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# SYNTHESIS OF A NEW CARBON-11–LABELED SULFAMATE DERIVATIVE AS A POTENTIAL PET TRACER FOR IMAGING OF BREAST CANCER AROMATASE AND STEROID SULFATASE EXPRESSION

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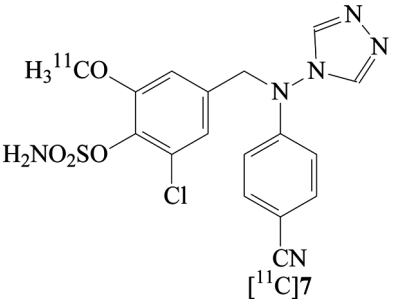
## GRAPHICAL ABSTRACT




**Abstract** *A carbon-11-labeled sulfamate derivative was designed and synthesized as a new potential positron-emission-tomography dual aromatase–steroid sulfatase inhibitor radiotracer for imaging of aromatase and steroid sulfatase expression in breast cancer. The target tracer 2-chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-6-[$^{11}$C]methoxyphenyl sulfamate ([$^{11}$C]**7**) was prepared from its corresponding precursor 2-chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-6-hydroxyphenyl sulfamate (**18**) with [$^{11}$C]$CH_3OTf$ under basic conditions through the O-[$^{11}$C]methylation and isolated by the reversed-phase high-performance liquid chromatography in 40–45% radiochemical yields based on [$^{11}$C]$CO_2$ and decay corrected to end of bombardment. The specific activity at end of synthesis was 111-185 GBq/μmol.*

**Keywords** Aromatase; cancer imaging; positron emission tomography; radiotracer; steroid sulfatase; sulfamate derivative

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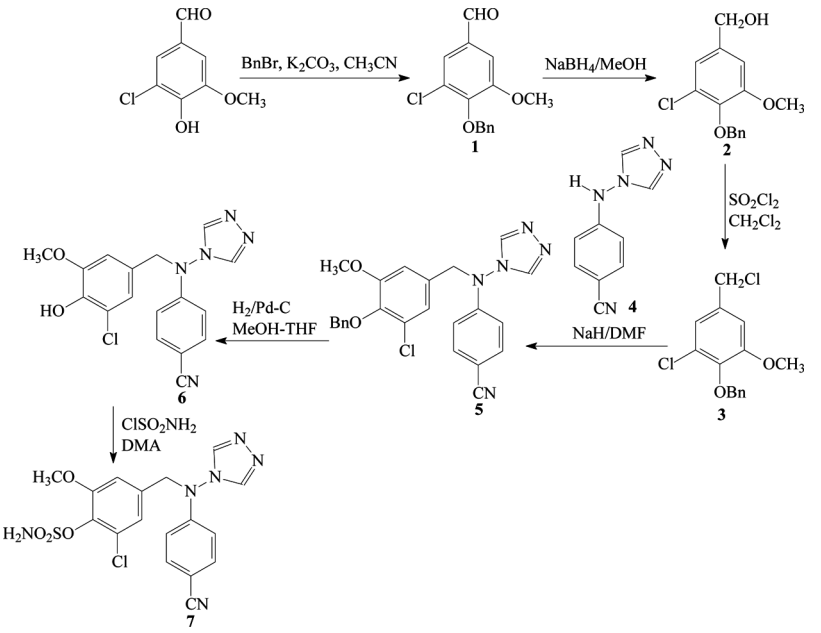
## INTRODUCTION

The enzymes aromatase and steroid sulfatase (STS) are particularly attractive targets in the treatment of estrogen receptor (ER)–positive breast cancer, and a novel series of sulfamate derivatives have been recently developed as potent dual aromatase–steroid sulfatase inhibitors (DASSIs).[1] The enzymes aromatase and STS also provide attractive targets for the development of enzyme-based breast cancer imaging agents for the biomedical imaging technique positron emission tomography (PET).[2] Sulfamate derivatives labeled with a positron-emitting radionuclide such as carbon-11 or fluorine-18 may enable noninvasive monitoring of the enzymes aromatase and STS and breast cancer response to DASSI treatment using PET. The selected title compound, 2-chloro-4-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)-methyl)-6-methoxyphenyl sulfamate (**7**), exhibited excellent biological activity: in vitro inhibition of aromatase and STS activity assessed using intact monolayers of JEG-3 cells with $IC_{50}$ (nM) $2.9 \pm 0.2$ and $536 \pm 38$, respectively.[1] Also, it has an *O*-methyl position amenable to labeling with carbon-11. These properties are often applied to development of a diagnostic radiotracer. We are interested in the development of enzyme- and/or receptor-based PET breast cancer imaging agents. A series of PET breast cancer imaging agents have been developed in this laboratory, including carbon-11-labeled aromatase inhibitors (NS-398 derivatives) for imaging of aromatase enzyme,[3] carbon-11-labeled cyclofenil derivatives as nonsteroidal estrogen radioligands for imaging of ER,[4] carbon-11-labeled tetrahydroisoquinoline derivatives as selective estrogen receptor modulator (SERM) radioligands for imaging of ER expression,[5] and carbon-11-labeled sulfamate derivatives as new DASSI radiotracers for imaging of aromatase and STS expression.[2] This ongoing study was to develop a new carbon-11-labeled chloro-containing sulfamate derivative, because this compound displayed better in vitro biological activity than other compounds previously reported[2] and opened an avenue to label sulfamate derivatives with another positron emitting radionuclide fluorine-18 through a halogen exchange reaction. Here, we report the design and synthesis of 2-chloro-4-(((4-cyanophenyl)(4*H*-1,2,4-triazol-4-yl)amino)methyl)-6-[$^{11}$C]methoxyphenyl sulfamate ([$^{11}$C]**7**), a new potential enzyme-based PET agent for imaging of breast cancer aromatase and STS expression.

