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Synthesis of [^{3}H]ABT-518, a matrix metalloproteinase inhibitor (MMPI) labeled in the phenyl rings

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A novel matrix metalloproteinase inhibitor, ABT-518, [*S*-(*R, *R**)]-*N*-[1-(2, 2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoromethoxy)-phenoxy]phenyl]sulfonyl]ethyl]-*N*-hydroxyformamide, was labeled with tritium in two phenyl rings in a seven-step synthesis. The overall radiochemical yield of [^{3}H]ABT-518 in seven steps starting from 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]benzene was 6.2% with the radiochemical purity of 99.4%.**

Keywords: matrix metalloproteinase inhibitors; MMPI; ABT-518; 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]benzene

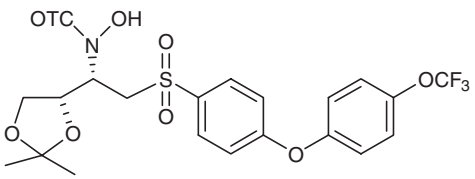
Introduction

The matrix metalloproteinases (MMPs) also known as matrixins play a vital role in remodeling and maintenance of normal tissue in biological processes. These are the family of enzymes containing zinc that degrade the extracellular matrix.[1] The disruption in a balance between the active enzymes and their natural inhibitors accelerates the destruction of the connective tissue, which is associated with diseases such as arthritis, cancer, multiple sclerosis, and cardiovascular diseases.[2] There are more than 20 different enzymes known to be in the MMP family and more are being discovered and characterized as MMPs.[1] The potential therapeutic agents that inhibit the MMP activity are referred to as matrix metalloproteinase inhibitors (MMPIs).

Our cancer research team had discovered two MMPIs from the retrohydroximate family, namely ABT-770 and ABT-518 (Figure 1). Both of these compounds are potent inhibitors of MMP-2 (gelatinase A) and MMP-9 (gelatinase B), which are involved in tumor growth and metastasis. The replacement of the ether linkage of ABT-770 with a sulfone group led to a substantial increase in the activity against MMP-2 and MMP-9.[3] Furthermore, toxicity studies revealed that ABT-770 has a number of adverse effects caused by metabolite accumulation in tissues.[4] It was found out that ABT-518 had 200-fold greater MMP-9 potency with a larger estimated therapeutic window and good pharmacokinetic characteristics and was as efficacious as ABT-770 in pre-clinical models.[5] We previously reported a radiosynthesis of [^{14}C]ABT-770.[6] To support the pre-clinical evaluation of ABT-518, ADME studies in laboratory animals were undertaken, which required radiolabeled ABT-518. The seven-step synthesis of [^{3}H]ABT-518 starting from 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]benzene (**4**) employed halogenation/tritiodehalogenation to introduce tritium label into both aromatic rings.

Results and discussion

Our initial attempts to make [^{3}H]ABT-518 from unlabeled compound using Crabtree's catalyst introduced tritium in the formyl group of **2**, which was confirmed by tritium NMR. *In vitro* metabolism studies indicated that this label was labile. Crabtree catalyst-mediated tritium/hydrogen exchange was attempted on sulfone **4** and obtained the intermediate **3** with a poor yield of radioactivity.



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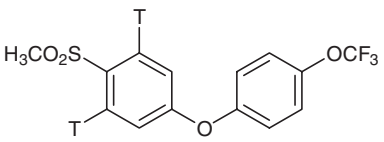

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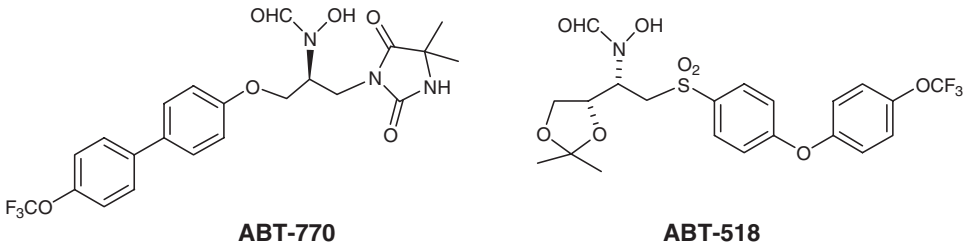
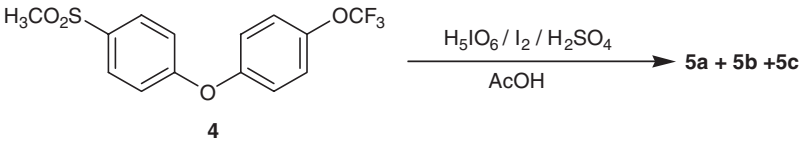


Figure 1. Chemical structures of MMPIs: ABT-770 and ABT-518.



