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# †Rapid Synthesis of F-18 and H-2 Dual-labeled Altanserin, A Metabolically Resistant PET Ligand For 5-$HT_{2A}$ Receptors

*Ping-Zhong Tan, Ronald M. Baldwin, Tao Fu, Dennis S. Charney and Robert B. Innis

Department of Psychiatry, Yale University School of Medicine-VA PET Center,

West Haven, CT 06516, USA

## Summary

F-18 and H-2 dual-labeled altanserin (**3**, [$^{18}$F]d-ALT), a novel PET tracer for 5-$HT_{2A}$ receptors with metabolically resistant properties, was synthesized by [$^{18}$F]fluoride displacement of the corresponding deuterated nitro precursor in 32% yield (EOB) in 108 min with radiochemical purity 95% and specific activity >1000 mCi/μmol (EOS). The key intermediate ethyl N-(2-chloroethyl-2,2-$d_2$)carbamate (**7**) was obtained by $LiAlD_4$ reduction of a glycine ester (93%), chlorination and carbamoylation (79%). 4-(4-Nitrobenzoyl)piperidine (**13**) was synthesized (60%) by improving the published coupling reaction of *p*-nitrophenyltrimethylstannane (**10**), obtained from *p*-iodonitrobenzene and $(CH_3)_6Sn_2$ (94%), with 1-benzoylisonipecotic acid chloride (**11**) followed by acid hydrolysis. **13** was alkylated with **7** (82%), hydrolyzed and condensed with methyl *o*-isothiocyanatobenzoyate to provide with the precursor deuteronitroaltanserin (**4**, 75%).

**Key words:** [$^{18}$F]altanserin, PET, 5-$HT_2$ receptor, deuterium isotope effect

## Introduction

[$^{18}$F]Altanserin (**1**) continues to be the radioligand of choice for PET studies of brain 5-$HT_{2A}$ receptors, compared to other PET ligands, such as [N-methyl-$^{11}$C]methyl-2-bromo-LSD, [$^{11}$C]3-N-methyl- and [$^{18}$F]3-N-2-fluoroethyl- spiperone, [$^{18}$F]setoperone (*1*) and the recently reported [$^{11}$C]MDL 100907 (*2, 3*). Advantages of [$^{18}$F]altanserin as a PET radiotracer are: ability to do equilibrium scans lasting several hours because of the 110-minute half life of $^{18}$F; high affinity and

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*For correspondence or reprints contact: Ping-Zhong Tan, Ph.D., Yale University School of Medicine, Department of Psychiatry-116A2, 950 Campbell Ave, West Haven, CT 06516. Phone: 203-932-5711 x3324 or 3590, fax: 203-937-3829, email: Tan@orpheus.med.yale.edu.

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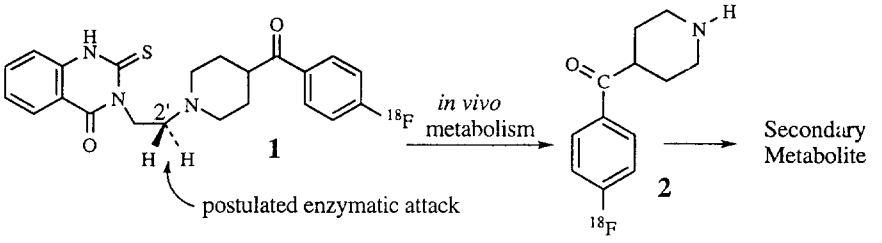
selectivity for the 5-$HT_{2A}$ receptors (*4, 5*); and a ratio of specific to non-specific binding of 2–2.5 (*6, 7*). A drawback of [$^{18}$F]altanserin is its rapid and extensive metabolism that may interfere with its kinetic modeling: four plasma radiometabolites were detected (*5, 8*), and only about 45% of parent tracer was present in the plasma after a bolus injection or in a constant infusion paradigm (*6, 7, 9, 10*).Tracer metabolism is generally undesirable because it decreases availability of tracer to target tissue; increases non-specific binding in background region and, as a result, decreases the specific brain uptake; and complicates the receptor quantification especially for kinetic modeling. Therefore, it is desirable to develop altanserin analogs that have reduced metabolism but retain its 5-$HT_{2A}$ binding affinity and specificity.

