Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

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Deciphering Aromatic Oligoamide Foldamer–DNA Interactions**

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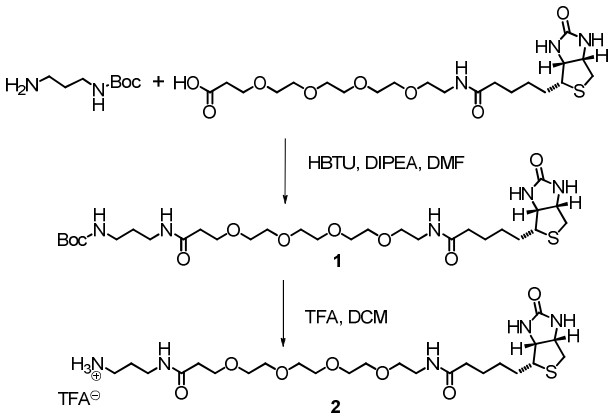
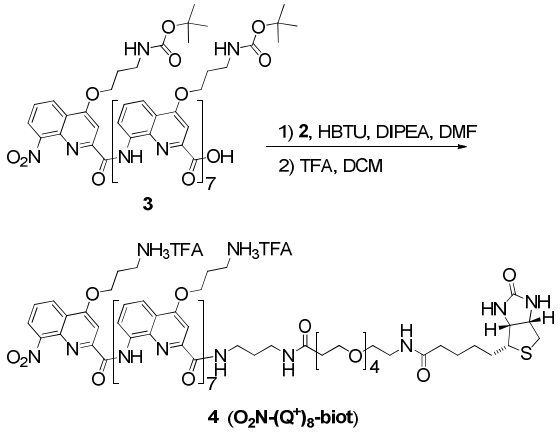
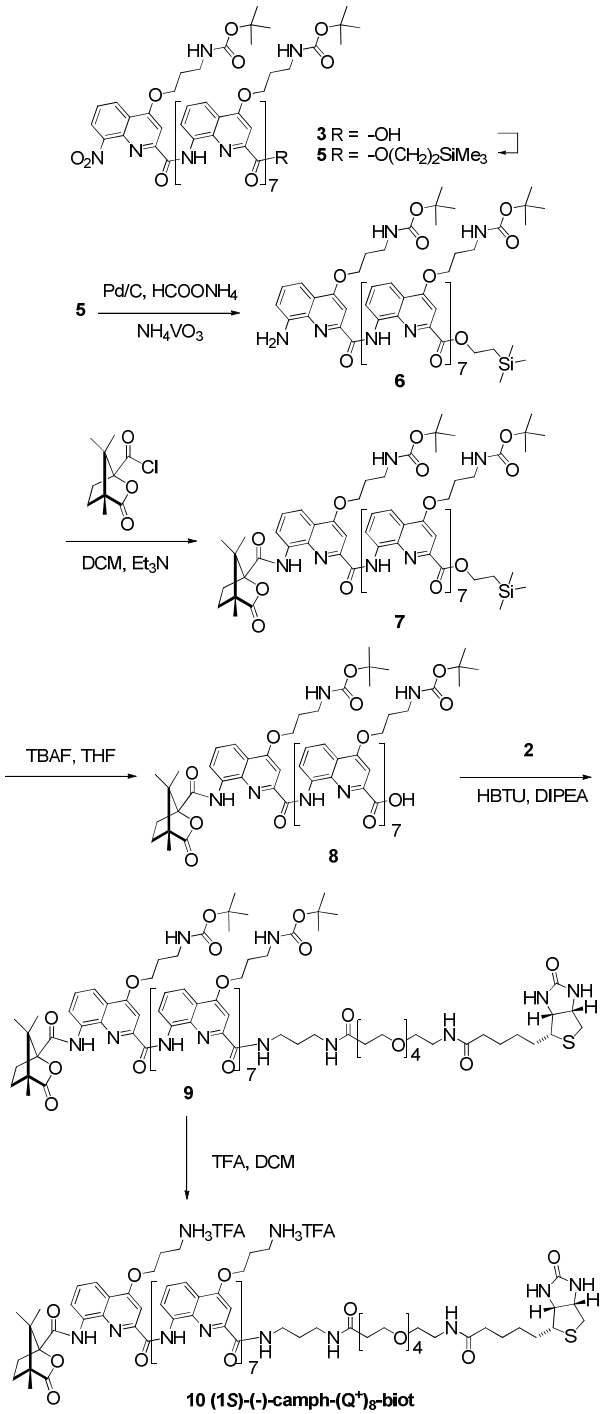
1. Synthetic Schemes



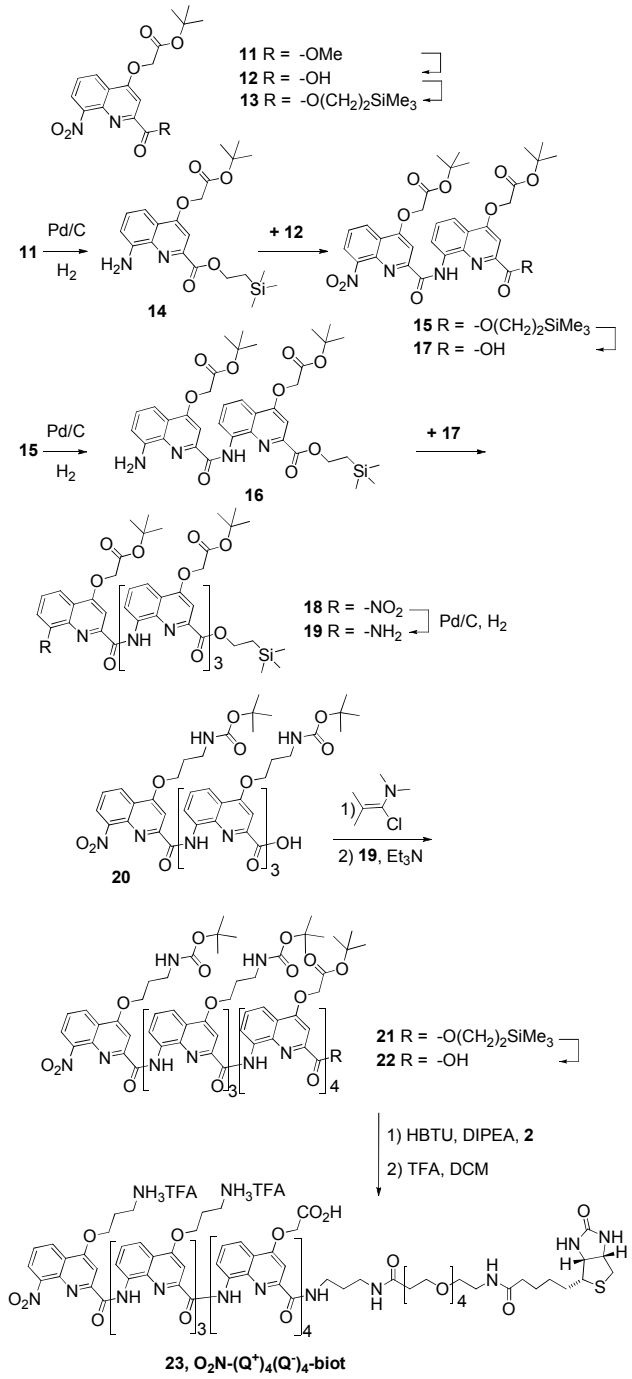
Scheme S1



Scheme S2



Scheme S3



Scheme S4

2. Investigation of aptamer and foldamer sequences

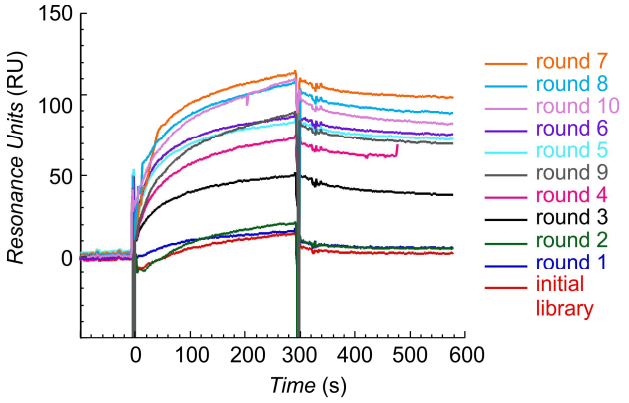


Figure S1. SPR sensorgrams in the selection buffer (20 mM HEPES pH 7.4, 140 mM potassium acetate, 20 mM sodium acetate and 3 mM magnesium acetate) of the DNA pool against O_2N-$(\mathbf{Q^+})_8$-**biot** immobilized on the sensorchip after each selection round.

```
7-1    TGGGGGGGTTGGTGGTTGTCCTTTCTTAC
7-11  TTCTCCTCGCCTGATCCCGCTTTTTCTTTC
7-20              TTCCCTCTCGTTCTTTATGTTTGGCCTAGT
7-29     GCGCTCTTTTATCCTCGTTCTTCTTGTTCA
7-41                  GCAAGTTCTTTCGTTTTTGGTGGTCGGTCG
10-1                GGCGGCCTTCTTGGTACCGAATTTCCTTTG
10-6              GGAGGTGGATTTCTTGTTCGGTGGTGGTGG
10-8     GGGATTTTCTCTCATTGTCTTTCTTGCTCC
10-11             GTAGTTCGCCCTTCTTCATCTTGCTTTTAC
10-13         GCCTCTTGTCTTCACCTTCTTATTCATCGG
10-19           GGCGGCGGGTTCTTCTTATTTCTTCACTCG
10-21          CGATTCTCTTTCGTTCTTTCTGTGTCCTTG
10-22    TTGGCCAACCCTCTTCCTTTTTCTTTTTGG
10-23  TCGTTGCTGGCCAACACTCTCTTTCTTTTG
10-25     GCAAAGTTGGGTGGTGGTGTTCTTCTTCTC
10-36    TGTATAGGCCAACCCTCTCTTTCTTTTTGG
10-38    CGGTCCCTGTACTTGGTTTTTTCTTCGTGT
10-40   GGTCCGATTCGGCCTTGGGGTTTCTTTTTG
10-45  CAAGAGGGGGGTGGGCGGTGGTTTCTTTTC
10-48      GTTCAGAGGCGAGCGTCTTTCTTCCTTCTC
10-55           CTGTTTTCACTCCTTCTTCTTTCACTTTTG
10-60                        GTTCTTCCCCTGTTTTGTATGGAGTTTCAG

7-30     GTATGATGGTTACTGCGTTTTCCGCTCGTG
7-41         GCAAGTTCTTTCGTTTTTGGTGGTCGGTCG
7-48                  CGGTTTTTCCTCTTGTCCTTATCCCTCCTG
7-59                  TTGTTTTTGGGTGGGTTGGTGGGTAATGTG
10-9       GAGGGTCTATTTTTGTTTTTCTCATCTTCA
10-18        GTTTCCACGTGTGTTTTACCCCCCTCTCG
10-24          GCGAGACGTCGTTTTTCATCACACATTCGG
10-38     CGGTCCCTGTACTTGGTTTTTTCTTCGTGT
10-42                  CGTTTTTGGGTGGAGGGTTGGGTGTCGTCG
10-43                  CGTTTTGCCCTCCCATCTGCGTCTTCTATC
10-55                 CTGTTTTCACTCCTTCTTCTTTCACTTTTG
10-59        CTAGCCTCTATCGTTTTTTTTCATGCCCTTC
10-60         GTTCTTCCCCTGTTTTGTATGGAGTTTCAG
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Figure S2. Aptamer sequences featuring a short conserved TTCT or GTTTT segment but no apparent secondary structure. Some of these sequences also are potential G-quadruplex forming (Figure 1)

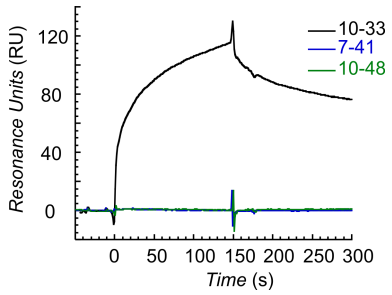

Figure S3. SPR sensorgrams of a G-rich aptamer sequence (**10-33**) and of aptamer sequences featuring a short conserved a TTCT (**10-48**) or GTTTT (**7-41**) motif, against O_2N–(**Q**$^+$)$_8$–**biot**.

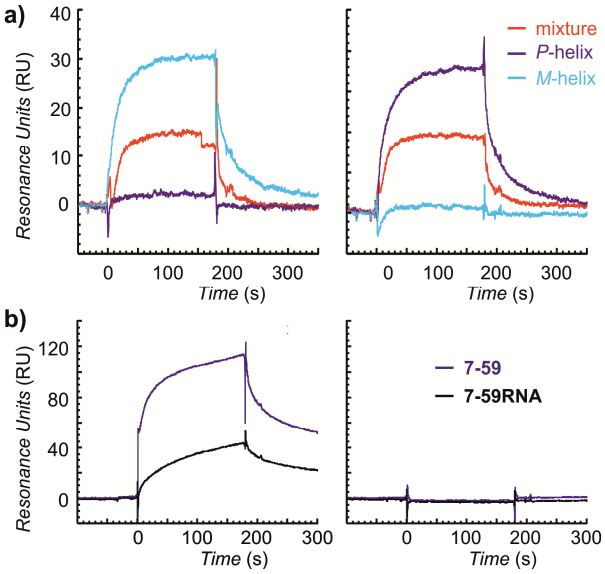

Figure S4. a) SPR sensorgrams of *D*-DNA **7-59-2G** (left) and *L*-DNA **7-59-2G** (right) against (1*S*)-(–)-**camph**-(**Q**$^+$)$_8$-**biot** (*P*-helix), (1*R*)-(+)-**camph**-(**Q**$^+$)$_8$-**biot** (*M*-helix) or a 1:1 mixture of the two. b) SPR sensorgrams of **7-59** and **7-59RNA** against O_2N–(**Q**$^+$)$_8$–**biot** (left) and O_2N–(**Q**$^+$)$_4$(**Q**$^-$)$_4$–**biot** (right).

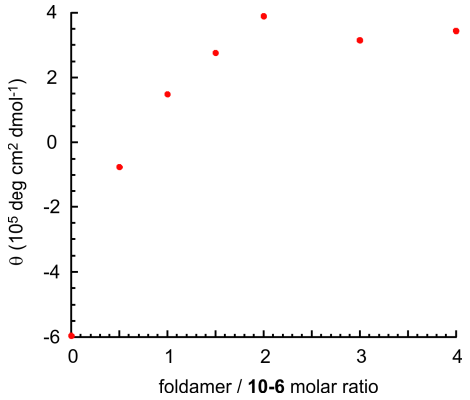

Figure S5. CD titration curve of **10-6** by O_2N-(**Q**$^+$)$_8$-OH representing changes in ellipticity monitored at 263 nm upon adding the foldamer.

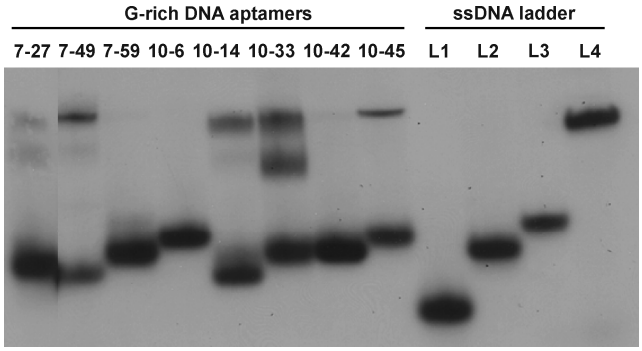

Figure S6. Electrophoretic analysis of quadruplex-forming aptamers on a 8% polyacrylamide in a TRIS buffer gel supplemented with 20 mM KCl. Single stranded DNA having 16, 30, 36 and 77 nucleotides respectively were used as markers (L1-L4).

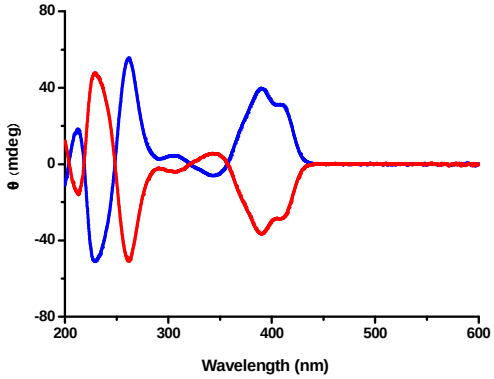

Figure S7. CD spectra of (1*S*)-(–)-**camph**-(**Q**$^+$)$_8$-**biot** (*P*-helix, blue line) and (1*R*)-(+)-**camph**-(**Q**$^+$)$_8$-**biot** (*M*-helix, red line) at 14 μM in H_2O at 20℃.

Table S1. Summary of the sequence, G-quadruplex structure and interactions with various foldamers of G-rich DNA aptamers and one RNA analogue. Some striking features are highlighted in blue.

