

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO			
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DEP:	2020 DIRECCION DE NUEVAS CREACIONES	EVE:	378 FASE NACIONAL INCLUIDO CAPITULO I
TRA:	11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS:	10
ACT:	519 PRESENTACION		

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

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Asunto: Radicación: 10-162853- -4
 Trámite: 11
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Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP09/004474				
Fecha de Presentación Internacional	20/06/2009				

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 6 a 36	Diciembre 27 de 2010
Reivindicaciones	Folio 37	Diciembre 27 de 2010
Prioridad:	DE 102008031285.5	Julio 2 de 2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

La solicitud cuenta solamente con 8 reivindicaciones, las cuales se incluyen dentro de la tasa pagada por concepto de la presentación de esta solicitud, por lo cual, todas estas serán objeto de estudio.

Título de la solicitud: “Nifurtimox para el tratamiento de enfermedades causadas por *Trichomonadida*”

El problema planteado en esta solicitud consiste en el uso de otros antihelmínticos para el tratamiento de *Trichomonadida*, particularmente en pavos.

Para resolver este problema técnico, la solicitud en estudio plantea el uso de composiciones farmacéuticas que contienen Nifurtimox y otro agente antihelmíntico ciclooctadepsipeptido para tratamiento de *Trichomonadida* en pavos.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/541; A61K38/15; A61P33/02

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 1 a 6 no es patentable de acuerdo al artículo 14.

5. De la solicitud de la Patente

En la primera página se presenta esta solicitud con el número de Publicación Internacional WO2009/000398, sin embargo, al realizar la búsqueda se encuentra que dicho numero no corresponde a esta solicitud. El número correcto de Publicación Internacional de esta solicitud es el WO2010/000398. Se solicita realizar dicha corrección.

Doble Patentabilidad

Junto a esta solicitud se presenta la solicitud CO2010/162857 con fecha de presentación en Colombia del 20 de Junio de 2010 con las siguientes reivindicaciones:

CO 2010/162853	CO 2010/162857
Reivindicación 1: Uso del Nifurtimox para la fabricación de fármacos para el tratamiento de enfermedades causadas por <i>Trichomonanida</i>	Reivindicación 1: Uso del Nifurtimox para la fabricación de medicamentos para el tratamiento de enfermedades causadas por <i>Giardias</i>
Reivindicación 2: Uso del Nifurtimox para el tratamiento de enfermedades causadas por <i>Histomonas</i>	Reivindicación 2: Uso del Nifurtimox para el tratamiento de enfermedades causadas por <i>Giardia Lamblia</i>
Reivindicación 3: Uso del Nifurtimox para el tratamiento de enfermedades causadas por <i>Histomonas meleagridis</i>	Reivindicación 3: Agente que contiene Nifurtimox y un antihelmintico
Reivindicación 4: Uso del Nifurtimox para el tratamiento de enfermedades causadas por <i>Tricomonas</i>	Reivindicación 4: Agente que contiene Nifurtimox y un desipéptido antihelmintico
Reivindicación 5: Uso del Nifurtimox para el tratamiento de enfermedades causadas por <i>Tricomonas</i>	
Reivindicación 6: Nifurtimox para el uso para el tratamiento de enfermedades causadas por <i>Trichomonanida</i>	
Reivindicación 7: Agente que contiene Nifurtimox y un antihelmintico	
Reivindicación 8: Agente que contiene	

Nifurtimox y un desipéptido antihelmintico	
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De acuerdo a lo establecido en el artículo 21 de la Decisión 486, el segundo uso de compuestos no es patentable (El Nifurtimox se usa para el tratamiento de la enfermedad de Chagas causada por el *Tripanosoma cruzi*). De manera tal que las reivindicaciones 1 a 6 de la solicitud CO 2010/162853 y las reivindicaciones 1 a 2 de la solicitud CO 2010/162857 no son patentables.

Por lo tanto, las reivindicaciones 7 a 8 de la solicitud CO 2010/162853 y las reivindicaciones 3 a 4 de la solicitud CO 2010/162857 serian patentables, pero estas reclaman la misma materia.