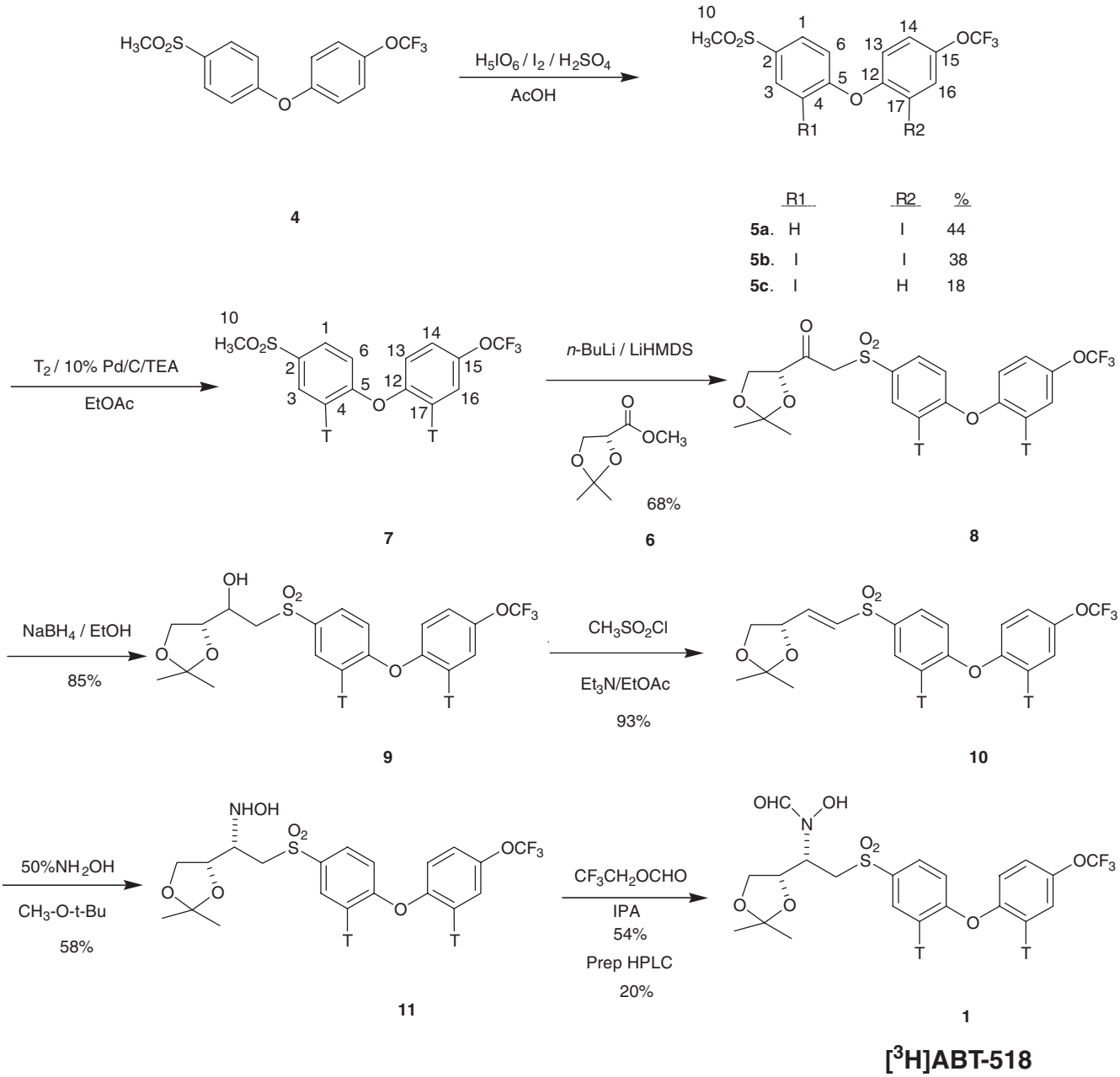
Scheme 1.

