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## 3.33 Main-Group Medicinal Chemistry Including Li and Bi\*

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### 3.33.1 Introduction

When discussing drugs and drug development it is usual for one to think of all-organic molecules rather than those containing a metal/main-group element. While it is estimated that about 70% of organic drugs are bioinspired or are derivatives of natural products,<sup>1</sup> putative metal-based drugs are normally synthetic. Metal-based drugs can offer considerable advantages over all-organic drug molecules in that they may function as carriers of otherwise unstable organic drugs (the so-called Trojan horse strategy), offer opportunities for controlled release of drugs, or, crucially, may in fact be the key to therapeutic benefit. Despite the dominance of organic molecules in chemotherapy, it is of interest that modern chemotherapy is widely acknowledged to have begun with the work of Paul Ehrlich who investigated the efficacy of arsenic compounds for the treatment of, for example, African trypanosomiasis.<sup>2</sup> While it is evident that metals featured prominently in traditional medicine of various societies, their adoption in contemporary medicine is not as well developed as it should be. This contention is supported by the fact that several metal-based drugs have dominant roles in modern chemotherapy. Perhaps most notable among these are cisplatin and second-generation platinum complexes that are used successfully for the treatment of various types of cancers. Other prominent elements include vanadium for the treatment of type 2 diabetes, gold for severe cases of rheumatoid arthritis, and more directly relevant to the present chapter, arsenic for the treatment of a specific form of leukemia, antimony for the treatment of the tropical

disease leishmaniasis, and bismuth for peptic and duodenal ulcers caused by *Helicobacter pylori*. While it is of some interest that specific metals appear to target specific diseases, a multitude of metal compounds are continuously being evaluated for efficacy against the full range of human afflictions and the literature describing this development is steadily growing. As such, a comprehensive literature is emerging. Two books dedicated to the topic 'metal-based drugs' have appeared in recent years.<sup>3,4</sup> These are complemented by numerous reviews with recent examples focusing on general aspects,<sup>5,6</sup> metal complexes for the treatment of cancer, which no doubt is the endeavor attracting most attention in this context,<sup>7-10</sup> tropical diseases,<sup>11</sup> diabetes,<sup>12</sup> and for enzyme inhibition.<sup>13</sup> Reflecting growing interest, reviews are also available describing the development of organometallic compounds as therapeutic agents<sup>14-16</sup> and, intriguingly, of metal-organic frameworks (MOFs) which may function as drug carriers, that is a new type of drug delivery system.<sup>17,18</sup>

In the present chapter, a brief overview of each of the heavier main-group elements is given followed by a description of the use, realized and potential, of the element in contemporary medicine. A discussion of lithium salts, which have been long used for the treatment of neurodegenerative disease, is also included after the description of the role of main-group elements in medicine. Emphasis will be placed on known biological targets and mechanism of action rather than comprehensive surveys of all main-group elements compounds evaluated for biological activity. Further, there is an emphasis on research from the recent literature, that is, from the last 5 years or so. The chapter is organized in terms of group by group of the periodic table, starting from gallium, and within each section, row by row. The chapter concludes with a description of lithium salts in medicine.

\*This chapter is dedicated to the memory of Edmunds Lukevics (1936–2009), an enthusiastic pioneer of drugs containing main-group elements.

### 3.33.2 Gallium and Indium

Gallium compounds have received significant attention in terms of therapeutic applications, in particular owing to their demonstrated anticancer activity, and their potential has been reviewed along with their use as diagnostic agents and their toxicity.<sup>19</sup> Considerably less attention has been devoted to indium compounds, although some promising trials have been reported. No therapeutic role has yet been identified for thallium compounds.

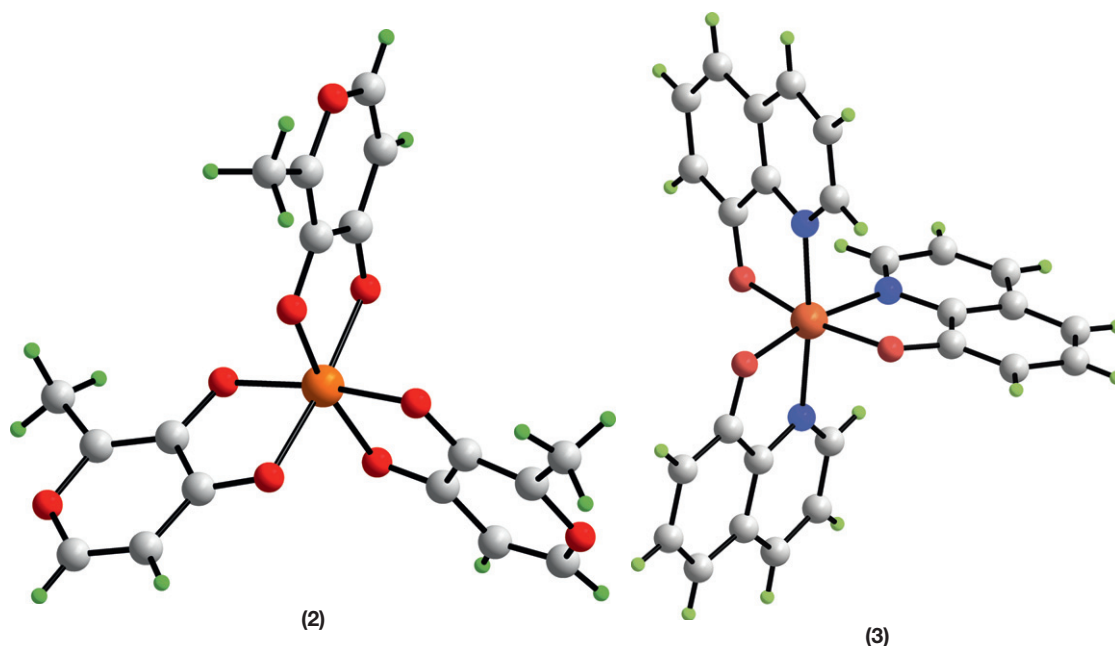
#### 3.33.2.1 Gallium

Gallium ( ${}_{31}\text{Ga}$ ) is of some historical importance as when it was discovered in 1875 by the Frenchman P.E. Lecoq de Boisbaudran, it was observed that gallium had the anticipated properties of 'eka-aluminum', the existence of which was predicted by Mendeleev 6 years earlier. As such, it was the first of Mendeleev's elements to be uncovered and it was this discovery that paved the way for the general acceptance of the periodic table.<sup>20</sup>

Gallium is dominated by the +III oxidation state and some of these compounds are very promising candidates for anticancer therapy, due to the similarity of the  $\text{Ga}^{3+}$  ion with  $\text{Fe}^{3+}$  in terms of, for example, electronegativity, electron affinity, ionic radius, and coordination geometry, but, not redox chemistry as  $\text{Ga}^{2+}$  is not readily accessible in biological media. These similarities suggest that  $\text{Ga}^{3+}$  ions can follow biochemical pathways similar to those found in iron metabolism.<sup>21–23</sup> Thus,  $\text{Ga}^{3+}$  is known to modify the three-dimensional structure of DNA and to inhibit its synthesis, to modulate protein synthesis, and to inhibit the activity of a number of enzymes, such as ATPases, DNA polymerases, ribonucleotide reductase, and tyrosine-specific protein phosphatase.<sup>24–28</sup>

Gallium was the second metal, after platinum, to be used in cancer treatment. Its anticancer properties were described for the first time in 1971.<sup>29,30</sup> Gallium nitrate,  $\text{Ga}(\text{NO}_3)_3$  (**1**; Ganite<sup>®</sup>), is an approved treatment for malignancy-associated hypercalcemia<sup>31</sup> and it is administered intravenously.  $\text{Ga}(\text{NO}_3)_3$  also activates the proapoptotic gene Bax and thereby induces apoptosis through the mitochondrial pathway.<sup>32</sup> In an important development, recent preclinical studies showed that a novel compound, tris(3-hydroxy-2-methyl-4*H*-pyran-4-onato)gallium(III) (gallium maltolate, **2**), having an octahedral geometry based on an  $\text{O}_6$  donor set defined by three chelating ligands (**Figure 1**) inhibits the growth of lymphoma cells resistant to **1** and has significantly greater antineoplastic activity than **1** against a panel of lymphoma cell lines.<sup>33</sup> Therefore, the development of gallium compounds with greater efficacy than **1** is of considerable interest and attracts increasing attention as it may advance the use of gallium in the clinic.

The hydrolytic stability and the ability to penetrate cell membranes impart gallium coordination complexes with improved intestinal absorption leading to increased plasma concentrations of gallium, compared to the gallium nitrate and chloride salts.<sup>34–36</sup> Gallium activity against tumors is thought to be due to its antiproliferative and antimetabolic effects. Once gallium gets into the cell, it exerts its antiproliferative effects by inhibiting ribonucleoside diphosphate reductase (RDR). Due to the competitive binding between  $\text{Ga}^{3+}$  and  $\text{Fe}^{3+}$ , gallium not only affects intracellular iron availability, but also interacts directly with RDR, displacing iron from the enzyme.<sup>32,37,38</sup> Tumor cells are more sensitive to the cytotoxic effects of RDR inhibition than normal cells because of the increased need of deoxynucleotide triphosphates for proliferation, and decreased adaptability and low responsiveness to regulatory signals. Thus, the enzyme has long been considered an excellent target for cancer chemotherapy. Owing to the benefits outlined above as well due to their better antiproliferative



**Figure 1** Molecular structures of gallium maltolate (**2**) and tris(8-quinolinolato)gallium(III) (**3**). Color code for this and subsequent diagrams: central main-group element, orange; oxygen, red; nitrogen, blue; carbon, gray; and hydrogen, green.



*Newport*,<sup>52</sup> and *Staphylococcus* species,<sup>53</sup> that is both Gram-negative and Gram-positive bacteria. The antimicrobial effect of gallium relates to its biochemical similarity to iron. As the ionic radii and other properties of  $\text{Ga}^{3+}$  and  $\text{Fe}^{3+}$  ions are very similar, as mentioned above,  $\text{Ga}^{3+}$  can substitute for  $\text{Fe}^{3+}$  in iron-dependent biological processes such as bacterial iron scavenging and transport systems as well as enzyme synthesis pathways.<sup>49,54</sup> In fact,  $\text{Ga}^{3+}$  is taken up preferentially over  $\text{Fe}^{3+}$  by some bacteria as it binds to ferric sites in transferrin and is also preferentially taken up by mononuclear phagocytes at sites of inflammation.<sup>21,55</sup> However, unlike  $\text{Fe}^{3+}$ ,  $\text{Ga}^{3+}$  is not reducible to the divalent form under physiological conditions. This precludes its participation in crucial bacterial iron-dependent DNA synthetic pathways, thereby accounting for gallium's antimicrobial activity.

As most pathogenic bacteria are dependent upon iron,<sup>37,56</sup> the use of gallium may represent a new treatment strategy against bacterial infection. Coordination of gallium(III) to organic ligands could also improve the antimicrobial action of gallium by increasing its lipophilicity and bioavailability.<sup>20</sup> In addition, by the use of appropriate ligands, metal–ligand synergism could occur. Thiosemicarbazones and their metal complexes present wide pharmacological versatility and their applications as antitumoral, antiviral, and antimicrobial agents have been extensively investigated.<sup>57</sup>

Recent studies suggest that coordination of various pyridine-substituted thiosemicarbazones with structures related to that of the cation in (4) but, with *trans* sulfur atoms, could be an interesting strategy for enhancing both metal and ligand activities on the antibacterial activity against the Gram-negative bacilli *P. aeruginosa*.<sup>58</sup> Moreover, since thiosemicarbazones are in general poorly active against Gram-negative bacteria,<sup>57</sup> coordination to gallium could be an efficient strategy to broaden their spectrum of antibacterial action. Using the siderophore, desferrioxamine, as a carrier for gallium also proved to be an effective strategy for combating *P. aeruginosa*.<sup>59</sup> Gallium(III) maltolate (2) has shown significant inhibitory effect on *in vitro* growth of *Staphylococcus aureus*, methicillin-resistant *S. aureus*, methicillin-resistant *S. pseudintermedius*,<sup>53,60</sup> and *R. equi*.<sup>61</sup> *S. aureus* is a major cause of surgical site infection and hospital-acquired bacteremia, and of subsequent life-threatening infection manifesting as necrotizing fasciitis, pneumonia, septic arthritis, osteomyelitis, and endocarditis.<sup>62,63</sup> This indicates that gallium maltolate may be useful in the treatment of *Staphylococcal* infections in veterinary species infected with *S. aureus*, particularly when used as a topical or local therapy, in addition to its known antitumor activity.<sup>62,63</sup>

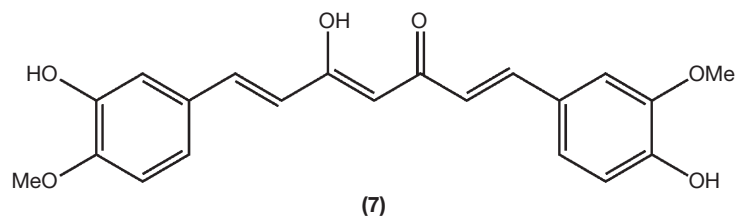
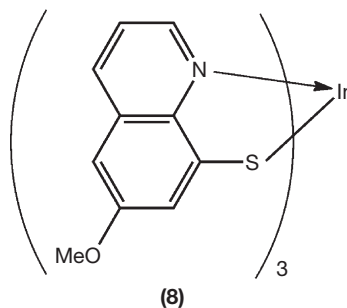
While not necessarily therapeutic agents, for completeness and reflecting the ever-growing interest in gallium for therapeutic applications, it is worth mentioning the incorporation of gallium in phosphate glasses for the slow release of  $\text{Ga}^{3+}$ .<sup>64</sup> Conversely, it was reported recently that bioceramics and gels

incorporating  $\text{Ga}^{3+}$  may be employed for the slow release of bioactive molecules such as curcumin (7),<sup>65</sup> the yellow antibacterial pigment which is the major component of turmeric.

