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Perspective

Phenols in Pharmaceuticals: Analysis of a Recurring Motif

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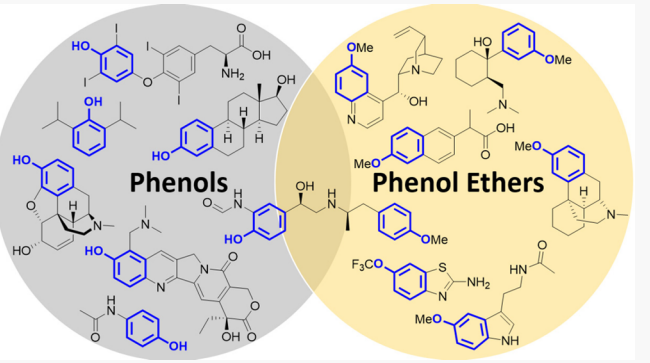
ABSTRACT: Phenols and phenolic ethers are significant scaffolds recurring both in nature and among approved small-molecule pharmaceuticals. This compendium presents the first comprehensive compilation and analysis of the structures of U.S. FDA-approved molecules containing phenol or phenolic ether fragments. This dataset comprises 371 structures, which are strongly represented by natural products. A total of 55 of the compounds described here are on the World Health Organization's list of essential medicines. Structural analysis reveals significant differences in the physicochemical properties imparted by phenols versus phenol ethers, each having benefits and drawbacks for drug developability. Despite trends over the past decade to increase the fraction of sp^3 centers in drug leads, thereby "escaping flatland", phenols and phenolic ethers are represented in 62% of small-molecule drugs approved in 2020, suggesting that this aromatic moiety holds a special place in drugs and natural products.



INTRODUCTION

Phenols and their derivatives are structural motifs appearing widely throughout the natural world in addition to being core scaffolds of countless important industrial products such as pharmaceuticals, agrochemicals, dyes, and flavor and fragrance components to name a few. Examples of phenols commonly found in the human body include the amino acid tyrosine, the neurotransmitter serotonin, and the thyroid hormone levothyroxine (Figure 1).

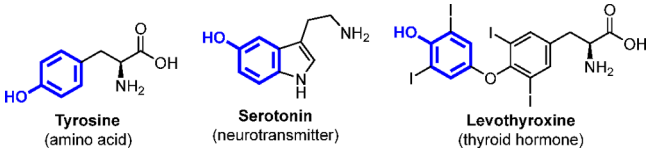


Figure 1. Examples of phenols found in humans.

Selected examples of natural phenol compounds found in significant quantities in commonly consumed food products are presented in Figure 2. These include epigallocatechin gallate and quercitin, which can be found in green tea and cranberries, respectively. Epigallocatechin gallate, which belongs to the catechin family of structures, has been studied extensively in clinical settings ranging from cardiovascular to cancer.[1,2] Resveratrol, which has gathered significant attention in recent years for its putative health benefits, is found in the skin of grapes as well as berries.

Phenols play important roles as flavoring and coloring agents. Examples of natural product flavoring agents containing

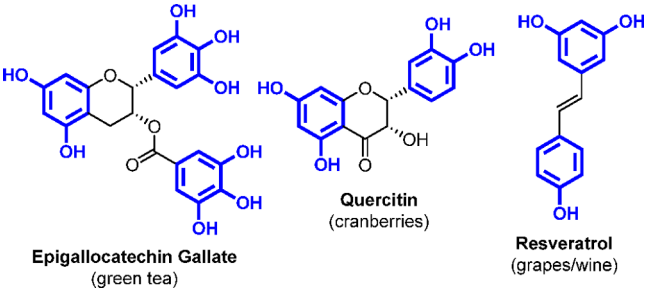


Figure 2. Examples of phenols in food.

phenols include eugenol, vanillin, and sesamol, which are responsible for the flavors of cloves, vanilla, and sesame seeds, respectively (Figure 3). The early years of the chemical industry are connected to the birth of synthetic dyes. Also highlighted are three phenol-containing coloring agents used to produce the colors green, yellow, and red. Nearly all food coloring agents contain phenol moieties. Although these are not approved as drugs by the U.S. FDA, at least two fluorescent compounds in this analysis are approved as ophthalmic diagnostics.

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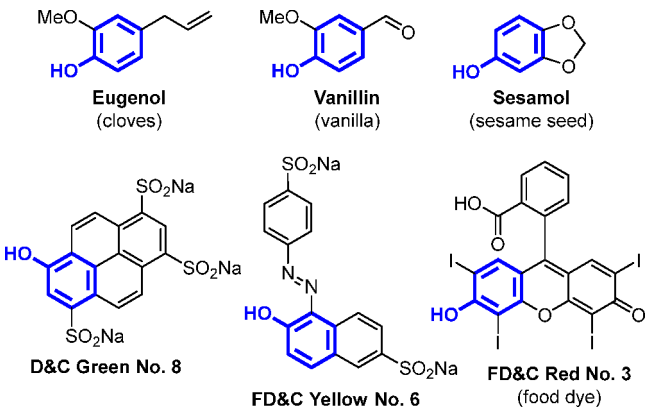

Figure 3. Examples of phenols used as flavoring and coloring agents.

Phenols appear in many agricultural industry products such as herbicides, insecticides, and fungicides (Figure 4). The dinitro-substituted phenols dinitro-*o*-cresol (DNOC), dinoseb, and dinoterb are herbicides whose origins date back to the 19th century.[3] Also displayed are the halogenated nitrile herbicides ioxynil and bromoxynil as well as bromofenoxim.

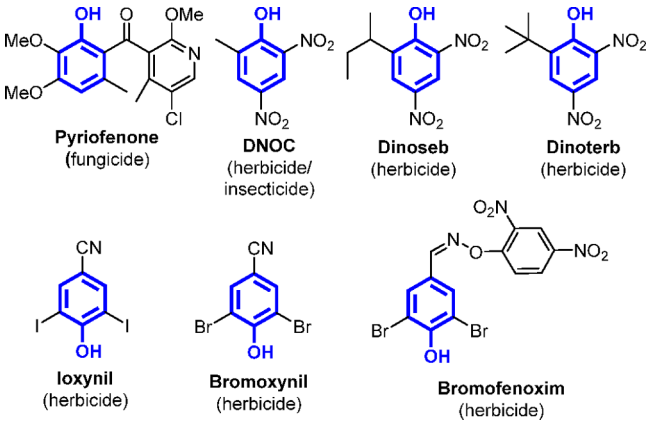

Figure 4. Examples of phenols used in the agricultural industry.

U.S. FDA-APPROVED PHENOL STRUCTURES

Natural products have historically served as excellent sources of drugs or drug leads.[4−8] Of the drugs approved by the FDA between 1980 and 2014, 49% were either natural products or derivatives thereof.[9] Only microbes produce more of the natural products associated with FDA-approved drugs than plants do. The largest group of plant secondary metabolites (natural products) consists of phenol-containing metabolites. These include abridged phenylpropanoids, simple phenols, quinones, xanthones, coumarins, flavonoids, tannins, and lignins.[10]

Our group has a long-standing interest in phenols as they relate to natural products, wherein we initially focused on using phenols as stable aromatic cores that could be dearomatized strategically for the purpose of synthesizing complex diterpenoid natural products.[11−14] More recently, we have investigated tailored decorations of phenols using dearomatization−rearomatization approaches to substitute C−H bonds[15,16] and an approach to generating densely substituted phenols *de novo* from simple starting materials.[17] This Perspective came about because of our continued interest in phenols and passion for communicating and analyzing the structures of approved pharmaceuticals.[18−24] We have further been excited to learn about the applications of phenols in the field of chemical biology, such as selective reactions with the phenol group of the amino acid tyrosine.[25−30] Our dataset of U.S. FDA-approved pharmaceuticals centered around phenols and phenol ethers comprises 371 structures. We decided to not limit our presentation and analysis to phenols but to also include both acyclic and cyclic phenolic ethers as well as a handful of phenolic esters and lactones. Phenols appear in 138 of these 371 structures, the rest being phenolic ethers and esters. Interestingly, 48 structures contain a phenol and a phenolic ether in the same drug. The first section is focused on presentation and analysis of phenols, which we have assembled into figures according to their approved indication and/or common structural cores. The second section is focused on phenolic ethers. Finally, we present a structural analysis of the 3D shape and physicochemical properties associated with drugs containing phenol moieties. To better aid the reader, we have highlighted the phenol core in blue in all figures.

In Figures 5−18 we present the structures of the 138 U.S. FDA-approved drugs containing a phenol. We have grouped these structures according to structural themes starting with the phenethylamine core in Figure 5. Tyrosine is a common

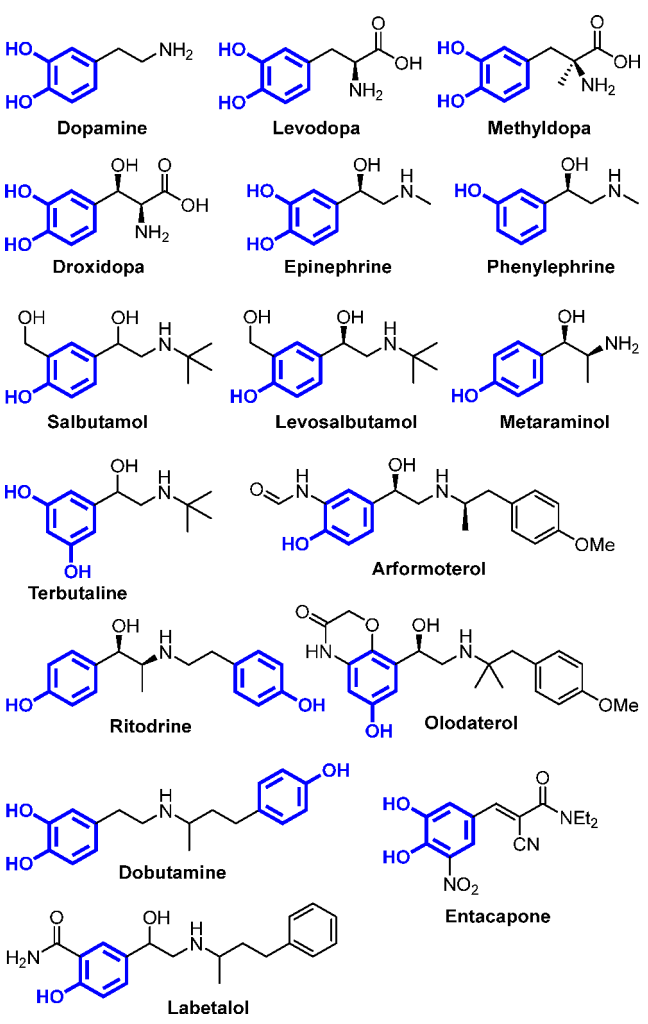

Figure 5. Phenol-containing phenethylamines that mimic dopamine and derivatives.

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building block that nature uses to make many natural products, including endogenous signaling molecules like dopamine and epinephrine. Drugs that are based on these structures (Figure 5) contain phenols, and many of these are recognizable as neurotransmitter analogs. Scaffolds based on the neurotransmitter dopamine or the hormone epinephrine are used to mimic the effects of the endogenous analogs. Indeed, both dopamine and epinephrine themselves are approved as drugs. Dopamine-derived structures like levodopa represent a major strategy in treating Parkinson's disease (PD).[31] Although it is structurally similar to levodopa, methyldopa is used as an antihypertensive. The β-hydroxyl groups of droxidopa and epinephrine impart adrenergic receptor activity, and the other adrenergic receptor agonists in this category can be identified by this feature.[32]

Analogs of naturally occurring thyroid hormones contain phenols with two or one iodine atoms on the phenyl ring as *S* and *R* enantiomers (Figure 6). Both dextrothyroxine and levothyroxine are on the World Health Organization (WHO)'s list of essential medicines.[33]

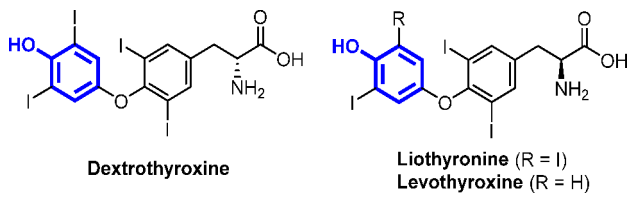

Figure 6. Phenol drugs used to treat hypothyroidism.

The β-lactam antibiotics are a critical class of drugs comprising more than 70 approved drugs. The five β-lactams shown in Figure 7 all contain phenols in various regions

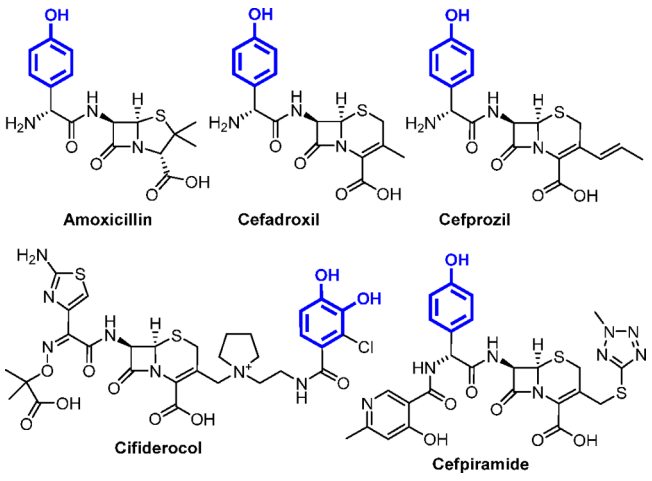

Figure 7. β-Lactam drugs containing phenol side chains.

around the β-lactam core. The phenol moieties of all four are incorporated in the structure by adding 4-hydroxyphenylglycine to culture media during fermentation. The phenol in cefiderocol is substituted with two hydroxy groups and a chlorine.

Another class of antibiotics, the tetracyclines, is highly represented in this analysis and is depicted in Figure 8, with 11 phenol-containing structures. Tetracyclines are among the most widely used antibiotics in both human and veterinary medicine, with over 3.9 million kg used in 2018 in agriculture

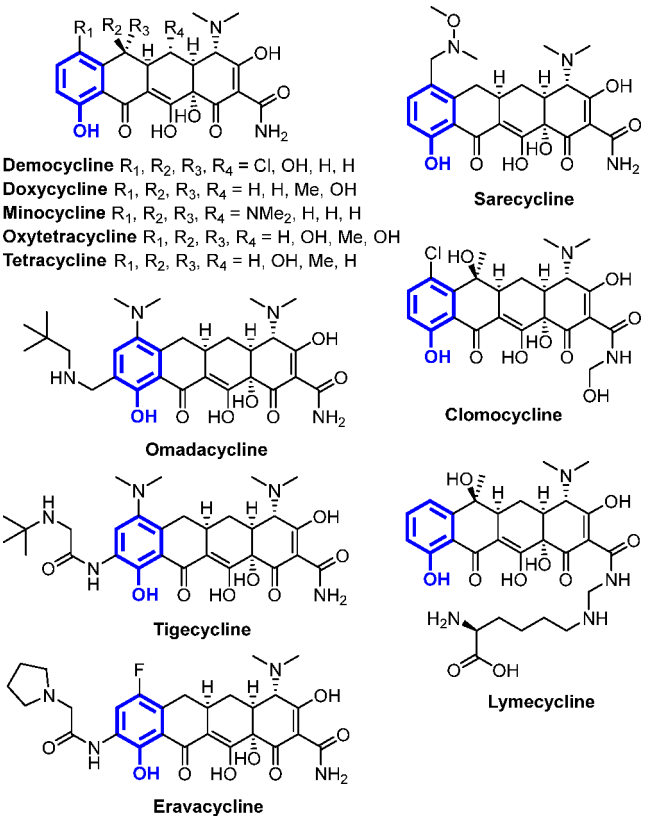

Figure 8. Phenol-containing tetracycline drugs.

alone. The compounds were originally isolated from *Streptomyces* species. Although it is not known what role the phenol moiety plays in the binding mechanism, all four rings are required for activity, as is the aromatic nature of the phenol ring.

Morphine and analogs based on the same morphinan core structure (Figure 9) contain a phenol ring, which is important for binding affinity to opioid receptors. Additional related compounds, including other morphinans (butorphanol and pentazocine) and aporphines (apomorphine), contain phenol and catechol moieties, respectively. In all these cases, the phenol ring is still attached to the skeletal remnants of tyrosine, from which these natural products are formed biosynthetically. The phenols in this category (with the exception of apomorphine) share a common polycyclic core which takes on a highly rigidified "T-shaped" molecule with few or no rotatable bonds, an attractive feature for a ligand. Morphine, hydromorphone, and oxycodone are opioid analgesics, which have gained attention for their potential for addiction.[34] Naloxone and naltrexone are used to reverse overdose of opiates as well as for treatment of opiate addiction, and nalmefene is used to treat alcohol dependence.[35] Chronic use of opiates can lead to opioid-induced constipation, and naloxegol, methylnaltrexone, and naldemedine are used to relieve this side effect.[36] Nalbuphine, nalorphine, and buprenorphine are all opioid analgesics used to treat pain. Butorphanol and pentazocine have structural homology with the morphine-based analgesics but lack the central 5-membered ether ring; both are used to treat pain. Apomorphine is central to late-stage treatment of PD, although the drug has been known since the late 1800s and has been explored for several indications.[37]

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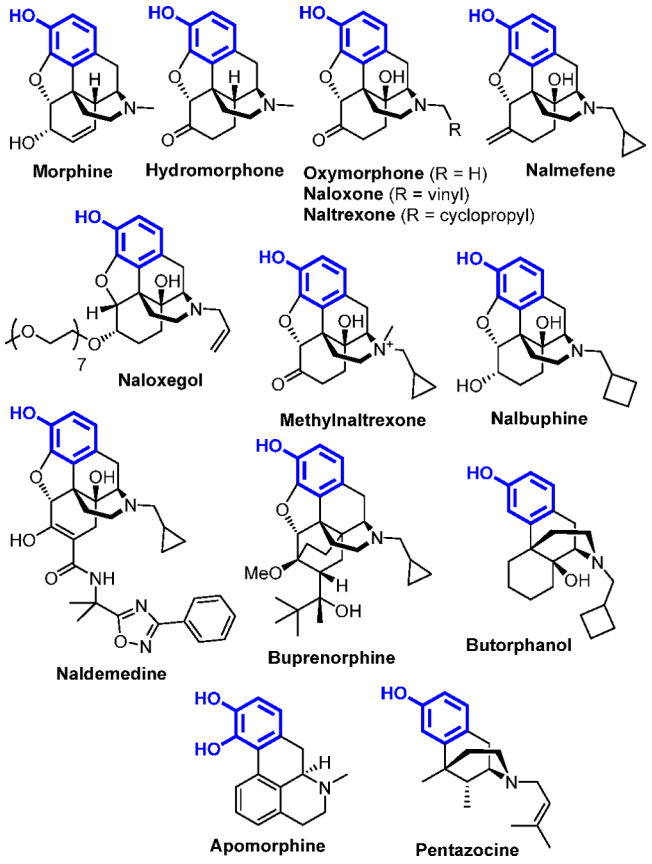

Figure 9. Phenol-containing morphinans and aporphines.

Nature commonly utilizes phenols in complex natural product structures, and the antibiotics in Figure 10 are an excellent example of this. The rifamycin-like antibiotics all contain a fused bis-phenol system with varying degrees of complexity. These compounds work by binding the DNA-dependent RNA polymerase. A related compound not approved by the FDA, rifamycin W, has been accessed by total synthesis. The activity of the rifamycin-type antibiotics is dependent upon the phenols. The orientation of the phenols in relation to the directly opposing hydroxyl groups is critical for activity.[38] Novobiocin is an aminocoumarin and is also called albamycin, cathomycin, and streptonivicin. It is isolated from *Streptomyces niveus* and works by binding bacterial DNA gyrase.[39]

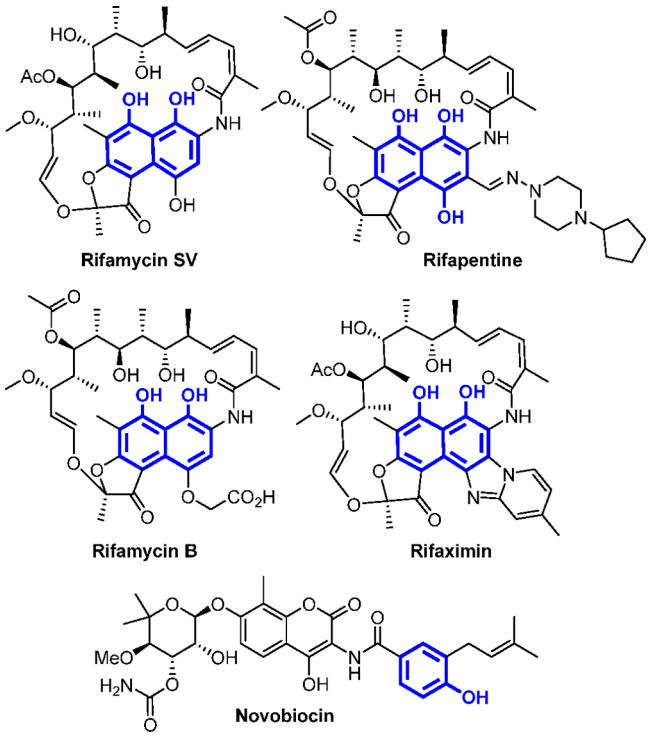

Figure 10. Novobiocin and phenol-containing rifamycins.

