Structure−Antitumor Activity Relationships of Tripodal Imidazolium-Amino Acid Based Salts. Effect of the Nature of the Amino Acid, Amide Substitution and Anion

Adriana Valls,[a] Belén Altava,*[a] Vladimir Aseyev,[b] Israel Carreira-Barral,[c] Laura Conesa,[a] Eva Falomir,[a] Eduardo García-Verdugo,[a] Santiago Vicente Luis,*[a] Roberto Quesada.[c]

[a] *Department of Inorganic and Organic Chemistry, ESTCE, University Jaume I, Av. Sos Baynat, s/n, 12004, Castellón, Spain. E-mail: altava@uji.es, luiss@uji.es*

[b] *Department of Chemistry, University of Helsinki, P.O. Box 55 (A413, A. I. Virtasen aukio 1), FIN-00014 HY Helsinki, Finland*

[c] *Department of Chemistry, Faculty of Science, Universidad de Burgos, 09001 Burgos, Spain*

Index.

1) Fluorescence experiments

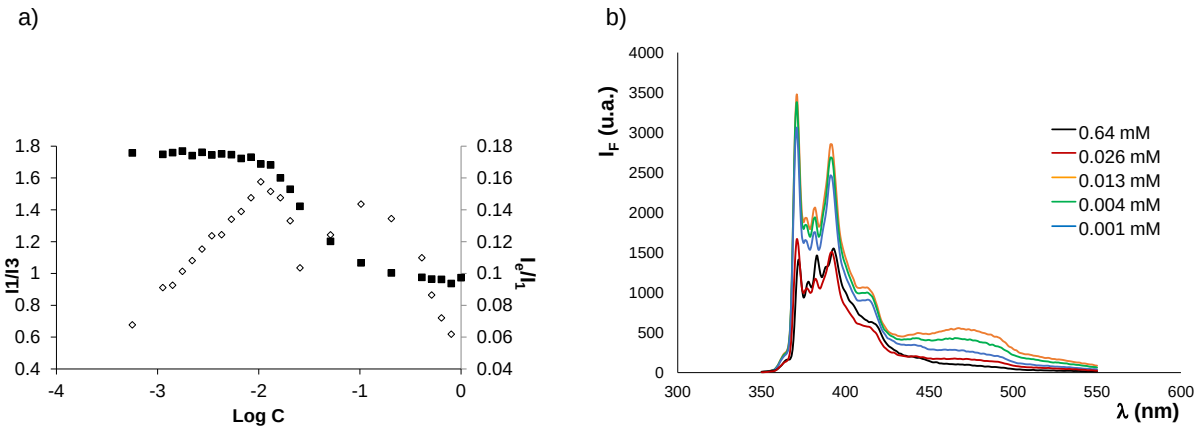


Figure S1. a) Plot of polarity ratio I_1/I_3 (dark squares, left axes) and Ie/I_1 (white diamonds, right axes) *vs* log C (mM) for **3b-Br** in H_2O at 25 ºC, b) Emission spectra of pyrene in H_2O in the presence of different amounts of **3b-Br**.

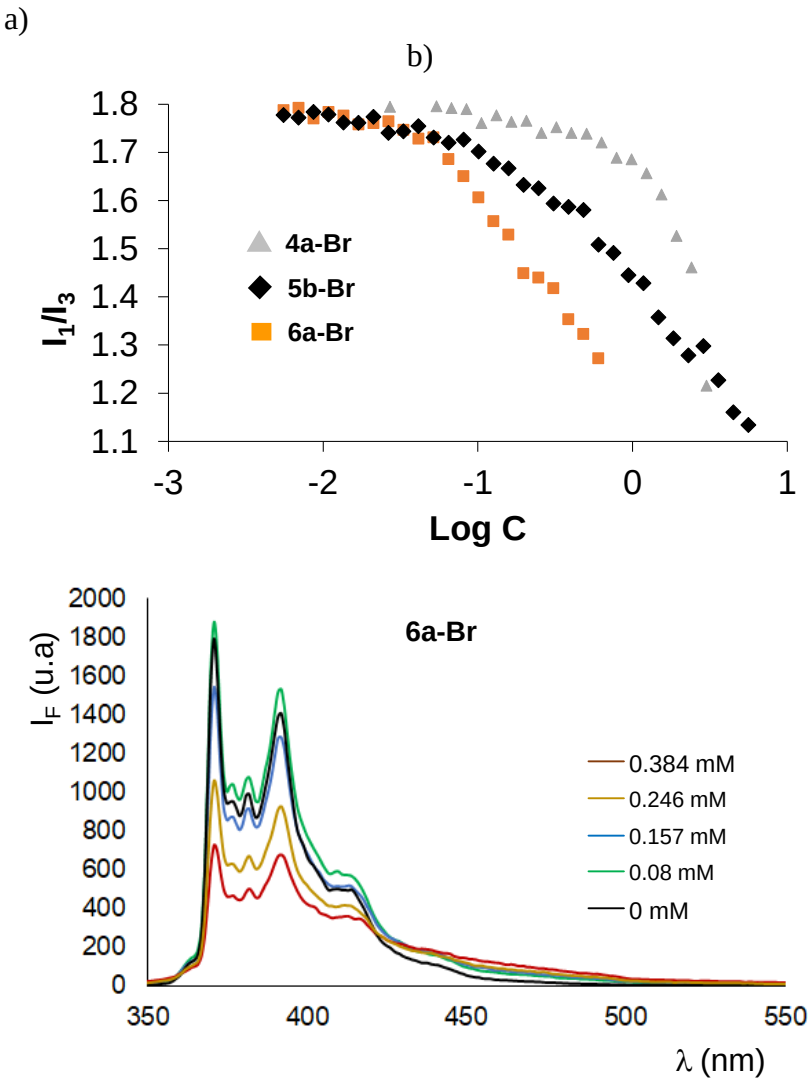


Figure S2. a) Plot of polarity ratio I_1/I_3 *vs* log C (mM) in H_2O at 25ºC for: **4a-Br**, **6a-Br** and **5b-Br.** b) Emission spectra of pyrene in H_2O in the presence of different amounts of **6a-Br**.

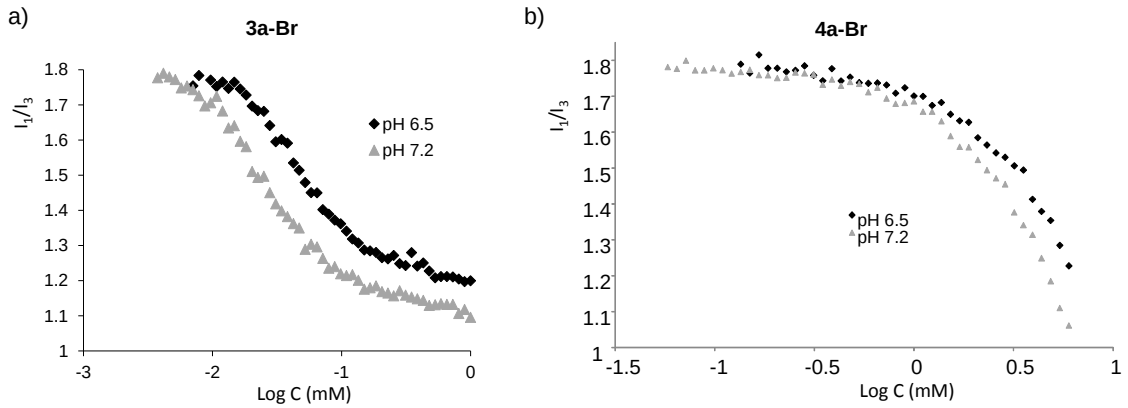


Figure S3. Plot of polarity ratio I_1/I_3 *vs* log C (mM) in buffer at different pHs at 25 ºC for: a) **3a-Br** and b) **4a-Br**

2) ^{1}H NMR experiments for aggregation studies

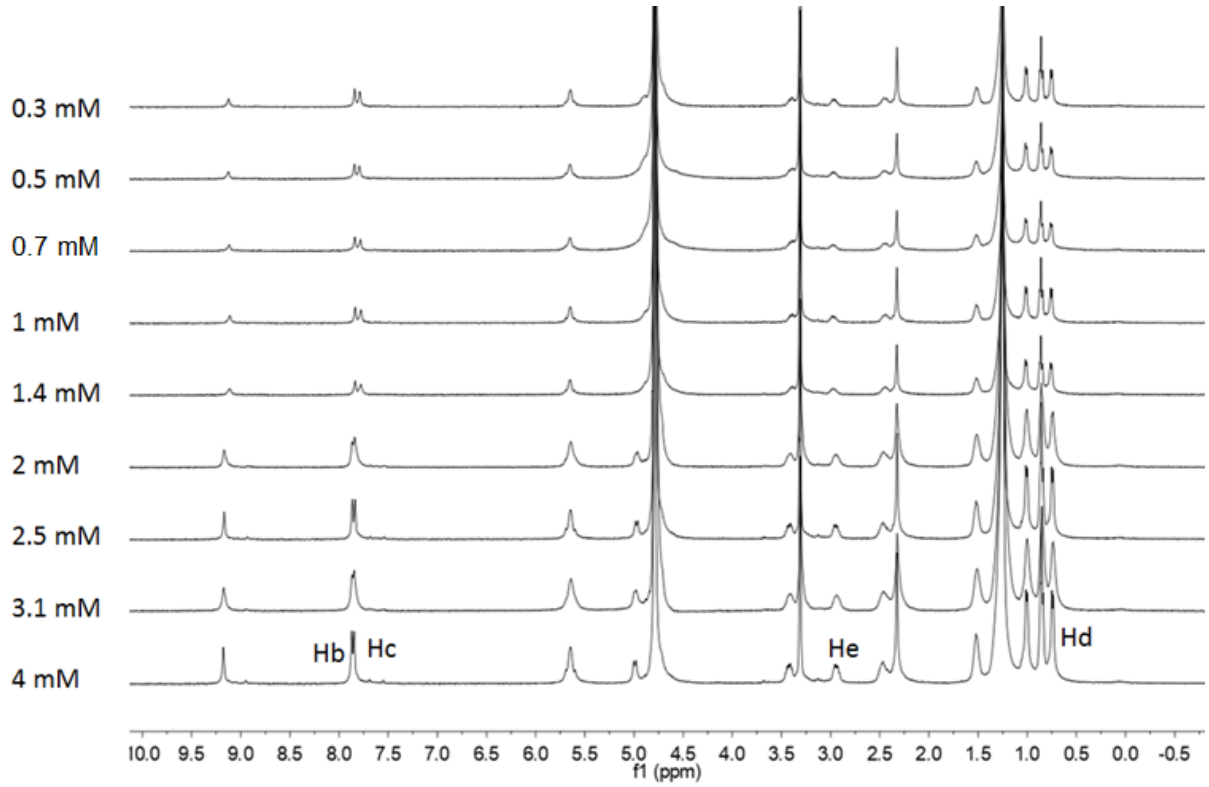


Figure S4. Partial ^{1}H NMR of tripodal compound **3b-Br** at different concentrations in CD_3OD/D_2O 1/1 v/v (400 MHz)

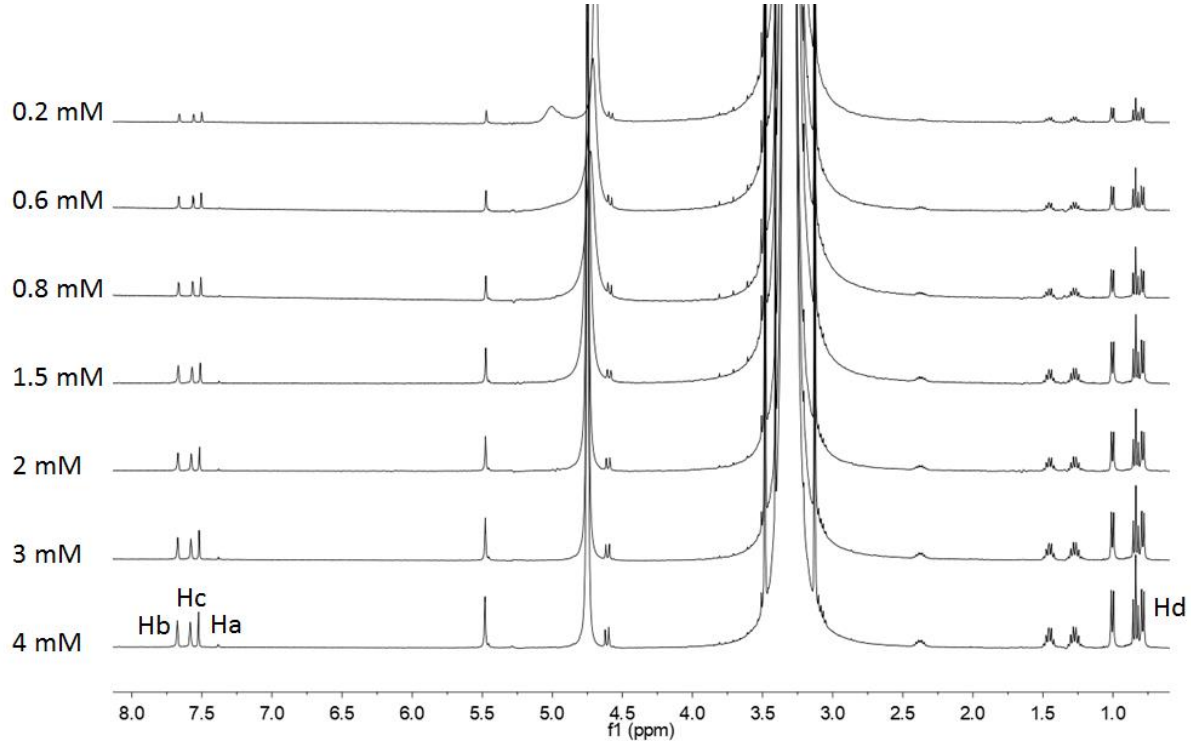


Figure S5. Partial 1H NMR of tripodal compound **4a-Br** at different concentrations in CD_3OD/D_2O 1/1 v/v (400 MHz)

3) LS experiments

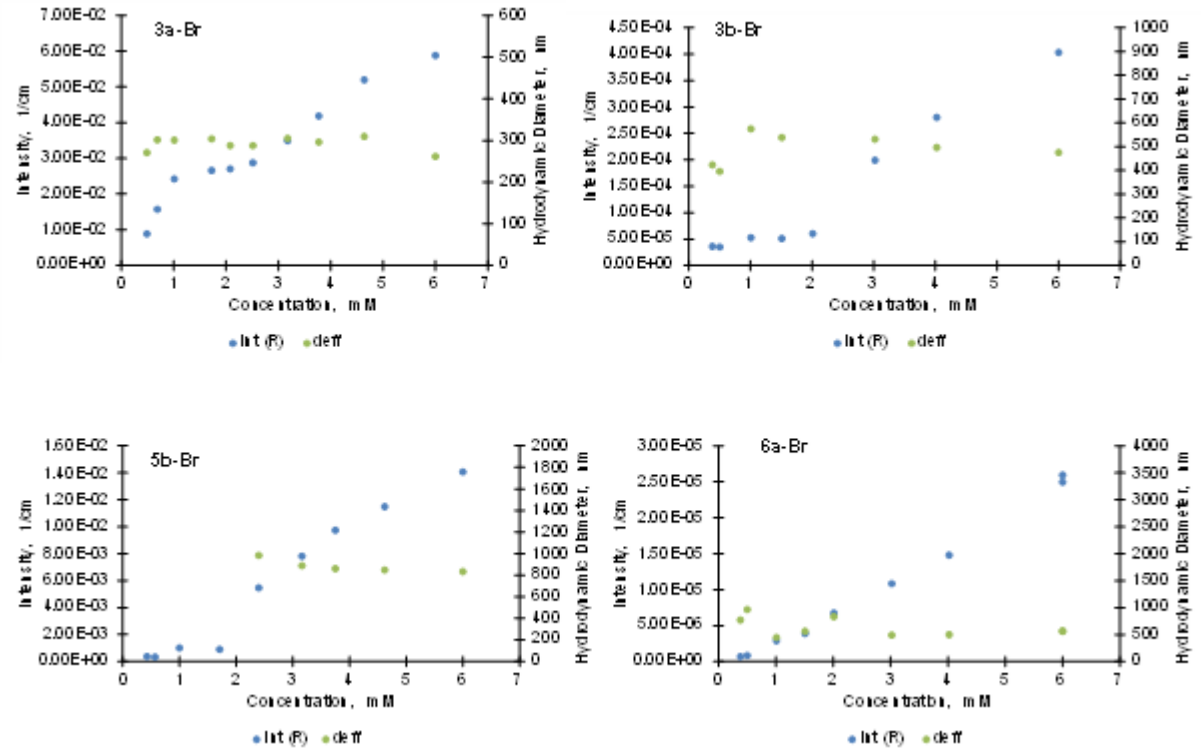


Figure S6. Hydrodynamic diameter (green circles, right axes) and intensity of the scattered light in absolute units ($1/cm^{-1}$) (blue circles, left axes) obtained with DLS for **3a-Br**, **3b-Br**, **5b-Br** and **6a-Br** in CH_3OH/H_2O (1/1 v/v) and presented as a function of the surfactant concentration.

4) Optical microscopy and SEM images

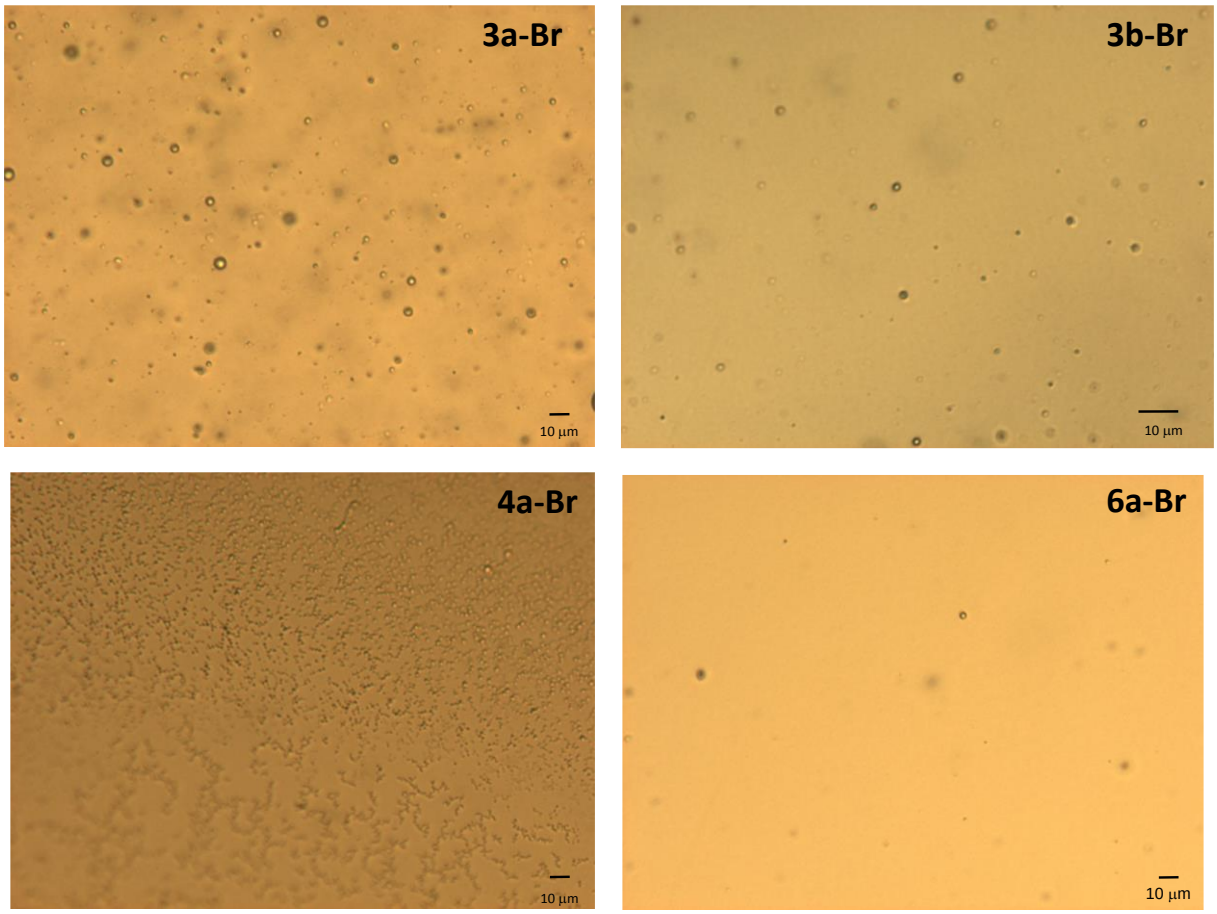


Figure S7. Optical microscopy images for some tripodal compounds (6 mM in H_2O/CH_3OH 1/1)

5) Chloride transport studies

Nitrate outside the vesicles

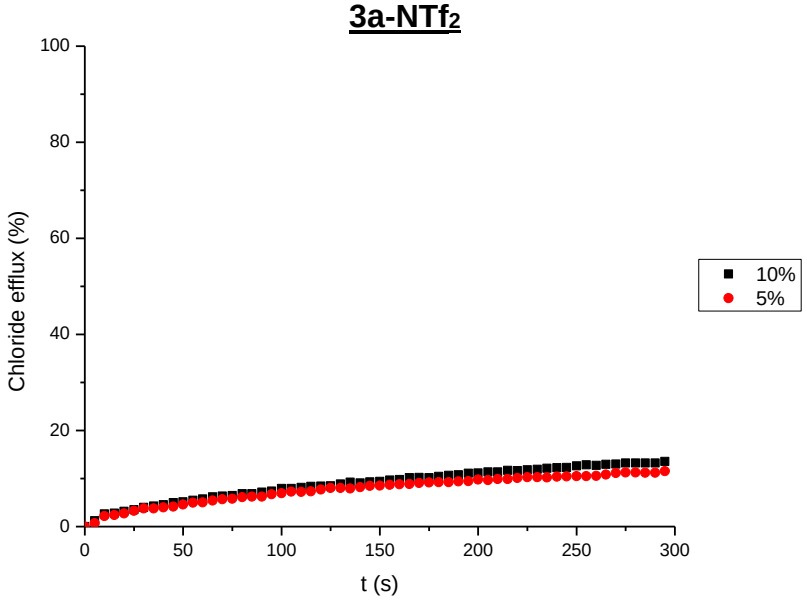


Figure S8. Chloride efflux promoted by **3a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. Vesicles loaded with 489 mM NaCl were buffered at pH 7.2 with 5 mM phosphate and dispersed in 489 mM $NaNO_3$ buffered at pH 7.2. Each trace represents the average of at least three trials, performed with three batches of vesicles.

