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A glimpse on biological activities of tellurium compounds

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ABSTRACT

Tellurium is a rare element which has been regarded as a toxic, non-essential trace element and its biological role is n clearly established to date. Besides of that, the biological effects of elemental tellurium and some of its inorganic a organic derivatives have been studied, leading to a set of interesting and promising applications. As an example, it can highlighted the uses of alkali-metal tellurites and tellurates in microbiology, the antioxidant effects of organotellurid and diorganoditellurides and the immunomodulatory effects of the non-toxic inorganic tellurane, named AS-10 and the plethora of its uses. Inasmuch, the nascent applications of organic telluranes (organotelluranes) as protea inhibitors and its applications in disease models are the most recent contribution to the scenario of the biological effec and applications of tellurium and its compounds discussed in this manuscript.

Key words: antitumorals, biological applications, enzyme inhibitors, organotellurium, proteases, tellurium.

INTRODUCTION

Tellurium is a rare element which has been regarded as a non-essential, toxic element. Several literature reports also stress that its compounds are highly toxic. Interestingly, selenium was also considered a highly poisonous element since the commencement of selenium related science, until it got the status of being an *absolute poison*. This pre-concept fell when selenium was identified as a micronutrient for bacteria, mammals and birds (Schwarz and Foltz 1957). Selenium was found in the active site of mammalian gluthathione peroxidase as the unique 21st amino acid, selenocysteine (Chambers et al. 1986, Hatfield and Gladyshev 2002). The number of known selenoenzymes greatly grew as well as the mechanisms by which those enzymes act. By now, *tellurium biology and biochemistry* face the same prejudice of selenium, before the recognition of its biological role. The chem tellurium has a plethora of reactivity patterns but chemistry is far less recognized than selenium. fore, there are plenty of opportunities for the d ment and establishment of tellurium participatio scenario of Biology and Medicine. Earlier, thoro views concerning other aspects of tellurium com were published, in relation to both their chemist masseto et al. 2007) and their pharmacological (Nogueira et al. 2004). This short review we herein has the aim to introduce a diversified view biological effects of tellurium compounds.

GENERALITIES AND DEFINITIONS

Tellurium comes from the Latin "*tellus*", m "earth", and was discovered by F.J. Mueller v chenstein in 1782 from ores mined in the gold d of Transylvania (Bragnall 1966, Cooper 1971)

In commemoration of the 75th anniversary of

occurred few years after the discovery of oxygen by J. Priestley and C.W. Scheele, though the periodic group relationship between the other chalcogens was not apparent until nearly a century later. Tellurium is occasionally found native, but is more often found as the telluride of gold (calaverite) or combined with other metals. In the environment, Te exists in its elemental (Te^0), inorganic -telluride ((Te^{2-}), tellurite (TeO_3^{2-}), and tellurate (TeO_4^{2-})), and organic (dimethyl telluride (CH_3TeCH_3)) forms (Cooper 1971). Of these, its oxyanion forms are more common than its non-toxic, elemental state (Summers and Jacoby 1977). Presently, sparse research into anthropogenic emissions of tellurium-based compounds has been conducted and the implications of Te in the air have yet to be investigated. Tellurium is a member of the family of chalcogens. The German chemist Wilhelm Blitz coined the term "chalcogen" ("ore formers" from chalcos, old Greek for "ore") for these elements, and "chalcogenides" for their compounds (Fischer 2001). Tellurium and selenium generate compounds that are structurally related to their sulfur analogues, but exhibit different properties and reactivities, being thus considerably more toxic. As one descends the column, the chalcogens become larger and more polarizable than sulfur. Selenium has a lower electronegativity and forms weaker bonds than sulfur (Whitham 1995). The chemists found that selenium can be easily introduced into molecules as a radical, a nucleophile, or an electrophile. Tellurium has even greater metal like properties and is a true metalloid. In part, due to its polarizability, the C-Se bond is weaker than C-S bonds; C-Te bonds are weaker yet, specially in the case of alkyl derivatives which tend to decompose under heat and light irradiation. This difference in bond energies may explain why telluromethionine and tellurocysteine amino acids have not been naturally found while selenocysteine (the 21st amino acid) has been found in many organisms.

Main Classes of Tellurium Compounds

Tellurium composes both inorganic and organic derivatives. An inorganic tellurium compound differs from an organic derivative because the former has at least one

can be divided in two distinct groups according to the oxidation state of tellurium. The first group contains the divalent derivatives. Tellurols are the analogues of alcohols and thiols and are readily susceptible to oxidation to ditellurides. Diorganotellurides are the analogues of ethers and tioethers, have a formal oxidation state of -2 and comprises the large set of studied organotellurium compounds. Diorganoditellurides are related to peroxides, being the products of oxidation of tellurols. The second major group is composed by the hypervalent derivatives in which tellurium has the oxidation states of +4 and +6, and the classes of *organotelluranes* composed by organotellurium trihalides, diorganotellurium dihalides, organotellurium oxides, organotellurates, and organopertelluranes (Chart 1).

