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[^{18}F]-labeled isoindol-1-one and isoindol-1,3-dione derivatives as potential PET imaging agents for detection of β-amyloid fibrils

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ABSTRACT

In this study a novel series of isoindol-1-one and isoindol-1,3-dione derivatives for β-amyloid-specific binding agents is described. Twelve compounds were synthesized and evaluated via a competitive binding assay with [^{125}I]TZDM against β-amyloid 1–42 (Aβ42) aggregates. Two new [^{18}F]-labeled isoindole derivatives were synthesized and evaluated as potential β-amyloid imaging probes based on the in vivo pharmacokinetic profiles. The preliminary results suggest that these [^{18}F]**18b** and [^{18}F]**18c** are promising positron emission tomography (PET) imaging probes for studying accumulation of Aβ fibrils in the brains of Alzheimer's disease (AD) patients.

Alzheimer's disease (AD) is a neurodegenerative brain disorder accompanying progressive memory loss and decline of cognitive functions. At present, clinical diagnosis of AD is performed via mental status tests, physical exam, diagnostic tests, neurological exam, and brain imaging. Brain imaging technologies utilize the verifying presence of β-amyloid (Aβ) peptide plaques and neurofibrillary tangles (NFTs) formed by tau proteins in the post-mortem brain tissue.[1–3] Accumulation of Aβ plaques in the AD brain is believed to be one of the most significant factors associated with the molecular etiology of the disease.[4] Therefore, development of Aβ plaque-specific binding agents for direct marking of Aβ aggregates in the living brain is a highly active research area in recent years and such technique is urgently desired for early diagnosis and monitoring of AD progress. In addition, an increasing focus on early identification and prevention highlights a need for non-invasive tools and robust biological markers. However, yet the diagnosis of this disease based on neurological observations is often difficult and unreliable.

Several research groups have reported biomarkers to visualize Aβ plaques in AD brains. Such Aβ-aggregate-specific radio-labeled imaging probes, using positron emission tomography (PET), are needed for pre-symptomatic detection or monitoring of the progression and effectiveness of AD treatments (Fig. 1).[5–7]

Recently, successful preliminary reports using a [^{11}C]-labeled benzothiazole derivative, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]PIB),[8,9] for plaque visualization in AD patients have demonstrated the potential utility of the in vivo imaging research. However, the short half-life ($t_{1/2}$ = 20 min) of ^{11}C may limit the use of [^{11}C]PIB for a wide variety of clinical applications. A [^{18}F]-labeled derivative of naphthalene, 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP), has been reported previously to bind SPs and NFTs in the brains of AD patients.[10,11] However,

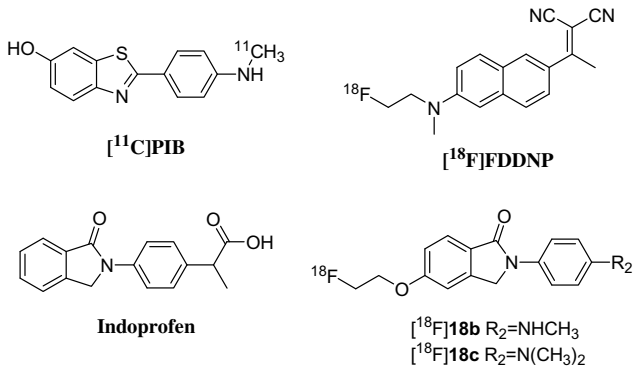

Figure 1. Structures of **PIB**, **FDDNP**, **Indoprofen**, [^{18}F]**18b**, and [^{18}F]**18c**.

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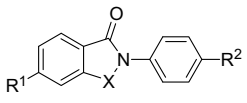


18a~f, 19a~f

18a : X=CH_2, R^1= $O(CH_2)_2F$, R^2=NH_2 **19a** : X=CO, R^1= $O(CH_2)_2F$, R^2=NH_2
18b : X=CH_2, R^1= $O(CH_2)_2F$, R^2=$NHCH_3$ **19b** : X=CO, R^1= $O(CH_2)_2F$, R^2=$NHCH_3$
18c : X=CH_2, R^1= $O(CH_2)_2F$, R^2=$N(CH_3)_2$ **19c** : X=CO, R^1= $O(CH_2)_2F$, R^2=$N(CH_3)_2$
18d : X=CH_2, R^1= $O(CH_2)_3F$, R^2=NH_2 **19d** : X=CO, R^1= $O(CH_2)_3F$, R^2=NH_2
18e : X=CH_2, R^1= $O(CH_2)_3F$, R^2=$NHCH_3$ **19e** : X=CO, R^1= $O(CH_2)_3F$, R^2=$NHCH_3$
18f : X=CH_2, R^1= $O(CH_2)_3F$, R^2=$N(CH_3)_2$ **19f** : X=CO, R^1= $O(CH_2)_3F$, R^2=$N(CH_3)_2$

Figure 2. Structures of **18a**–**f** and **19a**–**f**.

