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Invited review

Perspectives of antimony compounds in oncology

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Abstract

Antimony, a natural element that has been used as a drug for over more than 100 years, has remarkable therapeutic efficacy in patients with acute promyelocytic leukemia. This review focuses on recent advances in developing antimony anticancer agents with an emphasis on antimony coordination complexes, Sb (III) and Sb (V). These complexes, which include many organometallic complexes, may provide a broader spectrum of antitumoral activity. They were compared with classical platinum anticancer drugs. The review covers the literature data published up to 2007. A number of antimonials with different antitumoral activities are known and have diverse applications, even though little research has been done on their possibilities. It might be feasible to develop more specific and effective inhibitors for phosphatase-targeted, anticancer therapeutics through the screening of sodium stibogluconate (SSG) and potassium antimonyltartrate-related compounds, which are comprised of antimony conjugated to different organic moieties. For example, SSG appears to be a better inhibitor than suramin which is a compound known for its antineoplastic activity against several types of cancers.

Introduction

Antimony, a neutral substance that has been used as a drug for over 100 years, has remarkable therapeutic efficacy in patients with acute promyelocytic leukemia (APL). It exerts apoptosis in dose- and time-dependent manner. Advances in biocoordination chemistry are crucial for improving the design of compounds to reduce toxic side-effects and to understand their mechanisms of action. A great number of metallic complexes display a pronounced antitumoral activity, which makes them of a high interest for applications in the treatment of different types of cancer[1]. This research began in 1969 with the discovery of cisplatin by Rosenberg *et al*[2] in the treatment of testicle and ovary cancers, despite the fact that metal (oid)-containing compounds have been used historically as medicines for several thousands of years, especially in Chinese and Indian traditional medicine.

The clinical success of cisplatin and other platinum complexes is limited by the significant side-effects or intrinsic resistance[3]. Therefore, much attention has focused on designing new coordination compounds with improved pharmacological properties and a wide range of antitumoral activities. Strategies for developing new anticancer agents include the incorporation of carrier groups that can target tumor cells with high specificity. In an attempt to beat the resistance pathways that have evolved to eliminate the drug, developing new complexes that bind to DNA in a fundamentally different manner than cisplatin is also of interest. It has been widely accepted that the organic ligands associated with the metal atom in these complexes play an important role during their transport and assimilation at the membrane level and inside the cell.

To date, practically all transition and main group metals have been tested for antitumoral properties, and interestingly, a number of them have been shown marginal to good activity towards standard animal tumors[4-9]. Within the main group metal, inorganic and organometallic complexes of gallium, germanium[10,11], and tin have been the focus of most antitumoral studies. Gielen *et al* recently published antitumoral studies of a series of germanium rings against different human cancer cell lines. ID_{50} (Infectous dose 50) values

of most of the compounds were comparable with clinically employed drugs doxorubicin and cisplatin[12]. The same group has patented tin carboxylate complexes for their antitumoral properties that were later renewed[13,14]. Recently, chemical and biotechnological developments in organotin cancer chemotherapy emphasizing the coordinating ability of organotin compounds towards DNA and the action mode of organotins in cancer chemotherapy was reviewed[15]. In contrast, antimony compounds[16-17] appear to have not been as well documented as other metal-containing species, despite the fact that organoantimonials have been used successfully for more than half a century in the treatment of leishmaniases[18-21]. Leishmaniases are ineffective parasitic diseases that are injected into mammals via sand flies, which are endemic in 88 countries, and mainly affect developing countries. Pentavalent antimonials, including antimony *bis*-(4,5-dihydroxybenzene-3,5-disulphonate) Stibophen (Scientific coorp. USA), antimony (III) gluconate (Triostam; Canton Chem, USA), meglumine antimoniate (Glucantime; Aventis, France), and sodium stibogluconate (SSG; Pentostam; GlaxoSmithKline, US and UK) have been used for a long time as antileishmanial drugs. In spite of several limitations, including side-effects, need for daily parentral administration, and drug resistance, antimonials are still first-line drugs (Figure 1). The metabolism and mechanisms of action are still being investigated. It is not clear whether the final active form of pentavalent antimonials is Sb (V) or Sb (III), although recent studies suggest that pentavalent antimony acts as a prodrug that is converted to active and more toxic trivalent antimony, and thiols may act as a reducing agent in this conversion[22]. Some reports have suggested the intrinsic antileishmanial activity of Sb (V), which forms a complex with adenine ribonucleoside. Sb–ribonucleoside complexes may act as inhibitor of leishmania purine transporters or penetrate inside the parasite and then interfere with the purine nucleoside metabolism[23].

