Synthesis of telluroamino acid derivatives with remarkable GPx like activity†

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Received 28th August 2008, Accepted 3rd November 2008
First published as an Advance Article on the web 13th November 2008
DOI: 10.1039/b814990a

A series of modular telluroamino acid derivatives with remarkable GPx-like behavior was prepared in an efficient and short two-step synthesis.

Glutathione peroxidase enzymes (GPx) are excellent catalysts for antioxidant reactions. They protect our body against the potentially damaging effects of reactive oxygen species (ROS), such as hydrogen peroxide and some organic hydroperoxides, formed during aerobic metabolism. Several neurodegenerative diseases, including Alzheimer's and Parkinson's disease are linked to ROS activity.[1] Since the discovery that selenium plays a pivotal role in GPx enzymes, catalyzing the reduction of hydroperoxides at the expense of glutathione (GSH),[2] synthetic developments and design of new chalcogen-based catalytic antioxidants have attracted considerable attention.[3] Synthetic organoselenium and organotellurium compounds have emerged as excellent candidates to act as GPx mimics, due their well-known ability to undergo two-electron redox cycle between chalcogen (II) and (IV) species.[4]

The cyclic selenenamide ebselen **1** (Fig. 1), was the first synthetic compound suggested for hydrogen peroxide inactivating therapy in the presence of glutathione.[5]

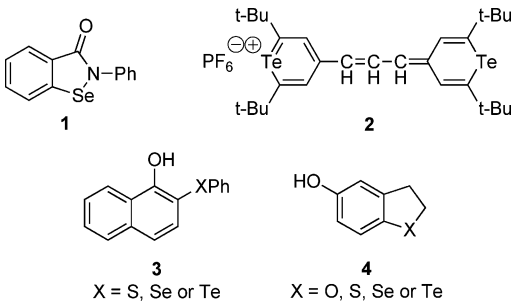


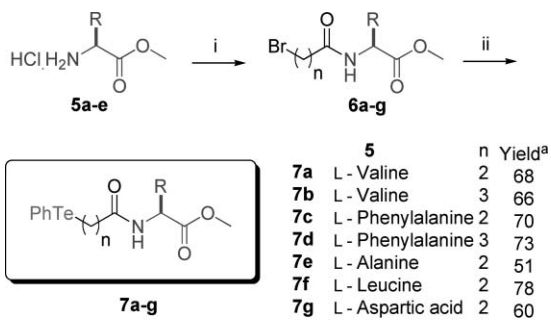
Fig. 1 Representative examples of GPx mimics.

Based on the recognized GPx like activity of ebselen, several papers have appeared describing simple synthetic organoselenium compounds with this property (*e.g.*, benzoselenazinones,[6] benzoselenazolinones,[7] camphor-derived selenenamide,[8] diaryl diselenides[9] and dendrimers with a diselenide core[10]).

On the other hand, the first organotellurium compound **2**, described as a GPx mimic, was reported by Detty.[11] After that, a series of diaryl ditellurides[12] and diaryl tellurides[13] have been reported. Engman and collaborators have developed the synthesis and studied the antioxidant properties of compounds **3**[14] and **4**.[15] A noteworthy characteristic of these compounds is the much improved antioxidant activity of tellurides, when compared with their selenium and sulfur analogues.

Amino groups that are capable of interacting with selenium, through Se–N nonbonded interactions, are known to play a significant role in modulating the redox proprieties of seleno-based antioxidants.[16] However, to the best of our knowledge, there are just a few reports concerning the synthesis and GPx like evaluations of aminoacid derivatives containing selenium[17] and none about tellurium. As part of our growing interest in aminoacid derivatives containing chalcogen,[3c,18] we report herein the synthesis of novel telluroaminoacid derivatives, easily obtained in a simple, modular and efficient two-step synthesis. We envisioned that this modular characteristic would allow us to investigate the structure–activity relationship of these compounds. Their GPx like activity was evaluated, and we promoted the variation of aminoacid residues, the chain length between the chalcogen atom and the aminoacid moiety in order to find a more efficient catalyst.

GPx mimics **7a–g** were prepared in two steps, in 51–78 overall yield, from readily available L-aminoesters and the appropriate bromo-carboxylic acid, as shown in Scheme 1.



	5	n	Yield[a]
7a	L - Valine	2	68
7b	L - Valine	3	66
7c	L - Phenylalanine	2	70
7d	L - Phenylalanine	3	73
7e	L - Alanine	2	51
7f	L - Leucine	2	78
7g	L - Aspartic acid	2	60

[a] Overall yields.

Scheme 1 Synthetic strategy to prepare compounds **7a–g**. *Reagents*: i) bromo-carboxylic acid, NMM, ethyl chloroformate, $CHCl_3$; ii) $PhTe)_2$, $NaBH_4$, THF, EtOH.

