

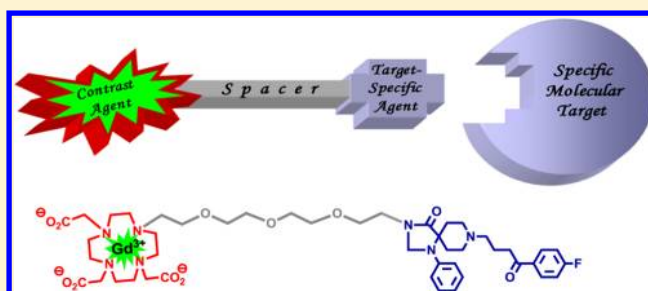
Target-Specific Ligands and Gadolinium-Based Complexes for Imaging of Dopamine Receptors: Synthesis, Binding Affinity, and Relaxivity

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S Supporting Information

ABSTRACT: Magnetic resonance imaging (MRI) and positron emission tomography (PET) are two extremely important imaging modalities with unlimited tissue penetration. Molecular imaging is a field by which specific targets or biological processes are imaged. MRI, which is used for functional imaging and for the diagnosis of a broad range of pathologic conditions, suffers from limited specificity and intrinsically low sensitivity. One possibility to alleviate partially these limitations is to use contrast agents (CAs) and more importantly target-specific CAs. We have developed a modular synthesis of novel ligands and gadolinium(III)-based target-specific MRI CAs with high relaxivity and high binding affinity toward the dopamine receptors. The prepared ligands and MRI CAs are based on spiperone as targeting moiety. The prepared target-specific CAs can potentially be used for *in vitro* and possibly *in vivo* MR imaging of dopaminergic receptors. Importantly the ligands prepared using the modular approach presented in this paper may also be useful for other imaging modalities such as PET (or SPECT) by just replacing, at the last stage of the synthesis, the gadolinium cation by other metal cations having relatively long half-lives, such as ^{64}Cu , ^{89}Zr , ^{111}In , and more.



INTRODUCTION

Magnetic resonance imaging (MRI) and positron emission tomography (PET) are two of the most important imaging modalities in biomedicine and in the clinics.¹ Molecular imaging, the field aimed at visualizing specific molecular targets or biological processes, is gaining increasing attention in recent years.² MRI is a very valuable imaging technique for studying tissue functions and for the diagnosis of a broad range of pathologies.^{1a} MRI has many advantages compared to other imaging techniques:^{1a,3} non-invasiveness, high tissue penetration, and relatively high temporal and spatial resolution.^{1a} In addition, MRI uses a variety of physical parameters as contrast mechanisms and can be combined with MR spectroscopy (MRS) of metabolites. However, the major drawbacks of MRI are the limited specificity and the intrinsically low sensitivity of the technique.^{1a}

One of the main possibilities to increase MRI specificity and, to a limited extent, the method's low sensitivity is to use contrast agents (CAs) with specific tissue distribution. Indeed such CAs, which first were mostly intravascular, have been prepared in the past three decades.⁴ A more challenging approach to increase MRI specificity, however, is to design target-specific MRI CAs⁵ with high affinity to a specific molecular target, thus expanding the scope of MRI into the field of molecular imaging.^{6,7} Such approach may, in principle, open the way for indirect MR imaging of specific receptors, enzymes, and other biological processes. Despite the recent progress in the design

of "smart" gadolinium CAs for imaging pH, temperature, and different metals,^{7a,8,9} MR imaging of specific receptors remained a formidable challenge.¹⁰ Nevertheless, during the past decade a few elegant demonstrations of the feasibility of this approach, using MRI methodology, have been reported.¹¹ These included, *inter alia*, an elegant example for indirect MR imaging of gene expressions^{11a,b} and imaging of the engineered version of the transferring receptor on the surface of 9L glioma cells.^{11c} These examples served as the first proof of concept for the potential uses of MRI in molecular imaging.^{11a-c} More recently new transgene reporters for *in vivo* MRI have been reported, and some gadolinium-based target-specific CAs were shown to operate even *in vivo*, most of them in cancer cells and tumors where specific receptors are overexpressed.¹² In contrast, PET, which has much higher sensitivity than MRI, has been used extensively in molecular imaging in general and for imaging of specific receptors in particular.^{1b} The main drawback of PET is that the methods rely on the use of radioactive tracers for achieving these goals.

In the present work we decided to develop a modular synthesis of ligands that have the potential to be used as target-specific CAs for imaging of the dopamine receptors (DRs) by MRI or PET. We selected the D3/D2 DRs as the target since the dopaminergic system is believed to be relevant to many

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(1) + 5eq **(2a): X = C(O);** **(2b): X = O.** $\xrightarrow{(i)}$ **(3a): X = C(O)** (93%); **(3b): X = O** (87%).

(3a) + **(4)** $\xrightarrow{(ii)}$ **(5a): X = C(O)** (81%); **(5b): X = O** (89%).

(5a) + **(6a): X = C(O)** (80%); **(6b): X = O** (74%). $\xrightarrow{(iii)}$

(7) $\xrightarrow{(iv)}$ **(8a): X = C(O)** (70%); **(8b): X = O** (76%).

(8a) + **(9a): X = C(O)** (~100%); **(9b): X = O** (~100%). $\xrightarrow{(v)}$

(10a): X = C(O) (~100%), Overall yield: ~45%; **(10b): X = O** (~100%), Overall yield: ~50%.

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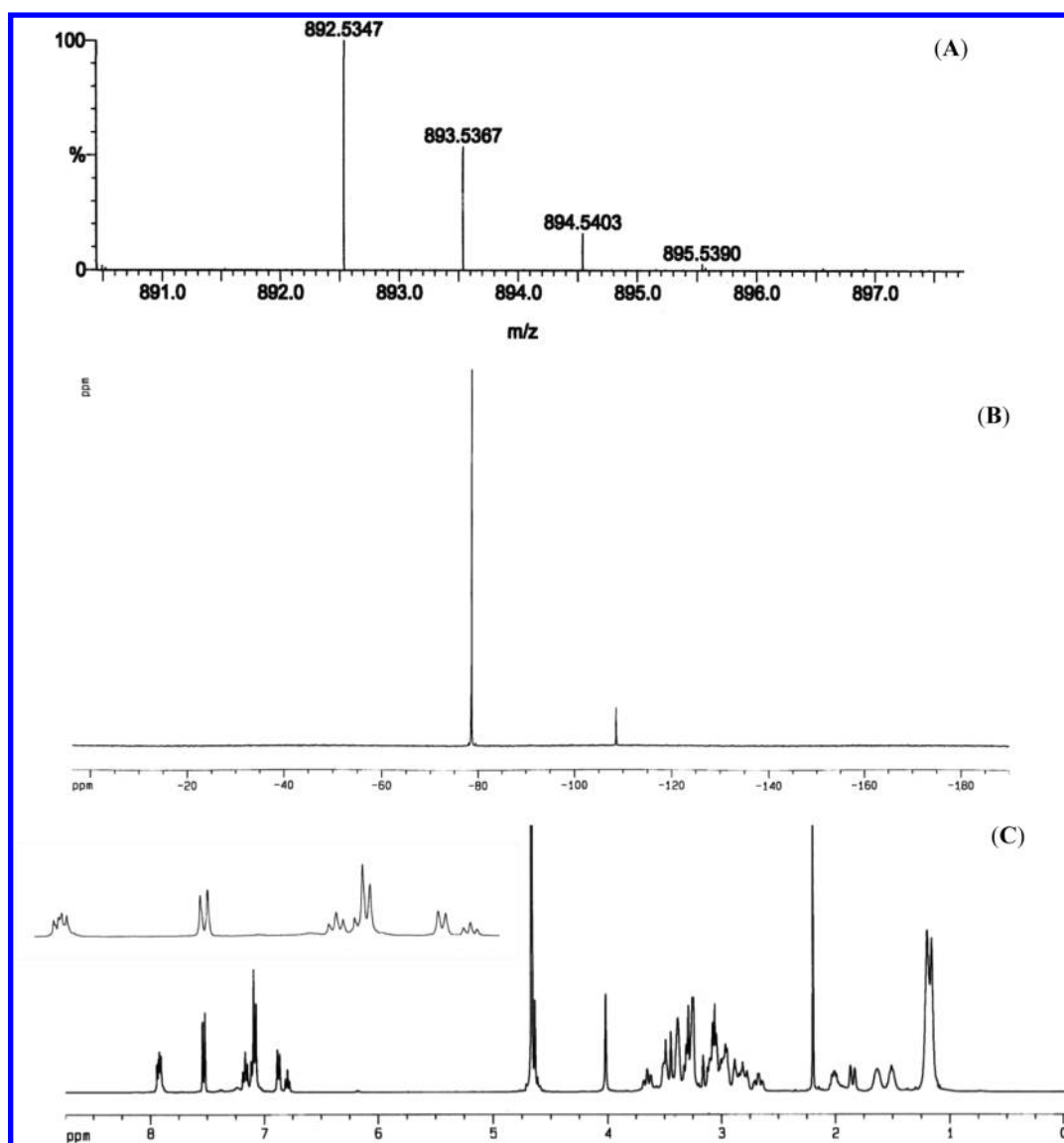


Figure 1. (A) HRMS (TOF MS ES negative), (B) ^{19}F NMR (376.3 MHz; CD_3OD , 25 $^\circ\text{C}$), and (C) ^1H NMR (400 MHz; CD_3OD , 25 $^\circ\text{C}$) spectra of **9a**.

ligands and the gadolinium-based CAs prepared thereof were derived from 8-[4-(4-fluorophenyl)-4-oxo-butyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, known also as spiperone (**3a** in Scheme 1), a strong ligand of the dopamine D3/D2 dopamine receptor^{17a} or its etheric analogue 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, known also as AMI-193 (**3b** in Scheme 1).^{17b,c} The paramagnetic moiety of the designed target-specific CAs is a Gd^{3+} -complex of 1,4,7,10-tetraazacyclododecane-1,4,7-tris-(acetate), known as DO3A, while the spacers were based on alkane and tri- and tetra(ethylene glycol) (triEG and tetraEG) moieties.

The ligands (**9a** and **9b**) and the gadolinium-based CAs with undecylenic spacers (**10a** and **10b** in Scheme 1) were synthesized from spiperone and AMI-193 (**3a** and **3b** in Scheme 1, respectively) in five steps with an overall yield of about 50% as outlined in Scheme 1. The starting compounds **3a** and **3b** were synthesized in high yields (of about 90%) by N-alkylation of the “spiro” compound 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one (**1**) at position 8 by the respective halides (**2a** and **2b**) under mild basic conditions, using a procedure similar to the one

used by us previously.¹⁶ Compounds **3a** and **3b** were then N-alkylated at position 3 by 11-bromo-1-undecanol (**4**) under basic conditions to afford the alcohols **5a** and **5b** in 81% and 89% yield, respectively. These alcohols were then tosylated in presence of *N,N*-dimethylaminopyridine to give the respective tosylates **6a** and **6b** in 80% and 74% yield, respectively. Subsequently compounds **6a** and **6b** were reacted with the commercially available compound **7** to give the triesters **8a** and **8b** in 70% and 76% yield, respectively. The triesters **8a** and **8b** were then nearly quantitatively deprotected by TFA to afford the ligands **9a** and **9b** as a penta-salt. These ligands were characterized by ^1H , ^{13}C , and ^{19}F NMR and high resolution mass spectrometry (see Figures 1 and 2 and Figures S33–S37 in the Supporting Information).

Ligands **15a–d**: Synthesis and Characterization.

