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Perspective

A Structural Analysis of the FDA Green Book-Approved Veterinary Drugs and Roles in Human Medicine

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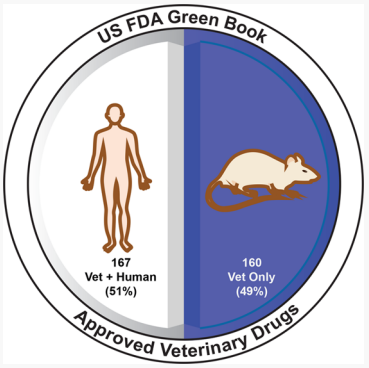
ABSTRACT: The FDA Green Book is a list of all drug products that have been approved by the FDA for use in veterinary medicine. The Green Book, as published, lacks structural information corresponding to approved drugs. To address this gap, we have compiled the structural data for all FDA Green Book drugs approved through the end of 2019. Herein we discuss the relevance of this data set to human drugs in the context of structural classes and physicochemical properties. Analysis reveals that physicochemical properties are highly optimized and consistent with a high probability of favorable drug metabolism and pharmacokinetic properties, including good oral bioavailability for most compounds. We provide a detailed analysis of this data set organized on the basis of structure and function. Slightly over half (51%) of vet drugs are also approved in human medicine. Combination drugs are biologics are also discussed.



INTRODUCTION

Veterinary medicine is an integral part of human life, not only ensuring the health and well-being of our companion animals but also improving agricultural yield and safety and playing a foundational role in drug discovery and development for human medicine. Agricultural medicine is responsible for the health and well-being of over 3 billion livestock and 50 billion poultry worldwide.[1] In 2018 nearly 12 million kg of antibiotics were administered to agricultural animals in the US.[2] In the same year, the global animal medicine market for agricultural and companion animals topped US$33.8 billion.[1] Of this total, 37.7% accounted for veterinary pharmaceuticals and 62.3% accounted for feed additives. The animal drug market has grown from $33.8 billion to $44.2 billion between 2018 and 2020 and is expected to grow to $54.2 billion by 2022. Despite the sizable economic impact of animal medicine, the human market is still over 30 times larger than all animal medicines combined. Drugs on the human market began the approval process based on data showing success in animal models. Although the testing of human drug candidates by treating pathology models in animals is not veterinary medicine, *per se*, veterinarians are responsible for the veterinary care of research animals and oversight of animal husbandry.[3]

Recent events such as the COVID-19 pandemic have emphasized the impact of zoonotic diseases on human health. Zoonotic diseases are passed from animals to humans and vice versa. The similarity between human and animal biology allows us to repurpose drugs from one species to another to treat infections shared across species. For example, nearly all of the antibiotics that are currently used in animals were first employed in humans. Furthermore, antiviral drugs that first showed efficacy in veterinary medicine are currently being investigated as potential drug candidates in humans.[4] On the other hand, the way that we use veterinary pharmaceuticals like antibiotics can also exacerbate the rise of drug resistant microbes, which have the potential to cause serious disease in humans. An understanding of the intersection of human and veterinary medicine can help foster mindfulness in the way in which we employ certain chemical matter and can increase the likelihood of a safe and healthy future.

For over 10 years, our group has been creating new educational and research content using the graphical language of organic chemistry.[5] Our analyses of FDA-approved drugs have highlighted the structural trends of drugs approved for use in humans.[6−10] We have recently taken on the challenge of curating a previously untapped data set of FDA-approved veterinary drugs, and with two data sets in hand, *comparing* structural and physicochemical features of human and veterinary drugs. The FDA states that the Green Book is primarily used by "companies wanting to manufacture and distribute" animal drugs and that it is a resource that can be

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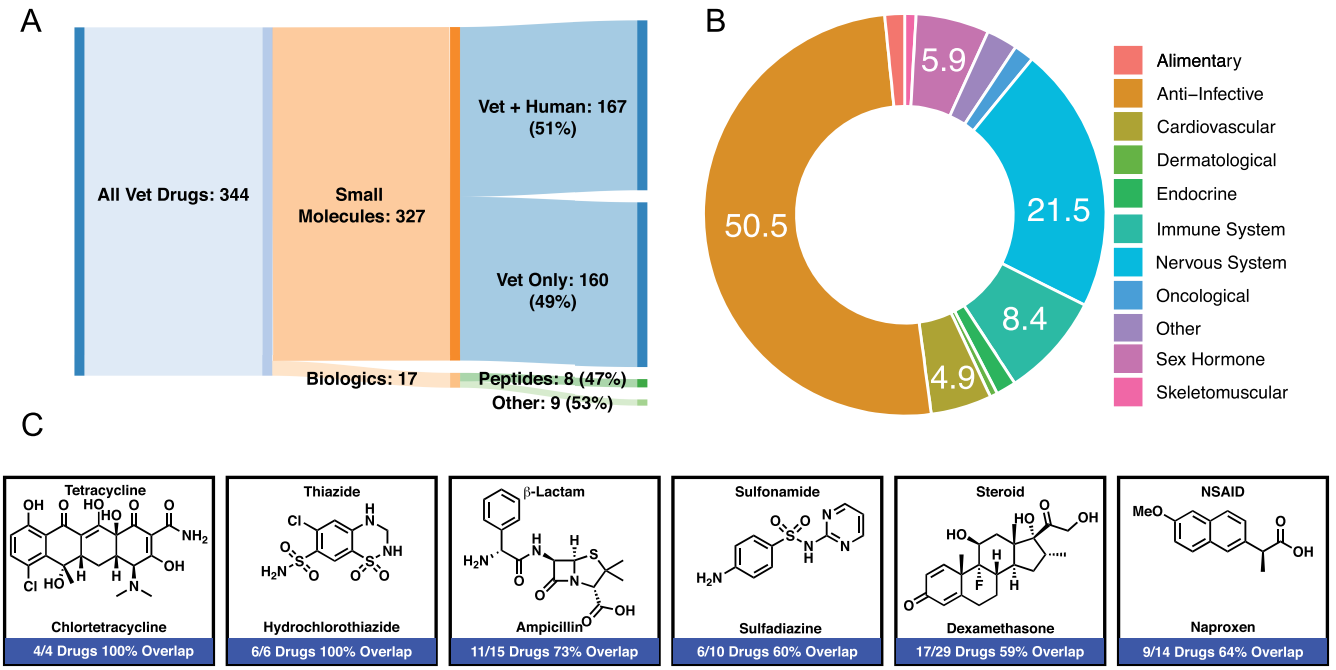

Figure 1. (A) Of the 327 small molecule drugs in the FDA Green Book, 51% are approved for use in animals and humans, and 49% are approved in animals only; 17 of the total vet drugs are biologics, including eight peptides and nine miscellaneous biologics. (B) Over 50% of the drugs in this analysis are anti-infectives, followed by 21.5% for nervous system drugs, 8.4% for immune system drugs, 5.9% for sex hormones, 4.9% for cardiovascular, 1.6% for each oncological, alimentary, and endocrine, 0.9% for skeletomuscular, and 0.6% for dermatological, with 2.5% remaining for other disorders. (C) 100% of chlortetracyclines, 100% of thiazides, 73% of β-lactams, 60% of sulfonamides, 59% of steroids, and 64% of NSAIDs are approved for use in animals are also approved for use in humans, respectively.

used by the public. As a further service to the scientific community and to the public, we have expanded this resource by augmenting the list of drug *names* with the *structures* of each active ingredient. We communicate the structures in a concise graphical format along with descriptions and commentary. This analysis is not intended to provide up-to-date information on veterinary medicine; some applications of drugs may be outdated.

To carry out this analysis, we have curated a brand-new data set that has never been described in structural detail. Through the FDA website, we downloaded an initial list of 2184 entries, which was narrowed to 344 unique entities.[11] The composition of this data set is described in Figure 1, with 327 unique small molecules, 49% of which are approved only for animals and 51% of which are approved for both animals and humans (Figure 1A). Of these compounds, 50.5% are anti-infective drugs (antiparasitic, antibacterial, and antifungal). Drugs active in the central nervous system make up 21.5%, immune system drugs 8.4%, sex hormones 5.9%, cardiovascular 4.9%, oncological, alimentary, and endocrine each 1.6%, skeletomuscular 0.9%, and dermatological 0.6%. Other categories make up 2.5%. In addition to the small molecules, 17 biologic drugs are approved. Some classes of drugs have more overlap between veterinary and animal approvals than others. For example, 100% of the tetracyclines and thiazide diuretics in this review are also approved for use in humans (Figure 1C). The β-lactams share 73% overlap, sulfonamides have 60% overlap, steroids have 59% overlap, and the nonsteroidal anti-inflammatory drugs (NSAIDs) have 64% overlap (Figure 1C). The fluoroquinolones are on the other end of the spectrum with 0% overlap, and of the 17 macrolide antibiotics approved by the FDA, only one (erythromycin) is approved for both animals and humans. Excluded from this data set are inorganic compounds (e.g., potassium chloride (KCl), bismuth subcarbonate ($(BiO)_2CO_3$), and activated attapulgite ($AlMgO_4Si^+$)). Veterinary vaccines are omitted from this analysis because they are regulated by the USDA not the FDA. We note that drugs approved for use in humans can be prescribed for use in companion animals by a veterinarian, although they are not specifically approved for use in animals. Drugs in this category are not covered here. Finally, the "index of legally marketed unapproved new animal drugs for minor species" is covered.[12] This list of 14 unique marketed formulations is narrowed down to eigh unique active ingredients in seven formulations (including three combination formulations). We cover this data set in order to completely cover veterinary drugs, but we treat it as a separate data set from the core analysis because the drugs therein are not explicitly approved by the FDA.

PROPERTY PROFILES OF VETERINARY DRUGS

The criteria employed for the design of human medicines also apply to the development of veterinary medicines. The drug substance still needs to possess good solubility, good permeability, and low metabolic clearance, arguably the three most important properties of successful drugs. There are obvious species differences and considerations to be made for drug metabolism (clearance) and gut absorption (permeability), but solubility is agnostic of species and a fundamental requirement for enhanced developability and probability of success. Physicochemical properties therefore are as important for the development of veterinary medicines as they are for

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human medicines and the principles employed for drug design are essentially the same.[13] In this section, we will assess the overall calculated physicochemical property landscape of veterinary drugs.

All structures were uploaded in AbbVie's internal design platform and a range of important physicochemical properties calculated; see Table 1. Overall, these highly optimized compounds have very good properties consistent with what one would expect for optimized drug-like chemical matter.[14] On average, these drugs are well within the limits of Lipinski's rules, with 72% of these compounds being fully Ro5 compliant (no more than 1 violation), with the largest contributor to failure attributed to molecular weight >500 (67%), then number of H-bond acceptors (NHBA) > 10 (54%), number of H-bond donors (NHBD) > 5 (31%), and cLogP > 5 (22%). In addition to very low cLogP, these compounds have a reasonably high TPSA, suggesting that they have an optimal balance of lipophilicity and hydrophilicity to effect desired permeability, solubility, and metabolism. Moreover, it is known from work by Pfizer that compounds with ClogP < 3 and TPSA > 75 are known to have significantly reduced odds of off-target promiscuity and in vivo toxicity.[15] Clearly, a significant proportion of these drugs pass the so-called Pfizer rule of 3/75, with 43% residing in this area of chemical space, again evidence of the successful optimization to drug candidates. To further assess the drug-likeness of this chemical matter, we calculated composite scoring functions known to indicate the likelihood of good drug-like properties in a multiparametric sense. Thus, the property forecast index (PFI),[16] the quantitative estimate of drug-likeness (QED),[17] and AbbVie's multiparametric scoring function (AB-MPS) were calculated for all compounds.[18] It is known from the work of GSK that compounds with a PFI ≤ 5 have a much higher probability of "developability" than compounds with a PFI > 5.[19] As is evident in the table, these compounds have low PFI with the upper quartile (Q3, 75% of compounds), passing this requirement for developability. If we look further, it is interesting to note that these compounds have a very low aromatic ring count (upper quartile (Q3) and a mean = 1.2). This, in combination with highly optimized and low log *D* (Q3 = 2.9, mean = 0.59), equates to an especially low PFI and therefore a high probability of developability, which we know is the case given that these are approved drugs. The low aromatic ring count contrasts with the mean total number of rings which includes all ring types in addition to aromatic rings. There are approximately twice as many nonaromatic rings, which suggests these types of rings had a positive effect on the overall optimization process.[19] We also conducted a more complex multiparametric assessment of drug-likeness by calculating QED, which takes into consideration eight different properties including structural alerts in its construction. Using Harrington desirability functions, based on the distributions of the properties of 771 drugs, QED was derived. Ultimately, a compound with a QED = 1 will have maximum desirability for all eight properties and any deviation equates to a QED < 1. Therefore, the closer the QED score is to 1, the more drug-like it is based on this set of 771 drugs. For veterinary drugs, the mean QED = 0.6 and Q3 = 0.8, which happens to be identical to the values obtained for the 771 drugs used in the above-mentioned analysis. The QED values therefore are in line with expectations for highly optimized drug-like chemical matter. In addition to PFI and QED, we also calculated AbbVie's AB-MPS. This MP score was derived based on the optimization of oral bioavailability of compounds beyond Rule of Five (i.e., failing the Rule of Five test), but we and others have also shown that this rubric is predictive of both permeability and oral absorption overall. In general, an AB-MPS ≤ 12 is a strong indicator of good permeability and oral absorption. Clearly, this cohort of compounds have low AB-MPS with 75% having an AB-MPS < 11.3, consistent with highly optimized compounds. Undoubtedly these compounds would be expected to have good solubility and ADME properties and good pharmacokinetic properties. This being the case, these properties are observed of the data set as a whole, which include oral and nonoral drugs; the authors do not distinguish between oral and nonoral drugs within this analysis.

Table 1. Statistics of the Physicochemical Property Profiles of Small Molecule Veterinary Drugs[a]

property	median	mean	Q1	Q3	IQR
molecular wt	334.2	397.5	264.3	440.2	175.9
cLogP	1.7	0.49	−1.1	3.2	4.3
log *D*	1.5	0.59	−0.45	2.9	3.35
TPSA	75	98	43	115	72
NHBD	2	2.6	1	3	2
NHBA	5	5.8	3	6	3
NAR	1	1.2	0	2	2
NR	3	2.8	2	4	2
NRB	4	5.6	2	7	5
Fsp^3	0.42	0.46	0.26	0.71	0.45
PFI	2.3	1.8	0.5	4.7	4.2
QED	0.7	0.6	0.4	0.8	0.4
AB-MPS	8	9.8	5.3	11.3	6

[a]cLogP: calculated BioByte log *P*. log *D*: calculated ChemAxon log *D*. TPSA = topological polar surface area (NO only). NHBD = number hydrogen bond donors. NHBA = number hydrogen bond acceptors. NAR = number of aromatic rings. NR = number of rings. NRB = number of rotatable bonds. Fsp^3 = fraction of sp^3 carbons. PF I =property forecast index. QED = quantitative estimate of drug-likeness. AB-MPS = AbbVie multiparametric score. Q1 = lower quartile. Q3 = upper quartile. IQR = interquartile range.

■ ANALYSIS OF 3D DESCRIPTORS AND SHAPE

In the past decade or so, there has been a paradigm shift in drug discovery away from synthesizing drug candidates with limited three dimensionality, due in part to the negative effect that "flatness" has on compound developability.[20] Emphasis has shifted from synthesizing as many compounds as possible, via combinatorial or parallel synthesis, to a situation now where novel chemistries and processes are being developed to purposely introduce 3D motifs into scaffolds and monomers in an effort to improve drug-like properties, particularly solubility.[21] This so-called "escape from flatland" lies as a major initiative for many pharmaceutical companies.[22] One of the reasons for this paradigm shift came out of a realization that a large majority of approved drugs have significant degrees of both saturation and three dimensionality. Indeed, many drugs are highly saturated with the fraction of sp^3 carbons (Fsp3) > 0.5, meaning that half of the carbon atoms are fully saturated. As can be observed in Table 1, veterinary drugs also have an appreciably high degree of Fsp^3 with a mean = 0.46 and Q3 = 0.71, which is consistent with what has been reported for human small molecule drugs. While Fsp^3 is a good descriptor of saturation, and to some degree 3D, it gives no indication of the absolute level of 3D and shape of molecules.

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To determine the level of 3D for these drugs two separate descriptors of 3D, namely the principal moments of inertia (PMI)[23] and plane of best fit score (PBF)[24] were calculated using methods reported in the literature. To qualify and visualize the extent of 3D, we used the method originally described by Firth et al.[24] Thus, we plotted the PBF scores versus the sum of the normalized principal moments of inertia. Using Firth's cut-offs for defining 3D space as ΣNPR > 1.07 and PBF score > 0.6, we calculated that 56% of these drugs sit in what can be considered 3D space by virtue of these two independent descriptors (see Figure 2). It is also possible using

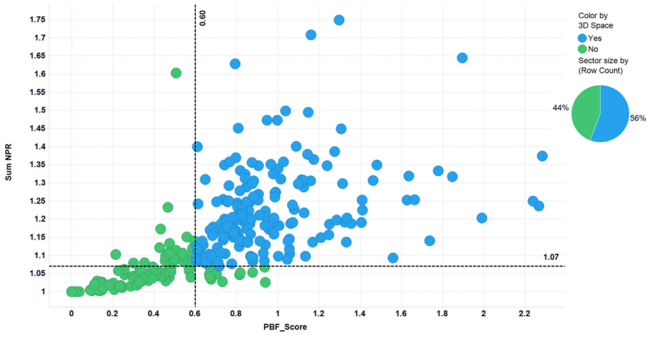

Figure 2. Plot of the sum NPR versus PBF score for vet drugs, 56% occupying 3D space.

calculated PMI values to approximate the shape of a given molecule. By plotting both normalized values of PMI NPR1 and NPR2, it is possible to roughly bin compounds into three different shape-types: namely, rod-like, disc-like, and sphere-like (see Figure 3).

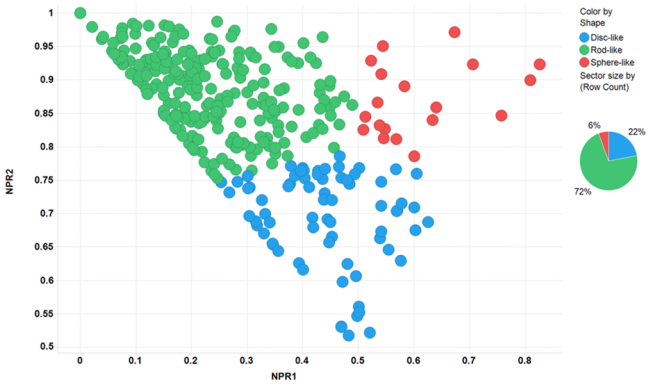

Figure 3. Plot of the normalized PMI for vet drugs with approximations given to shape based on these values.

The majority of veterinary drugs adopt a rod-like shape (73%), which is consistent with what is known for human drugs (68%, see below). Sphere-like shapes have the highest degree of 3D character with respect to PMI and also PBF scores, with all but one having a PBF score >0.6. Note that in order to compare, we calculated the same descriptors for 770 marketed human drugs by employing the same method as above. Both the 3D occupancy (52% for human, 56% for vet drugs) and shape distributions were very similar to veterinary drugs.

In conclusion, veterinary drugs, similarly to human drugs, have very good overall physicochemical properties that are consistent with what you would expect for highly optimized leads and ultimately drugs. Additionally, both the degree of shape and three-dimensionality, calculated using two independent 3D-descriptors, are very similar to human small molecule drugs.

Physiological and Metabolic Differences. It is important to consider that from a drug discovery perspective there are significant important physiological and metabolic differences across species. There are species differences in how xenobiotics are metabolized, (e.g., the canine CYP3A12 is different from the functionally similar human CYP3A4, and rabbits completely lack an analogue of the human CYP2D6, which metabolizes about a third of drugs), so ultimately there is not a one-to-one correlation between pathology and treatment across species.[25] Some natural and synthetic compounds that are safe for humans are known to be severely toxic to animals (e.g., xylitol, caffeine, and sulfur-containing natural products in onions and garlic are toxic to dogs). Furthermore, the gastric pH and gastrointestinal transit times also vary widely across species, and these are important considerations when designing oral drugs. While these topics (among others) are far beyond the scope of this analysis, the authors acknowledge important differences despite significant similarities between drug groups across species.

STRUCTURAL ANALYSIS OF VETERINARY DRUGS

Antiparasitics. Veterinary antiparasitics make up the largest class of drugs in the scope of this analysis, with 64 out of 327 total entities covered. Structures in this group are diverse and varied, ranging from complex natural products to small synthetic molecules. Often, medications from several classes are used in combination with one another in order to tackle infections by different types of parasites and to mitigate parasitic drug resistance.[26] Only eight of the 64 veterinary antiparasitics are approved in humans.

