Looking for the Rationale in Drug Substance Syntheses

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A brief summary will be provided on development of Drug Substances and New Chemical Entities with particular emphasis on Chemical Process Research & Development activities. In recent years, Chemical Process R&D has experienced revolutionary change through incorporation of (i) technical advances, such as automation and (ii) statistical tools such as DoE and QbD. These valuable tools assist accurate development of chemical processes, however, perhaps at the expense of innovation. Insight into reaction mechanisms and rational design of synthesis steps remain the most important factors for fast and efficient chemical development. This will be exemplified by two case studies: In the first case, a short and highly efficient synthesis of statins was achieved by theoretical evaluation of existing approaches supported by experimental design. The methodology was successfully applied to the synthesis of pitavastatin\(^1\). In the second case, the semi-synthesis of DB-67\(^2\), a camptothecin derivative, was investigated. Analysis of the reaction mechanism enabled the design of a tailor made catalyst, which improved the very low yield and also the reproducibility.

![Pitavastatin](image1.png)

![DB-67](image2.png)

References: