

COMMONWEALTH OF AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

In support of the (a) convention application made by
(b) The Upjohn Company

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

(hereinafter called "applicant(s)") for a patent (c) for an
invention entitled (d) Anthelmintic Acylhydrazones, Method of Use and
Compositions

(e) Insert FULL name(s) AND address(es) of declarant(s)
(See headnote*)

I/We (e) Robert A. Armitage, Vice President & Patent Counsel of
The Upjohn Company of 301 Henrietta Street, Kalamazoo, Michigan,
U.S.A.

do solemnly and sincerely declare as follows:

1. ~~I am/We are the applicant(s).~~
(or, in the case of an application by a body corporate)
1. I am/We are authorized to make this declaration on behalf of the applicant(s).
2. ~~I am/We are the actual inventor(s) of the invention.~~
(or, where the applicant(s) is/are not the actual inventor(s))
2. (f) Douglas L. Rector, George A. Conder, and Sylvester D. Folz,
residing at 6075 Litchfield Lane, Kalamazoo; 6835 East "F"
Avenue, Richland; and 6209 Enola Drive, Kalamazoo, respectively,
State of Michigan, U.S.A.

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s) derives title from actual inventor(s)
(See headnote**)

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

- (g) by virtue of assignments dated 30 April 1986, the applicant is the
assignee of the invention from the actual inventors.

(Note: Paragraphs 3 and 4 apply only to Convention applications)

(h) Insert country, filing date, and basic applicant(s) for the/each basic application

3. The basic application(s) for patent or similar protection on which the application is based
is/are identified by country, filing date, and basic applicant(s) as follows:

- (h) United States, 7 April 1986, Douglas L. Rector, George A. Conder,
and Sylvester D. Folz

(k) Insert PLACE of signing

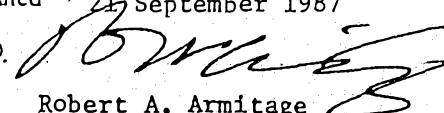
(l) Insert DATE of signing

Declared at (k) Kalamazoo, Michigan, U.S.A.

Dated (l) 21 September 1987

(m) Signature(s) of declarant(s)

X

(m) 
Robert A. Armitage
Vice President & Patent Counsel

Note: No legalization or other witness required

To: The Commissioner of Patents

PHILLIPS ORMONDE & FITZPATRICK

Patent and Trade Mark Attorneys
Melbourne, Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-72382/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 602140

(54) Title
ANTHELMINTIC ACYLHYDRAZONES, METHOD OF USE AND COMPOSITIONS

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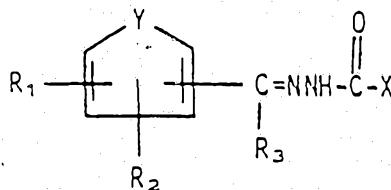
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(56) Prior Art Documents
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AU 72854/87 A01N 9/20
AU 55914/86 A61N 31/655

(57) Claim

1. A method of killing parasitic worms in humans and valuable warm-blooded domestic animals which comprises administering to humans or valuable warm-blooded domestic animals in need, a therapeutic or prophylactic dosage of an acylhydrazone, hydrate thereof or pharmaceutically acceptable salt thereof of the formula:



I

wherein X is (a) hydrogen; with the proviso that when X is hydrogen

and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-methyl and R_2 is hydrogen, R_3 is other than methyl; (b) C_1-C_{10} alkyl; with the proviso that when X is ethyl and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (c) C_2-C_5 alkenyl, preferably C_2-C_4 alkenyl; (d) C_2-C_5 alkynyl; (e) cyclo(C_3-C_{10})alkyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, trifluoromethyl, or halo; with the proviso that when X is cyclohexyl or chrysanthemyl and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (f) pyrrolidinyl; (g) piperidinyl; (h) 1-methylpyrrolidinyl; (i) 1-methylpiperidinyl; (j) C_2-C_5 alkoxyalkyl; (k) cyclo(C_3-C_{10})alkyl(C_1-C_4)alkyl; (l) phenyl(C_1-C_4)alkyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or trifluoromethyl; (m) cyano(C_1-C_3)alkyl; (n) naphthyl(C_1-C_3)alkyl optionally substituted with one or two C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or trifluoromethyl; (o) C_1-C_6 alkoxy, with the proviso that when X is methoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-methyl and R_2 is hydrogen, R_3 is other than methyl; with the proviso that when X is ethoxy or t-butoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; with the proviso that when X is ethoxy and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than phenyl or 4-ethoxyphenyl; (p) diphenylmethoxy; (q) cyclo(C_3-C_5)alkyloxy optionally substituted with one or two C_1-C_3 alkyl; (r) phenoxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or trifluoromethyl; with the proviso that when X is phenoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (s) benzyloxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or trifluoromethyl; with the proviso that when X is benzyloxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 4-methyl or 5-methyl and R_2 is hydrogen, R_3 is other than methyl; (t) heteroaromatic optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, or trifluoromethyl; (u) phenyl optionally

substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; with the proviso that when X is 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than hydrogen; with the proviso that when X is 3-chlorophenyl, 2-methylphenyl or 4-t-butylphenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than methyl; with the further proviso that when X is 2-nitrophenyl or 2-ethoxyphenyl and the compound is a 2-furanyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than methyl; with the further proviso that when X is phenyl and the compound is a 1-methyl-1H-pyrrol-2-yl acylhydrazone, R₁ and R₂ are hydrogen, R₃ is other than hydrogen; with the proviso that when X is 2-chlorophenyl or 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R₂ and R₃ are hydrogen, R₁ is other than 5-methyl; with the further proviso that when X is 2-nitrophenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than ethyl; with the further proviso that when X is 2-methylphenyl and the compound is a 1H-pyrrol-2-yl acylhydrazone, R₁ and R₂ are hydrogen, R₃ is other than hydrogen; (v) phenyl optionally substituted with the divalent C₁-C₂ alkylenedioxy; (w) naphthyl optionally substituted with one or 2 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro; (x) bridged polycyclic hydrocarbon substituents of six to 10 nuclear carbons, optionally substituted with one, 2 or 3 (C₁-C₃) alkyl groups; (y) perhalo(C₁-C₇)alkyl; (z) N-morpholinyl(C₁-C₄)alkyl; (aa) N-piperidinyl(C₁-C₄)alkyl; (bb) N-pyrrolidinyl(C₁-C₄)alkyl;

wherein Y is an oxygen atom; a sulfur atom; or a N-Z group;

wherein Z is hydrogen; C₁-C₄ alkyl; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; or phenyl(C₁-C₄)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl;

(11) AU-B-72382/87
(10) 602140

-4-

wherein R_1 and R_2 , being the same or different, are hydrogen; hydroxy; C_1-C_4 alkyl, preferably C_1-C_3 alkyl; C_1-C_3 alkoxy; C_1-C_3 alkylthio; halo or trifluoromethyl; with the proviso that R_1 and R_2 are not both halo; and

wherein R_3 is hydrogen; C_1-C_6 alkyl; cyclo(C_3-C_6)alkyl optionally substituted with one, 2 or 3 C_1-C_3 alkyl, preferably cyclo(C_3-C_5)alkyl optionally substituted; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, halo, trifluoromethyl, or C_1-C_3 alkoxy; phenyl(C_1-C_3)alkyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, halo, trifluoromethyl, or C_1-C_3 alkoxy; 1,3-dioxacyclohexan-5-yl; thienylvinyl; furanylvinyl; or phenylvinyl.

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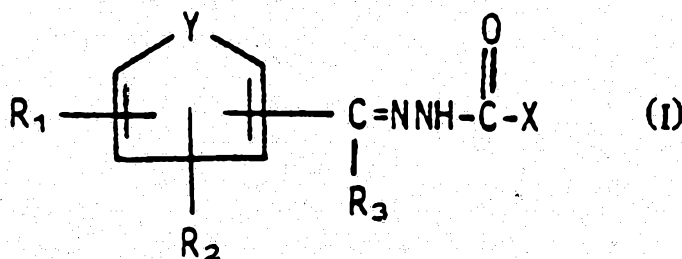
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(57) Abstract

Process for killing internal parasites, especially nematodes, trematodes and cestodes affecting warm blooded animals such as sheep, cattle, swine, goats, dogs, cats, horses and humans as well as poultry by administering an effective amount of a compound of formula (I). The compounds are readily prepared by conventional chemical reactions.

-1-

ANTHELMINTIC ACYLHYDRAZONES,
METHOD OF USE AND COMPOSITIONS

SUMMARY OF THE INVENTION

This invention pertains to a new method for killing and
5 controlling worms (Helminths), and new formulations for killing and
controlling worms in animals, and new chemical compounds. The
invention is more particularly directed to a new method for killing
and controlling parasitic worms in animals with certain
acylhydrazones, to new anthelmintic formulations comprising the same,
10 and to new acylhydrazones.

The anthelmintic acylhydrazones have the general structural
formula I.

BACKGROUND OF THE INVENTION

The diseases or groups of diseases described generally as
15 helminthiasis are due to infection of the animal with parasitic worms
known as helminths. Helminthiasis and helminthosis are prevalent and
may lead to serious economic problems in valuable domestic warm-
blooded animals such as sheep, swine, cattle, goats, dogs, cats,
horses, poultry and man. Among the helminths, the groups of worms
20 known as nematodes, trematodes and cestodes cause widespread and
often-times serious infections in various species of animals
including man. The most common genera of nematodes, trematodes and
cestodes infecting the animals referred to above are Dictyocaulus,
Haemonchus, Trichostrongylus, Ostertagia, Nematodirus, Cooperia,
25 Bunostomum, Oesophagostomum, Chabertia, Strongyloides, Trichuris,
Fasciola, Dicrocoelium, Enterobius, Ascaris, Toxascaris, Toxocara,
Ascaridia, Capillaria, Heterakis, Ancylostoma, Uncinaria,
Dirofilaria, Onchocerca, Taenia, Moniezia, Dipylidium,
Metastrongylus, Triodontophorus, Macracanthorhynchus, Hyoststrongylus,
30 and Strongylus. Some of these genera attack primarily the intestinal
tract while others, inhabit the stomach, lungs, liver and
subcutaneous tissues. The parasitic infections causing helminthiasis
and helminthosis lead to anemia, malnutrition, weakness, weight loss,
unthriftiness, severe damage to the gastrointestinal tract wall and,
35 if left to run their course, may result in death of the infected
animals.

The anthelmintic activity of acylhydrazones of formula I has not
been previously reported.

DETAILED DESCRIPTION OF THE INVENTION

The acylhydrazones of this invention, including hydrates or pharmaceutically acceptable salts thereof, are represented by Formula I wherein X is (a) hydrogen; with the proviso that when X is hydrogen and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-methyl and R₂ is hydrogen, R₃ is other than methyl; (b) C₁-C₁₀ alkyl; with the proviso that when X is ethyl and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is other than methyl; (c) C₂-C₆ alkenyl, preferably C₂-C₄ alkenyl; (d) C₂-C₆ alkynyl; (e) cyclo(C₃-C₁₀)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoxy, trifluoromethyl, or halo; with the proviso that when X is cyclohexyl or chrysanthemyl and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is other than methyl; (f) pyrrolidinyl; (g) piperidinyl; (h) 1-methylpyrrolidinyl; (i) 1-methylpiperidinyl; (j) C₂-C₆ alkoxyalkyl; (k) cyclo(C₃-C₁₀)alkyl(C₁-C₄)alkyl; (l) phenyl(C₁-C₄)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; (m) cyano(C₁-C₃)alkyl; (n) naphthyl(C₁-C₃)alkyl optionally substituted with one or two C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; (o) C₁-C₆ alkoxy, with the proviso that when X is methoxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-methyl and R₂ is hydrogen, R₃ is other than methyl; with the proviso that when X is ethoxy or t-butoxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is other than methyl; with the proviso that when X is ethoxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 4-methyl and R₂ is hydrogen, R₃ is other than methyl; with the proviso that when X is ethoxy and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than phenyl or 4-ethoxyphenyl; (p) diphenylmethoxy; (q) cyclo(C₃-C₆)alkoxy optionally substituted with one or two C₁-C₃ alkyl; (r) phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; with the proviso that when X is phenoxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is other than methyl; (s) benzyloxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; with the proviso that when X is benzyloxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 4-methyl or 5-methyl

-3-

and R_2 is hydrogen, R_3 is other than methyl; (t) heteroaromatic optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, or trifluoromethyl; (u) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, or trifluoromethyl; with the proviso that when X is 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than hydrogen; with the proviso that when X is 3-chlorophenyl, 2-methylphenyl or 4-t-butylphenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than methyl; with the further proviso that when X is 2-nitrophenyl or 2-ethoxyphenyl and the compound is a 2-furanyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than methyl; with the further proviso that when X is phenyl and the compound is a 1-methyl-1H-pyrrol-2-yl acylhydrazone, R_1 and R_2 are hydrogen, R_3 is other than hydrogen; with the proviso that when X is 2-chlorophenyl or 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R_2 and R_3 are hydrogen, R_1 is other than 5-methyl; with the further proviso that when X is 2-nitrophenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than ethyl; with the further proviso that when X is 2-methylphenyl and the compound is a 1H-pyrrol-2-yl acylhydrazone, R_1 and R_2 are hydrogen, R_3 is other than hydrogen; (v) phenyl optionally substituted with the divalent C_1-C_2 alkylenedioxy; (w) naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio, nitro; (x) bridged polycyclic hydrocarbon substituents of six to 10 nuclear carbons, optionally substituted with one, 2 or 3 (C_1-C_3) alkyl groups; (y) perhalo(C_1-C_7)alkyl; (z) N-morpholinyl(C_1-C_4)alkyl; (aa) N-piperidinyl(C_1-C_4)alkyl; (bb) N-pyrrolidinyl(C_1-C_4)alkyl;

wherein Y is an oxygen atom; a sulfur atom; or a N-Z group;

wherein Z is hydrogen; C_1-C_4 alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, or trifluoromethyl; or phenyl(C_1-C_4)alkyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or

trifluoromethyl;

wherein R_1 and R_2 , being the same or different, are hydrogen; hydroxy; C_1-C_4 alkyl, preferably C_1-C_3 alkyl; C_1-C_3 alkoxy; C_1-C_3 alkylthio; halo or trifluoromethyl; with the proviso that R_1 and R_2 are not both halo; and

wherein R_3 is hydrogen; C_1-C_6 alkyl; cyclo(C_3-C_6)alkyl optionally substituted with one, 2 or 3 C_1-C_3 alkyl, preferably cyclo(C_3-C_5)alkyl optionally substituted; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, halo, trifluoromethyl, or C_1-C_3 alkoxy; phenyl(C_1-C_3)alkyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, halo, trifluoromethyl, or C_1-C_3 alkoxy; 1,3-dioxacyclohexan-5-yl; thienylvinyl; furanylvinyl; or phenylvinyl.

$C_{\text{---}}-C_{\text{---}}$ means the carbon content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety. Thus (C_1-C_3) alkyl refers to alkyl of one to 3 carbon atoms, inclusive or methyl, ethyl, propyl, and isopropyl.

Halogen atom (halo) refers to a bromo, chloro, iodo or fluoro atom.

Heteroaromatic refers to an aromatic heterocycle of 5 to 10 members, containing one or two heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur and includes quinoline, pyrrole, indole, benzofuran, benzothiophene, quinazoline, quinoxaline, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyridazine, pyrimidine, pyrazine, benzimidazole, benzothiazole, benzoxazole, pyridine, thiophene or furan, as well as the N-oxides, hydrates and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacologically-toxicological point of view and to the manufacturing pharmaceutical chemist from a physical-chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

Examples of C_1-C_4 alkyl are methyl, ethyl, propyl, butyl and isomeric forms thereof. Examples of C_1-C_3 alkoxy are methoxy, ethoxy, propoxy and isomeric forms thereof. Examples of phenoxy substituted with one, 2 or 3 C_1-C_4 alkyl are (o-, m-, or p-)tolyl, (o-, m-, or p-)ethylphenyl, p-tert-butylphenyl, 2,5-dimethylphenyl,

2,6-dimethylphenyl, 2,4-dimethylphenyl, (2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 2,4,5-)trimethylphenyl.

Examples of C_2-C_6 dialkylamino are dimethylamino, diethylamino, methylethylamino, dipropylamino and ethylpropylamino.

5 Examples of phenyl(C_1-C_3)alkyl are benzyl, phenylethyl and phenylpropyl. Examples of phenyl(C_1-C_3)alkyl substituted with one, 2 or 3 C_1-C_4 alkoxy, halo or trifluoromethyl include 4-chlorobenzyl, 2-chlorophenylethyl, p-tolyethyl, 2-methylbenzyl, 4-methoxybenzyl. Examples of C_1-C_3 alkylthio include methylthio, ethylthio, and n-propylthio.

10 Examples of substituted cyclo(C_3-C_{10})alkyl are chrysanthemyl, 1-methylcyclopropyl and 2-methylcyclopropyl. Examples of cyclo(C_3-C_{10})alkyl(C_1-C_4)alkyl are 2-cyclohexylethyl and cyclohexylmethyl. An example of substituted cyclo(C_3-C_6)alkyloxy is menthyl.

15 Examples of naphthyl(C_1-C_3)alkyl include 2-naphthylmethyl and 1-naphthylethyl. Examples of substituted naphthyl(C_1-C_3)alkyl is (3,8-dichloro-1-naphthyl)methyl; (4-chloro-1-naphthyl)methyl; and (4-methoxy-1-naphthyl)methyl. Examples of substituted naphthyl include 3,6-dichloro-1-naphthyl; 3,5-dichloro-2-naphthyl; 6-methyl-2-naphthyl; and 4,6-dichloro-1-naphthyl.

20 Examples of bridged polycyclic hydrocarbon substituents of six to 10 nuclear carbons, optionally substituted with one, 2 or 3 (C_1-C_3) alkyl groups include exo or endo-2-norbornyl, bicyclo[2,2,2]oct-1-yl, and 1-adamantyl.

25 Examples of perhalo (C_1-C_7) alkyl include trifluoromethyl, n-heptafluoropropyl and n-undecafluoropentyl.

Preferred acylhydrazones of Formula I are 2-thienyl acylhydrazones (IA) or 2-furanyl acylhydrazones (IB).

Preferred R_1 and R_2 include hydrogen, methyl, or a chloro atom.

30 Preferred R_3 includes hydrogen, methyl or ethyl.

Preferred X include hydrogen; C_1-C_4 alkyl; cyclohexylethyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_2 alkoxy, trifluoromethyl and chloro; C_1-C_4 alkoxy; phenoxy optionally substituted with one, 2 or 3 C_1-C_2 alkyl, C_1-C_2 alkoxy, trifluoromethyl and chloro; cyclo(C_3-C_6)alkyl; pyridinyl; thienyl; furanyl; benzyloxy optionally substituted with one or 2 C_1-C_2 alkoxy; di(C_1-C_2)alkoxyphenylmethyl; N-morpholinylethyl; or 1-menthylO.

Preferred compounds of this invention are the compounds of Table

A represented by compound nos:

1, 6, 11, 18, 22, 25, 28, 30, 31, 32, 35, 45, 48, 49, 54, 55, 57, 58,
59, 60, 61, 62, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 81, 84, 85,
86, 87, 88, 89, 91, 94, 95, 97, 100, 108, 114, 115, 116, 118, 119,
5 120, 124, 126, 130, 131, 133, 137, 138, 144, 146, 148, 150, 154, 178,
186, 192, 201, 202, 203, 208, 209, 211, 224, 240, 241, 264, 266, 267,
268, 270, 271, 272, 274, 276, 279, 283, 285, 288, 289, 290, 291, 292,
293, 294, 296, 300, 301, 303, 305, 307, 311, 312, 313, 315, 317, 318,
320, 323, 324, 325, 327, 328, 329, 331, 343, 345, 346, 361, 363, 365,
10 366, 367, 370, 384, 386, 390, 391, 392, 394, 395, 397, 400, 402, 404,
406, 410, 411, 413, 422, 423, 424, 426, 429, 430, 432, 434, 435, 436,
437, 438, 439, 440, 441, 443, 445, 446, 450, 457, 483, 487, 494, 504,
506, 568, 569, 575, 585, 590, 591, 600, 604 and 605.

One embodiment of this invention includes, of course, the
15 anthelmintic use and anthelmintic compositions of compounds of
Formula I, IA, IB, or IC hydrates thereof or pharmaceutically
acceptable salts thereof.

Another embodiment of this invention are the novel compounds,
hydrates thereof or pharmaceutically acceptable salts thereof.
20 according to Formula I, IA, IB, and IC.

Another embodiment of this invention are the novel compounds of
Formula I, the hydrates thereof or pharmaceutically acceptable salts
thereof where X is (e) cyclo(C₃-C₁₀)alkyl optionally substituted with
one, 2 or 3 C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoxy,
25 trifluoromethyl, or halo; with the proviso that when X is cyclohexyl
and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂
is hydrogen, R₃ is other than methyl; (j) C₂-C₆ alkoxyalkyl; (k)
cyclo(C₃-C₁₀)alkyl(C₁-C₄)alkyl; (q) cyclo(C₃-C₆)alkyloxy optionally
substituted with one or two C₁-C₃ alkyl; (s) benzyloxy optionally
30 substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or tri-
fluoromethyl; with the proviso that when X is benzyloxy and the
compound is a 2-thienyl acylhydrazone, and R₁ is 4-methyl or 5-methyl
and R₂ is hydrogen, R₃ is other than methyl; or (u) phenyl
substituted with one, 2 or 3 C₁-C₃ alkoxy, phenoxy or
35 trifluoromethyl; with the proviso that when X is 2-ethoxyphenyl and
the compound is a 2-furanyl acylhydrazone, and R₁ and R₂ are
hydrogen, R₃ is other than methyl.

Still another embodiment of this invention are the novel

compounds of Table A represented by compound nos:

11, 22, 28, 30, 31, 32, 35, 45, 48, 49, 54, 55, 57, 58, 59, 60, 61,
62, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 81, 84, 85, 86, 87, 88,
89, 91, 94, 95, 97, 100, 108, 114, 116, 118, 119, 120, 124, 126, 130,
5 131, 133, 137, 138, 144, 146, 148, 150, 154, 178, 186, 192, 201, 202,
203, 208, 209, 211, 224, 240, 241, 264, 266, 267, 268, 270, 272, 274,
276, 279, 283, 285, 288, 289, 290, 291, 292, 293, 294, 296, 300, 301,
303, 305, 307, 311, 312, 313, 315, 317, 318, 320, 323, 325, 327, 328,
329, 343, 346, 361, 363, 365, 366, 384, 386, 390, 391, 392, 394, 395,
10 400, 402, 404, 406, 411, 413, 422, 423, 426, 429, 430, 432, 434, 435,
436, 437, 438, 439, 440, 441, 443, 445, 446, 450, 457, 483, 487, 494,
506, 568, 569, 575, 585, 590, 591, 600, 604 and 605.

Among the acylhydrazones of Formula I are the compounds of Table
A represented by compound nos: 1, 6, 7, 8, 12, 17, 18, 20, 24, 25,
15 26, 56, 115, 230, 265, 271, 275, 284, 324, 331, 332, 333, 345, 359,
367, 368, 369, 370, 385, 388, 396, 397, 398, 405, 409, 410, 421, 424,
425 and 504 are known.