The avermectins and milbemycins (Figure 4) are macrolactone anthelmintics used against nematodes and arthropods. The compounds in this class are used to treat internal parasites, but milbemycin oxime is also effective at treating ectoparasites (an endectocide). All of these compounds are produced by fermentation of *Streptomyces* species. They work by increasing the effects of γ-aminobutyric acid (GABA), which is an inhibitory neurotransmitter, causing flaccid paralysis in parasites. This allows the parasites to be eliminated via excretion. Because these drugs cannot cross the blood–brain barrier of mammals (necessary to act on GABA receptors), the drugs are selective for parasites and can be given safely in large doses. Because of toxicity in calves, ivermectin is sometimes given with picrotoxin, a noncompetitive GABA agonist.[27] Some dog breeds possess a mutation in the ABCB1 gene, which produces a nonfunctional P-glycoprotein, which results in toxicity from macrolactone accumulation when these drugs are administered. Of the six entities in this class, only ivermectin and moxidectin are approved for use in humans. Drug resistance that develops in agriculture is important for human health, and ivermectin-resistant strains of the nodular worm *Esophagostomum dentatum* have been identified in pigs, suggesting that the use of these drugs is driving evolutionary changes.[28]

Ivermectin is semisynthetically derived from avermectin, which is isolated from the actinomycete *Streptomyces avermetilis*. As the name *avermitilis* suggests, ivermectin is used to treat roundworms and hookworms, and the drug is also approved for use in humans. Ivermectin is a mixture of two

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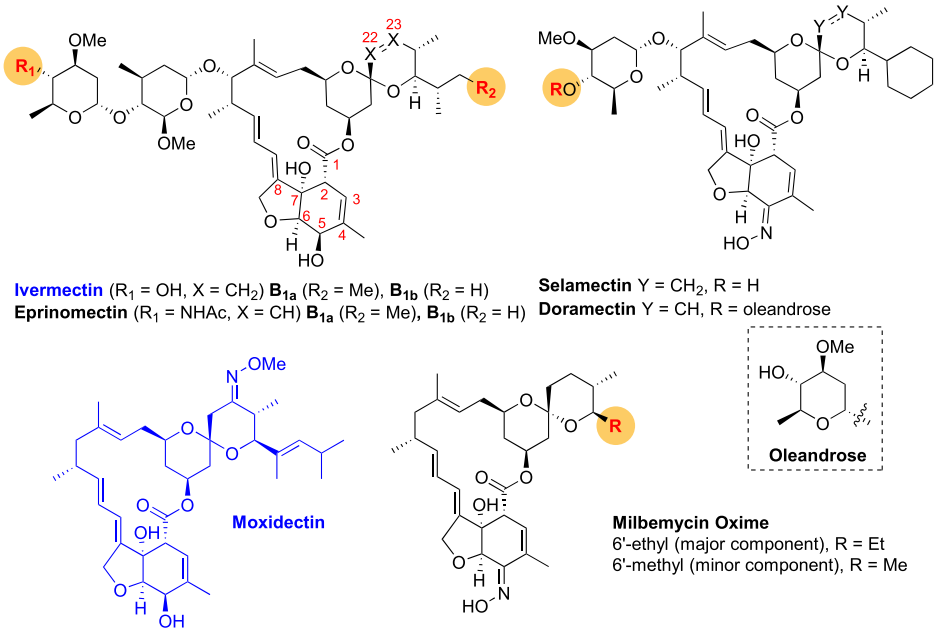

Figure 4. Veterinary antiparasitic natural products (drugs in blue are also approved in humans).

compound: ivermectin B_{1a} and B_{1b}, which only differ by a methyl group in the R_2 position for the former and a hydrogen atom for the latter. This macrolactone is appended by two consecutive L-oleandrose sugars. Eprinomectin, like ivermectin, is a mixture of two compounds, again the difference being a methyl group in the R_2 position. Eprinomectin differs from ivermectin in the presence of a double bond between C22 and C23 in the spiroacetal, and a −NHAc group on the oleandrose moiety, where ivermectin has −OH. Selamectin and doramectin share a high degree of structural similarity with ivermectin and eprinomectin. However, selamectin and doramectin have a cyclohexyl moiety on the spiroacetal rather than a *sec*-butyl or isopropyl, as the previous compounds have. Selamectin has only one oleandrose moiety while doramectin has two, and both compounds have an oxime on the bicyclic core, where ivermectin and eprinomectin have a hydroxyl group. Moxidectin and milbemycin oxime make up the milbemycins. These natural products lack the oleandrose moiety, which is characteristic of the previous compounds. Milbemycin oxime exists as a 7:3 ratio of major to minor products, between which the difference is an ethyl vs a methyl side chain, respectively.

Other Macrocyclic Antiparasitics. Emodepside (Figure 5) is a modern, symmetrical anthelmintic that acts at the neuromuscular junction of nematodes. This compound belongs to a structural class of peptides known as depsipeptides, in which several amide bonds have been replaced with esters. It is of note that all of the nitrogens in emodepside are tertiary, and no N−H bonds are present. Spinosad is a natural product produced by the bacterium *Saccharopolyspora spinosa*, which was originally isolated from sugar cane. The structure contains a 12-membered lactone fused with a tricyclic core, as well as a tri-*O*-methyl-L-rhamnose sugar and a D-forosamine amino sugar. It exists as a mixture of spinosyns A and D, in which the formed has a hydrogen atom at the R group, and the latter has a methyl group. Spinosin A is the major component of the mixture. Spinosad was approved for use in humans in 2011.

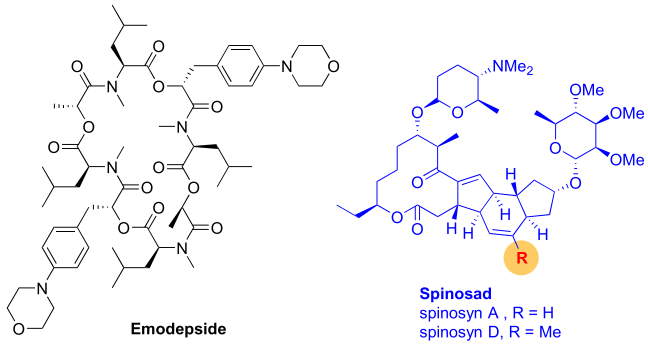

Figure 5. Synthetic and natural veterinary antiparasitics (drugs in blue are also approved in humans).

Phosphonates and Related Compounds. Phosphorthioates and organophosphates are insecticides that work by inhibiting acetylcholinesterase and pseudocholinesterase, causing paralysis (this allows the parasites to be eliminated via excretion). When these enzymes function naturally, during the hydrolysis of acetylcholine, the active-site serine is acetylated before the acetyl group leaves as acetic acid. However, when an organophosphate binds to the active site of the same enzyme, the serine residue is phosphorylated instead of acetylated, resulting in a highly stable state through which the enzyme is deactivated, in some cases reversibly.[29] A number of these pesticides have been approved by the FDA for use in animals and are depicted in Figure 6. Phosphorthioates are metabolized into their active organophosphate form by P450 enzymes, which convert the P═S bond into a P═O bond.[30,31] Humans and animals have acetylcholinesterases similar to those found in invertebrates and can experience sometimes fatal toxicity resulting from exposure to these compounds.

Trichlorfon and dichlorvos are separately approved entities, although trichlorfon is also a prodrug for dichlorvos and undergoes a dehalogenation/rearrangement under aqueous conditions (e.g., physiological conditions). Coumaphos and haloxon are both anthelmintic coumarin derivatives that bear a phosphorthioate and a phosphate ester at C7. Coumaphos is

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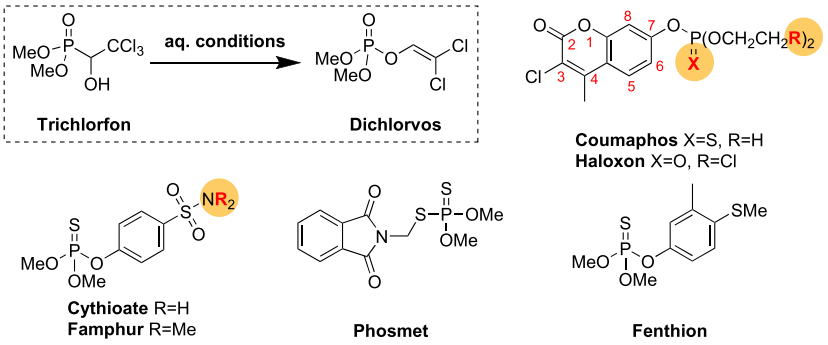

Figure 6. Veterinary phosphates, phosphonates, and thiophosphates to treat parasitic infections (drugs in blue are also approved in humans).

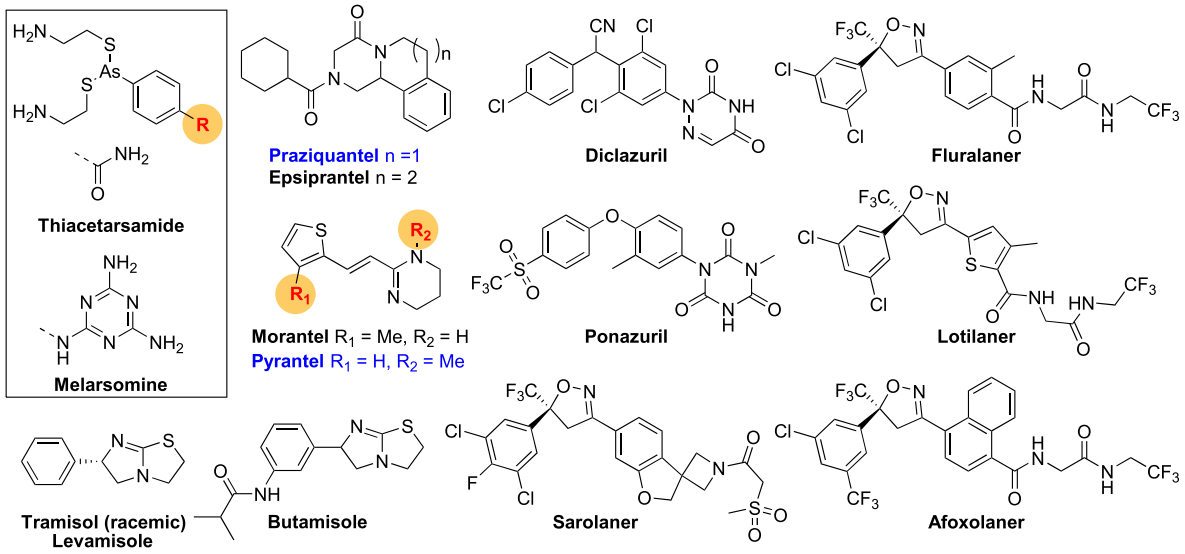

Figure 7. Miscellaneous veterinary antiparasitics (drugs in blue are also approved in humans).

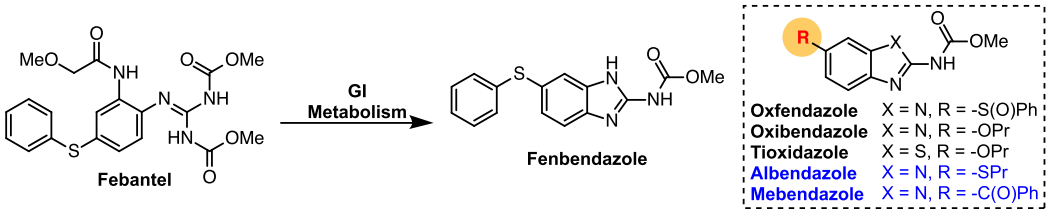

Figure 8. Veterinary antiparasitic benzimidazoles (drugs in blue are also approved in humans).

used to treat ticks in cattle, particularly those coming to the U.S. by land border, by dipping the animals into a solution of the compound. Phosmet is unique in this group in its phenylmaleimide and dithiophosphate moieties. It is used externally to treat fleas and ticks in dogs and as an insecticide in plant crops. Famphur and cythioate are used to kill fleas and ticks but have been shown to cause inadvertent toxicity in birds. The structures differ only in the alkyl groups on the sulfonamide. Fenthion shares structural similarity with the previous two compounds, with differences on the tolyl ring, including a thioether in place of a sulfonamide. The thioether (−SMe) becomes oxidized to the sulfoxide (−S(O)Me) *in vivo*, giving a chiral structure, and Gadepalli and co-workers have shown that the *R* enantiomer is nearly 20 times more active than the *S* enantiomer.[32]

Miscellaneous Antiparasitics I. Two drugs in this analysis contain arsenic: thiacetarsemide and melarsomine (Figure 7). Thiacetarsemide can be nephro- and hepatotoxic. Melarsomine toxicity can be reversed with dimercaprol. Both drugs have been used to treat heartworm (*Dirofilaria immitis*). Fluralaner, lotilaner, afoxolaner, and sarolaner are isoxazolines that are commonly used to prevent fleas and ticks in dogs. The mechanism of action of these compounds works through selectively inhibiting γ-butyric acid- and glutamate-gated chloride channels in arthropods.[33] Praziquantel and Epsiprantel are used to treat cestodes and work by increasing calcium permeability.[34] This prevents larvae from growing or reproducing. Praziquantel is also approved for use in humans to treat a number of parasitic worm infections. The "azuril" drugs are used as coccidiostats in a variety of species including chickens, horses, and lambs.[35,36] Both drugs can also be used as antiprotazoals in small animal medicine. Tramisol is effective against gastrointestinal and pulmonary parasites. First approved as a racemic mixture, it was later approved as the pure active isomer, levamisole. Butamisole is a closely related analogue. Tramisole, levamisole, and butamisole have chol-

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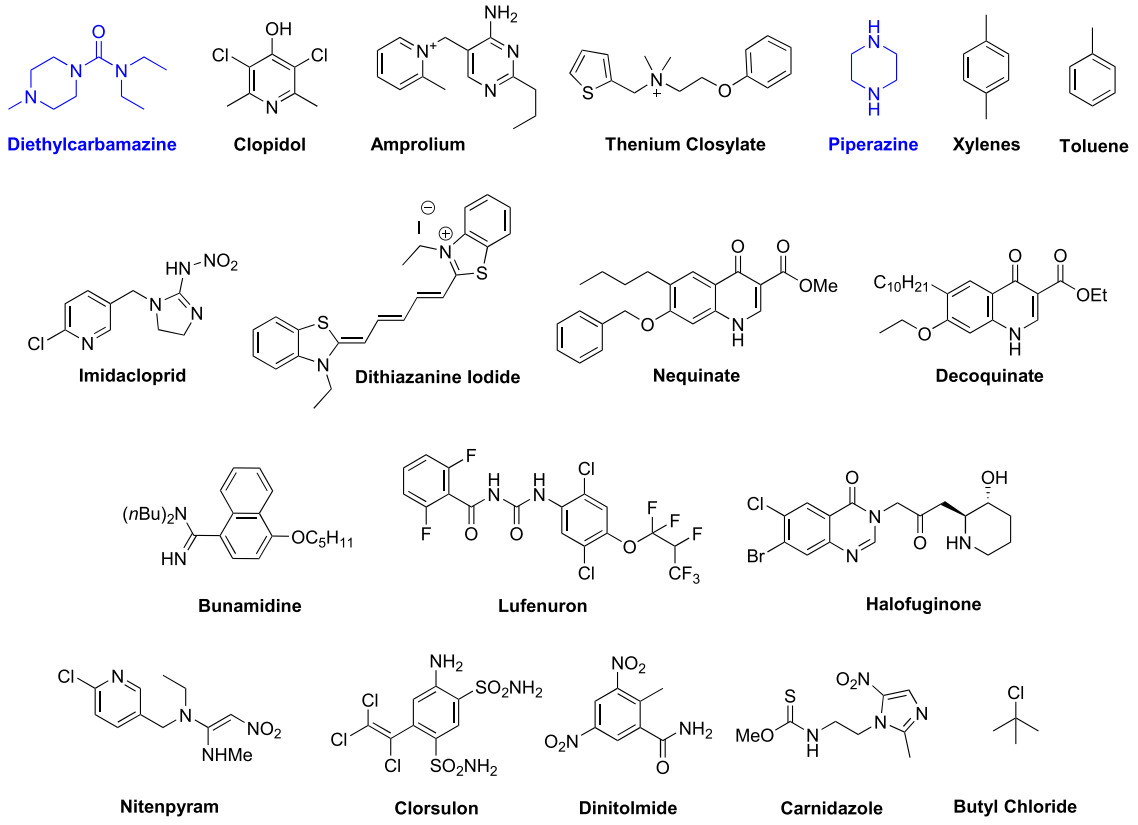

Figure 9. Diverse miscellaneous veterinary antiparasitics (drugs in blue are also approved in humans).

inergic activity that causes paralysis in nematodes and can cause toxicity in animals. Pyrantel and morantel are both anthelmintics of the tetrahydropyrimidine class and are used to treat pinworms, hookworms, and other parasites. Pyrantel and morantel are both L-type agonists, and pyrantel has 2 orders of magnitude higher binding affinity than acetylcholine. Oxantel (not shown, not approved), like nicotine and methyridine, is an N-type agonist.

Benzimidazole and Probenzimidazoles. Benzimidazole anthelmintics (Figure 8) were discovered in the 1960s and are used to treat roundworms, hookworms, whipworms, giardia, and some tapeworms. Benzimidazoles bind to β-tubulin with an affinity up to several hundred-fold higher in nematodes than in mammals. This prevents tubulin polymerization and leads to death. These compounds also bind to mammalian tubulin but are not toxic to the host, presumably due to differing pharmacokinetics. An alternative hypothesis for benzimidazole activity is that benzimidazoles bind to fumarate reductase, which results in uncoupling of oxidative phosphorylation in helminths. Febantel is a probenzimidazole which is metabolized into fenbendazole in the gastrointestinal (GI) tract.[37] All of these compounds have a high degree of structural similarity, with only the R group differing between various ethers, thioethers, phenylsulfoxide, or phenylketone and the X group being either nitrogen or sulfur. Two of these compounds, albendazole and mebendazole, have been approved for use in humans.

Miscellaneous Antiparasitics II. Nitrogen-containing heterocycles, amino groups, and nitro groups are highly represented in this group of compounds (Figure 9). The compounds in this category do not fit neatly into any other structural class and are used here to highlight the structural diversity of antiparasitic compounds. Piperazine and the related compound diethylcarbamazine are both approved for use in humans. Both of these compounds have been used for medicinal purposes since the mid-20th century. Piperazine works via GABA-ergic activity in parasites, and diethylcarbamazine disrupts the arachidonic acid biosynthesis pathway. Nitenpyram is a neonicotinoid compound. Thenium is a nicotinic receptor agonist.[34] Imadocloprid is a neonicotinoid that is neurotoxic to insects. Dithiazanine iodide is used in dogs to treat certain types of worm infections. Nequinate is a 4-hydroxy hydroquinolone antiprotazoan used as a coccidiostat in poultry and small animals. Decoquinate is structurally related to nequinate and is used to treat tapeworms in small animals. Bunamidine is used to treat tapeworms in small animals. Lefenuron inhibits the synthesis of chitin and is used to prevent fleas and ticks in small animals. Halofuginone is a coccidiostat derived from the natural product febrifugine, which has been used in Chinese medicine and is found in the plant *Dichroa febrifuga*. Butyl chloride is given orally to treat tapeworms in dogs and cats. Nitenpyram is a neonicotinoid that is neurotoxic to insects and is used in veterinary medicine as an antiparasitic. Chlorsulon inhibits phosphoglycerate kinase and phosphoglycerate mutase by mimicking 1,3-diphosphoglycerate.[34] Dinitolmide is used as a feed additive as a coccidiostat for poultry. Carnidazole is a nitroimidazole used as an antiprotazoal to treat *Trichomonas* infection.

Other Insecticides. The urea-derived antiparasitic drugs nicarbazin and imidocarb (Figure 10) are used to treat coccidia and protozoal infections in poultry and mammalian food animals, respectively.[38] Nicarbazin is a dinitrocarbanilide (or *N*,*N*′-diarylurea), which is formulated in complex with 2-hydroxy-4,6-dimethylpyramidine (not shown). While this

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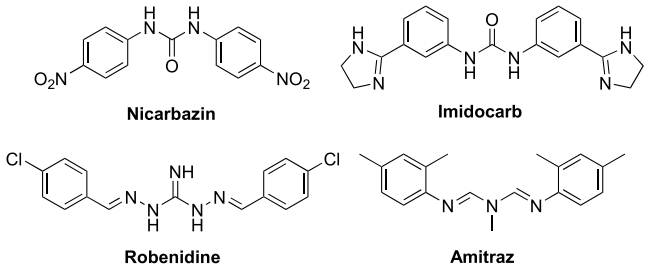

Figure 10. Structurally similar veterinary antiparasitics.

complexing agent has no activity on its own, this specific agent is important for absorption. Complexes with alternatives exhibited less potency. Robenidine is used in poultry feed to control coccidia and is often used in rotation with other coccidiostats to avoid drug resistance. Amitraz is an insecticide and acaricide, which likely works by binding to octopamine receptors in the target parasite.[39]

Antibiotics. The antibiotics group has the greatest overlap in the number of human approvals, and the use of veterinary antibiotics have the greatest impact (direct and indirect) on human health, so a few words of introduction are appropriate. Humans and animals are susceptible to similar bacterial infections, so it may come as no surprise and veterinary antibiotics largely resemble those of human antibiotics and that many of the entities in this section are approved for use in both humans and animals. Antibiotics and synthetic antimicrobials are used in agriculture to prevent infection, treat illness, and ensure maximal growth in livestock. However, the large-scale use of antibiotics in food animals serves as an evolutionary pressure for microbes to develop resistance against the same antibiotics that humans rely on to combat infection. Antibiotic resistance is a major concern to humans, and the use of human antibiotics in agriculture exacerbates the problem.[40] In 2018, nearly 12 million kg of antibiotics were used in agriculture in the U.S., down from an all-time high of nearly 16 million kg in 2015.[2] Concerns over antibiotic resistance have led to a 30% decrease in medically important antibiotic use in agriculture in the U.S. between the years of 2015 and 2019. The medically important antibiotics are ones that are commonly used in human medicine in life-threatening situations. Antibiotic resistance to these drugs could be disastrous to human health. With or without the use of agricultural antibiotics, resistant strains of pathogenic bacteria are becoming more common and cause serious problems for humans. Therefore, we often look to new classes of antibiotics that human pathogens may never have encountered. Polyethers are one class of veterinary drugs which may someday be repurposed for use in the clinic to treat multidrug resistant infections. Excessive use of antibiotics in human health and agriculture is also contributing to the mass extinction of bacterial species that are important to our well-being as constituents of our microbiomes.[41,42] This is perhaps a lesser known problem than that of drug-resistant microbes but one of equal or greater impact.

