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RADIOSYNTHESIS OF NEW CARBON-11-LABELED NIMESULIDE ANALOGS AS POTENTIAL PET SAER TRACERS FOR IMAGING OF AROMATASE EXPRESSION IN BREAST CANCER

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Carbon-11-labeled nimesulide analogs, N-[^{11}C]methyl-N-(2-benzyloxy-4-nitrophenyl)-methanesulfonamide ([^{11}C]4a), N-[^{11}C]methyl-N-[2-(4′-methylbenzyloxy)-4-nitrophenyl]-methanesulfonamide ([^{11}C]4b), N-[^{11}C]methyl-N-[2-(4′-fluorobenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]4c), N-[^{11}C]methyl-N-[2-(4′-nitrobenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]8a), N-[^{11}C]methyl-N-[2-(β-naphthylmethoxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]8b), and N-[^{11}C]methyl-N-[2-(2′-phenylbenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]8c), have been synthesized as new potential positron emission tomography (PET) selective aromatase expression regulator (SAER) radiotracers for imaging of aromatase expression in breast cancer. The target tracers were prepared by N-[^{11}C]methylation of their corresponding precursors using [^{11}C]CH_3OTf under basic conditions (NaH) and isolated by reversed-phase high-pressure liquid chromatography (HPLC) method in 30–50% radiochemical yields decay corrected to end of bombardment (EOB) with 25–30 min overall synthesis time and 111–148 GBq/μmol specific activity at end of synthesis (EOS).

Keywords: Aromatase expression; breast cancer; imaging; nimesulides; positron emission tomography (PET); radiosynthesis

Breast cancer is the most common cancer diagnosed in women and is the second leading cause of death in women after lung cancer in the United States. The exact cause of breast cancer remains unknown. Most breast cancer patients will survive after conventional treatment modalities such as surgery, radiation therapy, chemotherapy, and/or a combination thereof if the breast cancer can be detected at an early stage.[1] However, these treatments still fail to cure a significant number of patients. Rapid and accurate early detection is highly desirable so that various

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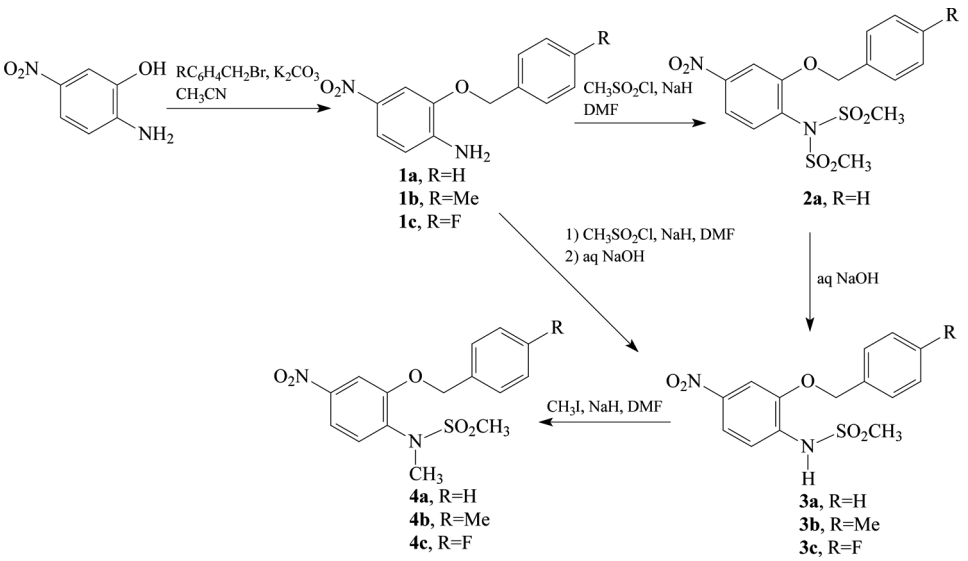
therapeutic regiments can be given before the primary tumors become widespread.[2] The improved therapies with fewer side effects and early detection with advanced imaging technology may help to decrease the overall death rate of breast cancer. Novel strategies are eagerly needed. To this end, aromatase inhibitor therapy has received wide attention in treating breast cancer,[3] because aromatase inhibitors are equivalent or superior to tamoxifen, a well-known selective estrogen receptor modulator currently in advanced clinical trials or on the market for treatment of hormone-dependent breast cancer, as a first-line therapy for metastatic breast cancer and as neoadjuvant treatment for primary breast cancer. Moreover, aromatase inhibitors can be administered instead of tamoxifen as a single agent for 5 years or sequentially with tamoxifen for 5 or 10 years as shown in the randomized studies.[4] The enzyme aromatase converts androgen to estrogen and is a particularly attractive target in the treatment of estrogen-receptor-positive breast cancer[5,6] and the development of enzyme-based cancer-imaging agents for a biomedical imaging technique, positron emission tomography (PET). Recently, a new series of nimesulide analogs has been developed as potent selective aromatase expression regulators (SAERs), which suppress aromatase enzyme activity and selectively decrease aromatase gene expression in breast cancer cells without causing cytotoxic or apoptotic effects.[5,6] We investigated whether ^{11}C-labeled analogs of nimesulides could be used to map breast cancer aromatase in vivo. In our previous work, we synthesized carbon-11-labeled sulfonanilides as potential PET breast cancer aromatase imaging agents and performed their preliminary biological evaluation.[7] In this ongoing study, we designed and synthesized carbon-11-labeled nimesulide analogs, *N*-[^{11}C]methyl-*N*-(2-benzyloxy-4-nitrophenyl)methanesulfonamide ([^{11}C]**4a**), *N*-[^{11}C]methyl-*N*-[2-(4′-methylbenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]**4b**), *N*-[^{11}C]methyl-*N*-[2-(4′-fluorobenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]**4c**), *N*-[^{11}C]methyl-*N*-[2-(4′-nitrobenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]**8a**), *N*-[^{11}C]methyl-*N*-[2-(β-naphthylmethoxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]**8b**), and *N*-[^{11}C]-methyl-*N*-[2-(2′-phenylbenzyloxy)-4-nitrophenyl]methanesulfonamide ([^{11}C]**8c**), as new potential PET SAER radiotracers for imaging of aromatase expression in breast cancer.