Our next approach was to prepare a halogenated precursor so that dehalogenation with tritium gas would give us access to a starting material with a tritium label in the aromatic core of the molecule. The halogenated precursor was prepared by the reaction of **4** with H_5IO_6 and I_2 in a mixture of AcOH and H_2SO_4 (Scheme 1).[7]

Proton NMR indicated that the major species, **5a,** had iodine *meta* to $-OCF_3$ (44%). The second most plentiful species (**5b**) contained two iodine atoms: the first iodine *meta* to the $-OCF_3$ group and the second iodine *meta* to the $-SO_2CH_3$ group (38%). The minor, **5c**, was a monoiodinated compound with the halogen *meta* to the $-SO_2CH_3$ group (18%). The mixture of **5a**–**c** was the key intermediate in the radiosynthesis of [^{3}H]ABT-518 (**1**). The general sequence of the synthesis is shown in the scheme. Thus, [^{3}H]ABT-518 (**1**) was synthesized by the catalytic dehalogenation of the mixture of iodo compounds **5a**–**c** in the presence of tritium gas, 10% Pd/C, and triethylamine in ethyl acetate to give 418 mCi of **7**. Both ^{1}H and ^{3}H-NMR indicated specific labeling consistent with reductive deiodination at the expected positions. Initially, the specific activity was lowered to approximately 800 mCi/mmol by mixing **7** with an unlabeled **7** in THF and was further lowered to approximately 500 mCi/mmol by mixing **8** with an unlabeled **8** in THF. The conversion of **7** to **8** was achieved by treating **7** at–78°C with 1.05 equivalents each of LiHMDS and *n*-butyllithium to generate the lithium anion, which was quenched with optically active 2,2′-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester **6** in THF.[8] To minimize the acetonide hydrolysis of **8** to form the diol, the reaction mixture was worked up with 10% CH_3COOH to yield 68% of **8**. Rapid reduction of **8** to alcohol **9** was achieved at room temperature (RT) by using sodium borohydride in ethanol and THF to give 85% of the alcohol **9**. To accomplish the dehydration of the alcohol **9** to vinyl sulfone **10**, alcohol **9** was treated with methanesulfonyl chloride and an excess of triethylamine at 0°C to give a 93% yield of vinyl sulfone products with **10** as the predominant isomer in a 1:10 *cis* to *trans* ratio. The 1,4-addition of hydroxylamine to the isomeric mixture of vinyl sulfone products was accomplished at a lower temperature by using 50% hydroxylamine solution, which proceeded with 5:1 selectivity in favor of the desired stereochemistry to give 58% of **11**. The desired isomer of **11** was purified by preparative high-performance liquid chromatography (HPLC) and was *N*-formylated to provide [^{3}H]ABT-518 (**1**). This was achieved by using 2,2,2-trifluoroethyl-formate as a formylating agent.[9] There is a kinetic competition between formylation on oxygen and nitrogen. The *N*-formyl isomer is favored thermodynamically. To enhance the rate of the interconversion of the *O*-formyl isomer to *N*-formyl isomer under the reaction conditions, a small amount of formic acid was added. The reaction medium was buffered with sodium formate to avoid acetonide hydrolysis of **11** to form a diol. The yield for this step was 54%. The overall radiochemical yield of [^{3}H]ABT-518 (**1**) after the HPLC purification was 6.2% (Scheme 2).

