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Candidate PET Radioligand Development for Neurofibrillary Tangles: Two Distinct Radioligand Binding Sites Identified in Postmortem Alzheimer's Disease Brain

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Abstract

[¹⁸F]THK-523 and [¹⁸F]807 are promising radioligands for imaging neurofibrillary tangles (NFTs) with positron emission tomography (PET) in neurodegenerative diseases, such as Alzheimer's disease (AD) and traumatic brain injury. Although [¹⁸F]THK-523 and [¹⁸F]T807 are considered high-affinity selective radioligands for NFTs, uncertainty has existed as to whether PET radioligands for imaging NFTs bind to the same molecular site because in vitro assays for ligands binding to NFTs have been lacking. We labeled THK-523 and T807 with tritium to serve as reference radioligands for in vitro binding assays with AD brain homogenates for newly synthesized ligands. With these radioligands, we identified two distinct binding sites for small molecules, one site with high affinity for THK-523 and the other with high affinity for T807. Moreover, binding assays with [³H]PIB confirmed that the two newly identified binding sites are also distinct from the thioflavin-T binding site where all current clinically useful PET radioligands for imaging β -amyloid plaque bind with high affinity. The two newly identified binding sites are considered to reside on NFTs rather than on β -amyloid plaques. Furthermore, we applied all three binding assays to a set of newly prepared compounds, based on chain modifications to THK-523. Some compounds with high affinity and selectivity for the THK-523 binding site emerged from this set, including one with amenability to labeling with fluorine-18, namely, ligand **10b**.

Graphical abstract

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Notes

The authors declare no competing financial interest.

Keywords

Radioligand; in vitro assay; tangle; tau; Alzheimer's disease; PET

Alzheimer's disease (AD) and other tauopathies constitute an increasingly enormous societal burden in terms of mortality, morbidity and cost, amidst a continuing absence of effective treatment strategies. Brain neurofibrillary tangles (NFTs) and neuritic plaques are two pathological hallmarks of AD.¹ NFTs are generated from abnormally hyperphosphorylated tau protein, whereas neuritic plaques are comprised primarily of β -amyloid. Human postmortem studies indicate that NFT deposition, unlike β -amyloid plaque deposition, correlates well with neurodegeneration and cognitive impairment.^{2–7} Furthermore, abundant NFTs are not observed in individuals who are cognitively unimpaired,⁵ in contrast to β -amyloid plaques which are nonetheless observed in some nondemented people.^{8–11} Moreover, tau and phospho-tau (ptau181) residing in cerebrospinal fluid are known to be useful biomarkers for the diagnosis of AD.^{12–15}

NFTs are also characteristic of many other tauopathies besides AD, such as sporadic corticobasal degeneration, progressive supranuclear palsy, Pick's disease, frontotemporal dementia Parkinsonism linked to chromosome 17, and Guamanian Parkinsonism dementia-amyotrophic lateral sclerosis complex.¹⁶ Tau aggregates are also the pathological hallmark of chronic traumatic encephalopathy, a neurodegenerative disorder that occurs as a consequence of traumatic brain injury.¹⁷ Aggregation of tau also arises from numerous forms of neuronal injury, including hypoxia, hyperglycemia, and heat shock.

Positron emission tomography (PET) may detect and quantify a low-density protein in living human brain when this imaging technique is used with an effective radioligand that penetrates brain to provide a robust and adequately high specific signal. Such radioligands are invariably labeled with either of two cyclotron-produced short-lived positron-emitters, namely, carbon-11 ($t_{1/2} = 20.4$ min) or fluorine-18 ($t_{1/2} = 109.8$ min). Over the past decade and a half, significant progress has been made on developing radioligands for PET imaging of β -amyloid plaques in diseased human brain (Chart 1). The radioligand from Eli Lilly, Amyvid (Florbetapir; [^{18}F]AV-45),^{18,19} is the first approved by the United States Food and Drug Administration (FDA) for human use. GE's Vizamy (Flutemetamol; [^{18}F]3'-F-PIB; GE-067)²⁰ is also now approved by the FDA. NeuraCeq (Florbetaben; [^{18}F]AV-1; [^{18}F]BAY94-9172)²¹ and [^{18}F]AZD4694²² are also proving clinically useful. Each of these radioligands, and also the progenitor radioligand [^{11}C]PIB,²³ binds with high affinity to the so-called "thioflavin-T binding site" on β -amyloid plaques.

By contrast with the PET imaging of β -amyloid plaques, the PET imaging of NFTs is much less advanced, mainly because candidate PET radioligands are still limited in efficacy.^{24,25} A high-performing PET radioligand for imaging brain NFTs would be useful not only to identify areas of neuronal damage but also to monitor the effectiveness of experimental therapies in AD, CTE, and other tauopathies. Indeed, several drugs that block phosphorylation and/or aggregation of tau are being developed for the possible treatment of these diseases.

Recent publications on [¹¹C]PBB3,²⁶ [¹⁸F]T807 (AV-1451),²⁷ [¹⁸F]T808,²⁸ and [¹⁸F]THK-523²⁵ (Chart 2) suggest that these radioligands have at least moderate selectivity for binding to NFTs over β -amyloid plaques, primarily on the basis of evidence gleaned from in vitro autoradiography of postmortem human brain. [¹¹C]PBB3,²⁶ [¹⁸F]T807,²⁷ and [¹⁸F]T808²⁸ have also shown moderate NFT-specific signals in PET imaging of human subjects. However, [¹¹C]PBB3 suffers from photoisomerization, which poses difficulties for regular practical application. Based on the initial report,²⁵ [¹⁸F]THK-523 gives a low PET signal and may suffer some other undesirable properties, such as low brain entry and radiodefluorination. However, radioligands that are structurally related to [¹⁸F]THK-523, namely, [¹⁸F]THK-5117²⁹ and [¹⁸F]THK-5351³⁰ (Chart 2), have recently entered clinical trials. Therefore, we also selected THK-523 as a lead compound in our search for more promising PET radioligands for imaging NFTs.

Multiple binding sites for PET radioligands that target β -amyloid plaques have been identified.^{31,32} This suggested to us that more than one ligand binding site might also exist in NFTs. Therefore, we produced both [³H]T807 and [³H]THK-523 to serve as reference radioligands for our in vitro assays on new candidate ligands for NFTs. As a result, we discovered that the binding sites for these two radioligands are distinct from each other, and that they are also distinct from the β -amyloid plaque binding site for thioflavins, such as [³H/¹¹C]PIB. In addition, a limited medicinal chemistry effort, based on chain extension and modification of THK-523, provided ligands with moderate lipophilicity and with high affinity and selectivity for the identified THK-523 binding site, including **10b** which is amenable to labeling with fluorine-18.

RESULTS

Chemistry

Ligand Synthesis—Specifically, we wished to explore whether the affinity of THK-523 for binding to NFTs could be enhanced by extension of its pendant 6-(2-fluoroethoxy) group and by structural variation at its terminus. The use of oxyethylene units to extend chains has been implemented previously as a promising strategy in PET radioligand development for imaging β -amyloid plaques, as apparent in the structures of Florbetapir¹⁹ and Florbetaben²¹ (Chart 1). Especially, this strategy allows radioligand lipophilicity to be kept within a desirably moderate range and can also be used to retain a terminal site for labeling with fluorine-18. We further considered that variation in the terminal substituent of the pendant chain, especially with a bulkier group having hydrogen bond acceptors or donors, might enhance binding affinity with NFTs through extra binding interactions. Therefore, we devised a general strategy to prepare THK-523 derivatives featuring chains composed of a

defined number of oxyethylene units (1–6) and with a fluoro, hydroxy, or larger substituent as a chain terminus. Our synthetic strategy was based on commercially available 2-chloro-6-methoxyquinoline (**1**) as starting material.

The first stage in the overall synthesis program was to replace the methoxy group in **1** with one or more oxyethylene units (Scheme 1). The phenol **2** was obtained in moderate yield (47%) by demethylation of **1** with boron tribromide. Various poly(oxyethylene)-bis-alcohols were monotosylated to give **3b–f** in low to moderate yields (29–53%). Treatment of **2** with the bromo compound **3a** or with one of the tosylates gave the hydroxyl terminated compounds with the desired number of oxyethylene units (**4a–f**) in good to excellent yields, except for **4a** (27%). This approach was also explored for preparing analogous compounds with a fluoro terminus, but succeeded only for compound **5** having a pendant 6-(2-fluoroethoxy) chain. Nonetheless, **5** was obtained in virtually quantitative yield (Scheme 1).

The next stage aimed to cross couple the prepared chloroquinolines (**4a–f** and **5**) with 4-(Boc-amino)-phenylboronic acid through Suzuki reactions. The preparation of the methoxy compound **6** from **1** (Scheme 2) was used as a model for establishing effective coupling conditions. We tried various combinations of phosphine ligand, palladium compound, and solvent, including 2'-phenyl-phenyl di-*t*-butyl phosphine plus Pd(OAc)₂ in THF or DMF, 1,1'-bis-(diisopropylphosphino)ferrocene plus Pd₂(dba)₃ in toluene, and Pd(PPh₃)₄ plus K₂CO₃ in DME-H₂O. The latter combination was most effective, giving virtually quantitative yield of **6**. K₂CO₃ was necessary for the reaction to proceed, and the proportion of water had to be kept below 50%. These coupling conditions delivered the *N*-protected hydroxy-terminated compounds (**7a–f**) plus the *N*-protected fluoro compound **8** in good to excellent yields (60–99%). Compounds **7a–f** were readily converted into their tosylates (**9a–f**) in excellent yields (83–90%) by treatment with tosyl chloride. Our prior attempts to insert the tosylate group into these compounds before Suzuki coupling did not succeed. Treatment of **8** with TFA gave THK-523 (**10a**) in quantitative yield (Scheme 2).

Treatment of the *N*-protected tosylates **9b–f** with TBAF in THF gave the target fluoro ligands **10b–f** in moderate to high yield (40–92%), without the need for a separate deprotection reaction (Scheme 3). The small amount of water in the commercial reagent was found to be critical for the success of these syntheses. If water was rigorously excluded from the reactions, products were obtained with a lower number of oxyethylene units.

Treatment of the Boc-protected tosylate **9b** with cyclohexane-1,3-dione, cyclopentane-1,3-dione or 2-aminoethanol in acetonitrile with potassium carbonate as base gave the variously chain-terminated compounds **11a** (79%), **11b** (59%) and **11f** (21%), respectively (Scheme 3). Treatment of **9b** with base plus one of the ketones, oxazolidin-2-one, imidazolidin-2-one or thiazoline-2-one gave the compounds **11c–e** with alternative bulky terminal groups in a similar range of yields (21–59%). The Boc group in each of the compounds **11a–f** was removed readily with BF₃·OEt₂ to give the target ligands **12a–f** in 35–72% yields (Scheme 3).

Synthesis of Halo Precursors for Tritiation—Treatment of THK-523 (**10a**) with NIS in chloroform–methanol at room temperature gave compound **13** with an iodo group at each

position ortho to the free amino group (Scheme 4). Any protective group at the amino group, such as an acetyl or formyl group, prevented iodination. We found that the two iodo substituents in **13** could be removed with hydrogen in the presence of Pd/C as catalyst to regenerate THK-523. Thus, [³H]THK-523 was obtained by treating **13** with tritium gas as a custom synthesis (Moravek Biochemicals & Radiochemicals, Inc.) (Scheme 4).

Attempt at an analogous iodination of T807 did not generate any tractable compound, and no further effort was made to synthesize an iodinated derivative of T807. Bromination of T807 with NBS generated the tribromo substituted derivative **14** (Scheme 5). We found that the three bromo substituents in **14** could be removed with hydrogen in the presence of Pd/C as catalyst to regenerate T807. Thus, [³H]T807 was obtained by treating **14** with tritium gas as a custom synthesis (Moravek Biochemicals & Radiochemicals, Inc.) (Scheme 5).

¹⁸F-Labeling of THK-523 and Derivatives—Because [¹⁸F] **10b–f** might be considered candidate PET radioligands, we were interested to test the feasibility of their labeling with no-carrier-added (NCA) cyclotron-produced [¹⁸F] fluoride ion. The *N*-Boc-protected tosylates, **9b–f**, were used as precursors for trial ¹⁸F-labeling (Scheme 6). After successful substitution of the tosylate group with [¹⁸F]fluoride ion, the Boc group was removed under acidic conditions. The labeled THK-523 derivatives [¹⁸F]**10b–f** were each neutralized and isolated with HPLC in 20–30% decay-corrected radiochemical yields.

Binding Assays for Human AD β -Amyloid Plaques and NFTs

We used three tritium-labeled compounds as reference radioligands (Chart 3) to measure the in vitro inhibition constants of new compounds with human AD brain homogenate as protein source. Protocols similar to those that have been used previously for assays of [³H]PIB binding to AD brain tissue did not generate any discernible inhibition curves for [³H]THK523 or [³H]T807 binding. We tried a variety of ways to improve the binding assays, including use of a variety of assay mediums, such as PBS, aq. DMSO (20%), aq. DMSO (40%), neat DMSO, aq. ethanol (20%), aq. ethanol (40%), neat ethanol, aq. BSA (0.1%), or Tween-20 (0.1%) in PBS, and a variety of washing solutions, such as PBS, Tris, aq. ethanol (20%), aq. ethanol (40%), or neat ethanol. The combination of conditions that gave reproducible results was as follows: (a) use of AD brain tissue homogenate that was rehomogenized after thawing the stock homogenate; (b) treatment of the rehomogenized suspension with a high-power ultrasonic probe; and (c) use of Tween-20 (0.1%) in PBS instead of PBS as the assay medium. After the best conditions were implemented, the washing solution was found to have little effect on measured K_i values (Figure 1).

Titration of AD Brain Homogenate with [³H]THK-523—The binding of the AD brain homogenate with [³H]THK-523 at different concentrations of THK-523 followed a typical saturation curve for a radioligand with a large proportion of nonspecific binding (Figure 2). The curve was fitted to the equation

$$[BF] = B_{\max} [F] / (K_D + [F]) + (NS [F]) + c$$

where [BF] is the concentration of bound radioligand, $B_{\max}$ is the concentration of maximal binding sites, [F] is the concentration of free radioligand plus THK-523, K_D is the equilibrium dissociation constant, NS is the coefficient of nonspecific binding, and c is the concentration of bound radioligand in background. The best fit was obtained with $K_D = 3.5 \pm 3.4$ nM, $B_{\max} = 1576 \pm 499$ dpm, $NS = 321 \pm 7$, and $c = 17.38 \pm 173$.

Titration of AD Brain Homogenate with [^{18}F]THK-523—The binding of the AD brain homogenate with [^{18}F]THK-523 at different concentrations of THK-523 also followed a typical saturation curve for a radioligand with a large proportion of nonspecific binding (Figure 3). The curve was fitted as in the analogous experiment with [^3H]THK-523. The best fit was obtained with $K_D = 4.6 \pm 1.8$ nM, $B_{\max} = 1639 \pm 235$ dpm, $NS = 169 \pm 3$, and $c = 57.7 \pm 65.2$.

