Synthesis and In Vitro Evaluation of Imidazo[1,2-b]-pyridazines as Ligands for β-Amyloid Plaques
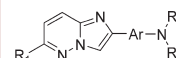
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ABSTRACT A series of imidazo[1,2-b]pyridazine derivatives were synthesized and evaluated for binding to amyloid plaques in vitro using synthetic aggregates of $A\beta_{1-40}$. Binding affinities of these compounds were found to range from 11.0 to > 1000 nM, depending on the various substitution patterns in the 6-position and 2-position. 2-(4′-Dimethylaminophenyl)-6-(methylthio)imidazo[1,2-b]pyridazine (**4**) showed high binding affinity (K_i = 11.0 nM) and might be useful for the development of novel positron emission tomography radiotracers for imaging Aβ plaques.

R_1 = F, Cl, I, OCH_3, SCH_3, OCH_2CH_2F, $OCH_2CH_2CH_2F$, SCH_2CH_2F, or $SCH_2CH_2CH_2F$;
Ar = phenyl, pyridinyl, or thiophenyl;
R_2, R_3 = CH_3 or H

KEYWORDS Imidazo[1,2-b]pyridazine, β-amyloid plaque, structure—activity relationship, positron emission tomography

Alzheimer's disease (AD) is a common cause of dementia, which is clinically characterized by progressive loss of memory and decline of cognitive function. The neuropathologic signature of AD generally revealed on postmortem brain examination is the massive deposit of β-amyloid plaques (Aβ) and neurofibrillary tangles (NFTs).[1−3] Therefore, amyloid-specific imaging agents would likely prove useful to identify and follow individuals at risk for AD and to assist in evaluating the efficacy of new therapeutic approaches that act early on the neurodegenerative progress and inhibit the accumulation of amyloid plaques and NFTs.[4−7]

The development of amyloid-specific imaging agents is generally based on conjugated dyes, such as Congo red, Chrysamine G, and thioflavin-T, which have been used in fluorescent staining of plaques and tangles in postmortem AD brain sections. Several radioligands for positron emission tomography (PET) and single photon emission computerized tomography (SPECT), including [^{11}C]PIB (Pittsburgh compound B),[8−10] [^{11}C]SB-13 (4-N-methylamino-4′-hydroxystilbene),[11] [^{11}C]AZD2184 (2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol),[12] [^{18}F]FDDNP (2-(1-{6-[(2-fluoroethyl)-(methyl)amino]-2-naphthyl}ethylidene)malononitrile),[13,14] [^{18}F]GE067 (2-(3′-fluoro-4′-(methylamino)phenyl)-6-hydroxybenzothiazole),[15] [^{18}F]BAY94-9172 (4-(N-methylamino)-4′-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)stilbene),[16] [^{18}F]AV-45 ((E)-4-(2-(6-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methyl benzenamine),[17,18] and [^{123}I]IMPY (2-(4′-dimethylamino-phenyl)-6-iodoimidazo[1,2-a]pyridine),[19] have been tested in clinical trials and demonstrated the potential utility as in

vivo imaging agents for Aβ plaque deposition in the living human brain (Figure 1).

In an attempt to develop more effective amyloid-specific imaging agents, we have chosen to investigate a novel series of imidazo[1,2-b]pyridazine derivatives. Imidazo[1,2-b]-pyridazines are designed to be isosteric analogues of IMPY, of which CH adjacent to N on the six-membered heterocyclic ring was replaced with N. We reasoned that substitution of aryl CH by an imino group might be effective in reducing ligand lipophilicity, thus reducing ligand nonspecific binding. Additionally, an appropriately substituted pyridazine ring lends itself well to easy attachment of different groups via heteroaromatic nucleophilic displacement reaction. We report here the synthesis and in vitro evaluation of imidazo-[1,2-b]pyridazines as potential imaging agents for detecting Aβ plaques.

