Bioorganic & Medicinal Chemistry Letters 19 (2009) 2258–2262

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and β-amyloid binding properties of rhenium 2-phenylbenzothiazoles

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ARTICLE INFO

Article history:
Received 9 January 2009
Revised 23 February 2009
Accepted 24 February 2009
Available online 27 February 2009

Keywords:
Technetium-99m
Rhenium
SPECT
PiB
β-Amyloid plaques
Alzheimer's disease

ABSTRACT

As a first step toward the development of ^{99m}Tc PiB analogs, we have synthesized six neutral Re 2-phenylbenzothiazoles via pendant or integrated approach. These Re compounds bind to $A\beta_{1-40}$ fibrils with fairly good affinities (K_i = 10.0–88.6 nM) and have moderate lipophilicities ($\log P_{C18}$ = 1.21–3.26). The Re compounds prepared via the integrated approach are smaller in size, and therefore their corresponding ^{99m}Tc analogs would have a greater chance of crossing the blood-brain barrier well. For potential clinical applications, further optimization on the structure–activity relationship to obtain Re 2-phenylbenzothiazoles with higher binding affinities (<10 nM) might be needed. The integrated approach reported here to obtain neutral, compact and lipophilic Re 2-phenylbenzothiazoles could to be applied to other high affinity pharmacophores as well as to generate ^{99m}Tc analogs that could hold promise for extending the use of Aβ imaging in living human brain to many more clinical settings because they could be used with SPECT.

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder characterized by irreversible memory impairment, continuous cognitive decline and behavioral disturbances. The production and accumulation of β-amyloid peptides (Aβ) is believed to be pivotal to the pathogenesis and progression of AD[1], and the formation of Aβ plaques precedes the appearance of clinical symptoms.[2] Research on the treatment of AD has focused on the anti-amyloid strategy and currently there are more than 10 anti-amyloid drugs in phase 1 to phase 3 clinical trials.[3] The development of Aβ plaque targeting radiotracers has enabled non-invasive imaging and quantification of Aβ deposition in living human brain. This technology could provide a useful tool for identifying preclinical cases of AD as candidates for early intervention and to follow the effectiveness of anti-amyloid therapy in individual patients. Among Aβ imaging agents[4–9] currently under clinical evaluation, 2-(4-[^{11}C]methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound-B, PiB)[5] has achieved highest signal-to-noise ratio, and has been adopted to perform AD-related research studies at more than 40 research centers worldwide. Unfortunately, due to its short half-life (20 min) the ^{11}C label on PiB limits its use to major academic PET (positron emission tomography) facilities with on-site cyclotrons and sophisticated radiochemistry laboratories. Derivatives of PiB[8] labeled with the longer half-life (110 min) radioisotope ^{18}F have recently been developed and could increase the availability of Aβ imaging to all PET facilities, but this still represents a minority of modern hospitals, as only a small fraction of hospitals have a PET scanner. However, many more hospitals have the capacity to perform single photon emission computed tomography (SPECT). Aβ imaging agents labeled with SPECT isotopes especially the inexpensive and readily available ^{99m}Tc will have more widespread clinical applicability especially in developing countries that can not afford expensive cyclotron and PET scanners.

The preparation of ^{99m}Tc-labeled Aβ imaging agents including antibody 10H3[10] and derivatives of Congo red and chrysamine G[11–13] have been reported. These radiotracers have limited clinical application due to poor brain uptake resulting from the bulky molecular size and/or charge of the Aβ-binding moiety. Recently several ^{99m}Tc-labeled tracers[14–16] based on small high affinity pharmacophores have been prepared. Among them, ^{99m}Tc-labeled biphenyl[14] and 2-phenylbenzothiazole[16] analogs showed good brain uptake in mice and their ability to bind to Aβ plaques were demonstrated via autoradiography[14] or fluorescent staining[16] using brain tissue from AD patients and/or transgenic mice. However, their binding affinities to aggregated Aβ in terms of the equilibrium dissociation constant K_d or inhibition constant K_i were not reported. With the success in the development of the PET radiotracer PiB, we were also interested in the development of its SPECT version labeled with ^{99m}Tc for more widespread use. Since there is no stable isotope of Tc available, we used Re, a congener of Tc, for our initial studies. Re and Tc both belong to the group VIIB of the periodic table of elements. Because of the lanthanide contraction, the chemical and physical properties of Re are similar to those of Tc. The methodologies developed to generate Re complexes are generally applicable to generate their corresponding Tc analogs. Therefore, Re has been widely used as a surrogate for Tc in

