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Metalloids: Semi as Metals yet Full of Antimicrobial Potential

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ABSTRACT

In the periodic table, the metalloids boron (B), silicon (Si), germanium (Ge), arsenic (As), antimony (Sb), and tellurium (Te) demarcate a borderline between the metals and non-metals. Also referred to as semi-metals, their behaviour is indeed characterized by inorganic ions, organometallic complexes, and covalent compounds. Yet despite this unique medley of inorganic and organic molecules, reactivities and activities, and century-old traditional uses, their pharmaceutical applications today are often underestimated or associated with outright toxicity. Still, recent research has taken a closer look at (some of) these elements and has encountered an amazing assortment of natural metalloid-containing products, many with distinct antimicrobial activities. At the same time, metalloid-containing complexes have been synthesized and tested successfully as ionophores, in ligand-exchange reactions with amino acids, such as cysteine, or as redox modulators triggering oxidative stress. This has been complemented by an extensive synthesis of organic metalloid-based compounds, even including bioisosteric replacements for carbon. Today, a few metalloid compounds are still or already used in therapy; others are in clinical trials, and many more are in the pipeline, clearly demanding full attention for the semi-metals and their many colourful compounds.

1 | Introduction

The sharp increase in antimicrobial resistance represents one of the most urgent pharmaceutical challenges of our time and necessitates the search for novel antimicrobial substances [1–3]. In the course of this search, a closer look should also be taken at elements that are currently rather neglected in drug development, such as the metalloids, a couple of main group *p*-block elements nested in the periodic table between the metals and the non-metals.

Indeed, the metalloids, or as they are sometimes called ‘semi-metals’, represent a very special group of elements in the periodic table and commonly include boron (B), silicon (Si), germanium (Ge), arsenic (As), antimony (Sb), and tellurium (Te). Together, they form a diagonal borderline between the metals to their left and non-metals to their right. Bismuth (Bi), polonium (Po), and astatine (At) are also sometimes included, as they would be the

logical followers in row 6 of the periodic table, yet these elements are de facto very metallic rather than semi-metallic, and in any case, with the possible exception of bismuth, play a very minor role in chemistry and the life sciences. As semi- or ‘half’-metals, and not to be confused with the *d*-block transition metals, the classic metalloids indeed exhibit various properties usually associated with metals, including a metallic appearance in some of their elemental modifications and the ability to form alloys, yet also share some of the typical non-metallic features, such as forming covalent bonds with carbon, nitrogen, oxygen, sulfur, and other elements [4, 5]. Other properties such as conducting heat and electricity, electronic band structure, ionization energy, and electronegativity fall between the metals and non-metals [4, 6]. Therefore, it is not unusual to find these elements at the centre of some typical inorganic chemistry, for instance as charged ions or in complexes, yet also in quite stable covalent organic – or shall we say *organometallic* – compounds.

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Intriguingly, these elements and their compounds have also found their ways into the life sciences not only as poisons but also as traditional medicines. The activities of some of them, such as the ones based on arsenic, are legendary and indeed such metalloid preparations have been used in medicine for thousands of years across the globe and still are today. Others, such as germanium, are more exotic yet still worth considering.

In this review, we shall therefore briefly explore the potential and current uses of metalloids in Medicine, with a focus on the antimicrobial activities associated with these elements and their various compounds. Apart from looking at more traditional applications of elements such as arsenic, boron, and antimony, we shall explore the specific molecular mechanisms and biochemical mode(s) of action associated with such metalloid molecules. Eventually, we shall try to answer the question if there is anything 'special' in the chemistry of semi-metals which may endow their compounds with specific properties, reactivities, and activities possibly not found in the case of 'real' metals or non-metals.

2 | Boron: Everything but Boring

In the periodic table, the first metalloid encountered is boron, the fifth element, located in the second row and framed between the distinctively metallic beryllium (Be) on the one side and carbon (C) on the other. As expected for such a semi-metal, boron shows metallic as well as non-metallic properties. On the one side, it forms ions (in oxidation state +3) and complexes, yet also various covalent compounds, for instance with carbon. Thanks to its electronegativity of 2.04, such organic boron compounds tend to be fairly stable. Since boron only has three valence electrons, reaching a full shell octet in covalent compounds tends to be tricky, and very unusual chemical structures such as three-centre two-electron systems, are not uncommon. From a purely chemical perspective, such exotic molecules may indeed drive you 'bananas', yet fortunately they do not play any notable role in Biology.

In Nature, boron occurs in its ionic B^{3+} form, usually as boric acid $B(OH)_3$ or esters of borate $[B(OH)_4]^-$. Boric acid has historically been used as an antiseptic, with its antiseptic properties largely due to its acidity [7]. Because of its toxicity, predominantly in infants, its application as an antiseptic has been discontinued [8]. Unlike typical oxoanions, such as phosphate (PO_4^{3-}), borate $[B(OH)_4]^-$ behaves more like a metal complex and does, for instance, readily exchange HO^- ligands for other organic or inorganic ligand anions, as we shall see in the case of boromycin and other natural boron-containing molecules.

Thanks to the complex chemistry of borate, natural boron compounds are not that uncommon either, and the first boron-containing natural product found by Huetter and coworkers in 1967, namely boromycin, even happens to be an antibiotic [9]. Boromycin (**1**; Figure 1) is a polyether-macrolide produced by *Streptomyces antibioticus* and shows antibiotic effects against Gram-positive bacteria, activity against HIV, and protozoan parasites [14]. Mechanistically, boromycin acts as an ionophore which causes the loss of potassium ions, resulting in cell cycle arrest and eventually cell death. The boric acid moiety appears to be essential for binding the ions, while a loss of the D-valine moiety does not affect the activity [10, 15]. Since the discovery of boromycin, other boron-containing ionophores have been

isolated from several soil bacteria, such as aplasmomycin (**2**) from *S. griseus* SS-20 and tartrolon B (**3**) from the cellulose-degrading myxobacterium, *Sorangium cellulosum* [16, 17]. Another recently discovered example of the boron-containing antibiotics of the tartrolon class is tartrolon E (**4**), produced by the symbiotic cellulose-degrading bacteria, *Teredinibacter turnerae*, which can be found in the gills of marine shipworms. Tartrolon E (**4**) shows antibacterial activity against *Pseudomonas aeruginosa* and methicillin-sensitive and methicillin-resistant *S. aureus* (MRSA) [18]. The mechanism underlying antimicrobial activities of tartrolon E still needs to be investigated further, although one may assume that it also acts as an ionophore [19]. It is worth noting that resistance already exists against such naturally occurring antibiotics. For example, Rolf Müller and colleagues were able to show that *Listeria monocytogenes* possesses an ATP-binding cassette-type multidrug resistance transporter, named TimAB which contributes to the resistance against tartrolon antibiotics [17].

Notably, these natural boron-containing antibiotics are based on esters of boronic acid, and the ensuing tetravalent boron complexes with oxygen-based ligands may therefore be considered as representatives of the inorganic side of this semi-metal. Employing organic synthesis, more eloquent compounds with classical covalent boron-carbon bonds and covalent boronic acid esters are possible and have been explored extensively. The antimicrobial compounds shown in Figure 2 represent such aromatic derivatives of boronic acid with a covalent boron-carbon bond. Some of them possess a free boronic acid moiety, while others are (cyclic) esters of boronic acid. There are, for instance, several boron-containing compounds specifically designed to tackle antibiotic resistance. One example is provided by the boronic acid-based class C β -lactamase inhibitors, which was designed by Waley and his coworkers at Oxford in 1983 [20]. Boronic acid-based β -lactamase inhibitors mimic the β -lactam structure and can inhibit β -lactamases by covalently binding to the active site serine and/or coordinating the zinc of zinc-dependent metallo- β -lactamases (Figure 2). This chemistry, in essence, represents a ligand exchange reaction at the boron atom whereby the HO^- ligand is replaced by a serine (Figure 2b). Thus, unlike in the natural ionophores based on boronic esters, the boron atom in these aromatic boronic acid derivatives is not just structurally yet actively involved in the inhibitory action. The combination of suitable β -lactamase inhibitors with β -lactam antibiotics is one of the most successful methods to address β -lactamase-mediated drug resistance [21]. To this day, vaborbactam **5** is the only FDA-approved boron-containing β -lactamase inhibitor which has been developed in 2015 by Hecker et al. at *Rempex Pharmaceuticals Inc.* [22, 23]. While most β -lactamase inhibitors only inhibit small sets of β -lactamases, vaborbactam has been developed to serve as a broad-spectrum inhibitor with specific potency against *Klebsiella pneumoniae* carbapenemase, a class of enzymes capable of inactivating nearly all β -lactams [24]. Notably, a combination of meropenem and vaborbactam has been approved by the FDA in 2017 for the treatment of patients with complicated urinary tract infections [23].

Since vaborbactam lacks the ability to inhibit metallo- β -lactamases, Hecker et al. reported the synthesis of QPX7728 (**6**), this time at *QPex Biopharma Inc.* in 2020, which inhibits a broad spectrum of β -lactamases, including metallo- β -lactamases [25, 26]. Paired with approved β -lactam antibiotics,

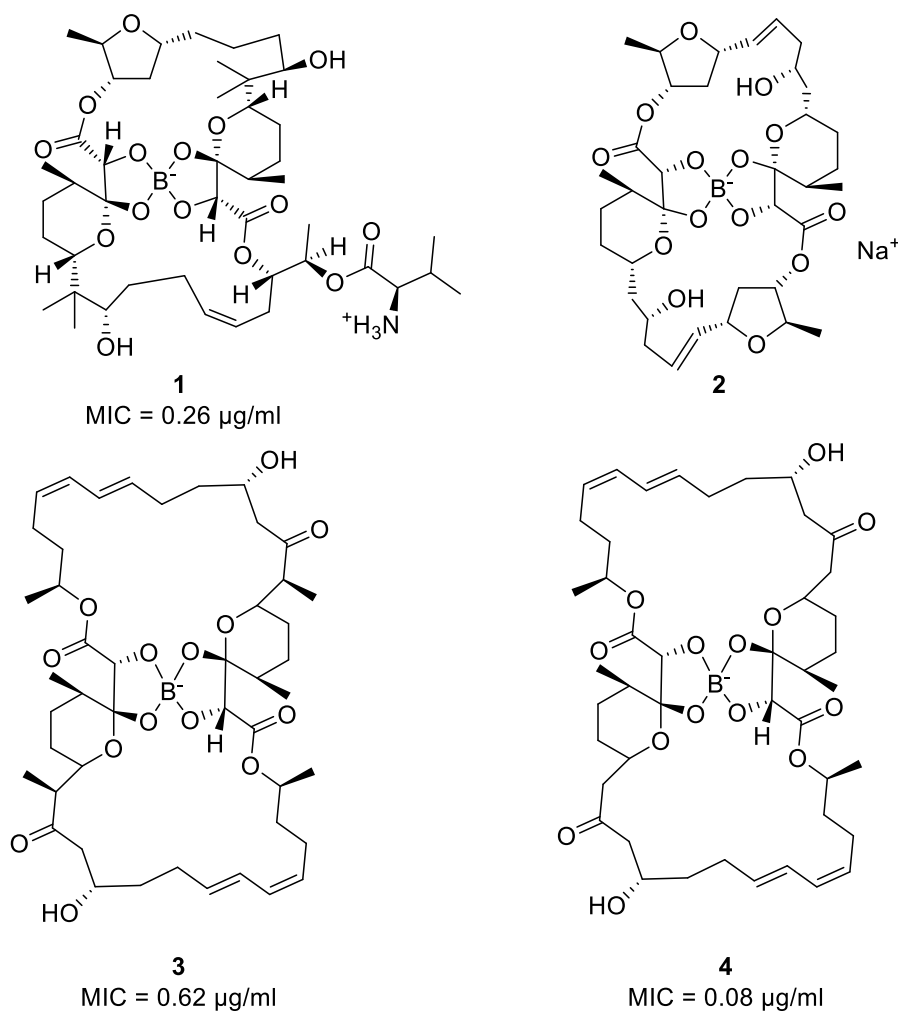


FIGURE 1 | Structures of boromycin (**1**), aplasmomycin (**2**), tartrolon B (**3**), and tartrolon E (**4**) and corresponding MIC values against methicillin susceptible *S. aureus*. For compound **2**, no MIC is reported. Nafcillin, as a first-line treatment for severe infections caused by methicillin-sensitive *S. aureus*, provided a MIC value of 0.5 $\mu\text{g/ml}$ [10–13].

QPX7728 is currently in Phase I trials for the combinational treatment of serious infections induced by Gram-negative pathogens [27]. At around the same time, Taniborbactam (**7**) has been developed by VenatoRx Pharmaceuticals bearing a similar scaffold as QPX7728. Taniborbactam (**7**) is the first pan-spectrum β -lactamase inhibitor which entered clinical trials and has successfully completed the Phase III clinical trial in combination with cefepime for the treatment of complicated urinary tract infections [26]. Intriguingly, the cefepime–taniborbactam combination has shown better antimicrobial activity compared to meropenem in the treatment of complicated urinary tract infections with acute pyelonephritis while exhibiting a similar safety profile as that of meropenem [28].

Benzoxaboroles form another subclass of aromatic boronic acid derivatives, which consists of compounds featuring a six-membered aromatic ring fused to a five-membered oxaborole ring. Members of Benzoxaboroles class generally exhibit a variety of biologically relevant activities including anti-fungal, anti-inflammatory, anti-malarial, anti-trypanosomal, ectoparasiticide, anticancer, and antibiotic activities, and there are even commercial ‘tool boxes’ available for benzoxaborole-based drug design [29]. These molecules exhibit prominent antimicrobial

activities against Gram-negative bacteria by inhibiting the editing site of the Leucyl-tRNA synthetase (LeuRS) enzyme which belongs to the aminoacyl-tRNA synthetases (aaRSs). In these pathogens, aaRSs provide raw materials for protein synthesis at the ribosome by catalyzing the covalent binding of amino acids to their corresponding tRNA. In essence, aaRSs are crucial for the survival of the pathogen and present a low rate of drug resistance. Some aaRSs are also structurally distinct from their eukaryotic equivalents, making them excellent drug targets. Mechanistically, benzoxaboroles form an adduct with the ribose 2' and 3'-OH groups of the terminal tRNA^{Leu} adenosine, thereby trapping the tRNA in the editing site of LeuRS (Scheme 1) [21, 30].