## RESULTS AND DISCUSSION

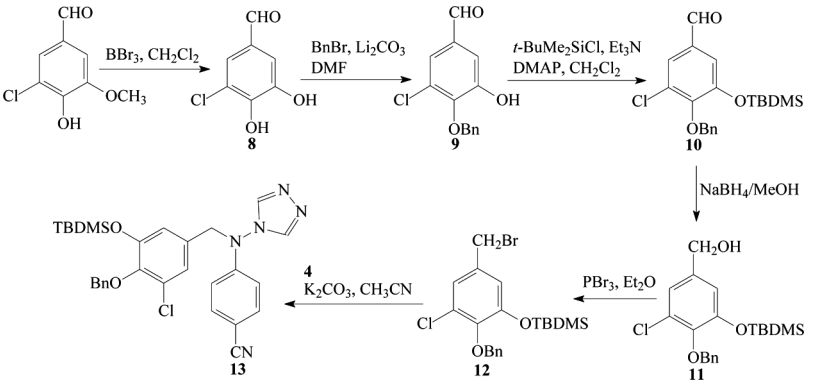
The synthesis of the reference standard **7** is outlined in Scheme 1 using slight modifications of the literature method.[1] The improvements included modified synthetic approaches with moderate to excellent chemical yields, more complete experimental procedures, and detailed spectral data. The phenolic hydroxyl group of 3-chloro-4-hydroxy-5-methoxybenzaldehyde was protected as benzyl ether with benzyl bromide in $CH_3CN$ using $K_2CO_3$ as a base to give **1** in 91% yield.[6] The benzyl protected aldehyde **1** was reduced to alcohol **2** using $NaBH_4$ in a mixture of $CH_2Cl_2$ and MeOH in 99% yield. The benzyl alcohol **2** was converted to benzyl chloride **3** with $SO_2Cl_2$ in $CH_2Cl_2$ in 71% yield. Coupling of the protected hydroxybenzyl chloride **3** and 4-((4-cyanophenyl)amino)-4*H*-1,2,4-triazole **4**, which was prepared from 4-fluorobenzonitrile and 4-amino-4*H*-1,2,4-triazole essentially following the literature method[7] in



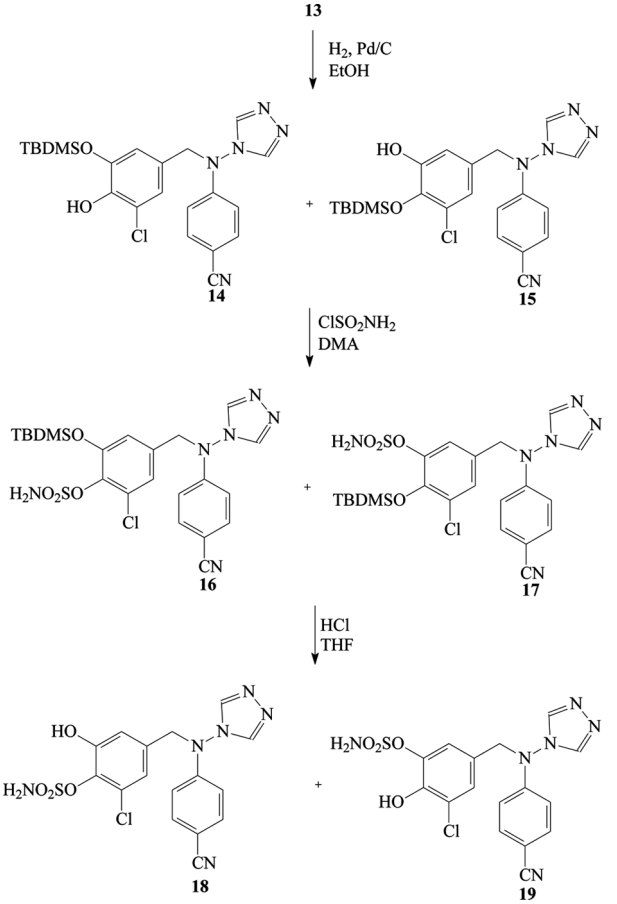

**Scheme 1.** Synthesis of a sulfamate derivative **7**.

42% yield, in dimethylformamide (DMF) with NaH as a base afforded the tertiary amine **5** in 56% yield. Deprotection of benzyl group of **5** by catalytic hydrogenation with 10% Pb/C in a mixture of MeOH and tetrahydrofuran (THF) provided phenol **6** in 65% yield. The resulting phenol **6** was reacted with an excess of sulfamoyl chloride in dimethylamine (DMA) to give the target compound **7** in 52% yield.