Because we observed that the water solubility of ligands **9a** and **9b** is not very high, we decided to prepare also a series of ligands with water-soluble spacers (see Scheme 2). We chose to prepare ligands **15a–d** that have water-soluble tri- and tetra(ethylene glycol) (EG) spacers. It should be noted that the ethylene glycol spacers may also make the compounds more

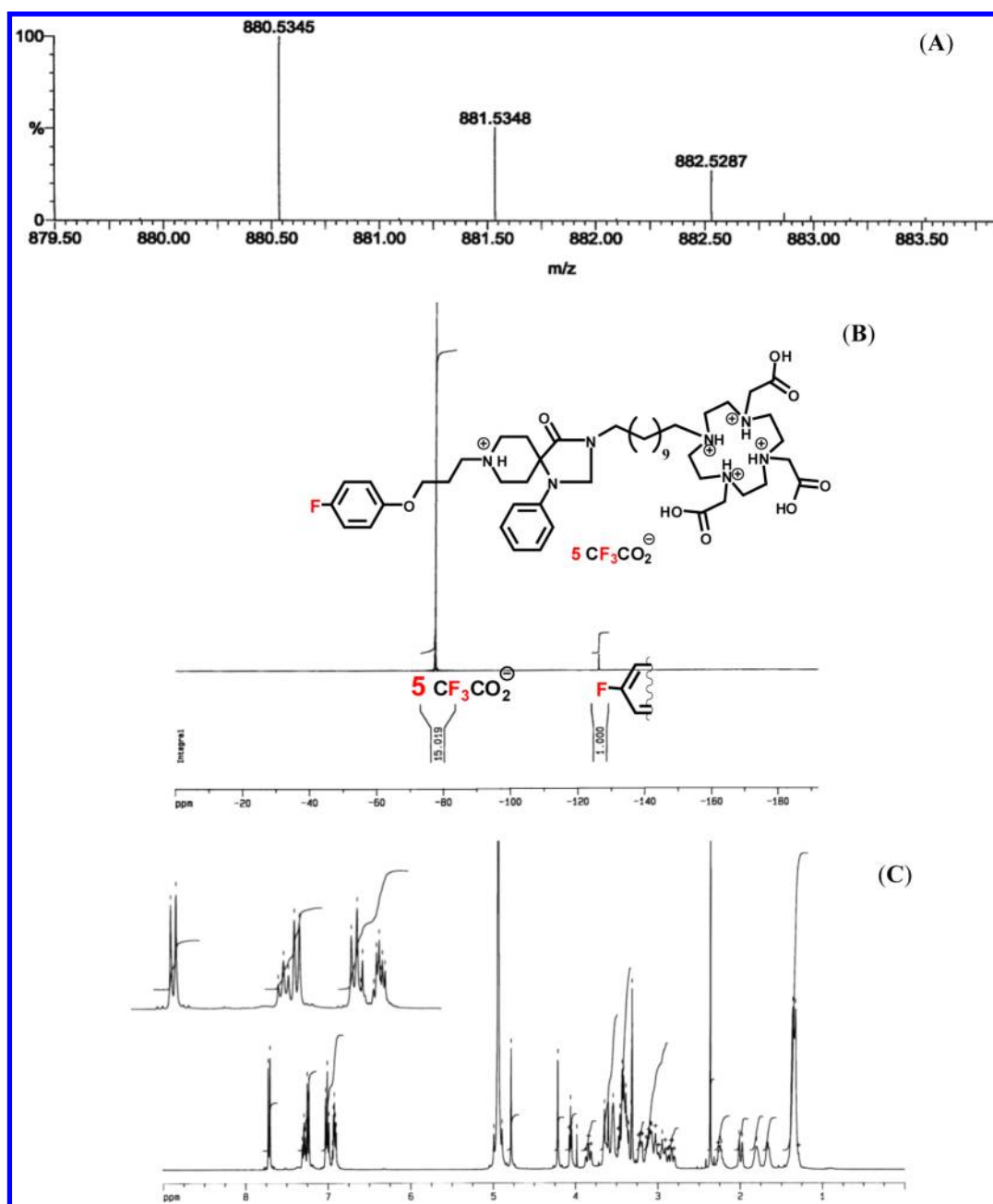


Figure 2. (A) HRMS (TOF MS ES negative), (B) ^{19}F NMR (376.3 MHz; CD_3OD , 25 $^\circ\text{C}$), and (C) ^1H NMR (400 MHz; CD_3OD , 25 $^\circ\text{C}$) spectra of **9b**.

biocompatible.¹⁹ The detailed synthesis of these ligands and the gadolinium complexes prepared thereof outlined in Scheme 2 shows that ligands **15a–d** were synthesized in five steps with an overall yields of about 45%.

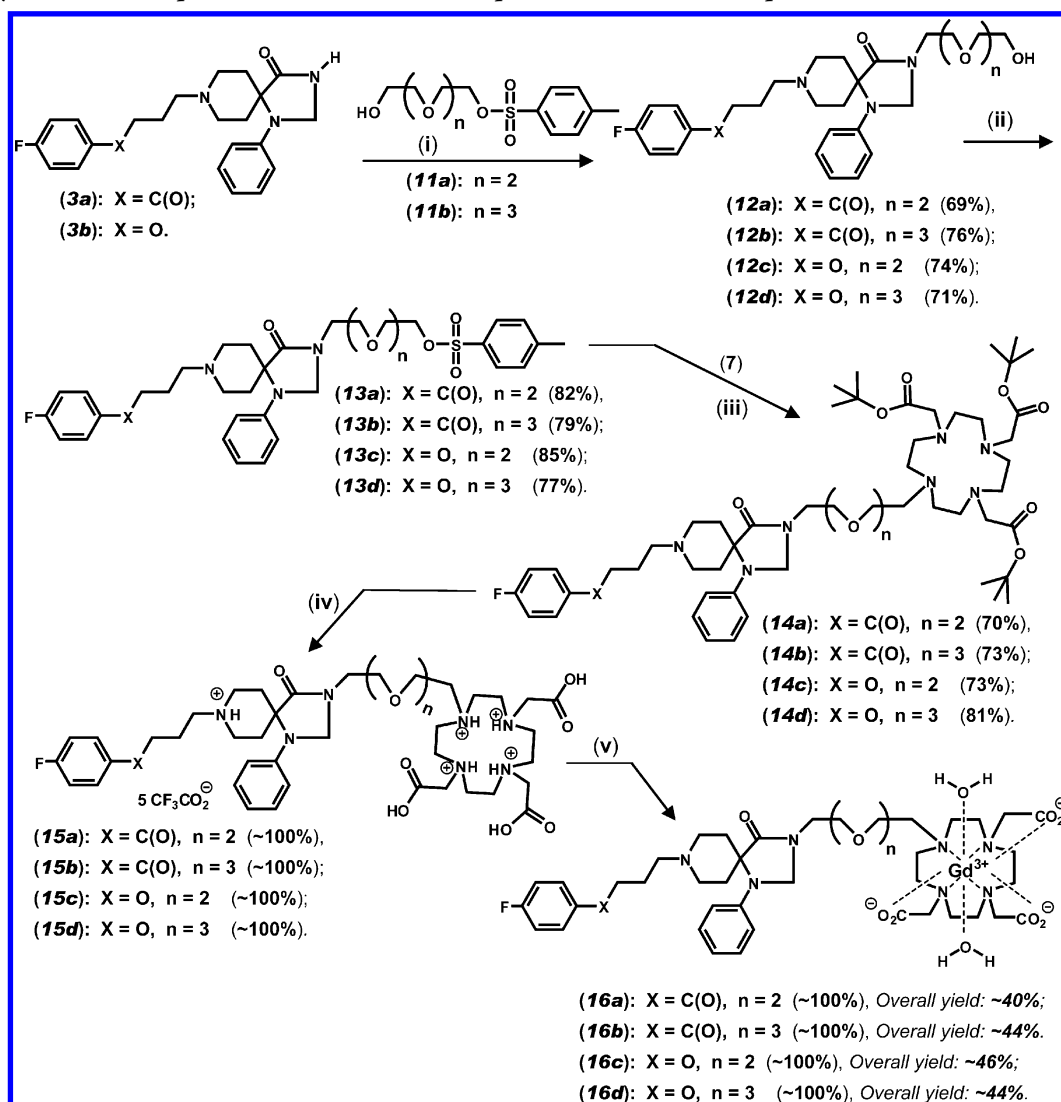
To obtain compounds **15a–d**, **3a** and **3b** were first reacted with 1.3 equiv of the respective oligo-EG monotosylate **11a**²⁰ or **11b**²⁰ in DMF with 1.3 equiv of KOH at 110 $^\circ\text{C}$ to afford alcohols **12a–d**, respectively in yields of over 70% (see Scheme 2). Compounds **12a–d** were then tosylated to give the respective tosylates **13a–d**, which were then reacted with the macrocyclic intermediate **7** affording the triesters **14a–d**, respectively. Compounds **14a–d** were deprotected by TFA to afford the *penta*-salts **15a–d**, respectively, and their full spectroscopic characterization is shown in Figures S93–S105 in Supporting Information.

The prepared ligands can be used to prepare metal-cation-based CAs like those used in PET, SPECT, and MRI. Although

both PET and SPECT are much more sensitive than MRI and hence are more suitable for imaging of receptors, both techniques use radioactive tracers, so we decided to concentrate on the preparation of gadolinium-based CAs suitable for MRI.

Gadolinium-Based Complexes: Synthesis and Characterization. Ligands **9a,b** were quantitatively converted to their respective gadolinium complexes **10a,b** by a known literature procedure (Scheme 1).¹⁹ Clear and conclusive evidence for the formation of the paramagnetic complexes **10a** and **10b** was obtained from high-resolution mass spectrometry (HRMS) (see Figure 3 and Supporting Information).

The same procedure was used to convert compounds **15a–d** to their Gd^{3+} paramagnetic complexes **16a–d** (Scheme 2). Clear evidence for the formation of the paramagnetic complexes was obtained from HRMS (TOF MS ESI) spectra (see Figure 4 and Supporting Information).

Scheme 2. Synthesis of Compounds 15a–d and Their Respective Gadolinium Complexes 16a–d^a

^a(i) 1.3 equiv oligoEG-monotosylate in DMF with 1.3 equiv KOH at 110 °C for 15 h; (ii) 2 equiv TsCl with DMAP (cat. amount) in dry DCM with 6 equiv TEA at 10 °C to rt for 3 h; (iii) 5 equiv K₂CO₃ in ACN at 80 °C for 4 h; (iv) TFA (excess) at rt for 4 h; (v) GdCl₃ in H₂O.

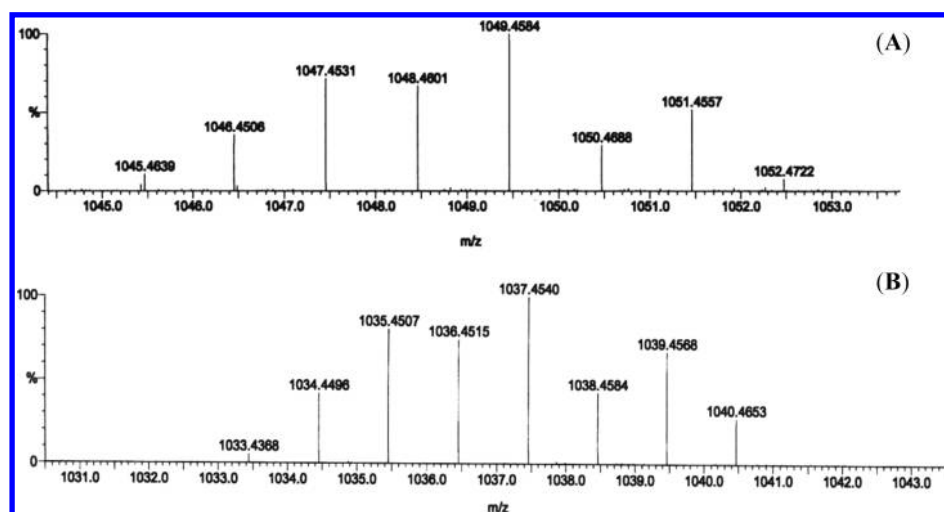


Figure 3. HRMS (TOF MS ES positive) of the isotope distribution of the experimental molecular peaks of (A) 10a and (B) 10b.