			SPR Interaction			
Entry	Sequence 5'→ 3'	G-quadruplex structure	**O_2N-$(Q^+)_8$-biot**	**O_2N-$(Q^+)_4(Q^-)_4$-biot**	**(1S)-(-)-camph-$(Q+)_8$-biot**	**(1R)-(+)-camph-$(Q+)_8$-biot**
7-27	TGGCTGCTTGGTGGGGGGTTGGGTATGTTG	parallel	+	–	–	–
7-49	GACTGACTTGGGGTGGTGGGGGGGTCCTCC	parallel	+	–	–	–
10-45	CAAGAGGGGGGTGGGCGGTGGTTTCTTTTC	parallel	+	–	–	–
10-6	GGAGGTGGATTTCTTGTTCGGTGGTGGTGG	anti-parallel	+	–	–	–
10-14	GAACAGAGGGGGTGGGTGGTGGTTGTGTA	parallel	+	–	–	–
10-33	GGGTTTGCATCAGGGGGGTGGGTGGAGGTT	parallel	+	–	–	–
10-42	CGTTTTTGGGTGGAGGGTTGGGTGTCGTCG	parallel	+	–	–	–
10-45	CAAGAGGGGGGTGGGCGGTGGTTTCTTTTC	parallel	+	–	–	–
7-59	TTGTTTTTGGGTGGGTTGGTGGGTAATGTG	parallel	+	–	–	–
7-59-RNA	UUGUUUUUGGGUGGGUUGGUGGGUAAUGUG	parallel	+	–	–	–
7-59-short	TTGGGTGGGTTGGTGGGTA	parallel	+	–	–	–
7-59-3G	TTGGGTGGGTTGGGTGGGTA	parallel	+	+	–	–
7-59-2G (*D*-DNA)	TTGGTGGTTGGTGGTA	parallel	+	–	–	**+**
7-59-2G (*L*-DNA)	TTGGTGGTTGGTGGTA	parallel	+	–	**+**	-

3. Experimental section

Oligonucleotides. The single stranded DNA library was purchased from Eurogentec. Each strand comprises fixed sequences at each extremity for the purpose of PCR amplification and a central random sequence of 30 nucleotides The overall sequences reads: $^{5'}$GCCTGTTGTGAGCCTCCTGTCGAA-N_{30}-TTGAGCGTTTATTCTTGTCTCCC$^{3'}$. The DNA aptamer sequences resulting from SELEX were purchased from Sigma-Aldrich, Eurofins MWG Operon, or Genecust Europe-labbx Luxemburg for the *L*-sequence. The RNA sequence of aptamer **7-59** was purchased from Thermoscientific. All oligonucleotides were purified by electrophoresis on denaturing polacrylamide gels.

Selection. Selection of DNA aptamers to foldamer O_2N–$(\mathbf{Q}^+)_8$–**biot** was performed using a DNA library having a 30 nucleotide random region. The initial round of selection started with 1.8 10^{14} DNA molecules (300 pmol). The DNA pool was heated at 70°C for 5 min in water, cooled down to 4°C for 4 min and left at room temperature for 15 min in the selection buffer (20 mM HEPES pH 7.4, 140 mM potassium acetate, 20 mM sodium acetate and 3 mM magnesium acetate). Prior to each selection round, a counterselection was performed against streptavidin magnetic beads alone (for the two first rounds) and against the biotinylated dimer O_2N–$(\mathbf{Q}^+)_2$–**biot** immobilized onto magnetic streptavidin beads (for all further rounds). The DNA pool was incubated for 30 min with free magnetic streptavidin beads or 10 pmol of O_2N–$(\mathbf{Q}^+)_2$–biot immobilized on beads. DNA candidates that were not retained at the counterselection step were then submitted to the selection during an incubation of 30 min with the foldamer O_2N–$(\mathbf{Q}^+)_8$–**biot** immobilized onto magnetic streptavidin beads at room temperature in a final volume of 100 µL in the selection buffer. The supernatant was magnetically separated from the beads that have captured DNA candidates complexed to biotinylated foldamers. The candidates were then eluted by heating 1 min at 75°C in water (100 µL). Selection conditions were made increasingly stringent throughout successive rounds upon reducing the concentration of both DNA and the foldamer from 300 to 48 pmol and from 10 to 1.6 pM, respectively. The two first rounds were carried out through a manual procedure and the others on an automated workstation

(TECAN Freedom EVO 150). To minimize unwanted backgound amplification, two types of beads were used: Dynabeads M-280 (Invitrogen) for the second round and streptavidin MagneSphere Paramagnetic beads (Promega) for all other rounds.

After each round of selection an enriched single stranded DNA library for the next round was generated by two different procedures. For the two manual rounds, single strands were obtained by PCR using heaviness-terminator-primer[S1] and for the automated rounds, we used asymmetric PCR with biotinylated reverse primer in lowest concentration. After PCR amplification, the products were filtered and incubated with streptavidin magnetic beads (Invitrogen) to separate biotinylated double strands and single strands without biotin.

Cloning and sequencing. DNA populations were amplified by PCR and dsDNAs were then cloned into a TOPO TA cloning vector (Invitrogen) and E. coli TOP 10 One Shot cells were transformed according to the manufacturer's instructions. PCR amplification was achieved on positive clones and PCR products were sequenced with BigDye Terminator version 3.1 Cycle Sequencing Kit (PE Applied Biosystem).

Melting temperature measurement and thermal difference spectra (TDS). Measurements were performed on an Uvikon XL spectrophotometer interface, with a Peltier effect device, using quartz cells of 10 mm optical path length. Samples were prepared at 1.5 or 10 μM in a cacodylate buffer (20 mM sodium cacodylate, 140 mM KCl (or LiCl), 20 mM NaCl, 3 mM $MgCl_2$, pH 7.4) using the same protocol as during the selection. Compared to the selection buffer, the cacodylate buffer contains cacodylate which replaces temperature-sensitive HEPES and chloride ions which replace acetate ions. Denaturation of the samples was achieved by increasing the temperature from 4°C to 95°C at 0.4°C/min and was monitored at 295 nm. Renaturation was then performed from 95°C to 4°C at 0.4°C/min. All results were baseline-corrected for signal contributions due to the buffer. The melting temperature T_m was defined as the maximum of the first derivative of the absorbance signal during the renaturation.

For TDS, absorbance spectra were recorded over a wavelength range of 220-330 nm at 4°C and 95°C. TDS was obtained by subtracting the 4°C spectrum from the 95°C spectrum.

Circular Dichroism (CD). CD spectra were recorded on a JASCO J-815 CD spectrometer using quartz cells of 10 mm optical path length. Scans were measured at 20°C, over a wavelength range of 230-320 nm, with a response time of 0.5 s and a scanning speed of 100 nm/min. The CD data represent an average of three scans. All CD were baseline-corrected for signal contributions due to the buffer. Samples were prepared at 1.5 μM in the cacodylate buffer (20 mM sodium cacodylate pH 7.4, 140 mM KCl, 20 mM NaCl, 3mM $MgCl_2$). CD experiments were achieved to follow the interactions between each cloned aptamer and the target foldamer by the addition of an increasing quantity of foldamer O_2N–$(\mathbf{Q}^+)_8$–OH to 1.5 μM of aptamer. Each CD spectrum was recorded 2h after each addition of foldamer.

Non denaturing gel electrophoresis. A 3 nmol aliquot of 5' end ^{32}P labelled DNA was loaded onto 8% acrylamide/ bisacrylamide (19/1) non-denaturing gel in a Tris buffer (50 mM TrisHCl, pH 7.4, 45 mM boric acid, 20 mM potassium acetate). Electrophoresis was performed at 4°C at 35 mA for 6h. The gel was fixed in 10% acetic acid-20% ethanol aqueous solution and dried at 80°C for 1h. The radioactive bands were visualized by autoradiography with Fuji X-ray films RX (Fujifilm). Four ssDNA of 16, 30, 36 and 77 bases were used as a DNA ladder (L1, L2, L3 and L4, respectively).

Surface Plasmon Resonance (SPR). The real-time measurement of the interaction between the target foldamer and the selected DNA was performed on a BIAcore 3000 biosensor system. For control experiments, an unrelated DNA sequence was used (ATCTTTATGCAGTTCGCATCCCCTCGCATA). O_2N–$(\mathbf{Q}^+)_8$–**biot** was immobilized on a streptavidin modified sensorchip SAD 200m (Xantec). Interaction analyses were performed at 23°C on high salt selection buffer (20 mM sodium phosphate pH 7.4, 1M KCl, 20 mM NaCl, 3 mM $MgCl_2$, 0.005% surfactant P20). The potassium ions concentration was increased to 1 M compared to 140 mM in the selection buffer to avoid non specific electrostatic interactions between anionic DNA and the octacationic foldamer. All DNA samples were prepared at 1 μM in this buffer and injected for 3 min at a rate of 20 μL/min. A blank flow cell was used to check for non-specific binding of DNA on the sensorchip. The interaction was estimated by subtracting the response units of the blank flow cell from the response of the foldamer immobilized flow cell.

General procedures and materials for synthesis. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. $CHCl_3$, CH_2Cl_2 and diisopropylethylamine (DIPEA) were distilled from CaH_2 prior to use. NMR spectra were recorded on a Bruker Avance 300MHz Spectrometer, and the chemical shifts were reported in ppm and are calibrated against residual solvent signals of $CDCl_3$ (δ 7.26, 77.2) and DMSO-d_6 (δ 2.50, 39.4). Coupling constants are reported in hertz (Hz). Electrospray ionization (ESI) was obtained in the positive ion mode and matrix assisted laser desorption ionization time of flight (MALDI) mass spectra were obtained in positive ion mode using α-cyanohydroxycinnamic acid as a matrix. The BOC protecting groups were cleanly removed using 1:1 TFA/CH_2Cl_2 as described in reference S2. Compound **3** (O_2N-$(\mathbf{Q}^+)_8$-OH) was prepared according to the synthetic procedures reported previously.[S2] Compound **1-12** were prepared by using typical coupling and protection/deprotection reactions. (1*R*)-(+)-**camph**-$(\mathbf{Q}^+)_8$-**biot** (*M*-helix) was synthesized using the same protocol as (1*S*)-(–)-**camph**-$(\mathbf{Q}^+)_8$-**biot** (*P*-helix). Although their are not enantiomers (they both possess the same biotin group), the characteristics of these compounds are identical except for their CD spectra (see section 4).

Synthesis of compound 1. Boc-protected 1,3-diaminopropoane (47 mg, 0.27 mmol) was dissolved in anhydrous DMF (1 mL) and was added to a solution of biotin (100 mg, 0.20 mmol), HBTU (102 mg, 0.27 mmol), and DIPEA (115 mg, 0.89 mmol) in anhydrous DMF (1 mL). The reaction mixture was allowed to stir at room temperature for 36 h. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (20 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with $CHCl_3$/MeOH (5:1, v/v) to afford the pure product (115 mg, 88%). IR (KBr) ν (cm^{-1}): 3327, 3230, 2936, 1709, 1474; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.48 (m, 2H), 1.61-1.76 (m, 7H), 2.23 (t, 2H), 2.48 (t, 2H), 2.72-2.76 (m, 1H), 2.91-2.95 (m, 1H), 3.15 (m, 2H), 3.28 (q, 2H), 3.44 (q, 2H), 3.57 (t, 2H), 3.63-3.65 (m, 12H), 3.73 (t, 2H), 4.33 (m, 1H), 4.51 (m, 1H), 5.09 (m, 1H), 5.21 (m, 1H), 5.94 (m, 1H), 6.59 (m, 1H), 6.93 (m, 1H); HRMS (ESI): calcd for $[M+H]^+$ ($C_{29}H_{54}N_5O_9S$): 648.3642; Found: 648.3646.

Synthesis of compound 2. TFA (0.5 mL) was added to a solution of compound **1** (10 mg) in CH_2Cl_2 (0.5 mL) and the reaction mixture was allowed to stir at room temperature for 2 h. All volatiles were removed and the residue was dried under the vacuum line for 5 h to afford the product amine (TFA salt) as a colorless solid in quantitative yield. This product was not characterized and directly used for the next coupling reaction without further purification.

Synthesis of compound 4 (O_2N-$(Q^+)_8$-biot). Compound **2** (5.3 mg, 0.0080 mmol) dissolved in anhydrous DMF (0.5 mL) was added to a mixture solution of octamer acid **3** (20 mg, 0.0072 mmol),[S2] HBTU (5.4 mg, 0.0143 mmol) and DIPEA (3.7 mg, 0.0286 mmol) in anhydrous DMF (0.5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 2 days. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with $CHCl_3$/MeOH (15:1, v/v) to afford the pure coupling product as a yellow solid. This material was dissolved in TFA/CH_2Cl_2 (1:1, vol/vol, 1 mL) and the reaction mixture was allowed to stir at room temperature for 2 h. All volatiles were removed and the residue was dried under the vacuum line for 5 h to afford the product amine (TFA salt). The product was further purified by semi-preparative reverse phase HPLC to yield **4** as a yellow solid (15 mg, 90%). IR (KBr) ν (cm^{-1}): 3342, 3218, 2961, 2942, 2925, 2872, 2853, 1713, 1686, ,1594, 1572, 1540, 1535, 1508, 1475, 1467, 1460, 1419, 1396, 1383, 1357, 1329, 1263, 1211, 1114, 1054; UV (λ, ε, in H_2O): 321 nm, 2.3×10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (m, 2H), 1.27 (m, 3H), 1.44 (m, 3H), 1.65 (m, 2H), 1.86 (m, 1H), 2.00 (m, 2H), 2.28 (m, 16H), 2.74 (m, 3H), 3.10-3.31 (m, 38H), 4.03 (m, 4H), 4.24 (m, 10H), 4.45 (m, 6H), 6.01 (s, 1H), 6.26 (s, 1H), 6.30 (s, 1H), 6.33 (s, 1H), 6.37 (s, 1H), 6.39 (s, 1H), 6.51 (s, 1H), 6.53 (s, 1H), 6.92 (s, 1H), 7.02 (s, 1H), 7.09 (m, 2H), 7.24 (d, 1H, *J* = 7.2), 7.32-7.48 (m, 10H), 7.54-7.64 (m, 3H), 7.71-8.23 (m, 15H), 8.37 (d, 1H, *J* = 7.2), 10.85 (s, 1H), 10.89 (m, 2H), 10.98 (s, 1H), 11.04 (s, 1H), 11.06 (s, 1H), 11.34 (s, 1H); MALDI-TOF MS: calcd for $[M+H-8\times TFA]^+$ ($C_{128}H_{148}N_{29}O_{25}S$): 2523.09; Found: 2523.11; Purity: > 98% HPLC pure.

Synthesis of compound 5: The alcohol 2-(trimethylsilyl)ethanol (32 mg, 0.271 mmol) was added to a solution of octamer acid **3** (383 mg, 0.137 mmol),[S2] HBTU (62 mg, 0.163 mmol) and DIPEA (89 mg, 0.689 mmol) in anhydrous DMF (3 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 3 days. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/EtOAc (1:1, v/v) to afford the pure product as a yellow solid (370 mg, 93 %). IR (KBr) ν (cm^{-1}): 2962, 2922, 2873, 2853, 1687, 1593, 1572, 1540, 1535, 1508, 1464, 1460, 1413, 1395, 1385, 1356, 1330, 1262, 1213, 1114, 1053; UV (λ, ε in $CHCl_3$): 321 nm, 2.3×10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): δ –0.58 (s, 9H), 0.31 (t, 2H), 1.44 (m, 18H), 1.45 (s, 9H), 1.47 (m, 18H), 1.50 (s, 9H), 1.53 (m, 18H), 2.18-2.38 (m, 16H), 3.40-3.68 (m, 16H), 4.18-4.47 (m, 16H), 4.15-5.12 (m, 3H), 5.34-5.75 (m, 2H), 6.21 (s, 1H), 6.34 (s, 1H), 6.48 (s, 1H), 6.57 (m, 2H), 7.01 (s, 1H), 7.08 (s, 1H), 7.10 (s, 1H), 7.20-7.47 (m, 11H), 7.54-7.70 (m, 3H), 7.78-8.29 (m, 13H), 8.50 (s, 1H), 9.04 (s, 1H), 11.05 (m, 4H), 11.36 (s, 1H), 11.51 (s, 1H), 12.03 (s, 1H); MALDI-TOF MS: calcd for $[M+H]^+$ ($C_{149}H_{181}N_{24}O_{35}Si$): 2894.29; Found: 2894.58.

Synthesis of compound 6. To a solution of **5** (360 mg, 0.124 mmol) in ethyl acetate (20 mL) and ethanol (5 mL), 10% Pd/C (20 mg) and a catalytic amount of was added at room temperature. The mixture was heated to reflux (90°C bath temperature) and a solution of ammonium formate (5 g) in water (10 mL) was added to the reaction mixture slowly in 3 intervals (each interval is about 15 minutes). Stirring under reflux was continued for 24 h. The mixture was then cooled down and filtered over celite. The filtrate was concentrated to remove all volatiles, taken up in $CHCl_3$ and washed with brine. The organic layer was dried with $MgSO_4$, and filtered over a small layer of silica. The filtrate was concentrated and dried under vacuum to yield a yellow solid (330 mg, 93%); ^1H NMR (300 MHz, $CDCl_3$): δ –0.54 (s, 9H), 0.33 (t, 2H, *J* = 7.2), 1.44 (s, 9H), 1.47 (m, 18H), 1.49 (s, 9H), 1.51 (s, 9H), 1.54 (m, 27H), 2.11-2.38 (m, 16H), 3.22 (m, 2H), 3.36-3.69 (m, 16H), 3.97-4.48 (m, 16H), 4.85-5.11 (m, 3H), 5.38 (m, 2H), 5.67 (m, 1H), 6.21 (s, 1H), 6.35 (s, 1H), 6.50-6.58 (m, 4H), 6.83 (m, 1H), 6.89 (m, 1H), 7.01 (m, 2H), 7.20-7.31 (m, 13H), 7.39 (m, 1H), 7.49 (m, 2H), 7.68 (m, 3H), 7.77-7.89 (m, 4H), 7.99 (m, 3H), 8.14 (m, 1H), 8.25 (m, 1H), 11.02 (s, 1H), 11.09 (m, 2H), 11.24 (s, 1H), 11.40 (m, 2H), 11.56 (s, 1H).