Se sugiere eliminar alguna de estas solicitudes.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 7 y 8 no son concisas porque al mencionar las expresiones “antihelmíntico” y “ciclooctadepsipeptido”, se incluyen una cantidad amplia de compuestos. Se sugiere citar los compuestos específicos objeto de las combinaciones con el Nifurtimox en las cantidades específicas efectivas para estas combinaciones para cada componente. Así mismo, se sugiere cambiar la palabra “agente” por la palabra “composición” que se considera más precisa para el objeto de dichas reivindicaciones.

En la primera página se pr¹esenta esta solicitud con el número de Publicación Internacional WO2009/000398, sin embargo, al realizar la búsqueda se encuentra que dicho numero no corresponde a esta solicitud. El número correcto de Publicación internacional de esta solicitud es el WO2010/000398. Se solicita realizar dicha corrección.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de la cual se invoca prioridad, es decir, el 2 de julio de 2008.

Consultadas las fuentes de información con que se cuenta, se encontró el siguiente documento que anticipa el objeto de esta solicitud.

Item	Documento	Título	Fecha de Publicación
D1	<i>Trends of Parasitology.</i> 2004; 20 (10); 456 - 461	Veterinary anthelmintics: old and new	Octubre 14 de 2004

El documento D1¹ divulga un compilado sobre diversos fármacos ampliamente utilizados como agentes antihelmínticos

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art 18 D 486)

La reivindicaciones 7 y 8 divulgan agentes que contienen Nifurtimox y un antihelmíntico, especialmente un ciclooctadepsipeptido (Folio 37, líneas 24 y 25)

¹http://ac.els-cdn.com/S1471492204002053/1-s2.0-S1471492204002053-main.pdf?_tid=240f91ea-1188-11e2-afc4-00000aacb360&acdnat=1349728899_690c3e88f063cabe1f5778fc8aa8d656

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1
Agente que contiene Nifurtimox y un antihelmítico (Reivindicacion 7)	Se divulga una combinación entre un Benzimidazol y Levamisol con una reducción de la resistencia de helmintos al 11%. De manera específica se divulga la combinación entre Albendazol (4.75mg/kg) y Levamisole (7.5mg/kg)
Agente que contiene Nifurtimox y un Ciclooctadepsipéptido (Reivindicación 8)	

D1 se considera el Estado de la Técnica más cercano a la invención definida en las reivindicaciones 7 y 8, porque divulga combinaciones de compuestos antihelmínticos, específicamente, dicha combinación la integran un Benzimidazol y Levamisol, para el tratamiento de enfermedades causadas por parásitos resistentes. (D1: Página 459, tabla 2)

La diferencia entre la invención y D1 consiste en que en para la invención las combinaciones propuestas la integran Nifurtimox y otro antihelmíntico, de manera preferible un ciclooctadepsipeptido, mientras que para D1 la combinación divulgada la integran un Benzimidazol y Levamisol.

Esta diferencia no parece conceder un efecto técnico inesperado o ventajoso a los compuestos de esta solicitud con respecto a lo divulgado en D1 y en el documento que aparece en pie de cuadro, porque en estos estados de la Técnica se divulga un resultado que evidencia la efectividad de esta combinación, mientras que en esta solicitud no se divulgan resultados que demuestren efectividad alguna de las combinaciones farmacéuticas que se reclaman en las reivindicaciones 7 y 8

El Problema Técnico Objetivo que se plantea en esta solicitud es: ¿Cómo modificar las combinaciones del Estado de la Técnica D1 para obtener nuevos tratamientos antihelmínticos?

D1 divulga el uso de combinaciones de antihelmínticos para aumentar la efectividad del tratamiento, aumentar el espectro de actividad antiparasitaria y retardar el proceso de resistencia por parte de los parásitos. Se establece que solo las combinaciones de fármacos con diferente mecanismo de acción y perfil farmacocinético, asegura la exposición de los parásitos, aumentando la efectividad y retardando la resistencia (D1: Página 458, columna 1, líneas 29 a 31 y columna 2, líneas 1 a 7)

Por lo tanto, para una persona versada en la materia y conocedora de los conceptos de D1, sin mayor esfuerzo puede utilizar otros antiparasitarios ampliamente difundidos en el Estado de la Técnica (en este caso el Nifurtimox, PF1022A y otros) para obtener combinaciones con actividad antiparasitaria para mejorar el perfil de efectividad del tratamiento, llegando de esta manera, a las combinaciones propuestas en esta solicitud, de manera obvia o evidente.