Polyethers. Polyether antibiotics are the only structural class in this section that has no counterparts approved for use in humans. Also called ionophores, they are used in animal feed as coccidiostats for poultry. In 2018, polyether antibiotics made up 82% of the "not medically important" antibiotics sold and 39% of all antibiotics sold for agricultural use at just over 4.5 million kg. Polyether antibiotics are effective against Gram-positive bacteria (as well as most animal cells), fungi, parasites (coccidia), viruses, and some tumor cell lines. They work by perturbing the ion gradient maintained by the cell membrane through a number of different mechanisms. Although these compounds kill bacterial cells at much lower concentrations than those needed to kill eukaryotes, their promiscuous activity may be the reason why none of these compounds have been approved for use in humans. Polyether antibiotics are natural products isolated mostly from *Streptomyces* species, and some fungi can also produce compounds with similar structures. Many more of these compounds have been described and studied, and only a small subset have been used medically. Their complex structures make them attractive and challenging targets for synthetic chemists, and great efforts have been put forth to complete numerous total syntheses.[43] The polyether antibiotics depicted in Figure 11 all contain a carboxylic acid moiety. The negative charge that this imparts is important for the molecules' orientation within the cell wall. Semduramicin and maduramicin are produced by fermentation of *Actinomadura* species.[44,45] Monensin, narasin, and salinomycin are

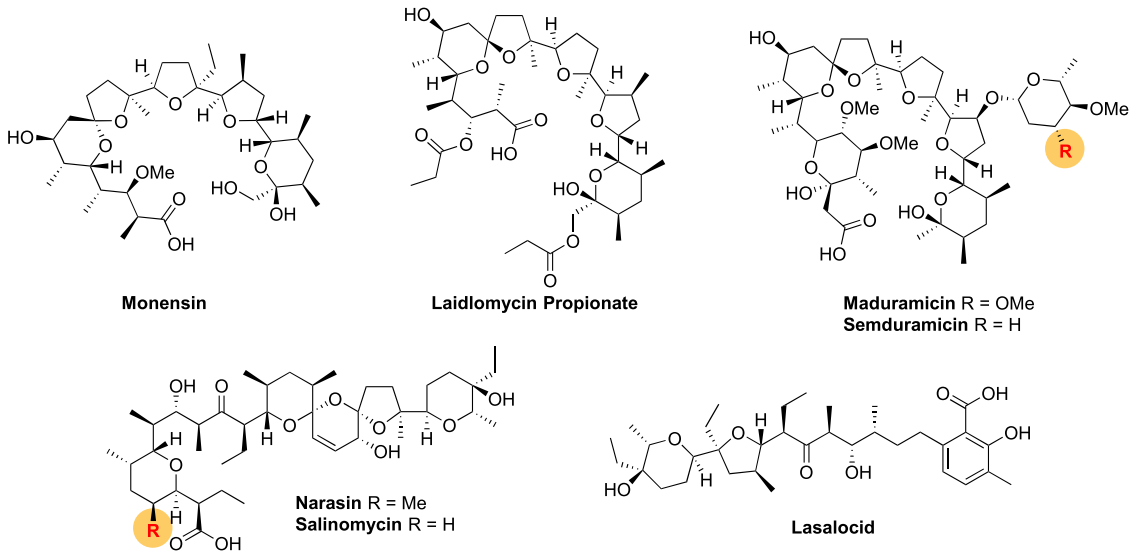

Figure 11. Polyether antibiotics or ionophores.

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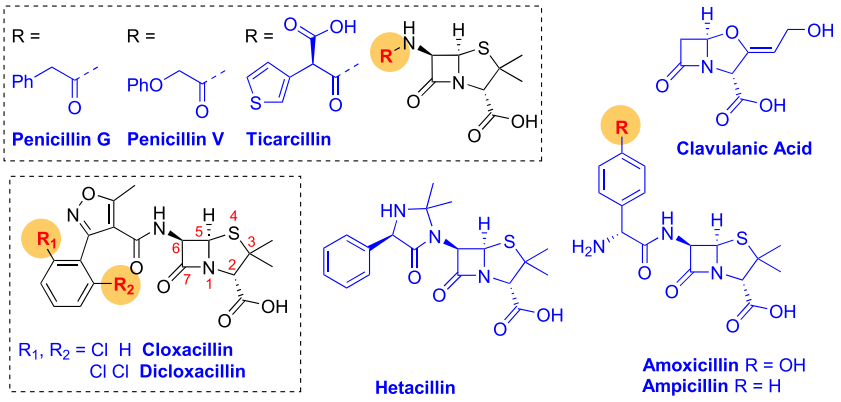

Figure 12. Penam antibiotics (all of these drugs are also approved in humans).

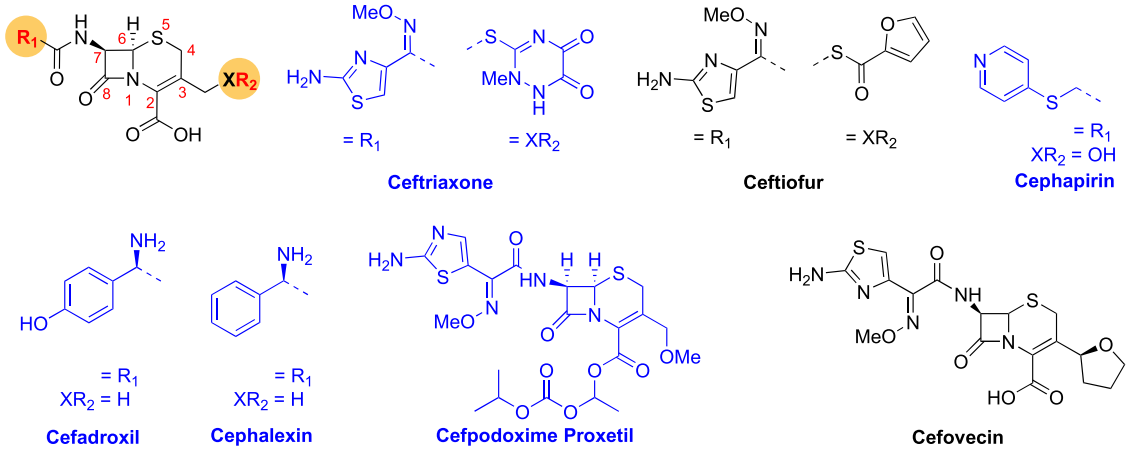

Figure 13. Cephem antibiotics (drugs in blue are also approved in humans).

common in agriculture and are common active ingredients in many of the combination drugs discussed below.

***β*-Lactams.** The discovery of penicillin in the 1930s ushered in one of the most successful groups of antibiotics: the *β*-lactams. Their success in human medicine was mirrored in agriculture, and these compounds still represent the second most used class of antibiotics by mass after tetracyclines (over 730 000 kg for penicillins and over 30 000 kg for cephalosporins in 2018). The *β*-lactams approved for use in medicine include penams, including penicillins (Figure 12) and cephems, including cephalosporins (Figure 13). The extensive use of these drugs combined with initially inappropriate dosing has contributed to the growing problem of resistant strains, notably methicillin resistant *Staphylococcus aureus* (MRSA).[46,47] Of the 15 compounds in this group, only two (ceftiofur and cefovecin) have not been approved for use in humans, although a handful have been withdrawn from the human market. The *β*-lactam antibiotics work by inhibiting penicillin-binding proteins (PBPs), which are critical for the final stages of peptidoglycan synthesis during bacterial cell-wall formation. These compounds are therefore bactericidal only in dividing cells. *β*-Lactamase enzymes represent the major resistance mechanism that bacteria possess. These enzymes open the *β*-lactam ring, rendering the compound incapable of inhibiting PBPs. These drugs are sometimes given in combination with clavulanic acid, which is not an antibiotic but works as a *β*-lactamase inhibitor to increase efficacy of the drug.

Penams. The penicillins (which are penams, Figure 12) were the first *β*-lactams to be discovered in the late 1920s. after *Penicillium* mold was observed to inhibit the growth of staphylococci on agar plates. When culturing some of these molds, different isolates bore varying side chains in the 6-position, and it was discovered that the identity of these side chains could be controlled by adding various organic acids to the growth media. For example, adding phenylacetic acid gave penicillin G, and adding phenoxyacetic acid gave penicillin V (see side chains in Figure 12). When the growth medium contains no side chain precursor, the isolated compound is 6-aminopenicillic acid (6-APA), which is not a potent antibacterial, although it serves as a precursor to many other derivatives. Some penicillins are readily hydrolyzed by gastric acids but can be administered by injection. Penicillin V is orally bioavailable and is approved as an oral drug.[46] Clavulanic acid is a *β*-lactamase inhibitor which has no antibacterial activity on its own but confers efficacy of *β*-lactam antibiotics by preventing resistance. Other *β*-lactamase inhibitors (like sulbactam and tazobactam) are approved in humans but not for animals.

Cephems. The cephem class of drugs is made up of cephaolosporins and cephamycins. All of the cephems in this review are cephalosporins. The first cephalosporins to be discovered were isolated from *Cephalosporium* species (now called *Acremonium*) in 1945 and were brought to the market some two decades later. While penams could not effectively penetrate the cell wall of Gram-negative bacteria, cephems showed activity against a number of these species.

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Furthermore, many of the β-lactamase enzymes that conferred resistance to penicillins were inactive against cephems.[46] The substituent in the XR_2 position has turned out to be an important factor in resistance to degradation by β-lactamases. In the ring-opening event, this group acts as a leaving group, and the poorer the leaving group the more stable the compound. The cephems in Figure 13 share a high degree of structural similarity and differ only in the R_1 and XR_2 moieties (cefpodoxime proxetil also has an esterified carboxylate). Four out of the seven cephems have an oxime appended with an aminothiazole moiety in the R_1 position.

Tetracyclines. The tetracyclines are the most commonly used antibiotics in agriculture, with over 3.9 million kilograms used in the U.S. in 2018. All four of the compounds in this section (Figure 14) are also approved for use in humans, so

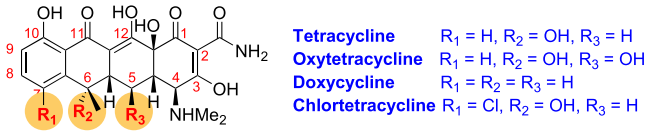

Figure 14. Tetracycline antibiotics (all of these drugs are also approved in humans).

their use in feed animals is of medical importance. Their use in agriculture peaked in 2015 and has since declined by nearly 50% due to consumer concerns about food quality and antibiotic resistance. As a point of contrast, the use of ionophores (which are not of medical importance) have dropped by less than 4% over the same time. Tetracyclines were one of the first broad spectrum antibiotics discovered and are active against both Gram positive and Gram negative bacteria.[48] The first generation of tetracyclines was isolated from *Streptomyces* species, but synthetic and semisynthetic techniques have given rise to second- and third-generation compounds, including glycyclines (not shown, not approved).[49] Tetracycines work by inhibiting protein synthesis by binding to the 16S RNA and S7 protein subunits of the 30S ribosome, preventing aminoacylated tRNA from coordinating with the ribosome. This causes bacteriostasis and eventually leads to bacterial cell death. The ketone at C1, the amide at C2, and the enol at C3 are required for antibiotic activity.[48] The substituents at C5−C7 affect solubility, and multivalent cations like calcium are chelated by the β-keto−enol at C11 and C12. Under physiological conditions, these compounds are zwitterionic and the net charge of zero aids in cell-wall permeability.

Sulfas. Sulfonamides were discovered to have antimicrobial activity when Bayer Laboratories investigated the diazo dye prontosil rubrum, even before penicillin was known. Liver metabolites of the dye in mice would evolve into the biologically active compounds that are sulfonamide antimicrobials. Sulfonamides, shown in Figure 15, work by disrupting the synthesis of folic acid.[50] The compounds bind to dihydropteroate synthase, competing with *para*-aminobenzoic acid (PABA), thereby preventing the addition of PABA to the folic acid molecule. This disruption results in bacteriostasis. Because humans and other animals receive dietary folic acid, but bacteria depend on biosynthesis, these drugs are selective for bacteria. Sulfa drugs make up 5% of antimicrobials used in agriculture, and nearly 300 000 kg were used in the U.S. in 2018. Sulfonamides are effective against Gram-positive and Gram-negative bacteria, protozoans, and toxoplasma. However, antimicrobial resistance has increased since the discovery of this class of compounds, potentially diminishing its value in medicine. Resistance mechanisms include reduced cell wall permeability, mutated dihydropteroate synthase, and/or increased production of PABA. Resistance is sometimes mitigated by coadministering sulfonamides with diaminopyrimidines like trimethoprim (depicted in Figure 21). Trimethoprim, like other diaminopyrimidines, also disrupts the folic acid biosynthesis pathway, but it works by inhibiting dihydrofolate reductase rather than dihydropteroate synthase. This prevents the reduction of dihydrofolate to tetrahydrofolate. When sulfonamides are used in combination with trimethoprim, a synergistic effect is observed, and chances of successful mutation conferring resistance to the pathogen are drastically reduced. Trimethoprim and other diaminopyrimidines will be discussed in greater detail in the "Miscellaneous Antimicrobials II" section.

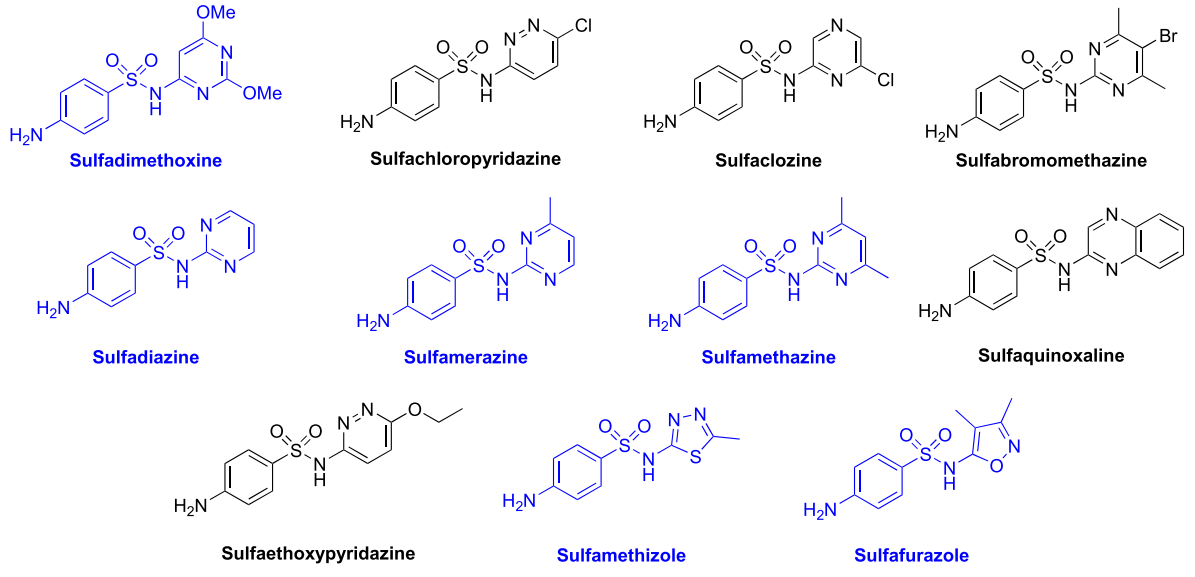

Figure 15. Sulfonamide antimicrobials (drugs in blue are also approved in humans).

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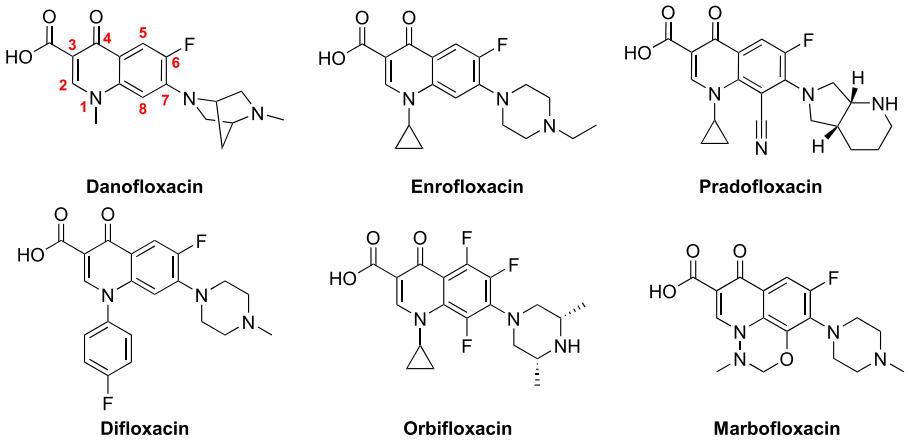

Figure 16. Fluoroquinolone antimicrobials.

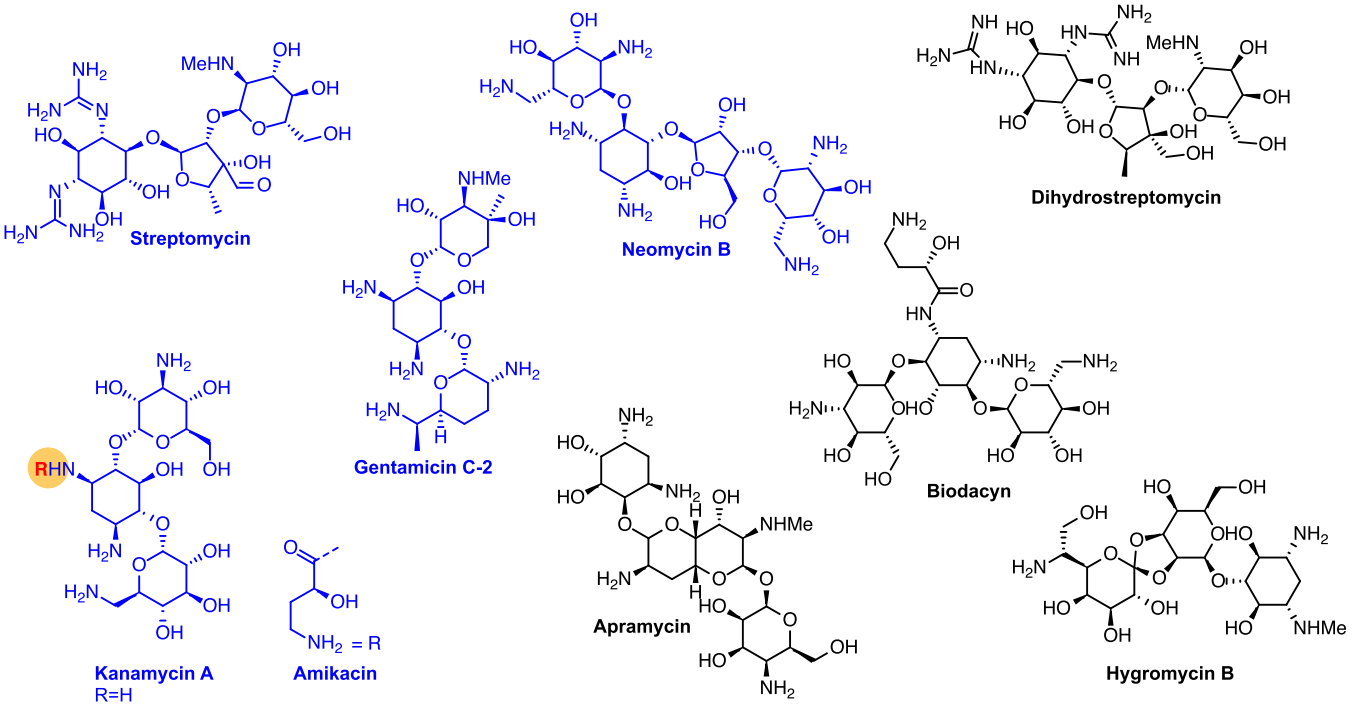

Figure 17. Aminoglycoside antibiotics (drugs in blue are also approved in humans).

Fluoroquinolones. Fluoroquinolones target DNA gyrase in bacteria, preventing chromosomal DNA from supercoiling, ultimately leading to cell death.[51] These compounds are effective against Gram-negative bacteria, mycoplasma, and a few Gram-positive bacteria. Fluoroquinolones are synthetic antibacterial drugs derived from nalidixic acid. Early analogues had solubility and potency issues, which were ultimately overcome by reducing the number of nitrogen atoms in the bicyclic core from two (like nalidixic acid) to one (resulting in the quinolone) and adding a fluorine to C6, leading to the hallmark core of these compounds (Figure 16).[52] The fluorine atom alone led to greater solubility, efficacy against Gram-negative bacteria, and greater cell-wall penetration. These drugs are widely known in both fields for their serious side effects, including phototoxicity and gastrointestinal toxicity as well as neurotoxicity at higher doses.[51] Cats are uniquely susceptible due to ABCG2 blood−retinal barrier protein transporter failure, which causes fluoroquinolones to build up in the eye, causing phototoxicity.[53] Curiously, fluoroquinolones are the only group of drugs in this review that are orthogonally approved in human and veterinary medicine. That is, all structures approved for use in animals are not approved for use in humans and vice versa. The reason for this is unclear. However, it the authors note that when comparing the structures of human and veterinary fluoroquinolones ($n = 6$ and $n = 10$, respectively), the veterinary data set on average has a 4.6% higher molecular weight, 8.7% lower topological polar surface area, 3.1% higher cLogP, 42.9% fewer hydrogen bond donors, and 2.2% more hydrogen bond acceptors. While it is not clear whether these parameters make a difference in oral biovailability across species, the differences in physicochemical properties are conspicuous. The SwissADME web tool was used to determine these parameters.[54]

Aminoglycosides. Aminoglycoside antibiotics (Figure 17) are natural products that exhibit excellent bactericidal activity against Gram-negative bacteria and staphylococci and are isolated from *Streptomyces* species.[55] Streptomycin was first in class and was approved for use in humans by the FDA in 1946.

