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REVIEW

Analysis of US FDA-Approved Drugs Containing Sulfur Atoms

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Abstract In this review, we discuss all sulfur-containing FDA-approved drugs and their structures. The second section of the review is dedicated to structural analysis and is divided into 14 subsections, each focusing on one type of sulfur-containing moiety. A concise graphical representation of each class features drugs that are organized on the basis of structural similarity, evolutionary relevance, and medical indication. This review offers a unique and comprehensive overview of the structural features of all sulfur-containing FDA-approved drugs to date.

Keywords Sulfonamide · Thioether · Sulfoxide · Sulfone · Sulfate · Sulfur heterocycle

Abbreviations

6-APA	6-Aminopenicillanic acid
ADP	Adenosine diphosphate
cGMP	Cyclic guanosine monophosphate
COX-2	Cyclooxygenase-2
GERD	Gastroesophageal reflux disease
GPCR	G protein-coupled receptor
HIV	Human immunodeficiency virus
mRNA	Messenger RNA
NSAID	Nonsteroidal anti-inflammatory drugs
SMN1	Survival motor neuron 1

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SMN2	Survival motor neuron 2
PBP-3	Penicillin binding protein 3
$P2Y_{12}$	A type of purinergic receptor
PDE5	Phosphodiesterase type 5
PET	Positron emission tomography
PPI	Proton pump inhibitor
US FDA	United States Food and Drug Administration

1 Introduction

Inspired by our recent survey of US FDA-approved sulfur- and fluorine-containing drugs [1], we decided to provide a comprehensive account of the small molecule structures of all sulfur drugs approved through December of 2016. Not included in our coverage are biologics/insulins containing cysteine, methionine, and S–S bonds. From our collection of US FDA-approved small molecule drugs we identified 249 unique structures to analyze.

Sulfur has been used in a medicinal context since antiquity. It is one of the earliest known elements and was known to the Greeks to have healing power. Magnesium sulfate was the first sulfur-containing compound approved by the nascent Food and Drug Administration (FDA), and sulfur-containing compounds were the hallmarks of several antibiotic breakthroughs that brought man into the modern antibiotic era. Several Nobel Prizes have been awarded for work done on sulfur-containing drugs. Sulfur-containing compounds continue to represent a large portion of new FDA approvals.

2 Diversity of Sulfur-Containing Functional Groups in US FDA Drugs

Sulfur commonly exists in five different oxidation states, enabling it to enjoy a diversity of forms. To guide our structural analysis, we have broken the sulfur-containing moieties into 14 substructure categories: sulfonamides, β-lactams, thioethers, thiazoles, thiophenes, phenothiazines, sulfoxides, S=C and S=P structures, thionucleotides, sulfones, sulfates, macrocyclic disulfides, and one category each for miscellaneous acyclic and cyclic sulfur-containing compounds (Fig. 1). Each category, where appropriate, is further divided into figures with similar structures.

2.1 Sulfonamides

With 72 of the 285 compounds, sulfonamides make up the largest group in the scope of this review. The sulfonamide moiety consists of a sulfur atom with two double bonds to oxygens, one S–C sigma bond, and one S–N sigma bond. The nitrogen can be bonded to two protons, two alkyl groups, or one of each. Sulfonamides are used in the treatment in a wide variety of indications, including high blood pressure, diabetes, bacterial infections, and human immunodeficiency virus (HIV).

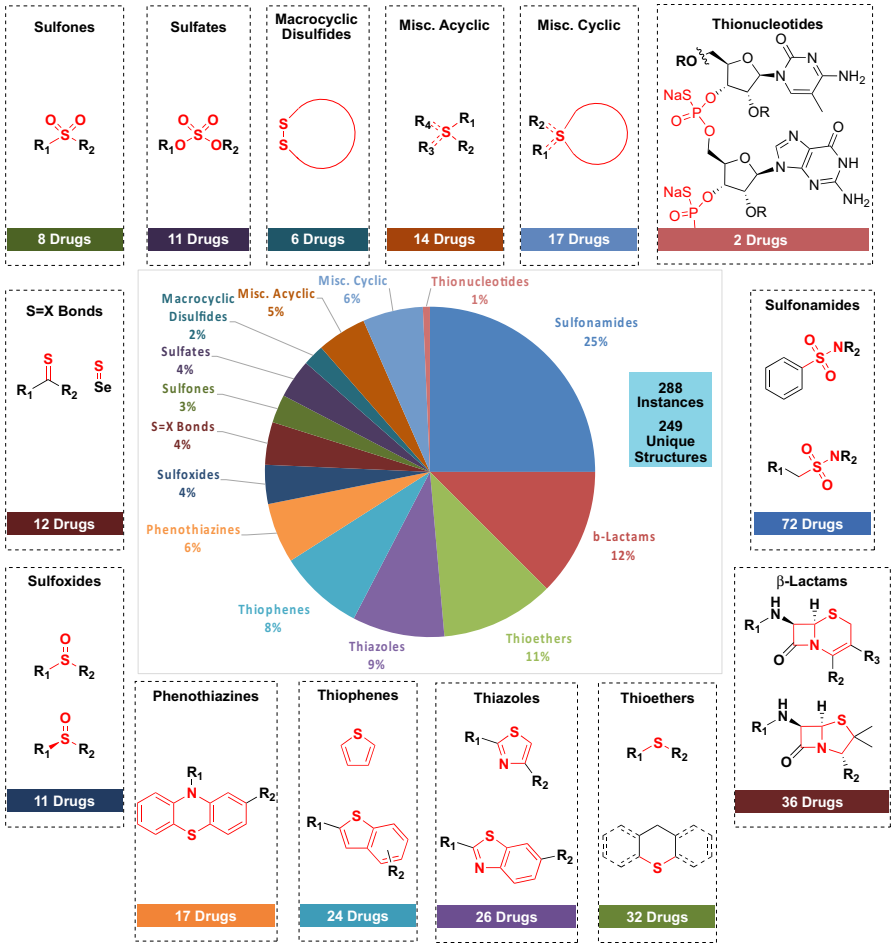

Fig. 1 Structural diversity of US FDA-approved sulfur-containing drugs

Chlorothiazide made its debut on the market in 1957, becoming the first FDA-approved member of the thiazide diuretics often used as treatment for hypertension. The six-membered heterocycle fused to the aromatic ring was discovered by chance, when the phenylamine was acylated, and the ring spontaneously cyclized [2–4]. In the decades following the approval of chlorothiazide, four structurally similar drugs were approved for the same indication: hydrochlorothiazide, methyclothiazide, cyclothiazide, and trichloromethiazide (Fig. 2). Chlorothiazide differs from the other members of this family in that the sulfur-bonded nitrogen in the thiazide ring harbors a C–N double bond, while the remaining members of the family bear a C–N single bond in this position. Bendroflumethiazide is structurally similar to these, excepting that the R group is benzyl and the chlorine on the core is changed to a trifluoromethyl group. The 1980s saw the approval of two thiazide-like diuretic

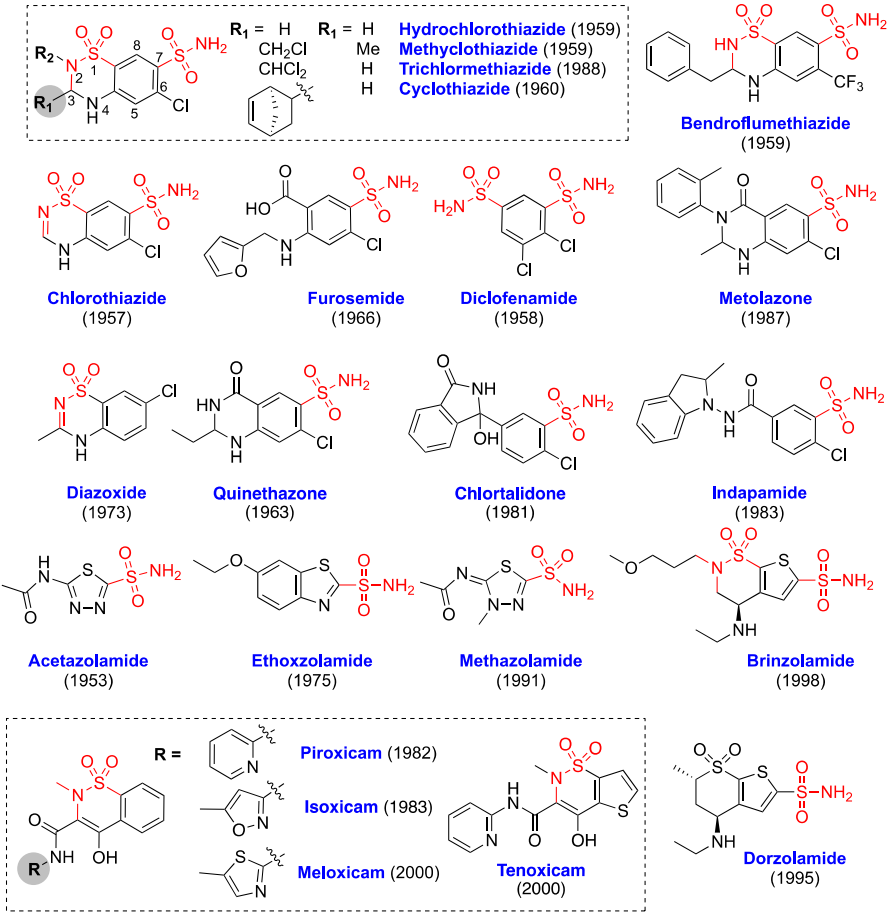

Fig. 2 Diuretics, carbonic anhydrase inhibitors, and NSAIDs: R_2NSO_3-aromatic sulfonamides

drugs, indapamide and metolazone. Indapamide has an open-chain indolinamide moiety rather than the heterocycle, and a carbonyl group in place of the sulfone that is typically in the 1-position. Metolazone still has a six-membered heterocycle that contains two nitrogen atoms, but has a carbonyl in place of a sulfone, in the same position as indapamide.

The electron-withdrawing group in the six-position is required for diuretic activity, with chloro and trifluoromethyl groups having been employed. The trifluoromethyl group has the added benefit of greater lipid solubility and half-life when compared with the chloro-analogue. The sulfonamide group in the 7-position is also crucial. A loss of diuretic activity is seen when this group is removed or modified. A saturation of the double bond in chlorothiazide and diazoxide, resulting in the 2,3-dihydro version, leads to a tenfold increase in activity. A hydrophobic substitution in the 3-position leads to greater diuretic potency. When

the core is decorated with haloalkyl, arylalkyl, or thioether groups, the lipid solubility is enhanced and the half-life is increased. Alkylation of the nitrogen in the 2-position decreases polarity and increases the longevity of diuretic effects.

The discovery of the aforementioned diuretics occurred serendipitously when researchers investigated compounds as carbonic anhydrase inhibitors. Acetazolamide was the first drug approved as a carbonic anhydrase inhibitor and was approved in 1953. Four others followed: ethoxzolamide, methazolamide, brinzolamide, and dorzolamide. The last two bear superficial structural similarities to the thiazide diuretics, but are in fact carbonic anhydrase inhibitors. All of these share the sulfonamide moiety bound to a heterocycle, most of them aromatic.

Piroxicam was introduced in 1982 as a nonsteroidal anti-inflammatory drug (NSAID) for treatment of pain and fever. The core structure consists of a six-membered sulfonamide-containing heterocycle fused with an aromatic ring, sharing similarities with the thiadiazines. In three of the four approved drugs, the fused aromatic ring is a benzene ring. Tenoxicam harbors a thiophene moiety in this position. The amide substitution is the variable that differentiates the remainder of the drugs, with either a pyridine, isoxazole, or thiazole moiety at that position.

Sulfonamides in which the sulfur atom is bonded to an aryl are further represented in Fig. 3. The sulfonylureas in the first two boxes make up an important component of this group, and comprise a broad class of antidiabetic drugs that work by stimulating insulin secretion by beta cells in the pancreas. Sulfonylureas were discovered to stimulate insulin secretion (and thus lower glucose levels in the blood) while compounds were being studied as a treatment for typhoid fever in the 1940s [5]. Previously known sulfonamide antibiotics were appended with a urea group in order to explore this application.

The first generation of oral hypoglycemics was introduced in 1958, and the second generation in 1984. Torasemide structurally belongs to the sulfonylureas, but is not an antidiabetic drug. The core of the first-generation antidiabetics consists of a benzenesulfonamide substituted with a lipophilic group in the 4-position (R_1), and a linear or cyclic lipophilic alkyl substituent on the urea in the R_2 position [6]. These increased with sophistication over time, beginning with a simple propyl group prior to using cyclohexyl, azepane, and fused bicyclic systems. The second-generation oral hypoglycemics is characterized by an extended chain on the 4-position of the benzenesulfonamide, with an amide moiety harboring a number of different heteroalkyl groups. These compounds are nearly two orders of magnitude more potent than the first generation. This is the result of the new substituent that replaces the previous R_1 with a longer *para*-(beta-arylcarboxyamidoethyl) group [7, 8]. The latest of these is glyburide, which has a substituted aryl ring at this position. The substitutions on the urea all contain a cyclohexane ring, with only glimepiride having a methyl group in the 4-position.