En consecuencia, la reivindicaciones 7 y 8, de acuerdo a lo divulgado en D1, carecen de Nivel Inventivo.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	<i>Trends of Parasitology.</i> 2004; 20 (10); 456 - 461	7 y 8	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2012-11-27

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Veterinary anthelmintics: old and new

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Between 1960 and 1980, extraordinary success was achieved in anthelmintic development for animals. In these 20 years, drugs with diverse structure, novel activity and enviable safety were produced for a global livestock industry leading to the productivity gains needed to support a human population that grew by 1.5 billion during the same period. The following 20 years have been spent refining existing molecules with niche activity (parasite and host specificity), improving delivery systems and worrying about the inexorable spread of drug resistance. The challenge for the next 20 years will be to use the technologies available to design and produce new drugs and biological controls. Then, to use the lessons of the past to ensure that the new drugs enjoy a longer useful lifespan and contribute to an animal health industry (livestock and companion) which enriches the lives of a global population. Old and new veterinary anthelmintics comprise a very large field, which could not be comprehensively reviewed in a short article. The present mini-review focuses on major chemical discoveries, formulation developments, administration strategies and new products.

Helminth infections of humans are clearly of considerable importance [1], yet arguably they are of even greater relative importance in our domestic animals [2]. The direct life cycles and access by grazing to infective stages of the parasites, aided by intensive farming practices, make herbivores an easy target for many nematode species. As a consequence, anthelmintics comprise the largest sector of the animal pharmaceutical industry by volume and value (see International Federation for Animal Health website: <http://www.ifahsec.org>). Anthelmintic research and development has thus demanded a very large share of the animal health pharmaceutical development effort and is probably the only area of such research where efforts and success in animal health exceed those in human health.

The electric years

Two centuries ago, treatment of animals for internal parasites was rudimentary where it existed at all, and most medicines were either metals or plant extracts that worked (if they did work) by mechanically irritating the parasites from their predilection sites or by removing the predilection site (for an illustration of this, see Ref. [3]). ‘Anthelmintics or worm medicines mechanically irritate the parasites by their speculi, or dislodge them by

removing the mucus of the bowels, as purgatives, or prove noxious to the worms themselves – tin or pewter, or iron filed fine, but not levigated, two or three ounces. Common salt, six to eight ounces. Oil of turpentine, two to three ounces, Savine, one to two ounces, Cowhage, half a dram, Calomel, a scruple, Arsenic, ten Grains. Aloes, till they purge’ (see Ref. [3]).

Over the next 120 years, progress was slow; arsenicals, nicotine sulfate, copper sulfate and carbon tetrachloride were all used, but all had substantial deficiencies in spectrum of activity, absolute efficacy and toxicity. The introduction of phenothiazine (1940) and piperazine (1954) as veterinary anthelmintics did provide compounds with real activity against target parasite species and with acceptable tolerance in the host animal species. However, major progress was made between 1960 and 1980 (Figure 1). The discoveries of thiabendazole and levamisole provided compounds with *in vivo* potency at milligram (per kg of body weight) rather than gram dosages and, in the case of thiabendazole, led to the discovery of a group of structural analogues, the benzimidazoles, with excellent broad-spectrum activity and safety. In 1981, a further major step forward was made in chemotherapy with the launch in the animal health market of ivermectin, which had activity in animals when administered at microgram per kg dosages, had excellent broad spectrum activity against nematodes and was also effective against several parasitic arthropods. However, almost as quickly as the new discoveries were being made, resistance was reported in the target parasites to each chemical group [4–6]. This stimulated research into the mechanisms of action of and resistance to the anthelmintics.

