Design, semi-synthesis and molecular docking of new antibacterial and antibiofilm triazole conjugates from hydroxy-triterpene acids and fluoroquinolones

Besma Boulila[†,‡], Mabrouk Horchani[†], Raphael Duval [§], Mohamed Othman[‡], Adam Daïch[‡], Hichem Ben Jannet[†], Anis Romdhane[†,*], Ata Martin Lawson[‡,*]

[†]University of Monastir, Faculty of Sciences of Monastir, Laboratory of Heterocyclic Chemistry, Natural Products and Reactivity (LR11ES39), Team: Medicinal Chemistry and Natural Products, Avenue of Environment, 5019 Monastir, Tunisia

[‡]Normandie Univ, UNILEHAVRE, URCOM, EA 3221, INC3M, FR 3038 CNRS, F-76600 Le Havre, France E-mail: lawsona@univ-lehavre.fr

[§]Université de Lorraine, CNRS, L2CM, F-54000 Nancy, France

Supporting Information

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I. General Experimental Details

Unless otherwise specified, all chemicals were purchased from commercial sources and used without further purification (Fisher scientific, Sigma-Aldrich, TCI).

All reactions were monitored by TLC on silica plates (0.20 mm silica gel 60 with UV_{254} indicator) and visualized using a combination of UV light and/or an ethanolic solution of p-anisaldehyde as a staining solution. Purifications were performed using an automated purification system Büchi C-815 puriflash, using 200-800 nm UV scan and ELSD as a detector. ^{1}H NMR (300 MHz), ^{13}C proton decoupling (75 MHz), and ^{19}F (282 MHz) spectra were recorded on a Bruker Advance III 300 MHz spectrometer using TMS as the internal standard (δ = 0). All chemical compounds were reported as δ values (ppm) and coupling constants (J) were expressed in Hz. Melting points were recorded on a scientific analyzer SMP 10 apparatus and are uncorrected. Optical rotations were measured on a JASCO PTC-262 polarimeter at 568.6 nm with a path length of 10 cm. [α] is expressed in $deg.cm^3.g^{-1}.dm^{-1}$, and c is expressed in g/100 cm^3. FT-IR spectra were recorded with a PerkinElmer Frontier. High-resolution mass spectra (HRMS) were measured on an Agilent 6530 QTOF-LC/MS mass analyzer in ESI^+.

II. General procedures for the synthesis of compounds 3-8

General procedure for the synthesis of benzyl maslinate 3

BnBr (1.32 mL, 11.10 mmol) was added to a mixture of MA (3.50 g, 7.40 mmol) and K_2CO_3 (1.53 g, 11.10 mmol) in DMF (30 mL). The reaction was stirred for 4 h at room temperature before it was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash column chromatography (cyclohexane/AcOEt 7/3) afforded compound **3** as a white solid (4.08 g, 98%), mp: 167-169 °C. **IR (ν_{max} / cm^{-1})**: 3266, 2943, 1731, 1156, 695. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.37 - 7.29 (m, 5H), 5.29 (t, *J* = 3.2 Hz, 1H), 5.12 - 5.02 (m, 2H), 3.73 - 3.64 (m, 1H), 3.01 - 2.97 (m, 1H), 2.94 - 2.88 (m, 1H), 2.32 - 2.29 (m, 2H), 2.03 - 1.86 (m, 4H), 1.75 - 1.48 (m, 8H), 1.44 - 1.17 (m, 7H), 1.12 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H), 0.60 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.6, 143.9, 136.5, 128.5 (x2), 128.1 (x2), 128.0, 122.4, 84.0, 69.1, 66.1, 55.4, 47.7, 46.8, 46.5, 46.0, 41.8, 41.5, 39.5, 39.3, 38.4, 34.0, 33.2, 32.7, 32.5, 30.8, 28.7, 27.7, 26.0, 23.8, 23.6, 23.2, 18.5, 17.0, 16.9, 16.7. **HRMS (ESI^+)**: Calcd for $C_{37}H_{54}NaO_4$ $[M+Na]^+$ 585.3920, found 585.3914.

General procedure for the synthesis of benzyl oleanolate 4

BnBr (1.37 mL, 11.49 mmol) was added to a mixture of OA (3.50 g, 7.66 mmol) and K_2CO_3 (1.59 g, 11.49 mmol) in DMF (30 mL). The reaction was stirred for 4 h at room temperature before it was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash column chromatography (cyclohexane/AcOEt 9/1) afforded compound **4** as a white solid (3.98 g, 95%), mp: 195-197 °C. **IR (ν_{max} / cm^{-1})**: 3583, 2921, 1725, 1162, 741. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H d 7.36 - 7.29 (m, 5H), 5.28 (t, *J* = 3.2 Hz, 1H), 5.12 - 5.01 (m, 2H), 3.22 - 3.12 (m, 1H), 2.95 - 2.88 (m, 1H), 2.03 - 1.92 (m, 1H), 1.86 - 1.82 (m, 2H), 1.77 - 1.46 (m, 12H), 1.42 - 1.16 (m, 8H), 1.12 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.77 (s, 3H), 0.60 (s, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.6, 143.8, 136.6, 128.6 (x2), 128.1 (x2), 128.0, 122.6, 79.2, 66.1, 55.4, 47.8, 46.9, 46.0, 41.8, 41.5, 39.4, 38.9, 38.6, 37.2, 34.0, 33.3, 32.9, 32.5, 30.9, 28.3, 27.8, 27.4, 26.0, 23.8, 23.6, 23.2, 18.5, 17.0, 15.7, 15.5. **HRMS (ESI$^+$)**: Calcd for $C_{37}H_{54}NaO_3$ $[M+Na]^+$ 569.3971, found 569.3973.

General procedure for the synthesis of compound 5

To a solution of benzyl maslinate **3** (3.00 g, 5.33 mmol), pyridine (1.29 mL, 16 mmol) and DMAP (cat.) in CH_2Cl_2 (50 mL) was added chloroacetyl chloride (1.28 mL, 16 mmol) dropwise over a period of 30 min at 0 °C. The reaction mixture was stirred at room temperature for 4 h then diluted with water and extracted with CH_2Cl_2. The organic layers were washed with saturated sodium bicarbonate solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash column chromatography (cyclohexane/AcOEt 8/2) gave compound **7** as a white solid (2.48 g, 65%), mp: 89-91 °C. **IR (ν_{max} / cm^{-1})**: 2946, 1729, 1159, 994, 695. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.37 - 7.30 (m, 5H), 5.27 (t, *J* = 3.2 Hz, 1H), 5.22 - 5.12 (m, 1H), 5.12 - 5.01 (m, 2H), 4.85 (d, *J* = 10.3 Hz, 1H), 4.04 (s, 2H), 3.95 (s, 2H), 2.91 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.94 - 1.82 (m, 2H), 1.72 - 1.49 (m, 8H), 1.45 - 1.39 (m, 5H), 1.34 - 1.20 (m, 4H), 1.11 (s, 3H), 1.03 (s, 3H), 0.92 (s, 9H), 0.90 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 167.3, 167.0, 144.0, 136.5, 128.5 (x2), 128.1 (x2), 128.1, 122.0, 82.4, 72.3, 66.1, 54.9, 47.6, 46.8, 45.9, 43.7, 41.8, 41.4, 41.0, 40.9, 39.7, 39.4, 38.3, 34.0, 33.2, 32.5, 32.4, 30.8, 28.5, 27.6, 26.0, 23.8, 23.6, 23.1, 18.3, 17.7, 16.9, 16.5. **HRMS (ESI$^+$)**: Calcd for $C_{41}H_{57}Cl_2O_6$ $[M+H]^+$ 715.3532, found 715.3515.

General procedure for the synthesis of compound 6

To a solution of benzyl oleanolate **4** (3.00 g, 5.48 mmol), pyridine (665 µL, 8.23 mmol) and DMAP (cat.) in CH_2Cl_2 (50 mL) was added chloroacetyl chloride (656 µL, 8.23 mmol)

dropwise over a period of 30 min at 0 °C. The reaction mixture was stirred at room temperature for 4 h then diluted with water and extracted with CH_2Cl_2. The organic layers were washed with saturated sodium bicarbonate solution and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated to give compound **6** as a white solid (2.56 g, 75%), mp: 168-170 °C. **IR (ν_{max} / cm^{-1})**: 2946, 1729, 1159, 994, 695. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H d 7.37 - 7.30 (m, 5H), 5.27 (t, *J* = 3.2 Hz, 1H), 5.22 - 5.12 (m, 1H), 5.12 - 5.01 (m, 2H), 4.85 (d, *J* = 10.3 Hz, 1H), 4.04 (s, 2H), 3.95 (s, 2H), 2.91 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.94 - 1.82 (m, 2H), 1.72 - 1.49 (m, 8H), 1.45 - 1.39 (m, 5H), 1.34 - 1.20 (m, 4H), 1.11 (s, 3H), 1.03 (s, 3H), 0.92 (s, 9H), 0.90 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 167.3, 167.0, 144.0, 136.5, 128.5 (x2), 128.1 (x2), 128.1, 122.0, 82.4, 72.3, 66.1, 54.9, 47.6, 46.8, 45.9, 43.7, 41.8, 41.4, 41.0, 40.9, 39.7, 39.4, 38.3, 34.0, 33.2, 32.5, 32.4, 30.8, 28.5, 27.6, 26.0, 23.8, 23.6, 23.1, 18.3, 17.7, 16.9, 16.5.**HRMS (ESI$^+$)**: Calcd for $C_{41}H_{57}Cl_2O_6$ $[M+H]^+$ 715.3532, found 715.3515.

General procedure for the synthesis of compound 7

Sodium azide (0.54 g, 8.38 mmol) was added portion-wise to a solution of compound **5** (2.00 g, 2.80 mmol). The reaction mixture was stirred for 6 h at 75 °C then quenched with water and extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (cyclohexane/AcOEt 8/2) to afford compound **7** as a yellow solid (1.53 g, 75%), mp: 93-95 °C. **IR (ν_{max} / cm^{-1})**: 2945, 2107, 1737, 1180, 739. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.38 - 7.32 (m, 5H), 5.29 - 5.18 (m, 2H), 5.12 - 5.02 (m, 2H), 4.87 (d, *J* = 10.2 Hz, 1H), 3.87 (s, 2H), 3.78 (s, 2H), 2.96 - 2.88 (m, 1H), 2.10 - 1.85 (m, 4H), 1.71 - 1.53 (m, 8H), 1.42 - 1.21 (m, 8H), 1.12 (s, 3H), 1.03 (s, 3H), 0.93 (s, 9H), 0.90 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C177.5, 168.3, 168.1, 144.0, 136.5, 128.6 (x2), 128.2 (x2), 128.1, 122.0, 82.4, 72.1, 66.1, 55.0, 50.7, 50.6, 47.7, 46.8, 46.0, 43.9, 41.9, 41.5, 39.7, 39.5, 38.4, 34.0, 33.2, 32.5, 32.5, 30.9, 29.8, 28.6, 27.6, 26.0, 23.8, 23.6, 23.1, 18.3, 17.8, 16.9, 16.5. **HRMS (ESI$^+$)**: Calcd for $C_{41}H_{56}N_6NaO_6$ $[M+Na]^+$ 751.4159, found 751.4167.

General procedure for the synthesis of compound 8

Sodium azide (0.31 g, 4.81 mmol) was added portion-wise to a solution of compound **6** (2.00 g, 3.20 mmol). The reaction mixture was stirred for 6h at 75 °C then quenched with water and extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography

(cyclohexane/AcOEt 9.5/0.5) to afford compound **8** as a white solid (1.41 g, 70%), mp: 138-140 °C. **IR (ν_{max} / cm^{-1})**: 2943, 2110, 1727, 1299, 689. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.37 - 7.30 (m, 5H), 5.26 (t, *J* = 3.7 Hz, 1H), 5.12 - 5.02 (m, 2H), 4.61 (t, *J* = 8.1 Hz, 1H), 3.85 (s, 2H), 2.90 (dd, *J* = 14.1, 4.5 Hz, 1H), 2.04 - 1.76 (m, 4H), 1.75 - 1.49 (m, 11H), 1.44 - 1.17 (m, 7H), 1.12 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.60 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 168.2, 143.8, 136.5, 128.5 (x2), 128.1 (x2), 128.0, 122.4, 83.3, 66.0, 55.3, 50.7, 47.6, 46.8, 45.9, 41.8, 41.4, 39.4, 38.1, 37.8, 37.0, 33.9, 33.2, 32.7, 32.4, 30.8, 28.2, 27.7, 25.9, 23.7, 23.6, 23.5, 23.1, 18.3, 16.9, 16.8, 15.4. **HRMS (ESI$^+$)**: Calcd for $C_{39}H_{55}N_3NaO_4$ $[M+Na]^+$ 652.4090, found 652.4068

III. General procedure for the synthesis of compounds 11a–k

A mixture of the appropriate aniline **9a-k** (25 mmol) and diethyl ethoxymethylenemalonate (5.55 mL, 27.5 mmol) was stirred and heated at 120 °C for 2 h. After cooling, the reaction mixture was put under reduced pressure to evaporate the ethanol formed during the reaction and to yield compounds **10a-k** which were used in the next step without any further purification. The intermediate malonate esters **10a-k** above were added portion-wise to 50 mL of boiling diphenyl ether. The solution was refluxed at 250 °C between 2 and 6 hours. After cooling to room temperature, cyclohexane (50 mL) was added and the formed solid precipitate was filtrated and washed with cyclohexane (3 x 30 mL). The product was then stirred for 20 min in ethanol (100 mL) and filtered again to ensure that diphenyl ether was fully removed. The desired quinolone derivatives **11a-k** were obtained in good yields ranging from 48 to 92%.
It was difficult to characterize the chemical structure of compounds **11a-k** by ^{1}H NMR and ^{13}C NMR spectra due to their poor solubility even in DMSO-*d*$_6$.

IV. General procedure for the synthesis of compounds 12a–k

A mixture of the appropriate quinolone derivative **11a-k** (3 mmol) and DIPEA (4.5 mmol) in anhydrous DMF (10 mL) was stirred at 70 °C for 30 min until all solid was dissolved. Propargyl bromide (4.5 mmol) was then added dropwise and the solution was heated at 70 °C for 12h. Water (10 mL) was then added to the reaction mixture and extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using cyclohexane /ethyl acetate (3/7) as eluent to obtain the title compounds **12a-k**.
(12a) Yield: 83%, mp: 197-199 °C. **IR (ν_{max} / cm^{-1})**: 3211, 1717, 1312, 1104, 820. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.53 (s, 1H), 8.71 (d, *J* = 2.6 Hz ,1H), 7.64 (dd, *J* = 8.9, 2.6 Hz, 1H),

7.51 (d, J = 9.0 Hz, 1H), 4.89 (d, J = 2.6 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.62 (t, J = 2.5 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.2, 165.2, 148.6, 137.1, 133.1, 132.0, 130.1, 127.4, 117.7, 111.9, 77.6, 75.0, 61.2, 43.8, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{30}H_{24}Cl_2N_2NaO_6$ $[2M+Na]^+$ 601.0909, found 601.0947.

(12b) Yield: 88%, mp: 205-207 °C. **IR (ν_{max} / cm^{-1})**: 3171, 1671, 1318, 1174, 815. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.57 (s, 1H), 8.17 - 8.11 (m, 1H), 7.61 – 7.57 (m, 1H), 7.48 – 7.42 (m, 1H), 4.91 (s, 2H), 4.39 (q, J = 7.3 Hz, 2H), 2.62 (s, 1H), 1.40 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.6, 165.4, 160.3 (d, J = 251.3 Hz), 148.5, 135.1, 131.0, 121.2 (d, J = 24.3 Hz), 118.3 (d, J = 9.0 Hz), 113.2 (d, J = 22.2 Hz), 110.0, 77.6, 75.0, 61.2, 43.9, 14.6. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{13}FNO_3$ $[M+H]^+$ 274.0879, found 274.0895.

(12c) Yield: 82%, mp: 190-192 °C. **IR (ν_{max} / cm^{-1})**: 3191, 1670, 1312, 1120, 821. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.72 (d, J = 2.1 Hz ,1H), 8.57 (s, 1H), 7.89 (dd, J = 8.9, 2.2 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 4.95 (d, J = 2.5 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.63 (t, J = 2.5 Hz, 1H), 1.39 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.6, 164.8, 149.2, 140.6, 129.1 (q, J = 3.3 Hz), 128.8, 127.6 (q, J = 33.6 Hz), 125.7 (q, J = 4.0 Hz), 123.7 (q, J = 272.3 Hz), 117.1, 112.6, 77.8, 74.8, 61.3, 43.8, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{16}H_{13}F_3NO_3$ $[M+H]^+$ 324.0848, found 324.0864.

(12d) Yield: 80%, mp: 194-196 °C. **IR (ν_{max} / cm^{-1})**: 3317, 1727, 1312, 1096, 808. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.71 (d, J = 2.1 Hz ,1H), 8.57 (s, 1H), 7.88 (dd, J = 8.8, 2.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 4.96 (d, J = 2.5 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 2.64 (t, J = 2.3 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.6, 164.7, 149.2, 140.5, 129.1 (q, J = 3.3 Hz), 128.7, 127.6 (q, J = 33.7 Hz), 125.7 (q, J = 4.0 Hz), 123.6 (q, J = 270.5 Hz), 117.1, 112.5, 77.8, 74.8, 61.3, 43.9, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{16}H_{12}F_3NNaO_4$ $[M+Na]^+$ 362.0616, found 362.0487.

(12e) Yield: 78%, mp: 152-154 °C. **IR (ν_{max} / cm^{-1})**: 3222, 1690, 1311, 1147, 785. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.55 (s, 1H), 8.34 – 8.31 (m, 1H), 7.47 – 7.34 (m, 2H), 5.09 (t, J = 2.7 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 2.58 (t, J = 2.5 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.1, 165.3, 152.0 (d, J = 250.2 Hz), 150.4, 131.8, 128.0 (d, J = 7.3 Hz), 125.8 (d, J = 8.3 Hz), 124.0 (d, J = 3.5 Hz), 120.0 (d, J = 22.8 Hz), 111.9, 76.9, 76.2, 61.3, 47.2

(d, *J* = 17.6 Hz), 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{13}FNO_3$ $[M+H]^+$ 274.0879, found 274.0885.

(12f) Yield: 73%, mp: 52-54 °C. **IR (ν_{max} / cm^{-1})**: 3262, 1713, 1305, 1125, 778. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 9.36 (s, 1H), 8.54 (d, *J* = 8.4 Hz ,1H), 8.09 (d, *J* = 7.2 Hz ,1H), 7.59 (t, *J* = 7.9 Hz, 1H), 5.02 (d, *J* = 2.4 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 164.2, 162.7, 153.0, 147.4, 130.1 (q, *J* = 5.5 Hz), 128.6, 127.6 (q, *J* = 29.2 Hz), 125.7, 124.9, 123.8 (q, *J* = 274.1 Hz), 115.2, 77.9, 77.4, 63.3, 61.9, 14.2. **HRMS (ESI$^+$)**: Calcd for $C_{16}H_{13}F_3NO_3$ $[M+H]^+$ 324.0848, found 324.0867.

(12g) Yield: 49%, mp: 159-161 °C. **IR (ν_{max} / cm^{-1})**: 3262, 1679, 1326, 1169, 786. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.57 (s, 1H), 8.46 (dd, *J* = 8.0, 1.6 Hz ,1H), 7.62 - 7.58 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 2.5 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.56 (t, *J* = 2.5 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.0, 164.9, 151.4, 138.2 (q, *J* = 1.6 Hz), 132.0, 131.8, 126.8, 125.5, 125.0 (q, *J* = 1.7 Hz), 120.6 (q, *J* = 260.6 Hz), 112.3, 76.9, 75.9, 61.3, 47.5, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{16}H_{12}F_3NNaO_4$ $[M+Na]^+$ 362.0616, found 362.0631.

(12h) Yield: 66%, mp: 174-176 °C. **IR (ν_{max} / cm^{-1})**: 3317, 1693, 1315, 1115, 799. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.65 (s ,1H), 8.63 (d, *J* = 9.5 Hz ,1H), 7.84 (s ,1H), 7.68 (d, *J* = 8.3 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.66 (t, *J* = 2.5 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.5, 165.1, 149.3, 138.5, 134.5 (q, *J* = 31.7 Hz), 129.5, 129.4 (q, *J* = 245.5 Hz), 125.3, 121.8 (q, *J* = 3.4 Hz), 113.7 (q, *J* = 4.2 Hz), 112.6, 78.1, 74.6, 61.4, 43.8, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{16}H_{13}F_3NO_3$ $[M+H]^+$ 324.0848, found 324.0858.

(12i) Yield: 52%, mp: 166-168 °C. **IR (ν_{max} / cm^{-1})**: 3243, 1680, 1316, 1160, 804. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H d 8.49 (s ,1H), 8.33 (dd, *J* = 2.3, 1.2 Hz, 1H), 7.51 (dd, *J* = 13.3, 2.4 Hz,1H), 5.06 (d, *J* = 2.7 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.60 (t, *J* = 2.5 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 171.6, 164.5, 151.6 (d, *J* = 257.1 Hz), 150.3, 132.2, 127.0 (d, *J* = 7.2 Hz), 126.5 (d, *J* = 3.6 Hz), 123.2 (d, *J* = 26.0 Hz), 118.5 (d, *J* = 9.5 Hz), 111.8, 77.1, 75.9, 61.2, 47.2 (d, *J* = 17.1 Hz), 14.4. **HRMS (ESI$^+$)**: Calcd for $C_{30}H_{22}Br_2F_2N_2NaO_6$ $[2M+Na]^+$ 724.9710, found 724.9737.

(12j) Yield: 48%, mp: 155-157 °C. **IR (ν_{max} / cm^{-1})**: 3195, 1687, 1310, 1173, 803. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H d 8.57 – 8.56 (m, 1H), 8.50 (s, 1H), 7.69 (dd, *J* = 13.2, 2.1 Hz, 1H), 5.06 (d, *J* = 2.7 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.60 (t, *J* = 2.4 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 171.4, 164.5, 151.2 (d, *J* = 253.7 Hz), 150.3, 132.9 (d, *J* = 3.2 Hz), 132.3 (d, *J* = 2.4 Hz), 128.5 (d, *J* = 25.3 Hz), 127.7 (d, *J* = 7.2 Hz), 112.1 (d, *J* = 3.2 Hz), 88.3 (d, *J* = 8.2 Hz), 77.1, 75.9, 61.2, 47.2 (d, *J* = 17.1 Hz), 14.4. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{12}FINO_3$ $[M+H]^+$399.9846, found 399.9876.

(12k) Yield: 81%, mp: 175-177 °C. **IR (ν_{max} / cm^{-1})**: 3221, 1681, 1322, 1065, 808. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.54 (s, 1H), 8.19 – 8.13 (m, 1H), 5.07 (t, *J* = 3.0 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 2.5 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 171.5, 164.8, 150.8, 148.8 (ddd, *J* = 253.5, 11.0, 2.2 Hz), 143.7 (td, *J* = 257.8, 15.8 Hz), 141.7 (ddd, *J* = 255.8, 14.3, 2.4 Hz), 125.8, 125.6, 110.1 (dd, *J* = 18.8, 3.1 Hz), 77.5, 75.4 (d, *J* = 2.6 Hz), 61.5, 47.0 (d, *J* = 16.3 Hz), 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{11}F_3NO_3$ $[M+H]^+$ 310.0691, found 310.0695.

IV. General procedure for the synthesis of compounds 13a-k

To a mixture of propargylated quinolone **12a-k** (0.30 mmol) and azide **(**0.11 g, 0.15 mmol**)** in CH_2Cl_2 (1 mL) and H_2O (1 mL) were added $CuSO_4 \cdot 5H_2O$ (15.09 mg, 0.06 mmol) and sodium ascorbate (23.92 mg, 0.12 mmol). The reaction mixture was stirred at room temperature for 8-10 h then diluted with water and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified using silica gel flash column chromatography.

(13a) White solid, yield: 92%, mp > 290 °C. $[\alpha]_D^{24}$ +47 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2932, 1720, 1619, 1486, 1227, 1161, 1108, 815, 749, 697. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.69 (s, 1H), 8.67 (s, 1H), 8.25 (s, 1H), 8.22 (s, 1H), 8.14 - 7.86 (m, 2H), 7.67 - 7.46 (m, 4H), 7.37 - 7.29 (m, 5H), 5.58 - 5.41 (m, 4H), 5.23 (t, *J* = 3.5 Hz, 1H), 5.19 - 5.00 (m, 6H), 4.95 - 4.85 (m, 1H), 4.49 (d, *J* = 10.1 Hz, 1H), 4.29 (q, *J* = 6.7 Hz, 4H), 2.88 (dd, *J* = 12.7, 3.9 Hz, 1H), 2.01 - 1.87 (m, 3H), 1.77 - 1.47 (m, 9H), 1.41 - 1.28 (m, 9H), 1.24 - 1.14 (m, 5H), 1.09 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H), 0.57 (s, 3H), 0.53 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.6, 173.6, 165.8, 165.5, 165.3, 165.3, 149.5, 149.5, 144.0, 142.3, 142.2, 137.4, 137.4, 136.5, 133.2, 133.1, 131.9, 131.9, 131.7, 131.7, 128.5 (x2), 128.1 (x2), 128.1, 127.0, 127.0, 125.3, 125.3, 121.8, 118.7, 118.7, 111.6, 111.5, 82.8, 72.2, 66.1, 61.2, 61.2, 54.7,

51.1, 51.0, 49.9, 49.8, 47.5, 46.8, 45.9, 41.8, 41.4, 39.6, 39.4, 38.3, 34.0, 33.2, 32.5, 32.4, 30.8, 29.8, 28.4, 27.6, 26.0, 23.8, 23.5, 23.1, 18.2, 17.4, 16.9, 16.5, 14.5, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{71}H_{81}Cl_2N_8O_{12}$ $[M+H]^+$ 1307.5351, found 1307.5358.

(13b) White solid, yield: 94%, mp: 263-265 °C. $[\alpha]_D^{24}$+51 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2943, 1720, 1616, 1492, 1261, 1211, 1152, 818, 716, 696. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.74 (s, 1H), 8.71 (s, 1H), 8.05 - 7.96 (m, 3H), 7.84 (s, 1H), 7.68 - 7.60 (m, 2H), 7.40 - 7.29 (m, 7H), 5.53 (s, 1H), 5.51 (s, 1H), 5.25 - 4.99 (m, 7H), 4.90 (td, *J* = 10.2, 4.4 Hz, 1H), 4.44 (d, *J* = 10.2 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 4H), 2.88 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.01 - 1.85 (m, 3H), 1.82 - 1.73 (m, 2H), 1.71 - 1.40 (m, 7H), 1.35 (t, *J* = 7.0 Hz, 6H), 1.29 - 1.13 (m, 6H), 1.09 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H), 0.57 (s, 3H), 0.53 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.8, 173.7, 165.7, 165.6, 165.5, 165.4, 160.2 (d, *J* = 248.5 Hz), 160.1 (d, *J* = 248.7 Hz), 149.3, 149.3, 144.1, 142.4, 142.3, 136.5, 135.4 (d, *J* = 5.2 Hz), 135.4 (d, *J* = 5.1 Hz), 131.1 (d, *J* = 7.0 Hz), 131.0 (d, *J* = 7.3 Hz), 128.6 (x2), 128.2 (x2), 128.1, 125.1, 125.0, 121.8, 121.3 (d, *J* = 25.2 Hz), 121.2 (d, *J* = 24.6 Hz), 119.2 (d, *J* = 6.9 Hz), 119.1 (d, *J* = 7.4 Hz), 112.8 (d, *J* = 23.5 Hz), 112.8 (d, *J* = 23.3 Hz), 110.8, 110.8, 82.8, 72.2, 66.1, 61.2, 61.2, 54.7, 51.1, 51.0, 50.0, 49.9, 47.6, 46.8, 45.9, 43.7, 41.8, 41.4, 39.5, 39.4, 38.3, 34.0, 33.2, 32.4, 30.8, 29.8, 28.4, 27.6, 25.9, 23.8, 23.5, 23.1, 18.2, 17.4, 16.9, 16.4, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -114.5, -114.6. **HRMS (ESI$^+$)**: Calcd for $C_{71}H_{81}F_2N_8O_{12}$ $[M+H]^+$ 1275.4942, found 1275.4995.

(13c) White solid, yield: 93%, mp: 174-176 °C. $[\alpha]_D^{24}$+40 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2939, 1723, 1611, 1501, 1231, 1157, 1124, 806, 731, 698. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.75 (s, 2H), 8.69 - 8.60 (m, 2H), 7.99 (s, 1H), 7.90 (s, 1H), 7.87 - 7.74 (m, 4H), 7.37 - 7.29 (m, 5H), 5.55 (s, 4H), 5.24 - 4.86 (m, 8H), 4.53 (d, *J* = 10.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 4H), 2.88 (dd, *J* = 14.0, 4.3 Hz, 1H), 2.03 - 1.96 (m, 1H), 1.90 - 1.74 (m, 3H), 1.67 - 1.46 (m, 8H), 1.38 - 1.31 (m, 7H), 1.27 - 1.21 (m, 7H), 1.07 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H), 0.57 (s, 3H), 0.52 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 174.0, 173.9, 165.8, 165.5, 165.0, 165.0, 150.2, 150.2, 144.0, 142.0, 141.9, 141.0, 140.9, 136.4, 129.2, 129.2, 128.8, 128.7, 128.5 (x2), 128.1 (x2), 128.1, 127.4 (q, *J* = 33.8 Hz), 127.4 (q, *J* = 33.6 Hz), 125.4, 125.4, 125.3, 125.2, 123.5 (q, *J* = 271.2 Hz), 123.4 (q, *J* = 271.4 Hz), 121.7, 118.0, 117.9, 112.3, 112.3, 82.9, 72.2, 66.1, 61.3, 61.3, 54.6, 51.0, 50.9, 49.7, 47.5, 46.8, 45.9, 43.6, 43.6, 41.8, 41.4, 39.6, 39.3, 38.2, 37.8, 33.9, 33.2, 32.4, 30.8, 29.8, 28.4, 27.6, 25.9, 23.7, 23.5, 22.8,

18.2, 17.4, 16.8, 16.4, 14.4, 14.4. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.2, -62.2. **HRMS (ESI^+)**: Calcd for $C_{73}H_{80}F_6N_8NaO_{12}$ $[M+Na]^+$ 1397.5698, found 1397.5706.

(13d) White solid, yield: 91%, mp > 290 °C. $[\alpha]_D^{24}$ +57 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2937, 1725, 1610, 1502, 1231, 1156, 1124, 820, 730, 698. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.75 (s, 2H), 8.64 - 8.59 (m, 2H), 8.03 (s, 1H), 7.94 (s, 1H), 7.83 - 7.73 (m,4H), 7.37 - 7.29 (m, 5H), 5.56 (s, 4H), 5.22 (t, *J* = 3.9 Hz, 1H), 5.16 - 4.87 (m, 7H), 4.54 (d, *J* = 10.1 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 4H), 2.88 (dd, *J* = 13.4, 4.5 Hz, 1H), 1.99 - 1.85 (m, 2H), 1.80 - 1.41 (m, 10H), 1.35 - 1.14 (m, 14H), 1.06 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.79 (s, 3H), 0.58 (s, 3H), 0.52 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 173.8, 173.7, 165.8, 165.5, 164.9, 164.9, 150.1, 150.1, 144.1, 144.1, 142.0, 142.0, 141.0, 141.0, 136.5, 129.2, 129.1, 128.9, 128.9, 128.5 (x2), 128.2 (x2), 128.1, 127.4 (x2) (q, *J* = 33.8 Hz), 125.5, 125.5, 125.1, 125.0, 123.7 (x2) (q, *J* = 271.9 Hz), 121.8, 117.9, 117.8, 112.5, 112.5, 83.0, 72.2, 66.1, 61.2, 61.2, 54.7, 51.1, 51.0, 49.8, 49.7, 47.6, 46.8, 46.0, 43.7, 41.8, 41.5, 39.6, 39.4, 38.3, 34.0, 33.2, 32.4, 30.8, 29.8, 28.4, 27.7, 25.9, 23.7, 23.5, 23.1, 18.2, 17.4, 16.9, 16.4, 14.4, 14.4. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.2, -62.2. **HRMS (ESI^+)**: Calcd for $C_{73}H_{80}F_6N_8NaO_{14}$ $[M+Na]^+$ 1429.5596, found 1429.5623.

(13e) White solid, yield: 88%, mp: 278-280 °C. $[\alpha]_D^{24}$ +38 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2962, 1692, 1623, 1492, 1205, 1164, 1111, 801, 739, 703. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.80 (s, 1H), 8.78 (s, 1H), 8.32 - 8.23 (m, 2H), 7.99 (s, 1H), 7.86 (s, 1H), 7.41 - 7.28 (m, 9H), 5.74 - 5.57 (m, 4H), 5.25 (t, *J* = 3.2 Hz, 1H), 5.20 - 4.98 (m, 6H), 4.92 - 4.48 (m, 1H), 4.43 - 4.30 (m, 5H), 2.89 (dd, *J* = 10.3, 2.9 Hz, 1H), 2.00 - 1.88 (m, 2H), 1.79 - 1.52 (m, 8H), 1.41 - 1.33 (m, 8H), 1.28 - 1.14 (m, 8H), 1.10 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H), 0.55 (s, 3H), 054 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 173.3, 173.3, 165.6, 165.4, 165.4, 165.3, 151.9 (d, *J* = 249.3 Hz), 151.9 (d, *J* = 248.9 Hz), 151.7, 151.7, 144.1, 143.0, 143.0, 136.5, 132.0, 131.8, 128.6 (x2), 128.5 (d, *J* = 20.2 Hz), 128.4 (d, *J* = 22.9 Hz), 128.1 (x2), 128.1, 125.5 (d, *J* = 8.0 Hz), 125.4 (d, *J* = 7.5 Hz), 124.8, 124.6, 124.1 (d, *J* = 5.3 Hz), 124.0 (d, *J* = 4.5 Hz), 121.9, 120.0 (d, *J* = 23.1 Hz), 119.8 (d, *J* = 23.3 Hz), 111.8, 111.8, 82.5, 72.2, 66.1, 61.2, 61.2, 54.8, 52.8 (d, *J* = 15.4 Hz), 52.7 (d, *J* = 15.5 Hz), 51.1, 51.0, 47.6, 46.8, 46.0, 43.6, 41.9, 41.5, 39.5, 39.5, 38.3, 34.0, 33.2, 32.5, 30.8, 29.8, 28.4, 27.7, 26.0, 23.8, 23.6, 23.1, 18.2, 17.3, 16.9, 16.5, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -121.5. **HRMS (ESI^+)**: Calcd for $C_{71}H_{81}F_2N_8O_{12}$ $[M+H]^+$ 1275.5942, found 1275.6002.

(13f) White solid, yield: 86%, mp: 192-194 °C. $[\alpha]_D^{24}$+25 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2963, 1736, 1620, 1494, 1218, 1147, 1111, 803, 722, 702. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 9.38 (s, 2H), 8.47 - 8.43 (m, 2H), 8.14 - 8.03 (m, 4H), 7.57 - 7.51 (m, 2H), 7.37 - 7.29 (m, 5H), 5.51 - 5.42 (m, 4H), 5.27 (t, *J* = 3.6 Hz, 1H), 5.21 - 5.01 (m, 7H), 4.76 (d, *J* = 10.2 Hz, 1H), 4.51 - 4.41 (m, 4H), 2.90 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.06 - 1.97 (m, 2H), 1.89 - 1.80 (m, 2H), 1.72 - 1.53 (m, 9H), 1.47 - 1.37 (m, 8H), 1.29 - 1.14 (m, 5H), 1.10 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H), 0.89 (s, 6H), 0.82 (s, 3H), 0.57 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 166.1, 165.8, 164.4, 164.4, 163.6, 163.5, 153.1 (x2), 147.6, 147.6, 144.1, 143.5, 143.5, 136.5, 130.2 (x2) (q, *J* = 5.4 Hz), 128.5 (x2), 128.5, 128.4, 128.1 (x2), 128.1, 127.6, 127.6, 126.2, 126.2, 125.9, 125.9, 124.7, 124.7, 123.9 (x2) (q, *J* = 274.5 Hz), 121.8, 115.2, 115.1, 84.3, 72.5, 69.1, 69.1, 66.1, 62.0, 62.0, 54.9, 51.2, 51.1, 47.6, 46.8, 46.0, 43.7, 41.8, 41.4, 39.7, 39.4, 38.4, 33.9, 33.2, 32.4, 30.8, 29.8, 28.6, 27.7, 26.0, 23.8, 23.6, 23.1, 18.3, 17.6, 16.9, 16.5, 14.4, 14.4. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -60.2.**HRMS (ESI$^+$)**: Calcd for $C_{73}H_{80}F_6KN_8O_{12}$ $[M+K]^+$ 1413.5437, found 1413.5458.

(13g) White solid, yield: 84%, mp: 167-169 °C. $[\alpha]_D^{24}$+44 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2936, 1716, 1620, 1491, 1211, 1164, 1110, 803, 738, 701. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.77 (s, 1H), 8.76 (s, 1H), 8.49 - 8.44 (m, 2H), 7.82 (s, 1H), 7.69 (s, 1H), 7.55 - 7.51 (m, 2H), 7.41 - 7.28 (m, 7H), 5.78 - 5.64 (m, 4H), 5.25 (t, *J* = 3.5 Hz, 1H), 5.14 - 4.85 (m, 7H), 4.46 (d, *J* = 10.2 Hz, 1H), 4.40 - 4.32 (m, 4H), 2.89 (dd, *J* = 10.7, 3.7 Hz, 1H), 2.00 - 1.87 (m, 2H), 1.79 - 1.49 (m, 10H), 1.43 - 1.33 (m, 8H), 1.29 - 1.15 (m, 5H), 1.10 (s, 3H), 1.04 - 0.99 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.89 (s, 3H), 0.77 (s, 3H), 0.57 (s, 3H), 055 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C177.4, 173.1, 173.1, 165.6, 165.4, 165.2, 165.1, 152.8, 152.8, 144.1, 142.8, 142.7, 138.0, 137.9, 136.5, 132.4, 132.3, 132.2, 132.0, 128.6 (x2), 128.1 (x2), 128.1, 127.2, 127.2, 125.7, 125.6, 125.3, 125.3, 124.5, 124.3, 121.8, 120.6 (x2) (q, *J* = 260.7 Hz), 112.5, 112.4, 82.6, 72.1, 66.1, 61.3, 61.2, 54.7, 52.9, 52.8, 51.0, 50.9, 47.6, 46.8, 45.9, 43.6, 41.8, 41.4, 39.5, 39.4, 38.3, 33.9, 33.2, 32.4, 30.8, 28.3, 27.6, 26.0, 23.8, 23.5, 23.5, 23.1, 18.2, 17.3, 16.9, 16.5, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -56.7, -56.7. **HRMS (ESI$^+$)**: Calcd for $C_{73}H_{80}F_6N_8NaO_{14}$ $[M+Na]^+$ 1429.5596, found 1429.5596.

(13h) White solid, yield: 91%, mp: 256-258 °C. $[\alpha]_D^{24}$+36 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2937, 1725, 1619, 1490, 1218, 1169, 1132, 802, 741, 699. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H d 8.84 - 8.69 (m, 2H), 8.58 - 8.41 (m, 2H), 8.13 - 7.80 (m, 4H), 7.59 - 7.50 (m, 2H), 7.36 - 7.29 (m, 5H), 5.77 - 5.43 (m, 4H), 5.24 (t, *J* = 4.2 Hz, 1H), 5.16 - 4.89 (m, 7H), 4.49 (d, *J* = 9.8 Hz,

1H), 4.41 - 4.22 (m, 4H), 2.89 (dd, *J* = 14.1, 4.4 Hz, 1H), 2.00 - 1.88 (m, 2H), 1.82 - 1.52 (m, 10H), 1.43 - 1.33 (m, 8H), 1.28 - 1.14 (m, 6H), 1.09 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H), 0.65 (s, 3H), 0.54 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C177.5, 173.9, 173.8, 165.7, 165.4, 165.3, 165.2, 150.3, 150.3, 144.1, 141.7, 141.7, 139.0, 138.9, 136.5, 134.3 (q, *J* = 33.0 Hz), 134.3 (q, *J* = 32.9 Hz), 129.5 (x2) (q, *J* = 242.3 Hz), 129.1, 129.1, 128.5 (x2), 128.1 (x2), 128.1, 125.3, 125.2, 121.8, 121.6, 121.6, 121.4, 121.4, 114.4, 114.3, 112.3, 112.2, 82.8, 72.3, 66.1, 61.3, 61.3, 54.6, 51.2, 51.0, 49.3, 49.3, 47.5, 46.8, 45.9, 43.5, 41.8, 41.4, 39.5, 39.4, 38.2, 34.0, 33.2, 32.4, 30.8, 29.8, 28.4, 27.6, 25.9, 23.7, 23.5, 23.1, 18.2, 17.4, 16.9, 16.4, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.5, -62.7. **HRMS (ESI$^+$)**: Calcd for $C_{73}H_{80}F_6N_8NaO_{12}$ $[M+Na]^+$ 1397.5698, found 1397.5684.

(13i) White solid, yield: 87%, mp: 202-204 °C. $[\alpha]_D^{24}$+54 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2936, 1711, 1622, 1485, 1259, 1231, 1152, 804, 733, 698. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.76 (s, 1H), 8.74 (s, 1H), 8.33 - 8.25 (m, 2H), 8.13 (s, 1H), 8.06 (s, 1H), 7.51 - 7.44 (m, 2H), 7.36 - 7.28 (m, 5H), 5.62 (s, 4H), 5.29 - 5.00 (m, 7H), 4.93 - 4.85 (m, 1H), 4.54 (d, *J* = 10.2 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 4H), 2.88 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.81 - 1.76 (m, 2H), 1.71 - 1.52 (m, 7H), 1.37 - 1.32 (m, 6H), 1.27 - 1.15 (m, 9H), 1.09 (s, 3H), 0.90 (s, 3H), 0.88 (s, 6H), 0.78 (s, 3H), 0.58 (s, 3H), 0.53 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C177.4, 172.0, 172.0, 165.7, 165.5, 164.8, 164.8, 151.8, 151.8, 151.7 (d, *J* = 254.7 Hz), 151.6 (d, *J* = 254.6 Hz), 144.0, 142.4, 142.3, 136.4, 132.4, 132.3, 128.5 (x2), 128.1 (x2), 128.1, 127.5 (d, *J* = 12.8 Hz), 127.4 (d, *J* = 12.7 Hz), 126.6, 126.6, 125.0 (d, *J* = 3.1 Hz), 124.9 (d, *J* = 3.0 Hz), 123.3 (d, *J* = 26.5 Hz), 123.2 (d, *J* = 26.3Hz), 121.8, 118.3 (d, *J* = 9.8 Hz), 118.2 (d, *J* = 9.8 Hz), 111.6, 111.6, 82.5, 72.1, 66.1, 61.3, 61.3, 54.7, 52.9, 52.7, 51.1, 51.0, 47.5, 46.7, 46.4, 45.9, 43.6, 41.8, 41.4, 39.5, 39.4, 38.3, 33.9, 33.2, 32.4, 30.8, 29.8, 28.3, 27.6, 26.0, 23.8, 23.5, 23.1, 18.2, 17.3, 16.9, 16.6, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -114.5. **HRMS (ESI$^+$)**: Calcd for $C_{71}H_{79}Br_2F_2N_8O_{12}$ $[M+H]^+$ 1431.4152, found 1431.5258.

