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Synthesis and evaluation of fluoroethyl cyclofenil analogs: Models for potential estrogen receptor imaging agent

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ABSTRACT

Cyclofenil analogs (**2a–2f**) and their fluorine-containing derivatives (**3a–3f**) were synthesized and evaluated as candidate ligands for positron emission tomography (PET) imaging of estrogen receptors. Most of them show relatively high binding affinities comparable with estradiol (E_2). (4-Fluoroethoxyphenyl)-(4-hydroxyphenyl) methylenecyclopentane (**3a**) showed both the highest binding affinity for ERs (88.6 for ERβ, 13.8 for ERα) and highest β/α ratio (β/α for 6.4-fold). The radioactive compound [^{18}F]**3a** was prepared via displacement of the corresponding mesylate precursor **4** with [^{18}F]fluoride (^{18}F: β^+; 96.7%, $T_{1/2}$ = 109.8 min). The biodistribution studies in immature female SD rats demonstrated that the uptake in the uterus and ovaries were 1.358 ± 0.089% ID/g, 1.439 ± 0.214% ID/g, respectively, both of the ratios of uterus/blood and ovaries/blood was less than 2:1. Micro-PET imaging of immature female SD rats has also been reported.

1. Introduction

Estrogen receptor (ER), which is widely distributed in many tissues and human breast tumors, is a member of the super family of ligand-regulated nuclear transcription factors that mediates the actions of estrogens [1,2]. The development of estrogen derivatives is an attractive target for the diagnosis and treatment of breast cancer [3]. There are two structurally similar subtypes ERα or ERβ with different biological properties [4,5]. It is important to find subtype-specific imaging of ERα or ERβ because the level of ERβ relative to that of ERα declines with breast cancer progression [6–10].

As one of the most important endogenous ligands for estrogen receptors, 17-estradiol and its derivatives have been received much attention. A series of estradiol derivatives labeled with ^{18}F, ^{77}Br, ^{125}I and ^{11}C have been developed as PET imaging agents [11–18]. While most of these agents are based on steroidal estrogens, a few investigations have focused on selective ER modulators [19–22].

Cyclofenil and its derivatives, having high binding affinity for ERs and ERβ selectivity as well as estrogen agonist/antagonist activity, have been used to treatment of scleroderma, hepatitis, haemolytic, anaemia, and ovulation [23–27]. Furthermore, cyclofenil-type ligands labeled with radionuclide may enable non-invasive monitoring ER expression in breast cancer by PET and single-photon emission computed tomography (SPECT) imaging. The examples of ^{18}F labeled cyclofenil analogs ([^{18}F]FCF) and ^{11}C labeled cyclofenil-ester ([^{11}C]CCFE) have been reported for subtype-specific imaging of ERα or ERβ by PET (Fig. 1). However, these high affinity ligands for the ER failed to show receptor-mediated uptake into the uterus [28,29].

Structural studies on the ERs have suggested there is ample unoccupied space within the ligand binding pocket (Fig. 1) [30,31]. Recently we investigated the ^{99m}Tc cyclofenil compounds as potential breast cancer imaging agents by SPECT [31]. And we also made great effort to synthesis and labeling of cyclofenil with ^{18}F as PET probes [32,33]. In the study reported here, we not only undertook investigation of substituted cyclofenil ligands to establish a structure–activity relationship (SAR) relating ERα/ERβ binding affinities but radio-synthesis, evaluation of ^{18}F labeled cyclofenil analogs as potential PET image agents.

2. Results and discussion

2.1. Chemical synthesis

The compounds we have synthesized can be divided into three types (Scheme 1). First series of analogs (type I, compounds **2a–c**)

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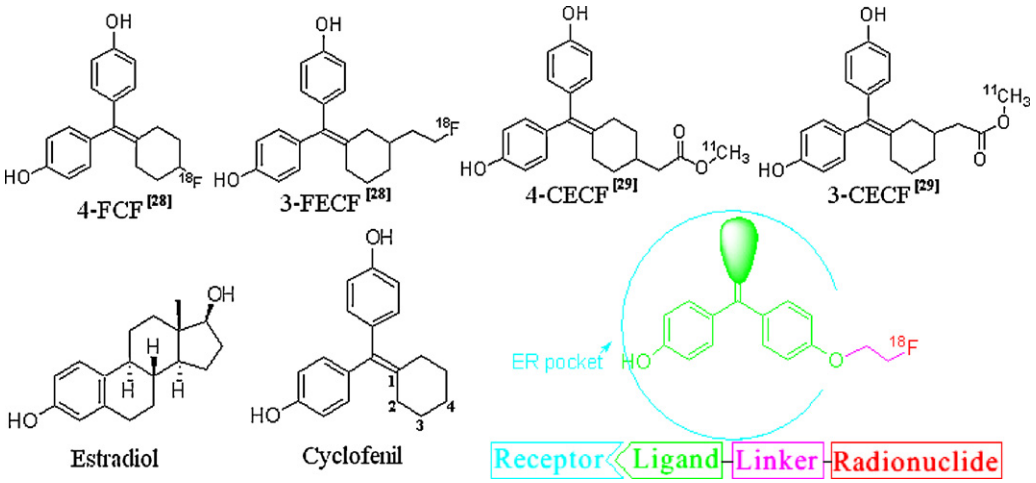


