

A cathepsin-B inhibitor: crystal and docking studies.

I.Caracelli^a, Julio Zukerman-Schpector^b, R.L.O.R.Cunha^c, I.L.S.Tersariol^d, J.V.Comasseto^c.

^a Physics Dept. F.C. *Universidade Estadual Paulista/UNESP-Bauru*, Brazil;

^b Chemistry Dept. *Universidade Federal de São Carlos*, 13565-905 São Carlos, SP, Brazil;

^cIQ-*Universidade de São Paulo*, Brazil; ^d*Universidade de Mogi das Cruzes*, SP, Brazil.

Introduction

Clinical investigations showed that cathepsin B is a highly predictive indicator for prognosis and diagnosis of cancer. It has been postulated that its inhibition is directly responsible for the abrogation of the invasion process in the human prostate cancer cell lines and in other tumor cells. In view of this, the development of protease inhibitors has paramount importance in the search of chemotherapeutic agents. Following the discovery by Albeck *et al.* (Inorg. Chem., 37, 1998, 1704) that Te^{IV} compounds present protease inhibitory activity, the title compound was synthesized and its inhibitory activity towards human cathepsin B investigated (Cunha *et al.*, Bioorg. Med. Chem. Lett., 15, 2005, 755.)

Crystallographic Studies

An *E* configuration of the double bond was found (Fig. 1). The Te atom makes one intramolecular secondary bond, to the oxygen atom:

Te...O = 2.476(3) Å, and three intermolecular:

Te...Cl1a = 3.610(1);

Te...Cl2b = 3.777(1) and

Te...Cl4c = 3.715(1) Å.

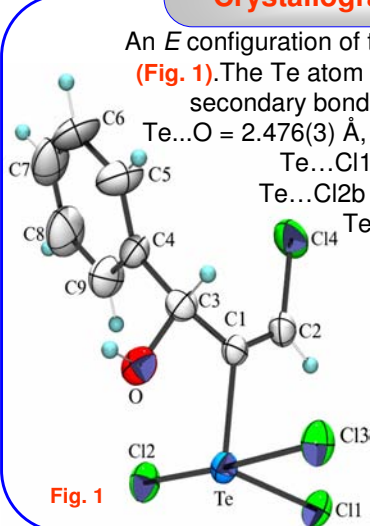


Fig. 1

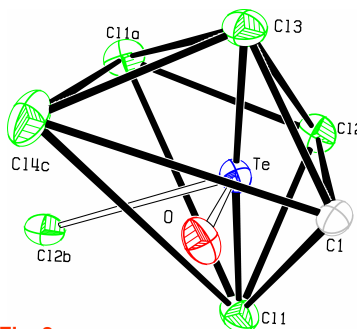


Fig. 2

Due to the intra and intermolecular secondary interactions, the polyhedron (Fig. 2) around the tellurium can be best described as a distorted bicapped octahedron, with an eight-coordinated tellurium(IV) (not counting the lone pair), with O capping Cl1-Cl4 face and Cl2b capping the Cl1-Cl1a-Cl4c face. This type of coordination polyhedron has not been described earlier

The Te...O distance is rather short, indeed a search in the CSD showed that the shortest distances found were 2.419 Å and 2.643 Å.

The molecules are associated in an helical fashion with a Te...Te pitch of 6.3492(6) Å

(Fig. 3).

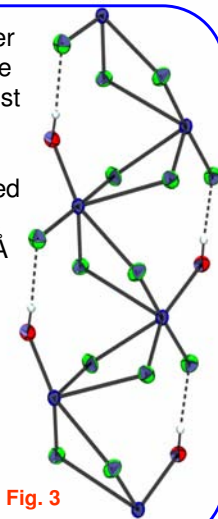


Fig. 3

Docking studies

The coordinates of human cathepsin B were downloaded from PDB (1GMY). The rigid docking methodology through the DOCK 3.5 program (J. Mol. Biol. 161, 1982, 269; idem, 221, 1991, 327) was employed. As the inactivation of cathepsin B by organotellurium(IV) compounds can be due to the high nucleophilic character of the thiol residue at the active site combined with the electrophilic character of the Te atom, we focused on the residue Cys C29.

Three consecutive approaches were used, first the docking was performed with the neutral ligand and involving contacts and forcefield, this positioned the Te and SG at a distance of 7.84 Å (Fig. 4a). The same calculation was done but now with a charged ligand, that is, one of the chlorine atoms attached to Te was removed, obtaining a Te...SG distance of 5.97 Å (Fig. 4b).

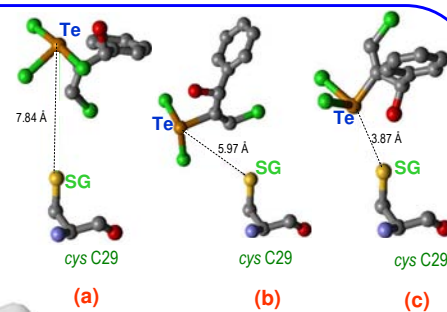
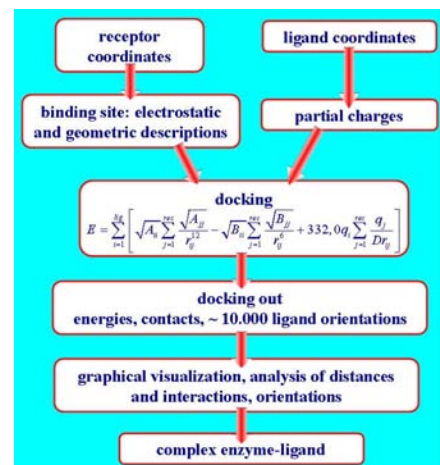


Fig. 4



The next docking calculation was performed considering only contacts, the ligand still charged, in this case the Te...SG distance obtained was of 3.87 Å (Figs. 4c and 5), which is less than the sum of their van der Waals radii.

Starting from this position, molecular mechanics calculation were performed, resulting in a 2.39 Å distance, a value close to those found for the covalent Te-S bond.

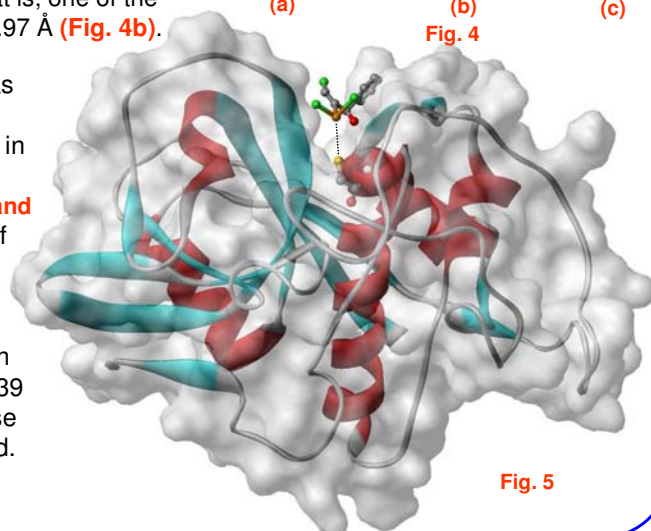


Fig. 5