Synthesis and Structure−Affinity Relationships of New 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-dimethylbenzeneamine Derivatives as Ligands for Human β-Amyloid Plaques

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A new and extensive set of 4-(6-iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-dimethylbenzeneamine (IMPY) derivatives was synthesized and assayed for affinity toward human Aβ plaques. 6-Ethylthio- (**12h**), 6-cyano- (**12e**), 6-nitro- (**12f**), and 6-*p*-methoxybenzylthio- (**15d**) analogues were discovered to have high affinity (K_I < 10 nM). However, introduction of a hydrophilic thioether group in the 6-position (**15a**−**c, 15e**−**g**) reduced or abolished affinity. In secondary *N*-methyl analogues, a bromo substituent in the adjacent ring position (**14a**) imparted high affinity (K_I = 7.4 nM) whereas a methyl substituent did not (**14c**). The tolerance for nonhydrophilic thioether substituents in the 6-position opens up the possibility of developing new sensitive positron emission tomography radioligands for imaging human Aβ plaques in Alzheimer's disease, especially in view of the amenability of thioethers to be labeled with carbon-11 or fluorine-18 through S-alkylation reactions. The structure−activity relationships revealed in this study extends insight into the topography of the binding site for IMPY-like ligands in human Aβ plaques.

Introduction

Alzheimer's disease (AD[a]) is characterized by several features, including cerebral plaques formed from amyloid β-peptide (Aβ), neuronal loss, and intracellular deposits denoted as neurofibrillary tangles, an aggregated form of hyperphosphorylated forms of the microtubule-associated tau protein.[1] A major contemporary hypothesis for the biochemical changes underlying the progression of AD is the "β-amyloid cascade hypothesis"[2] in which brain Aβ peptide is processed through various stages to form the plaques eventually responsible for the morbid clinical symptoms of the disease. An ability to detect this process in human brain in vivo at an early stage, ideally preceding the presentation of clinical symptoms, would be a valuable tool for testing the underlying hypothesis and also for monitoring potential therapeutic interventions.

Three radioligands for positron emission tomography (PET)[3−5] and one for single photon emission computed tomography (SPECT)[6] imaging of Aβ plaques have reached the clinical stage: ([^{11}C]2-(4-(methylamino)phenyl)benzo[*d*]thiazol-6-ol ([^{11}C]-PIB), [^{11}C](*E*)-4-(4-(methylamino)styryl)phenol ([^{11}C]SB-13), [^{18}F]2-(1-(6-((2-fluoroethyl)(methyl)amino)naphthalen-2-yl)ethylidene)malononitrile ([^{18}F]FDDNP), and [^{123}I]**12a** ([^{123}I]IMPY) (Figure 1). The development of such radioligands is challenging because animal models of AD, for example, those using transgenic mice that express various genes for overexpression of Aβ, do not necessarily present Aβ plaques with the same molecular properties and density of ligand binding sites as those found in human AD subjects.[7] These models therefore turn out to have limited value in the PET or SPECT radioligand development process.

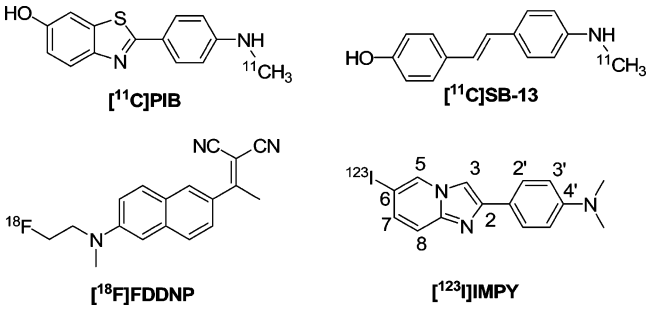

Figure 1. Four radioligands for imaging Aβ plaques in clinical research.

It is generally considered that candidate radioligands for Aβ plaques should have high affinity with K_D below 20 nM,[8] and the radioligands shown in Figure 1 meet this criterion. Generally, the pharmacokinetic properties of high-affinity (K_I < 10 nM) radioligands in normal animals (monkeys, mice, rats) appear quite predictive of such properties in AD subjects in vivo. Fast and high entry of radioligand into brain followed by fast washout is considered desirable, since this should permit long-lasting strong interactions between radioligand and plaque to be imaged with high contrast against weaker nonspecific interactions. Ligand lipophilicity is one important parameter that may influence brain pharmacokinetics, with ideal lipophilicity usually lying in the Log$P_{7.4}$ range 2.5−3.5.[9−11] However, ligand brain pharmacokinetics may also be influenced strongly by the action of efflux pumps (e.g., P-gp) at the blood−brain barrier and also by peripheral metabolism and ligand clearance. Ideally, ligands

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[a] Abbreviations: PET, positron emission tomography; AD, Alzheimer's disease; SPECT, single photon emission computed tomography; nM, nano molar; P-gp, P-glycoprotein; SAR, structure−activity relationship; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; cLogP, calculated logarithm of lipophilicity coefficients; ACD, advanced chemistry development; SD, standard deviation; ppm, parts per million; TLC, thin-layer chromatography; FCC, flash column chromatography; HRMS, high-resolution mass spectra; SPE, solid-phase extraction; y, year; h, hour.

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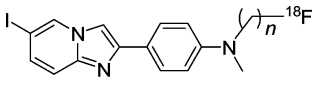


n = 2, [^{18}F]FEM-IMPY
n = 3, [^{18}F]FPM-IMPY

Figure 2. Structures of [^{18}F]FEM-IMPY and [^{18}F]FPM-IMPY.

should not be substrates for brain efflux pumps and should be cleared rapidly from the periphery. The ratios of the radioactivity in normal animal brains at 2 and 30 min or between 2 and 60 min have become used as indexes to predict the signal-to-noise ratio achievable in humans when Aβ plaques are present.[8] This radioactivity should represent the parent radioligand and be uncontaminated by radiometabolites. [^{123}I]**12a** is one of few ligands showing a high ratio of radioactivity between 2 and 30 min (11)[12,13] similar to the ratio for [^{11}C]PIB (12), the most extensively studied radioligand for Aβ plaque imaging.[3,14]

The study of structure−affinity relationships (SAR) in **12a** analogues is a useful first step for identifying potentially more sensitive radioligands for imaging Aβ plaques in vivo. Only limited SAR studies of **12a** derivatives have been reported[15,16] (for a recent summary of SAR in all classes of Aβ plaque ligands, see Cai et al.[17]). Substituents at the 4′- and 6-positions are critical for maintaining high binding affinity for Aβ plaques.[15] Strong electron-donating groups are needed at the 4′-position. Tertiary arylamino groups are preferred over secondary amino groups. A 4′-hydroxyl group is not tolerated.[18] Heavier halides, such as iodo and bromo, are needed at the 6-position, while electron-donating groups, such as tertiary amino, are not tolerated. A substituent at the 3-position abolishes affinity.

We have previously evaluated the tertiary amines, ^{18}F-labeled FEM-IMPY [*N*-(2-fluoroethyl)-4-(6-iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-methylbenzeneamine], and its 3-fluoropropyl analogue, ^{18}F-labeled FPM-IMPY (Figure 2), as PET radioligands for Aβ plaques.[18] These analogues have somewhat lower affinity than **12a** itself (Table 1). After intravenous injection of either radioligand into rodent or monkey, there was rapid and high uptake of radioactivity into the brain followed by biphasic clearance comprising fast and very slow components. Metabolism was rapid and shown to involve dealkylation of the tertiary arylamino group plus defluorination, culminating respectively in residual activity from radiometabolites in brain and high uptake of radioactivity ([^{18}F]fluoride ion) in bone, including skull. Both metabolic features would confound attempts to measure brain radioligand-Aβ binding accurately in vivo. Here, we report the synthesis and evaluation in vitro of a further extensive series of **12a** derivatives in our continuing effort to develop more effective PET radioligands for imaging Aβ plaques in AD patients.

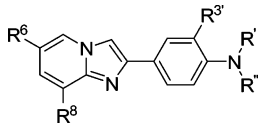
Results and Discussion

Chemistry. In all cases the imidazo[1,2-*a*]pyridine nucleus was created through condensation of an α-bromoketone with a 2-aminopyridine or 2-aminopyrazine in the manner described previously for the synthesis of **12a**.[18] A variety of substituents are acceptable in either reactant.

Syntheses of α-Bromoketones. α-Bromoketone **4a** was prepared by ortho bromination of 1-(4-methylaminophenyl)-ethanone (**1**)[18] with *N*-bromosuccinimide (NBS),[19] N-protection with a trifluoroacetyl group, and finally α-bromination[20] with copper(II) bromide (Scheme 1).

α-Bromoketones **4b** and **4c** were prepared by protecting the arylamino groups in **5b** and **5c** with a trifluoroacetyl group and

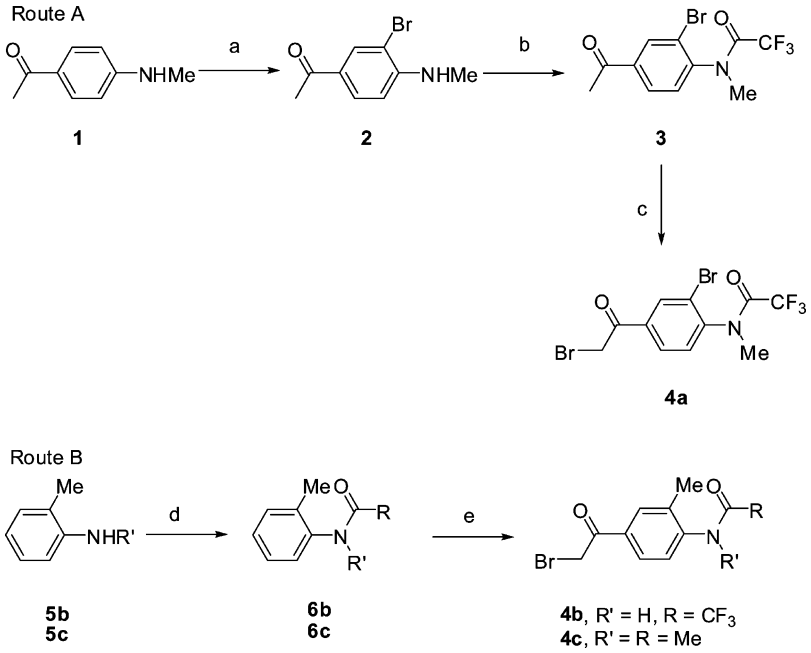
Table 1. Binding Affinity (K_I Values) of **12a** Derivatives (imidazopyridines)



ligand	R′	R″	R$^{3'}$	R^6	R^8	cLogD$_{7.4}$ [a]	K_I (nM)[b]
12a (IMPY)	Me	Me	H	I	H	4.37 ± 0.88	8.9 ± 0.7
12b	Me	Me	H	Br	H	4.11 ± 0.88	5.9 ± 0.4
12c	Me	Me	H	Cl	H	3.93 ± 0.84	24.2 ± 5.6
12d	Me	Me	H	F	H	3.38 ± 0.88	13.0 ± 1.6
12e	Me	Me	H	CN	H	2.80 ± 1.31	8.2 ± 1.0
12f	Me	Me	H	NO_2	H	3.09 ± 1.30	7.6 ± 0.7
12g	Me	Me	H	OMe	H	3.05 ± 1.30	38.5 ± 5.0
12h	Me	Me	H	SEt	H	4.24 ± 1.31	8.3 ± 0.5
12i	Me	Me	H	Br	I	5.17 ± 0.93	183 ± 61
12j	Me	Me	H	Br	CN	3.28 ± 1.35	>180
12k	Me	Me	H	OH	H	1.26 ± 1.29	177 ± 31
13a	CF_3CO	Me	Br	Br	H	4.88 ± 1.16	>1000
13b	CF_3CO	H	Me	Br	H	4.78 ± 1.06	>1000
13c	MeCO	Me	Me	Br	H	3.44 ± 0.91	>1000
14a	H	Me	Br	Br	H	4.30 ± 0.94	7.4 ± 0.6
14b	H	H	Me	Br	H	3.28 ± 0.87	658 ± 47
14c	H	Me	Me	Br	H	4.16 ± 0.88	>1000
15a	H	Me	H	SCH_2CONH_2	H	1.59 ± 1.33	1840 ± 497
15b	H	Me	H	$S(CH_2)_2OH$	H	2.54 ± 1.35	645 ± 75
15c	Me	Me	H	SCH_2CONH_2	H	2.02 ± 1.33	391 ± 76
15d	Me	Me	H	$SCH_2C_6H_4$*p*-OMe	H	4.76 ± 1.35	8.3 ± 1.8
15e	Me	Me	H	$S(CH_2)_2OH$	H	2.96 ± 1.35	88 ± 6
15f	H	Me	Me	SCH_2CONH_2	H	2.12 ± 1.33	>1000
15g	H	Me	Me	$S(CH_2)_2OH$	H	3.07 ± 1.35	>1000
FEM-IMPY	Me	$(CH_2)_2F$	H	I	H	4.52 ± 0.92	31 ± 5
FPM−IMPY	Me	$(CH_2)_3F$	H	I	H	4.90 ± 0.92	41 ± 5

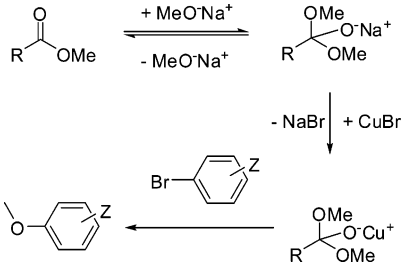
[a] Calculated with ACD/LogD, version 9.02 (Advanced Chemistry Development, Inc., Toronto, Canada). [b] Measured in triplicate with results given as the mean ± SD.