The discovery of sulfanilamide in the 1930s led to the first successful class of synthetic antimicrobials. Prontosil rubrum is a sulfonamide belonging to the diazo dyes that was investigated by Bayer Laboratories in 1932. While the dye was not active in vitro, the urine of the animals treated with the dye was found to have antimicrobial activity. A reduced liver-metabolite, the benzenesulfonic acid amide

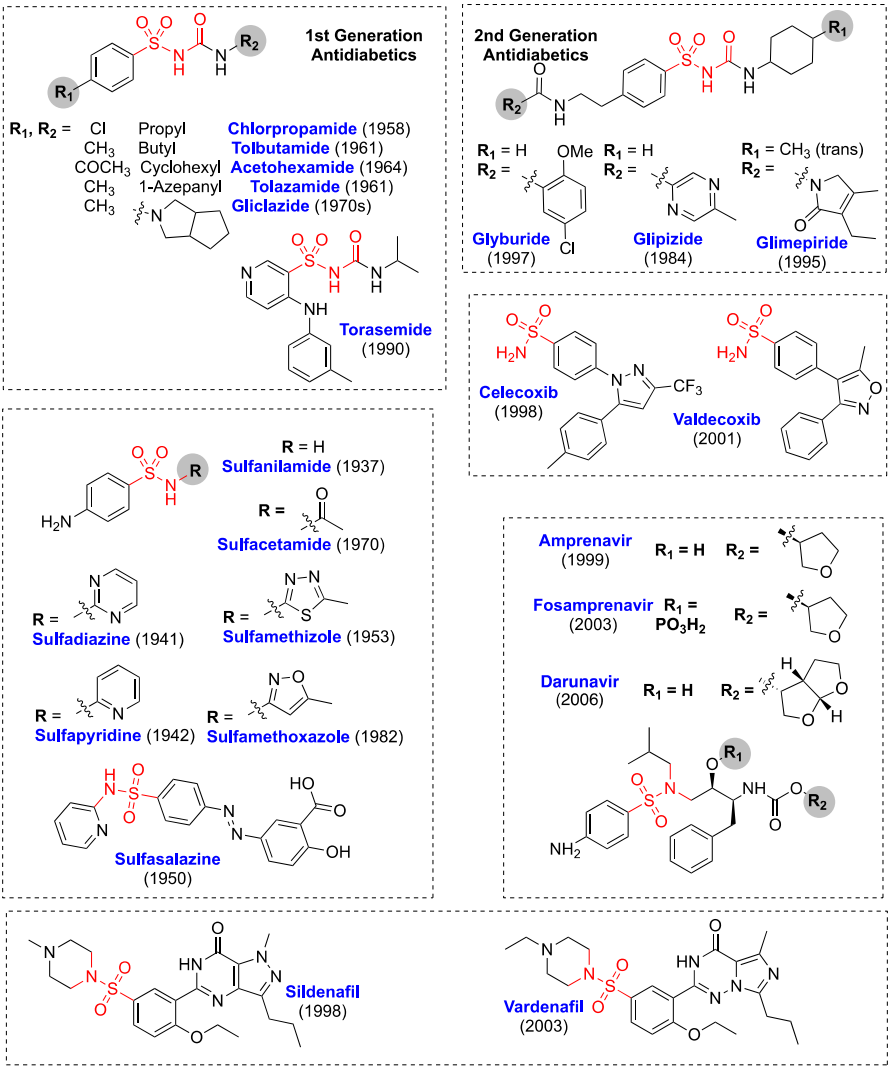

Fig. 3 Antidiabetics, antibacterials, and other drugs containing R_2NSO_3-aromatic sulfonamides

(sulfanilamide) of the dye, was found to be antimicrobially active, and the class was born [9].

Sulfonamide antibiotics are commonly referred to as sulfa drugs, and are responsible for the majority of allergic reactions against sulfur-containing drugs. Sulfonamide antibiotics inhibit bacterial dihydropteroate synthase, which is essential for the biosynthesis of folates. This inhibition prevents thymidine biosynthesis, a process required for DNA synthesis, resulting in bacteriostasis [10]. The strongly electron-withdrawing SO_2 group decreases the pK_a of the nitrogen protons. When one of these protons is replaced with an electron-withdrawing hetero-aromatic ring, the

pK_a of the remaining proton is decreased even further, increasing the potency of the drug. In addition to increasing potency, these changes increase solubility under biological conditions. Sulfasalazine is a prodrug that undergoes hydrolysis at the N=N bond, resulting in the anilino-sulfonamide, which is capped with a pyridine moiety. While it is grouped with the sulfonamide antibiotics structurally, it is used to treat inflammatory disorders.

Celecoxib and valdecoxib get their names from the fact that they are cyclooxygenase-2 (COX-2)-inhibiting NSAIDs. Both drugs contain a five-membered heterocyclic core with two aromatic moieties, including a benzenesulfonamide. The major metabolism of these drugs involves the cytochrome P450 enzyme CYP2C9, which oxidizes the methyl group to a carboxylic acid. The acid is then glucuronidated before excretion.

Sildenafil and vardenafil were developed separately, are structurally very similar, and are both blockbuster drugs used to treat erectile dysfunction. Their discovery was the fortuitous result of research in a different medical arena: the pursuit of drugs to reduce blood pressure. Both drugs are cGMP-specific phosphodiesterase type 5 (PDE_5) inhibitors. The guanine-like core of both compounds plays a role in the binding mechanism to PDE_5. Aside from the shift of a single nitrogen atom within the core, the only difference between these compounds is the N-alkyl substituent (methyl vs. ethyl). The former of these differences accounts for the greater potency of vardenafil [11]. The sulfur moiety of these drugs is an N-alkyl-piperazyl-sulfonamide, which, mechanistically, constitutes what is known as the "lid region" of the compound.

The seven remaining drugs that contain a sulfonamide in which the sulfur atom is connected to an aromatic moiety and the nitrogen is connected to an alkyl or acyl group, or hydrogen are depicted in Fig. 4. The oldest, probenecid, is structurally

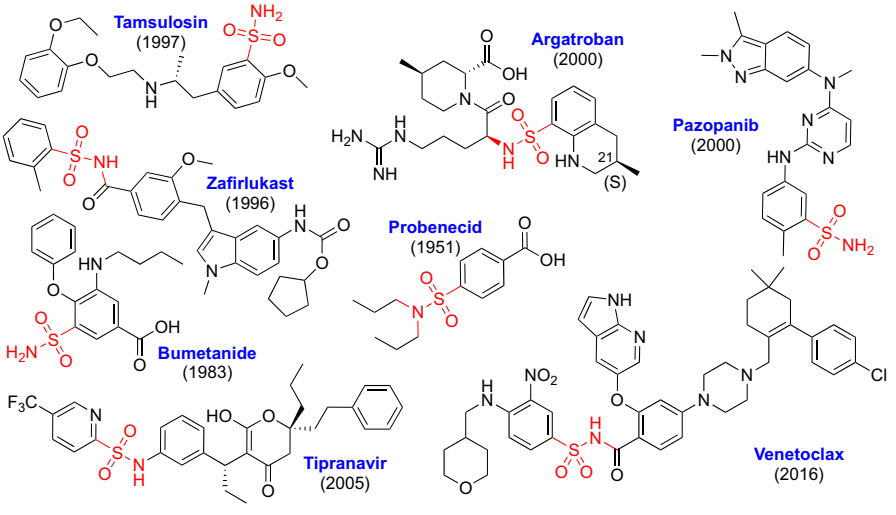

Fig. 4 Other drugs containing R_2NSO_3-aryl sulfonamides

simple. The most recent drug in this category is venetoclax, a leukemia drug with considerably greater complexity, including a modern pyrrolopyridine. Argatroban is notable for its four stereocenters, and is sold as a mixture of 21-(*R*) and 21-(*S*) isomers, with the (*S*)-isomer possessing about twofold higher activity [12].

Amprenavir, fosamprenavir, darunavir, and simeprevir (Figs. 3, 5) are all antiretroviral sulfonamides used to treat HIV, and the peptidomimetic argatroban (Fig. 4) was approved in 2000 as a thrombin inhibitor. These sulfonamides share a structural feature in their peptide backbone, although simeprevir is unique within this group, in that the sulfur atom is attached to a cyclopropyl group rather than a phenyl ring.

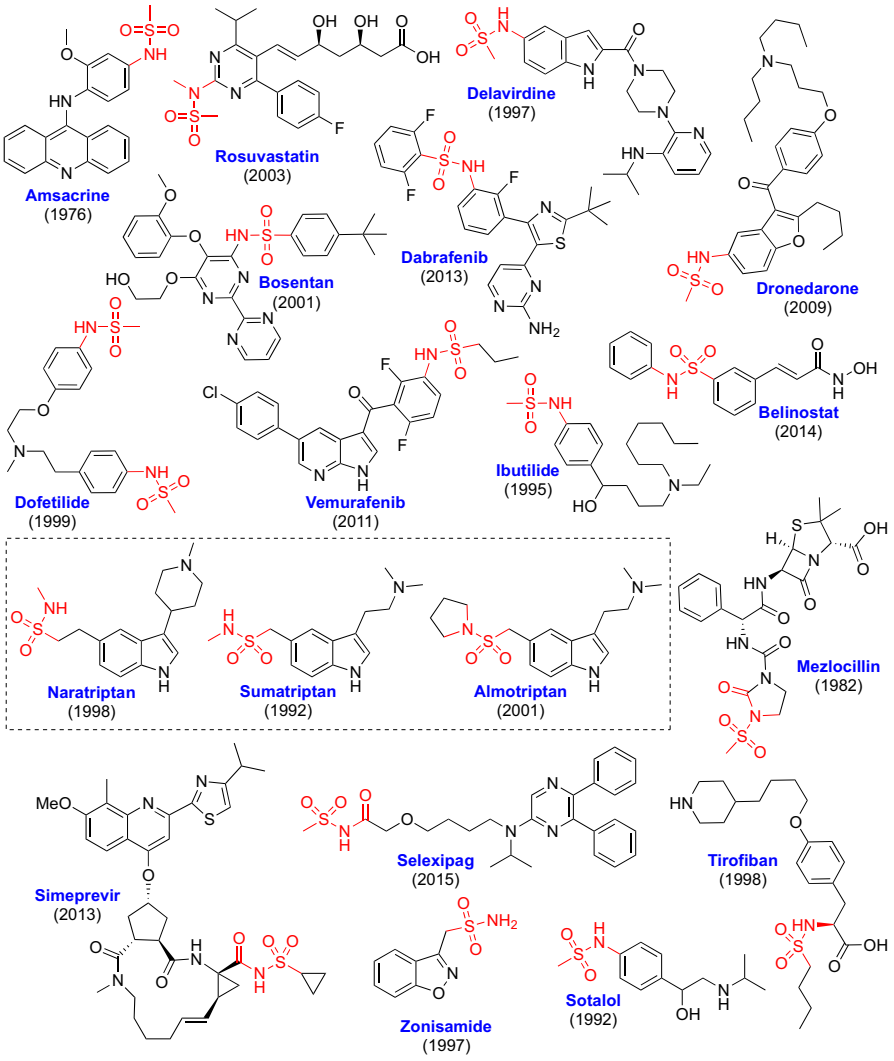

Fig. 5 Drugs containing R_2NSO_2-alkyl groups

Simeprevir is the most complex structure within this group, with five stereocenters and a number of unique moieties. Fosamprenavir is a prodrug of amprenavir and contains a stereocenter bearing a phosphate group which is cleaved by serum phosphatase, releasing the active compound. Amprenavir was the fifth protease inhibitor approved for the treatment of HIV, but the first with a sulfonamide moiety.

Three of the drugs in this class belong to the triptan class of migraine medications: naratriptan, sumatriptan, and almotriptan (Fig. 5, box). While there are other triptans, these (along with eletriptan in Sect. 2.10) are the only ones containing sulfur atoms. Each of the three in this category has a sulfonamide attached to a tryptophan-like core, which is shared by all triptans. Of the 17 remaining sulfonamides in Fig. 5, 11 of them have the nitrogen atom attached to an aryl or hetero-aryl moiety, four are part of an amide or cyclic amide, one is attached to an alkyl group, and one exists as an NH_2 terminal moiety. Of these 17 drugs, the sulfur atom is most often attached to a methyl group (ten instances), though five others are attached to sp^3 alkyl moieties, including propyl, butyl, cyclopropyl, and one methylene benzisoxazole. Rosuvastatin is a top-selling drug for the treatment of hypertension, and contains two stereogenic centers, each with a secondary alcohol. Dronedarone and vemurafenib have superficially similar structures with 5,6-fused ring systems and a phenyl ketone in the 2-position. Closer inspection of the two drugs reveals differences, however, and they are used to treat arrhythmias and cancer, respectively.

