Review Article

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A Review of FDA-Approved Antiparasitic Drugs in USA for Sheep and Goats: Their Synthesis and Pharmaceutical Use

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Abstract

This review describes the Food and Drug Administration (FDA)-approved antiparasitic drugs for sheep and goats in the USA updated to 2021. The emerging drug resistance is posing a significant burden for the treatment of parasitic infections in these small ruminants and the need for novel antiparasitic drugs is urgent. Sheep and goats are producing every year important resources such as milk and wool, among others. This work incorporates the OneHealth approach which focuses not only on human health, but also on animal health and the environment in an interdependent modus operandi. The dynamic equilibrium among these three sectors plays a fundamental role in general healthcare. Drug discovery (e.g., a novel benzimidazole recently identified) and drug delivery (incorporation of the antiparasitic agent into the proper carrier to increase effectiveness) have provided some promising results in recent time. This should go hand-in-hand with the scientific awareness. Education is key in spreading the word about the responsible use of antiparasitic drugs. The synthesis of the currently approved drugs will be provided including synthetic procedures which date from 1961 to 2021. More synthetic pathways, when available, will be described. Their mechanism of action and ecotoxicological data will be presented as well.

Keywords: Parasites, FDA, Drugs, Synthesis, Sheep, Goats.

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1. Introduction

Sheep and goats represent an important source of raw materials and contribute significantly to the world economy. Milk, wool and leather are just some examples of resources that can be obtained from these small ruminants.

Several health hazards, among the most known of which are goat pox and sheep pox are endangering lives of these animals leading to an economic loss and to ecosystem unbalance (1). Sheeppox and goatpox are both systemic diseases, with cell-associated viral infection preceding the appearance of lesions and marked lymphadenopathy (2).

Another example, the roundworm Haemonchus contortus is a blood-sucking parasite which causes severe disease in sheep and goats. This result in such signs as decreased activity level, decreased to no appetite, reduced growth, a very low red blood cell count (severe anemia), and death. When H. contortus become resistant to previously effective antiparasitic drugs, the herds experience increased health problems and the producer experiences greater economic losses (3). Parasites are often called “worms”. A parasite is a pathogen that simultaneously injures and gets sustenance from its host (4).

Besides the economic point of view, the healthcare is impacted. Several animal infections

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pose zoonotic threats to human health, and diseases in one species may act as reservoirs for infections in other species (5). According to the United States Department of Agriculture (USDA) all sheep and lambs inventory in the United States on January 1, 2021 totaled 5.17 million head, down 1 % from 2020. Shorn wool production in the United States during 2020 was 23.1 million pounds, down 4 percent from 2019 (6).

Despite the relatively low number of small ruminants in the USA compared to other continents such as Oceania (3), sheep and goat have a high need for effective antiparasitic drugs. Parasitic infections can harm animal health, can lead to economic crisis and last, but not the least, can affect human health.

Australia and New Zealand have already adopted some preventive measures in order to tackle the antiparasitic resistance, that is the ability of a parasite to survive a dose of an antiparasitic drug that would normally be expected to kill them. Among these measures are the avoidance of treating every animal in the flock or herd, by avoiding to treat all animals at the same time, and by using drugs that are effective based on recent diagnostic test results and approved for the particular parasites present on the farm.

Also, leaving some internal parasites unexposed to an antiparasite drug could help slow down the development of resistance (3). Given the critical and current situation of antiparasitic spreading resistance, FDA launched in 2012 the Antiparasitic Resistance Management Strategy (ARMS). This initiative promotes selective use of antiparasitic drugs together with sustainable management practices to maintain the effectiveness of antiparasitic drugs in grazing livestock species (7). A three-concepts approach underpins the program: education, research, and regulation.

Stated in the program are the therapeutic indication and target parasite for the used drugs. Attention has to be paid by veterinarians and farmers in order to overcome the problem of antiparasistic resistance.

Although there is urgent need for novel antiparasite agent for sheep and goats, the antiparasitic drug discovery is declining for various reasons, namely little incentive to invest in researching and developing new antiparasitic drugs (3). Nearly 75% of all emerging infectious diseases that impact or threaten human health are zoonotic, that is originated by animals (8).

Given this picture, novel antiparasitic drugs are needed (possibly with novel mechanism of action) and the purpose of this review is to show the chemistry of recently FDA-approved antiparasitic molecules.