Inhibition of Binding to Human AD β -Amyloid Plaques and NFTs—When we used the three binding assays with AD brain homogenates to screen compounds for inhibition of radioligand binding at 1 μmol concentration, we found that the reference radioligands occupied distinctly different binding sites. Thus, T807 failed to inhibit [^3H]THK-523 binding (Figure 4), and THK-523 failed to inhibit [^3H]T807 binding (Figure 5). Similar mutually exclusive inhibition behavior was also observed for [^3H]PIB (data not shown). These graphical demonstrations of multiple binding sites were also confirmed by the K_i values measured for THK-523, T807 and the newly synthesized compounds at the three different binding sites (Table 1). For the new fluoro compounds **10b–f**, only the compound with two oxyethylene units (**10b**) showed high affinity ($K_i = 28$ nM) and selectivity for binding to the “THK binding site”. None of these compounds showed high affinity for the “T807 binding site”, whereas compound **12e**, which has five oxyethylene units, showed high affinity ($K_i = 43$ nM) and selectivity for binding to the “PIB binding site”. Some variations in the terminal group were quite well tolerated among other compounds having two oxyethylene units. Thus, whereas compound **12a** and **12b** showed greatly decreased K_i values, compounds **12c–f** retained both high affinity and selectivity for the THK binding site. Notably, **12e** and **12f** showed higher affinities (lower K_i values) than THK-523 itself in the same assay.

Computed Lipophilicity

Computation indicated that $\text{clog}D$ for all the prepared target ligands was held within a moderate range (1.3–3.74), except for compounds **12a** and **12f**.

DISCUSSION

We overcame many obstacles to establish in vitro assays for measuring the relative binding affinities of small molecules for NFTs. The challenges that we met came from three main issues: (1) Ligand solubility is low in PBS; for example, THK-523 is insoluble in water or PBS; even its high fluorescence is not observed in water, reflecting its limited solubility in common media used for binding assays. (2) NFTs from AD brain homogenate are poorly accessible to small molecules; they exist as aggregates within neurons, unlike β -amyloid

plaques, which exist outside neurons. (3) NFTs are highly heterogeneous, and on standing they precipitate within 5–10 min.

Effective conditions for binding assays on human AD brain tissue were achieved by taking three measures: (1) substituting PBS with 0.1% Tween-20 in PBS as the assay medium; (2) rehomogenizing the brain tissue homogenate before each experiment; and (3) ultrasound treatment of the tissue after the rehomogenization. With regard to the ligand solubility issue, we tried adding organic solvent, such as ethanol or DMSO, at various concentrations, to the binding assay medium. We also tried adding BSA. However, we did not obtain an appreciable signal for specific binding of radioligand, and the small dubious signal was also irreproducible. Although a low concentration of Tween-20 (0.001%) in PBS was ineffective, it was found that a much higher concentration 0.1% promoted complete dissolution of the ligands in aqueous media. The other two measures were designed to address the issue of poor NFT accessibility to small molecules. Rehomogenization before an assay experiment helped to break down the chunk of brain tissue into smaller pieces, thereby exposing individual neurons to the highest degree. Subsequent ultrasound treatment then helped to break the neuronal cell membranes, exposing the NFTs to small molecules.

During our initial efforts to work up assay conditions, we hypothesized that the specific radioligand binding signal was obscured by high nonspecific binding to the brain tissue homogenate. Therefore, various washing agents were tested to reduce radioligand nonspecific binding, such as PBS or Tris-buffer, or various concentrations of ethanol, DMSO, acetic acid, or formic acid in water. However, it was found that, after deploying the revised combination of conditions for the binding assay, the nature of the washing agent no longer affected the K_i measurement (Figure 2).

The K_D value for THK-523 for binding to AD brain homogenate was also measured by titration. K_D was found to be 3.5 ± 3.4 and 4.6 ± 1.8 nM with [^3H]THK-523 (Figure 3) and [^{18}F]THK-523 (Figure 4) as radioligands, respectively. These measurements are clearly in good agreement. However, the K_i value measured from the competitive inhibition experiment was much lower at 51 ± 22 nM. This discrepancy may derive from error that is intrinsic to the titration experiments, where the specific binding signals are only a small fraction of the total binding.

The principal discovery of this study is the plurality of distinct binding sites on NFTs. Both [^{18}F]THK-523 and [^{18}F]T807, and their close analogues, are considered to be radioligands that bind selectively to NFTs, based on ample evidence from autoradiography, immunohistochemistry, and the use of brain tissue from different disease origins.^{25,28,33,34} Therefore, in this study, we assumed that the binding of THK-523 analogues to AD tissue homogenate was entirely to binding sites on NFTs, rather than to other binding sites on β -amyloid plaques or to other proteins in AD brain homogenate. When we analyzed the binding data, we assumed a single-site model, to which the data fit quite well. No compelling reason to fit the data to two or more binding sites was found. The mutually exclusive binding behaviors of [^3H]THK-523, [^3H]T807 and of some of the prepared ligands (e.g., **10b**, **12c**, **12e**; Table 1) showed that they occupy different binding sites within NFTs. Although multiple binding sites have been observed on β -amyloid plaques,^{31,32,35} only

radioligands that bind to the thioflavin T site (Chart 1) have so far become useful for clinical PET imaging. Nonetheless, for biomedical research on the various NFTs in tauopathies, radioligands that bind to different sites on NFTs may well find distinct applications.

From only a small set of synthesized THK-523 derivatives, three compounds (**10b**, **12e**, and **12f**) emerged with high affinity (<50 nM) and selectivity for the THK-523 binding site (Table 1). These contained two oxyethylene units. Some five-membered rings were well tolerated as chain terminal groups, as in **12c** and **12e**. Compounds with more than two oxyethylene units showed no appreciable binding at the THK-523 site ($K_i > 1000$ nM), although **10e** with five oxyethylene units showed high affinity and selectivity for binding to the PIB site ($K_i > 4.3$ nM). Compound **10b** appears of special interest because of (i) its demonstrated amenability to labeling with fluorine-18, (ii) high affinity ($K_i = 28$ nM) on par with that of THK-523 itself in the same assay ($K_i = 51$ nM), and (iii) a moderate lipophilicity ($\log D$, 3.74) that computes to be only 0.44 clog D units greater than that of THK-523 (Table 1).

CONCLUSIONS

We developed reliable in vitro binding assays to measure the binding affinities of small molecules proposed as possible radioligands for PET imaging of NFTs. Through tritium-labeling of THK-523 and T807, we identified two different kinds of binding sites on NFTs. These two binding sites are also different from that of PIB. Use of these three assays expands the scope for developing new PET radioligands for NFTs by bringing a variety of binding sites into consideration. Moreover, chain modifications in THK-523 were successful in producing compounds with high affinity and selectivity for the THK binding site, accompanied by moderate lipophilicity compatible with further development as PET radioligands.

METHODS

Materials

Water was purified with a system comprising two filters, one Rio, one reservoir, and one Milli-Q synthesis system (Millipore; Bedford, MA). Common solvents were obtained from Fisher Scientific (Pittsburgh, PA). Literature methods were used to prepare PIB,²³ T807,³⁶ 2-fluoroethyl 4-methylbenzenesulfonate,³⁷ and 2-hydroxyethyl 4-methylbenzenesulfonate.³⁸ [³H]PIB was purchased from Moravek Biochemicals Inc. (Brea, CA) as a custom radiosynthesis. 2-Chloro-6-methoxyquinoline (**1**) was obtained from Ark Pharma Inc. (Libertyville, IL). Other chemicals, including 2-bromoethanol (**3a**) were purchased from Aldrich Chemical Co. (Milwaukee, WI), Fluka Chemical Co. (Milwaukee, WI), Acros (Hampton, NH), or Strem Chemicals (Newburyport, MA), and were used without further purification.

Instruments and General Methods

Analytical TLC was performed on precoated aluminum plates (silica gel 60, F254) and compounds were visualized under UV light at 254 or 365 nm. Reaction products were purified with flash column chromatography on silica gel 60 (230–400 mesh), and EtOAc-

hexane-MeOH was used as mobile phase. Analytical HPLC was performed with a reversed phase column (X-bridge C18; 5 μ m; 10.0 $\times$ 250 mm; Waters Corp.; Milford, MA) eluted with *c.* NH₃ (0.025%) in MeCN-H₂O at 6.2 mL/min. The chromatography system was fitted with a continuous wavelength UV-vis detector (System Gold 168 Detector; Beckman; Fullerton, CA) and an autosampler (System Gold 508; Beckman). For semi-preparative HPLC, a reversed phase column (Atlantis C18; 5 μ m; 30 $\times$ 150 mm; Waters Corp.) or silica gel column (10 μ m; 30 $\times$ 250 mm; Phenomenex; Torrance, CA) was eluted at 30 mL/min. The HPLC system was fitted with a manual injector (5 mL loop) and a third delivery pump using MeCN or EtOAc as mobile phase at 1 mL/min. The purities of compounds were determined with HPLC monitored for absorbance at 254 nm and expressed as area percentage of all peaks. All compound purities exceeded 95%.

The ¹H and ¹³C NMR spectra of all compounds were acquired on a DRX 400 instrument (400 MHz ¹H and 100 MHz ¹³C; Bruker; Billerica, MA), using the chemical shifts of residual deuterated solvent as the internal standard; chemical shift (δ) data for the proton and carbon resonances are reported in parts per million (ppm) downfield relative to the signal for TMS (δ = 0). Mass spectra were acquired using a Velos Pro LC-MS instrument (Thermo Fisher Scientific; Waltham, MA) fitted with a Luna C18 column (5 μ m; 2.0 $\times$ 150 mm; Phenomenex) eluted at 150 μ L/min with a MeOH-H₂O mixture. High-resolution mass spectra (HRMS) were acquired from the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL). Either electron spray ionization (ESI) or electron ionization (EI) was used. Melting points were measured with a Mel-Temp (Electrothermal; Thermo Fisher Scientific) or SMP-30 (Stuart; Staffordshire, UK) manual melting point apparatus and were uncorrected. cLog*D* was computed with Pallas for Windows software version 3.8 in default option (CompuDrug; Bal Harbor, FL). A Discover apparatus (CEM; Matthews, NC) was used for microwave synthesis.

Brain Tissue

Postmortem brain tissues from an autopsy-confirmed AD case and a healthy control were obtained from the Human Brain Collection Core (HBCC), NIH.

Ligand Syntheses

2-Chloroquinolin-6-ol (2)—2-Chloro-6-methoxyquinoline (**1**; 10 g; 52 mmol) was dissolved in DCM (200 mL), and BBr₃ (12 mL; 126 mmol) was added through a large needle syringe. Some off-white precipitate formed quickly and accumulated during the reaction. The mixture was stirred at RT overnight, and then quenched slowly by adding MeOH until heat and gas generation stopped. The solution was basified by adding NaHCO₃ until gas generation stopped. The mixture was then extracted with DCM (200 mL $\times$ 3). The collected organic phase was dried (MgSO₄), and the solvent was removed to give **2** as a brown solid (4.8 g; 47%) that was pure enough for subsequent reactions: ¹H NMR (CD₃OD) δ 8.11 (d, 1H, ³*J*_{HH} = 8.6 Hz, ArH), 7.78 (d, 1H, ³*J*_{HH} = 9.2 Hz, ArH), 7.38 (m, 2H, ArH), 7.15 (d, ⁴*J*_{HH} = 2.6 Hz, 1H, ArH); *m/z* (ESI-MS): 180.3 (100%, [M + H]⁺), 182.2 (30%, [M + H]⁺), 190.1 (22%); HRMS (TOF⁺): calcd for C₉H₇ClNO [M + H]⁺, 180.0216; found, 180.0215. Error (ppm): -2.5.

2-(2-Hydroxyethoxy)ethyl 4-Methylbenzenesulfonate (3b)—2,2'-Oxybis(ethan-1-ol) (1.7 g, 16 mmol) was dissolved in DCM (10 mL). *p*-TsCl (1.0 g, 5.3 mmol) and pyridine (1.2 mL, 16 mmol) were added sequentially. The reaction mixture was stirred at RT for 2 days, and then partitioned between DCM (100 mL) and brine (100 mL). The aq. phase was extracted twice with DCM (100 mL). The combined organic phase was dried (MgSO₄), and the solvent was removed to leave a colorless oil, which was dissolved in DCM. Silica gel (4 mL) was added, and the mixture was dried by rotary evaporation. The dry powder was loaded onto a silica gel column with silica gel–hexane (100 mL). Oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) eluted in EtOAc–hexane (1:3). Elution with EtOAc–hexane (1:1) followed by removal of solvent gave **3b** as a colorless oil (0.57 g; 42%): ¹H NMR (CDCl₃) δ 7.77 (dm, ³J_{HH} = 8.3 Hz, 2H, ArH), 7.32 (dm, ³J_{HH} = 8.6 Hz, 2H, ArH), 4.17–4.15 (m, 2H, OCH₂), 3.67–3.63 (m, 4H, OCH₂), 2.42 (s, 3H, CH₃); ¹³C NMR (CDCl₃) δ 145.1, 133.0, 130.0, 128.0, 72.7, 69.4, 68.8, 61.8, 21.8 (s, 1C, CH₃); *m/z* (ESI-MS): 371.1 (30%, [TsO(C₂H₄O)₄H + Na]⁺), 349.1 (30%, TsO(C₂H₄O)₄H + H]⁺), 283.1 (100%, [M + Na]⁺), 278.1 (34%, [M + H₂O]⁺), 261.1 (100%, [M + H]⁺), 235.1 (30%), 89.1 (40%, [CH₂CH₂OCH₂CH₂OH]⁺); HRMS (TOF⁺) calcd for C₁₁H₁₆O₅S, 261.0797 [M + H]⁺; found, 261.0792. Error (ppm): –1.9.