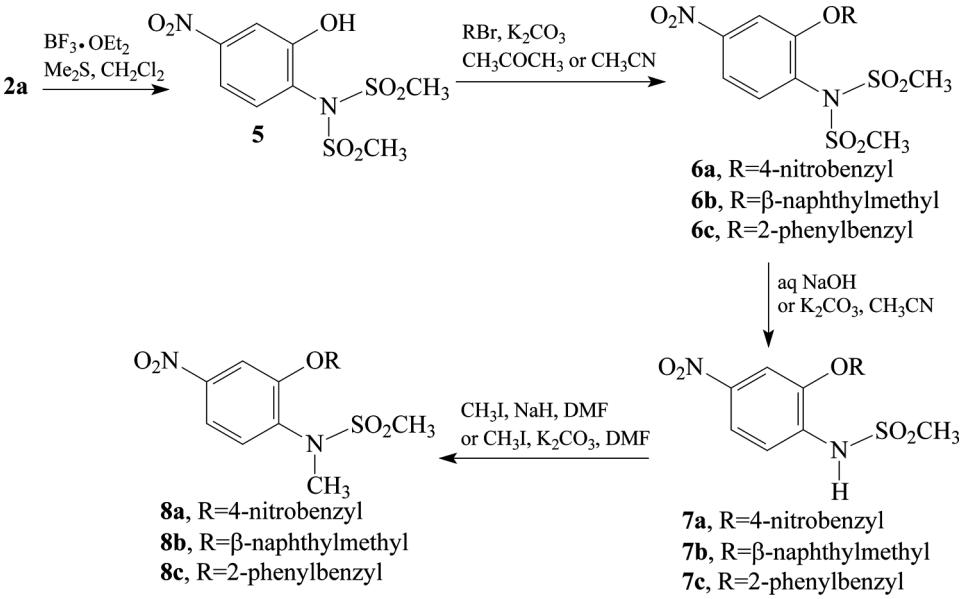
The precursors (**3a–c**, **7a–c**) and their corresponding standard compounds (**4a–c**, **8a–c**) were synthesized as shown in Schemes 1 and 2 with a modification of the literature procedure.[6] As outlined in Scheme 1, the synthesis started with benzylation of 2-amino-5-nitrophenol by various substituted benzyl bromides in the presence of K_2CO_3 to provide 2-benzyloxy-4-nitroanilins **1a–c**. Compound **1a** reacted with excess of methanesulfonyl chloride under basic conditions (NaH) in dimethylformamide (DMF) to afford *N,N*-bimethanesulfonimide **2a**, which was hydrolyzed with 3 N NaOH under reflux to provide monomethanesulfonamide **3a**. However, compound **1b** or **1c** reacted with excess of methanesulfonyl chloride, resulting in a mixture of *N,N*-bimethanesulfonimide and *N*-methanesulfonamide. The mixture was hydrolyzed with 3 N NaOH to obtain monomethanesulfonamide **3b** or **3c**. Methylation of the precursors **3a–c** with CH_3I in the presence of NaH in DMF to provide standard compounds **4a–c**.

