ACS Medicinal Chemistry Letters

In This Issue

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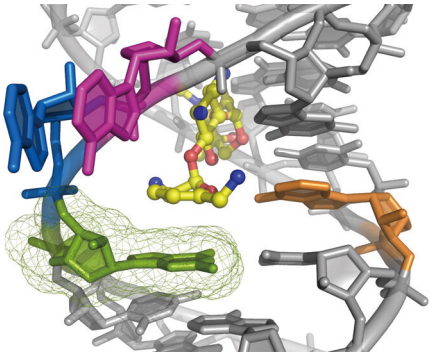
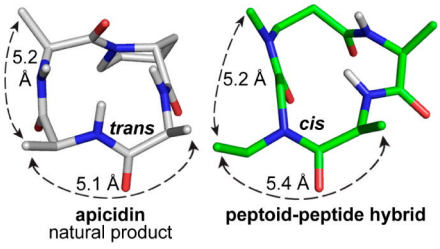
BINDING MODE OF SISOMICIN REVEALED



Given the increasing incidence of bacterial resistance to current antimicrobial agents, scientists continue to search for new antibacterial agents with novel mechanisms. Aminoglycoside antibiotics specifically recognize the ribosomal decoding site mainly through a sugar base pseudo pair and a stacking interaction between their ring I and specific RNA residues. Sisomicin, an aminoglycoside with one of the highest antibacterial activities, possesses unsaturated ring I, which is usually saturated in other aminoglycosides. This suggests a different binding mode for sisomicin.

In this issue, Kondo et al. (DOI: 10.1021/ml300145y) reveal that ring I of sisomicin with a characteristic structure can share its π-electron density with one of the RNA residues and fits well within the A-site helix. The binding mode has never been observed before and will be useful for structure-based drug design of new aminoglycosides with high activities against antibacterial-resistant bacteria and parasitic protozoa.

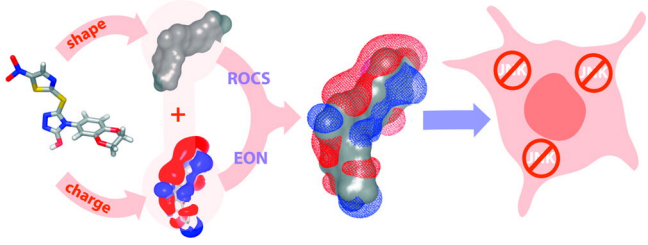
PEPTOID–PEPTIDE HYBRIDS MIMIC APICIDIN SCAFFOLD



Histone deacetylase (HDAC) is a family of enzymes responsible for the deacetylation of lysine residues on histone and nonhistone proteins, which eventually leads to the inhibition of gene expression. This makes HDAC inhibitors promising agents for anticancer chemotherapy.

Here, Olsen et al. (DOI: 10.1021/ml300162r) describe the synthesis and functional analyses of the first macrocyclic peptoid-containing HDAC inhibitors, which are inspired by the macrocyclic natural product apicidin. The authors report a family of compounds in which peptoid residues were introduced with the goal of accessing novel side chain spatial arrangements and backbone conformations not available in simple α- or β-peptides. One inhibitor showed equivalent potency to apicidin against K-562 cells but was more cytoselective across a panel of cancer cell lines.

VIRTUAL SCREEN REVEALS JNK–JIP BINDING INHIBITORS



c-Jun N-terminal kinases (JNKs) have been recognized as important enzymes in the pathogenesis of different diseases. As such, several efforts have been made to design drugs that inhibit JNK signaling. However, despite its potential medical significance as a target for the treatment of diseases such as diabetes, Alzheimer's disease, and Parkinson's disease, no JNK inhibitors have been approved for use in humans.

In this work, Kaoud et al. (DOI: 10.1021/ml300129b) describe how they used shape-based virtual screening to discover new JNK-selective inhibitors that do not compete with ATP. They have previously reported a compound that specifically inhibits JNK but which is not stable in cells. Here, the authors identified new scaffolds with potential for development as agents that target protein-docking interactions mediated by JNK. They identified the natural product (−)-zuonin A as a highly selective inhibitor of JNK with activity in cells.

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