Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 319-327 (1998)

THE SYNTHESIS OF SEVERAL TRITIATED NON-NUCLEOSIDE, HIV-1 REVERSE TRANSCRIPTASE INHIBITORS.

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Summary

The synthesis of three tritiated reverse transcriptase inhibitors is described herein. These compounds contained the benzoxazole ring linked to a 2-pyridinone ring by an aminomethylene group. The tritiated compounds were synthesized by hydrogenolysis of bromobenzoxazole precursors. The final tritiated compounds had specific activities ranging from 3-10 Ci/mmol.

Keywords: HIV-1, reverse transcriptase inhibitors, reductive debromination, tritium NMR, L-696,040, L-697,639, L-697,661.

Introduction

Because of the rapid spread of AIDS, caused by the human immunodeficiency virus type 1 (HIV-1), a large effort has been directed towards finding an effective antiviral drug to treat this disease (1). There are several unique viral enzymes that are necessary for viral propagation and these have become potential targets for therapy against HIV-1 (2). One enzyme crucial for the virus to replicate is reverse transcriptase (RT), a DNA polymerase responsible for the transcription of single stranded viral RNA into double stranded DNA for incorporation into the host chromosomes. Because RT is essential for viral replication it is an attractive target for drug development (3).

At present there are nucleoside reverse transcriptase inhibitors (4), such as 3'-azidothymidine (AZT) and dideoxyinosine (ddI), which are used to treat HIV-1 infections. Use of these compounds however, leads to resistant viral strains (5) and side effects (6) which are brought on by the concomitant inhibition of host DNA synthesis. Because of these problems, efforts have focused on identifying selective, non-nucleoside HIV-1 RT inhibitors.

Among the known classes of non-nucleoside HIV-1 RT inhibitors (3), the 2-pyridinone series (7) are examples developed at Merck. During the course of their development, it became necessary to radiolabel several of these compounds for preliminary absorption, distribution, metabolism and excretion (ADME) studies. Since high specific activity material was desired, we chose to label these compounds with tritium (8).

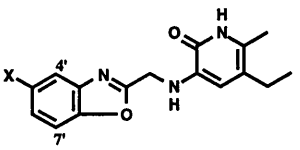
CCC 0362–4803/98/040319–09$17.50

Received 28 October 1997
Revised 9 December 1997

Discussion

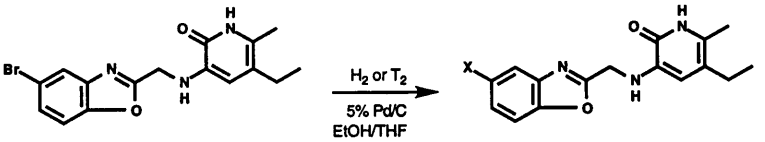
The tritiated compounds that were synthesized are shown in Figure 1. Among several options considered, we chose to synthesize precursors **1c**, **2c** and **3c** containing the brominated benzoxazole moiety so that tritium could be incorporated in the final synthetic step via reductive debromination.

Figure 1



Substituent		
L-696,040	none	1a, X=H 1b, X=T 1c, X=Br
L-697,661	4',7'-Cl_2	2a, X=H 2b, X=T 2c, X=Br
L-697,639	4',7'-Me_2	3a, X=H 3b, X=T 3c, X=Br

Equation 1: Synthesis of L-696,040 via bromobenzoxazole 1c.