To obtain a phenolic precursor, we envisioned that **18** could be prepared by *O*-demethylation of compound **7**. A variety of protocols[8] were screened for this purpose, including protic acid (HBr), Lewis acids ($BBr_3$, $AlCl_3$/EtSH, LiCl/DMF), and base (EtSNa). However, in all cases, the demethylated product was obtained with very poor yield. As a result of these unsuccessful attempts, an alternative strategy was first investigated as we were interested in the development of the precursor chemistry with readily available starting material. As shown in Scheme 2, demethylation of 3-chloro-4-hydroxy-5-methoxybenzaldehyde with $BBr_3$ in $CH_2Cl_2$ gave 3-chloro-4,5-dihydroxybenzaldehyde **8** in 91% yield.[9,10] To generate differentially protected hydroxyl groups at 4- and 5-positions, selective benzylation[11] of the more acidic 4-hydroxyl group by pretreatment of catechol **8** with $Li_2CO_3$ as a base in DMF prior to addition of benzyl bromide was achieved to provide **9** in 89% yield. Silylation of the 5-hydroxyl group of **9** as *tert*-butyldimethylsilyl (TBDMS) ether with *tert*-butyldimethylsilyl chloride, triethylamine, and dimethylaminopyradine (DMAP) in $CH_2Cl_2$ afforded **10** in 89% yield. Redution of the protected aldehyde **10** with $NaBH_4$ in MeOH provided the resulting alcohol **11** in 84% yield. Bromination of compound **11** with $PBr_3$ in $Et_2O$ gave benzyl bromide **12** in 89% yield. Benzyl bromide **12** was reacted with **4** in $CH_3CN$ using $K_2CO_3$ as a base to afford a key intermediate tertiary amine **13** in 13% yield. As indicated in Scheme 3, debenzylation




**Scheme 2.** Synthesis of a key intermediate **13**.



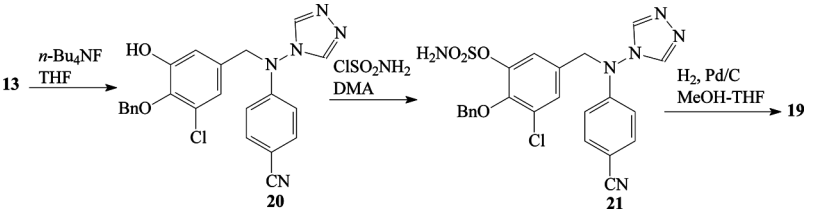

**Scheme 3.** Synthesis of a sulfamate derivative precursor **18** and its regioisomer **19**.

of compound **13** by catalytic hydrogenation yielded two phenols as a 3:1 mixture of regioisomers **14** and **15** in 86% yield. It was difficult to separate and purify the mixture of two regioisomers by silica-gel thin-layer chromatography (TLC) or flash column chromatography, and the ratio of the resulting regioisomers was determined by $^1$H NMR. The phenol **15** is the product of 1,2-*O,O*-TBDMS migration of the phenol **14**.[12] Without separation, the mixture was sulfamoylated in DMA to give two sulfamates **16** and **17** in 51% yield. Likewise, these two regioisomers were not separable by silica gel. Initial removal of TBDMS groups (desilylation) of compounds **16** and **17** with tetra-*n*-butylammonium fluoride (TBAF) was unsuccessful. However, 6 N HCl in THF[13] proved to cleanly cleave the silicon–oxygen bond to give the separable alcohols **18** and **19** in 47% and 13% yields, respectively.

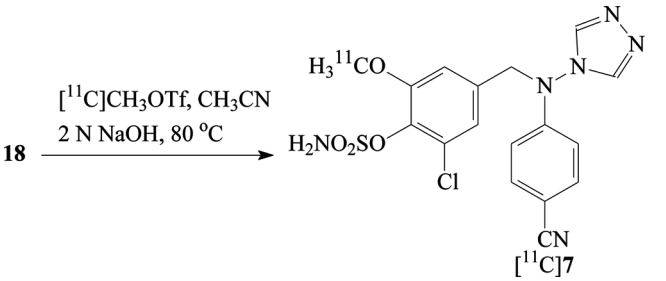
It is noteworthy that desilylation of amine **13** with TBAF in THF took place rapidly to give phenol **20** in 35% yield. Sulfamoylation of phenol **20** with sulfamoyl chloride in DMA afforded sulfamate **21** in 68% yield, which in turn was deprotected by catalytic hydrogenation to give free phenol **19** in 75% yield. The synthetic approach was outlined in Scheme 4. This also confirmed that the compound **19** was formed due to 1,2-*O,O*-TBDMS migration.

Synthesis of the target radiotracer [$^{11}$C]**7** is indicated in Scheme 5. Precursor **18** was labeled by a reactive [$^{11}$C]methylating agent, [$^{11}$C]methyl triflate ([$^{11}$C]$CH_3OTf$)[14,15] prepared from [$^{11}$C]$CO_2$, in the presence of 2 N NaOH in acetonitrile through the *O*-[$^{11}$C]methylation and isolated by semipreparative reversed-phase high-performance liquid chromatography (HPLC) to provide target tracer [$^{11}$C]**7** in 40–45% radiochemical yields, decay corrected to end of bombardment (EOB), based on [$^{11}$C]$CO_2$. The synthesis was performed in an automated multipurpose $^{11}$C-radiosynthesis module, allowing measurement of specific activity during synthesis.[16,17] The specific activity of [$^{11}$C]**7** was in a range of 222–370 GBq/μmol at EOB measured by the on-the-fly technique using semipreparative HPLC during synthesis[17] and 111–185 GBq/μmol at the end of synthesis (EOS) determined by analytical HPLC,[18] respectively. Chemical purity and radiochemical purity were determined by analytical HPLC.[18] The chemical purity of the precursor **18** and reference standard **7** was >96%. The radiochemical purity of the target tracer [$^{11}$C]**7** was >99% determined by radio-HPLC through γ-ray (PIN diode) flow detector, and the chemical purity of the target tracers [$^{11}$C]**7** was >95% determined by reversed-phase HPLC through an ultraviolet (UV) flow detector.

