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Perspective

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From Oxiranes to Oligomers: Architectures of U.S. FDA Approved Pharmaceuticals Containing Oxygen Heterocycles

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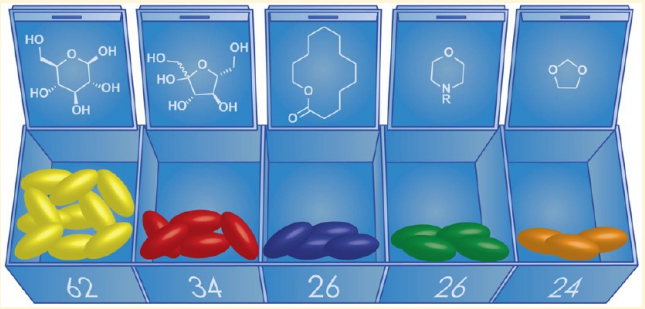
ABSTRACT: Oxygen heterocycles are the second most common type of heterocycles that appear as structural components of U.S. Food and Drug Administration (FDA) approved pharmaceuticals. Analysis of our database of drugs approved through 2017 reveals 311 distinct pharmaceuticals containing at least one oxygen heterocycle. Most prevalent among these are pyranoses, with furanoses, macrolactones, morpholines, and dioxolanes rounding off the top five. The main body of this Perspective is organized according to ring size, commencing with three- and four-membered rings and ending with macrocycles, polymers, and unusual oxygen-containing heterocycles. For each section, all oxygen heterocycle-containing drugs are presented along with a brief discussion about structural and drug application patterns.



INTRODUCTION

Inspired by how much was learned by assembling and analyzing the 640 small molecule drugs containing nitrogen heterocycles[1] as well as other educational endeavors,[2] a similar study for oxygen heterocycles has now been completed. Analysis of our drug database (through 2017) unearthed a total of 311 unique oxygen heterocycle-containing pharmaceuticals, which is a significant representation (about 27% of unique approved small molecules and 15% of all approved drugs). In comparison, our group's 2016 top 200 pharmaceutical prescription and retail sales posters reveal 17% and 16% representation of oxygen-heterocycle containing pharmaceuticals, respectively.[3] Many of these drugs contain more than one oxygen heterocycle with a total of 389 oxygen heterocycles being part of these 311 drugs. For example, recently approved eteplirsen and mipomersen contain 30 and 20 oxygen heterocycles, respectively. In the context of the evolutionarily selected structures carbohydrates and nucleosides, it is unsurprising that pyranoses and furanoses are the top two most frequently employed oxygen heterocycles. In this Perspective, all 311 U.S. FDA approved drugs containing oxygen heterocycles are presented, analyzed, and discussed in sections organized according to ring size or unique common structural features.

The breakdown of the 389 oxygen heterocycles that are components of the 311 identified oxygen heterocyclic drugs is presented according to ring size and presence or absence of aromaticity in Figure 1. The majority (89%) of the oxygen heterocycles are nonaromatic; 95% of aromatic are five-membered rings. These numbers are significantly higher than for their nitrogen heterocyclic counterparts where 70% are nonaromatic and 60% of the aromatic heterocycles are five-membered rings. With respect to ring size, five- and six-membered rings reign supreme (84% total) with 46% and 38%

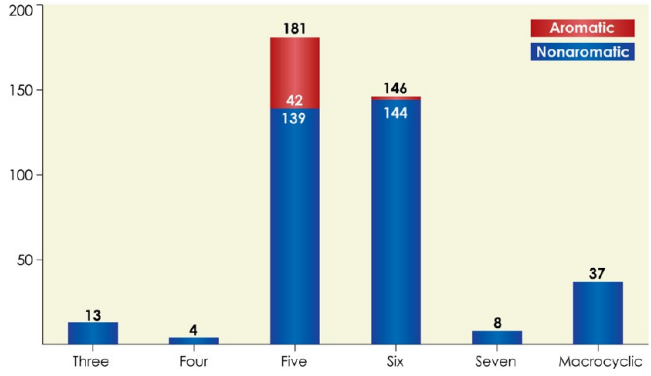


Figure 1. Distribution of oxygen heterocycles according to ring size and aromaticity.

representation, respectively. Rounding off the top five are macrocycles (10%) followed by three-membered (3%), seven-membered (2%), and four-membered (1%) rings.

A closer look at the 311 unique oxygen heterocycle containing U.S. FDA approved drugs reveals the majority (71%) are substituted with only one oxygen heterocycle (Figure 2), with 13% and 6% consisting of two and three oxygen heterocycles, respectively. A decent number (3%) of these drugs are decorated with greater than eight oxygen heterocycles. Although the atomic composition of the rings of these oxygen heterocycles primarily comprises one oxygen atom and carbon atoms (64%) as one would find in pyranoses, furanoses, etc., a large number (26%) also contain nitrogen, sulfur, boron, and even metal

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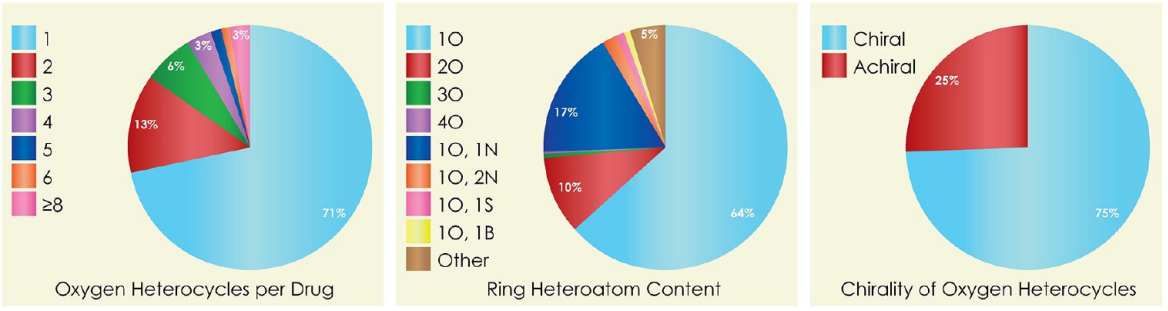

Figure 2. Frequency and structural content of oxygen heterocycles.

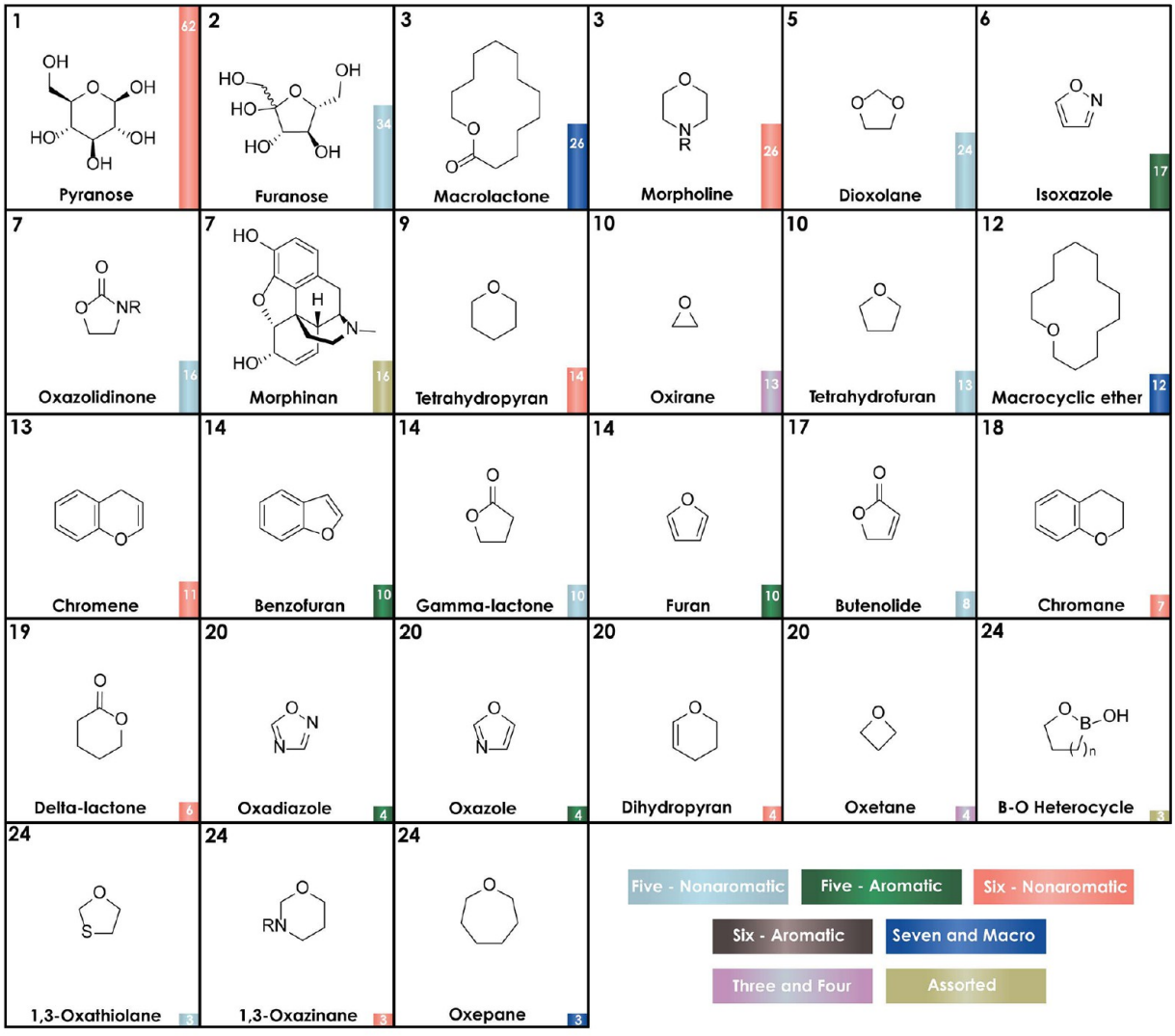

Figure 3. Most frequent oxygen heterocycles in U.S. FDA approved drugs.

atoms, and 10% contain a second oxygen atom. The most common of these are rings composed of one oxygen and one nitrogen atom, which are represented by members such as oxazoles and morpholines and their isomeric variants. Finally, most (75%) of these oxygen heterocycles are chiral.

Our analysis led us to identify the top 27 most frequently occurring oxygen heterocycles in the FDA pharmaceutical library (Figure 3). Analysis of the 389 oxygen heterocycles contained within the 311 unique oxygen heterocycle-containing drugs revealed that pyranoses are number 1 with 62 appearances (16%) followed by furanoses in a distant second place (9%). Macrolactones, morpholines, and dioxolanes account for the remaining top five. These data for oxygen heterocycles are far more top heavy in favor of one heterocycle (pyranose) when compared with nitrogen heterocycles, with a 45% decrease between #1 (pyranose) and #2 (furanose) compared to 14% drop between (#1) piperidine and (#2) pyridine. In assembling this top 27 list and deciding how to best convey the diversity of

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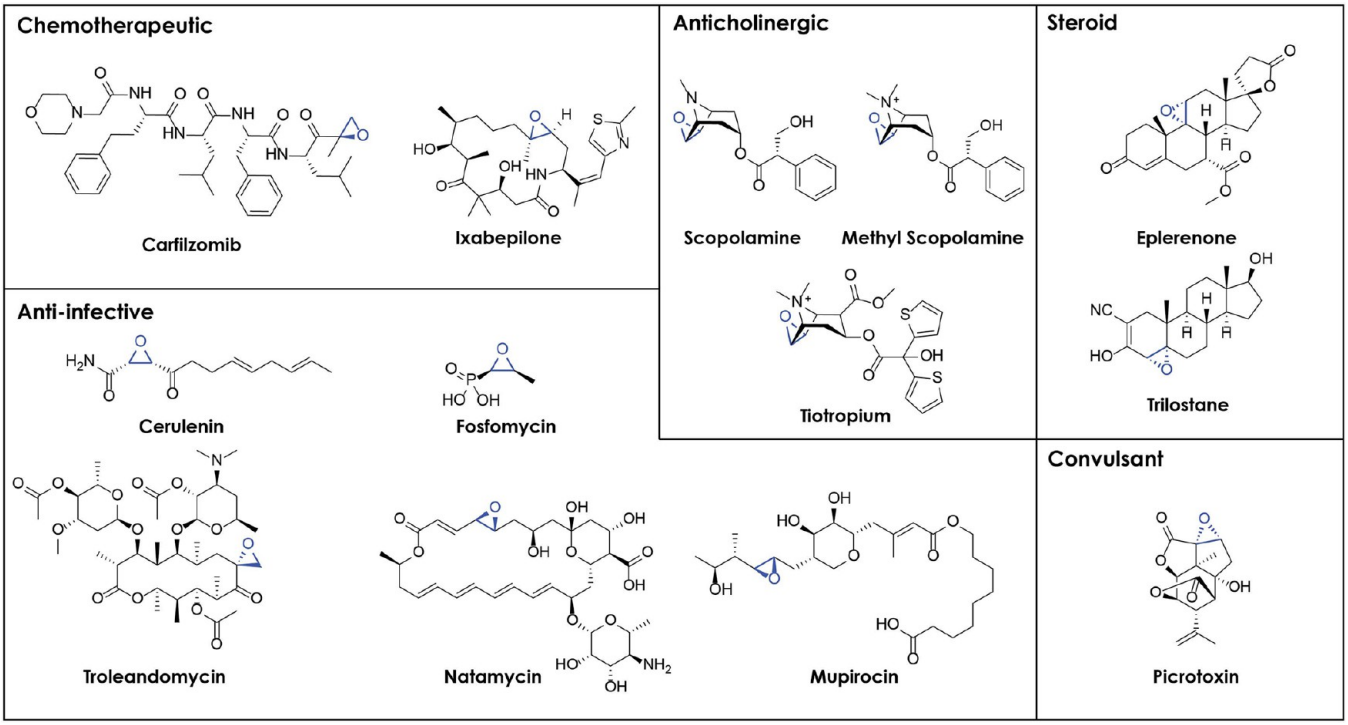

Figure 4. Pharmaceuticals containing oxiranes.

oxygen heterocycles presented in later sections, similar ring types are organized according to their degree and location of unsaturation as well as exact location of heteroatoms within a given ring and fusion with other rings. For example, pyranoses are not the only six-membered rings containing a single oxygen atom in the top 27. Also belonging to this broad category would be tetrahydropyrans, chromenes, chromanes, δ-lactones, and dihydropyrans. Similarly, isoxazole and oxazole were categorized separately. Macrolactones (#3) make it into the top 10, which is in stark contrast to nitrogen heterocycles, for which no macrocycles make it into the top 27. This is perhaps not entirely surprising as macrocyclic drugs are commonly natural products or derivatives that usually contain 14- to 20-membered lactones. Dioxolanes, which chemists typically associate with carbonyl protecting groups, are quite a surprise at #5 being part of 24 approved drugs. Oxiranes appear highly on this list; this is not the case for the three-membered nitrogen heterocycle aziridine, which is only seen in a single U.S. FDA approved drug. Only 5 (19%) of the top 27 oxygen heterocycles are aromatic, with isoxazole (#6) being the most commonly occurring. Two (1,3-oxathiolane and boron−oxygen heterocycles) of these top structures contain atoms other than carbon, oxygen, or nitrogen as part of their rings. Four fused ring types (morphine, chromene, benzofuran, and chromane) are represented, which is far fewer than for nitrogen heterocycles where 11 fused rings are highly ranked. Oxadiazoles are the only oxygen heterocycle in the top 27 with two additional heteroatoms as part of the core ring. Furthermore, 13 (48%) of the top 27 oxygen heterocycles are five-membered; 8 (30%) are six-membered.

In the sections that follow, all of the 311 unique oxygen heterocycle-containing drugs are presented according to their ring size, from small to large starting with oxiranes and continuing all the way to macrocyclic structures, with the final two sections focused on oxygen oligomers and unusual oxygen heterocycles. To achieve comprehensive coverage of all relevant structures, drugs that contain more than one oxygen heterocycle appear in more than one section. For each section, the oxygen heterocycle of focus is highlighted in blue and drug structures are organized based on common disease indications. For drug families with high structural similarity, alphabetized colored circles are employed to signify structural deviations from the common core.

THREE-MEMBERED OXYGEN HETEROCYCLES

Oxiranes appear in 13 U.S. FDA approved drugs (Figure 4). With respect to oxirane substitution arrangements, only di- (69%) and trisubstituted oxiranes are represented. Three of the trisubstituted rings are part of fused natural product-type ring systems (eplerenone, trilostane, and picrotoxin), while one (ixabepilone) is nonfused. The disubstituted oxiranes can be further broken down into three categories: 1,1-disubstituted (carfilzomib and troleandomycin), 1,2-trans-disubstituted (natamycin and mupirocin), and 1,2-cis-disubstituted (scopolamine, methyl scopolamine, tiotropium, cerulenin, and fosfomycin). These oxirane-containing drugs are structurally diverse with origins in natural products. Troleandomycin, natamycin, mupirocin, scopolamine, and picrotoxin are natural products, while eplerenone, trilostane, tiotropium, and methyl scopolamine are natural products derived from steroids and tropanes, respectively. Scopolamine, methyl scopolamine, and tiotropium are anticholinergic drugs used to treat a variety of conditions such as nausea, peptic ulcers, irritable bowel syndrome, and chronic obstructive pulmonary disease (COPD).[4,5] These drugs are easily recognizable by their tropane ring. Fosfomycin, isolated from *Streptomyces fradiae*, is a broad-spectrum antibiotic effective against both Gram-negative and Gram-positive bacteria. Intriguingly, fosfomycin, with its small size and phosphonic acid substitution at a reactive oxirane site, shares no structural similarities to any other natural product antibiotics.[6] Cerulenin is an antifungal agent that inhibits fatty

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acid and sterol biosynthesis. The reactive epoxide interacts with fatty acid synthase through the formation of a covalent adduct with a cysteine residue.[7] Trilostane, which inhibits steroid biosynthesis, is used to combat Cushing's syndrome (hyperadrenocorticism) in both humans and dogs.[8] Mupirocin and troleandomycin are both antibiotics, with troleandomycin having also been investigated as an alternative to steroids in the treatment of asthma.[9] Mupirocin, which is easily hydrolyzed and therefore can only be applied topically, is primarily used to combat streptococcal and staphylococcal infections. Natamycin is an antifungal available as eye drops to treat fungal infections around the eye.[10] Carfilzomib, a selective proteasome inhibitor, is an analog of the natural product epoxomicin. Epoxomicin and carfilzomib contain a unique pharmacophore epoxyketone that is responsible for the drug's mechanism of action. The epoxyketone undergoes a double nucleophilic attack by a threonine residue, thereby forming a morpholine ring.[11]

FOUR-MEMBERED OXYGEN HETEROCYCLES

Oxetane's importance as a valuable structural motif in drug discovery has increased in recent years. Oxetanes possess high polarity and the ability to act as hydrogen bond acceptors while contributing to metabolic and chemical stability of their host molecule. As a result of these attractive physiochemical properties, oxetanes have been investigated as isosteres to gem-dimethyl and carbonyl groups.[12] As depicted in Figure 5,

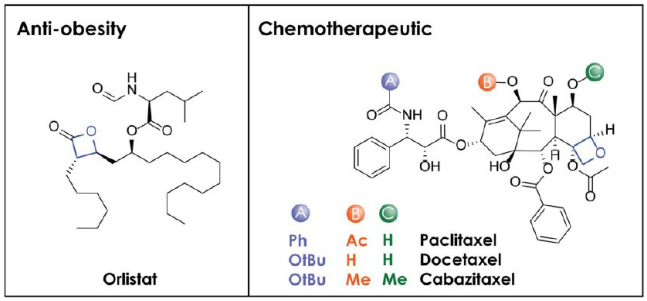

Figure 5. Pharmaceuticals containing oxetanes.