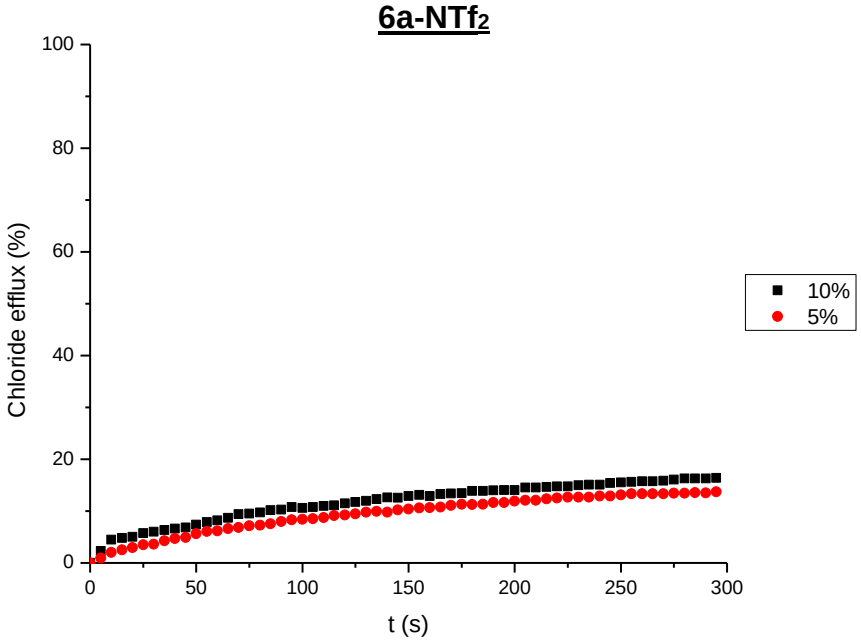


Figure S9. Chloride efflux promoted by **6a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. Vesicles loaded with 489 mM NaCl were buffered at pH 7.2 with 5 mM phosphate and dispersed in 489 mM $NaNO_3$ buffered at pH 7.2. Each trace represents the average of at least three trials, performed with three batches of vesicles.

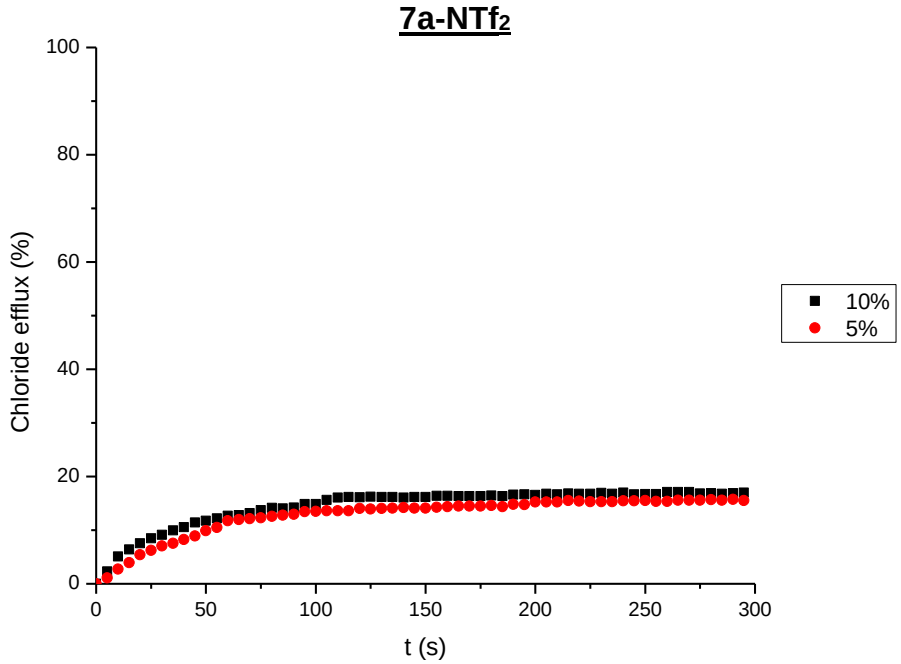


Figure S10. Chloride efflux promoted by **7a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. Vesicles loaded with 489 mM NaCl were buffered at pH 7.2 with 5 mM phosphate and dispersed in 489 mM $NaNO_3$ buffered at pH 7.2. Each trace represents the average of at least three trials, performed with three batches of vesicles.

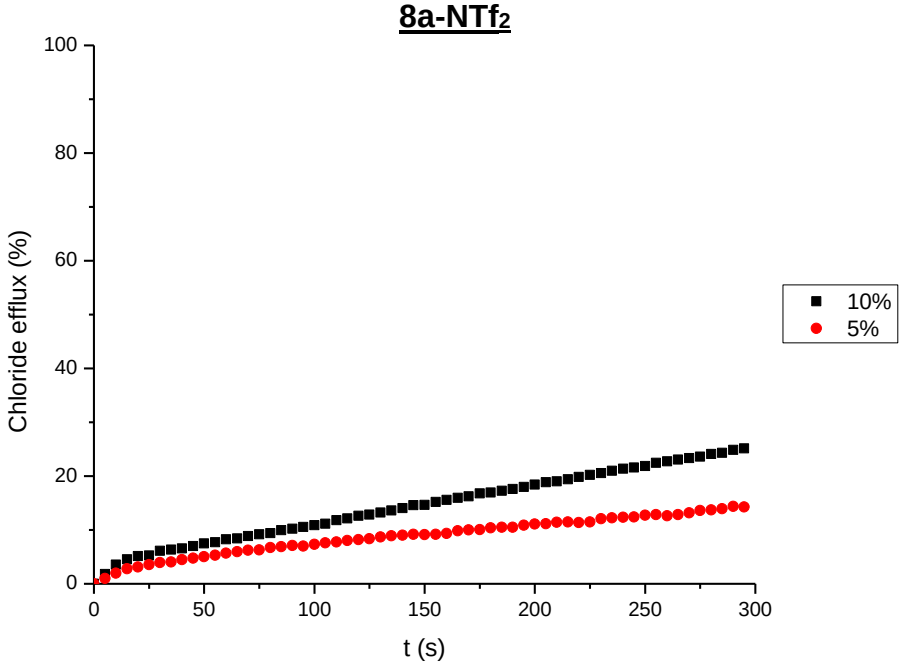


Figure S11. Chloride efflux promoted by **8a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. Vesicles loaded with 489 mM NaCl were buffered at pH 7.2 with 5 mM phosphate and dispersed in 489 mM $NaNO_3$ buffered at pH 7.2. Each trace represents the average of at least three trials, performed with three batches of vesicles.

Bicarbonate/sulfate outside the vesicles

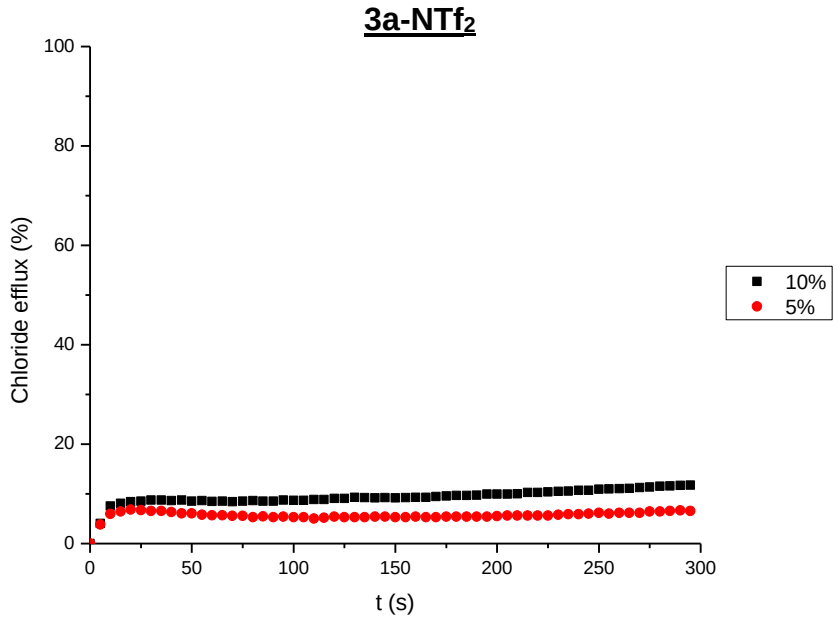


Figure S12. Chloride efflux promoted by **3a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4, 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). Each trace represents an average of at least three different experiments, performed with three batches of vesicles.

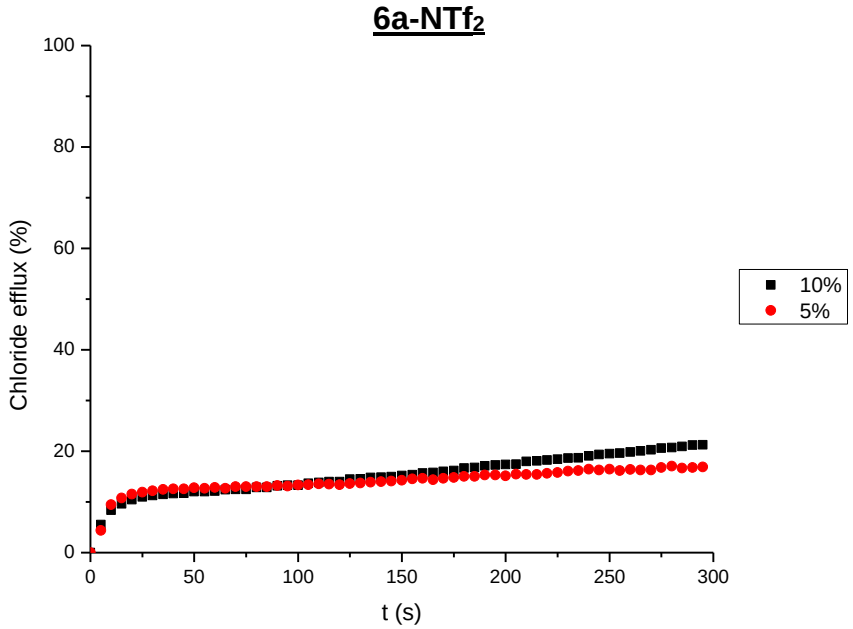


Figure S13. Chloride efflux promoted by **6a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4, 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). Each trace represents an average of at least three different experiments, performed with three batches of vesicles.

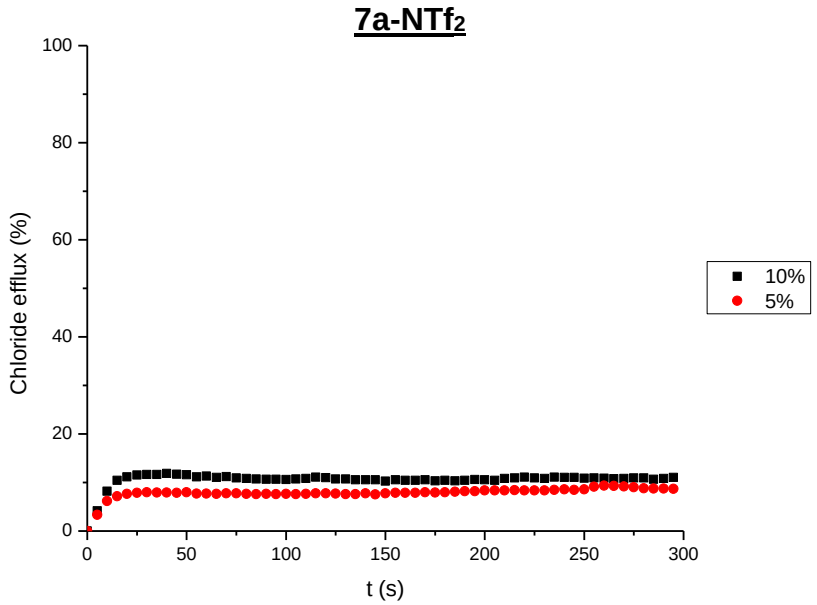


Figure S14. Chloride efflux promoted by **7a-NTf$_2$** (50 μM - 10%; 25 μM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4, 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). Each trace represents an average of at least three different experiments, performed with three batches of vesicles.

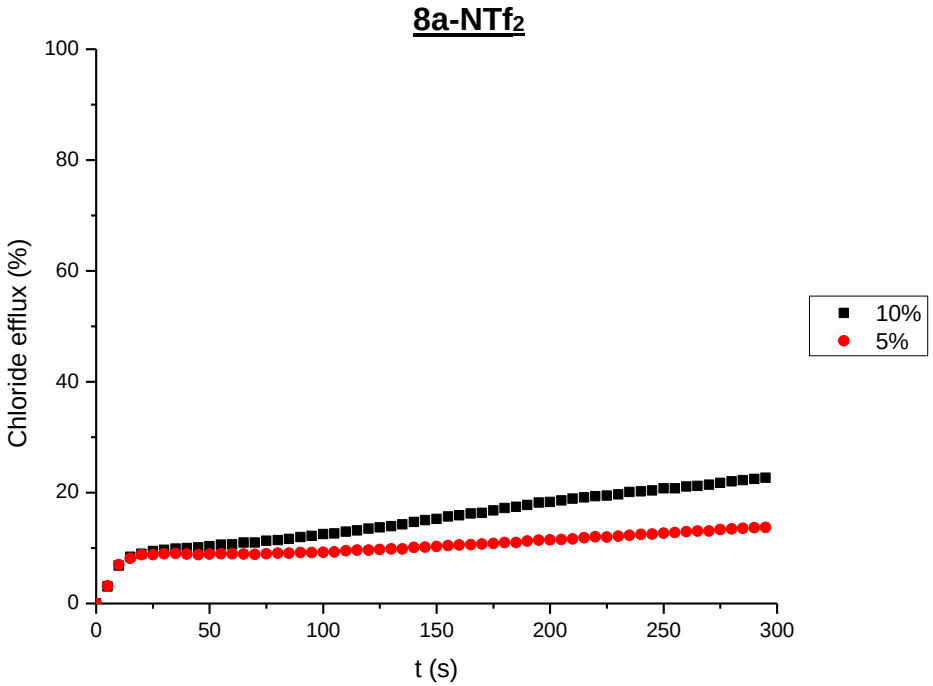


Figure S15. Chloride efflux promoted by **8a-NTf$_2$** (50 μM - 10%; 25 μM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4, 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). Each trace represents an average of at least three different experiments, performed with three batches of vesicles.

Sulfate outside the vesicles

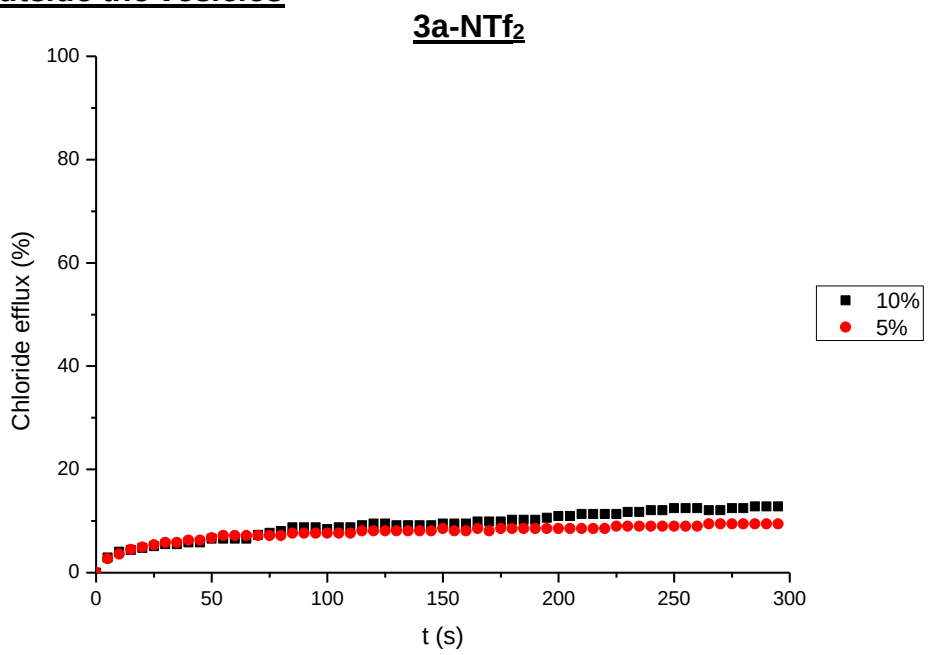


Figure S16. Chloride efflux promoted by **3a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4 and 20 mM phosphate buffer, pH 7.2). Each trace corresponds to one experiment.

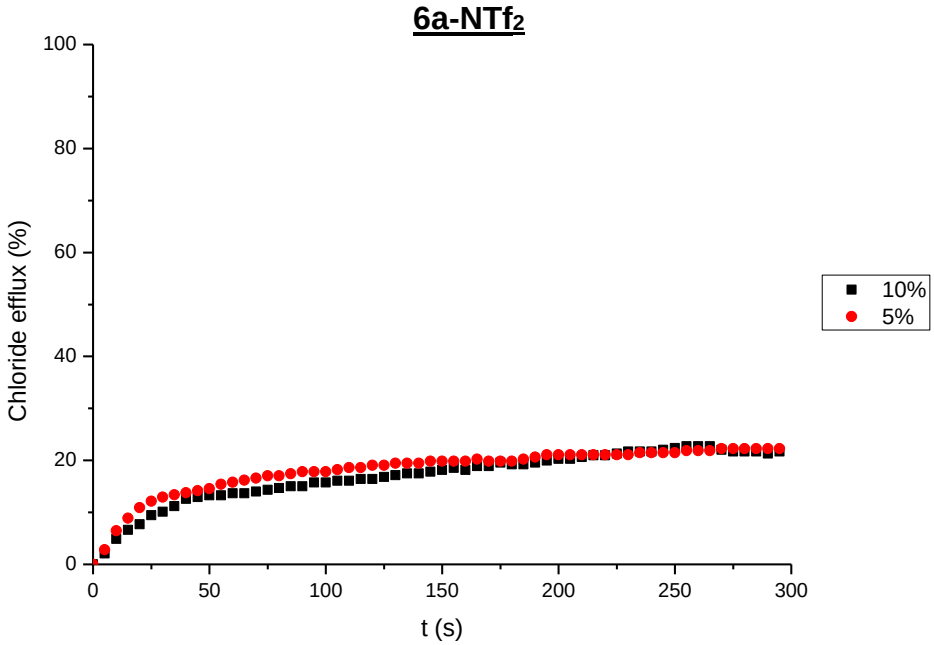


Figure S17. Chloride efflux promoted by **6a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4 and 20 mM phosphate buffer, pH 7.2). Each trace corresponds to one experiment.