2.2 β-Lactams

Alexander Fleming's observation that *Penicillium* mold had the ability to inhibit the growth of bacterial colonies led to the first β-lactam, the penicillins, the first of which to approved being ampicillin in 1965. The Nobel Prize for medicine, in the same year, was awarded to Fleming, Chain, and Florey for their work. Through a combination of fermentation and semisynthesis, hundreds of thousands of analogues have been made, leading to a respectable number of FDA-approved drugs containing the β-lactam core. Efforts to increase potency, spectrum, and to combat antibiotic resistance have given rise to several generations of β-lactam antibiotics, which can be grouped into penams, cephems, and monobactams. Penams are represented by penicillins and carbapenems, cephems by cephalosporins and cephamycins, and monobactams make up the third category of β-lactam antibiotics. Collectively, these have been the most successful antibiotics known to man. Because the fused heterocyclic core of penams and cephems contains sulfur atoms, this section will focus only on these structures, and monobactams will be addressed in Sect. 2.13.

The earliest FDA-approved β-lactam antibiotics are penems belonging to the penicillin group of drugs (Fig. 6). Penam antibiotics share a bicyclic core made of a five-membered thiazolidine ring fused to a β-lactam ring. All 13 drugs in this category share the same core, and differ only by the side chain of the amide. Four drugs share a substituted isoxazole moiety, six of them a substituted benzyl moiety, and the three remaining drugs have unique side chains.

Penicillins were first isolated through solid media fermentation of the fungus *Penicillium chrysogenum.* Various penicillin isolates were determined to have

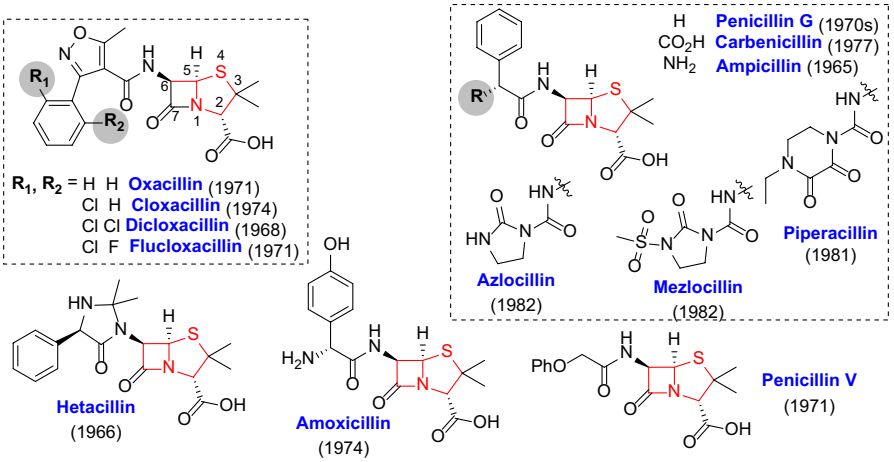

Fig. 6 Penam core-containing β-lactam antibiotics

varying side chains in the 6-position. It was noted that when certain organic acids were added to the media they were incorporated at this position. This method gave control over side-chain identity. For example, phenylacetic acid afforded penicillin G, and phenoxyacetic acid penicillin V. When side-chain precursors are absent from media, the penicillin core 6-aminopenicillanic acid (6-APA) is produced. While 6-APA has only modest antibacterial activity, it serves as a chemical precursor to many derivatives, which are produced by converting the acid to a desired amide.

Oxacillin derivatives all contain a methylisoxazole moiety, which is appended with a 2,5-disubstituted phenyl ring (except oxacillin, which has two hydrogen atoms at those positions). The three analogues of oxacillin have combinations of chlorine and fluorine at these positions (Fig. 6). Derivatives of penicillin G all contain an N-substituted phenylglycine amide for the side chain, all of which contain an (*R*)-stereocenter. Hetacillin, amoxicillin, and penicillin V have variations of the aforementioned substitutions.

Cephalosporin C was first isolated from fungus of the genus *Acremonium*, and characterized in 1961 [13]. Cephalosporins and cephamycins contain the cephem core, which consists of a β-lactam ring fused to a six-membered dihydrothiazine ring, in which carbons 2 and 3 share a double bond. The six-membered dihydrothiazine ring is more stable than the five-membered thiazolidine ring of the penicillin analogues, rendering the cephems less susceptible to hydrolysis by β-lactamases. The mechanism for hydrolysis requires the substituent on carbon 3 to act as a leaving group; therefore, poor leaving groups in this position result in greater resistance to degradation. Cephalosporins have seen a number of analogues developed over five generations of the core, beginning with the development of cephalexin in 1969 and FDA approval in 1971 (Fig. 7). Cephalexin remains one of the top prescribed antibiotics worldwide. Early cephalosporins did not have great potency, although they did exhibit activity against strains that were resistant to penicillin.

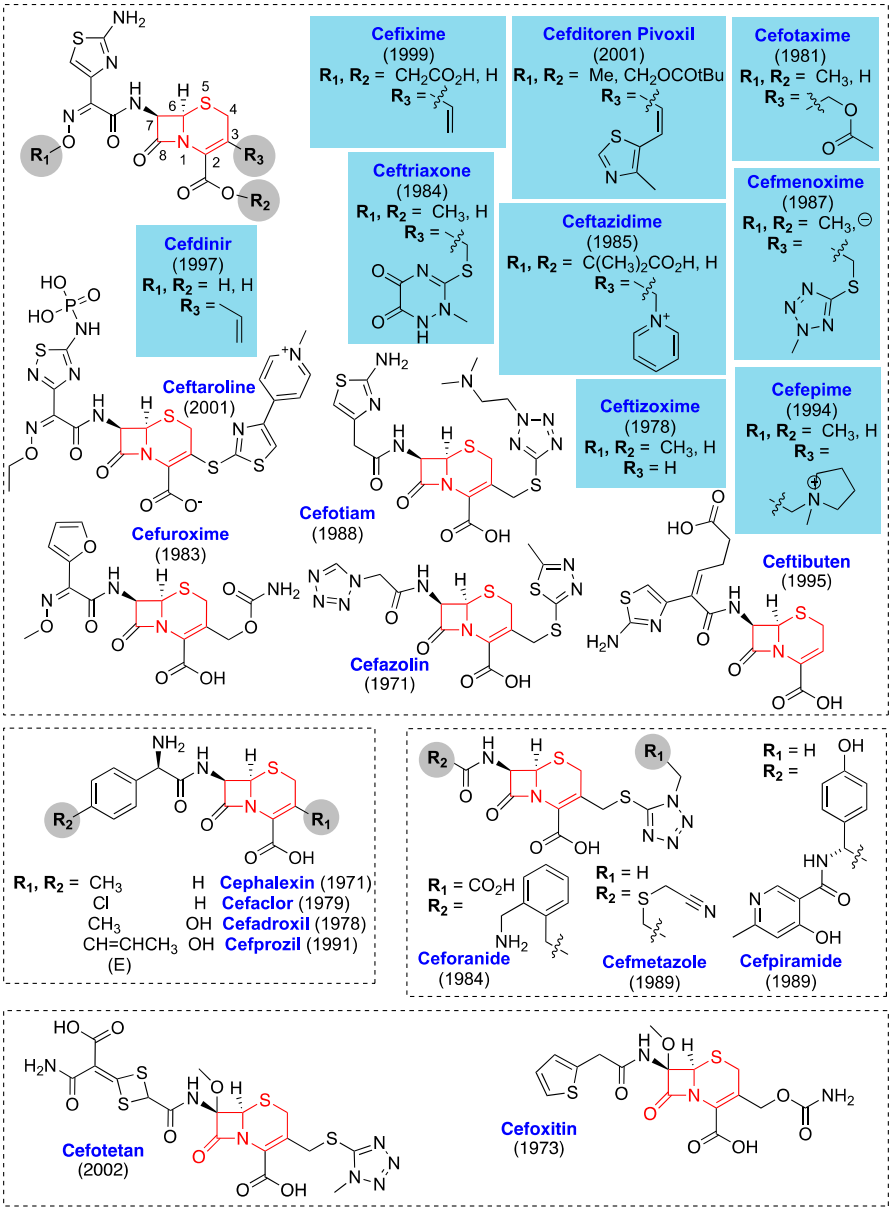

Fig. 7 Cephem core-containing β-lactam antibiotics

Like the penams, cephems share a large degree of structural homology (Fig. 7). Nine of these have the same extended cephem core, with different side chains on the oxime (R_1), the ester (R_2), and the C3 side chain (R_3). All nine of these compounds are equipped with an aminothiazole moiety adjacent to the oxime. Ceftaroline is the

only cephem with a heteroatom directly attached to the C3 carbon, and also has a pyridinium moiety connected to the thiazole in the 4-position, imparting a constitutive positive charge. Ceftibuten resembles the nine oxime-containing drugs but has a carbon–carbon double bond in that position. Four drugs have no group on the carboxylate side chain and exist as the acid rather than the ester. Another three more modern cephems are also carboxylates, and have various alkyl substituents on the amide (R_2) as well as thiotetrazole substituent at R_1. Cefmetazole, a more recently approved cephem, contains a thioether moiety (discussed in the next section), linking the core to a nitrile, a unique feature in this group. Cefoxitin and cefotetan are notable in that these are the only two β-lactams which have a substituent in the 7-position in addition to the amine. Each has a methoxy group in this position.

2.3 Thioethers

Thioethers are characterized as an R–S–R′ moiety in which R and R′ are alkyl or aryl groups. This group contains 31 drugs: 12 belong to the β-lactam group (Fig. 8), and of the remaining 19 (Fig. 9), two drugs contain thiazoles in addition to thioethers. Two of the drugs in this section contain more than one thioether: cangrelor has two, and sugammadex has eight. Twelve of the 30 drugs contain C_{sp3}–S–C_{sp3} thioethers, 15 contain C_{sp3}–S–C_{sp2} thioethers, and the remaining six contain C_{sp2}–S–C_{sp2}

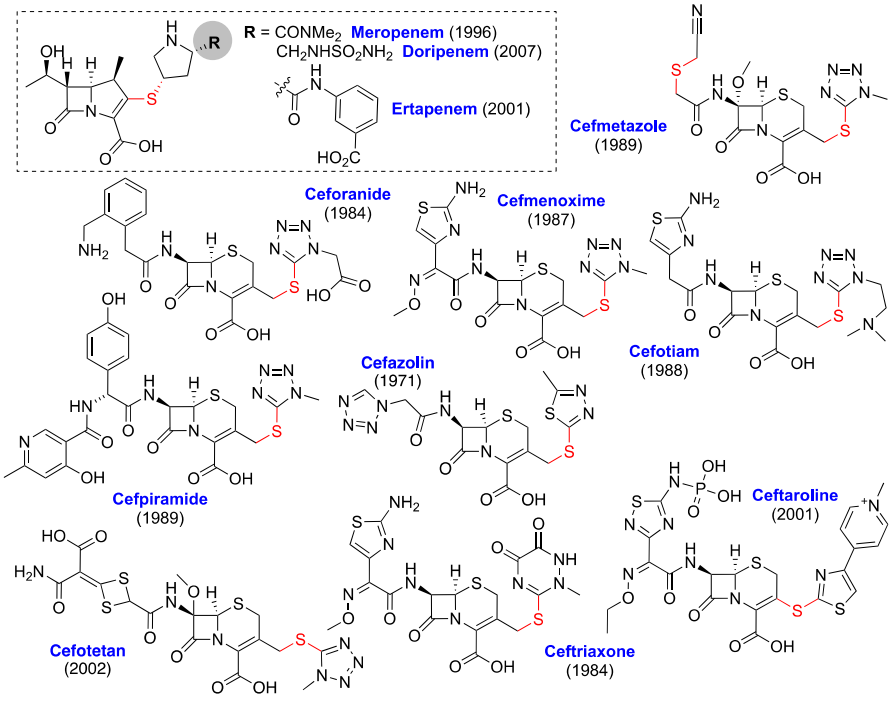

Fig. 8 β-Lactam antibiotics containing thioethers

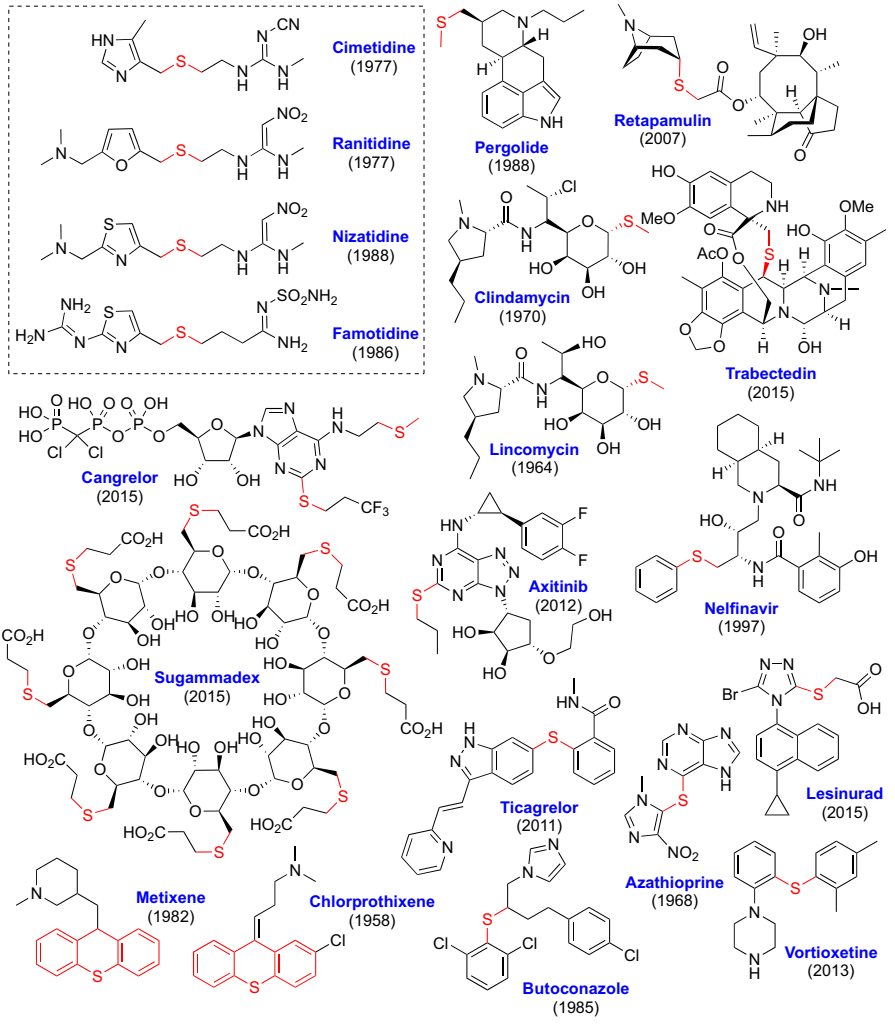

Fig. 9 Other drugs containing thioethers

thioethers. In total, there are 31 different thioether moieties in this section because cangrelor has two *different* types of thioether.