four U.S. FDA approved drugs contain an oxetane. Paclitaxel (Taxol) and its two derivatives (docetaxel and cabazitaxel), which are antimitotic agents, contain a trisubstituted oxetane fused to the cyclohexyl C-ring. The paclitaxel family of drugs has proven to be successful in treating cancers like breast, lung, and ovarian. The oxetane ring in this family of drugs orients the adjacent acetyl group in the hydrophobic binding pocket for optimal interactions.[13] Orlistat, an antiobesity drug, contains a β-lactone ring. Orlistat is a semisynthetic derivative of the natural product lipstatin and acts as an irreversible inhibitor of pancreatic lipase, thereby reducing fatty acid absorption from the GI tract. The reactive electrophilic β-lactone moiety is critical for irreversible acylation of the serine residue in lipase.[14]

FIVE-MEMBERED OXYGEN HETEROCYCLES: NONAROMATIC

Furanose. The furanose ring appears in 34 U.S. FDA approved pharmaceuticals of which 31 contain a single furanose (Figure 6) with the remaining being oligomers (Figure 33). The majority (74%) of furanose containing drugs are nucleosides. This number increases to 79% if the nucleoside component of vitamin B12 derivatives is included. A closer look at these nucleosides reveals that 52% of nucleobases contain the pyrimidine core, 36% contain the purine core, while pentostatin and ribavirin contain ring-expanded or ring-contracted nucleobases. Several of the nucleobases are substituted with halogens in the form of iodine (idoxuridine), fluorine (floxuridine, fludarabine, and capecitabine), trifluoromethyl (trifluridine), and a 1-thio-3,3,3-trifluoropropyl (Cangrelor) substituent. With respect to the substitution and stereochemical patterns of the furanose component, all but one of these nucleoside drugs contain a 2,5-cis-substitution with the same stereochemistry. The exception to this is telbivudine, which is the enantiomer of thymidine. Four common furanose cores are highlighted in Figure 6, with the rest differing in their substitutions or lack thereof at the 3- and 4-positions. The majority (68%) contain substituents at 3- and 4-positions, with 26% lacking a substituent at the 3-position, two being unsubstituted (didanosine and zalcitabine) and, interestingly, none lacking a substituent at the 4-position. Most fascinating of these are zidovudine, clofarabine, gemcitabine, and sofosbuvir, which are decorated with fluorine atoms or an azide at these positions. Many of these drugs are antimetabolite agents used to combat cancer and viruses. These antimetabolite drugs act as imposter substrates and entice nucleotide biosynthesis enzymes to select them over endogenous substrates. Once this occurs, the antimetabolites irreversibly bind the enzymes, thereby halting DNA synthesis. Cyanocobalamin and hydroxcobalamin, which are synthetic derivatives of vitamin B_{12}, are used to treat vitamin B_{12} deficiencies as well as related conditions such as pernicious anemia.[15] Non-nucleoside furanoses appear in five drugs (neomycin, paromomycin, streptomycin, lactulose, and sucralfate). All these furanoses contain at least one highly decorated pyranose component as well. Neomycin, paromomycin, and streptomycin are natural product antibiotics. Lactulose, a disaccharide of fructose and galactose, is used to treat constipation as well as hepatic encephalopathy by lowering ammonia levels. Because it is a synthetic sugar, lactulose is not metabolized by humans.[16] Sucralfate is most notable for the unique aluminum sulfate decoration of all its hydroxyl groups.

Dioxolane. The dioxolane heterocycle appears in 24 drugs (Figure 7). Three unique drug families, corticosteroids, podophyllotoxins, and conazoles, all contain dioxolanes. 83% of dioxolanes are part of fused rings, with 38% of those being aromatic (1,3-benzodioxole). Of these nine 1,3-benzodioxoles, only lumacaftor is substituted at the ketal carbon (two fluorine atoms). This is in clear contrast to the cyclic and acyclic alkyl ones, which all contain either one (13%) or two (87%) carbon substituents at the ketal carbon atom. Topiramate is noteworthy as the only drug containing two dioxolanes, while guanadrel is structurally the simplest member of this family. The nine steroids shown contain a dioxolane fused to the D-ring at carbons 16−17 with two methyl groups substituted at the ketal carbon (acetonide) for most members. Otherwise, these steroids differ primarily in their C−F substitutions or if the primary hydroxyl group is acylated. The dioxolane (cyclic ketal) helps increase the lipophilicity and potency of these topical corticosteroids. The conazoles, a class of antifungals, contain a nonfused trisubstituted dioxolane ring with a chiral quaternary center. Ketoconazole was the first oral antifungal azole to be discovered, but as a result of more effective antifungals becoming available, its use is currently limited to shampoos and creams. Podophyllotoxin (podofilox), a natural product extracted from *Podophyllum* species, is used to treat genital warts. Podofilox functions by destabilizing microtubules. Remarkably, two

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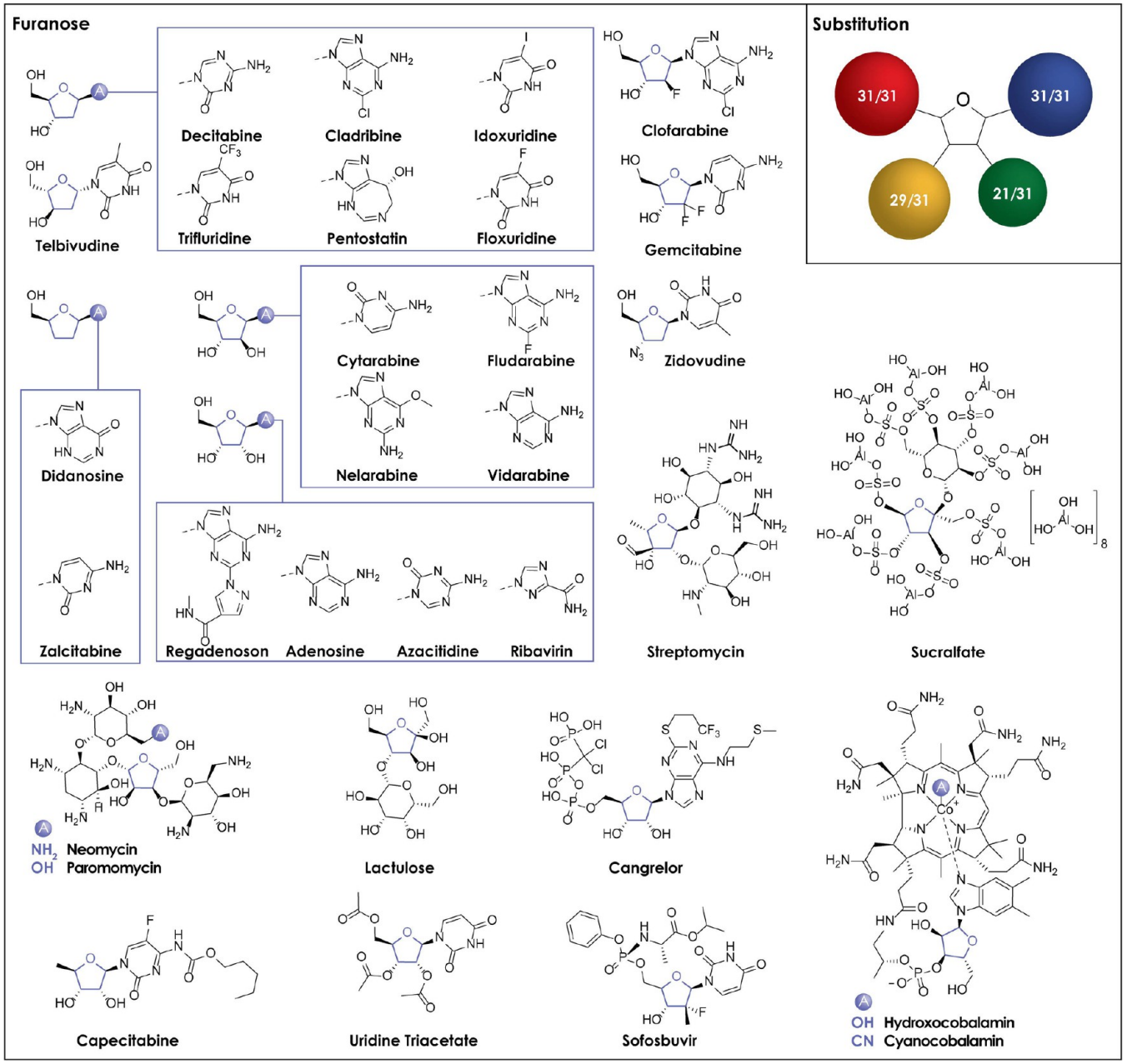

Figure 6. Pharmaceuticals containing furanose.

semisynthetic derivatives of podofilox (etoposide and teniposide) function as topoisomerase II poisons and are prescribed for treatment of numerous cancers.[17] Guanadrel contains both a spirocyclic dioxolane and guanidine component. Guanadrel is structurally and pharmacologically similar to guanethidine; both are used as antihypertensives.[18] The dioxolane moiety appears in drugs used to treat a variety of conditions including depressive and anxiety disorders (paroxetine), erectile dysfunction (tadalafil), epilepsy (topiramate), cancer (trabectedin and omacetaxine mepesuccinate), and cystic fibrosis (lumacaftor). Lumacaftor contains cyclopropane and difluoromethylene moieties, both of which are being seen more frequently in pharmaceuticals.

Dihydrofuran-2(3*H*)-one (γ-Lactones). γ-Lactones appear in 10 U.S. FDA approved pharmaceuticals (Figure 8), of which six are fused, three are spiro, and one (pilocarpine) is not attached to a ring. The γ-lactone of mycophenolate mofetil is the only one that contains unsaturation and lacks any stereocenters. Natural product motifs play a key role in this category, with two natural products (podofilox and picrotoxin) and all the rest except pilocarpine being derivatives of natural products. The spirolactone class of steroids contain spirocyclic γ-lactones at the C17 junction. These drugs are mineralocorticoid receptor antagonists that help to increase sodium excretion and potassium retention. Both the lactone ring and enone-decorated A-ring are crucial for activity.[19] Picrotoxin contains an additional γ-lactone as part of its pentacyclic core. Vorapaxar, a derivative of the natural product himbacine, is a thrombin receptor antagonist indicated for patients with past myocardial infarctions.[20] Pilocarpine, a disubstituted cholinergic dihydrofuran-2(3*H*)-one that contains an additional imidazole component, is used to treat glaucoma and xerostomia (dry mouth).[21] Mycophenolate mofetil, which is a prodrug of mycophenolic acid, helps prevent transplant rejection.[22]

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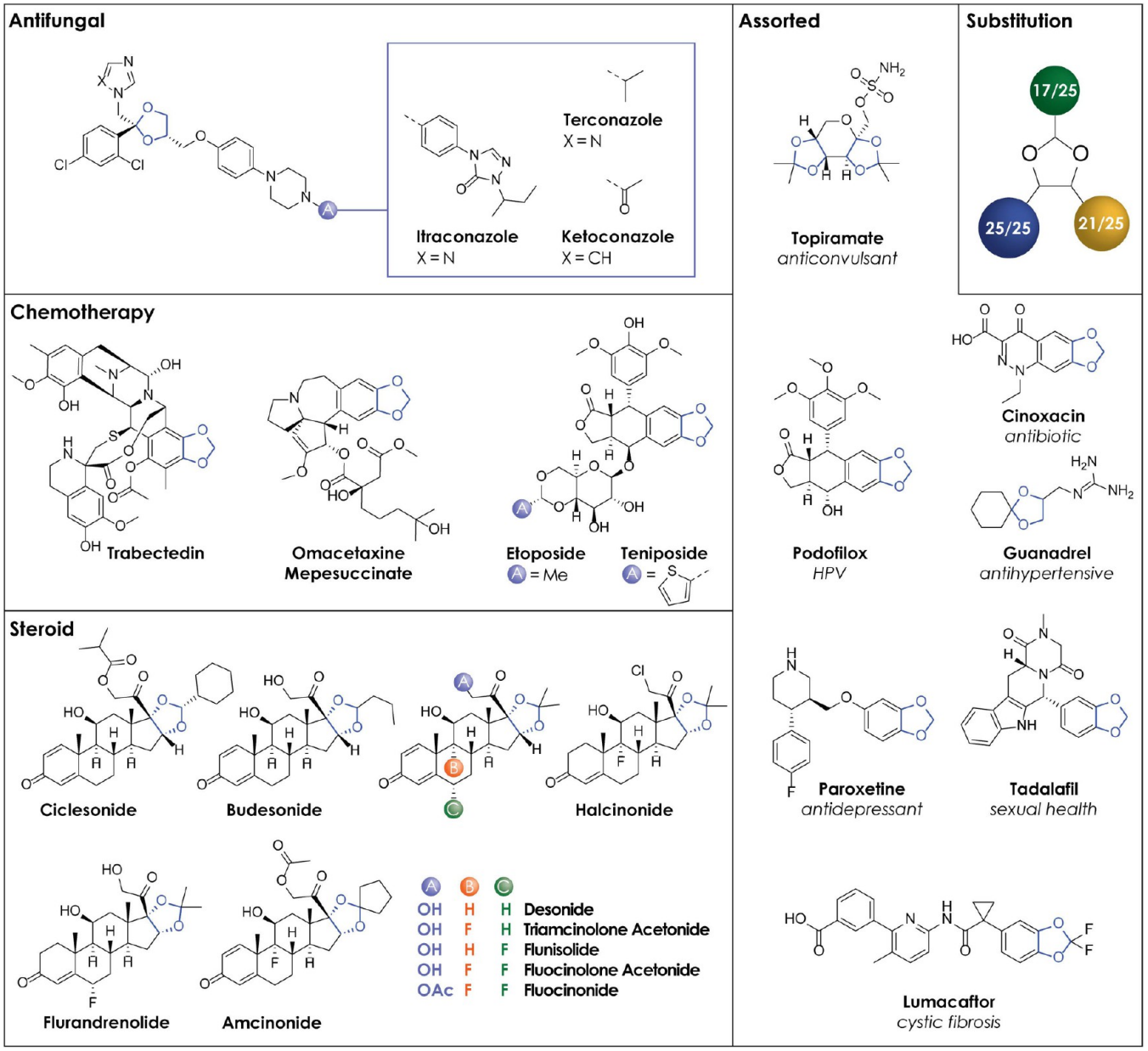

Figure 7. Pharmaceuticals containing dioxolanes.

Furan-2(5*H*)-one (Butenolides). Butenolides appear in the eight drugs presented in Figure 9 of which six are steroids. The digoxin family, indicated for a myriad of heart-related conditions, contains a chiral butenolide attached at C17 on the D-ring of their glycosylated steroid core.[23] Rofecoxib, an anti-inflammatory, contains a 1,2-diaryl substituted butenolide. Fluorescein is a fluorescent dye that is used as a tracer in a variety of procedures. It is commonly used in the medical field of ophthalmology as a diagnostic tool for corneal conditions.

Oxazolidinones. Oxazolidinone family members appear in 16 U.S. FDA approved drugs (Figure 10). These 16 oxazolidinones can be broken into four structural categories. Oxazolidine-2-ones are mostly commonly seen in this family, appearing in eight (50%) of these drugs. Most members (tedizolid, linezolid, furazolidone, and telithromycin) are antibiotics. In particular, oxazolidine-2-ones make up a class of antimicrobial drugs that inhibit protein synthesis at the P site of the 50S ribosomal subunit of Gram-positive bacteria.[24] Within the oxazolidine-2-one family, all but metaxalone have a nitrogen atom substituent. Furazolidone is the least substituted oxazolidine-2-one member, while telithromycin is the most (tetrasubstituted). The isomeric oxazolidine-4-ones appear in four (25%) drugs, which are small components of the ergot alkaloids, which are used to treat migraines. The oxazolidine-2,4-dione moiety is present in three (19%) drugs (pemoline, trimethadione, and paramethadione). Finally, cycloserine, an intriguing constrained version of the amino acid serine, is the lone isoxazolidin-3-one. Cycloserine, a partial NMDA-agonist initially developed to combat tuberculosis, has been investigated for use in treating neuropsychiatric illnesses such as schizophrenia.[25]

Tetrahydrofurans. Tetrahydrofuran-containing drugs are prescribed as treatments for various diseases including cardiovascular, infectious, urinary, cancer, and diabetes (Figure 11). Cyclic ethers have been used in drug design as bioisosteres of amide/peptide bonds in protease inhibitors to help combat

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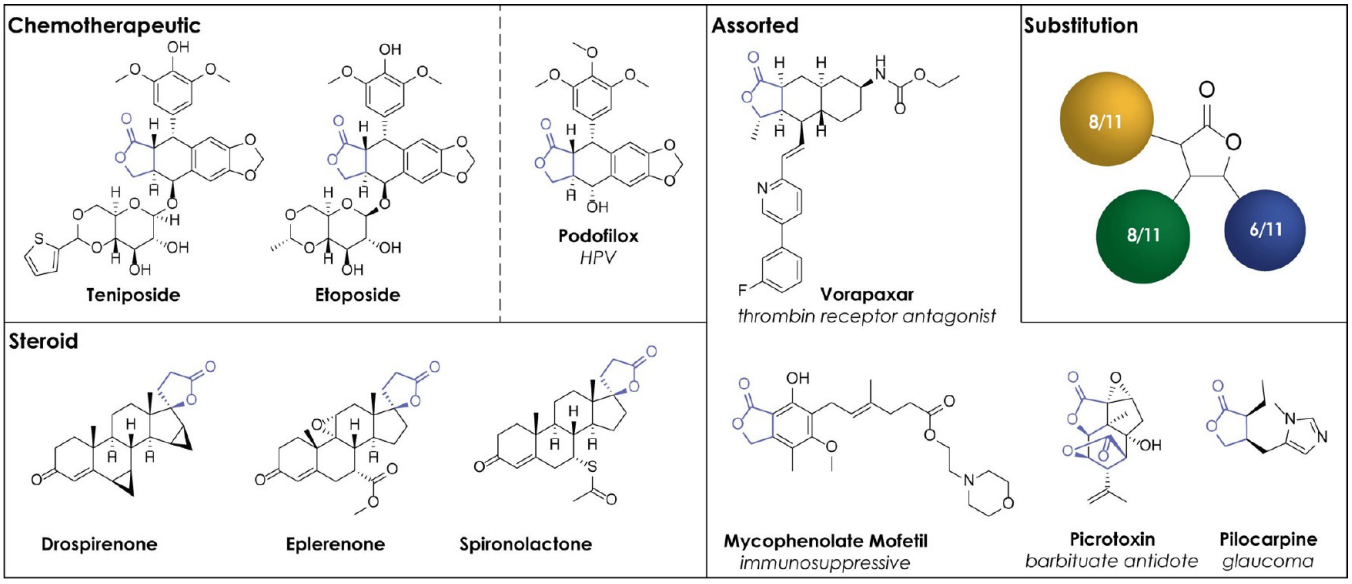

Figure 8. Pharmaceuticals containing dihydrofuran-2(3*H*)-one (γ-lactones).