Figure 11 displays four examples of spectacularly complex natural product antibiotics that contain phenol moieties.

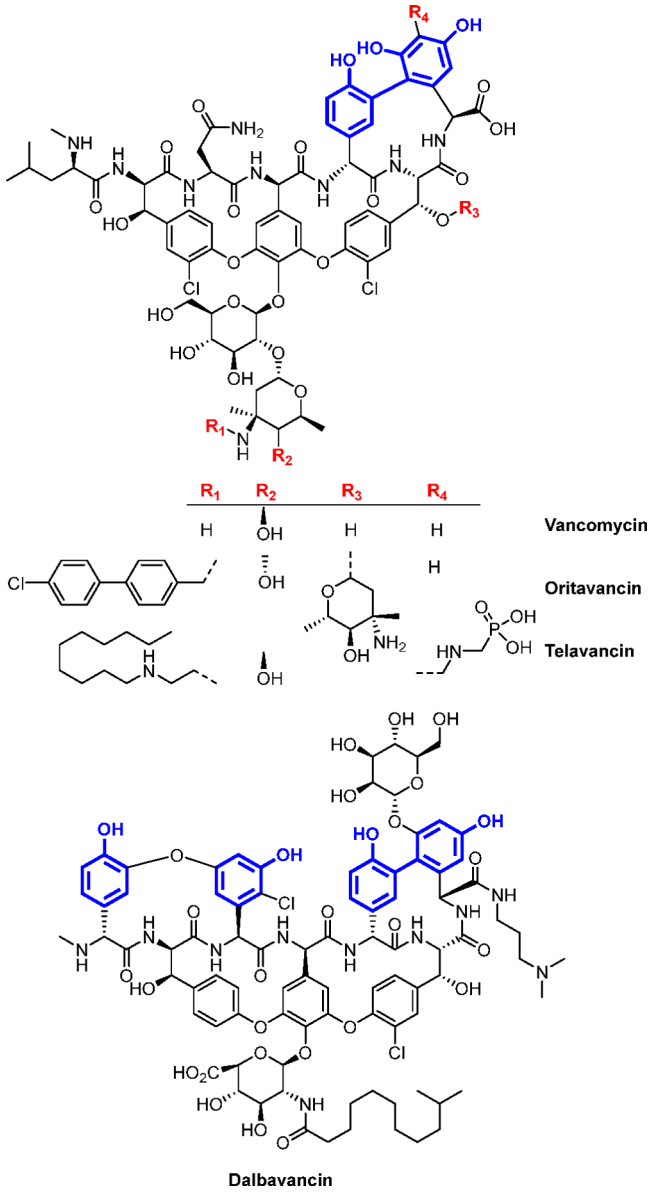

Figure 11. Vancomycin, oritavancin, televancin, and dalbavancin.

Vancomycin and related antibiotics are critical for treating infections caused by bacteria that are resistant to frontline drugs. Because of this, vancomycin is on the WHO's list of essential medicines. The common core structure contains a bisphenol connected by an aryl−aryl σ bond. It has been determined that the phenol in the center of the core containing

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the *O*-glycoside has a greater impact on the structure−activity relationship (SAR), which is discussed further in relation to Figure 38.[40]

Steroid hormones are another major class of important biomolecules of which many have found successes as drugs, and Figure 12 shows the ones that contain phenols in which

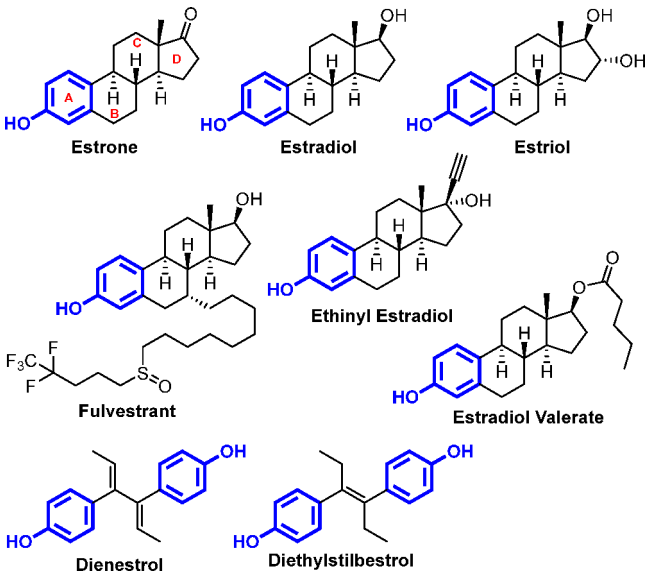

Figure 12. Phenol-containing steroids and related structures.

the A ring is aromatized. Fulvestrant has an interesting side chain containing a highly fluorinated terminal moiety and a sulfoxide group mid-chain.[41] Dienestrol and diethylstilbestrol are included in this group as non-steroidal estrogens, which are used for several indications from preventing miscarriage to treating prostate cancer in men and breast cancer in women.[42]

Just as many of the antimicrobials we have discussed so far are natural products, so are the important cancer therapeutics depicted in Figure 13. Doxorubicin, daunorubicin, idarubicin, valrubicin, and epirubicin all contain 1,4-benzenediol (phenol) moieties that are characteristic of the "-rubicin" core scaffold.[43] The majority of "antibiotic" chemotherapeutics (so named because they were originally discovered in soil bacteria) contain core phenolic moieties. The benzoquinone core is also

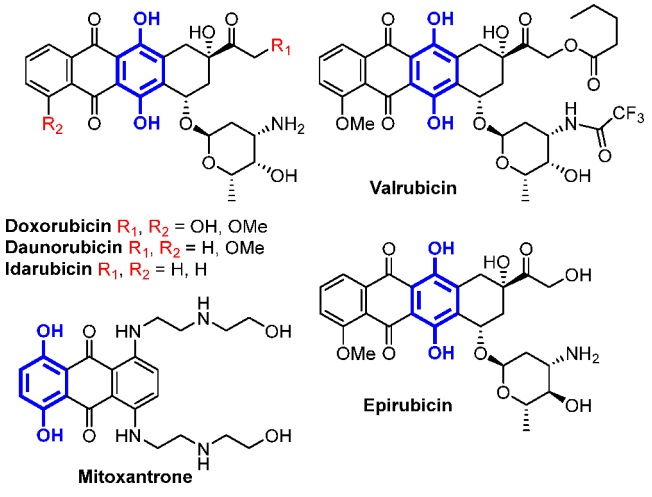

Figure 13. Phenol-containing "antibiotic" chemotherapeutics.

a strong chromophore, and these drugs are often noted for their intense red coloration. Mitoxantrone is a topoisomerase II inhibitor, which superficially resembles the "-rubicins", and is also used to treat cancers.

The additional cancer drugs presented in Figure 14 are also largely natural products or derivatives thereof. Trabactedin and

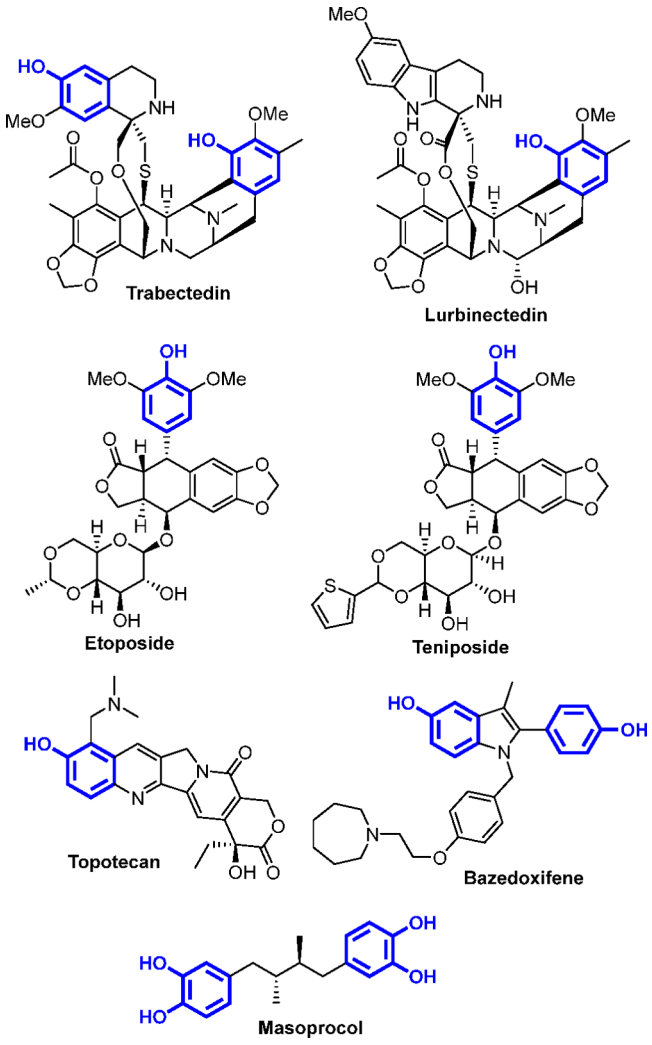

Figure 14. Phenol-containing "antibiotic" chemotherapeutics.

lurbinectedin are natural product chemotherapeutics that block DNA binding to the FUS-CHOP transcription factor.[44] Both compounds share a highly substituted fused monomethyl-catechol ring, and trabectedin has a second monomethyl-catechol. Etoposide and teniposide are structurally related cancer drugs (they only differ in the acetal group substituent). Both compounds contain a 4-hydroxy-3,5-dimethoxybenzene moiety reminiscent of the gallates, which is attached to a sp^3 stereocenter. Topotecan is another cancer drug and a derivative of the natural product camptothecin. Bazedoxifine is a synthetic estrogen receptor modulator used to increase bone density and strength (and is being explored to prevent breast cancer proliferation).[45] Masoprocol is a symmetrical compound that absorbs sunlight in the prevention of skin cancer growths.[46]

Figure 15 depicts miscellaneous antimicrobial drugs: hexachlorophene is an antibacterial disinfectant, nelfinavir is an antiviral used to treat human immunodeficiency virus

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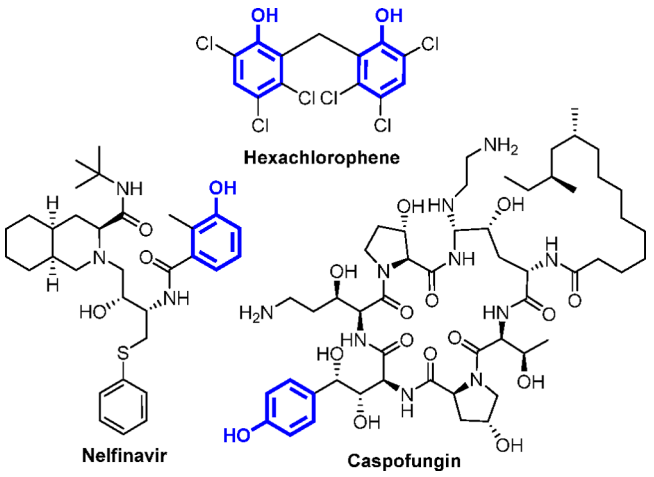

Figure 15. Miscellaneous phenol-containing antimicrobial drugs.

(HIV), and caspofungin is a complex antifungal. Hexachlorophene was approved as a disinfectant, but the label was withdrawn due to toxicity.

Figure 16 depicts a collection of non-steroidal anti-inflammatory drugs (NSAIDs) used to treat pain, anesthetics,

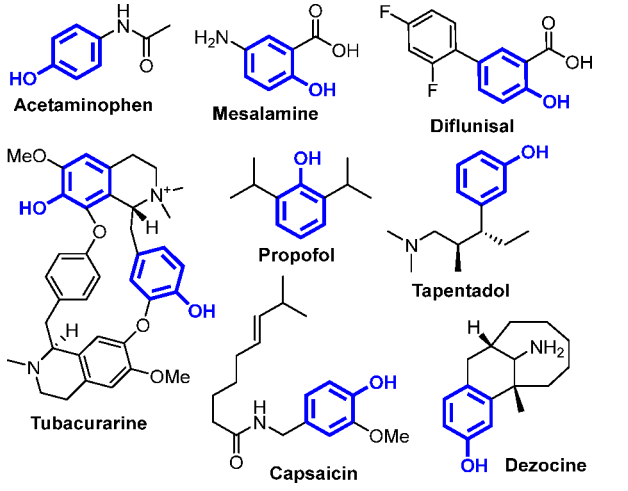

Figure 16. Phenol-containing anti-inflammatory, anesthetic, and analgesic drugs.

and other pain medications. Acetaminophen (Tylenol, paracetamol) is a pain reliever and fever reducer. Mesalamine and diflunisal bear some structural similarity with acetaminophen, and both exhibit anti-inflammatory activity. Tubacurarine was originally used as an arrow poison that causes paralysis, and its propensity to relax skeletal muscle made it useful as an anesthetic.[47] Propofol is an anesthetic used in surgery and is structurally a simple 2,6-diisopropylphenol. Tapentadol is an opioid analgesic with high propensity for addiction. Capsaicin is isolated from *Capsicum* species and is used as a topical pain reliever. The mode of action of this interesting phenol is not completely understood, but it acts differently when compared with other pain relievers. Dezocine is another opioid analgesic.

Figure 17 depicts the first set of miscellaneous phenol-containing drugs. The range of diversity in this group is immense, from cannabidiol to the fluorescent dye fluorescein. Cannabidiol and its synthetically derived nabilone are structurally related, and both contain a substituted resorcinol

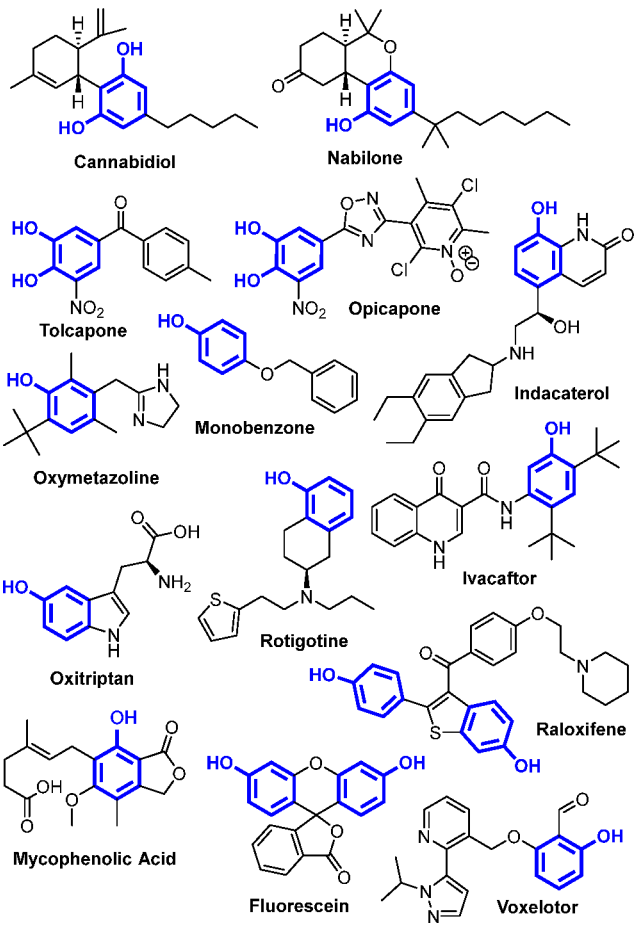

Figure 17. Miscellaneous phenol-containing drugs: part 1.

moiety (1,3-dihydroxybenzene derivative).[48] Tolcapone and opicapone are catechol *O*-methyltransferase inhibitors that are used in combination with the levodopa/carbidopa combination in the treatment of PD.[49] Oxymetazoline is used as a nasal decongestant and features a nearly fully alkyl-substituted phenol. Indocaterol is used to treat chronic obstructive pulmonary disease (COPD) and has a structure similar to those of other respiratory drugs like salbutamol. Rotigotine is a dopamine agonist used for treating PD. Ivacaftor is used to treat cystic fibrosis, and its co-approvals elexacaftor and tezacaftor are discussed below in Figures 49 and 42, respectively. Oxitriptan is also known as 5-hydroxytryptophan, or 5-HTP, and is used to treat depression, sleep disorders, and other indications. Raloxifene is used to treat postmenopausal osteoporosis, working as a selective estrogen receptor modulator.[50] Mycophenolic acid is an immunosuppressant used after organ transplant surgery. Fluorescein's highly conjugated phenols give it fluorescence properties, and its sodium salt is used as an ophthalmic diagnostic. Voxelotor is an oxygen affinity modulator used to treat sickle cell disease.[51]

Figure 18 depicts the second set of miscellaneous phenol-containing drugs. Sulfasalazine and balsalazide are used to treat inflammatory bowel disease.[52] Both drugs are azosalicylic acid derivatives (the fragment containing the phenol) and are conjugated with 2-aminopyridine and β-alanine, respectively, by way of a linker. Crofelemer is a polymeric polyphenol that is used to treat diarrhea caused by other drug treatments such as HIV protease and reverse transcriptase inhibitors.[53] Ezetimibe, which lowers cholesterol, contains a *trans*-disubstituted β-

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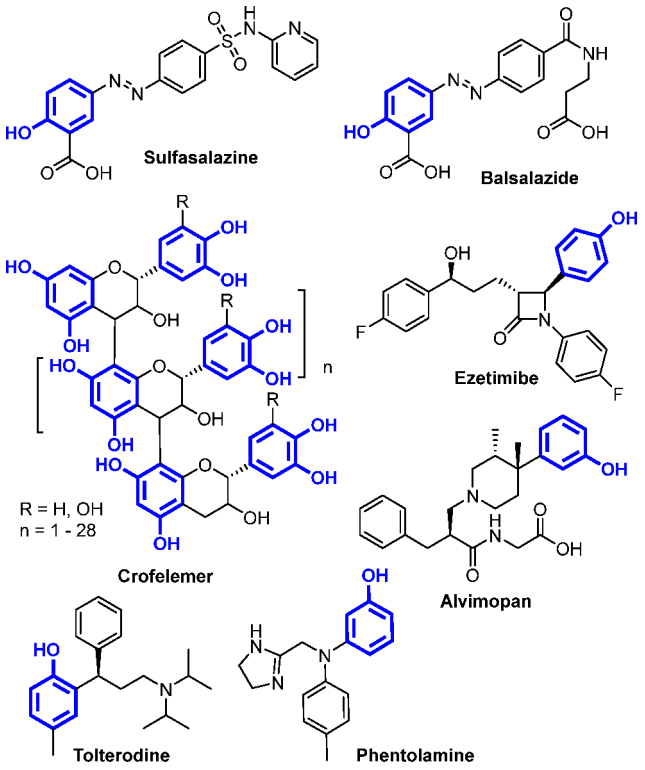

Figure 18. Miscellaneous phenol-containing drugs: part 2.

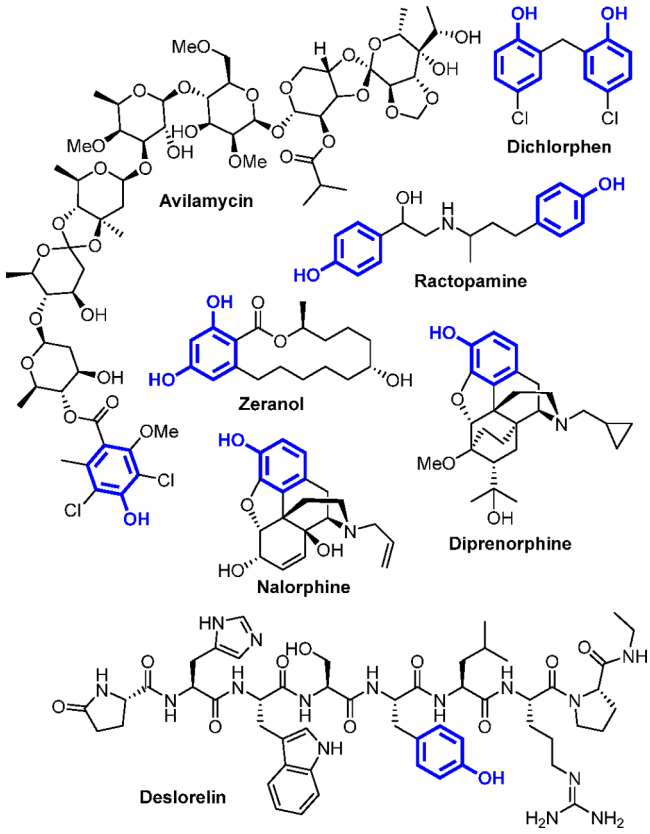

Figure 19. Phenol-containing drugs approved for veterinary use only.

lactam, in which the β-substitution is the phenol. Alvimopan is a μ-opioid receptor agonist used to treat ileus after operation.[54] Tolterodine is used to treat urinary problems ranging from incontinence to urgency. Phentolamine is an α-adrenergic receptor antagonist used to induce vasodilation.