2. FDA-approved antiparasitic drugs (as of 2021) for use in sheep and goats in USA

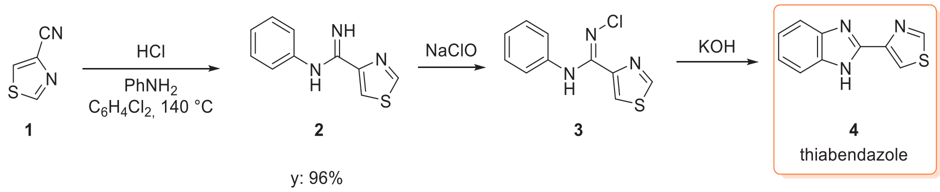
The approved active ingredients in USA (updated to April 2021) are: thiabendazole, albendazole, fenbendazole, morantel tartate, levamisole, ivermectin and moxidectin (3). The classification of these molecules was made according to their chemical structure. When possible, multiple synthetic pathways are provided. The reported synthesis are presented in a date range from 1961 to the more recent 2021. The mechanism of action for each drug is discussed. The most striking data these presented approved drugs have in common is that resistance has developed to each active ingredient. Resistance has developed to each active ingredient described in the paper, including to moxidectin, which was approved in 2005 and it is the newest antiparasitic drug on the market (3).

The emergence of resistance to currently available antiparasitic drugs is a concerning issue. It highlights the need for the development of novel and effective treatments against parasitic infections.

2.1 Thiabendazole

Thiabendazole (**4**, brand name Mintezol®) (9) was first introduced as an anthelmintic in sheep in 1961. This drug proved to be an extremely effective broad-spectrum anthelmintic and has been used widely in many geographical locations for treatment of parasitic helminths. Efficacy against Haemonchus in sheep ranged as high as 96-100% (10). It was also noted that thiabendazole was highly effective against other worm parasites including Trichostrongylus and Ostertagia (11).

Owned by Boehringer lngelheim Animal Health USA, it is reccomended for control of infections of gastrointestinal roundworms in sheep



Scheme 1. Preparation of thiabendazole (4) according to Merck patent (15).

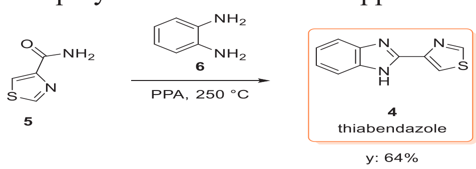
and goats (12).

Although the mechanism of action of thiabendazole remains unknown, it is presumed to specifically inhibit fumarate reductase, a helminth-specific enzyme (13). The inhibition of this enzyme leads to the block of mitochondrial respiration and ultimately to helminth's death. In addition, it has been suggested that thiabendazole may lead to inhibition of microtubule polymerization by binding to β-tubulin (14).

Chemically, thiabendazole is a benzimidazole and one of its first commercial synthetic procedure was released by Merck in 1967 (Scheme 1) [15]. This employs 4-cyanothiazole (**1**) as strating material. This is treated with hydrogen chloride and aniline in o-dichlorobenzene ($C_6H_4Cl_2$) as solvent at 140 °C to give amidine 2 in high yield (96%). The treatment of **2** with sodium hypochlorite (NaClO) afforded the N-chloro derivative **3** which was eventually converted into thiabendazole (**4**) in the presence of potassium hydroxide (KOH) via a nitrene intermediate.

Few years earlier (1961), a shorter synthetic pathway was reported involving the only 4-thiazolecarboxamide **5** with o-phenylenediamine **6** in polyphosphoric acid (PPA) at 250 °C (Scheme 2) (16).

A more recent, one-pot synthesis of thiabendazole has been reported (Scheme 3) (17). Conditions employ 2-iodo- or 2-bromoanilines **7** (1.0 equiv), aldehydes (**8** in our example, 1.2 equiv), NaN_3 (2.0 equiv), 5 mol% of copper chloride (CuCl), and 5 mol% of tetramethylethylenediamine (TMEDA) in DMSO as solvent at 120 °C for 12 h. The proposed mechanism is supposed to progress via halobenzimine followed by insertion of copper and cyclization with consequent loss of gaseous nitrogen. DMSO outperformed other polar solvents such as NMP, DMF, DMAc. The oxidation state of copper was not a factor, as Cu (I) and Cu (II) salts showed similar performance. Yield was excellent when starting from 2-iodoaniline (97%) but satisfactory as well when using 2-bromoaniline (88%) (17).



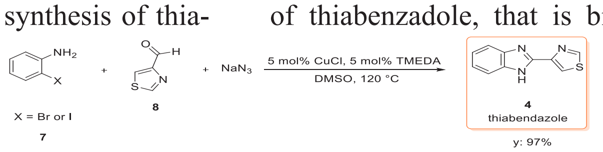
Scheme 2. Preparation of thiabendazole published in 1961 (16).

2.2 Albendazole

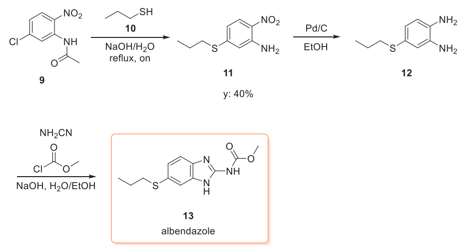
Albendazole (**13**, brand name Valbazen®) is used against numerous animal and human parasites and it is chemically related to thiabenzadole as the name suggests. Discovered in 1961 by Brown and his team, it exhibited potent activity against gastrointestinal nematodes (18, 19).

