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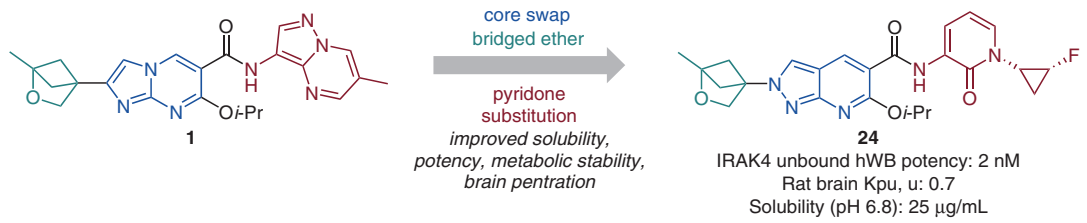
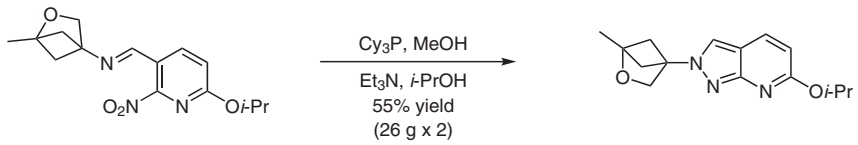
A Tiny Pocket Packs a Punch: Leveraging Pyridones for the Discovery of CNS-Penetrant Aza-indazole IRAK4 Inhibitors
ACS Med. Chem. Lett. **2024**, *15*, 714–721, DOI: 10.1021/acsmedchemlett.4c00102.

Discovery and Development of CNS-Penetrant IRAK4 Inhibitors



Cadogan cyclization enables scalable and regioselective installation of bridged ether ring:



Significance: Interleukin-1 Receptor Associated Kinase 4 (IRAK4) inhibitors are emerging therapeutics for the treatment of neurological disorders. In this work, Bolduc, Peterson and co-workers describe the property driven optimization of previous lead compound **1** to compound **24**, which has improved potency, solubility and brain penetration. Challenging chemistry was enabled to the synthesis of the bridged ether ring and access complex 3-amino-2-pyridone analogues, leading to identification of the potent *cis*-fluorocyclopropyl pyridone structure in compound **24**.

Comment: Compounds were designed to decrease lipophilicity and increase F_{sp}^3, with the goal of improving solubility and brain penetration. Swapping the imidazolopyrimidine 5,6-heterocyclic core in **1** with an azaindazole core improved potency, solubility, and MDR1 efflux ratio. The bridged ether ring improved potency, metabolic stability, and solubility. A challenging Cadogan cyclization was optimized to enable the scalable installation of the bridged ether onto the azaindazole core in 55% yield. Replacement of pyrazolopyrimidine amide in **1** with an *N*-alkylpyridone reduced eLogD and introduced an opportunity to increase F_{sp}^3. A one-pot Knoevenagel, Michael addition and nitro reduction approach developed in a previous report by the authors (*Org. Lett.* **2022**, *24*, 6133) was utilized to access diverse 3-amino-2-pyridone analogues leading to identification of the potent *cis*-fluorocyclopropyl derivative **24**.

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Category
Innovative Drug Discovery and Development

Key words
IRAK4
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Synfact of the Month