(13j) White solid, yield: 86%, mp: 243-245 °C. $[\alpha]_D^{24}$+63 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2930, 1728, 1607, 1472, 1231, 1151, 1124, 803, 731, 698. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.79 (s, 1H), 8.77 (s, 1H), 8.65 - 8.51 (m, 2H), 7.86 (s, 1H), 7.83 (s, 1H), 7.66 - 7.59 (m, 2H), 7.38 - 7.30 (m, 5H), 5.73 - 5.56 (m, 4H), 5.26 (t, *J* = 3.7 Hz, 1H), 5.19 - 4.94 (m, 6H), 4.88 - 4.78 (m, 1H), 4.50 (d, *J* = 10.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 4H), 2.90 (dd, *J* = 13.2, 4.4 Hz, 1H), 1.98 - 1.88 (m, 2H), 1.83 - 1.76 (m, 2H), 1.71 - 1.53 (m, 9H), 1.44 - 1.33 (m, 8H), 1.27 - 1.21 (m, 5H), 1.11 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.77 (s, 3H), 0.55 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 177.5, 171.7, 171.6, 165.6, 165.4, 165.4, 165.0, 151.8, 151.8, 151.2 (d, *J* = 245.1 Hz), 151.1 (d, *J* = 245.2 Hz),144.1, 142.8, 142.8, 136.5, 133.2, 133.2, 132.8, 132.7, 128.6 (x2), 128.5 (d, *J* = 25.4 Hz), 128.5 (d, *J* = 25.4 Hz), 128.2 (x2), 128.1, 128.0, 128.0, 125.2, 125.2, 121.8, 112.3, 112.2, 88.1, 88.0, 82.7, 72.1, 66.1, 61.4, 61.3, 54.7, 52.9, 52.8, 51.1, 51.1, 47.6, 46.8, 46.0, 43.6, 41.9, 41.8, 41.4, 39.5, 39.4, 38.3, 34.0, 33.2, 32.4, 30.8, 29.8, 28.4, 27.6, 26.1, 23.8, 23.5, 23.1, 18.2, 17.3, 16.9, 16.6, 14.5, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -56.6. **HRMS (ESI$^+$)**: Calcd for $C_{71}H_{79}F_2I_2N_8O_{12}$ $[M+H]^+$ 1527.3875, found 1527.3849.

(13k) White solid, yield: 90%, mp: 150-152 °C. $[\alpha]_D^{24}$+32 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2948, 1725, 1617, 1485, 1261, 1199, 1158, 803, 733, 697. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.88 (s, 2H), 8.15 - 8.07 (m, 2H), 7.97 (s, 1H), 7.83 (s, 1H), 7.38 - 7.30 (m, 5H), 5.76 - 5.59 (m, 4H), 5.26 (t, *J* = 3.4 Hz, 1H), 5.18 - 4.95 (m, 6H), 4.87 (td, *J* = 11.1, 4.3 Hz, 1H), 4.42 - 4.32 (m, 4H), 4.28 (d, *J* = 10.2 Hz, 1H), 2.90 (dd, *J* = 13.9, 4.2 Hz, 1H), 1.98 - 1.87 (m, 2H), 1.72 - 1.52 (m, 9H), 1.42 - 1.36 (m, 7H), 1.28 - 1.21 (m, 8H), 1.11 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.73 (s, 3H), 0.62 (s, 3H), 0.55 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.4, 171.5, 171.5, 165.4, 165.3, 164.9, 164.8, 152.2, 152.2,148.4 (ddd, *J* = 252.5, 19.7, 10.3 Hz), 148.3 (ddd, *J* = 252.4, 19.2, 9.8 Hz), 144.1, 143.3 (ddd, *J* = 256.6, 32.2, 15.8 Hz), 143.2 (ddd, *J* = 257.3, 33.0, 16.5 Hz), 142.3, 142.2, 141.6 (dd, *J* = 253.7, 14.3 Hz), 141.6 (dd, *J* = 254.4, 14.7 Hz), 136.4, 128.5 (x2), 128.1 (x2), 128.0, 126.1 (d, *J* = 6.9 Hz), 126.1 (d, *J* = 7.0 Hz), 125.7 (dd, *J* = 14.4, 6.0 Hz), 125.7 (dd, *J* = 14.2, 6.0 Hz), 124.8, 124.7, 121.7, 111.2, 111.1, 109.9 (dd, *J* = 17.2, 5.4 Hz), 109.9, (dd, *J* = 17.3, 5.5 Hz), 82.5, 72.0, 66.0, 61.3, 61.3, 54.7, 52.4 (d, *J* = 14.9 Hz), 52. (d, *J* = 14.6 Hz), 51.0, 50.8, 47.5, 46.7, 45.9, 43.6, 41.7, 41.4, 39.4, 33.9, 33.2, 32.4, 30.8, 29.8, 28.2, 27.6, 25.8, 23.7, 23.5, 23.0, 18.2, 17.2, 16.8, 16.3, 14.4, 14.4. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -134.7 (dd, *J* = 22.6, 4.7 Hz), -134.9 (dd, *J* = 22.2, 4.9 Hz), -142.7 - -142.8 (m, 2F), -150.2 (dd, *J* = 22.3, 18.1 Hz), -150.4 (dd, *J* = 22.7, 18.3 Hz). **HRMS (ESI$^+$)**: Calcd for $C_{71}H_{77}F_6N_8O_{12}$ $[M+H]^+$ 1347.5565, found 1347.5540.

V. General procedure for the synthesis of compounds 14a-k

To a mixture of propargylated quinolone **12a-k** (0.19 mmol) and azide **(**0.12 g, 0.19 mmol**)** in CH_2Cl_2 (1 mL) and H_2O (1 mL) were added $CuSO_4 \cdot 5H_2O$ (9.48 mg, 0.038 mmol) and sodium ascorbate (15.05 mg, 0.076 mmol). The reaction mixture was stirred at room temperature for 8-10 h then diluted with water and extracted with CH_2Cl_2. The organic layers were washed with

brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified using silica gel flash column chromatography.

(14a) White solid, yield: 94%, mp: 272-274 °C. $[\alpha]_D^{24}$+24 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2235, 1723, 1626, 1485, 1227, 1160, 1110, 815, 1133, 696. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.63 (s, 1H), 8.42 - 8.36 (m, 1H), 7.72 (s, 1H), 7.67 - 7.55 (m, 2H), 7.36 - 7.28 (m, 5H), 5.50 (s, 2H), 5.27 (t, *J* = 3.4 Hz, 1H), 5.14 (s, 2H), 5.11 - 5.01 (m, 2H), 4.52 (dd, *J* = 10.6, 4.5 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.04 - 1.93 (m, 2H), 1.83 - 1.80 (m, 2H), 1.70 - 1.52 (m, 9H), 1.46 - 1.34 (m, 7H), 1.28 - 1.21 (m, 5H), 1.10 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.74 (s, 3H), 0.60 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.2, 165.7, 165.1, 149.1, 143.9, 141.9, 137.4, 136.5, 133.1, 131.9, 130.2, 128.5 (x2), 128.1 (x2), 128.0, 127.3, 124.3, 122.4, 118.4, 111.7, 84.3, 66.1, 61.2, 55.3, 51.4, 49.8, 47.6, 46.8, 46.0, 41.8, 41.5, 39.4, 38.1, 37.8, 36.9, 34.0, 33.2, 32.7, 32.5, 30.8, 29.8, 28.2, 27.7, 26.0, 23.8, 23.5, 23.2, 18.2, 17.0, 16.5, 15.4, 14.5. **HRMS (ESI$^+$)**: Calcd for $C_{54}H_{68}ClN_4O_7$ $[M+H]^+$ 919.4777, found 919.4749.

(14b) White solid, yield: 96%, mp: 195-196 °C. $[\alpha]_D^{24}$+16 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2934, 1731, 1618, 1492, 1213, 1551, 1124, 816, 735, 698. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.64 (s, 1H), 8.12 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.71 (dd, *J* = 9.4, 4.0 Hz, 1H), 7.68 (s, 1H), 7.40 - 7.30 (m, 6H), 5.51 (s, 2H), 5.27 (t, *J* = 3.5 Hz, 1H), 5.13 (s, 2H), 5.11 - 5.01 (m, 2H), 4.52 (dd, *J* = 10.9, 4.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.84 - 1.80 (m, 2H), 1.67 - 1.52 (m, 11H), 1.43 - 1.37 (m, 5H), 1.28 - 1.20 (m, 6H), 1.10 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H), 0.61 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.5 (d, *J* = 2.1 Hz), 165.6, 165.5, 160.2 (d, *J* = 248.3 Hz), 149.0, 143.9, 142.1, 136.5, 135.3 (d, *J* = 1.6 Hz), 131.2 (d, *J* = 6.0 Hz), 128.5 (x2), 128.1 (x2), 128.1, 124.0, 122.3, 121.3 (d, *J* = 25.0 Hz), 118.9 (d, *J* = 7.8 Hz), 113.1 (d, *J* = 22.9 Hz), 111.1, 84.3, 66.1, 61.3, 55.3, 51.4, 50.0, 47.6, 46.8, 46.0, 41.8, 41.5, 39.4, 38.0, 37.8, 36.9, 34.0, 33.2, 32.7, 32.5, 30.8, 29.8, 28.2, 27.7, 26.0, 23.8, 23.5, 23.1, 18.2, 17.0, 16.6, 15.4, 14.6.**^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -114.7.**HRMS (ESI$^+$)**: Calcd for $C_{54}H_{68}FN_4O_7$ $[M+H]^+$ 903.5072, found 903.5054.

(14c) White solid, yield: 92%, mp: 169-171 °C. $[\alpha]_D^{24}$+30 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2048, 1726, 1610, 1503, 1157, 1125, 1098, 824, 732, 697. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.70 (s, 1H), 8.66 (s, 1H), 7.85 - 7.79 (m, 3H), 7.37 - 7.29 (m, 5H), 5.54 (s, 2H), 5.26 (t, *J* = 3.5

Hz, 1H), 5.15 (s, 2H), 5.11 - 5.01 (m, 2H), 4.51 (dd, *J* = 10.5, 4.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.88 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.83 - 1.78 (m, 2H), 1.70 - 1.48 (m, 10H), 1.41 - 1.32 (m, 6H), 1.28 - 1.16 (m, 6H), 1.09 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H), 0.58 (s, 3H), 0.57 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.4, 165.6, 164.8, 149.8, 143.9, 141.7, 140.9, 136.5, 129.2 (q, *J* = 3.2 Hz), 128.9, 128.5 (x2), 128.1 (x2), 128.0, 127.5 (q, *J* = 33.7 Hz), 125.7 (q, *J* = 4.0 Hz), 124.3, 123.4 (q, *J* = 272.9 Hz), 122.3, 117.6, 112.6, 84.3, 66.0, 61.3, 55.2, 51.4, 49.7, 47.6, 46.8, 46.0, 41.8, 41.5, 39.3, 38.0, 37.8, 36.9, 34.0, 33.2, 32.6, 32.5, 30.8, 29.8, 28.1, 27.7, 25.9, 23.7, 23.5, 23.1, 18.2, 16.9, 16.5, 15.4, 14.5.**^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.3. **HRMS (ESI^+)**: Calcd for $C_{55}H_{68}F_3N_4O_7$ $[M+H]^+$ 953.5040, found 953.5033

(14d) White solid, yield: 93%, mp: 213-215 °C. $[\alpha]_D^{24}$+48 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2927, 1726, 1610, 1500, 1231, 1157, 1125, 806, 749, 699. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.78 - 8.73 (m, 1H), 8.67 (s, 1H), 7.87 - 7.82 (m, 2H), 7.75 - 7.70 (m, 1H), 7.39 - 7.30 (m, 5H), 5.53 (s, 2H), 5.26 (t, *J* = 3.8 Hz, 1H), 5.14 (s, 2H), 5.11 - 5.01 (m, 2H), 4.52 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.84 - 1.79 (m, 2H), 1.67 - 1.52 (m, 11H), 1.44 - 1.39 (m, 6H), 1.29 - 1.21 (m, 5H), 1.09 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.73 (s, 3H), 0.58 (s, 3H), 0.57 (s, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.6, 165.6, 165.1, 149.7, 143.9, 141.8, 140.9, 136.6, 129.3 (q, *J* = 3.1 Hz), 129.0, 128.6 (x2), 128.1 (x2), 128.1, 127.6 (q, *J* = 34.1 Hz), 125.9 (q, *J*= 4.0 Hz), 124.1, 123.8 (q, *J* = 271.0 Hz), 122.4, 117.5, 112.3, 84.3, 66.1, 61.3, 55.3, 51.5, 49.8, 47.6, 46.9, 46.0, 41.8, 41.5, 39.4, 38.1, 37.8, 37.0, 34.0, 33.2, 32.7, 32.5, 30.8, 29.8, 28.2, 27.8, 26.0, 23.8, 23.5, 23.2, 18.2, 17.0, 16.6, 15.4, 14.6. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.3. **HRMS (ESI^+)**: Calcd for $C_{55}H_{67}F_3N_4NaO_8$ $[M+Na]^+$ 991.4809, found 991.4825.

(14e) White solid, yield: 89%, mp: 141-143 °C. $[\alpha]_D^{24}$+21 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2937, 1724, 1608, 1493, 1227, 1160, 1030, 804, 749, 697. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.66 (s, 1H), 8.29 (dd, *J* = 5.9, 1.9 Hz, 1H), 7.74 (s, 1H), 7.40 - 7.27 (m, 7H), 5.62 (d, *J* = 3.1 Hz, 2H), 5.26 (t, *J* = 3.5 Hz, 1H), 5.14 (s, 2H), 5.10 - 5.00 (m, 2H), 4.51 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.88 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.83 - 1.79 (m, 2H), 1.70 - 1.51 (m, 9H), 1.45 - 1.31 (m, 7H), 1.28 - 1.14 (m, 4H), 1.09 (s, 3H), 1.03 - 0.96 (m, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.73 (s, 3H), 0.57 (s, 3H), 0.56 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.1, 165.7, 164.9, 151.8 (d, *J* = 249.6 Hz), 151.3, 143.9, 142.8, 136.5, 131.8, 128.5 (x2), 128.4 (d, *J* = 31.8 Hz), 128.1 (x2), 128.0, 125.4 (d, *J* = 7.7 Hz),

124.2 (d, *J* = 3.4 Hz), 123.9 (d, *J* = 6.6 Hz), 122.3, 119.8 (d, *J* = 22.0 Hz), 111.9, 84.1, 66.0, 61.1, 55.2, 52.6 (d, *J* = 15.9 Hz), 51.3, 47.6, 46.8, 45.9, 41.8, 41.5, 39.3, 38.0, 37.7, 36.9, 33.9, 33.2, 32.6, 32.4, 30.8, 28.1, 27.7, 25.9, 23.7, 23.5, 23.5, 23.1, 18.2, 16.9, 16.4, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -122.0. **HRMS (ESI$^+$)**: Calcd for $C_{54}H_{68}FN_4O_7$ $[M+H]^+$ 903.5072, found 903.5106.

(14f) White solid, yield: 87%, mp: 234-236 °C. $[\alpha]_D^{24}$+39 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2930, 1728, 1620, 1458, 1213, 1149, 1110, 786, 724, 699. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 9.43 (s, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 7.91 (s, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.39 - 7.29 (m, 5H), 5.48 (s, 2H), 5.28 (t, *J* = 3.5 Hz, 1H), 5.19 (s, 2H), 5.11 - 5.01 (m, 2H), 4.61 - 4.54 (m, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.90 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.03 - 1.92 (m, 1H), 1.88 - 1.80 (m, 2H), 1.71 - 1.57 (m, 9H), 1.52 - 1.38 (m, 6H), 1.34 - 1.18 (m, 5H), 1.11 (s, 3H), 1.06 - 0.99 (m, 2H), 0.91 (s, 3H), 0.89 (s, 6H), 0.84 (s, 3H), 0.75 (s, 3H), 0.59 (s, 3H).**^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.6, 165.9, 164.4, 163.6, 153.1, 147.6, 143.9, 143.5, 136.5, 130.3 (q, *J* = 5.4 Hz), 128.5 (x2), 128.4, 128.1 (x2), 128.0, 127.7, 126.0, 125.3, 124.7, 123.9 (q, *J* = 271.3 Hz), 122.4, 115.2, 84.2, 69.2, 66.1, 62.0, 55.3, 51.3, 47.6, 46.9, 46.0, 41.8, 41.5, 39.4, 38.1, 37.9, 37.0, 34.0, 33.2, 32.7, 32.5, 30.8, 28.3, 27.7, 26.0, 23.8, 23.6, 23.5, 23.2, 18.3, 17.0, 16.7, 15.5, 14.4. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -60.2. **HRMS (ESI$^+$)**: Calcd for $C_{55}H_{68}F_3N_4O_7$ $[M+H]^+$ 953.5040, found 953.5078.

(14g) White solid, yield: 85%, mp: 183-185 °C. $[\alpha]_D^{24}$+18 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2935, 1723, 1620, 1492, 1229, 1153, 1030, 803, 738, 699. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.66 (s, 1H), 8.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.64 (s, 1H), 7.57 - 7.52 (m, 1H), 7.42 - 7.29 (m, 6H), 5.67 (s, 2H), 5.26 (t, *J* = 3.6 Hz, 1H), 5.13 - 5.01 (m, 4H), 4.52 (dd, *J* = 10.9, 4.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.7, 4.3 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.84 - 1.78 (m, 2H), 1.71 - 1.49 (m, 9H), 1.46 - 1.37 (m, 6H), 1.32 - 1.15 (m, 5H), 1.09 (s, 3H), 1.04 - 0.94 (m, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H), 0.61 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.1, 165.6, 164.7, 152.5, 143.9, 142.4, 137.8 (q, *J* = 1.6 Hz), 136.5, 132.2, 132.0, 128.5 (x2), 128.0 (x2), 128.0, 127.4, 125.7, 125.4, 123.7, 122.3, 120.8 (q, *J* = 260.6 Hz), 112.5, 84.1, 66.0, 61.2, 55.2, 52.7, 51.3, 47.6, 46.8, 45.9, 41.8, 41.5, 39.3, 38.0, 37.8, 36.9, 33.9, 33.2, 32.6, 32.4, 30.8, 28.1, 27.7, 25.9, 23.7, 23.5, 23.5, 23.1, 18.2, 16.9, 16.5, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -119.1. **HRMS (ESI$^+$)**: Calcd for $C_{55}H_{67}F_3N_4NaO_8$ $[M+Na]^+$ 991.4809, found 991.4825.

(14h) White solid, yield: 93%, mp: 155-157 °C. $[\alpha]_D^{24}$+42 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2939, 1718, 1613, 1475, 1216, 1168, 1126, 803, 742, 694. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.71 (s, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 7.99 (s,1H), 7.83 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.37 - 7.29 (m, 5H), 5.55 (s, 2H), 5.26 (t, *J* = 3.6 Hz, 1H), 5.16 (s, 2H), 5.10 - 5.01 (m, 2H), 4.51 (dd, *J* = 10.7, 4.8 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.88 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.84 - 1.75 (m, 2H), 1.70 - 1.47 (m, 9H), 1.42 - 1.30 (m, 6H), 1.28 - 1.14 (m, 5H), 1.09 (s, 3H), 1.02 - 0.96 (m, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H), 0.57 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 173.5, 165.6, 164.9, 149.9, 143.8, 141.4, 138.8, 136.5, 134.4 (q, *J* = 33.7 Hz), 129.5 (q, *J* = 252.7 Hz), 129.3, 128.5 (x2), 128.1 (x2), 128.0, 125.2, 124.3, 122.3, 121.5 (q, *J* = 3.2 Hz), 114.0 (q, *J* = 3.7 Hz), 112.4, 84.2, 66.0, 61.2, 55.2, 51.4, 49.4, 47.6, 46.8, 45.9, 41.8, 41.4, 39.3, 38.0, 37.7, 36.9, 33.9, 33.2, 32.6, 32.4, 30.8, 29.8, 28.1, 27.7, 25.9, 23.7, 23.4, 23.1, 18.2, 16.9, 16.4, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -62.8.**HRMS (ESI$^+$)**: Calcd for $C_{55}H_{68}F_3N_4O_7$ $[M+H]^+$ 953.5040, found 953.5040.

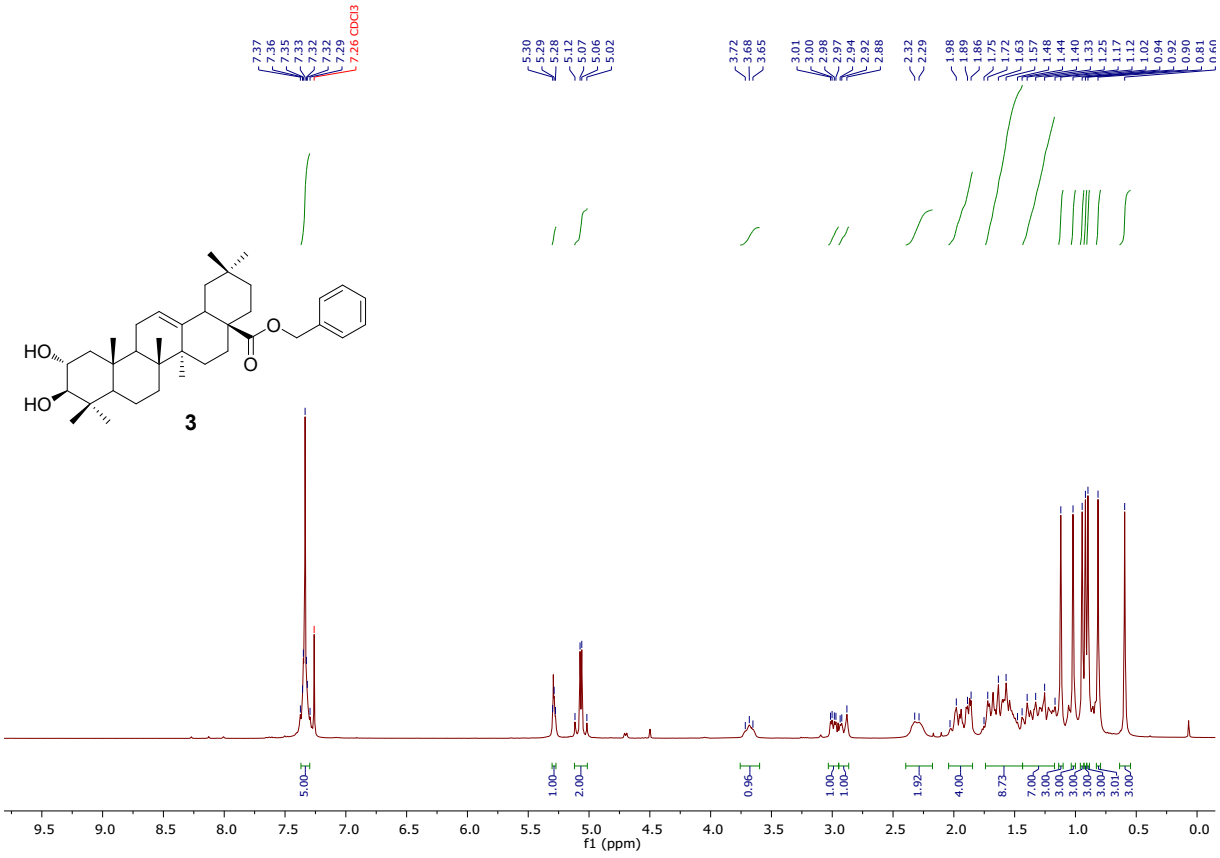
(14i) White solid, yield: 86%, mp: 251-253 °C. $[\alpha]_D^{24}$+35 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2937, 1724, 1606, 1490, 1211, 1160, 1124, 803, 747, 697. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.65 (s, 1H), 8.42 (s, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.50 (dd, *J* = 13.7, 2.4 Hz, 1H), 7.37 - 7.29 (m, 5H), 5.60 (d, *J* = 3.1 Hz, 2H), 5.27 (t, *J* = 3.6 Hz, 1H), 5.14 (s, 2H), 5.11 - 5.01 (m, 2H), 4.53 (dd, *J* = 11.1, 4.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.01 - 1.91 (m, 1H), 1.84 - 1.80 (m, 2H), 1.71 - 1.67 (m, 2H), 1.62 - 1.46 (m, 8H), 1.42 - 1.32 (m, 5H), 1.30 - 1.15 (m, 5H), 1.10 (s, 3H), 1.04 - 0.97 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H), 0.57 (s, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 171.7, 165.7, 164.5, 151.6 (d, *J* = 252.6 Hz), 151.4, 143.9, 142.4, 136.5, 132.6, 128.5 (x2), 128.1 (x2), 128.0, 127.3 (d, *J* = 6.2 Hz), 127.0 (d, *J* = 3.1 Hz), 124.0, 123.1 (d, *J* = 26.3 Hz), 122.3, 118.2 (d, *J* = 9.8 Hz), 112.2, 84.2, 66.1, 61.3, 55.2, 52.6 (d, *J* = 15.7 Hz), 51.4, 47.6, 46.8, 46.0, 41.8, 41.5, 39.4, 38.0, 37.8, 36.9, 34.0, 33.2, 32.6, 32.5, 30.8, 28.1, 27.7, 25.9, 23.8, 23.5, 23.5, 23.1, 18.2, 16.9, 16.5, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -56.6.**HRMS (ESI$^+$)**: Calcd for $C_{54}H_{67}BrFN_4O_7$ $[M+H]^+$ 981.4177, found 981.4130.

(14j) White solid, yield: 88%, mp: 177-179 °C. $[\alpha]_D^{24}$+45 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2933, 1720, 1475, 1217, 1150, 1078, 802, 747, 696. **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.66 (s, 1H), 8.62 (d, *J* = 1.3 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.66 (dd, *J* = 13.6, 1.9 Hz, 1H), 7.39 - 7.28 (m, 5H), 5.59 (d, *J* = 3.1 Hz, 2H), 5.27 (t, *J* = 3.8 Hz, 1H), 5.14 (s, 2H), 5.11 - 5.01 (m, 2H), 4.53 (dd, *J* = 11.3, 4.6 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 13.3, 4.4 Hz, 1H),

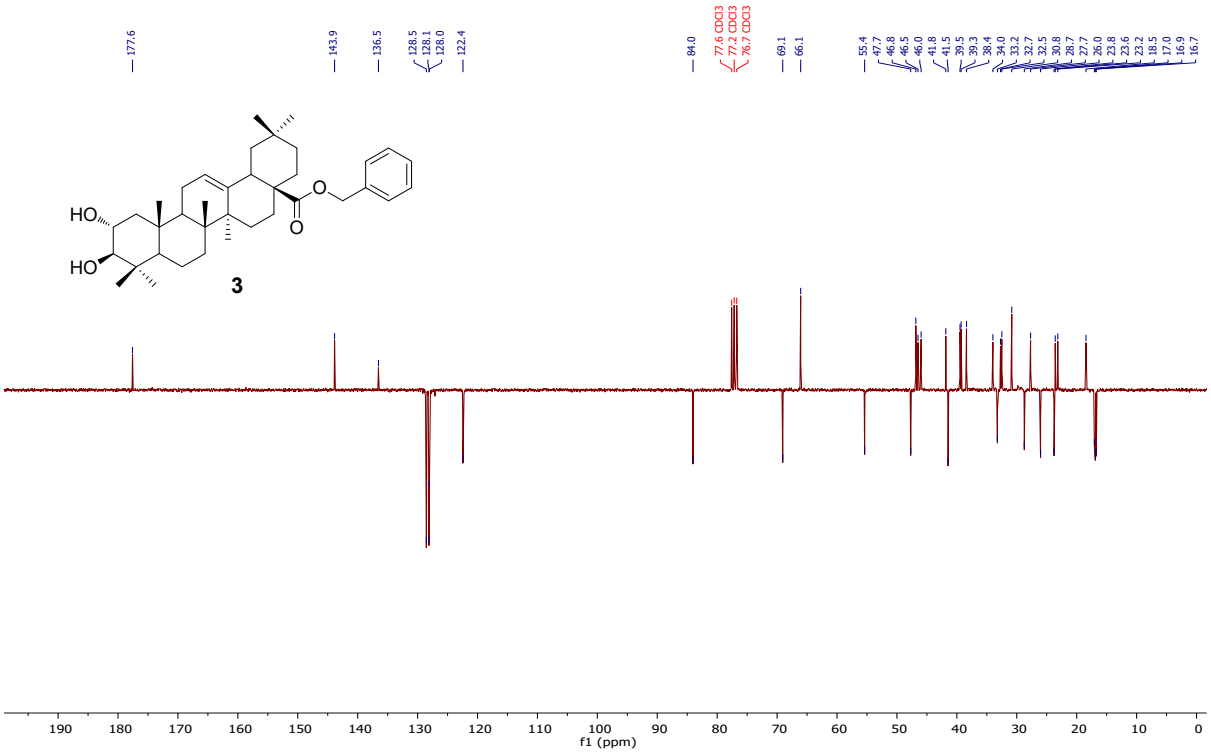
2.02 - 1.91 (m, 1H), 1.86 - 1.79 (m, 2H), 1.71 - 1.46 (m, 11H), 1.42 - 1.33 (m, 5H), 1.28 - 1.15 (m, 4H), 1.10 (s, 3H), 1.05 - 0.97 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H), 0.74 (s, 3H), 0.58 (s, 3H), 0.56 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 171.4, 165.7, 164.4, 151.3, 151.1 (d, *J* = 254.3 Hz), 143.8, 142.3, 136.5, 133.2 (d, *J* = 3.4 Hz), 132.6, 128.5 (x2), 128.4 (d, *J* = 24.9 Hz), 128.1 (x2), 128.0, 127.9 (d, *J* = 6.8 Hz), 124.0, 122.3, 112.3, 87.9 (d, *J* = 8.5 Hz), 84.1, 66.0, 61.2, 55.2, 52.6 (d, *J* = 15.2 Hz), 51.3, 47.6, 46.8, 45.9, 41.8, 41.5, 39.4, 38.0, 37.7, 36.9, 33.9, 33.2, 32.6, 32.4, 30.8, 29.8, 28.1, 27.7, 25.9, 23.7, 23.5, 23.1, 18.2, 16.9, 16.4, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -119.9.**HRMS (ESI$^+$)**: Calcd for $C_{54}H_{67}FIN_4O_7$ $[M+H]^+$ 1029.4038, found 1029.4081.

(14k) White solid, yield: 91%, mp: 199-201 °C. $[\alpha]_D^{24}$+27 (*c* 0.05, $CHCl_3$). **IR (ν_{max} / cm^{-1})**: 2936, 1724, 1619, 1488, 1211, 1156, 1104, 803, 746, 696.**^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.68 (s, 1H), 8.17 - 8.11 (m, 1H), 7.77 (s, 1H), 7.37 - 7.26 (m, 5H), 5.60 (d, *J* = 2.9 Hz, 2H), 5.27 (t, *J* = 3.7 Hz, 1H), 5.11 - 5.01 (m, 2H), 4.54 (dd, *J* = 10.7, 5.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.89 (dd, *J* = 14.1, 4.4 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.85 - 1.79 (m, 2H), 1.68 - 1.50 (m, 10H), 1.44 - 1.36 (m, 5H), 1.28 - 1.18 (m, 5H), 1.10 (s, 3H), 1.05 - 0.97 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.5, 171.4, 165.6, 164.5, 151.8,148.6 (d, *J* = 242.2 Hz), 143.9, 143.5 (d, *J* = 256.4 Hz), 142.0, 141.5 (d, *J* = 250.5 Hz), 136.5, 128.5 (x2), 128.1 (x2), 128.0, 126.0 (d, *J* = 2.3 Hz), 125.7 (dd, *J* = 5.0, 2.5 Hz), 123.9 (d, *J* = 5.1 Hz), 122.3, 111.5, 110.3 (dd, *J* = 18.1, 3.2 Hz), 84.3, 66.1, 61.4, 55.3, 52.2 (d, *J* = 15.0 Hz), 51.4, 47.6, 46.8, 46.0, 41.8, 41.5, 39.4, 38.1, 37.8, 36.9, 34.0, 33.2, 32.7, 32.5, 30.8, 29.8, 28.1, 27.7, 26.0, 23.8, 23.5, 23.1, 18.2, 17.0, 16.5, 15.4, 14.5. **^{19}F NMR (282 MHz, $CDCl_3$)**: δ_F -134.7 (dd, *J* = 22.8, 5.6 Hz), -143.1 (dd, *J* = 18.6, 5.5 Hz), -150.0 (dd, *J* = 23.0, 18.5 Hz). **HRMS (ESI$^+$)**: Calcd for $C_{54}H_{66}F_3N_4O_7$ $[M+H]^+$ 939.4884, found 939.4875.

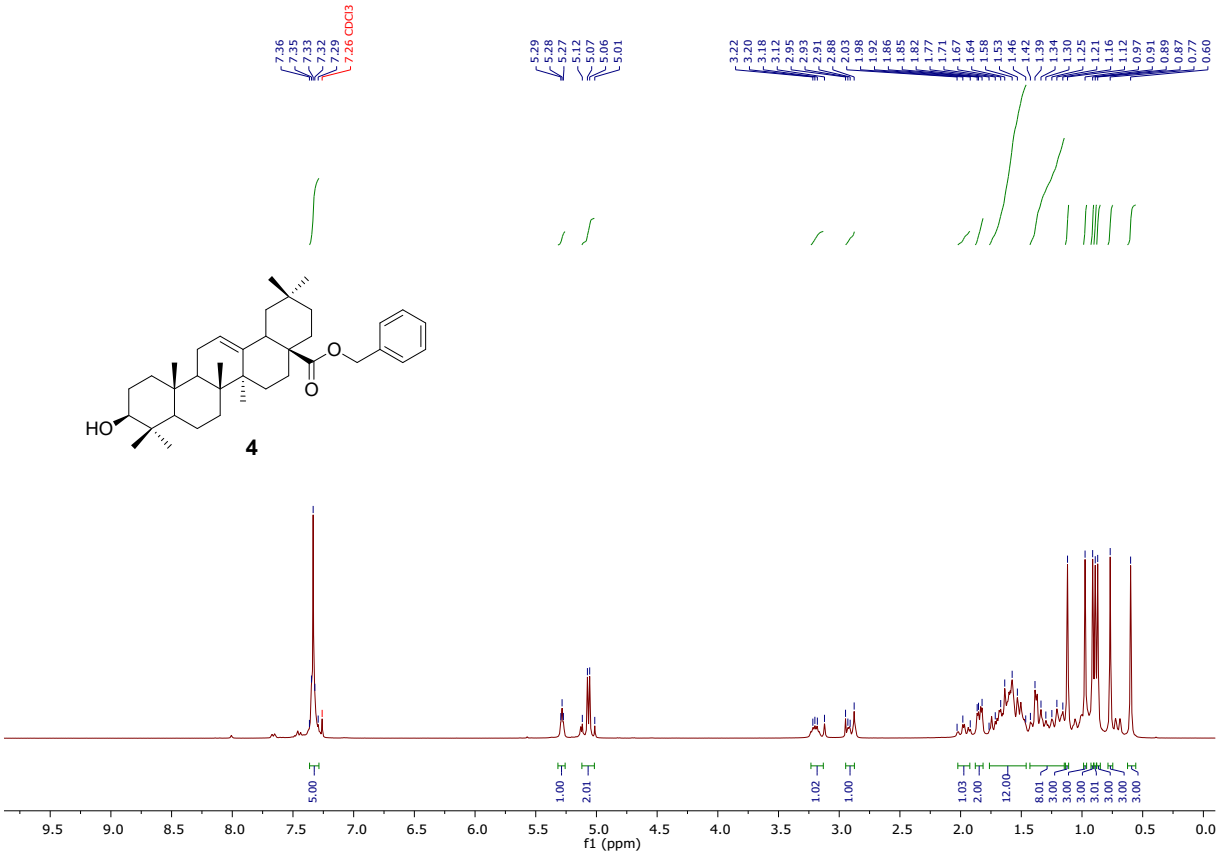
VI. NMR Spectra



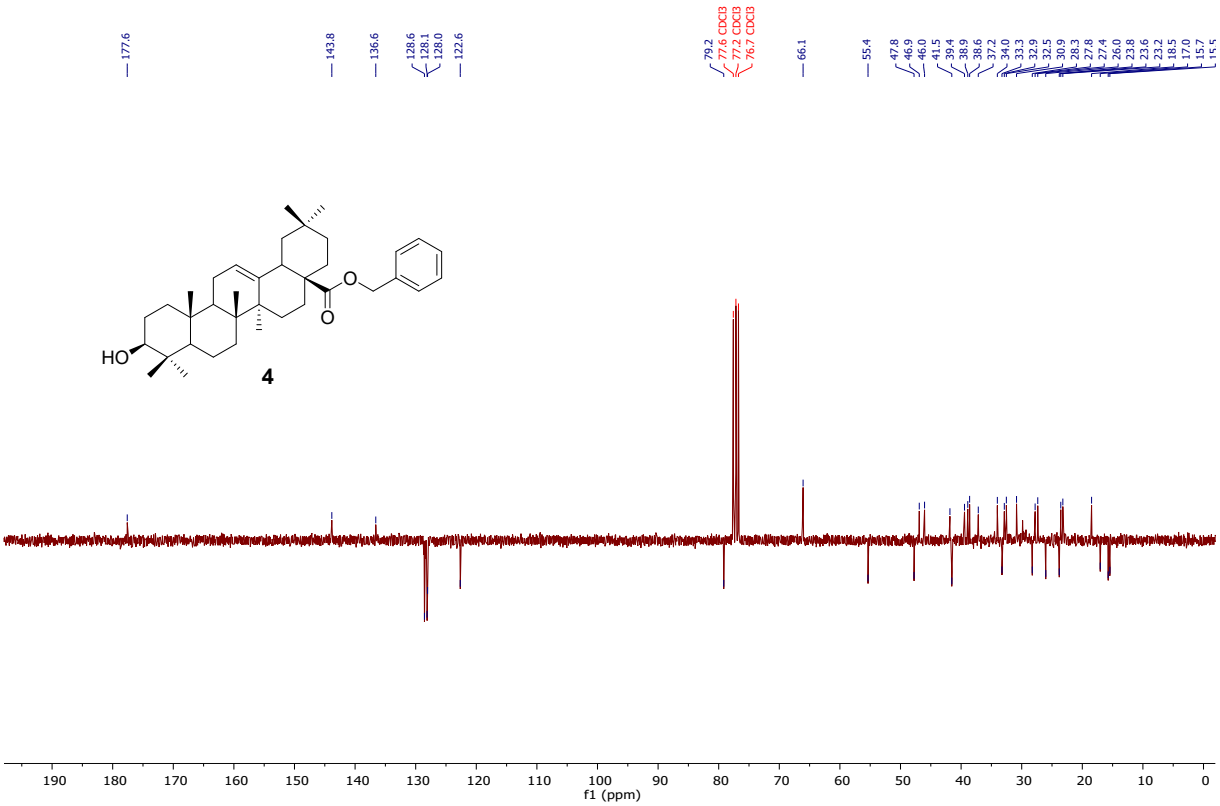
^{1}H NMR (300 MHz, $CDCl_3$)



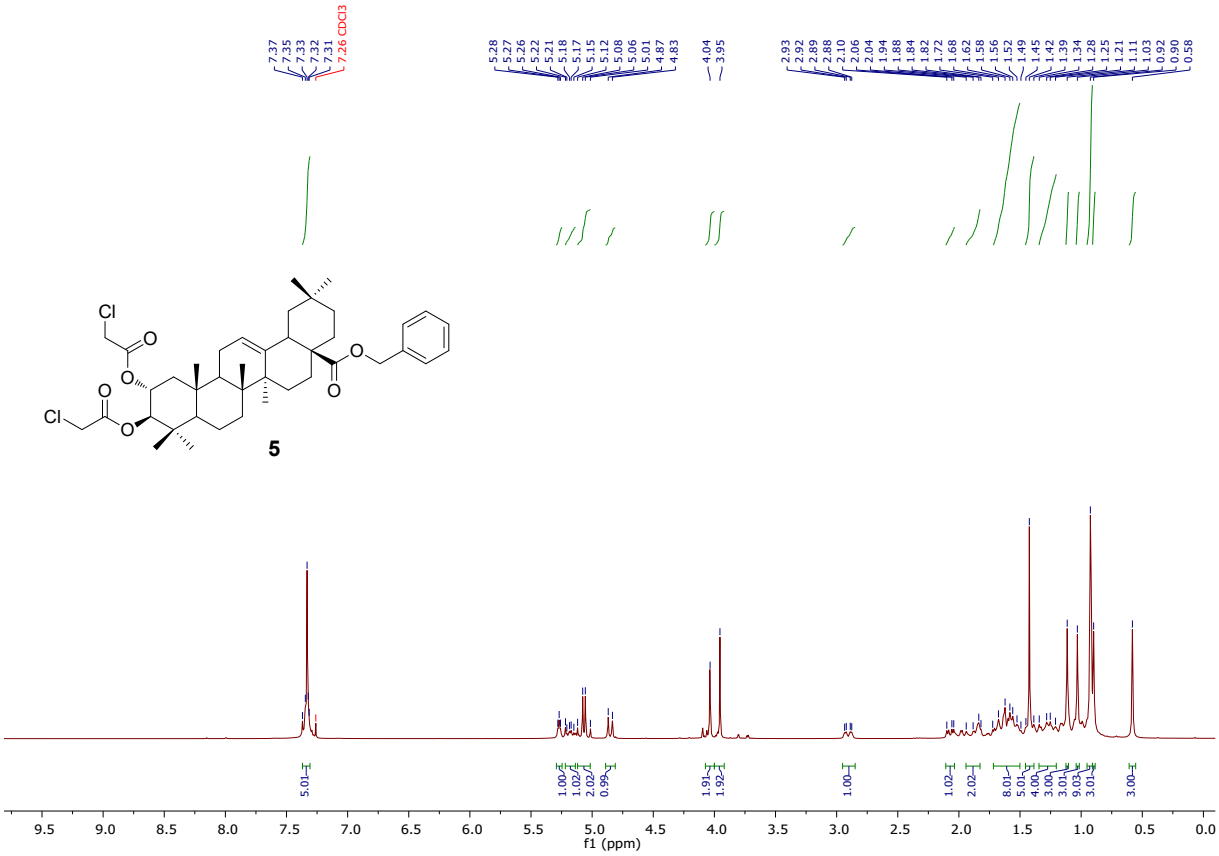
^{13}C NMR (75 MHz, $CDCl_3$)