Fig. 1. ER ligands and proposed cyclofenil-ER pharmacophore model.

have different cycloalkyl core units, ranging from cyclopentane to cycloheptane. Second series (type II, compounds **2d–e**) have a fixed cyclohexyl moiety onto which we have introduced methyl substituent at the C3 or C4 position. Type III (compound **2f**) has an isobutyl core unit. Under the optimized conditions, a series of reference compounds, cyclofenil-FEts were synthesized in high yields as molecular probe precursors of ERs.

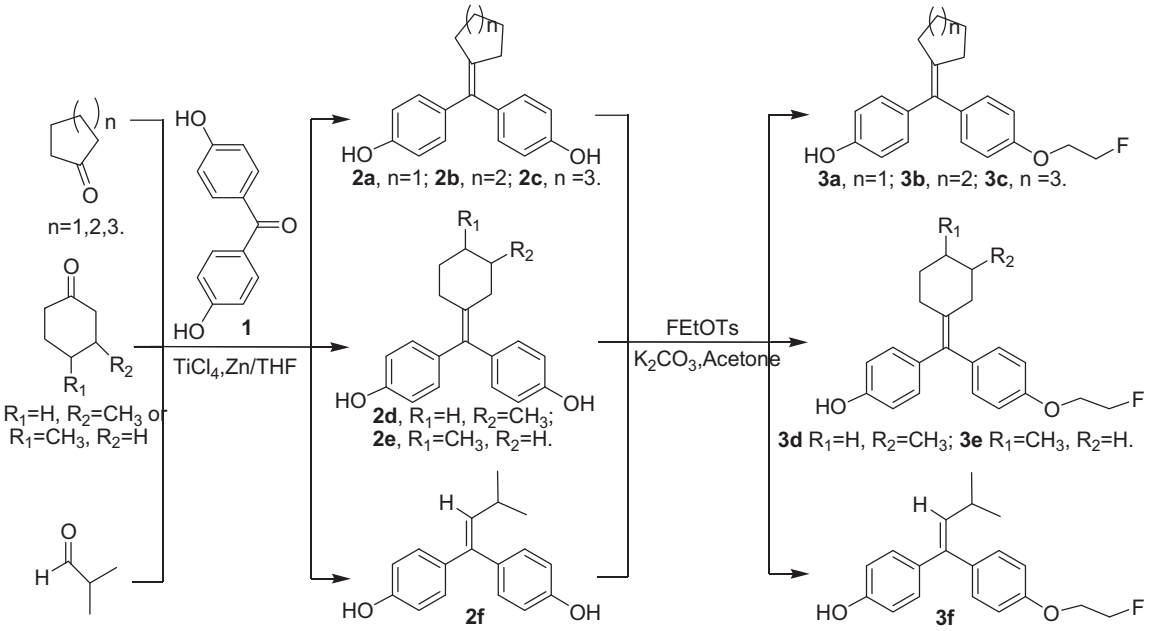
2.2. Estrogen receptor binding assay

The [^{3}H]-E_2 binding inhibition curves were established for each cyclofenil-FEt compound shown in Fig. 2. The effective concentration (EC 50) values of estradiol and cyclofenil derivatives were calculated by Graphpad Prism software shown in Table 1. The relative binding affinity (RBA) was expressed as the binding affinity relative to that of estradiol (100%) [30–32]. RBA values of the twelve cyclofenil derivatives (**2a–2f** and **3a–3f**) are listed in Table 2.

Structural studies on the ERs have suggested that there is ample unoccupied space within the ligand binding pocket. By our previous work, the modification of one hydroxyl function and keep the other was successful, we found cyclofenil-Re(CO)$_3$ compounds bind to ERs with an affinity comparable to that of estradiol [31]. Preliminary result of synthesis and evaluation of cyclofenil-FEt derivatives showed potential radioactive PET image agents [32,33]. However, it was not obvious what effect the ring size core units with the same substituted hydroxyl group had on binding affinity.

