SUMMARY OF Ph.D. DISSERTATION

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Title

Discovery of orally active PDE4 inhibitors based on bicycle[3.3.0]octane, pyrazolopyridine, and piperidine scaffolds

Abstract

Phosphodiesterase type 4 (PDE4) is an enzyme that is mainly expressed in airway smooth muscle and inflammatory cells, where it catalyzes hydrolysis of the second messenger adenosine 3',5'-monophosphate. Inhibition of PDE4 results in elevation of the intracellular cAMP level, which in turn downregulates the inflammatory response. Accordingly, the potential of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma and chronic obstructive pulmonary disease has received considerable attention. However, no selective PDE4 inhibitor has come into clinical use yet because the early compounds had dose-limiting side effects like nausea and vomiting.

Cilomilast is a selective PDE4 inhibitor with a unique arrangement of three functional groups (carboxylic acid, benzylic nitrile, and 3-cyclopentyloxy-4-methoxyphenyl moieties) on its cyclohexane ring, and it was in pre-registration for COPD as of February 2003. As studies of PDE4 enzyme have continued to advance, the crystal structure of PDE4B was first reported by Xu et al in 2000.

This report concerns efforts to discover a compound with a superior therapeutic index to that of Cilomilast. To obtain effective PDE4 inhibitors with fewer side effects, three strategies have been tried: 1) use of a bicycle[3.3.0]octane template (to achieve more rigid spatial arrangement of the three functional groups within their optimized stereochemistry); 2) use of a pyrazolopyridine template (as a different approach to the chemical modification of catechol derivatives); and 3) use of a piperidine template (to reduce penetration into the central nervous system). Several compounds were synthesized based on these strategies and their structure-activity relationships, biological properties, and pharmacokinetics were investigated. As a result, three compounds were selected as clinical candidates. The role of the three functional groups on bicyclooctane and/or piperidine templates was investigated by using in silico docking studies.