ACS Medicinal Chemistry Letters

In This Issue

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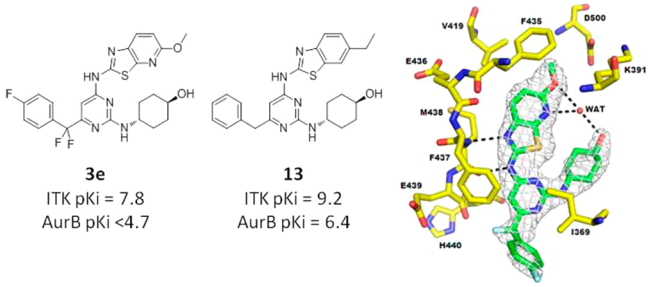
IDENTIFICATION OF NEW ITK INHIBITORS

Interleukin-2 inducible tyrosine kinase (Itk) is a nonreceptor protein tyrosine kinase predominantly expressed in T cells, which plays a dominant role in T-cell development, differentiation, and signaling. ITK plays a pivotal role in the secretion of key inflammatory cytokines and has been shown to regulate the response during allergic asthma. While Itk is a significant target, there are currently no drugs available in the market.

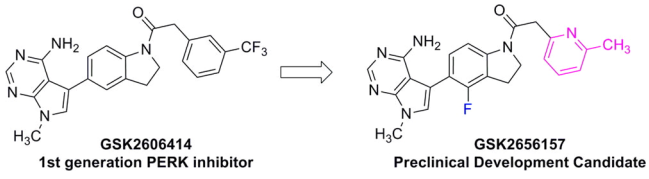
In this issue, Alder et al. (DOI: 10.1021/ml400206q) describe the identification and initial optimization of diaminopyrimidine-based Itk inhibitors that showed Aurora selectivity using a template-hopping strategy. Using modeling and crystallography, the authors were able to rationalize the selectivity of these inhibitors and formulate strategies to further improve their potency against Itk.



PERK INHIBITOR FOR PRECLINICAL DEVELOPMENT

Endoplasmic reticulum (ER) stress is associated with several debilitating conditions such as neurodegeneration, heart disease, diabetes, and cancer. The ER-induced unfolded protein response (UPR) gets activated when misfolded proteins accumulate in the ER and restores ER homeostasis. (PKR)-like ER kinase (PERK) is one of three primary effectors of the UPR, activating stress sensors that lead to transcriptional reprogramming of the cells. Thus, inhibiting PERK in cancer cells may lead to apoptosis or tumor growth inhibition.

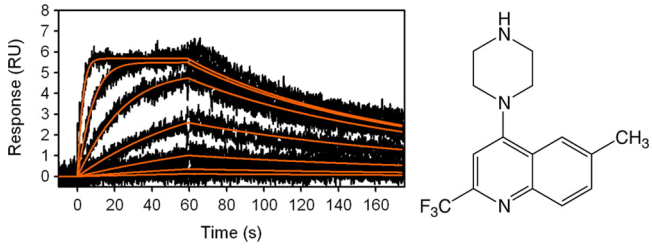
The letter by Axten et al. (DOI: 10.1021/ml400228e) elegantly describes the discovery and optimization of inhibitors of PERK and characterization of the lead compounds. The novel compounds were designed using protein crystal structures, improving the metabolic liabilities, pharmacokinetics, and physicochemical properties of the first generation inhibitors. One compound was selected as a preclinical development candidate. This compound can potentially serve as a valuable tool compound in exploring the emerging area of UPR.



USE OF SPR IN DISCOVERING NOVEL GPCR LIGANDS

In recent years, biophysical methods have progressed immensely for utilization in studying membrane-bound G-protein coupled receptors (GPCRs). The elucidation of X-ray crystallographic structures of human GPCRs has opened up these difficult membrane proteins to new drug discovery approaches such as structure-based drug design and virtual screening.

The technology note by Aristotelous et al. (DOI: 10.1021/ml400312j) describe the effort to develop, validate, and reduce to practice a new cell-free, label-free surface plasmon resonance (SPR) assay method for low molecular weight compounds screening against wild-type sequence GPCRs. Herein, the authors demonstrate the application of SPR to the discovery of fragment-based antagonists of the β2-adrenergic receptor. The hits from the assay are characterized, validated, and profiled in a variety of assays. This screening method provides a new approach to the discovery of novel GPCR ligands.



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