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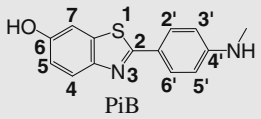
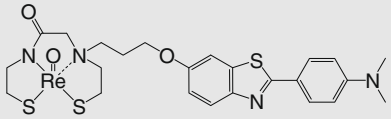
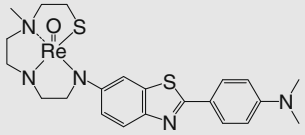
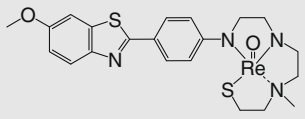
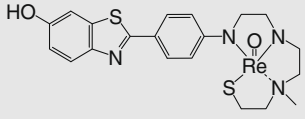
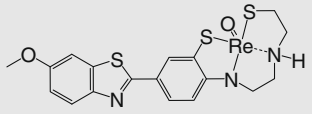
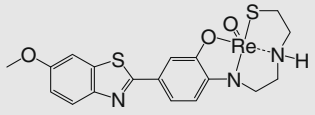
doi:10.1016/j.bmcl.2009.02.096

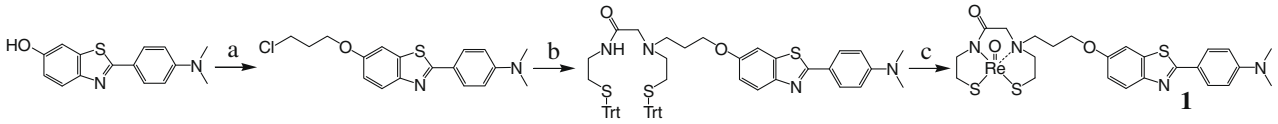
radiotracer development for characterization of complex structure and determination of binding affinity.[12,14,17] Here we report the synthesis and Aβ binding properties of six neutral Re 2-arylbenzothiazoles as our first step toward the development of ^{99m}Tc PiB analogs for use with SPECT. Based on our previous work with PiB, we targeted compounds with a $K_i \leqslant 10$ nM and a logP_{oct} (P_{oct}: octanol–water partition coefficient) between 1 and 3.[18]

Compound **1** (Table 1) was synthesized in three steps from 2-(4-dimethylaminophenyl)-6-hydroxybenzothiazole[19] as illustrated in Scheme 1. The dimethylamino substitution at the 4′-position was used to increase the binding affinity to aggregated Aβ as we have demonstrated previously that substitutions at the 6- and 4′-position of 2-phenylbenzothiazole with electron-donating groups such as amino, methylamino, dimethylamino, hydroxyl or alkoxyl groups led to analogs with high binding affinity to aggregated Aβ.[19] The oxorhenium core $[Re(V)O]^{3+}$ was chelated by a monoamide-monoamine-dithiol (MAMA) tetradentate chelator, and the overall charge was balanced by the loss of three protons from one amide N–H group and two thiol S–H groups. The Re-MAMA chelate was connected to the 6-position of 2-phenylbenzothiazole pharmacophore via a 3-C pendant to minimize its interference on the binding of 2-(4-dimethylaminophenyl)benzothiazole to aggregated Aβ. Compound **1** was lipophilic (logP_{C18} = 3.26; P_{C18}: estimation of P_{oct} by a reverse phase HPLC method[19]) and showed high binding affinity (K_i = 10.0 nM) to Aβ_{1-40} fibrils as determined by previously published procedures[19–21] using [^{3}H]BTA-1 as the radioactive control compound. However, there are concerns that the corresponding ^{99m}Tc analog of **1** may not cross the blood-brain barrier satisfactorily due to its high molecular weight (617 Da). Furthermore, ^{99m}Tc complexes derived from amino chelators such as diaminedithiol (DADT) typically show higher brain uptake than those derived from tetradentate chelators containing amide groups such as MAMA.[14,22] Therefore, in addition to the pendant approach used for the preparation of **1**, we also designed and synthesized **2**–**6** (Table 1) with a tetradentate chelator integrated into the 2-phenylbenzothiazole pharmacophore to lower the overall molecular

Table 1
Properties of Re 2-phenylbenzothiazoles including molecular weight (MW), binding affinity (K_i) to Aβ_{1-40}, and lipophilicity (logP_{C18})

Compound number	Structure	MW	K_i (nM)	LogP_{C18}
–	 PiB	256	4.3	1.23
1		704 (617*)	10.0	3.26
2		629 (542*)	30.0	2.59
3		616 (528*)	86.9	2.52
4		602 (514*)	88.6	1.21
5		591 (503*)	43.0	2.30
6		575 (487*)	29.7	1.65

* Molecular weight of their corresponding Tc analogs.



