



## Development of alkoxy styrylchromone derivatives for imaging of cerebral amyloid- $\beta$ plaques with SPECT

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### ARTICLE INFO

#### Article history:

Received 14 March 2015

Revised 15 May 2015

Accepted 18 May 2015

Available online 27 May 2015

#### Keywords:

Alzheimer's disease

Amyloid- $\beta$  plaque

Styrylchromone

Single photon emission computed tomography (SPECT)

### ABSTRACT

We report here the development of radioiodinated styrylchromone derivatives with alkoxy groups as single photon emission computed tomography (SPECT) imaging probes for cerebral amyloid- $\beta$  ( $A\beta$ ) plaques. Among the derivatives, the methoxy derivative **14** and the dimethoxy derivative **15** displayed relatively high affinity for the  $A\beta$ (1–42) aggregates with  $K_i$  values of 22 and 46 nM, respectively. Fluorescent imaging demonstrated that **14** and **15** clearly labeled thioflavin-S positive  $A\beta$  plaques in the brain sections of Tg2576 transgenic mice. In the in vivo studies, [<sup>125</sup>I]**14** and [<sup>125</sup>I]**15** showed high initial brain uptake expressed as the percentage of the injected dose per gram (2.25% and 2.49% ID/g at 2 min, respectively) with favorable clearance (0.12% and 0.20% ID/g at 180 min, respectively) from the brain tissue of normal mice. Furthermore, in vitro autoradiography confirmed that [<sup>125</sup>I]**15** binds thioflavin-S positive regions in Tg2576 mouse brain sections. The derivative **15** may be a potential scaffold for the development of in vivo imaging probes targeting  $A\beta$  plaques in the brain. In particular, further structural modifications are required to improve the compounds binding affinity for  $A\beta$ .

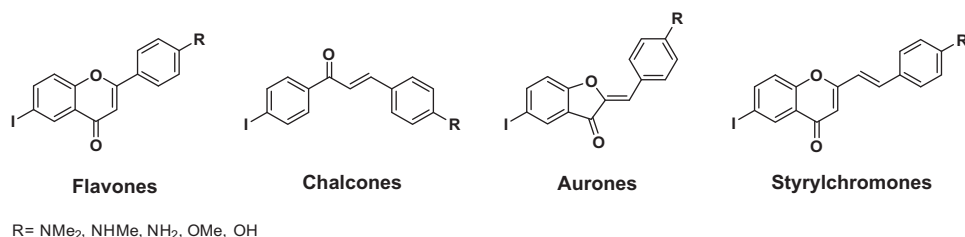
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Alzheimer's disease (AD), which is the most common cause of dementia in the elderly, is characterized by the progressive decline of cognition including learning and memory.<sup>1</sup> It is estimated that the number of patients with AD will increase to over 100 million by the year 2050 and, for this reason, effective therapies need to be developed to prevent the collapse of global health-care systems.<sup>2</sup>  $A\beta$  plaques have been detected in patients prior to the appearance of the clinical symptoms of AD. This implies that the detection and early initiation of treatment targeting  $A\beta$  deposits could be an effective therapeutic option to improve the symptoms of AD patients in the early disease stage.<sup>2,3</sup> Nuclear medicine imaging techniques have been accepted as useful tools for the early detection of cerebral  $A\beta$  plaque deposits.<sup>4</sup> Numerous studies have reported the development of positron emission tomography (PET) and SPECT imaging probes of  $A\beta$  plaques in the living brain.<sup>5–7</sup> In particular, <sup>18</sup>F-flutemetamol, <sup>18</sup>F-florbetapir and <sup>18</sup>F-florbetaben have demonstrated highly correlated brain distribution patterns with post-mortem existence of  $A\beta$  plaques.