The acylhydrazones of this invention (Formula I) are readily
prepared by reacting the appropriate ketone/aldehyde (II) with the
20 acylhydrazide/carbazate (III) (Chart A, Scheme A) or by heating the
heteroaromatic ketone/aldehyde (II) with the appropriate hydrazine
(IV) to form the hydrazone intermediate (V) which is then acylated
with the halide or anhydride (VI) to form the acylhydrazone (I)
(Chart A, Scheme B).

25 The reaction of Scheme A is carried out in the presence of a
suitable solvent, for example, water, alcohols, ethers, halogenated
hydrocarbons, hydrocarbons and include methanol, ethanol,
isopropanol, propanol, hexane, tetrahydrofuran, dioxane, methylene
chloride, and preferably ethanol. A catalyst such as glacial acetic
30 acid, hydrochloric acid, sulfuric acid or p-toluenesulfonic acid can
be utilized to enhance the yield/rate of the reaction, particularly
when R_3 is alkyl of 3 or more atoms, arylalkyl or aryl.

The acylation reaction of Scheme B is carried out in the
presence of a suitable base such as an organic tertiary amine, or
35 inorganic base, for example, triethylamine or sodium carbonate or
preferably, pyridine. The base may also be the solvent.

The starting compounds are known or can be readily prepared by
known methods. R. L. Frank and C. Weatherbee, J. Am. Chem. Soc., 70,

3482-3 (1948); N. B. Mahishi, et al., J. Indian Chem. Soc., 42, 67-74 (1965) and M. Ogata and H. Kano, Chem. Pharm. Bull (Tokyo), 11, 32 (1963).

5 The following detailed examples/procedures describe how to prepare various acylhydrazones of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants as well as to reaction conditions and
10 techniques.

Procedure 1 Preparation of benzoic acid (2-thienylmethylene)-hydrazide, Compound 1.

A mixture of 6.81 gm (0.05 mole) of benzoic acid hydrazide, 5.6 gm (0.05 mole) of 2-thiophenecarboxaldehyde and 100 ml of absolute
15 ethanol is refluxed 8 hr. Sufficient dioxane is added at boiling to furnish a solution. The hot solution is filtered. The filtrate is cooled and then chilled. The product is collected and dried to yield 7.68 gm (67%) of the title compound having a melting point of 203.3°C.

20 Analysis Calcd: C, 62.61; H, 4.35.

Found: C, 62.34; H, 4.36.

Procedure 2 Preparation of 4-methylbenzoic acid (2-thienylmethylene)hydrazide, Compound 3.

A mixture of 3.36 gm (0.03 mole) of 2-thiophenecarboxaldehyde,
25 4.51 gm (0.03 mole) of 4-methylbenzoic acid hydrazide, ten drops of concentrated hydrochloric acid and 100 ml of absolute ethanol is refluxed 6 hr. Sufficient dioxane is added to the boiling mixture to furnish as solution. The hot solution is filtered. The filtrate is cooled to room temperature, then chilled. The product is collected,
30 washed with Skellysolve B and dried to yield 5.01 gm (69%) of the title compound having a melting point of 219.1°C.

Analysis Calcd: C, 63.93; H, 4.92; N, 11.45.

Found: C, 63.77; H, 5.00; N, 11.59.

Procedure 3 Preparation of cyanoacetic acid (2-thienylmethylene)-hydrazide. Compound 12.

35 A mixture of 2.97 gm (0.03 mole) of cyanoacetylhydrazide, 3.36 gm (0.03 mole) of 2-thiophenecarboxaldehyde and 200 ml of absolute ethanol is refluxed 6 hr. Sufficient dimethylformamide is added to

give a solution. The hot solution is filtered. The filtrate is cooled and then chilled. The product is collected, washed with Skellysolve B and dried to yield 3.23 gm (56%) of the title compound having a melting point of 158.0°C.

5 Analysis Calcd: C, 49.74; H, 3.63.

 Found: C, 50.00; H, 3.70.

Procedure 4 Preparation of 3-nitrobenzoic acid [1-(2-thienyl)-ethylidene]hydrazide. Compound 14.

10 A mixture of 3.62 gm (0.02 mole) of 3-nitrobenzoic acid hydrazide, 2.24 gm (0.02 mole) of 2-acetylthiophene, 1 ml of glacial acetic acid and 100 ml of absolute ethanol is refluxed 10 hr. A sufficient amount of dimethylformamide is added to the boiling mixture to furnish a solution. The solution is filtered. The filtrate is diluted with water to the cloud point and cooled, then
15 chilled. The product is collected, washed with ether and dried to yield 4.3 gm (75%) of the title compound having a melting point of 223.1°C.

 Analysis Calcd: C, 53.98; H, 3.81; N, 14.53.

 Found: C, 54.27; H, 3.96; N, 14.49.

20 Procedure 5 Preparation of ethyl (2-thienylmethylene)carbazate. Compound 18.

 A mixture of 3.36 gm (0.03 mole) of 2-thiophenecarboxaldehyde, 3.12 gm (0.03 mole) of ethyl carbazate and 100 ml of absolute ethanol is refluxed 8 hr. The hot solution is filtered. The filtrate is
25 diluted with water, cooled to room temperature and then chilled. The product is collected, washed with water and dried to yield 4.32 gm (73%) of the title compound having a melting point of 102.0°C.

 Analysis Calcd: C, 48.48; H, 5.05; N, 14.14.

 Found: C, 48.35; H, 5.15; N, 14.09.

30 Procedure 6 Preparation of benzyl [1-(5-methyl-2-furanyl)ethylidene]-carbazate. Compound 36.

 To 9.14 gm (0.055 mole) of benzylcarbazate dissolved in 100 ml warm water is added 6.82 gm (0.055 mole) of 2-acetyl-5-methylfuran in 30 ml of ethanol. The mixture is refluxed 16 hr. The solid which
35 separates is collected. The product is recrystallized from absolute ethanol to yield 9.81 gm (66%) of the title compound having a melting point of 110.3°C.

 Analysis Calcd: C, 66.18; H, 5.88; N, 10.29.

-10-

Found: C, 66.21; H, 5.87; N, 10.44.

Procedure 7 Preparation of 1-menthyl[1-(2-thienyl)ethylidene]-carbazate. Compound 38.

A mixture of 6.31 gm (0.05 mole) of 2-acetylthiophene, 10.72 gm (0.05 mole) of 1-menthylcarbazate, 100 ml of ethanol and 5 drops of concentrated hydrochloric acid is refluxed 20 hr. The hot solution is filtered. The filtrate is cooled to room temperature and then chilled. The product is collected, washed with Skellysolve B and dried to yield 12.11 gm (75%) of the title compound having a melting point of 168.0°C.

Analysis Calcd: C, 63.35; H, 8.08; N, 8.70; S, 9.94.

Found: C, 63.46; H, 8.14; N, 8.83; S, 10.02.

Procedure 8 Preparation of 4-dimethylaminobenzoic acid [1-(2-thienyl)ethylidene]hydrazide. Compound 49.

A mixture of 6.31 gm (0.05 mole) of 2-acetylthiophene, 8.99 gm (0.05 mole) of 4-dimethylaminobenzoic acid hydrazide, 5 drops of glacial acetic acid and 100 ml of ethanol is refluxed 20 hr. The mixture is cooled and then chilled. The product is collected, washed with Skellysolve B and dried to yield 12.28 gm (85%) of the title compound having a melting point of 175.3°C.

Analysis Calcd: C, 62.72; H, 5.92; N, 14.63.

Found: C, 62.30; H, 6.25; N, 15.15.

Procedure 9 Preparation of formic acid [(3-methyl-2-thienyl)-methylene]hydrazide. Compound 57.

A mixture of 6.31 gm (0.05 mole) of 3-methylthiophene-2-carboxaldehyde, 3.00 gm (0.05 mole) of formic acid hydrazide and 100 ml of ethanol is refluxed 10 hr. The reaction mixture is treated with Darco decolorizing carbon and filtered. The filtrate is cooled to room temperature and then chilled. The product is collected to yield 2.34 gm (28%) of the title compound having a melting point of 125.2°C.

Analysis Calcd: C, 50.00; H, 4.76; N, 16.67; S, 16.10.

Found: C, 49.93; H, 4.91; N, 16.10; S, 16.26.

Procedure 10 Preparation of 3-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide. Compound 71.

A mixture of 6.31 gm (0.05 mole) of 3-methylthiophene-2-carboxaldehyde, 8.53 gm (0.05 mole) of 3-chlorobenzhydrazide and 100 ml of ethanol is refluxed 10 hr. The mixture is cooled and chilled. The

-11-

tan product is collected, then crystallized from isopropyl alcohol (decolorized with Darco) to yield 3.99 gm (59%) of the title compound having a melting point of 208.8°C.

Analysis Calcd: C, 56.01; H, 3.95; N, 10.05; Cl, 12.75; S, 11.91.

Found: C, 55.89; H, 4.07; N, 9.91; Cl, 12.95; S, 11.77.

Procedure 11 Preparation of 4-dimethylaminobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide. Compound 77.

A mixture of 6.31 mg (0.05 mole) of 3-methylthiophene-2-carboxaldehyde, 8.99 gm (0.05 mole) of 4-dimethylaminobenzoic acid hydrazide and 100 ml of ethanol is refluxed 6 hr. The solvent is removed. The crude product is suspended in 90 ml of boiling isopropyl alcohol and sufficient dimethylformamide added to give a solution. The solution is treated with Darco decolorizing carbon and filtered. The filtrate is diluted with water to the cloud point and chilled. The product is collected, washed with water and dried to yield 10.5 gm (73%) of the title compound having a melting point of 231.5°C.

Analysis Calcd: C, 62.72; H, 5.92; N, 14.63; S, 11.15.

Found: C, 62.48; H, 5.94; N, 14.50; S, 11.19.

Procedure 12 Preparation of 4-nitrobenzoic acid [(5-methyl-2-thienyl)methylene]hydrazide. Compound 112.

A mixture of 6.31 gm (0.05 mole) of 5-methylthiophene-2-carboxaldehyde, 9.06 gm (0.05 mole) of 4-nitrobenzoic acid hydrazide and 100 ml of ethanol is refluxed 12 hr. The solvent is evaporated. The crude product is suspended in boiling isopropyl alcohol. Sufficient dimethylformamide is added to furnish a solution. The solution is filtered and the filtrate diluted with water to the cloud point and chilled. The product is collected, washed with water and dried to yield 14.45 gm (100%) of the title compound having a melting point of 224.8°C.

Analysis Calcd: C, 53.98; H, 3.81; N, 14.53; S, 11.07.

Found: C, 53.82; H, 3.86; N, 14.31; S, 11.14.

Procedure 13 Preparation of 2-chlorobenzoic acid [1-(5-chloro-2-thienyl)ethylidene]hydrazide. Compound 170.

A mixture of 8.03 gm (0.05 mole) of 2-acetyl-5-chlorothiophene, 8.53 gm (0.05 mole) of 2-chlorobenzhydrazide, 100 ml of ethanol and 5

-12-

drops of concentrated hydrochloric acid is refluxed 20 hr. The mixture is cooled to room temperature and then chilled. The product is collected, washed with water and dried to yield 8.53 gm (55%) of the title compound having a melting point of 229.9°C (decomposition).

Analysis Calcd: C, 49.84; H, 3.19; Cl, 22.68; N, 8.95; S, 10.72

Found: C, 50.06; H, 3.31; Cl, 23.01; N, 8.86; S, 10.42

Procedure 14 Preparation of 2,4,5-trichlorophenoxyacetic acid [1-(2-thienyl)ethylidene]hydrazide. Compound 261.

A mixture of 4.04 gm (0.015 mole) of 2,4,5-trichlorophenoxyacetic acid, 1.89 gm (0.015 mole) of 2-acetylthiophene, 100 ml of dioxane and 1 ml of glacial acetic acid is refluxed 4 hr. Sufficient dimethylformamide is added to furnish a solution. The hot solution is filtered and filtrate diluted with water to the cloud point. The mixture is cooled and then chilled. The product is collected, washed with methanol and dried to yield 4.11 gm (73%) of the title compound having a melting point of 221.4°C.

Analysis Calcd: C, 44.50; H, 2.91; N, 7.42

Found: C, 44.72; H, 3.11; N, 7.51

Procedure 15 Preparation of β -morpholinopropanoic acid (2-thienylmethylene)hydrazide. Compound 263.

A mixture of 3.46 gm (0.02 mole) of β -morpholinopropanoic acid hydrazide, 2.24 gm (0.02 mole) of 2-thiophenecarboxaldehyde and 100 ml of ethanol is refluxed 16 hr. The solvent is evaporated. The residue is dissolved in boiling ethyl acetate. The solution is treated with Darco decolorizing carbon and filtered. The filtrate is diluted with Skellysolve B, cooled, then chilled. The product is collected, washed with cold ether and dried to yield 3.35 (63%) of the title compound having a melting point of 160.7°C.

Analysis Calcd: C, 53.93; H, 6.37; N, 15.73; S, 11.99

Found: C, 53.49; H, 6.75; N, 16.13; S, 11.79

Procedure 16 Preparation of methyl(2-furanylmethylene)carbazate. Compound 265.

A mixture of 2.70 gm (0.03 mole) of methyl carbazate, 2.88 gm (0.03 mole) of 2-furaldehyde and 50 ml of methanol is refluxed 8 hr. The hot solution is filtered. The filtrate is diluted with water, cooled and chilled. The product is collected, washed with water and

-13-

dried to yield 3.07 gm (61%) of the title compound having a melting point of 124.5°C with decomposition.

Analysis Calcd: C, 50.00; H, 4.76; N, 16.67

Found: C, 49.90; H, 4.79; N, 16.51

- 5 Procedure 17 Preparation of 4-methylbenzoic acid [(5-methyl-2-furanyl)-methylene]hydrazide. Compound 317.

To a mixture of 5.50 gm (0.05 mole) of 5-methyl-2-furaldehyde in 100 ml of ethanol is added 7.51 gm (0.05 mole) of 4-methylbenzoic acid hydrazide. The mixture is refluxed 6 hr and chilled. The product is collected, washed with cold ethanol and dried to yield 11.18 gm (92%) of the title compound having a melting point of 187.5°C.

Analysis Calcd: C, 69.41; H, 5.82; N, 11.56

Found: C, 69.11; H, 5.82; N, 11.49

- 15 Procedure 18 Preparation of cyclohexylacetic acid [1-(2-furanyl)-ethylidene]hydrazide. Compound 322.

A mixture of 5.50 gm (0.05 mole) of 2-acetylfuran in 100 ml of ethanol is added 7.81 gm (0.05 mole) of cyclohexylacetic acid hydrazide and 10 drops of glacial acetic acid. The mixture is refluxed 18 hr and diluted with water to the cloud point. The mixture is cooled and then chilled. The product is collected, washed with water, and dried to yield 9.41 gm (76%) of the title compound having a melting point of 132.1°C.

Analysis Calcd: C, 67.72; H, 8.12; N, 11.27

- 25 Found: C, 67.40; H, 8.16; N, 11.05

Procedure 19 Preparation of 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylic acid (2-furanylmethylene)-hydrazide. Compound 195.

A mixture of 28.83 gm (0.3 mole) of 2-furaldehyde, 54.6 gm (0.3 mole) of 2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid hydrazide and 400 ml of absolute ethanol is refluxed 5 hr. The solvent is removed in vacuo to give an oil which crystallizes on standing in a freezer for 16 hours. The product is slurried with Skellysolve B and filtered to yield 23.0 gm (29%) of the title compound having a melting point of 133.0°C.

Analysis Calcd: C, 69.21; H, 7.74; N, 10.76

Found: C, 68.86; H, 7.84; N, 10.76

Procedure 20 Preparation of butyric acid [1-(1H-pyrrol-2-

yl)ethylidene]hydrazide. Compound 196.

A solution of 8.73 gm (0.080 mole) of 2-acetylpyrrole, 8.17 gm (0.08 mole) of n-butyric acid hydrazide, 0.30 gm of p-toluenesulfonic acid and 200 ml of tetrahydrofuran is refluxed for 8 hours. The reaction is chilled. The insoluble material is filtered off and discarded. The filtrate is diluted with water and chilled. The product separates and is collected and dried to yield 9.01 gm (58%) of the title compound having a melting point of 115.0°C.

Analysis Calcd: C, 62.15; H, 7.82; N, 21.74

Found: C, 61.75; H, 7.53; N, 21.52

The compounds prepared according to Procedures 1-20 are tabulated in Table A along with other illustrative compounds of the invention prepared following the general procedure indicated (Procedures 1-20) and making non-critical variations, except starting with the appropriate ketone/aldehyde (II) and acylhydrazide/carbazate (III).

The acylhydrazones of this invention (Formula I) are effective against parasitic worms, particularly those of valuable domestic warm-blooded animals and more particularly helminth parasites in ovines (sheep) and bovines (cattle).

Observations in sheep experimentally infected with Haemonchus contortus in accordance with Procedure 1, generally confirm anthelmintic activity at 100 mg/kg of body weight upon oral and/or parenteral administration as set forth in Table I. Acylhydrazones which are toxic at 100 mg/kg are expected to exhibit anthelmintic activity at a lower non-toxic dose. Further observations in sheep naturally infected with various helminths also confirmed broad-spectrum anthelmintic activity of acylhydrazones of this invention. See Procedure 2 and the results as set forth in Tables IIA-G.

Procedure No. 1

In individual experiments all sheep are treated identically, however non-critical variations occur between experiments. All of the sheep used in this procedure are treated twice with levamisole hydrochloride orally at 8 mg/kg or once each with ivermectin parenterally at 200 µg/kg and levamisole hydrochloride orally at 8 mg/kg. The second treatment in each case is administered 4-7 days after the first treatment. Two weeks after the second treatment all sheep are inoculated per os with ~3,500 to ~7,500 infective larvae of

H. contortus. Rectal fecal samples are taken from each sheep 26-41 days post-inoculation (PI), and these samples are examined for eggs of H. contortus using the McMaster counting chamber technique. All sheep harboring good infections of H. contortus are randomly allocated to a treatment group; those which do not exhibit suitable infections are dropped from the study. One-three days later on days 27-42 PI each sheep remaining in the study (excluding the nontreated controls) is treated with a test compound (orally or parenterally at 100 mg/kg unless indicated otherwise) or a standard (levamisole hydrochloride orally at 8 mg/kg) or is used as an untreated control. All sheep received food and water ad lib. throughout the experiment.

Prior to administration, all solid compounds are finely ground using a mortar and pestle. Oral compounds are suspended in 20-30 ml of sterile vehicle #98 (each ml contains: carboxymethylcellulose - 10 mg, polysorbate 80-4 mg, propylparaben - 0.42 mg) using a sonicator and administered along with a tap water wash via a stomach tube. The parenteral compounds are similarly suspended in 20-30 ml of the sterile vehicle and given by intraperitoneal injection using a 13 gauge, 2 inch needle and a 50 ml syringe. All test compounds are given to a single sheep/route of administration. Two or more sheep are treated with levamisole hydrochloride and five are used as nontreated controls. All animals are monitored for signs of toxicity following treatment.

The sheep are sacrificed 7-12 days after treatment (days 35-49 PI), and the abomasum is ligated and removed from each sheep. Each abomasum is longitudinally sectioned and rinsed into an 80 mesh sieve. Sieve contents are collected in individual containers and fixed in formol-alcohol. Later each sample is transferred to a 1000 or 2000 ml beaker and the volume brought to 400-1000 ml with tap water. The total number of worms in a 40-100 ml aliquot (10%) is determined. When no worms are found in the 10% aliquot, the entire sample is examined. Total worm number/sheep and percentage clearance for each treatment are calculated. Percentage clearance for a particular test compound in a given trial is determined according to the following formula:

Percentage Clearance = $\frac{[(\text{Mean number of worms recovered from nontreated control sheep} - \text{Number of worms recovered from treated sheep}) / \text{Mean number of worms recovered from nontreated control sheep}] \times 100}{100}$

x 100.

Sheep which die within 24 hr following treatment are not examined for worms (Toxic), while any that die between 24 hr post-treatment and necropsy are examined in an identical manner as that described above. The results of various trials are combined and reported in Table I as percentage clearance.

Procedure No. 2

Parasitized sheep are randomly assigned to groups of five animals based on parasitic burden, sex, and farm origin. Sheep are double ear-tagged, weighed, housed in a barn in community pens, fed hay supplemented with 1/2 lb corn/head/day. Water is given ad lib. Animals are allowed to acclimate for one-two weeks prior to treatment.

Each group of sheep receives a test compound either orally or parenterally at a dosage rate of 100 mg/kg. A group of sheep is treated with 8 mg/kg of levamisole hydrochloride and another group serves as an untreated control group. Orally administered compounds are suspended in 20-30 ml of sterile vehicle #98 (each ml contains: carboxymethylcellulose - 10 mg, polysorbate 80-4 mg, propylparaben - 0.42 mg) using a sonicator and administered along with a tap water wash via a stomach tube. For parenteral administration, compounds are similarly suspended in 20-30 ml of the sterile vehicle and given by intraperitoneal injection using a 20 gauge, 1 inch needle and a 50 ml syringe. Following treatment, all animals are observed for signs of toxicity.

The number and classification of helminth eggs per gram of feces (e.p.g.) are determined for each sheep during the acclimation period and in some cases at necropsy. Egg counts are made using the McMaster counting chamber technique and rectal fecal samples. Animals dying during the 24 hours immediately following dosing are not subjected to necropsy. Sheep that die 1-6 days posttreatment are posted and complete worm counts performed. All remaining animals are sacrificed on days 7-8 posttreatment. Each sheep is euthanised and bled out prior to opening the abdominal cavity. Ligatures are placed at the reticulo-omasal junction, the pyloric valve, and the ileocecal junction. The abomasum and small intestine are freed of fat and mesenteric attachments, longitudinally opened, and their contents placed in individual containers. The mucosal surface of each is

washed with tap water, rubbed clean, and rinsed several times. Washings and ingesta for each organ are made up to 1 liter and a 10% aliquot in formalin is stored for later examination. The cecum, large intestine, and colon are freed of mesenteric attachments, each is longitudinally opened, and their contents washed, collected, and made up to 1 liter in 10% formalin. The entire sample is stored. All carcasses are incinerated.

Ten percent of the total contents collected from the abomasum and small intestine and the entire contents of the large intestine, cecum, and colon are examined under stereoscopic magnification (40X). All worms are identified to genus and in some instances species. Separate adult and larval counts are determined.

The mean percentage clearance against specific helminths in the test sheep is calculated by subtracting the mean number of helminths observed in the treated sheep at necropsy from the mean number observed in the nontreated controls at necropsy, dividing the remainder by the latter mean number and multiplying by 100. The mean percentage clearances against the various helminths identified in the test sheep are calculated. The results for acylhydrazones of Formula I are set forth in Tables IIA-G.

From an evaluation of the test results set forth in Tables I and IIA-G, it is clear that the acylhydrazones of this invention (Formula I) are broad-spectrum anthelmintic agents.