Synthesis of compound 7. To a solution of **6** (92 mg, 0.032 mmol) in dry CH_2Cl_2 (3 mL) was added Et_3N (20 mg, 0.198 mmol). The (1*S*)-(–)-camphanyl acid chloride (14 mg, 0.065 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and transferred to the above solution by syringe. The mixture was stirred for 2 days at room temperature under a nitrogen atmosphere. Volatiles were removed under vacuum. The residue was diluted with $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/EtOAc (1:1, v/v) to afford the pure compound as yellow solid (97 mg, 99 %). IR (KBr) ν (cm^{-1}): 2964, 2921, 2872, 2853, 1686, 1593, 1571, 1542, 1536, 1508, 1463, 1461, 1413, 1396, 1383, 1356, 1331, 1262, 1211, 1114, 1054; UV (λ, ε, in $CHCl_3$): 321 nm, 2.3×10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): δ –0.55 (s, 9H), 0.11 (s, 3H), 0.32 (t, 2H), 0.56 (s, 3H), 0.59 (s, 3H), 1.42 (s, 9H), 1.47 (m, 18H), 1.52 (m, 27H), 1.56 (m, 18H), 2.19-2.38 (m, 16H), 2.94 (m, 3H), 3.38-3.67 (m, 16H), 3.96-4.44 (m, 16H), 4.97 (m, 2H), 5.15 (m, 1H), 5.39 (m, 2H), 5.69 (m, 1H), 6.11 (m, 1H), 6.34 (s, 1H), 6.46 (m, 1H), 6.57 (m, 2H), 6.96 (m, 2H), 7.07 (m, 2H), 7.19 (m, 8H), 7.31 (m, 3H), 7.38 (t, 1H, *J* =8.1 Hz), 7.47 (t, 1H, *J* =8.1), 7.69 (m, 7H), 7.81 (m, 3H), 7.97 (m, 3H), 8.12 (m, 1H), 8.22 (m, 1H), 9.37 (s, 1H), 11.03 (m, 3H), 11.22 (s, 1H), 11.38 (s, 1H), 11.43 (s, 1H), 11.52 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ -1.9, 9.4, 14.2, 15.8, 15.9, 16.1, 21.0, 28.4, 28.5, 28.6, 29.0, 29.3, 29.7, 37.3, 38.0, 53.9, 54.4, 60.4, 63.6, 66.4, 66.5, 66.6, 77.3, 79.2, 79.3, 79.4, 91.5, 97.2, 97.5, 99.9, 115.4, 115.5, 115.8, 116.2, 116.3, 116.4, 121.1, 121.2, 121.3, 121.6, 121.7, 121.9, 125.9, 126.0, 126.1, 126.2, 126.3, 127.3, 127.6, 127.7, 132.3, 132.7, 133.0, 133.1, 133.2, 133.6, 137.0, 137.3, 137.5, 137.6, 137.8, 138.6, 145.2, 148.3, 148.7, 149.8, 150.2, 155.9, 156.0, 156.1, 156.2, 156.3, 158.9, 160.4, 160.6, 160.7, 161.4, 161.8, 162.4, 162.5, 162.7, 163.7, 164.3, 171.1, 176.1; MALDI-TOF MS: calcd for $[M+H]^+$ ($C_{159}H_{195}N_{24}O_{36}Si$): 3044.39; Found: 3043.55

Synthesis of compound 8. To a solution of **7** (100 mg, 0.033 mmol) in dry THF (2 mL) was added tetra-*n*-butylammonium fluoride (TBAF, 17 mg, 0.066 mmol, 1M in dry THF). The

reaction mixture was stirred at room temperature overnight. Volatiles were removed under vacuum. The residue was diluted in $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/EtOAc (13:20, v/v) to afford the pure compound as yellow solid (95 mg, 99 %). IR (KBr) ν (cm^{-1}): 2963, 2922, 2872, 2852, 1687, 1593, 1572, 1541, 1535, 1508, 1463, 1460, 1412, 1394, 1383, 1355, 1332, 1262, 1212, 1114, 1053; UV (λ, ε, in $CHCl_3$): 321 nm, 2.3 × 10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.54 (s, 3H), 0.56 (s, 3H), 1.47 (m, 36H), 1.52 (m, 18H), 1.56 (m, 18H), 2.10-2.35 (m, 16H), 3.37-3.48 (m, 17H), 4.01-4.40 (m, 16H), 5.04 (m, 2H), 5.19 (m, 2H), 5.71 (m, 2H), 6.10 (m, 1H), 6.29 (m, 1H), 6.40 (s, 1H), 6.49 (m, 2H), 6.63 (m, 1H), 6.94-7.30 (m, 12H), 7.43-7.94 (m, 18H), 8.19 (m, 2H), 9.34 (s, 1H), 10.85 (s, 1H), 11.02 (m, 3H), 11.20 (s, 1H), 11.28 (s, 1H), 11.40 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 9.4, 13.5, 14.1, 14.2, 15.9, 16.1, 21.0, 28.4, 28.5, 28.6, 29.2, 29.3, 29.7, 37.3, 37.4, 37.7, 37.8, 37.9, 38.0, 38.1, 53.9, 54.4, 60.4, 66.0, 66.1, 66.5, 66.6, 66.7, 66.8, 66.9, 77.3, 79.2, 79.4, 79.5, 91.5, 97.5, 97.9, 98.0, 98.1, 98.6, 98.8, 99.1, 99.2, 99.3, 115.1, 115.2, 115.4, 115.5, 115.6, 115.9, 116.0, 116.1, 116.2, 116.3, 116.4, 116.5, 121.3, 121.4, 121.5, 121.7, 121.8, 126.0, 126.1, 126.2, 126.3, 127.5, 127.6, 132.1, 132.5, 132.6, 132.7, 132.9, 133.0, 137.0, 137.1, 137.4, 137.6, 137.7, 144.3, 147.9, 149.3, 149.7, 150.2, 156.0, 156.1, 156.2, 156.3, 156.4, 158.8, 160.4, 160.5, 160.6, 162.3, 162.4, 162.5, 162.6, 162.7, 162.8, 164.3, 171.1, 176.1; MALDI-TOF MS: calcd for $[M+H]^+$ ($C_{154}H_{183}N_{24}O_{36}$): 2944.32; Found: 2944.56.

Synthesis of compound 9. Compound **2** (5 mg, 0.0076 mmol) dissolved in anhydrous DMF (0.5 mL) was added to a solution of **8** (20 mg, 0.0068 mmol), HBTU (5.1 mg, 0.0134 mmol) and DIPEA (3.5 mg, 0.0271 mmol) in anhydrous DMF (0.5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 2 days. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/MeOH (12:1, v/v) to afford the pure compound as yellow solid (15 mg, 64%). IR (KBr) ν (cm^{-1}): 3351, 3220, 2960, 2941, 2923, 2872, 2852, 1714, 1685, ,1593, 1572, 1540, 1536, 1508, 1474, 1468, 1460, 1419, 1397, 1383, 1356, 1329, 1262, 1211, 1113, 1053; UV (λ, ε): 321 nm, 2.3 × 10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.56 (s, 3H), 0.58 (s, 3H), 1.42 (s, 9H), 1.43 (s, 9H), 1.47 (m, 18H), 1.52 (m, 27H), 1.56 (s, 9H), 2.09-2.35 (m, 32H), 3.20-3.67 (m, 39H), 4.10-4.43 (m, 16H), 5.19 (m, 3H), 5.77 (m, 3H), 6.11 (m, 3H), 6.40 (m, 2H), 6.51 (m, 4H), 6.70 (m, 2H), 6.96-7.19 (m, 12H), 7.29-7.86 (m, 17H), 7.95 (m, 1H), 8.13 (m, 2H), 9.37 (s, 1H), 11.00 (s, 1H), 11.06 (m, 3H), 11.23 (s, 1H), 11.45 (s, 1H), 11.53 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 9.4, 12.3, 14.1, 15.9, 16.1, 22.7, 23.5, 23.9, 24.9, 28.4, 28.5, 28.6, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 35.3, 37.8, 37.9, 43.0, 53.4, 53.9, 54.4, 55.0, 55.3, 60.1, 66.7, 66.8, 69.1, 69.2, 69.3, 77.2, 79.1, 79.3, 79.4, 91.5, 97.8, 98.3, 99.2, 115.5, 116.2, 116.3, 116.4, 121.1, 121.5, 121.7, 121.8, 126.1, 126.2, 126.3, 132.1, 132.4, 132.5, 136.9, 137.0, 137.1, 137.2, 137.3, 137.4, 137.6, 137.7, 137.8, 138.6, 139.2, 148.4, 148.5, 148.7, 156.1, 156.2, 156.3, 156.4, 156.5, 158.8, 160.0, 160.7, 160.8, 162.1, 162.7, 162.8, 163.2, 164.3, 173.2,176.2; MALDI-TOF MS: calcd for $[M+H]^+$ ($C_{178}H_{226}N_{29}O_{42}S$): 3473.62; Found: 3473.20.

Synthesis of compound 10 (1*S*)-(-)-**camph**-($\mathbf{Q}^+$)$_8$-**biot** (*P*-helix). Compound **9** (10 mg, 0.00288 mmol) was dissolved in TFA/CH_2Cl_2 (1:1, vol/vol, 1 mL) and the reaction mixture was allowed to stir at room temperature for 2 h. Volatiles were removed and the residue was dried further under a vacuum line for 5 h to afford the product (TFA salt). Purification was achieved by semi-preparative reversed phase HPLC to yield the pure product as a yellow solid (7 mg, 68%). IR (KBr) ν (cm^{-1}): 3349, 3220, 2962, 2941, 2926, 2872, 2851, 1714, 1685, ,1594, 1572, 1542, 1535, 1507, 1475, 1466, 1460, 1421, 1396, 1385, 1356, 1330, 1263, 1212, 1113, 1053; UV (λ, ε, in H_2O): 321 nm, 2.3 × 10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; HRMS: calcd for $[M+H-8\times TFA]^+$ ($C_{138}H_{162}N_{29}O_{26}S$): 2673.1967; Found: 2673.1996; Purity: > 99% HPLC pure; Found: 2673.31; Purity: > 99% HPLC pure.

Compound 11 was synthesized as in reference S3. To a solution of methyl 8-nitro-(1H)-4-quinolinone-2-carboxylate[4](5g, 20 mmol) in a mixture of Acetone/DMF (160 mL, 15:1 v/v) was added sodium carbonate (4.14 g, 30 mmol), sodium iodide (0.6 g, 4 mmol) and *ter*-butyl-bromoacetate (3,57mL, 24.2 mmol) under a nitrogen atmosphere. The solution was stirred overnight at 70°C. Acetone was removed under reduced pressure and the residue was diluted in ethyl acetate (200 mL). The organic layer was successively washed (2 × each) with water (20 mL), with a 0.5 M solution of HCl (20 mL) and with brine (20 mL), dried over sodium sulfate and evaporated under vacuum to yield **4** (77%) which was recrystallized in $CHCl_3$/MeOH (150 mL, 1:4 v/v). ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 9H), 4.04 (s, 3H), 4.87 (s, 2H), 7.57 (s, 1H), 7.69 (t, 1H, *J* =7.4), 8.13 (d, 1H, *J* = 7.4), 8.57 (d, 1H, *J* = 8.4); ^{13}C NMR (75 MHz, CDCl3): δ 21.9, 28.0, 30.0, 53.4, 66.0, 83.6, 102.3, 125.2, 126.5, 128.4, 132.0, 151.0, 161.6, 165.4, 165.8; HRMS: calcd. for $[M+H]^+$ ($C_{17}H_{19}N_2O_7$): 363.1192; Found: 363.1196.

Compound 12 was synthesized as in reference S3. To a solution of nitro quinoline methyl ester **4** (1.5 g, 4.1 mmol) in THF (115 mL) was added a 0.2 N solution of lithium hydroxide in water (31 mL) and the solution was stirred for 30 min. Acetic acid was then added and the reaction mixture was taken up with DCM (200 mL). The organic layer was successively washed once with water (20 mL) and with brine (20 mL), dried over sodium sulfate, filtered and evaporated under vacuum to give **12** as a yellow solid (1.21g, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H), 4.92 (s, 2H), 7.64 (s, 1H), 7.76 (t, 1H, *J* = 7.3, 8.5), 8.26 (d, 1H, *J* = 7.5), 8.65 (d, 1H, *J* = 7.5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 28.0, 30.3, 66.1, 84.0, 100.4, 123.3, 125.5, 126.9, 138.4, 146.0, 149.1, 163.1, 163.4, 165.5, 176.2; HRMS: calcd. for $[M+H]^+$ ($C_{16}H_{17}N_2O_7$): 349.1030; Found: 349.1026.

Synthesis of compound 13. In a dry 50 mL round-bottomed flask, carboxylic acid **12** (1.5 g, 4.3 mmol), HBTU (1.96 g, 5.2 mmol) and DIPEA (3.75 mL, 21.5 mmol) were dissolved in 10 mL anhydrous DMF. The flask was then kept under N_2 during the reaction time. After adding 2-(trimethylsilyl)ethanol (0.92 mL, 6.4 mmol), the mixture was stirred at room temperature overnight. The solution was taken up in 150 mL EtOAc and the organic layer was washed with brine (3 x 70 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. After purification by flash column chromatography eluting with pure CH_2Cl_2, the product was obtained as a light yellow solid (1.45 g, 75%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 1.19-1.28 (m, 2H), 1.54 (s, 9H), 4.50-4.58 (m, 2H), 4.88 (s, 2H), 7.58 (s, 1H), 7.69 (dd, 1H, *J* = 7.5, 8.4), 8.12 (1H, dd, *J* = 1.3, 7.5), 8.57 (dd, 1H, *J* = 1.3,

8.4); ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.64, 14.1, 16.3, 20.5, 28.0, 30.4, 66.2, 84.0, 100.3, 123.3, 125.6, 126.9, 138.4, 146.1, 149.1, 163.1, 163.4, 165.5, 176.8; HRMS: calcd. for $[M+H]^+$ ($C_{21}H_{29}N_2O_7Si$): 449.1744; Found: 449.1759.

Synthesis of compound 14. In a 250 mL round-bottomed flask, a mixture of compound **13** (3 g, 6.7 mmol) and 10% Pd/C (0.3 g) in EtOAc (80 mL) was stirred overnight at room temperature under a 1 bar hydrogen atmosphere. The solution was filtered through celite which was washed with EtOAc. The filtrate was rotary evaporated and the residue dried under reduced pressure to yield the product as a flashy yellow solid which was not stored and used immediately in the next step (2.74 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 1.19-1.27 (m, 2H), 1.53 (s, 9H), 4.50-4.58 (m, 2H), 4.80 (s, 2H), 5.12 (bs, 2H), 6.96 (dd, 1H, *J* = 1.1, 7.5), 7.37-7.44 (m, 2H), 7.60 (dd, 1H, *J* = 1.1, 8.5).

Synthesis of compound 15. To a solution of carboxylic acid **12** (1.0 g, 2.87 mmol) in dry $CHCl_3$ (15 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.48 mL, 3.5 mmol), and the solution was kept stirring for 3 hours. Then, all volatiles were removed under vacuum, and the residue was dissolved in dry $CHCl_3$ (10 mL) and transferred to a solution of amine **14** (1.17 g, 2.80 mmol) and DIPEA (2.42 mL, 14 mmol) in dry $CHCl_3$ (10 mL) by syringe at 0°C (ice bath) under a N_2 atmosphere. The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (20 mL), and washed with brine several times. The organic layer was collected and dried over MgSO4. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with 100% CH_2Cl_2 to afford the pure product as a pale yellow solid (1.84 g, 88%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 9H), 1.26 (m, 2H), 1.52 (s, 9H), 1.54 (s, 9H), 4.72 (m, 2H), 4.84 (s, 2H), 4.93 (s, 2H), 7.50 (s, 1H), 7.69 (m, 2H), 7.85 (s, 1H), 8.09 (d, 1H, *J* = 8.4), 8.23 (d, 1H, *J* = 7.5), 8.63 (d, 1H, *J* = 8.4), 9.05 (d, 1H, *J* = 7.8), 11.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ –1.5, 17.6, 28.1, 64.8, 65.8, 65.9, 83.2, 83.6, 100.3, 101.5, 116.9, 119.0, 121.9, 123.1, 125.7, 125.8, 126.9, 128.1, 134.8, 139.5, 140.0, 147.7, 148.8, 153.9, 161.6, 162.1, 162.2, 165.9, 166.0, 166.4; EI MS: calcd for $[M+H]^+$ ($C_{37}H_{45}N_4O_{11}Si$): 749.29; Found: 749.30.

Synthesis of compound 16. A mixture of compound **15** (1.0 g, 1.34 mmol) and 10% Pd/C (0.15 g) in EtOAc (40 mL) was stirred overnight at room temperature under a 1 bar hydrogen atmosphere. The solution was filtered through celite which was washed with EtOAc. The filtrate was rotary evaporated and the residue dried under reduced pressure to yield the product as a green solid which was not stored and used immediately ion the next step (0.94 g, 98%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.14 (s, 9H), 1.23 (m, 2H), 1.52 (s, 9H), 1.54 (s, 9H), 4.57 (m, 2H), 4.83 (s, 2H), 4.87 (s, 2H), 5.58 (s, 2H), 7.02 (d, 1H, *J* = 7.5), 7.41 (t, 1H, *J* = 8.4), 7.44 (s, 1H), 7.62 (d, 1H, *J* = 8.4), 7.66 (s, 1H), 7.68 (d, 1H, *J* = 7.5), 8.02 (d, 1H, *J* = 8.4), 9.04 (d, 1H, *J* = 7.8), 12.73 (s, 1H); EI MS: calcd for $[M+H]^+$ ($C_{37}H_{47}N_4O_9Si$): 719.31; Found: 719.40.

Synthesis of compound 17. To a solution of **15** (1.0 g, 1.34 mmol) in dry THF (20 mL) was added TBAF (0.70 g, 2.7 mmol, 1M in dry THF). The reaction mixture was stirred at room temperature overnight. Volatiles were removed under vacuum. The residue was diluted in $CHCl_3$ (20 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with $CHCl_3$/MeOH (10:1, v/v) to afford the pure product as yellow solid (0.84 g, 97 %). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.54 (s, 9H), 1.55 (s, 9H), 4.90 (s, 2H), 4.95 (s, 2H), 7.72 (m, 3H), 7.85 (s, 1H), 8.16 (d, 1H, *J* = 8.4), 8.30 (d, 1H, *J* = 7.5), 8.65 (d, 1H, *J* = 8.4), 9.17 (d, 1H, *J* = 7.8), 10.80 (s, 1H), 11.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 65.9, 66.0, 83.6, 83.8, 100.1, 100.3, 117.4, 119.8, 122.7, 123.1, 126.1, 126.2, 127.5, 128.8, 134.1, 138.7, 139.3, 146.6, 147.2, 153.2, 161.8, 162.5, 162.8, 164.4, 165.9, 166.1; EI MS: calcd for $[M+H]^+$ ($C_{32}H_{33}N_4O_{11}$): 649.21; Found: 649.40.