Scheme 1. Synthesis of α-Bromoketones[a]

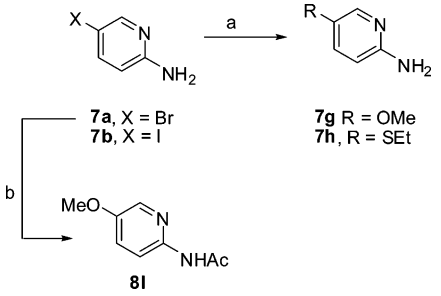


[a] Reagents and conditions: (a) NBS, CH_2Cl_2, room temp, 91%; (b) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, room temp, 96%; (c) $CuBr_2$, EtOAc, reflux, 4 h, 34%; (d) $(RCO)_2O$, Et_3N, CH_2Cl_2, 90−95% for both **6b** and **6c**; (e) $BrCH_2COBr$, $AlCl_3$, reflux, overnight, 38% for **4b**, 48% for **4c**.

Scheme 2. Copper(I) and Ester-Catalyzed Methoxide Substitution



Scheme 3. Synthesis of New 2-Aminopyridine Derivatives[a]

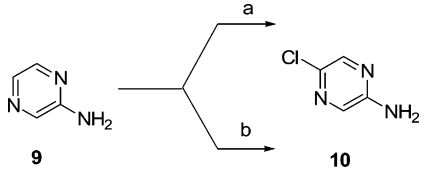


[a] Reagents and conditions: (a) For **7g**: **7a**, RNa, Cu powder, methanol, 135 °C, 14 h, 36%, or RNa, Cu powder, DMF, microwave, 75 W, 140 °C, 30 min, 17%. For **7h**: **7b**, RNa, Cu powder, ethylene glycol, 150 °C, 26 h, 76%. (b) AcOEt, CuCl, MeONa, MeOH.

acetyl group, respectively, followed by Friedel−Crafts acylation with bromoacetyl bromide catalyzed by $AlCl_3$ in CS_2[21−23] (Scheme 1).

Syntheses of 2-Aminopyridines and 2-Aminopyrazines. Attempts to prepare 5-methoxypyridin-2-amine (**7g)** by nucleophilic aromatic displacement of a bromo substituent with a methoxy group, catalyzed conventionally by copper powder[24] with microwave heating or with an ultrasound bath, were frustrated by lack of reactivity in the starting 2-amino-5-bromopyridine (**7a)**. Another procedure[25] for performing aromatic substitution with the methoxy anion was therefore

Scheme 4. Synthesis of 5-Chloro-2-aminopyrazine[a]



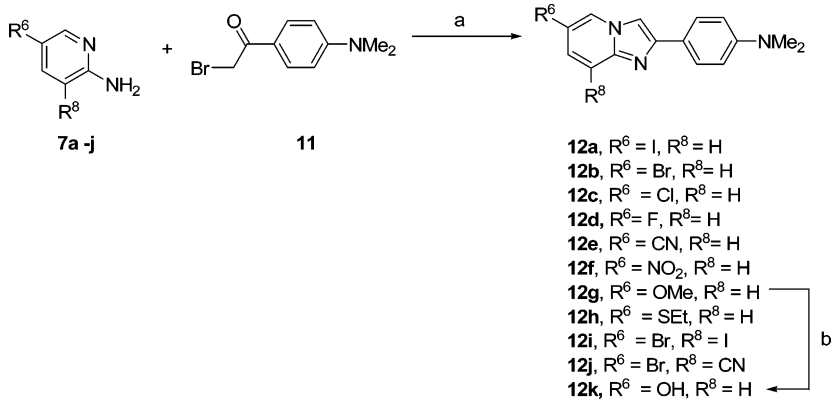
[a] Reagents and conditions: (a) NCS (0.5 equiv), $CHCl_3$, reflux 2 h, 26%; (b) NCS (0.6 equiv), $CHCl_3$, microwave, 60 W, 10 min, 70 °C, 45%.

attempted. This method uses a copper(I) salt and a small amount of ester to form a stabilized tetrahedral adduct that acts as a powerful methoxide donor (Scheme 2). Unfortunately, because of the presence of the free amino group in **7a** and the use of ethyl acetate as cocatalyst, the reaction produced the undesired acetamide **8l** (Scheme 3). We considered that the copper(I) had been inactivated by coordination to the nitrogen atoms of the substrate. By increasing the number of equivalents of catalyst, we obtained the expected product **7g** in 36% yield after a 14 h reaction (Scheme 3). A significant amount of starting material remained together with black polymers. The reaction was quenched after 14 h to avoid further polymerization and product degradation. In order to decrease the reaction time, the transformation in Scheme 3 was also performed with microwave irradiation but at the cost of lower yield.

A previously reported synthesis of 5-(ethylthio)pyridine-2-amine **7h**[26,27] made use of copper as catalyst and methanol as solvent at 150 °C under pressure.[28] The inconvenience of this procedure prompted us to evaluate other solvents to replace the low boiling point methanol. Ethylene glycol has been noted to be beneficial as a solvent in other copper or copper(I) catalyzed reactions.[29] We found ethylene glycol to be an excellent solvent for the reaction of **7b** to give a high yield of **7h** (Scheme 3).

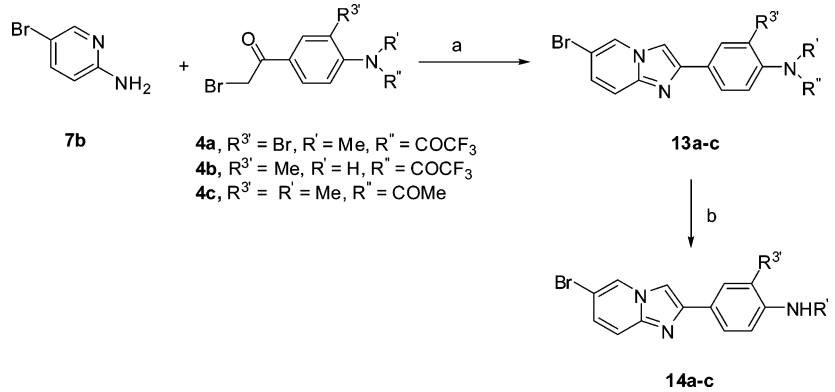
The synthesis of 5-chloro-2-aminopyrazine **10** described in the literature is an inefficient multistep process.[30] Direct chlorination of 2-aminopyrazine with *N*-chlorosuccinimide (NCS) in refluxing chloroform gave a black polymer after a few minutes, with undesired 3,5-dichloro-2-aminopyrazine as

Scheme 5. Synthesis of Tertiary Amino **12a** Derivatives[a]



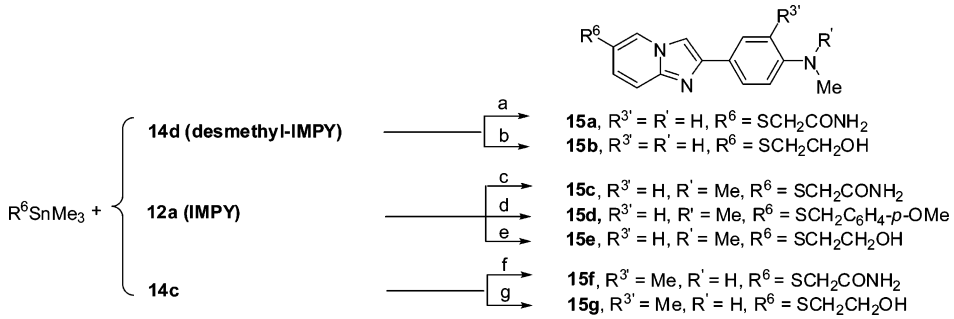
[a] Reagents and conditions: (a) $NaHCO_3$, ethanol or acetonitrile, 5−11 h, reflux, yields 23−65%; (b) BBr_3, CH_2Cl_2, room temp for 2 h, 70%.

Scheme 6. Synthesis of Secondary Amino "Isosteres" of **12a**[a]



[a] Reagents and conditions: (a) $NaHCO_3$, ethanol, 8−12 h, reflux, yields 28−59%; (b) K_2CO_3 or KOH, EtOH, 8−12 h, reflux, yields 77−80%.

Scheme 7. Synthesis of 6-Thioether **12a** Derivatives from 6-Halo-IMPY Derivatives[a]



[a] Reagents and conditions: The general conditions are $Me_3Sn-NMe_2$, $Pd_2(dba)_3$, DiPPF, toluene, and microwave; (a) $HSCH_2CONH_2$, 78%; (b) $HSCH_2CH_2OH$, 91%; (c) $HSCH_2CONH_2$, 85%; (d) $HSCH_2C_6H_4OCH_3$, 85%; (e) $HSCH_2CH_2OH$, 89%; (f) $HSCH_2CONH_2$, 69%; (g) $HSCH_2CH_2OH$, 69%.

the main product (14%) after 2 h. Only a low yield of **10** (4%) was isolated. To avoid overchlorination, milder conditions were examined. No reaction was observed at room temperature, but even at 50 °C complete transformation into 3,5-dichloro-2-aminopyrazine occurred. Pretreatment of the solvent, distilled chloroform, by passage over basic alumina drastically reduced the formation of black polymers. When NCS was added slowly into the refluxing 2-aminopyrazine, **10** was isolated in 26% yield. Moreover, when microwave irradiation was used at 70 °C for 10 min, the yield reached 45% (Scheme 4).

Syntheses of 12a Derivatives. Most of the new **12a** derivatives (**12a**−**j**, **13a**−**c**) were synthesized through direct condensations of α-bromoketones with 2-amino-pyridines (Scheme 5).[18] In examples where a trifluoroacetyl group was used to protect the arylamino group (**13a**,**b)**, no base was needed for the condensation.

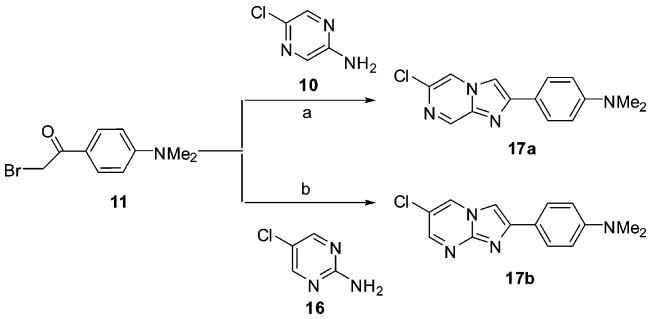
The synthesis of the 6-hydroxy compound **12k** was through demethylation of the methoxy group in **12g**. The most effective reagent to perform the reaction was BBr_3 in CH_2Cl_2 (Scheme 5).[31]

The *N*-trifluoroacetyl group in **13a**,**b** or acetyl group in **13c** was easily removed under basic conditions (Scheme 6). This provided an excellent method for the synthesis of **12a** derivatives with a secondary (**14a**,**c**) or primary (**14b**) amino group.