The synthesis of imidazo[1,2-b]pyridazine derivatives is shown in Schemes 1 and 2. In all cases, the formation of imidazo[1,2-b]pyridazine backbone was accomplished through a condensation reaction between an α-bromoketone and a 3-amino-6-halopyridazine under a mild basic condition such as sodium bicarbonate. In fact, the successful formation of imidazo[1,2-b]pyridazine rings in good yield was due to the introduction of a halogen in the pyridazine ring. In 3-aminopyridazine, the ring nitrogen that is not adjacent to the amino group is the most nucleophilic. Thus, alkylation by the α-bromoketone takes place preferentially
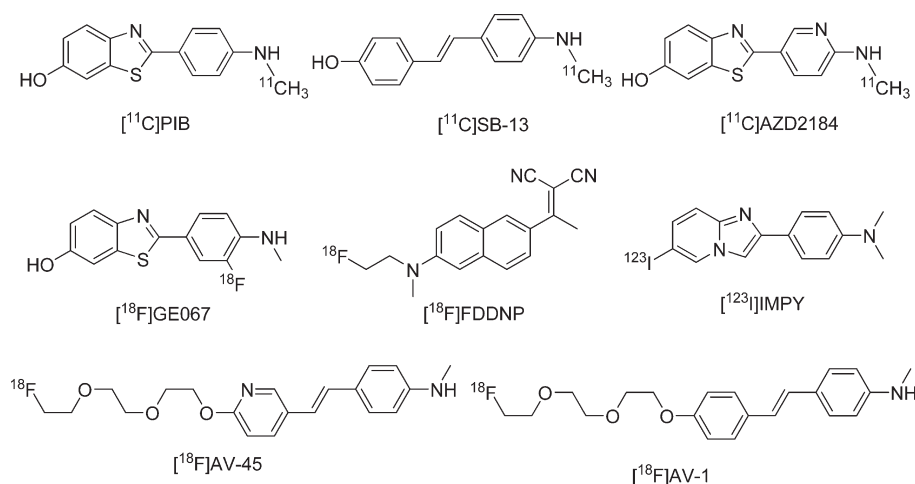
Figure 1. Radioligands for Aβ plaque imaging with PET and SPECT in clinical trials.

at this site, hampering an effective synthesis of the desired bicyclic product. This was overcome by placing a halogen in the ring, adjacent to the offending nitrogen, thus greatly reducing the nucleophilicity of this nitrogen and returning the preferential site of alkylation to the ring nitrogen adjacent to the amino function.

The synthesis of 6-substituted-2-phenylimidazo[1,2-b]-pyridazines is shown in Scheme 1. 3-Amino-6-chloropyridazine[20] and 3-amino-6-fluoropyridazine[21] were prepared from 3,6-dichloro- and 3,6-difluoropyridazine by reaction with aqueous ammonia at 130 °C, respectively. While 3-amino-6-iodopyridazine could also be prepared from 3,6-diiodopyridazine using the same method, the yield was very low, and 3,6-diaminopyridazine was the major product. Alternatively, 3-amino-6-iodopyridazine was obtained in 81% yield by refluxing 3-amino-6-chloropyridazine in 57% HI solution.[22] α-Bromoketone **1** was prepared from 4′-dimethylaminoacetophenone through dibromination and debromination procedures reported previously.[23] Nucleophilic substitution of the 6-chloro derivative **2b** by methoxide, thiomethoxide, and deprotonated fluoroethanol, fluoropropanol, 2-mercaptoethanol, and 3-mercaptopropanol afforded **3−8** in good to excellent yields. 2-Fluoroethylthio and 3-fluoropropylthio compounds (**9** and **10**) were obtained by the treatment of **7** and **8** with DAST, respectively.

The free amino derivatives, **12a−c**, were readily prepared from **11a−c** by reduction with SnCl$_2$. Conversion of **12a** and **12c** to their N-methylamino derivatives was achieved by a selective monomethylation reaction using sodium methoxide and paraformaldehyde, followed by a reduction reaction with NaBH$_4$. However, the 6-chloro group of **12b** was also converted to methoxyl group under the same condition to give **13b** as the only product. Alternatively, **14** was prepared by methylation by MeI in the present of K$_2$CO$_3$, while dimethylation product **2b** was also observed in this reaction.

The synthesis of 6-halogen-2-pyridinylimidazo[1,2-b]pyridazines and 6-halogen-2-thiophenylimidazo[1,2-b]pyridazines, based on the similar method shown above for 6-substituted-2-phenylimidazo[1,2-b]pyridazines, is outlined in Scheme 2. α-Bromoketone **15** was prepared by α-bromination of 1-(5-(dimethylamino)pyridin-2-yl)ethanone with pyridinium tribromide. α-Bromoketone **17** was prepared by bromination of 2-acetyl-5-nitrothiophene with copper(I) bromide.[24]