Scheme 1. Synthesis of **1**. Reagents and conditions: (a) 1-bromo-3-chloropropane, K_2CO_3, acetone, 63 h, reflux, 76%; (b) N-[2-[(triphenylmethyl)thio]ethyl]-2-[[2-[(triphenylmethyl)thio]ethyl]amino]acetamide, K_2CO_3, KI, CH_3CN, 67 h, reflux, 68%; (c) (1) TFA, Et_3SiH, 5 min, rt; (2) $ReO(PPh_3)_2Cl_3$, NaOAc, MeOH, 20 h, 75 °C, 7%.

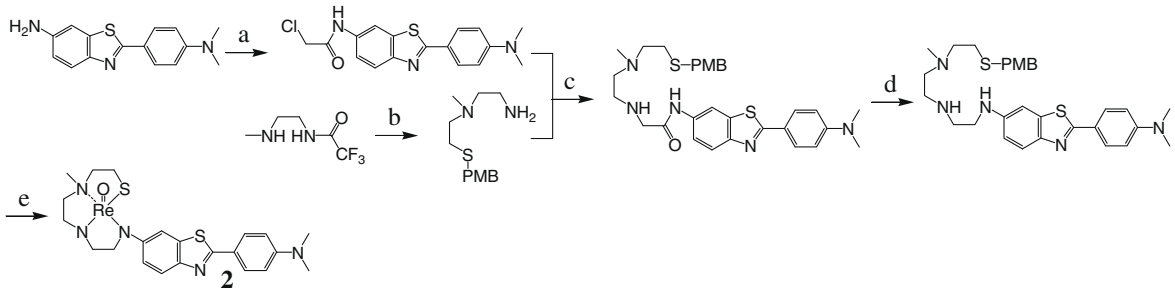
weight of their corresponding ^{99m}Tc analogs to <550 Da. All the nitrogen moieties in the integrated tetradentate chelators are amino groups, in hopes that the ^{99m}Tc analogs of **2**–**6** would show rapid and high brain entry.

Compounds **2**–**4** were synthesized with an integrated triamine-thiol chelator as depicted in Schemes 2 and 3. The lateral amino group of the triamine-thiol chelator was integrated into the 6-position at the benzothiazole ring in **2** or the 4′-position at the phenyl ring in **3** and **4**. This triamine-thiol chelating system was modified from a previously reported mercaptoacetylglycylglycylglycylaminobenzene SN3 system.[23] In the mercaptoacetylglycylglycylglycylaminobenzene SN3 system, complexation with $[Re(V)O]^{3+}$ led to a Re chelate with one negative charge due to the loss of four protons from three amide N–H groups and one thiol S–H group. It is well documented that charged Tc complexes do not cross the blood-brain barrier. Therefore, we modified the original SN3 chelating system by replacing the three amide groups with three amino groups for potentially higher brain uptake. We also added a small methyl group to one of the aliphatic amino groups in order to obtain neutral Tc/Re complexes. Through such modification the overall charge was balanced by losing all three protons (from two amino N–H groups and one thiol S–H group) after $[Re(V)O]^{3+}$ complexation reaction and the desired neutral compounds **2**–**4** were obtained.