1c

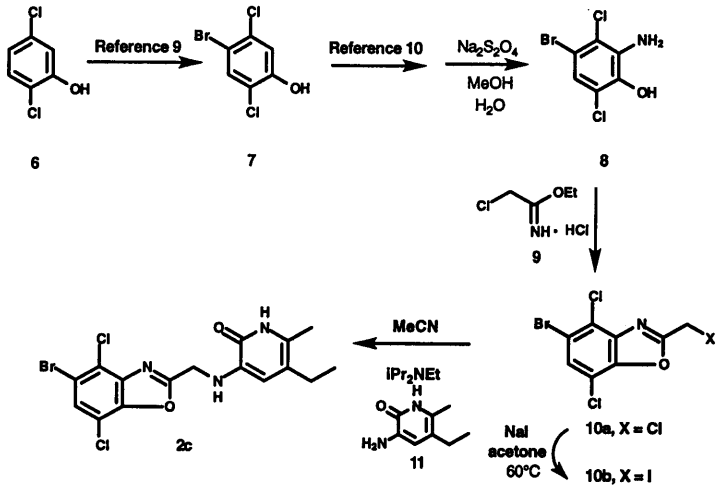
L-696,040
1a, X=H
1b, X=T

In the reverse transcriptase program, the initial compound labelled was L-696,040, **1a**, shown in equation 1. As part of this development work several analogs of L-696,040 had been synthesized, and the bromo analog **1c** was available (9). To test the feasibility of using these brominated precursors, catalytic hydrogenation conditions were developed for the conversion of **1c** to **1a**. As shown in equation 1, catalytic hydrogenation of **1c** using 5% Pd/C as the catalyst in EtOH:THF gave **1a**. The aromatic region of the ^1H NMR of the crude reaction mixture was identical with the ^1H NMR of the authentic sample. This hydrogenation reaction went to completion better in a 1:1 mixture of EtOH/THF than in THF alone. The corresponding tritiation reaction was carried out for 4 hours at room temperature, and a ^1H decoupled ^3H NMR of the crude reaction mixture showed a singlet at δ7.4. Purification gave**1b** with a radiochemical purity of 99% and a specific activity of 10 Ci/mmol.

Because brominated benzoxazole **1c** was successfully converted to [^3H]L-696,040, as the need arose to label other compounds in this class, the requisite brominated benzoxazoles had to be synthesized. We next turned our attention to [^3H]L-697,661, **2b**. This required the

synthesis of **2c** for the precursor. This introduced the potential problem of selective reduction of the bromine in preference to the chlorine, but previous work in our laboratory had shown that a chlorobenzoxazole similar to L-697,661 required somewhat harsher reaction conditions than bromobenzoxazoles for reduction of the chlorobenzoxazoles.

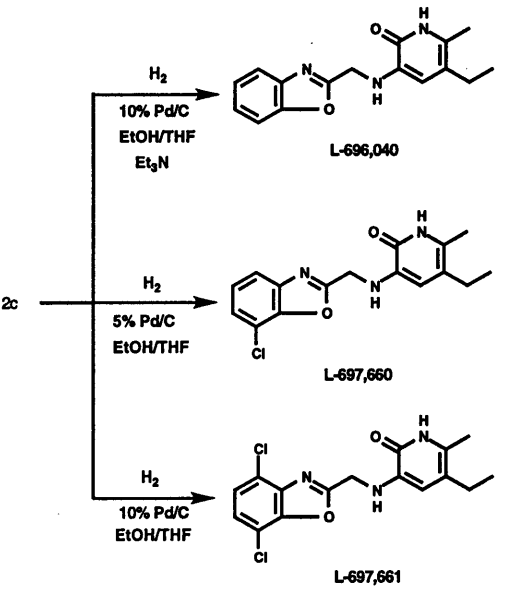
Equation 2: Synthesis of trihalobenzoxazole 2c.



As shown in equation 2, commercially available 2,5-dichlorophenol **6** was chosen as the starting material for **2c**. Several procedures were attempted for the initial bromination, and the best results were obtained using Br_2/I_2 (10). Nitration (11) and reduction of **7** gave aminophenol **8**, which could be purified or used directly in the cyclization step. Reaction of aminophenol **8** with ethyl (chloroimino)acetate hydrochloride, **9**, gave cyclized chloromethylbenzoxazole **10a**. This material could be either used directly or converted to iodide **10b** for the coupling reaction. In either case, coupling with aminopyridinone **11** gave the desired **2c.**

Model reduction reactions were then carried out to explore the conditions necessary for the reductive debromination of **2c**. These are shown in equation 3. The reaction system used was 5% or 10% Pd/C in THF/EtOH. Not surprisingly, as shown in equation 3, care had to be taken to avoid loss of chlorine (12). In the presence of triethylamine, using 5% or 10% Pd/C and the solvent EtOH/THF at room temperature, complete overreduction occurred within one hour to give L-696,040 as the major product, as determined by HPLC coelution with an authentic standard. When 5% Pd/C was used without triethylamine, L-697,661 was formed, but the major product was L-696,660 (coelution with an authentic standard). When 10% Pd/C was used without triethylamine, after three hours at room temperature, integration of the HPLC chromatogram showed 80% of L-697,661 had formed with 14% of the unreacted starting material remaining. Longer reaction times consumed the starting material but overreduced compounds were also formed.