DETAILED DESCRIPTION (cont'd)

The acylhydrazones of Formula I can be used as the pure compounds or as mixtures of pure compounds but for practical reasons the compounds are preferably formulated as anthelmintic compositions and administered as a single or multiple dose, alone or in combination with other anthelmintics (e.g. avermectins, benzimidazoles, levamisole, praziquantel, etc.). For example, aqueous or oil suspensions can be administered orally, or the compounds can be formulated with a solid carrier for feeding. Furthermore, an oil suspension can be converted into an aqueous emulsion by mixing with water and injecting the emulsion intramuscularly, subcutaneously or into the peritoneal cavity. In addition, the active compound(s) can be administered topically to the animal in a conventional pour-on formulation.

Pure compounds, mixtures of the active compounds, or

combinations thereof with a solid carrier can be administered in the animal's food, or administered in the form of tablets, pills, boluses, wafers, pastes, and other conventional unit dosage forms, as well as sustained release dosage forms which deliver the active compound over an extended period of days, weeks or months. All of these various forms of the active compounds of this invention can be prepared using physiologically acceptable carriers and known methods of formulation and manufacture.

Representative solid carriers conveniently available and satisfactory for physiologically acceptable, unit dosage formulations include corn starch, powdered lactose, powdered sucrose, talc, stearic acid, magnesium stearate, finely divided bentonite, and the like. The active agent can be mixed with a carrier in varying proportions from, for example, about 0.001 percent by weight in animal feed to about 90 or 95 percent or more in a pill or capsule. In the latter form, one might use no more carrier than sufficient to bind the particles of active compound.

In general, the compounds can be formulated in stable powders or granules for mixing in an amount of feed for a single feeding or enough feed for one day and thus obtain therapeutic efficacy without complication. It is the prepared and stored feeds or feed premixes that require care. A recommended practice is to coat a granular formulation to protect and preserve the active ingredient. A prepared hog-feed containing about 0.2 percent of the active compound will provide a dosage of about 100 mg per kg body weight for each 100 lb pig in its daily ration.

A solid diluent carrier need not be a homogeneous entity, but mixtures of different diluent carriers can include small proportions of adjuvants such as water; alcohols; protein solutions and suspensions like skimmed milk; edible oils; solutions, e.g., syrups; and organic adjuvants such as propylene glycols, sorbitol, glycerol, diethyl carbonate, and the like.

The solid carrier formulations of the inventions are conveniently prepared in unit dosage forms, to facilitate administration to animals. Accordingly, several large boluses (about 20 g weight) amounting to about 54 g of active compound would be required for a single dosage to a 900 lb horse at a dosage rate of 50 mg/kg of body weight. Similarly, a 60 lb lamb at a dosage rate of

100 mg/kg of body weight would require a pill, capsule, or bolus containing about 2.7 g of active compound. A small dog, on the other hand, weighing about 20 lbs. would require a total dosage of about 225 mg at a dosage rate of 25 mg/kg of body weight. The solid, unit dosage forms can be conveniently prepared in various sizes and concentrations of active ingredient, to accomodate treatment of the various sizes of animals that are parasitized by worms.

Liquid formulations can also be used. Representative liquid formulations include aqueous (including isotonic saline) suspensions, oil solutions and suspensions, and oil in water emulsions. Aqueous suspensions are obtained by dispersing the active compound in water, preferably including a suitable surface-active dispersing agent such as cationic, anionic, or non-ionic surface-active agents. Representative suitable ones are polyoxyalkylene derivatives of fatty alcohols and of sorbitan esters, and glycerol and sorbitan esters of fatty acids. Various dispersing or suspending agents can be included and representative ones are synthetic and natural gums, tragacanth, acacia, alginate, dextran, gelatin, sodium carboxymethylcellulose, methylcellulose, sodium polyvinylpyrrolidone, and the like. The proportion of the active compound in the aqueous suspensions of the invention can vary from about 1 percent to about 20 percent or more.

Oil solutions are prepared by mixing the active compound and an oil, e.g. an edible oil such as cottonseed oil, peanut oil, coconut oil, modified soybean oil, and sesame oil. Usually, solubility in oil will be limited and oil suspensions can be prepared by mixing additional finely divided compound in the oil.

Oil in water emulsions are prepared by mixing and dispersing an oil solution or suspension of the active compound in water preferably aided by surface-active agents and dispersing or suspending agents as indicated above.

In general, the formulations of this invention are administered to animals so as to achieve therapeutic or prophylactic levels of the active compound. At present, it is known that a dose of 100 mg/kg of body weight in sheep of a acylhydrazone of this invention will effectively combat a wide variety of parasites. Much lower effective dosages of various compounds are contemplated, e.g., in the range of 1 to 75 mg/kg of body weight.

In other animals, and for other kinds of parasitic worms,

-20-

definitive dosages can be proposed. Contemplated are dosage rates of about 1 mg to about 800 mg/kg of body weight. A preferred, contemplated range of dosage rates is from about 5 mg to about 400 mg/kg of body weight. In this regard, it should be noted that the concentration of active compound in the formulation selected for administration is in many situations not critical. One can administer a larger quantity of a formulation having a relatively low concentration and achieve the same therapeutic or prophylactic dosage as a relatively small quantity of a relatively more concentrated formulation. More frequent small dosages will likewise give results comparable to one large dose. One can also administer a sustained release dosage system (protracted delivery formulation) so as to provide therapeutic and/or prophylactic dosage amounts over an extended period. Unit dosage forms in accordance with this invention can have anywhere from less than 1 mg to 500 g of active compound per unit.

Although the anthelmintic agents of this invention will find their primary use in the treatment and/or prevention of helminth parasitisms in valuable warm-blooded domesticated animals such as sheep, cattle, horses, dogs, swine, goats and poultry, they are also effective in treatment that occurs in other warm blooded animals including man. The optimum amount to be employed for best results will, of course, depend upon the particular compound employed, species of animal to be treated, the regimen treatment and the type and severity of helminth infection. Generally good results are obtained with compounds of Formula I by the oral or parenteral route of administration of about 1 to 300 mg/kg of animal bodyweight (such total dose being given at one time, in a protracted manner or in divided doses over a short period of time such as 1-4 days). The technique for administering these materials to animals are known to those skilled in the veterinary and medical fields.

It is contemplated that the acylhydrazones of Formula I can be used to treat various helminth diseases in humans, including those caused by Ascaris, Enterobius, Ancylostoma, Trichuris, Strongyloides, Fasciola, Taenia, and/or Onchocerca or other filaria at a dose of from 1 mg/kg to 300 mg/kg of body weight upon oral and/or parenteral administration.

DEFINITIONS

The definitions and explanations below are for the terms as used throughout the entire patent application including both the specification and claims.

All temperatures are in degrees Celsius.

5 TLC refers to thin-layer chromatography.

Brine refers to an aqueous saturated sodium chloride solution.

When solvent pairs are used, the ratio of solvents used are volume/volume (v/v).

TABLE A

	<u>C</u>	<u>Y</u>	<u>a</u>	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>X</u>	<u>m.p. (°C)</u>	<u>P</u>	<u>H</u>
5	1	S	2	H	H	H	Ph	203.3	1	-
	2	NCH ₃	2	H	H	H	4-CF ₃ Ph	197.4	5	-
	3	S	2	H	H	H	4-CH ₃ Ph	219.1	2	-
	4	NCH ₃	2	H	H	H	Ph	176.8	2	-
	5	S	2	H	H	H	4-pyridinyl	235.9d	2	-
	6	S	2	H	H	H	3-pyridinyl	300.5d	2	-
10	7	S	2	H	H	H	2-ClPh	177.0	2	-
	8	S	2	H	H	H	4-ClPh	203.8	2	-
	9	NPh	3	2-CH ₃	5-CH ₃	H	CH ₃ CH ₂ CH ₂	140.3	5	-
15	10	NPh	3	2-CH ₃	5-CH ₃	H	4-pyridinyl	140.4	5	+
	11	NPh	3	2-CH ₃	5-CH ₃	H	CH ₃ CH ₂ O	176.2	5	-
	12	S	2	H	H	H	NCCH ₂	158.0	3	-
	13	NCH ₃	2	H	H	H	NCCH ₂	199.2	2	-
	14	S	2	H	H	CH ₃	3-NO ₂ Ph	223.1	4	-
	15	O	2	H	H	H	3-NO ₂ Ph	197.7	4	-
20	16	NCH ₃	2	H	H	H	3-NO ₂ Ph	204.8	4	+
	17	O	2	H	H	H	NCCH ₂	indef.	3	-
	18	S	2	H	H	H	CH ₃ CH ₂ O	111.0	5	-
	19	O	2	H	H	H	CH ₃ CH ₂ O	135.5	5	-
	20	NCH ₃	2	H	H	H	CH ₃ CH ₂ O	94.2	5	-
	21	S	2	H	H	H	PhCH ₂	167.1	5	-
25	22	NCH ₃	2	H	H	H	PhCH ₂	131.4	5	-
	23	S	2	H	H	H	c-C ₃ H ₅	154.6	5	-
	24	S	2	H	H	CH ₃	NCCH ₂	163.4d	5	-
	25	S	2	H	H	H	CH ₃	152.1	5	-
	26	O	2	H	H	H	CH ₃	135.9	5	-
	27	S	2	H	H	H	N-morpholino- CH ₂ (CH ₃)CH	146.7	5	-
30	28	S	2	H	H	H	H	132.0	5	-
	29	NCH ₃	2	H	H	H	H	99.8d	5	-
	30	NH	2	H	H	CH ₃	CH ₃ CH ₂ O	128.7	8	-
35	31	S	2	H	H	H	CH ₃ CH ₂ CH ₂	120.3	5	-
	32	S	2	H	H	CH ₃	CH ₃ CH ₂ CH ₂	128.4	5	-
	33	S	2	H	H	CH ₃	PhCH ₂ O	146.0	5	-
	34	O	2	H	H	CH ₃	PhCH ₂ O	134.2	5	-
	35	O	2	5-CH ₃	H	CH ₃	CH ₃ CH ₂ O	106.0	5	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
	36	O	2	5-CH ₂	H	CH ₃	PhCH ₂ O	110.3	6	-
	37	O	2	5-CH ₃	H	CH ₃	Ph ₂ CHO	175.0	6	-
5	38	S	2	H	H	CH ₃	1-menthylO	168.0	7	-
	39	S	2	H	H	CH ₃	4-CH ₃ OPhCH ₂ O	174.1	7	-
	40	S	2	H	H	CH ₃	Ph	189.0	7	-
	41	S	2	H	H	CH ₃	2-ClPh	129.0	7	-
	42	S	2	H	H	CH ₃	3-ClPh	192.4	7	-
10	43	S	2	H	H	CH ₃	4-ClPh	210.2	7	-
	44	S	2	H	H	CH ₃	2-CH ₃ Ph	191.0	7	-
	45	S	2	H	H	CH ₃	3-CH ₃ Ph	158.1	7	-
	46	S	2	H	H	CH ₃	4-CH ₃ Ph	185.3	7	-
	47	S	2	H	H	CH ₃	4-CF ₃ Ph	221.8	7	-
15	48	S	2	H	H	CH ₃	4-CH ₃ OPh	169.6	7	-
	49	S	2	H	H	CH ₃	4-(CH ₃) ₂ NPh	175.3	8	-
	50	S	2	H	H	CH ₃	4-t-C ₄ H ₉ Ph	162.8	7	-
	51	S	2	H	H	CH ₃	3,4-(CH ₃ O) ₂ PhCH ₂	174.5	7	-
	52	S	2	H	H	CH ₃	PhCH ₂	143.0	7	-
20	53	S	2	H	H	CH ₃	1-naphthylCH ₂	170.5	7	-
	54	S	2	H	H	CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	84.5	7	-
	55	S	2	H	H	CH ₃	2-thienyl	206.1	7	-
	56	S	2	H	H	CH ₃	4-pyridinyl	225.5	8	-
	57	S	2	3-CH ₃	H	H	H	125.2	9	-
25	58	S	2	3-CH ₃	H	H	CH ₃	112.7	9	-
	59	S	2	3-CH ₃	H	H	CH ₃ CH ₂	97.4	5	-
	60	S	2	3-CH ₃	H	H	i-C ₃ H ₇	140.7	5	-
	61	S	2	3-CH ₃	H	H	CH ₃ CH ₂ CH ₂	89.9	5	-
	62	S	2	3-CH ₃	H	H	c-C ₄ H ₇	109.9	5	-
30	63	S	2	3-CH ₃	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	111.6	5	-
	64	S	2	3-CH ₃	H	H	CH ₃ O	117.2d	5	-
	65	S	2	3-CH ₃	H	H	CH ₃ CH ₂ O	85.2	5	-
	66	S	2	3-CH ₃	H	H	t-C ₄ H ₉ O	158.6	5	-
	67	S	2	3-CH ₃	H	H	1-menthylO	137.2	5	-
35	68	S	2	3-CH ₃	H	H	4-CH ₃ OPhCH ₂ O	102.1	5	-
	69	S	2	3-CH ₃	H	H	Ph	162.7	5	-
	70	S	2	3-CH ₃	H	H	2-ClPh	180.7	7	-
	71	S	2	3-CH ₃	H	H	3-ClPh	211.3	10	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	72	S	2	3-CH ₃	H	H	4-ClPh	192.7	10	-
	73	S	2	3-CH ₃	H	H	2-CH ₃ Ph	156.8	10	-
	74	S	2	3-CH ₃	H	H	3-CH ₃ Ph	199.8	10	-
	75	S	2	3-CH ₃	H	H	4-CH ₃ Ph	205.5	10	-
	76	S	2	3-CH ₃	H	H	4-CH ₃ OPh	184.1	9	-
10	77	S	2	3-CH ₃	H	H	4-(CH ₃)NPh	231.5	11	-
	78	S	2	3-CH ₃	H	H	4-t-C ₄ H ₉ Ph	217.2	9	-
	79	S	2	3-CH ₃	H	H	2-PhOPh	146.7	9	-
	80	S	2	3-CH ₃	H	H	2-CH ₃ OPh	156.3	9	-
	81	S	2	3-CH ₃	H	H	PhCH ₂	127.2	9	-
15	82	S	2	3-CH ₃	H	H	3,4-(CH ₃ O) ₂ PhCH ₂	157.2	9	-
	83	S	2	3-CH ₃	H	H	1-naphthylCH ₂	168.6	10	-
	84	S	2	3-CH ₃	H	H	2-thienyl	169.4	5	-
	85	S	2	3-CH ₃	H	H	3-pyridinyl	178.3	5	-
	86	S	2	5-CH ₃	H	H	H	146.9	5	-
20	87	S	2	5-CH ₃	H	H	CH ₃	155.3	5	-
	88	S	2	5-CH ₃	H	H	CH ₃ CH ₂	138.6	5	-
	89	S	2	5-CH ₃	H	H	i-C ₃ H ₇	173.9	5	-
	90	S	2	5-CH ₃	H	H	CH ₃ CH ₂ CH ₂	126.2	5	-
	91	S	2	5-CH ₃	H	H	c-C ₄ H ₇	134.0	5	-
25	92	S	2	5-CH ₃	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	128.8	5	-
	93	S	2	5-CH ₃	H	H	CH ₃ O	147.1	5	-
	94	S	2	5-CH ₃	H	H	CH ₃ CH ₂ O	118.8	5	-
	95	S	2	5-CH ₃	H	H	t-C ₄ H ₉ O	158.9	5	-
	96	S	2	5-CH ₃	H	H	1-menthylO	156.6	5	-
30	97	S	2	5-CH ₃	H	H	4-CH ₃ OPhCH ₂ O	133.5	5	-
	98	S	2	5-CH ₃	H	H	Ph	172.4	5	-
	99	S	2	5-CH ₃	H	H	2-ClPh	211.9	5	-
	100	S	2	5-CH ₃	H	H	3-ClPh	172.4	5	-
	101	S	2	5-CH ₃	H	H	4-ClPh	228.1	5	-
35	102	S	2	5-CH ₃	H	H	2-CH ₃ Ph	179.5	5	-
	103	S	2	5-CH ₃	H	H	3-CH ₃ Ph	170.4	5	-
	104	S	2	5-CH ₃	H	H	4-CH ₃ Ph	232.5	5	-
	105	S	2	5-CH ₃	H	H	2-CH ₃ CH ₂ OPh	158.7	5	-
	106	S	2	5-CH ₃	H	H	4-CH ₃ CH ₂ OPh	201.0	5	-
	107	S	2	5-CH ₃	F	H	2-furanyl	181.5	5	-

-25-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
	108	S	2	5-CH ₃	H	H	3-pyridinyl	219.6	5	-
	109	S	2	5-CH ₃	H	H	2-PhOPh	158.8	5	-
5	110	S	2	5-CH ₃	H	H	chrysanthemyl	117.3d	5	-
	111	S	2	5-CH ₃	H	H	PhCH ₂	161.5	5	-
	112	S	2	5-CH ₃	H	H	4-NO ₂ Ph	224.8	12	-
	113	S	2	5-CH ₃	H	H	2,5-(CH ₃ O) ₂ Ph	154.4	7	-
	114	S	3	H	H	CH ₃	H	141.5	7	-
10	115	S	3	H	H	CH ₃	CH ₃	148.0	7	-
	116	S	3	H	H	CH ₃	CH ₃ CH ₂	129.8	7	-
	117	S	3	H	H	CH ₃	i-C ₃ H ₇	161.2	7	-
	118	S	3	H	H	CH ₃	CH ₃ CH ₂ CH ₂	129.2	7	-
	119	S	3	H	H	CH ₃	CH ₃ O	152.0	7	-
15	120	S	3	H	H	CH ₃	CH ₃ CH ₂ O	139.1	7	-
	121	S	3	H	H	CH ₃	t-C ₄ H ₉ O	167.7	7	-
	122	S	3	H	H	CH ₃	PhO	164.1	7	-
	123	S	3	H	H	CH ₃	1-menthylo	171.2	7	-
	124	S	3	H	H	CH ₃	Ph	173.4	7	-
20	125	S	3	H	H	CH ₃	2-ClPh	125.9	7	-
	126	S	3	H	H	CH ₃	4-ClPh	196.7	7	-
	127	S	3	H	H	CH ₃	2-CH ₃ CH ₂ OPh	143.5	7	-
	128	S	3	H	H	CH ₃	4-CH ₃ CH ₂ OPh	189.4	7	-
	129	S	2	H	H	CH ₂ CH ₃	H	101.5	7	-
25	130	S	2	H	H	CH ₂ CH ₃	CH ₃	106.7d	7	-
	131	S	2	H	H	CH ₂ CH ₃	CH ₃ CH ₂	130.4	7	-
	132	S	2	H	H	CH ₂ CH ₃	i-C ₃ H ₇	171.4	7	-
	133	S	2	H	H	CH ₂ CH ₃	CH ₃ CH ₂ CH ₂	122.9	7	-
	134	S	2	H	H	CH ₂ CH ₃	c-C ₆ H ₁₁	214.4	7	-
30	135	S	2	H	H	CH ₂ CH ₃	c-C ₆ H ₁₁ CH ₂	139.4	7	-
	136	S	2	H	H	CH ₂ CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	113.0	7	-
	137	S	2	H	H	CH ₂ CH ₃	CH ₃ O	154.4	7	-
	138	S	2	H	H	CH ₂ CH ₃	CH ₃ CH ₂ O	144.4	7	-
	139	S	2	H	H	CH ₂ CH ₃	t-C ₄ H ₉ O	171.4	7	-
35	140	S	2	H	H	CH ₂ CH ₃	1-menthylo	151.7	7	-
	141	S	2	H	H	CH ₂ CH ₃	4-CH ₃ OPhCH ₂ O	140.0	7	-
	142	S	2	H	H	CH ₂ CH ₃	2-furanyl	142.1	7	-
	143	S	2	H	H	CH ₂ CH ₃	2-thienyl	186.4	7	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
	144	S	2	H	H	CH ₂ CH ₃	Ph	161.2	7	-
	145	S	2	H	H	CH ₂ CH ₃	2-ClPh	151.9	7	-
5	146	S	2	H	H	CH ₂ CH ₃	4-ClPh	154.6	7	-
	147	S	2	H	H	CH ₂ CH ₃	2-CH ₃ CH ₂ OPh	127.4	7	-
	148	S	2	H	H	CH ₂ CH ₃	4-CH ₃ CH ₂ OPh	135.1	7	-
	149	S	2	H	H	CH ₂ CH ₃	2-NO ₂ Ph	194.4	7	-
	150	S	2	H	H	CH ₂ CH ₃	4-CH ₃ Ph	165.0	7	-
10	151	S	2	H	H	CH ₂ CH ₃	3,4-(CH ₃ O)PhCH ₂	152.3	7	-
	152	S	2	H	H	CH ₂ CH ₃	4-t-C ₄ H ₉ Ph	143.6	7	-
	153	S	2	5-Cl	H	CH ₃	H	171.4d	7	-
	154	S	2	5-Cl	H	CH ₃	CH ₃	183.0	7	-
	155	S	2	5-Cl	H	CH ₃	CH ₃ CH ₂	167.5	7	-
15	156	S	2	5-Cl	H	CH ₃	i-C ₃ H ₇	204.6	7	-
	157	S	2	5-Cl	H	CH ₃	CH ₃ CH ₂ CH ₂	163.0	7	-
	158	S	2	5-Cl	H	CH ₃	c-C ₆ H ₁₁	201.1	7	-
	159	S	2	5-Cl	H	CH ₃	c-C ₆ H ₁₁ CH ₂	164.0	7	-
	160	S	2	5-Cl	H	CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	134.0	7	-
20	161	S	2	5-Cl	H	CH ₃	CH ₃ O	175.2	7	-
	162	S	2	5-Cl	H	CH ₃	CH ₃ CH ₂ O	165.8	7	-
	163	S	2	5-Cl	H	CH ₃	t-C ₄ H ₉ O	188.3	7	-
	164	S	2	5-Cl	H	CH ₃	PhO	166.9	7	-
	165	S	2	5-Cl	H	CH ₃	1-menthylO	196.6	7	-
25	166	S	2	5-Cl	H	CH ₃	2-furanyl	200.7	7	-
	167	S	2	5-Cl	H	CH ₃	2-thienyl	192.4	7	-
	168	S	2	5-Cl	H	CH ₃	3-pyridinyl	203.2	8	-
	169	S	2	5-Cl	H	CH ₃	Ph	213.8	7	-
	170	S	2	5-Cl	H	CH ₃	2-ClPh	229.9d	13	-
30	171	S	2	5-Cl	H	CH ₃	4-ClPh	225.2	13	-
	172	S	2	5-Cl	H	CH ₃	2-CH ₃ CH ₂ OPh	193.3	13	-
	173	S	2	5-Cl	H	CH ₃	4-CH ₃ CH ₂ OPh	206.2	13	-
	174	S	2	5-Cl	H	CH ₃	4-CH ₃ Ph	207.6	13	-
	175	S	2	5-Cl	H	CH ₃	4-t-C ₄ H ₉ Ph	211.8	13	-
35	176	S	2	5-Cl	H	CH ₃	chrysanthemyl	186.4	7	-
	177	NH	2	H	H	CH ₃	3-pyridinyl	219.6	8	-
	178	NH	2	H	H	CH ₃	CH ₃ O	119.0	8	-
	179	NH	2	H	H	CH ₃	4-ClPh	197.5	8	+