Biological Effects of Elemental Tellurium and its Inorganic Derivatives

Tellurium found historical applications in the treatment of microbial infections prior to the discovery of antibiotics. Early documentation in 1926 reports its use in the treatment of syphilis and leprosy (De Meio and Henriques 1947). Its oxyanion tellurite, TeO_3^{2-}, has been used in microbiology since the 1930s when Alexander Fleming reported its antibacterial properties (Fleming 1932, Fleming and Young 1940). In 1984, it was suggested that TeO_3^{2-} could be a potential antisickling agent of red blood cells in the treatment of sickle cell anemia (Asakura et al. 1984). In 1988, tellurium-containing immunomodulating drugs were proposed as treatment agents for AIDS; however, little has been done on it since then (Jacobs 1989). This compound, AS-101, inhibits the production of IL-10, IFN-γ, IL-2R, and IL-5 (Shohat et al. 2005), and also exhibits protection of bone marrow stem cells during chemotherapy (Guest and Uetrecht 2001). More recently, it has been found other diverse activities of AS-101, such as the induction of hair growth in both nude mice and in teenagers with alopecia (Sredn et al. 2004); the inhibition of IL-1β converting enzyme (caspase-1) (Brodsky et al. 2007); protection against homocysteine-promoted apoptosis (Okun et al. 2007a); the enhancement of neuronal survival in an ischemic stroke animal model (Okun et al.

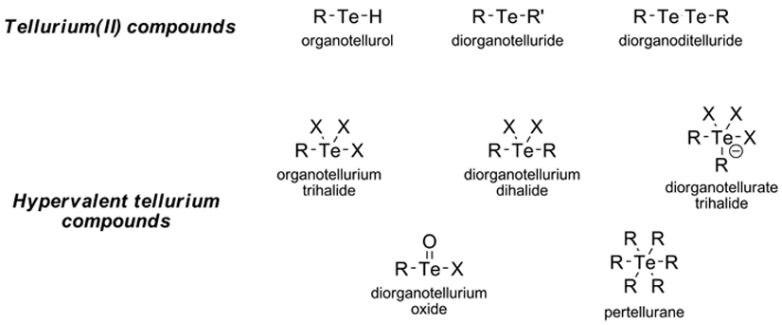


Chart 1 – Classes of tellurium compounds mainly explored for the study of biological effects.

Tellurium biochemistry in the context of animal and human toxicology was last reviewed by Taylor (1996). Despite many chemical homologies between selenium and tellurium, a nutritional role has never been identified for tellurium. Moreover, tellurium, at low concentrations, induces both acute and chronic toxicity in a variety of organisms. Nevertheless, several studies have shown that trace amounts of tellurium are present in body fluids, such as blood and urine (Goulle' et al. 2005). Tellurocysteine and telluromethionine can be found in bacteria (Boles et al. 1995, Budisa et al. 1995, 1997), yeast (Yu et al. 1993), and fungi (Ramadan et al. 1989) as a result of misincorporation of tellurium in place of sulfur or selenium, thus allowing the expression of protein analogs useful for protein structural studies (Moroder 2005).

The toxicology of tellurium has been received less attention than that of selenium. This may be a result of the less frequent contact of man and animals with this element and its compounds. Tellurium is less soluble than selenium in physiological pH and the oxidation to tellurite (TeO_3^{2-}), tellurate (TeO_4^{2-}) or TeO_2 occurs easily. Tellurium dioxide is practically insoluble in water at physiological pH. The reduced form of tellurium, H_2Te, more readily decomposes, by light or air, than H_2Se; for this reason, some authors attribute to tellurium a lower potential toxicity than selenium (Sadeh 1987).

Both tellurium and/or its oxyanion forms act on the enzyme squalene monooxygenase, the second enzyme in the committed pathway for cholesterol biosyn-

same effect has been observed with selenite an
methylselenium compounds (Gupta and Porter
The sensitivity of squalene monooxygenase to te
and selenium compounds is due to the binding c
compounds to vicinal cysteines; the methylation
lurium *in vivo* may enhance the toxicity of telluri
this enzyme (Laden and Porter 2001). It has als
observed that tellurite (TeO_3^{2-}) ions induce th
ation of the erythrocyte membrane and this act
thiol-dependent as well (Deuticke et al. 1992). I
most of the Te(IV) derivatives are also able to ina
cysteine proteases, but not other families of pro
This seems to be related to the ability of Te(IV
pounds to react with the thiolcatalytic site of c
proteases. Te(VI) compounds do not exhibit an
inhibitory activity as they are inert towards thio
eties (Albeck et al. 1998). Overall, the above wo
gests that tellurium compounds interact with bio
systems by specific chemical interaction with e
nous thiols. More recently, another inorganic te
compound, named SAS, was synthesized, and
hibitory activity toward papain and cathepsin B de
as more potent than AS-101 as cysteine prote
hibitor (Yosef et al. 2007).

