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Deuterium Editing of Small Molecules: A Case Study on Antitumor Activity of 1,4-Benzodiazepine-2,5-dione Derivatives
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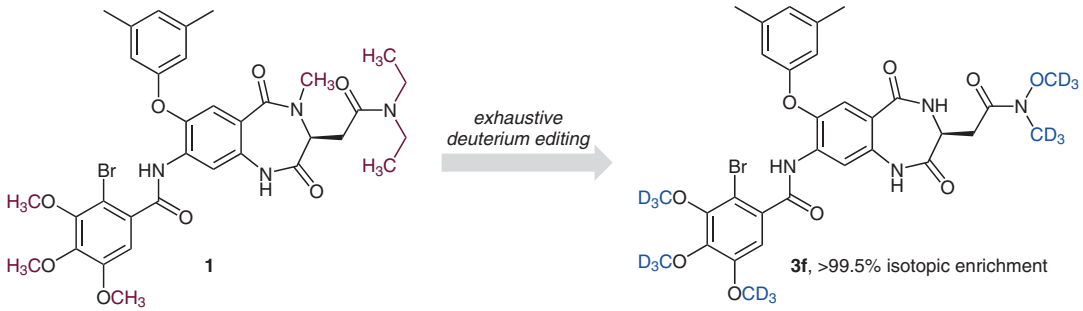
Exhaustive Deuterium Editing Study of 1,4-Benzodiazepine-2,5-dione Derivatives



Significance: Deuterium substitution is an emerging strategy to alter the metabolic profile of pharmaceutical compounds amongst other drug properties. In this work, Zheng and Liu exhaustively investigate the effect of deuterium substitution at multiple metabolic sites of protein translation inhibitor **1**. These studies culminated in 15-deuterated derivative **3f** which exhibited improved clearance and demonstrated efficacy in vivo. Impressively, GMP-grade **3f** was produced for IND-filing with >99.5% isotopic enrichment.

Comment: CYP3A4 was found to be the primary metabolic enzyme for **1**. The major metabolic pathways for **1** are oxidative dealkylation of the diethylamide, oxidation of the 3,5-dimethylbenzene, and oxidation of the methoxy functional groups. Additionally, it was found that the *N*-4 methyl group played a key role in mediating oxidative deethylation of **1**. An exhaustive study was performed investigating the effect of selective deuteration on the intrinsic clearance and primary site of metabolism. These studies lead to identification of **3f**, which exhibited 9.3-fold reduction in intrinsic clearance. Albumin-bound nanoparticles of **3f** demonstrated an 8.33 h and 9.36 h $t_{1/2}$ in bone marrow and tumor tissue, respectively, and exhibited dose-dependent inhibition in mouse models of various cancer types. Synthesis of GMP-grade **3f** was accomplished with >99.5% isotopic enrichment in 51% yield.

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Synfact of the Month