DOI: 10.1002/ejoc.201101449

A Synthetic Overview of Radiolabeled Compounds for β-Amyloid Targeting

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Keywords: Medicinal chemistry / Imaging agents / Radiopharmaceuticals / Isotopic labeling / Alzheimer's disease / β-Amyloid peptide aggregation

The formation of β-amyloid plaques is considered a histopathological hallmark of Alzheimer's disease (AD), a neurodegenerative disorder that affects millions of people worldwide. For effective treatment of AD, diagnosis at an earlier stage of the degenerative process is essential. Therefore, in the last few years significant efforts to find probes for in vitro and/or in vivo imaging of β-amyloid deposits have been made. This work presents an overview of different small molecules explored as fluorescent or radioactive probes for targeting β-amyloid deposits. It focuses mainly on the different synthetic approaches used for their synthesis or radiosynthesis but their biological behaviour is also briefly discussed when appropriate.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that affects millions of people worldwide.[1] The impact on public health is considerable, with the tendency to increase as the population gets older. The most common symptoms

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of AD are decline in the cognitive functions, irreversible memory loss, and disorientation. AD diagnosis is based mainly on the patient's history and on neuropsychological tests. However, the overlapping of early AD symptoms with normal signs of aging make such diagnosis difficult. Histopathologically, AD is characterized by the presence of plaques (aggregates of β-amyloid protein) and neurofibrillary tangles (NFTs) (highly phosphorylated tau protein). At present, definitive confirmation of AD is only possible through post-mortem histopathologic studies with use of dyes such as thioflavin T (**ThT**, Figure 1), congo red (**CR**), or chrysamine G (**CG**) that stain β-amyloid (Aβ) deposits.[2]

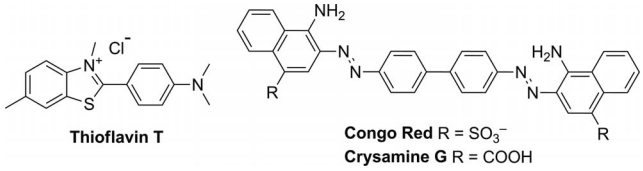


Figure 1. Chemical structures of fluorescent dyes: thioflavin T (ThT), congo red (CR), and chrysamine G (CG).

Although the molecular processes underlying the pathology are still unknown, deposition of Aβ protein is thought to be an early and specific event in the pathogenesis of AD.[3] Aβ is a soluble extracellular peptide consisting of either 40 ($Aβ_{1–40}$) or 42 ($Aβ_{1–42}$) amino acids. It is formed from transmembranar amyloid precursor protein (APP) through the action of β and γ secretases (Figure 2, A).[4] In vivo imaging agents that can specifically demonstrate the locations and densities of Aβ deposits in the AD brain should therefore be useful for early and conclusive diagnosis of AD (Figure 2, B). Moreover, these agents should help in the finding and monitoring of novel AD therapies, especially those based on the dissolution of the Aβ plaques.

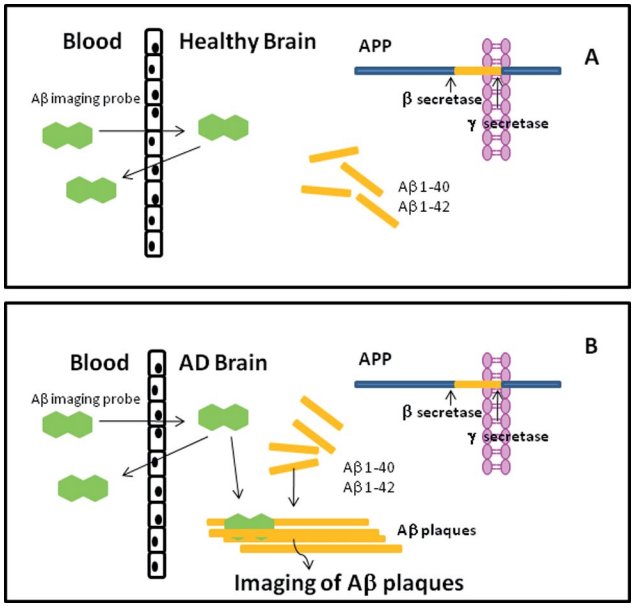


Figure 2. Schematic representation of behavior of Aβ imaging probes in control and AD brain.

Among all the molecular imaging modalities (e.g., nuclear imaging, magnetic resonance imaging, computed tomography, ultrasound, bioluminescence, and fluorescence imaging) the nuclear techniques, which include SPECT and PET, have the advantage of high intrinsic sensitivity and unlimited depth penetration. PET has the additional advantage of being fully quantitative and providing higher spatial resolution than SPECT. The PET and SPECT molecular imaging modalities need the use of nuclear probes containing positron or γ emitters, respectively. Table 1 presents some examples of relevant radionuclides for PET and SPECT imaging.

Table 1. Examples of relevant radionuclides for PET and SPECT imaging.

Nuclides	Production	Half-life $t_{1/2}$	Mode of decay (keV)
PET			
^{11}C	cyclotron	20.4 min	$β^+$(511)
^{18}F	cyclotron	110 min	$β^+$(511)
^{124}I	cyclotron	4.2 days	25%$β^+$(511)
SPECT			
^{123}I	cyclotron	13 h	EC (159)[a]
^{99m}Tc	$^{99}Mo/^{99m}Tc$ generator	6 h	IT (140)
^{67}Ga	cyclotron	78.2 h	EC (93, 185, 300)
^{111}In	cyclotron	2.8 days	EC (171, 245)

[a] EC: Electronic capture; IT: Isomeric transition.

SPECT measurements are based mainly on the use of radiometals: namely ^{99m}Tc, the most widely used SPECT radionuclide to date. ^{99m}Tc offers several advantages such as its ideal nuclear properties, low cost, and availability from commercial $^{99}Mo/^{99m}Tc$ generators. However, the design of ^{99m}Tc-based radioprobes for in vivo targeting of Aβ plaques usually requires the use of a bifunctional chelator (BFC) for the complexation of the metal and for conjugation to a suitable amyloid-avid molecule, and constructs of this type sometime have limited capability to cross the blood–brain barrier (BBB), an essential requisite for targeting Aβ plaque deposits in the brain. For this reason, progress with ^{99m}Tc complexes is quite limited[5] and is not reported in this contribution. So far, the most promising SPECT radioprobes for in vivo imaging of Aβ plaques are compounds containing the γ emitter ^{123}I (Table 1). This radiohalogen is a cyclotron-produced radionuclide with a relatively short half-life ($t_{1/2}$ = 13 h) and can readily be incorporated into amyloid-avid molecules.

The radionuclides most intensively explored for amyloid PET imaging are the cyclotron-produced carbon-11 (^{11}C) and fluorine-18 (^{18}F) (Table 1). In the past few years, a plethora of ^{11}C- and ^{18}F-labeled compounds have been synthesized and evaluated and some of them have undergone clinical trials to assess their potential for in vivo diagnosis of AD. Labeling with ^{11}C frequently involves the introduction of a [^{11}C]methyl group into the biomolecule through selective *N*- and *O*-methylation.[6] However, the very short

life of this radionuclide ($t_{1/2}$ = 20.4 min) limits its use to on-site cyclotron facilities, and requires rapid one-step radiosynthesis. The longer half-life of ^{18}F ($t_{1/2}$ = 110 min) allows for multistep radiosynthesis, longer in vivo investigation, and commercial distribution to other clinical PET centers. Radiofluorination reactions can be achieved with either electrophilic or nucleophilic radioactive fluoride. Reactions with the less reactive nucleophilic radiofluoride, however, are more selective and provide ^{18}F-labeled compounds in higher yields and with higher specific activities.[6]

Several entities (small molecules, antibodies, small peptides) have been designed to interact with the oligomeric or fibrillar forms of the Aβ peptide, either for its in vivo detection or for promoting its desaggregation in a therapeutic approach. A common requirement for these compounds is the ability to cross the BBB to reach the intracerebral target. Moreover, a good radiotracer for in vivo imaging of Aβ plaques by PET or SPECT must allow a fast washout from the normal brain, to ensure a good target/non-target ratio. Small, aromatic, and planar nonpeptidic molecules have been the most widely explored type of compounds in the design of PET or SPECT probes for in vivo detection of amyloid deposits. The planarity allows for insertion into the β sheet structure of Aβ plaques, ensuring good binding affinity. The design of these aromatic and planar compounds for the targeting of Aβ plaques has been based mainly on the highly conjugated systems present in the structures of the **ThT** and **CR** dyes (Figure 1). In several instances, the intrinsic fluorescence of the developed compounds, conferred by the presence of highly conjugated systems, has also been explored for the in vitro fluorescence staining of the Aβ plaques. These fluorescent probes, however, are unsuitable for in vivo human imaging, due to the short penetration of light photons into biological tissues in comparison with the γ photons emitted by radionuclides.

In recent years, a number of reviews has already covered the research done on aromatic and planar nonpeptide organic compounds in the design of fluorescent and/or radioactive probes for in vitro or in vivo imaging of Aβ plaques.[7] These reviews, though, have focused mainly on the biological properties of the radiocompounds, specifically on their in vitro interaction with Aβ plaques and their biodistribution in AD animal models.[7] Unlike those predecessors, this review intends to cover, in a comprehensive way, the most relevant chemical and radiochemical challenges involved in the design of ^{11}C-, ^{18}F-, and ^{123}I-probes. Nevertheless, their biological properties are also discussed when pertinent. For this reason, some overlap with the predecessors is unavoidable.

