ACS Medicinal Chemistry Letters

In This Issue

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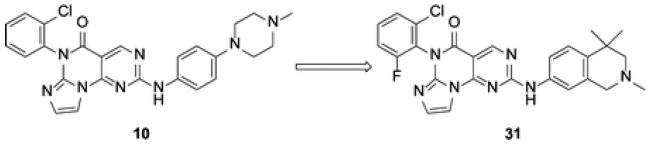
■ ORAL INHIBITORS OF WEE1 KINASE

Cells utilize checkpoints to ensure genomic integrity. Wee1 kinase is a key player in the process as it enables repair of damaged DNA in G2 phase prior to mitosis. As such, Wee1 inhibitors have been employed in preventing the activation of the G2 cell cycle checkpoint to enhance the antitumor activity of DNA damaging agents.

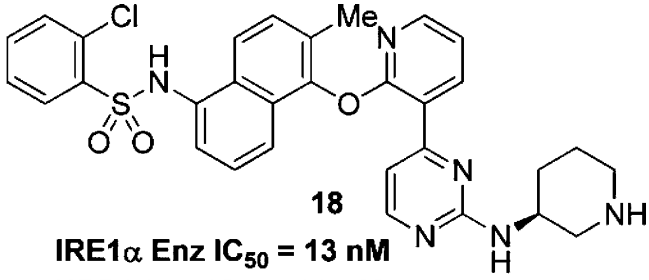
The research featured on the cover of this Special Issue discloses a novel class of potent and efficacious Wee1 inhibitors. Tong et al. (DOI: 10.1021/ml5002745) present the SAR studies and in vivo biomarker and efficacy data of a novel class of inhibitors. The SAR studies could give further insight into the active site of the Wee1 kinase.



■ RETHINKING THE ROLE OF IRE1αIN CANCER THERAPY

Target validation efforts in drug discovery are often hampered by the potency and selectivity of the tool compound used, with compounds interacting with other cellular targets resulting in misperceived readouts.

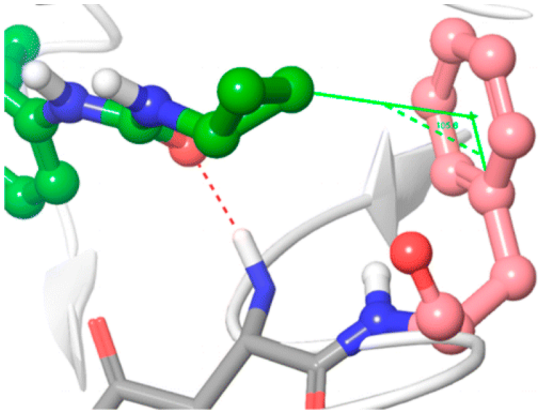
In this Special Issue, Harrington et al. (DOI: 10.1021/ml500315b) address the previously reported potential of the enzyme IRE1α as an anticancer target. The group identified potent and selective molecules that inhibit the endonuclease function of IRE1α in cells and demonstrate surprising results showing that the enzyme inhibition has minimal impact on the tumor cell lines. These results may suggest a revision of the reported value of IRE1α inhibition in cancer therapy.



■ BINDING MODE OF POTENTIAL ANTICANCER DRUG LENVATINIB

Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor that is currently under clinical investigation in solid tumors. Lenvatinib selectively inhibits vascular endothelial growth factor receptor 2 (VEGFR2) and is being developed as an anticancer drug. Lenvatinib recently achieved the primary end point in a phase 3 clinical trial in patients with differentiated thyroid cancer.

Here, Okamoto et al. (DOI: 10.1021/ml500394m) discuss the analysis of the interaction kinetics between lenvatinib and VEGFR2, which revealed the rapid association rate constant and a relatively slow dissociation rate constant of lenvatinib in complex with VEGFR2.



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