2-(2-(2-Hydroxyethoxy)ethoxy)ethyl 4-Methylbenzenesulfonate (3c)—2,2'-(Ethane-1,2-diylbis(oxy))bis(ethan-1-ol) (15.5 g, 103 mmol) was dissolved in DCM (50 mL). *p*-TsCl (6.2 g, 32.5 mmol) and pyridine (8.0 mL, 99 mmol) were added sequentially. The reaction mixture was stirred at RT for 2 days, and then silica gel (60 mL) was added. The mixture was dried by rotary evaporation. The dry powder was loaded onto a silica gel column with silica gel–hexane (600 mL). The bis-tosylate eluted with EtOAc–hexane (1:3). Elution with EtOAc–hexane (1:1) followed by removal of solvent gave **3c** as a colorless oil (5.2 g; 53%). ¹H NMR (CDCl₃) δ 7.79 (d, ³J_{HH} = 8.4 Hz, 2H), 7.35 (d, ³J_{HH} = 8 Hz, 2H), 4.16 (m, 2H), 3.69 (m, 4H), 3.59 (s, 4H), 3.56 (m, 2H), 2.85 (s, 1H), 2.45 (s, 3H); ¹³C {¹H} NMR (CDCl₃) δ 144.9, 132.8, 129.9, 127.9, 72.5, 70.7, 70.2, 69.3, 68.6, 61.6, 21.6; *m/z* (ESI-MS): 459.2 (50%, [TsO(C₂H₄O)₆H + Na]⁺), 454.1 (26%, [TsO(C₂H₄O)₆H + H₂O]⁺), 437.2 (28%, [TsO(C₂H₄O)₆H + H]⁺), 415.2 (11%), 343.1 (16%), 327.1 (97%, [M + Na]⁺), 454.1 (34%, [M + H₂O]⁺), 305.1 (100%, [M + H]⁺), 301.1 (20%), 199.0 (17%), 181.0 (14%), 133.1 (23%); HRMS (TOF⁺) calcd for C₁₃H₂₁O₆S, 305.1059 [M + H]⁺; found, 305.1056. Error (ppm): –1.0.

2-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)ethyl 4-Methylbenzene-sulfonate (3d)—The method for **3c** was applied to 2,2'-((oxybis-(ethane-2,1-diyl))bis(oxy))bis(ethan-1-ol) (10.2 g, 52.5 mmol) and gave **3d** as a colorless oil (3.2 g; 43%): ¹H NMR (CDCl₃) δ 7.79 (d, ³J_{HH} = 8.4 Hz, 2H), 7.35 (d, ³J_{HH} = 8 Hz, 2H), 4.16 (m, 2H), 3.65 (m, 14H), 2.61 (s, 1H), 2.45 (s, 3H); ¹³C NMR (CDCl₃) δ 144.9, 132.9, 129.8, 128.0, 72.5, 70.7, 70.6, 70.4, 70.3, 69.3, 68.7, 61.7, 21.6; *m/z* (ESI-MS): 547.2 (27%, [TsO(C₂H₄O)₈H + Na]⁺), 542.3 (34%, [TsO(C₂H₄O)₈H + H₂O]⁺), 525.2 (28%, [TsO(C₂H₄O)₈H + H]⁺), 371.1 (70%, [M + Na]⁺), 349.1 (100%, [M + H]⁺); HRMS (TOF⁺) calcd for C₁₅H₂₅O₇S, 349.1321 [M + H]⁺; found, 349.1323. Error (ppm): +0.6.

14-Hydroxy-3,6,9,12-tetraoxatetradecyl 4-Methylbenzenesulfonate (3e)—*p*-TsCl (19.15 g, 108 mmol), KI (557 mg, 3.36 mmol), and silver(I) oxide (9.34 g, 40.3 mmol) were added to a solution of pentaethylene glycol (8 g, 33.6 mmol) in DCM (150 mL), and the mixture was stirred overnight and then filtered over Celite. The filtrate was washed with H₂O and extracted three times with DCM, dried (MgSO₄), and filtered. The solvent was evaporated off from the filtrate and the residue was purified with flash chromatography (acetone-hexane-triethylamine; 39.9:60:0.1) to give **3e** as a colorless oil (4.08 g; 31%): ¹H NMR (CDO₃) δ 7.79 (d, ³J_{HH} = 8.4 Hz, 2H), 7.35 (d, ³J_{HH} = 8 Hz, 2H), 4.16 (m, 2H), 3.65 (m, 18H), 2.88 (s, 1H), 2.45 (s, 3H); ¹³C NMR (CDCl₃) δ 144.8, 132.9, 129.8, 127.9, 72.5, 72.5, 70.7, 70.5, 70.5, 70.5, 70.2, 69.3, 68.6, 61.6, 21.6. HRMS (TOF⁺) calcd for C₁₇H₂₉O₈S, 393.1583 [M + H]⁺; found, 393.1591. Error (ppm): +2.0.

17-Hydroxy-3,6,9,12,15-pentaoxaheptadecyl 4-Methylbenzene-sulfonate (3f)—The method for **3e** was applied to hexaethylene glycol (8 g, 28.3 gave **3f** as a colorless oil (3.57 g; 29%): ¹H NMR (CDCl₃) δ 7.79 (m, 2H), 7.35 (d, *J* = 8 Hz, 2H), 4.16 (m, 2H), 3.66 (m, 22H), 2.81 (s, 1H), 2.45 (s, 3H); ¹³C NMR (CDCl₃) δ 144.81, 132.94, 129.83, 127.96, 72.50, 70.69, 70.58, 70.53, 70.51, 70.49, 70.30, 69.28, 68.64, 61.68, 21.64; HRMS (TOF⁺) calcd for C₁₉H₃₃O₉S, 437.1845 [M + H]⁺; found, 437.1845. Error (ppm): +0.0.

2-((2-Chloroquinolin-6-yl)oxy)ethan-1-ol (4a)—Compound **2** (0.10 g, 0.56 mmol), 2-bromoethanol (**3a**; 0.20 mL, 1.7 mmol), and Cs₂CO₃ (0.9 g, 2.8 mmol) were suspended in DMF (1.0 mL) and stirred at RT for 2 d. Conversion of the starting material was 90%. The mixture was microwaved (100c5m50w250 psi). After the reaction was found to be 95% complete by HPLC, the mixture was partitioned between EtOAc and brine. The combined organic phase was dried (MgSO₄). After removing solvent, the crude product was dissolved in DCM and mixed with silica gel (4.0 mL). Solvent was then removed. Chromatography of the residual powder on silica gel (EtOAc-hexane, 1:1) gave **4a** as a white solid (34 mg; 27%): ¹H NMR (CDCl₃) δ 7.96 (d, 1H, 8.8 Hz, ArH), 7.91 (d, 1H, ³J_{HH} = 9.2 Hz, ArH), 7.37 (dd, 1H, ³J_{HH} = 9.2 Hz, ⁴J_{HH} = 2.8 Hz, ArH), 7.33 (d, ³J_{HH} = 8.6 Hz, 1H, ArH), 7.07 (d, ⁴J_{HH} = 2.8 Hz, 1H, ArH), 4.21–4.19 (m, 2H, OCH₂), 4.07–4.05 (m, 2H, OCH₂), 2.35 (brs, 1H, OH); ¹³C NMR (CD₃OD) δ 157.1, 147.0, 143.0, 138.7, 128.0, 127.4, 123.3, 122.4, 106.8, 70.0, 59.4; *m/z* (ESI-MS): 226.0, 224.0 (100%, [m + H]⁺), 182.0, 180.0 (10%, [M + H – C₂H₄O]⁺); HRMS (TOF⁺): calcd for C₁₁H₁₀ClNO₂ [M + H]⁺, 224.0478; found, 224.0481. Error (ppm): +1.3.

2-(2-((2-Chloroquinolin-6-yl)oxy)ethoxy)ethan-1-ol (4b)—Compound **2** (0.10 g, 0.56 mmol), **3b** (0.26 g, 1.0 mmol), and Cs₂CO₃ (0.55 g, 1.7 mmol) were suspended in DMF (1.0 mL) within a nitrogen-filled glovebox. The mixture was microwaved (100c30m50w250 psi). HPLC showed greater than 90% conversion of starting material. The mixture was partitioned between EtOAc and brine. The combined organic phase was dried (MgSO₄). The solvent was removed to give **4b** as an oil (0.15 g; 100%): ¹H NMR (CDCl₃) δ 7.91 (d, ³J_{HH} = 8.5 Hz, 1H, ArH), 7.85 (d, ³J_{HH} = 9.2 Hz, 1H, ArH), 7.34 (dd, ³J_{HH} = 9.2 Hz, ⁴J_{HH} = 2.8 Hz, 1H, ArH), 7.27 (d, ³J_{HH} = 8.6 Hz, 1H, ArH), 7.01 (d, ⁴J_{HH} = 2.8 Hz, 1H, ArH), 4.20–4.17 (m, 2H, OCH₂), 3.89–3.87 (m, 2H, OCH₂), 3.76–3.73 (m, 2H, OCH₂), 3.67–3.64 (m, 2H, OCH₂); ¹³C NMR (CDCl₃) δ 157.3, 148.3, 143.9, 137.9, 130.1, 127.9, 123.3, 122.7, 106.4,

72.9, 69.6, 67.9, 61.9; m/z (ES-MS): 310.1 (10%), 279.1 (12%), 268.1 (100%, $[M + H]^+$), 270.1 (34%, $[M + H]^+$); HRMS (TOF⁺) calcd for C₁₃H₁₅ClNO₃, 268.0740 $[M + H]^+$; found, 268.0747. Error (ppm): +2.6.

2-(2-(2-((2-Chloroquinolin-6-yl)oxy)ethoxy)ethoxy)ethan-1-ol (4c)—The method for **4b** was applied to **3c** (0.34 g, 1.1 mmol) and gave **4c** as an oil (0.18 g; 100%): ¹H NMR (CDCl₃) δ 7.96 (d, ³ J_{HH} = 8.4 Hz, 1H), 7.90 (d, ³ J_{HH} = 9.2 Hz, 1H), 7.41 (dd, ³ J_{HH} = 6.8 Hz, 6.8 Hz, 1H), 7.32 (d, ³ J_{HH} = 8.4 Hz, 1H), 7.07 (d, ⁴ J_{HH} = 2.4 Hz, 1H), 4.24 (m, 2H), 3.93 (m, 2H), 3.73 (m, 6H), 3.62 (t, ³ J_{HH} = 4 Hz, 2H), 2.68 (s, 1H); ¹³C NMR (CDCl₃) δ 157.2, 148.1, 143.8, 137.7, 129.9, 127.8, 123.3, 122.5, 106.2, 72.5, 70.9, 70.4, 69.6, 67.7, 61.7; HRMS (TOF⁺) calcd for C₁₃H₁₉ClNO₄, 312.1003 $[M^+ + H]^+$; found, 312.1010. Error (ppm): +2.2.

2-(2-(2-((2-Chloroquinolin-6-yl)oxy)ethoxy)ethoxy)ethan-1-ol (4d)—The method for **4b** was applied to **3d** (0.39 g, 1.1 mmol) and gave **4d** as an oil (0.16 g; 78%): ¹H NMR (CDCl₃) δ 7.97 (d, ³ J_{HH} = 8.4 Hz, 1H), 7.90 (d, ³ J_{HH} = 9.2 Hz, 1H), 7.41 (dd, ³ J_{HH} = 9.6 Hz, 9.6 Hz, 1H), 7.32 (d, ³ J_{HH} = 8.8 Hz, 1H), 7.08 (d, ⁴ J_{HH} = 2.8 Hz, 1H), 4.24 (m, 2H), 3.93 (m, 2H), 3.68 (m, 12H), 2.91 (s, 1H); ¹³C NMR (CDCl₃) δ 157.2, 148.1, 143.8, 137.7, 129.8, 127.8, 123.3, 122.5, 106.2, 72.5, 70.8, 70.6, 70.6, 70.3, 69.6, 67.8, 61.7; m/z (ESI-MS): 536.2 (7%, $[M - Cl + (OCH_2CH_2)_4OH + Na]^+$), 532.2 (16%, $[M - Cl + (OCH_2CH_2)_4OH + H_2O + H]^+$), 514.3 (28%, $[M - Cl + (OCH_2CH_2)_4OH + H]^+$), 378.1 (32%, $[M + Na]^+$), 380.1 (11%), 356.1 (100%, $[M + H]^+$), 358.1 (30%), 320.2 (9%, $[M - Cl]^+$); HRMS (TOF⁺) calcd for C₁₇H₂₃ClNO₅, 356.1265 $[M + H]^+$; found, 356.1267. Error (ppm): +0.6.

14-((2-Chloroquinolin-6-yl)oxy)-3,6,9,12-tetraoxatetradecan-1-ol (4e)—

Compound **3e** (4.0 g, 10.2 mmol) and Cs₂CO₃ (16.6 g, 51 mmol) were added to a solution of **2** (1.53 g, 8.05 mmol) in DMF (15 mL) in a microwave tube loaded with a stirrer bar, and the mixture was microwaved (95°C/60 min/30 min) with stirring. The reaction mixture was washed with brine and extracted three times with EtOAc, dried (MgSO₄), and filtered. The solvent was evaporated off, and the residue was purified with flash chromatography (EtOAc-hexane-MeOH; 90:5:5) to give **4e** as a yellowish-white solid (2.07 g, 52%): ¹H NMR (CDCl₃) δ 7.98 (d, ³ J_{HH} = 8.4 Hz, 1H), 7.91 (d, ³ J_{HH} = 9.2 Hz, 1H), 7.41 (dd, ³ J_{HH} = 9.2 Hz, 9.2 Hz, 1H), 7.33 (d, ³ J_{HH} = 8.4 Hz, 1H), 7.09 (d, ⁴ J_{HH} = 2.4 Hz, 1H), 4.25 (m, 2H), 3.93 (m, 2H), 3.76 (m, 2H), 3.68 (m, 12H), 3.60 (m, 2H), 2.68 (s, 1H); ¹³C NMR (CDCl₃) δ 157.3, 148.1, 143.8, 137.7, 129.9, 127.9, 123.4, 122.5, 106.2, 72.5, 70.9, 70.6, 70.6, 70.6, 70.5, 70.3, 69.6, 67.8, 61.7; HRMS (TOF⁺) calcd for C₁₉H₂₇ClNO₆, 400.1527 $[M + H]^+$; found, 400.1527. Error (ppm): +0.0.

17-((2-Chloroquinolin-6-yl)oxy)-3,6,9,12,15-pentaoxaheptadecan-1-ol (4f)—

The method for **4e** was applied to **3f** (819 mg, 1.87 mmol). Flash chromatography (EtOAc-MeOH-hexane; 85:10:5) of the crude product gave **4f** as a yellow-white solid (373 mg, 54%): ¹H NMR (CDCl₃) δ 7.98 (d, ³ J_{HH} = 8 Hz, 1H), 7.89 (d, ³ J_{HH} = 12 Hz, 1H), 7.41 (dd, ³ J_{HH} = 6.8 Hz, ³ J_{HH} = 6.8 Hz, 1H), 7.32 (d, ³ J_{HH} = 8 Hz, 1H), 7.32 (d, ⁴ J_{HH} = 4 Hz, 1H), 7.07 (d, ⁴ J_{HH} = 2.4 Hz, 1H), 4.24 (m, 2H), 3.92 (m, 2H), 3.93 (m, 20H), 2.68 (s,

1H); ^{13}C NMR (CDCl_3) δ 157.3, 148.1, 143.8, 137.7, 130.0, 127.9, 123.4, 122.5, 106.2, 72.6, 70.9, 70.6, 70.6, 70.5, 70.5, 70.2, 69.6, 67.8, 61.7; HRMS (TOF^+) calcd for $\text{C}_{21}\text{H}_{31}\text{ClNO}_7$, 444.1789 $[\text{M} + \text{H}]^+$; found, 444.1784. Error (ppm): -1.1.