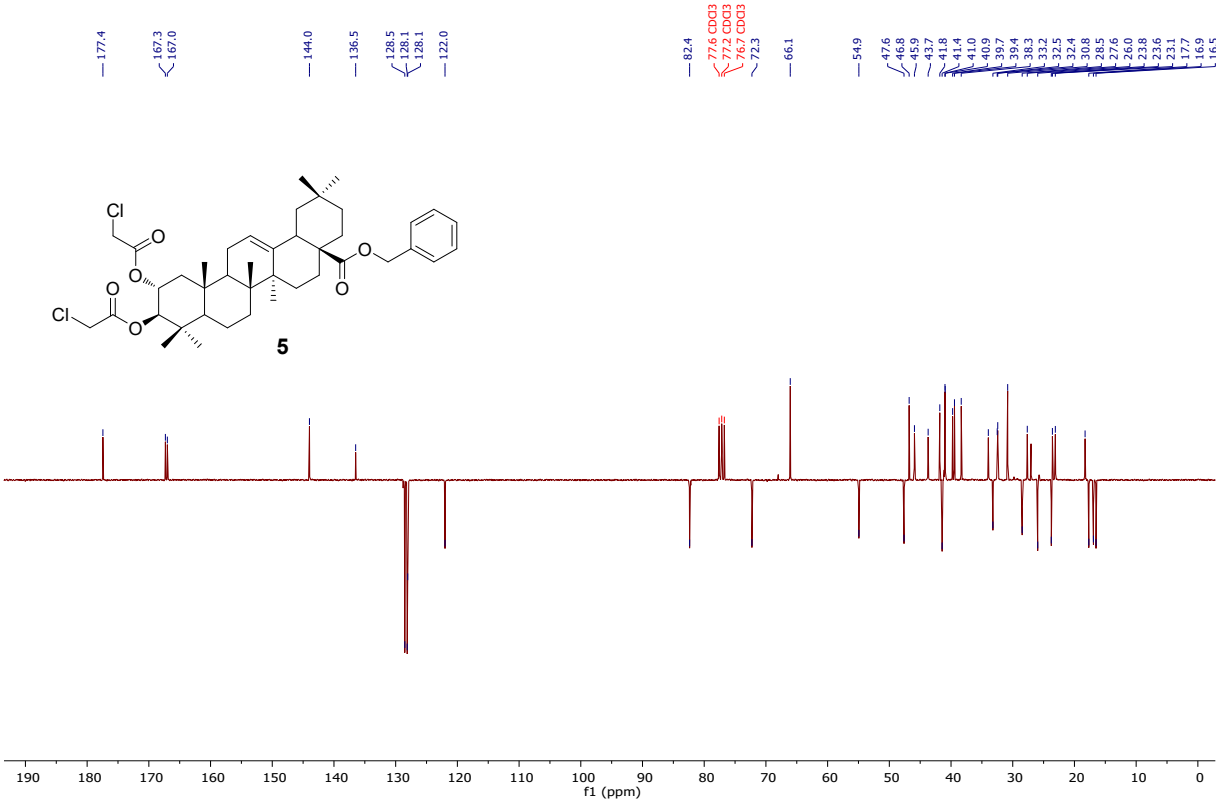
^{1}H NMR (300 MHz, $CDCl_3$)



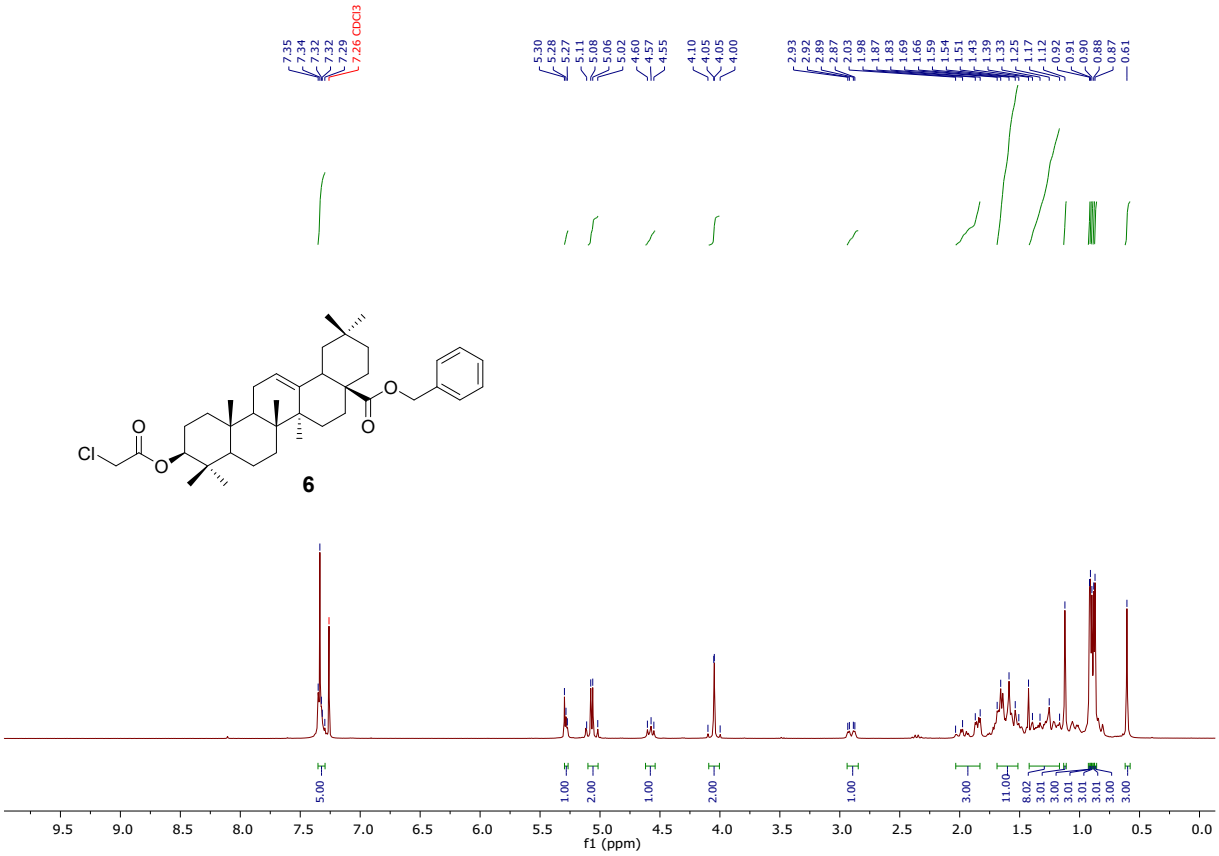
^{13}C NMR (75 MHz, $CDCl_3$)



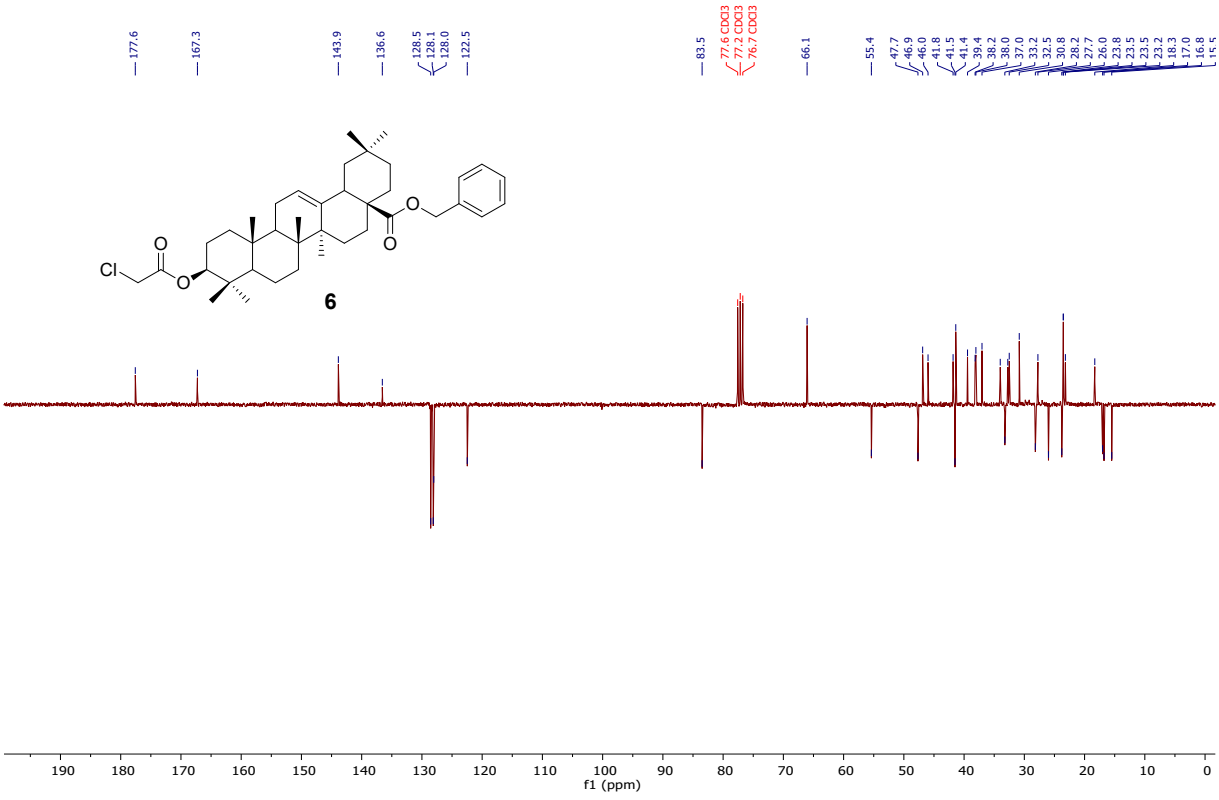
^{1}H NMR (300 MHz, $CDCl_3$)



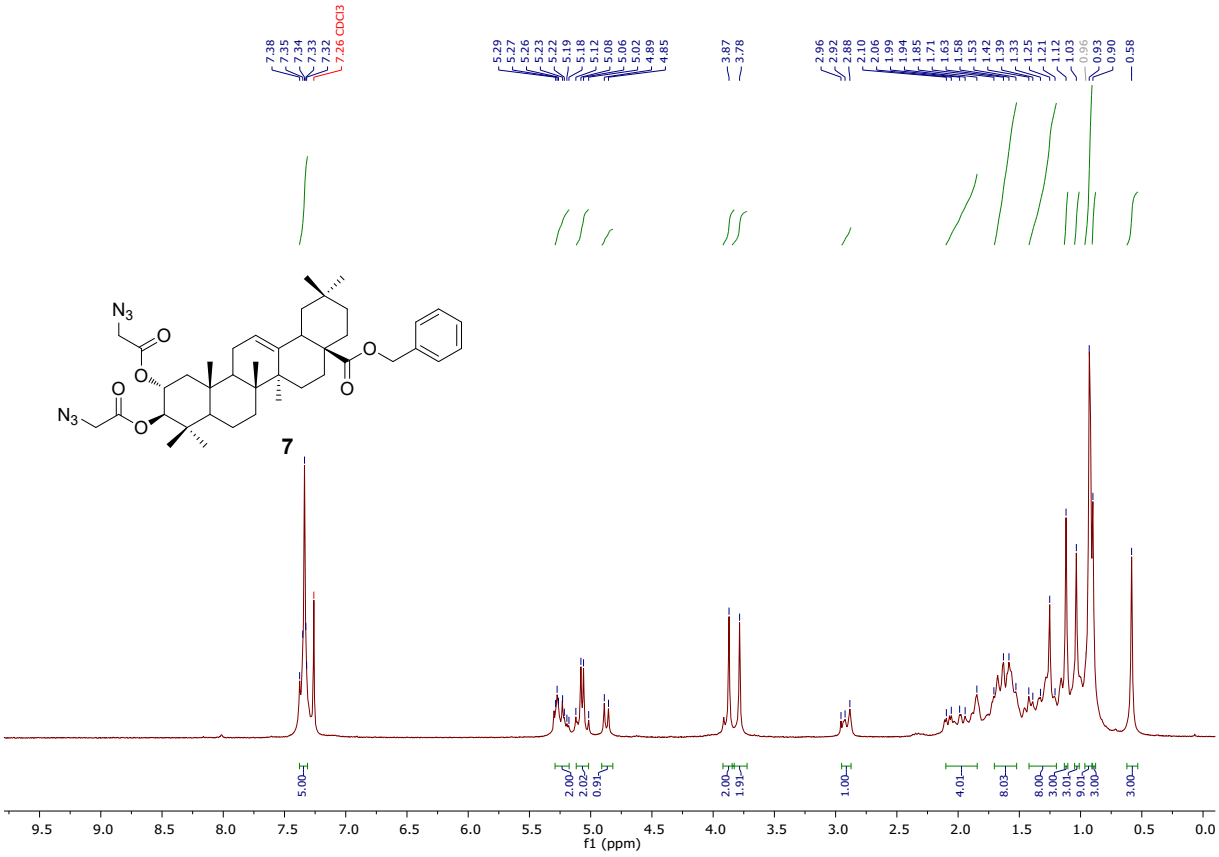
^{13}C NMR (75 MHz, $CDCl_3$)



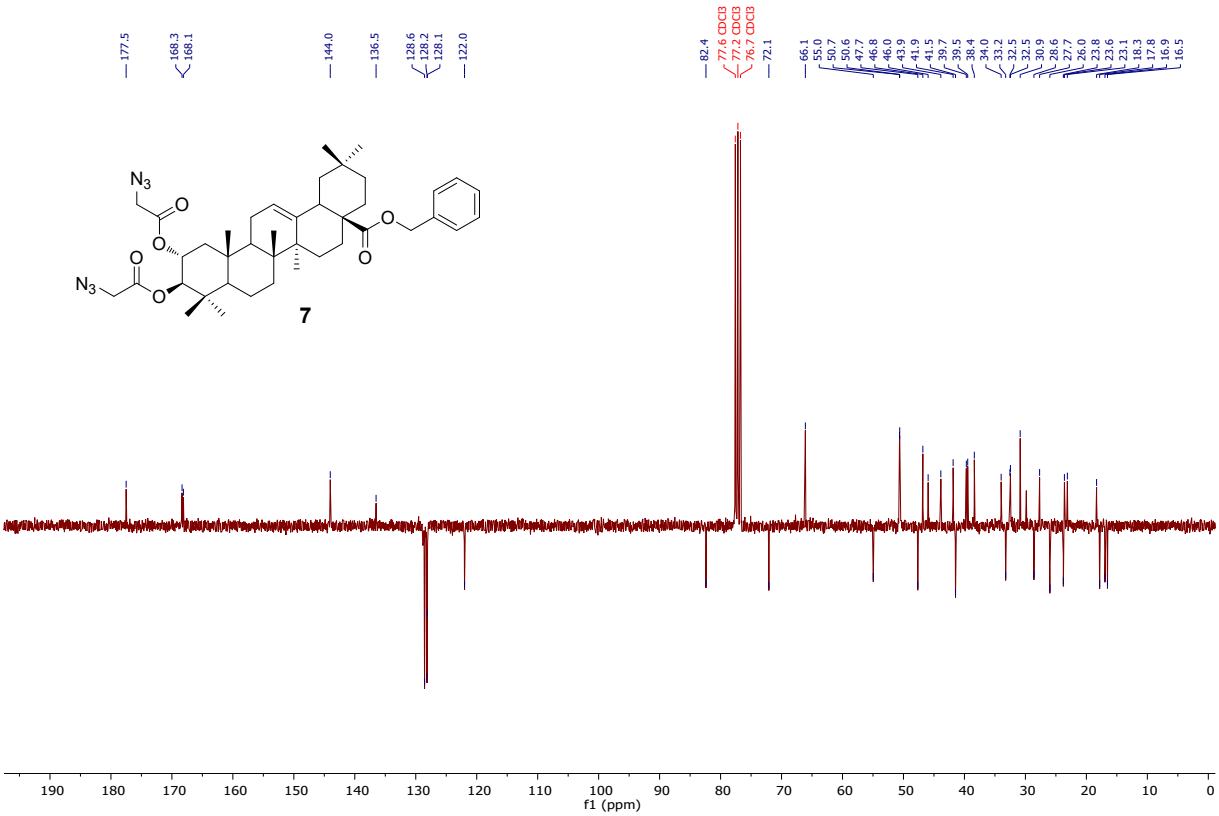
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



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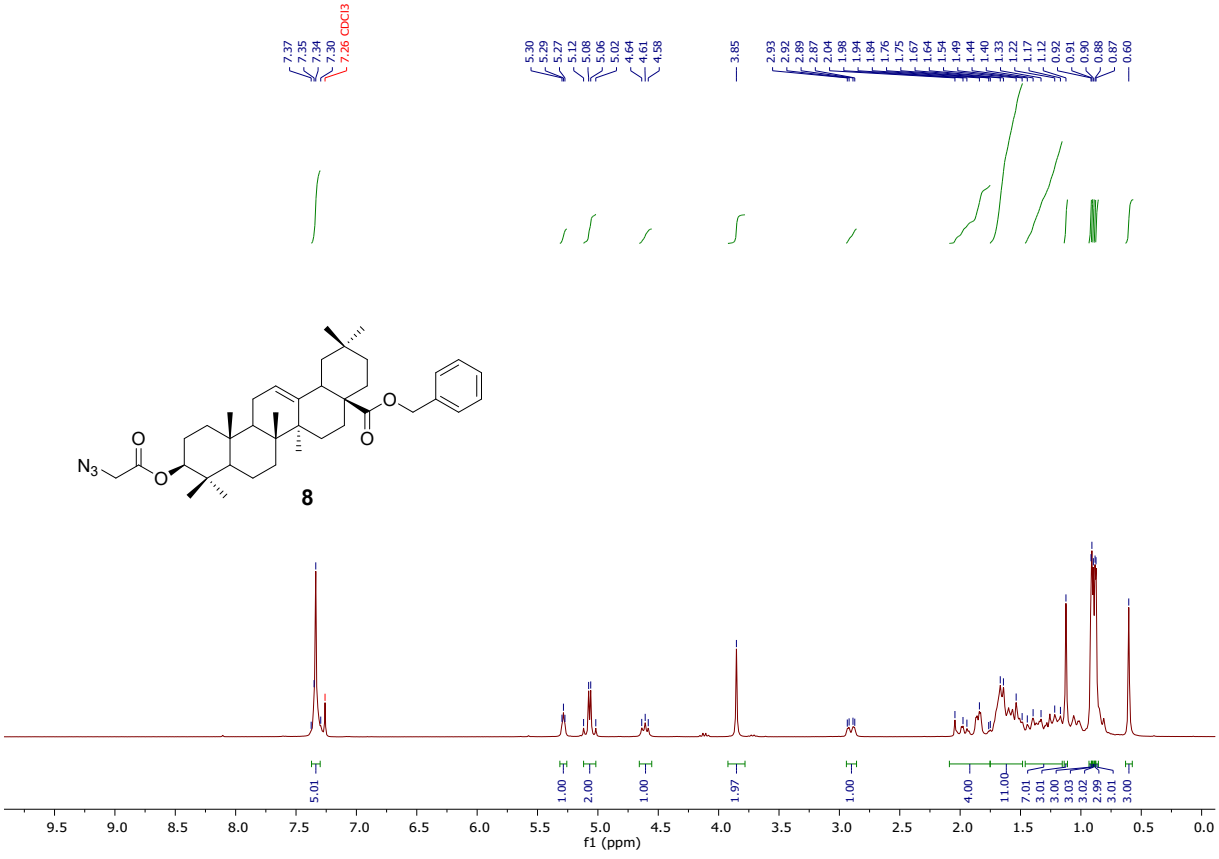
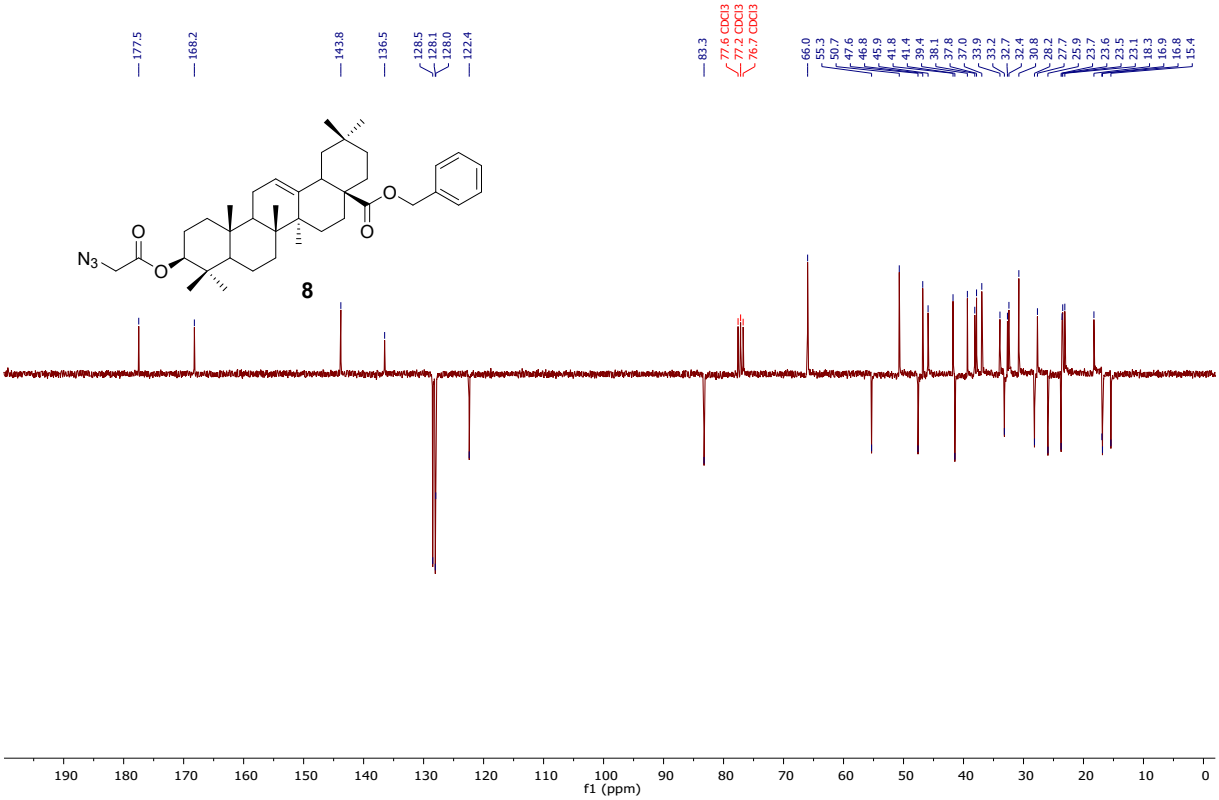
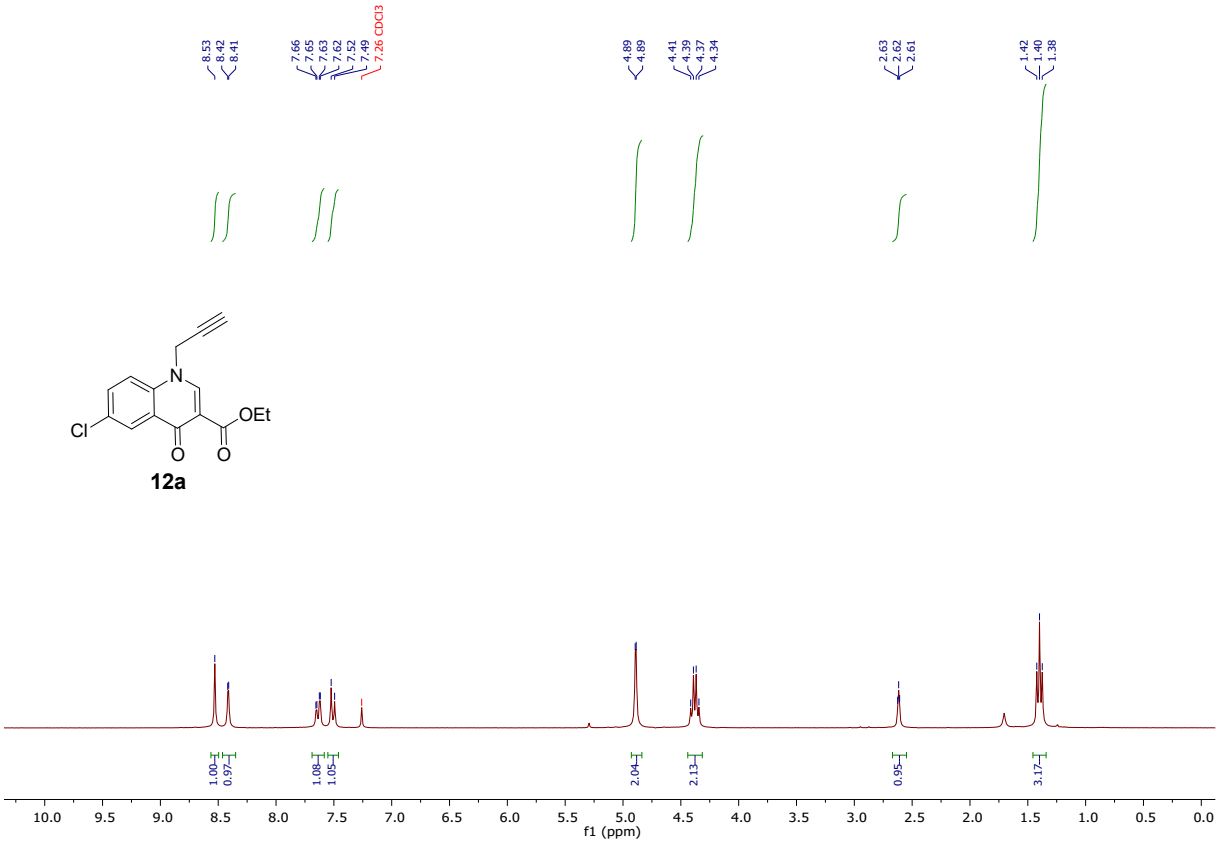


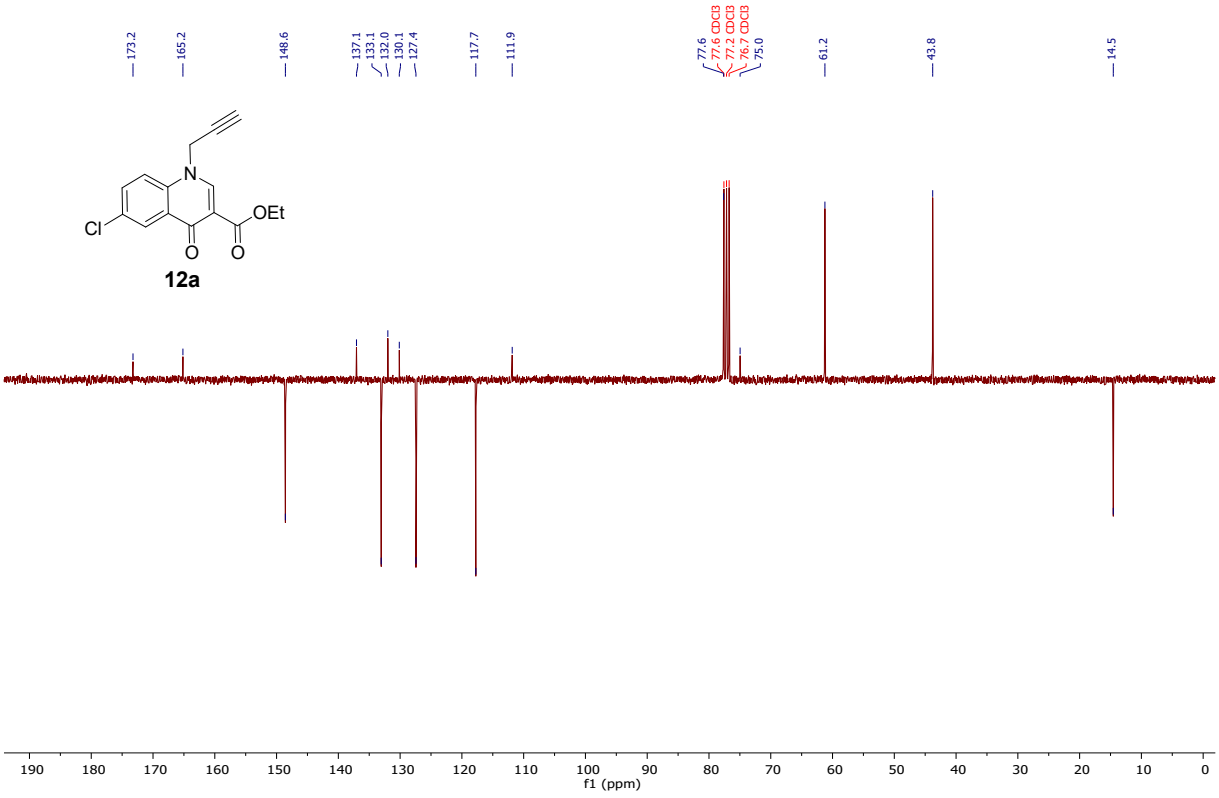
^{1}H NMR (300 MHz, $CDCl_3$)



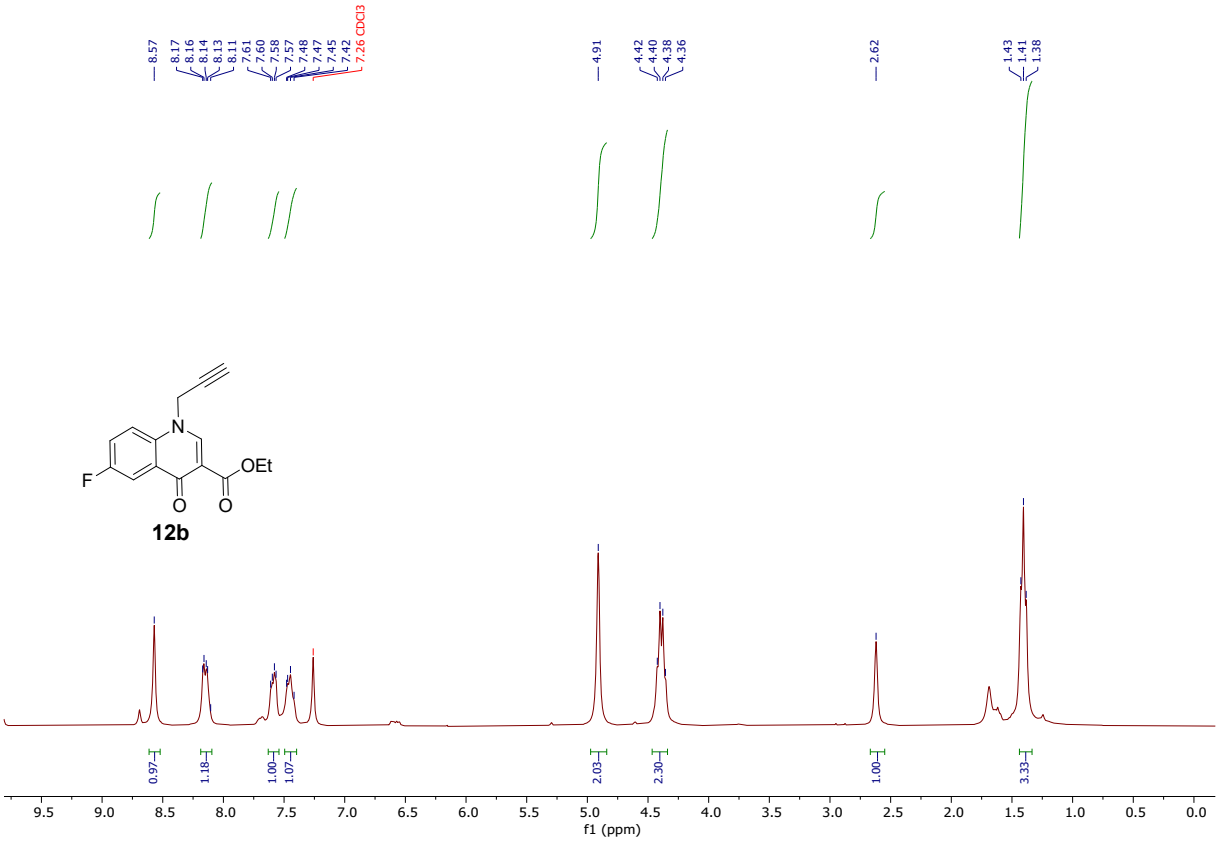
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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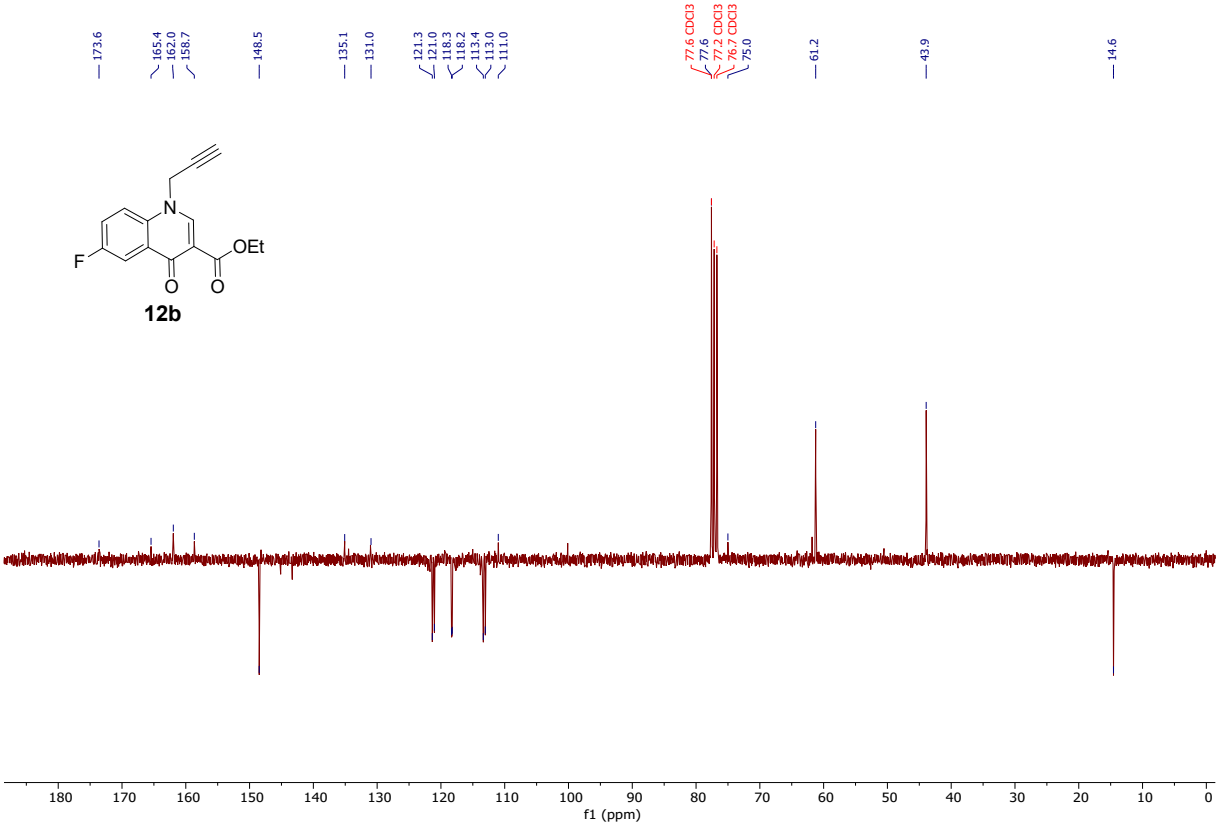
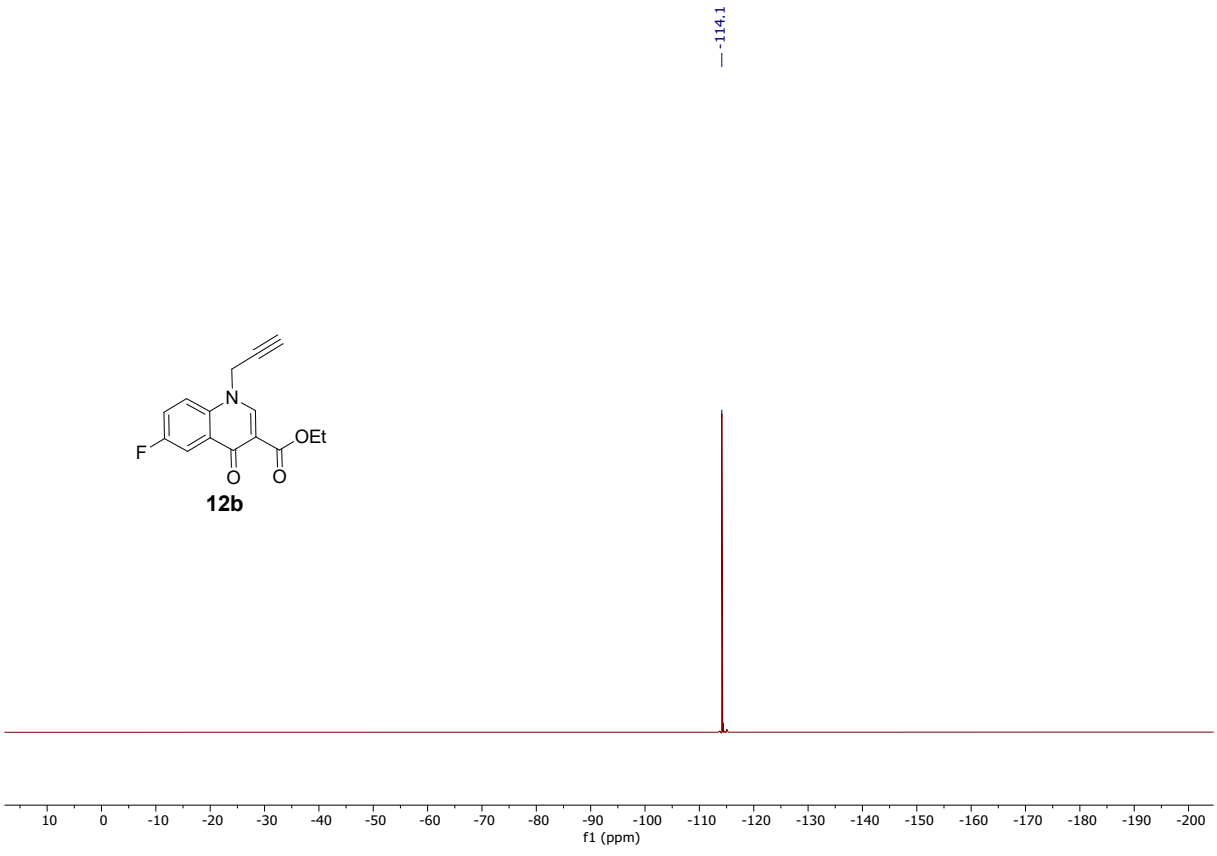
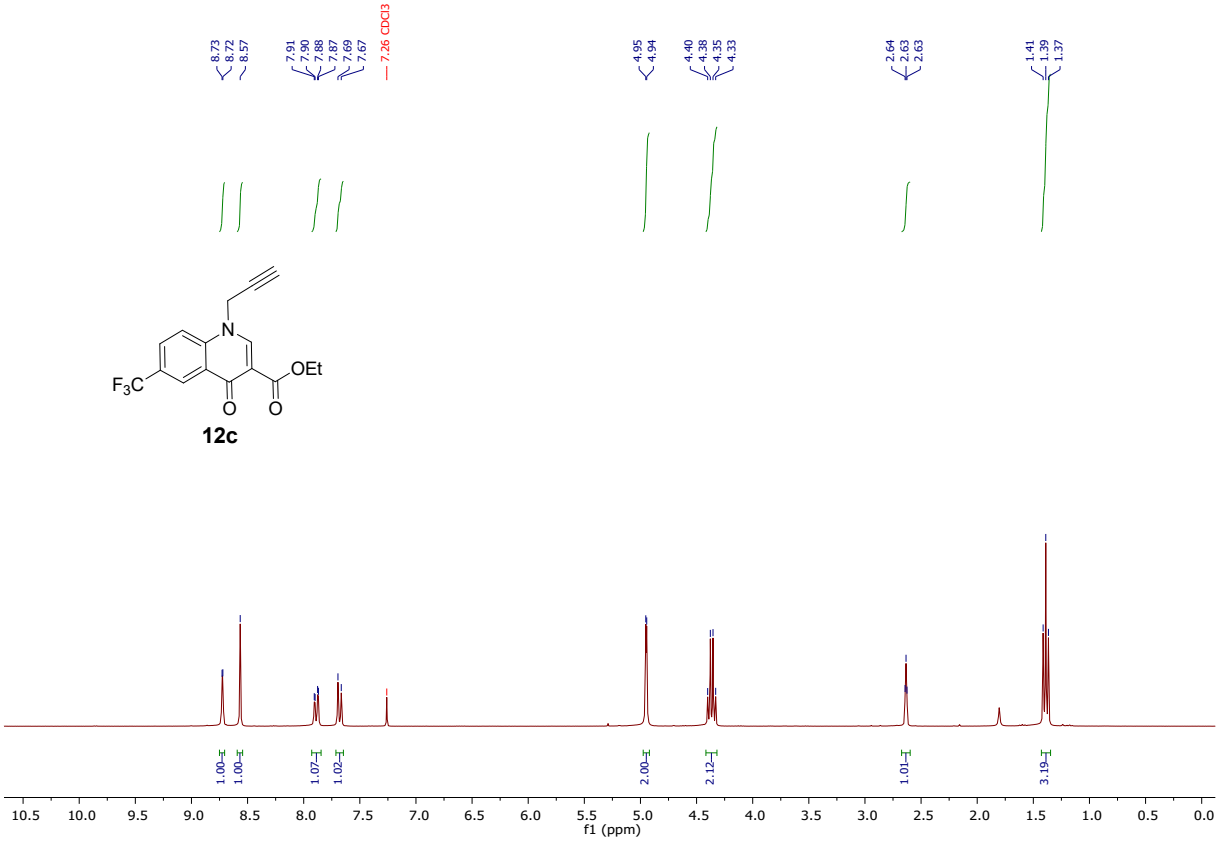