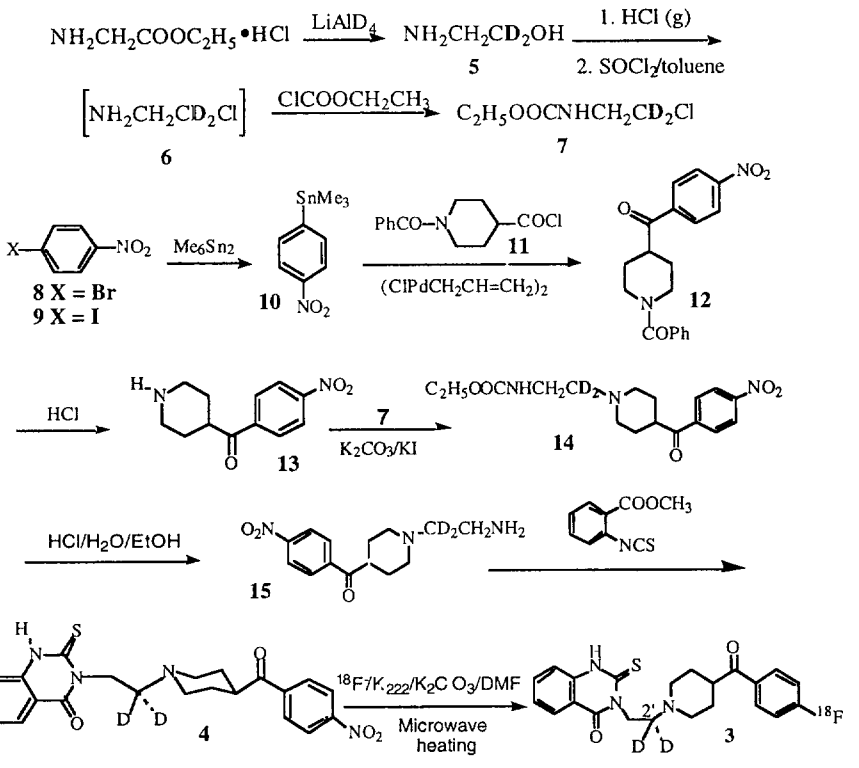
**Scheme 1 N-Dealkylation Metabolism of Altanserin**




A major metabolic pathway of altanserin is N-dealkylation (or deamination), giving [$^{18}$F]4-(4-fluorobenzoyl)piperidine (**2**, [$^{18}$F]FBP) and its secondary metabolite (**Scheme 1**) (*5, 11*). Reducing the rate of this metabolic step should reduce the formation of radiometabolites. In general, metabolic deamination of amines (*12*) occurs by attack at the carbon-hydrogen bond alpha to the amine nitrogen followed by subsequent degradation in several steps to break the C-N bond (*13*), forming the amine (**2**, FBP, **Scheme 1**) and a carbonyl compound. The carbonyl fragment does not contain fluorine and is therefore not detected by $^{18}$F radioactivity, but the carboxylic acid was identified for the structurally similar ketanserin (*14*). If carbon-hydrogen bond breaking is involved in the rate determining step, substituting deuterium ($^{2}$H) at the alpha methylene group should reduce the rate of *N*-dealkylation due to the greater strength of the C-D bond (see: for example (*15*)). This isotope effect has been observed in practice for *(+)-N*-[$^{2}$H]isopropylamphetamine (*16*) and has been successfully applied to PET studies of neurotransmission using [$^{2}$H,$^{11}$C]deprenyl (*17*) and [$^{2}$H,$^{18}$F]fluorodopamine (*18*). We therefore hypothesized that [$^{18}$F]deuteroaltanserin (**3**, **Scheme 2**), in which the 2'-hydrogens alpha to the piperidine nitrogen are replaced with deuterium, will generate reduced amount of radiometabolites than its hydrogen-1 form.