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	180	NH	2	H	H	CH ₃	c-C ₆ H ₁₁	135.7	8	-
	181	NH	2	H	H	CH ₃	CH ₃	172.7	8	-
	182	NH	2	H	H	CH ₃	PhCH ₂	169.6	8	-
	183	NH	2	H	H	CH ₃	4-CH ₃ CH ₂ OPh	188.2	8	+
	184	NH	2	H	H	CH ₃	t-C ₄ H ₉ O	161.0	8	-
10	185	NH	2	H	H	CH ₃	2-ClPh	126.0	8	-
	186	NPh	3	2-CH ₃	5-CH ₃	H	CH ₃	200.1	17	-
	187	NPh	3	2-CH ₃	5-CH ₃	H	4-CF ₃ Ph	227.0	17	-
	188	O	2	H	H	H	2-thienyl	168.4	17	-
	189	O	2	H	H	H	3,4,5-(CH ₃ O) ₃ Ph	175.9	17	-
15	190	NPh	3	2-CH ₃	5-CH ₃	H	c-C ₆ H ₁₁	194.9	17	-
	191	NPh	3	2-CH ₃	5-CH ₃	H	CH ₃ CH ₂	184.3	17	-
	192	NH	2	H	H	CH ₃	PhCH ₂ O	172.5	18	-
	193	NH	2	H	H	CH ₃	c-C ₄ H ₇	169.0	18	-
	194	NH	2	H	H	CH ₃	c-C ₆ H ₁₁ CH ₂ CH ₂	109.4	18	-
20	195	O	2	H	H	H	chrysanthemyl	133.0	19	-
	196	NH	2	H	H	CH ₃	CH ₃ CH ₂ CH ₂	115.0	20	-
	197									
	198									
	199									
25	200	S	2	3-CH ₃	H	CH ₃	H	101.6	7	-
	201	S	2	3-CH ₃	H	CH ₃	CH ₃	149.5	7	-
	202	S	2	3-CH ₃	H	CH ₃	CH ₃ CH ₂	108.6	7	-
	203	S	2	3-CH ₃	H	CH ₃	i-C ₃ H ₇	111.4	7	-
	204	S	2	3-CH ₃	H	CH ₃	CH ₃ CH ₂ CH ₂	94.2	7	-
30	205	S	2	3-CH ₃	H	CH ₃	c-C ₃ H ₅	132.8	7	-
	206	S	2	3-CH ₃	H	CH ₃	c-C ₆ H ₁₁	131.2	7	-
	207	S	2	3-CH ₃	H	CH ₃	c-C ₆ H ₁₁ CH ₂	104.7	7	-
	208	S	2	3-CH ₃	H	CH ₃	CH ₃ O	71.5	7	-
	209	S	2	3-CH ₃	H	CH ₃	CH ₃ CH ₂ O	79.9	7	-
35	210	S	2	3-CH ₃	H	CH ₃	t-C ₄ H ₉ O	101.9	7	-
	211	S	2	3-CH ₃	H	CH ₃	Ph	102.8	7	-
	212	S	2	3-CH ₃	H	CH ₃	4-CH ₃ CH ₂ OPh	128.7	7	-
	213	S	2	5-CH ₃	H	CH ₃	H	164.1	7	-
	214	S	2	5-CH ₃	H	CH ₃	CH ₃	157.7	7	-
	215	S	2	5-CH ₃	H	CH ₃	CH ₃ CH ₂	146.4	7	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	216	S	2	5-CH ₃	H	CH ₃	i-C ₃ H ₇	177.5	7	-
	217	S	2	5-CH ₃	H	CH ₃	CH ₃ CH ₂ CH ₂	134.9	7	-
	218	S	2	5-CH ₃	H	CH ₃	c-C ₃ H ₅	181.0	7	-
	219	S	2	5-CH ₃	H	CH ₃	c-C ₆ H ₁₁	190.7	7	-
	220	S	2	5-CH ₃	H	CH ₃	c-C ₆ H ₁₁ CH ₂	167.1	7	-
10	221	S	2	5-CH ₃	H	CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	119.3	7	-
	222	S	2	5-CH ₃	H	CH ₃	PhCH ₂	180.0	7	-
	223	S	2	5-CH ₃	H	CH ₃	CH ₃ O	156.3	7	-
	224	S	2	5-CH ₃	H	CH ₃	CH ₃ CH ₂ O	133.5	7	-
	225	S	2	5-CH ₃	H	CH ₃	t-C ₄ H ₉ O	163.7	7	-
15	226	S	2	5-CH ₃	H	CH ₃	1-menthylO	163.2	7	-
	227	S	2	5-CH ₃	H	CH ₃	PhCH ₂ O	147.0	7	-
	228	S	2	5-CH ₃	H	CH ₃	2-furanyl	183.3	7	-
	229	S	2	5-CH ₃	H	CH ₃	2-thienyl	199.4	7	-
	230	S	2	5-CH ₃	H	CH ₃	4-pyridinyl	210.4	7	-
20	231	S	2	5-CH ₃	H	CH ₃	Ph	179.5	7	-
	232	S	2	5-CH ₃	H	CH ₃	4-CH ₃ Ph	185.9	7	-
	233	S	2	5-CH ₃	H	CH ₃	4-ClPh	215.7	7	-
	234	S	2	5-CH ₃	H	CH ₃	4-CH ₃ CH ₂ OPh	173.2	7	-
	235	S	2	5-CH ₃	H	CH ₃	4-(CH ₃) ₂ NPh	237.2	8	-
25	236	S	2	5-CH ₃	H	CH ₃	2,5-(Cl) ₂ Ph	212.0	7	-
	237	S	2	5-CH ₃	H	CH ₃	2-PhOPh	177.1	7	-
	238	S	3	2-CH ₃	5-CH ₃	CH ₃	H	110.0d	7	-
	239	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃	144.9	7	-
	240	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ CH ₂	134.4	7	-
30	241	S	3	2-CH ₃	5-CH ₃	CH ₃	i-C ₃ H ₇	124.0	7	-
	242	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ CH ₂ CH ₂	92.7d	7	-
	243	S	3	2-CH ₃	5-CH ₃	CH ₃	c-C ₃ H ₅	131.6d	7	-
	244	S	3	2-CH ₃	5-CH ₃	CH ₃	chrysanthemyl	123.2	7	-
	245	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	94.3d	7	-
35	246	S	3	2-CH ₃	5-CH ₃	CH ₃	c-C ₆ H ₁₁	151.5	7	-
	247	S	3	2-CH ₃	5-CH ₃	CH ₃	c-C ₆ H ₁₁ CH ₂	101.2	7	-
	248	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ O	104.3	7	-
	249	S	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ CH ₂ O	90.0	7	-
	250	S	3	2-CH ₃	5-CH ₃	CH ₃	t-C ₄ H ₉ O	118.6	7	-
	251	S	3	2-CH ₃	5-CH ₃	CH ₃	PhCH ₂ O	93.5	7	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	252	S	3	2-CH ₃	5-CH ₃	CH ₃	PhCH ₂	95.9	7	-
	253	S	3	2-CH ₃	5-CH ₃	CH ₃	2-thienyl	138.3	7	-
	254	S	3	2-CH ₃	5-CH ₃	CH ₃	3-pyridinyl	135.6	8	-
	255	S	3	2-CH ₃	5-CH ₃	CH ₃	2-CH ₃ CH ₂ OPh	154.0	7	-
	256	S	3	2-CH ₃	5-CH ₃	CH ₃	3-CH ₃ CH ₂ OPh	125.9	7	-
10	257	S	3	2-CH ₃	5-CH ₃	CH ₃	4-CH ₃ CH ₂ OPh	144.9	7	-
	258	S	3	2-CH ₃	5-CH ₃	CH ₃	2-CH ₃ Ph	141.6	7	-
	259	S	3	2-CH ₃	5-CH ₃	CH ₃	3-CH ₃ Ph	128.1	7	-
	260	S	3	2-CH ₃	5-CH ₃	CH ₃	4-CH ₃ Ph	128.5	7	-
	261									
15	262									
	263	S	2	H	H	H	N-morpholino- CH ₂ CH ₂	160.7	15	-
	264	O	2	H	H	H	N-morpholino- CH ₂ CH ₂	126.0	15	-
	265	O	2	H	H	H	CH ₃ O	124.5d	16	-
	266	S	3	H	H	H	H	123.1	5	-
20	267	S	3	H	H	H	CH ₃	148.9	5	-
	268	S	3	H	H	H	CH ₃ CH ₂	109.2	5	-
	269	S	3	H	H	H	CH ₃ CH ₂ CH ₂	148.5	5	-
	270	S	3	H	H	H	i-C ₃ H ₇	142.4	5	-
	271	S	3	H	H	H	Ph	198.8	5	-
25	272	S	3	H	H	H	c-C ₆ H ₁₁	184.3	5	-
	273	S	3	H	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	110.6	5	-
	274	S	3	H	H	H	c-C ₄ H ₇	137.7	5	-
	275	S	3	H	H	H	4-ClPh	211.5	5	-
	276	S	3	H	H	H	4-CH ₃ OPh	187.0	5	-
30	277	S	3	H	H	H	CH ₃ CH ₂ O	131.9	5	-
	278	S	3	H	H	H	t-C ₄ H ₉ O	164.0	5	-
	279	S	3	H	H	H	PhO	166.3	5	-
	280	S	3	H	H	H	4-(CH ₃) ₂ NPh	261.8	5	-
	281	S	3	H	H	H	3-pyridinyl	222.3	5	-
35	282	S	3	H	H	H	2-thienyl	211.1	5	-
	283	S	2	H	H	CH ₃	H	140.4	7	-
	284	S	2	H	H	CH ₃	CH ₃	162.7	7	-
	285	S	2	H	H	CH ₃	CH ₃ CH ₂	123.5	7	-

TABLE A

	<u>C</u>	<u>Y</u>	<u>a</u>	<u>R</u> ₁	<u>R</u> ₂	<u>R</u> ₃	<u>X</u>	<u>m.p.</u> (°C)	<u>P</u>	<u>H</u>
5	286	S	2	H	H	CH ₃	i-C ₃ H ₇	150.9	7	-
	287	S	2	H	H	CH ₃	c-C ₆ H ₁₁	173.2	7	-
	288	S	2	H	H	CH ₃	c-C ₆ H ₁₁ CH ₂ CH ₂	95.2	7	-
	289	S	2	H	H	CH ₃	c-C ₄ H ₇	143.7	7	-
	290	S	2	H	H	CH ₃	PhO	147.4	7	-
10	291	O	2	5-CH ₃	H	H	H	143.3	5	-
	292	O	2	5-CH ₃	H	H	CH ₃	129.9	5	-
	293	O	2	5-CH ₃	H	H	CH ₃ CH ₂	141.7	5	-
	294	O	2	5-CH ₃	H	H	CH ₃ CH ₂ CH ₂	99.6	5	-
	295	O	2	5-CH ₃	H	H	i-C ₃ H ₇	161.1	5	-
15	296	O	2	5-CH ₃	H	H	c-C ₆ H ₁₁	184.2	5	-
	297	O	2	5-CH ₃	H	H	c-C ₆ H ₁₁ CH ₂	125.9	5	-
	298	O	2	5-CH ₃	H	H	c-C ₃ H ₅	177.0	5	-
	299	O	2	5-CH ₃	H	H	CH ₃ CH ₂ OCH ₂ CH ₂	89.2	5	-
	300	O	2	5-CH ₃	H	H	CH ₃ O	165.5	5	-
20	301	O	2	5-CH ₃	H	H	CH ₃ CH ₂ O	141.0	5	-
	302	O	2	5-CH ₃	H	H	t-C ₄ H ₉ O	149.3	5	-
	303	O	2	5-CH ₃	H	H	PhO	203.1	5	-
	304	O	2	5-CH ₃	H	H	1-menthylO	129.5	5	-
	305	O	2	5-CH ₃	H	H	PhCH ₂ O	108.1	5	-
25	306	O	2	5-CH ₃	H	H	Ph	163.7	5	-
	307	O	2	5-CH ₃	H	H	4-ClPh	196.1	5	-
	308	O	2	5-CH ₃	H	H	3-ClPh	177.8	5	-
	309	O	2	5-CH ₃	H	H	2-ClPh	203.0	5	-
	310	O	2	5-CH ₃	H	H	2,5-(Cl) ₂ Ph	218.9	5	-
30	311	O	2	5-CH ₃	H	H	3,4-(CH ₃ O) ₂ PhCH ₂	167.4	5	-
	312	O	2	5-CH ₃	H	H	4-CH ₃ Ph	187.5	17	-
	313	O	2	5-CH ₃	H	H	3-CH ₃ Ph	168.3	17	-
	314	O	2	5-CH ₃	H	H	2-CH ₃ Ph	205.1	17	-
	315	O	2	5-CH ₃	H	H	4-CH ₃ CH ₂ OPh	214.7	17	-
35	316	O	2	5-CH ₃	H	H	2-CH ₃ CH ₂ OPh	106.0	5	-
	317	O	2	5-CH ₃	H	H	2-furanyl	165.2	17	-
	318	O	2	5-CH ₃	H	H	2-thienyl	171.0	17	-
	319	O	2	5-CH ₃	H	H	4-t-C ₄ H ₉ Ph	243.3	17	-
	320	O	2	5-CH ₃	H	H	2-PhOPh	142.9	8	-
	321	O	2	5-CH ₃	H	H	2-NO ₂ Ph	194.0	17	-

-31-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
	322	0	2	H	H	CH ₃	c-C ₆ H ₁₁ CH ₂	132.1	18	-
	323	0	2	H	H	CH ₃	H	143.6	17	-
5	324	0	2	H	H	CH ₃	CH ₃	150.0	17	-
	325	0	2	H	H	CH ₃	CH ₃ CH ₂	136.4	5	-
	326	0	2	H	H	CH ₃	CH ₃ CH ₂ CH ₂	140.1	5	-
	327	0	2	H	H	CH ₃	i-C ₃ H ₇	140.1	5	-
	328	0	2	H	H	CH ₃	c-C ₆ H ₁₁	171.5	5	-
10	329	0	2	H	H	CH ₃	c-C ₃ H ₅	204.2	17	-
	330	0	2	H	H	CH ₃	CH ₃ CH ₂ OCH ₂ CH ₂	91.7	17	-
	331	0	2	H	H	CH ₃	CH ₃ O	139.7	5	-
	332	0	2	H	H	CH ₃	CH ₃ CH ₂ O	149.8	5	-
	333	0	2	H	H	CH ₃	c-C ₄ H ₉ O	155.5	5	-
15	334	0	2	H	H	CH ₃	1-menthylO	171.8	17	-
	335	0	2	H	H	CH ₃	Ph	147.4	7	-
	336	0	2	H	H	CH ₃	3-ClPh	120.7	7	-
	337	0	2	H	H	CH ₃	2-ClPh	122.1	7	-
	338	0	2	H	H	CH ₃	2,5-(Cl) ₂ Ph	174.7	7	-
20	339	0	2	H	H	CH ₃	3,4-(CH ₃ O) ₂ PhCH ₂	159.4	7	-
	340	0	2	H	H	CH ₃	4-CH ₃ Ph	153.0	18	-
	341	0	2	H	H	CH ₃	3-CH ₃ Ph	176.6	18	-
	342	0	2	H	H	CH ₃	2-CH ₃ Ph	160.2	18	-
	343	0	2	H	H	CH ₃	4-CH ₃ CH ₂ OPh	157.2	18	-
25	344	0	2	H	H	CH ₃	2-CH ₃ CH ₂ OPh	183.3	17	-
	345	0	2	H	H	CH ₃	2-furanyl	172.3	17	-
	346	0	2	H	H	CH ₃	2-thienyl	197.8	17	-
	347	0	2	H	H	CH ₃	4-t-C ₄ H ₉ Ph	179.3	17	-
	348	0	2	H	H	CH ₃	2-PhOPh	175.4d	5	-
30	349	0	2	H	H	CH ₃	2-NO ₂ Ph	183.6	5	-
	350	0	2	H	H	H	CH ₃ CH ₂	120.4	5	-
	351	0	2	H	H	H	CH ₃ CH ₂ CH ₂	116.3	5	-
	352	0	2	H	H	H	i-C ₃ H ₇	159.7	5	-
	353	0	2	H	H	H	c-C ₃ H ₅	175.4	5	-
35	354	0	2	H	H	H	c-C ₆ H ₁₁	187.9	5	-
	355	0	2	H	H	H	c-C ₆ H ₁₁ CH ₂	145.0	5	-
	356	0	2	H	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	106.7	5	-
	357	0	2	H	H	H	CH ₃ CH ₂ OCH ₂ CH ₂	89.8	5	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	358	0	2	H	H	H	PhCH ₂	158.5	5	-
	359	0	2	H	H	H	1-naphthylCH ₂	192.0	5	-
	360	0	2	H	H	H	<i>o</i> -C ₆ H ₅ O	168.5	5	-
	361	0	2	H	H	H	PhO	149.7	5	-
	362	0	2	H	H	H	1-menthylO	156.2	5	-
10	363	0	2	H	H	H	PhCH ₂ O	131.9	5	-
	364	0	2	H	H	H	4-CH ₃ OPhCH ₂ O	163.3	5	-
	365	0	2	H	H	CH ₃	PhO	158-160	5	-
	366	0	2	H	H	CH ₃	4-ClPh	189.0	18	-
	367	0	2	H	H	H	Ph	184.0	5	-
15	368	0	2	H	H	H	2-ClPh	164.8	5	-
	369	0	2	H	H	H	3-ClPh	186.9	17	-
	370	0	2	H	H	H	4-ClPh	216.0	17	-
	371	0	2	H	H	H	2,5-(Cl) ₂ Ph	202.9	17	-
	372	0	2	H	H	H	2-CH ₃ OPh	160.5	17	-
20	373	0	2	H	H	H	2-CH ₃ CH ₂ OPh	138.0	5	-
	374	0	2	H	H	H	4-CH ₃ CH ₂ OPh	229.9	17	-
	375	0	2	H	H	H	2-PhOPh	181.8	17	-
	376	0	2	H	H	H	2,5-(CH ₃ O) ₂ Ph	164.7	17	-
	377	0	2	H	H	H	3,5-(CH ₃ O) ₂ Ph	196.0	17	-
25	378	0	2	H	H	H	4- <i>o</i> -C ₆ H ₅ Ph	229.3	17	-
	379	0	2	H	H	H	4-CF ₃ Ph	233.8	17	-
	380	0	2	H	H	H	4-(CH ₃) ₂ NPh	236.5	17	-
	381	0	2	H	H	H	3,4-(CH ₃ O) ₂ Ph	196.2	17	-
	382	0	2	H	H	H	2-CH ₃ Ph	172.5	5	-
30	383	0	2	H	H	H	3-CH ₃ Ph	151.0	5	-
	384	0	2	H	H	H	4-CH ₃ Ph	206.2	17	-
	385	0	2	H	H	H	2-furanyl	204.3	5	-
	386	0	2	H	H	H	4-CH ₃ OPh	211.9	17	-
	387	0	2	H	H	H	3-CH ₃ OPh	181.5	17	-
35	388	0	2	H	H	H	3-pyridinyl	192.0	17	-
	389	0	2	H	H	H	4-pyridinyl	222.4	5	-
	390	N-CH ₃	2	H	H	H	4-pyridinyl	215.7	5	-
	391	N-CH ₃	2	H	H	H	<i>c</i> -C ₆ H ₁₁	157.1	5	-
	392	N-CH ₃	2	H	H	H	<i>c</i> -C ₆ H ₁₁ CH ₂	149.5	5	-
	393	N-CH ₃	2	H	H	H	CH ₃ O	130.4	5	-

TABLE A

	<u>C</u>	<u>Y</u>	<u>a</u>	<u>R</u> ₁	<u>R</u> ₂	<u>R</u> ₃	<u>X</u>	<u>m.p.</u> (°C)	<u>P</u>	<u>H</u>
	394	NH	2	H	H	CH ₃	Ph	170.0	18	-
	395	NH	2	H	H	H	CH ₃ CH ₂ CH ₂	192.3d	5	-
5	396	NH	2	H	H	H	Ph	197.2d	5	+
	397	NH	2	H	H	H	4-ClPh	238.8d	5	+
	398	NH	2	H	H	H	CH ₃ CH ₂ O	151.2d	5	-
	399	NH	2	H	H	H	4-CH ₃ CH ₂ OPh	207.2d	5	+
	400	NH	2	H	H	H	c-C ₄ H ₇	199.5d	5	-
10	401	NH	2	H	H	H	CH ₃ CH ₂	176.9d	5	-
	402	NH	2	H	H	H	i-C ₃ H ₇	166.0	5	+
	403	NH	2	H	H	H	t-C ₄ H ₉ O	181.5d	5	-
	404	NH	2	H	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	162.9	5	-
	405	NH	2	H	H	H	CH ₃	193.9	5	-
15	406	NH	2	H	H	H	CH ₃ CH ₂ CH ₂	194.9	5	-
	407	NH	2	H	H	H	c-C ₃ H ₅	207.7d	5	+
	408	NH	2	H	H	H	4-CF ₃ Ph	239.6d	5	-
	409	NH	2	H	H	H	3-ClPh	197.3d	5	-
	410	NH	2	H	H	H	2-ClPh	102.7	5	-
20	411	NH	2	H	H	H	1-menthyl	163.5	5	-
	412	NH	2	H	H	H	2-thienyl	255.1d	12	-
	413	NH	2	H	H	H	4-CH ₃ Ph	230.4d	5	-
	414	NH	2	H	H	H	3-CH ₃ Ph	199.2	5	-
	415	NH	2	H	H	H	2-CH ₃ Ph	94.3	5	-
25	416	NH	2	H	H	H	4-t-C ₄ H ₉ Ph	133.0	5	-
	417	NH	2	H	H	H	2-furanyl	253.4d	5	-
	418	NH	2	H	H	H	2-CH ₃ CH ₂ OPh	162.8	5	-
	419	NH	2	H	H	H	PhOPh	156.8	5	-
	420	NH	2	H	H	H	2-CH ₃ OPh	130.9	5	+
30	421	NH	2	H	H	H	1-naphthylCH ₂	213.6	5	-
	422	NH	2	H	H	H	3,4-(CH ₃ O) ₂ PhCH ₂	164.3	5	-
	423	NH	2	H	H	H	4-CH ₃ OPhCH ₂ O	134.7	5	-
	424	NH	2	H	H	H	3-pyridinyl	240.2d	5	-
	425	NH	2	H	H	H	PhCH ₂	228.3d	5	-
35	426	NH	2	H	H	H	PhCH ₂ O	125.4	5	-
	427	NH	2	H	H	H	c-C ₆ H ₁₁	210.2d	-	-
	428	NH	2	H	H	H	c-C ₆ H ₁₁ CH ₂	203.2	5	-
	429	NH	2	H	H	H	4-pyridinyl	220.6d	5	+

