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# Octa-*O*-bis-(*R,R*)-Tartarate Ditellurane (SAS)—a Novel Bioactive Organotellurium(IV) Compound: Synthesis, Characterization, and Protease Inhibitory Activity**

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*Octa-O-bis-(R,R)-Tartarate Ditellurane (SAS) is a new $Te^{IV}$ compound, comprised of two tellurium atoms, each liganded by four oxygen atoms from two carboxylates and two alkoxides of two tartaric acids. Unlike many other $Te^{IV}$ compounds, SAS was highly stable in aqueous solution. It interacted with thiols to form an unstable $Te(SR)_4$ product. The product of the interaction of SAS with cysteine was isolated and characterized by mass spectroscopy and elemental analysis. SAS selectively inactivated cysteine proteases, but it did not inactivate other families of proteolytic enzymes. It displayed selectivity towards the cysteine protease cathepsin B, a human enzyme of pharmaceutical interest, with a second order rate constant $k_i/K_i = 5900\ M^{-1}s^{-1}$.*

## Introduction

Tellurium is a relatively rare element, which is found in small amounts (up to 600 mg) in the human body,[1] though its physiological functions are not clear.[2]

Several synthetic tellurium compounds exhibit biological activity. Compounds of the form $R_2TeCl_n$ exhibit anthelmintic activity[3] whereas tellurite ions ($TeO_3^{-2}$) induce alterations of the erythrocyte membrane.[4] Ammonium trichloro(dioxoethylene-*O,O'*)tellurate (AS101)[5] is probably the synthetic tellurium compound most studied from the standpoint of its biological activity. It is a potent immunomodulator (both in vitro and in vivo) with a variety of potential therapeutic applications.[6–8] AS101 was shown to have beneficial effects in diverse preclinical and clinical studies. It exhibits protective effects in mouse models of parasitic and viral diseases,[9] in autoimmune diseases,[10] in septic mice,[11] in kidney diseases,[12] and in protecting dopaminergic neurons and enhancing their function in animal models of Parkinson's disease.[13] AS101 was also shown to mediate bone marrow sparing in phase II clinical trials in cancer patients.[14,15]

Most of the activities of AS101 have been primarily attributed to the direct inhibition of the anti-inflammatory cytokine, interleukin 10 (IL-10).[16] AS101 was also shown to inhibit cysteine proteases,[17] and in particular caspase 3 and 8 activities in vitro,[13] and caspase 1 and 3 in vivo,[13,18] potentially enabling the compound to exert both anti-inflammatory and antiapoptotic properties.

Much of the biological activity of AS101 is directly related to its specific chemical interactions with endogenous thiols. Such tellurium-thiol compounds may be important for the manifestation of the biological function itself or for transportation of the tellurium species to its target location.[19] Formation of a tellurium-thiol chemical bond may initiate a biological activity, which is naturally promoted by an endogenous effector.[13] Alternatively, it may lead to complete loss of the biological activity by thiol inactivation, as is the case of cysteine proteases.[13,17,18] In a previous study, we clarified several mechanistic aspects of the chemistry of AS101, and discussed its relationship to its biological activity.[17]

The wealth of biological activities exhibited by AS101 prompted us to further develop additional organotellurium compounds, which may present a different activity profile. Such compounds may expand the arsenal of beneficial activities, or demonstrate a more narrowed profile with higher selectivity. Furthermore, the new compounds may possess different molecular properties such as stability, solubility, and permeability. Thus, we describe herein a novel organotellurium compound, octa-*O*-bis-(*R,R*)-tartarate ditellurane (SAS), and report preliminary studies of its biological activity as a selective cysteine protease inhibitor.