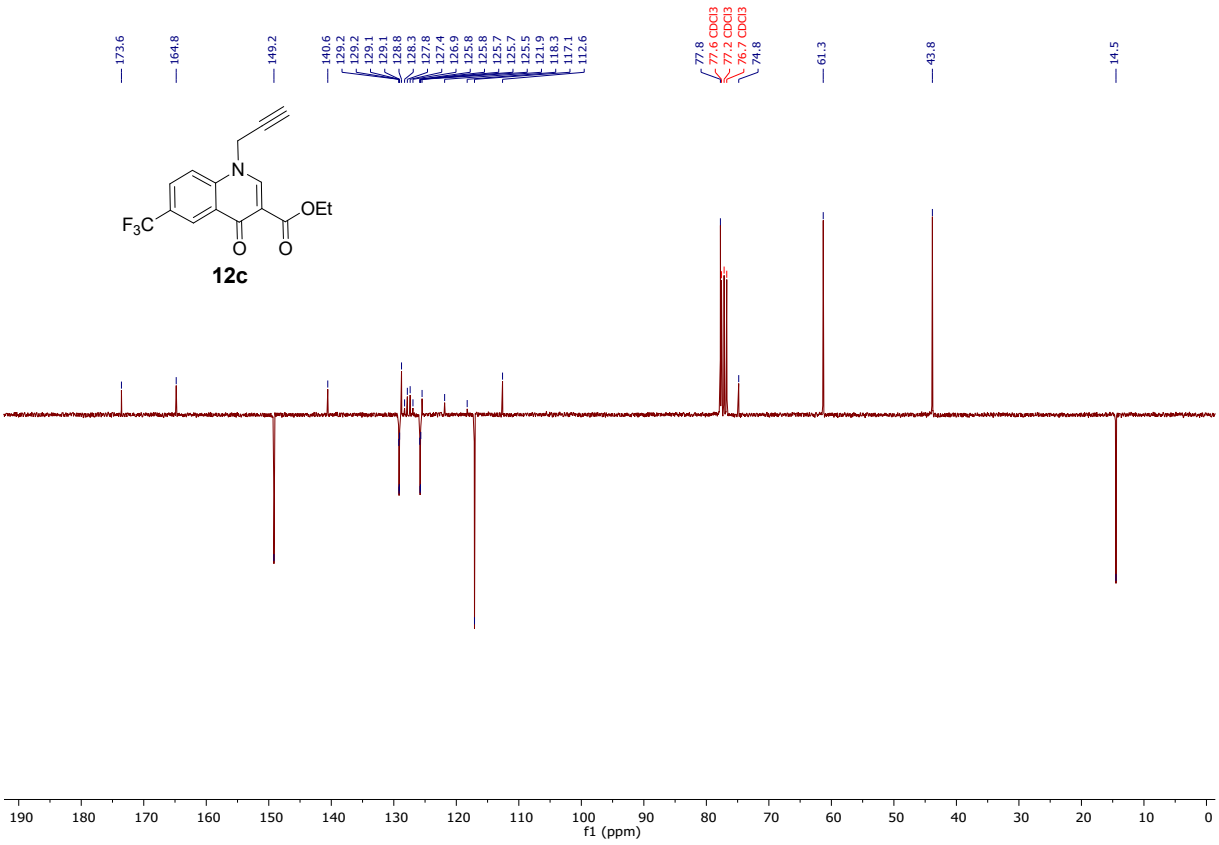
^{13}C NMR (75 MHz, $CDCl_3$)



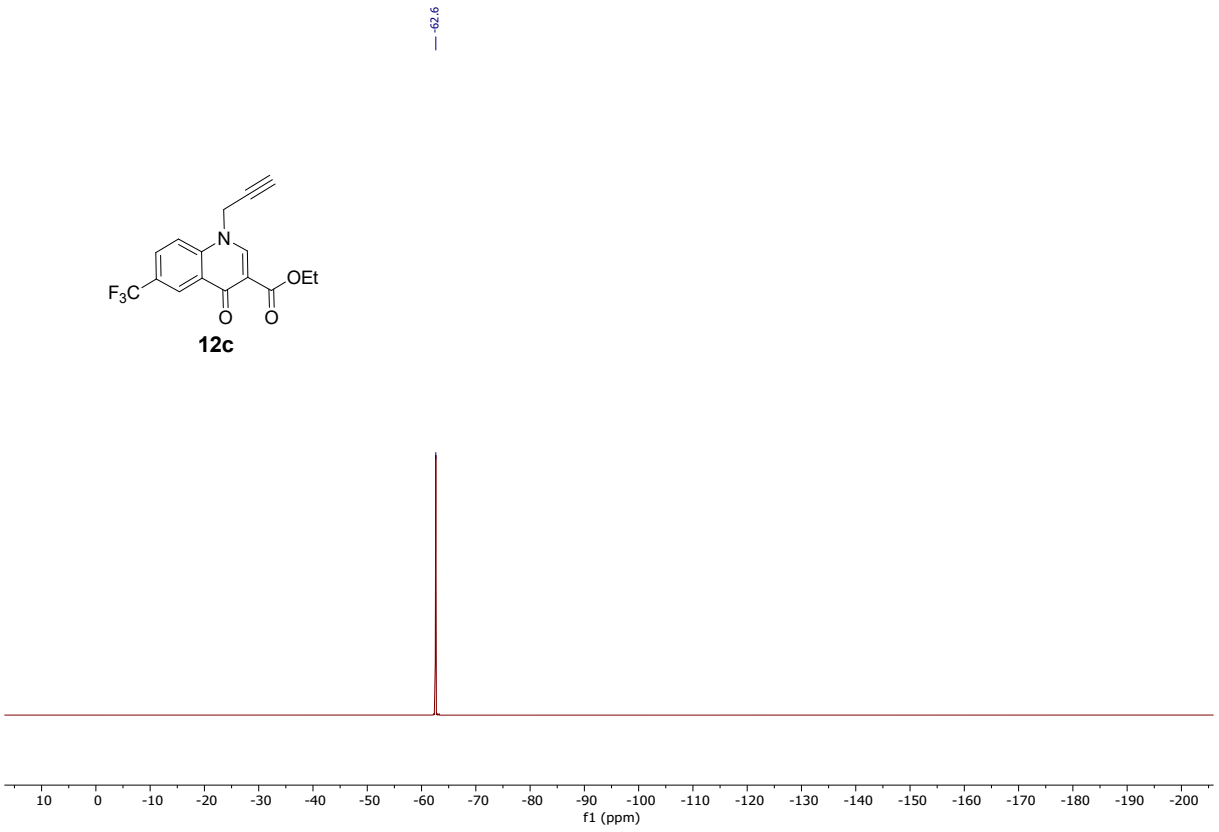
^{19}F NMR (282 MHz, $CDCl_3$)



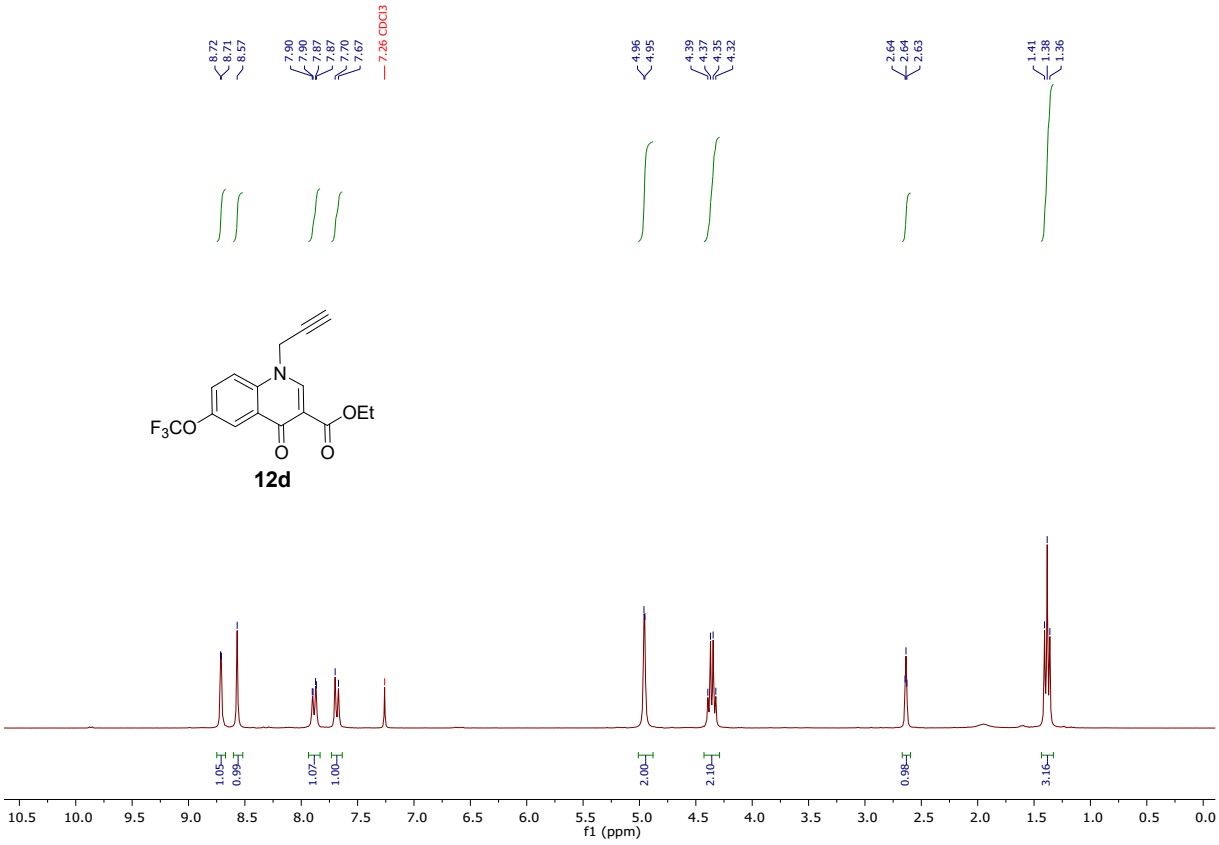
^{1}H NMR (300 MHz, $CDCl_3$)



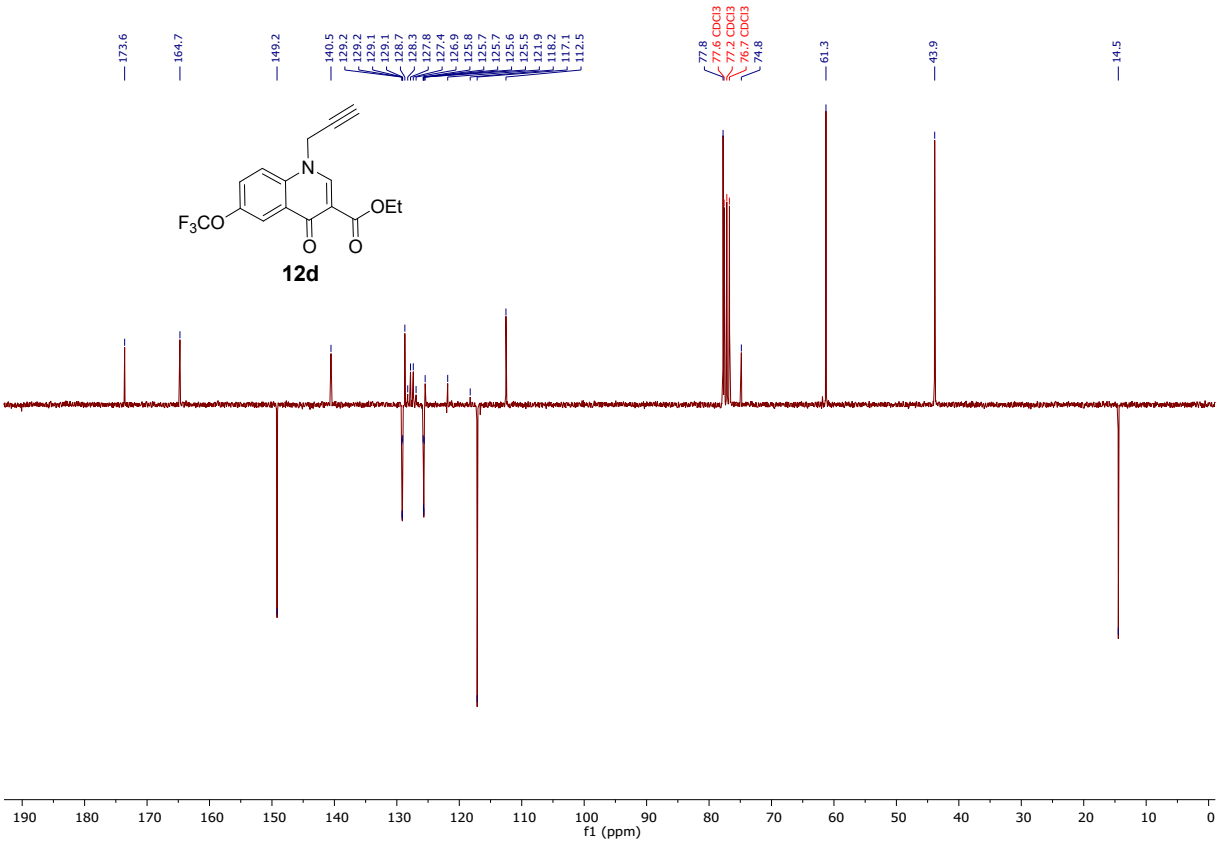
^{13}C NMR (75 MHz, $CDCl_3$)



^{19}F NMR (282 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



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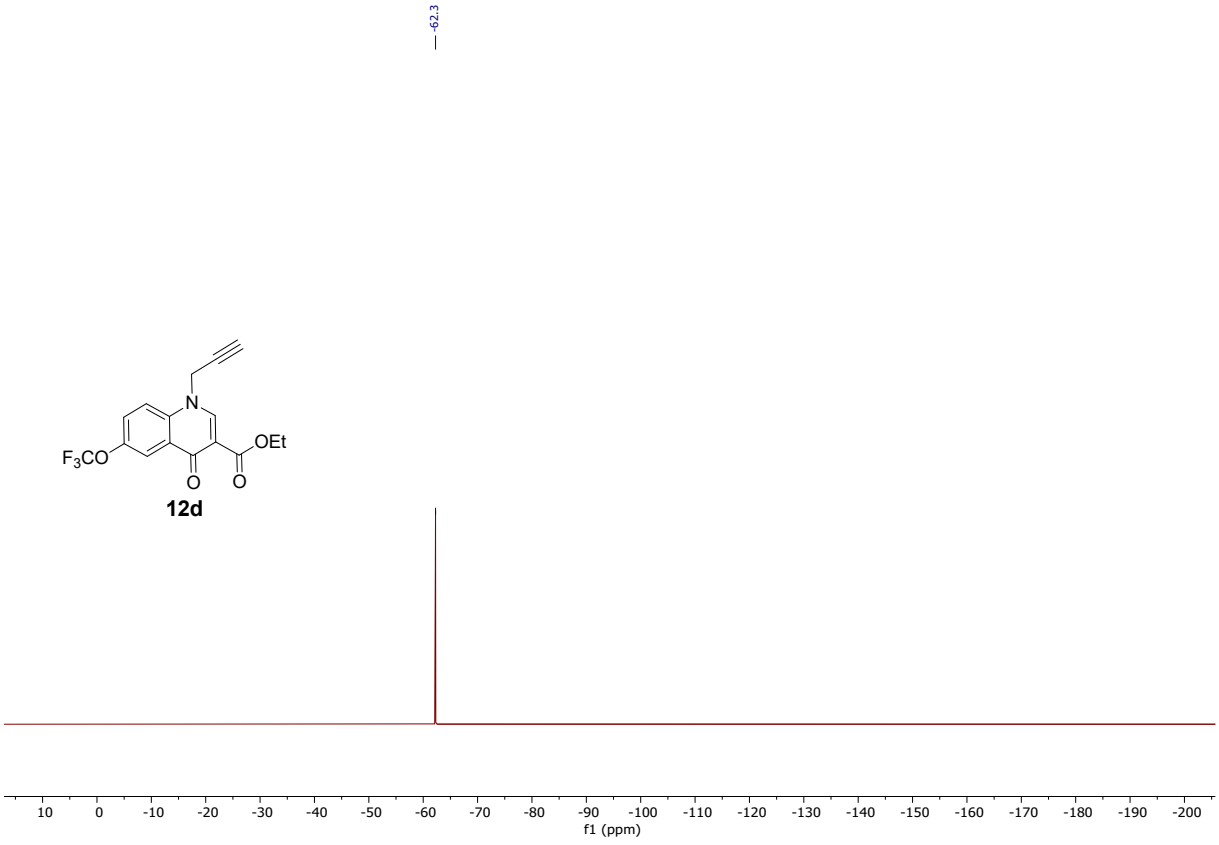

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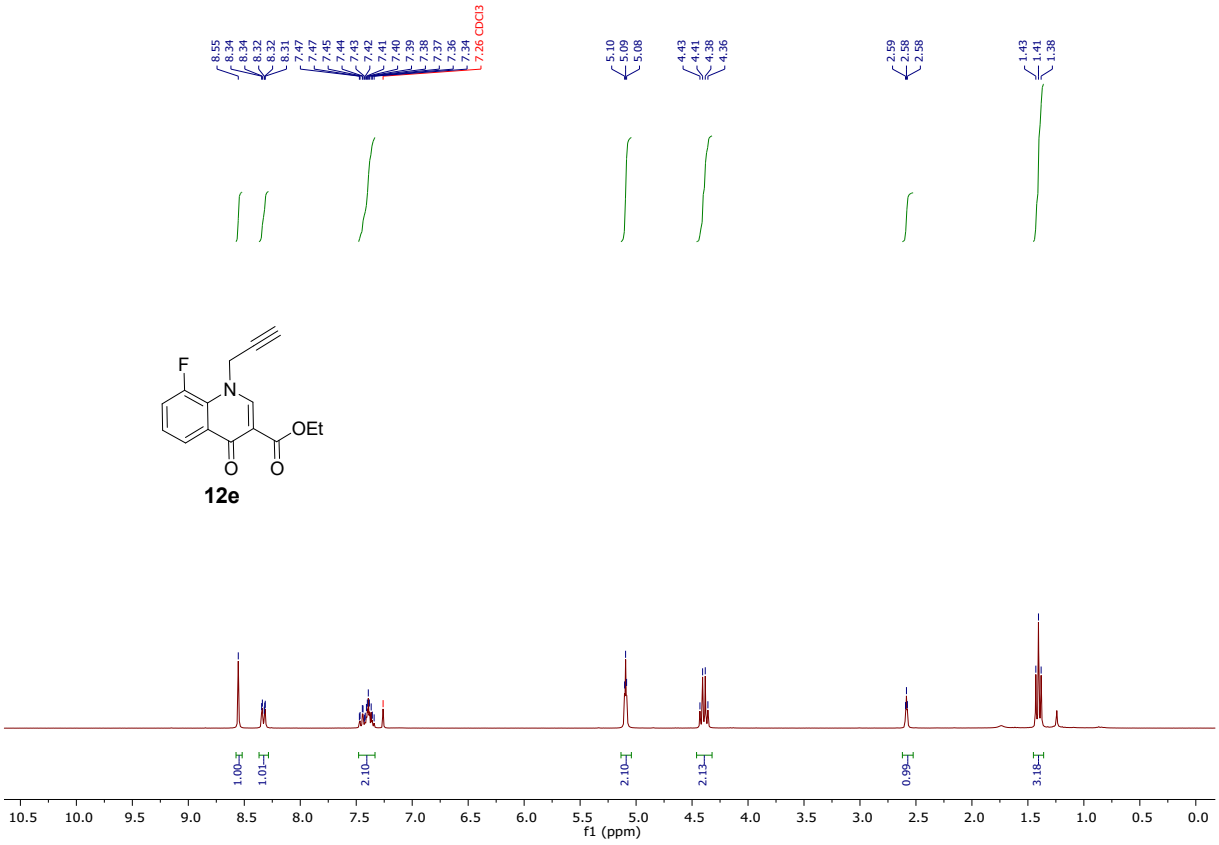

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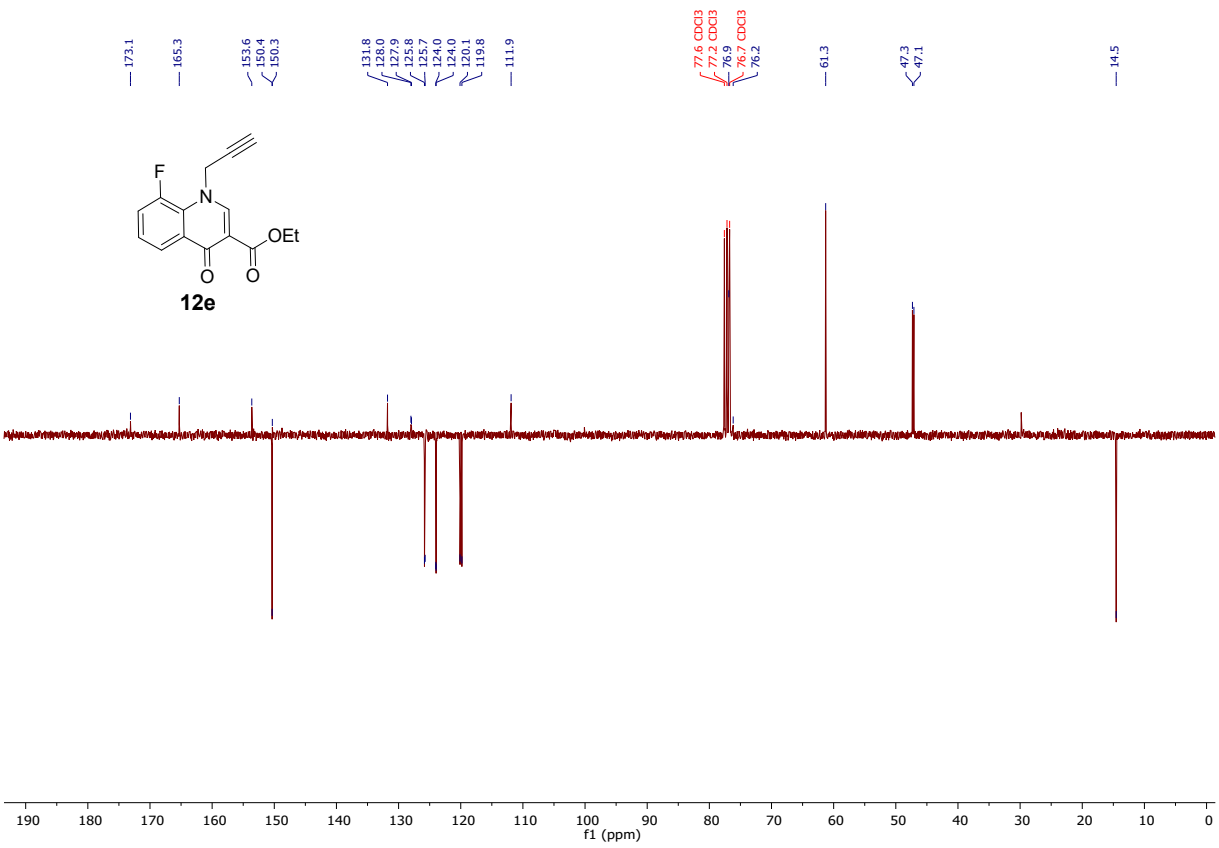

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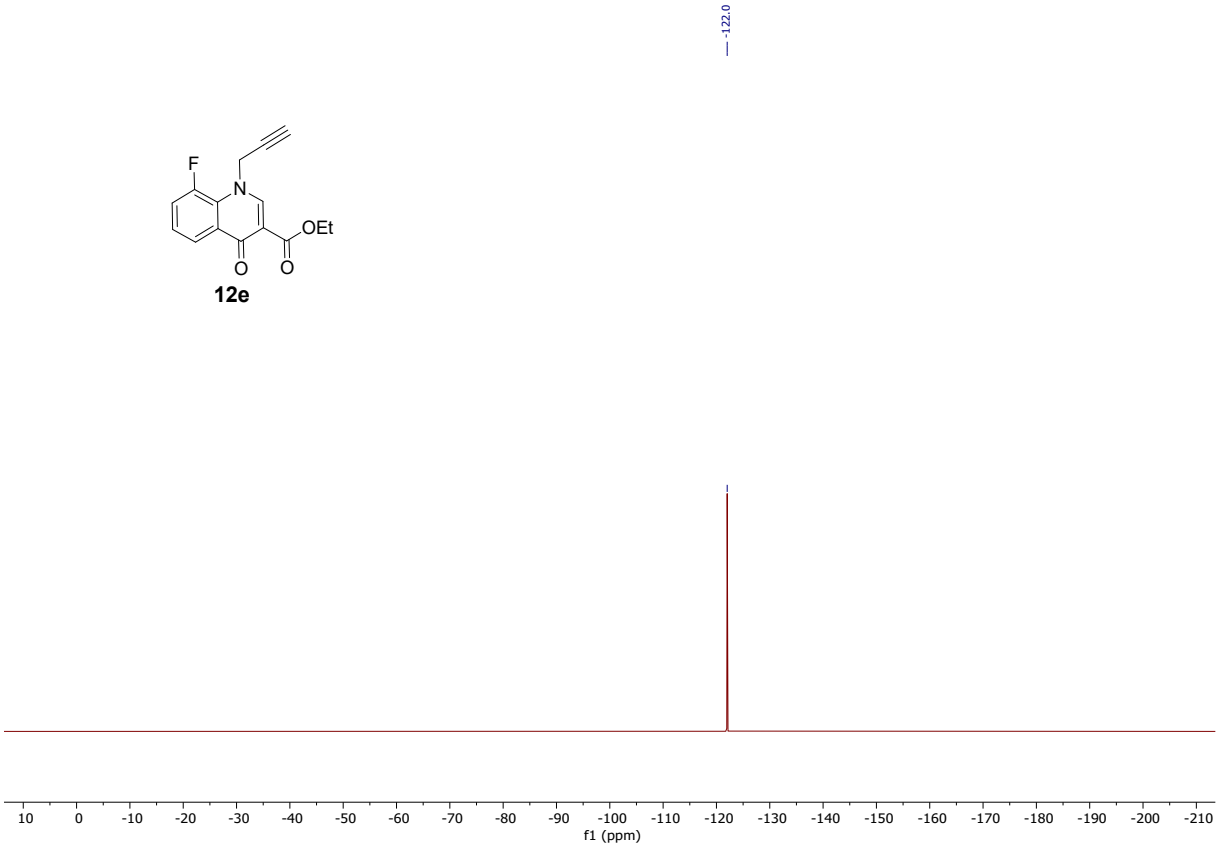
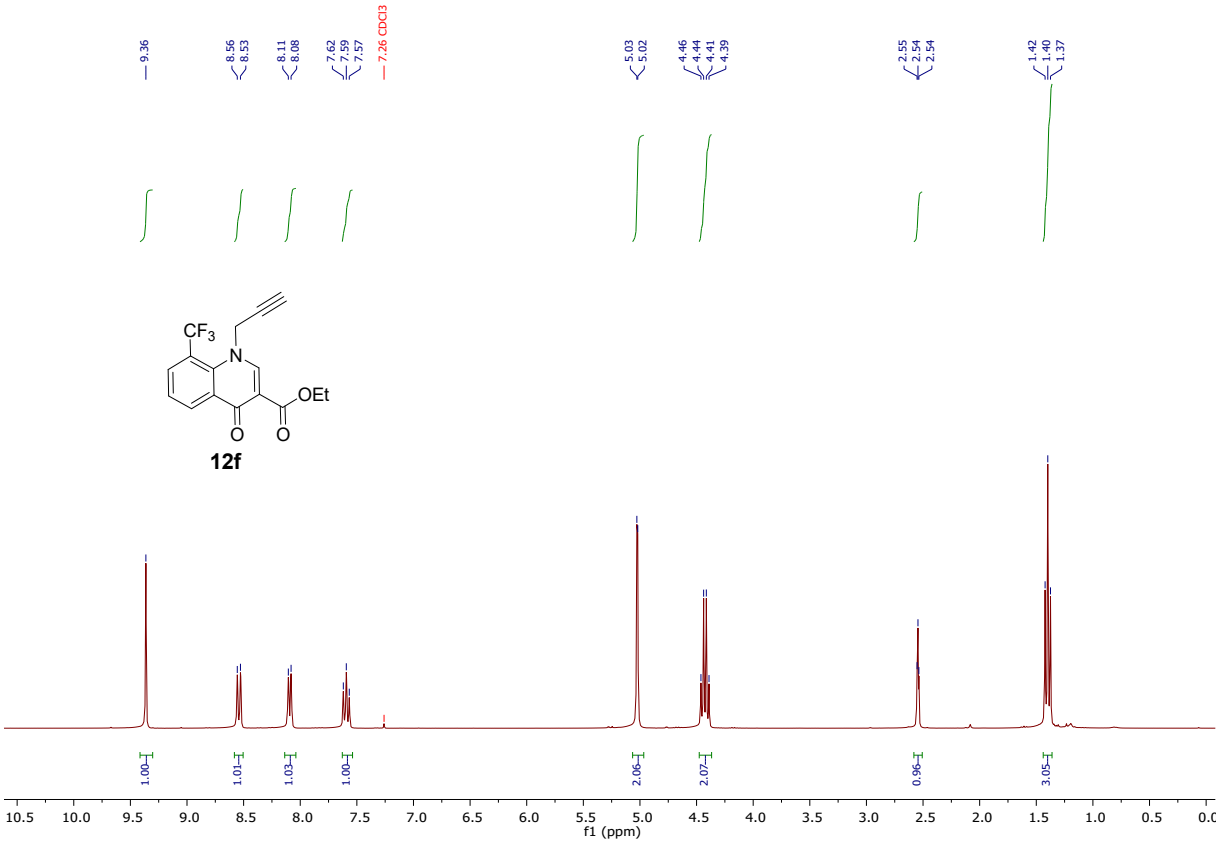
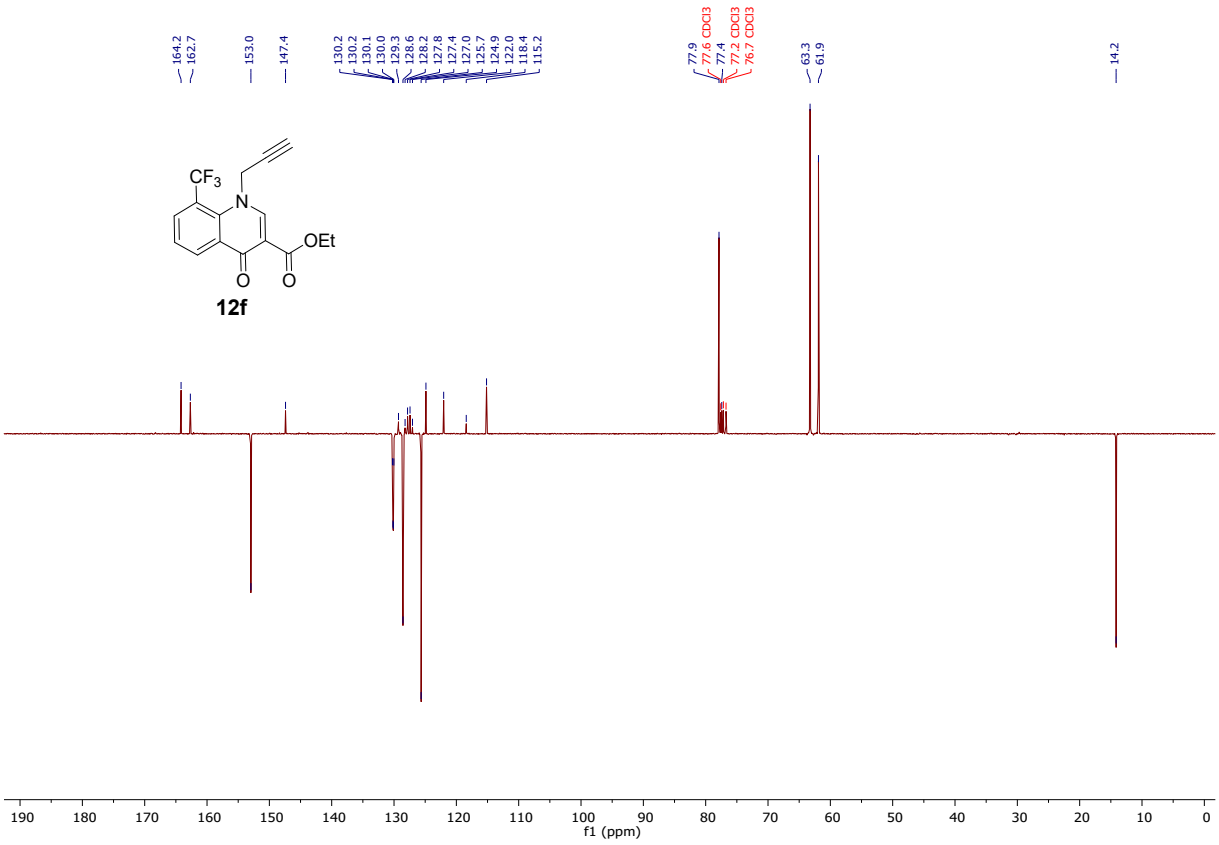


12e

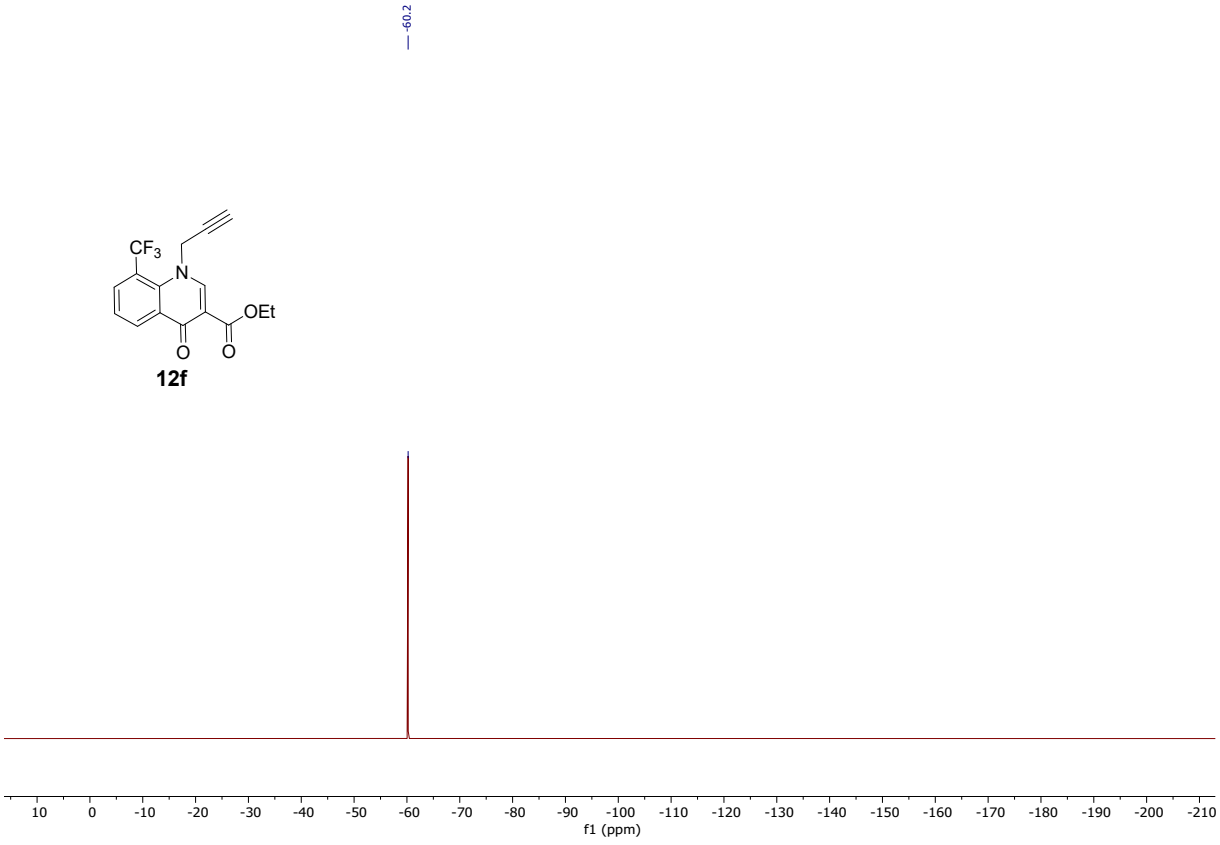
^{19}F NMR (282 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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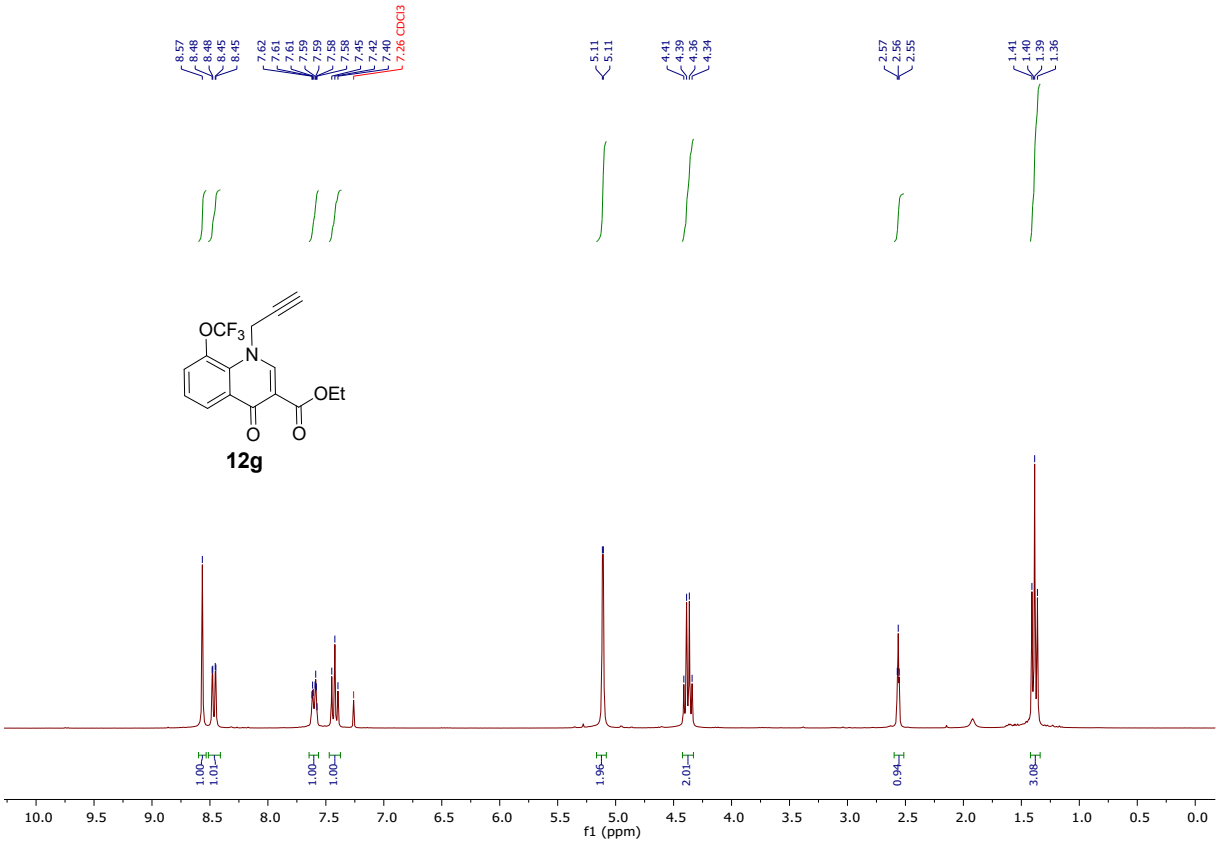
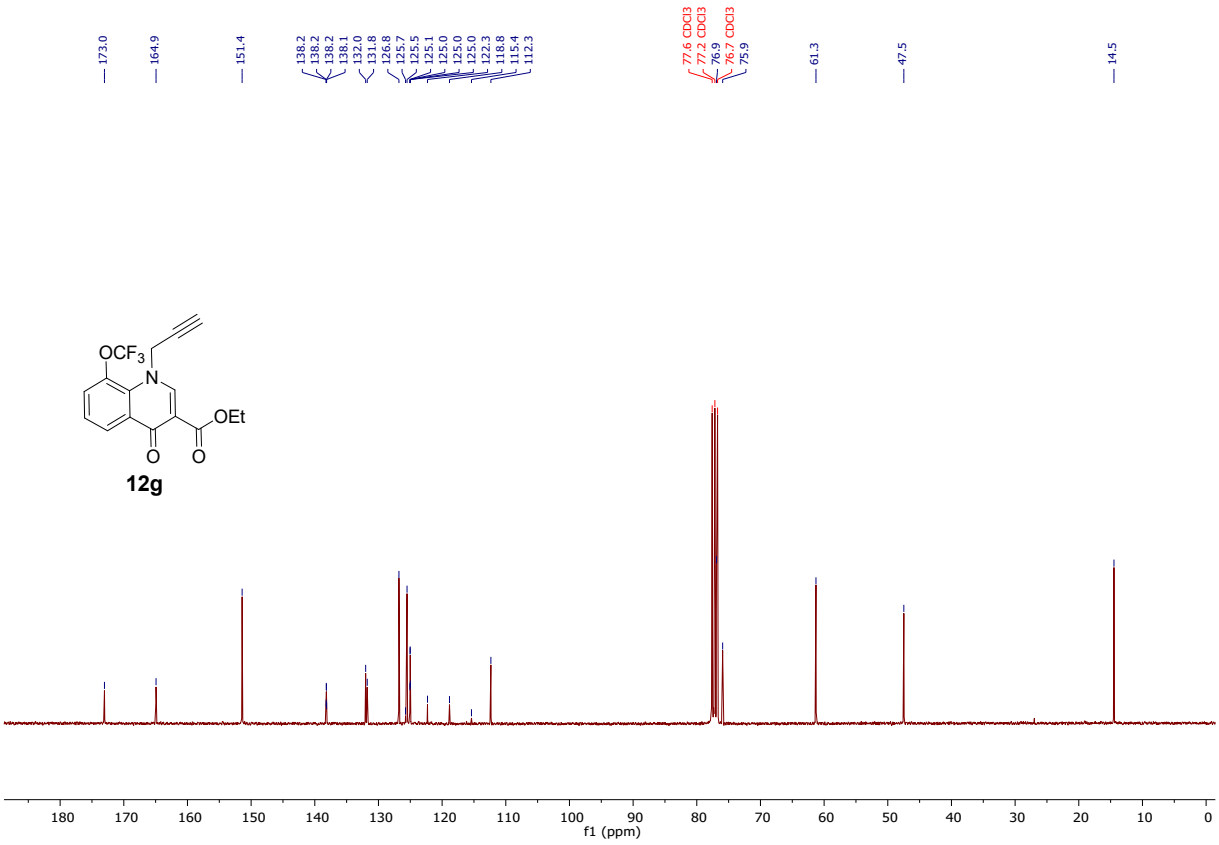
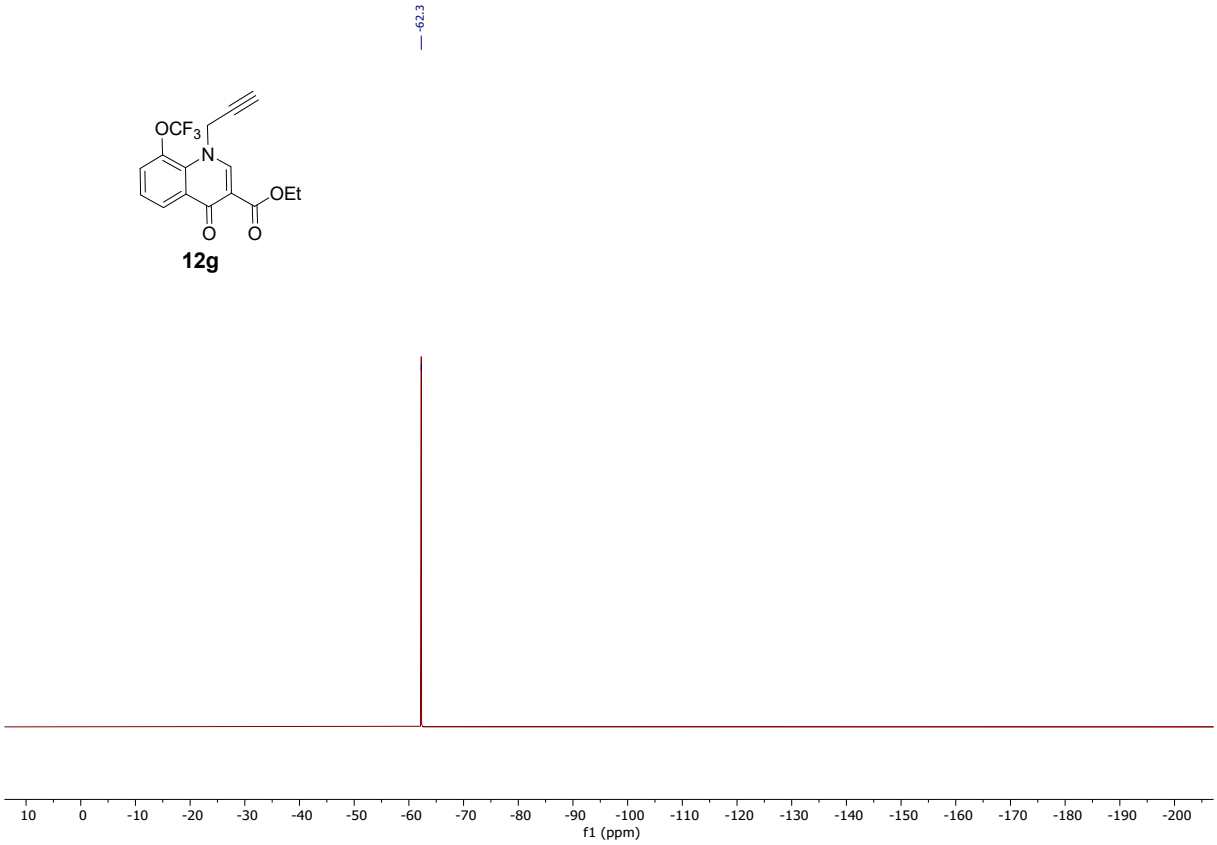