2-Chloro-6-(2-fluoroethoxy)quinoline (5)—Compound **2** (0.50 g, 2.8 mmol), 2-fluoroethyl tosylate (0.90 g, 4.1 mmol), and Cs_2CO_3 (4.6 g, 14.1 mmol) were suspended in THF (5.0 mL). The mixture was stirred overnight. After the reaction was found to be complete with HPLC, the mixture was partitioned between EtOAc and brine. The combined organic phase was dried (MgSO_4). After removing solvent from the filtrate, the crude product was dissolved in DCM and mixed with silica gel (4.0 mL). Solvent was then removed. Chromatography of the residual powder on silica gel (EtOAc-hexane) gave **5** as a white solid (0.63 g; 100%): ^1H NMR (CD_3OD) δ 7.97 (d, 1H, $^3J_{\text{HH}} = 8.5$ Hz, ArH), 7.92 (d, 1H, $^3J_{\text{HH}} = 9.2$ Hz, ArH), 7.42 (dd, 1H, $^3J_{\text{HH}} = 9.2$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, ArH), 7.33 (d, $^3J_{\text{HH}} = 8.6$ Hz, 1H, ArH), 7.07 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 4.88–4.86 (m, 1H, FCH_2), 4.76–4.74 (m, 1H, FCH_2), 4.36–4.34 (m, 1H, OCH_2), 4.29–4.27 (m, 1H, OCH_2); m/z (ESI-MS): 272.0, 270.0 (40%, $[\text{M} - \text{Cl} + \text{Br}]$), 226.2 (100%, $[\text{M} + \text{H}]^+$), 228.2 (30%, $[\text{M} + \text{H}]^+$); HRMS (TOF^+): calcd for $\text{C}_{11}\text{H}_9\text{ClFNO}$ $[\text{M} + \text{H}]^+$, 226.0435; found, 226.0437. Error (ppm): +0.9.

***t*-Butyl (4-(6-Methoxyquinolin-2-yl)phenyl)carbamate (6)**—Compound **1** (0.10 g, 0.52 mmol), (4-((*t*-Boc)amino)phenyl)boronic acid (0.137 g, 0.67 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.026 g, 0.023 mmol), and K_2CO_3 (0.122 g, 1.04 mmol) were suspended in DME- H_2O (4:1; 10 mL). The mixture was microwaved (80c60m50w250 psi). After the reaction was found to be complete by HPLC, the mixture was partitioned between EtOAc and brine (100 mL $\times$ 3). The combined organic phase was dried (MgSO_4). After the solvent was removed, the crude product was dissolved in DCM, and silica gel (4 mL) was added, and dried. Chromatography of the residual powder on silica gel (100 mL; EtOAc-hexane, 1:3) gave **6** as a white solid (0.16 g; 100%): ^1H NMR (acetone- d_6) δ 8.58 (brs, 1H, NH), 8.25 (d, 1H, $^3J_{\text{HH}} = 8.9$ Hz, ArH), 8.22 (dm, 2H, $^3J_{\text{HH}} = 9.2$ Hz, ArH), 8.01 (d, 1H, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.97 (d, $^3J_{\text{HH}} = 9.2$ Hz, 1H, ArH), 7.72 (d, $^3J_{\text{HH}} = 8.9$ Hz, 1H, ArH), 7.38 (dd, $^3J_{\text{HH}} = 9.5$ Hz, $^4J_{\text{HH}} = 2.6$ Hz, 1H, ArH), 7.32 (d, $^4J_{\text{HH}} = 2.9$ Hz, 1H, ArH), 3.95 (s, 3H, OCH_3), 1.51 (s, 9H, CH_3); ^1H NMR (CDCl_3) δ 8.07 (dm, 2H, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 8.05 (d, 1H, Hz, ArH), 8.01 (d, 1H, $^3J_{\text{HH}} = 8.9$ Hz, ArH), 7.78 (d, 1H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 7.49 (d, 2H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 7.34 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 7.05 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 6.62 (s, 1H, NH), 3.92 (s, 3H, OCH_3), 1.52 (s, 9H, CH_3); ^{13}C NMR (CDCl_3) δ 157.7, 154.6, 152.8, 144.5, 141.3, 139.4, 135.7, 134.5, 131.2, 128.2, 128.1, 122.4, 119.1, 118.6, 105.2, 80.9, 77.9, 55.7, 29.9, 28.6; m/z (ESI-MS): 350.9 (100%, $[\text{M} + \text{H}]^+$), 295.2 (38%, $[\text{M} - \text{C}(\text{CH}_3)_3 + \text{H}]^+$); HRMS (TOF^+): calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$, 351.1709; found, 351.1704. Error (ppm): 1.4.

***t*-Butyl (4-(6-(2-Hydroxyethoxy)quinolin-2-yl)phenyl)carbamate (7a)**—The method for **6** was applied to **4a** (0.700 g, 3.13 mmol) and gave **7a** as a white solid (0.714 g; 60%): ^1H NMR (CDCl_3) δ 8.09 (d, 2H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 8.05 (d, 2H, $^3J_{\text{HH}} = 9.2$ Hz, ArH), 7.81 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.51 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H, ArH), 7.39 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 7.10 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 6.60 (brs, 1H, NH), 4.24–4.21 (m, 2H, OCH_2), 4.06–4.04 (m, 2H, OCH_2), 1.55 (s, 9H, CH_3); m/z (ESI-MS):

381.2 (100%, $[M + H]^+$), 325.1 (81%, $[M - C_4H_8 + H]^+$); HRMS (TOF⁺): calcd for $C_{22}H_{24}N_2O_4$ $[M + H]^+$, 381.1814; found, 381.1812. Error (ppm): -0.5.

t-Butyl (4-(6-(2-(2-Hydroxyethoxy)ethoxy)quinolin-2-yl)phenyl)-carbamate (7b)

—The method for **6** was applied to **4b** (0.15 g, 0.56 mmol) and gave **7b** as a white solid (0.24 g; 99%): ¹H NMR (CDCl₃) δ 8.06 (d, 2H, ³J_{HH} = 8.6 Hz, ArH), 8.04 (d, 2H, ³J_{HH} = 9.0 Hz, ArH), 8.03 (d, 1H, ³J_{HH} = 8.7 Hz, ArH), 8.02 (d, ³J_{HH} = 9.1 Hz, 1H, ArH), 7.77 (d, ³J_{HH} = 8.7 Hz, 1H, ArH), 7.48 (d, ³J_{HH} = 8.5 Hz, 1H, ArH), 7.37 (dd, ⁴J_{HH} = 9.2 Hz, ⁴J_{HH} = 2.7 Hz, 1H, ArH), 7.06 (d, ⁴J_{HH} = 2.7 Hz, 1H, ArH), 6.62 (brs, 1H, NH), 4.26–4.24 (m, 2H, OCH₂), 3.94–3.92 (m, 2H, OCH₂), 3.79–3.76 (m, 2H, OCH₂), 3.71–3.69 (m, 2H, OCH₂), 1.52 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 156.8, 154.8, 152.8, 144.6, 139.5, 135.7, 134.5, 131.3, 128.2, 128.1, 122.6, 119.1, 118.7, 106.3, 81.0 (CO), 72.9 (CO), 69.8 (CO), 67.9 (CO), 62.0 (CO), 28.6 (CH₃); *m/z* (ESI-MS): 425.2 (93%, $[M + H]^+$), 310.1 (10%), 279.1 (100%); HRMS (TOF⁺): calcd for $C_{24}H_{29}N_2O_5$ $[M + H]^+$, 425.2076; found, 425.2073. Error (ppm): -0.7.

t-Butyl (4-(6-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)quinolin-2-yl)phenyl)carbamate (7c)

—The method for **6** was applied to **4c** (0.18 g, 0.56 mmol) and gave **7c** as a white solid (0.26 g; 99%): ¹H NMR (CDCl₃) δ 8.02 (m, 4H), 7.71 (d, ³J_{HH} = 8.8 Hz, 1H), 7.50 (d, ³J_{HH} = 8.4 Hz, 2 H), 7.37 (dd, ³J_{HH} = 6.8 Hz, 6.8 Hz, 1H), 7.02 (d, ⁴J_{HH} = 2.4 Hz, 1H), 6.89 (s, 1H), 4.24 (m, 2H), 3.91 (m, 2H), 3.73 (m, 6H), 3.62 (m, 2H), 2.71 (s, 1H), 1.53 (s, 9H); ¹³C NMR (CDCl₃) δ 156.5, 154.5, 152.7, 144.3, 139.4, 135.5, 134.2, 130.9, 127.9, 127.8, 122.4, 118.8, 118.5, 106.0, 80.6, 72.5, 70.9, 70.4, 69.7, 67.6, 61.7, 28.4; *m/z* (ESI-MS): 469.2 (100%, $[M + H]^+$), 470.2 (30%); HRMS (TOF⁺): calcd for $C_{26}H_{33}N_2O_6$ $[M + H]^+$, 469.2339; found, 469.2331. Error (ppm): -1.7.

t-Butyl (4-(6-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)quinolin-2-yl)phenyl)carbamate (7d)

—The method for **6** was applied to **4d** (0.18 g, 0.45 mmol) and gave **7d** as a white solid (0.23 g; 99%): ¹H NMR (CDCl₃) δ 8.05 (m, 4H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.39 (dd, *J* = 6.8 Hz, 6.8 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.63 (s, 1H), 4.27 (m, 2H), 3.93 (m, 2H), 3.68 (m, 12H), 1.53 (s, 9H); ¹³C NMR (CDCl₃) δ 154.7, 152.7, 150.7, 142.5, 137.4, 133.6, 132.4, 129.1, 126.1, 126.0, 120.6, 117.0, 116.6, 104.2, 78.8, 70.7, 69.0, 68.8, 68.7, 68.4, 67.8, 65.8, 59.9, 26.5; *m/z* (ESI-MS): 535.2 (9%, $[M + Na]^+$), 513.3 (100%, $[M + H]^+$); HRMS (TOF⁺): calcd for $C_{28}H_{37}N_2O_7$, $[M + H]^+$, 513.2601; found, 513.2595. Error (ppm): -1.2.

t-Butyl (4-(6-((14-Hydroxy-3,6,9,12-tetraoxatetradecyl)oxy)-quinolin-2-yl)phenyl)carbamate (7e)

—4-(*N*-Boc-amino)-phenylboronic acid (1.42 g, 6.02 mmol), K₂CO₃ (1.38 g, 10 mmol), and Pd(PPh₃)₄ (288 mg, 0.25 mmol) were added to a solution of **4e** (2.0 g, 5 mmol) in DME-H₂O (4:1; 15 mL) and then microwaved (80°C/40 m/80 w) with stirring. The reaction mixture was washed with brine and extracted with three times with EtOAc, dried (MgSO₄), and filtered. The solvent was evaporated off from the filtrate, and the residue was purified by flash chromatography (EtOAc–hexane–MeOH; 90:7:3) to give **7e** as a yellowish-white solid (1.86 g, 67%): ¹H NMR (CDCl₃) δ 8.02 (m, 4H), 7.71 (d, ³J_{HH} = 8.8 Hz, 1H), 7.50 (d, ³J_{HH} = 8.4 Hz, 2 H), 7.37 (dd, ³J_{HH} = 6.8 Hz, 6.8 Hz, 1H), 7.02

(d, $^4J_{\text{HH}} = 2.4$ Hz, 1H), 6.89 (s, 1H), 4.24 (m, 2H), 3.91 (m, 2H), 3.73 (m, 6H), 3.62 (m, 2H), 2.71 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (CDCl_3) δ 156.5, 154.5, 152.7, 144.3, 139.4, 135.5, 134.2, 130.9, 127.9, 127.8, 122.4, 118.8, 118.5, 106.0, 80.6, 72.5, 70.9, 70.4, 69.7, 67.6, 61.7, 28.4; HRMS (TOF⁺): calcd for $\text{C}_{30}\text{H}_{41}\text{N}_2\text{O}_8$, $[\text{M} + \text{H}]^+$, 557.2863; found, 557.2869. Error (ppm): +0.6.

t-Butyl (4-(6-((17-Hydroxy-3,6,9,12,15-pentaoxaheptadecyl)oxy)-quinolin-2-yl)phenyl)carbamate (7f)—The method for **6** was applied to **4f** (1.225 g, 2.04 mmol) and gave **7f** as a yellowish white solid (1.01 g, 83%): ^1H NMR (CDCl_3) δ 8.03 (m, 4H), 7.73 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 7.52 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 7.38 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 9.2$ Hz, 1H), 7.04 (m, 2H), 4.22 (m, 2H), 3.9 (m, 2H), 3.69 (m, 18H), 3.57 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (CDCl_3) δ 156.6, 154.5, 152.7, 144.2, 139.5, 135.5, 134.1, 130.8, 127.9, 127.8, 122.5, 118.8, 118.5, 106.0, 80.6, 72.7, 70.8, 70.6, 70.6, 70.5, 70.5, 70.4, 70.2, 69.6, 67.7, 61.6, 28.4. HRMS (TOF⁺): calcd for $\text{C}_{32}\text{H}_{45}\text{N}_2\text{O}_9$, $[\text{M} + \text{H}]^+$, 601.3125; found, 601.3143. Error (ppm): +3.0.

t-Butyl (4-(6-(2-Fluoroethoxy)quinolin-2-yl)phenyl)carbamate (8)—The method for **6** was applied to compound **5** (0.727 g, 3.22 mmol) and gave 0.831 g; 67%): ^1H NMR (acetone- d_6) δ 8.59 (brs, 1H, NH), 8.25 (d, 1H, $^3J_{\text{HH}} = 9.7$ Hz, ArH), 8.23 (dm, 2H, $^3J_{\text{HH}} = 9.0$ Hz, ArH), 8.02 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 8.00 (d, $^3J_{\text{HH}} = 10.4$ Hz, 1H, ArH), 7.72 (d, $^3J_{\text{HH}} = 8.7$ Hz, 1H, ArH), 7.44 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 7.36 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 4.92–4.91 (m, $^2J_{\text{HF}} = 43.9$ Hz, 1H, FCH_2), 4.81–4.79 (m, $^2J_{\text{HF}} = 43.9$ Hz, 1H, FCH_2), 4.49–4.47 (m, $^2J_{\text{HF}} = 29.1$ Hz, 1H, OCH_2), 4.42–4.4 (m, $^2J_{\text{HF}} = 29.1$ Hz, 1H, OCH_2), 1.52 (s, 9H, CH_3); ^{13}C NMR (CDCl_3) δ 156.5, 155.0, 152.8, 144.7, 139.5, 135.7, 134.4, 131.4, 128.0, 122.5, 119.2, 118.7, 106.4, 82.1 ($^2J_{\text{CF}} = 169.8$ Hz, CF), 81.0 (CO), 67.6 ($^3J_{\text{CF}} = 20.7$ Hz, CCF), 28.6 (CH_3); m/z (ESI-MS): 383.2 (100%, $[\text{M} + \text{H}]^+$), 327.2 (20%, $[\text{M} - \text{C}_4\text{H}_8 + \text{H}]^+$); HRMS (TOF⁺): calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_2\text{O}_3$ $[\text{M} + \text{H}]^+$, 383.1771; found, 383.1770. Error (ppm): -0.3.