The precursor has the potential to methylate either at the nitrogen or at the oxygen position. The radio-HPLC chromatogram of the radiosynthesis did show




**Scheme 4.** Synthesis of a sulfamate derivative regioisomer **19**.




**Scheme 5.** Synthesis of a carbon-11–labeled sulfamate derivative [$^{11}$C]**7**.



other radiolabeled minor by-products, because the methylation of the precursor at the nitrogen position is a potential competing reaction. However, the evidence provided by the radio-HPLC chromatogram of the radiosynthesis showed that the precursor is mainly methylated at the oxygen position to produce the major target radiotracer compared to the retention time of the reference standard. These results are consistent with the theoretical explanation that the deprotonization at the oxygen position of the precursor is easier than at the nitrogen position under basic conditions (2 N NaOH) because the acidity of HO- of the precursor is greater than the acidity of $H_2NO_2SO$- of the precursor, and the methylation of the precursor will prefer to occur at the oxygen position rather than at the nitrogen position. More strongly basic conditions such as NaH may increase the yield of the methylated product at the nitrogen position.[19] Compared to the acidic HO- of the precursor, $H_2NO_2SO$- of the precursor tends to be basic.

## CONCLUSIONS

In summary, an efficient and convenient synthesis of a new carbon-11-labeled sulfamate derivative has been developed. The new precursor synthetic methodology employed organic reactions such as selective benzylation and debenzylation, reduction, bromination, coupling reaction, protecting and deprotecting reactions, and sulfamoylation to prepare a series of new sulfamate derivative precursors. The target radiotracer was prepared by the *O*-[$^{11}$C]methylation of its corresponding phenolic precursor using a reactive [$^{11}$C]methylating agent, [$^{11}$C]$CH_3OTf$, and isolated by a HPLC procedure in high radiochemical yields, short overall synthesis time, and high specific radioactivities. These chemistry results combined with the reported in vitro biological data[1] encourage further in vivo biological evaluation of this new carbon-11-labeled DASSI as a candidate PET radiotracer for imaging of enzymes aromatase and STS in breast cancer.

## EXPERIMENTAL

All commercial reagents and solvents from Sigma-Aldrich and Fisher Scientific were used without further purification. [$^{11}$C]$CH_3OTf$ was prepared according to a literature procedure.[15] Melting points were determined on a Mel-Temp II capillary

tube apparatus and were uncorrected. $^1$H NMR spectra were recorded on Bruker Avance II 500-MHz NMR spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants ($J$) were reported in hertz (Hz). The low-resolution mass spectra (LRMS) were obtained using a Bruker Biflex III matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer, and the high resolution mass spectra (HRMS) were obtained using a Thermo MAT 95XP-Trap spectrometer. Chromatographic solvent proportions are indicated as volume/volume ratio. TLC was run using Analtech silica-gel GF uniplates ($5 \times 10\,cm^2$). Plates were visualized under UV light. Preparative TLC was run using Analtech silica gel UV 254 plates ($20 \times 20\,cm^2$). Normal phase flash column chromatography was carried out on EM Science silica gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described next. All moisture- and/or air-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Analytical HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 4.6 × 250 mm; 3:1:1 $CH_3CN$ / MeOH / 20 mM, pH 6.7 phosphate (buffer solution) mobile phase; flow rate 1.5 mL/min; and UV (254 nm) and γ-ray (PIN diode) flow detectors. Semipreparative HPLC was performed using a YMC-Pack ODS-A, S-5 μm, 12 nm, 10 × 250 mm C-18 column; 3:1:1 $CH_3CN$ / MeOH / 20 mM, pH 6.7 phosphate (buffer solution) mobile phase; 5.0 mL/min flow rate; UV (254 nm) and γ-ray (PIN diode) flow detectors. Sterile Millex-GS 0.22-μm vented filter unit was obtained from Millipore Corporation, Bedford, MA.



### 4-(Benzyloxy)-3-chloro-5-methoxybenzaldehyde (1)

Benzyl bromide (15.3 mL, 129 mmol) was added to a mixture of 3-chloro-4-hydroxy-5-methoxybenzaldehyde (10.0 g, 53.6 mmol) and $K_2CO_3$ (18.6 g, 134 mmol) in $CH_3CN$ (160 mL). The mixture was stirred, heated at reflux for 6 h, and then allowed to cool to ambient temperature. After the inorganic powder was filtered off, the filtrate was concentrated in vacuo. Water was added to the residue and extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with column chromatography (1:4 EtOAc/hexanes) to give **1** (13.4 g, 91%) as a pale yellow solid, mp 42–43 °C (lit.[6] mp 43–44 °C). $^1$H NMR ($CDCl_3$): δ 9.84 (s, 1H), 7.51–7.50 (m, 3H), 7.39–7.33 (m, 4H), 5.17 (s, 2H), 3.94 (s, 3H).

### (4-(Benzyloxy)-3-chloro-5-methoxyphenyl)methanol (2)

$NaBH_4$ (2.2 g, 58.3 mmol) was added to a stirred solution of **1** (13.0 g, 47.1 mmol) in $CH_2Cl_2$ (8 mL) and MeOH (80 mL) portionwise at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was concentrated in vacuo. Cooled water was added to the residue and extracted with EtOAc. The combined organic layer was washed with brine and dried ($Na_2SO_4$). Concentration in vacuo afforded **2** (13.0 g, 99%) as a white solid, which was used for the next step in the reaction without further purification. $^1$H NMR ($CDCl_3$): δ 7.53–7.52 (m, 2H), 7.39–7.31 (m, 3H), 6.96 (d, $J = 1.5$ Hz, 1H), 6.85 (d, $J = 1.5$ Hz, 1H), 5.02 (s, 2H), 4.61 (s, 2H), 3.87 (s, 3H).