Palencia et al. developed a series of 20 benzoxaboroles based on the lead structure AN2679 (**8**; Figure 3) as LeuRS inhibitors [31]. The compounds presented decent biochemical potency as well as excellent whole-cell activity against *Mycobacterium tuberculosis*. The compounds also exhibited good oral bioavailability which led to the in vivo efficacy not only in acute but also in chronic mouse models of TB. Interestingly, the potency of these benzoxaboroles was comparable to isoniazid, the drug of choice. Epetraborole (**9**; GSK2251052) is another example of

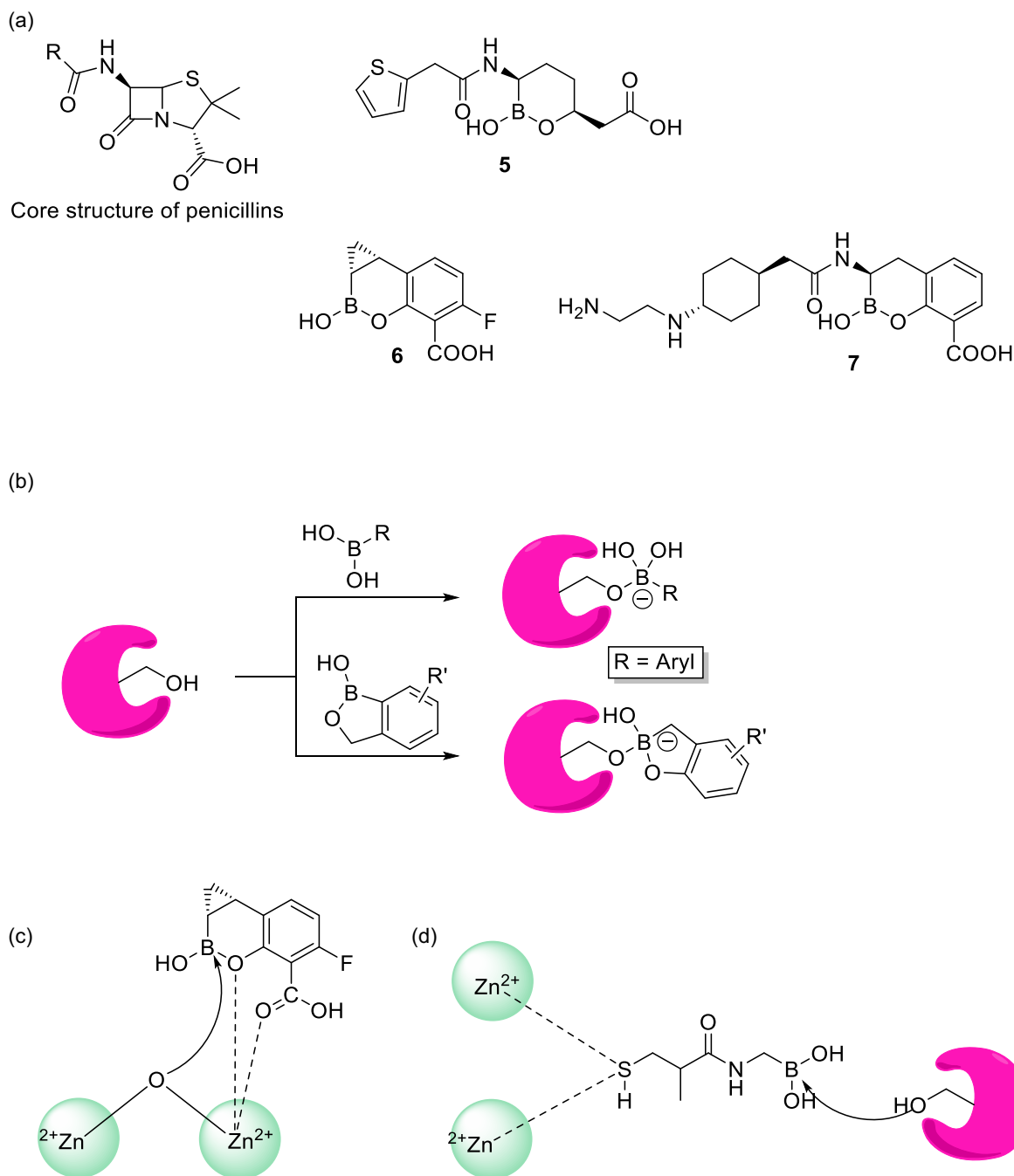
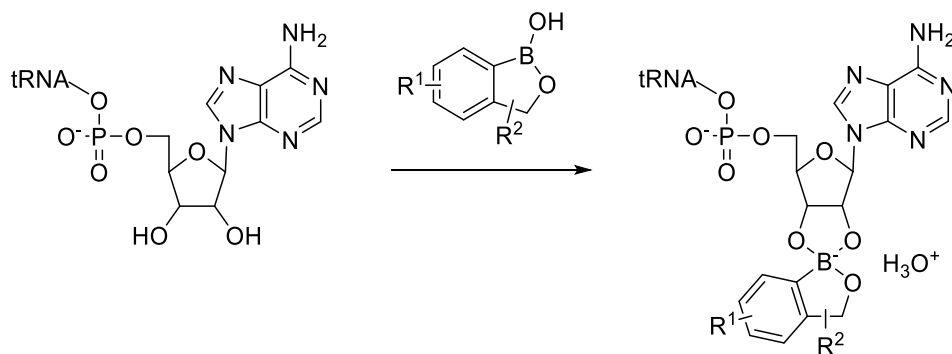


FIGURE 2 | Chemical structures of β -lactamase inhibitors and different mechanisms of β -lactamase inhibition. (a) Structures of vaborbactam (5), QPX7728 (6), taniborbactam (7) and core structure of penicillins. (b) Inhibitors binding at the active site. (c) Inhibitors coordinating zinc. (d) Inhibitors employing both modes of action.

benzoxaboroles which inhibits LeuRS function ($IC_{50} = 0.31 \mu\text{mol/l}$) by binding to the 3'-terminus of tRNA^{Leu} located in the editing active site of LeuRS to form a tetrahedral complex and ultimately leading to bactericidal activity [30, 32]. Epetraborole could not find its way in clinical application due to emergence of microbial resistance in Phase II clinical trial for the treatment of complicated urinary tract infections and inner-abdominal infections [33]. Currently, ganfeborole (10; GSK3036656) has reached in Phase II clinical trials for the treatment of tuberculosis [33]. DS86760016 (11) is another promising LeuRS inhibitor which exhibits good activity against extended-spectrum drug-resistant *P. aeruginosa* and other multidrug-resistant Gram-negative

bacteria (e.g., *E. coli*, *K. pneumoniae*) and found its way in preclinical trials [34]. Zhou and coworkers have also screened benzoxaborole analogues for their activity against LeuRS in *S. pneumoniae* and identified compounds 12 and 13 bearing thiol moiety with promising activity [35]. Although no antibacterial benzoxaborole has reached the milestone of getting the status of an approved drug yet, the anti-fungal benzoxaborole tavaborole (14) is approved for the treatment of onychomycosis, where it also acts as a LeuRS inhibitor [21].

Another approach to tackle drug resistance involves the inhibition of the NorA efflux pump, a factor responsible for antibiotic



SCHEME 1 | Mechanism of benzoxaborole tRNA-binding.

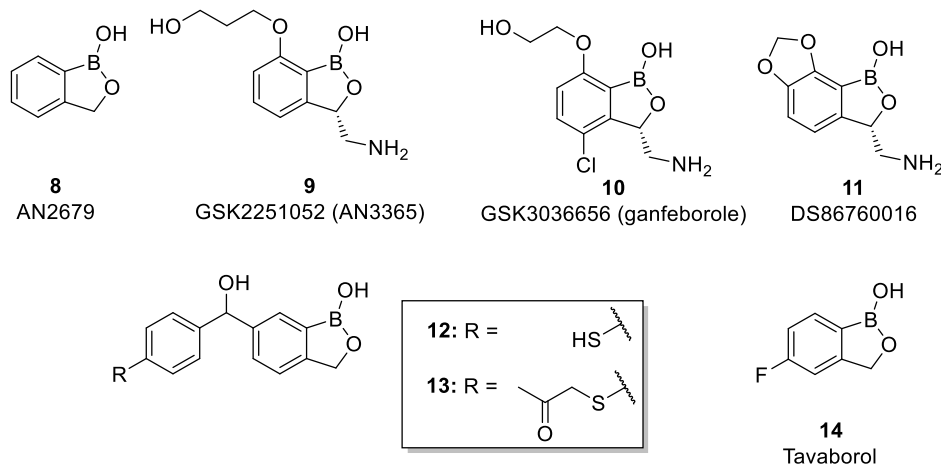


FIGURE 3 | Structures of benzoxaboroles 8–14.

resistance in MRSA. Here again, we find boronic acid derivatives playing a crucial role (Figure 4). These compounds are able to restore the activity of ciprofloxacin and inhibit the resistant *S. aureus* 1199B strain with a minimum modulatory concentration between 0.5 and 128 $\mu\text{g/ml}$. Boron is crucial for anti-resistance activity, with pyridine-3-boronic compounds showing the best activity [36, 37]. The exact mechanism of inhibition has not yet been unveiled, but an interaction with a serine or threonine residue, as in the case of β -lactamase inhibitors, is quite likely.

A recent strategy to combat bacterial infections involves the utilization of boron clusters, such as carboranes or metallocarboranes, which inhibit the growth of various microbes such as *S. aureus* and *M. tuberculosis* [38, 39]. Boron clusters exhibit diverse morphologies, and consequently, a variety of mechanisms which contribute to an overall excellent antimicrobial activity. Boron clusters, for instance, can disrupt the cell membrane due to their hydrophobic surface. Some other boron clusters, on the other hand, can pass through the cell membrane

without disrupting it and inhibit target enzymes via linked organic residues [40]. Furthermore, boron clusters are biologically inert, making it difficult for microbial defence mechanisms to develop resistance [41]. The diverse chemistry of boron clusters is beyond the scope of this review and has been recently reviewed in detail by Fink et al. and Price et al. [40, 41].

Zhang et al. have employed a rather interesting approach by constructing a covalent organic framework (COF) based on benzene diboronic acid, which acts as a photocatalyst to promote the release of ROS. The boron-based COF serves as multifunctional photocatalyst and effectively kills *E. coli* and *S. aureus* under white light irradiation without exhibiting cytotoxicity [42].

Taken together, this brief yet informative excursion into the bioinorganic and bioorganic chemistry of boron supports our notion that semi-metals may combine the best of both sides, inorganic ionic and complex chemistry on the one side and covalent organic chemistry on the other. This special role and potential of metalliods as interlocutors between inorganic and organic

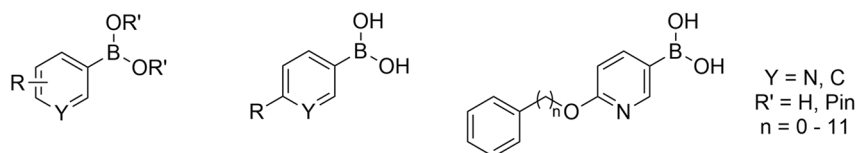


FIGURE 4 | General structures of the aromatic boronic acids with potential antimicrobial activity against MRSA.

chemistry is nicely exemplified by the benzoxaboroles and becomes even more apparent once we turn to the next semi-metal in the periodic table, namely silicon.

3 | Silicon: Silicon Dreams in the Drug Pipeline

Indeed, silicon, formally the closest relative of carbon in the periodic table, is an element that stands for a pronounced inorganic chemistry, often associated with silicate SiO_4^{3-} , glass and, as far as physiology is concerned, healthy skin, hair and fingernails [43]. Amazingly, silicon is even the third most abundant trace element in human body, after zinc and iron. Inorganic, silicate-based molecules are taken up by humans from food, water, and other beverages, such as beer. Since several forms of silicon are rather insoluble, these compounds need to be converted to orthosilicate (OSA) in the acidic environment of the stomach [43–45]. Once taken up, OSA is incorporated in tissues, such as bones, hair, fingernails, and skin where it is bound to glycosaminoglycans and plays an important role in the formation of cross-links between collagen and proteoglycans [46]. Although such inorganic SiO_4^{3-} forms of silicon are quite important for the human body and indeed many other organisms, animals, and plants alike, silicates are not very reactive and thus also hardly of pharmaceutical relevance. Nevertheless, incorporation of silicon into organic drug scaffolds affords several advantages. For instance, the increased bond-length of Si–C compared to C–C provides the room for different architectures of the scaffolds [47]. Furthermore, the electropositive nature of silicon enhances hydrogen bonding abilities. Last but not least, silicon is able to form octahedral complexes due to its empty d-orbitals [47]. Complexes of silicon with imine rather than HO^- ligands in some ways therefore form the next, logical step in the development

Si-based therapeutics. Such complexes, for instance compound **15** (Figure 5), have been synthesized and indeed surpass the activity of streptomycin against *S. aureus* [48]. Notably, they also provide antifungal activity comparable to fluconazole. Molecular docking studies suggest that these complexes bind to the active site of DNA gyrase, a type II topoisomerase with the ability to alter DNA topology. Noteworthy, the silicon does not directly interact with the enzyme, and its importance is more of structural nature [48].

In a similar approach, Liao, and coworkers have developed silicon analogues of ruthenium complexes as less toxic and more stable complexes with antifungal activity. The octahedral silicon complex (**16**), for instance, inhibits the growth of *Cryptococcus neoformans* significantly [49].

