

***In Vivo* Dearomatization of the Potent Antituberculosis Agent BTZ043 via Meisenheimer Complex Formation.**

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Abstract

Nitrobenzothiazinones are among the most potent antituberculosis agents. Herein, we disclose an unprecedented in vivo reduction process that affords Meisenheimer complexes of the clinical candidates BTZ043 and PBTZ169. The reduction is reversible, occurs in all mammalian species investigated, has a profound influence on the in vivo ADME characteristics, and has considerable implications for the design and implementation of clinical studies. The reduction was confirmed by chemical studies that enabled the complete characterization of the Meisenheimer complex and its subsequent chemistry. Combination of the in vivo and chemical studies with LC-MS characterization and assay development also provides a basis for rational lead optimization of this very promising class of antituberculosis agents.

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