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Discovery of Epigenetic Regulator I-BET762: Lead Optimization to Afford a Clinical Candidate Inhibitor of the BET Bromodomains


**Synthesis of Epigenetic Regulator I-BET762 (GSK525762)**

**Significance:** I-BET762 (GSK525762) has entered phase I/II clinical trials for the treatment of the aggressive NUT midline carcinoma and other cancers. It disrupts the function of the bromodomain and extra-terminal domain (BET) family of proteins. The synthesis depicted features the construction of the 1,4-benzodiazepine skeleton with incorporation of an (S)-aspartic acid moiety.

**Comment:** For a synthesis of benzophenone **A**, see: C.-w. Chung et al. *J. Med. Chem.* **2011**, 54, 3827. The easy epimerization of the stereogenic center that occurs in the thionation reaction (**B** → **C**) was suppressed by conducting the reaction in the presence of sodium carbonate. The (R)-enantiomer is biologically inactive as a BET inhibitor.