### 3.33.2.2 Indium

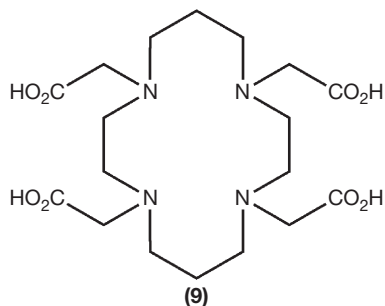
While the relatively rare element indium ( $_{49}\text{In}$ ) is considered nontoxic by most sources, it is only relatively recently that research into potential medical and radiodiagnostic applications of indium compounds has emerged in the literature. While the general phobia against the heavier elements might be partly responsible for this inactivity, just like  $\text{Ga}^{3+}$ ,  $\text{In}^{3+}$  is known to interact with transferrins, iron-binding blood plasma glycoproteins that control the level of free iron in biological fluids, thereby providing a likely mechanism for transport of  $\text{In}^{3+}$  across a cell membrane. When  $^{111}\text{In}$ -labeled compounds are administered with weakly bound ligands or in acidic solutions, more than 95% of the  $\text{In}^{3+}$  is found to bind to proteins, mainly transferrin.<sup>66</sup> This is crucial as when a transferrin protein loaded with iron encounters a transferrin receptor (TFR) on the surface of a cell, it binds to it and is transported into the cell in a vesicle by receptor-mediated endocytosis suggesting that indium-loaded transferrins can similarly transport  $\text{In}^{3+}$ .<sup>67,68</sup> Although  $\text{In}^{3+}$  transferrin binds the TFR as well as diferric transferrin, the transport of  $\text{In}^{3+}$  across the cell membrane is much slower than in the case of  $\text{Ga}^{3+}$ . However,  $\text{In}^{3+}$  still tends to accumulate in tissues that have high levels of TFR, and it seems likely that transferrin is a mediator for the delivery of  $\text{In}^{3+}$  to tumors.<sup>69</sup> In any case, it is clear that indium(III) compounds will use the first steps of the classical iron pathway after reaching the blood stream and this may have important consequences in relation to the toxicological or radiopharmaceutical roles of these compounds.

In terms of biological screening, reports are few. In a rare trial involving indium(III) and other metal 8-quinolinethiolates against a variety of human cell lines,<sup>70</sup> most compounds proved cytotoxic not only against cancer cell lines investigated but also against normal cell lines. A notable exception was tris(6-methoxy-8-quinolinethiolate)indium(III), (8), which is likely to have a mer distribution of nitrogen atoms as for tris(8-quinolinolato)gallium(III) (3).



Compound 8 has lower cytotoxicity against murine hepatoma MG-22A tumor cells compared to the other metal complexes evaluated (for example, rhodium, osmium, iridium, antimony, and bismuth) but considerably lower cytotoxicity (that is, 22–44 times) against normal NIH 3T3 fibroblasts, indicating selectivity.<sup>70</sup>

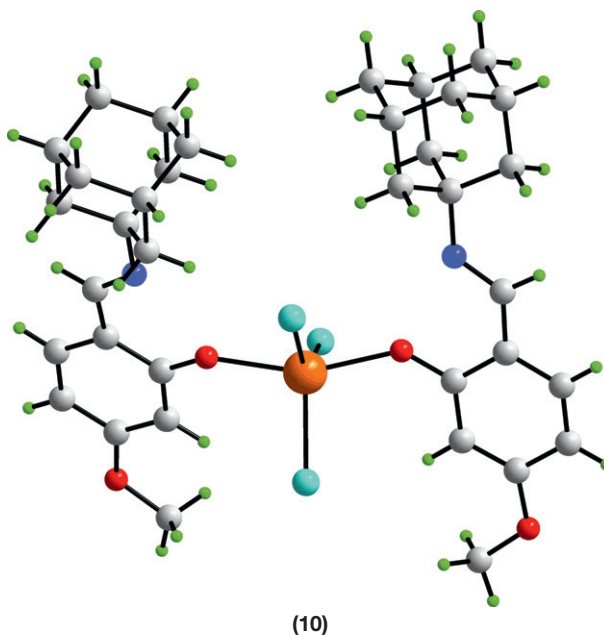
The inhibitory activity against *Mycobacterium tuberculosis* of a selection of metal ions coadministered with macrocyclic compounds including 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (9) proved the efficacy of indium(III).<sup>71</sup> When equimolar concentrations of the free cations of  $V^{4+}$ ,  $As^{3+}$ ,  $Fe^{3+}$ ,  $In^{3+}$ , and  $Bi^{3+}$  with 9 were tested *in vitro* against *M. tuberculosis*, the metal compounds exhibited greater activity than the uncoordinated macrocycles. Further, radiometric inhibition ranged from 80% to 99%, with compounds of vanadium(IV), bismuth(III), and indium(III), in order of increasing activity. The highest radiometric inhibition levels were obtained with the  $[In(9-H_2)]^-$  compound, which caused drops of up to 4 log units in cellular viability.<sup>71</sup>



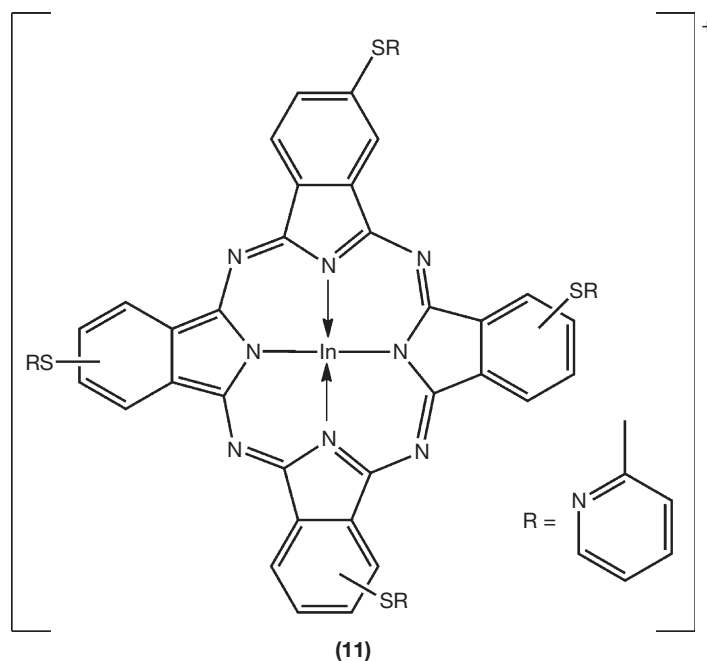
As mentioned above, curcumin (7) is a natural antibacterial agent. Its indium(III) compound displays enhanced activity compared with 7 against a variety of bacteria including *S. aureus* and *Escherichia coli*.<sup>72</sup> These two bacteria also featured in a separate trial where indium(III) compounds with neutral Schiff base molecules containing the adamantane residue, for

example, trigonal bipyramidal (10) with *trans* oxygen atoms (Figure 3), were evaluated. In all cases, the indium(III) compound proved more active than the uncoordinated Schiff base molecules proving the importance of the metal, particularly at higher concentrations.<sup>73</sup>

Finally, and for completeness, several recent studies have reported the efficacy of indium(III) phthalocyanine compounds, including water-soluble cationic derivatives such as (11), for use in photodynamic therapy (PDT), for example, in the treatment of cancer.<sup>74–76</sup>



**Figure 3** Molecular structure of bis[2-((adamantan-1-ylimino)methyl)-5-methoxyphenolato]-trichloridoindium(III) (10). Additional color code: chloride, cyan.



From the aforementioned, the evaluation of indium(III) compounds for biological activity is clearly in its infancy. Given the initial promising results, additional studies are clearly warranted.

### 3.33.3 Germanium, Tin, and Lead

Of all the main-group element compounds covered in this chapter, tin(IV) compounds, in particular, organotin(IV) compounds, have attracted the most attention, especially for their putative antitumor potential. Despite these efforts, this potential remains largely unrealized. Other biological activities, for example, antimicrobial, antiviral, and antifungal, have also attracted considerable attention. By contrast, the potential efficacy of germanium(IV) compounds have received much less attention even though some specific derivatives have undergone clinical evaluation; of those evaluated, no significant toxicity has been found (see below). Not surprisingly, owing to its known toxicity a very limited number of studies have appeared on the potential of lead compounds as therapeutic agents.

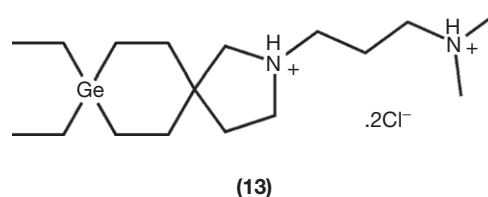
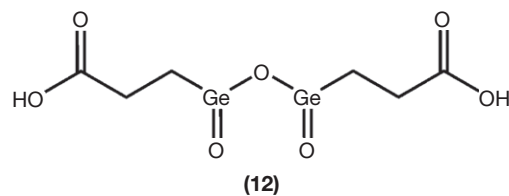
#### 3.33.3.1 Germanium

Germanium ( ${}_{32}\text{Ge}$ ) is a metalloid known for its semiconducting properties. Owing to its low natural abundance, germanium was discovered relatively recently, as with gallium. Interestingly, and again as for gallium, Mendeleev predicted its existence and named it 'ekasilicon'. Germanium(IV), either as molecular compounds or in inorganic forms, may modulate immune response,<sup>77,78</sup> reduce mutagenicity and genotoxicity of toxicants,<sup>79–81</sup> and even possess antimicrobial activity.<sup>82</sup> Although there are reports revealing the clinical effects of germanium(IV) compounds, the cellular and molecular responses to the molecules are not well understood. Further studies are required to explore the biological impact of germanium(IV) compounds in consideration of their demonstrated biological activities.

Several DNA-damaging agents can arrest the transition of the G2- to M-phase cell cycle. The delay at the G2 phase is hypothesized to enable the repair of damaged DNA.<sup>83</sup> Cyclin-dependent kinases (CDKs) are key regulators in mammalian cell cycle and their regulation occurs through cyclin production, destruction, relocation, inhibitory, and activating phosphorylation events.<sup>84</sup> CDK1 kinase activity is critical for cell-cycle progression through mitosis and as such it is recognized as a valid anticancer target. It has been reported that CDK1 inhibitors effectively arrest tumor cell growth prompting recent interest in the discovery and development of new CDK1 inhibitors.<sup>85</sup> In 2002, germanium oxide ( $\text{GeO}_2$ ) was found to block cell-cycle progression at G2 phase for Chinese hamster ovary cells. Surprisingly, this delay was not due to DNA damage but due to the reduction of CDK1 activity after  $\text{GeO}_2$  treatment.<sup>86</sup> Despite these encouraging results, most attention has been directed toward evaluating the anticancer potential of molecular germanium(IV) compounds.

Prominent organogermanium(IV) compounds found to exhibit significant antiproliferative activity against human tumors include bis(2-carboxyethylgermanium)sesquioxide (12), also

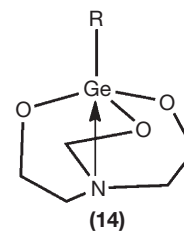
known as organic germanium and Ge-132, and 3-(8,8-diethyl-3-aza-8-germaspiro[4.5]decan-3-yl)-*N,N*-dimethylpropan-1-amine dihydrochloride (13), commonly known as spirogermanium.

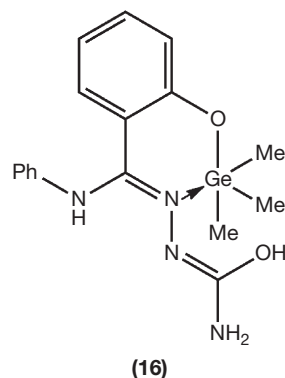
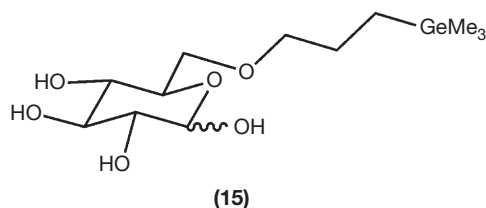


Both 12 and 13 inhibit the growth of diverse fluid and solid tumors.<sup>87</sup> Toxicity does not appear to be a major issue as 12 is used widely as a dietary supplement.<sup>88</sup> In early clinical studies, 13 displayed activity against advanced ovarian carcinomas and lymphocytic lymphoma.<sup>89</sup> Compound 12 has been reported to enhance several cytokines (such as interferon-gamma ( $\text{INF-}\gamma$ ) and interleukin-2 ( $\text{IL-2}$ )), which may be due to its antioxidant effects.<sup>90</sup> Compound 12 facilitates oxygen entry as the primary electron acceptor into red blood cells. In cancer cells, which cannot utilize oxygen, which actually appear to be oxygen sensitive, the presence of an oxygen catalyst could have deleterious effects and likely therapeutic value.<sup>91</sup> The exact anticancer mechanism of these compounds remains unclear, however. A recent study that evaluated the cytotoxicity of hydroxyl derivatives of 12 suggested these may possess DNA-binding specificity, like cisplatin, to inhibit cancer cell proliferation.<sup>92</sup>

The next group of biologically active organogermanium compounds that have attracted considerable attention are germatranes; see (14) for the archetypical structure. Germatranes are tetracoordinated and contain hypervalent germanium owing to the formation of a transannular bond from nitrogen, a feature which imparts chemical stability to the molecule.<sup>93</sup> The nature of the R substituent at the germanium atom influences the strength of the  $\text{N}\rightarrow\text{Ge}$  bond and biological properties.<sup>94</sup> Biological investigations have demonstrated that certain bromobenzylgermatranes have low toxicity ( $\text{LD}_{50} > 1000 \text{ mg kg}^{-1}$ ) and have high anesthetic and anti-Corazol activity.<sup>95</sup> Further they may improve memory processes and completely prevent animals from retrogradal amnesia caused by electroshock.<sup>95</sup>

Beyond these studies, other investigations for biological activity are comparatively rare and sporadic. In a recent study, compound 12 has been demonstrated to enhance





protoporphyrin IX, therefore pointing to a possible role in the treatment of chronic hepatitis.<sup>96,97</sup> A trimethylgermanium(IV) sugar derivative (15) was originally synthesized with the desire to reduce contamination by inorganic germanium in drug formulations of 12.<sup>98</sup> Trials showed that 15 was more effective than 12 in inducing INF- $\gamma$  with the concomitant enhancement of antiproliferative activity.<sup>98</sup> Finally, complexation of diorganogermanium(IV) by Schiff base derivatives, for example, trigonal bipyramidal (16), and screening for antifungal and antibacterial activity showed that the germanium-containing compounds were more effective than the uncoordinated ligands but not as effective as standard antimicrobial agents.<sup>99</sup>

### 3.33.3.2 Tin

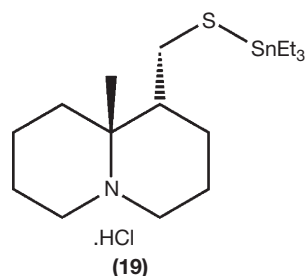
Tin ( ${}_{50}\text{Sn}$ ) compounds, more often than not organotin(IV) compounds, have arguably, among all main-group elements surveyed herein, attracted the greatest attention in terms of attempts at drug discovery, in particular as potential antitumor agents. The reasons for this attention are varied; however, it is fair to state that with one or two notable exceptions, the attention received by these compounds has not resulted in significant breakthroughs in terms of new drugs. Also disappointing is the lack of knowledge of possible biological mechanisms that could drive rational drug discovery.