Recently, these PET tracers were approved by the US Food and Drug Administration (FDA) for the specific detection of  $A\beta$  plaques in clinical practice.<sup>8–10</sup> In contrast, there are currently no effective SPECT probes for detecting  $A\beta$  plaques despite their convenience and widespread utilization. SPECT is widely available in most hospitals, and is generally less expensive, as compared to PET.<sup>11,12</sup> Accordingly, the development of clinically useful SPECT imaging probes for  $A\beta$  can facilitate and encourage the initial diagnosis of AD in elderly people. Previously, we have developed flavonoid derivatives such as flavones, chalcones, aurones, and styrylchromones as prospective  $A\beta$  imaging probes (Fig. 1), although clinically available compounds have not yet been developed.<sup>13–22</sup> We found that radioiodinated styrylchromones (SCs) with amino groups (NH<sub>2</sub>, NHMe, and NMe<sub>2</sub>) bind to  $A\beta$  aggregates with high binding affinities. However, their initial uptake and washout from normal mice brain tissue were inadequate for in vivo imaging.<sup>22</sup> Therefore, we hypothesized that the structural modification of SCs may improve the in vivo brain distribution and thereby, provide useful  $A\beta$  imaging agents. Previously, we reported that radioiodinated flavonoids such as flavone, chalcone, and aurone derivatives with alkoxy groups at the *p*-position of the phenyl ring showed good initial brain uptake and washout from the normal brain without crucial decline in binding affinity for  $A\beta$ .<sup>13,19,21</sup>

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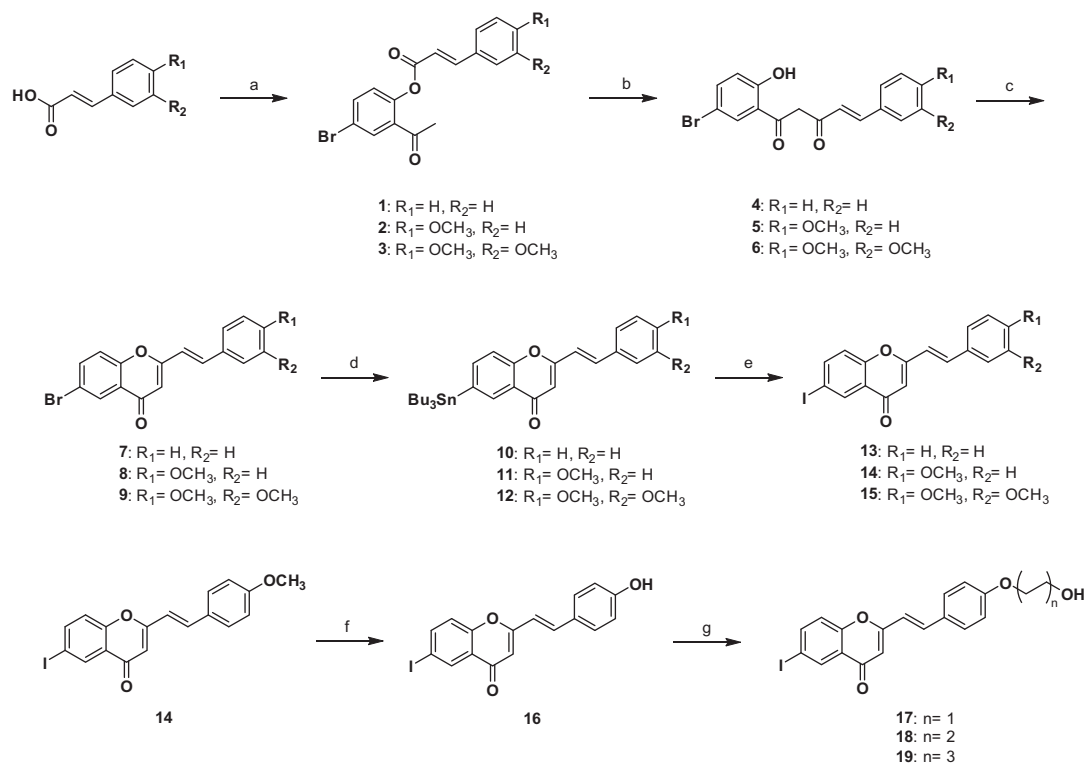
**Figure 1.** Chemical structures of flavonoid derivatives reported as A $\beta$  imaging probes.

