ACS Medicinal Chemistry Letters

IN THIS ISSUE

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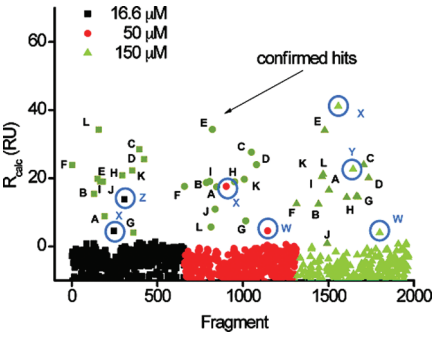
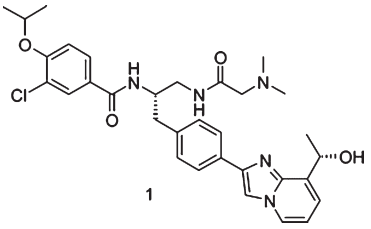
Screening Fragments

Fragment-based drug discovery, which uses as starting points very small, low molecular weight drug fragments, is now widely used in pharma and academia. To realize its true potential, the technique requires new tools to make it faster, to use less expensive reagents, and to expand its scale. In particular, new tools are needed to rapidly distinguish true ligands from artifacts. Now, Navratilova and Hopkins (DOI: 10.1021/ml900002k) present a practical method to virtually eliminate false positive binders and thereby improve the cost effectiveness of fragment screening strategies. The authors screen 650+ fragments by surface plasmon resonance against carbonic anhydrase II, looking for ways to distinguish true ligands from artifacts. The authors screen affinity and ligand efficiency. At the same time, they counter-screen against another target (a kinase) to remove many of the false positives that they find. The results indicate that this biosensor-based screening method shows significant advances over current biophysical methods employed in fragment-based drug discovery.



Inhibiting Motor Function

Cancer cells are characterized by uncontrolled cell division. Specific macromolecules involved in cell division have long been therapeutic targets of anticancer drugs. Kinesin motor proteins are of particular interest because their known functions are limited to dividing cells. One kinesin protein, centromere-associated protein E (CENP-E), is responsible for movement of the mammalian chromosomes and/or spindle elongation during mitosis. Now, Qian et al. (DOI: 10.1021/ml900018m) identify a highly potent and selective inhibitor of CENP-E. GSK923295 (3-chloro-*N*-{(1*S*)-2-[(*N*,*N*-dimethylglycyl)amino]-1-[(4-{8-[(1*S*)-1-hydroxyethyl]imidazo[1,2-*a*]pyridin-2-yl}phenyl)methyl]ethyl}-4-[(1-methylethyl)oxy]benzamide) induces mitotic arrest in human tumor cells and tumor regression *in vivo*. It is currently in human clinical trials for the treatment of solid tumor cancer.



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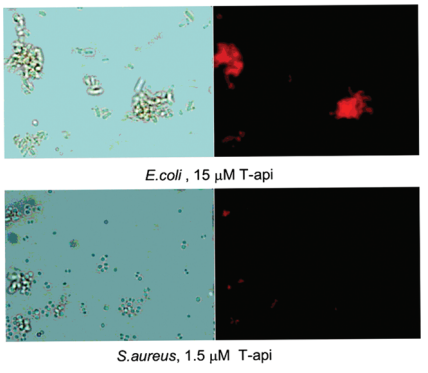
Blue Light Special

Photodynamic therapy combines a drug (photosensitizer) with visible light to produce reactive oxygen species that kill cells. It is used in the medical field to treat certain types of cancer as well as superficial and localized bacterial infections. It is effective against Gram-positive bacteria but much less so against Gram-negative bacteria. Dosselli et al. (DOI: 10.1021/ml900021y) synthesize a new conjugate between the antimicrobial peptide apidaecin (a Pro-Arg rich antimicrobial peptide) and a porphyrin-based photosensitizer that, by activation with light, exhibit broad spectrum bacteriacidal activity. This novel antibacterial agent significantly reduced the number of colony-forming units of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria when irradiated with blue



E.coli , 15 μM T-api

S.aureus, 1.5 μM T-api

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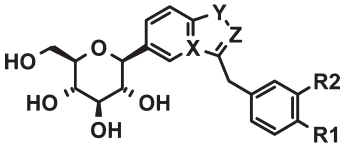
light. These findings open new developments in the field of modification of antimicrobial peptides. The results are promising in view of developing novel antibacterial compounds that could find application, for instance, in the sterilization of infected wounds by photodynamic therapy.

Controlling Sugar Uptake

Sodium glucose cotransporter 2 (SGLT2) is a trans-membrane protein located in the proximal tubule of the kidney. It is responsible for the reuptake of glucose from the glomerular filtrate to the plasma. In the clinic, inhibitors of SGLT2 prevent the reabsorption of glucose, resulting in reduced blood glucose levels and modest weight loss in diabetic patients. These characteristics suggest that SGLT2 inhibitors will be effective in the treatment of type 2 diabetes and obesity. Known inhibitors of SGLT2 are carbohydrate-derived glycosides originating from the natural product phlorizin, a nonselective *O*-glucoside inhibitor. Now, Zhou et al. (DOI: 10.1021/ml900010b) use a Pd-catalyzed cross-coupling reaction to synthesize a series of benzisothiazole- and indolizine-β-D-glucopyranoside inhibitors of human SGLT2 with an IC_{50} of 10 nM. The authors also show that high oral bioavailability of their compounds could be achieved without utilizing a prodrug strategy. The results described by the authors lead the way to optimization of these C-linked heterocyclic glucoside inhibitors for use in the treatment of metabolic disorders such as diabetes.



X=C, Y=S, Z=N
X=N, Y=C, Z = C
X=N, Y=N, Z=C

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