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	430	N-CH ₃	2	H	H	H	CH ₃	155.0	5	-
	431	N-CH ₃	2	H	H	H	CH ₃ CH ₂	143.1	5	-
	432	N-CH ₃	2	H	H	H	CH ₃ CH ₂ CH ₂	101.7	5	-
	433	N-CH ₃	2	H	H	H	i-C ₃ H ₇	124.5	5	-
	434	N-CH ₃	2	H	H	H	c-C ₆ H ₁₁ CH ₂ CH ₂	116.6	5	-
10	435	N-CH ₃	2	H	H	H	4-ClPh	202.7	5	-
	436	N-CH ₃	2	H	H	H	3-ClPh	182.2	5	-
	437	N-CH ₃	2	H	H	H	2-ClPh	173.5	5	-
	438	N-CH ₃	2	H	H	H	4-CH ₃ CH ₂ OPh	195.1	5	-
	439	N-CH ₃	2	H	H	H	3-pyridinyl	80.1	5	-
15	440	N-CH ₃	2	H	H	H	4-CH ₃ Ph	207.4	5	-
	441	N-CH ₃	2	H	H	H	4-t-C ₄ H ₉ Ph	220.7	5	-
	442	N-CH ₃	2	H	H	H	t-C ₄ H ₉ O	167.4d	5	+
	443	N-CH ₃	2	H	H	H	4-CH ₃ OPh	214.7	5	-
	444	N-Ph	3	2-CH ₃	5-CH ₃	H	Ph	216.9	5	-
20	445	N-Ph	3	2-CH ₃	5-CH ₃	H	CH ₃ CH ₂ O	175.3	5	-
	446	N-Ph	3	2-CH ₃	5-CH ₃	H	CH ₃ CH ₂ CH ₂	140.6	5	-
	447	S	2	H	H	2-thienyl-CHCH	CH ₃ O	155.5	7	-
	448	S	2	4-CH ₃	H	CH ₃	4-CH ₃ CH ₂ OPh	168.1	7	-
	449	S	2	4-CH ₃	H	CH ₃	4-ClPh	183.6	7	-
25	450	S	2	4-CH ₃	H	CH ₃	Ph	170.6	7	-
	451	S	2	4-CH ₃	H	CH ₃	c-C ₆ H ₁₁ CH ₂	139.2	7	-
	452	S	2	4-CH ₃	H	CH ₃	PhCH ₂ O	150.9	7	-
	453	S	2	4-CH ₃	H	CH ₃	CH ₃ CH ₂ O	132.0	7	-
	454	S	2	4-CH ₃	H	CH ₃	CH ₃ O	156.9	7	-
30	455	S	2	4-CH ₃	H	CH ₃	i-C ₃ H ₇	178.6	7	-
	456	S	2	4-CH ₃	H	CH ₃	CH ₃ CH ₂ CH ₂	127.8	7	-
	457	S	2	4-CH ₃	H	CH ₃	CH ₃ CH ₂	138.7	7	-
	458	S	2	H	H	c-C ₃ H ₅	4-CH ₃ CH ₂ OPh	141.0	7	-
	459	S	2	H	H	4-CH ₃ OPh	PhCH ₂ O	132.0	7	-
35	460	S	2	H	H	4-CH ₃ OPh	CH ₃ CH ₂ O	120.6	7	-
	461	S	2	H	H	4-CH ₃ OPh	CH ₃ O	125.0	7	-
	462	S	2	H	H	Ph	2-CH ₃ OPh	178.3	7	-
	463	S	2	H	H	Ph	2-NO ₂ Ph	194.3	7	-
	464	S	2	H	H	Ph	2-PhOPh	170.2	7	-

-35-

TABLE A

	<u>C</u>	<u>Y</u>	<u>a</u>	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>X</u>	<u>m.p. (°C)</u>	<u>P</u>	<u>H</u>
5	465	S	2	H	H	Ph	2,5-(Cl) ₂ Ph	146.0	7	-
	466	S	2	H	H	Ph	2-furanyl	150.7	7	-
	467	S	2	H	H	Ph	3,4-(CH ₃ O) ₂ Ph	157.6	7	-
	468	S	2	H	H	Ph	4-CF ₃ Ph	143.2	7	-
	469	S	2	H	H	Ph	3-ClPh	140.5	7	-
10	470	S	2	H	H	Ph	2-ClPh	98.2	7	-
	471	S	2	H	H	Ph	4-CH ₃ Ph	140.8	7	-
	472	S	2	H	H	Ph	3-CH ₃ Ph	72.9	7	-
	473	S	2	H	H	Ph	2-CH ₃ Ph	93.2	7	-
	474	S	2	H	H	Ph	4-CH ₃ CH ₂ OPh	118.1	7	-
15	475	S	2	H	H	Ph	2-CH ₃ CH ₂ OPh	173.0	7	-
	476	S	2	H	H	Ph	PhCH ₂ O	107.0	7	-
	477	S	2	H	H	Ph	CH ₃ CH ₂ O	115.2	7	-
	478	S	2	H	H	Ph	CH ₃ O	121.9	7	-
	479	S	2	H	H	Ph	c-C ₆ H ₁₁ CH ₂	100.7	7	-
20	480	S	2	H	H	Ph	c-C ₆ H ₁₁	118.2	7	-
	481	S	2	H	H	Ph	c-C ₃ H ₅	126.0	7	-
	482	S	2	H	H	Ph	CH ₃ CH ₂ CH ₂	71.2	7	-
	483	S	3	2-CH ₃	5-CH ₃	CH ₃	Ph	163.3	7	-
	487	NCH ₃	2	H	H	H	c-C ₄ H ₇	115.2	5	-
25	488	NCH ₃	2	H	H	H	c-C ₃ H ₅	153.7	5	-
	489	NCH ₃	2	H	H	H	3-CH ₃ Ph	186.2	17	-
	490	NCH ₃	2	H	H	H	2-CH ₃ Ph	158.5	17	-
	491	NCH ₃	2	H	H	H	1-naphthylCH ₂	166.3	17	-
	492	NCH ₃	2	H	H	H	3,4-(CH ₃ O) ₂ PhCH ₂	167.4	17	-
30	493	NCH ₃	2	H	H	H	4-CH ₃ OPhCH ₂ O	126.8	5	-
	494	NCH ₃	2	H	H	H	PhCH ₂ O	109.6	5	-
	495	NCH ₃	2	H	H	H	2-thienyl	174.8	17	-
	496	NCH ₃	2	H	H	H	2-furanyl	147.5	17	-
	497	NCH ₃	2	H	H	H	3-CH ₃ OPh	133.0	17	-
35	498	NCH ₃	2	H	H	H	3,5-(CH ₃ O) ₂ Ph	156.3	17	-
	499	NCH ₃	2	H	H	H	1-naphthyl	196.3	17	-
	500	NCH ₃	2	H	H	H	2-CH ₃ CH ₂ OPh	139.2	5	-
	501	NCH ₃	2	H	H	H	2,4-(Cl) ₂ Ph	139.9	17	-
	502	NCH ₃	2	H	H	H	2-pyridinyl	138.5	5	-
	503	NH	2	H	H	H	4-CH ₃ OPh	169.7	5	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
	504	NH	2	H	H	H	H	166.9	5	-
	505	NH	2	H	H	H	3-CH ₃ OPh	103.2	5	-
5	506	NCH ₃	2	H	H	H	PhO	133.6	5	-
	507	NCH ₃	2	H	H	H	1-menthylO	118.1	5	-
	508	NPh	3	2-CH ₃	5-CH ₃	H	CH ₃ O	173.2	5	-
	509	NPh	3	2-CH ₃	5-CH ₃	H	4-ClPh	218.2	17	-
	510	NPh	3	2-CH ₃	5-CH ₃	H	4-CH ₃ CH ₂ OPh	239.6	17	-
10	511	NCH ₃	2	H	H	CH ₃	4-CH ₃ Ph	139.6	13	-
	512	NCH ₃	2	H	H	CH ₃	3-CH ₃ Ph	141.1	13	-
	513	NCH ₃	2	H	H	CH ₃	1-naphthylCH ₂	220.2	13	-
	514	NCH ₃	2	H	H	CH ₃	2-CH ₃ CH ₂ OPh	143.6	13	-
	515	NCH ₃	2	H	H	CH ₃	4-CH ₃ CH ₂ OPh	142.4	13	-
15	516	NCH ₃	2	H	H	CH ₃	CH ₃ CH ₂ O	90.1	13	-
	517	NCH ₃	2	H	H	CH ₃	c-C ₆ H ₁₁	141.7	13	-
	518	NCH ₃	2	H	H	CH ₃	c-C ₃ H ₅	155.0	13	-
	519	NCH ₃	2	H	H	CH ₃	c-C ₄ H ₇	123.6	13	-
	520	NCH ₃	2	H	H	CH ₃	1-menthylO	100.4	13	-
20	521	NCH ₃	2	H	H	CH ₃	2,5-(Cl) ₂ Ph	224.9	13	-
	522	NPh	3	2-CH ₃	5-CH ₃	H	t-C ₄ H ₉ O	173.7	17	-
	523	NPh	3	2-CH ₃	5-CH ₃	H	3-pyridinyl	171.7	17	-
	524	NPh	3	2-CH ₃	5-CH ₃	H	2-ClPh	163.8	17	+
	525	NPh	3	2-CH ₃	5-CH ₃	H	3-ClPh	194.7	17	-
25	526	NPh	3	2-CH ₃	5-CH ₃	H	c-C ₆ H ₁₁ CH ₂ CH ₂	179.8	17	-
	527	NPh	3	2-CH ₃	5-CH ₃	H	c-C ₆ H ₁₁ CH ₂	164.3	17	-
	528	NPh	3	2-CH ₃	5-CH ₃	H	i-C ₃ H ₇	175.5	17	+
	529	NPh	3	2-CH ₃	5-CH ₃	H	4-CH ₃ OPh	217.3	17	-
	530	NPh	3	2-CH ₃	5-CH ₃	H	4-t-C ₄ H ₉ Ph	>300	17	-
30	531	NPh	3	2-CH ₃	5-CH ₃	H	PhCH ₂	171.7	17	-
	532	NPh	3	2-CH ₃	5-CH ₃	H	4-CH ₃ Ph	216.3	17	-
	533	NPh	3	2-CH ₃	5-CH ₃	H	c-C ₄ H ₇	170.6	17	-
	534	NPh	3	2-CH ₃	5-CH ₃	H	3-CH ₃ Ph	243.5	17	-
	535	NPh	3	2-CH ₃	5-CH ₃	H	2-CH ₃ Ph	204.6	17	-
35	536	NPh	3	2-CH ₃	5-CH ₃	H	2-CH ₃ CH ₂ OPh	172.9	17	-
	537	NPh	3	2-CH ₃	5-CH ₃	H	1-menthylO	151.1	5	-
	538	NPh	3	2-CH ₃	5-CH ₃	H	2-PhOPh	200.5	17	-
	539	NPh	3	2-CH ₃	5-CH ₃	H	2-CH ₃ OPh	194.5	17	-

TABLE A

	C	Y	a	R ₁	R ₂	R ₃	X	m.p. (°C)	P	H
5	540	NPh	3	2-CH ₃	5-CH ₃	H	1-naphthylCH ₂	213.1	17	-
	541	NPh	3	2-CH ₃	5-CH ₃	H	3,4-(CH ₃ O) ₂ PhCH ₂	172.7	17	+
	542	NPh	3	2-CH ₃	5-CH ₃	H	4-CH ₃ OPhCH ₂ O	153.0	17	-
	543	NPh	3	2-CH ₃	5-CH ₃	H	3-CH ₃ OPh	217.8	17	-
	544	NPh	3	2-CH ₃	5-CH ₃	H	3,5-(CH ₃ O) ₂ Ph	263.0	17	-
10	545	NPh	3	2-CH ₃	5-CH ₃	H	2,5-(CH ₃ O) ₂ Ph	228.7	17	-
	546	NPh	3	2-CH ₃	5-CH ₃	H	2-thienyl	201.1	17	-
	547	NPh	3	2-CH ₃	5-CH ₃	H	2-furanyl	>300	17	+
	548	NCH ₃	2	H	H	H	2,5-(Cl) ₂ Ph	166.9	17	-
	549	NH	2	H	H	H	CH ₃ O	138.5	5	-
15	550	NH	2	H	H	H	3,5-(CH ₃ O) ₂ Ph	220.6	5	-
	551	NH	2	H	H	H	2,5-(CH ₃ O) ₂ Ph	241.3	17	-
	552	NCH ₃	2	H	H	H	2-PhOPh	111.3	17	+
	553	NCH ₃	2	H	H	H	2,5-(CH ₃ O) ₂ Ph	118.0	5	-
	554	NH	2	H	H	H	2,5-(Cl) ₂ Ph	185.4	5	+
20	555	NH	2	H	H	H	3,4-(CH ₃ O) ₂ Ph	215.9	17	+
	556	NCH ₃	2	H	H	H	3,4,5-(CH ₃ O) ₃ Ph	191.7	17	+
	557	NCH ₃	2	H	H	CH ₃	3,4-(CH ₃ O) ₂ PhCH ₂	137.3	13	-
	558	NCH ₃	2	H	H	H	2-CH ₃ OPh	65.9	5	+
	559	NCH ₃	2	H	H	CH ₃	2-ClPh	173.8	13	-
25	560	NCH ₃	2	H	H	CH ₃	2-CH ₃ Ph	129.3	13	-
	561	NCH ₃	2	H	H	CH ₃	PhCH ₂ O	103.0	13	-
	562	NH	2	H	H	H	4-(CH ₃) ₂ NPh	263.1	17	-
	563	NH	2	H	H	H	3,4,5-(CH ₃ O) ₃ Ph	232.1	17	+
	564	NCH ₃	2	H	H	H	4-(CH ₃) ₂ NPh	225.5	17	-
30	565	NCH ₃	2	H	H	H	3-CH ₃ CH ₂ O, 4-HOPh	268.1	17	-
	566	NH	2	H	H	H	C ₂ H ₅ OCH ₂ CH ₂	107.1	5	-
	567	O	3	2-CH ₃	5-CH ₃	CH ₃	CH ₃ CH ₂ O	96.7	13	-
	568	O	3	2-CH ₃	5-CH ₃	CH ₃	n-C ₃ H ₇	104.3	13	-
	569	O	3	2-CH ₃	5-CH ₃	CH ₃	Ph	155.1	13	-
35	570	O	3	2-CH ₃	5-CH ₃	CH ₃	4-pyridinyl	152.8	18	-
	571	O	3	2-CH ₃	5-CH ₃	CH ₃	c-C ₆ H ₁₁	144.4	13	-
	572	O	3	2-CH ₃	5-CH ₃	CH ₃	c-C ₆ H ₁₁ CH ₂ CH ₂	107.8	13	-
	573	O	3	2-CH ₃	5-CH ₃	CH ₃	PhCH ₂ O	106.5	13	-
	574	O	3	2-CH ₃	5-CH ₃	CH ₃	2-ClPh	160.7	13	-
	575	O	3	2-CH ₃	5-CH ₃	CH ₃	C ₂ H ₅	116.3	13	-

TABLE A

	<u>C</u>	<u>Y</u>	<u>a</u>	<u>R</u> ₁	<u>R</u> ₂	<u>R</u> ₃	<u>X</u>	<u>m.p.</u> (°C)	<u>P</u>	<u>H</u>
	576	O	3	2-CH ₃	5-CH ₃	CH ₃	4-CH ₃ Ph	158.0	13	-
	577	O	3	2-CH ₃	5-CH ₃	CH ₃	4-CH ₃ CH ₂ OPh	138.0	13	-
5	578	O	3	2-CH ₃	5-CH ₃	CH ₃	3,5-(CH ₃ O) ₂ Ph	155.0	13	-
	579	O	3	2-CH ₃	5-CH ₃	CH ₃	4- <i>t</i> -C ₄ H ₉ Ph	110-112	13	-
	580	O	3	2-CH ₃	5-CH ₃	CH ₃	4-CF ₃ Ph	144.0	13	-
	581	O	3	2-CH ₃	5-CH ₃	CH ₃	4-CH ₃ CH ₂ OPh	157.0	5	-
	582	O	3	2-CH ₃	5-CH ₃	CH ₃	2-furanyl	125.0	13	-
10	583	O	3	2-CH ₃	5-CH ₃	CH ₃	2-thienyl	155.0	13	-
	584	O	2	5-C ₂ H ₅	H	H	C ₂ H ₅ O	112.3	13	-
	585	O	2	5-C ₂ H ₅	H	H	Ph	188.7	13	-
	586	O	2	5-C ₂ H ₅	H	H	4-pyridinyl	195.5	17	-
	587	O	2	5-C ₂ H ₅	H	H	<i>c</i> -C ₆ H ₁₁	164.9	13	-
15	588	O	2	H	H	<i>n</i> -C ₅ H ₁₁	Ph	164.3	13	-
	589	O	2	H	H	<i>n</i> -C ₅ H ₁₁	<i>c</i> -C ₆ H ₁₁	180.1	13	-
	590	O	2	5-C ₂ H ₅	H	H	<i>n</i> -C ₃ H ₇	108.2	13	-
	591	O	2	H	H	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₃ H ₇	102.3	13	-
	592	S	2	H	H	Ph	2-thienyl	154.8	13	-
20	593	S	2	H	H	4-CH ₃ OPh	4-C ₂ H ₅ OPh	167.7	13	-
	594	S	2	H	H	<i>c</i> -C ₃ H ₅	CH ₃ O	119.9	13	-
	595	S	2	H	H	CH ₃	2,4,5-(Cl) ₃ PhOCH ₂	221.4	14	-
	596	S	2	H	H	H	2,4,5-(Cl) ₃ PhOCH ₂	242.4	14	-
	597	S	2	H	H	H	4-(CH ₃) ₂ NPh	206.0	17	-
25	598	S	2	H	H	H	4- <i>t</i> -C ₄ H ₉ Ph	228.3	17	-
	599	S	2	H	H	H	PhO	167.2	17	-
	600	S	2	H	H	H	CH ₃ O	154.1	5	-
	601	S	2	H	H	H	2-CH ₃ OPh	173.0	5	-
	602	S	2	H	H	H	4-CH ₃ OPh	213.3	5	-
30	603	S	2	H	H	H	2-CH ₃ CH ₂ OPh	144.8	5	-
	604	S	2	H	H	H	<i>c</i> -C ₆ H ₁₁ CH ₂ CH ₂	131.5	5	-
	605	S	2	H	H	H	<i>c</i> -C ₆ H ₁₁	209.9	5	-
	606	S	2	H	H	H	<i>i</i> -C ₃ H ₇	156.3	5	-

TABLE I
H. Contortus

		% Clearance	
	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	1	100	100
	2	N.T.	N.T.
	3	N.T.	N.T.
	4	0	N.T.
	5	N.T.	N.T.
10	6	100	98.3
	7	72.7	N.T.
	8	0	N.T.
	9	N.T.	N.T.
	10	N.T.	N.T.
15	11	95.9	N.T.
	12	N.T.	N.T.
	13	N.T.	N.T.
	14	N.T.	N.T.
	15	N.T.	N.T.
20	16	N.T.	N.T.
	17	N.T.	N.T.
	18	90.9	N.T.
	19	Toxic	N.T.
	20	N.T.	N.T.
25	21	N.T.	N.T.
	22	98.8	99.9-99.8
	23	27.3	N.T.
	24	N.T.	N.T.
	25	100	Toxic
30	26	N.T.	N.T.
	27	N.T.	N.T.
	28	100	100
	29	N.T.	N.T.
	30	99.2	N.T.
35	31	99.1	N.T.

-40-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	32	100	100
	33	N.T.	37.7
	34	67.5	N.T.
	35	100	81.1-95.7
	36	N.T.	N.T.
10	37	N.T.	N.T.
	38	N.T.	N.T.
	39	2.8	47.8
	40	*	N.T.
	41	59.3	N.T.
15	42	0	N.T.
	43	72.9	N.T.
	44	0	N.T.
	45	97.4	N.T.
	46	72.1	22.7
20	47	12.1	14.0.
	48	97.7	N.T.
	49	92.6	N.T.
	50	0	N.T.
	51	45.5	43.6
25	52	64.5	N.T.
	53	75.2	N.T.
	54	98.1	N.T.
	55	97.1	N.T.
	56	93.7 ^a	N.T.
30	57	94.9 ^b	N.T.
	58	100	N.T.
	59	100	N.T.
	60	99.7	N.T.
	61	99.6	N.T.
35	62	100	N.T.

-41-

TABLE I (cont'd)
H. Contortus

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	63	N.T.	N.T.
	64	99.8	100
	65	*	N.T.
	66	97.0	99.4
	67	0	68.3
10	68	99.5	N.T.
	69	99.2	N.T.
	70	98.7	N.T.
	71	85.7	N.T.
	72	98.9	N.T.
15	73	96.6	6.4
	74	99.4	N.T.
	75	97.9	N.T.
	76	*	N.T.
	77	17.6	N.T.
20	78	19.7	N.T.
	79	N.T.	N.T.
	80	72.9	N.T.
	81	99.4	N.T.
	82	28.9	N.T.
25	83	60.4	N.T.
	84	99.7	N.T.
	85	99.7	N.T.
	86	100	N.T.
	87	99.9	N.T.
30	88	96.4	N.T.
	89	100	N.T.
	90	N.T.	N.T.
	91	92.7 ^b	N.T.
	92	*	N.T.
35	93	N.T.	N.T.
	94	99.7	N.T.

-42-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	95	81.8	N.T.
	96	N.T.	N.T.
	97	98.6	N.T.
	98	74.5	N.T.
	99	0	N.T.
10	100	99.2	N.T.
	101	0	N.T.
	102	N.T.	N.T.
	103	N.T.	N.T.
	104	68.9	N.T.
15	105	N.T.	N.T.
	106	N.T.	N.T.
	107	N.T.	N.T.
	108	99.5	N.T.
	109	15.2	N.T.
20	110	N.T.	N.T.
	111	N.T.	N.T.
	112	N.T.	N.T.
	113	N.T.	N.T.
	114	99.4	N.T.
25	115	99.4	N.T.
	116	96.4	N.T.
	117	N.T.	N.T.
	118	100	N.T.
	119	100	N.T.
30	120	99.5	N.T.
	121	N.T.	N.T.
	122	76.8	N.T.
	123	N.T.	N.T.
	124	100	N.T.
35	125	N.T.	N.T.
	126	99.5	N.T.

-43-

TABLE I (cont'd)

H. Contortus

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	127	N.T.	N.T.
	128	N.T.	N.T.
	129	*	N.T.
	130	98.9	N.T.
	131	85.4	N.T.
10	132	N.T.	N.T.
	133	100	N.T.
	134	N.T.	N.T.
	135	N.T.	N.T.
	136	N.T.	N.T.
15	137	100	N.T.
	138	100	N.T.
	139	N.T.	N.T.
	140	N.T.	N.T.
	141	N.T.	N.T.
20	142	N.T.	N.T.
	143	N.T.	N.T.
	144	99.6	N.T.
	145	N.T.	N.T.
	146	94.9	N.T.
25	147	N.T.	N.T.
	148	100	N.T.
	149	0	N.T.
	150	84.7	N.T.
	151	N.T.	N.T.
30	152	N.T.	N.T.
	153	*	N.T.
	154	96.4	N.T.
	155	0	N.T.
	156	*	N.T.
35	157	N.T.	N.T.
	158	0	N.T.