The catalytic activity of tellurides **7a–g**, as a GPx model enzyme, was evaluated according to the Tomoda method[15] using benzenethiol as a glutathione alternative. The reduction of H_2O_2 was monitored through the UV absorption increase at 305 nm, due to diphenyl disulfide formation.

Our prime concern in the evaluation of these compounds as GPx mimics was the influence of the chain length between the tellurium atom and aminoacid moiety. It should be noted that compounds **7a** ($n = 2$) and **7b** ($n = 3$) derived from L-Valine

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† Electronic supplementary information (ESI) available: General procedures, ^1H and ^{13}C NMR spectra of selected compounds. See DOI: 10.1039/b814990a

showed the same activity. Linear increases in absorbance (Fig. 2) were observed by mixing MeOH, catalyst **7a–d** (2.6 mol%), PhSH and H_2O_2. Taking advantage of the modular characteristic of our synthetic route, we explored the influence of the aminoacid residue in the reduction of hydrogen peroxide in the presence of an excess of thiol. Compounds **7c** ($n = 2$) and **7d** ($n = 3$) derived from L-Phenylalanine were tested in the same conditions. Compound **7c**, with a shorter chain length, showed the same catalytic activity that compounds **7a** and **7b**. However, **7d** was less effective in the reduction of hydrogen peroxide.

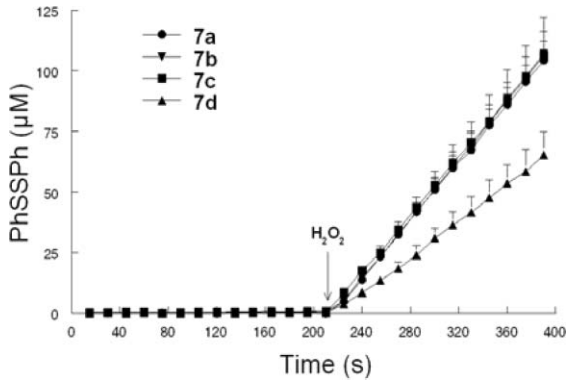
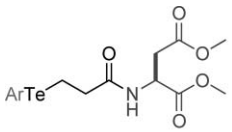


Fig. 2 GPx like behavior of compounds **7a-d**.

The time required to reduce the thiol concentration to a half (T_{50}) is shown in Table 1. Compounds **7a** ($n = 2$) and **7b** ($n = 3$), derived from L-valine and **7c** ($n = 2$) from L-phenylalanine showed almost the same T_{50}, near to 13 min (Entries 1–3). For compound **7d** ($n = 3$) derived from L-phenylalanine it was 21.61 min (Entry 4).

On the basis of these initial observations, we used telluroaminoacids with $n = 2$ as standard catalysts, and promoted the variation of amino acid moiety to enhance their ability to mimic the glutathione peroxidase enzyme. L-Alanine **7e** (Entry 5) and L-leucine **7f** (Entry 6) derivatives showed T_{50} of 10.41 and 12.75 min. respectively, and to our delight we found that telluride **7g** derived from L-aspartic acid (Entry 7) was the best catalyst, promoting the reduction of H_2O_2 concentration to a half in 8.15 min. On the other hand, a seleno derivative **7h** (Entry 8) was not able to promote the reduction of H_2O_2 in an appreciable rate ($T_{50} = 1543$ min). Diphenyl ditelluride was also employed as reducing agent, and it was found that it is less effective than compounds **7a–g**, ($T_{50} = 16.73$ (±0.26) min). We also investigated if the tellurium moiety remains intact after reaction with H_2O_2. To address this issue we performed a GC analysis of telluride **7g**, and another one with the reaction of GPx using **7g** as catalyst (see supporting information). To our delight, compound **7g** was also present after its application in the standard reaction. Apart from the main product, diphenyldisulfide, some minor side products are formed which may originate in some decomposition of the catalyst or of other components involved.

Encouraged by these results, we next explored the effects of substituents in the aryl group attached to tellurium in **7g** derivatives. A new series of telluroaminoacids were prepared with electron donating **7i–k**, electron withdrawing **7l** and **7m**, as well as with steric hindrance substituents **7n** and **7o** (Fig. 3).



7i-o

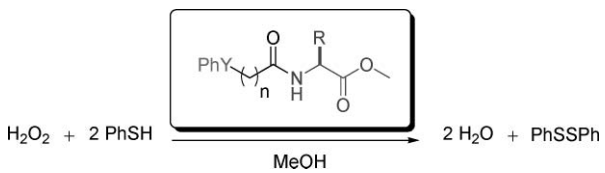
	Ar	Yield[a]
7i	*p*-tolyl	52
7j	*o*-tolyl	54
7k	4-methoxyphenyl	48
7l	4-chlorophenyl	59
7m	2-chlorophenyl	46
7n	2-naphthalene	58
7o	1-naphthalene	36

[a] Overall yields.