Mechanisms of action

The benzimidazole drugs bind nematode tubulin, thus inhibiting the formation of microtubules, which are subsequently unable to transport secretory granules or secrete enzymes within the cell cytoplasm; this eventually results in cell lysis [7]. Reduced affinity for β tubulin appears to be associated with benzimidazole resistance, and identification of the genes involved in resistance determination has permitted the production of a PCR to identify early resistance in parasite populations [8]. This is of considerable importance in the implementation of control programmes in that the other methods for detecting resistance are either cumbersome (egg hatch assay [9]), or cumbersome and insensitive (faecal egg count reduction test [10]). The faecal egg count reduction test detects resistance only when >25% of the parasite population expresses resistance genes [11]. The mode of action of

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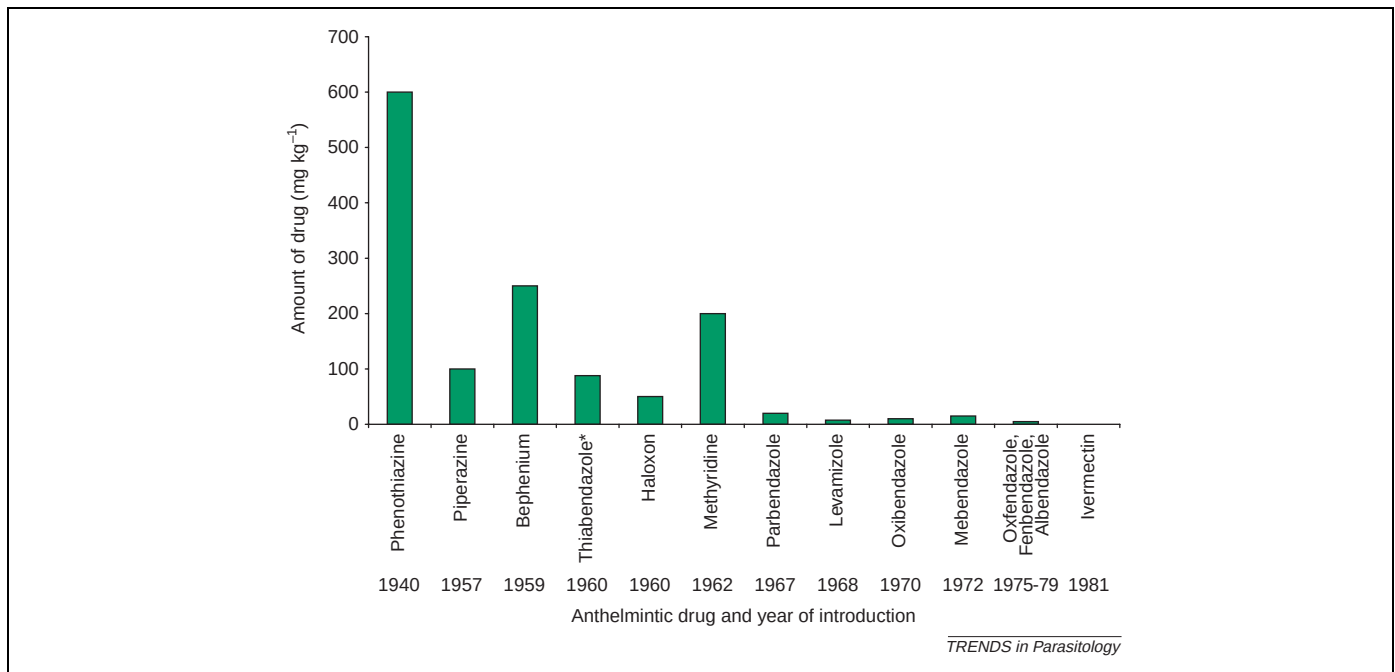


Figure 1. Chronological introduction of anthelmintic compounds and effective dose for the treatment of parasitic gastroenteritis in sheep. Compounds introduced from the mid-1960s have effective dose rates that are many-fold lower than the earliest developed compounds.

