Note

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Radiosynthesis of [^{3}H]-ABP688 using [^{3}H]-methyl nosylate: a non-volatile alternative methylating agent

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Tritiated ABP688 was synthesized from desmethyl ABP688 with [^{3}H]-methyl nosylate in high radiochemical yield. The results demonstrate that [^{3}H]-methyl nosylate is a good alternative methylating agent for radiosynthesis.

Keywords: tritiation; radiosynthesis; methylation; mGlu5 receptor antagonist

Introduction

ABP688 (**1**,3-((6-methylpyridin-2-yl)ethynyl)cyclohex-2-enone *O*-methyl oxime, Figure 1) was reported as a selective and high affinity ligand for the mGlu5 receptor and was proposed to act as a negative allosteric modulator.[1] Tritiated ABP688 was proposed to be useful for receptor occupancy and other studies in drug discovery programs at Wyeth. The radiosyntheses of ABP688, in both tritiated and carbon-11 forms, have been reported using radiolabeled iodomethane with desmethyl ABP688 (**2**,3-((6-methylpyridin-2-yl)ethynyl)cyclohex-2-enone oxime).[1,2] However, a better radiosynthesis strategy was warranted because the existing reactions were carried out at high temperature and iodomethane is a volatile reagent. Methyl nosylate (Methyl 4-nitrobenzenesulfonate) was investigated because it is a non-volatile methylating reagent and tritiated methyl nosylate is commercially available.[3] Herein, we report our results on the preparation of [^{3}H]-ABP688 using tritiated methyl nosylate.

Results and discussion

In our study, desmethyl ABP688 (**2**) was deprotonated with potassium bis(trimethylsilyl)amide (KHMDS), and then treated with methyl nosylate at room temperature. ABP688 was obtained with excellent yield after silica gel flash chromatography. Interestingly, very high *E/Z* isomer ratio (12:1) was obtained under the new reaction conditions, while the *E/Z* isomer ratio of the starting material was about 8:1. The *E/Z* ratios of the ABP688 and desmethyl ABP688 were measured by HPLC UV area percent at 220 nm (major isomer undetermined). It was observed that excess KHMDS did not adversely affect the reaction or the product, but changed the excess starting material *E/Z* ratio to about 1:1 (by LC/MS mass chromatogram area integration). The obtained ABP688 *E/Z* mixture was tested in the binding assay and performed very well. With the success of the cold run, [^{3}H]-ABP688 (**4**) was prepared using tritiated methyl nosylate (**3**) in a similar manner (Figure 2). Excellent radiochemical yield (90%) and purity (>98%) were obtained, whereas the yield was not provided in the previously reported [^{3}H]-ABP688 synthesis. This study clearly demonstrated that methyl nosylate is a good, non-volatile methylating agent. It is especially beneficial in the field of radiosynthesis for avoiding personnel exposure and reducing emissions of radioactive material. Moreover, the obtained [^{3}H]-ABP688 *E/Z* isomer ratio was about 22:1 (by radio HPLC area percent, major isomer undetermined). The highest reported *E/Z* isomer ratio for preparation of radiolabeled ABP688 was 10:1.[1]

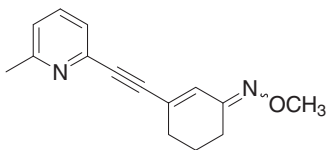

Figure 1. Structure of ABP688 (**1**).

Experimental

General: Radioactivity was measured with a Wallac 1450 Microbeta Trilux. UV, radiochemical purity and Mass spectra were obtained by LC/MS (Shimadzu LCMS 2010EV with an IN/US β-Ram model 4 radioflow detector). Aldrich 200–400 mesh 60 Å silica gel was used for column chromatography. All reactions were done under a nitrogen atmosphere with anhydrous solvents. Tritiated methyl nosylate was obtained from Perkin Elmer (100 mCi in 5 mL toluene solution, 75 Ci/mmol). Desmethyl ABP688 and ABP688 reference material were prepared by a Wyeth authorized vendor. All other reagents and solvents were obtained from standard commercial sources and used without additional purification.

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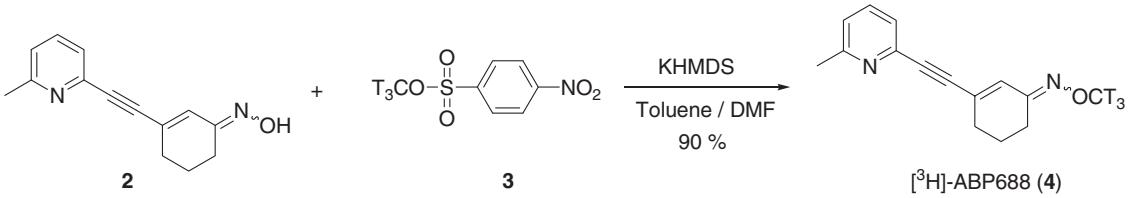

Figure 2. Synthesis of [^{3}H]-ABP688 (**4**) using [^{3}H]-Methyl Nosylate (**3**).

3-((6-Methylpyridin-2-yl)ethynyl)cyclohex-2-enone *O*-methyl oxime (ABP688, 1)

In a 10 mL pear flask, desmethyl ABP688 (12.5 mg, 0.055 mmol) was dissolved in DMF (1 mL) to give a colorless solution. KHMDS (0.5 M in toluene, 0.11 mL, 0.055 mmol) was added. After 15 min, methyl nosylate (3 mg, 0.014 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, and the residue purified by flash chromatography with 10% EtOAc/toluene to give ABP688 (3.4 mg, quantitative). The material was confirmed by comparison to the reference material with LCMS (Nucleosil 100-3 C18 HD column, 150 × 4.6 mm; mobile phase A: 5% ACN/H_2O, mobile phase B: 100% ACN; 50% B to 95% B over 15 min, 1 mL/min, 40°C; t_R = 6.5 and 7.2 min).

[^{3}H]-3-((6-Methylpyridin-2-yl)ethynyl)cyclohex-2-enone *O*-methyl oxime ([^{3}H]-ABP688, 4)

In a 50 mL pear flask, methyl nosylate [methyl-^{3}H] (100 mCi/5 mL in toluene) and desmethyl ABP688 (25 mg/100 mL solution in DMF, 4.85 mL, 5.34 μmol) were combined to give a colorless solution. KHMDS (0.5 M in toluene, 10.68 μL, 5.34 μmol) was added. After 1 h, additional potassium bis(trimethylsilyl)amide (0.5 M in toluene, 10.68 μL, 5.34 μmol) was added to ensure complete consumption of tritiated methyl nosylate. The reaction mixture was stirred at room temperature for 4 h and then concentrated *in vacuo*. The residue was purified by flash chromatography with 10% EtOAc/toluene to give [^{3}H]-ABP688 (90.2 mCi, 90%). Specific activity (84.9 Ci/mmol) was determined by MS. Chemical purity and radiochemical purity were determined to be greater than 98% by HPLC (same method as the cold run with radioflow detector).

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