-44-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	159	N.T.	N.T.
	160	*	N.T.
	161	9.6	N.T.
	162	0	N.T.
	163	0	N.T.
10	164	0	N.T.
	165	N.T.	N.T.
	166	*	N.T.
	167	*	N.T.
	168	63.5	N.T.
15	169	*	N.T.
	170	N.T.	N.T.
	171	67.2	N.T.
	172	N.T.	N.T.
	173	*	N.T.
20	174	N.T.	N.T.
	175	N.T.	N.T.
	176	0	N.T.
	177	N.T.	N.T.
	178	99.4	N.T.
25	179	N.T.	N.T.
	180	N.T.	N.T.
	181	75.1	N.T.
	182	N.T.	N.T.
	183	N.T.	N.T.
30	184	N.T.	N.T.
	185	N.T.	N.T.
	186	99.9	N.T.
	187	N.T.	N.T.
	188	N.T.	N.T.
35	189	N.T.	N.T.
	190	N.T.	N.T.

-45-

TABLE I (cont'd)

H. Contortus

		% Clearance	
	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	191	N.T.	N.T.
	192	99.5	N.T.
	193	N.T.	N.T.
	194	N.T.	N.T.
	195	N.T.	N.T.
10	196	N.T.	N.T.
	197		
	198		
	199		
	200	*	N.T.
15	201	99.4	N.T.
	202	83.2	N.T.
	203	99.7	N.T.
	204	*	N.T.
	205	N.T.	N.T.
20	206	N.T.	N.T.
	207	N.T.	N.T.
	208	98.9	N.T.
	209	93.2	N.T.
	210	*	N.T.
25	211	89.1	N.T.
	212	N.T.	N.T.
	213	0	N.T.
	214	82.5	N.T.
	215	N.T.	N.T.
30	216	N.T.	N.T.
	217	N.T.	N.T.
	218	N.T.	N.T.
	219	N.T.	N.T.
	220	N.T.	N.T.
35	221	N.T.	N.T.
	222	N.T.	N.T.

-46-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	223	0	N.T.
	224	96.4	N.T.
	225	N.T.	N.T.
	226	N.T.	N.T.
	227	0	N.T.
10	228	N.T.	N.T.
	229	N.T.	N.T.
	230	N.T.	N.T.
	231	*	N.T.
	232	N.T.	N.T.
15	233	41.2	N.T.
	234	N.T.	N.T.
	235	N.T.	N.T.
	236	N.T.	N.T.
	237	N.T.	N.T.
20	238	*	N.T.
	239	N.T.	N.T.
	240	100	N.T.
	241	100	N.T.
	242	N.T.	N.T.
25	243	N.T.	N.T.
	244	N.T.	N.T.
	245	N.T.	N.T.
	246	N.T.	N.T.
	247	*	N.T.
30	248	Toxic	N.T.
	249	74.5	N.T.
	250	N.T.	N.T.
	251	Toxic	N.T.
	252	N.T.	N.T.
35	253	N.T.	N.T.
	254	N.T.	N.T.

-47-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	255	N.T.	N.T.
	256	N.T.	N.T.
	257	N.T.	N.T.
	258	N.T.	N.T.
	259	N.T.	N.T.
10	260	N.T.	N.T.
	261		
	262		
	263	N.T.	N.T.
	264	95.9	99.9-100
15	265		
	266	99.8	N.T.
	267	Toxic	99.9
	268	Toxic	100
	269	N.T.	N.T.
20	270	99.7	N.T.
	271	99.6	96.2
	272	99.9	98.7
	273	78.1	N.T.
	274	99.9	N.T.
25	275	30.3	N.T.
	276	96.0	77.4
	277	Toxic	N.T.
	278	*	N.T.
	279	98.9	N.T.
30	280	71.0	4.1
	281	N.T.	N.T.
	282	N.T.	N.T.
	283	100	N.T.
	284	Toxic	Toxic
35	285	99.4	N.T.

-48-

TABLE I (cont'd)
H. Contortus

		% Clearance	
	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	286	*	N.T.
	287	78.1	N.T.
	288	99.8	N.T.
	289	99.9	99.2
	290	99.7	N.T.
10	291	100	N.T.
	292	94.6	N.T.
	293	100	N.T.
	294	99.6	N.T.
	295	N.T.	N.T.
15	296	100	N.T.
	297	N.T.	N.T.
	298	N.T.	N.T.
	299	Toxic	N.T.
	300	97.7	N.T.
20	301	96.4	N.T.
	302	N.T.	N.T.
	303	96.4 ^c	N.T.
	304	N.T.	N.T.
	305	92.8	N.T.
25	306	N.T.	N.T.
	307	79.9	N.T.
	308	N.T.	N.T.
	309	76.7	N.T.
	310	N.T.	N.T.
30	311	94.6	N.T.
	312	100	N.T.
	313	99.5	N.T.
	314	N.T.	N.T.
	315	91.0	N.T.
35	316	N.T.	N.T.
	317	94.6	N.T.

-49-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	318	100	N.T.
	319	64.2	N.T.
	320	96.7	N.T.
	321	44.4	N.T.
	322	N.T.	N.T.
10	323	100	N.T.
	324	98.3	N.T.
	325	99.1	N.T.
	326	N.T.	N.T.
	327	94.6	N.T.
15	328	100	N.T.
	329	100	N.T.
	330	N.T.	N.T.
	331	98.9	N.T.
	332	N.T.	N.T.
20	333	N.T.	N.T.
	334	30.0	N.T.
	335	N.T.	N.T.
	336	N.T.	N.T.
	337	N.T.	N.T.
25	338	N.T.	N.T.
	339	N.T.	N.T.
	340	N.T.	N.T.
	341	N.T.	N.T.
	342	N.T.	N.T.
30	343	100	N.T.
	344	0	N.T.
	345	100	N.T.
	346	99.8	N.T.
	347	31.9	N.T.
35	348	N.T.	N.T.
	349	0	N.T.

-50-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	350	N.T.	N.T.
	351	N.T.	N.T.
	352	N.T.	N.T.
	353	N.T.	N.T.
	354	N.T.	N.T.
10	355	N.T.	N.T.
	356	N.T.	N.T.
	357	N.T.	N.T.
	358	N.T.	N.T.
	359	N.T.	N.T.
15	360	N.T.	N.T.
	361	100	N.T.
	362	N.T.	N.T.
	363	99.9	N.T.
	364	N.T.	N.T.
20	365	100	N.T.
	366	100	N.T.
	367	99.6	N.T.
	368	N.T.	N.T.
	369	N.T.	N.T.
25	370	99.4	N.T.
	371	N.T.	N.T.
	372	N.T.	N.T.
	373	N.T.	N.T.
	374	N.T.	N.T.
30	375	N.T.	N.T.
	376	N.T.	N.T.
	377	N.T.	N.T.
	378	N.T.	N.T.
	379	20.9	N.T.
35	380	N.T.	N.T.
	381	N.T.	N.T.

-51-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	382	N.T.	N.T.
	383	N.T.	N.T.
	384	100	N.T.
	385	N.T.	N.T.
	386	99.9	N.T.
10	387	N.T.	N.T.
	388	N.T.	N.T.
	389	N.T.	N.T.
	390	100	N.T.
	391	99.9	N.T.
15	392	95.8	N.T.
	393	N.T.	N.T.
	394	99.5	N.T.
	395	100	N.T.
	396	N.T.	N.T.
20	397	85.7	N.T.
	398	Toxic	N.T.
	399	53.4	N.T.
	400	100	N.T.
	401	N.T.	N.T.
25	402	100	N.T.
	403	N.T.	N.T.
	404	95.0	N.T.
	405	62.4	N.T.
	406	100	N.T.
30	407	71.8	N.T.
	408	71.3	N.T.
	409	N.T.	N.T.
	410	80.3	N.T.
	411	85.0	N.T.
35	412	22.9	N.T.
	413	83.9	N.T.

-52-

TABLE I (cont'd)

H. Contortus

* Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	414	N.T.	N.T.
	415	0	N.T.
	416	N.T.	N.T.
	417	N.T.	N.T.
	418	74.9	N.T.
10	419	N.T.	N.T.
	420	49.8	N.T.
	421	N.T.	N.T.
	422	89.2	N.T.
	423	97.8	N.T.
15	424	96.4	N.T.
	425	N.T.	N.T.
	426	98.2	N.T.
	427	N.T.	N.T.
	428	N.T.	N.T.
20	429	100	N.T.
	430	100	N.T.
	431	Toxic	N.T.
	432	100	N.T.
	433	Toxic	N.T.
25	434	91.6	N.T.
	435	91.0	N.T.
	436	92.0	N.T.
	437	99.9	N.T.
	438	93.3	N.T.
30	439	99.8	N.T.
	440	98.9	N.T.
	441	83.9	N.T.
	442	N.T.	N.T.
	443	97.9	N.T.
35	444	60.0	N.T.
	445	89.6	N.T.

-53-

TABLE I (cont'd)

H. Contortus

& Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	446	98.7	N.T.
	447	N.T.	N.T.
	448	N.T.	N.T.
	449	N.T.	N.T.
	450	99.6	N.T.
10	451	N.T.	N.T.
	452	0	N.T.
	453	0	N.T.
	454	N.T.	N.T.
	455	N.T.	N.T.
15	456	N.T.	N.T.
	457	100	N.T.
	458	N.T.	N.T.
	459	40.4	N.T.
	460	0	N.T.
20	461	N.T.	N.T.
	462	N.T.	N.T.
	463	N.T.	N.T.
	464	N.T.	N.T.
	465	N.T.	N.T.
25	466	N.T.	N.T.
	467	N.T.	N.T.
	468	N.T.	N.T.
	469	N.T.	N.T.
	470	N.T.	N.T.
30	471	N.T.	N.T.
	472	N.T.	N.T.
	473	N.T.	N.T.
	474	N.T.	N.T.
	475	N.T.	N.T.
35	476	38.5	N.T.
	477	0	N.T.

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	478	N.T.	N.T.
	479	N.T.	N.T.
	480	N.T.	N.T.
	481	N.T.	N.T.
	482	N.T.	N.T.
10	483	99.2	N.T.
	487	99.9	N.T.
	488	N.T.	N.T.
	489	N.T.	N.T.
	490	N.T.	N.T.
15	491	N.T.	N.T.
	492	N.T.	N.T.
	493	N.T.	N.T.
	494	100	N.T.
	495	N.T.	N.T.
20	496	N.T.	N.T.
	497	N.T.	N.T.
	498	N.T.	N.T.
	499	N.T.	N.T.
	500	N.T.	N.T.
25	501	N.T.	N.T.
	502	N.T.	N.T.
	503	N.T.	N.T.
	504	87.8 ^d	N.T.
	505	N.T.	N.T.
30	506	100	N.T.
	507	N.T.	N.T.
	508	N.T.	N.T.
	509	N.T.	N.T.
	510	N.T.	N.T.
35	511	N.T.	N.T.
	512	N.T.	N.T.
	513	N.T.	N.T.
	514	N.T.	N.T.

-55-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	515	N.T.	N.T.
	516	N.T.	N.T.
	517	N.T.	N.T.
	518	N.T.	N.T.
	519	N.T.	N.T.
10	520	N.T.	N.T.
	521	N.T.	N.T.
	522	N.T.	N.T.
	523	N.T.	N.T.
	524	N.T.	N.T.
15	525	N.T.	N.T.
	526	N.T.	N.T.
	527	N.T.	N.T.
	528	N.T.	N.T.
	529	N.T.	N.T.
20	530	N.T.	N.T.
	531	N.T.	N.T.
	532	N.T.	N.T.
	533	N.T.	N.T.
	534	N.T.	N.T.
25	535	N.T.	N.T.
	536	N.T.	N.T.
	537	N.T.	N.T.
	538	N.T.	N.T.
	539	N.T.	N.T.
30	540	N.T.	N.T.
	541	N.T.	N.T.
	542	N.T.	N.T.
	543	N.T.	N.T.
	544	N.T.	N.T.
35	545	N.T.	N.T.
	546	N.T.	N.T.
	547	N.T.	N.T.
	548	N.T.	N.T.

-56-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	549	N.T.	N.T.
	550	N.T.	N.T.
	551	N.T.	N.T.
	552	N.T.	N.T.
	553	N.T.	N.T.
10	554	N.T.	N.T.
	555	N.T.	N.T.
	556	N.T.	N.T.
	557	N.T.	N.T.
	558	N.T.	N.T.
15	559	N.T.	N.T.
	560	N.T.	N.T.
	561	N.T.	N.T.
	562	N.T.	N.T.
	563	N.T.	N.T.
20	564	N.T.	N.T.
	565	N.T.	N.T.
	566	N.T.	N.T.
	567	N.T.	N.T.
	568	99.9	N.T.
25	569	97.9	N.T.
	570	N.T.	N.T.
	571	N.T.	N.T.
	572	N.T.	N.T.
	573	N.T.	N.T.
30	574	N.T.	N.T.
	575	99.5	N.T.
	576	N.T.	N.T.
	577	N.T.	N.T.
	578	N.T.	N.T.
35	579	N.T.	N.T.
	580	N.T.	N.T.
	581	N.T.	N.T.
	582	N.T.	N.T.

-57-

TABLE I (cont'd)

H. Contortus

% Clearance

	<u>Compound No.</u>	<u>P.O.</u>	<u>I.P.</u>
5	583	N.T.	N.T.
	584	N.T.	N.T.
	585	99.7	N.T.
	586	N.T.	N.T.
	587	N.T.	N.T.
10	588	N.T.	N.T.
	589	N.T.	N.T.
	590	100	N.T.
	591	99.2	N.T.
	592	N.T.	N.T.
15	593	N.T.	N.T.
	594	N.T.	N.T.
	595	0	N.T.
	596	N.T.	N.T.
	597	N.T.	N.T.
20	598	N.T.	N.T.
	599	56.2	N.T.
	600	93.7	97.5
	601	N.T.	N.T.
	602	N.T.	N.T.
25	603	N.T.	N.T.
	604	89.1	N.T.
	605	99.2	97.5
	606	N.T.	N.T.

30 N.T. - not tested

— - —, means the compound was tested two or more times and the extreme values reported (for example, 23.7 - 26.6)

I.P. - Intraperitoneal administration

P.O. - oral administration

35 ^a 45 mg/kg dose^b 85 mg/kg dose^c 80 mg/kg dose^d 31 mg/kg dose

-58-

* Tested, Data inconclusive (due to failure of untreated controls)
Toxic - Sheep died within 24 hr following treatment and were not
examined for worms.

TABLE IIA

Percentage Clearance (Adult Worms) of Compound #35 at 100 mg/kg

5			
	<u>Parasite</u>	<u>Percentage Clearance</u>	<u>Route</u>
	<u>Haemonchus</u>	93.6	Oral
10		62.8	IP
	<u>Ostertagia</u>	46.5	Oral
		38.2	IP
15	<u>Trichostrongylus axei</u>	27.2	Oral
		0	IP
	<u>Trichostrongylus colubriformis</u>	33.5	Oral
		0	IP
20	<u>Nematodirus</u>	81.8	Oral
		55.2	IP
	<u>Cooperia</u>	35.4	Oral
25		21.6	IP
	<u>Strongyloides</u>	78.6	Oral
		0	IP
30	<u>Trichuris</u>	0	Oral
		22.8	IP

*Oral Data for Compound 35 is based on 4 lambs.

TABLE IIB

Percentage Clearance (Adult Worms)
of Compound #22 and 264 (100 mg/kg)

	<u>Parasite</u>	<u>Percentage Clearance (Compound 22)</u>	<u>Percentage Clearance (Compound 264)</u>	<u>Route</u>
5				
10	<u>Haemonchus</u>	100 80.0	100 100	Oral IP
15	<u>Ostertagia</u>	0 0	2.5 70.5	Oral IP
	<u>Nematodirus</u>	68.1 68.1	76.3 97.0	Oral IP
20	<u>Cooperia</u>	30.9 0	45.5 50.9	Oral IP
	<u>Moniezia</u>	45.0 65.0	0 60.0	Oral IP
25	<u>Trichuris</u>	66.7 33.3	100 66.7	Oral IP

-61-

TABLE IIC

Percent Clearance (Adult Worms) of Compound #6
at 100 mg/kg (IP)

5		
	<u>Parasite</u>	<u>Percentage Clearance</u>
10	<u>Haemonchus</u>	92.8
	<u>Ostertagia</u>	53.5
15	<u>Trichostrongylus axei</u>	27.0
	<u>Trichostrongylus colubriformis</u>	0
20	<u>Cooperia</u>	0
	<u>Nematodirus</u>	72.2
25	<u>Strongyloides</u>	35.8
	<u>Trichuris</u>	9.6
	<u>Oesphagostomum</u>	0
30		

TABLE IID

Percentage Clearance (Adult Worms) of Compound #19
at 100 mg/kg (Orally)

5		
	<u>Parasite</u>	<u>Percentage Clearance</u>
10	<u>Haemonchus contortus</u>	98.3
	<u>Ostertagia circumcincta</u>	95.0
	<u>T. axei</u>	88.0
15	<u>T. colubriformis</u>	0
	<u>Cooperia curticei</u>	1.0
20	<u>N. folicollis</u>	0
	<u>Strongyloides</u>	0

TABLE IIE

Percentage Clearance (Adult Worms) of Compound #17 at 100 mg/kg (IP)

5	<u>Parasite</u>	<u>Percentage Clearance</u>
	<u>Haemonchus contortus</u>	84.3
10	<u>Ostertagia circumcincta</u>	69.3
	<u>T. axei</u>	75.6
15	<u>T. colubriformis</u>	0
	<u>Cooperia curticei</u>	14.7
	<u>N. folicollis</u>	54.4
20	<u>Strongyloides</u>	9.6
	<u>Trichuris ovis</u>	0
25		

-64-

TABLE IIF

Percentage Clearance (Adult Worms) of Compound #22
at 100 mg/kg (Orally)

5		
	<u>Parasite</u>	<u>Percentage Clearance</u>
10	<u>Haemonchus</u>	95.8
	<u>Ostertagia</u>	86.8
	<u>T. axei</u>	0
15	<u>T. colubriformis</u>	93.5
	<u>Cooperia</u>	0
20	<u>Nematodirus</u>	89.0
	<u>Bunostomum</u>	0
	<u>Strongyloides</u>	9.5
25	<u>Trichuris</u>	0
	<u>Oesophagostomum</u>	64.4
30		

-65-

TABLE IIG

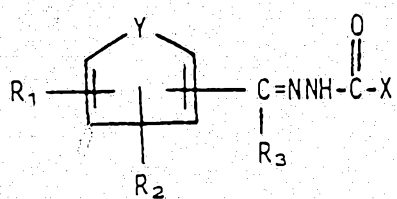
Percentage Clearance (Adult Worms) of Compound #13
at 75 mg/kg (Orally)

5

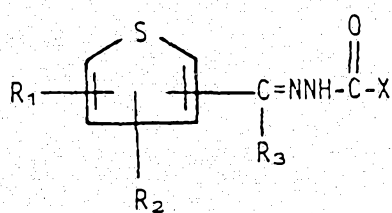
	<u>Parasite</u>	<u>Percentage Clearance</u>
10	<u>Haemonchus contortus</u>	91.7
	<u>Ostertagia circumcincta</u>	0
	<u>Trichostrongylus</u>	62.1
15	<u>Nematodirus</u>	65.4
	<u>Oesophagostomum</u>	0
20	<u>Trichuris</u>	0
	<u>Moniezia</u>	0

25

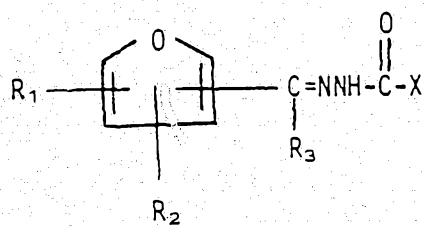
FORMULAE



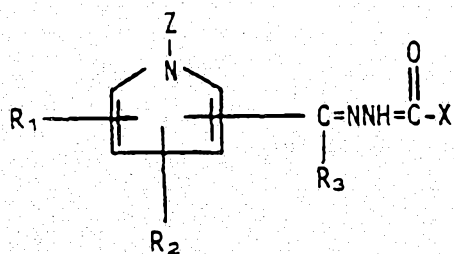
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IA



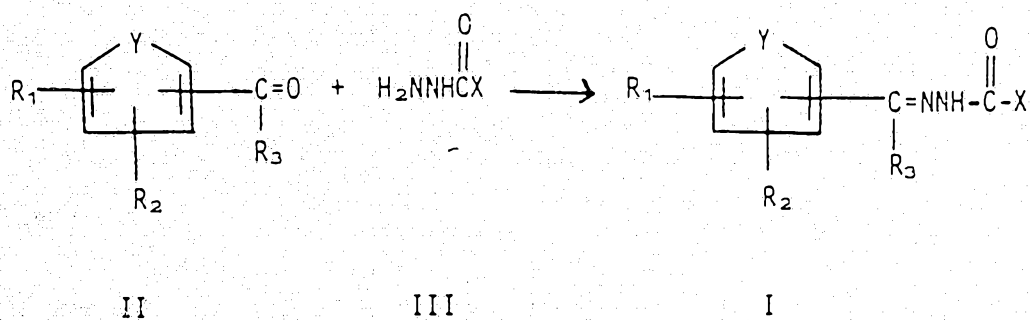
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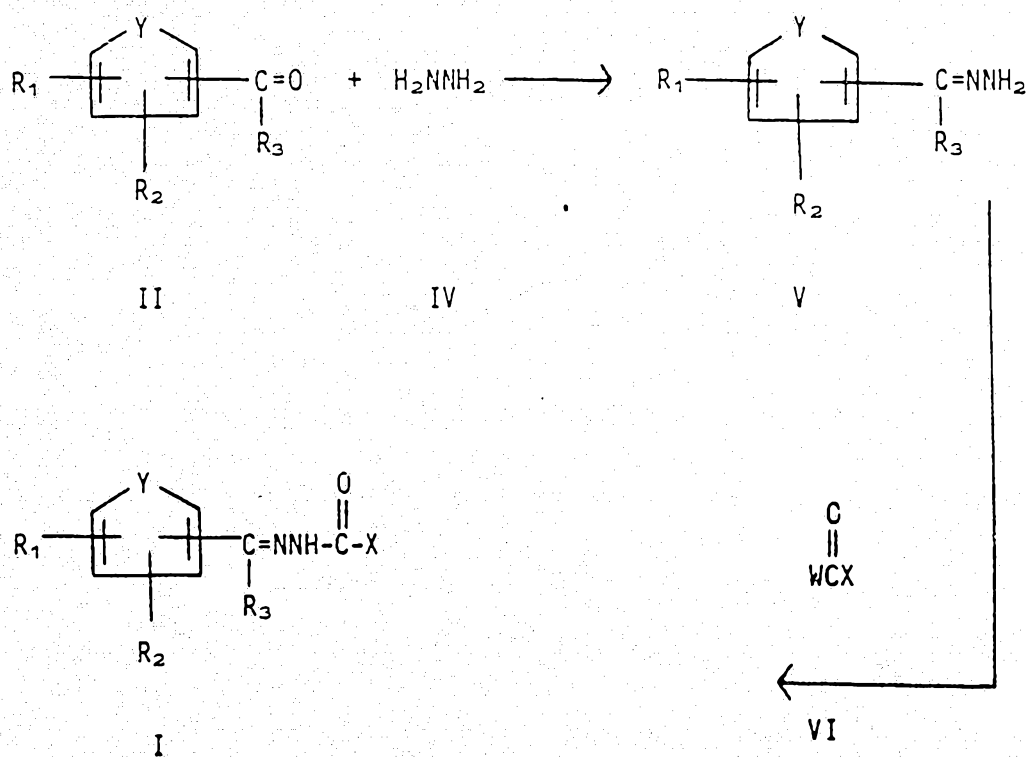
IC