In vitro binding affinity of imidazo[1,2-b]pyridazines for Aβ plaques was determined via the binding competition with [³H]BTA-1 (2-(4′-(dimethylamino)phenyl)benzothiazole) using synthetic aggregates of Aβ$_{1−40}$. IMPY and PIB were also screened under the same assay system for comparison. Initially, we prepared 6-halogen N,N-dimethylamino, N-methylamino, and primary amino analogues. Comparison of the K_i values (Table 1) reveals that the tertiary amino analogues typically have a higher affinity than their secondary amino analogues (**2a** vs **13a**, **2b** vs **14**, and **2c** vs **13c**), in accord with the previous data on the tertiary and secondary amino analogues of IMPY,[25] while the corresponding primary amino analogues show a much lower affinity. Therefore, we decided to focus our efforts on tertiary analogues and synthesized several 6-substituent N,N-dimethylamino analogues. The 6-iodo N,N-dimethylamino analogue has a higher affinity than the 6-chloro or 6-fluoro analogue, and this trend was repeated in the corresponding secondary amino and primary amino analogues (**2c** vs **2b** vs **2a**, **12c** vs **12b**, and **13c** vs **14** vs **13a**). This indicates that the size and electronegativity of the halogen atom presumably influence the binding of these ligands. Substitution of aryl CH of IMPY by an imino group as in **2c** is effective in reducing ligand lipophilicity (compare cLog P value with that of IMPY) but slightly reduced binding affinity. The 6-methylthio analogue (**4**) shows a higher affinity over the 6-methoxyl analogue (**3**). Incorporation of ω-fluoroethyl or ω-fluoropropyl group, as reflected in **5**, **6**, **9**, and **10**, decreases binding affinity. To further study the structure−activity relationship (SAR) of imidazo[1,2-b]pyridazines, we synthesized **16a**, **16b**, **16c**, **20a**, and **20b** with the replacement of phenyl ring with pyridinyl or thiophenyl ring. Unfortunately, these ligands show significantly reduced binding affinity, indicating that the phenyl ring might be required to retain high binding

Scheme 1[a]
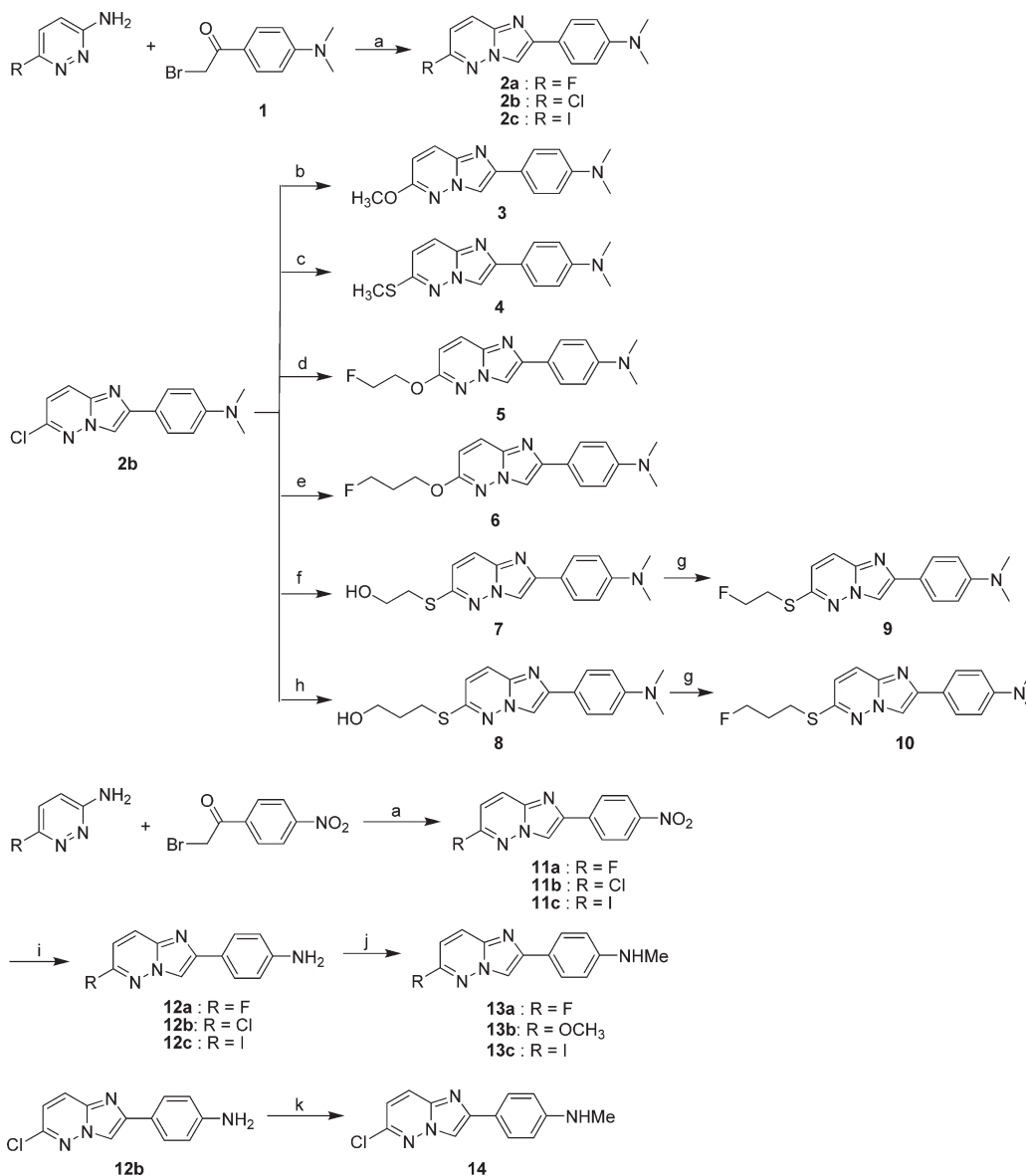
[a] Reagents and conditions: (a) EtOH, reflux, 2 h; NaHCO$_3$, reflux, 5 h, 52−81 %. (b) NaOCH$_3$, EtOH, reflux, 18 h, 62 %. (c) NaSCH$_3$, EtOH, reflux, 18 h, 78 %. (d) FCH$_2$CH$_2$OH, Bu$_4$NOH, DMF, room temperature, 18 h, 54 %. (e) FCH$_2$CH$_2$CH$_2$OH, Bu$_4$NOH, DMF, room temperature, 48 h, 44 %. (f) HOCH$_2$CH$_2$SH, Bu$_4$NOH, DMF, room temperature, 1 h, 83 %. (g) DAST, CH$_2$Cl$_2$, −78 °C to room temperature, 1 h, 21 %. (h) HOCH$_2$CH$_2$CH$_2$SH, Bu$_4$NOH, DMF, room temperature, 1 h, 86 %. (i) SnCl$_2$·2H$_2$O, EtOH, reflux, 2 h, 54−61 %. (j) NaOMe, CH$_3$OH, (CH$_2$OH)$_n$, NaBH$_4$, reflux, 3 h, 42−57 %. (k) MeI, K$_2$CO$_3$, DMSO, 100 °C, 16 h, 24 %.