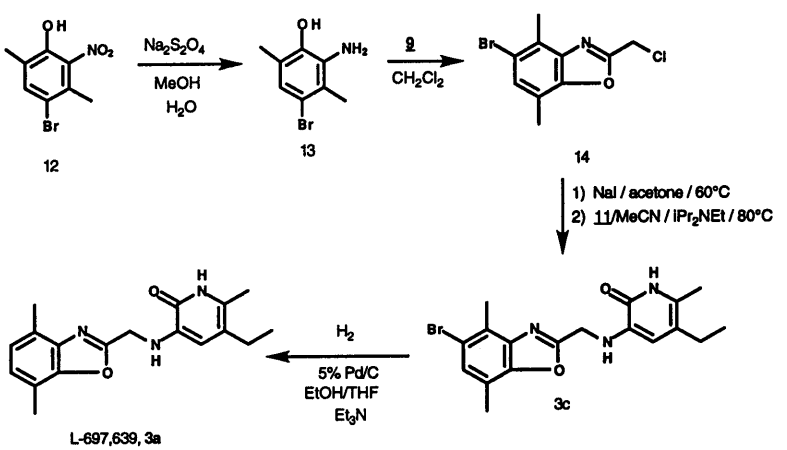
Equation 3: Synthesis of L-697,661 from trihalobenzoxazole 2c.



Repeating this reduction procedure with tritium gas and 10% Pd/C without triethylamine gave [^{3}H]L-697,661. The ^{1}H decoupled ^{3}H NMR of the crude material showed a singlet at δ7.4, and the ^{1}H coupled ^{3}H NMR showed a doublet with J_{HT}=9 Hz, indicating a single tritium atom had been incorporated into the aromatic ring. After purification, this material had a radiochemical purity of 99% and a specific activity of 3 Ci/mmol determined by mass spectrometry and 4-6 Ci/mmol determined by UV spectrometry.

The precursor for [^{3}H]L-697,639, **3c**, was synthesized in a similar fashion as shown in equation 4. As in the previous routes, nitrophenol **12** (13) was converted to **3c**. Model reductions using hydrogen gas were used to optimize the conditions for the reduction reaction.

Equation 4: Synthesis of L-697,639 via bromobenzoxazole 3c.



Optimal conditions were found to be 5% Pd/C in EtOH/THF with triethylamine present and a reaction time of one hour. When the tritiation reaction was carried out using these conditions, HPLC purification gave [^{3}H]L-697,639, which had a radiochemical purity of 99% and a specific activity of 6 Ci/mmol as measured by mass spectrometry or UV spectrometry.

Use of these various brominated benzoxazoles proved to be a useful and general method for tritium labelling of various reverse transcriptase inhibitors.

Experimental

^{1}H NMR were recorded using a Varian Infinity-300 spectrometer operating at 300 MHz. The samples were dissolved in $CDCl_3$ with tetramethylsilane as the internal reference or in D_2O with 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt (DSS) as the internal reference. ^{3}H NMR were recorded using a Varian VXR 400S spectrometer operating at 426.6 MHz with a tritium probe tuned to tritium. Samples were placed in a 5mm teflon sleeve which was then secured in a 10mm glass NMR tube. Tritium chemical shifts were measured by ghost-referencing from internal non-tritiated TMS. Melting points were measured using a Thomas Hoover capillary melting point apparatus. Analytical and preparative HPLC were carried out using a Waters 600E Powerline Multi Solvent Delivery System with 100 µL heads, a Rheodyne 7125 injector and a Waters 990 Photodiode Array Detector. A Gilson FC203 Microfraction collector was used for sample collection. The acetonitrile used for the HPLC analyses was Fisher Optima grade. The HPLC radiodetector used was a Beckman 171 Radioisotope detector with a Beckman 110B solvent delivery system and Beckman Ready Flow III liquid scintillation cocktail was used. A Waters C-18 µ Bondapak column, 3.9 X 150 or 300 mm was used for HPLC analysis and purification of the tritiated compounds. Solutions of radioactivity were concentrated using a Jouan vacuum centrifuge. Calibration curves and chemical concentrations were determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer. Sample radioactivities were determined in an LKB Wallac 1410 liquid scintillation counter. The identity of labelled compounds were determined by HPLC coelution with authentic compounds. Reagents were purchased from Aldrich Chemical Co. unless otherwise noted.