During the last decade, there has been progress made towards the improvement of antimonial chemotherapy for leishmaniases, but the application of antimonials as antitumoral agents needs attention.

Trivalent antimony compounds

In the mid 1960s, Hsu *et al*[24–26] reported the antitumoral activity of inorganic compounds of antimony and demonstrated that some Sb(III) with aminopolycarboxy ligands increased the life span of mice bearing the Ehrlich ascites tumor and spindle sarcoma. It was later reported that some tungstoantimonates with complicated compositions exhibited antitumoral activity[27,28].

Nitrogen mustard cyclophosphamide (Figure 2) is an alkylating agent reported to possess significant antitumoral activity in selected malignant neoplasms; however, its 1:1 adduct with $SbCl_3L$ presented no activity against L1210 leukemia and Ehrlich ascites tumor, similar to the inactivity of other metal coordination compounds[29].

A series of antimony (III) complexes along with other metal ion complexes, that is, Co, Ni, Sn, and Pb with different polydentate carboxylic acids have also been investigated for their antitumoral action. Preliminary results have indicated that the uncoordinated ligands as such are not as potent as antimony complexes with these ligands, showing the presence of Sb (III) for activity. Of the other metal ions investigated with these ligands, only the antimony (III) species have shown activity[30,31].

The cytotoxicity of NH_4(Sb[Hdtpa]) was examined in human promyelocytic leukemia (HL-60) cells. Complexes at 1, 10, and 100 μg/mL showed 18%, 70%, and 100% cell inhibition within 24 h, respectively. The antitumoral activity of NH_4(Sb[Hdtpa]) (Figure 3) (30 mg/kg) towards solid experimental animal tumors (S180) in mice reduced the weight of the tumors to 74% of that of the control values on d 9 after tumor transplantation[30].

In vitro antitumoral activity of antimony (III) nitrilotriacetate complexes (nitriloacetate compound shown in Figure 4) against Ehrlich adenocarcinoma (EAC) in mice was studied. Compound $(NH_4)_2Sb(Nta)(HNta)\text{-}nH_2O$ (I) and $Na_2Sb(Nta)(HNta)\times 2H_2O$ (II) produced a significant (60%–90%) increase in the survival rate of test mice with ascetic EAC, at an optimum therapeutic dose of 25–50 mg/kg in the absence of significant toxicity in this dose range. The results showed good prospects in the search for new antitumoral agents among Sb(III) complexes with aminopolycarboxy ligands[32].

Similarly, antimony (s-benzyldithiocarbazate) complexes display antitumoral agents against melanoma (skin cancer cells)[33].

The toxicity of a novel water stable antimony (III) complex with heterocyclic thioamide, 2-mercaptopyrimidine (pmtH) (Figure 5) of formula $Sb(pmt)_3]0.5(CH_3OH)$, against tumor pleiomorphic cells was studied. Pleiomorphic cells were isolated from a leiomyosarcoma tumor in the Wistar rat (chemical carcinogenesis using 3,4-benzopyrene BaP). The result showed that the compound did not destroy or prevent multiplication *in vitro* leiomyosarcoma cells at low doses. The antimetastatic capability study showed that the compound had shown inhibition of cancer cell-induced aggregation up to the value of 10% in all mmol/L concentrations tested[34].