Still, the famous ‘Silicon Dream’ actually refers less to such inorganic or organometallic complexes of silicon, yet takes advantage of the organic side of this semi-metallic element. Silicon, chemically often in cahoots with carbon, is not only relevant to plumbers and DIY enthusiasts; although silicon-based cosmetic and medical implants have gained considerable popularity already, other organic silicon-carbon compounds have also recently attracted the interest of pharmaceutical chemists.

Various derivatives of silatrane (**17–21**), for instance, provide antimicrobial activity against Gram-negative and, even more so, Gram-positive bacteria, particularly *Enterococcus durans* and *Bacillus subtilis* [50]. The γ -aminopropylsilatrane derivative (**20**) shows high antifungal activity against *Aspergillus fumigatus*, *Penicillium chrysogenum* and *Fusarium* (MIC = 0.08 $\mu\text{g}/\text{ml}$) while not being antibacterial. Further modifications of the scaffold have already yielded compounds with activity against the unicellular parasites *Giardia lamblia*, *Trichomonas vaginalis*, and *Entamoeba histolytica* [51–53]. Mechanistically, the silatrane-moiety

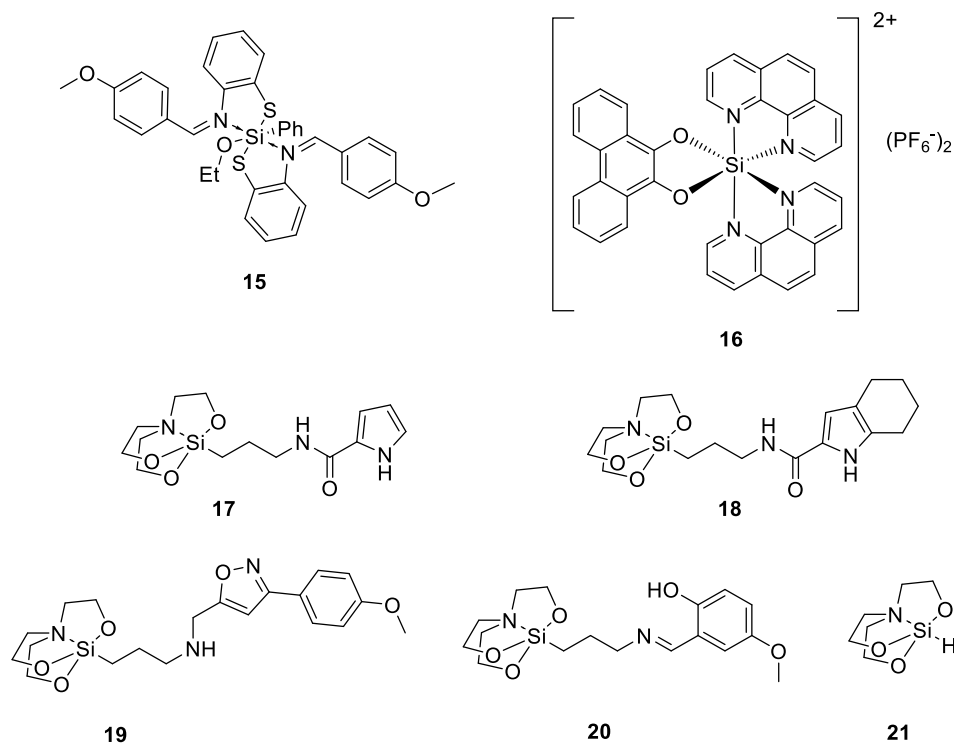


FIGURE 5 | Silicon complexes (**15–21**) provide strong antibacterial and antifungal activities.

can easily be adsorbed to the cell membranes, due to hydrogen bonds and dipole–dipole interactions with polar groups of proteins and lipids, thus finding its way inside the target microbes. Consequently, they primarily serve to transport the organic residue into the cell [54]. In this context, silica nanoparticles should also be mentioned. Although they do not exhibit antimicrobial activity themselves, they can significantly facilitate the transport of drugs across the cell membrane and thus the antimicrobial activity of established drugs [55].

Whilst silatranes may still be considered as organometallic complexes of Si with O, N and H ligands, organic silicon-carbon compounds, such as alkylsilanols (Figure 6), clearly represent the organic side of silicon. In 2006, simple trialkylsilanols, such as triethylsilanol (**22**), have been reported to exhibit antimicrobial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *Enterococcus faecalis* due to increased lipophilicity and O–H acidity compared to the corresponding alcohols [56]. Similarly, choline derivatives **23** and **24**, in which the tertiary nitrogen is replaced by silicon, show good activity against Gram-positive and two Gram-negative bacterial strains [57]. These compounds also display antifungal activity against *Candida tropicalis* and *Candida albicans*.

Since carbon and silicon share the same group in the periodic table, an isosteric replacement of silicon for carbon seems to be feasible, at least in theory. Indeed, Reddy and coworkers have focused on this interesting strategy in known antimicrobial compounds to yield novel silicon derivatives. Some of the most active resulting silicon compounds are presented in Figure 6 whilst their antimicrobial activities are summarized in Table 1 [58, 59]. Compound **25**, for instance, is an analogue of the antifungal drug fenpropimorph and acts on Δ^{14} -reductase and sterol- Δ^7 - Δ^8 -isomerase, leading to ergosterol depletion and accumulation of the intermediates ignosterol and lichesterol. As a result, the bacterial membrane integrity is compromised which

TABLE 1 | Antimicrobial activities of compounds 25–27.

Compounds	Target microorganisms	MIC (µg/ml)
25	<i>C. albicans</i> ATCC 24433	0.125
	<i>C. albicans</i> ATCC 10231	0.5
	<i>C. neoformans</i> ATCC 34664	0.125
	<i>Candida glabrata</i> NCYC 388	0.125
	<i>Candida tropicalis</i> ATCC 750	0.5
	<i>Aspergillus niger</i> ATCC 10578	2
26	<i>M. tuberculosis</i>	0.031
27	<i>M. tuberculosis</i> H37Rv	0.03125
	<i>M. tuberculosis</i> DR-TB	0.0625 – 0.5

leads to cessation of growth [58]. Regarding the rimonabant analogue **26**, the authors suggest that this compound binds to a mycolic acid transporter called mycobacterial membrane protein large 3 (MmpL3). The increased binding affinity of **26** compared to rimonabant is actually linked to the increased lipophilicity due to the incorporation of silicon [60].

Based on these studies, Wen et al. have developed triazole derivatives as inhibitors of MmpL3 for the treatment of *M. tuberculosis* [61]. In a series of 37 compounds, the most promising drug candidate **27** showed >90% inhibition at concentrations as low as 31.25 ng/ml and with negligible cytotoxicity [61].

In yet another rather elegant approach towards the facet-rich silicon chemistry, Hegyes et al. have exploited the ability of silicates to form Si–O–Si anhydrides and have synthesized the basic disilicate efflux-pump inhibitor SILA-421 (**28**; Figure 6) [62]. This compound exhibits excellent bactericidal activity against 21 clinical *M. tuberculosis* isolates in in vitro studies, including drug- and multidrug-resistant strains in a concentration and time dependent manner. SILA-421 can also enhance the activity of isoniazid (2–4 mg/l SILA-421 with 0.063 mg/l isoniazid) and rifampicin (2–4 mg/l SILA-421 with 0.015 mg/l RIF) when applied in combination [63].

To date, there are no studies explaining the fate of silicon-based antimicrobials after metabolic degradation. However, Tacke et al. were able to demonstrate that sila-haloperidol, a silicon analogue of the dopamine (D2) receptor antagonist haloperidol, degrades via a completely different pathway than its carbon-based counterpart, and unlike haloperidol, does not produce any toxic intermediates. It is quite likely that this difference in degradation also applies to the degradation of other silicon analogues [64].

This specific silicate chemistry is certainly worth exploring further, as indeed is most of the biological chemistry associated with this often-ignored trace element, especially since silicon has, unlike the other metalloids, no intrinsic ‘element-specific’ toxicity [47].

4 | Germanium: One of the Forgotten Elements in the Periodic Table

Unlike silicon, germanium is less present in chemistry, daily life, and also biological systems. Indeed, an international conference

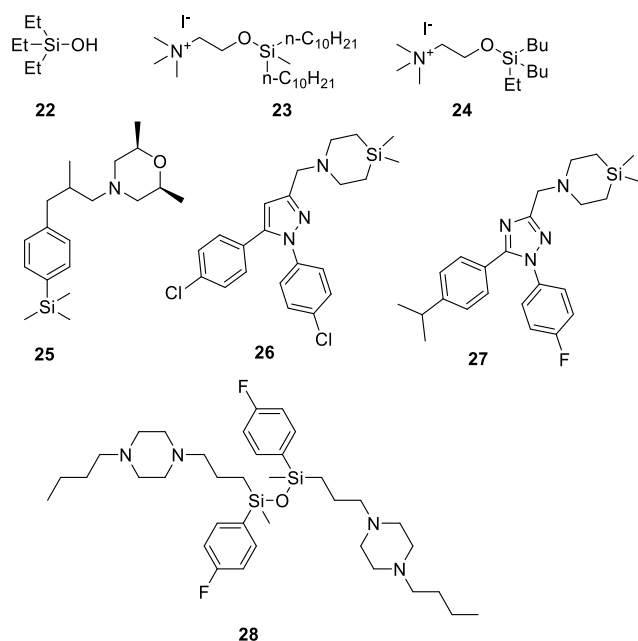


FIGURE 6 | Examples of trialkylsilanols (**22**) and silicon-analogues of choline (**23**) and colamine (**24**), fenpropimorph analogue (**25**), rimona-bant analogue (**26**), MmpL3 inhibitor (**27**) and the efflux-pump inhibitor SILA-421 (**28**).

on germanium chemistry may be held in your garage, and a meeting on biological aspects of this metal may turn out to be a one (wo)man show!

Like the other metalloids discussed so far, germanium can be divided into two main forms: inorganic and organic germanium – and the respective compounds. Whilst inorganic germanium is mostly linked to semiconductor materials and optical fibres, some groups have also reported antimicrobial activities of inorganic germanium materials, such as GeO_2 incorporated into silicocarnotite ceramics [65]. Interestingly, these ceramics exhibit good antibacterial activity against *E. coli* and *S. aureus* with the GeO_2 content of 0.05 wt.% or higher [65]. In this context, other forms of GeO_2 also play a major role in the ‘biochemistry’ of germanium. Inorganic MgO-GeO_2 nanocomposite powders, for instance, exhibit antimicrobial activity against *E. coli* and *S. aureus* [66]. Furthermore, GeO_2 can be incorporated in ternary silicate glass structures, yielding an antimicrobial glass which can be used for dental applications [67].

Moreover, a chitosan-PVA-germanium dioxide (Cs-PVA-GeO_2) composite exhibits broad-spectrum antibacterial activity against Gram-positive (*S. aureus*, *E. faecalis*) and Gram-negative (*E. coli*, *P. aeruginosa*) pathogens. As for the underlying mechanism(s) associated with this activity, and based on molecular docking studies, the authors propose strong binding affinities of Cs-PVA-GeO_2 with key bacterial enzymes, including DNA gyrase, penicillin-binding proteins and dihydropteroate synthase, suggesting a

multi-target inhibitory mechanism [68]. Similarly, GeO_2 in the form of a typical organometallic complex with 2-amino-3-hydroxybutanoic acid (**29**; Figure 7) provides both bacteriostatic as well as bactericidal activities against *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, *E. faecalis*, and *Acinetobacter baumannii*, which indeed are interesting targets since they have developed a pronounced antibiotic resistance [69]. Also, a complex of folic acid and Ge(IV) (**30**; Figure 7) shows an increased antibacterial and antifungal activities when compared to the free ligand [70]. It is assumed that these metal ions enhance the antibacterial and antifungal activities by increasing lipophilicity, thus facilitating the penetration of the metal complex across the cell membrane [70]. Furthermore, monometallic complexes of Ge(IV) with macrocyclic ligands, such as complex **31** depicted in Figure 7, show a broad spectrum of antimicrobial activity against both Gram-positive and Gram-negative human pathogenic bacterial isolates [71].

In the field of (mixed) organometallic germanium chemistry, a number of germanium-containing organotin(IV) compounds with the general formula $(\text{Me})_2\text{Sn}(\text{OCOCHR}^3\text{CHR}^2\text{GeR}^1_3)_2$, where $\text{R}^1 = \text{Ph}$, 4- MeC_6H_4 , $\text{R}^2 = \text{N}(\text{CH}_2\text{CH}_2\text{O})_3$, $\text{R}^3 = \text{Ph}$, H, Me, 4- MeOC_6H_4 , 4- ClC_6H_4 , 4- MeC_6H_4 and $\text{R}^3 = \text{Me}$, have been screened against various fungal strains such as *Trichophyton longifusus*, *C. albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani*, and *Candida glabrata*. It was found that these compounds, in concentrations of 400 $\mu\text{g/ml}$, are active against these fungi, except for *A. flavus* [72, 73].