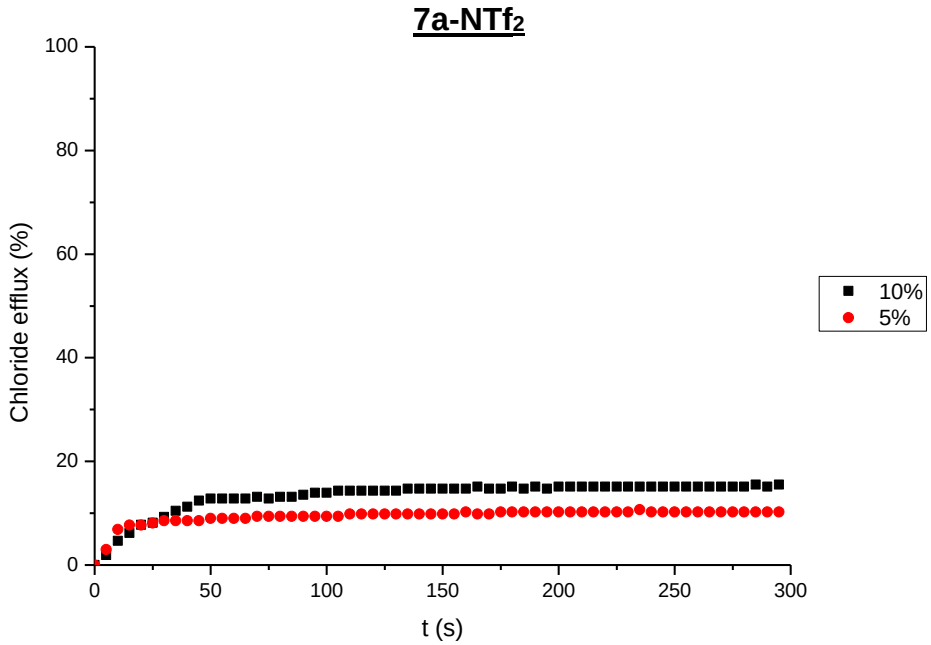


Figure S18. Chloride efflux promoted by **7a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4 and 20 mM phosphate buffer, pH 7.2). Each trace corresponds to one experiment.

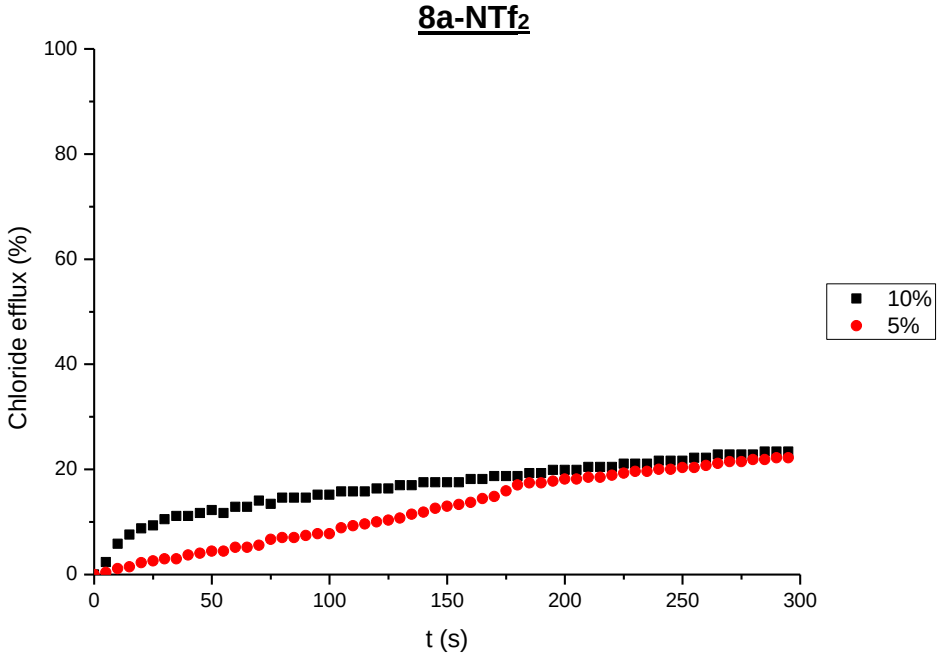


Figure S19. Chloride efflux promoted by **8a-NTf$_2$** (50 µM - 10%; 25 µM - 5% mol carrier to lipid concentration) in unilamellar POPC vesicles. The vesicles, which contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2), were immersed in Na_2SO_4 (150 mM Na_2SO_4 and 20 mM phosphate buffer, pH 7.2). Each trace corresponds to one experiment.

6) Chloride ^{1}H NMR titration experiments

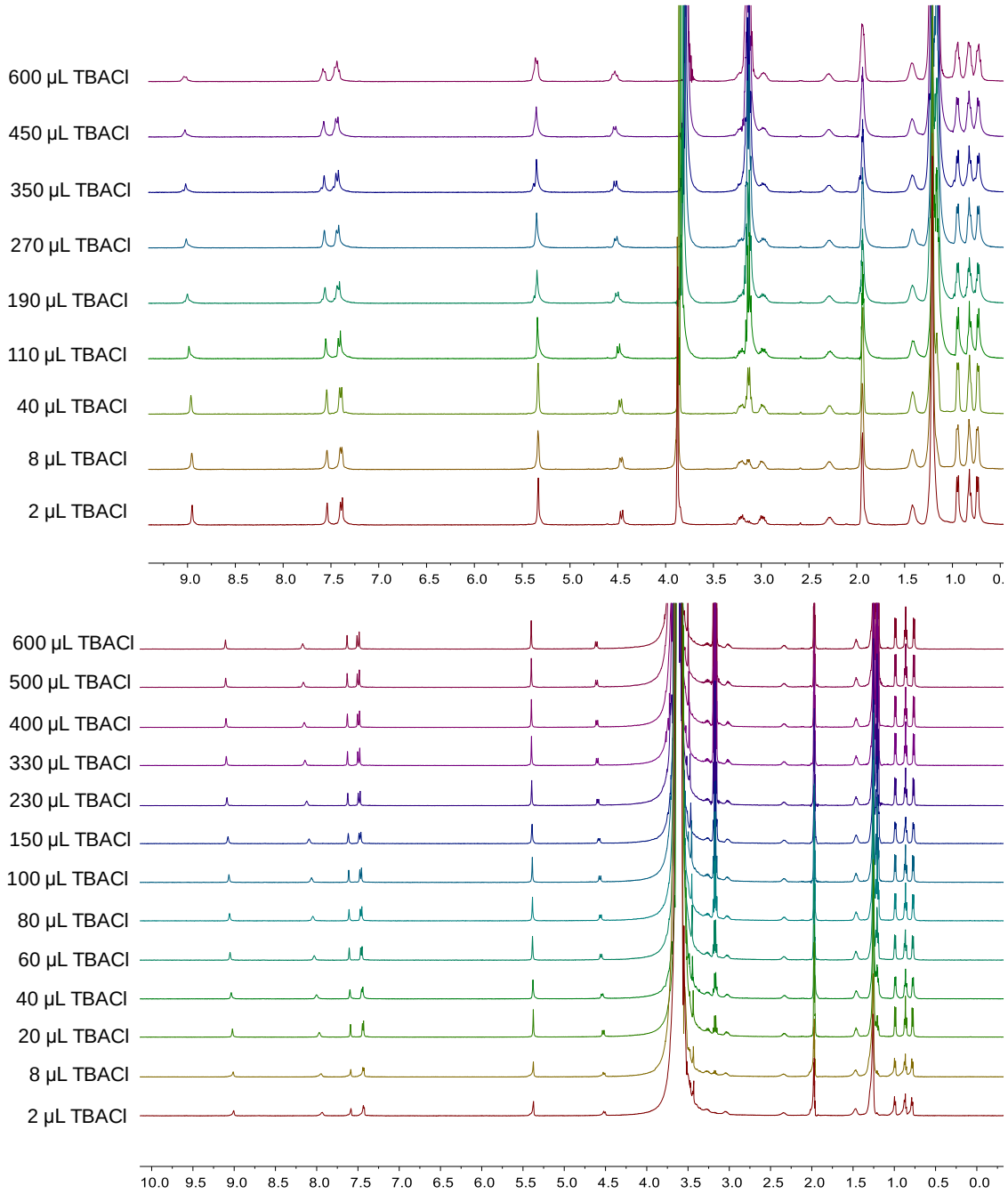


Figure S20. Partial ^{1}H NMR spectra (400 MHz, CD_3CN/D_2O 8/2 v/v) for **3a-NTf$_2$** (6 mM) obtained upon addition of different aliquots of a 60 mM solution of TBACl

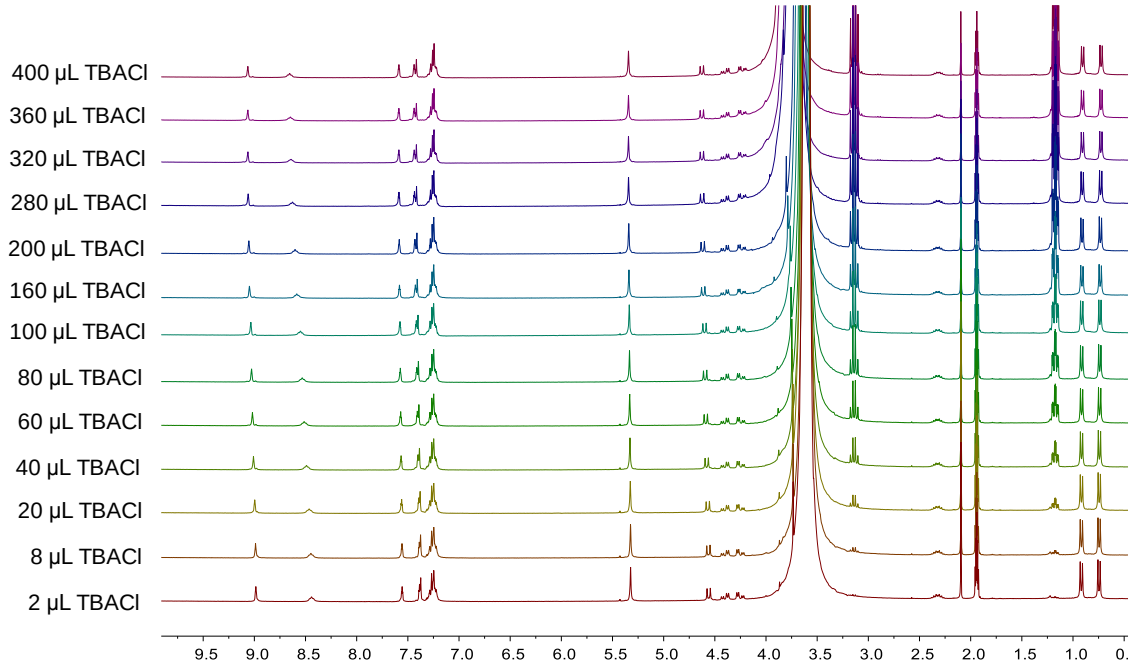


Figure S21. Partial ^{1}H NMR spectra (300 MHz, CD_3CN/D_2O 8/2 v/v) for **6a-NTf$_2$** (6 mM) obtained upon addition of different aliquots of a 60 mM solution of TBACl

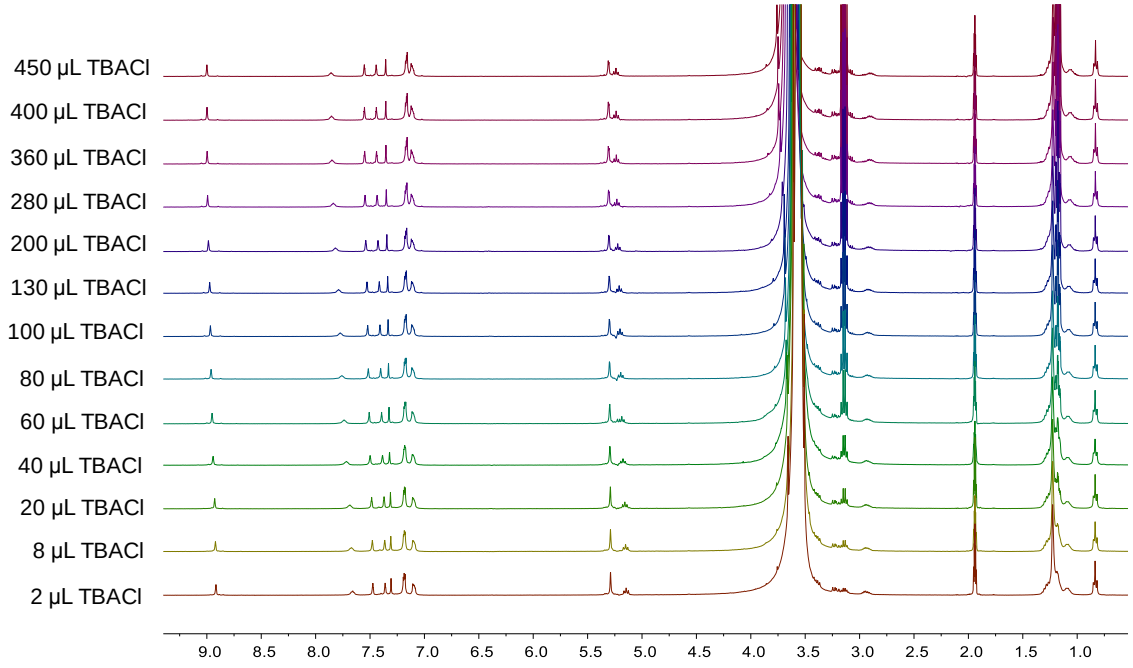


Figure S22. Partial ^{1}H NMR spectra (400 MHz, CD_3CN/D_2O 8/2 v/v) for **7a-NTf$_2$** (6 mM) obtained upon addition of different aliquots of a 60 mM solution of TBACl

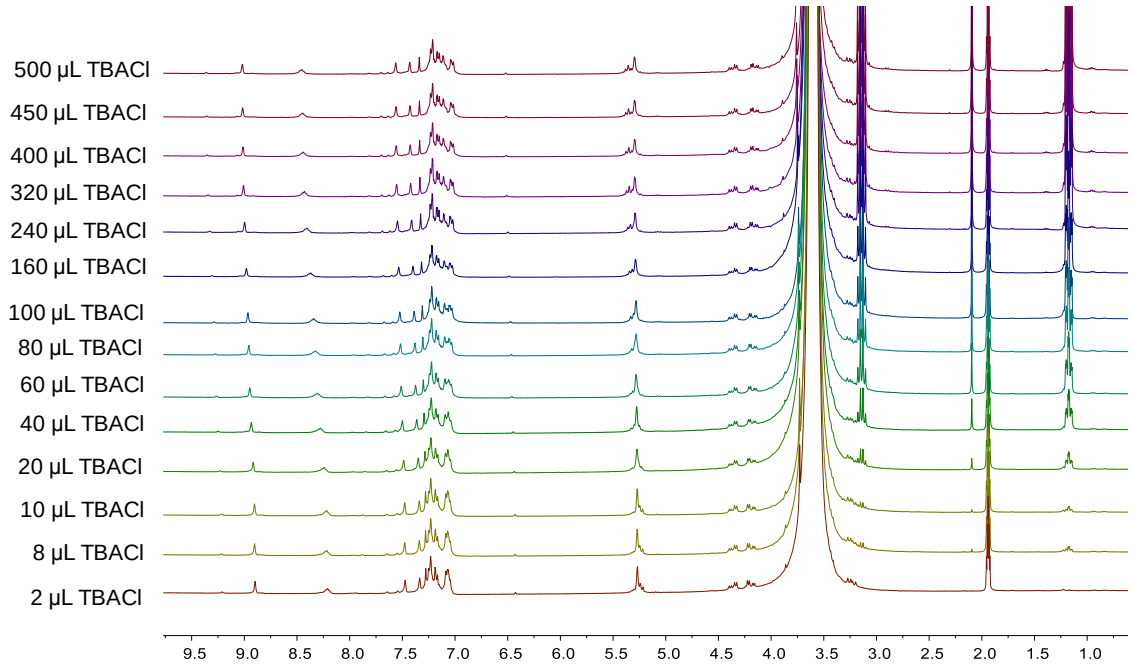


Figure S23. Partial ^{1}H NMR spectra (300 MHz, CD_3CN/D_2O 8/2 v/v) for **8a-NTf$_2$** (6 mM) obtained upon addition of different aliquots of a 60 mM solution of TBACl

7) Fitted binding isotherms

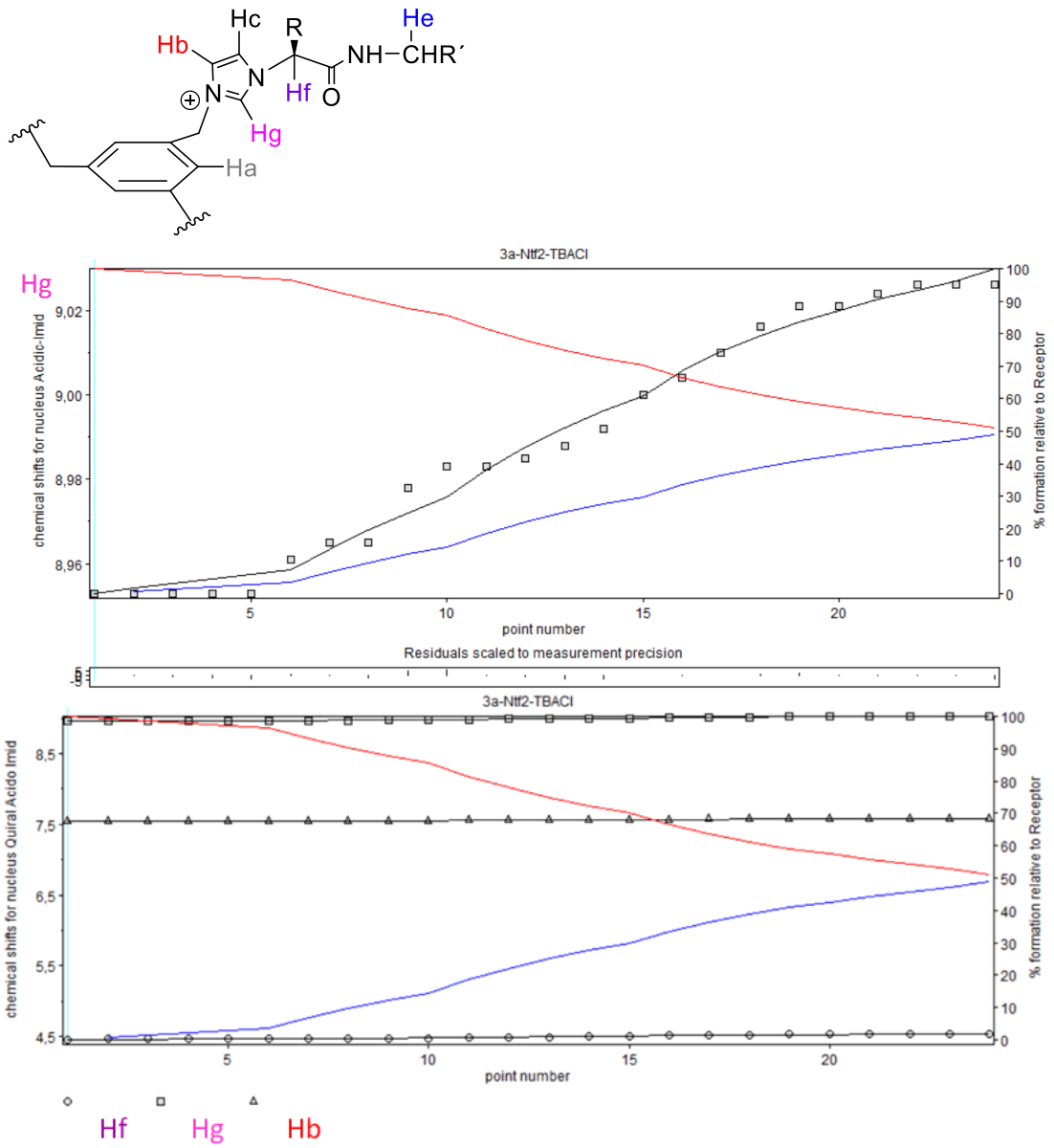


Figure S24. Fitted binding isotherms obtained for the titration of a 6 mM solution of compound **3a-NTf$_2$** with a 60 mM solution of TBACl (CD_3CN/D_2O 8/2). In order to avoid the dilution effect, the latter was prepared with the former. The graph shows the change in chemical shift of the signals corresponding to imidazolium H_g, H_f, H_b protons of the molecule, fitted to the 1:1 binding model.

