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In This Issue

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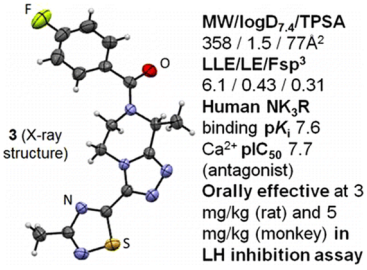
EFFECTIVE REGULATION OF SEX HORMONES

Polycystic ovary syndrome and uterine fibroids are disorders characterized by an imbalance of sex hormones. Release of these sex hormones is regulated in part by signaling via the neurokinin-3 receptor (NK_3R), thus making NK_3R an attractive target for therapy.

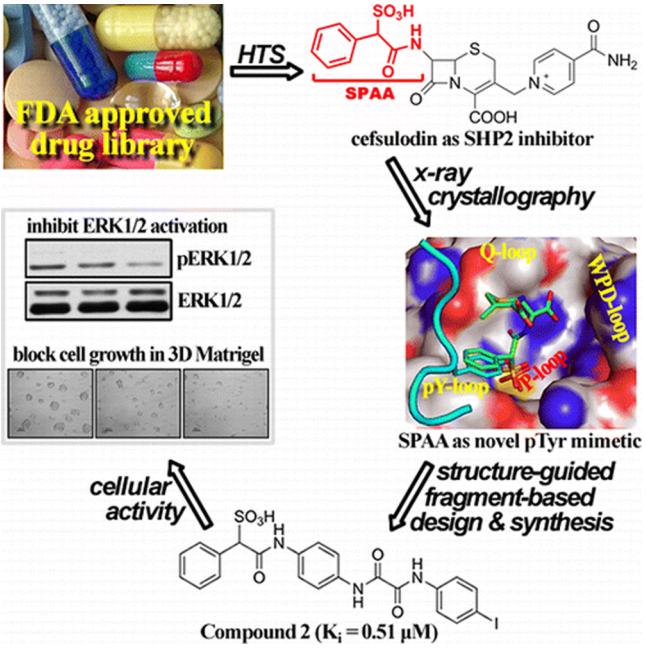
In this Featured Letter, Hoveyda et al. (DOI: 10.1021/acsmedchemlett.5b00117) describe lead optimization of NK_3R antagonists. Using animal models to investigate bioactivity and safety profiles of the NK_3R antagonists, the authors identify a single highly selective and efficacious compound that has progressed to phase 2 clinical trials for the treatment of polycystic ovary syndrome and uterine fibroids.



TURNING AN ANTIBIOTIC INTO A CANCER THERAPEUTIC

Activating mutations in the protein tyrosine phosphatase (PTP) SHP2 have been identified in both leukemia and solid tumor cells. Inhibition of SHP2 presents a novel strategy to target cancer cells; however, the conserved PTP active site presents a challenge for the development of small molecule inhibitors of SHP2. While a number of PTP inhibitors have been developed, poor bioavailability has limited their development as therapeutics.

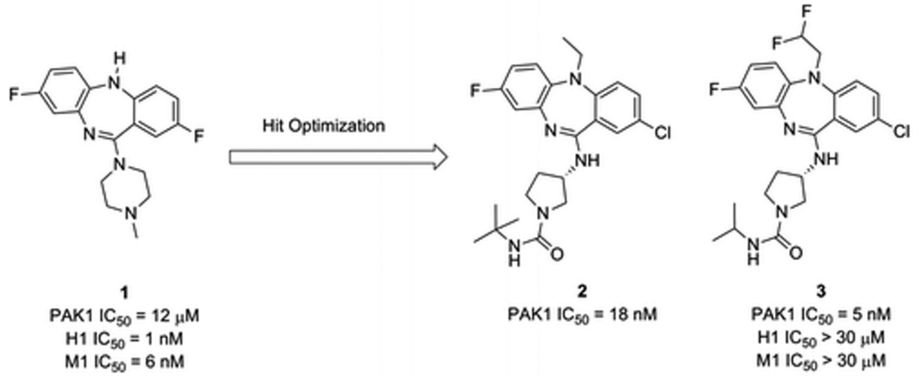
In this issue, He et al. (DOI: 10.1021/acsmedchemlett.5b00118) screen an FDA-approved drug collection for SHP2 inhibitory activity. The authors identify cefsulodin, an antibiotic with good bioavailability, as a candidate for further development. Using a structure-guided and fragment-based approach, the authors develop several cefsulodin-based compounds demonstrating antiproliferative activity in cancer cell lines. By using currently approved drugs as a starting point for screening and optimization, the authors successfully circumvent many challenges of therapeutic development such as poor bioavailability.



DEVELOPING SELECTIVE TOOLS TO INVESTIGATE KINASE ACTIVITY

Altered activity of the p21-activated kinase PAK1 has been suggested to play a role in a wide variety of diseases including neurological diseases such as Alzheimer's and Huntington's disease; and various cancers such as breast cancer and pancreatic cancer. Despite its importance in a number of diseases, a thorough understanding of PAK1 activity has been limited by a lack of selective kinase inhibitors available to dissect biological activities.

Here, Karpov et al. (DOI: 10.1021/acsmedchemlett.5b00102) use a benzodiazepine hit, discovered by fragment-based screening, as a starting point for the development of two compounds that demonstrate potent and selective activity against PAK1. These compounds present novel tools that will serve to further the understanding of PAK1 biological activity.



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