### 4-(Benzyloxy)-3-chloro-5-methoxybenzyl chloride (3)

$SOCl_2$ (9.0 mL, 123.7 mmol) was added to a stirred solution of **2** (13.0 g, 46.8 mmol) in $CH_2Cl_2$ (75 mL) dropwise. After stirring at room temperature for 4 h, the reaction mixture was concentrated in vacuo. The oily residue was poured onto ice and extracted with $Et_2O$. The combined organic layer was washed with saturated $NaHCO_3$, water, and brine; dried ($Na_2SO_4$); filtered; and concentrated in vacuo. The crude product was purified by trituration from $CH_2Cl_2$ by addition of hexanes to afford **3** (9.9 g, 71%) as a white solid, mp 39–40 °C (lit.[1] mp 39–41 °C). $^1$H NMR ($CDCl_3$): δ 7.53–7.52 (m, 2H), 7.40–7.32 (m, 3H), 7.02 (d, $J = 2.0$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 5.04 (s, 2H), 4.51 (s, 2H), 3.88 (s, 3H).

### 4-((4-Cyanophenyl)amino)-4H-1,2,4-triazole (4)

4-Amino-4*H*-1,2,4-triazole (16.8 g, 200 mmol) was added portionwise to a stirred suspension of potassium *tert*-butoxide (22.4 g, 200 mmol) in DMSO (100 mL) at 0 °C. After stirring at room temperature for 0.5 h, a solution of 4-fluorobenzonitrile (12.2 g, 100 mmol) in DMSO (30 mL) was added dropwise below 30 °C. The mixture was stirred for another 0.5 h at room temperature, then poured into water, and neutralized with 1 N HCl. The precipitate was filtered and recrystallized from water to afford **4** (7.8 g, 42%) as a white solid, mp 202–204 °C (lit.[7] mp 206–208 °C). $^1$H NMR (DMSO-$d_6$): δ 10.22 (s, 1H), 8.84 (s, 2H), 7.69 (d, $J = 9.0$ Hz, 2H), 6.56 (d, $J = 9.0$ Hz, 2H).

### 4-((4-(Benzyloxy)-3-chloro-5-methoxybenzyl)(4H-1,2,4-triazole-4-yl)amino)benzonitrile (5)

Compound **4** (4.0 g, 21.6 mmol) was added portionwise to a stirred suspension of NaH (60% dispersion in mineral oil, 950 mg, 23.8 mmol) in DMF (45 mL) at 0 °C. After stirring at room temperature for 0.5 h, a solution of **3** (7.06 g, 23.8 mmol) in DMF (15 mL) was added, and the mixture was heated at 90 °C overnight. The reaction mixture was cooled, poured into water, and extracted with EtOAc. The combined organic layer was washed with brine and dried ($Na_2SO_4$). Concentration in vacuo gave an orange residue, which was recrystallized from *i*-PrOH to afford **5** (5.2 g, 56%) as a white solid, mp 178–180 °C (lit.[1] mp 177–178 °C). $^1$H NMR (DMSO-$d_6$): δ 8.85 (s, 2H), 7.78 (d, $J = 9.0$ Hz, 2H), 7.44–7.42 (m, 2H), 7.39–7.31 (m, 3H), 6.97 (s, 2H), 6.78 (d, $J = 9.0$ Hz, 2H), 5.00 (s, 2H), 4.96 (s, 2H), 3.81 (s, 3H).

### 4-((3-Chloro-4-hydroxy-5-methoxybenzyl)(4H-1,2,4-triazol-4-yl)amino)benzonitrile (6)

To a stirred solution of **5** (4.0 g, 9.3 mmol) in THF (200 mL) and MeOH (100 mL) was added 10% Pd/C (400 mg). The flask was charged with a balloon filled with $H_2$ gas and stirred at room temperature overnight. The catalyst was removed by filtration through celite. The filtrate was concentrated in vacuo to give a beige residue, which was recrystallized from EtOH to give **6** (2.1 g, 65%) as a white solid, mp 235 °C (dec) [lit.[1] mp > 230 °C (dec)]. $^1$H NMR (DMSO-$d_6$): δ 9.50 (s, 1H), 8.79

(s, 2H), 7.77 (d, $J = 9.0$ Hz, 2H), 6.84 (s, 1H), 6.82 (s, 1H), 6.79 (d, $J = 9.0$ Hz, 2H), 4.92 (s, 2H), 3.77 (s, 3H).

### 2-Chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-6-methoxyphenyl Sulfamate (7)

Sulfamoyl chloride (729 mg, 6.31 mmol) was added to a stirred solution of **6** (660 mg, 1.86 mmol) in dimethylamine (DMA) (6 mL) at 0 °C under a nitrogen atmosphere. After stirring at room temperature overnight, the mixture was poured into ice water and extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The crude product was purified with column chromatography (1:7 MeOH/$CHCl_3$) to give **7** (420 mg, 52%) as a white solid, mp 217 °C (dec) [lit.[1] mp > 210 °C (dec)]. $^1$H NMR (DMSO-$d_6$): δ 8.91 (s, 2H), 7.98 (s, 2H), 7.78 (d, $J = 9.0$ Hz, 2H), 7.08 (s, 1H), 7.05 (s, 1H), 6.75 (d, $J = 9.0$ Hz, 2H), 5.06 (s, 2H), 3.77 (s, 3H).

