



Synthesis and phosphonate binding of guanidine-functionalized fluorinated amphiphiles

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ABSTRACT

We report herein convenient procedures for the use of highly fluorinated α,ω -diols (e.g. **1**) as building blocks for the rapid assembly of amphiphilic materials containing a fluororous phase region. We describe expedient conversion of the parent diols to both symmetrically and asymmetrically substituted amphiphiles via the installation of an intermediate trifluoromethanesulfonyl ester. These sulfonate esters are versatile and easily manipulated intermediates, which can be readily converted to a variety of nitrogen, halogen, and carbon groups. Moreover, we show that for guanidine-terminated fluororous amphiphiles, these molecules can bind phosphonic acid groups in aqueous media. Thus, these materials offer a new strategy for decorating phosphorylated biomolecules with fluorine-rich coatings.

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1. Introduction

We are developing a general and convenient synthetic route to guanidine functionalized, fluororous-phase amphiphiles. Fluorinated amphiphiles are important because of their tendency to self-assemble into nanostructures such as monolayers [1,2], micelles, or vesicles [3], in a fashion distinct from their hydrocarbon-based counterparts [4]. Particularly, amine and guanidine-terminated molecules in this class can potentially decorate phosphate-rich biomolecules through selective non-covalent interactions such as hydrogen bonding. While syntheses of several highly fluorinated amphiphiles or surfactants have been reported [4–6], amine- and guanidine-functionalized fluorocarbons remain largely under addressed despite the potential synthetic utility of nitrogen-containing groups as functionalization handles and biochemical tools. The known synthetic routes to highly fluorinated amines have drawbacks: for example, highly fluorinated amines can be prepared from routes such as fluoroalkylation of ammonia with an alkyl chloride [7], hydrogenation of fluoro-organic azides [8], and the Gabriel synthesis [9], with the latter two involving high-temperature displacement of fluoroalkyl tosylates. These methods are of limited scope or involve harsh conditions incompatible with some biologically relevant substrates.

We present here a concise approach to the preparation of guanidine-terminated fluororous amphiphiles based on displacement

of convenient fluoroalkyl trifluoromethanesulfonate intermediates. The syntheses proceed from commercially available fluorinated diols, which are available as byproducts of Teflon[®] synthesis [10]. Carbon–nitrogen bond formation is achieved through the intermediacy of remarkably stable and versatile alkyl triflate intermediates, which are prepared through a convenient sulfonation procedure. Both are amenable to bidirectional syntheses of fluorocarbon-centered moieties as well. Guanylation of the resulting fluoroalkyl amines proceeds smoothly under mild conditions with practical yields.

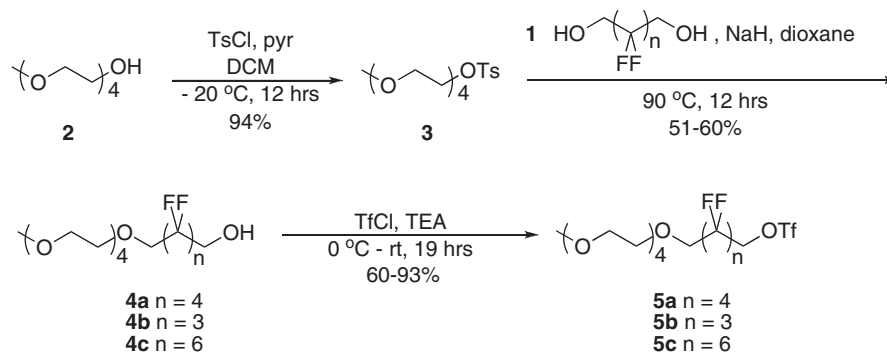
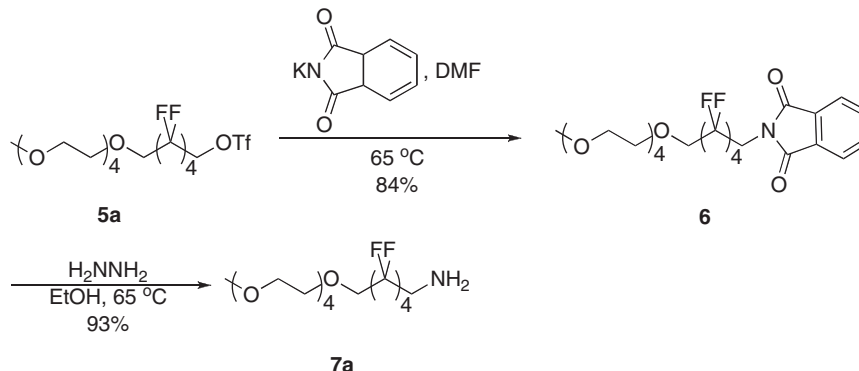
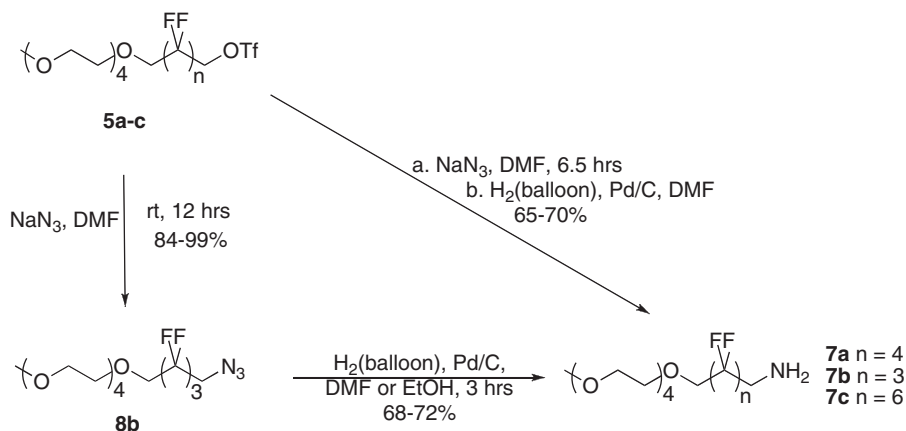
These products are of the general structure guanidine-fluorocarbon-poly(ethylene glycol), to allow for potential assembly of a fluororous coating around a phosphate-coated surface. The nearest known relatives to these structures are thiol-fluorocarbon-poly(ethylene glycol) moieties that can decorate gold surfaces via covalent S–Au bonds [5]. We will show with ³¹P NMR data that our guanidine-fluorocarbon-poly(ethylene glycol) moieties can bind to a phosphonic acid in aqueous solution, presumably through a guanidinium–phosphonate double hydrogen bond.

2. Synthesis of fluorinated amphiphiles

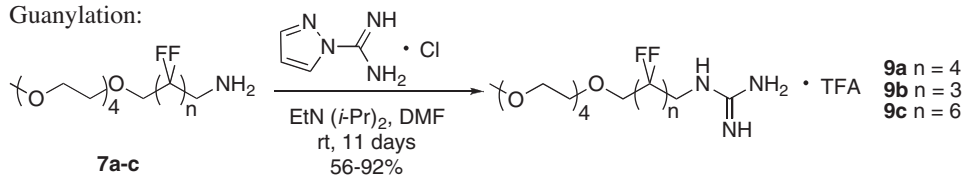
We expected that fluororous amphiphiles could be constructed by attaching a fluororous diol, such as **1**, to a poly(ethylene glycol) (PEG) fragment. A general outline of this operation is shown in Scheme 1. Accordingly, a tosylate-functionalized PEG fragment (**3**) is used to effect selective mono-alkylation of **1** in the presence of sodium hydride. The resulting PEG-functionalized fluororous alcohol can be further elaborated. We chose to install a triflate to mediate further functionalization, although several sulfonate esters are known to

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Amine Synthesis *via* phthalimide:Amine Synthesis *via* azide:

Guanylation:

Scheme 1. Synthesis of PEG-functionalized amphiphiles from diols **1a–c**.

transfer polyfluoroalkyl groups [11]. We presumed that the added reactivity of the triflate would be important to effect efficient displacement reactions. Sulfonation of fluorinated alcohols is often carried out in dichloromethane [12], yet sulfonation of **5a** in dichloromethane was relatively slow. A simple change of solvent to tetrahydrofuran accelerated the rate of the reaction, affording triflate **5a** in excellent yield. C–N bond formation can be affected by triflate displacement with either (i) potassium phthalimide or (ii) sodium azide. Hydrogenation of the azide was more convenient in our hands.

Guanylation of amines **7a–c** is challenging because the proximal fluorine atoms reduce the nucleophilicity of the precursor amine [6]. Nonetheless, successful guanylation was realized with an excess of guanylpzrazole and Hünig's base. We chose 1H-pyrazole-1-carboximidamide due to its mild guanylation conditions and ease of use [13,14]. Remarkably, these guanylation reactions proceed to completion despite the attenuated nucleophilicity of the fluoroalkyl amines. This route can be generalized to generate homologs of **9a** featuring different lengths of the fluorocarbon (Table 1, entries 16–18).

Table 1
Synthesis of fluorinated amphiphiles.


