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Original article

Synthesis and preliminary biological evaluation of new carbon-11 labeled tetrahydroisoquinoline derivatives as SERM radioligands for PET imaging of ER expression in breast cancer

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Abstract

The estrogen receptors (ERs) are attractive targets in the treatment of breast cancer and the development of receptor-based breast cancer imaging agents for diagnostic use in biomedical imaging technique positron emission tomography (PET). Tetrahydroisoquinoline derivatives are a class of selective estrogen receptor modulators (SERMs) with high binding affinity and specificity exhibiting up to 50 folds for ERα over ERβ. New carbon-11 labeled tetrahydroisoquinoline derivatives, [^{11}C]methyl 1-(2-(4-(2-(4-fluorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)piperidine-4-carboxylate ([^{11}C]**10a**) and [^{11}C]methyl 1-(2-(4-(2-(4-chlorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)piperidine-4-carboxylate ([^{11}C]**10b**), have been first designed, synthesized and evaluated. The target tracers were prepared by *O*-[^{11}C]methylation of their corresponding precursors using [^{11}C]CH_3OTf and isolated by solid-phase extraction (SPE) purification procedure in 40–60% radiochemical yields, which were decay corrected to the end of bombardment (EOB), based on [^{11}C]CO_2. The overall synthesis time was 15–20 min from EOB. The radiochemical purity was >99%, and specific activity was in a range of 74–111 GBq/μmol at the end of synthesis (EOS). Preliminary findings from in vitro biological assay indicate that the synthesized derivatives displayed similar potencies in the MCF-7 human breast cancer cell line in comparison with 4-hydroxytamoxifen, a well-known potent SERM. These results encourage further in vivo evaluation of carbon-11 labeled tetrahydroisoquinoline derivatives as new potential SERM radioligands for PET imaging of ER expression in breast cancer.

Keywords: Carbon-11; Tetrahydroisoquinoline derivatives; Positron emission tomography (PET); Estrogen receptors; Selective estrogen receptor modulators (SERMs); Cancer imaging

1. Introduction

The estrogen receptors (ERs) are attractive targets in the treatment of breast cancer and the development of receptor-based breast cancer imaging agents for diagnostic use in biomedical imaging technique positron emission tomography (PET) [1,2]. The positron labeled steroidal estrogen 16α-[^{18}F]fluoro-17β-estradiol, a 17β-estradiol derivative and a well-known ER radioligand as indicated in Fig. 1, has been developed as a PET breast cancer ER imaging agent [3]. A number of selective estrogen receptor modulators (SERMs) such as tamoxifen and 4-hydroxytamoxifen (Fig. 1) are currently in advanced clinical trials or in the market for the treatment of

Abbreviations: SERMs, selective estrogen receptor modulators; PET, positron emission tomography; ERs, estrogen receptors; SPE, solid-phase extraction; EOB, end of bombardment; EOS, end of synthesis; PPA, polyphosphoric acid; HPLC, high pressure liquid chromatography; rt, room temperature; ERE, estrogen response element; SAR, structure–activity relationship; TMS, tetramethylsilane; LRMS, low resolution mass spectra; HRMS, high resolution mass spectra; RDS, radionuclide delivery system; OD, optical density; INGEN, Indiana Genomics Initiative.

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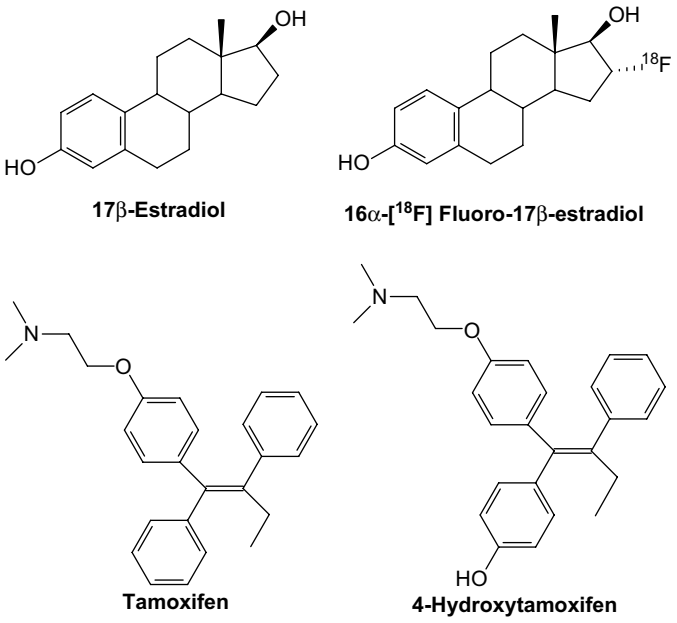


Fig. 1. Chemical structures of estrogens and SERMs.

hormone-dependent breast cancer [4]. Recently, a series of tetrahydroisoquinoline derivatives have been developed as new and potent SERMs, and they are found to bind with high affinity to the two currently known ERs, ERα and ERβ, and specificity exhibiting up to 50 folds for ERα over ERβ [5,6]. Tetrahydroisoquinoline derivatives labeled with a positron emitting radionuclide carbon-11 or fluorine-18 may enable non-invasive monitoring of ER expression in breast cancer and breast cancer response to hormone therapy. We are interested in the development of PET breast cancer imaging agents. In our previous works, we have developed carbon-11 labeled cyclofenil derivatives as new potential PET nonsteroidal estrogen radioligands for imaging ER expression in breast cancer [7]. This ongoing study was to develop new SERM radioligands. To further develop therapeutic agent for diagnostic use, we have first designed, synthesized and evaluated carbon-11 labeled tetrahydroisoquinoline derivatives, [^{11}C]methyl 1-(2-(4-(2-(4-fluorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)piperidine-4-carboxylate ([^{11}C]**10a**) and [^{11}C]methyl 1-(2-(4-(2-(4-chlorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy) ethyl)piperidine-4-carboxylate ([^{11}C]**10b**) as new potential SERM radioligands for PET imaging of ER expression in breast cancer.