2. Compounds for β-Amyloid Targeting

As mentioned in the Introduction, the design of fluorescent or radioactive probes for in vitro and/or in vivo imaging of Aβ plaques was initially mainly based on the structures of the conjugated dyes (e.g., **ThT**, **CR**) used to stain the plaques in histopathological studies. Those studies led to a variety of aromatic and heteroaromatic compounds with different core structures, but sharing common features such as planarity, low molecular weight, and lipophilicity. In the next sections, the chemical/radiochemical strategies explored to synthesize aromatic/heteroaromatic compounds relevant as amyloid probes are reviewed.

2.1. Naphthalene Derivatives

The compound **[^{18}F]FDDNP** (Figure 3) was the first radiolabeled probe successfully used for in vivo molecular imaging of Aβ plaques.[8] This compound belongs to the family of (6-amino-2-naphthyl)ethene derivatives. It is considered structurally related to the fluorescent probe **DDNP** (Figure 3) and to the diazo-naphthyl core of **CR**.[9] **FDDP** is a neutral and lipophilic probe developed for fluorescence spectroscopy.[10] However, PET imaging showed that **[^{18}F]FDDNP** labels both Aβ plaques and NFTs in the AD brain. In addition, its lipophilicity (log P = 3.92) contributed to high nonspecific binding in normal mouse brain.[9]

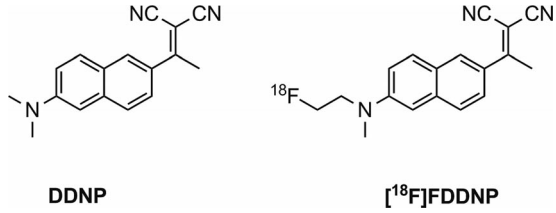
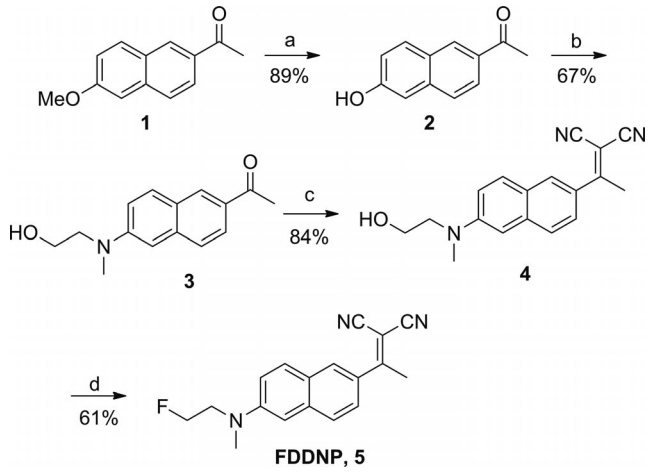


Figure 3. Chemical structures of naphthalene-based compounds.

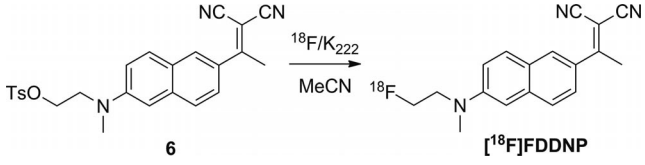
A detailed description of the synthesis of **[^{18}F]FDDNP** was only reported in 2006, by Barrio's group, together with its improved automated radiosynthesis.[11] The synthesis of the cold **FDDNP** started with commercially available 1-(6-methoxy-2-naphthyl)ethan-1-one (**1**), which was converted into ketone **2** by demethylation in hydrochloric acid (37%) at reflux (Scheme 1). A Bucherer reaction between **2** and 2-(methylamino)ethanol, followed by a Knoevenagel condensation between the resulting amine derivative **3** and ma-



Scheme 1. Synthesis of **FDDNP**.[11] Reagents: a) HCl (37%); b) $CH_3NHCH_2CH_2OH$, Na_2SO_3, H_2O; c) $CH_2(CN)_2$, pyridine; d) DAST, pyridine, CH_2Cl_2.

lononitrile, yielded the dicyano compound **4**. Compound **4** was then converted into **FDDNP** by fluorination with DAST. Knoevenagel condensation reactions between malononitrile and carbonyl derivatives were further explored for the synthesis of other compounds, such as fluorescent probes of the dicyanomethylene type bearing the bithiophene motif[12] or the styrylbenzothiazole motif.[13]

The radiosynthesis of **[^{18}F]FDDNP** involved a SN_2-type reaction with tosylate as the leaving group. Compound **4** was transformed into the tosylated precursor **6** (Scheme 2), which then reacted with radioactive fluoride ion ($^{18}F^-$) in the presence of kryptofix 2.2.2. (K_{222}) to yield **[^{18}F]FDDNP** (Scheme 2). This type of aliphatic nucleophilic radiofluorination, carried out under strictly anhydrous conditions, is the commonest method used to prepare radiofluorinated agents. The ^{18}F fluoride ion is produced in the cyclotron by irradiation of oxygen-18-enriched water, through the $^{18}O(p,n)^{18}F$ reaction, being obtained in aqueous solution.[14] The fluoride ions display poor nucleophilicity in aqueous medium and therefore need to be dried and activated. This involves the complete exclusion of water by azeotropic drying of an aqueous ^{18}F-fluoride solution in dry acetonitrile at high temperature under a stream of nitrogen. Further activation of ^{18}F-fluoride is achieved through the use of cryptands in combination with alkali (K, Cs, Rb) salts or tetra-*n*-butylammonium cation. The aminopolyether Kryptofix 2.2.2. (K_{222}) complex is the most commonly used cryptand.[6]



Scheme 2. Radiosynthesis of **[^{18}F]FDDNP**.[11]

2.2. Styryl-Based Compounds

More than a decade ago, an simplified form of **CG**, **X-34** (Figure 4), was produced by replacement of the diazo and diphenyl) groups of **CG** with vinyl and phenyl groups, respectively. However, no report describing its synthesis was published. Later on, the synthesis of the congener halogenated distyrylbenzenes **BSB** and **ISB** (Figure 4) was reported.[15] The key step for the synthesis of these compounds was a Wittig or Wittig-type (Horner–Wadsworth–Emmons) reaction between aldehyde **11** (prepared from 5-formylsalicylic acid) and either triphenylphosphonium salt **12** or bis(diethyl phosphonate) **13**, respectively (Scheme 3).[15] When the triphenylphosphonium salt **12** was used for the reaction, all four possible isomers [(*E*,*E*)-**14**, (*Z*,*Z*)-**14**, (*Z*,*E*)-**14**, and (*E*,*Z*)-**14**] were formed. Alternatively, when the bis(diethyl phosphonate) **13** was used in a Horner–Wadsworth–Emmons reaction, the *trans*-*trans* isomer (*E*,*E*-**14**) was the only one formed, in 45% yield. Additionally, in vitro binding assay showed that all four isomers of **BSB** displayed similar high binding affinities to $A\beta_{1-40}$ plaques. Moreover, the same authors have also demonstrated the ability of the isomer (*Z*,*Z*)-**BSB** to isomerize into (*E*,*E*)-**BSB** under strongly basic conditions.[16]

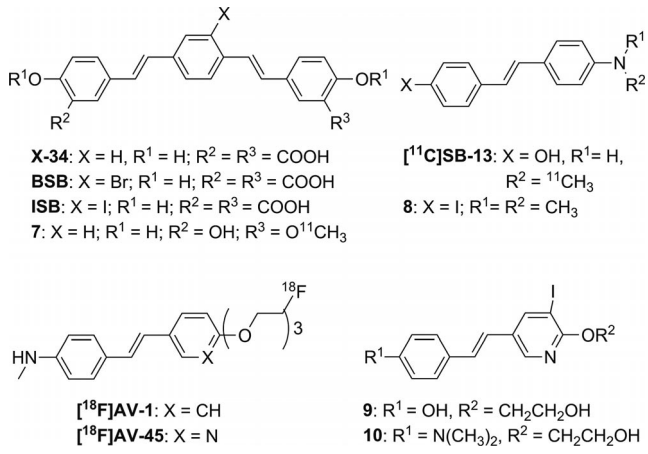
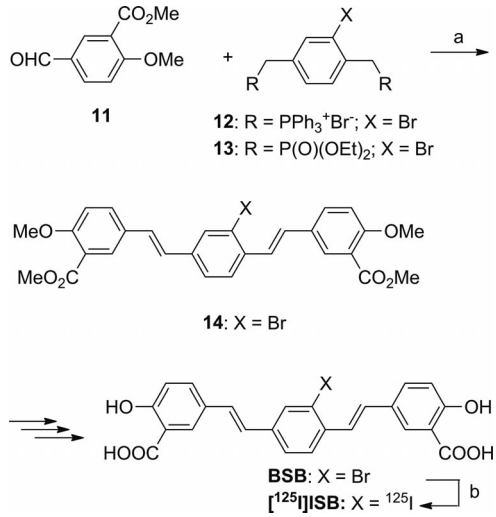


Figure 4. Chemical structures of styrylbenzene and styrylpyridine derivatives.



Scheme 3. Key step for the synthesis of distyryl benzenes, according to ref.[15] Reagents: a) NaOMe, MeOH; b) i. Pd^0, $(SnBu_3)_2$; ii. $Na^{125}I$, H_2O_2.