### 3-Chloro-4,5-dihydroxybenzaldehyde (8)

$BBr_3$ (12.1 mL, 130 mmol) was added to a stirred solution of 3-chloro-4-hydroxy-5-methoxybenzaldehyde (20.0 g, 110 mmol) in $CH_2Cl_2$ (350 mL) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 0.5 h and at room temperature for 3 h, the mixture was cooled to 0 °C, and MeOH (100 mL) was added carefully. The solvent was concentrated in vacuo, and the residue was added MeOH (100 mL). This process was repeated three times. The residue was diluted with $CH_2Cl_2$, and the precipitate was filtered and washed with $CH_2Cl_2$ to give **8** (16.8 g, 91%) as a pink solid, mp 235 °C (dec). $^1$H NMR (DMSO-$d_6$): δ 10.4 (s, 2H), 9.70 (s, 1H), 7.43 (d, $J = 2.0$ Hz, 1H), 7.22 (d, $J = 2.0$ Hz, 1H).

### 4-(Benzyloxy)-3-chloro-5-hydroxybenzldehyde (9)

$Li_2CO_3$ (13.4 g, 180.8 mmol) was added to a stirred solution of **8** (12.0 g, 69.54 mmol) in DMF (120 mL). After stirring and heating at°C for 1 h, benzyl bromide (21.5 mL, 180.8 mmol) was added dropwise. The mixture was stirred at 45 °C for another 1 h and then cooled to 0 °C. The reaction was quenched with 1 N HCl and extracted with EtOAC. The combined organic layer was washed with water and brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with column chromatography (1:9 hexanes/$CH_2Cl_2$) to give **9** (16.2 g, 89%) as an off-white solid, mp 45–47 °C. $^1$H NMR ($CDCl_3$): δ 9.80 (s, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.44–7.37 (m, 5H), 7.32 (d, $J = 2.0$ Hz, 1H), 5.19 (s, 2H). HRMS (CI, $m/z$): calc. for $C_{14}H_{12}O_3Cl$ ($[M + H]^+$), 263.0469; found, 263.0459.

### 4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-chlorobenzaldehyde (10)

Triethylamine (44.6 mL, 320 mmol) was added to a stirred solution of **9** (12.0 g, 45.7 mmol) and DMAP (1.68 g, 13.7 mmol) in $CH_2Cl_2$ (200 mL), followed by *tert*-butyldimethylsilyl chloride (20.7 g, 137.1 mmol), at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 1 h and at room temperature for 2 h, the reaction

mixture was washed with saturated $NH_4Cl$. The organic layer was washed with water and brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with column chromatography (1:9 hexanes/$CH_2Cl_2$) to give **10** (15.4 g, 89%) as a pale yellow oil. $^1H$ NMR ($CDCl_3$): δ 9.82 (s, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.49–7.48 (m, 2H), 7.39–7.33 (m, 3H), 7.30 (d, $J = 2.0$ Hz, 1H), 5.12 (s, 2H), 1.02 (s, 9H), 0.23 (s, 6H). HRMS (CI, $m/z$): calc. for $C_{20}H_{26}O_3ClSi$ ($[M + H]^+$), 377.1334; found, 377.1333.

### (4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-chlorophenyl)methanol (11)

$NaBH_4$ (2.6 g, 68.7 mmol) was added to a stirred solution of **10** (14.6 g, 38.7 mmol) in MeOH (40 mL) portionwise at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was concentrated in vacuo. Cooled water was added to the residue and extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with column chromatography (1:100 MeOH/$CH_2Cl_2$) to give **11** (12.3 g, 84%) as a white solid, mp 37–39 °C. $^1H$ NMR ($CDCl_3$): δ 7.51–7.50 (m, 2H), 7.39–7.31 (m, 3H), 7.01 (d, $J = 2.0$ Hz, 1H), 6.81 (d, $J = 2.0$ Hz, 1H), 5.00 (s, 2H), 4.58 (s, 2H), 1.00 (s, 9H), 0.19 (s, 6H). HRMS (CI, $m/z$): calc. for $C_{20}H_{27}O_3ClSi$ ($[M]^+$), 378.1415; found, 378.1413.

### 4-(Benzyloxy)-3-(*tert*-Butyldimethylsilyloxy)-5-chlorobenzyl Bromide (12)

$PBr_3$ (3.0 mL, 31.9 mmol) was added to a stirred solution of **11** (11.5 g, 30.3 mmol) in $Et_2O$ (150 mL) dropwise at 0 °C. After stirring at room temperature for 7 h, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic layer was washed with water and brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo to afford **12** (11.9 g, 89%) as a pale yellow oil. This material was used for the next step in the reaction without further purification. $^1H$ NMR ($CDCl_3$): δ 7.51–7.49 (m, 2H), 7.39–7.33 (m, 3H), 7.04 (d, $J = 2.0$ Hz, 1H), 6.83 (d, $J = 2.0$ Hz, 1H), 5.01 (s, 2H), 4.37 (s, 2H), 1.00 (s, 9H), 0.20 (s, 6H). HRMS (CI, $m/z$): calc. for $C_{20}H_{27}O_2BrClSi$ ($[M]^+$), 441.0647; found, 441.0641.