We have recently developed the palladium-catalyzed substitution of halides by thiolate as a process that avoids halide reduction.[32] This new method was applied to the synthesis of several **12a** derivatives (**15a**−**g**) with a thiolate group in the 6-position (Scheme 7).

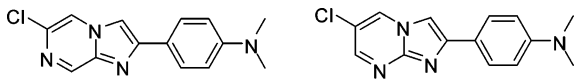
The imidazopyrazine **12a** analogue **17a** was synthesized through condensation of chloropyrazine **10** with the α-bromoacetophenone **11** (Scheme 8). Although **10** was very soluble

Scheme 8. Syntheses of 6-Chloroimino **12a** Analogues[a]



[a] Reagents and conditions: (a) $NaHCO_3$, MeCN, reflux, 9 h, 7%; (b) $NaHCO_3$, MeCN−DMF, reflux, 9 h, 23%.

Table 2. Affinity (K_I Values) of **12a** Derivatives (N for CH Analogues)



compd	$cLogD_{7.4}$ [a]	K_I (nM)[b]
17a	2.54 ± 1.30	88 ± 22
17b	3.14 ± 1.43	147 ± 20

[a] Calculated with ACD/LogD, version 9.02 (Advanced Chemistry Development, Inc., Toronto, Canada). [b] Measured in triplicate with results given as the mean ± SD.

in acetonitrile, it was very unreactive; **17a** was obtained in only 7% yield. Longer reaction times and stronger bases such as triethylamine failed to improve the yield.

Separation was difficult in the synthesis of the imidazopyrimidine **12a** analogue **17b**. When excess amine was used, the product could not be separated from the starting amine. When excess α-bromoketone was used, starting pyrimidine persisted. A small amount of DMF was added to the reaction mixture to dissolve the amine completely and to induce precipitation of the product. By filtering this solution while hot, even before the reaction was complete, we were able to isolate the desired **17b** in a 23% yield (Scheme 8).

In Vitro Assay. Determination of the binding affinities of new ligands for Aβ plaques is the first step in selecting candidate radioligands for PET studies in humans. Three types of Aβ plaques have been used to assay ligand binding affinity in vitro, namely, (i) synthetic aggregates of $A\beta_{1-40}$ or $A\beta_{1-42}$, (ii) Aβ plaques from transgenic rodents, and (iii) amyloid plaques from human AD brain tissue. Binding site concentration varies across the three types of plaques and between different batches of synthetic aggregates.[14] These findings may reflect variations in binding site architecture, although no significant difference in ligand binding affinity has been detected between synthetic aggregates and human Aβ plaques for the binding site typical of PIB.[33] Since our ultimate goal is to develop a sensitive radioligand for imaging Aβ plaques in the human AD brain, in vitro evaluation using human AD brain tissue, as described and used in this study, is clearly the most appropriate.

Structure−Affinity Relationships. The binding affinities (K_I values) at human Aβ plaques are listed in Tables 1 and 2 for **12a** and its derivatives. Comparison of the K_I values in direct analogues of **12a**−**h**,**k** and **15c**−**e** in which the 6-substituent was varied reveals that the binding site in Aβ plaques tolerates bulky thioether substituents [e.g., SEt (**12h**), $SCH_2C_6H_4$–*p*-OMe (**15d**)], provided that they are not hydrophilic [e.g., SCH_2CONH_2 (**15c**), $S(CH_2)_2OH$ (**15e**)]. An alkyl thiolate group appears to mimic the effect of an iodo or bromo substituent well, as reflected in the very close binding affinities of **12a**, **12b**, and **12h**. The polarizability of the sulfur atom is likely important because previously described **12a** derivatives bearing 2-fluoroethyl and 3-fluoropropyl substituents in the 6-position have a much lower affinity than **12a** itself.[16]

From the standpoint of developing new PET radioligands, the discovery that even bulky thioether substituents may be tolerated in the 6-position has considerable importance. A light alkyl thiolate group imparts hydrophobicity similar to that of the iodo substituent in **12a** (cf. cLogP values for **12a** and **12h**, Table 1). Furthermore, a thioalkyl functional group provides a site for convenient and efficient labeling with a positron emitter, such as carbon-11 or fluorine-18, for example, by S-alkylation with such well-known labeling agents as [^{11}C]iodomethane,[34,35] [^{11}C]methyl triflate,[36] ω-[^{18}F]fluoroalkyl halides,[37] or ω-[^{18}F]-fluoroalkyl tosylates.[38]

Steric bulk in the 6-position is not, however, a requirement for high affinity, since the 6-fluoro analogue (**12d)** has only marginally less affinity than the highest affinity compounds. Polarizable [e.g., Br (**12b**), I (**12a**)] or electron-withdrawing 6-substituents [e.g., F (**12d**), CN (**12e**), NO_2 (**12f**)] favor high affinity, while strongly electron-donating substituents [e.g., OMe (**12g**), OH (**12k**)] reduce affinity, as observed previously for Me and NMe_2 substituents.[15] The nitrile **12e** is of special interest with respect to PET radioligand development, since it has a high affinity similar to that of **12a** itself, lower computed lipophilicity ($cLogD_{7.4}$, Table 1), and the potential for labeling with carbon-11, either in the nitrile group with cyclotron-produced [^{11}C]cyanide[39−43] or in the *N*-methyl position with [^{11}C]methyl triflate.[44]

Generally, the tertiary *N*,*N*-dimethylamino analogues of **12a** were found to have a much higher affinity than their secondary methylamino analogues (cf. **12b** vs **14c**, **15c** vs **15a**, **15e** vs **15b**), in accord with the previously limited data on tertiary and secondary amino analogues.[17] An exceptionally high-affinity secondary amino analogue was found to be that with a bromo substituent in the 3′-position (i.e., ortho to the secondary amino group) (**14a**). This analogue may be regarded as "isosteric" with the tertiary amino analogue with hydrogen as the 3′-substituent (**12b**). However, the binding affinity is abolished in the secondary amino analogue bearing a methyl group in the 3′-position (**14c**). The detrimental effect of a 3′-methyl group was repeated in the secondary amino analogues **15f** and **15g** (cf. with the corresponding tertiary amines **15c** and **15e**, respectively). In fact, **15f** and **15g** had lower affinity than the corresponding analogues bearing hydrogen in the 3′-position, namely, **15a** and **15b**, respectively. Since a methyl group is almost isosteric with a bromo substituent, the beneficial effect of the 3′-bromo substituent in **14a** must involve one or more properties other than steric (e.g., substituent electronics or polarizability). The secondary arylamino group in **14a** is expected to be more robust to oxidative metabolism in vivo than the tertiary amino group in **12a**. Hence, **14a**, labeled with carbon-11 in the *N*-methyl position, may be of interest for evaluation as a prospective PET radioligand.

The effect of a substituent at the 8-position was evaluated in **12i** and **12j**. Both iodo and cyano substituents reduced the binding affinity dramatically, indicating low tolerance of the binding site for even moderately bulky substituents in this position.

Increasing the size of substituents on the arylamino group decreases binding affinity, as reflected in **12a**, FEM-IMPY, and FPM-IMPY.[18] This shows moderate tolerance for steric bulk at

this location. An amido group at this position as in **13a**−**c** is not, however, tolerated.

Substitution of aryl CH by an imino group as in **17a** and **17b** is effective in reducing ligand lipophilicity **(**compare $cLogD_{7.4}$ values with that of the analogue **12c**, Table 1) but drastically reduces binding affinity, regardless of the position of nitrogen atom insertion.

Binding Site Topography. Knowledge of the topography of the binding site in Aβ plaques for **12a**-like ligands would be helpful for the design of improved ligands. Although the detailed structure of Aβ plaques is unknown, a model derived from solid-state NMR has been proposed.[45] Also, computer modeling of the binding interaction between *trans*-stilbene derivatives, similar to SB13, and the Aβ plaque model has been reported recently.[46] A strong quantitative correlation between ligand binding affinity and molecular properties (HOMO energy, charge, molecular volume, and cLogP) has been established. There are multiple binding sites in Aβ plaques,[17] and the computer modeling study only considered one type of binding site, that for stilbenes. However, the observed SAR of **12a** derivatives has striking similarities with that observed and computed for the stilbenes. For example, the highest affinity compounds carry a *p*-*N*,*N*-dimethylamino group. Bulkier amino groups or those containing ω-fluoroalkyl groups tend to have lower affinity, as do primary amino groups or nonbasic groups. This correspondence in SAR supports the notion that **12a** and stilbene-type ligands (e.g., SB13) occupy the same binding site within the Aβ plaques. By inference, PIB also occupies the same binding site, since **12a** and stilbene derivatives compete with PIB for binding. According to findings from this and previous SAR studies, this site appears to be hydrophobic, flat, and narrow. There is little tolerance for an extra hydrophilic feature within the molecular core or for substituents that may disrupt coplanarity. There is a high restriction on the molecular width of the ligand, since substantial changes in only the 6- or 3′-position substituents of **12a** are tolerated. This study shows that ligands elongated with hydrophobic 6-substituents bonded to the molecular core with a polarizable sulfur atom retain high affinity. This indicates the binding site to be an extensive narrow channel. The long axis of the ligand most likely aligns with the long axis of peptide chains, as previously proposed for stilbene ligands.[46] Such a parallel alignment would probably favor $\pi-\pi$ interactions and electron transfer between ligand and plaque.

Conclusions

We have identified synthetic strategies to overcome problems encountered in our initial investigation of **12a** derivatives as PET radioligands for imaging β-amyloid. High-affinity ligands, including those with thiolate substituents in the 6-position, have been discovered, opening up possibilities for developing new easily labeled candidate radioligands for imaging human Aβ plaques in vivo. These possibilities are now actively pursued. The SAR findings aid further in demonstrating the topography of the ligand binding site in human Aβ plaques.

Experimental Procedures

Reagents and Chemicals. Common reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI), Fluka Chemical Company (Milwaukee, WI), Acros (Hampton, NH), or Strem Chemicals (Newburyport, MA) and were used without further purification unless otherwise indicated. DiPPF (1,1′-bis(diisopropylphosphino)ferrocene) was from Strem Chemicals. *o*-Toluidine (**5b**), 5-bromopyridin-2-amine (**7a**), 5-iodopyridin-2-amine (**7b**), 5-chloro-2-aminopyridine (**7c**), 5-fluoro-2-aminopyridine (**7d**), pyrazin-2-amine (**9**), 2-mercaptoethanol, 2-bromoacetyl bromide, *N*-methyl-*N*-(trimethylstannyl)methanamine, sodium methoxide, and Pd_2dba_3 were from Aldrich. 2-Mercaptoacetamide and 6-aminopyridine-3-carbonitrile (**7e**) were from Acros. 5-Chloropyrimidin-2-imine (**16**) was from Alfa Aesar (Ward Hill, MA). 4-(6-Bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (**12b)** was obtained from Bioassay Systems (Hayward, CA). Water was purified through a Millipore purification system, comprising two filters, one Rio, one reservoir, and one Milli-Q synthesis system (Bedford, MA). Common solvents were obtained from Fisher Scientific (Pittsburgh, PA). Brain tissue from deceased AD patients was obtained from the Brain Collection of the Clinical Brain Disorders Branch, National Institute of Mental Health, National Institutes of Health (see below).

