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Radiosynthesis of [5-[^{11}C]methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5-(tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-methanone ([^{11}C]RO5013853), a novel PET tracer for the glycine transporter type I (GlyT1)

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The glycine transporter type 1 (GlyT1) has emerged as a key novel target for the treatment of schizophrenia. We have recently discovered and developed [^{11}C]RO5013853 as a novel positron emission tomography tracer for GlyT1 for which a reliable five-step synthetic route was established. The incorporation of the radioisotope was achieved in the final step through methylation of a sodium sulfinate precursor, itself easily accessible upon reduction of the corresponding sulfonyl-chloride analog. [^{11}C]RO5013853 was prepared with high specific activity (>49 GBq/μmol) and high radiochemical purity (100%). A validation study of [^{11}C]RO5013853 in animal imaging studies is in progress.

Keywords: [^{11}C]RO5013853; carbon-11; PET; GlyT1; glycine; transporter; radiolabeling

Introduction

The glycine transporter type 1 (GlyT1) is a selective transporter of the neurotransmitter glycine. It belongs to the Na^+/Cl^--dependent neurotransmitter transporter superfamily and its distribution in the central nervous system (CNS) overlaps the expression pattern of the *N*-methyl-D-aspartate (NMDA) receptors for which glycine is an obligatory co-agonist.[1,2] GlyT1 provides tight regulation of the extracellular glycine concentration at this receptor. Inhibition of glycine reuptake via selective blockade of GlyT1 leads to an increase in local glycine concentration and potentiation of the NMDA receptor synaptic activity.[3] Compelling evidence suggests that impairment in NMDA neurotransmission is involved in the pathophysiology of schizophrenia.[4] This hypothesis originated from the observation that selective NMDA-R blockers are able to reproduce, in healthy subjects, the positive, negative, and cognitive symptoms of schizophrenia. Thus, normalization of NMDA receptor neurotransmission by increasing the availability of glycine at its modulatory site on the receptor may provide a novel therapeutic intervention to this severe CNS disorder for which there is a strong need to identify more efficacious and safer agents than the currently marketed dopaminergic-based drugs. As a result, considerable effort has been focused, over the last decade, on the discovery and development of selective glycine reuptake inhibitors for schizophrenia. Several of these have entered clinical trial stage.[5] In 2009, Roche disclosed positive phase II results with RG1678 in schizophrenic patients, effectively providing for the first time a proof-of-concept for glycine reuptake inhibition as a therapeutic approach.[6,7]

A positron emission tomography (PET) ligand for GlyT1 is an important imaging tool that may serve to improve the understanding of the pathology of schizophrenia as well as to facilitate the development of therapeutic candidates for this target. We have recently described the identification of benzoylisoindolines as a novel class of glycine reuptake inhibitors.[8] From this series, [5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5-(tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-methanone (RO5013853, Figure 1) was found to exhibit properties that supported its further evaluation as a potential PET ligand candidate: high target affinity for human GlyT1 (hGlyT1 EC_{50}: 14 nM), high

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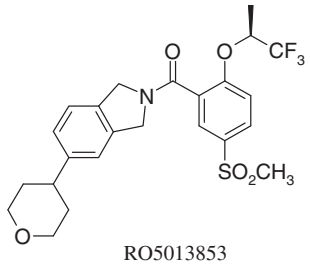

Figure 1. Chemical structure of [5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5-(tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-methanone (RO5013853).

target selectivity (≫100-fold selectivity for human GlyT1 versus GlyT2 and versus a CEREP panel of 92 receptors), moderate lipophilicity (clogP: 2.91), good brain penetration (rat brain/plasma: 0.6), and the possibility for radiolabeling employing readily available PET chemistry synthons such as [^{11}C]methyl iodide (*vide infra*).

We report herein on the development of a suitable synthetic route to [^{11}C]RO5013853, an essential prerequisite for its evaluation as a GlyT1 PET radiotracer.

