ACS Medicinal Chemistry Letters

In This Issue

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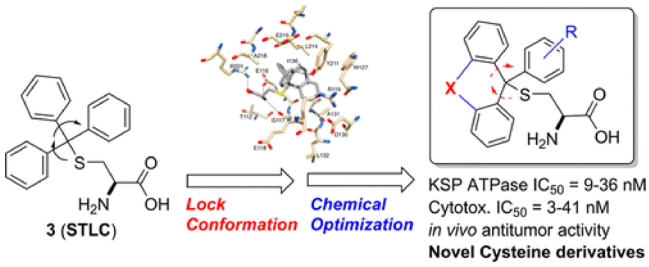
ARRESTING SPINDLE FORMATION

Arresting cell division with antimitotic agents, which act directly on microtubules, has become a promising strategy for treatment of various cancers. However, activity of antimitotic agents is associated with neurotoxicity and peripheral neuropathy. New agents with reduced potential for neurotoxic effects are being developed that indirectly target microtubules by inhibiting kinesin spindle protein (KSP).

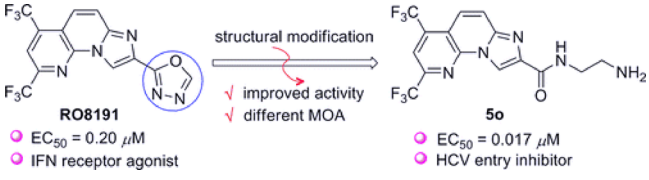
In this issue, Ogo et al. (DOI: 10.1021/acsmedchemlett.5b00221) use a structure-guided approach to design a series of derivative compounds that are evaluated for KSP inhibitory activity. The authors conduct a thorough investigation of structure−activity relationships and use modeling to further understand the interactions contributing to improved KSP inhibition by the derivative compounds.



TARGETING HCV ENTRY WITH IFN-LIKE SMALL MOLECULES

Infection with hepatitis C virus (HCV) can lead to the development of serious liver diseases including chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Prior to the recent approval of agents that directly target HCV, treatment for HCV infection involved a combination of pegylated-interferon-α and ribavirin. Despite the drastic improvements in patient outcomes with the direct acting antivirals for HCV, there is still a need for therapeutics with improved resistance profiles and fewer side effects. Recently, a novel small molecule interferon-like (IFN-like) agent was discovered that exhibits potent activity against HCV.

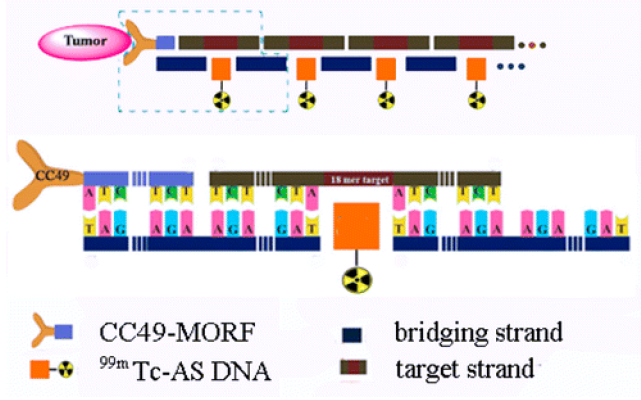
In this issue, Wang et al. (DOI: 10.1021/acsmedchemlett.5b00159) use the IFN-like compound as a lead for further development of a series of potential anti-HCV agents. The authors successfully develop several compounds that demonstrate improved anti-HCV activity over the lead agent. Notably, the work suggests that in contrast to the lead compound, which acts via an indirect route by binding the type I IFN receptor, the newly developed compounds directly inhibit viral entry.



IMPROVING TUMOR DETECTION WITH DNA BASED PRETARGETING

Pretargeting is a multistep noninvasive method used to specifically radiolabel tumors for imaging. In conventional pretargeting procedures, a slow clearing antibody is administered followed by a fast clearing radiolabeled effector that will specifically bind the antigen. This strategy promotes specific localization of the radiolabeled effector in the tumor, while rapid clearance from the bloodstream reduces toxicity.

Here, Li et al. (DOI: 10.1021/acsmedchemlett.5b00265) design a DNA based system for amplification of pretargeting signal. The authors use a DNA polymer with multiple binding sites between the injection of the antibody and the labeled effector to successfully amplify the signal compared to conventional pretargeting. The in vitro cell and plate based assays conducted here serve as a proof of concept for potential enhancement of sensitivity when performing SPECT or PET imaging.



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