FDDNP has some disadvantage in practical use due to its considerable amount of non-specific binding in normal brain tissue.[12] There have been several previous attempts generating [^{18}F]-labeled radioligands, such as [^{18}F]FPPIP,[13] [^{18}F]FEM-IMPY,[14] [^{18}F]FPEG-stilbene[15] and [^{18}F]FPEGN3-styrylpyridine,[16] but, unfortunately, most of them displayed low-binding affinities to Aβ plaques. Our focus is to develop [^{18}F]-labeled plaque-specific imaging agents utilizing the benefit of ^{18}F allowing use of radioligands over a long period of time due to its longer half-life ($t_{1/2}$ = 110 min), along with a sufficient blood–brain barrier (BBB) penetration property to reach Aβ plaques. The radio-labeled imaging agents should also have adequate affinity toward the target and show rapid clearance of free and non-specific bound compounds from the brain. We have worked to develop Aβ fibril-binding agents which have indoprofen moiety as non-steroidal anti-inflammatory drugs (NSAIDs), of which analogues were associated with delaying the formation of Aβ fibril caused by their good binding affinity to Aβ.[17–20] Therefore, we have focused our efforts on the development of [^{18}F]-labeled imaging probes containing indoprofen moiety (Fig. 2).

In the beginning, we designed fluoroethyl- and fluoropropyl-substituted **18a**–**f** and **19a**–**f** compounds. All the synthesized compounds were evaluated by competitive binding assays against Aβ aggregates using [^{125}I]TZDM.

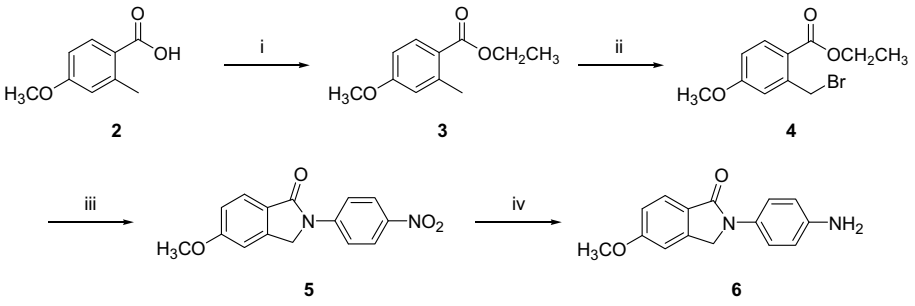
Syntheses of 2,3-dihydroisoindol-1-one derivatives are outlined in Scheme 1. The first step of 2-bromomethyl-4-methoxybenzoic acid ethyl ester **4** was achieved with *N*-bromosuccinimide and 2-methyl-4-methoxybenzoic acid via esterification and bromination. 2,3-Dihydroisoindol-1-one compound **5** was readily prepared from compound **4** and 4-nitroaniline.[21] Synthesis of 5-methoxy-2-(4-aminophenyl)isoindol-1,3-dione **10** was performed as described in Scheme 2.

Phthalic acid **7** upon a reaction with thionyl chloride in the presence of 1,4-diazabicyclo[2.2.0]octane gave phthalic anhydride **8**, which was then treated with 4-nitroaniline to afford the corresponding **9**.

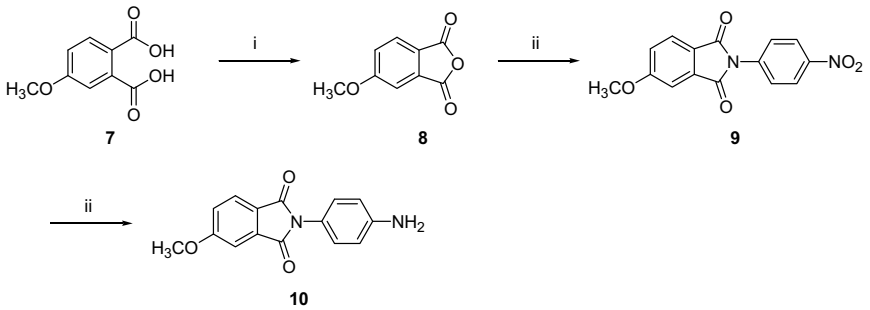
The free amino derivatives, **6** and **10** were prepared from the nitro compounds **5** and **9** via reduction with $SnCl_2$. Conversion of **6** to the monomethylamino derivative **11** was achieved via a method previously reported reductive amination.[22–24] **6** and **10** were also converted to dimethylamino derivatives, compounds **13** and **14**, via an efficient method with paraformaldehyde, sodium cyanoborohydride and acetic acid. The monomethylamino compound **12** was achieved via alkylation with iodomethane. The *O*-methyl groups were demethylated by reacting with BBr_3 to give **15a**–**c** and **16a**–**c**. Compounds **15b** and **15c** were alkylated with ethylene glycol di-*p*-tosylate to give the tosylethyl precursors **17b** and **17c**.