Therefore, we considered that the introduction of alkoxy groups to the structure of SCs could improve their in vivo brain distribution. For this reason, we designed new radioiodinated SCs derivatives, which have alkoxy groups introduced into the 2-phenyl ring of the original structure. We envisaged that this structural modification would enable their application in SPECT diagnosis.

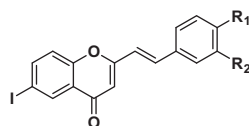
The synthesis of the alkoxy SC derivatives is presented in Scheme 1. O-acylation of the 5'-bromo-2'-hydroxyacetophenone with the appropriate cinnamoyl chlorides provided phenyl cinnamates **1–3**. The Baker–Venkataraman rearrangement of the phenyl cinnamates using KOH gave the corresponding 1,3-diketones **4–6**. The treatment of these 1,3-diketones with a mixture of H<sub>2</sub>SO<sub>4</sub> and AcOH led to their cyclodehydration yielding (*E*)-2-styrylchromones **7–9**. These styrylchromones were converted to tributyltin derivatives **10–12** using a bromo-to-tributyltin exchange reaction catalyzed by Pd(0). The resulting tributyltin derivatives were reacted with iodine in CHCl<sub>3</sub> to form the target iodo derivatives **13–15**. Methoxy derivative **14** was converted to phenol derivative **16** by demethylation with BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>. Alkylation of **16** with ethylene chlorohydrin, ethylene glycol mono-2-chloroethyl ether, or 2-[2-(2-chloroethoxy)ethoxy]ethanol using potassium

carbonate resulted in oligoethyleneoxy derivatives **17**, **18**, and **19**, respectively.

In vitro binding experiments to evaluate the binding affinity of the SC derivatives for A $\beta$  were performed. We used suspensions of A $\beta$ (1–42) aggregates with <sup>125</sup>I-labeled 4-dimethylamino-4'-iodo-styrylchromone (**20**), which showed high binding affinity for A $\beta$  aggregates (*K*<sub>d</sub> = 8.7 nM) in our previous studies.<sup>22</sup> The inhibition constant (*K*<sub>i</sub>) values of the SCs for the A $\beta$  aggregates ranged from 21.9 to 553 nM (Table 1). Derivative **13**, which contained an unsubstituted 2-phenyl ring, displayed weak affinity for A $\beta$  aggregates (*K*<sub>i</sub> = 198 nM). In contrast, methoxy derivative **14** (*K*<sub>i</sub> = 21 nM) showed a 9-fold improvement in binding affinity versus **13**, displaying comparable affinity to dimethylamino derivative **20** (*K*<sub>i</sub> = 22 nM). Accordingly, the presence of a methoxy group at R<sub>1</sub> may have a crucial role in binding interactions with A $\beta$  aggregates. Dimethoxy derivative **15** had a reasonable binding affinity (*K*<sub>i</sub> = 46 nM), suggesting that the introduction of a methoxy group at the R<sub>2</sub> position can retain binding affinity. However, introduction of a hydroxyl group at the R<sub>1</sub> position did not improve the binding affinity. Indeed, hydroxyl derivative **16** displayed a negligible A $\beta$  binding affinity (*K*<sub>i</sub> = 121 nM). The oligoethyleneoxy



**Scheme 1.** Synthesis of styrylchromone derivatives. Reagents and conditions: (a) (1) SOCl<sub>2</sub>, DMF, reflux 1 h, (2) 5'-bromo-2'-hydroxyacetophenone, pyridine, reflux, 3 h; (b) pyridine, KOH, reflux, 1 h; (c) H<sub>2</sub>SO<sub>4</sub>, AcOH, reflux, 1 h then rt, 1 h; (d) (SnBu<sub>3</sub>)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>N, dioxane, reflux, 7 h, (e) I<sub>2</sub>, CHCl<sub>3</sub>, rt, 30 min (f) CH<sub>2</sub>Cl<sub>2</sub>, BBr<sub>3</sub>, rt, 24 h; (g) H(OCH<sub>2</sub>CH<sub>2</sub>)<sub>n</sub>Cl, K<sub>2</sub>CO<sub>3</sub>, DMF.