2. Results and discussion

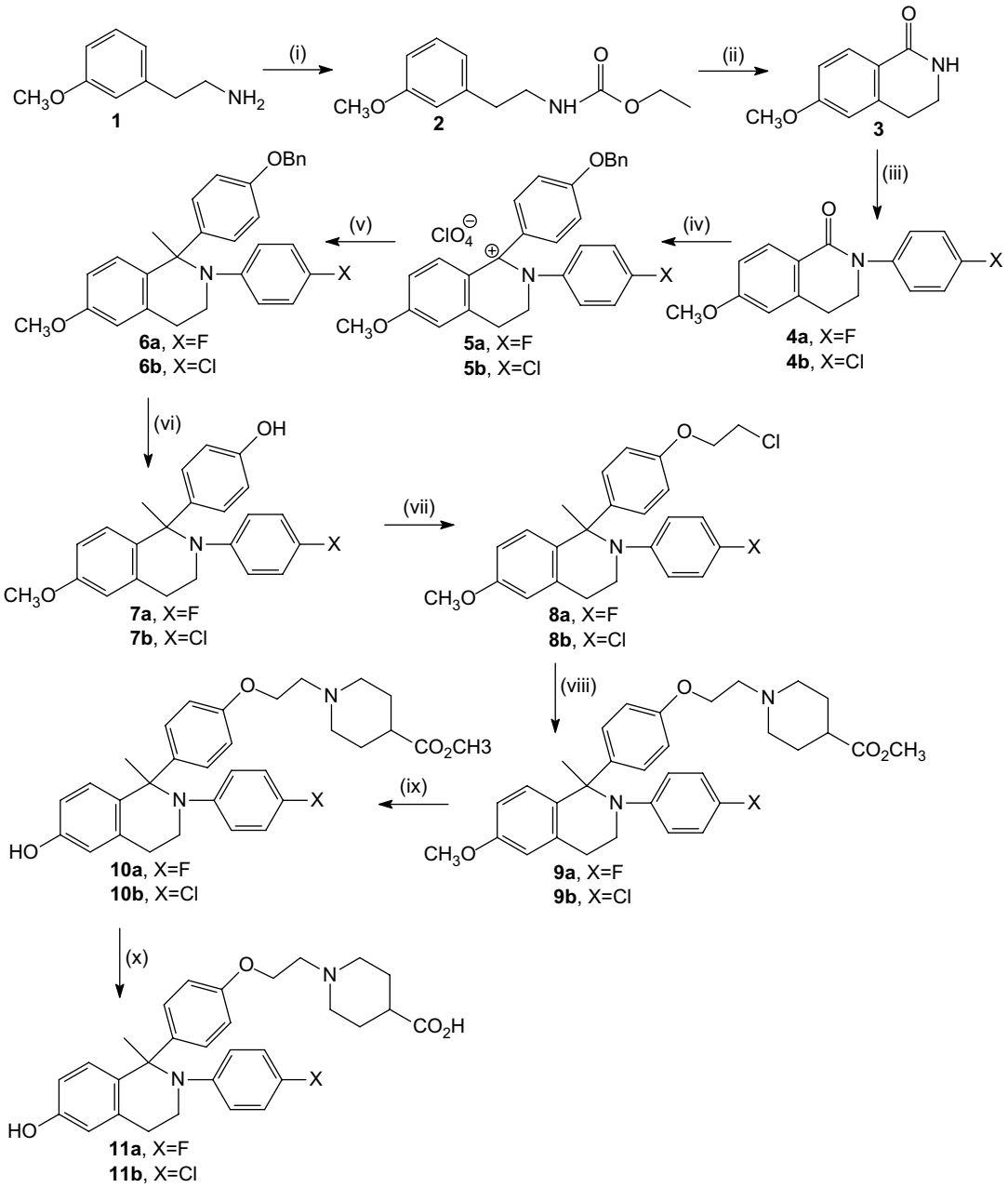
2.1. Chemistry

Synthesis of precursors and reference standards was designed and accomplished through chemical modification of the previously reported procedures [5,6,8]. The synthetic approach is outlined in Scheme 1. 2-(3-Methoxyphenyl)-1-ethanamine (**1**) was treated with ethyl chloroformate to furnish carbamate compound **2** in 96% yield. The subsequent cyclization of compound **2** with polyphosphoric acid (PPA) provided bicyclic lactam compound **3** in 77% yield. *N*-Arylation of compound **3** with 1-fluoro-4-iodobenzene or 1-chloro-4-iodobenzene under Ullmann-type conditions using CuI in DMF afforded compounds **4a**,**b** in 91% and 90% yields, respectively. Treatment of compounds **4a**,**b** with benzyloxyphenyllithium and subsequent acidic workup with $HClO_4$ gave intermediate iminium salts **5a**,**b** in quantitative yield. The iminium salts **5a**,**b** were subsequently treated with MeMgBr in THF to give 1-methyl-tetrahydroisoquinolines **6a**,**b** in 75% and 73% yields, respectively. $AlCl_3$-mediated debenzylation in the presence of Me_2NPh in CH_2Cl_2 of compounds **6a**,**b** yielded phenols **7a**,**b** in 70% and 72% yields, respectively. Alkylation of compounds **7a**,**b** with $BrCH_2CH_2Cl$ or $ClCH_2CH_2OTs$ furnished compounds **8a**,**b** in 52–68% yields. Compounds **8a**,**b** were treated with methyl piperidine-4-carboxylate to give esters **9a**,**b** in 92% and 91% yields, respectively. The cleavage of the methyl ether of compounds **9a**,**b** in the presence of $AlCl_3$ and EtSH provided target tetrahydroisoquinoline compounds **10a**,**b** as reference standards in 41% and 36% yields, respectively. The hydrolysis of compounds **10a**,**b** afforded acids **11a**,**b** as precursors in 88% and 86% yields, respectively.

Compounds **10a**,**b** were selected as the lead candidates for PET radioligand development for reasons of ERα selectivity, potency and feasibility of chemical modification to incorporate an *O*-methyl group at the ester moiety. The *O*-methyl group serves as a platform for radiolabeling of this series of methyl ester compounds with a positron emitting radioisotope carbon-11 as potential PET radiopharmaceuticals. Compounds **10a**,**b** (**10a**, X = F; **10b**, X = Cl) are halo-tetrahydroisoquinoline compounds, and they are amenable to labeling with another positron emitting radioisotope fluorine-18 by a conventional nucleophilic substitution with K [^{18}F]F/Kryptofix 2.2.2 [9] to be new fluorine-18 PET agents. In this regard, compound **10b** could be the precursor for compound **10a** in fluorine-18 radiolabeling reaction.