benzimidazoles is also of clinical significance in susceptible parasite populations because the duration of exposure of the parasite to drug is a key determinant of efficacy. Consequently, strategies have been developed both experimentally and commercially to extend this exposure period through the development of sustained delivery systems and by modifying the metabolism of the drug in the host species. Sustained delivery systems (such as intraruminal boluses) have the added advantage, for which many were originally designed, that they provide control over most of the grazing period, thus improving the efficacy of the operation. Potentiation of an anthelmintic by metabolic inhibition was first demonstrated experimentally by the co-administration of two benzimidazoles: oxfendazole and parbendazole. Parbendazole reduced the hepatic metabolism and biliary secretion of oxfendazole, and increased its extra-biliary secretion and thus prolonged the exposure of parasites in the gastrointestinal (GI) tract to effective oxfendazole concentrations [12]. Targeted metabolic inhibition of the flavine monooxygenase (by methimazole) and the cytochrome P450 (by metyrapone and piperonyl butoxide) enzymes, responsible for the sulfoxidation and sulfonation of sulfide benzimidazoles has also been shown to improve the efficacy of benzimidazoles. None of these combinations has yet reached the market because the cost of producing the required information for authorization, including toxicity, safety residues and withdrawal period data make them commercially unattractive for livestock [13–15].

Levamisole acts as a cholinergic agonist at nicotinic neuromuscular junctions in nematode parasites, first by opening and then blocking acetylcholine receptor-mediated cation channels [16]. Receptor desensitization might occur at high concentrations of levamisole, and increasing the dose might not be therapeutically advantageous. Because levamisole also acts as a nicotinic agonist in mammals, it

has a rather narrower therapeutic index than that by the other popular broad-spectrum anthelmintics, and some care is required when medicating a flock of animals with a large range of body weights.

Avermectins (and milbemycins, which are deglycosylated analogues), the macrocyclic lactones were thought to induce the release of the neurotransmitter gamma amino butyric acid (GABA), which interferes with neuronal transmission in parasites, but they are now known to potentiate the effect of GABA in parasitic nematodes [17,18]. The avermectins also have a receptor-mediated effect on glutamate-gated chloride ion channels which has been directly correlated to nematocidal activity and which is considered their major mode of action [19,20]. The selective toxicity of avermectins for parasites and not their mammalian hosts remained something of a mystery, although it was apparent that, despite their high solubility for lipids, they did not distribute well into the central nervous system (CNS) [21]. The explanation appears to be associated with P-glycoproteins, which have a significant role in transmembrane exclusion of avermectins from the CNS. P-glycoprotein knockout mice are ~100 times more sensitive to the toxicity of avermectins when compared with fully P-glycoprotein competent mice [22,23]. The P-glycoprotein transport proteins are also present in the gut and hepatobiliary tract, and could account for reduced oral bioavailability of some avermectins. P-glycoprotein inhibitors have been used to increase the oral absorption of macrocyclic lactones and thus to improve their efficacy [24]. Parasites are also endowed with P-glycoproteins, which might have a role in anthelmintic exclusion in resistant worms [25,26].

Other anthelmintics

There are several other anthelmintics of some importance including; (i) triclabendazole, a benzimidazole effective

against adult and immature *Fasciola hepatica*, but with no nematocidal activity; and (ii) the salicylanilides (e.g. closantel) which are active against *F. hepatica* and *Haemonchus contortus*. The pyrazinainisoquinoline praziquantel has been extensively used in dogs and cats because of its excellent activity against many cestode species including all intestinal stages of *Echinococcus granulosus*. It is also used for tapeworm control in horses and ruminants in many parts of the world. Praziquantel has excellent activity against trematodes of the genus *Schistosoma* for which it is more commonly used in humans and in which there is now evidence of emerging resistance [27]. Nevertheless, it is the broad-spectrum activity and safety of sulfide benzimidazoles, levamisole and the avermectins and milbemycins that accounts for their popularity (Table 1).

Anthelmintic resistance

Resistance within a chemical group tends to be common to all members of the group, although differences in potency mean that some drugs retain activity even when overt resistance has been recorded to others in their group [28]. Resistance to all three groups, benzimidazoles, levamisole and the avermectins, has now been recorded in many parts of the world, and nematode parasite populations have been found with multiple resistance to all three major groups of drugs. Resistance is a particular problem in sheep, goat and horse parasites, and strategies have been developed to slow its evolution, limit its spread and sustain livestock in its presence [9–11]. The use of anthelmintic combinations has been predicted to be the most effective way of delaying resistance emergence [29],

and many combinations have been used in animals to extend the spectrum of antiparasitic activity of the combination products. Only combinations of drugs with different mechanisms of action against common target parasites and with pharmacokinetic characteristics that ensure simultaneous exposure of the parasite populations are likely to be effective in delaying resistance. Resistance of *F. hepatica* to triclabendazole and of *H. contortus* to salicylanilides has also been recorded (Table 2). The use of anthelmintics that had less commercial success because of their limited spectrum of activity, but acted by different mechanisms (e.g. buphenium; a cholinergic agonist at non-levamisole nicotinic receptors [30]; organophosphates; acetylcholinesterase inhibitors [31]), could be used for parasites resistant to the major anthelmintic groups.