Scheme 2 presents an alternative pathway for achieving the precursors **7a–c** and standard compounds **8a–c**. Benzyl ether **2a** was debenzylated with $BF_3 \cdot OEt_2$-Me_2S in CH_2Cl_2 to give the corresponding parent phenol **5** in a good yield.[8]

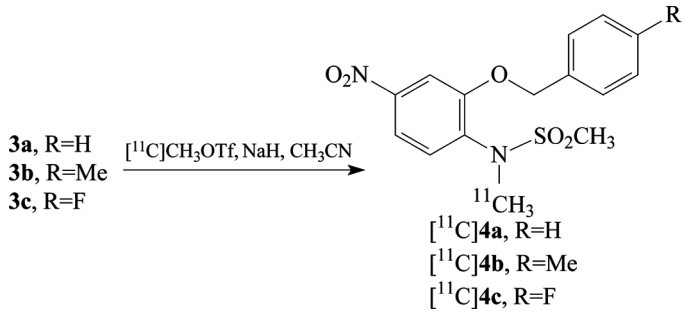


Scheme 1. Synthesis of nimesulide precursors and standards **3a–c** and **4a–c**.

Alkylation of the phenolic hydroxyl group of compound **5** by substituted benzyl or naphthylmethyl bromides provided compounds **6a–c**. Hydrolysis of *N,N*-bimethanesulfonimides (**6a** with K_2CO_3 in CH_3CN and **6b** and **6c** with 3 N NaOH) gave monomethanesulfonamides **7a–c**. The precursors **7a–c** reacted with CH_3I in the presence of NaH or K_2CO_3 in DMF to form their corresponding standard compounds **8a–c**.



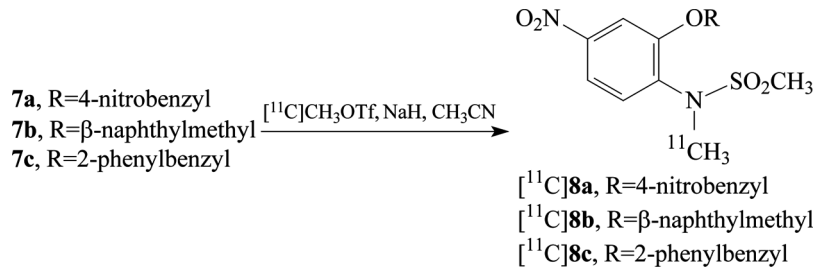
Scheme 2. Synthesis of nimesulide precursors and standards **7a–c** and **8a–c**.



Scheme 3. Synthesis of carbon-11-labeled nimesulides [^{11}C]**4a–c**.