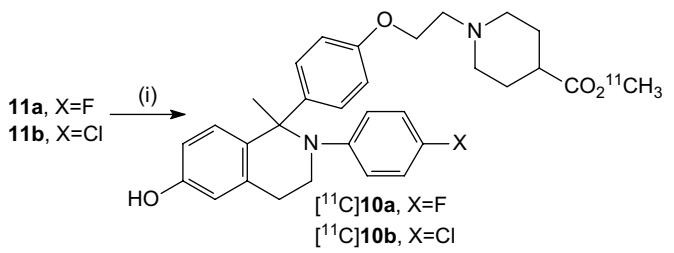
2.2. Radiochemistry

Synthesis of the target tracers, carbon-11 labeled tetrahydroisoquinoline derivatives [^{11}C]**10a**,**b** is outlined in Scheme 2. The precursor **11a** or **11b** was labeled by [^{11}C]methyl triflate ([^{11}C]CH_3OTf) [10,11] through *O*-[^{11}C]methylation [12] and isolated by a simplified solid-phase extraction (SPE) purification [13] to produce corresponding pure target radiolabeled compound [^{11}C]**10a** or [^{11}C]**10b** with 40–60% radiochemical yields, based on [^{11}C]CO_2, decay corrected to end of bombardment (EOB). The large polarity difference between the acid precursor and the labeled *O*-methylated ester product permitted the use of SPE technique for purification of labeled product from radiolabeling reaction mixture. Either a light C-18 Sep-Pak cartridge or a semi-prep C-18 guard cartridge column was used in SPE purification technique. The reaction mixture was loaded onto the cartridge by gas pressure. The cartridge was washed with water to remove non-reacted [^{11}C]CH_3OTf, acid precursor and reaction solvent, and then



Scheme 1. Synthesis of tetrahydroisoquinoline derivatives. Reagents and conditions: (i) $ClCO_2Et$, Et_3N, CH_2Cl_2, rt, 5 h. (ii) PPA, 120 °C, 2 h. (iii) ArI, CuI, K_2CO_3, DMF, reflux, 4 d. (iv) [LiArOBn] (generated from *p*-BrArOBn or *p*-ArOBn and *n*-BuLi), THF, −78 °C, 3 h; $HClO_4$, 15 min. (v) MeMgBr, THF, 0 °C to rt, 3 h. (vi) $AlCl_3$, Me_2NPh, CH_2Cl_2, rt, 1.5 h. (vii) $BrCH_2CH_2Cl$, K_2CO_3, CH_3CN, reflux, 3 d; or $ClCH_2CH_2OTs$, 2-butanone, K_2CO_3, reflux, 2 d. (viii) Methyl piperidine-4-carboxylate, K_2CO_3, CH_3CN, reflux, 3 d. (ix) $AlCl_3$, EtSH, CH_2Cl_2, 0 °C to rt, 3 h. (x) KOH, MeOH, rt, 12 h, HCl.

final labeled product was eluted with ethanol. Overall synthesis time was 15–20 min from EOB. SPE technique is fast, efficient and convenient and works very well for the *O*-methylated tracer production. The radiosynthesis was performed in an automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific activity during synthesis [14,15]. The specific activity was estimated in a range of 74–111 GBq/μmol at the end of synthesis (EOS) based on other compounds produced using the same targetry conditions which have been measured by the on-the-fly technique [15,16]. The actual measurement of specific activity at EOS by analytical high pressure liquid chromatography (HPLC) method [17] is in agreement with this estimation. The specific activity obtained in our automated synthesis module was high, since the methylation reagent we used was no-carrier-added (high specific activity) $[^{11}C]CH_3OTf$, which was produced by the gas-phase production method [11] from $[^{11}C]CO_2$ through $[^{11}C]CH_4$ and $[^{11}C]CH_3Br$ with silver triflate (AgOTf) column. In addition, we used very small amount of the precursor **11a** or **11b** (0.1–0.3 mg) in radiosynthesis, which also improved the specific activity data. Chemical purity and radiochemical purity were determined by analytical HPLC method. The chemical purity of precursors and reference standards was >95%. The radiochemical purity of target tracers was >99%



Scheme 2. Synthesis of carbon-11 labeled tetrahydroisoquinoline derivatives. Reagents and conditions: (i) [^{11}C]CH_3OTf, CH_3CN, 3 N NaOH.

determined by radio-HPLC through γ-ray (NaI) flow detector, and the chemical purity of target tracers was >95% determined by reversed-phase HPLC through UV flow detector.

The *O*-[^{11}C]methylation of phenolic hydroxyl position on the precursor to form undesired radiolabeled ether byproduct is a potential competing reaction, however, our previous results [18] have indicated that the *O*-[^{11}C]methylation of acid position on the precursor to form desired radiolabeled ester product will be a major reaction. These results are consistent with the theoretical explanation that the deprotonization at the acid position of the precursor is much easier than at the phenolic hydroxyl positions of the precursor, since the acidity of HO− at the acid position of the precursor is greater than at the phenolic hydroxyl position of the precursor, and the *O*-[^{11}C]methylation of the precursor will prefer to occur at the acid position rather than at the phenolic hydroxyl position. In addition, the minimal formation of the undesired labeled byproduct, estimated to be <5%, will be washed out with non-reacted [^{11}C]CH_3OTf, acid precursor and reaction solvent by water during the SPE purification, since their polarities are very similar. To prove that alkylation indeed occurred at the carboxylate-O and not the phenylate-O, a control experiment was designed and conducted using a previously reported procedure from our laboratory [19]. Briefly, the precursor **11a** or **11b** (0.1–0.3 mg) was dissolved in CH_3CN (0.5 mL). To this solution were added 3 N NaOH (2 μL) and 20 mM CH_3OTf (50 μL). The mixture was stirred at room temperature (rt) for 10 min, and the reaction was monitored by the analytical HPLC method aforementioned. The results showed that precursor **11a** or **11b** was completely converted to compound **10a** or **10b**, respectively, as indicated by their retention times (t_R **11a** = 1.69 min, t_R **10a** = 4.03 min; and t_R **11b** = 1.71 min, t_R **10b** = 3.06 min) on HPLC chromatograms. These chromatographic data support our conclusion.