The precise biochemical explanation for th
city of oxyanions of the different chalcogens r
largely unknown in bacteria. In general, it has b
sumed that the toxicity of tellurite is a consequ
the strong oxidizing properties that lead to the
tion of deleterious reactive oxygen species (Trem

way. Some living organisms display can process non-essential tellurium. As a form of defense, some bacteria and fungi strains are able to metabolize tellurium salts in their reductive metabolism, leading to biologically inert Te^0 or tellurolate (Te^{2-}), which is methylated to volatile, garlic smelling $(H_3C)_2Te$, in such a way that tellurium is eliminated from the medium where the microorganism is. The reduction and methylation of tellurium occur also in mammals including humans. The injection of tellurium salt solutions in animals lead to the formation of Te^0 and $(H_3C)_2Te$, which are eliminated by breath, urine and sweat (Chasteen and Bentley 2003).

Tellurate (TeO_4^{2-}) is about 2- to 10-fold less toxic than tellurite in most organisms studied (Harrison et al. 2004). However, due to its poor solubility in aqueous conditions, very little has been done with this form of tellurium. Finally, as another effect of an inorganic form of tellurium, it has been reported that tellurium tetrachloride is a reversible inhibitor of Zn^{2+} glicerolphosphocoline coline phosphodiesterase by tellurium tetrachloride (Sok and Kim 1992). This enzyme is found in the nervous system and is related with the myelin basal membrane homeostasis. It should be noted that tellurium tetrachloride readly hydrolyses in water and, because of this, the tellurium specie responsible for the inhibition was not clarified.

Aspects of the effects of selenium and tellurium in microorganisms were recently covered in an excelent review (Zannoni et al. 2008). An interesting application of TeO_3^{2-} consists in its use as an additive to growth media for the selection and identification of various microorganisms, particularly those resistant to tellurite, for almost 90 years. It is often employed in selective media to isolate a wide range of pathogens including: *Corynebacterium diphtheriae*, *Vibrio cholerae* (Shimada et al. 1990), *Shigella spp.* (Rahaman et al. 1986), and verocytotoxigenic *E. coli* O157:H7 (the "hamburger disease" bacterium) (Zadic et al. 1993, Kormutakova et al. 2000). Considerable work has been focused on the pathogenic *E. coli* O157:H7 since this strain is highly tolerant to metalloid anions. This allows the use of tellurite-enriched media for its identification and isolais also used in media to select Shiga toxin-producing *E. coli* (STEC) O26 (Hiramatsu et al. 2002). However, a study on *E. coli* O46 and O15:H7 strains suggest that there is no correlation between the tellurium resistance and the ability to produce Shiga toxin (Taylor et al. 2002). In addition to *E. coli* strains, tellurite has been used in selection media for other organisms, including *Mycobacterium avium* complex (Afghani and Fujiyama 2001), methicillin-resistant *Staphylococcus aureus* (MSRA) (Zadic et al. 2001), pathogenic *Vibrio spp.* (Donovan and van Netten 1995). Cefixime-tellurite media has been used for isolating organisms from minced beef (Dogan et al. 2003), rectal swabs of cattle (Yilmaz et al. 2002), raw vegetables (Fujisawa et al. 2002), and sprouts (Fujisawa et al. 2000).

Tellurite and tellurate have also been proposed for use in selective media for identification of fecal *Streptococci* (Saleh 1980). It is clear that tellurite has proven to be a useful amendment for selection media in clinical laboratory settings and will continue to do so. However, this approach should be used with caution since non-pathogenic strains can acquire tellurite resistance determinants, thereby appearing in many clinical assays as false positives.

A noteworthy possibility of exploring the microorganism tellurium resistance is highlighted if one considers the unique challenges of the use of microorganisms in environmental sciences. The exploitation of microorganisms for the bioremediation of contaminated areas is nowadays of particular interest. The use of antibiotic resistance markers in usual molecular biology techniques may have deleterious consequences in the spread of multi-drug resistance strains. It has been show that the tellurium resistance genes can be used to follow *Pseudomonas putida* following environmental release for organic degradation (Sanchez-Romero et al. 1998). Tellurite has also been used to detect and quantify the release of *Pseudomonas pseudoalcaligenes* KF707 in soils for polychlorinated biphenyl (PCB) degradation (Zanaroli et al. 2002). Bacteria can mediate bioremediation of tellurium either through direct sequestration, bioreduction, or biomethylation. In sequestration, bac-

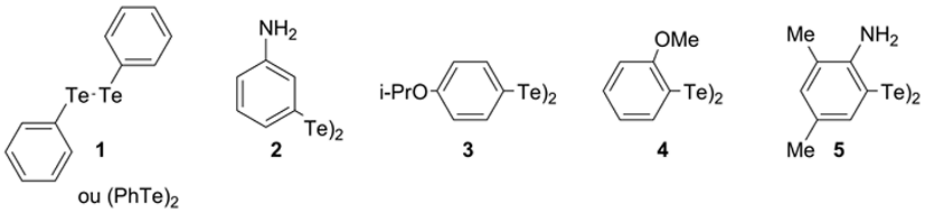


Fig. 1 – Molecular structures of diorgano ditellurides used in toxicological studies.

acting in the form of an ion-exchange matrix. Bioreduction instead reduces the more toxic oxyanion forms to the "non-toxic" Te^0. This process usually occurs intracellularly, leading to the precipitation of the metallic form within the cell. Biomethylation leads to volatile methyl derivatives that disperse into the atmosphere. Thus, the chalcogen can travel considerable distances providing detoxification of local contamination sites through dilution by diffusion.

