CONVENTION APPLICATION FOR A STANDARD PATENT

We, CIBA-GEIGY AG, of Klybeckstrasse 141, 4002 Basle, Switzerland hereby apply for the grant of a standard patent for an invention entitled:

"N-3-(5-TRIFLUOROMETHYL)PYRIDYL-2-OXY)PHENYL-N'-BENZOYLUREAS FOR CONTROLLING HELMINTHS IN PRODUCTIVE LIVESTOCK"

which is described in the accompanying complete specification.

DETAILS OF BASIC APPLICATION(S)

Number(s) of Basic Application(s):-

222/86-0; 1362/86-9 and 5053/86-5

Name of Convention Country in which Basic Application(s) were filed:-
Switzerland

Date(s) of Basic application(s):-

21 January, 1986; 8 April, 1986 and 17 December, 1986, respectively

Our address for service is:-

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Sydney New South Wales Australia

DATED this TWENTIETH day of JANUARY 1989

CIBA-GEIGY AG

By:


TO: THE COMMISSIONER OF PATENTS

AUSTRALIA

SBR/JS/0003U
In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

"N-3-(5-Trifluoromethylpyridyl-2-oxy)phenyl-N'-benzoylureas for controlling helminths in productive livestock"

We, Arnold Seiler and care of CIBA-GEIGY AG, Klybeckstrasse 141, 4002 Basle, Switzerland do solemnly and sincerely declare as follows:

1. We are authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was(were) made in Switzerland:
   - on January 21, 1986,
   - on April 8, 1986 and
   - on December 17, 1986

3. Walter Hausermann, En Sendey, 1867 Ollon, Switzerland,
   Max Maurer, Mühleweg 16, 3280 Murten, Switzerland and
   Thomas Friedel, Lot 32, The High Road, East Blaxland, N.S.W. 2774, Australia

is(are) the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The said applicant is the assignee of the actual inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was(were) the first application(s) made in a Convention country in respect of the invention the subject of the application.

DECLARED at Basle, Switzerland on January 12, 1987

To: The Commissioner of Patents

Arnold Seiler / Ernst Altherr
Claim

1. A method of controlling helminths in productive livestock, which comprises the use of a compound of formula I

\[
\text{R}_1 \text{CONHCONH} \text{R}_2 \text{CF}_3
\]

wherein

- \( \text{R}_1 \) is hydrogen, \( \text{C}_1-\text{C}_2 \) alkoxy, \( \text{C}_1-\text{C}_2 \) alkylthio, \( \text{C}_1-\text{C}_2 \) alkyl or halogen,
- \( \text{R}_2 \) is hydrogen or halogen,
- \( \text{R}_3 \) is hydrogen or halogen,
- \( \text{R}_4 \) is hydrogen, \( \text{C}_1-\text{C}_2 \) alkyl or halogen, and
- \( \text{R}_5 \) is hydrogen or halogen.

11. A process for the preparation of an anthelmintic composition for administration to productive livestock, which comprises mixing a compound of formula I
13. An anthelmintic veterinary composition for administration to animals, which contains at least one compound of formula I

\[
\begin{align*}
R_1 & \quad \text{CONHCONH} \quad \text{R}_4 \\
R_2 & \quad \text{O-} \quad \text{N-} \\
R_3 & \quad \text{CF}_3
\end{align*}
\]

wherein
- \( R_1 \) is hydrogen, \( C_1-C_2 \) alkoxy, \( C_1-C_2 \) alkylthio, \( C_1-C_2 \) alkyl or halogen,
- \( R_2 \) is hydrogen or halogen,
- \( R_3 \) is hydrogen or halogen,
- \( R_4 \) is hydrogen, \( C_1-C_2 \) alkyl or halogen, and
- \( R_5 \) is hydrogen or halogen,
with suitable formulation adjuvants.

10. A method according to claim 1 in which the active ingredient of the formula I is administered as a feed additive to the solid or liquid feed of domestic animals so that the ready prepared feed contains the active ingredient in a concentration of about 0.0005 to 0.02 percent by weight.
The following statement is a full description of this invention, including the best method of performing it known to us
N-3-(5-Trifluoromethylpyridyl-2-oxy)phenyl-N'-benzoylureas for controlling helminths in productive livestock

The present invention relates to N-3-(5-trifluoromethylpyridyl-2-oxy)phenyl-N'-benzoylureas as defined in formula I below for controlling helminths, especially nematodes and trematodes, in domestic animals and productive livestock, preferably in warm-blooded animals and, first and foremost, in mammals.