2-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)ethyl 4-methyl-benzenesulfonate (9a)—Compound **7a** (0.21 g, 0.55 mmol) and TsCl (0.24 g, 1.3 mmol) were dissolved in DCM (10 mL). Triethylamine (0.5 mL, 3.6 mmol) was added slowly. The mixture was stirred overnight. After the reaction was found to be complete by HPLC, the mixture was partitioned between EtOAc and brine (50 mL $\times$ 3). The combined organic phase was dried (MgSO_4). After the solvent was removed, the crude product was dissolved in DCM, and silica gel (2 mL) was added, and dried. Chromatography of the residual powder on silica gel (50 mL; EtOAc–hexane, 1:3) gave **9a** as a white solid (0.26 g; 89%): ^1H NMR (CDCl_3) δ 8.09 (d, 2H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 8.02 (vt, 2H, $^3J_{\text{HH}} = 9.4$ Hz, ArH), 7.83 (d, 2H, $^3J_{\text{HH}} = 8.0$ Hz, ArH), 7.80 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.51 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H, ArH), 7.33 (d, $^3J_{\text{HH}} = 8.0$ Hz, 2H, ArH), 7.21 (dd, $^3J_{\text{HH}} = 8.8$ Hz, $^4J_{\text{HH}} = 3.2$ Hz, 1H, ArH), 6.97 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 6.62 (s, 1H, NH), 4.47–4.44 (m, 2H, OCH_2), 4.29–4.27 (m, 2H, OCH_2), 2.42 (s, 3H, CH_3), 1.54 (s, 9H, CH_3); ^{13}C NMR (CDCl_3) δ 155.8 (CO), 154.8, 152.5, 145.0, 144.5, 139.4, 135.5, 134.2, 132.9, 131.2, 130.0, 128.03, 127.99, 127.7, 122.1, 119.0, 118.4, 106.1, 80.8 (COtBu), 68.0, 65.6, 28.4 ($\text{C}(\text{CH}_3)_3$), 21.7 (CH_3); m/z (ESI-MS): 589.1 (10%), 535.2 (100%, $[\text{M} + \text{H}]^+$), 479.1 (12%), 263.1 (14%); HRMS (TOF⁺):

calcd for $C_{31}H_{35}N_2O_7S$, $[M + H]^+$, 579.2165; found, 579.2155. Error (ppm): -1.7. m/z (ESI-MS): 535.2 (100%, $[M + H]^+$), 536.2 (34%); HRMS (TOF⁺): calcd for $C_{29}H_{31}N_2O_6S$ $[M + H]^+$, 535.1903; found, 535.1899. Error (ppm): -0.7.

2-(2-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)ethoxy)ethyl 4-methylbenzenesulfonate (9b)—

The method for **9a** was applied to **7b** (0.24 g, 0.55 mmol) and gave **9b** as a white solid (0.29 g; 90%): ¹H NMR (CDCl₃) δ 8.12 (d, 2H, ³J_{HH} = 8.9 Hz, ArH), 8.09 (d, 1H, ³J_{HH} = 9.2 Hz, ArH), 8.05 (d, 1H, ³J_{HH} = 9.5 Hz, ArH), 7.83 (d, 1H, ³J_{HH} = 8.5 Hz, ArH), 7.81 (d, ³J_{HH} = 8.2 Hz, 2H, ArH), 7.53 (d, ³J_{HH} = 9.2 Hz, 2H, ArH), 7.37 (dd, ³J_{HH} = 9.5 Hz, ⁴J_{HH} = 3.0 Hz, 1H, ArH), 7.30 (d, ³J_{HH} = 9.2 Hz, 2H, ArH), 7.08 (d, ⁴J_{HH} = 3.0 Hz, 1H, ArH), 6.60 (s, 1H, NH), 4.24 (m, 2H, OCH₂), 4.20 (m, 2H, OCH₂), 3.89 (m, 2H, OCH₂), 3.82 (m, 2H, OCH₂), 2.40 (s, 3H, CH₃), 1.56 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 156.5 (CO), 154.6, 152.6, 144.8, 144.4, 139.3, 137.7, 135.5, 134.3, 133.0, 131.1, 129.8, 128.0, 127.9, 122.4, 118.9, 118.4, 106.1, 80.7 (COtBu), 69.8, 69.2, 69.0, 67.7, 28.4 (C(CH₃)₃), 21.6 (CH₃); m/z (ESI-MS): 579.2 (100%, $[M + H]^+$), 580.2 (36%), 422.1 (9%); HRMS (TOF⁺): calcd for $C_{31}H_{35}N_2O_7S$, $[M + H]^+$, 579.2165; found, 579.2155. Error (ppm): -1.7.

2-(2-(2-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)ethoxy)-ethoxy)ethyl 4-methylbenzenesulfonate (9c)—

p-TsCl (3.05 g, 16 mmol) and excess triethylamine were added to a solution of **7c** (300 mg, 0.64 mmol) in DCM (100 mL) and stirred at RT overnight. The reaction mixture was washed with brine and extracted three times with EtOAc, dried (MgSO₄), and filtered. Solvent was evaporated off. Flash chromatography (EtOAc–hexane 1:1) of the residue gave **9c** as a yellowish-white solid (354 mg, 89%): ¹H NMR (CDCl₃) δ 8.04 (m, 4H), 7.77 (m, 3H), 7.51 (d, ³J_{HH} = 8.8 Hz, 2H), 7.37 (dd, ³J_{HH} = 6.4 Hz, 6.4 Hz, 1H), 7.29 (d, ³J_{HH} = 8 Hz, 2H), 7.06 (d, ⁴J_{HH} = 2.8 Hz, 1H), 6.74 (s, 1H), 4.23 (m, 2H), 4.15 (m, 2H), 3.89 (m, 2H), 3.70 (m, 4H), 3.64 (m, 2H), 2.40 (s, 3H), 1.54 (s, 9H); ¹³C NMR (CDCl₃) δ 156.6, 154.5, 152.6, 144.8, 144.4, 139.3, 135.5, 134.3, 132.9, 131.0, 129.8, 128.0, 127.9, 127.9, 80.7, 70.8, 70.8, 69.7, 69.3, 68.8, 67.7, 28.4, 21.6; m/z (ESI-MS): 623.2 (100%, $[M + H]^+$), 624.2 (38%); HRMS (TOF⁺): calcd for $C_{33}H_{39}N_2O_8S$, $[M + H]^+$, 623.2427; found, 623.2418. Error (ppm): -1.4.

2-(2-(2-(2-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)ethoxy)-ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (9d)—

The method for **9c** was applied to **7d** (1.18 g, 2.3 mmol). Flash chromatography (acetone–hexane–triethylamine; 30:69:1) of the crude product gave **9d** as a yellowish-white solid (1.26 g, 83%): ¹H NMR (CDCl₃) δ 8.06 (m, 4H), 7.77 (d, ³J_{HH} = 8.4 Hz, 3H), 7.51 (d, ³J_{HH} = 8.4 Hz, 2H), 7.38 (dd, ³J_{HH} = 9.2 Hz, 9.2 Hz, 1H), 7.3 (d, ³J_{HH} = 8 Hz, 2H), 7.07 (d, ⁴J_{HH} = 2.8 Hz, 1H), 6.73 (s, 1H), 4.24 (m, 2H), 4.14 (m, 2H), 3.92 (m, 2H), 3.75 (m, 2H), 3.67 (m, 4H), 3.59 (m, 4H), 2.40 (s, 3H), 1.54 (s, 9H); ¹³C NMR (CDCl₃) δ 156.7, 154.4, 152.6, 144.8, 144.0, 139.4, 135.8, 134.0, 132.9, 130.7, 128.0, 122.7, 118.9, 118.4, 106.0, 80.7, 70.9, 70.8, 70.7, 70.6, 69.7, 69.3, 68.7, 67.7, 28.4, 21.6. HRMS (TOF⁺): calcd for $C_{35}H_{43}N_2O_9S$, $[M + H]^+$, 667.2689; found, 667.2675. Error (ppm): -2.1.

14-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (9e)—The method for **9c** was applied to **7e** (1.8 g, 3.2 mmol) and after flash chromatography (EtOAc–hexane–triethylamine; 80:19:1) of the crude product gave **9e** as a yellowish-white solid (1.88 g, 83%): ^1H NMR (CDCl_3) δ 8.04 (m, 4H), 7.77 (m, 3H), 7.51 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2H), 7.38 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 9.2$ Hz, 1H), 7.30 (d, $^3J_{\text{HH}} = 8$ Hz, 2H), 7.06 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.71 (s, 1H), 4.24 (m, 2H), 4.14 (m, 2H), 3.92 (m, 2H), 3.76 (m, 2H), 3.65 (m, 8H), 3.56 (m, 4H), 2.41 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (CDCl_3) δ 156.8, 154.3, 152.5, 144.8, 139.6, 136.1, 133.0, 130.4, 129.8, 128.1, 128.0, 127.9, 122.9, 119.0, 118.4, 106.0, 80.8, 70.9, 70.7, 70.7, 70.6, 70.5, 69.7, 69.3, 68.7, 67.8, 28.4, 21.6; HRMS (TOF $^+$): calcd for $\text{C}_{37}\text{H}_{47}\text{N}_2\text{O}_{10}\text{S}$, $[\text{M} + \text{H}]^+$, 711.2951; found, 711.2932. Error (ppm): –2.7 ppm.

17-((2-(4-((t-Boc)amino)phenyl)quinolin-6-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate (9f)—The method for **9c** was applied to **7f** (300 mg, 0.50 mmol) and after flash chromatography (EtOAc–hexane–MeOH; 8:1:1) of the crude product gave **9f** (316 mg, 84%) as a yellowish-white solid: ^1H NMR (CDCl_3) δ 8.04 (m, 4H), 7.77 (m, 3H), 7.51 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 7.38 (dd, $^3J_{\text{HH}} = 6.4$ Hz, $^3J_{\text{HH}} = 6.4$ Hz, 1H), 7.31 (d, $^3J_{\text{HH}} = 8$ Hz, 2H), 7.06 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.82 (s, 1H), 4.24 (m, 2H), 4.13 (m, 2H), 3.92 (m, 2H), 3.76 (m, 2H), 3.63 (m, 16H), 2.42 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (CDCl_3) δ 156.6, 154.5, 152.6, 144.8, 144.3, 142.8, 141.5, 139.4, 135.5, 134.2, 132.9, 130.9, 129.8, 129.7, 128.0, 127.9, 127.9, 125.4, 125.3, 122.5, 118.8, 118.4, 106.0, 80.6, 70.9, 70.7, 70.6, 70.6, 70.6, 70.6, 70.5, 69.9, 69.7, 69.3, 68.7, 67.7, 28.4, 21.7; HRMS (TOF $^+$): calcd for $\text{C}_{39}\text{H}_{51}\text{N}_2\text{O}_{11}\text{S}$, $[\text{M} + \text{H}]^+$, 755.3214; found, 755.3209. Error (ppm): –0.7 ppm.

4-(6-(2-Fluoroethoxy)quinolin-2-yl)aniline (10a)—Compound **8** (0.21 g; 0.549 mmol) was dissolved in DCM (12 mL) and TFA (1 mL) was added. The mixture became a pale brown solution. After the reaction was confirmed to be complete, the mixture was partitioned between EtOAc and brine (100 mL $\times$ 3). The combined organic phase was dried (MgSO_4). Removal of solvent gave **10a** as a white solid (0.155 g; 100%): ^1H NMR ($\text{DMSO}-d_6$) δ 8.17 (d, 1H, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.96 (d, 2H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 7.92 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.87 (d, 1H, $^3J_{\text{HH}} = 9.1$ Hz, ArH), 7.38 (dd, 1H, $^3J_{\text{HH}} = 9.1$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, ArH), 7.34 (d, 1H, $^4J_{\text{HH}} = 2.7$ Hz, ArH), 6.68 (d, 1H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 5.49 (brs, 2H, NH_2), 4.82 (dm, $^2J_{\text{HH}} = 47.8$ Hz, 2H, CH_2F), 4.36 (dm, $^3J_{\text{HH}} = 30.0$ Hz, 2H, CH_2O); ^{13}C NMR ($\text{DMSO}-d_6$) δ 155.3, 154.5, 150.2, 143.6, 135.4, 130.2, 127.9, 127.1, 126.0, 121.7, 118.0, 113.7, 106.7, 82.1 ($^2J_{\text{HH}} = 166$ Hz, CF), 67.4 ($^3J_{\text{CF}} = 18.9$ Hz, CCF); m/z (ESI-MS): 283.1 (100%, $[\text{M} + \text{H}]^+$), 284.1 (27%); HRMS (TOF $^+$): calcd for $\text{C}_{17}\text{H}_{16}\text{FN}_2\text{O}$, $[\text{M} + \text{H}]^+$, 283.1247; found, 283.1240. Error (ppm): –2.5.

4-(6-(2-(2-Fluoroethoxy)ethoxy)quinolin-2-yl)aniline (10b)—TBAF solution (1 M in THF, 0.20 mL, 0.20 mmol) was added to a solution of **9b** (100 mg, 0.16 mmol) in DMF (10 mL) and microwaved (120°C/20 min/80 W). The reaction mixture was partitioned between ethyl acetate and brine, and the aqueous layer was extracted with EtOAc. The combined organic phase was dried (MgSO_4) and filtered. The solvent was evaporated off. HPLC purification of the residue gave **10b** as a white solid (45 mg, 75%): ^1H NMR (CDCl_3) δ 8.04 (d, $^3J_{\text{HH}} = 8.4$

Hz, 2H), 7.99 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 7.76 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 7.38 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 2.8$ Hz, 1H), 7.08 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.80 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 4.68 (m, 1H), 4.56 (m, 1H), 4.28 (m, 2H), 3.97 (m, 2H), 3.90 (m, 1H), 3.83 (m, 1H); ^{13}C NMR (CDCl_3) δ 156.4, 155.1, 147.6, 144.3, 135.6, 130.7, 130.0, 128.6, 127.6, 122.3, 118.7, 115.2, 106.2, 84.1, 82.4, 70.8, 70.6, 69.9, 67.8. m/z (ESI-MS): 415.2 (36%), 371.2 (21%), 355.1 (21%), 327.2 (100%, $[\text{M} + \text{H}]^+$); HRMS (TOF $^+$): calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{F}$, $[\text{M} + \text{H}]^+$, 327.1509; found, 327.1513. Error (ppm): +1.2.