The tellurite resistance determinants *kilAtelAB*, *ter*, *tehAB*, and *arsABC* were investigated for use in tellurite remediation. The use of the plasmid borne tellurite resistance determinant *tehAB* was found to facilitate the largest amount of uptake of tellurite from the external media (Turner et al. 1994). Highly resistant microbes could also potentially be used for Te bioremediation. Strains of marine purple non-sulfur bacteria with resistance to 5mM tellurite were found to decrease the concentration of tellurite in the external media 100-fold and led to accumulation of elemental tellurium deposits in cells (Yamada et al. 1997). The bioreduction of toxic inorganic forms of tellurium may have promising use for aquifer contamination sites and the same techniques are also applicable for other metalloid derivatives as well.

Biological Effects of Organotellurium Compounds

There are just a few reports on the toxicology of organotellurium compounds. Albeit the organotellurium compounds were considered less toxic than the selenium derivatives (Engman 1985), recent studies indicate the contrary (Nogueira et al. 2004). It must be pointed that research efforts are focused mainly on the effects of

Diphenylditelluride, (PhTeTePh) (**1**) have b
tensively used in toxicological studies. The adm
tion of doses of **1** to test animals showed an exp
toxicity – $LD_{50} < 1\mu$mol/kg (rat); $LD_{50} \approx 150\mu$
(mice). Mice survived for 72h after the adminis
of doses of 500μmol/kg of **1** whereas 75%
treated with doses of 0.75μmol/kg died. Inasmu
administration to rats of shorter dosed of diphen
luride (0.5μmol/kg) showed an increase of alan
aspartate aminotransferase activities in serum ind
of an induction of alteration in the normal func
liver and kidney of the testing animals (Meott
2003).

The toxicology of organotellurium compoun
been studied mainly by empirical methods based
relative toxicity observed in animals, or the evalua
effects in tissues or by the inhibition of cellular
(Sailer et al. 2004). For these reasons, Chaste
coworkers evaluated the toxicity of a series of
ditellurides (**2-5**, Fig. 1) to HL-60 cells by mea
the induction of apoptosis by cell cytometry (Sail
2003). The ditellurides showed a meaningful ap
induction in doses of 1μM, except for the ditell
which minimal dose was of 10μM.

Despite the toxic effects demonstrated fo
pounds **1-5**, applications of other classes of orga
lurium compounds have been studied. Among
the most thoughtfully described effect is the anti
properties of organic tellurides.

GSH acts as a reductor and as substrate of GS
oxidases (GPx) and transferases. The GPx enzym
tain selenium as selenocysteine at its active site a
in conjunction with GSH to avoid or minimize ox

gen peroxide to water. The GPx catalytic selenol (EnzSeOH) is oxidized by hydroperoxides (ROOH) to selenilic acid (EnzSeOH), leading also to the reduced form of the hydroperoxide (ROH). The oxidized GPx (EnzSeOH) reacts with GSH, leading to the mixed dichalcogenide (EnzSeSG) which reacts with another GSH molecule, forming oxidized gluthathione (GSSG) and restoring the catalytic active GPx (Fig. 2).

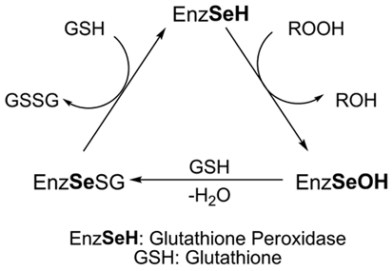
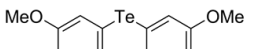
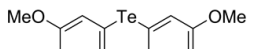


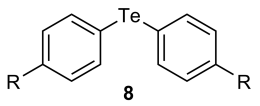
Fig. 2 – Catalytic cycle of gluthathione peroxidases showing the reduction of an organic hydroperoxide.

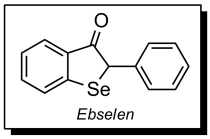
Since this process is related to the chemical reactivity of the catalytic selenium, the exploitation of organoselenides and organotellurides as GPx mimetics are well covered in the literature. Due to the fundamental relevance of this process in aging and the potential use of antioxidants as prospective drugs for oxidative stress-related diseases, several studies have been undertaken with selenium compounds that act as mimics of GPx enzymes such as aromatic selenides and diselenides, selenium heterocycles containing Se-N moiety, the artificial selenosubtilysin, and selena-peptides among other selenium derivatives (Mugesh et al. 2001). The substitution of selenium for tellurium in arylic derivatives greatly improves the antioxidant activity. Andersson and coworkers (1994) described the antioxidant activity of organotellurium compounds *in vitro*. It was observed the improvement on efficacy of tellurides **6** and **7** in the inhibition of lipid peroxidation of cells induced by oxidative conditions (Fig. 3).