1-(4-(Methylamino)phenyl)ethanone (**1**),[18] *N*,2-dimethylbenzenamine (**5c**),[47,48] 2,2,2-trifluoro-*N*-*o*-tolylacetamide (**6b**),[49] *N*-methyl-*N*-*o*-tolylacetamide (**6c**),[50] 4-bromoacetyl-*N*,*N*-dimethylbenzeneamine (**11**),[18] 5-bromo-3-iodopyridin-2-amine (**7i**),[51] 2-amino-5-bromonicotinonitrile (**7j**),[20] IMPY (**12a**),[15] desmethyl-IMPY (**14d**),[18] and PIB (2-(4′-methylaminophenyl)-6-hydroxybenzothiazole)[14] were synthesized as reported. [^{3}H]PIB ([*N*-methyl-$^3H_3$]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, 80 Ci per mmol) was obtained from GE Healthcare (www.customlabelling.com).

Instruments and General Conditions. Analytical HPLC was performed with a reverse-phase column (X-Terra C18, 5 μm, 10.0 mm × 250 mm; Waters, Milford, MA) eluted with concentrated ammonia (0.25%) in acetonitrile−water at 6.2 mL/min. The chromatography system was fitted with an autosampler (System Gold 508 model, Beckman; Fullerton, CA) and a continuous wavelength UV−vis detector (System Gold 168 model, Beckman). For semipreparative HPLC, a Beckman system was fitted with a manual injector (5 mL injection loop) and a third delivery pump eluted at 1 mL/min. For reverse-phase semipreparative HPLC, an X-Terra C18 column (5 μm, 19 mm × 250 mm, Waters) was eluted with concentrated ammonia (0.25%) in acetonitrile−water at 20 mL/min. Acetonitrile was used as delivery solvent. For normal phase semipreparative HPLC, a silica gel column (10 μm, 21.2 mm × 250 mm, Phenomenex; Torrance, CA) was eluted with triethylamine (0.25%) in chloroform−ethyl acetate at 30 mL/min. Ethyl acetate was used as the delivery solvent. The purity of the compounds was determined with HPLC monitored for UV absorbance at 280 nm (for **12a** derivatives) or 254 nm (for other aromatic compounds) and expressed as an area percentage of all peaks. The ^{1}H and ^{13}C NMR spectra of all compounds were acquired on a Jeol GSX 270 (270 MHz ^{1}H), Bruker DRX 300 (300 MHz ^{1}H), Bruker DRX 400 (400 MHz ^{1}H and 100 MHz ^{13}C), or Bruker AM500 (500 MHz ^{1}H and 125 MHz ^{13}C) instrument, using the chemical shifts of residual deuterated solvent as the internal standard. Chemical shift (δ) data for the proton and carbon resonances were reported in parts per million (ppm) relative to the internal standard. Thin-layer chromatography (TLC) was performed with silica gel 60 F254 plates (EM Science), and compounds were visualized under UV light (250 or 360 nm). Flash column chromatography (FCC) was performed with a Horizon HPFC system (Biotage; Charlottesville, VA; column sizes 12 mm × 150 mm, 25 mm × 150 mm, 40 mm × 150 mm) with hexanes−ethyl acetate mixtures as eluents; all later mentioned solvent proportions are expressed as volume per volume. Mass spectra were acquired using either a LCQ^{DECA} LC−MS instrument (Thermo Finnigan; San Jose, CA) fitted with a Luna C18 column (5 μm, 2.0 mm × 150 mm; Phenomenex) and with elution with a methanol−water mixture at 150 μL/min or a PolarisQ GC−MS instrument (Thermo Finnigan; San Jose, CA) equipped with a capillary RTX-5ms column (30 m × 0.25 mm; flow rate: 1 mL/min, carrier gas: He), or VG Micromass 7070E and AutoSpec-Q spectrometers. High-resolution mass spectra (HRMS) were acquired from the Mass Spectrometry Laboratory, University of Illinois at Urbana−Champaign (Urbana, IL). Melting points were measured using a Mel-Temp manual melting point apparatus (Electrothermal, Fisher Scientific) and are uncorrected. A Discover microwave apparatus (CEM, Matthews, NC) was used for microwave-promoted synthesis.

1-(3-Bromo-4-(methylamino)phenyl)ethanone (2). 1-(4-Methylaminophenyl)ethanone[18] (**1**, 2.98 g, 20 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 4 °C with an ice−water bath. *N*-Bromosuccinimide (NBS, 3.65 g, 20.5 mmol) was added portionwise. The reaction mixture was warmed to room temperature and stirred for 2 h. Reaction progress was monitored with TLC until completion. At the end of reaction, water (50 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried with Na_2SO_4. The solvent was removed to leave the crude product, which was further purified on silica gel (ethyl acetate−petroleum ether (1: 3)) to give **2** (4.15 g, 91%): mp 80−83 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.81 (dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 6.65 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar−H), 6.22 (m, 1H, N−H), 2.83 (d, $^3J_{HH}$ = 4.8 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 198.1 (s, 1C, CO), 151.9, 134.3, 131.6, 127.4, 110.2, 109.3, 30.3 (CH_3), 26.0 (CH_3). *m*/*z* (EI-MS): 230.0 (5%), 229.0 (48%), 228.0 (7%), 227.0 (50%, $[M + H]^+$), 215.0 (10%), 214.0 (96%), 213.0 (10%), 212.0 (100%), 186.0 (7%), 184.0 (8%), 105.1 (25%), 104.1 (13%), 77.1 (12%), 63.0 (8%). HRMS *m*/*z* (EI^+): calcd $C_9H_{10}ONBr$ = 226.9946. Found: 226.9942. Error (ppm): −0.4.

***N*-(4-Acetyl-2-bromophenyl)-2,2,2-trifluoro-*N*-methylacetamide (3).** 1-(3-Bromo-4-(methylamino)phenyl)ethanone (**2**, 1.4 g, 6.14 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Trifluoroacetic anhydride (1.9 g, 9.21 mmol) and Et_3N (0.93 g, 9.21 mmol) were added sequentially. The mixture was stirred at room temperature for 3 h, washed thrice with water, and dried over Na_2SO_4. The solvent was removed and the residue dried to afford **3** (1.9 g, yield 96%) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ isomer α (amide rotamers) (82%) 8.32 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.07 (dd, $^3J_{HH}$ = 8.2 Hz,$^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.90 (s, 1H, Ar−H), 7.65 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar−H), 3.32 (s, 3H, CH_3), 2.64 (s, 3H, CH_3). Isomer β (18%) 8.31(d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.09 (dd, $^3J_{HH}$ = 8.2 Hz,$^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.90 (s, 1H, Ar−H), 7.58 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar−H), 3.31 (q, $^5J_{FH}$ = 1.6 Hz, 3H, CH_3), 2.63 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ isomer α 197.7 (s, 1C, CO), 157.7 (q, $^2J_{CF}$ = 36.4 Hz, 1C, CO), 144.6, 140.6, 134.6, 131.6, 130.0, 124.8, 117.6 (q, $^1J_{CF}$ = 288 Hz, 1C, CF_3), 38.4 (s, 1C, CH_3), 26.9 (s, 1C, CH_3). Isomer β 197.9 (s, 1C, CO), 157.7 (q, $^2J_{CF}$ = 36.4 Hz, 1C, CO), 146.2, 140.1, 134.7, 131.6, 130.5, 123.1, 117.6 (q, $^1J_{CF}$ = 288 Hz, 1C, CF_3), 38.3 (s, 1C, CH_3), 26.0 (s, 1C, CH_3). *m*/*z* (ES-MS): 348.0 (11%), 346 (11%), 343.0 (7%), 341.0 (10%), 326.0 (87%), 324.0 (100%, $[M + H]^+$), 269.1 (4%), 268.1 (61%), 263.1 (13%), 246.1 (83%). HRMS *m*/*z* (TOF^+): calcd $C_{11}H_{10}NO_2F_3Br$ = 323.9847. Found: 323.9843. Error (ppm): −1.2.

***N*-(2-Bromo-4-(2-bromoacetyl)phenyl)-2,2,2-trifluoro-*N*-methylacetamide (4a).** $CuBr_2$ (6.0 g, 26.9 mmol) was suspended in ethyl acetate (20 mL) and heated to reflux. A solution of *N*-(4-acetyl-2-bromophenyl)-2,2,2-trifluoro-*N*-methylacetamide (**3**, 4.5 g, 13.9 mmol) in $CHCl_3$ (20 mL) was added. The mixture was refluxed for 4 h and filtered. The solvent was removed from the filtrate to give an orange solid, which was purified by silica gel column chromatography (ethyl acetate−petroleum ether from 1:100 to 1:50) to afford **4a** (1.9 g, yield 34%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ isomer α (80%) 8.33 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.02 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.48 (dd, $^3J_{HH}$ = 8.2 Hz, $^5J_{HH}$ = 0.5 Hz, 1H, Ar−H), 4.46 (AB, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2), 4.42 (AB, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2), 3.36 (d, $^4J_{HF}$ = 0.4 Hz, 3H, CH_3). Isomer β (20%) 8.33 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 8.05 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.44 (dd, $^3J_{HH}$ = 8.2 Hz, $^5J_{HH}$ = 0.5 Hz, 1H, Ar−H), 4.46 (AB, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2), 4.42 (AB, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2), 3.49 (q, $^4J_{HF}$ = 1.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ isomer α 189.0 (s, 1C, CO), 156.5 (q, $^2J_{CF}$ = 34.6 Hz, 1C, CO), 143.9, 135.7, 134.3, 130.4, 129.0, 124.1, 115.9 (q, $^1J_{CF}$ = 287 Hz, 1C, CF_3), 37.9 (s, 1C, CH_3), 30.0 (s, 1C, CH_2). Isomer β 189.1 (s, 1C, CO), 156.5 (q, $^2J_{CF}$ = 34.6 Hz, 1C, CO), 145.5, 135.4, 134.6, 129.5, 129.3, 123.8, 116.2 (q, $^1J_{CF}$ = 287 Hz, 1C, CF_3), 37.7 (s, 1C, CH_3), 29.9 (s, 1C, CH_2). *m*/*z* (EI-MS): 406.0 (<1%), 404.9 (<1%), 403.0, (<1%), 401.9 (<1%, $[M + H]^+$), 401.0 (<1%), 399.9 (<1%), 325.0 (12%), 324.0 (79%), 323.0 (12%), 322.0 (81%), 310.0 (26%), 308.0 (27%), 244.1 (32%), 215.1 (8%), 201.1 (14%), 170.0 (3%), 132.1 (5%), 110.0 (100%), 77.1 (11%). HRMS *m*/*z* (EI^+): calcd $C_{11}H_9NO_2F_3Br_2$ = 401.8952. Found: 401.8954. Error (ppm): +0.2. Calcd $C_{11}H_8NO_2F_3Br_2$ = 401.8874. Found: 401.8874. Error (ppm): 0.0.

***N*-(4-(2-Bromoacetyl)-2-methylphenyl)-2,2,2-trifluoroacetamide (4b).** 2,2,2-Trifluoro-*N*-*o*-tolylacetamide (**6b**, 5.0 g, 24.6 mmol) was dissolved in CS_2 (20 mL) and cooled below 10 °C. Bromoacetyl bromide (10.1 g, 50.0 mmol) was added dropwise. $AlCl_3$ (10.0 g, 75.0 mmol) was added in portions, with a drying tube attached to the reaction flask. The reaction mixture was refluxed overnight. After the reaction was complete as monitored by TLC, the upper CS_2 layer was removed. The lower layer was added to ice−water (7.0 mL) and concentrated HCl (1.0 mL). The product was extracted into CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed and the solid was dried to afford crude product (5.0 g), which was purified by silica gel column chromatography to afford **4b** (3.0 g, yield 38%) as a yellow solid: mp 127−130 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H, Ar−H), 7.83 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.78 (s, 1H, NH), 7.39 (d, $^3J_{HH}$ = 7.8 Hz, 1H, Ar−H), 4.41 (s, 2H, $-CH_2-$Br), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (s, 1C, CO), 155.3 (q, $^2J_{CF}$ = 37.6 Hz, 1C, CO), 137.1, 133.4, 133.1, 131.6, 127.6, 124.1, 115.8 (q, $^1J_{CF}$ = 289 Hz, 1C, CF_3), 30.6 (s, 1C, CH_2), 17.9 (s, 1C, CH_3). *m*/*z* (ES-MS): 353.4 (5%), 352.9 (23%), 352.4 (12%), 351.9 (50%), 351.4 (8%), 350.9 (24%), 326.0 (94%), 324.0 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{11}H_{10}NO_2F_3Br$ = 323.9847. Found: 323.9853. Error (ppm): +1.9.