The fluorinated compounds **18a**–**f**[32] and **19a**–**f** were prepared from **15a**–**c** and **16a**–**c** by a nucleophilic substitution reaction with 1-fluoro-2-tosyloxyethane or 1-fluoro-3-tosyloxypropane (Scheme 3).[25] To make the desired [^{18}F]-labeled [^{18}F]**18b** and [^{18}F]**18c**, the tosylates **17b** and **17c** were employed as precursors (Scheme 4), and each tosylate was mixed with [^{18}F]TBAF in CH_3CN/*t*-amyl alcohol and heated to 120 °C for 10 min.[26]

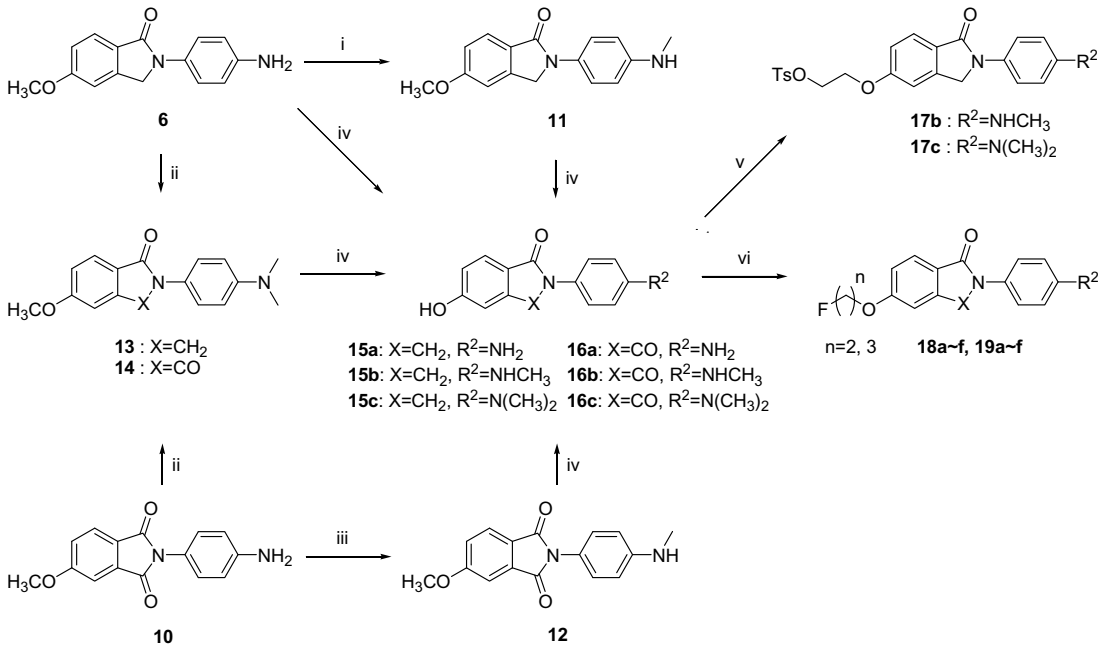
Specific binding affinities of synthesized compounds to Aβ42 fibrils were evaluated by an in vitro fibril-binding assay. The in vitro competition binding assay using pre-formed Aβ42 aggregates



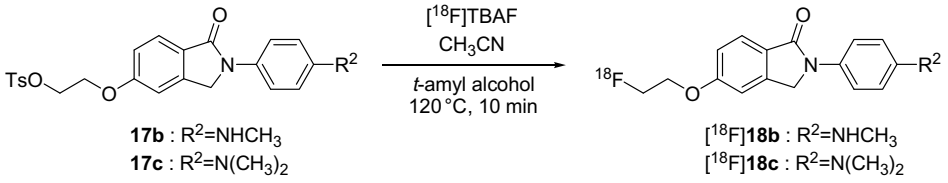
Scheme 1. Reagent and reaction conditions: (i) $SOCl_2$, EtOH, reflux, 4 h, 98%; (ii) *N*-bromosuccinimide, CCl_4, reflux, 6 h, 49%; (iii) 4-nitroaniline, acetic acid, reflux, 12 h, 50%; (iv) $SnCl_2$, EtOH, reflux, 3 h, 95%.