In light of our recent analysis of veterinary drugs,[22] veterinary drugs containing phenols that are not approved for human use have been grouped together for the reader's observation in Figure 19. Veterinary drugs largely resemble human drugs, and 50% of them are separately approved for human use (dual approval). The veterinary drugs that contain phenols, as the structures in Figure 19 do not belong to a class of drugs that has a human counterpart. Avilamycin is a complex orthosomycin antibiotic that is approved in veterinary medicine in two combination drugs, one with narasin and one with monensin, both antimicrobial feed additives. It is isolated from *Streptomyces* species and acts by binding to the 30S ribosome.[55] Avilamycin contains both a phenol and a phenolic ether on the same ring, which is fully substituted with two chlorine atoms and two alkyl groups. Dichlorphen is used as an antimicrobial. The former contains a dimer of 4-chlorophenols, and the latter is a fully substituted pyridylphenol. Zeranol is a non-steroidal estrogen that is used to promote weight gain in cattle and contains a resorcinol moiety. Ractopamine is a TAAR1 and β-adrenergic receptor agonist used as a feed additive to promote leanness and is approved in no fewer than five combination drugs as a feed additive. Nalorphine and diprenorphine are morphine analogs.

What Is the Origin of Phenol Moieties in Drugs? Phenol-containing U.S. FDA-approved drugs are significantly represented by natural products, which in turn have catalyzed drug discovery efforts, with later approved phenol-containing structures being derivatives or fully synthetic versions inspired by the natural product. Since these phenolic drugs originated from screening natural products, many of which were identified decades ago, there was no drug discovery design philosophy associated with their selection, and therefore, at that point, whether a phenol was part of the molecule or not was less critical than it might be today. In the preceding Figures 5−19, phenols appeared in small-molecule natural products, amino acids, catechins, polyketides, opioids, steroids, and many other natural motifs, which begs the question, What are the common biosynthetic origin points for the phenol fragments of these drugs? The amino acids tyrosine and phenylalanine, both of which originate from aromatization of shikimic acid via the shikimate pathway, represent a biosynthetic origin for multiple families of phenol-containing drugs and their many derivatives: serotonin; levothyroxine;[56] L-DOPA and dopamine;[57] ephinephrine; morphine, codeine, and all opioids;[58] capsaicin; vancomycin;[59] tubacurine; camptothecin[60] (topotecan); and trabectedin,[61] lurbinectedin, and others. The phenolic A-ring of the steroids estrone, estradiol, and their derivatives originates from aromatization of the cyclohexenone cores of androstenedione and testosterone, which are derived from cholesterol via squalene cyclization leading back to acetyl-coenzyme A.[62] Many of the more complex multi-ring fused phenol-containing natural products (tetracycline,[63] doxorubicin,[64] rifamycin,[65] cannabidiol,[66] mycophenolic acid,[67] etc.) are made via polyketide synthesis mechanisms wherein the aromatic fragments, including phenolic ones, are made from acyclic precursors via a series of condensations and tautomerizations.

Physicochemical Property Landscape of Phenolic Drugs. Assessment of the *in silico* physicochemical property profiles of phenolic drugs was performed using AbbVie's internal molecular design platform. A range of important

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physicochemical properties were calculated with the statistics shown in Table 1.

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

property	median	mean	Q1	Q3	IQR
MW	363.4	510.5	270.4	558.6	288.2
AlogP	1.68	1.61	−0.42	3.84	4.26
LogD	1.2	0.83	−1.6	3.3	4.8
TPSA	87.0	150.7	57.5	176.6	119.1
NHBD	4	5	2	5	3
NHBA	5	7.4	3	10	7
NAR	1	2.1	1	2	1
NR	3	3.7	2	5	3
NRB	4	8.1	2	7	5
Fsp^3	0.42	0.40	0.30	0.52	0.22
PFI	3.2	2.6	−0.2	5	5.2
QED	0.48	0.44	0.22	0.68	0.45
AB-MPS	9.3	13.3	6.3	13.1	6.8

[a]AlogP, atom-based LogP; LogD, calculated ChemAxon LogD; TPSA, topological polar surface area (NO only); NHBD, number of hydrogen-bond donors; NHBA, number of hydrogen-bond acceptors; NAR, number of aromatic rings; NR, number of rings; NRB, number of rotatable bonds; Fsp^3, fraction of sp^3 carbons; PFI, property forecast index; QED, quantitative estimate of drug-likeness; AB-MPS, AbbVie multi-parametric score; Q1, lower quartile; Q3, upper quartile; IQR, interquartile range.

Lipinski's Rule of Five (Ro5) comprises guidelines used to determine how drug-like a candidate molecule might be based on its molecular mass (less than 500 Da), number of hydrogen bonds (5 or less), number of hydrogen-bond acceptors (10 or less), and partition coefficient (clog P equal to or less than 5).[68] Overall, these drugs have good physicochemical properties which are, on average, well within Ro5. Indeed, we found that 73% of these drugs are Ro5 compliant, with the largest contributor to non-compliance equating to molecular weight >500 (96%), followed by the number of hydrogen-bond donors (NHBD) > 10 (72%) and number of hydrogen-bond acceptors (NHBA) > 5 (68%), with very few violations for lipophilicity AlogP > 5 (<1%). For Ro5-compliant drugs, 72% of this cohort are orally delivered, compared with 36% for the non-Ro5-compliant cohort. The distribution of the routes of administration for both Ro5-pass and Ro5-fail drugs is shown in Figure 20.

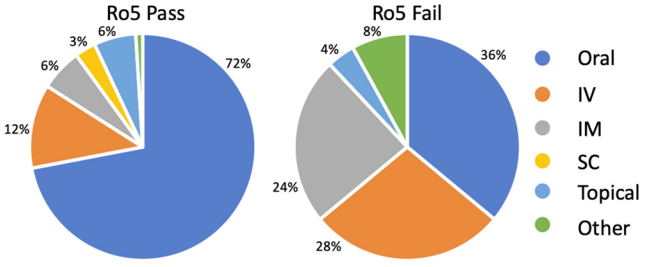

Figure 20. Distribution of the routes of administration for phenolic drugs that pass and fail Ro5. IV, intravenous delivery; IM, intramuscular delivery; SC, subcutaneous delivery. "Other" refers to less frequently used routes of delivery such as vaginal, implant, and inhaled delivery.

Note that drugs that fail Ro5 have overall very high molecular weight and low AlogP (large and not greasy), with over half having a molecular weight over 1000 Da. The bulk of these drugs are either natural products or derivatives thereof, such as vancomycin and the semi-synthetic variant telavancin. In addition, to very low AlogP, these drugs have a 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 than compounds within the property space defined by CLogP < 3 and TPSA > 75 are known to have significantly reduced odds of off-target promiscuity and *in vivo* toxicity.[69] Clearly these drugs, on average, pass the so-called Pfizer Rule of 3/75, with 46% residing in this area of chemical space, and again consistent with the optimization of successful drugs. To further assess the drug-likeness of this chemical matter, we calculated the composite scoring functions known to indicate the likelihood of good drug-like properties in a multi-parametric sense. Thus, the property forecast index (PFI),[70] the quantitative estimate of drug-likeness (QED),[71] and AbbVie's multi-parametric scoring function (AB-MPS) were calculated for all compounds.[72] 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.[73] As is evident in the table, these compounds have low PFI, with the upper quartile (Q3, 75% of compounds) passing this requirement for developability. The fact that this set of drugs has good overall PFI values is not a surprise, given the low LogD and aromatic ring count. So, despite the overall relatively high average molecular weight, these drugs have good drug-like properties, particularly the set of drugs that passes Ro5. We also conducted a more complex multi-parametric assessment of drug-likeness by calculating the QED, which derives desirability based on eight different properties. Using Harrington desirability functions based on the distributions of the properties of 771 drugs, the 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 unity, the more drug-like it is based on this set of 771 drugs. For phenolic drugs, the mean QED = 0.44 and Q3 = 0.68, which are significantly lower than the average values given in the original paper for 771 orally available drugs (mean = 0.6, Q3 = 0.8). If we calculate the QED distribution of orally delivered phenolic drugs, however, we only note a slight increase in overall QED values (mean QED = 0.48, Q3 = 0.68), suggesting that phenolic drugs have properties different from those of other chemotype-specific drugs. In addition to PFI and QED, we calculated AbbVie's AB-MPS. This MP score was derived based on the optimization of oral bioavailability of compounds beyond Ro5. We (and others) have shown that this rubric is predictive of both permeability and oral absorption, irrespective of Ro5 compliance. In general, an AB-MPS ≤ 12 is a strong indicator of good permeability and oral absorption. Phenolic drugs have a very broad range of AB-MPS. However, 75% (Q3) of these drugs have an AB-MPS < 13, which improves significantly for orally delivered phenolic drugs (Q3, AB-MPS < 10.3), which again is consistent with highly optimized compounds with a greater probability of drug-like properties. Undoubtedly these drugs would be expected to have good solubility and absorption, distribution, metabolism, and excretion (ADME) properties, and therefore good pharmacokinetic properties.

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U.S. FDA-APPROVED PHENOL ETHER STRUCTURES

For the larger phenol ether-containing structures (281 drugs), we elected to group them according to their common acyclic ether and cyclic ether features, starting with the simplest acyclic ones, represented by phenol methyl ethers, before progressing to more complex acyclic ethers. Cyclic ethers are grouped together according to their ring size, saturation, and oxygenation.

The drugs in Figure 21 feature a single methyl ether group and one other substituent on the phenol ether core. They

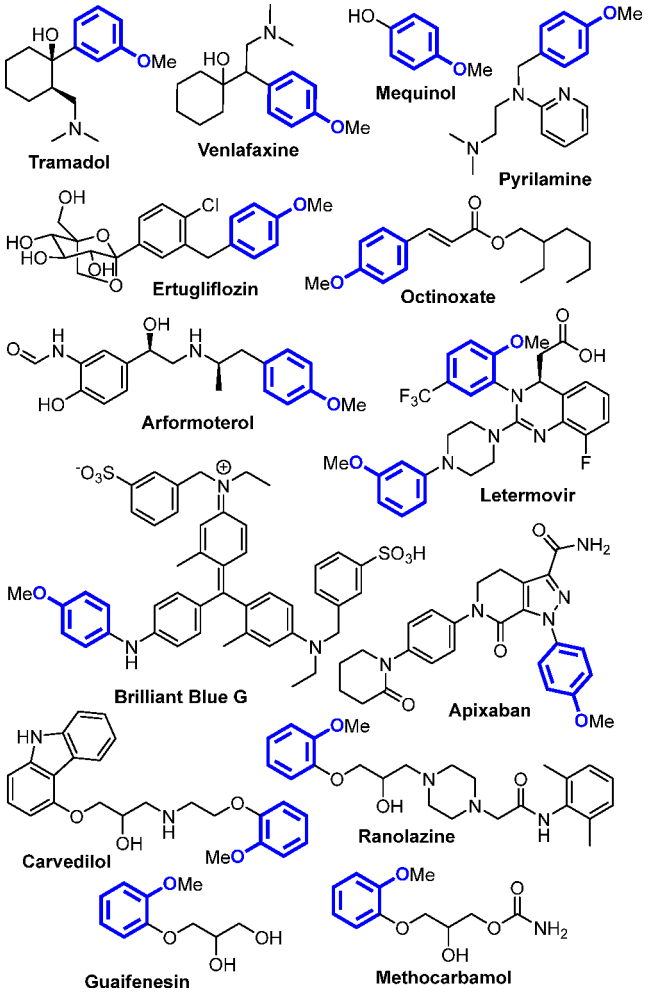

Figure 21. Mono-substituted phenol methyl ether-containing drugs.

represent a wide variety of indications, including pain (tramadol), diabetes (ertugliflozin), viral infection (letermovir), and congestion (guaifenesin). Venlafaxine is used to treat nerve pain and depression. Mequinol is a very simple 1,4-disubstituted phenol and methyl phenol ether used to treat skin depigmentation. Pyrilamine is a first-generation antihistamine used to treat allergies. Etrugliflozin is structurally interesting because of the tethered sugar moiety but also stands out from the other "-gliflozin" drugs in that it contains a phenolic ether. Octinoxate is a derivative of cinnamic acid and prevents skin damage caused by the sun when it is used in sunscreens. Arformoterol is a beta agonist that works as a bronchodilator in asthma treatment. Letermovir contains two methyl phenolic ethers and is used to prevent cytomegalovirus infection in stem cell transplant patients. Brilliant blue G is used for ophthalmic staining. Apixaban is an anti-coagulant used to treat blood clots and prevent stroke. Carvedilol and ranolazine are both heart medications that reduce blood pressure, and guaifenesin and methocarbamol are used to treat chest pain and spasms.

Figure 22 depicts drugs that, in addition to a single methyl ether, are also decorated with two other substituents on the

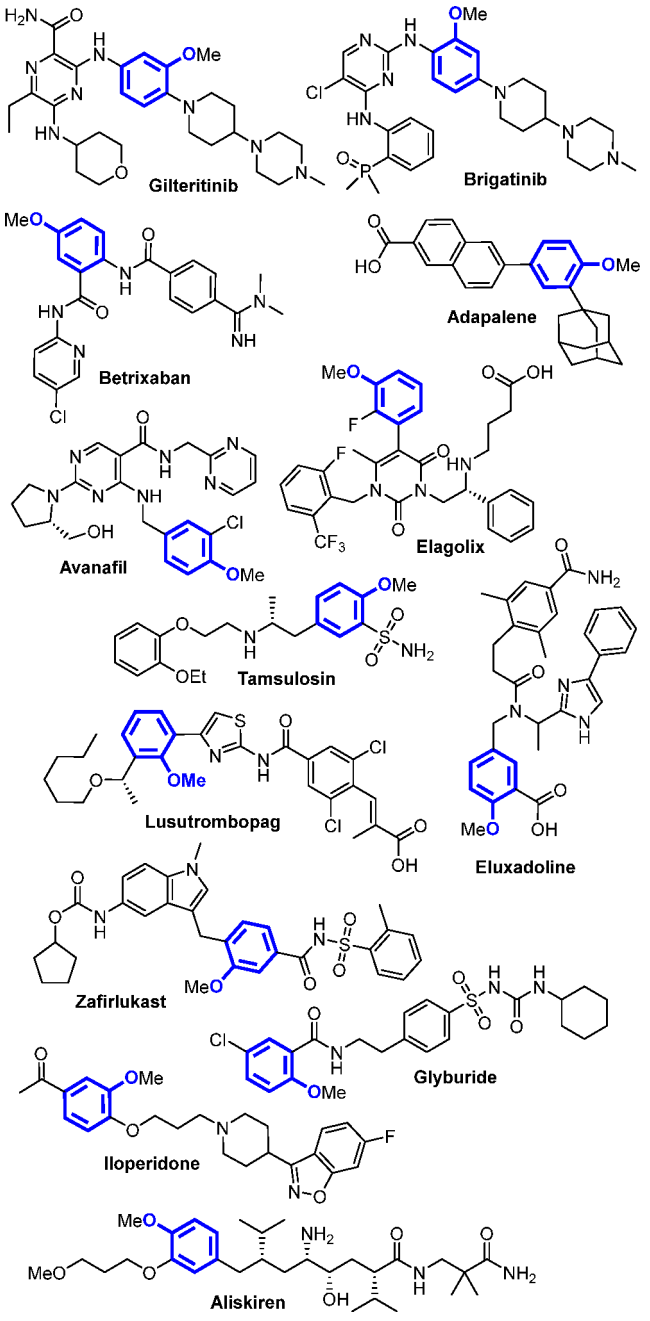

Figure 22. Disubstituted phenol methyl ether-containing drugs.

phenolic ether ring. Gilteritinib and brigatinib are both kinase inhibitors used for cancer therapy. Betrixaban is a factor Xa inhibitor used as an anti-coagulant. Adapalene, used to treat acne, has an adamantane ring in the 2-position of the phenol ether.[74] Avanafil is a phosphodiesterase 5 inhibitor used as a treatment for erectile dysfunction and has a chlorine atom in

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the position *ortho* to the phenolic ether. Elagolix, an antagonist of gonadrotropin-releasing hormone receptor used to treat symptoms of menopause, contains a fluorine *ortho* to the phenolic ether.[75] Tamsulosin is a treatment for urinary retention, with a sulfonamide group ortho to the phenolic ether. Lusutrombopag is a thrombopoietin agonist used to treat thrombocytopenia and contains a phenolic ether connected to a thiazole.[76] Zafirlukast is a leukotriene receptor antagonist that is used to treat chronic asthma through its anti-inflammatory effects. Eluxadoline can treat diarrhea and abdominal pain by acting as a μ- and κ-opioid agonist and a δ-opioid antagonist.[77] Glyburide contains a phenolic ether with a chlorine in the position *para* to the phenol and is used to treat type 2 diabetes, working by inhibiting the inhibitory regulatory subunit sulfonyl receptor-1 on adenosine triphosphate-sensitive potassium channels.[78] Iloperidone is an atypical anti-psychotic that contains a catechol ether (two adjacent phenolic ethers on the same ring). Aliskiren is an anti-hypertensive that works by inhibiting renin.[79]

The drugs displayed in Figure 23 contain one methyl ether and three or four other substituents on the phenolic ether ring.

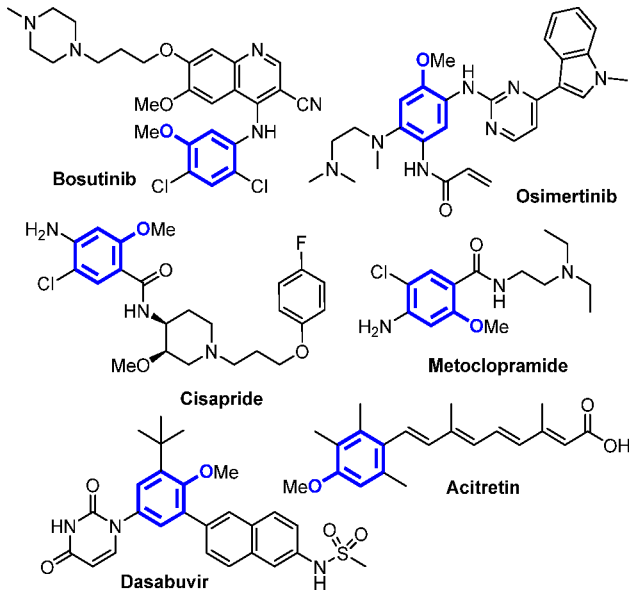

Figure 23. Tri- and tetrasubstituted phenol methyl ether-containing drugs.

In two of these structures, bosutinib and osimertinib, all four substituents are heteroatoms, consisting of nitrogen and chlorine. Two other structures, cisapride and metoclopramide, each have a nitrogen and a chlorine substitution on the phenol ring, as well as an acyl group. Finally, the phenol in dasabuvir has a nitrogen heterocycle, an aromatic ring, and an alkyl group appended, and acitretin has all alkyl groups: three methyl and an olefin.

Figure 24 depicts monomethyl phenolic ethers that are fused to another ring. The "-rubicin" compounds (doxorubicin, daunorubicin, epirubicin, and valrubicin) were first presented in Figure 13, and are classic chemotherapeutics derived from soil bacteria. Naproxen and nabumetone are both NSAIDs used to treat pain. Hydrocodone, codeine, and oxycodone are also used to treat pain and belong to the morphine class of drugs. Dextromethorphan is structurally related to the previous three but belongs to the morphinan class of drugs. Lenvatinib

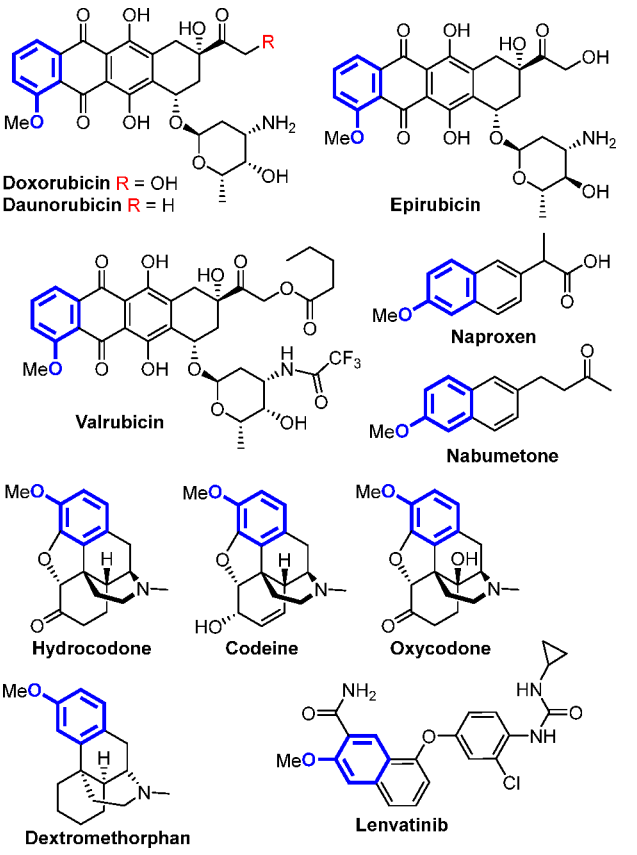

Figure 24. Aryl- and cyclohexyl-fused aryl methyl ether-containing drugs.

is a cancer drug that works by inhibiting a number of kinases, including vascular endothelial growth factors (VEGFR1−3), fibroblast growth factors (FGFR1−4), and platelet-derived growth factor receptor (PDGFR).

