Discovery of LOU064 (Remibrutinib), a Potent and Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase

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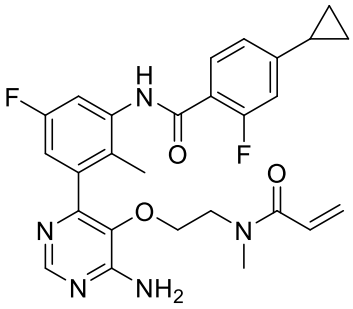
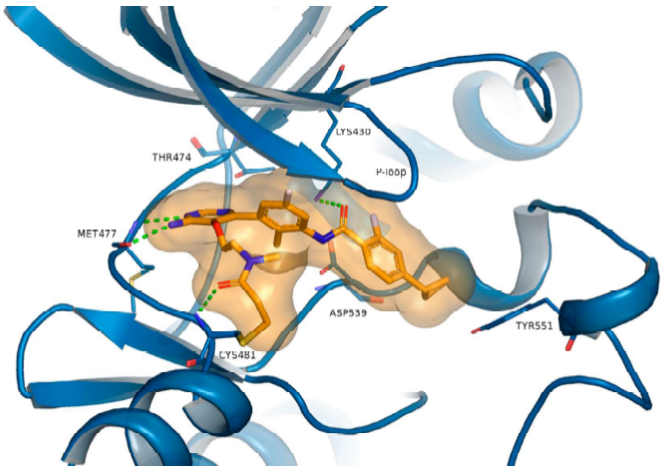
Bruton's Tyrosine Kinase (BTK), a cytoplasmic tyrosine kinase, is selectively expressed in a subset of immune cells, including macrophages, mast cells, and B cells. BTK is a key regulator of B cell antigen receptor signaling in B cells and of Fc receptor signaling in mast cells and macrophages. Due to its central role in immunity, it is likely that a BTK inhibitor will have a positive impact on autoimmune diseases which are caused by autoreactive B cells and immune-complex driven inflammation.
We describe the discovery, synthesis, and preclinical profile of LOU064 (remibrutinib), a potent, highly selective covalent BTK inhibitor. LOU064 exhibits an exquisite kinase selectivity due to binding to an inactive conformation of BTK and has the potential for a best-in-class covalent BTK inhibitor for the treatment of autoimmune diseases.[1]
LOU064 is currently being tested in phase 3 clinical studies for chronic spontaneous urticaria and multiple sclerosis and in phase 2 studies for Sjoegren's syndrome.



LOU064
(remibrutinib)



[1] Angst, D. et al *J. Med. Chem.* **2020**, *63*, 10, 5102-5118.