In the face of increasing level of resistance, it might seem surprising that new anthelmintics with novel mechanisms of action have not been marketed for over 20 years, as there is a clear need for them in the major sheep-rearing areas of the world. The reasons are probably manifold. First, the avermectins and milbemycins are so effective (98–99%) against a very broad spectrum of susceptible parasites that it is unlikely that novel anthelmintic compounds could be produced with a significant commercial advantage in terms of either efficacy or spectrum, although some scope exists for compounds with combined nematode, cestode and trematode activity. Second, resistance has not yet become a major problem in cattle and, in the animal health market, cattle products accounted for >55% of the global anthelmintic market in 2002 (see: <http://www.ifahsec.org>). Third, the potential of new technologies to develop new anthelmintics have not

Table 1. Major anthelmintics used in veterinary medicine^a

Class	Representative drugs	General activity
Avermectin ^b	Ivermectin, abamectin, doramectin, eprinomectin, selamectin	GI nematodes (many host species, including hypobiotic nematodes ^a); lung nematodes; migrating strongyles in horses; dirofilaria in dogs.
Milbemycin ^b	Moxidectin, milbemycin oxime	Broadly similar to avermectins.
Pro-benzimidazoles	Febantel, netobimin, thiophanate	GI nematodes (many host species; some with activity against hypobiotic nematodes); lung nematodes; tapeworms; liver fluke (<i>Netobimin</i> only).
Benzimidazole (thiazoles)	Thiabendazole, cambendazole	GI nematodes (many host species).
Benzimidazole (carbamates)	Albendazole (oxide), fenbendazole, mebendazole, oxfendazole, parbendazole, triclabendazole, oxibendazole, flubendazole	Broadly similar to pro-benzimidazoles. Albendazole and triclabendazole (exclusively) have activity against liver fluke.
Imidazothiazole	Levamisole, tetramisole	GI nematodes (ruminants); lung nematodes.
Tetrahydropyrimidine	Morantel Pyrantel	GI nematodes (ruminants, horses, dogs and cats). Tapeworms in horses.
Organophosphate	Trichlorphon, haloxon, dichlorvos, naphthalophos	GI nematodes ^c
Salicylanilide	Closantel, oxyclozanide, rafoxanide, niclosamide	Liver fluke (ruminant). Closantel is also active against <i>Haemonchus</i> .
Nitrophenolic compounds	Nitroxylnil, Nitroscanate	Liver fluke and <i>Haemonchus</i> in sheep Tapeworms and GI nematodes in dogs.
Benzoenedisulphonamide	Clorsulon	Liver fluke (ruminants)
Pyrazinainisoquinoline	Praziquantel, epsiprantel	Tapeworms including <i>Echinococcus</i> (many host species).
Heterocyclic compounds	Piperazine diethylcarbamazine, Dichlorophen Phenothiazine	GI roundworms in dogs and cats Lungworms in cattle Tapeworms in dogs GI nematodes in several species
Arsenical	Thiacetarsamide, melorsamine, arsenamide	<i>Dirofilaria</i> in dogs

^aThe above table provides information on general activity. There are significant differences between members of each class. Furthermore, authorizations differ between countries (both for host and target species). Please refer to the authorized data sheet for specific product information and indication. Abbreviation: GI, gastrointestinal.

^bActivity against some ectoparasites, horse bots and sheep bots.

