ACS Medicinal Chemistry Letters

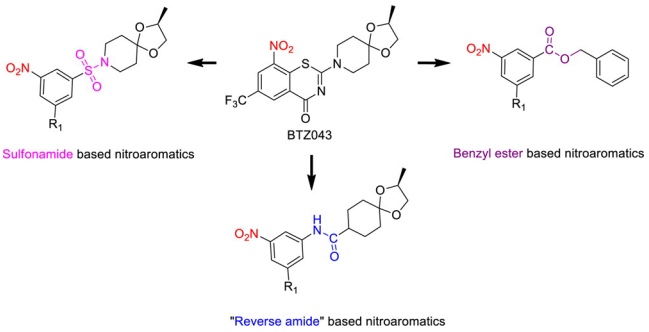
In This Issue

pubs.acs.org/acsmedchemlett

SIMPLIFIED ANTI-TB AGENTS

Currently, more than two billion people on earth are infected with tuberculosis (TB). With the development of drug resistant forms of TB and ease of dissemination through the air, the development of new potential anti-TB agents is of paramount importance.

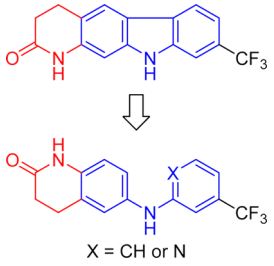
Here, Tiwari et al. (DOI: 10.1021/ml500039g) describe the design and syntheses of the simplified anti-TB agents based on the reactive nitroaromatic core of the recently discovered potent anti-TB agent, BTZ043, and its molecular interaction with its target enzyme, DprE1. The study explores the effect of functional groups such as sulfonamide, reverse-amide, and esters that are attached to the nitroaromatic rings on their anti-TB activity. This work highlights the importance of the electronic character of the nitroaromatic ring as a central theme in these nitroaromatic anti-TB agents.



MORE SOLUBLE KSP INHIBITORS

The kinesin spindle protein (KSP) plays a critical role in mitosis, mediating the formation of the bipolar spindle during cell division. Inhibition of KSP function leads to mitotic arrest and subsequent cell death. Thus, KSP is considered to be a promising drug target for cancer therapy. To date, a number of KSP inhibitors are in clinical trials and offer new opportunities for the development of novel anticancer therapeutics.

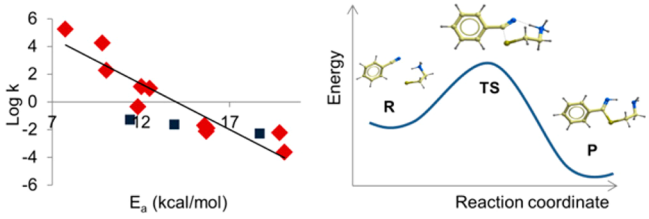
Herein, Takeuchi et al. (DOI: 10.1021/ml500016j) describe the design and synthesis of diaryl amine containing KSP inhibitors with improved solubility over carbazole-type KSP inhibitors. One derivative showed four times greater solubility than the parent carbazoles. The authors further investigated the inhibitory mechanism and binding mode of these novel KSP inhibitors and studied the improved solubility using physicochemical data, crystal structures, and computational studies.



PREDICTING THE REACTIVITY OF NITRILE-CARRYING COMPOUNDS

Nitrile is one of the most common chemical groups in nature. A growing interest around the use of the nitrile group in drug discovery has recently arisen; about 30 nitrile-carrying drugs are currently in use for different pathological conditions, and around 20 novel nitrile-containing drug candidates are in clinical development. As such, understanding and predicting nitrile reactivity is important to properly address the design of novel covalent drugs and help improve the toxicological profile of biologically active nitrile-containing compounds.

In this issue, Berteotti et al. (DOI: 10.1021/ml400489b) report on a combined study using density functional theory (DFT) calculations and experimental work to investigate nitrile reactivity with the cysteine residue of nitrile-carrying compounds. The agreement between computational and experimental results shows how the DFT-based approach can be used as a straightforward tool in predicting nitrile reactivity in covalent drug discovery and how it can be utilized to investigate the reactivity of nucleophilic agents toward nitriles.



Published: May 8, 2014

dx.doi.org/10.1021/ml500152n | ACS Med. Chem. Lett. 2014, 5, 452−452