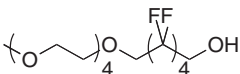
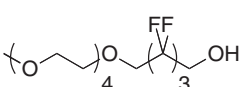
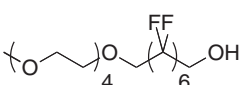
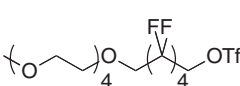
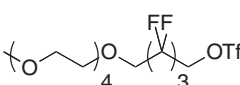
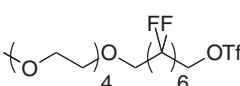
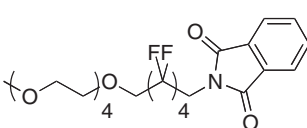
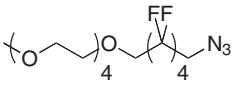
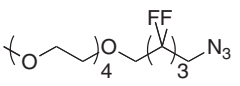
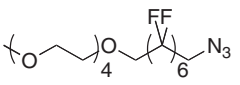
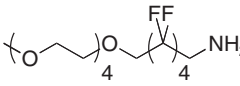
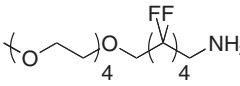
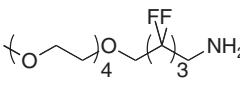
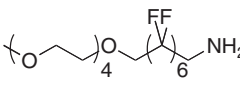
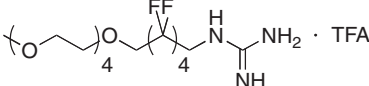
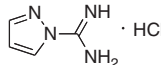
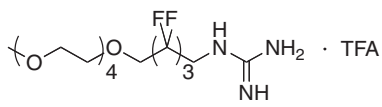
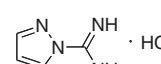
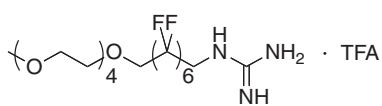
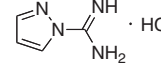
Entry	Starting material	Product	Conditions	Yield
1	2		3 TsCl, pyridine, DCM, –20 °C	94%
2	1a		4a NaH, dioxane, 90 °C	62%
3	1b		4b NaH, dioxane, 90 °C	51%
4	1c		4c NaH, dioxane, 90 °C	60%
5	4a		5a TfCl, THF, 0 °C–rt	81% ^a
6	4b		5b TfCl, THF, 0 °C–rt	60%
7	4c		5c TfCl, THF, 0 °C–rt	93% ^a
8	5a		6 KN(phthal), DMF, 85 °C	84%
9	5a		8a NaN ₃ , DMF, rt	84%
10	5b		8b NaN ₃ , DMF, rt	>99%
11	5c		8c NaN ₃ , DMF, rt	87%
12	6		7a H ₂ NNH ₂ , EtOH, 65 °C	93%
13	5a		7a a. NaN ₃ , DMF, b. H ₂ (balloon), Pd/C, rt	70%
14	6b		7b H ₂ (balloon), Pd/C, rt	72%
15	5c		7c a. NaN ₃ , DMF, b. H ₂ (balloon), Pd/C, rt	65%
16	7a		9a  EtN(<i>i</i> -Pr) ₂ , DMF, rt	92%

Table 1 (Continued)

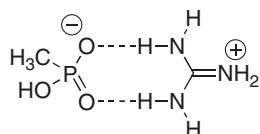
Entry	Starting material	Product	Conditions	Yield
17	7b	 9b	 EtN(<i>i</i> -Pr) ₂ , DMF, rt	57%
18	7c	 9c	 EtN(<i>i</i> -Pr) ₂ , DMF, rt	56%

^a 95% conversion.

3. Binding of fluorinated amphiphiles to a phosphonic acid

Guanidinium binds to phosphonate through a salt bridge that is buttressed by a bidentate hydrogen bonding system (Fig. 1). This interaction is generally stable within a wide range of pH values [15]. Thus, guanidinium-functionalized amphiphiles **9a–c** should form complexes with phosphonates in aqueous buffer. We show here the interaction between **9a** and MePO₃K₂ using ³¹P NMR (Fig. 2, Table 2) [16], which has been used as a probe for phosphate binding to several types of cations [17]. Fig. 2A shows that as **9a** is added to a solution of phosphonate, the ³¹P chemical shift of the phosphonate moves only slightly, but broadens significantly. This broadening effect is more pronounced as additional **9a** is added. The change in the shape of the peak is consistent with reduced tumbling associated with increased size or reversible association of **9a** with MePO₃K₂, which indicates complexation between the guanidinium species and the phosphonate group. By contrast, Fig. 2B shows that in the presence of HCl, a strong Brønsted acid, protonated MePO₃H₂ remains sharp and shifts downfield to 30.4 ppm. Thus, guanidinium **9a** is not merely protonating the phosphonate in Fig. 2A. Treatment of MePO₃K₂ with NH₄Cl resulted in a small downfield shift like HCl, but did not broaden the signal like HCl. Urea is structurally similar to guanidinium and can potentially complex a phosphonate in a manner similar to **9a** (Fig. 1B). In the presence of HCl, similar chemical behavior is expected when MePO₃K₂ is treated with urea as when it is treated with **9a**. Interestingly, these peaks do not broaden as is observed with the apparent MePO₃K₂–**9a** complex (Fig. 2D). Overall, these spectra show that **9a** complexes methylphosphonate as indicated by NMR properties which different from those of the corresponding free phosphonate, phosphonic acid, or a putative urea-phosphonate complex.

A. Guanidinium-Phosphonate Dimer



B. Urea as a Guanidine Homolog

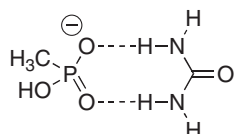


Fig. 1. The guanidinium–phosphate interaction.

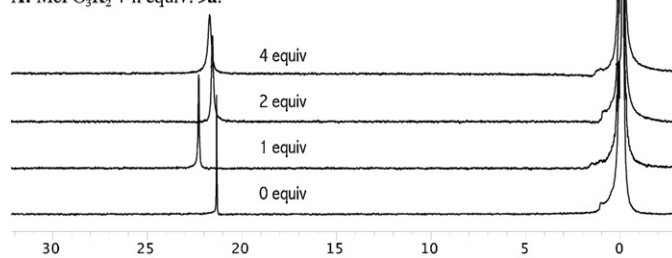
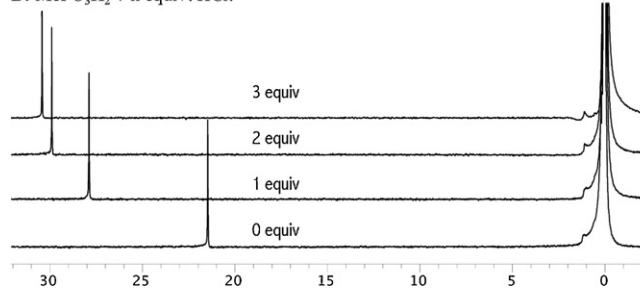
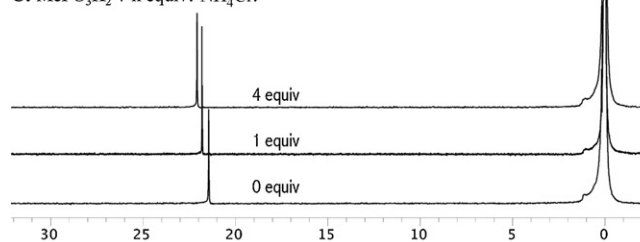
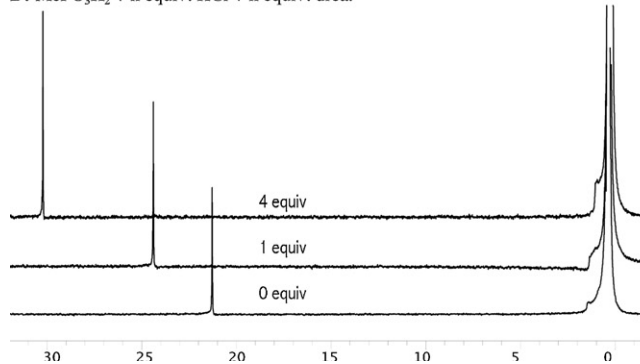
A: MePO₃K₂ + n equiv. **9a**:B: MePO₃K₂ + n equiv. HCl:C: MePO₃K₂ + n equiv. NH₄Cl:D: MePO₃K₂ + n equiv. HCl + n equiv. urea:Fig. 2. ³¹P NMR spectra showing chemical shift perturbation of samples delimited in Table 2. Temp = 25 °C. [MePO₃K₂] = 25 mM. Solvent: 10% D₂O/H₂O.

Table 2

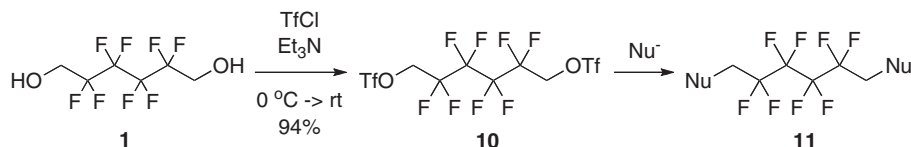
NMR evidence for guanidinium–phosphate binding.