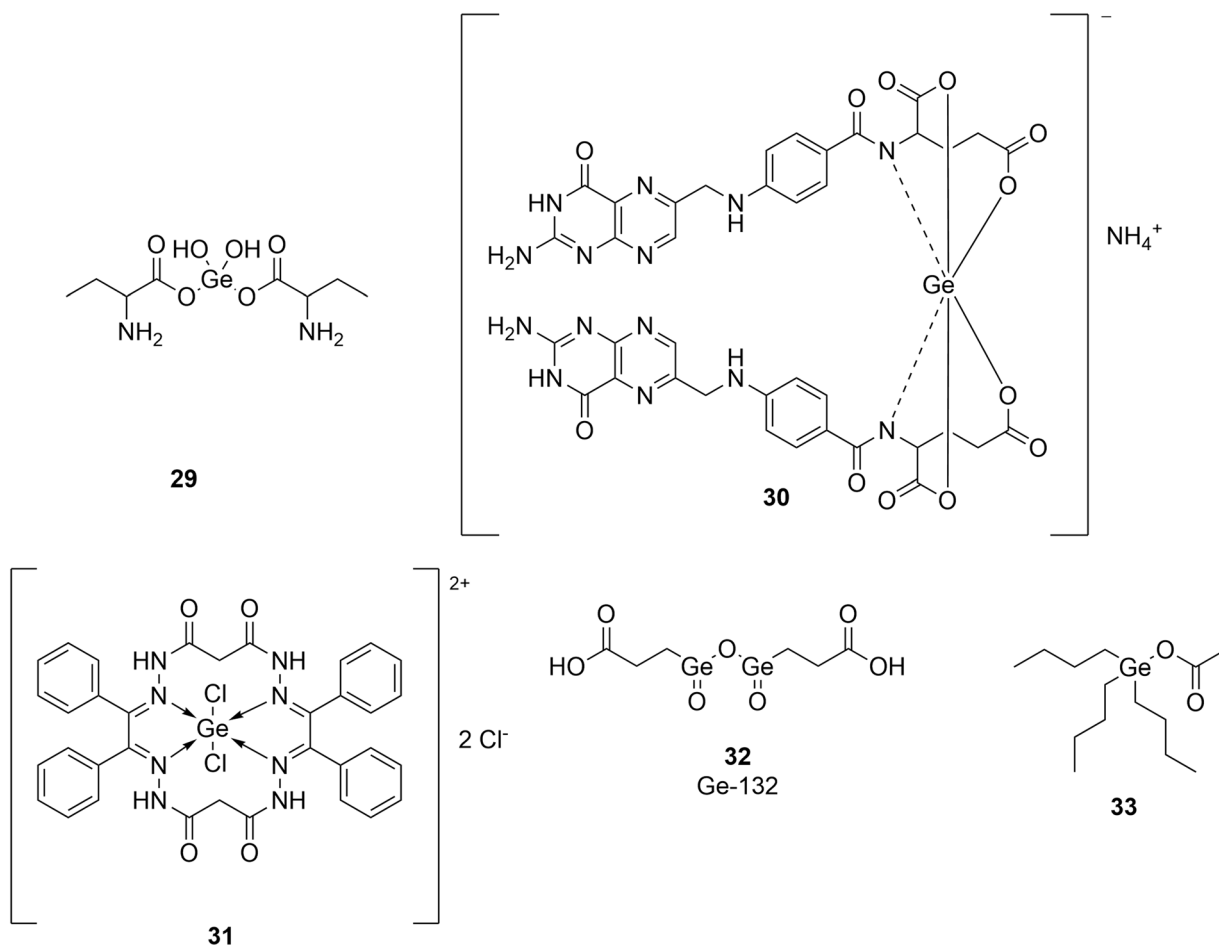


FIGURE 7 | Structures of GeO_2 in complex with 2-aminobutanoic acid (**29**), Ge(IV) folic acid complex (**30**, proposed structure) macrocyclic Ge(IV) complex (**31**), Ge-132 (**32**), and tributylgermanium acetate (**33**).

With regard to organic germanium compounds, to date, not many compounds with biological activity have been reported. Nonetheless, *bis*-(carboxyethylgermanium) sesquioxide (Ge-132; **32**; Figure 7) may be mentioned in this context. This compound was reported first by Mironov et al. in 1967, and later Asai and coworkers discovered its potential as a drug [74]. Several in vivo studies have shown that Ge-132 exhibits antiviral, analgesic, antitumorigenic, and antioxidant activities [75]. Concerning Ge-containing organic antimicrobials, trialkylgermanium acetates, such as tributylgermanium acetate (**33**), inhibits bacterial and fungal growth of several strains in concentrations of 2–5 µg/ml, although the presence of blood or blood serum in the nutrient medium can counteract this effect [76, 77]. Mechanistically, these compounds seem to follow the similar mechanism of action like their tin-analogues while being less toxic. These compounds are expected to interfere with the oxidative phosphorylation through the inhibition of F₁F₀-ATPase and disrupt the membrane of bacteria [78–80]. Furthermore, a soft ligand exchange with cysteine-containing proteins is conceivable as a mechanism, but there is a lack of scientific evidence. In any case, the specific antimicrobial potential and underlying mechanisms of this class of compounds have not been thoroughly investigated yet.

Taken together, these findings highlight the fact that when it comes to pharmaceutical applications, germanium is a promising, albeit somewhat neglected metalloid element. Still, it may be incorporated into novel antimicrobial drugs, either as an inorganic ion in complexes, as active ingredient of metalloorganic or indeed as main player in organic compounds. In this context, the field of organic germanium compounds has been neglected in the search for new antimicrobials.

5 | Arsenic: Old Cures and New Challenges

Indeed, moving down the periodic table brings us into ever more ‘metallic’ territory, also for the metalloids, and this is often reflected in the mode(s) of action which become(s) more metal and thus complex-like. This also holds true for arsenic, one of the most traditional elements in ancient and medieval medicine.

Arsenic was described first by Albertus Magnus (1200–1280) around the year 1250 and thus is the only element in the periodic table which has been discovered by a renowned Philosopher. Its initial applications have been less philosophical though, as some of its compounds can be quite poisonous and have also been used as such throughout the centuries. Curiously, arsenic (As) as an element is non-toxic to humans. Even after the ingestion of 10 g of elemental As, the patients in question survived without any severe complications [81]. Intriguingly, its namesake arsenic (As₂O₃) is a notorious toxin, even in very low doses of 1–2.5 mg/kg [82].

The infamous toxicity of As₂O₃ (arsenic trioxide) is primarily attributed to its covalent interactions with individual cysteine residues, cysteine clusters, zinc finger motifs, and RING finger domains in proteins. These interactions not only disrupt protein function but also contribute to the development and progression of various diseases [83]. Intriguingly, these same properties also make As₂O₃ a promising candidate for antimicrobial applications; for instance, incorporating As₂O₃ into polymer composites has shown to effectively inhibit bacterial growth of *E. coli* and *S. aureus* [84].

In the early 1900s, organic arsenicals became a prosperous field in medical research with an astonishing number of approximately 32,000 As compounds being synthesized over the years. Some of these compounds exhibit antimicrobial activities and have also been used as medications. One example is the pentavalent organic arsenical atoxyl (Figure 8; **34**), which was used in the early 1900s by Robert Koch (1843–1910) to treat sleeping sickness yet caused optic atrophy due to its high arsenic content [86]. Nonetheless, the organic arsenic compound melarsoprol (**35**), which was developed in 1949, is still in use today to cure sleeping sickness caused by *Trypanosoma brucei rhodesiense*. It targets trypanothione, which is found exclusively in trypanosomes. Melarsoprol forms an adduct with the thiol groups of two trypanothione molecules. This adduct can no longer cross the cell membrane and thus accumulates in the parasite. Furthermore, melarsoprol acts as an inhibitor of trypanothione reductase. Together, these two mechanisms lead to the loss of the parasite's

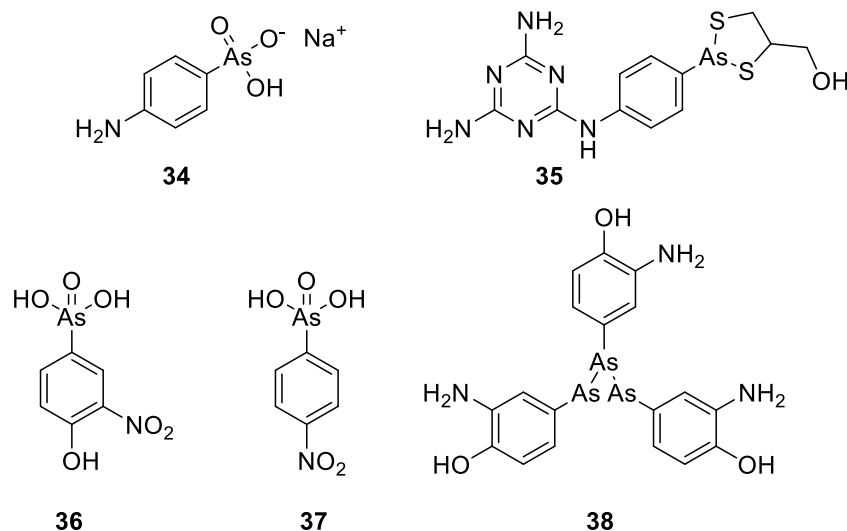


FIGURE 8 | Structures of different historically used arsenic drugs (**34–38**). Arsphenamine (**38**) is depicted in its trimeric form as proposed by Lloyd et al. [85].

ability to reduce oxidative stress [87]. In poultry farming, the use of atoxyl and the related synthetic aromatic arsenicals roxarsone (36) and nitarosone (37) to prevent *Coccidia* and *Histomonas* infections is still common [88]. These compounds disrupt the DNA repair process and energy metabolism by inhibiting ATP synthesis of the parasites [89].

More famous than these organic arsenic compounds is Paul Ehrlich's (1854–1915) "magic bullet", arsphenamine (38), also known as Salvarsan. This unusual tri- or pentacyclic structure was used from 1910 onwards to treat human syphilis until it was replaced by penicillin in the 1940s [90, 91]. Arsphenamine itself serves as a prodrug which is oxidized in vivo. Although the mechanism of action is still unclear, it can be assumed that cysteine bonding plays an important role, since As(III) has a high affinity for thiols [85, 92, 93].

Despite the phasing out of most of these early arsenic compounds, the pharmaceutical interest and fascination with this element have never entirely faded. And indeed, even Nature itself provides some unusual arsenic compounds with a pronounced antimicrobial activity.

A simple yet amazing natural As-containing organic product is the highly toxic antibiotic methylarsenite (MAs(III); 39; Figure 9), which is produced by methylation of inorganic As(III) by the enzyme As(III) S-adenosylmethionine (SAM) methyltransferase, termed ArsM in microbes and AS3MT in animals. The methylation of As is catalyzed by four conserved cysteines [94]. Just like arsinothricin, which will be discussed later, it is produced by soil bacteria to kill other bacteria. Due to the high reactivity of MAs(III), no single target could be identified that applies in every cell [95]. Nevertheless, one target for MAs(III) was recently identified in *Shewanella putrefaciens* 200 [96]. MAs(III), unlike inorganic As(III), effectively inhibits the enzyme MurA (uridine diphosphate (UDP)-N-acetylglucosamine enolpyruvyl transferase) [95]. MurA is a cytoplasmic enzyme involved in the synthesis of the key precursor of the peptidoglycan, UDP-N-acetylmuramate (UNAM), which is only essential to prokaryotes [97]. This makes MurA an excellent target for antibiotics. So far, only fosfomycin is approved as an antibiotic that acts against MurA. Fosfomycin inhibits MurA by alkylation of the highly conserved catalytic cysteine residue in the active site. In some microbes, the relevant cysteine residue is replaced by an aspartate, leading to resistance to fosfomycin [98]. MAs(III) could possibly overcome this resistance since it still shows activity against the Cys-to-Asp mutants, indicating a different mechanism of inhibition, most likely by binding to a different cysteine residue [96, 99]. Thence MAs(III) could be the starting point of a new generation of antibiotic drugs.

This brings us to one of the most fascinating natural As-compounds, arsenicin A (2,4,6-trioxa-1,3,5,7-tetrasatricyclo [3.3.1.1.3,7] decane; 40) ($C_3H_6As_4O_3$) from the marine sponge

Echinochalina bargibanti, where As literally holds the key to a complex adamantane system and a pronounced antimicrobial activity, especially against *S. aureus*, *E. coli*, and *C. albicans* [100]. The adamantane bridgeheads in arsenicin A are replaced by As and three methylene groups are replaced by oxygen. Even though research on arsenicin A has been more focused on its anticancer activity, arsenicin A, and the two sulfur-containing metabolites arsenicin B (41) and arsenicin C (42) also exhibit strong antimicrobial activities, especially against *S. aureus* [101].

L-AST but not least, and in addition to these complexes, new impetus has been provided by the discovery of organic As compounds in microorganisms, such as the recently discovered pentavalent arsenic (V)-containing arsinothricin (2-amino-4-(hydroxymethylarsinoyl)butanoate, L-AST; 43), produced by the rice rhizosphere microbe *Burkholderia gladioli* and exhibiting broad-spectrum antibiotic activity while possessing acceptable cytotoxicity. The mechanism underlying the activity of this compound is rather interesting, as it seemingly serves as a non-proteogenic analogue of glutamate, thereby inhibiting glutamate synthase leading to a potent broad spectrum antimicrobial activity [88]. Notably, L-AST inhibits the growth of Gram-negative bacteria more than Gram-positive bacteria. It also inhibits the growth of *E. coli* more strongly compared to the inorganic As(III) and almost similar to that of highly toxic trivalent methylarsenite (MAs(III)). The high toxicity of L-AST is particularly interesting, since pentavalent arsenicals are generally much less toxic than their trivalent counterparts, making L-AST the only known pentavalent arsenic compound, apart from thiolated species, which exhibits such a pronounced toxicity [102]. Intriguingly, L-AST, compared to its phosphorus analogue L-PPT, which differs just by one atom (P instead of As), also provides better antimicrobial activity, especially against the pathogenic mycobacterial strain *M. bovis* [88]. Moreover, L-AST effectively inhibits the growth of carbapenem-resistant *Enterobacter cloacae* (ATCC BAA-2341), classified within the highest priority category of the World Health Organization (WHO)'s global priority pathogens list. In comparison, other glutamine synthetase inhibitors (L-PPT and methionine sulfoximine) fail to affect the growth of *E. cloacae*. The efficacy of L-AST against the resistant microbes highlights its potential as a promising candidate for the development of novel antimicrobial drugs.

Despite having interesting antimicrobial activities, the As containing compounds face a major challenge due to narrow therapeutic windows (therapeutic indices of 2, 10, and 50–100 for atoxyl, arsphenamine, and melarsoprol, respectively), severe side effects and resistances resulting from widespread uses in animal breeding [103–105].

