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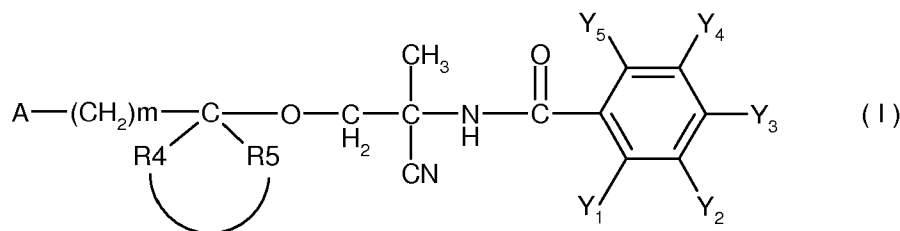
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(54) Title: THE USE OF AMINOACETONITRIL COMPOUNDS IN THE CONTROL OF ENDOPARASITES IN WARM-BLOOD ANIMALS.



(57) Abstract: The invention relates to the use of aminoacetonitrile compounds of formula (I) wherein A, R4, R5, m, Y1, Y2, Y3, Y4 and Y5 have the significances given in claim 1, in the control of endoparasites, especially helminths, in warm-blooded productive livestock and domestic animals.



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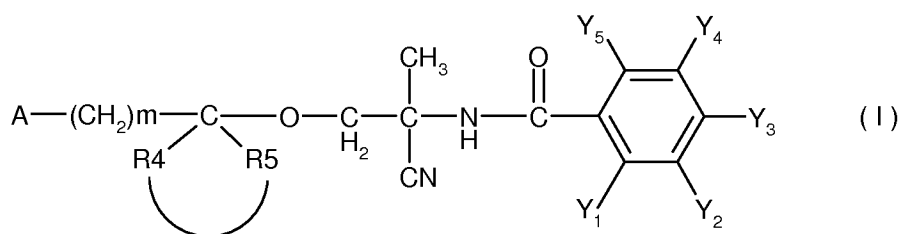
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THE USE OF AMINOACETONITRIL COMPOUNDS IN THE CONTROL OF ENDOPARASITES IN WARM-BLOOD ANIMALS .

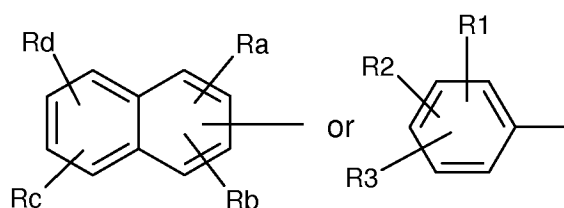
The present invention relates to veterinary compositions comprising as active ingredient a aminoacetonitrile compound of the formula I or an enantiomers thereof, as defined below and to the use of the compounds of the formula I for the preparation of said veterinary compositions and for combating endoparasites in animals, preferably nematodes. Thus the focus of the present invention is on the use of known aminoacetonitrile compounds in the control of endo- and ectoparasites, especially helminths, in and on warm-blooded productive livestock, domestic animals and fishes.

the control of endoparasites, especially helminthes, in warm-blooded productive livestock and domestic animals.

Said active ingredients have the formula I



wherein A is hydrogen,



R1, R2, R3, Ra, Rb, Rc, Rd, Y1, Y2, Y3, Y4 and Y5 is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, halo-C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, halo-C₁-C₆-alkylsulfonyl, di-C₁-C₆-alkylamino and a cyclic moiety M; whereby M is a cyclic moiety selected from the group consisting of unsubstituted or once to three time substituted C₃-C₆-cycloalkyl, phenyl, phenoxy and pyridyloxy, and whereby the substituents are independently of each other selected from the group consisting of halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio; or A stands for hetaryl that is unsubstituted or carries one, two or three substituents selected from the group defined for R1;

R4 and R5 are independently of each other hydrogen, C₁-C₆-alkyl, or for a saturated C₃-C₆-cycloalkylalkyl, and

m is 0, 1, 2, 3, 4, 5 or 6.

Substituted amidoacetonitrile compounds with pesticidal action are disclosed in EP0953565, for example. The active ingredients specifically revealed therein may not, however, always meet the requirements concerning strength and activity spectrum. There consequently exists a need for active ingredients with improved pesticidal properties. It has now been found that the amidoacetonitrile compounds of the formula I have outstanding pesticidal properties, in particular against endo- and ectoparasites in and on productive livestock, domestic animals fishes and plants.

An important aspect of the present invention is a veterinary composition comprising a compound of the formula I and a physiologically acceptable carrier.

Alkyl - as group per se and as structural component of other groups and compounds, for example of haloalkyl, alkoxy, alkylthio, alkylsulfinyl and alkylsulfonyl, - is, in each case giving due consideration to the number of carbon atoms which the relevant group or compound has in each individual case, either straight-chain, i.e. methyl, ethyl, propyl, butyl, pentyl or hexyl, or branched, e.g. isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl or isohexyl.

Cycloalkyl - as group per se and as structural component of other groups and compounds, for example of a substituted cycloalkylgroup, - is, in each case giving due consideration to the number of carbon atoms which the relevant group or compound has in each individual case, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Aryl is phenyl or naphthyl, preferably phenyl.

Hetaryl is heteroaromatic ring that is bound to the basic molecule through a C-C bond and is selected from the group consisting of pyridyl, pyrimidyl, s-triazinyl, 1,2,4-triazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, triazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, benzothienyl, benzofuranyl, benzothiazolyl, indolyl and indazolyl, preferably from pyridyl, pyrimidyl, s-triazinyl and 1,2,4-triazinyl, in particular from pyridyl and pyrimidyl.

Halogen - as group per se and as structural component of other groups and compounds, such as of haloalkyl, haloalkoxy, haloalkylthio, haloalkylsulfinyl and haloalkylsulfonyl, - is fluorine, chlorine, bromine or iodine, in particular fluorine, chlorine or bromine, especially fluorine or chlorine.

Halogen-substituted carbon-comprising groups and compounds, such as haloalkyl, halo-

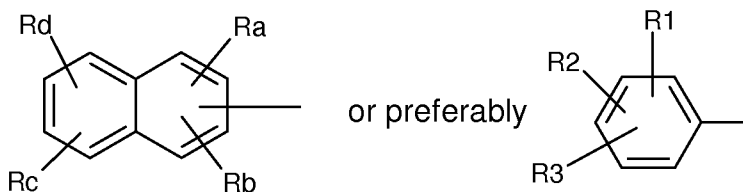
alkoxy, haloalkylthio, haloalkylsulfinyl and haloalkylsulfonyl, can be partially halogenated or perhalogenated, it being possible, in the case of polyhalogenation, for the halogen substituents to be identical or different. Examples of haloalkyl - as group per se and as structural component of other groups and compounds, such as of haloalkoxy or haloalkylthio, - are methyl substituted up to three times by fluorine, chlorine and/or bromine, such as CHF_2 or CF_3 ; ethyl substituted up to five times by fluorine, chlorine and/or bromine, such as CH_2CF_3 , CF_2CF_3 , CF_2CCl_3 , CF_2CHCl_2 , CF_2CHF_2 , CF_2CFCl_2 , CF_2CHBr_2 , CF_2CHClF , CF_2CHBrF or CClFCHClF ; propyl or isopropyl substituted up to seven times by fluorine, chlorine and/or bromine, such as $\text{CH}_2\text{CHBrCH}_2\text{Br}$, $\text{CF}_2\text{CHFCH}_2\text{Br}$, $\text{CH}_2\text{CF}_2\text{CF}_3$ or $\text{CH}(\text{CF}_3)_2$; butyl or one of its isomers substituted up to nine times by fluorine, chlorine and/or bromine, such as $\text{CF}(\text{CF}_3)\text{CHFCF}_3$ or $\text{CH}_2(\text{CF}_2)_2\text{CF}_3$; pentyl or one of its isomers substituted up to eleven times by fluorine, chlorine and/or bromine, such as $\text{CF}(\text{CF}_3)(\text{CHF})_2\text{CF}_3$ or $\text{CH}_2(\text{CF}_2)_3\text{CF}_3$; and hexyl or one of its isomers substituted up to thirteen times by fluorine, chlorine and/or bromine, such as $(\text{CH}_2)_4\text{CHBrCH}_2\text{Br}$, $\text{CF}_2(\text{CHF})_4\text{CF}_3$, $\text{CH}_2(\text{CF}_2)_4\text{CF}_3$ or $\text{C}(\text{CF}_3)_2(\text{CHF})_2\text{CF}_3$.

Alkoxy groups preferably have a chain length of 1 to 6 carbon atoms. For example, alkoxy is methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, and also the pentyloxy and hexyloxy isomers; preferably methoxy and ethoxy. Haloalkoxy groups preferably have a chain length of 1 to 6 carbon atoms. Haloalkoxy is, e.g., fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2-difluoroethoxy and 2,2,2-trichloroethoxy; preferably difluoromethoxy, 2-chloroethoxy and trifluoromethoxy.

Preferred subgroups compounds within the formula I consist of:

(1) Compounds of the formula I, wherein R4 and R5 are independently of each other hydrogen or methyl, and the other substituents are as previously defined under formula I.

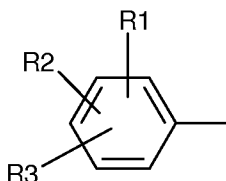
(2) Compounds of the formula I, wherein A is hydrogen,



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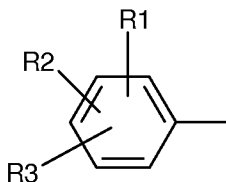
R1, R2, R3, Ra, Rb, Rc, Rd, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl and C₁-C₆-alkylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, preferably hydrogen; and m is 1 or preferably 0.

(3) Compounds of the formula I, wherein A is



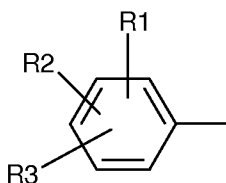
R1, R2, and R3 independently of each other is hydrogen, chlorine, fluorine, nitro, cyano, methyl, ethyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, chlorine, fluorine, nitro, cyano, methyl, methoxy, methylthio, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, preferably hydrogen; and m is 1 or preferably 0.

(4) Compounds of the formula I, wherein A is



R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, preferably hydrogen; and m is 0 or 1.

(5) Compounds of the formula I, wherein A is



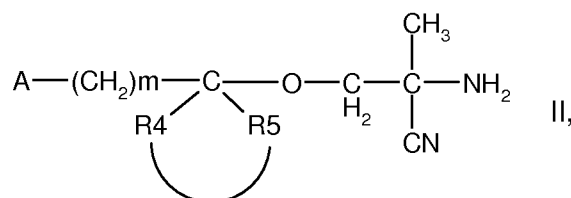
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R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, and Y₅ are hydrogen; Y₄ is trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, preferably hydrogen; and m is 0.

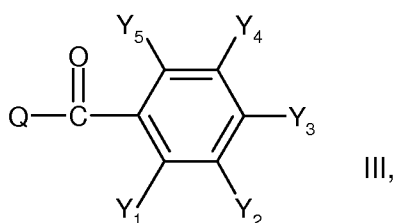
(6) Compounds of the formula I, wherein A is a hetaryl selected from the group consisting of pyridyl, pyrimidyl, s-triazinyl, 1,2,4-triazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, triazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, benzothienyl, benzofuranyl, benzothiazolyl, indolyl and indazolyl, preferably from pyridyl, pyrimidyl, s-triazinyl and 1,2,4-triazinyl, in particular from pyridyl and pyrimidyl that is unsubstituted or carries one, two or three substituents selected from the group hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy; Y₁, Y₂, Y₃, and Y₅ are hydrogen; Y₄ is trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, preferably hydrogen; and m is 0.