Synthesis of compound 18. To a solution of carboxylic acid **17** (0.50 g, 0.77 mmol) in dry $CHCl_3$ (10 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.13 mL, 0.92 mmol), and the solution was kept stirring for 3 hours. All volatiles were removed under vacuum, and the residue was dissolved in dry $CHCl_3$ (6 mL) and transferred to a solution mixture of amine **16** (0.54 g, 0.75 mmol) and DIPEA (0.67 mL, 3.85 mmol) in dry $CHCl_3$ (6 mL) by syringe at 0°C (ice bath) under a N_2 atmosphere. The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (15 mL), and washed with brine several times. The organic layer was collected and dried over MgSO4. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with $CHCl_3$/EtOAc (10:1, v/v) to afford the pure product as pale yellow solid (0.94 g, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ –0.21 (s, 9H), 0.68 (t, 2H, *J* = 8.4), 1.54 (s, 9H), 1.55 (s, 9H), 1.61 (s, 9H), 1.62 (s, 9H), 3.93 (m, 2H), 4.64 (m, 2H), 4.70 (s, 2H), 4.93 (s, 2H), 5.01 (s, 2H), 6.59 (s, 1H), 6.81 (s, 1H), 7.36 (t, 1H, *J* = 8.1), 7.41 (s, 1H), 7.48 (t, 1H, *J* = 7.8), 7.63 (t, 1H, *J* = 8.1), 7.70 (d, 1H, *J* = 7.5), 7.75 (s, 1H), 7.78 (t, 1H, *J* = 7.8), 8.04 (d, 1H, *J* = 7.8), 8.10 (m, 2H), 8.21 (d, 1H, *J* = 7.8), 8.36 (d, 1H, *J* = 7.8), 8.66 (d, 1H, *J* = 8.4), 9.18 (d, 1H, *J* = 7.8), 11.64 (s, 1H), 11.87 (s, 1H), 12.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ –1.6, 16.5, 28.1, 64.0, 65.8, 66.2, 66.3, 83.0, 83.1, 83.5, 97.8, 99.2, 100.1, 100.3, 116.2, 116.4, 116.9, 117.0, 118.0, 121.6, 121.8, 123.3, 125.2, 126.8, 127.5, 128.0, 128.2, 128.3, 128.5, 128.8, 133.6, 133.9, 135.0, 138.4, 138.9, 139.0, 139.1, 145.1, 145.9, 149.0, 150.8, 153.2, 160.2, 160.9, 161.2, 161.9, 162.0, 162.4, 162.5, 163.4, 166.3, 166.4, 166.5; EI MS: calcd for $[M+H]^+$ ($C_{69}H_{77}N_8O_{19}Si$): 1349.51; Found: 1349.50.

Synthesis of compound 19. A mixture of compound **18** (0.90 g, 0.67 mmol) and 10% Pd/C (0.15 g) in 40 mL EtOAc was stirred overnight at room temperature under a 1 bar hydrogen atmosphere. The solution was filtered through celite which was washed with EtOAc. The filtrate was rotary evaporated and the residue dried under reduced pressure to yield the product as a green solid (0.85 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ –0.17 (s, 9H), 1.26 (m, 2H), 1.55 (bs, 18H), 1.61 (s, 9H), 1.62 (s, 9H), 3.83 (s, 2H), 3.96 (m, 2H), 4.64 (s, 2H), 4.68 (s, 2H), 4.93 (s, 2H), 4.95 (s, 2H), 6.01 (d, 1H, *J* = 7.5), 6.59 (s, 1H), 6.83 (s, 1H), 7.07 (t, 1H, *J* = 7.8), 7.24 (s, 1H), 7.34 (t, 1H, *J* = 7.8), 7.60 (d, 1H, *J* = 7.8), 7.63 (s, 1H), 7.68 (t, 1H, *J* = 8.1), 7.75 (t, 1H, *J* = 8.1), 7.97 (d, 1H, *J* = 8.4), 8.08 (m, 3H), 8.47 (d, 1H, *J* = 7.8), 9.05 (d, 1H, *J* = 7.8), 11.79 (s, 1H), 11.92 (s, 1H), 12.45 (s, 1H); EI MS: calcd for $[M+H]^+$ ($C_{69}H_{79}N_8O_{17}Si$): 1319.53; Found: 1319.48.

Synthesis of compound 21. To a solution of tetramer acid **20**[S2] (0.10 g, 0.070 mmol) in dry $CHCl_3$ (3 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.019 mL, 0.14 mmol), and the solution was kept stirring for 3 hours. Then, volatiles were removed under vacuum, and the residue was dissolved in dry $CHCl_3$ (3 mL) and transferred to a solution

mixture of amine **19** (0.092 g, 0.070 mmol) and DIPEA (0.67 mL, 3.85 mmol) in dry $CHCl_3$ (4 mL) by syringe at 0°C (ice bath) under a N_2 atmosphere. The solution mixture was allowed to stir overnight at room temperature. The solvent was removed under vacuum. The residue was diluted in $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was collected and dried over MgSO4. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/EtOAc (3:1, v/v) to afford the pure product as pale yellow solid (74 mg, 39%). ^{1}H NMR (300 MHz, DMSO-d_6): δ −0.56 (s, 9H), 0.25 (m, 2H), 1.40 (m, 18H), 1.42(s, 9H), 1.45 (s, 9H), 1.49 (m, 18H), 1.64 (s, 9H), 1.74 (s, 9H), 2.11-2.28 (m, 8H), 3.18 -3.55 (m, 8H), 3.95 (m, 2H), 4.13-4.45 (m, 10H), 4.63 (m, 1H), 4.74-4.82 (m, 6H), 4.95 (s, 2H), 5.00 (m, 1H), 5.93 (s, 1H), 6.19 (s, 1H), 6.26 (s, 2H), 6.49 (s, 1H), 6.56 (s, 1H), 6.93-7.25 (m, 7H), 7.31-7.70 (m, 10H), 7.75-7.95 (m, 6H), 8.00 (d, 1H, *J* = 7.8), 8.14 (d, 1H, *J* = 8.1), 8.31 (d, 1H, *J* = 7.2), 10.69 (s, 1H), 10.84 (m, 3H), 11.01 (s, 1H), 11.10 (s, 1H), 11.26 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ -1.6, 16.0, 27.7, 27.9, 28.0, 28.2, 28.3, 28.6, 28.8, 28.9, 29.0, 29.2, 29.4, 29.5, 30.1, 31.7, 35.5, 36.9, 37.0, 37.4, 37.5, 37.6, 37.8, 65.3, 65.4, 65.7, 65.9, 66.0, 66.8, 66.9, 67.0, 79.2, 79.3, 79.4, 83.1, 83.2, 83.3, 83.4, 97.2, 97.3, 97.5, 97.6, 98.0, 98.1, 98.3, 98.4, 99.0, 99.2, 99.4, 99.5, 99.6, 99.8, 100.4, 115.4, 115.6, 115.7, 115.8, 115.9, 116.0, 116.1, 116.2, 116.3, 116.4, 116.5, 116.7, 116.8, 116.9, 117.1, 117.3, 121.1, 121.2, 121.5, 121.7, 122.0, 122.1, 123.2, 124.1, 125.8, 126.2, 126.3, 126.4, 126.6, 126.7, 126.8, 126.9, 127.4, 127.7, 127.8, 128.0, 132.0, 132.1, 132.6, 132.8, 132.9, 133.0, 133.4, 137.1, 137.2, 137.3, 137.6, 137.7, 137.9, 138.1, 138.3, 144.4, 148.0, 148.2, 148.4, 148.9, 149.8, 152.7, 156.6, 156.7, 156.9, 158.8, 159.0, 159.1, 159.5, 160.1, 160.3, 160.6, 160.9, 161.0, 161.4, 161.7, 161.9, 162.5, 162.7, 162.8, 166.2, 166.4, 167.4; ESI MS calcd for $[M+H]^+$ ($C_{141}H_{161}N_{20}O_{35}Si$): 2722.11; Found: 2722.60.

Synthesis of compound 22. To a solution of **21** (64 mg, 0.0235 mmol) in dry THF (2 mL) was added TBAF (14 mg, 0.054 mmol, 1M in dry THF). The reaction mixture was stirred at room temperature overnight. Volatiles were removed under vacuum. The residue was diluted in $CHCl_3$ (8 mL), and washed with brine several times. The organic layer was collected and dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/MeOH (10:1, v/v) to afford the product as a pale yellow solid (50 mg, 81%). ^{1}H NMR (300 MHz, 3:1 = $CDCl_3$/CD_3OD): δ 1.33 (m, 27H), 1.37 (m, 27H), 1.52 (s, 9H), 1.61 (s, 9H), 2.01-2.25 (m, 8H), 3.23-3.64 (m, 8H), 3.84-4.75 (m, 20H), 6.00-6.42 (m, 6H), 6.91-7.38 (m, 13H), 7.61-7.82 (m, 9H), 7.97 (d, 1H, *J* = 8.1), 8.06 (m, 2H), 8.18 (d, 1H, *J* = 8.1), 10.93 (s, 1H), 11.01 (m, 4H), 11.14 (s, 1H), 11.31 (s, 1H); ^{13}C NMR (75 MHz, 3:1=$CDCl_3$/CD_3OD): δ 27.7, 27.8, 27.9, 28.1, 28.2, 28.3, 28.5, 28.6, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.5, 30.1, 31.7, 35.5, 36.9, 37.0, 37.4, 37.5, 37.6, 37.8, 65.3, 65.4, 65.7, 65.9, 66.0, 66.8, 66.9, 67.0, 79.2, 79.3, 79.4, 83.0, 83.1, 83.2, 83.3, 97.2, 97.3, 97.4, 97.6, 98.0, 98.1, 98.2, 98.3, 99.0, 99.3, 99.4, 99.5, 99.6, 99.7, 100.4, 115.5, 115.6, 115.7, 115.8, 115.9, 116.0, 116.1, 116.2, 116.3, 116.4, 116.6, 116.7, 116.8, 116.9, 117.1, 117.3, 121.1, 121.2, 121.5, 121.7, 122.0, 122.1, 123.2, 124.1, 125.8, 126.2, 126.3, 126.4, 126.6, 126.7, 126.8, 126.9, 127.4, 127.5, 127.8, 127.9, 132.0, 132.1, 132.7, 132.8, 132.9, 133.0, 133.4, 137.1, 137.2, 137.3, 137.6, 137.7, 137.9, 138.1, 138.3, 144.4, 148.1, 148.2, 148.3, 148.9, 149.8, 152.7, 156.6, 156.7, 156.8, 158.8, 159.0, 159.1, 159.5, 160.1, 160.2, 160.6, 160.9, 161.0, 161.6, 161.7, 161.9, 162.5, 162.6, 162.57, 166.4, 166.5, 167.3; ESI MS: calcd for $[M+H]^+$ ($C_{136}H_{149}N_{20}O_{35}$): 2622.04; Found: 2622.56.

Synthesis of compound 23. Compound **2** (5.0 mg, 0.0076 mmol) dissolved in anhydrous DMF (0.5 mL) was added to a solution of octamer acid **22** (20 mg, 0.0076 mmol), HBTU (6.0 mg, 0.0158 mmol) and DIPEA (3.9 mg, 0.0302 mmol) in anhydrous DMF (0.5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 2 days. The solvent was removed under vacuum. The residue was diluted with $CHCl_3$ (10 mL), and washed with brine several times. The organic layer was dried over $MgSO_4$. After filtration, all volatiles were removed and the residue was purified by chromatography (silica gel) eluting with CH_2Cl_2/MeOH (12:1, v/v) to afford the adduct as a yellow solid. This compound was dissolved in TFA/CH_2Cl_2 (1 mL, 1:1 vol/vol) and the reaction mixture was allowed to stir at room temperature for 2 h. All volatiles were removed under vacuum and the residue was dried under vacuum for 5 h to afford the product (TFA salt) which was further purified by semi-preparative reversed-phase HPLC to yield a yellow solid (11 mg, 49%). IR (KBr) ν (cm^{-1}): 3346, 3225, 2962, 2943, 2925, 2872, 2853, 1711, 1687, ,1595, 1572, 1541, 1535, 1508, 1472, 1467, 1459, 1420, 1396, 1383, 1357, 1330, 1263, 1212, 1114, 1053; UV (λ, ε, H_2O): 321 nm, 2.3×10^4 $L \cdot mol^{-1} \cdot cm^{-1}$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.90 (m, 1H), 1.26 (m, 1H), 1.47 (m, 1H), 1.66 (m, 2H), 1.91 (m, 3H), 2.27 (m, 12H), 2.72 (m, 2H), 3.10-3.31 (m, 32H), 4.02-4.96 (m, 20H), 6.01 (m, 1H), 6.16 (m, 1H), 6.20 (m, 1H), 6.27 (m, 1H), 6.50 (m, 2H), 6.89 (m, 2H), 7.19 (m, 2H), 7.41-7.62 (m, 11H), 7.65-8.09 (m, 16H), 8.30 (d, 1H), 10.63 (s, 1H), 10.71 (s, 1H), 10.73 (s, 1H), 10.78 (s, 1H), 10.81 (s, 1H), 11.03 (s, 1H), 11.19 (s, 1H); HRMS: calcd for $[M+H-4\times TFA]^+$ ($C_{124}H_{128}N_{25}O_{33}S$):2526.8827; Found: 2526.8843; Purity: > 99% (HPLC).