Results and discussion

The strategy we followed was to label the methyl-sulfone substituent of RO5013853 with ^{11}C. The methyl-sulfone moiety has already been reported by several groups as a useful position for the labeling of PET ligands.[9,10] In these published studies, the labeling strategy typically involves the methylation of a thiol group followed by the double oxidation of the resulting methyl sulfide. This approach suffers nevertheless from several limitations and drawbacks: (1) the thiol is often not very stable and is prone to dimerization to form the corresponding disulfide; (2) the radioisotope is not incorporated in the last step of the synthesis; and (3) the final oxidation step is often incomplete and leads to a mixture of sulfone and sulfoxides. Recently, an alternative approach was introduced by Perrio *et al.*,[11] in which the starting thiol is first oxidized with *N*-sulfonyloxaziridine to a lithium sulfinate intermediate, which is then, in the final step, S-methylated with [^{11}C]methyl iodide at 150°C in a THF/H_2O solvent mixture. This method, which allows the introduction of the methyl group in the final step, still suffers however from the utilization of a potentially unstable thiol as a starting material. To circumvent this issue, we proposed to prepare the intermediate sulfinate by reduction of a sulfonyl-chloride. This reaction is well described and can be performed under very mild condition in the presence of sodium sulfite.

Thus, the synthesis of RO5013853 (Figure 2) was started with commercially available 2-fluorobenzoic acid (**1**), which, upon treatment at 100°C with the sodium salt of (*S*)-1,1,1-trifluoro-propan-2-ol[12], provided 2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (**2**) with excellent yield. Coupling of (**2**) with 5-(tetrahydro-pyran-4-yl)-2,3-dihydro-1*H*-isoindole[13] using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as an acid activating agent afforded amide (**3**). Friedel-Crafts chlorosulfonylation of (**3**) proceeded in a fully regioselective manner at the most activated aromatic position to provide the desired sulfonyl-chloride intermediate (**4**). Reduction of (**4**) proceeded uneventfully in the presence of sodium sulfite at 40°C. After basification with sodium bicarbonate and purification on a reverse-phase column, the sulfinate sodium salt (**5**) was