Scheme 2. Reagents and reaction conditions: (i) 1,4-diazabicyclo[2.2.2]octane, $SOCl_2$, CH_2Cl_2, 0 °C–rt, 1 h, 78%; (ii) 4-nitroaniline, acetic acid, reflux, 12 h, 92%; (iv) $SnCl_2$, EtOH, reflux, 3 h, 95%.



Scheme 3. Syntheses of **18a–f** and **19a–f**. Reagent and reaction conditions: (i) *p*-formaldehyde, NaOMe, MeOH/THF, $NaBH_4$, reflux, 3 h; (ii) *p*-formaldehyde, $NaBH_3CN$, acetic acid, rt, 12 h; (iii) CH_3I, K_2CO_3, DMSO, 100 °C, 5 h, 36%; (iv) BBr_3, CH_2Cl_2, reflux, 12 h 58–68%; (v) ethylene glycol di-*p*-tosylate, K_2CO_3, DMF, 90 °C, 2 h, 75%; (vi) 1-fluoro-2-tosyloxyethane or 1-fluoro-3-tosyloxypropane, K_2CO_3, DMF, 90 °C, 2 h, 68–90%.



Scheme 4. Radiosynthesis of [^{18}F]**18b** and [^{18}F]**18c**.

demonstrated that **18a–f** and **19a–f** competed against radioligands such as [^{125}I]TZDM.[27–29]

The results shown in Table 1 demonstrated that most of the synthesized compounds displayed lower K_i values (K_i = 0.30–0.91 nM) than PIB. In structure-activity relationship, isoindol-1-one derivatives, **18a–f**, showed slightly higher binding affinities than isoindol-1,3-dione derivatives, **19a–f**. Among the isoindol derivatives evaluated, it is evident that compound **18c** displayed higher binding affinities (K_i = 0.30 nM) so that **18c** with **18b** (secondary amine), for its closest structural similarity to **18c** (tertiary amine), was chosen to measure brain pharmacokinetic profiles.

In vivo biodistribution and micro-PET studies showed favorable characteristics (Table 2). The novel [^{18}F]-labeled compounds, both *N*-monomethyl, [^{18}F]**18b**, and *N*,*N*-dimethyl, [^{18}F]**18c**, tested in normal mice and exhibited excellent brain penetrations (9.1% and 11.1% ID/g at maximum peaked post-injection for [^{18}F]**18b** and [^{18}F]**18c**, respectively). The clearance rate test of these compounds displayed rapid washout (3.0% and 3.7% ID/g at 30-min post-injection for [^{18}F]**18b** and [^{18}F]**18c**, respectively). Therefore, the ratio peak/

Table 1
K_i values of **18a–f** and **19a–f** against [^{125}I]TZDM for binding affinities to Aβ42 aggregates

Compound	K_i[a] (nM)
18a	0.61
18b	0.91
18c	0.30
18d	0.40
18e	0.51
18f	0.71
19a	0.59
19b	0.60
19c	0.69
19d	0.74
19e	0.78
19f	0.85
PIB	0.77

[a] K_i was calculated by the Cheng–Prusoff equation ($K_i = IC_{50}/(1+[L]/K_d)$)[30] using *Graphpad Prism* software.

Table 2
Biodistributions of [^{18}F]**18b** and [^{18}F]**18c** after iv injection in normal mouse (% ID/g)

Compound	$Peak_{max}$	30 min	60 min	120 min
[^{18}F]**18b**				
Cerebrum	9.1	3.0	3.3	3.2
Cerebellum	11.0	3.3	3.4	3.0
Bone	4.9	4.1	4.8	6.6
Lung	13.3	3.0	2.6	2.5
Soft tissue	3.1	2.9	2.0	2.3
Liver	18.1	5.0	3.1	2.5
[^{18}F]**18c**				
Cerebrum	11.1	3.7	3.9	3.7
Cerebellum	14.4	3.7	3.9	3.8
Bone	8.2	4.3	5.1	6.0
Lung	18.1	3.2	2.9	2.8
Soft tissue	3.1	3.3	3.0	2.6