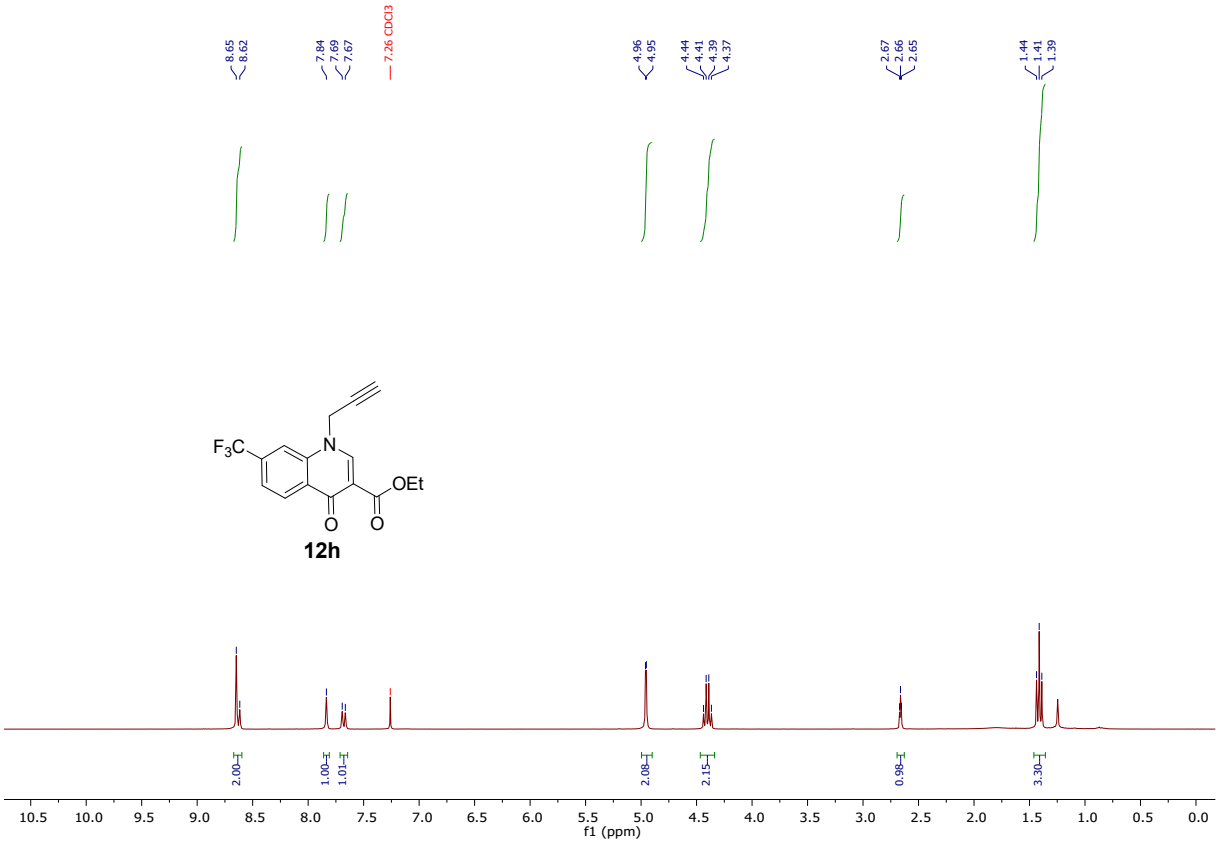
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



^{19}F NMR (282 MHz, $CDCl_3$)



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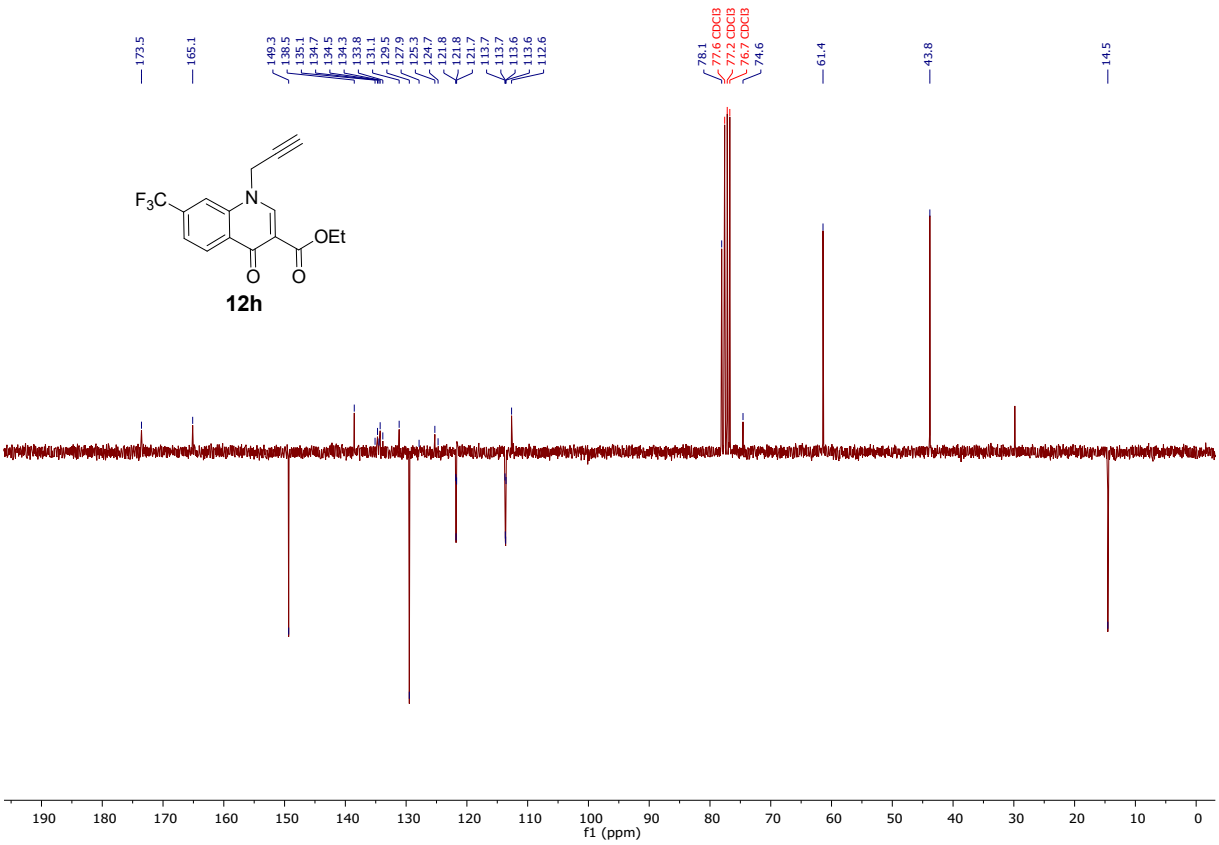

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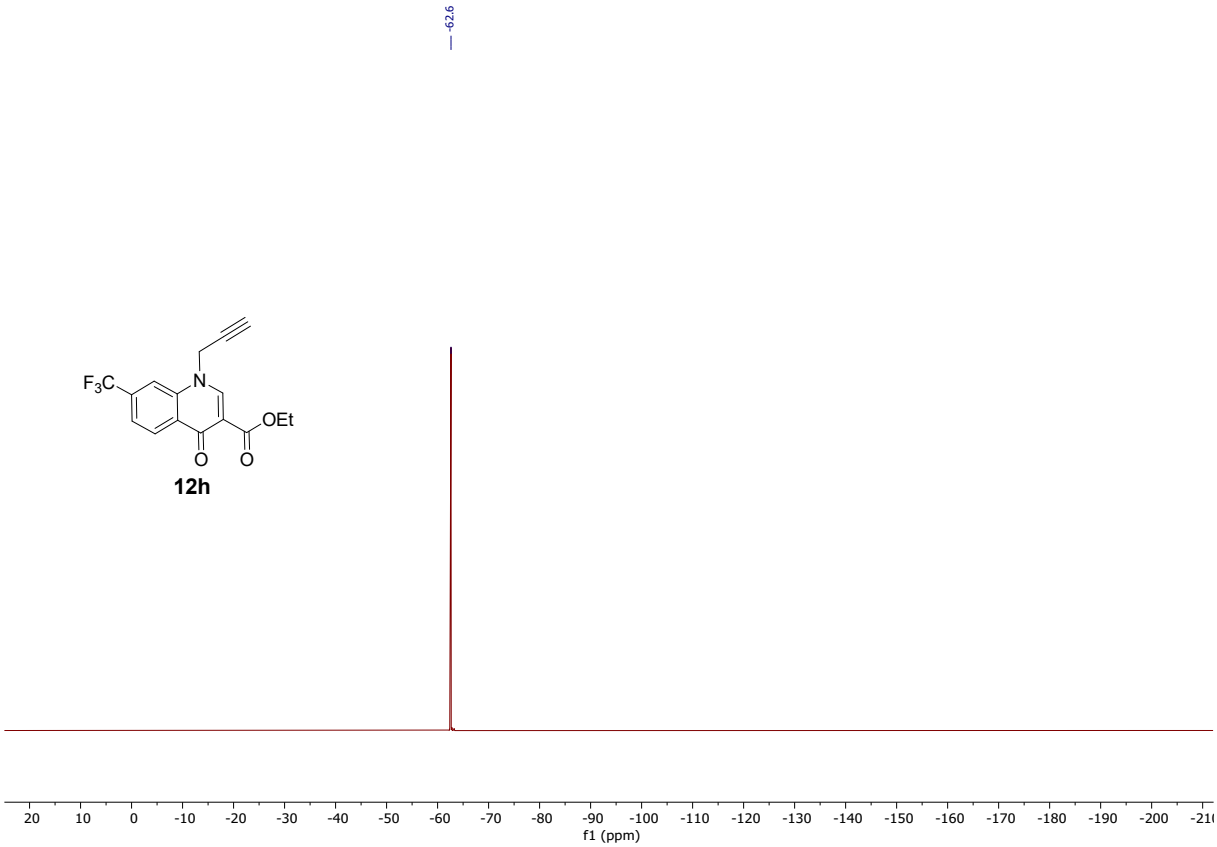

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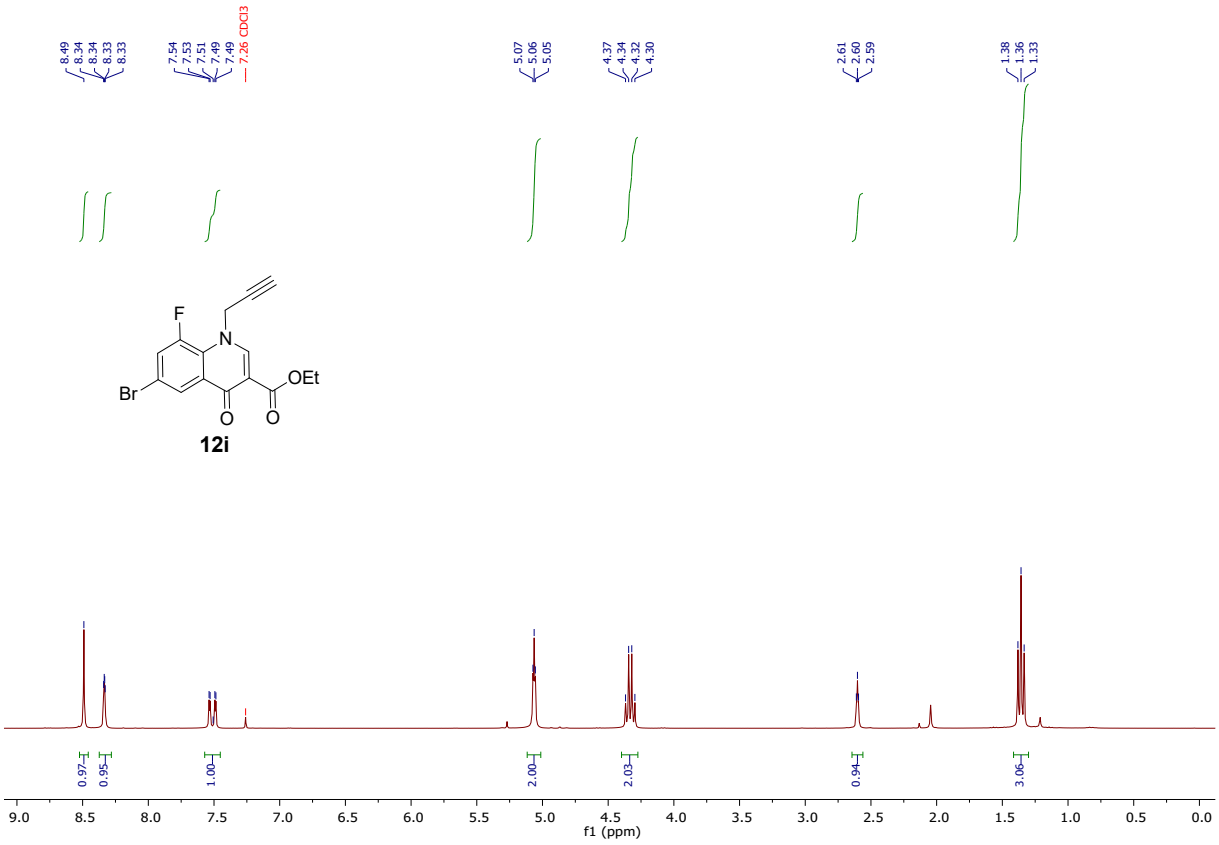

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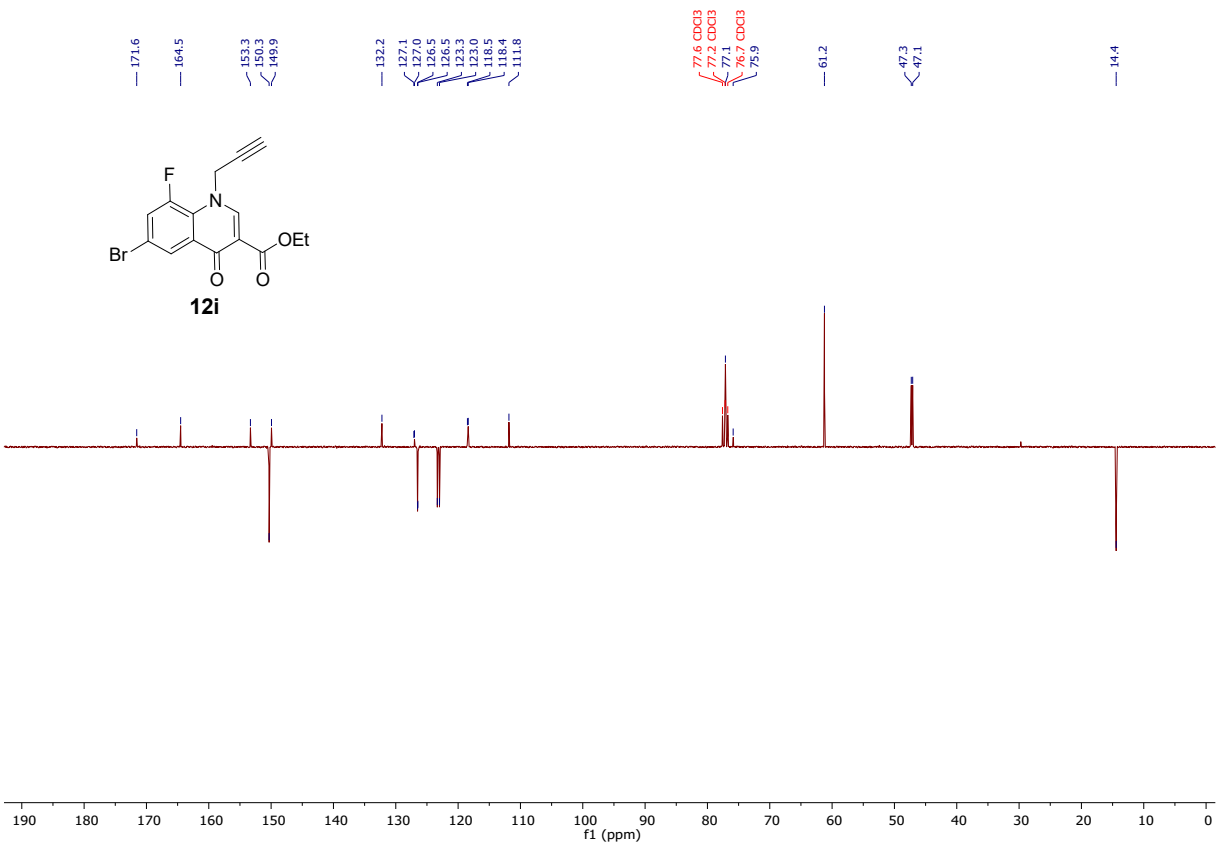

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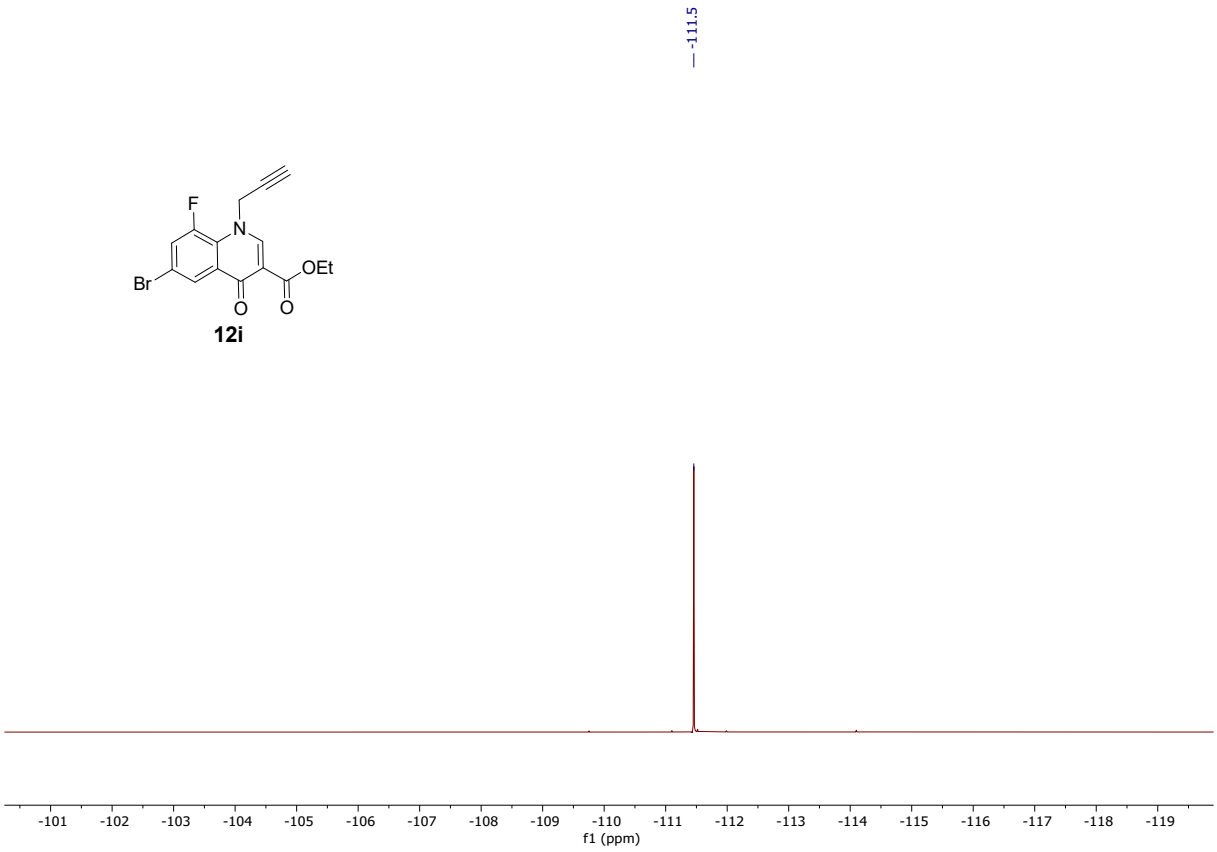
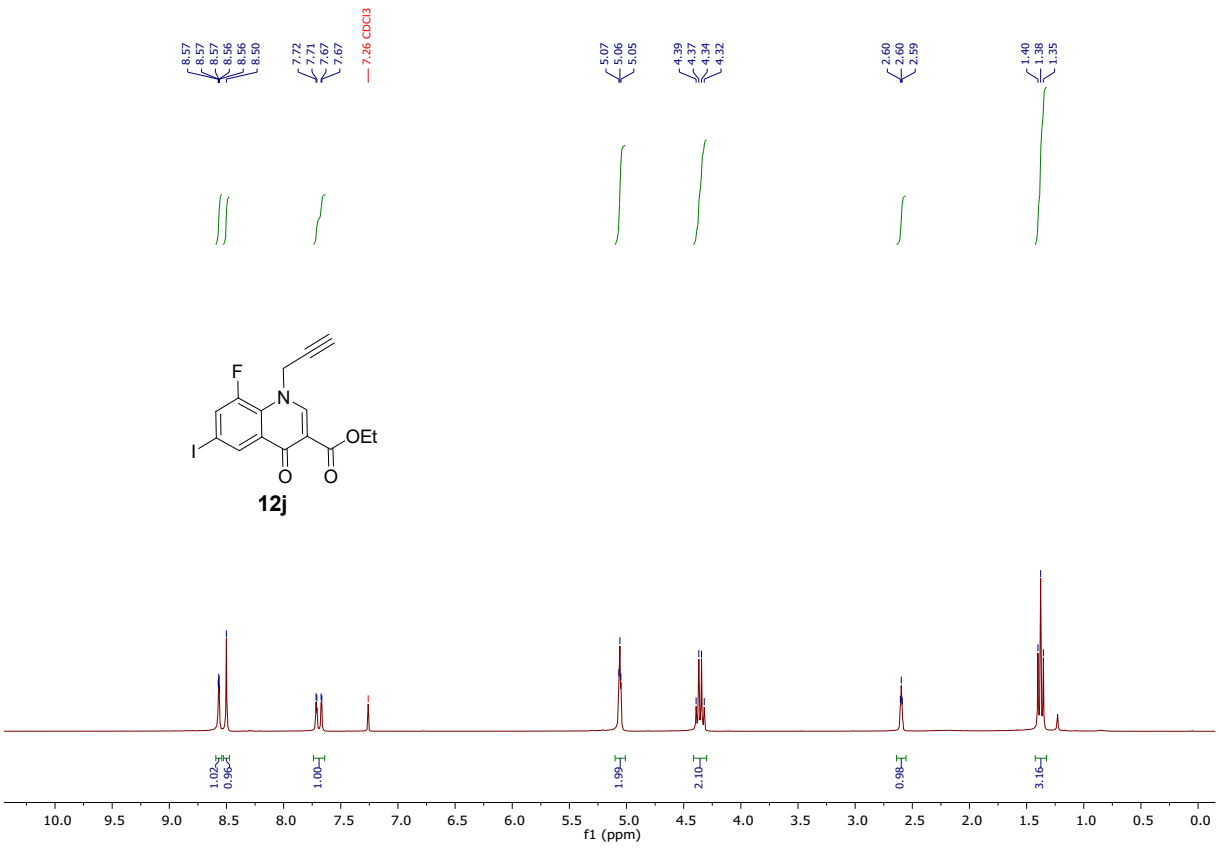


^{19}F NMR (282 MHz, $CDCl_3$)



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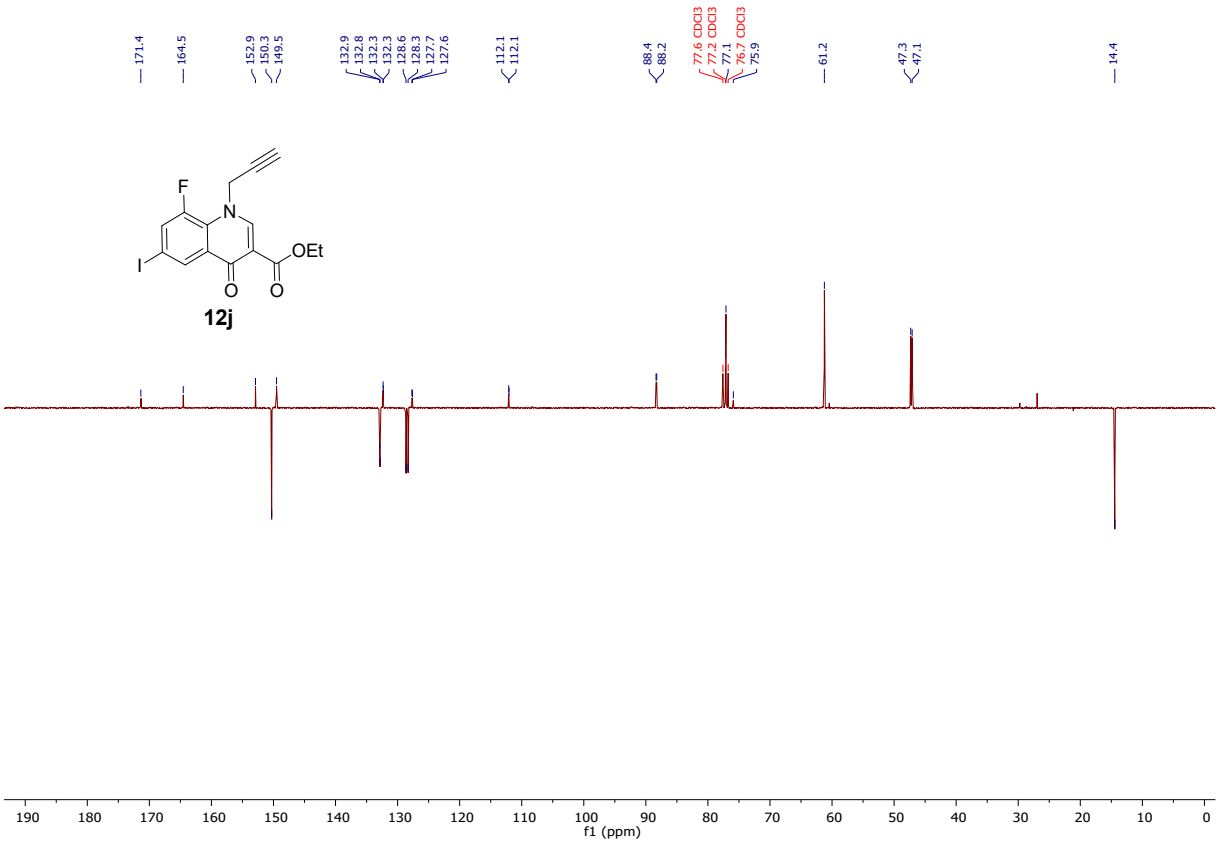

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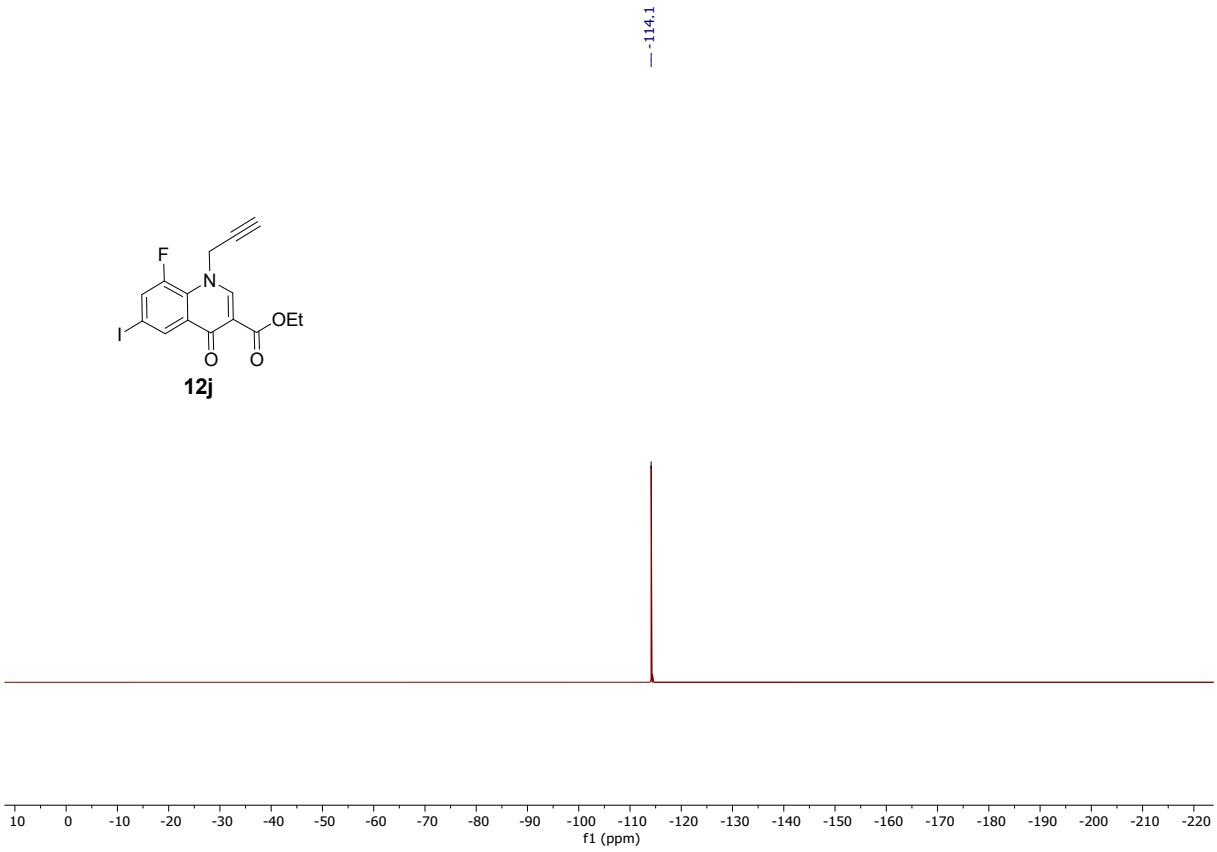

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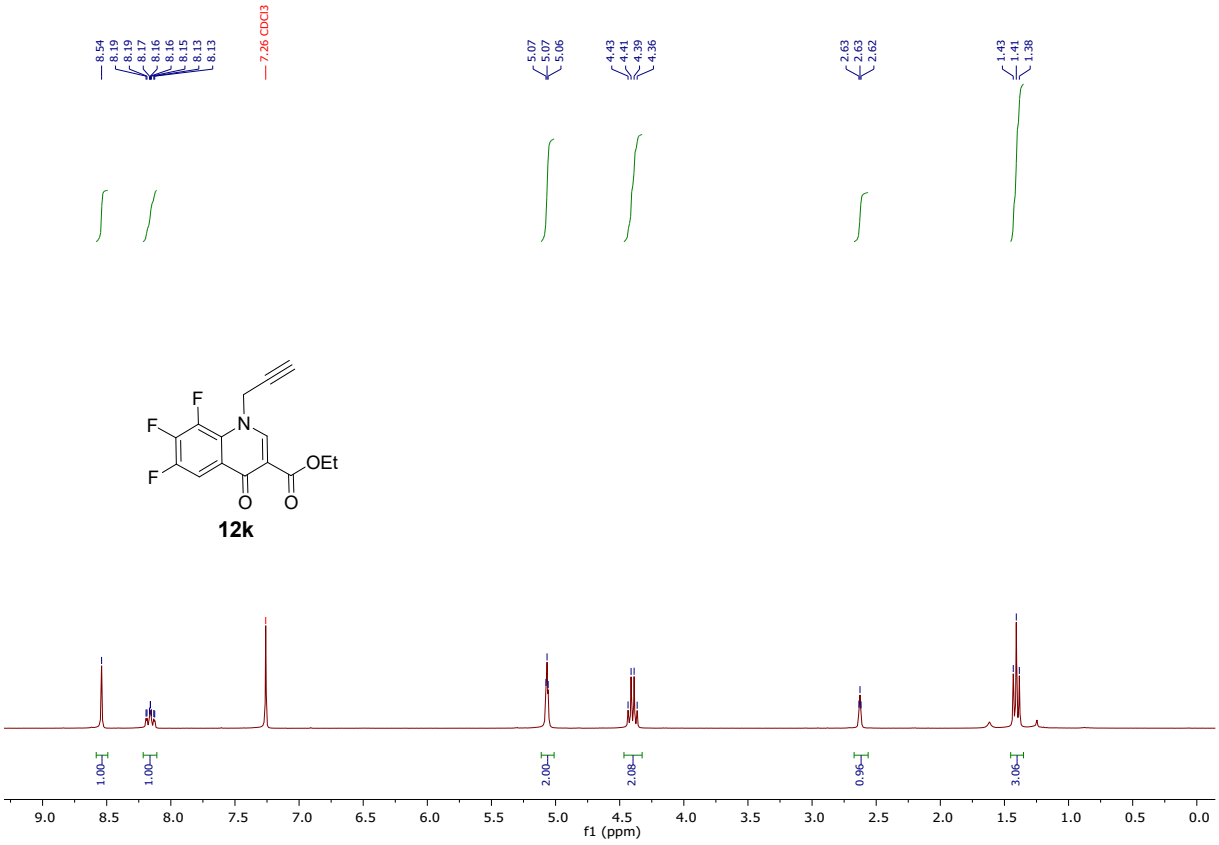

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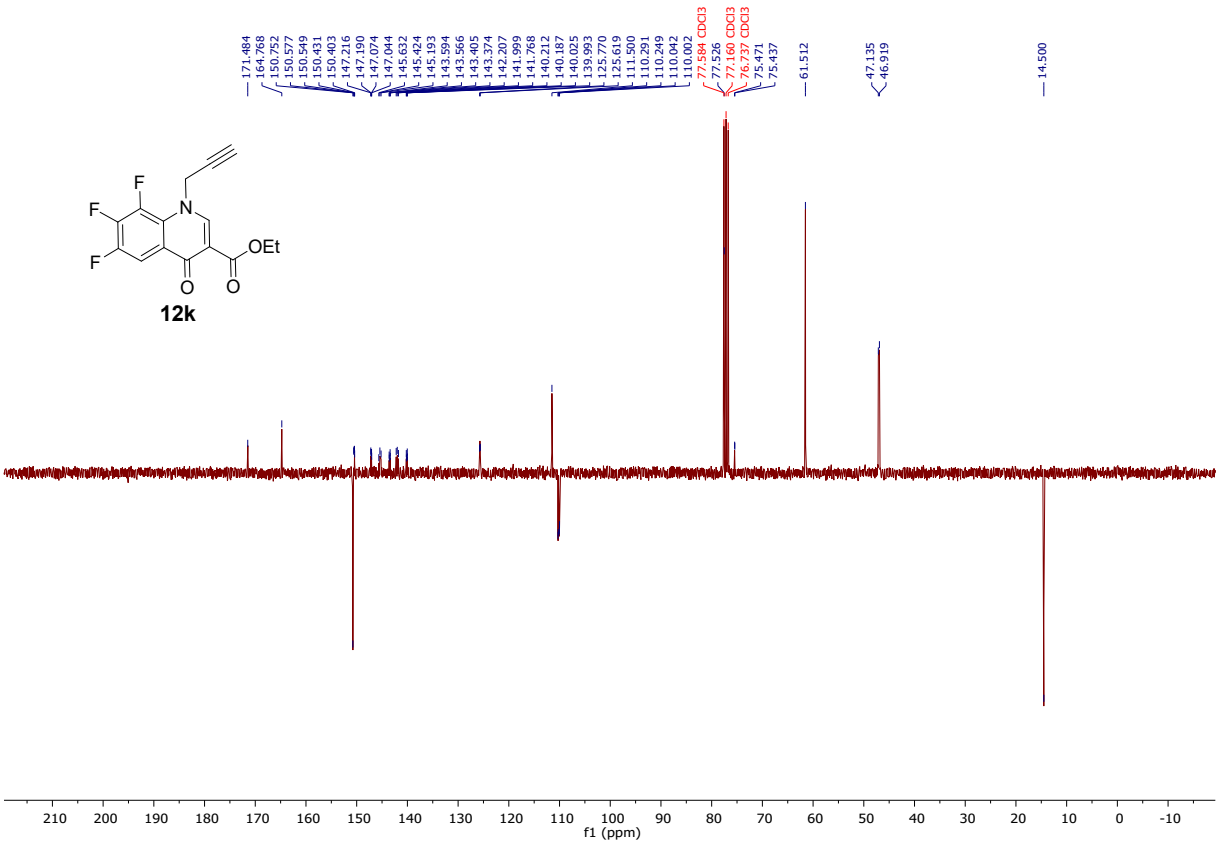