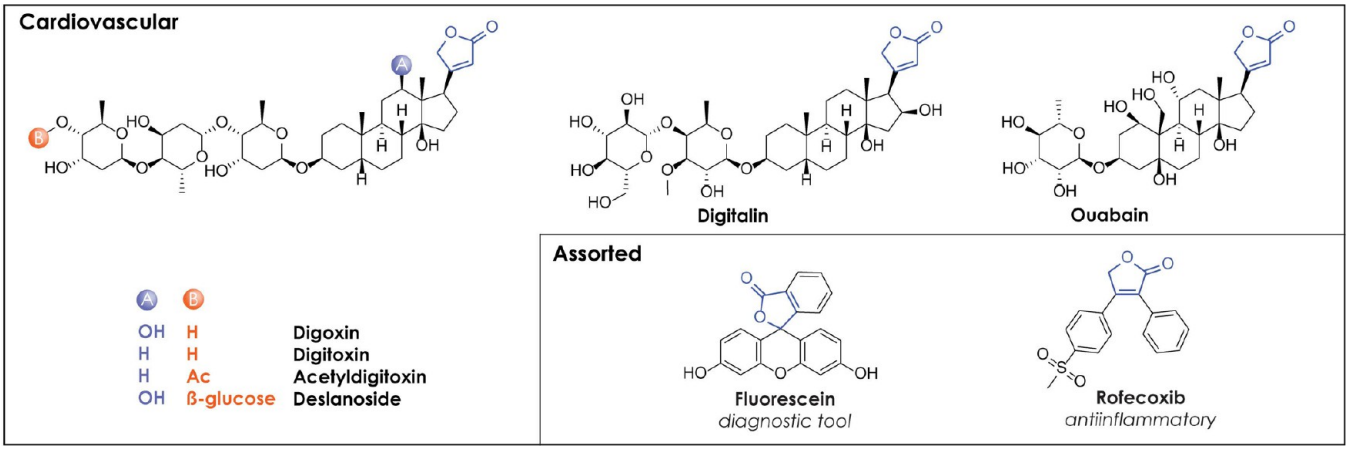

Figure 9. Pharmaceuticals containing furan-2(5*H*)-one (butenolides).

drug-resistant viral strains. The ether's oxygen can form hydrogen bonds (like peptides), thereby enhancing binding affinity. In addition, replacing a peptide bond with a tetrahydrofuran helps increase the bioavailability of the drug, as it will no longer be susceptible to protease degradation.[26,27] These approaches have been shown to be effective with amprenavir and darunavir in treating HIV infection. Our analysis reveals 13 tetrahydrofuran-containing drugs. Four of these drugs contain two tetrahydrofuran units, three of which are fused bis-tetrahydrofurans (darunavir, isosorbide dinitrate, and isosorbide mononitrate). All tetrahydrofurans contain a stereocenter, with terazosin and alfuzosin being sold as racemates. Ivermectin and epoprostenol (prostaglandin I2) are the only bona fide natural products with eribulin being a synthetic analog of the natural product halichondrin B.[28] Posaconazole, a recent antifungal of the azole family, contains a trisubstituted tetrahydrofuran with a chiral quaternary center. Posaconazole is preferred over earlier azoles such as ketoconazole, as it is effective against *Aspergillus* as well as other fungal infections resistant to previous antifungals.[29]

1,3-Oxathiolane. Three drugs contain an 1,3-oxathiolane heterocycle (Figure 12). All three are chiral and are substituted at C2 and C4 positions. Cevimeline, whose 1,3-oxathioloane is spiro-connected to a quinuclidine, is a muscarinic agonist indicated for treatment of dry mouth.[30] Lamivudine, a cytidine nucleoside analog, is an antiretroviral medication used to treat HIV/AIDS and hepatitis B. Its fluorinated analog, emtricitabine, is a nucleoside reverse transcriptase inhibitor also utilized for the treatment of HIV.[31] Emtricitabine is prescribed in combination with tenofovir.

FIVE-MEMBERED OXYGEN HETEROCYCLES: AROMATIC

Furans. The aromatic furan heterocycle appears in 10 drugs (Figure 13) of which six (60%) are disubstituted and four (40%) are monosubstituted. All these furans are substituted at C2 with six (67%) being also substituted at C5. Fluticasone furoate is the only furan drug without a benzylic amine/imine in the 2-position. The nitrofurans are a class of drugs almost exclusively used as antibiotics. Nitrofurantoin, available since World War II, is used to treat urinary tract infections.[32] However, dantrolene is used as a muscle relaxant.[7] Lapatinib, a human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR) mixed inhibitor, contains a disubstituted furan.[33] Prazosin, originally used as an antihypertensive, has also been

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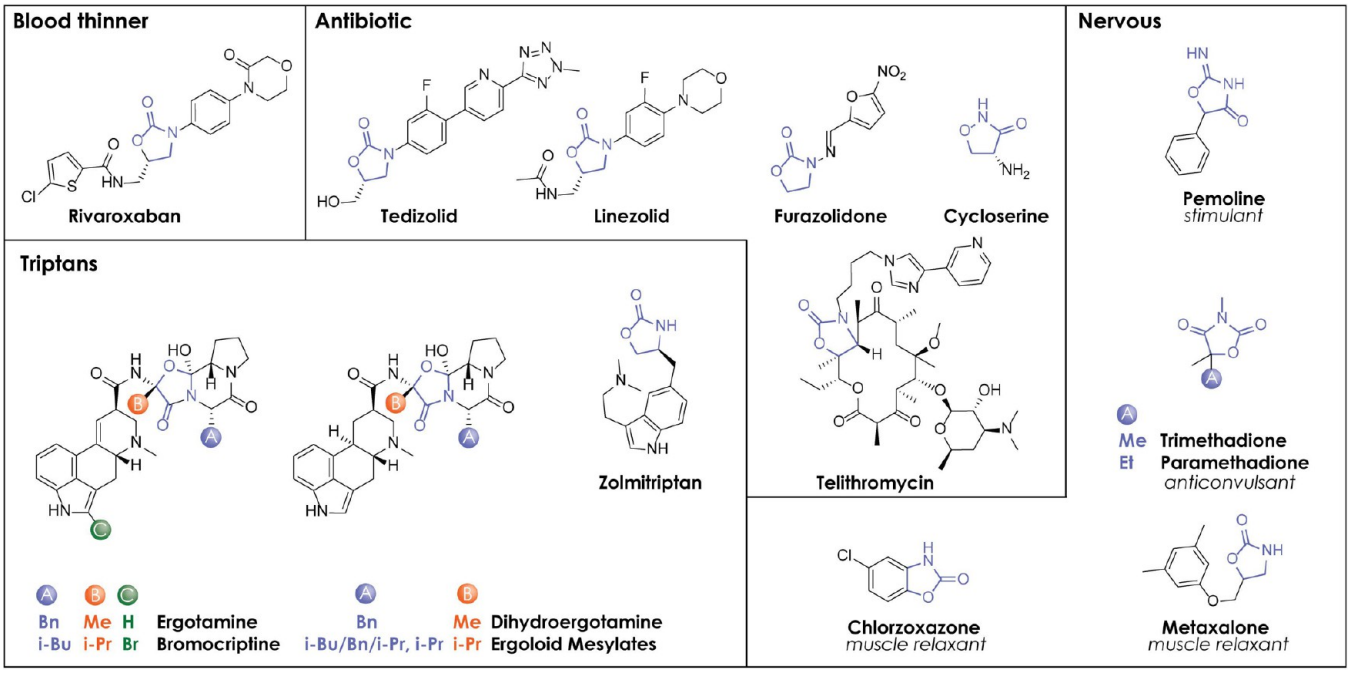

Figure 10. Pharmaceuticals containing oxazolidinones.

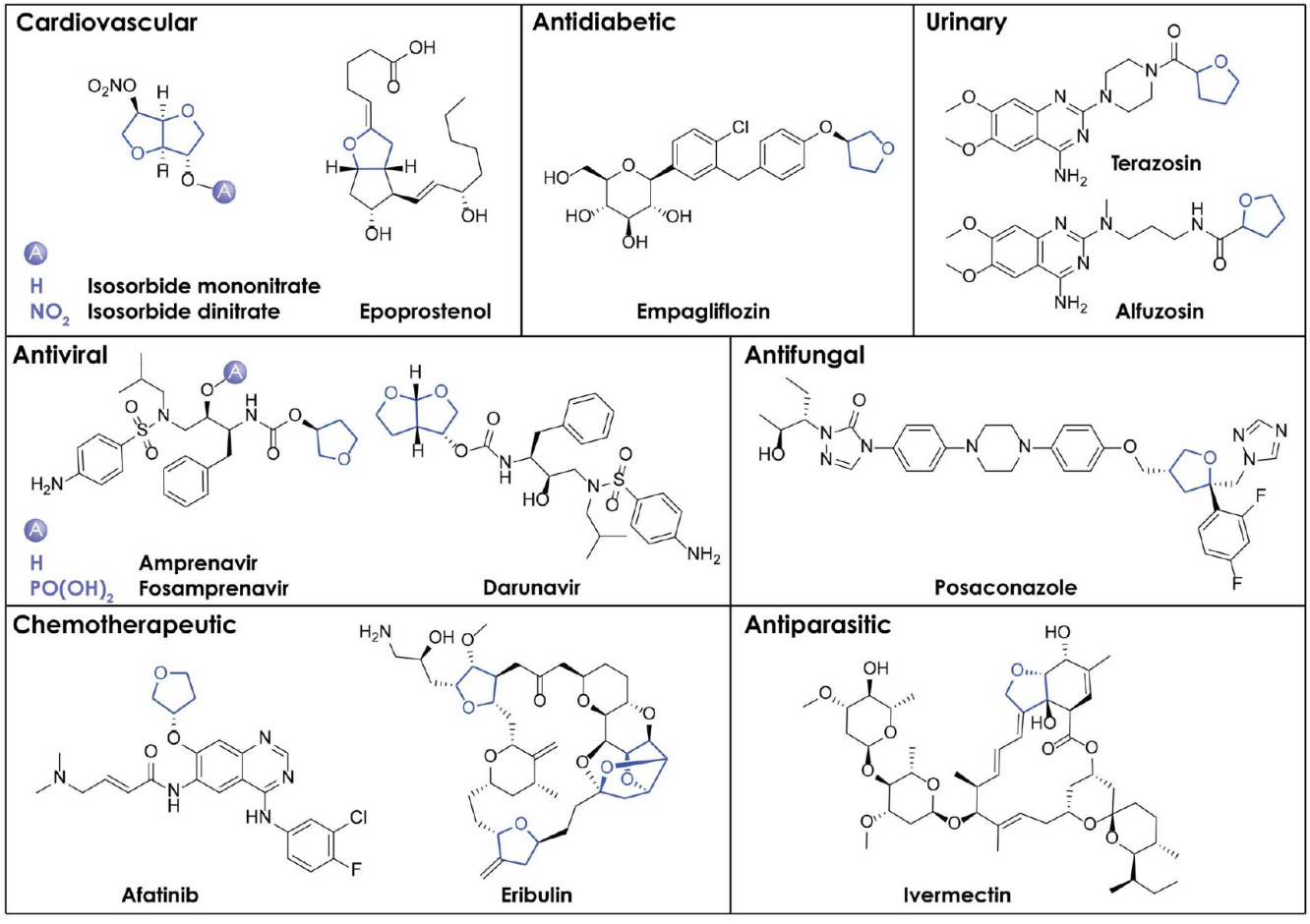

Figure 11. Pharmaceuticals containing tetrahydrofurans.

evaluated as candidate for treating nightmares, especially post-traumatic stress disorder (PTSD) related.[34] Ranitidine, an antacid (histamine H2 receptor antagonist) FDA approved in 1983, became one of the first drugs to total $1 billion in sales.[35]

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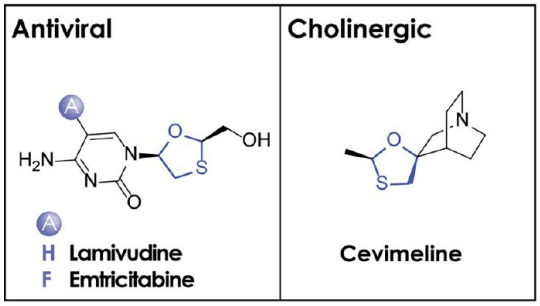

Figure 12. Pharmaceuticals containing 1,3-oxathiolane.

At first glance, it may seem surprising that such a common heterocycle only appears in nine drugs. It is worth noting however that both furans and thiophenes can display hepatotoxicity when bioactivated to electrophilic *cis*-2-butene-1,4-dials in vivo.[36,37]

Isoxazoles. Our database reveals 17 drugs containing an isoxazole (Figure 14) of which three (risperidone, paliperidone, and zonisamide) are benzisoxazoles. Substitution pattern analysis reveals that 65% of these isoxazoles are trisubstituted with the rest being disubstituted. All isoxazoles are substituted at C5, and all but two (danazol and leflunomide) are substituted at C3. Isoxazole-containing drugs display a broad range of biological activity as exemplified by the various indications.[38,39] The β-lactam oxacillin family, sulfisoxazole (acetyl) and sulfamethoxazole are all antibiotics. Isoxicam and valdecoxib are anti-inflammatory drugs, while isocarboxazid is an antidepressant of the monoamine oxidase inhibitor (MAOI) class. Leflunoamide is an immunosuppressant, whereas risperidone and paliperidone are antipsychotics. Micafungin is an antifungal natural product of the echinocandin family.

Oxazoles. In juxtaposition to the 17 isoxazoles approved, its isomer oxazole only appears in two approved drugs oxaprozin and suvorexant (Figure 15). Also included in Figure 15 are dihydro- (deflazacort) and tetrahydro- (clavulanate) oxazole drugs. Various drug types including anti-inflammatory, sleep agents, antibiotics, and glucocorticoids are represented by these four drugs. Deflazacort, which was approved in 2017 for the treatment of Duchenne muscular dystrophy, contains a dihydrooxazole fused at C16−C17 of its D-ring steroid core. Suvorexant, which contains three types of heterocycles, was approved in 2014 for the treatment of insomnia. Clavulanate, a β-lactamase inhibitor, contains a unique oxa-penam (clavam) core wherein the sulfide common to penams has been replaced with an ether.

Oxadiazoles. Oxadiazoles, which are frequently used in drug discovery as bioisosteres of amides and esters as well as to confer solubility benefits,[40] are represented by three isomeric forms and appear in four U.S. FDA approved drugs (Figure 16). The antiretroviral remedy raltegravir contains a 1,2,5-oxadiazole core, and the high blood pressure medication isradipine is decorated with a benzo-variant. In naldemedine, which is approved to treat opioid-induced constipation, one of the nitrogen atoms is in a different position (1,2,4-oxadiazole) while in the hypertension drug azilsartan medoxomil the heterocycle is no longer aromatic (1,2,3-oxadiazole-3-one) as a carbonyl group has been added.

SIX-MEMBERED OXYGEN HETEROCYCLES: NONAROMATIC

Pyranose. The pyranose family constitutes the largest family of U.S. FDA approved drugs containing oxygen heterocycles, with 62 drugs containing at least one pyranose. Natural products, oligosaccharides, and more traditional synthetic drugs are all encompassed in this diverse family. Given the size of this data set and the fact that many of these drugs are large and occupy significant space when drawn, the discussions about the pyranoses are split into three sections. Part 1 (Figure 17) is focused on chemotherapeutic, cardiovascular, antidiabetic, and antifungal agents, part 2 (Figure 18) is dedicated to antibiotics, and part 3 (Figure 19) covers an assortment of pyranoses.

Pyranoses in part 1 are components of nine chemotherapeutic, six cardiovascular, five antidiabetic, and four antifungal agents (Figure 17). Pyranoses in these series are common components of terpenoids, glycosylated macrolactones, and anthracyclines. The anthracycline family is easily recognized by their linearly fused tetracyclic core. These anticancer agents, which are extracted from *Streptomyces* bacteria, are all decorated with an L-daunosamine carbohydrate (pyranose). The anthracyclines intercalate with DNA, thereby inhibiting topoisomerase II.[41] Streptozocin, a glucosamine-nitrosourea compound, is a natural product currently used to treat pancreatic islet cell cancer. As with other nitroso-containing compounds, streptozocin is an alkylating agent, thereby acting as a DNA synthesis inhibitor.[42] Midostaurin, a derivative of staurosporine, is part of the indolocarbazole family

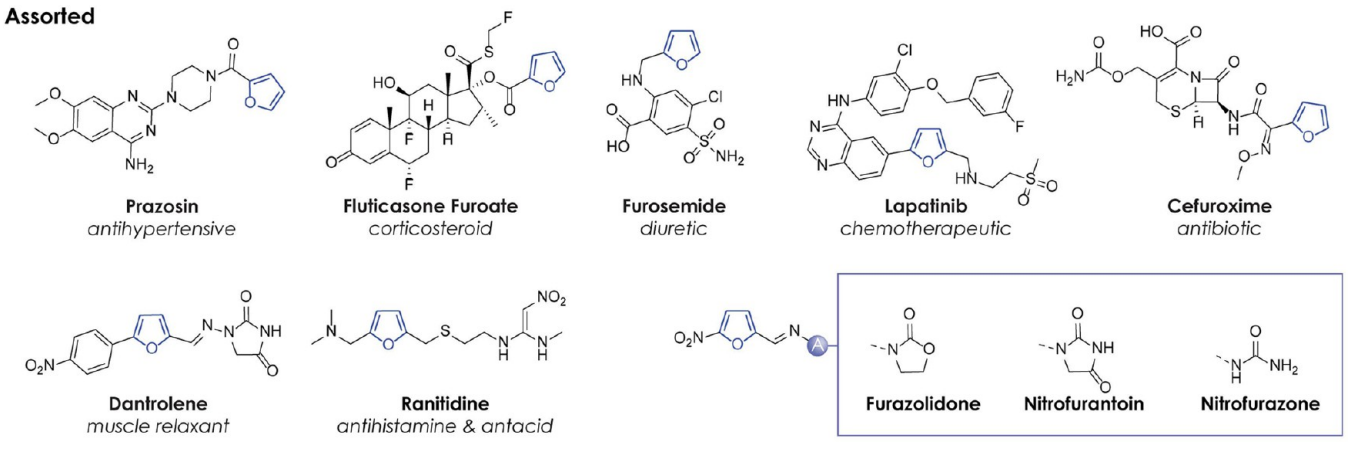

Figure 13. Pharmaceuticals containing furans.

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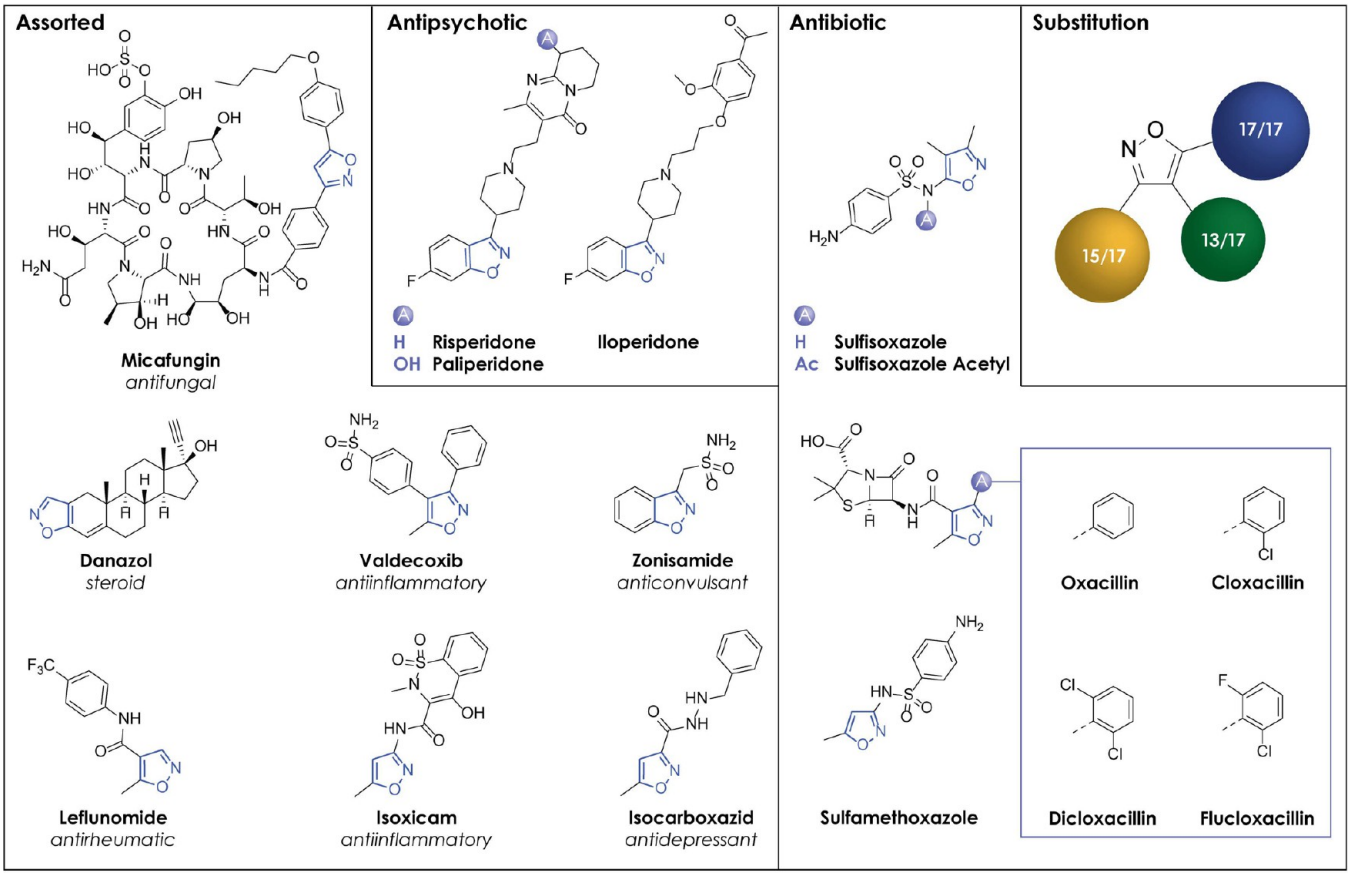

Figure 14. Pharmaceuticals containing isoxazoles.