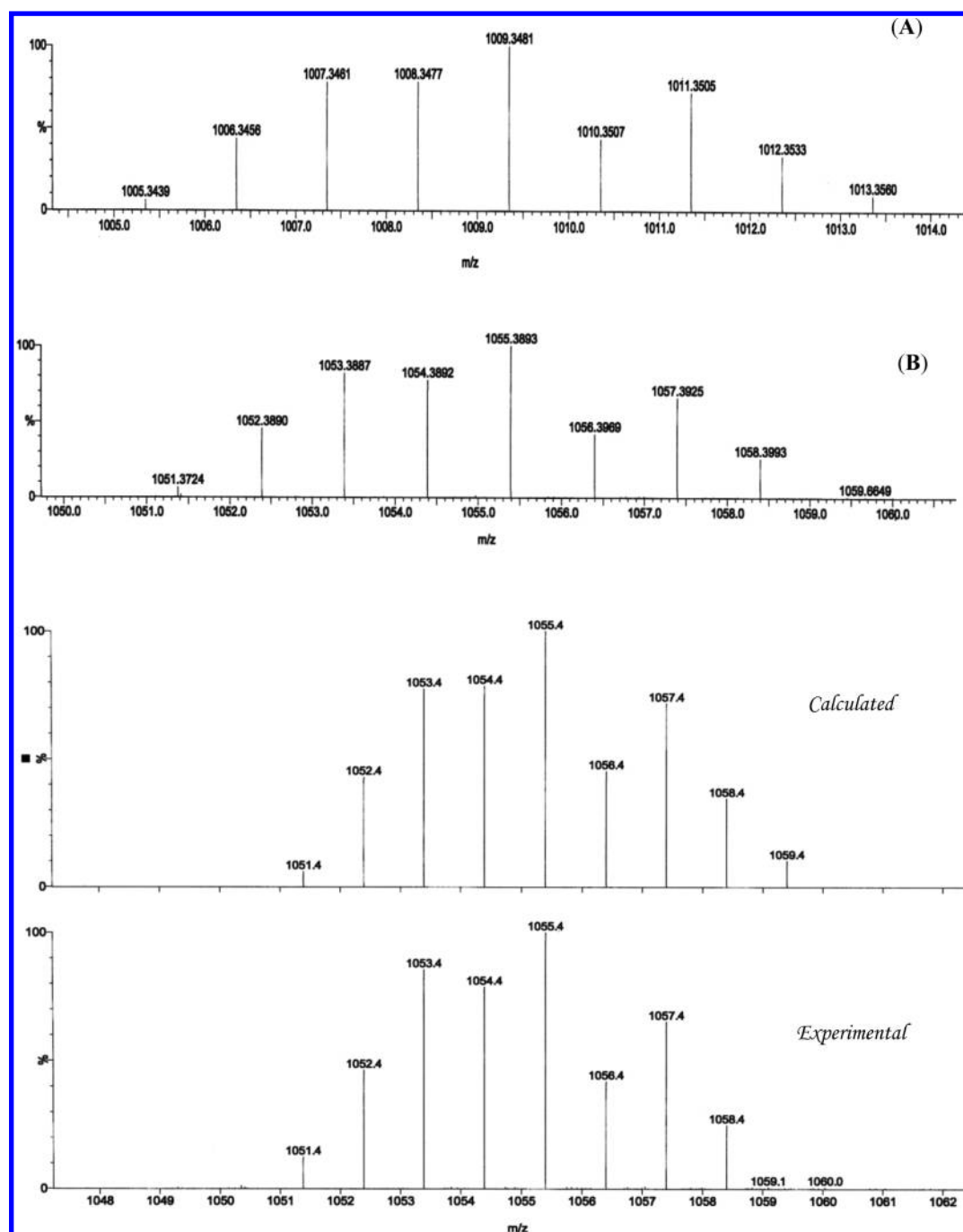


Figure 4. (A) HRMS (TOF MS ES negative) of the isotope distribution of molecular peak of **16a** and (B) HRMS (TOF MS ES positive) of the isotope distribution of the calculated and experimental molecular peak of **16b**.

Binding Affinity to the Dopamine Receptor and Relaxivity of the Target-Specific CAs **10a,b** and **16a–d**.

As a first stage we tested the binding affinity of our gadolinium-based CAs to the dopamine receptors and then evaluated their relaxivity (longitudinal relaxivity R_1 and transverse relaxivity R_2). To assess the affinity of the obtained target-specific CAs to the D3/D2 DRs, we have performed an assay of [^3H]-spiperone binding [5×10^{-10} M] to isolated mouse striatal membranes as we described previously.^{16,21} In our assay we measured the concentration that induces 50% inhibition as compared to ^3H -spiperone.²¹ The binding affinity values of **10a** and **10b** were found to be much higher than the previously reported ones for the “spiro”-based CAs, which were previously found to be about

(10^{-5} – 10^{-6} M; see Table 1).¹⁶ The binding results for the AMI-193-based CAs, however, were less satisfying. Indeed, **16d** was found to have a binding affinity close to that previously reported for the “spiro”-based compound with the relatively long (C_8) spacer.¹⁶ The spiperone-based CAs **10a** and **16b**, however, were found to have very high binding affinities toward the dopamine receptors (close to that of spiperone itself). Thus, the 50% inhibition of ^3H -spiperone binding (5×10^{-10} M) was obtained at concentrations of 1×10^{-8} M and 5×10^{-9} M for **16b** and **10a**, respectively (see Table 1).

The results obtained in the present study together with those reported previously¹⁶ shed light on the structural requirements to obtain high affinity ligands and complexes for dopamine

Table 1. Comparative Binding Affinity (50% Inhibition Concentration) and Relaxivity (R_1 and R_2 Values) of Spiperone-Based (10a and 16b), AMI-193-Based (16d), and Previously Prepared “Spiro”-Based (C_3 -Spacered and C_8 -Spacered) CAs¹⁶

	10a	16b	16d	“spiro”-based C_3 -spacered CA ¹⁶	“spiro”-based C_8 -spacered CA ¹⁶
D2 binding affinity [M]	5×10^{-9}	1×10^{-8}	10^{-6}	10^{-5}	10^{-6}
R_1 [mM ⁻¹ s ⁻¹]	5.5	7.8	a	5.9	8.3
R_2 [mM ⁻¹ s ⁻¹]	23.6	28.8	a	18.1	22.6

^aBecause of the low binding affinity of 16d to the DRs its R_1 and R_2 were not be measured.

receptors in the spiperone family. Our results show that the “spiro” part of the spiperone is not sufficient for effective binding to the dopamine receptors. Even changing the carbonyl group of the spiperone to an etheric moiety resulted in a much lower affinity toward the dopamine receptors. Indeed, despite the many different ligands that bind strongly to the DRs, our results clearly show that the entire spiperone is needed for effective binding to these receptors and that binding of even a large chemical moiety through the N3 position (see Scheme 1) of the spiperone does not reduce considerably the binding affinity to the dopamine receptors. This indeed indicates that the N3 position is the best position to modify the spiperone moiety without compromising the binding affinity to receptors. It is interesting to note also that compound 10a with a *hydrophobic* C_{11} spacer has higher binding affinity than its analogue 16b with a *hydrophilic* tetraEG spacer (see Table 1). For the target-specific gadolinium complexes that were found to have high binding affinities to the dopamine receptors (10a and 16b), we evaluated also their relaxivity. The R_1 and R_2 relaxivity of 10a were found to be 5.5 and 23.6 mM⁻¹ s⁻¹, respectively, while those of 16b were found to be 7.8 and 28.8 mM⁻¹ s⁻¹, respectively. These values are somewhat higher than those reported previously for the “spiro”-based CAs¹⁶ and are also significantly higher than those of Gd-DOTA.²²

It is interesting to note that the R_1 of 10a is lower than the R_1 of 16b. One possible explanation for this observation may well be that the long chain connecting the spiperone moiety in 10a is not fully extended in water or may even be folded so that water has less access to the Gd³⁺ in 10a as compared to 16b. It is even more important to note that the R_2 relaxivities of both 10a and 16b are higher than 20 mM⁻¹ s⁻¹. These values imply that these target-specific MR gadolinium complexes may also be used as “negative” or T_2/T_2^* contrast agents.

To image specific receptors that are not overexpressed by MR methods is rather challenging and requires not only high binding affinity to the targets but also significant amplification. Therefore it is very important that our modular synthesis provides ligands (9a and 15b) that can, relatively easily, be transformed into positron PET and SPECT active CAs by just introducing, in the last step of the synthesis, other metal cations having relatively long half-lives, such as ⁶⁴Cu, ¹¹¹In, ⁹⁹Tc, and more.²³ This will transform our new ligands into target-specific PET agents that are extremely important by themselves.¹ Because of the much higher sensitivity of PET and SPECT as compared to MRI, it is clear that our ligands should enable one to map the dopamine receptors as in the case of ¹¹C-methylspiperone.¹⁷ The much longer half-lives of the metal cation PET agents as compared to ¹¹C PET agents (20 min compared to 12.7 h and 3 days in the case of ⁶⁴Cu and ⁸⁹Zr, respectively, for example) imply that our new ligands, 9a and 15b, may also open new avenues of applications in the field of PET imaging.

CONCLUSION

We designed and prepared a series of spiperone and AMI-193-targeted ligands from which we prepared a series of

gadolinium-based MRI CAs all by an efficient modular synthesis. The target-specific gadolinium-based complexes were found to have high R_1 and R_2 relaxivity. Most importantly the spiperone-based CAs were found to have excellent binding affinity to dopamine receptors, while their “spiro”- and even AMI-193-based analogues did not. Therefore, the spiperone-based CAs (10a, 16a, and 16b) have the potential to be used as target-specific MRI contrast agents, which may enable *in vitro* and possibly *in vivo* MR mapping of dopamine receptors in experimental models. *In vitro* MRI experiments along these lines are now underway. The binding affinity of the different complexes prepared shed light on crucial structural requirements to preserve high binding affinity and enabled us to identify the structural modifications allowed to maintain strong binding to the dopamine receptors. Importantly the modular approach presented in the present paper should, in principle, allow the preparation of target-specific CAs to be used by other imaging modalities such as PET and SPECT, by just replacing the gadolinium cation, in the last step of the synthesis, by other cations such as ⁶⁴Cu, ⁸⁹Zr, ¹¹¹In, ⁹⁹Tc, and more. This will enable mapping of the dopamine receptors with PET and SPECT tracers having long half-lives.

EXPERIMENTAL SECTION

General. [³H]-Spiperone (91 Ci/mmol) was purchased from Amersham Bio Science UK. ¹H, ¹⁹F, and ¹³C NMR spectra and T_1 and T_2 relaxation experiments were all acquired on a 400 MHz (9.4T) NMR spectrometer operating at 400.13, 376.3, and 100.6 MHz for ¹H, ¹⁹F, and ¹³C, respectively. MS were obtained by FAB-MS, and the HRMS were collected on a time-of-flight analyzer (TOF) (ionization mode ESI).