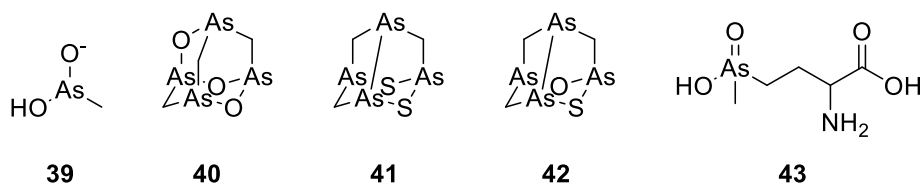


FIGURE 9 | Structures of naturally occurring As-compounds (39–43) which provide pronounced antimicrobial activity.

6 | Antimony: Antimicrobial and Traditionally Worth its Money

Unlike the more synthetic metalloid compounds, many of which are currently under pre-clinical investigation, the use of naturally occurring inorganic antimony compounds as antimicrobial agents dates back as far as the Egyptians and Assyrians, who used elementary antimony and antimony trisulfide as a treatment for fevers and skin irritation [106–108]. A modern inorganic approach to exploit the antimicrobial properties of antimony involves the utilisation of antimony-doped tin (IV) oxide nanoparticles (ATO NPs). These ATO NPs are capable of significantly inhibiting the biofilm formation by uropathogenic *E. coli* (UPEC), *S. aureus*, and dual-species biofilms, as well as reducing their main virulence attributes, such as the cell surface hydrophobicity of UPEC and haemolysis of *S. aureus* [109].

Regarding organic antimony compounds, a rather infamous compound is antimony potassium tartrate (Figure 10; **44**), an Sb(III) complex also known as tartar emetic [112]. It was promoted by no one less than Paracelsus (ca. 1494–1541) as an agent against ulcers and was said to have cured King Louis XIV of France (1638–1715) from typhoid fever. Nonetheless, it is also known for its severe side effects, including vomiting, diarrhoea, hepatitis, renal failure, red cell toxicity, cardiovascular collapse, and even death, which brings us to a major drawback of antimony-containing drugs. Most of them provide severe side effects and toxicity, which dramatically limit their medical uses [112].

Nonetheless, some antimony-containing drugs are still in use today, especially in the field of neglected tropical diseases, such as leishmaniasis [113]. Antimony potassium tartrate (**44**) has been used until the 1970s for the treatment of schistosomiasis [114–116]. And indeed, for the treatment of leishmaniasis, the pentavalent antimonials sodium stibogluconate (**45**) and meglumine antimonate (**46**) are still in use today, even though they are not the first choice.

Interestingly, the mechanisms and modes of actions underlying these activities have been studied in more detail, and there are models of activity now for antimony-based drugs available which so far are notably lacking for many of the other metalloid-based molecules. The first model for the antimicrobial activity of pentavalent antimonials assumes that their +5 forms are being reduced within the organism to the +3 oxidation state, and that these reduced compounds exhibit a higher toxicity, due to their ability to bind to thiols which in turn act as soft ligands for Sb^{3+} [117]. They may, for instance, inhibit the reduction of

trypanothione, an analogue of glutathione solely present in some parasitic protozoa, as antimony might bind to the sulfur atom of the catalytic Cys of trypanothione reductase [117]. Simultaneously, Sb(III) actively decreases the thiol buffering capacity of the parasites by inducing rapid efflux of intracellular trypanothione [118]. As a result, reactive oxygen species (ROS) can not be reduced by the parasite, eventually leading to cell death [117, 119, 120]. Furthermore, pentavalent antimonials may inhibit the expression of genes needed for the survival of the parasite [120]. A second model suggests that type I DNA topoisomerase of the parasite is directly inhibited by stibogluconate and not by meglumine antimonate, indicating that antimony itself is not involved in the mechanism [121]. Pentavalent antimonials have also been reported to bind to ribonucleosides and reduce the levels of ATP and GTP [122]. In short, they cut a major pathway for energy generation and, once again, induce oxidative stress [120].

As for the underlying chemistry is concerned, each of the pentavalent antimonials features antimony in an SbO_6 environment, yet recent studies have shown that Sb-C bonds are favourable when compared to such Sb-O bonds in terms of reducing side effects whilst increasing activity. Not surprisingly, this has led to renewed interest in antimony-based drugs. Gerasimchuk et al., for instance, have synthesized a series of organic tetraphenyl-antimony(V) cyanoximates, which exhibit antimicrobial activity [123]. The tetraphenyl-antimony(V) cyanoximate SbPh_4ACO (**47**) inhibits the bacterial pathogens including *P. aeruginosa*, *E. coli*, and *S. aureus* with MIC values ranging from 50 to 100 $\mu\text{g}/\text{ml}$, whilst not being cytotoxic. The presence of a lipophilic organometallic fragment provides favourable kinetics for the intake of tetraphenyl-antimony(V) cyanoximates into cells, which facilitates the delivery of biologically active cyanoxime [123]. Although SbPh_4ACO (**47**) has been shown to disrupt the bacterial membrane yet the underlying mechanism still has to be investigated [106].

If, when and how such antimony drugs and materials may reach clinical trials and practical applications are, of course, relevant questions and one needs to see if antimony-based drugs can indeed make it again into the clinics or not.

7 | Tellurium: The Most Metallic of the Lot

This brings us to the – arguably – last and perhaps most down-to-earth and metallic of the semi-metals, as we shall not include Bi

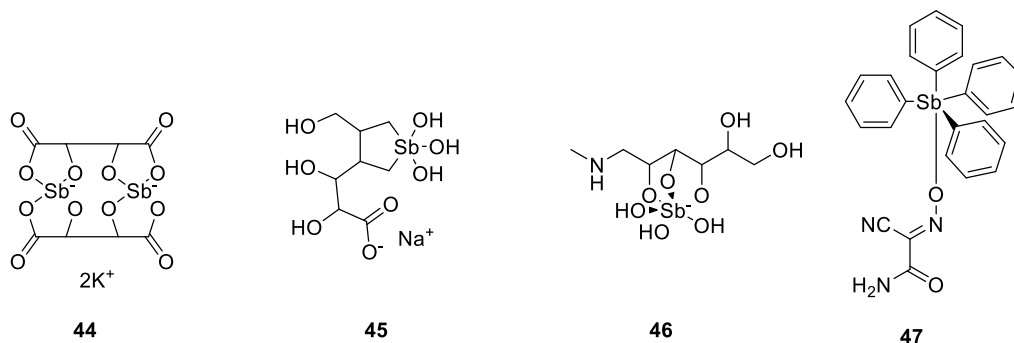


FIGURE 10 | Structures of antimony potassium tartrate (**44**), sodium stibogluconate (**45**), meglumine antimonate (**46**), and tetraphenyl-antimony(V) cyanoximate (**47**) [110, 111].

and ignore Po and At because of limited relevance and abundance, respectively. Even though the antibiotic properties of Te have been known in the past, this element can be considered as another 'forgotten' player in drug development [124]. Interestingly, tellurium is also found in form of tellurocysteine and telluromethionine in proteins of bacteria, yeast, and fungi [125].

Inorganic salts of tellurium can be rather toxic, and historically, TeO_3^{2-} was used extensively in research – albeit not in medicine – to inhibit the growth of many microorganisms as a “benchmark antibiotic” similar to ciprofloxacin and fluconazol today. Alexander Fleming (1881–1955), for instance, compared the antibacterial activities of penicillin and TeO_3^{2-} and found that most penicillin-insensitive bacteria are sensitive to TeO_3^{2-} and *vice versa*, indicating a certain selectivity of tellurite [124].

Today, inorganic tellurium salts such as TeO_3^{2-} and TeO_4^{2-} have mostly vanished from the Life Sciences altogether. TeO_3^{2-} may not be the most sophisticated drug candidate, still it can enhance the efficacy of antibiotics, possibly in combination therapies whilst reducing antibiotic burden. Therefore, TeO_3^{2-} may enter the scene again as a player in a promising strategy for combating drug-resistant bacterial infections, yet this needs to be investigated and studied in the future [126].

As far as the mode(s) of action of TeO_3^{2-} and its derivatives are concerned, it is likely that they interact with cysteine residues in proteins and enzymes, by complex formation and potentially also by oxidation. Indeed, tellurium, as the most metallic of the metalloids, tends to form complex-like structures, and the immunomodulator ammonium trichloro[1,2-ethanediolato-*O,O'*]-tellurate (AS101; **48**; Figure 11) is one prominent example within the community. AS101 has been found to be active against

several parasitic, viral, and bacterial infections, including, for instance, *Leishmania* [127, 128]. In *Enterobacteriaceae* species AS101 damages the cytoplasmic membrane and the pumps connected to it provoking the influx of sodium and potassium ions into the cell and leakage of ATP, nucleotides, and proteins [128]. Even though several tellurium compounds are considered highly toxic, AS101 is in fact non-toxic, demonstrating that it is possible to develop non-toxic tellurium-based drugs [129]. More recently, a set of novel organotellurium(IV) complexes employing a newly developed Schiff base (1,1'-(((2,4,6-trimethyl-1,3-phenylene))bis(azaneylylidene))bis(methaneylylidene))bis (naphthalen-2-ol), HNTD) (**49,50**), has been developed and tested for their activities against *Plasmodium* and other microbes. The study has identified different HNTDs to exhibit antimalarial, antifungal, and antibacterial activities [130].

Besides such complexes, organo-tellurium compounds are also active against parasitic organisms, although their chemical and especially metabolic stability is always in question. *Plasmodium falciparum*, for instance, which causes malaria, is sensitive to naphthoquinone couples with a selenium or tellurium moiety [131]. The rather selective toxicity against plasmodia may be due to the fact many tellurium agents are redox active and they increase levels of oxidative stress, while plasmodia lack certain antioxidant defence systems and hence are especially sensitive to this condition [124]. Tellurium-based compounds may therefore hold some promise to target organisms with a weak(er) oxidative defence rather efficiently and selectively.

A recent study by Souza et al. reports the anti-protozoal activity of organotellurium compounds especially **51–53**, which have exhibited IC_{50} values in the low micromolar range against

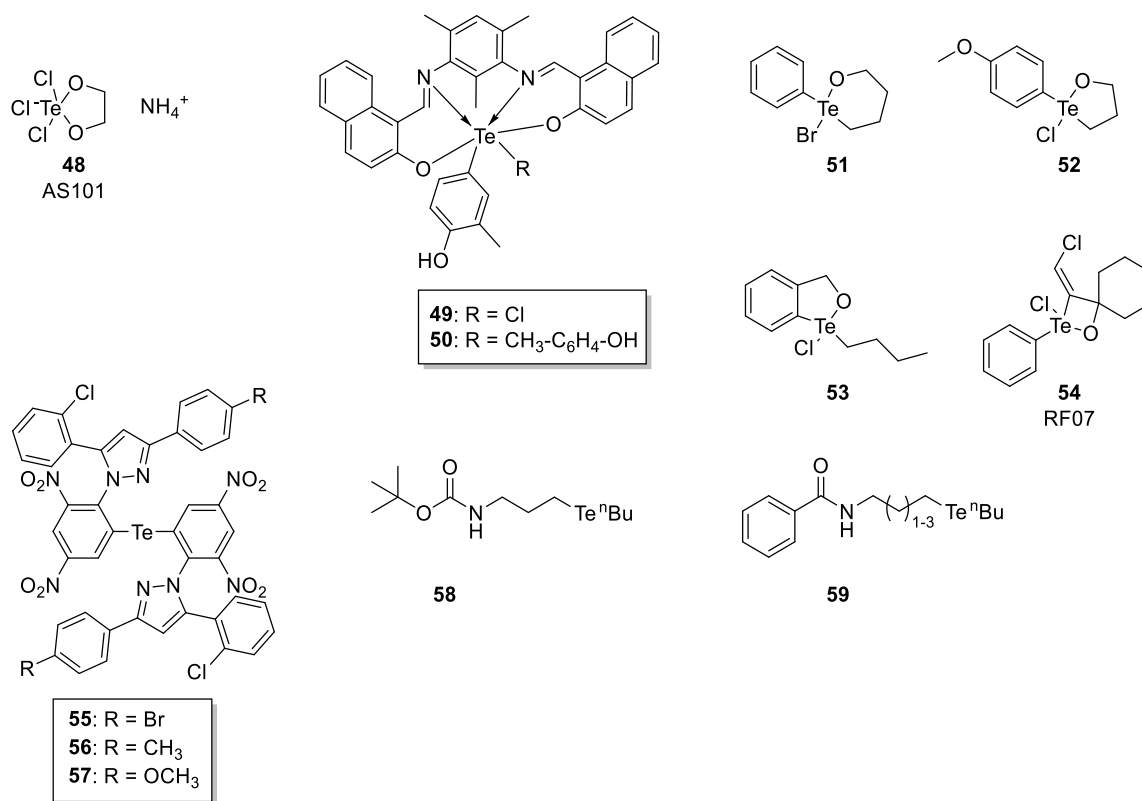
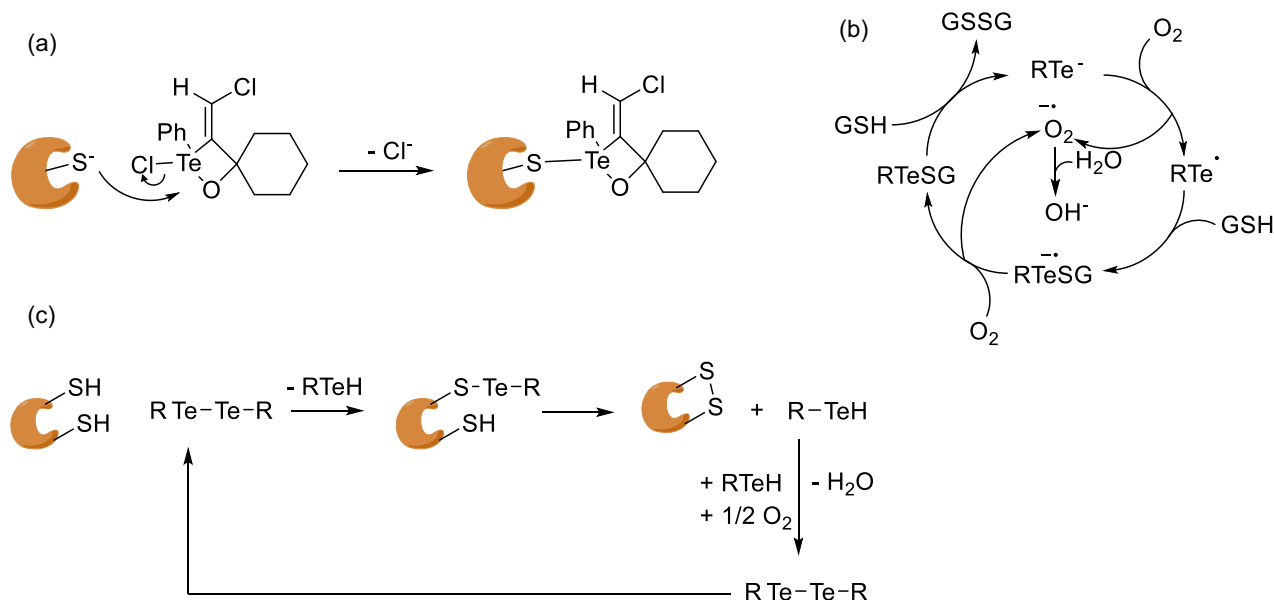


FIGURE 11 | Complexes of tellurium (**48–50**) as well as organotellurium compounds (**51–59**) provide antimicrobial activity.