After this first report, the antioxidant activity of a series of arylic tellurides **8a-k** was compared with the selenium heterocycle Ebselen, the first selenium compound which the GPx-like activity was demonstrated in chemical and biochemical systems (Fig. 4). The used diaryltellurides were found to efficiently inhibit peroxidation in rat hepatocytes, rat liver microssomes and an organic solution of phosphatidylcholine (Andersson et al. 1994).





R: NH_2(**a**), OH(**b**), OMe(**c**), F(**d**), H(**e**), NMe_2(**f**), Me(**g**), CF_3(**h**), Cl(**i**), Br(**j**), NO_2(**k**)

Fig. 4 – Arylic tellurides used in the first demonstration of their GPx-like activity.

The mechanism of the thiol-peroxidase activity of organotellurides was studied further by Engman and coworkers (1994). It was proposed that the organotelluroxide in the hydrate form reacts with thiols, producing disulfides and regenerating the initial diorganotelluride as shown in Figure 5.

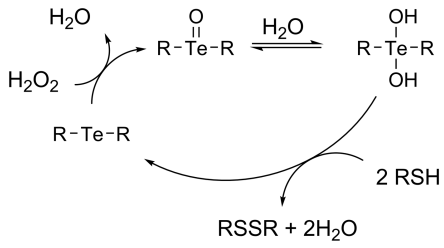


Fig. 5 – Proposed mechanism of the GPx-like activity of diorganotellurides (adapted from Engman et al. 1994).

From these initial studies, several groups have been reporting the antioxidant activity of several organic tellurides. A common observed feature consists in the great antioxidant efficacy of tellurium derivatives in comparison to sulfur or selenium analogues. It is noteworthy that diaryl tellurides inhibit lipid peroxidation much

lurium compounds were also demonstrated in complex cellular systems, in which the abrogation of radical chain reactions and the decomposition of peroxides were observed (Wieslander et al. 1998). These make this class of organotellurium compounds promising candidates for the use in the developing antioxidant therapies. As an example, the inhibition of thioredoxin/thioredoxin reductase system (TrxR) and cancer cell growth by antioxidant organotellurium compounds structurally related to vitamin E was reported (Engman et al. 2003). TrxR system is a promising redox target for cancer therapy (Urig and Becker 2006).

Another class of organotellurium compounds which showed antioxidant activity is the diorgano ditellurides (Fig. 6). Tellurium dichalcogenides are more efficient antioxidants than selenium counterparts. Engman and coworkers (1992) proposed a mechanism for the thiol-peroxidase activity performing a series of elegant NMR experiments. The ditellurides which presents in its structure coordinating nitrogen groups exhibits a strong secondary interaction between tellurium and nitrogen atoms. Interestingly, it was observed an inverse linear correlation among the force of the Te•••N secondary interaction and the GPx-like activity: as the secondary interaction gets stronger, the GPx-like activity diminishes.

Furthermore, more complex organotellurium compounds with antioxidant activities were also described, being the case of semisynthetic tellurosubtilisin (Mao et al. 2005), dendrimeric organotellurides (Francavilla et al. 2001, Ahsan et al. 2003); and tellurium-based polymeric surfactants. The thiol-peroxidase activity of these systems was more active than the previously described semi-synthetic tellurosubtilisin (Huang et al. 2006). In a more sophisticated report, a nanoenzyme model with glutathione peroxidase-like active site was built on polystyrene nanoparticle via microemulsion polymerization (Huang et al. 2008). The nanoenzyme mimics showed to be highly efficient, but the major achievement was the demonstration that polymeric nanoparticles can be developed as excellent models for combining most of catalytic factors of enzyme into one scaffold.

thirty-five years and had acquired regulatory appr
several countries for carcinomas of the lung, di
tract, and genitourinary tract. PDT cancer treatr
also in development for head, neck and pancreas c
mas. The principle of this therapy is based in the
a sensitizer agent which is capable to interact wi
producing cytotoxic species or a cytotoxic reac
tumoral carcinoma, typically singlet oxygen ($^1O_2$
peroxide from molecular oxygen (Leonard et al.
The sensitizer agent is generally porphirins, phth
nines or dyes, and may ideally present a prefe
interaction with tumoral cells. Detty and cowork
ported the *in vitro* production of $^1O_2$ by the irradia
an oxygen saturated solution of chalcogen-based c
shown in Figure 7 (Detty et al. 1990). In this first
a series of chalcogena-pyrilium salts were prepar
characterized as inhibitors of cytochrome c oxi
tumoral cells. The damage induced by **9c** was v
by pronunciated morphological changes in mitoch
from human glyoma cells. This report is noteworr
cause it compares all possible chalcogen derivativ
it was verified that the selenium and tellurium deri
were more efficient sensitizers.

More recently, Brennan and coworkers (20
veloped a novel class of chalcogena-pyrilium dyc
more resistant to hydrolysis and structurally rel
the tio-pyrilium salt AA1, which has a defined a
cific action on mitochondria (Fig. 8).

