Organic Telluranes: A Novel Class of Protease Inhibitors.


1 Depto. de Biofísica, UNIFESP, SP.
2 Centro Interdisciplinar de Investigação Bioquímica, UMC, Mogi das Cruzes, SP.
3 Depto. de Química Fundamental, IQUSP, SP.
4 Depto. de Química, UFSCar, SP.
5 Depto. de Física, UNESP-Bauru, SP.

Although the biological role of tellurium is still unknown, biological applications of tellurium compounds have been continuously investigated. As a representative example, the glutathione reductase-like activity of organic tellurides is well established, however, for the organic telluranes which are the oxidized form of organic tellurides, there is no general application developed yet. On the basis of the unique reactivity of telluranes with thiols, we recently demonstrated that organic telluranes constitutes a new class of specific cysteine protease inhibitors. We performed inactivation studies of both papain and cathepsin B with different classes of organic telluranes and observed that they exhibited high specific second-order inactivation constants towards these enzymes. A chloro oxytelluroxetane was the most active compound tested showing a second-order inactivation constants of $36 \times 10^{-3} \text{M}^{-1}\text{s}^{-1}$ and $34 \times 10^{-6} \text{M}^{-1}\text{s}^{-1}$ for cathepsin B and papain, respectively. In order to better understand the inactivation of these proteases, a more detailed study of the model reactions with dithiothreitol and cysteine was performed and analyzed by UV-Vis, ESI-MS/MS, $^{125}$Te NMR techniques. The obtained results of both kinetic and model reaction studies are consistent with an irreversible inhibition, time and concentration dependent. Chiral derivatives of aromatic telluranes were also prepared to probe the influence of chirality on the inhibition of cysteine-proteases. We observed that the configuration of an esterogenic center in the tellurane molecule influenciates the inactivation. Docking studies were done with one tellurane and cathepsin B. All these results will allow the planning and synthesis of new derivatives to increase the inhibition activity and selectivity towards cysteine proteases. In summary, we presented and elucidated the first general application of organic telluranes towards biological targets.

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