Fig. 3

A new set of experiments to screen the GPx activity of these new catalysts was performed with **7i–o** (2 mol%), in a more concentrated solution (Table 2). It was found that the GPx behavior is strongly influenced by steric effects. The T_{50} of *para* substituted compounds were lower when compared with the *ortho* analogues (Entries 2 and 3, 5 and 6). The changing of electronic environment at the tellurium atom did not produce a pronounced change to the thiol peroxidase activity of these compounds. The T_{50} of **7g** (Ar = Ph, Entry 1), **7i** (Ar = *p*-tolyl, Entry 2), **7k** (Ar = 4-$MeOC_6H_4$, Entry 4), and **7l** (Ar = 4-ClC_6H_4, Entry 5) was between 2.11 and 2.98 min.

Table 1



Entry[a]	Catalyst[b]	Y	*n*	R	T_{50}[c,d]
1	**7a**	Te	2	i-Pr	13.43 (±0.15)
2	**7b**	Te	3	i-Pr	13.14 (±0.27)
3	**7c**	Te	2	Bn	13.43 (±0.31)
4	**7d**	Te	3	Bn	21.61 (±1.10)
5	**7e**	Te	2	Me	10.41 (±0.52)
6	**7f**	Te	2	i-Bu	12.75 (±1.03)
7	**7g**	Te	2	CH_2COOMe	8.15 (±0.61)
8	**7h**	Se	2	i-Pr	1543 (±1.82)

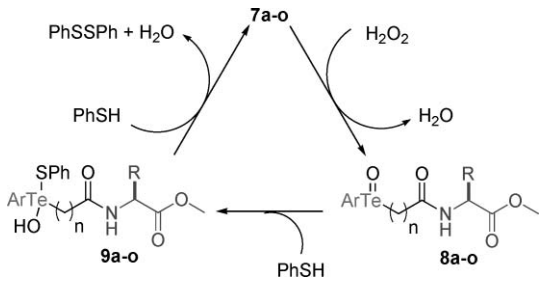
[a] Under this condition addition of H_2O_2 in the absence of telluride did not produce any significant oxidation of PhSH. [b] MeOH (1 mL); catalyst [0.05 mmol L^{-1}]; PhSH [1.9 mmol L^{-1}]; H_2O_2 [8.8 mmol L^{-1}]. [c] T_{50} is the time required, in min, to reduce the thiol concentration with 50% after the addition of H_2O_2; [d] Data in parentheses: experimental error.

Table 2

Entry[a]	Catalyst[b]	Ar	T_{50}[c,d]
1	**7g**	phenyl	2.98 (±0.21)
2	**7i**	*p*-tolyl	2.78 (±0.20)
3	**7j**	*o*-tolyl	4.78 (±0.12)
4	**7k**	4-methoxyphenyl	2.11 (±0.24)
5	**7l**	4-chlorophenyl	2.94 (±0.19)
6	**7m**	2-chlorophenyl	8.14 (±1.52)
7	**7n**	2-naphthalene	3.65 (±0.18)
8	**7o**	1-naphthalene	4.27 (±0.32)

[a] Under this condition addition of H_2O_2 in the absence of telluride did not produce any significant oxidation of PhSH. [b] MeOH (1 mL); catalyst [0.1 mmol L^{-1}]; PhSH [5 mmol L^{-1}]; H_2O_2 [5 mmol L^{-1}]. [c] T_{50} is the time required, in min, to reduce the thiol concentration with 50% after the addition of H_2O_2. [d] Data in parentheses: experimental error.

Concerning mechanistic aspects, and in agreement with Detty's study,[19] we believe that initially Te(II) compounds **7a-o** react with H_2O_2 to form the Te(IV) oxides **8a–o**, and H_2O (Scheme 2). Addition of one equivalent of PhSH to these compounds generate tellurenyl sulfides **9a–o** which react with another equivalent of PhSH to regenerate **7a–o** to the catalytic cycle and produce PhSSPh and H_2O.



Scheme 2

In conclusion, we have prepared a series of telluroamino acid derivatives, in a short, modular and efficient synthetic route. These compounds were tested as GPx mimics, catalyzing the reduction of H_2O_2 to water at expense of thiophenol using a very low amount of catalyst. We found that the time required to reduce the concentration of the PhSH to a half, T_{50}, is strongly influenced by the aminoacid residue, as well as by steric effects. New studies to investigate the influence of amino acid residues of telluroamino acid derivatives have been performed in our lab using glutathione as reducing agent.

Acknowledgements

The authors thank CNPq, CAPES, and FAPERGS for financial support.

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