BSB displayed exquisite properties as a fluorescent probe for highly specific labeling of fibrillar Aβ plaques,[17] but the radioactive counterpart **[^{125}I]ISB** penetrates only poorly into the brain, most likely due to the presence of the two ionizable carboxylic groups.[15] To overcome this problem, the neutral unsymmetrical distyrylbenzene (*E*,*E*)-**7** (Figure 4) was prepared by the same synthetic strategy.[18]

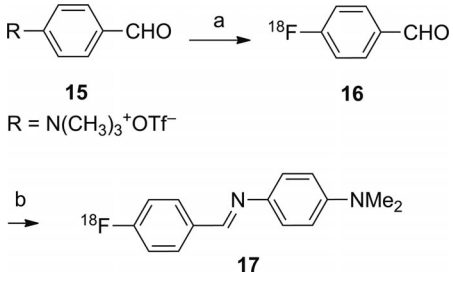
A series of simple stilbenes (Figure 4) were also prepared and investigated as probes for SPECT and PET imaging of Aβ plaques, with the goal of enhancing brain uptake relative to that observed for higher molecular weight distyrylbenzenes. The exclusive formation of the geometric *trans* isomers in the Horner–Wadsworth–Emmons reactions made this reaction the method of choice to synthesize the

stilbenes.[19] Of these compounds, **[^{11}C]SB-13** showed the better profile as an Aβ plaque imaging agent, presenting a good binding affinity and higher brain uptake than the radioiodinated congener **8**, as well as a lower nonspecific binding.[19b] *O*-Alkylation of **SB-13** produced a series of pegylated and radiofluorinated stilbene derivatives (e.g., **[^{18}F]AV-1**, Figure 4).[20] The polyethylene glycol (PEG) was tethered on the 4-hydroxy group of **SB-13** and the fluorine was attached at the end of the PEG chain. The PEG was used to circumvent the excessive lipophilicity conferred by the fluoroalkyl group.

The fluoropegylation approach has been extended to the preparation of alternative ^{18}F-labeled tracers with different backbone structures, such as the styrylpyridine derivative **[^{18}F]AV-45** (Figure 4). The introduction of a vinyl group into a compound of this type was also accomplished through a Horner–Wadsworth–Emmons reaction, between diethyl 4-(dimethylamino)benzylphosphonate and 6-chloronicotonaldehyde.[21] Alternatively, the styrylpyridine backbones in a series of iodinated derivatives, such as **9** and **10** (Figure 4), were assembled through palladium-catalyzed Heck couplings between 1,2-disubstituted 4-iodopyridinyl derivatives and 4-substituted styrenes.[22]

Of the stilbene and styrylpyridine derivatives evaluated, the compounds **[^{11}C]SB-13**, **[^{18}F]AV-1**, and **[^{18}F]AV-45** are clinically the most relevant for Aβ plaque PET imaging. Currently, **[^{18}F]AV-1** and **[^{18}F]AV-45** are undergoing phase II and phase III clinical studies, respectively. Several efforts have been made to produce clinical doses of these radioactive compounds under GMP guidance.[23]

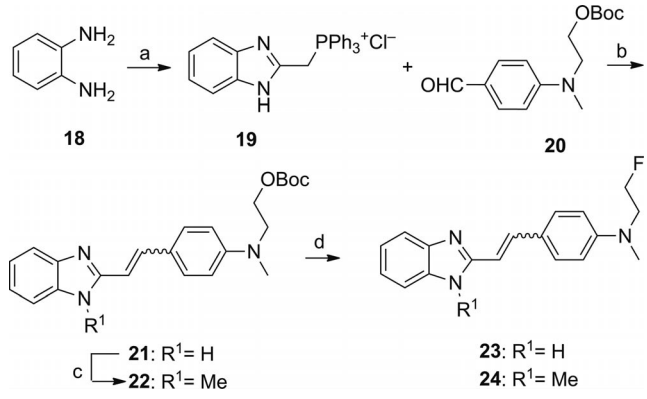
A series of fluorinated benzylideneaniline derivatives (e.g., compound **17**, Scheme 4) structurally related to the above reviewed stilbenes were recently reported. Their synthesis involved base-promoted reactions between the commercially available 4-fluorobenzaldehyde and substituted anilines.[24] Interestingly, the radiosynthesis of the corresponding ^{18}F-labeled congeners has been achieved by use of the prosthetic group ^{18}F-fluorobenzaldehyde (**16**) as depicted in Scheme 4, representing a unique example of the use of such an approach to obtain a potential radiofluorinated A*β* imaging agent. The prosthetic group **16** was prepared by the nucleophilic aromatic substitution of the ammonium triflate component in compound **15** with [^{18}F]-fluoride (Scheme 4).[24] The presence of the electron-withdrawing carbaldehyde substituent on the aromatic system of **15** facilitated the nucleophilic aromatic substitution, which is usually quite a difficult process.



Scheme 4. Synthesis of ^{18}F-labeled benzylideneaniline derivatives.[24] Reagents: a) TBA^{18}F, DMSO; b) 1-(dimethylamino)benzene-4-amine, EtOH.

A series of ^{11}C- and ^{18}F-labeled styrylbenzoxazoles were also reported and evaluated as Aβ imaging agents. In these compounds, the styryl motifs were constructed either through Knoevenagel reactions between substituted 2-methylbenzoxazole and substituted benzaldehyde[25] or by the coupling of *O*-aminophenol with substituted cinnamic acids catalyzed by polyphosphoric acid trimethylsilyl ester.[25a] More recently, Cui et al. explored Wittig reactions between 2,2′-bithiophene-5-carbaldehyde and substituted benzyltriphenylphosphonium salts to prepare, in excellent yields, a series of (*E*)-5-styryl-2,2′-bithiophene derivatives as ligands for Aβ plaques. Interestingly, no *Z* isomers were described, in contrast with the results obtained with distyrylbenzenes.[26]

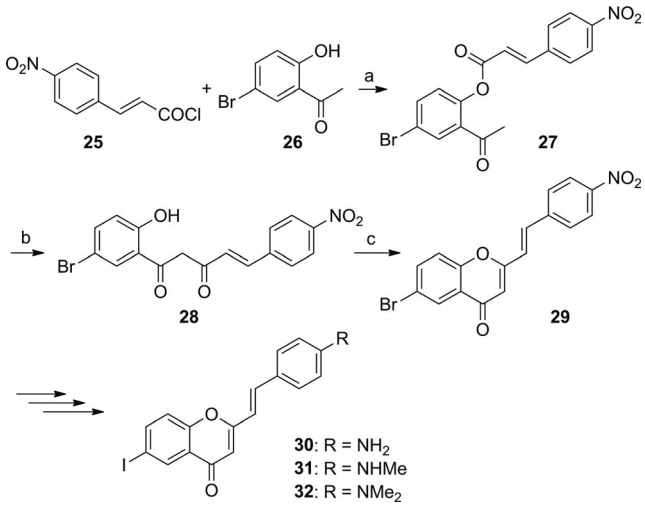
In our group, we have also designed the fluorinated 2-styrylbenzo[*d*]imidazole derivatives **23** and **24** (Scheme 5). We reasoned that the presence of the NH groups in the imidazole rings should reduce the lipophilicity conferred by the styryl moieties, while also allowing the introduction of pharmacokinetic modifiers. The styryl moiety was fashioned through a Wittig reaction between triphenylphosphonium salt **19** and substituted benzaldehyde **20** in good yield (η = 67%). As expected, use of the nonstabilized phosphonium salt **19** led to the formation of both *E* and *Z* isomers. However, the *E* isomer was converted almost exclusively into the *Z* isomer after exposure to light, so the selection of an alternative olefination method, such as the Horner–Wadsworth–Emmons reaction, would be useless for prevention of the formation of the *Z* isomer.[27]



Scheme 5. Synthesis of 2-styrylbenzylimidazoles **23** and **24**.[27] Reagents: a) i. chloroacetic acid, HCl (4 N); ii. PPh_3, CH_3CN; b) NaOMe, MeOH; c) MeI, NaOH, acetone/H_2O; d) i. TFA/CH_2Cl_2; ii. *p*TsCl, Et_3N, CH_2Cl_2; iii. TBAF, THF.

A series of styrylchromone derivatives were also prepared (**30**–**32**); the key step for their synthesis involved the Baker–Venkataraman rearrangement.[28] Specifically, 2-hydroxyacetophenone **26** was first converted into the 2-cinn-

amoyl-*O*-hydroxyacetophenone **27** as a way to incorporate the styryl motif. Intermediate **27** was further rearranged to **29** on treatment with base followed by acid-promoted cyclodehydration of the resulting unsaturated 1,3-diketone **28** (Scheme 6). The final iodinated styrylchromone derivatives **30**–**32** exhibited binding affinities to Aβ plaques in the nanomolar range (8.7 to 32.0 nM).[28]



Scheme 6. Synthetic route to styrylchromone derivatives **30**–**32**.[28] Reagents: a) pyridine; b) pyridine, KOH; c) H_2SO_4, AcOH.