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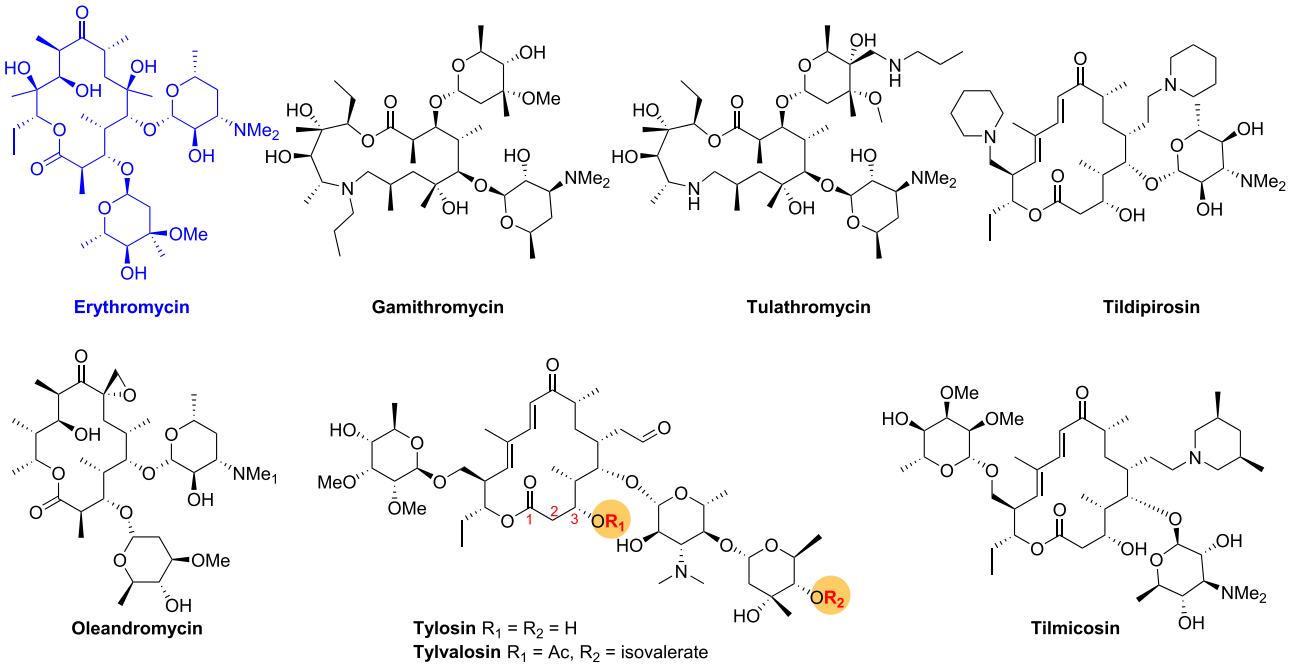

Figure 18. Macrolide antibiotics (drugs in blue are also approved in humans).

This class of drugs made up 5% of medically important antibiotics used in agricultural in the U.S. in 2018 at nearly 300 000 kg. Aminoglycosides can be potentiated by coadministering an antibiotic that disrupts cell-wall synthesis, like the β-lactams. The mechanism by which aminoglycosides cause bacterial death is by binding to the 30S subunit of the ribosome, causing misreading and therefore halting normal protein biosynthesis. The cell wall is subsequently compromised, allowing more of the antibiotic to enter the cell, eventually leading to cell death. Aminoglycoside uptake by Gram-negative species is oxygen-dependent, and therefore these drugs are not effective under anaerobic conditions. Pathogenic bacteria can develop resistance via a number of enzymes that modify aminoglycosides. These enzymes can be classified as phosphotransferases, acetyltransferases, and adenyltransferases, which modify the antibiotics at the amines or the alcohols to prevent them from binding to the ribosome.[55] This resistance mechanism is plasmid mediated and therefore can be exchanged between bacteria. Other resistance mechanisms include reduced cell-wall permeability and reduced aminoglycoside uptake. Streptomycin, neomycin B, and dihydrostreptomycin all consist of a highly substituted central furanose appended with one pyranose and one substituted cyclohexane. Neomycin has an additional pyranose appended to the cyclohexane, which the other two structures do not have. Gentamicin C-2, amikacin, kanamycin A, and biodacin consist of the same 4,6-diamino-2,3,4-cyclohexanetriol, appended with two pyranose moieties. Kanamycin is isolated from *Streptomyces kanamyceticus*, and kanamycin A is a semisynthetic derivative thereof, in which the R group is removed from the amine. Hygromycin B has an intriguing and unique structure within this group, in that the central pyranose forms an acetal, which is fused with the adjacent pyranose through a highly oxidized spiro center. Hygromycin B is produced by *Streptomyces hygroscopicus* and is used primarily as an anthelmintic in chicken feed. Apramycin, also known as nebramycin II, also has a unique structure in its central fused dipyran ring. It is produced by *Streptomyces tenebarius* and is effective against *Escherichia coli*, *Klebsiella*, and *Pseudomonas* strains.[56] Five out of the nine aminoglycosides in Figure 15 are approved in humans and animals (shown in blue) and four are only approved for veterinary medicine (shown in black). An additional three (tobramycin, netimicin, and paromomycin) are approved in humans only (not shown here).

Macrolides. Macrolide antibiotics consist of 14, 15, or 16-membered lactone rings appended with various glycosides (Figure 18). The 16-membered species are widely used in veterinary medicine and are absent from human medicine. The 14-membered erythromycin is the only drug in this group that is approved for human use. Macrolides are one of the most commonly used antibiotics in agriculture, with nearly 475 000 kg used in the U.S. in 2018. Most of these macrolides bind to the 50S ribosome and cause premature termination of polypeptide strands, leading to bacteriostasis.[57] Resistance can occur through efflux, enzymatic deactivation of the macrolides, or RNA methylation.[58] Enzymatic deactivation works through two identified esterases and six identified phosphorylases. The RNA methylation mechanism also confers resistance to lincosamides and streptogramin B. Many macrolides deactivate cytochrome P450 enzymes, requiring increased doses of coadministered drugs that rely on CYP3A activation. Gamithromycin and tulathromycin are unique in that they contain a nitrogen atom within the macrocyclic ring. Oleandromycin is isolated from *Streptomyces antibioticus* and is structurally similar to erythromycin, with the two having been discovered around the same time. Unique structural features of oleandromycin include an α-oxirane, and an oleandrose sugar moiety, which is also common in the avermectins covered earlier in this analysis (see Figure 2). Tylosin is one of the most frequently used drugs in combination with other drugs. It appears together with at least one of the following in unique combinations: melengestrol, ractopamine, monensin, zilpaterol, salinomycin, and pyrantel. Tylvalosin is structurally very similar to tylosin, except for an acetate ester at C3 and an isovalerate ester on the terminal glycoside. Tilmicosin is a semisynthetic macrolide

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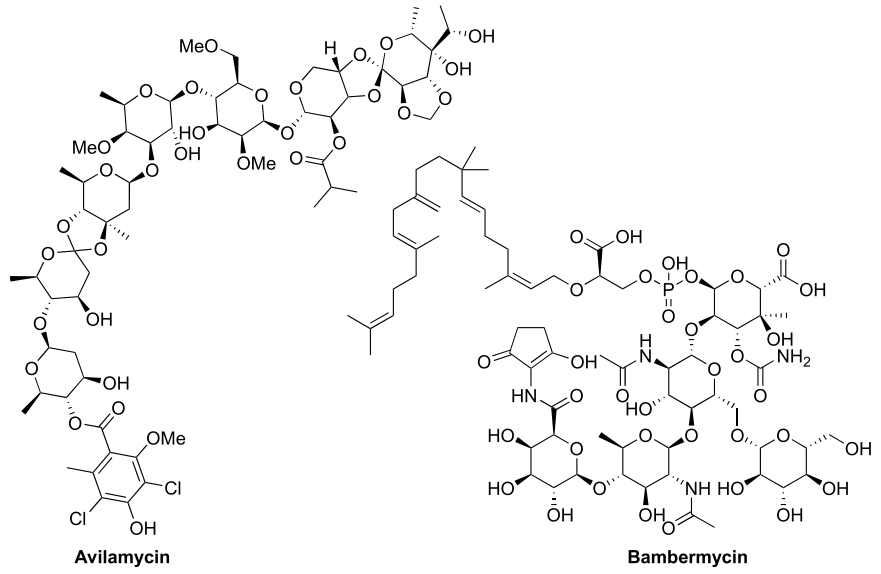

Figure 19. Miscellaneous natural product antibiotics.

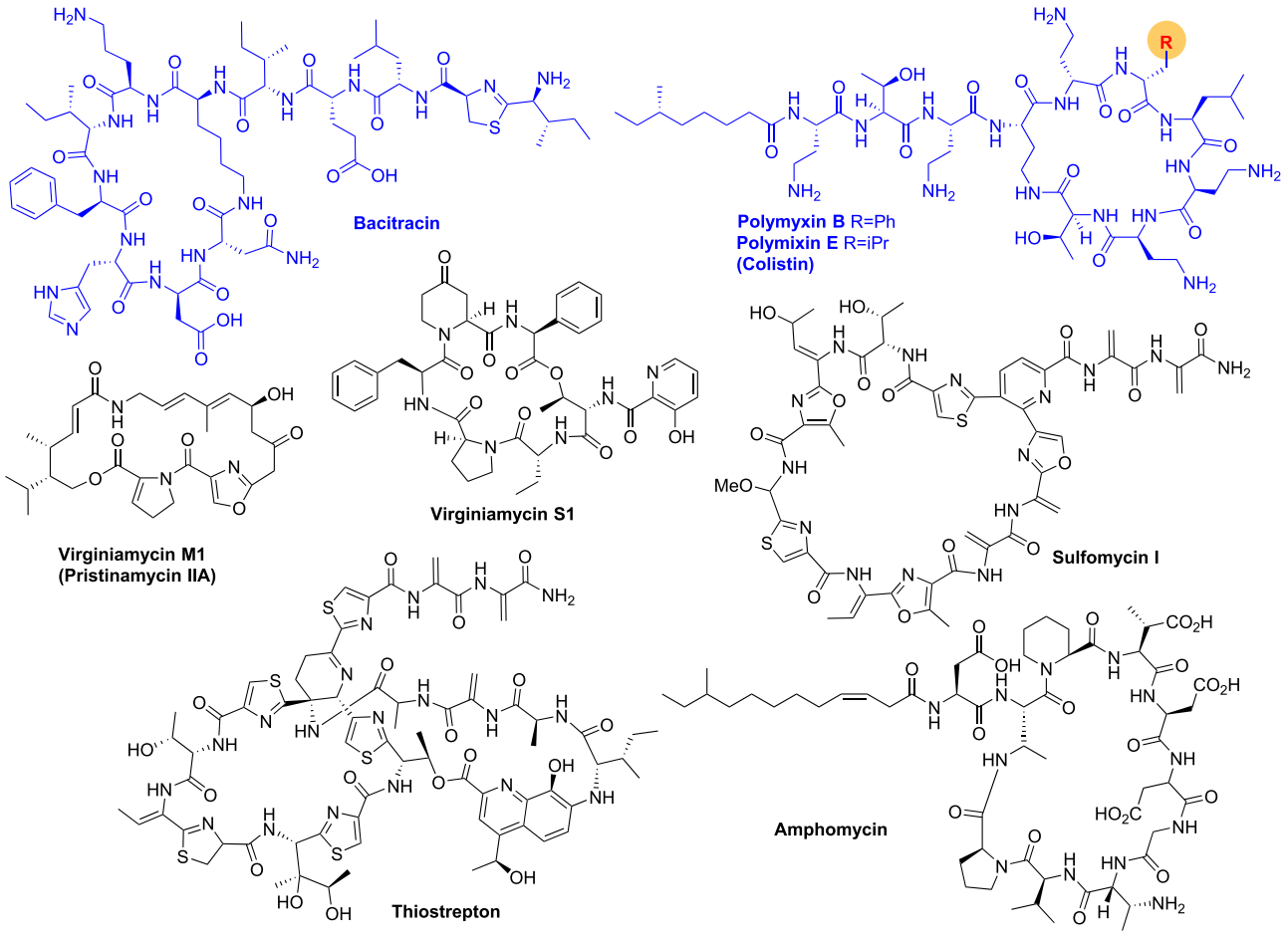

Figure 20. Macrocyclic antibiotics (drugs in blue are also approved in humans).

that was discovered in 1987 and is primarily used as a feed additive to prevent swine, bovine, and ovine bacterial infections.

Other Glycan Antibiotics. Avilamycin is an orthosomycin antibiotic that has no structural analogue in human medicine (Figure 19). It is approved in two combinations, one with narasin and the other with monensin. It is a natural product isolated from *Streptomyces* and inhibits Gram-positive bacterial growth by binding to the 30S subunit of the ribosome.[59] Bambermycin (also known as flavomycin), like avilamycin, is a polysaccharide, but its long lipophilic tail and phosphate headgroup make it a glycolipid antibiotic. It is used as a feed

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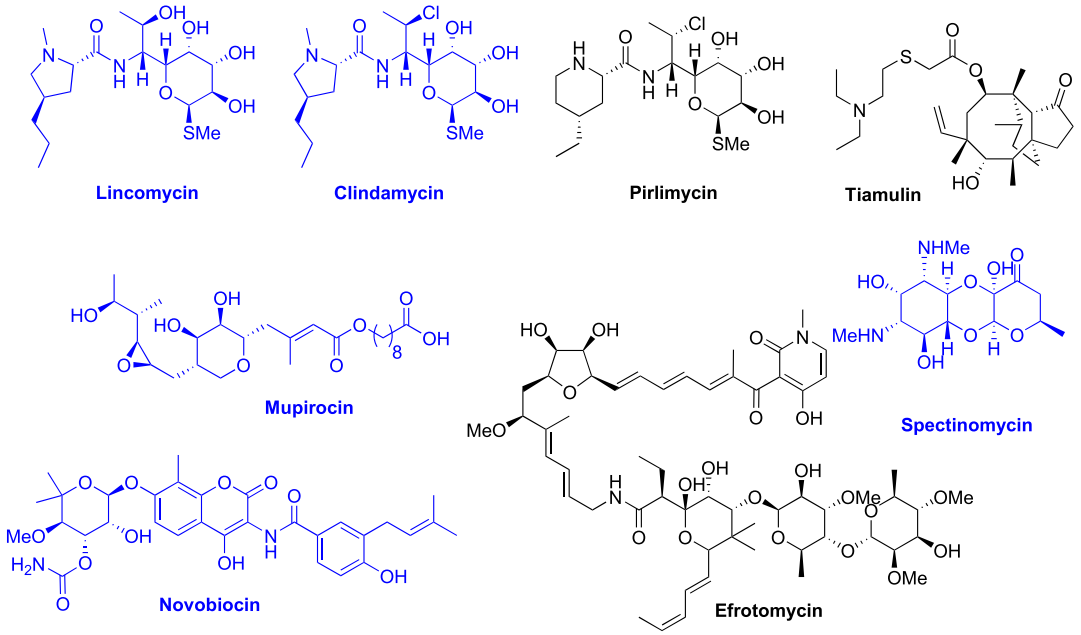

Figure 21. Miscellaneous antibiotics (drugs in blue are also approved in humans).

additive and is approved in combination with salinomycin and is effective at treating and preventing *Salmonella* infections.[60] Bambermycin is isolated from *Streptomyces bambergiensis* and *fridae* strains (and perhaps others) which also produce the antibiotic tylosin.

Cyclic Peptides. Bacitracin (Figure 20) was first isolated from *Bacillus subtilis* in 1943. It has bactericidal effects against Gram-positive bacteria and works by inhibiting peptidoglycan formation. Polymyxins B and E (known as colistin) were originally isolated from *Bacillus polymyxa colistinus*. In the 1940s, these compounds were valued for their ability to treat *Pseudomonas aeruginosa* infections, and they are now being investigated for their activity against carbapenem-resistant Gram-negative bacterial infections.[61] Polymyxins are bactericidal and displace magnesium or calcium ions, disrupting the phospholipid membrane and increasing cell permeability. Resistance mechanisms include cell membrane modification and efflux. Virginiamycin (factor M1 and factor S) is a natural product belonging to the streptogramin class and was originally isolated from *Streptomyces virginiae*. Virginiamycin is effective against aerobic and anaerobic Gram-positive bacteria but ineffective against most Gram-negative bacteria except some *Mycoplasma*. Streptogrammins (including virginiamycin) bind to the 50S ribosome subunit irreversibly and either prevent peptide chain elongation or cause early termination.[62] Methylation of the 23S rRNA leads to resistance against B type streptogramins, lincosamides, and macrolides. Because A type and B type streptogramins bind synergistically to unique sites on the ribosome, resistance is uncommon. Efflux represents an additional mode of resistance. Thiostrepton is isolated from various species of *Streptomyces* and was first described in 1955. It is used topically to treat Gram-positive bacterial infections in animals and is not approved for use in humans. Sulfomycin I is structurally related to thiostrepton. It was first described in 1988 and is produced by *Streptomyces viridochromogenes* and demonstrates strong inhibitory activity against Gram-positive bacteria.[63] Amphomycin is active against Gram positive bacteria and works by inhibiting peptidoglycan synthesis.[64]

Other Antibiotics 1. Antibiotics without a unifying category are depicted in Figure 21. The diterpene lincomycin was the first lincosamide to be isolated from *Streptomyces* species in 1963. Semisynthetic efforts toward improving the compound gave rise to clindamycin and pirlimycin. Pirlimycin is the only lincosamide not approved for humans. Lincosamides bind to the 50S ribosome (in a similar fashion to macrolides, streptogramins, and chloramphenicol), and bacteriostatic or bactericidal effects are dose dependent.[62] These compounds exhibit activity against Gram-positive bacteria but are not active against most Gram-negative species. Spontaneous mutations in the ribosomal peptidyltransferace can lead to resistance against lincomycins, although it is much more common for resistance to arise via cross-resistance from macrolides and streptogramins. Tiamulin is semisynthetically derived from pleuromutilin (not shown, approved in humans) and is active against Gram-positive anaerobic bacteria and mycoplasma as well as some Gram-negative species. Valnemulin (not shown, not approved) is a related species with high structural homology to the pleuromutilins and is twice as active as tiamulin. The pleuromutilins bind to the 50S ribosome at a different binding site than erythromycin. Bacterial strains that have developed resistance to tiamulin are completely resistant to tylosin, but cross-resistance in the other direction does not appear to occur as readily, with tylosin-resistant strains being only slightly resistant to tiamulin.[62] Mupirocin is a natural product isolated from *Pseudomonas fluorescens* and inhibits the growth of *Staphylococcus* and *Streptococcus* species by binding to the isoleucyl tRNA synthetase, preventing protein synthesis.[65] Spectinomycin is an aminocyclitol natural product that was first isolated from *Streptomyces spectabilis* in 1961 and works by binding to the 16S subunit of the ribosome, preventing protein synthesis.[66] Efrotomycin is a natural product that was first isolated from *Streptomyces lactamdurans* (which also produces cephamycin C), and described in 1972.[67] Novobiocin (also called albamycin, cathomycin, and streptonivicin) is a natural product belonging to the aminocoumarin class. It was first isolated from

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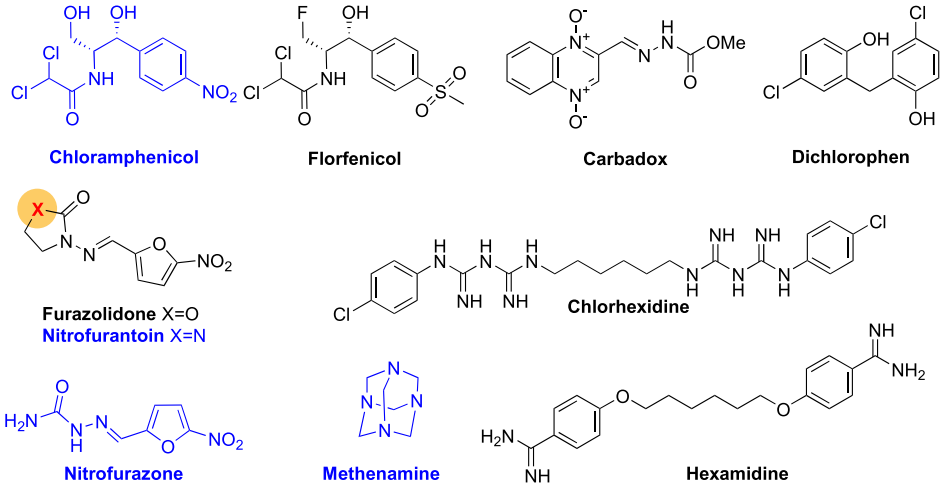

Figure 22. Miscellaneous antibiotic and antimicrobial drugs (drugs in blue are also approved in humans).

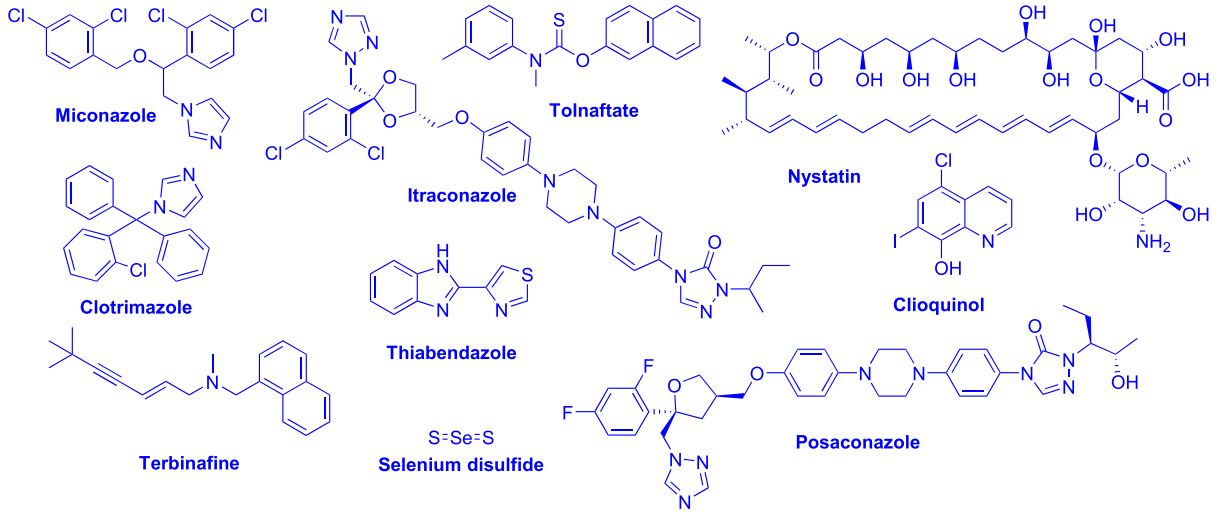

Figure 23. Antifungal drugs (all of these drugs are also approved in humans).

Streptomyces niveus.[68] It works by tightly binding to bacterial DNA gyrase.