All of the cyclofenil **2b** and all of their derivatives (**2a**, **2c–f**) were selected due to affinities in previous report. In general, the RBA values range from 19.5 to 335 for ERβ and from 17.7 to 114.6 for ERα.

In short, the RBA values of **3a–f** range from less than 0.01 to 88.6 for ERβ and from 13.8 to 26.3 for ERα. In all cases, any substitution at phenol-hydroxyl group reduced binding affinity to both ERs, however the degree to which binding was lowered depended on substituent size and polarity. In general, groups that were small had the highest binding affinity. Of greatest interest to this study, the cyclopentyl compound (**3a**) still had good binding affinity compared to the cyclofenil parent (**2a,** approximately 75% of that of



Scheme 1. Synthesis of cyclofenil (**2a–2f**) and cyclofenil-FEt (**3a–3f**).

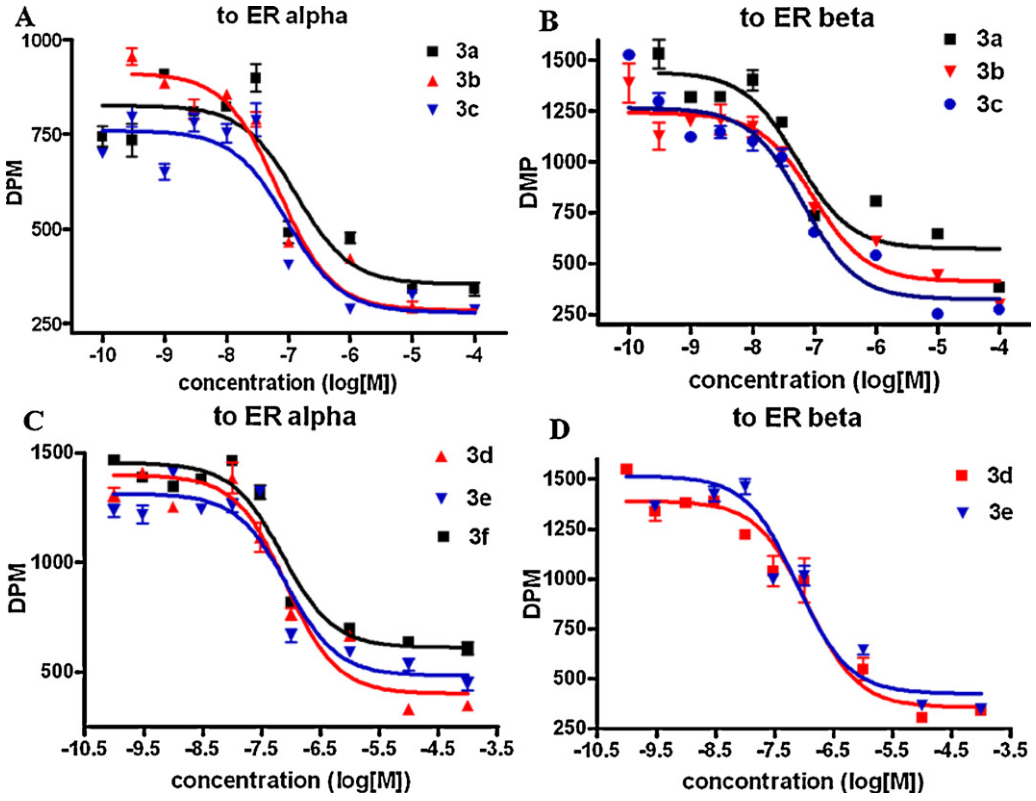


Fig. 2. Determination of specific binding of cyclofenil-FEt (**3a–3f**) compounds in purified full-length human ER. (A) **3a–3c** for ERα; (B) **3a–3c** for ERβ; (C) **3d–3f** for ERα; and (D) **3d–3f** for ERβ. Each data point was from the average of three measurements and the bar represents the standard deviation.

lead structure). While others compounds (**3b–3e)** after the modification of hydroxyl group with a carbon side chain, the RBA was moiety reduced (approximately 25% of that of lead structure, **2b–2e**). The isobutyl compound (**3f**) show the greatly reduction in ERβ, dropped about 2000-fold, due to its Z/E structure. However, the modification structure **3f** might be a good ERα selectivity compound.

In all, the principal interest to the study is the fact that we have identified cyclofenil-FEt compound **3a**, that has a binding affinity for ERβ nearly comparable to that of estradiol. It is a competitive candidate for PET imaging of ERs in breast cancer.