2.3. Benzothiazoles and Related Compounds

Benzothiazole-based compounds represent one of the most promising family of agents for imaging of Aβ plaques. Interestingly, compounds of this class were also found to inhibit tyrosine kinase, a useful target for treatment of certain types of cancers. As a result of this inhibitory capability, a number of compounds containing the benzothiazole scaffold were developed and evaluated either as potential anticancer agents or as PET probes for tumor detection.[29]

The preference for the benzothiazole scaffold is based on its structural similarity to **ThT** (Figure 1). Moreover, removal of the methyl group from the heterocyclic nitrogen of **ThT** provided neutral and lipophilic fluorescent compounds with high affinities for Aβ plaques. A large number of benzothiazole aniline (BTA) derivatives (Figure 5, Table 2) have been developed over the last decade.[15,30] In 2003, Klunk's group at the University of Pittsburgh developed a series of BTAs, of which the ^{11}C-labeled 6-hydroxy-2-[4′-(methylamino)phenyl]benzothiazole {[*N*-methyl-^{11}C]6-OH-BTA-1, known as **[^{11}C]PIB** or Pittsburgh compound-B}, demonstrated good binding properties towards Aβ plaques and excellent pharmacokinetics. Retention of **[^{11}C]PIB** in frontotemporal and hippocampal areas of the brain in patients with AD is selectively higher than in non-AD controls. **[^{11}C]PIB** is nowadays the radiotracer of choice for imaging of Aβ plaques in the brains of suspected AD patients.[31]

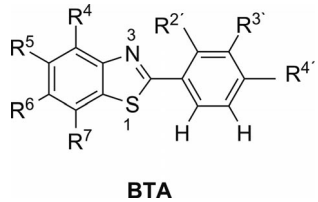


Figure 5. Chemical structures of benzothiazole aniline (BTA) derivatives. In the shorthand nomenclature,[32] the position and substituent in the benzothiazole ring is written before "BTA" and the number of methyl groups on the 4′-amino group and the position and substituent in the aryl ring are written after "BTA" (e.g., 6-OH-BTA-1–3′-I; R^6 = OH; $R^{4'}$ = NHMe; $R^{3'}$ = I).

Various synthetic approaches have been explored with the goal of obtaining benzothiazole-containing compounds

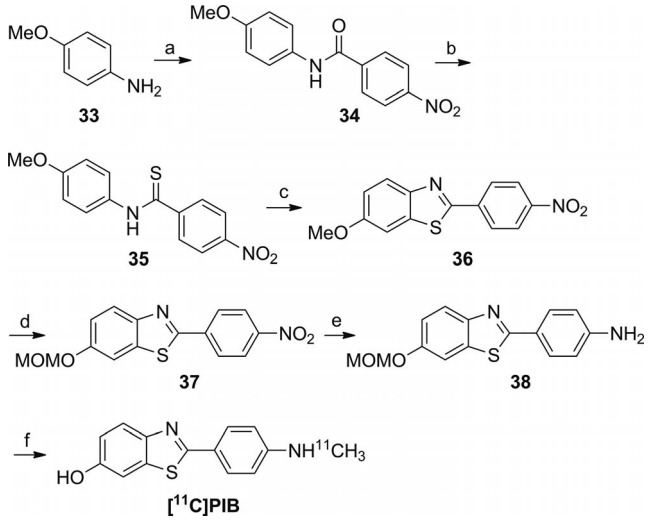
Table 2. Benzothiazole-aniline derivatives (BTAs).

Compound	R^4	R^5	R^6	R^7	$R^{2'}$	$R^{3'}$	$R^{4'}$	K_i [nM][ref.]
6-I-BTA-2 (**TZDM**)	H	H	I	H	H	H	NMe_2	0.9 ± 0.2[15]
6-OH-BTA-1 (**PIB**)	H	H	OH	H	H	H	NHMe	4.3[30a]
6-OH-BTA-2 (**39**)	H	H	OH	H	H	H	NMe_2	4.4[30a]
6-MeO-BTA-1 (**40**)	H	H	OMe	H	H	H	NHMe	4.9[30a]
BTA-1 (**41**)	H	H	H	H	H	H	NHMe	11 ± 1[30b]
4-OH-BTA-1 (**42**)	OH	H	H	H	H	H	NHMe	18.8 ± 3.8[30k]
5-OH-BTA-1 (**43**)	H	OH	H	H	H	H	NHMe	11.5 ± 3[30k]
7-OH-BTA-1 (**44**)	H	H	H	OH	H	H	NHMe	11.2 ± 5[30k]
6-FEtO-BTA-1 (**45**)	H	H	OEtF	H	H	H	NMHe	7.2 ± 7[30h]
BTA-1–3′-FEtO (**46**)	H	H	H	H	H	OEtF	NHMe	> 600[30h]
6-FPrO-BTA-0 (**47**)	H	H	OPrF	H	H	H	NH_2	14.5 ± 5[30l]
BTA-0–2′-FPrO (**48**)	H	H	H	H	OPrF	H	NH_2	> 4000[30l]
BTA-0–4′-F (**49**)	H	H	H	H	H	H	F	9.0 ± 2[30n]
6-COOH-BTA-0–4′-F (**50**)	H	H	COOH	H	H	H	F	> 4000[30j]
6-Me-BTA-0–4′-F (**51**)	H	H	Me	H	H	H	F	5.7 ± 1.8[30j]
6-OH-BTA-0–4′-F (**52**)	H	H	OH	H	H	H	F	22.5 ± 4.5[30j]
6-OH-BTA-1–3′-I (**53**)	H	H	OH	H	H	I	NHMe	7.1[30d]
6-NH2-BTA-0–4′-F (**54**)	H	H	NH_2	H	H	H	F	10.0 ± 1[30m]
6-NHMe-BTA-0–4′-F (**55**)	H	H	NHMe	H	H	H	F	4.1 ± 0.3[30m]
6-F-BTA-1 (**56**)	H	H	F	H	H	H	NHMe	5.5 ± 0.2[30g]
6-F-BTA-0 (**57**)	H	H	F	H	H	H	NH_2	26.2[30g]

as potential markers of Aβ plaques. One of the methods consisted of direct condensations of substituted 2-aminothiophenols either with substituted benzaldehydes in DMSO[15,30a,30g] or with substituted benzoic acids.[30b,30f,30h,30n]

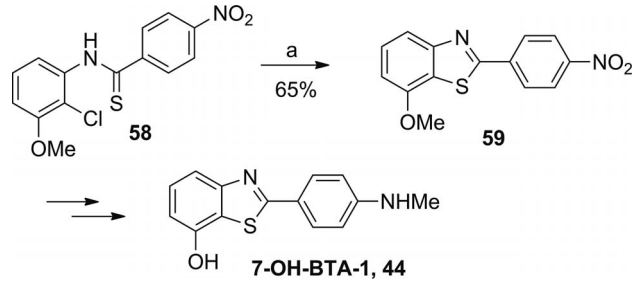
Such condensation reactions with aldehydes have usually been catalyst-free. However, Henriksen et al. prepared a series of benzothiazole dyes from aromatic and heteroaromatic aldehydes, in which the condensations were catalyzed either by a lanthanide-based Lewis acid or by silica under microwave irradiation conditions.[30i] Condensations catalyzed by polyphosphoric acid (PPA) were also used for substituted benzoic acids, but this process involved harsh conditions, difficult workup, and low yields, which was tackled in some cases by use of the corresponding benzoyl chlorides.[30n,33]

An alternative approach (Scheme 7) was developed to construct the benzothiazole core in the **PIB** compound.[30a] Basically, commercially available 4-methoxyaniline (**33**) was treated with *p*-nitrobenzoyl chloride in pyridine. The resulting benzamide derivative **34** was further converted into the corresponding thiobenzamide **35** by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,3-disulfide] as a thiation reagent.[34] Compound **35** was cyclized to its corresponding aryl benzothiazole **36** by a Jacobsen synthesis with use of the oxidizing agent potassium ferricyanide in aqueous sodium hydroxide. The *O*-methyl group in **36** was replaced by a more acid-labile protective group (MOM), followed by reduction of the nitro group to an amine with $SnCl_2$. This time-consuming protective group chemistry was necessary to avoid *O*-methylation when [^{11}C]methyl iodide was used as the labeling agent. Potassium hydroxide proved to be superior to potassium carbonate for promoting the [^{11}C]*N*-methylation of the protected precursor **38**. At the end of the synthesis (EOS), **[^{11}C]PIB** was obtained in low RCY (15%).



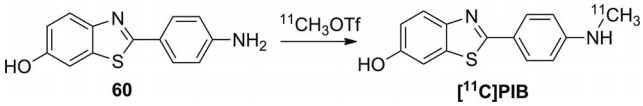
Scheme 7. Synthesis of [^{11}C]6-OH-BTA-1 (**[^{11}C]PIB**).[30a] Reagents: a) *p*-nitrobenzoyl chloride, pyridine; b) Lawesson's reagent; c) $K_3Fe(CN)_6$, NaOH, EtOH; d) i. BBr_3; ii. CH_3OCH_2Cl, K_2CO_3; e) $SnCl_2$, EtOH; f) i. $^{11}CH_3I$, KOH, DMSO; ii. HCl, MeOH.

The Jacobsen cyclization approach is highly versatile, allowing the use of a wide variety of commercially available 2- and 4-substituted anilines, and other BTAs have been prepared accordingly.[30f,30j,30l] For the synthesis of BTAs such as **44** (Scheme 8), in which cyclization of thiobenzamides derived from 3- and 5-substituted anilines could lead to formation of two regioisomers, however, a modification of this procedure was explored. In this modified procedure, thiobenzamide **58** was treated with sodium hydride and *N*-methyl-2-pyrrolidone (NMP) instead of potassium ferricyanide, leading to a ring closure specifically at the position of the halogen (Scheme 8).[30k]



Scheme 8. Synthesis of 7-OH-BTA-1 **44**.[30k] Reagents: a) NaH, NMP.