**Table 1**Inhibition constant ( $K_i$ ) for A $\beta$ (1–42) aggregates and log*P* values of styrylchromone derivatives

- 13:  $R_1 = H$ ,  $R_2 = H$   
 14:  $R_1 = OMe$ ,  $R_2 = H$   
 15:  $R_1 = OMe$ ,  $R_2 = OMe$   
 16:  $R_1 = OH$ ,  $R_2 = H$   
 17:  $R_1 = OCH_2CH_2OH$ ,  $R_2 = H$   
 18:  $R_1 = (OCH_2CH_2)_2OH$ ,  $R_2 = H$   
 19:  $R_1 = (OCH_2CH_2)_3OH$ ,  $R_2 = H$   
 20:  $R_1 = N(CH_3)_2$ ,  $R_2 = H$

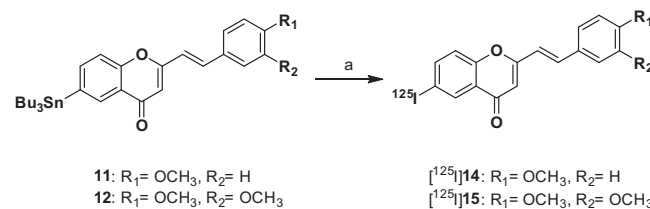
Compounds	$K_i^a$ (nM)	Mw	log <i>P</i> <sup>b</sup>
<b>13</b>	198 ± 48.0	374.1	—
<b>14</b>	21.9 ± 5.10	404.2	2.15
<b>15</b>	45.5 ± 10.7	434.2	2.14
<b>16</b>	121 ± 20.8	390.2	1.87
<b>17</b>	446 ± 100	434.2	—
<b>18</b>	415 ± 64.5	478.3	—
<b>19</b>	553 ± 135	522.3	—
<b>20</b>	21.8 ± 3.35	417.3	2.65 <sup>c</sup>

<sup>a</sup> Inhibition constant of styrylchromone derivatives were determined using [<sup>125</sup>I]**20** as the ligand in A $\beta$  aggregates. Each value (mean ± SEM) was determined by 3–6 independent experiments.

<sup>b</sup> The partition coefficient between *n*-octanol and sodium phosphate buffer at pH 7.4 was determined by a conventional flask shaking method ( $n = 3$ ).

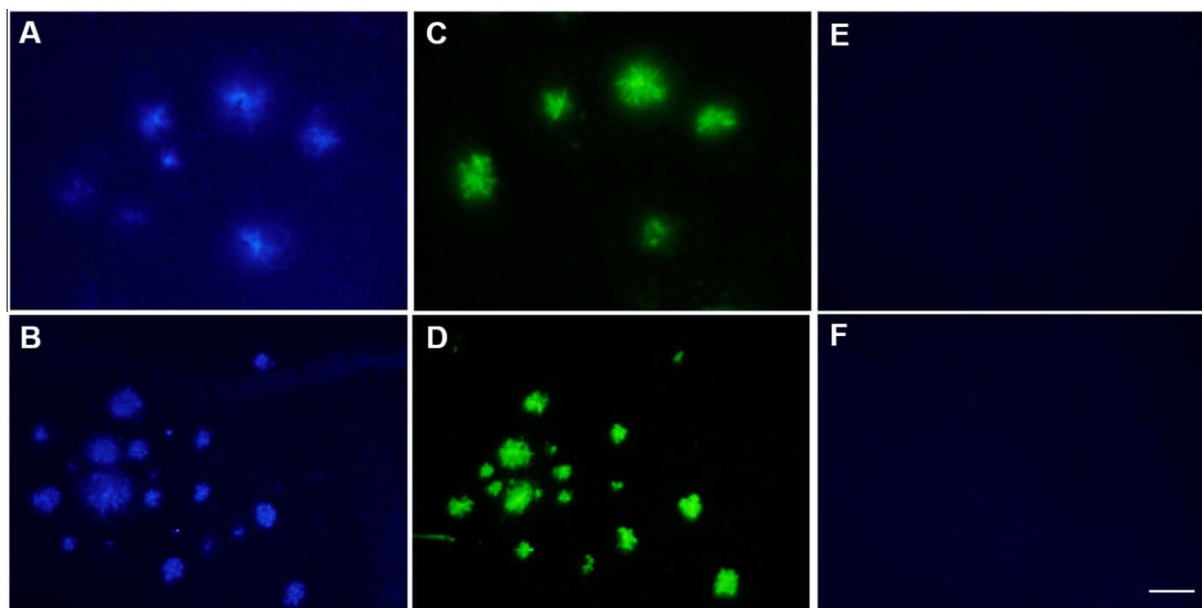
<sup>c</sup> The log*P* values have been reported in our previous studies.<sup>22</sup>