Figure 25 depicts monomethyl phenolic ethers that are fused to an indole or an indoline ring. Vinorelbine, vinblastine, and vincristine are structurally related complex vinca alkaloid natural products that are all used as chemotherapeutics.[80] Reserpine is a natural product first isolated from Indian snakeroot (*Rauvolfia serpentina*) in 1952. It is used to treat high blood pressure. Melatonin is an analog of serotonin that is naturally produced by the human body and is used to treat sleeplessness. Indomethacin is an NSAID.

Figure 26 depicts monomethyl phenolic ethers that are fused to aromatic nitrogen heterocycles (pyridines, pyrazines, and pyrimidines). Voxilaprevir, grazoprevir, and glecaprevir are combination drug components of recently approved hepatitis C virus medications. Tafenoquine and the diastereomers quinidine and quinine share a structural core and are all used as anti-malarials. Dacomitinib, gefitinib, vandetanib, and bosutinib are all kinase inhibitors used to treat different types of cancer.

Figure 27 depicts monomethyl phenolic ethers that are fused to non-aromatic heterocycles. Moxifloxacin and gatifloxacin are both fluoroquinolone antibacterial drugs. Galantamine bears significant structural similarity with morphine-based drugs, but it is used as a cognitive enhancer in dementia patients. Tubacurarine is an anesthetic based on a toxin isolated from arrow frogs. Elvitegravir is an integrase inhibitor that is used to treat HIV infection. Lurbinectidin and trabectedin are natural

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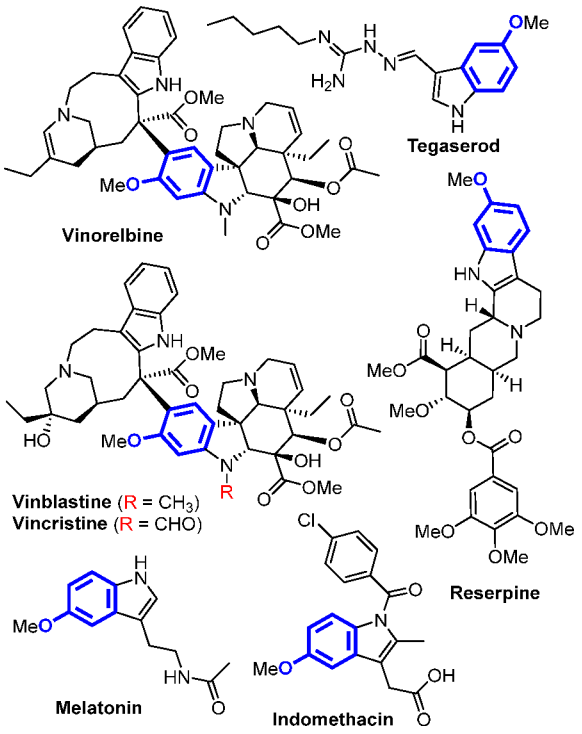

Figure 25. Indole and indoline methyl ether drugs.

products used to treat cancer. Mycophenolic acid and its ester derivative mycophenolate mofetil are immunosuppressants. Copanlisib is used to treat specific lymphomas. Omeprazole is a proton pump inhibitor.

The drugs in Figure 28 contain two methyl ethers. Istradefylline is a selective adenosine A_{2A} receptor antagonist used to treat PD.[81] Verapamil is an important drug used to treat high blood pressure and angina and acts as a calcium-channel blocker. Teniposide is a drug already discussed in the context of its free phenol and here highlighted for its two methyl ethers.

Figure 29 displays drugs with two methyl phenolic ethers fused to another ring. Prazosin, terazosin, doxazosin, and alfuzosin share a high degree of structural similarity and are all used to treat high blood pressure. Tetrabenazine and its deuterated analog deutetrabenazine, as well as valbenazine, are used to treat uncontrolled movements. Moexipril is an angiotensin-converting enzyme inhibitor used to treat hypertension. Ivabradine has notable structural features, with two dimethyl phenolic ethers fused to a 7-membered ring and a 4-membered ring. Cisatracurium is a symmetric dimer of benzyltetrahydroisoquinolonium moieties, each of which contains two catechol ethers (phenolic ethers with two adjacent oxygens), that is used as a skeletal muscle relaxant and acts by blocking neuromuscular junctions.[82]

Figure 30 contains drugs with three methyl phenolic ethers on a single ring. Reserpine and deserpidine belong to a class called rauwolfia alkaloids and are used to calm the nervous system (reserpine was covered in the monomethyl section). Podofilox is a natural product called podophyllotoxin isolated from *Podophyllum* species and is used to treat warts.[83] Colchicine is an anti-inflammatory natural product isolated from the plant *Colchicum autumnale* used to treat gout.[84] Trimethoprim and trimetrexate are quinazoline dihydrofolate reductase inhibitors used to treat bacterial infections.

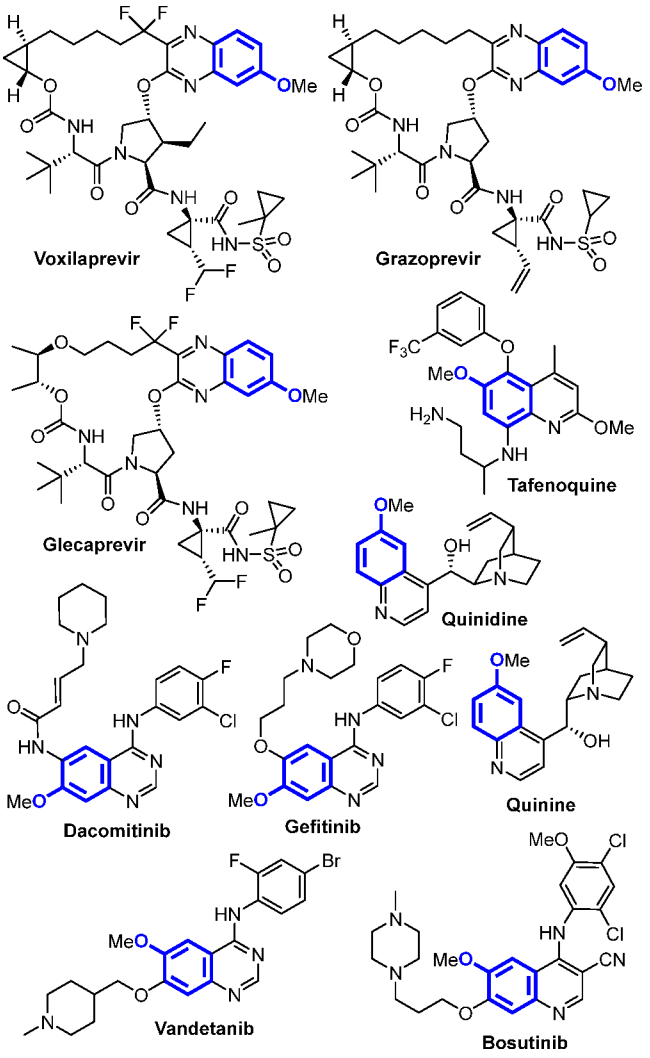

Figure 26. Pyridine-, pyrazine-, and pyrimidine-fused aryl methyl ether drugs.

Figure 31 depicts phenolic ethers with primary alkyl groups. Vardenafil is used to treat erectile dysfunction. Repaglinide and dapagliflozin are both used in type 2 diabetes treatments (as well as the structurally related ertugliflozin in the monomethyl group). Anidulafungin is an antifungal drug that belongs to the echinocandin class. Pentamidine is a symmetric antimicrobial drug used to treat several different parasitic infections. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor that prevents TNF-α production for the treatment of psoriasis and psoriatic arthritis.[85] Febuxostat is used to treat gout. Pimavanserin is a dopamine agonist approved for treating PD. Proparacaine is an anesthetic, similar in structure and function to other "-caine" anesthetics like benzocaine and lidocaine.

Each drug in Figure 32 features prominent fluorine atoms. Pretomanid is a nitroimidazole antibacterial drug, which features a trifluoromethyl phenolic ether. Sonidegib also contains a trifluoromethyl phenolic ether and disrupts the hedgehog signaling pathway for cancer treatment.[86] The trifluoromethyl group in riluzole is attached to a phenol whose aromatic portion is a benzothiazole, and the drug is used in treating amyotrophic lateral sclerosis. Florbetaben contains the ^{18}F isotope and is used to image β-amyloid plaques in the brain by positron emission tomography.[87]

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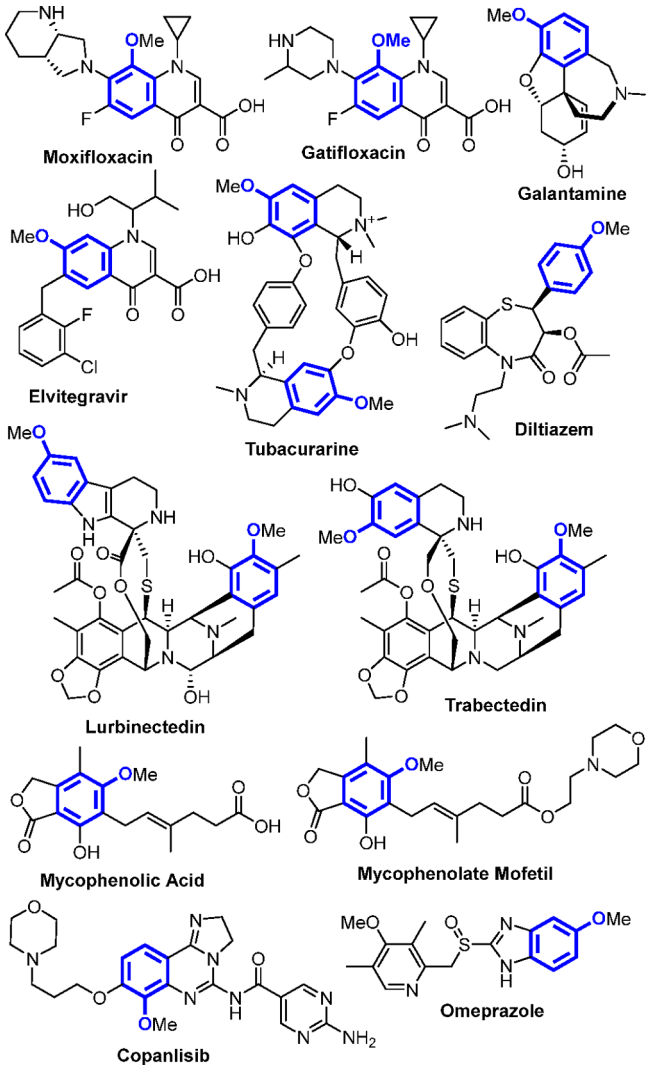

Figure 27. Fused non-aromatic heterocyclic aryl methyl ether drugs.

Flecainide is an anti-arrhythmic drug used to treat tachycardia. Silodosin is an α_1-adrenergic antagonist used to treat benign prostatic hyperplasia.[88] Pantoprazole is a proton pump inhibitor used to treat stomach ulcers and other stomach issues. Roflumilast is a PDE4 inhibitor used to treat COPD and other inflammatory lung conditions. Tafluprost is a fluorinated prostaglandin drug used to treat glaucoma or ocular hypertension.[89]

The drugs in Figure 33 contain a shared central structure consisting of a trisubstituted propylene group (except isoxsuprine), and most of them bind to adrenergic receptors. The drugs whose names end in "-lol" are beta blockers. Most of the phenols in this category have either a 1,4-disubstitution or a fused ring system. Acebutolol and cromolyn are trisubstituted. Ranolazine is a sodium channel blocker used to treat angina. Cromolyn is used to treat asthma by stabilizing mast cells. Isoxsuprine is a beta agonist that increases blood circulation.[90]

The drugs in Figure 34 contain primary alkyl aryl ethers. Tamoxifen, toremifene, clomifene, and ospemifene are all highly homologous estrogen receptor modulators used to treat breast cancer.[91] Amiodarone is a class III anti-arrhythmic.[92] Raloxifene was discussed earlier (Figure 17) in the context of its two phenols, and here it is highlighted for its ethylamine

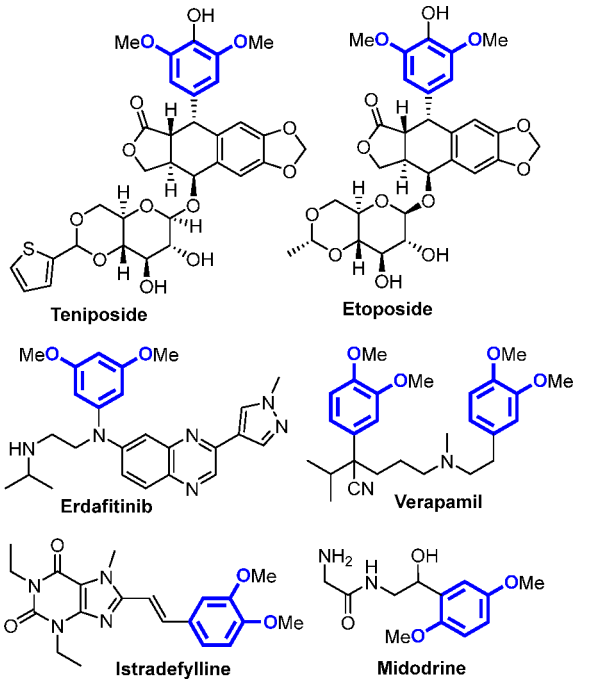

Figure 28. Non-fused aryl dimethyl ether drugs.

phenyl ether. Fedratinib is a kinase inhibitor used to treat myeloproliferative diseases.[93] Penicillin V contains a phenolic ether, which is incorporated into the structure by fermentation with 2-phenoxyacetic acid. Mexiletine is a class IB anti-arrhythmic which is also used to treat neuropathy associated with diabetes and works as a non-selective voltage-gated sodium channel blocker.[94] Dofetilide is an anti-arrhythmic drug. Phenoxybenzamine is an irreversible α-adrenergic receptor agonist used to treat high blood pressure associated with adrenal gland tumors. Nefazodone is an atypical antidepressant that works as a serotonin antagonist and reuptake inhibitor.[95] Olodaterol is an ultra-long-acting β-blocker, whose structure differs from the compounds in Figure 33 because the aromatic moiety is connected to the central structure by a carbon−aromatic bond rather than a phenol ether bond. Trifarotene is a selective retinoic acid receptor-γ agonist used to treat certain types of acne.[96] Lopinavir is an antiviral prescribed with ritonavir (which has a thiazole in place of the phenolic moiety) for treatment of HIV.[97]

Figure 35 depicts primary alkyl ethers that terminate in an amino group. Gefitinib, vandetanib, and bosutinib are structurally related kinase inhibitors used to treat certain cancers, including lung and breast cancers, by targeting epidermal growth factor receptor (EGFR) kinase.[98] Copanlisib is used under specific conditions to treat follicular lymphoma and works by inhibiting phosphatidylinositol-3-kinase in malignant B cells.[99] Cisapride is a 5-HT_4 agonist used to induce gut motility. Aripiprazole, brexipiprazole, and tirofiban are anti-psychotic drugs used to treat a variety of disorders, including schizophrenia. Paroxetine is a selective serotonin reuptake inhibitor that is used in treating depression.[100] Metaxalone is a muscle relaxer. Tirofiban is a blood thinner. Iloperidone is an atypical anti-psychotic. Aclidinium is a muscarinic receptor agonist used to treat COPD. Dronedarone is an anti-arrhythmic.[101]

Figure 36 shows benzylic, glycerol, and hydroxyacetic acid aryl ethers. Itraconazole, posaconazole, terconzaole, and

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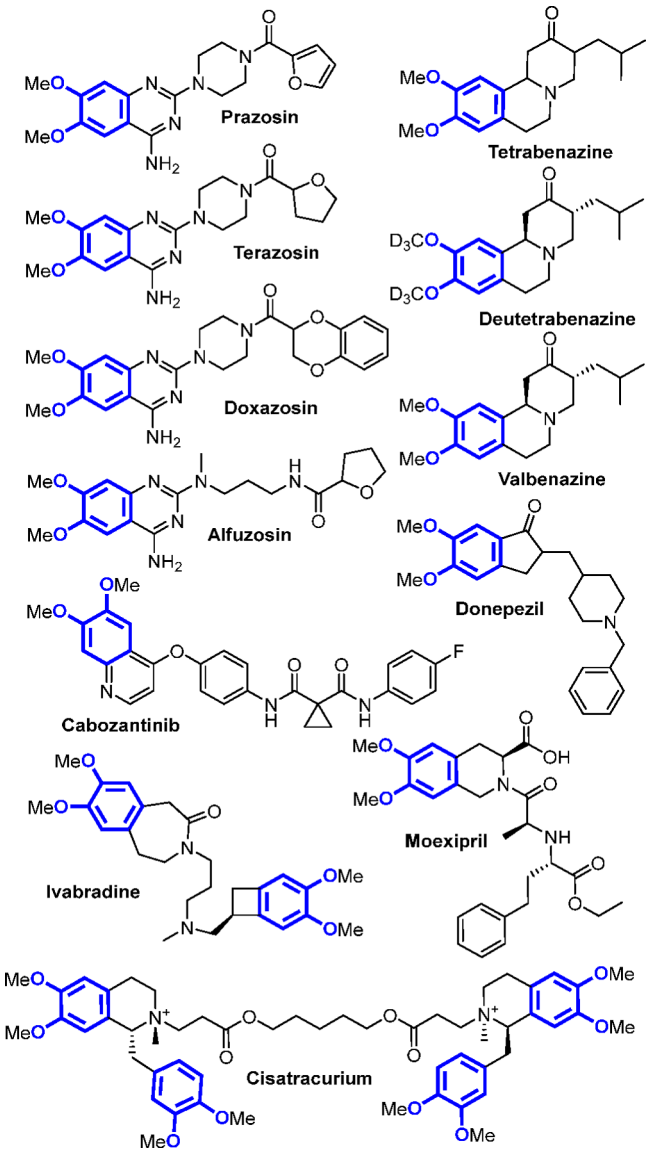

Figure 29. Fused aryl dimethyl ether drugs.

ketoconazole are azole antifungal drugs with broad-spectrum activity.[102] Lepatinib is a kinase inhibitor used to treat certain cancers. Monobenzone is a structurally simple compound used in treating skin over-pigmentation. Voxelotor is used to treat sickle cell disease, acting as a hemoglobin S polymerization inhibitor.[103] Safinamide is a selective monoamine oxidase-B inhibitor used in PD treatment regimens.[104] Rifamycin B is a natural product antibiotic with a number of analogs, the structures of which are covered in other sections in this analysis. Treprostinil is a synthetic prostacyclin analog used as a vasodilator to treat pulmonary arterial hypertension.[105] Ethacrynic acid is an interesting dichlorophenolic ether used to treat edema by acting as a loop diuretic.[106]

Figure 37 depicts miscellaneous alkyl aryl ethers, including aliskiren, an anti-hypertensive, and the prostanoid travoprost, a glaucoma medication that works by relieving pressure inside the eye. Cilostazol is a phosphodiesterase 3 (PDE3) inhibitor used to inhibit platelet aggregation and treat claudication.[107] Pioglitazone is used to treat diabetes and works by activating the nuclear peroxisome proliferator-activated receptor-γ.

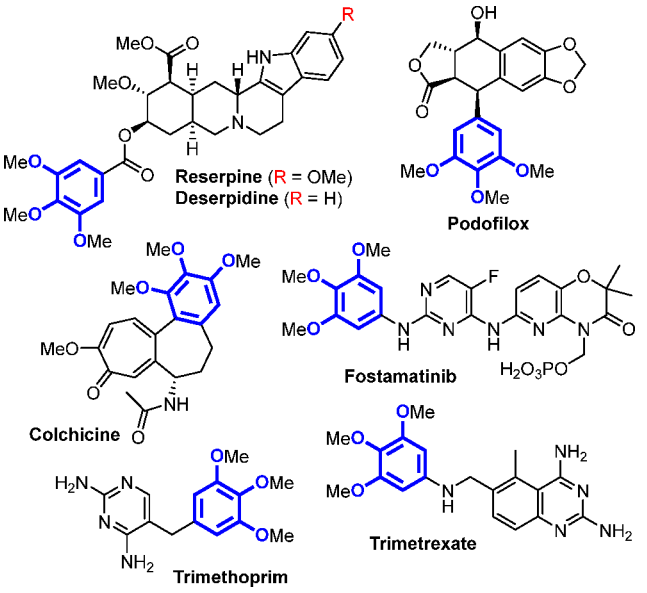

Figure 30. Aryl trimethyl ether drugs.