2.3. Radio-synthesis of [^{18}F]3a

As shown in Scheme 2. The synthesis strategy of **4** was similar to that in synthesis of cyclofenil-FEt with a nucleophilic substitution of phenol-hydroxyl group. It was estimated that the –OMs or –Br group at 2-methanesulfony bromoethyl would be replaced by hydroxyl group. However, when we used conditions with the reaction mixture stirred for 3 h at 52 °C, the pure compound **4** was obtained as a main product. This interesting result made it possible that cyclofenil-OMs could directly react with fluorine-18 ions with high labeling yield and simple purification procedure in certain conditions.

Total radiochemical yield of [^{18}F]**3a** was 30% (start from ^{18}F anion, total synthetic time of 50 min, decay-corrected end of synthesis (EOS), measured by radio-HPLC). The aimed product was identified by radio-HPLC, The retention time of [^{18}F]**3a** (Fig. 3D) was about 9.8 min (the same as reference compound **3a**, Rt = 9.75 min, Fig. 3B) and well separated from other chemical

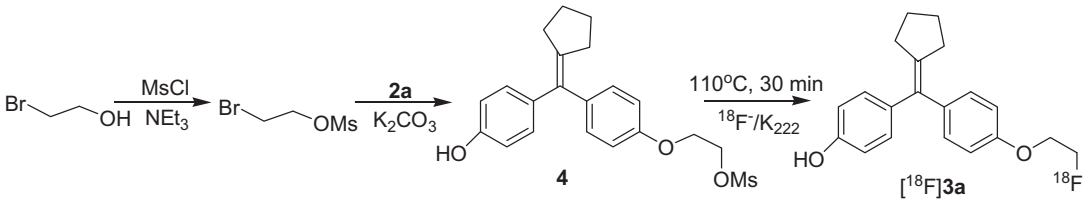
Table 1
Effective concentration (EC 50) value of cyclofenil derivatives at 25 °C.

Compounds	EC 50 value	
	ERα	ERβ
E2	1.48E−08	4.07E−08
2a	8.36E−08	3.34E−08
2b	1.29E−08	1.48E−08
2c	1.46E−08	1.20E−08
2d	1.35E−08	1.84E−08
2e	2.45E−08	1.82E−08
2f	2.13E−08	2.09E−07
3a	1.07E−07	4.59E−08
3b	5.63E−08	8.22E−08
3c	7.67E−08	5.64E−08
3d	6.61E−08	9.83E−08
3e	6.82E−08	6.67E−08
3f	5.76E−08	4.07E−08

Table 2
Relative binding affinities (RBA) of cyclofenil and its derivatives at 25 °C.

Compounds	RBA (E_2 = 100)[a]		β/α[b]
	ERα	ERβ	
2a	17.7 ± 1.8	121.8 ± 8.0	6.9
2b	114.6 ± 15.0	274.8 ± 15.0	2.4
2c	101.3 ± 12.0	339.0 ± 19.0	3.3
2d	109.5 ± 8.0	220.8 ± 10.0	2.0
2e	60.5 ± 8.2	224.0 ± 18.2	3.7
2f	69.5 ± 3.0	19.5 ± 2.0	0.28
3a	13.8 ± 2.2	88.6 ± 6.8	6.4
3b	26.3 ± 2.8	49.5 ± 3.0	1.9
3c	19.3 ± 1.2	72.2 ± 4.6	3.7
3d	22.4 ± 1.8	41.4 ± 4.4	1.9
3e	21.7 ± 2.0	61.0 ± 3.2	2.8
3f	25.7 ± 3.3	<0.01	<0.004

[a] Determined by a competitive radiometric binding assay with [^{3}H] estradiol, using full-length human ERα and ERβ.
[b] Under these conditions, the Kd of estradiol is 0.4 nM for ERα and 1.0 nM for ERβ.