2.3. MCF-7 cell proliferation assay

Compounds **10a**,**b** were designed and synthesized through a slight structural modification based on a novel series of tetrahydroisoquinoline derivatives, potent SERMs, recently developed by Renaud et al., which have been fully evaluated by radioligand binding assay and estrogen response element (ERE) assay to ERα and ERβ, and inhibition of MCF-7 cell proliferation assay [5,6]. Thus, we can assume that the slight structural modification of compounds **10a**,**b** would not significantly change their biological activity in light of the structure–activity relationship (SAR). The preliminary biological evaluation of the synthesized new tetrahydroisoquinoline derivatives **10a**,**b** was performed via an MCF-7 cell proliferation assay [5,6,20] and compared to 4-hydroxytamoxifen. 4-Hydroxytamoxifen (IC_{50} 8.5 ± 8.0 nM in MCF-7 cells) is a more potent SERM than its parent compound tamoxifen (IC_{50} 580 ± 160 nM in MCF-7 cells) [5], and MCF-7 cell line is an ER positive human breast cancer cell line [21,22]. The results are shown in Fig. 2. As indicated in Fig. 2, proliferation of MCF-7 cells was inhibited by 0.625 nM of 4-hydroxytamoxifen, also by higher concentrations. MCF-7 cell proliferation was inhibited only by 0.625 nM of compound **10a**, but not by higher concentrations. Similar to 4-hydroxytamoxifen, proliferation of MCF-7 cells was inhibited by 0.3125–0.625 nM of compound **10b**, also by higher concentrations. Taken collectively, these results suggest that the new compounds **10a**,**b** were proved to be potent SERMs

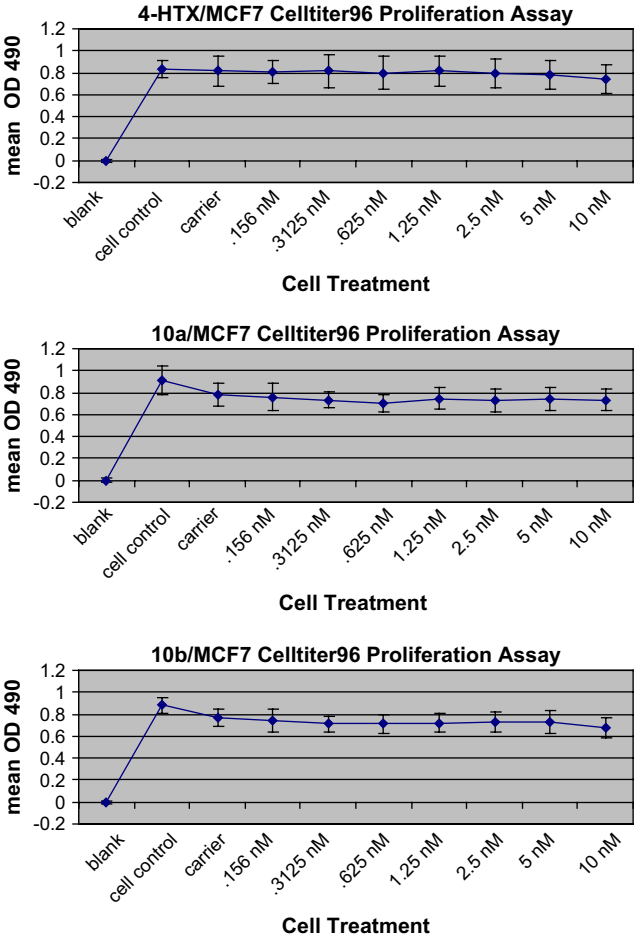


Fig. 2. MCF-7 cell proliferation assay of 4-hydroxytamoxifen (4-HTX), and new tetrahydroisoquinoline derivatives **10a** and **10b**. The *X*-axis represents blank, cell control, carrier and different concentrations (0.156–10 nM) of 4-HTX and **10a**,**b**, and the *Y*-axis represents their average inhibition intensity in MCF-7 cells measured under optical density (OD) 490 nm. Celltiter96 assay demonstrated that new tetrahydroisoquinoline derivatives **10a** and **10b** have similar potencies in the MCF-7 human breast cancer cell line compared to the reference compound 4-HTX.

with very high binding affinity to ER, comparable to that of the reference compound 4-hydroxytamoxifen under our assay conditions.

3. Conclusion

An efficient and convenient synthesis of new carbon-11 labeled tetrahydroisoquinoline derivatives has been well developed. The synthetic methodology employed classical organic chemistry such as cyclization, arylation, debenzylation, alkylation, demethylation and hydrolysis reactions to synthesize unlabeled tetrahydroisoquinoline derivatives. Carbon-11 labeling at oxygen position of the precursor through *O*-[^{11}C] methylation was incorporated efficiently using [^{11}C]CH_3OTf, a signature reaction of carbon-11 radiochemistry from our laboratory. Radiosynthesis produced new radioligands in amounts and purity suitable for the preclinical application in animal studies using PET. Labeled products are suitable for injection, with the higher specific radioactivities in a range of 74–111 GBq/μmol at EOS, and can be obtained within 20 min from EOB including fast and efficient SPE purification and formulation. Preliminary findings from in vitro biological assay indicate that the synthesized new tetrahydroisoquinoline derivatives displayed similar potencies in the MCF-7 human breast cancer cell line in comparison with reference compound 4-hydroxytamoxifen. These results encourage further in vivo evaluation of carbon-11 labeled tetrahydroisoquinoline derivatives as new potential SERM radioligands for PET imaging of ER expression in breast cancer.