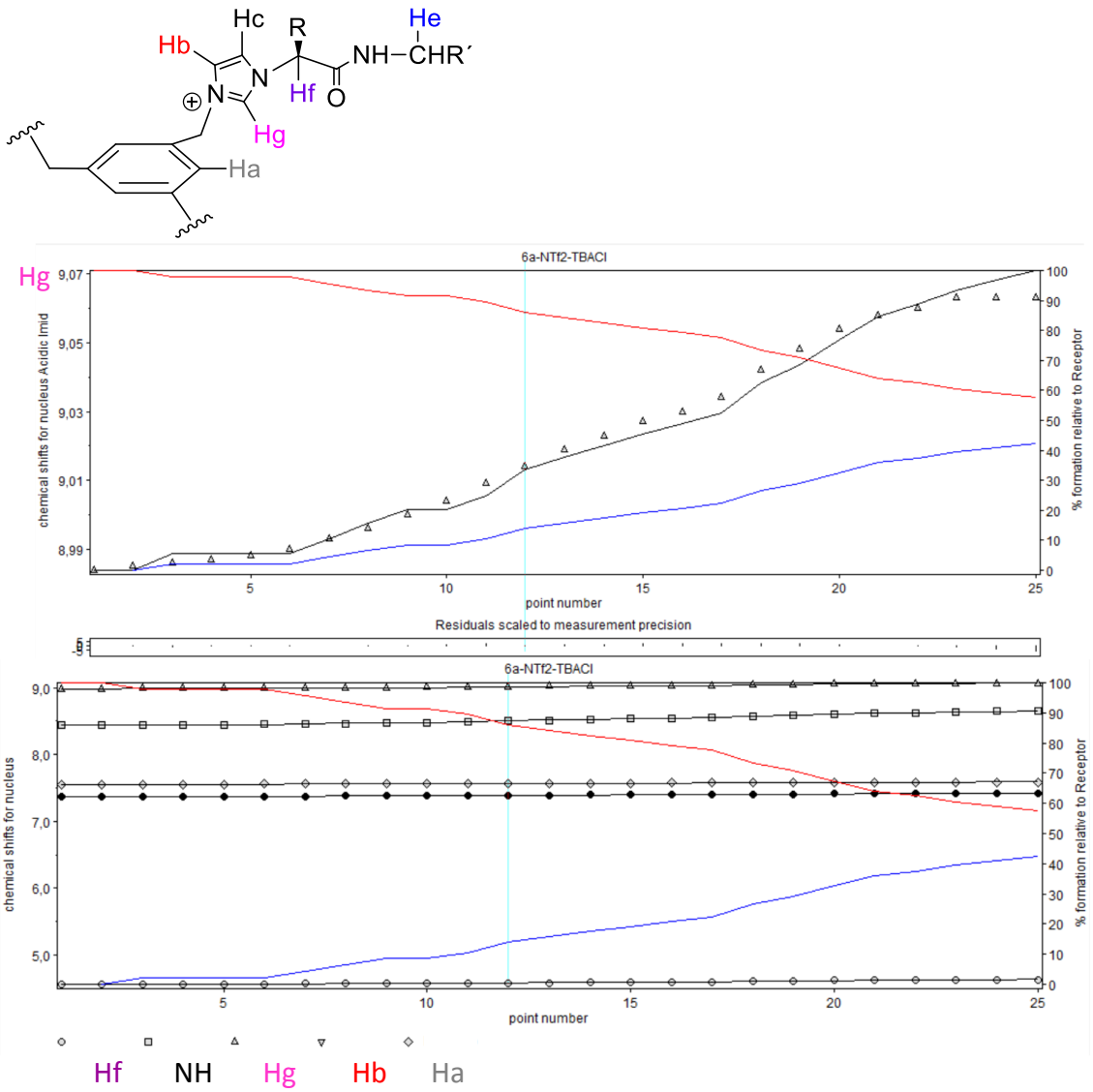


Figure S25. Fitted binding isotherms obtained for the titration of a 6 mM solution of compound **6a-NTf$_2$** with a 60 mM solution of TBACl (CD_3CN/D_2O 8/2). In order to avoid the dilution effect, the latter was prepared with the former. The graph shows the change in chemical shift of the signals corresponding to H_g, H_f, NH, H_b, H_a protons of the molecule, fitted to the 1:1 binding model.

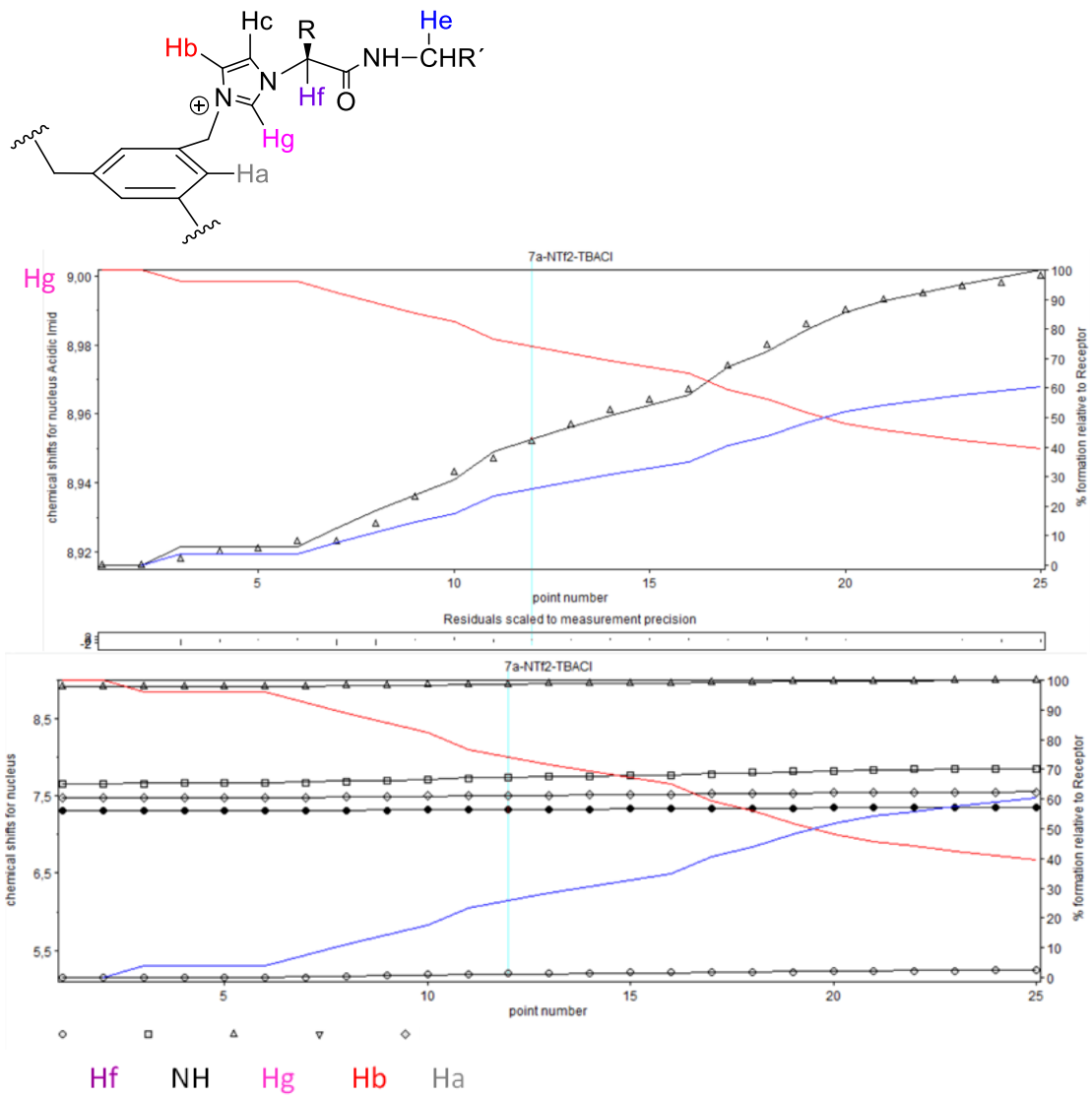


Figure S26. Fitted binding isotherms obtained for the titration of a 6 mM solution of compound **7a-NTf$_2$** with a 60 mM solution of TBACl (CD_3CN/D_2O 8/2). In order to avoid the dilution effect, the latter was prepared with the former. The graph shows the change in chemical shift of the signals corresponding to H_g, H_f, NH, H_b, H_a protons of the molecule, fitted to the 1:1 binding model.

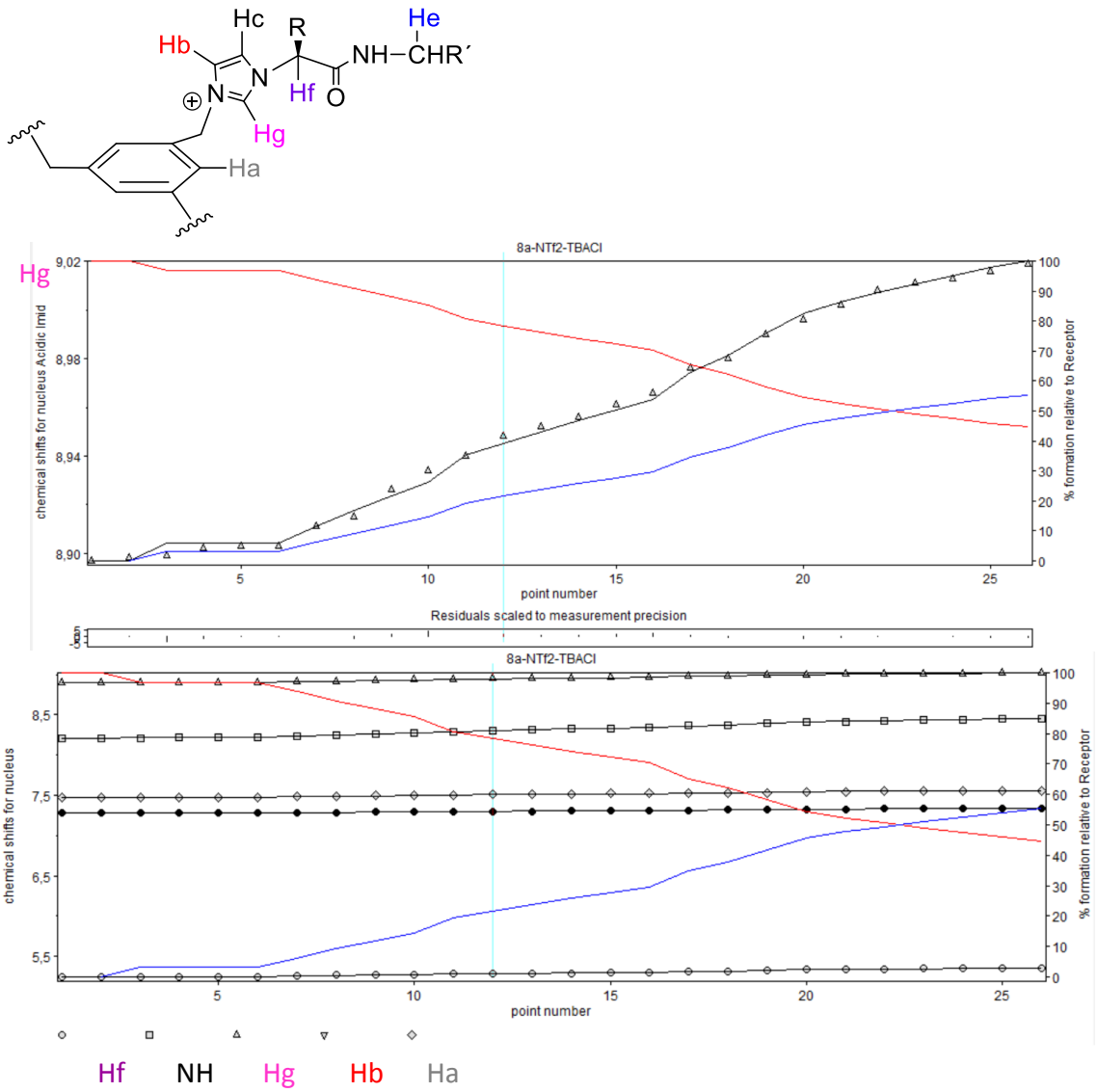


Figure S27. Fitted binding isotherms obtained for the titration of a 6 mM solution of compound **8a-NTf$_2$** with a 60 mM solution of TBACl (CD_3CN/D_2O 8/2). In order to avoid the dilution effect, the latter was prepared with the former. The graph shows the change in chemical shift of the signals corresponding to H_g, H_f, NH, H_b, H_a protons of the molecule, fitted to the 1:1 binding model.

8) Carboxyfluorescein transport studies

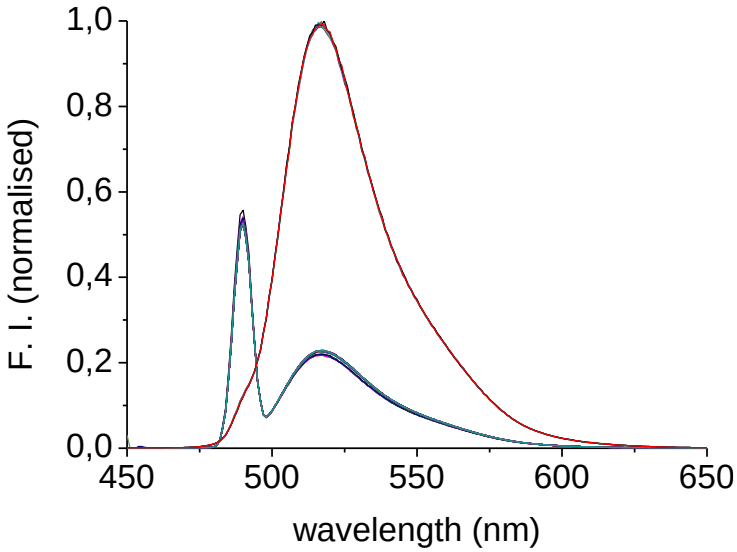


Figure S28. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **DMSO**, the blank, to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s DMSO was added (10 μL), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of three trials, carried out with three different batches of vesicles.

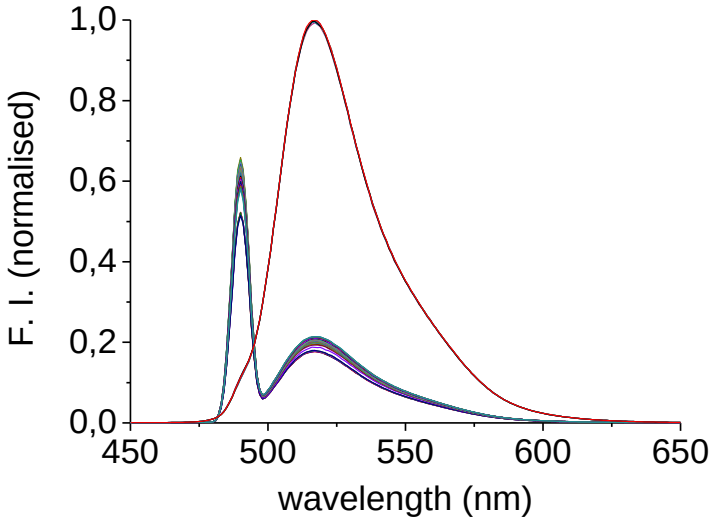


Figure S29. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **3a-NTf$_2$** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of three trials, carried out with three batches of vesicles.

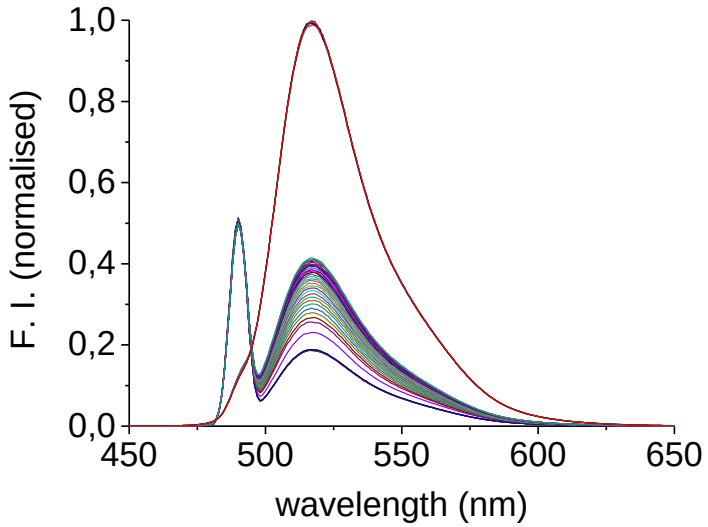


Figure S30. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **6a**-**NTf**$_2$ to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of three trials, carried out with three batches of vesicles.

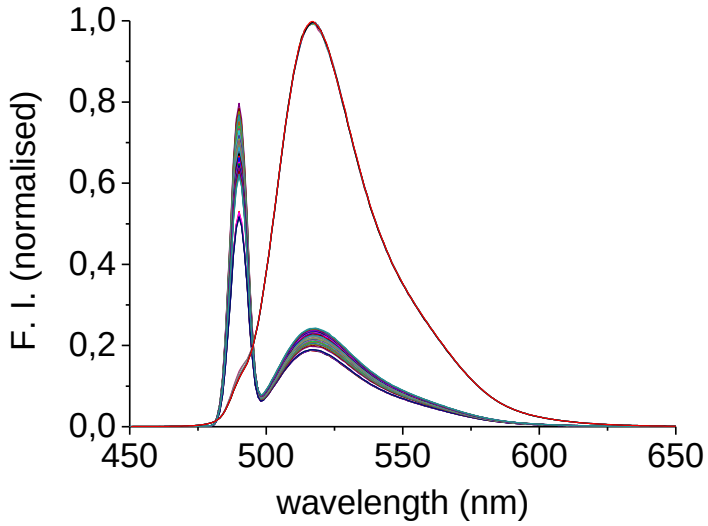


Figure S31. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **7a**-**NTf**$_2$ to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of three trials, carried out with three batches of vesicles.

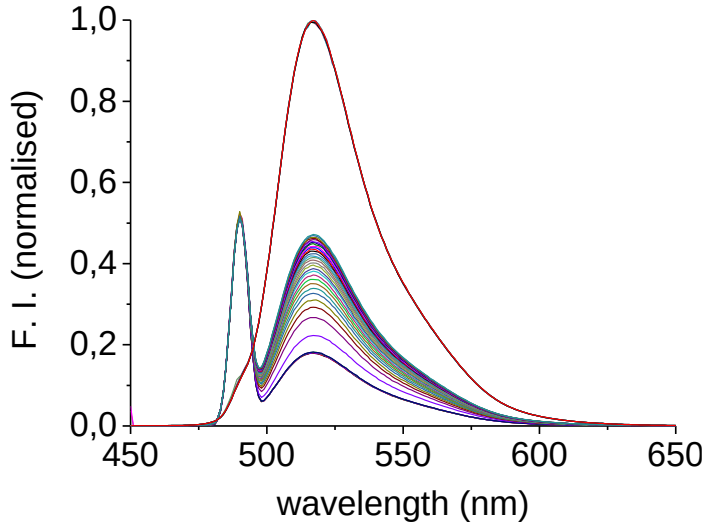


Figure S32. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **8a-NTf$_2$** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of three trials, carried out with three batches of vesicles.

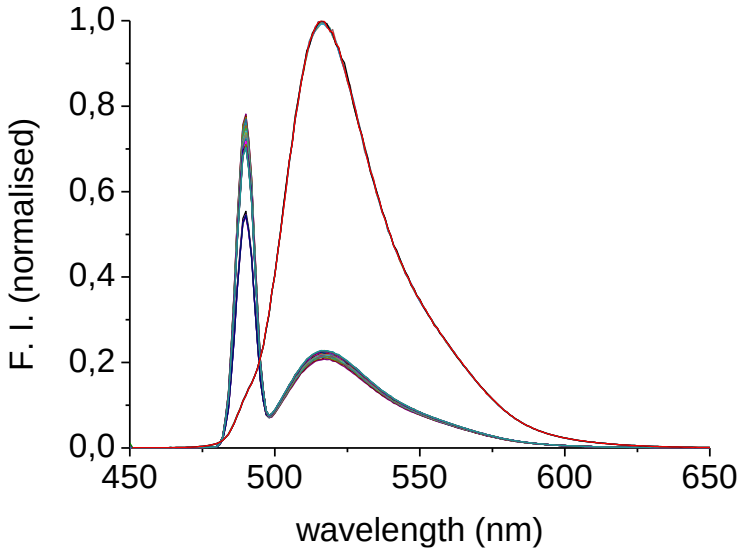


Figure S33. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **3a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of average of least three trials, carried out with three different batches of vesicles.

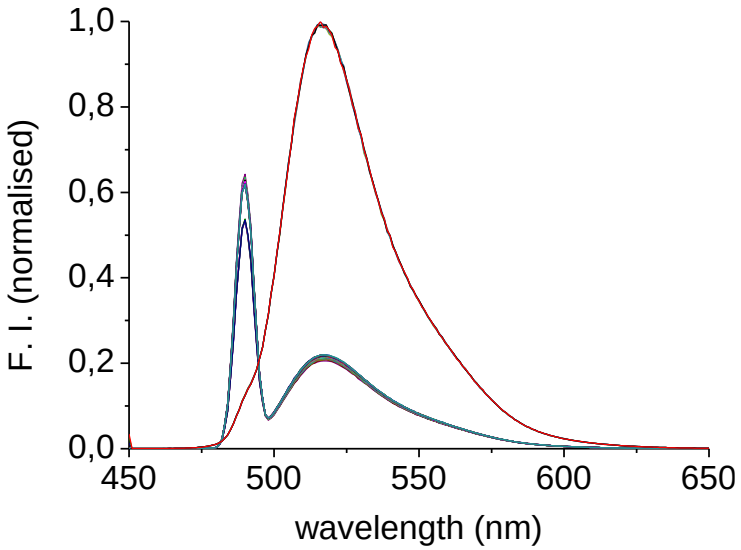


Figure S34. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **3b-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three trials, carried out with three different batches of vesicles.

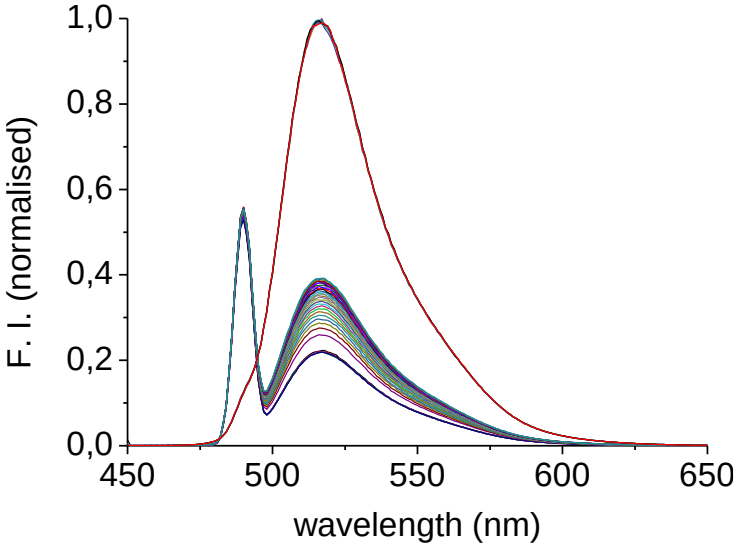


Figure S35. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **4a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three trials, carried out with three different batches of vesicles.

