Title:
Advancing a Clinical Candidate Targeting IRAK4 from a Fragment Lead

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Abstract:
Interleukin-1 receptor-associated kinase 4 (IRAK4) is an essential signal transducer downstream of the IL-1 family receptors (IL-1R, IL-18R, and IL-33R), and the Toll-like receptors (TLRs) that detect bacterial and viral pathogens. Activation of the signaling cascade leads to the production of pro-inflammatory cytokines such as TNFα and IL-6. It is an attractive target for the treatment of auto-immune diseases such as rheumatoid arthritis and lupus. At Pfizer, we identified small fragments as leads based on biophysical and biochemical screening. These were subsequently developed into a highly ligand efficient and kinome selective first-in-class IRAK4 inhibitor through an integrated approach that included structural, biochemical, computational and medicinal chemistry techniques. I will discuss how our lead clinical compound evolved from the starting fragment based on structure-based drug design.