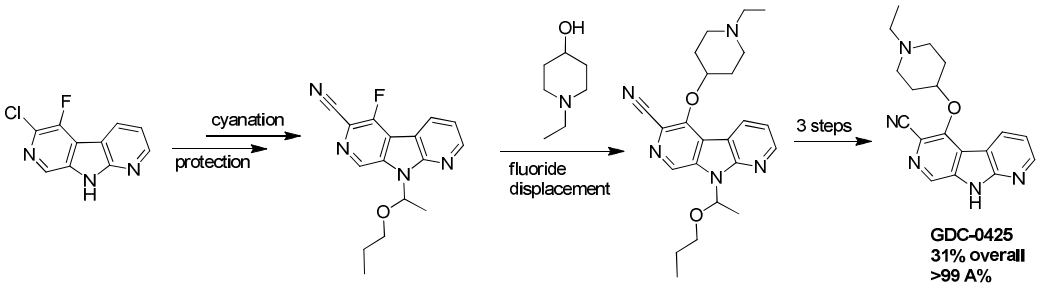
Development of an Expedient Process for the Multi-Kilogram Synthesis of Chk1 Inhibitor GDC-0425

Andreas Stumpf, Zhigang Ken Cheng, Remy Angelaud, Lewis Gazzard

Genentech, San Francisco, CA, USA



As part of a recent drug development program for the orally active ChK1 inhibitor GDC-0425, we required multi kilogram amounts of active pharmaceutical ingredient (API) to support human clinical studies. The initial discovery chemistry synthesis involved a multi-step conversion from 6-chloro-5-fluoro-9H-pyrrolo[2,3-b:5,4-c']dipyridine **1**. This route effectively provided initial quantities of API but used undesirable reagents (SEM, NaH, TBAF), high catalyst loadings and required tedious workup and isolation procedures. We set out do develop a first generation process to manufacture ChK1 inhibitor GDC-0425 on multi-kilogram scale. An important part of our process development also needed to address the removal of heavy metals and the development of a crystallization process for the isolation of the penultimate API in high purity.

This presentation will discuss our efforts to secure an efficient and scalable route to the API and steps taken to lead us to the optimal route for GDC-0425 as shown in the scheme below. Highlights of the talk will be the discussion of the (1) carbazole protection strategy, (2) development of an efficient Pd catalyzed cyanation of aryl chloride **2**; (3) optimization of the SNAr fluoride displacement of **3**; (4) development of the recrystallization process for GDC-0425. The optimized process delivered highly pure API (>99 A% by HPLC) with the desired crystal form in an overall yield of 31 %.