References

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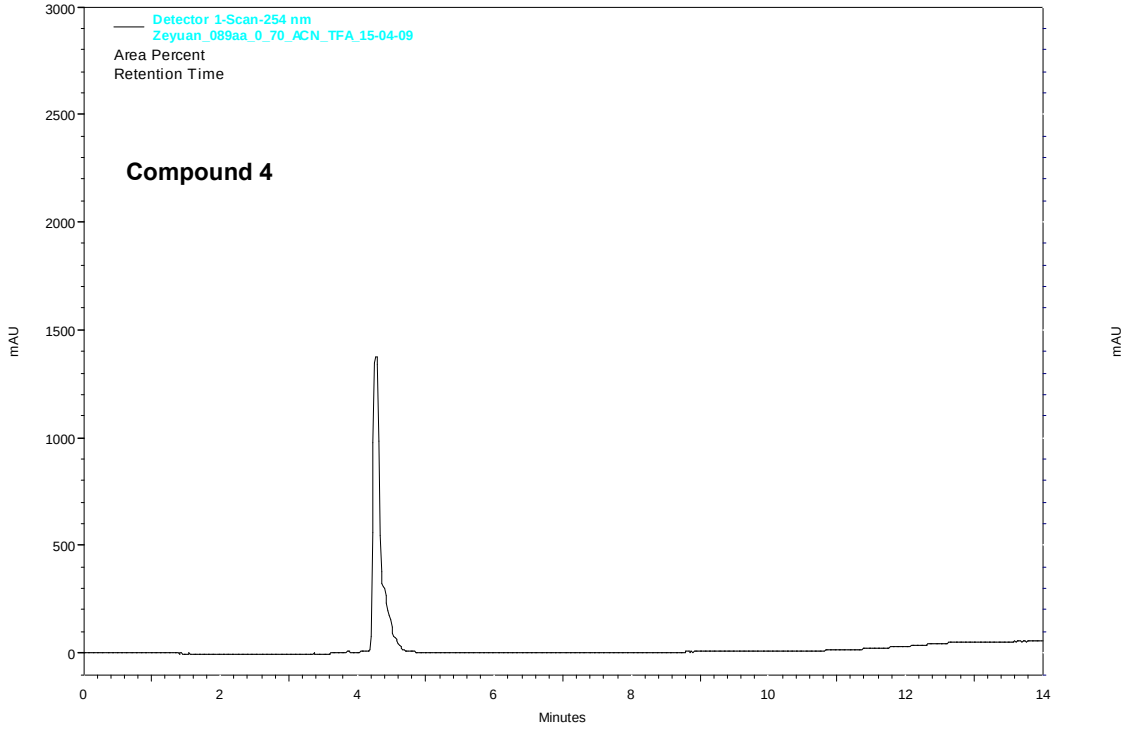
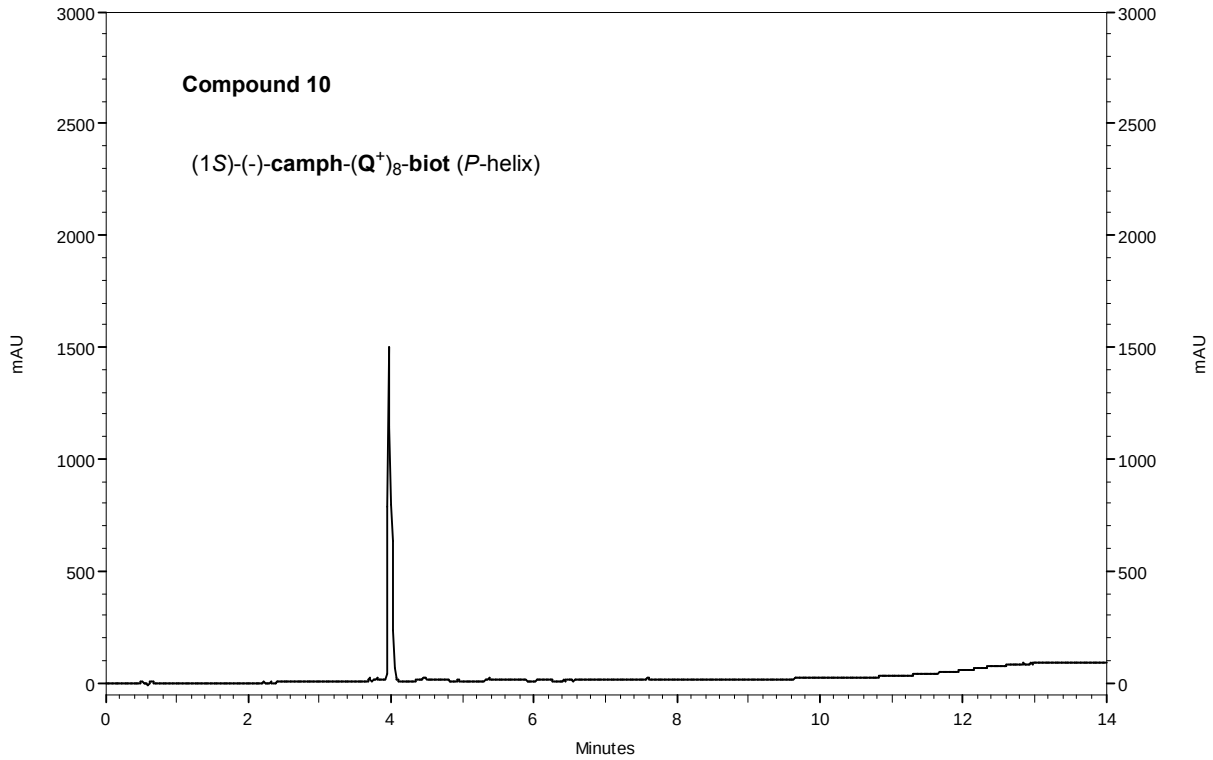
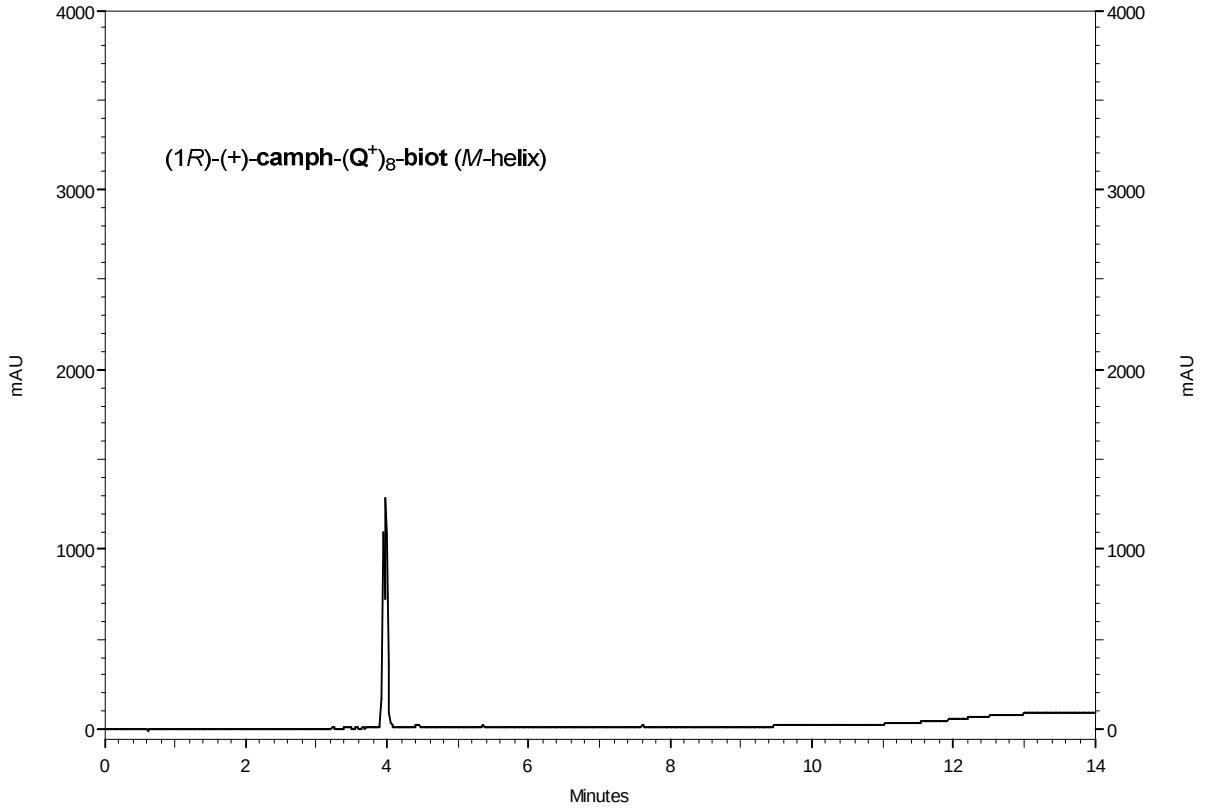
5. Chromatographic data



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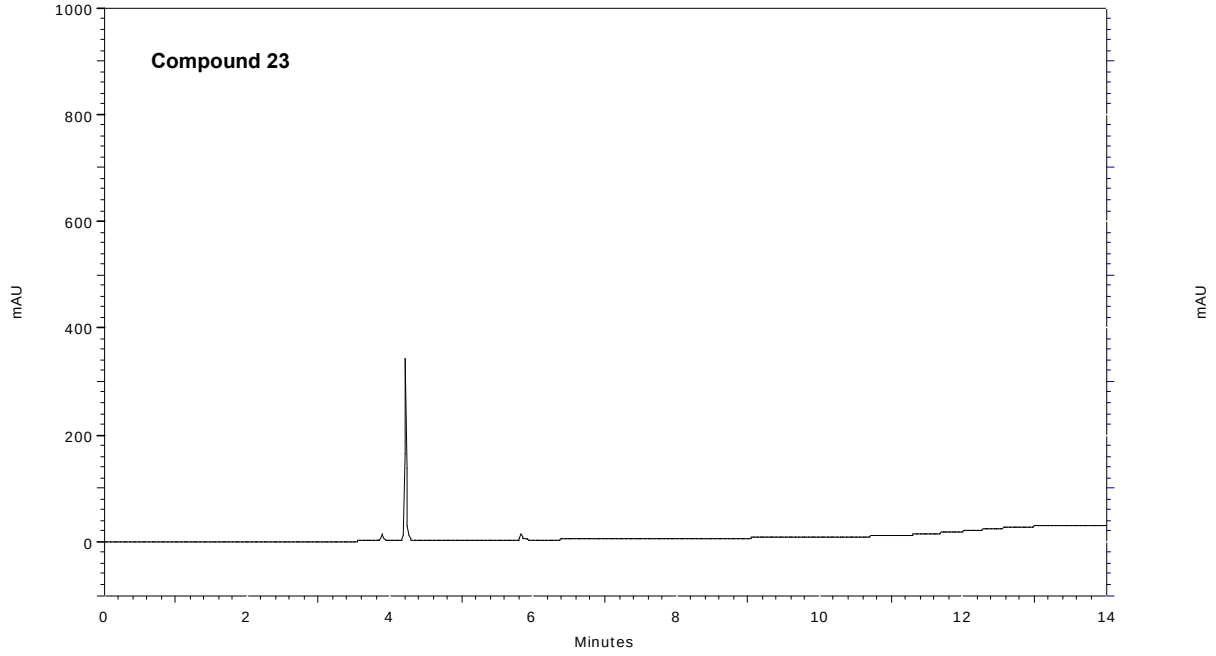
Compound 23
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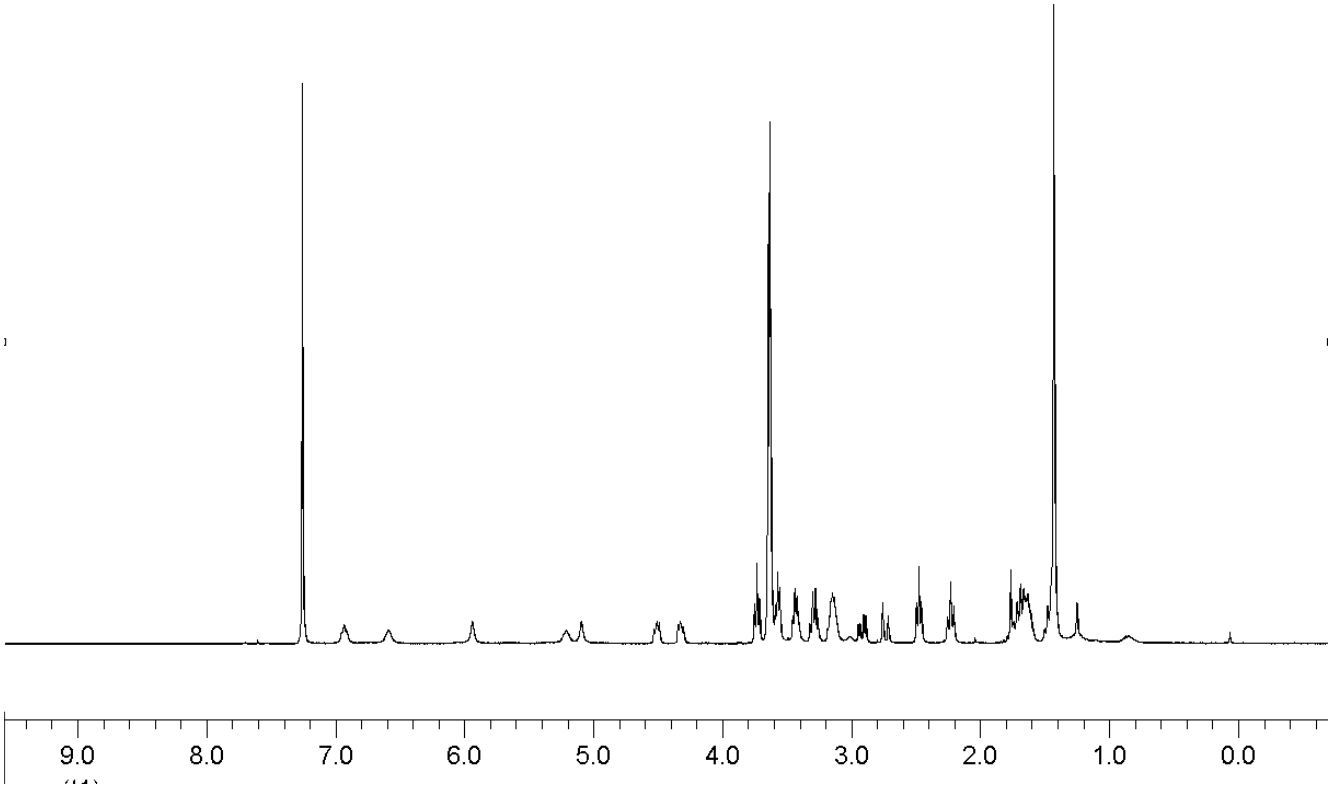
8
10
12
14

6. NMR spectra

Compound 1