It is manufactured and distributed by Zoetis Inc. as a broad spectrum dewormer (20).

The mechanism of action is similar to that of thiabenzadole, that is binding selectively on



Scheme 3. Preparation of thiabendazole via copper-catalyzed reaction (17).



Scheme 4. Preparation of albendazole by SmithKline (24).

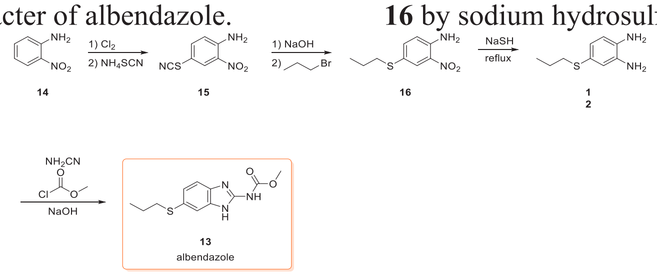
β-tubulin of nematodes. Albendazole produces the starvation of the nematodes by intestinal disruption and inhibits egg production (21). It is additionally a fumarate reductase flavoprotein subunit inhibitor (22).

Structurally, albendazole differs from thiabendazole for having a mercaptopropyl chain on the position 6 of benzimidazole ring and a methyl carbamate instead of a thiazole ring.

The overall lipophilicity (calculated using ChemDraw16.0) (23) for albendazole (logP: 2.55) is higher compared to that of thiabendazole (logP: 2.03). The mercaptopropyl is mostly responsible for the lipophilic character of albendazole.

A very first patent about the synthetic preparation (Scheme 4) of albendazole was reported in 1976 by SmithKline Corporation (24). The authors used 3-chloro-6-nitroacetanilide (9) as starting material. This is tretaed with propylmercaptan **10** in the presence of NaOH with consequent hydrolysis at the acetamide site to give the mercaptopropyl derivative **11** (yield: 40%). The reduction of nitro group of **11** by catalytic hydrogenation afforded di-aniline **12**. Eventually, **12** was converted into albendazole **13** upon addition of electrophilic cyanamide (NH_2CN) and methylchloroformate in a solvent mixture of ethanol/water.

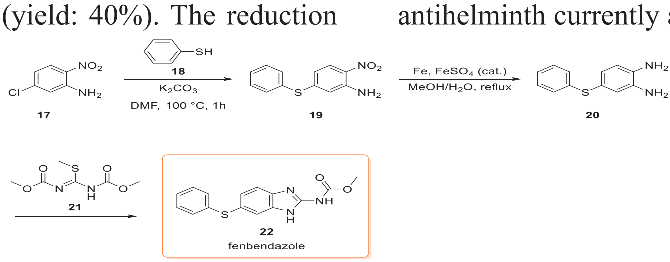
An alternative, multi-scale pathway (Scheme 5) (25), has been reported in more recent years. This involves the use of o-nitroaniline **14** as starting material. This was treated with molecular chlorine and ammonium thiocyanate to give 2-nitro-4-thiocyanatoaniline **15**. Treatment of **15** with NaOH and propyl bromide gave the mercaptopropyl derivative **16**. Reduction of nitro group of **16** by sodium hydrosulfite (NaSH) gave di-aniline **12** which was converted into albendazole **13** upon consequent addition of cyanamide and methyl chloroformate.



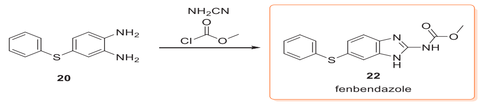
Scheme 5. Alternative multi-scale preparation of albendazole (25).

2.3 Fenbendazole

Fenbendazole (22, brand name Safe-Guard®) (26) is a broad-spectrum benzimidazole antihelminth currently approved for use in numer-



Scheme 6. Early synthesis of fenbendazole (22) (31).



Scheme 7. Alternative final step approach for the preparation of fenbendazole 22 (32).

ous animal species, including small ruminants (27). It is effective against a number of gastrointestinal parasites including giardia, roundworms, hookworms and whipworms (28).

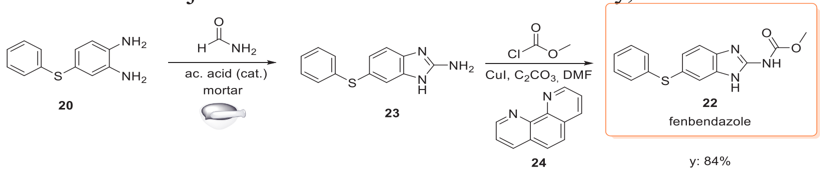
Its anthelmintic activity is linked to the inhibition of microtubule in parasites. Moreover, it displays preclinical activity in leukemia and myeloma and therefore anticancer potentialities (29,30).

Structurally, it is related to albendazole, but possessing a mercaptophenyl substituent instead of the mercaptopropyl of albendazole.