SCHEME 2 | (a) Covalent protein binding of RF-07 as proposed by Cunha et al. [134]. (b) ROS generation through tellurium-containing compounds. (c) Dimerization of vicinal cysteine residues through ditellurites.

L. amazonensis promastigotes [132]. Moreover, compound RF-07 (54) has been reported to exhibit the biological activity in sub-micromolar concentrations against *L. chagasi*, with a selectivity index of 10 [133]. Compound RF-07 is an inhibitor of cysteine protease cathepsin B, which also exists in leishmania [132]. The overall biological activity is most probably achieved by binding covalently to the cysteine residue of the active site of cathepsin B as depicted in Scheme 2a [134].

As far as the antibacterial activity of organotellurium compounds is concerned, Sabti and coworkers have synthesized a series of compounds (55–57) based on pyrazole derivatives, some of which show better antimicrobial activity compared to amoxicillin [135]. Reis de Sá and coworkers have also synthesized a series of tellurium-based organic compounds to target the efflux pumps of *C. albicans* in order to overcome fluconazole resistance. Indeed, compounds 58 and 59 have been able to somewhat restore the fluconazole sensitivity of *S. cerevisiae* strains overexpressing *C. albicans* Cdr1p and Mdr1p, by inhibiting CaCdr1p ATPase activity, while exhibiting no cytotoxicity to human cell lines [136].

Although the mechanisms of the antimicrobial activity of the tellurium containing compounds are still unclear, tellurium, as a chalcogen, is highly redox-active. Thus, tellurium containing compounds are not limited to soft ligand interactions with cysteine yet are also capable of actively generating ROS by reacting with oxygen and glutathione (GSH) as depicted in Scheme 2b [125]. Furthermore, ditellurides, for instance, can dimerize vicinal cysteine residues in proteins (Scheme 2c).

Apart from the studies presented here, the research on the antimicrobial activities of small-molecule organotellurium compounds has been rather scarce. In other approaches, tellurium has been implemented into polymeric materials like chitosan-fabricated tellurium nanoparticles (CS-Te NPs) or tellurium-loaded polymeric fibre meshes [137, 138]. The latter approach has yielded a material capable of effectively inhibiting bacterial growth of *E. coli* and therefore can be used as an antibacterial

fibre. CS-Te NPs exhibit strong antimicrobial activity not only against bacteria, fungi, and yeast but also inhibit Gram-positive and Gram-negative biofilm formation. Mechanistically, Te NPs are capable of generating ROS through their unique electronic environment. Once in contact with water or oxygen Te can transfer electrons to molecular oxygen, thus forming superoxide anions ($O_2^{\cdot-}$) and thereby starting a cascade of ROS formation leading to microbial cell death [139].

Taken together, these results highlight the potential of tellurium-containing compounds as antimicrobial agents. However only one of the presented compounds, namely AS101, has found its way into clinical trials, as a immunomodulating drug, i.e. for a non-antimicrobial application [140].

8 | Summary and Outlook

This brief and necessarily incomplete look at the six traditional metalloid elements, a few of their more interesting compounds and respective biological activities has underlined the versatility and potential uses of some of them. Together, these semi-metals combine benefits from the inorganic, ionic and complex chemistry on the one side and the covalent, organic chemistry on the other, and therefore bestow their respective compounds with considerable flexibility and diversity in reactivity and modes of action. Notably, several of these compounds, from boric acid and silicate to arsenic and antimony have been and still are being used in the therapy of certain diseases, such as parasitic infections. Others have been superseded by modern antibiotics and yet several others are being in the pipeline for possible resistance-busting antimicrobial drugs or to fight some of the more neglected and perhaps exotic diseases where mainstream pharmaceutical research has not yet provided efficient solutions.

In the future, one should therefore keep an eye on these metalloids, as they reflect a distinct chemistry between the metals and

non-metals and thus may be able to carry out tasks neither classic metals nor non-metals can do easily on their own, just like fixing your bathtub with silicone.

Author Contributions

Kevin Böhm: conceptualization (supporting), data curation (equal), validation (equal), writing – original draft (equal). **Muhammad Jawad Nasim:** formal analysis (lead), supervision (lead), validation (lead), writing – original draft (supporting), writing – review & editing (supporting). **Claus Jacob:** conceptualization (lead), formal analysis (equal), supervision (lead), visualization (equal), writing – original draft (lead), writing – review & editing (equal).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. C. S. Ho, C. T. H. Wong, T. T. Aung, et al., “Antimicrobial Resistance: A Concise Update,” *Lancet Microbe* 6 (2025): 100947.
2. N. Van Rhijn and J. Rhodes, “Evolution of Antifungal Resistance in the Environment,” *Nature Microbiology* 10 (2025): 1804–1815.
3. P. Chambial, N. Thakur, P. L. Bhukya, A. Subbaiyan, and U. Kumar, “Frontiers in Superbug Management: Innovating Approaches to Combat Antimicrobial Resistance,” *Archives of Microbiology* 207 (2025): 60.
4. D. Wei, L. Wang, Y. Zhang, et al., “Metalloid Substitution Elevates Simultaneously the Strength and Ductility of Face-Centered-Cubic High-Entropy Alloys,” *Acta Materialia* 225 (2022): 117571.
5. T. Řezanka and K. Sigler, “Biologically active compounds of semi-metals,” in *Studies in Natural Products Chemistry* (Elsevier, 2008), 835–921.
6. R. E. Vernon, “Which Elements Are Metalloids?,” *Journal of Chemical Education* 90 (2013): 1703–1707.
7. I. Adriztina, L. I. Adenin, and Y. M. Lubis, “Efficacy of Boric Acid as a Treatment of Choice for Chronic Suppurative Otitis Media and Its Ototoxicity,” *Korean Journal of Family Medicine* 39 (2018): 2.
8. R. A. Hamilton and B. C. Wolf, “Accidental Boric Acid Poisoning Following the Ingestion of Household Pesticide,” *Journal of Forensic Sciences* 52 (2007): 706–708.
9. R. Hütter, W. Keller-Schien, F. Knüsel, et al., “Stoffwechselprodukte von Mikroorganismen. 57. Mitteilung. Boromycin,” *Helvetica Chimica Acta* 50 (1967): 1533–1539.
10. W. Moreira, D. B. Aziz, and T. Dick, “Boromycin Kills Mycobacterial Persisters without Detectable Resistance,” *Frontiers in Microbiology* 7 (2016), <https://doi.org/10.3389/fmicb.2016.00199>.
11. H. Irschik, D. Schummer, K. Gerth, G. Höfle, and H. Reichenbach, “Antibiotics from Gliding Bacteria. No.60. The Tartrolons, New Boron-Containing Antibiotics from a Myxobacterium, Sorangium Cellulosum,” *Journal of Antibiotics* 48 (1995): 26–30.
12. S. I. Elshahawi, A. E. Trindade-Silva, A. Hanora, et al., “Boronated Tartrolon Antibiotic Produced by Symbiotic Cellulose-Degrading

Bacteria in Shipworm Gills,” *Proceedings of the National Academy of Sciences* 110 (2013), <https://doi.org/10.1073/pnas.1213892110>.

13. L. I. Mortin, T. Li, A. D. G. Van Praagh, S. Zhang, X.-X. Zhang, and J. D. Alder, “Rapid Bactericidal Activity of Daptomycin against Methicillin-Resistant and Methicillin-Susceptible, *Staphylococcus aureus*, Peritonitis in Mice as Measured with Bioluminescent Bacteria,” *Antimicrobial Agents and Chemotherapy* 51 (2007): 1787–1794.
14. L. P. De Carvalho, S. Groeger-Otero, A. Kreidenweiss, P. G. Kremsner, B. Mordmüller, and J. Held, “Boromycin Has Rapid-Onset Antibiotic Activity Against Asexual and Sexual Blood Stages of *Plasmodium falciparum*,” *Frontiers in Cellular and Infection Microbiology* 11 (2022): 802294.
15. W. Pache and H. Zähler, “Metabolic Products of Microorganisms: 77. Information Studies on the Mechanism of Action of Boromycin,” *Archives of Microbiology* 67 (1969): 156–165.
16. K. Sato, T. Okazaki, K. Maeda, and Y. Okami, “New Antibiotics, Aplasmomycins B and C,” *Journal of Antibiotics* 31 (1978): 632–635.
17. T. Engelgeh, J. Herrmann, R. Jansen, R. Müller, and S. Halbedel, “Tartrolon Sensing and Detoxification by the *Listeria monocytogenes* *timABR* Resistance Operon,” *Molecular Microbiology* 120 (2023): 629–644.
18. D. A. Dias, K. A. Kouremenos, D. J. Beale, D. L. Callahan, and O. A. H. Jones, “Metal and Metalloid Containing Natural Products and a Brief Overview of Their Applications in Biology, Biotechnology and Biomedicine,” *Biometals* 29 (2016): 1–13.
19. L. Chery-Karschney, R. Patrapuvich, D. G. Mudeppa, et al., “Tartrolon E, a Secondary Metabolite of a Marine Symbiotic Bacterium, Is a Potent Inhibitor of Asexual and Sexual *Plasmodium falciparum*,” *Antimicrobial Agents and Chemotherapy* 68 (2024): e00684–e00623.
20. T. Beesley, N. Gascoyne, V. Knott-Hunziker, et al., “The Inhibition of Class C β -Lactamases by Boronic Acids,” *Biochemical Journal* 209 (1983): 229–233.
21. Z. Huang, L. Bai, J. Liu, and Y. Luo, “Boron-Containing Compounds as Antimicrobial Agents to Tackle Drug-Resistant Bacteria,” *Ph Fronts* 06 (2024): e336–e354.
22. S. J. Hecker, K. R. Reddy, M. Totrov, et al., “Discovery of a Cyclic Boronic Acid β -Lactamase Inhibitor (RPX7009) with Utility Vs Class A Serine Carbapenemases,” *Journal of Medicinal Chemistry* 58 (2015): 3682–3692.
23. T. Hillyer and W. S. Shin, “Meropenem/Vaborbactam—A Mechanistic Review for Insight into Future Development of Combinational Therapies,” *Antibiotics* 13 (2024): 472.
24. O. Lomovskaya, D. Sun, D. Rubio-Aparicio, et al., “Vaborbactam: Spectrum of Beta-Lactamase Inhibition and Impact of Resistance Mechanisms on Activity in Enterobacteriaceae,” *Antimicrobial Agents and Chemotherapy* 61 (2017): e01443–e01417.
25. S. J. Hecker, K. R. Reddy, O. Lomovskaya, et al., “Discovery of Cyclic Boronic Acid QPX7728, an Ultrabroad-Spectrum Inhibitor of Serine and Metallo- β -Lactamases,” *Journal of Medicinal Chemistry* 63 (2020): 7491–7507.
26. B. Liu, R. E. L. Trout, G.-H. Chu, et al., “Discovery of Taniborbactam (VNRX-5133): A Broad-Spectrum Serine- and Metallo- β -Lactamase Inhibitor for Carbapenem-Resistant Bacterial Infections,” *Journal of Medicinal Chemistry* 63 (2020): 2789–2801.
27. M. P. Hernández-Mitre, S. C. Wallis, J. S. Loutit, D. C. Griffith, and J. A. Roberts, “Phase 1, Randomized, Double-Blind, Placebo-Controlled, Ascending Single- and Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous Xeruborbactam (QPX7728) in Healthy Adult Subjects,” *Antimicrobial Agents and Chemotherapy* 69 (2025): e00784–e00725.
28. F. M. Wagenlehner, L. B. Gasink, P. C. McGovern, et al., “Cefepime–Taniborbactam in Complicated Urinary Tract Infection,” *New England Journal of Medicine* 390 (2024): 611–622.