An alternative approach for the radiosynthesis of **[^{11}C]PIB**[35] and related BTAs was developed[30k] with the aims of increasing the unsatisfactory low RCY and of avoiding a two-step radiosynthesis. In this approach, the [^{11}C]*N*-radiomethylation was performed directly on the unprotected precursor **60** (Scheme 9) with use of [^{11}C]methyl triflate as the labeling agent, in the absence of base. The higher reactivity of [^{11}C]methyl triflate, relative to [^{11}C]methyl iodide, towards the aniline nitrogen avoided the need for protection of the phenol group, the [^{11}C]*N*-methylation being predominant over the [^{11}C]*O*-methylation. Only a small amount (<5%) of [*O*-methyl-^{11}C]6-MeO-BTA-0 was obtained as byproduct. The RCY of **[^{11}C]PIB** was significantly improved by use of increased temperatures, reaching a maximum of 60% at 80 °C (Table 3).[35] The position of the hydroxy group on the benzothiazole ring also affected the RCYs of similar radiolabeled BTAs when [^{11}C]methyl triflate was used as the labeling agent (Table 3).[30k]



Scheme 9. Improved radiosynthesis of **[^{11}C]PIB**.[35]

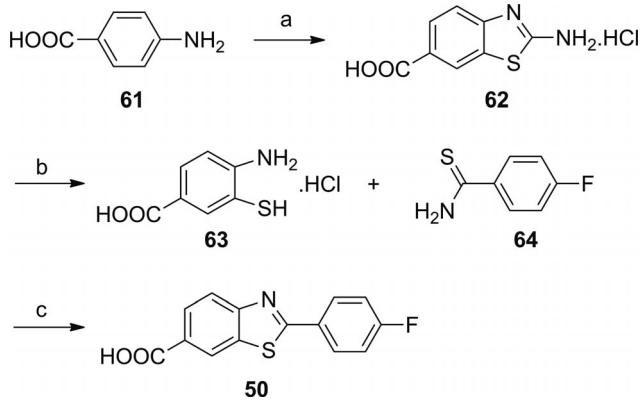
Direct couplings of commercially available substituted 1,3-benzothiazoles with aryl bromide in the presence of $Pd(OAc)_2$, Cs_2CO_3, and CuBr/P(*t*Bu)$_3$ also provided a series of 2-arylbenzothiazole derivatives.[30e,30m] This method allowed the introduction of a variety of substituents, including free amines, and led to better yields than in the case of Suzuki cross-coupling.[30e] Recently, Svensson et al. have also demonstrated the suitability of this direct

Table 3. RCYs (d.c.) of [^{11}C]BTAs under different experimental conditions.

Compound	Reagents and conditions	RCY (%)
[^{11}C]6-OH-BTA-1	[^{11}C]MeI, KOH, DMSO, 95 °C, 5 min	12
[^{11}C]6-OH-BTA-1	[^{11}C]MeOTf, MEK, 20 °C, 1 min	16
[^{11}C]6-OH-BTA-1	[^{11}C]MeOTf, acetone, 80 °C, 1 min	60
[^{11}C]4-OH-BTA-1	[^{11}C]MeOTf, ACN, room temp., 0.5 min	25
[^{11}C]5-OH-BTA-1	[^{11}C]MeOTf, ACN, room temp., 0.5 min	5
[^{11}C]7-OH-BTA-1	[^{11}C]MeOTf, ACN, room temp., 0.5 min	7

coupling to prepare 2-pyridylbenzothiazole derivatives, but only with fair yields (η = 24%).[36]

In addition to the above methods, cyclization of 4-aminobenzoic acid (**61**, Scheme 10) with sodium thiocyanate and bromine promoted the formation of 2-aminobenzothiazole-6-carboxylic acid (**62**).[30j] Upon basic hydrolysis, compound **62** was converted into the corresponding 4-amino-3-mercaptobenzoic acid (**63**). Transformations of the same type have been reported for related substituted 2-aminobenzothiazole derivatives[26,30d,30f] or 2-methylbenzothiazole derivatives[30k] and have emerged as a convenient strategy for obtaining poorly commercially available substituted *o*-aminothiophenols. Further condensation of **63** with *p*-fluorothiobenzamide (**64**) in NMP in the presence of concentrated hydrochloric acid resulted in the desired 2-arylbenzothiazole-6-carboxylic acid derivative (6-COOH-F-BTA-0–4′-F, **50**, Scheme 10), although with an unsatisfactory yield (η = 13%).[30j] Wang et al. reported a similar



Scheme 10. Synthesis of 6-COOH-F-BTA-0–4′-F (**50**).[30j] Reagents: a) NaSCN, Br_2; b) KOH; c) NMP, concd. HCl.

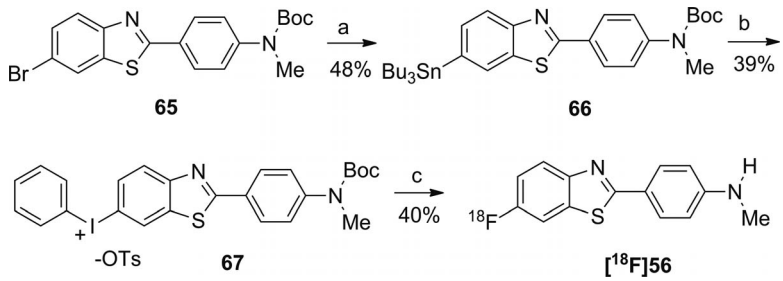
strategy for the preparation of 2-arylbenzothiazole-6-carboxylic acid derivatives, but with the coupling of **63** with benzoyl chlorides instead of thiobenzamides, affording BTAs with improved yields (η = 83%).[37]

As mentioned above, aromatic radiofluorination is more challenging than aliphatic radiofluorination. Serdons et al., however, recently reported the radiosynthesis of the [^{18}F]-labeled congener of **43**, as well as of related BTAs (**42**–**48**, Table 2), based on aromatic radiofluorination reactions. The radiosynthesis involved the direct aromatic nucleophilic substitution of nitro precursors [substituted 2-(4′-nitrophenyl)-1,3-benzothiazole derivatives] with [^{18}F]-fluoride. The presence of the electron-withdrawing benzothiazole group at the *para* position of the nitrophenyl ring facilitated the exchange of the nitro group with the ^{18}F.[30j,30m,30n]

More recently, Lee et al. reported the preparation of ^{18}F-6-fluoro-4-substituted benzothiazole derivatives (e.g., [^{18}F]-**56** and [^{18}F]**57**, Scheme 11) by an alternative approach based on diaryliodonium salt precursors.[30g] In exploring such an approach, these authors kept in mind the fact that diaryliodonium salts are good precursors for achieving ^{18}F-labeling of deactivated aryl compounds.[38] As demonstrated for [^{18}F]**56** (Scheme 11), suitable aryliodonium salt precursors were prepared by treatment of tributyltin analogues with the commercially available [hydroxyl(tosyloxy)-iodo]benzene (Koser's reagent).[30g] In the radiosynthesis of these compounds, *n*-butylammonium [^{18}F]fluoride proved to be a more efficient radiofluorinating agent than cesium [^{18}F]fluoride or potassium [^{18}F]fluoride/kryptofix 2.2.2. In addition, the radical scavenger TEMPO was found to be necessary to stabilize the iodonium tosylate salts and, therefore, to increase the efficiency of the ^{18}F-labeling reaction.

To overcome difficulties in aromatic radiofluorination, ^{18}F-labeling of several BTA analogues by aliphatic nucleophilic radiofluorination was attempted. Interestingly, Neumaier et al. found that the yields of these reactions depend on the position chosen to incorporate the aliphatic chain carrying the ^{18}F-label. Higher yields were obtained when the incorporation was at the 2′-position of the aryl ring (RCY = 32%), rather than the 6-position (RCY = 14%) of the more electron-rich benzothiazole component.[30h]

Attempts to refine the pharmacokinetics (brain uptake and retention) of some BTAs through isosteric substitution of the sulfur by oxygen resulted in a few examples of compounds featuring the benzoxazole core (Figure 6). The



Scheme 11. Synthesis of ^{18}F-labeled benzothiazole aniline derivatives.[30g] Reagents: a) Sn_2Bu_6, Pd^0, THF; b) Koser's reagent; c) i. $nBu_4N[^{18}F]$, TEMPO, MW; ii. HCl.

benzoxazole nucleus was formed in fair to good yields through boronic-acid-catalyzed condensations of the corresponding aminonitrophenols with 4-(dimethylamino)-benzoic acid.[39] The yields of a series of 2-arylbenzoxazole derivatives were improved up to threefold by the palladium-catalyzed arylation of 1,3-benzoxazole with aryl bromides.[30e] Oxidative cyclization of a phenolic Schiff base with DDQ as oxidant afforded the required key intermediate for the synthesis of 2-pyridylbenzoxazole derivatives (e.g., **69**, Figure 6).[36]

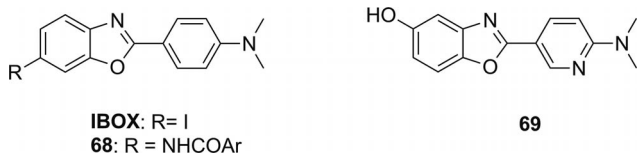


Figure 6. Chemical structures of benzoxazole derivatives.