Its early synthesis (Scheme 6) was reported in 1975 (31). It starts from 5-chloro-2-nitroaniline **17** which is treated with thiophenol **18** and potassium carbonate (K_2CO_3) in DMF to give the nitro intermediate **19**. This is subjected to treatment with iron (and catalytic amount of $FeSO_4$) under methanolic reflux to give di-aniline 20. Lastly, **20** was converted to fenbendazole (22) upon via condensation with 1,3-Bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (21).

Intermediate 20 was otherwise condensed with cyanamide and methyl chloroformate as reported in a later patent (32).

A more green, mechanochemical method involving the condensation of aldehydes and dianilines has been reported (33). Authors used the intermediate to synthesize fenbendazole (Scheme 8) (22).



Scheme 8. Alternative final step approach for the preparation of fenbendazole 22 (32).

In detail, intermediate **20** was grinded with formamide in the presence of acetic acid as catalyst in a mortar to give benzimidazole-2-amine **23**. The eventual carbamoylation of **23** with methyl chloroformate, copper iodide (CuI), cesium carbonate and 1,10-phenanthroline **24** in DMF provided fenbendazole (**22**) in high yield (84%).

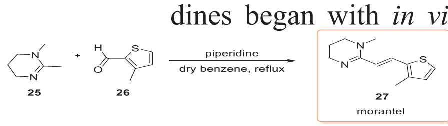
2.4 Morantel

Differently from the three benzimidazoles (thiabendazole, albendazole, fenbendazole) described above, morantel (brand name Rumatel®) (3) belongs to the class tetrahydropyrimidine which act as commonly grouped together as nicotinic acetylcholine receptor (nAChR) agonists (34).

Recently, morantel was shown to act as an agonist of the nAChR subtype in H. contortus or quine roundworm Parascaris equorum (35). Also, allosteric modulation by morantel leading to an increased channel gating of neuronal nicotinic acetylcholine has been reported (36).

Therefore, the main mechanism of action for morantel is the cholinergic agonisms at nervous system level (leading to muscular spasms). Moreover, it has been shown that this drug may also interfere with the glucose metabolism of the worms (37).

The discovery of the tetrahydropyrimidines began with *in vivo* screening programs in



Scheme 9. Synthesis of morantel according to Pfizer's patent (39).

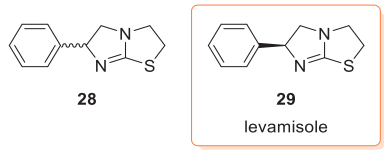


Figure 1. Chemical structures of tetramisole (28) and levamisole (29).

the late-1950s by Pfizer scientists leading to the synthesis of morantel and related compounds (pyrantel and oxantel) (38).

The synthesis of morantel reported by Pfizer (Scheme 9) (39) is carried out via Knoevenagel-type condensation of 1,2-Dimethyl-1,4,5,6-tetrahydropyrimidine **25** with 3-methyl-2-thiophenecarboxaldehyde **26** in the presence of piperidine and dry benzene as solvent under reflux to give the trans-product morantel (**27**).

2.5 Levamisole

Levamisole (**29**, brand name Ergamisol®) (40) belongs to imidazothiazole class of antiparasitic agents. Similarly to morantel, it causes spastic paralysis in parasites due its binding to nAChRs of the muscles that belong to the body wall of the parasite (41). Racemic tetramisole (**28**) was the first generation compound of this group and was followed by the use of levamisole which is the levorotatory enantiomer of tetramisole (Figure 1). The original patent for the preparation of tetramisole was released by Janssen in 1967 (42).

The two-steps synthesis starts from 1-phenylethane-1,2-diamine (**30**) that is reacted with carbon disulfide (CS2) in the presence of alkaline water to afford imidazole-2-thiol 31. Eventually, this was cyclized by adding 1,2-dibromoethane to give tetramisole 28 (Scheme 10).

The chiral resolution of tatramisole to provide pure levamisole was released in 1968 as well. It was accomplished by using d-10-camphorsulfonic acid (**32**) as a resolving agent in chloroform as solvent (43). Both levamisole and its isomer **33** were isolated (Scheme 11).

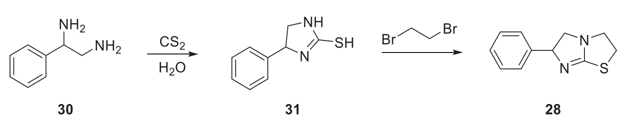
Several alternative preparations of tetramisole were described among which some are herein described (Scheme 12) (44). It originates from α-bromoacetophenone mixed with 2-imino-1,3-thiazolidine to give 2-imino-1,3-thiazolidine **35**. This was treated with acetic anhydride to afford acetyl intermediate **36**. The reduction of keto group of **36** by $NaBH_4$ yielded racemic alcohol **37**. Treatment of **36** with thionyl chloride ($SOCl_2$) in boiling acetic anhydride as a solvent gave tetramisole (**28**).