Preparation of 3a and 3b. To a solution of 1 (1.04 g, 4.5 mmol, 1 equiv) in dry dimethylformamide (DMF; 25 mL) and dry diisopropylamine (DIPA; 4.5 g, 6.4 mL, 45 mmol, 10 equiv) was added 4-chloro-4'-fluorobutyl-phenone (2a) (4.5 g, 3.7 mL, 22.5 mmol, 5 equiv) or 3-(4-fluorophenoxy)propyl chloride (2b) (4.2 g, 3.5 mL, 22.4 mmol, 5 equiv) under argon. After stirring for 17 h at 80 °C the reaction mixture was cooled to room temperature (rt) and then was poured into water (50 mL). Thereafter, the aqueous phase was extracted with chloroform (4 × 50 mL). The combined organic phase was dried with magnesium sulfate, filtered, and evaporated under reduced pressure (first, the chloroform was evaporated with an evaporator, and then DMF in a high vacuum system with liquid nitrogen). The obtained grayish powdery solid was purified by trituration from methanol or by column chromatography over silica starting with chloroform as eluting solvent and changing it to 5:95 methanol/chloroform to afford 3a as white powdery solid; yield 1.66 g (4.2 mmol, 93%); mp 201–202 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ_{ppm} 8.00–8.04 (m, 2H), 7.24–7.28 (m, 2H), 7.13 (t, J = 8.6 Hz, 2H), 6.85–6.91 (m, 3H), 4.73 (s, 2H), 3.02 (t, J = 7.1 Hz, 2H), 2.70–2.90 (m, 4H), 2.40–2.70 (m, 4H), 1.98 (t, J = 7 Hz, 2H), 1.68–1.76 (m, 2H); ¹³C NMR (100.6 MHz, CDCl₃, 25 °C) δ_{ppm} 198.6, 177.9, 165.6 (d, J = 254 Hz), 143.1, 133.6, 130.7 (d, J = 9 Hz), 129.2, 119.1, 115.7, 115.6 (d, J = 21 Hz), 59.4, 59.2, 57.5, 49.6, 36.4, 29.1, 21.8; ¹⁹F NMR (376.3 MHz, CDCl₃, 25 °C) δ_{ppm} -106.1; FAB⁺-MS m/z 396.2 [M + H]⁺.

Compound 3b was obtained as a white powdery solid; yield 1.50 g, (3.9 mmol, 87%); mp 171–172 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C) δ_{ppm} 7.25–7.29 (m, 2H), 6.83–6.99 (m, 7H), 6.59 (bs, NH,

1H), 4.74 (s, 2H), 4.021 (t, $J = 6.4$ Hz, 2H), 2.79–2.85 (m, 4H), 2.58–2.70 (m, 4H), 1.96–2.00 (m, 2H), 1.70–1.78 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 177.8, 157.1 (d, $J = 238$ Hz), 155.2, 143.2, 129.2, 119.1, 115.8 (d, $J = 23$ Hz), 115.7, 115.4 (d, $J = 8$ Hz), 67.0, 59.4, 59.1, 54.9, 49.7, 29.2, 27.1; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.8; FAB⁺-MS m/z 384.1 $[\text{M} + \text{H}]^+$.

Preparation of 5a and 5b. To a solution of 3a (1.00 g, 2.53 mmol, 1 equiv) or 3b (0.97 g, 2.53 mmol, 1 equiv) in dry DMF (30 mL) and potassium hydroxide (KOH; 0.21 g, 3.80 mmol, 1.5 equiv) was added 11-bromo-1-undecanol (4) (0.76 g, 3.04 mmol, 1.2 equiv) under argon. After stirring for 18–20 h at 120 °C the reaction mixture was cooled and poured into water (70 mL). Thereafter, the aqueous phase was extracted with dichloromethane (DCM; 3 × 70 mL). The combined organic phase was dried with magnesium sulfate, filtered, and evaporated under reduced pressure (first, the dichloromethane was evaporated in an evaporator, and then DMF in a high vacuum system with liquid nitrogen). The residue was purified by column chromatography over silica. The eluting chloroform solvent was changed to 3:97 methanol/chloroform (R_f of the product was 0.2) to afford 5a as clear very viscous liquid; yield 1.16 g (2.05 mmol; 81%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 8.00–8.04 (m, 2H), 7.23–7.27 (m, 2H), 7.10–7.15 (m, 2H), 6.82–6.90 (m, 3H), 4.66 (s, 2H), 3.63 (t, $J = 6.6$ Hz, 2H), 3.41 (t, $J = 7.3$ Hz, 2H), 3.02 (t, $J = 7.2$ Hz, 2H), 2.8–2.9 (bm, 4H), 2.6 (bm, 2H), 2.5 (bm, 2H), 1.93–1.99 (m, 2H), 1.52–1.66 (m, 6H), 1.25–1.35 (bm, 14H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.6, 174.3, 165.6 (d, $J = 254$ Hz), 143.0, 133.6, 130.7 (d, $J = 9$ Hz), 129.2, 118.8, 115.6 (d, $J = 22$ Hz), 115.2, 63.4, 63.0, 60.7, 57.6, 49.6, 40.8, 36.4, 32.8, 29.47, 29.40, 29.36, 29.35, 29.35, 29.10, 27.3, 26.7, 25.7, 21.9; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.2; FAB⁺-MS m/z 537.3 $[\text{M} + \text{H}]^+$.

Compound 5b was obtained as a very viscous clear liquid; yield 1.24 g, (2.25 mmol, 89% yield); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.25–7.29 (m, 2H), 6.83–6.98 (m, 7H), 4.66 (s, 2H), 4.00 (t, $J = 6.3$ Hz, 2H), 3.61 (t, $J = 6.6$ Hz, 2H), 3.41 (t, $J = 7.2$ Hz, 2H), 2.59–2.89 (bm, 8H), 1.97–2.01 (m, 2H), 1.53–1.68 (bm, 6H), 1.27–1.32 (bm, 14H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.3, 157.1 (d, $J = 238$ Hz), 155.1, 142.9, 129.2, 118.7, 115.6 (d, $J = 23$ Hz), 115.4 (d, $J = 8$ Hz), 115.1, 66.9, 63.3, 62.7, 60.6, 54.9, 49.6, 40.7, 32.7, 29.4, 29.32, 29.32, 29.27, 29.27, 29.1, 27.3, 26.8, 26.6, 25.7; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.7; FAB⁺-MS m/z 554.3 $[\text{M} + \text{H}]^+$.

Preparation of 6a and 6b. A solution of 5a (0.97 g, 1.81 mmol, 1 equiv) or 5b (1.00 g, 1.81 mmol, 1 equiv) with dry triethylamine (TEA; 1.46 g, 2.0 mL, 14.5 mmol, 8 equiv) in dry DCM (45 mL) was cooled to 0 °C, and then tosyl chloride (0.69 g, 3.62 mmol, 2 equiv) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added. The solution was stirred for about 3 h (until TLC indicated the disappearance of 5a or 5b) at 10 °C. Water (70 mL) was added, and the organic layer was separated. After extraction with DCM (3 × 70 mL), the combined organic phase was dried over magnesium sulfate, filtered, and evaporated under reduced pressure, and the residue was purified by column chromatography over silica. The eluting solvent was exchanged from chloroform to 2% methanol in chloroform (R_f of the product was 0.1) to afford 6a as a very viscous clear liquid; yield 1.04 g (1.45 mmol, 80%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 8.00–8.04 (m, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.22–7.27 (m, 2H), 7.12 (t, $J = 8.6$ Hz, 2H), 6.81–6.90 (m, 3H), 4.65 (s, 2H), 4.00 (t, $J = 6.5$ Hz, 2H), 3.40 (t, $J = 7.3$ Hz, 2H), 3.01 (t, $J = 7.2$ Hz, 2H), 2.83 (bs, 4H), 2.63 (bm, 2H), 2.49–2.53 (m, 2H), 2.44 (s, 3H), 1.96 (t, $J = 7.0$ Hz, 2H), 1.58–1.65 (bm, 6H), 1.10–1.31 (bm, 14H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.6, 174.3, 165.6 (d, $J = 254$ Hz), 144.6, 143.0, 133.6, 133.2, 131.7 (d, $J = 9$ Hz), 129.8, 129.2, 127.8, 118.8, 115.6 (d, $J = 22$ Hz), 115.2, 70.7, 63.4, 60.6, 57.6, 49.6, 40.8, 36.4, 29.36, 29.31, 29.27, 29.11, 28.85, 28.77, 27.6, 27.3, 26.7, 25.3, 21.9, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.9; FAB⁺-MS m/z 720.3 $[\text{M} + \text{H}]^+$.

Compound 6b was obtained as a very viscous clear liquid; yield 0.95 g (1.34 mmol, 74%); ^1H (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.78 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.24–7.29 (m, 2H), 6.83–6.98 (bm, 7H), 4.67 (s, 2H), 4.01 (t, $J = 6.4$ Hz, 4H), 3.38–3.43 (m,

2H), 2.86 (m, 4H), 2.58–2.70 (m, 4H), 2.44 (s, 3H), 1.95–2.05 (m, 2H), 1.58–1.74 (m, 6H), 1.22–1.32 (m, 14H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.3, 157.1 (d, $J = 238$ Hz), 155.1, 144.6, 143.0, 133.3, 129.7, 129.2, 127.8, 118.8, 115.7 (d, $J = 23$ Hz), 115.4 (d, $J = 8$ Hz), 115.2, 70.6, 67.0, 63.4, 60.6, 54.9, 49.7, 40.8, 29.39, 29.37, 29.35, 29.31, 29.27, 29.1, 28.86, 28.79, 27.3, 26.7, 25.3, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.8; FAB⁺-MS m/z 708.2 $[\text{M} + \text{H}]^+$.

Preparation of 8a and 8b. 1,4,7,10-Tetraazacyclododecane-1,4,7-tris(*tert*-butylacetate) (7) (0.36 g, 0.70 mmol, 1 equiv) was added to a stirred solution of 6a (0.50 g, 0.70 mmol, 1 equiv) or 6b (0.50 g, 0.70 mmol, 1 equiv) and K_2CO_3 (0.48 g, 3.50 mmol, 5 equiv) in acetonitrile (ACN; 10 mL). The solution was heated to 80 °C for 6 h. The precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica. The eluting solvent was changed from chloroform to 10% methanol in chloroform (R_f of the product was 0.5) to afford 8a as a very viscous liquid; yield 0.52 g (0.49 mmol, 70%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.95–8.01 (m, 2H), 7.79 (d, $J = 8.0$ Hz, 2H; tosylate anion), 7.19 (t, $J = 7.9$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 8.2$ Hz, 2H; tosylate anion), 6.85 (d, $J = 8.3$ Hz, 2H), 6.80 (t, $J = 7.3$ Hz, 1H), 4.63 (s, 2H), 3.33 (t, $J = 7.3$ Hz, 2H), 1.90–3.33 (bm, 41H; includes s of tosylate anion), 1.10–1.80 (bm, 45H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.3, 174.0, 173.4, 172.5, 165.9 (d, $J = 254$ Hz), 144.2, 142.7 (tosylate anion), 138.4 (tosylate anion), 133.4, 130.6 (d, $J = 9$ Hz), 129.2, 128.2 (tosylate anion), 126.2 (tosylate anion), 118.8, 115.5 (d, $J = 22$ Hz), 115.1, 82.4, 82.1, 63.3, 60.2, 57.3, 56.2, 55.6, 54.3, 50.2, 49.4, 40.7, 36.2, 29.5, 29.5, 29.4, 29.4, 29.1, 28.9, 27.82, 27.83, 27.83, 27.83, 27.84, 27.7, 27.7, 27.7, 27.2, 26.7, 21.2 (tosylate anion); ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.1; FAB⁺-MS m/z 1084.7 $[\text{M} + \text{Na}]^+$.