The ability to inhibit cancer cells by organotins has been known for about 80 years.<sup>100</sup> Much of the tremendous impetus to study organotin compounds rests with the high *in vitro* cytotoxicity they exhibit compared with cisplatin, the benchmark metal-based anticancer drug, especially used for treating testicular, ovarian, bladder, and head/neck cancers.<sup>101</sup> Several comprehensive reviews on the potential antitumor activity of tin compounds have appeared in recent years and these uniformly highlight the diverse range of organic molecules coordinated to the tin center, normally in organotin compounds,<sup>102–104</sup> including a review of organotin derivatives coordinated by molecules that function as drugs in their own right.<sup>105</sup> Even so, identification of definitive structural relationships and mechanisms of action is still wanting.<sup>106</sup> As tin(IV) is a hard metal center, it is no surprise that tin compounds prefer to bind to phosphate-oxygen of the polyanionic structure of DNA forcing conformational changes.<sup>107,108</sup> Tin compounds are also known to act as strong apoptotic directors, activating apoptosis directly via the p53 tumor suppressor pathway, TNF-related apoptosis-inducing ligand (TRAIL) receptor, caspases, and the Bcl-2 family of proteins. Since there are two primary modes of apoptosis,

metal-induced apoptosis is thought to be initiated intracellularly with the mitochondria being most pertinent in mediating apoptosis via metal-induced reactive oxygen species (ROS).<sup>109</sup> In the following, brief summaries of studies are given where potential activity was coupled with investigations of possible mechanisms of action.

Early *in vitro* studies on di-*n*-butyltin dichloride (17) and tri-*n*-butyltin chloride (18) showed these to induce apoptosis in rat thymocytes, inhibiting DNA synthesis and increasing RNA synthesis.<sup>110</sup> The apoptotic pathway induced by 17 and 18 commences with an increase in concentration of  $\text{Ca}^{2+}$  ions. This is followed by the release of mitochondrial cytochrome *c*, activation of caspases, and finally results in DNA fragmentation.<sup>111</sup> More recent studies are available on organotin compounds carrying organic ligands.

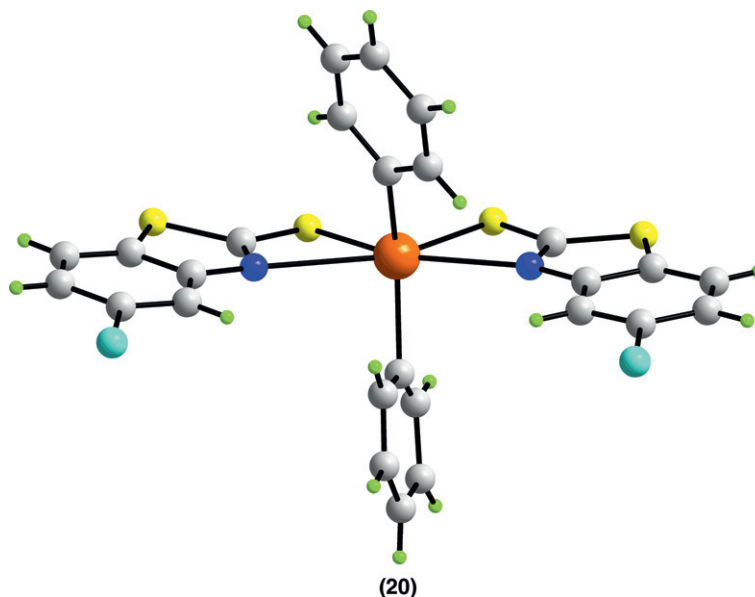
A compound attracting early attention was triethyltin(IV)lupinylsulfide hydrochloride (19), a quinolizidine derivative, which was developed as a potential antitumor agent.<sup>112</sup> This compound exhibited potent antiproliferative effects on different human cancer cell lines but it appears that DNA is not the primary target for 19. Rather, perturbation of homeostasis, impairment of mitochondrial functions, and inhibition of protein synthesis may be primarily responsible for cytotoxicity.<sup>112</sup>



Triphenyltin(IV) compounds such as diphenyltin(IV) bis(5-chloro-2-benzothiazole thiolate) (20), having a skew-trapezoidal bipyramidal coordination geometry with the phenyl rings lying over the weaker Sn–N bonds (Figure 4), displayed an interesting correlation between cytotoxicity and inhibition of lipoxygenase-induced peroxidation of linoleic acid.<sup>113</sup>

Organotin carboxylates have received significant attention in terms of their ability to exhibit promising cytotoxicity profiles.<sup>102–104</sup> A series of tricyclohexyltin carboxylates, as exemplified by the pentacoordinated tin compound (21), which features an asymmetrically coordinating carboxylate ligand (Figure 5), were evaluated against the daunomycin-resistant





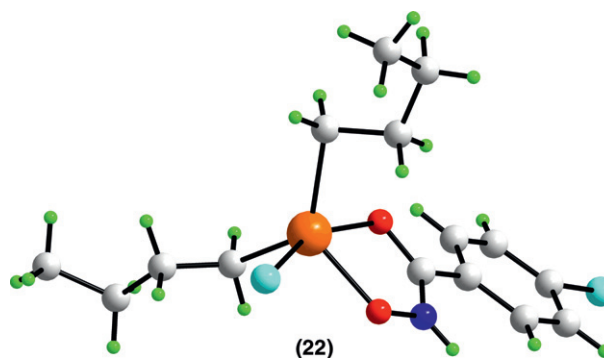
**Figure 4** Molecular structure of diphenyltin(IV) bis(5-chloro-2-benzothiazole thiolate) (20).



**Figure 5** Molecular structure of tricyclohexyltin(IV) 2,5-dimethyl-3-furoate (21).

K562/R cell line which is known to express P-glycoprotein.<sup>114</sup> The studied compounds were shown not to be substrates of the protein efflux pump, a key indicator that these compounds do not induce multidrug resistance.<sup>114</sup> As mentioned above, *in vivo* studies are comparatively rare for tin compounds. However, some recent reports have emerged.

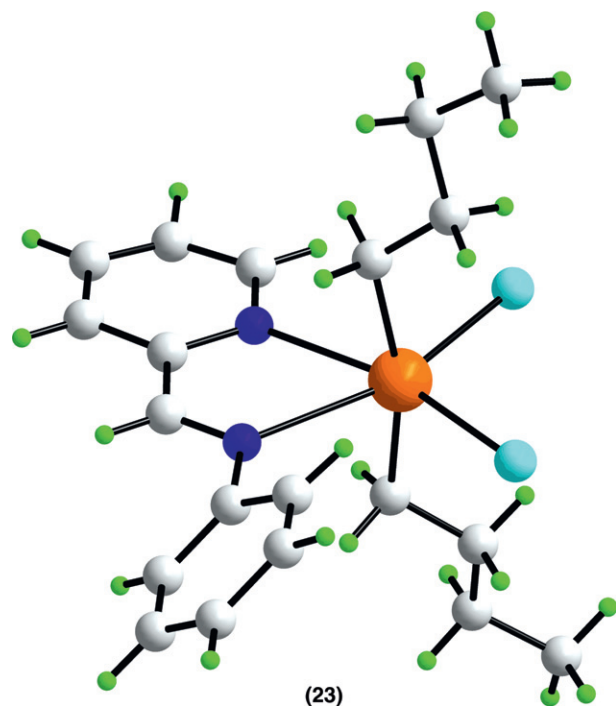
An *in vivo* study was carried out on di-*n*-butylchloridotin(IV) 4-chlorobenzohydroxamate, (22), which is illustrated in **Figure 6** and which exhibits a trigonal bipyramidal geometry with one oxygen and the chloride atoms in the axial positions.<sup>115</sup> Compound 22 was shown to display a good dose–effect relationship against liver tumor H22 and sarcoma S180, close to that exhibited by cisplatin, as well as a dose dependency on mice Ehrlich's ascites tumor.<sup>115</sup>



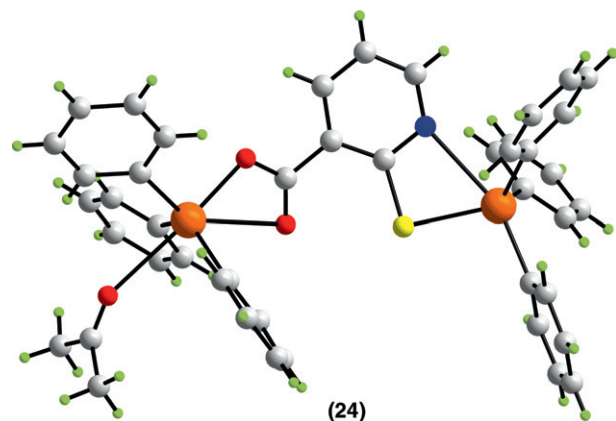
**Figure 6** Molecular structure of di-*n*-butylchloridotin(IV) 4-chlorobenzohydroxamate (22).

In a more recent study, another series of diorganotin compounds were found to cause apoptotic death via different pathways. In particular, one of these, antiproliferative and antitumor active di-*n*-butyldichloridotin(IV) 2-(phenylimino-methyl)pyridine (23), featuring an octahedral  $C_2Cl_2N_2$  coordination geometry (**Figure 7**), was shown to significantly block cell-cycle progression, induce chromosome aberrations, and sister chromatid exchanges in human lymphocytes raising the levels of p53 and p21 proteins.<sup>116</sup>

Antitumor potential has been explored for dinuclear compound 24 featuring two triphenyltin(IV) residues connected to a bridging 2-mercaptonicotinate dianion, one via the chelating N,S group, giving rise to a trigonal bipyramidal tin center. The other is chelated by the oxygen atoms of the asymmetrically coordinating carboxylate group and the distorted octahedral coordination geometry is completed by an oxygen atom from the solvent acetone molecule (**Figure 8**).<sup>117</sup> In this study it was reported that the cytotoxic effects exerted by 24 might be in part due to apoptosis in both leiomyosarcoma and human breast adenocarcinoma (MCF-7) cell lines. Apoptotic death caused by 24 was also confirmed by the DNA fragmentation analysis, in which the typical



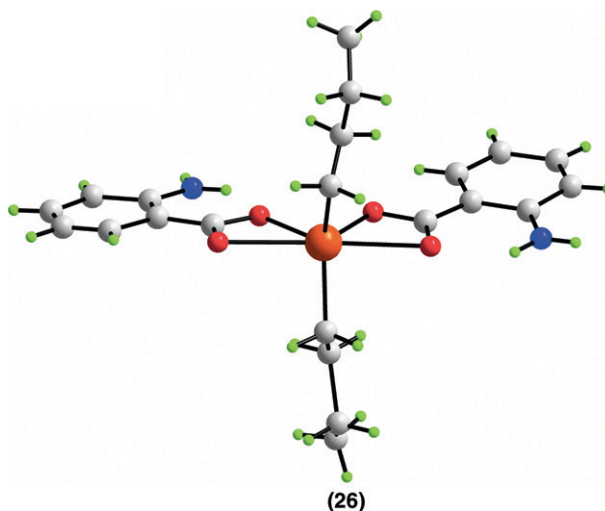
**Figure 7** Molecular structure of di-*n*-butylchloridotin(IV) 2-(phenyliminomethyl)pyridine (**23**).



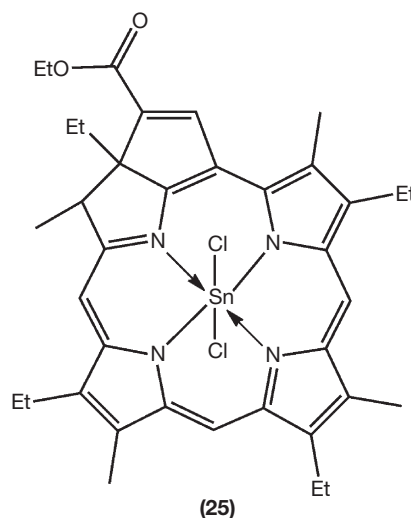
**Figure 8** Molecular structure of bis(triphenyltin(IV))( $\mu_2$ -2-mercaptocotinate) acetone (**24**).

pattern of the oligonucleosomal-sized fragments was also observed. Mean survival times of up to 200% were observed in Wistar rats inoculated with **24**, accompanied by reduced cancer volume and complete cure in 30% of the animals.<sup>117</sup>

Rather than operating as a potential drug for the treatment of cancer, a tin(IV) porphyrin compound, (**25**), commonly known as tin ethyl etiopurpurin, has been employed as a photosensitizing agent in PDT. Clinical trials have shown efficacy in the treatment of cutaneous basal cell cancer, breast metastasis to the chest wall, and Kaposi sarcoma.<sup>118,119</sup> While this photosensitizer has demonstrated great promise and produced excellent preliminary clinical results, it has not been brought to commercial realization.<sup>120</sup> While thus far the focus in this section has been upon cancer, tin compounds have also been evaluated for their activity against other diseases.