A similar approach, but employing styrene oxide 38 as starting material was reported (Scheme 13) (44). **38** was subjected to the nucleophilic attack of 2-imino-1,3-thiazolidine to give alcohol 39. This underwent cyclization medaited by thionyl chloride ($SOCl_2$) in acetic anhydride to give tetramisole (**28**).

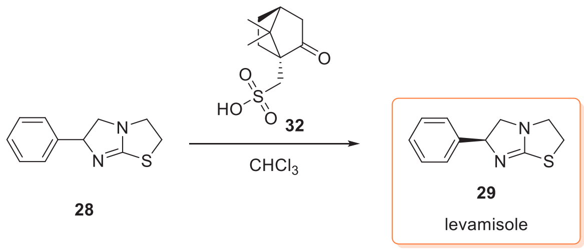
An approach to give the desired product levamisole was reported involving the use of chiral starting diamine (Scheme 14) (45). It originates from β-nitro para-tosyl protected amine 40 which is converted into mono para-tosyl protected diamine **41** by catalytic hydrogenation (Pd/C in methanol). The removal of tosyl group (compound **42**) was accomplished by using magnesium powder. Compound **42** was treated firstly with carbon disulfide and lastly with 1,2-dibromoethane to afford levamisole in a good yield (65%) (**29**).

2.6 Ivermectin

Ivermectin (**43** and **44**, brand name Stromectol®) (**46**) is a semisynthetic macrocyclic



Scheme10. Original synthesis of tetramisole by Janssen (42).



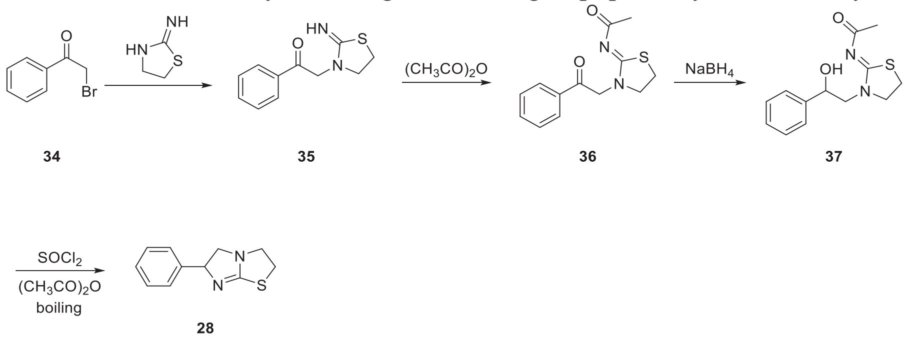
Scheme 11. Optical resolution of tetramisole (28) operated by d-10-camphorsulfonic acid 32.

lactone whose precursor (avermectin B1) is produced by an actinomycete, Streptomyces avermitilis. It is active at extremely low dosage against a wide variety of parasites including worms, and its mechanism of action was found to bind selectively and with high affinity to glutamate-gated chloride channels, commonly found in invertebrate nerve and muscle cells (**47**). Moreover, it is hypothesized a binding to gamma-aminobutyric acid receptor (**48**). It immobilizes nematodes by blocking the signal transmission from the central command interneurons to the peripheral motoneurons (49). It was discovered by Merck scientists (50) and it is essentially a mixture of two compounds ivermectin component B1a (**43**, Figure 2) and Ivermectin component B1b (**44**, Figure 2) (46). William C. Campbell, won the 2015 Nobel Prize in physiology or medicine with his collaborator on ivermectin, Satoshi Ōmura (51).

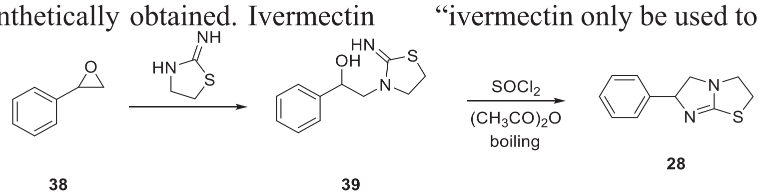
Avermectin B1a and avermectin B1b (Scheme 15) are the precursors from which ivermectin is semi-synthetically obtained. Ivermectin exists as a mixture of component B1a which is dominant over the component B1b (not less than 80% and not more than 20%, respectively).

Catalytic hydrogenation of avermectin components B1a and B1b 45 and 46, using Wilkinson's catalyst $[RhCl(PPh_3)_3]$ in toluene, selectively reduces the double bond at $C_{22\text{-}23}$ to a single bond to form ivermectin (Scheme 15, compounds **43** and **44**) (**47**). A peculiar pentacyclic scaffold, high lipophilicity and a hexahydrobenzofuran segment is a common trait in both avermectin B1 and ivermectin B1. These features together with the potent antiparasitic activities have gained the attention of several organic chemistry groups in order to obtain ivermectin derivatives (52).

