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Isoindol-1,3-dione and isoindol-1-one derivatives with high binding affinity to β-amyloid fibrils

Hyu Ji Lee,[a,b] Soo Jeong Lim,[c] Seung Jun Oh,[c] Dae Hyuk Moon,[c] Dong Jin Kim,[a] Jinsung Tae[b] and Kyung Ho Yoo[a,*]

[a]*Life Sciences Research Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea*
[b]*Department of Chemistry, Yonsei University, Seodaemun-gu, Seoul 120-749, Republic of Korea*
[c]*Department of Nuclear Medicine, Asan Medical Center, 388-1, Pungnap-2-Dong, Songpa-Gu, Seoul 138-736, Republic of Korea*

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Abstract—Based on the structural features of Indoprofen and PIB, a series of isoindol-1,3-diones **1a**–**k** and isoindol-1-ones **2a**–**l** were designed and synthesized. These 23 compounds were evaluated by competitive binding assay against aggregated Aβ42 fibrils using [^{125}I]TZDM. All the isoindolone derivatives showed very good binding affinities with K_i values in the subnanomolar range (0.42–0.94 nM). Among them, isoindol-1,3-diones **1i** and **1k** and isoindol-1-ones **2c** and **2i** exhibited excellent binding affinities (K_i = 0.42–0.44 and 0.46–0.49 nM) than those of Indoprofen (K_i = 0.52 nM) and PIB (K_i = 0.70 nM). These results suggest that isoindolones could be served as a scaffold for potential AD diagnostic probes to monitor Aβ fibrils.

Alzheimer's disease (AD) is a progressive neuro degenerative disease that is characterized by the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles in the brain of AD patients.[1–3] Fibrillar β-amyloid (Aβ), which is one of the main components of senile plaques, is cleaved from β-amyloid precursor protein (APP) by secretase to produce Aβ40 and Aβ42, resulting in neurotoxic activity both in vitro and it in vivo.[4,5]

It has suggested that the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) from epidemiological studies reduces the relative risk[6–8] or delays the onset of AD.[9] Since then, 2-(1-{6-[(2-[^{18}F]fluoro ethyl)(methyl)amino]-2-naphthyl}ethylidene)malono nitrile ([^{18}F]FDDNP) as a molecular imaging probe was developed for detection of senile plaques and neurofibrillary tangles in the living brain of AD patients using positron emission tomography (PET).[10] Recently, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxy benzothiazole ([^{11}C]PIB)[11,12] as an in vivo PET β-sheet imaging agent exhibited high affinity for Aβ, good brain entry and clearance. For early diagnosis or monitoring of β-amyloid formation and aggregation in AD brain, a variety of radiolabeled compounds as imaging probes have been developed.[13–18] The development of ligands specifically binding to β-amyloid aggregates is very important for labeling agents as in vivo diagnostic tools.

In an effort to develop the small molecules with high affinity to Aβ aggregates, isoindolones based on the structural combination of Indoprofen as a NSAID and PIB were designed as shown in Figure 1. We report here the synthesis and evaluation of a series of isoindol-1,3-dione and isoindol-1-one derivatives with high affinities for β-amyloid fibrils.

The synthesis of isoindol-1,3-dione derivatives **1a**–**k** was outlined in Scheme 1. Phthalic acids **3a** and **3b** with thionyl chloride in the presence of 1,4-diazabicyclo[2.2.0]octane gave phthalic anhydrides **4a** and **4b** (**4c**–**e**, commercially available), which were then treated with aminobenzene compounds **7** to afford the corresponding **1a**–**k**, respectively. Compounds **7b**–**d** (**7a**, commercially available) were obtained in good yields by first reductive amination of nitrobenzenes **5b**–**d** with *p*-formaldehyde and sodium cyanoborohydride[19,20] and subse-

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* Corresponding author. Tel.: +82 2 958 5152; fax: +82 2 958 5189; e-mail: khyoo@kist.re.kr