Compound 8b was obtained as a very viscous liquid; yield 0.56 g (0.53 mmol, 76%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.82 (d, $J = 8.0$ Hz, 2H; tosylate anion), 7.25 (t, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H; tosylate anion), 6.89–7.00 (m, 4H), 6.80–6.87 (m, 3H), 4.68 (s, 2H), 4.01 (t, $J = 6.1$ Hz, 2H), 3.42 (t, $J = 7.4$ Hz, 2H), 3.0–3.2 (bm, 8H), 2.77 (bs, 8H), 2.2–2.4 (bm, 9H; includes s of tosylate anion), 2.08 (bs, 2H), 1.66–1.73 (m, 2H), 1.59–1.65 (m, 2H), 1.20–1.55 (m, 53H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.0, 173.4, 172.6, 157.1 (d, $J = 238$ Hz), 154.9, 143.9, 142.6 (tosylate anion), 138.6 (tosylate anion), 129.3, 128.3 (tosylate anion), 126.1 (tosylate anion), 118.9, 115.7 (d, $J = 23$ Hz), 115.4 (d, $J = 8$ Hz), 115.0, 82.5, 82.2, 77.2, 66.6, 63.4, 60.1, 56.3, 55.6, 54.9, 54.3, 50.2, 49.5, 40.8, 29.6, 29.44, 29.42, 29.1, 28.8, 28.1, 28.0, 27.9, 27.9, 27.8, 27.7, 27.5, 27.3, 26.7, 26.6, 21.2 (tosylate anion); ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.6; FAB⁺-MS m/z 1072.5 $[\text{M} + \text{Na}]^+$.

Preparation of 9a and 9b. Compound 8a or 8b was dissolved in trifluoroacetic acid (TFA). After stirring at ambient temperature for 4 h the solution was evaporated in vacuum. Methanol was added and evaporated, and then chloroform was added and evaporated (until the complete disappearance of TFA). Compound 9a was obtained nearly quantitatively as a light brown viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 7.91–7.97 (m, 2H), 7.68 (d, $J = 8.1$ Hz, 2H; tosylate anion), 7.32 (t, $J = 7.9$ Hz, 2H), 7.10–7.28 (m, 4H; includes d of tosylate anion in 7.24), 7.03 (d, $J = 8.3$ Hz, 2H), 6.95 (t, $J = 8.0$ Hz, 1H), 4.79 (s, 2H), 4.17 (s, 2H), 3.80 (dt, $J = 13$ Hz, $J = 5$ Hz, 2H), 3.49–3.70 (m, 8H), 3.33–3.49 (bm, 8H), 3.06–3.30 (bm, 8H), 2.88–3.06 (bm, 4H), 2.82 (dt, $J = 14$ Hz, $J = 6$ Hz, 2H), 2.35 (s, 3H; tosylate anion), 2.15–2.18 (m, 2H), 2.00 (d, $J = 15$ Hz, 2H), 1.79 (m, 2H), 1.66 (m, 2H), 1.25–1.45 (m, 16H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 199.9, 174.8, 174.5, 168.9, 167.3 (d, $J = 254$ Hz), 162.8 (q, $J = 34$ Hz; TFA), 143.3 (tosylate anion), 142.9 (tosylate anion), 142.1, 134.2, 132.1 (d, $J = 9.5$ Hz), 130.6, 130.0 (tosylate anion), 126.8 (tosylate anion), 121.8, 118.2, 117.7 (q, $J = 291$ Hz; TFA), 116.8 (d, $J = 22$ Hz), 64.8, 60.1, 57.6, 56.1, 55.9, 53.6, 53.0, 51.1, 50.4, 49.7, 49.3, 42.1, 36.0, 30.39, 30.36, 30.36, 30.1, 30.0, 28.5, 28.0, 27.6, 27.5, 24.7, 21.4 (tosylate anion); ^{19}F NMR (376.3 MHz, CD_3OD , 25 °C) δ_{ppm} –78.6, –108.6; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{48}\text{H}_{71}\text{N}_7\text{O}_8\text{F}^-$ $[\text{M} - \text{H}]^-$ 892.5348, found 892.5347.

Compound 9b was obtained nearly quantitatively as a light brown viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 7.71

(d, $J = 8.1$ Hz, 2H; tosylate anion), 7.28 (t, $J = 7.9$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H; tosylate anion), 6.96–7.14 (m, 4H), 6.88–6.95 (m, 3H), 4.78 (s, 2H), 4.21 (s, 2H), 4.05 (t, $J = 5.7$ Hz, 2H), 3.84 (dt, $J = 13$ Hz, $J = 5$ Hz, 2H), 3.49–3.70 (m, 8H), 3.33–3.49 (m, 10H), 3.16–3.24 (m, 2H), 2.88–3.16 (m, 6H), 2.83 (dt, $J = 11$ Hz, $J = 5$ Hz, 2H), 2.36 (s, 3H; tosylate anion), 2.15–2.30 (m, 2H), 1.99 (d, $J = 15$ Hz, 2H), 1.73–1.86 (m, 2H), 1.60–1.71 (m, 2H), 1.25–1.46 (m, 16H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 174.8, 174.3, 168.7, 162.2 (q, $J = 36$ Hz; TFA), 158.9 (d, $J = 234$ Hz), 156.1, 143.58, 143.53 (tosylate anion), 141.8 (tosylate anion), 130.5 (tosylate anion), 129.9, 127.0 (tosylate anion), 121.6, 118.2, 117.8 (q, $J = 291$ Hz; TFA), 116.8 (d, $J = 23$ Hz), 116.8 (d, $J = 8$ Hz), 66.5, 64.8, 60.0, 56.1, 56.0, 55.9, 53.4, 53.1, 51.2, 50.8, 42.1, 30.57, 30.58, 30.58, 30.59, 30.33, 30.27, 28.7, 28.2, 27.9, 27.7, 25.4, 24.7, 21.3 (tosylate anion); ^{19}F NMR (376.3 MHz, CD_3OD , 25 °C) δ_{ppm} -77.5, -126.2; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{47}\text{H}_{71}\text{N}_7\text{O}_8\text{F}^-$ [$\text{M} - \text{H}$] $^-$ 880.5348, found 880.5345.

Preparation of 10a and 10b. A concentrated methanolic solution of **9a** (220 mg, 0.15 mmol) or **9b** (220 mg, 0.15 mmol) was mixed with an aqueous solution of gadolinium(III) chloride hexahydrate (155 mg, 0.15 mmol). The pH of the obtained solution was adjusted to 7.8, and the solution was stirred at room temperature (rt) for 1 week, during which the pH was measured and readjusted to 7.8. After lyophilization **10a** was obtained as a brown solid. The reaction proceeded nearly quantitatively; HRMS (TOF MS ES positive) m/z calcd for $\text{C}_{48}\text{H}_{70}\text{N}_7\text{O}_8\text{F}^{155}\text{Gd}^+$ [$\text{M} + \text{H}$] $^+$ 1046.4496, found 1046.4506.

Compound **10b** was obtained nearly quantitatively as a brown solid; HRMS (TOF MS ES positive) m/z calcd for $\text{C}_{47}\text{H}_{70}\text{N}_7\text{O}_8\text{F}^{155}\text{Gd}^+$ [$\text{M} + \text{H}$] $^+$ 1034.4496, found 1034.4496.

Preparation of 11a and 11b. Solution of tosyl chloride (TsCl; 6.3 g, 33.4 mmol, 1 equiv) in dry DCM (25 mL) at rt was dropwise (during 0.5 h) added into a cooled (0 °C) solution of triEG (25.0 g, 167 mmol, 5 equiv) or tetraEG (32.4 g, 167 mmol, 5 equiv) and dry TEA (9.2 mL, 6.7 g, 67 mmol, 2 equiv) in dry DCM (100 mL). The resulting mixture was stirred at rt for 1.5 h. After washing with water, extracting with chloroform, drying with magnesium sulfate, filtering, and evaporation, a colorless viscous liquid was obtained. It was purified by column chromatography over silica. The eluting solvent was exchanged from chloroform to 5% methanol in chloroform (R_f of the monotosylated product **11a** was 0.35; R_f of the ditosylated product was 0.8; triEG stayed near the start line; the TLC was exposed by solution of potassium permanganate) to afford **11a** as a clear, colorless viscous liquid; yield 7.2 g (23.7 mmol; 71%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.79 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 4.16 (t, $J = 4.7$ Hz, 2H), 3.69 (t, $J = 4.6$ Hz, 4H), 3.53–3.61 (m, 6H), 2.44 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 144.6, 132.5, 129.5, 127.5, 72.2, 70.3, 69.8, 69.0, 68.2, 61.2, 21.2; $\text{FAB}^+\text{-MS}$ m/z 305.1 [$\text{M} + \text{H}$] $^+$, 327.1 [$\text{M} + \text{Na}$] $^+$.

Compound **11b** was purified by column chromatography over silica. The eluting solvent was exchanged from chloroform to 5% methanol in chloroform (R_f of the monotosylated product was 0.4; R_f of the ditosylated product was 0.75; R_f of **11b** was 0.1, when TLC of **11b** was exposed in the manner of **11a**) to afford **11b** as a clear, colorless viscous liquid; yield 7.2 g (20.7 mmol, 62%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.76 (d, $J = 8.1$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.12 (t, $J = 4.7$ Hz, 2H), 3.35–3.80 (m, 14H), 2.41 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 144.7, 132.8, 129.7, 127.8, 72.3, 70.6, 70.5, 70.3, 70.2, 69.2, 68.5, 61.5, 21.5; $\text{FAB}^+\text{-MS}$ m/z 349.0 [$\text{M} + \text{H}$] $^+$, 371.0 [$\text{M} + \text{Na}$] $^+$, 387.0 [$\text{M} + \text{K}$] $^+$.

Preparation of 12a, 12b, 12c, and 12d. Compound **11a** (0.50 g, 1.65 mmol, 1.3 equiv) or **11b** (0.57 g, 1.65 mmol, 1.3 equiv) was added under argon to a solution of **3a** (0.50 g, 1.27 mmol, 1 equiv) or **3b** (0.49 g, 1.27 mmol, 1 equiv) and KOH (0.092 g, 1.65 mmol, 1.3 equiv) in dry DMF (15 mL), and the mixture was heated at 110 °C for 20 h. Water (60 mL) and chloroform (50 mL) were added, and the organic layer was separated. After extraction with chloroform (3 \times 60 mL), the combined organic phase was dried over magnesium sulfate, filtered, and evaporated under reduced pressure (first, the chloroform was evaporated in an evaporator, and then the DMF in high vacuum system with liquid nitrogen). The obtained viscous liquid

was purified by column chromatography over silica. The eluting solvent was changed from chloroform to 3% methanol in chloroform, to afford **12a** as a very viscous colorless liquid; yield 0.46 g (0.87 mmol, 69%); ^1H NMR (200 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.94–8.10 (m, 2H), 7.22–7.38 (m, 3H), 7.13 (t, $J = 8.6$ Hz, 1H), 6.81–6.95 (m, 3H), 4.79 (s, 2H), 3.47–3.80 (m, 12H), 3.03 (t, $J = 7.0$ Hz, 2H), 2.75–2.90 (m, 4H), 2.35–2.75 (m, 4H), 1.98 (q, $J = 7.0$ Hz, 2H), 1.60–1.75 (m, 2H); ^{13}C NMR (50.3 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.5, 174.6, 165.6 (d, $J = 254$ Hz), 143.1, 133.5, 130.6 (d, $J = 9$ Hz), 129.1, 119.1, 115.8, 115.5 (d, $J = 21$ Hz), 72.4, 70.3, 69.2, 64.7, 61.6, 60.4, 57.5, 49.5, 40.9, 36.3, 29.6, 29.1, 21.7; ^{19}F NMR (188.15 MHz, CDCl_3 , 25 °C) δ_{ppm} -106.2; $\text{FAB}^+\text{-MS}$ m/z 528.1 [$\text{M} + \text{H}$] $^+$.