2.4. Imidazo[1,2-*a*]pyridine Derivatives

Inspired by the encouraging results found for some BTA derivatives, a series of related compounds containing the imidazo[1,2*a*]pyridine scaffold (Figure 7) were synthesized and studied as radioactive probes for SPECT or PET imaging of Aβ plaques.[30a,40]

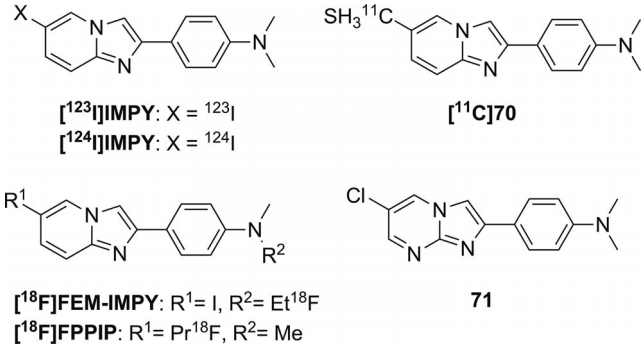
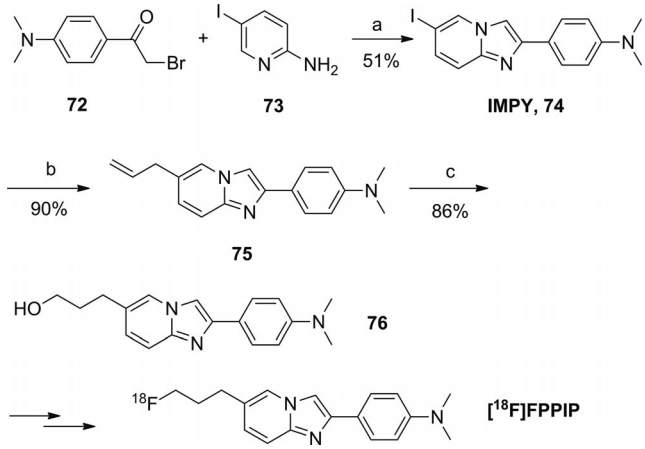


Figure 7. Chemical structures of imidazo[1,2-*a*]pyridine-based derivatives.

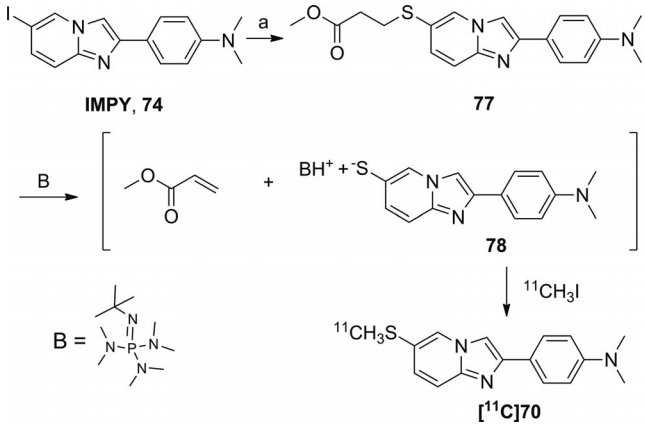
The first compounds were labeled with $^{123}I/^{125}I$. Among the resulting radioiodinated compounds, **[^{123}I]IMPY** (Figure 7) was the best characterized in vivo.[40a] Currently, **[^{123}I]IMPY** is considered one of the most promising SPECT probes for imaging of Aβ plaques. Recently, **IMPY** was also radiolabeled with iodine-124 with the goal of obtaining a congener PET probe.[40f] Both ^{18}F- and ^{11}C-labeled imidazo[1,2-*a*]pyridine derivatives were also prepared. ^{18}F-labeled IMPY derivatives in which the ^{18}F-fluoroalkyl group was introduced at the aromatic amino group (e.g., **[^{18}F]FEM-IMPY**) were found to undergo in vivo *N*-dealkylation and were therefore considered unsuitable probes.[40b] More metabolically stable compounds, such as **[^{18}F]FPPIP**,[40c] could be obtained by introducing the ^{18}F-label in another position but their binding affinities to synthetic Aβ plaques were five to 17 times lower than that displayed by the original **IMPY**. Furthermore, the 6-iodo substituent in IMPY was replaced by a thiol group, to open the possibility of labeling with ^{11}C {e.g., **[^{11}C]70** (Figure 7)} or ^{18}F, while tackling the in vivo *N*-demethylation reported for **[^{18}F]FEM-IMPY**.[40e]

Formation of the imidazo[1,2-*a*]pyridine ring was readily accomplished by condensation, under mild basic conditions, between an α-bromo ketone, such as bromoacetophenone **72**, and a suitable 2-aminopyridine derivative, as illustrated in Scheme 12. In the same way, the synthesis of imidazopyrazine **71** (Figure 7) was also achieved by condensation of **72** with 5-chloropyrazine-2-amine.[40d] This versatile condensation reaction was also applied in the synthesis of derivatives bearing various substituents on the ring system.



Scheme 12. Synthesis of imidazo[1,2*a*]pyridine derivatives **IMPY** and **[^{18}F]FPPIP**.[40c] Reagents: a) EtOH, $NaHCO_3$; b) $Bu_3SnCH_2CH{=}CH_2$, $(PPh_3)_4Pd$, Et_3N; c) 9-BBN, NaOH (3 N), H_2O_2 (30%).

As depicted in Scheme 12 and Scheme 13, **IMPY** has been the starting material for the synthesis of ^{18}F- or ^{11}C-labeled compounds. Palladium-catalyzed Stille coupling between **IMPY** and allyltributyltin, followed by hydroboration/oxidation of alkene **75**, produced the hydroxypropyl compound **76**. Non-radioactive **FPPIP** was readily obtained by treatment of **76** with DAST. For the synthesis of



Scheme 13. Synthesis of [^{11}C]-labeled imidazo[1,2*a*]pyridine derivative **[^{11}C]70**.[40e] Reagents: a) $HSCH_2CH_2COOMe$, Me_2SnNMe_2, $Pd_2(dba)_3$, DiPPF ligand.

[^{18}F]FPPIP, compound **76** was transformed into the corresponding tosylate, which was then radiofluorinated (Scheme 12).[40c] Interestingly, the radiosynthesis of **[^{18}F]FEM-IMPY** was accomplished by treatment of the *N*-monomethyl analogue of **IMPY** (HM-IMPY) with ethylene glycol ditosylate and [^{18}F/K_{222}] (in situ production of 2-[^{18}F]fluoroethyl tosylate).[40b] This "one-pot" method for *N*-[^{18}F]fluoroalkylation was developed when it became clear that 2-fluoroethyl tosylate or the corresponding triflate were more efficient *N*-alkylating agents than ethylene glycol ditosylate.

Selective *S*-[^{11}C]methylation could be achieved in the radiosynthesis of **[^{11}C]70** through treatment of the methyl sulfanyl-γ-propionate **77** (Scheme 13) with [^{11}C]iodomethane under basic conditions, as previously reported for the synthesis of ^{11}C-labeled ligands for imaging of brain norepinephrine transporters.[40e,41] The use of the large, strong organic base *tert*-butylimino-tris(dimethylamino)phosphorane, instead of potassium *tert*-butoxide or inorganic bases such as NaOH, KOH, Cs_2CO_3, or K_2CO_3, allowed the synthesis of **[^{11}C]70** with higher RCYs. Under anhydrous conditions, use of this base avoided unwanted ester hydrolysis and favored removal of the β-proton to generate the free thiolate ion with the desired high reactivity towards [^{11}C]iodomethane. The synthesis of **[^{11}C]70** involved the *S*-alkylated precursor **77**, which was used to generate the free thiolate in situ. The synthesis of the non-radioactive form of **70** was carried out in a similar way with sodium methanethiolate and trimethyltin chloride as reagents.[40e] Compound **77** was obtained by palladium-catalyzed aromatic substitution of the iodo group in **IMPY** by the thiol group of methyl 3-mercaptopropionate. No reduced byproducts were formed with this homogeneous catalytic reaction.[42]

More recently, two independent research groups have developed structurally related compounds bearing a common 2-arylimidazo[2,1-*b*]benzothiazole core (IBTs, Figure 8). IBTs are considered mix-condensed analogues of **PIB** and **IMPY**, and the influence of various hydrogen-bond-donating and -accepting substituents on their lipophilicities and binding properties to synthetic Aβ plaques was investigated. The 2-arylimidazo[2,1-*b*]benzothiazole scaffold was built by a condensation similar to that employed in the synthesis of the imidazo[1,2*a*]pyridine ring, but with use of 2-aminobenzothiazole instead of 2-aminopyridine.[43]

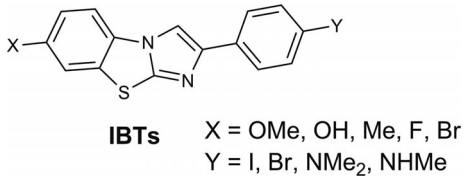


Figure 8. Chemical representation of 2-arylimidazo[2,1-*b*]benzothiazole derivatives.

