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Novel (*E*)-5-styryl-2,2′-bithiophene derivatives as ligands for β-amyloid plaques

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ABSTRACT

In continuation of our investigation on the bithiophene structure as potential β-amyloid probes, a series of (*E*)-5-styryl-2,2′-bithiophene (SBTP) derivatives was designed and synthesized. *In vitro* binding showed that all of them displayed high binding affinities to Aβ$_{1-42}$ aggregates ($K_i = 0.10-41.05$ nM). Moreover, two radio-iodinated probes, [^{125}I]-(*E*)-5-(4-iodostyryl)-2,2′-bithiophene ([^{125}I]**8**) and [^{125}I]-(*E*)-5-iodo-5′-(4-methoxystyryl)-2,2′-bithiophene ([^{125}I]**31**) were prepared. Both of them displayed specific labeling of Aβ plaques in the brain sections of AD model mice with low background. *In vivo* biodistribution in normal mice indicated that [^{125}I]**8** exhibited high initial brain uptake (2.11% ID/g at 2 min) and rapid clearance (0.41% ID/g at 30 min). These preliminary results suggest that SBTP derivatives may be served as novel β-amyloid imaging probes.

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1. Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder characterized by progressive decline in cognitive function of brain and behavior. Histopathologically, β-amyloid plaques (Aβ) and neurofibrillary tangles (NFTs) are found in the brain of patients suffering from AD [1]. Although the etiology of AD is not completely understood, the most widely accepted theory concerning the etiology of AD is the amyloid cascade hypothesis [2,3]. The clinical diagnosis of this disease is made through the neurological observations and history of patients, which is often difficult and unreliable. To facilitate the early diagnosis of AD, functional imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been employed. For this purpose, a radionuclide-labeled probe that specifically binds to Aβ plaques in the brain may greatly facilitate the diagnosis of AD [4,5].

During the past decade, several attempts have been made to develop specific radiotracers for *in vivo* imaging Aβ plaques with PET and SPECT. Most of the reported probes are based on the core structure of Congo Red (CR), Thioflavin T (ThT) and DDNP. Several PET tracers such as 2-(4′-[^{11}C]methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]PIB) [6,7], [^{18}F]-2-(1-(2-(*N*-(2-fluoroethyl)-*N*-methylamino)-naphthalene-6-yl)ethylidene)malononitrile ([^{18}F]FDDNP) [8–10], 4-*N*-[^{11}C]methylamino-4′-hydroxystilbene ([^{11}C]SB-13) [11,12], [^{18}F]-4-(*N*-methylamino)-4′-(2-(2-(2-fluoroethoxy)ethoxy) ethoxy)-stilbene ([^{18}F]BAY94-9172) [13] and [^{18}F]-(*E*)-4-(2-(6-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylaniline ([^{18}F]AV-45) [14,15] have been evaluated in human studies. Some of the candidates have already moved into Phase II, Phase III and even finalization stages (such as Florbetapir, [^{18}F]AV-45, is waiting for the approval from FDA). On the other hand, to the best of our knowledge, the only SPECT tracer tested in human studies is [^{123}I]-6-iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine ([^{123}I]IMPY) [16–18]. However, some undesirable properties including high lipophilicity, *in vivo* instability together with insufficient target-to-background ratio may account for the failure of [^{123}I]IMPY in clinical trials. After that, there is no report of any Aβ imaging candidate for SPECT moving into clinical trial. For the routine clinical applications, imaging with SPECT has some advantages over PET such as more widespread availability, no need for an on-site cyclotron and lower cost. From this point of view, there is an urgent need for developing Aβ imaging agents for SPECT. In the past few years, lots of the research related to Aβ imaging agents for SPECT have been reported. For example, Qu et al. reported radio-iodinated aza-diphenylacetyllenes [19] and styrylpyridines [20] as SPECT imaging agents for Aβ plaque detection. Ono et al. designed and synthesized radio-iodinated aurone derivatives [21,22], chalcones and their related derivatives [23,24], as well as ^{99m}Tc labeled flavonoids including chalcone [25], flavone and aurone [26] as probes for SPECT imaging of Aβ plaques.

In a search on novel Aβ binding probes, Nesterov et al. first proposed, synthesized and evaluated bithiophene type molecules as fluorescent imaging markers for Aβ plaques [27]. A bithiophene molecule, NIAD-4 had been screened out as a simple fluorescent

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marker for optical imaging of amyloid plaques in brain (Fig. 1). Later, Nilsson et al. identified that a class of luminescent conjugated polythiophenes (LCPs) with a striking specificity for Aβ plaques as shown in Fig. 1 [28–30]. In our previous work, a series of benzothiazole derivatives based on the bithiophene structure (TZBP) was evaluated for the imaging of Aβ plaques. These derivatives displayed excellent binding affinity to Aβ aggregates [31]. Inspired by these successful results we decided to perform extensive research on the ligands with bithiophene structure, which may play an important role in maintaining the specific binding ability to Aβ plaques. Herein, we report a series of bithiophene derivatives combined with a vinylbenzene structure [(*E*)-5-styryl-2,2′-bithiophene (SBTP)] as novel Aβ imaging agents.