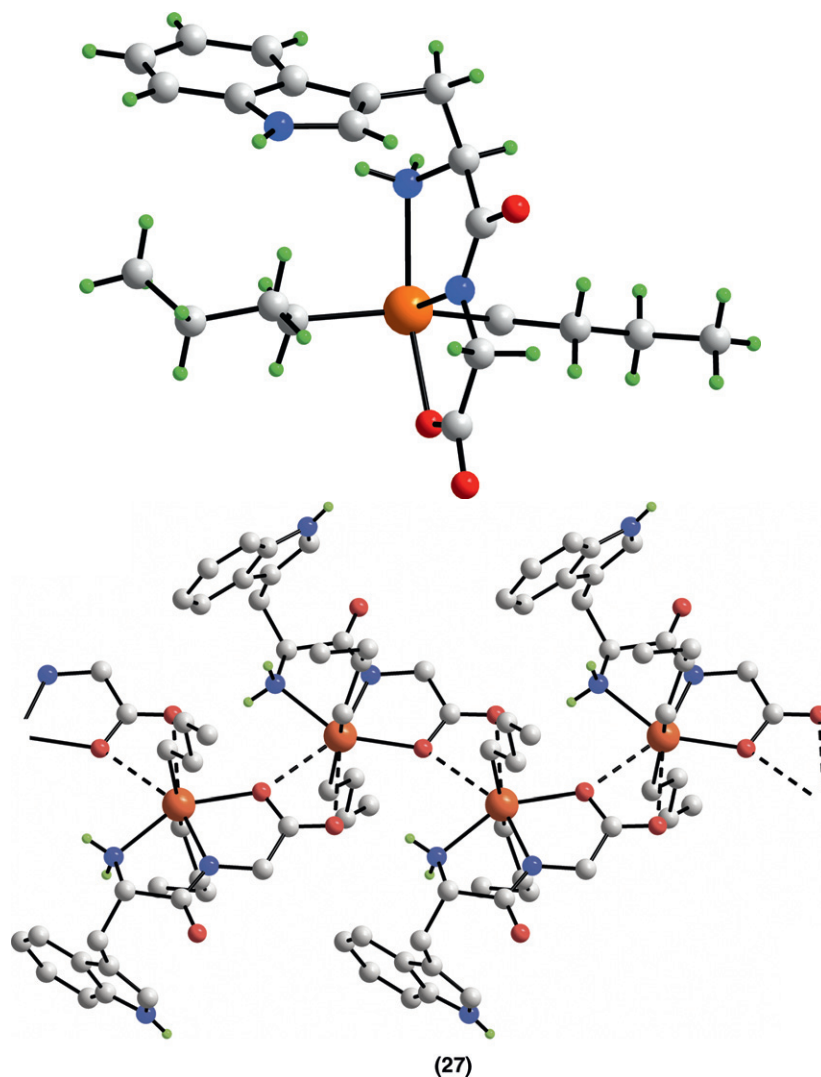


**Figure 9** Molecular structure of di-*n*-butyltin(IV) bis(aminobenzoate) (**26**).



Organotin(IV) compounds have attracted attention also for their wide variety of biological activities which includes bactericidal, acaricidal, and fungicidal, with aspects of these being reviewed recently.<sup>121,122</sup> Mechanistic studies are still rare but a recent study is exceptional in this regard.<sup>123</sup> Several organotin compounds, including di-*n*-butyltin(IV) bis(aminobenzoate) (**26**), having a skew-trapezoidal bipyramidal geometry with the tin-bound organic groups lying over the weaker Sn–O bonds (**Figure 9**), were evaluated against *Candida albicans*. No changes in DNA integrity or in mitochondria function were observed. However, all of the organotin compounds surveyed were found to reduce ergosterol biosynthesis and caused severe damage to *C. albicans* cells compromising the cellular integrity, suggesting that the organotin complexes act on the cell membrane in view of cytoplasm leaking and cellular deformation. The study also indicated that the mechanism of action of these organotin compounds is similar to that of the azole drugs, such as ketconazole or fluconazole, normally used in *Candida* infections.<sup>123</sup>

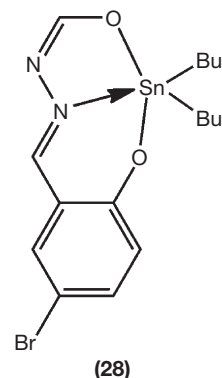
A recent study described the anti-inflammatory activity of organotin(IV) tryptophanylglycinates, exemplified by di-*n*-butyltin(IV) tryptophanylglycinate (**27**), exhibiting, to a first



**Figure 10** Molecular structure of di-*n*-butyltin(IV) tryptophanylglycinate (**27**) (upper view), and supramolecular chain mediated by hypervalent Sn...O interactions (C-bound hydrogen atoms omitted) leading to a  $\Psi$ -pentagonal bipyramidal geometry (lower view).

approximation, a trigonal bipyramidal geometry with the carboxylate-O and amine-N atoms defining the axial positions (**Figure 10**).<sup>124</sup> This coordination geometry has a rather large void (the C–Sn–C angle is approximately  $152^\circ$ ) and this is occupied by two carboxylate-O atoms (Sn–O = 2.8 Å) from another molecule leading to a supramolecular chain and hence to a tin atom coordination geometry based on a  $\psi$ -pentagonal bipyramid. Biological screening of these compounds indicated good anti-inflammatory activity with limited side effects on the cardiovascular system/blood pressure.<sup>124</sup>

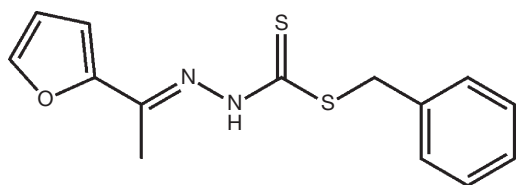
Finally, anti-leishmanial activity has been demonstrated for some organotin compounds<sup>125,126</sup> with that exhibited by di-*n*-butyltin(IV) 5-bromo-2-oxidobenzylidene formylhydrazine (**28**), in which the trigonal bipyramidal tin center is coordinated by the tridentate dianion, having activity comparable to the standard drug, Amphotericin B (that is,  $0.41 \pm 0.05$  vs.  $0.50 \pm 0.02$  mg ml<sup>-1</sup>).<sup>126</sup>



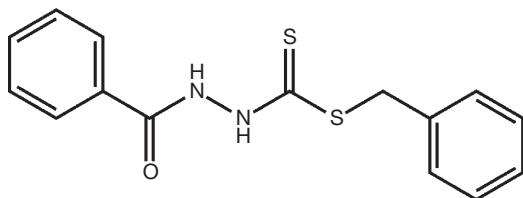
### 3.33.3.3 Lead

The least studied of the elements of this group are compounds of lead ( $s_2\text{Pb}$ ). It is the well-known toxicity (also see

Chapter 3.04) of lead/lead compounds that has undoubtedly limited interest in exploring their potential as therapeutics. Thus, with the exception of results from the Crouse group,<sup>127,128</sup> which has investigated the lead(II) and other heavy element dithiocarbazates, virtually no recent studies have been reported. When lead(II) is complexed by the monoanion derived from 29 the product is highly cytotoxic against leukemic cells (CEM-SS) with an  $IC_{50}$  of  $3.25 \mu\text{g cm}^{-3}$ , whereas the  $PbNO_3$  salt is inactive under the same conditions.<sup>127</sup> In another study, when lead(II) is coordinated to dithiocarbazate derived from 30, the product displayed marked cytotoxicity against human myeloid leukemia (HL-60) with an  $IC_{50}$  of  $1.54 \mu\text{g cm}^{-3}$ .<sup>128</sup>



(29)



(30)

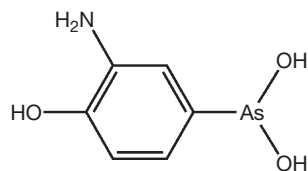
While not downplaying the very real difficulties associated with toxic elements such as lead, possible drugs may emerge if a therapeutic window can be identified that allows beneficial doses to be administered. This idea is no better illustrated in the next section where the therapeutic use of arsenic is outlined.

### 3.33.4 Arsenic, Antimony, and Bismuth

In contrast to the elements belonging to the other groups covered in this survey, each member of this group plays a prominent role in contemporary medicine with arsenic, antimony, and bismuth compounds having clinical applications in cancer, leishmaniasis, and stomach ulcers, respectively, as detailed below. Over and above these, each of the elements has been evaluated for a range of biological efficacies and brief mention of these will also be made.

#### 3.33.4.1 Arsenic

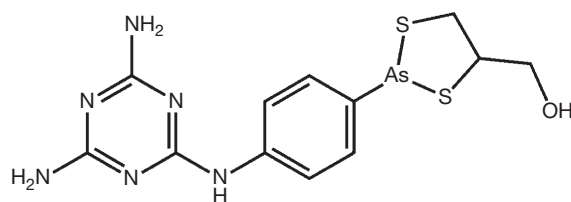
Arsenic ( $_{33}\text{As}$ ) compounds have been used in medicine for more than 2400 years with ailments such as ulcers, the plague, and malaria being targeted by arsenic formulations during this period.<sup>129,130</sup> Indeed, arsenic played an important role in development of modern chemotherapy<sup>2</sup> being a key component of Paul Ehrlich's magic bullet 'Salvarsan', now known to be a prodrug that releases the therapeutically active species,



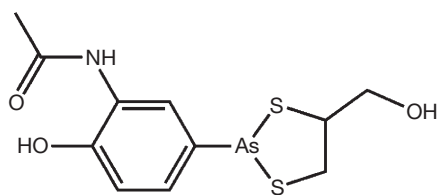
(31)

(3-amino-4-hydroxyphenyl)arsinous acid (31).<sup>131</sup> As with many compounds prepared at that time, Salvarsan was developed to eradicate *Treponema pallidum*, the causative bacterium of syphilis. Indeed, its use continued until supplanted by penicillin.<sup>132</sup> Arsenic compounds have also been long known to exhibit anticancer activity as summarized in a recent bibliographic review.<sup>133</sup> In 1878, Fowler's solution, comprising potassium arsenite ( $KAsO_2$ , 32), better known as a rodenticide, was reported to be active against leukemia and its use in the clinic continued until the middle of the twentieth century when it was replaced by busulfan (butane-1,4-diyl dimethanesulfonate) in the 1950s.<sup>134,135</sup> As mentioned above, arsenic compounds, either alone or in combination with other drugs, have been used for the treatment of a range of diseases including syphilis, psoriasis, trypanosomiasis (human African sleeping sickness), pernicious anemia, and Hodgkin's disease.<sup>136,137</sup>

Some of these clinically utilized arsenic compounds have subsequently been evaluated for anticancer potential. Prominent among these are the trypanocide, melarsoprol (33),<sup>138</sup> and the amebicidal and bactericidal, arsthinol (34).<sup>139</sup> While each exhibits antitumor potential, by far the greatest attention has been devoted to arsenic trioxide ( $As_2O_3$ , 35), distributed as Trisenox<sup>®</sup>,<sup>140</sup> which until recently was used as a primary drug for combating chronic myeloid leukemia as well as other leukemias.<sup>141</sup>



(33)



(34)

$As_2O_3$  (35) is a naturally occurring substance that has attracted increasing attention since the discovery of its clinical efficacy in acute promyelocytic leukemia (APL) reported by Chinese investigators who discovered 35 to be a key component of traditional Chinese medicine.<sup>140,141</sup> At present, the drug is indicated as a broad-spectrum anticancer medicine by

apoptosis induction for a variety of cancers including APL, other myeloid leukemia cells (HL-60, NB4, and U937),<sup>142</sup> human breast cancer cell line (MDA-231),<sup>143</sup> hepatoma-derived cell lines (SK-Hep-1, HepG2, and HuH7),<sup>144</sup> and gall bladder,<sup>145</sup> esophageal,<sup>146</sup> prostate,<sup>147</sup> and ovarian carcinomas.<sup>148</sup>

Current research indicates that the chemotherapeutic effectiveness of 35 arises due to its ability to modulate several pathways in cancer cells. This attribute leads to increased apoptosis, enhanced differentiation, inhibition of cell proliferation, and angiogenesis.<sup>141</sup> As<sub>2</sub>O<sub>3</sub> is also known to target mitochondria in cancer cell lines resulting in decreased mitochondrial membrane potential, induction of ROS, release of cytochrome *c*, and activation of several cell death pathways.<sup>143,149,150</sup>

As<sub>2</sub>O<sub>3</sub> (35) is also known to interact with genes. Most patients suffering with APL tend to overexpress the PML-RAR $\alpha$  fusion gene resulting from the translocation of the t(15;17) chromosome,<sup>151,152</sup> and therefore it is important that 35 can induce the inactivation or degradation of PML-RAR $\alpha$  as this gene is known to inhibit the expression of genes associated in myeloid differentiation.<sup>153</sup> Some literature reports indicate that 35 also decreases the expression of genes involved with angiogenesis (vascular endothelial growth factor (VEGF)), cell proliferation (Cyclin D1), and survival (bcl-2 and NF $\kappa$ B) in cancer cell lines.<sup>154,155</sup> It is noteworthy that some currently used anticancer drugs, such as curcumin, betulinic acid, and tolfenamic acid, function similarly by decreasing the expression of these genes.<sup>156</sup> This effect is ascribed to the decreased expression of specificity protein transcription factors (Sp), Sp1, Sp3, and Sp4, which are overexpressed in many tumors and are known to bind to the guanine/cytosine-rich promoter elements in Sp regulated genes.<sup>157</sup> The expression of genes such as VEGF, Cyclin D1, bcl-2, and NF $\kappa$ B is also decreased in cancer cells which are transfected with a mixture (iSp) of small inhibitory RNAs for Sp1, Sp3, and Sp4.<sup>156</sup> The ability of 35 to interact with genes has implications for patients suffering from gall bladder carcinoma.