The compounds of the formula I listed in Table 1 are particularly preferred within the context of the invention and very particularly those presented with physical parameters.

A further subject-matter of the invention is the process for the preparation of the compounds of the formula I, which comprises the reaction of a compound of the formula



which is known or can be prepared by analogy to relevant known compounds and in which A, R4, R5 and m are as defined above in the formula I, with a compound of the formula



which is known or can be prepared by analogy to relevant known compounds and in which Y₁, Y₂, Y₃, Y₄ and Y₅ are as defined as in the formula I and Q is a leaving group, if desired in

the presence of a basic catalyst.

If desired, one can convert a compound of the formula I obtainable according to this process or in another way, from the free form to a salt form, or to another compound of the formula I. One can also separate the mixture of isomers isolate the desired isomer.

The reactants can be reacted with one another as such, i.e. without addition of a solvent or diluent, e.g. in the molten form. For the most part, however, it is advantageous to add an inert solvent or diluent or a mixture thereof. Mention may be made, as examples of such solvents or diluents, of: aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, such as benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene or tetrachloroethene; ethers, such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tert-butyl methyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol dimethyl ether, dimethoxydiethyl ether, tetrahydrofuran or dioxane; ketones, such as acetone, methyl ethyl ketone or methyl isobutyl ketone; amides, such as N,N-dimethylformamide, N,N-diethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethylphosphoramide; nitriles, such as acetonitrile or propionitrile; and sulfoxides, such as dimethyl sulfoxide.

Preferred leaving groups Q are OH, halogens, tosylates, mesylates and triflates, particularly preferably halogens, especially chlorine.

Suitable bases for facilitating the reaction are, e.g., alkali metal or alkaline earth metal hydroxides, hydrides, amides, alkoxides, acetates, carbonates, dialkylamides or alkylsilylamides, alkylamines, alkylenediamines, if desired N-alkylated and saturated or unsaturated, cycloalkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. Mention may be made, by way of examples, of sodium hydroxide, sodium hydride, sodamide, sodium methoxide, sodium acetate, sodium carbonate, potassium tert-butoxide, potassium hydroxide, potassium carbonate, potassium hydride, lithium diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, triethylamine, diisopropylethylamine, triethylenediamine, cyclohexylamine, N-Cyclohexyl-N,N-dimethylamine, N,N-diethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, quinuclidine, N-methylmorpholine, benzyltrimethylammonium hydroxide and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU).

The reaction is advantageously carried out at a temperature from approximately 0 °C to approximately +150 °C, preferably from approximately 20 °C to approximately +100 °C.

According to the method or reaction conditions, the compounds I with salt-forming properties can be obtained in the free form or in the form of salts.

The compounds I can also be obtained in the form of their hydrates and/or can incorporate other solvents, which might, for example, be used in the crystallization of compounds existing in the solid form.

The compounds I can exist in the form of one of the possible isomers or as a mixture of the same, e.g., according to the number, absolute and relative configuration of the asymmetric carbon atoms, as pure isomers, for example optical isomers and/or diastereoisomers, or as mixtures of isomers, such as mixtures of enantiomers, e.g. racemates, mixtures of diastereoisomers or racemate mixtures; the invention relates both to the pure isomers and to all possible mixtures of isomers and is to be correspondingly understood in each case heretofore and hereinafter, even if stereochemical details are not specifically referred to in every case.

Mixtures of diastereoisomers and mixtures of racemates of compounds I obtainable according to the process - depending on the choice of the starting materials and operating methods - or otherwise obtainable can be separated in a known way into the pure diastereoisomers or racemates on the basis of the physicochemical differences of the components, for example by fractional crystallization, distillation and/or chromatography. Correspondingly obtainable mixtures of enantiomers, such as racemates, can be resolved into the optical isomers by known methods, for example by recrystallization from an optically active solvent, by chromatography on chiral adsorbents, e.g. high performance liquid chromatography (HPLC) on acetylcellulose, with the help of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion complexes, e.g. by using chiral crown ethers, in which only one enantiomer is complexed.

In addition to through separation of the corresponding mixtures of isomers, pure diastereoisomers or enantiomers according to the invention can also be obtained through generally known methods of diastereoselective or enantioselective synthesis, e.g. by carrying out the process according to the invention with educts with correspondingly suitable stereochemistry.

Advantageously, the biologically more effective isomer, e.g. enantiomer, or mixture of isomers, e.g. mixture of enantiomers, is isolated or synthesized each time, provided that the individual components have different biological activity.

In the process of the present invention, use is preferably made of such starting materials and intermediates which result in the compounds I described at the beginning as particularly valuable.

The invention in particular relates to the preparation process described in the example. Starting materials and intermediates used according to the invention for the preparation of the compounds I which are novel, their use and processes for their preparation likewise form a subject-matter of the invention.

In the context of the present invention, ectoparasites are understood to be in particular insects, acari (mites and ticks), and crustaceans (sea lice). These include insects of the following orders: *Lepidoptera*, *Coleoptera*, *Homoptera*, *Hemiptera*, *Heteroptera*, *Diptera*, *Dictyoptera*, *Thysanoptera*, *Orthoptera*, *Anoplura*, *Siphonaptera*, *Mallophaga*, *Phthiraptera*, *Thysanura*, *Isoptera*, *Psocoptera* and *Hymenoptera*. However reference may in particular be made to ectoparasites which are a nuisance to man or animals and which transmit pathogens, for example flies such as *Musca domestica*, *Musca vetustissima*, *Musca autumnalis*, *Fannia canicularis*, *Sarcophaga carnaria*, *Lucilia cuprina*, *Lucilia sericata*, *Hypoderma bovis*, *Hypoderma lineatum*, *Chrysomya chloropyga*, *Dermatobia hominis*, *Cochliomyia hominivorax*, *Gasterophilus intestinalis*, *Oestrus ovis*, biting flies such as *Haematobia irritans irritans*, *Haematobia irritans exigua*, *Stomoxys calcitrans*, horse-flies (Tabanids) with the subfamilies of Tabanidae such as *Haematopota* spp. (e.g. *Haematopota pluvialis*) and *Tabanus* spp. (e.g. *Tabanus nigrovittatus*) and *Chrysopsinae* such as *Chrysops* spp. (e.g. *Chrysops caecutiens*); Hippoboscids such as *Melophagus ovinus* (sheep ked); tsetse flies, such as *Glossinia* spp.; other biting insects like midges, such as *Ceratopogonidae* (biting midges), *Simuliidae* (Blackflies), *Psychodidae* (Sandflies); but also blood-sucking insects, for example mosquitoes, such as *Anopheles* spp, *Aedes* spp and *Culex* spp, fleas, such as *Ctenocephalides felis* and *Ctenocephalides canis* (cat and dog fleas), *Xenopsylla cheopis*, *Pulex irritans*, *Ceratophyllus gallinae*, *Dermatophilus penetrans*, blood-sucking lice (*Anoplura*) such as *Linognathus* spp, *Haematopinus* spp, *Solenopotes* spp, *Pediculus humanis*; but also chewing lice (*Mallophaga*) such as *Bovicola (Damalinia) ovis*, *Bovicola (Damalinia) bovis* and other *Bovicola* spp.

Compounds of the formula I can also be used against hygiene pests, especially of the order *Diptera* of the families *Muscidae*, *Sarcophagidae*, *Anophilidae* and *Culicidae*; the orders *Orthoptera*, *Dictyoptera* (e.g. the family *Blattidae* (cockroaches), such as *Blatella germanica*, *Blatta orientalis*, *Periplaneta Americana*), *Isoptera* (termites) and *Hymenoptera* (e.g. the families *Formicidae* (ants) and *Vespidae* (wasps)).

The compounds I also have lasting activity in the case of phytoparasitic mites and insects. In the case of spider mites of the order *Acarina*, they are active against eggs, nymphs and adults of *Tetranychidae* (*Tetranychus* spp. and *Panonychus* spp.).

They are highly active in the case of the sucking insects of the order Homoptera, in particular against pests of the families Aphididae, Delphacidae, Cicadellidae, Psyllidae, Loccidae, *Diaspididae* and *Eriophyidae* (e.g. citrus rust mite); of the orders Hemiptera, Heteroptera and Thysanoptera, and in the case of the phytophagous insects of the orders Lepidoptera, *Coleoptera*, *Diptera* and *Orthoptera*.

They are also suitable as soil insecticides against pests in the soil.

The compounds of the formula I are accordingly active against all development stages of sucking and feeding insects on crops such as cereals, cotton, rice, maize, soya beans, potatoes, vegetables, fruit, tobacco, hops, citrus fruit, avocados and others.

Ectoparasites also include members of the order Acarina, such as mites (e.g. *Chorioptes bovis*, *Cheyletiella* spp., *Dermanyssus gallinae*, *Demodex canis*, *Sarcoptes scabiei*, *Psoroptes ovis* and *Psorergates* spp. and ticks. Known representatives of ticks are, for example, *Boophilus*, *Amblyomma*, *Anocentor*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, *Rhipicentor*, *Margaropus*, *Rhipicephalus*, *Argas*, *Otobius* and *Ornithodoros* and the like, which preferably infest warm-blooded animals including farm animals, such as cattle, horses, pigs, sheep and goats, poultry such as chickens, turkeys, guinea fowls and geese, fur-bearing animals such as mink, foxes, chinchillas, rabbits and the like, as well as domestic animals such as cats and dogs, but also humans.

Ticks may be divided into hard and soft ticks, and are characterized by infesting one, two or three host animals. They attach themselves to a passing host animal and suck the blood or body fluids. Fully engorged female ticks drop from the host animal and lay large amounts of eggs (2000 to 3000) in a suitable crack in the floor or in any other protected site where the larvae hatch. These in turn seek a host animal, in order to suck blood from it. Larvae of ticks which only infest one host animal molt twice and thus become nymphs and finally adult ticks without leaving the host they have selected. Larvae of ticks which infest two or three host animals leave the animal after feeding on the blood, molt in the local environment and seek a second or third host as nymphs or as adult ticks, in order to suck its blood.

Ticks are responsible world-wide for the transmission and spread of many human and animal diseases. Because of their economic influence, the most important ticks are *Boophilus*, *Rhipicephalus*, *Ixodes*, *Hyalomma*, *Amblyomma* and *Dermacentor*. They are carriers of bacterial, viral, rickettsial and protozoal diseases and cause tick-paralysis and tick-toxicosis. Even a single tick can cause paralysis whereby its saliva penetrates into the host animal during ingestion. Diseases caused by ticks are usually transmitted by ticks, which infest several host animals. Such diseases, for example babesiosis, anaplasmosis, theileriasis and heart water disease, are responsible for the death or impairment of a large number of

domestic and farm animals in the entire world. In many countries of temperate climate, Ixodid ticks transmit the agent of the chronically harmful Lyme's disease from wild animals to humans. Apart from the transmission of disease, the ticks are responsible for great economic losses in livestock production. Losses are not confined to the death of the host animals, but also include damage to the pelts, loss of growth, a reduction in milk production and reduced value of the meat.