***N*-(4-(2-Bromoacetyl)-2-methylphenyl)acetamide (4c).** The synthetic procedure was the same as that for **4b** but started from **6c**. Yield 48%; mp 144−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ isomer α (93%) 7.85 (dd, $^3J_{HH}$ = 7.9 Hz,$^4J_{HH}$ = 1.8 Hz, 1H. Ar−H), 7.74 (d, $^4J_{HH}$ = 1.8 Hz, 1H. Ar−H), 7.41 (d, $^3J_{HH}$ = 8.0 Hz, 1H. Ar−H), 4.40 (AB, $^2J_{HH}$ = 11.6 Hz, 1H, CH_2), 4.34 (AB, $^2J_{HH}$ = 11.7 Hz, 1H, CH_2), 3.15 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 1.73 (s, 3H, CH_3). Isomer β (7%) 7.82 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.9 Hz, 1H. Ar−H), 7.72 (d, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.33 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 4.65 (AB, $^2J_{HH}$ = 14.4 Hz, 1H, CH_2), 4.61 (AB, $^2J_{HH}$ = 14.4 Hz, 1H, CH_2), 3.29 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.73 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ isomer α 190.3 (s, 1C, CO), 170.5 (s, 1C, CO), 143.8, 142.6, 133.6, 132.2, 128.9, 128.8, 36.0 (s, 1C, CH_2), 30.5 (s, 1C, CH_3), 22.2 (s, 1C, CH_3), 17.9 (s, 1C, CH_3). Isomer β 190.2 (s, 1C, CO), 170.6 (s, 1C, CO), 143.8, 142.7, 133.9, 131.7, 128.5, 128.4, 45.7 (s, 1C, CH_2), 39.1 (s, 1C, CH_3), 30.9 (s, 1C, CH_3), 18.2 (s, 1C, CH_3). *m*/*z* (CI−MS): 358.0 (7%), 332.1 (36%), 330.1 (39%), 302.1 (19%), 300.1 (19%), 287.1 (14%), 286.1 (93%), 285.1 (15%), 284.1 (99%, $[M + H]^+$), 250.2 (9%), 236.1 (28%), 218.1 (14%), 206.1 (57%), 205.1 (13%), 204.1 (40%), 190.1 (7%), 176.1 (4%), 148.1 (9%), 134.1 (3%), 120.1 (4%), 91.1 (4%), 77.1 (2%), 55.9 (10%). HRMS *m*/*z* (EI^+): calcd $C_{12}H_{14}NO_3Br$ = 283.0208. Found: 283.0210. Error (ppm): 0.2.

5-Methoxypyridin-2-amine (7g). Method a. 2-Amino-5-bromopyridine (**7a**, 0.10 g, 0.58 mmol), sodium methoxide (0.16 g, 2.9 mmol), and nanosized activated copper powder (0.11 g, 1.74 mmol) were introduced in a screw-cap vial (Pyrex glass) together with anhydrous MeOH (2.0 mL) and a stirrer bar. The vial was closed and put in an oil bath at 135 °C and stirred for 14 h. The mixture was cooled, diluted with MeOH (5.0 mL), and filtered through an SPE silica gel cartridge, and the product eluted with AcOEt. The fractions were collected and evaporated giving crude product (92 mg), which was further purified by FCC (CH_2Cl_2/AcOEt = 1:1) to give **7g** (26 mg, yield 36%) as a brown oil.

Method b. 2-Amino-5-bromopyridine (**7a**, 0.10 g, 0.58 mmol), sodium methoxide (0.16 g, 2.9 mmol), and nanosized activated copper powder (0.11 g, 1.74 mmol) were introduced into a microwave glass tube with anhydrous DMF (1.5 mL) and sealed. The tube was introduced into the microwave cavity and heated for 30 min at 140 °C (140C30M75W300Psi). Although DMF is a high boiling solvent, high pressure was observed, probably caused by

the partial methanolysis of the DMF, resulting in low-boiling products such as methyl formate and dimethylamine. The mixture was diluted with 2 M NH_4Cl solution (10 mL) and extracted thrice with AcOEt. The organic phase was washed twice with 2 M NH_4-Cl solution and once with water to remove the remaining DMF, dried on Na_2SO_4, and filtered. After the solvent was removed, the crude product was purified by FCC (AcOEt) to afford **7g** (12 mg, yield 17%) as a brown oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74 (1 H, d, $^3J_{HH}$ = 3.0 Hz), 7.06 (1H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 3.0 Hz), 6.45 (1 H, d, $^3J_{HH}$ = 9.0 Hz), 3.95 (2H, bs, NH_2), 3.74 (3H, s, OCH_3). *m*/*z* (EI-MS): 124 (M^+), 109 ([M − CH_3]$^+$).

5-(Ethylthio)pyridin-2-amine (7h).[28] 2-Amino-5-iodopyridine (**7b**, 2.20 g, 10 mmol), sodium ethanethiolate 80% (1.7 g, 16 mmol), and copper powder (190 mg, 3.00 mmol) were loaded into a 100 mL round-bottom flask under nitrogen. Ethylene glycol (40 mL, 0.25 mol) was added, and the solution was stirred at 150 °C for 26 h. The cooled solution was filtered and twice partitioned between ethyl acetate and water. The organic layer was dried over barium oxide and filtered and the solvent removed in vacuo to afford **7h** (1.2 g, yield 76%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.06 (1H, d, $^4J_{HH}$ = 2.1 Hz, Ar−H), 7.48 (1H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.4 Hz, Ar−H), 6.42 (1H, dd, $^3J_{HH}$ = 8.7 Hz, $^5J_{HH}$ = 0.6 Hz, Ar−H), 2.68 (2H, q, $^3J_{HH}$ = 7.3 Hz, CH_2), 1.15 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3).

5-Chloropyrazin-2-amine (10). Method a. In a double-necked dry flask equipped with condenser and dropping funnel under dinitrogen flow were added 2-aminopyrazine (**9**, 0.50 g, 5.25 mmol) and anhydrous $CHCl_3$ (13 mL) previously passed over basic Al_2O_3. This solution was heated at 60 °C with stirring. A solution of *N*-chlorosuccinimide (NCS, 0.35 g, 2.12 mmol) in anhydrous $CHCl_3$ (7 mL) was added to the mixture through a dropping funnel over 1.5 h. After another 30 min, the reaction was stopped and the solvent evaporated off. The residue was dissolved in methanol and adsorbed on silica gel (2 g). This crude product was purified by FCC (hexane/CH_2Cl_2/AcOEt, 1:1) to afford **10** (73 mg, yield 26%) as a yellow solid.

Method b. 2-Aminopyrazine (0.10 g, 1.05 mmol) and NCS (80 mg, 0.60 mmol) were added to a microwave tube with anhydrous $CHCl_3$ (1.5 mL) and sealed. The tube was placed in the microwave cavity and heated at 70 °C for 10 min (70C10M60W300Psi). After the workup, the crude product (0.15 g) was purified by FCC (hexane/CH_2Cl_2/AcOEt, 1: 1: 1) to afford **10** (35 mg, yield 45%) as a yellow solid. ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.99 (1H, s, H-6), 7.67 (1H, s, H-3), 6.65 (2H, bs, NH_2). *m*/*z* (EI-MS): 129 (M^+), 99, 94 ([M − Cl]$^+$).

4-(6-Chloro-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (12c). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)phenylethanone (**11)** (1.21 g, 5.00 mmol) and 5-chloro-2-aminopyridine (**7c**) (0.668 g, 5.20 mmol) were used to give **12c** (0.65 g, yield 48%): mp 234−236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, Ar−H), 7.81 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 7.70 (s, 2H, Ar−H), 7.19 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 6.76 (d, $^3J_{HH}$ = 8.6 Hz, 2H, Ar−H), 3.00 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.6, 144.0, 127.2 (s, 2C), 125.6, 123.2, 121.4, 120.2, 117.4, 112.6 (s, 2C), 107.1, 40.6 (s, 2C, NCH_3). *m*/*z* (ES-MS): 275.1 (4%), 274.1 (51%), 273.1 (18%), 272.1 (100%, [M + H]$^+$). HRMS *m*/*z* (TOF$^+$): calcd $C_{15}H_{15}N_3Cl$ = 272.0955. Found: 272.0960. Error (ppm): + 1.8.

4-(6-Fluoro-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (12d). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)phenylethanone (**11)** (1.21 g, 5.00 mmol) and 5-fluoro-2-aminopyridine (**7d**) (0.583 g, 5.17 mmol) were stirred in reflux ethanol (50 mL) for 4 h. Pale-yellow precipitate formed. $NaHCO_3$ (0.41 g, 4.9 mmol) was added to the reaction mixture after cooling (15 min). The mixture was refluxed again for another 2 h. After the mixture was cooled, the solvents were removed. The solid was washed with water, CH_2Cl_2, and recrystallized from ethyl acetate to give 0.42 g of product. Yield 33%; mp 228−229 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (m,$^3J_{FH}$ = 4.2 Hz, $^4J_{HH}$ = 2.4 Hz, $^5J_{HH}$ = 0.7 Hz, 1H, Ar−H), 8.03 (d, $^4J_{HH}$ = 0.3 Hz, 1H, Ar−H), 7.76−7.72 (m, 2H, Ar−H), 7.51 (m, $^3J_{HH}$ = 9.8 Hz, $^4J_{FH}$ = 5.0 Hz, $^5J_{HH}$ = 0.6 Hz, 1H, Ar−H), 7.24 (m, $^3J_{HH}$ = 9.8 Hz, $^3J_{FH}$ = 8.3 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 6.84−6.80 (m, 2H, Ar−H), 2.99 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, $^1J_{FC}$ = 236.4 Hz, 1C, Ar), 150.2 (s, 1C, Ar), 147.7 (s, 1C, Ar), 143.3 (s, 1C, Ar), 127.2 (s, 2C, Ar), 121.4 (s, 1C, Ar), 117.4 (d, $^3J_{FC}$ = 9.3 Hz, 1C, Ar), 116.2 (d, $^2J_{FC}$ = 25.4 Hz, 1C, Ar), 112.6 (s, 2C, Ar), 112.2 (d, $^2J_{FC}$ = 40.6 Hz, 1C, Ar), 108.1 (d, $^4J_{FC}$ = 1.8 Hz, 1C, Ar), 40.7 (s, 2C, CH_3). *m*/*z* (ES-MS): 257.1 (7%), 256.1 (100%, [M + H]$^+$). HRMS *m*/*z* (TOF$^+$): calcd $C_{15}H_{15}N_3F$ = 256.1250. Found: 256.1261. Error (ppm): +4.3.

2-(4-(Dimethylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridine-6-carbonitrile (12e). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)-phenylethanone (**11)** (1.21 g, 5.00 mmol) and 6-aminopyridine-3-carbonitrile (**7e)** (0.63 g, 5.3 mmol) were used to give **12e** (0.85 g, yield 65%): mp 269−271 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, $^4J_{HH}$ = 1.6 Hz, $^5J_{HH}$ = 0.6 Hz, 1H, Ar−H), 7.81−7.78 (m, 2H, Ar−H), 7.77 (s, 1H, Ar−H), 7.63−7.60 (m, 1H, Ar−H), 7.20 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, Ar−H), 6.77−6.74 (m, 2H, Ar−H), 3.00 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 149.3, 144.9, 131.1, 127.5 (s, 2C, Ar), 124.2, 120.4, 117.8, 117.0, 112.4 (s, 2C, Ar), 107.4, 98.1, 40.5 (s, 2C, CH_3). *m*/*z* (ES-MS): 364.0 (8%), 264.1 (29%), 263.1 (100%, [M + H]$^+$). HRMS *m*/*z* (TOF$^+$): calcd $C_{16}H_{15}N_4$ = 263.1297. Found: 263.1303. Error (ppm): +2.3.