Spectrum	Content	Chemical shift (ppm)	Half-height width (Hz)
A, 4 equiv.	MePO ₃ K ₂ + 4 equiv. 9a	21.6	35.5
A, 2 equiv.	MePO ₃ K ₂ + 2 equiv. 9a	21.6	20.0
A, 1 equiv.	MePO ₃ K ₂ + 1 equiv. 9a	22.4	11.2
A, 0 equiv.	MePO ₃ K ₂	21.4	4.2
B, 3 equiv.	MePO ₃ K ₂ + 3 equiv. HCl	30.4	3.4
B, 2 equiv.	MePO ₃ K ₂ + 2 equiv. HCl	29.9	3.4
B, 1 equiv.	MePO ₃ K ₂ + 1 equiv. HCl	27.8	3.8
B, 4 equiv.	MePO ₃ K ₂	21.4	4.2
C, 1 equiv.	MePO ₃ K ₂ + 4 equiv. NH ₄ Cl	22.1	4.2
C, 0 equiv.	MePO ₃ K ₂ + 1 equiv. NH ₄ Cl	21.8	3.6
C, 0 equiv.	MePO ₃ K ₂	21.4	4.2
D, 4 equiv.	MePO ₃ K ₂ + 4 equiv. urea + 2 equiv. HCl	27.7	3.6
D, 1 equiv.	MePO ₃ K ₂ + 1 equiv. urea + 2 equiv. HCl	27.6	3.3
D, 0 equiv.	MePO ₃ K ₂	21.4	4.2

4. Bi-directional functionalization of fluorinated diols

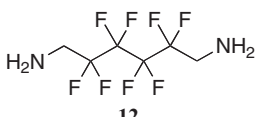
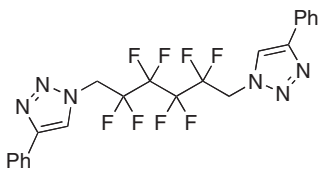
The methods developed above for the synthesis of fluorinated amphiphiles also have utility in bidirectional applications. Our general route to doubly functionalized fluorinated materials is sketched in Table 3 [12]. Thus, treatment of diols such as **1** with trifluoromethanesulfonyl chloride gives easy access to bis(sulfonic) esters **10**, which are remarkably stable and easily manipulated

building blocks. Entries 1–5 of Table 3 illustrate conditions for the double displacement of triflate **10**. Since dehydrofluorination is facile in many fluorous compounds in the presence of stronger bases, only weakly basic nucleophiles were used here [18]. For example, bromide can displace the triflate easily to give **11a** in 81% yield. Treatment of **10** with potassium malonate results in selective cyclization to give octa(fluoro)cycloheptane **11b**. While fluorocarbon chains are known to be more rigid than their hydrocarbon

Table 3Synthesis and derivatization of fluorinated bis(sulfonic) ester **10**.

Entry	Starting material	Nucleophile or reagent	Conditions	Product	Yield ^a
1	10	KBr	DMF, 18-crown-6, rt		81%
2	10		DMF, rt		57%
3	10		DMF, 85 °C		89%
4	10	NaN ₃	DMF, rt		>99%

Table 3 (Continued)

Entry	Starting material	Nucleophile or reagent	Conditions	Product	Yield ^a
5	11c	H ₂ NNH ₂	EtOH, 65 °C		76%
6	11d	H ₂	H ₂ (balloon), EtOH, Lindlar, rt		13%
7	11d	H ₂	H ₂ (balloon), EtOH, Lindlar, quinoline, rt		59%
8	11d	Ph—C≡C—H	DMF, CuI, 70 °C		85%

^a All yields are isolated yields.

counterparts [19], the formation of this seven-membered ring indicates that the octafluoro-precursor is reasonably flexible [20]. We found C–N bond formation with **10** to proceed smoothly under multiple conditions: both phthalimide and azide react with **10** to generate the respective intermediates **11c** and **11d** in high yield (entries 3 and 4). Compound **11d** forms with less apparent degradation of the fluorocarbon group. Installation of an intermediate triflate in the synthesis of **11d** seems essential: attempts to obtain **11d** directly using diphenylphosphoryl azide left diol **1** unreacted [21]. Direct hydrogenation of **11d** using Pd/C led to extensive degradation while little or no product was formed. By contrast, using the Lindlar catalyst afforded **12** with satisfying yield in the presence of quinoline (entry 7). **11d** participates in double Huisgen cycloaddition under traditional conditions in high yield (entry 8).

5. Summary

Triflate esters, which are easily prepared from the corresponding commercially available diols, are effective building blocks for nitrogen substituted fluororous-phase amphiphiles that are not easily prepared through other methods. These reactions are high yielding, operationally simple, and afford easy access to highly fluorinated materials. Among these compounds, guanidine-terminated amphiphiles have special value because they present an interesting approach to binding phosphate-covered molecules or materials in aqueous solution. Ongoing research in our laboratories involves the application of these materials to the control of nanoparticle solubility and self-assembly.

6. Experimental

6.1. General procedures

All water sensitive procedures were carried out using standard Schlenk techniques under nitrogen when indicated. All reagents were purchased from Alfa Aesar or TCI and used without further purification. Dry solvents were obtained from EMD. All other solvents were reagent grade and used as received. Distilled water was purchased from Arrowhead.

Deuterated NMR solvents were purchased from Cambridge Isotopes Labs.

Chloroform-*d* (CDCl₃) was used as received; NMR spectra were obtained on a Varian Mercury 400, Varian VNMRS 500, or Varian VNMRS 600 MHz spectrometer. All chemical shifts are reported in units of ppm and referenced to the residual ¹H solvent. Data are

reported as follows: chemical shift (ppm); multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, h: heptet, m: multiplet, br: broad, tm: triplet of multiplet, tq: triplet of quintet); integration; coupling constants (Hz); assignment. ¹³C NMR spectra were referenced to the solvent chemical shift at 77.0 ppm for CDCl₃. ¹⁹F NMR spectra were referenced to CFCl₃ as an external standard at 0.0 ppm. All NMR spectra were taken at 25 °C unless otherwise indicated.

Mass spectra were obtained by electrospray ionization (ESI).

MALDI mass spectra were obtained on an Applied Biosystems Voyager spectrometer using the evaporated drop method on a coated 96 well plate. The 2,5-dihydroxybenzoic acid from Aldrich was used as a matrix. In a standard preparation, ca. 1 mg of analyte and ca. 20 mg of matrix were dissolved in a 1 mL of suitable solvent and spotted on the plate with a micropipette.

6.2. PEG tosylate **3**

To a solution of tetraethyleneglycol monomethyl ether (**2**) (10.0 g, 48.0 mmol) and pyridine (84 mL) in CH₂Cl₂ (170 mL), solid *p*-toluenesulfonyl chloride (22.0 g, 115.4 mmol) was added portion-wise at –20 °C under nitrogen. The resulting reaction mixture was stirred for 2 days at –20 °C. Then, the reaction mixture was allowed to warm to room temperature and water (200 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (150 mL × 3). The combined organic fractions were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica (1:1 EtOAc:hexanes; *R*_f = 0.3) to yield **3** as a colorless oil, 16.4 g, 94%.

¹H NMR (500 MHz, CDCl₃): δ = 7.80 (d, Ar, 2H), 7.34 (d, Ar, 2H), 4.16 (t, 2H), 3.66 (t, 2H), 3.62–3.65 (m, 6H), 3.58 (s, 4H), 3.532–3.56 (m, 2H), 3.34 (s, 3H), 2.43 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 144.71 (s, CSO₂O), 132.94 (s, CH₃CCH), 129.74 (s, CHCHCSO₂), 127.89 (s, CCHCH), 71.79, 70.57, 70.46, 70.44, 70.38, 70.36, 69.20, 68.52, 58.94 (CH₃OCH₂), 21.56 (CH₃CHCH). Data was consistent with a previously reported compound [5].

6.3. PEG-fluorinated alcohol **4abc**

6.3.1. **4a**

To a solution of diol **1** (10.85 g, 41.4 mmol) in dry dioxane (236 mL), NaH powder (0.563 g, 23.46 mmol) was added under nitrogen and stirred for 30 min at room temperature. The reaction flask was then placed in 90 °C oil bath and continued to stir for 2 h. A solution of **3** (5 g, 13.8 mmol) in dry dioxane (20 mL) was then added drop wise. The mixture stirred overnight. Then the reaction was cooled down and quenched by hydrochloric acid (2 M in

diethyl ether, 4.33 mL), and the solvent was removed under reduced pressure. The crude compound was dissolved in dichloromethane (200 mL) and a white precipitate was removed via filtration. After solvent removal, the crude product was purified by flash chromatography (1:2 ethyl acetate:hexanes, R_f = 0.5) to yield the monosubstituted product as a clear oil, 3.86 g, 62%.

