ACS Medicinal Chemistry Letters

In This Issue

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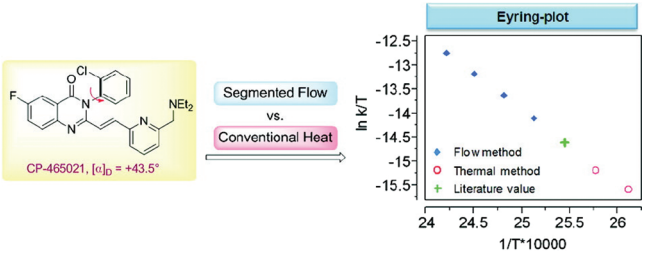
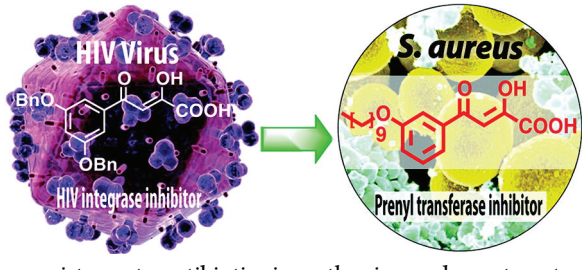
NEW TOOL FOR STUDYING ATROPISOMERS



By definition, atropisomers are stereoisomers with very high steric strain barrier to rotation that allows for their isolation. The prevalence of atropisomers has increased due to current methods available that allow for ease of their formation. In drug discovery, the different isomers can have an impact ranging from bioactivity to toxicity. Thus, measuring the activation parameters would be useful in looking at the atropo isomerization kinetics.

Here, Davoren et al. (DOI: 10.1021/ml2003108) describe how segmented flow technology can be used as a convenient and reproducible method for performing rapid and semiautomated kinetics experiments as opposed to traditional thermal methods. Segmented flow technology is appropriate for measuring thermal interconversion kinetics and allows for maintenance of reaction temperature. Because it is programmable, an experimental run can be performed overnight without human intervention. This method was validated for accuracy and could find general use among chemists.

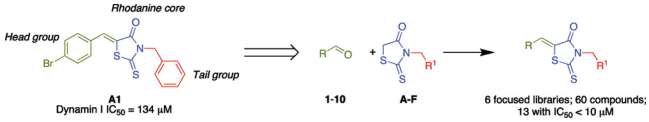
FROM ANTIVIRAL TO ANTIBACTERIAL



Drug resistance to antibiotics is on the rise, and new targets and leads are needed. Isoprenoid biosynthesis serves as a striking target due to the sheer number of enzymes involved in the pathway to which drug discovery efforts can be directed.

In this issue, Zhang et al. (DOI: 10.1021/ml300038t) display an interesting "integrase inhibitor-inspired" approach to antibacterial drug discovery. This approach shows the feasibility of using HIV drugs in developing drug leads that target staph infections and anthrax. Specifically, HIV-1 integrase inhibitors can be turned into antibacterial drugs that target isoprenoid biosynthesis since the enzymes involved similarly contain aspartate and magnesium clusters that are essential for catalysis. The best lead compounds are shown to be active against *S. aureus* and several other Gram-positive bacteria, while they are shown to have low toxicity to human cells.

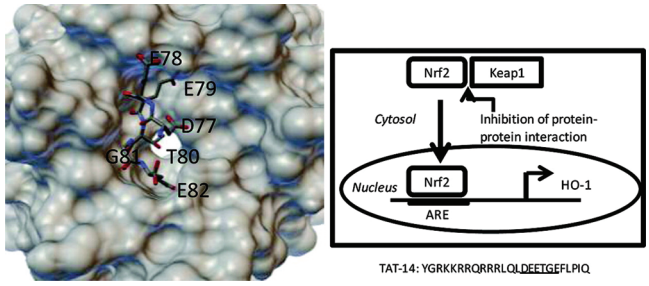
RHODANINE-BASED INHIBITORS OF DYNAMIN



Dynamin is a member of Rho family of guanosine triphosphate hydrolase enzymes that is essential for clathrin-dependent coated-vesicle formation. However, dynamin is also involved in clathrin-independent endocytosis, phagocytosis, and caveolae internalization and has been implicated in a plethora of cellular processes. Thus, dynamin inhibition presents a novel strategy for disease treatment by inhibiting endocytosis and membrane trafficking.

In this work, Robertson et al. (DOI: 10.1021/ml200284s) present the discovery of a new family of potent inhibitors of dynamin. The authors focus on six rhodanine core inhibitors, which they have expanded to different libraries. These Rhodadyn series serve as an addition to the expanding palette of current dynamin inhibitors.

PEPTIDE AS NEW ANTI-INFLAMMATORY AGENT



New approaches to the development of anti-inflammatory agents are continually being sought as they may prove useful in the treatment of various diseases. One main target is nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which plays a crucial role in redox homeostasis under oxidative stress.

In this paper (DOI: 10.1021/ml300041g), Steel et al. demonstrate that there may be multiple approaches to targeting the interaction between the proteins involved in the inflammatory response. While intensive research has focused on the activation of the Nrf2 using small molecules that form links to its protein partner, Kelch-like ECH-associated protein 1 (Keap1), the authors show that it is possible to activate Nrf2 in living cells without forming these links but through reversible binding to a specific site on Keap1. This reversible binding is often felt to be preferable to forming irreversible links in drug design and paves the way for new anti-inflammatory agents, such as a peptide, which can activate Nrf2 described here. This peptide constitutes a useful chemical biology tool with potential therapeutic applications.

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