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[**] *CCDC 645094 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.*

  

## Results

### Synthesis

Octa-*O*-bis-(*R*,*R*)-tartarate ditellurane (SAS) (Figure 1a) was synthesized in a single step from tellurium tetraisopropoxide[20] and (*R*,*R*)-tartaric acid in either ethanol or DMSO. The white crystalline product (mp 210–225 °C (d)) was obtained in good yield. Its structure was determined by X-ray crystallography (Figure 1b). The compound is comprised of two tellurium atoms and two tartarate molecules. Each tellurium$^{IV}$ atom is liganded by four oxygen atoms, the alkoxide and the carboxylate atoms of the two tartarate molecules. When crystallized from DMSO, each SAS molecule is surrounded by four DMSO molecules. One of these solvent molecules is ordered, whereas the other three are disordered. The crystallographic data can be found in the Supporting Information.

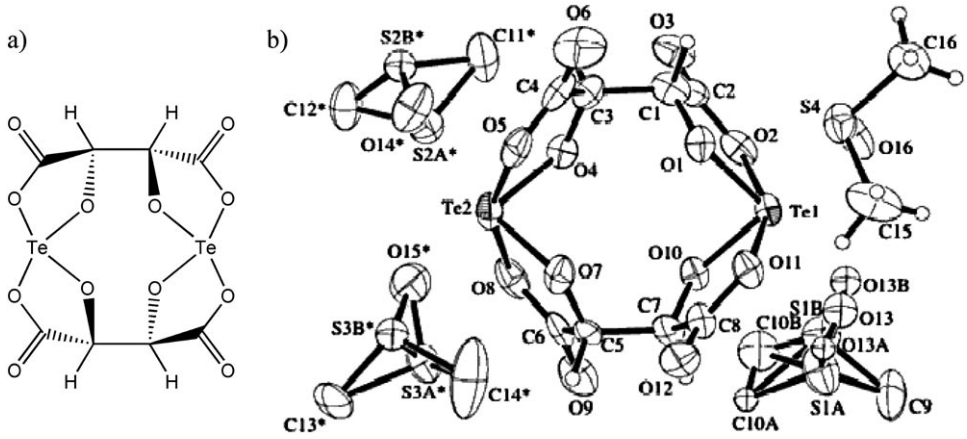


**Figure 1.** a) The chemical structure and b) X-ray crystal structure of SAS. There are four solvent molecules (DMSO) per SAS molecule in the crystal, one of which is ordered while the other three are disordered.

### Interaction with thiols

SAS was reacted with L-cysteine in a glove box under $N_2$ atmosphere in the dark, yielding a yellow solid material that was identified, both by mass spectroscopy and elemental analysis, as the Te$^{IV}$-thiol compound Te(cysteine)$_4$ (Figure 2a). In addition, the mass spectrum of the reaction mixture exhibited a set of peaks at *m*/*z* 1033, 913, 793, and 673. These peaks could be assigned to Te$_2$(tartarate)$_2$(cysteine)$_4$ ($MH^+$), and the products of the consecutive loss of one, two, and three cysteines, respectively (Figure 2b).

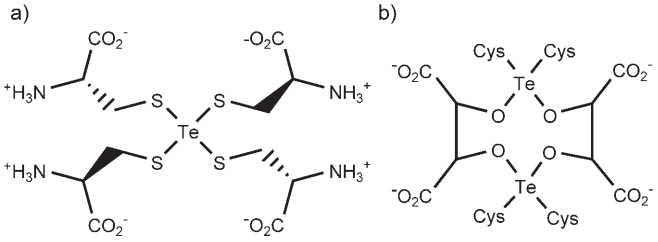


**Figure 2.** The chemical structure of a) the Te(cysteine)$_4$ product of the interaction between SAS and cysteine and b) the Te$_2$(tartarate)$_2$(cysteine)$_4$ intermediate of this reaction.

### Interaction with proteolytic enzymes

SAS was tested as a potential inhibitor of the four families of proteases. No inhibition of serine proteases (chymotrypsin, trypsin, subtilisin, and elastase - characterized by different substrate selectivities), aspartic proteases (pepsin), or metallo proteases (carboxypeptidase A) was detected, even upon long incubation (1 h) at a high concentration (1.5 mM) of SAS (data not shown).