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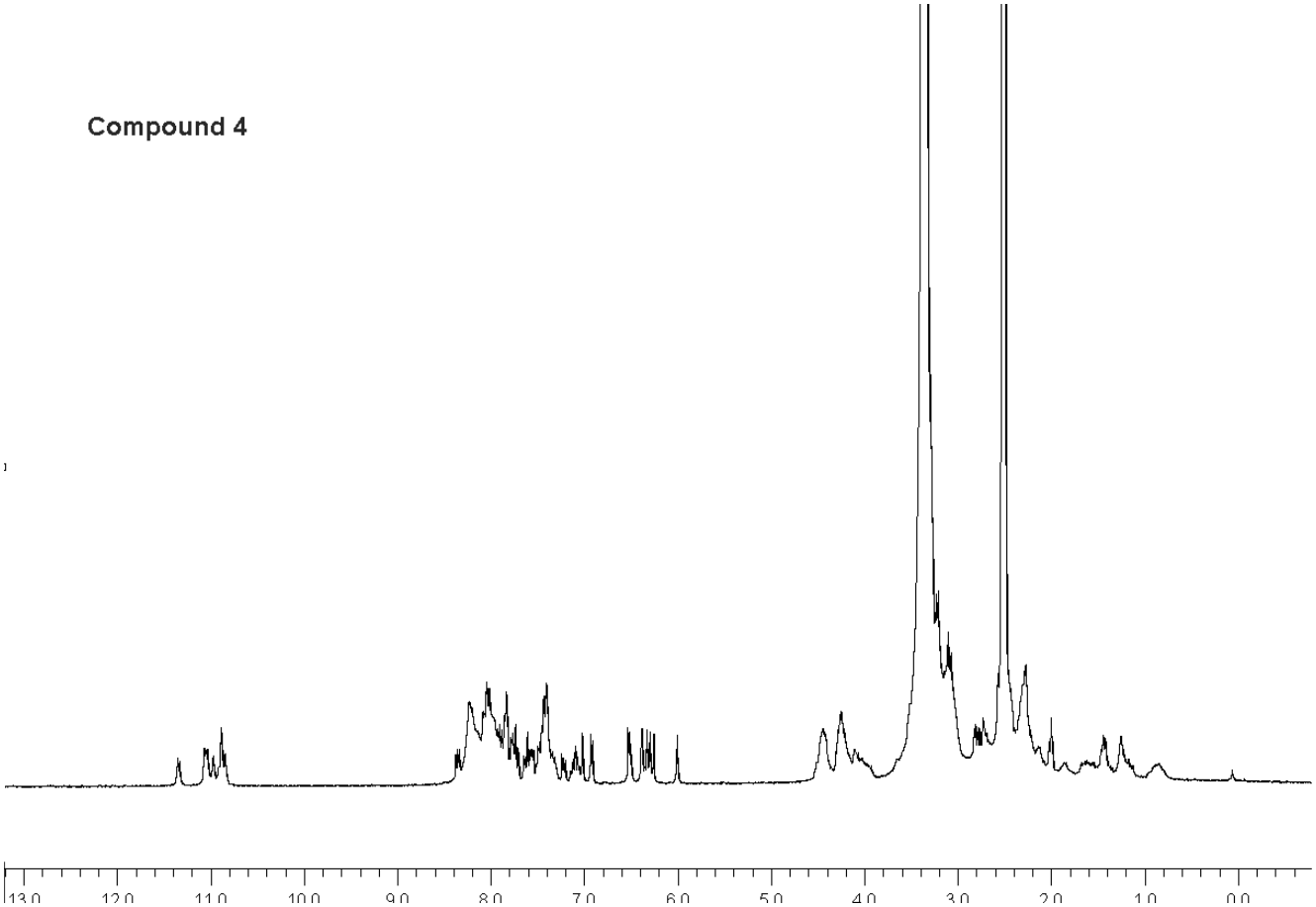

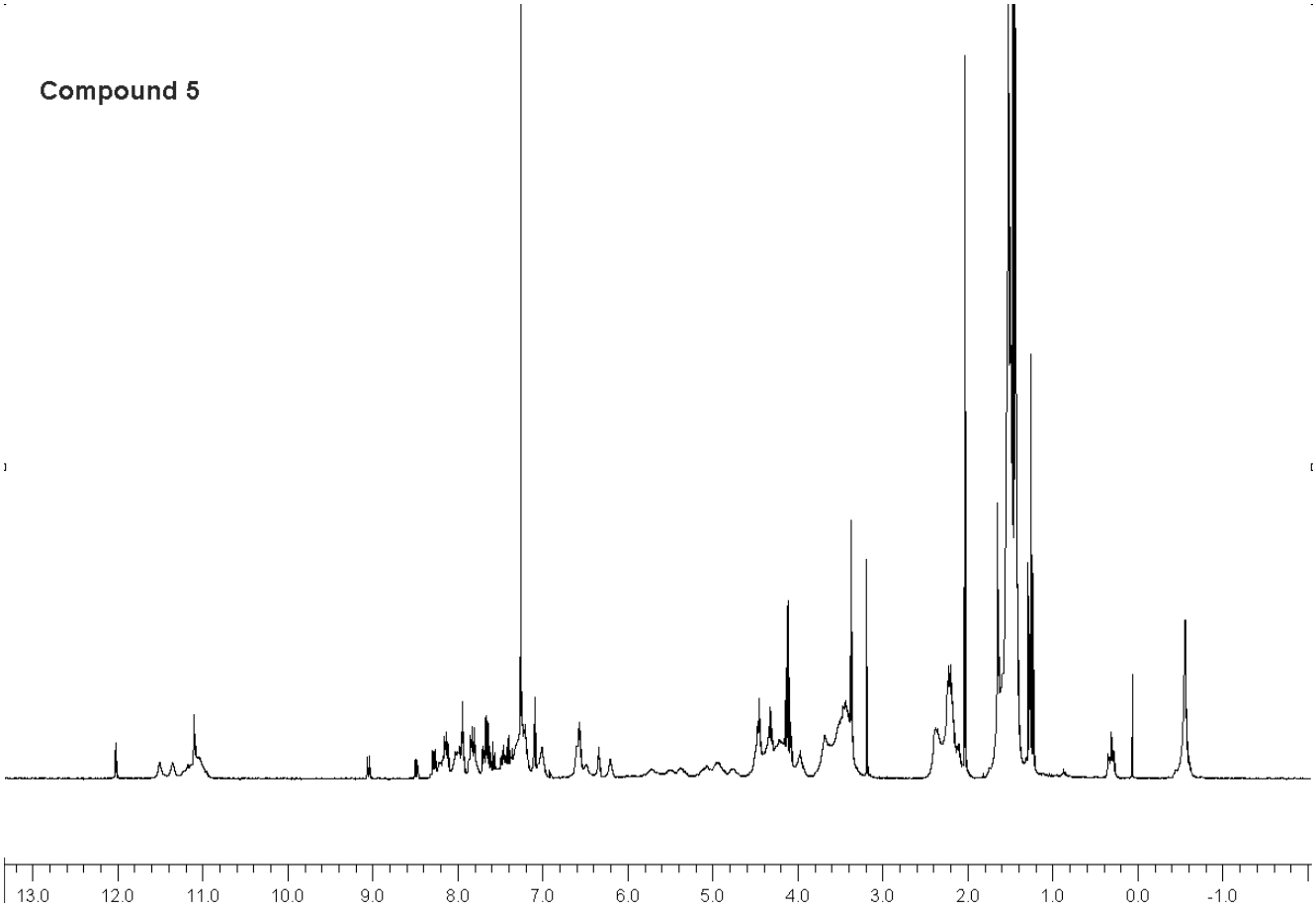
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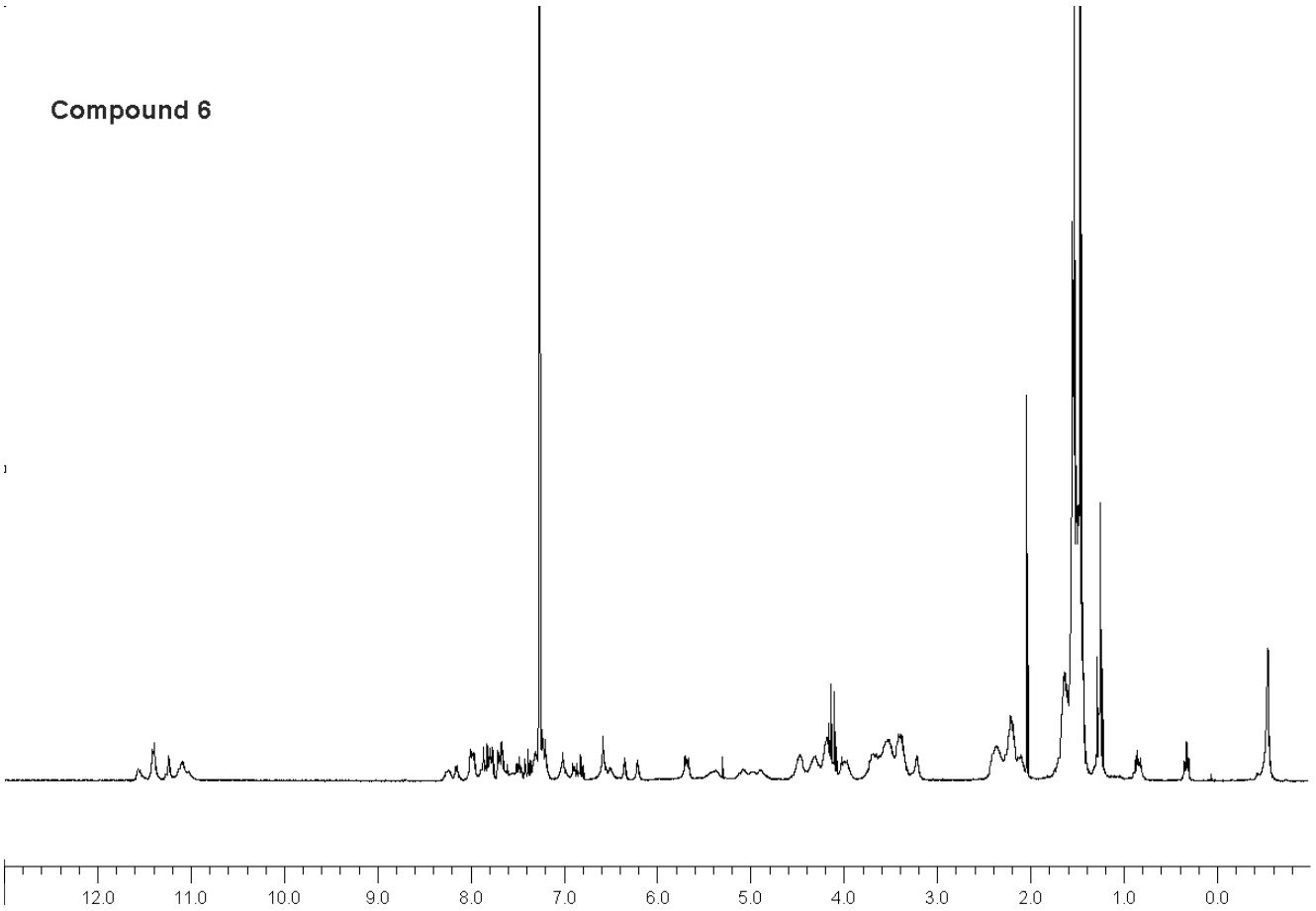
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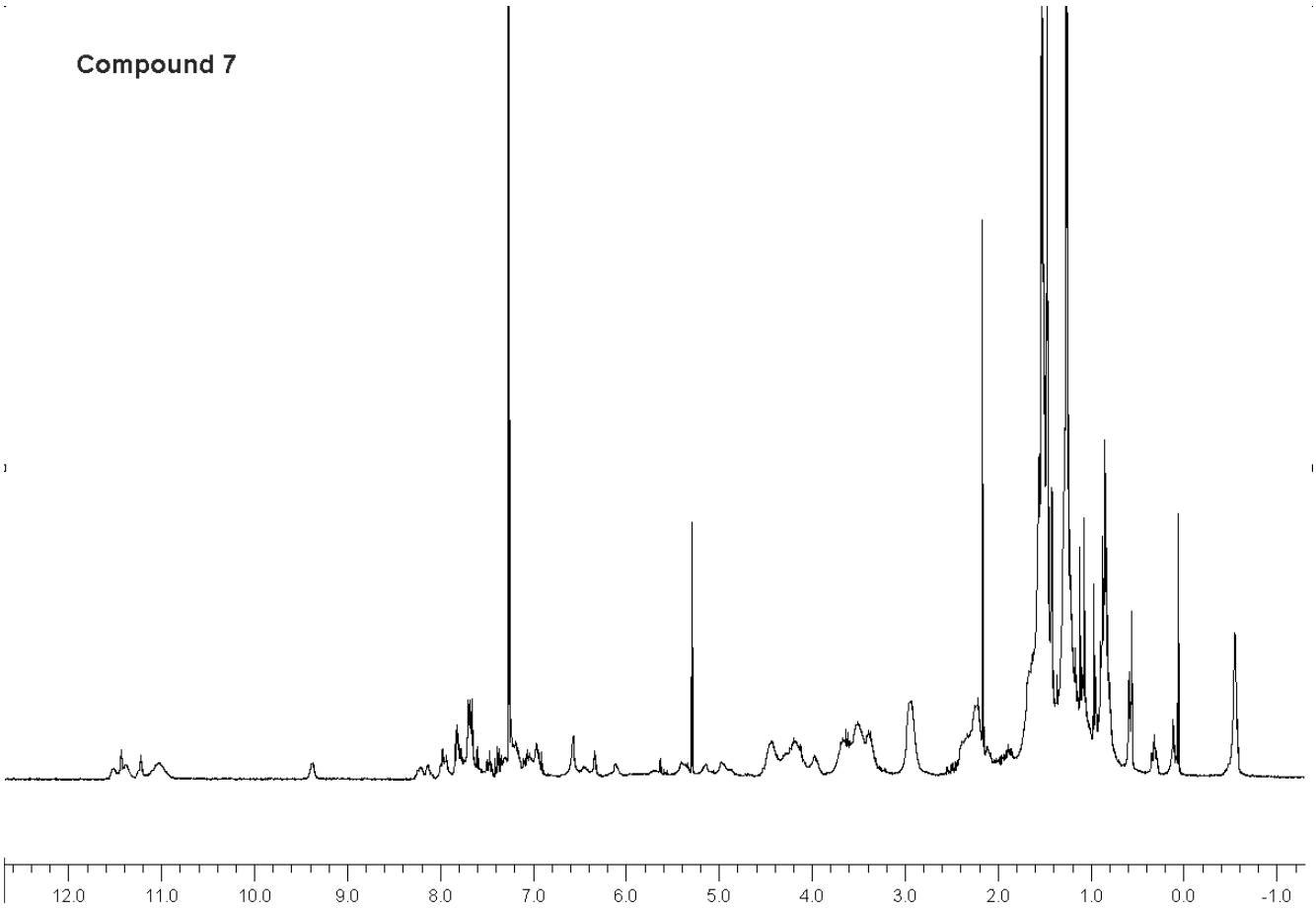
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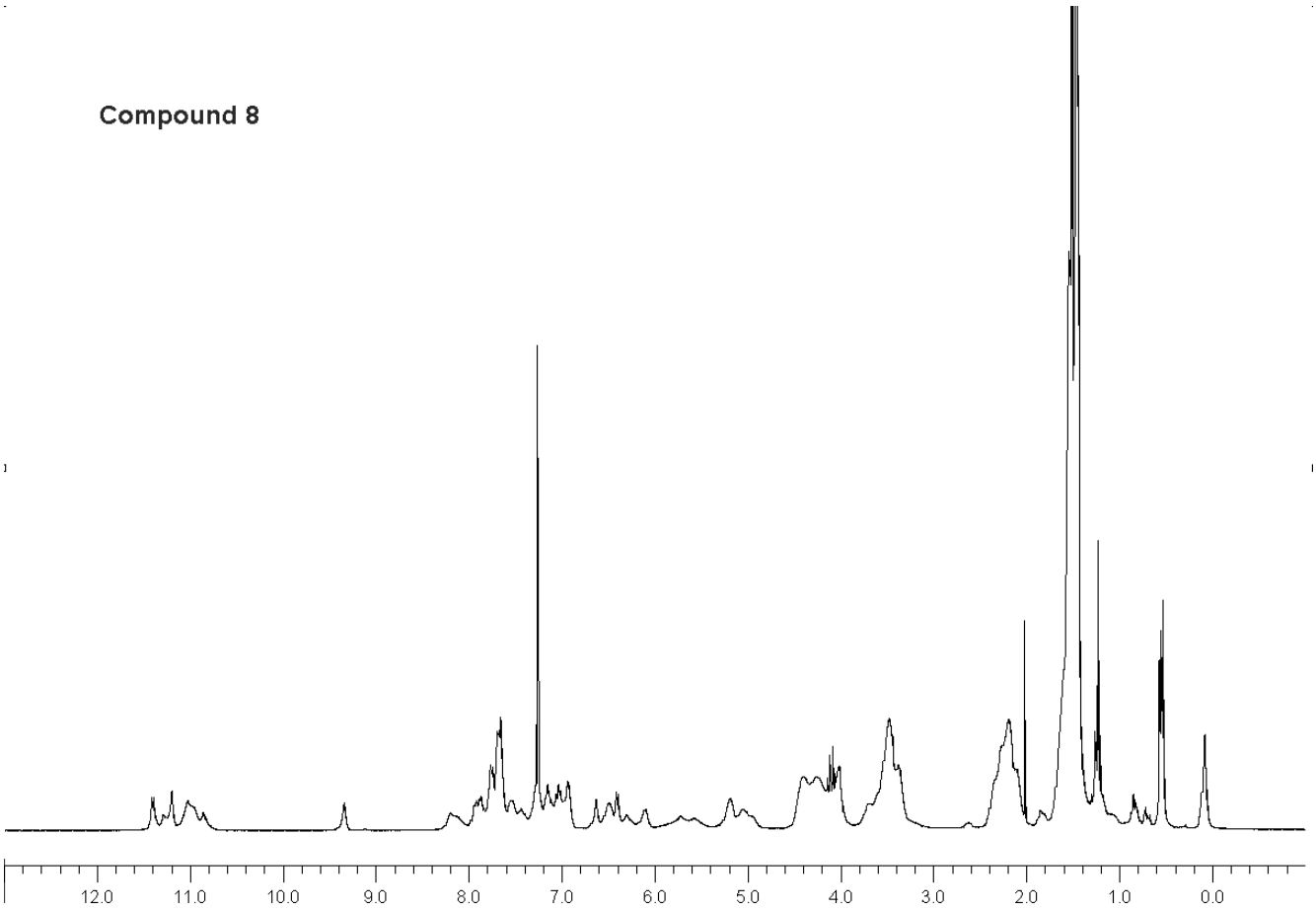
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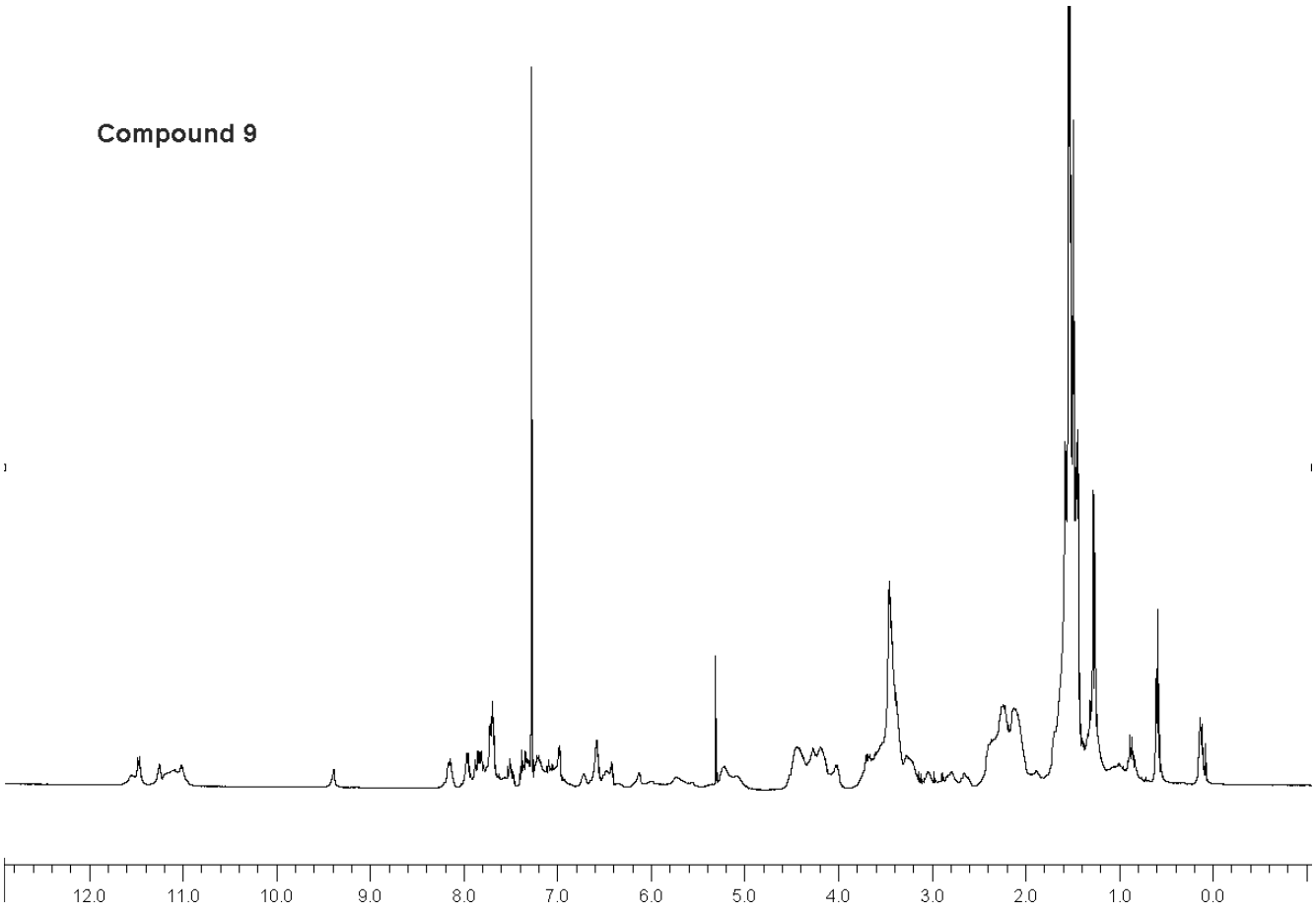