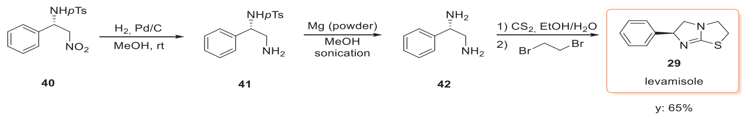
Recently, ivermectin has been associated with a possible inhibitory effect on the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in the early stages of infection but the possible antiviral mechanism is still debated (53). However, WHO advises that "ivermectin only be used to treat COVID-19 with-



Scheme 12. Alternative synthesis of tetramisole (44).



Scheme 13. Alternative synthesis of tetramisole (44).



Scheme 14. Synthesis of levamisole using chiral β-nitro tosyl-protected amine as starting material (45).

in clinical trials" (54).

2.7 Moxidectin

Moxidectin (47) is a potent, broad-spectrum endectocide (antiparasitic that is active against endo- and ecto-parasites) with activity against nematodes, insects, and acari (55).

The exact antiparasitic mechanism of action of moxidectin (brand name Cydectin®).

However, studies indicate that the primary mode of action results from binding to glutamate-gated chloride channels in the parasites (56).

The high lipophilicity, the macrolactonic core, mechanism of moxidectin is shared with ivermectin, but structural differences exist. These include the absence of a disaccharide at position C13 of the macrocyclic ring in moxidectin, the presence of a C23-methoxyimino group and the olefinic substituent at position C25 (Figure 3).

Its precursor, nemadectin (48), is produced by Streptomyces cyaneogriseus subspecies noncyanogenus (57). A semi-synthetic preparation of moxidectin starting from nemadectin involves classical sequential steps of organic chemistry such as protection of alcohol, oxidation, deprotection and final oximation (Scheme 16) (58). In detail, the hydroxyl group at position C5 of 48 is selectively protected with p-nitrobenzoyl halide (such as p-nitrobenzoyl iodide) in the presence of organic base (e.g., triethylamine) to give intermediate 49. Then, pyridinium dichromate (PDC) and acetic anhydride were used to oxidize secondary alcohol at C_{23} to afford ketone 50. The deprotection stage was achieved by adding alkaline sodi-

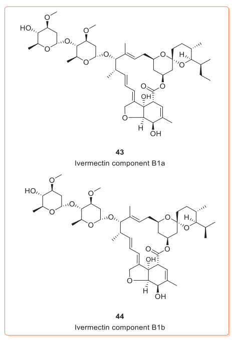
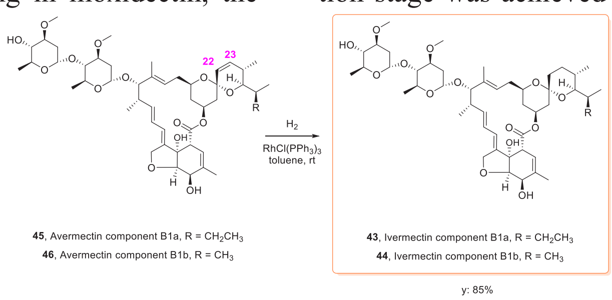


Figure 2. Chemical structures of the two components of ivermectin: Ivermectin component B1a (43) and Ivermectin component B1b (44).



Scheme 15. Synthesis of ivermectin (ivermectin component B1a 43 and ivermectin component B1b 44) starting from avermectin B1 (45 and 46). The reduction occurs at positions C22-C23 (highlighted in bold pink) of avermectin B1 (47).

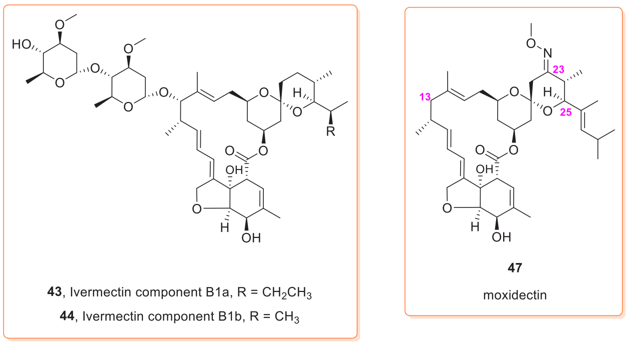


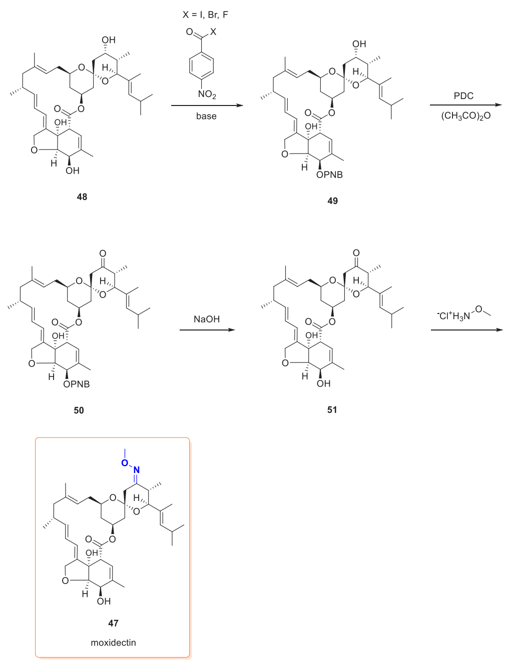
Figure 3. Chemical structures of ivermectin [(B1a, 43) and (B1b, 44)] and of moxidectin (47). The carbon sites in pink highlights the sites where differences exist between the two drugs.