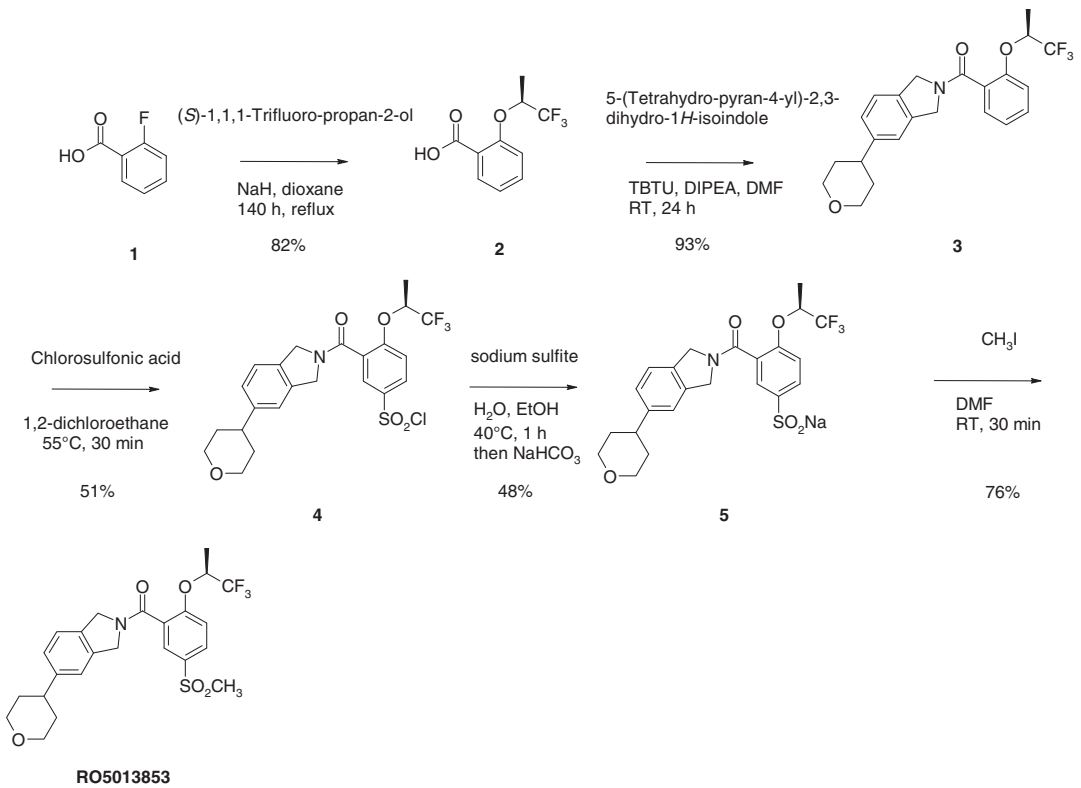

Figure 2. Chemical synthesis of RO5013853.

isolated with 48% yield as a pure and stable white solid. The reaction of (**5**) in solution with one equivalent of methyl iodide in dimethylformamide (DMF) provided RO5013853 in excellent yield (76%). The reaction was rapid: the full conversion of sulfinate (**5**) was reached in less than 30 min at room temperature. Moreover, under these reaction conditions, the formation of the corresponding sulfinic methylester resulting from the competing O-alkylation was not detected, making the purification of RO5013853 very straightforward.

The methylation reaction conditions established for sulfinate precursor (**5**) were then applied to the preparation of [^{11}C]RO5013853. [^{11}C]RO5013853 was synthesized remotely using a captive solvent system by reaction of [^{11}C]methyl iodide with the nor-methyl precursor (**5**) in DMF (Figure 3). After the reaction, the product was purified by semi-preparative HPLC. Figure 4 shows a typical semi-preparative chromatogram. [^{11}C]RO5013853 was collected in water, concentrated on a reverse-phase SPE, eluted through a sterile filter into a sterile vial with absolute ethanol, and then diluted with sterile saline. A typical synthesis produced 4.13±1.46 GBq (111.7±39.6 mCi; n=95) of final [^{11}C]RO5013853. Based on a calculated production of 56 GBq [^{11}C]carbon dioxide, the radiochemical yield was approximately 7% (calculated at end of synthesis, not corrected for decay). The average time of synthesis was 33 min (from end-of-bombardment to radiotracer product in vial). The average specific radioactivity was 49.3±29.6 GBq/μmol (13342±7998 mCi/μmol) calculated at end of synthesis. Analytical HPLC (Figure 5) demonstrated the product to be radiochemically pure (100%). [^{11}C]RO5013853 co-eluted with an authentic non-radioactive standard of the product. The radiotracer was sterile and free from pyrogens (<5 EU/mL) by standard analytical tests.

Conclusions

We have established a reliable and convenient synthesis of [^{11}C]RO5013853, a PET ligand of GlyT1. The incorporation of the radioisotope was achieved in the final step through radiomethylation with [^{11}C]methyl iodide of a sodium sulfinate precursor, itself easily accessible by reduction of the corresponding sulfonyl-chloride analog. Results from the evaluation of [^{11}C]RO5013853 in baboon and human PET studies will be reported in due course.

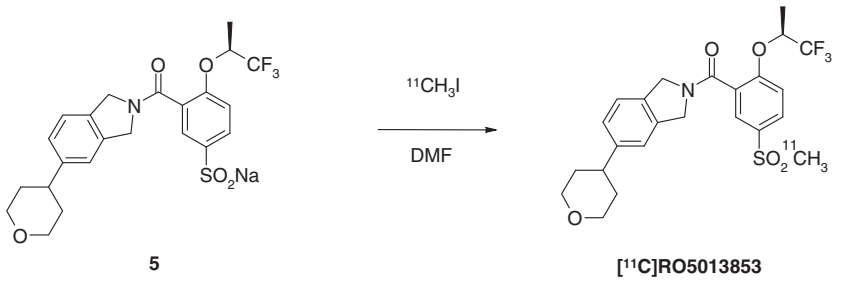

Figure 3. Radiosynthesis of [^{11}C]RO5013853.