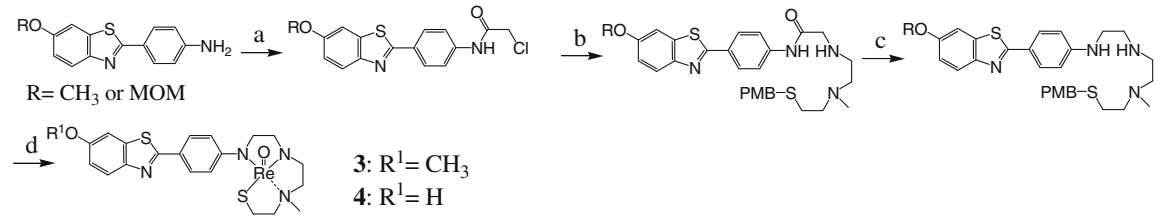
To further reduce the molecular weight we also prepared **5** and **6** in which two electron-donating groups of a tetradentate chelating system were incorporated into the phenyl ring at the 3′- and 4′-position as shown in Scheme 4. The semi-rigid XH-diamine-thiol (X = O in **5** and X = S in **6**) chelators used for our studies were modified from the XH-diamide-thiol chelators reported by Le Gal and coworkers.[24] The complexation of $[Re(V)O]^{3+}$ with Le Gal's XH-diamide-thiol chelators led to Re complexes with one negative charge due to the loss of four protons. In order to produce neutral Re complexes and have higher brain uptake of their ^{99m}Tc analogs, we replaced the two amide groups with two amino groups. Our results showed that, after Re complexation, only three protons were lost (from the phenol O–H, the thiol S–H, and the aromatic amino N–H group for **5**; from the aromatic amino N–H and two thiol S–H groups for **6**). With relatively higher pK_a value, the aliphatic amino N–H group was not deprotonated after Re complexation reaction, and therefore, the overall charge was balanced.

The last step in the preparation of **1**–**6** involved a two-stage reaction.[25] The tetradentate chelating systems were first restored by removing the trityl (Trt), *p*-methoxybenzyl (PMB) and/or methoxymethyl (MOM) protecting groups under acidic conditions, followed by an exchange labeling reaction using a labile Re complex $Re(V)O(PPh_3)_2Cl_3$. During the reaction, the oxorhenium core $[Re(V)O]^{3+}$ chelated by weak ligands triphenylphosphine and chloride was transferred to the stronger tetradentate chelating systems. Compounds **1**–**6** were isolated in 7–41% yields. In spite of potential existence of *cis*- and *anti*-isomers, only one single isomer was isolated in the preparation of **1**–**6**. The chemical identities of **1**–**6** were confirmed by NMR[26] and HRMS,[27] but their absolute configurations have not yet been determined by X-ray crystallography.

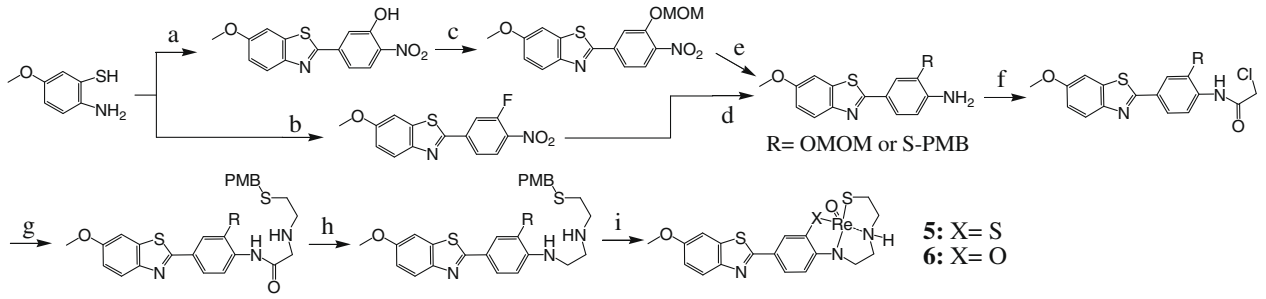
Compounds **2**–**6** were designed to be neutral, lipophilic and compact by integrating the Re chelate into the 2-phenylbenzo-



Scheme 2. Synthesis of **2**. Reagents and conditions: (a) 2-chloroacetyl chloride, K_2CO_3, THF, 14 h, rt, 92%; (b) (1) 2-(4-methoxybenzylthio)ethyl bromide, CH_2Cl_2, 18 h, reflux; (2) NaOH, H_2O, MeOH, 4 h, rt, 67%; (c) KI, K_2CO_3, CH_3CN, 14 h, reflux, 68%; (d) LAH, THF, 17 h, rt, 44%; (e) (1) TFA, anisole, CH_3SO_3H, 1 h, rt; (2) $ReO(PPh_3)_2Cl_3$, NaOAc, MeOH, 24 h, 75 °C, 17%.