^1H NMR (400 MHz, CDCl_3): δ = 4.09–3.96 (m, 4H, $\text{OCH}_2(\text{CF}_2)_4\text{CH}_2\text{OH}$), 3.78–3.74 (m, 2H), 3.67–3.61 (m, 12H), 3.55–3.52 (m, 2H), 3.36 (s, 3H, OCH_3), 3.12 (t, $^3J_{\text{H,H}}$ = 7.2 Hz, 1H, CH_2OH). ^{13}C NMR (125 MHz, CDCl_3): δ = 118.08–109.06 (m, CF_2), 72.37, 72.00, 70.80, 70.77, 70.67, 70.63, 70.53, 68.3 (t, $^2J_{\text{C,F}}$ = 24.9 Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 60.59 (t, $^2J_{\text{C,F}}$ = 25.4 Hz, $\text{CF}_2\text{CH}_2\text{OH}$), 59.07 (s, CH_3O). ^{19}F NMR (376 MHz, CDCl_3): δ = –124.1 to –124.1 (m, 4F), –123.0 (p, $^3J_{\text{F,F}}$ = 214.8 Hz, 2F), –120.4 (p, $^3J_{\text{F,F}}$ = 13.3 Hz, 2F). FT-IR (cm^{-1} , neat): ν = 3415, 2882, 1457, 1351, 1177–1119, 946, 865, 762. MALDI-TOF for $\text{C}_{15}\text{H}_{24}\text{F}_8\text{O}_6$ $[\text{MNa}]^+$: calculated 475.13 g/mol, found 475.10 g/mol.

6.3.2. 4b

4b was prepared in the same way as **4a** with 51% yield.

^1H NMR (400 MHz, CDCl_3): δ = 4.07 (td, $^3J_{\text{H,H}}$ = 15.32 Hz, $^3J_{\text{H,H}}$ = 7.3, 4H, $\text{HOCH}_2(\text{CF}_2)_3$), 4.00 (t, $^3J_{\text{H,H}}$ = 14.3 Hz, 4H, $\text{HOCH}_2(\text{CF}_2)_3\text{CH}_2$), 3.77–3.76 (m, 2H), 3.68–3.63 (m, 12H), 3.56–3.54 (m, 2H), 3.38 (s, 3H, OCH_3), 2.91 (t, $^3J_{\text{H,H}}$ = 7.3 Hz, 1H, CH_2OH). ^{13}C NMR (126 MHz, CDCl_3): δ = 118.19–109.41 (m, CF_2), 72.06, 71.94, 70.66–70.48 ($\text{OCH}_2\text{CH}_2\text{O}$), 68.20 (t, $^2J_{\text{C,F}}$ = 25.4 Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 60.31 (t, $^2J_{\text{C,F}}$ = 25.4 Hz, $\text{CF}_2\text{CH}_2\text{OH}$), 59.01 (s, CH_3O). ^{19}F NMR (376 MHz, CDCl_3): δ = –120.46 (m, 2F), –123.05 (m, 2F), –127.47 (m, 2F). FT-IR (cm^{-1} , neat): ν = 3421, 2881, 1460, 1350, 1285–1307, 937, 886, 850, 771, 668. MALDI-TOF for $\text{C}_{14}\text{H}_{24}\text{F}_6\text{O}_6$ $[\text{MNa}]^+$: 425.14 g/mol, found 425.03 g/mol.

6.3.3. 4c

4c was prepared in the same way as **4a** with 60% yield.

^1H NMR (400 MHz, CDCl_3): δ = 4.09 (td, $^3J_{\text{H,H}}$ = 14.3 Hz, $^3J_{\text{H,H}}$ = 7.6, 4H, $\text{HOCH}_2(\text{CF}_2)_6$), 4.04 (t, $^3J_{\text{H,H}}$ = 14.2 Hz, 4H, $\text{HOCH}_2(\text{CF}_2)_6\text{CH}_2$), 3.79–3.77 (m, 2H), 3.69–3.63 (m, 12H), 3.56–3.54 (m, 2H), 3.38 (s, 3H, OCH_3), 2.19 (t, $^3J_{\text{H,H}}$ = 7.6 Hz, 1H, CH_2OH). ^{13}C NMR (126 MHz, CDCl_3): δ = 117.82–108.76 (m, CF_2), 72.41, 72.00, 70.82–70.56 ($\text{OCH}_2\text{CH}_2\text{O}$), 68.44 (t, $^2J_{\text{C,F}}$ = 24.4 Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 60.60 (t, $^2J_{\text{C,F}}$ = 25.4 Hz, $\text{CF}_2\text{CH}_2\text{OH}$), 59.08 (s, CH_3O). ^{19}F NMR (470 MHz, CDCl_3): δ = –120.25 (m, 2F), –122.60 (m, 4F), –122.83 (m, 2F), –124.08 (m, 4F). FT-IR (cm^{-1} , neat): ν = 3408, 2884, 1645, 1457, 1197–1106, 944, 846, 758–726. MALDI-TOF for $\text{C}_{17}\text{H}_{24}\text{F}_{12}\text{O}_6$ $[\text{MNa}]^+$: 575.13 g/mol, found 575.08 g/mol.

6.4. PEG-fluorinated triflate 5

6.4.1. 5a

To a solution of **4a** (1 g, 2.21 mmol) in dry THF (3.3 mL), triethylamine (0.68 mL, 4.862 mmol) was added under N_2 atmosphere. The mixture was stirred for 10 min, after which the flask was cooled to 0 °C. Trifluoromethanesulfonyl chloride (0.47 mL, 4.42 mmol) was then added and the reaction mixture was stirred for 14 h. The solvent was removed under reduced pressure. The crude product was dissolved in ether and filtered to remove a white solid. The solvent of the filtrate was removed under reduced pressure. The crude product was purified by flash chromatography (2:1 ethyl acetate:hexanes, R_f = 0.42) to give **5a** as a clear, oily liquid (1.05 g). Yield: 81%, conversion: 95%.

^1H NMR (400 MHz, CDCl_3): δ = 4.79 (t, $^3J_{\text{H,H}}$ = 12.6 Hz, 2H, $\text{CF}_3\text{SO}_2\text{OCH}_2\text{CF}_2$), 4.01 (t, $^3J_{\text{H,H}}$ = 13.9 Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.77–3.73 (m, 2H), 3.66–3.59 (m, 12H), 3.53–3.50 (m, 2H), 3.35 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, CDCl_3): δ = 118.4 (q, $^1J_{\text{C,F}}$ = 318.9 Hz, SO_2CF_3), 117.89–110.77 (m, CF_2), 72.2, 71.8, 70.62, 70.59, 70.51, 70.49, 70.42, 68.45 (t, $^2J_{\text{C,F}}$ = 27.3 Hz, CH_2OTf), 68.16 (t,

$^2J_{\text{C,F}}$ = 24.9 Hz, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 58.9 (s, CH_3O). ^{19}F NMR (376 MHz, CDCl_3): δ = –124.0 (m, 4F), –120.5 (p, 2F, $^2J_{\text{C,F}}$ = 12.4 Hz, OCH_2CF_2), –120.3 (m, 2F, $\text{CF}_2\text{CH}_2\text{OTf}$), –74.6 (s, 3F, CF_3SO_2). FT-IR (cm^{-1} , neat): ν = 2885, 1428, 1215–1134, 1017, 958, 838, 611. MALDI-TOF for $\text{C}_{16}\text{H}_{23}\text{F}_{11}\text{O}_8\text{S}$ $[\text{MNa}]^+$: calculated 607.08 g/mol, found 606.85 g/mol.

6.4.2. 5b

5b was prepared in a similar way as **5a** to afford 60% yield (100% conversion).

^1H NMR (500 MHz, CDCl_3): δ = 4.82 (t, $^3J_{\text{H,H}}$ = 13.2 Hz, 2H, $\text{CF}_3\text{SO}_2\text{OCH}_2\text{CF}_2$), 4.03 (t, $^3J_{\text{H,H}}$ = 14.2 Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.77–3.76 (m, 2H), 3.67–3.63 (m, 12H), 3.55–3.53 (m, 2H), 3.37 (s, 3H, CH_3O). ^{13}C NMR (126 MHz, CDCl_3): δ = 118.57 (q, $^1J_{\text{C,F}}$ = 318.6 Hz, SO_2CF_3), 117.4–108.8 (m, CF_2), 72.35, 72.07, 70.83, 70.76, 70.74, 70.71, 70.65, 69.03 (t, $^2J_{\text{C,F}}$ = 26.4 Hz, CH_2OTf), 68.14 (t, $^2J_{\text{C,F}}$ = 26.4 Hz, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 58.9 (s, CH_3O). ^{19}F NMR (470 MHz, CDCl_3): δ = –123.9 to –124.1 (m, 4F, $\text{CF}_2\text{CF}_2\text{CH}_2$), –120.5 (p, 2F, $^3J_{\text{C,F}}$ = 12.4 Hz, OCH_2CF_2), –120.2 to –120.35 (m, 2F, $\text{CF}_2\text{CH}_2\text{OTf}$), –74.6 (s, 3F, CF_3SO_2). FT-IR (cm^{-1} , neat): ν = 2878, 1427, 1216, 1144 1008, 969, 613. MALDI-TOF for $\text{C}_{15}\text{H}_{23}\text{F}_9\text{O}_8\text{S}$ $[\text{MNa}]^+$: calculated 557.09 g/mol, found 556.90 g/mol.