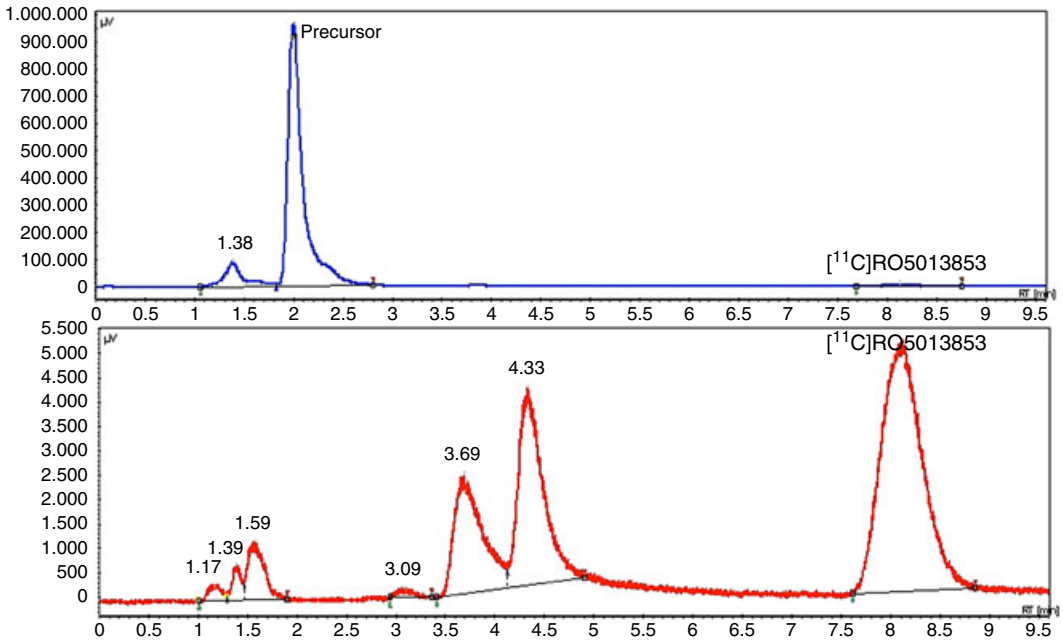

Figure 4. Semi-preparative HPLC of reaction mixture. Top panel, UV chromatogram. Bottom panel, radiochromatogram. [^{11}C]RO5013853 elutes at approximately 8 min.

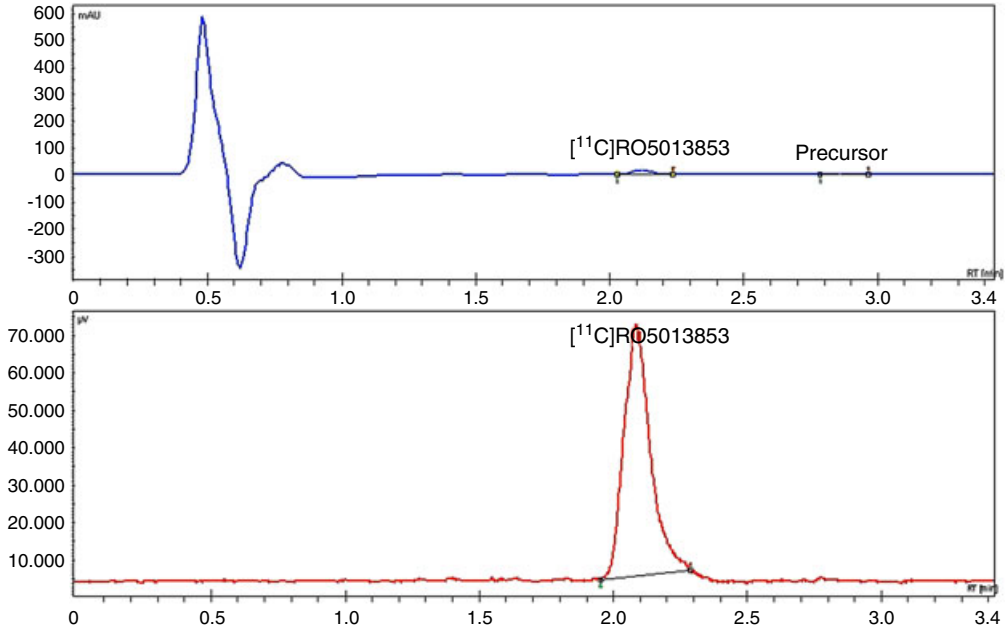

Figure 5. Analytical HPLC of final radiotracer product. Top panel is UV chromatogram. Bottom panel is radiochromatogram. [^{11}C]RO5013853 elutes at approx. 2.1 min.