4-(6-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)quinolin-2-yl)aniline (10c)—TBAF solution (1 M in THF, 10 mg, 0.038 mmol) was added to a solution of **9c** (20 mg, 0.032 mmol) in DMF (2 mL) and microwaved (120c20m80w). The reaction mixture was washed with H_2O and extracted three times with EtOAc, dried (MgSO_4), and filtered. Solvent was evaporated off. HPLC of the residue gave **10c** as a white solid (9.1 mg, 77%): ^1H NMR (CDCl_3) δ 7.99 (m, 4H), 7.75 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 7.37 (dd, $^3J_{\text{HH}} = 6.4$ Hz, 6.4 Hz, 1H), 7.06 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.79 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2H), 4.63 (m, 1H), 4.51 (m, 1H), 4.26 (m, 2H), 3.94 (m, 2H), 3.76 (m, 6H); ^{13}C NMR (CDCl_3) δ 156.4, 155.1, 147.5, 144.3, 135.4, 130.8, 130.0, 128.5, 127.5, 122.3, 118.6, 115.2, 106.1, 84.0, 82.3, 70.9, 70.9, 70.6, 70.4, 69.8, 67.7. HRMS (TOF $^+$): calcd for $\text{C}_{21}\text{H}_{24}\text{FN}_2\text{O}_3$, $[\text{M} + \text{H}]^+$, 370.1771; found, 371.1766. Error (ppm): -1.3.

4-(6-(2-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethoxy)quinolin-2-yl)aniline (10d)—The method for **10c** was applied to **9d** (20 mg, 0.030 mmol) and gave **10d** as a white solid (11.4 mg, 92%). ^1H NMR (CDCl_3) δ 8.39 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 2H), 7.99 (t, $J = 9.6$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.39 (dd, $J = 9.2$ Hz, 9.2 Hz, 1H), 6.97 (d, $J = 2.8$ Hz, 1H), 4.58 (m, 1H), 4.46 (m, 1H), 4.18 (m, 2H), 3.92 (m, 2H), 3.73 (m, 10H); ^{13}C NMR (CDCl_3) δ 156.90, 153.50, 144.17, 137.35, 135.99, 135.70, 130.93, 128.09, 122.82, 120.66, 118.65, 105.82, 83.95, 82.27, 70.90, 70.79, 70.77, 70.66, 70.48, 70.29, 69.67, 67.70; HRMS (TOF $^+$): calcd for $\text{C}_{23}\text{H}_{28}\text{FN}_2\text{O}_4$, $[\text{M} + \text{H}]^+$, 415.2033; found, 415.2034. Error (ppm): 0.2.

4-(6-((14-Fluoro-3,6,9,12-tetraoxatetradecyl)oxy)quinolin-2-yl)-aniline (10e)—The method for **10c** was applied to **9e** (20 mg, 0.028 mmol) and gave **10e** as a white solid (8.7 mg, 68%): ^1H NMR (CDCl_3) δ 8.00 (m, 4H), 7.75 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 7.37 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 9.2$ Hz, 1H), 7.06 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.80 (m, 2H), 4.63 (m, 1H), 4.49 (m, 1H), 3.93 (m, 2H), 3.75 (m, 3H), 3.68 (m, 11H); ^{13}C NMR (CDCl_3) δ 156.4, 155.1, 147.5, 144.3, 135.4, 130.8, 130.0, 128.5, 127.5, 122.3, 118.6, 115.2, 106.1, 84.0, 82.3, 70.9, 70.8, 70.7, 70.7, 70.6, 70.5, 70.3, 69.7, 67.7. HRMS (TOF $^+$): calcd for $\text{C}_{25}\text{H}_{32}\text{FN}_2\text{O}_5$, $[\text{M} + \text{H}]^+$, 459.2295; found, 459.2294. Error (ppm): -0.1.

4-(6-((17-Fluoro-3,6,9,12,15-pentaoxaheptadecyl)oxy)quinolin-2-yl)aniline (10f)—The method for **10c** was applied to **9f** (20 mg, 0.039 mmol) and gave **10f** as a white solid (7.8 mg, 40%): ^1H NMR ($\text{DMSO}-d_6$) δ 8.00 (m, 4H), 7.75 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 7.37 (dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 9.2$ Hz, 1H), 7.07 (d, $^4J_{\text{HH}} = 2.8$ Hz, 1H), 6.80 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2H), 4.61 (m, 1H), 4.49 (m, 1H), 4.26 (m, 2H), 3.93 (m, 2H), 3.76 (m, 3H), 3.68 (m, 15H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 155.6, 154.3, 150.1, 135.6, 130.0, 127.8, 127.1, 121.8, 117.9,

113.7, 106.6, 83.8, 82.2, 69.9, 69.8, 69.8, 69.5, 68.8, 67.4; HRMS (TOF⁺): calcd for C₂₇H₃₆N₂O₆, [M + H]⁺, 503.2557; found, 503.2556. Error (ppm): -0.2.

t-Butyl (4-(6-(2-(2-(2,6-Dioxocyclohexyl)ethoxy)ethoxy)quinolin-2-yl)phenyl)carbamate (11a)—Compound **9a** (21.2 mg, 0.0367 mmol), cyclohexane-1,3-dione (9.4 mg, 0.0838 mmol), and K₂CO₃ (67 mg, 0.485 mmol) were suspended in MeCN (1.0 mL). The mixture was microwaved (120c40m30w250 psi). After the reaction was found to be complete by HPLC, semipreparative HPLC gave **11a** as a white solid (15 mg; 79%): ¹H NMR (CDCl₃) δ 8.07 (d, 2H, ³J_{HH} = 9.1 Hz, ArH), 8.04 (d, 1H, ³J_{HH} = 9.4 Hz, ArH), 8.01 (d, 1H, ³J_{HH} = 9.4 Hz, ArH), 7.79 (d, 1H, ³J_{HH} = 9.1 Hz, ArH), 7.49 (d, ³J_{HH} = 8.1 Hz, 1H, ArH), 7.38 (dd, ³J_{HH} = 9.4 Hz, ⁴J_{HH} = 2.6 Hz, 1H, ArH), 7.07 (d, ⁴J_{HH} = 2.6 Hz, 1H, ArH), 6.56 (s, 1H, NH), 5.35 (s, 1H, CH), 4.27 (m, 2H, OCH₂), 4.01 (m, 2H, OCH₂), 3.95 (m, 2H, OCH₂), 3.90 (m, 2H, OCH₂), 2.40 (m, 2H, CH₂), 2.31 (m, 2H, CH₂), 1.95 (m, 2H, CH₂), 1.52 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 199.9 (C=O), 177.9 (C=O), 156.7, 154.8, 152.8, 144.6, 139.5, 135.7, 134.5, 131.3, 128.2, 128.0, 122.6, 119.1, 118.6, 106.3, 103.2, 80.9 (CO), 70.1 (CO), 69.4 (CO), 68.0 (CO), 67.9 (CO), 36.9 (CH), 29.1 (CH₂), 28.6 (CH₃), 21.4 (CH₂); *m/z* (ESI-MS): 519.2 (100%, [M + H]⁺), 520.3 (25%); HRMS (TOF⁺): calcd for C₃₀H₃₅N₂O₆, [M + H]⁺, 519.2495; found, 519.2495. Error (ppm): 0.0.

t-Butyl (4-(6-(2-(2-(2,5-Dioxocyclopentyl)ethoxy)ethoxy)quinolin-2-yl)phenyl)carbamate (11b)—The method for **11a** was applied to **9b** (27.0 mg, 0.0497 mmol) and cyclopentane-1,3-dione (12.8 mg, 0.130 mmol) under 120c60m100w250 psi conditions and gave **11b** as a white solid (14 mg; 59%): ¹H NMR (CDCl₃) δ 8.07 (d, 2H, ³J_{HH} = 8.7 Hz, ArH), 8.04 (d, 1H, ³J_{HH} = 9.5 Hz, ArH), 8.02 (d, 1H, 10.2 Hz, ArH), 7.79 (d, 1H, ³J_{HH} = 8.6 Hz, ArH), 7.49 (d, ³J_{HH} = 8.6 Hz, 1H, ArH), 7.37 (dd, ³J_{HH} = 9.2 Hz, ⁴J_{HH} = 2.7 Hz, 1H, ArH), 7.07 (d, ⁴J_{HH} = 2.8 Hz, 1H, ArH), 6.57 (s, 1H, NH), 5.31 (s, 1H, CH), 4.27 (m, 2H, OCH₂), 4.15 (m, 2H, OCH₂), 3.96 (m, 2H, OCH₂), 3.92 (m, 2H, OCH₂), 2.62 (m, 2H, CH₂), 2.42 (m, 2H, CH₂), 1.52 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 205.9 (C=O), 190.0 (C=O), 156.5, 154.6, 152.6, 144.4, 139.3, 135.5, 134.2, 131.1, 128.0, 127.8, 122.3, 118.9, 118.4, 106.1, 105.1, 80.7 (CO), 71.1 (CO), 69.9 (CO), 69.1 (CO), 67.7 (CO), 34.1 (CH), 28.5 (CH₂), 28.4 (CH₃); *m/z* (ESI-MS): 505.2 (100%, [M + H]⁺), 506.2 (30%), 449.3 (35%), 450.3 (12%); HRMS (TOF⁺): calcd for C₂₉H₃₃N₂O₆, [M + H]⁺, 505.2339; found, 505.2327. Error (ppm): -2.4.

t-Butyl (4-(6-(2-(2-(2-Oxooxazolidin-3-yl)ethoxy)ethoxy)quinolin-2-yl)phenyl)carbamate (11c)—Compound **9c** (12.1 mg, 0.0209 mmol), oxazolidin-2-one (5.3 mg, 0.0609 mmol), and Li₂O (5 mg, 0.167 mmol) were suspended in DMF (1.0 mL). The mixture was microwaved (80c10m60w250 psi). After the reaction was found to be complete by HPLC, semipreparative HPLC gave **11c** as a white solid (6.0 mg; 58%): ¹H NMR (CDCl₃) δ 8.07 (d, 2H, ³J_{HH} = 8.9 Hz, ArH), 8.05 (d, 1H, ³J_{HH} = 9.2 Hz, ArH), 8.01 (d, 1H, ³J_{HH} = 9.2 Hz, ArH), 7.79 (d, 1H, ³J_{HH} = 9.2 Hz, ArH), 7.49 (d, ³J_{HH} = 8.9 Hz, 1H, ArH), 7.34 (dd, ³J_{HH} = 9.2 Hz, ⁴J_{HH} = 3.2 Hz, 1H, ArH), 7.06 (d, ⁴J_{HH} = 2.9 Hz, 1H, ArH), 6.61 (s, 1H, NH), 4.26–4.21 (m, 2H, OCH₂), 3.89–3.86 (m, 2H, OCH₂), 3.75 (t, ³J_{HH} = 5.2 Hz, 1H, CH₂), 3.70–3.66 (m, 2H, OCH₂), 3.48 (t, ³J_{HH} = 5.2 Hz, 1H, CH₂), 1.52 (s, 9H,

CH₃); ¹³C NMR (CDCl₃) δ 158.6, 156.6, 154.6, 152.6, 144.4, 1393.3, 135.5, 134.2, 131.1, 128.0, 127.9, 122.3, 118.9, 118.4, 106.1, 80.7 (CO), 69.9 (CO), 69.4 (CO), 67.6 (CO), 62.0 (CO), 46.0 (CN), 44.1 (CN), 28.4 (CH₃); *m/z* (ESI-MS): 494.2 (100%, [M + H]⁺), 495.2 (30%); HRMS (TOF⁺): calcd for C₂₇H₃₂N₃O₆, [M + H]⁺, 494.2291; found, 494.2298. Error (ppm): +1.4.

t-Butyl (4-(6-(2-(2-(2-Oxoimidazolidin-1-yl)ethoxy)ethoxy)-quinolin-2-yl)phenyl)carbamate (11d)—The method for **11c** was applied to **9d** (20.0 mg, 0.0346 mmol) and imidazolidin-2-one (15.0 mg, 0.174 mmol) and gave **11d** as a white solid (3.5 mg; 21%): ¹H NMR (CDCl₃) δ 8.08 (d, 2H, ³*J*_{HH} = 8.7 Hz, ArH), 8.06 (d, 1H, ³*J*_{HH} = 9.0 Hz, ArH), 8.01 (d, 1H, ³*J*_{HH} = 9.4 Hz, ArH), 7.79 (d, 1H, ³*J*_{HH} = 9.0 Hz, ArH), 7.49 (d, ³*J*_{HH} = 9.0 Hz, 1H, ArH), 7.36 (dd, ³*J*_{HH} = 9.4 Hz, ⁴*J*_{HH} = 2.9 Hz, 1H, ArH), 7.08 (d, ⁴*J*_{HH} = 2.6 Hz, 1H, ArH), 6.58 (s, 1H, NH), 4.23 (tm, ³*J*_{HH} = 4.5 Hz, 2H, OCH₂), 3.88 (tm, ³*J*_{HH} = 4.5 Hz, 2H, OCH₂), 3.72 (tm, ³*J*_{HH} = 5.3 Hz, 2H, OCH₂), 3.56 (tm, ³*J*_{HH} = 7.9 Hz, 2H, OCH₂), 3.41 (tm, ³*J*_{HH} = 5.3 Hz, 2H, OCH₂), 3.33 (tm, ³*J*_{HH} = 7.9 Hz, 2H, OCH₂), 1.52 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 162.9, 156.9, 154.8, 152.8, 144.6, 139.5, 135.7, 134.5, 131.3, 128.2, 128.1, 122.6, 119.1, 118.7, 106.3, 81.0 (CO), 70.6 (CO), 69.5 (CO), 67.9 (CO), 46.7 (CN), 43.6 (CN), 38.5 (CN), 28.6 (CH₃); *m/z* (ESI-MS): 493.2 (100%, [M + H]⁺), 494.2 (28%), 437.3 (26%); HRMS (TOF⁺): calcd for C₂₇H₃₃N₄O₅, [M + H]⁺, 493.2451; found, 493.2441. Error (ppm): −2.0.