The N-3-(5-trifluoromethylpyridyl-2-oxy)phenyl-N'benzoylureas of this invention have the formula I

\[
\begin{align*}
\text{CONHCONH} & \quad \text{I} \\
\text{CONHCONH} & \\
\end{align*}
\]

wherein
- \( R_1 \) is hydrogen, \( C_1-C_2 \)-alkoxy, \( C_1-C_2 \)-alkylthio, \( C_1-C_2 \)-alkyl or halogen,
- \( R_2 \) is hydrogen or halogen,
- \( R_3 \) is hydrogen or halogen,
- \( R_4 \) is hydrogen, \( C_1-C_2 \)-alkyl or halogen, and
- \( R_5 \) is hydrogen or halogen.

Preferred compounds of formula I are those wherein
- \( R_1 \) is fluorine, chlorine, methoxy, methylthio or methyl,
- \( R_2 \) is hydrogen, fluorine or chlorine,
- \( R_3 \) is hydrogen, 2-fluoro or 2-chloro,
- \( R_4 \) is hydrogen, fluorine, chlorine, bromine or methyl, and
- \( R_5 \) is fluorine or chlorine.
Particularly preferred compounds of formula I are those wherein
R₁ is fluorine, methoxy or methylthio,
R₂ is fluorine,
R₃ is hydrogen,
R₄ is fluorine, chlorine or bromine, and
R₅ is chlorine.

C₁₋₂Alkyl by itself or as moiety of alkoxy or alkylthio is methyl
or ethyl, so that C₁₋₂alkoxy is ethoxy or methoxy and C₁₋₂alkyl-
thio is ethylthio or methylthio. Halogen is fluorine, chlorine,
bromine or iodine, with fluorine, chlorine or bromine being
preferred.

Preferred individual compounds of formula I are e.g.:
Further typical representatives of compounds of formula I are:
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<th>Compound No.</th>
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In PCT patent application WO-86/03941, the entire chemical field of acylureas is broadly claimed for controlling endo- and ectoparasites in warm-blooded animals. However, biological data are cited for only a few individual compounds of specific structural types. This publication makes no reference to the outstanding anthelmintic properties of N-3-(5-trifluoromethylpyridyl-2-oxy)phenyl-N'-benzoylureas of formula I above. PCT patent application WO-86/03941 anticipates the instant compounds of formula I neither with respect to structure nor activity.

The compounds of formula I are known from European patent application EP-79311 as parasiticides for controlling ectoparasites of the class of insects as well as of the order Acarina, or they can be prepared as disclosed therein.

Thus, for example, a compound of formula I can be obtained by reacting

\[
\text{a) a compound of formula II} \quad \begin{array}{c}
\text{CF}_3 \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{R}_4 \\
\text{R}_5 \\
\text{NH}_2
\end{array}
\]

\[
\text{with a compound of formula III} \quad \begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{CO-N=C=O}
\end{array}
\]

or by reacting
b) a compound of formula IV

\[
\begin{align*}
\text{CF}_3 & \quad \text{N} \\
\text{R}_5 & \quad \text{O} \\
\text{R}_4 & \quad \text{N}=\text{C}=\text{O} \\
\text{R}_3 & \quad \text{R}_2 \quad \text{R}_1
\end{align*}
\]

(IV)

with a compound of formula V

\[
\begin{align*}
\text{R}_1 & \quad \text{CO-NH}_2 \\
\text{R}_2 & \quad \text{R}_2
\end{align*}
\]

(V),

in the absence or presence of an organic or inorganic base,

or by reacting

c) a compound of formula II with a compound of formula VI

\[
\begin{align*}
\text{R}_1 & \quad \text{CO-NH-COOR} \\
\text{R}_2 & \quad \text{R}_2
\end{align*}
\]

(VI),

In the formulae II to VI above, the substituents \( R_1 \) to \( R_5 \) are as defined for formula I and \( R \) is a \( C_1-C_8 \) alkyl radical or a halogen-substituted \( C_1-C_8 \) alkyl radical.

The above processes a), b) and c) may conveniently be carried out under normal pressure and in the presence of an organic solvent or diluent. Examples of suitable solvents or diluents are: ethers and ethereal compounds such as diethyl ether, dipropyl ether, dibutyl ether, dioxane, dimethoxyethane and tetrahydrofuran; \( N,N \)-dialkylated carboxamides; aliphatic, aromatic and halogenated hydrocarbons, especially benzene, toluene, xylene, chloroform, methylene chloride, carbon tetrachloride and chlorobenzene; nitriles such as acetonitrile or propionitrile; dimethyl sulfoxide; and ketones, e.g. acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl
isobutyl ketone. Process a) is normally carried out in the temperature range from \(-10^\circ\) to \(+100^\circ\)C, preferably from \(15^\circ\) to \(25^\circ\)C, and if desired in the presence of an organic base, e.g. triethylamine. Process b) is carried out in the temperature range from \(0^\circ\) to \(150^\circ\)C, preferably at the boiling point of the solvent employed and, if desired, in the presence of an organic base such as pyridine, and/or with the addition of an alkali metal or alkaline earth metal, preferably sodium. For the reaction of the urethane of formula VI with the aniline of formula II according to process c), a temperature range from about \(60^\circ\) to the boiling point of the reaction mixture is preferred, and the solvent employed is preferably an aromatic hydrocarbon such as toluene, xylene, chlorobenzene or the like.