**Scheme 2 Synthesis of F-18 and H-2 dual labeled altanserin**




Our initial pharmacokinetic comparison in human subjects demonstrated that [$^{18}$F]deuteroaltanserin gave significantly higher plasma parent-to-metabolites ratio (29% ) than [$^{18}$F]altanserin in the elimination phase (*19*). In keeping with the pharmacokinetic results, PET imaging studies in baboons showed that $V_3$" (ratio of specific brain uptake to uptake in a reference region) of [$^{18}$F]deuteroaltanserin was 35% higher than [$^{18}$F]altanserin, supporting our hypothesis (*20*). We would like to report in this paper the rapid synthesis of F-18 and H-2 dual labeled-altanserin (3) and its deuterated nitro-precursor.

## Results and Discussion

The approach to radiolabeling and the precursor deuteronitroaltanserin (4) is similar to the synthesis of [$^{18}$F]altanserin (*21*) (**Scheme 2**). To regiospecifically introduce the deuterium isotope, the ethyl ester of glycine was reduced with excess lithium aluminum deuteride (98 atom %

D) in 93% yield. The hydrochloride salt of the resulting deuterium-labeled ethanolamine (**5**) was converted to the ß-chloroethylamine-$d_2$ (**6**) with thionyl chloride in toluene. The free base **6** was not isolated from the aqueous solution, and the amino group was protected as its carbamate **7** in 79% yield for these two steps (**Scheme 2**).

Azizian et al. reported a 34% yield of p-nitrophenyltrimethylstannane (**10**) when p-nitrobromobenzene (**8**) reacted with hexamethylditin in toluene in the presence of tetrakis(triphenylphosphine)palladium complex (*22*), and this procedure gave 17-33% yield in our hand. However, when using the more reactive *p*-iodonitrobenzene (**9**) as the starting halide and conducting the reaction in N,N-dimethylformamide (DMF) in the presence of pi-allyl palladium chloride dimer as catalyst, the desired crystalline trimethylstannyl product **10** was obtained in 94% yield (*23*). To synthesize 4-(4-nitrobenzoyl)-1-benzoylpiperidine (**12**), we tested the published method (*24*). However, the black oily acid chloride **11**, obtained by heating the mixture of 1-benzoylisonipecotic acid (**16**) with neat thionyl chloride under reflux, did not couple with the trimethylstannyl compound **10** following the reported conditions (*24*). We therefore developed an alternative method to prepare the acid chloride **11**. Reaction of 1-benzoylisonipecotic acid with thionyl chloride in ethyl ether in the presence of sodium carbonate and 4 Å molecular sieves gave acid chloride **11** as a colorless oil in quantitative yield. Coupling of the colorless acid chloride **11** with the tin compound **10** gave 40% of **12**, in keeping with the reported results (*24*). A less polar side product was also isolated from the reaction, which was identified by its NMR spectrum and melting point to be 4,4'-dinitrobiphenyl, a product from the intermolecular coupling of p-nitrophenyltrimethylstannane. We reasoned that a reaction mixture containing diluted stannane compound would reduce the formation of side product. Indeed, the yield increased to 60% when adding anhydrous tetrahydrofuran solution of the stannane **10** dropwise to the stirring acid chloride. Hydrolysis of 1-benzoylpiperidine compound **12** gave **13** as a hydrochloride salt (70%).

N-alkylation with deuterium alkylating agent **7** in 4-methylpentanone in the presence of $K_2CO_3$ and a catalytic amount of potassium iodide afforded pure **14** after repeated flash chromatography. The carbamate **14** was hydrolyzed by 12 M HCl to give the corresponding free amine, which easily condensed with methyl *o*-isothiocyanatobenzoate to give the deuterium-labeled nitro precursor **4** as a pale solid (**Scheme 2**). HPLC analysis indicated 99.9% purity (E. Merck RP Sel-B, 10 µ, 250 x 4.6 mm, 2.5 ml/min, 32.5/67.5 THF/80 mM NaOAc, pH 5.0, UV 291 nm). The final

deuterium labeled nitroaltanserin was identified by comparing the NMR spectrum with that of the corresponding protio compound: the 2' protons of nitroaltanserin(δ, 2.65 ppm, $J$ = 7.3 Hz) disappeared and the triplet peak of the 1' protons (4.54 ppm, J = 7.3 Hz) changed to a sharp singlet in the spectrum of deuteronitroaltanserin (**4**).