Scheme 2. Radiosynthesis of [^{18}F]**3a.**

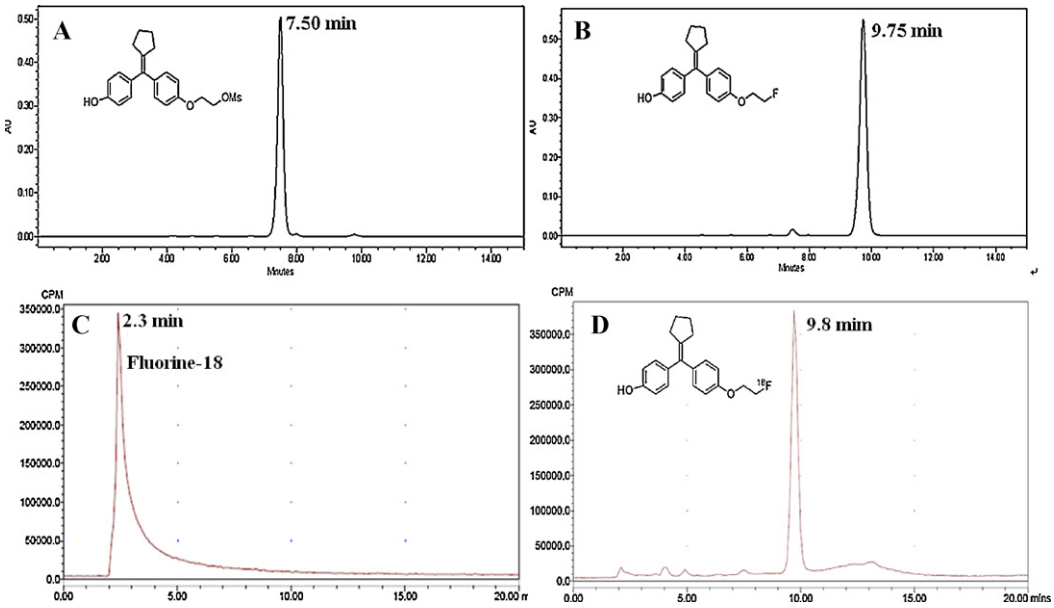


Fig. 3. HPLC analyses of cyclofenil and its derivatives. (A) Precursor compound **4**; (B) Reference compound **3a**; (C) fluorine-18 ions; and (D) [^{18}F]**3a**.

species (for precursor compound **4a**, Rt = 7.5 min, Fig. 3A; $^{18}F^{-}$, Rt = 2.3 min, Fig. 3C).

Then the reaction products were purified by semi-preparative HPLC column. The analytical HPLC and radio-thin layer chromatography (TLC) were used for quality control (radiochemical purity of [^{18}F]**3a** was >95%, Fig. 3D). The effective specific activity estimated by comparing UV peak (UV = 254 nm) intensity of purified [^{18}F]**3a** and corresponding radioactivity was 380 Ci/mmol.

2.4. In vitro stability studies and partition coefficients

As shown in Fig. 4, the radio-labeled compound [^{18}F]**3a** keeps excellent in vitro stability both in PBS and fetal calf serum (FCS) at 37 °C within 180 min, and at least 80% of compound [^{18}F]**3a** still keeps the original structures in serum.

According to the research by Prossnitz and coworkers, the appropriately reducing lipophilicity can be favorable to target tissues uptake in ER-expressing tumors [34]. The value of log *P* for compound [^{18}F]**3a** is 2.19, while the reported value of log *P* is 3.30 for estradiol [35,36].

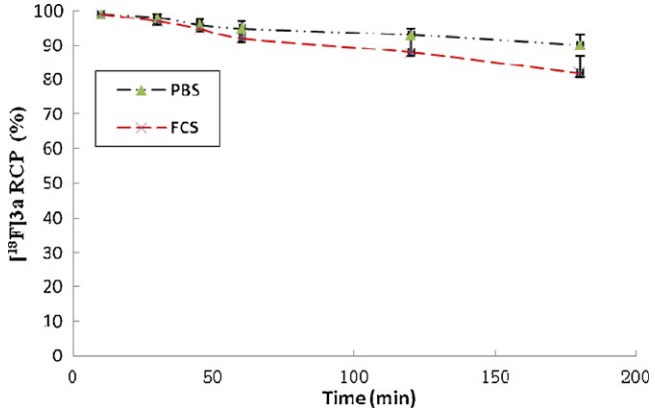


Fig. 4. In vitro stability of [^{18}F]**3a** in PBS and FES.

2.5. Biodistribution study

From the biodistribution studies shown in Table 3, the compound [^{18}F]**3a** showed selective uptake in target tissue (uterus and ovaries), its target/nontarget (blood, muscle and brain) ratio

Table 3
Biodistribution of [^{18}F]**3a** in immature SD female rats (%ID/g).

Tissue	%ID/g	
	1 h	2 h
Heart	0.657 ± 0.072	0.398 ± 0.049
Liver	1.78 ± 0.122	0.851 ± 0.164
Spleen	0.711 ± 0.050	0.411 ± 0.033
Lung	0.905 ± 0.122	0.419 ± 0.016
Kidney	0.775 ± 0.101	0.338 ± 0.022
Bone	1.054 ± 0.194	0.863 ± 0.162
Muscle	0.619 ± 0.025	0.360 ± 0.070
Intestine	0.880 ± 0.137	0.558 ± 0.202
Brain	0.556 ± 0.079	0.257 ± 0.036
Fats	0.628 ± 0.140	0.333 ± 0.094
Blood	0.818 ± 0.104	0.391 ± 0.061
Thymus	0.587 ± 0.090	0.332 ± 0.020
Ovaries	1.439 ± 0.214	0.897 ± 0.108
Uterus	1.358 ± 0.089	0.720 ± 0.078