The starting materials of formulae II to VI are known and can be prepared by methods analogous to known ones. Some of the starting compounds of formula II and IV are novel compounds which can be prepared by methods that are known per se (q.v. for example US patent specifications 3 705 170 and 3 711 486).

5-Trifluoromethylpyridyl-2-oxyanilines of formula II can be prepared as follows:

\[
\text{CF}_3-\text{C}-\text{N}^\text{Cl} + \text{R}_4-\text{R}_3-\text{N}^\text{NH}_2 \rightarrow (\text{II}).
\]

This reaction is carried out in the temperature range from \(20^\circ-180^\circ\)C, preferably from \(50^\circ-160^\circ\)C, in the presence of an acid acceptor, e.g. a hydroxide or hydride of an alkali metal or alkaline earth metal, preferably KOH or NaOH, as well as of an inert organic solvent, preferably dimethylformamide or dimethylsulfoxide. Further, an aniline of formula II can be obtained by a process analogous to that described in J. Org. Chem. 29 (1964), 1, by hydrogenating the corresponding nitro compounds (cf. the literature cited therein).
Anilines of formula II are also obtainable by chemical reduction (e.g. with Sn(II) chloride/HCl) of a corresponding nitro compound (cf. Houben-Weyl, Methoden d. org. Chemie, 11-1, 422):

\[ \text{hydrogenation or reduction} \rightarrow \text{(II).} \]

Benzoylisocyanates of formula III can be obtained, inter alia, as follows (q.v. J. Agr. Food Chem. 21, 348 and 993; 1973):

\[ \begin{array}{c}
\text{R}_1 \\
\text{H}_2\text{SO}_4/\text{H}_2\text{O} \\
\text{R}_2 \\
\text{H}_2\text{O} \\
\text{C}_\text{O}-\text{NH}_2 \\
\text{ClO}_2-\text{COC}_1 \rightarrow \text{(III).} \\
\text{CH}_2\text{Cl}_2
\end{array} \]

A 3-(5-trifluoromethylpyridyl-2-oxy)phenylisocyanate of formula IV can be prepared e.g. by phosgenating an aniline of formula II by conventional methods. The starting benzamides of formula V are known (q.v. for example Boilstein, Handbuch der organischen Chemie, Vol. 9, p. 336).

Urethanes of formula VI can be obtained in a manner known per se by reacting a benzoylisocyanate of formula III with an appropriate alcohol or by reacting a benzamide of formula V in the presence of a basic compound with a corresponding ester of chloroformic acid.

Surprisingly, the compounds of formula I have a very useful activity spectrum against parasiticising helminths in the animal organism, especially in warm-blooded animals, most particularly in mammals. They can be used very successfully against nematodes and trematodes. A distinguishing feature of these compounds is in particular that they are fully effective against species which are resistant to benzimidazoles, especially to thiabendazole. By "thiabendazole" is meant e.g. the compound 2-[4-thiazolyl]benzimidazole as well as related compounds of this class. The anthelmintic activity of the
compounds of formula I rests less on controlling adult, parasitic forms in the body of the host animal than on inhibiting the development of larvae and on the eggs excreted with the faeces, so that the life cycle of the parasite is effectively interrupted.

Among the endoparasites which occur in warm-blooded animals, the helminths cause severe damage. For example, animals attacked by these parasites are not only retarded in their growth, but in some cases suffer such harmful physiological effects that they die. It is therefore of great importance to develop therapeutic agents which are suitable for controlling helminths and their development stages and to prevent attack by these parasites. Particularly dangerous helminth infestations are those caused in the gastrointestinal tract and other organs by parasitic nematodes, cestodes and trematodes, and especially in ruminants such as sheep, cattle and goats, as well as horses, pigs, deer, dogs, cats and poultry.

The damage caused by helminthiases can be substantial whenever herds of cattle fall victim to chronic and, in particular, to epidemic attack. Such damage takes the form, inter alia, of diminution of useful performance, weakened resistance and increased mortality. The control and prevention of helminth infestation are therefore of the utmost importance to avoid or reduce such damage, especially damage having serious economic consequences.