Carbapenem antibiotics belong to the penem class of β-lactams, but are differentiated from the penems by the absence of a sulfur atom in the fused heterocyclic core that is characteristic of the family. Three carbapenems, however, contain a sulfur atom in the form of a thioether. These are meropenem, doripenem, and ertapenem. Seven of the cephalosporins also contain a sulfur atom in the form of a thioether, each are part of the linker on carbon 3. These sulfur atoms are all attached to an sp^3 carbon atom attached to the core, and then either to a tetrazole (ceforanide, cefmetazole, cefpiramide, cefmenoxime, cefotiam, and cefotetan), a thiazole (ceftaroline), a

thiadiazole (cefazolin), or a triazinedione (ceftriaxone), each of which is substituted as shown in Fig. 8.

The 1960s saw the discovery and development of two new antibiotics: lincomycin and clindamycin (Fig. 9). Both compounds contain a thioether at the anomeric carbon of a sugar-derived backbone, and differ only in the C-7 substitution, with an (*R*)-OH group for the former, and the inverted (*S*)-Cl in the latter [10]. Chloro-substitution results in greater lipophilicity and bioavailability.

Retapamulin is a notable semisynthetic diterpene belonging to the class of pleuromutilin antibacterials that are extracted from the fungus *Pleurotus mutilus* [10]. Two structurally similar drugs, valnemulin and tiamulin, contain thioethers and would be grouped with retapamulin, but these are veterinary drugs that have not been approved for use in humans. Retapamulin works by inhibiting the 50S subunit of bacterial ribosomes [14].

Ticagrelor and cangrelor are irreversible inhibitors of $P2Y_{12}$ receptor inhibitors [15]. Both are antiplatelet drugs with a purine (cangrelor) or a purine-like (ticagrelor) core. Ticagrelor has an alkyl thioether attached to C-2 on the purine-like core, and cangrelor has two thioethers: one attached to C-2, and one within the chain attached to C6 on the purine core. Adenosine diphosphate (ADP) plays a critical role in platelet aggregation. As such, it is no surprise that both compounds resemble the adenosine core, with cangrelor even containing a non-hydrolyzable biomimetic triphosphate group.

Metixene and chlorprothixene are the only drugs in this section to contain a cyclic thioether, linking two phenyl rings, a structure known as a thioxanthene. Though structurally related to the phenothiazine (Fig. 15) antipsychotics discussed in Sect. 2.6, metixene is an anticholinergic prescribed to treat Parkinson's disease. The core of this drug differs from the phenothiazines in that it contains an sp^3 carbon atom in the place of the nitrogen atom in the latter. Chlorprothixene also has a carbon atom in this position, but it is sp^2 hybridized. To be active, chlorprothixene must be in the *Z*-orientation in order to achieve a conformation that allows the terminal nitrogen to be near the chloro-substituted phenyl ring. Unlike metixene, chlorprothixene *does* belong to the typical antipsychotics class, and is used to treat schizophrenia, and other psychotic disorders.

Azathioprine is a drug that was developed in the 1960s largely through work by Gertrude Elion and George Herbert Hitchings [16]. It can be taken orally or intravenously as an immunosuppressant, or to treat rheumatoid arthritis, Crohn's disease, or ulcerative colitis. The thioether in this drug acts as a prodrug moiety, with the side chain being removed during metabolism, leaving the active 6-mercaptopurine.

Sugammadex is a γ-cyclodextrin with eight identical thioethers that connect propionic acid moieties to linked hexoses. It is used to reverse a general anesthetic called rocuronium. This is done by reversing neuromuscular blockade [17]. Sugammadex is used alone in anesthetic reversal because cholinergic effects are not seen; other drugs, like neostigmine, act as acetylcholine esterases and must therefore be coadministered with an antimuscarinic agent.

Cimetidine, ranitidine, nizatidine, and famotidine are H_2 antagonists that are designed to decrease gastric acid secretion and are prescribed to treat gastroesophageal reflux disease (GERD). Each of these was developed from histamine-like

compounds, and each contains a thioether that connects a heterocycle to an alkyl urea, or urea-like compound. Ranitidine and nizatidine contain a substituted ethylenediamine appended with a nitro group. When carbon or oxygen takes the place of sulfur, the activity is drastically reduced [10].

Trabadectin is a complex natural product that contains a thioether within a 10-membered bridged hetero-lactone, as well as three tetrahydroisoquinoline structures, and eight rings in total. Its biosynthetic pathway was used as a blueprint for E. J. Corey's total synthesis of the molecule in 1996 [18]. It is prescribed as an antitumor chemotherapeutic to treat soft tissue sarcoma.

Pergolide is the only member of the ergot-type dopamine receptor antagonists to contain a thioether, and is the first drug of the class that does not contain a peptide linkage at that position [19]. It is a D_1 and D_2 dopamine receptor agonist, and was approved by the FDA in 1988 as a treatment for Parkinson's disease, though it has since been removed from the market because of links to heart disease [20].

2.4 Thiazoles

The term thiazole typically refers to 1,3-thiazole, a five-membered nitrogen- and sulfur-containing heterocycle. Twenty-three of the drugs in this group contain at least one thiazole (Figs. 10, 11), and three of the drugs in this group contain

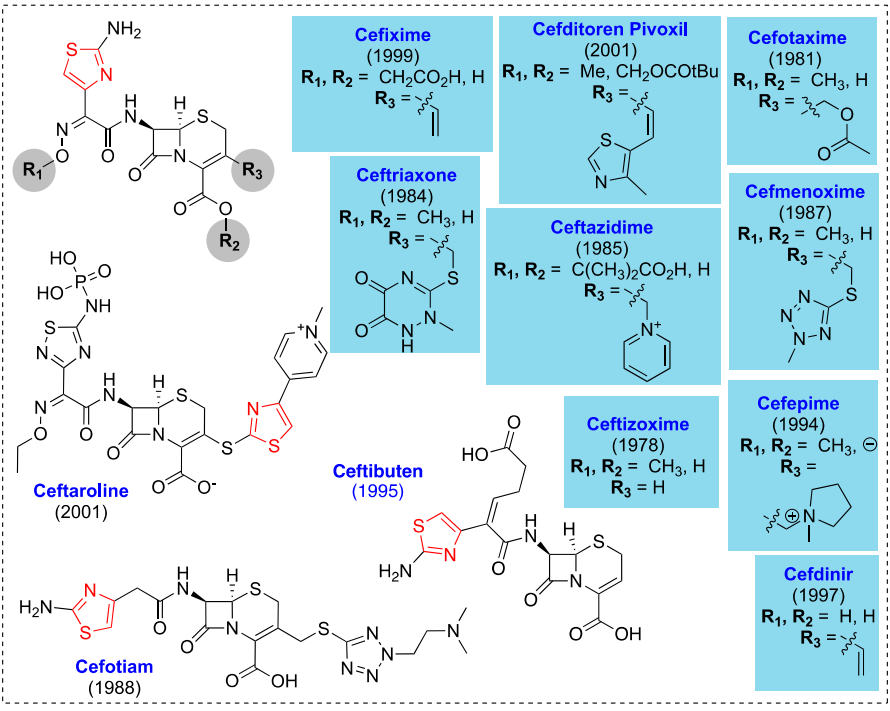

Fig. 10 β-Lactam antibiotics containing thiazoles

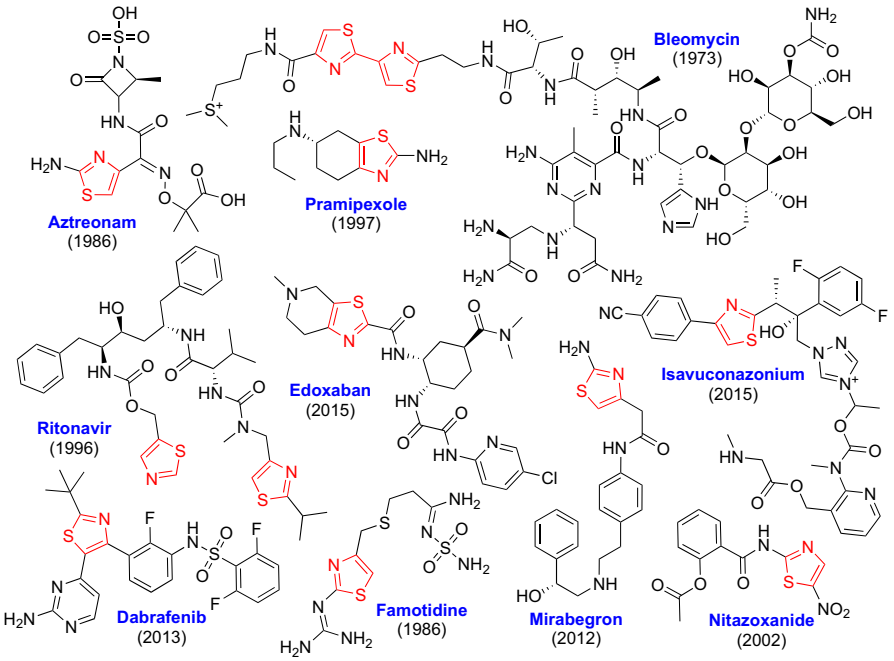

Fig. 11 Other drugs containing thiazoles

benzothiazoles (Fig. 12). It is notable that more than half of the cephem antibiotics contain thiazoles (Fig. 10). Nineteen of the 23 (not including benzothiazoles) are 2,4-substituted, one is substituted only in the 5-position, one is substituted in a 2,4,5-pattern, one is 2,5-disubstituted, and two drugs are 2,4,5-trisubstituted, in which the 4,5-disubstitution is part of a non-aromatic ring. This count includes bleomycin, which has two 2,4-disubstituted moieties, and ritonavir, which has one

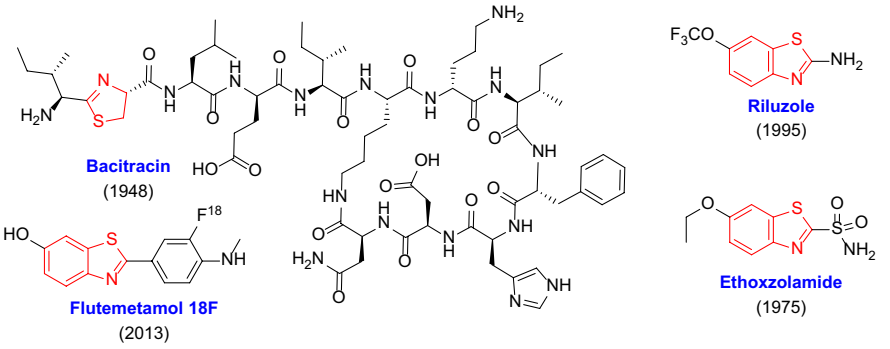

Fig. 12 Bacitracin and the benzothiazoles

2-substituted and one 2,4-disubstituted moieties. Fifteen of the nineteen 2,4-disubstituted moieties have a heteroatom at the 2-position, with 12 of those bearing an sp^2 center at the 4-position and only three bearing an sp^3 center at the 4-position. Notably, aminothiazoles are common within this substitution.