6.4.3. 5c

5c was prepared in a similar way as **5a** to afford 93% yield (95% conversion).

^1H NMR (500 MHz, CDCl_3): δ = 4.80 (t, $^3J_{\text{H,H}}$ = 12.2 Hz, 2H, $\text{CF}_3\text{SO}_2\text{OCH}_2\text{CF}_2$), 4.02 (t, $^3J_{\text{H,H}}$ = 13.4 Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.77–3.75 (m, 2H), 3.66–3.60 (m, 12H), 3.53–3.51 (m, 2H), 3.35 (s, 3H, CH_3O). ^{13}C NMR (126 MHz, CDCl_3): δ = 118.52 (q, $^1J_{\text{C,F}}$ = 320.7 Hz, SO_2CF_3), 118.03–108.41 (m, CF_2), 72.41, 72.02, 70.82–70.60, 68.37 (t, $^3J_{\text{C,F}}$ = 28.9 Hz, CH_2OTf), 68.13 (t, $^3J_{\text{C,F}}$ = 28.9 Hz, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 59.0 (s, CH_3O). ^{19}F NMR (470 MHz, CDCl_3): δ = –120.16 (m, 4F), –122.5 (m, 2F), –122.48 (m, 2F), –123.43 (m, 2F), –74.4 (s, 3F, CF_3SO_2). FT-IR (cm^{-1} , neat): ν = 2884, 1427, 1203, 1142, 1012, 956, 821, 612. MALDI-TOF for $\text{C}_{18}\text{H}_{23}\text{F}_{15}\text{O}_8\text{S}$ $[\text{MNa}]^+$: calculated 707.08 g/mol, found 706.73 g/mol.

6.5. PEG-fluorinated phthalimide 6

Potassium phthalimide (4.12 g, 22.3 mmol) was added to a solution of **5a** (6.5 g, 11.1 mmol) in DMF (223 mL). The reaction was stirred at 65 °C overnight under nitrogen. The reaction was then cooled to room temperature and solvent was removed under reduced pressure. Chloroform (200 mL) was added and a white precipitate was filtered. The solvent was removed under reduced pressure. The compound was then purified on a silica gel column with a solvent gradient (in 4:1 ethyl acetate:hexanes R_f = 0.4) to yield a clear oil 5.4 g, 84%.

^1H NMR (400 MHz, CDCl_3): δ = 7.92 (q, $^3J_{\text{H,H}}$ = 2.8 Hz, Ar, 4H), 7.78 (q, $^3J_{\text{H,H}}$ = 2.8 Hz, Ar, 4H), 4.35 (t, $^3J_{\text{H,H}}$ = 15.8 Hz, 2H, NCH_2CF_2), 4.03 (t, $^3J_{\text{H,H}}$ = 14.4 Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.80–3.75 (m, 2H), 3.69–3.61 (m, 12H), 3.56–3.51 (m, 2H), 3.36 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.9 (s, Ar), 134.5 (s, Ar), 131.6 (s, Ar), 123.9 (s, Ar), 118.4–109.2 (m, CF_2), 72.3, 71.9, 70.71, 70.67, 70.64, 70.58, 70.56, 70.52, 70.48, 70.44, 68.3 (t, $^2J_{\text{C,F}}$ = 24.9 Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 58.97 (s, CH_3O), 37.45 (t, $^2J_{\text{C,F}}$ = 23.5 Hz, $\text{CF}_2\text{CH}_2\text{N}$). ^{19}F NMR (376 MHz, CDCl_3): δ = –124.13 (m, 2F), –123.73 (m, 2F), –120.35 (m, 2F), –116.6 (m, 2F). FT-IR (cm^{-1} , in CDCl_3): ν = 3154, 2985, 2903, 2254, 1793, 1472, 1378, 1382, 1099, 910, 733. MALDI-TOF for $\text{C}_{23}\text{H}_{27}\text{F}_8\text{NO}_7$ $[\text{MNa}]^+$: calculated 604.1557 g/mol, found 603.8150 g/mol.

6.6. PEG-fluorinated amine 7

6.6.1. 7a

Compound **6** (3.8 g, 6.5 mmol) was treated with hydrazine (2.05 mL, 65.2 mmol) in anhydrous ethanol (150 mL) at 65 °C and

stirred overnight under nitrogen. The reaction was cooled to room temperature. White precipitate was filtered and washed with CHCl_3 . The solvent was removed under reduced pressure. Chloroform (200 mL) was then added and stirred for 30 min. More white precipitate was obtained, and the precipitate was filtered. The solvent was removed to yield the product as light yellow oil, 2.74 g, 93%.

Alternative route to prepare **7a** via a one-pot hydrogenation of azide **8a**: to a solution of **5a** (190 mg, 0.33 mmol) in DMF (1.5 mL), sodium azide (26.6 mg, 0.41 mmol) was added under nitrogen. The reaction mixture was stirred for 6.5 h. Then Pd/C (2.4 mg, 10%, w/w) was added and the reaction was purged under hydrogen gas. A balloon filled with hydrogen gas was attached to the reaction, which was then stirred for 3 h. Then the Pd/C was filtered out on a pad of Celite. The reaction mixture was poured over 1 M aqueous HCl (2 mL) and, washed with ether (1.5 mL \times 2). The pH of the aqueous phase was adjusted to 12 with saturated NaOH solution, and extracted with ether (2 mL \times 3). The combined organic fractions were dried over MgSO_4 . The solvent was removed under reduced pressure to afford **7a** as a yellow, oily liquid (102.8 mg). Yield: 70%.

^1H NMR (400 MHz, CDCl_3): δ 4.02 (t, $^3J_{\text{H,F}} = 14.3$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.80–3.75 (m, 2H), 3.69–3.61 (m, 12H), 3.56–3.51 (m, 2H), 3.37 (s, 3H, CH_3O), 3.24 (t, $^3J_{\text{H,F}} = 15.8$ Hz, 2H, NCH_2CF_2), 1.36–1.21 (br, 2H, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{13}C NMR (100 MHz, CDCl_3): δ = 118.4–109.6 (m, CF_2), 72.3, 71.9, 70.71, 70.68, 70.65, 70.59, 70.57, 70.50, 68.3 (t, $^3J_{\text{C,F}} = 24.6$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 58.99 (s, CH_3O), 42.92 (t, $^3J_{\text{C,F}} = 24.1$ Hz, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{19}F NMR (376 MHz, CDCl_3): δ = –124.5 (m, 2F), –124.21 (m, 2F), –122.17 (m, 2F), –120.50 (m, 2F). FT-IR (cm^{-1} , in CDCl_3): ν = 3409, 3340, 2878, 1632, 1460, 1352, 1232–1115, 956, 858. MALDI-TOF for $\text{C}_{15}\text{H}_{25}\text{F}_8\text{NO}_5$ $[\text{MH}]^+$, calculated 452.17 g/mol, found 451.96 g/mol.

6.6.2. 7b

7b was prepared from the azide precursor **8b**, which was first purified and subjected to two different conditions for hydrogenation. Both conditions gave the product as a clear oil. Using EtOH as a solvent gave **7b** with 68% yield. Using DMF as a solvent gave **7b** with 72% yield.

^1H NMR (500 MHz, CDCl_3): δ 3.99 (t, $^3J_{\text{H,F}} = 14.3$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.78–3.76 (m, 2H), 3.70–3.63 (m, 12H), 3.56–3.54 (m, 2H), 3.39 (s, 3H, CH_3O), 3.31 (t, $^3J_{\text{H,F}} = 15.3$ Hz, 2H, NCH_2CF_2), 1.56 (br, 2H, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{13}C NMR (126 MHz, CDCl_3): δ = 120.26–109.56 (m, CF_2), 72.34, 72.02, 70.79–70.60, 68.36 (t, $^2J_{\text{C,F}} = 24.5$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 59.08 (s, CH_3O), 43.05 (t, $^3J_{\text{C,F}} = 24.6$ Hz, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{19}F NMR (470 MHz, CDCl_3): δ = –119.84 (m, 2F), –121.62 (m, 2F), –122.04 to 122.01 (m, 2F), –122.15 (m, 2F), –123.56 (m, 2F), –123.70 (m, 2F). FT-IR (cm^{-1} , in CHCl_3): ν = 3408, 3340, 2875, 1632, 1456, 1350, 1284, 1234, 1141, 956, 881. MALDI-TOF for $\text{C}_{14}\text{H}_{25}\text{F}_6\text{NO}_5$ $[\text{MH}]^+$: calculated 402.17 g/mol, found 402.04 g/mol.