Throughout this specification, the term "helminths" will be understood as meaning in particular parasitic worms which belong to the Phyla Platyhelminthes (cestodes, trematodes) and Nemathelminthes (nematodes and related species), i.e. cestodes, trematodes and nematodes of the gastrointestinal tract and other organs (e.g. liver, lungs, kidneys, lymphatic vessels, blood etc.). Although a range of compounds having anthelmintic activity are known and have been proposed for controlling the different helminth species, they are not entirely satisfactory, either because it is not possible to exploit their activity spectrum fully when administered in well tolerated doses or because they exhibit undesirable side-effects or
characteristics when administered in therapeutic doses. In this regard, the increasing resistance being encountered at the present time to specific classes of compound is an ever more significant factor. Although, for example, the commercial compound "albendazole" (British Patent specification 1 464 326; Am. J. Vet. Res. 38, 1425-14 (1977); Am. J. Vet. Res. 37, 1515-1516 (1976); Am. J. Vet. Res. 38, 807-808 (1977); Am. J. Vet. Res. 38, 1247-1248 (1977)) has a limited activity spectrum as anthelmintic when administered to ruminants, its activity e.g. against benzimidazole-resistant nematodes and adult liver flukes is inadequate. In particular, the pathologically important immature migratory forms of the last mentioned parasites are not attacked when the compound is administered in doses which are tolerated by the host animal.

Surprisingly, it has now been found that the compounds of formula I have not only - as already mentioned - a potent anthelmintic activity with a broad activity spectrum against nematodes, cestodes and trematodes, but, in addition, a low toxicity to warm-blooded animals.

The eligible compounds of formula I are suitable e.g. for controlling parasitic nematodes of the orders (according to the classification of K.I. Skrajabin)

- Rhabditida
- Ascaridida
- Spirurida
- Trichocephalida

or for controlling cestodes of the orders (according to the classification of Wardle and McLeod)

- Cyclophyllidae
- Pseudophyllidae

or for controlling trematodes of the order

- Digenea

in domestic animals and product livestock such as cattle, sheep, goats, horses, pigs, cats, dogs and poultry. The compounds of formula I can be administered to the animals in both individual and
repeated doses. Depending on the species of animal, the individual doses are preferably administered in amounts ranging from 1 to 500 mg per kg of body weight. A better activity is sometimes achieved by protracted administration, or lower doses may suffice.

The compounds of the formula I are preferably used together with the adjuvants conventionally employed in the art of formulation, and can therefore be formulated in known manner to emulsifiable concentrates, directly sprayable or dilutable solutions, dilute emulsions, wettable powders, soluble powders, dusts, granulates, and also encapsulations in e.g. polymer substances, and to tablets, pellets or boluses.

The formulations, i.e. the compositions containing one or more anthelmintic compounds of formula I and, where appropriate, solid or liquid adjuvants, are prepared in known manner, e.g. by homogenously mixing and/or grinding the active ingredient with extenders, e.g. solvents, solid carriers and, in some cases, surface-active compounds (surfactants).

The following formulation adjuvants are employed for preparing the anthelmintic compositions of the invention: solid carriers, e.g. kaolin, talc, bentonite, common salt, calcium phosphate, carbohydrates, cellulose powder, cottonseed meal, polyethylene glycol ether, optionally binders such as gelatin, soluble cellulose derivatives, if desired with the addition of surface-active compounds such as ionic or non-ionic dispersants; natural mineral fillers such as calcite, montmorillonite or attapulgite. To improve the physical properties it is also possible to add highly dispersed silicic acid or highly dispersed adsorbent polymers. Suitable granulated adsorptive carriers are porous types, for example pumice, broken brick, sepiolite or bentonite; and suitable nonsorbent carriers are materials such as calcite or sand. In addition, a great number of pregranulated materials of inorganic or organic nature can be used, e.g. especially dolomite or pulverised plant material.
Suitable solvents are: aromatic hydrocarbons, preferably the fractions containing 8 to 12 carbon atoms, e.g. xylene mixtures or substituted naphthalenes, phthalates such as dibutyl phthalate or dioctyl phthalate, aliphatic hydrocarbons such as cyclohexane or paraffins, alcohols and glycols and their ethers and esters, such as ethanol, ethylene glycol, ethylene glycol monomethyl or monoethyl ether, ketones such as cyclohexanone, strongly polar solvents such as N-methyl-2-pyrrolidone, dimethyl sulfoxide or dimethylformamide, as well as vegetable oils or epoxidised vegetable oils such as epoxidised coconut oil or soybean oil; or water.

Suitable surface-active compounds are nonionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. The term "surfactants" will also be understood as comprising mixtures of surfactants.

Suitable anionic surfactants can be water-soluble soaps as well as water-soluble synthetic surfactants.