In contrast to its inertness towards serine, aspartic, and metallo proteases, SAS displayed time- and concentration-dependent inhibition of the cysteine proteases papain and cathepsin B (Figure 3). The kinetic parameters for the inhibition process were: $K_i = 2.5\ \mu M$, $k_i = 3.4 \times 10^{-2}\ min^{-1}$ and $k_i/K_i = 225\ M^{-1}s^{-1}$ for papain inactivation and $K_i = 0.13\ \mu M$, $k_i = 4.7 \times 10^{-2}\ min^{-1}$ and $k_i/K_i = 5900\ M^{-1}s^{-1}$ for cathepsin B inactivation.

## Discussion

### Synthesis and characterization

We previously synthesized a variety of Te$^{IV}$ and Te$^{VI}$ compounds,[17] but SAS is the first organotellurium compound of this series that contains two tellurium atoms. This is quite unusual, as we applied a simple general synthesis that usually yields the monotellurium compounds with other ligands. Therefore, we expected the synthetic procedure to yield Te(tartarate)$_2$ as the major product. Indeed, NMR spectra ($^1H$, $^{13}C$, and $^{125}Te$) indicated that SAS is a symmetrical compound, consistent with a Te(tartarate)$_2$ structure, analogous to the other compounds prepared in the same way. However, elemental analysis indicated an approximately 1:1 Te:tartarate composition, and the actual Te$_2$(tartarate)$_2$ structure was only revealed by X-ray crystallography (Figure 1). Four DMSO molecules surround each SAS molecule in this crystal structure. SAS could be prepared either in DMSO or in EtOH. Extensive solvent evacuation under vacuum left two DMSO molecules or one EtOH molecule per SAS molecule in the crystalline product.

The solubility of SAS in PBS is almost identical to that of AS101 (0.50 mM and 0.54 mM, respectively), but SAS delivers two equivalents of Te$^{IV}$ per molecule. Therefore, in terms of tellurium equivalents, SAS is twice as soluble as AS101. In addition, SAS is much more stable in aqueous solutions; whereas

  