The antitumoral activity of the of the thiatell
bocyanine iodide **11** (Fig. 9) was found from a
ing of 1000 lipophilic cationic compounds demor
by Sun and coworkers (1996). Lipophilic cationi
pounds were found to be a class of antitumoral
due to its selective localization, accumulation a
tention within the mitochondria of certain tumor
(Sun et al. 1996). Certain selectivity toward t
cells was observed *in vitro* assays, in which **11** v
fold more toxic to the CX-1 carcinoma cells in co
son to the epithelial CV-1 cell line. Regarding the
studies, the administration of **11** significantly pro
the survival of mice implanted with tumors. The
of **11** on mitochondria was attributed by similarity

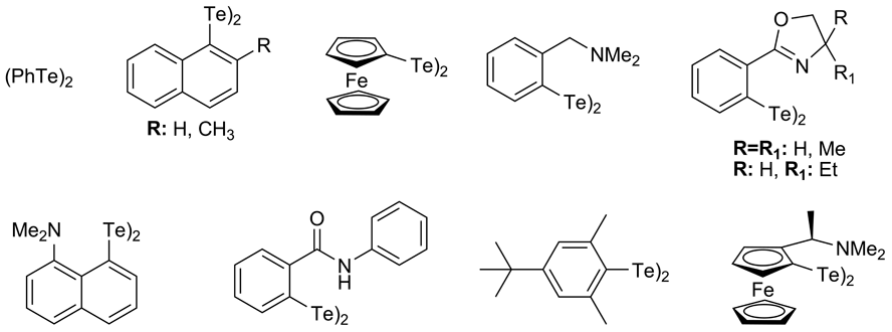
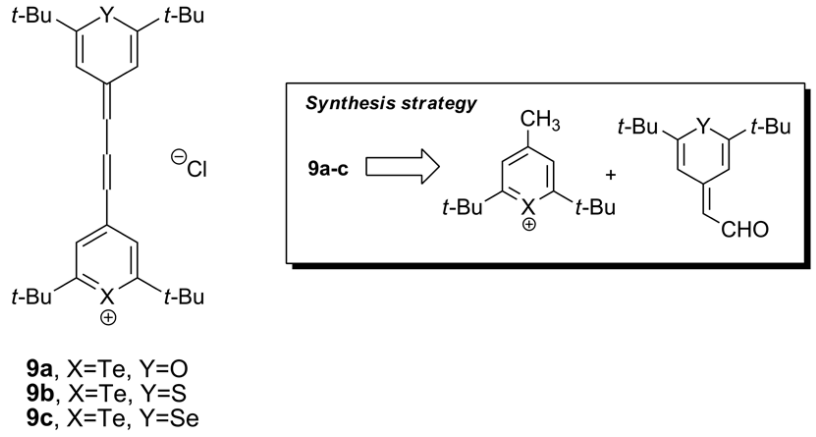
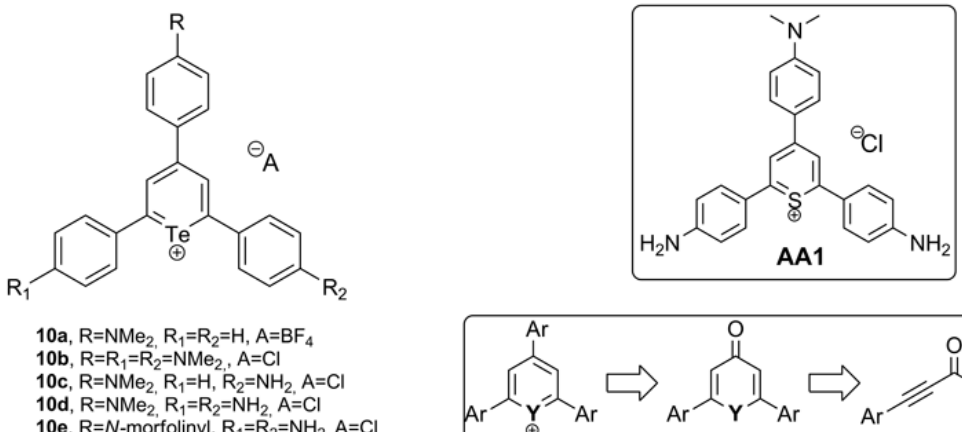


Fig. 6 – Diorganil ditellurides with mimetic GPx activity.



9a, X=Te, Y=O
9b, X=Te, Y=S
9c, X=Te, Y=Se

Fig. 7 – Molecular structure of chalcogena-pyrilium salts and the main strategy for its preparation.



10a, R=NMe_2, R_1=R_2=H, A=BF_4
10b, R=R_1=R_2=NMe_2, A=Cl
10c, R=NMe_2, R_1=H, R_2=NH_2, A=Cl
10d, R=NMe_2, R_1=R_2=NH_2, A=Cl
10e, R=*N*-morfolinyl, R_1=R_2=NH_2, A=Cl

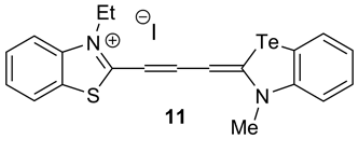
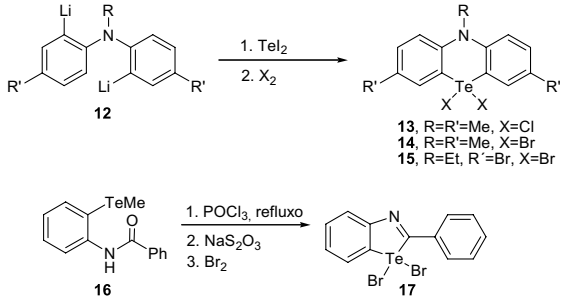


Fig. 9 – Molecular structure of the thiatelluracarbocyanine iodide **11**.