3-[2-benzoxazolylmethyl]amino-5-ethyl-6-methyl-1H-pyridine-2-one (1a):
A solution of 6 mg (15µmol) of **1c** (8) in 2 mL of anhydrous1:1 EtOH/THF was treated with 6 mg of 5% Pd/C and the mixture was degassed and stirred under hydrogen (balloon) overnight at room temperature. The reaction mixture was filtered through celite to remove the catalyst, and concentrated to give **1a**.

[^{3}H]-3-[2-benzoxazolylmethyl]amino-5-ethyl-6methyl-1H-pyridine-2-one (1b):
The tritiation of **1c** was carried out by NEN using the same procedure as described for **1a** with a four hour reaction time. The ^{1}H decoupled ^{3}H NMR of the crude reaction mixture showed a singlet at δ7.4 indicating a single tritium atom had been incorporated into the aromatic ring. A portion of the crude product mixture containing **1b** was purified by HPLC [Waters C-18 µBondapak, 3.9 x 300 mm, 40:60 Acetonitrile:H_2O (0.1% TFA), 1 mL/min, 254 nm, t_R=12 minutes] to yield **1b** with a radiochemical purity of 98.9% and a specific activity of 10.4 Ci/mmol.

2-Amino-4-Bromo-3,6-dichlorophenol (8): The nitration reaction of **7** (9) was carried out according to the literature procedure (10) to give 4-bromo-2,5-dichloro-6-nitrophenol. A clear yellow solution of 1 g (3.49 mmol) of 4-bromo-2,5-dichloro-6-nitrophenol in 34 mL of methanol at room temperature was treated with a solution of 4.26 g (24.5 mmol) of $Na_2S_2O_4$ in 14 mL of H_2O via addition funnel over approximately 10 minutes, giving a yellow opaque mixture slightly warm to the touch. HPLC analysis at 10 minutes (Zorbax RX C-8, 4.6 x 250 mm, 52% acetonitrile:H_2O (0.1% TFA), 1.5 mL/min, 210 nm) indicated no unreacted 4-bromo-2,5-dichloro-6-nitrophenol. After stirring 20 minutes at room temperature, the white opaque mixture was concentrated via rotary evaporation, giving a white gelatinous material. This was triturated several times with methylene chloride and then decanted. The methylene chloride layers were combined, dried ($MgSO_4$), filtered and concentrated to give 593 mg (66%) of **8** as a white solid which was the sole chemical component by ^1H NMR (δ, $CDCl_3$): 7.02 (1H, s), 5.54 (1H, s), 1.61 (2H, br. s). (The signals at δ5.54 and δ1.61 disappeared when shaken with D_2O); MS m/e 258 (M+2, 100%) This material could be purified by radial chromatography (hexane to 20% ether/hexane) but was generally used without purification.

