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Development of a Green and Sustainable Manufacturing Process for Gefapixant Citrate (MK-7264) Part 1: Introduction and Process Overview

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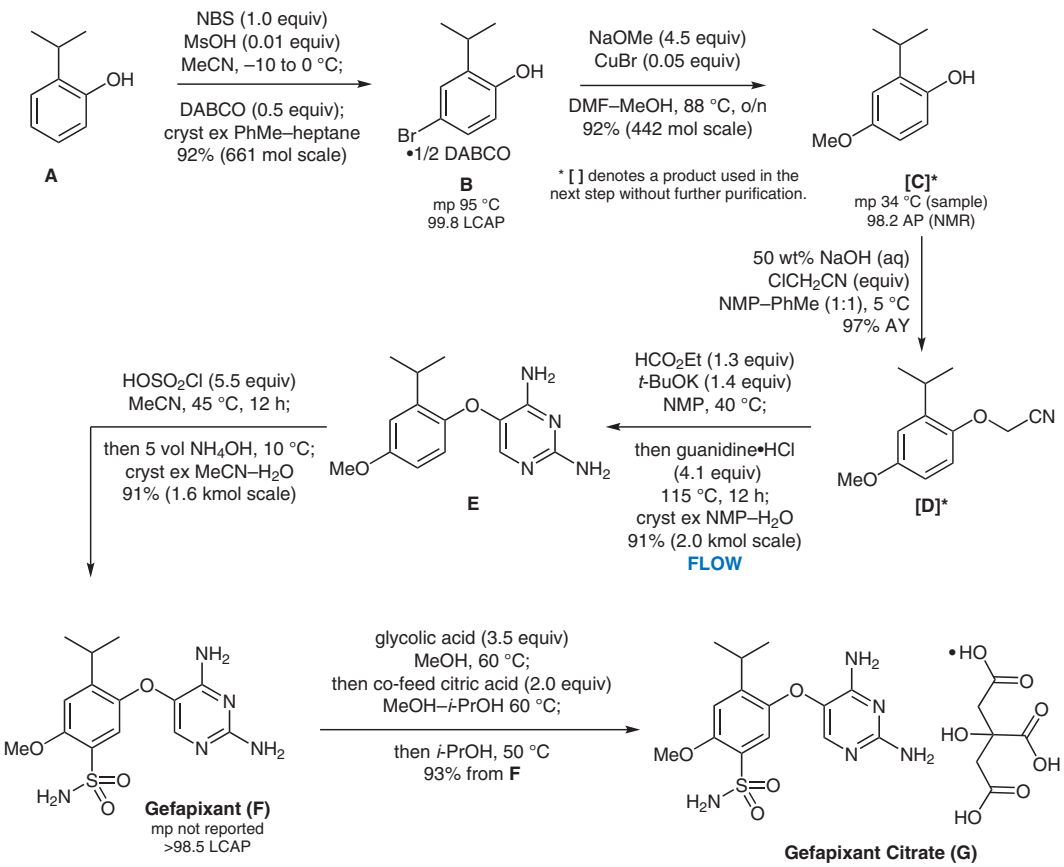
Synthesis of Gefapixant



Significance: Gefapixant citrate (MK-7264) is a P2X3 receptor antagonist that reduces the frequency of cough in patients with refractory chronic cough. The six-step synthesis of gefapixant citrate (**G**) is described in forensic detail in six back-to-back papers. Part 1 provides an overview of the commercial manufacturing process. Parts 2–6 elaborate the process development of each step. Compared with the clinical supply route, this route has a much improved overall process mass intensity from commodity raw materials resulting in a five-fold reduction compared to the clinical supply route. In addition, a higher overall yield (60% vs 16%) and a six-fold reduction in raw material costs were realized.

Comment: Salient features of the synthesis are (1) a highly efficient two-step methoxyphenol synthesis (**A** → **C**), (2) an innovative pyrimidine synthesis in flow (**D** → **E**), and (3) a simplified sulfonamidation reaction using chlorosulfonic acid (**E** → **F**). In order to address adverse solubility and form issues, the free base **F** was transiently converted into a highly soluble glycolate salt enabling complete dissolution, from which direct crystallization of the final citrate salt occurred in a high yield through salt metathesis.

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