The Discovery of Orally Active Inhibitors of Respiratory Syncytial Virus

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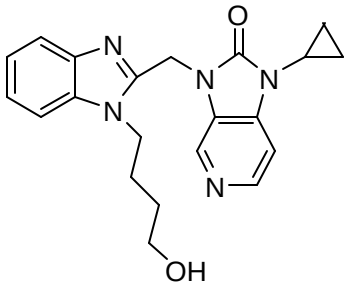
Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection that circulates predominantly in the winter season and infects virtually all children in the first 2 years of life. Whilst for the majority of patients, RSV infection is restricted to the upper respiratory tract and recovery is without complication, in those who are immunosuppressed or have underlying cardiopulmonary problems, RSV infection is a significant cause of morbidity and mortality. In addition, RSV has been implicated as a contributor to otitis media infections and is an underestimated pathogen in the elderly, where it is frequently misdiagnosed as influenza. RSV infections can recur throughout life, a consequence of an immune response of limited durability.

Using a tissue cell culture screen, a series of benzimidazole derivatives were identified as selective RSV inhibitors and subsequently optimized for increased potency whilst introducing drug-like properties in order to produce compounds that demonstrated oral bioavailability in animals and antiviral activity in models of RSV infection. BMS-433771 emerged from this work as a potent, orally bioavailable inhibitor of RSV that interferes with the virus-host cell fusion process. Studies using a photoaffinity probe determined that the mode of action of this class of RSV inhibitor involves interfering with the assembly of the virus fusion protein into a functional six-helix bundle arrangement that is an essential step in RSV entry. A model of BMS-433771 bound to the trimeric RSV F protein N-terminal helical region identified potential opportunities for establishing additional interactions between the drug and its target.



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