As<sub>2</sub>O<sub>3</sub> has been reported to inhibit the proliferation of gall bladder carcinoma *in vitro* and *in vivo* as well as the transcription of cell-cycle-related protein Cyclin D1. The overexpression of Cyclin D1 inhibited the negative role of 35 in cell-cycle progression. Furthermore, the Sp1 transcription factor was downregulated by 35, with a corresponding decrease in Cyclin D1 promoter activity. Taken together, these results suggested that 35 inhibited gall bladder carcinoma cell proliferation via downregulation of Cyclin D1 transcription in an Sp1-dependent manner, which provides a new mechanism of 35-involved cell proliferation and may have important therapeutic implications in gall bladder carcinoma patients.<sup>154</sup>

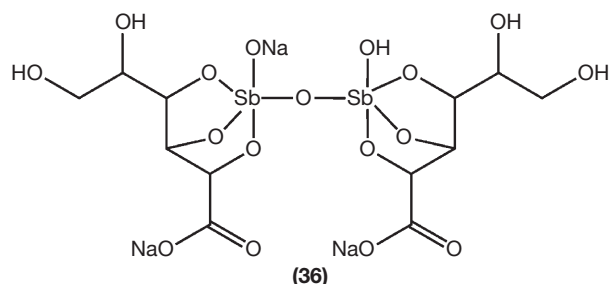
As<sub>2</sub>O<sub>3</sub> has some single-agent activity in myeloma. In a single-agent (0.15 mg kg<sup>-1</sup> day<sup>-1</sup> for 60 days) phase II trial in multiple myeloma patients with advanced, extensively pretreated and refractory disease, 2 of the 14 patients achieved partial responses.<sup>158</sup> In addition, there is preclinical evidence for a synergistic interaction between 35 and doxorubicin as 35 has been shown to increase the intracellular accumulation of doxorubicin in hepatocellular carcinoma.<sup>159</sup> More recent studies have shown that for the 35/microtubule-stabilizing agent and paclitaxel (PTX) combination, treatment at low concentrations could synergistically inhibit proliferation and

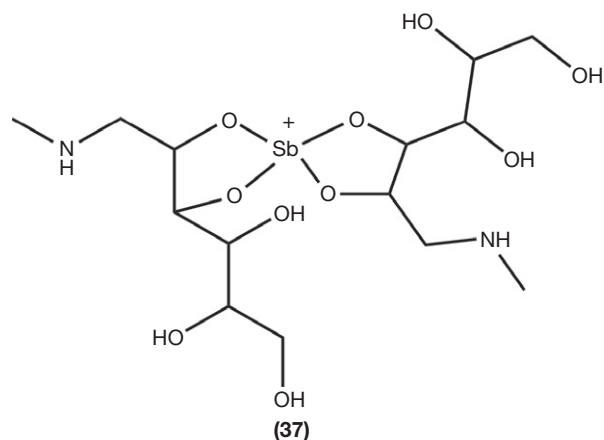
decrease cell viability in lymphocytic leukemia cells by enhanced mitotic arrest through the activation of Cdk1 and spindle checkpoint. This suggests that clinical trials of the combined regimen of 35 and PTX deserve to be performed in the refractory patients with acute lymphoblastic leukemia.<sup>160</sup> Finally, recent research revealed that treatment with 35 reduces CD133 expression at transcriptional levels.<sup>161</sup> CD133<sup>+</sup> tumor cells are responsible for the initiation, propagation, and recurrence of tumors, which are highly resistant to conventional chemotherapy. As<sub>2</sub>O<sub>3</sub> effectively induces CD133<sup>+</sup> gall bladder carcinoma cell apoptosis. Furthermore, the ectopic expression of CD133 is attenuated by the apoptotic effect of 35 on cells through activation of AKT (protein kinase B) signaling pathways. In summary, 35 effectively targets CD133 in gall bladder carcinoma, providing a new mechanism of 35-induced cell apoptosis and a better understanding of drug resistance in gall bladder carcinoma.<sup>161</sup>

### 3.33.4.2 Antimony

Despite the fact that antimony (<sub>51</sub>Sb) compounds have been at the forefront of the treatment of leishmaniasis for many decades, the exploration of other therapeutic uses of antimony has not attracted significant interest. While this may be because of the real and anticipated toxic side effects associated with antimony compounds, as indicated above by the discussion of therapeutic arsenic, this does not necessarily mitigate against therapeutic applications.

Antimony(V)-containing compounds, such as sodium stibogluconate (Pentostam<sup>®</sup>; 36) and meglumine antimonite (Glucantime<sup>®</sup>; 37), as well as the antimony(III) compounds sodium antimony(III) gluconate (Triostam<sup>®</sup>; 38) and potassium antimony(III) tartrate (Tartar emetic<sup>®</sup>; 39), have been widely used for the treatment of leishmaniasis.<sup>162,163</sup> Leishmaniasis is a disease of both temperate and tropical countries and manifests in skin lesions (cutaneous and mucocutaneous leishmaniasis). Another form, visceral leishmaniasis, may affect vital organs and can be fatal. The disease is spread by bites from specific species of sandfly that infects the host with parasites. The use of antimony compounds for the treatment of leishmaniasis notwithstanding, the mechanism of action of the antimonial drugs is not yet completely understood, a situation not made easier by the fact that the precise chemical structures of these drugs are not known – the chemical structures shown for 36–39 being more representative of the chemical composition only.





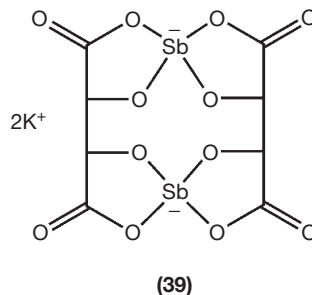
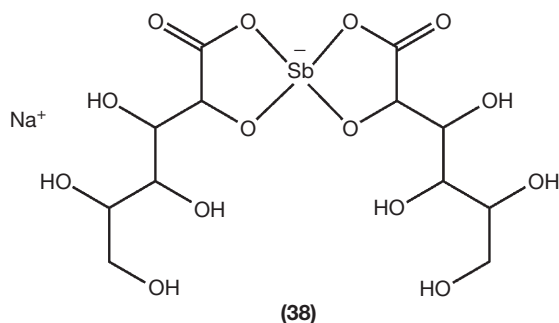
It has been proposed that the anti-leishmanial activity of antimony(V) compounds depends on its reduction to antimony(III) inside parasites by the tripeptide, glutathione (GSH,  $\gamma$ -L-Glu-L-Cys-Gly), or by trypanothione (T(SH)<sub>2</sub>), a conjugation of glutathione and the polyamine spermine, *N*<sup>1</sup>,*N*<sup>8</sup>-bis(glutathionyl)spermidine;<sup>164,165</sup> hence, antimony (V) drugs should be considered as less toxic prodrugs. The more toxic antimony(III) compounds display anti-leishmanial activity owing to the ability of antimony to coordinate to trypanothione reductase (TR), an enzyme which is responsible for various trypanosome protections against free radicals and therefore essential for the survival of the parasite and for its virulence;<sup>166</sup> TR is absent in mammalian cells.

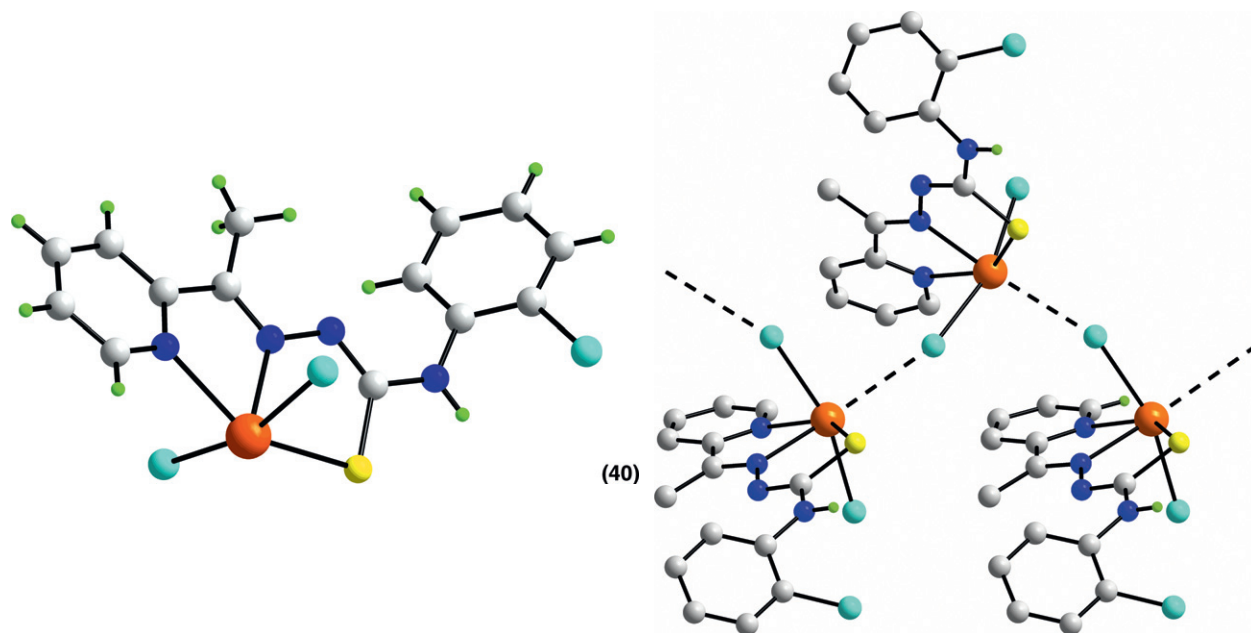
Recent studies indicate that the combination of suboptimal doses of **38** and diperoxovanadate compound K[VO(O<sub>2</sub>)<sub>2</sub>(H<sub>2</sub>O)] may be beneficial for the treatment of **38**-resistant visceral leishmaniasis patients.<sup>167</sup> From the significant reduction in organ parasite burden, this combination is highly effective in combating experimental infection of BALB/c mice with *Leishmania donovani*, known to be antimony resistant. It was also of interest that such treatment allowed clonal expression of anti-leishmanial T-cells together with a robust surge of IFN- $\gamma$  with a concomitant decrease in IL-10 production. The splenocytes from the treated animals generated significantly higher amounts of IFN- $\gamma$ -inducible parasitocidal effector molecules, such as superoxide and nitric oxide, when compared to the infected group.<sup>167</sup>

In keeping with the ability of antimony(III) to interact with TR (see above) and the fact that TR also occurs in trypanosoma, it has been suggested that TR might be a most promising

target for the development of trypanocidal drugs, that is, for the treatment of sleeping sickness and Chagas disease,<sup>168</sup> and thereby open another opportunity for antimony(III) compounds. Accordingly, an investigation of the antitrypanosomal activity of antimony(III) thiosemicarbazone compounds was carried out, as exemplified by dichloridoantimony(III) *N*-2-chlorophenyl-2-acetylpyridinethiosemicarbazone (40) (Figure 11) in which the immediate environment of the antimony(III) atom comprises N<sub>2</sub>S donor atoms of the uninegative tridentate ligand, and two chloride atoms which define a highly distorted trigonal bipyramidal coordination geometry. Supramolecular association via Sb...Cl interactions (3.3 Å) led to a polymeric chain and to a distorted octahedral coordination geometry (Figure 11) based on a mer-Cl<sub>3</sub>N<sub>2</sub>S donor set. *In vitro* trials revealed excellent inhibition action on *Trypanosoma cruzi* growth.<sup>169</sup> The antitrypanosomal mechanism of action of the antimony(III) thiosemicarbazone compounds could be due to a synergistic effect involving both antimony (III) and the ligand molecules as the latter were also active in their own right and are thought provide the additional function as carriers of antimony(III) into the cell.<sup>168</sup>

Although the major clinical use of antimony compounds is as a treatment for leishmaniasis, the antitumor potential of some antimony compounds has been reported in several studies.<sup>133</sup> In particular, antimony(III) compounds are now being proposed as a novel therapy for APL, discussed above in terms of therapeutic arsenic compounds. In early studies, the effects of antimony(III) drugs on glutathione homeostasis, oxidative stress, and apoptosis in the THP-1 (human acute monocytic leukemia cell line) monocyte cells were investigated.<sup>169</sup> It was shown that when treated with antimony(III), THP-1 macrophage cells exhibited high levels of ROS and showed the early signs of apoptosis.<sup>169</sup> Other studies showed that antimony trioxide (Sb<sub>2</sub>O<sub>3</sub>, **41**) induces growth inhibition in patient-derived APL cell lines. It was demonstrated that treatment with **41** inhibits the growth of several malignant cell lines including those derived from both hematologic malignancies and solid tumors.<sup>170</sup> In most malignant cells tested, this growth inhibition is due to an increase in apoptosis as well as caspase activation, although in APL cells, **41** also induces a significant amount of granulocytic differentiation.<sup>170</sup> When treated with **41**, the signaling pathway of APL cells is associated with increased apoptosis as well as differentiation markers. Sb<sub>2</sub>O<sub>3</sub>-induced ROS correlated with increased apoptosis. In addition, **41** induces c-jun kinase (JNK) activity in APL cells and fibroblasts, and that an intact





**Figure 11** Molecular structure of dichloridoantimony(III) *N*-2-chlorophenyl-2-acetylpyridinethiosemicarbazonate (**40**) (left-hand view), and supramolecular chain mediated by hypervalent Sb...Cl interactions (C-bound hydrogen atoms omitted) leading to a pseudo-octahedral geometry (right-hand view).

