Category

Synthesis of Natural Products and Potential Drugs

Key words

I-BET762

GSK525762

1,4-benzodi-azepines

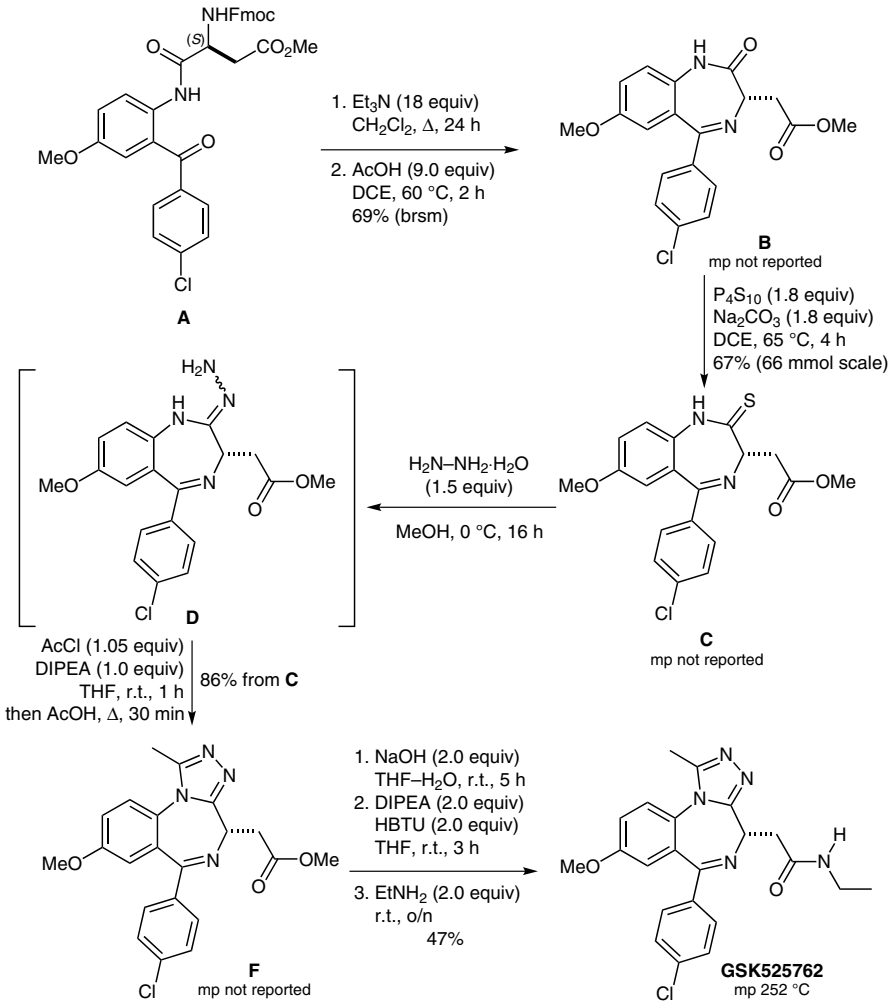
1,2,4-triazoles

O. MIRGUET,* N. PARR* ET AL. (GLAXOSMITHKLINE R&D, VILLEBON-SUR-YVETTE, FRANCE AND STEVENAGE, UK)

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

J. Med. Chem. **2013**, *56*, 7501–7515.

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.

SYNFACTS Contributors: Philip Kocienski
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