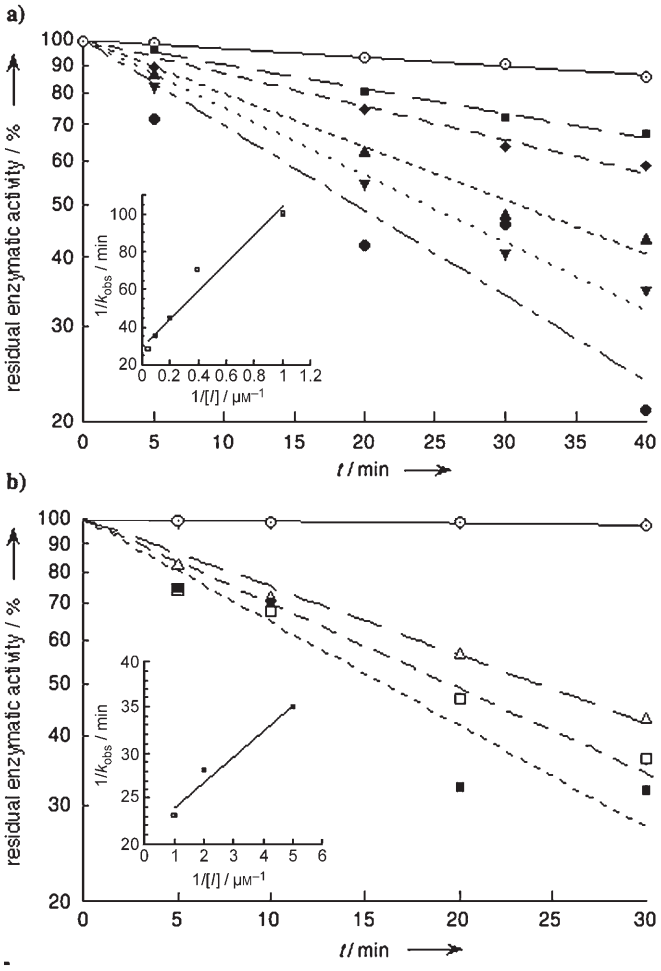


**Figure 3.** Representative time course of inactivation of a) papain and b) cathepsin B by SAS. Inhibitor concentration: (○) 0 μM; (△) 0.2 μM; (□) 0.5 μM; (■) 1.0 μM; (◆) 2.5 μM; (▲) 5 μM; (▼) 10 μM; (●) 20 μM. The lines represent the calculated exponential fit to the experimental data points. The insets show the corresponding replots of $1/k_{obs}$ versus $1/[I]$.

AS101 hydrolyzes in water to an unidentified complex of $TeO_2$, SAS remains stable for days. Finally, in addition to the tellurium atom, SAS is comprised of only tartaric acid, which is a natural ingredient in food. In light of the biological activities and pharmaceutical value of AS101, and the distinct properties SAS possesses, the latter could be a good candidate for drug development.

### Interaction with thiols

$Te^{IV}$ compounds such as $TeX_4$ or $Te(OR)_4$ interact readily with nucleophiles such as alcohols, thiols, and carboxylates, yielding $Te(Nu)_4$ products.[21,22] The latter may engage in further ligand exchange or eventually, hydrolyze in aqueous solution to $TeO_2$. Contrary to this simple chemistry, $Te(SR)_4$ compounds undergo an oxidation-reduction disproportionation reaction:[23,24]

$$Te(SR)_4 \rightarrow Te(SR)_2 + RSSR \quad (1)$$

$Te(SR)_2$ may further react to form a second disulfide and elemental tellurium. The chemistry of AS101 with thiols was previously studied in detail.[17] Herein, we isolated the product of the interaction between SAS and cysteine, and determined its structure as $Te(cysteine)_4$, based on its mass spectrum and elemental analysis. It should be noted that this stoichiometry does not necessarily imply the formation of Te–S bonds. On the other hand, this interaction between SAS and cysteine eventually leads to the reduction of the tellurium atom to $Te^0$ and oxidation of the thiol functional group to a disulfide (as was previously demonstrated by the thiol-specific reagent DTNB[17]). These observations, together with our previous studies of the interaction of AS101 with thiols,[17] strongly suggest that the formation of the $Te(SR)_4$ species involves Te–S bonds.

The mass spectrum of the reaction mixture of SAS with cysteine exhibited a set of peaks that could be assigned to $Te_2(tartarate)_2(cysteine)_4$ (Figure 2b) and its MS degradation products. This compound may be an intermediate in the reaction of SAS with cysteine, in which four thiols of cysteine molecules replace the four Te-carboxylate bonds, while the four Te-alkoxide bonds remain intact. From the point of view of the central tellurium atoms, we identified a $Te(OR)_2(SR')_2$ intermediate of the reaction

$$Te(OR)_4 \rightarrow Te(OR)_2(SR')_2 \rightarrow Te(SR)_4 \quad (2)$$

As indicated above, compounds such as $Te(tartarate)_2(cysteine)_2$ or $Te(cysteine)_4$ may mediate the actual biological activity of SAS and other Te-based compounds such as AS101, or the transportation of the tellurium species to the site of its biological action.

