Title

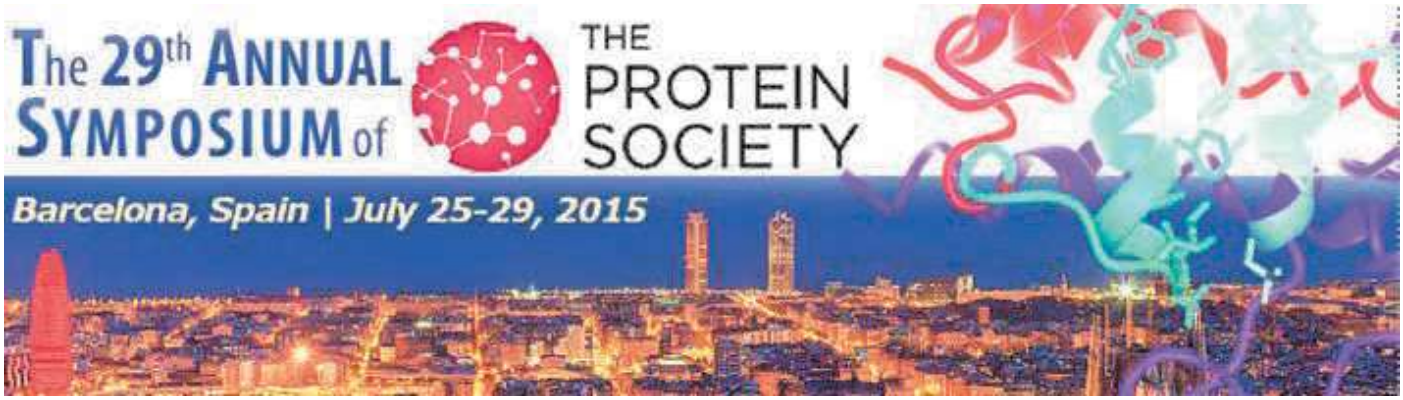
Subtle Differences Between NOS Active Sites Lends Towards the Development of a Bacterial NOS Specific Inhibitor

Authors

Holden, Jeffrey K
Kang, Soosung
Silverman, Richard B
et al.

Publication Date

2014



POSTER ABSTRACTS

POST 10-70

Subtle Differences Between NOS Active Sites Lends Towards the Development of a Bacterial NOS Specific Inhibitor

Jeffrey K. Holden[1], Soosung Kang[3], Richard B. Silverman[3], Thomas L. Poulos[1, 2]

[1]Molecular Biology and Biochemistry, University of California-Irvine, Irvine, California, US, [2]Pharmaceutical Sciences, University of California-Irvine, Irvine, California, US, [3]Departments of Chemistry and Molecular Biosciences, Northwestern University, Evanston, Illinois, US

Nitric oxide synthase (NOS) catalyzes the oxidation of L-Arg into nitric oxide (NO) and is found in both mammals and select bacteria. Previous work by our group and others has established the bacterial NOS as an excellent antibacterial target for pathogens *Staphylococcus aureus* and *Bacillus anthracis*. Since all currently known NOS' share a near identical active site architecture (composed of a heme prosthetic group, substrate binding site and co-substrate binding site) the design of an isoform specific inhibitor design is not a trivial task. Recently, we designed a series of inhibitors that take advantage of the bacterial NOS Ile218 and His128 residues; mammalian equivalents are Val and Ser, respectively. From x-ray crystal structures we have found the binding mode of these inhibitors to both be constrained sterically and favored by the noncovalent interactions afforded by the bulkier Ile218 and His128 active site residues. Moreover, kinetic analyses of these inhibitors reveal them to not only be more potent against the bacterial form of NOS then the mammalian forms but also to have antibiotic-like properties.