6.6.3. 7c

7c was prepared in the same way as **7a** via one flask hydrogenation of the corresponding azide, and was isolated as a yellow oil in 65% yield.

^1H NMR (500 MHz, CDCl_3): δ 4.02 (t, $^3J_{\text{H,F}} = 14.0$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.77–3.75 (m, 2H), 3.66–3.61 (m, 12H), 3.53–3.52 (m, 2H), 3.36 (s, 3H, CH_3O), 3.24 (t, $^3J_{\text{H,F}} = 15.8$ Hz, 2H, NCH_2CF_2), 1.28 (br, 2H, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{13}C NMR (126 MHz, CDCl_3): δ = 118.78–108.75 (m, CF_2), 72.43, 72.03, 70.83–70.58, 68.43 (t, $^2J_{\text{C,F}} = 25.43$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 59.08 (s, CH_3O), 42.96 (t, $^3J_{\text{C,F}} = 23.5$ Hz, $\text{CF}_2\text{CH}_2\text{NH}_2$). ^{19}F NMR (470 MHz, CDCl_3): δ = –119.84 (m, 2F), –121.62 (m, 2F), –122.04 to 122.01 (m, 2F), –122.15 (m, 2F), –123.56 (m, 2F), –123.70 (m, 2F). FT-IR (cm^{-1} , in CHCl_3): ν = 3411, 3348, 2881, 1632, 1458, 1351, 1200–1141, 960, 840. MALDI-TOF for $\text{C}_{17}\text{H}_{25}\text{F}_{12}\text{NO}_5$ $[\text{MNa}]^+$: calculated 574.14 g/mol, found 574.12 g/mol.

6.7. PEG-fluorinated azide **8**

6.7.1. 8a

To a solution of **5a** (194 mg, 0.34 mmol) in DMF (1.5 mL), sodium azide (26.7 mg, 0.41 mmol) was added under nitrogen. The reaction mixture was stirred for 6.5 h. The reaction mixture was poured over H_2O (2 mL) and extracted with Et_2O (2 mL \times 3). The combined organic fraction was washed with H_2O (6 mL \times 3) and dried over MgSO_4 . The solvent was removed under reduced pressure to obtain **8a** as a light-yellow liquid (136 mg, 84%).

^1H NMR (500 MHz, CDCl_3): δ 4.02 (t, $^3J_{\text{H,F}} = 14.3$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.79–3.77 (m, 2H), 3.75 (t, $^3J_{\text{H,F}} = 14.6$ Hz, 2H, $\text{N}_3\text{CH}_2\text{CF}_2$), 3.68–3.63 (m, 12H), 3.55–3.53 (m, 2H), 3.38 (s, 3H, CH_3O). ^{13}C NMR (125 MHz, CDCl_3): δ = 117.97–108.79 (m, CF_2), 72.38, 72.00, 70.79, 70.75, 70.68, 70.66, 70.58, 68.38 (t, $^3J_{\text{C,F}} = 24.6$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 59.04 (s, CH_3O), 50.18 (t, $^3J_{\text{C,F}} = 23.9$ Hz, CH_2N_3). ^{19}F NMR (470 MHz, CDCl_3): δ = –118.08 (m, 2F), –120.32 (m, 2F), –123.95 (m, 2F), –124.11 (m, 2F). FT-IR (cm^{-1} , in CDCl_3): ν = 2881, 2113, 1456, 1123, 960, 857. MALDI-TOF for $\text{C}_{15}\text{H}_{24}\text{F}_8\text{N}_3\text{O}_5$ $[\text{MH}]^+$, calculated 478.16 g/mol, found 478.02 g/mol.

6.7.2. 8b

8b was prepared in a similar way as **8a** to afford >99% yield.

^1H NMR (500 MHz, CDCl_3): δ 4.01 (t, $^3J_{\text{H,F}} = 14.4$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.78–3.75 (m, 2H), 3.77 (t, $^3J_{\text{H,F}} = 14.6$ Hz, 2H, $\text{N}_3\text{CH}_2\text{CF}_2$), 3.68–3.63 (m, 12H), 3.55–3.53 (m, 2H), 3.37 (s, 3H, CH_3O). ^{13}C NMR (125 MHz, CDCl_3): δ = 117.97–108.58 (m, CF_2), 72.13, 71.84, 70.68, 70.60, 70.54, 70.51, 70.49, 70.41, 68.04 (t, $^3J_{\text{C,F}} = 24.9$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 58.83 (s, CH_3O), 50.06 (t, $^3J_{\text{C,F}} = 23.5$ Hz, CH_2N_3). ^{19}F NMR (470 MHz, CDCl_3): δ = –118.30 (m, 2F), –120.21 (m, 2F), –126.43 (m, 2F). FT-IR (cm^{-1} , in CDCl_3): ν = 2881, 2114, 1653, 1457, 1306, 1148, 956. MALDI-TOF for $\text{C}_{14}\text{H}_{24}\text{F}_6\text{N}_3\text{O}_5$ $[\text{MH}]^+$, calculated 428.1620 g/mol, found 428.1664 g/mol.

6.7.3. 8c

8c was prepared in a similar way as **8a** to afford 87% yield.

^1H NMR (500 MHz, CDCl_3): δ 4.04 (t, $^3J_{\text{H,F}} = 14.0$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CF}_2$), 3.80–3.77 (m, 2H), 3.77 (t, $^3J_{\text{H,F}} = 15.6$ Hz, 2H, $\text{N}_3\text{CH}_2\text{CF}_2$), 3.68–3.63 (m, 12H), 3.56–3.54 (m, 2H), 3.38 (s, 3H, CH_3O). ^{13}C NMR (125 MHz, CDCl_3): δ = 117.97–108.58 (m, CF_2), 72.13, 71.84, 70.68, 70.60, 70.54, 70.51, 70.49, 70.41, 68.04 (t, $^3J_{\text{C,F}} = 24.9$ Hz, $\text{CF}_2\text{CH}_2\text{OCH}_2$), 58.83 (s, CH_3O), 50.06 (t, $^3J_{\text{C,F}} = 23.5$ Hz, CH_2N_3). ^{19}F NMR (470 MHz, CDCl_3): δ = –117.88 (m, 2F), –120.19 (m, 2F), –122.30 (m, 2F), –122.50 (m, 2F), –123.66 (m, 2F), –123.88 (m, 2F). FT-IR (cm^{-1} , in CDCl_3): ν = 2881, 2114, 1456, 1142, 958. MALDI-TOF for $\text{C}_{17}\text{H}_{24}\text{F}_{12}\text{N}_3\text{O}_5$ $[\text{MH}]^+$, calculated 578.1524 g/mol, found 577.9730 g/mol.

6.8. PEG-fluorinated-guanyldinium mono TFA salts **9**

6.8.1. 9b

To a solution of compound **7b** (161.6 mg, 0.4 mmol) in DMF (0.4 mL), Hünig's base (0.14 mL, 0.8 mmol) and 1H-pyrazole-1-carboxamide hydrochloride (117.3 mg, 0.8 mmol) were added and the reaction was stirred vigorously. Another addition of Hünig's base and 1H-pyrazole-1-carboxamide hydrochloride was made at 72 h. Another aliquot of Hünig's base and 1Hpyrazole-1-carboxamide hydrochloride was added at 6 days and every 24 h thereafter to drive the reaction to completion. NMR and MALDI confirmed the completion of the reaction at 11 days. The solvent was removed under reduced pressure. The crude product was obtained as a yellow gum, which was then suspended in H_2O and passed through an IRN-78 ion-exchange column to neutralize the hydrochloride. The resulting crude product was separated with

reverse phase chromatography (MeOH/H₂O, 0.1% TFA) to afford a light yellow oil as the product in mono-TFA salt form (126.8 mg, 57%).

¹H NMR (500 MHz, 55 °C, CDCl₃): δ 8.62 (br, 1H, H₂NCNHNH₂), 7.37 (br, 4H, H₂NCNHNH₂), 3.96 (t, ³J_{H,F} = 13.4 Hz, 2H, CH₂OCH₂CF₂), 3.92 (NHCH₂CF₂), 3.77–3.75 (m, 2H), 3.65–3.62 (m, 12H), 3.55–3.53 (m, 2H), 3.34 (s, 3H, CH₃O). ¹³C NMR (126 MHz, CDCl₃): δ = 158.9 (s, C=N), 117.9–109.2 (m, CF₂CF₂CF₂), 72.3, 71.8, 70.5–70.2, 68.2 (t, ²J_{C,F} = 26.0 Hz, CF₂CH₂OCH₂), 58.7 (s, CH₃O), 42.1 (t, ²J_{C,F} = 22.1 Hz, CF₂CH₂NH₂). ¹⁹F NMR (470 MHz, CDCl₃): δ = −75.78 (s, 3F, HOOCFCF₃), −117.86 (m, 2F), −119.32 (m, 2F), −127.35 (m, 2F). FT-IR (cm^{−1}, in CHCl₃): ν = 3354–3015, 2921, 1684, 1457, 1204, 1150–1136, 755. MALDI-TOF for C₁₅H₂₇F₆N₃O₅ [MH]⁺: calculated 444.19 g/mol, found 444.07 g/mol.