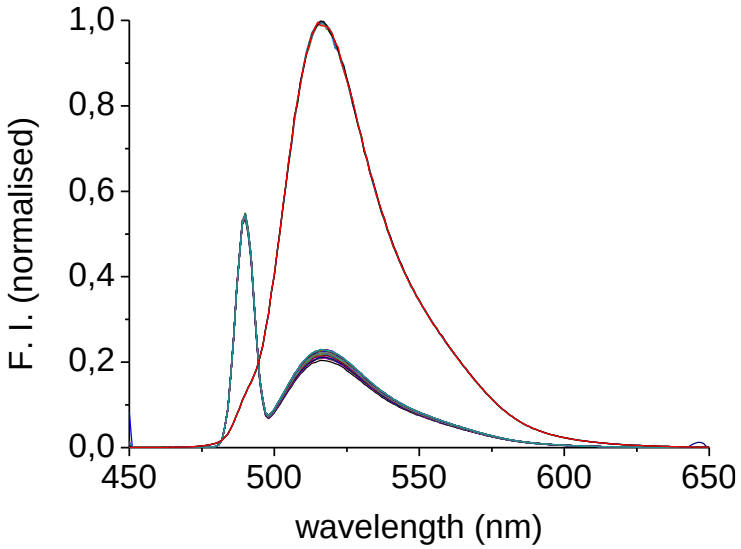


Figure S36. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **5b-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three trials, carried out with three different batches of vesicles.

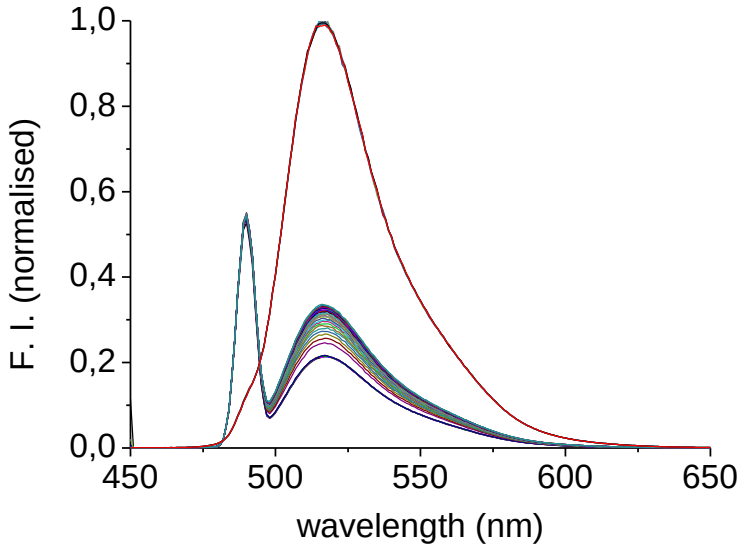


Figure S37. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **6a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three trials, carried out with three different batches of vesicles.

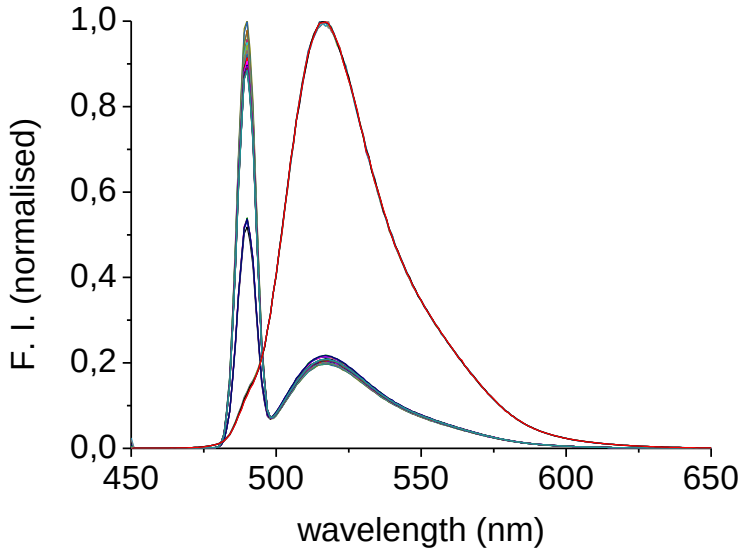


Figure S38. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **7a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three, carried out with three different batches of vesicles.

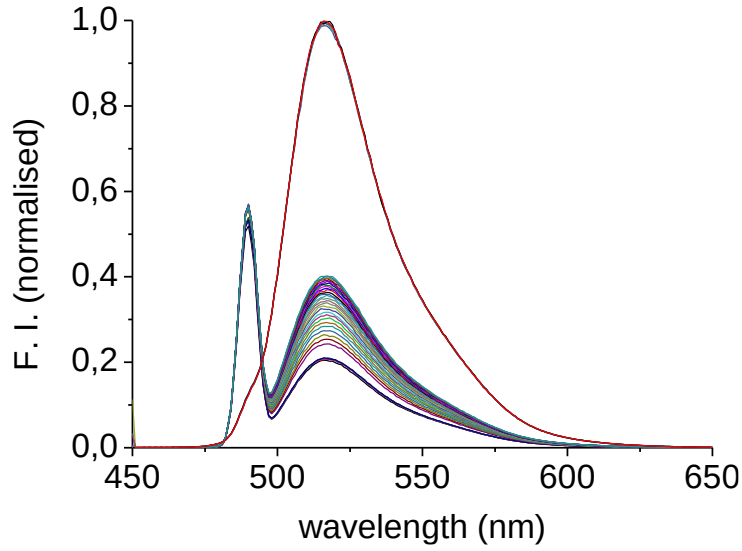


Figure S39. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **8a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of least three, carried out with three different batches of vesicles.

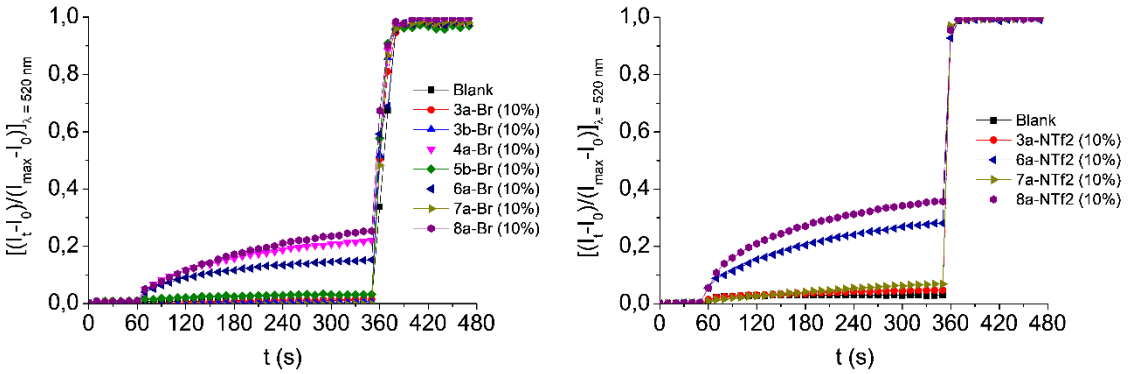


Figure S40. Carboxyfluorescein leakage observed upon addition of the studied compounds to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 7.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. The blank is DMSO (10 μL). Each trace represents the average of least three, carried out with three different batches of vesicles

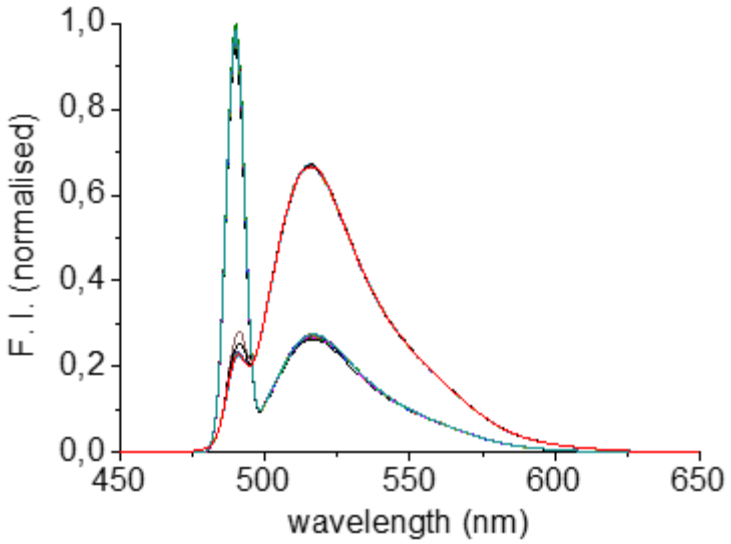


Figure S41. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **DMSO**, the blank, to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s DMSO was added (10 µL), while at t = 360 s the detergent (20 µL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

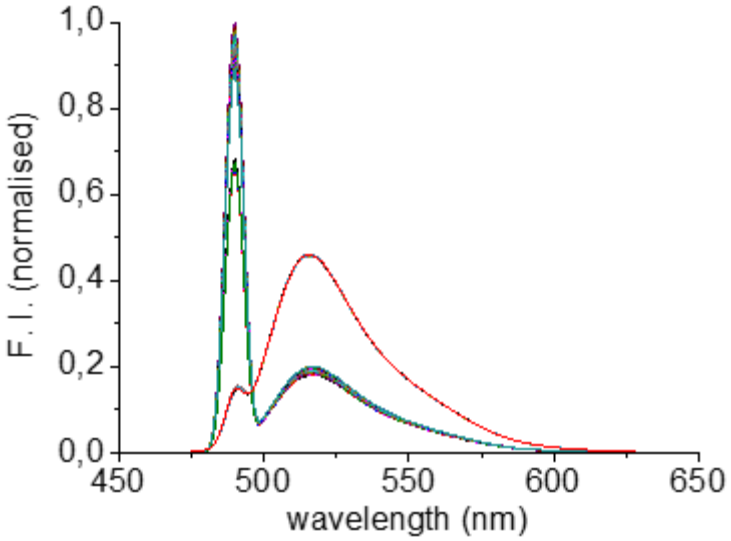


Figure S42. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **3a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 µL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

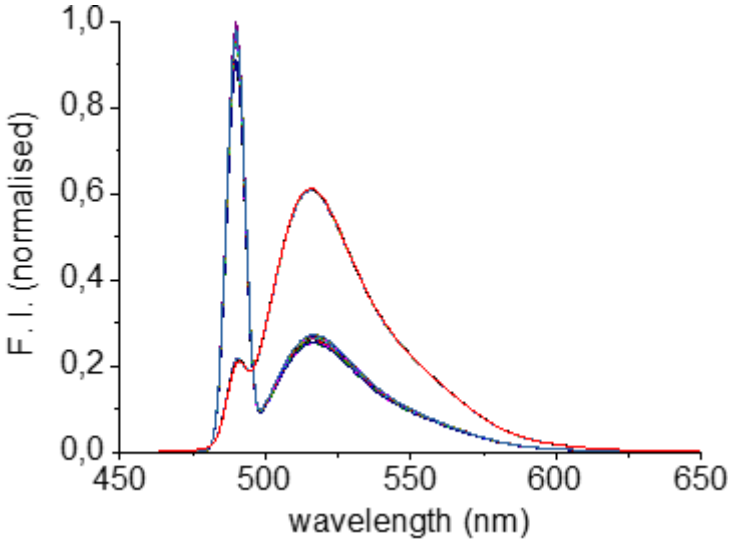


Figure S43. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **3b-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 µL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

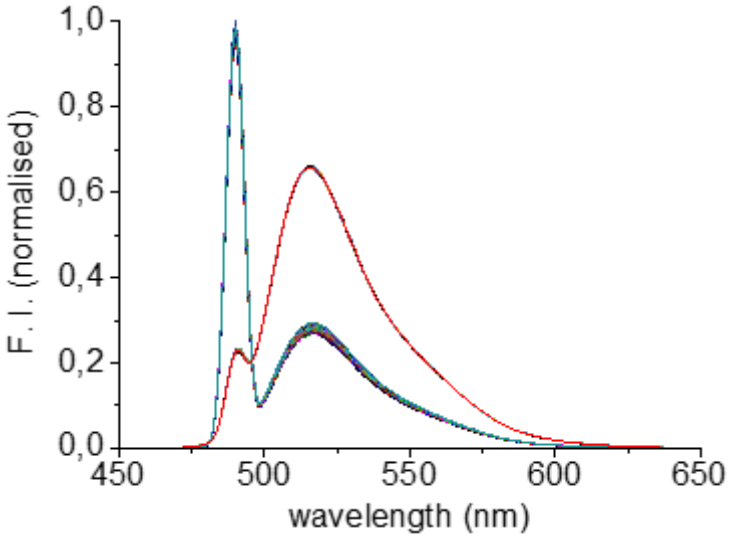


Figure S44. Carboxyfluorescein normalised fluorescence intensity recorded upon addition of **4a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 µL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

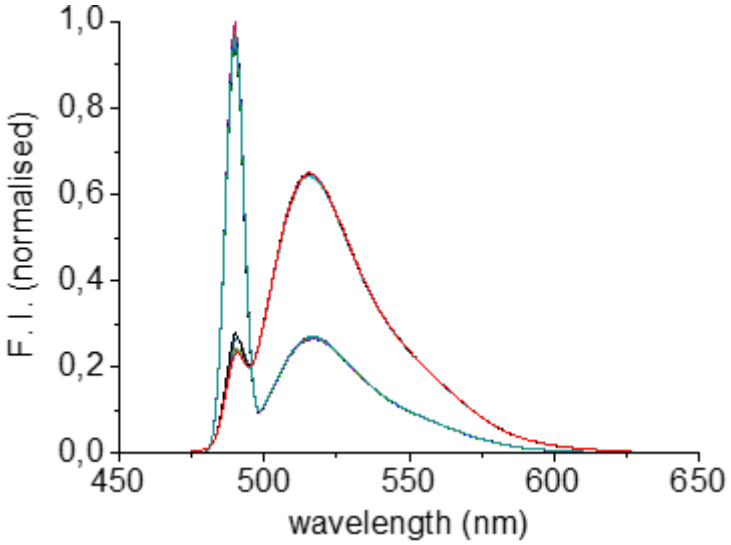


Figure S45. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **5b-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

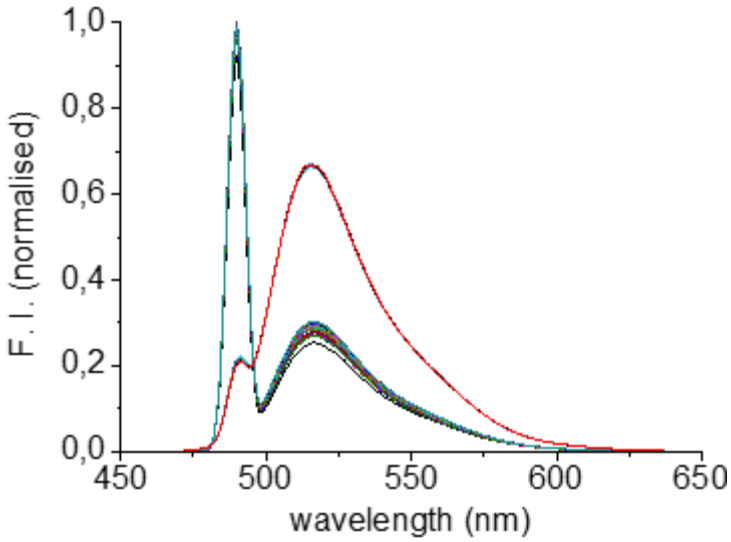


Figure S46. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **6a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 mL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

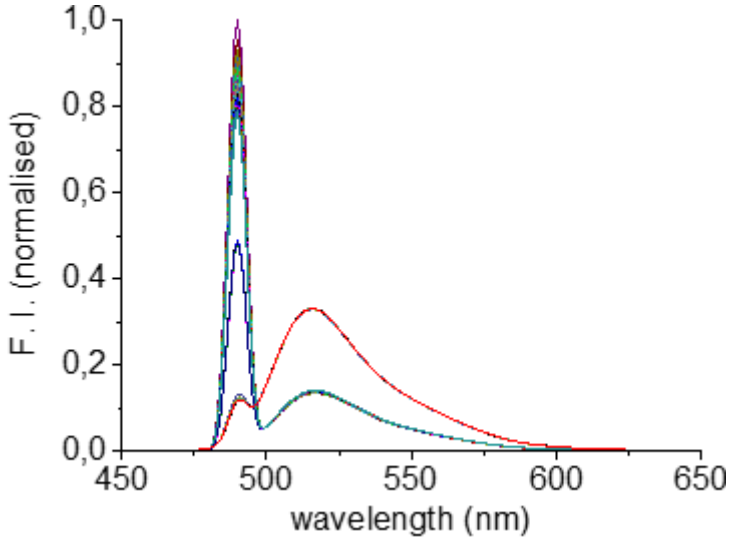


Figure S47. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **7a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 mL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

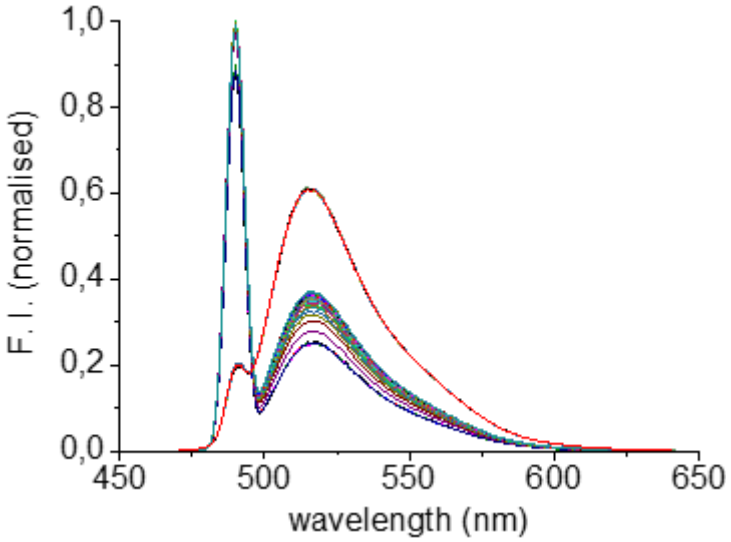


Figure S48. Carboxyfluorescein normalized fluorescence intensity recorded upon addition of **8a-Br** to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 mL) was added. Each spectrum represents the average of at least three trials, carried out with three batches of vesicles.

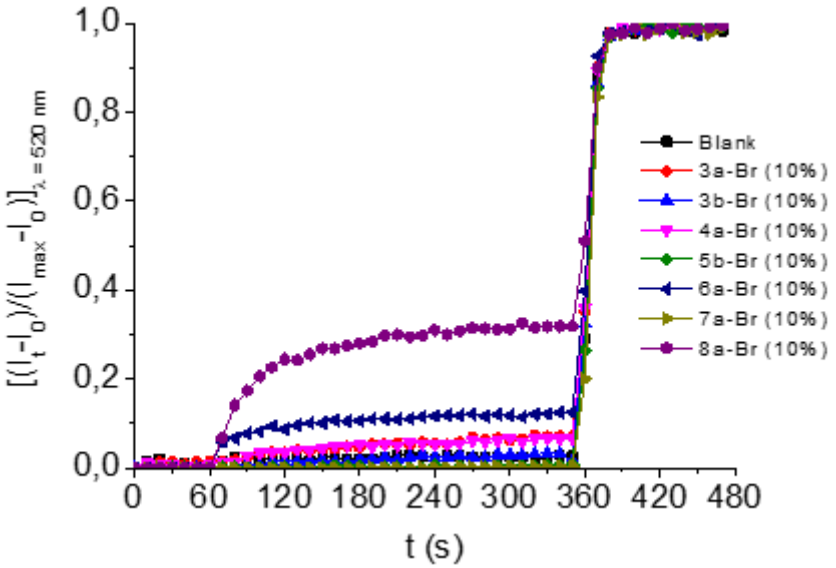


Figure S49. Carboxyfluorescein leakage observed upon addition of **3a-Br** (red trace), **3b-Br** (light blue trace), **4a-Br** (pink trace), **5b-Br** (green trace), **6a-Br** (dark blue trace), **7a-Br** (gold trace) and **8a-Br** (purple trace) to POPC vesicles (0.05 mM). Vesicles (loaded with 451 mM NaCl buffered at pH 7.2 with 20 mM phosphate, and containing 50 mM CF; I.S. 500 mM) were suspended in Na_2SO_4 (150 mM, buffered at pH 6.2 with 20 mM phosphate; I.S. 500 mM). At t = 60 s the compound was added (10% mol carrier to lipid), while at t = 360 s the detergent (20 μL) was added. The blank is DMSO (10 μL). Each trace represents the average of at least three trials, carried out with three batches of vesicles.