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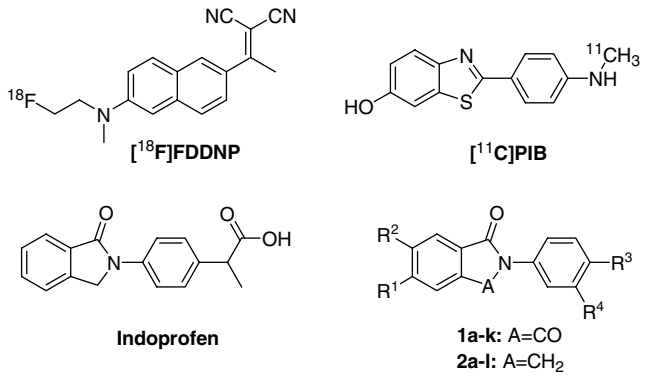


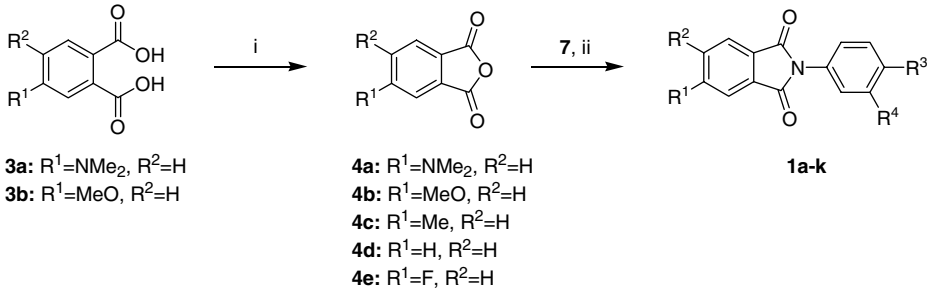
Figure 1. Structures of FDDNP, PIB, Indoprofen and isoindolone derivatives.

quent reduction of nitro group with tin chloride[21] (Scheme 2).

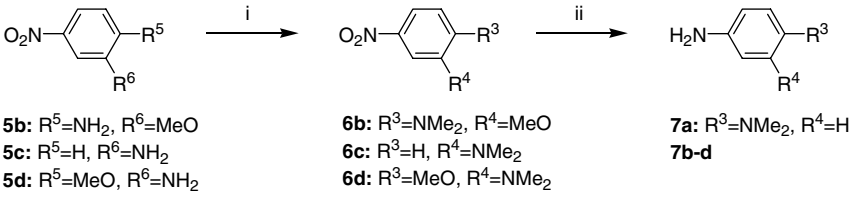
Isoindol-1-one derivatives **2a**–**l** were prepared in three steps using benzoic acids **8a**–**h** as starting materials (Scheme 3). Conversion of **8a**–**e**, **8g** and **8h** to ester compounds **9a**–**e**, **9g** and **9h** followed by bromination with *N*-bromosuccinimide provided bromomethylbenzoic esters **10a**–**e**, **10g** and **10h**, which were transformed into the corresponding **2a**–**l**, respectively.[22] Compound **9f**, which was prepared by bromination of **8f** with *N*-bromosuccinimide in the presence of benzoyl peroxide, was esterified to give **10f** for the synthesis of **2f**.

Table 1 shows the in vitro binding affinities (K_i values) of isoindol-1,3-diones **1a**–**k** and isoindol-1-ones **2a**–**l** against aggregated Aβ42 fibrils together with those of Indoprofen and PIB as reference compounds. All the synthesized compounds were evaluated by competitive binding assays against Aβ42 fibrils using [^{125}I]TZDM.[23]

