

PATENT SPECIFICATION

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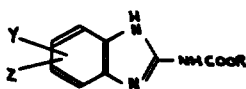


(54) BENZIMIDAZOLE CARBAMATES

(71) We, SMITHKLINE CORPORATION, of 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101, United State of America, a Corporation organised under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to anthelmintic compounds, to processes for their preparation, to compositions comprising the compounds and to methods of treatment of animals infected by certain parasites.

In our Specification No. 1123317 we described a large generic class of Compounds of the following formula I:



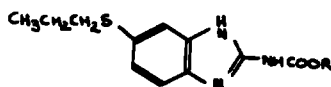
FORMULA I

wherein R is straight or branched alkyl group containing from one to six carbon atoms; Y is hydrogen, alkyl straight or branched containing from one to fifteen carbon atoms, alkoxy straight or branched containing from one to fifteen carbon atoms, phenyl, hydroxy-alkyl containing from one to six carbon atoms, trifluoromethyl, halogen, hydroxy, lower alkylthio, alkylamino, dialkylaminoalkyl, dialkylamino, cyano, carboxy or carbalkoxy containing from two to seven carbon atoms, with the alkyl substituents not specifically defined having one to seven carbon atoms; and Z is hydrogen, alkyl containing from one to six carbon atoms or alkoxy containing from one to six carbon atoms; provided that Y and Z are not both hydrogen.

We have now unexpectedly found that certain compounds within the above class are

extremely active as anthelmintic agents not only against the gastrointestinal parasites as disclosed by the Specification No. 1123317 but also against lungworm infections of animals. These parasites are of the Dictyocaulidae, Metastrongylidae, Protostrongylidae, and Filaroididae families, especially the genus Dictyocaulus which are prevalent in sheep, cattle and horses. They are particularly resistant to standard anthelmintic agents. Metastrongylus is important in pigs, Protostrongylus in sheep and goats, and Filaroides in cats and dogs. Certain lungworms have been reported to be vectors for the influenza virus in swine.

Accordingly we provide compounds of the following formula II:



FORMULA II

wherein R¹ is an alkyl group containing from one to eight carbon atoms such as methyl, ethyl or propyl; furyl; or benzyl.

A particularly useful compound of the invention is that wherein R¹ is methyl i.e. methyl 5-propylthio-2-benzimidazolecarbamate.

The following study in sheep demonstrates the unexpected nature of the activity of the propylthio compound of this invention compared with its oxygen congener (oxibendazole) and/or its methylthio congener which are both within the scope of the disclosure (the former is specifically disclosed) of Specification No. 1123317.

Thirty-one (31) susceptible lambs were dehelminthized using thiabendazole drench (66 mg/kg), then levamisole drench (7.5 mg/kg) to eliminate unwanted nematodes. Fecal counts confirmed the wormfree nature

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of the test animals which were maintained in clean quarters and fed alfalfa pellets and watered *ad libitum*. Each lamb was infected orally with filariform larvae as follows:

- 5 *Haemonchus* 5000/head for 2 days.
 Nematodirus 3500/head for 2 days.
 Dictyocaulus 600/head for 2 days.

coprocultures of donor animals carrying monospecific infections of the three parasites.

On the 24th day, egg counts were made using the modified Stoll method to confirm the patency of the infection. Fecal pellets were Baermannized to recover the *Dictyocaulus* larvae. The infected sheep were divided into control and treated groups. They were sacrificed and processed by standard helminthological procedures to give the following results.

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The infected larvae were prepared from

TABLE 1

Lamb #	Weight Kg.	Worms Recovered		
		<i>Haemonchus</i>	<i>Nematodirus</i>	<i>Dictyocaulus</i>
CONTROL				
519	16.0	5100	3040	102
536	15.9	9850	5280	297
522	20.6	5140	5320	281
538	16.2	1700	1820	70
516	24.1	3300	5270	138
512	18.9	4630	5090	149
Mean		4953	4303	173
METHYL 5-PROPYLOXY-2-BENZIMIDAZOLECARBAMATE - 15 mg./kg.				
540	15.5	110	2610	137
534	21.9	0	100	284
521	23.4	220	590	60
515	19.3	10	230	277
523	13.8	Died 4/27/74 - no worm recovery.		
Mean		85	883	190
% Reduction		98.3	79.5	0
METHYL 5-METHYLTHIO-2-BENZIMIDAZOLECARBAMATE - 5 mg./kg.				
513	22.6	3760	5350	109
517	15.6	1100	5850	400
514	13.6	2600	240	300
Mean		2487	3813	270
% Reduction		49.8	11.4	0
METHYL 5-PROPYLTHIO-2-BENZIMIDAZOLECARBAMATE - 2.5 mg./kg.				
512	18.0	160	760	80
518	24.2	0	80	2
537	20.1	810	0	107
524	27.3	120	10	11
531	16.4	100	720	189
528	27.6	0	10	115
Mean		198	263	84
% Reduction		96.0	93.9	51.4

