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Synthesis and biological evaluation of (*E*)-3-styrylpyridine derivatives as amyloid imaging agents for Alzheimer's disease

Masahiro Ono[a,*], Mamoru Haratake[a], Morio Nakayama[a], Yoshikazu Kaneko[a], Koichi Kawabata[b], Hiroshi Mori[b], Mei-Ping Kung[c], Hank F. Kung[c]

[a]*Department of Hygienic Chemistry, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*
[b]*Department of Neuroscience, Osaka City University Medical School, Osaka 545-8585, Japan*
[c]*Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA*

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Abstract

A new series of (*E*)-3-styrylpyridine derivatives as potential diagnostic imaging agents targeting amyloid plaques in Alzheimer's disease (AD) were synthesized and examined. When in vitro binding studies using AD brain homogenates were carried out with a series of styrylpyridine derivatives, (*E*)-2-Bromo-5-(4-dimethylaminostyryl)pyridine (**7**) with a dimethylamino group showed the highest binding affinity. Compound **7** intensely stained neuritic and diffused plaques and cerebrovascular amyloids on postmortem AD brain sections. (*E*)-2-Iodo-5-(4-dimethylaminostyryl)pyridine (**9**), the iodo derivative of compound **7**, also stained senile plaques in human AD sections. The radioiodinated ligand [^{125}I]**9** was successfully prepared through an iododestannylation reaction from the corresponding tributyltin derivatives using hydrogen peroxide as the oxidant in high yields and with high radiochemical purity. A biodistribution study in normal mice after an intravenous injection of [^{125}I]**9** displayed high brain uptake and fast washout. Taken together, the data suggest that the new radio tracer, [^{125}I]**9**, may be useful as a radioiodinated imaging agent for mapping Aβ plaques in the brains of patients with AD.

Keywords: Alzheimer's disease; Amyloid plaques; Amyloid imaging; Styrylpyridine; Stilbene

1. Introduction

Amyloid plaques and neurofibrillary tangles (NFTs) are proposed to play key roles in the pathogenesis of Alzheimer's disease (AD) [1]. Currently, the only definitive confirmation of AD relies on postmortem histopathological examination of amyloid plaques and/or NFTs in the brain. Early appraisal of clinical symptoms for diagnosis of AD is often difficult and unreliable. Therefore, a specific marker for amyloid plaques and/or NFTs is required for the accurate evaluation of AD diagnosis. Such a specific marker will be useful for early detection and monitoring the progression and effectiveness of AD treatment [2].

Recently, many agents based on Congo red (CR) and Chrysamine G (CG) derivatives have been synthesized and evaluated for in vivo positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging probes of amyloid deposition in the AD brain (Fig. 1) [3–6]. Thioflavin analogs, such as TZDM [6], IBOX [7], IMPY [8], BTA-1 [9], 6-OH-BTA-1 [10] and others [11] (Fig. 1), showing high binding affinity toward Aβ aggregates, have been reported as potential imaging agents. The relatively high brain penetrations of neutral thioflavin derivatives make them more attractive candidates compared to CR and CG analogs for plaque imaging.

Another neutral and highly lipophilic tracer, fluorine-18-labeled FDDNP, for binding both amyloid plaques and NFTs, has recently been reported (Fig. 1) [12]. A preliminary study in humans appear to suggest that [^{18}F]FDDNP showed a higher retention in regions of the brain suspected of having tangles and plaques [13].

Furthermore, stilbene derivatives, which possess the basic structure of the styrylbenzene backbone, have been developed as probes for in vivo evaluation of amyloid plaques in the AD brain (Fig. 1) [14,15]. The stilbene derivatives penetrate BBB and maintain binding affinity for amyloid

* Corresponding author. Tel.: +81 95 819 2443; fax: +81 95 819 2442.
E-mail address: mono@net.nagasaki-u.ac.jp (M. Ono).