30 min in the normal brain is 3.0, which means that within 30 min over 50% radioligand not bound to Aβ aggregates is cleared out in the brain and which is believed to be a promising pharmacokinetic property for early detection of amyloid plaques in the AD brain.[31]

In conclusion, a series of novel fluoroethyl- and fluoropropyl-substituted compounds were successfully synthesized and these isoindole derivatives displayed excellent binding affinities to Aβ aggregates. Two new [^{18}F]-labeled isoindole derivatives were synthesized and evaluated as potential Aβ imaging probes based on in vivo pharmacokinetic profiles using micro-PET. In addition, they displayed high initial brain uptake and rapid washout from brains after injection in normal mice. The combination of high-binding affinities to Aβ fibrils, high brain uptake, and excellent clearance of [^{18}F]-labeled compounds provides a series of potential probe candidates for PET imaging to diagnose accumulation of Aβ aggregate in AD patients.

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26. [^{18}F]fluoride was produced from a cyclotron (IBA Cyclone 18/9, Belgium) and eluted with a solution of 20 μL tetra-butylammonium bicarbonate ($TBAHCO_3$), 300 μL of H_2O, and 300 μL of CH_3CN after collection of [^{18}F]fluoride on a PS–HCO_3 cartridge (Macherey-Nagel, Germany). The solvent was removed under a stream of nitrogen at 120 °C and the residue was azeotropically dried with anhydrous CH_3CN (3× 500 μL) at 120 °C under nitrogen stream. We dried [^{18}F]fluoride and then added 10 mg of precursor, 50 μL of CH_3CN, and 500 μL of *t*-amyl alcohol. Reaction time and temperature for [^{18}F]fluorination was 10 min at 120 °C. We checked [^{18}F]fluorination yield with radio thin-layer chromatography (radio-TLC) using EtOH/ethyl acetate, 1:1 as developing solvent. After [^{18}F]fluorination, we removed solvent and diluted with 1.0 mL CH_3CN and filtered to syringe filter. The residue was injected to HPLC for purification [C_8 apollo (250 mm, 10 mm), CH_3CN/5 mM dimethylglutaric acid; flow rate 4 mL/min]. After product was diluted with 20 mL water, it was passed through the C_{18} Sep-Pak. (Waters, USA) The product was trapped and eluted with 0.5 mL of EtOH.
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29. We estimated K_d value (0.13 nM) of [^{125}I]TZDM for Aβ42 aggregates. For inhibition studies, The reaction mixture contained 50 μL of Aβ42 aggregates (11.5 nM in the final concn), 50 μL of inhibitors (10^{-6}–10^{-12} M in DMSO), 50 μL of [^{125}I]TZDM (in 40% EtOH, 0.05 nM in the final concn) and 10% EtOH in a final volume of 1 mL. Non-specific binding was defined by adding 2 μM Th-T for [^{125}I]TZDM binding. The mixture was incubated at room temperature for 3 h and the bound and the free radioactivity were separated by a vacuum filtration through Whatman GF/B filters using a Brandel M-24R cell harvester followed by 2× 3 mL washes of 10% EtOH at room temperature. Filters containing the bound radioligand were counted in a gamma-counter (Cobra-II). The result of inhibition assays were subjected to nonlinear regression analysis using software *Graphpad Prism* by K_i values was calculated.
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32. *Selected data* **18b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.68 (d, J = 4.7 Hz, 3H), 4.35 (dt, J = 3.4, 29.9 Hz, 2H), 4.77 (dt, J = 3.5, 40.1 Hz, 2H), 5.59 (m, NH), 6.58 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 29.92, 50.73, 67.42, 67.61, 81.18, 82.84, 108.38, 111.55, 115.36, 121.54, 124.34, 125.71, 128.47, 143.24, 147.01, 161.20, 165.66; HRMS m/z Calcd for $C_{17}H_{17}FN_2O_2$ $(M)^+$ 300.1274, found 300.1265. *Compound* **18c**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.88 (s, 6H), 4.34 (dt, J = 3.4, 30.1 Hz, 2H), 4.78 (dt, J = 3.5, 49.1 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 7.09 (dd, J = 1.9, 8.5 Hz, 1H), 7.20 (d, J = 1.9 Hz, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ) 30.67, 50.54, 67.38, 67.63, 80.90, 83.10, 108.37, 112.63, 115.39, 120.99, 124.40, 125.62, 129.21, 143.25, 147.51, 161.26, 165.76; HRMS m/z Calcd for $C_{18}H_{19}FN_2O_2$ $(M)^+$ 314.1431, found 314.1431.