2. Results and discussion

2.1. Chemistry

The synthetic route of the SBTP derivatives is outlined in Scheme 1. The key step was the base-catalyzed Wittig reaction between substituted triphenyl phosphonium ylide and 5′-substituted-2,2′-bithiophene-5-carbaldehydes. The substituted triphenyl phosphonium ylides reacted with 5′-substituted-2,2′-bithiophene-5-carbaldehydes in the presence of CH_3ONa under reflux in THF to form the target SBTP derivatives. The chemical yields of compounds **4**–**33** were ranged from 14% to 90%. Reduction of the nitro group of **9** provided the amino-substituted compound **10**. The synthetic route of the tributyltin precursors (**34**, **35**) is shown in Scheme 2. The yields of **34** and **35** from the corresponding bromo compounds (**7**, **23**) under a bromo to tributyltin exchange reaction catalyzed by $Pd(PPh_3)_4$ were 21.7% and 39.3%, respectively. The tributyltin derivatives can be readily used as starting materials to prepare the radio-iodinated ligands.

2.2. Binding studies using Aβ aggregates in solution

The affinity of these SBTP derivatives (**4**–**33**) for $A\beta_{1-42}$ aggregates was determined by competition binding assay using [^{125}I]TZDM as radio-ligand. The K_i values shown in Table 1 suggest that all of these new compounds inhibit the binding of [^{125}I]TZDM in a dose-dependent manner with a high binding affinity for $A\beta_{1-42}$ aggregates ($K_i < 10$ nM) except for compound **10** ($K_i = 41.05$ nM). The affinity was increased by bromination or iodination of the 2 position of bithiophene moiety (e.g., **4**–**5**, **15**–**16**, **26**–**27**). Bromination or iodination of the *para* position of phenyl ring also increased the binding affinity. The tertiary *N*,*N*-dimethylamino analogs of **11** and **21** were found to have a higher affinity than the primary amino analog **10**, which is in accord with the previously limited data on tertiary and primary amino analogs [5,23]. Methylation of the hydroxy group improved the binding affinity [e.g., OH (**22**) versus OCH_3 (**23**)]. The ligands with both electron-withdrawing substituents [e.g., NO_2 (**9**, **20**)] and electron-donating substituents [e.g., OCH_3 (**12**, **23**), $N(CH_3)_2$ (**11**, **21**)] showed high affinities to Aβ aggregates, especially compound **20** with a nitro group displayed the highest affinity ($K_i = 0.10$ nM).

In addition, the high affinities of compounds **14**, **25** and **33** containing a bulk *tert*-butyl group indicated high tolerance for steric bulk on the *para* position of phenyl ring. A long polyethylene glycol chain, which is used to improve the pharmacokinetic properties of ^{18}F labeled radiotracers [32], may be introduced at this position to design new SBTP PET probes. More importantly, it is possible to design ^{99m}Tc labeled SBTP SPECT probes for Aβ imaging.

2.3. Radiochemistry

Due to the high binding affinities observed for iodinated ligands **8** ($K_i = 0.92$ nM) and **31** ($K_i = 0.30$ nM), these two ligands were chosen for radiolabeling and further biological evaluations. The novel radio-iodinated ligands [^{125}I]**8** and [^{125}I]**31** were prepared via an iododestannylation reaction using hydrogen peroxide as an oxidant. The reaction was quenched with saturated $NaHSO_3$. The resulting mixture was purified by HPLC. The radioactive product was co-injected and co-eluted with the corresponding nonradioactive compound. The radio-iodinated products were obtained in 39.8–46.3% radiochemical yields with radiochemical purities of >98% after purification by HPLC. It is anticipated that the specific activity of the no-carrier-added preparation was comparable to that of [^{125}I]NaI (2200 Ci/mmol). Under the experimental conditions, the log *D* values of [^{125}I]**8** and [^{125}I]**31** were 3.31 ± 0.10 and 3.07 ± 0.08, respectively (measured by a partition between 1-octanol and pH 7.4 phosphate buffer), which is desirable for blood-brain barrier (BBB) penetration.

2.4. Neuropathological staining on brain sections of double transgenic model mice

To confirm the specific binding of these SBTP derivatives to Aβ plaques, *in vitro* neuropathological staining was performed on the brain sections of a transgenic model mouse (C57, APP/PS1, 12 months). As shown in Fig. 2, compounds **11**, **14**, **20** and **21** distinctively stained Aβ plaques on the brain sections with low background (Fig. 2A–D). The similar pattern of Aβ plaques was consistent with that stained with thioflavin-S using the adjacent sections (Fig. 2E–H). The results from neuropathological staining indicate that the binding of these SBTP derivatives is specific for Aβ plaques.

2.5. Autoradiography in vitro using brain sections of double transgenic model mice

Next, the radio-iodinated probes [^{125}I]**8** and [^{125}I]**31** were investigated for their binding to Aβ plaques by *in vitro* autoradiography in the brain sections of a transgenic model mouse (C57, APP/PS1, 12 months). As shown in Fig. 3 autoradiographic images of [^{125}I]**8** and

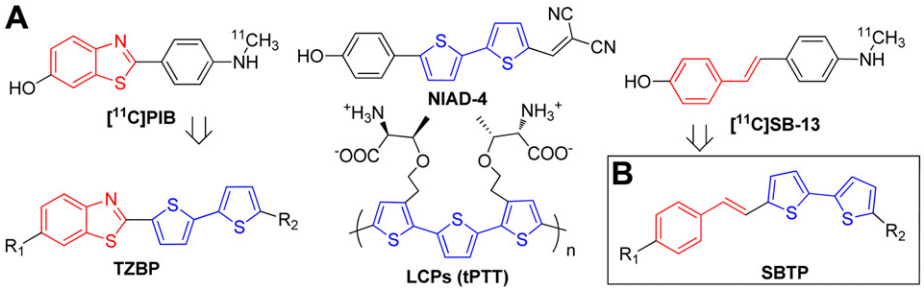

Fig. 1. (A) Structures of [^{11}C]PIB, [^{11}C]SB-13, LCPs (tPTT) and TZBP; (B) Structure of the designed SBTP derivatives.

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