TABLE 1 - continued

Lamb #	Weight Kg.	Worms Recovered		
		<i>Haemonchus</i>	<i>Nematodirus</i>	<i>Dictyocaulus</i>
METHYL 5-PROPYLTHIO-2-BENZIMIDAZOLECARBAMATE – 5 mg./kg.				
543	20.3	140	1410	63
535	16.8	0	0	58
539	19.1	150	10	12
520	18.7	10	0	21
514	19.5	80	10	0
533	17.0	0	0	19
Mean		63	238	29
% Reduction		98.7	94.5	83.2
METHYL 5-PROPYLTHIO-2-BENZIMIDAZOLECARBAMATE – 10 mg./kg.				
529	23.7	10	30	34
526	14.4	0	0	0
511	21.6	0	0	17
525	24.7	0	0	0
542	22.3	10	0	0
Mean		4	6	10
% Reduction		99.9	99.9	94.2

5 The recorded worm recoveries indicate that the propylthio compound at 15 mg./kg. showed no activity against the lungworm, *Dictyocaulus* and 98% and 80% activity against *Haemonchus* and *Nematodirus*, respectively. 35

10 The methylthio compound at 5mg./k. demonstrated very slight activity against the gastrointestinal worms and no activity against the lungworm. The propylthio active ingredient of this invention showed extremely high efficacy against *Haemonchus* and *Nematodirus* at all doses. Against lungworm it was active at 51.4% at 2.5 mg./kg.; 83.2% at 5 mg./kg.; 15 and 94.2% at 10 mg./kg.

Earlier studies in lambs drenched with a 10 mg./kg., 5% suspension in carboxymethyl-cellulose solution gave 100% elimination of *Dictyocaulus filaria*; a similar drench at 5 mg./kg. against *Nematodirus spathiger* in sheep gave 99.5% elimination compared to 89% for the standard thiabendazole (50 mg./kg.) and 98% for levamisole (7.5 mg./kg.); a similar drench at 5 mg./kg. in sheep 20 against *Haemonchus contortus* gave 100% reduction of eggs per gram of faeces and 99.7% in worm elimination compared to 65.8% and 84.2% for thiabendazole (50 mg./kg.); at 0.05% of diet against the migrating stages of *Ascaris suum* in mice, 25 mean lung lesions were reduced to 1.5 over

infected controls of 2.7 with no deaths in the propylthio treated animals and only three survivors out of ten in the infected controls. In another study four lambs treated with a 35 10% drench of the propylthio congener of the prior art at 30 mg./k. gave no effect on *Dictyocaulus* (lungworm).

The data show that the active ingredient of this invention afford dual activity against 40 helminths at two different sites, the gastrointestinal tract and the lungs.

The active ingredient, methyl 5-propylthio-2-benzimidazolecarbamate, is prepared by reacting carbo-methoxycyanamide with 4- 45 propylthio-*o*-phenylene diamine or an acid addition salt thereof usually in an aqueous miscible solvent in which the reactants are soluble, such as aqueous acetone, water, pyridine-water, ethanol or mixtures of various water-miscible solvents. The reaction is often 50 run at about room temperature up to the boiling point of the solvent mixture used and if necessary alkali may be added.

As an alternative, the diamine is reacted 55 with cyanamide to give the intermediate, 2-amino-5-propylthiobenzimidazole, which is then reacted with methyl-chloroformate to form the desired compound. This is the same reaction as above but carried out in two 60 distinct steps.

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The following is a specific example of the preparation of the compound of this invention.

A mixture of 6.65 g. of 3-chloro-6-nitroacetanilide, 3.2 ml. of propylmercaptan, 5.6 g. of 50% sodium hydroxide and 100 ml. of water is heated at reflux overnight. The cooled mixture is filtered to give the desired 2-nitro-5-propylthioaniline, m.p. 69.5—71.5°C. after recrystallization from ethanol then hexane-ether. N.M.R. (CDCl₃) 40%.

The aniline (2.5 g.) is hydrogenated with 1.9 ml. of concentrated hydrochloric acid, 100 ml. ethanol and 5% palladium-on-charcoal to give 4-propylthio-*o*-phenylene-diamine hydrochloride.