derivatives **17–19** exhibited reduced binding affinities ( $K_i = 415$ – $553$  nM), which were over 20-fold lower than **14**. In our previous study, the introduction of oligoethyleneoxy groups to the phenyl ring of radioiodinated aurones did not considerably alter A $\beta$  aggregate binding.<sup>21</sup> In this study, we observed the opposite effect, in that the presence of oligoethyleneoxy groups on the 2-phenyl ring of the SCs clearly had a deleterious effect on A $\beta$  aggregate binding affinity. These facts suggest that SCs and aurones may exhibit different binding interactions with A $\beta$  aggregates, although the mechanisms remain largely unclear.

**Scheme 2.** Radiosynthesis of <sup>125</sup>I-labeled styrylchromone derivatives. Reagents and conditions: (a) [<sup>125</sup>I]NaI, H<sub>2</sub>O<sub>2</sub>, HCl, EtOH, 3 min.

Based on the *in vitro* results, we selected **14** and **15** for further biological evaluation. Fluorescence imaging experiments with the SCs were performed using brain slices from a transgenic mouse (Tg2576) model of A $\beta$  deposition. A number of fluorescence spots denoting derivatives **14** and **15** were observed in the mouse brain slices (Fig. 2A and B). The labeling patterns of these compounds corresponded to the fluorescence signals obtained with thioflavin-S staining (Fig. 2C and D). In contrast, there was no significant fluorescence for **14** and **15** in the brain slices from wild-type mice (Fig. 2E and F). There was no marked autofluorescence detected in any brain slices (data not shown). These results indicate that **14** and **15** have specific binding potential to A $\beta$  plaques in the mouse brain.

For the biodistribution study and *in vitro* autoradiography, <sup>125</sup>I-labeled SC derivatives ([<sup>125</sup>I]**14**, [<sup>125</sup>I]**15**) were synthesized by an iododestannylation reaction of tributyltin derivatives (**11** and **12**) with hydrogen peroxide as an oxidant (Scheme 2). Using HPLC systems, the radioligands were purified, and the radiochemical qualities of these ligands were analyzed by co-injection of non-radioactive compounds. The radioiodinated products were obtained in radiochemical yields of 40–75% with a radiochemical purity of >95%. Clinically available SPECT imaging probes for the A $\beta$  plaque should show a high initial brain uptake and rapid clearance from non-target regions in the brain. Therefore, biodistribution studies of [<sup>125</sup>I]**14** and [<sup>125</sup>I]**15** were conducted in normal mice and expressed as % of injected dose per gram (% ID/g) (Table 2). The compounds [<sup>125</sup>I]**14** and [<sup>125</sup>I]**15** exhibited a high initial brain uptake (2.3% and 2.5% ID/g at 2 min, respectively) and a favorable brain clearance (0.1% and 0.2% ID/g at 180 min,

**Figure 2.** Neuropathological staining of styrylchromone derivatives **14** (A) and **15** (B) in 10  $\mu$ m sections of Tg2576 mice brain. Labeled plaques were confirmed by staining of the adjacent sections with thioflavin-S (C and D). Fluorescence images of **14** (E) and **15** (F) in the age-matched control mouse brain sections. Scale bar = 50  $\mu$ m.