Radiolabeling was carried out in a completely remote controlled system, which used a microwave oven, an HPLC module and a solid phase extraction-formulation system (*25*) (**Scheme 2**). [$^{18}$F]Fluoride, generated by $^{18}$O[p,n]$^{18}$F reaction in a silver target, was transferred along with a solution of kryptofix-222 and $K_2CO_3$ to an open reaction vessel in the chamber of a microwave oven. [$^{18}$O]Water was evaporated with acetonitrile under a stream of argon by microwave heating, and then deuteronitroaltanserin (**4**) in DMF was added to the vessel. The fluoro-nitro exchange reaction was conducted by heating with microwave oven for 3 min at 50% power. The reaction mixture was diluted with water, and loaded directly onto a HPLC. Purification was carried out on two sequentially connected HPLC columns (E. Merck RP sel-B, 250 x10) and eluted with 32.5:67.5 THF/80 mM NaOAc (pH 5.0) at a flow rate of 5.0 ml/min. The product fraction (retention time 54 min), as indicated by the gamma-detector, was collected, diluted with water, and passed through a C-18 Sep-Pak cartridge. The radioactivity trapped by the cartridge was then eluted with ethanol (1.0 -1.5 ml), and formulated with L-ascorbic acid (0.2 mg) and normal saline (20 ml). The labeling yield was 44%, overall yield was 32% (EOB) with a total synthesis time 108 min, including formulation. HPLC analysis (RP Sel-B, 250 x 4.6, 10 μ, 32.5:67.5 THF/80 mM NaOAc, 2.5 ml/min) indicated radiochemical purity of >95%, free of starting precursor and with a specific activity of >1000 mCi/μmol.

In summary, we have developed an efficient synthetic method for deuteronitroaltanserin (**4**) as a precursor for radiolabeling. Radiofluorination of this precursor in a remote control system gave [$^{18}$F]deuteroaltanserin (**3**) in high purity and good yield.

## Experimental

Melting points were determined on a Thomas Hoover Capillary Apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer FT 1600 instrument. $^1$H NMR was conducted on a Bruker AM 500 MHz Spectrometer; chemical shifts are reported in parts per million downfield

from internal tetramethylsilane and the coupling constants, in hertz. HPLC analyses were carried out on a Spectra-Physics HPLC system with a UV- (291 nm) and radio-detector. Zorbax Eclipse XDB-C8 semi-preparative (250 x 9.4, 5 μ) and analytical (250 x 4.6, 5 μ) HPLC columns were purchased from Mac-Mod Analytical, Inc., Chadds Ford, PA. [$^{18}$F]Fluoride was produced with an RDS-112 11 MeV negative ion cyclotron (CTI, Oak Ridge, TN) by the nuclear reaction $^{18}O(p,n)^{18}F$ in a silver target. High resolution mass spectroscopy was conducted on Q-Tof from Micromass, UK, using electrospray method with positive ion source. Altanserin was synthesized from 4-(4-fluorobenzoyl)piperidine (Fisher Scientific, Pittsburgh, PA) using a procedure described for synthesis of nitro-altanserin (*21*). Kryptofix-222 was purchased from Research Biochemicals, Int., Natick, MA. The other reagents were from Aldrich and were used as received.

