“Overcoming Electronics with Strategy: Development of an Efficient Synthesis of a Novel Antiretroviral”

Abstract. The appearance of resistant HIV-1 variants has necessitated the identification of therapeutic agents with novel modes of action. Recent efforts at Bristol-Myers Squibb have been directed toward the identification of potent, orally active antiretrovirals with a unique mechanism of action. HIV-1 attachment inhibitors are a new class of viral entry inhibitors which bind to the gp120 envelope protein of the virus and interfere with the attachment to CD4 receptors of the host cell. This presentation will describe the evolution of the synthesis of a promising clinical candidate, from a fit for purpose process that was used to prepare over a metric ton of BMS-663068, a phosphonooxymethyl prodrug of the small-molecule inhibitor BMS-626529, to a completely revised and improved preparation of the entire molecule. The new approach, that includes a de novo preparation of the azaindole core, provides a significantly more efficient and robust synthesis of BMS-663068.