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Synthesis and evaluation of pyridylbenzofuran, pyridylbenzothiazole and pyridylbenzoxazole derivatives as ^{18}F-PET imaging agents for β-amyloid plaques

Britt-Marie Swahn [a,*], Johan Sandell [a], David Pyring [a], Margareta Bergh [a], Fredrik Jeppsson [b], Anders Juréus [b], Jan Neelissen [c], Peter Johnström [a,d], Magnus Schou [a,d], Samuel Svensson [b]

[a] Department of Medicinal Chemistry, AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden
[b] Department of Neuroscience, AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden
[c] Department of DMPK, AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden
[d] Department of Clinical Neuroscience, Karolinska Institutet, S-171 76 Stockholm, Sweden

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ABSTRACT

The synthesis and SAR of new β-amyloid binding agents are reported. Evaluation of important properties for achieving good signal-to-background ratio is described. Compounds **27**, **33**, and **36** displayed desirable lipophilic and pharmacokinetic properties. Compound **27** was further evaluated with autoradiographic studies in vitro on human brain tissue and in vivo in Tg2576 mice. Compound **27** showed an increased signal-to-background ratio compared to flutemetamol **4**, indicating its suitability as PET ligand for β-amyloid deposits in AD patients. The preparation of the corresponding ^{18}F-labeled PET radioligand of compound **27** is presented.

Alzheimer's disease (AD) is a neurodegenerative brain disorder characterized clinically by progressive decline of cognitive function. Pathologically AD is characterised by amyloid plaques[1] containing Aβ peptide(s), and by neurofibrillary tangles (NFTs) containing hyper-phosphorylated tau protein. Aβ peptides are produced from membrane-bound β-amyloid precursor protein (APP) by the sequential proteolytic cleavage of two aspartyl proteases, β- and γ-secretase. Amyloid plaques accumulate prior to the onset of clinical symptoms. Detection of amyloid pathology early in disease progression, even before a clinical diagnosis of AD can be established, is therefore a key objective of current research in AD diagnosis. Biochemical measures of Aβ and tau in CSF have been shown to have utility as potential diagnostic tools, but there is also a need for Aβ plaque specific binding agents that can be used as PET (positron emission tomography) ligands for early diagnosis and monitoring of AD progression in the living brain.

Several types of β-amyloid imaging agents have been synthesized and evaluated including PIB **1**,[2] SB-13 **2**,[3] AZD2184 **3**,[4] flutemetamol **4**,[5] FDDNP **5**[6] and AV45 **6**[7] (Fig. 1). The reporting of several additional core structures that are not mutually displaceable, suggests that there are a number of different binding sites on β-amyloid in the Aβ plaques of AD patients.[8] The most examined compound, PIB **1**, has been tested clinically and demonstrated in ^{11}C-PET studies to be a potential biomarker for the visualization of A plaques in AD brains.[2b,9] However, ^{11}C has a short half-life ($t_{1/2}$ = 20 min) and the supply of ^{11}C agents will likely be limited to facilities with an on-site cyclotron. To broaden the utility of Aβ plaque detecting agents, the focus has turned into developing ^{18}F-labeled imaging agents ($t_{1/2}$ = 110 min).[10]

In order to obtain good sensitivity and allow for detection of low levels of Aβ plaques, and thus monitor β-amyloid lowering therapies with high sensitivity, the non-specific binding of Aβ PET ligands must be minimized.

We have previously concluded that it is essential to keep lipophilicity as low as possible in order to decrease non-specific binding and increase the wash out rate of non-specific binding.[11] Thus we have continued to focus on pyridine derivatives. In the search for suitable ^{18}F-labeled PET ligands we explored three different compound series with regard to binding affinity to Aβ(1-40) fibrils, lipophilicity ($e\log D$), and iv pharmacokinetic properties.

First we set out to examine compounds having side chains fluorinated in positions where we predicted that it would be possible to conduct the ^{18}F-labelling. This approach was warranted by

* Corresponding author. Tel.: +46 8 553 264 74.
E-mail address: britt-marie.swahn@astrazeneca.com (B.-M. Swahn).