6.8.2. 9a

9a was prepared in a way similar to **9b** to give the corresponding mono TFA salt product as a light yellow oil in 92% yield.

¹H NMR (500 MHz, 55 °C, CDCl₃): δ 8.28 (br, 1H, H₂NCNHNH₂), 7.34 (br, 4H, H₂NCNHNH₂), 3.97 (t, ³J_{H,F} = 14.0 Hz, 2H, CH₂OCH₂CF₂), 3.93 (NHCH₂CF₂), 3.74–3.73 (m, 2H), 3.66–3.60 (m, 12H), 3.54–3.52 (m, 2H), 3.33 (s, 3H, CH₃O). ¹³C NMR (126 MHz, CDCl₃): δ = 158.72 (s, C=N), 117.82–108.96 (m, CF₂CF₂CF₂CF₂), 72.21, 71.78, 70.50–70.13, 68.24 (t, ²J_{C,F} = 24.3 Hz, CF₂CH₂OCH₂), 58.55 (s, CH₃O), 41.84 (t, ²J_{C,F} = 23.54 Hz, CF₂CH₂NH₂). ¹⁹F NMR (376 MHz, CDCl₃): δ = −75.98 (s, 3F, HOOCFCF₃), −117.81 (m, 2F), −119.72 (m, 2F), −123.55 (m, 2F), −123.58 (m, 2F). FT-IR (cm^{−1}, in CHCl₃): ν = 3356–3014, 2920, 1684, 1457, 1177, 1132, 759. MALDI-TOF for C₁₆H₂₇F₈N₃O₅ [MNa]⁺: calculated 494.19 g/mol, found 494.06 g/mol.

6.8.3. 9c

9c was prepared in a way similar to **9b** to give the corresponding mono TFA salt product as a light yellow oil in 56% yield.

¹H NMR (500 MHz, 55 °C, CDCl₃): δ 8.34 (br, 1H, HOOCFCF₃), 7.41 (br, 4H, H₂NCNHNH₂), 3.97 (t, ³J_{H,F} = 13.4 Hz, 2H, CH₂OCH₂CF₂), 3.93 (NHCH₂CF₂), 3.75–3.73 (m, 2H), 3.65–3.59 (m, 12H), 3.53–3.51 (m, 2H), 3.33 (s, 3H, CH₃O). ¹³C NMR (126 MHz, 55 °C, CDCl₃): δ = 158.88 (s, C=N), 118.15–108.56 (m, CF₂CF₂CF₂CF₂CF₂), 72.31, 71.86, 70.61–70.26, 68.33 (t, ²J_{C,F} = 24.4 Hz, CF₂CH₂OCH₂), 58.60 (s, CH₃O), 41.75 (t, ²J_{C,F} = 25.16 Hz, CF₂CH₂NH₂). ¹⁹F NMR (470 MHz, 55 °C, CDCl₃): δ = −76.07 (s, SCF₃), −117.875 (m, 2F), −119.74 (m, 2F), −121.81 (m, 2F), −122.02 (m, 2F), −123.22 (m, 2F), −123.57 (m, 2F). FT-IR (cm^{−1}, in CHCl₃): ν = 3360–3184, 3020, 2904, 1684, 1216–1144, 761. MALDI-TOF for C₁₈H₂₇F₁₂N₃O₅ [MH]⁺: calculated 594.18 g/mol, found 593.99 g/mol.

6.9. Triflate 10

To a solution of diol **1** (5.0 g, 19.1 mmol) in dry dichloromethane (200 mL), trifluoromethanesulfonyl chloride (4.9 mL, 45.8 mmol) was added under nitrogen atmosphere in an ice bath. Triethylamine (10.7 mL, 76.3 mmol) was then added drop wise. A yellow precipitate was observed. The mixture was stirred at room temperature overnight. The solvent was then removed and the crude compound was dissolved in ethyl acetate (200 mL) and washed twice with water (100 mL). The phases were separated, and the organic phase was washed sequentially with 1 M HCl (200 mL), NaHCO₃ (200 mL), and brine and then dried with MgSO₄ and filtered. The solvent was removed under reduced pressure to yield a yellow oil. It was then crystallized from 3:1 hexanes:ethyl acetate to yield **8** as clear crystals (9.4 g, 94%). Mp. 57.5–58.5 °C.

¹H NMR (400 MHz, CDCl₃): δ = 4.82 (t, ³J_{H,F} = 12.1 Hz, 4H, CF₃SO₂OCH₂CF₂). ¹³C NMR (150 MHz, CDCl₃): δ = 118.42 (q,

¹J_{C,F} = 320.1 Hz, CF₃SO₂), 115.5 (t, CF₂), 113.6–112.6 (m, CF₂), 111.3–109.9 (m, CF₂), 108.0 (t, ²J_{C,F} = 32.9 Hz, CF₂), 68.07 (t, ²J_{C,F} = 28.4 Hz, OCH₂). ¹⁹F NMR (376 MHz, CDCl₃): δ = −123.35 (m, 4F, CF₂CF₂CH₂), −120.1 (m, 4F, CF₂CH₂O), −74.3 (s, 6F, CF₃SO₂). FT-IR (cm^{−1}, in CHCl₃): ν = 3683, 3020, 2400, 1519, 1429, 1220, 931, 761. Anal. Calc'd for C₈H₄F₁₄O₄S₂: C, 18.26; H, 0.77. Found: C, 19.87; H, 0.77.

6.10. Dibromide 11a

To a solution of compound **10** (100 mg, 0.18 mmol) in DMF (1.2 mL), potassium bromide (50.8 mg, 0.43 mmol) and 18-crown-6 (14.6 mg, 0.054 mmol) were added under N₂ atmosphere. After 6 h of stirring, KBr (25 mg) was added and the reaction was allowed to continue for another 26 h. The reaction mixture was poured over H₂O (3.6 mL), extracted with ether (2.4 mL × 3), washed with H₂O (7.2 mL × 3) and dried over MgSO₄. Solvent was removed under reduced pressure to afford the **3a** as a clear oil (56.1 mg, 81%).

¹H NMR (500 MHz, CDCl₃): δ = 3.76 (t, ³J_{H,F} = 15.6 Hz, 4H, BrCH₂CF₂). ¹³C NMR (126 MHz, CDCl₃): δ = 113.99 (tt, ¹J_{C,F} = 257.25 Hz, ²J_{C,F} = 31.8 Hz, CH₂CF₂), 110.91 (tq, ¹J_{C,F} = 268.01 Hz, ²J_{C,F} = 31.3 Hz, CH₂CF₂CF₂), 26.05 (t, ²J_{C,F} = 25.4 Hz, BrCH₂). ¹⁹F NMR (470 MHz, CDCl₃): δ = −113.10 (m, 4F, CF₂CF₂CH₂), −122.03 (m, 4F, CF₂CF₂CH₂). FT-IR (cm^{−1}, in CHCl₃): ν = 2987, 2961, 2932, 1727, 1428, 1287–1072, 875. EI GC/MS for C₆H₄Br₂F₈ [M]⁺: calculated 385.8552 g/mol, found 385.8544 g/mol.

6.11. Malonocycloheptane 11b

In a 3-neck round bottom flask, potassium hydride (26.8 mg, 0.67 mmol, in mineral oil) was washed with pentane. DMF (1.8 mL) was then added. To this suspension of KH in DMF under vigorous stirring, dimethylmalonate (88.2 mg, 0.67 mmol) was added slowly. After 1 h, compound **10** (150 mg, 0.27 mmol) was added to the resulting enolate and the reaction was stirred for 12 h. After that, another aliquot of enolate was added, and the reaction was allowed to stir for 24 h longer. The reaction mixture was poured over H₂O (3.6 mL) and extracted with ether (3.6 mL × 3). The combined organic fractions were washed with H₂O (9 mL × 3) and dried over MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by chromatography (7:1 benzene:ethyl acetate, R_f = 0.74) to separate unreacted starting material, then further purified by a second chromatography (4:1 hexanes:ethyl acetate, R_f = 0.59) to obtain a clear liquid, which crystallized on standing. The crystal sublimes at room temperature. Yield: 54.3 mg, 57%, mp. 67.5–69 °C.