9) NMR spectra, ESI-MS (+) and DSC data

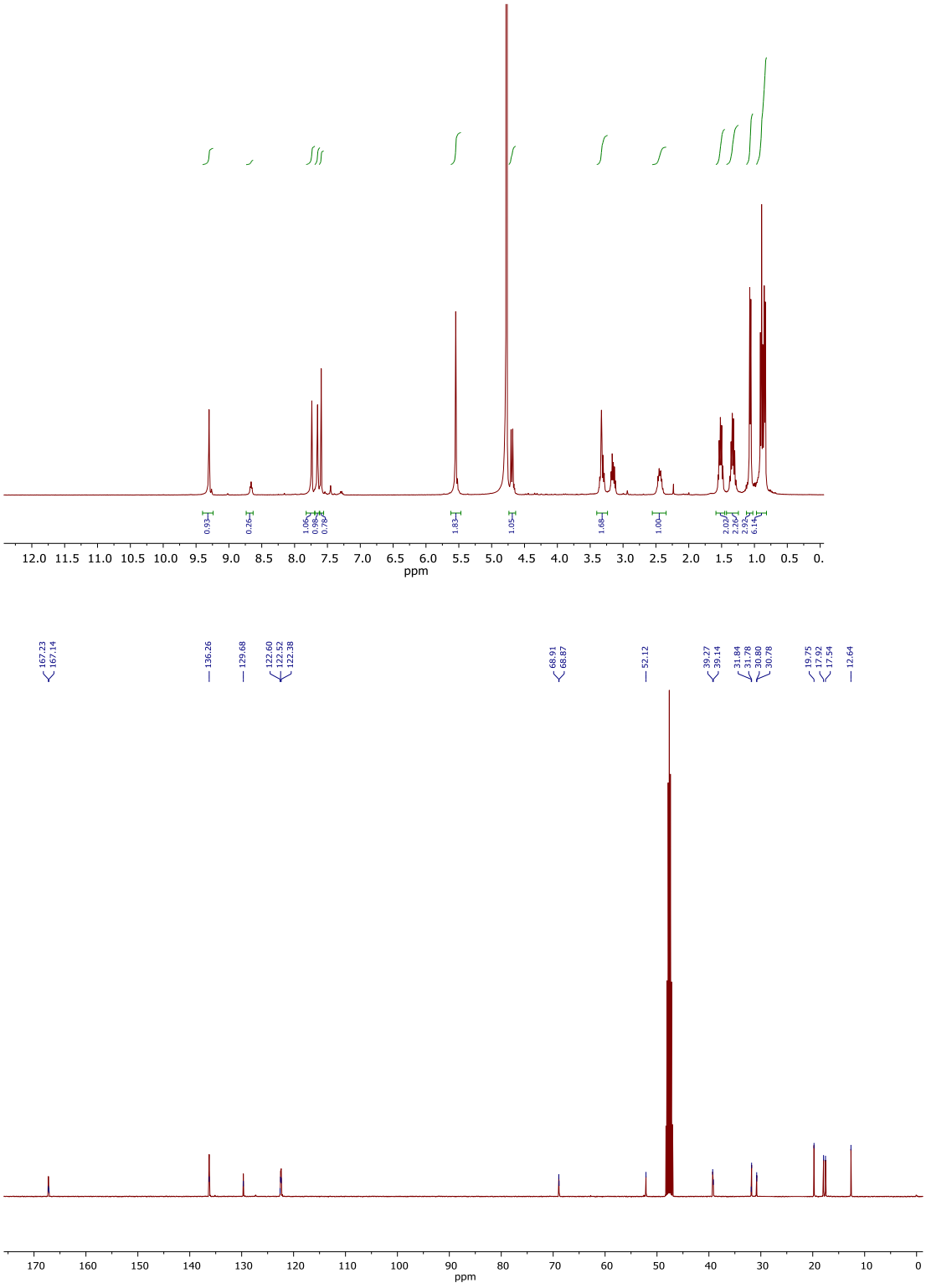


Figure S50. ^{1}H NMR (400 MHz, Methanol-d_4,) and ^{13}C-NMR (101 MHz, Methanol-d_4) of compound **4a-Br**

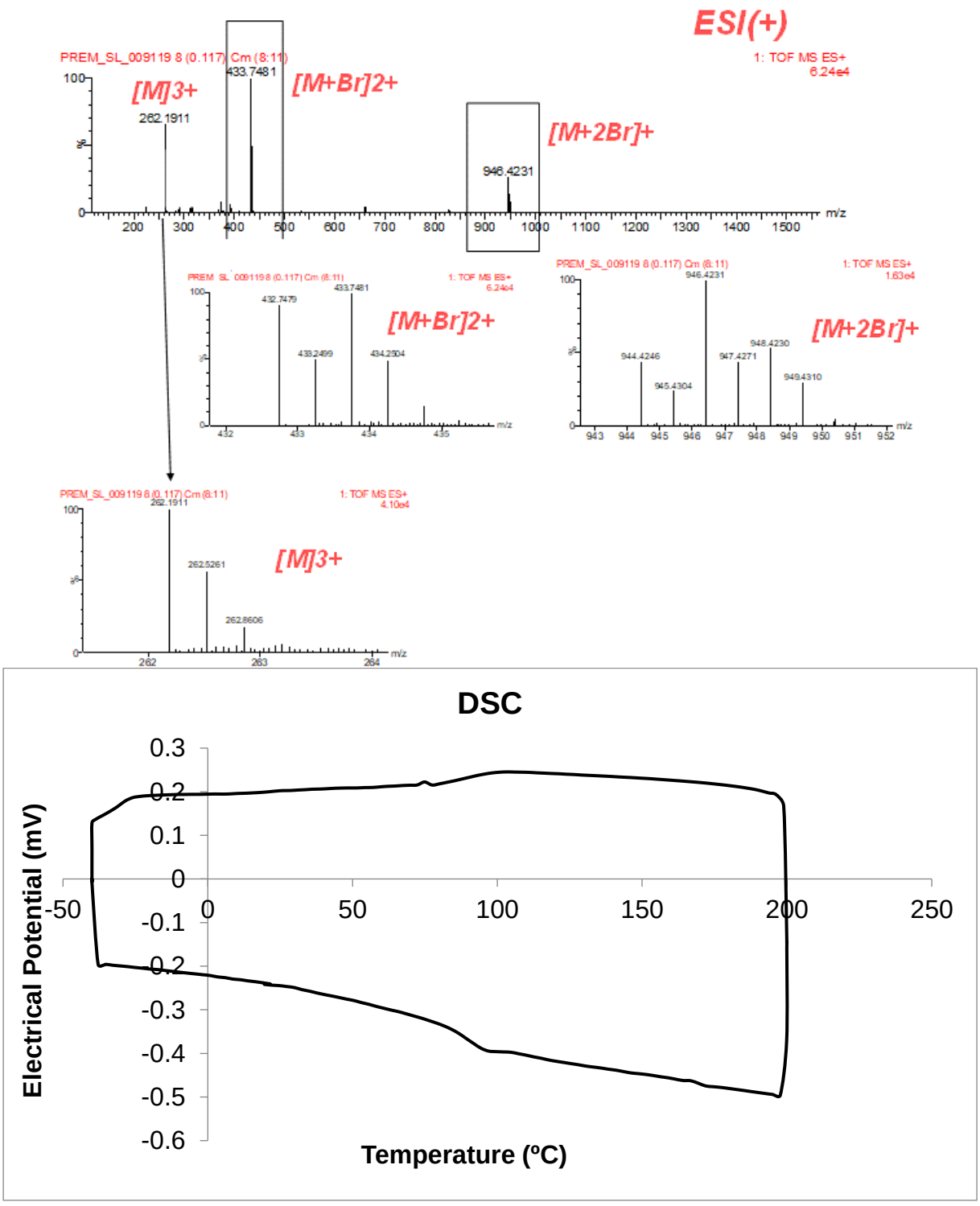


Figure S51. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **4a-Br.**

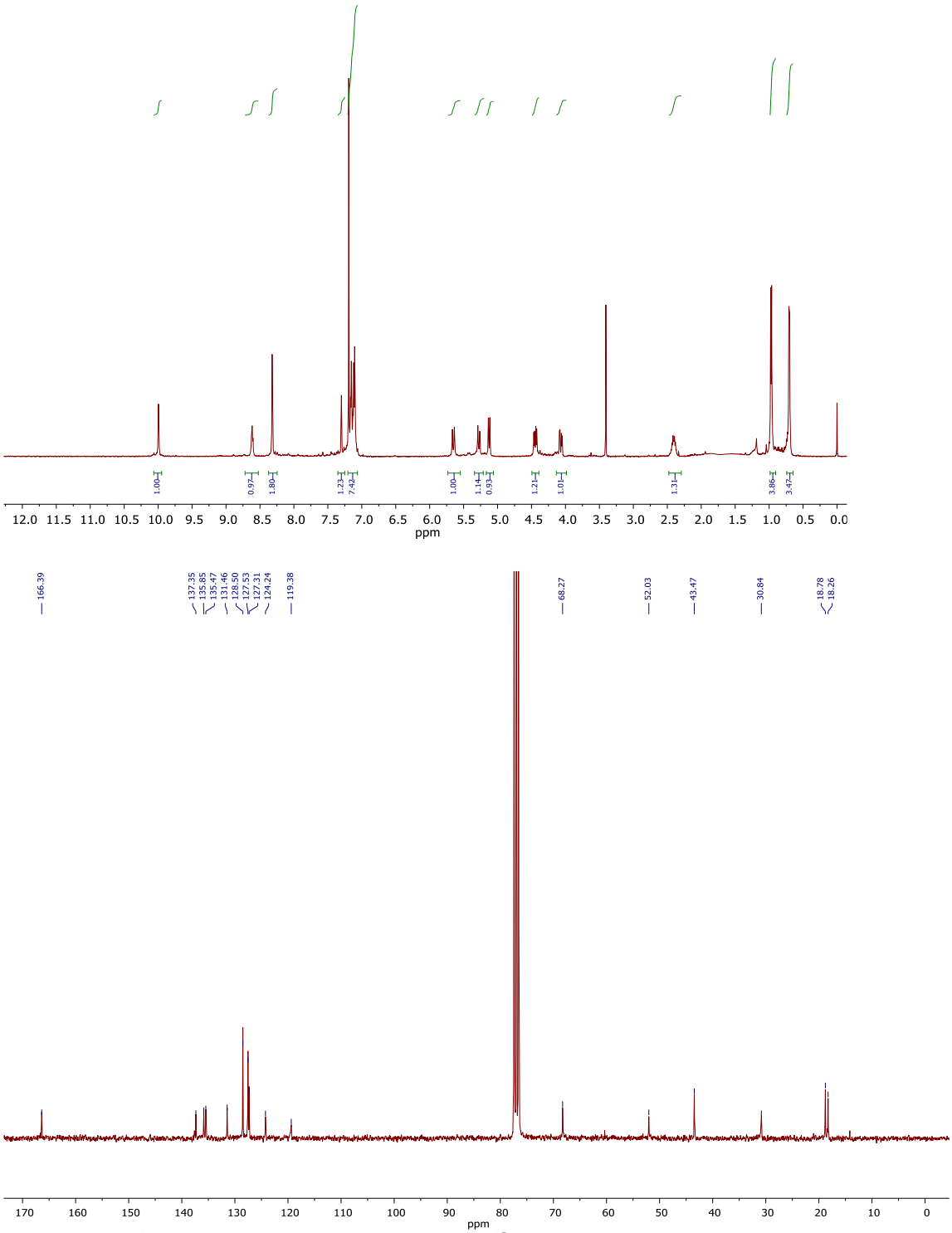
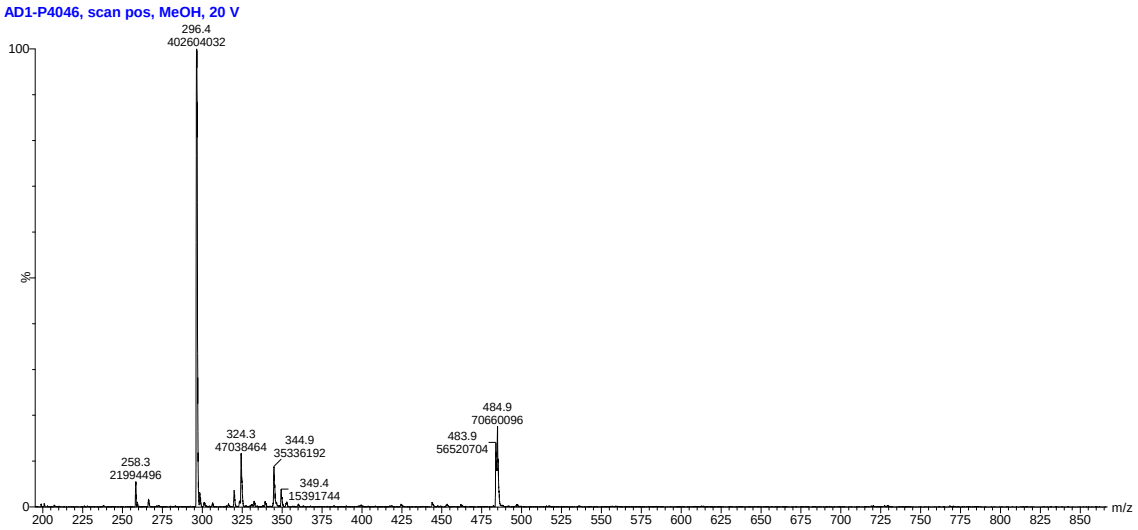


Figure S52. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$) of compound **6a-Br**