Synthesis of the tracers [^{11}C]**4a–c** and [^{11}C]**8a–c** is outlined in Schemes 3 and 4. The precursors **3a**–**c** and **7a–c** were labeled by [^{11}C]methyl triflate ([^{11}C]CH_3OTf)[9,10] through *N*-[^{11}C]methylation and isolated by reversed-phase high-performance liquid chromatography (HPLC)[7] to produce the corresponding pure radiolabeled compounds [^{11}C]**4a–c** and [^{11}C]**8a–c** in 30–50% radiochemical yields, based on [^{11}C]CO_2 with decay corrected to end of bombardment (EOB). Overall synthesis time was 25–30 min from EOB. The radiosynthesis was performed in an automated multipurpose ^{11}C-radiosynthesis module, allowing measurement of specific activity during synthesis.[11,12] The specific activity measured by the on-the-fly technique was in a range of 222–296 GBq/μmol at EOB and 111–148 GBq/μmol at the end of synthesis (EOS), respectively. Chemical purity and radiochemical purity were determined by analytical HPLC method.[13] The chemical purity of the precursors and reference standards was >95%. The radiochemical purity of the target tracers was >99%, determined by radio-HPLC through γ-ray (PIN diode) flow detector, and the chemical purity of the target tracers was >93% determined by reversed-phase HPLC through an ultraviolet (UV) flow detector.

In conclusion, an efficient and convenient synthesis of new carbon-11-labeled nimesulide analogs has been developed. The synthetic methodology employed classical organic chemistry such as benzylation, methanesulfonylation, debenzylation, alkylation, hydrolysis, and methylation to produce nimesulide precursor and standard compounds. Carbon-11-labeled nimesulides were prepared by *N*-[^{11}C]methylation of their corresponding monomethanesulfonamide precursors using



Scheme 4. Synthesis of carbon-11-labeled nimesulides [^{11}C]**8a–c**.

a reactive [^{11}C]methylating agent, [^{11}C]CH_3OTf, and isolated by HPLC purification procedure in high radiochemical yields, short overall synthesis time, and great specific radioactivities. These results combined with the reported in vitro biological data[5,6] encourage further in vivo biological evaluation of new carbon-11-labeled nimesulide analogs as potential PET SAER radiotracers for imaging of breast cancer aromatase expression.

EXPERIMENTAL

All commercial reagents and solvents from Aldrich and Sigma were used without further purification. [^{11}C]CH_3OTf was prepared according to a literature procedure.[10] Melting points were determined on a Mel-Temp II capillary tube apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance II 500-MHz NMR spectrometer 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). Thin-layer chromatography (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 chromatographic solvent proportions (volume–volume). 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. Semi-preparative HPLC was performed using a YMC-Pack ODS-A, S 5 μm, 12 nm, 10×250 mm i.d. (Waters) C-18 column; 3:1:1 CH_3CN/MeOH/20 mM, pH 6.7 phosphate mobile phase, 5.0 mL/min flow rate, UV (254 nm) and γ-ray (PIN diode) flow detectors. Sterile vented Millex-GS 0.22-μm filter unit was obtained from Millipore Corporation, Bedford, MA.

2-Benzyloxy-4-nitroaniline (1a)

Yellow solid, 86% yield, mp 144–145 °C (lit.[6] 148–149 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, $J = 2.5$, 8.5 Hz, 1H, Ar-H), 7.79 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.47–7.35 (m, 5H, Ar-H), 6.78 (d, $J = 8.5$ Hz, 1H, Ar-H), 5.16 (s, 2H, $PhCH_2O$).

2-(4′-Methylbenzyloxy)-4-nitroaniline (1b)

Yellow solid, 86% yield, mp 145–146 °C (lit.[6] 149–150 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, $J = 2.3$, 8.5 Hz, 1H, Ar-H), 7.78 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.35 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.20 (d, $J = 7.5$ Hz, 2H, Ar-H), 6.78 (d, $J = 8.7$ Hz, 1H, Ar-H), 5.16 (s, 2H, $PhCH_2O$), 2.38 (s, 3H, $PhCH_3$).

2-(4′-Fluorobenzyloxy)-4-nitroaniline (1c)

Yellow solid, 84% yield, mp 120–121 °C (lit.[6] 125–127 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.74 (dd, $J = 2.0$, 9.0 Hz, 1H, Ar-H), 7.69 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.58 (t, $J = 7.3$ Hz, 2H, Ar-H), 7.23 (t, $J = 9.0$ Hz, 2H, Ar-H), 6.69 (d, $J = 9.0$ Hz, 1H, Ar-H), 6.44 (br s, 2H, NH_2), 5.22 (s, 2H, $PhCH_2O$).