Compound **12b** was obtained as a very viscous colorless liquid; yield 0.55 g (0.97 mmol, 76%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.90–7.99 (m, 2H), 7.18 (t, $J = 7.5$ Hz, 2H), 7.06 (t, $J = 8.2$ Hz, 2H), 6.87 (d, $J = 8.1$ Hz, 2H), 6.77 (t, $J = 7.2$ Hz, 1H), 4.72 (s, 2H), 3.34–3.75 (m, 16H), 2.70–3.05 (m, 6H), 2.55–2.70 (m, 2H), 2.45–2.55 (m, 2H), 1.87–2.00 (m, 2H), 1.56–1.68 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.1, 174.1, 165.3 (d, $J = 254$ Hz), 142.8, 133.2, 130.4 (d, $J = 9$ Hz), 128.9, 118.7, 115.4 (d, $J = 22$ Hz), 115.3, 72.3, 70.3, 70.2, 70.03, 69.95, 68.9, 64.5, 61.2, 59.9, 57.2, 49.2, 40.7, 36.0, 28.6, 21.1; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -106.0; $\text{FAB}^+\text{-MS}$ m/z 572.3 [$\text{M} + \text{H}$] $^+$.

Compound **12c** was obtained as a very viscous colorless liquid; yield 0. (0.94 mmol, 74%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.27 (t, $J = 8$ Hz, 2H), 6.94 (t, $J = 8$ Hz, 4H), 6.80–6.90 (m, 3H), 4.79 (s, 2H), 4.00 (t, $J = 6.3$ Hz, 2H), 3.52–3.75 (m, 12H), 2.75–2.95 (m, 4H), 2.55–2.75 (m, 4H), 1.93–2.05 (m, 2H), 1.63–1.74 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.7, 157.1 (d, $J = 238$ Hz), 155.1, 143.1, 129.2, 119.1, 115.7, 115.7 (d, $J = 23$ Hz), 115.4 (d, $J = 8$ Hz), 72.5, 70.4, 70.4, 69.1, 66.9, 64.7, 61.6, 60.4, 54.9, 49.6, 41.0, 29.2, 26.9; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -124.7; $\text{FAB}^+\text{-MS}$ m/z 516.2 [$\text{M} + \text{H}$] $^+$.

Compound **12d** was obtained as a very viscous colorless liquid; yield 0.50 g (0.90 mmol, 71%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.26 (t, $J = 7.6$ Hz, 2H), 6.91–6.99 (m, 4H), 6.81–6.89 (m, 3H), 4.78 (s, 2H), 4.00 (t, $J = 6.2$ Hz, 2H), 3.57–3.73 (m, 14H), 3.53 (t, $J = 4.3$ Hz, 2H), 2.80–2.93 (m, 4H), 2.57–2.71 (m, 4H), 1.93–2.04 (m, 2H), 1.64–1.73 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.5, 157.0 (d, $J = 238$ Hz), 155.0, 143.0, 129.0, 118.9, 115.6, 115.5 (d, $J = 23$ Hz), 115.3 (d, $J = 8$ Hz), 72.4, 70.4, 70.3, 70.1, 70.0, 69.0, 66.8, 64.6, 61.4, 60.3, 54.8, 49.5, 40.8, 29.0, 26.7; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -124.7; $\text{FAB}^+\text{-MS}$ m/z 560.3 [$\text{M} + \text{H}$] $^+$.

Preparation of 13a, 13b, 13c, and 13d. TsCl (0.14 g, 0.76 mmol, 2 equiv) and a catalytic amount of DMAP were added to a cooled (10 °C) solution of **12a** (0.20 g, 0.38 mmol, 1 equiv), **12b** (0.22 g, 0.38 mmol, 1 equiv), **12c** (0.20 g, 0.38 mmol, 1 equiv), or **12d** (0.21 g, 0.38 mmol, 1 equiv) and TEA (0.3 mL, 2.3 mmol, 6 equiv) in dry DCM (10 mL). After about 3 h of stirring at rt, water (20 mL) and DCM (15 mL) were added. The organic layer was separated, and after extraction with dichloromethane (2 \times 25 mL) the combined organic phase was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography over silica. The eluting solvent was changed from chloroform to 3% methanol in chloroform to afford **13a** as a viscous liquid; yield 0.21 g (0.31 mmol, 82%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.98–8.06 (m, 2H), 7.77 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.23 (t, $J = 8.3$ Hz, 2H), 7.13 (t, $J = 8.6$ Hz, 2H), 6.82–6.90 (m, 3H), 4.75 (s, 2H), 4.11 (t, $J = 4.8$ Hz, 2H), 3.67 (t, $J = 4.8$ Hz, 4H), 3.56–3.62 (m, 6H), 3.02 (t, $J = 7.1$ Hz, 2H), 2.75–2.90 (m, 4H), 2.45–2.65 (m, 4H), 2.44 (s, 3H), 1.97 (q, $J = 6.5$ Hz, 2H), 1.61–1.70 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.5, 174.6, 165.6 (d, $J = 254$ Hz), 144.8, 144.8, 143.1, 132.9, 130.7 (d, $J = 9$ Hz), 129.8, 129.2, 127.9, 118.9, 115.6, 115.5 (d, $J = 22$ Hz), 70.7, 70.7, 70.3, 69.4, 69.1, 68.7, 64.7, 57.6, 49.6, 40.9, 36.4, 29.7, 29.2, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -106.2; $\text{FAB}^+\text{-MS}$ m/z 682.1 [$\text{M} + \text{H}$] $^+$.

Compound **13b** was obtained as a viscous liquid; yield 0.22 g (0.30 mmol, 79%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.97–8.05 (m, 2H), 7.77 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.23 (t, $J = 7.7$ Hz, 2H), 7.12 (t, $J = 8.3$ Hz, 2H), 6.90 (d, $J = 8.1$ Hz, 2H),

6.83 (t, $J = 7.2$ Hz, 1H), 4.77 (s, 2H), 4.09 (t, $J = 4.7$ Hz, 2H), 3.48–3.71 (m, 14H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.75–2.99 (m, 4H), 2.45–2.75 (m, 4H), 2.43 (s, 3H), 2.00 (q, $J = 6.8$ Hz, 2H), 1.62–1.71 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.5, 174.6, 165.6 (d, $J = 254$ Hz), 144.7, 143.1, 130.6 (d, $J = 9$ Hz), 129.8, 129.8, 129.2, 127.9, 118.9, 115.6 (d, $J = 22$ Hz), 115.6, 115.5, 70.6, 70.5, 70.4, 70.3, 69.2, 69.1, 68.6, 64.7, 60.2, 57.4, 49.5, 41.0, 36.3, 29.6, 29.0, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.1; FAB⁺-MS m/z 726.3 $[\text{M} + \text{H}]^+$.

Compound **13c** was obtained as a viscous liquid; yield 0.22 g (0.32 mmol, 85%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.76 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 7.4$ Hz, 2H), 6.95 (d, $J = 8.3$ Hz, 2H), 6.91 (d, $J = 8.1$ Hz, 2H), 6.81–6.88 (m, 3H), 4.76 (s, 2H), 4.11 (t, $J = 4.7$ Hz, 2H), 4.01 (t, $J = 6.3$ Hz, 2H), 3.64–3.69 (m, 4H), 3.56–3.62 (m, 6H), 2.75–2.95 (m, 4H), 2.55–2.75 (m, 4H), 2.43 (s, 3H), 1.95–2.05 (m, 2H), 1.64–1.71 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.5, 157.1 (d, $J = 238$ Hz), 155.1, 144.8, 143.0, 132.9, 129.8, 129.1, 127.8, 118.9, 115.6 (d, $J = 23$ Hz), 115.5, 115.4 (d, $J = 8$ Hz), 70.7, 70.2, 69.2, 69.1, 68.7, 66.9, 64.6, 60.3, 54.9, 49.6, 40.9, 29.2, 26.8, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.7; FAB⁺-MS m/z 670.1 $[\text{M} + \text{H}]^+$.

Compound **13d** was obtained as a viscous liquid; yield 0.21 g (0.29 mmol, 77%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.78 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.24 (t, $J = 7.5$ Hz, 2H), 6.95 (d, $J = 8.2$ Hz, 2H), 6.90 (d, $J = 8.0$ Hz, 2H), 6.80–6.87 (m, 3H), 4.78 (s, 2H), 4.10 (t, $J = 4.8$ Hz, 2H), 4.01 (t, $J = 6.4$ Hz, 2H), 3.40–3.75 (m, 16H), 2.75–2.95 (m, 2H), 2.55–2.75 (m, 2H), 2.44 (s, 3H), 1.90–2.10 (m, 2H), 1.60–1.85 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.5, 157.1 (d, $J = 238$ Hz), 155.1, 144.8, 143.1, 133.0, 129.8, 129.2, 127.9, 118.9, 115.7 (d, $J = 23$ Hz), 115.6, 115.5 (d, $J = 8$ Hz), 70.7, 70.6, 70.6, 70.5, 70.4, 69.3, 69.2, 68.7, 67.0, 64.7, 60.3, 55.0, 49.7, 49.7, 41.1, 29.7, 29.3, 21.6; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.8; FAB⁺-MS m/z 714.3 $[\text{M} + \text{H}]^+$.

Preparation of 14a, 14b, 14c, and 14d. Compound **7** (0.08 g, 0.15 mmol, 1 equiv) was added to a stirred solution of **13a** (0.10 g, 0.15 mmol, 1 equiv), **13b** (0.11 g, 0.15 mmol, 1 equiv), **13c** (0.10 g, 0.15 mmol, 1 equiv), or **13d** (0.11 g, 0.15 mmol, 1 equiv) and K_2CO_3 (0.10 g, 0.75 mmol, Seq.) in ACN (4 mL). After heating at 80 °C for 3.5 to 4 h the precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over silica. The eluting solvent was changed from chloroform to 20% methanol in chloroform to afford **14a** as a viscous liquid; yield 0.107 g (0.105 mmol, 70%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.90–8.10 (m, 2H), 7.70–7.90 (m, 2H), 7.21 (t, $J = 7.8$ Hz, 2H), 7.03–7.16 (m, 4H), 6.87 (d, $J = 8.2$ Hz, 2H), 6.83 (t, $J = 7.8$ Hz, 1H), 4.73 (s, 2H), 3.44–3.70 (m, 8H), 1.8–3.3 (m, 41H; includes s of tosylate anion in 2.29), 1.61–1.70 (m, 2H), 1.30–1.60 (m, 27H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.5, 174.2, 173.1, 172.7, 165.6 (d, $J = 254$ Hz), 144.3, 142.8, 138.6, 132.9, 130.7 (d, $J = 9$ Hz), 129.3, 128.3, 126.2, 119.2, 115.6 (d, $J = 22$ Hz), 115.6, 82.1, 82.0, 70.1, 70.0, 69.0, 68.1, 64.6, 57.3, 56.3, 55.7, 52.4, 50.7, 50.5, 50.4, 50.1, 49.7, 49.4, 40.9, 36.2, 29.6, 28.9, 28.0, 27.9, 21.2; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.1; FAB⁺-MS m/z 1046.5 $[\text{M} + \text{Na}]^+$.