Other Antibiotics 2. Additional antibiotics without a unifying category are depicted in Figure 22. Chloramphenicol is a natural product first isolated from *Streptomyces venezuelae*, and florfenicol is a synthetic derivative thereof. Both compounds work by irreversibly binding to the 50S subunit of the bacterial ribosome at the same site as macrolides. An off-target effect in mammalian cells is inhibition of mitochondrial protein synthesis in bone marrow.[69] These compounds have broad spectrum efficacy against both Gram-negative and Gram-positive bacteria. Chloramphenicol acyltransferases are enzymes used by resistant strains to acylate the hydroxyl groups, preventing the molecules from binding to the ribosome. Phosphorylation of the drugs, efflux, cell-wall permeability, and active site mutations are other less common modes of resistance.[69] Chloramphenicol is approved for animals and humans, and in humans the nitrophenyl group has been associated with idiosyncratic aplastic anemia. Thiamphenicol (not shown) is a related compound not approved by the FDA but has a methanesulfonyl group in place of the nitro group and does not cause the same side effect in humans. Thiamphenicol is up to two times less active than chloramphenicol. Florphenicol has a methanesulfonyl group in place of the nitro group, as well as a fluorine in place of the hydroxyl group (Figure 22), and is generally as active as chloramphenicol and has a wider range of antimicrobial activity. The conclusion can be drawn that the change from nitro to sulfonyl reduces activity, but the change from hydroxy- to fluoro- increases activity. Carbadox is used to prevent swine dysentery and is effective for a number of other indications including enteritis and roundworms (*Acaris suum*). Dichlorophen is an antimicrobial with broad spectrum efficacy against fungi and parasites and is used in combination with toluene to treat various worms in dogs and cats. Trimethoprim is a diaminopyrimidine that was first discussed as a potentiator of sulfanilamides earlier in this analysis. Ormetorpim and pyrimethamine are structurally related compounds that are also approved. Of these, only ormetoprim is not approved for use in humans. All of these compounds target bacterial dihydrofolate reductase, and while mammals also have a version of this enzyme, bacteria rely on them for survival and therefore these compounds do not affect the host. Furazolidone, nitrofurantoin, and nitrofurazone are nitrofuran antimicrobials that have been used to treat Gram-positive and Gram-negative bacterial as well as *Trypanosoma*.[70] They are now widely prohibited due to carcinogenic properties and residual metabolites in food animals and due to the

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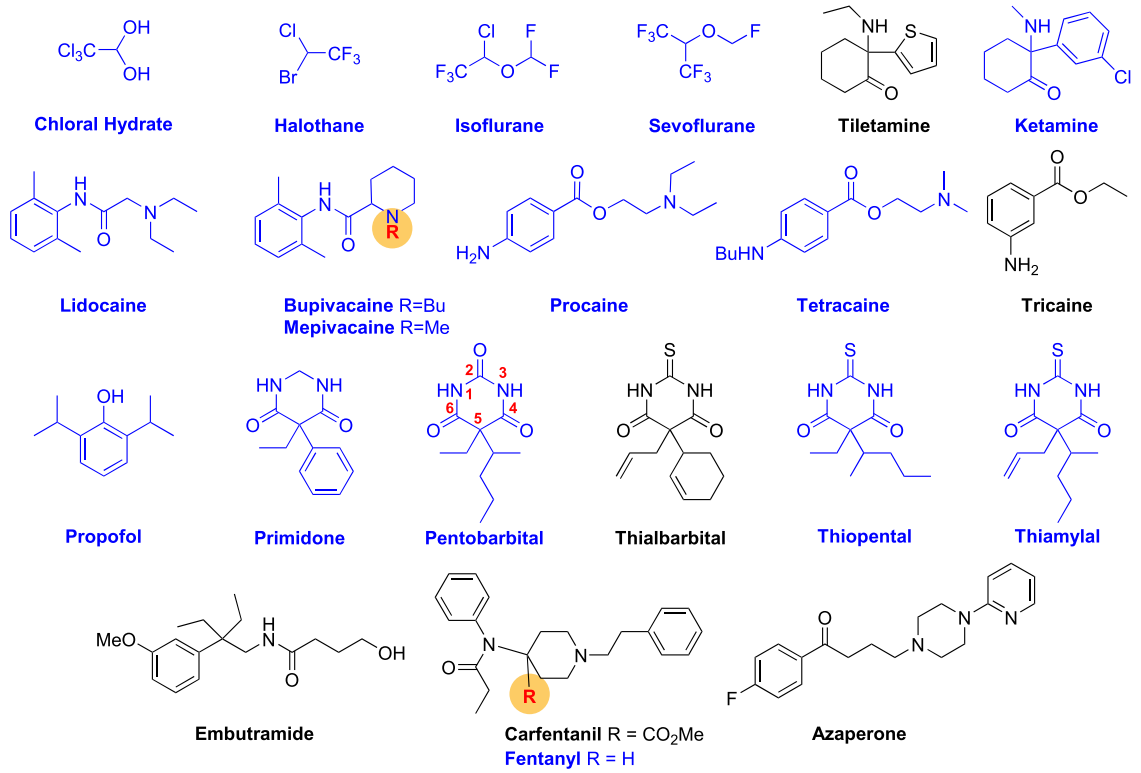

Figure 24. CNS-active drugs anesthetics and sedatives (drugs in blue are also approved in humans).

development of safer alternatives. These compounds are believed to act by inhibiting DNA synthesis, but the mechanism is not fully understood. Chlorhexidine and hexamidine are used as topical antiseptics. Methanamine is an antibacterial agent that is used orally to treat urinary tract infections. It is synthesized from ammonia and formaldehyde, and under acidic conditions of the urinary tract it is hydrolyzed back into ammonia and formaldehyde. Formaldehyde acts as a potent antibacterial agent.[71]

Antifungal Drugs. Fungal infections present a fundamental challenge from a drug discovery perspective because fungi and animals (including humans) are eukaryotes which share many cellular characteristics and potential drug targets.[72] Fungal infections, in animals as in humans, present increasing health risks as drug resistance becomes more common. All of the compounds in this section (Figure 23) are approved for use in animals and in humans, and all are synthetic except for the natural product nystatin. Azoles are a first line of defense in antifungal therapy with great clinical importance and make up the majority of the drugs in this section. The imidazoles (miconazole, clotrimazole, and thiabendazole) and triazoles (itraconazole and posaconazole) work by inhibiting 14α-demethylase, which is a critical enzyme in the ergosterol biosynthesis pathway.[72] Ergosterol is the fungal analogue of mammalian cholesterol and is critical for cell-wall integrity. Inhibition of 14α-demethylase not only leads to a depletion of ergosterol, but it also leads to toxic levels of methylated sterols. Resistance mechanisms include mutation to the gene that encodes for 14α-demethylase (ERG11), and by overexpression of the same gene, as well as multidrug efflux; efforts to suppress these resistance mechanisms have seen progress.[73,72] Tolnaftate is a thiocarbamate that is believed to exhibit antifungal effects by inhibiting squalene epoxidase, a critical enzyme in the ergosterol biosynthesis pathway.[74] Nystatin is a polyketide appended with a mycosamine glycoside moiety and was first isolated in 1950 from *Streptomyces noursei*. This compound is approved for use in animals and humans and belongs in the same structural class as natamycin, candidicin, and amphotericin B (not shown), which are not approved in veterinary medicine but are of clinical importance. All of these drugs disrupt the cell membrane by binding to ergosterol. They have low affinity for cholesterol (the mammalian analogue of ergosterol) and are therefore selective for fungi, with little effect on the host. These polyenes are toxic to eukaryotic cells, but not bacteria, because their activity requires the presence of sterols in the cell membrane. Terbinafine belongs to the allylamine family of drugs, which inhibit squalene epoxidase, disrupting the ergosterol biosynthesis pathway.[74] Clioquinol is a hydroxyquinoline that is used as an antifungal and antiprotazoal and also exhibits antiviral activity.[75] Selenium disulfide is used externally to treat a variety of skin conditions, including dandruff in humans, and acts as an antifungal in the treatment of *Pityriasis versicolor*.[8]

Anesthetics. The first four compounds in this section (Figure 24) are highly halogenated, low molecular weight compounds used for anesthesia. Chloral hydrate is a sedative and hypnotic given orally and is converted to trichloroethanol, the active compound, in the liver.[76] Halothane, isoflurane, and sevoflurane are given by inhalation.[77] Ketamine is approved for use in humans, and tiletamine is a structural analogue in which the chlorophenyl group has been replaced by an aromatic thiophene.[78] Lidocaine, bupivacaine, and mepivacaine are aminamides used for local anesthesia, often in combination with other anesthetics.[79] Procaine, tricaine, and tetracaine are aminoesters also used for anesthesia. Propofol is used as an anesthetic for surgery in both animals and humans.[80] Primidone, pentobarbital, thialbarbital, thiopental, and thiamylal are derivatives of barbituric acid (barbiturates).

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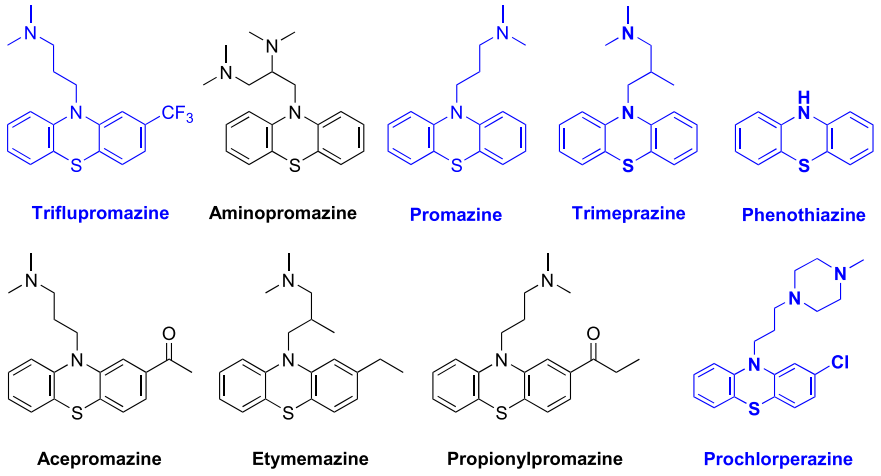

Figure 25. Veterinary phenothiazines (drugs in blue are also approved in humans).

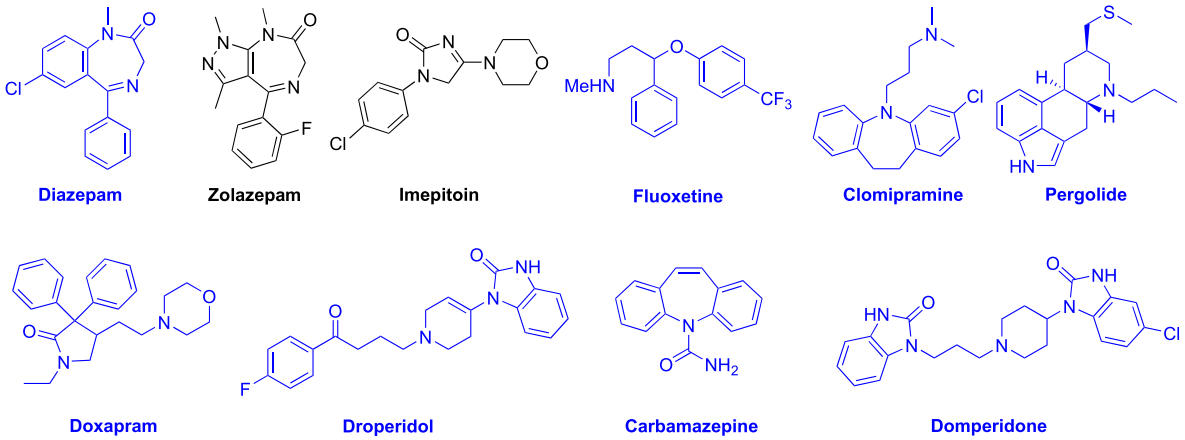

Figure 26. Miscellaneous CNS-active drugs (drugs in blue are also approved in humans).

Primidone is lacking the carbonyl group at C2 and is an anticonvulsant. The remaining four compounds are sedatives used for anesthesia in surgery. The prefix "thi" in the latter three compounds refers to the thiocarbonyl (C═S) at C2. Embutramide is an opioid that is used as a sedative, however, its narrow therapeutic window makes it dangerous to use, and it is mainly used for euthanasia.[81] Embutramide is structurally related to the human drug methadone (not shown). Carfentanyl and fentanyl are potent opioids used for anesthesia. Fentanyl is approved in humans and is used for pain management as well; remifentanil (not shown) is a structurally related drug approved for humans but not in veterinary medicine. Azaperone is a butyrophenone neuroleptic that is used as a sedative and tranquilizer.[82] It is not approved for use in humans although it has been investigated.

Phenothiazines. Phenothiazines made their breakthrough in medicine as antipsychotics. Many of these compounds also have sedative properties and are often used as tranquilizers in veterinary medicine. The hallmark of the structure consists of a tricyclic core with a nitrogen and sulfur atom across from each other in a six-membered thiazine heterocycle between two aromatic rings (Figure 25). The nitrogen atom is appended with a dialkylaminopropyl group, whose structure varies and can change the properties of the drug. Trifluprom azine is an antipsychotic that is used as an antipsychotic in veterinary medicine. Acepromazine is commonly used as a sedative in companion animals. Prochlorperazine is used to treat nausea.

Miscellaneous CNS Drugs 1. The compounds in this section do not conveniently fit into their own category. All but one of the drugs in this section (Figure 26) are approved for use in both animals and humans. Diazepam is a benzodiazepine that can be used to treat anxiety or as a tranquilizer. Zolazepam is structurally related, although it is not a typical benzodiazepine, which requires the aromatic ring fused with the azepine ring including the halide for activity. Zolazepam is used as a sedative in veterinary medicine and is not approved in humans. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used as an antidepressant in humans and for separation anxiety in companion animals. Doxapram is used to stimulate breathing during anesthesia. Droperidol is a butyrophenone dopamine receptor antagonist that is used as an antiemetic at low doses and can have antipsychotic properties at high doses. It shares some structural properties with droperidol, which also acts as a dopamine receptor antagonist. Although they have other uses, both drugs are typically used as antiemetics, especially during and after anesthesia. Carbamazepine is used to treat seizures and neuropathic pain. Pergolide is derived from ergot and has been used as a dopamine receptor agonist in Parkinson's disease and to treat Cushing's disease in horses.[83] Clomipramine belongs to the tricyclic antidepressant class of drugs and is used to treat separation anxiety in companion animals.[84]

Miscellaneous CNS Drugs 2. As a continuation of the previous category, the compounds in Figure 27 do not all

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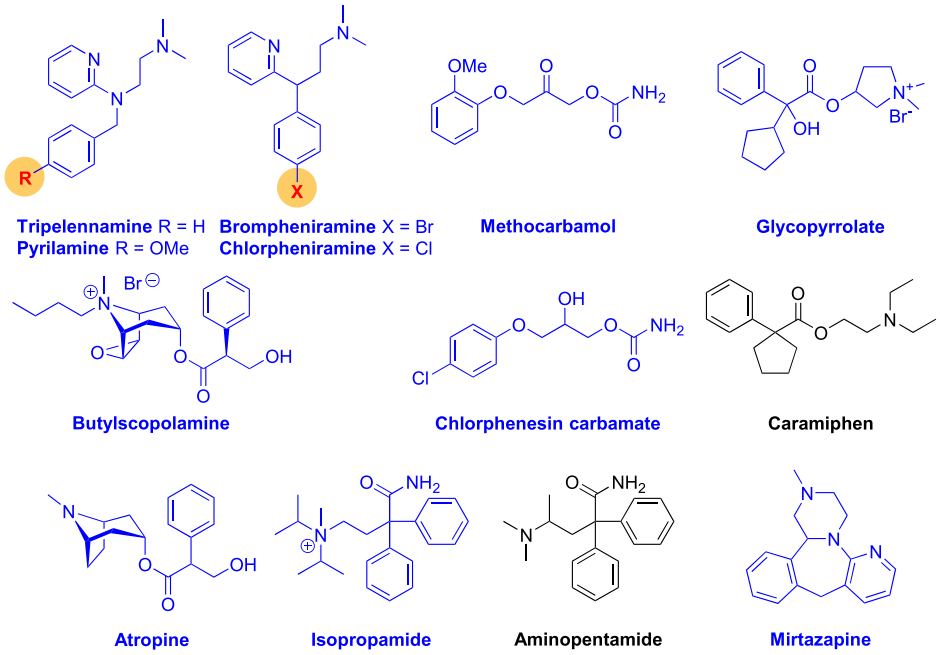

Figure 27. Additional miscellaneous CNS-active drugs (drugs in blue are also approved in humans).

belong to a major class of drugs, with all but two approved for use in humans. Tripelennamine, pyrilamine, and bromophenir-amine are antihistamine drugs. Methocarbamol and chlor-ophensin carbamate are muscle relaxers. Butylscopolamine (also known as hyoscine butyl bromide) and atropine are both anticholinergics derived from the tropine core structure. Both drugs are competitive agonists of the muscarinic acetylcholine receptor. Butylscopolamine is made semisynthetically from the natural product hyoscyamine. It is used to treat spasms and abdominal cramps, including menstrual cramps, in humans. In veterinary medicine, it is used as an antispasmodic. Atropine is used to reduce salivation and bronchial secretions during anesthesia.[85] Isopropamide is an anticholinergic drug with a quaternary amine and is used to treat gastrointestinal disorders that are associated with hyperacidity.[86] Similarly, amino-pentamide is used as an anticholinergic in small animals as a smooth-muscle antispasmodic. Caramiphen is an anticholiner-gic used to treat cough and other respiratory symptoms in veterinary medicine. Although it is not approved by the FDA for use in humans, caramiphen has been used on an investigational basis to treat Parkinson's disease. Glycopyrro-late is a structurally related compound that is approved in humans. It acts as an anticholinergic drug used to treat peptic ulcers and to control drooling and excessive secretions during anesthesia.

Opioids. The first four compounds in this group (Figure 28) are directly derived from the backbone of the opiate morphine and its analogues, in which the C ring has various oxidation states. Naltrexone is used in human and veterinary medicine to reverse opioid overdose, but it is also used in veterinary medicine to treat pain. Buprenorphine and diprenorphine are structurally nearly identical, except for the R group on the side chain at C7, in which buprenorphine has a *tert*-butyl group and diprenorphine has a methyl group. Both compounds are used as analgesics in veterinary medicine, but only buprenorphine is approved for use in humans for treating drug addiction. Nalorphine (also called *N*-allylmorphine) is structurally nearly identical to morphine, except it has an allyl

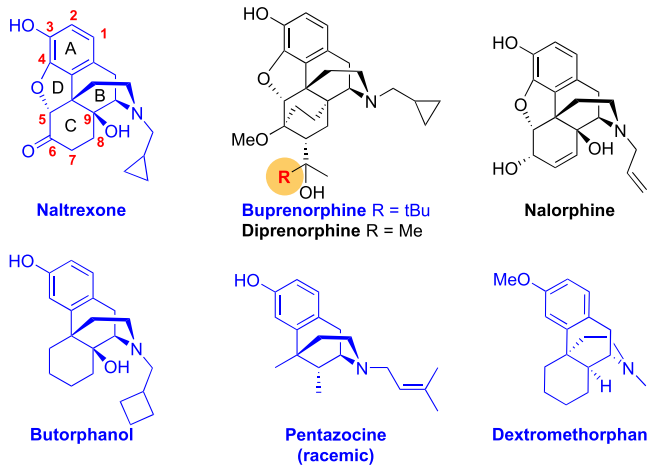

Figure 28. Opioids and morphinans (drugs in blue are also approved in humans).

group on the nitrogen atom where morphine has a methyl group. It is a used to treat pain in animals and is not approved for use in humans. The remaining three compounds (butorphanol, pentazocine, and dextromethorphan) are also morphinan opioid analgesics although they are not based on the morphine structure. Butorphanol and pentazocine are structurally related compounds that are used as pain relievers. They are both approved for human and veterinary medicine. Dextromethorphan belongs to the morphinans, like butorpha-nol and pentazocine, but it exists as the opposite enantiomer as butorphanol. Although it is an opioid, it is used as a cough suppressant.

Adrenergic Receptor Modulators. The compounds in this group are α- and β-adrenergic receptor modulators, which work as sympathomimetics in the central nervous system (shown in Figure 29). The β-agonists are used to build muscle and enhance leanness in agricultural animals, and the α-agonists are used as sedatives. Yohimbine is the only α-antagonist here and is used to reverse sedative effects of α-

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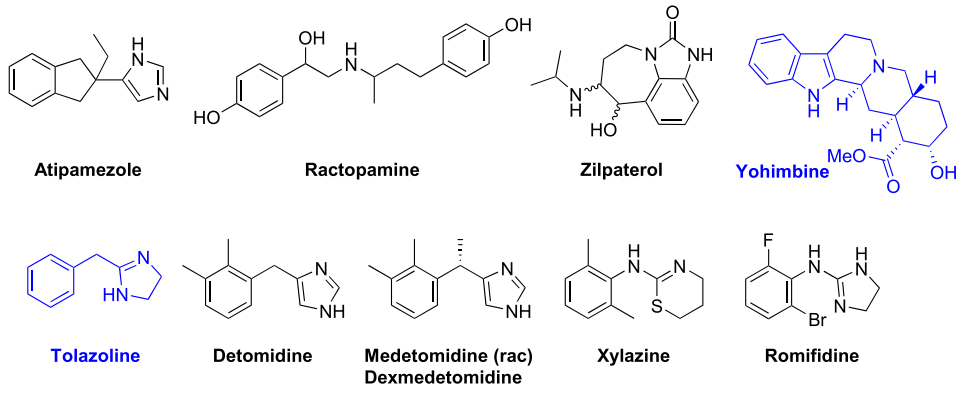

Figure 29. Adrenergic receptor modulators (drugs in blue are also approved in humans).

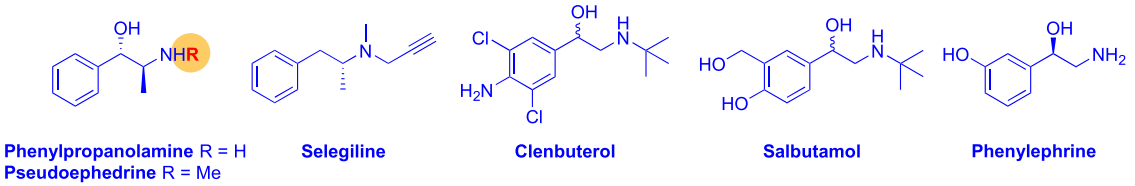

Figure 30. Veterinary phenethylamines (all of these drugs are also approved in humans).