Experimental

Chemistry

All solvents and reagents were obtained from commercial sources and were used as received. All reactions were followed by thin layer chromatography (TLC) (TLC plates F254, Merck) or liquid chromatography-mass spectrometry (LCMS) analysis. Proton NMR spectra were obtained on a Bruker 300- or 400-MHz instrument with chemical shifts (δ in ppm) reported relative to tetramethylsilane as internal standard. NMR abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; sext, sextuplet; hept, heptuplet; m, multiplet; br, broadened. Elemental analyses were performed by Solvias AG (Mattenstrasse, Postfach, CH-4002 Basel, Switzerland). Column chromatography was carried out on silica gel 60 (32–60 mesh, 60 Å) or on prepacked columns (Isolute Flash Si). Mass spectra were recorded on a SSQ 7000 (Finnigan-MAT) spectrometer using electron impact ionization.

Radiochemistry

For radiochemical syntheses, DMF was stirred over barium oxide for 24 h and then vacuum distilled. Carbon-11-labeled carbon dioxide was produced by proton bombardment of nitrogen-14 gas in a General Electric PETtrace 18 MeV cyclotron. Carbon-11-labeled methyl iodide ([^{11}C]CH_3I) was synthesized using a General Electric MeI Microlab gas phase system. A Bioscan Autoloop® (software version 1.0.233) captive solvent methylation system was used to trap and react the [^{11}C]methyl iodide with the precursor. Semipreparative chromatography (connected in concert with the Autoloop) was performed with a Waters 610 pump, Waters 486 UV detector (254 nm), and a Bioscan Flow-Count module with a diode radioactivity detector. The semi-preparative HPLC column was a Waters XTerra C18 5 μm, 19 × 100 mm column eluted with a mixture of 40:60 acetonitrile/water containing 0.1 N ammonium formate at a flow rate of 18 mL/min. The analytical chromatography system consisted of a Varian Prostar 210 pump with a Prostar 410 autosampler, a Varian Prostar 325 LC detector (205 nm), and a Bioscan Flow-Count module with a diode radioactivity detector. The analytical HPLC column was a Phenomenex Luna C-18(2) 5 μm, 4.6 × 150 mm column thermoregulated to a temperature of 30 °C, eluted with a mixture of 50:50 acetonitrile/water containing 0.2% formic acid at a flow rate of 3 mL/min. Chromatographic data were acquired and analyzed on a Varian Galaxie chromatography data system (version 1.9.302.952). Radioactivity measurements were made using a Capintec CRC-15R dose calibrator.

2-((*S*)-2,2,2-Trifluoro-1-methyl-ethoxy)-benzoic acid (2)

(*S*)-1,1,1-Trifluoro-propan-2-ol[12] (36.0 g, 316 mmol) was added to a cooled (0 to 5 °C) suspension of NaH (60% dispersion in mineral oil) (17.0 g, 425 mmol) in dioxane (200 mL). The suspension was stirred at room temperature for 0.5 h and then cooled (0 to 5 °C), and a solution of 2-fluoro-benzoic acid (20.0 g, 143 mmol) in dioxane (100 mL) was added. The mixture was stirred for 0.5 h at room temperature and then for 140 h under reflux. The mixture was poured into water (800 mL), washed with methyl-*t*-butylether (MTBE) (300 mL), and then acidified to pH 2 with hydrochloric acid; the product was extracted with MTBE. The solvent was evaporated *in vacuo*, and the residue was crystallized from ethanol/water to provide 27.3 g (82%) of the desired product (**2**) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.3 (br, 1H), 8.15 (m, 1H), 7.56 (m, 1H), 7.22 (m, 1H), 7.07 (m, 1H), 4.86 (m, 1H), 1.62 (d, J = 6.6 Hz, 3H). MS (EI) *m/e*: 234.1 $[M]^+$.