**2-Hydroxyethylamine-2,2-$d_2$ (5)** To a stirred suspension of lithium aluminum deuteride (98 atom % D, 10.0 g, 238.2 mmol) and THF (distilled from $LiAlH_4$, 200 mL) was added, in portions, glycine ethyl ester hydrochloride (8.4 g, 60 mmol) at 0°C. The resulting mixture was stirred at room temperature for 4 h. Water (10 ml), 3 N NaOH (10 mL) and water (30 mL) were added sequentially dropwise with vigorous stirring. The resulting white residue was removed by filtration under reduced pressure and washed with THF (200 mL) to give a colorless filtrate, which was concentrated on a rotary evaporator to give a light yellow oil (1.8 g). Extraction of the residue with THF on a Soxhlet extractor for 4 days gave a second crop of product (1.7 g) with a combined yield of 93%. Bulb-to-bulb distillation under reduced pressure provided the pure product as a colorless oil. The IR spectrum was identical to that of the corresponding protiocompound.

**Ethyl N-(2-chloroethyl-2,2-$d_2$)carbamate (7)** HCl(g) was bubbled through a solution of **5** (3.22 g, 51.1 mmol) in toluene (40 mL) for 10 min. The resulting heterogeneous mixture was made anhydrous by distillation of toluene under reduced pressure to a small volume (about 20 mL). Thionyl chloride (6.24 g, 52.4 mmol) was added dropwise in 5 min. The resulting heterogeneous mixture was heated at 70-75°C with vigorous stirring under dry argon atmosphere for 3 h. Another portion of thionyl chloride (1.60 g, 13.4 mmol) was added and heated for 30 min to drive the chlorination to completion. The mixture was cooled to room temperature and water (50 mL) was added to quench the reaction. The toluene layer was separated, the aqueous layer was extracted with ether, and the acidic aqueous solution was neutralized with sodium carbonate (5.0 g) to give the free base 2-chloroethyl amine-2,2-$d_2$ (**6**)

To the neutral aqueous solution of 2-chloroethylamine-2,2-$d_2$ (**6**) was added dropwise, simultaneously, ethyl chloroformate (5.0 mL, 52 mmol) and 10% sodium carbonate solution (60 mL) in 5 min. The resulting solution (pH 8-9) was stirred for 30 min. The product was extracted with ethyl ether (100 mL, 2 x 50 mL), dried ($Na_2SO_4$) and the ether was evaporated. Bulb-to-bulb distillation of the remaining residue gave the final product **7** as a colorless oil (6.21 g, 79% for two steps). IR (neat) 3334, 2981, 1701, 1528, 1257, 1155, 1081, 1035 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 5.21 (br, 1 H, NH), 4.14 (q, 2 H, $J$ = 7.0, $OCH_2$), 3.51 (2 H, d, $J$ = 5.5, $CH_2NH$), 1.25 (3 H, t, $J$ = 7.0, $CH_3$).

**1-Benzoyl isonipecotic acid chloride (11)** Thionyl chloride (3.2 mL, 44 mmol, distilled before use) was added to a stirring mixture of 1-benzoyl isonipecotic acid (9.22 g, 40 mmol), anhydrous sodium carbonate (6.36 g, 60 mmol) and ethyl ether (400 mL, distilled from $LiAlH_4$) under argon. The mixture was stirred for 22 h at room temperature, filtered through Celite, washed with anhydrous ether and concentrated under reduced pressure to give a colorless oil (10.38 g, 100%). This product was dissolved in THF (80 mmol) to make a solution of 0.5 mmol/mL and stored over 4 Å molecular sieves and sodium carbonate for future use.

**p-Nitrophenyltrimethylstannane (10)** *p*-Nitroiodobenzene (**9**, 6.0 g, 24 mmol), hexamethylditin (10 g, 30 mmol) and pi-allyl palladium chloride dimer (48 mg) in DMF (anhydrous, 100 mL) was stirred at room temperature for 4 h. DMF was evaporated under reduced pressure. The residue was crystallized from MeOH-$H_2O$ to give the product as an orange-yellow solid (5.69 g, 94%). MP 51-52 °C (lit. 41-43°, (*22*)).