### Interaction with proteolytic enzymes

Based on the unique chemistry of $Te(SR)_4$ compounds, which undergo redox disproportionation, we expected that $Te^{IV}$ compounds should irreversibly inactivate cysteine proteases by promoting oxidation of their catalytic thiols, whereas they might interact nonspecifically and reversibly with serine, metallo, and aspartic proteases.[17] Indeed, SAS did not inactivate any of the enzymes tested from the three serine, aspartic, and metallo protease families. On the other hand, time- and concentration-dependent inhibition was observed upon its incubation with the cysteine proteases papain and cathepsin B. In a previous study, we demonstrated that this inactivation could be reversed by the introduction of reducing agents such as excess thiols, supporting the suggestion that inactivation occurs through the oxidation of the catalytic thiol.[17]

The inhibition kinetics could be interpreted according to the minimal inhibition scheme:

$$E + I \overset{K_i}{\rightleftharpoons} E \cdot I \overset{k_i}{\rightarrow} E{-}I \quad (3)$$

and fit to the equation[25]

$$1/k_{obs} = (K_i/k_i)(1/[I]) + 1/k_i \quad (4)$$

  

It should be emphasized that the above kinetic scheme does not describe the actual inhibition mechanism, which is much more complicated and involves multistep ligand replacement at the tellurium center and subsequent redox disproportionation.[17] Nevertheless, the above kinetic scheme is a useful approximation to a set of chemical transformations in which the first step is rate limiting. Indeed, we have previously demonstrated that this is the case in the reaction in solution of $Te^{IV}$ compounds with four equivalents of thiol.[17] We expect this to apply to the enzyme inhibition reaction as well.

The cysteine protease target tested was cathepsin B. This human enzyme is implicated in a variety of pathologies, including tumor invasion, metastasis, and angiogenesis,[26–29] neuronal cell death,[30,31] arthritis,[32,33] muscle dystrophy,[34] pancreatitis,[35] and apoptosis and necrosis.[36–38] Therefore, cathepsin B is an attractive target for drug development.

In a previous study, we showed that the $Te^{IV}$ compound AS101 inactivates the cysteine proteases cathepsin B and papain, with second order rate constants $k_i/K_i = 37\ M^{-1}s^{-1}$ and $310\ M^{-1}s^{-1}$, respectively.[17] Cathepsin B and papain are also inactivated by peptidyl epoxides with similar binding affinities.[39] On the other hand, SAS exhibits selectivity towards cathepsin B; it inactivates cathepsin B with a second order rate constant an order of magnitude higher than the corresponding inhibition constant of papain ($k_i/K_i = 5900\ M^{-1}s^{-1}$ and $225\ M^{-1}s^{-1}$, respectively). These results reflect a 220-fold difference in the selectivity towards cathepsin B between AS101 and SAS. Further analysis of the inactivation parameters indicates that the stronger interaction with cathepsin B stems solely from the binding affinity ($K_i = 0.13\ \mu M$ and $2.5\ \mu M$ for cathepsin B and papain, respectively), whereas the first order rate constants, reflecting the chemical step, are very similar for the inactivation of the two enzymes ($k_i = 4.7\times10^{-2}\ min^{-1}$ and $3.4\times10^{-2}\ min^{-1}$ for cathepsin B and papain, respectively).

## Conclusions

In this report we introduce a novel $Te^{IV}$ compound, Octa-*O*-bis-(*R*,*R*)-Tartarate Ditellurane (SAS), which exhibits improved properties (solubility and stability) relative to the extensively studied immunomodulator AS101. SAS exhibits a protease inhibition profile similar to AS101; they are both selective inactivators of cysteine proteases, but inert towards serine, metallo, and aspartic proteases. However, SAS displays different selectivity within the family of cysteine proteases. Thus, we anticipate that SAS will have a unique biological activity profile which we hope to characterize in future studies.

## Experimental Section

### General

Enzymes and their substrates were obtained from Sigma Chemical Company and used without further purification. $^{125}Te$, $^{13}C$, and $^{1}H$ NMR spectra were recorded at 189, 75, and 300 MHz, respectively, in [$D_6$]DMSO. Chemical shifts are reported with tellurium tetraisopropoxide as an external reference for the $^{125}Te$ NMR[20] and solvent resonance as an internal reference in the $^{13}C$ and $^{1}H$ NMR measurements. Elemental analyses were carried out by Prof. Dr. H. Malissa und G. Reuter GmbH (Kaiserau, 51789 Lindlar, Germany). Gel permeation chromatography was carried out on Sephadex G-15 from Pharmacia.