N,N-(2-Benzyloxy-4-nitrophenyl)dimethanesulfonamide (2a)

Pale yellow solid, 98% yield, mp 186–187 °C (lit.[6] 188–189 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.03 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.91–7.86 (m, 2H, Ar-H), 7.53 (d, $J = 7.0$ Hz, 2H, Ar-H), 7.42 (t, $J = 7.0$ Hz, 2H, Ar-H), 7.38–7.35 (m, 1H, Ar-H), 5.40 (s, 2H, $PhCH_2O$), 3.46 (s, 6H, $2 \times SO_2CH_3$).

N-(2-Benzyloxy-4-nitrophenyl)methanesulfonamide (3a)

Yellow solid, 87% yield, mp 158–160 °C (lit.[6] 150–152 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (dd, $J = 2.3$, 8.8 Hz, 1H, Ar-H), 7.89 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.68 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.47–7.40 (m, 5H, Ar-H), 7.23 (br s, 1H, NH), 5.21 (s, 2H, $PhCH_2O$), 3.07 (s, 3H, SO_2CH_3).

N-[2-(4′-Methylbenzyloxy)-4-nitrophenyl]methanesulfonamide (3b)

Yellow solid, 55% yield, mp 152–153 °C (lit.[6] 151–152 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (dd, $J = 2.3$, 8.8 Hz, 1H, Ar-H), 7.89 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.66 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.30 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.24 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.22 (br s, 1H, NH), 5.16 (s, 2H, $PhCH_2O$), 3.06 (s, 3H, SO_2CH_3), 2.39 (s, 3H, $PhCH_3$).

N-[2-(4′-Fluorobenzyloxy)-4-nitrophenyl]methanesulfonamide (3c)

Yellow solid, 71% yield, mp 155–157 °C (lit.[6] 162–164 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (dd, $J = 2.3$, 8.8 Hz, 1H, Ar-H), 7.88 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.67 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.42–7.40 (m, 2H, Ar-H), 7.21 (br s, 1H, NH), 7.16–7.12 (m, 2H, Ar-H), 5.17 (s, 2H, $PhCH_2O$), 3.08 (s, 3H, SO_2CH_3).

N-Methyl-*N*-(2-benzyloxy-4-nitrophenyl)methanesulfonamide (4a)

Pale yellow solid, 66% yield, mp 131–133 °C (lit.[6] 138–140 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.89 (dd, $J = 2.5$, 8.5 Hz, 1H, Ar-H), 7.55 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.45–7.41 (m, 5H, Ar-H), 5.21 (s, 2H, $PhCH_2O$), 3.26 (s, 3H, SO_2CH_3), 2.81 (s, 3H, NCH_3).

N-Methyl-*N*-[2-(4′-methylbenzyloxy)-4-nitrophenyl]methanesulfonamide (4b)

Yellow solid, 76% yield, mp 116–118 °C (lit.[6] 123–124 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.87 (dd, $J = 2.5$, 8.5 Hz, 1H,

Ar-H), 7.54 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.32 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.24 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.16 (s, 2H, $PhCH_2O$), 3.25 (s, 3H, SO_2CH_3), 2.80 (s, 3H, NCH_3), 2.39 (s, 3H, $PhCH_3$).

N-Methyl-*N*-[2-(4′-fluorobenzyloxy)-4-nitrophenyl]-methanesulfonamide (4c)

Yellow solid, 72% yield, mp 168–169 °C (lit.[6] 168–169 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.89 (dd, $J = 2.3$, 8.8 Hz, 1H, Ar-H), 7.54 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.45–7.42 (m, 2H, Ar-H), 7.15–7.12 (m, 2H, Ar-H), 5.18 (s, 2H, $PhCH_2O$), 3.25 (s, 3H, SO_2CH_3), 2.82 (s, 3H, NCH_3).

N,N-(2-Hydroxy-4-nitrophenyl)dimethanesulfonamide (5)

Yellow solid, 82% yield, mp 251 °C (dec.) [lit.[6] 249–253 °C (dec.)]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.63 (s, 1H, OH), 7.76–7.74 (m, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 7.69 (dd, $J = 2.5$, 9.0 Hz, 1H, Ar-H), 3.55 (s, 6H, $2 \times SO_2CH_3$).