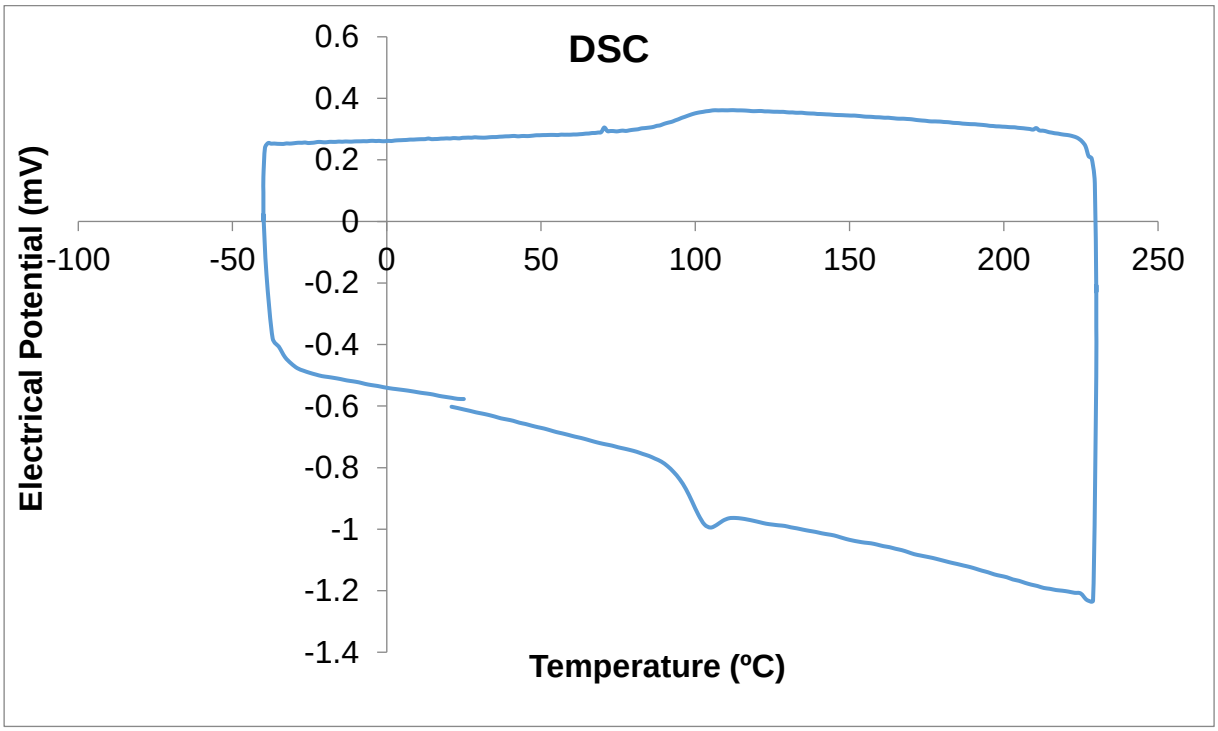


Figure S53. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **6a-Br.**

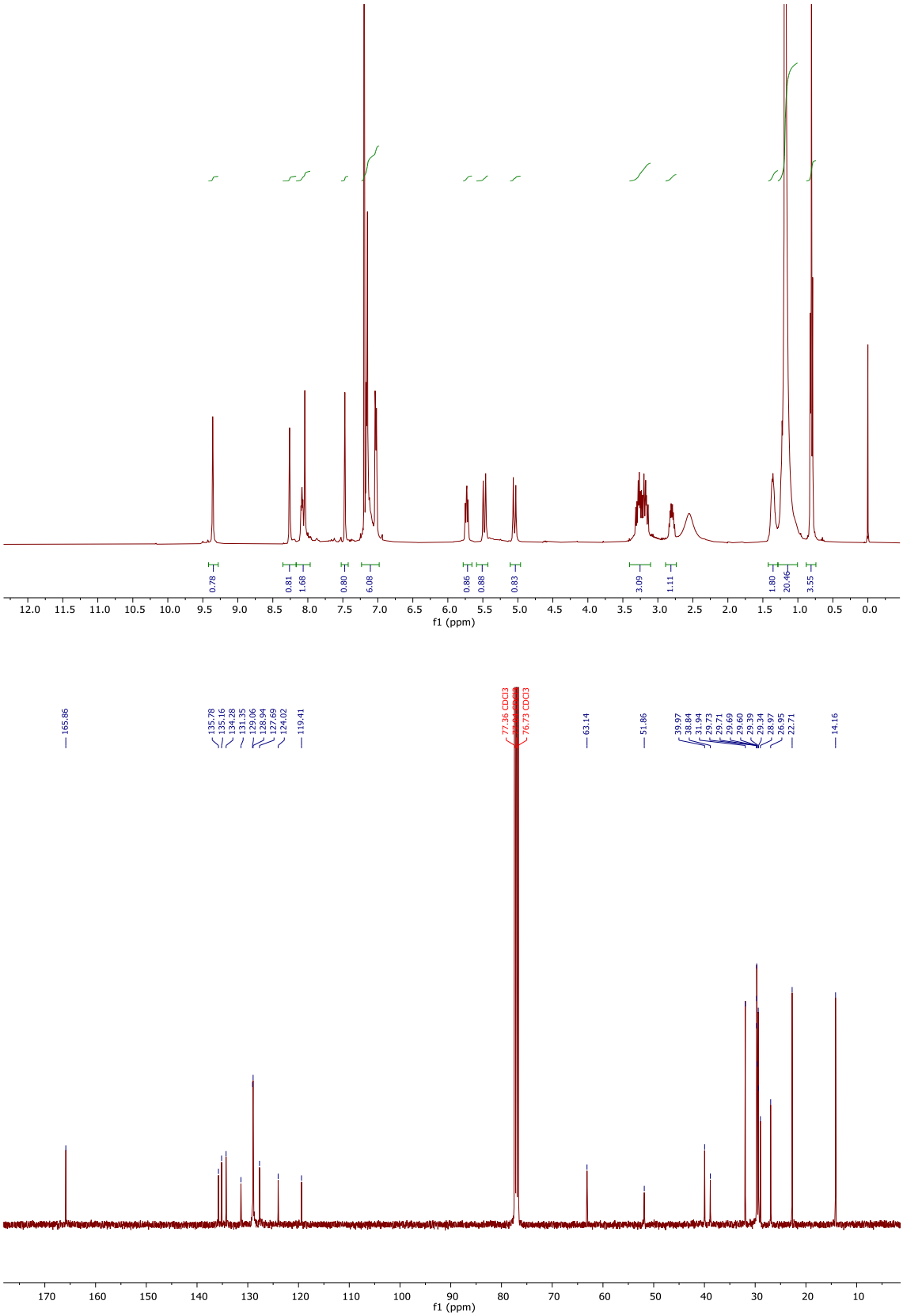


Figure S54. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **7a-Br**

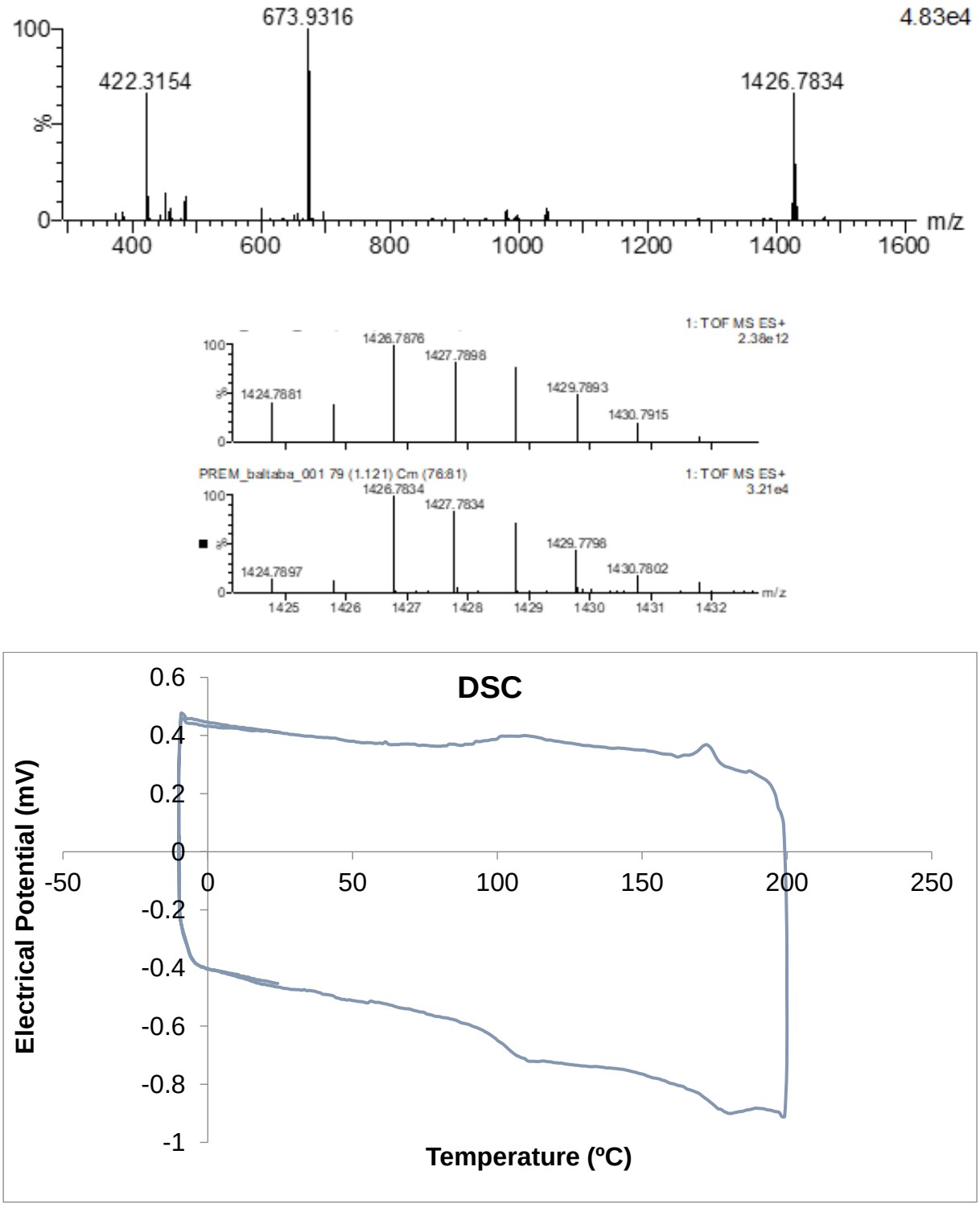


Figure S55. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **7a-Br.**

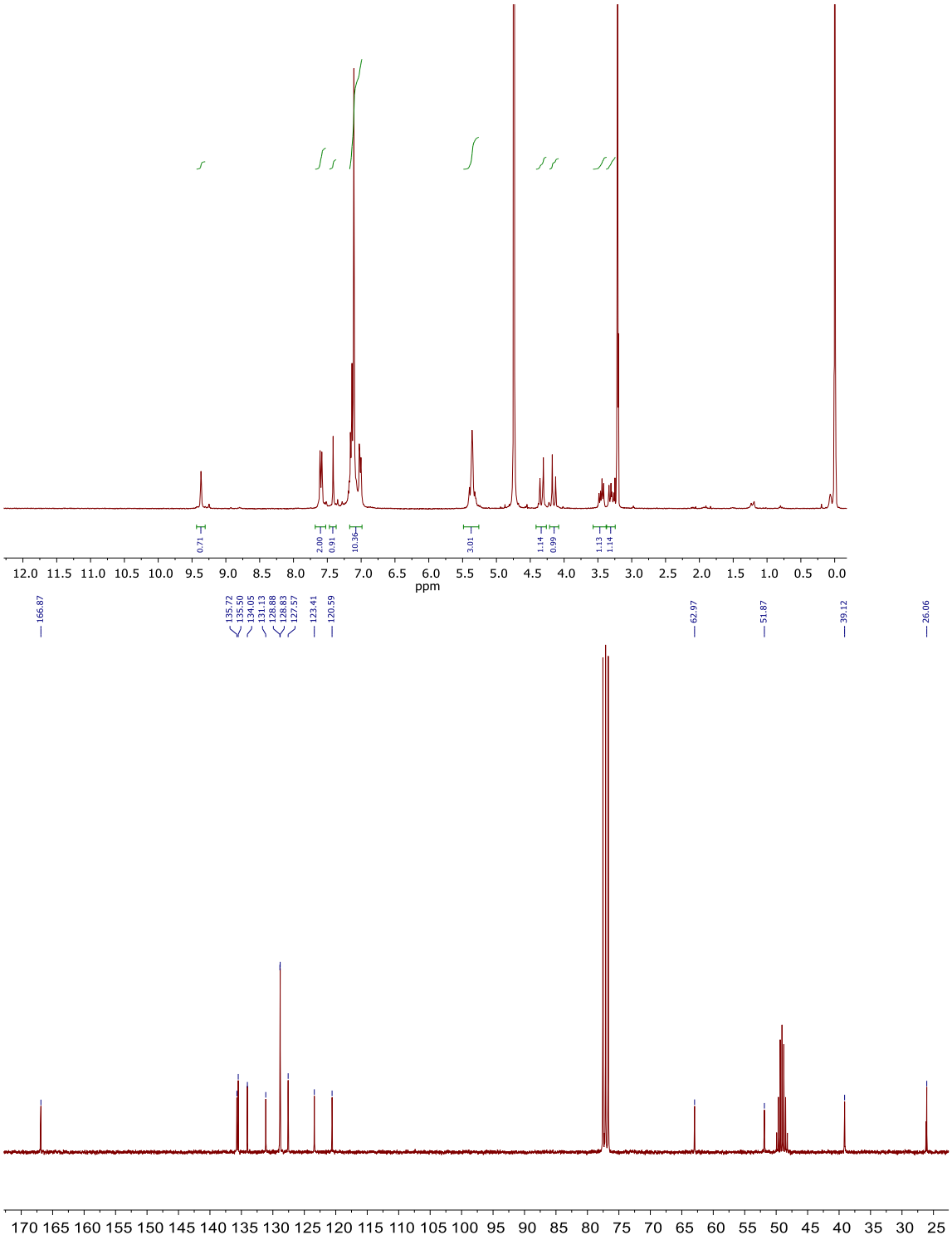


Figure S56. ^{1}H NMR (400 MHz, methanol-d_4/$CDCl_3$) and ^{13}C-NMR (75 MHz, methanol-d_4/$CDCl_3$) of compound **8a-Br.**

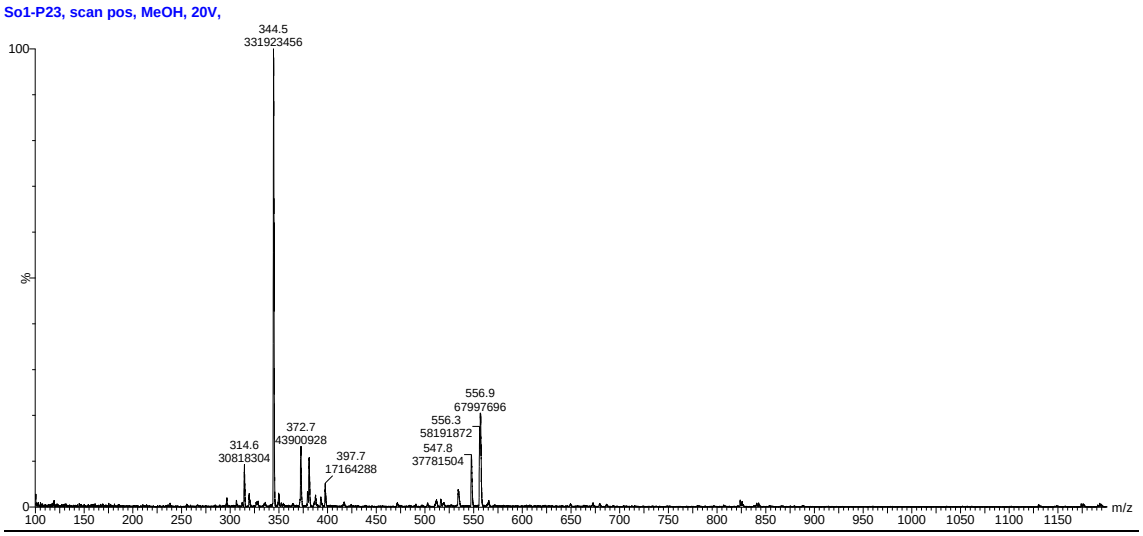


Figure S57. ESI-MS (+) of compound **8a-Br.**

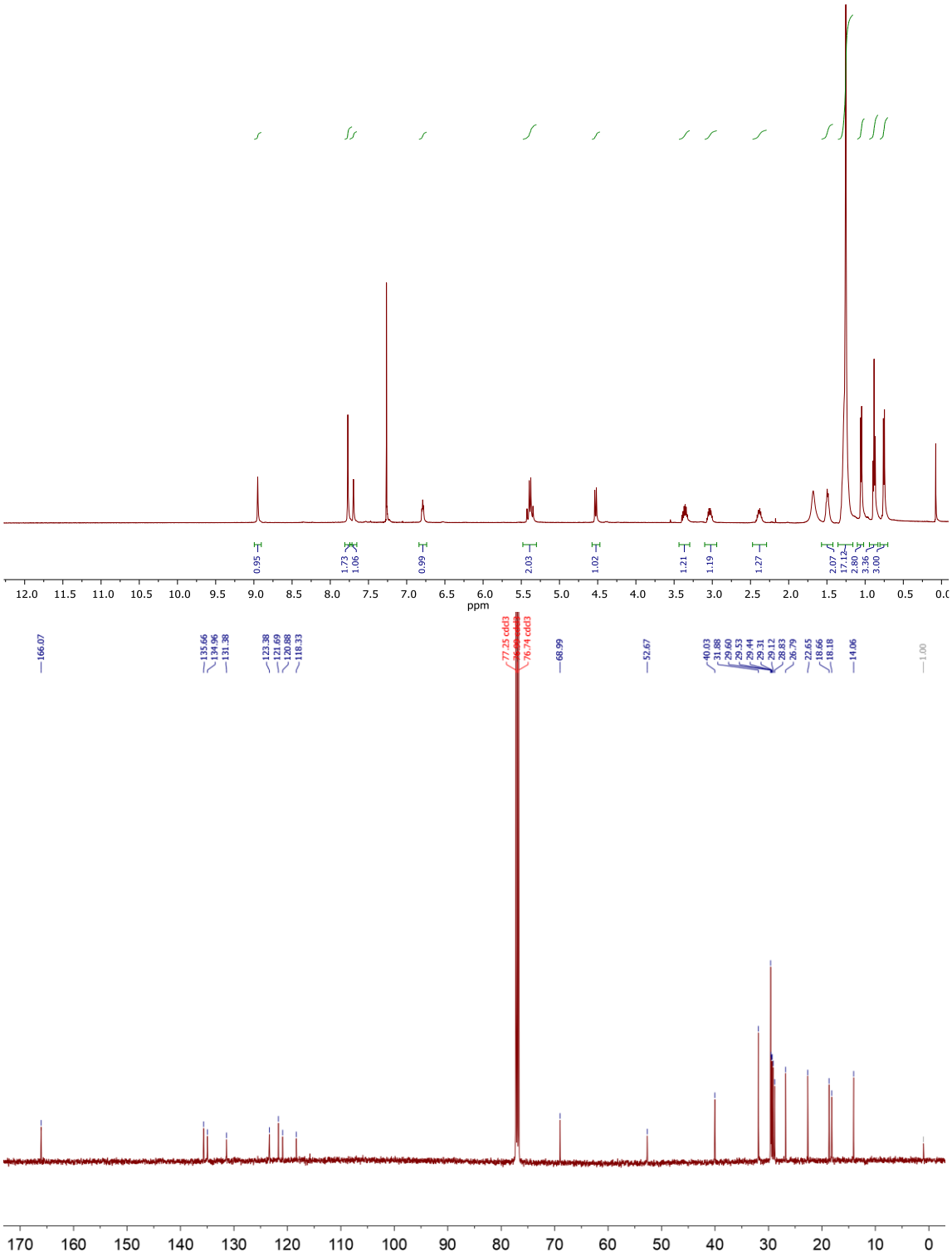


Figure S58. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (126 MHz, $CDCl_3$) of compound **3a-NTf$_2$.**

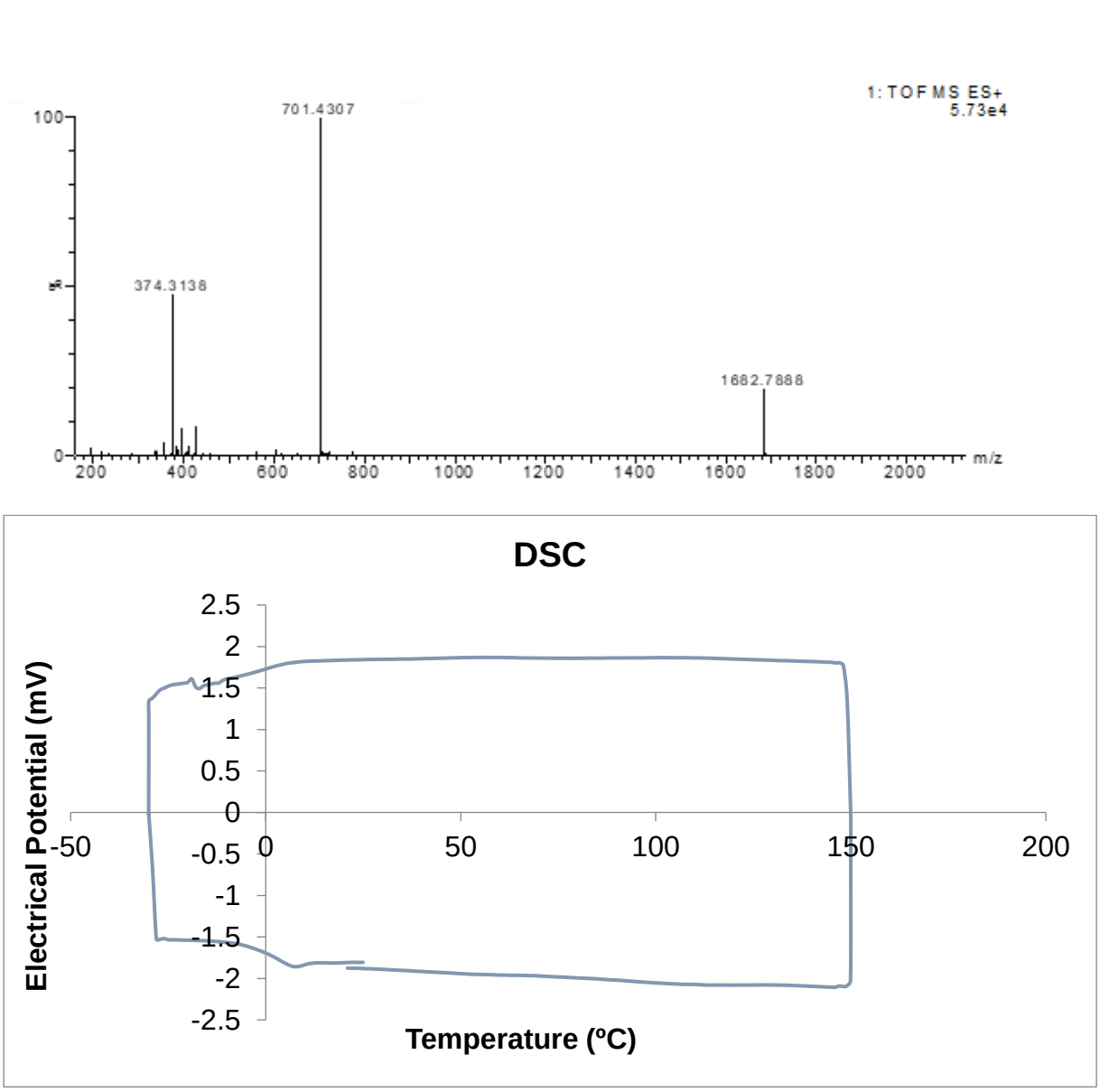


Figure S59. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **3a-NTf$_2$.**

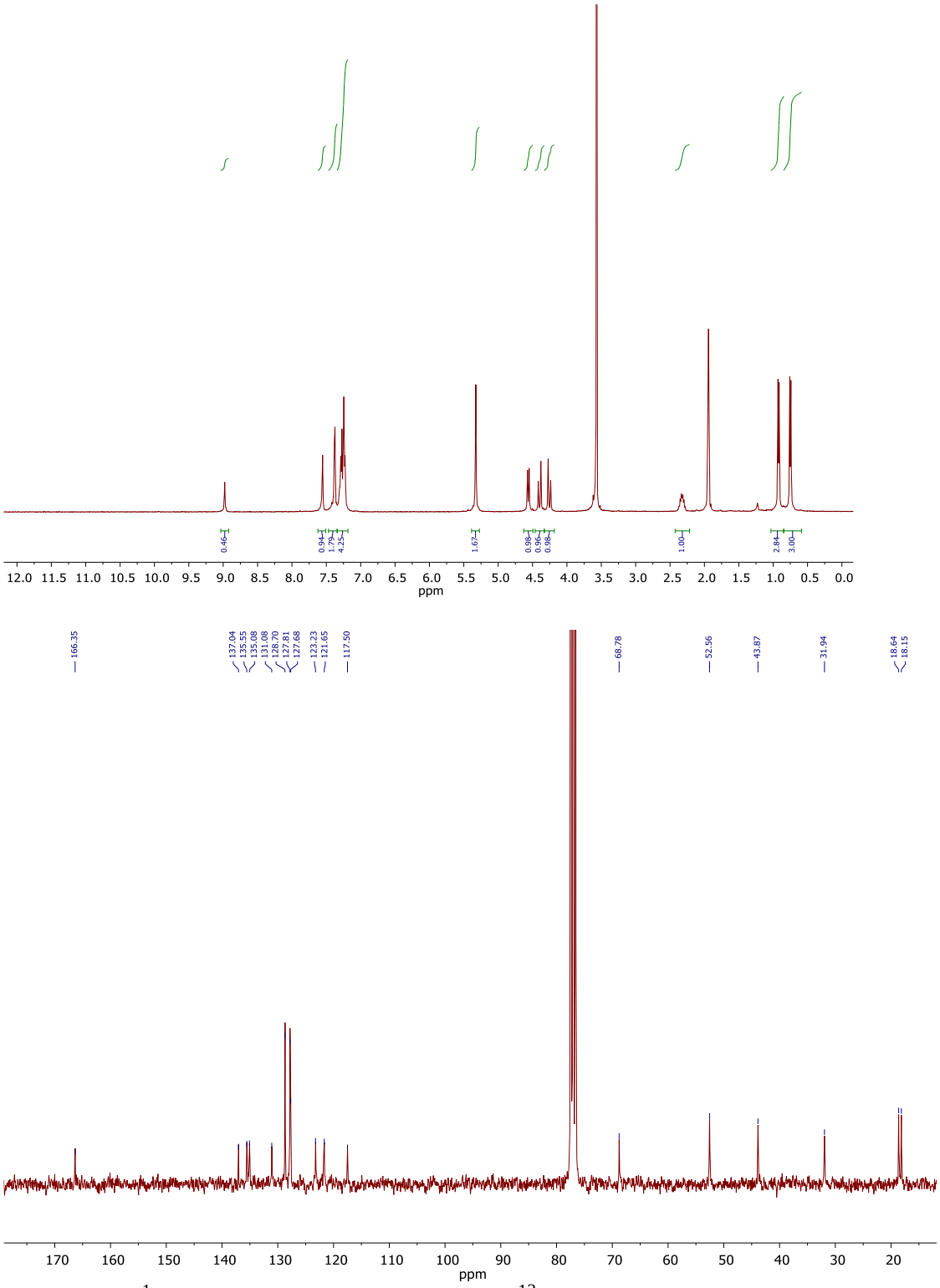
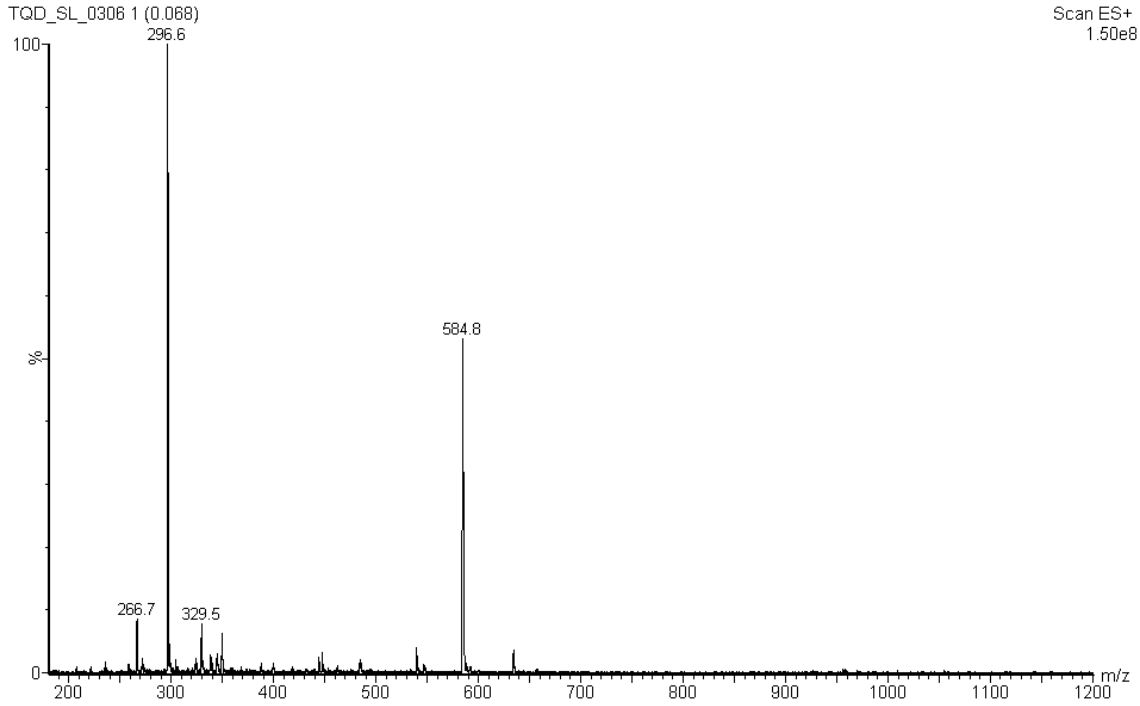