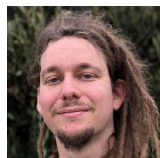
29. B. Dhawan, G. Akhter, H. Hamid, P. Kesharwani, and M. S. Alam, "Benzoxaboroles: New Emerging and Versatile Scaffold with a Plethora of Pharmacological Activities," *Journal of Molecular Structure* 1252 (2022): 132057.
30. M. Wang, Y. He, S. A. Cohen, et al., "Time-Dependent Inhibition of Leucyl-tRNA-Synthetase (LeuRS): Insight into Target Vulnerability," *ACS Infectious Diseases* 11 (2025): 977–985.
31. A. Palencia, X. Li, W. Bu, et al., "Discovery of Novel Oral Protein Synthesis Inhibitors of Mycobacterium Tuberculosis That Target Leucyl-tRNA Synthetase," *Antimicrobial Agents and Chemotherapy* 60 (2016): 6271–6280.
32. J. A. Sutcliffe, "Antibiotics in Development Targeting Protein Synthesis," *Annals of the New York Academy of Sciences* 1241 (2011): 122–152.
33. K. P. Purnapatre, M. Rao, M. Pandya, et al., "In Vitro and, In Vivo, Activities of DS86760016, a Novel Leucyl-tRNA Synthetase Inhibitor for Gram-Negative Pathogens," *Antimicrobial Agents and Chemotherapy* 62 (2018): e01987–e01917.
34. A. H. Diacon, C. E. Barry, A. Carlton, et al., "A First-in-Class Leucyl-tRNA Synthetase Inhibitor, Ganfaborole, for Rifampicin-Susceptible Tuberculosis: A Phase 2a Open-Label, Randomized Trial," *Nature Medicine* 30 (2024): 896–904.
35. G. Hao, H. Li, F. Yang, et al., "Discovery of Benzhydryl-Oxaborole Derivatives as Streptococcus Pneumoniae Leucyl-tRNA Synthetase Inhibitors," *Bioorganic and Medicinal Chemistry* 29 (2021): 115871.
36. F. Fontaine, A. Héquet, A.-S. Voisin-Chiret, et al., "Boronic Species as Promising Inhibitors of the Staphylococcus Aureus NorA Efflux Pump: Study of 6-Substituted Pyridine-3-Boronic Acid Derivatives," *European Journal of Medicinal Chemistry* 95 (2015): 185–198.
37. F. Fontaine, A. Hequet, A.-S. Voisin-Chiret, et al., "First Identification of Boronic Species as Novel Potential Inhibitors of the, Staphylococcus aureus, NorA Efflux Pump," *Journal of Medicinal Chemistry* 57 (2014): 2536–2548.
38. C. Selg, T. Grell, A. Brakel, P. C. Andrews, R. Hoffmann, and E. Hey-Hawkins, "Fusing Bismuth and Mercaptocarboranes: Design and Biological Evaluation of Low-Toxicity Antimicrobial Thiolato Complexes," *ChemPlusChem* 89 (2024): e202300759.
39. D. Różycka, M. Korycka-Machała, A. Żaczek, et al., "Novel Isoniazid-Carborane Hybrids Active In Vitro against Mycobacterium Tuberculosis," *Pharmaceuticals* 13 (2020): 465.
40. W. J. P. Cunliffe, P. J. Rutledge, and L. M. Rendina, "Recent Advances in the Antimicrobial Potential of Boron Cluster Compounds," *RSC Medicinal Chemistry* 17 (2026): 65–79.
41. K. Fink and M. Uchman, "Boron Cluster Compounds as New Chemical Leads for Antimicrobial Therapy," *Coordination Chemistry Reviews* 431 (2021): 213684.
42. Y. Zhang, X. Xu, Q. Liao, et al., "New Potential of Boron-Based COFs: The Biocompatible COF-1 for Reactive Oxygen Generation and Antimicrobial Applications," *Journal of Materials Chemistry B* 10 (2022): 3285–3292.
43. L. A. D. Araújo, F. Addor, and P. M. B. G. M. Campos, "Use of Silicon for Skin and Hair Care: An Approach of Chemical Forms Available and Efficacy," *Anais Brasileiros De Dermatologia* 91 (2016): 331–335.
44. R. Jugdaohsingh, S. H. Anderson, K. L. Tucker, et al., "Dietary Silicon Intake and Absorption," *American Journal of Clinical Nutrition* 75 (2002): 887–893.
45. A. Boguszewska-Czubara and K. Pasternak, "Silicon in Medicine and Therapy," *Journal of Elementology* (2011), <https://doi.org/10.5601/jelem.2011.16.3.13>.
46. C. T. Price, K. J. Koval, and J. R. Langford, "Silicon: A Review of Its Potential Role in the Prevention and Treatment of Postmenopausal Osteoporosis," *International Journal of Endocrinology* 2013 (2013): 1–6.
47. A. K. Franz and S. O. Wilson, "Organosilicon Molecules with Medicinal Applications," *Journal of Medicinal Chemistry* 56 (2013): 388–405.
48. N. Dhingra, J. B. Singh, and H. L. Singh, "Synthesis, Spectroscopy, and Density Functional Theory of Organotin and Organosilicon Complexes of Bioactive Ligands Containing Nitrogen, Sulfur Donor Atoms as Antimicrobial Agents: In Vitro and in Silico Studies," *Dalton Transactions* 51 (2022): 8821–8831.
49. C. Fu, B. Fu, X. Peng, and G. Liao, "Discovery of an Octahedral Silicon Complex as a Potent Antifungal Agent," *Molecules* 22 (2017): 637.
50. J.-L. Panayides, D. L. Riley, F. Hasenmaile, and W. A. L. Van Otterlo, "The Role of Silicon in Drug Discovery: A Review," *RSC Medicinal Chemistry* 15 (2024): 3286–3344.
51. G. Singh, A. Singh, K. Chowdhary, et al., "Synthesis, Characterization, Hydrolytic Stability, Nickel(II) Chloride Complex and Anti-Parasitic Activity of Pyrene-Tethered Silatranes," *Polycyclic Aromatic Compounds* 41 (2021): 173–183.
52. G. Singh, A. Arora, P. Kalra, et al., "A Strategic Approach to the Synthesis of Ferrocene Appended Chalcone Linked Triazole Allied Organosilatranes: Antibacterial, Antifungal, Antiparasitic and Antioxidant Studies," *Bioorganic and Medicinal Chemistry* 27 (2019): 188–195.
53. G. Singh, A. Singh, J. Singh, et al., "First Synthesis of Pyrene-Functionalized Silatranes for Mechanistic Insights into Their Potential Anti-Parasitic and Anti-Oxidation Activities," *New Journal of Chemistry* 41 (2017): 15165–15172.
54. N. N. Chipanina, S. N. Adamovich, A. M. Nalibayeva, et al., "Supramolecular Structure of Sulfonamide-Substituted Silatranes: Quantum Chemical DFT Calculations," *International Journal of Molecular Sciences* 25 (2024): 11920.
55. M. Vallet-Regí, F. Schüth, D. Lozano, M. Colilla, and M. Manzano, "Engineering Mesoporous Silica Nanoparticles for Drug Delivery: Where Are We after Two Decades?," *Chemical Society Reviews* 51 (2022): 5365–5451.
56. Y. Kim, S. Farrah, and R. H. Baney, "Structure–antimicrobial Activity Relationship for Silanols, a New Class of Disinfectants, Compared with Alcohols and Phenols," *International Journal of Antimicrobial Agents* 29 (2007): 217–222.
57. A. Zablotskaya, I. Segal, Y. Popelis, et al., "Silyl Modification of Biologically Active Compounds. 12. Silyl Group as True Incentive to Antitumour and Antibacterial Action of Choline and Colamine Analogues," *Applied Organometallic Chemistry* 20 (2006): 721–728.
58. G. R. Jachak, R. Ramesh, D. G. Sant, et al., "Silicon Incorporated Morpholine Antifungals: Design, Synthesis, and Biological Evaluation," *ACS Medicinal Chemistry Letters* 6 (2015): 1111–1116.
59. R. Ramesh, R. D. Shingare, V. Kumar, et al., "Repurposing of a Drug Scaffold: Identification of Novel Sila Analogues of Rimnabant as Potent Antitubercular Agents," *European Journal of Medicinal Chemistry* 122 (2016): 723–730.
60. N. Vasudevan, Z. Motiwala, R. Ramesh, et al., "Synthesis, Biological Evaluation and Docking Studies of Silicon Incorporated Diarylpyrroles as MmpL3 Inhibitors: An Effective Strategy towards Development of Potent Anti-Tubercular Agents," *European Journal of Medicinal Chemistry* 259 (2023): 115633.
61. Y. Wen, S. Lun, Y. Jiao, et al., "Design, Synthesis, and Biological Evaluation of 1,2,4-Triazole Derivatives as Potent Antitubercular Agents," *Chinese Chemical Letters* 35 (2024): 108464.
62. J. Molnar, I. Mucsi, J. Nacs, et al., "New Silicon Compounds as Resistance Modifiers against Multidrug-Resistant Cancer Cells," *Anticancer Research* 24 (2004): 865.
63. G. J. De Knecht, I. A. J. M. Bakker-Woudenberg, D. Van Soolingen, R. Aarnoutse, M. J. Boeree, and J. E. M. De Steenwinkel, "SILA-421 Activity In Vitro against Rifampicin-Susceptible and Rifampicin-

- Resistant Mycobacterium Tuberculosis, and In Vivo in a Murine Tuberculosis Model,” *International Journal of Antimicrobial Agents* 46 (2015): 66–72.
64. R. Tacke, F. Popp, B. Müller, et al., “Sila-Haloperidol, a Silicon Analogue of the Dopamine (D₂) Receptor Antagonist Haloperidol: Synthesis, Pharmacological Properties, and Metabolic Fate,” *ChemMedChem* 3 (2008): 152–164.
65. Y. Ji, S. Yang, J. Sun, and C. Ning, “Realizing Both Antibacterial Activity and Cytocompatibility in Silicocarnotite Bioceramic via Germanium Incorporation,” *Journal of Functional Biomaterials* 14 (2023): 154.
66. C. P. Avanzato, J. M. Follieri, I. A. Banerjee, and K. R. Fath, “Biomimetic Synthesis and Antibacterial Characteristics of Magnesium Oxide—Germanium Dioxide Nanocomposite Powders,” *Journal of Composite Materials* 43 (2009): 897–910.
67. T. M. Tiama, M. A. Ibrahim, M. H. Sharaf, and A. F. Mabied, “Effect of Germanium Oxide on the Structural Aspects and Bioactivity of Bioactive Silicate Glass,” *Scientific Reports* 13 (2023): 9582.
68. A. F. Mabied, T. M. Tiama, A. F. El-Sayed, and M. A. Ibrahim, “Structural Characterizations, DFT, and Docking of Novel Chitosan/PVA/Germanium Oxide as a Potent Antimicrobial Agent,” *International Journal of Biological Macromolecules* 322 (2025): 146577.
69. A. V. Kadomtseva, G. M. Mochalov, M. A. Zasovskaya, and A. M. Ob’edkov, “Synthesis, Structure, and Biological Activity of the Germanium Dioxide Complex Compound with 2-Amino-3-Hydroxybutanoic Acid,” *Inorganics* 12 (2024): 83.
70. A. A. El-Habeeb, “Novel Gallium(III), Germanium(IV), and Hafnium(IV) Folate Complexes and Their Spectroscopic, Thermal Decomposition, Morphological, and Biological Characteristics,” *Bioinorganic Chemistry and Applications* 2020 (2020): 1–12.
71. A. Chaudhary, A. Singh, and E. Rawat, “Synthesis, Characterization and Biological Activity of Monometallic Complexes of Germanium,” *International Journal of Current Research in Chemistry and Pharmaceutical Sciences* 3 (2016): 35–43.
72. A. V. Kadomtseva, G. M. Mochalov, and O. V. Kuzina, “Biologically Active Coordination Compounds of Germanium. Synthesis and Physicochemical Properties,” *Russian Journal of Organic Chemistry* 57 (2021): 879–888.
73. M. K. Khosa, M. Mazhar, S. Ali, and S. Dastgir, “Synthesis, Characterisation, and Structural Elucidation by Spectral Investigation (FT-IR, Multinuclear NMR, Mass Spectrometry) of Biologically Active Organotin(IV) Compounds Containing Germanium,” *Turkish Journal of Chemistry* (2010), <https://doi.org/10.3906/kim-0904-10>.
74. X. Luo, J. Sun, D. Kong, et al., “The Role of Germanium in Diseases: Exploring Its Important Biological Effects,” *Journal of Translational Medicine* 21 (2023): 795.
75. T. Wada, T. Hanyu, K. Nozaki, et al., “Antioxidant Activity of Ge-132, a Synthetic Organic Germanium, on Cultured Mammalian Cells,” *Biological and Pharmaceutical Bulletin* 41 (2018): 749–753.
76. A. K. Sijpesteijn, F. Rijkens, G. J. M. V. D. Kerk, and A. Manten, “Antimicrobial Activity of Organogermanium Derivatives,” *Nature* 201 (1964): 736–736.
77. A. K. Sijpesteijn, “Growth Inhibition of Bacteria by Tributylgermanium Acetate and Its Reversal by Blood Constituents,” *Antonie van Leeuwenhoek* 34 (1968): 85–92.
78. G. M. Gadd, “Microbial Interactions with Tributyltin Compounds: Detoxification, Accumulation, and Environmental Fate,” *Science of the Total Environment* 258 (2000): 119–127.
79. S. Nesci, V. Ventrella, and A. Pagliarini, “Modulation of the F₁ F₀ -ATPase Function by Butyltin Compounds,” *Applied Organometallic Chemistry* 27 (2013): 199–205.
80. J. S. Thayer, “Organometallic Compounds and Living Organisms,” *Journal of Organometallic Chemistry* 76 (1974): 265–295.
81. K. Baumgartner, D. B. Liss, M. E. Mullins, A. J. Strand, S. P. Boley, and J. B. Cole, “Two Cases of Deliberate Elemental Arsenic Ingestion with No Apparent Toxicologic Consequences,” *Clinical Toxicology* 63 (2025): 442–444.
82. “Arsenic, Medical Management Guidelines, Toxic Substance Portal, ATSDR,” n.d., accessed October 23, 2025 <https://www.cdc.gov/TSP/MMG/MMGDetails.aspx?mmgid=1424&toxid=3>.
83. C. A. Vergara-Gerónimo, A. L. D. Río, M. Rodríguez-Dorantes, P. Ostrosky-Wegman, and A. M. Salazar, “Arsenic-Protein Interactions as a Mechanism of Arsenic Toxicity,” *Toxicology and Applied Pharmacology* 431 (2021): 115738.
84. W. Brostow, M. Gahutishvili, A. W. Wren, et al., “Antibacterial Efficacy of Silver or Arsenic Doped Polymer Composites Against Several Kinds of Bacteria,” *Chemistry and Chemical Technology* 16 (2022): 42–50.
85. N. C. Lloyd, H. W. Morgan, B. K. Nicholson, and R. S. Ronimus, “The Composition of Ehrlich’s Salvarsan: Resolution of a Century-Old Debate,” *Angewandte Chemie International Edition* 44 (2005): 941–944.
86. J. Stein, S. Mogk, C. N. Mudogo, et al., “Drug Development Against Sleeping Sickness: Old Wine in New Bottles?,” *Current Medicinal Chemistry* 21 (2014): 1713–1727.
87. A. H. Fairlamb, G. B. Henderson, and A. Cerami, “Trypanothione Is the Primary Target for Arsenical Drugs against African Trypanosomes,” *Proceedings of the National Academy of Sciences* 86 (1989): 2607–2611.
88. V. S. Nadar, J. Chen, D. S. Dheeman, et al., “Arsinothricin, an Arsenic-Containing Non-Proteinogenic Amino Acid Analog of Glutamate, Is a Broad-Spectrum Antibiotic,” *Communications Biology* 2 (2019): 131.
89. “Recent Advancements on Alternative Control Measures of Histomonas Meleagridis,” *International Journal of Veterinary Science* (2024): 510–516.
90. D. M. Jolliffe, “A History of the Use of Arsenicals in Man,” *Journal of the Royal Society of Medicine* 86 (1993): 287–289.
91. “Alexander Fleming Discovery and Development of Penicillin - Landmark,” n.d., accessed October 23, 2025, <https://www.acs.org/education/whatischemistry/landmarks/flemingpenicillin.html>.
92. S. B. Christensen, “Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and β -Lactams,” *Molecules* 26 (2021): 6057.
93. B. Chen, Q. Liu, A. Popowich, et al., “Therapeutic and Analytical Applications of Arsenic Binding to Proteins,” *Metallomics* 7 (2015): 39–55.
94. S. Y. Mersaoui, C. Guilbert, H. Chou, et al., “Arsenic 3 methyltransferase (AS3MT) Automethylates on Cysteine Residues In Vitro,” *Archives of Toxicology* 96 (2022): 1371–1386.
95. N. P. Paul, A. E. Galván, K. Yoshinaga-Sakurai, B. P. Rosen, and M. Yoshinaga, “Arsenic in Medicine: Past, Present and Future,” *Biometals* 36 (2023): 283–301.
96. L. D. Garbinski, B. P. Rosen, and M. Yoshinaga, “Organoarsenicals Inhibit Bacterial Peptidoglycan Biosynthesis by Targeting the Essential Enzyme MurA,” *Chemosphere* 254 (2020): 126911.
97. A. Sonkar, H. Shukla, R. Shukla, J. Kalita, T. Pandey, and T. Tripathi, “UDP-N-Acetylglucosamine Enolpyruvyl Transferase (MurA) of Acinetobacter Baumannii (AbMurA): Structural and Functional Properties,” *International Journal of Biological Macromolecules* 97 (2017): 106–114.
98. K. A. L. De Smet, K. E. Kempell, A. Gallagher, K. Duncan, and D. B. Young, “Alteration of a Single Amino Acid Residue Reverses Fosfomycin Resistance of Recombinant MurA from Mycobacterium