Compound **14b** was obtained as a viscous liquid; yield 0.12 g (0.11 mmol, 73%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.95–8.03 (m, 2H), 7.80 (d, $J = 8.0$ Hz, 2H), 7.20 (t, $J = 7.8$ Hz, 2H), 7.05–7.15 (m, 4H), 6.89 (d, $J = 8.2$ Hz, 2H), 6.82 (t, $J = 7.8$ Hz, 1H), 4.75 (s, 2H), 3.43–3.69 (m, 18H), 1.90–3.35 (m, 35H; includes s of tosylate anion in 2.29), 1.63–1.73 (d, 2H), 1.30–1.60 (m, 27H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 198.4, 174.1, 173.0, 172.6, 165.5 (d, $J = 254$ Hz), 144.2, 142.7, 138.7, 133.3, 130.7 (d, $J = 9$ Hz), 129.3, 128.3, 126.2, 119.1, 115.6 (d, $J = 22$ Hz), 115.5, 82.1, 82.0, 77.2, 70.3, 70.1, 70.0, 69.8, 68.9, 67.6, 64.6, 56.3, 55.6, 52.2, 50.6, 50.6, 49.7, 49.4, 40.9, 36.1, 29.6, 28.0, 28.0, 27.8, 27.8, 21.2, 21.2; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –106.1; FAB⁺-MS m/z 1090.3 $[\text{M} + \text{Na}]^+$.

Compound **14c** was obtained as a viscous liquid; yield 0.11 g (0.11 mmol, 73%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.82 (d, $J = 8.1$ Hz, 0.5H; tosylate anion), 7.24–7.29 (m, 2H), 7.09 (d, $J = 8.1$ Hz, 0.5H; tosylate anion), 6.89–7.02 (m, 4H), 6.81–6.89 (m, 3H), 4.75 (s, 2H), 4.02 (t, $J = 6.2$ Hz, 2H), 3.57–3.67 (m, 8H), 3.55 (t, $J =$

5.2 Hz, 2H), 3.47 (s, 2H), 2.10–3.40 (bm, 27H; includes s of tosylate anion (0.75H) in 2.31), 2.03 (q, $J = 6.8$ Hz, 2H), 1.62–1.70 (m, 2H), 1.37–1.55 (m, 31H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 174.4, 172.9, 172.6, 157.1 (d, $J = 238$ Hz), 155.0, 144.3, 142.9, 138.4, 129.2, 128.2, 126.2, 119.2, 115.7 (d, $J = 23$ Hz), 115.6, 115.4 (d, $J = 8$ Hz), 82.2, 82.1, 70.1, 70.0, 69.0, 68.0, 66.8, 64.5, 60.2, 56.3, 56.3, 55.6, 54.9, 52.4, 50.5, 49.7, 49.5, 49.5, 40.9, 29.1, 28.1, 28.0, 27.8, 21.2; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.7; FAB⁺-MS m/z 1034.3 $[\text{M} + \text{Na}]^+$.

Compound **14d** was obtained as a viscous liquid; yield 0.13 g (0.12 mmol, 81%); ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ_{ppm} 7.81 (d, $J = 8.1$ Hz, 2H; tosylate anion), 7.22 (t, $J = 7.8$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H; tosylate anion), 6.90–6.99 (m, 4H), 6.78–6.86 (m, 3H), 4.79 (s, 2H), 4.01 (t, $J = 6.1$ Hz, 2H), 3.70 (t, $J = 4.9$ Hz, 2H), 3.53–3.65 (m, 10H), 3.49 (t, $J = 5.2$ Hz, 2H), 1.90–3.40 (bm, 27H; includes s of tosylate anion (3H) in 2.31), 1.71 (bs, 12H), 1.36–1.53 (m, 27H); ^{13}C NMR (100.6 MHz, CDCl_3 , 25 °C) δ_{ppm} 173.0, 172.6, 172.6, 157.2 (d, $J = 238$ Hz), 154.9, 144.0, 142.8, 138.7, 129.4, 128.4, 126.2, 119.1, 115.8 (d, $J = 23$ Hz), 115.4 (d, $J = 8$ Hz), 115.4, 82.1, 82.0, 77.2, 70.4, 70.4, 70.2, 70.0, 69.9, 69.0, 67.7, 64.6, 56.4, 56.4, 55.7, 55.0, 52.3, 49.7, 49.5, 41.0, 28.6, 28.0, 27.9, 27.9, 21.3; ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} –124.5; FAB⁺-MS m/z 1078.5 $[\text{M} + \text{Na}]^+$.

Preparation of 15a, 15b, 15c, and 15d. Compound **14a** (0.10 g, 0.10 mmol, 1 equiv), **14b** (0.11 g, 0.10 mmol, 1 equiv), **14c** (0.10 g, 0.10 mmol, 1 equiv), or **14d** (0.11 g, 0.10 mmol, 1 equiv) was dissolved in TFA (1.5 g, 1 mL, 8.8 mmol, 88 equiv). After stirring at ambient temperature for 4 h the solution was evaporated in reduced pressure. Methanol was added and evaporated, and then chloroform was added and evaporated (until the complete disappearance of TFA) to afford **15a** nearly quantitatively as a grayish viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 7.90–8.05 (m, 2H), 7.60 (d, $J = 7.5$ Hz, tosylate anion), 7.19 (t, $J = 7.4$ Hz, 2H), 7.12 (d, $J = 7.5$ Hz, tosylate anion), 7.10–7.16 (m, 2H), 6.91 (d, $J = 7.8$ Hz, 2H), 6.75–6.85 (m, 1H), 4.75 (s, 2H), 4.07 (bs, 4H), 2.60–3.80 (m, 38H), 2.24 (s, tosylate anion), 1.94–2.10 (m, 4H), 1.82–1.94 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 198.7, 174.5, 174.2, 168.9, 167.3 (d, $J = 254$ Hz), 162.8 (q, $J = 36$ Hz; TFA), 143.7 (tosylate anion), 143.5 (tosylate anion), 141.9, 134.4, 132.0 (d, $J = 9$ Hz), 130.6, 130.0 (tosylate anion), 126.9 (tosylate anion), 121.4, 117.7, 117.6 (q, $J = 291$ Hz; TFA), 116.6 (d, $J = 22$ Hz), 71.7, 71.0, 70.8, 69.1, 65.4, 59.8, 57.6, 55.6, 53.5, 52.8, 52.3, 50.4, 49.9, 42.0, 36.0, 28.5, 21.3 (tosylate anion), 19.5; ^{19}F NMR (376.3 MHz, CD_3OD , 25 °C) δ_{ppm} –78.6, –109.1; HRMS (MALDI-TOF) m/z calcd for $\text{C}_{43}\text{H}_{63}\text{N}_7\text{O}_{10}\text{F}^+$ $[\text{M} + \text{H}]^+$ 856.4620, found 856.4556; m/z calcd for $\text{C}_{43}\text{H}_{62}\text{N}_7\text{O}_{10}\text{FNa}^+$ $[\text{M} + \text{Na}]^+$ 878.4440, found 878.4473.

Compound **15b** was obtained nearly quantitatively as a grayish viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 8.01–8.08 (m, 2H), 7.68 (d, $J = 8.0$ Hz, tosylate anion), 7.28 (t, $J = 7.8$ Hz, 2H), 7.21 (d, $J = 7.8$ Hz, tosylate anion), 7.15–7.19 (m, 2H), 7.00 (d, $J = 8.1$ Hz, 2H), 6.90 (t, $J = 7.2$ Hz, 1H), 4.85 (s, 2H), 4.15 (bs, 2H), 2.80–3.90 (m, 46H), 2.33 (s, tosylate anion), 2.05–2.26 (m, 2H), 1.95–2.05 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 198.7, 174.5, 174.2, 168.9, 167.0 (d, $J = 254$ Hz), 160.9 (q, $J = 36$ Hz; TFA), 143.8 (tosylate anion), 143.5 (tosylate anion), 141.8, 134.4, 132.0 (d, $J = 9$ Hz), 130.7, 129.9 (tosylate anion), 127.0 (tosylate anion), 121.4, 117.8, 117.2 (q, $J = 291$ Hz; TFA), 116.7 (d, $J = 22$ Hz), 71.7, 71.4, 71.3, 71.2, 71.1, 69.2, 65.6, 59.8, 57.7, 55.6, 53.5, 52.8, 52.3, 50.5, 49.9, 49.8, 42.1, 36.0, 28.5, 28.3, 21.3 (tosylate anion), 19.5; ^{19}F NMR (376.3 MHz, CD_3OD , 25 °C) δ_{ppm} –78.5, –109.0; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{45}\text{H}_{65}\text{N}_7\text{O}_{11}\text{F}^-$ $[\text{M} - \text{H}]^-$ 898.4726, found 898.4725.

Compound **15c** was obtained nearly quantitatively as a grayish viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 7.68 (d, $J = 8.0$ Hz, 1H; tosylate anion), 7.28 (t, $J = 7.4$ Hz, 2H), 7.21 (d, $J = 7.9$ Hz, 1H; tosylate anion), 6.93–7.02 (m, 4H), 6.80–6.93 (m, 3H), 4.78 (s, 2H), 3.95–4.17 (m, 4H), 2.60–3.90 (m, 38H), 2.34 (s, 1.5H; tosylate anion), 2.05–2.31 (m, 4H), 1.95–2.04 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 174.6, 174.2, 169.1, 162.4 (q, $J = 36$ Hz; TFA), 158.9 (d, $J = 237$ Hz), 156.1, 143.7, 143.5 (tosylate anion),

141.9 (tosylate anion), 130.8 (tosylate anion), 129.9, 127.0 (tosylate anion), 121.8, 118.3, 117.9 (q, $J = 291$ Hz; TFA), 116.8 (d, $J = 23$ Hz), 116.8 (d, $J = 8$ Hz), 71.8, 71.0, 69.2, 66.5, 65.6, 59.8, 55.8, 55.3, 53.6, 52.3, 50.6, 42.1, 28.7, 25.4, 21.3 (tosylate anion); ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -77.5, -126.2; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{42}\text{H}_{61}\text{N}_7\text{O}_{10}\text{F}^- [\text{M} - \text{H}]^-$ 842.4464, found 842.4463.