4. Experimental

4.1. General

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 [11]. Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker QE 300 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). The low resolution mass spectra (LRMS) were obtained using a Bruker Biflex III 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 in a volume:volume ratio. Thin layer chromatography was run using Analtech silica gel GF uniplates (5×10 cm^2). Plates were visualized under UV light. Normal phase flash 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 below. 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; 3:1:3 CH_3CN:MeOH:20 mM, pH 6.7 $KHPO_4^-$ (buffer solution) mobile phase; flow rate 1.5 mL/min; and UV (254 nm) and γ-ray (NaI) flow detectors. Light C-18 Sep-Pak cartridges were obtained from Waters Corporate Headquarters, Milford, MA. Semi-prep C-18 guard cartridge column 1×1 cm was obtained from E. S. Industries, Berlin, NJ, and part number 300121-C18-BD 10 μm. Sterile Millex-GS 0.22 μm vented filter unit was obtained from Millipore Corporation, Bedford, MA.

4.2. Ethyl 3-methoxyphenethylcarbamate (**2**)

2-(3-Methoxyphenyl)-1-ethanamine (**1**, 50 g, 330 mmol) was dissolved in dichloromethane (500 mL) with Et_3N (51 mL, 360 mmol) at 0 °C. Ethyl chloroformate (35 mL, 360 mmol) was added and stirring was continued at rt for 5 h. The reaction mixture was washed with water (100 mL × 2), dried with $MgSO_4$, and filtered. The organic phase was evaporated under reduced pressure to give oily compound **2** (64.0 g, 96%), $R_f = 0.85$ (1:19 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, $J = 7.0$ Hz, 3H, CH_3), 2.78 (t, $J = 7.0$ Hz, 2H, CH_2CH_3), 3.40 (dd, $J = 7.0$, 14.0 Hz, 2H, CH_2CH_2), 3.79 (s, 3H, OCH_3), 4.08 (dd, $J = 7.0$, 14.0 Hz, 2H, CH_2CH_2), 4.71 (s, 1H, CONH), 6.74–6.79 (m, 3H, Ph-H), 7.21 (t, $J = 7.8$ Hz, 1H, Ph-H).

4.3. 6-Methoxy-3,4-dihydroisoquinolin-1(2H)-one (**3**)

Compound **2** (30 g, 135 mmol) was treated with polyphosphoric acid (PPA, 100 g) at 120 °C under N_2 atmosphere for 2 h. After the reaction mixture was cooled down to rt, ice-water was added (300 mL), and then extracted with EtOAc (100 mL × 3) and CH_2Cl_2 (100 mL × 2), washed with brine, and dried with Na_2SO_4. Combined organic layer was evaporated, and the residue was recrystallized from EtOAc or purified by column chromatography with silica gel to afford colorless solid **3** (18.4 g, 77%), mp 136–138 °C, $R_f = 0.35$ (EtOAc). ^{1}H NMR ($CDCl_3$) δ: 2.95 (t, $J = 6.6$ Hz, 2H, CH_2), 3.54 (dt, $J = 2.6$, 6.6 Hz, 2H, CH_2N), 3.84 (s, 3H, OCH_3), 6.70 (d, $J = 2.6$ Hz, 1H, Ph-H), 6.83 (d, $J = 2.4$ Hz, 1H, Ph-H), 6.86 (d, $J = 2.4$ Hz, 1H, Ph-H), 8.02 (d, $J = 8.6$ Hz, 1H, NHCO).

4.4. 6-Methoxy-2-(4-flurophenyl)-3,4-dihydro-2H-isoquinolin-1-one (**4a**)

A mixture of compound **3** (8.16 g, 46 mmol), 1-fluoro-4-iodobenzene (20 g, 90 mmol), K_2CO_3 (6.36 g, 46 mmol), and CuI (1.75 g, 9.2 mmol) in DMF (90 mL) was heated at 160 °C for 48 h under N_2 atmosphere. After that, a second portion of CuI (876 mg, 4.6 mmol) was added, and heating was continued for another 48 h. Then the mixture was poured into aqueous NH_4OH (350 mL) and EtOAc (350 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (350 mL × 3). The combined organic phases were washed with brine (500 mL), dried with Na_2SO_4, and

concentrated in vacuo until the crystallization started. Hexanes were added slowly to the solution. The crystallization provided white solid **4a** (11.35 g, 91%), mp 132–134 °C, $R_f = 0.29$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 3.09 (t, $J = 6.4$ Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.92 (t, $J = 6.4$ Hz, 2H, CH_2), 6.71 (d, $J = 2.4$ Hz, 1H, Ph-H), 6.85 (dd, $J = 2.4$, 8.6 Hz, 1H, Ph-H), 7.06 (t, $J = 8.6$ Hz, 2H, Ph-H), 7.31 (dd, $J = 4.8$, 9.0 Hz, 2H, Ph-H), 8.05 (d, $J = 8.8$ Hz, 1H, Ph-H).

*4.5. 6-Methoxy-2-(4-chlorophenyl)-3,4-dihydro-2H-isoquinolin-1-one (**4b**)*

According to the procedure for preparation of **4a**, compound **4b** was prepared from compound **3** and 1-chloro-4-iodobenzene in 90% yield as white solid, mp 169–171 °C, $R_f = 0.31$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 3.10 (t, $J = 6.4$ Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.94 (t, $J = 6.4$ Hz, 2H, CH_2), 6.72 (d, $J = 2.4$ Hz, 1H, Ph-H), 6.86 (dd, $J = 2.4$, 8.8 Hz, 2H, Ph-H), 7.25–7.39 (m, 4H, Ph-H), 8.06 (d, $J = 8.8$ Hz, 1H, Ph-H).