Experimental

All chemicals and solvents were reagent grade or better and purchased from commercial suppliers. They were used without further purification. Tritium gas was purchased from American Radiolabeled Chemicals, St. Louis, MO. IN/US Systems, Inc. TRI-SORBER (tritium manifold system) was used for the tritiation. 1-(Methylsulfonyl)-4-[4-(trifluoromethyl)phenoxy]benzene **4** was obtained from the Abbott process chemistry group. The identity of intermediates was confirmed by comparison with authentic samples supplied by the Abbott process chemistry group. Liquid scintillation counting was performed on LKB-Wallac 1214 Rack Beta 'Excel' counter. TLC plates were coated with Kieselgel 60 (0.25 mm, Merck) and were scanned for radioactivity with a Radiomatic RS chromatograph. The ^{3}H-NMR spectrum was recorded at 501 MHz and chemical shifts are reported in ppm (δ). Preparative HPLC on **11** was performed using Shimadzu LC system consisting of a Shimadzu SIL-10A autosampler, Shimadzu FRC-10A fraction collector, and two Shimadzu LC-8A pumps. Peak detection and chromatograms were obtained with a Shimadzu SPD-10A VP variable wavelength UV detector set at 210 nm and Shimadzu Ezchrom software. The compound **11** was analyzed using Hitachi L-7000 series analytical HPLC system consisting of an autosampler, a pump, a variable wavelength UV detector, and Packard A-500 liquid scintillation radioactivity flow detector (Packard Instruments, 0.5 mL flow cell, 3:1 ratio of Packard Ultima-Flo M scintillant to effluent). A Perkin Elmer 250 analytical HPLC system (Zorbax Rx-C8 column, 4.6 × 250 mm, 5 μm, UV at 220 nm, flow rate = 1 mL/min, 30% CH_3CN/0.1% H_3PO_4 to 90% CH_3CN/0.1%



Scheme 2.

H_3PO_4 over 15 min, hold at this concentration for 5 min, and back to the initial concentration in 1 min), an Applied Biosystems UV detector, and the same liquid scintillation radioactivity flow detector as above were used to analyze **7**, **9**, **10**, **11**, and **1**. Preparative HPLC on [^{3}H]ABT-518 (**1**) was performed using an Agilent 1100 series HPLC system. Peak detection and chromatograms were obtained with a Agilent variable wavelength UV detector set at 210 nm and Agilent Chemstation software. Fractions of the [^{3}H]ABT-518 (**1**) peak were collected using an Agilent fraction collector. [^{3}H]ABT-518 (**1**) was analyzed using an Agilent 1100 series HPLC system consisting of an Agilent variable wavelength UV detector set at 210 nm, Chemstation software, and the same Packard A-500 radiodetector as above.

Iodination of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]benzene (5a–c)

Into a mixture containing **4** (0.156 g, 0.5 mmol), H_5IO_6 (0.025 g, 0.11 mmol), and iodine (0.051 g, 0.2 mmol) was added a solution of concentrated sulfuric acid (0.5 mL) and water (0.3 mL) in acetic acid (1.5 mL). The resulting solution was heated at 90°C for 27 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water and brine solution (20 mL each). The solvent was removed on a rotary evaporator. The crude product obtained was purified by preparative silica gel plates (2 × 2000 μm, 20 × 20 cm, 60% pentane in ethyl acetate). The bands corresponding to the product were scraped and

extracted with ethyl acetate (4 × 45 mL). The solvent was removed on a rotary evaporator to give approximately 50 mg of a mixture of **5a–c** containing mono- and di-iodo aromatic substituted analogues as they were observed from ^{1}H and ^{13}C-NMR spectra.[10]

[^{3}H] - 1 - (methylsulfonyl) - 4 - [4 -(trifluoromethoxy)phenoxy]-benzene (7)

A mixture of iodo compounds **5a–c** (7.7 mg), 10% Pd/C (10.9 mg), triethylamine (100 μL), and ethyl acetate (2 mL) was placed in a 5 mL round-bottom flask. The flask was attached to the tritium manifold (TRI-SORBER) and degassed by freeze–pump–thaw. Tritium gas (0.063 mmol, 3.65 Ci) was introduced and the mixture was vigorously stirred at RT for 2.4 h. The excess gas was removed to a charcoal trap cooled in a liquid nitrogen bath, the catalyst was filtered, and the labile tritium was removed by three evaporations of methanol (10 mL each) to yield 418 mCi of **7**. HPLC analysis (t_R = 12.9 min) indicated the presence of **7** in 97% radiochemical purity. ^{1}H-NMR (501 MHz, CD_3OD): δ 7.95 (d, *J* = 8.9 Hz, 2H, *H*(*1*), *H*(*3*)), 7.37 (d, *J* = 8.9 Hz, 2H, *H*(*14*), *H*(*16*)), 7.20 (d, *J* = 8.9, 2H, *H*(*13*), *H*(*17*)), 7.17 (d, *J* = 8.9 Hz, 2H, *H*(*4*), *H*(*6*)), 3.11 (s, 3H, *CH*$_3$). ^{3}H-NMR (534 MHz, CD_3OD): δ 7.20 (^{3}H(*17*)), 7.17 (^{3}H(*4*)).