Suitable soaps are the alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts of higher fatty acids (C₁₀-C₂₂), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures which can be obtained e.g. from coconut oil or tall oil.

Frequently, however, so-called synthetic surfactants are used, especially fatty sulfonates, fatty sulfates, sulfonated benzimidazole derivatives or alkylaryl sulfonates.

The fatty sulfonates or sulfates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and contain a C₉-C₂₂ alkyl radical which also includes the alkyl moiety of acyl radicals, e.g. the sodium or calcium salt of lignosulfonic acid, or dodecyl sulfate or of a mixture of fatty alcohol sulfates obtained from natural fatty acids. These compounds also comprise the salts of sulfated and sulfonated
fatty alcohol/ethylene oxide adducts. The sulfonated benzimidazole derivatives preferably contain 2 sulfonic acid groups and one fatty acid radical containing 8 to 22 carbon atoms. Examples of alkylarylsulfonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulfonic acid, dibutynaphthalenesulfonic acid or of a condensate of naphthalenesulfonic acid and formaldehyde. Also suitable are corresponding phosphates, e.g. salts of the phosphoric acid ester of an adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide, or phospholipids.

Non-ionic surfactants are preferably polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, or saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols.

Further suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediamine-propylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit.

Representative examples of non-ionic surfactants are nonylphenol-polyethoxyethanols, castor oil polyglycol ethers, polypropylene-/polyethylene oxide adducts, tributylphonoxypropyethoxyethanol, polyethylene glycol and octylphenoxypropyethoxyethanol. Fatty acid esters of polyoxyethylene sorbitan, e.g. polyoxyethylene sorbitan trioleate, are also suitable non-ionic surfactants.

Cationic surfactants are preferably quaternary ammonium salts which contain, as N-substituent, at least one C₆-C₂₂alkyl radical and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl or hydroxy-lower alkyl radicals. The salts are preferably in
the form of halides, methylsulfates or ethylsulfates, e.g. stearyl-trimethylammonium chloride or benzyldi(2-chloroethyl)ethylammonium bromide.

The surfactants customarily employed in the art of formulation are described e.g. in

"McCutcheon's Detergents and Emulsifiers Annual"
Helmut Stache, "Tensid-Taschenbuch" (Handbook of Surfactants), Carl Hanser Verlag, Munich/Vienna, 1981.

Suitable binders for tablets and boluses are chemically modified natural polymers which are soluble in water or alcohol, e.g. starch, cellulose or protein derivatives (e.g. methyl cellulose, carboxymethyl cellulose, ethyl hydroxyethyl cellulose, proteins such as zein, gelatin and the like), as well as synthetic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone etc. Tablets too contain fillers (e.g. starch, microcrystalline cellulose, sugar, lactose etc.), glidants and disintegrators.

If the anthelmintic compositions are in the form of feed concentrates, then suitable carriers are for example production feeds, cereal feeds or protein concentrates. In addition to the active ingredient, such feeds can contain additives, vitamins, antibiotics, chemotherapeutical agents or other pesticides, in particular bacteriostats, fungistats, coccidiostats or also hormone preparations, substances having anabolic action or other substances which promote growth, enhance the quality of the flesh of slaughter animals, or which are otherwise beneficial to the organism. If the compositions or the compound of formula I contained therein are added direct to the solid or liquid feed, then the ready prepared feed contains the active ingredient preferably in a concentration of about 0.0005 to 0.02 percent by weight (5-200 ppm).
The compositions of the invention are administered to the animals to be treated perorally, parenterally, subcutaneously or topically, and are in the form of solutions, emulsions, suspensions (drenches), powders, tablets, boluses and capsules.

The anthelmintic compositions usually contain 0.1 to 99 % by weight, preferably 0.1 to 95 % by weight, of a compound of formula I, 99.9 to 1 % by weight, preferably 99.9 to 5 % by weight, of a solid or liquid adjuvant, and 0 to 25 % by weight, preferably 0.1 to 25 % by weight, of a surfactant.

Whereas commercial products will be preferably formulated as concentrates, the end user will normally employ dilute formulations.

The compositions may also contain further ingredients such as stabilisers, antifoams, viscosity regulators, binders, tackifiers as well as fertilisers or other active ingredients for obtaining special effects.

Such anthelmintic compositions employed by the end user likewise constitute an object of the present invention.

The invention is illustrated in more detailed by the following non-limitative Examples.