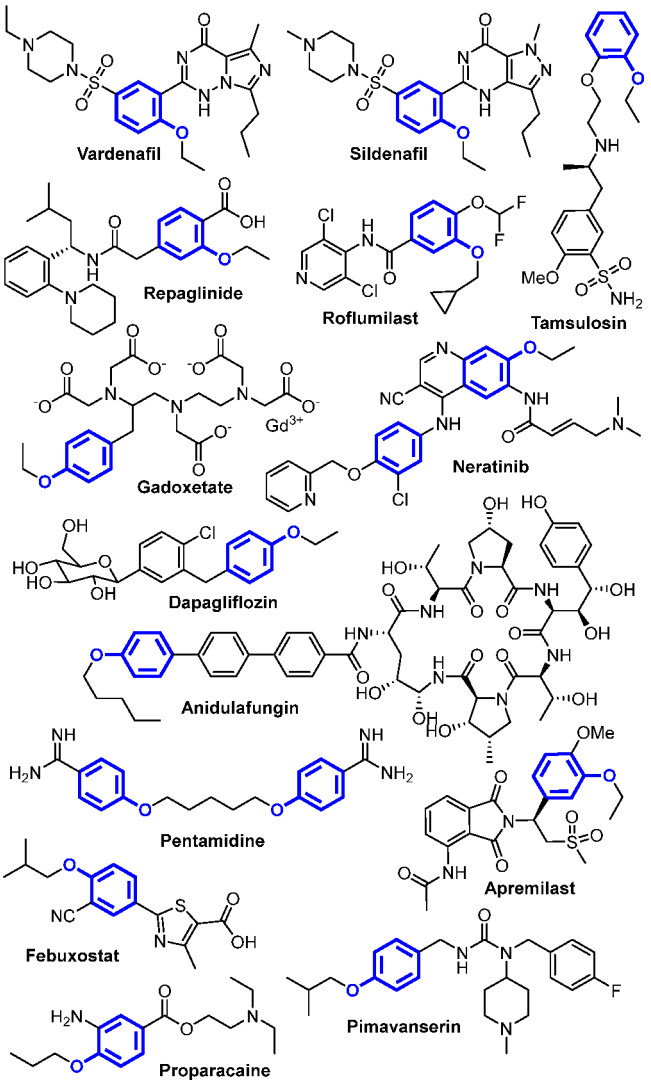

Figure 31. Alkyl aryl ether drugs.

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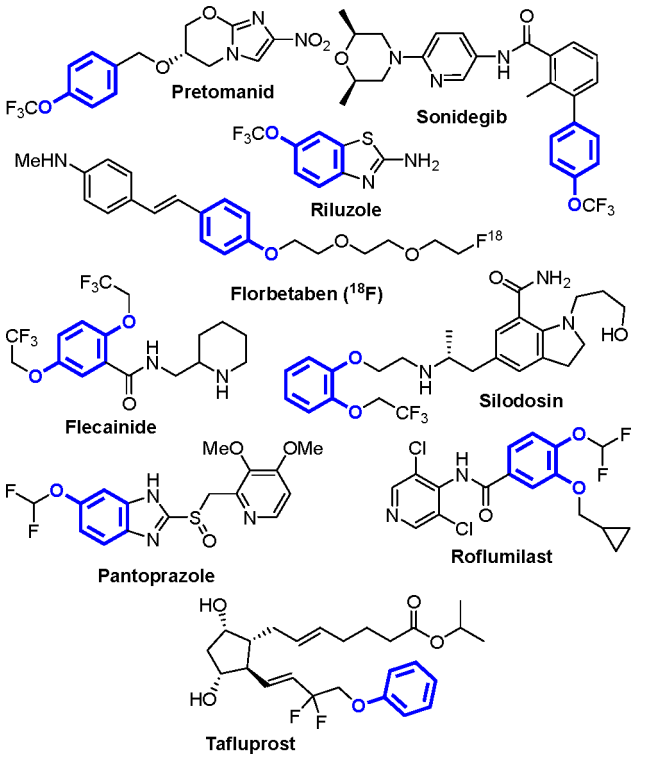

Figure 32. Fluorinated alkyl aryl ether drugs.

Gemfibrozil is used to lower lipid levels, although the mechanism by which it does so is unclear.[108]

The drugs in Figure 38 depict secondary alkyl aryl ethers. Vancomycin and related antibiotics were covered in the phenol section but are revisited here, this time for the *O*-glycoside phenolic ether. This moiety has the greatest impact on SAR and is also the region of greatest variability between analogs. Afatinib is a dual kinase inhibitor used to treat non-small-cell lung carcinoma and targets human epidermal growth factor receptor 2 (Her2) and EGFR kinases by covalent inhibition.[109] Ceritinib is a kinase inhibitor used for treating metastatic non-small-cell lung cancer. Lofexidine, fluoxetine, and atomoxetine are structurally related drugs used to treat high blood pressure and opioid withdrawal, depression, and attention deficit hyperactivity disorder, respectively.[110] Fenofibrate activates the peroxisome proliferator receptor alpha and is used to lower triglyceride and cholesterol levels.[111] Novobiocin is an aminocoumarin antibiotic which was seen previously in the context of its phenol moiety but is revisited here to highlight the *O*-glycoside phenolic ether.

A number of important drugs contain phenyl phenyl ethers, and some of them are depicted in Figure 39. Notable drugs in this category include the thyroid hormones levothyroxine and liothyronine, as well as NSAIDs like fenoprofen. Crisaborole is used to treat dermatitis and is one of very few approved drugs that contain a boron atom.[112] Ibrutinib and zanubritinib are covalent inhibitors that target Bruton's tyrosine kinase for cancer treatment and are part of a resurgence in covalent drugs.[113] Tafenoquine is used both as a prophylaxis and as a treatment for malaria.[114] Lenvatinib and sorafenib are kinase inhibitors used to treat a number of different cancers. Tubocurarine is an anesthetic that is covered in two other sections of this analysis for its phenol and monomethyl phenolic ether moieties. Oftasceine is an ophthalmic dye used

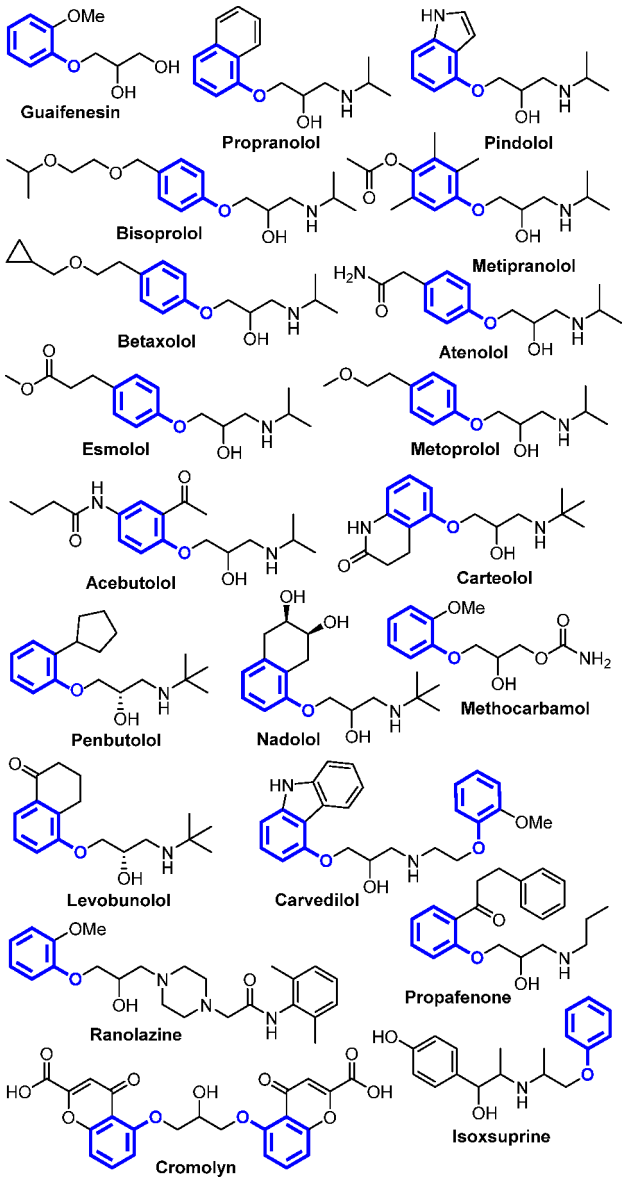

Figure 33. Primary aryl ether beta blockers and related drugs.

for diagnosis, similar in structure to fluorescein. Lenvatinib is used to treat thyroid cancers by targeting multiple kinases, including VEGFR1−3.[115]

Figure 40 highlights the bisphenyl ethers found in vancomycin and related antibiotics, which have been covered in previous sections. In this case the highlighted moiety is a structurally interesting tris-phenol which acts as part of two fused cyclic peptides. The benzene rings of the meta-connected phenolic ethers are perpendicular to one another, resulting in an interesting three-dimensional structure.

Figure 41 shows phenolic esters as well as phenolic carbamate drugs and includes aspirin and estradiol acetate. Not surprisingly, this is a small category among phenol-containing drugs, as phenolic esters and phenolic carbamates are far more prone to hydrolysis than their alkyl ester and carbamate counterparts. Bisacodyl is used as a laxative. Metipranolol is a *β*-blocker used to treat hypertension. Dipivefrin is a prodrug of epinephrine. Neostigmine is used to treat myasthenia gravis and can be used to reverse some anesthetics; it has also been used for other indications like

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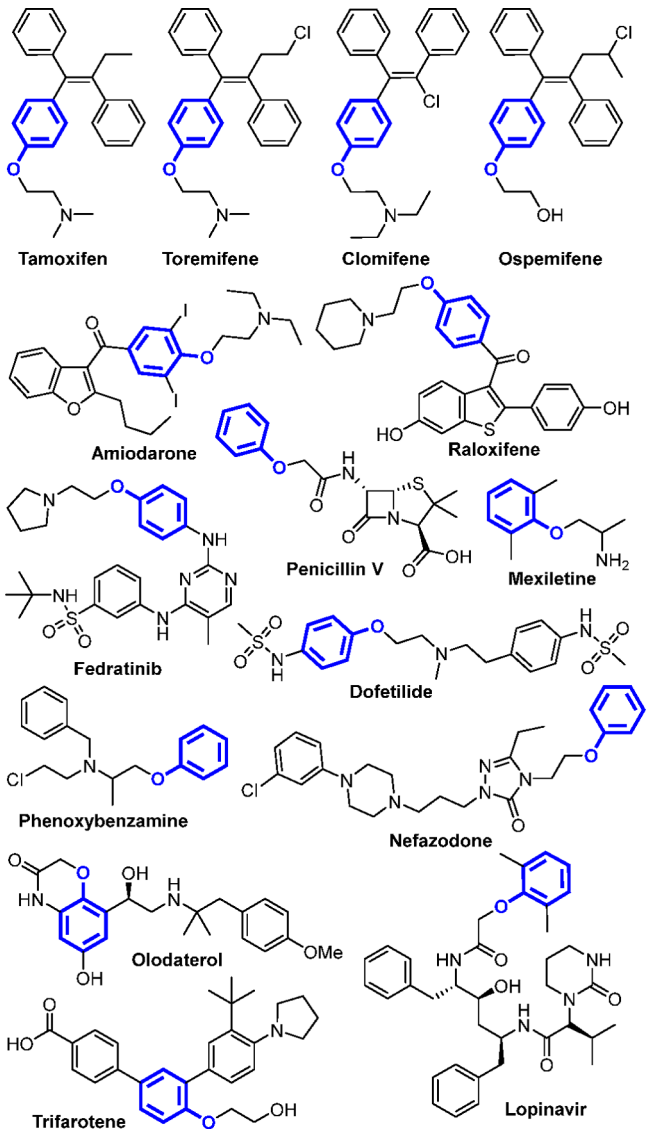

Figure 34. Primary ethanolamine and ethylene glycol aryl ether drugs.

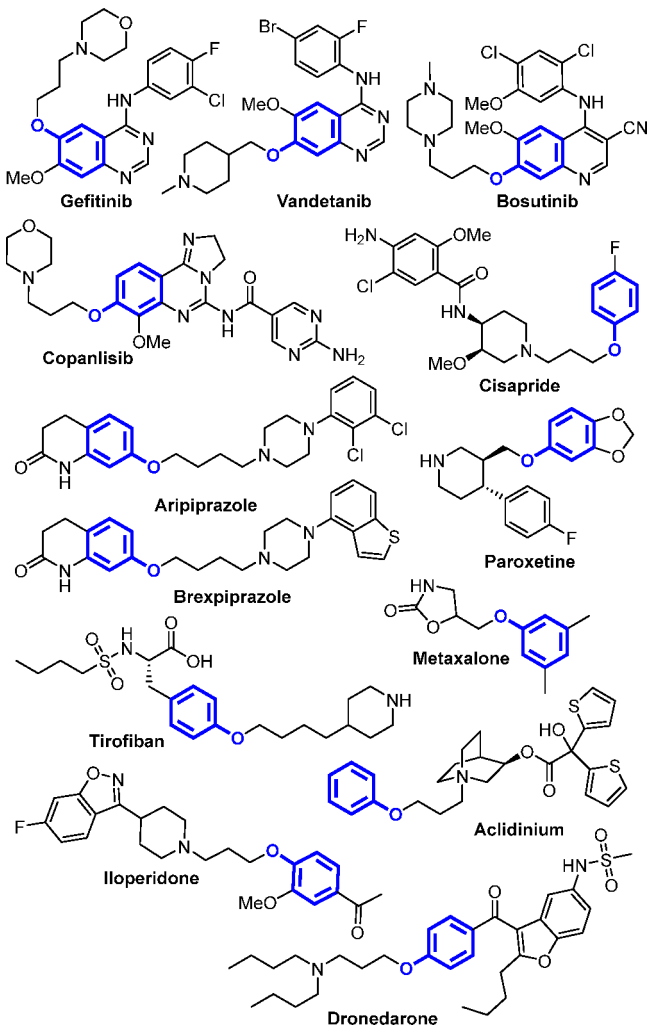

Figure 35. Primary aryl ether drugs terminating with an amino group.

acute colon obstruction because it enhances excitatory parasympathetic activity.[116] Neostigmine, estramustine, and irinotecan contain a phenolic carbamate group, which is rare among phenolic drug architectures but common for alkyl carbamates, as nicely documented by Ghosh.[117] Trabectedin and lurbinectedin are natural products used to treat cancers and were covered in previous sections.

Figure 42 depicts phenolic ethers that contain benzodioxole moieties. Among these are lumacaftor and tezacaftor, which are used to treat cystic fibrosis. Teniposide and etoposide are structurally nearly identical and are used to treat cancers. Podofilox, which is the natural product podophyllotoxin (derived from *Podophyllum* species), exhibits structural similarity with the previous two drugs but is used topically to treat warts. Stiripentol is an anti-seizure medication with no elucidated mechanism of action. Omacetaxine is a chemotherapeutic used to treat chronic myeloid leukemia. Trabectedin and lurbinectedin are structurally analogous chemotherapeutics. Paroxetine is used to treat depression. Stiripentol is an anti-convulsant used to treat epilepsy. Tadalafil is used to treat erectile dysfunction.[118]

Figure 43 depicts benzofurans, dihydrobenzofurans, and benzoxazoles. Amiadarone and dronedarone are structurally related and are both class III anti-arrythmic drugs. Vilazodone is an anti-depressant.[119] Lifitegrast is used to treat keratojunctivitis (dry eye) and works by downregulating T lymphocyte-mediated inflammation.[120] Darifenacin is a muscarinic acetylcholine receptor antagonist used for treating urinary incontinence.[121] Methoxsalen was covered previously in this analysis and is used for treating skin pigmentation disorders such as vitiligo. Ramelteon is an analog of serotonin and is used to treat insomnia. Iloperidone is an anti-psychotic used to treat schizophrenia. Tafamidis is used in treatment of neuropathies. Chlorzoxazone is a muscle relaxant, although its mechanism of action is unclear.

Figure 44 displays the morphine-based opiates previously described in Figure 9. Here we highlight a different structural feature, the benzofuran that contributes to the famous rigidity of the morphinan core. This ether moiety is formed by the fused A and E rings and is central to the morphine core. Recall that this moiety is what set these compounds apart from the analgesics butorphanol and pentazocine in Figure 9.

Figure 45 shows benzofuran-3(2*H*)-one-containing drugs, which all share the interesting feature of a phenol moiety that exists as an ether bonded to a fully substituted sp^3 carbon. The first six of these, which are analogs of rifamycin, are natural

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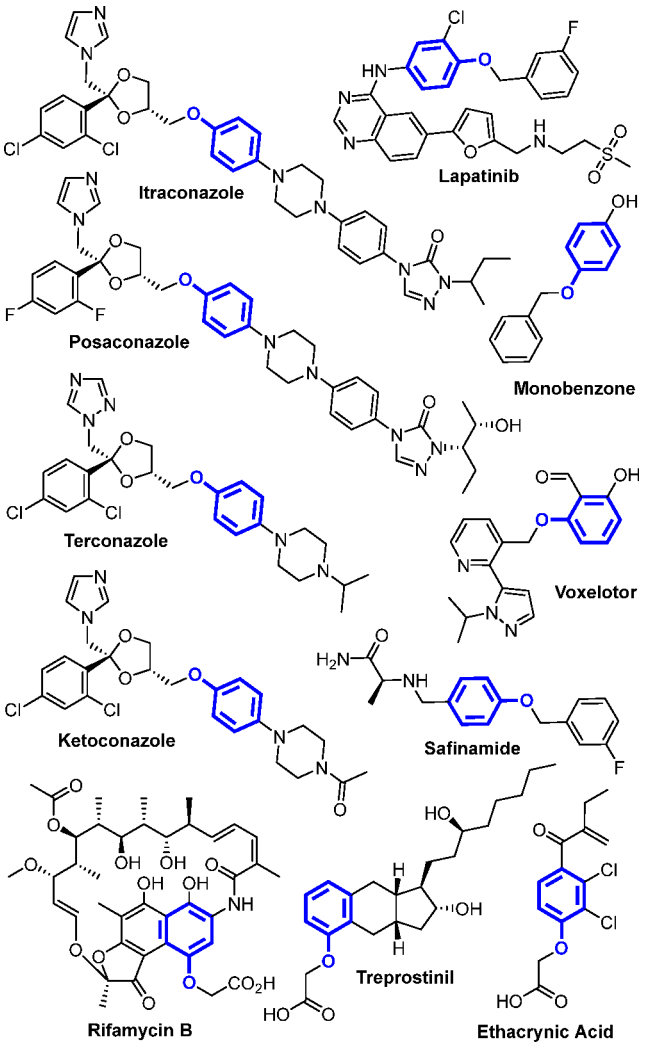

Figure 36. Primary benzylic, glycerol, and hydroxyacetic acid ether drugs.

