A. C. SPIVEY,* C.-C. TSENG, T. C. JONES, A. D. KOHLER, G. J. ELLAMES (IMPERIAL COLLEGE, LONDON AND SANOFI-AVENTIS, ALNWICK, UK)

A Method for Parallel Solid-Phase Synthesis of Iodinated Analogues of the CB_1 Receptor Inverse Agonist Rimonabant

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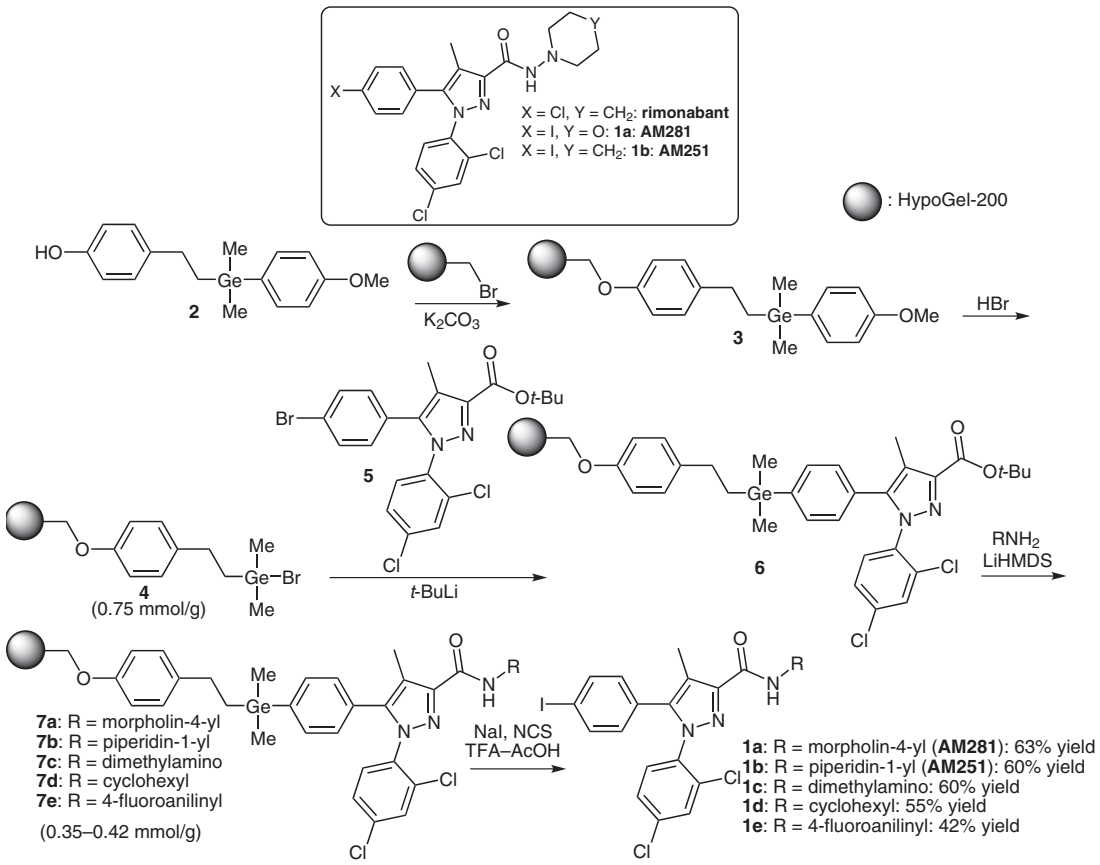
Parallel Solid-Phase Synthesis of Iodinated Analogues of Rimonabant



Significance: A novel method for the parallel solid-phase synthesis of iodinated analogues of the CB_1 receptor inverse agonist rimonabant was described. HypoGel-bound 1,5-diarylpyrazole *tert*-butyl ester **6** was prepared by employing HypoGel-bound gelmanium bromide **4** via transmetalation. Parallel amidation of **6** with hydrazines and amines gave HypoGel-bound 1,5-arylpyrazolyl hydrazides/amides **7a**–**e**. Cleavage of the Ge linker with concomitant *ipso*-iodination afforded iodinated rimonabant analogues **1a**–**e** (5 examples, 42–63% yield, 1–6 h).

Comment: Rimonabant (marketed as Acomplia) is a CB_1 receptor inverse agonist first approved for the treatment of obesity by European Medicines Agency in 2006, and then withdrawn from the market in 2008 following the emergence of psychiatric disorders among patients. Various ^{11}C-labeled, ^{18}F-labeled, and $^{123/124}I$-labeled rimonabant derivatives (e.g., **1a**: [^{123}I] AM281 and **1b**: [^{123}I] AM251) have proved to be viable for positron emission tomography (PET) and single photon emission computerized tomography (SPECT) imaging of central nervous system (CNS) activity.

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Category

Polymer-Supported Synthesis

Key words

solid-phase synthesis

HypoGel

germane linker

rimonabant