Preparatory Examples

Example 1: Preparation of N-3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-chlorophenyl-N'-2,6-difluorobenzoylurea

![Chemical Structure](I)
With stirring, a solution of 3.7 g of 2,6-difluorobenzoylisocyanate in 25 ml of anhydrous toluene is added dropwise to 6.5 g of 3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-chloroaniline in 50 ml of anhydrous toluene. After the initially exothermic reaction has subsided, the reaction mixture is allowed to stand for ca. 24 hours at room temperature, whereupon colourless crystals precipitate. These crystals are isolated by filtration, washed with hexane and recrystallised from toluene/hexane, affording 4.1 g of N-3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-chlorophenyl-N'-2,6-difluorobenzoylurea with a melting point of 217°-218°C (compound 17).

Example 1.1: Preparation of N-3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-methylphenyl-N'-2,6-difluorobenzoylurea

A solution of 2.7 g of 2,6-difluorobenzoylisocyanate in 20 ml of anhydrous toluene is added to 4.5 g of 3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-methylaniline in 50 ml of anhydrous toluene. After the initially exothermic reaction has subsided, the mixture is left to stand overnight. The precipitate is isolated by filtration and washed with hexane, affording white crystals of N-3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-methylphenyl-N'-2,6-difluorobenzoylurea with a melting point of 178°-179°C (compound 1).

Preparation of the starting material:
A solution of 15.3 g of 2-methyl-5-nitrophenyl in 30 ml of dimethylsulfoxide is added dropwise to a mixture of 6.4 g of potassium hydroxide in 30 ml of dimethylsulfoxide. When the exothermic reaction has subsided, 19.9 g of a mixture of 2-fluoro-3-chloro-5-trifluoromethylpyridine (40% by weight) and 2,3-dichloro-5-trifluoromethylpyridine (60% by weight) are slowly added dropwise. After this exothermic reaction too has subsided, the reaction
mixture is stirred for 10 hours, then poured into ice-water and extracted with dichloromethane. The organic extract is dried and concentrated by evaporation. The residue is chromatographed with a mixture of dichloromethane and hexane (in the volume ratio 35:15) over silica gel, using pure dichloromethane as eluant at the start and at the conclusion of chromatography, to give 3-(3-chloro-5-trifluoromethylpyridyl)-2-oxy)-4-methylnitrobenzene as a white crystalline powder with a melting point of 93°-94°C. This compound is then hydrogenated in dioxane using Raney nickel as catalyst. The catalyst is removed by filtration and the reaction solution obtained as filtrate is washed with dichloromethane and chromatographed over silica gel, affording 3-(3-chloro-5-trifluoromethylpyridyl-2-oxy)-4-methylaniline as a white crystalline powder which melts at 55°C.

Formulation Examples

Formulation Examples for compounds of formula I
(throughout, percentages are by weight)

2.1 Emulsifiable concentrate

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound 17</td>
<td>10 %</td>
</tr>
<tr>
<td>castor oil thioxilate</td>
<td>25 %</td>
</tr>
<tr>
<td>butanol</td>
<td>15 %</td>
</tr>
<tr>
<td>ethyl acetate</td>
<td>50 %</td>
</tr>
</tbody>
</table>

Emulsions of any required concentration can be obtained from this concentrate by dilution with water.

2.2 Solutions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound 17</td>
<td>10%</td>
</tr>
<tr>
<td>ethylene glycol monomethyl ether</td>
<td>a) 5%</td>
</tr>
<tr>
<td>polyethylene glycol (mol.wt.400)</td>
<td>b) -</td>
</tr>
<tr>
<td>N-methyl-2-pyrrolidone</td>
<td>20%</td>
</tr>
<tr>
<td>epoxidised coconut oil</td>
<td>a) 1%</td>
</tr>
<tr>
<td>petroleum distillate (boiling range 160-190°)</td>
<td>b) 94%</td>
</tr>
</tbody>
</table>
These solutions are suitable for application in the form of micro-drops.

### 2.3 Granulates

<table>
<thead>
<tr>
<th>Component</th>
<th>a)</th>
<th>b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound 17</td>
<td>5 %</td>
<td>10 %</td>
</tr>
<tr>
<td>kaolin</td>
<td>94 %</td>
<td>-</td>
</tr>
<tr>
<td>highly dispersed silicic acid</td>
<td>1 %</td>
<td>-</td>
</tr>
<tr>
<td>attapulgite</td>
<td>-</td>
<td>90 %</td>
</tr>
</tbody>
</table>

The active ingredient is dissolved in methylene chloride, the solution is sprayed onto the carrier, and the solvent is subsequently evaporated off in vacuo.