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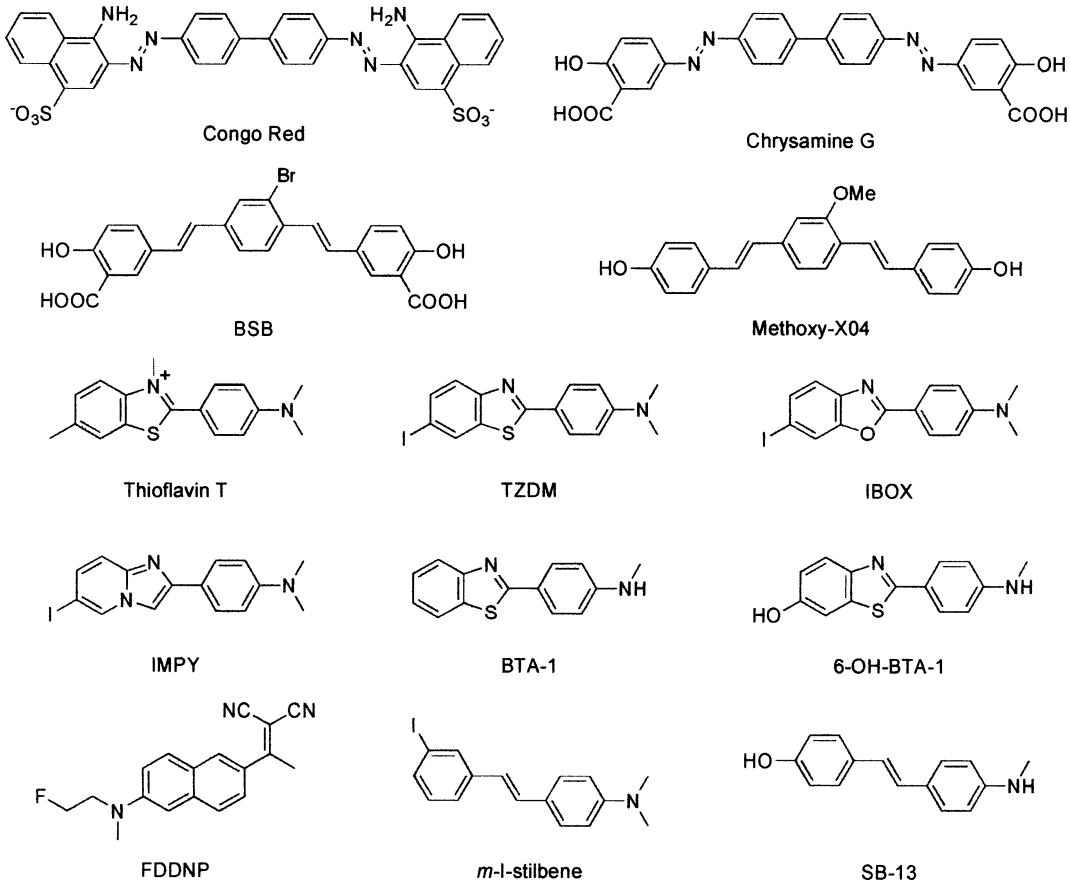

Fig. 1. Chemical structure of amyloid imaging agents previously reported.

fibrils, despite their lower molecular weight compared to CR and CG derivatives. This leads to flexibility when designing new probes that show specific binding for amyloid deposits. Indeed, we have reported that a simple stilbene derivative, ^{11}C-labeled 4-methylamino-4′-hydroxystilbene (SB-13, Fig. 1), showed a very good binding affinity to Aβ aggregates. In addition, excellent labeling of Aβ plaques in transgenic AD mouse brain sections was observed by in vitro autoradiography [15]. This PET tracer displayed moderate lipophilicity and showed very good brain penetration and washout from the normal rat brain after intravenous injection, a highly desirable property for an Aβ-aggregate-specific imaging agent. However, radioiodinated 3-iodo-4′-dimethylaminostilbene (*m*-I-stilbene, Fig. 1) for SPECT imaging showed slow brain washout in normal mice, resulting in high background-to-noise ratios due to its highly lipophilic properties [14].

In an attempt to further develop new radioiodinated ligands for SPECT imaging of Aβ plaques in AD, we evaluated a series of (*E*)-3-styrylpyridine derivatives. (*E*)-3-Styrylpyridine derivatives, which replace one of two benzene rings of stilbene with one pyridine ring (Fig. 2), are designed to have moderate lipophilicity and facilitate nonspecific binding clearance from the brain by decreasing lipophilicity compared to stilbene derivatives. To our knowledge, this is the first time (*E*)-3-styrylpyridines have been proposed as imaging agents for detecting AD. Described herein is the synthesis and characterization of this series of compounds.

2. Materials and methods

All reagents used in syntheses were commercial products and were used without further purification unless otherwise indicated. ^{1}H-NMR spectra were obtained on Varian Gemini 300 spectrometer with TMS as an internal standard. Coupling constants are reported in hertz. The multiplicity is defined by s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet). Mass spectra were obtained on a JEOL IMS-DX instrument.

2.1. Chemistry

*2.1.1. 6-Bromo-3-pyridinecarboxyaldehyde (**2**)*

A solution of 4-dibromopyridine (**1**) (2.0 g, 8.44 mmol) in Et_2O (20 ml) was cooled to −78°C and stirred for 5 min. *n*-BuLi in hexanes (3.52 ml, 2.64 M) was added dropwise via

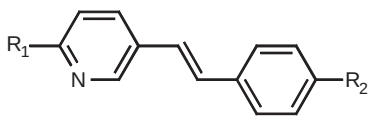

Fig. 2. Chemical structure of (*E*)-styrylpyridine derivatives. Compounds reported here include the following: R_1=Br, I; R_2=NH_2, $NH(CH_3)$, $N(CH_3)_2$.