Cui et al. recently synthesised a series of 6-iodinated 2-phenyl-1*H*-benzo[*d*]imidazole (BZMZ) derivatives (Figure 9) similar to **IMPY** (Figure 7). The 2-phenylbenzimidazole backbone was introduced in an efficient way through intermolecular cyclizations between 4-bromobenzene-1,2-diamine and substituted benzaldehydes in the presence of $Na_2S_2O_5$ as oxidant.[44] Competitive in vitro binding studies of **79**–**83** for the Aβ plaque, with [^{125}I]IMPY as competitor, demonstrated that these compounds have binding affinities in the range of 9.8 nM to 901 nM. The K_i values decreased with the electron-donating capacity of the substituent at the *para* position of the aryl group. The radioactive form of **79** (**[^{125}I]79**) was evaluated in vivo and showed high initial brain uptake followed by a fast washout from normal mice brain. The brain clearance was better than that seen with **[^{125}I]IMPY**. In vitro autoradiographic studies of AD brain sections with **[^{125}I]79** and in vivo studies with transgenic mouse models of AD demonstrated the specificity of this compounds for Aβ plaques.[44]

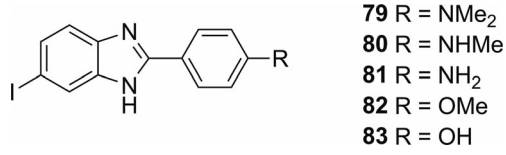


Figure 9. Chemical structures of 2-phenylbenzimidazole derivatives.

2.5. Benzofurans and Related Compounds

In 2002, a number of 5- and 6-iodobenzofuran derivatives with different *para*-substituted phenyl groups at their 2-positions (Figure 10) were reported as isosteric analogues of the benzoxazole derivative IBOX (Figure 6), with replacement of the heterocyclic nitrogen atom by a CH group.[45] These benzofuran derivatives were labeled either with carbon-11 or with fluorine-18, the most promising ones being displayed in Figure 10.

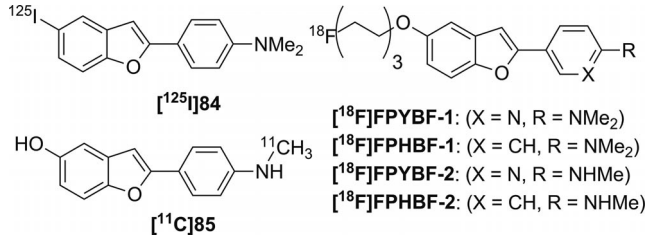
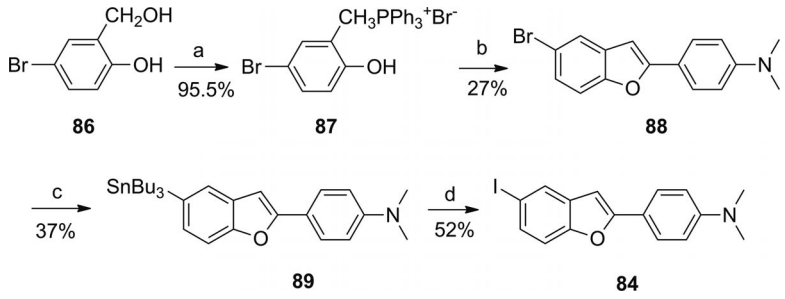


Figure 10. Chemical structures of benzofuran derivatives.

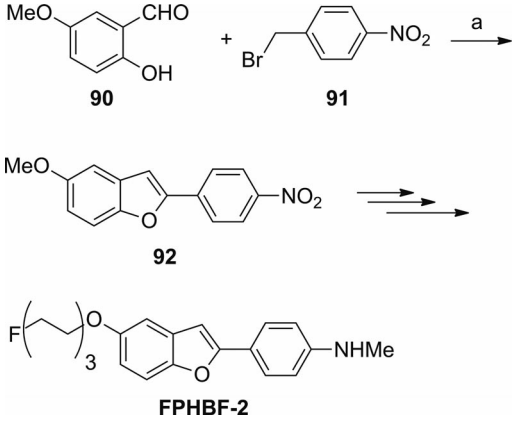
Formation of the benzofuran backbone in iodinated benzofuran derivatives was accomplished through intramolecular Wittig reactions between triphenylphosphonium salts and 4-substituted benzoyl chlorides, as outlined in Scheme 14 for compound **84**. Interestingly, preparation of the triphenylphosphonium salt **87** involved a one-pot conversion of 5-bromo-2-hydroxybenzyl alcohol (**86**) into the corresponding 5-bromo-2-hydroxybenzyl bromide followed by treatment with triphenylphosphane. The synthesis of **84** consisted of the preparation of the stannylated precursor **89** by treatment of the brominated compound **88** with bis(tributyltin) in the presence of Pd^0 as catalyst, followed by iododestannylation of **89** with iodine, a common methodol-



Scheme 14. Synthesis of benzofuran derivative **84**.[45] Reagents: a) PPh_3·HBr; b) 4-aminobenzoyl chloride; c) bis(tributyltin), $(PPh_3P)_4Pd$; d) iodine.

ogy for the preparation of iodophenyl derivatives of this type.[45] The syntheses of the radioiodinated congeners, such as **[^{125}I]84**, were also performed by electrophilic radioiodination of the correspondent tributyltin derivatives, in the presence of hydrogen peroxide as oxidant. These compounds exhibited excellent in vitro binding to Aβ plaques (K_i values in the subnanomolar range), but washed out slowly from normal mouse brain, suggesting high in vivo nonspecific binding.

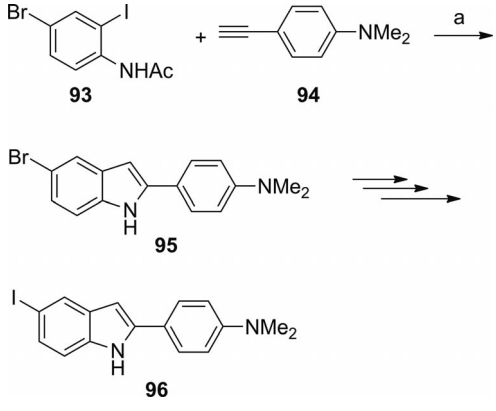
The phenylbenzofuran backbones in compounds **[^{11}C]85** and **[^{18}F]FPHBF-1** (Figure 10) were also constructed through intramolecular Wittig reactions, as outlined in Scheme 14 for compound **84**.[46] In contrast, the same backbone was introduced in **FPHBF-2** (Scheme 15) through the base-promoted condensation of 2-hydroxy-5-methoxybenzaldehyde (**90**) with 4-nitrobenzyl bromide (**91**).[47] These compounds exhibited good affinities for Aβ plaques but pharmacokinetic profiles with unfavorable target/non-target ratios.



Scheme 15. Key step for the synthesis of phenylbenzofuran **FPHBF-2**.[47] Reagents: a) K_2CO_3, DMF.

Searching to overcome the unfavorable in vivo properties of the compounds, the same authors developed less lipophilic fluorinated pyridyl-benzofuran derivatives (**FPYBF-1** and **FPYBF-2**), by replacing the phenyl moiety by a pyridyl group (Figure 10). The key step in the formation of **FPYBF-1** and **FPYBF-2** was achieved by Suzuki coupling between 5-methoxybenzofuran-2-boronic acid and 1-amino-5-iodopyridine.[47–48] Although compound **FPYBF-2** shows a weaker binding affinity to Aβ plaques than **FPYBF-1** (2.41 nM vs. 0.95 nM), the former displays improved brain uptake and faster clearance from normal mouse brain, and is currently the first [^{18}F]-benzofuran-based compound in preparation for clinical trials.[47]

As alternatives to benzofuran-based compounds, the benzothiophene and indole scaffolds were also investigated as potential Aβ imaging agents. Once again, the intramolecular Wittig reaction proved to be a suitable strategy to provide phenylbenzothiophene derivatives (isosteric analogues of BTAs) in good yields (η = 54%).[49] On the other hand, Sonogashira coupling (Pd^0/Cu^I-catalyzed reaction) was explored for the preparation of indolylphenylacetylene[50] and 2-phenyl-1*H*-indoles (2-PI, e.g., **96**, Scheme 16).[51] It is worth mentioning that for the preparation of **96** the Sonogashira reaction was followed by an intramolecular cyclization in a one-pot, two-step method. Additionally, the phenyl group was also introduced at the 1-position of the indole through the copper-mediated coupling of substituted indoles with substituted phenylboronic acids.[51] This method, developed by Cham et al., constitutes an alternative use of boronic acids, in addition to the well-known Suzuki coupling, to form heteroatom-carbon bonds.[52]



Scheme 16. Key step for the synthesis of phenylindoles.[51] Reagents: a) CuI, $PdCl_2(PPh_3)_2$, TBAF, THF.

2.6. Diphenyl-Substituted Compounds

As a result of the promising results obtained with distyrylbenzene and stilbene structures (Figure 4), several authors have also explored alternative diphenyl-substituted deriva-

tives (Figure 11) in which the double bond is replaced by a cyclic moiety or an unsaturated motif in order to maintain the conjugation of the electronic density and to refine pharmacokinetics.

