Gold complexes as metallo-β-lactamase inhibitors

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Zinc containing metallo-β-lactamases (MBLs) are recognized targets for antibacterial chemotherapy research due to their key role on most resistant bacterial infections and the absence of clinically useful inhibitors against them[1]. Many organic compounds, that are able to successfully block enzyme active site, have been studied as MBL inhibitors, but none has been found to be clinically useful yet[1]. Metal complexes have been so far neglected as possible MBL inhibitors, despite the significant loss of MBL activity shown by different metal ion substitution as Ni(II), Fe(II), Cd(II) and Hg(II).[2,3] On the other hand, both Au(I) and Au(III) complexes have demonstrated to act as Lewis acid electrophiles, binding to cysteines and histidines coordinated to zinc in zinc proteins, particularly zinc-fingers.[4]

We have studied the MBL inhibitory activity of different Au(I), Au(III), Pd(II) and Pt(II) complexes in a commercial MBL from *B. cereus* (BcII). The initial rate (v0) of Nitrocefin hydrolysis by BcII was followed by UV-Vis Spectroscopy in the presence of different potential inhibitors. Au(I)-phosphine complexes have shown relevant inhibitory activities. Among them the novel water-soluble phosphine-Au(I) complex, with the ligand tris-(2-carboxyethyl)phosphine (AuTCEP) showed important inhibitory activity. The ligand is a widely used reducing agent, and did not show alone any significant MBL inhibitory activity. Its water solubility allowed NMR studies that also pointed for MBL interaction (Figure 1). Surprisingly AuTCEP showed a slow reactivity with zinc-fingers. The results can suggest that the mechanism of interaction of AuTCEP with zinc protein is different of the usual electrophilic attack to cysteines.

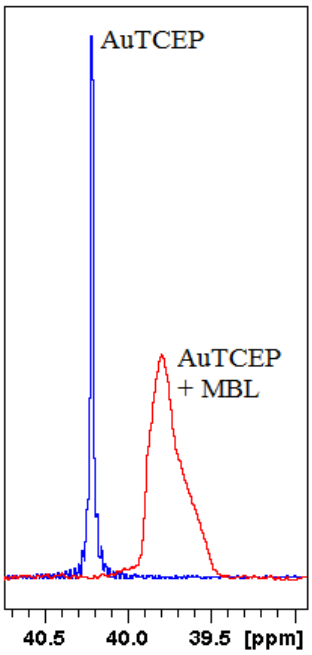

Figure 1: ^{31}P NMR spectra from AuTCEP and its interaction with MBL.

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