[5-(Tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-[2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone (3)

To a solution of **2** (0.9 g, 3.8 mmol) in DMF (9 mL) under argon at room temperature was added TBTU (1.4 g, 4.2 mmol), *N*-ethyldiisopropylamine (3.3 mL, 19.2 mmol), and finally 5-(tetrahydro-pyran-4-yl)-2,3-dihydro-1*H*-isoindole (0.8 g, 3.8 mmol).[13] The mixture was stirred at room temperature overnight. The

solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate. The solution was washed twice with water and twice with sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash-column chromatography on silica eluting with a gradient formed from heptane and ethylacetate to provide 1.5 g (93%) of the desired product (**3**) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.28 (m, 2H), 7.21–6.99 (m, 5H), 4.96 (m, 2H), 4.69–4.50 (m, 3H), 4.16–4.04 (m, 2H), 3.58–3.47 (m, 2H), 2.82–2.73 (m, 1H), 1.86–1.72 (m, 4H), 1.45 (d, *J*=6.6 Hz, 3H). MS (EI) *m/e*: 420.2 $[M+H]^+$.

3-[5-(Tetrahydro-pyran-4-yl)-1,3-dihydro-isoindole-2-carbonyl]-4-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonyl chloride (4)

A solution **3** (0.2 g, 0.47 mmol) in 1,2-dichloroethane (2 mL) was added dropwise to chlorosulfonic acid (0.32 mL, 4.7 mmol) under ice-bath cooling. The mixture was stirred at room temperature for 30 min and then at 55 °C for 30 min. The mixture was cooled in an ice bath, and water (2 mL) was added dropwise. Dichloromethane was also added. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined dichloromethane extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting foam was stirred with ethylacetate. The solid was removed by filtration. The filtrate was washed twice with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 0.12 g (51%) of the desired product (**4**) as a light yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13–8.06 (m, 2H), 7.32–6.91 (m, 4H), 4.98 (m, 2H), 4.99–4.86 (m, 1H), 4.63–4.54 (m, 2H), 4.13–4.05 (m, 2H), 3.58–3.47 (m, 2H), 2.80–2.76 (m, 1H), 1.86–1.73 (m, 4H), 1.55 (d, *J*=6.6 Hz, 3H). MS (EI) *m/e*: 517.1 $[M]^+$.

3-[5-(Tetrahydro-pyran-4-yl)-1,3-dihydro-isoindole-2-carbonyl]-4-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfinate sodium salt (5)

Na_2SO_3 (1.15 g, 8.94 mmol) and Na_2HPO_4 hydrate (1.70 g, 9.60 mmol) were dissolved in water (13 mL). An ethanolic solution of **4** (2.40 g, 4.63 mmol) was added. The reaction mixture was stirred at 35 to 40 °C for 1 h and then at room temperature overnight. Speedex (1.3 g) was added; the reaction mixture was filtered; and the filtrate was concentrated *in vacuo*. The crude product was treated with aqueous citric acid/NaCl solution and then extracted with MTBE/THF (1:1). The organic solvent was evaporated, and the residue was dissolved in MeOH/water (2:1) and then treated with $NaHCO_3$ (800 mg, 9.52 mmol). Speedex (1 g) was added, and the reaction mixture was filtrated and concentrated *in vacuo*. The residue was purified by chromatography on a reverse-phase column (RP-18, water/methanol) to provide 1.12 g (48%) of the desired product (**5**) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51–7.14 (m, 6H), 5.21 (m, 1H), 4.78 (m, 2H), 4.43 (m, 2H), 3.93 (m, 2H), 3.41 (m, 2H), 2.73 (m, 1H), 1.70–1.64 (m, 4H), 1.35 (d, *J*=6.0 Hz, 3H). MS (EI) *m/e*: 484.3 $[M+H]^+$.