**Table 2**Biodistribution of radioactivity after iv injection of  $^{125}\text{I}$  labeled styrylchromone derivatives in normal mice

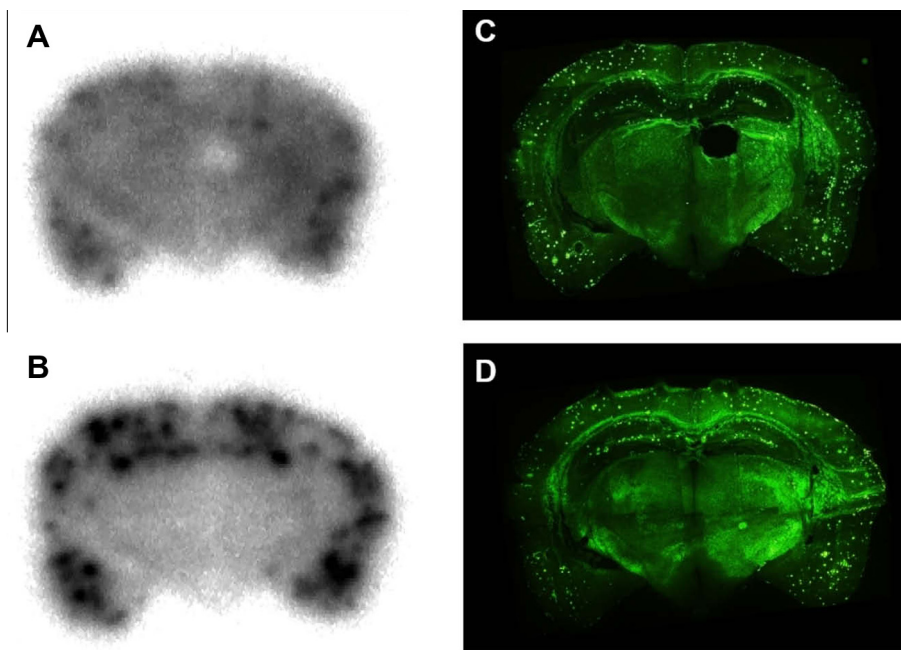
Organ	Time after injection (min)				
	2	30	60	120	180
$[^{125}\text{I}]\mathbf{14}$					
Blood	2.22 (0.31)	0.76 (0.09)	0.56 (0.13)	0.36 (0.08)	0.29 (0.04)
Liver	20.90 (3.32)	14.72 (3.73)	9.10 (2.58)	6.53 (3.63)	3.38 (0.59)
Kidney	10.06 (1.94)	4.50 (1.55)	2.20 (0.41)	1.28 (0.40)	0.85 (0.12)
Intestine	1.70 (0.67)	10.41 (3.60)	18.57 (7.07)	22.64 (6.14)	18.82 (3.81)
Spleen	3.81 (1.11)	1.19 (0.20)	0.82 (0.17)	0.70 (0.26)	0.55 (0.32)
Lung	6.12 (1.61)	1.77 (0.33)	1.17 (0.28)	0.78 (0.18)	0.60 (0.19)
Stomach	0.96 (0.26)	1.22 (0.88)	2.58 (2.09)	5.03 (4.15)	4.19 (1.37)
Pancreas	5.26 (0.84)	1.44 (0.22)	1.06 (0.44)	0.82 (0.74)	0.68 (0.72)
Heart	5.50 (1.08)	1.09 (0.08)	0.67 (0.15)	0.37 (0.10)	0.26 (0.08)
Brain	2.25 (0.38)	1.00 (0.12)	0.56 (0.11)	0.23 (0.06)	0.12 (0.02)
$[^{125}\text{I}]\mathbf{15}$					
Blood	3.42 (0.32)	1.25 (0.16)	0.74 (0.10)	0.61 (0.14)	0.33 (0.05)
Liver	15.07 (1.39)	7.42 (1.46)	4.98 (1.39)	3.50 (0.82)	4.26 (0.80)
Kidney	12.28 (1.43)	4.74 (0.70)	2.37 (0.33)	1.51 (0.18)	1.09 (0.20)
Intestine	1.71 (0.47)	12.19 (4.91)	15.93 (8.64)	27.37 (4.85)	23.16 (3.95)
Spleen	4.86 (0.69)	1.62 (0.31)	1.04 (0.16)	0.80 (0.49)	1.33 (1.19)
Lung	7.00 (0.99)	2.31 (0.31)	1.46 (0.18)	0.95 (0.11)	1.68 (2.48)
Stomach	1.39 (0.18)	2.75 (2.17)	1.77 (0.53)	5.15 (3.29)	3.67 (2.82)
Pancreas	7.17 (1.62)	2.95 (0.90)	1.13 (0.17)	0.76 (0.34)	0.42 (0.20)
Heart	6.96 (0.93)	1.68 (0.23)	0.96 (0.13)	0.52 (0.08)	0.32 (0.08)
Brain	2.49 (0.39)	1.39 (0.16)	0.76 (0.12)	0.36 (0.05)	0.20 (0.12)
$[^{125}\text{I}]\mathbf{20}$					
Blood	2.24 (0.43)	1.20 (0.17)	1.02 (0.16)	1.07 (0.19)	1.09 (0.29)
Liver	12.3 (2.65)	8.36 (2.01)	5.84 (1.18)	7.46 (2.61)	4.36 (1.29)
Kidney	8.68 (2.05)	3.36 (1.25)	1.59 (0.66)	1.35 (0.55)	1.37 (0.41)
Intestine	1.20 (0.48)	11.83 (2.26)	9.90 (5.68)	13.43 (5.52)	10.03 (2.58)
Spleen	3.88 (1.94)	2.65 (0.45)	1.82 (0.45)	2.01 (0.89)	2.04 (0.29)
Lung	8.83 (2.51)	3.85 (0.69)	2.54 (0.82)	2.27 (0.55)	1.96 (0.89)
Stomach	1.01 (0.31)	1.88 (0.79)	1.79 (0.66)	3.15 (1.46)	3.38 (2.68)
Pancreas	3.37 (0.59)	1.44 (0.58)	0.84 (0.14)	0.81 (0.31)	0.59 (0.21)
Heart	5.51 (1.33)	1.26 (0.31)	0.66 (0.13)	0.63 (0.14)	0.64 (0.17)
Brain	1.20 (0.23)	1.13 (0.21)	0.62 (0.10)	0.44 (0.11)	0.38 (0.11)