t-Butyl (4-(6-(2-(2-(2-Oxothiazolidin-3-yl)ethoxy)ethoxy)-quinolin-2-yl)phenyl)carbamate (11e)—The method for **11c** was applied to **9e** (17.9 mg, 0.0310 mmol) and thiazolidin-2-one (24.6 mg, 0.239 mmol) and gave **11e** as a white solid (11 mg; 70%): ¹H NMR (CD₃OD) δ 8.28 (d, 2H, ³*J*_{HH} = 8.8 Hz, ArH), 8.02 (d, 1H, ³*J*_{HH} = 8.9 Hz, ArH), 8.00 (d, 1H, ³*J*_{HH} = 9.4 Hz, ArH), 7.92 (d, 1H, ³*J*_{HH} = 8.9 Hz, ArH), 7.60 (d, ³*J*_{HH} = 9.4 Hz, 1H, ArH), 7.44 (dd, ³*J*_{HH} = 9.4 Hz, ⁴*J*_{HH} = 2.8 Hz, 1H, ArH), 7.33 (d, ⁴*J*_{HH} = 2.8 Hz, 1H, ArH), 4.30 (m, 2H, OCH₂), 3.92 (m, 2H, OCH₂), 3.82 (t, ³*J*_{HH} = 7.9 Hz, 2H, NCH₂), 3.71 (m, 2H, OCH₂), 3.54 (m, 2H, SCH₂), 3.26 (t, ³*J*_{HH} = 7.9 Hz, 2H, SCH₂), 1.54 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 172.5, 156.8, 154.8, 152.8, 144.6, 139.5, 135.7, 134.4, 131.3, 128.2, 128.1, 122.5, 119.1, 118.6, 106.3, 81.0 (CO), 70.1 (CO), 69.7 (CO), 67.8 (CO), 50.2 (CN), 44.9 (CN), 28.6 (CH₃), 26.2 (C–S); *m/z* (ESI-MS): 510.1 (100%, [M + H]⁺), 511.1 (30%), 454.3 (40%); HRMS (TOF⁺): calcd for C₂₇H₃₂N₃O₅S, [M + H]⁺, 510.2063; found, 510.2073. Error (ppm): +2.0.

t-Butyl (4-(6-(2-(2-((2-Hydroxyethyl)amino)ethoxy)ethoxy)-quinolin-2-yl)phenyl)carbamate (11f)—The method for **11a** was applied to **9f** (20 mg, 0.0346 mmol) and 2-aminoethanol (10 μL, 0.165 mmol) under microwave conditions (120c30m300w250 psi) and gave **11f** as a white solid (12 mg; 74%): ¹H NMR (CDCl₃) δ 8.07 (d, 2H, ³*J*_{HH} = 8.8 Hz, ArH), 8.04 (d, 1H, ³*J*_{HH} = 9.5 Hz, ArH), 8.01 (d, 1H, ³*J*_{HH} = 9.3 Hz, ArH), 7.78 (d, 1H, ³*J*_{HH} = 8.6 Hz, ArH), 7.48 (d, ³*J*_{HH} = 8.7 Hz, 1H, ArH), 7.37 (dd, ³*J*_{HH} = 9.2 Hz, ⁴*J*_{HH} = 2.8 Hz, 1H, ArH), 7.07 (d, ⁴*J*_{HH} = 2.8 Hz, 1H, ArH), 6.58 (s, 1H, NH), 4.26–4.21 (m, 2H, OCH₂), 3.91–3.49 (m, 2H, OCH₂), 3.74–3.72 (m, 2H, OCH₂), 3.68–3.64 (m, 2H, OCH₂), 2.92–2.89 (m, 2H, NCH₂), 2.86–2.82 (m, 2H, NCH₂), 1.52 (s, 9H, CH₃); ¹³C NMR (CDCl₃) δ 156.5, 154.6, 152.6, 144.4, 139.3, 135.5, 134.3, 131.1,

128.0, 127.8, 122.3, 118.9, 118.5, 106.2, 105.1, 80.8 (CO), 69.6 (CO), 67.6 (CO), 59.9 (CO), 50.9 (CN), 48.4 (CN), 28.4 (CH₃); *m/z* (ESI-MS): 468.3 (60%, [M + H]⁺), 437.7 (20%), 425.2 (27%), 311.1 (15%), 234.6 (18%), 206.6 (100%), 197.6 (14%); HRMS (TOF⁺): calcd for C₂₆H₃₄N₃O₅, [M + H]⁺, 468.2498; found, 468.2511. Error (ppm): +2.8.

2-(2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-cyclohexane-1,3-dione (12a)—BF₃·OEt₂ (20 μL) was added to a solution of **11a** (20.2 mg; 0.0390 mmol) in CHCl₃ (1.0 mL). The mixture became an orange-yellowish solution. After the reaction was found to be complete by HPLC, the solution was partitioned between EtOAc and brine (10 mL × 3). The combined organic phase was dried (MgSO₄). Removal of solvent gave **12a** as a white solid (11 mg; 67%): ¹H NMR (CDCl₃) δ 8.84 (d, 2H, ³J_{HH} = 8.4 Hz, ArH), 8.27 (d, 1H, ³J_{HH} = 9.9 Hz, ArH), 8.12 (d, 1H, ³J_{HH} = 8.4 Hz, ArH), 7.97 (d, 2H, ³J_{HH} = 8.4 Hz, ArH), 7.78 (dd, ³J_{HH} = 9.2 Hz, ⁴J_{HH} = 2.7 Hz, 1H, ArH), 7.54 (d, ³J_{HH} = 8.4 Hz, 2H, ArH), 7.43 (d, ⁴J_{HH} = 2.7 Hz, 1H, ArH), 6.56 (s, 1H, NH), 4.39 (m, 2H, OCH₂), 4.09 (m, 2H, OCH₂), 3.98 (m, 2H, OCH₂), 3.88 (m, 2H, CCH₂), 2.89 (m, 2H, CH₂), 2.70 (m, 2H, CH₂), 2.18 (m, 2H, CH₂); ¹³C NMR (CDCl₃) δ 199.9, 177.9, 156.4, 155.4, 147.7, 144.6, 135.5, 131.1, 130.2, 128.7, 127.7, 122.3, 118.9, 115.4, 106.4, 103.2, 70.1, 69.4, 68.0, 67.9, 36.9, 29.2, 21.4; *m/z* (ESI-MS): 419.4 (100%, [M + H]⁺), 420.4 (20%); HRMS (TOF⁺): calcd for C₂₅H₂₇N₂O₄, [M + H]⁺, 418.1971; found, 418.1974. Error (ppm): 0.7.

2-(2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-cyclopentane-1,3-dione (12b)—Compound **11b** (21.2 mg; 0.0420 mmol) was suspended in dioxane (1.0 mL). After ultrasound treatment, a cloudy milky suspension formed. BF₃·OEt₂ (20 μL, 3.9 equiv) was added. The mixture became an orange-yellowish suspension. After 2 to 5 min a bright yellow solution formed and then a yellow precipitate. After the reaction was found to be complete by HPLC, *c.* NH₃ solution (0.5 mL) was added to the mixture, which then changed from yellow to white, with some residue of a white solid. The mixture was partitioned between EtOAc and brine (10 mL × 3). The combined organic phase was dried (MgSO₄). Removal of solvent gave **12b** as a white solid (5.9 mg, 35%): ¹H NMR (CDCl₃) δ 8.01 (d, 1H, ³J_{HH} = 8.6 Hz, ArH), 7.99 (d, 1H, ³J_{HH} = 9.1 Hz, ArH), 7.96 (d, 2H, ³J_{HH} = 8.6 Hz, ArH), 7.74 (d, 1H, ³J_{HH} = 8.6 Hz, ArH), 7.35 (dd, ³J_{HH} = 9.7 Hz, ⁴J_{HH} = 2.8 Hz, 1H, ArH), 7.05 (d, ⁴J_{HH} = 2.8 Hz, 2H, ArH), 6.78 (d, ³J_{HH} = 8.6 Hz, 2H, ArH), 4.26 (m, 2H, OCH₂), 4.16 (m, 2H, OCH₂), 3.96–3.91 (m, 4H, OCH₂ + CCH₂), 2.60 (m, 2H, CCH₂), 2.40 (m, 2H, CH₂); ¹³C NMR (CDCl₃) δ 205.8, 190.0, 156.2, 155.3, 147.5, 144.4, 135.3, 130.9, 130.0, 128.5, 127.5, 122.1, 118.7, 115.2, 106.2, 105.1, 71.1, 70.0, 69.1, 67.7, 34.1, 28.5; *m/z* (ESI-MS): 405.4 (100%, [M + H]⁺), 406.4 (30%); HRMS (TOF⁺): calcd for C₂₄H₂₅N₂O₄, [M + H]⁺, 404.1814; found, 404.1814. Error (ppm): 0.

3-(2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-oxazolidin-2-one (12c)—Compound **11c** (18.9 mg; 0.0383 mmol) was suspended in MeCN (1.0 mL) with the help of ultrasound to form a milky solution and BF₃·OEt₂ (24 μL, 5 equiv) was added in one portion. The mixture became an orange-yellowish solution and was stirred at RT for 1 h. The reaction was found to be complete by HPLC. *c.* NH₃ in ethylene glycol (1:4; 0.5 mL) was added and stirred for 10 min. Preparative HPLC gave **12c** as a white solid (10.9 mg; 72%): ¹H NMR (DMSO-*d*₆) δ 8.17 (d, 1H, ³J_{HH} = 8.8 Hz, ArH), 7.95 (d, 2H, ³J_{HH} = 8.6

Hz, ArH), 7.91 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.86 (d, 1H, $^3J_{\text{HH}} = 9.0$ Hz, ArH), 7.35 (dd, $^3J_{\text{HH}} = 9.0$ Hz, $^4J_{\text{HH}} = 2.8$ Hz, 1H, ArH), 7.33 (d, $^4J_{\text{HH}} = 2.7$ Hz, 1H, ArH), 6.67 (d, 2H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 5.48 (brs, 2H, NH₂), 4.24–4.20 (m, 4H, NCH₂ + OCH₂), 3.83–3.81 (m, 2H, OCH₂), 3.64 (t, 2H, $^3J_{\text{HH}} = 5.4$ Hz, OCH₂), 3.62–3.58 (m, 2H, OCH₂), 3.36 (m, 2H, NCH₂); ^{13}C NMR (DMSO-*d*₆) δ 206.8 (C=O), 158.0, 155.6, 154.4, 150.1, 143.6, 135.4, 130.1, 127.9, 127.1, 126.1, 121.8, 117.9, 113.7, 106.6, 68.5, 68.1, 67.4, 62.8, 61.7, 44.7, 43.3; *m/z* (ESI-MS): 394.2 (100%, [M + H]⁺), 395.2 (39%); HRMS (TOF⁺): calcd for C₂₂H₂₄N₃O₄, [M + H]⁺, 394.1767; found, 394.1760. Error (ppm): –1.8.

1-(2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-imidazolidin-2-one (12d)—Compound **11d** (8.2 mg; 0.0166 mmol) was suspended in MeCN (1.0 mL) with the help of ultrasound to form a milky suspension, and BF₃·OEt₂ (11 μL , 5 equiv) was added in one portion. The mixture became an orange-yellowish solution. After stirring the mixture for 1 h at RT, the reaction was found to be complete by HPLC. *c.* NH₃ in ethylene glycol (1:4; 0.5 mL) was added and stirred for 10 min. Preparative HPLC of the mixture gave **12d** as a white solid (3.6 mg; 55%): ^1H NMR (DMSO-*d*₆) δ 8.29 (brd, $^3J_{\text{HH}} = 8.2$ Hz, 1H, ArH), 8.00–7.92 (m, 4H, ArH), 7.44–7.41 (m, 2H, ArH), 6.71 (d, $^3J_{\text{HH}} = 8.5$ Hz, 2H, ArH), 6.52 (brs, 1H, NH), 6.28 (brs, 1H, NH), 4.25–4.23 (m, 2H, OCH₂), 3.83–3.80 (m, 2H, OCH₂), 3.58 (t, 2H, $^3J_{\text{HH}} = 5.5$ Hz, OCH₂), 3.39 (t, 2H, $^3J_{\text{HH}} = 7.8$ Hz, NCH₂), 3.32 (t, 2H, $^3J_{\text{HH}} = 5.6$ Hz, OCH₂), 3.18 (t, 2H, $^3J_{\text{HH}} = 7.8$ Hz, NCH₂); *m/z* (ESI-MS): 393.2 (100%, [M + H]⁺), 394.2 (26%), 325.2 (34%), 223.9 (58%), 195.9 (33%), 178.9 (43%), 116.0 (45%); HRMS (TOF⁺): calcd for C₂₂H₂₅N₃O₃, [M + H]⁺, 393.1927; found, 393.1928. Error (ppm): 0.3.

3-(2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-thiazolidin-2-one (12e)—Compound **11e** (20.1 mg; 0.0394 mmol) was added to MeCN (1.0 mL) with the help of ultrasound to form a milky suspension, and BF₃·OEt₂ in MeCN solution (1:9, 280 μL , 5 equiv) was added. The mixture became a yellowish-orange solution. The mixture was stirred for 1 h at RT for 1 h. The reaction was found to be complete by HPLC. *c.* NH₃ in ethylene glycol (1:4; 0.5 mL) was added and stirred for 10 min. Preparative HPLC of the mixture gave **12e** as a white solid (12.3 mg; 76%): ^1H NMR (DMSO-*d*₆) δ 8.50 (d, 1H, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 8.22 (d, 1H, $^3J_{\text{HH}} = 8.0$ Hz, ArH), 8.13 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 8.05 (d, 2H, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.55 (dd, $^3J_{\text{HH}} = 8.7$ Hz, $^4J_{\text{HH}} = 2.0$ Hz, 1H, ArH), 7.53 (s, 1H, ArH), 6.80 (d, $^3J_{\text{HH}} = 8.6$ Hz, 2H, ArH), 4.26 (m, 2H, NCH₂), 3.83 (m, 2H, SCH₂), 3.70 (t, 2H, $^3J_{\text{HH}} = 7.3$ Hz, OCH₂), 3.63 (t, 2H, $^3J_{\text{HH}} = 5.4$ Hz, OCH₂), 3.42 (t, 2H, $^3J_{\text{HH}} = 5.4$ Hz, NCH₂), 3.26 (t, 2H, $^3J_{\text{HH}} = 7.3$ Hz, OCH₂); ^{13}C NMR (DMSO-*d*₆) δ 170.9, 162.3, 156.7, 152.7, 151.1, 139.5, 138.2, 129.7, 127.4, 125.7, 123.9, 119.4, 114.5, 107.4, 68.4, 68.0, 67.6, 48.8, 43.8, 25.4; *m/z* (ESI-MS): 410.2 (100%, [M + H]⁺), 411.2 (26%); HRMS (TOF⁺): calcd for C₂₄H₂₄N₂O₄, [M + H]⁺, 410.1538; found, 410.1535. Error (ppm): –0.7.