The compounds of the formula I according to the invention are also active against all or individual development stages of animal pests showing normal sensitivity, as well as those showing resistance to widely used parasiticides. This is especially true for resistant insects and members of the order *Acarina*. The insecticidal, ovicidal and/or acaricidal effect of the active substances of the invention can manifest itself directly, i.e. killing the pests either immediately or after some time has elapsed, for example when moulting occurs (growth regulators), or by destroying their eggs, or indirectly, e.g. reducing the number of eggs laid and/or the hatching rate, good efficacy corresponding to a pesticidal rate (mortality) of at least 50 to 60%.

The compounds I also have lasting activity in the case of phytoparasitic mites and insects. In the case of spider mites of the order *Acarina*, they are active against eggs, nymphs and adults of *Tetranychidae* (*Tetranychus spp.* and *Panonychus spp.*).

They are highly active in the case of the sucking insects of the order *Homoptera*, in particular against pests of the families *Aphididae*, *Delphacidae*, *Cicadellidae*, *Psyllidae*, *Loccidae*, *Diaspididae* and *Eriophyidae* (e.g. citrus rust mite); of the orders *Hemiptera*, *Heteroptera* and *Thysanoptera*, and in the case of the phytophagous insects of the orders *Lepidoptera*, *Coleoptera*, *Diptera* and *Orthoptera*.

They are also suitable as soil insecticides against pests in the soil.

The compounds of the formula I are accordingly active against all development stages of sucking and feeding insects on crops such as cereals, cotton, rice, maize, soya beans, potatoes, vegetables, fruit, tobacco, hops, citrus fruit, avocados and others.

The compounds are particularly active against helminths, among which the endoparasitic nematodes and trematodes can be the cause of serious diseases in mammals, fish and poultry, e.g. in sheep, pigs, goats, cattle, horses, donkeys, dogs, cats, guinea pigs, salmonids, cods and ornamental birds. Typical nematodes of this indication are:

Haemonchus, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Chabertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*,

Heterakis, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. Mention may specifically be made, among the trematodes, of the family of the Fasciolidae, in particular *Fasciola hepatica*.

The particular advantage of the compounds of the formula I is their activity against such parasites, which are resistant to benzimidazole-based active ingredients and to macrocyclic lactones.

Certain species of the genera *Nematodirus*, *Cooperia* and *Oesophagostomum* infect the intestinal tract of the host animal, while others of the genera *Haemonchus* and *Ostertagia* parasitize in the stomach and others of the genus *Dictyocaulus* parasitize in lung tissue. Parasites of the families Filariidae and Setariidae are found in internal cell tissue and in organs, e.g. the heart, blood vessels, lymph vessels and subcutaneous tissue. Mention may particularly be made here of the dog heartworm, *Dirofilaria immitis*.

The compounds of the formula I are highly effective against these parasites.

The pests which can be controlled with the compounds of the formula I also include, from the class Cestoda (tapeworms), the families Mesocestoidae, in particular the genus *Mesocestoides*, especially *M. lineatus*; Dilepididae, in particular *Dipylidium caninum*, *Joyeuxiella* spp., especially *Joyeuxiella pasquali*, and *Diplopylidium* spp.; and Taeniidae, in particular *Taenia pisiformis*, *Taenia cervi*, *Taenia ovis*, *Taenia hydatigena*, *Taenia multiceps*, *Taenia taeniaeformis*, *Taenia serialis* and *Echinococcus* spp., particularly preferably *Taenia hydatigena*, *Taenia ovis*, *Taenia multiceps*, *Taenia serialis*; *Echinococcus granulosus*, *Echinococcus multilocularis*, and *Multiceps multiceps*.

In a very particularly preferred way, *Taenia hydatigena*, *Taenia pisiformis*, *Taenia ovis*, *Taenia taeniaeformis*, *Multiceps multiceps*, *Joyeuxiella pasquali*, *Dipylidium caninum*, *Mesocestoides* spp., *Echinococcus granulosus* and *E. multilocularis* are controlled simultaneously with *Dirofilaria immitis*, *Ancylostoma* spp., *Toxocara* spp. and/or *Trichuris vulpis* on or in dogs and cats. Also in a preferred way, *Ctenocephalides felis* and/or *Ctenocephalides canis* are controlled simultaneously with the abovementioned nematodes and cestodes.

The compounds of the formula I are also suitable for controlling parasites which are pathogenic to man, among which may be mentioned, as typical representatives occurring in the digestive tract, those of the genera *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris* and *Enterobius*. The compounds of the present invention are also active against parasites of the genera *Wuchereria*, *Brugia*, *Onchocerca* and *Loa* from the family of the Filariidae, which occur in the blood, in tissue and in various organs, and also

against *Dracunculus* and parasites of the genera *Strongyloides* and *Trichinella*, which specifically infect the gastrointestinal tract.

The compounds of the formula I are also active against plant nematodes of the genera *Meloidogyne*, *Heterodera*, *Pratylenchus*, *Ditylenchus*, *Radopholus*, *Rizoglyphus* and others.

The compounds of the formula I are used as such or preferably together with the auxiliaries conventional in formulation technology and can accordingly be processed in a known way, for example to liquid formulations such as solutions, suspensions, emulsions, emulsifiable concentrates, dilutable solutions or solid formulations such as soluble powders, granules, tablets, capsules. The application methods as well as the compositions are chosen in accordance with the intended aims and the prevailing circumstances.

The formulation, i.e. the compositions, preparations or combinations comprising the active ingredient of the formula I, or combinations of these active ingredients with other active ingredients, and, if desired, a solid or liquid additive, is prepared in a known way, for example by dissolving, intimately mixing and/or grinding the active ingredients with extenders, for example with solvents, solid carriers and other excipients with required properties like surface-active compounds (surfactants), solubilizers, stabilizers, preservatives.

Preferred application forms for use in warm-blooded animals for controlling helminths include oral liquid formulations (drenches) such as solutions, emulsions, suspensions, emulsion concentrates, directly dilutable solutions, oral solid formulations such as feed additives, powders, tablets, including effervescent tablets, boluses, capsules, microencapsulations and topically applied pour-on formulations such as solutions, suspensions, emulsions, emulsion concentrates, solution concentrates, and parenterally or subcutaneously administered formulations such as solutions, suspensions, emulsions or long acting parenteral formulations like microparticles, implants or injectable depots; care having to be taken over the physiological compatibility of the formulation auxiliaries.

The following are possible as solvents: alcohols, such as ethanol, propanol or butanol, and glycols, and their ethers and esters, such as propylene glycol, dipropylene glycol ether, ethylene glycol, ethylene glycol monomethyl ether or ethylene glycol monoethyl ether, ketones, such as cyclohexanone, isophorone or diacetone alcohol, strongly polar solvents, such as N-methyl-2-pyrrolidone, dimethyl sulfoxide, dimethylformamide or water, vegetable and mineral oils, such as rapeseed oil, castor oil, coconut oil, soybean oil or medium chain triglycerides; and, if desired, silicone oils.

Suitable binders for tablets and boluses are chemically modified polymeric natural products which are soluble in water or alcohol, such as starch, cellulose or protein derivatives (e.g.,

methylcellulose, carboxymethylcellulose, ethylhydroxyethylcellulose, proteins, such as zein, gelatin, and the like), and synthetic polymers, for example polyvinyl alcohol, polyvinylpyrrolidone, and the like. Tablets also comprise fillers (e.g., starch, microcrystalline cellulose, sugar, lactose, and the like), glidants, lubricants and disintegrating agents. If the anthelmintic compositions are present in the form of feed concentrates, then high-performance feed, feed cereals or protein concentrates, for example, are used as carriers. Such feed concentrates or compositions can, in addition to the active ingredients, also comprise additives, vitamins, antibiotics, chemotherapeutics, or other pesticides, mainly bacteriostats, fungistats, coccidiostats, or also hormone preparations, anabolics or substances which promote growth, influence the quality of meat from animals for slaughter or are useful to the organism in another way. If the compositions or the active ingredients of the formula I present therein are added directly to the feed or to the drinking water for the animals, the finished feed or the finished drinking water comprises the active ingredients preferably in a concentration from approximately 0.0005 to 0.02% by weight (5-200 ppm).

The compounds of the formula I according to the invention can be used alone or in combination with other biocides. They can, e.g., be combined with pesticides possessing the same direction of action, in order to enhance the action, or can be combined with substances possessing another direction of action, in order to broaden the activity spectrum. It may also make sense to add substances which repel, known as repellents. If it is desired to expand the activity spectrum with regard to endoparasites, for example worms, the compounds of the formula I are appropriately combined with substances having endoparasitocidal properties. They can also, naturally, be used in combination with antibacterial compositions. Since the compounds of the formula I represent adulticides, i.e. since they are effective in particular against the adult stages of the target parasites, the addition of pesticides which are more likely to attack the juvenile stages of parasites can be highly advantageous. In this way, most of those parasites causing great economic damage are namely included. In addition, a substantial contribution is also made as well to avoiding the formation of resistance. Some combinations can also lead to synergistic effects, i.e. that the total amount of active substance consumed can be reduced, which is desirable from an ecological viewpoint. Preferred groups of combination participants and particularly preferred combination participants are mentioned subsequently, which combinations can, in addition to a compound of the formula I, comprise one or more of these participants. Suitable participants in the mixture include biocides, for example the insecticides and acaricides with different mechanisms of action mentioned subsequently and sufficiently

known to a person skilled in the art, for example chitin synthesis inhibitors, growth regulators; active ingredients which act as juvenile hormones; active ingredients which act as adulticides; broad spectrum insecticides, broad spectrum acaricides and nematocides; but also the sufficiently known anthelmintics and substances which repel insects and/or members of the Acarina, known as repellents or detachers.