^cVariable efficacy against equine cyathostomes

Table 2. Resistance against broad- and narrow-spectrum anthelmintics, and combinations^a

Country	Prevalence of resistance (%)						Refs
	Bz	Lev	MI	Bz/Lev	Clos	Rfx	
Australia	90	80	60	60	60	-	[45]
South Africa	79	73	73	-	-	89	[46]
Argentina	40	22	6	11	-	-	[47]
Brazil	90	84	13	73	20	-	[48]
Paraguay	73	68	73	-	-	-	[49]
Uruguay	80	71	1	-	-	-	[50]

^aThe prevalence of resistance is indicted by the percentage of sheep farms tested. Resistance in sheep parasites to the major anthelmintic drugs available has become endemic throughout many regions of the southern hemisphere. Abbreviations: -, not tested; Bz, benzimidazole; Lev, levamisole; MI, macrocyclic lactone; Clos, closantel; Rfx, rafoxanide.

been realized – thus designer molecules for specific target receptors have not materialized and the high-throughput screening of potential new drugs has not markedly increased the number of candidate molecules progressing to clinical testing. Finally, it is probable that the high regulatory hurdles, which increase the cost and the risk associated with the development and manufacture of new products, decrease the enthusiasm of pharmaceutical companies to progress with anything short of the ‘spectacular’ candidate!

This is not to say that technologies have not made their mark – the development of designer analogues of existing molecules, particularly the avermectins and milbemycins, has been exceptional. Doramectin was produced by mutational biosynthesis whereby a mutant of *Streptomyces avermitilis* was used to generate novel molecules with substitutions on the previously chemically inaccessible C-25 position [32]. Extensive research on the avermectin molecule indicated that the milk partitioning coefficient could be altered in dairy cattle by selection of analogues with an unsaturated C-22,23 position: this was a substantial achievement for a highly lipophilic molecule of this type [33]. It has since been shown that only 0.1% of an administered dose of the C-4'-epi-acetyl amino analogue (eprinomectin) is eliminated in milk compared with 5% for ivermectin or moxidectin [34]. Eprinomectin has been authorized for use in lactating cattle with no milk withholding period. Monosaccharide avermectins have been identified with excellent activity against fleas in dogs and cats, and selamectin was selected for commercialization because it retained activity against heartworms and GI nematodes, and was safe when administered topically in collie dogs, which were known to have an idiosyncratic susceptibility to avermectin toxicity [35,36].

Production systems for cattle and sheep have become increasingly competitive as international trade has increased, and national subsidies and tariffs have been reduced. Anthelmintic usage has contributed to this by reducing production losses associated with parasites. More efficient ways of delivering the anthelmintics have been developed, which are prophylactic rather than therapeutic, and provide epidemiological control, whereby delivery is convenient and labour saving. The epidemiology of the most common and important nematode parasites of ruminants depends on parasite life cycles with prepatent periods of approximately three weeks. Delivery of anthelmintic at a three-week inter-dosing interval or extended persistence of anthelmintic in the animal at nematocidal concentrations such that nematodes do

not reach the egg-laying adult stage therefore provides a mechanism to reduce pasture contamination. This has been exploited by the production of a variety of ingenious delivery systems and by the development of anthelmintic chemicals with extended persistence in the host animal. Delivery systems have been developed which are administered orally to cattle and sheep, and which are retained in the rumen by virtue of their specific gravity or geometry. They release anthelmintic at three weekly intervals, or in a sustained manner over a period (generally three months or longer), which provides protection over a season in temperate areas. Osmotic pumps, sacrificial metallic corrosion and matrix diffusion have all been exploited in the delivery mechanisms. Excipients have also been used to provide extended delivery of anthelmintics administered by subcutaneous injection, and strategies devised which require treatment at intervals equivalent to the prepatent period of the parasite plus the period during which the drug remains at therapeutic concentrations in the animal. The innate characteristics of the anthelmintic itself can provide the essential requirements for epidemiological control. Moxidectin is highly lipid soluble (~100 times that of ivermectin*) and, following administration by either the oral or subcutaneous routes, it rapidly distributes to fat tissue which acts as a reservoir from which it is released into the blood and is redistributed to the parasite predilection site. Moxidectin thus confers activity against incoming challenge with *Ostertagia* spp. (35 days) and against *Dictyocaulus viviparus* (42 days).

Although no chemical entities with novel activity have been marketed since 1981, there has been continued research interest in this area and in 2003 alone there were >60 patent applications published on novel anthelmintic compounds. Admittedly these included several extensions to established patents, several which might better be described as vaccine candidates and some creative ideas around interleukin (IL) 6 inhibitors, mature dendritic cells and vectors for RNA interference.