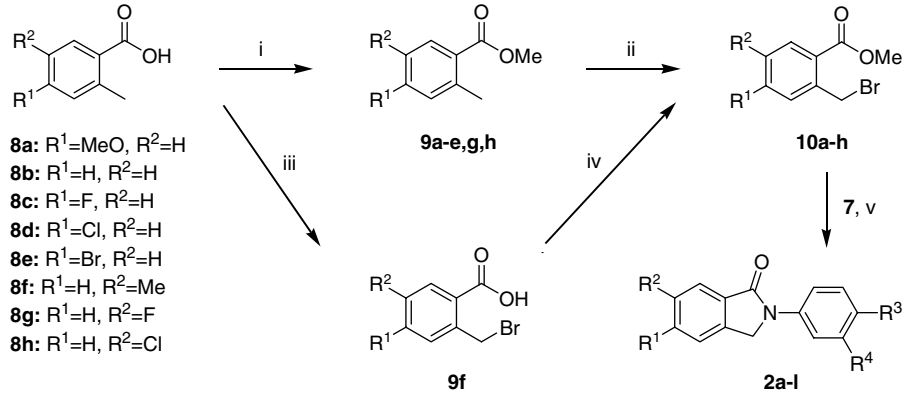
Binding affinities of the evaluated isoindolones ranged from 0.42 to 0.94 nM, and 13 compounds displayed higher affinity (lower K_i values) to Aβ42 fibrils than that of PIB (K_i = 0.70 nM). Especially, isoindol-1,3-diones **1i**



Scheme 1. Reagents and reaction conditions: (i) 1,4-diazabicyclo[2.2.2]octane, $SOCl_2$, CH_2Cl_2, 0 °C–rt, 1 h, 75% (for **4a**), 77% (for **4b**); (ii) acetic acid, reflux, 3–4 h, 46–99% (for **1a**–**k**).



Scheme 2. Reagents and reaction conditions: (i) $(CH_2O)n$, $NaBH_3CN$, AcOH, 0 °C–rt, 3 h, 75–99% (for **6b**–**d**); (ii) $SnCl_2$, EtOH, reflux, 3 h, 79–95% (for **7b**–**d**).



Scheme 3. Reagent and reaction conditions : (i) $SOCl_2$, MeOH, reflux, 4 h, 79–97%; (ii) *N*-bromosuccinimide, CCl_4, reflux, 6 h, 34–59% (for **10a**–**e**, **10g** and **10h**); (iii) *N*-bromosuccinimide, CCl_4, benzoyl peroxide, reflux, 1 h, 36%; (iv) THF, MeOH, 2 M trimethylsilyl diazomethane–hexane solution, rt, 4 h, 61% (for **10f**); (v) acetic acid, reflux, 3–4 h, 9–33% (for **2a**–**l**).

Table 1. In vitro binding affinities of isoindol-1,3-diones **1a–k** and isoindol-1-ones **2a–l** against Aβ42 fibrils using [^{125}I]TZDM

Compound	A	R^1	R^2	R^3	R^4	K_i[a] (nM)
1a	CO	NMe_2	H	NMe_2	H	0.70
1b	CO	MeO	H	NMe_2	H	0.71
1c	CO	Me	H	NMe_2	H	0.50
1d	CO	H	H	NMe_2	H	0.69
1e	CO	F	H	NMe_2	H	0.56
1f	CO	H	H	NMe_2	MeO	0.66
1g	CO	F	H	NMe_2	MeO	0.78
1h	CO	Cl	H	NMe_2	MeO	0.70
1i[25]	CO	Br	H	NMe_2	MeO	0.42
1j	CO	H	H	H	NMe_2	0.46
1k[25]	CO	H	H	MeO	NMe_2	0.44
2a	CH_2	MeO	H	NMe_2	H	0.94
2b	CH_2	H	H	NMe_2	H	0.58
2c[25]	CH_2	F	H	NMe_2	H	0.49
2d	CH_2	Cl	H	NMe_2	H	0.76
2e	CH_2	Br	H	NMe_2	H	0.81
2f	CH_2	H	Me	NMe_2	H	0.76
2g	CH_2	H	F	NMe_2	H	0.93
2h	CH_2	H	Cl	NMe_2	H	0.50
2i[25]	CH_2	H	Me	NMe_2	MeO	0.46
2j	CH_2	H	H	NMe_2	MeO	0.90
2k	CH_2	H	H	H	NMe_2	0.57
2l	CH_2	H	H	MeO	NMe_2	0.65
Indoprofen	—	—	—	—	—	0.52
PIB	—	—	—	—	—	0.70