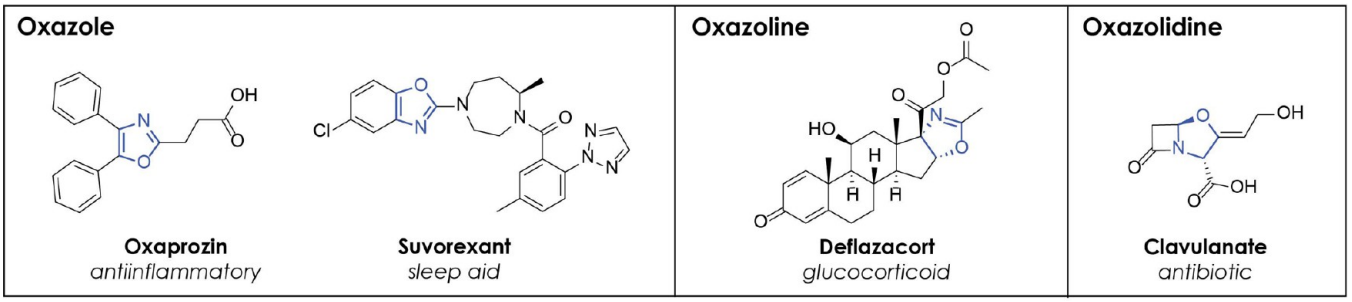

Figure 15. Pharmaceuticals containing oxazoles.

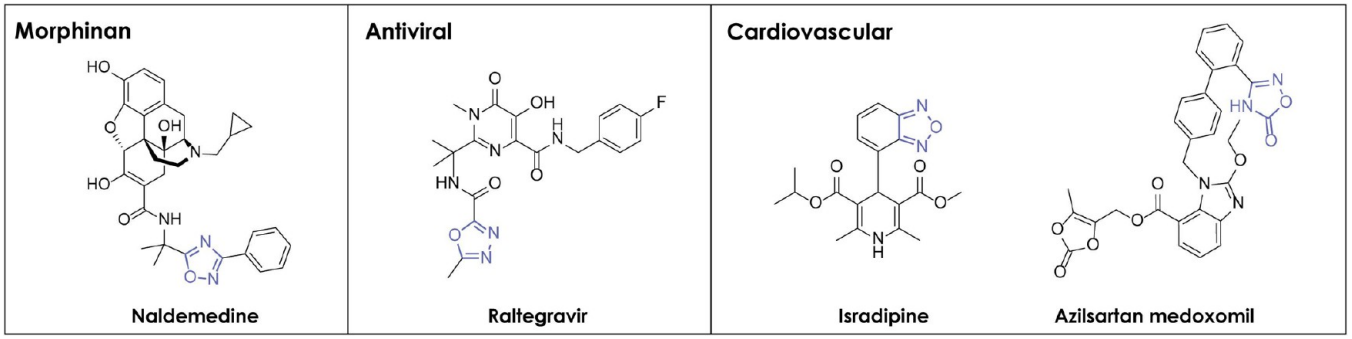

Figure 16. Pharmaceuticals containing oxadiazoles.

and was recently approved as an anticancer agent.[43] Bleomycin is a glycopeptide of antitumor antibiotic class used to treat a variety of cancers. The bis-thiazole in bleomycin is involved in intercalating DNA, helping to facilitate the single- and double-stranded breaks.[44] The digitalis glycosides, isolated from *Digitalis* (foxglove), are a family of drugs used to treat

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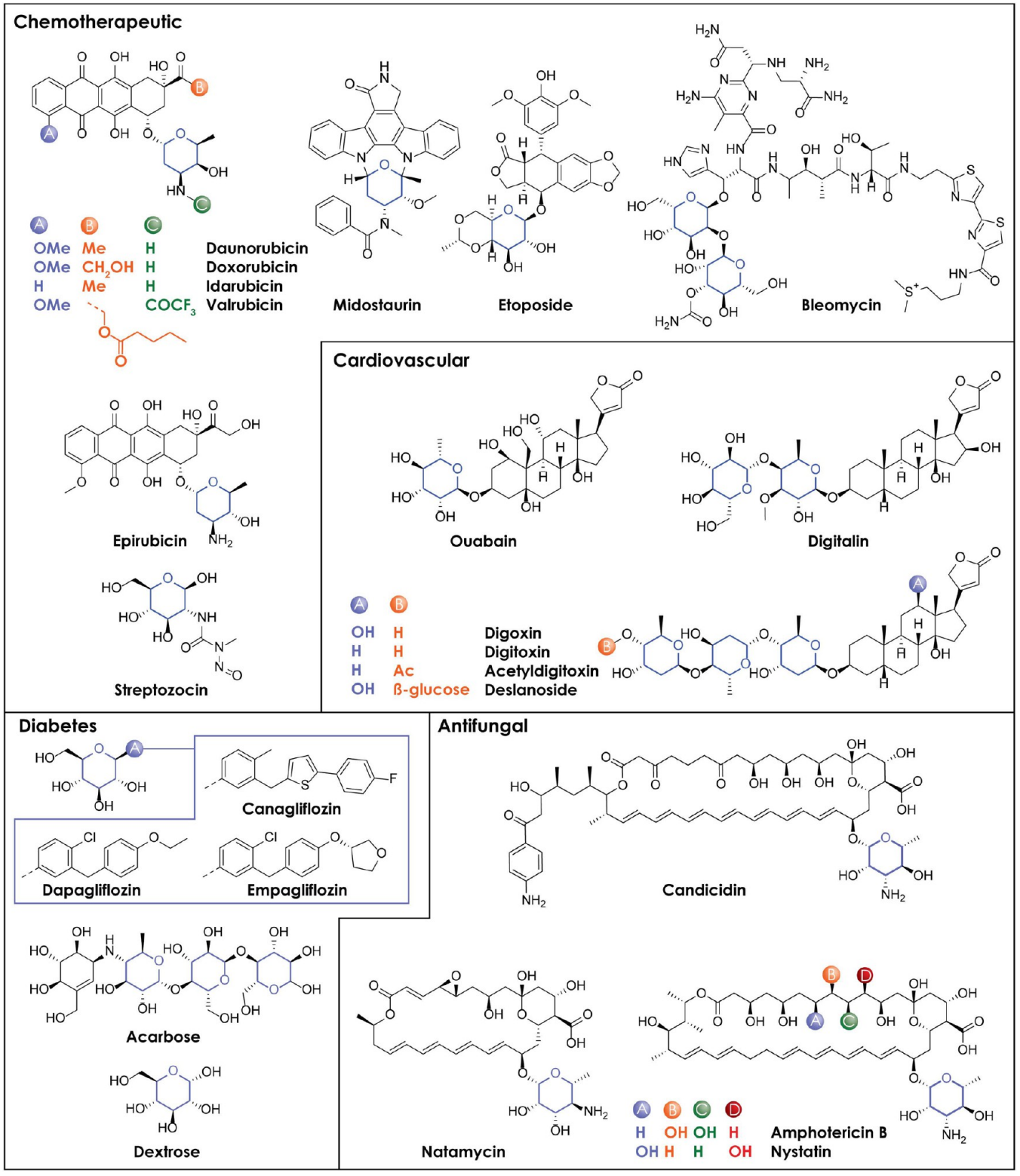

Figure 17. Pharmaceuticals containing pyranoses (part I).

cardiovascular conditions such as heart failure.[45] The six approved digitalis glycosides share a common steroid core, notably substituted with a butenolide on its D-ring and glycosides at C3 on the A-ring. Ouabain and digitalin are decorated with one and two glycosides, respectively, while digoxin, digitoxin, and acetyldigitoxin all contain a common triglycoside, and deslanoside is substituted with a tetraglycoside.

Glycosylated macrolactones are a significant presence. Amphotericin B, nystatin, candicidin, and natamycin are polyene antifungals with many structural similarities. Five antidiabetic drugs are represented; three are members of the gliflozin family, which are inhibitors of sodium-glucose transport protein 2 (SGLT2), used to treat type 2 diabetes.[46] These members, dapagliflozin, canagliflozin, and empagliflozin, share a common

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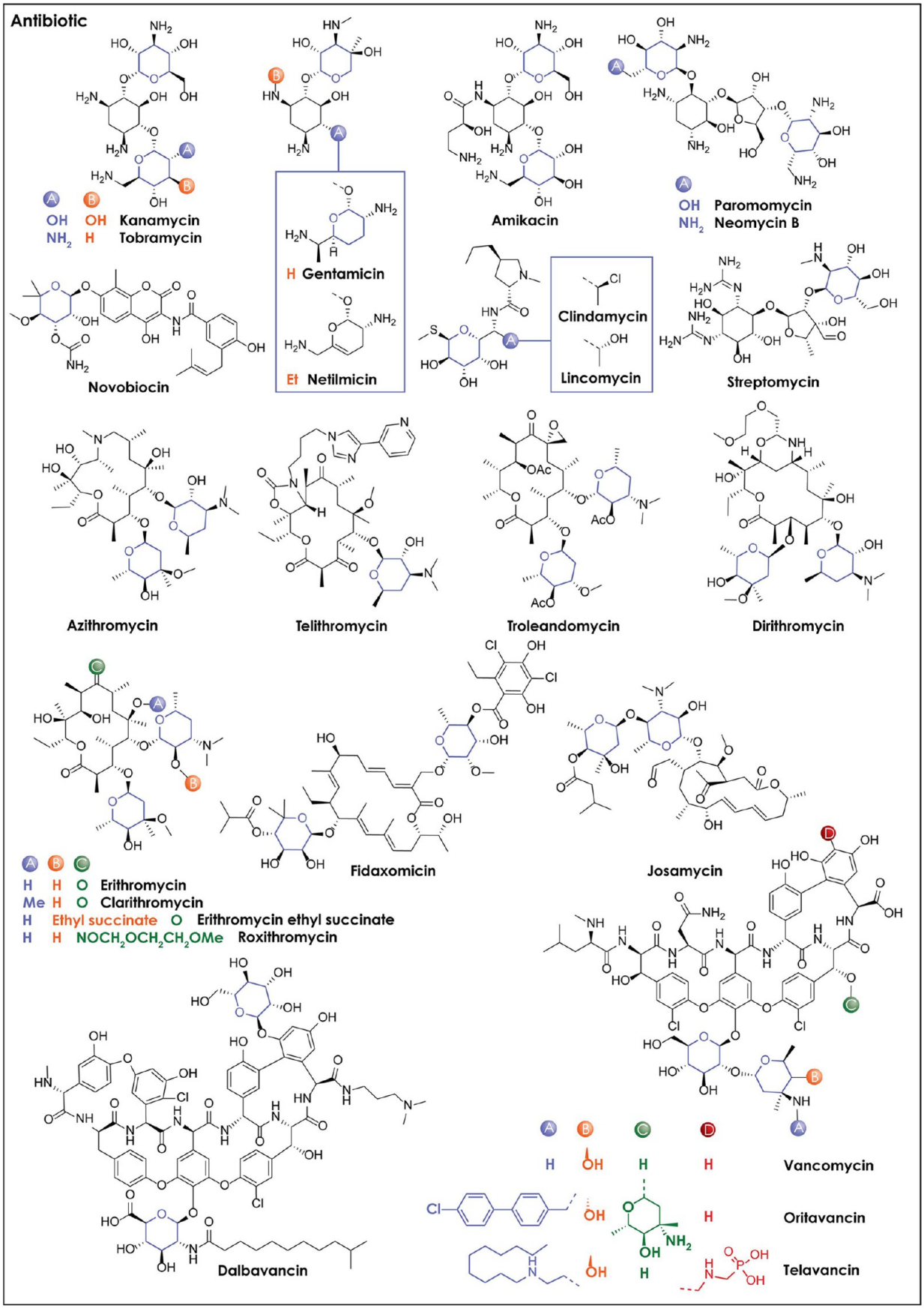

Figure 18. Pharmaceuticals containing pyranoses (part II).

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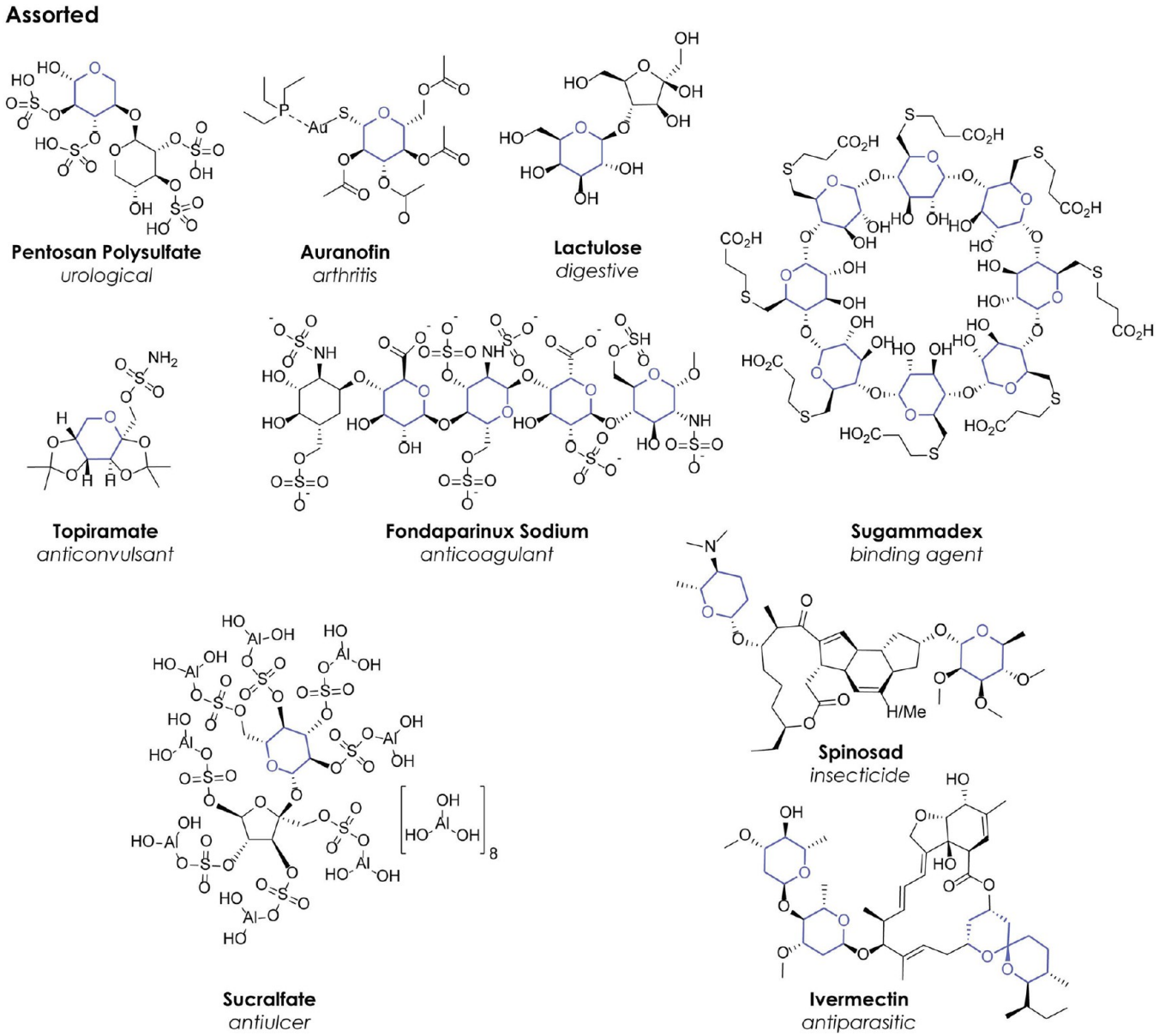

Figure 19. Pharmaceuticals containing pyranoses (part III).

pyranose core as well other structural similarities. Acarbose, a trisaccharide linked to an interesting heavily substituted cyclohexene fragment, is an antidiabetic drug of the α-glucosidase inhibitor class used to treat type 2 diabetes.[47]

Part 2 presents antibiotics which contain pyranoses (Figure 18). Natural products and their derivatives are heavily represented in this category with erythromycin, vancomycin, and streptomycin being among the more notable polyketide (macrolactone), nonribosomal peptide, and aminoglycoside members. The glycopeptide vancomycin, produced by fermenting *Amycolatopsis orientalis,* is a glycosylated hexapeptide effective against Gram-positive bacteria.[48] Oritavancin and telavancin are natural product derivatives whose structures marginally deviate in the positions shown, while dalbavancin is significantly different. The natural product erythromycin and related macrolide members are used as antibiotics to treat a range of bacterial infections. Most of these macrolide antibiotics contain a characteristic 14-membered ring with two pyranose sugars, usually a cladinose and desosamine, appended at common hydroxyl groups. Unlike erythromycin, josamycin has a 16-membered ring.[49] Fidaxomicin, which contains an 18-membered ring, is a narrow spectrum antibiotic prescribed for *Clostridium difficile* infection (CDI).[50] Eight pyranose containing drugs belong to the aminoglycoside family, which have traditionally been used as antibiotics against Gram-negative bacteria.[51] However, aminoglycosides are also effective against Gram-positive bacteria. Aminoglycoside members are easily recognizable by their 1,3-diaminoinositol pharmacophore, usually a 2-deoxystreptamine. Streptomycin contains a streptidine ring instead.[52] Most (88%) aminoglycosides contain two highly substituted pyranose moieties. Lincomycin and its derivative clindamycin are lincosamide antibiotics that are mostly effective against Gram-positive bacteria. This family functions by binding to rRNA, blocking microbial protein synthesis. Clindamycin has recently found an important use in the treatment of *Staphylococcus aureus*.[53]

Part 3 covers the remaining pyranose-containing drugs (Figure 19). Sugammadex is the first selective relaxant binding