Of the chemical compounds that have surfaced since the discovery of the avermectins and milbemycins, the cyclodepsipeptides and the paraherquamide class of drug look the most promising.

Cyclodepsipeptides are cyclic chains of amino acids with unique mode of activity [37]. The most promising molecules have an 18-membered cyclic ring incorporating hydroxy-amino acids that confer protease resistance and

* Hayes, P.W. (1994) Moxidectin: understanding the unique persistent anthelmintic activity of the second generation macrocyclic lactone. In: *Australian Veterinarians in Industry, Australian Veterinary Association Annual Conference 1994*, Canberra, Australia

thus oral bioavailability. Cyclodepsipeptides have been produced by the fermentation of several bacteria and fungi, and the product of the fungus *Mycelia sterilia* comprising four N-methyl-(S)-leucine residues, two 3-phenyl-(R)-lactate units and two (R)-lactate moieties.

The cyclooctadepsipeptide PF1022A appears to have particularly attractive anthelmintic properties. It has high lipophilicity, which could give it pharmacokinetic characteristics appropriate for therapy in animals [38]. Its mode of activity has not been fully elucidated, although its paralytic effects have been shown not to be associated with GABAergic activity or antagonism of cholinergic receptors [39]. There is now evidence that the cyclodepsipeptides could act by interacting with a nematode-specific latrotoxin-induced Ca^{2+} influx at latrophilin receptors, thus inhibiting pharyngeal pumping [40]. Latrotoxin is a neurotoxic protein produced by the black widow spider. Cyclodepsipeptides might also confer some ionophoric activity affecting the translocation of metal cations, which could in turn affect oxidative phosphorylation, however, this activity is not thought to be responsible for their anthelmintic effects [41]. PF1022A has been shown to have good activity against *Ancylostoma caninum* in dogs, cyathostomes in horses, *Trichostrongylus colubriformis* and *H. contortus* in sheep, and *D. viviparus* in cattle [42].

The paraherquamide compounds have been classified as diketopiperazines and include: (i) marcfortine, a metabolite of *Penicillium roqueforti*; (ii) paraherquamide A, a metabolite of *Penicillium paraherquei*; and (iii) 2-desoxoparaherquamide A (PNU-141962), a semi-synthetic derivative. The activity of paraherquamide has been recognized since 1990 [43], however the excellent activity and apparent tolerance of 2-desoxoparaherquamide A might make it a more attractive potential candidate for commercialization. Members of this group probably have a common mechanism of action, which involves blockade of cholinergic neuromuscular transmission. 2-desoxoparaherquamide causes paralysis in *H. contortus* at lower concentrations (IC_{50}) than those required to block nicotinic stimulation at mammalian ganglionic, muscle and CNS receptors, suggesting a reason for parasite selectivity. 2-desoxoparaherquamide has shown excellent activity in models of *H. contortus*, *T. colubriformis*, and *O. ostertagi* and, in a dose titration study, was shown to have greater potency against *H. contortus* than other members of the group [44].

Concluding remarks

It is an unfortunate paradox that as we progress to a scientific era, which could deliver designer molecules to solve the worsening global problem of anthelmintic resistance, the societal will and economic drive have been insufficient to realize that goal. However, the increasing prevalence of anthelmintic resistance could provide the pharmaceutical industry with sufficient encouragement to develop, register and launch anthelmintics with a new mode of action.

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NIH launches expanded health information website

The National Institutes of Health (<http://www.nih.gov>) has recently launched an expanded health information website. The site now includes three new feature sections. 'Healthy Lifestyles' highlights links to popular topics such as seasonal health concerns, nutrition and weight loss. 'Research in Action' directs users to cutting-edge scientific information on topics such as stem cells and genetics, plus it provides readers with an opportunity to meet scientists ranging from high school students to Nobel Laureates. 'Now Online' emphasizes interactive features and web exhibits, such as the Portion Distortion quiz, the Household Products Database, and the Milk Matters campaign.

Of particular interest to parasitologists are the general infectious diseases page (<http://health.nih.gov/result.asp/367>) and the parasitic diseases page (<http://health.nih.gov/result.asp/499>).

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