Nonlimiting examples of suitable insecticides and acaricides are:

1. Abamectin	29. Carbaryl	57. Dioxathion
2. AC 303 630	30. Carbofuran	58. DPX-MP062
3. Acephate	31. Carbophenothion	59. Edifenphos
4. Acrinathrin	32. Cartap	60. Emamectin
5. Alanycarb	33. Cloethocarb	61. Endosulfan
6. Aldicarb	34. Chlorethoxyfos	62. Esfenvalerate
7. -Cypermethrin	35. Chlorfenapyr	63. Ethiofencarb
8. Alphamethrin	36. Chlorfluazuron	64. Ethion
9. Amitraz	37. Chlormephos	65. Ethofenprox
10. Avermectin B ₁	38. Chlorpyrifos	66. Ethoprophos
11. AZ 60541	39. Cis-Resmethrin	67. Etrifos
12. Azinphos E	40. Clocythrin	68. Fenamiphos
13. Azinphos-methyl	41. Clofentezine	69. Fenazaquin
14. Azocyclotin	42. Cyanophos	70. Fenbutatin oxide
15. <i>Bacillus subtil.</i> toxin	43. Cycloprothrin	71. Fenitrothion
16. Bendiocarb	44. Cyfluthrin	72. Fenobucarb
17. Benfuracarb	45. Cyhexatin	73. Fenothiocarb
18. Bensultap	46. D 2341	74. Fenoxycarb
19. -Cyfluthrin	47. Deltamethrin	75. Fenpropathrin
20. Bifenthrin	48. Demeton M	76. Fenpyrad
21. BPMC	49. Demeton S	77. Fenpyroximate
22. Brofenprox	50. Demeton-S-methyl	78. Fenthion
23. Bromophos E	51. Dichlofenthion	79. Fenvalerate
24. Bufencarb	52. Dicliphos	80. Fipronil
25. Buprofezin	53. Diethion	81. Fluazinam
26. Butocarboxim	54. Diflubenzuron	82. Fluazuron
27. Butylpyridaben	55. Dimethoate	83. Flucycloxuron
28. Cadusafos	56. Dimethylvinphos	84. Flucythrinate

85. Flufenoxuron
86. Flufenprox
87. Fonofos
88. Formothion
89. Fosthiazate
90. Fubfenprox
91. HCH
92. Heptenophos
93. Hexaflumuron
94. Hexythiazox
95. Hydroprene
96. Imidacloprid
97. Insect-active fungi
98. Insect-active nematodes
99. Insect-active viruses
100. Iprobenfos
101. Isofenphos
102. Isoprocab
103. Isoxathion
104. Ivermectin
105. -Cyhalothrin
106. Lufenuron
107. Malathion
108. Mecarbam
109. Mesulfenfos
110. Metaldehyde
111. Methamidophos
112. Methiocarb
113. Methomyl
114. Methoprene
115. Metolcarb
116. Mevinphos

117. Milbemectin
118. Moxidectin
119. Naled
120. NC 184
121. NI-25, Acetamiprid
122. Nitenpyram
123. Omethoate
124. Oxamyl
125. Oxydemeton M
126. Oxydeprofos
127. Parathion
128. Parathion-methyl
129. Permethrin
130. Phenthoate
131. Phorate
132. Phosalone
133. Phosmet
134. Phoxim
135. Pirimicarb
136. Pirimiphos E
137. Pirimiphos M
138. Promecarb
139. Propaphos
140. Propoxur
141. Prothiofos
142. Prothoate
143. Pyraclofos
144. Pyridaphenthion
145. Pyresmethrin
146. Pyrethrum
147. Pyridaben
148. Pyrimidifen
149. Pyriproxyfen

150. RH-5992
151. RH-2485
152. Salithion
153. Sebufos
154. Silafluofen
155. Spinosad
156. Sulfotep
157. Sulprofos
158. Tebufenozide
159. Tebufenpyrad
160. Tebupirimfos
161. Teflubenzuron
162. Tefluthrin
163. Temephos
164. Terbam
165. Terbufos
166. Tetrachlorvinphos
167. Thiafenox
168. Thiodicarb
169. Thiofanox
170. Thionazin
171. Thuringiensin
172. Tralomethrin
173. Triarathene
174. Triazamate
175. Triazophos
176. Triazuron
177. Trichlorfon
178. Triflumuron
179. Trimethacarb
180. Vamidothion
181. XMC (3,5-xylyl methylcarbamate)

182. Xylylcarb
183. YI 5301/5302
184. -Cypermethrin
185. Zetamethrin

Nonlimiting examples of suitable anthelmintics are mentioned subsequently, in which some representatives, in addition to the anthelmintic activity, also have an insecticidal and acaricidal activity and are already included in the above list:

- (A1) Praziquantel = 2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1- α]isoquinoline
- (A2) Closantel = 3,5-Diiodo-N-[5-chloro-2-methyl-4-(α -cyano-4-chlorobenzyl)phenyl]-salicylamide
- (A3) Triclabendazole = 5-Chloro-6-(2,3-dichlorophenoxy)-2-methylthio-1H-benzimidazole
- (A4) Levamisole = L-(-)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole
- (A5) Mebendazole = Methyl 5-benzoyl-1H-benzimidazol-2-ylcarbamate
- (A6) Omphalotin = a macrocyclic fermentation product from the fungus *Omphalotus olearius* disclosed in WO 97/20857
- (A7) Abamectin = Avermectin B1
- (A8) Ivermectin = 22,23-Dihydroavermectin B1
- (A9) Moxidectin = 5-O-Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino)milbemycin B
- (A10) Doramectin = 25-Cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)avermectin A1a
- (A11) Milbemectin = Mixture of Milbemycin A3 and Milbemycin A4
- (A12) Milbemycin oxime = 5-Oxime of Milbemectin

Nonlimiting examples of suitable repelling substances (repellents or detachers) are:

- (R1) DEET (N,N-Diethyl-m-toluamide)
- (R2) KBR 3023 N-Butyl-2-oxycarbonyl-2-(2-hydroxyethyl)piperidine
- (R3) Cymiazole = N-2,3-Dihydro-3-methyl-1,3-thiazol-2-ylidene-2,4-xylylidine

The participants in the mixture which are mentioned are very well known to a person skilled in the art. Most are described in the various editions of The Pesticide Manual, The British Crop Protection Council, London, others in the various editions of The Merck Index, Merck & Co. Inc., Rahway, New Jersey, USA, or in the patent literature. The following listing is accordingly restricted to a few references by way of examples.

- (I) 2-Methyl-2-(methylthio)propionaldehyde O-methylcarbamoyloxime (Aldicarb), from The Pesticide Manual, 13th Ed. (2001), The British Crop Protection Council, London, page 26;
- (II) S-(3,4-Dihydro-4-oxobenzo[d][1,2,3]triazin-3-ylmethyl) O,O-dimethyl phosphorodithioate (Azinphos-methyl), from The Pesticide Manual, 13th Ed. (2001), The British Crop Protection Council, London, page 67;

- (III) Ethyl N-[2,3-dihydro-2,2-dimethylbenzofuran-7-yloxycarbonyl(methyl)aminothio]-N-isopropyl- β -alaninate (Benfuracarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 96;
- (IV) 2-Methylbiphenyl-3-ylmethyl (*Z*)-(1*RS*)-*cis*-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate (Bifenthrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 118;
- (V) 2-tert-Butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one (Buprofezin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 157;
- (VI) 2,3-Dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate (Carbofuran), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 186;
- (VII) 2,3-Dihydro-2,2-dimethylbenzofuran-7-yl (dibutylaminothio)methylcarbamate (Carbosulfan), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 188;
- (VIII) *S,S'*-(2-Dimethylaminotrimethylene) bis(thiocarbamate) (Cartap), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 193;
- (IX) 1-[3,5-Dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenyl]-3-(2,6-difluorobenzoyl)-urea (Chlorfluazuron), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 213;
- (X) *O,O*-Diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate (Chlorpyrifos), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 235;
- (XI) (*RS*)- α -Cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (Cyfluthrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 293;
- (XII) Mixture of (*S*)- α -cyano-3-phenoxybenzyl (*Z*)-(1*R*,3*R*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate and (*R*)- α -cyano-3-phenoxybenzyl (*Z*)-(1*S*,3*S*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate (Lambda-Cyhalothrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 300;
- (XIII) Racemate consisting of (*S*)- α -cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (*R*)- α -cyano-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (Alpha-cypermethrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 308;

- (XIV) A mixture of the stereoisomers of (*S*)- α -cyano-3-phenoxybenzyl (1*RS*,3*RS*,1*RS*,3*RS*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (zeta-Cypermethrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 314;
- (XV) (*S*)- α -Cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (Deltamethrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 344;
- (XVI) 1-(4-Chlorophenyl)-3-(2,6-difluorobenzoyl)urea (Diflubenzuron), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 395;
- (XVII) (1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-en-2,3-ylenebismethylene) sulfite (Endosulfan), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 459;
- (XVIII) α -Ethylthio-*o*-tolyl methylcarbamate (Ethiofencarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 479;
- (XIX) *O,O*-Dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate (Fenitrothion), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 514;
- (XX) 2-*sec*-Butylphenyl methylcarbamate (Fenobucarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 516;
- (XXI) (*RS*)- α -Cyano-3-phenoxybenzyl (*RS*)-2-(4-chlorophenyl)-3-methylbutyrate (Fenvalerate), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 539;
- (XXII) *S*-[Formyl(methyl)carbamoylmethyl] *O,O*-dimethyl phosphorodithioate (Formothion), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 625;
- (XXIII) 4-Methylthio-3,5-xylyl methylcarbamate (Methiocarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 813;
- (XXIV) 7-Chlorobicyclo[3.2.0]hepta-2,6-dien-6-yl dimethyl phosphate (Heptenophos), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 670;
- (XXV) 1-(6-Chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine (Imidacloprid), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 706;
- (XXVI) 2-Isopropylphenyl methylcarbamate (Isoprocab), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 729;

- (XXVII) *O,S*-Dimethyl phosphoramidothioate (Methamidophos), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 808;
- (XXVIII) *S*-Methyl *N*-(methylcarbamoyloxy)thioacetimidate (Methomyl), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 815;
- (XXIX) Methyl 3-(dimethoxyphosphinoyloxy)but-2-enoate (Mevinphos), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 844;
- (XXX) *O,O*-Diethyl *O*-4-nitrophenyl phosphorothioate (Parathion), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 926;
- (XXXI) *O,O*-Dimethyl *O*-4-nitrophenyl phosphorothioate (Parathion-methyl), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 928;
- (XXXII) *S*-6-Chloro-2,3-dihydro-2-oxo-1,3-benzoxazol-3-ylmethyl *O,O*-diethyl phosphorodithioate (Phosalone), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 963;
- (XXXIII) 2-Dimethylamino-5,6-dimethylpyrimidin-4-yl dimethylcarbamate (Pirimicarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 985;
- (XXXIV) 2-Isopropoxyphenyl methylcarbamate (Propoxur), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1036;
- (XXXV) 1-(3,5-Dichloro-2,4-difluorophenyl)-3-(2,6-difluorobenzoyl)urea (Teflubenzuron), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1158;
- (XXXVI) *S*-tert-Butylthiomethyl *O,O*-diethyl phosphorodithioate (Terbufos), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1165;
- (XXXVII) Ethyl (3-*tert*-butyl-1-dimethylcarbamoyl-1*H*-1,2,4-triazol-5-ylthio)acetate, (Triazamate), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1224;
- (XXXVIII) Abamectin, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 3;
- (XXXIX) 2-sec-Butylphenyl methylcarbamate (Fenobucarb), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 516;
- (XL) *N*-*tert*-Butyl-*N*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide (Tebufenozide), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1147;

- (XLI) ($\pm$)-5-Amino-1-(2,6-dichloro- α,α,α -trifluoro-p-tolyl)-4-trifluoromethylsulfinylpyrazole-3-carbonitrile (Fipronil), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 545;
- (XLII) (*RS*)- α -Cyano-4-fluoro-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (beta-Cyfluthrin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 295;
- (XLIII) (4-Ethoxyphenyl)[3-(4-fluoro-3-phenoxyphenyl)propyl](dimethyl)silane (Silafluofen), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1105;
- (XLIV) *tert*-Butyl (*E*)- α -(1,3-dimethyl-5-phenoxy-pyrazol-4-ylmethyleneamino-oxy)-p-toluate (Fenpyroximate), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 530;
- (XLV) 2-*tert*-Butyl-5-(4-*tert*-butylbenzylthio)-4-chloropyridazin-3(2*H*)-one (Pyridaben), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1161;
- (XLVI) 4-[[4-(1,1-Dimethylethyl)phenyl]ethoxy]quinazoline (Fenazaquin), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 507;
- (XLVII) 4-Phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether (Pyriproxyfen), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1073;
- (XLVIII) 5-Chloro-*N*-{2-[4-(2-ethoxyethyl)-2,3-dimethylphenoxy]ethyl}-6-ethylpyrimidin-4-amine (Pyrimidifen), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1070;
- (XLIX) (*E*)-*N*-(6-Chloro-3-pyridylmethyl)-*N*-ethyl-*N*-methyl-2-nitrovinylidenediamine (Nitenpyram), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 880;
- (L) (*E*)-*N*¹-[(6-Chloro-3-pyridyl)methyl]-*N*²-cyano-*N*¹-methylacetamidine (NI-25, Acetamiprid), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 9;
- (LI) Avermectin B₁, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 3;
- (LII) An insect-active extract from a plant, in particular (2*R*,6*aS*,12*aS*)-1,2,6,6*a*,12,12*a*-hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-*b*]furo[2,3-*h*]chromen-6-one (Rotenone), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection

- Council, London, page 1097; and an extract from *Azadirachta indica*, in particular azadirachtin, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 59;
- (LIII) A preparation comprising insect-active nematodes, preferably *Heterorhabditis bacteriophora* and *Heterorhabditis megidis*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 671; *Steinernema feltiae*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1115, and *Steinernema scapterisci*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1116;
- (LIV) A preparation obtainable from *Bacillus subtilis*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 72; or from a *Bacillus thuringiensis* strain except for compounds isolated from GC91 or from NCTC11821; The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 73;
- (LV) A preparation comprising insect-active fungi, preferably *Verticillium lecanii*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1266; *Beauveria brogniartii*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 85; and *Beauveria bassiana*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 83;
- (LVI) A preparation comprising insect-active viruses, preferably *Neodiprion Sertifer NPV*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1342; *Mamestra brassicae NPV*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 759; and *Cydia pomonella granulosus virus*, from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 291;
- (CLXXXI) *N*-tert-Butyl-*N*'-(3,5-dimethylbenzoyl)-3-methoxy-2-methylbenzohydrazide (RH-2485, Methoxyfenozide), from The Pesticide Manual, 11thEd. (1997), The British Crop Protection Council, London, page 1094;
- (CLXXXII) Isopropyl *N*'-[4-methoxybiphenyl-3-yl]hydrazinecarboxylate (D 2341), from Brighton Crop Protection Conference, 1996, 487- 493; and
- (R2) Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (1996), AGRO-020. Publisher: American Chemical Society, Washington, D.C. CONEN: 63BFAF.
- As a consequence of the above details, a further essential aspect of the present invention relates to combination preparations for the control of parasites on warm-blooded animals, characterised in that they contain, in addition to a compound of formula I, at least one further active ingredient having the same or different sphere of activity and at least one

physiologically acceptable carrier. The present invention is not restricted to two-fold combinations.

Especially preferred combination partners for the compounds of the formula I of the present inventions are the more modern natural or chemically modified macrocyclic lactones (macrolides), such as avermectins, milbemycins and derivatives thereof, including prominent representatives such as Ivermectin, Doramectin, Moxidectin, Selamectin, Emamectin, Eprinomectin, Milbemectin, Abamectin, Milbemycin oxime, Nemadectin, and a derivative thereof, in the free form or in the form of a physiologically acceptable salt.

The combination of these two different classes of compounds leads to several advantageous effects. In the first instant, one observes a broadening of the activity spectrum with regard to the endo-parasites. The combination product is highly active against all sorts of commercially important worms and, what is really surprising, also against metabolic active larval stages. Investigations concerning arrested larval stages are still ongoing but it could well turn out that the combination product will also be effective against these stages.

A further advantage of the combination product is the pest resistance management, meaning that the occurrence of resistance against the compounds of the formula I can drastically be delayed by the administration of the combination product instead of applying the compounds of formula I only. Another advantage is that the combination product can successfully be used even in those cases where the worm population has already developed resistance against a macrocyclic lactones.

Beyond this, a major advantage of the compounds of the formula I is their exhibiting full efficacy against worms resistant to commonly used products such as representatives of the macrocyclic lactones, e.g. Ivermectin or Moxidectin, and to Levamisole or representatives of the benzimidazole class of anthelmintics.

The macrocyclic lactones are most preferred because they exhibit a broad spectrum of activity. Most of them exhibit ecto- and in parallel endo-parasitocidal activity. Therefore, they are also called endectocides. Macrocyclic lactones bind to glutamated chlorine channels causing paralysis of the parasites in the first instance, followed by their death.

Especially preferred combination partners are Ivermectin, Abamectin and Moxidectin.

The anthelmintic compositions according to the invention generally comprise 0.1 to 99% by weight, in particular 1 to 95% by weight, of active ingredient of the formula I or mixtures thereof, and 99.9 to 1% by weight, in particular 99 to 5% by weight, of solid or liquid additives

The compositions according to the invention can be applied topically, perorally, parenterally or subcutaneously to the animals to be treated. The compositions include topically applied pour-on formulations such as solutions, suspensions, emulsions, emulsion concentrates, solution concentrates; oral liquid formulations (drenches) such as solutions, emulsions, suspensions, emulsion concentrates, directly dilutable solutions; oral solid formulations such as feed additives, powders, tablets, including effervescent tablets, boluses, capsules, microencapsulations and parenterally or subcutaneously administered formulations such as solutions, suspensions, emulsions or long acting parenteral formulations like microparticles, implants or injectable depots; care having to be taken over the physiological compatibility of the formulation auxiliaries.

The pour-on or spot-on method consists in applying the compound of the formula I to a locally restricted part of the skin or fur, advantageously on the neck or back of the animal. This is carried out, e.g., by applying a spot or dash of the pour-on or spot-on formulation to a relatively small area of the fur, from where the active substance spreads out virtually unaided over wide regions of the fur because of the spreading components of the formulation and supported by the movements of the animal.

It is advantageous for pour-on or spot-on formulations to comprise carriers which promote speedy distribution on the surface of the skin or in the fur of the host animal and which are generally described as spreading oils. Suitable carriers are, e.g., oily solutions; alcoholic and isopropanolic solutions, for example solutions of 2 octyldodecanol or oleyl alcohol; solutions in esters of monocarboxylic acids, such as isopropyl myristate, isopropyl palmitate, lauric acid oxal ester, oleyl oleate, decyl oleate, hexyl laurate, capric acid esters of saturated fatty alcohols with a chain length of C12 C18; solutions of esters of dicarboxylic acids, such as dibutyl phthalate, diisopropyl isophthalate, diisopropyl adipate or di(n-butyl) adipate, or also solutions of esters of aliphatic acids, e.g. glycols. It can be advantageous if a dispersant known from the pharmaceutical or cosmetics industry is additionally present. Examples are 2 pyrrolidone, 2 (N-alkyl)pyrrolidone, acetone, polyethylene glycol and ethers and esters thereof, propylene glycol or synthetic triglycerides.

The oily solutions include, e.g., vegetable oils, such as olive oil, groundnut oil, sesame oil, pine oil, linseed oil or castor oil. The vegetable oils can also be present in epoxidized form. Paraffin oils and silicone oils can also be used.

In general, a pour-on or spot-on formulation comprises 1 to 20% by weight of a compound of the formula I, 0.1 to 50% by weight of dispersant and 45 to 98.9% by weight of solvent.

The pour-on or spot-on method can be used particularly advantageously with gregarious animals, such as cattle, horses, sheep or pigs, where it is difficult or time-consuming to treat all the animals orally or via injection. Because of its simplicity, this method can naturally also be used with all other animals, including individual domestic animals or pets, and is very popular with animal owners because it can often be implemented without the expert assistance of a veterinary surgeon.

While concentrated compositions are more preferred as commercially available products, the end user generally uses dilute compositions.

Such compositions can comprise yet further additives, such as stabilizers, antifoaming agents, viscosity regulators, binders, deposit builders and other active ingredients to obtain specific effects.

Such anthelmintic compositions used by the end user likewise form part of the present invention.

In each of the methods according to the invention for controlling pests or of the pesticides according to the invention, the active ingredients of the formula I can be used in all their steric configurations or mixtures thereof.

The invention also includes a method for the prophylactic protection of warm-blooded animals, in particular of productive livestock, domestic animals and pets, against parasitic helminths, which comprises applying the active ingredients of the formula I or the active ingredient formulations prepared therefrom as a feed additive or drinking water additive or also in the solid or liquid form, orally, by injection or parenterally, to the animals. The invention also includes the compounds of the formula I according to the invention for use in one of the methods mentioned.

The following examples serve merely to illustrate the invention, without limiting it, the term "active ingredient" represents a substance listed in Table 1, for example compound No. 29.

Preferred formulations are in particular composed in the following way:

(% = per cent by weight)

Formulation examples

1. Granules

	a)	b)
Active ingredient	5%	10%
Kaolin	94%	-
Highly dispersed silica	1%	-
Attapulgate	-	90%

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The active ingredient is dissolved in methylene chloride and sprayed onto the carrier, and the solvent is subsequently evaporated under reduced pressure. Such granules can be added to the animal feed.

2. Granules

Active ingredient	3%
Polyethylene glycol (MW 200)	3%
Kaolin	94%

(MW = molecular weight)

The finely milled active ingredient is applied evenly in a mixer to the kaolin, which has been moistened with polyethylene glycol. In this way, dust-free coated granules are obtained.

3. Tablets or Boluses

- | | | |
|----|-------------------------|--------|
| I | Active ingredient | 33.00% |
| | Methylcellulose | 0.80% |
| | Highly dispersed silica | 0.80% |
| | Maize starch | 8.40% |
| II | Cryst. lactose | 22.50% |
| | Maize starch | 17.00% |
| | Microcryst. cellulose | 16.50% |
| | Magnesium stearate | 1.00% |
- I Methylcellulose is stirred into water. After the material has swollen, silica is stirred in and the mixture is homogeneously suspended. Active ingredient and maize starch are mixed. The aqueous suspension is incorporated in this mixture and kneaded to a dough. The substance thus obtained is granulated through a 12 M sieve and dried.
- II All 4 auxiliaries are intimately mixed.
- III The premixes obtained according to I and II are mixed and pressed to give tablets or boluses.

4. Injectables

A. Oily vehicle (slow release)

- | | | |
|----|-------------------|-----------|
| 1. | Active ingredient | 0.1-1.0 g |
| | Groundnut oil | ad 100 ml |
| 2. | Active ingredient | 0.1-1.0 g |
| | Sesame oil | ad 100 ml |

Preparation: The active ingredient is dissolved in a portion of the oil with stirring and, if

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desired, gentle heating, made up to the required volume after cooling and sterilely filtered through a suitable membrane filter with a size of 0.22 μ m.

B. Water-miscible solvent (medium release rate)

1. Active ingredient	0.1-1.0 g
4-Hydroxymethyl-1,3-dioxolane (glycerol formal)	40 g
1,2-Propanediol	ad 100 ml
2. Active ingredient	0.1-1.0 g
Glycerol dimethyl acetal	40 g
1,2-Propanediol	ad 100 ml

Preparation: The active ingredient is dissolved in a portion of the solvent with stirring, made up to the required volume and sterilely filtered through a suitable membrane filter with a size of 0.22 μ m.