***N*,*N*-Dimethyl-4-(6-nitro-*H*-imidazo[1,2-*a*]pyridin-2-yl)benzenamine (12f).** 2-Bromo-1-(4-(dimethylamino)phenylethanone (**11**) (0.40 g, 1.65 mmol) and 5-nitropyridin-2-amine (**7f**) (0.30 g, 2.15 mmol) were stirred in refluxing anhydrous acetonitrile (25 mL) at 90−95 °C and dinitrogen for 2 h. $NaHCO_3$ (0.25 g, 2.97 mmol) was added to the reaction mixture after cooling (15 min). The mixture was refluxed for another 9 h. After cooling, the mixture was filtered through a Busch funnel. The precipitate was washed with acetonitrile and water to afford 0.11 g of the red product. Yield 23%; mp 275−277 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (dd, $^4J_{HH}$ = 2.3 Hz, $^5J_{HH}$ = 0.8 Hz, 1H, Ar−H), 8.41 (s, 1H, Ar−H), 7.90 (dd, $^3J_{HH}$ = 9.8 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, Ar−H), 7.82−7.79 (m, 2H, Ar−H), 7.67−7.654 (m, 1H, Ar−H), 6.82−6.79 (m, 2H, Ar−H), 2.96 (s, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 148.5, 144.9, 136.0, 127.3, 126.9 (s, 2C, Ar), 120.2, 118.4, 115.2, 112.2 (s, 2C, Ar), 109.3, 40.2 (s, 2C, CH_3). *m*/*z* (ES-MS): 284.1 (29%), 283.1 (100%, [M + H]$^+$). HRMS *m*/*z* (TOF$^+$): calcd $C_{15}H_{15}N_4O_2$ = 283.1195. Found: 283.1206. Error (ppm): +3.9.

4-(6-Methoxy-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (12g). In a two-necked round-bottom flask equipped with a condenser and under dinitrogen flow were introduced 5-methoxypyridin-2-amine (**7g**) 0.15 g, 1.17 mmol), 2-bromo-4′-dimethylaminoacetophenone (**11**) (0.31 g, 1.29 mmol), and absolute EtOH (14 mL). The reaction mixture was stirred at reflux for 2 h. After the reaction mixture had cooled down, $NaHCO_3$ (0.15 g, 1.75 mmol) was added and the mixture refluxed for another 6 h. Solvent was removed and the residue dissolved in AcOEt. The organic phase was washed with water, dried over $MgSO_4$, and filtered. The solvent was removed to afford crude product (0.271 g), which was purified by FCC (CH_2Cl_2/AcOEt, 1:1) to give **12g** (0.129 g, yield 41%) as a yellow solid: mp 182−184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, $^4J_{HH}$ = 2.2 Hz, 1H, Ar−H), 8.10 (s, 1H, Ar−H), 7.76−7.72 (m, 2H, Ar−H), 7.44 (d, $^3J_{HH}$ = 9.7 Hz, 1H, Ar−H), 6.98 (dd, $^3J_{HH}$ = 9.7 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, Ar−H), 6.79−6.75 (m, 2H, Ar−H), 3.79 (s, 3H, O−CH_3), 2.94 (s, 6H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 152.0, 150.8, 147.0, 143.7, 127.8 (s, 2C), 123.2, 121.2, 116.8, 113.8 (s, 2C), 109.7, 109.4, 56.7 (s, 1C, OCH_3), 40.8 (s, 2C, NCH_3). *m*/*z* (ES-MS): 269.1 (18%), 268.1 (100%, [M + H]$^+$). HRMS *m*/*z* (TOF$^+$): calcd $C_{16}H_{18}N_3O$ = 268.1450. Found: 268.1453. Error (ppm): +1.1.

4-(6-(Ethylthio)-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (12h). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)-

phenylethanone (**11**) (1.21 g, 5.00 mmol) and 5-(ethylthio)pyridin-2-amine (**7h**) (0.80 g, 5.2 mmol) were used to give **12h** (0.91 g, yield 61%): mp 168−171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (dd, $^4J_{HH}$ = 1.9 Hz, $^5J_{HH}$ = 0.9 Hz, 1H, Ar−H), 8.14 (s, 1H, Ar−H), 7.78−7.74 (m, 2H, Ar−H), 7.51−7.49 (m, 1H, Ar−H), 7.23 (dd, $^3J_{HH}$ = 9.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 6.76 (m, 2H, Ar−H), 2.94 (s, 6H, CH_3), 2.92 (q, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2), 1.21 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.1, 145.7, 143.6, 128.0, 127.3, 126.5 (s, 2C, Ar), 121.5, 118.3, 116.1, 112.2 (s, 2C, Ar), 107.1, 40.0 (s, 2C, CH_3), 28.4 (s, 1C, CH_2), 14.4 (s, 1C, CH_3). *m*/*z* (ES-MS): 300.1 (6%), 299.1 (39%), 298.1 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{17}H_{20}N_3S$ = 298.1378. Found: 298.1386. Error (ppm): +2.7.

4-(6-Bromo-8-iodoindolizin-2-yl)-*N*,*N*-dimethylbenzenamine (12i). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)phenylethanone (**11**) (1.21 g, 5.00 mmol) and 2-amino-3-iodo-5-bromopyridine (**7i**) (1.58 g, 5.3 mmol) were used to give **12i** (1.21 g, yield 55%): mp 218−220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $^4J_{HH}$ = 1.7 Hz, 1H, Ar−H), 7.85−7.81 (m, 2H, Ar−H), 7.79 (s, 1H, Ar−H), 7.66 (d, $^4J_{HH}$ = 1.7 Hz, 1H, Ar−H), 6.79 (d, $^3J_{HH}$ = 7.9 Hz, 2H, Ar−H), 2.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.9, 143.9, 135.8, 127.5 (s, 2C, Ar), 125.4, 121.5, 112.8 (s, 2C, Ar), 108.8, 106.0, 84.0 (s, 1C, Ar−I), 40.9 (s, 1C, CH_3). *m*/*z* (ES-MS): 444.9 (6%), 443.9 (99%), 442.9 (9%), 441.9 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{15}H_{14}N_3BrI$ = 441.9416. Found: 441.9398. Error (ppm): −4.1.

6-Bromo-2-(4-(dimethylamino)phenyl)indolizine-8-carbonitrile (12j). The synthetic procedure is analogous to that used in the synthesis of **12a**.[15,16] 2-Bromo-1-(4-(dimethylamino)phenylethanone (**11**) (1.21 g, 5.00 mmol) and 2-amino-5-bromonicotinonitrile (**7j**) (1.03 g, 5.2 mmol) were used to give **12j** (0.77 g, yield 45%): mp 240−246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 8.32 (s, 1H, Ar−H), 8.13 (d, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.81 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 6.79 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 2.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 147.4, 141.3, 133.6, 131.1, 127.0 (s, 2C, Ar), 119.9, 114.8, 112.1 (s, 2C, Ar), 109.0, 103.5, 99.9, 39.9 (s, 2C, NCH_3). *m*/*z* (ES-MS): 443.9 (4%), 441.9 (3%), 344.0 (11%), 343.0 (98%), 342.0 (11%), 341.0 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{16}H_{14}N_4Br$ = 341.0402. Found: 341.0389. Error (ppm): - 3.8.

2-(4-(Dimethylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ol (12k). To a dried 10 mL flask under dinitrogen flow was added 4-(6-methoxy-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (**12g**, 62 mg, 0.22 mmol) and anhydrous CH_2Cl_2 (2 mL). The solution was stirred and cooled to −78 °C with a CO_2/acetone bath and then BBr_3 (80 mg, 0.32 mmol) was added dropwise from a disposable syringe. (Caution! BBr_3 reacts violently with water). The reaction mixture was allowed to stir at room temperature for 2 h and poured into ice−water (15 mL). A mixture of CH_2Cl_2 and MeOH (15:1) was added and the mixture stirred for 10 min. The organic phase was separated, dried over $MgSO_4$, and filtered. Solvent was removed to give **12k** (39 mg, yield 70%) as a yellow solid: mp 262−264 °C. ^{1}H NMR (270 MHz, DMSO-d_6), δ 9.70 (s, 1H, OH), 8.16 (s, 1H, H-3), 8.01 (s, 1H, H-5), 7.71 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 7.45 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 7.03 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 6.78 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 2.95 (s, 6H, NCH_3). ^{13}C NMR (125 MHz, DMSO-d_6), δ 150.2, 146.2, 143.2, 140.3, 126.4 (Ph-2,6), 120.7 (C7), 120.4, 115.3 (C8), 112.4 (Ph-3,5), 110.5 (C3), 107.8 (C5), 39.9 (NCH_3). *m*/*z* (CI-MS): 254 ($[M + 1]^+$), 238 ($[M - CH_3]^+$). *m*/*z* (ES-MS): 355.1 (6%), 268.1 (4%), 260.1 (6%), 255.1 (12%), 254.1 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{15}H_{16}N_3O$ = 254.1293. Found: 254.1299. Error (ppm): +2.4.

***N*-(2-Bromo-4-(6-bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)phenyl)-2,2,2-trifluoro-*N*-methylacetamide (13a).** *N*-(2-Bromo-4-(2′-bromoacetyl)phenyl)-2,2,2-trifluoro-*N*-methylacetamide (**4a**) (4.0 g, 9.93 mmol) and 5-bromopyridin-2-amine (**7b**) (1.7 g, 9.83 mmol) were dissolved in MeOH (20 mL). The reaction mixture was refluxed for 8 h and solvent then removed. A small amount of CH_2Cl_2 was added and the resultant precipitate filtered off to afford **13a** (2.8 g, yield 59%) as a yellow solid: mp 95−98 °C. ^{1}H NMR (400 MHz, CD_3OD) δ isomer α (84%) 8.73−8.72 (m, 1H, Ar−H), 8.34−8.31 (m, 2H, Ar−H), 8.01 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.58 (d, $^3J_{HH}$ = 8.3 Hz, 1H, Ar−H), 7.55−7.52 (m, 1H, Ar−H), 7.45 (dd, $^3J_{HH}$ = 9.6 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 2.66 (s, 3H, CH_3). Isomer β (16%) 8.73−8.72 (m, 1H, Ar−H), 8.34−8.31 (m, 2H, Ar−H), 8.03 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.55−7.52 (m, 1H, Ar−H), 7.51 (d, $^3J_{HH}$ = 8.3 Hz, 1H, Ar−H), 7.44 (dd, $^3J_{HH}$ = 9.6 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ isomer α 155.5 (q, $^2J_{CF}$ = 35.1 Hz, 1C, CO),143.5, 142.3, 137.9, 136.3, 130.8, 129.8, 128.6, 125.8, 122.8, 117.9, 115.9 (q, $^1J_{CF}$ = 286 Hz, 1C, CF_3), 111.1, 106.5, 37.7 (s, 1C, CH_3). Isomer β 155.5 (q, $^2J_{CF}$ = 35.1 Hz, 1C, CO), 143.4, 142.6, 139.8, 135.6, 129.9, 129.4, 128.4, 127.1, 126.3, 121.3, 117.8, 115.9 (q, $^1J_{CF}$ = 286 Hz, 1C, CF_3), 110.8, 109.4, 37.7 (s, 1C, CH_3). *m*/*z* (ES-MS): 479.9 (27%), 477.9 (100%, $[M + H]^+$), 475.9 (28%). HRMS *m*/*z* (TOF^+): calcd $C_{16}H_{11}N_3OF_3Br_2$ = 475.9221. Found: 475.9228. Error (ppm): +1.5.