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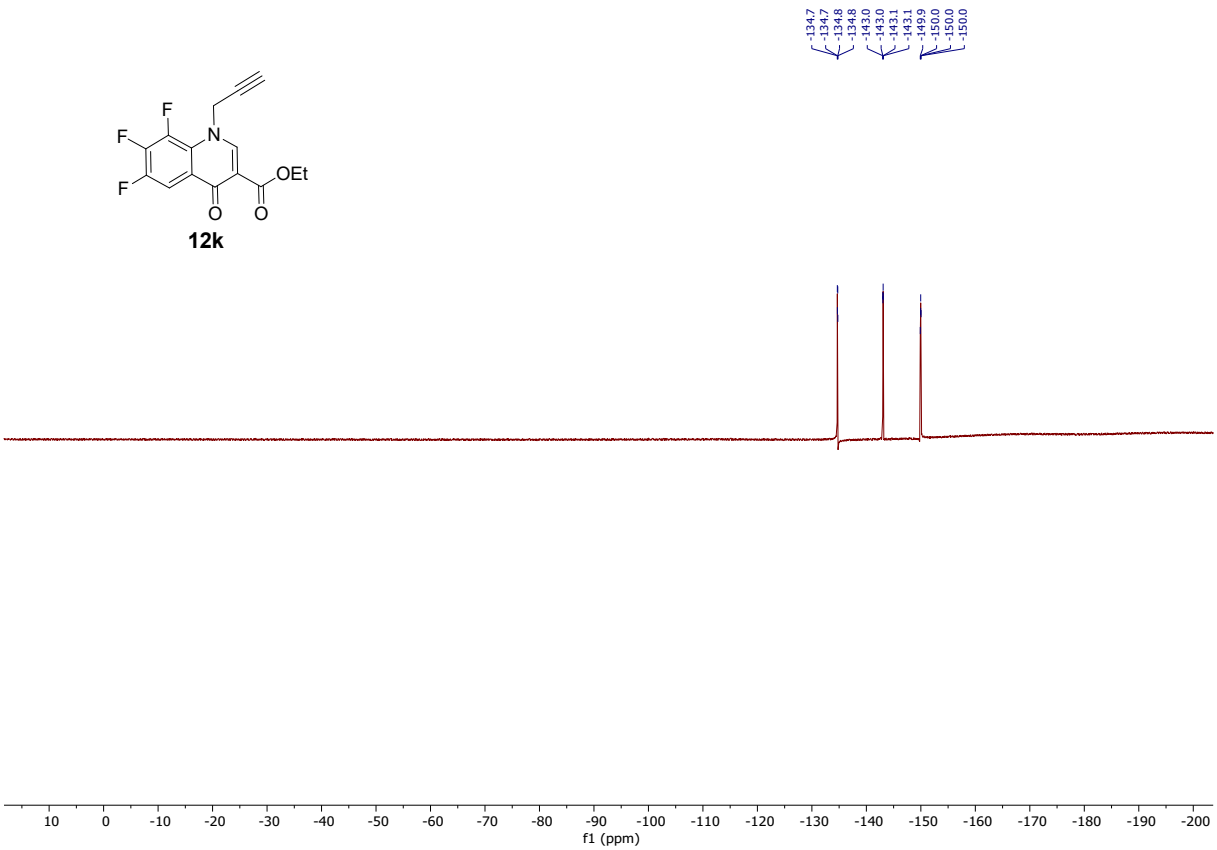

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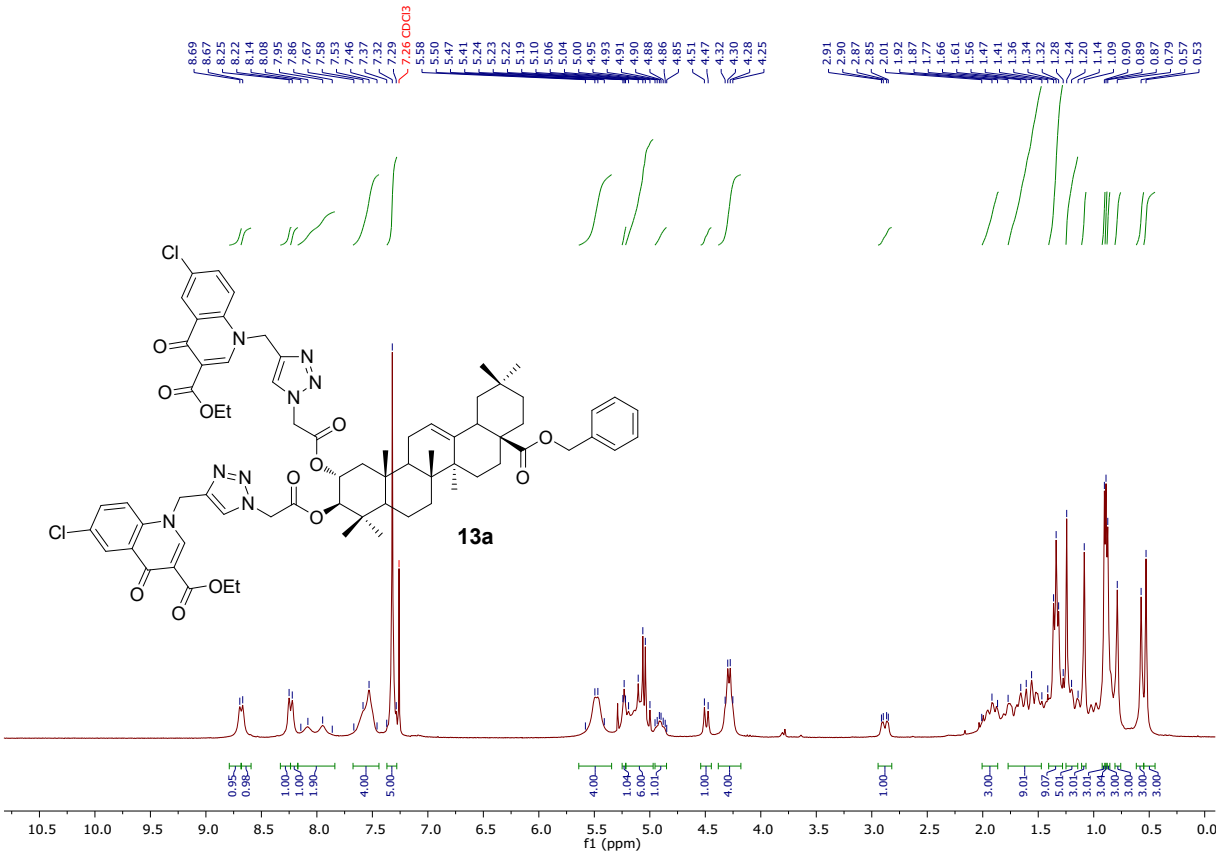

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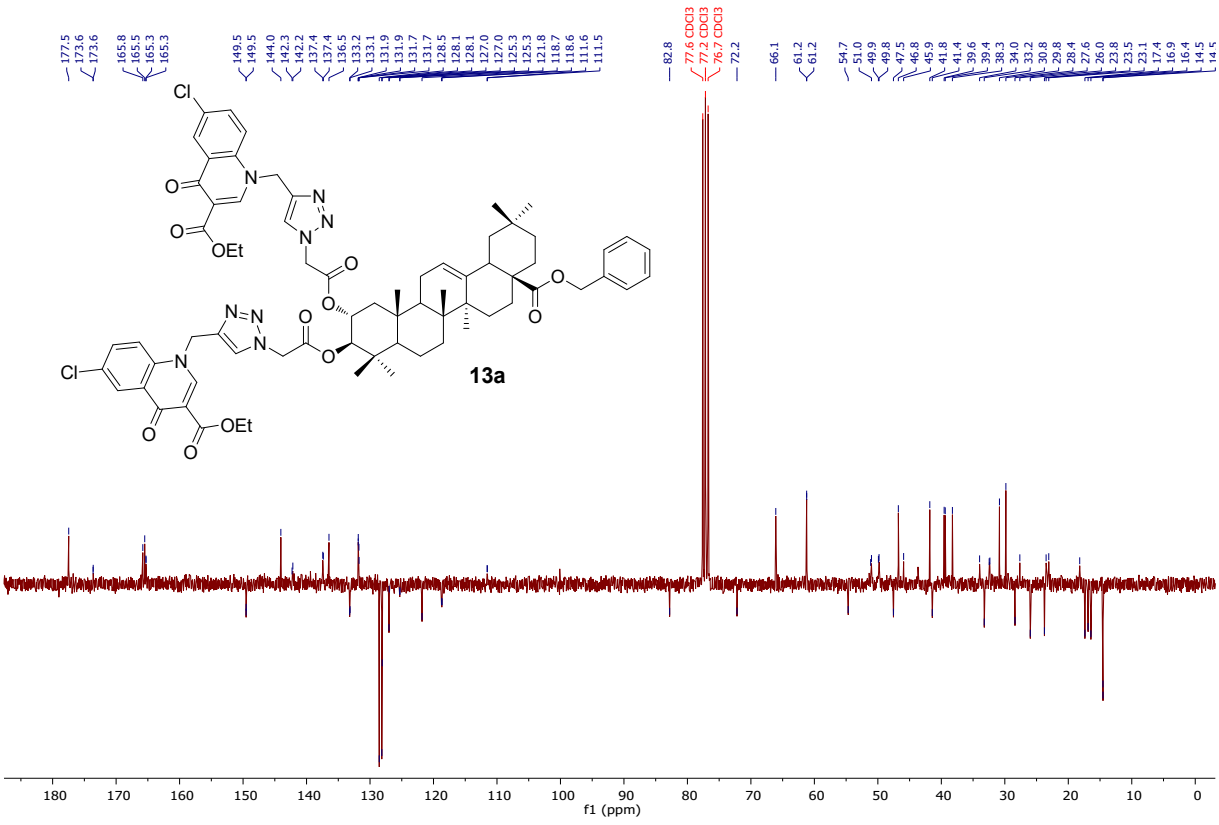
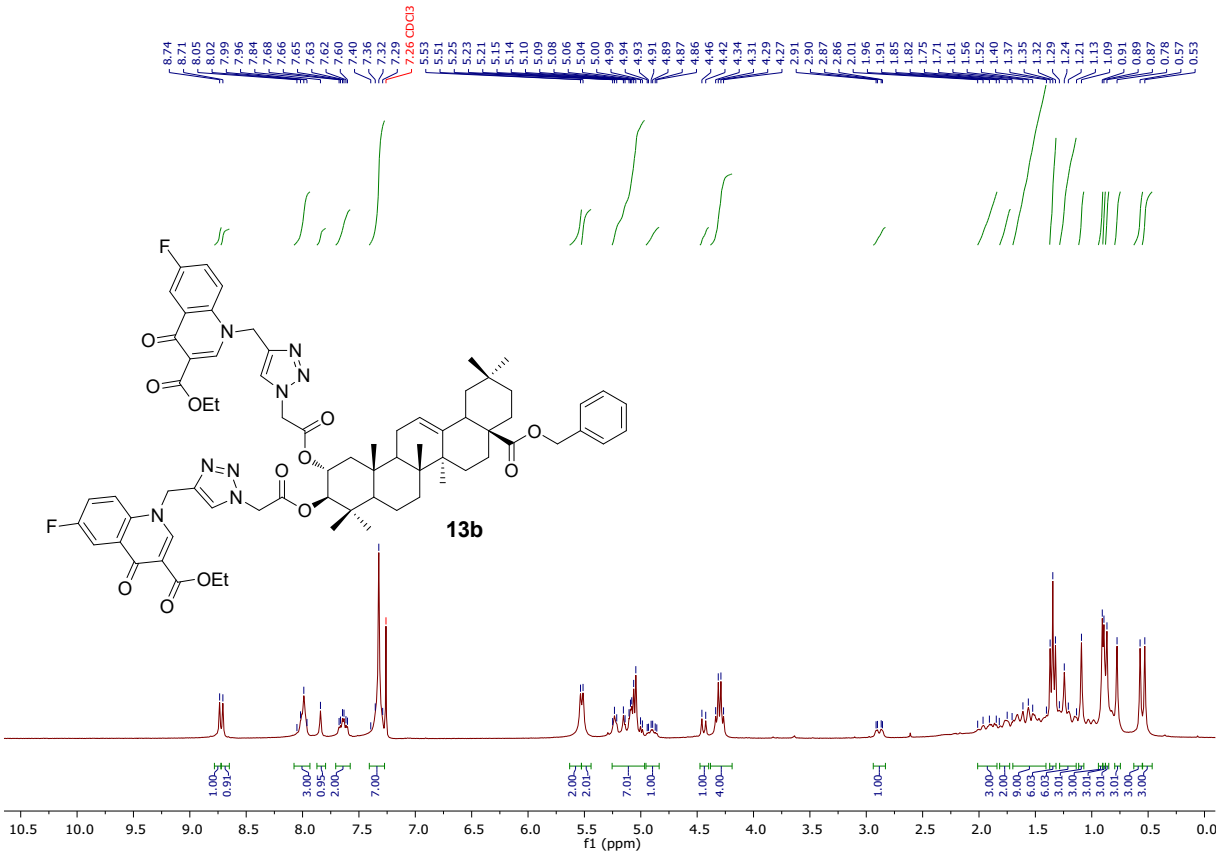


^{13}C NMR (75 MHz, $CDCl_3$)



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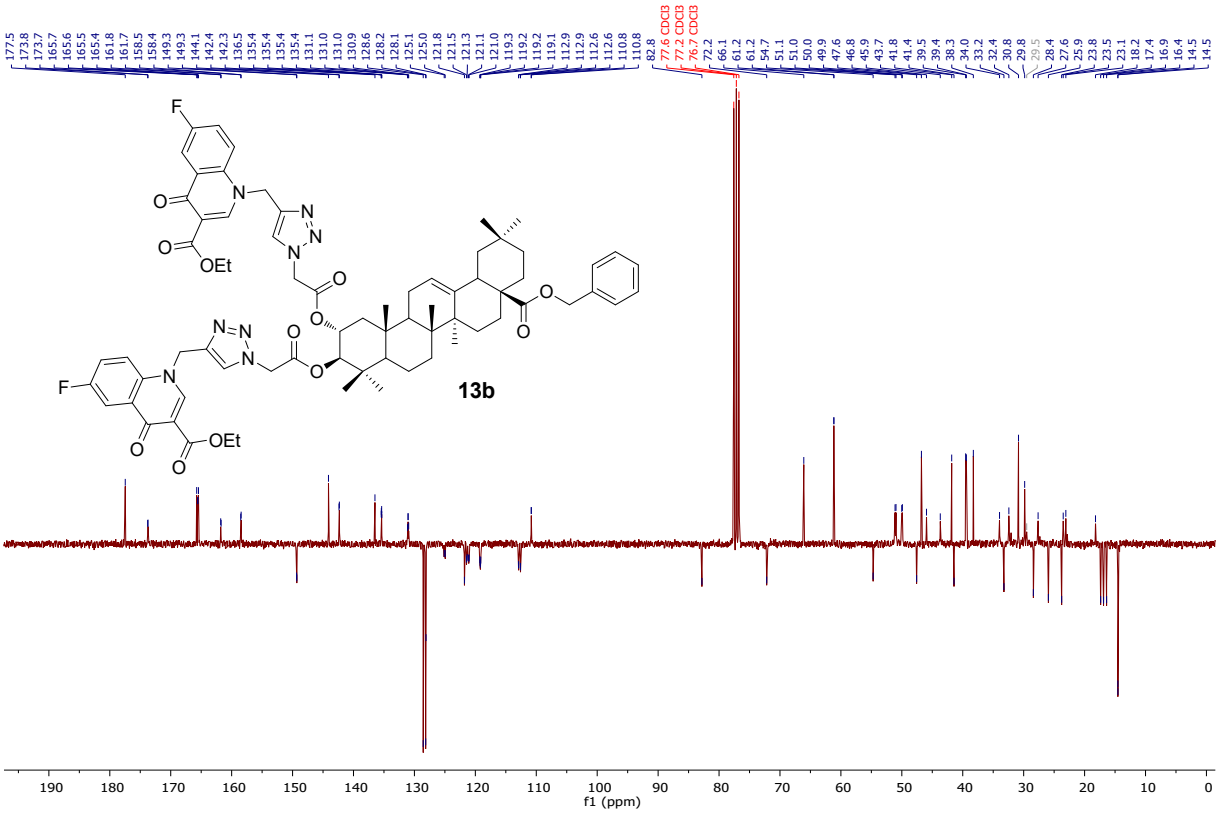
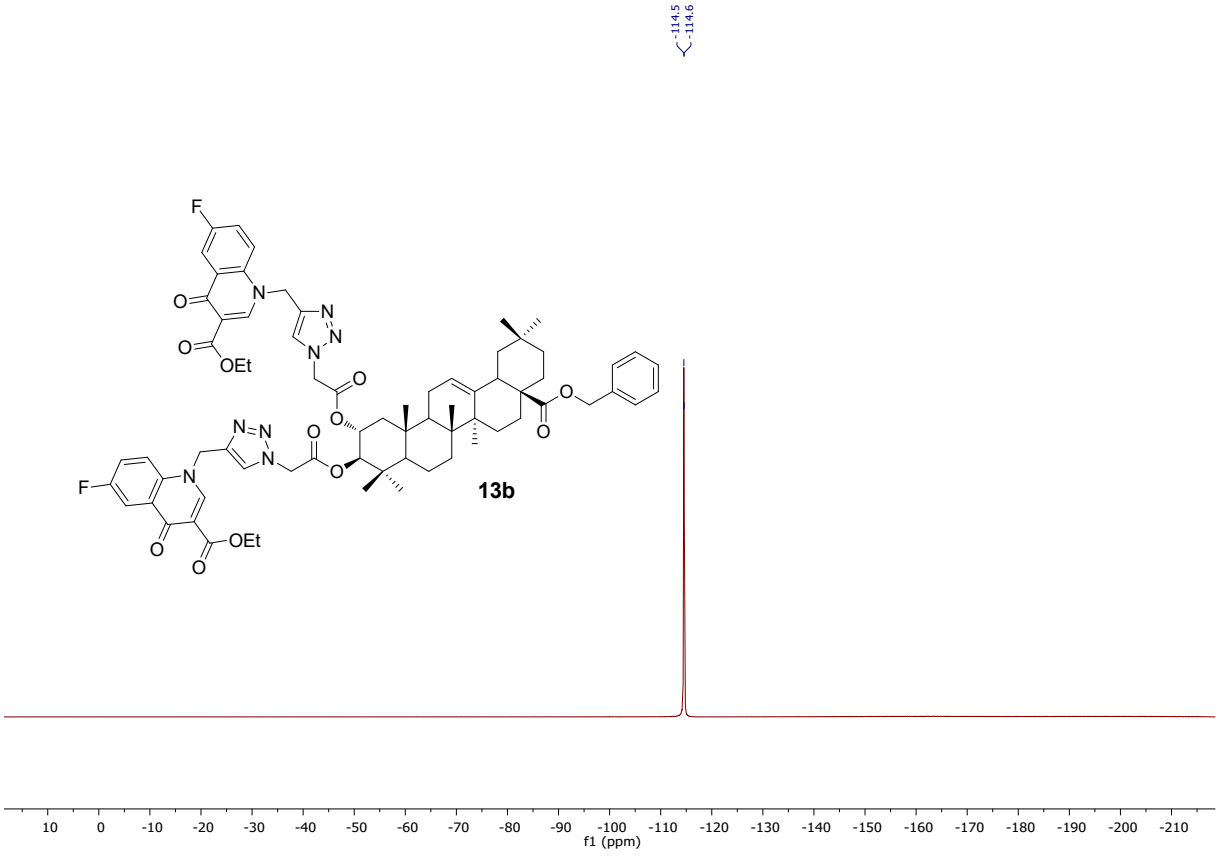
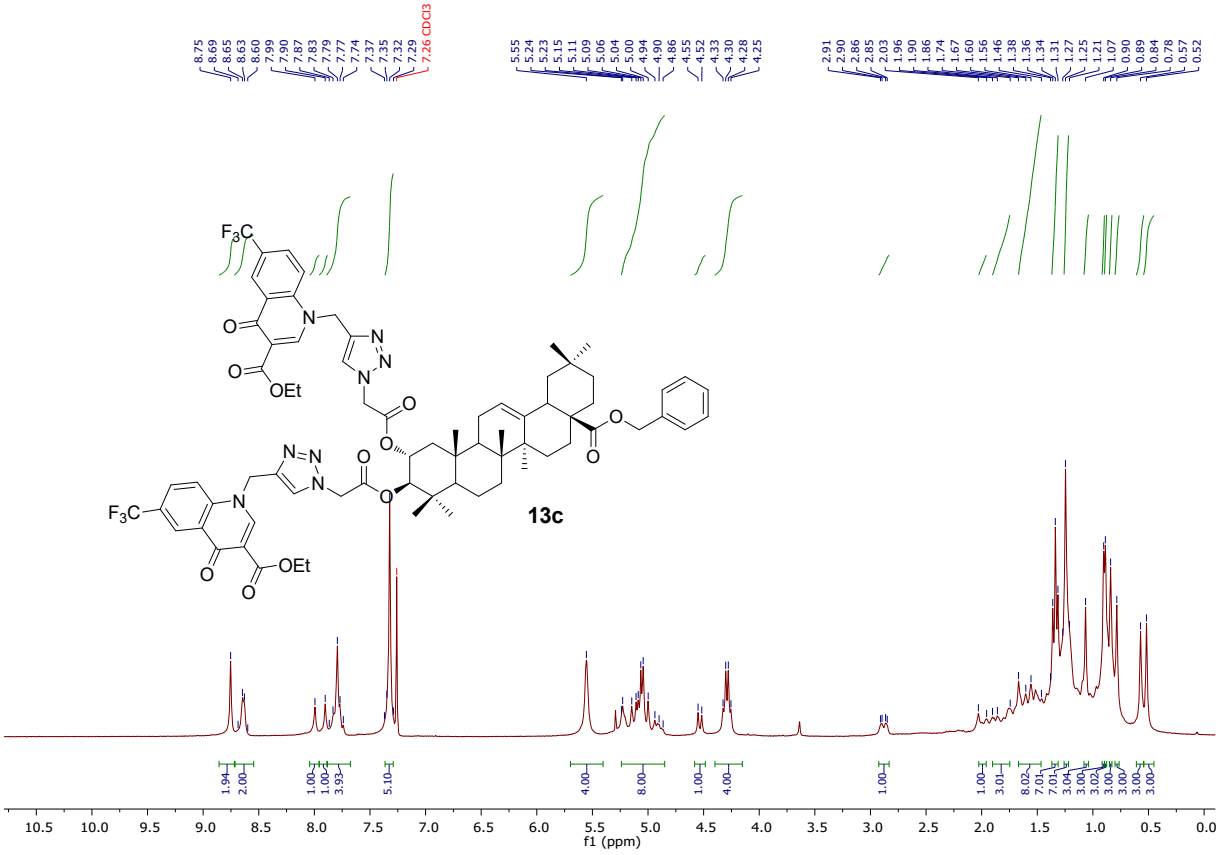


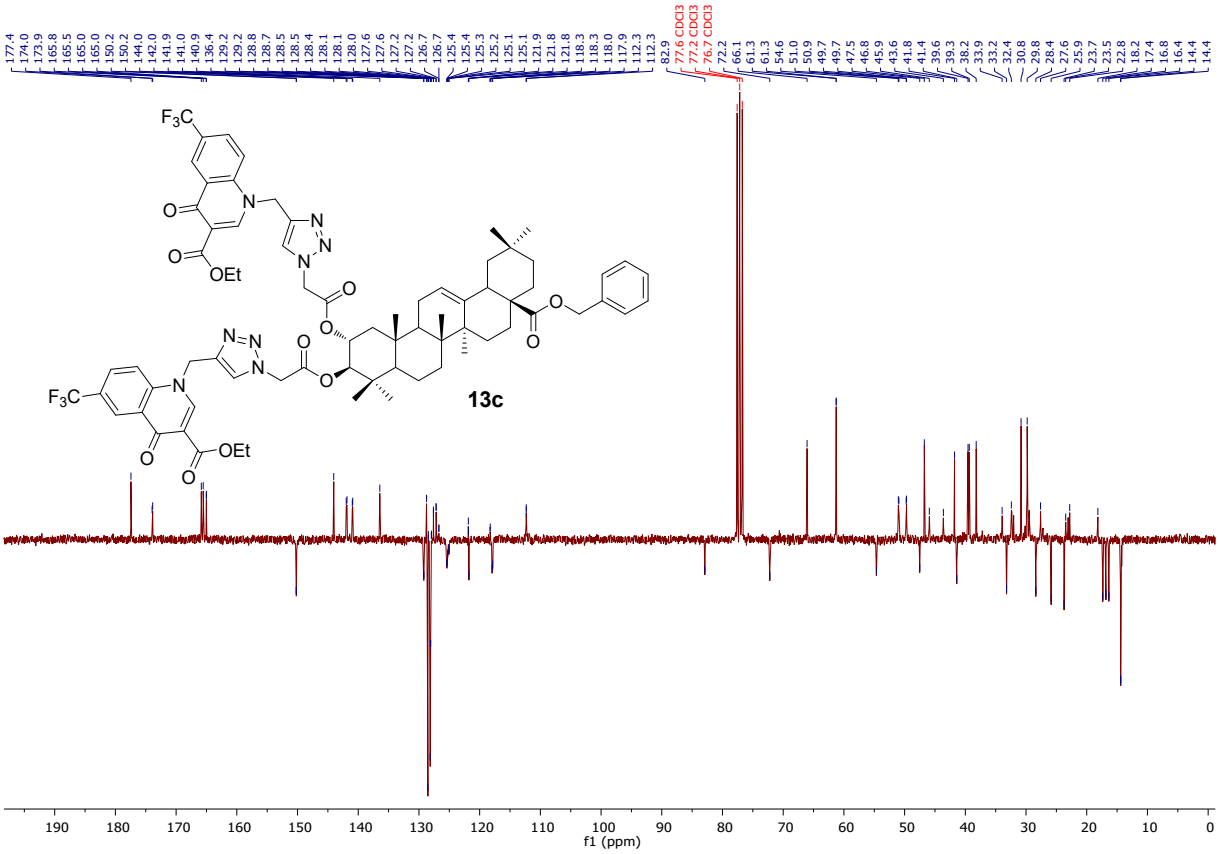
^{13}C NMR (75 MHz, $CDCl_3$)



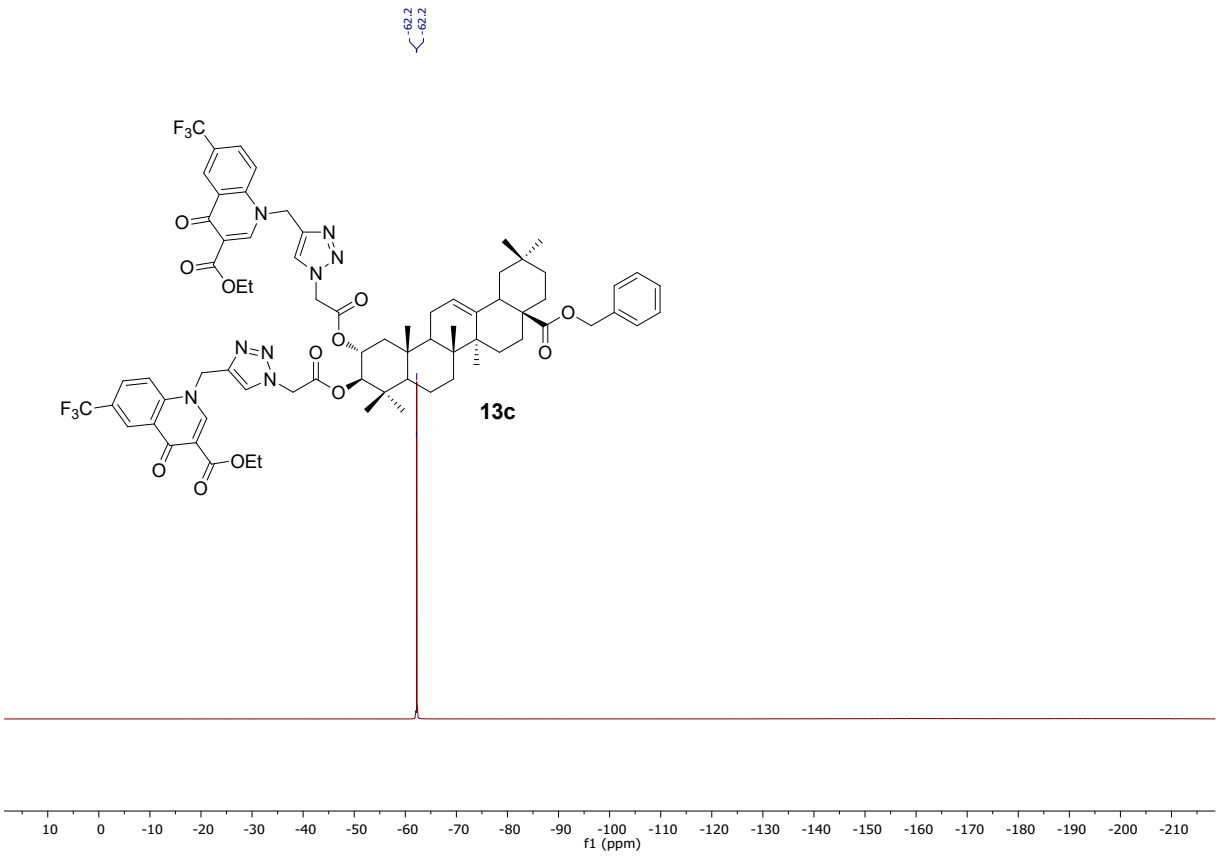
^{19}F NMR (282 MHz, $CDCl_3$)



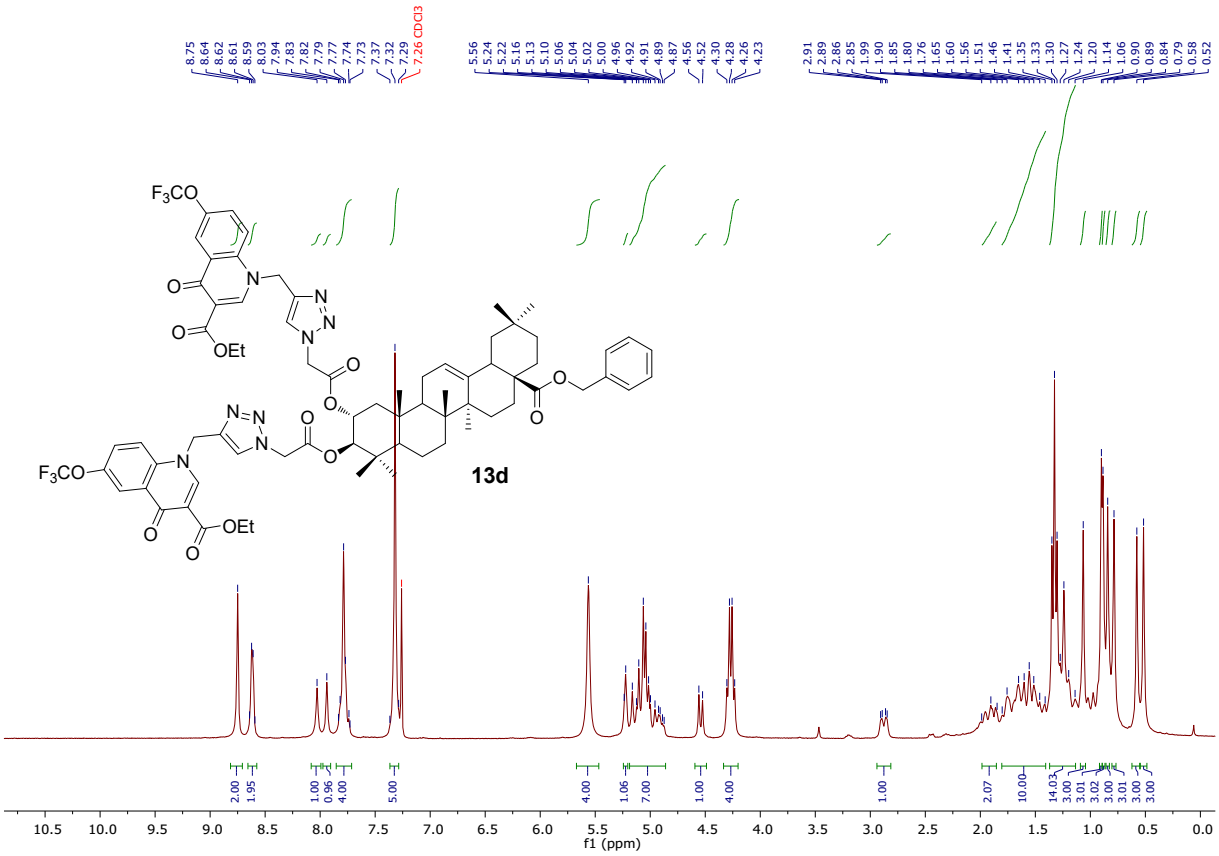
^{1}H NMR (300 MHz, $CDCl_3$)



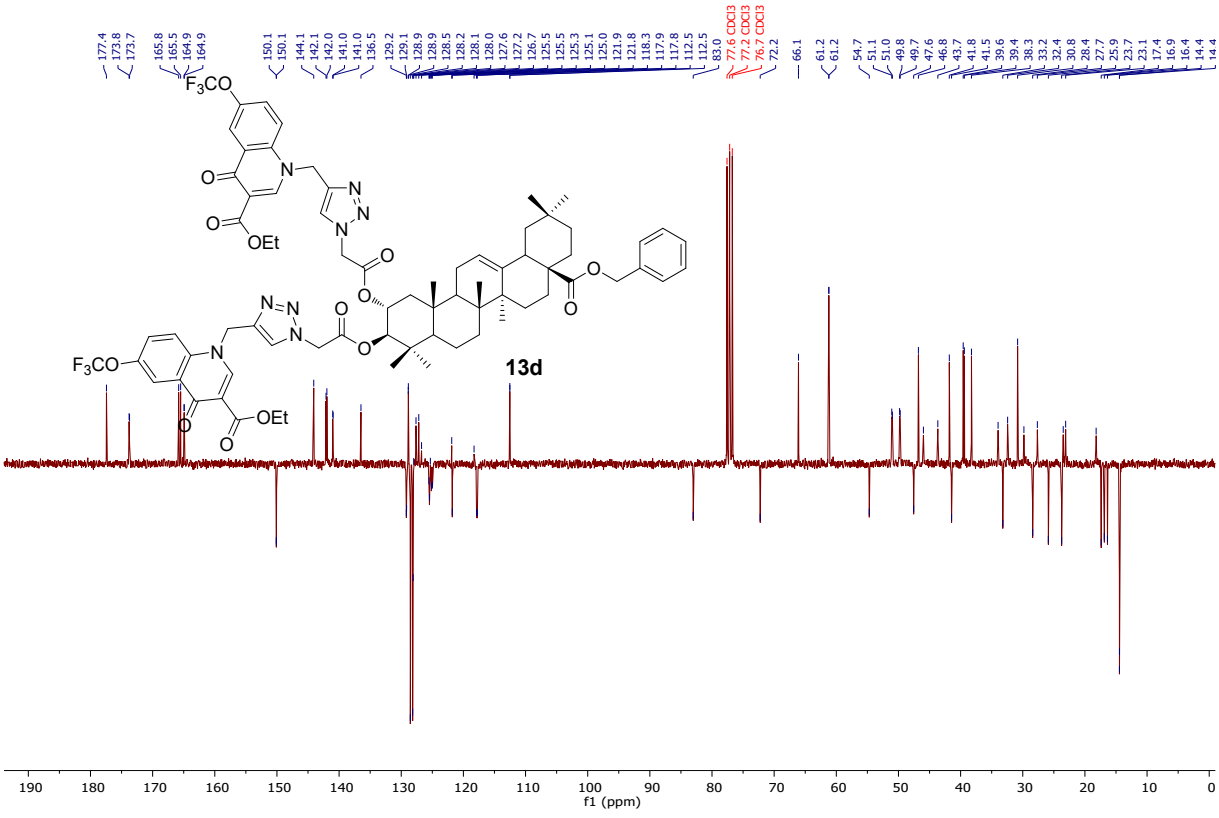
^{13}C NMR (75 MHz, $CDCl_3$)



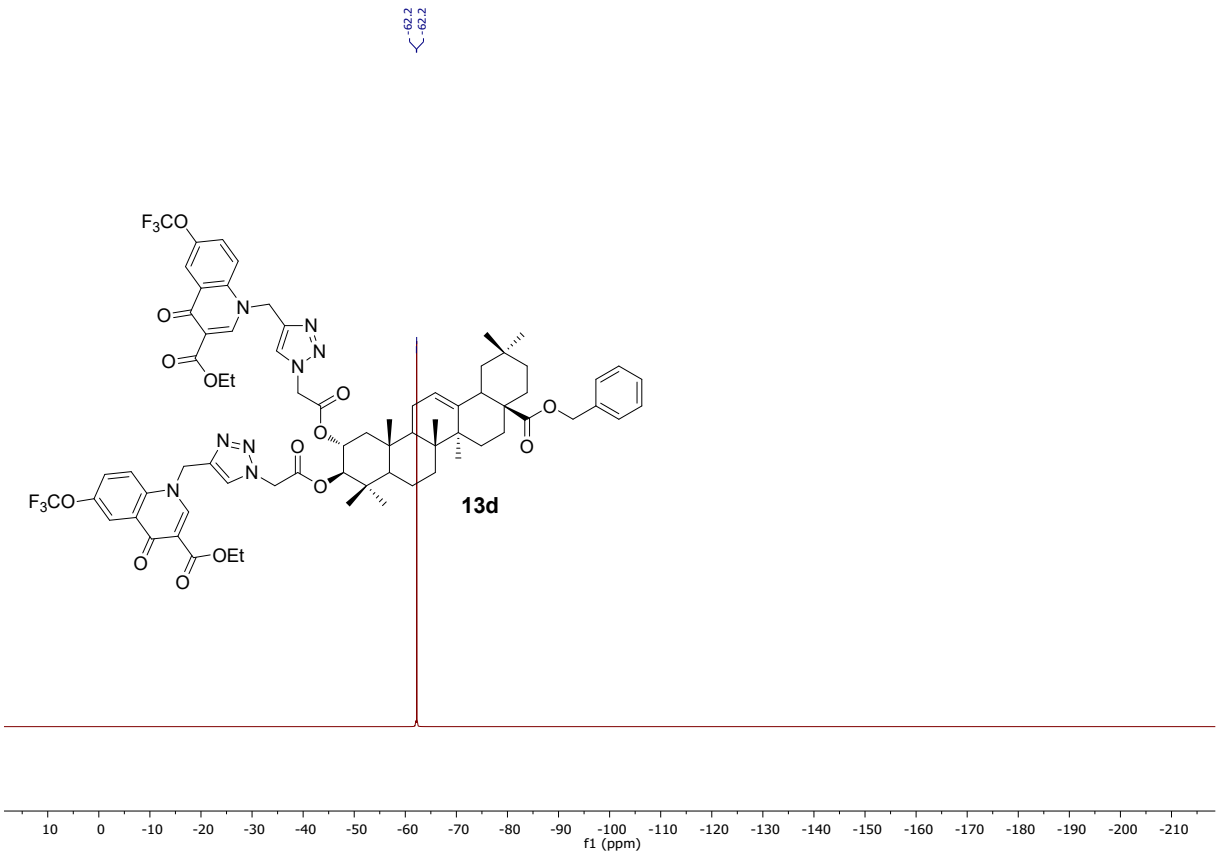
^{19}F NMR (282 MHz, $CDCl_3$)



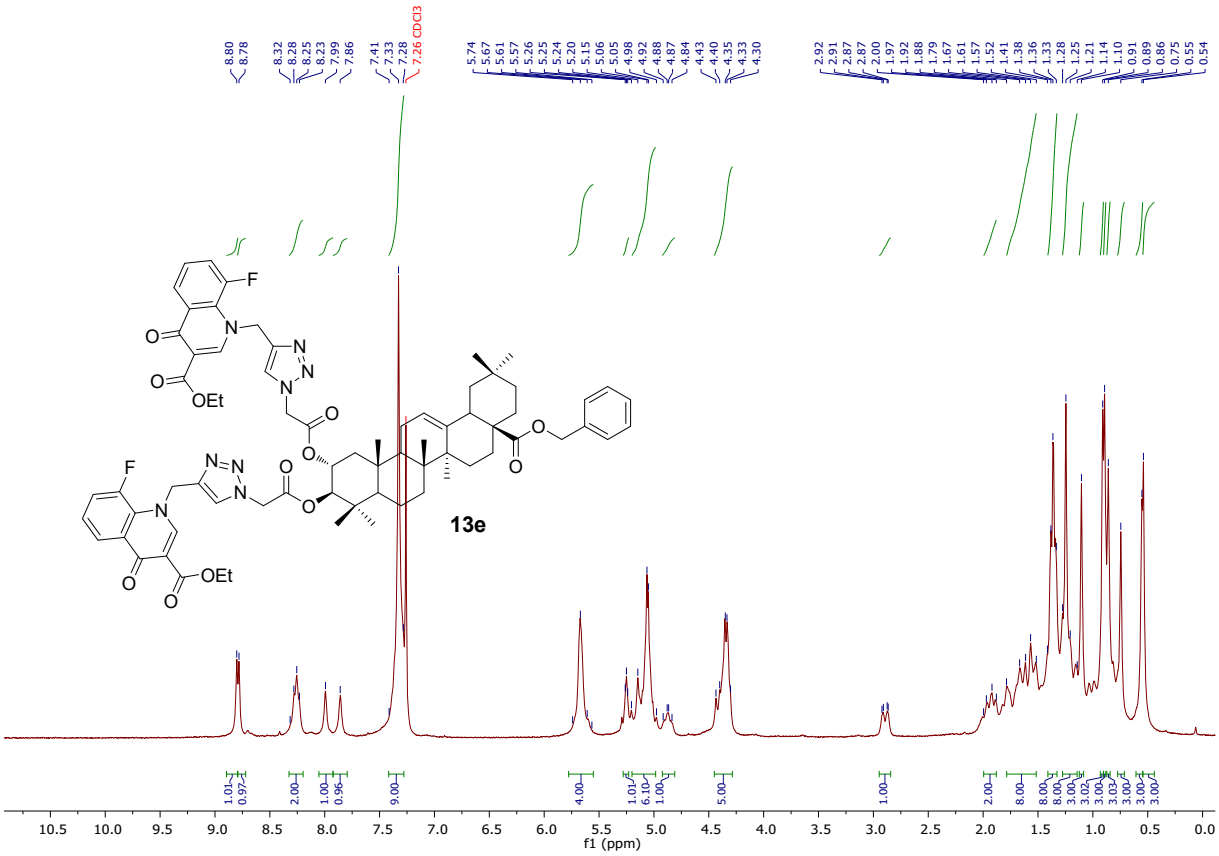
^{1}H NMR (300 MHz, $CDCl_3$)