Recently, new antimony (III) complexes with the hetero-

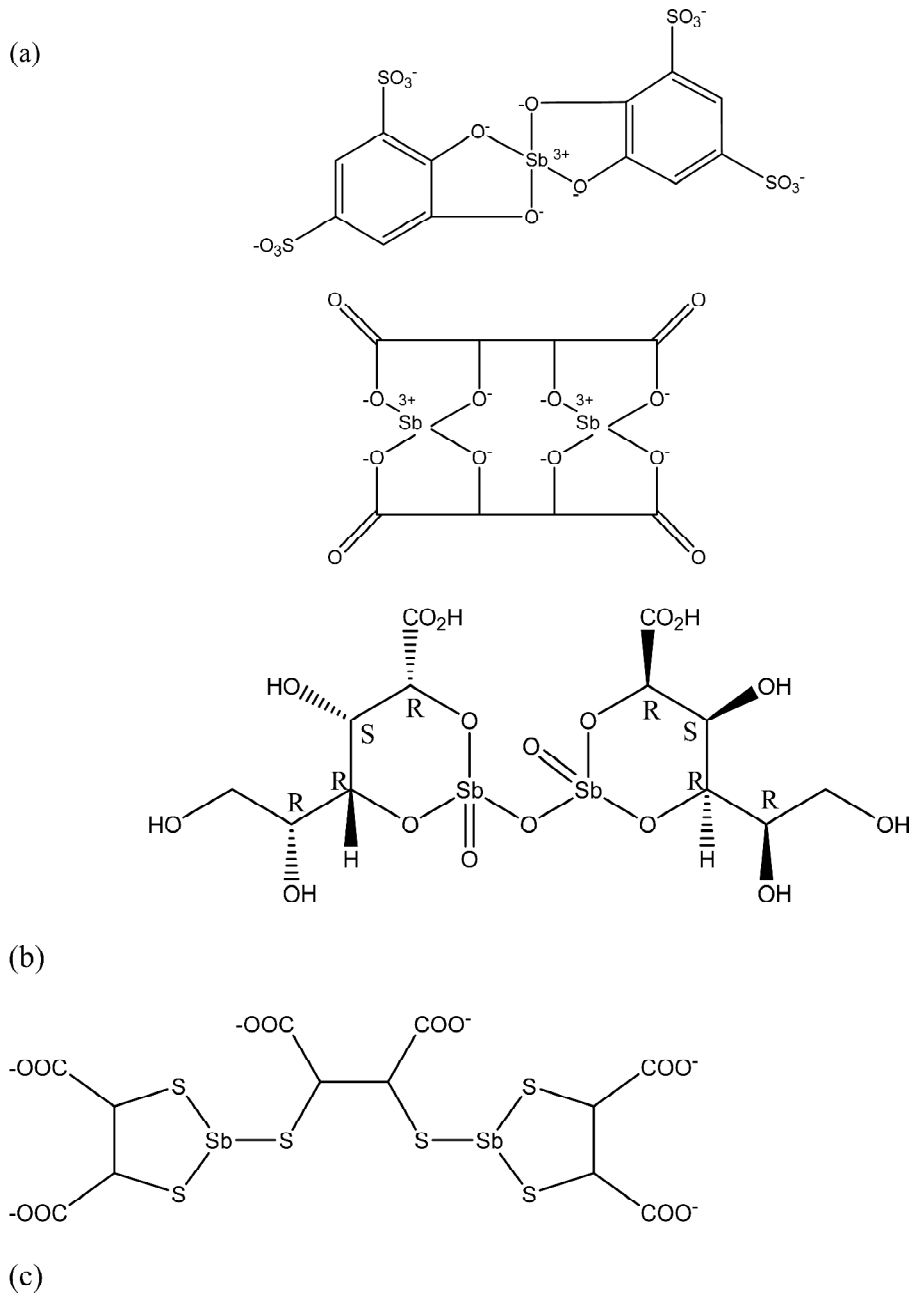


Figure 1. Some antileishmanial compounds of antimony (a) Antimony *bis*(4,5-dihydroxybenzene-3,5-disulphonate) (Stibophen) and Antimony (III) tartarate (Tartar emetic), (b) SSG (Pentostam), (c) Antimony-2,3-dimercaptosuccinate (Astiban).

cyclic thiones 2-mercapto-benzimidazole, 5-ethoxy-2-mercapto-benzimidazole, 2-mercapto-thiazolidine, and 2-mercapto-3,4,5,6-tetrahydro-pyrimidine were tested *in vitro* for their inhibitory effects on the proliferation of murine leukemia cells (L1210), murine mammary carcinoma cells (FM3A), human T-lymphocyte cells (Molt4/C8, CEM), and human cervix carcinoma cells (HeLa)[35]. Complexes showed a pronounced cytostatic activity against these tumor cell lines. Surprisingly, antimony (III) thione complexes consistently showed selective antiproliferative activity against HeLa cells. Their antiproliferative activity against cervix carcinoma (HeLa) cells was 2–3 to >10-fold stronger than against leukemia and lymphocyte cells. In particular the $\{[SbCl_2(MBZIM)_4]^+ \cdot Cl^- \cdot 2H_2O \cdot (CH_3OH)\}$ complex showed stronger activity against cancerous HeLa cells, 6 times higher than that of carboplatin.