Ethyl chloroimine acetate hydrochloride (9): In a 100 mL three neck flask with a magnetic stirrer and a thermometer, a clear colorless solution of 4.2 mL (66.3 mmol) of chloroacetonitrile and 4.3 mL (73.8 mmol) of a freshly opened bottle of absolute ethanol, in 50 mL of anhydrous ether was cooled in an acetone/ice bath to -10°C and HCl(g) was bubbled through the reaction. The temperature rose to 25-30°C and then began to drop. When the temperature fell below 20°C (about 10 minutes) the HCl(g) addition was stopped. The resulting clear colorless solution was cooled in the freezer, resulting in formation of a white precipitate. The precipitate was collected by filtration and rinsed with cold ether. The filtrate was cooled as above and a second crop of crystals was obtained. A third crop was possible but was not collected. The product was dried by vacuum in the presence of KOH pellets and P_2O_5 to give 7.53 g from the first crop and 1.30 g from the second crop (84%) as white solids: ^1H NMR (δ, d_6 DMSO): 4.66 (2H, d, J=0.5Hz), 4.5 (2H, q, J=7Hz), 1.37 (3H, t, J=7Hz); mp 89-90.

2-Chloromethyl-5-bromo-4,7-dichlorobenzoxazole (10a): A solution of 520 mg (2.02 mmol) of **8** in 35 mL of methylene chloride was treated with 573 mg (3.6 mmol) of **9** and the resulting slurry was stirred under argon overnight at room temperature. TLC analysis of the reaction mixture (10% ether/hexane) showed some starting material (R_f 0.08) along with the desired product (R_f 0.33). The mixture was filtered through a celite pad and concentrated to give 823 mg of a yellow solid. This material was purified by radial chromatography (hexane to 5% ether/hexane) to give 467 mg (73%) of **10a** as a white solid: ^1H NMR (δ, $CDCl_3$): 7.70 (1H, s), 4.79 (2H, s); mp 106.5-108. MS m/e 316 (M+1, 100%).

3-[2-(5-Bromo-4,7-dichlorobenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (2c): A 2 mL Wheaton reaction vial was charged with 200 mg (0.63 mmol) of **10a**, 96 mg (0.63 mmol) of **11** (7c), 143 µL (3.57 mmol) of diisopropyl ethyl amine and 900 µL of acetonitrile. The yellow slurry was placed in an 80-85°C oil bath and heated overnight giving a dark brown liquid containing a tan precipitate. The reaction mixture was cooled to 0°C, filtered

and the filter cake was rinsed with cold acetonitrile. Drying the tan solid under vacuum gave 185 mg (68%) of **2c** as a tan solid: ^{1}H NMR (δ, d_6 DMSO): 11.27 (1H, s), 8.01 (1H, s), 6.33 (1H, s), 5.91 (1H, t, J=6.1 Hz), 4.67 (2H, d, J=6.1 Hz), 2.24 (2H, q, J=7.3 Hz), 2.04 (3H, s), 0.98 (3H, t, J=7.3 Hz). With a D_2O shake, the δ11.27 and δ5.91 signals disappear and the δ4.67 doublet becomes a singlet; mp 214-217; MS m/e 432 (M+1, 100%).

3-[2-(4,7-Dichlorobenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (2a): A mixture of 1.1 mg of **2c** and 1.1 mg of 10% Pd/C in 200 μL of anhydrous THF and 200 μL of absolute ethanol was degassed and stirred under hydrogen (balloon) for 3 hours at room temperature. HPLC analysis [40:60 acetonitrile:H_2O (0.1% TFA), 1 mL/min, 254 nm, Waters C-18 μBONDAPAK, 3.9mm X 150mm] shows a small quantity of **2c** (t_R=23 minutes) along with **2a** (t_R=11.5 minutes). The reaction mixture was filtered through a pad of celite, rinsed with methanol and concentrated to dryness.

[^{3}H]-3-[2-(4,7-Dichlorobenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (2b): The tritiation reaction was carried out at New England Nuclear (NEN) following the above procedure. Purification of a portion of the crude reaction mixture by HPLC [50:50 Acetonitrile:H_2O(0.1M NH_4HCO_3),1 mL/min, Waters C-18 μBondapak, 3.9x300mm, 254 nm, t_R = 10 minutes] yielded 20 mCi of [^{3}H]L-697,661 with a specific activity of 6 Ci/mmol, as measured by UV spectrometry versus a calibration curve at 254 nm. This material was also analyzed by electron ionization mass spectrometry and was found to have 11 % tritium enrichment. The ^{1}H decoupled ^{3}H NMR of the crude [^{3}H]L-697,661 showed a singlet at δ7.44 and the ^{1}H coupled ^{3}H NMR showed a doublet with J_{HT}=9.02Hz, indicating a single tritium atom had been incorporated into the aromatic ring.