### 2.4 Dusts

<table>
<thead>
<tr>
<th>Component</th>
<th>a)</th>
<th>b)</th>
<th>c)</th>
<th>d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound 17</td>
<td>2 %</td>
<td>5 %</td>
<td>5 %</td>
<td>8 %</td>
</tr>
<tr>
<td>highly dispersed silicic acid</td>
<td>1 %</td>
<td>5 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>talcum</td>
<td>97 %</td>
<td>-</td>
<td>95 %</td>
<td>-</td>
</tr>
<tr>
<td>kaolin</td>
<td>-</td>
<td>90 %</td>
<td>-</td>
<td>92 %</td>
</tr>
</tbody>
</table>

Ready-for-use dusts are obtained by intimately mixing the carriers with the active ingredient.

### 2.5 Wettable powders

<table>
<thead>
<tr>
<th>Component</th>
<th>a)</th>
<th>b)</th>
<th>c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound 17</td>
<td>20 %</td>
<td>50 %</td>
<td>75 %</td>
</tr>
<tr>
<td>sodium lignosulfonate</td>
<td>5 %</td>
<td>5 %</td>
<td>-</td>
</tr>
<tr>
<td>sodium lauryl sulfate</td>
<td>3 %</td>
<td>-</td>
<td>5 %</td>
</tr>
<tr>
<td>sodium diisobutylnaphthalenesulfonate</td>
<td>-</td>
<td>6 %</td>
<td>10 %</td>
</tr>
<tr>
<td>octylphenol polyethylene glycol ether (7-8 moles of ethylene oxide)</td>
<td>-</td>
<td>2 %</td>
<td>-</td>
</tr>
<tr>
<td>highly dispersed silicic acid</td>
<td>5 %</td>
<td>10 %</td>
<td>10 %</td>
</tr>
<tr>
<td>kaolin</td>
<td>67 %</td>
<td>27 %</td>
<td>-</td>
</tr>
</tbody>
</table>
The active ingredient is thoroughly mixed with the adjuvants and the mixture is thoroughly ground in a suitable mill, affording wettable powders which can be diluted with water to give suspensions of the desired concentration.

2.6 Extruder granulate
compound of formula 17 10 %
sodium lignosulfonate 2 %
carboxymethylcellulose 1 %
kaolin 87 %

The active ingredient is mixed and ground with the adjuvants, and the mixture is subsequently moistened with water. The mixture is extruded and then dried in a stream of air.

2.7 Coated granulate
compound 17 3 %
polyethylene glycol (mol.wt.200) 3 %
kaolin 94 %

2.8 Suspension concentrate
compound 17 40 %
ethylene glycol 10 %
nonylphenol polyethylene glycol (15 moles of ethylene oxide) 6 %
sodium lignosulfonate 10 %
carboxymethylcellulose 1 %
37 % aqueous formaldehyde solution 0.2 %
silicone oil in the form of a 75 % aqueous emulsion 0.8 %
water 32 %

The finely ground active ingredient is intimately mixed with the adjuvants, giving a suspension concentrate from which suspensions of any desired concentration can be obtained by dilution with water.
2.9 Pellets or boluses

I
- compound 17: 33.0 %
- methyl cellulose: 0.80 %
- highly dispersed silic acid: 0.80 %
- maize starch: 8.40 %

II
- crystalline lactose: 22.50 %
- maize starch: 17.00 %
- microcrystalline cellulose: 16.50 %
- magnesium stearate: 1.00 %

I
The methyl cellulose is stirred in water and allowed to swell. Then the silicic acid is stirred in to give a homogeneous suspension. The active ingredient and the maize starch are mixed and the aqueous suspension is added to the mix, which is kneaded to a paste. This paste is granulated through a 12M sieve and the granulate is dried.

II
All 4 adjuvants are thoroughly mixed.

III
Phases I and II are mixed and compressed to tablets or boluses.

3. Biological Examples

The following trials were carried out to determine the anthelmintic activity:

3.1 Trials with sheep infected with Haemonchus contortus

3.11 Activity against larval development in the host

A specific amount of the test compound was administered daily with a stomach probe for 10 days. The dose varied from 1 to 10 mg/kg body weight. Infection with infective H. contortus larvae was made on the second day after the start of treatment.
Evaluation of activity was made by counting the eggs in faecal samples taken from the sheep rectally 21 to 35 days after infection. Confirmation of activity was that, compared with control animals, no eggs were present in the faecal samples taken from sheep treated with a compound of formula I, e.g. compounds 1, 4, 5, 9, 15 to 18, 25, 26, 30, 31, 35 and 36. The absence of eggs showed that H. contortus was unable to develop normally and can be fully controlled by the used compounds.

3.12 Activity against H. contortus eggs in sheep infected with adult H. contortus

A compound of formula I, e.g. compounds 1, 4, 5, 9, 15 to 18, 25, 26, 30, 31, 35 and 36, was administered daily at a dose of 10 mg/kg body weight with a stomach probe to sheep heavily infected with adult H. contortus.