Potassium antimonyl tartrate (PAT) inhibited human

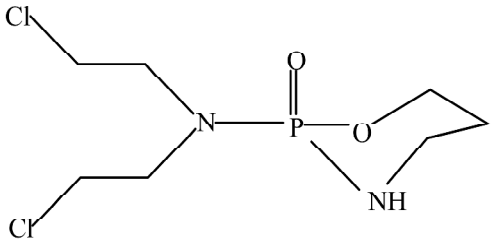


Figure 2. Chemical structure of cyclophosphamide.

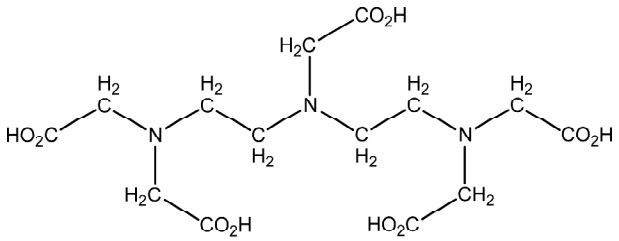


Figure 3. Chemical structure of diethylenetriaminepentaacetic acid (Hdtpa).

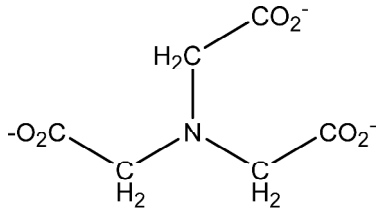


Figure 4. Chemical structure of nitrilotriacetate.

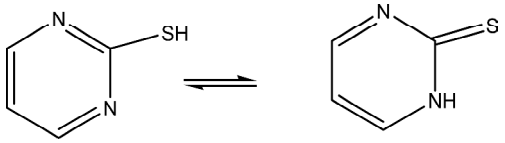


Figure 5. Chemical structure of heterocyclic thioamide 2-mercaptopyrimidine.

gastric cancer cells SGC-7901 growth significantly in a dose- and time-dependent manner. PAT displayed prominent inhibitory effects with 20 and 40 μmol/L at 72 h, and the cancer cell growth inhibition rates reached 54.1% and 66.6%, respectively[16, 36]. *In vitro,* this compound was found to be cytotoxic to various lung cancer cell lines with the IC_{50} [half maximal (50%) inhibitory concentration] ranging from 4.2 to 322 μg/mL (Table 1). The complex was as effective as clinically used anticancer drugs, such as cisplatin and doxorubicin[16].

Like As_2O_3, antimony compounds have also been used

Table 1. Antimony potassium tartrate cytotoxicity against different tumor cell lines.

Cell line	IC_{50} (μg/mL)
AD-A	4.6
BK-T	15.3
HG-E	33.1
JN-M	70.0
JO-E	66.0
LD-T	12.8
LG-T	39.3
Mar	11.2
MM-I	11.9
MO-A	9.1
NCI-H_{69}	4.2
NCI-H_{128}	24.7
NCI-H_{209}	14.9
OS-A	322
RG-I	14.0
SHP-77	53.4
SV-E	276
WL-E	6.4

for a long time in traditional Chinese medicines for the treatment of many diseases, and they have been shown to be clinically active in APL. In eukaryotic cells, resistance to arsenic and antimony is conferred by membrane transport proteins of the multidrug resistance-associated protein (MRP)1 family, which is a drug transport pump. Human MRP1, a member of the MRP family, is frequently amplified in cancer cells. It is well known that MRP1-overexpressing cells accumulate less As and Sb because of increased cellular efflux which is dependent on the presence of glutathione [37]. This is a possible mechanism by which human cells can avoid cytotoxic effects of heavy metals administered as drugs. Such a mechanism of resistance may be important for the clinical efficiency of antimonials used in the treatment of some leukemias[17, 37].