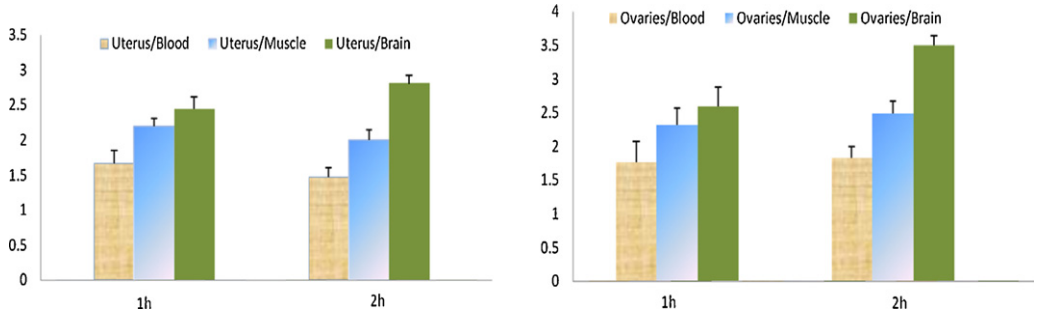


Fig. 5. The uptake in target tissue [uterus (left), ovaries (right)] compared with nontarget tissue [blood, muscle and brain].

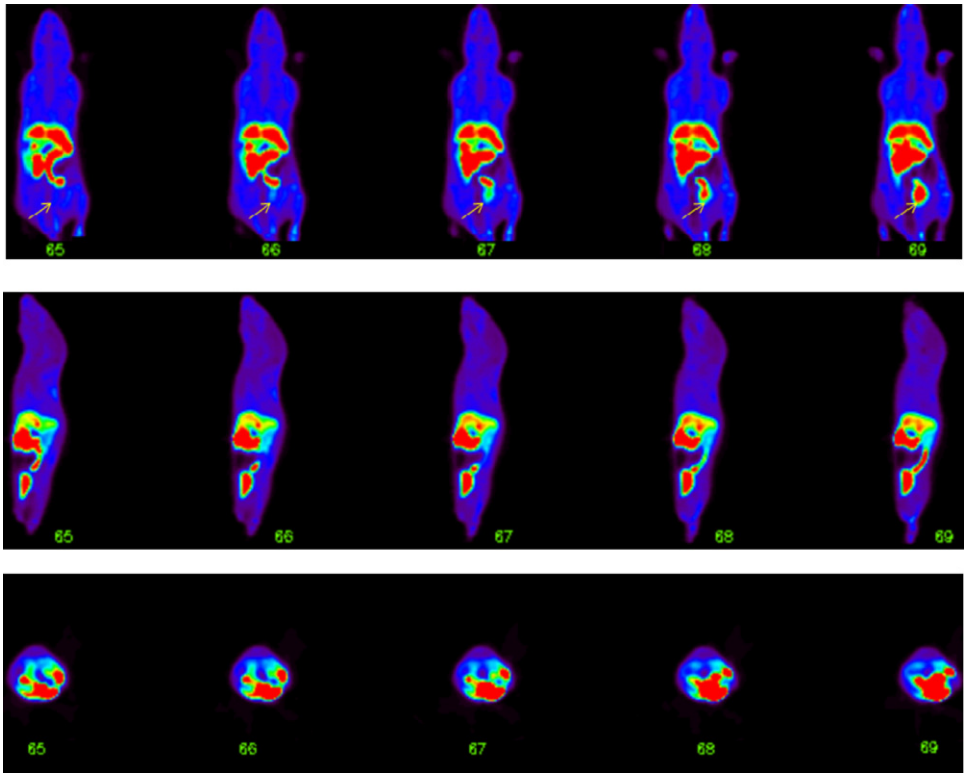


Fig. 6. Representative summed images of 65–69 frames in immature female SD rats. Injection of 100 μCi [^{18}F]**3a** coronal (up); sagittal (middle); horizontal (down) in 30 min.

was calculated between 1.7 and 2.6 at 1 h and 2 h after injection, and the ovaries/brain ratio was up to 3.5 at 2 h as shown in Fig. 5 [28,34]. The radiolabeled compound accumulated in ER-positive tissues such as kidneys, spleen, ovaries, and uterus. As a small molecular probe, it showed some accumulation in brain due to its ability to penetrate the blood–brain barrier.

We noticed that Seo et al. found some uterine selective uptake while no specific receptor mediated uptake using different cyclofenil analogs [28]. We began with the selective modification of phenolic hydroxyl group. We focused on the design, synthesis and revaluation of ^{18}F labeled cyclofenil. However, at present we have no experiment data whether it is receptor mediated uptake using this kind of cyclofenil analogs despite it is uterine selective uptake.