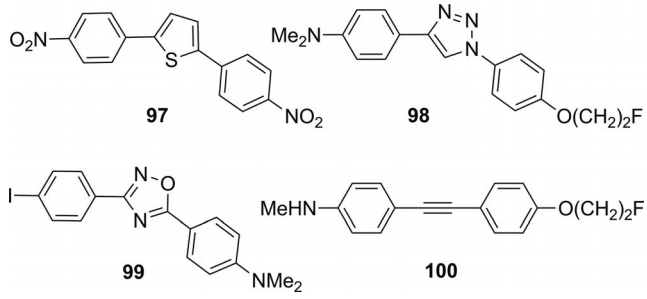
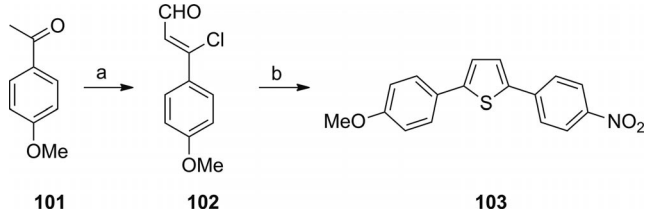


Figure 11. Chemical structures of diphenyl-substituted derivatives.

The thiophene ring, which can be also regarded as a diene in the *s-cis* conformation, was attached to phenyl systems by Kung and co-workers.[53] Symmetrical diphenylthiophene derivatives (e.g., **97**, Figure 11) were produced by Suzuki coupling of 2,5-dibromothiophene with the corresponding phenylboronic acids in one-step fashion. Alternatively, sequential treatment of β-chloroacrolein **102** (Scheme 17) with sodium sulfide nonahydrate and 4-nitrobenzyl bromide, followed by cyclization with sodium methoxide, afforded the unsymmetrically substituted diphenylthiophene **103**.[53] Later on, the same authors employed the "click chemistry" method to produce 1,4-diphenyltriazoles (e.g., **98**, Figure 11) as probes for targeting Aβ plaques.[54]



Scheme 17. Key step in the synthesis of the unsymmetrically substituted diphenylthiophene **103**.[53] Reagents: a) PCl_3/DMF; b) i. Na_2S/DMF; ii. 4-nitrobenzyl bromide; iii. NaOMe.

Oxadiazole ring systems were also considered as linkers between two phenyl rings. Depending on the substitution pattern, two diphenyl-oxadiazole ring systems were synthesised: the 3,5-diphenyl-1,2,4-oxadiazole (1,2,4-DPOD) type (e.g., **99**, Figure 11) and the less lipophilic structural isomer 2,5-diphenyl-1,3,4-oxadiazole (1,3,4-DPOD) type. Condensations of 4-bromobenzamide oxime with 4-substituted benzoic acids in the presence of conjugation agents were the key step for the preparation of 1,2,4-DPOD derivatives,[55] whereas CAN-mediated (cerium ammonium nitrate) condensations of 4-bromobenzahydrazide with 4-substituted benzaldehydes yielded 1,3,4-DPOD derivatives.[56]

Diphenylacetylenes such as **100** (Figure 11) are relatively rigid structures with limited freedom around their triple bonds. This was expected to led to tight fits with the binding pockets at the β sheet. The key step for the synthesis of the diphenylacetylene core involved Sonogashira couplings of suitable substituted iodobenzenes with substituted phenylacetylenes. Depending on the substitution pattern of the phenylacetylene component, these coupling reactions were carried out under reducing atmospheres (hydrogen in argon, 10 to 50%) to circumvent the excessive formation of dimers as byproducts.[57] Similarly, the same coupling reaction was the method selected for the production of a series of aza-diphenylacetylenes designed as less lipophilic analogues of diphenylacetylenes.[58]

A series of diphenyltriene derivatives was also prepared for investigation of the influence of the distance between the two phenyl groups on the binding to Aβ plaques. In these derivatives, the polyene moieties were fashioned through Horner–Wadsworth–Emmons reactions between but-2-ene-1,4-bis(diethyl phosphonate) and various benzaldehydes, albeit in low yields.[59]

2.7. Flavonoids

It was found that polyhydroxyflavones can interact with Aβ plaques after their investigation as antiamyloidogenic agents.[60] This finding prompted Ono's group to investigate flavonoid-type compounds, including flavones (2-arylchromones),[61] aurones,[62] and chalcones[63] (Figure 12), as novel core structures for amyloid imaging agents. Although not structurally related to classical probes such as **DDNP**, **ThT**, or **CR**, these compounds showed excellent characteristics as new amyloid targeting agents.

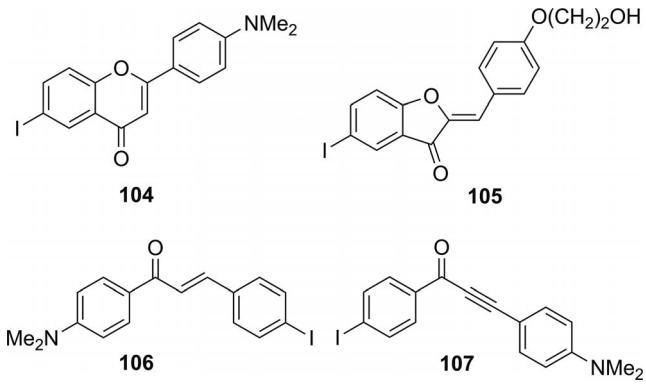


Figure 12. Chemical structures of flavonoid-based derivatives.

The Baker–Venkataraman rearrangement, already used to obtain styrylchromone derivatives as illustrated in Scheme 6, is the commonest method for formation of the chromone (1,4-benzopyrone) ring in flavones and was explored for the preparation of iodo- and fluoro-substituted flavones such as **104**.[61] The aurone backbone in **105** was produced through aldol condensations of 5-bromo-3-benzofuranone with substituted benzaldehydes in the presence of Al_2O_3.[62] On the other hand, condensation reac-

tions between acetophenones and substituted benzaldehydes or heterocyclic aldehydes were also the method of choice for the production of a series of chalcones (e.g., **106**) and chalcone-like compounds.[63]

The promising results with chalcones prompted the same group to prepare a series of chalcone derivatives (diphenylpropynones), in which the double bond was replaced with a triple bond (e.g., **107**). The diphenylpropynone scaffold was prepared in single-step fashion through palladium-catalyzed Sonogashira-like reactions between 4-bromobenzoyl chloride and substituted phenylacetylenes in the presence of triethylamine as base. Interestingly, no ligand, or copper, or solvent were used to promote this cross-coupling.[64]

3. Concluding Remarks

In this review we have presented an overview of the different synthetic methods used to obtain aromatic and heteroaromatic compounds with potential relevance as PET, SPECT, or optical amyloid imaging agents. In general, depending on the designed scaffold, intermolecular and intramolecular condensation, olefination, catalyst-mediated C–C bond formation, or aldol condensation have been the most widely used synthetic strategies. A large number of compounds have been produced with satisfactory overall yields, with the goal of biological screening to establish structure–affinity relationships (SARs). A variety of these compounds have been labeled with ^{11}C, ^{18}F (PET), or ^{123}I (SPECT). Some of them have presented encouraging properties for in vivo imaging of amyloid aggregates, and the so-called Pittsburgh compound-B (**[^{11}C]PIB**) has emerged as the most promising radiotracer for imaging Aβ plaques in the brains of suspected AD patients. Despite this progress, compounds with matched half-life, improved initial brain uptake, and rapid clearance from the regions of brain without Aβ plaques are still needed. Another drawback of the classical Aβ probes is their lack of selectivity towards the different types of amyloid deposits. All together, these limitations still need to be addressed, which is a motivation for research in this area. There is no doubt that chemistry and radiochemistry are the fuel for in vivo molecular imaging of Aβ plaques. Despite the interest of small organic molecules such as those reviewed here, peptidic compounds are also promising and deserve to be explored. These peptidic molecules would be expected to exhibit the highest selectivity in their interactions with amyloid plaques. This new generation of ligands might also help in answering some of the basic scientific questions relating to "protein misfolding disorders", such as AD, which remain elusive.

4. Abbreviations

Abbreviations and acronyms used in the article are listed in Table 4.

Table 4. Abbreviations and acronyms.

ACN	acetonitrile
BSB	bromostyrylbenzene
BZMZ	2-phenyl-1*H*-benzo[*d*]imidazole
DAST	(diethylamino)sulfur trifluoride
d.c.	decay-corrected
DDNP	2-{1-[6-(dimethylamino)-2-naphthyl] ethylidene}malononitrile
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
FDDNP	2-(1-{6-[(2-fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile
FEM-IMPY	6-iodo-2-[4′-*N*-(2-fluoroethyl)methylamino]phenylimidazo[1,2-*a*]pyridine
FPPIP	6-(3′-fluoropropyl)-2-(4′-dimethylamino)-phenylimidazol[1,2-*a*]pyridine
GMP	good manufacturing practice
IBOX	iodobenzoxazole
ISB	iodostyrylbenzene
IMPY	iodoimidazo[1,2-*a*]pyridine
FPHBF	fluorinated phenylbenzofuran
FPYBF	fluorinated pyridylbenzofuran
MEK	methyl ethyl ketone
MW	microwave
NFTs	neurofibrillar tangles
PET	positron emission tomography
RCY	radiochemical yield
SPECT	single photon emission computed tomography
TBAF	tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Acknowledgments

We thank the Portuguese Fundação para a Ciência e Tecnologia (FCT) for financial support (PTDC/QUI/102049/2008 and the Ciência 2008 program). Fatima Marques is also thanked for technical support in the preparation of the figures.

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Received: October 4, 2011
Published Online: December 28, 2011