Evaluation of activity was made by counting the infective larvae in incubated faecal samples taken from the sheep rectally on the 3rd and 21st day after the start of treatment. Confirmation of activity was that larvae developed from eggs laid between the 3rd and 14th day of treatment, whereas larvae did develop from eggs laid in untreated control animals and from eggs laid after treatment had been interrupted.

3.13 Activity against eggs of the liver fluke Fasciola hepatica

F. hepatica eggs in aqueous medium were treated with concentrations of 7.5, 75 and 750 ppm of a compound of formula I and kept in the dark for 15 days at room temperature.

Microscopic examination of the eggs after 15 days showed that no miracidia developed at the two higher concentrations and that the eggs were totally deformed.
In all three trials 3.11, 3.12 and 3.13, compounds of formula I, especially compounds 1, 4, 5, 9, 15 to 18, 25, 26, 30, 31, 35 and 36, strongly inhibited egg hatchability and larval and miracidial viability (95-100 % inhibition compared with untreated hosts).
What is claimed is:

The claims defining the invention are as follows:

1. A method of controlling helminths in productive livestock, which comprises the use of a compound of formula I

\[
\text{CONICONH} - \text{R}_1 - \text{R}_2 - \text{R}_3 - \text{R}_4 - \text{R}_5 - \text{CF}_3
\]

wherein

R\(_1\) is hydrogen, C\(_1\)-C\(_2\)alkoxy, C\(_1\)-C\(_2\)alkylthio, C\(_1\)-C\(_2\)alkyl or halogen,
R\(_2\) is hydrogen or halogen,
R\(_3\) is hydrogen or halogen,
R\(_4\) is hydrogen, C\(_1\)-C\(_2\)alkyl or halogen, and
R\(_5\) is hydrogen or halogen.

2. A method according to claim 1 which comprises the use of a compound of formula I, wherein

R\(_1\) is fluorine, chlorine, methoxy, methylthio or methyl,
R\(_2\) is hydrogen, fluorine or chlorine,
R\(_3\) is hydrogen, 2-fluoro or 2-chloro,
R\(_4\) is hydrogen, fluorine, chlorine, bromine or methyl, and
R\(_5\) is fluorine or chlorine.

3. A method according to claim 2 which comprises the use of a compound of formula I, wherein

R\(_1\) is fluorine, methoxy or methylthio,
R\(_2\) is fluorine,
R\(_3\) is hydrogen,
R\(_4\) is fluorine, chlorine or bromine, and
R\(_5\) is chlorine.

4. A method according to claim 2 which comprises the use of a compound of formula
5. A method according to claim 2 which comprises the use of a compound of formula

6. A method according to claim 2 which comprises the use of a compound of formula

7. A method according to claim 2 which comprises the use of a compound of formula

8. A method according to claim 2 which comprises the use of a compound of formula

9. A method according to claim 2 which comprises the use of a compound of formula
10. A method according to claim 1 in which the active ingredient of the formula I is administered as a feed additive to the solid or liquid feed of domestic animals so that the ready prepared feed contains the active ingredient in a concentration of about 0.0005 to 0.02 percent by weight.

11. A process for the preparation of an anthelmintic composition for administration to productive livestock, which comprises mixing a compound of formula I

\[
\begin{align*}
\text{R}_1 & \quad \text{CONHCONH} & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{CONHCONH} & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{CONHCONH} & \quad \text{R}_6 \\
\end{align*}
\]


wherein
\( R_1 \) is hydrogen, \( C_1-C_2 \) alkoxy, \( C_1-C_2 \) alkylthio, \( C_1-C_2 \) alkyl or halogen,
\( R_2 \) is hydrogen or halogen,
\( R_3 \) is hydrogen or halogen,
\( R_4 \) is hydrogen, \( C_1-C_2 \) alkyl or halogen, and
\( R_5 \) is hydrogen or halogen,
with suitable formulation adjuvants.

12. A process according to claim 11, wherein the compound of formula I is a compound as claimed in any one of claims 2 to 8.

13. An anthelmintic veterinary composition for administration to animals, which contains at least one compound of formula I
wherein

R₁ is hydrogen, C₁-C₂alkoxy, C₁-C₂alkylthio, C₁-C₂alkyl or halogen,
R₂ is hydrogen or halogen,
R₃ is hydrogen or halogen,
R₄ is hydrogen, C₁-C₂alkyl or halogen, and
R₅ is hydrogen or halogen,
together with formulation adjuvants.

FO 7.5 HL/bg*

DATED this NINETEENTH day of JANUARY, 1987
CIBA-GEIGY AG

Patent Attorneys for the Applicant
SPRUSON & FERGUSON