um hydroxide in organic solvents (e.g., toluene, 1,4-dioxane) to yield 51. Eventually, the addition of methoxylamine hydrochloride salt in the presence of sodium acetate gave moxidectin (47). It is worth mentioning that oxidants other than PDC can be used. For example, aluminum t-butoxide and o-benzoquinone; phosphorous pentoxide and dimethyl sulfoxide; chromium trioxide, potassium dichromate; FeBr3 and H_2O_2; dicyclohexylcarbodiimide and dimethyl sulfoxide; manganese dioxide; acetic anhydride and dimethyl sulfoxide; and manganese dioxide are all valid options (58).

The overview of the described, approved antiparasitic drugs for sheep and goats is given in Table 1.

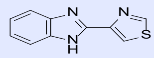
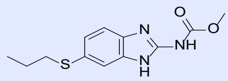
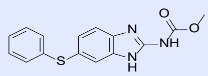
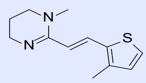
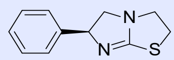
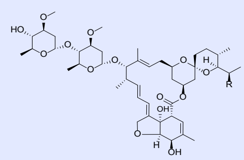
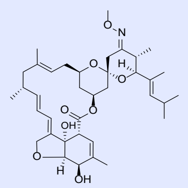
3. OneHealth Paradigm: sheep and goats and the surrounding ecosystem

A variety of zoonotic agents can be transmitted from small ruminants to farmers. These include bacterial, fungal, viral and protozoan. Pathogen transmission can take place through direct contact with the infected animals, although other modes or transmission, e.g., via aerial route, can also occur (59). Among the various infections, brucellosis (Brucella melitensis) is likely the most



Scheme 16. Synthesis of moxidectin (47) starting from nemadectin (48). Methoxyimino group highlighted in blue (58).

Table 1. Names of the active ingredients presented in this work together with their chemical class, chemical structure and their mechanism of action.

Name of active ingredient/ chemical class		Chemical structure	Mechanism of action
thiabendazole	benzimidazoles		Inhibition of fumarate reductase
albendazole			Binding selectively on β-tubulin of nematodes Inhibition of fumarate reductase
fenbendazole			inhibition of microtubule synthesis
morantel	tetrahydropyrimidine		nicotinic acetylcholine receptor (nAChR) agonist
levamisole	imidazothiazole		nicotinic acetylcholine receptor (nAChR) agonist
ivermectin	semisynthetic macrocyclic lactone	 Ivermectin component B1a, R = CH_2CH_3 Ivermectin component B1b, R = CH_3	binding to glutamate-gated chloride channels
moxidectin	semisynthetic macrocyclic lactone		binding to glutamate-gated chloride channels

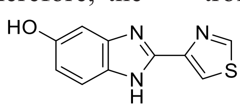
important related to sheep and goats, due to high incidence of human infections (59).

Environment, as well, is part of the One-Health vision. For example, climatic catastrophes, can provide new opportunities for diseases to pass to animals. In turn, animal could spread the disease to human in a sort of vicious cycle (60).

Differently from drugs addressed to humans, antimicrobial agents and antiparasitic drugs for veterinary use are administered to all animals of the same herd or flock for purposes not only of curing infected animals but also of preventing infections and promoting growth. Therefore, the amount consumed could represent a serious burden for environment (61). Antiparasitic drugs are released either intact or as metabolites onto fields or wastewaters, for example.

The impact on the environment of antiparasitic substances depends on the deleterious effect which the agent or its metabolites have on organisms in the place of the excretion, the amount of active agent excreted and the time-stability of the excretion (62).

The commonly used compounds are generally metabolized to some extent either in the gastrointestinal tract or by hepatic metabolism follow-



5-hydroxythiabendazole

Figure 4. Chemical structures of 5-hydroxythiabendazole.

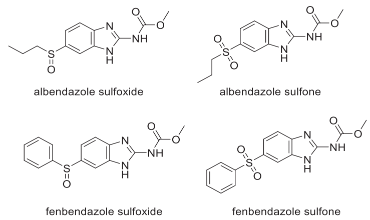


Figure 5. Chemical structures of albendazole sulfoxide, sulphone and of fenbendazole sulfoxide and sulphone.

ing absorption (62).