Scheme 3. Synthesis of **3** and **4**. Reagents and conditions: (a) 2-chloroacetyl chloride, K_2CO_3, THF, 15 h, rt, 83–92%; (b) *N*-methyl-*N*-[2-[(4-methoxybenzyl)thio]ethyl]-1,2-ethanediamine, KI, K_2CO_3, CH_3CN, 14 h, reflux, 87–88%; (c) LAH, THF, 20 h, rt, 43–58%; (d) (1) TFA, anisole, CH_3SO_3H, 1 h, rt; (2) $ReO(PPh_3)_2Cl_3$, NaOAc, MeOH, 24 h, 75 °C, 27–41%.



Scheme 4. Synthesis of **5** and **6**. Reagents and conditions: (a) 3-hydroxy-4-nitrobenzaldehyde, DMSO, 31 h, 125 °C, 65%; (b) 3-fluoro-4-nitrobenzoyl chloride, NMP, 23 h, 125 °C, 73%; (c) MOMCl, DIEA, THF, 16 h, reflux, 51%; (d) (1) 4-methoxy-α-toluenethiol, K_2CO_3, DMF, 17 h, 95 °C; (2) $SnCl_2$, THF, EtOH, 3 h, reflux, 56%; (e) $Cu(OAc)_2$, $NaBH_4$, EtOH, 17 h, rt, 100%; (f) 2-chloroacetyl chloride, K_2CO_3, THF, 18 h, rt, 81–82%; (g) 2-(4-methoxybenzylthio)ethylamine, KI, K_2CO_3, CH_3CN, 18 h, reflux, 75–98%; (h) LAH, THF, 20 h, rt, 45–81%; (i) (1) TFA, anisole, CH_3SO_3H, 1 h, rt; (2) $ReO(PPh_3)_2Cl_3$, NaOAc, MeOH, 24 h, 75 °C, 17–23%.

thiazole pharmacophore. In addition, they also have electron-donating groups substituted at both 6- and 4′-position to promote high binding affinity to aggregated Aβ. The integration of a tetradentate chelator into the benzothiazole ring provides an electron-donating group at the 6-position (compound **2**) whereas the integration of a tetradentate chelator into the phenyl ring provides an electron-donating group at the 4′-position (compounds **3**–**4**) or at both the 3′- and 4′-position (compounds **5**–**6**). In vitro binding assays showed that **2**–**6** also bind aggregated Aβ with good affinities (29.7–88.6 nM). In addition, **2**–**6** are all lipophilic with the $\log P_{C18}$ values in the range of 1.21 to 2.59. Comparing **3** with **4**, the binding affinity did not change (86.9 vs 88.6 nM) when the methoxy group at the 6-position was replaced with a hydroxyl group, but its $\log P_{C18}$ value was reduced from 2.52 to 1.21. The −1.3 unit reduction in $\log P_{C18}$ value when replacing the 6-position methoxy group of 2-phenylbenothiazole with a hydroxyl group was consistent with our previous observation during the development of PiB.[19] Comparing **5** with **6**, the replacement of a thiol group at the 3′-position with a more hydrophilic and electron-donating hydroxyl group reduced its $\log P_{C18}$ value (2.30 vs 1.65) and slightly enhanced its binding affinity to aggregated Aβ (43.0 vs 29.7 nM). MAMA[13] (in **1**) and semi-rigid SH-diamine-thiol[28] (in **6**) chelating systems have previously been used for the preparation of neutral Tc/Re complexes. However, to the best of our knowledge, neutral Tc/Re complexes derived from the triamine-thiol (in **2**–**4**) and semi-rigid OH-diamine-thiol (in **5**) chelating systems used for our studies have never been reported before. While triamine-thiol and semi-rigid XH-diamine-thiol (X = S or O) chelators all form neutral Re complexes, the use of different tetradentate chelators or the same chelator integrated at different positions combined with substitutions of electron-donating groups at other positions might generate compact Tc/Re 2-phenylbenzothiazoles with different binding affinity, lipophilicity and in vivo pharmacokinetics. A more systematic exploration on the structure-activity relationship is likely to provide the desired 2-phenylbenzothiazole to be labeled with ^{99m}Tc for imaging Aβ deposition with SPECT.