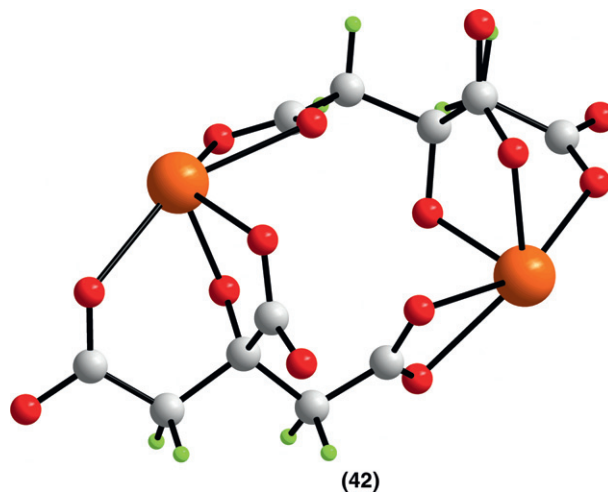
JNK signaling pathway involving SEK1 is important to 41-induced growth inhibition. Therefore, a complete SEK1/JNK pathway is required for 41 to induce activator protein-1 binding, which leads to apoptosis.<sup>171</sup>

### 3.33.4.3 Bismuth

Bismuth ( $_{83}\text{Bi}$ ) compounds have played a prominent role in chemotherapy for more than 200 years with early reports documenting the use of bismuth formulations for the treatment of gastrointestinal disorders.<sup>163,172</sup> Today, bismuth therapy is extensively used for duodenal and peptic ulcers. Peptic ulcers may be treated by administration of colloidal bismuth subcitrate (De-Nol<sup>®</sup>, **42**) and along with bismuth subsalicylate (Pepto-Bismol<sup>®</sup>, **43**) is used for both the prevention and treatment of gastric and duodenal ulcers. A more recently developed compound, ranitidine bismuth citrate (Tritec<sup>®</sup> and Pylorid<sup>®</sup>, **44**), is also available for treatment.<sup>163,172</sup> As for the antimony-based drugs employed for the treatment of leishmaniasis, the precise chemical structures of the bismuth-based drugs are largely unknown and the chemical structures shown for **42**–**44** are far from conclusive. The image shown in **Figure 12** represents the supposed core in **41**, where two bismuth(III) centers are linked by two pentadentate citrate anions; these units are connected to neighboring building blocks to generate an oligomeric aggregate. In **43**, the ranitidine molecules are accommodated within channels defined by the three-dimensional framework and so represents a functional example of the use of MOFs as drug carriers.<sup>17,18</sup>

While the lack of precise structural information is common to both antimony and bismuth drugs, by contrast to the situation for antimony, significantly more is known about the biological targets of therapeutic bismuth and their mechanism of action.

The effectiveness of bismuth has been attributed to its bactericidal action against the Gram-negative bacterium



**Figure 12** Proposed  $[\text{Bi}(\text{citrate})_2\text{Bi}]^{2-}$  core in (**42**).

*H. pylori* (the bacterium associated with the mucus layer of ulcers).<sup>173,174</sup> Bismuth is known to engage in exchange reactions with thiols and thereby inactivate membrane-bound enzymes involved in respiration, such as the F1-ATPase of *H. pylori*.<sup>175</sup> The antimicrobial activity of bismuth compounds towards Gram-negative bacteria has been reported to be dependent on the iron-uptake system.<sup>176</sup> As iron is essential for the growth of *H. pylori*, efficient iron acquisition is thought to be an important virulence factor for this bacterium. Bismuth is primarily present in red blood cells, possibly binding to glutathione with the remainder in serum or plasma.<sup>177</sup> Recently, it has been demonstrated that binding of bismuth(III) to transferrin (hTF) is much stronger than human albumin in blood plasma. Most of the  $\text{Bi}^{3+}$  was associated with transferrin in the presence of a large excess of albumin.<sup>178</sup> This suggests that transferrin is the major target for bismuth(III) in blood plasma.

Lactoferrin (hLF) is another major iron-binding protein in the transferrin family and is present in significant amounts in stomach secretions of patients with gastritis. Bismuth(III) binds to human lactoferrin in the two iron-specific sites in the presence of either carbonate or oxalate;<sup>176</sup> the presence of ATP facilitates the release of bismuth(III) from the lactoferrin complex. The Bi<sub>2</sub>-hLF complex blocks iron uptake to intestinal cells. Consequently, bismuth(III) may be released inside the cells and inhibit target enzymes, including enzymes essential for the survival of bacteria.<sup>176</sup> Furthermore, Bi<sup>3+</sup> inhibits the biological activity of glycine extended gastrin-17 (Ggly), a gastrointestinal hormone.<sup>179</sup> The biological activity of gastrin-17 is associated with its binding to high-affinity Fe<sup>3+</sup> ions.<sup>18,179</sup> Bismuth(III) inhibits the action of gastrin by blocking its effects on cell proliferation and cell migration in the gastrointestinal tract.

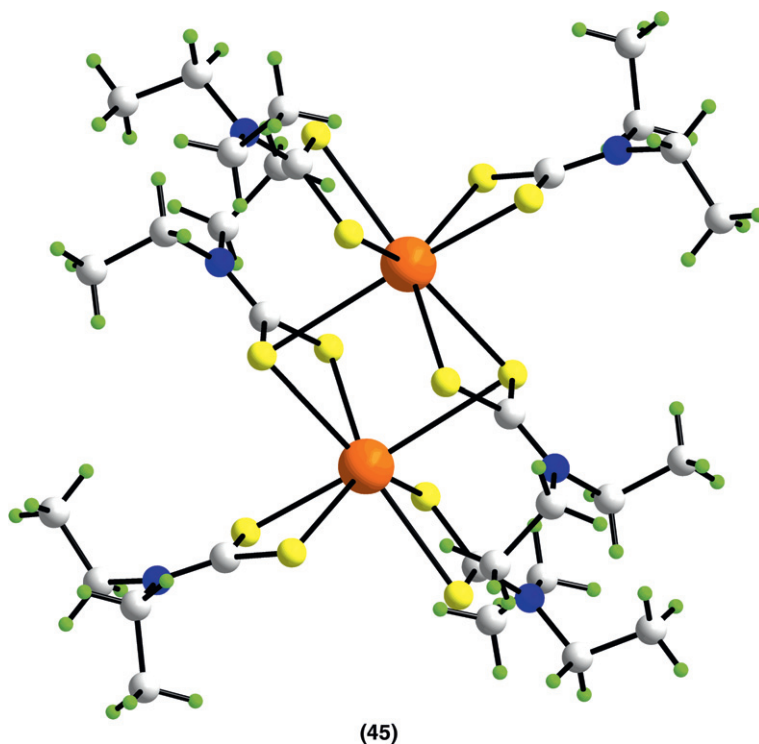
Gastrin is a gastrointestinal peptide hormone that was originally identified as a stimulant of acid secretion. Proteolytic processing in the secretory vesicles of the antral G cell generates a number of intermediate, nonamidated progastrin-derived peptides, including Ggly.<sup>180</sup> Removal of the C-terminal glycine and amidation of the penultimate phenylalanine yields amidated gastrin (Gamide). Gamide, acting through the cholecystokinin-2 receptor, is the major hormonal regulator of gastric acid secretion,<sup>181</sup> and is a mitogen for normal gastric epithelium and some gastric cancers *in vitro* and *in vivo*.<sup>182</sup> By contrast, progastrin and Ggly have little direct effect on gastric acidity but potentiate the effects of Gamide on acid secretion.<sup>183</sup> The major physiological role of progastrin and Ggly is in the colon, as progastrin and Ggly stimulate proliferation of a colonic cell line *in vitro* and of the normal mucosa *in vivo*. Such nonamidated gastrins may also act as growth factors in colorectal cancer.<sup>184</sup>

Other bismuth compounds have been demonstrated to be extremely effective inhibitors of nonamidated gastrins and

were able to completely reverse the stimulatory effects of Ggly and progastrin in animal models. It was suggested that bismuth selectively inhibits the proliferative effects of nonamidated gastrins in the normal colorectal mucosa of both rats and mice.<sup>185</sup> Together with its safe dosing, antioxidant and mucosal healing qualities, bismuth is a good candidate as an all-round gastrointestinal protective agent.

Concerning other potential therapeutic applications, various research groups have shown that bismuth compounds display potent activities against a wide range of pathogens including *E. coli*, *Legionella pneumophila*, *Klebsiella pneumoniae*, *Clostridium difficile*, *Pseudomonas aeruginosa*, *S. aureus* (including multiresistant strains), *S. epidermidis* (including methicillin-resistant strains), and the protozoa responsible for leishmaniasis.<sup>186-188</sup> However, the mode(s) of action of these bismuth agents is not known but perhaps they interfere with iron transport, thereby starving the pathogen of the needed iron for cellular energy-producing enzymatic redox transformations, and also bind to thiol-containing bacterial enzymes necessary for the maintenance of the organism within the host. A recent report highlighted the ability of bismuth compounds, including ranitidine bismuth citrate (44) to inhibit the SARS Coronavirus.<sup>189</sup> Strong inhibition of the ATPase activity of the SARS Coronavirus helicase protein characterized 44, and this was also shown to inhibit the DNA duplex unwinding. Helicase, specifically the cysteine residues, was reported to be the intracellular target for bismuth.<sup>189</sup>

Screening for potential anticancer activity of bismuth compounds has been recently reviewed.<sup>133</sup> While most results focus upon *in vitro* cytotoxicity results, an *in vivo* study demonstrated that bismuth thiolates, such as bismuth(III) tris(diethylthiocarbamate) (45) (Figure 13), have antitumor activity.<sup>190</sup> Compound 45 self-associates into a dimeric aggregate in the solid state via Bi···S interactions so that the



**Figure 13** Molecular structure of dimeric bis[bismuth(III) tris(diethylthiocarbamate)] (45).



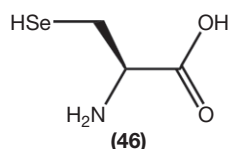
coordination geometry is based on a pentagonal bipyramid but with a void that is thought to accommodate a stereochemically active lone pair of electrons. In trials on mice inoculated with an ovarian cancer cell line (OVCAR-3) or a colon carcinoma cell line (HT-29), tumor growth was arrested in the former and slowed in the latter.<sup>190</sup>

### 3.33.5 Selenium and Tellurium

Of the elements covered in the present chapter, it is only selenium that is known to be bioessential. Complementing selenium supplements to maintain good health (a topic not covered herein), a number of therapeutic applications of selenium are emerging. Tellurium compounds also attract interest in this context with early experiments exploring antimicrobial activity described by Sir Alexander Fleming.

#### 3.33.5.1 Selenium

Selenium ( $^{34}\text{Se}$ ) is an essential micronutrient that is important for various aspects of human health including proper thyroid hormone metabolism, cardiovascular health, prevention of neurodegeneration and cancer, and optimal immune responses.<sup>191</sup> Selenocysteine (46) is the 21st amino acid and is usually the form in which selenium is found in selenoproteins.<sup>192,193</sup> As with most of the other elements covered in this chapter, the effects of selenium compounds, both as supplements and chemotherapeutic agents, have attracted significant attention for cancer treatment.



The first human intervention trials using sodium selenite ( $\text{Na}_2\text{SeO}_3$ , 47) as a dietary supplement to prevent cancer were performed in China. In all, 20 847 subjects received table salt containing 47, so that each subject received 30–50 mg of selenium per day for 8 years. The incidence of primary liver cancer was significantly reduced.<sup>194</sup> It is thought that 47 induces apoptosis by generation of ROS through the mitochondrial-dependent pathway,<sup>195</sup> based on studies into the 47-induced cell death in cervical carcinoma cells during 24 h of exposure in the HeLa Hep-2 cell line. Compound 47 produced time- and dose-dependent suppression of DNA synthesis and induced DNA damage which resulted in phosphorylation of histone H2A.X. Subsequently, 47 activated the p53-dependent pathway as evidenced by the appearance of phosphorylated p53 and accumulation of p21 in the treated cells. Concurrently, 47 activated the p38 pathway.<sup>195</sup> The p53- and p38-dependent signaling led to the accumulation of the protein responsible for the generation of the Bax proapoptotic gene. It appears that mitochondria in 47-treated cells had their dynamics changed and initiated caspase-independent apoptosis, which was confirmed by the assay of caspase-3 activity. It was concluded that 47 induces caspase-independent apoptosis in cervical carcinoma cells mostly by ROS-mediated activation of p53 and p38 pathways, and other selenite-mediated effects, in

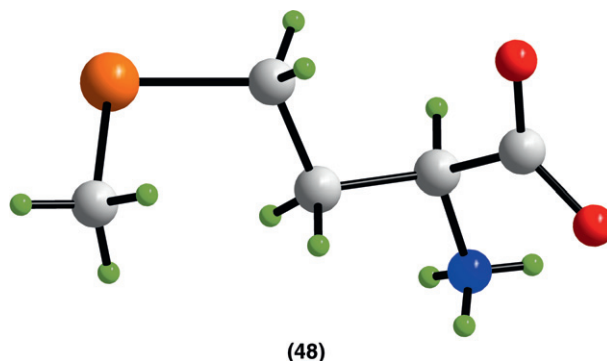
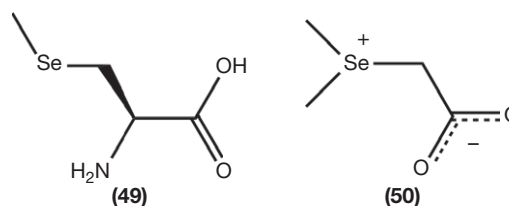


Figure 14 Molecular structure of zwitterionic selenomethionine (48).

particular in mitochondria-specific cells, are also involved.<sup>195,196</sup> The versatility of selenium is evidenced by the fact that amino acid analogs also display protective action against cancer.

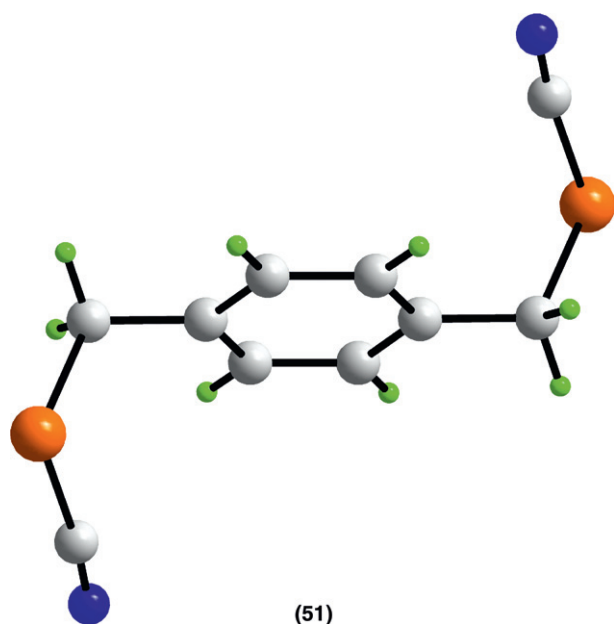
For example, it has been reported that selenomethionine (48), having a V-shape geometry at the selenium atom (Figure 14), may protect against cancer by activating the tumor suppressor protein p53 in human lung cancer cells by transformation of p53 from the oxidized to the reduced form.<sup>197</sup> Methylated selenium-modified amino acids such as selenobetaine (49) and Se-methylselenocysteine (50), through the action of cysteine conjugate  $\beta$ -lyase or related lyases, function as prodrugs to release methylselenol or methylselenenic acid,<sup>198</sup> and have chemopreventive effects at very low concentrations in transformed cells, *in vitro*. In this way, these species serve as a reservoir of monomethylated selenium compounds to maintain a sufficient concentration to inhibit cell growth. It is also known that 50 leads to a significant reduction in angiogenesis<sup>201,200</sup> as detected by intratumoral microvessel density and a VEGF in mammary carcinomas.<sup>199</sup> With this background in mind, it is not surprising that synthetic selenium compounds, often organoselenium compounds, have been evaluated for their anticancer potential.<sup>201</sup>



Upon administration to 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary rat tumors (the immunosuppressor DMBA is a powerful laboratory carcinogen that functions by making mutations to DNA), 1,4-phenylenebis(methylene) selenocyanate (51), a dinuclear molecule with a bent geometry at each selenium center (Figure 15), suppressed the formation of DMBA–DNA adducts at doses of  $80 \text{ mg kg}^{-1}$ . The chemopreventive activity of 51 may be explained in part by the inhibition of DNA adduct formation as 51 inhibited the formation of  $\text{O}^6$ -methylguanine and 7-methyl guanine in the lung, while 47 at  $5 \text{ mg kg}^{-1}$  had no effect against lung tumor induction.<sup>202</sup> Complimenting the above are indications that selenium compounds can be useful when coadministered with other drugs.