Pramipexole (Fig. 11) is one of the leading drugs for management of Parkinson's disease [21]. It contains a thiazole fused to a cyclohexene ring as the central core of the molecule. Ritonavir is an HIV protease inhibitor prescribed as an antiretroviral. Like other drugs in this class, it is a peptidomimetic, and contains a thiazol-5-ylmethyl carbamate as the terminal moiety, and an isopropyl thiazole at the other end of the molecule [22]. Famotidine is a histamine H_2 receptor antagonist used to treat GERD. It contains a thiazole with an exocyclic guanidine group. Owing to its lack of cytochrome P450 inhibition and induction, and lack of interaction with other drugs, it is sometimes preferred over cimetidine [23].

Bacitracin (Fig. 12) is a cyclic peptide antibiotic that is produced by the bacterium *Bacillus subtilis.* While the aminoalkyl dihydrothiazole core is always the same, the product is actually a mixture of peptides. The drug inhibits peptidoglycan synthesis and treats Gram-positive bacteria, including staphylococci resistant to typical treatments.

Flutemetamol ^{18}F is notable because it is the only drug in this review that contains a radioactive isotope, in this case ^{18}F, used as a PET scanning contrast agent. It contains a 6-hydroxybenzothiazole core with a fluoro-aniline at the 2-position. Riluzole also contains fluorine in the form of a trifluoromethoxy group at the 6-position, as well as a 2-aminobenzothiazole. The drug is prescribed to treat amyotrophic lateral sclerosis, and delays onset of tracheostomy and ventilator-dependence by up to 3 months [24]. Finally, dabrafenib and isavuconazonium also contain fluorine atoms, in this case on phenyl rings.

2.5 Thiophenes

Thiophenes are a five-membered sulfur-containing aromatic heterocycle, the sulfur variant of furan. This section is comprised of 21 thiophene-containing drugs (Fig. 13), and an additional four benzothiophene-containing drugs (Fig. 14). Three of the 21, tiagabine, aclidinium, and tiotropium, have two thiophene moieties. Three drugs in this section, brinzolamide, dorzolamide, and tenoxicam, were discussed in Sect. 2.1. Eight of the 21 thiophenes are fused to a six-membered ring, with seven of those being heterocycles, including one with two nitrogens, three with one nitrogen, and three with both a nitrogen and a sulfur. Nine of the 21 thiophenes are monosubstituted, eight of them are disubstituted (including fused rings), and only four are trisubstituted.

Brinzolamide and dorzolamide are both carbonic anhydrase inhibitors. This time we see them in the context of the thiophene moiety, which is fused to the central cyclic sulfonamide or sulfone core, respectively. The alkylamine present in both of these molecules bears a positive charge under biological conditions, and the thiophene moiety presumably confers enough lipophilic character to penetrate the

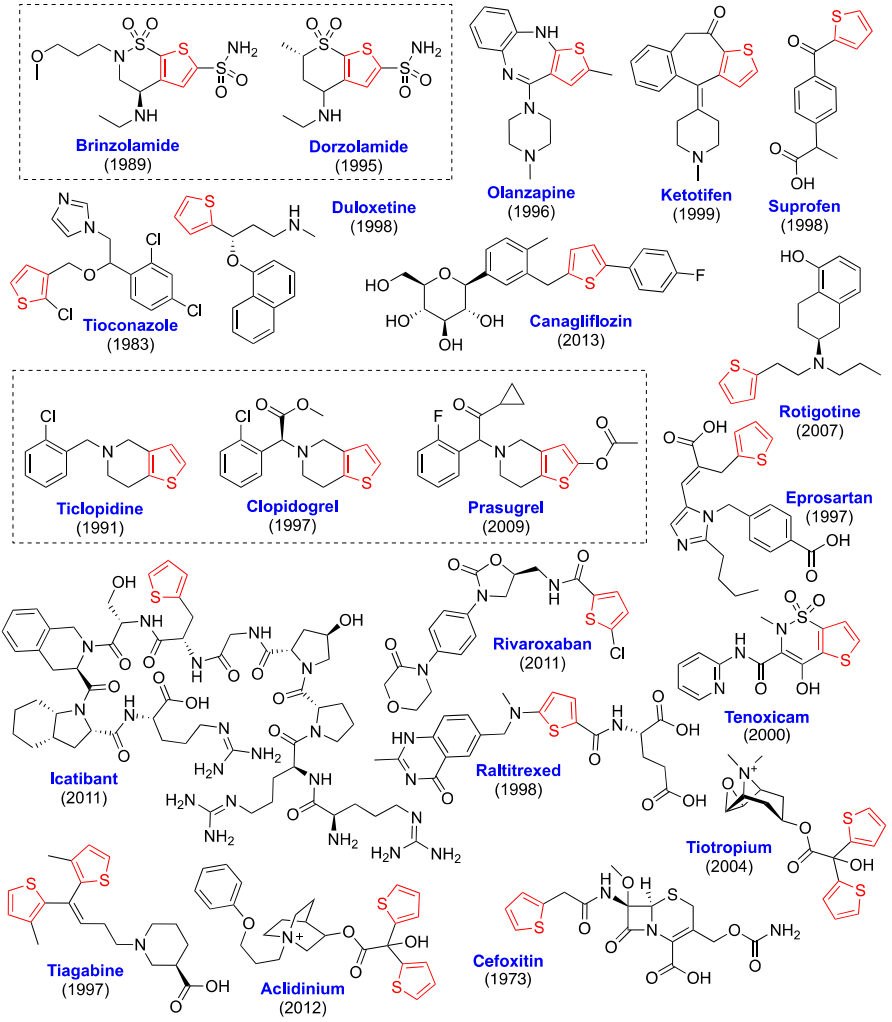

Fig. 13 Drugs containing thiophenes

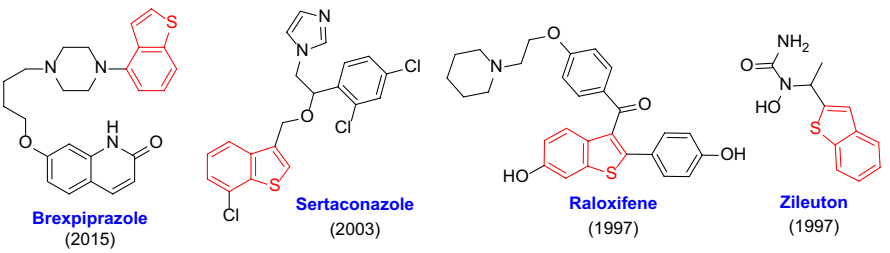

Fig. 14 Drugs containing benzothiophenes

cornea. Tenoxicam is an oxicam drug with a similar core structure, with the exception that the orientation of the fused thiophene moiety is inverted.

Ticlopidine, clopidogrel, and prasugrel are thienopyridines that consist of a thiophene fused to a piperidine, with the nitrogen substituted with a halobenzyl group, a halophenylacetate connected at the alpha position, or a 1-cyclopropyl-2-phenylethan-1-one connected at the 2-position, respectively. All three are antiplatelet drugs that inhibit the ADP receptor $P2Y_{12}$ irreversibly and that need to be metabolized into their active forms by cytochrome P450. Ticlopidine and clopidogrel are oxidized during metabolism, which leaves a thiol free to form a disulfide bond with a cysteine on the target enzyme; this is an irreversible step in the inhibition mechanism [25, 26]. Prasugrel acts via a similar mechanism, although in this case cleavage of the ester on the thiophene ring serves as the activation to the thiolactone, rather than oxidation.

The remaining thiophene structures are a diverse group, including a benzodiazepine (olanzapine), a monosaccharide (canagliflozin), a synthetic peptide (icatibant), a tropane and a quinicludinium (tiotropium and aclidinium) both with constitutive charges, and an oxicam (tenoxicam), to name a few.

In addition to thiophenes, their fused aromatic counterpart (benzothiophene) is represented by the four drugs zileuton, raloxifene, sertaconazole, and brexpiprazole (Fig. 14) all of which were approved in the last 20 years.

2.6 Phenothiazines

The 14 drugs in the phenothiazine class share a tricyclic core with nitrogen and sulfur atoms across from one another (Fig. 15). The substitution at the R_1 position of the core is important to the antipsychotic activity of these drugs. Only one of the antipsychotics in this class, promazine, has a hydrogen atom at this position. Another four drugs in this structural class also have a hydrogen at this position, but they are not antipsychotics. Ten of the 14 drugs in this section make up the typical antipsychotic drugs (only three atypical antipsychotics are covered in this review: sulpiride, a sulfonamide, and ziprasidone and lurasidone, both miscellaneous cyclic sulfur-containing compounds). The other four include an antipruritic (trimeprazine), a sedative (promethazine), and two antihistamine/anticholinergics (methdilazine and mequitazine). All of these drugs have a number of side effects due to their affinity to a number of important G protein-coupled receptors (GPCRs) [27]. All 14 drugs have an alkyl linker attached to the nitrogen atom of the core, which is, in turn, attached to another nitrogen atom. This is important for psychoactive phenothiazine derivatives to achieve conformational states similar to dopamine. In phenothiazines, crystal structures depict a *trans*-rotamer, with the side chain preferring to rotate toward the substituted phenyl ring [28]. That phenyl ring can be superimposed onto that of dopamine, putting the nitrogens of the respective side chains in a similar position. It is likely that this is the basis for the psychoactive properties of antischizophrenic drugs, which are thought to mainly bind at D_2-type dopamine receptors. Promethazine has a two-carbon linker, but the other 16 drugs have a three-carbon linker. All of the side-chain nitrogens are trisubstituted. Four drugs contain a dimethyl side-chain

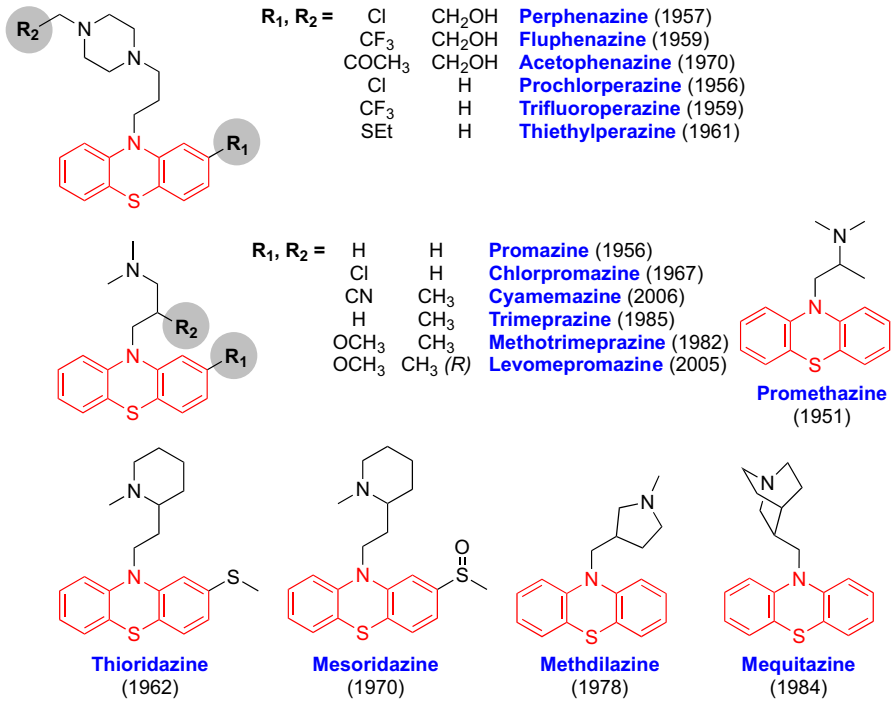

Fig. 15 Drugs containing phenothiazines

nitrogen, six contain a piperazine moiety, and four contain cyclic alkyl nitrogens. Of the latter, methdilazine contains a methyl-pyrrolidine, and mequitazine contains a bridged quinuclidine side chain. Thioridazine and mesoridazine have the same methylpiperidine side chain. Thioridazine and mesoridazine differ only in the oxidation state of the sulfur atom at the R_1 position. They are likely metabolic by-products of one another, and both have been withdrawn from the market because of severe cardiac arrhythmia side effects.

The first synthesis of phenothiazine was published by Bernthsen in 1883 and was found early on to have antiparasitic properties [29]. Phenothiazines were discovered to have antipsychotic properties by chance [30]. Bovet was initially looking for antihistamine activity in benzodioxanes, and did not investigate phenothiazines until the sixth generation of molecules [31]. These structures were investigated for mental illness related indications in the 1950s in France. These drugs were found to have anxiolytic and sedative properties, and to improve symptoms of psychosis [32].

2.7 Sulfoxides

Sulfoxides are unique from other sulfur moieties in this review because the sulfur atom in this oxidation state has a lone pair of electrons that result in a chiral center at the sulfur atom. This class consists of 11 drugs, with four approved entities being

racemic or enantiopure versions of the same two structures. Only three of the 11 sulfoxides are bound to two sp^3 carbons, while the other eight are bound to one sp^3 and one sp^2 carbon (Fig. 16).