The effects of organotellurium(II) compounds were described above. Another important group of organotellurium compounds, the hypervalent organotellurium compounds (organotelluranes), with described and nascent applications, is described below. The biological applications of organotelluranes are far less studied than those of organotellurium(II) compounds.

The antihelminic of four organotelluranes (**13-17**) was demonstrated against *Trichinella spiralis* infected mice (Ordyntseva et al. 1988). The organotelluranes **13-15** were prepared by the reaction of the aryllithium reagent **12** and TeI_2 followed by the oxidation of the obtained organotellurides with chlorine or bromine. The fourth organotellurane was prepared by the reaction of the organotelluride **16** with phosphorous oxychloride, followed by the sequence of reduction and oxidation with bromine which lead to **17** (Scheme 1). The effect of these compounds was compared with mebedazol; compound **15** did not show any activity, whereas **13** and **14** were less effective than mebedazol; **17** showed similar activity.



Scheme 1 – Synthesis of organotelluranes with anti-helmintic activity.

Soni and coworkers (2005) recently showed the antibacterial activity of a series of unsymmetrical diorganyltellurium dichlorides (**18-22**) (Fig. 10). It has been found the antibacterial effect against gram-positive (*Baclilus subtilis*, *Staphylococcus aureus*) and gram-negative naphtyl series (**20-22**) were most effective, but nism of this effect was not demonstrated.

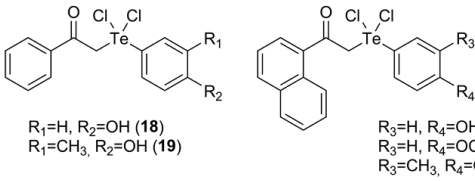


Fig. 10 – Organotelluranes with gram-negative antibacterial

Inorganic and organic tellurium derivativ highly toxic for the central nervous system of (Maciel et al. 2000). Compounds **23**, **24**, and **25** (are potent inhibitors of either purified squalene oxigenase (Laden and Porter 2001) and also for it ity in cells (Goodrum 1998), causing a dramatic re in cholesterol biosynthesis and leading to the d tion of myelin and further demyelinization of per nerves. The inactivation of squalene monooxigen curs by the interaction of the telluranes and a vicinal thiols from the catalytic cysteine in the e Dimethyltellurium dichloride **23** is the most po hibitor of this enzyme, and its effects on nerve c very similar to those observed in the Te^0-induce ropathy.

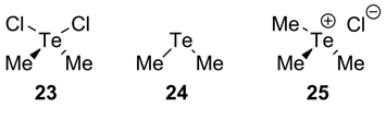


Fig. 11 – Tellurium-based inhibitors of cholesterol biosyn

Finally, organotelluranes have been studied tease inhibitors. The first description of this effe reported for inorganic telluranes (Albeck et al. In this first seminal report, tellurium(IV), telluri compounds and the effect on the activity of t main classes of proteases were studied. It ha found that just the inorganic tellurium(IV) com exhibited a specific inhibitory activity towards c proteases papain and cathepsin B from bovine More recently, an inorganic tellurane obtained fr taric acid, named SAS, was also reported to be potent inhibitor of papain and cathepsin B than

any formal carbon-tellurium bond, it should be correctly classified as inorganic tellurium compounds.

In comparison to those and other inorganic telluranes, the organotelluranes has a particular advantage. Once the inorganic ones are limited to the availability of the ligand, the organic ones can be obtained by the oxidation of every organotellurium(II) compound which can have a plethora of structural motifs. Taking this into account, a small set of organotelluranes was evaluated as inhibitors of recombinant human cathepsin B (Cunha et al. 2005). It was therefore observed that the organotelluranes were potent inactivators of cathepsin B (Fig. 13). The inactivation of cathepsin B was time- and concentration- dependent and involves the modification of enzyme´s catalytic thiol. The most interesting feature of the organotellurane inhibition consists in the recovery of the enzyme activity by the use of reducing agents such as dithiothreitol (DTT). Docking studies have been carried out using these and other organotellurium compounds (Cunha et al. 2006). It is anticipated that the information collected from this studies may be useful to plan specific and more potent derivatives.