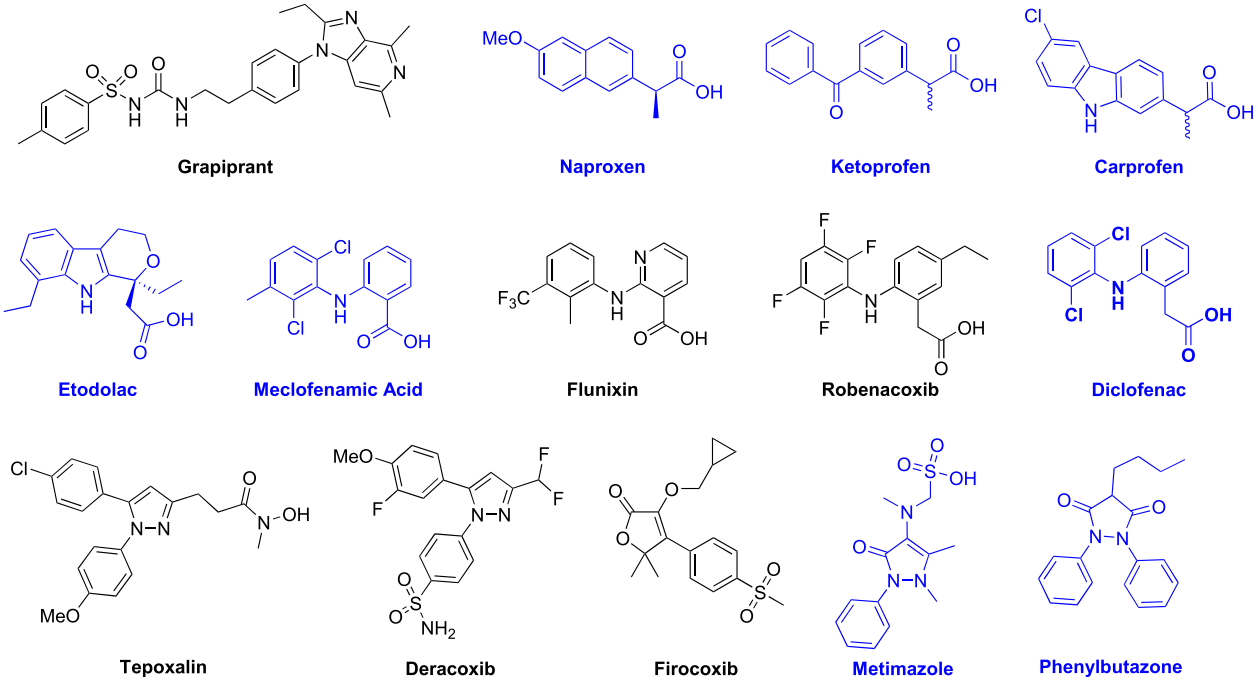

Figure 31. Nonsteroidal anti-inflammatory drugs (drugs in blue are also approved in humans).

agonists. Atipemazine, detomidine, medetomidine, and dexmedetomidine are structural analogues that are all α-adrenergic receptor agonists. Medetomidine has only one extra methyl group than detomidine, making it chiral. Dexmedetomidine is the active isomer of medetomidine, and both compounds are used to maintain anesthesia during surgery.[87] Romifidine is also used as an anesthetic during veterinary surgery.[88] It is structurally related to dexmedetomidine but bears a nitrogen in the position at which dexmedetomidine has a chiral carbon center. Xylazine is a structural analogue of romifidine and is used as a muscle relaxer and a sedative.[89] Both compounds are α2 adrenergic receptor agonists for which yohimbine is used as an antidote. Isolated from several tropical tree species, the indole alkaloid natural product yohimbine is an α2-antagonist and is used to reverse the effects of the α-agonists described in this section.

Phenethylamines. The structural feature that the compounds in this group share is the phenethylamine moiety (Figure 30), giving the immediate impression of similarity with a number of neurotransmitters. All of the compounds in this section are also approved for use in humans. Phenylpropanolamine is used in decongestant formulations in humans, and in veterinary medicine it is used to treat urinary incontinence in companion animals (urethral sphincter mechanism incom-

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petence). Pseudoephedrine only differs from phenylpropanolamine in the methyl group on the nitrogen atom and is used in nasal decongestants and induces vasoconstriction by acting on α-adrenergic receptors.[90] Seleginiline is an irreversible monamine oxidase inhibitor in animals and in humans. In animals, it is used to treat cognitive dysfunction and Cushing's disease, and in humans it is used as part of Parkinson's disease treatments to inhibit monoamine oxidase. Clenbuterol is a smooth-muscle relaxer used as a bronchodilator, and in veterinary medicine it is sometimes used to relax abdominal muscles, especially during labor in cattle.[91] Salbutamol has the same effect as clenbuterol and is used to treat asthma in humans and in animals. The *tert*-butyl group on the nitrogen of both drugs makes them more selective for the β2-adrenergic receptor, and they are both sold as racemic mixtures. However, the *R* enantiomer is the active form but tends to racemize under biological conditions.[92]

NSAIDs. Grapiprant is an analgesic and anti-inflammatory drug used to treat osteoarthritis in dogs which works by blocking the prostaglandin EP4 receptor.[93] Although grapiprant is not approved for use in humans, more than half of the other nonsteroidal anti-inflammatory drugs (NSAIDs) in this category are. The remaining drugs in this category work by disrupting prostaglandin biosynthesis through inhibition of cyclooxygenase 1 and/or 2 (COX-1 and/or COX-2), although details of the mechanism are unclear. Ketoprofen is the only drug in this group that also inhibits leukotriene synthesis and leukocyte migration into joints. The first eight compounds in Figure 31 (first two rows) belong to or are derived from a class of drugs known as aryl- and heteroarylacetic acids. With the exception of etodolac, these compounds feature an aryl or heteroaryl ring attached to a carboxylic acid, either directly (meclofenamic acid and flunixin) or with a single methylene group in between (diclofenac, robenacoxib, naproxen, ketoprofen, and carprofen). Naproxen, ketoprofen, and carprofen all have a methyl substituent at the methylene spacer, making them chiral. Although naproxen is the only one sold as purely the active isomer, the *S* enantiomer is the active form in all three cases. Compounds bearing this α-methyl moiety have been dubbed the "profens" by the U.S. Adopted Name Council. Etodolac shares structural similarities with the heteroarylacetic acids but is classified as a pyranocarboxylic acid due to its six-membered oxygen heterocycle. Although it is sold as a racemic mixture, like the arylacetic acids, it is the *S* enantiomer that is active. The methoxy substitution of the naphthalene ring of naproxen represents the most potent substitution at the best position of the ring in the assays that led to the drug's development.[94] Structurally related to the arylacetic acid NSAIDs, the second row of compounds belongs to the anthranilic acid class of drugs, which are known as the "fenamic acids". They are direct analogues of salicylic acid, from which they were derived. It is believed that the *ortho*-dichloro substitution on the phenyl ring of diclofenac forces the ring out of the plane, giving it higher binding affinity for the COX enzymes. The same logic holds true for meclofenamic acid and robenacoxib and at least partially for flunixin. All four of these drugs lack substitution on the anthranilic acid ring because any substitution reduces activity. The "coxibs" were the first selective COX-2 inhibitors. Metimazole is approved for use in animals and humans and is the latest NSAID to hit the animal market in 2019. Although phenylbutazone appears similar to the coxibs, it disrupts prostaglandin biosynthesis by inhibiting prostaglandin synthase, not COX enzymes. Meloxicam is a sulfonamide NSAID which inhibits COX-2 slightly more than COX-1 and appears in Figure 38 (with other sulfonamides).

Thyroid. The thyroid gland produces a small number of iodized tyrosine analogues which serve as thyroid hormones. When the body is not able to produce sufficient levels, hypothyroidism results, and artificial hormones can be given as a supplement in order to treat the disorder. Thyroxine (T_4) is a hormone produced by the thyroid gland in mammals, and levothyroxine is the structurally identical synthetic version of the hormone (Figure 32). The drug can be given to animals

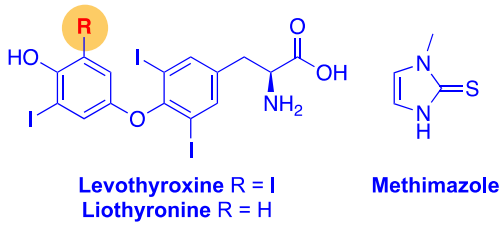

Figure 32. Thyroid hormones (all of these drugs are also approved in humans).

(including humans) who do not produce enough of the compound naturally. Triiodothyronine (T_3) is also a thyroid hormone which has only one iodine fewer than thyroxine, and liothyronine is the synthetic version. Metimazole is an antithyroid that is used to treat hyperthyroidism, a condition in which the thyroid gland produces too much of the previously described hormones.

Steroids. Steroids are hormones that play complicated roles in biology. When taken as drugs, they are used to treat the most wide-ranging conditions out of any structural class of drugs. Hormones are incredibly potent and are only needed in small doses. Because of their potency, most steroid treatments must be limited to short timeframes in order to avoid serious side effects. The biosynthesis and secretion of these hormones is at least partially regulated by adrenocorticotrophin-releasing hormone (ACTH), which is covered in the peptides section (see Figure 41).

Anti-inflammatory Steroids. The 13 drugs in this section (Figure 33) are corticosteroids (anti-inflammatory steroids), and all but two are approved for use in humans. All of the compounds in this group share a high degree of structural similarity. These drugs share the pregnane steroid core with an α,β-unsaturated ketone on ring A and additional unsaturation between C1 and C2 as well as a β-hydroxyketone on C17. All compounds except prednisolone have a hydroxy group at C11; prednisolone has a ketone in this position but is metabolized into an alcohol (prednisone) in the body. Prednisolone is used to treat allergies and infections.[95] Eight compounds have fluorine atoms at C9, and two of these have a fluorine atom at C6 as well. Betamethasone has two additional analogues, the phosphate and the valerate. Isoflupredone acetate is a corticosteroid that was never approved for use in humans but is used to treat heaves in horses.[96] Prednisolone is a structural analogue of cortisone (not pictured, not approved), which is a naturally occurring steroid. The difference is that prednisolone has a C1−C2 double bond. Cortisone is the inactive form of cortisol and is activated by 11β-hydroxysteroid dehydrogenase, which converts the C11 ketone into the β-alcohol. The active alcohol form of cortisone is cortisol, which

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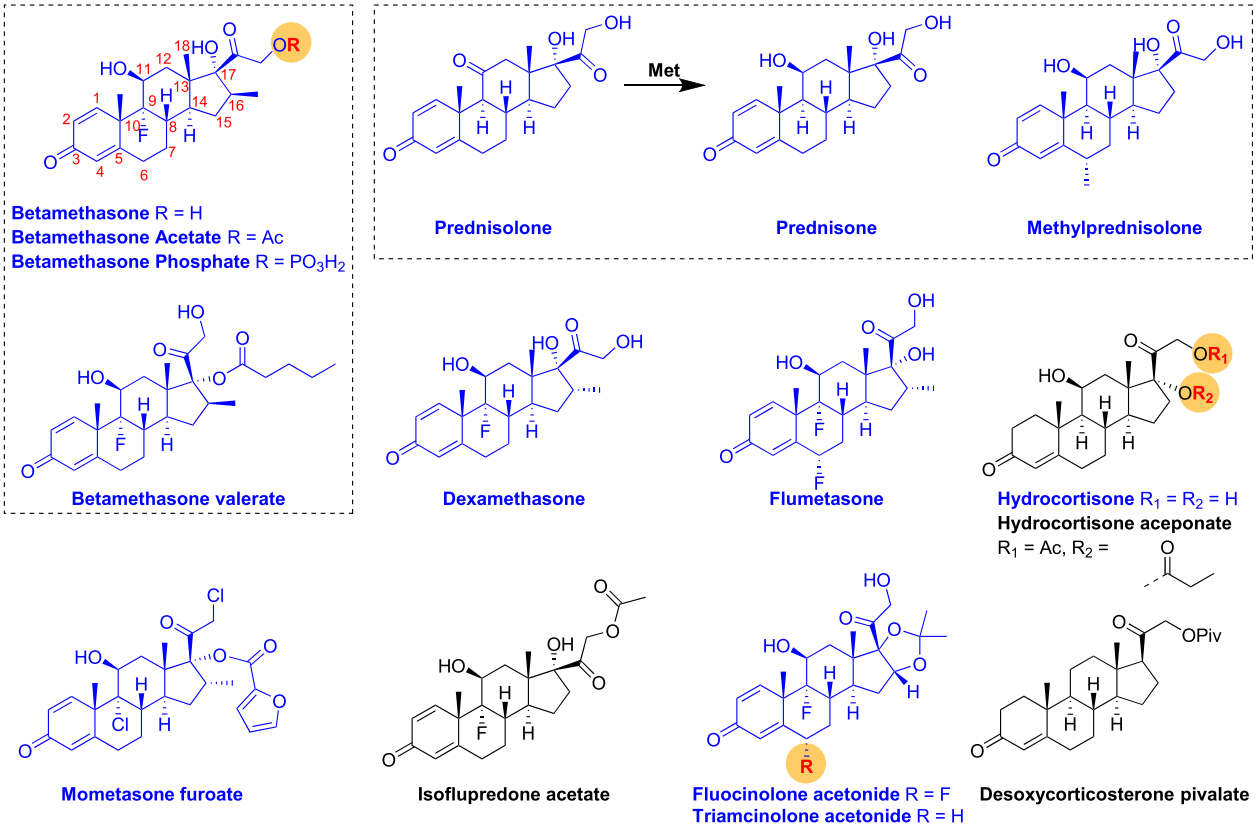

Figure 33. Antiinflammatory steroids (drugs in blue are also approved in humans).

is also approved and known as hydrocortisone. Interestingly, 11β-hydroxysteroid dehydrogenase also converts hydrocortisone back into cortisone. In a similar conversion, prednisolone is converted to its active form (prednisone) by reduction of the C11 ketone into the β-alcohol, but it is not converted back. Hydrocortisone aceponate ester is an analogue of the naturally occurring steroid hydrocortisone and is used in veterinary medicine. The structurally related desoxyhydrocortisone pivalate lacks the two hydroxyl groups at C11 and C17 that hydrocortisone and its analogues have. The pivalate ester improves physicochemical properties including absorption. Desoxyhydrocortisone pivalate is used to treat hypoadrenocorticism.[97]

Miscellaneous Steroids. A considerable amount of care goes into ensuring that farm animals have a healthy weight to maximize food production. Feed additives that contain antiparasitics and antibiotics to prevent animals from losing mass to infection also contain steroids to promote proper growth (these combination approvals are covered below). Three of the six drugs in this group are steroids intended for weight gain (the other three are grouped here on a structural basis). Melengestrol acetate (Figure 34) is a common cattle feed additive and can be used to control ovulation as well.[98] It is approved with one or more of each of the following drugs: lasalocid, tylosin, zilpaterol, and ractopamine (the first two are antibiotics and the last two are adrenergic receptor modulators). Melengestrol is a synthetic progesterone analogue that works as a progesterone receptor agonist.[99] It is structurally similar to megestrol acetate (covered in the next section, Figure 34), with the exception of an additional methylene group at C18, which dramatically changes its activity. Alfaxalone is unique for steroids in that it is

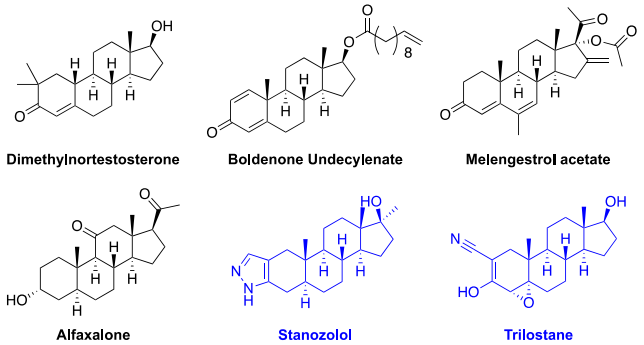

Figure 34. Miscellaneous steroids (drugs in blue are also approved in humans).

neuroactive; it is used as an anesthetic.[100] The core of the structure is based on progesterone. Stanazolol is a synthetic steroid that is used in humans and animals to treat hereditary angioedema and is also used as an adrogenic steroid with effects similar to those of boldenone.[101] The methyl group in the 17α position (where all of the other steroids in this review have either a hydrogen atom or an oxygen atom) enhances oral bioavailability. The pyrazole moiety fused to ring A is also a unique feature. Trilostane is used in humans and animals to treat Cushing's disease. This disease is characterized by an overactive thyroid gland, known as hypercortisolism. The drug works by inhibiting the biosynthesis of natural steroids. Trilostane is the only steroid with a nitrile functional group.[102]

Reproductive Steroids. The steroids in this section (Figure 35) closely resemble natural steroid hormones that are central to critical signaling pathways in animals and humans. Progesterone is used in veterinary medicine to

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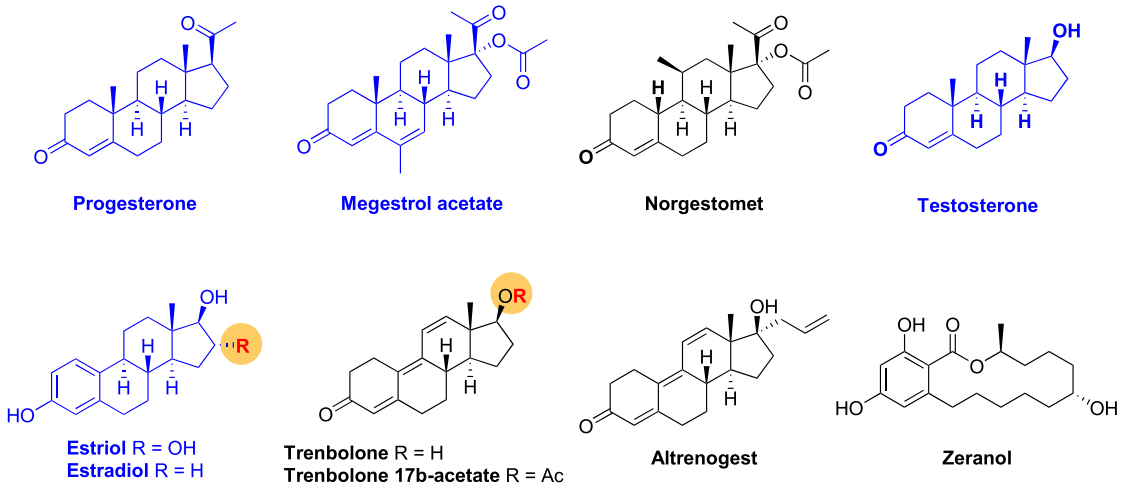

Figure 35. Reproductive steroids and hormone receptor modulators (drugs in blue are also approved in humans).

stimulate estrus and aid in the breeding of animals. Megestrol acetate is a close relative of progesterone and is used to postpone estrus in small animals.[103] It can also be used to treat certain skin conditions and has been used in humans as part of cancer treatment regimens and to stimulate appetite for weight gain. Norgestomet is prescribed in combination with estradiol to control ovulation and estrus in cattle.[104] Testosterone is approved in two separate combinations: one with estradiol and tylosin, and the other with estradiol, progesterone, and trenbolone. In both cases, the combinations are used to promote weight gain. Trenbolone is approved in animals as both the free alcohol and the 17b-acetate. Estriol is used in veterinary medicine to restore estrogen levels and is used in humans for hormone replacement therapies. Altrenogest is a progestin used to synchronize or suppress estrus in hogs and horses and is not approved for use in humans. Zeranol is not a steroid, but it is a nonsteroidal estrogen that is used to promote weight gain in cattle. It is structurally related to a class of mycoestrogens that are isolated from various fungi.

Prostaglandins. Control over reproductive timing is important in the agricultural industry, and prostaglandins help control over reproductive cycles. All of the structures in this group are direct analogues of naturally occurring prostaglandins with only one drug in this section (dinoprost) being approved for use in humans. All of the drugs in this category (Figure 36) are $PDF_{2\alpha}$ analogues, which induce luteolysis (degradation of the corpus luteum) and are administered to animals to restart the ovulation cycle and thereby control the timing of pregnancy.[105] When given to pregnant mares, these prostaglandins can act as abortifacients. The classification of prostaglandins is determined by the substitution pattern of the ring. The designation of Fα (PGFα) is given for the cyclohexane with 9,11-diol and a single bond between C8 and C12, with *trans*-configuration for the R_1 and R_2 chains. The carboxylate at the end of the R_1 chain is always designated as C1. Most of the compounds in this group feature a *Z* double bond between C5 and C6, but fenprostalene has an allene (two consecutive double bonds) between C5 and C7. Fenprostalene is also unique in that it exists as the methyl ester rather than the free carboxylate. Luprostiol is unique in that a sulfur atom replaces C13, giving a thioether. Fenprostalene, fluprostenol, cloprostenol, and luprostiol all have a phenolic ether at the end of R_2, and the latter three have either a trifluoromethyl or a chloro group in the *meta*-position of that ring. Dinoprost is the naturally occurring $PGF_{2\alpha}$.

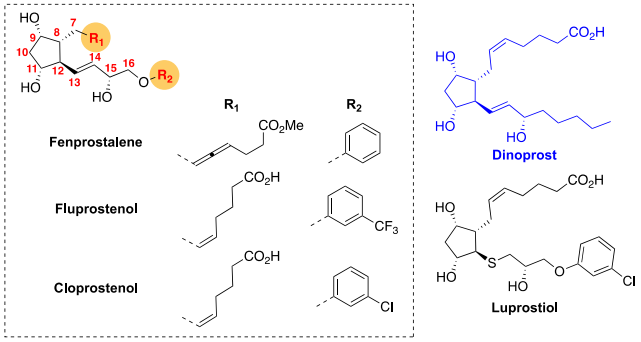

Figure 36. Veterinary prostaglandins (drugs in blue are also approved in humans).