### 4-((4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-5-chlorobenzyl)(4H-1,2,4-triazole-4-yl)amino)benzonitrile (13)

A mixture of **4** (4.1 g, 22.3 mmol), **12** (9.8 g, 22.3 mmol), and $K_2CO_3$ (6.2 g, 44.5 mmol) in $CH_3CN$ (180 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layer was washed with water and brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with column chromatography (1:30 MeOH/$CH_2Cl_2$) to afford **13** (1.6 g, 13%) as a yellow solid, mp 58–60 °C. $^1H$ NMR ($CD_3COCD_3$): δ 8.58 (s, 2H), 7.74–7.71 (m, 2H), 7.55–7.33 (m, 5H), 7.15 (d, $J = 2.0$ Hz, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.88–6.85 (m, 2H), 5.11 (s, 2H), 5.03 (s, 2H), 0.98 (s, 9H), 0.18 (s, 6H). HRMS (TOF ES+, $m/z$): calc. for $C_{29}H_{33}N_5O_2ClSi$ ($[M + H]^+$), 546.2092; found, 546.2105.

### 4-((3-(*tert*-Butyldimethylsilyloxy)-5-chloro-4-hydroxybenzyl)(4H-1,2,4-triazol-4-yl)amino)benzonitrile (14) and 4-((4-(*tert*-Butyldimethylsilyloxy)-3-chloro-5-hydroxybenzyl)(4H-1,2,4-triazol-4-yl)amino)benzonitrile (15)

To a stirred solution of **13** (500 mg, 0.92 mmol) in EtOH (5 mL) was added 10% Pd/C (50 mg). The flask was charged with a $H_2$ balloon and stirred at room temperature overnight. The catalyst was removed by filtration through celite. The filtrate was concentrated in vacuo and then purified with preparative TLC plate (1:30 MeOH/$CH_2Cl_2$) to afford a nonseparable mixture of regioisomers **14** and **15** (360 mg, 86%) as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 9.93, 9.07 (s, 1H), 8.74, 8.71 (s, 2H), 7.76 (d, $J = 9.0$ Hz, 2H), 6.92–6.64 (m, 4H), 4.90 (s, 2H), 0.99, 0.92 (s, 9H), 0.17, 0.11 (s, 6H). HRMS (TOF ES+, $m/z$): calc. for $C_{22}H_{27}N_5O_2ClSi$ ($[M + H]^+$), 456.1623; found, 456.1634.

### 2-(*tert*-Butyldimethylsilyloxy)-6-chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)phenyl Sulfamate (16) and 2-(*tert*-Butyldimethylsilyloxy)-3-chloro-5-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)phenyl Sulfamate (17)

Sulfamoyl chloride (227 mg, 1.97 mmol) was added to a stirred solution of a mixture of two regioisomers **14** and **15** (300 mg, 0.66 mmol) in DMA (3 mL) at 0 °C under a nitrogen atmosphere. After stirring at room temperature overnight, ice water was added, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with preparative TLC plate (1:30 MeOH/$CH_2Cl_2$) to afford a nonseparable mixture of regioisomers **16** and **17** (179 mg, 51%) as a pale yellow solid. $^1$H NMR (DMSO-$d_6$): δ 8.83, 8.78 (s, 2H), 8.17, 8.02 (s, 2H), 7.77 (d, $J = 9.0$ Hz, 2H), 7.34 (d, $J = 2.0$ Hz, 1H), 7.30 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 9.0$ Hz, 2H), 4.97 (s, 2H), 0.98, 0.92 (s, 9H), 0.20, 0.13 (s, 6H). HRMS (TOF ES+, $m/z$): calc. for $C_{22}H_{28}N_6O_4SClSi$ ($[M + H]^+$), 535.1351; found, 535.1361.

### 2-Chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-6-hydroxyphenyl Sulfamate (18) and 3-Chloro-5-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-2-hydroxyphenyl Sulfamate (19)

To a stirred solution of a mixture of two regioisomers **16** and **17** (38 mg, 0.07 mmol) in THF (0.5 mL) was added 6 N HCl (1 mL). After stirring at room temperature for 1 h, the reaction mixture was diluted with water and extracted with EtOAC. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with preparative TLC plate (1:7 MeOH/$CH_2Cl_2$) to afford **18** (14 mg, 47%) as a pale yellow solid and **19** (4 mg, 13%) as a pale yellow solid. Compound **18**, mp 170 °C (dec). $^1$H NMR (DMSO-$d_6$): δ 8.85 (s, 2H), 7.77 (d, $J = 9.0$ Hz, 2H), 6.94 (d, $J = 2.0$ Hz, 1H), 6.83 (d, $J = 2.0$ Hz, 1H), 6.72 (d, $J = 9.0$ Hz, 2H), 5.00 (s, 2H). HRMS (TOF ES+, $m/z$): calc. for $C_{16}H_{14}N_6O_4SCl$ ($[M + H]^+$), 421.0486; found, 421.0481. Compound **19**, mp

112–114 °C.$^1$H NMR (DMSO-$d_6$): δ 8.78 (s, 2H), 7.76 (d, $J = 9.0$ Hz, 2H), 7.25 (d, $J = 2.0$ Hz, 1H), 7.23 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 9.0$ Hz, 2H), 4.97 (s, 2H). HRMS (TOF ES+, $m/z$): calc. for $C_{16}H_{14}N_6O_4SCl$ ($[M + H]^+$), 421.0486; found, 421.0498.