In summary, we have synthesized six neutral Re 2-phenylbenzothiazoles and measured their binding affinity to aggregated Aβ. Synthesized via the pendant approach, compound **1** displayed high binding affinity to aggregated Aβ (K_i = 10 nM). However, the introduction of a 3-C aliphatic linker also resulted in higher molecular weight (>550 Da) and lipophilicity ($\log P_{C18}$ = 3.26) that exceeded our target range of 1–3. Both high molecular weight and lipophilicity might limit the passage of ^{99m}Tc analog of compound **1** across the blood-brain barrier. Synthesized via the integrated approach, **2**–**6** were smaller in size and displayed moderate lipophilicities ($\log P_{C18}$ = 1.21–2.59) that fell into our target range and binding affinities to aggregated Aβ (K_i = 29.7–88.6 nM) that were near our target of $K_i \leqslant 10$ nM. By simply replacing only the Re atom on **2**–**6** with a ^{99m}Tc isotope, the resulting ^{99m}Tc 2-phenylbenzothiazoles are expected to retain the high binding affinity to aggregated Aβ. Since these ^{99m}Tc 2-phenylbenzothiazoles would be small (<550 Da), neutral and lipophilic as well, they are likely to cross the blood-brain barrier and enter the brain. However, for clinical application, further modification to obtain Tc/Re 2-phenylbenzothiazoles with ever higher binding affinity might be needed since most of the Aβ imaging agents currently in clinical evaluation have binding affinities less than 10 nM. Nevertheless, the binding affinities of **1**–**6** presented here are the first Aβ binding data of Re complexes derived from PiB ever to be reported. In addition, our preliminary results also have demonstrated that it is feasible to obtain small, neutral, and lipophilic Re 2-phenylbenzothiazoles with fairly good binding affinity to aggregated Aβ through the integrated design introduced here. Further optimization on the structure-activity relationship of 2-phenylbenzothiazole and the application of this approach to other high affinity pharmacophores such as stilbene[6] and diphenylacetylene[29] have great potential to generate promising ^{99m}Tc analogs for imaging Aβ deposition in living human brain with SPECT.

Acknowledgments

This work was supported by the National Institutes of Health (R01 AG018402, P50 AG005133, R01 AG020226, R37 AG025516, and P01 AG025204), the Alzheimer's Association (TLL-01-3381), and the US Department of Energy (DE-FD02-03 ER63590).

References and notes

1. Hardy, J.; Selkoe, D. J. *Science* **2002**, *297*, 353.
2. Pike, K. E.; Savage, G.; Villemagne, V. L.; Ng, S.; Moss, S. A.; Maruff, P.; Mathis, C. A.; Klunk, W. E.; Masters, C. L.; Rowe, C. C. *Brain* **2007**, *130*, 2837.
3. Pangalos, M. N.; Jacobsen, S. J.; Reinhart, P. H. *Biochem. Soc. Trans.* **2005**, *33*, 553.
4. Shoghi-Jadid, K.; Small, G. W.; Agdeppa, E. D.; Kepe, V.; Ercoli, L. M.; Siddarth, P.; Read, S.; Satyamurthy, N.; Petric, A.; Huang, S. C.; Barrio, J. R. *Am. J. Geriatr. Psychiatry* **2002**, *10*, 24.
5. Klunk, W. E.; Engler, H.; Nordberg, A.; Wang, Y. M.; Blomqvist, G.; Holt, D. P.; Bergstrom, M.; Savitcheva, I.; Huang, G. F.; Estrada, S.; Ausen, B.; Debnath, M. L.; Barletta, J.; Price, J. C.; Sandell, J.; Lopresti, B. J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C. A.; Langstrom, B. *Ann. Neurol.* **2004**, *55*, 306.
6. Verhoeff, N. P. L. G.; Wilson, A. A.; Takeshita, S.; Trop, L.; Hussey, D.; Singh, K.; Kung, H. F.; Kung, M. P.; Houle, S. *Am. J. Geriatr. Psychiatry* **2004**, *12*, 584.
7. Kudo, Y.; Okamura, N.; Furumoto, S.; Tashiro, M.; Furukawa, K.; Maruyama, M.; Itoh, M.; Iwata, R.; Yanai, K.; Arai, H. *J. Nucl. Med.* **2007**, *48*, 553.
8. Mathis, C.A. *Abstract of Papers*, 54th Society of Nuclear Medicine Annual Meeting, Washington, DC. Society of Nuclear Medicine: Reston, VA, 2007; Abstract 187.
9. Rowe, C.C. *Abstract of Papers*, 54th Society of Nuclear Medicine Annual Meeting, Washington, DC. Society of Nuclear Medicine: Reston, VA, 2007; Abstract 188.
10. Friedland, R. P.; Majocha, R. E.; Reno, J. M.; Lyle, L. R.; Marotta, C. A. *Mol. Neurobiol.* **1994**, *9*, 107.
11. Han, H.; Cho, C. G.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, 118: 4506.
12. Zhen, W.; Han, H.; Anguiano, M.; Lemere, C. A.; Cho, C. G.; Lansbury, P. T. *J. Med. Chem.* **1999**, *42*, 2805.