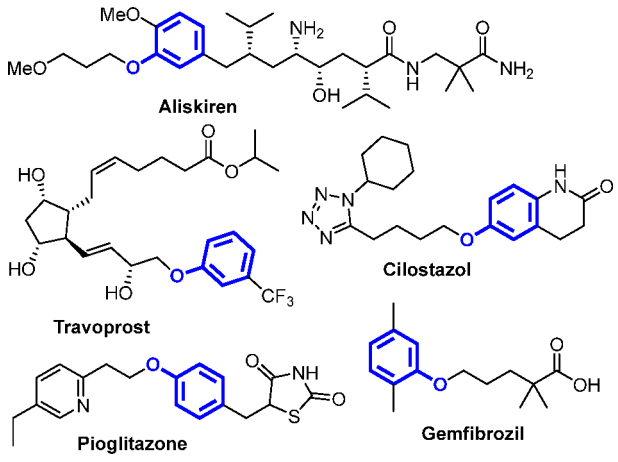

Figure 37. Miscellaneous primary alkyl ether drugs.

product antibiotics, four of which were covered previously in Figure 10, and highlighted here for a different phenolic moiety within the same structure: the benzofuranone. Griseofulvin is an antifungal drug isolated from various penicillium species, whose structure contains a spirocyclic phenolic ether core, the aromatic ring of which is nearly fully oxidized.[122]

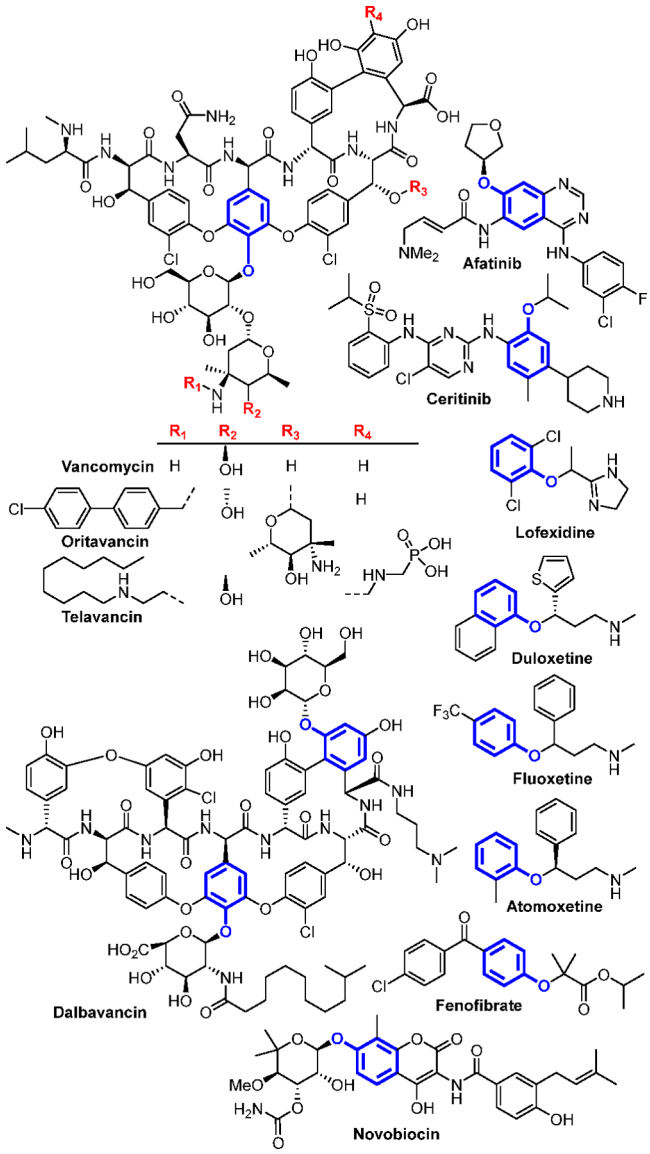

Figure 38. Secondary and tertiary alkyl ether drugs.

Figure 46 shows chromenone- and dihydrobenzopyran-containing drugs. The first three compounds in this section—phenprocoumon, warfarin, and acenocoumarol—are all coumarin-derived vitamin K agonists used for treating blood clotting.[123] Dicoumarol is a structural analog that works via the same mechanism as the previous three compounds and exists as a symmetric coumarin-derived dimer. Novobiocin is an aminocoumarin antibiotic. Methoxsalen was covered earlier in this analysis and is used to treat skin pigmentation disorders such as vitiligo. Cromolyn is also called cromoglicic acid and is used to treat asthma by preventing mast cells from releasing histamine. Flavoxate relaxes the muscles of the bladder and is used to treat frequent urination. Pranlukast prevents bronchospasms that occur as the result of allergen exposure.[124] Nedocromil is a structurally related drug used for the same indication as pranlukast. Amlexanox is an anti-inflammatory immunomodulator used to treat several diseases, including canker sores.[125] Velpatasvir is prescribed with sofosbuvir to treat hepatitis C. Crofelemer was covered previously in the context of its polyphenol moiety and is used to treat digestive issues associated with the side effects of other drugs. Nabilone

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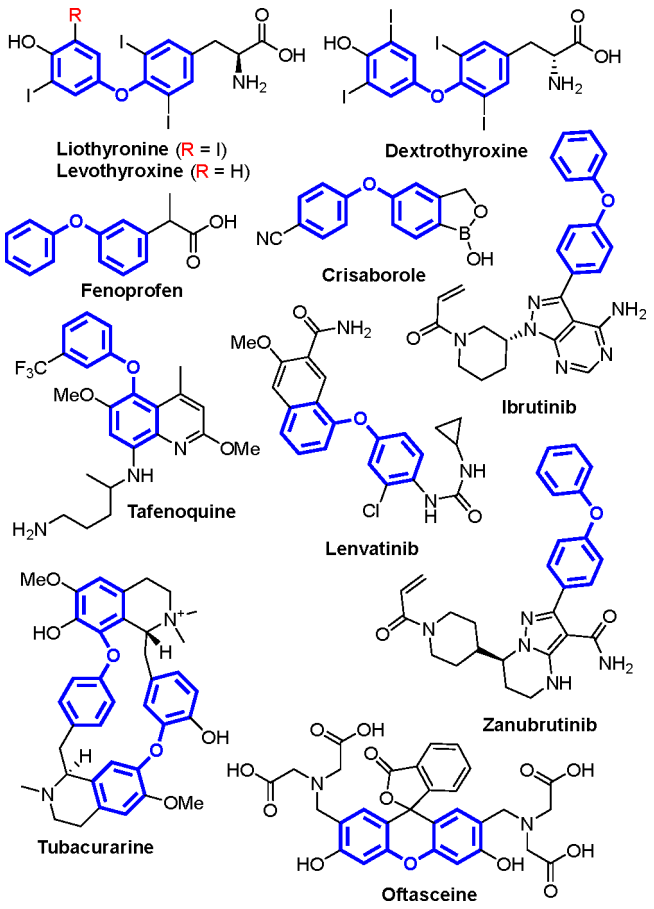

Figure 39. Bisphenyl ether drugs: part 1.

was also covered earlier in this analysis as a synthetic analog of cannabidiol. Oftasceine, an ocular diagnostic, shares structural homology with fluorescein.

Figure 47 shows six-membered fused phenolic ethers. Levofloxacin and orfloxaxin belong to the fluoroquinolone antibacterial drugs and represent a pair, in which the former is the enantiopure form of the latter.[126] Elbasvir is an antiviral used to treat hepatitis C and contains a phenolic oxygen connected to a stereogenic sp^3 center. Doxazosin is an antihypertensive, and eliglustat is used to treat Gaucher's disease. Both of these drugs contain a catechol moiety in which the oxygens are bridged by an ethylene group (a dihydrobenzo-[1,4]dioxine). Dactinomycin is a complex natural product used to treat cancer, especially a form known as Wilms's tumor, and contains a phenol fused with a nitrogen-containing heterocycle, collectively called a phenoxazinone.[127]

Figure 48 shows the five oxepane drugs in this analysis. These five compounds are the only members of this analysis containing the 7-membered oxygen heterocycle, and they also contain two different kinds of phenolic ethers. The first two, doxepin and olopatadine, contain a phenyl benzyl ether and have anxiolytic and antidepressive properties. The other three, asenapine, amoxapine, and loxapine, contain *O*-aryl phenol ethers. The latter three drugs share an electron-withdrawing chlorine in the 4-position of the phenol. Asenapine contains a rigidified nitrogen atom. Doxepin and amoxapine are antidepressant and nerve pain drugs, whereas doxepin, asenapine, and loxapine are anti-psychotics. Olopatadine resembles the other structures but is used as an anti-histamine to teat redness in the eyes.

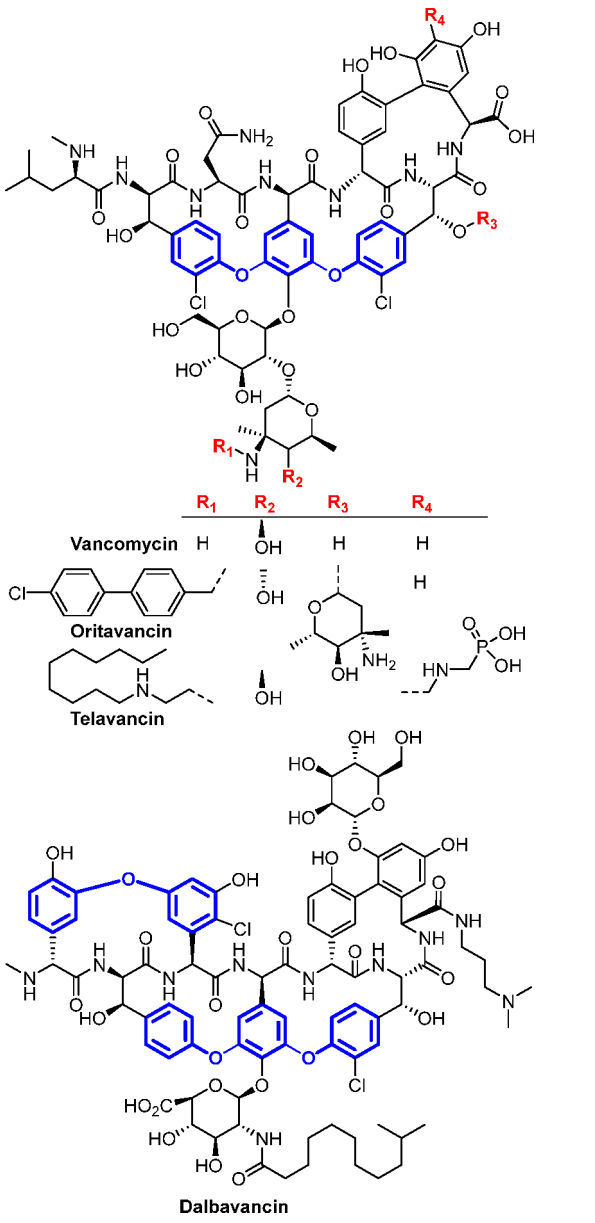

Figure 40. Bisphenyl ether drugs: part 2.

Also included in this review are the structures of important U.S. FDA-approved aromatic nitrogen heterocycles substituted with ether groups (heteroarylphenols). The first four drugs in Figure 49 depict these motifs within intriguing macrocyclic frameworks. These include three antiviral drugs (glecaprevir, voxilaprevir, and grazoprevir) and a kinase inhibitor (lorlatinib). The antiviral drugs in this category (ending in the suffix "-vir") are used to treat hepatitis C and contain many unique structural features, most notably two side-chain cyclopropyl groups.[128] Lorlatinib is an anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 inhibitor used to treat ALK-positive non-small-cell lung cancer and contains a pyridyl phenolic ether.[129] Omeprazole and pantoprazole are proton pump inhibitors whose structural cores are nearly identical, differing on the 4-methoxypyridine moiety, with one containing a 3-methoxy group and the other 3,5-dimethyl groups. Sulfadimethoxine is an antibacterial drug in the sulfonamide class and gets part of its name from the two methyl ethers on the pyrazine ring. Telotristat ethyl is a

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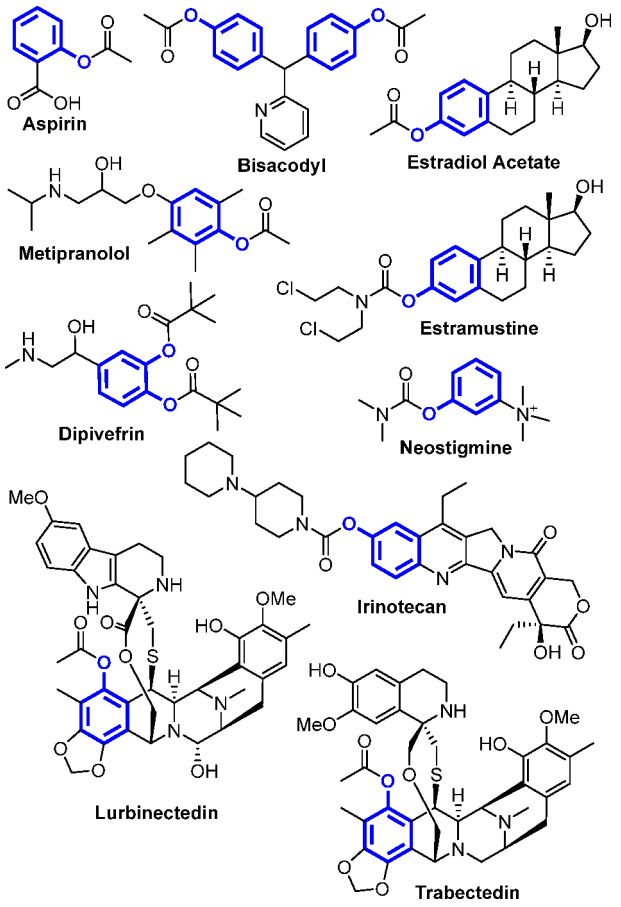

Figure 41. Acyclic phenolic ester and carbamate drugs.

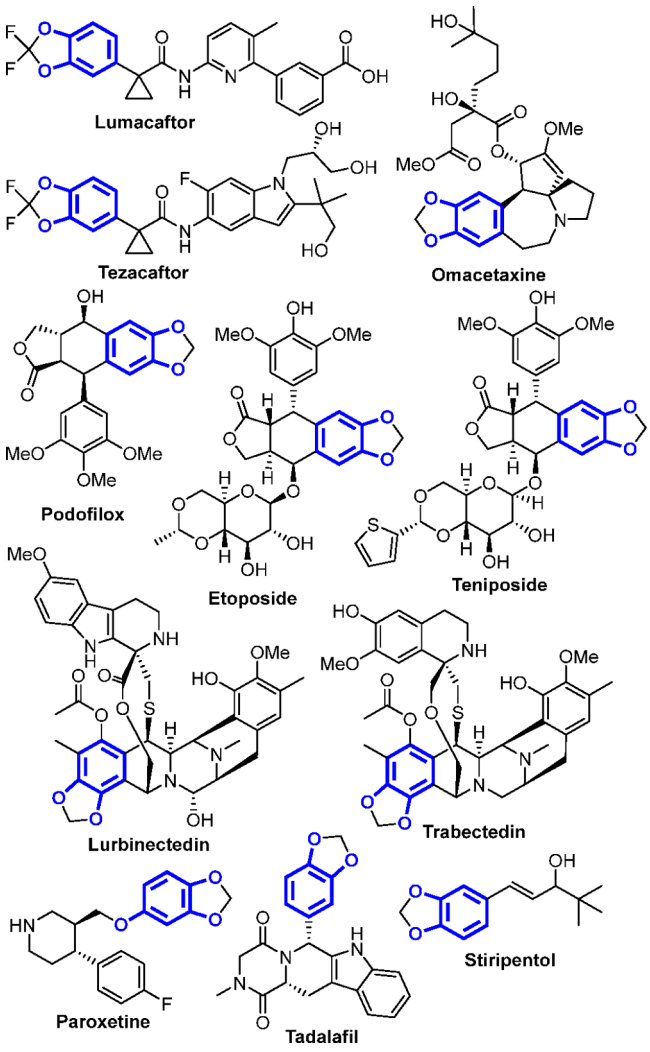

Figure 42. 1,3-Benzodioxole drugs.

tryptophan hydroxylase inhibitor and contains a unique aminopyrimidine as well as a stereogenic trifluoromethyl group. Lemborexant includes a chiral cyclopropane at its core and is used to treat insomnia.[130] Elexacaftor is used to treat cystic fibrosis. Etravirine is a non-nucleoside reverse transcriptase inhibitor used for treating HIV. Regorafenib is a multi-kinase inhibitor that prevents angiogenesis for cancer treatment.[131] Venetoclax is used to treat lymphatic leukemia. Sorafenib is a kinase inhibitor used to treat number of cancers, including advanced renal cell carcinoma and hepatocellular carcinoma.

As previously demonstrated in the phenol section, inspired by our recent veterinary drug analysis, the phenolic ethers approved only in veterinary medicine are shown in Figure 50. This group includes drugs for a wide variety of indications from anthelmintics (tioxidazole and oxibendazole) to control of fertility (cloprostenol, fluprostenol, luprostiol, and fenprostalene). The structural trends of veterinary drugs largely mirror those of human drugs.[22] Accordingly, most of the approved phenol-containing veterinary drugs belong to major drug classes in human medicine. Obvious outliers are the insecticide drugs coumaphos, haloxon, cythioate, famphur, and fenthion. These compounds contain phenolic moieties that are part of an organophosphate or phosphorthioate, which act as inhibitors of acetylcholinesterase and pseudocholinesterase, causing paralysis in invertebrates (this allows parasites to be excreted). Fenthion is activated by metabolism, by which the phenyl methyl thioether is oxidized to the sulfoxide, whose *R* enantiomer is nearly 20 times more active than the *S* enantiomer.[132] Tioxidazole and oxibendazole contain phenolic ethers that are part of benzothiazole and benzimidazole structures, respectively. Hezamidine is a symmetric disinfectant that consists of two phenols with an amidine in the 4-position, connected by a 6-carbon linker. Cloprostenol, fluprostenol, luprostiol, and fenprostalene are all prostaglandins used to control reproductive cycles in animals.[133] The phenolic ether is central to these structures, with only minor modifications, including electron-withdrawing groups being added in more recent approvals. Lufenuron contains a 2,5-dichloro-4-aminophenol with a highly fluorinated propane group on the phenol oxygen. Maropitant contains a disubstituted methyl phenolic ether and acts as a neurokinin-1 receptor agonist in treating motion sickness. Bunamidine contains a naphthyl phenolic ether and is used as an anti-helminthic. Thenium closylate is a nicotinic receptor agonist used to treat parasites.[134] Tepoxalin and deracoxib are both NSAIDs used to treat pain and contain a methyl phenolic ether. Marbofloxacin belongs to the fluoroquinolone antibiotics and is the only one of the veterinary fluoroquinolones with a phenolic moiety. Nequinate and decoquinate are structurally related compounds belonging to the hydroquinolone class of anti-parasitics. Pimobendan is a PDE3 inhibitor used to treat dogs with congestive heart failure and contains a methyl phenyl ether appended with a benzimidazole in the 4-position.[135] Ponazuril contains a

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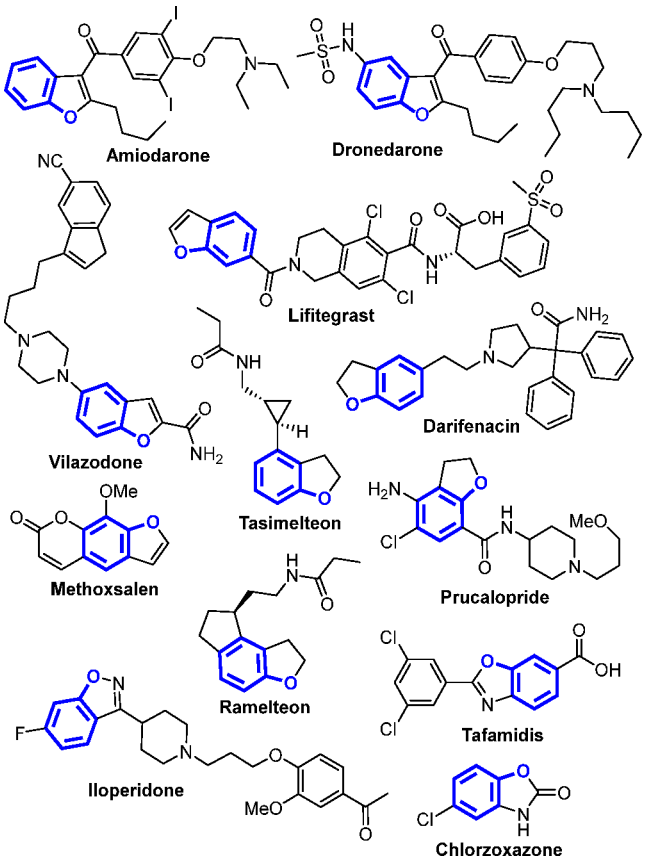

Figure 43. Benzofuran-, dihydrobenzofuran-, and benzoxazole-containing drugs.

phenyl phenyl ether and is used to treat equine protozoal myeloencephalitis.[136]

Physicochemical Property Landscape of Phenolic Ether Drugs. In contrast to phenolic drugs, phenolic ether drugs have a significantly higher percentage approved for oral delivery (84%), and this is reflected in their comparatively superior physicochemical properties. Given this fact, overall Ro5 compliance is high (86%), with a very slight enhancement in Ro5 compliance (87%) for oral phenol ether drugs versus other routes of administration. Statistics of the physicochemical properties of small-molecule phenol ether drugs are presented in Table 2.

The largest contributor to non-compliance of Ro5 for phenolic ether drugs is molecular weight, with all non-compliant drugs having a molecular weight greater than 500 Da, and unlike non-compliant phenolic drugs, a significant percentage of non-compliant phenolic ethers are lipophilic (ALogP > 5 (62%)), followed by number of H-bond acceptors (NHBA > 10 (44%)) and number of H-bond donors (NHBD > 5 (6%)). This profile of contributions to Ro5 non-compliance is very different from that for phenolic drugs and will be further discussed later in this analysis. For the Ro5-compliant phenolic ether drugs, 86% are orally delivered, compared with 76% of the non-Ro5 set, indicating a high degree of favorable drug-like properties for both sets of drugs, irrespective of mode of delivery.