### Synthesis

*Tellurium tetraisopropoxide* was synthesized as previously described.[20]

*Octa-O-bis-(R,R)-tartarate ditellurane (SAS).* Tellurium tetra-isopropoxide (0.73 g, 2 mmol) was added to a solution of (*R*,*R*)-tartaric acid (0.3 g, 2 mmol) in dry EtOH (3 mL) under Ar atmosphere at RT. The reaction mixture was kept at 60 °C for 4 h. The product SAS precipitated as a white solid. It was collected by centrifugation, washed with EtOH, and dried under vacuum (0.1 mm/Hg, 25 °C, 48 h), affording the clean product at 86% yield. mp 210–225 °C (d). $^{1}H$ NMR: $\delta = 4.69$ ppm (s). $^{13}C$ NMR: $\delta = 76.62$ (CH), 173.89 ppm ($CO_2$). $^{125}Te$ NMR: $\delta = 1463.1$ ppm (s). MS *m/z* 553 [$MH^+$], 436, 407, 277. Elemental analysis for $C_{10}H_{10}O_{13}Te_2$ (SAS + EtOH)%: C 20.44 (20.28), H 1.83 (1.53), Te 44.51 (43.08)

*Tellurium tetracysteine.* A solution of cysteine (100 mg, 0.83 mmol) in degassed distilled water (2 mL) was added to a solution of SAS (100 mg, 0.18 mmol) in degassed distilled water (2 mL) under $N_2$ atmosphere in a glove box. A yellow solid precipitated. After stirring for 15 h, the solid was collected by centrifugation and washed with distilled water. It was then removed from the glove box and dried under vacuum (0.1 mm/Hg, 25 °C, 48 h), affording the insoluble clean product in 65% yield. mp 165–190 °C (d). MS *m/z* 611 [$MH^+$], 548, 458, 442, 429, 354, 327. Elemental analysis for $C_{12}H_{24}N_4O_8S_4Te$%: C 23.58 (23.68), H 3.90 (3.95), N 9.07 (9.21), O 21.27 (21.05) Te 20.80 (21.05).

### X-ray crystallography

A wet single transparent crystal coated with vaseline was placed quickly inside a glass capillary and mounted on the KappaCCD diffractometer. Data collection was performed with graphite monochromatized MoK$\alpha$ radiation using $\phi$ and $\omega$ scans to cover the Ewald sphere. Programs used for data collection and processing were KappaCCD server software[40] and DENZO-SMN,[41] respectively. The structure was solved by direct methods using the program package "maXus"[42] and refined with SHELXL-97.[43] The Te cluster was refined anisotropically and its four hydrogens were placed at calculated positions and refined isotropically using the riding model. At this stage, four DMSO molecules were located from the Fourier difference maps. One was found ordered and three disordered with the S atoms disposed with various occupancies above and below the plane defined by the oxygen and two methyl groups. The occupancies were 0.8, 0.2; 0.8, 0.2; 0.925, 0.075. The ordered DMSO molecule was refined anisotropically and its six hydrogens isotropically, using the riding model. S1A, S2A, S3A, C9, C11, C12, O14, C13, C14, and O15 were refined anisotropically and S1B, S2B S3B, C10A, C10B, O13, O13A, O13B isotropically until refinement reached convergence at $R = 0.04$. Software used for material publication: SHELXL-97.[43] Software used for molecular graphics: ORTEP, TEXRAY structure analysis package.[44]

### Enzymatic assays

All enzymatic assays were carried out at 25 °C, by following substrate hydrolysis spectrophotometrically by an ELISA reader (unless otherwise specified). A 60 μL substrate solution (in the indicated concentration and solvent) was dissolved in 120 μL buffer. The catalytic reaction was initiated by addition of 4 μL enzyme solution. The concentration of the enzymes was set such that, under substrate saturation ($V_{max}$) conditions, the initial velocity of hydrolysis was about $10^{-3}$ O.D./s.