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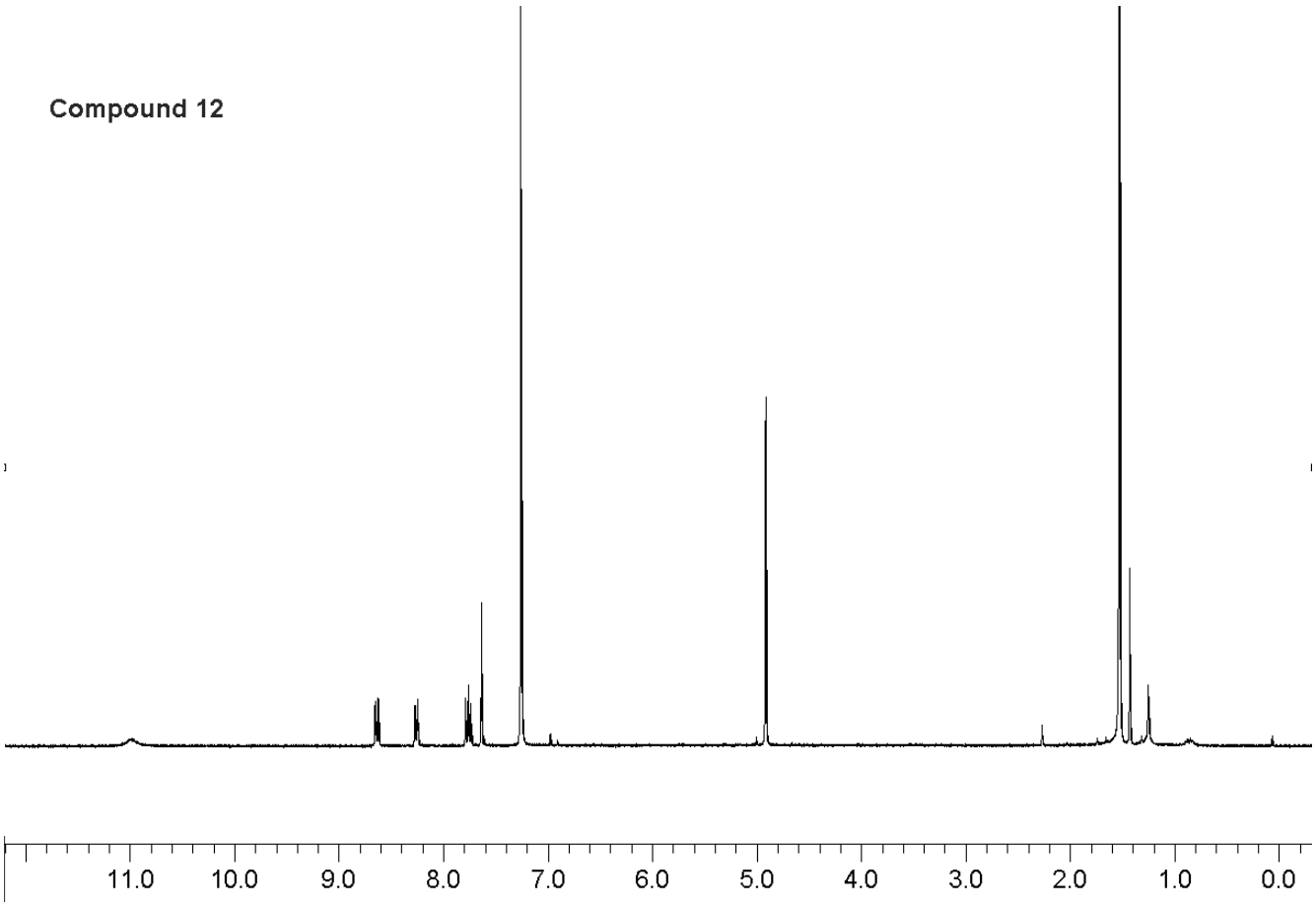
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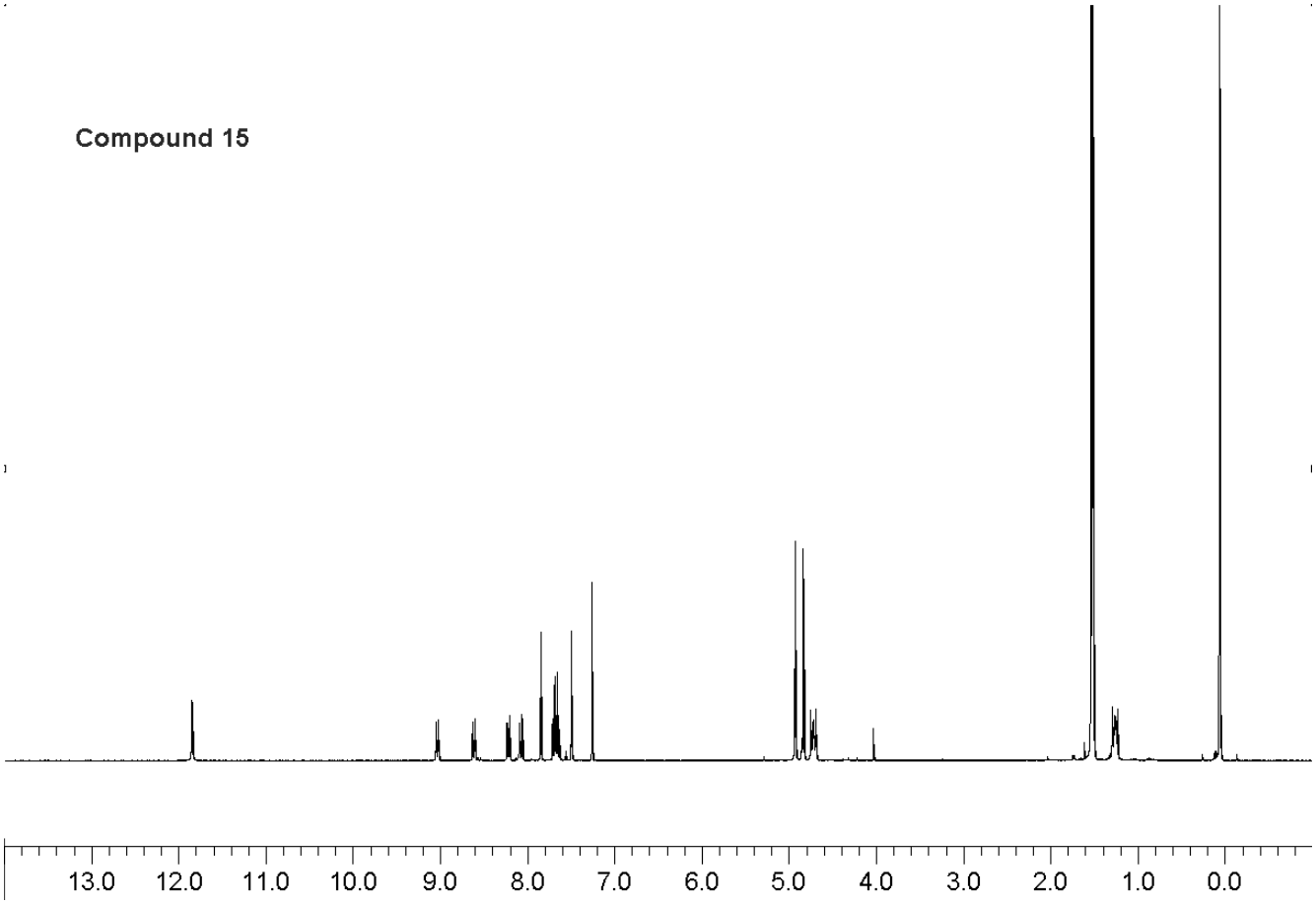
Compound 15



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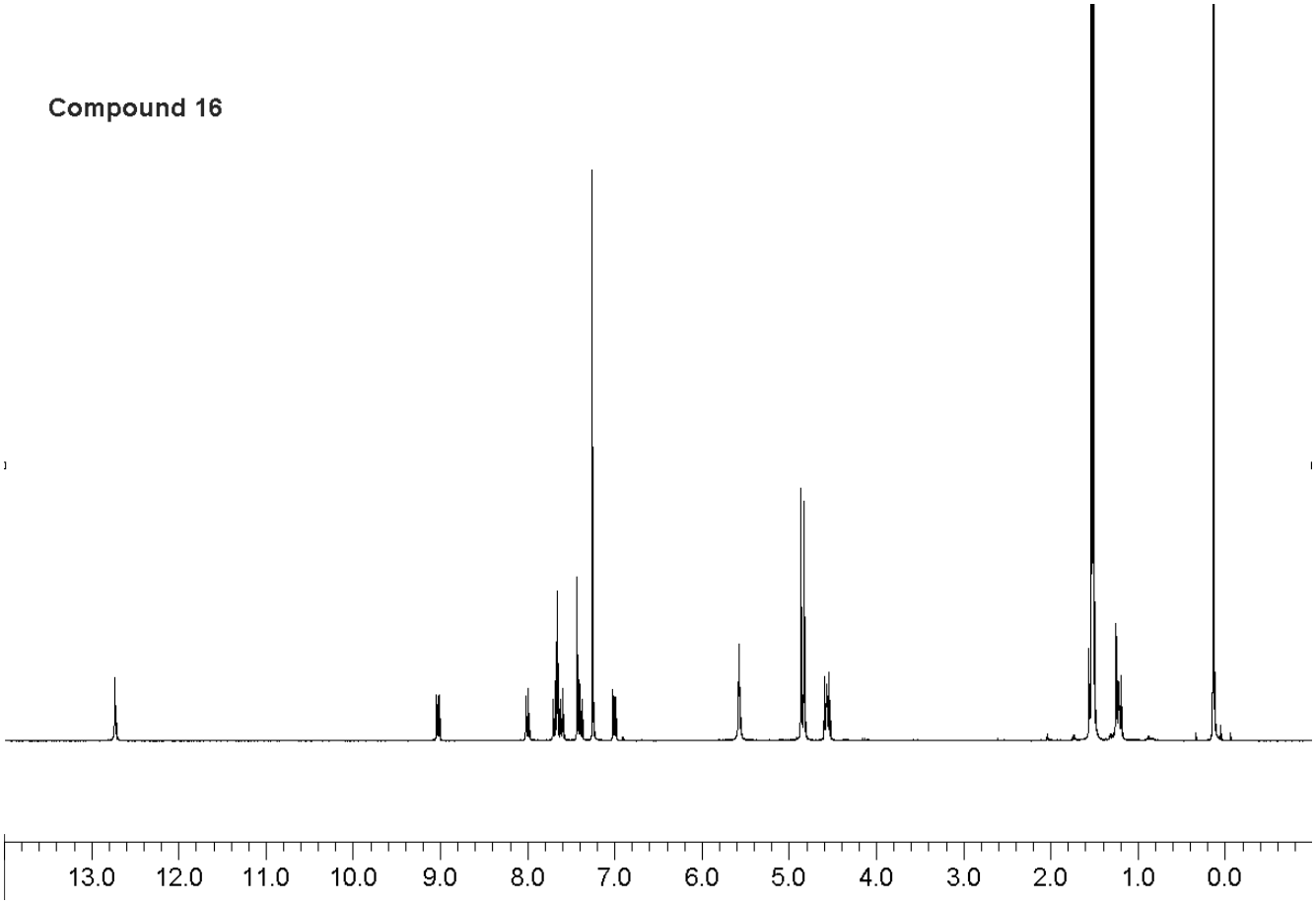

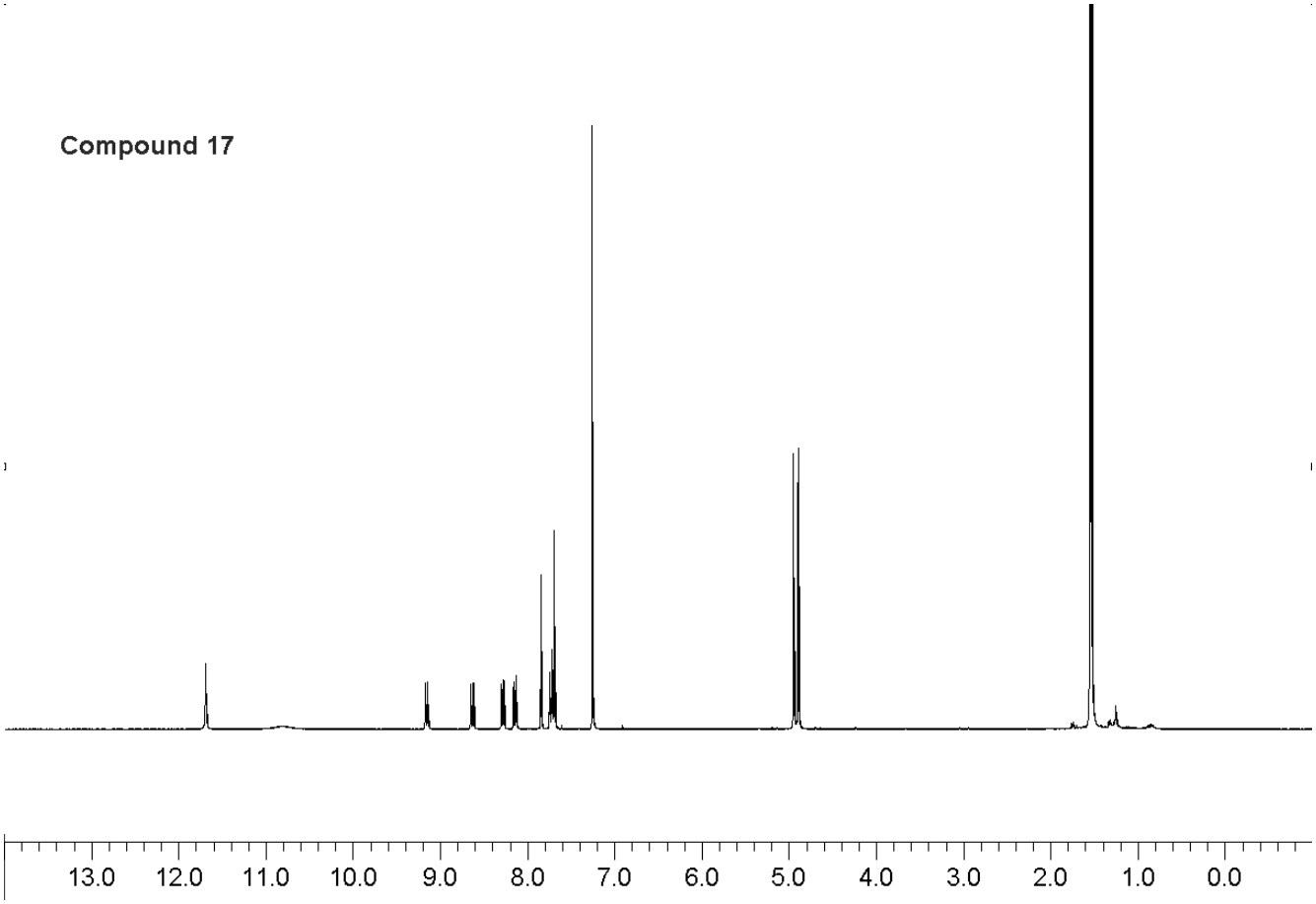
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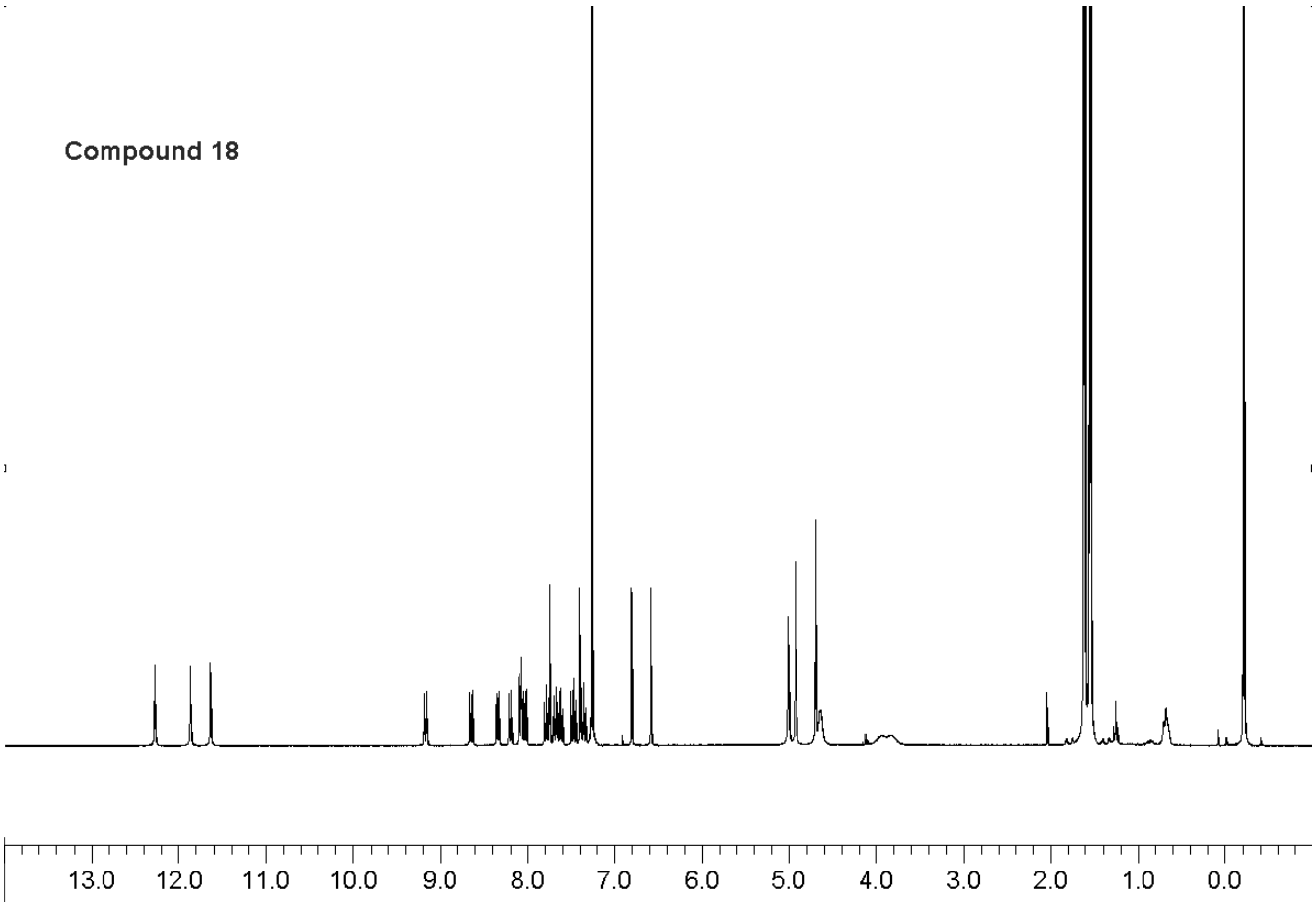
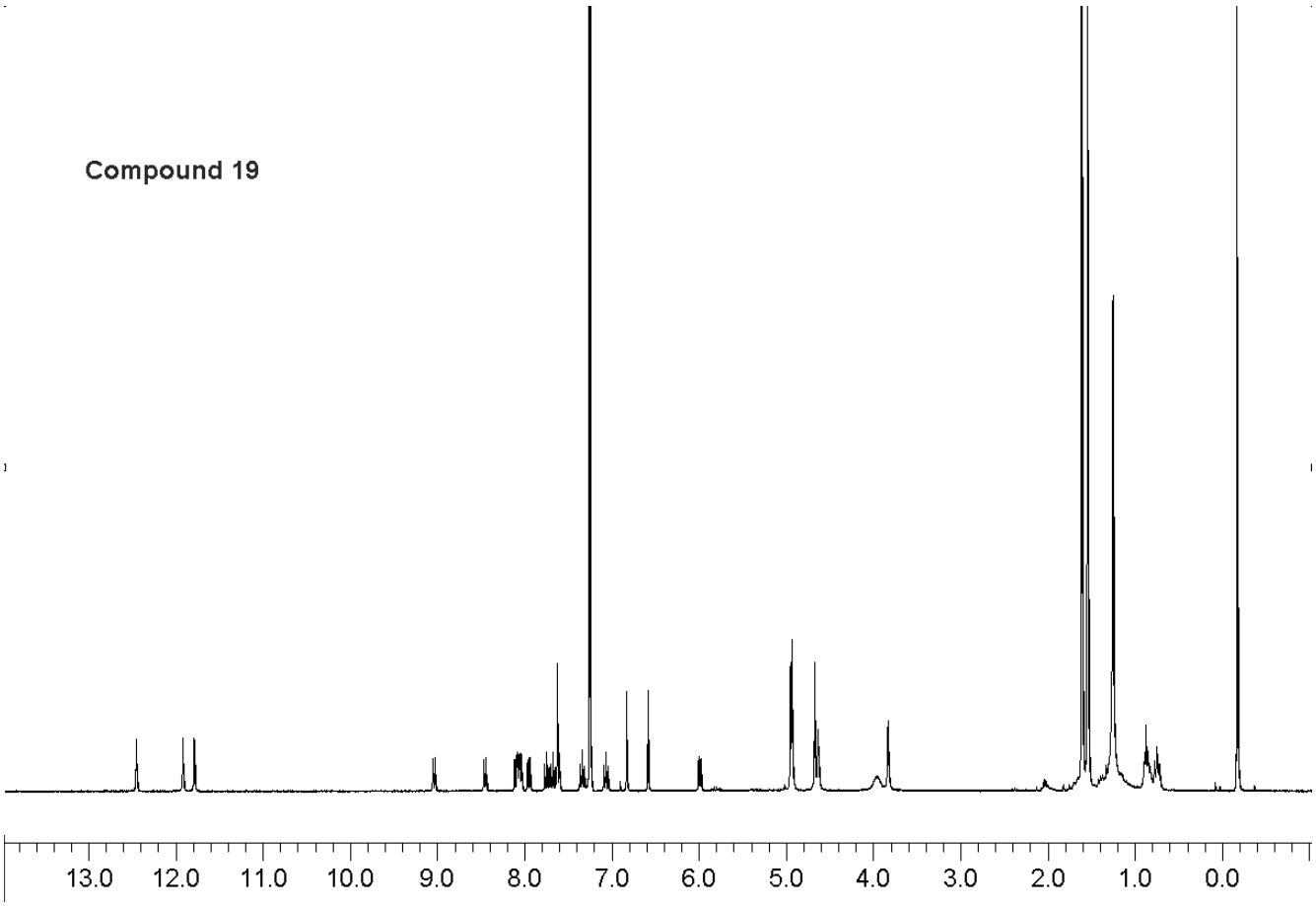
