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In This Issue

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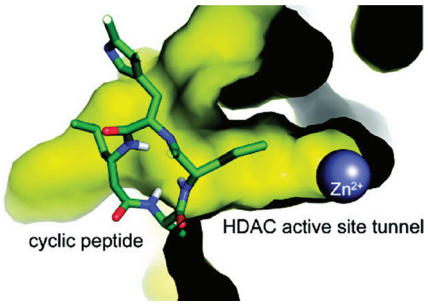
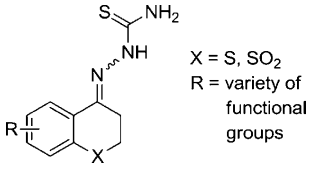
HDAC INHIBITORS LACKING THE METAL ION-BINDING GROUP



Histone deacetylases (HDACs) are among the key players in the complex epigenetic regulation of cellular processes and, consequently, are important targets for therapeutic approaches in several chronic diseases, including neurodegenerative disorders and cancer. However, natural and synthetic HDAC inhibitors generally derive their strong binding affinity and high potency from a key functional group that binds to the Zn^{2+} ion within the enzyme active site. Yet, this feature also carries the potential liability of undesirable off-target interactions with other metalloenzymes, which is arguably a significant contributor to the known problems of dose-limiting toxicity and narrow therapeutic index associated with most clinically relevant HDAC inhibitors.

In this issue, Vickers et al. (DOI: 10.1021/ml300081u) describe the design, structure–activity optimization, and characterization of potent histone deacetylase (HDAC) inhibitors that lack the Zn^{2+}-binding group. They report tetrapeptide HDAC inhibitors with *in vitro* potency against class 1 HDACs and in tissue culture against various human cancer cell lines. The discovery of these HDAC inhibitors lacking the metal ion-binding group provides an important proof of principle example that might guide and inspire future efforts in the design of a new generation of less toxic therapeutics.

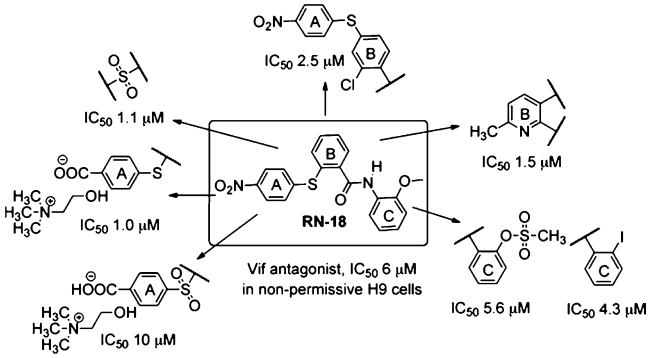
NEW INHIBITORS OF CATHEPSIN L



Cathepsin L, a cysteine proteinase, represents an exciting and emerging target for the discovery and development of small-molecule therapeutics that have the potential to limit or arrest cancer metastasis. While inhibitors of cathepsin K, another cysteine proteinase, have been quite extensively evaluated, primarily in terms of the treatment of osteoporosis, the research landscape as it relates to antimetastatic agents that inhibit cathepsin L is in its very early stages. Small-molecule inhibitors of cathepsin L represent an exciting new area of research based primarily on their potential to function as antimetastatic agents.

In this issue, Song et al. (DOI: 10.1021/ml200299g) detail the synthesis and biochemical/biological evaluation of a small library of 36 thiochromanone thiosemicarbazone analogues and selected corresponding sulfone derivatives as inhibitors of the cysteine protease cathepsin L. Nine of the compounds inhibit cathepsin L in nanomolar concentrations. The study provides entry into a largely unexplored molecular space that is rich for the design and synthesis of new thiosemicarbazone analogues.

WATER-SOLUBLE ANALOGUES OF VIF INHIBITOR



The HIV-AIDS epidemic is one of the most pressing healthcare issues worldwide. The current standard of treatment has significantly reduced AIDS-related mortality but is still beset with problems, including toxic side effects and the acquisition of multidrug-resistant variants. There is a need to developed new anti-HIV drugs targeting additional viral enzymes and host–virus interactions. The host restriction factor, human APOBEC3G (A3G), is one of the most potent inhibitors of HIV-1, but its antiviral activity is overcome by the HIV-1 virion infectivity factor (Vif). Thus, inhibition of Vif is a promising approach for developing small molecule therapeutics against HIV-1.

Here, Mohammed et al. (DOI: 10.1021/ml300037k) report the design, synthesis, and structure–activity relationship studies of a series of new analogues of a small molecule, RN18, that inhibits Vif function and HIV-1 replication by targeting Vif-A3G interactions. Most importantly, potent water-soluble analogues have been disclosed in this study.

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