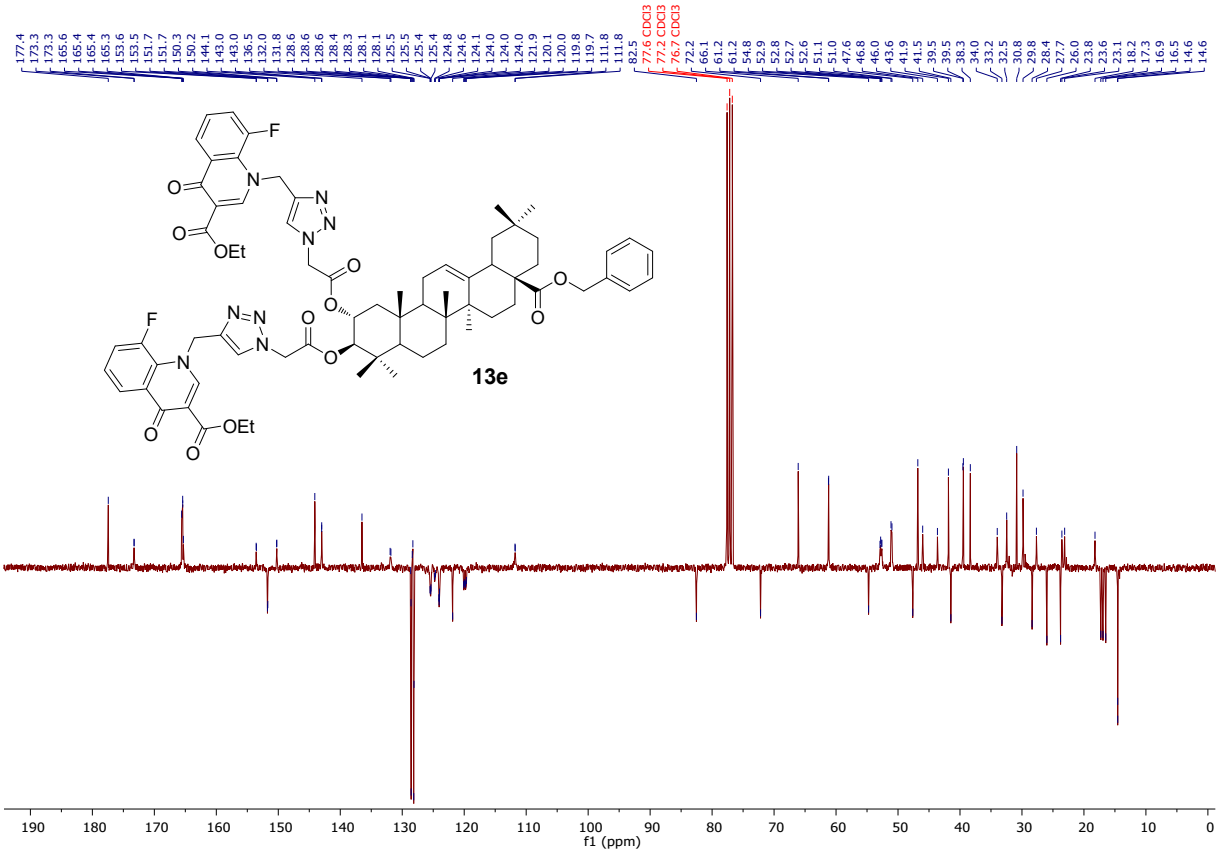
^{13}C NMR (75 MHz, $CDCl_3$)



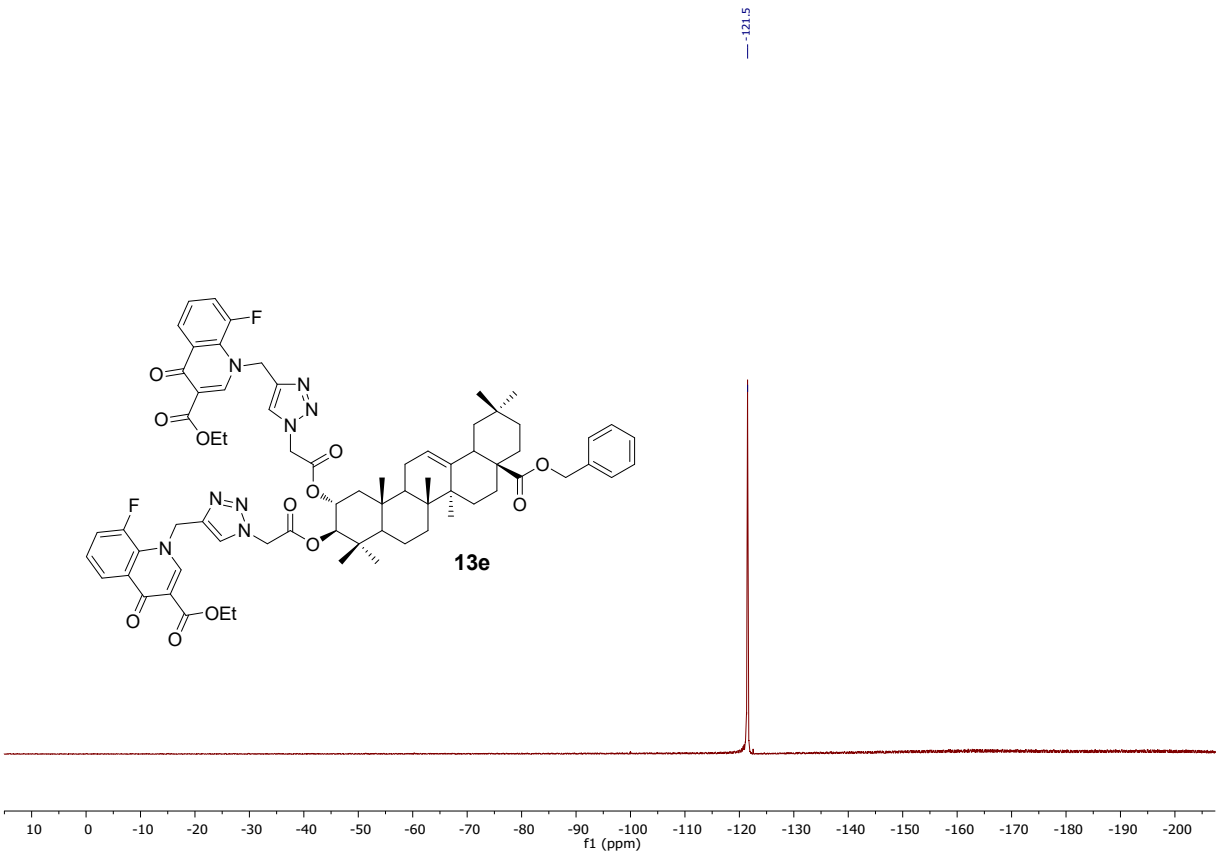
^{19}F NMR (282 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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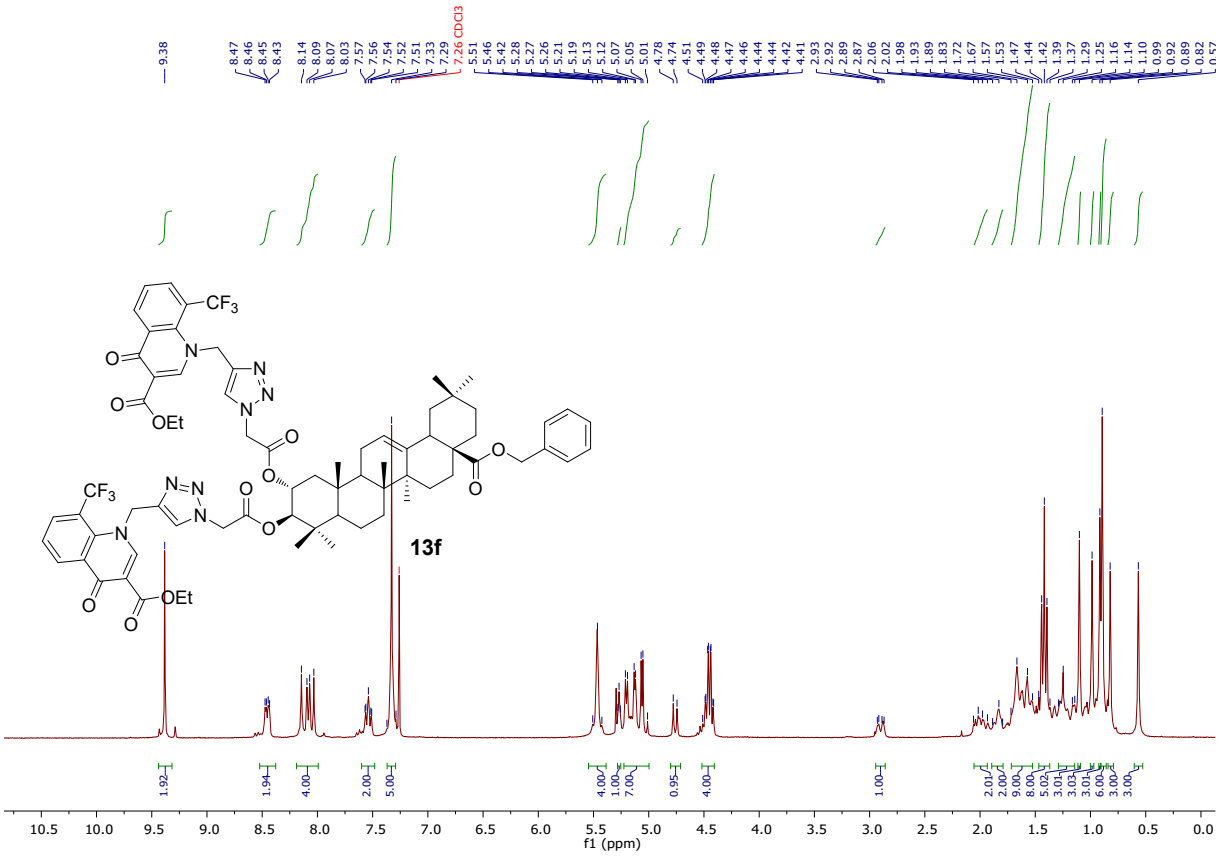
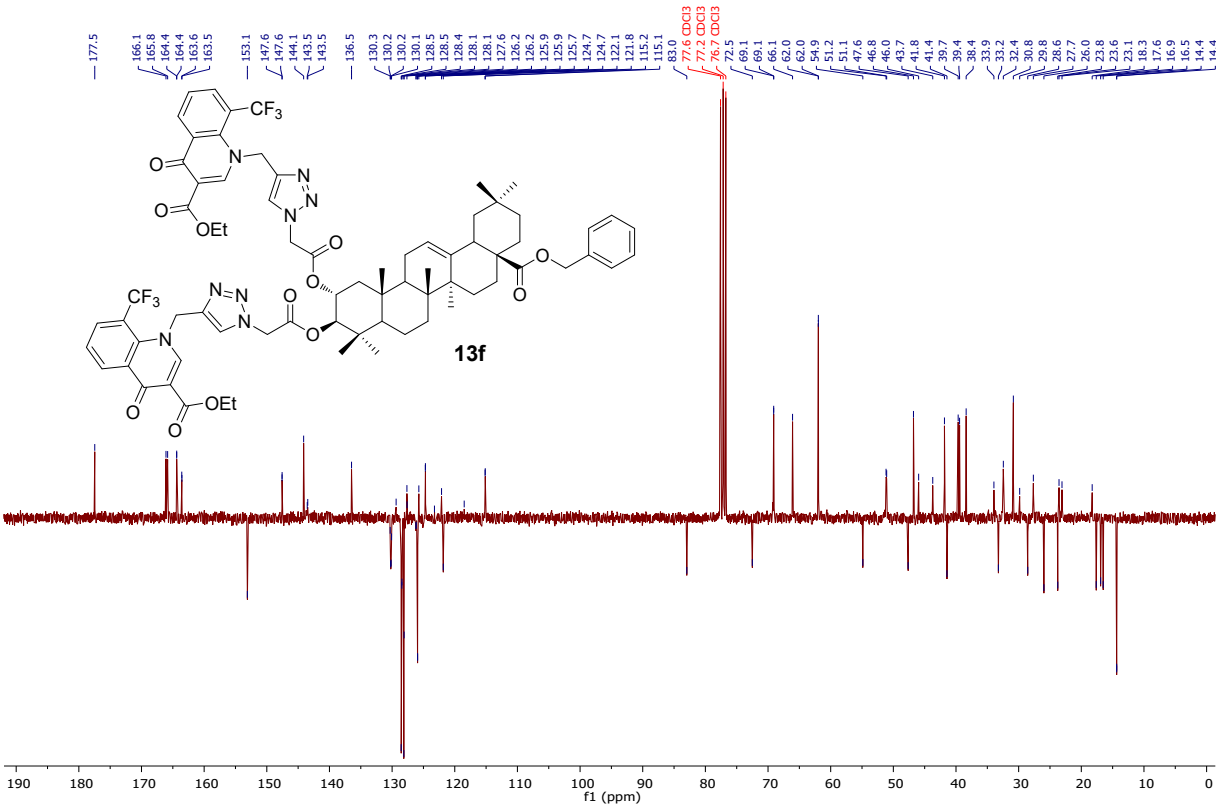


^{1}H NMR (300 MHz, $CDCl_3$)



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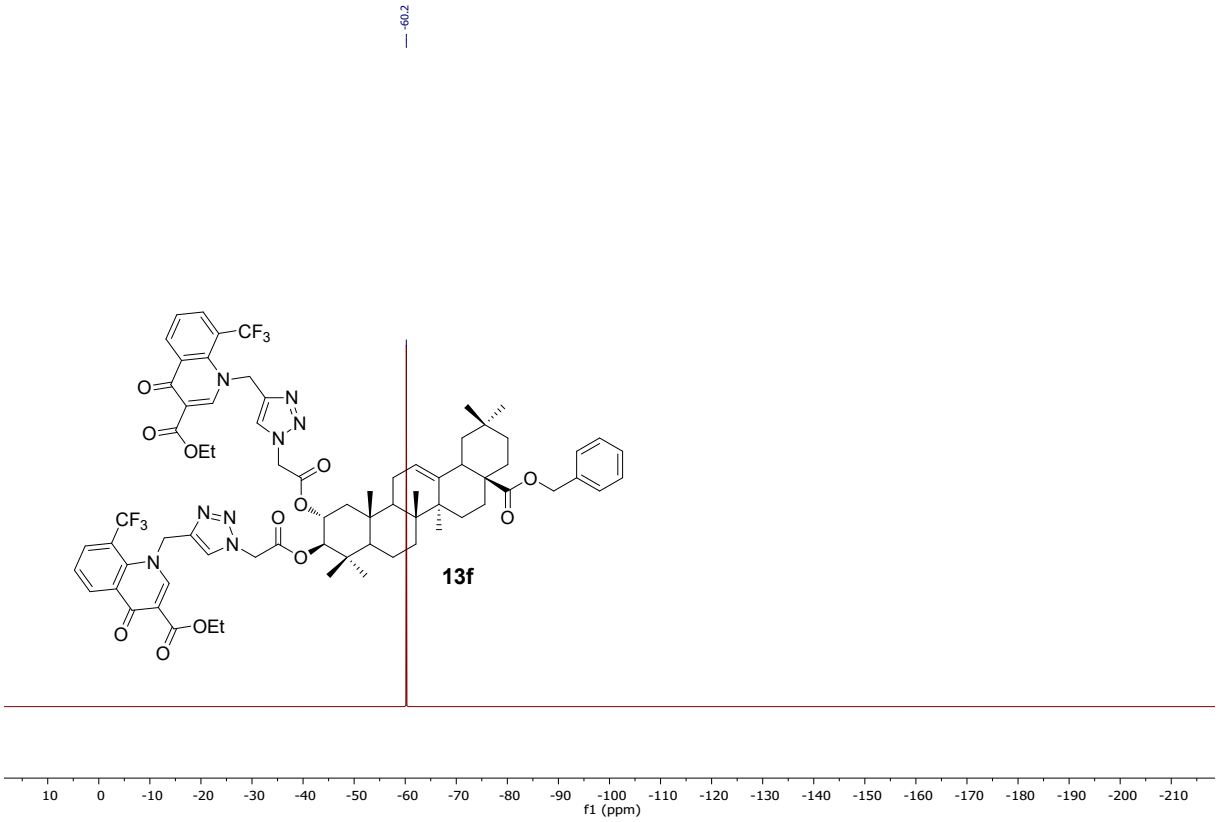
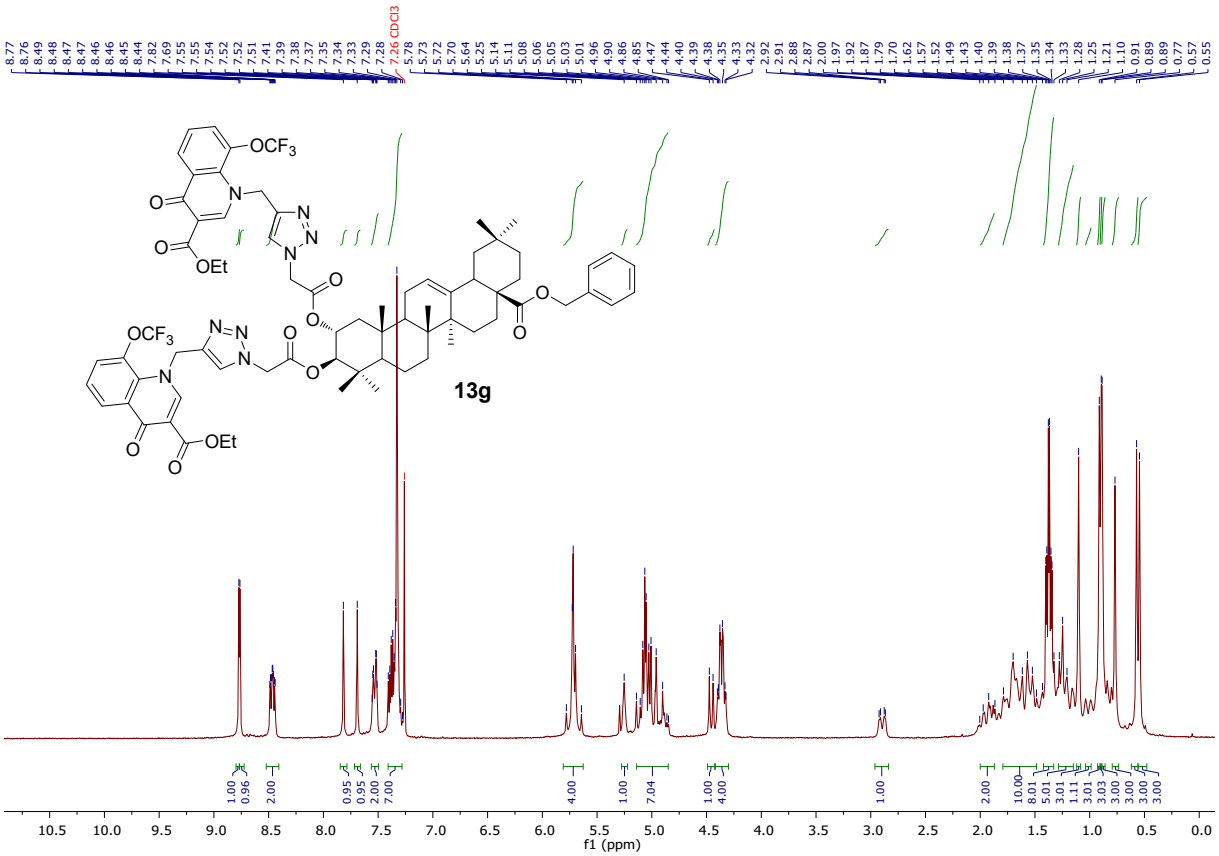
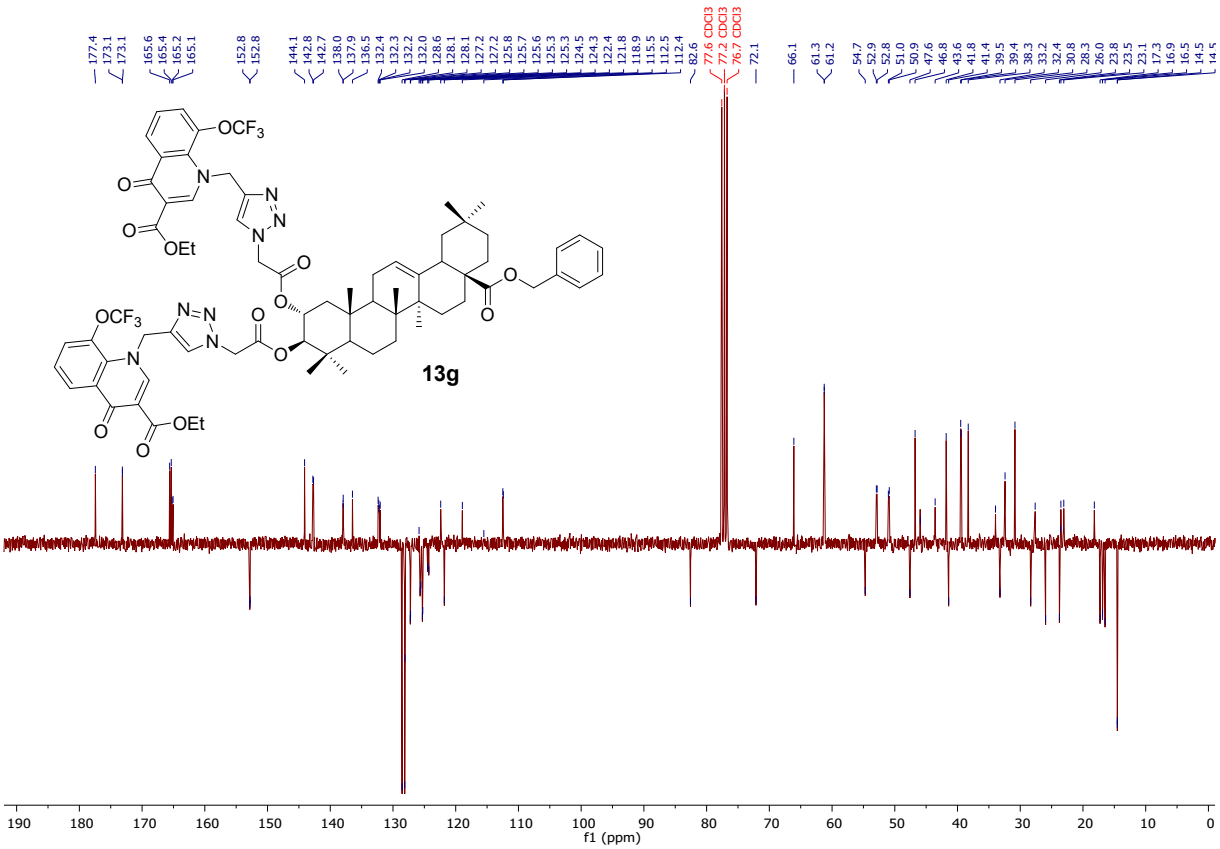


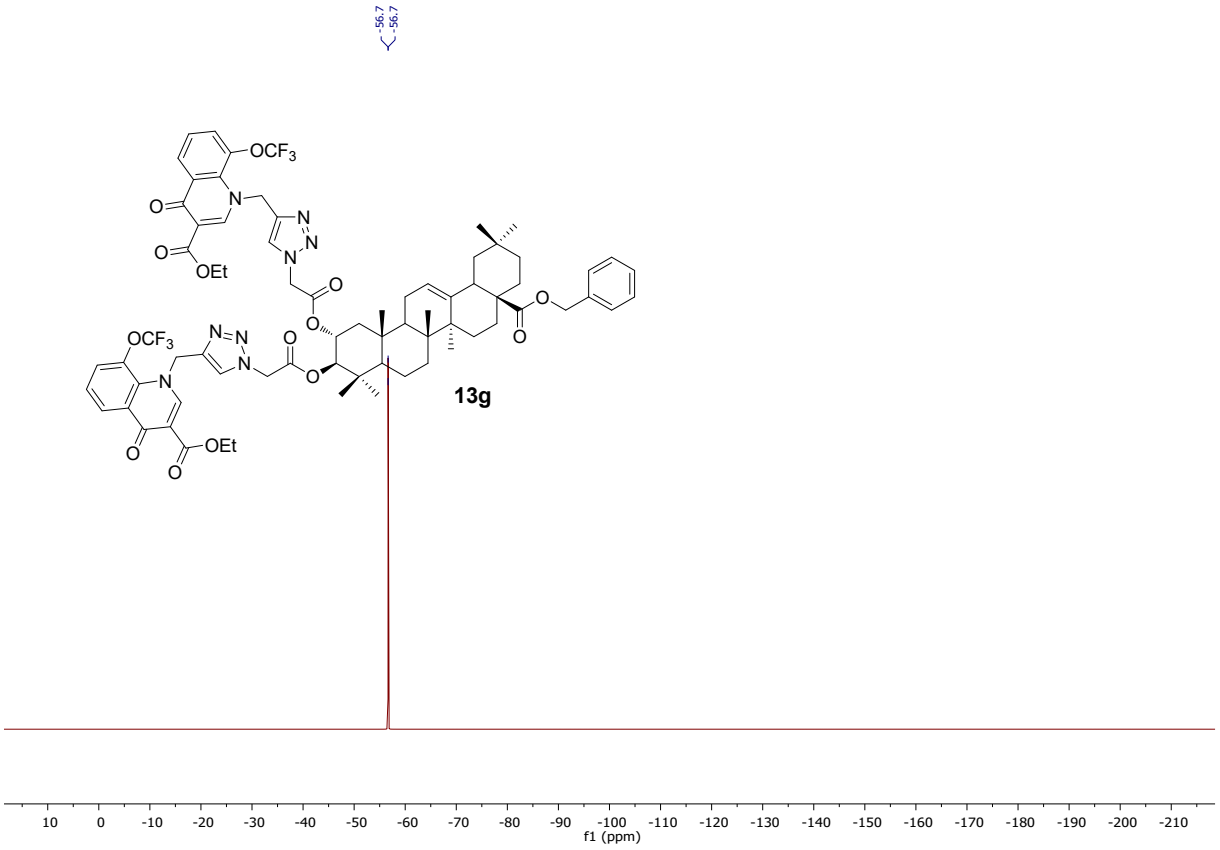
^{19}F NMR (282 MHz, $CDCl_3$)



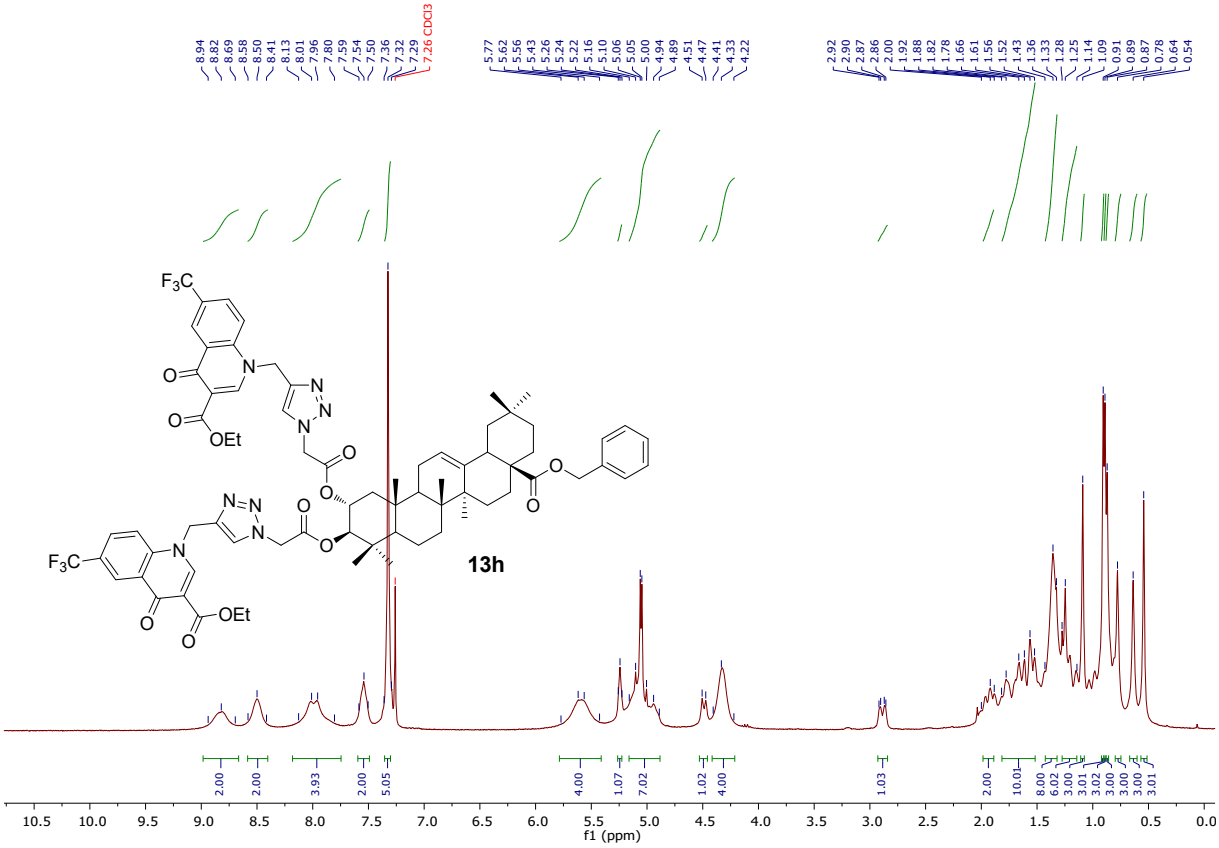
^{1}H NMR (300 MHz, $CDCl_3$)



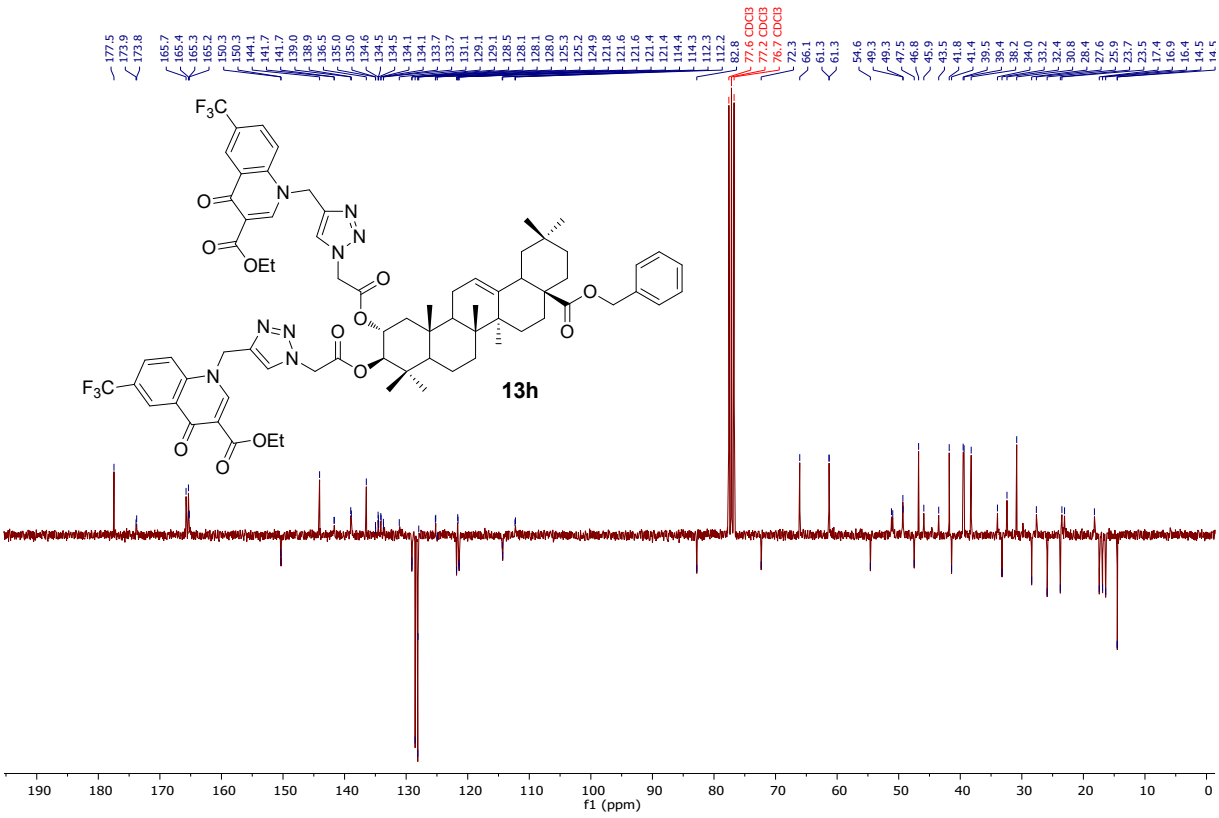
^{13}C NMR (75 MHz, $CDCl_3$)



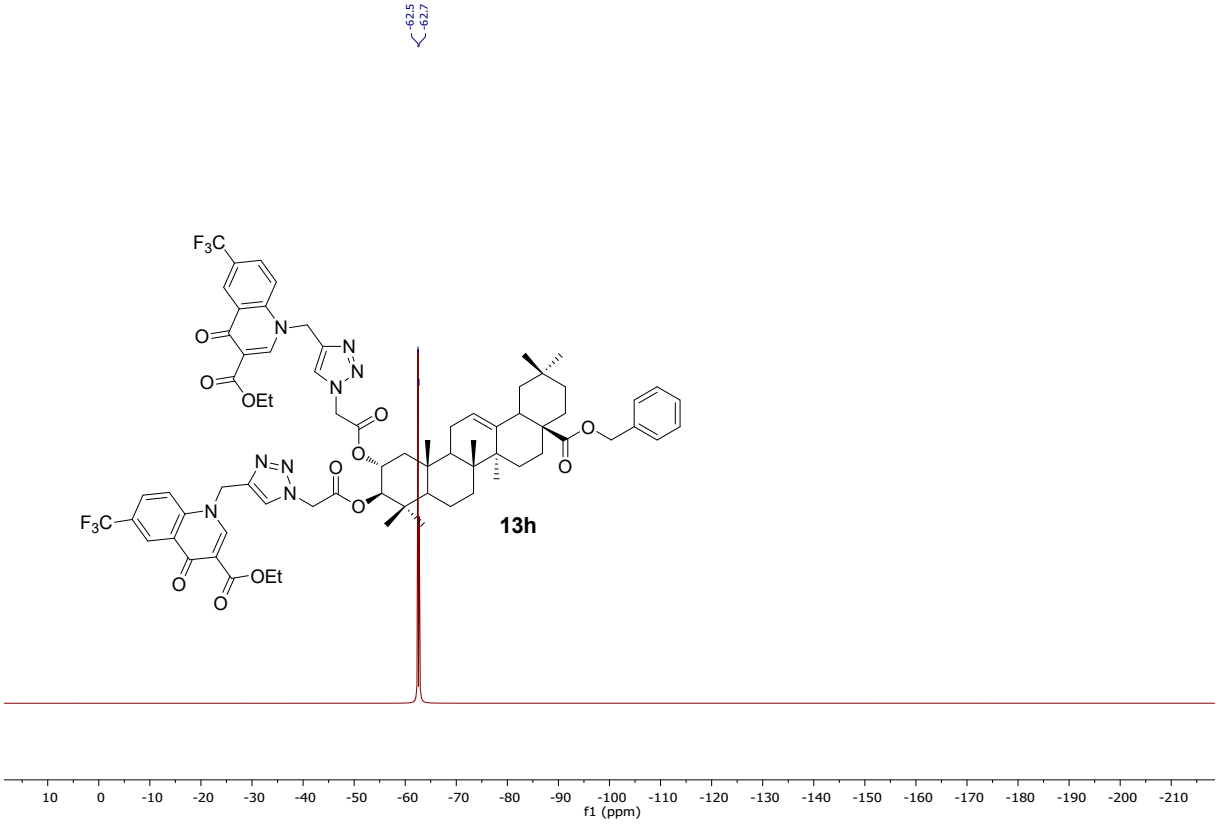
^{19}F NMR (282 MHz, $CDCl_3$)



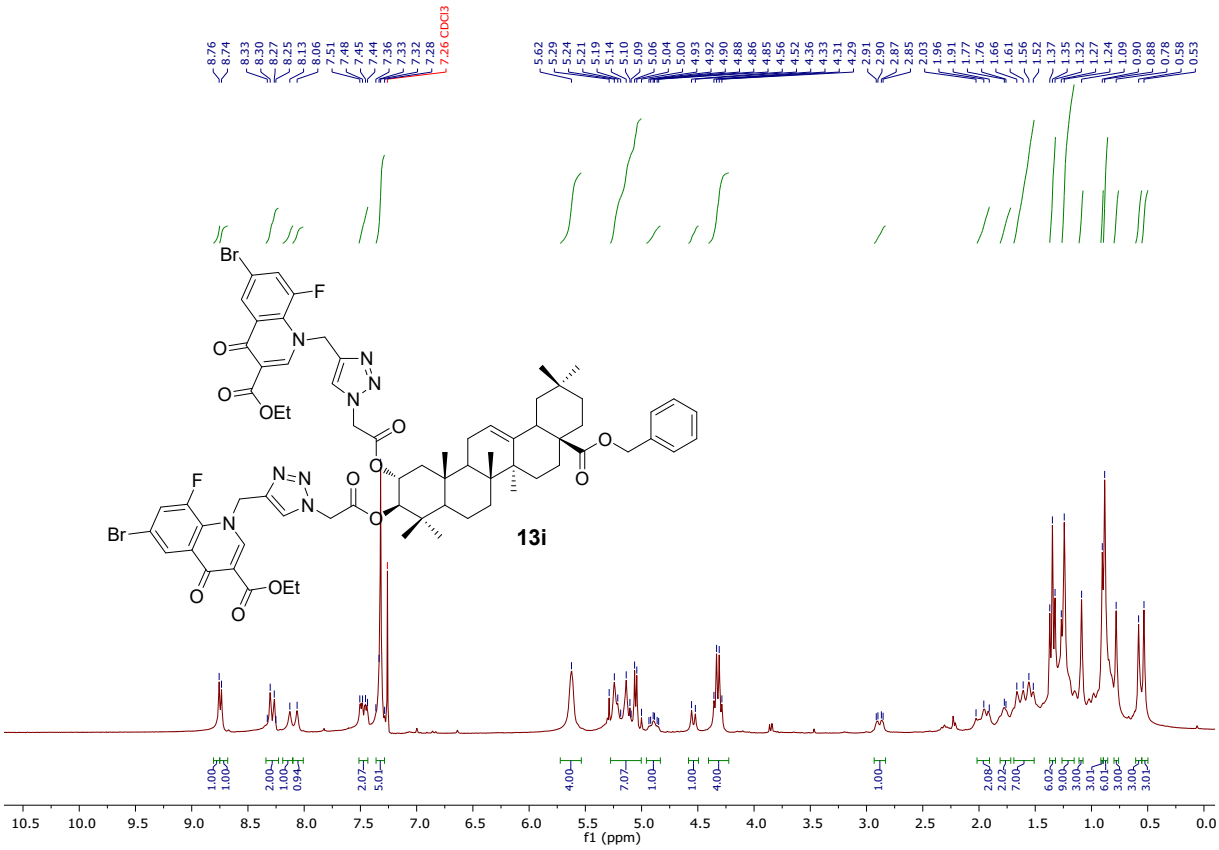
^{1}H NMR (300 MHz, $CDCl_3$)



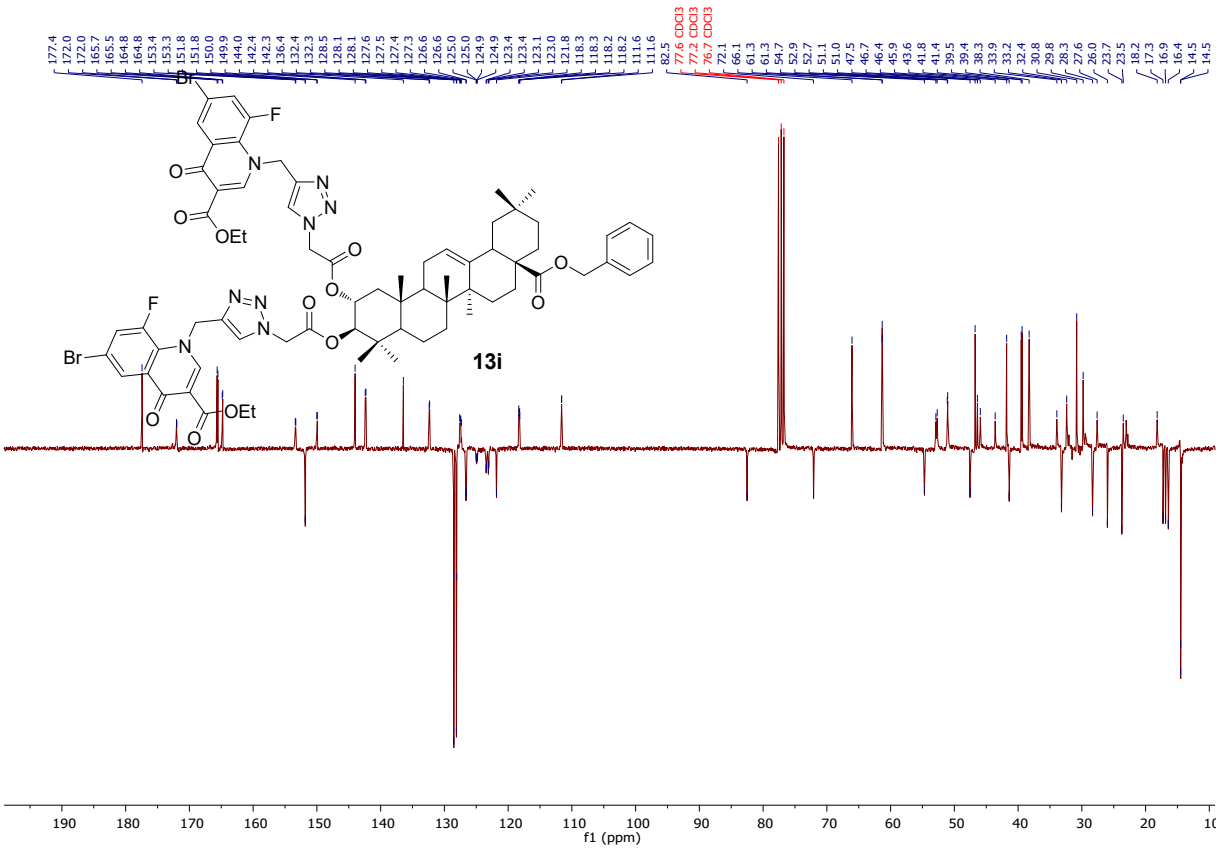
^{13}C NMR (75 MHz, $CDCl_3$)