[^{3}H] - 1 - (2,2 - dimethyl - [1,3]dioxolan - 4 - yl) - 2 -[4-(4-trifluoromethoxy-phenoxy)-benzenesulfonyl] ethanone (8)

Into a solution of [^{3}H]-1-(methylsulfonyl)-4-[4-(trifluoromethoxy)-phenoxy]benzene (**7**, 210 mCi, ∼1 mg) and unlabeled **7** (102 mg, 0.31 mmol to give a specific activity of ∼0.8 Ci/mmol) in THF (3 mL) under N_2 at −78°C was added 1 M LiHMDS in THF (0.33 mL, 0.33 mmol) followed by 1.55 M *n*-BuLi in hexanes (0.22 mL, 0.33 mmol). The reaction mixture was stirred at −78°C for 2 h. A solution of 2,2′-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**6**, 0.060 g, 0.37 mmol) in 60 μL of THF was added to the reaction mixture and stirring was continued for 1 h. The TLC analysis (silica gel, 10% acetic acid in ethyl acetate) showed 60% of **8**. Additional 2,2′-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**6**, 0.01 g, 0.063 mmol) was added and the mixture was stirred at −78°C for 1.5 h. The reaction mixture was diluted with 10% CH_3COOH and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine solution (2 × 20 mL) and the solvent was removed on a rotary evaporator. The crude product was purified on preparative silica gel plates (2 × 2000 μm, 20 × 20 cm, 60% pentane in ethyl acetate). The bands corresponding to the product were scraped and extracted with ethyl acetate (4 × 45 mL). The solvent was removed on a rotary evaporator to give 142 mCi of **8** in 68% yield. TLC analysis (silica gel, 50% pentane in ethyl acetate, R_f ∼ 0.5) indicated radiochemical purity > 99%.

[^{3}H] - 1 -(2, 2 - dimethyl - [1, 3dioxolan - 4 - yl) - 2 - [4-(4-trifluoromethoxy-phenoxy)-benzenesulfonyl]-ethanol (9)

Into a solution of ketone (**8**, 140 mCi, ∼2 mg) and unlabeled **8** (114 mg, 0.247 mmol to give a specific activity of ∼0.5 Ci/mmol) in THF (0.5 mL) and EtOH (1.6 mL) was added sodium borohydride (72 mg, 1.9 mmol). The reaction mixture was stirred at RT for 1.5 h, quenched with 10% CH_3COOH (10 mL), and was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (3 × 25 mL) and brine solution (3 × 25 mL). The solvent was removed on a rotary evaporator to give 131 mCi of **9**. HPLC analysis (t_R = 13 min) showed 96% of **9**. The crude product was purified by preparative silica gel plates (1000 μm, 20 × 20 cm, 60% pentane in ethyl acetate). The bands corresponding to the product were scraped and extracted with ethyl acetate (4 × 35 mL). The solvent was removed on the rotary evaporator to give 120 mCi of **9** in 85% yield.

[^{3}H] - (*S,E*) - 2, 2 - dimethyl - 4 -(2-([3-3H]-4-([2-3H]-4-(trifluoromethoxy)phenylsulfonyl)vinyl)1,3-dioxolane (10)

