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Molecular docking studies of dithiocarbamates compounds interactions with jack-bean urease

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ABSTRACT

Molecular docking studies concerning the inclusion of dithiocarbamates compounds inside the jack-bean urease enzyme (JBU) are reported. The compounds are dimethyldithiocarbamate (MDTC), diethyldithiocarbamate (EDTC) and pyrrolidinedithiocarbamate (PDTC) and they present inhibitory activity against urease, justifying the structural investigation. Interaction energies of each dithiocarbamate inside the distinct enzyme domains are calculated and the active sites for the inhibitors are determined. The lowest electrostatic intermolecular energy (ΔE) for every compound was obtained within the C-terminal $(\alpha\beta)_8$ domain containing the Tyr442 residue, originally corresponding to the enzymatic catalytic site. EDTC and PDTC compounds have similar ΔE and MDTC has a comparatively higher ΔE. It was observed that the stability of inclusion increases with the carbon chain of the molecules and from the ΔE perspective the relative inhibitors efficiencies are in order PDTC $\approx$ EDTC $>$ MDTC. However, interactions of the dithiocarbamates with water molecules allowed determining a precise order of activity as EDTC $>$ PDTC $>$ MDTC. Data are supplied in this article.

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Specifications table

Subject area	*Computational Chemistry and Biochemistry.*
Compounds	*Jack-bean urease, dimethyldithiocarbamate, diethyldithiocarbamate and pyrrolidinedithiocarbamate.*
Data category	*Computational simulations.*
Data acquisition format	*3D structure of JBU at 2.05 Å resolution was obtained from the Protein Data Bank (code 3LA4) and the dithiocarbamates 3D structures were built with a PC Spartan® software. The AM1 semiempirical molecular orbital method was used to calculate partial atomic charges. Docking energies of the inhibitors inside the available enzyme domains were found through the software Molegro Virtual Docker® (MVD).*
Data type	*Experimental and Theoretical.*
Procedure	*In the present article the interaction of the enzyme jack-bean urease (JBU) with three different dithiocarbamates compounds namely dimethyldithiocarbamate (MDTC), diethyldithiocarbamate (EDTC) and pyrrolidinedithiocarbamate (PDTC), is studied with the molecular docking method. These studies are carried out to investigate interaction energies of the dithiocarbamates in different JBU domains allowing determination of the active sites.*
Data accessibility	*State.*

1. Rationale

From a structural perspective, urease inhibitors can be classified in groups such as hydroxamic acids and its derivatives, thiolate anions, phosphodiamidates, chelators of nickel and metal ions [1–3]. Dithiocarbamates contain a monoanionic 1,1-dithiolate group and some of them, which can bind metals due to presence of $R_1R_2NCS^{2-}$ species, have been tested as metalloenzyme inhibitors. They can coordinate a variety of metal ions having a role in manufacture of rubber products and pesticides [4]. Clinical applications are reported as well; disulfiram (tetraethylthiuram disulfide) works as alcohol aversive drug and diethyldithiocarbamate acts as auxiliary drug in preventing cisplatin nephrotoxicity and is also used in chelation therapy for metal intoxication [5–7].

Dithiocarbamates compounds inhibit metalloenzymes such as carbonic anhydrases (CAs) and superoxide dismutases (SODs) both associated with important biological processes; it was reported before the inhibitory activity of anionic dithiocarbamates against human CAs involved in pathologies like glaucoma and cancer [8]. Crystalline adducts of three dithiocarbamates with a human CA enzyme were characterized by using single-crystal X-ray diffraction, indicating their coordination to the enzymatic metal ion at a monodentate mode involving one sulfur atom directly linked to Zn(II) [8]. Molecular mimicry is also possible; for instance, morpholyldithiocarbamate and diethyldithiocarbamate can mimic the SOD enzyme suppressing its activity [9]. However, few data about urease interactions with dithiocarbamates have been published so far. Urease is a metalloenzyme with two nickel ions forming an active center and it has 840 amino acid residues per unit. It can be found in plants, fungi and bacteria. It catalyzes the urea hydrolysis producing ammonia and carbon dioxide [10, 11]. The urease from jack bean (Canavalia ensiforms), JBU, was the first enzyme to be crystallized in 1926 [12]. This enzyme is essential in nitrogen release processes and as insecticidal agent. Therefore, the production of urease by plants is a main step for the nitrogen bioavailability course. On the other hand, in agriculture, a high urease activity induces plant damages during soil fertilization by urea, due to ammonia toxicity [13].

Medically, the urea degradation can be a nitrogen source, necessary for proliferation of pathogenic microorganisms. Microbial ureases have been implicated in pathologies such as urinary and gastrointestinal diseases [14]. For instance, Helicobacter pylori bacterium is a microbiological carcinogenic agent that produces urease, generating ammonia and increasing the human pH stomach and this is a central factor in its proliferation [15]. The study of new urease inhibitors is indeed crucial to protect soils from pH elevation during fertilization processes and in searching of alternative therapies for ureolytic and gastric infections. Hence, structural and energetic analysis regarding interactions between urease and its potential inhibitors are imperative steps in a deep understanding about the whole in-

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