2-((2-(2-((2-(4-Aminophenyl)quinolin-6-yl)oxy)ethoxy)ethyl)-amino)ethan-1-ol (12f)—Compound **11f** (12.4 mg; 0.0265 mmol) was added to MeCN (1.0 mL) to form a milky suspension and BF₃·OEt₂ (13 μL , 5 equiv) was added. The mixture became a yellowish-orange solution. After 2 h at RT, the concentration of the starting material was less than that of an impurity, as monitored by HPLC. Semipreparative HPLC of the reaction mixture gave **12f** as a white solid (6.7 mg; 69%): ^1H NMR (CDCl₃) δ 8.01 (d, 1H, $^3J_{\text{HH}} =$

8.8 Hz, ArH), 7.99 (d, 1H, $^3J_{\text{HH}} = 9.4$ Hz, ArH), 7.96 (d, 2H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.75 (d, 1H, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.36 (dd, $^3J_{\text{HH}} = 9.4$ Hz, $^4J_{\text{HH}} = 3.0$ Hz, 1H, ArH), 7.06 (d, $^4J_{\text{HH}} = 2.7$ Hz, 1H, ArH), 6.79 (d, $^3J_{\text{HH}} = 9.1$ Hz, 2H, ArH), 4.24 (m, 2H, OCH₂), 3.89 (m, 2H, OCH₂), 3.83 (s, 2H, OH +NH), 3.69 (m, 2H, OCH₂), 3.61 (m, 2H, OCH₂), 2.84 (m, 2H, NCH₂), 2.79 (m, 2H, NCH₂); ^{13}C NMR (DMSO-*d*₆) δ 155.5, 154.4, 150.1, 143.6, 135.4, 130.1, 127.9, 127.1, 126.0, 121.8, 118.0, 113.7, 106.6, 68.9, 67.3, 66.9, 57.3, 49.6, 46.8; *m/z* (ESI-MS): 368.3 (100%, [M + H]⁺), 369.3 (30%), 325.2 (5%), 281.1 (62%, [M – C₂H₄NHC₂H₄O + H]⁺), 237.1 (62%, [M – C₂H₄OC₂H₄NHC₂H₄O + H]⁺), 184.6 (82%), 175.6 (52%); HRMS (TOF⁺): calcd for C₂₁H₂₆N₃O₃, [M + H]⁺, 368.1974; found, 368.1974. Error (ppm): 0.

4-(6-(2-Fluoroethoxy)quinolin-2-yl)-2,6-diiodoaniline (13)—THK-523 (**12a**; 109 mg, 0.386 mmol) and NIS (175 mg, 0.778 mmol) were dissolved in CHCl₃–MeOH (1:1; 5 mL) and stirred overnight. HPLC showed a 1:1 ratio of mono and di-iodo substituted products. More NIS (55 mg, 0.245 mmol) was added and the reaction mixture was stirred for another 5 days, or until the reaction was found to be complete by HPLC. The mixture was partitioned between EtOAc and brine (50 mL $\times$ 3). The combined organic phase was dried (MgSO₄). After removal of solvent, the crude product was dissolved in DCM, and silica gel (2 mL) was added, and dried. Chromatography of the resultant powder on a silica gel column (50 mL; EtOAc–hexane: 1:1) gave **13** as a dark solid (0.11 g; 53%): ^1H NMR (CDCl₃) δ 8.46 (s, 2H, ArH), 8.10 (brs, 1H, ArH), 8.07 (d, 1H, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 7.70 (d, 2H, $^3J_{\text{HH}} = 8.5$ Hz, ArH), 7.42 (dd, 1H, $^3J_{\text{HH}} = 9.8$ Hz, $^4J_{\text{HH}} = 2.9$ Hz, ArH), 7.08 (d, $^4J_{\text{HH}} = 2.6$ Hz, 1H, ArH), 4.89–4.87 (m, $^2J_{\text{HF}} = 47.4$ Hz, 1H, FCH₂), 4.83 (brs, 2H, NH₂), 4.77–4.75 (m, $^2J_{\text{HF}} = 47.4$ Hz, 1H, FCH₂), 4.38–4.36 (m, $^2J_{\text{HF}} = 27.6$ Hz, 1H, OCH₂), 4.31–4.29 (m, $^2J_{\text{HF}} = 27.6$ Hz, 1H, OCH₂), 1.52 (s, 9H, CH₃); ^{13}C NMR (DMSO-*d*₆) δ 156.0, 151.2, 148.1, 143.6, 137.7, 136.3, 131.0, 130.6, 127.9, 122.5, 118.4, 106.8, 82.3 ($^1J_{\text{CF}} = 166.2$ Hz, CF), 81.9 (CI), 67.6 ($^2J_{\text{CF}} = 19.2$ Hz, CCF); *m/z* (ESI-MS): 535.0 (100%, [M + H]⁺), 536.0 (18%); HRMS (TOF⁺): calcd for C₁₇H₁₄FI₂N₂O [M + H]⁺, 534.9180; found, 534.9185. Error (ppm): +0.9.

4,6,9-Tribromo-7-(6-fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole (14)—A solution of T807 (66 mg; 0.25 mmol) in DCM (3 mL) was treated with NBS (1.0 mmol) at 0 °C. The reaction mixture was stirred at RT (48 h) until starting materials had disappeared, as evidenced by TLC. A small amount of silica gel was added and the solvent was evaporated off under reduced pressure. Flash chromatography of the residue on silica gel (EtOAc) gave **14** as a colorless solid (19 mg; 15%): mp 176–178 °C; ^1H NMR (CDCl₃): δ 7.10 (dd, $^4J_{\text{HH}} = 4$ Hz, $^3J_{\text{HH}} = 8$ Hz, 1H), 7.76 (dt, $^4J_{\text{HH}} = 4$, $^3J_{\text{HH}} = 8$ Hz, 1H), 8.19 (s, 1H), 8.42 (s, 1H), 8.61 (brs, 1H), 8.72 (s, 1H), 9.23 (s, 1H); HRMS (EI): *m/z* calcd for C₁₆H₈Br₃FN₃ (M⁺): 497.8257; found: 497.8252. Error (ppm): +1.0.

Tritiated Ligands

[³H]T807 (1850 GBq per mmol, radiochemical purity > 97%) and [³H]THK-523 (³[H]**10a**; 1665 GBq per mmol, radiochemical purity > 99%) were obtained through custom syntheses at Moravex Biochemicals & Radiochemicals, Inc. (Brea, CA) based on hydrogenation of the halo precursors **13** and **14**, respectively.

In Vitro Binding Assays

Human AD brain tissue was homogenized in assay medium (0.1% Tween-20 in PBS) at 1:500 dilution in volume, and aliquots of this suspension (100 μL) were added to each of four tubes (total 48 in a rack). A solution of tritiated radioligand ($[^3\text{H}]\text{THK-523}$, $[^3\text{H}]\text{T807}$ or $[^3\text{H}]\text{PIB}$; 10 Bq/ μL) in assay medium (100 μL) was added to each tube. Nonradioactive ligand (THK-523, T807 or PIB) or test compound was dissolved in DMSO to give a 1 mM stock solution, which was further diluted with DMSO to give solutions ranging in concentration from 1×10^{-5} to 10^{-10} M. A volume of 10 μL of each solution was added to each tube. After assembly of the components listed above in each tube (made up to a total volume of 1.0 mL with assay medium), the tubes were vortexed and then incubated for 2 h at 37 °C. After separation of tube contents with a cell harvester, the filter paper (GF/B; Whatman; pretreated with 0.5% polyethylenimine solution) was washed with PBS (3 mL $\times$ 3). The filters were placed in 7 mL plastic vials and then scintillation fluid (4 mL) added to each. Each vial was vortexed until the filter was floating. After overnight incubation, the scintillation vials were counted for radioactivity. The collected data were analyzed with GraphPad Prism 4 version 4.03 (GraphPad Software; San Diego, CA) with “One site competition” curve-fitting. K_i values were calculated according to the Cheng–Prusoff equation:³⁹

$$K_i = \text{IC}_{50} / (1 + [L]/K_D)$$

where $[L]$ is the concentration (0.4 nM) and K_D is the equilibrium dissociation constant of the reference radioligand. K_D was determined with “Scatchard analysis of homologous displacement” from multiple runs with self-displacement from AD brain tissue.

Preparation of $[^{18}\text{F}]\text{THK-523}$ ($[^{18}\text{F}]\text{10a}$) and $[^{18}\text{F}]\text{10b-f}$

The general method is exemplified for the radiosynthesis of $[^{18}\text{F}]\text{THK-523}$ ($[^{18}\text{F}]\text{10a}$), as follows. No-carrier-added (NCA) $[^{18}\text{F}]\text{fluoride}$ ion was obtained from the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction by the proton irradiation of ^{18}O -enriched water (>95 atom %) ⁴⁰ at the NIH Clinical Center. NCA $[^{18}\text{F}]\text{fluoride}$ ion (3.7–9.25 GBq in 0.25 mL of H_2^{18}O) was added to kryptofix 2.2.2 (5 mg, 13.3 μmol) and K_2CO_3 (0.5 mg; 3.6 μmol) in MeCN–water (95:5; 0.1 mL), and dried azeotropically by four addition–evaporation cycles of MeCN (1 mL each cycle). Precursor **9a** (2.0 mg) was loaded into a 1.5 mL closed vial. $[^{18}\text{F}]\text{Fluoride ion-K}^+$ -kryptofix 2.2.2 in dry DMF (0.7 mL) was then added. The reaction mixture was heated at 120 °C for 15 min, and the solvent then removed by blowing nitrogen through the mixture at 120 °C for 5 min. A solution of *c.* HCl–ethylene glycol solution (0.5 mL; 1:9 v/v) was added, heated at 120 °C for 5 min, and then cooled to below 40 °C. The reaction was quenched with a solution (0.5 mL) of *c.* NH_3 (33%)-water (1:4 v/v). The reaction mixture was loaded onto a HPLC column (X-Bridge C-18; 19 $\times$ 150 mm, 10 μm particle; Waters) eluted at 10.0 mL/min with a mixture of A (0.1 M ammonium formate) and B (MeCN), with B increased from 20 to 40% over 60 min. Eluate was monitored for absorbance at 350 nm and radioactivity (NaI(Tl) Flow Count detector; Bioscan). The radioactive fraction with the same retention time as the respective reference ligand was collected and diluted with water (~100 mL). This solution was passed through a C-18 Sep-Pak cartridge (Waters; Milford, MA),

which was washed at least twice with water. The radioactive product was washed out of the cartridge with absolute ethanol (1.0 mL) into saline (0.9% w/v; 10 mL) plus Ethanol USP (0.9 mL) containing Polysorbate 80 (20 mg), and then sterile-filtered into a sterile and pyrogen-free dose vial.

The formulated radioligand was analyzed with HPLC on an X-bridge C18 column (10 μ m, 4.6 $\times$ 250 mm; Waters) eluted with 40% acetonitrile in water at 1.75 mL/min over 15 min. Eluate was monitored for absorbance at 350 nm and for radioactivity.

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ABBREVIATIONS

NCA	no-carrier-added
NFTs	neurofibrillary tangles
PIB	Pittsburgh Compound B
RCY	decay-corrected radiochemical yield
SD	standard deviation

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Figure 1.

Lack of effect of different washing agents on the K_i measured for THK-523 in the in vitro binding assay with [^3H]THK-523 as reference radioligand. The data points are means $\pm$ SD of three measurements (error bars not shown are within symbol size). The determined K_i values are 45 ± 12 nM with neat ethanol wash; 28 ± 6 nM for 20% ethanol wash; and 52 ± 14 nM for Tris-buffer (pH 7.2) wash.

Figure 2. Binding of [³H]THK-523 to AD brain homogenate versus concentration of [³H]THK-523 plus THK-523. The data points are means of four measurements, and SDs are within symbol size. The curve was fitted to the equation $[BF] = B_{\max}[F]/(K_D + [F]) + (NS[F]) + c$, giving $K_D = 3.5 \pm 3.4$ nM.

Figure 3.

Binding of [¹⁸F]THK-523 to AD brain tissue homogenate versus concentration of THK-523 plus [¹⁸F]THK-523. The data are means from four measurements, and SDs are within symbol size. The curve was fitted to the equation $[BF] = B_{\max}[F]/(K_D + [F]) + (NS[F]) + c$, giving $K_D = 4.6 \pm 1.8$ nM.

Figure 4.

Percentages of specific binding of [³H]THK-523 to AD brain tissue homogenate inhibited by each of 13 compounds (**10a–f**, **12a–f**, and T807) at 1 μ M concentration. THK-523 (**10a**) gave full inhibition, whereas T807 gave very low inhibition. The data are mean $\pm$ SD from three measurements.

Figure 5.

Percentages of specific binding of [³H]T807 to AD brain tissue homogenate inhibited by each of 13 compounds (**10a–f**, **12a–f**, and T807) at 1 μ M concentration. T807 gave full inhibition, whereas THK-523 (**10a**) gave very low inhibition. The data are mean $\pm$ SD from three measurements.

Scheme 1.
Synthesis of Hydroxy Compounds 4a–f and Fluoro Compound 5

Scheme 2.
Syntheses of Tosylates 9a–f and THK-523 (10a)

Scheme 3.

Syntheses of THK-523 Analogues with Poly(oxyethylene) Chains and Various Terminal Groups

Scheme 4.
Synthesis of $[^3\text{H}]\text{THK-523}$ ($[^3\text{H}]\text{10a}$)

Scheme 5.
Synthesis of $[^3\text{H}]\text{T807}$

Scheme 6.
Radiosyntheses of $[^{18}\text{F}]\text{10b-f}$

Chart 1.
Clinically Useful PET Radioligands for Imaging β -Amyloid Plaques

Chart 2.
Candidate PET Radioligands for Imaging NFTs

Chart 3.
Three Reference Radioligands Used for in Vitro Binding Assays on AD Brain Tissue Homogenates

Table 1
cLogD and K_i Values for Ligands at Three Binding Sites in AD Brain Tissue Homogenates^a

Compound	Structure	cLogD	K_i (nM) at		
			THK-523 site	T807 site	PIB site
T807		2.91	>1000	2.6 ± 0.7	>1000
PIB		2.30	>1000	>1000	34 ± 3
THK-523 (10a)		3.30	51 ± 22	425 ± 383	>1000
10b		3.74	28 ± 8	>1000	>1000
10c		3.33	>1000	>1000	>1000
10d		2.62	>1000	>1000	>1000
10e		2.70	>1000	N.d.	43 ± 39
10f		2.29	>1000	N.d.	>500
12a		-0.38	358 ± 381	>1000	502 ± 143
12b		1.79	>1000	>1000	>1000
12c		2.87	35 ± 19	>1000	>1000

Compound	Structure	cLogD	K_i (nM) at		
			THK-523 site	T807 site	PIB site
12d		2.16	78 ± 7	> 1000	> 1000
12e		3.30	21 ± 6	> 1000	> 1000
12f		0.38	22 ± 3	< 1000	< 1000

^a K_i values are average of five measurements for THK-523, T807, and PIB. K_i values for other compounds are mean ± SD from three measurements. N.d. = K_i , not determined; see Figure 5 for percentage inhibition of [³H]T807 binding at 1 μ M concentration.