2.6. Micro-PET imaging of immature female SD rats

The micro-PET imaging was obtained by injection of 100 μCi of [^{18}F]**3a** into immature female SD rats. The representative summed images of 65–69 frames in immature female SD rats in Fig. 6 also showed the major uptake of [^{18}F]**3a** in liver, ovaries, and uterus from different views (coronal (up); sagittal (middle); horizontal (down)). Prominent up take of [^{18}F]**3a** was observed in the liver-kidneys and urinary bladder, suggesting that this radiotracer might be mainly excreted through the renal route. These preliminary results might provide valuable information for exploring ER mediated PET imaging agents.

3. Conclusion

By design, synthesis, and revaluation of cyclofenil derivatives, we undertook an investigation of substituted cyclofenil ligands to establish a structure–activity relationship (SAR) relating ERα/ERβ binding affinities to the substituted group. Compound **3a** with high binding affinity for ERs was labeled by ^{18}F in good radiochemical purity. The biodistribution studies in immature female SD rats demonstrated that the uptake in the uterus and ovaries was $1.358 \pm 0.089\%$ ID/g, $1.439 \pm 0.214\%$ ID/g, respectively, both uterus/blood and ovaries/blood ratios were less than 2:1.

These preliminary results suggested that the cyclofenil analogs might be potential PET imaging agents for ERs. Further structure modification and detailed evaluation is underway and will be reported in due course.

4. Experimental

All experiments were performed under the specified temperature conditions. ^{1}H NMR was recorded on a Bruker AC-500 (400 MHz) instrument with Me_4Si as an internal standard in the indicated solution described below, respectively. High resolution mass spectrums Electron (HRMS) were obtained on Micromass GCTTM. IR spectra were recorded on an Avataar 370 FT-IR spectrometer (250–4000 cm^{-1}).

Purified full-length human ERα and ERβ were purchased from PanVera/Invitrogen (Carlsbad, CA, USA). [6,7-^{3}H]Estra-1,3,5(10)-triene-3,17-β-diol ([^{3}H]-E_2), 44.8 Ci/mmol, was from Perkin Elmer (Boston, MA, USA). Hydroxyapatite (HAP) was from Aladdin (China). Borosilicate glass tubes were from VWR International (West Chester, PA, USA). Fluorine-18 was obtained from the ^{18}O (p, n)^{18}F reaction on an enriched water target (Sumitomo Heavy Industries, Co. Ltd.). High performance liquid chromatography (HPLC) analyses of the fluorine-18 analogs were performed using a Dionex P680 system equipped with a tunable absorption detector and a PDA-100 photodiode-array detector.

4.1. Synthesis of reference compounds 3a–f

The synthesis of cyclofenils (**2a–f** and **3a–f**) is shown in Scheme 1. Cyclofenils (**2a–f**) were prepared from 4,4′-dihydroxybenzophenone **1** and ketones by McMurry reaction [30,31].

Compounds **3a–f** were synthesized according to the following general procedure:

The reaction of cyclofenils (**2a–f**) with 2-fluoroethyl-4-methylbenzenesulfonate (FEtOTs, 1.5 equivalents) in the presence of K_2CO_3 afforded FEt-cyclofenils (**3a–f**) in high yields [32,33].

4.2. Synthesis of precursor compound 4

A flask containing cyclofenil **2a** (1.0 mmol), 2-methanesulfony bromoethyl-sulfonate (240 mg, 1.2 mmol), K_2CO_3 (205 mg, 1.5 mmol) was fitted with a reflux condenser, and charged with nitrogen gas. After acetone (5 mL) was added, the solution was stirred and heated to 50 °C for 3 h. Purified by column chromatography (EtOAc/hexane = 1/5) to afford the product **4**. Yield 51.0%, colorless oil. UV (EtOH): λ 228, 275 nm; IR (KBr): ν 3210, 2855, 1319, 1169, 1161, 908, 652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.10 (2H, d, J = 8.6 Hz, aromatic), 7.02 (2H, d, J = 8.5 Hz, aromatic), 6.81 (2H, d, J = 8.6 Hz, aromatic), 6.75 (2H, d, J = 8.5 Hz aromatic), 4.56 (2H, t, J = 4.4 Hz, –CH_2OMs), 4.22 (2H, t, J = 4.4 Hz, –OCH_2–), 3.08 (3H, s, OMs), 2.36–2.38 (4H, m, C_2–H), 1.64–1.70 (4H, m, C_3–H); ESI-HRMS calcd. for $C_{21}H_{24}O_5SNa$ [M+Na]$^+$: 411.1242; found: 411.1240.