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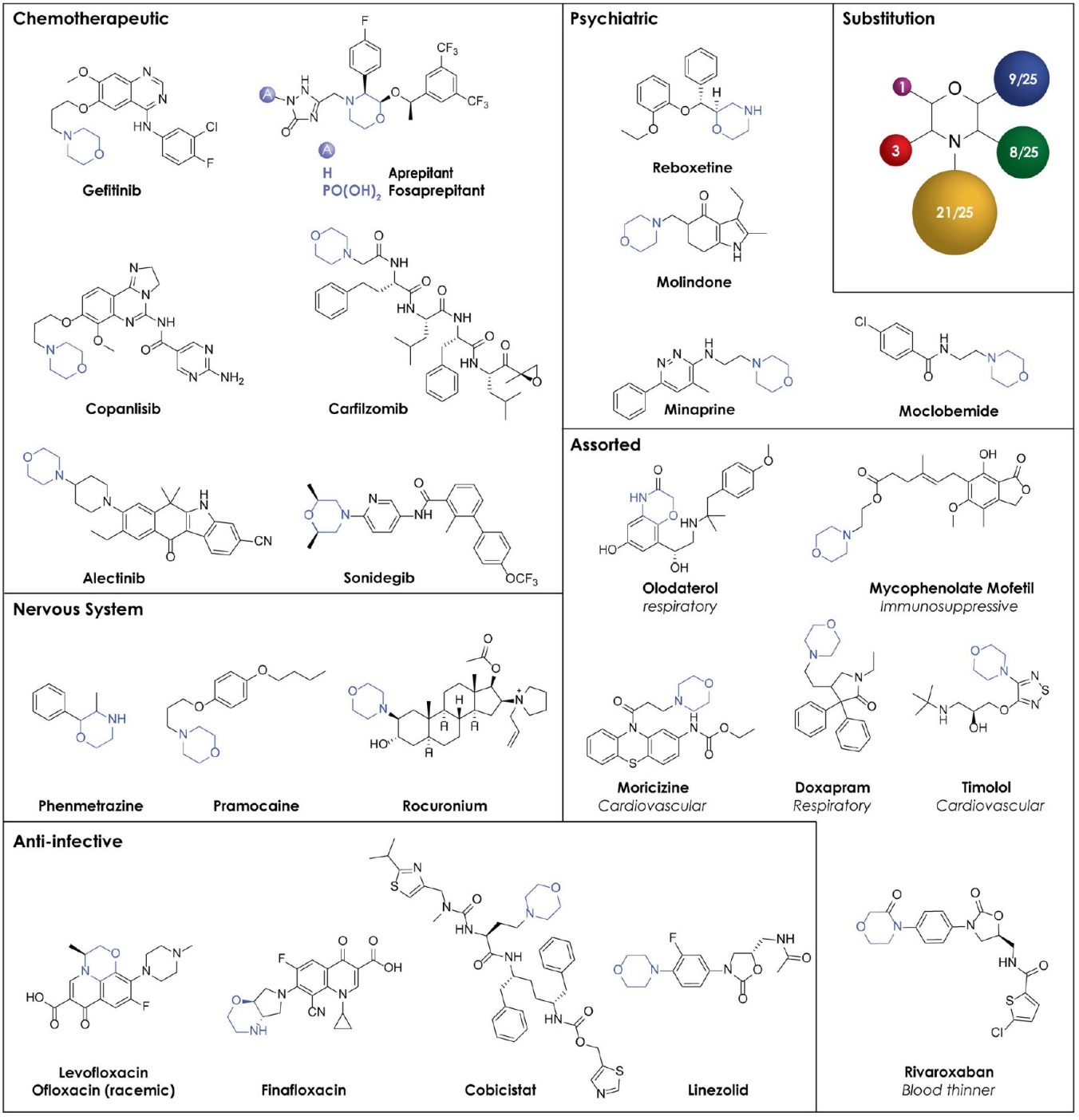

Figure 20. Pharmaceuticals containing morpholines.

agent (SRBA) indicated to reverse neuromuscular blockage effects of rocuronium in anesthesia. Structurally, sugammadex is a γ-cyclodextrin derivative with eight carboxyl thioether groups substituted at the C6 of the pyranose moieties.[54] Fondaparinux, a synthetic pentasaccharide structurally similar to low molecular weight heparins, is an anticoagulant. Among the more interesting structures in this category is auranofin, which is an organogold tetra-acetylated pyranose indicated for treatment of rheumatoid arthritis.[55] Sucralfate is a sucrose sulfate−aluminum complex used to treat various gastrointestinal conditions. Spinosad, an antiparasitic, is used to treat head lice in humans and fleas in cats and dogs. Interestingly, spinosad is also a widely used insecticide. Spinosad contains a unique tetracyclic core with two pyranoses (D-forosamine and a tri-*O*-methyl-L-rhamnose).[56] Ivermectin, a member of the avermectin family, is an antiparasitic agent used to treat a wide range of diseases such as head lice, river blindness, strongyloidiasis, and scabies. As a result of ivermectin's revolutionary impact in the world, it is often referred to as a "wonder drug".[57] A Nobel Prize was awarded in 2015 to William C. Campbell and Satoshi Ōmura for their ivermectin discoveries.[58]

Morpholine. Morpholine, which contains both a secondary amine and a ether, is a valuable building block for synthesizing drug-like molecules. Morpholine also finds utility as common solvent in organic synthesis. With a pK_a of 8.7, morpholine can be readily alkylated at its N4 atom in substitution reactions.

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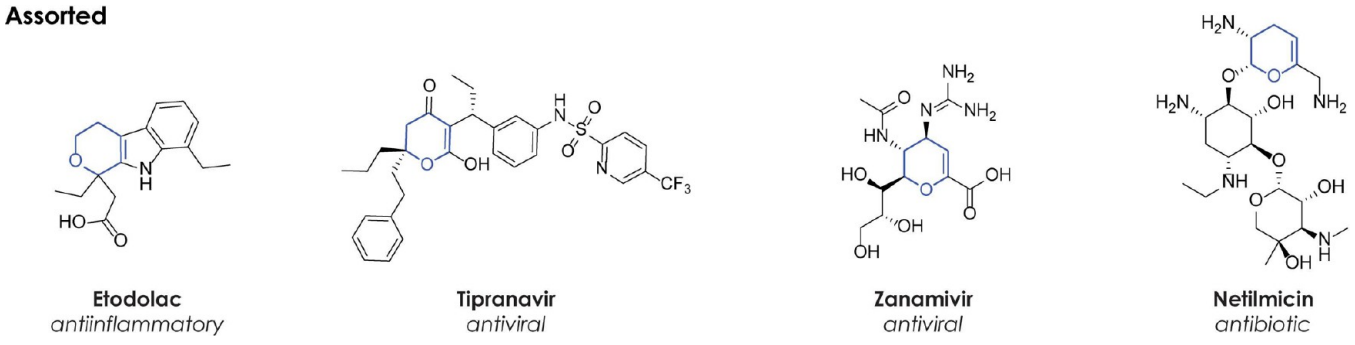

Figure 21. Pharmaceuticals containing dihydropyran.

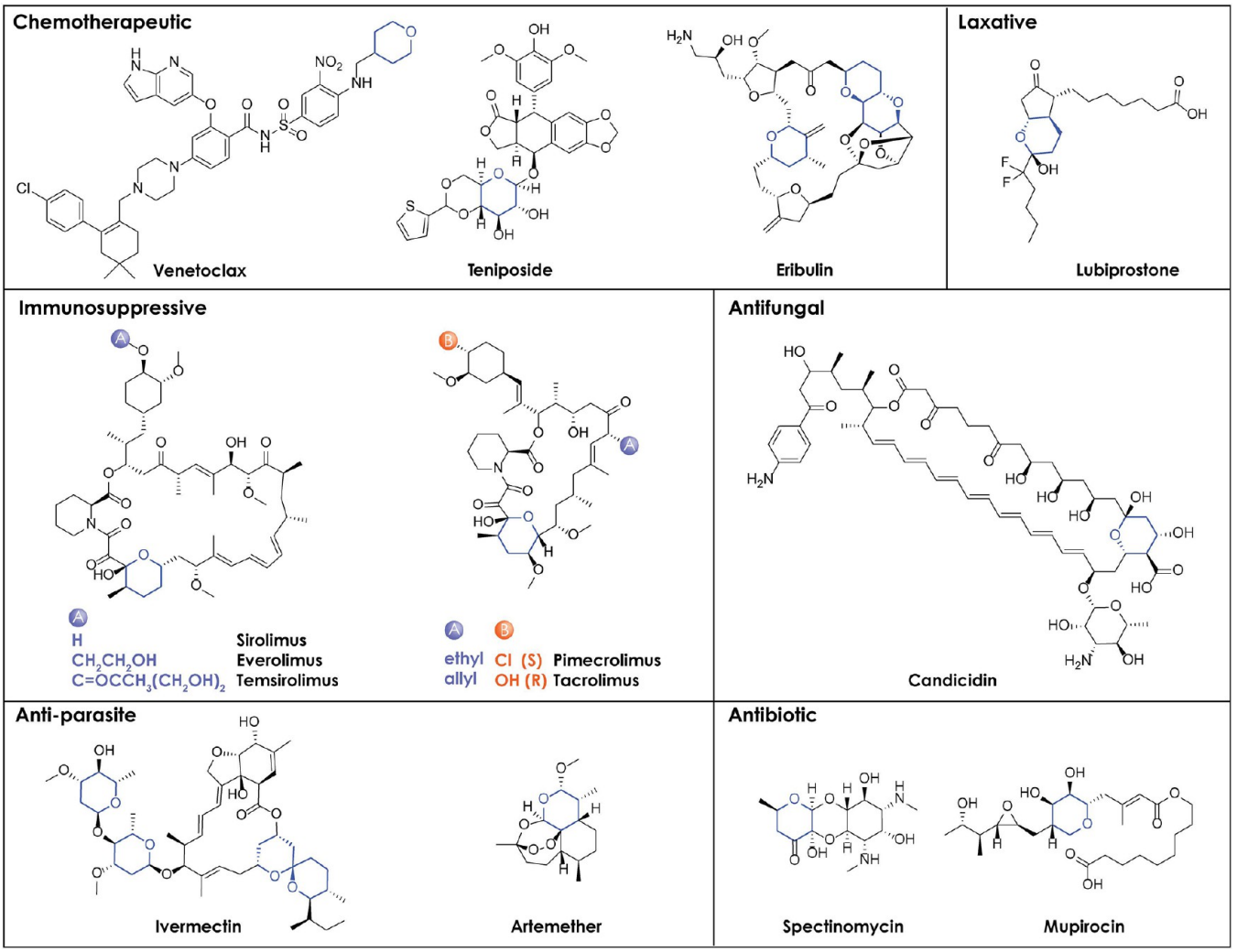

Figure 22. Pharmaceuticals containing tetrahydropyran.

Morpholine-containing drugs are used to treat a wide variety of diseases.[59] In addition, morpholine can fine-tune the physicochemical properties such as polarity and solubility of drugs. The secondary amine on morpholine can enhance selectivity through hydrogen bond donating and accepting; the ether moiety acts as a hydrogen bond acceptor.[60] Anticancer agents (alectinib, carfilzomib, gefitinib, and sonidegib), antiemetics (aprepitant), stimulants (phenmetrazine), glaucoma (timolol), antivirals (cobicistat), and antibiotics (linezolid) are represented to name a few. Our drug analysis (Figure 20) confirms 25 small molecule drugs that contain a morpholine heterocycle. An additional morpholino oligomer (eteplirsen) is shown in Figure 33. Further inspection of these morpholine substitution patterns reveals that most (84%) are substituted at N4, with the 2-position and 3-positions substituted in 36% and 32% of the drugs, respectively. The majority (64%) are monosubstituted with levofloxacin and ofloxacin being most substituted.

Dihydropyran. As shown in Figure 21, four highly decorated dihydropyrans appear among U.S. FDA approved drugs, including the antivirals tipranavir and zanamivir. Zanamivir is a neuraminidase inhibitor used to combat influenza A and B virus.[61] Netilimicin is an antibiotic, while etodolac is an

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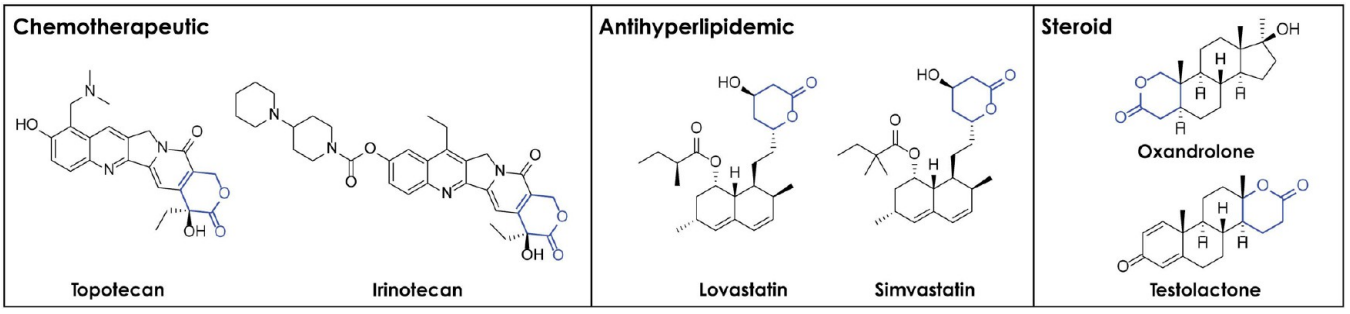

Figure 23. Pharmaceuticals containing δ-lactones.

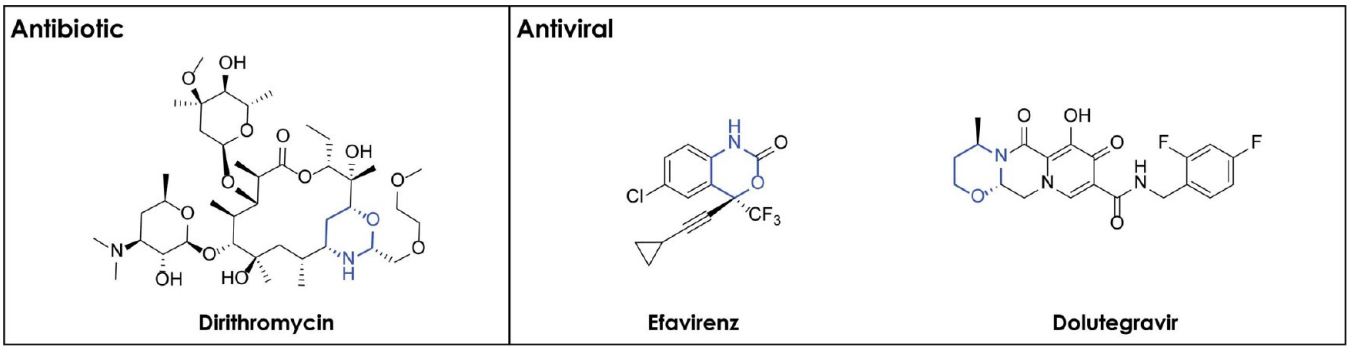

Figure 24. Pharmaceuticals containing 1,3-oxazinanes.

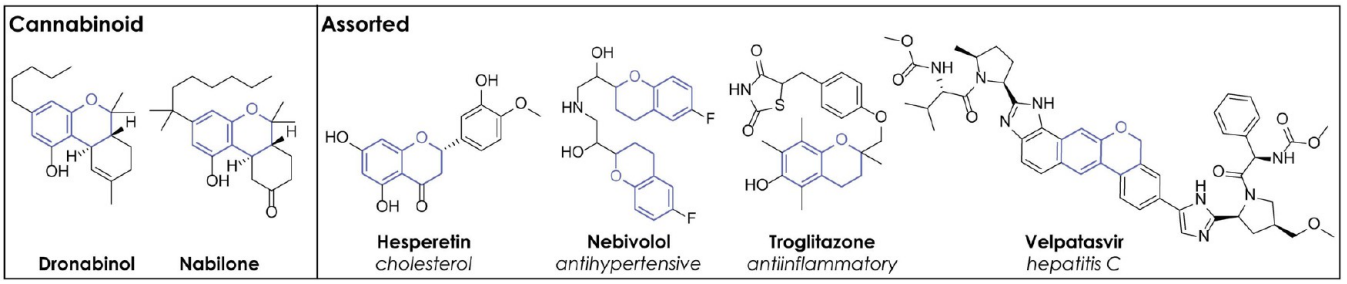

Figure 25. Pharmaceuticals containing chromanes.

anti-inflammatory drug. Etodolac is the only 3,6-dihydropyran of the four and the rest are 3,4-dihydropyrans, which is a reactive group used as a reagent for protecting hydroxyls (THP protecting group).

Tetrahydropyran. Tetrahydropyrans appear in 14 U.S. FDA approved drugs (Figure 22). Three of these drugs (candicidin, eribulin, and ivermectin) are decorated with multiple tetrahydropyrans, fused in eribulin and spirocyclic in ivermectin. Candicidin, an antifungal, contains two tetrahydropyrans of which one is part of the macrolactone. A variety of diseases are treated by these drugs. For example, the natural products rapamycin (sirolimus) and FK-506 (tacrolimus) and their derivatives are immunosuppressive drugs. In addition to their use as immunosuppressive agents, everolimus and temsirolimus have oncological applications such as in the treatment of advanced renal cell carcinoma (RCC), subependymal giant cell astrocytoma (SEGA), mantle cell lymphoma (MCL) as well as hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.[62] The prostaglandin derivative lubiprostone is a laxative. Teniposide and eribulin are all chemotherapy agents, while mupirocin and spectinomycin are antibiotics. Venetoclax targets the B-cell lymphoma-2 (Bcl-2) protein and is used to treat chronic lymphocytic leukemia (CLL).[63]

δ-Lactones. δ-Lactones appear in six drugs (Figure 23) all of which are natural products (lovastatin) or are derived or inspired from ones (camptothecin, steroids, and lovastatin). The camptothecin family contains a pentacyclic structural core with the δ-lactone occupying the E-ring. The camptothecin family of drugs are topoisomerase I poisons, which irreversibly damage DNA, so it is unable to be replicated. The parent compound containing the δ-lactone is more active than the hydrolyzed hydroxy acid metabolite. Both topotecan and irinotecan are tetrasubstituted δ-lactones fused to a 2-pyridone.[64] Lovastatin, the first of the statins to be approved, and its derivative simvastatin both contain disubstituted δ-lactones. The statins are a family of antihyperlipidemics, which act as HMG-CoA reductase inhibitors.[65] Two steroids contain δ-lactones as replacements for their cyclohexyl A-ring or cyclopentyl D-rings. Testolactone, a modified androstenedione, is an irreversible aromatase inhibitor used to treat late-stage breast cancer,[66] while oxandrolone is an anabolic steroid.