Compound **15d** was obtained nearly quantitatively as a grayish viscous substance; ^1H NMR (400 MHz, CD_3OD , 25 °C) δ_{ppm} 7.71 (d, $J = 8.0$ Hz, 1H; tosylate anion), 7.26–7.36 (m, 2H), 7.23 (d, $J = 7.9$ Hz, 1H; tosylate anion), 6.96–7.06 (m, 4H), 6.87–6.96 (m, 3H), 4.81 (s, 2H), 4.07 (bs, 4H), 2.70–3.95 (m, 44H), 2.36 (s, 1.5H; tosylate anion), 2.13–2.35 (bs, 2H), 1.95–2.13 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD , 25 °C) δ_{ppm} 174.6, 173.9, 169.1, 162.9 (q, $J = 35$ Hz; TFA), 158.9 (d, $J = 238$ Hz), 156.1, 143.8, 143.6 (tosylate anion), 141.8 (tosylate anion), 130.6 (tosylate anion), 129.9, 127.0 (tosylate anion), 119.6, 118.1, 117.9 (q, $J = 291$ Hz; TFA), 116.8 (d, $J = 23$ Hz), 116.8 (d, $J = 8$ Hz), 71.6, 71.4, 71.3, 71.1, 69.1, 68.9, 66.5, 65.6, 60.1, 55.8, 55.1, 54.0, 52.5, 52.3, 42.1, 40.2, 33.1, 30.7, 30.5, 25.4, 23.7, 21.3 (tosylate anion); ^{19}F NMR (376.3 MHz, CDCl_3 , 25 °C) δ_{ppm} -77.4, -126.1; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{44}\text{H}_{65}\text{N}_7\text{O}_{11}\text{F}^- [\text{M} - \text{H}]^-$ 886.4726, found 886.4722.

Preparation of 16a, 16b, 16c, and 16d. A concentrated aqueous solution of **15a**, **15b**, **15c**, or **15d** (0.15 mmol of each one) was mixed with an equimolar aqueous solution of gadolinium(III) chloride hexahydrate (155 mg, 0.15 mmol). The pH of the obtained solution was adjusted to 7.8, and the solution was stirred at rt for 1 week, during which the pH was measured and readjusted to 7.8. After lyophilization **16a** was obtained as a grayish solid. The reaction proceeded nearly quantitatively; HRMS (TOF MS ES negative) m/z calcd for $\text{C}_{43}\text{H}_{58}\text{N}_7\text{O}_{10}\text{F}^{158}\text{Gd}^- [\text{M} - \text{H}]^-$ 1009.3470, found 1009.3481.

Compound **16b** was obtained nearly quantitatively as a brown solid; HRMS (TOF MS ES positive) m/z calcd for $\text{C}_{45}\text{H}_{64}\text{N}_7\text{O}_{11}\text{F}^{158}\text{Gd}^+ [\text{M} + \text{H}]^+$ 1055.3889, found 1055.3893.

Compound **16c** was obtained nearly quantitatively as a brown solid; HRMS (TOF MS ES positive) m/z calcd for $\text{C}_{42}\text{H}_{60}\text{N}_7\text{O}_{10}\text{F}^{155}\text{Gd}^+ [\text{M} + \text{H}]^+$ 996.3612, found 996.3615.

Compound **16d** was obtained nearly quantitatively as a brown solid; HRMS (TOF MS ES positive) m/z calcd for $\text{C}_{44}\text{H}_{64}\text{N}_7\text{O}_{11}\text{F}^{155}\text{Gd}^+ [\text{M} + \text{H}]^+$ 1040.3874, found 1040.3868.

Dopamine receptor binding was evaluated according to known protocol.²¹ Striatal tissues was isolated from C57 bl. mouse and homogenized in 100 vol of ice-cold Tris-HCl 50 mM pH 7.4 buffer, using Brinkman Polytron. The homogenate was centrifuged three times (and resuspended twice in equal volumes of buffer) for 20 min at 3000 rpm. Final reconstitution of the pellet was done to yield a tissue concentration of 10 mg wt weight per mL buffer. To analyze the dopamine receptor binding, 0.1 mL of [^3H]-spiperone (5×10^{-10} M) was added to 0.1 mL of striatal membranes and 0.8 mL Tris-HCl buffer and incubated at 25 °C. One hour later, the mixture was diluted in 3 mL of ice-cold buffer and filtered under vacuum through glass fiber filters (Whatman GF/C). The filters were washed three times with 3 mL of ice-cold buffer. The bound radioactivity was counted in a liquid scintillation cocktail (Optifluor) using a scintillation counter (Tri carb 300c Packard). The specific binding was defined as the difference between the binding in the presence and absence of 1 μM sulpiride.

■ ASSOCIATED CONTENT

■ Supporting Information

NMR spectra, MS or HRMS of all compounds prepared, as well as HRMS of the gadolinium complexes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) *Magnetic Resonance Imaging*, 3rd ed.; Stark, D. D., Bradley, Jr. W. G., Eds.; Mosby: Philadelphia, 1999. (b) *Positron Emission Tomography: Basic Sciences*; Bailey, D., Townsend, D. W., Valk, P. E., Maisey, M. N., Eds.; Springer, New York, 2005.
- (2) (a) *Molecular Imaging*; Weissleder, R., Ross, B. D., Rehemtulla, A., Gambhir, S. S., Eds.; People's Medical Publishing House: Beijing, 2010. (b) *Molecular Imaging in Oncology*; Schober, O., Riemann, B., Eds.; Springer: New York, 2013. (c) *Molecular Imaging*; Schaller, B., Ed.; in Tech Publishing: Croatia, 2012.
- (3) Weissleder, R.; Pittet, M. J. *Nature* **2008**, 452, 580–589.
- (4) (a) Lauffer, R. B. *Chem. Rev.* **1987**, 87, 901–927. (b) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, 99, 2293–2352. (c) *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*; Merbach, A. E., Toth, E., Eds.; John Wiley & Sons: Chichester, 2001.
- (5) (a) Jacques, V.; Desreux, J. F. *Top. Curr. Chem.* **2002**, 221, 123–164. (b) Lanza, G. M.; Winter, P.; Caruthers, S.; Schneider, A.; Crowder, K.; Morawski, A.; Zhang, H. Y.; Scott, M. J.; Wickline, S. A. *Curr. Pharm. Biotechnol.* **2004**, 5, 495–507.
- (6) (a) Woods, M.; Woessner, D. E.; Sherry, D. *Chem. Soc. Rev.* **2006**, 35, 500–511. (b) Caravan, P. *Acc. Chem. Res.* **2009**, 42, 851–862. (c) Louie, A. *Chem. Rev.* **2010**, 110, 3146–3195.
- (7) (a) Weissleder, R.; Mahmood, U. *Radiology* **2001**, 219, 316–333. (b) Graves, E. E.; Weissleder, R.; Ntziachristos, V. *Curr. Mol. Med.* **2004**, 4, 419–430. (c) Gross, S.; Piwnicka-Worms, D. *Cancer Cell* **2005**, 7, 5–15. (d) Doubrovina, M.; Serganova, I.; Mayer-Kuckuk, P.; Ponomarev, V.; Blasberg, R. G. *Bioconjugate Chem.* **2004**, 15, 1376–1388. (e) Modo, M. M. J.; Bulte, J. W. M. *Molecular and Cellular MR Imaging*, CRC Press: Boca Raton, 2007.
- (8) (a) De-Leon Rodriguez, L. M.; Lubag, A. J. M.; Malloy, C. R.; Martinez, G. V.; Gillies, R. J.; Sherry, A. D. *Acc. Chem. Res.* **2009**, 42, 948–957. (b) Major, J. L.; Meade, T. J. *Acc. Chem. Res.* **2009**, 42, 893–903.
- (9) (a) Que, E. L.; Chang, C. J. *Chem. Soc. Rev.* **2010**, 39, 51–60. (b) De-Leon Rodriguez, L. M.; Lubag, A. J. M.; Sherry, A. D. *Inorg. Chem. Acta* **2012**, 393, 12–23.
- (10) Zhou, Z.; Lu, Z.-R. *Nanomed. Nanobiotechnol.* **2013**, 5, 1–18.
- (11) (a) Moats, R. A.; Fraser, S. E.; Meade, T. J. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 726–728. (b) Louie, A. Y.; Huber, M. M.; Ahrens, E. T.; Rothbacher, U.; Moas, R.; Jacobs, P. e.; Fraser, S. E.; Meade, T. J. *Nat. Biotechnol.* **2000**, 18, 321–325. (c) Weissleder, R.; Moore, A.; Mahmood, U.; Bhorade, R.; Benveniste, H.; Chiocca, E. A.; Basilion, J. P. *Nat. Med.* **2000**, 6, 351–355.
- (12) (a) Genove, G.; DeMarco, U.; Xu, H.; Goins, W.; Ahrens, E. T. *Nat. Med.* **2005**, 11, 450–454. (b) Park, J. A.; Lee, J. J.; Jung, J. C.; Yu, D. Y.; Ha, S.; Kim, T. J.; Chang, Y. M. *ChemBioChem.* **2008**, 9, 2811–2813. (c) Qiao, J.; Li, S.; Wei, L.; Jiang, J.; Long, R.; Mao, H.; Wang, L.; Yang, H.; Grossniklaus, H. E.; Liu, Z.-R.; Yang, J. J. *PlosOne* **2011**, 6, e18103.
- (13) (a) *Molecular Neurobiology of the Mammalian Brain*, 2nd ed.; McGeer, P. L., Eccles, J. C., McGeer, E. G., Eds.; Plenum Press: New York, 1987; Chapter 9, p 284. (b) Blum, D.; Torch, S.; Lambeng, N.; Nissou, M. F.; Benabid, A. L.; Sadoul, R.; Verna, J. M. *Prog. Neurobiol.*

2001, 65, 135–172. (c) Davis, K. L.; Kahn, R. S.; Ko, G.; Davidson, M. *Am. J. Psychiatry* **1991**, 148, 1474–1486. (d) Nunn, A. D.; Linder, K. E.; Tweedle, M. F. Q. *J. Nucl. Med.* **1997**, 41, 155–162. (e) Zhen, J.; Antonio, T.; Dutta, A. K.; Reith, M. E. A. *J. Neurosci. Methods* **2010**, 189, 32–38.

(14) Moore, H.; West, A. R.; Grace, A. A. *Biol. Psychiatry* **1999**, 46, 40–48.

(15) 1-Phenyl-1,3,8-triazaspiro[4.5]decan-4-one. For a series of its substituted derivatives, see: Lavieri, R. R.; Scott, S. A.; Selvy, P. E.; Kim, K.; Jadhav, S.; Morrison, R. D.; Daniels, J. S.; Brown, H. A.; Lindsley, C. W. *J. Med. Chem.* **2010**, 53, 6706–6719.

(16) Zigelboim, I.; Offen, D.; Melamed, E.; Panet, H.; Rehavi, M.; Cohen, Y. *J. Incl. Phenom. Macrocycl. Chem.* **2007**, 59, 323–329.

(17) (a) Wagner, H. N., Jr.; Burns, H. D.; Dannals, R. F.; Wong, D. F.; Langstrom, B.; Duelfer, T.; Frost, J. J.; Ravert, H. T.; Links, J. M.; Rosenbloom, S. B.; Lukas, S. E.; Kramer, A. V.; Kuhar, M. J. *Science* **1983**, 221, 1264. (b) Baxter, G. S. *Behav. Brain Res.* **1996**, 73, 149–152. (c) Czoty, P. W.; Howell, L. L. *Pharmacol., Biochem. Behav.* **2000**, 67, 257–264.

(18) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Sirvastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, 30, 1265–1269.

(19) Lee, J. H.; Lee, H. B.; Andrade, J. D. *Prog. Polym. Sci.* **1995**, 20, 1043–1079.

(20) TriEG monotosylate **11a** and tetraEG monotosylate **11b** were prepared by reaction of tosyl chloride with 5-fold excess of triEG and tetraEG, respectively.

(21) Gordon, I.; Weizman, R.; Rehavi, M. *Eur. J. Pharmacol.* **1996**, 298, 27–30.

(22) Stasiuk, G. J.; Long, N. J. *Chem. Commun.* **2013**, 49, 2732–2746.

(23) DOTA and its derivatives were shown to form very stable complexes with ^{64}Cu , ^{68}Ga , other lanthanides, and transition metal cations as shown in ref 22 and the references therein.