Sulfinpyrazone was the first sulfoxide-containing drug to be approved by the FDA. Sulfinpyrazone is structurally similar to phenylbutazone, and both are commonly synthesized using a similar route [33]. The structural difference is that sulfinpyrazone has a terminal phenylsulfoxide. This drug acts as an antiplatelet compound, and the anti-inflammatory effects of phenylbutazone are diminished with the addition of the sulfoxide moiety. This drug undergoes extensive metabolism, in which the sulfur can be either reduced to the thioether or oxidized to the sulfone.

Omeprazole was the first of a series of proton pump inhibitors (PPI) approved for the treatment of GERD, acid reflux disease, and Zollinger–Ellison syndrome [10]. All pre-2017 GERD drugs in this category except esomeprazole are sold as racemic mixtures [34]. Esomeprazole is structurally identical to omeprazole with the exception that it is exclusively in its (*S*)-form; development of a single enantiomer of a racemic drug is known as a chiral switch [35]. Interestingly, the chirality does not lead to a more potent drug: the compounds must first undergo a rearrangement to achieve the active form, which is not chiral. The rearrangement can only occur under acidic conditions, and forms a disulfide bond with a cysteine residue [36, 37]. While esomeprazole is the only enantio-pure PPI on the market, enantio-enriched forms

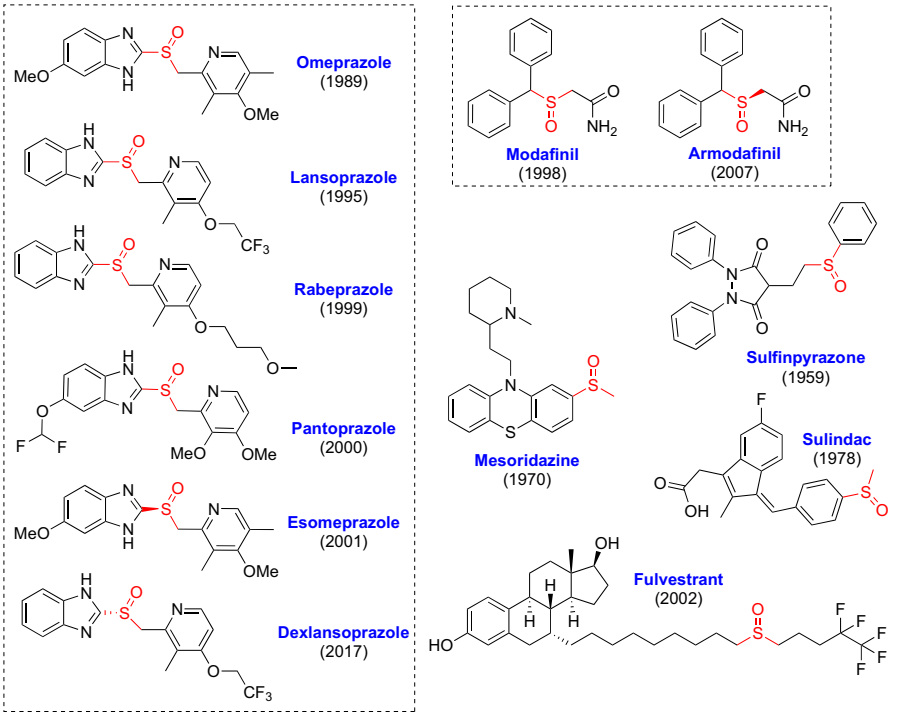

Fig. 16 Sulfoxide containing drugs

of other PPIs have been investigated, and have been found to have some favorable attributes, such as greater bioavailability and better metabolism.

Modafinil and armodafinil are an additional example of a chiral switch, with the latter being the (*R*)-enantiomer of the former, a racemic mixture. The two are weak dopamine reuptake inhibitors used to treat sleep disorders. Both contain a diphenylmethylene group tethered to an ethanamide via a sulfoxide. This structure superimposes nicely onto diphenhydramine, a common ingredient in allergy medications that is also used to treat insomnia, though the latter compound has oxygen instead of a sulfoxide, and no carbonyl.

Although the scope of this review contains the drugs approved through the end of 2016, it is fitting to include dexlansoprazole, which is an enantiopure version of the racemic lansoprazole approved in the second half of 2017. These drugs are unique among the proton pump inhibitors in that they contain a trifluoroethoxy group on the pyridine ring.

Sulindac was discovered when indomethacin analogues were explored as anti-inflammatory agents. First, the indole was changed to an indane, then the methoxy group was replaced with a fluorine atom (which increased potency), and finally, the chlorine atom was replaced with a sulfonyl group, increasing solubility. The isomer with the *Z*-double bond is the more active of the two. The stereocenter at the sulfoxide loses its chirality when it is reduced to a sulfide, so it is sold as a racemic mixture. Fulvestrant is used to treat certain breast cancers. It is unique within this group in that it contains a steroid core derived from 17β-estradiol and contains five fluorine atoms.

2.8 C=S and P=S Structures

This class is made up of ten drugs that contain C=S (thiocarbonyl) bonds. In the five drugs that are nucleobase analogues, the C=S structure acts as a surrogate for the natural C=O analogue (Fig. 17). Seven drugs contain a thiourea, three

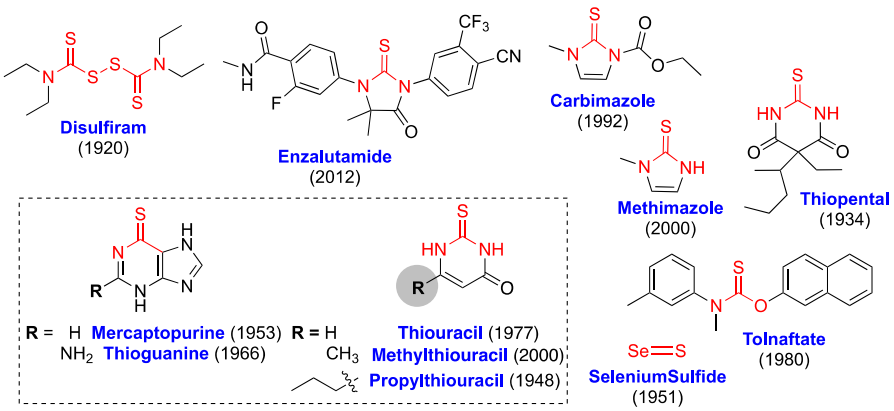

Fig. 17 C=S and Se=S containing drugs

within a five-membered ring and four within a six-membered ring. Disulfiram exists as a carbamodithioate, tolnaftate as an O-substituted carbamothioate, and selenium sulfide as a mixture of compounds. Notably, five of the drugs in this category are analogues of nucleobases in which sulfur has replaced oxygen.

Mercaptopurine and thioguanine are both artificial nucleobase analogues used to treat leukemia. The former works by preventing purine nucleotide biosynthesis and the latter by mistaken incorporation into DNA. Because mistaken incorporation can cause unwanted side effects in non-cancerous cells, mercaptopurine is associated with less risk [38]. Thiouracil, methylthiouracil, and propylthiouracil are also artificial nucleobases, which are also used as antithyroid medications and to treat Grave's disease.

Carbimazole is a prodrug for methimazole, which is used to treat hyperthyroidism. The prodrug contains a carbamate, which is cleaved, leaving the cyclic core in its active form. When carbimazole is ineffective, the structurally similar propylthiouracil is sometimes prescribed in its stead. Both of these drugs work by oxidizing iodide anions to iodine and other species, allowing the iodine to transfer to the protein thyroglobulin [39, 40]. The structural difference between methimazole and propylthiourea is the change from a five- to a six-membered heterocycle, a thioxodihydropyrimidinone, the core structure of thiouracil. These structures are related to thioamides and thioureylenes, and can exist in thioketo or thioenol forms.

Enzalutamide is a thiohydantoin nonsteroidal antiandrogen for the treatment of prostate cancer [41]. It shares structural similarities with other nonsteroidal androgens like flutamide, nilutamide, and bicalutamide. Bicalutamide is the only other sulfur-containing member of these four drugs and is featured in the "Sulfones" section; enzalutamide is unique in its sulfur-containing core.

Disulfiram is a symmetrical dimer of tetraethylthiurams that is used to treat alcoholism by inhibiting acetaldehyde dehydrogenase [42]. This mechanism results in the inability for the natural metabolism of ethanol and results in a general malaise in the case of alcohol consumption. It is the only drug in this group that contains two unique sulfur moieties, and the only drug in this review that contains a carbamodithioic acid (in this case, a dimer).

Tolnaftate is a topical squalene epoxidase inhibitor used to treat fungal infections [43]. The naphthyl moiety is common to all members of this class of drugs, though the central thiocarbamate makes this one unique in containing a sulfur moiety. In addition to fungi, mammals also use squalene oxidase (in the cholesterol biosynthesis pathway). However, the fungal enzymes are sufficiently different that the drugs are selective against the pathogens [44].

Selenium disulfide is the active ingredient in dandruff shampoos, used to treat seborrheic dermatitis and pityriasis versicolor [45]. Selenium disulfide exists as a mixture, and although the structure is statistically nearly one-to-two, the ratio is closer to 1:1.2, depending on the formulation [46]. It is the structurally simplest drug discussed in this review.

2.9 Thionucleotides

Mipomersen (Fig. 18) is a second-generation antisense oligonucleotide used to treat high cholesterol [47]. It works by binding to the mRNA encoding apolipoprotein B-100, which makes up the majority of low-density lipoprotein. This prevents the protein from being transcribed. Mipomersen is distinct from natural antisense nucleotides in that the typical phosphodiester linkages have been replaced with phosphorothioate groups, which help to prevent cleavage by nucleases. Additionally, the nucleobases are unnatural analogues of the natural nucleobases.

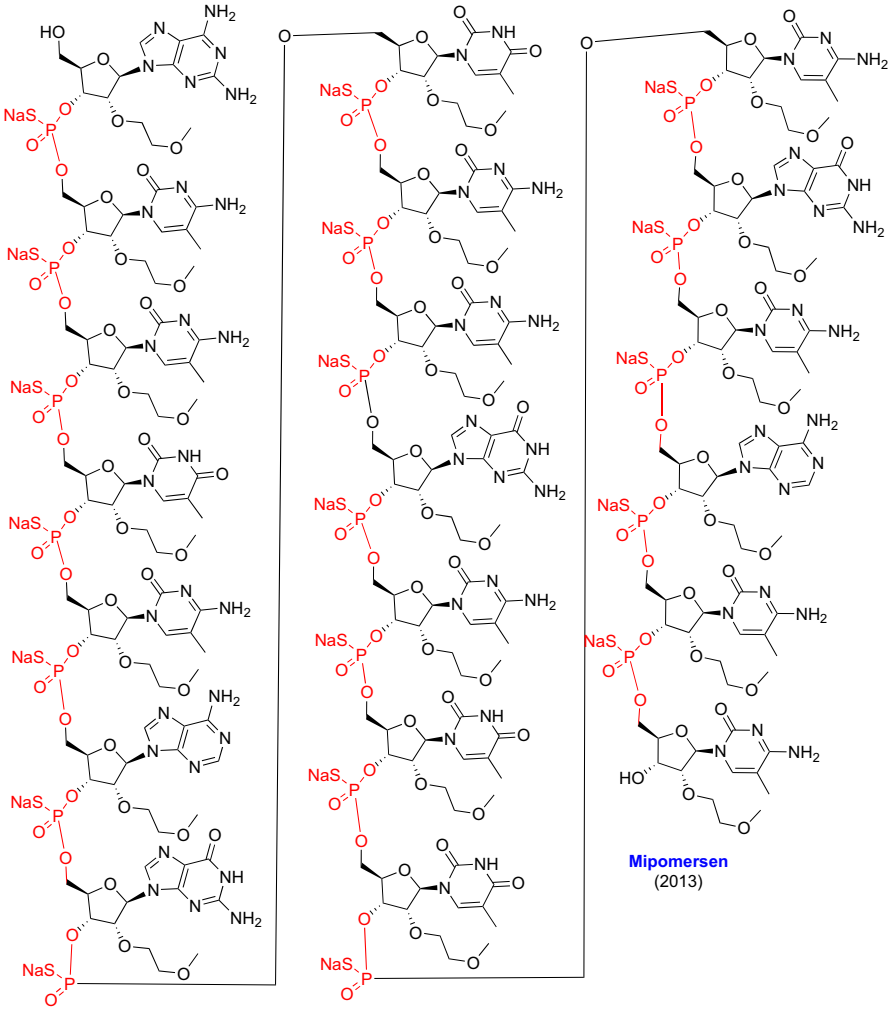

Fig. 18 Mipomersen contains multiple P–SNa groups

Nusinersen (Fig. 19) uses the same phosphorothioate approach as mipomersen, and became the first drug to treat spinal muscular atrophy in 2016 [48]. It works by changing the splicing in the survival motor neuron 2 (SMN2) gene into the survival motor neuron 1 (SMN1) gene, which is mutated in spinal muscular atrophy patients