When combined with a chemotherapeutic agent, selenium compounds may also provide protection from toxic side effects. For example, when each of 48 and 50 was coadministered with several chemotherapeutic agents such as irinotecan, fluorouracil, oxaliplatin, cisplatin, taxol, and doxorubicin, the maximum tolerated dose was raised.<sup>202</sup>

Arguably, one of the most prominent selenium-containing compounds that has attracted significant attention for therapeutic potential is Ebselen (2-phenyl-1,2-benzoselenazol-3-one, 52). As illustrated in (Figure 16), individual molecules assemble into supramolecular chains in the solid state via hypervalent Se···O interactions (2.57 Å). The presence of 46 in glutathione peroxidase, an antioxidant, has stimulated significant additional research for synthetic selenium analogs that are capable of inactivating ROS species such as hydroperoxides and peroxynitrite, and led to the discovery of 52.<sup>203</sup>

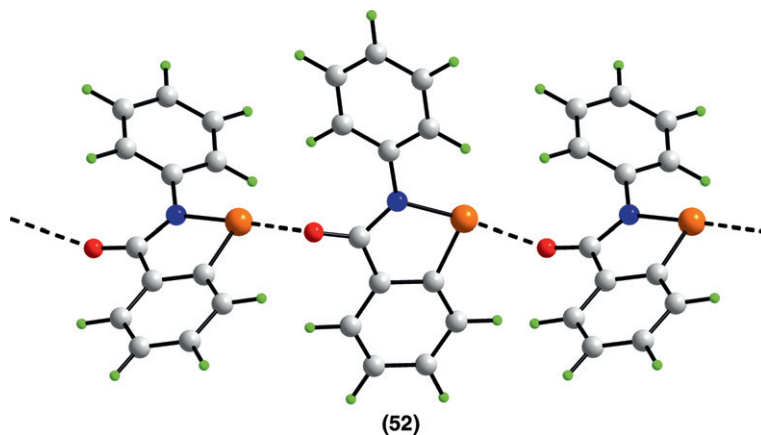


**Figure 15** Molecular structure of 1,4-phenylenebis(methylene)selenocyanate (51).

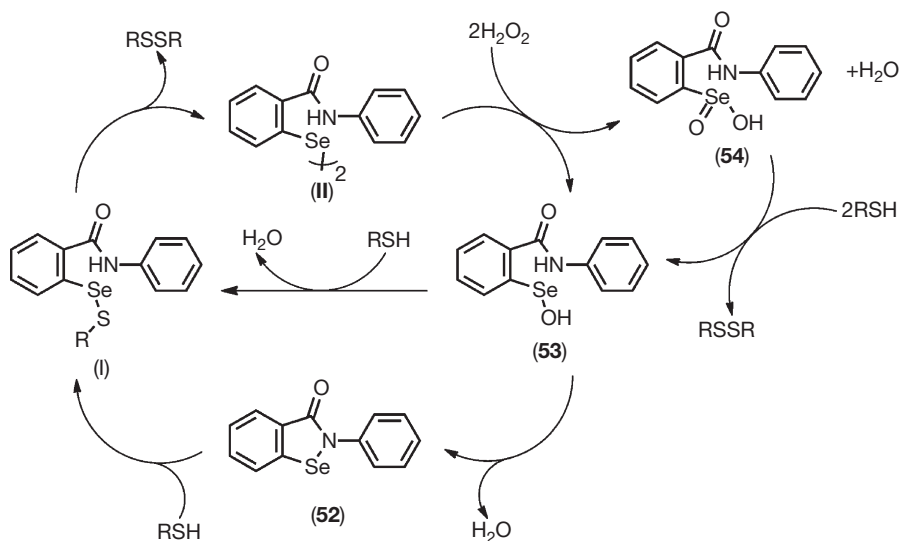
Subsequent work has been motivated by the proposed catalytic cycle for 52 (Figure 17).<sup>203</sup> Compound 52 can catalyze the inactivation of ROS by using a variety of thiols as the substrate, including glutathione. Reaction with the thiol cosubstrate gives the ring-opened product owing to breaking of the Se–N bond. Disproportionation to the diselenide, the rate-determining step, is followed by reaction with H<sub>2</sub>O<sub>2</sub> to produce a selenium-containing acid, either selenenic acid (53) or seleninic acid (54). Any 54 formed reacts with thiol to give 53 which, following dehydrogenation, regenerates 52, and so completes the catalytic cycle.<sup>203</sup> Structure–activity studies suggest that three key factors are important for efficacy, namely (1) the presence of a Se–C(aromatic) bond that is sufficiently stable to prevent release of selenium, (2) the presence of a Se–N bond that ensures activity akin to that exhibited by glutathione peroxidase, and (3) the presence of a N–C(=O) moiety to provide coordination donors to stabilize the various intermediates in the catalytic cycle.<sup>203</sup>

With this background into the antioxidant potential of selenium compounds, it is not surprising that considerable effort has been devoted to discovering synthetic selenium-based compounds that may function as anti-inflammatory agents, in particular given the insolubility of 52.<sup>204</sup> The diselenyl compound 51, mentioned above, has demonstrated the ability to disrupt the normal functions of cyclooxygenase-2 (COX-2) through its ability to inhibit the redox active transcription factor NF-κN.<sup>205</sup> The hope of combining the preventative action of selenium with the COX-2 inhibiting ability of Celecoxib<sup>®</sup> (55), to generate enhanced therapeutic benefit, led to selenium derivatives of 55, such as 56 where the CF<sub>3</sub> group of 55 has been substituted by a methyleneselenylcarbonitrile residue.<sup>206</sup> Compound 55 inhibited COX-2 in macrophages, diminished COX-2 protein expression, and suppressed the activation of NF-κN.<sup>206</sup>

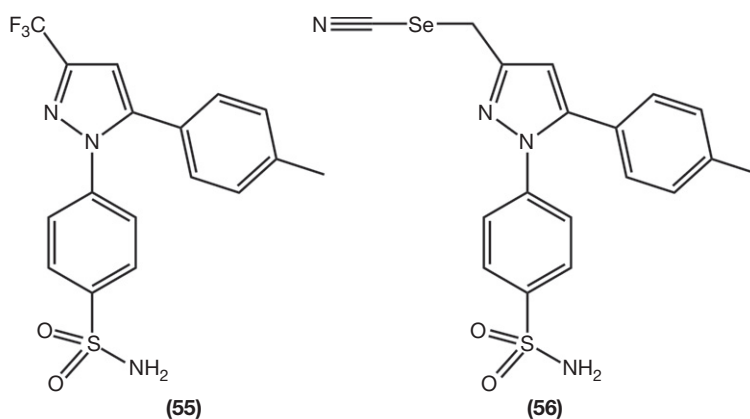
The 21st amino acid selenocysteine (46) is also found in the catalytic sites of the iodothyronine deiodinases, lactoperoxidase, and other enzymes associated with the normal functions of the thyroid gland.<sup>207</sup> The key role of selenium is to facilitate the deiodination of thyroxine but the mechanism is yet to be determined. What is known is that during deiodination a selenenyl iodide intermediate is formed that reacts with a thiol cofactor.<sup>207</sup> The selenium compound 1-methyl-



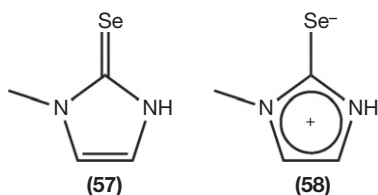
**Figure 16** Structure of Ebselen (2-phenyl-1,2-benzoselenazol-3-one) (52), whereby mononuclear molecules associate into supramolecular chains via hypervalent Se···O interactions.



**Figure 17** Proposed catalytic cycle showing the ability of **52** to inactivate  $H_2O_2$ . Compound **53** is selenenic acid and **54** is seleninic acid. The thiol in the above cycle is not necessarily glutathione but may be another thiol.

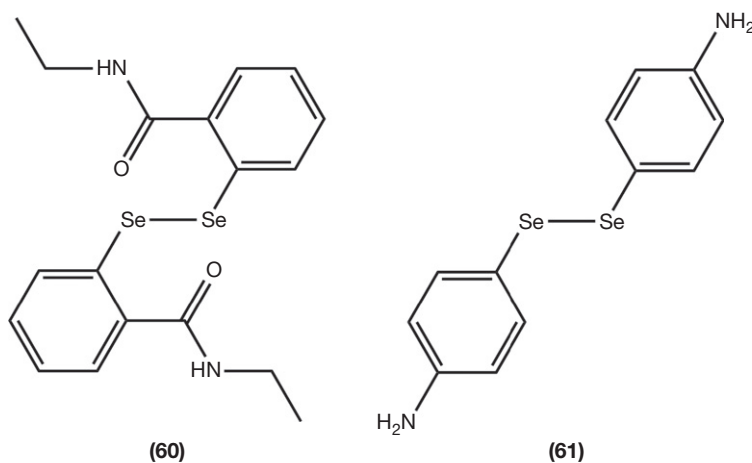
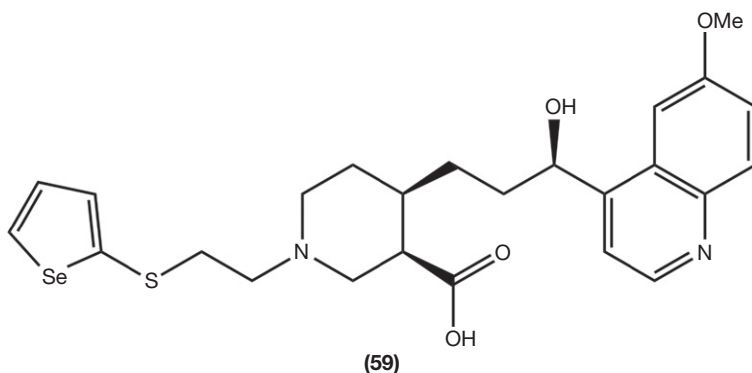


3*H*-imidazole-2-selenone (**57**), an analog of the sulfur drug Methimazole<sup>®</sup>, effectively inhibits lactoperoxidase-catalyzed reactions relating to oxidation, in a mechanism likely to involve the reduction of  $H_2O_2$ , and iodination.<sup>208</sup> A chemical reason has been proposed to account for the differences between the sulfur and selenium antithyroid drugs, namely based on the greater nucleophilicity of selenium.<sup>209</sup> While the sulfur analog of **57** exists primarily as a thione, the greater nucleophilicity of selenium sees a significant contribution of zwitterionic **58** to the overall electronic structure. Thus, while **57** is readily oxidized to the diselenide, important for the inhibition thyroid hormone synthesis, the same is not true for the sulfur drugs. *In vivo*, glutathione and other thiols can reduce the diselenide to form charged and highly reactive species.



Selenium compounds including **52** have been evaluated for antimicrobial potential.<sup>204</sup> There are indications that selenium compounds are more effective against Gram-positive strains as opposed to Gram-negative strains.<sup>210</sup> A notable recent study described the effective antistaphylococcal activity of **59** which is the selenium analog of a 2-thienyl containing drug (AVE6971) which is known as a topoisomerase poison.<sup>211</sup> The presence of selenium in the noncytotoxic molecule gave rise to a more potent antistaphylococcal species and the lowest potential in expressing the hERG gene, the gene (KCNH2) that codes for the Kv11.1 potassium ion channel protein. Such studies point to the potential efficacy of selenium in therapeutic medicine and other diseases have been targeted in some very recent studies. A very brief overview of these is given below.

Having selenium present in molecules such as diselenide (**60**; *N*-ethyl-2-[[2-(ethylcarbamoyl)phenyl]diselanyl]benzamide) gave rise to compounds that were effective antiviral agents, that is effective against Human herpes virus type 1 and Encephalomyocarditis virus compared to their sulfur analogs.<sup>212</sup> Another diselenide (**61**; 4-[[4-(4-aminophenyl)diselanyl]aniline) was the most potent of a series of selenocyanates and diselenides explored as a new therapy for the treatment of leishmaniasis.<sup>213</sup>



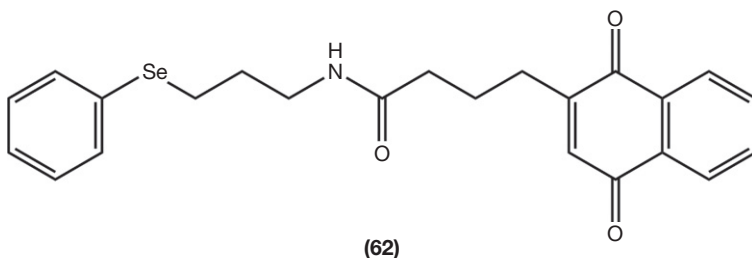
Compound **61** displayed potency against promastigotes (*Leishmania infantum*) found in the sandfly host as well in a model for amastigotes found in the infected human.