Each value represents mean (SD) for 5 or 6 mice at each interval.

respectively). The brain<sub>2min</sub>/brain<sub>60min</sub> ratio of  $^{18}\text{F}$  has been used as an index of brain washout.<sup>23,24</sup> The brain<sub>2min</sub>/brain<sub>60min</sub> ratio of clinically used [ $^{18}\text{F}$ ]Florbetapir ([ $^{18}\text{F}$ ]AV-45) and [ $^{18}\text{F}$ ]Florbetaben ([ $^{18}\text{F}$ ]BAY94-917218) was reported to be 3.8<sup>23</sup> and 4.8,<sup>25</sup> respectively. Since the brain<sub>2min</sub>/brain<sub>60min</sub> ratio of [ $^{125}\text{I}$ ]**14** and [ $^{125}\text{I}$ ]**15** was calculated to be 4.5 and 3.3, respectively, the washout index of these [ $^{125}\text{I}$ ]SC derivatives seems to be comparable to the aforementioned PET probes. Additionally, because the half-life of radioactive iodine  $^{125}\text{I}$ , used for SPECT, is much longer than that of  $^{18}\text{F}$  (13.2 h vs 110 min), the brain<sub>2min</sub>/brain<sub>180min</sub> ratio can be used as another index of brain washout in this study. The brain<sub>2min</sub>/brain<sub>180min</sub> ratios of [ $^{125}\text{I}$ ]**14** and [ $^{125}\text{I}$ ]**15** were 18.8 and 12.5, respectively, indicating that these two  $^{125}\text{I}$ -labeled SC derivatives have promising in vivo pharmacokinetics. Furthermore, the collective in vivo results suggested that the washout of [ $^{125}\text{I}$ ]**14** from the normal brain tissue was faster than that of [ $^{125}\text{I}$ ]**15**. Both [ $^{125}\text{I}$ ]**14** and [ $^{125}\text{I}$ ]**15** demonstrated increased radioactivity in the stomach over time, and peaked at 5.0% and 5.2% ID/g at 60 min, respectively, suggesting that these SCs were gradually deionidated in vivo. Since brain uptake of these tracers rapidly declined with time, it is unlikely that the metabolites could easily penetrate the blood brain barrier. Consistent with our previous study,<sup>22</sup> relatively low initial brain uptake and high brain retention of the dimethylamino derivative [ $^{125}\text{I}$ ]**20** (1.20% ID/g at 2 min and 0.38% ID/g at 180 min) was observed, compared with the methoxy derivatives. It is reported that radiotracers with a low molecular weight (<500 Da) and a moderate lipophilicity (log $D_{7.4}$  values, 2.0–3.5) show optimal passive brain entry in vivo.<sup>26,27</sup> Although the molecular weights of the  $^{125}\text{I}$ -labeled compounds in this study