**4-(4-Nitrobenzoyl)-1-benzoylpiperidine (12)** To a solution of freshly-made 1-benzoyl isonipecotic acid chloride (50 mL, 25 mmol) and pi-allyl palladium chloride dimer (130 mg) was added dropwise *p*-nitrophenyltrimethylstannane (4.925 g, 19.6 mmol) in THF (250 mL) with stirring under argon. The mixture was stirred for another 3 h, filtered through Celite, and washed with THF. The yellow filtrate was concentrated *in vacuo* and the residue was flash-chromatographed (silica, 2:2:0.5 hexane/AcOEt/$Et_3N$) to give two fractions. Evaporation of the solvent in the second fraction under reduced pressure gave the desired product as yellow crystals (3.65 g,

60%). MP 151.5-152.5 °C. $^1$H NMR ($CDCl_3$) δ 1.81 (d, 4 H), 3.12 (d, 2 H), 3.55 (d, 1 H), 3.85 (d, 1 H), 4.71 (d, 1 H), 7.42 (s, 5 H), 8.10 (d, 2 H), 8.34 (d, 2 H). IR (neat), 1689, 1616 cm-1.

In the coupling reaction of p-nitrobromobenzene with hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium (*22*), a side product was isolated as a yellow needle, which was identified as 4, 4'-dinitrobiphenyl, MP 232-233 °C (lit 239-243 °C (*27*)). $^1$H NMR ($CDCl_3$) δ 7.79 (dd, 4 H, *J* = 1.8, 6.9, ArH), 8.37 (dd, 4 H, *J* = 1.8, 6.9, ArH).

**4-(4-Nitrobenzoyl)piperidine hydrochloride (13).** A mixture of **12** (1.55 g, 4.58 mmol), ethanol (40 mL) and 12 M HCl (60 mL) was heated under reflux for 15 h and concentrated under reduced pressure. The resulting yellow solid was crystallized from EtOH-$Et_2O$ to give the product as a yellow powder (0.879 g, 70%), MP 240 °C (dec.). $^1$H NMR ($D_2O$) δ 1.93 (m, 2 H), 2.18 (m, 2 H), 3.23 (dt, 2 H, *J* = 3.1, 12.7), 3.53 (dt, 2 H, *J* = 3.5, 13.0), 3.88 (t, 1 H, *J* = 11.0, 3.6), 8.19 (dd, 2 H, *J* = 2.0, 7.0), 8.39 (dd, 2 H, *J* = 2.0, 7.0).

**Ethyl N-(2-(4-(4-nitrobenzoyl)-piperidin-1-yl)-ethyl-2,2-$d_2$)carbamate (14)** 4-(4-Nitrobenzoyl)piperidine hydrochloride (**13**, 130 mg, 0.5 mmol) was dissolved in $H_2O$ (30 mL), basified with 15 M $NH_4OH$, extracted with $CH_2Cl_2$ (5 x 20 mL), dried ($K_2CO_3$ and 4 Å molecular sieve), filtered and concentrated to give the free base as an oil. To the residue was added 4-methyl-2-pentanone (5.0 mL, dried with $Na_2SO_4$ and 4 Å molecular sieve), ethyl N-(2-chloroethyl-2,2-$d_2$)carbamate (**7**, 115 mg, 0.75 mmol), $K_2CO_3$ (100 mg, 0.7 mmol) and KI (10 mg). The resulting mixture was heated under reflux for 20 h, filtered, concentrated and purified by flash chromatography (10:0.5 AcOEt-$Et_3N$) to give the product as a brown oil (114 mg, 82%). IR (neat) 3339, 2945, 1692, 1602, 1524, 1263. $^1$H NMR δ 1.25 (t, 3 H, *J* = 7.1), 1.95 (m, 2 H), 2.48 (m, 2 H), 3.08 (m, 2 H), 3.39 (m, 3 H), 3.64 (s, 2 H), 4.10 (q, 2 H, *J* = 7.1), 5.60 (br, 1 H, NH), 8.07 (d, 2 H, *J* = 7.0), 8.32 (d, 2 H, *J* = 7.0).