13. Dezutter, N. A.; Dom, R. J.; de Groot, T. J.; Bormans, G. M.; Verbruggen, A. M. *Eur. J. Nucl. Med.* **1999**, *26*, 1392.
14. Zhuang, Z. P.; Kung, M. P.; Hou, C.; Ploessl, K.; Kung, H. F. *Nucl. Med. Biol.* **2005**, *32*, 171.
15. Kung, H.F. *Abstract of Papers*, 16th International Symposium on Radiopharmaceutical Chemistry, Sydney, Australia. Society of Radiopharmaceutical Sciences: Reston, VA, 2005; Abstract 251.
16. Chen, X.; Yu, P.; Zhang, L.; Liu, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1442.
17. Le Gal, J.; Latapie, L.; Gressier, M.; Coulais, Y.; Dartiguenave, M.; Benoist, E. *Org. Biomol. Chem.* **2004**, *2*, 876.
18. Mathis, C. A.; Wang, Y.; Klunk, W. E. *Curr. Pharm. Des.* **2004**, *10*, 1469.
19. Mathis, C. A.; Wang, Y. M.; Holt, D. P.; Huang, G. F.; Debnath, M. L.; Klunk, W. E. *J. Med. Chem.* **2003**, *46*, 2740.
20. Klunk, W. E.; Wang, Y. M.; Huang, G. F.; Debnath, M. L.; Holt, D. P.; Mathis, C. A. *Life Sci.* **2001**, *69*, 1471.
21. Mathis, C. A.; Bacskai, B. J.; Kajdasz, S. T.; McLellan, M. E.; Frosch, M. P.; Hyman, B. T.; Holt, D. P.; Wang, Y. M.; Huang, G. F.; Debnath, M. L.; Klunk, W. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 295.
22. Oya, S.; Plossl, K.; Kung, M. P.; Stevenson, D. A.; Kung, H. F. *Nucl. Med. Biol.* **1998**, *25*, 135.
23. Hansen, L.; Cini, R.; Taylor, A., Jr.; Marzilli, L. G. *Inorg. Chem.* **1992**, *31*, 2801.
24. Le Gal, J.; Tisato, F.; Bandoli, G.; Gressier, M.; Jaud, J.; Michaud, S.; Dartiguenave, M.; Benoist, E. *Dalton Trans.* **2005**, *23*, 3800.
25. (a) *Synthesis of compound* **1**: To a solution of the trityl-protected precursor (198 mg, 0.2 mmol) in trifluoroacetic acid (3 mL), triethylsilane was added dropwise until the color of the solution became colorless. The mixture was stirred for 5 min at rt, and then trifluoroacetic acid was removed under reduced pressure. $ReO(Ph_3)_2Cl_3$ (208 mg, 0.25 mmol) and NaOAc methanolic solution (1.0 M, 20 mL) were added to the residue, and the resulting solution was heated at 75 °C for 20 h. After cooling to rt, the solution was diluted with water (50 mL), and extracted with ethyl acetate (50 mL). The ethyl acetate phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with 10:90 methanol/ethyl acetate to give the title compound **1** as a brown powder (10 mg, 7%). (b) *Synthesis of compounds* **2**–**6**: To a solution of the respective *p*-methoxybenzyl-protected precursor (0.27 mmol) in trifluoroacetic acid (3 mL) and anisole (0.2 mL), methanesulfonic acid (1.5 mL) was added dropwise. The mixture was stirred for 1 h at rt, and then cooled in ice/water bath. The solution was neutralized with NH_4OH, and then extracted with ethyl acetate (10 mL × 3). The ethyl acetate phases were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. $ReO(Ph_3)_2Cl_3$ (208 mg, 0.25 mmol) and NaOAc methanolic solution (1.0 M, 20 mL) were added to the residue, and the resulting solution was heated at 75 °C for 24 h. After cooling to rt, the solution was diluted with water (50 mL), and extracted with ethyl acetate (50 mL). The ethyl acetate phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with 10:90 methanol/ethyl acetate to give the expected product in 17–41% yields.