Into a solution of **9** (120 mCi, 0.111 g) in ethyl acetate (1.5 mL) under nitrogen was added Et_3N (200 μL, 1.4 mmol). The reaction mixture was cooled in an ice bath, methane sulfonyl chloride (0.044 g, 0.38 mmol) was added slowly, and the mixture was stirred for 45 min. The ice bath was removed and stirring was continued at RT for 2.5 h. To complete the reaction, Et_3N (20 μL, 14 mmol) and methane sulfonyl chloride (0.010 g, 0.09 mmol) were added and the reaction mixture was stirred at RT for 1.2 h. The reaction mixture was worked up by adding 10% citric acid (2.5 mL, pH = 4), EtOAc (10 mL), and water (2 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2.5 mL) and brine solution (30 mL). The solvent was removed on a rotary evaporator to give 120 mCi of **10**. The crude product was purified by preparative silica gel plates (2 × 1000 μm, 20 × 20 cm, 2% ethyl acetate in methylene chloride). The bands corresponding to the product were scraped and extracted with EtOAc (4 × 35 mL). The solvent was removed on a rotary evaporator to yield 112 mCi of **10** in 93% yield. TLC analysis (silica gel, 2% ethyl acetate in methylene chloride, R_f ∼ 0.4) and HPLC analysis (t_R = 14.8 min) showed radiochemical purity > 92%.

[^{3}H] - *N* - 1 -(2,2-dimethyl-[1,3]dioxolan-4-yl)-2-[4-(4-trifluoromethoxy-phenoxy)-benzenesulfonyl]-ethyl-hydroxylamine (11)

A solution of **10** (60 mCi, 0.053 g) in methyl *t*-butyl ether (1.5 mL) under N_2 was cooled to −15°C and 50% hydroxylamine (185 μL) was added. The reaction mixture was stirred for 4 h. An aliquot was analyzed by HPLC (t_R = 11.9 min) showing 77% of **11**. The reaction mixture was diluted with EtOAc (40 mL) and brine solution (15 mL). The organic layer was separated. The solvent was removed on a rotary evaporator to give 56 mCi of **11** that was further purified by preparative HPLC (Phenomenex Luna C8 column, 21.2 × 250 mm, 5 μm, UV at 210 nm, flow rate = 20 mL/min, 65% CH_3CN and 35% water, isocratic t_R = 8.7 min) to give 35 mCi of **11** in 58% yield with radiochemical purity > 99%.

[^{3}H]ABT-518 (1)

A solution containing **11** (35 mCi, 0.045 g), 2,2,2-trifluoroethyl-formate (135 μL), isopropyl acetate (500 μL), 96% formic acid (12 μL), and sodium formate (0.005 g) was heated at 65°C for 3 h. The reaction mixture was diluted with 5% $NaHCO_3$ solution (5 mL) and extracted with EtOAc (30 mL). The organic layer was concentrated on a rotary evaporator to yield 28.5 mCi of **1**. The crude product was purified by preparative silica gel plates (1000 and 2000 μm, 20 × 20 cm, 55% methanol in methylene chloride). The bands corresponding to the product were scraped and extracted with ethyl acetate (4 × 30 mL). The solvent was removed on the rotary evaporator to give 19 mCi of **1**.

HPLC analysis ($t_R = 12$ min) and TLC analysis (silica gel, 5% methanol in methylene chloride, $R_f \sim 0.1$) showed radiochemical purity of 94%.

Purification by preparative HPLC

Approximately 19 mCi of crude [^{3}H]ABT-518 (**1**) was added to 1 mL of CH_3CN and 0.5 mL of H_2O. Each 0.1 mL of the sample preparation was injected onto a Zorbax Rx-C8 column (5 μm, 250 × 4.6 mm ID) using an Agilent 1100 series HPLC system. [^{3}H]ABT-518 (**1**) was eluted at a flow rate of 1 mL/min with isocratic elution of 50% acetonitrile. Peaks were detected and chromatograms were obtained using an Agilent variable wavelength UV detector set at 210 nm and Chemstation software. The fractions containing [^{3}H]ABT-518 (**1**) were collected at approximately 11 min using an Agilent fraction collector. Fractions were further purified using Phenomenex Luna C18 (2) column (5 μm, 250 × 4.6 mm ID) and Agilent 1100 series HPLC system. [^{3}H]ABT-518 (**1**) was eluted at a flow rate of 1 mL/min with isocratic elution of 65% MeOH. Peaks were detected and chromatograms were obtained using an Agilent UV detector set at 210 nm. The fractions containing [^{3}H]ABT-518 (**1**) were collected at approximately 22 min using an Agilent fraction collector. The product-containing fractions were pooled and solvents were evaporated *in vacuo* to yield 7.1 mCi of **1**.

