Parallel Solid-Phase Synthesis of Iodinated Analogues of Rimonabant

Significance: A novel method for the parallel solid-phase synthesis of iodinated analogues of the CB₁ receptor inverse agonist rimonabant was described. HypoGel-bound 1,5-diarylpyrazole tert-butyl ester 6 was prepared by employing HypoGel-bound germanium bromide 4 via transmetalation. Parallel amidation of 6 with hydrazines and amines gave HypoGel-bound germanium 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 CB₁ receptor inverse agonist first approved for the treatment of obesity by European Medicines Agency in 2006, and then withdrawn from the market in 2008 following the emergence of psychiatric disorders among patients.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 ¹¹C-labeled, ¹⁸F-labeled, and ¹²³/¹²⁴I-labeled rimonabant derivatives (e.g., 1a: [¹²³I] AM281 and 1b: [¹²³I] 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.