Into detail, benzimidazoles are poorly soluble in water, but their metabolites are clearly more water-friendly. Short residence times following single oral administration are typical for benzimidazoles (62). For example, thiabendazole is metabolized to 5-hydroxythiabendazole (Figure 4) (63). 5-hydroxythiabendazole is very toxic to aquatic life (64).

Albendazole and fenbendazole are metabolized to sulfoxide and subsequently to sulphone (Figure 5) metabolites. The sulphones have little antiparasitic activity (65, 66). It has been estimated that in sheep and goats up to 50% of an administered dose of fenbendazole is excreted as unmetabolized sulfide (67).

Morantel is quickly metabolized in the liver. After oral administration to cattle and goats (10 mg/kg) morantel cannot be detected in plasma. In lactating goats, morantel is not detectable in the milk (38).

Levamisole is quickly absorbed following oral, subcutaneous or topical administration and is rapidly excreted. It is believed that little metabolism occurs and is largely excreted unchanged in urine (68).

A high ecotoxicological risk has been associated with ivermectin. In particular, ivermectin should be considered a contaminant of high concern due to its potential to affect the survival of aquatic invertebrates as well as its effects on nutrient cycling (69).

Demethylated and hydroxylated ivermectin were the main human *in vivo* metabolite in humans (Figure 6) (70).

A possible solution to overcome ivermectin toxicity could be provided by aqueous micellar formulations for subcutaneous administration with excretory profiles, which would reduce the period of production of contaminated faeces by treated animals (71).

Moxidectin has been shown to be toxic for aquatic invertebrates. A study demonstrate that moxidectin was lethal for amphipod Hyalella curvispina (72) which is often employed in ecotoxicological assessments.

Moreover, despite the scarcity of data on toxicity to freshwater invertebrates, moxidectin strongly binds to organic matter and thereby may be consumed in aquatic food chains (72).

These data, together with the fact majority of infectious diseases that impact human health are zoonotic, represent an alarm and immediate intervention (e.g., accelerated drug discovery projects and care from veterinarians) is needed. Also, novel formulations could be a valid strategy to reduce environmental pollution and the toxicity (e.g., aquatic).

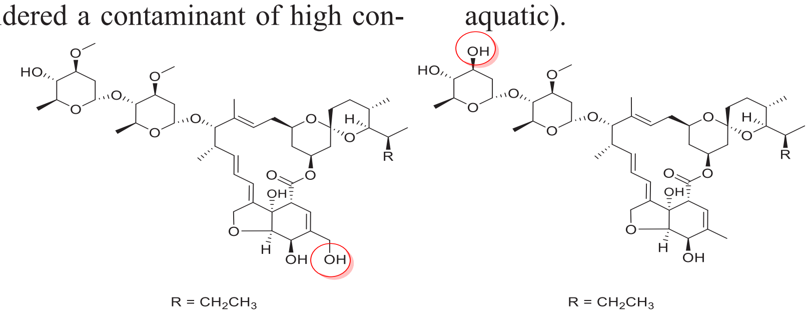


Figure 6. Chemical structures of two main ivermectin metabolites found in humans. Main sites of metabolism (hydroxylation on left side and demethylation on right side) are highlighted in red.

4. Concluding remarks and future outlook

This review describes the recently FDA-approved antiparasitic drugs, focusing especially on the chemical structures and mechanisms of action, for sheep and goats.

The importance of sheep and goats for the world economy is relevant to world economy and is highlighted in this review. Data about ecotoxicology was provided for each of the presented drugs. Alongside the fear for the progressing resistance and environmental hazards, there has been also a spark of optimism; the search for novel compounds has afforded already some successful candidates. A benzimidazole, for example, was found to be really effective *in vivo* against Haemonchus contortus in sheep (73). The wide chemical space will likely allow chemists to find new drug candidates, either belonging to the chemical classes presented herein or, even better in terms of circumventing resistance, to new chemical classes.

Also, drug delivery has provided good results. For instance, dinitroaniline analogues incorporated in liposomes were found as promising means to further improve the antileishmanial activity of those compounds (74). Another recent example describes a statin, pitavastatin, which has been loaded in nanoparticles suitable for ophthalmic administration and designed for the management of *Acanthamoeba keratitis*. Nanoparticles were effective in killing these parasites (75).

Online initiatives, such as webinars (76), are also encouraging farmers to use wisely drugs and to develop deeper relationship with veterinarians.

The chemistry presented in this work should be only one piece of the puzzle that brings together experts from different sectors (chemists, biologists, veterinarians, and ecologists) in order to tackle antiparasitic drug resistance for the health of every organism in a holistic vision.

Overall, the One Health approach relies heavily on the creation and sensible application of antiparasitic medications. We can safeguard human health, animal welfare, and the environment by dealing with parasite illnesses in animals, promoting a holistic and linked approach to health.

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Declaration of Competing Interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Conflict of Interest

The authors declare no conflict of interest.

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