*4.6. 1-(4-(Benzyloxy)phenyl)-2-(4-fluorophenyl)-6-methoxy-3,4-dihydro-2H-isoquinolinium (**5a**)*

To a cold solution (−78 °C) of 4-benzyloxybromobenzene (6.7 g, 25.4 mmol) in anhydrous THF (70 mL) was added a solution of *n*-BuLi (2.5 M, 11.2 mL, 28 mmol) over a period of 30 min. After the resultant suspension was stirred at −78 °C for 40 min, a solution of compound **4a** (5.2 g, 19.1 mmol) in anhydrous THF (100 mL) was added over 30 min. Stirring was continued for 50 min. The reaction mixture was poured into water (220 mL) and EtOAc (220 mL). $HClO_4$ (70%, 5.0 mL) was added, and the mixture was stirred for 20 min. The pH value of aqueous layer was adjusted to 5 by addition of aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc (180 mL × 3). The combined organic layers were washed with brine (220 mL) and dried with $MgSO_4$, and the solution was concentrated in vacuo to obtain yellowish solid **5a** (8.36 g, 100%), which was used directly in the next step without further purification, mp 133–135 °C, $R_f = 0.62$ (1:9 CH_3OH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 3.45 (t, $J = 7.5$ Hz, 2H, CH_2), 3.95 (s, 3H, OCH_3), 4.54 (t, $J = 7.5$ Hz, 2H, CH_2), 5.05 (s, 2H, OCH_2Ph), 6.81–7.05 (m, 6H, Ph-H), 7.24 (t, $J = 2.4$ Hz, 2H, Ph-H), 7.28 (d, $J = 2.4$ Hz, 1H, Ph-H), 7.34–7.40 (m, 7H, Ph-H). MS (ESI): 438 (M^+, 100%).

*4.7. 1-(4-(Benzyloxy)phenyl)-2-(4-chlorophenyl)-6-methoxy-3,4-dihydro-2H-isoquinolinium (**5b**)*

According to the procedure for preparation of **5a**, compound **5b** was prepared from compound **4b** in 100% yield as yellowish solid, mp 154–156 °C, $R_f = 0.64$ (1:9 CH_3OH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 3.44 (t, $J = 7.4$ Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.53 (t, $J = 7.4$ Hz, 2H, CH_2), 5.05 (s, 2H, OCH_2Ph), 6.80–6.96 (m, 4H, Ph-H), 7.22–7.31 (m, 7H, Ph-H), 7.36–7.42 (m, 5H, Ph-H). MS (ESI): 454 (M^+, 100%).

*4.8. 1-(4-Benzyloxyphenyl)-6-methoxy-2-(4-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6a**)*

To a cold solution (0 °C) of compound **5a** (8.36 g, 19.1 mmol) in anhydrous THF (150 mL) was added a solution of MeMgBr in Et_2O (3.0 M, 11 mL, 33 mmol) over 15 min. The resultant mixture was stirred at 0 °C for 30 min and was allowed to warm up to rt. The suspension was poured into saturated aqueous NH_4Cl (250 mL) after being stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (250 mL × 3). The combined organic phases were washed with brine (220 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was recrystallized from EtOAc/hexanes or purified by column chromatography with silica gel to provide white solid **6a** (6.49 g, 75%), mp 114–115 °C, $R_f = 0.82$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 3H, CH_3), 2.85–3.13 (m, 2H, CH_2), 3.21–3.42 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 5.03 (s, 2H, OCH_2), 6.50–6.83 (m, 9H, Ph-H), 7.03 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.31–7.41 (m, 5H, Ph-H).

*4.9. 1-(4-Benzyloxyphenyl)-6-methoxy-2-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6b**)*

According to the procedure for preparation of **6a**, compound **6b** was prepared from compound **5b** in 73% yield as white solid, mp 148–150 °C, $R_f = 0.81$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H, CH_3), 2.89 9 (dt, $J = 4.4$, 16.2 Hz, 1H, C*H*H), 3.16 (ddd, $J = 4.4$, 9.6, 15.1 Hz, 1H, CH*H*), 3.30–3.37 (m, 1H, C*H*H), 3.41–3.49 (m, 1H, CH*H*), 3.77 (s, 3H, OCH_3), 5.03 (s, 2H, OCH_2), 6.49 (d, $J = 8.9$ Hz, 1H, Ph-H), 6.61–6.71 (m, 3H, Ph-H), 6.80 (d, $J = 8.9$ Hz, 2H, Ph-H), 6.98 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.08 (d, $J = 8.6$ Hz, 2H, Ph-H), 7.32–7.45 (m, 5H, Ph-H).

*4.10. 4-[6-Methoxy-2-(4-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-yl]phenol (**7a**)*

A solution of compound **6a** (5.38 g, 11.86 mmol), $AlCl_3$ (4.74 g, 35.58 mmol) and Me_2NPh (14.3 g, 118.6 mmol) in CH_2Cl_2 (270 mL) was stirred at rt for 1.5 h. Water (90 mL) and CH_2Cl_2 (350 mL) were added to the reaction mixture, and the pH value of aqueous layer was adjusted to 5 with aqueous $NaHCO_3$. The layer was separated, aqueous layer was extracted with CH_2Cl_2 (250 mL × 2) and then EtOAc (280 mL × 3). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The resultant oil was purified by column chromatography with silica gel to afford white solid product **7a** (3.01 g, 70%), mp 56–57 °C, $R_f = 0.47$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 3H, CH_3), 2.87 (dt, $J = 4.4$, 15.8 Hz, 1H, C*H*H), 3.06–3.19 (m, 1H, CH*H*), 3.21–3.48 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.96 (s, 1H, OH), 6.51–6.61 (m, 2H, Ph-H), 6.65–6.79 (m, 7H, Ph-H), 6.98 (d, $J = 8.8$ Hz, Ph-H).

*4.11. 4-[6-Methoxy-2-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-yl]phenol (**7b**)*

According to the procedure for preparation of **7a**, compound **7b** was prepared from compound **6b** in 72% yield as white solid, mp 110–112 °C, $R_f = 0.48$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H, CH_3), 2.86 (dt, $J = 4.0$, 15.6 Hz, 1H, C*H*H), 3.08–3.21 (m, 1H, CH*H*), 3.28–3.51 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.71 (1H, OH), 6.50 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.60–6.74 (m, 5H, Ph-H), 6.98–7.06 (m, 4H, Ph-H).