4.3. Radio-synthesis of [^{18}F]3a

The solution with [^{18}F] fluoride radioactivity was transferred to an automated synthesis unit (Type PET-MF-2V-IT-I) that contained Kryptofix-2.2.2 (18 mg, 48 μmol) and K_2CO_3 (4.5 mg, 30 μmol). The reaction product was dissolved in acetonitrile (1.0 mL) and transferred to a test tube that contained precursor **4** (3.8 mg, 10.0 μmol) and a glass bead. The test tube was capped in a reactor at 110 °C for 30 min. The reaction mixture was purified by RP-HPLC (Agilent 300SB-C3 Semi-Prep HPLC Column 250 mm × 9.4 mm, 5 μm, 60% CH_3CN/40% H_2O, flow rate 5.0 mL/min) to give ^{18}F labeled compound [^{18}F]**3a**.

4.4. Estrogen receptor binding affinity test

The ERα and ERβ were diluted to 2 nM in binding buffer (50 mM Tris–HCl, pH 7.4, 150 mM KCl, 1 mM EDTA). [^{3}H]-E_2 was extracted with ethanol and diluted in Tris–HCl to 0.5–30 nM for saturation binding affinity and to 5 nM for competition binding affinity respectively in which HAP was used to absorb the receptor–ligand conjugate. The compound (**3a–3f** or **2a–2f**) was dissolved respectively in DMF, and then diluted with binding buffer to obtain concentrations ranging from 0.1 nM to 1 mM. Then 30 μL of the ER solution, [^{3}H]-E_2 solution, estradiol and the synthetic compound was added to the test tube followed by buffer to a final volume of 300 μL. The mixture was incubated at 25 °C for 2 h. HAP slurry (30% solution) was added and the mixture was vortexes and centrifuged. The supernatant was removed and discarded and the pellet was washed three times with Tris–HCl (0.05 M, pH 7.4). The radioactivity was counted the next day in the scintillation counter (Beckman) with 43% counting efficiency. All numeric data were expressed as the mean of the values ± the SEM. Graphpad Prism, Version 4, was used for statistical analysis.

4.5. In vitro stability studies and partition coefficients

Stability of the [^{18}F]**3a** was evaluated by measuring the radiochemical purity using radio-HPLC at different time intervals. [^{18}F]**3a** was added to a test tube containing phosphate buffered saline (PBS) solution or fetal calf serum. The mixture was incubated by shaking at 37 °C in a Thermo-mixer. The radiochemical purity was measured at 10 min, 30 min, 45 min, 60 min, 120 min and 180 min by radio-HPLC (Hypersil BDS C-18 reversed-phase column (250 mm × 4.6 mm, 5 μm), 60% CH_3CN/40% H_2O, and flow rate 1.0 mL/min).

For partition coefficients, the mixture of 10 μL aliquot of aqueous solution of labeled compound, 1 mL n-octanol and 1 mL PBS was vigorous shaken for 3 min at room temperature using a vortex miner, then the solution was incubated for 30 min. This workup was conducted for five times. The organic layer and the phosphate buffer solution were collected, and the radioactivity was measured with γ counter.

4.6. Biodistribution studies

Immature female SD rats were used for biodistribution studies. The radioactivity was injected via tail vein under isoflurane anesthesia, 200 μCi of [^{18}F]**3a** was dissolved in 200 μL ethanol and diluted with 1.8 mL of saline (10% ethanol/saline solution). Two sets of animals (n = 5) were injected with 20 μCi/200 μL of [^{18}F]**3a** and sacrificed at the noted time points (1 h, 2 h). Radioactivity was counted in a Wallac (Perkin-Elmer) 1470 Wizard Gamma Counter, and activity in each tissue was calculated as % ID per gram {organ uptake = [organ radioactivity/(total radioactivity ×organ weight)] × 100%}.

4.7. Micro-PET imaging

Micro-PET scans and image analysis were performed using an Inveon Dedicated PET (DPET) scanner (Siemens Medical Solutions, Malvern, PA). The scanner has a computer controlled bed and 12.7 cm trans axial fields of view (FOVs) and 1.4 mm of resolution at the center of FOV. All rats were injected via the tail vein with 100 μCi of [^{18}F]**3a** and anesthetized by inhalation of isoflurane/oxygen, placed head first prone for imaging, and the acquisition time was set for 30 min. The acquired data were rebinned with a 2D ordered-subsets expectation maximum (OSEM) algorithm. Representative images shown are static scans of single mouse (arrows indicate target tissue), which is representative of 3 mice tested in each group.

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