***N*-(4-(6-Bromoindolizin-2-yl)-2-methylphenyl)-2,2,2-trifluoroacetamide (13b).** *N*-(4-(2′-Bromoacetyl)-2-methylphenyl)-2,2,2-trifluoroacetamide (**4b**) (3.0 g, 9.26 mmol) and 5-bromopyridin-2-amine (**7b**) (1.5 g, 8.67 mmol) were dissolved in ethanol (20 mL). The mixture was refluxed overnight and the solvent removed. CH_2Cl_2 was added to precipitate a solid, which was filtered and washed with CH_2Cl_2 to afford **13b** (1.0 g, yield 28%) as a yellow powder: mp 306−309 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 9.09 (dd, $^4J_{HH}$ = 1.7 Hz, $^5J_{HH}$ = 0.9 Hz, 1H, Ar−H), 8.53 (s, 1H, Ar−H), 8.08 (dd, $^3J_{HH}$ = 9.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.87 (d, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.84 (dd, $^3J_{HH}$ = 9.5 Hz, $^5J_{HH}$ = 0.7 Hz, 1H, Ar−H), 7.78 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.56 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar−H), 2.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.4 (q, $^2J_{CF}$ = 36.6 Hz, 1C, CO), 139.7, 136.6, 136.4, 134.9, 134.3, 131.9, 128.8, 125.6, 125.1, 124.5, 116.1 (q, $^1J_{CF}$ = 289 Hz, 1C, CF_3), 113.9, 111.2, 110.1, 17.4 (CH_3). *m*/*z* (ES-MS): 401.0 (7%), 400.0 (93%), 399.0 (7%), 398.0 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{16}H_{12}N_3OF_3Br$ = 398.0116. Found: 398.0099. Error (ppm): −4.3.

***N*-(4-(6-Bromoindolizin-2-yl)-2-methylphenyl)-*N*-methylacetamide (13c).** The synthetic procedure is analogous to that used in the synthesis of **13a**. *N*-(4-(2′-Bromoacetyl)-2-methylphenyl)-*N*-methylacetamide (**4c**) (1.0 g, 3.52 mmol) and 5-bromopyridin-2-amine (**7b**) (0.73 g, 4.22 mmol) were used. Yield 37%; mp 197−198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ isomer α (90%) 8.88 (dd, $^4J_{HH}$ = 2.0 Hz, $^5J_{HH}$ = 0.8 Hz, 1H, Ar−H), 8.39 (d, $^5J_{HH}$ = 0.4 Hz, 1H, Ar−H), 7.89 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.84 (d, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.43 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.37 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 3.11 (s, 3H, NCH_3), 2.21 (s, 3H, Ar−CH_3), 1.70 (s, 3H, CH_3). Isomer β (10%) 8.87 (dd, $^4J_{HH}$ = 1.9 Hz, $^5J_{HH}$ = 0.8 Hz, 1H, Ar−H), 8.32 (d, $^5J_{HH}$ = 0.3 Hz, 1H, Ar−H), 7.76 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.73 (d, $^4J_{HH}$ = 1.8 Hz, 1H, Ar−H), 7.56−7.53 (m, 1H, Ar−H), 7.36 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.31 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 3.28 (s, 3H, NCH_3), 2.13 (s, 3H, Ar−CH_3), 1.70 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ isomer α 169.0 (s, 1C, CO), 144.2, 143.3, 143.2, 134.7, 133.0, 131.7, 127.9, 126.9, 125.3, 125.1, 117.6, 109.8, 106.0, 35.3 (s, 1C, NCH_3), 21.6 (s, 1C, CH_3), 16.7 (s, 1C, Ar−CH_3). Isomer β 169.6 (s, 1C, CO), 144.6, 143.8, 143.2, 134.8, 132.2, 130.9, 127.8, 126.8, 124.5, 124.1, 117.5, 109.3, 105.9, 38.7 (s, 1C, NCH_3), 21.9 (s, 1C, CH_3), 17.1 (s, 1C, Ar−CH_3). *m*/*z* (ES-MS): 361.0 (4%), 360.0 (100%, $[M + H]^+$), 359.0 (47%), 358.0 (96%). HRMS *m*/*z* (TOF^+): calcd $C_{17}H_{17}N_3OBr$ = 358.0555. Found: 358.0557. Error (ppm): +0.6.

2-Bromo-4-(6-bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-methylbenzenamine (14a). *N*-(2-Bromo-4-(6-bromo-*H*-imidazo[1,2-*a*]-pyridin-2-yl)phenyl)-2,2,2-trifluoro-*N*-methylacetamide (**13a**, 1.0 g, 2.10 mmol) and K_2CO_3 (2.0 g, 14.5 mmol) were suspended in ethanol (30 mL) and water (15 mL). The mixture was refluxed for 8 h. The organic solvent was removed and CH_2Cl_2 added. The

organic phase was washed twice with water and dried over $MgSO_4$. The solvent was removed to afford **14a** (0.60 g, yield 80%) as a yellow solid: mp 226−228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (dd, $^4J_{HH}$ = 1.8 Hz, $^5J_{HH}$ = 0.9 Hz, 1H, Ar−H), 8.21 (s, 1H, Ar−H), 8.01 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar−H), 7.78 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.0 Hz, 1H. Ar−H), 7.51 (dt, $^3J_{HH}$ = 8.9 Hz, $^5J_{HH}$ = 0.7 Hz, 1H, Ar−H), 7.32 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 6.68 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar−H), 5.55 (m, 1H, N−H), 2.81 (d, $^3J_{HH}$ = 4.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.0, 144.7, 143.1, 129.3, 127.47, 126.5, 126.2, 122.2, 117.1, 110.1, 108.4, 107.9, 105.5, 30.1 (s, 1C, NCH_3). *m*/*z* (ES-MS): 383.9 (42%), 383.4 (6%), 381.9 (100%, $[M + H]^+$), 379.9 (47%). HRMS *m*/*z* (TOF^+): calcd $C_{14}H_{12}N_3Br_2$ = 379.9398. Found: 379.9396. Error (ppm): −0.5.

4-(6-Bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-2-methylbenzenamine (14b). *N*-(4-(6-Bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-2-methylphenyl)-2,2,2-trifluoroacetamide (**13b**, 1.0 g, 2.51 mmol) and K_2CO_3 (4.0 g, 29.0 mmol) were suspended in ethanol (30 mL) and water (15 mL). The mixture was refluxed overnight. The solvent was removed, and CH_2Cl_2 was added. The organic phase was washed twice with H_2O and dried over $MgSO_4$. The solvent was removed to afford a solid, which was purified by silica gel column chromatography to give **14b** (0.60 g, yield 79%) as a yellow solid: mp 183−187 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (dd, $^4J_{HH}$ = 1.9 Hz, $^5J_{HH}$ = 0.9 Hz, 1H, Ar−H), 8.06 (s, 1H, Ar−H), 7.46 (dt, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = $^5J_{HH}$ = 0.76 Hz, 1H, Ar−H), 7.37 (dd, $^3J_{HH}$ = 9.5, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.26 (d, $^4J_{HH}$ = 1.8 Hz, 1 H, Ar−H), 7.17 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, Ar−H), 7.06 (d, $^3J_{HH}$ = 7.7 Hz, 1H, Ar−H), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 146.1, 143.0, 131.6, 130.2, 127.3, 126.6, 121.2, 117.4, 113.7, 111.2, 108.6, 105.5, 17.3 (CH_3). *m*/*z* (ES-MS): 305.0 (21%), 304.0 (99%), 303.0 (24%), 302.0 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{14}H_{13}N_3Br$ = 302.0293. Found: 302.0298. Error (ppm): +1.7.

4-(6-Bromo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,2-dimethylbenzenamine (14c). The synthetic procedure is analogous to that used in the synthesis of **14a**. *N*-(4-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-2-methylphenyl)-*N*-methylacetamide (**13c**, 1.0 g, 2.79 mmol) and KOH (1.0 g, 17.8 mmol) were used, to afford 0.68 g. Yield 77%; mp 165−166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (dd, $^4J_{HH}$ = 1.8 Hz, $^5J_{HH}$ = 0.7 Hz, 1H, Ar−H), 8.27 (s, 1H, Ar−H), 7.56 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.33 (dd, $^3J_{HH}$ = 9.5 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, Ar−H), 7.10−7.09 (m, 2H, Ar−H), 7.01 (dd, $^3J_{HH}$ = 8.3 Hz, $^5J_{HH}$ = 0.32 Hz, 1H, Ar−H), 5.12 (s, 1H, N−H), 2.82 (s, 1H, CH_3), 2.10 (s, 1H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.8, 146.4, 143.1, 131.9, 129.8, 127.3, 126.6, 121.8, 117.5, 113.2, 108.9, 105.7, 105.6, 30.2 (s, 1C, N−CH_3), 17.5 (s, 1C, Ar−CH_3). *m*/*z* (ES-MS): 319.0 (17%), 318.0 (96%), 317.0 (22%), 316.0 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{15}H_{15}N_3Br$ = 316.0449. Found: 316.0453. Error (ppm): +1.3.

General Procedure for Thiolate Substitution. A 10 mL microwave tube was charged with Pd_2dba_3 (13−58 mg, 0.014−0.063 mmol, 10−20 mol % Pd), DiPPF (6−27 mg, 0.014−0.063 mmol, 10−20 mol %), **12a** derivative (0.14−0.32 mmol), and tin thiolate (0.29−0.63 mmol). The tube was capped and put in a microwave system for the desired temperature and time as specified in the text. A small sample of the resulting suspension was analyzed by HPLC to confirm the conversion. The suspension was partitioned between $CHCl_3$ and K_2CO_3 solution. The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was dissolved in DMSO and loaded on a reversed-phase HPLC. After the correct band had been collected, the solvents were removed and the product was dried by addition and evaporation of MeCN.

2-(2-(4-(Methylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)acetamide (15a). 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-methylbenzenamine (**14d**) (100 mg, 0.29 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (60 mg, 0.29 mmol), 2-mercaptoacetamide (26 mg, 0.29 mmol), $Pd_2(dba)_3$ (26.2 mg, 0.029 mmol), DiPPF (12 mg, 0.029 mmol), and 8.0 mL of toluene were used. Yield 78%; mp 198−202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, $^4J_{HH}$ = 4.4 Hz, 1H, Ar−H), 8.11 (s, 1H, Ar−H), 7.68 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 7.48 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 7.26 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 6.59 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 5.86 (s, 2H, NH_2), 3.53 (s, 2H, CH_2S), 2.71 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8 (−CO−N), 149.8, 146.2, 143.6, 128.0, 127.7, 126.6, 120.9, 118.2, 115.9, 111.6, 106.8, 38.5 (C−S), 29.6 (NCH_3). *m*/*z* (LC−MS): 314.3 (21%), 313.2 (100%, $[M + H]^+$), 255.5 (32%, $[M - CH_2CONH_2]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{16}H_{17}N_4OS$ = 313.1123. Found: 313.1126. Error (ppm): +0.9.

2-(2-(4-(Methylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)ethanol (15b). 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*-methylbenzenamine (**14d**) (100 mg, 0.29 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (60 mg, 0.29 mmol), 2-mercaptoethanol (23 mg, 0.29 mmol), $Pd_2(dba)_3$ (28 mg, 0.031 mmol), DiPPF (22 mg, 0.039 mmol), and toluene (5.0 mL) were used. Yield 91%; mp 158−161 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H, Ar−H), 7.95 (s, 1H, Ar−H), 7.68 (d, $^3J_{HH}$ = 8.6 Hz, 2H, Ar−H), 7.45 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar−H), 7.34 (d, $^3J_{HH}$ = 8.6 Hz, 1H, Ar−H), 6.67 (d, $^3J_{HH}$ = 8.6 Hz, 2H, Ar−H), 3.69 (t,$^3J_{HH}$ = 6.5 Hz, 2H, OCH_2), 3.01 (t,$^3J_{HH}$ = 6.5 Hz, 2H, SCH_2), 2.81 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 151.8, 148.0, 145.7, 130.9, 129.5, 128.1, 122.6, 121.2, 116.5, 113.4, 108.5, 61.5 (C−O), 38.8 (C−S), 30.6 (NCH_3). *m*/*z* (LC−MS): 302.2 (5%), 301.3 (15%), 300.2 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{16}H_{18}N_3OS$ = 300.1171. Found: 300.1163. Error (ppm): −2.5.