*4.12. 1-(4-(2-Chloroethoxy)phenyl)-2-(4-fluorophenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**8a**)*

Method A: a solution of compound **7a** (363 mg, 1 mmol), 1-bromo-2-chloroethane (789 mg, 5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (50 mL) was heated to reflux for 3 days. The reaction mixture was filtered, and concentrated. The residue was purified by column chromatography with silica gel to give white solid **8a** (221 mg, 52%). *Method B*: a solution of compound **7a** (1.82 g, 5 mmol), 2-chloroethyl 4-methylbenzenesulfonate (1.76 g, 7.5 mmol) and K_2CO_3 (1.38 g, 10 mmol) in 2-butanone (120 mL) was heated to reflux for 3 days. The reaction mixture was filtered, and concentrated. The residue was purified by column chromatography with silica gel to give white solid **8a** (1.44 g, 68%), mp 119–121 °C, $R_f = 0.78$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 3H, CH_3), 2.87 (dt, $J = 4.4$, 15.6 Hz, C*H*H), 3.07–3.23 (m, 1H, CH*H*), 3.26–3.47 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.80 (t, $J = 6.0$ Hz, 2H, CH_2Cl), 4.20 (t, $J = 6.0$ Hz, 2H, CH_2O), 6.51–6.64 (m, 4H, Ph-H), 6.69–6.79 (m, 5H, Ph-H), 7.04 (d, $J = 8.8$ Hz, 2H, Ph-H).

*4.13. 1-(4-(2-Chloroethoxy)phenyl)-2-(4-chlorophenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**8b**)*

According to the Method B for preparation of **8a**, compound **8b** was prepared from compound **7b** in 66% yield as white solid, mp 138–140 °C, $R_f = 0.78$ (1:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H, CH_3), 2.88 (dt, $J = 4.4$, 15.4 Hz, 1H, C*H*H), 3.12–3.21 (m, 1H, CH*H*), 3.30–3.49 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.80 (t, $J = 5.9$ Hz, 2H, CH_2Cl), 4.20 (t, $J = 5.9$ Hz, OCH_2), 6.50 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.60–6.64 (m, 3H, Ph-H), 6.77 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.02 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.12 (d, $J = 8.8$ Hz, 2H, Ph-H).

*4.14. Methyl 1-(2-(4-(2-(4-fluorophenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylate (**9a**)*

A solution of compound **8a** (852 mg, 2 mmol), methyl piperidine-4-carboxylate (572 mg, 4 mmol) and K_2CO_3 (691 mg, 5 mmol) in CH_3CN (60 mL) was heated to reflux for 3 days. The reaction mixture was filtered, and concentrated. The residue was purified by column chromatography with silica gel to give white solid **9a** (980 mg, 92%), mp 104–106 °C, $R_f = 0.34$ (1:1 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 3H, CH_3), 1.75–1.93 (m, 4H), 2.13–2.36 (m, 3H), 2.77 (t, $J = 6.0$ Hz, 2H, NCH_2), 2.87–2.99 (m, 3H), 3.11–3.41 (m, 3H), 3.67 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.06 (t, $J = 6.0$ Hz, 2H, OCH_2), 6.50–6.57 (m, 2H, Ph-H), 6.60–6.78 (m, 7H, Ph-H), 7.01 (d, $J = 8.8$ Hz, Ph-H). MS (CI): 533 ($[M + H]^+$, 100%), 532 (M^+, 48%). HRMS (CI): calcd for $C_{32}H_{38}O_4N_2F$, 533.2810, found, 533.2816.

*4.15. Methyl 1-(2-(4-(2-(4-chlorophenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylate (**9b**)*

According to the procedure for preparation of **9a**, compound **9b** was prepared from compound **8b** in 91% yield as white solid, mp 76–78 °C, $R_f = 0.33$ (1:1 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H, CH_3), 1.75–1.94 (m, 4H), 2.12–2.36 (m, 3H), 2.78 (t, $J = 5.8$ Hz, 2H, NCH_2), 2.86–2.99 (m, 3H), 3.11–3.23 (m, 1H), 3.28–3.49 (m, 2H), 3.67 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.06 (t, $J = 5.8$ Hz, 2H, OCH_2), 6.48 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.60–6.64 (m, 2H, Ph-H), 6.69–6.75 (m, 2H, Ph-H), 6.98 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.05 (d, $J = 8.8$ Hz, 2H, Ph-H). MS (CI): 549 ($[M + H]^+$, 100%), 548 (M^+, 48%). HRMS (CI): calcd for $C_{32}H_{38}O_4N_2Cl$, 549.2515, found, 549.2502.

*4.16. Methyl 1-(2-(4-(2-(4-fluorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylate (**10a**)*

To a cold solution (0 °C) of compound **9a** (212 mg, 0.4 mmol) and EtSH (0.3 mL) in CH_2Cl_2 (15 mL) was added $AlCl_3$ (213 mg, 1.6 mmol). The mixture was stirred at 0 °C for 1 h, and then at rt for 3 h. The reaction was quenched by adding some water, and the pH value of the solution was adjusted to 6 with aqueous $NaHCO_3$. Then the mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography with silica gel to afford white solid **10a** (85 mg, 41%), mp 95–97 °C, $R_f = 0.76$ (1:9 CH_3OH/CH_2Cl_2). ^{1}H NMR (CD_3OD) δ: 1.62 (s, 3H, CH_3), 1.83–2.00 (m, 5H), 2.40–2.50 (m, 3H), 2.78–2.98 (m, 3H), 3.09–3.22 (m, 3H), 3.26–3.41 (m, 1H), 3.67 (s, 3H, OCH_3), 4.14 (t, $J = 6.0$ Hz, 2H, OCH_2), 6.49–6.64 (m, 5H, Ph-H), 6.70–6.79 (m, 4H, Ph-H), 7.03 (d, $J = 8.8$ Hz, 2H, Ph-H). MS (ESI): 519 ($[M + H]^+$, 100%). HRMS (CI): calcd for $C_{31}H_{36}O_4N_2F$, 519.2654, found, 519.2643.

*4.17. Methyl 1-(2-(4-(2-(4-chlorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylate (**10b**)*

According to the procedure for preparation of **10a**, compound **10b** was prepared from compound **9b** in 36% yield as white solid, mp 72–74 °C, $R_f = 0.76$ (1:9 CH_3OH/CH_2Cl_2).