affinity. Among all of the ligands tested, the 6-methylthio analogue (**4**), which exhibits a high binding affinity (K_i = 11.0 nM) comparable to the values for PIB and IMPY, might be of interest for evaluation as a prospective PET radioligand if labeled with carbon-11 in N-methyl or S-methyl position. Four is also expected to have a higher target-to-background ratio for plaque labeling of an AD brain with regard to its reduced lipophilicity, as compared to IMPY and its derivatives. It is interesting to mention that the 6-methylthio IMPY derivative was reported to have a low retention to Aβ in AD patients.[26]

In summary, we have synthesized a series of imidazo-[1,2-b]pyridazines with various substitution patterns in the 6-position and 2-position. The SAR studies of these compounds with regard to Aβ showed that 2-N,N-dimethyl-aminophenyl moiety might be a requirement for these compounds to exhibit desirable binding affinities. The K_i values of 2-dimethylaminophenyl imidazo[1,2-b]pyrida-zines with different substituents in the 6-position range from 10 to 50 nM, indicating moderate tolerance for modification at this location. The 6-methylthio analogue (**4**) exhibited high binding to Aβ plaques in vitro and might

Scheme 2[a]
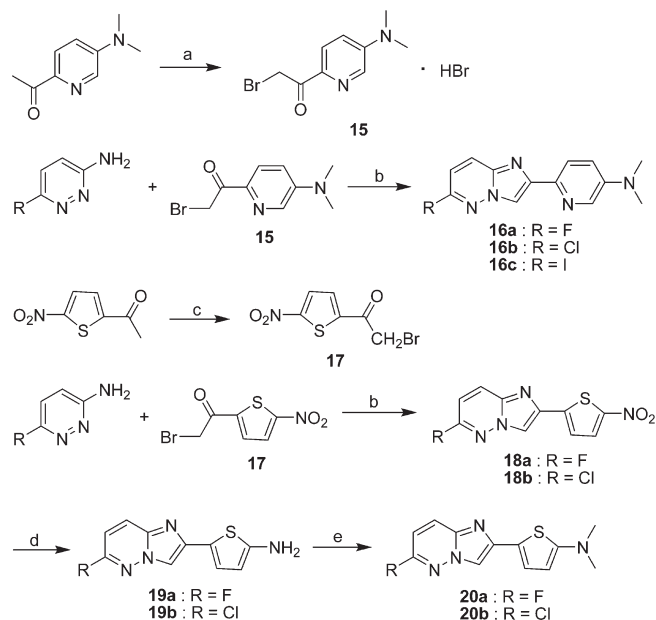
[a] Reagents and conditions: (a) HBr, pyridinium tribromide, HOAc, 40 °C, 18 h, 37%. (b) EtOH, reflux, 2 h; NaHCO₃, reflux, 5 h, 41–56%. (c) CuBr, EtOAc, reflux, 18 h, 60%. (d) SnCl₂·2H₂O, EtOH, concentrated HCl, 0 °C to room temperature, 1 h, 57%. (e) MeI, NaH, DMSO, room temperature, 1 h, 22%.

be interest for evaluation as a prospective PET radioligand if labeled with carbon-11 in the *N*-methyl or *S*-methyl position.

SUPPORTING INFORMATION AVAILABLE Procedure for the preparation of new ligands, analytical data, and in vitro binding assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS AD, Alzheimer's disease; Aβ, β-amyloid plaques; NFTs, neurofibrillary tangles; PET, positron emission tomography; SPECT, single photon emission computerized tomography; PIB, Pittsburgh compound B; SB-13, 4-*N*-methylamino-4′-hydroxystilbene; FDDNP, 2-(1-{6-[(2-fluoroethyl)-(methyl)amino]-2-naphthyl}ethylidene)malononitrile; GE067, 2-(3′-fluoro-4′-(methylamino)phenyl)-6-hydroxybenzothiazole; BAY94-9172, 4-(*N*-methylamino)-4′-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)stilbene; AV-45, (*E*)-4-(2-(6-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methyl benzenamine; IMPY, 2-(4′-dimethylaminophenyl)-6-iodo-imidazo[1,2-*a*]pyridine; AZD2184, 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol; BTA-1, 2-(4′-(dimethylamino)phenyl)benzothiazole; SAR, structure–activity relationship.

Table 1. Inhibition Constant (*K*ᵢ Values) of Imidazo[1,2-*b*]pyridazines for Binding Synthetic Amyloid Plaques Aβ 1−40
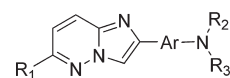
ligand	R₁	R₂	R₃	Ar	K_i (nM)[a]	cLog P[b]
2a	F	CH₃	CH₃	phenyl	41.4 ± 1.8	3.00
2b	Cl	CH₃	CH₃	phenyl	34.2 ± 1.2	3.57
2c	I	CH₃	CH₃	phenyl	18.4 ± 0.4	3.98
3	OCH₃	CH₃	CH₃	phenyl	18.3 ± 3.3	3.06
4	SCH₃	CH₃	CH₃	phenyl	11.0 ± 1.2	3.54
5	O(CH₂)₂F	CH₃	CH₃	phenyl	32.0 ± 1.8	3.32
6	O(CH₂)₃F	CH₃	CH₃	phenyl	47.5 ± 1.8	3.54
9	S(CH₂)₂F	CH₃	CH₃	phenyl	35.5 ± 9.9	3.80
10	S(CH₂)₃F	CH₃	CH₃	phenyl	38.8 ± 1.2	4.03
12b	Cl	H	H	phenyl	470 ± 10	1.68
12c	I	H	H	phenyl	280 ± 46	2.66
13a	F	CH₃	H	phenyl	91.4 ± 4.2	2.42
13c	I	CH₃	H	phenyl	34.0 ± 1.1	3.40
14	Cl	CH₃	H	phenyl	78.8 ± 2.5	2.99
16a	F	CH₃	CH₃	pyridinyl	>1000	2.24
16b	Cl	CH₃	CH₃	pyridinyl	280 ± 6	2.81
16c	I	CH₃	CH₃	pyridinyl	233 ± 6	3.22
20a	F	CH₃	CH₃	thiophenyl	550 ± 23	2.93
20b	Cl	CH₃	CH₃	thiophenyl	336 ± 11	3.50
PIB					11.0 ± 0.2	3.99
IMPY					9.0 ± 0.9	4.91

[a] Measured in at least three independent experiments, each performed in triplicate with results given as the mean ± SD. [b] Calculated in ChemDraw Ultra 11 (CambridgeSoft, Cambridge, MA).

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