N,N-[2-(4′-Nitrobenzyloxy)-4-nitrophenyl]-dimethanesulfonamide (6a)

Yellow solid, 68% yield, mp 265 °C (dec.) [lit.[6] 265–269 °C (dec.)]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.28 (d, $J = 9.0$ Hz, 2H, Ar-H), 8.04 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.94 (dd, $J = 2.0$, 8.5 Hz, 1H, Ar-H), 7.89 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.80 (d, $J = 9.0$ Hz, 2H, Ar-H), 5.59 (s, 2H, $PhCH_2O$), 3.50 (s, 6H, $2 \times SO_2CH_3$).

N,N-[2-(β-Naphthylmethoxy)-4-nitrophenyl]-dimethanesulfonamide (6b)

Pale yellow solid, 90% yield, mp 185–186 °C (lit.[6] 184–185 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (d, $J = 2.5$ Hz, 2H, Ar-H), 7.97 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.95–7.88 (m, 3H, Ar-H), 7.64 (dd, $J = 1.5$, 8.5 Hz, 1H, Ar-H), 7.57–7.53 (m, 2H, Ar-H), 5.58 (s, 2H, $PhCH_2O$), 3.50 (s, 6H, $2 \times SO_2CH_3$).

N,N-[2-(2′-Phenylbenzyloxy)-4-nitrophenyl]-dimethanesulfonamide (6c)

White solid, 90% yield, mp 184–185 °C (lit.[6] 182–184 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87 (d, $J = 1.0$ Hz, 2H, Ar-H), 7.79 (s, 1H, Ar-H), 7.71 (dd, $J = 1.0$, 7.5 Hz, 1H, Ar-H), 7.50–7.38 (m, 8H, Ar-H), 5.20 (s, 2H, $PhCH_2O$), 3.45 (s, 6H, $2 \times SO_2CH_3$).

N-[2-(4′-Nitrobenzyloxy)-4-nitrophenyl]methanesulfonamide (7a)

Yellow solid, 70% yield, mp 151–152 °C (lit.[6] 168–169 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.75 (s, 1H, NH), 8.29 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.92

(s, 1H, Ar-H), 7.90 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.87 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.61 (d, $J = 8.0$ Hz, 1H, Ar-H), 5.51 (s, 2H, $PhCH_2O$), 3.17 (s, 3H, SO_2CH_3).

N-[2-(β-Naphthylmethoxy)-4-nitrophenyl]methanesulfonamide (7b)

Pale yellow solid, 83% yield, mp 143–144 °C [lit.[6] 239–243 °C (dec.)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H, Ar-H), 7.94–7.92 (m, 2H, Ar-H), 7.89–7.87 (m, 3H, Ar-H), 7.68 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.56–7.53 (m, 2H, Ar-H), 7.50 (dd, $J = 1.5$, 8.5 Hz, 1H, Ar-H), 5.37 (s, 2H, $PhCH_2O$), 3.06 (s, 3H, SO_2CH_3).

N-[2-(2′-Phenylbenzyloxy)-4-nitrophenyl]methanesulfonamide (7c)

Pale yellow solid, 55% yield, mp 138–140 °C (lit.[6] 116–119 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, $J = 2.5$, 9.0 Hz, 1H, Ar-H), 7.61 (s + d, $J = 7.0$ Hz, 2H, Ar-H), 7.51–7.34 (m, 9H, Ar-H), 7.02 (br s, 1H, NH), 5.16 (s, 2H, $PhCH_2O$), 3.02 (s, 3H, SO_2CH_3).

N-Methyl-*N*-[2-(4′-nitrobenzyloxy)-4-nitrophenyl]-methanesulfonamide (8a)

Pale yellow solid, 68% yield, mp 215–216 °C (lit.[6] 209–211 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.30 (d, $J = 9.0$ Hz, 2H, Ar-H), 8.00 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.89 (dd, $J = 2.5$, 8.5 Hz, 1H, Ar-H), 7.81 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.64 (d, $J = 8.5$ Hz, 1H, Ar-H), 5.53 (s, 2H, $PhCH_2O$), 3.22 (s, 3H, SO_2CH_3), 3.04 (s, 3H, NCH_3).