2.10 Sulfones

Sulfones are structurally comprised of a sulfonyl group bonded to two carbon groups. The group of sulfone-containing compounds consists of eight drugs, for all of which the sulfone is the only sulfur-containing moiety. Sulfones are similar to

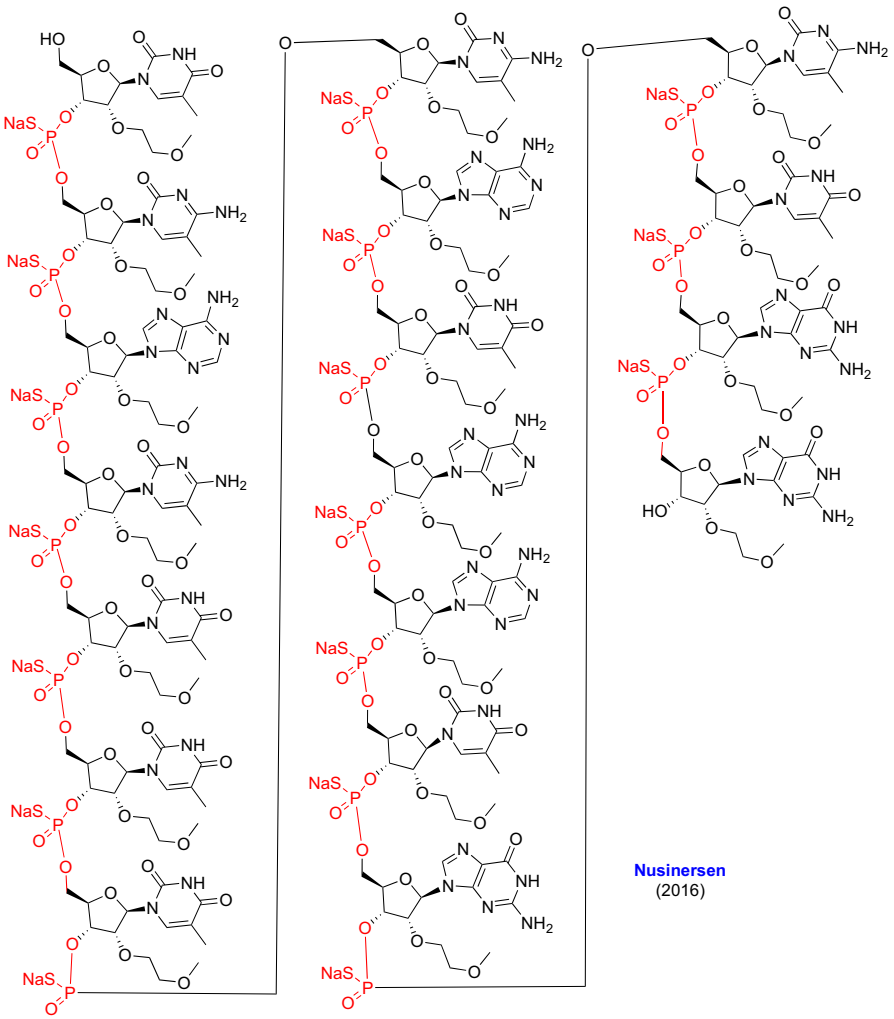

Fig. 19 Nusinersen contains multiple P–SNa groups

thioethers in that they contain two S–C bonds. Six of the sulfones are connected to one sp^3 and one sp^2 carbon, and the other two are connected to two sp^3 carbons (Fig. 20).

Chlormezanone contains a cyclic sulfone that is part of a six-membered nitrogen heterocycle and is used as an anxiolytic and muscle relaxant [49]. It is the only cyclic member of the sulfones, and at first glance, has some similarity to the oxicams and with carbonic anhydrase inhibitors like dorzolamide.

Eletriptan is a second-generation triptan that is used to treat migraines [50]. It acts as a serotonin receptor agonist and is taken after the onset of a migraine, rather than prophylactically. Other triptans were discussed with the sulfonamide drugs, though the sulfone moiety here is unrelated, serving as a linker between the triptan core and a phenyl group. Four of the remaining six drugs have the sulfur atom bonded to one sp^2 and one sp^3 carbon, and the other two to two sp^3 carbons.

2.11 Sulfates

The sulfate moiety is characterized by an $ROSO_3^-$ group, in which R is an alkyl group. Of the 11 drugs in this group, nine contain sp^3 carbon centers as the R group, one has an sp^2 carbon center, and magnesium sulfate has no carbon atoms at all (Fig. 21).

The first six drugs in this group are linear polysaccharides, and are all used as blood thinners. The sulfate moieties make these drugs highly water soluble. Enoxaparin, dalteparin, and tinzaparin are low molecular weight heparin derivatives, and fondaparinux is closely related to these. Fondaparinux is unique from the other polysaccharides in that, at five subunits, it is relatively small. Additionally, fondaparinux has non-traditional linkages between subunits. These drugs are based on heparan sulfate, which is found in animal tissues, and are used to prevent blood clots [51]. These analogues of natural heparan sulfate are resistant to hydrolysis by heparanase.

Sucralfate, as the name hints at, is a sulfated sucrose with aluminum moieties complexed with the sulfate groups. This is a unique drug within this review in that

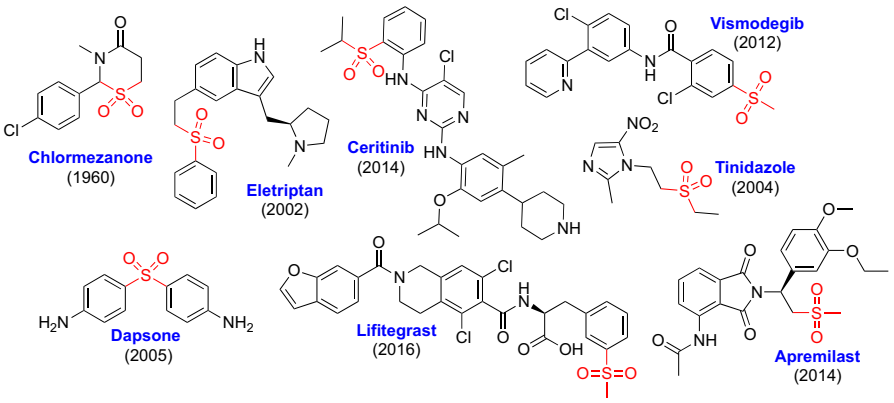

Fig. 20 Sulfone-containing drugs

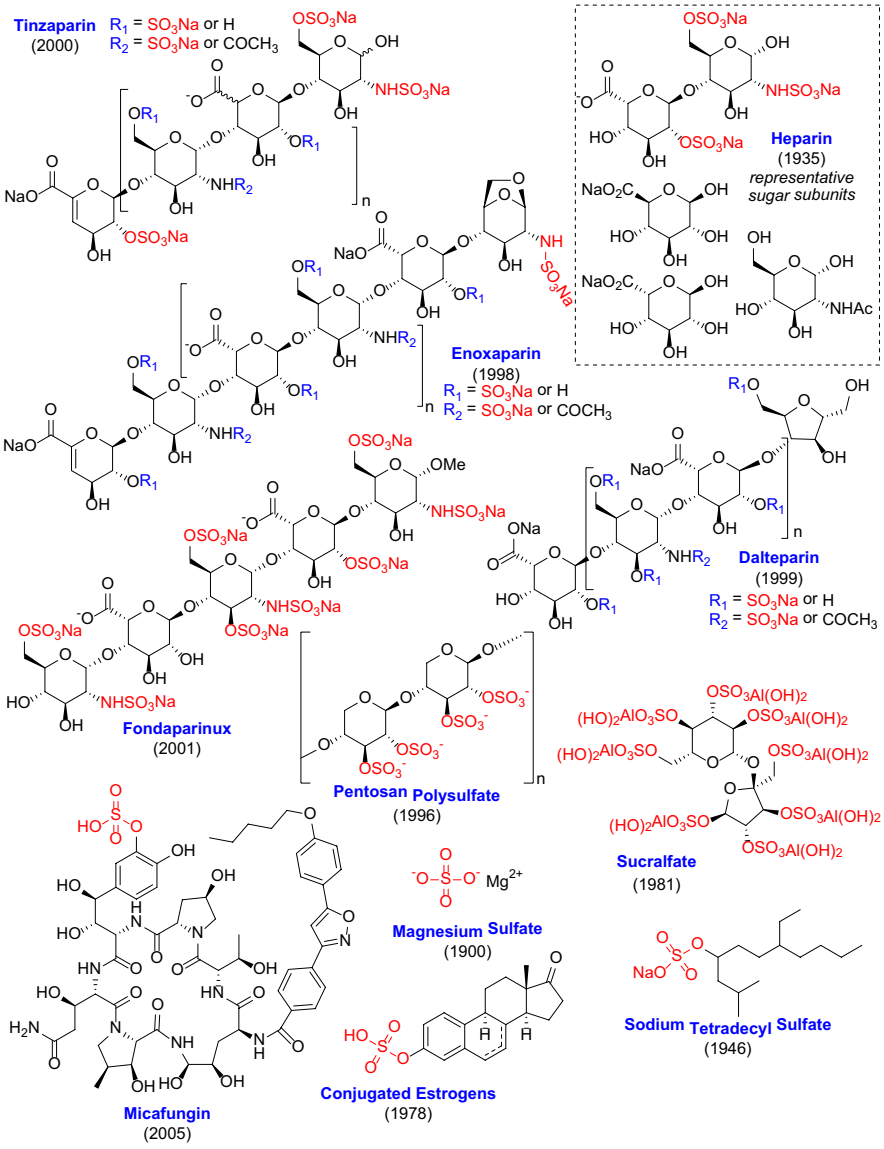

Fig. 21 Sulfate-containing drugs

it contains aluminum. It is used to treat GERD. Another unique drug in this section is sodium tetradecylsulfate. As might be expected by visual inspection of the structure, sodium tetradecylsulfate is a surfactant, and is used in the treatment of varicose veins.

Magnesium sulfate is the earliest FDA-approved drug within this review (approved in 1900), and for this reason, the sulfates span the largest timeframe in

terms of FDA approvals, with the antifungal micafungin having been approved in 2005. Curiously, the last 10 years have not seen the approval of any non-biological sulfate-containing drugs.

2.12 Macrocyclic Disulfides

The first four of the macrocyclic disulfides are either natural hormones, in the cases of vasopressin and oxytocin, or derivatives thereof, in the cases of urofollitropin and desmopressin. Romidepsin and lanreotide are synthetic cyclic peptides that also both contain disulfide bonds, with the former being a bridged compound. While these drugs could be considered biological drugs, the author feels that the nature of the latter drugs and their relative structural simplicity warrant their discussion here.

Desmopressin and urofollitropin are synthetic analogues of the human antidiuretic hormone, or vasopressin, which is similar to oxytocin. Desmopressin is only different from vasopressin in that the arginine on the 8-position in its D-form (as opposed to the natural L-form), and is missing the amine at the R_2 position (Fig. 22). When the amine is absent, the half-life of the drug is increased. These structures are highly similar but they are used to treat different ailments. Oxytocin is used to induce contractions during labor, and can help to control bleeding. Urofollitropin is used to help with ovulation and fertility. Vasopressin and desmopressin are both antidiuretic drugs.

Romidepsin is a natural product isolated from the bacterium *Chromobacterium violaceum*, and is used as a cancer treatment [52]. In 1994, Li and coworkers synthesized this cyclic peptide, which harbors an impressive 15-member disulfide ring [53]. Lanreotide is also a disulfide-containing synthetic peptide used to treat acromegaly and neuroendocrine tumor symptoms [54].

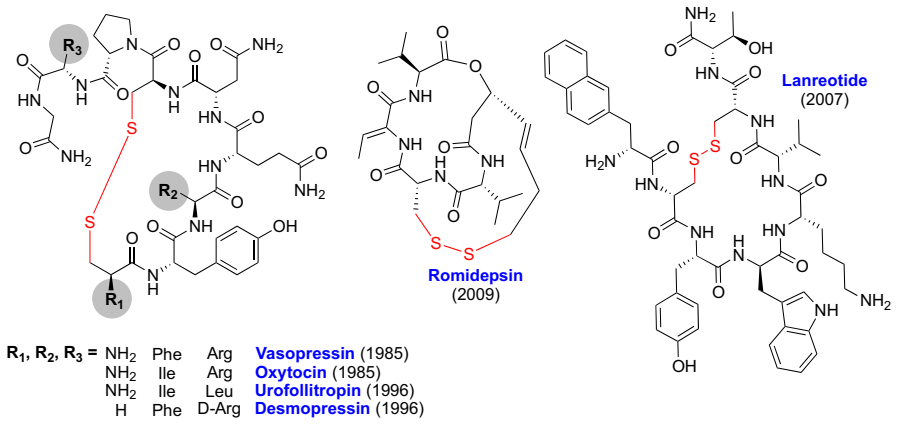

Fig. 22 Macrocyclic disulfide-containing drugs

2.13 Miscellaneous Acyclic Sulfur Functional Groups

This section addresses the acyclic functional groups that do not fit into any other category. This category contains 14 drugs that include two organosulfonates, one thiophosphate, one thiol, two sulfuric diamides, one trialkyl sulfonium, two thioesters, one carbamodithioic acid dimer, and sulfur hexafluoride (Fig. 23).