Similarly, other antileishmanial agents, such as SSG and other trivalent antimonials, including antimony trioxide (the reported toxicity of $SbCl_3$ or Sb_2O_3 not withstanding), could induce acute promyelocytic leukemia cell NB4 apoptosis in a dose- and time-dependent manner and present therapeutic benefits to patients[38,39]. It was found that SSG is a potent inhibitor of protein tyrosine phosphatase (PTPases) *in vitro* and *in vivo*, and augments responses in hemopoietic cell lines. It was shown that induction of cellular protein tyrosine phosphorylation was less pronounced with prolonged drug incubation suggesting that either the instability of the drug under experimental conditions or the drug

may sequentially inactivate PTPases with opposite effects on the phosphorylation of the cellular proteins. The intracellular Sb (V) to Sb (III) transformation of stibogluconate can result in the inactivation of the PTPases inhibitor and may account for the modest and transient induction of tyrosine phosphorylation by the drug. SSG inhibited the growth of human cancer cell lines *in vitro* in synergy with interferon (IFN) in IFN-resistant cancer cells. The activity of Src homology PTPase1 (SHP-1) was almost completely inhibited by SSG at 10 μg/mL, which is comparable to the serum concentration of *Leishmania* treatment (~10 μg/mL). The mechanism by which the drug inhibits PTPase is likely by targeting the PTPase catalytic domain of the enzymes. The drug forms a stable complex with SHP-1 *in vitro*, but it is not clear whether this was due to docking of the drug into a pocket structure in the PTPase domain or whether a covalent bond formation is involved. Interference with intracellular tyrosine phosphorylation resulted in the disruption of cell proliferation, differentiation, and signaling activities. Consequentially, antitumoral activity based on the finding that SSG inhibited SHP-1, anti-renal cell carcinoma (anti-RCC) potential, and the action mechanism of SSG and SSG/interleukin (IL)-2 in combination were investigated in a murine renal cancer model (Renca). Despite its failure to inhibit Renca cell proliferation in cultures, SSG induced 61% growth inhibition of Renca tumors in BALB/c mice which coincided with a 2-fold increase in tumor-infiltrating macrophages (Mϕ). The combination of SSG and IL-2 was more effective in inhibiting tumor growth (91%) and inducing tumor-infiltrating Mϕ (4-fold), whereas IL-2 alone had little effect[40-44].

No organoantimony compounds appear to have been screened for their antitumoral activity until the 1990s when Silvestru *et al*[45-47] started working on this direction. Now the most studied antimony compounds in the context of antitumoral activity are organometallic-presenting antimony–carbon bonds.

Some diphenylantimony (III) and diphenyltin (IV) thiolates were tested both *in vitro* and *in vivo* for antitumoral activity. *In vitro*, against Ehrlich ascites tumors, all these compounds were almost equally effective in the inhibition of cell proliferation and viability and protein synthesis. However, the cell respiration and Ca-ATPase and lactate dehydrogenase (LDH) enzymatic activities were considerably impaired. The effects were dose and exposure time dependent. The compounds containing antimony (III) were more active than their organotin congeners[45-47].

In vivo, tests were carried out on mice bearing Ehrlich ascites tumors and P388 leukemias. The results are shown in Table 2, where it was found that all these compounds exhibited antitumoral properties. Three of the antimony compounds had shown marginal activity (T/C <125%) and were less active than cisplatin in this model. The $Ph_2SbS_2P(OPr^i)_2$ compound was most active, but presented increased toxicity at higher doses (Figure 6).

Table 2. Biological evaluation of diphenylantimony (III) thiolates against P388 leukemia *in vivo*.

Compound	Total dose (mg/kg)[a]	T/C(%)[b]
Control	-	100
NH_3PtCl_2 (Cisplatin)	4	245
Ph_2SbL_1	10	123
	5	118
Ph_2SbL_2	10	118
	5	136

[a]Doses were administered on d 1, 2, and 3 after P388 leukemia tumor cells were transplanted into mice. [b]Median survival rate of mice versus median survival rate of controls was expressed as a percentage.

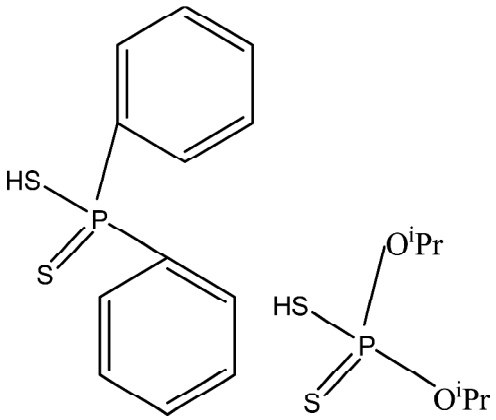


Figure 6. Diphenyldithiophosphinic acid diisopropyldithiophosphoric acid.

