LNP023 / iptacopan: Discovery and Synthesis Development of a First-in-Class, Oral Factor B Inhibitor for the Treatment of Rare Renal and Hematological Diseases

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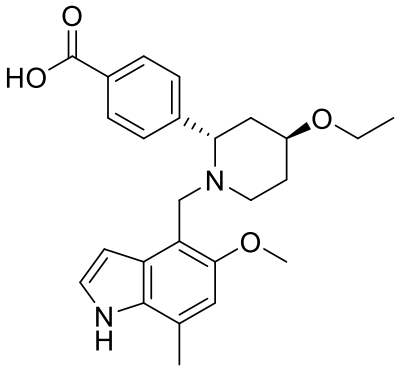
Complement is a key component of the innate immune system; however, its dysregulation due to genetic mutations or the presence of autoantibodies can cause a number of diseases including age-related macular degeneration, paroxysmal nocturnal hemoglobinuria, and C3 glomerulopathy. The alternative pathway acts as an amplification loop of the complement system. It is triggered by the activation of factor B, the proteolytically active component of the C3 and C5 convertases. We report the discovery of LNP023, a highly selective small-molecule inhibitor of factor B by structure-based design. It efficiently blocks the alternative pathway in vivo, ex vivo in patient samples and in PNH patients. To support clinical development of LNP023 / iptacopan, the diversity oriented research synthesis has been transformed into a scalable manufacturing process.



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