C. Aqueous solubilisate (rapid release)

1. Active ingredient	0.1-1.0 g
Polyethoxylated castor oil (40 ethylene oxide units)	10 g
1,2-Propanediol	20 g
Benzyl alcohol	1 g
Water for injections	ad 100 ml
2. Active ingredient	0.1-1.0 g
Polyethoxylated sorbitan monooleate (20 ethylene oxide units)	8 g
4-Hydroxymethyl-1,3-dioxolane (glycerol formal)	20 g
Benzyl alcohol	1 g
Water for injections	ad 100 ml

Preparation: The active ingredient is dissolved in the solvents and the surfactant and made up to the required volume with water. Sterile filtration is carried out through a suitable membrane filter with a pore diameter of 0.22 μ m.

5. Pour-on

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A.

Active ingredient	5 g
Isopropyl myristate	10 g
Isopropanol	ad 100 ml

B.

Active ingredient	2 g
Hexyl laurate	5 g
Triglycerides of medium chain length	15 g
Ethanol	ad 100 ml

C.

Active ingredient	2 g
Oleyl oleate	5 g
N-Methylpyrrolidone	40 g
Isopropanol	ad 100 ml

The aqueous systems can preferably also be used for oral and/or intraruminal administration.

The compositions can also comprise further additives, such as stabilizers, e.g. epoxidized or nonepoxidized vegetable oils (epoxidized coconut oil, rapeseed oil or soybean oil), antifoaming agents, e.g. silicone oil, preservatives, viscosity regulators, binders, deposit builders and fertilizers or other active ingredients to obtain specific effects.

Further biologically active substances or additives which are neutral towards the compounds of the formula I and have no adverse effect on the host animal to be treated, and mineral salts or vitamins, can also be added to the compositions described.

6. Spot on

A.

active ingredient	10-15 g
diethyleneglycol monoethylether	ad 100 ml

B

active ingredient	10-15 g
octyl palmitate	10 g

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isopropanol	ad 100 ml
C	
active ingredient	10-15 g
isopropanol	20 g
benzyl alcohol	ad 100 ml
<u>7. Spray on</u>	
A.	
active ingredient	1 g
isopropanol	40 g
propylene carbonate	ad 100 ml
B	
active ingredient	1 g
propylene glycol	10 g
isopropanol	ad 100 ml

The aqueous systems may also preferably be used for oral and/or intraruminal application.

The compositions may also contain further additives, such as stabilisers, e.g. where appropriate epoxidised vegetable oils (epoxidised coconut oil, rapeseed oil, or soybean oil); antifoams, e.g. silicone oil, preservatives, viscosity regulators, binders, tackifiers, as well as fertilisers or other active ingredients to achieve special effects.

Further biologically active substances or additives, which are neutral towards the compounds of formula I and do not have a harmful effect on the host animal to be treated, as well as mineral salts or vitamins, may also be added to the described compositions.

The following examples serve to illustrate the invention. They do not limit the invention. The letter 'h' stands for hour. The starting substances used may be produced by methods described in literature or are commercially available.

7. Tablets: (each containing a total of 0.0183 g active ingredient) are prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	183.00 g
Lactose	290.80 g
Potato starch	274.70 g
Stearic acid	10.00 g
Talc	217.00 g
Magnesium stearate	2.50 g
Colloidal silica	32.00 g
Ethanol	q.s.

A mixture of the active ingredient, the lactose and 274.70 g potato starch is wetted with an ethanolic solution of stearic acid and granulated through a sieve. After drying, the remaining potato starch, the talc, the magnesium stearate, and the colloidal silica are added and the mixture compressed to form tablets of 0.1 g each in weight, which – if so desired – can be scored to allow for a finer adjustment of the dose.

8. Capsules: each containing a total of 0.022 g active ingredient can be prepared as follows:

Composition (for 1000 capsules)

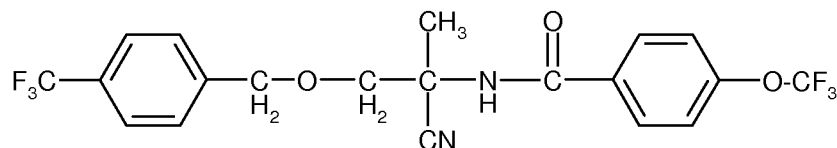
Active ingredient	22.00 g
Lactose	249.80 g
Gelatin	2.00 g
Corn starch	10.00 g
Talc	15.00 g
Water	q.s.

The active ingredient is mixed with the lactose, the mixture wetted evenly with an aqueous solution of the gelatine and granulated through a sieve with a mesh size of 1.2–1.5 mm. The granulate is mixed with the dried cornstarch and the talc, and portions of 300 mg are filled into hard gelatine capsules (size 1).

The following examples serve to clarify the invention. They do not limit the invention. The symbol 'h' denotes hour.

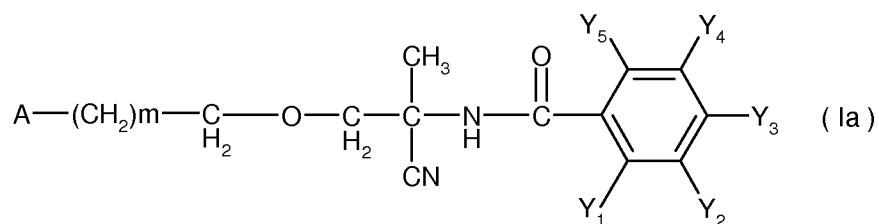
Preparation examplesExample 1:

N-[1-Cyano-1-methyl-2-(4-trifluoromethyl-benzyloxy)-ethyl]-4-trifluoromethoxy-benzamide



- a) In 40 ml of water are added 2.22 g of ammonium chloride, 2.04 g of sodium cyanide before adding dropwise 4.62 g of hydroxyacetone over 15 minutes. The reaction mixture is stirred for 19 h at RT, cooled to 0 °C and 4.36 g of sodium bicarbonate and 10 ml of ethylacetate are added. Over 30 minutes are added dropwise a solution of 4.49 g of 4-(trifluoromethoxy)benzylchloride in 10 ml of ethylacetate. The reaction mixture is stirred for 90 minutes at 0 °C and then washed successively with a saturated solution of sodium bicarbonate (2x), with water and with brine. The organic phases are dried on magnesium sulphate, filtered and concentrated. The residue is purified by chromatography to afford 3.97 g of N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-trifluoromethoxy-benzamide.
- b) 144 mg of N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-trifluoromethoxy-benzamide are dissolved in 1 ml of THF, a solution of 112 mg of potassium tert-butoxyde in 1 ml of THF is added followed by 0.155 ml of 4-(trifluoromethyl)benzyl bromide. The reaction mixture is stirred for an hour and then washed with brine. The organic phase is concentrated and the residue purified by chromatography to afford 78 mg of N-[1-Cyano-1-methyl-2-(4-trifluoromethyl-benzyloxy)-ethyl]-4-trifluoromethoxy-benzamide, melting point is 102-103 °C.

Table 1 Compounds of the formula Ia



$Y_1, Y_2, Y_3,$ and Y_5 are hydrogen, Me stands for methyl

No.	A	m	Y_3	m.p.
1.	4-Cl-C ₆ H ₄ -	0	4-CF ₃	
2.	4-Cl-C ₆ H ₄ -	0	4-OCF ₃	
3.	4-Cl-C ₆ H ₄ -	0	4-SCF ₃	
4.	-	3	4-OCF ₃	
5.	4-MeO-C ₆ H ₄ -	0	4-OCF ₃	
6.	3-MeO-C ₆ H ₄ -	0	4-OCF ₃	93-94 °C
7.	4-CN-C ₆ H ₄ -	0	4-OCF ₃	
8.	3-CN-C ₆ H ₄ -	0	4-OCF ₃	110-112 °C
9.	2-CN-C ₆ H ₄ -	0	4-OCF ₃	109-111 °C
10.	2-Cl-C ₆ H ₄ -	0	4-OCF ₃	
11.	3-Cl-C ₆ H ₄ -	0	4-OCF ₃	92-93 °C
12.	2-Cl,4-F-C ₆ H ₃ -	0	4-OCF ₃	88-90 °C
13.	2-CF ₃ ,4-F-C ₆ H ₃ -	0	4-OCF ₃	69-70 °C
14.	3-CF ₃ ,4-F-C ₆ H ₃ -	0	4-OCF ₃	95-96 °C
15.	3-CF ₃ ,2-F-C ₆ H ₃ -	0	4-OCF ₃	83-84 °C
16.	5-CF ₃ ,2-F-C ₆ H ₃ -	0	4-OCF ₃	101-102 °C
17.	5-CF ₃ ,3-F-C ₆ H ₃ -	0	4-OCF ₃	87-89 °C
18.	4-CF ₃ ,3-F-C ₆ H ₃ -	0	4-OCF ₃	69-70 °C
19.	2-CF ₃ ,5-F-C ₆ H ₃ -	0	4-OCF ₃	82-84 °C
20.	2-OCF ₃ -C ₆ H ₄ -	0	4-OCF ₃	61-62 °C
21.	3-OCF ₃ -C ₆ H ₄ -	0	4-OCF ₃	76-77 °C
22.	4-OCF ₃ -C ₆ H ₄ -	0	4-OCF ₃	110-112 °C
23.	4-F-C ₆ H ₄ -	0	4-OCF ₃	100-101 °C
24.	3-F-C ₆ H ₄ -	0	4-OCF ₃	88-89 °C
25.	2-F-C ₆ H ₄ -	0	4-OCF ₃	106-108 °C

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26.	4-Me-C ₆ H ₄ -	0	4-OCF ₃	120-121 °C
27.	3-Me-C ₆ H ₄ -	0	4-OCF ₃	90-91 °C
28.	2-Me-C ₆ H ₄ -	0	4-OCF ₃	121-123 °C
29.	4-CF ₃ -C ₆ H ₄ -	0	4-OCF ₃	102-103 °C
30.	3-CF ₃ -C ₆ H ₄ -	0	4-OCF ₃	77-79 °C
31.	2-CF ₃ -C ₆ H ₄ -	0	4-OCF ₃	73-74 °C
32.	4-MeO-C ₆ H ₄ -	0	4-CF ₃	
33.	3-MeO-C ₆ H ₄ -	0	4-CF ₃	
34.	4-CN-C ₆ H ₄ -	0	4-CF ₃	
35.	3-CN-C ₆ H ₄ -	0	4-CF ₃	
36.	2-CN-C ₆ H ₄ -	0	4-CF ₃	
37.	2-Cl-C ₆ H ₄ -	0	4-CF ₃	
38.	3-Cl-C ₆ H ₄ -	0	4-CF ₃	
39.	2-Cl,4-F-C ₆ H ₃ -	0	4-CF ₃	
40.	2-CF ₃ ,4-F-C ₆ H ₃ -	0	4-CF ₃	
41.	3-CF ₃ ,4-F-C ₆ H ₃ -	0	4-CF ₃	
42.	3-CF ₃ ,2-F-C ₆ H ₃ -	0	4-CF ₃	
43.	5-CF ₃ ,2-F-C ₆ H ₃ -	0	4-CF ₃	
44.	5-CF ₃ ,3-F-C ₆ H ₃ -	0	4-CF ₃	
45.	4-CF ₃ ,3-F-C ₆ H ₃ -	0	4-CF ₃	
46.	2-CF ₃ ,5-F-C ₆ H ₃ -	0	4-CF ₃	
47.	2-OCF ₃ -C ₆ H ₄ -	0	4-CF ₃	
48.	3-OCF ₃ -C ₆ H ₄ -	0	4-CF ₃	
49.	4-OCF ₃ -C ₆ H ₄ -	0	4-CF ₃	
50.	4-F-C ₆ H ₄ -	0	4-CF ₃	
51.	3-F-C ₆ H ₄ -	0	4-CF ₃	
52.	2-F-C ₆ H ₄ -	0	4-CF ₃	
53.	4-Me-C ₆ H ₄ -	0	4-CF ₃	
54.	3-Me-C ₆ H ₄ -	0	4-CF ₃	
55.	2-Me-C ₆ H ₄ -	0	4-CF ₃	
56.	4-CF ₃ -C ₆ H ₄ -	0	4-CF ₃	
57.	3-CF ₃ -C ₆ H ₄ -	0	4-CF ₃	
58.	2-CF ₃ -C ₆ H ₄ -	0	4-CF ₃	
59.	4-MeO-C ₆ H ₄ -	0	4-SCF ₃	