[a] K_i was calculated by the Cheng–Prusoff equation ($K_i = IC_{50}/(1 = [L]/K_d)$[24] using *Graphpad Prism* software.

and **1k** and isoindol-1-ones **2c** and **2i** exhibited excellent binding affinities (K_i = 0.42–0.44 and 0.46–0.49 nM, respectively) compared to reference compounds. In general, isoindol-1,3-diones **1** showed slightly better potency in binding to Aβ42 fibrils than isoindol-1-ones **2**. Positional effect according to R^1 and R^2 substituents and modification of electron-donating groups to electron withdrawing groups at isoindolone nucleus did not make any significant difference of binding affinity. Compounds **1d**, **1f** and **2b**, **2i** having NMe_2, OMe at R^3, R^4 positions possessed slightly lower affinities as compared to compounds **1j**, **1k** and **2k**, **2l** with OMe, NMe_2 at R^3, R^4 positions, respectively.

In conclusion, all the isoindolone derivatives based on the structural features of Indoprofen and PIB exhibited very good binding affinities to aggregated Aβ42 fibrils. These isoindolones with high affinity provide the possibility of a scaffold for potential molecular imaging agents to monitor Aβ fibrils in the brain of AD patients.

Acknowledgment

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23. 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 conc.), 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 conc.) 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 was subjected to nonlinear regression analysis using software *Graphpad Prism* by K_i values was calculated.
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25. Selected data **1i**: Mp 167.5–168.5 °C; IR (KBr): 3678, 1724, 1514, 1334, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 1.2 Hz, 1H), 7.93 (dd, J = 7.9, 7.9 Hz, 1H), 7.82 (dd, J = 7.9, 0.3 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.4, 2.2 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.80, 166.26, 152.45, 137.36, 133.45, 130.42, 129.25, 127.01, 125.03, 119.06, 118.16, 109.77, 55.61, 43.15; MS m/z 375 (M^+).
Compound **1k**: Mp 154.0–155.0 °C; IR (KBr): 3671, 1716, 1512, 1389, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97–7.94 (m, 2H), 7.81–7.78 (m, 2H), 7.02 (dd, J = 8.6, 2.2 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 3.94 (s, 3H), 2.83 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.71, 152.16, 143.02, 134.26, 131.90, 124.42, 123.62, 120.65, 117.03, 111.14, 55.63, 43.15; MS m/z 296 (M^+).
Compound **2c**: Mp 238.5–239.5 °C; IR (KBr): 3674, 1673, 1527, 1357, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (dd, J = 9.1, 5.1 Hz, 1H), 7.61 (dd, J = 6.9, 2.2 Hz, 2H), 7.21–7.16 (m, 2H), 6.78 (dd, J = 6.9, 2.2 Hz, 2H), 4.78 (s, 2H), 2.96 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.83, 166.09, 163.50, 148.24, 142.64, 142.50, 129.59, 128.88, 126.00, 125.87, 121.70, 116.20, 115.89, 113.00, 110.08, 109.76, 51.01, 50.98, 40.80; MS m/z 270 (M^+).
Compound **2i**: Mp 153.0–154.0 °C; IR (KBr): 3671, 1678, 1514, 1392, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (s, 1H), 7.69 (s, 1H), 7.38 (s, 2H), 6.70 (s, 2H), 4.78 (s, 2H), 3.96 (s, 3H), 2.81 (s, 6H), 2.46 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 167.54, 152.64, 138.41, 137.30, 135.16, 133.44, 132.99, 124.12, 122.27, 118.25, 110.86, 104.19, 55.54, 50.90, 43.50, 21.40; MS m/z 296 (M^+).