Poster

X-ray crystallography deciphers the inhibition of thione-based compounds on NDM-1 β- lactamase

F. Vascon[1,#], M. Bersani[2], E. Gianquinto[2], A. Legru[3], F. Verdirosa[4], L. Gavara[3], D. Tondi[5], F. Spyrakis[2], L. Lazzarato[2], J.F. Hernandez[3], J.D. Docquier[4], L. Cendron[1]

[1]Department of Biology, University of Padua, Via Ugo Bassi 58b, 35121 Padova, Italy, [2]Department of Drug Science and Technology, University of Turin, Torino, Italy, [3]IBMM, CNRS, ENSCM, University of Montpellier, Montpellier, France, [4]Department of Medical Biotechnologies, University of Siena, Siena, Italy, [5]Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy.

[#] filippo.vascon@unipd.it

Over a decade ago, the 1,2,4-triazole-3-thione scaffold was discovered to directly bind the active site zinc cations of metallo-β-lactamases (MBLs). Since then, extensive research has been conducted on this molecular scaffold's potential as a source of MBL inhibitors through comprehensive screenings of analogs with diverse lateral substituents. Analysis of their binding mode via X-ray crystallography has illuminated favorable interactions within MBLs catalytic pockets, facilitating the rational design of improved antagonists.

This study reports a novel targeted screening of 1,2,4-triazole-3-thione derivatives against the clinically concerning NDM-1 β-lactamase, exploring previously untested combinations of substituent groups. Among the compounds synthesized and evaluated *in vitro*, several ones exhibited inhibitory constants (K_i) in the low micromolar range. These K_i values demonstrated a strong correlation with the synergistic bactericidal activity of the inhibitors when combined with the meropenem β-lactam, as evidenced by antimicrobial susceptibility testing on resistant bacterial strains [1,2]. Furthermore, X-ray structures of NDM-1 in binary complexes with the most potent inhibitors have been resolved, uncovering a previously unreported binding mode in one instance. This finding could potentially pave the way for the development of new compound series.

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[2] Bersani, M., Failla, M., Vascon, F., Gianquinto, E., Bertarini, L., Baroni, M., Cruciani, G., Verdirosa, F., et al., Tondi, D. (2023). *Pharmaceuticals*, **16** (12), 1682. Doi: 10.3390/ph16121682