CHART A

Scheme A:



Scheme B:

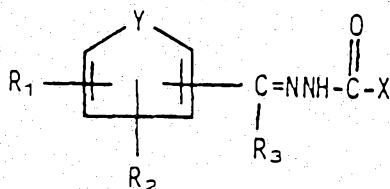


W is a halogen atom or other active group, for example, an anhydride

CLAIMS

1. A method of killing parasitic worms in humans and valuable warm-blooded domestic animals which comprises administering to humans or valuable warm-blooded domestic animals in need, a therapeutic or prophylactic dosage of an acylhydrazone, hydrate thereof or pharmaceutically acceptable salt thereof of the formula:

10



I

- 15 wherein X is (a) hydrogen; with the proviso that when X is hydrogen and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-methyl and R_2 is hydrogen, R_3 is other than methyl; (b) C_1 - C_{10} alkyl; with the proviso that when X is ethyl and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (c) C_2 - C_6 alkenyl, preferably C_2 - C_4 alkenyl; (d) C_2 - C_6 alkynyl; (e) cyclo(C_3 - C_{10})alkyl optionally substituted with one, 2 or 3 C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy, trifluoromethyl, or halo; with the proviso that when X is cyclohexyl or chrysanthemyl and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (f) pyrrolidinyl; (g) piperidinyl; (h) 1-methylpyrrolidinyl; (i) 1-methylpiperidinyl; (j) C_2 - C_6 alkoxyalkyl; (k) cyclo(C_3 - C_{10})alkyl(C_1 - C_4)alkyl; (l) phenyl(C_1 - C_4)alkyl optionally substituted with one, 2 or 3 C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, or trifluoromethyl; (m) cyano(C_1 - C_3)alkyl; (n) naphthyl(C_1 - C_3)alkyl optionally substituted with one or two C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, or trifluoromethyl; (o) C_1 - C_6 alkoxy, with the proviso that when X is methoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-methyl and R_2 is hydrogen, R_3 is other than methyl; with the proviso that when X is ethoxy or t-butoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; with the proviso that when X is ethoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 4-methyl and R_2 is hydrogen, R_3 is other than methyl; with the proviso

that when X is ethoxy and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than phenyl or 4-ethoxyphenyl; (p) diphenylmethoxy; (q) cyclo(C₃-C₆)alkyloxy optionally substituted with one or two C₁-C₃ alkyl; (r) phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; with the proviso that when X is phenoxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is other than methyl; (s) benzyloxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; with the proviso that when X is benzyloxy and the compound is a 2-thienyl acylhydrazone, and R₁ is 4-methyl or 5-methyl and R₂ is hydrogen, R₃ is other than methyl; (t) heteroaromatic optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, or trifluoromethyl; (u) phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; with the proviso that when X is 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than hydrogen; with the proviso that when X is 3-chlorophenyl, 2-methylphenyl or 4-t-butylphenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than methyl; with the further proviso that when X is 2-nitrophenyl or 2-ethoxyphenyl and the compound is a 2-furanyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than methyl; with the further proviso that when X is phenyl and the compound is a 1-methyl-1H-pyrrol-2-yl acylhydrazone, R₁ and R₂ are hydrogen, R₃ is other than hydrogen; with the proviso that when X is 2-chlorophenyl or 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R₂ and R₃ are hydrogen, R₁ is other than 5-methyl; with the further proviso that when X is 2-nitrophenyl and the compound is a 2-thienyl acylhydrazone, and R₁ and R₂ are hydrogen, R₃ is other than ethyl; with the further proviso that when X is 2-methylphenyl and the compound is a 1H-pyrrol-2-yl acylhydrazone, R₁ and R₂ are hydrogen, R₃ is other than hydrogen; (v) phenyl optionally substituted with the divalent C₁-C₂ alkylenedioxy; (w) naphthyl optionally substituted with one or 2 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro; (x) bridged polycyclic

hydrocarbon substituents of six to 10 nuclear carbons, optionally substituted with one, 2 or 3 (C₁-C₃) alkyl groups; (y) perhalo(C₁-C₇)alkyl; (z) N-morpholinyl(C₁-C₄)alkyl; (aa) N-piperidinyl(C₁-C₄)alkyl; (bb) N-pyrrolidinyl(C₁-C₄)alkyl;

5 wherein Y is an oxygen atom; a sulfur atom; or a N-Z group;

wherein Z is hydrogen; C₁-C₄ alkyl; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; or phenyl(C₁-C₄)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl;

wherein R₁ and R₂, being the same or different, are hydrogen; hydroxy; C₁-C₄ alkyl, preferably C₁-C₃ alkyl; C₁-C₃ alkoxy; C₁-C₃ alkylthio; halo or trifluoromethyl; with the proviso that R₁ and R₂ are not both halo; and

wherein R₃ is hydrogen; C₁-C₆ alkyl; cyclo(C₃-C₆)alkyl optionally substituted with one, 2 or 3 C₁-C₃ alkyl, preferably cyclo(C₃-C₅)alkyl optionally substituted; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; phenyl(C₁-C₃)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; 1,3-dioxacyclohexan-5-yl; thienylvinyl; furanylvinyl; or phenylvinyl.

25 2. The method according to Claim 1 wherein the compound, hydrate or pharmaceutically acceptable salt thereof is a thienyl or furanyl acylhydrazone.

30 3. The method according to Claim 1 wherein X is hydrogen; C₁-C₄ alkyl; cyclohexylethyl; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₂ alkoxy, trifluoromethyl and chloro; C₁-C₄ alkoxy; phenoxy optionally substituted with one, 2 or 3 C₁-C₂ alkyl, C₁-C₂ alkoxy, trifluoromethyl and chloro; cyclo(C₃-C₆)alkyl; pyridinyl; thienyl; furanyl; benzyloxy optionally substituted with one or 2 C₁-C₂ alkoxy; di(C₁-C₂)alkoxyphenylmethyl; N-morpholinylethyl; or 1-menthyl.

4. The method according to Claim 1 wherein R₁ and R₂ are selected

from the group consisting of hydrogen, methyl or a bromo atom.

5. The method according to Claim 1 wherein R₃ is hydrogen.

5 6. The method according to Claim 1 wherein the compound, hydrate or pharmaceutically acceptable salt thereof is selected from the group consisting of:

benzoic acid (2-thienylmethylene)hydrazide (Cpd 1);

nicotinic acid (2-thienylmethylene)hydrazide (Cpd 6);

10 ethyl [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-carbazate (Cpd 11);

ethyl (2-thienylmethylene)carbazate (Cpd 18);

benzeneacetic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide (Cpd 22);

15 acetic acid (2-thienylmethylene)hydrazide (Cpd 25);

formic acid (2-thienylmethylene)hydrazide (Cpd 28);

ethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 30);

butyric acid (2-thienylmethylene)hydrazide (Cpd 31);

butyric acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 32);

20 ethyl [1-(5-methyl-2-furanyl)ethylidene]carbazate (Cpd 35);

3-methylbenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 45);

4-methoxybenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 48);

25 4-dimethylaminobenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 49);

3-ethoxypropanoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 54);

30 2-thiophenecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 55);

nicotinic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 56);

formic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 57);

acetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 58)

35 59);

2-methylpropanoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 60);

butyric acid [(3-methyl-2-thienyl)methylene]hydrazide

- (Cpd 61);
cyclobutanecarboxylic acid [(3-methyl-2-thienyl)methylene]-
hydrazide (Cpd 62);
methyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd 64);
5 1,1-dimethylethyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd
66);
4-methoxyphenylmethyl [(3-methyl-2-thienyl)methylene]carbazate
(Cpd 68);
benzoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 69);
10 2-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 70);
3-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 71);
4-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
15 (Cpd 72);
2-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 73);
3-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 74);
20 4-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 75);
benzeneacetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
81);
2-thiophenecarboxylic acid [(3-methyl-2-thienyl)methylene]-
25 hydrazide (Cpd 84);
nicotinic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
85);
formic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 86);
acetic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 87);
30 propanoic acid [(5-methyl-2-thienyl)methylene]hydrazide
(Cpd 88);
2-methylpropanoic acid [(5-methyl-2-thienyl)methylene]hydrazide
(Cpd 89);
cyclobutane carboxylic acid [(5-methyl-2-thienyl)methylene]-
35 hydrazide (Cpd 91);
ethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd 94);
1,1-dimethylethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd
95);

4-methoxyphenylmethyl [(5-methyl-2-thienyl)methylene]carbazate
(Cpd 97);

3-chlorobenzoic acid [(5-methyl-2-thienyl)methylene]hydrazide
(Cpd 100);

5 nicotinic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd
108);

formic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 114);

acetic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 115);

propanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 116);

10 butanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 118);

methyl [1-(3-thienyl)ethylidene]carbazate (Cpd 119);

ethyl [1-(3-thienyl)ethylidene]carbazate (Cpd 120);

benzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 124);

15 4-chlorobenzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd
126);

acetic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 130);

propanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 131);

butanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 133);

methyl [1-(2-thienyl)propylidene]carbazate (Cpd 137);

20 ethyl [1-(2-thienyl)propylidene]carbazate (Cpd 138);

benzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 144);

4-chlorobenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd
146);

25 4-ethoxybenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd
148);

4-methylbenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd
150);

acetic acid [1-(5-chloro-2-thienyl)ethylidene]hydrazide
(Cpd 154);

30 methyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 178);

acetic acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-
hydrazide (Cpd 186);

phenylmethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 192);

35 acetic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
201);

propanoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
202);

2-methylpropanoic acid [1-(3-methyl-2-thienyl)ethylidene]-

- hydrazide (Cpd 203);
methyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 208);
ethyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 209);
benzoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
5 211);
ethyl [1-(5-methyl-2-thienyl)ethylidene]carbazate (Cpd 224);
propanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide
(Cpd 240);
2-methylpropanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]-
10 hydrazide (Cpd 241);
3-(N-morpholinyl)propanoic acid (2-furanylmethylene)hydrazide
(Cpd 264);
formic acid (3-thienylmethylene)hydrazide (Cpd 266);
acetic acid (3-thienylmethylene)hydrazide (Cpd 267);
15 propanoic acid (3-thienylmethylene)hydrazide (Cpd 268);
2-methylpropanoic acid (3-thienylmethylene)hydrazide (Cpd 270);
benzoic acid (3-thienylmethylene)hydrazide (Cpd 271);
cyclohexanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
272);
20 cyclobutanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
274);
4-methoxybenzoic acid (3-thienylmethylene)hydrazide (Cpd 276);
phenyl (3-thienylmethylene)carbazate (Cpd 279);
formic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 283);
25 propanoic acid [1-(2-thienyl)ethylene]hydrazide (Cpd 285);
cyclohexanepropanoic acid [1-(2-thienyl)ethylidene]hydrazide (-
Cpd 288);
cyclobutanecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 289);
30 phenyl [1-(2-thienyl)ethylidene]carbazate (Cpd 290);
formic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 291);
acetic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 292);
propanoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
293);
35 butyric acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 294);
cyclohexanecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 296);
methyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 300);

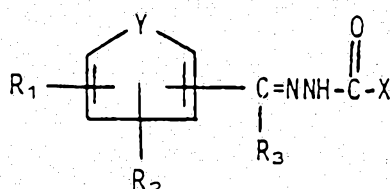
- ethyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 301);
phenyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 303);
benzyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 305);
4-chlorobenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
5 (Cpd 307);
3,4-dimethoxyphenylacetic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 311);
4-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 312);
10 3-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 313);
4-ethoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 315);
2-furoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
15 317);
2-thiophenecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 318);
2-phenoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 320);
20 formic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 323);
acetic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 324);
propanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 325);
2-methylpropanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
327);
25 cyclohexanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 328);
cyclopropanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 329);
ethyl [1-(2-furanyl)ethylidene]carbazate (Cpd 331);
30 4-ethoxybenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
343);
2-furoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 345);
2-thiophenecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 346);
35 phenyl (2-furanylmethylene)carbazate (Cpd 361);
phenylmethyl (2-furanylmethylene)carbazate (Cpd 363);
phenyl [1-(2-furanyl)ethylidene]carbazate (Cpd 365);
4-chlorobenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd

- 366);
- benzoic acid (2-furanylmethylene)hydrazide (Cpd 367);
- 4-chlorobenzoic acid (2-furanylmethylene)hydrazide (Cpd 370);
- 4-methylbenzoic acid (2-furanylmethylene)hydrazide (Cpd 384);
5. 4-methoxybenzoic acid (2-furanylmethylene)hydrazide (Cpd 386);
- isonicotinic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide (Cpd 390);
- cyclohexanecarboxylic acid (1-methyl-1H-pyrrol-2-ylmethylene)-hydrazide (Cpd 391);
- 10 cyclohexanecarboxylic acid (1-methyl-1H-pyrrol-2-ylmethylene)-hydrazide (Cpd 392);
- benzoic acid [1-(1H-pyrrol-2-yl)ethylidene]hydrazide (Cpd 394);
- butyric acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 395);
- 4-chlorobenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd
- 15 397);
- cyclobutanecarboxylic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 400);
- 2-methylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 402);
- 20 3-cyclohexylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 404);
- butanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 406);
- 2-chlorobenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 410);
- 25 1-menthyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 411);
- 4-methylbenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 413);
- 3,4-dimethoxyphenylacetic acid (1H-pyrrol-2-ylmethylene)-hydrazide (Cpd 422);
- 30 4-methoxyphenylmethyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 423);
- nicotinic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 424);
- phenylmethyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 426);
- isonicotinic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 429);
- 35 acetic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 430);
- butyric acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 432);

- cyclohexanepropanoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 434);
- 4-chlorobenzoic acid (1-methyl-1H-pyrrol-2-yl)methylene)hydrazide (Cpd 435);
- 5 3-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 436);
- 2-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 437);
- 4-ethoxybenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
- 10 hydrazide (Cpd 438);
- nicotinic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 439);
- 4-methylbenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 440);
- 15 4-(1,1-dimethylethyl)benzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 441);
- 4-methoxybenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 443);
- 20 butyric acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-hydrazide (Cpd 446);
- benzoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 450);
- propanoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 457);
- 25 benzoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide (Cpd 483);
- cyclobutanecarboxylic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 487);
- phenylmethyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd
- 30 494);
- formic acid [1-(1H-pyrrol-2-yl)methylene] hydrazide (Cpd 504);
- phenyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd 506);
- butanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 568);
- 35 benzoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 569);
- propanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 575);

benzoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 585);
 butanoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 590);
 butanoic acid [1-(2-furanyl)hexylidene]hydrazide (Cpd 591);
 methyl (2-thienylmethylene)carbazate (Cpd 600);
 5 cyclohexanepropanoic acid (2-thienylmethylene)hydrazide (Cpd
 604);
 or
 cyclohexanecarboxylic acid (2-thienylmethylene)hydrazide (Cpd
 605).

10 7. A compound, hydrate thereof or pharmaceutically acceptable salt
 thereof of the formula



15 where X is (e) cyclo(C₃-C₁₀)alkyl optionally substituted with one, 2
 or 3 C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoxy, trifluoromethyl, or
 halo; with the proviso that when X is cyclohexyl and the compound is
 a 2-thienyl acylhydrazone, and R₁ is 5-Cl and R₂ is hydrogen, R₃ is
 20 other than methyl; (j) C₂-C₆ alkoxyalkyl; (k) cyclo(C₃-C₁₀)alkyl(C₁-
 C₄)alkyl; (q) cyclo(C₃-C₆)alkyloxy optionally substituted with one or
 two C₁-C₃ alkyl; (s) benzyloxy optionally substituted with one, 2 or
 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl; with the
 proviso that when X is benzyloxy and the compound is a 2-thienyl
 30 acylhydrazone, and R₁ is 4-methyl or 5-methyl and R₂ is hydrogen, R₃
 is other than methyl; or (u) phenyl substituted with one, 2 or 3 C₁-
 C₃ alkoxy, phenoxy or trifluoromethyl; with the proviso that when X
 is 2-ethoxyphenyl and the compound is a 2-furanyl acylhydrazone, and
 R₁ and R₂ are hydrogen, R₃ is other than methyl;

35 wherein Y is an oxygen atom; a sulfur atom; or a N-Z group;
 wherein Z is hydrogen; C₁-C₄ alkyl; phenyl optionally
 substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo,
 trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or

phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; or phenyl(C₁-C₄)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl;

5 wherein R₁ and R₂, being the same or different, are hydrogen; hydroxy; C₁-C₄ alkyl, preferably C₁-C₃ alkyl; C₁-C₃ alkoxy; C₁-C₃ alkylthio; halo or trifluoromethyl; with the proviso that R₁ and R₂ are not both halo; and

10 wherein R₃ is hydrogen; C₁-C₆ alkyl; cyclo(C₃-C₆)alkyl optionally substituted with one, 2 or 3 C₁-C₃ alkyl, preferably cyclo(C₃-C₅)alkyl optionally substituted; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; phenyl(C₁-C₃)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; 1,3-dioxacyclohexan-5-yl; thienylvinyl; furanylvinyl; or phenylvinyl;

15 or a compound ^{as hereinbefore defined} selected from the group consisting of:

11, 22, 28, 30, 31, 32, 35, 45, 48, 49, 54, 55, 57, 58, 59, 60, 61, 62, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 81, 84, 85, 86, 87, 88, 89, 91, 94, 94, 95, 97, 100, 108, 114, 116, 118, 119, 120, 124, 126, 20 130, 131, 133, 137, 138, 144, 146, 148, 150, 154, 178, 186, 192, 201, 202, 203, 208, 209, 211, 224, 240, 241, 264, 266, 267, 268, 270, 272, 274, 276, 279, 283, 285, 288, 289, 290, 291, 292, 293, 294, 296, 300, 301, 303, 305, 307, 311, 312, 313, 315, 317, 318, 320, 323, 325, 327, 328, 329, 343, 346, 361, 363, 365, 366, 384, 386, 390, 391, 392, 394, 25 395, 400, 402, 404, 406, 411, 413, 422, 423, 426, 429, 430, 432, 434, 435, 436, 437, 438, 439, 440, 441, 443, 445, 446, 450, 457, 483, 487, 494, 506, 568, 569, 575, 585, 590, 591, 600, 604 or 605.

8. A compound, hydrate or pharmaceutically acceptable salt thereof
30 according to Claim 7 wherein X is selected cyclohexylethyl; phenyl optionally substituted with one, 2 or 3 C₁-C₂ alkoxy, or trifluoromethyl.

9. A compound, hydrate or pharmaceutically acceptable salt thereof,
35 according to Claim 7 wherein Y is N-Z and Z is hydrogen.

10. A compound, hydrate or pharmaceutically acceptable salt thereof,
according to Claim 7 wherein R₁ and R₂ are selected from the group



consisting of hydrogen, methyl or a bromo atom.

11. A compound, hydrate or a pharmaceutically acceptable salt thereof, according to Claim 7 wherein R₃ is hydrogen.

5

12. A compound, hydrate or pharmaceutically acceptable salt thereof, according to Claim 7 selected from the group consisting of

ethyl [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-
carbazate (Cpd 11);

10 phenylacetic acid (1-methylpyrrol-2-ylmethylene)hydrazide (Cpd
22);

formic acid (2-thienylmethylene)hydrazide (Cpd 28);

ethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 30);

butyric acid (2-thienylmethylene)hydrazide (Cpd 31);

15 butyric acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 32);

ethyl [1-(5-methyl-2-furanyl)ethylidene]carbazate (Cpd 35);

3-methylbenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd
45);

20 4-methoxybenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd
48);

4-dimethylaminobenzoic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 49);

3-ethoxypropanoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd
54);

25 2-thiophenecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 55);

formic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 57);

acetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 58)

30 propanoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
59);

2-methylpropanoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 60);

butyric acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 61);

35 cyclobutanecarboxylic acid [(3-methyl-2-thienyl)methylene]-
hydrazide (Cpd 62);

methyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd 64);

1,1-dimethylethyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd

- 66);
4-methoxyphenylmethyl [(3-methyl-2-thienyl)methylene]carbazate
(Cpd 68);
benzoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 69);
5 2-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 70);
3-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 71);
4-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
10 (Cpd 72);
2-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 73);
3-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 74);
15 4-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 75);
benzeneacetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
81);
2-thiophenecarboxylic acid [(3-methyl-2-thienyl)methylene]-
20 hydrazide (Cpd 84);
nicotinic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
85);
formic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 86);
acetic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 87);
25 propanoic acid [(5-methyl-2-thienyl)methylene]hydrazide
(Cpd 88);
2-methylpropanoic acid [(5-methyl-2-thienyl)methylene]hydrazide
(Cpd 89);
cyclobutane carboxylic acid [(5-methyl-2-thienyl)methylene]-
30 hydrazide (Cpd 91);
ethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd 94);
1,1-dimethylethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd
95);
4-methoxyphenylmethyl[(5-methyl-2-thienyl)methylene]carbazate
35 (Cpd 97);
4-methoxyphenylmethyl[(5-methyl-2-thienyl)methylene]carbazate (Cpd
97);
3-chlorobenzoic acid [(5-methyl-2-thienyl)methylene]hydrazide

- (Cpd 100);
nicotinic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 108);
formic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 114);
5 propanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 116);
butanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 118);
methyl [1-(3-thienyl)ethylidene]carbazate (Cpd 119);
ethyl [1-(3-thienyl)ethylidene]carbazate (Cpd 120);
benzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 124);
10 4-chlorobenzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 126);
acetic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 130);
propanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 131);
butanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 133);
15 methyl [1-(2-thienyl)propylidene]carbazate (Cpd 137);
ethyl [1-(2-thienyl)propylidene]carbazate (Cpd 138);
benzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 144);
4-chlorobenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 146);
20 4-ethoxybenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 148);
4-methylbenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 150);
acetic acid [1-(5-chloro-2-thienyl)ethylidene]hydrazide
25 (Cpd 154);
methyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 178);
acetic acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-
hydrazide (Cpd 186);
phenylmethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 192);
30 acetic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd 201);
propanoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd 202);
2-methylpropanoic acid [1-(3-methyl-2-thienyl)ethylidene]-
35 hydrazide (Cpd 203);
methyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 208);
ethyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 209);
benzoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd

211);

ethyl [1-(5-methyl-2-thienyl)ethylidene]carbazate (Cpd 224);

propanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide
(Cpd 240);

5 2-methylpropanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]-
hydrazide (Cpd 241);

3-(N-morpholinyl)propanoic acid (2-furanylmethylene)hydrazide
(Cpd 264);

formic acid (3-thienylmethylene)hydrazide (Cpd 266);