A mixture of 2.5 ml. of 50% sodium hydroxide in 5 ml. of water is added to a mixture of 1.9 g. of cyanamide, 2.2 g. of methyl chloroformate, 3.5 ml. of water and 3 ml. of acetone over 45 minutes below 10°C. and the pH raised to 6.5. A molar equivalent solution of the diamine in 100 ml. of ethanol is added. The mixture is heated until the easily volatile solvents are expelled, to about 85°C., then maintained at this temperature with some water added for one-half hour. The product, methyl 5-propylthio-2-benzimidazolecarbamate, is separated, washed to give a colourless crystalline solid, m.p. 208—210°C. N.M.R. and T.L.C. consistent.

The methods of this invention for treating parasitically infected or exposed animals comprise the oral administration of an effective but nontoxic quantity of methyl 5-propylthio-2-benzimidazolecarbamate to said animals. The animals most usually treated are swine, sheep, cattle or horses but any infected commercial or pet animal can be the subject of these new methods. The subject animals may have either gastorintestinal infestation of the type disclosed in U.K. Patent No. 1123317 or preferably lungworm infections. In effect, the new methods give a dual activity against gastrointestinal and lung parasites at the same dose levels.

The administration may be by any of the commonly used oral veterinary methods for anthelmintic treatment, such as by bolus, tablet, drench and top dressing. Animals of low weight are treated with unit doses ranging no higher than a few milligrams; whereas animals of high body weight, such as ruminants as sheep or cattle, require proportionately larger unit doses ranging up to several grams. Preferably, a single dose is administered from 1—5 times or preferably once or twice to clear the animals or sometimes daily for each animal species.

The amount of ingredient administered will therefore depend on the weight of the host, but will usually be between 1 mg./kg. and 100 mg./kg., preferably 5—15 mg./kg., of body weight per dose.

The method may be applied as a curative to infected animals or in somewhat lower

doses prophylactically to animals potentially exposed to internal parasites. Most advantageously the methods of this invention comprise the oral administration for curative or prophylactic purposes to animals infected with or exposed to a lungworm, for example a Dictyocaulidae, preferably in sheep, cattle or horses.

In addition to lungworm infection as noted below, the 5-propylthio-2-benzimidazolecarbamate of this invention has most useful general anthelmintic properties, that is, broad spectrum activity against gastrointestinal parasites of warm blooded animals, including both mature and immature parasitic forms. In particular, this compound has high activity against various helminthic infections of the intestinal tract of economically important animals, coupled with low systemic toxicity to the host animal.

For example, the disclosed compounds are generally effective in clearing mice of worm infections for laboratory purposes, among others: *Syphacia obvelata* and *Aspicularis tetraptera* (mouse pinworm), *Nematospiroides dubius* (mouse hookworm), and the migratory stages of *Ascaris suum*.

Other susceptible helminths include *Toxocara canis*, found in naturally infested dogs. Also, parasitic to this host are *Ancylostoma canium*, *Trichuris vulpis* (whipworm), and *Physalaptera spp.*

These compounds are efficacious against parasites of pigs, such as the migratory stages of *Ascaris suum*, thus preventing the development of verminous pneumonia.

Among the gastrointestinal parasites in sheep and cattle which are susceptible are *Haemonchus contortus*, *Ostertagia spp.*, *Trichostrongylus spp.*, *Nematodirus spp.*, *Trichuris ovis*, *Cooperia spp.*, and *Strongyloides papillosus*, *Bunostomum spp.*, *Chabertia sp.* and *Oesophagostomum spp.*, are other important parasites of sheep.

In practice, the active propylthio compound is usually formulated with a nontoxic animal veterinary or feed carrier thereof to give the anthelmintic compositions of this invention. The carrier may be a standard animal feed composition based on a feed carrier or an orally ingestible container for the active ingredient, for example, a hard or soft gelatin capsule; or it may be a pharmaceutically acceptable diluent or excipient of the kind normally used in the production of medications, ready for use, for example maize starch, terra alba, lactose, sucrose, calcium phosphate, gelatin, talcum stearic acid, magnesium stearate, dextrin, agar, pectin or acacia.

Exemplary of liquid carriers are peanut oil, olive oil, sesame oil, and water. Similarly, the carrier or diluent may include a time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical or veteri-

nary forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule, compounded in the form of a salt block, as a powder for drench or gavage use, whole feed or top dressing mixed with standard animal feed carrier as noted in U.S. Patent No. 3,812,255. The amount of solid veterinary carrier will vary widely but preferably will be from 25 mg. to 3 gm. for the nonfeed carriers. If a liquid carrier is used, the preparation may be in a soft gelatin capsule, in an ampule or in liquid suspension.