Later studies showed that these thiophosphinate derivatives had mutagenic potential with compound 4 at a greater extent[48, 49].

Our group[50,51] has published reports on the antitumoral activity of organostibine containing heterocycles; for example, selenophenyl or substituted thienyl ring (Figure 7). The compound *tris*(2-selenophenyl)stibine and *tris*(3-methyl-2-thienyl)stibine showed a significant selectivity (>85%) for carcinogenic cell K and U growth inhibition. For compound *tris*(5-chloro-2-thienyl)stibine, 85% of carcinogenic cell growth inhibition (U, K, and H) was observed, but these

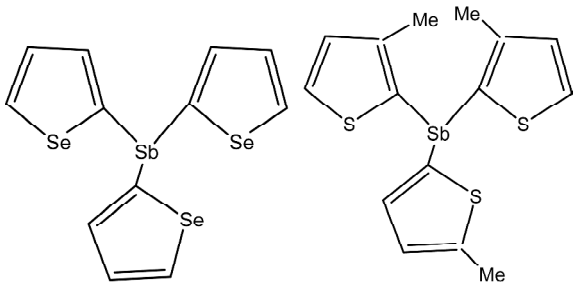


Figure 7. 2-Selenophenylstibine 3-methyl-2-thienylstibine.

compounds are highly toxic for the growth of normal lymphocytes with approximately 95% lethality.

Pentavalent antimony compounds

The trimethylantimony compounds were tested *in vitro* against human tumor cell lines and were found to be inactive[52].

Cytotoxicity of antimony (V) compounds are reported in literature and one of the reports on the cytotoxicity of antimony (V) compounds focuses on the inhibitory effects of a series of triphenylantimony (V) polyamines[53]. The different polyamines used are shown in Figure 8. Almost all the compounds displayed some inhibition, and increased inhibition was associated with increased doses. 2,6-Diaminoanthraquinone adenine has shown higher potential against the 3 cell lines BHK-21, L929, and HeLa, while the dianion derived from 2,4,-diamino-5(3,4-dimethoxybenzil)pyrimidine showed greater selectivity against BHK-21.

Recently Li *et al* published reports on the *in vitro* antitumoral activities of some arylantimony derivatives of demethylcantharimide[54] (LH=*N*-hydroxy-demethyl dehydrogencantharimide, LH=*N*-hydroxy-demethyl-cantharimide, n=3, 4; Ar=C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-