OTHER DRUG CLASSES

Cancer. Veterinary oncology for companion animals has recently garnered great interest for human medical studies. The reasoning behind this is that naturally occurring tumors in companion animals resemble human tumors much more closely than xenograft models due to oncogene expression, vasculature, and other factors.[106] Thus, being on the *qui vive* with studies may lead to the repurposing of cancer drugs from animals to humans or vice versa. Clodronate (Figure 37) is a bisphosphonate that is used to treat high levels of calcium, which is sometimes associated with secondary bone cancers. Rabacfosadine is used to treat lymphoma in dogs and works by inducing S phase arrest through DNA synthesis inhibition which leads to apoptosis.[107] Masitinib is a tyrosine kinase inhibitor used to treat mast cell tumors in dogs.[108] Like masitinib, toceranib treats mast cell tumors in dogs but targets a receptor tyrosine kinase.[109]

Cardiovascular. Chlorothiazide diuretics (Figure 38) were developed in the first half of the 20th century and remain some of the most commonly prescribed medicines to treat blood pressure. Some of the compounds in this group also exhibit carbonic anhydrase inhibition and are used to treat other conditions like glaucoma. Trichlormethiazide is approved in combination with dexamethasone as a diuretic/anti-inflammatory. Meloxicam is an NSAID that works by inhibiting COX

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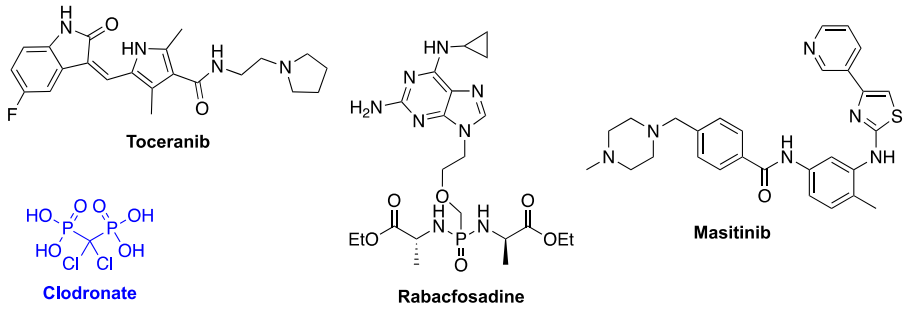

Figure 37. Oncological drugs (drugs in blue are also approved in humans).

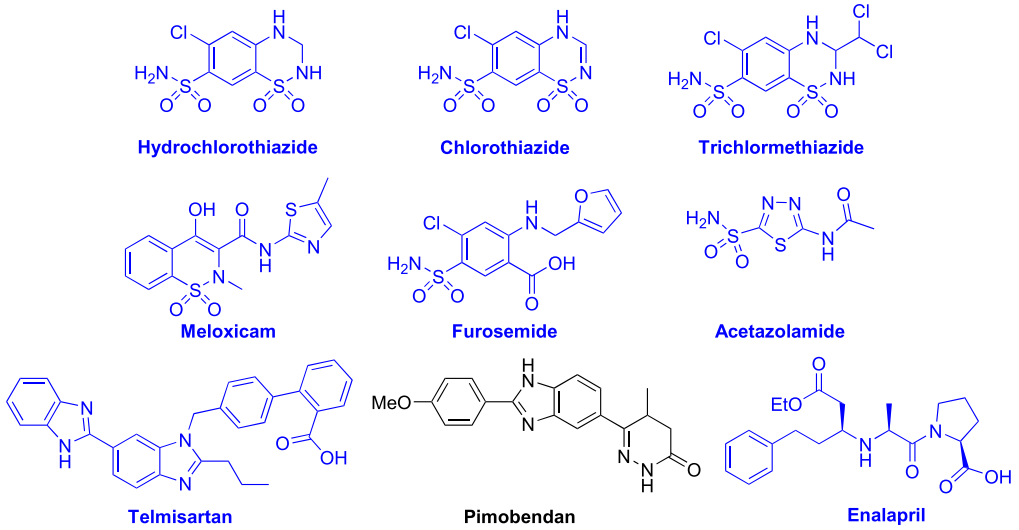

Figure 38. Cardiovascular drugs (drugs in blue are also approved in humans).

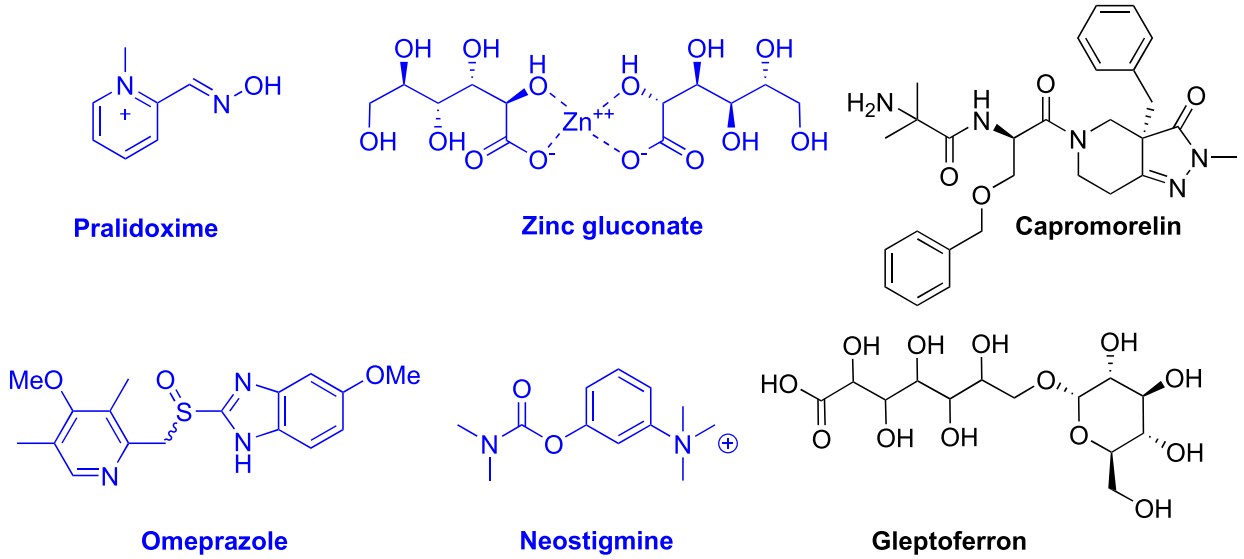

Figure 39. Miscellaneous drugs (drugs in blue are also approved in humans).

enzymes. It is listed in this figure on a structural basis and is not a cardiovascular drug (indeed, it can have cardiovascular side effects). Acetazolamide is a sulfonamide diuretic like the other sulfonamides in this group, but it is used to treat glaucoma not cardiovascular disorders and acts as a carbonic anhydrase inhibitors.[110] In humans, it is also used to treat epilepsy. Pimobendan is a phosphodiesterase 3 (PDE3) inhibitor and is not approved in humans.[111] Enalapril is an inhibitor of the angiotensin converting enzyme (ACE).[112] Angiotensin is a peptide regulator of blood pressure which works in the renin−angiotensin pathway by activation via cleavage by ACE. Ace inhibitors prevent the activation of angiotensin and reduce blood pressure.

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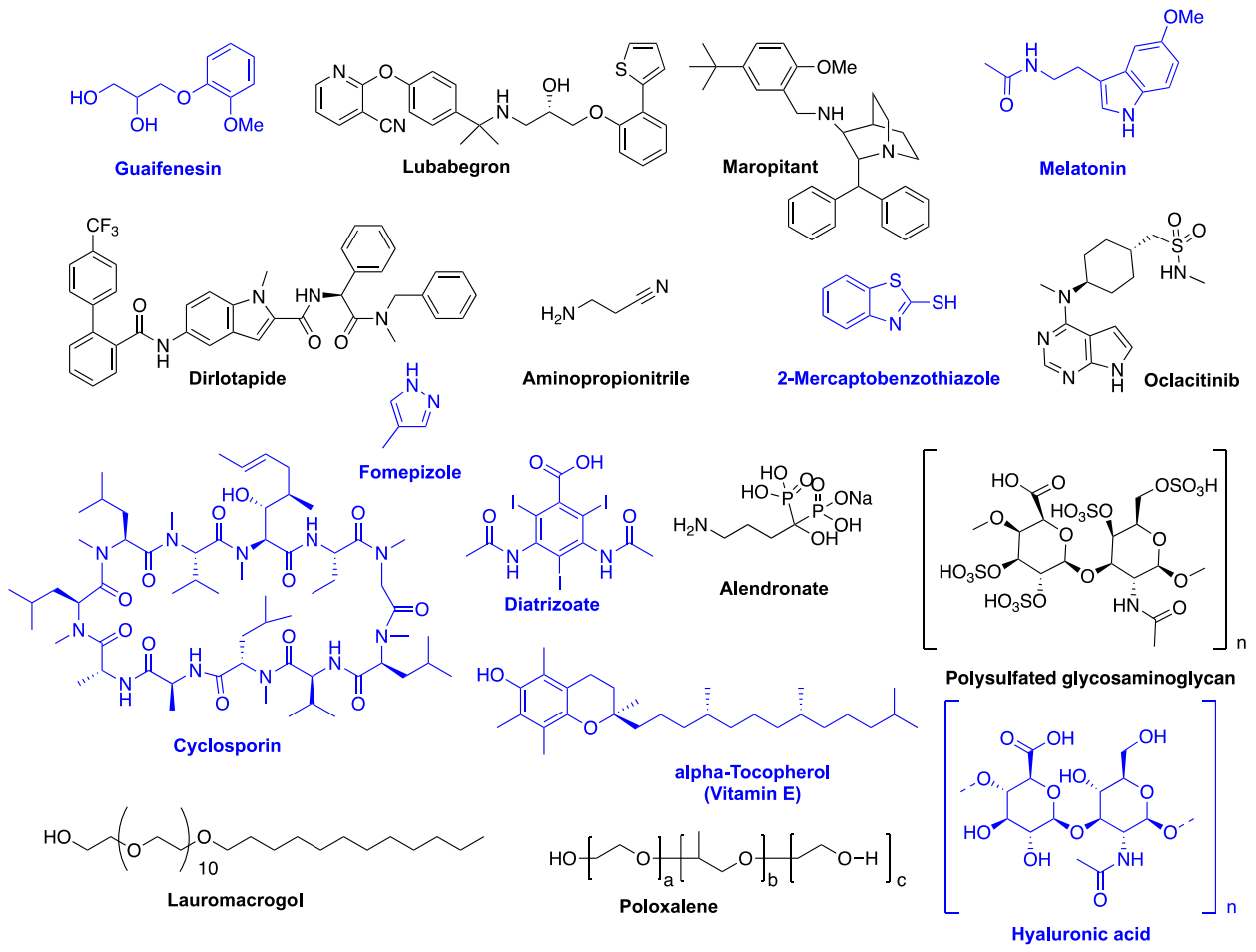

Figure 40. Additional miscellaneous drugs (drugs in blue are also approved in humans).

Miscellaneous Drugs 1. The drugs in this category do not fit neatly into a structural classification. Pralidoxime (Figure 39) is used to reverse nerve agent poisoning by binding to acetylcholinesterase enzymes that have been activated by organophosphates.[113] Zinc gluconate is comprised of two gluconic acids ligated to a zinc atom and is used by injection to chemically castrate dogs by acting as a sclerosing agent.[114] It is also used as a dietary zinc supplement. Gleptoferron is used to increase iron levels to treat anemia and has recently been explored as a combination drug with toltrazuril to treat *Cystoisospora* infections in piglets.[115,116] Capromorelin is a ghrelin mimic used as an appetite stimulant.[117] Omeprazole is a proton pump inhibitor used to treat gastric disorders and is one of the most commonly prescribed drugs for the same disorder in humans.[118] Neostigmine is used to reverse anesthesia in a number of species and to increase reticular motility in ruminants.[119]

Miscellaneous Drugs 2. Guaiafensin (Figure 40) is commonly used to treat cough.[120] Lubabegron is used to reduce ammonia emissions in cattle.[121] Maropitant is a neurokinin-1 receptor antagonist that is used as an antiemetic in dogs.[122] Dirlotapide is used to treat obesity in dogs.[123] Fomepizole is used to treat methanol or antifreeze (ethylene glycol) poisoning in companion animals as well as in humans.[124,125] Melatonin is a natural hormone produced by mammals and is used in dogs and other companion animals to treat sleep disorders and stimulate coat growth.[126] The antirheumatic drug β-aminopropionitrile is found naturally in plants of the genus *Lathyrus* and has been used to treat skeletomuscular diseases in companion animals.[127] It works by inhibiting lysyl oxidase, which is responsible for cross-linking collagen. The organosulfur drug 2-mercaptobenzothiazole is used to treat the skin condition known as moist dermatitis.[128] Diatrizoate is a contrast agent used in X-rays.[129] Alendronate is used to treat osteoporosis, osteosarcoma, and Paget's disease of the bone.[130] Cyclosporin is an immunosuppressant natural product used for a number of different indications in human and veterinary medicine. It is used in dogs as an immunomodulatory drug to treat keratojunctivitis sicca. Vitamin E (α-tocopherol) is given as a dietary supplement, especially in performance animals like racing dogs. It is also used to treat vitamin deficiencies. Polysulfated glycosaminoglycan is used as an injection to treat pain and lameness associated with arthritis in dogs and horses as well as hip dysplasia in dogs.[131] Lauromacrogol is used as an injection to treat vericose sclerosation. Recent reports have described some success in treating cysts by direct injection into the tissue. Poloxalene is added to bloat blocks as a surfactant to prevent bloating in cattle.[132] Hyaluronic acid is used in human and veterinary medicine to treat a number of conditions, including wound healing and joint disease.

Combination Drugs. The FDA Green Book data set contains 327 small molecules, and 86 of these are approved as combination drugs to make 95 unique combinations. In Figure 41, each ellipse contains the structure of a unique drug (or in the case of virginiamycin, two structures that make up a single

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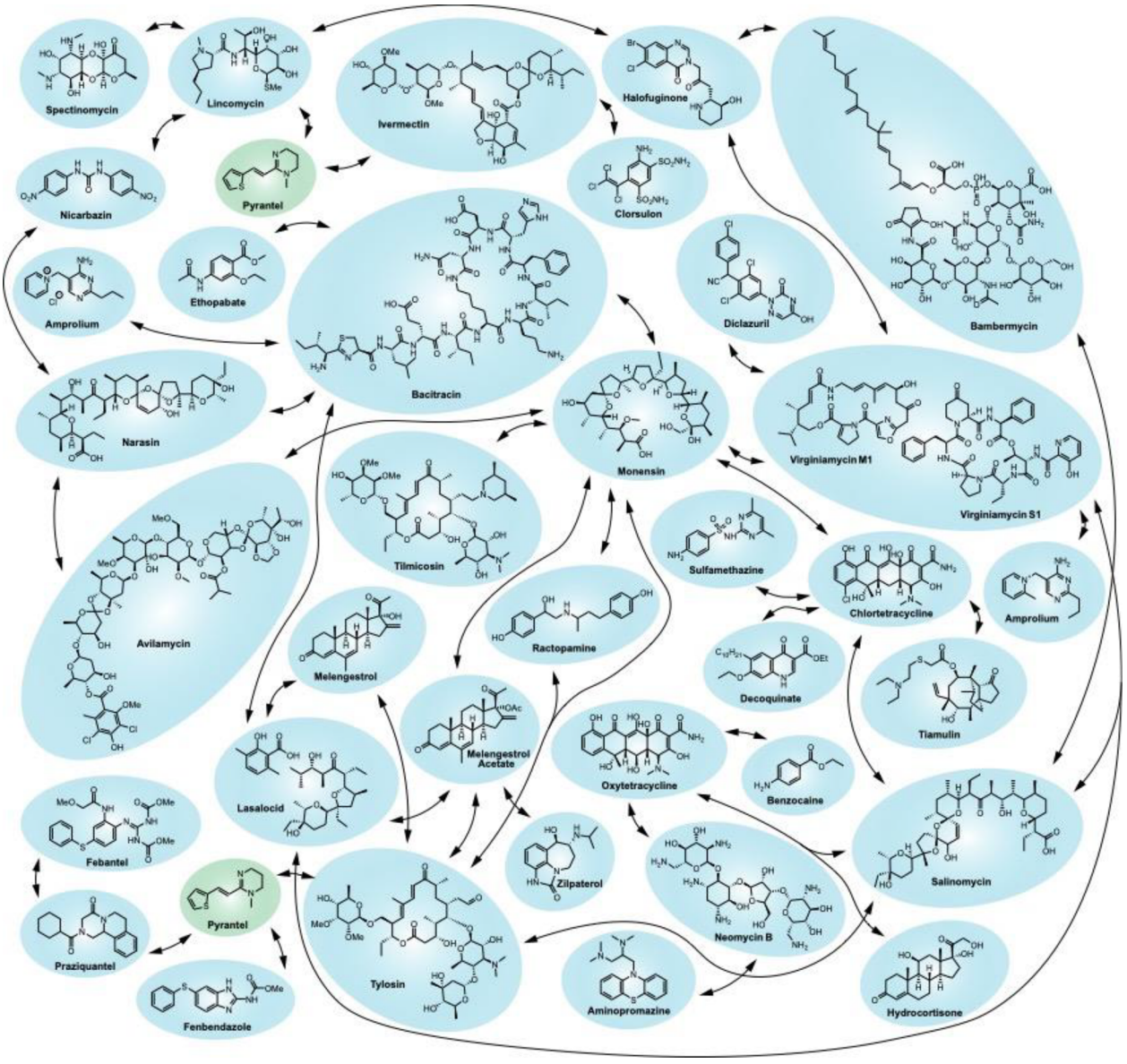

Figure 41. Two-drug combinations; pyrantel is shown in green to highlight that it is shown twice separately.

drug). Each arrow that connects two ellipses represents a unique combination of drugs. Interestingly, all 46 unique structures in Figure 41 can be arranged to represent 46 unique two-drug combinations. In this figure, monensin is approved in eight combinations, more than any other drug.

Figure 42 contains combinations that do not share structures with other combinations. Figures 43 and 44 contain three- and four-drug combinations in which drugs overlap across several approvals. The most highly represented drugs in combinations of three or four drugs are tylosin, melengestrol and its acetate, zilpaterol, and ractopamine, all of which are used as feed additives to promote weight gain in cattle. Figure 45 depicts the remaining three-drug combinations that do not overlap across approvals.

Peptide Hormones. The biologics that are approved in veterinary medicine have direct analogues in human medicine. Deslorelin, gonadorelin, and triptorelin (Figure 46) are gonadotropin-releasing hormone (GnRH) agonists. All three of these peptide hormones are used in fertility treatment to aid in breeding programs.[133] These peptides share a high degree of structural homology. Deslorelin and gonadorelin only differ by the R group at the N terminus. Triptorelin has an additional amino acid, a tryptophan (hence the name), between the phenylalanine and the valine. GnRHs have also been used as experimental drugs in certain types of cancer. Adrenocorticotrophin-releasing hormone is naturally produced in mammals and is used to diagnose hypo- and hyperadrenocorticism in animals. This is done by injecting the hormone and observing the effects on the adrenal glands. In humans it is used to treat multiple sclerosis. Thyrotropin releasing hormone is used to diagnose hypothyroidism and pituitary pars intermedia dysfunction (PPID) by administering the hormone to animals and observing the response.[134] Oxytocin is a naturally occurring hormone that is used to stimulate uterine contractions in animals, as it is in humans. Both human and porcine insulins are approved for use in veterinary medicine with the two insulin structures differing by a single residue. The 30th amino acid on the B chain is threonine in humans and alanine in pigs.

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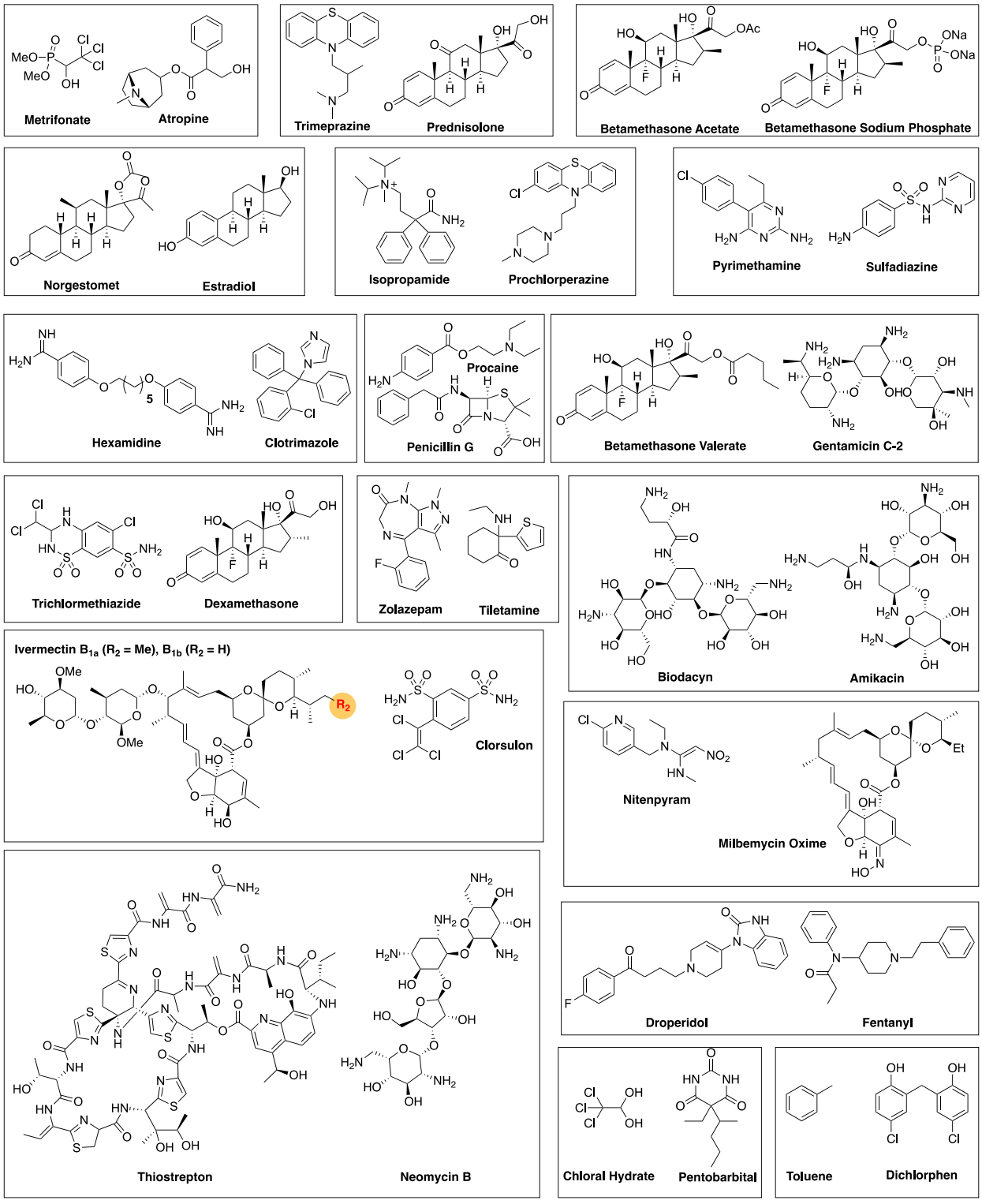

Figure 42. Additional two-drug combinations.

