OR01 – A Robust Kilo-Scale Synthesis of Doravirine

Peter Maligres, Qinghao Chen, Danny Gauvreau, Mélina Girardin, Kevin Belyk, Lushi Tan, Paul D. O'Shea, Louis-Charles Campeau


b Process Research and Development, Merck Frosst Center for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Quebec, Canada H3C 3J7

E-mail: peter_maligres@merck.com

Doravirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) currently in phase III clinical trials for the treatment of HIV infection. Herein we describe a robust kilo-scale synthesis for its manufacture used to supply pre-clinical and clinical supplies. The structure and origin of major impurities was determined and their fate and purge studied. This resulted in a re-design of the route to introduce the key nitrile functionality via a copper catalyzed cyanation in order to ensure all impurities were controlled to an adequate level. The limited availability of 3-chloro-5-iodo-phenol prompted us to develop a meta-selective iridium catalyzed C–H borylation-oxidation sequence which readily afforded the desired phenol. Overall, the synthesis could be scaled to prepare Doravirine in >90 kg batches and was used to prepare all pre-clinical and clinical material up to phase III. The synthesis affords high quality material in a longest linear sequence of 6 steps and 37% overall yield.