- Tuberculosis the EMBL Accession Number for the Sequence in This Paper Is X96711," *Microbiology* 145 (1999): 3177–3184.
99. L. D. Garbinski, B. P. Rosen, and M. Yoshinaga, in *Arsenic in the Environment: Bridging Science to Practice for Sustainable Development As2021* (CRC Press, 2024), 260–261.
 100. I. Mancini, G. Guella, M. Frostin, et al., "On the First Polyarsenic Organic Compound from Nature: Arsenicin A from the New Caledonian Marine Sponge *Echinochalina Bargibanti*," *Chemistry – A European Journal* 12 (2006): 8989–8994.
 101. P. Tähtinen, G. Guella, G. Saielli, C. Debitus, E. Hnawia, and I. Mancini, "New Sulfur-Containing Polyarsenicals from the New Caledonian Sponge *Echinochalina Bargibanti*," *Marine Drugs* 16 (2018): 382.
 102. C. Fan, G. Liu, Y. Long, B. Rosen, and Y. Cai, "Thiolation in Arsenic Metabolism: A Chemical Perspective," *Metallomics* 10 (2018): 1368–1382.
 103. H. P. De Koning, "The Drugs of Sleeping Sickness: Their Mechanisms of Action and Resistance, and a Brief History," *Tropical Medicine and Infectious Disease* 5 (2020): 14.
 104. A. H. Fairlamb and D. Horn, "Melarsoprol Resistance in African Trypanosomiasis," *Trends in Parasitology* 34 (2018): 481–492.
 105. J. Oliver, "The Relative Therapeutic Efficiency of Arsphenamine and Gelatin-Arsphenamine," *Experimental Biology and Medicine* 20 (1922): 56–59.
 106. T. Salpadoru, K. E. Pinks, J. A. Lieberman, et al., "Novel Antimony-Based Antimicrobial Drug Targets Membranes of Gram-Positive and Gram-Negative Bacterial Pathogens," *Microbiology Spectrum* 12 (2024): e04234–e04223.
 107. A. M. Metwaly, M. M. Ghoneim, I. H. Eissa, et al., "Traditional Ancient Egyptian Medicine: A Review," *Saudi Journal of Biological Sciences* 28 (2021): 5823–5832.
 108. J. B. Christopherson, "Discussion on the Special Uses of Antimony," *Journal of the Royal Society of Medicine* 22 (2016): 559–568.
 109. I. Park, A. Jailani, J.-H. Lee, B. Ahmed, and J. Lee, "The Antibiofilm Effects of Antimony Tin Oxide Nanoparticles against Polymicrobial Biofilms of Uropathogenic *Escherichia Coli* and *Staphylococcus Aureus*," *Pharmaceutics* 15 (2023): 1679.
 110. D. Kumari, S. Perveen, R. Sharma, and K. Singh, "Advancement in Leishmaniasis Diagnosis and Therapeutics: An Update," *European Journal of Pharmacology* 910 (2021): 174436.
 111. F. Frézard, C. Demicheli, and R. R. Ribeiro, "Pentavalent Antimonials: New Perspectives for Old Drugs," *Molecules* 14 (2009): 2317–2336.
 112. J. Duffin and P. René, "Anti-moine; Anti-biotique: The Public Fortunes of the Secret Properties of Antimony Potassium Tartrate (Tartar Emetic)," *Journal of the History of Medicine and Allied Sciences* 46 (1991): 440–456.
 113. L. N. Gonzalez-Garcia, A. M. Rodríguez-Guzmán, C. M. Vargas-León, et al., "Genomic Characterization of *Leishmania* (V.) *Braziliensis* Associated with Antimony Therapeutic Failure and Variable In Vitro Tolerance to Amphotericin B," *Scientific Reports* 15 (2025): 12973.
 114. R. A. Wilson, "Schistosomiasis Then and Now: What Has Changed in the last 100 years?," *Parasitology* 147 (2020): 507–515.
 115. K. C. Shekhar, "Schistosomiasis Drug Therapy and Treatment Considerations," *Drugs* 42 (1991): 379–405.
 116. R. Bergquist, J. Utzinger, and J. Keiser, "Controlling Schistosomiasis with Praziquantel: How much Longer without a Viable Alternative?," *Infectious Diseases of Poverty* 6 (2017): 74.
 117. A. K. Haldar, P. Sen, and S. Roy, "Use of Antimony in the Treatment of Leishmaniasis: Current Status and Future Directions," *Molecular Biology International* 2011 (2011): 1–23.
 118. S. Wyllie, M. L. Cunningham, and A. H. Fairlamb, "Dual Action of Antimonial Drugs on Thiol Redox Metabolism in the Human Pathogen *Leishmania Donovanii*," *Journal of Biological Chemistry* 279 (2004): 39925–39932.
 119. K. Singh, G. Garg, and V. Ali, "Current Therapeutics, Their Problems and Thiol Metabolism as Potential Drug Targets in Leishmaniasis," *Current Drug Metabolism* 17 (2016): 897–919.
 120. A. Augusto, I. Costa, J. Conceição, and M. L. S. Cristiano, "Targeting Trypanothione Synthetase and Trypanothione Reductase: Development of Common Inhibitors to Tackle Trypanosomatid Disease," *Pharmaceutics* 18 (2025): 1182.
 121. J. Walker and N. G. Saravia, "Inhibition of *Leishmania Donovanii* Promastigote Dna Topoisomerase I and Human Monocyte DNA Topoisomerases I and II By Antimonial Drugs and Classical Antitopoisomerase Agents," *Journal of Parasitology* 90 (2004): 1155–1162.
 122. J. H. No, "Visceral Leishmaniasis: Revisiting Current Treatments and Approaches for Future Discoveries," *Acta Tropica* 155 (2016): 113–123.
 123. N. Gerasimchuk, K. Pinks, T. Salpadoru, et al., "Non-Antibiotic Antimony-Based Antimicrobials," *Molecules* 27 (2022): 7171.
 124. L. A. Ba, M. Döring, V. Jamier, and C. Jacob, "Tellurium: An Element with Great Biological Potency and Potential," *Organic and Biomolecular Chemistry* 8 (2010): 4203.
 125. D. S. Avila, A. Soares, and W. G. Salgueiro, "Toxicology and pharmacology of organotellurium compounds," in *Tellurium: Properties, Uses and Research*, ed. D. Grey (2017), 137–169.
 126. W. Peng, Y. Fu, Y. Wang, et al., "The Antibacterial Effect of Tellurite Is Achieved through Intracellular Acidification and Magnesium Disruption," *mLife* 4 (2025): 423–436.
 127. P. Vishwakarma, N. Parmar, P. Chandrakar, et al., "Ammonium Trichloro [1,2-Ethanedithiolato-O, O']-Tellurate Cures Experimental Visceral Leishmaniasis by Redox Modulation of *Leishmania Donovanii* Trypanothione Reductase and Inhibiting Host Integrin Linked PI3K/Akt Pathway," *Cellular and Molecular Life Sciences* 75 (2018): 563–588.
 128. M. Daniel-Hoffmann, B. Sredni, and Y. Nitzan, "Bactericidal Activity of the Organo-Tellurium Compound AS101 against *Enterobacter Cloacae*," *Journal of Antimicrobial Chemotherapy* 67 (2012): 2165–2172.
 129. M. Hayun, Y. Naor, M. Weil, et al., "The Immunomodulator AS101 Induces Growth Arrest and Apoptosis in Multiple Myeloma: Association with the Akt/Survivin Pathway," *Biochemical Pharmacology* 72 (2006): 1423–1431.
 130. M. Dalal, N. Antil, B. Kumar, and S. Garg, "Unveiling the Therapeutic Potential of Organotellurium(IV) Schiff Base Complexes through Structural Elucidation, Antimalarial, Antioxidant and Antimicrobial Studies," *Journal of Molecular Structure* 1313 (2024): 138558.
 131. S. Mecklenburg, S. Shaaban, L. A. Ba, et al., "Exploring Synthetic Avenues for the Effective Synthesis of Selenium- and Tellurium-Containing Multifunctional Redox Agents," *Organic and Biomolecular Chemistry* 7 (2009): 4753.
 132. J. P. A. Souza, L. R. A. Menezes, F. P. Garcia, et al., "Synthesis, Mechanism Elucidation and Biological Insights of Tellurium(IV)-Containing Heterocycles," *Chemistry: A European Journal* 27 (2021): 14427–14437.
 133. I. A. S. Pimentel, C. D. S. Paladi, S. Katz, W. A. D. S. Júdice, R. L. O. R. Cunha, and C. L. Barbiéri, "In Vitro and In Vivo Activity of an Organic Tellurium Compound on *Leishmania* (*Leishmania*) Chagasi," *PLoS ONE* 7 (2012): e48780.
 134. R. L. O. R. Cunha, M. E. Urano, J. R. Chagas, et al., "Tellurium-Based Cysteine Protease Inhibitors: Evaluation of Novel Organotellurium(IV) Compounds as Inhibitors of Human Cathepsin B," *Bioorganic and Medicinal Chemistry Letters* 15 (2005): 755–760.

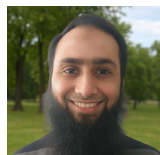
135. A. B. Sabti, A. A. Al-Fregi, and M. Y. Yousif, "Synthesis and Antimicrobial Evaluation of Some New Organic Tellurium Compounds Based on Pyrazole Derivatives," *Molecules* 25 (2020): 3439.
136. L. F. R. De Sá, F. T. Toledo, A. C. Gonçalves, et al., "Synthetic Organotellurium Compounds Sensitize Drug-Resistant *Candida Albicans* Clinical Isolates to Fluconazole," *Antimicrobial Agents and Chemotherapy* 61 (2017): e01231–e01216.
137. R. K. Matharu, Z. Charani, L. Ciric, U. E. Illangakoon, and M. Edirisinghe, "Antimicrobial Activity of Tellurium-Loaded Polymeric Fiber Meshes," *Journal of Applied Polymer Science* 135 (2018): 46368.
138. A. Sathiyaseelan, X. Zhang, J. Lin, and M.-H. Wang, "In Situ, Synthesis of Chitosan Fabricated Tellurium Nanoparticles for Improved Antimicrobial and Anticancer Applications," *International Journal of Biological Macromolecules* 258 (2024): 128778.
139. A. S. Ajayi, P. Adanigbo, J. T. Olaifa, et al., "Tellurium Nanoparticles as Antimicrobial Agents for Multi-Drug-Resistant Infections," *RSC Advances* 15 (2025): 36272–36299.
140. L. Chiaverini, T. Marzo, and D. La Mendola, "AS101: An Overview on a Leading Tellurium-Based Prodrug," *Inorganica Chimica Acta* 540 (2022): 121048.

Biographies



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