**1-(2-Aminoethyl-1,1-$d_2$)-4-(4-nitrobenzoyl)piperidine (15).** Ethyl N-(2-(4-nitrobenzoyl)-1-piperidinyl)-ethyl)carbamate (**14**, 114 mg , 0.41 mmol) and 12 M HCl solution was

heated under reflux for 24 h. The cooled solution was extracted with $Et_2O$ (2 x 25 m), the aqueous solution was basified with 15 M $NH_4OH$, extracted with $CH_2Cl_2$ (4 x 25 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to give (15) as a yellow brown residue (104 mg).

**3-(2-(4-(4-Nitrobenzoyl)-piperidin-1-yl)-ethyl-2,2-$d_2$)-1,2-dihydro-2-thioxo-quinazolinone (Nitrodeuteroaltanserin,** 4) The free amine (15) obtained above was dissolved in anhydrous THF (5.0 mL), methyl 2-isothiocyanatobenzoate (236 mg) was added and the solution was stirred at room temperature for 1 h. The resulting mixture was concentrated and purified by flash chromatography (7/3/0.5, $CH_2Cl_2$/AcOEt/MeOH) to give a white pale solid (135 mg, 75% for two steps). MP 240-243°C. $^1$H NMR (DMSO-$d_6$) δ 1.54 (m, 2 H), 1.77 (d, 2 H, $J$ = 11.4), 2.33 (dd, 2 H, $J$ = 9.8, 11.3), 2.99 (d, 2 H, $J$ = 11.3), 3.43 (tt, 1 H, $J$ = 3.5, 11.3), 4.53 (s, 2 H), 7.73 (ddd, 1 H, $J$ = 1.5, 7.2, 8.3), 7.95 (dd, 1 H, $J$ = 1.2, 8.0), 8.18 (d, 2 H, $J$ = 8.9), 8.32 (d, 2 H, $J$ = 8.9). Exact mass for $C_{22}H_{21}D_2N_4O_4S$ ($MH^+$): calcd, 441.1563; found, 441.1569. Analytical HPLC showed >99.9% purity.

**[$^{18}$F]Deuteroaltanserin** (3) Aqueous $^{18}F^-$ solution (0.3 mL) was delivered to a 1-mL vial containing a solution of kryptofix-222 and $K_2CO_3$ placed in a dose calibrator to measure the starting radioactivity. The $^{18}$F solution was transferred through a Teflon tube to an open reaction vessel affixed on the floor of a commercial microwave oven. Water was removed by azeotropic distillation with $CH_3CN$. Nitrodeuteroaltanserin (4, 4.5 mg) in DMF (1.0 mL) was added and the mixture was heated at power level 5 for 3 min. After cooling with water, the reaction mixture was diluted with $H_2O$ (1.0 mL) and loaded onto a 5-mL HPLC sample loop. Prep HPLC purification was carried out on two semi-prep columns connected in series (EM RP Select-B, 250 x 10 mm, 10 μm) and eluted with THF/0.08 M NaOAc buffer (35/65, pH 5) at a flow rate of 5.0 mL/min. The retention time of [$^{18}$F]deuteroaltanserin was 54 min and that of the nitro precursor was >80 min. The fraction corresponding to [$^{18}$F]deuteroaltanserin was collected, diluted with water (300 mL) and passed through two stacked C-18 solid phase extraction cartridge (Sep-Pak plus, Millipore). After washing with water (10 mL), the trapped radioactivity was eluted with EtOH (1.0 mL) and collected in a vial containing 0.9% NaCl (20 mL) and L-ascorbic acid (250 μg), and filtered through a 0.2 μm membrane filter. The radiochemical purity and specific activity were determined by HPLC (EM RP Select-B, 250 x 4.6 mm, 10 μm, THF/0.08 M NaOAc, 35/65 (pH 5.0) at 2.5

mL/min). The synthesis time was 108 min, the radiochemical yield was 32% at the end of synthesis with radiochemical purity of 95% and specific activity of >1000 mCi/μmol at the end of synthesis. Sterility (*26*) and apyrogenicity (LAL test, Endosafe, Charleston, NC) were assured for each batch by compendia tests.

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