ACS Medicinal Chemistry Letters

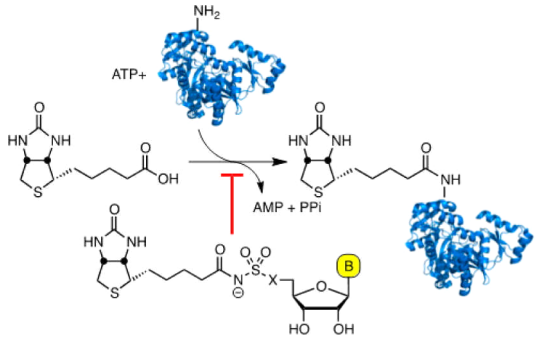
In This Issue

pubs.acs.org/acsmedchemlett

CHEMICALLY STABLE INHIBITORS AGAINST *MYCOBACTERIUM TUBERCULOSIS*

Tuberculosis remains the leading cause of death due to a single infectious agent. This disease is caused by members of the *Mycobacterium tuberculosis* (Mtb) complex, for which the current treatment for susceptible strains requires at least 6 months of drug therapy using a combination of four drugs discovered over 40 years ago. Thus, there is an urgent need for new tuberculosis drugs with novel mechanisms of action.

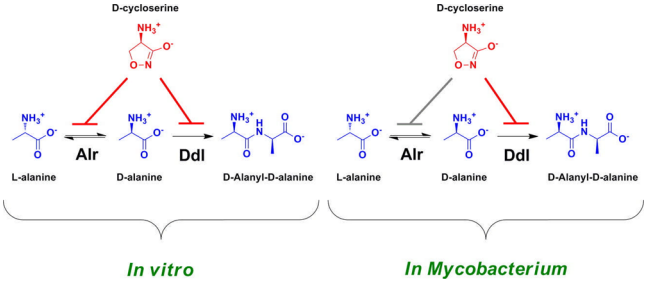
The letter by Shi et al. (DOI: 10.1021/ml400328a) presents the synthesis and biochemical and biological evaluation of a systematic series of rationally designed nucleoside analogues targeting the biotin protein ligase for treatment of tuberculosis. The study addresses past limitations stemming from lack of biostability of inhibitors. Important analogues showed significant chemical stability and high affinities to biotin protein ligase.



METABOLOMICS TELLS A DIFFERENT STORY

Amidst the increasing number of infectious diseases, low success rates in drug discovery effort, and drug resistance reaching a crisis stage, new approaches are required to identify new drugs and features important for potency and specificity. Metabolomics, the study of a cell's metabolite profiles, is a powerful and emerging field that can assist in this direction.

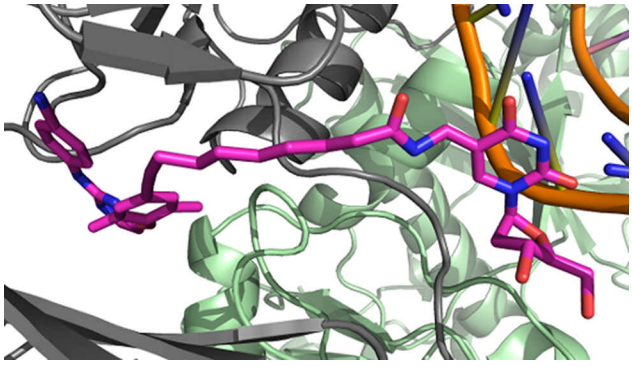
Here, Prosser and de Carvalho (DOI: 10.1021/ml400349n) demonstrate by using mass-spectrometry-based metabolomics that the primary target of D-cycloserine, an important second-line drug used for the treatment of tuberculosis, is D-alanine-D-alanine ligase (Ddl) and not L-alanine racemase. These results suggest that drug discovery efforts should be refocused to targeting D-alanine-D-alanine ligase, which is a more tractable target than D-alanine racemase.



NOVEL BIFUNCTIONAL INHIBITOR OF REVERSE TRAINSCRIPTASE

Human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT) is a major target for currently approved anti-HIV drugs because this viral polymerase is essential for virus replication. Chimeric inhibitors containing both nucleoside and non-nucleoside moieties are ideal against RT due to the close proximity of the nucleoside reverse transcriptase inhibitor and non-nucleoside reverse transcriptase inhibitor binding sites.

Herein, Iyidogan et al. (DOI: 10.1021/ml4002979) describe a new class of chimeric HIV-1 RT inhibitors and illustrate the synthesis and biochemical evaluation of novel two-site binding RT inhibitors, including two molecules that are linked via a linker entity and bind to their respective binding sites on RT simultaneously. The metabolically active triphosphate of the novel chimeric inhibitor is successfully incorporated into a growing DNA chain in a base-specific manner and inhibits the polymerization activity of the HIV-1 RT.



Published: December 12, 2013

dx.doi.org/10.1021/ml400461r | *ACS Med. Chem. Lett.* 2013, 4, 1125−1125