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Short Research Article

Synthesis of two isotopically labeled 5-HT_{1B} antagonists†

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Introduction

Serotonin (5-HT) is a neurotransmitter, and dysfunctions of its transmission have been implicated in a large number of disease states including migraines, anxiety, depression, and obesity.[1] 5-HT_{1B} antagonists have been suggested as potential treatments for depression and anxiety and have been shown to be effective in animal models of these disease states.[2] During development of 5-HT_{1B} antagonists, C-14 labeled AR-A000002 and tritium labeled M-549865 were required and their syntheses will be discussed herein.

Results and discussion

M-549865 was required in tritium labeled form for use in internal studies with a specific activity >20 Ci/mmol. Exchange methodology using several catalysts was probed using deuterium gas (500 mbar) in CH_2Cl_2 (Scheme 1).[3] Complex product mixtures were obtained from these exchange reactions, and the products and isotopic incorporation of the products varied considerably with catalyst. With catalyst **5**, two peaks were observed in addition to M-549865 by the LC/MS; those peaks' retention time and mass spectra were consistent with *cis* and *trans* **2** which could have arisen by reduction of the *p*-diamino ring to the corresponding diaminocyclohexane. Furthermore, investigation of the peak due to M-549865 showed a mixture of compounds with *m/Z* of parent, parent +2 and parent +4. We hypothesized that the M+2 compound resulted from reduction of chromenone to the chromanone and M+4 from further reduction to the chromanol. Since these impurities would consume a considerable amount of tritium gas in a non-productive manner, we decided to investigate alternate catalysts. Attempted exchange with two other catalysts and Crabtree's catalyst gave results similar to those obtained with **5**.

Reaction of M-549865 with *N*-iodosuccinimide in neat TFA gave iodide **1** and tritiodehalogenation of **1** (2.3 mg of 5% Pd/C, 1.6 mg of **1** and 950 mCi of $^3H_2$) proceeded cleanly to afford 24 mCi of [^{3}H]M-549865 in 79% radiochemical purity. Purification gave 17 mCi in 99% radiochemical purity with a specific activity of 21 Ci/mmol (Scheme 2). ^{3}H NMR confirmed the site of labeling.

The synthesis of [^{14}C]AR-A000002 has been previously reported by[^{14}C]cyanation of 1-iodo-4-morpholinebenzene.[4] We used a similar route (depicted in Scheme 3) to give the HBr salt of [^{14}C]AR-A000002 in 29% radiochemical yield.

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3. For examples of T-H exchange reactions see Garman RN, Hickey MJ, Kingston LP, McAuley B, Jones JR, Lockley WJS, Mather AN, Wilkinson DJ. *J Label Compd Radiopharm* 2005; **48**: 75 and references therein.
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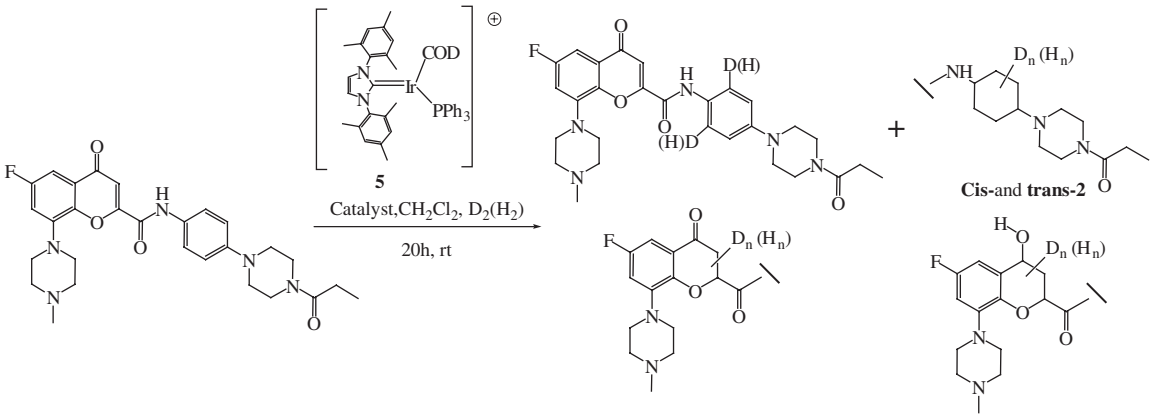
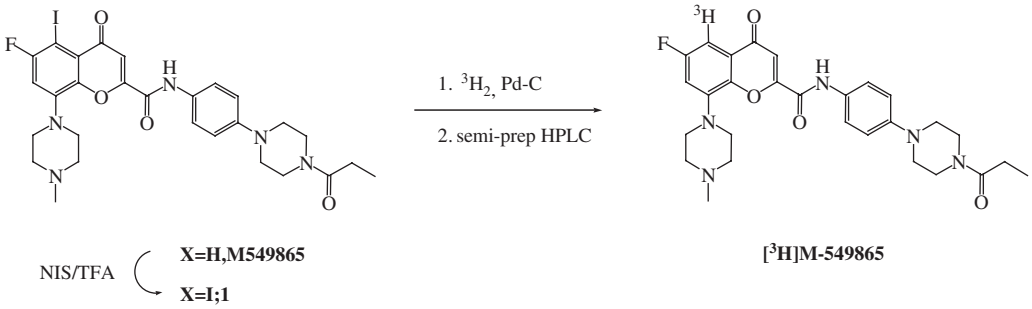
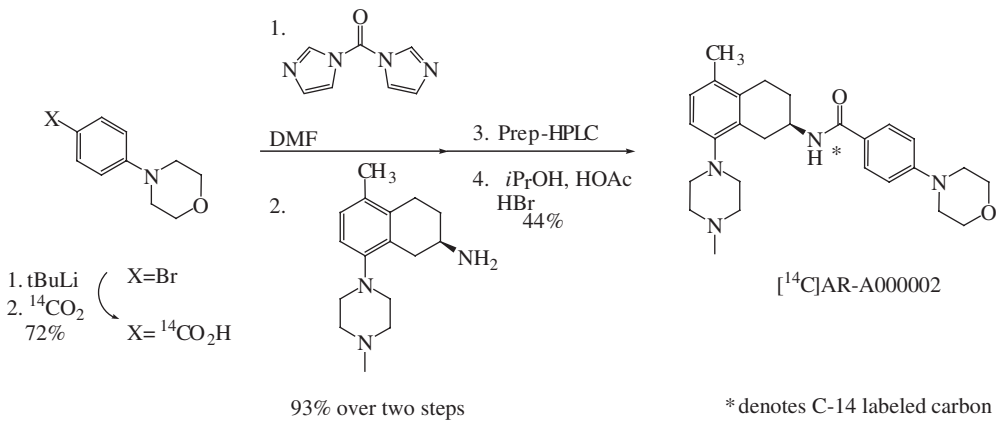


Scheme 1



Scheme 2



Scheme 3

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