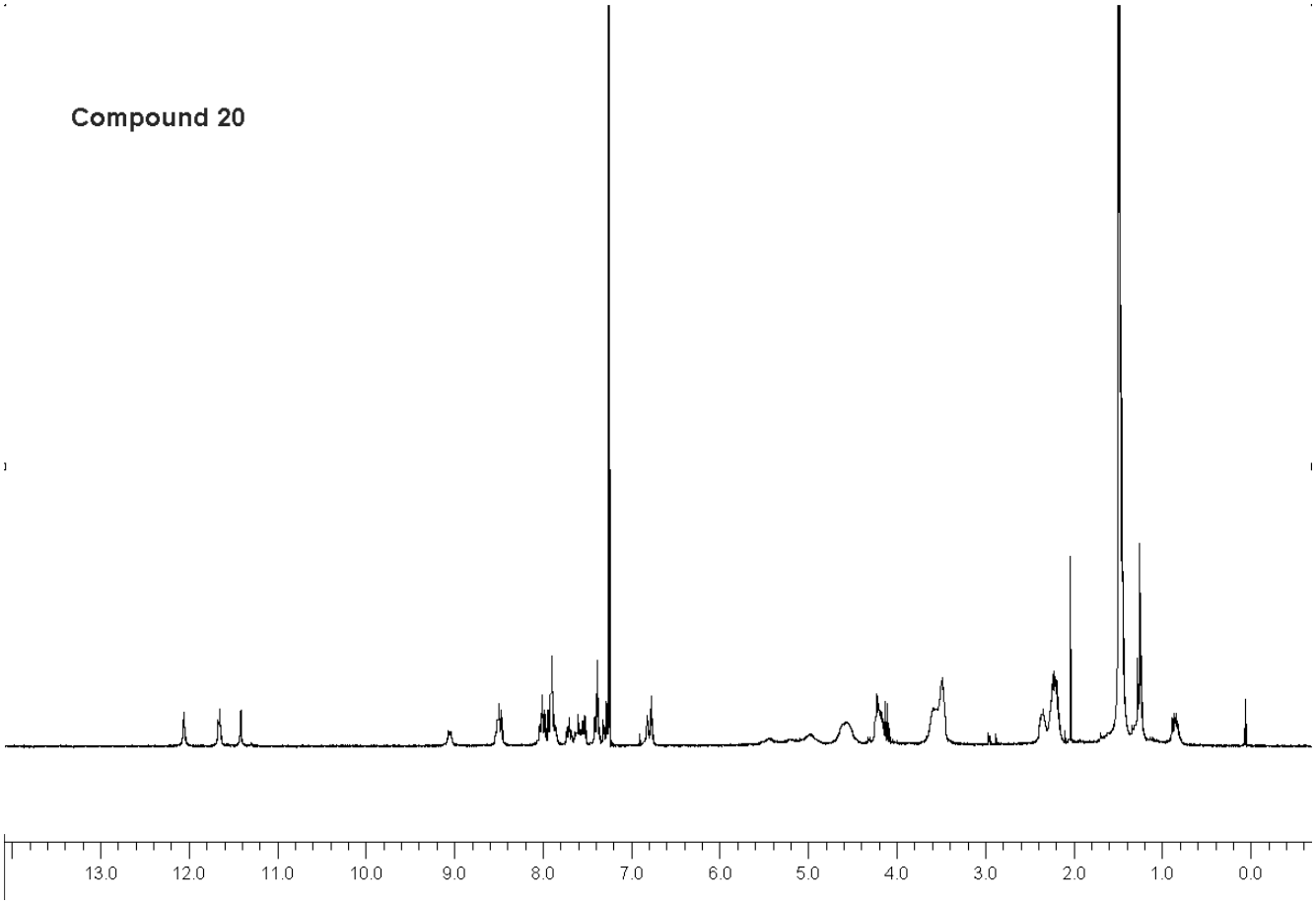
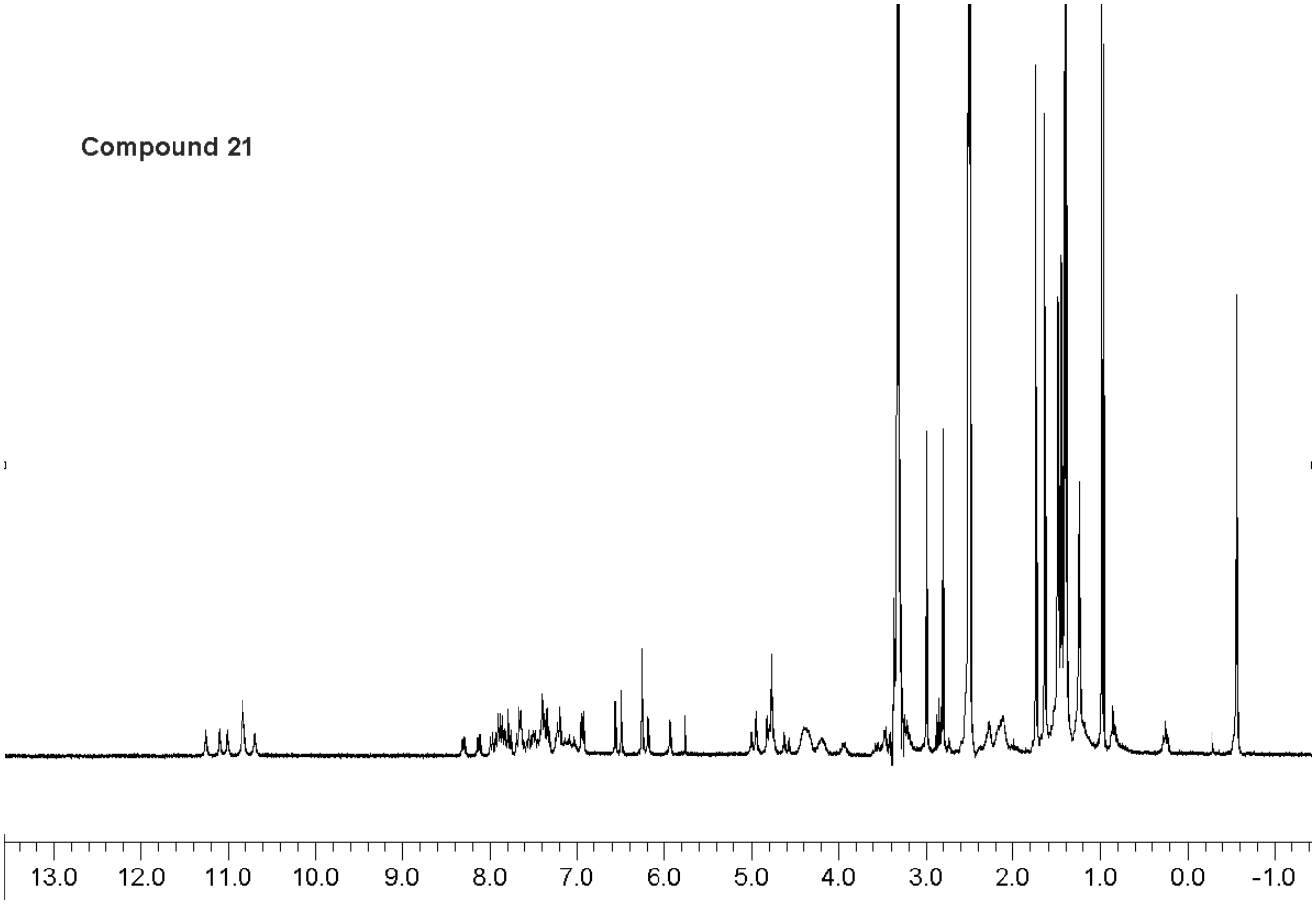

Compound 18
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

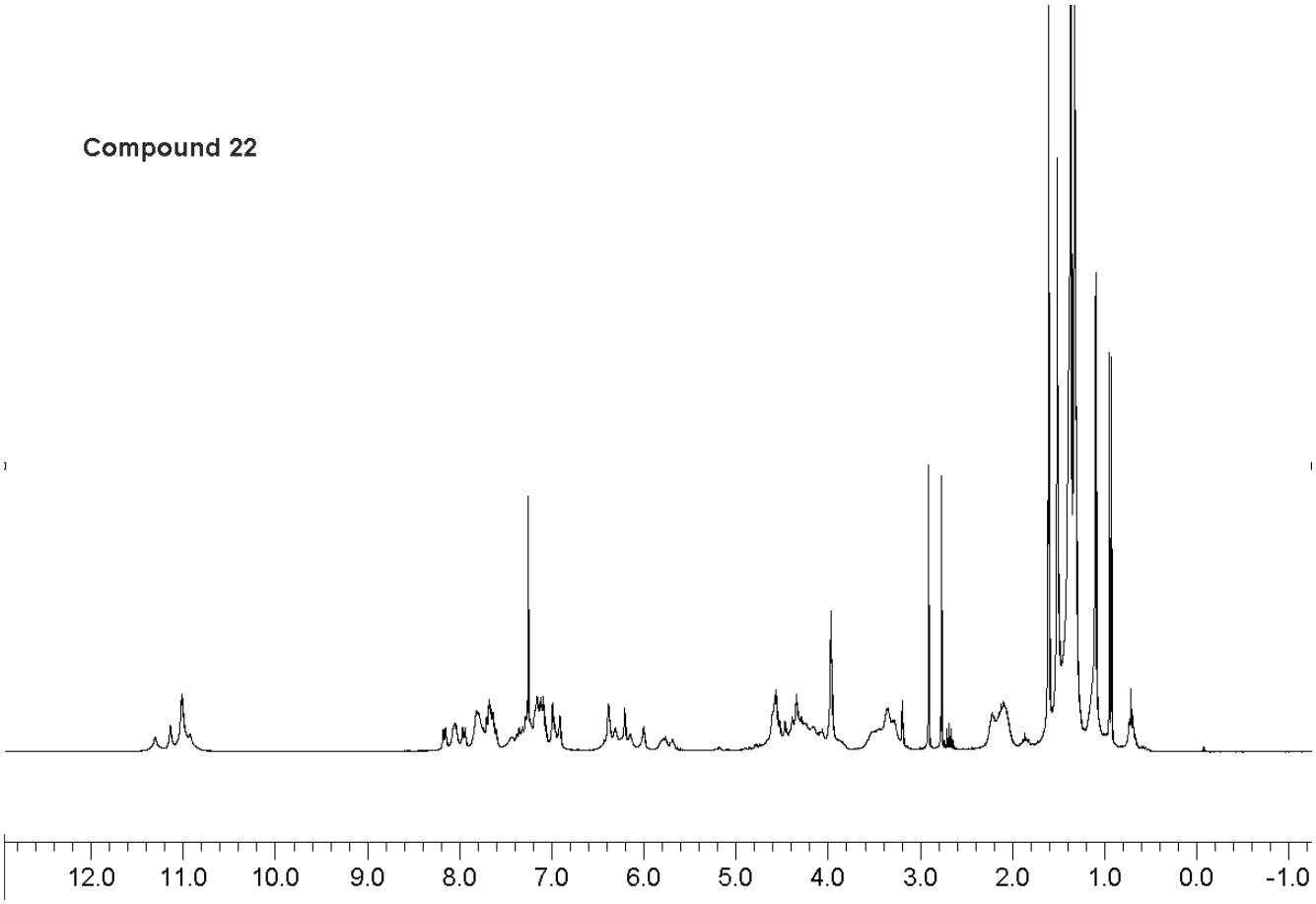

Compound 19
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

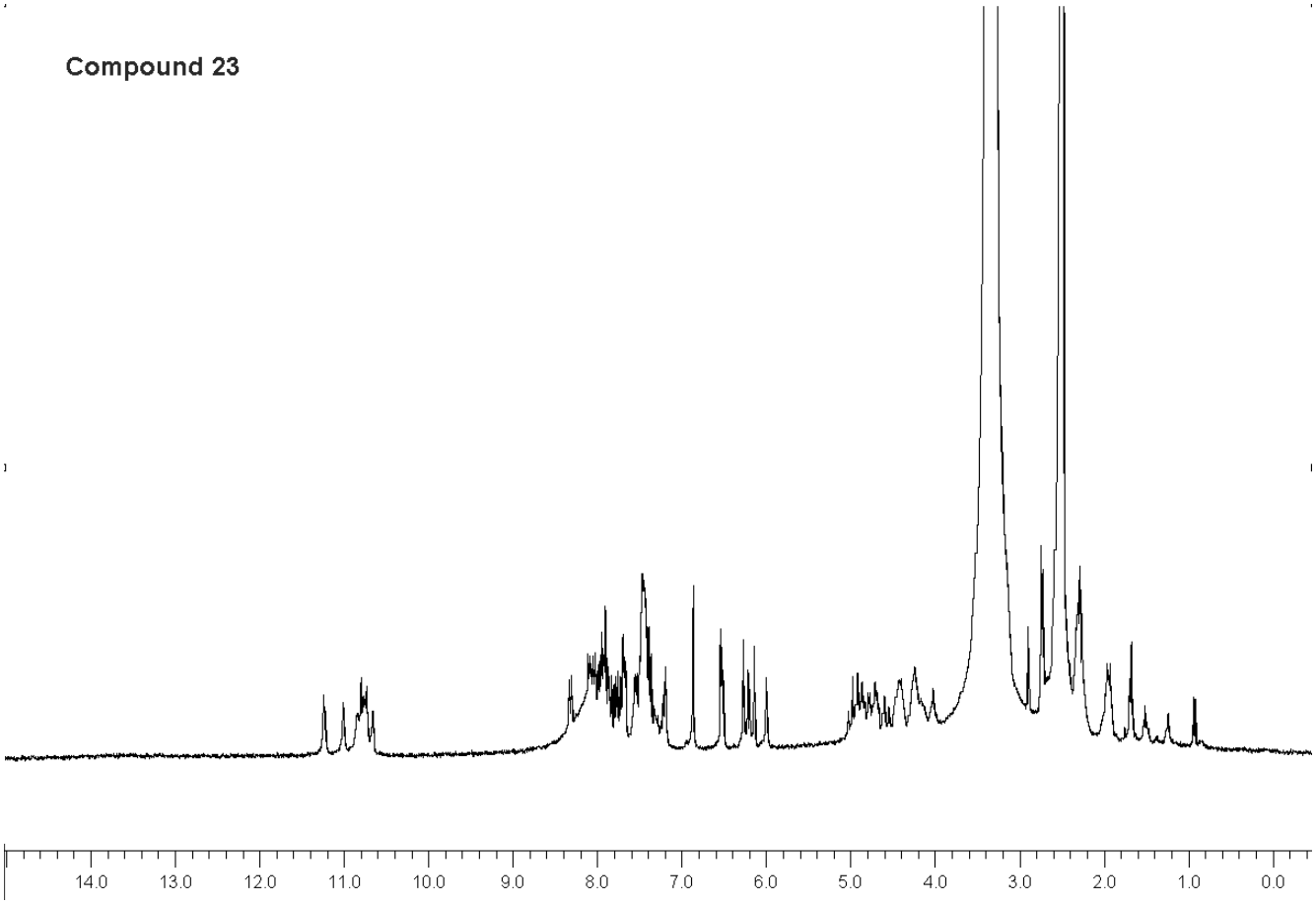

Compound 20
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Compound 21



Compound 22




Compound 23
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0