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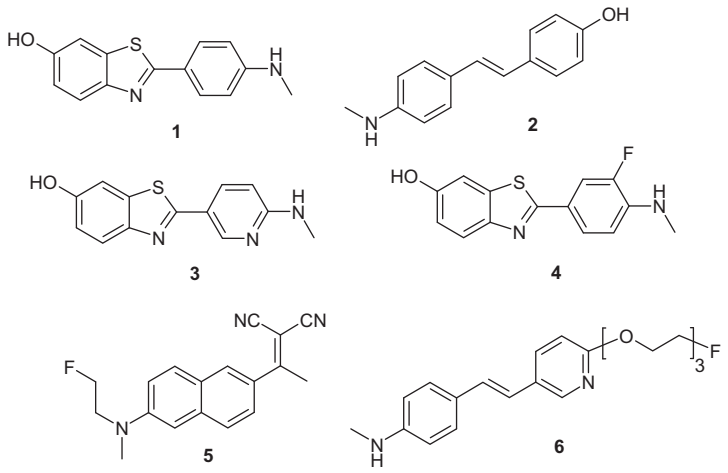
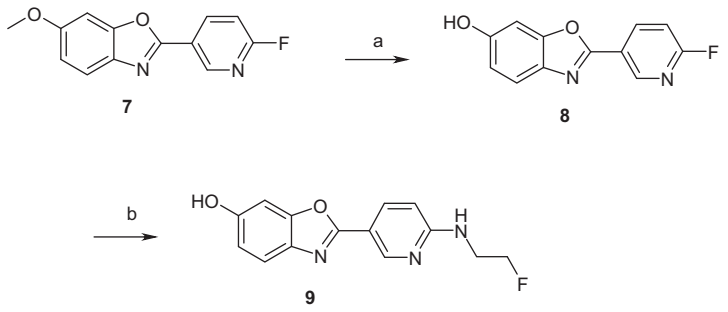
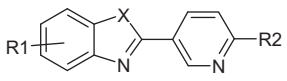


Figure 1. Examples of reported β-amyloid imaging agents.



Scheme 1. Reagents and conditions: (a) BBr_3, CH_2Cl_2, rt, 24%. (b) F-ethylamine, Et_3N, THF, 60 °C, 24 h, 26%.

Table 1
IC_{50} values, $e\log D$[15] and iv-PK properties[16] for compounds **1**, **3** and **9–13**



9-13

	R1	R2	X
9	6-OH	NHCH2CH2F	O
10	6-OMe	NHCH2CH2F	O
11	6-OH	NHCH2CH2CH2F	O
12	6-OH	NHCH2CH2F	S
13	6-OH	NHCH2CH2CH2F	S

Compound	IC_{50}[a] (nM)	$e\log D$	$t_{1/2}$ (min)	Dose in brain at 2 min (%)
1	19	2.8	9.8	1.3
3	22	1.8	6.8	1.0
9	158	1.2	<6.0	0.3
10	35	2.9	10.9	0.4
11	395	1.5	n.d.	n.d.
12	33	1.6	8.0	0.5
13	66	n.d.	n.d.	n.d.

n.d. denotes not determined.
[a] Values are means of $n \geqslant 2$ determinations, absolute value of standard deviation $\leqslant$10%.

the fact that $e\log D$ is not generally increased by the introduction of fluorine in alkyl chains contrary to the substitution of hydrogen by fluorine in aromatic rings. A low $e\log D$ value has been shown[11] to be essential in order to avoid high non-specific binding.

The 2-(pyridyl)-benzothiazole and 2-(pyridyl)-benzoxazole cores were synthesized as previously described[11–13] and the F-alkyl moiety was introduced in the last step via substitution with the corresponding amine, as shown for the example in Scheme 1. In vitro binding affinities to human Aβ(1-40) fibrils were determined by a competition radioligand binding assay using a fixed concentration of Aβ(1–40) fibrils (2 μM) and [^{3}H]-AZD2184 (3 nM).[4,14] As previously discussed,[11] keeping the lipophilicity low (as measured by $e\log D$[15]), and the wash-out rate of non-specific in vivo binding in the same range as for PIB **1** (as measured by $t_{1/2}$[16] in wild type rats), should produce a low non-specific binding in brain tissue. Suitable properties for a candidate ^{18}F-ligand would be high affinity for