26. NMR spectra were recorded using a Bruker AVANCE 300 MHz NMR spectrometer, and were reported in parts per million downfield from internal tetramethylsilane. *Compound* **1** (DMSO-d_6): 1.48–1.60 (m, 1H), 2.16–2.38 (m, 2H), 2.80–3.10 (m, 3H), 2.99 (s, 6H), 3.32–3.72 (m, 3H), 3.92–4.17 (m, 4H), 4.29 (d, *J* = 16.8 Hz, 1H), 4.34–4.43 (m, 1H), 5.02 (d, *J* = 16.8 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 7.08 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.77–7.83 (m, 3H); *Compound* **2** ($CDCl_3$): 2.10–2.20 (m, 1H), 2.55–2.70 (m, 2H), 3.06 (s, 6H), 3.20–3.41 (m, 3H), 3.29 (s, 3H), 3.61–3.82 (m, 2H), 3.90–4.03 (m, 2H), 4.21–4.33 (m, 1H), 4.80–4.89 (m, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 7.41 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.88–7.99 (m, 3H); *Compound* **3** ($CDCl_3$): 2.11–2.21 (m, 1H), 2.60–2.71 (m, 2H), 3.20–3.40 (m, 3H), 3.38 (s, 3H), 3.56–3.68 (m, 1H), 3.70–3.82 (m, 1H), 3.89 (s, 3H), 3.90–4.03 (m, 2H), 4.13–4.25 (m, 1H), 4.76–4.85 (m, 1H), 7.05 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.28–7.36 (m, 3H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 2H); *Compound* **4** (DMSO-d_6): 2.09–2.20 (m, 1H), 2.70–2.81 (m, 1H), 3.19 (s, 3H), 3.20–3.52 (m, 5H), 3.60–3.72 (m, 1H), 3.80–4.03 (m, 3H), 4.58–4.70 (m, 1H), 6.92 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.72–7.89 (m, 3H), 9.75 (s, 1H); *Compound* **5** (DMSO-d_6): 2.02–2.14 (m, 1H), 2.81–3.00 (m, 2H), 3.30–3.46 (m, 2H), 3.84 (s, 3H), 3.89–3.98 (m, 1H), 4.27–4.43 (m, 2H), 7.08 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 8.1 (s, 1H), 9.64 (s, 1H); *Compound* **6** (DMSO-d_6): 2.09–2.21 (m, 1H), 2.81–2.92 (m, 1H), 2.95–3.03 (m, 1H), 3.14–3.24 (m, 1H), 3.60–3.71 (m, 1H), 3.83 (s, 3H), 3.85–4.03 (m, 2H), 4.34–4.44 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 9.45 (s, 1H).
27. HRMS experiments were performed at the Department of Chemistry Mass Spectrometry Facility, University of Pittsburgh, on a Waters LC/Q-Tof mass spectrometer using electronspray ionization method. *Compound* **1**: *m/z* calcd for $C_{24}H_{30}N_4O_3ReS_3$ (M+H) 705.1038, found 705.1032; *Compound* **2**: *m/z* calcd for $C_{22}H_{29}N_5OReS_2$ (M+H) 630.1371, found 630.1350; *Compound* **3**: *m/z* calcd for $C_{21}H_{26}N_4O_2ReS_2$ (M+H) 617.1055, found 617.1055; *Compound* **4**: *m/z* calcd for $C_{20}H_{24}N_4O_2ReS_2$ (M+H) 603.0898, found 603.0895; *Compound* **5**: *m/z* calcd for $C_{18}H_{19}N_3O_2ReS_3$ (M+H) 592.0197, found 592.0198; *Compound* **6**: *m/z* calcd for $C_{18}H_{19}N_3O_3ReS_2$ (M+H) 576.0426, found 576.0432.
28. Kagotani, H. Japan Patent 2000219674, 2000.
29. Chandra, R.; Oya, S.; Kung, M.-P.; Hou, C.; Jin, L.-Y.; Kung, H. F. *J. Med. Chem.* **2007**, *50*, 2415.