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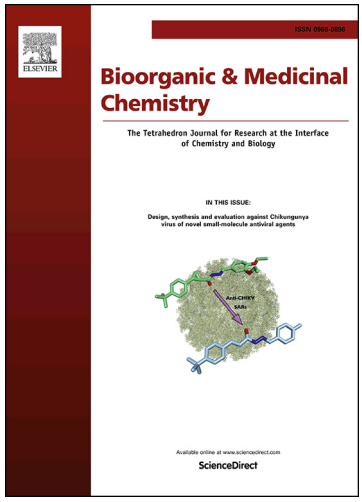

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Structure activity relationship studies on rhodanines and derived enethiol inhibitors of metallo-β-lactamases

Dong Zhang[a], Marios S. Markoulides[a], Dmitrijs Stepanovs[a,1], Anna M. Rydzik[a,2], Ahmed El-Hussein[a,c3] Corentin A. M. Bon[a,4], Jos J. A. G. Kamps[a], Klaus-Daniel Umland[a,5], Patrick M. Collins[b], Samuel T. Cahill[a], David Y. Wang[a], Timothy D. W. Claridge[a], Jürgen Brem[a], Michael A. McDonough[a], and Christopher J. Schofield[a,*]

[a] *Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, United Kingdom.*
[b] *Diamond Light Source, Harwell Science and Innovation Campus, Didcot, OX11 0DE, United Kingdom.*
[c] *The National Institute of Laser Enhanced Science, Cairo University, Egypt.*

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ABSTRACT

Metallo-β-lactamases (MBLs) enable bacterial resistance to almost all classes of β-lactam antibiotics. We report studies on enethiol containing MBL inhibitors, which were prepared by rhodanine hydrolysis. The enethiols inhibit MBLs from different subclasses. Crystallographic analyses reveal that the enethiol sulphur displaces the di-Zn(II) ion bridging 'hydrolytic' water. In some, but not all, cases biophysical analyses provide evidence that rhodanine/enethiol inhibition involves formation of a ternary MBL enethiol rhodanine complex. The results demonstrate how low molecular weight active site Zn(II) chelating compounds can inhibit a range of clinically relevant MBLs and provide additional evidence for the potential of rhodanines to be hydrolysed to potent inhibitors of MBL protein fold and, maybe, other metallo-enzymes, perhaps contributing to the complex biological effects of rhodanines. The results imply that any medicinal chemistry studies employing rhodanines (and related scaffolds) as inhibitors should as a matter of course include testing of their hydrolysis products.

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* Corresponding author. Tel.: +44 (0)1865 285 000; fax: +44 (0)1865 285 002; e-mail: christopher.schofield@chem.ox.ac.uk.
[1] Present address: Latvian Institute of Organic Synthesis, Aizkraukles Str. 21 Riga, LV-1006, Latvia.
[2] Present address: Boehringer Ingelheim Pharma GmbH & Co KG Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany.
[3] Present address (on leave from): The National Institute of Laser Enhanced Science, Cairo University, Egypt.
[4] Present address: École polytechnique université, Paris saclay Route de Saclay, 91128 Palaiseau.
[5] Present address: Bleichestrasse 10, 8400 Winterthur, Switzerland.

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