1,3-Oxazinanes. Three approved drugs contain a 1,3-oxazinane heterocycle (Figure 24). All three drugs are chiral,

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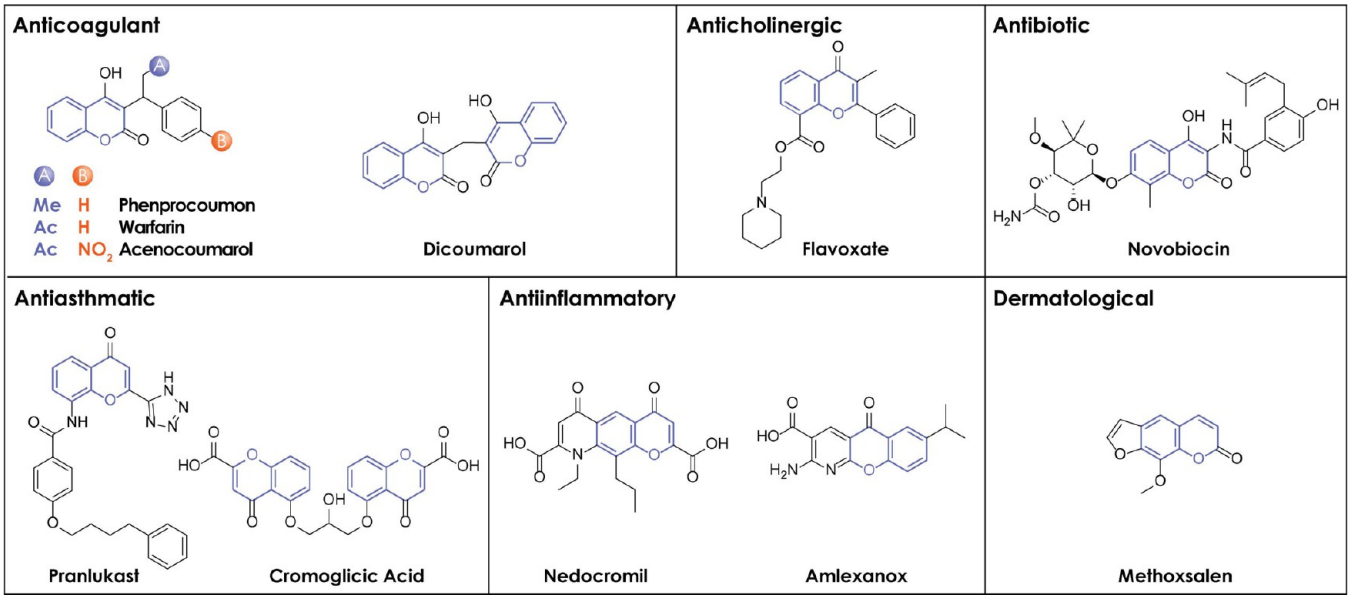

Figure 26. Pharmaceuticals containing chromenes.

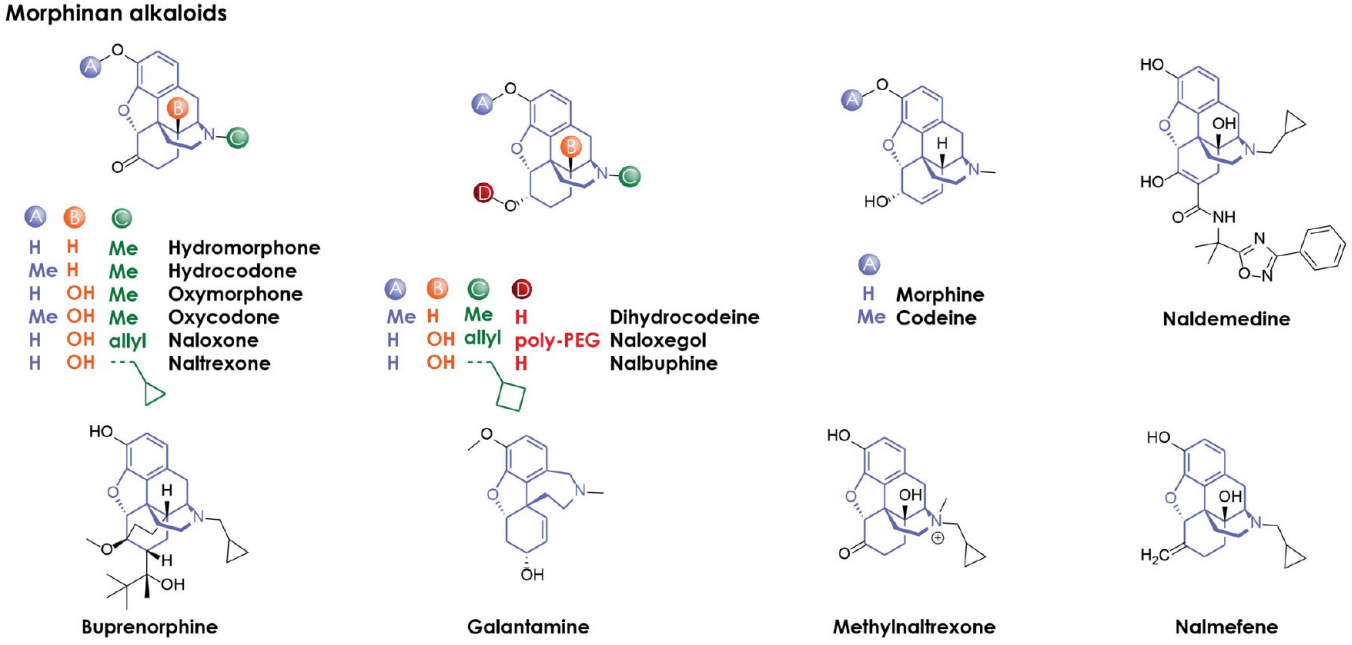

Figure 27. Pharmaceuticals containing morphinan alkaloids.

with the ethereal oxygen atom being part of a secondary or tertiary stereocenter and fused to another ring. Both dolutegravir and efavirenz are antiretrovirals indicated for treatment of HIV/AIDS. Dolutegravir is also used as a combination drug with abacavir and lamivudine for the same indication.[67] Dirithromycin is an antibiotic of the macrolide glycopeptide family. The oxazinane, which is a hemiaminal, of dirithromycin is hydrolyzed in vivo to form erythromycylamine.[68]

SIX-MEMBERED OXYGEN HETEROCYCLES: AROMATIC

Chromanes. Seven U.S. FDA approved drugs contain a chromane heterocycle; six are small molecules (Figure 25), and one (crofelemer) is an oligomer (Figure 33). Diverse drug types such as antidiabetic and anti-inflammatory (troglitazone), antiviral (velpatasvir), and synthetic cannabinoids (dronabinol and nabilone) are represented by these structures. Most notable among these is the natural product dronabinol and velpatasvir, which are used in combination with sofosbuvir to treat hepatitis C.

Chromenes. The chromenes, of which coumarins and chromones belong, are privileged scaffolds in drug discovery (Figure 26). These heterocycles, widely seen in natural products, have been extensively investigated for diverse pharmacological drug properties.[69] Eleven U.S. FDA approved pharmaceuticals were found to contain a chromene heterocycle, of which six are coumarins. Indications include asthma (cromoglicic acid and pranlukast), blood clots (warfarin family and dicumarol), skin diseases (methoxsalen), and bacterial infections (novobiocin) among others. Warfarin, phenprocou-

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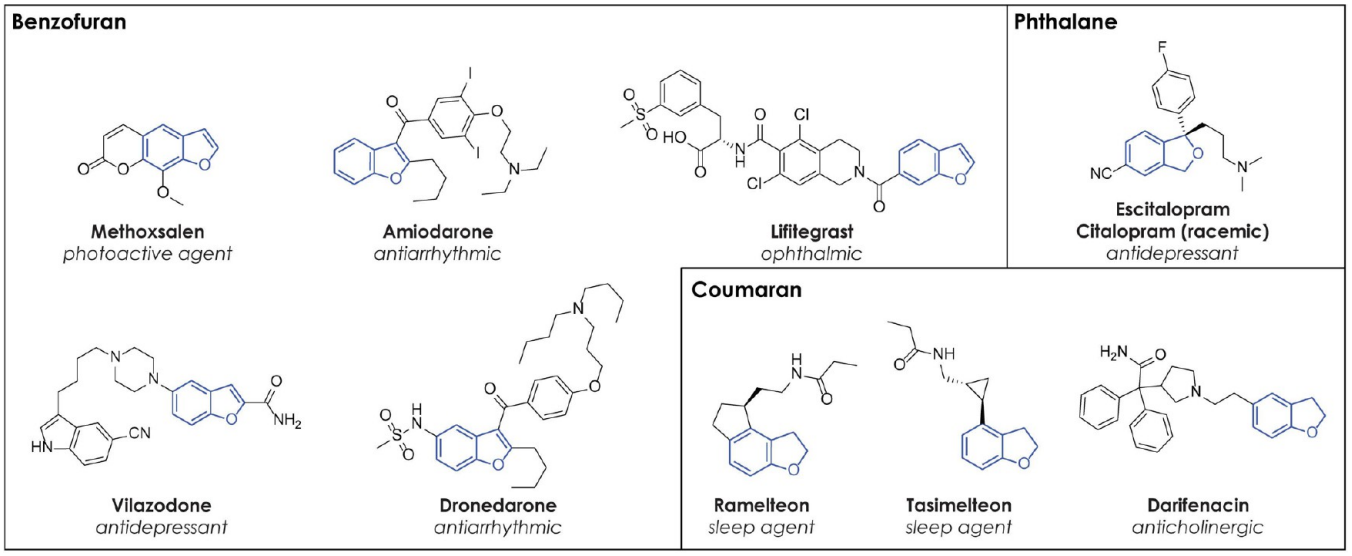

Figure 28. Pharmaceuticals containing benzofurans.

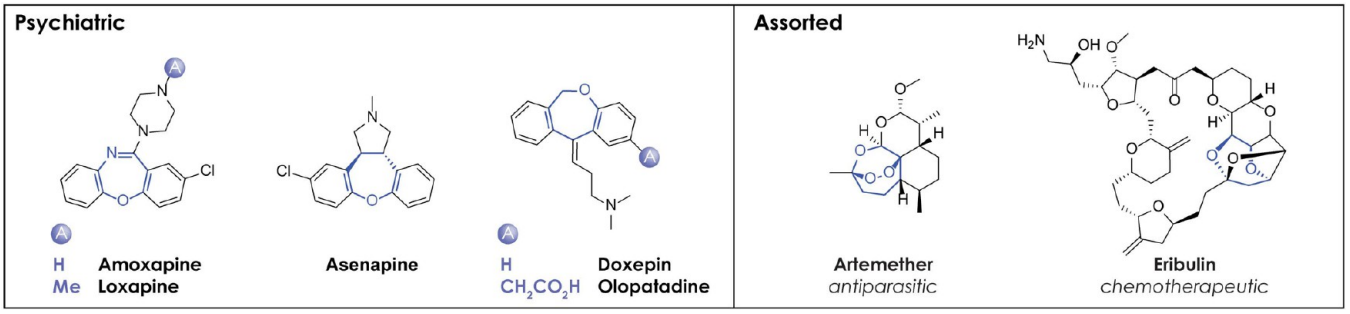

Figure 29. Pharmaceuticals containing various seven-membered rings.

mon, and acenocoumarol are structurally similar, differing slightly in their substitution at the two positions shown. Novobiocin and methoxsalen are also decorated with pyranose and furan oxygen heterocycles, respectively. Cromoglicic acid and dicoumarol are rare examples of drugs that are symmetrical dimers.

Morphinan Alkaloids. Sixteen U.S. FDA approved morphinan-type drugs, distinguished by their unique pentacyclic natural product core, are displayed in Figure 27. The E-ring contains a tetrahydrofuran moiety. Morphine and its methylated version codeine are the only ones that contain a C7−C8 double bond, while 12 derivatives are saturated at C7−C8. Naldemedine is different as it contains a C6−C7 enol. Galantamine, although not a morphinan per se, contains very similar architecture with an azepane in place of the bridged bicyclic piperidine. Galantamine, a natural product alkaloid, is an acetylcholinesterase (AChE) inhibitor indicated to treat cognitive degeneration in Alzheimer's disease.[70] 44% of the morphinans contain a C6 ketone, while the others are either in reduced hydroxy form or contain an olefin (nalmefene). All 16 members are substituted at the core nitrogen atom, with an unusual methylene cyclopropane substituent appearing in five derivatives. Buprenorphine stands out as the most complex approved morphinan with its C14−C6 bridged carbon chain as well as additional substitution at C7.

Benzofuran Family. Ten U.S. FDA approved benzofuran (five), coumaran (three), and phthalane- (two) containing drugs are presented in Figure 28. Our coverage of benzofuran[71,72] is combined with that of its reduced (2,3-dihydrobenzofuran = coumaran and 1,3-dihydroisobenzofuran = phthalane) members. These ten drugs have been approved as antiarrhythmic agents (amiodarone and dronedarone), antidepressants (vilazodone, citalopram, and escitalopram), and sleep agents (ramelteon and tasimelteon) as well as for conditions such as urinary incontinence (darifenacin), skin disease (methoxsalen), and dry eye (lifitegrast). Dronedarone and amiodarone share a common central benzofuran differing slightly in their heteroatom substitutions and amine tether lengths. The same can be said for ramelteon and tasimelteon, whose dihydrobenzofuran core is the same. The two phthalanes are particularly notable as they are the same compound, with one being sold as a racemate (citalopram) and the other (escitalopram) as single enantiomer. Escitalopram, the *S*-(+)-enantiomer, was developed after studies showed that this enantiomer was responsible for nearly all of the serotonin reuptake inhibition. Furthermore, in vitro studies in rat brains concluded that the *S*-(+)-enantiomer is 150 times more potent than the *R*-(−)-enantiomer.[73] Interestingly, arylnitriles are featured in three (vilazodone, citalopram, and escitalopram) of these drugs.

■ VARIOUS SEVEN-MEMBERED RINGS

Seven U.S. FDA approved oxygen heterocycle-containing drugs are seven-membered rings (Figure 29). Most of these drugs are used for psychiatric conditions. Loxapine, a typical antipsychotic, and amoxapine (N-demethylated version), an anti-

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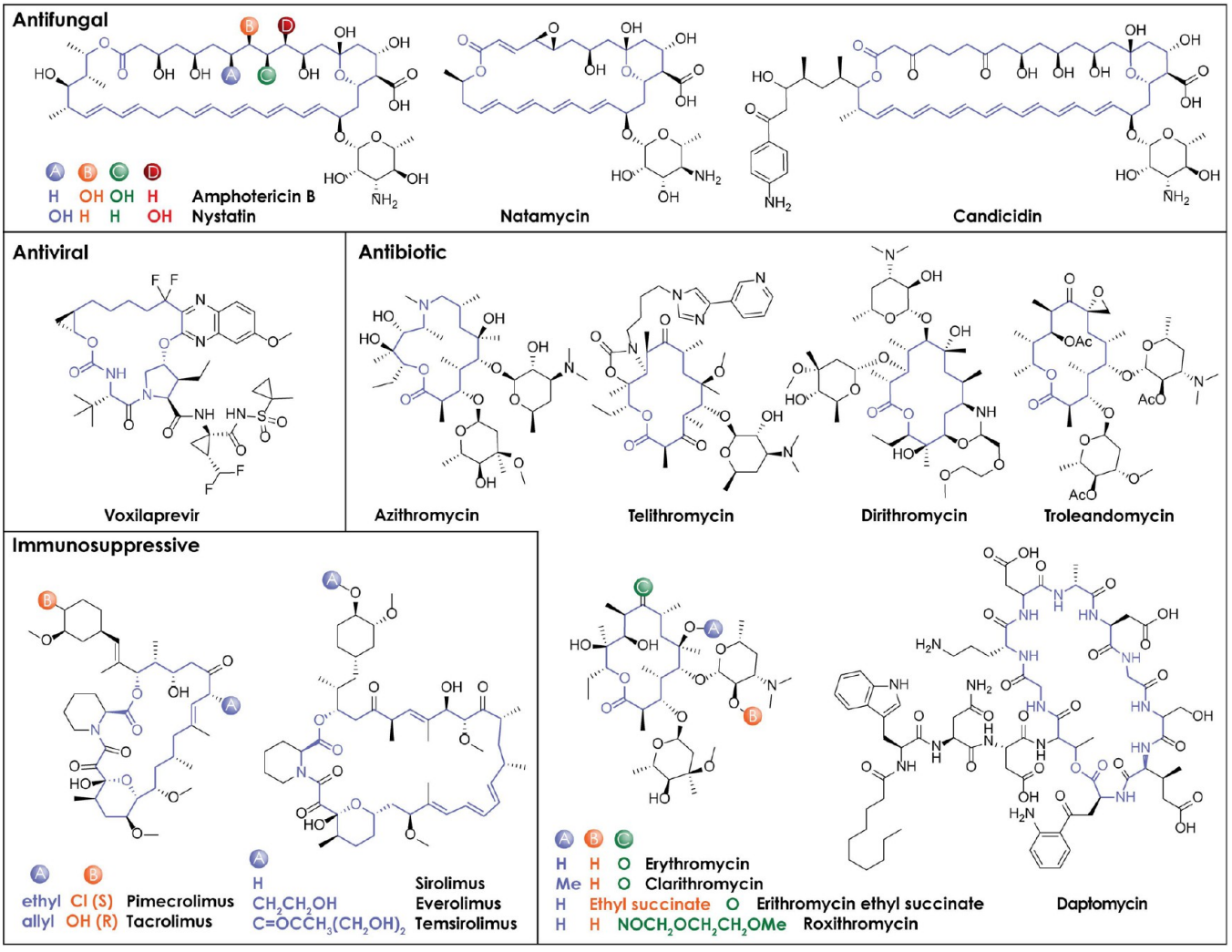

Figure 30. Pharmaceuticals containing macro-lactones (part I).

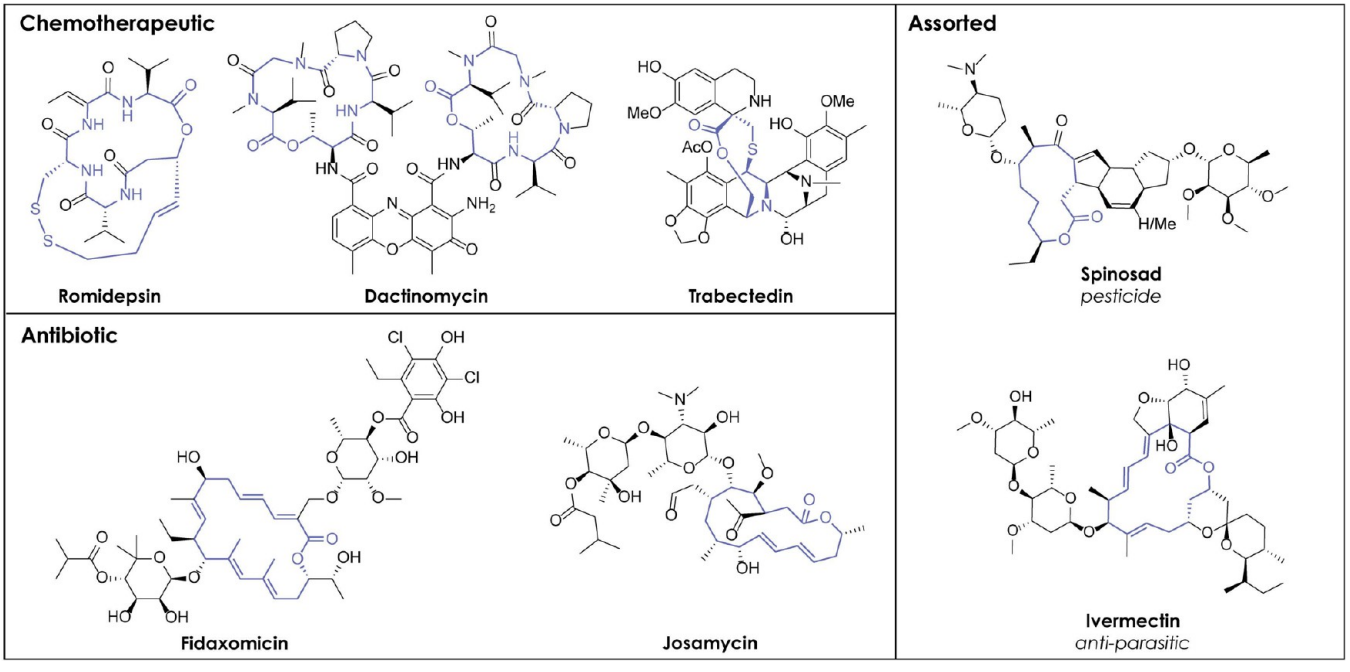

Figure 31. Pharmaceuticals containing macro-lactones (part 2).

