ACS Infectious Diseases

In This Issue

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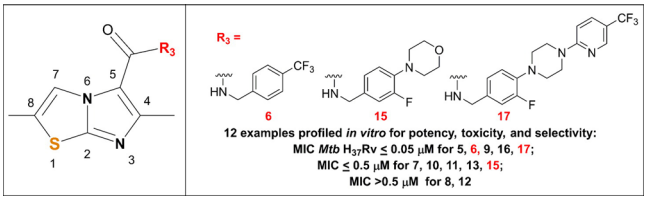
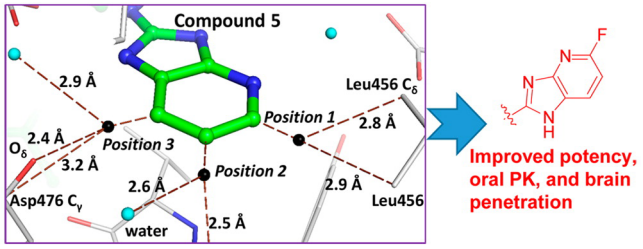
ARMING AGAINST MDR-TB



Tuberculosis (TB) has been one of the most devastating diseases throughout history, and it remains a major threat to global health. In 2014, approximately 1.5 million deaths were attributed to TB, and an estimated one-third of the world's population was infected with latent TB. As a growing number of TB cases are multi-drug-resistant and do not respond to current chemotherapy, the modern day global TB challenge is greater than ever. With only two recently approved TB treatments, bedaquiline and delamanid, in the last 40 years, heroic efforts in research are needed to contain the spread of TB.

The research presented on the cover of this month's issue (DOI: 10.1021/acsinfecdis.5b00154) focuses on the design, synthesis, and activities of novel anti-TB agents. Here, Moraski et al. develop agents with potent and selective activity against TB. The authors demonstrate that the compounds have a novel target and mechanism of action and are also practical to synthesize. The imidazothiazoles described in this article provide exciting leads for the development of much needed new anti-TB agents.

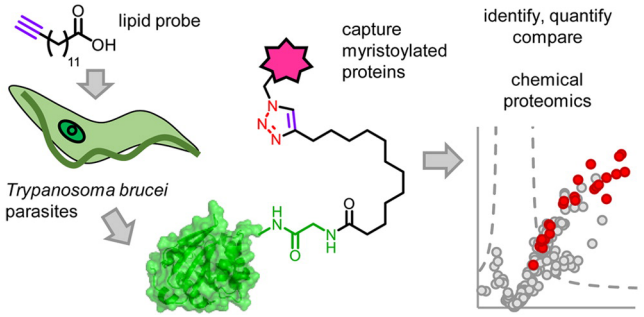
HATS OFF TO FLUORINE



Human African trypanosomiasis (HAT) is a neglected tropical disease caused by the protozoan parasite *Trypanosoma brucei*. The disease progresses in two stages, with parasites circulating in host blood during the early stage and invading the central nervous system during late-stage infection. Treatment of *T. brucei* infection is currently hampered by the high cost of certain treatment options, toxicity, and emerging resistance to available drugs, and new therapeutic agents with oral availability that are able to penetrate the central nervous system are urgently needed.

Methionyl-tRNA synthetase (MetRS) has previously been demonstrated to be a potential target for the development of therapeutics to treat Human African trypanosomiasis; however, early potent compounds against this target derived from bacterial MetRS inhibitors exhibited poor oral and CNS bioavailability. In this issue, Zhang et al. (DOI: 10.1021/acsinfecdis.6b00036) present work aimed at improving membrane permeability and therefore oral and CNS bioavailability of earlier MetRS inhibitors by adding a fluorine atom using a structure-guided approach. The authors demonstrate the activity of the fluorinated inhibitors in murine models of *T. brucei* infection and present lead compounds for further development as drugs for treating HAT.

DEFINING ACTION OF NMT INHIBITORS IN *T. BRUCEI*



Protein *N*-myristoylation is the attachment of the lipid myristate to the N-terminus of select proteins in eukaryotes. This modification modulates protein function, structure, and/or localization and is catalyzed by the enzyme *N*-myristoyltransferase (NMT). NMT is currently under investigation as a potential drug target in several parasitic diseases and cancer. Previous work has used genetic and chemical knockdown to validate NMT as a drug target in *T. brucei*, yet only a handful of proteins have been experimentally validated as myristoylated in the parasite. As the scope of myristoylation in *T. brucei* is not yet defined, the mechanisms by which the inhibition of NMT leads to antiparasitic activity are poorly understood.

Here, Wright et al. (DOI: 10.1021/acsinfecdis.6b00034) employ an alkyne-functionalized myristate analogue to metabolically tag lipidated proteins in insect vector and host life stages of *T. brucei*. The authors present a series of experiments aimed at visualizing and quantifying myristoylation in *T. brucei*. Overall, this study provides a set of tools and methodologies for demonstrating a mechanism of action of NMT inhibitors in live cells and a rich data set for understanding the complex and pleiotropic effects of NMT inhibition in *T. brucei*.

Received: May 26, 2016
Published: June 10, 2016

DOI: 10.1021/acsinfecdis.6b00091
ACS Infect. Dis. 2016, 2, 377−377