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In This Issue

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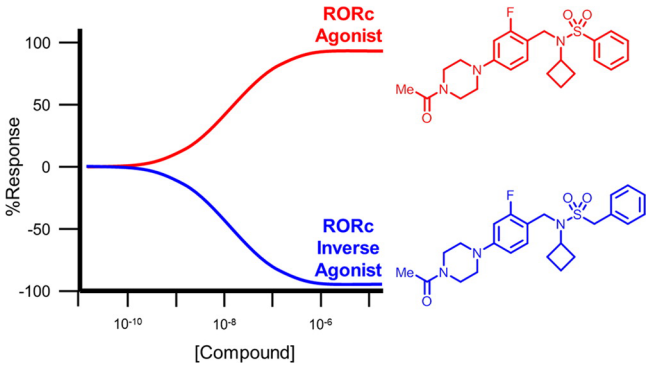
SMALL STRUCTURAL CHANGE LEADS TO BIG MECHANISM OF ACTION CHANGE

Interleukin-17 (IL-17) is a critical driver of several autoimmune diseases. The retinoic acid receptor-related orphan receptor gamma (RORγ or RORc) is a key nuclear receptor that has been implicated in the production and regulation of IL-17. Thus, RORc ligands have received significant attention due to their potential pharmaceutical significance.

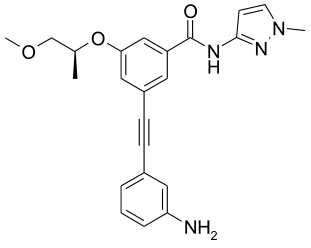
Featured on the cover is the work by Rene et al. (DOI: 10.1021/ml500420y), which demonstrates that a minor structural change to tertiary sulfonamide RORc ligands led to opposite mechanisms of action in both biochemical and primary human blood cell assays. X-ray cocrystal structural data was used to identify and characterize the two distinct binding modes consistent with the biochemical and cellular modes of action.



NEW GLUCOKINASE ACTIVATORS FOR DIABETES TREATMENT

Type 2 diabetes mellitus (T2DM) now affects over 300 million people worldwide. To date, currently available antidiabetic agents have limited long-term efficacy or has associated side effects. Thus, great research efforts have been made to develop new therapeutics that focus on safety and efficacious glycemic control.

Glucokinase activator (GKA) is associated with a dual mechanism for lowering blood glucose concentrations and increasing insulin secretion. Therefore, glucokinase has become an attractive target for antidiabetic therapy. Park et al. (DOI: 10.1021/ml5004712) report the synthesis and activity screening of acetylenyl-containing benzamide derivatives, looking at increases in glucokinase activity and glucose uptake in rat liver cells. Lead optimization led to the discovery of several active compounds. One compound was identified as a potent glucokinase activator and was selected as a candidate for further preclinical development for the treatment of type 2 diabetes.



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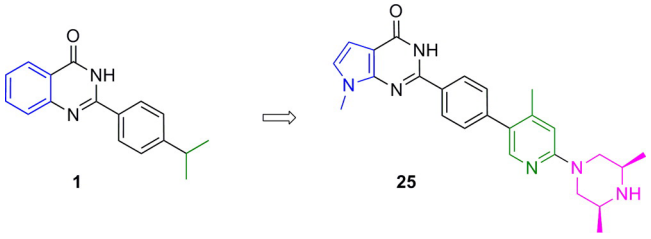
GK EC_{50} = 27 nM, AUC reduction in OGTT = 47.4% (30 mg/kg)

SELECTIVE TANKYRASE AND WNT PATHWAY INHIBITORS

There is a strong link between mutations to the Wnt signaling pathway and cancer, and recent literature has shown that inhibition of the tankyrases can block mutant Wnt signaling in certain cancer cell lines. This has led to the hypothesis that a tankyrase inhibitor could have great potential to treat cancer patients with tumors that harbor Wnt mutations. Further, it points to the need for drug-like probe compounds with suitable properties for hypothesis testing in preclinical species.

In this issue, Johannes et al. (DOI: 10.1021/ml5003663) describe the optimization of a series of tankyrase inhibitors for desirable primary target potency, enzyme family selectivity, permeability, aqueous solubility, and pharmacokinetics. These efforts have resulted in a lead compound that can be used to test the hypothesis of tankyrase inhibition in mouse xenograft models of cancer for antitumor efficacy and tolerability.



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