^{1}H NMR (CD_3OD) δ: 1.63 (s, 3H, CH_3), 1.72–1.95 (m, 4H), 2.21–2.44 (m, 4H), 2.79–2.87 (m, 3H), 2.99–3.05 (m, 3H), 3.34–3.45 (m, 1H), 3.67 (s, 3H, OCH_3), 4.09 (t, $J = 5.8$ Hz, 2H, OCH_2), 6.43–6.60 (m, 5H, Ph-H), 7.74 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.95 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.06 (d, $J = 8.8$ Hz, 2H, Ph-H). MS (ESI): 535 ($[M + H]^+$, 100%). HRMS (CI): calcd for $C_{31}H_{36}O_4N_2Cl$, 535.2358, found, 535.2349.

*4.18. 1-(2-(4-(2-(4-Fluorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylic acid (**11a**)*

A solution of compound **10a** (52 mg, 0.1 mmol), potassium hydroxide (56 mg, 1 mmol) and methanol (15 mL) was stirred at rt for 12 h. The mixture was evaporated in vacuo, added water (5 mL) and adjusted pH to 5–6 with 1 N HCl. The mixture solution was extracted with EtOAc (50 mL × 3), washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography to give yellow compound **11a** (44 mg, 88%), mp 185–187 °C, $R_f = 0.40$ (2:1 CH_3OH/CH_2Cl_2). ^{1}H NMR (CD_3OD) δ: 1.62 (s, 3H, CH_3), 1.80–2.02 (m, 4H), 2.19–2.31 (m, 1H), 2.53–2.63 (m, 3H), 2.80–2.88 (m, 1H), 2.98–3.01 (m, 3H), 3.20–3.46 (m, 3H), 4.18 (t, $J = 5.6$ Hz, 2H, OCH_2), 6.44–6.61 (m, 4H, Ph-H), 6.63–6.87 (m, 5H, Ph-H), 7.03 (d, $J = 8.8$ Hz, Ph-H). MS (ESI): 505 ($[M + H]^+$, 100%). HRMS (CI): calcd for $C_{30}H_{34}O_4N_2F$, 505.2497, found, 505.2503.

*4.19. 1-(2-(4-(2-(4-Chlorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)-piperidine-4-carboxylic acid (**11b**)*

According to the procedure for preparation of **11a**, compound **11b** was prepared from compound **10b** in 86% yield as yellow solid, mp 174–176 °C, $R_f = 0.40$ (2:1 CH_3OH/CH_2Cl_2). ^{1}H NMR (CD_3OD) δ: 1.65 (s, 3H, CH_3), 1.86–2.06 (m, 5H), 2.26–2.34 (m, 1H), 2.78–2.88 (m, 5H), 3.19–3.45 (m, 4H), 4.24 (t, $J = 5.2$ Hz, OCH_2), 6.43–6.62 (m, 5H, Ph-H), 6.80 (d, $J = 8.8$ Hz, 2H, Ph-H), 9.96 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.11 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.97 (s, 1H, OH). MS (ESI): 521 ($[M + H]^+$, 100%). HRMS (CI): calcd for $C_{30}H_{34}O_4N_2Cl$, 521.2202, found, 521.2216.

*4.20. General method for the preparation of carbon-11 labeled tetrahydroisoquinoline derivatives, [^{11}C]methyl 1-(2-(4-(2-(4-fluorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)piperidine-4-carboxylate ([^{11}C]**10a**) and [^{11}C]methyl 1-(2-(4-(2-(4-chlorophenyl)-6-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenoxy)ethyl)piperidine-4-carboxylate ([^{11}C]**10b**)*

[^{11}C]CO_2 was produced by the ^{14}N(p,α)^{11}C nuclear reaction in 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). The acid precursor **11a** or **11b** (0.1–0.3 mg) was dissolved in CH_3CN (300 μL). To this solution was added 3 N NaOH (2 μL). The mixture was transferred to a small reaction vial. [^{11}C]CH_3OTf that was produced from [^{11}C]CO_2 through [^{11}C]CH_4 and [^{11}C]CH_3Br with AgOTf column was passed into the reaction vial, which was cooled to 0 °C, 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). The reaction tube was connected to either a light C-18 Sep-Pak cartridge or a semi-prep C-18 guard cartridge column. The labeled product mixture solution was passed onto the cartridge for SPE purification by gas pressure. The cartridge was washed with H_2O (3 mL × 2), and the aqueous washing was discarded. The product was eluted from the column with EtOH (3 mL × 2), and then passed onto a rotatory evaporator. The solvent was removed by evaporation under vacuum. The labeled product [^{11}C]**10a** or [^{11}C]**10b** was formulated with saline, sterile-filtered through a sterile vented Millex-GS 0.22 μm cellulose acetate membrane and collected into a sterile vial, whose volume was dependent upon the use of the labeled product in tissue biodistribution studies (~6 mL, 2 mL × 3) or in PET imaging studies (1–3 mL). Total radioactivity was assayed and the total volume (1.0–6.0 mL) was noted. The overall synthesis time including SPE purification and formulation was 15–20 min. The radiochemical yields were 40–60% decay corrected to EOB from [^{11}C]CO_2 and 20–30% at EOS, respectively. Retention times in the analytical HPLC system were: t_R **11a** = 1.69 min, t_R **10a** = 4.03 min, t_R [^{11}C]**10a** = 4.03 min; and t_R **11b** = 1.71 min, t_R **10b** = 3.06 min, t_R [^{11}C]**10b** = 3.06 min.

4.21. MCF-7 cell proliferation assay

MCF-7 cell proliferation assay was performed following a literature procedure [20]. Briefly, cell proliferation was performed using Celltiter96 kits. For proliferation assays, 100 μL of medium containing 5000 MCF-7 breast cancer cells was plated in a 96-well flat-bottom microplate (Becton Dickinson & Co., Lincoln Park, NJ) and was incubated at 37 °C for 24 h in the presence of 0.156–10 nM of reference compound 4-hydroxytamoxifen, and synthesized new compounds **10a**,**b**. Following treatment, 20 μL of the reagent, the tetrazolium compound MTS (Promega, Madison, WI), was added to each well, and incubation was continued at 37 °C for 1 h. The absorbance was measured at a wavelength of 490 nm. Control cells were not incubated with 4-hydroxytamoxifen and **10a**,**b**. Each series was performed in triplicate.

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