Another parasite, namely *Plasmodium falciparum*, was targeted in trials for new antimalarials with compound (**62**; 4-(1,4-dioxonaphthalen-2-yl)-N-[3-(phenylselenanyl)propyl]butanamide), which feature the redox-modulating quinone residue, being the most effective.<sup>214</sup>

### 3.33.5.2 Tellurium

Unlike selenium, there is no known natural biological function for tellurium ( $_{52}\text{Te}$ ). Also unlike selenium, tellurium has a relatively long history in terms of biological evaluation where tellurium, in the form of potassium tellurite  $2\text{K}^+ \text{TeO}_3^{2-}$  (**63**), attracted early attention as an antibiotic. Sir Alexander Fleming,

in 1932, established that **63** was active in penicillin-insensitive bacteria and, by contrast, penicillin was active in tellurium-insensitive bacteria.<sup>215</sup> Despite this selectivity, the evaluation of tellurium as a therapeutic agent did not really progress significantly from that point in time, perhaps owing to perceived problems with toxicity.<sup>216,217</sup> As mentioned above on several occasions, this should not be a deterrent in evaluating tellurium compounds for therapeutic potential. This point is particularly apposite in consideration of the wide range of useful biological properties exhibited by another anion, trichlorido(dioxoethylene)tellurate(IV) (**64**), found in its ammonium salt. The molecular structure comprises a pentacoordinate tellurium atom coordinated by two oxygen atoms derived from the chelating alkoxide ligand and three chloride atoms (Figure 18). The coordination geometry is based on a square pyramid with the stereochemically active lone pair of

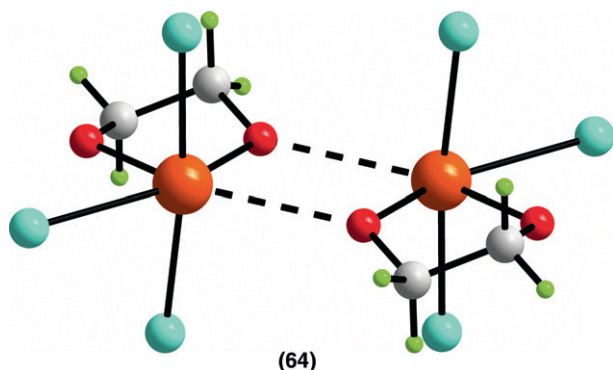


electrons projected to occupy the space opposite the axial oxygen atom. Symmetry-related molecules associate into supramolecular dimers via  $\text{Te} \cdots \text{O}$  (2.76 Å) interactions.

The anion in **64** is reported to be a nontoxic and potent immunomodulator.<sup>218</sup> While displaying a variety of potential therapeutic applications, **64** has attracted most attention in terms of its potential anticancer activity based on diverse pre-clinical and clinical studies, and its anticancer effects have been reviewed recently.<sup>219</sup> The direct inhibition of the anti-inflammatory cytokine, IL-10, with a concomitant enhancement of particular cytokine levels is thought responsible for the activity of **64**. When patients with advanced cancer were treated with **64** in phase I clinical trials, it was observed that the increased production and secretion of certain cytokines resulted in a dominance and decrease in TH1 and TH2 responses, respectively. The effects of **64** on IL-10 might explain the mechanism by which it sensitizes tumor cells to chemotherapy. While Stat3 is the main target of IL-10, it is known that to a lesser extent PI3-kinase can be activated by this cytokine. As the upregulation of survivin gene expression in malignant cells requires the convergence of constitutive Stat3 activation and PI3K/Akt signaling, in IL-10-producing tumors it is feasible that inhibition of IL-10 ultimately results in the inhibition of pStat3 and subsequent repression of survivin. Supporting this proposal is the observation that **64** inhibits survivin protein expression in myeloma cells.<sup>220</sup>

Compound **64** and other species such as bis(*R,R*-tartrato)-di-tellurium(IV) (**65**), a dinuclear compound featuring tetra-coordinated tellurium(IV) atoms and stereochemically active lone pairs of electrons (Figure 19), do not effect aspartic-, serine-, and metallo-proteases but selectively inactive cysteine proteases,<sup>216</sup> indicating a selectivity for proteins reliant upon the redox status of cysteine for biological activity. This characteristic of **64** and **65** enables the inhibition of  $\alpha\text{V}\beta\text{3}$  integrin located on endothelial cells and accounts for their antiangiogenic properties.<sup>219</sup> It should also be noted that **64** functions as a protective agent against homocysteine toxicity by its ability to oxidize homocysteine to the less toxic disulfide, homocystine.<sup>221</sup>

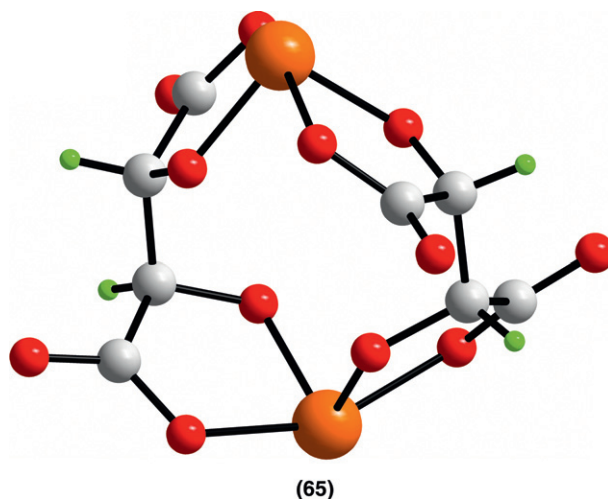
Compound **64** has also demonstrated potential in neuro-generative disease (for example, Parkinson's disease),<sup>222</sup> autoimmune disease,<sup>223</sup> induced mesangial proliferation in the



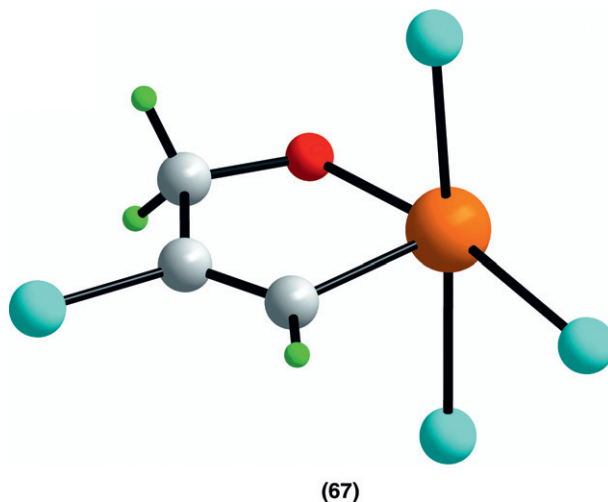
**Figure 18** Molecular structure of trichlorido(dioxoethylene)tellurate (IV) (**64**), whereby mononuclear molecules associate into supramolecular dimers via hypervalent  $\text{Te} \cdots \text{O}$  interactions. The ammonium cations have been omitted.

kidney,<sup>224</sup> viral and parasitic diseases,<sup>225</sup> and dermatitis.<sup>226</sup> With such a wide range of potential therapeutic applications, it is not surprising that other tellurium compounds are under investigation,<sup>204</sup> with an emphasis on the specific targeting of relevant biological sites, such as cathepsin B. Figuring prominently among these are organotellurium compounds, both charged and neutral.

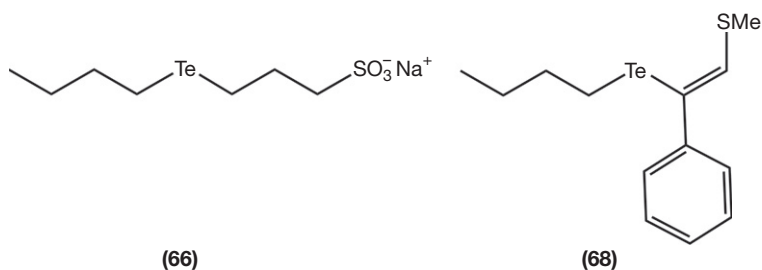
Malaria has been targeted in several studies with the tellurium analog of species such as selenium containing **62** having measurably greater potency than the selenium compound against *P. falciparum*.<sup>214</sup> The charged species 3-(butyltellanyl)propane-1-sulfonate (**66**) was designed to target low-molecular-weight thioredoxin reductases in complementary trials for effective antimalarials.<sup>227</sup> Another charged species, 2,2,2,4-tetrachloro-2,5-dihydro-1,2 $\lambda^4$ -oxatelluro-2-uide (**67**), featuring (Figure 20) a square-pyramidal tellurium(IV) atom but no significant hypervalent interactions owing to the presence of the organo substituent in contrast to closely related **64** (Figure 18), was trialed for anti-leishmaniasis potential in an *in vivo*



**Figure 19** Molecular structure of bis(*R,R*-tartrato)-di-tellurium(IV) (**65**).



**Figure 20** Molecular structure of 2,2,2,4-tetrachloro-2,5-dihydro-1,2 $\lambda^4$ -oxatelluro-2-uide (**67**). The ammonium cation has been omitted.



model and demonstrated activity against flagellate and non-flagellate forms of the parasite.<sup>228</sup> Neutral organotellurium(II) compounds such as [(Z)-1-(butyltellanyl)-2-(methylsulfanyl)ethenyl]benzene (68) display potential as excitotoxic agents owing to their antioxidant abilities.<sup>229</sup>

From the foregoing, tellurium compounds, in either +II or +IV oxidation states, as coordination or organotellurium compounds, charged or neutral, offer significant potential for drug development.

### 3.33.6 Lithium

Having a density only half that of water, lithium ( ${}^6\text{Li}$ ) is the lightest of all metals and is not known to have any natural biological function. Lithium salts, most commonly in the form of  $\text{Li}_2\text{CO}_3$  (68; Lithicarb<sup>®</sup>, Quilonum<sup>®</sup>, Eskalith<sup>®</sup>, Lithobid<sup>®</sup>, Lithonate<sup>®</sup>, and Lithotabs<sup>®</sup>) but also as  $\text{Li}_2\text{SO}_4$  (69) or  $\text{Li}_3(\text{citrate})$  (70), are well known as psychopharmacological agents.<sup>230–232</sup> Lithium is known to influence neurotransmitter receptor-mediated signaling, signal transduction cascades, the regulation of hormonal and circadian cycles, ion transport, and gene expression. With this range of activity, lithium salts have been the standard pharmacological treatment for bipolar disorder for more than 60 years. Despite the emergence of other drugs, lithium salts continue to be used as the first-line treatment against acute mania, and used prophylactically for recurrent manic and depressive episodes. Clinically, lithium salts can also be used as an adjunctive with mood-stabilizing drugs, antidepressants, and antipsychotics in order to optimize their therapeutic benefits. It is also known that lithium salts have strong antisuicidal properties. Despite being prescribed clinically for the treatment of several neurodegenerative conditions for over half a century, the precise mechanisms of action/biological targets of 'lithium' are still subject to debate.

There is considerable evidence to indicate that lithium exerts significant neuroprotective/neurotrophic properties against various insults. Based on pharmacological and gene manipulation studies, the main mechanisms of action for lithium appear to be the inhibition of glycogen synthase kinase-3 and the induction of brain-derived neurotrophic factor-mediated signaling. These lead to pathways for enhanced cell survival and alteration of various downstream effectors.<sup>233</sup> Lithium also contributes to calcium homeostasis by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx and by suppressing calcium-dependent activation of proapoptotic signaling pathways.<sup>234</sup> Lithium has also been implicated in a recently identified process touted as a novel mechanism for inducing autophagy, that is, by inhibiting phosphoinositol

phosphatases. Lithium decreases inositol 1,4,5-trisphosphate concentrations. Whatever the precise mechanism/mechanisms of action, it is clear that therapeutic doses of lithium are able to defend neuronal cells against diverse forms of death insults. Lithium has been known for many years to improve behavioral traits and cognitive deficiencies in patients suffering from neurodegenerative diseases, including stroke, amyotrophic lateral sclerosis, fragile X syndrome, as well as Huntington's, Alzheimer's, and Parkinson's diseases.<sup>230–232</sup> With such therapeutic utility, it is perhaps surprising that significant research and development into exploring new forms of lithium and modes of administration is not apparent.

### 3.33.7 Conclusion

Herein, the use and potential therapeutic use of main-group elements (including lithium) have been surveyed. It is evident that these compounds present a diverse range of clinical outcomes, with certain types of cancer being treated by arsenic and gallium-containing species, leishmaniasis by antimony compounds, gastric ulcers by bismuth formulations, and neurodegenerative disease by lithium salts. Despite these current applications, it is acknowledged that precise molecular structures, let alone mechanisms of action, are often not known for compounds that entered into the pharmacopoeia before the more stringent regulations of modern times. Perhaps with greater knowledge of structure and mechanism of action, more effective drugs can be designed. As clearly indicated in the known crystal structures of many of the biologically active molecules described herein, supramolecular aggregation through hypervalent metal  $\cdots X$  (donor atom) interactions is apparent. This indicates a possible and consistent mode of action whereby the metal center in a putative drug can anchor onto a target biomolecule through such interactions. Great potential is obvious for all main-group element compounds as therapeutic windows might be available for elements once dismissed as being too toxic to provide pharmacological benefit, with the obvious outstanding example being that of arsenic. This change in paradigm obligates further research into elements that have been neglected owing to perceived problems with toxicity. However, such research should be reliant on complementary *in vivo* studies and include a quest to discover biological targets and mechanisms – studies proving 'potential' by *in vitro* studies are often incomplete and ambiguous. A full range of disease can be tackled, that is, from cancer to microbial disease. With the latter, overcoming drug resistance may be possible using 'out of the ordinary' main-group elements with no known biological

function. Inspirations from traditional medicine should not be ignored, as after all Chinese traditional medicine inspired studies into therapeutic arsenic. With an emphasis on molecular compounds, nanoparticles of main-group elements have not been covered to any significant extent in the present survey and this remains an almost uncharted frontier deserving of greater investigation.<sup>235</sup>

In summary, main-group-element-containing species are deserving of greater attention and new therapeutic agents will undoubtedly be discovered on the road less traveled.

## Acknowledgments

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