2-Chloromethyl-5-bromo-4,7-dimethylbenzoxazole (14): Synthesized as **10a** starting with 250 mg (1.02 mmol) of **12** (13) to give 300 mg of **13** and 252 mg of **14**. Purification by column chromatography (2% MeOH/$CHCl_3$) gave 105 mg (28%) of **14** as a white solid: ^{1}H NMR (δ, CD_3OD): 7.06 (2H, s), 4.77 (2H, s), 2.57 (3H, s), 2.50 (3H, s).

3-[2-(5-Bromo-4,7-dimethylbenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (3c): A mixture of 105 mg of **14** (0.38 mmol) in 10 mL of acetone and 217 mg of NaI (1.44 mmol) was heated to reflux for 4 hours. The mixture was cooled to room temperature, diluted with ether, filtered and concentrated to dryness. Purification by flash chromatography (10:1 hexane:ether) gave 258 mg of 2-iodomethyl-5-bromo-4,7-dimethylbenzoxazole as an off white solid. This was converted to **3c** using the procedure for the conversion of **10b** to **2c**. The resulting solid was purified using flash chromatography (5% MeOH/CH_2Cl_2) to give 32 mg (12%) of **3c** as a tan solid: ^{1}H NMR (δ, $CDCl_3$): 11.05 (1H, br. s), 7.30 (1H, s), 6.47 (1H, s), 5.39 (1 H, t, J=6.4 Hz), 4.60 (2 H, d, J= 6.4 Hz), 2.59 (3H, s), 2.36 (2H, q, J=7.5 Hz), 2.20 (3H, s), 1.09 (3H, t, J=7.5 Hz).

[2-(4,7-Dimethylbenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (3a): A mixture of 1 mg of **3c** (2.6 μmol) in 400 μL of 1:1 EtOH:THF with 1 mg of 5% Pd/C and 1 equivalent of Et_3N was degassed and stirred under 1 atmosphere (balloon) of hydrogen gas. HPLC analysis of the reaction (Waters C-18 μBondapak, 3.9 x 300 mm, 40% acetonitrile:0.1M NH_4HCO_3 in H_2O, 1 mL/min, 254 nm) after 1 hour showed no starting material (t_R=19.7 minutes) but a peak with a retention time of 10 minutes which coeluted with an authentic standard of L-697,639. The reaction was filtered through celite, rinsed with ethanol and concentrated to give an off-white residue.

[^{3}H]-3-[2-(4,7-Dimethylbenzoxazolyl)methyl]amino-5-ethyl-6-methyl-1H-pyridin-2-one (3b): The tritiation reaction was carried out at Chemsyn Science Laboratories using the above procedure. The reaction was run for a total of 5 hours to give 46 mCi of crude [^{3}H]L-697,639 with a radiochemical purity of 21%. Approximately half of the activity was concentrated to near dryness, dissolved in 75 μL of EtOH and purified by HPLC (Waters C18 μBondapak, 3.9x300 mm, 1 mL/min, 45% acetonitrile:H_2O (0.1 M NH_4HCO_3), 254 nm, t_R=12.5 minutes). Several of the fractions containing the purest material were pooled, concentrated and diluted with ethanol to give 565 μCi of [^{3}H]L-697,639 with a radiochemical purity of 99% and a specific activity of 6 Ci/mmol, as measured versus a calibration curve in ethanol at 254 nm. This material was also analyzed by electron ionization mass spectrometry and was found to have 22% tritium enrichment.

Acknowledgment

The authors wish to thank John Lola (NEN/Dupont) for conducting the tritiation reactions for [^{3}H]L-697,661 and [^{3}H]L-696,040 and for obtaining the ^{3}H NMR spectra of [^{3}H]L-697,661; Bob Roth (Chemsyn Science Laboratories) for conducting the tritiation reaction for [^{3}H]L-697,639 and Hari Ramjit (Medicinal Chemistry, Merck) for conducting the mass spectral analyses of [^{3}H]L-697,639 and [^{3}H]L-697,661.

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