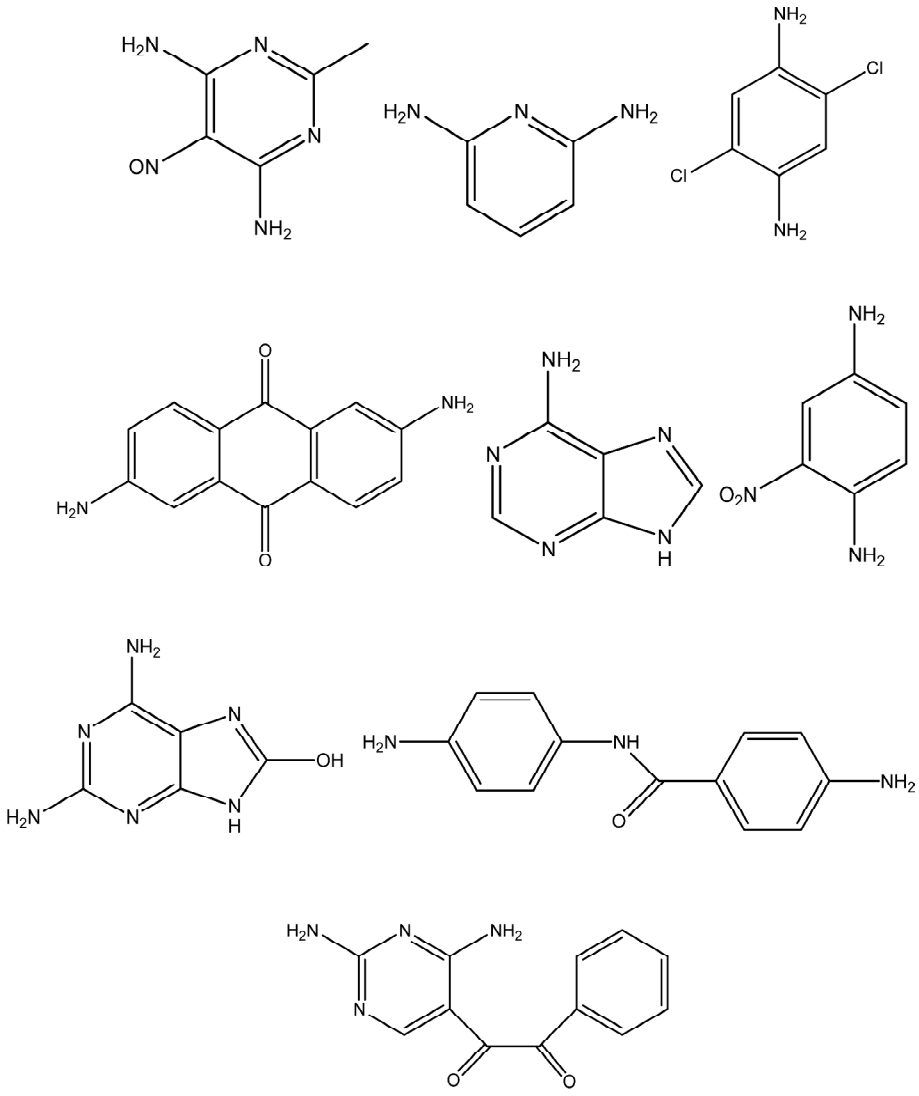


Figure 8. Chemical structures of amines.

$CH_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4), arylhydroxamates (LH=hydroxamic acid; Figure 4)[55], and a series of derivatives of exo-7–oxa-bicyclo(2,2,1)heptane(ene)-3-arylamide-2-acid[56], which are analogs of demethylcantharidin, and demethyldehydrogencantharidin[57].

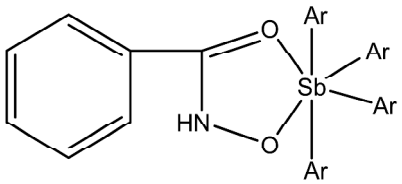
Tetraarylantimony derivatives of demethylcantharimide have relatively higher antitumoral activity against the 6 cancer cells (HL-60, PC-3MIE8, Human Gastric Carcinoma (BGC-823), Breast Tumor MDA-MB-435, Bel-7402, HeLa) than the triarylantimony derivatives of demethylcantharimide. When Ar is 4-ClC_6H_4, compounds c and e have relatively higher antitumoral activity. When compared with cisplatin, compound a and tetraarylantimony derivatives of demethylcantharimide, namely compounds b, c, d, and h, have very high antitumoral activity against some cancer cells[54].

The results of the bioassay showed that these derivatives exhibited antitumoral activities against the different human cancer cells *in vitro*[55]. The antitumoral activities are also affected by the nature of the arylantimony. The tetraarylantimony benzohydroxamate, namely compound a, has much higher antitumoral activity against the 3 human cancer cells (HL-60, BGC-823, MDA-MB-435) than the triarylantimony benzohydroxamates. In addition, compound $(HNEt_3)^+(Ar_3Sb\ [arylhydroxamate]_2)^-$, where Ar is 4-$ClC_6H_4$, is more potent against BGC-823 cells (Figure 9).

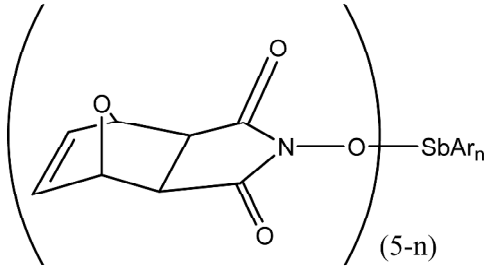
Five human neoplastic cell lines (HL-60, KB, Bel-7402, BGC-823, and HCT-8) were used to screen derivatives of exo-7–oxa-bicyclo(2,2,1)heptane(ene)-3-arylamide-2-acid. The results indicated that these compounds at 10 μmol/L show certain antitumoral activities *in vitro*[56].

Preliminary antitumoral activity tests show that tetraphenylantimony (V) derivatives of demethylcantharidin and demethyldehydrogencantharidin have significant antitumoral activities *in vitro* against 5 human neoplastic cell lines[57].