[5-Methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5-(tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-methanone; RO5013853

To a solution of **5** (20 mg, 0.040 mmol) in DMF (0.5 mL) was added dropwise at room temperature iodomethane (5.6 mg, 0.040 mmol) in solution in DMF. The mixture was stirred at room temperature for 30 min, and the solvent was evaporated *in vacuo*. The residue was purified by flash-column chromatography on silica eluting with a gradient formed from heptane and ethylacetate to provide 15 mg (76%) of the desired product (RO5013853) as a white solid. $[\alpha]_D^{20}$ −5.96° (*c*=1.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dt, *J*=8.7, 2.2 Hz, 1H), 7.95 (d, *J*=2.2 Hz, 1H) 7.31–7.00 (m, 4H), 4.97 (m, 2H), 4.82 (quint., *J*=6.1 Hz, 1H), 4.61–4.53 (m, 2H), 4.12–4.05 (m, 2H), 3.58–3.47 (m, 2H), 3.07 (s, 3H), 2.80–2.75 (m, 1H), 1.86–1.73 (m, 4H), 1.53 (d, *J*=6.5 Hz, 3H). MS (EI) *m/e*: 498.4 $[M+H]^+$. Anal. calcd. for $C_{24}H_{26}F_3NO_5S$: C, 57.94; H, 5.27; N, 2.82; S, 6.44; F, 11.46. Found: C, 57.77; H, 5.32; N, 2.93; S, 6.48; F, 11.64. HPLC, analytical Chiralpack AD® column (flow rate: 1 mL/ min, pressure: 25 bar, detection at 254 nm) using heptane/isopropanol (80:20) as eluant, retention time: 14.4 min ee > 99%.

The *R*-enantiomer was independently prepared, and the retention time under the above HPLC conditions is 7.8 min.

[5-[^{11}C]Methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5-(tetrahydro-pyran-4-yl)-1,3-dihydro-isoindol-2-yl]-methanone; [^{11}C]RO5013853

At end of bombardment (EOB), the [^{11}C]carbon dioxide was released from the target into the GE MeI Microlab system, and the [^{11}C]methyl iodide module was started. At approximately 7 min post-EOB, between 0.5 and 1 mg of **5** in DMF (100 μL) was added to the cleaned loop of the Bioscan Autoloop® system. At approximately 10 min post-EOB, [^{11}C]methyl iodide was released from the Microlab system in a stream of helium at a flow rate of 20 mL/min through the loop methylation system until the radioactivity reached a plateau (approximately 2 min). Upon reaching a plateau, the reaction was kept at room temperature in the loop for 4.5 min. The reaction mixture was automatically injected into the preparative HPLC column. [^{11}C]RO5013853 (retention time of approximately 8 min) was collected in a reservoir containing water (50 mL). After collection, the reservoir was emptied through a reverse-phase SPE (Waters C-18 SepPak Plus) cartridge previously conditioned with absolute ethanol (10 mL) followed by water (10 mL). The SPE cartridge was then washed with sterile saline (10 ml) that was sent to waste. The output of the SPE cartridge was connected to a sterile filter (Millipore Millex-FG, 0.2 μm, 25 mm diameter). Absolute ethanol (1 ml) was passed through the SPE cartridge to elute the [^{11}C]RO5013853 into a sterile vial previously charged with sterile saline (4 mL). The SPE cartridge was further washed with sterile saline (10 mL) into same sterile vial. Before an aliquot was aseptically removed for quality control, the radioactivity content of the sterile product vial was assayed. Radiochemical purity, chemical purity, chemical identity, and specific activity were determined by analytical HPLC (retention time (RO5013853)= 2.12 min; retention time (**5**)=2.86 min). The final pH was approximately 5. The product was assayed by gas chromatography (method not presented here) and determined to have considerably less than 20 ppm of residual acetonitrile and DMF. Pyrogen testing using an Endosafe PTS® (Charles River Laboratories, MA) was performed. Sterility testing was performed according to the United States Pharmacopeia, Chapter 71.

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