Figure S60. ^{1}H NMR (400 MHz, ACN-d_3) and ^{13}C-NMR (75 MHz, $CDCl_3$) of compound **6a-NTf$_2$.**



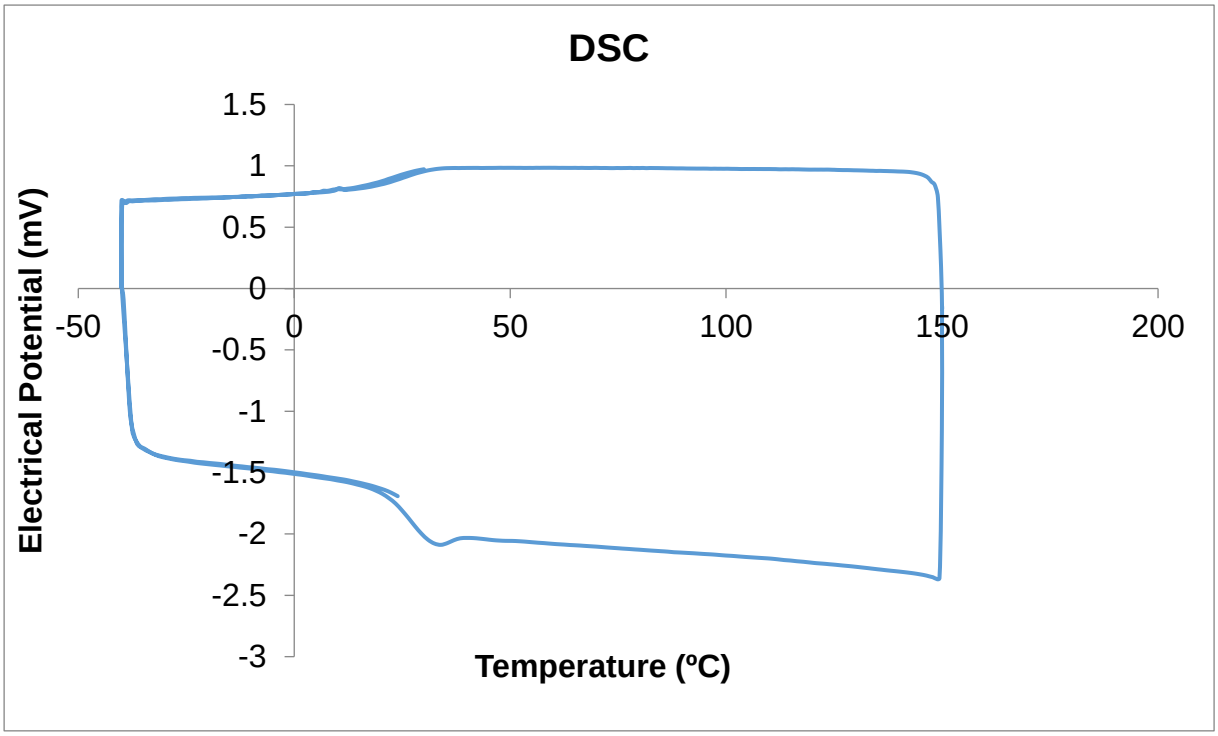


Figure S61. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **6a-NTf$_2$.**

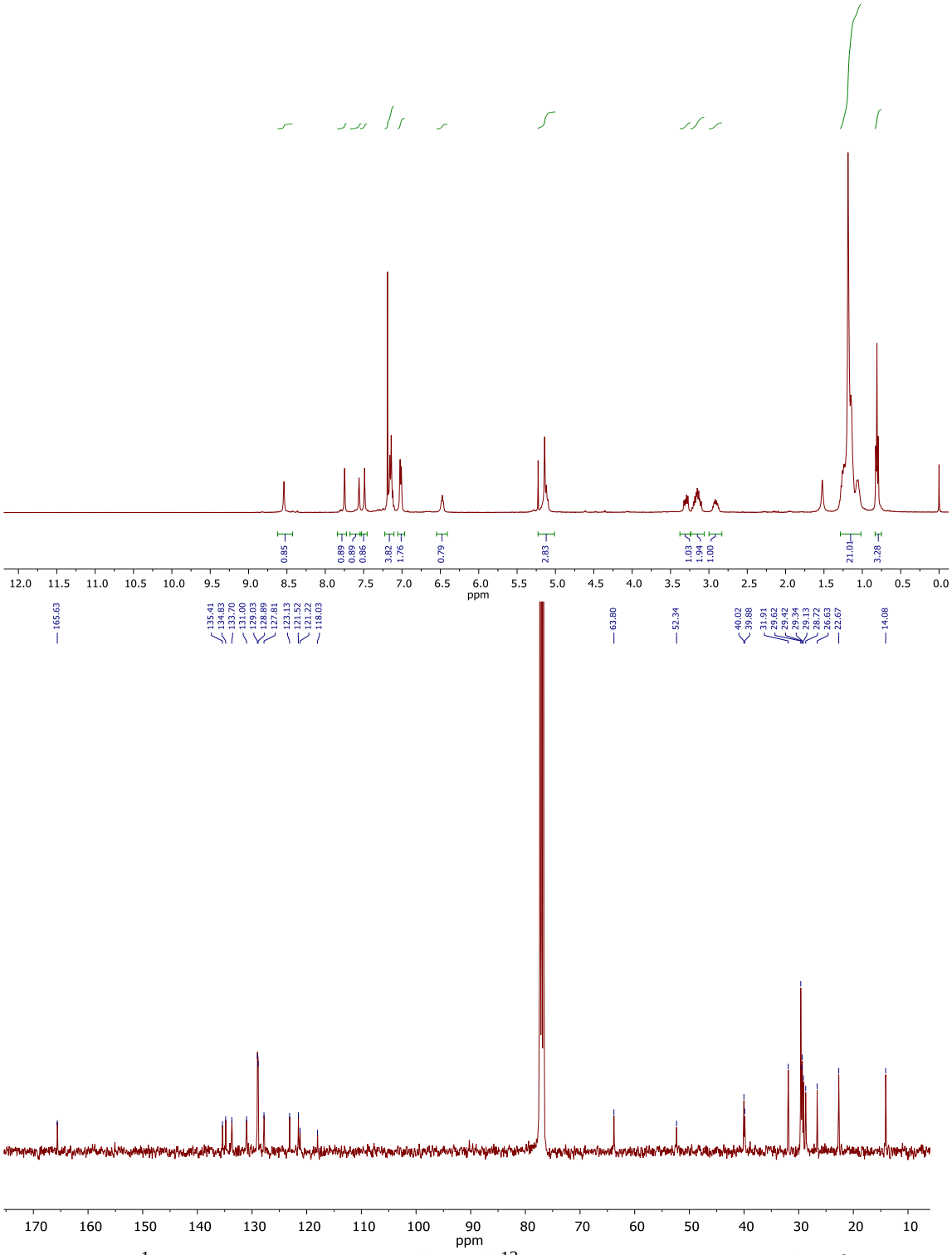


Figure S62. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (101 MHz, $CDCl_3$) of compound **7a-NTf$_2$.**

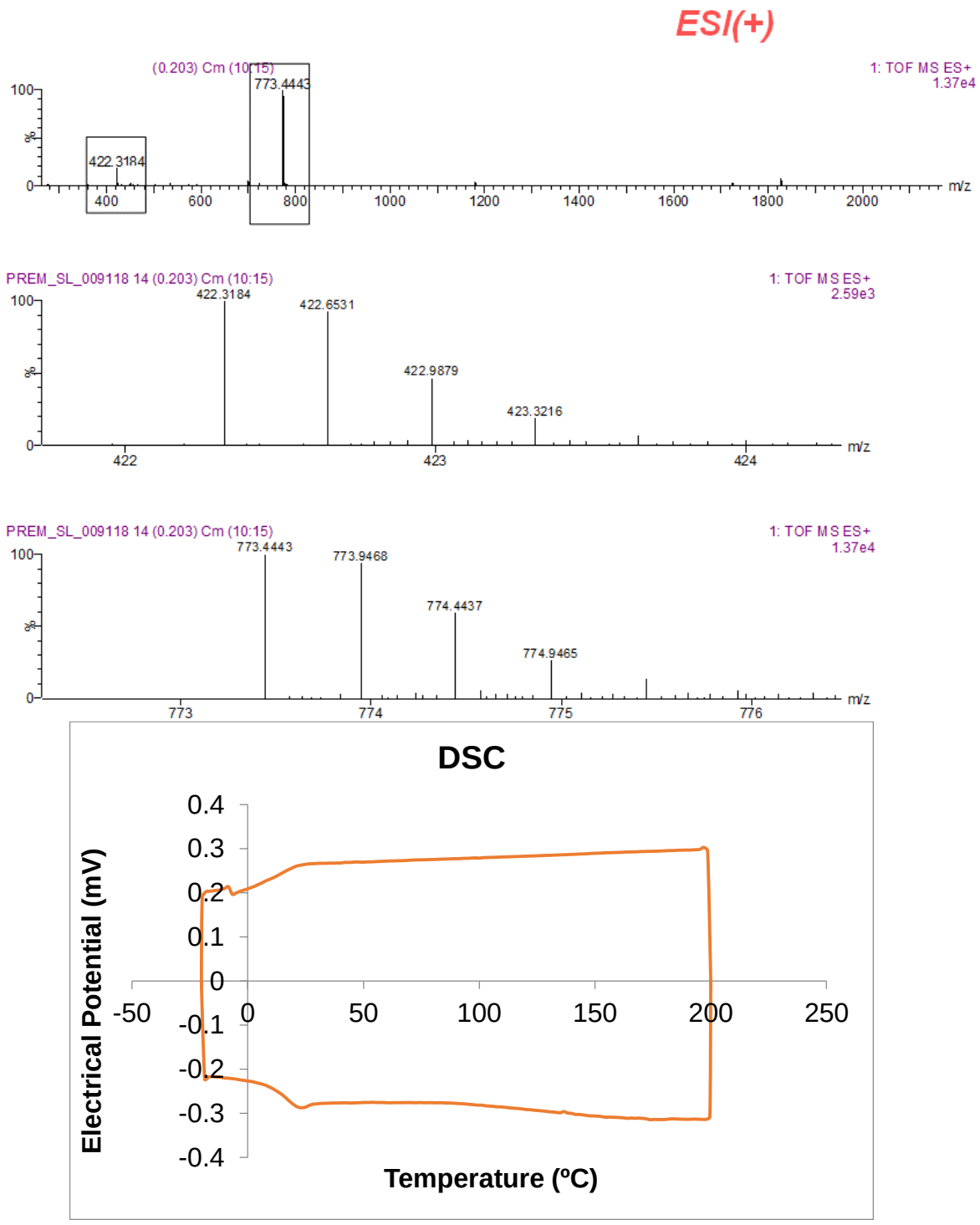


Figure S63. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **7a-NTf$_2$.**

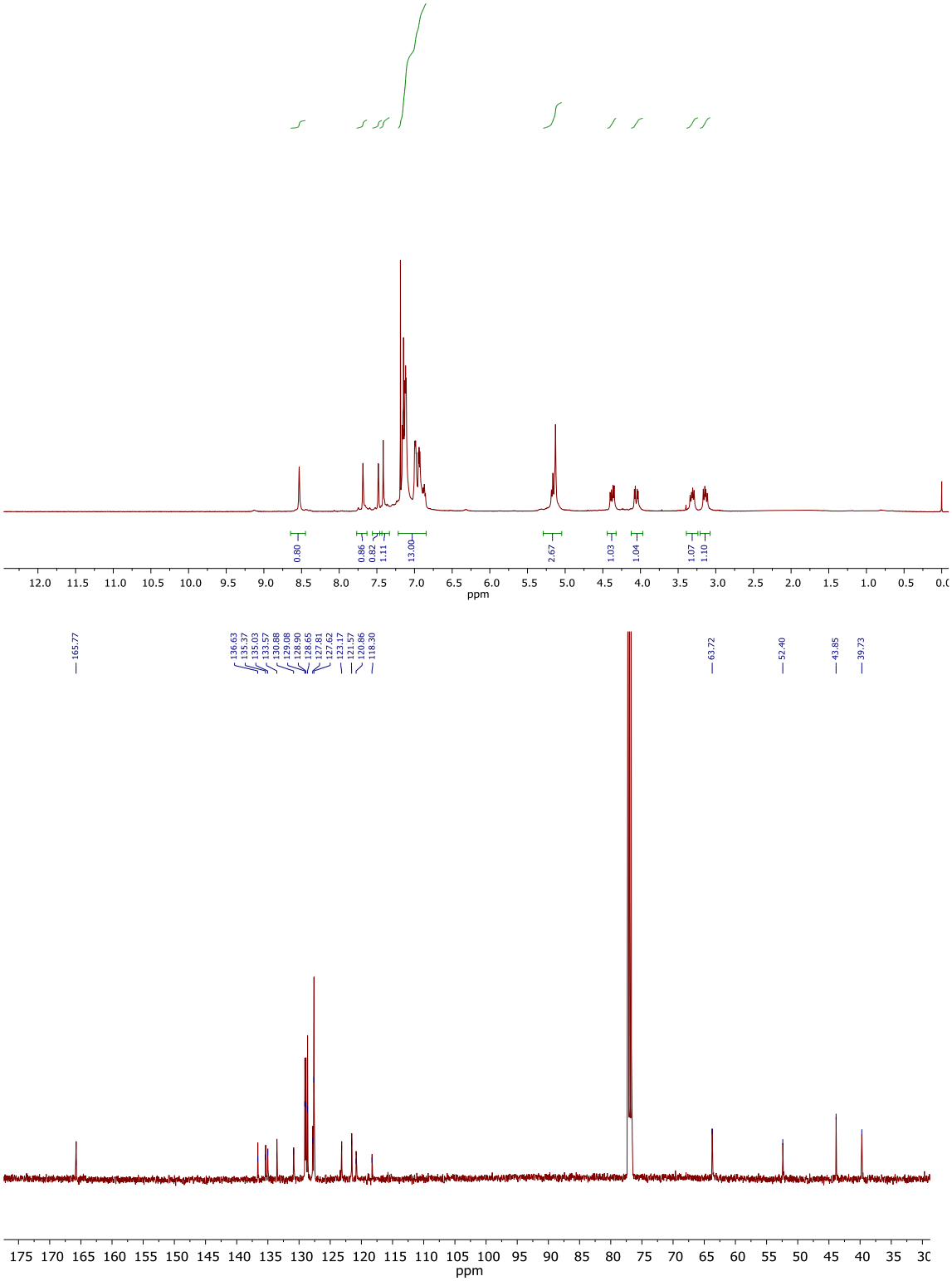
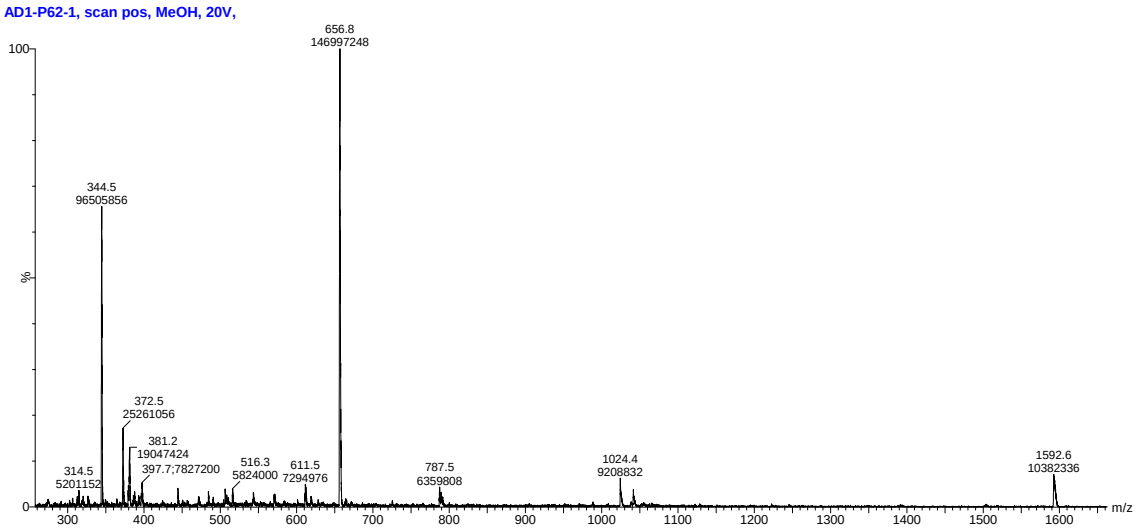


Figure S64. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (126 MHz, $CDCl_3$) of compound **8a-NTf$_2$.**



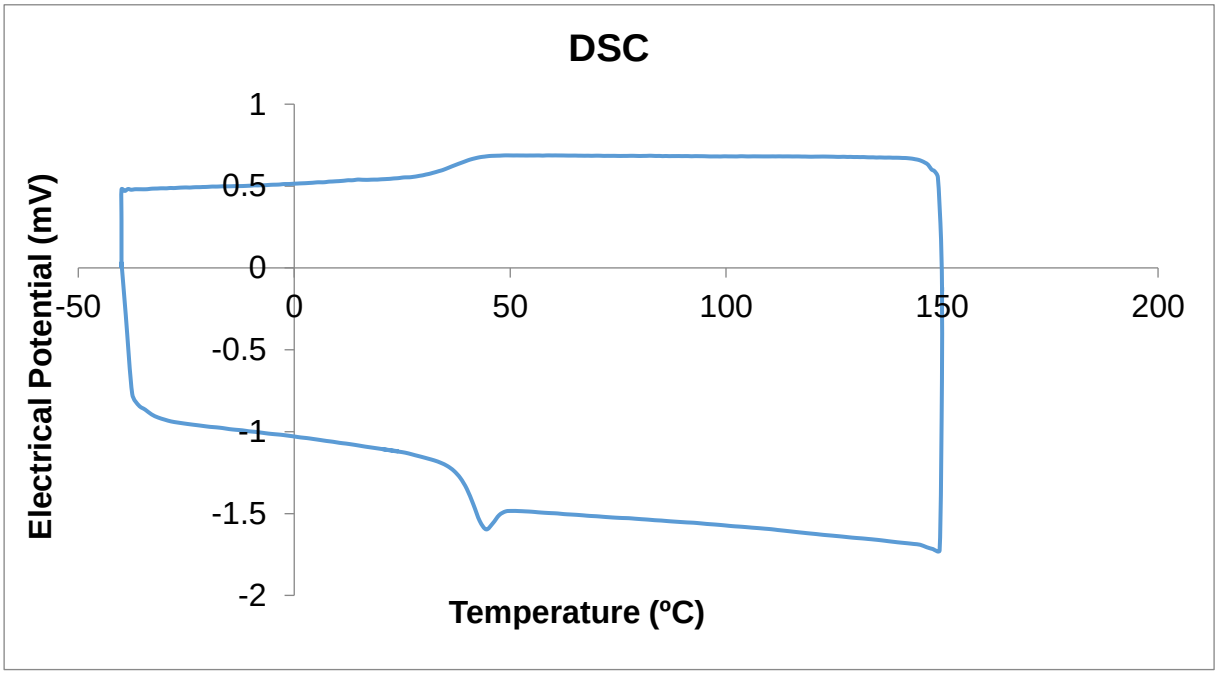


Figure S65. ESI-MS (+) and DSC (second heating and cooling cycle) of compound **8a-NTf$_2$.**