### 4-((4-(Benzyloxy)-3-chloro-5-hydroxybenzyl)(4H-1,2,4-triazol-4-yl)amino)benzonitrile (20)

To a stirred solution of **13** (252 mg, 0.46 mmol) in THF (2 mL) was added a 1.0 M solution of TBAF in THF (2.0 mL, 2.0 mmol) slowly at 0 °C under nitrogen atmosphere. After stirring at room temperature for 1 h, the reaction mixture was poured into ice water and extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo, and then purified with preparative TLC plate (1:8 MeOH/$CH_2Cl_2$) to afford **20** (70 mg, 35%) as a yellow solid, mp 225 °C (dec). $^1$H NMR (DMSO-$d_6$): δ 10.04 (s, 1H), 8.80 (s, 2H), 7.77 (d, $J = 9.5$ Hz, 2H), 7.46 (d, $J = 7.0$ Hz, 2H), 7.37 (t, $J = 7.0$ Hz, 2H), 7.34–7.31 (m, 1H), 6.86 (d, $J = 1.5$ Hz, 1H), 6.77 (d, $J = 1.5$ Hz, 1H), 6.74 (d, $J = 9.0$ Hz, 2H), 4.97 (s, 2H), 4.95 (s, 2H). HRMS (TOF ES+, $m/z$): calc. for $C_{23}H_{19}N_5O_2Cl$ ($[M + H]^+$), 432.1227; found, 432.1231.

### 2-(Benzyloxy)-3-chloro-5-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)phenyl Sulfamate (21)

Sulfamoyl chloride (170 mg, 1.47 mmol) was added to a stirred solution of **20** (60 mg, 0.14 mmol) in DMA (0.5 mL) at 0 °C under nitrogen atmosphere. After stirring at room temperature overnight, ice water was added, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried ($Na_2SO_4$), filtered, concentrated in vacuo, and then purified with preparative TLC plate (1:30 MeOH/$CH_2Cl_2$) to afford **21** (48 mg, 68%) as a pale yellow solid, mp 159–161 °C. $^1$H NMR (DMSO-$d_6$): δ 8.82 (s, 2H), 8.35 (s, 2H), 7.78 (d, $J = 9.0$ Hz, 2H), 7.48 (d, $J = 7.5$ Hz, 2H), 7.41–7.34 (m, 5H), 6.75 (d, $J = 9.0$ Hz, 2H), 5.07 (s, 2H), 5.06 (s, 2H). HRMS (TOF ES+, $m/z$): calc. for $C_{23}H_{20}N_6O_4SCl$ ($[M + H]^+$), 511.0955; found, 511.0932.

### 3-Chloro-5-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-2-hydroxyphenyl Sulfamate (19)

To a stirred solution of **21** (39 mg, 0.08 mmol) in MeOH (0.3 mL) and THF (0.5 mL) was added 10% Pd/C (11 mg). The flask was charged with a hydrogen balloon and stirred at room temperature for 3 h. The catalyst was removed by filtration through celite. The filtrate was concentrated in vacuo and then purified with preparative TLC plate (1:30 MeOH/$CH_2Cl_2$) to afford **19** (24 mg, 75%) as a pale yellow solid, mp 110–112 °C. $^1$H NMR (DMSO-$d_6$): δ 8.78 (s, 2H), 7.76 (d, $J = 9.0$ Hz, 2H), 7.24 (d, $J = 2.0$ Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 9.0$ Hz, 2H), 4.97 (s, 2H). LC-MS (ESI, $m/z$): calc. for $C_{16}H_{14}N_6O_4SCl$ ($[M + H]^+$), 421.0; found, 421.1.

### 2-Chloro-4-(((4-cyanophenyl)(4H-1,2,4-triazol-4-yl)amino)methyl)-6-[$^{11}$C]methoxyphenyl Sulfamate ([$^{11}$C]7)

[$^{11}$C]$CO_2$ was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction in a small-volume (9.5-$cm^3$) aluminum gas target (CTI) from 11-MeV proton cyclotron on research purity nitrogen (+1% $O_2$) in a Siemens radionuclide delivery system (Eclipse RDS-111). In a small reaction vial (5 mL), the precursor **18** (0.1 mg) was dissolved in $CH_3CN$ (300 μL). To this solution was added 2 N NaOH (2 μL). No carrier-added (high specific activity) [$^{11}$C]$CH_3OTf$ that was produced by the gas-phase production method[15] from [$^{11}$C]$CO_2$ through [$^{11}$C]$CH_4$ and [$^{11}$C]$CH_3Br$ with a silver triflate (AgOTf) column was passed into the reaction vial at room temperature, until radioactivity reached a maximum (~2 min), and then the reaction vial was isolated and reacted at 80 °C for 3 min. The contents of the reaction vial were diluted with $NaHCO_3$ (1 mL, 0.1 M) and injected onto the semipreparative HPLC column with 2-mL injection loop. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product, [$^{11}$C]**7**, was formulated in saline, sterile-filtered through a sterile vented Millex-GS 0.22-μm cellulose acetate membrane, and collected into a sterile vial. Total radioactivity was assayed, and total volume was noted for tracer dose dispensing. The overall synthesis, purification, and formulation time was 20–25 min from EOB. Retention times in the analytical HPLC system were $t_R$ **18** = 3.45 min, $t_R$ **7** = 6.58 min, and $t_R$ [$^{11}$C]**7** = 6.58 min. Retention times in the semipreparative HPLC system were $t_R$ **18** = 5.76 min, $t_R$ **7** = 8.02 min, and $t_R$ [$^{11}$C]**7** = 8.02 min. The radiochemical yields were 40–45% decay corrected to EOB, based on [$^{11}$C]$CO_2$.



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