As this set of drugs has a significantly higher degree of lipophilicity and much lower TPSA compared to phenolic drugs, it is not surprising that the overall compliance to Pfizer's Rule of 3/75 is significantly lower (29% versus 46%) for

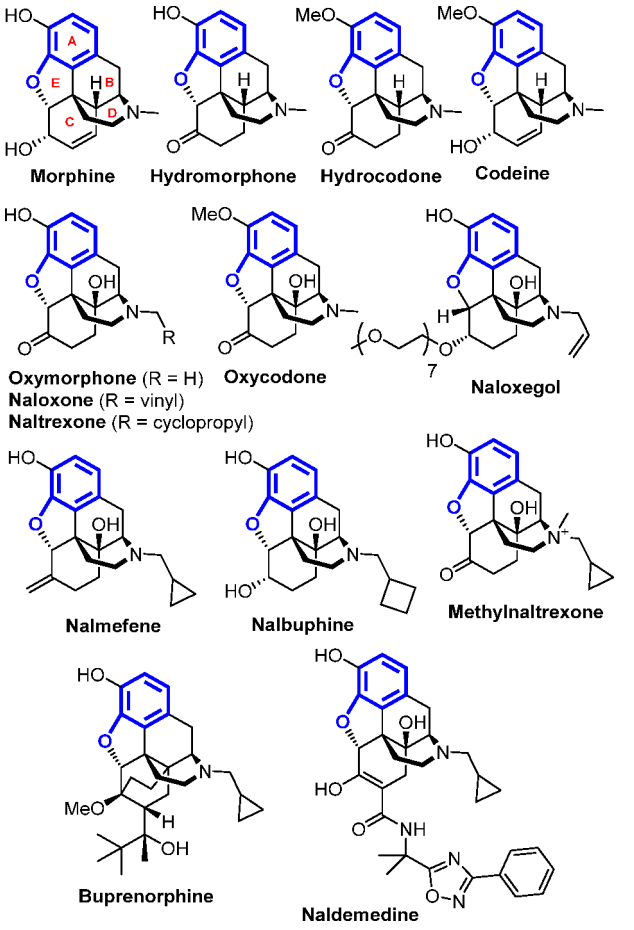

Figure 44. Dihydrobenzofuran-containing opioid drugs.

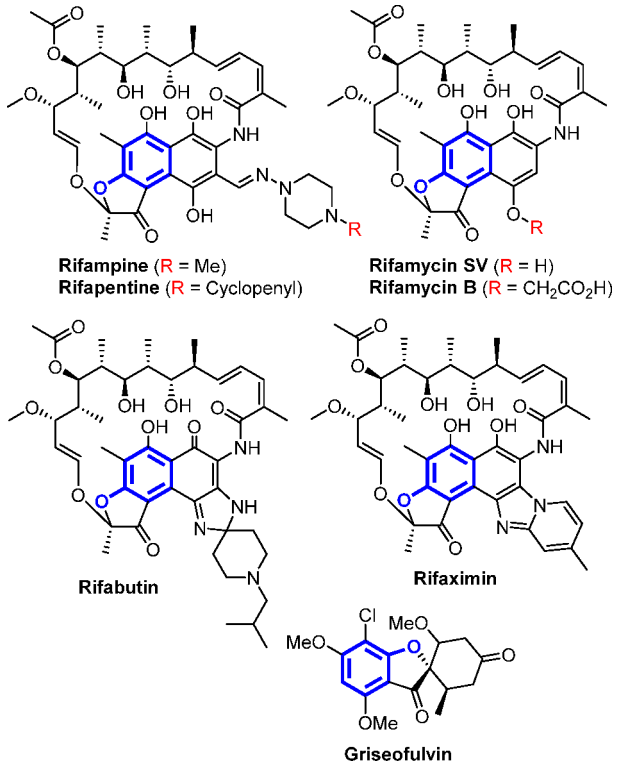

Figure 45. Benzofuran-3(2*H*)-one-containing opioid drugs.

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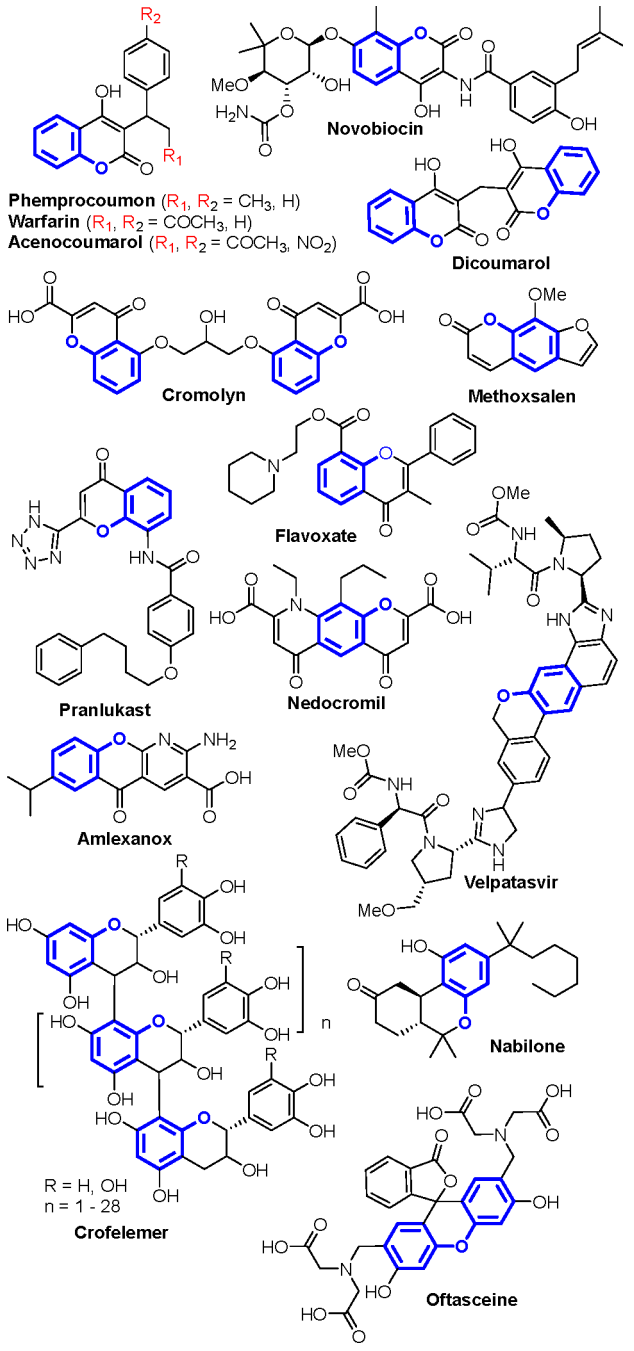

Figure 46. Chromenone- and dihydrobenzopyran-containing drugs.

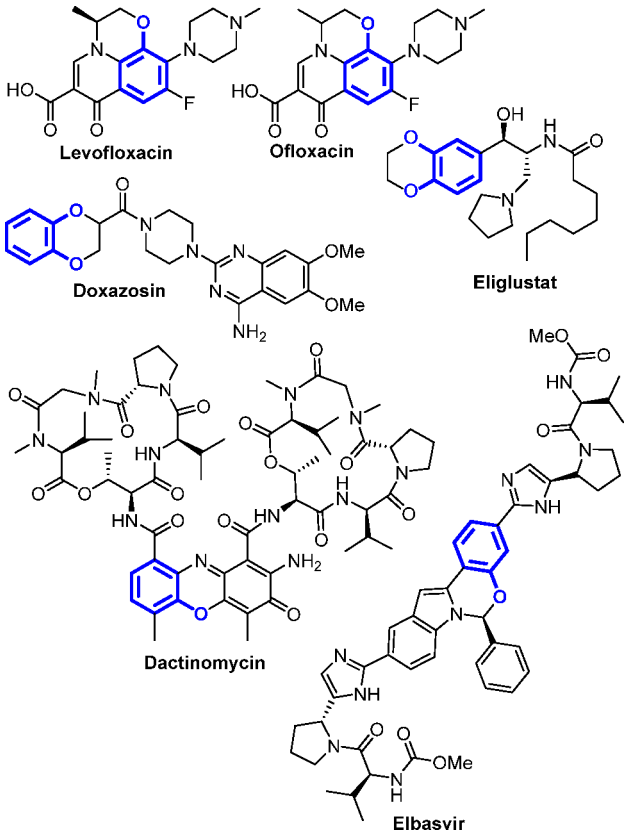

Figure 47. Miscellaneous six-membered fused phenol ether drugs.

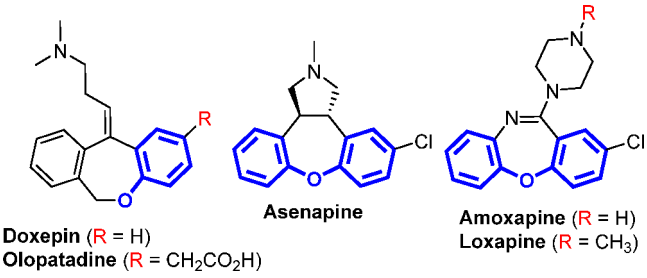

Figure 48. Benzoxepane-type drugs.

phenolic drugs (Figure 51). In terms of drug-likeness composite scores, the average values were higher for QED (0.55 vs 0.44) and lower for AB-MPS (10.9 vs 13.3) compared with those of phenolic ethers; however, PFI was higher (5 vs 2.6) for phenolic ethers versus phenolic drugs. This suggests that the overall physicochemical profiles of these sets for drugs are differentiated, which will be discussed in more detail later.

Brief Survey of U.S. FDA-Approved Peptide Hormones Containing Phenols. In each one of our groups' earlier drug analyses, drawing a line of molecular weight cutoff has been difficult, in part because it is difficult to justify the inclusion of macrocyclic peptide antibiotics but not peptide hormones, for example, and in part because no matter where the line is somewhat arbitrarily drawn, the drugs just beyond that line are just as important as the ones that precede the cutoff. Short peptide hormone drugs are important and have numerous applications, from treating diabetes (semaglutide) to inducing labor (oxytocin), and most of them contain the amino acid tyrosine, which is a phenol-containing structure. Over the past decade, biologics have been rapidly displacing small molecules as a proportion of FDA-approved entities, and we feel that a brief treatment is warranted here, even if the analysis is not complete or in-depth. Indeed, over 80 peptide drugs have been approved. Some of the most important phenol-containing peptides are depicted in Figure 52.

OVERALL COMPARISON OF PHENOL- AND PHENOL ETHER-CONTAINING DRUGS

The *in silico* physicochemical property profiles of phenol and phenol ether drugs on average are very different with respect to several important drug-like properties. The relative distributions of physicochemical properties in which there is a statistical significance in the averages of the distributions are shown in the box plots in Figure 53. Phenolic drugs are

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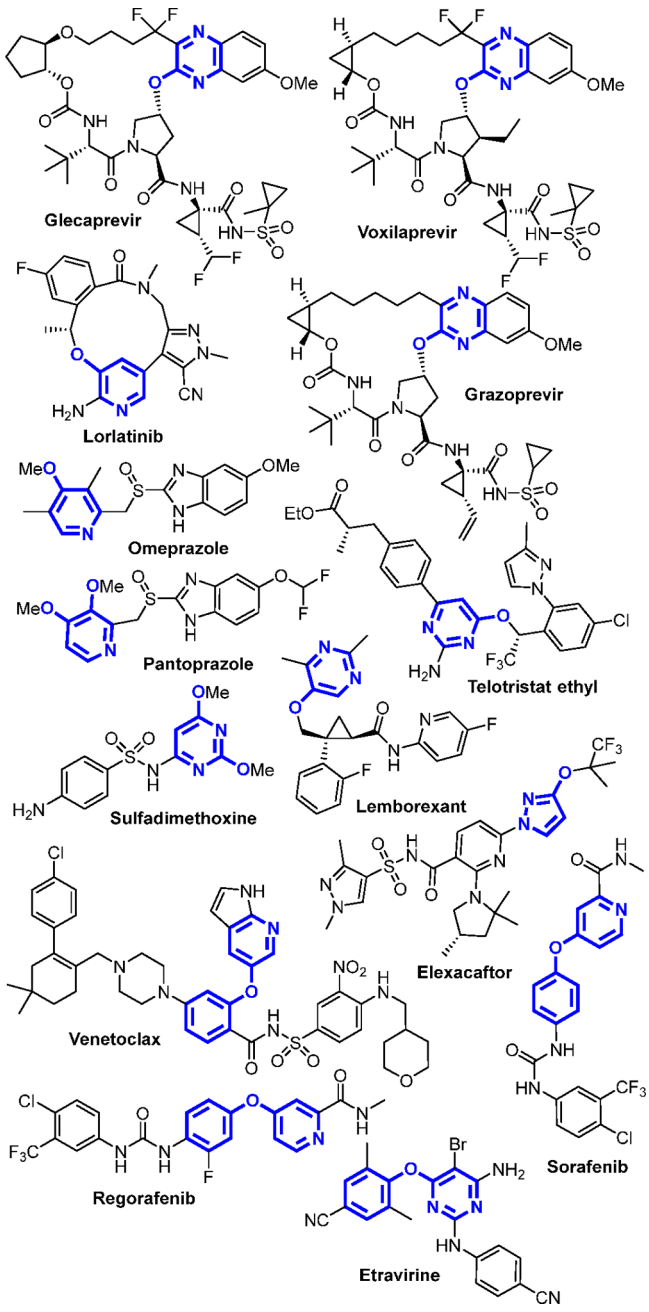

Figure 49. Heteroaryloxy drugs.

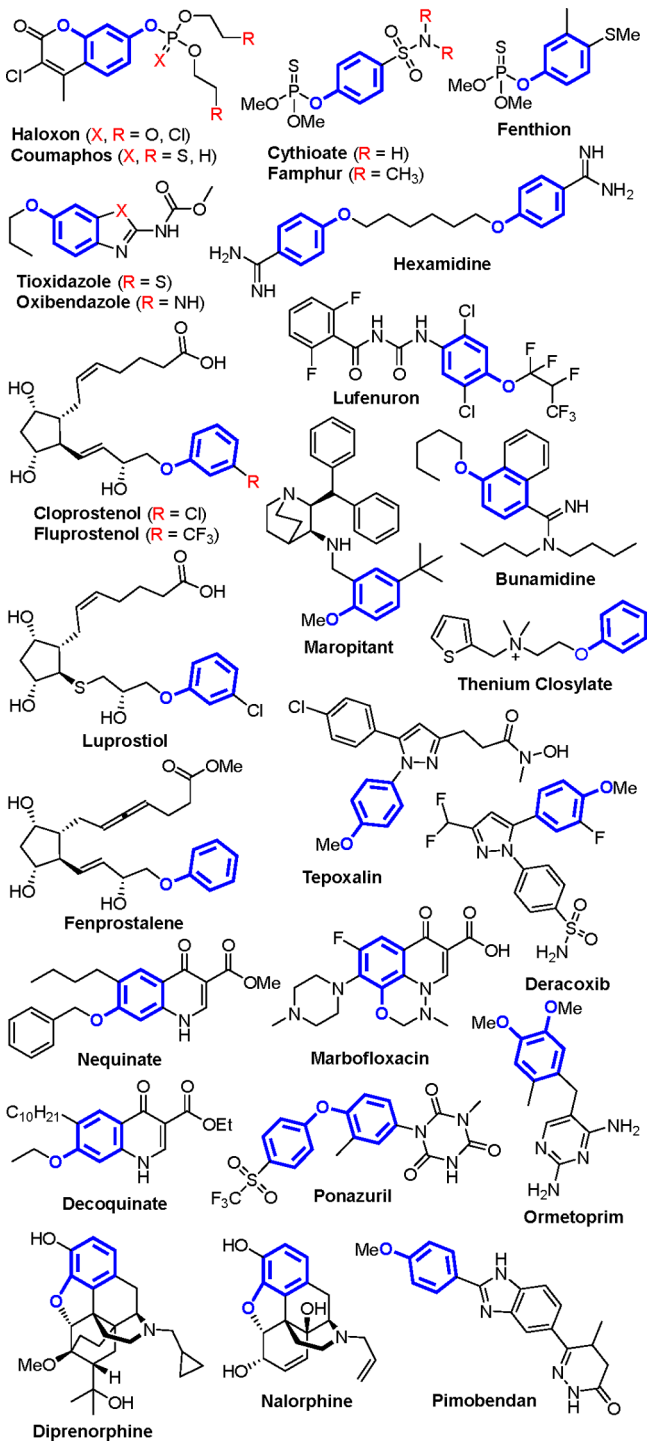

Figure 50. Phenol ether structures approved for veterinary use only.

significantly less lipophilic than phenolic ethers, as evidenced by both the calculated log of the partition (ALogP) and the distribution (LogD) coefficients. As mentioned earlier, this set of phenolic drugs has much higher numbers of hydrogen-bond donors, which likely contributes to the appreciably higher TPSA over phenolic ethers. Given the associated acidity of phenols, it is not surprising that this contributes to an enhancement in hydrophilicity, hence the difference seen with the less acidic phenolic ethers.

These differences in physicochemical properties are manifest when the ionization state distributions are compared for both sets of drugs (Figure 54). Note that the ionization state of each compound was calculated using AbbVie's property design platform. Phenols have a much greater percentage of zwitterions and acids (44%) than phenol ethers (19%), albeit phenol ethers have a greater percentage of acids, but appreciably fewer zwitterions than phenols do. This is consistent with phenols having significantly greater TPSA and NHBD compared with phenol ethers. Phenol ethers, on the other hand, are more basic and neutral, consistent with observed higher lipophilicity and PFI compared with phenols.

Another observation is that, while the phenolic ethers have much higher compliance with Ro5, have a greater percentage that are orally delivered, and have a higher and statistically significant QED than phenols, their PFI is significantly higher, which translates into a theoretically lower degree of developability versus phenols. Of course, we know that these

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Table 2. Statistics of the Physicochemical Property Profiles of Small-Molecule Phenolic and Heteroaryloxy Ether Drugs[a]

property	median	mean	Q1	Q3	IQR
MW	401.5	422.6	309.4	474.8	165.4
AlogP	3.40	3.37	2.27	4.52	2.25
LogD	2.8	2.9	1.8	4.2	2.4
TPSA	77.0	83.2	50.7	106.5	55.8
NHBD	1	1.6	1	2	1
NHBA	5	5.6	4	7	3
NAR	2	2.2	1	3	2
NR	3	3.4	2	4	2
NRB	7	7.3	5	10	5
Fsp^3	0.38	0.39	0.28	0.52	0.23
PFI	4.9	5.0	3.4	6.9	3.5
QED	0.59	0.55	0.34	0.76	0.42
AB-MPS	10.3	10.9	8.0	13.2	5.1

[a]AlogP, atom-based LogP; LogD, calculated ChemAxon LogD; TPSA, topological polar surface area (NO only); NHBD, number of hydrogen-bond donors; NHBA, number of hydrogen-bond acceptors; NAR, number of aromatic rings; NR, number of rings; NRB, number of rotatable bonds; Fsp^3, fraction of sp^3 carbons; PFI, property forecast index; QED, quantitative estimate of drug-likeness; AB-MPS, AbbVie multi-parametric score; Q1, lower quartile; Q3, upper quartile; IQR, interquartile range.

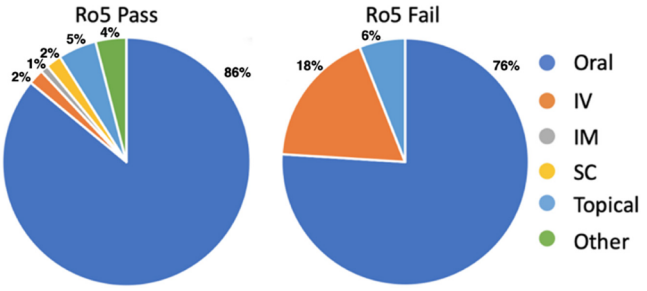

Figure 51. Distribution of the routes of administration for phenolic ether drugs that pass and fail Lipinski's rules. IV, intravenous delivery; IM, intramuscular delivery; SC, subcutaneous delivery. "Other" refers to less common routes of delivery for these drugs such as vaginal, implant, and inhaled delivery.

phenolic ethers are approved drugs, so they must have achieved developability. However, perhaps the path to approval was hampered by deleterious effects, such as poor solubility, as an unwanted consequence of high PFI.

If you look at the reasons why both phenols and phenol ethers fail Lipinski's rules, you can see different sets of parameters that are causative of violations that necessitate non-compliance (Table 3). For both Ro5 non-compliant phenols and phenol ethers, molecular weight is the greatest percentage violator. In stark contrast, however, only 1% of Ro5 non-compliant phenol drugs violate ALogP > 5, as opposed to 62% of the Ro5 non-compliant phenol ethers. Additionally, there is a similar gulf in the percentage of Ro5 non-compliant compounds that violate the NHBD (>5), with only 6% of the phenol ethers versus 72% of the phenolic drugs in violation. This implies that the properties of phenols and phenol ether drugs are significantly different, suggesting an interesting dynamic in the overall molecular diversity or similarity of the two sets of drugs.

