ACS Medicinal Chemistry Letters

In This Issue

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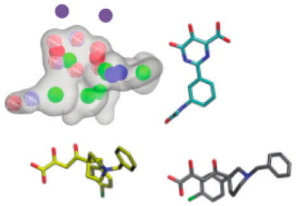
COMPUTATION-GUIDED DISCOVERY OF INFLUENZA ENDONUCLEASE INHIBITORS

Influenza causes as many as forty thousand deaths annually. While vaccination can be an effective prophylactic in healthy adults, there is generally a six-month lag time between the recognition of a new viral strain and the dissemination of an effective vaccine. Currently available small molecule antivirals are also in clinical use, but emerging viral resistance is threatening their long-term efficacy.

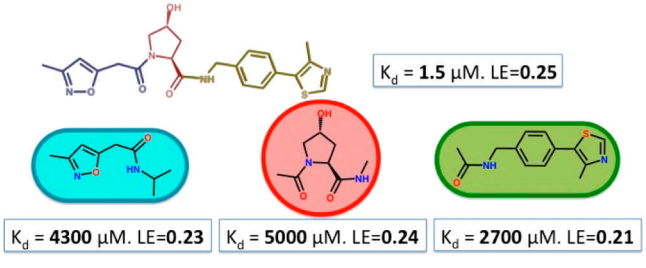
Influenza endonuclease is an enzyme required for viral replication and an appealing drug target. In this issue, Chen et al. (DOI: 10.1021/ml4003474) report the development and utilization of a computational model to discover compounds with the ability to inhibit influenza endonuclease activity and viral replication. In total, sixteen endonuclease inhibitors were found, of which, two inhibited viral replication with negligible cell toxicity.



FINE-TUNING NMR FRAGMENT SCREENING

Fragment screening by NMR spectroscopy is widely used in modern drug discovery to identify low molecular weight compounds that bind weakly to a protein target, as a first step to make an improved and more potent drug-like molecule. Unfortunately, researchers can spend a lot of time screening libraries and still miss compounds that could be very promising, as false negatives. This caveat is often exacerbated when targeting protein−protein interactions (PPIs), as useful fragments that could bind to PPI sites may exhibit too weak affinities to be reliably detected in a screen.

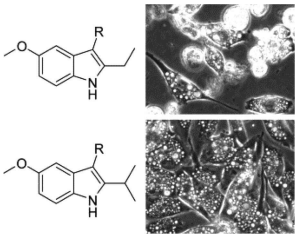
Here, Dias et al. (DOI: 10.1021/ml400296c) have pushed the limits of binding detectability in fragment screening by NMR spectroscopy against a model PPI. The authors show that a revision of the experimental set-ups in the NMR screen leads them to rescue as true hits three fragments that form part of a high-affinity drug-like compound and that had otherwise escaped binding detection as false negatives under standard conditions. The lessons learned from this study could prove useful to improve hit rates and successes when targeting other PPIs by NMR fragment screening.



FURTHER INSIGHTS ON METHUOSIS

Gliobstoma multiforme (GBM) is one of the most aggressive brain cancers, showing limited response to the standard chemotherapy drugs, Temozolomide and Gliadel. This is partly because tumors harbor genetic mutations that dull the apoptotic process. In recent years, a number of novel cell death pathways distinct from apoptosis have been discovered. Of particular interest is methuosis, characterized by extensive cytoplasmic vacuolization, which leads to loss of membrane integrity and eventual rupturing of the cell.

In this issue, Trabbic et al. (DOI: 10.1021/ml4003925) bring further insight into the SAR of methuosis by indolyl-substituted pyridinylpropenones. The authors show that increasing the size of aliphatic substituents does not reduce vacuolization but substantially reduces cytotoxicity. Such insights on structural requirements needed for cell death are essential for development of this class of compounds toward preclinical anticancer trials.



Published: January 9, 2014