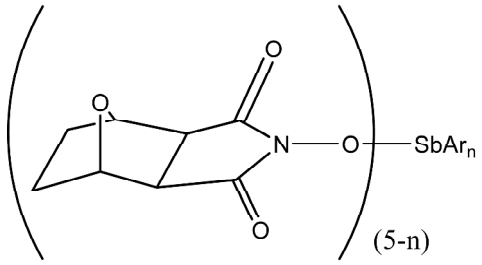
In an another report, the antitumoral potential of different triarylantimony derivatives of triphenylgermanyl propionate were investigated[58]. These compounds have relatively higher antitumoral activities against cancer cells *in vitro* than triphenylgermanylpropionic acid. The results indicate that the antitumoral activities are affected by the nature of the aryl and the triphenylgermanylpropionic acids. The same group[59,60] extended their studies to antimony ferrocenylcarboxylate and N-phenylglycinate derivatives. Three human neoplastic cell lines (HCT-8, Bel-7402, and KB) were used to screen these compounds. The results indicated that these complexes at 5 μmol/L show relatively good antitumoral activities *in vitro*. When the ferrocenylcarboxylate group is $C_5H_5FeC_5H_4C(Me)=CHCOO^-$, it has relatively higher antitumoral activities, in particular, the activity of compound



Compound (**a**) Ar = 4-$CH_3C_6H_4$



Compounds (**b**) Ar=C_6H_5, (**c**) 4-ClC_6H_4



Compounds (**d**) Ar=C_6H_5, (**e**) 4-ClC_6H_4

Figure 9. General structures of antimony (V) compounds.

tris-(*p*-chlorophenyl)antimony(ferrocenylcarboxylate) against HCT-8 cells is higher than that of cisplatin.

Carraher *et al*[61] synthesized polymers containing metal complex formed from triphenylantimony dichloride and thiopyrimidine, and preliminary evaluation showed that these polymers exhibited both antitumoral and antibacterial properties. The polymers showed inhibition of BalK/3T3 cells at concentrations below 10 μg/mL. Additionally, products from Ph_3SbBr_2 and cephalexin showed good inhibition of Balb/3T3 cells to 2 μg/mL, and those from Me_3SbBr_2 and cephalexin show good inhibition to 15 μg/mL. The structure for the Ph_3SbCl_2 and cephalexin product is given later (Figure 10).

A number of antimony (V) polyamines were synthesized, and it was found that these materials also effectively inhibited HeLa cells at concentrations of approximately 5 μg/mL.

Conclusion

A variety of antimonials with different antitumoral activi-

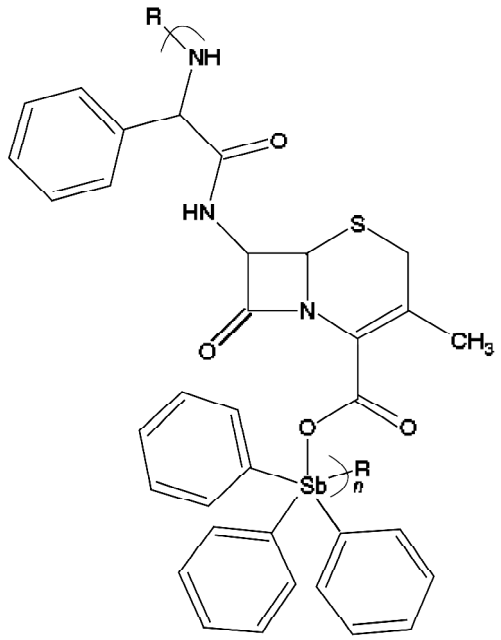


Figure 10. Ph_3SbCl_2 and cephalexin compound.

ties are known. These antimonials have a diverse application, even though little research has been done on their possibilities in this respect. It might be feasible to develop more specific and effective inhibitors for phosphatase-targeted anticancer therapeutics through the screening of SSG-related compounds comprised of antimony conjugated to different organic moieties. SSG is a potent PTPases inhibitor, and as an enhancer of cytokine signaling, appears to be a better inhibitor than suramin. This suggests potential novel clinical applications of the drug in a variety of situations where increased cytokine responses are beneficial. It is clear that the exploration of the antitumoral activity of antimony compounds appear to hold the promise, and therefore, is an area certainly deserving of more research effort.

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