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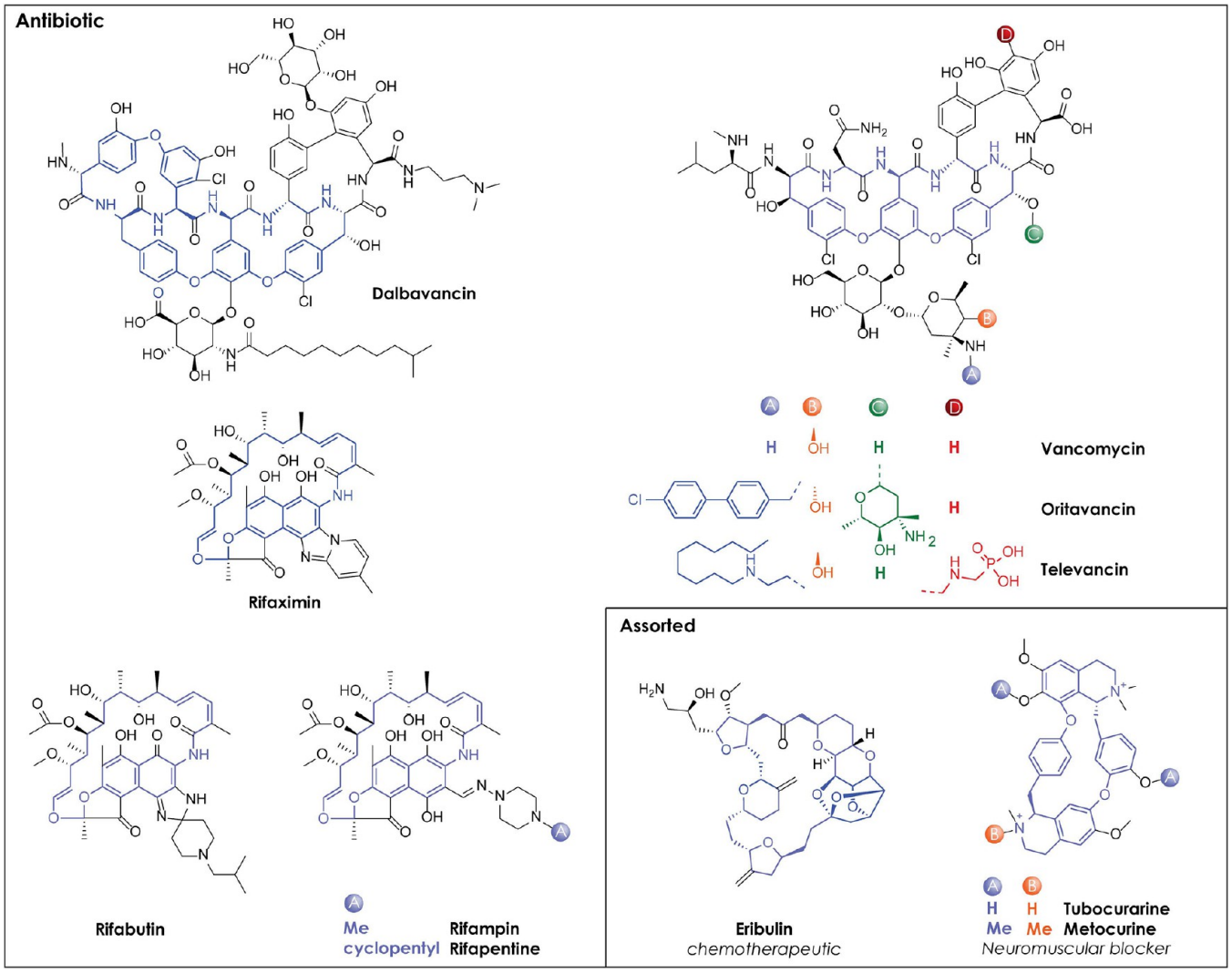

Figure 32. Pharmaceuticals containing macrocyclic ethers.

depressant, both contain a 1,4- oxazepine heterocycle fused between two aryl rings. Asenapine, doxepin, and olopatadine share similar isomeric dibenzooxepine cores as part of their rigid central architecture. Artemether, an artemisinin derivative, is a sesquiterpene lactone, which contains a truly unique seven-membered peroxide bridge as well as a fused oxepane ring. The artemisinin family of drugs is used to treat malaria. The endoperoxide is thought to play a role in killing parasites through a free radical mechanism.[74]

MACRO-LACTONES

Macro-lactones are encompassed in 26 U.S. FDA approved drugs, 19 of which are shown in Figure 30. These drugs are generally natural products or natural-product-derived structures with complex highly substituted architectures. As discussed previously, amphotericin B, nystatin, candicidin, and natamycin are all polyene antifungal agents. The nystatin family contains a 36-membered lactone ring, while natamycin contains a 24-membered lactone ring. Sirolimus (rapamycin) and its derivatives act as immunosuppressants in preventing organ transplant rejection. Temsirolimus is utilized as an anticancer agent.[75,76] The sirolimus (rapamycin) family contains a 29-membered ring with four trans double bonds. Pimecrolimus and tacrolimus are calcineurin inhibitors that act as immunosuppressive agents and contain a 21-membered lactone ring.[77] The erythromycin family, a class of broad-spectrum antibiotics, contains a 14-membered lactone ring.

Figure 31 displays the seven additional pharmaceuticals containing a macrolactone. Dactinomycin, a chemotherapeutic agent, contains two separate 16-membered macrolactones. Trabectedin, a chemotherapy agent, contains a structurally unique 10-membered macrolactone.[78] Romidepsin, another anticancer agent, contains a unique structural moiety in the form of a disulfide in addition to a 16-membered ring. Furthermore, this disulfide linkage is responsible for its mechanism of action. The disulfide is reduced in vivo to a thiol, which reversibly interacts with a zinc atom in the histone deacetylase binding pocket.[79] Ivermectin, a 16-membered antiparasitic agent, and the antibiotics josamycin (16-membered ring) and fidaxomycin (18 membered ring) each contain highly decorated pyrans as part of their architectures. Dactinomycin, an anticancer agent, contains a unique oxazine ring fused to a benzene ring and a 2,5-cyclohexadienone. It is worth noting that the *p*-benzoquinone imine component of dactinomycin is reactive and electrophilic. Therefore, dactinomycin is susceptible to NADPH/CYP450 reductase. Furthermore, single-stranded DNA breaks can occur as result of free radicals produced.[80]

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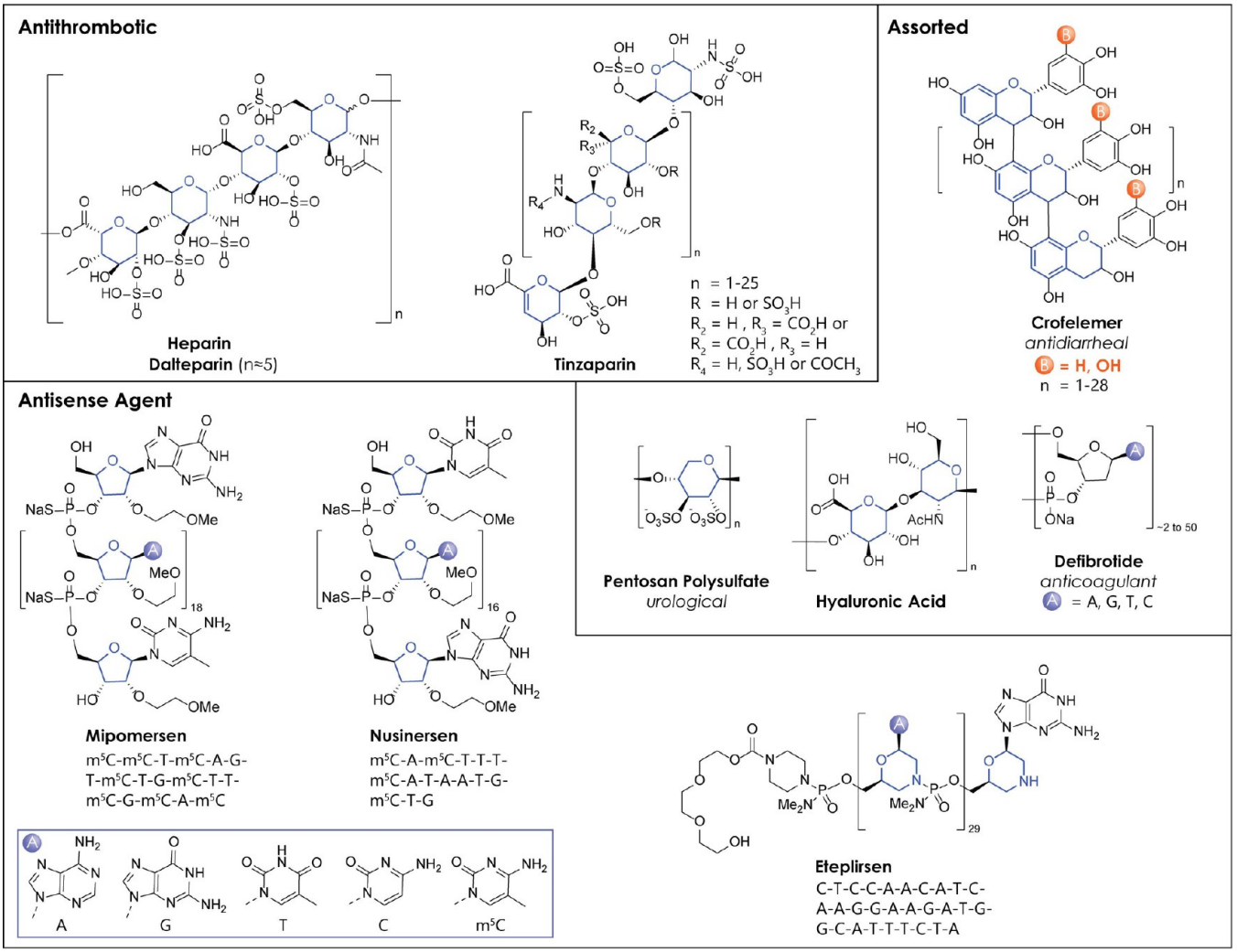

Figure 33. Pharmaceuticals containing oligomers and polymers.

■ MACROCYCLIC ETHERS

Macrocyclic ethers appear in 12 U.S. FDA approved drugs (Figure 32). The majority of macrocyclic ether drugs are antibiotics, with the 30- and 25-membered ether rings of the vancomycin and rifamycin families representing all eight members. Voxilaprevir, an 18-membered antiviral, and eribulin, a 22-membered anticancer agent, also contain macrocyclic ethers.[81] Tubocurarine, a benzyl isoquinoline derivative, is a naturally occurring 18-membered quaternary alkaloid that was once used as an arrow poison. Although rarely used currently, tubocurarine was used as a combination drug with an anesthetic for its muscle relaxing properties.[82] However, metocurine, a trimethylated analog of tubocurarine, is currently used as a muscle relaxant.

■ OLIGOMERS AND POLYMERS

The U.S. FDA approved oxygen heterocycle-containing oligomers and polymers are shown in Figure 33. Recently approved mipomersen and nusinersen are antisense oligonucleotides indicated for treatments of familial hypercholesterolemia and spinal muscular atrophy, respectively.[83] Interestingly, the nucleotides are linked by phosphorothioate linkages as opposed to phosphodiester. This modification aids in its resistance to nuclease degradation. The methoxyethyl substitution helps increase binding affinity and potency.[84] Mipomersen is a 20-mer, and nusinersen is an 18-mer. Distribution analysis of the nitrogenous bases of mipomersen reveals 5-methylcytosine (m^5C, 45%) is most prevalent, followed by thymine (T, 25%), guanine (G, 20%), and adenine (A, 10%). However, in the case of nusinersen, thymine (T, 39%) is most prevalent, followed by adenine (A, 22%), 5-methylcytosine (m^5C, 22%), and guanine (G, 17%). Furthermore, both mipomersen and nusinersen contain predominately pyrimidine architectures at 70% and 61%, respectively. Eteplirsen's unique and innovative structure stands out from the rest. Eteplirsen, an oligomorpholine, targets regional mutations thought to cause Duchenne muscular dystrophy (DMD). DMD, a recessive X-linked neuromuscular disorder in males, results from mutations of the DMD gene that codes for dystrophin. Dystrophin is a vital protein needed for strengthening muscle structure. Mutations in this protein lead to muscle degeneration, loss of ambulation, and ultimately death, usually in the 20s. Eteplirsen, a 30-mer nucleotide morpholino oligomer, acts as an exon-skipping therapeutic, specifically targeting deletions ending at exon 50 and beginning at exon 52. About 14% of all DMD patients are covered by this exon skipping range.[85] The heparins are glycosaminoglycans used as anticoagulants. Structurally, heparin contains a sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine disaccharide.

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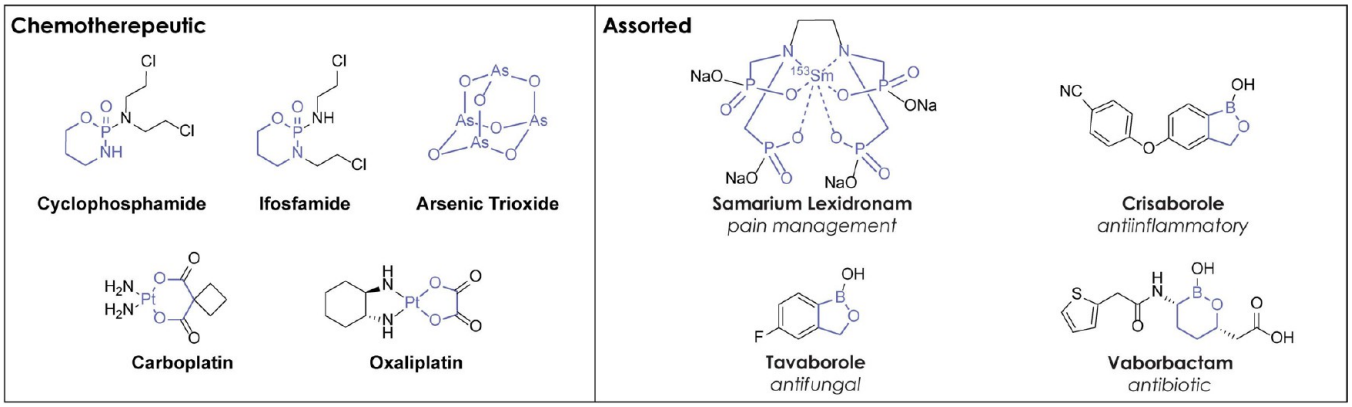

Figure 34. Pharmaceuticals containing boron, phosphorus, and metal oxacycles.

Dalteparin, enoxaparin, and tinzaparin are additional members of the heparin family also indicated as anticoagulants.[86] Pentosan polysulfate, a semisynthetic xylan, is a heparin-like, sulfated polysaccharide indicated for thrombus and interstitial cystitis in humans.[87] Hyaluronic acid, a glycosaminoglycan-like heparin, is commonly used in cosmetic surgery as a dermal filler, for skin care, and as a dietary supplement. However, hyaluronic acid is nonsulfated unlike the heparin family.[88] Defibrotide is an oligonucleotide used to treat hepatic veno-occlusive disease. Defibrotide is derived from the porcine intestinal mucosa.[89]

BORON, PHOSPHORUS, AND METAL OXACYCLES

There are nine unique boron, phosphorus, and metal oxacycles (Figure 34), which have received U.S. FDA approval. The pharmaceutical industry has shown increased interest in boron in drugs, with recent developments showing boron-containing drugs having therapeutic effects against a wide range of disease pathologies. A breakthrough with boron-containing drugs was the development of bortezomib as a treatment for multiple myeloma.[90] Currently, there are three U.S. FDA-approved boron−oxygen containing heterocycles of which two are oxaborolanols and one is an oxaborinanol. Tavaborole is an antifungal. The boron atom of tavaborole binds to cytoplasmic leucyl-transfer ribonucleic acid (tRNA) synthetase, a fungal enzyme needed for protein synthesis.[91] Crisaborole is a nonsteroidal topical for atopic dermatitis; the boron atom in crisaborole helps to facilitate increased skin penetration. In addition, the boron is critical for the drug's mechanism of action. The boronate mimics a phosphate of cyclic adenosine monophosphate (cAMP), thereby targeting and inhibiting phosphodiesterase 4 (PDE4).[92] Vaborbactam is a non-β-lactam β-lactamase inhibitor. The boron atom in vaborbactam is necessary for the drug's mechanism of action as a tetrahedral transition state mimic targeted against β-lactamases.[93] Platinum-based drugs continue to find uses as anticancer agents. The electrophilic platinum atom in carboplatin and oxaliplatin is attacked by the nucleophilic DNA.[94] Cyclophosphoramide and ifosfamide contain a unique oxazaphosphinane heterocycle, which is required for their mechanism of action in generating aziridines in vivo.[95] Despite the inherit toxicity of arsenic, arsenic-containing drugs have had a major impact over the years. For example, arsphenamine was used to treat syphilis in the past century. Arsenic trioxide, which is an adamantane-type oxygen−arsenic heterocycle, is used as an anticancer agent.[96] Samarium has found a unique medical use, with samarium lexidronam being used in pain management of cancers which have spread to the bone.[97] Structurally, this drug contains a unique heterocycle with five different elements.

SUMMARY

In conclusion, this Perspective offers the first compilation and detailed analysis of oxygen-containing heterocycles in U.S. FDA approved pharmaceuticals. As is evident from the discussion, the 311 drugs containing oxygen heterocycles have a dramatic impact in the treatment of a wide variety of medical conditions. It is quite remarkable how numerous types of oxygen heterocycles appear in approved drug architectures. This comprehensive overview is meant to give the reader an up-to-date analysis of the frequency as well as substitution patterns of all oxygen-heterocycles in drugs using a minimalistic graphical presentation approach. The heterocyclic moieties successfully incorporated into approved drugs should provide some valuable insight for prospective drug hunters. It is our hope that this analysis also serves to inspire the development of novel methods and reactions for constructing oxygen heterocycles, especially underrepresented or yet-to-be synthesized oxygen heterocycles. For example, seeing boron-containing heterocycles incorporated in drugs has been a true testament to the creativity of the synthetic community in pushing the boundaries beyond classically successful oxygen heterocycles such as furanoses and pyranoses.