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60.	3-MeO-C ₆ H ₄ -	0	4-SCF ₃
61.	4-CN-C ₆ H ₄ -	0	4-SCF ₃
62.	3-CN-C ₆ H ₄ -	0	4-SCF ₃
63.	2-CN-C ₆ H ₄ -	0	4-SCF ₃
64.	2-Cl-C ₆ H ₄ -	0	4-SCF ₃
65.	3-Cl-C ₆ H ₄ -	0	4-SCF ₃
66.	2-Cl,4-F-C ₆ H ₃ -	0	4-SCF ₃
67.	2-CF ₃ ,4-F-C ₆ H ₃ -	0	4-SCF ₃
68.	3-CF ₃ ,4-F-C ₆ H ₃ -	0	4-SCF ₃
69.	3-CF ₃ ,2-F-C ₆ H ₃ -	0	4-SCF ₃
70.	5-CF ₃ ,2-F-C ₆ H ₃ -	0	4-SCF ₃
71.	5-CF ₃ ,3-F-C ₆ H ₃ -	0	4-SCF ₃
72.	4-CF ₃ ,3-F-C ₆ H ₃ -	0	4-SCF ₃
73.	2-CF ₃ ,5-F-C ₆ H ₃ -	0	4-SCF ₃
74.	2-OCF ₃ -C ₆ H ₄ -	0	4-SCF ₃
75.	3-OCF ₃ -C ₆ H ₄ -	0	4-SCF ₃
76.	4-OCF ₃ -C ₆ H ₄ -	0	4-SCF ₃
77.	4-F-C ₆ H ₄ -	0	4-SCF ₃
78.	3-F-C ₆ H ₄ -	0	4-SCF ₃
79.	2-F-C ₆ H ₄ -	0	4-SCF ₃
80.	4-Me-C ₆ H ₄ -	0	4-SCF ₃
81.	3-Me-C ₆ H ₄ -	0	4-SCF ₃
82.	2-Me-C ₆ H ₄ -	0	4-SCF ₃
83.	4-CF ₃ -C ₆ H ₄ -	0	4-SCF ₃
84.	3-CF ₃ -C ₆ H ₄ -	0	4-SCF ₃
85.	2-CF ₃ -C ₆ H ₄ -	0	4-SCF ₃

Biological examples

1. Activity in vitro against *Haemonchus contortus* & *Trichostrongylus colubriformis* (Gastro-intestinal nematodes).

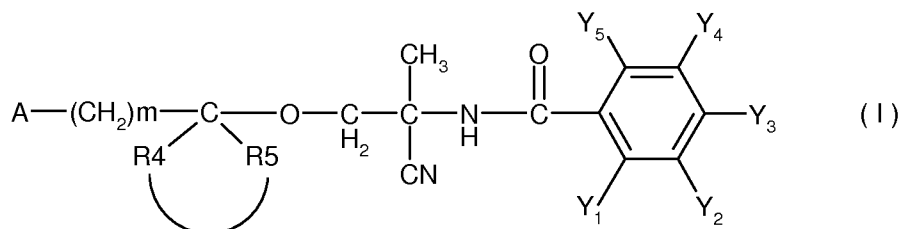
Freshly harvested and cleaned nematode eggs are used to seed a suitably formatted 96-well plate containing the test substances to be evaluated for antiparasitic activity. Each compound is tested by serial dilution in order to determine its MED. The test compounds are embedded in an agar-based nutritive medium allowing the full development of eggs through to 3rd instar larvae. The plates are incubated for 6 days at 25 °C and 60% relative humidity (RH). Egg-hatching and ensuing larval development are recorded to identify a possible nematicidal activity. Efficacy is expressed in percent reduced egg hatch, reduced development of L3, or paralysis & death of larvae of all stages. In above HTS assay (5.), a given compound has to exhibit a nematicidal efficacy of higher than 99% at a concentration of 32 ppm in order to qualify for further testing. This result is achieved by the compounds Nos. 1, 4, 5, 6, 7, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31.

2. In vivo test against *Trichostrongylus colubriformis* and *Haemonchus contortus* in Mongolian gerbils (*Meriones unguiculatus*) by peroral administration

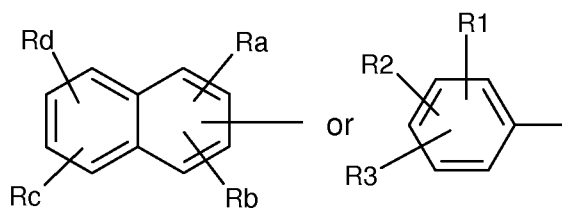
Six- to eight-week-old Mongolian gerbils are infected, using manufactured feed, with in each case approximately 2 000 larvae of the 3rd stage of *T. colubriformis* and *H. contortus*. Six days after infecting, the gerbils are lightly anaesthetized with N₂O and are treated by peroral administration with the test compounds, dissolved in a mixture of 2 parts of DMSO and 1 part of polyethylene glycol (PEG 300), with amounts of 100, 32 and 10 – 0.1 mg/kg. On day 9 (3 days after treating), when most of the *H. contortus* larvae still existing are in the late 4th stage and most of the *T. colubriformis* are immature adults, the gerbils are sacrificed in order to count the worms. The activity is calculated in % reduction in the number of worms in each gerbil by comparison with the geometric mean of the number of worms from 8 infected and untreated gerbils. In this test, a large decrease in the nematode infestation is obtained with compounds of the formula I, in particular from Table 1, more specifically compounds Nos. 1, 4, 5, 7, 10, 11, 13, 18, 22, 26, 29.

The following embodiments A to L are especially preferred within the present invention:

A. The use of compounds the formula I



wherein A is hydrogen,

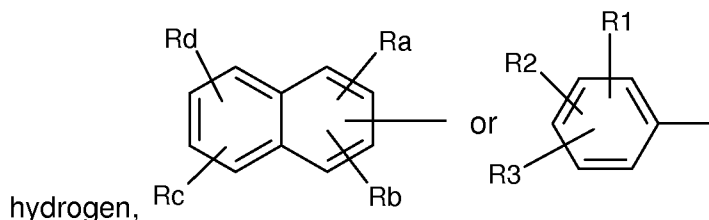


R1, R2, R3, Ra, Rb, Rc, Rd, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, halo-C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, halo-C₁-C₆-alkylsulfonyl, di-C₁-C₆-alkylamino and a cyclic moiety M; whereby M is a cyclic moiety selected from the group consisting of unsubstituted or once to three time substituted C₃-C₆-cycloalkyl, phenyl, phenoxy and pyridyloxy, and whereby the substituents are independently of each other selected from the group consisting of halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio; or A stands for hetaryl that is unsubstituted or carries one, two or three substituents selected from the group defined for R1;

R4 and R5 are independently of each other hydrogen, C₁-C₆-alkyl, or for a saturated C₃-C₆-cycloalkylalkyl, and

m is 0, 1, 2, 3, 4, 5 or 6, and optionally enantiomers thereof, as such or in combination with at least one suitable carrier in the control of endoparasitic pests in warm-blooded productive livestock and domestic animals or the use of said compounds for the preparation of a veterinary composition.

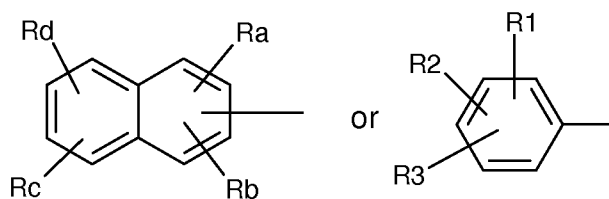
B. Said use of compound of the formula I, whereby in the compound of the formula I, A is



; R1, R2, R3, Ra, Rb, Rc, Rd, Y₁, Y₂,

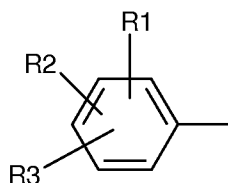
Y_3 , Y_4 and Y_5 is each independently of each other hydrogen, halogen, nitro, cyano, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, halo- C_1 - C_6 -alkylthio, C_1 - C_6 -alkylsulfinyl, halo- C_1 - C_6 -alkylsulfinyl, C_1 - C_6 -alkylsulfonyl, halo- C_1 - C_6 -alkylsulfonyl, di- C_1 - C_6 -alkylamino and a cyclic moiety M; whereby M is a cyclic moiety selected from the group consisting of unsubstituted or once to three time substituted C_3 - C_6 -cycloalkyl, phenyl, phenoxy and pyridyloxy, and whereby the substituents are independently of each other selected from the group consisting of halogen, nitro, cyano, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, halo- C_1 - C_6 -alkylthio; or A stands for hetaryl that is unsubstituted or carries one, two or three substituents selected from the group defined for R_1 ; R_4 and R_5 are independently of each other hydrogen or methyl, and m is 0, 1, 2, 3, 4, 5 or 6.

C. Said use of compound of the formula I, whereby in the compound of the formula I, A is hydrogen,



R_1 , R_2 , R_3 , R_a , R_b , R_c , R_d , Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is each independently of each other hydrogen, halogen, nitro, cyano, C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, halo- C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, halo- C_1 - C_6 -alkylthio, C_1 - C_6 -alkylsulfinyl and C_1 - C_6 -alkylsulfonyl; R_4 and R_5 are independently of each other hydrogen or methyl; and m is 0 or 1.

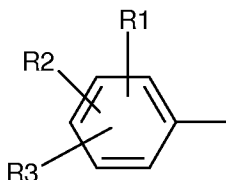
D. Said use of compound of the formula I, whereby in the compound of the formula I, A is



R_1 , R_2 , and R_3 independently of each other is hydrogen, chlorine, fluorine, nitro, cyano, methyl, ethyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is each independently of each other hydrogen, chlorine, fluorine, nitro, cyano, methyl, methoxy, methylthio, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; R_4 and R_5 are independently of each other hydrogen or methyl, and m is 0 or 1.

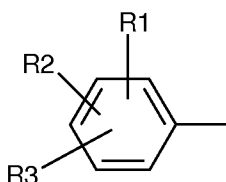
E. Said use of compound of the formula I, whereby in the compound of the formula I, A is

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R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, trifluoromethyl, trifluormethoxy, trifluormethylthio, trifluormethylsulfinyl or trifluormethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, and m is 0 or 1.

F. Said use of compound of the formula I, whereby in the compound of the formula I, A is



R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, and Y₅ are hydrogen; Y₄ is trifluoromethyl, trifluormethoxy, trifluormethylthio, trifluormethylsulfinyl or trifluormethylsulfonyl; R4 and R5 are hydrogen, and m is 0.