The compositions are most often made up in a form suitable for oral administration and may therefore take the form of a liquid, for example, an emulsion or a solution or suspension in water, oil, such as arachis oil, or other liquid.

The compositions are advantageously made up in a dosage unit form adapted for the desired mode of administration. Thus for the preferred oral administration, the dosage unit may take the form of a suspension, top dressing, tablet, packaged powder, bolus or encapsulated powder. The quantity of active ingredient in each dosage unit will be such that one or more units are required for each therapeutic administration.

Where tableting is used, the resulting tablets may then be coated with methyl methacrylate to form an enteric coating, i.e., a coating which is substantially insoluble in gastric secretion but substantially soluble in intestinal fluids.

The compositions thusly prepared are administered, usually orally, to an infected or susceptible host from 1—5 times daily for curative or prophylactic anthelmintic activity.

The following examples illustrate specific aspects of the invention which may be employed in formulating the compositions of the invention but are not considered to limit the scope of the invention described herebefore.

EXAMPLE 1.

Typical Cattle Bolus.

Methyl 5-propylthio-2-benzimidazolecarbamate	0.15 grams
Calcium Phosphate	2.5 grams
Maize Starch	0.54 grams
Talcum	0.14 grams
Gum Arabic	0.15 grams
Magnesium Stearate	0.5 grams

The calcium phosphate and the anthelmintic compounds are thoroughly mixed, and the mixture reduced to a particle size finer than 60 mesh. About one-half of the starch is added, as an aqueous paste, and the resulting mixture granulated. The granules are passed through a 10 mesh screen and dried at 100°—130°F. for about eight hours. The dried materials are then passed through a No. 16

mesh screen. The guar gum and the balance of the starch are added and the mixture thoroughly blended. Finally, the remainder of the ingredients are added and the entire mass thoroughly mixed and compressed into a bolus. The magnesium stearate, talcum and gum acacia are of a particle size to pass a No. 10 mesh screen.

EXAMPLE 2.

<i>Sheep Drench</i>	Parts by Weight
Methyl 5-propylthio-2-benzimidazolecarbamate	60
Terra Alba English	35.5
Tragacanth, U.S.P.	3.0
Sodium Lauryl Sulfate	1.5
Water	

The above solid components are thoroughly mixed, giving a water dispersible powder. This powder can be directly admixed with water in concentrations on the order of 10.5 g. of powder to 5 cc. of water.

EXAMPLE 3.

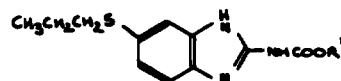
<i>Sheep Drench</i>	
Methyl 5-propylthio-2-benzimidazolecarbamate	2 grams
0.1N HCl Solution	Quantum sufficient to make 1 liter.

It will be understood that the novel part of the structure of the compounds of Formula II which gives enhanced anthelmintic activity against gastrointestinal helminths and unique activity against lungworms is the propylthio group.

The methods and compositions of this invention using methyl 5-propylthio-2-benzimidazolecarbamate are also applicable to ruminants especially cattle and sheep infected or exposed to tapeworms (cestodes). For example, at 10 and 15 mg/kg complete control of *Moniezia* and *Avitellina* in sheep was achieved. In sheep at 50 mg/kg complete elimination of flukes was achieved after artificial infection with 300 metacercariae of *Fasciola hepatica*.

WHAT WE CLAIM IS:—

1. A compound of the following formula:



wherein R¹ is an alkyl group containing from one to eight carbon atoms; furyl or benzyl.

2. Methyl 5-propylthio-2-benzimidazolecarbamate.

3. A process for the preparation of the



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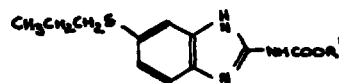
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1. A compound of the following formula:



wherein R¹ is an alkyl group containing from one to eight carbon atoms; furyl or benzyl.

2. Methyl 5-propylthio-2-benzimidazolecarbamate.

3. A process for the preparation of the

X. CN

4. A process according to claim 3 wherein X is NHCOOCH_3 and the compound of formula:



5. A process according to claim 4 as hereinbefore described.

7. An anthelmintic composition for animals comprising a veterinary or feed carrier and dispersed uniformly therein a compound according to any one of claims 1, 2 and 6.

9. An anthelmintic composition according to claim 8 as hereinbefore described in any one of Examples 1 to 3.

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13. A method according to any one of claims 10 to 12 in which the quantity is chosen from the range of 1—100 mg/kg per dose based in the animal weight.

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17. A method according to claim 10 in which the helminths are present in both the gastrointestinal tract and in the lungs.

R. A. R. HURST,
Agent for the Applicants.