Other Biologics. Biologics that are larger than the peptides described in the previous section are described here. Pegbovigrastim (recombinant endogenous bovine granulite-colony stimulating factor, or G-CSF) stimulates production of neutrophils and is used to prevent mastitis and other postpartum disorders in cows without using antibiotics (Table 2).[135] Mastitis is one of the most important dairy diseases worldwide and accounts for 80% of antimicrobials used in dairy farming.[136] Dairy cows produce more milk when treated with *n*-methionyl bovine somatotropin (nBST, or bovine growth hormone), a growth hormone which is marketed as sometribove. Porcine pituitary follitropin is used as an injectable to stimulate ovulatory response in agricultural animals including cattle.[137] Similarly, chorionic gonadotropin is used to stimulate ovulation in mares.[138] Pituitary luteinizing hormone is also used to induce ovulation.[105] Trypsin is used to

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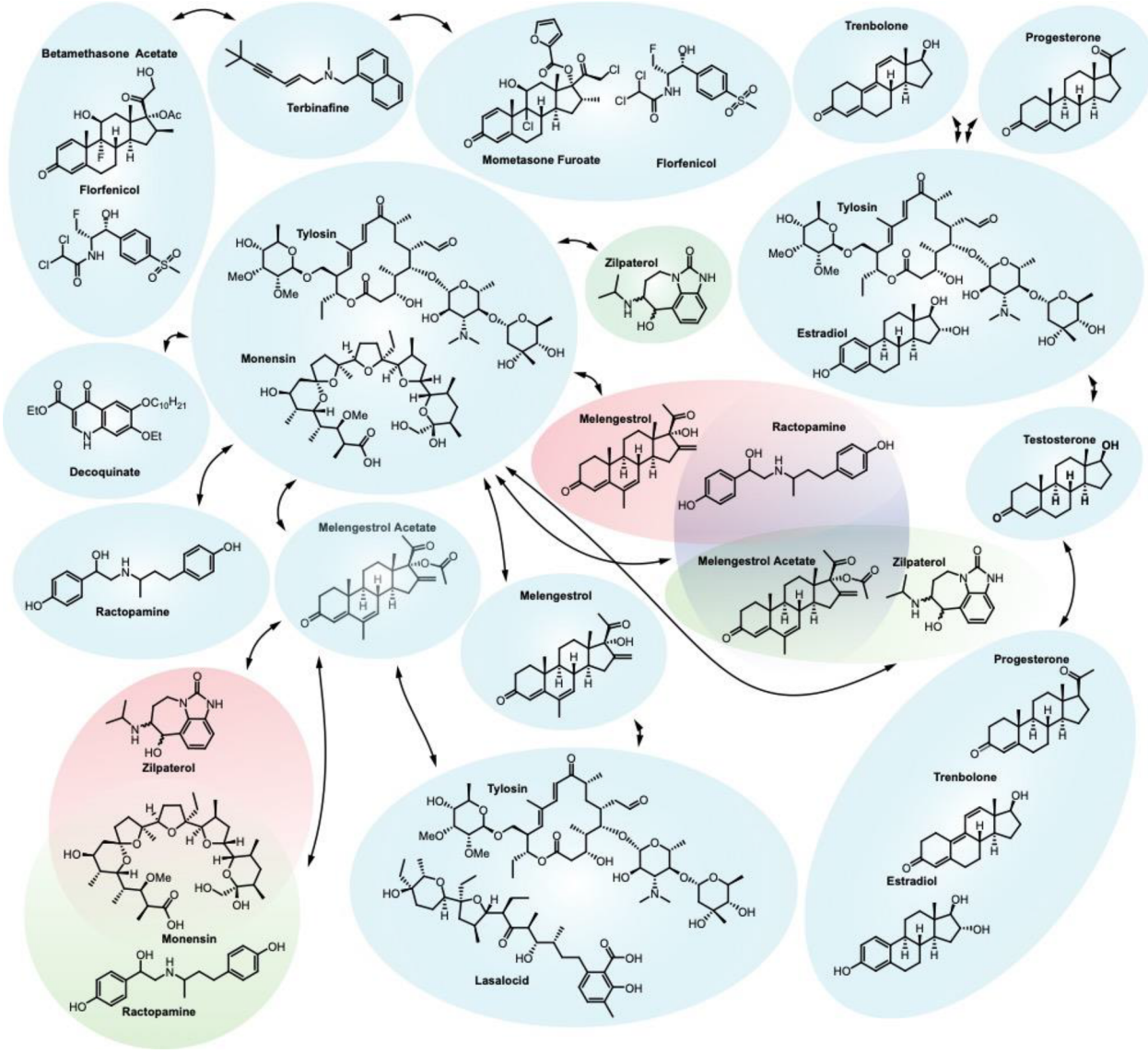

Figure 43. Three- and four-drug combinations; colors have been added to facilitate distinction between structures.

treat external wounds in companion and agricultural animals. Improvest, a gonadotropin factor analogue−diphtheria toxoid conjugate, is used to chemically castrate farm animals.[139] Iodinated casein is a feed additive that stimulates milk production in cows and has also been used to increase weight and egg production in chickens.[140,141]

Unapproved Drugs. The index of legally marketed unapproved new animal drugs is a short list of drugs that veterinarians can legally use in animal medicine but which have not been approved by the FDA (Table 3). The list was created in part to provide veterinarians with treatment options for minor species (species not common in the veterinary clinic) while ameliorating the high cost associated with clinical trials. Although there are 14 drugs on this list, a number of them have already been discussed and are approved by the FDA. A total of six unique small molecules (including two combinations) and three biologics make up the remainder of this list. Thiafentanil is a sedative that is used in minor hoofstock.[142] Metomidate is used in ornamental fish for anesthesia.[143] Benzalkonium chloride is used as an antiseptic and exists in two combinations, one with polyhexanide only and the other with polyhexanide and cypermethrin. Both combinations are used as topical antiseptics in a wide variety of species including mammals, birds, and reptiles. Poly acetyl-argenyl-glucosamide is used in elephants and rhinoceros as a topical to clean wounds. Salmon gonadotropin releasing hormone (sGnRHa) is used in combination with domperidone (a dopamine receptor agonist) and is used in ornamental fish to induce spawning.[144] Bovine hemoglobin is used in a number of species including mustelids, rodents, and raptors and is used as a blood substitute.

■ CONCLUSIONS

Humans have been in close contact with animals since we began domesticating them for agriculture, transport, and companionship. We have looked after our animals and sought to keep them healthy using contemporary methods of treatment that we used for ourselves throughout history. Zoonotic diseases have also been part of human pathology for at least as long, so in addition to remedies, we share a history of diseases with animals.[145] In fact, there is a correlation between the length of time an animal has been domesticated

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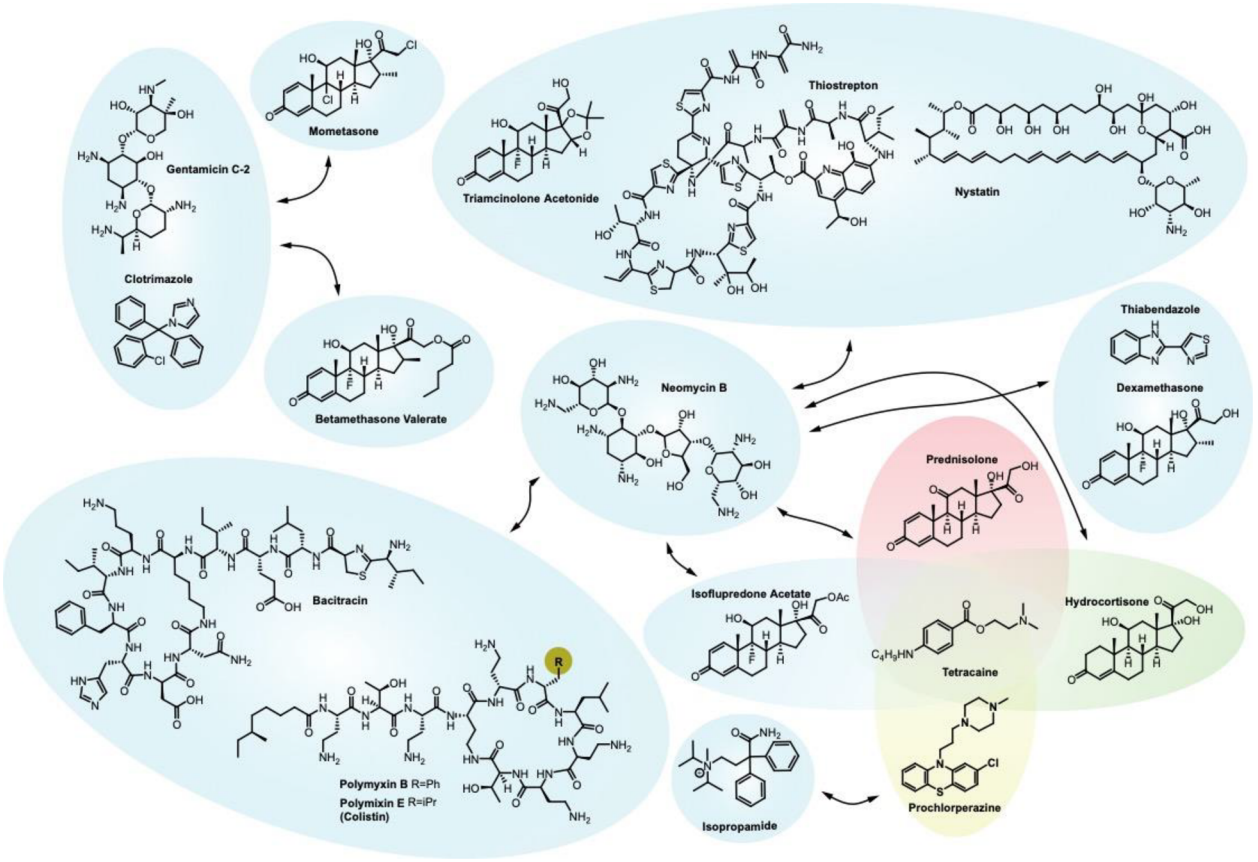

Figure 44. Additional three- and four-drug combinations; colors have been added to facilitate distinction between structures.

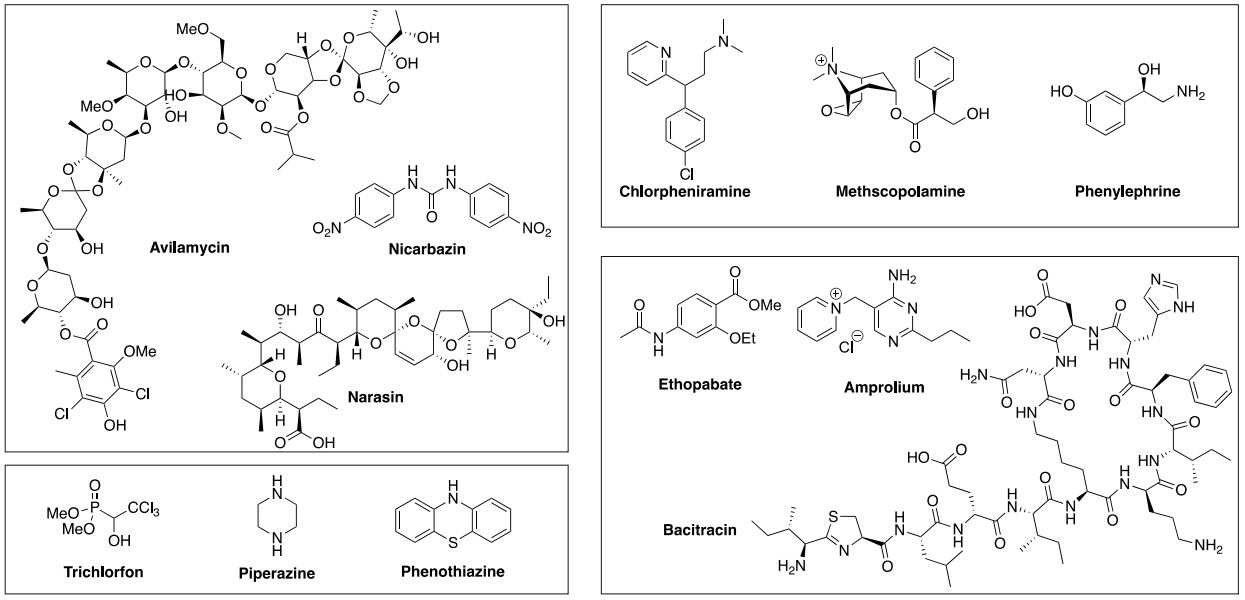

Figure 45. Three-drug combinations without overlapping drugs.

and the number of parasites and pathogens we share with them.[146] Until the late 1700s, academic studies did not distinguish between human and animal medicine.[147] Nearly a century after the epistemological split, Rudolf Virchow observed that humans and swine sometimes suffer from the same diseases and coined the term *zoonosis*. Virchow once again suggested that "one medicine," a single field of study, can encompass the pathologies of all animals (including humans) and that we can benefit from studying human and veterinary medicine together; the idea has been gaining momentum in recent years.[148,149] Today's pharmacists are responsible for dispensing both human and veterinary drugs and are required to have a deep understanding of both; medicinal chemists may also benefit from an awareness of both fields.

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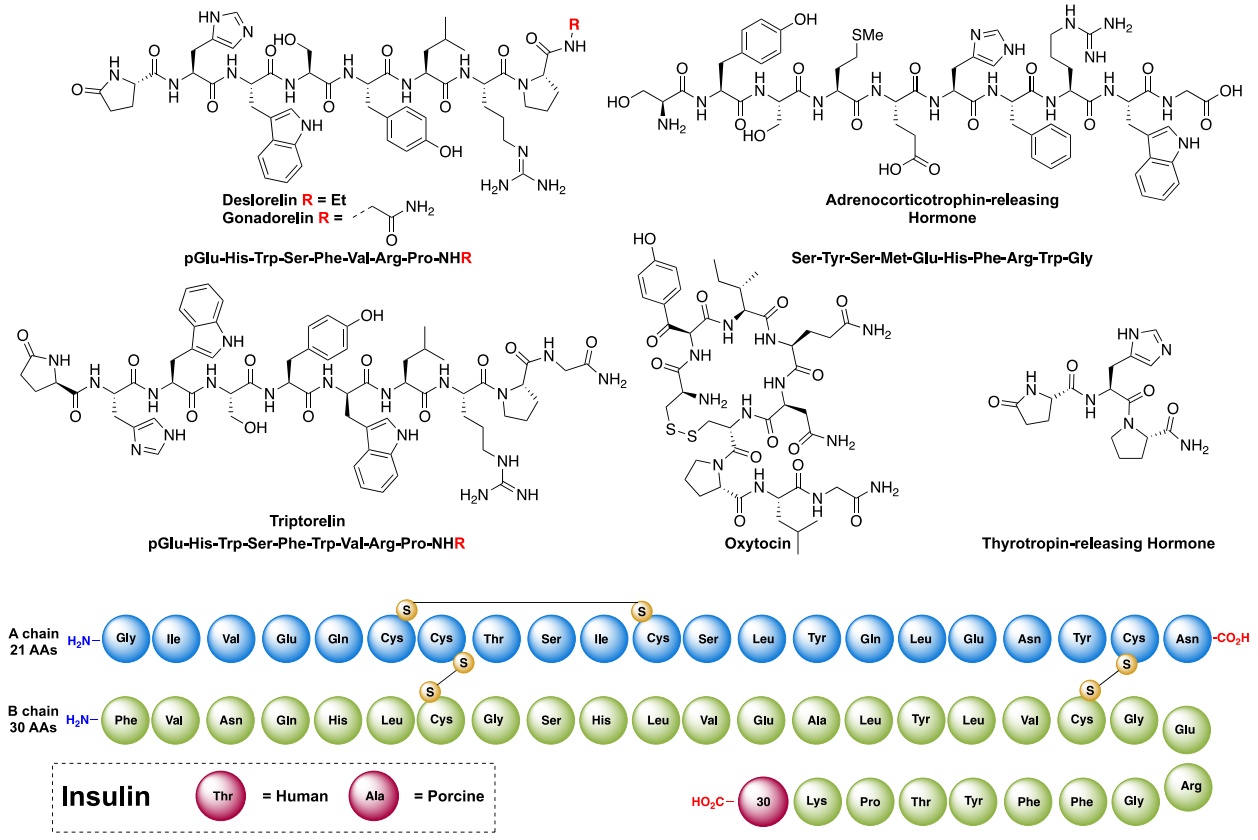

Figure 46. Veterinary peptide hormones.

Table 2. A Total of Eight Biologics beyond the Peptide Hormones Are Listed by Indication

drug name	classification	indication
recombinant endogenous bovine granulite-colony stimulating factor (G-CSF)	biologic	treats mastitis
n-methionyl bovine somatotropin (nBST)	biologic	growth hormone
porcine pituitary follitropin	biologic	reproductive
chorionic gonadotropin	biologic	reproductive
pituitary luteinizing hormone	biologic	reproductive
trypsin	biologic	wound-healing
gonadotropin factor analogue−diphtheria toxoid conjugate	biologic	reproductive (castration)
iodinated casein	biologic	feed additive

Drug products approved for veterinary use largely resemble human drugs in class, structure, and physicochemical properties. This comes as no surprise, as humans and animals (especially mammals) share much of their anatomy, physiology, and pathology. Anatomy and physiology will determine factors such as absorption, metabolism, and blood−brain barrier penetrance. These factors in turn dictate, at least in part, what kinds of structures are successful. Overlapping pathologies naturally lead to similar drug types in both fields. Similar drug types often have similar structures (as structure determines function), and previous successes of drugs often influence work on future drugs. The list of vet drug structures expands the data set of drugs that we look to in order to understand what kinds of structures are "drug-like." While the argument for "one medicine" is beyond the scope of this analysis, the clear connection and intersection between human and veterinary drug structures warrants further investigation.

Table 3. Index of Legally Marketed Unapproved Drugs Are Used to Treat Indications in Minor Species, For Which It Would Be Too Costly to Undergo Clinical Trials

drug name	classification	indication
thiafentanil	small molecule	anesthetic
metomidate	small molecule	anesthetic
benzalkonium chloride	small molecule	antiseptic
polyhexanide	small molecule	antiseptic
pypermethrin	small molecule	antiseptic
domperidone	small molecule	reproductive
poly acetyl-argenyl-glucosamide	biologic	wound-healing
salmon gonadotropin releasing hormone (sGnRHa)	biologic	reproductive
bovine hemoglobin	biologic	blood substitute

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Notes

The authors declare no competing financial interest.

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Munaum H. Qureshi received a B.S. in chemistry from The University of Texas at Austin in 2016. Munaum entered the graduate program in chemistry at The University of Arizona in August of 2016 and in January of 2017 joined the research group of Professor Njardarson.

Philip B. Cox is a Research Fellow at AbbVie. Phil received a B.Sc. (Hons) degree in chemistry from the University of Salford in 1987, then a Ph.D. at the University of Exeter in 1991 (Prof. Stan Roberts). After two postdoctoral fellowships at WSU and CWRU (Prof. Phil Garner), Phil began his industrial career in 1997 with Evotec as a project leader overseeing discovery chemistry collaborations. Phil then moved to Pharmacia and subsequently Pfizer, Ann Arbor, MI, where he was a member of the lead discovery group. In 2007, Phil moved to Abbott Laboratories (now AbbVie), where he has worked in many leadership roles in med chem and currently in cheminformatics. Phil is also an adjunct faculty in the Department of Chemistry at Washington State University.

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■ ABBREVIATIONS USED

6-APA, 6-aminopenicillic acid; AB-MPS, AbbVie multiparametric score; ACE, angiotensin converting enzyme; ACTH, adrenocorticotrophin-releasing hormone; cLogP, calculated BioByte log *P*; CNS, central nervous system; COX1, cyclooxygenase 1; COX2, cyclooxygenase 2; CYP3A, cytochrome P450 3A; FDA, Food and Drug Administration; Fsp^3, fraction of sp^3 carbons; GABA, γ-aminobutyric acid; G-CSF, granulite colony stimulating factor; GI tract, gastrointestinal tract; GnRH, gonadotropin releasing hormone; IQR, interquartile range; log *D*, calculated ChemAxon log *D*; MRSA, methicillin resistant *Staphylococcus aureus*; NAR, number of aromatic rings; nBST, *N*-methionyl bovine somatotropin; NHBA, number of hydrogen bond acceptors; NHBD, number of hydrogen bond donors; NR, number of rings; NRB, number of rotatable bonds; NSAID, nonsteroidal anti-inflammatory drug; PABA, *para*-aminobenzoic Acid; PBP, penicillin binding protein; PDE3, phosphodiesterase 3; PFI, property forecast index; PGF_{α}, prostaglandin F_{α}; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PPID, pituitary pars intermedia dysfunction; Q1, lower quartile; Q3, upper quartile; QED, quantitative estimate of drug-likeness; SSRI, selective serotonin reuptake inhibitor; TPSA, topological polar surface area; tRNA, transfer RNA; USDA, United States Department of Agriculture

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