Purity and specific activity determination by HPLC

[^{3}H]ABT-518 (**1**) was analyzed by reverse-phase HPLC and compared with authentic ABT-518. Each sample was injected onto a Zorbax Rx-C8 column, 4.6 × 250 mm, 5 μm, and eluted at 1 mL/min with mobile phase consisting of 0.1% trifluoroacetic acid and 50% acetonitrile. Peaks were detected with a UV detector at 210 nm and a liquid scintillation radioactivity flow detector. Greater than 99% of radioactivity corresponded to the UV peak of ABT-518 at 11.8 min. An assay of the effluent showed that greater than 99% of the activity was recovered from the column. The specific activity of the product was calculated by relative proportions of UV-detected signal from the radioactive product and an unlabeled reference. It was found to be 381.6 mCi/mmol.

Conclusion

[^{3}H]ABT-518 (**1**) was synthesized in seven steps from 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]benzene (**4**) in 6.2% radiochemical yield. The radioactivity was introduced in the second step. The radiochemical purity was >99% and the specific activity was 381.6 mCi/mmol. This material was suitable for use in *in vivo* and *in vitro* metabolism studies.

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[10] For **5a**: ^{1}H-NMR (501 MHz, $CDCl_3$): δ 7.92 (d, $J = 9.0$ Hz, 2H, *H*(*1*), *H*(*3*)), 7.79 (d, $J = 2.6$ Hz, 1H, *H*(*16*)), 7.29 (dd, $J = 8.8$, 2.6 Hz, 1H, *H*(*14*)), 7.05 (d, $J = 9.0$ Hz, 2H, *H*(*4*), *H*(*6*)), 7.02 (d, $J = 8.8$ Hz, 1H, *H*(*13*)), 3.07 (s, 3H, CH_3). ^{13}C-NMR (125.2 MHz, $CDCl_3$): δ 132.87 (*C*(*16*)), 129.98 (*C*(*1*), *C*(*3*)), 122.86 (*C*(*14*)), 121.41 (*C*(*13*)), 117.54 (*C*(*4*), *C*(*6*)), 44.78 (CH_3). For **5b**: ^{1}H-NMR (501 MHz, $CDCl_3$): δ 8.45 (d, $J = 2.4$ Hz, 1H, *H*(*3*)), 7.83 (dd, $J = 8.5$, 2.4 Hz, 1H, *H*(*1*)), 7.77 (d, $J = 2.7$ Hz, 1H, *H*(*16*)), 7.29 (ds, $J = 8.9$, 2.7 Hz, 1H, *H*(*14*)), 7.06 (d, $J = 8.9$ Hz, 1H, *H*(*13*)), 6.68 (d, $J = 8.5$ Hz, 1H, *H*(*6*)), 3.06 (s, 3H, CH_3). ^{13}C-NMR (125.2 MHz, $CDCl_3$): δ 139.61 (*C*(*3*)), 132.87 (*C*(*16*)), 129.28 (*C*(*1*)), 122.86 (*C*(*14*)), 121.65 (*C*(*13*)), 115.92 (*C*(*4*)), 44.78 (CH_3). For **5c**: ^{1}H-NMR (501 MHz, $CDCl_3$): δ 8.43 (d, $J = 2.2$ Hz, 1H, *H*(*3*)), 7.84 (dd, $J = 8.6$, 2.2 Hz, 1H, *H*(*1*)), 7.29 (d, $J = 9.1$ Hz, 2H, *H*(*13*), *H*(*17*)), 7.09 (d, $J = 9.1$ Hz, 2H, *H*(*14*), *H*(*16*)), 6.87 (d, $J = 8.6$ Hz, 1H, *H*(*6*)), 3.07 (s, 3H, CH_3). ^{13}C-NMR (125.2 MHz, $CDCl_3$): δ 139.45 (*C*(*3*)), 129.28 (*C*(*1*)), 122.86 (*C*(*13*), *C*(*17*)), 121.09 (*C*(*14*), *C*(*16*)), 117.01 (*C*(*6*)), 44.78 (CH_3).