  

Chymotrypsin (from bovine pancreas, EC 3.4.21.1) was assayed in 100 mM potassium phosphate buffer pH 7.0, by following the hydrolysis of BTEE (50 μM in DMSO:buffer 2:58) at 260 nm.[45]
Subtilisin (Sigma Type XXVII) was assayed in 100 mM potassium phosphate buffer pH 7.0, by following the hydrolysis of Succ-AAPF-pNA (50 μM in DMSO:buffer 2:58) at 410 nm.[46]
Elastase (from porcine pancreas, EC 3.4.21.36) was assayed in 100 mM Tris·HCl buffer pH 8.0 containing 0.15 M NaCl, by following the hydrolysis of Succ-AAA-pNA (20 μM in the same buffer) at 410 nm.[47]
Trypsin (EC 3.4.21.4) was assayed in 100 mM Tris·HCl buffer pH 8.3 containing 10 mM $CaCl_2$, by following the hydrolysis of BAEE (40 μM in DMSO:buffer 2:58) at 260 nm.[48]
Carboxypeptidase A (from bovine pancreas, EC 3.4.17.1) was dissolved in 10% aqueous LiCl for stock solution and was assayed in 25 mM Tris·HCl buffer pH 7.5 containing 0.5 M NaCl, by following the hydrolysis of hyppuryl-L-phenylalanine (1.4 mM in the same buffer) at 260 nm.[49]
Pepsin (pepsin A from porcine stomach mucosa, EC 3.4.23.1) was assayed for its ability to digest hemoglobin, according to a published procedure.[50]
Papain (EC 3.4.22.2) and cathepsin B (from bovine spleen, EC 3.4.22.1) were activated at 25 °C for one hour in 100 mM potassium phosphate buffer pH 7.0, containing 1 mM DTT and 1 mM EDTA, followed by gel filtration to remove excess DTT (see below). They were assayed in 100 mM potassium phosphate buffer pH 7.0, by following the hydrolysis of Cbz-Gly-ONp (50 μM in $CH_3CN$:buffer 1:2) at 405 nm.[51]

**Inactivation studies**

The discontinuous method was applied.[25] Typically, the enzyme in buffer (200 μL) was incubated at 25 °C with SAS dissolved in DMSO (10 μL). Aliquots (20 μL) were removed periodically, diluted into assay solution containing the substrate, and the residual enzymatic activity was measured. A control preincubation solution, containing all of the ingredients except for the inhibitor itself, was run and assayed in parallel. Values of $k_{obs}$ (The apparent inactivation rate constant) were calculated from semilog plots of percentage residual enzymatic activity versus time (by fitting the graphs to the exponential equation % activity$_t = 100\,e^{-k_{obs}t}$). Replot of $1/k_{obs}$ versus $1/[I]$ yielded the inactivation kinetic parameters $k_i$ and $K_i$ .[25]

**Gel permeation chromatography**

A 0.5 mL solution of activated papain or cathepsin B was loaded on a 1×8 cm Sephadex G-15 column, pre-equilibrated with 100 mM potassium phosphate buffer pH 7.0 containing 0.1 mM EDTA. The enzyme was eluted with the same buffer (degassed) at 0.5 mL min$^{-1}$ and 1 mL fractions were collected. The $A_{280}$ of each fraction was measured. Subsequently, 300 μL aliquots were removed, mixed with DTNB (20 μL of 0.1 mM in DMSO) and $A_{410}$ was measured.

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**Keywords:** biological activity · cysteine proteases · enzyme inhibitors · tellurium · thiol oxidation

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