¹H NMR (400 MHz, CDCl₃): δ = 3.83 (s, 6H, CH₃COC), 3.20 (t, ³J_{H,F} = 15.1 Hz, 4H, CCH₂CF₂). ¹³C NMR (126 MHz, CDCl₃): δ = 168.42 (s, CH₃COC), 117.78–113.72 (tt, ¹J_{C,F} = 254.4 Hz, ²J_{C,F} = 27.9 Hz, CH₂CF₂), 111.38–107.08 (tq, ¹J_{C,F} = 229.8 Hz, ²J_{C,F} = 27.8 Hz, CH₂CF₂CF₂), 54.44 (s, CH₃CO), 33.02 (t, ²J_{C,F} = 24.7 Hz, CH₂CF₂). ¹⁹F NMR (470 MHz, CDCl₃): δ = −111.41 (m, 4F, CF₂CF₂CH₂), −120.1 (m, 4F, CF₂CH₂O), −74.3 (s, 6F, CF₃SO₂). FT-IR (cm^{−1}, in CHCl₃): ν = 3021, 2958, 1748, 1438, 1345, 1282, 1216, 1180, 1117, 1076, 1016, 932, 756, 668. GC/MS for C₁₀H₇F₈O₃ [M–OMe]⁺ calculated 327.03, found 327.08 g/mol; C₉H₇F₈O₂ [M–CO₂Me]⁺ calculated 299.03, found 299.08 g/mol.

6.12. Phthalimide 11c

To a solution of **10** (3.0 g, 5.7 mmol) in dry *N,N*-dimethylformamide (300 mL), potassium phthalimide (2.53 g, 13.7 mmol) was added under nitrogen atmosphere. The mixture was stirred at 85 °C overnight. The reaction mixture was cooled down to room temperature and 300 mL of brine was added. The product

precipitated as a white solid and was collected by filtration (2.6 g, 89%). Decomp. temp and mp. 260.5–262 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.93 (q, $^3J_{\text{H,H}}$ = 2.8 Hz, Ar, 4H), 7.78 (q, $^3J_{\text{H,H}}$ = 2.8 Hz, Ar, 4H), 4.38 (t, $^3J_{\text{H,F}}$ = 15.6 Hz, 4H, NCH_2CF_2). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.8 (s, Ar), 134.5 (s, Ar), 131.8 (s, Ar), 123.9 (s, Ar), 37.6 (t, $^3J_{\text{C,F}}$ = 25.1 Hz, NCH_2). ^{19}F NMR (376 MHz, CDCl_3): δ = –123.5 to –123.6 (m, 4F, $\text{CF}_2\text{CF}_2\text{CH}_2$), –116.4 to –116.6 (m, 4F, $\text{CF}_2\text{CH}_2\text{N}$). Anal. Calc'd for $\text{C}_{13}\text{H}_{13}\text{O}_4\text{N}$: C, 50.78; H, 2.32; N, 5.38. Found: C, 50.73; H, 2.03; N, 5.05. FT-IR (cm^{-1} , in CHCl_3): ν = 3019, 2400, 1522, 1424, 1216, 930, 759.

Data are consistent with a previously reported compound [9].

6.13. Diazide 11a

To a solution of compound **10** (150 mg, 0.267 mmol) in DMF (1.8 mL), NaN_3 (41.6 mg, 0.64 mmol) was added under N_2 atmosphere. The reaction was stirred for 3 h. The reaction mixture was then poured over of H_2O (3.6 mL) and extracted with ether (3.6 mL \times 3). The combined organic fractions were then washed with H_2O (10 mL \times 3) and dried over MgSO_4 . The solvent was removed under reduced pressure to yield a colorless oil (83.3 mg, >99%).

^1H NMR (500 MHz, CDCl_3): δ = 3.77 (t, $^3J_{\text{H,H}}$ = 14.7 Hz, 4H, $\text{CH}_2\text{CF}_2\text{CF}_2$). ^{13}C NMR (150 MHz, CDCl_3): δ = 115.73 (tt, $^1J_{\text{C,F}}$ = 258.9 Hz, $^2J_{\text{C,F}}$ = 30.1 Hz, $\text{N}_3\text{CH}_2\text{CF}_2$), 111.82 (tt, $^1J_{\text{C,F}}$ = 265.87 Hz, $^2J_{\text{C,F}}$ = 33.52 Hz, $\text{NH}_2\text{CH}_2\text{CF}_2\text{CF}_2$), 50.20 (t, $^2J_{\text{C,F}}$ = 24.3 Hz, CH_2N_3). Data are consistent with a previously reported compound [8].

6.14. Diamine 12

Compound **11c** (2.3 g, 4.4 mmol) was treated with hydrazine (1.4 mL, 44.4 mmol) in anhydrous ethanol (300 mL) under reflux overnight. After cooling to room temperature, the reaction mixture was filtered to remove the white precipitate. The solvent was then removed under vacuum. The crude product was then stirred in 200 mL chloroform and re-filtered to remove white precipitate. Chloroform was removed by rotary evaporation, and the product was obtained as a white solid. It was sublimated to obtain clear crystals, 0.87 g, 76%. Mp. 47–48 °C.

^1H NMR (400 MHz, CDCl_3): δ = 3.24 (t, $^3J_{\text{H,H}}$ = 16.0 Hz, 4H, $\text{CH}_2\text{CF}_2\text{CF}_2$), 1.35–1.18 (b, 4H, $\text{NH}_2\text{CH}_2\text{CF}_2$). ^{13}C NMR (150 MHz, CDCl_3): δ = 118.4–117.8 (m, CF_2), 116.5–116.1 (m, CF_2), 114.6 (t, $^3J_{\text{C,F}}$ = 28.5 Hz, CF_2), 113.4 (t, $^3J_{\text{C,F}}$ = 35.1 Hz, CF_2), 111.7 (q, $^3J_{\text{C,F}}$ = 35.1 Hz, CF_2), 109.9 (t, $^3J_{\text{C,F}}$ = 35.1 Hz, CF_2), 42.9 (t, $^2J_{\text{C,F}}$ = 24.6 Hz, CH_2NH_2). ^{19}F NMR (376 MHz, CDCl_3): δ = –124.2 to –124.4 (m, 4F, $\text{CF}_2\text{CF}_2\text{CH}_2$), –122.1 to –122.3 (m, 4F, $\text{CF}_2\text{CH}_2\text{NH}_2$). FT-IR (cm^{-1} , in CHCl_3): ν = 3020, 1215, 756.

Data are consistent with a previously reported compound [8,9].

12 can also be prepared via direct hydrogenation using the following procedure:

To a solution of **11d** (53 mg, 0.17 mmol) and quinoline (0.8 mg) in EtOH (0.85 mL), Lindlar (2.6 mg) was added under nitrogen. A balloon filled with H_2 was immediately attached to the reaction. After 6 h 45 min of stirring, the balloon was removed and the reaction mixture was filtered over a pad of Celite. It was then poured over 1 mL of HCl and extracted with ether (2 mL \times 1). After adjusting the pH to 13 with saturated NaOH solution, the aqueous phase was extracted with ether (2 mL \times 3) and dried over MgSO_4 . The crude product was separated using flash-chromatography (chloroform:MeOH = 1:12, R_f = 0.33) to give **12** as clear crystals which sublimes at room temperature. 26.2 mg, Yield: 59%.

6.15. (Bis)triazole 13

To a solution of **11d** (100 mg, 0.32 mmol) in DMF (1 mL), phenylacetylene (78.4 mg, 0.768 mmol), and CuI (9.1 mg,

0.048 mmol) were added sequentially. The reaction was heated at 70 °C for 12 h. The solution was cooled and the solvent was removed under reduced pressure. The greenish crude product was then re-dissolved in a minimal amount of acetone and passed through a plug of silica gel. The eluent was collected and solvent was removed under reduced pressure to obtain a yellowish solid, which was then triturated with ethyl acetate and hexanes to obtain **13** as a white, fluffy solid, 147 mg, 89%. Mp. 242.5–245.5 °C.

^1H NMR (599.804 MHz, DMSO): δ = 8.74 (s, 1H, NCHC), 7.91–7.90 (m, 2H, Ar, CHCHCH), 7.48–7.49 (m, 2H, Ar, CHCHCHN), 7.38–7.36 (m, 1H, Ar, CHCHCH), 5.62 (t, 4H, $^3J_{\text{H,F}}$ = 15.9 Hz, 4H, $\text{CH}_2\text{CF}_2\text{CF}_2$). ^{13}C NMR (150.837 MHz, DMSO): δ = 146.79 (s, CCNCH), 130.02 (s, CHCC), 128.98 (s, Ar, CHCHCH), 128.25 (s, Ar, CHCHCH), 125.34 (s, Ar, CHCHC), 123.50 (s, CCHN), 116.3–112.9 (tm, $^1J_{\text{C,F}}$ = 260.5, CF_2), 112.5–109.0 (tm, $^1J_{\text{C,F}}$ = 270.3, CF_2), 48.5 (t, $^2J_{\text{C,F}}$ = 22.5 Hz, CH_2N). ^{19}F NMR (470 MHz, DMSO): δ = –115.93 (m, 4F, $\text{CF}_2\text{CF}_2\text{CH}_2$), –122.43 (m, 4F, CF_2CH_2). FT-IR (cm^{-1} , in CH_2Cl_2): ν = 3052, 2988, 1419, 1265, 897, 737. MALDI-TOF for $\text{C}_{22}\text{H}_{17}\text{F}_8\text{N}_6$ $[\text{MH}]^+$: calculated 517.14 g/mol, found 517.04 g/mol.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.12.011.

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