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■ ABBREVIATIONS USED

AIDS, acquired immunodeficiency syndrome; CYP450, cytochrome P450; δ, delta; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; FDA, Federal Drug Administration; GI, gastrointestinal; HIV, human immunodeficiency virus; HMG-CoA reductase, 3-hydoxy-3-methylglutaryl-coenzyme A reductase; NADPH, nicotinamide adenine dinucleotide phosphate; N-heterocycle, nitrogen heterocycle; NMDA, *N*-methyl-D-aspartic acid; O-heterocycle, oxygen heterocycle; PTSD, post-traumatic stress disorder

■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.
(2) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-mining for sulfur and fluorine: an evaluation of pharmaceuticals to reveal opportunities for drug Design and discovery. *J. Med. Chem.* **2014**, *57*, 2832−2842.
(3) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical journey of innovative organic architectures that have improved our lives. *J. Chem. Educ.* **2010**, *87*, 1348−1349.
(4) ZuWallack, A. R.; ZuWallack, R. L. Tiotropium bromide, a new, once-daily inhaled anticholinergic bronchodilator for chronic-obstructive pulmonary disease. *Expert Opin. Pharmacother.* **2004**, *5*, 1827−1835.
(5) Grynkiewicz, G.; Gadzikowska, M. Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs. *Pharmacol. Rep.* **2008**, *60*, 439−463.
(6) Raz, R. Fosfomycin: an old−new antibiotic. *Clin. Microbiol. Infect.* **2012**, *18*, 4−7.
(7) Kawaguchi, A.; Tomoda, H.; Nozoe, S.; Omura, S.; Okuda, S. Mechanism of action of cerulenin on fatty acid synthetase. Effect of cerulenin on iodoacetamide-induced malonyl-CoA decarboxylase activity. *J. Biochem.* **1982**, *92*, 7−12.
(8) Arenas, C.; Melián, C.; Pérez-Alenza, M. D. Evaluation of 2 trilostane protocols for the treatment of canine pituitary-dependent hyperadrenocorticism: twice daily versus once daily. *J. Vet. Intern. Med.* **2013**, *27*, 1478−1485.
(9) Evans, D. J.; Cullinan, P.; Geddes, D. M.; Walters, E. H.; Milan, S. J.; Jones, P. Troleandomycin as an oral corticosteroid steroid sparing agent in stable asthma. *Cochrane Database Syst. Rev.* **2000**, *2*, Cd002987.
(10) Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W. *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lippincott Williams & Wilkins: Baltimore, MD, 2013; p 1163.
(11) Kim, K. B.; Crews, C. M. From epoxomicin to carfilzomib: chemistry, biology, and medical outcomes. *Nat. Prod. Rep.* **2013**, *30*, 600−604.
(12) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetanes in drug discovery: structural and synthetic insights. *J. Med. Chem.* **2010**, *53*, 3227−3246.
(13) Gueritte, F. General and recent aspects of the chemistry and structure activity relationships of taxoids. *Curr. Pharm. Des.* **2001**, *7*, 1229−1249.
(14) Hadvary, P.; Sidler, W.; Meister, W.; Vetter, W.; Wolfer, H. The lipase inhibitor tetrahydrolipstatin binds covalently to the putative active site serine of pancreatic lipase. *J. Biol. Chem.* **1991**, *266*, 2021−2027.
(15) Chan, C. Q. H.; Low, L. L.; Lee, K. H. Oral vitamin B12 replacement for the treatment of pernicious anemia. *Front. Med.* **2016**, *3*, 38.
(16) Chen, X.; Zhai, X.; Kang, Z.; Sun, X. Lactulose: an effective preventive and therapeutic option for ischemic stroke by production of hydrogen. *Med. Gas Res.* **2012**, *2*, 3−6.
(17) Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W. *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lippincott Williams & Wilkins: Baltimore, MD, 2013; pp 924, 1165−1168, 1221−1224.
(18) Palmer, J. D.; Nugent, C. A. Guanadrel Sulfate: A Postganglionic sympathetic inhibitor for the treatment of mild to moderate hypertension. *Pharmacotherapy* **1983**, *3*, 220−227.
(19) Peterfalvi, M.; Torelli, V.; Fournex, R.; Rousseau, G.; Claire, M.; Michaud, A.; Corvol, P. Importance of the lactonic ring in the activity of steroidal antialdosterones. *Biochem. Pharmacol.* **1980**, *29*, 353−357.
(20) Chackalamannil, S.; Wang, Y.; Greenlee, W. J.; Hu, Z.; Xia, Y.; Ahn, H.-S.; Boykow, G.; Hsieh, Y.; Palamanda, J.; Agans-Fantuzzi, J.; Kurowski, S.; Graziano, M.; Chintala, M. Discovery of a novel, orally active himbacine-based thrombin receptor antagonist (SCH 530348) with potent antiplatelet activity. *J. Med. Chem.* **2008**, *51*, 3061−3064.
(21) Geyer, O.; Wolf, A.; Arev-Fishelzon, T.; Levinger, E.; Wolfson, Y. The effect of a single dose of oral pilocarpine (Salagen) on the intraocular pressure and pupil diameter in glaucoma Patients. *Invest. Ophthalmol. Visual Sci.* **2006**, *47*, 448.
(22) Allison, A. C.; Eugui, E. M. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* **2000**, *47*, 85−118.
(23) Hauptman, P. J.; Kelly, R. A. Digitalis. *Circulation* **1999**, *99*, 1265−1270.
(24) Bozdogan, B.; Appelbaum, P. C. Oxazolidinones: activity, mode of action, and mechanism of resistance. *Int. J. Antimicrob. Agents* **2004**, *23*, 113−119.
(25) Schade, S.; Paulus, W. D-Cycloserine in neuropsychiatric diseases: a systematic review. *Int. J. Neuropsychopharmacol.* **2016**, *19*, pyv102.
(26) Ghosh, A. K.; Anderson, D. D. Tetrahydrofuran, tetrahydropyran, triazoles and related heterocyclic derivatives as HIV protease inhibitors. *Future Med. Chem.* **2011**, *3*, 1181−1197.
(27) Ghosh, A. K.; Ramu Sridhar, P.; Kumaragurubaran, N.; Koh, Y.; Weber, I. T.; Mitsuya, H. Bis-tetrahydrofuran: a privileged ligand for darunavir and a new generation of hiv protease inhibitors that combat drug resistance. *ChemMedChem* **2006**, *1*, 939−950.
(28) McBride, A.; Butler, S. K. Eribulin mesylate: a novel halichondrin B analogue for the treatment of metastatic breast cancer. *Am. J. Health-Syst. Pharm.* **2012**, *69*, 745−755.
(29) Torres, H. A.; Hachem, R. Y.; Chemaly, R. F.; Kontoyiannis, D. P.; Raad, I. I. Posaconazole: a broad-spectrum triazole antifungal. *Lancet Infect. Dis.* **2005**, *5*, 775−785.
(30) Yasuda, H.; Niki, H. Review of the pharmacological properties and clinical usefulness of muscarinic agonists for xerostomia in patients with sjogren's syndrome. *Clin. Drug Invest.* **2002**, *22*, 67−73.
(31) Ford, N.; Shubber, Z.; Hill, A.; Vitoria, M.; Doherty, M.; Mills, E. J.; Gray, A. comparative efficacy of lamivudine and emtricitabine: a systematic review and meta-analysis of randomized trials. *PLoS One* **2013**, *8*, e79981.
(32) Salvaris, M. Treatment of urinary infections with nitrofurantoin (furadantin). *BJU Int.* **1958**, *30*, 303−309.

DOI: 10.1021/acs.jmedchem.8b00876
J. Med. Chem. 2018, 61, 10996−11020

(33) Moy, B.; Kirkpatrick, P.; Kar, S.; Goss, P. Lapatinib. *Nat. Rev. Drug Discovery* **2007**, *6*, 431.
(34) Kung, S.; Espinel, Z.; Lapid, M. I. Treatment of nightmares with prazosin: A systematic review. *Mayo Clin. Proc.* **2012**, *87*, 890−900.
(35) Wright, R. How Zantac became the best-selling drug in history. *J. Health Care Mark.* **1996**, *16*, 24−29.
(36) Hamberger, C.; Kellert, M.; Schauer, U. M.; Dekant, W.; Mally, A. Hepatobiliary toxicity of furan: identification of furan metabolites in bile of male f344/n rats. *Drug Metab. Dispos.* **2010**, *38*, 1698−1706.
(37) Peterson, L. A. Reactive metabolites in the biotransformation of molecules containing a furan ring. *Chem. Res. Toxicol.* **2013**, *26*, 6−25.
(38) Barmade, M. A.; Murumkar, P. R.; Sharma, M. K.; Yadav, M. R. Medicinal chemistry perspective of fused isoxazole derivatives. *Curr. Top. Med. Chem.* **2016**, *16*, 2863−2883.
(39) Zhang, H.-Z.; Zhao, Z.-L.; Zhou, C.-H. Recent advance in oxazole-based medicinal chemistry. *Eur. J. Med. Chem.* **2018**, *144*, 444−492.
(40) Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T. Oxadiazoles in medicinal chemistry. *J. Med. Chem.* **2012**, *55*, 1817−1830.
(41) McGowan, J. V.; Chung, R.; Maulik, A.; Piotrowska, I.; Walker, J. M.; Yellon, D. M. Anthracycline chemotherapy and cardiotoxicity. *Cardiovasc. Drugs Ther.* **2017**, *31*, 63−75.
(42) Eleazu, C. O.; Eleazu, K. C.; Chukwuma, S.; Essien, U. N. Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *J. Diabetes Metab. Disord.* **2013**, *12*, 60.
(43) Sanchez, C.; Mendez, C.; Salas, J. A. Indolocarbazole natural products: occurrence, biosynthesis, and biological activity. *Nat. Prod. Rep.* **2006**, *23*, 1007−1045.
(44) Goodwin, K. D.; Lewis, M. A.; Long, E. C.; Georgiadis, M. M. Crystal structure of DNA-bound Co(III)·bleomycin B(2): Insights on intercalation and minor groove binding. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 5052−5056.
(45) Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W. *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lippincott Williams & Wilkins: Baltimore, MD, 2013; pp 701−705.
(46) Nair, S.; Wilding, J. P. H. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 34−42.
(47) Hanefeld, M. The role of acarbose in the treatment of non-insulin-dependent diabetes mellitus. *J. Diabetes Complicat.* **1998**, *12*, 228−237.
(48) Bruniera, F. R.; Ferreira, F. M.; Saviolli, L. R.; Bacci, M. R.; Feder, D.; da Luz Goncalves Pedreira, M.; Sorgini Peterlini, M. A.; Azzalis, L. A.; Campos Junqueira, V. B.; Fonseca, F. L. The use of vancomycin with its therapeutic and adverse effects: a review. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 694−700.
(49) Arsic, B.; Barber, J.; Cikos, A.; Mladenovic, M.; Stankovic, N.; Novak, P. 16-membered macrolide antibiotics: a review. *Int. J. Antimicrob. Agents* **2018**, *51*, 283−298.
(50) Zhanel, G. G.; Walkty, A. J.; Karlowsky, J. A. Fidaxomicin: A novel agent for the treatment of clostridium difficile infection. *Can. J. Infect. Dis. Med. Micriobiol.* **2015**, *26*, 305−312.
(51) Hermann, T. Aminoglycoside antibiotics: old drugs and new therapeutic approaches. *Cell. Mol. Life Sci.* **2007**, *64*, 1841−1852.
(52) Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. 2-Deoxystreptamine: central scaffold of aminoglycoside antibiotics. *Chem. Rev.* **2005**, *105*, 775−792.
(53) Morar, M.; Bhullar, K.; Hughes, D. W.; Junop, M.; Wright, G. D. Structure and mechanism of the lincosamide antibiotic adenylyltransferase LinB. *Structure* **2009**, *17*, 1649−1659.
(54) Nag, K.; Singh, D. R.; Shetti, A. N.; Kumar, H.; Sivashanmugam, T.; Parthasarathy, S. Sugammadex: A revolutionary drug in neuromuscular pharmacology. *Anesth. Essays Res.* **2013**, *7*, 302−306.
(55) Roder, C.; Thomson, M. J. Auranofin: repurposing an old drug for a golden new age. *Drugs R&D* **2015**, *15*, 13−20.
(56) Snyder, D. E.; Meyer, J.; Zimmermann, A. G.; Qiao, M.; Gissendanner, S. J.; Cruthers, L. R.; Slone, R. L.; Young, D. R. Preliminary studies on the effectiveness of the novel pulicide, spinosad, for the treatment and control of fleas on dogs. *Vet. Parasitol.* **2007**, *150*, 345−351.
(57) Crump, A.; Omura, S. Ivermectin, "wonder drug" from Japan: the human use perspective. *Proc. Jpn. Acad., Ser. B* **2011**, *87*, 13−28.
(58) Tambo, E.; Khater, E. I. M.; Chen, J. H.; Bergquist, R.; Zhou, X. N. Nobel prize for the artemisinin and ivermectin discoveries: a great boost towards elimination of the global infectious diseases of poverty. *Infect. Dis. Poverty* **2015**, *4*, 58−65.
(59) Naim, M.; Alam, O.; Alam, J.; Alam, P.; Shrivastava, N. A review on pharmacological profile of Morpholine derivatives. *Int. J. Pharmacol. Pharm. Sci.* **2015**, *3*, 40−51.
(60) Rupak, K.; Vulichi, S. R.; Suman, K. Emphasizing morpholine and its derivatives (MAID): typical candidate of pharmaceutical importance. *Int. J. Chem. Sci.* **2016**, *14*, 1777−1788.
(61) Stiver, G. The treatment of influenza with antiviral drugs. *Can. Med. Assoc. J.* **2003**, *168*, 49−57.
(62) Martelli, A. M.; Buontempo, F.; McCubrey, J. A. Drug discovery targeting the mTOR pathway. *Clin. Sci.* **2018**, *132*, 543−568.
(63) Anderson, M. A.; Deng, J.; Seymour, J. F.; Tam, C.; Kim, S. Y.; Fein, J.; Yu, L.; Brown, J. R.; Westerman, D.; Si, E. G.; Majewski, I. J.; Segal, D.; Heitner Enschede, S. L.; Huang, D. C. S.; Davids, M. S.; Letai, A.; Roberts, A. W. The bcl2 selective inhibitor venetoclax induces rapid onset apoptosis of cll cells in patients via a tp53-independent mechanism. *Blood* **2016**, *127*, 3215−3224.
(64) Sriram, D.; Yogeeswari, P.; Thirumurugan, R.; Bal, T. R. Camptothecin and its analogues: a review on their chemotherapeutic potential. *Nat. Prod. Res.* **2005**, *19*, 393−412.
(65) Pasha, M. K.; Muzeeb, S.; Basha, S. J.; Shashikumar, D.; Mullangi, R.; Srinivas, N. R. Analysis of five HMG-CoA reductase inhibitors–atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin: pharmacological, pharmacokinetic and analytical overview and development of a new method for use in pharmaceutical formulations analysis and in vitro metabolism studies. *Biomed. Chromatogr.* **2006**, *20*, 282−293.
(66) Dunkel, L. Use of aromatase inhibitors to increase final height. *Mol. Cell. Endocrinol.* **2006**, *254*−*255*, 207−216.
(67) Kandel, C. E.; Walmsley, S. L. Dolutegravir − a review of the pharmacology, efficacy, and safety in the treatment of HIV. *Drug Des., Dev. Ther.* **2015**, *9*, 3547−3555.
(68) Brogden, R. N.; Peters, D. H. (1994). Dirithromycin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* **1994**, *48*, 599−616.
(69) Reis, J.; Gaspar, A.; Milhazes, N.; Borges, F. Chromone as a privileged scaffold in drug discovery: recent advances. *J. Med. Chem.* **2017**, *60*, 7941−7957.
(70) Scott, L. J.; Goa, K. L. Galantamine: a review of its use in Alzheimer's disease. *Drugs* **2000**, *60*, 1095−1122.
(71) Nevagi, R. J.; Dighe, S. N.; Dighe, S. N. Biological and medicinal significance of benzofuran. *Eur. J. Med. Chem.* **2015**, *97*, 561−581.
(72) Hiremathad, A.; Patil, M. R.; K. R., C.; Chand, K.; Santos, M. A.; Keri, R. S. Benzofuran: an emerging scaffold for antimicrobial agents. *RSC Adv.* **2015**, *5*, 96809−96828.
(73) Sanchez, C. The pharmacology of citalopram enantiomers: the antagonism by R-citalopram on the effect of S-citalopram. *Basic Clin. Pharmacol. Toxicol.* **2006**, *99*, 91−95.
(74) Meshnick, S. R. Artemisinin: mechanisms of action, resistance and toxicity. *Int. J. Parasitol.* **2002**, *32*, 1655−1660.
(75) Seto, B. Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. *Clin Transl Med.* **2012**, *1*, 29.
(76) Abraham, R. T.; Wiederrecht, G. J. Immunopharmacology of rapamycin. *Annu. Rev. Immunol.* **1996**, *14*, 483−510.
(77) Ashcroft, D. M.; Dimmock, P.; Garside, R.; Stein, K.; Williams, H. C. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ.* **2005**, *330*, 516.
(78) Recine, F.; Bongiovanni, A.; Riva, N.; Fausti, V.; De Vita, A.; Mercatali, L.; Liverani, C.; Miserocchi, G.; Amadori, D.; Ibrahim, T.

DOI: 10.1021/acs.jmedchem.8b00876
J. Med. Chem. 2018, 61, 10996−11020

Update on the role of trabectedin in the treatment of intractable soft tissue sarcomas. *OncoTargets Ther.* **2017**, *10*, 1155−1164.
(79) VanderMolen, K. M.; McCulloch, W.; Pearce, C. J.; Oberlies, N. H. Romidepsin (Istodax®, NSC 630176, FR901228, FK228, Depsipeptide): a natural product recently approved for cutaneous T-cell lymphoma. *J. Antibiot.* **2011**, *64*, 525−531.
(80) Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W. *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lippincott Williams & Wilkins: Baltimore, MD, 2013; pp 1230−1231.
(81) Voaklander, R.; Jacobson, I. M. Sofosbuvir, velpatasvir and voxilaprevir combination for the treatment of hepatitis C. *Expert Rev. Gastroenterol. Hepatol.* **2017**, *11*, 789−795.
(82) Raghavendra, T. Neuromuscular blocking drugs: discovery and development. *J. R. Soc. Med.* **2002**, *95*, 363−367.
(83) Corey, D. R. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. *Nat. Neurosci.* **2017**, *20*, 497−499.
(84) Crooke, S. T.; Geary, R. S. Clinical pharmacological properties of mipomersen (Kynamro), a second generation antisense inhibitor of apolipoprotein B. *Br. J. Clin. Pharmacol.* **2013**, *76*, 269−276.
(85) Lim, K. R. Q.; Maruyama, R.; Yokota, T. Eteplirsen in the treatment of duchenne muscular dystrophy. *Drug Des., Dev. Ther.* **2017**, *11*, 533−545.
(86) Alquwaizani, M.; Buckley, L.; Adams, C.; Fanikos, J. Anticoagulants: a review of the pharmacology, dosing, and complications. *Curr. Emerg. Hosp. Med. Rep.* **2013**, *1*, 83−97.
(87) Anderson, V. R.; Perry, C. M. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* **2006**, *66*, 821−835.
(88) Papakonstantinou, E.; Roth, M.; Karakiulakis, G. Hyaluronic acid: A key molecule in skin aging. *Derm.-Endocrinol.* **2012**, *4*, 253−258.
(89) Richardson, P. G.; Smith, A. R.; Triplett, B. M.; Kernan, N. A.; Grupp, S. A.; Antin, J. H.; Lehmann, L.; Shore, T.; Iacobelli, M.; Miloslavsky, M.; Hume, R.; Hannah, A. L.; Nejadnik, B.; Soiffer, R. J. Defibrotide for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome: interim results from a treatment IND study. *Biol. Blood Marrow Transplant.* **2017**, *23*, 997−1004.
(90) Hunter, P. Not boring at all. Boron is the new carbon in the quest for novel drug candidates. *EMBO Rep.* **2009**, *10*, 125−128.
(91) Elewski, B. E.; Aly, R.; Baldwin, S. L.; González Soto, R. F.; Rich, P.; Weisfeld, M.; Wiltz, H.; Zane, L. T.; Pollak, R. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: Results from 2 randomized phase-III studies. *J. Am. Acad. Dermatol.* **2015**, *73*, 62−69.
(92) Zane, L. T.; Chanda, S.; Jarnagin, K.; Nelson, D. B.; Spelman, L.; Gold, L. S. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy* **2016**, *8*, 853−866.
(93) Docquier, J. D.; Mangani, S. An update on β-lactamase inhibitor discovery and development. *Drug Resist. Updates* **2018**, *36*, 13−29.
(94) Raymond, E.; Faivre, S.; Woynarowski, J. M.; Chaney, S. G. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol.* **1998**, *25* (2, Suppl.5), 4−12.
(95) Giraud, B.; Hebert, G.; Deroussent, A.; Veal, G. J.; Vassal, G.; Paci, A. Oxazaphosphorines: new therapeutic strategies for an old class of drugs. *Expert Opin. Drug Metab. Toxicol.* **2010**, *6*, 919−938.
(96) Antman, K. H. Introduction: the history of arsenic trioxide in cancer therapy. *Oncologist* **2001**, *6* (Suppl. 2), 1−2.
(97) Sartor, O. Overview of samarium Sm 153 lexidronam in the treatment of painful metastatic bone disease. *Rev. Urol.* **2004**, *6* (Suppl. 10), S3−S12.

DOI: 10.1021/acs.jmedchem.8b00876
J. Med. Chem. 2018, 61, 10996−11020