2-(2-(4-(Dimethylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)acetamide (15c). 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (**12a**, 50 mg, 0.14 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (30 mg, 0.14 mmol), 2-mercaptoacetamide (13 mg, 0.14 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol), DiPPF (6 mg, 0.014 mmol), and toluene (5.0 mL) were used. Yield 85%; mp 180−183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H, Ar−H), 8.17 (s, 1H, Ar−H), 7.77 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 7.50 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ar−H), 7.27 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 7.13 (brs, 2H, NH_2), 6.78 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar−H), 3.54 (s, 2H, CH_2S), 2.94 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7 (−CO−N), 149.0, 144.7, 142.5, 129.4, 127.8, 126.9, 126.6, 125.3, 120.3, 117.2, 114.9, 111.1, 109.5, 106.1, 38.5 (C−S), 37.3 (NCH_3). *m*/*z* (LC−MS): 329.3 (7%), 328.2 (18%), 327.2 (100%, $[M + H]^+$), 325.1 (12%), 323.4 (7%), 321.7 (7%), 320.9 (5%), 269.4 (14%, $[M - CH_2CONH_2]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{17}H_{19}N_4OS$ = 327.1280. Found: 327.1278. Error (ppm): −0.5.

4-(6-(4-Methoxybenzylthio)-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (15d). 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (**12a**, 80 mg, 0.22 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (46 mg, 0.22 mmol), (4-methoxyphenyl)methanethiol (34 mg, 0.22 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), DiPPF (18.4 mg, 0.044 mmol), and toluene (5.0 mL) were used. Yield 85%; mp 184−186 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H, Ar−H), 8.10 (s, 1H, Ar−H), 7.75 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.47 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.16 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar−H), 6.83 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 6.77 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 4.13 (s, 2H, CH_2S), 3.71 (s, 3H, CH_3O), 2.94 (s, 6H, NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 150.0, 145.6, 143.5, 129.9, 129.2, 128.2, 127.7, 126.3, 121.3, 118.0, 115.8, 113.9, 112.1, 107.0, 54.8 (OCH_3), 39.9 (NCH_3), 38.3 (C−S). *m*/*z* (LC−MS): 392.1 (7%), 391.1 (23%), 390.1 (100%, $[M + H]^+$). HRMS *m*/*z* (TOF^+): calcd $C_{23}H_{24}N_3OS$ = 390.1640. Found: 390.1634. Error (ppm): −0.6.

2-(2-(4-(Dimethylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)ethanol (15e). 4-(6-Iodo-*H*-imidazo[1,2-*a*]pyridin-2-yl)-*N*,*N*-dimethylbenzenamine (**12a**, 50 mg, 0.14 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (29 mg, 0.14 mmol), 2-mercaptoethanol (11 mg, 0.14 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol), DiPPF (6 mg, 0.014 mmol), and toluene (5.0 mL) were used. Yield 89%; mp 183−185 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H, Ar−H), 8.05 (s, 1H, Ar−H), 7.78 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 7.45 (d, $^3J_{HH}$ = 8.9 Hz, 1H, Ar−H), 7.35 (d, $^3J_{HH}$ = 8.9 Hz, 1H, Ar−

H), 6.83 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 3.70 (t, $^3J_{HH}$ = 6.7 Hz, 2H, OCH_2), 3.03 (t, $^3J_{HH}$ = 6.7 Hz, 2H, SCH_2), 3.00 (s, 6H, NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.1, 145.7, 143.6, 128.1, 127.4, 126.4, 121.5, 118.5, 116.1, 112.2, 107.1, 59.8 (C−O), 55.9 (C−S), 37.2 (NCH_3). *m/z* (LC−MS): 316.1 (5%), 315.2 (23%), 314.2 (100%, $[M + H]^+$). HRMS *m/z* (TOF^+): calcd $C_{17}H_{20}N_3OS$ = 314.1327. Found: 314.1317. Error (ppm): −3.4.

2-(2-(3-Methyl-4-(methylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)acetamide (15f). 4-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-*N*,2-dimethylaniline (**14c**) (100 mg, 0.32 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (99 mg, 0.48 mmol), 2-mercaptoacetamide (43 mg, 0.48 mmol), $Pd_2(dba)_3$ (43 mg, 0.048 mmol), DiPPF (20 mg, 0.048 mmol), and toluene (6.0 mL) were used. Yield 69%; mp 181−182 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H, Ar−H), 8.10 (s, 1H, Ar−H), 7.49 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.41 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.17 (s, 1H, Ar−H), 7.12 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.06 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 3.46 (s, 1H, NH), 3.55 (s, 2H, SCH_2), 2.93 (s, 3H, NCH_3), 2.16 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7 (−CO−), 146.6, 144.9, 142.4, 131.0, 128.6, 127.1, 126.6, 120.5, 117.5, 115.3, 112.0, 107.5, 104.5, 37.2 (CH_2S), 29.0 (NCH_3), 16.3 (CH_3). *m/z* (LC−MS): 329.2 (6%), 328.3 (22%), 327.2 (100%, $[M + H]^+$). HRMS *m/z* (TOF^+): calcd $C_{17}H_{19}N_4OS$ = 327.1280. Found: 327.1278. Error (ppm): −0.4.

2-(2-(3-Methyl-4-(methylamino)phenyl)-*H*-imidazo[1,2-*a*]pyridin-6-ylthio)ethanol (15g). 4-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-*N*,2-dimethylaniline (**14c**) (100 mg, 0.32 mmol), *N*-methyl-*N*-(trimethylstannyl)methanamine (132 mg, 0.63 mmol), 2-mercaptoethanol (50 mg, 0.63 mmol), $Pd_2(dba)_3$ (58 mg, 0.063 mmol), DiPPF (27 mg, 0.063 mmol), and toluene (6.0 mL) were used. Yield 69%; mp 149−153 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H, Ar−H), 8.10 (s, 1H, Ar−H), 7.50 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.38 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.18 (s, 1H, Ar−H), 7.15 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 7.08 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar−H), 3.80 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2O), 3.03 (t, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2S), 2.94 (s, 3H, NCH_3), 2.16 (s, 3H, Ar−CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.7, 146.0, 143.4, 132.2, 129.7, 128.2, 127.4, 121.6, 118.8, 116.5, 113.1, 108.6, 105.6, 59.5 (OCH_2), 37.1 (CH_2S), 30.1 (NCH_3), 17.5 (CH_3). *m/z* (LC−MS): 329.2 (6%), 328.3 (22%), 327.2 (100%, $[M + H]^+$). *m/z* (LC−MS): 316.2 (8%), 315.2 (24%), 314.2 (100%, $[M + H]^+$). HRMS *m/z* (TOF^+): calcd $C_{17}H_{20}N_3OS$ = 314.1327. Found: 314.1316. Error (ppm): −3.5.

4-(6-Chloroimidazo[1,2-*a*]pyrazin-2-yl)-*N*,*N*-dimethylbenzenamine (17a). 5-Chloro-2-aminopyrazine (**10**) (61 mg, 0.47 mmol), 2-bromo-4′-dimethylaminoacetophenone (**11**) (170 mg, 0.71 mmol), and anhydrous MeCN (7 mL) were introduced under dinitrogen flow into a double-necked round-bottomed flask equipped with a condenser. The reaction mixture was refluxed for 3 h and allowed to cool. $NaHCO_3$ (71 mg, 0.85 mmol) was added. The mixture was refluxed for another 6 h. The solvent was removed and the crude product (221 mg) purified by FCC (hexane/CH_2Cl_2/AcOEt, 2: 2: 1) to afford **17a** (9 mg, yield 7%) as a yellow solid. ^{1}H NMR (270 MHz, $CDCl_3$), δ 8.82 (s, 1H, Ar−H), 8.09 (s, 1H, Ar−H), 7.822 (s, 1H, Ar−H), 7.818 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 6.77 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar−H), 3.02 (s, 6H, NCH_3). *m/z* (CI-MS): 273 ($[M + 1]^+$), 261, 239 ($[M - Cl + 1]^+$). *m/z* (ES-MS): 275.1 (41%), 274.1 (10%), 273.1 (100%, $[M + H]^+$). HRMS *m/z* (TOF^+): calcd $C_{14}H_{14}N_4Cl$ = 273.0907. Found: 273.0908. Error (ppm): +0.4.

4-(6-Chloroimidazo[1,2-*a*]pyrimidin-2-yl)-*N*,*N*-dimethylbenzenamine (17b). 2-Amino-5-chloropyrimidine (**16**) (0.150 g, 1.16 mmol), 2-bromo-4′-dimethylaminoacetophenone (**11**) (0.56 g, 2.32 mmol), and anhydrous MeCN (16 mL) were added to a double-necked flask equipped with a condenser under dinitrogen. A small amount of anhydrous DMF (0.5 mL) was added to dissolve the amine completely. The mixture was stirred and refluxed for 3 h and cooled and $NaHCO_3$ (0.19 g, 2.32 mmol) added. The reaction mixture was refluxed for another 6 h and filtered *hot* on a Busch funnel. The solid was washed sequentially with EtOH, water, and EtOH and finally dried overnight to afford 72 mg (yield 23%) of **17b** as a yellow powder: mp 260−262 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.97 (d, $^4J_{HH}$ = 2.5 Hz, 1H, Ar−H), 8.45 (d, $^4J_{HH}$ = 2.5 Hz, 1H, Ar−H), 8.02 (s, 1H, Ar−H), 7.82−7.79 (m, 2H, Ar−H), 6.84−6.81 (m, 2H, Ar−H), 3.01 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ 150.5, 149.3, 147.9 (C7), 147.0, 129.6 (C5), 127.5 (Ph-2,6), 117.5, 112.8 (Ph-3,5), 106.2 (C−Cl), 104.8 (C3), 40.7 (NCH_3). *m/z* (CI-MS): 273 ($[M \pm 1]^+$), 239 ($[M - Cl + 1]^+$). *m/z* (ES-MS): 355.1 (6%), 275.1 (27%), 274.1 (9%), 273.1 (100%, $[M + H]^+$). HRMS *m/z* (TOF^+): calcd $C_{14}H_{14}N_4Cl$ = 273.0907. Found: 273.0920. Error (ppm): +4.8.

In Vitro Binding Assay. Postmortem brain tissue was obtained from a female AD patient at the age of 80 years (postmortem interval, 7.5 h). Consent for donation was obtained from the next of kin, and the brain was removed. The clinical diagnosis was confirmed after autopsy by macro- and microscopic examination, including Bielschowsky's silver stain adapted for paraffin sections. The cerebrum was sectioned into 1 cm coronal sections, which were rapidly frozen in a 50:50 mixture of dry ice and isopentane, and the frozen sections were transferred to plastic bags and stored at −76 °C until used. One day before the experiment, bags of selected brain tissue were removed from the freezer and transferred to a −20 °C freezer; 3 h before the experiment these sections were placed on wet ice. While on ice, the leptomeninges were first removed and the white matter was dissected away. Then the gray matter was cut into 3 mm × 3 mm pieces with a sharp scalpel and placed into plastic bags. The tissue was rapidly frozen on dry ice and stored in a freezer (−70 °C) for further use.

The AD brain tissue was homogenized in PBS (1:50 in vol) to generate a suspension, which was dispensed into 1.0 mL and stored in a −70 °C freezer for further use. For each assay, a new vial with 1.0 mL of suspension was thawed, vortexed, and diluted with PBS until 10.0 mL. An amount of 100 μL of suspension was used in each tube. [^{3}H]PIB solution (1 mCi/mL) was diluted with PBS to give an intermediate stock solution (10 nCi/μL), which was further diluted with PBS to yield a dilute stock solution (1 nCi/μL). An amount of 100 μL was used in each tube. Nonradioactive PIB or other displacer was dissolved in DMSO to give a stock solution (1 mM), which was further diluted with DMSO to give serial solutions in the concentration range of 1×10^{-4} to 10^{-10} M, and 10 μL was used in each tube. Quadruplets were used for each concentration. The assembled reaction mixtures were vortexed and incubated for 2 h at 37 °C. After separation using a cell harvester, the filter paper (GF/B filter paper pretreated with 0.5% polyimine solution) was washed with PBS (3 × 3 mL). The filters were placed in 7 mL plastic vials, and scintillation fluid (4 mL each) was added. The samples were counted after overnight incubation. The data were analyzed using GraphPad Prism 4.

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Supporting Information Available: A table listing the analytical techniques used to determine degree of purity for all target compounds, a table of elemental analysis data, and some NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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