are all within the specified range (Table 2), the most lipophilic [ $^{125}\text{I}$ ]**20** showed a relatively low blood–brain barrier permeability. Taken together, these results indicate that the substitution of a dimethylamino group with methoxy groups at the 2-phenyl ring position of the SCs structure improves its brain distribution for in vivo imaging.

To further characterize [ $^{125}\text{I}$ ]**14** and [ $^{125}\text{I}$ ]**15** as possible imaging probes for specifically targeting A $\beta$  plaques, in vitro autoradiography was performed using brain sections from the Tg2576 mice. Although some [ $^{125}\text{I}$ ]**14** spots in the brain slices corresponded to thioflavin-S stained regions, the overall [ $^{125}\text{I}$ ]**14** image was inconsistent with the existence of A $\beta$  plaques (Fig. 3A and C). In contrast, clear [ $^{125}\text{I}$ ]**15** autoradiographic images were observed in the thioflavin-S positive regions (Fig. 3B and D). The discrepancy between the fluorescence and autoradiographic images of these SC derivatives could have been caused by the different concentration of the compounds. The concentration of the SCs was 100  $\mu\text{M}$  for the fluorescence staining while only 0.3 nM of  $^{125}\text{I}$  labeled SCs was used in the autoradiography studies. It is unclear why only the [ $^{125}\text{I}$ ]**15** displayed a clear autoradiograph for A $\beta$  plaques, despite the fact that derivative **15** possesses a lower binding affinity for the A $\beta$  aggregates than **14** (Table 1). Several factors may have contributed to these results, including the selectivity for A $\beta$  plaques over other brain components, degree of nonspecific binding, and conformation differences between the A $\beta$  aggregates and A $\beta$  plaques in the brain of Tg2576 mice. Regardless, the [ $^{125}\text{I}$ ]**15** may be a potential lead compound for the development of in vivo imaging probes for A $\beta$  plaques in the brain. Further structural modification of the SC derivatives can provide promising A $\beta$  imaging probes.



**Figure 3.** In vitro autoradiograms of styrylchromone derivatives [ $^{125}\text{I}$ ]**14** (A) and [ $^{125}\text{I}$ ]**15** (B) in the brain sections of Tg2576 mouse brain. Fluorescence images of thioflavin-S in the adjacent section (C and D).

In conclusion, we demonstrated that radioiodinated styrylchromone derivatives with methoxy groups had preferable pharmacokinetics for in vivo imaging without significant reduction in binding affinity for the A $\beta$  aggregates. In particular, both fluorescent imaging and autoradiography showed that the dimethoxy derivative [ $^{125}\text{I}$ ]**15** labeled the thioflavin-S positive A $\beta$  plaques in sections of the Tg2576 mouse brain. Further structural modifications based on derivative **15** may facilitate the development of clinically useful A $\beta$  imaging probes.

### Acknowledgment

Financial support was provided by a Grant-in-Aid for Scientific Research (B) (Grant No. 21390348) from Japan Society for the Promotion of Science (JSPS).

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2015.05.048>.

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