ACS Medicinal Chemistry Letters

In This Issue

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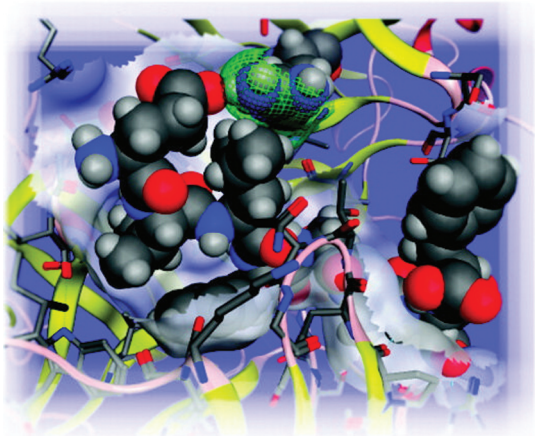
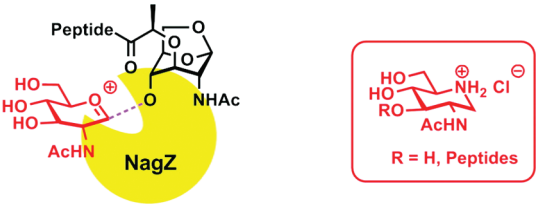
TURNING THE SUBSTRATE INTO INHIBITORS



β-Secretase enzyme has been implicated in Alzheimer's disease pathogenesis and serves as a promising molecular target for therapeutic intervention. This enzyme initiates the production and subsequent accumulation of β-amyloid peptides that play a key role in the progression of Alzheimer's disease. Thus, there is tremendous interest in developing peptidic and nonpeptidic inhibitors of β-secretase.

In this issue, Hamada et al. (DOI: 10.1021/ml2002373) describe the design and synthesis of peptides showing β-secretase inhibitory activity. From the hypothesis that a specific amino acid in the enzyme binding pocket interacts with its substrates and inhibitors via different attractive forces, specific peptides were synthesized. Some of these inhibitors, which are structurally similar to the substrate, exhibited potent activity. Understanding the specific interactions with inhibitors may be important in developing the next generation of β-secretase inhibitors.

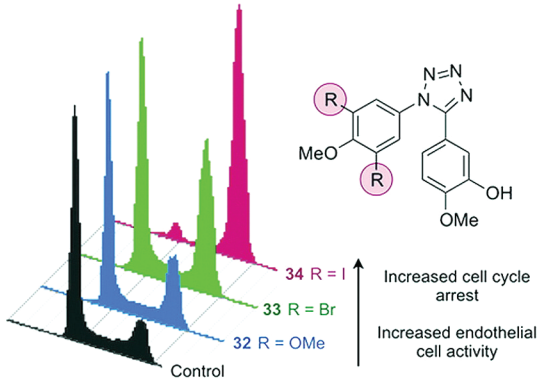
INTERMEDIATE MIMICRY



Cell wall recycling is an integral component of bacterial growth but is also a response to damage from antibiotics. Two enzymes involved in this multistep process, the periplasmic lytic transglycosylases and cytoplasmic β-*N*-acetylglucosaminidase (NagZ), are proposed to go through oxocarbenium ion intermediates in their respective disparate reactions.

Here, Yamaguchi et al. (DOI: 10.1021/ml2002746) explore the existence of these enzyme intermediates by inhibiting NagZ using oxocarbenium mimics. Four iminosaccharide compound mimics were synthesized and evaluated. One compound was found to be a competitive inhibitor exhibiting nanomolar activity. This inhibitor class and oxocarbenium mimics could help in deciphering the pathways involved in bacterial cell wall recycling and may have significance in designing broad-spectrum antibiotics.

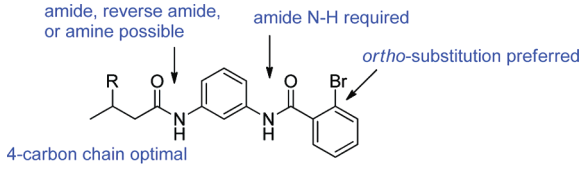
UNUSUAL SUBSTITUTION LEADS TO INCREASE IN POTENCY



Solid tumors require a blood supply to survive, and a relatively new field of cancer treatment involves the disruption of this blood supply using small molecules. Combretastatin, isolated from the African willow tree, is a potent vascular disrupting agent that can cut off tumor blood flow. Combretastatin analogues are in development to come up with optimal antitumor drugs.

In this work, Beale et al. (DOI: 10.1021/ml200149g) describe their discovery of new highly potent combretastatin derivatives that target the cell skeleton of tumors. These derivative compounds possess an unusual substitution pattern that gives them a 5-fold increase in potency against cancer cells. Unlike other compounds in this class, these combretastatin analogues are crystalline, stable, and soluble and are therefore promising agents for further drug development.

NEW SELECTIVE INHIBITORS OF PLATELET ACTIVATION



R = H: IC_{50} = 0.26 uM (**ML161**)
R= Me: IC_{50} = 0.29 uM *improved plasma stability*

Platelets are small, anucleated cells that circulate in the bloodstream that become activated by a variety of signals, leading the formation of blood clots. In some circumstances, these clots can contribute to heart attack and stroke. New antiplatelet drugs that act on new targets are required for improved treatment of cardiovascular disease. One such target is protease-activated receptor 1, a receptor embedded in the surface of platelets that responds to the clotting factor thrombin and activates platelets.

Here, Dockendoff et al. (DOI: 10.1021/ml2002696) outline a new series of compounds that inhibit select features of platelet activation through protease-activated receptor 1. This selective mode of action might enable future antithrombotic agents to be used with a reduced risk of serious bleeding events, which is a significant problem with the current treatments.

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