Acamprosate is a simple three-carbon chain with an acylated amine at one terminus and a sulfonate moiety at the other. It is used to treat alcohol dependence, especially effects associated with alcohol withdrawal [55]. Bleomycin is a complex natural product that was first isolated from *Streptomyces verticillus* in 1962 and was synthesized by Aoyagi and coworkers 20 years later [56]. Structurally it contains elements of peptides, saccharides, and polyketides. These features make it, arguably, the most diverse structure within this review. Bleomycin contains two types of sulfur moiety: two thiazoles (discussed previously) and a constitutively charged trialkyl sulfonium. It is used to treat several types of cancer by inducing DNA strand breaks [57].

Four of the drugs in this section consist of simple alkyl chains with sulfur moieties at the end. Amifostine is an organic thiophosphate prodrug that undergoes dephosphorylation to make the active aminothiol in vivo. It is used to reduce neutrophenia-related fever that can be caused by certain types of chemotherapeutics and

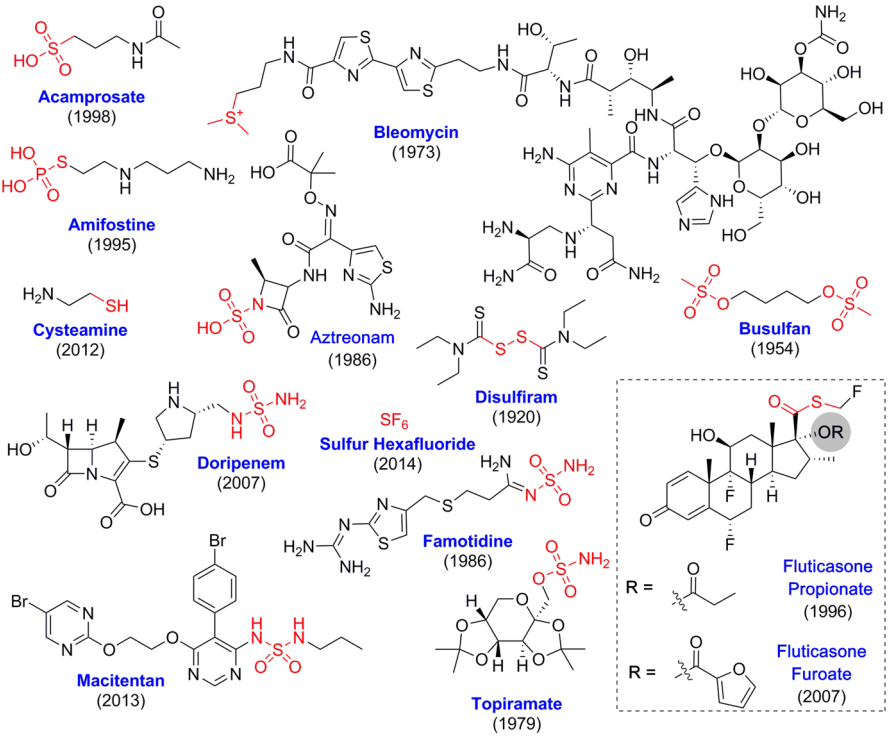

Fig. 23 Miscellaneous acyclic sulfur-containing drugs

radiotherapy during cancer treatment [58]. Cystamine is a three-carbon aminothiol that is used to treat cystinosis, which occurs when the amino acid cysteine builds up in lysosomes [59]. It is produced biosynthetically by mammals by breaking down coenzyme A.

Aztreonam is a drug that was briefly covered in the thiazole section, though its monobactam moiety is more characteristic of this drug's classification. Monocyclic β-lactam antibiotics were discovered via chemical modification of natural products isolated from the fermentation of unconventional bacteria [60]. Aztreonam is a synthetic drug that came out of these studies, and is used to treat Gram-negative bacterial infections. Perhaps as a result of some structural similarity to the more typical β-lactam antibiotics, aztreonam is able to inhibit some β-lactamases, the enzymes responsible for conferring antibiotic resistance against the class. The methyl group in the C-2 position aids in β-lactamase inhibition. Not surprisingly, its mode of action is similar to that of the typical β-lactams, through inhibition of penicillin-binding protein 3 (PBP-3). Hydrolysis of the lactam ring is faster than in β-lactam antibiotics as a result of the strongly electron-withdrawing sulfamide group.

Sulfur hexafluoride is an interesting entity within this review for its simplicity and for its use. It is used in eye surgery as a gas bubble to plug a hole during retinal detachment. It is eventually absorbed into the blood [61]. Its inert properties within the eye make it an ideal choice for this procedure.

The remaining drugs in this group are varied. Acamprosate, amifostine, cysteamine, and busulfan are simple linear chains with varying sulfur moieties at the termini. Topiramate is an anticonvulsant that consists of a sugar derivative with two acetonides and a terminal sulfamate. Fluticasone has been approved as two different esters of the same steroid backbone: the propionate and the furoate. Macitentan is an endothelin receptor antagonist that contains a propyl sulfuric diamide, which is dealkylated to give its active form [62].

2.14 Miscellaneous Cyclic Sulfur Functional Groups

Cyclic sulfur-containing drugs that do not fit into other categories have approval dates that span from 1953 to 2013, and are showcased in Fig. 24. This category contains 17 drugs with 13 unique sulfur moieties. Some of these include non-traditional benzothiazole and thiazole moieties that did not fit into the appropriate previous sections.

Lamivudine and emtricitabine are structurally similar antiretroviral drugs used to treat HIV infection. They differ only by the substitution on the aminopyrimidinone, with a fluorine and an amine, respectively. Both drugs contain a substituted, stereogenic oxathiolane moiety, which is used as an unnatural sulfur-containing analogue of the ribose normally found in nucleobases [63].

Ziprasidone and lurasidone are atypical antipsychotic drugs belonging to the benzothiazole family. Along with the older typical antipsychotics, they are used to treat schizophrenia [64].

Pioglitazone and rosiglitazone share a core, as the comprising members of thiazolidinedione hypoglycemic used to treat diabetes. Ciglitazone is the prototype for

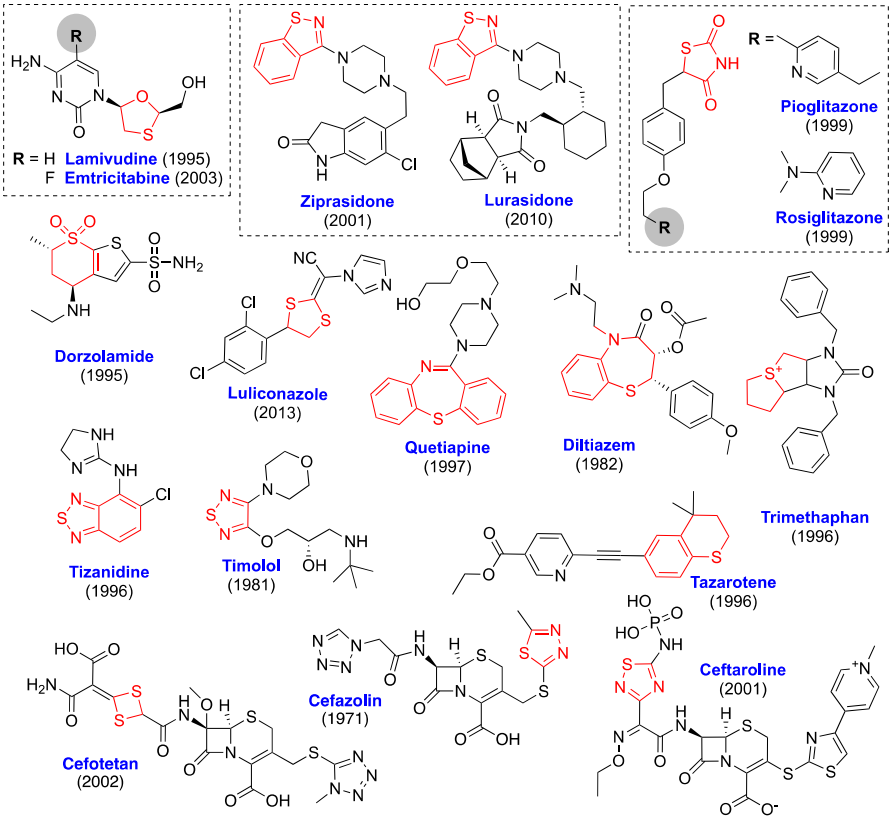

Fig. 24 Miscellaneous cyclic sulfur-containing drugs

this family of drugs, although it was never approved by the FDA [65]. These drugs are a considerable departure from the sulfonylureas addressed in the beginning of the review, which served as the early antidiabetic drugs.

Quetiapine and diltiazem are both benzothiazepine structures. The former contains an N=C bond within the ring while the latter contains a single bond at that position. These are notable because they are the only approved drugs that contain sulfur within a seven-membered heterocycle. Quetiapine is an atypical antipsychotic and diltiazem is a calcium-channel blocker used to treat hypertension. Diltiazem is also notable for the two stereocenters on the thiazepine ring.

Timolol and tinazidine are structurally similar in that they both have a thiadiazole moiety. The former is used to treat high intraocular pressure, and the latter is a muscle relaxant used to treat spasms [66, 67]. These structures are unique in that these are the only ones to have sulfur, in this oxidation state, bound to two nitrogen atoms. Trimethaphan contains two fused five-membered rings with a sulfonium at the bridgehead, which bears a constitutive positive charge. Because of its permanent charge, it cannot cross lipid bilayers, but the drug is used as a

ganglionic blocker and given to treat hypertension in emergencies. Although this is the second trialkyl-sulfonium we have seen, this one is unique in the positioning of the sulfur between two rings. Three cephems in this category have unique structures that land them in this group. Cefazolin and ceftaroline have 1,3,4- and 1,2,4-thiadiazole moieties, respectively, but with different substitution patterns. Cefotetan is the most recently approved cephem drug, and contains an interesting four-membered heterocycle containing two sulfur atoms: a dithietane.

3 US FDA Drugs Containing Multiple Sulfur Atoms

Of the 249 unique structures reviewed in this review, only 68 have more than one sulfur atom. Forty-six drugs contain two sulfur atoms, nine drugs contain three sulfur atoms, and three drugs contain four sulfur atoms (Fig. 25). Only three drugs contain eight, one contains 17, one contains 19, and five contain more than 20 sulfur atoms.

4 Presence of Sulfur Atoms in Combination Drugs

Sulfur-containing small molecules are found in more than 70 approved combination drugs (Fig. 26). Several drugs appear in multiple combination therapies. Therefore, the diversity of sulfur moieties within the combination drugs dataset is not as extensive as the entire sulfur drug dataset. The most commonly used sulfur-containing structures found in combination drugs are shown in the scheme below.

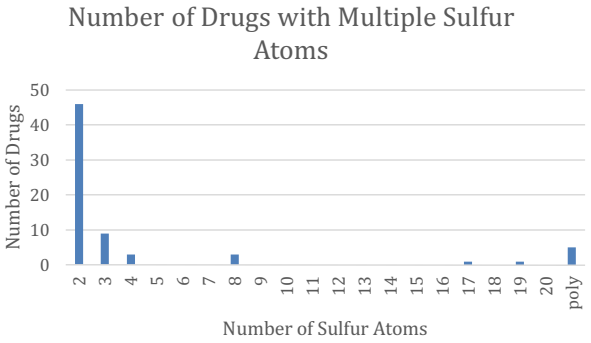

Fig. 25 Distribution and number of drugs containing more than one sulfur atom

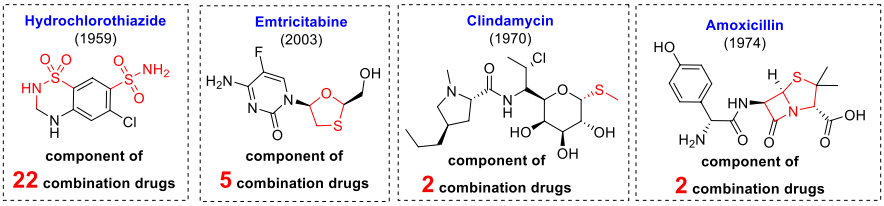

Fig. 26 Examples of sulfur-containing drugs approved by the FDA for use in combination therapies

5 Conclusion

To date in 2017, a total of 23 unique sulfur-containing structures were approved by the FDA, with only one of these structures being novel (the others have been approved before and appear in this review). The novel structure is dexlansoprazole, a proton pump inhibitor, and is the enantiopure (or chiral switch) form of lansoprazole. This overview of the sulfur-containing drugs approved from 1900 to 2016 attests to the importance of the sulfur atom in modern medicine. Sulfur is a versatile element that exists in many unique forms, in 14 different categories including five different oxidation states. The graphical analyses of these drugs present a unique opportunity to visually analyze which sulfur-containing moieties are important on the basis of their frequency, as well as to gain an overview of the evolution of drug design.

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