N-Methyl-*N*-[2-(β-naphthylmethoxy)-4-nitrophenyl]-methanesulfonamide (8b)

Pale yellow solid, 54% yield, mp 119–120 °C (lit.[6] 119–121 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.91–7.86 (m, 4H, Ar-H), 7.57–7.52 (m, 4H, Ar-H), 5.37 (s, 2H, $PhCH_2O$), 3.27 (s, 3H, SO_2CH_3), 2.81 (s, 3H, NCH_3).

N-Methyl-*N*-[2-(2′-phenylbenzyloxy)-4-nitrophenyl]-methanesulfonamide (8c)

Pale yellow solid, 87% yield, mp 124–125 °C (lit.[6] 128–129 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, $J = 2.5$, 8.5 Hz, 1H, Ar-H), 7.64 (d, $J = 2.0$ Hz, 1H, Ar-H), 7.54 (dd, $J = 1.0$, 7.5 Hz, 1H, Ar-H), 7.51–7.39 (m, 9H, Ar-H), 5.17 (s, 2H, $PhCH_2O$), 3.22 (s, 3H, SO_2CH_3), 2.81 (s, 3H, NCH_3).

General Method for the Preparation of the Carbon-11-Labeled Nimesulide Analogs

[^{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 an 11-MeV proton cyclotron on

research-purity nitrogen (+1% O_2) in a Siemens radionuclide delivery system (Eclipse RDS-111). The precursor (**3a**, **3b**, **3c**, **7a**, **7b**, or **7c**) (0.1–0.3 mg) was dissolved in CH_3CN (300 μL). NaH (0.5–1 mg) was added to this solution. The mixture was transferred to a small reaction vial. No-carrier-added (high specific activity) [^{11}C]CH_3OTf [produced by the gas-phase production method[10] from [^{11}C]CO_2 through [^{11}C]CH_4 and [^{11}C]CH_3Br with silver triflate (AgOTf) column] was passed into the reaction vial until radioactivity reached a maximum (~2 min), and then the reaction vial was isolated and heated 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 semi-preparative HPLC column with a 2-mL injection loop. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product, [^{11}C]**4a**, [^{11}C]**4b**, [^{11}C]**4c**, [^{11}C]**8a**, [^{11}C]**8b**, or [^{11}C]**8c**, was formulated in saline, 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 25–30 min from EOB. The radiochemical yields decay-corrected to EOB, from [^{11}C]CO_2, were 30–50%. Retention times in the analytical HPLC system were t_R **3a** = 2.80 min, t_R **4a** = 3.13 min, t_R [^{11}C]**4a** = 3.13 min; t_R **3b** = 3.23 min, t_R **4b** = 3.80 min, t_R [^{11}C]**4b** = 3.80 min; t_R **3c** = 2.75 min, t_R **4c** = 3.03 min, t_R [^{11}C]**4c** = 3.03 min; t_R **7a** = 2.73 min, t_R **8a** = 3.05 min, t_R [^{11}C]**8a** = 3.05 min; t_R **7b** = 3.80 min, t_R **8b** = 4.13 min, t_R [^{11}C]**8b** = 4.13 min, and t_R **7c** = 4.35 min, t_R **8c** = 4.80 min, and t_R [^{11}C]**8c** = 4.80 min. Retention times in the semi-preparative HPLC system were t_R **3a** = 5.12 min, t_R **4a** = 7.33 min, t_R [^{11}C]**4a** = 7.33 min; t_R **3b** = 6.55 min, t_R **4b** = 8.23 min, t_R [^{11}C]**4b** = 8.23 min; t_R **3c** = 5.35 min, t_R **4c** = 7.28 min, t_R [^{11}C]**4c** = 7.28 min; t_R **7a** = 4.98 min, t_R **8a** = 6.75 min, t_R [^{11}C]**8a** = 6.75 min; t_R **7b** = 5.34 min, t_R **8b** = 8.03 min, t_R [^{11}C]**8b** = 8.03 min; and t_R **7c** = 6.18 min, t_R **8c** = 8.54 min, t_R [^{11}C]**8c** = 8.54 min.

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