G. A veterinary composition comprising as active ingredient an aminoacetonitrile compound of the formula I as defined above or an enantiomers thereof and a suitable physiologically acceptable carrier.

H. Said veterinary composition consisting of a solution, emulsion, suspension, feed additive, powder, tablet, bolus, capsule, microencapsule, pour-on, spray-on, spot-on, drench or an injectable formulation.

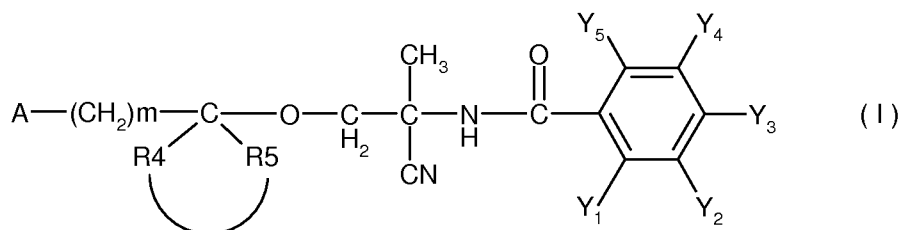
I. The use of a compound of formula I as defined above in a process for controlling endoparasites on warm-blooded animals.

K. The use of a compound of formula I as defined above in the preparation of a veterinary composition against endoparasites.

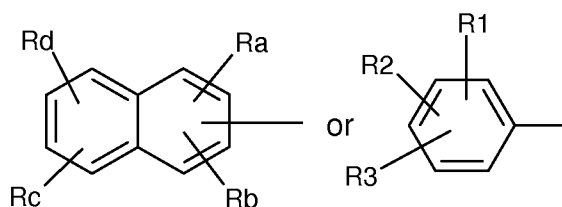
L. A method of controlling endoparasites on warm-blooded animals comprising the administration of a pesticidally amount of a compound as defined above to the endoparasite.

What is claimed is:

1. Use of compounds the formula I



wherein A is hydrogen,

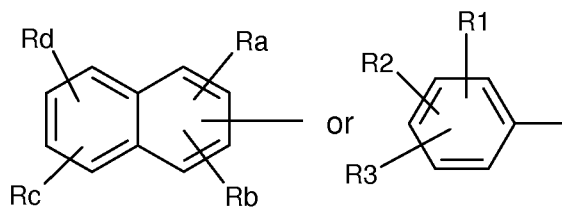


R1, R2, R3, Ra, Rb, Rc, Rd, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, halo-C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, halo-C₁-C₆-alkylsulfonyl, di-C₁-C₆-alkylamino and a cyclic moiety M; whereby M is a cyclic moiety selected from the group consisting of unsubstituted or once to three time substituted C₃-C₆-cycloalkyl, phenyl, phenoxy and pyridyloxy, and whereby the substituents are independently of each other selected from the group consisting of halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio; or A stands for hetaryl that is unsubstituted or carries one, two or three substituents selected from the group defined for R1;

R4 and R5 are independently of each other hydrogen, C₁-C₆-alkyl, or for a saturated C₃-C₆-cycloalkylalkyl, and

m is 0, 1, 2, 3, 4, 5 or 6, and optionally enantiomers thereof, in the control of endoparasitic pests in warm-blooded productive livestock and domestic animals

2. Use according to claim 1, whereby in the compound of the formula I, A is hydrogen,

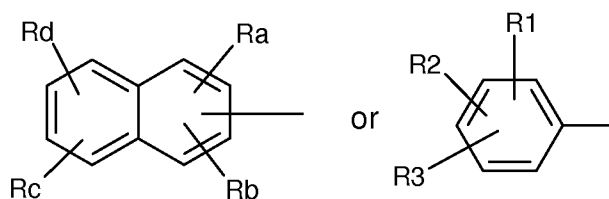


- 40 -

R₁, R₂, R₃, R_a, R_b, R_c, R_d, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, halo-C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, halo-C₁-C₆-alkylsulfonyl, di-C₁-C₆-alkylamino and a cyclic moiety M; whereby M is a cyclic moiety selected from the group consisting of unsubstituted or once to three time substituted C₃-C₆-cycloalkyl, phenyl, phenoxy and pyridyloxy, and whereby the substituents are independently of each other selected from the group consisting of halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio; or A stands for hetaryl that is unsubstituted or carries one, two or three substituents selected from the group defined for R₁;

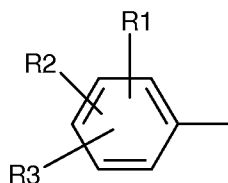
R₄ and R₅ are independently of each other hydrogen or methyl, and m is 0, 1, 2, 3, 4, 5 or 6.

3. Use according to claim 1, whereby in the compound of the formula I, A is hydrogen,



R₁, R₂, R₃, R_a, R_b, R_c, R_d, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, halogen, nitro, cyano, C₁-C₆-alkyl, halo-C₁-C₆-alkyl, C₁-C₆-alkoxy, halo-C₁-C₆-alkoxy, C₁-C₆-alkylthio, halo-C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl and C₁-C₆-alkylsulfonyl; R₄ and R₅ are independently of each other hydrogen or methyl; and m is 0 or 1.

4. Use according to claim 1, whereby in the compound of the formula I, A is

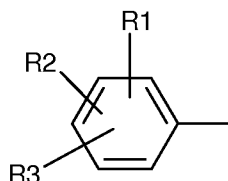


R₁, R₂, and R₃ independently of each other is hydrogen, chlorine, fluorine, nitro, cyano, methyl, ethyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfinyl or trifluoromethylsulfonyl; Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, chlorine, fluorine, nitro, cyano, methyl, methoxy, methylthio, trifluoromethyl, trifluoromethoxy,

- 41 -

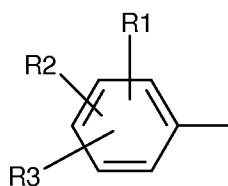
trifluormethylthio, trifluormethylsulfinyl or trifluormethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, and m is 0 or 1.

5. Use according to claim 1, whereby in the compound of the formula I, A is



R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, Y₄ and Y₅ is each independently of each other hydrogen, trifluoromethyl, trifluoromethoxy, trifluormethylthio, trifluormethylsulfinyl or trifluormethylsulfonyl; R4 and R5 are independently of each other hydrogen or methyl, and m is 0 or 1.

6. Use according to claim 1, whereby in the compound of the formula I, A is



R1, R2, and R3 independently of each other is hydrogen, cyano, chlorine, fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy, Y₁, Y₂, Y₃, and Y₅ are hydrogen; Y₄ is trifluoromethyl, trifluoromethoxy, trifluormethylthio, trifluormethylsulfinyl or trifluormethylsulfonyl; R4 and R5 are hydrogen, and m is 0.

7. Veterinary composition comprising as active ingredient an aminoacetonitrile compound of the formula I as defined in claims 1 to 6 or an enantiomers thereof and a suitable physiologically acceptable carrier.

8. Veterinary composition according to claim 7 consisting of a solution, emulsion, suspension, feed additive, powder, tablet, bolus, capsule, microencapsule, pour-on, spray-on, spot-on, drench or an injectable formulation.

9. Use of a compound of formula I according to claim 1 in a process for controlling endoparasites on warm-blooded animals.

10. Use of a compound of formula I according to claim 1 in the preparation of a veterinary composition against endoparasites.

11. Method of controlling endoparasites on warm-blooded animals comprising the administration of a pesticidally amount of a compound as defined in claim 1 to the endoparasite.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/062614

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/277 A61P33/14 A61P33/10

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)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 953 565 A2 (NIHON NOHYAKU CO LTD [JP]) 3 November 1999 (1999-11-03) page 24; table 3 page 49, line 37 - page 50, line 12	7-8
X	EP 1 445 251 A1 (NIHON NOHYAKU CO LTD [JP]) 11 August 2004 (2004-08-11) page 23; table 3 page 36, line 58 - page 37, line 53	7,8
Y	WO 02/49641 A2 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; DUCRAY PIERRE [FR]) 27 June 2002 (2002-06-27) page 16; table 2 page 1, paragraph 1	1-11
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

8 January 2008

Date of mailing of the international search report

04/02/2008

Name and mailing address of the ISA/

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Authorized officer

Young, Astrid

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/062614

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/102155 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; DUCRAY PIERRE [FR] 27 December 2002 (2002-12-27) page 1, paragraph 1 page 4; table 1 -----	1-11
Y	WO 2004/000793 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DUCRAY PIERRE [FR]; GOEBE) 31 December 2003 (2003-12-31) page 17, lines 31-33 page 36; table 1 -----	1-11
Y	WO 2005/121075 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; GAUVRY NOELLE [FR]; DUCRA) 22 December 2005 (2005-12-22) page 16, lines 19-22 page 39; table 1 -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/062614

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-6 and 9-11 are directed to a method of treatment of the human/animal body (Article 53(c) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/062614

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0953565	A2	03-11-1999	AU 752112 B2 05-09-2002
		AU 2602799 A 11-11-1999	
		CN 1234177 A 10-11-1999	
		DE 69919930 D1 14-10-2004	
		DE 69919930 T2 08-09-2005	
		DE 69934617 T2 15-11-2007	
		TW 585849 B 01-05-2004	
		US 6239077 B1 29-05-2001	
EP 1445251	A1	11-08-2004	NONE
WO 0249641	A2	27-06-2002	AT 354360 T 15-03-2007
		AU 3458802 A 01-07-2002	
		BR 0116326 A 06-07-2004	
		CA 2432388 A1 27-06-2002	
		CN 1531426 A 22-09-2004	
		DE 60126838 T2 08-11-2007	
		DK 1392281 T3 11-06-2007	
		EP 1392281 A2 03-03-2004	
		ES 2281453 T3 01-10-2007	
		JP 2004521097 T 15-07-2004	
		MX PA03005701 A 06-10-2003	
		NZ 526538 A 23-12-2005	
		RU 2286775 C2 10-11-2006	
		US 2004082624 A1 29-04-2004	
		ZA 200304331 A 28-04-2004	
WO 02102155	A	27-12-2002	AT 365455 T 15-07-2007
		BR 0210926 A 08-06-2004	
		CA 2449854 A1 27-12-2002	
		CN 1529552 A 15-09-2004	
		DK 1401277 T3 27-08-2007	
		EP 1401277 A1 31-03-2004	
		ES 2287289 T3 16-12-2007	
		JP 2004530711 T 07-10-2004	
		MX PA03011630 A 05-04-2004	
		NZ 530120 A 30-09-2005	
		RU 2294640 C2 10-03-2007	
		TW 236341 B 21-07-2005	
		US 2004209950 A1 21-10-2004	
		ZA 200309672 A 04-08-2004	
WO 2004000793	A2	31-12-2003	AU 2003279395 A1 06-01-2004
		BR 0312435 A 19-04-2005	
		CA 2489842 A1 31-12-2003	
		EP 1517885 A2 30-03-2005	
		JP 2005529968 T 06-10-2005	
		MX PA04012971 A 16-05-2005	
		NZ 537665 A 27-07-2007	
		US 2006128801 A1 15-06-2006	
		ZA 200410232 A 23-06-2005	
WO 2005121075	A	22-12-2005	AR 049391 A1 26-07-2006
		AU 2005251917 A1 22-12-2005	