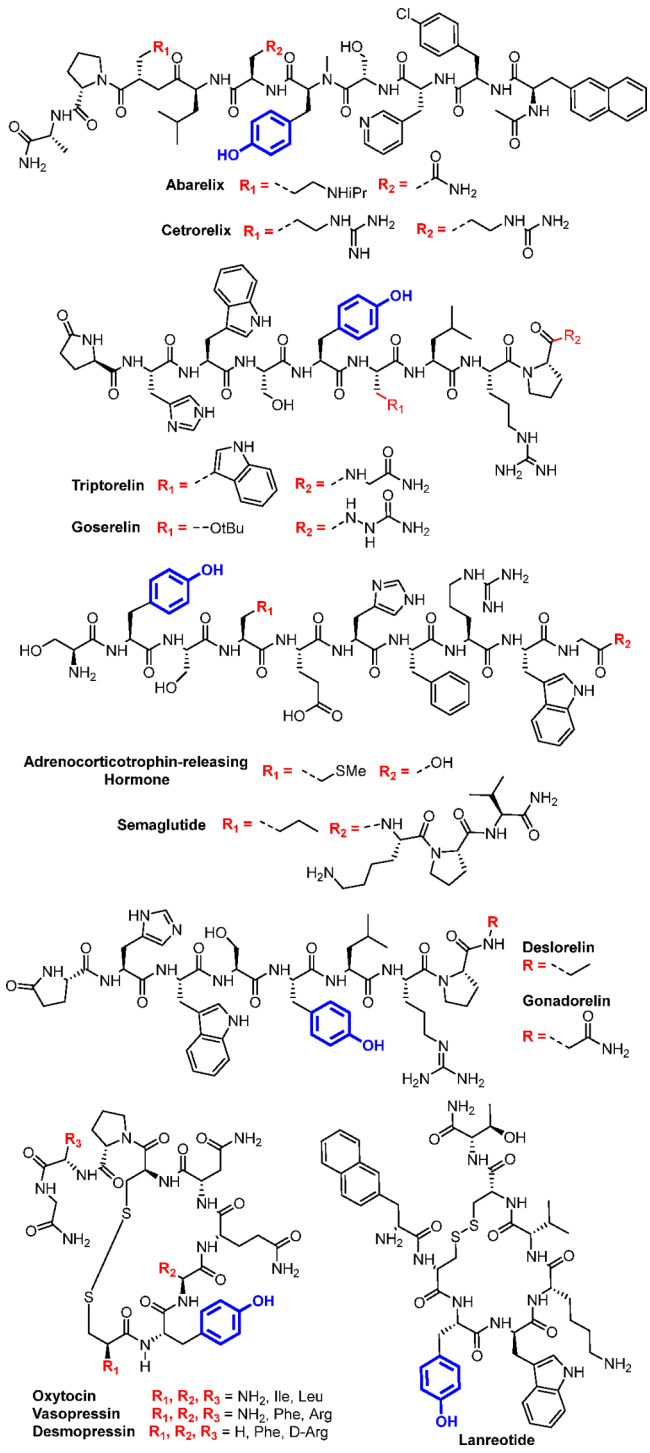

Figure 52. Examples of phenol ether-containing peptides.

In order to determine the relative similarity of diversity of both sets of drugs, we combined the list of phenols and phenol ether drugs and calculated the nearest-neighbor (NN) similarity using extended connectivity fingerprints (ECFP-4) in Pipeline Pilot. The distributions of the Tanimoto coefficients are shown in Figure 55. Phenols are the least diverse of the two sets of drugs with an average Tanimoto similarity of 0.15, which contrasts with phenolic ethers with an average Tanimoto similarity of 0.12. What is clear from this analysis is that the NN similarity of the combined sets (phenol vs phenol ether and phenol ether vs phenol, which are

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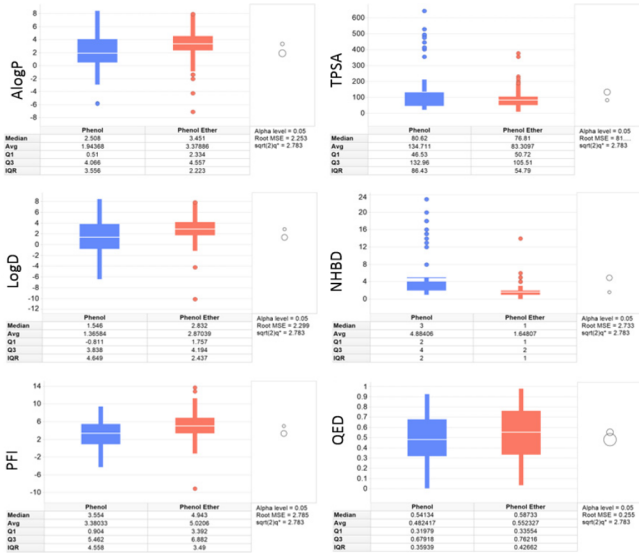

Figure 53. Comparative distributions of properties of phenolic and phenolic ether drugs with differentiated average statistical significances.

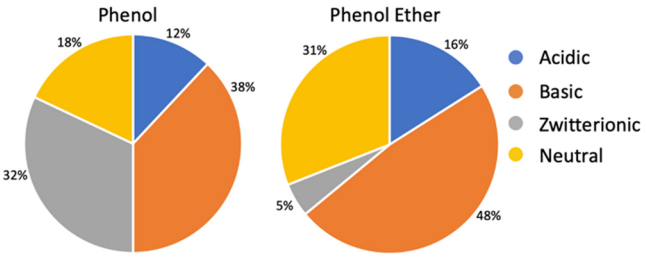

Figure 54. Comparative distributions of the ionization states of phenolic and phenolic ether drugs.

Table 3. Comparison of Ro5 Compliance and Percentage of Properties Responsible for Violating Ro5 for Phenols and Phenol Ethers

property	phenols	phenol ethers
number of drugs	93	236
% fail Ro5	27	14
% violate MW_t > 500	96	100
% violate AlogP > 5	1	62
% violate NHBD > 5	72	6
% violate NHBA > 10	68	44

identical) is significantly lower and therefore more diverse compared to both the phenol vs phenol and phenol ether vs phenol ether alone, with an average Tanimoto coefficient of 0.09. This suggests that phenols and phenol ethers are differentiated in terms of their molecular structures, too, as the overall NN similarity decreased for the combined list, suggesting greater diversity and, therefore, differentiation.

World Health Organization List of Essential Medicines Designation. Phenols are also highly represented in some of the most essential medicines as designated by the WHO. This list of drugs contains medications considered to be safe and effective for treating the most important diseases. Of the 363 structures covered in this analysis, 55 (15%) are on the WHO list of essential medicines. Table 4 presents the list of

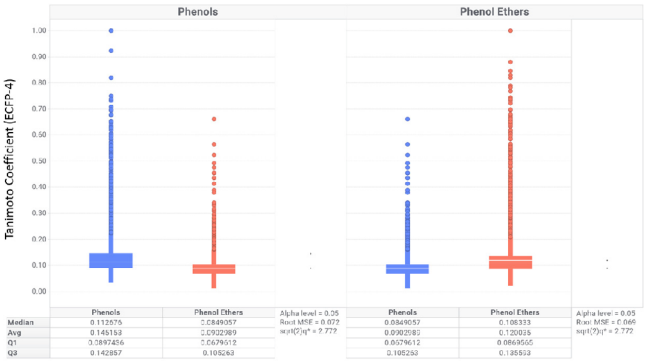

Figure 55. Box plot showing the relative nearest-neighbor similarity (ECFP-4) of phenols vs phenols, phenol ethers vs phenol ethers, phenol ethers vs phenols, and phenols vs phenol ethers.

drugs that are on this list. A recent review by Pirali discusses this important list of drugs in greater detail.[137]

Table 4. Phenol- or Phenolic Ether-Containing Drugs on the WHO List of Essential Medicines and Their Oral Administration[a]

Drug	Oral?	Drug	Oral?
Amiodarone	Yes	Methyldopa	Yes
Apixaban	Yes	Metoclopramide	Yes
Atenolol	Yes	Metoprolol	Yes
Bisoprolol	Yes	Morphine	Yes
Buprenorphine	Yes	Moxifloxacin	Yes
Carvedilol	Yes	Naloxone	Yes
Clomifene	Yes	Neostigmine	Yes
Codeine	Yes	Ofloxacin	Yes
Dactinomycin	No	Omeprazole	Yes
Dasabuvir	Yes	Oxycodone	Yes
Daunorubicin	No	Propofol	No
Demeclocycline	Yes	Propranolol	Yes
Dopamine	No	Quinine	Yes
Doxorubucin	No	Rifabutin	Yes
Epinephrine	Yes	Rifapentine	Yes
Ethinyl Estradiol	Yes	Salbutamol	Yes
Etoposide	Yes	Sulfasalazine	Yes
Fluorescein	No	Tamoxifen	Yes
Fluoxetine	Yes	Tetracycline	Yes
Gefitinib	Yes	Trimethoprim	Yes
Glecaprevir	Yes	Vancomycin	Yes
Griseofulvin	Yes	Velpatasvir	Yes
Hydromorphone	Yes	Verapamil	Yes
Itraconazole	Yes	Vinblastine	No
Levodopa	Yes	Vincristine	No
Levofloxacin	Yes	Vinorelbine	Yes
Levothyroxine	Yes	Warfarin	Yes
Lopinavir	Yes		

[a]Names of drugs containing only phenols or phenol ether/ester/carbamates are highlighted in blue and red, respectively, with drugs containing both functional groups highlighted in both colors.

Metabolism of Phenol-Containing Drugs. The metabolism of phenol-containing drugs is complex and dependent on structural context. Orally bioavailable drugs containing phenols undergo typical phase I and phase II metabolism, as do their natural counterparts found in plant-based foods. Phenolic ethers, on the other hand, will typically undergo phase I metabolism but not phase II, because the oxygen atom, which is conjugated in phase II metabolism, is masked by an alkyl or aryl group. In some cases, the metabolism of phenols and their ether counterparts leads to rapid elimination from the body or to inactive metabolites of the drug. In other cases, the resulting metabolite can have toxic effects. In yet other cases,

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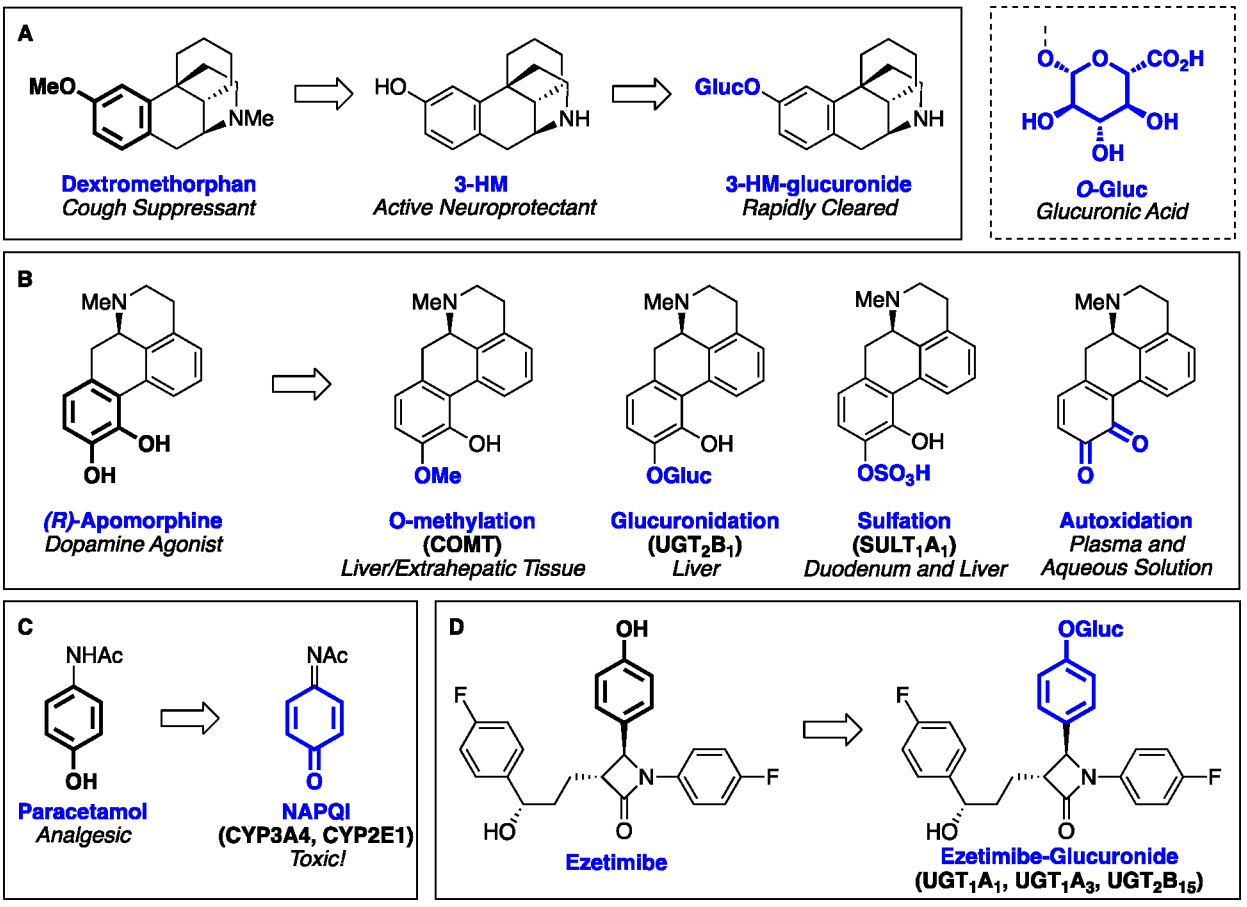

Figure 56. Examples of phenol drug metabolisms. (A) Dextromethorphan is metabolically demethylated to give 3-HM, a potent neuroprotectant, which is further metabolized by *O*-glucuronidation, among other pathways. (B) Apomorphine undergoes extensive metabolism in various tissues and by several pathways and, as a result, is administered subcutaneously to avoid first-pass metabolism. (C) A minor metabolic pathway of paracetamol leads to the toxic byproduct DAPQI. (D) The cholesterol-lowering activity of ezetimibe is dependent on glucuronidation.

metabolism of the phenol moiety is required for activation of the drug compounds. The metabolism of phenols proceeds via multiple enzymes in various tissues and organs that are beyond the scope of this Perspective. However, this section gives an overview, outlines considerations, and discusses cases that are broadly representative of phenol metabolism.

Phenols from plant-derived food sources have recently gained interest as antioxidants. Studies investigating the bioavailability and metabolism of these compounds may provide insights that can be extended more broadly to phenol-containing drug leads, particularly in the sense that similar structures tend to undergo similar metabolic transformations.[138−141] Of particular interest is that many of these plant secondary metabolites seem to be highly bioavailable, and the concentrations of specific metabolites can be quantitatively detected in plasma. In some cases, the active metabolites of phenols and phenolic ethers possess a greater potency than the active ingredient in a drug or are neofunctionalized. However, such transformations can have a give-and-take effect: while an active metabolite may have a more potent or novel effect, the body may clear it more quickly. For example, 3-hydroxymorphinan (3-HM), an active metabolite of the approved drug dextromethorphan, exhibits greater neuroprotective effects in dopamine neurotoxicity studies, but 3-HM is further metabolized via *O*-glucuronidation (Figure 56A), is rapidly cleared from the body, and suffers from low oral bioavailability on its own.[142] Dextromethorphan is an example that raises the important consideration of phase II metabolism of phenols and their ethers by demonstrating that, when the *O*-alkyl substituent is as simple as a methyl group, the bond is often cleaved. The resulting phenol is then susceptible to phase II metabolism. In a mechanism similar to demethylation, drugs for which the phenol is critical for binding can be demethylated or deacetylated in phase I metabolism to unmask the active component of a drug. Examples of this are morphine analogs such as codeine (a methylphenol) and heroin (an acetylated phenol).[143] In each of these cases, the prodrug version (alkylated or acetylated) more readily enters the central nervous system before enzymatic activation allows the drug to bind to its target. Apomorphine undergoes extensive metabolism and is administered by subcutaneous injection to avoid extensive first-pass metabolism. The major metabolic transformations of the catechol moiety are highlighted in Figure 56B (other metabolic pathways such as demethylation and racemization metabolisms are not shown).[144] Catechols are particularly sensitive to autoxidation and readily form quinones upon oxidation in air or plasma. Taken together, the rapid metabolic degradation and clearance as well as the serious side effects of apomorphine have been detrimental to the drug's success. The metabolism of phenol-containing drugs, however, can be more detrimental than simple deactivation or rapid clearance of the drug. A well-known example is the P450 oxidation of paracetamol (acetaminophen) to the toxic reactive species *N*-acetyl *p*-

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benzoquinone (NAPQI, Figure 56C).[145] Although the major pathway of metabolic inactivation of paracetamol is *O*-glucuronidation, and other minor pathways include *O*-sulfation and sulfation, the small amount of the toxic byproduct is detoxified in the liver by conjugation with glutathione. High levels of NAPQI can lead to liver failure and death. In contrast to both previous examples, some drugs require metabolic activation to achieve the active drug component. Ezetimibe, for example, contains a phenolic moiety that must be glucuronidated in order to have activity involving the NPC1L1 transporter protein to lower cholesterol (Figure 56D).[146]

The diverse mechanisms by which phenols are metabolized mirror the wide away of structures within which they are found. Phenols abound in nature, particularly as plant secondary metabolites, and have a long evolutionary relationship with higher eukaryotes. The high bioavailability and extensive metabolism may be the result of this coexistence. The physicochemical properties of phenols offer benefits and disadvantages with seemingly equal alacrity both in nature and in pharmaceutical science, and in accordance with the large overlap between natural products and the modern pharmacopeia, it is no surprise that phenols continue to be highly represented. The topic of phenol metabolism is only briefly discussed here, but the reader is directed to the wealth of literature on metabolism.

CONCLUSION

Nature tends to use easily diversified and energetically inexpensive starting materials to generate complex secondary metabolites. Phenols and their derivatives are probably the most highly represented plant secondary metabolites known to humans. Since natural products and their derivatives are the greatest source of drugs and drug leads, it is no surprise that phenols are also highly represented in the FDA-approved drug dataset. Phenols still make frequent appearances in approved drugs, as evidenced by the 17 out of 29 (62%) small molecules approved in 2020 which contain phenol moieties. Understanding the common modalities and connectivity of phenols to other functional groups in drug structures informs on structural combinations that have led to FDA approval in the past. Through structural analysis, we have shown that there is a significant difference between the physicochemical properties of phenols and phenol ethers, with benefits and drawbacks to each.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00223.

List of the names of the compounds featured in this Perspective along with their SMILES strings (PDF)

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Notes

The authors declare no competing financial interest.

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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 (Professor Stan Roberts). After two postdoctoral fellowships at WSU and CWRU (Professor 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 medicinal chemistry and currently in cheminformatics. Phil is also an adjunct faculty member in the Department of Chemistry at Washington State University.

Jon T. Njardarson received his Ph.D. at Yale University in 2001 with Professor John L. Wood. Following postdoctoral training with Professor Samuel J. Danishefsky at The Memorial Sloan-Kettering Cancer Center, he started his independent career in 2004 at Cornell University. In 2010, Professor Njardarson moved his research group to The University of Arizona.

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ABBREVIATIONS USED

AB-MPS, AbbVie multi-parametric score; ALK, anaplastic lymphoma kinase; AlogP, atom-based LogP; CHOP, C/EBP homologous protein; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; DNA, deoxyribonucleic acid; DNOC, dinitro-*o*-cresol; EGFR, epidermal growth factor receptor; EFCP, extended connectivity fingerprints; FDA, Food and Drug Administration; FGFR, fibroblast growth factor; Fsp^3, fraction of sp^3 carbons; FUS, fused in sarcoma; Her2, human epidermal growth factor receptor 2; 3-HM, 3-hydroxymorphinan; IQR, interquartile range; NAPQI, *N*-acetyl *p*-benzoquinoneimine; NAR, number of aromatic rings; NHBA, number of hydrogen-bond acceptors; NHBD, number of hydrogen-bond donors; NN, nearest-neighbor; NPC1L1, Niemann−Pick C1-like 1; NR, number of rings; NRB, number of rotatable bonds; NSAID, non-steroidal anti-inflammatory drug; PD, Parkinson's disease; PDE3,4,

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phosphodiesterases 3 and 4; PFI, property forecast index; PDGFR, platelet-derived growth factor; Q1, lower quartile; Q3, upper quartile; QED, quantitative estimate of drug-likeness; RNA, ribonucleic acid; Ro5, Rule of Five; SAR, structure−activity relationship; TAAR1, trace amine-associated receptor 1; TPSA, topological polar surface area; VEGFR, vascular endothelial growth factor; WHO, World Health Organization

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