10 acetic acid (3-thienylmethylene)hydrazide (Cpd 267);

propanoic acid (3-thienylmethylene)hydrazide (Cpd 268);

2-methylpropanoic acid (3-thienylmethylene)hydrazide (Cpd 270);

cyclohexanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
272);

15 cyclobutanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
274);

4-methoxybenzoic acid (3-thienylmethylene)hydrazide (Cpd 276);

phenyl (3-thienylmethylene)carbazate (Cpd 279);

formic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 283);

20 propanoic acid [1-(2-thienyl)ethylene]hydrazide (Cpd 285);

cyclohexanepropanoic acid [1-(2-thienyl)ethylidene]hydrazide (-
Cpd 288);

cyclobutanecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 289);

25 phenyl [1-(2-thienyl)ethylidene]carbazate (Cpd 290);

formic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 291);

formic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 291);

acetic acid[(5-methyl-2-furanyl)methylene]hydrazide (Cpd 292);

30 propanoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
293);

butyric acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 294);

cyclohexanecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 296);

methyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 300);

35 ethyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 301);

phenyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 303);

benzyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 305);

4-chlorobenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide

(Cpd 307);

3,4-dimethoxyphenylacetic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 311);

4-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide

5 (Cpd 312);

3-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide

(Cpd 313);

4-ethoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide

(Cpd 315);

10 2-furoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
317);

2-thiophenecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 318);

2-phenoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide

15 (Cpd 320);

formic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 323);

propanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 325);

2-methyl-propanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
327);

20 cyclohexanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 328);

cyclopropanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide

(Cpd 329);

4-ethoxybenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd

25 343);

2-thiophenecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide

(Cpd 346);

phenyl (2-furanylmethylene)carbazate (Cpd 361);

phenylmethyl (2-furanylmethylene)carbazate (Cpd 363);

30 phenyl [1-(2-furanyl)ethylidene]carbazate (Cpd 365);

4-chlorobenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
366);

4-methylbenzoic acid (2-furanylmethylene)hydrazide (Cpd 384);

4-methoxybenzoic acid (2-furanylmethylene)hydrazide (Cpd 386);

35 isonicotinic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide
(Cpd 390);

cyclohexanecarboxylic acid (1-methyl-1H-pyrrol-2-ylmethylene)-
hydrazide (Cpd 391);

- cyclohexaneacetic acid (1-methylpyrrol-2-ylmethylene)hydrazide (Cpd 392);
- benzoic acid (1-(1H-pyrrol-2-yl)ethylidene]hydrazide (Cpd 394);
- butyric acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 395);
- 5 cyclobutanecarboxylic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 400);
- 2-methylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 402);
- 3-cyclohexylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 404);
- 10 butanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 406);
- 1-menthyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 411);
- 4-methylbenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 413);
- 15 3,4-dimethoxyphenylacetic acid (1H-pyrrol-2-ylmethylene)-hydrazide (Cpd 422);
- 4-methoxyphenylmethyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 423);
- phenylmethyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 426);
- 20 isonicotinic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 429);
- acetic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 430);
- butyric acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 432);
- 25 cyclohexanepropanoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 434);
- 4-chlorobenzoic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide (Cpd 435);
- 30 3-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 436);
- 2-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 437);
- 4-ethoxybenzoic acid (1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 438);
- 35 nicotinic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 439);
- 4-methylbenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-hydrazide (Cpd 440);

4-(1,1-dimethylethyl)benzoic acid [(1-methyl-1H-pyrrol-2-yl)-methylene]hydrazide (Cpd 441);

4-methoxybenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 443);

5 butyric acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]hydrazide (Cpd 446);

benzoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 450);

10 propanoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 457);

benzoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide (Cpd 483);

cyclobutanecarboxylic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 487);

15 phenylmethyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd 494);

phenyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd 506);

butanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 568);

20 benzoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 569);

propanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide (Cpd 575);

benzoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 585);

25 butanoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 590);

butanoic acid [1-(2-furanyl)hexylidene]hydrazide (Cpd 591);

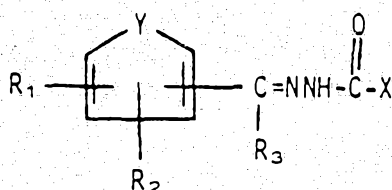
methyl (2-thienylmethylene)carbazate (Cpd 600);

cyclohexanepropanoic acid (2-thienylmethylene)hydrazide (Cpd 604);

30 or

cyclohexanecarboxylic acid (2-thienylmethylene)hydrazide (Cpd 605).

13. An anthelmintic composition for administration to animals
35 comprising a physiologically acceptable carrier and adjuvants, and at least an effective anthelmintic amount of a acylhydrazone, hydrate or pharmaceutically acceptable salt thereof of the formula:



wherein X is (a) hydrogen; with the proviso that when X is hydrogen
 and the compound is a 2-thienyl acylhydrazone, and R_1 is 5-methyl and
 R_2 is hydrogen, R_3 is other than methyl; (b) C_1 - C_{10} alkyl; with the
 proviso that when X is ethyl and the compound is a 2-thienyl
 acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than
 methyl; (c) C_2 - C_6 alkenyl, preferably C_2 - C_4 alkenyl; (d) C_2 - C_6
 alkynyl; (e) cyclo(C_3 - C_{10})alkyl optionally substituted with one, 2 or
 3 C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkoxy, trifluoromethyl, or halo;
 with the proviso that when X is cyclohexyl or chrysanthemyl and the
 compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is
 hydrogen, R_3 is other than methyl; (f) pyrrolidinyl; (g) piperidinyl;
 (h) 1-methylpyrrolidinyl; (i) 1-methylpiperidinyl; (j) C_2 - C_6
 alkoxyalkyl; (k) cyclo(C_3 - C_{10})alkyl(C_1 - C_4)alkyl; (l) phenyl(C_1 -
 C_4)alkyl optionally substituted with one, 2 or 3 C_1 - C_4 alkyl, C_1 - C_4
 alkoxy, halo, or trifluoromethyl; (m) cyano(C_1 - C_3)alkyl; (n)
 naphthyl(C_1 - C_3)alkyl optionally substituted with one or two C_1 - C_4
 alkyl, C_1 - C_4 alkoxy, halo, or trifluoromethyl; (o) C_1 - C_6 alkoxy, with
 the proviso that when X is methoxy and the compound is a 2-thienyl
 acylhydrazone, and R_1 is 5-methyl and R_2 is hydrogen, R_3 is other
 than methyl; with the proviso that when X is ethoxy or t-butoxy and
 the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is
 hydrogen, R_3 is other than methyl; with the proviso that when X is
 ethoxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 4-
 methyl and R_2 is hydrogen, R_3 is other than methyl; with the proviso
 that when X is ethoxy and the compound is a 2-thienyl acylhydrazone,
 and R_1 and R_2 are hydrogen, R_3 is other than phenyl or 4-
 ethoxyphenyl; (p) diphenylmethoxy; (q) cyclo(C_3 - C_6)alkyloxy
 optionally substituted with one or two C_1 - C_3 alkyl; (r) phenoxy
 optionally substituted with one, 2 or 3 C_1 - C_4 alkyl, C_1 - C_4 alkoxy,
 halo, or trifluoromethyl; with the proviso that when X is phenoxy and

the compound is a 2-thienyl acylhydrazone, and R_1 is 5-Cl and R_2 is hydrogen, R_3 is other than methyl; (s) benzyloxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, or trifluoromethyl; with the proviso that when X is benzyloxy and the compound is a 2-thienyl acylhydrazone, and R_1 is 4-methyl or 5-methyl and R_2 is hydrogen, R_3 is other than methyl; (t) heteroaromatic optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, or trifluoromethyl; (u) phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, or trifluoromethyl; with the proviso that when X is 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than hydrogen; with the proviso that when X is 3-chlorophenyl, 2-methylphenyl or 4-t-butylphenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than methyl; with the further proviso that when X is 2-nitrophenyl or 2-ethoxyphenyl and the compound is a 2-furanyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than methyl; with the further proviso that when X is phenyl and the compound is a N-methylpyrrol-2-yl acylhydrazone, R_1 and R_2 are hydrogen, R_3 is other than hydrogen; with the proviso that when X is 2-chlorophenyl or 4-chlorophenyl and the compound is a 2-thienyl acylhydrazone, and R_2 and R_3 are hydrogen, R_1 is other than methyl; with the further proviso that when X is 2-nitrophenyl and the compound is a 2-thienyl acylhydrazone, and R_1 and R_2 are hydrogen, R_3 is other than ethyl; with the further proviso that when X is 2-methylphenyl and the compound is a pyrrol-2-yl acylhydrazone, R_1 and R_2 are hydrogen, R_3 is other than hydrogen; (v) phenyl optionally substituted with the divalent C_1-C_2 alkylenedioxy; (w) naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluoromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio, nitro; (x) bridged polycyclic hydrocarbon substituents of six to 10 nuclear carbons, optionally substituted with one, 2 or 3 (C_1-C_3) alkyl groups; (y) perhalo(C_1-C_7)alkyl; (z) N-morpholinyl(C_1-C_4)alkyl; (aa) N-piperidinyl(C_1-C_4)alkyl; (bb) N-pyrrolidinyl(C_1-C_4)alkyl;

wherein Y is an oxygen atom; a sulfur atom; or a N-Z group;

wherein Z is hydrogen; C_1-C_4 alkyl; phenyl optionally

substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, trifluoromethyl, C₂-C₆ dialkylamino, C₁-C₃ alkylthio, nitro, or phenoxy optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, or trifluoromethyl; or phenyl(C₁-C₄)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, or trifluoromethyl;

wherein R₁ and R₂, being the same or different, are hydrogen; hydroxy; C₁-C₄ alkyl, preferably C₁-C₃ alkyl; C₁-C₃ alkoxy; C₁-C₃ alkylthio; halo or trifluoromethyl; with the proviso that R₁ and R₂ are not both halo; and

wherein R₃ is hydrogen; C₁-C₆ alkyl; cyclo(C₃-C₆)alkyl optionally substituted with one, 2 or 3 C₁-C₃ alkyl, preferably cyclo(C₃-C₅)alkyl optionally substituted; phenyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; phenyl(C₁-C₃)alkyl optionally substituted with one, 2 or 3 C₁-C₄ alkyl, halo, trifluoromethyl, or C₁-C₃ alkoxy; 1,3-dioxacyclohexan-5-yl; thienylvinyl; furanylvinyl; or phenylvinyl.

14. The composition of Claim 13 in which the compound, hydrate or pharmaceutically acceptable salt thereof is selected from the group consisting of

benzoic acid (2-thienylmethylene)hydrazide (Cpd 1);
nicotinic acid (2-thienylmethylene)hydrazide (Cpd 6);
ethyl [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-

carbazate (Cpd 11);
ethyl (2-thienylmethylene)carbazate (Cpd 18);
benzeneacetic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide (Cpd 22);

acetic acid (2-thienylmethylene)hydrazide (Cpd 25);
formic acid (2-thienylmethylene)hydrazide (Cpd 28);
ethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 30);
butyric acid (2-thienylmethylene)hydrazide (Cpd 31);
butyric acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 32);
ethyl [1-(5-methyl-2-furanyl)ethylidene]carbazate (Cpd 35);

3-methylbenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 45);

4-methoxybenzoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 48);

- 4-dimethylaminobenzoic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 49);
- 3-ethoxypropanoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd
54);
- 5 2-thiophenecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 55);
- nicotinic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 56);
- formic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 57);
- acetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 58)
- 10 propanoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
59);
- 2-methylpropanoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 60);
- butyric acid [(3-methyl-2-thienyl)methylene]hydrazide
- 15 (Cpd 61);
- cyclobutanecarboxylic acid [(3-methyl-2-thienyl)methylene]-
hydrazide (Cpd 62);
- methyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd 64);
- 1,1-dimethylethyl [(3-methyl-2-thienyl)methylene]carbazate (Cpd
20 66);
- 4-methoxyphenylmethyl [(3-methyl-2-thienyl)methylene]carbazate
(Cpd 68);
- benzoic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 69);
- 2-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
- 25 (Cpd 70);
- 3-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 71);
- 4-chlorobenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 72);
- 30 2-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 73);
- 3-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
(Cpd 74);
- 4-methylbenzoic acid [(3-methyl-2-thienyl)methylene]hydrazide
- 35 (Cpd 75);
- benzeneacetic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd
81);
- 2-thiophenecarboxylic acid [(3-methyl-2-thienyl)methylene]-

hydrazide (Cpd 84);

nicotinic acid [(3-methyl-2-thienyl)methylene]hydrazide (Cpd 85);

formic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 86);

acetic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 87);

propanoic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 88);

2-methylpropanoic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 89);

cyclobutane carboxylic acid [(5-methyl-2-thienyl)methylene]-hydrazide (Cpd 91);

ethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd 94);

1,1-dimethylethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd 95);

4-methoxyphenylmethyl [(5-methyl-2-thienyl)methylene]carbazate (Cpd 97);

3-chlorobenzoic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 100);

nicotinic acid [(5-methyl-2-thienyl)methylene]hydrazide (Cpd 108);

formic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 114);

acetic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 115);

propanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 116);

butanoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 118);

methyl [1-(3-thienyl)ethylidene]carbazate (Cpd 119);

ethyl [1-(3-thienyl)ethylidene]carbazate (Cpd 120);

benzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 124);

4-chlorobenzoic acid [1-(3-thienyl)ethylidene]hydrazide (Cpd 126);

acetic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 130);

propanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 131);

butanoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 133);

methyl [1-(2-thienyl)propylidene]carbazate (Cpd 137);

ethyl [1-(2-thienyl)propylidene]carbazate (Cpd 138);

benzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 144);

4-chlorobenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd 146);

4-ethoxybenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd

- 148);
4-methylbenzoic acid [1-(2-thienyl)propylidene]hydrazide (Cpd
150);
acetic acid [1-(5-chloro-2-thienyl)ethylidene]hydrazide
5 (Cpd 154);
methyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 178);
acetic acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-
hydrazide (Cpd 186);
phenylmethyl [1-(1H-pyrrol-2-yl)ethylidene]carbazate (Cpd 192);
10 acetic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
201);
propanoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
202);
2-methylpropanoic acid [1-(3-methyl-2-thienyl)ethylidene]-
15 hydrazide (Cpd 203);
methyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 208);
ethyl [1-(3-methyl-2-thienyl)ethylidene]carbazate (Cpd 209);
benzoic acid [1-(3-methyl-2-thienyl)ethylidene]hydrazide (Cpd
211);
20 ethyl [1-(5-methyl-2-thienyl)ethylidene]carbazate (Cpd 224);
propanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide
(Cpd 240);
2-methylpropanoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]-
hydrazide (Cpd 241);
25 3-(N-morpholinyl)propanoic acid (2-furanylmethylene)hydrazide
(Cpd 264);
formic acid (3-thienylmethylene)hydrazide (Cpd 266);
acetic acid (3-thienylmethylene)hydrazide (Cpd 267);
propanoic acid (3-thienylmethylene)hydrazide (Cpd 268);
30 2-methylpropanoic acid (3-thienylmethylene)hydrazide (Cpd 270);
benzoic acid (3-thienylmethylene)hydrazide (Cpd 271);
cyclohexanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
272);
cyclobutanecarboxylic acid (3-thienylmethylene)hydrazide (Cpd
35 274);
4-methoxybenzoic acid (3-thienylmethylene)hydrazide (Cpd 276);
phenyl (3-thienylmethylene)carbazate (Cpd 279);
formic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 283);

propanoic acid [1-(2-thienyl)ethylidene]hydrazide (Cpd 285);
cyclohexanepropanoic acid [1-(2-thienyl)ethylidene]hydrazide (-
Cpd 288);

5 cyclobutanecarboxylic acid [1-(2-thienyl)ethylidene]hydrazide
(Cpd 289);

formic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 291);

phenyl [1-(2-thienyl)ethylene]carbazate (Cpd 290);

acetic acid[(5-methyl-2-furanyl)methylene]hydrazide (Cpd 292);

10 propanoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
293);

butyric acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd 294);

cyclohexanecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 296);

methyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 300);

15 ethyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 301);

phenyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 303);

benzyl [(5-methyl-2-furanyl)methylene]carbazate (Cpd 305);

4-chlorobenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 307);

20 3,4-dimethoxyphenylacetic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 311);

4-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 312);

3-methylbenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
25 (Cpd 313);

4-ethoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 315);

2-furoic acid [(5-methyl-2-furanyl)methylene]hydrazide (Cpd
317);

30 2-thiophenecarboxylic acid [(5-methyl-2-furanyl)methylene]-
hydrazide (Cpd 318);

2-phenoxybenzoic acid [(5-methyl-2-furanyl)methylene]hydrazide
(Cpd 320);

formic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 323);

35 acetic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 324);

propanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 325);

2-methylpropanoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
327);

- cyclohexanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 328);
cyclopropanecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
(Cpd 329);
5 ethyl [1-(2-furanyl)ethylidene]carbazate (Cpd 331);
4-ethoxybenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
343);
2-furoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd 345);
2-thiophenecarboxylic acid [1-(2-furanyl)ethylidene]hydrazide
10 (Cpd 346);
phenyl (2-furanylmethylene)carbazate (Cpd 361);
phenylmethyl (2-furanylmethylene)carbazate (Cpd 363);
phenyl [1-(2-furanyl)ethylidene]carbazate (Cpd 365);
4-chlorobenzoic acid [1-(2-furanyl)ethylidene]hydrazide (Cpd
15 366);
benzoic acid (2-furanylmethylene)hydrazide (Cpd 367);
4-chlorobenzoic acid (2-furanylmethylene)hydrazide (Cpd 370);
4-methylbenzoic acid (2-furanylmethylene)hydrazide (Cpd 384);
4-methoxybenzoic acid (2-furanylmethylene)hydrazide (Cpd 386);
20 isonicotinic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide
(Cpd 390);
cyclohexanecarboxylic acid (1-methyl-1H-pyrrol-2-ylmethylene)-
hydrazide (Cpd 391);
cyclohexaneacetic acid (1-methyl-1H-pyrrol-2-ylmethylene)-
25 hydrazide (Cpd 392);
benzoic acid (1-(1H-pyrrol-2-yl)ethylidene]hydrazide (Cpd 394);
butyric acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 395);
4-chlorobenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd
397);
30 cyclobutanecarboxylic acid (1H-pyrrol-2-ylmethylene)hydrazide
(Cpd 400);
2-methylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd
402);
3-cyclohexylpropanoic acid (1H-pyrrol-2-ylmethylene)hydrazide
35 (Cpd 404);
butanoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 406);
2-chlorobenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd
410);

- 1-methyl(1H-pyrrol-2-ylmethylene)carbazate (Cpd 411);
4-methylbenzoic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 413);
3,4-dimethoxyphenylacetic acid (1H-pyrrol-2-ylmethylene)-
5. hydrazide (Cpd 422);
4-methoxyphenylmethyl (1H-pyrrol-2-ylmethylene)carbazate (Cpd 423);
nicotinic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 424);
phenylmethyl (1H-pyrrol-2-ylmethylene)carbazate (Cpd 426);
10. isonicotinic acid (1H-pyrrol-2-ylmethylene)hydrazide (Cpd 429);
acetic acid (1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 430);
butyric acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide (Cpd 432);
15. cyclohexanepropanoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 434);
4-chlorobenzoic acid (1-methyl-1H-pyrrol-2-ylmethylene)hydrazide
(Cpd 435);
3-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
20. hydrazide (Cpd 436);
2-chlorobenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 437);
4-ethoxybenzoic acid (1-methyl-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 438);
25. nicotinic acid [(1-methyl-1H-pyrrol-2-yl)methylene]hydrazide
(Cpd 439);
4-methylbenzoic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 440);
4-(1,1-dimethylethyl)benzoic acid [(1-methyl-1H-pyrrol-2-yl)-
30. methylene]hydrazide (Cpd 441);
4-methoxybenzoic acid [(1-methyl)-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 443);
butyric acid [(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)methylene]-
hydrazide (Cpd 446);
35. benzoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 450);
propanoic acid [1-(4-methyl-2-thienyl)ethylidene]hydrazide (Cpd 457);

benzoic acid [1-(2,5-dimethyl-3-thienyl)ethylidene]hydrazide
(Cpd 483);

cyclobutanecarboxylic acid [(1-methyl-1H-pyrrol-2-yl)methylene]-
hydrazide (Cpd 487);

5 phenylmethyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd
494);

formic acid [1-(1H-pyrrol-2-yl)methylene] hydrazide (Cpd 504);

phenyl [(1-methyl-1H-pyrrol-2-yl)methylene]carbazate (Cpd 506);

10 butanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide
(Cpd 568);

benzoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide
(Cpd 569);

propanoic acid [1-(2,5-dimethyl-3-furanyl)ethylidene]hydrazide
(Cpd 575);

15 benzoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 585);

butanoic acid [(5-ethyl-2-furanyl)methylene]hydrazide (Cpd 590);

butanoic acid [1-(2-furanyl)hexylidene]hydrazide (Cpd 591);

methyl (2-thienylmethylene)carbazate (Cpd 600);

20 cyclohexanepropanoic acid (2-thienylmethylene)hydrazide (Cpd
604);

or

cyclohexanecarboxylic acid (2-thienylmethylene)hydrazide (Cpd
605).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/00699

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
4 A 61 K 1/655; C 07 D 333/22; C 07 D 333/28; C 07 D 307/52; IPC: C 07 D 207/32; C 07 D 409/12; C 07 D 405/12; C 07 D 401/12; C 07 D 407/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	A 61 K 31/00; C 07 D 333/00; C 07 D 307/00; C 07 D 207/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US, A, 3733319 (D.W. HENRY) 15 May 1973 see the whole document --	7,13
A	US, A, 4064262 (A. SERBAN) 20 December 1977 see columns 1,2 and claims --	7,13
A	EP, A, 0172031 (ROHM AND HAAS) 19 February 1986 see claims --	7,13
A	US, A, 2639287 (J.V. SCUDI) 19 May 1953 see the whole document --	7,13
A	GB, A, 1581675 (SHELL) 17 December 1980 see claims --	7,13
P,A	EP, A, 0183398 (FISONS) 4 June 1986 see claims -----	7,13
¹⁰ 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 "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		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
26th June 1987	- 3 AUG 1987	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL 	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

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

1. ☒ Claim numbers 1-6.... because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv):

Method for treatment of the human or animal body by means of surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers....., 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. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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 all searchable claims of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ 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 claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO.

PCT/US 87/00699 (SA 16790)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/07/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3733319	15/05/73	None	
US-A- 4064262	20/12/77	None	
EP-A- 0172031	19/02/86	AU-A- 4610285 JP-A- 61093155	20/02/86 12/05/86
US-A- 2639287		None	
GB-A- 1581675	17/12/80	BE-A- 867584 NL-A- 7805805 FR-A, B 2392985 DE-A- 2823362 JP-A- 53149941 OA-A- 5974 CH-A- 637920	29/11/78 04/12/78 29/12/78 07/12/78 27/12/78 30/06/81 31/08/83
EP-A- 0183398	04/06/86	JP-A- 61143349	01/07/86

For more details about this annex :

see Official Journal of the European Patent Office, No. 12/82