A larger collection of organotelluranes was further assayed with recombinant cathepsins B, L, S and K to seek for selectivity aspects on the inhibition of closely related cysteine proteases (R.L.O.R. Cunha, I.E. Gouveia et al., unpublished data). It was observed interesting inhibition profiles using these cathepsins which revealed selective inactivation of each cathepsin with a different organotelluranes, especially for cathepsins S and K. Since the effect upon a biological target was established, further exploration of the effects of organotelluranes, on more complex models where the activity of cysteine proteases is associated, has been explored. As examples, it was described the effect of organotelluranes in angiogenesis and the cytotoxicity on several cancer cell lineages (R.L.O.R. Cunha, T. Paschoalin et al., unpublished data); the induction of apoptosis in human HL-60 cells (Abondanza et al. 2008). The protective effect of an organotelluroxetane in an animal model of epilepsy was also demonstrated. The pre-administration of the organotelluranes avoided the establishment of the *status* with the organotelluxetane, anionic organotelluranes and AS-101. Once again, the organotelluranes were better inactivators in comparison to AS-101. Finally, the effect of organotelluranes in isolated mitochondria was investigated (Pessoto et al. 2007). It was found that these compounds induce the formation of a transition pore in mitochondria inner membrane (but avoids the oxidative damage which usually arises); this was explained by the formation of organotellurium(II) species from the interaction of the organotelluranes with membrane proteins.

CONCLUSIONS

Albeit the conventional prejudice concerning tellurium and its compounds, the role of tellurium at the stage of biology is at its beginning. Tellurium compounds have a particular chemistry with thiol which is related to many of the biological effects observed so far. Besides of this, there are a lot of information and possible new concepts waiting to be addressed to allow a rational development of the uses of tellurium compounds in biology and medicine. In particular, the fate of organotellurium(II) in biological media, the reactivity of tellurium compounds towards bionucleophiles and a broad knowledge on other possible targets must be clarified before further developments.

ACKNOWLEDGMENTS

Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) are acknowledged for research grants and scholarships. RLORC thanks to FAPESP for a post-doctoral scholarship (process no. 04/14426-0).

RESUMO

O telúrio é um elemento não-essencial raro que vem sendo considerado tóxico, e o seu papel biológico é ainda pouco esclarecido. Apesar disso, os efeitos biológicos do telúrio elementar e de alguns derivados inorgânicos e orgânicos que têm sido estudados revelam um conjunto de aplicações diversificadas interessantes e promissoras. Como exemplo, pode-se destacar

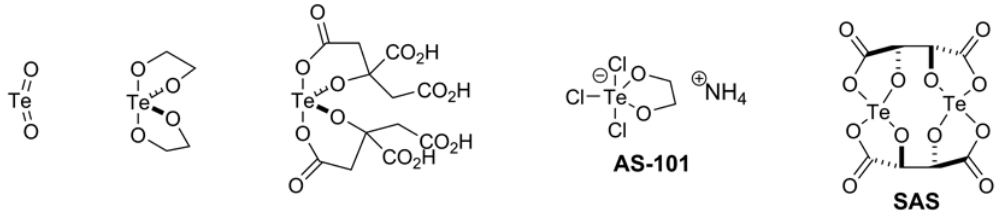


Fig. 12 – Inorganic telluranes as specific cysteine protease inhibitors.

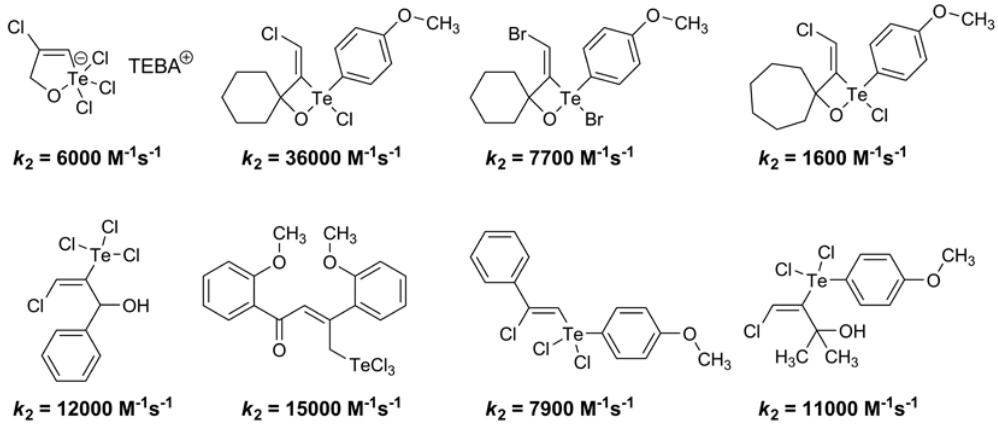


Fig. 13 – Organotelluranes with potent irreversible inactivation of recombinant human cathepsin B, above the molecular structures the order inactivation rate constants determined for each compound is indicated.

relacionados a este efeito de uma telurana inorgânica denominada AS-101. Ademais, as aplicações de teluranas orgânicas (organoteluranas) como inibidoras de proteases e as aplicações em modelos de doenças compõem a mais recente contribuição ao cenário dos efeitos e aplicações biológicas do telúrio e seus compostos discutidas neste manuscrito.

Palavras-chave: antitumorais, aplicações biológicas, enzimas inibidoras, compostos orgânicos de telúrio, proteases, telúrio.

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