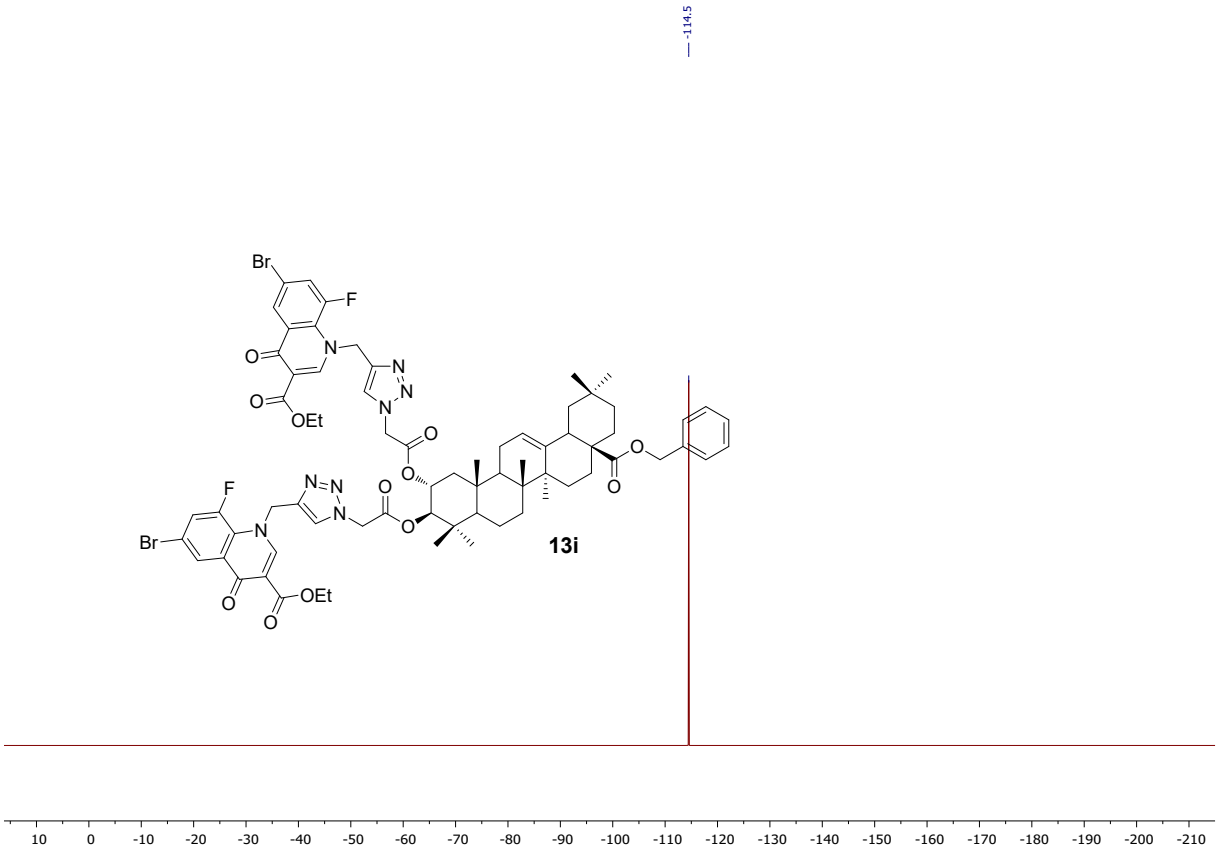
^{19}F NMR (282 MHz, $CDCl_3$)



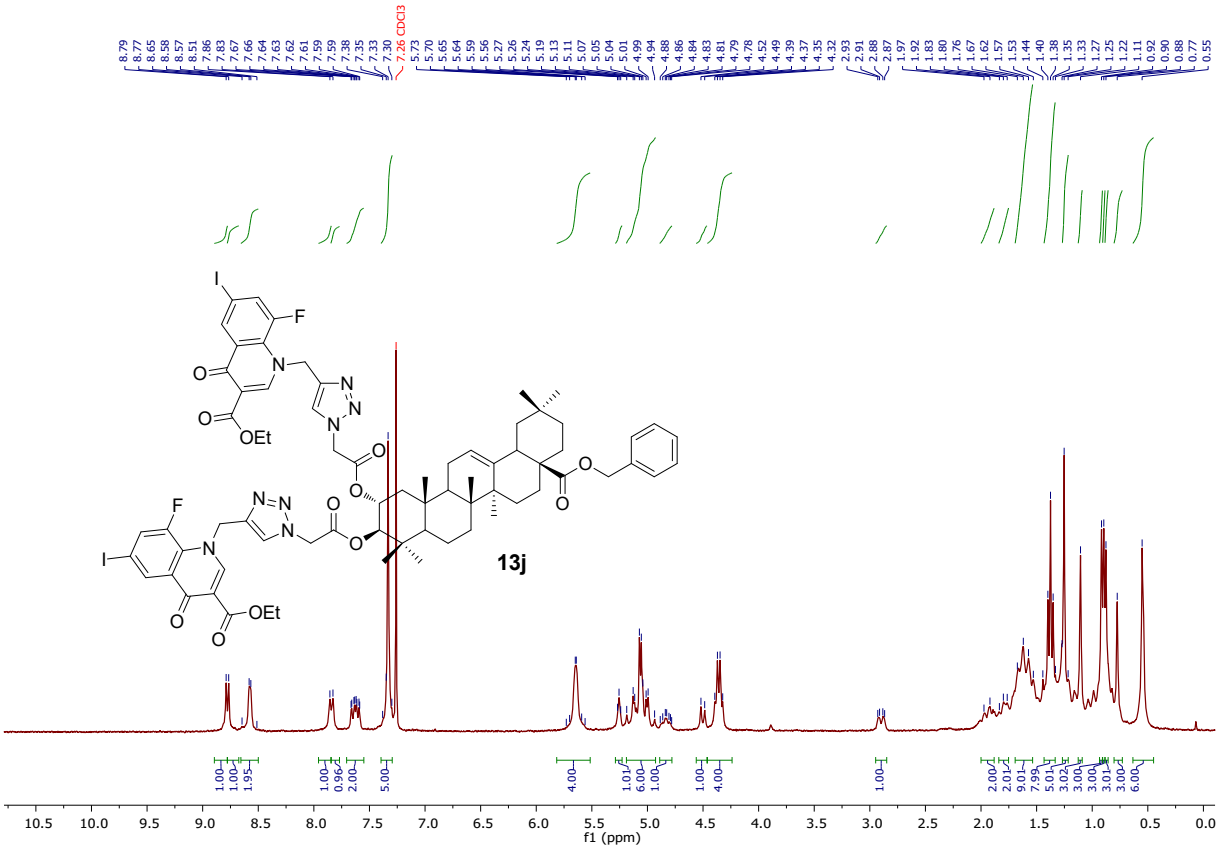
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



^{19}F NMR (282 MHz, $CDCl_3$)



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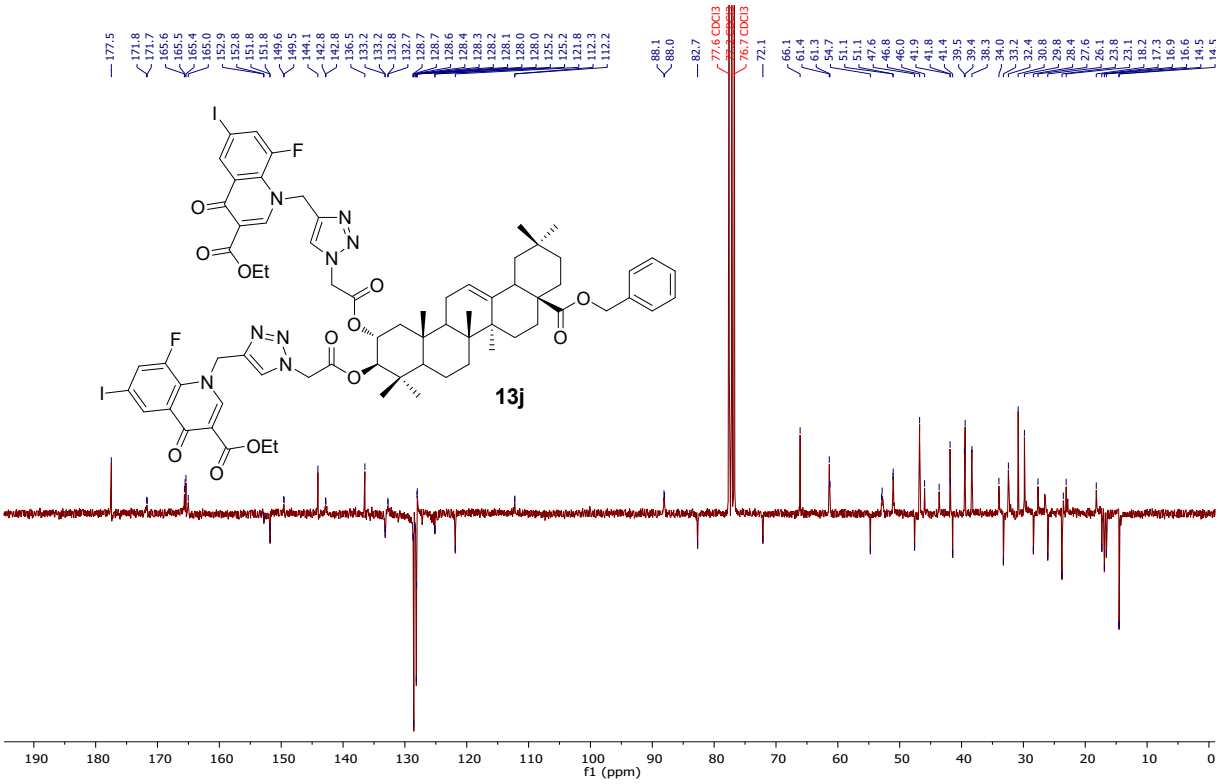
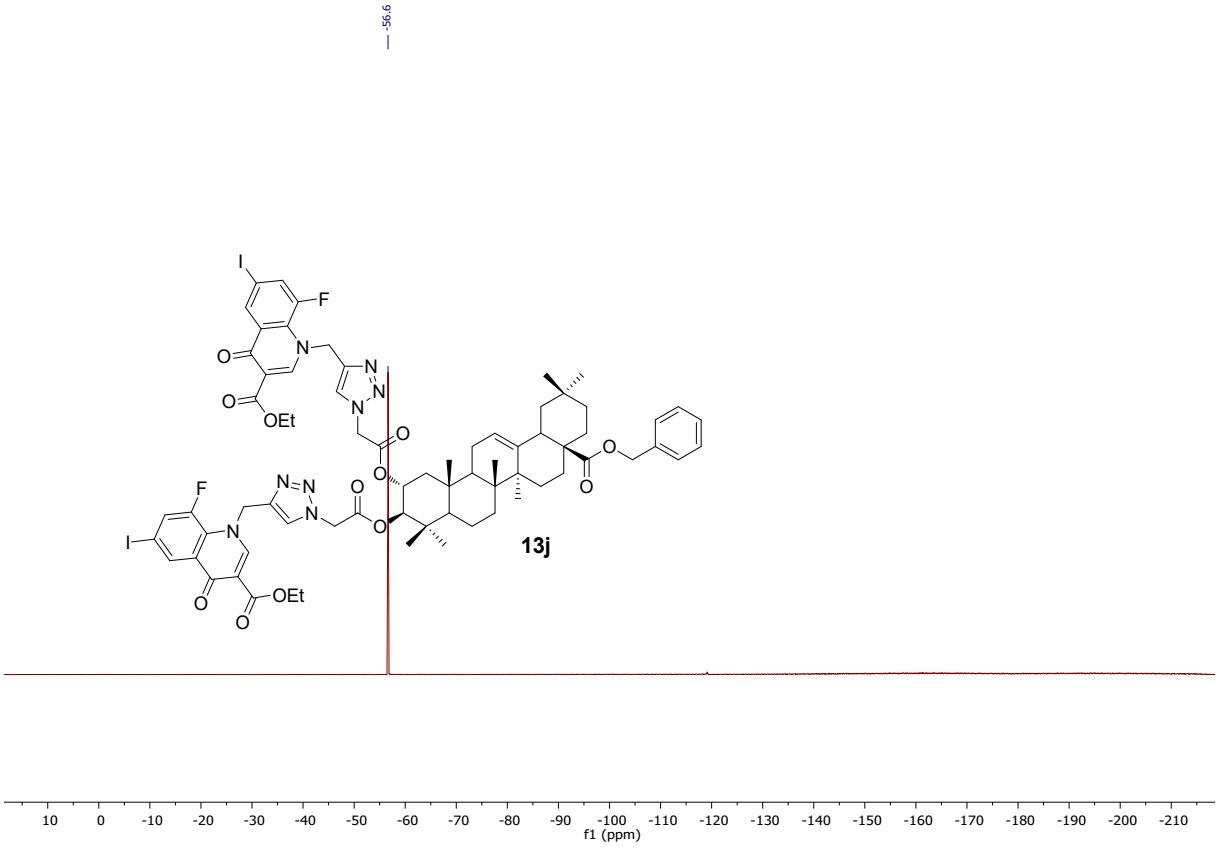


^{13}C NMR (75 MHz, $CDCl_3$)



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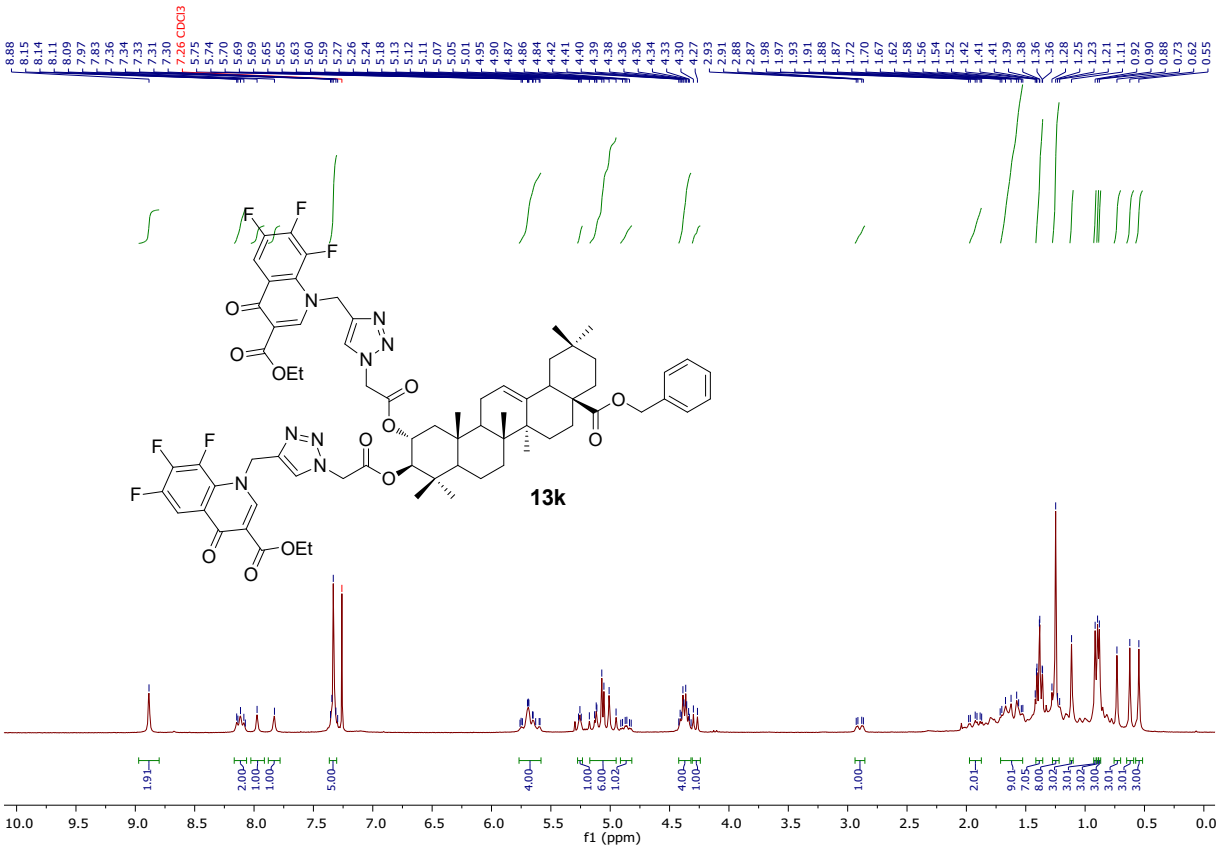

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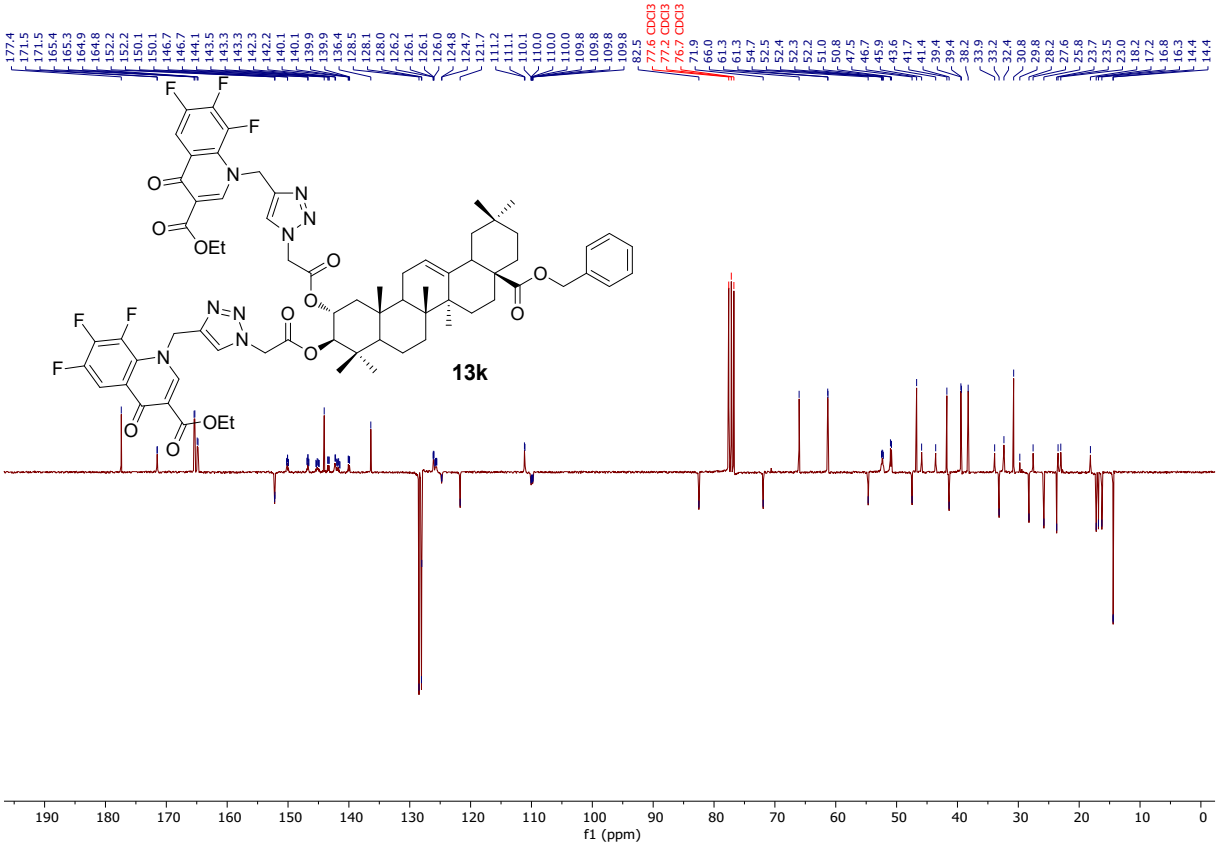

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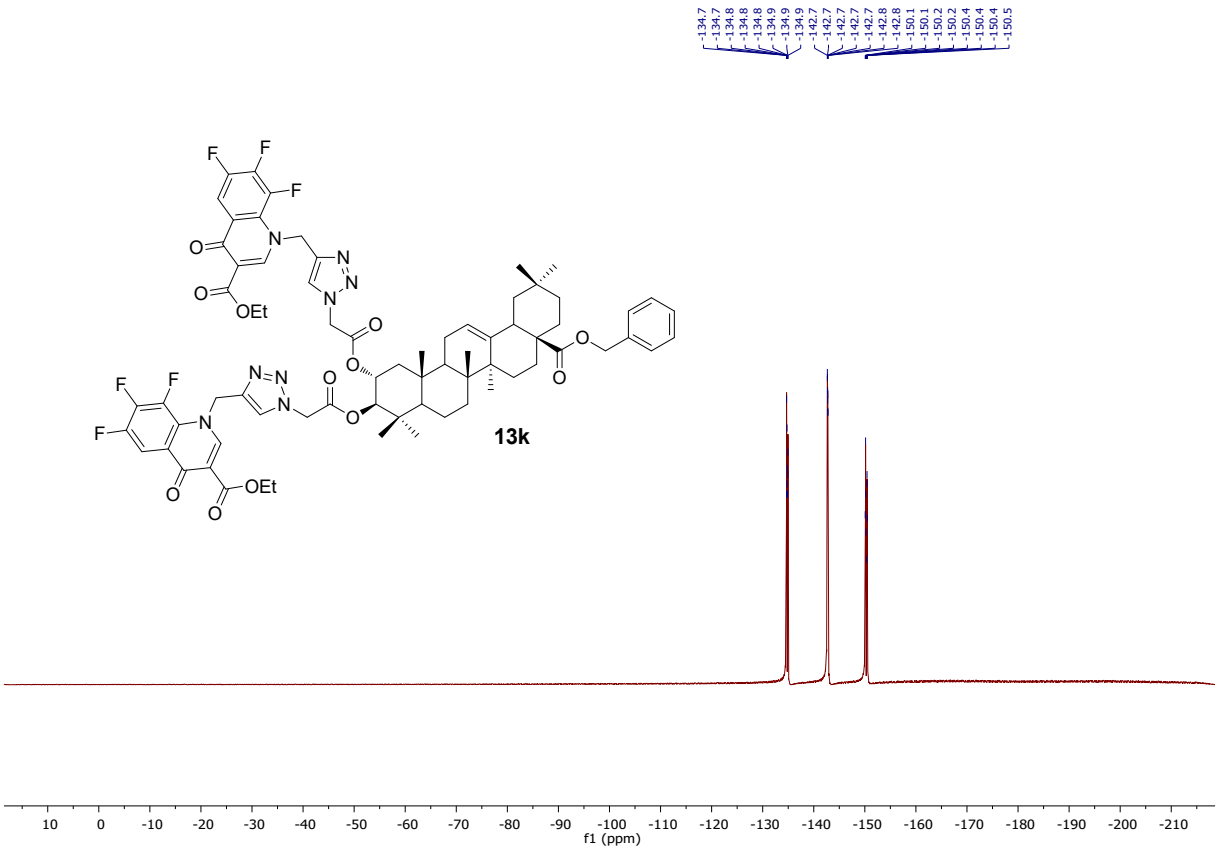

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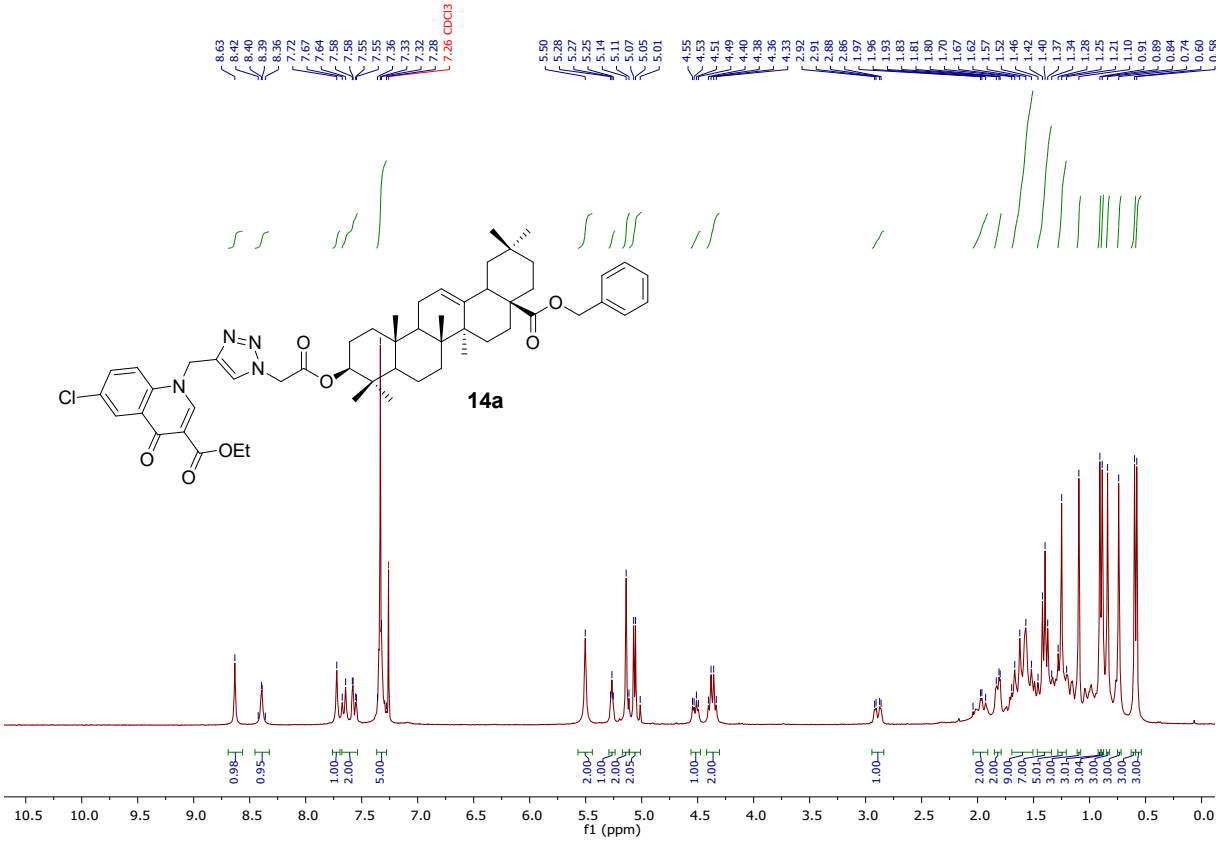

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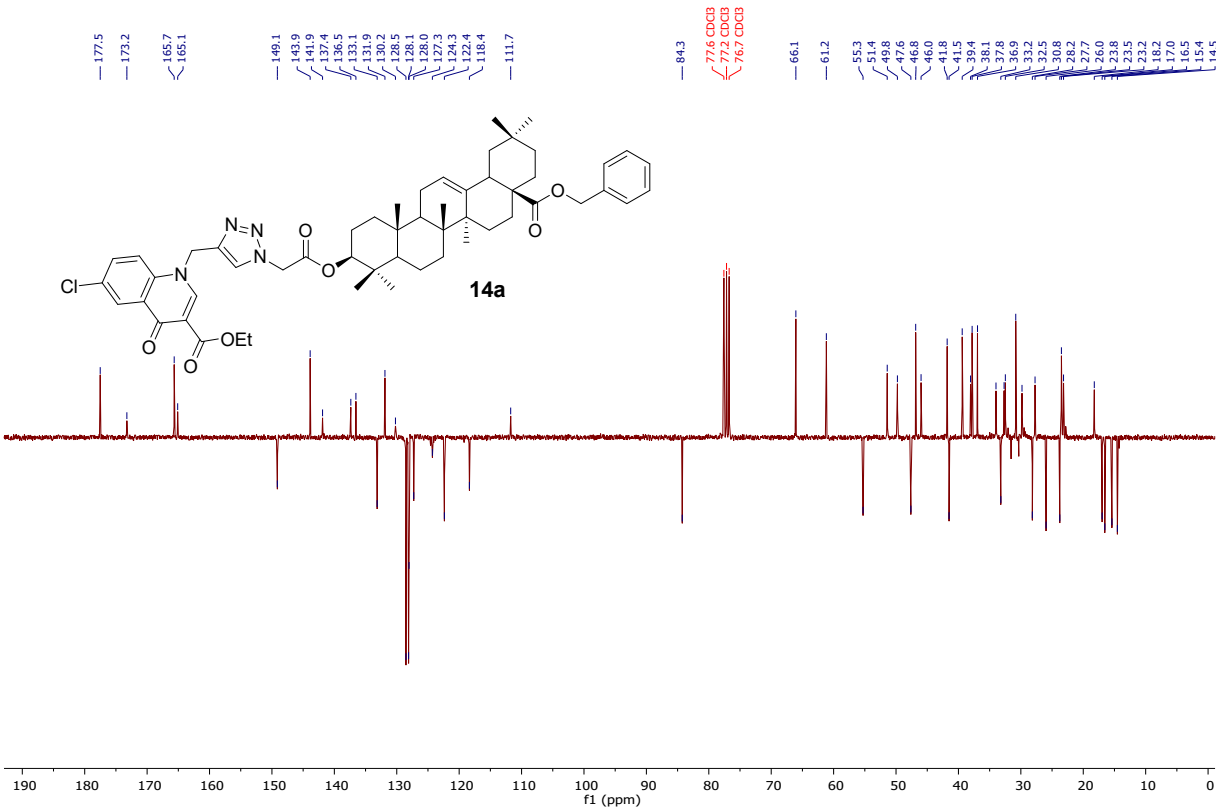

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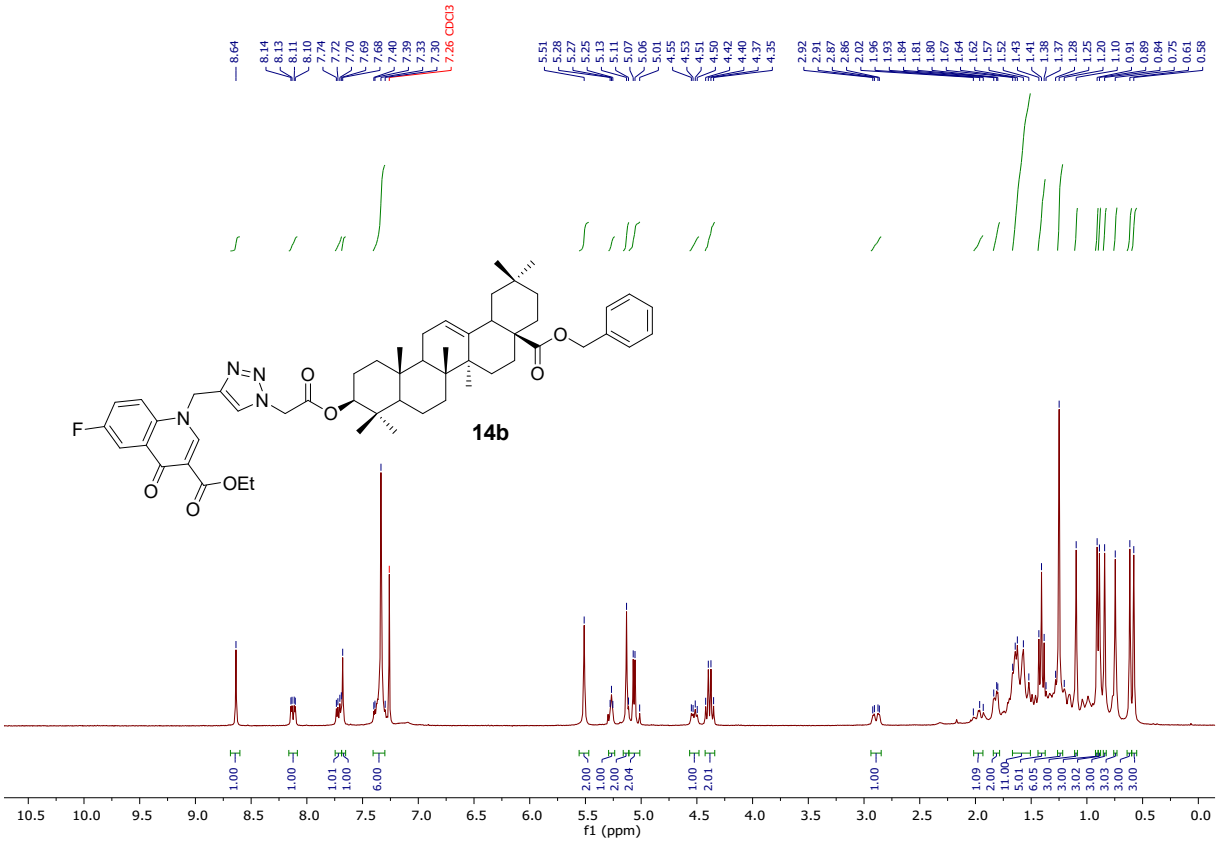

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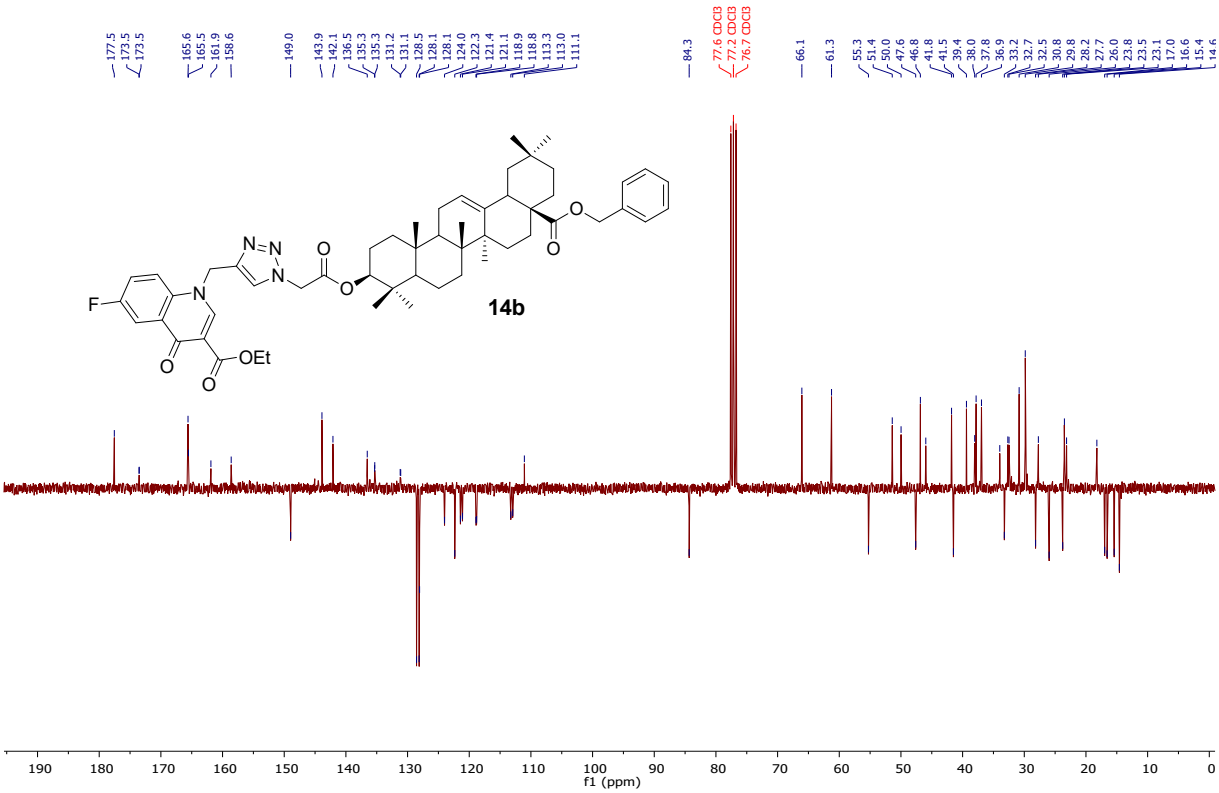
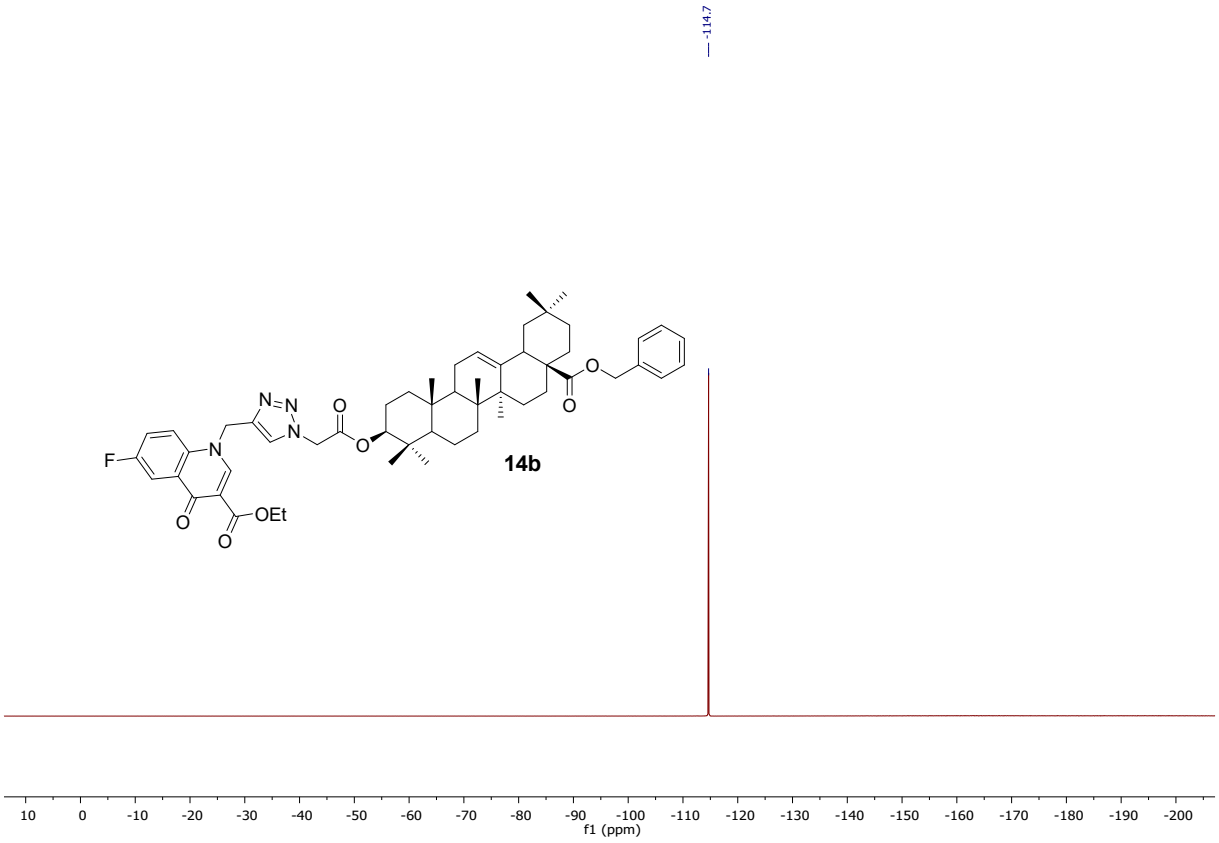
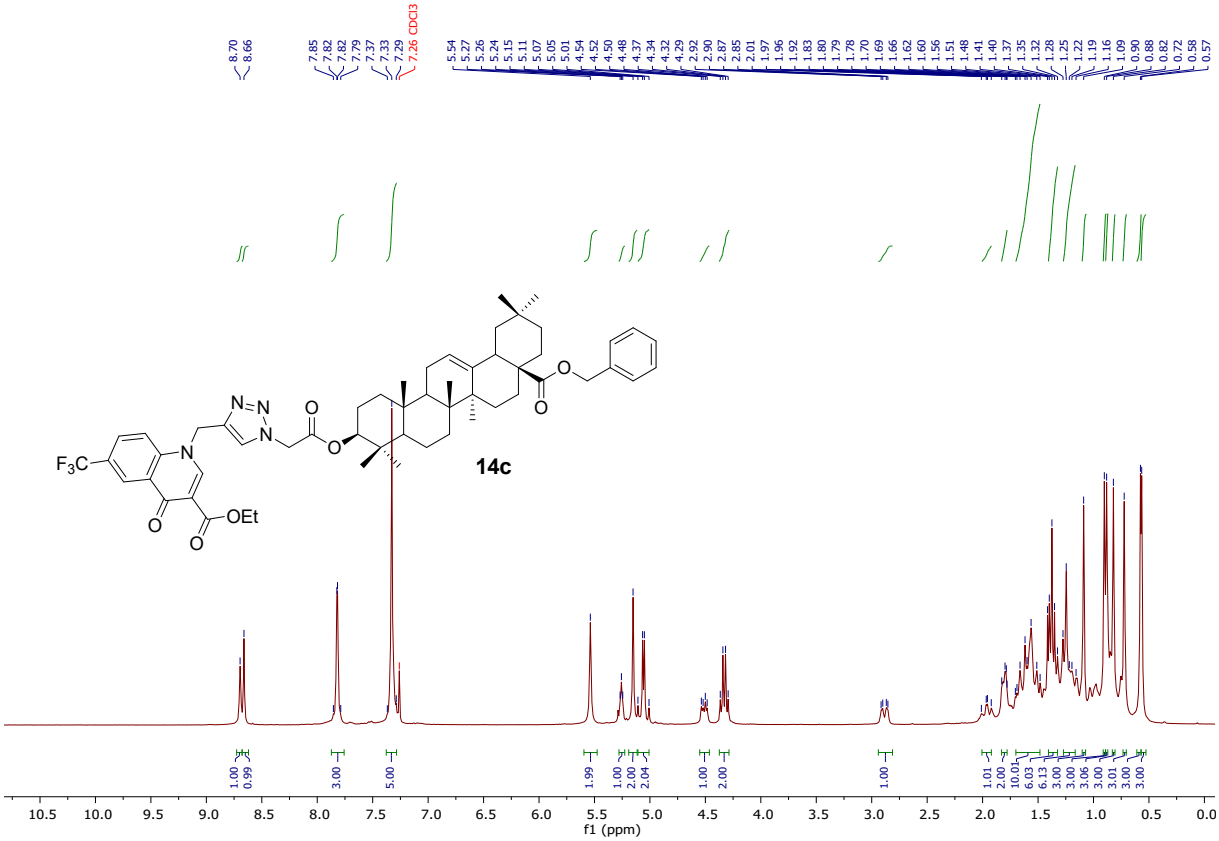


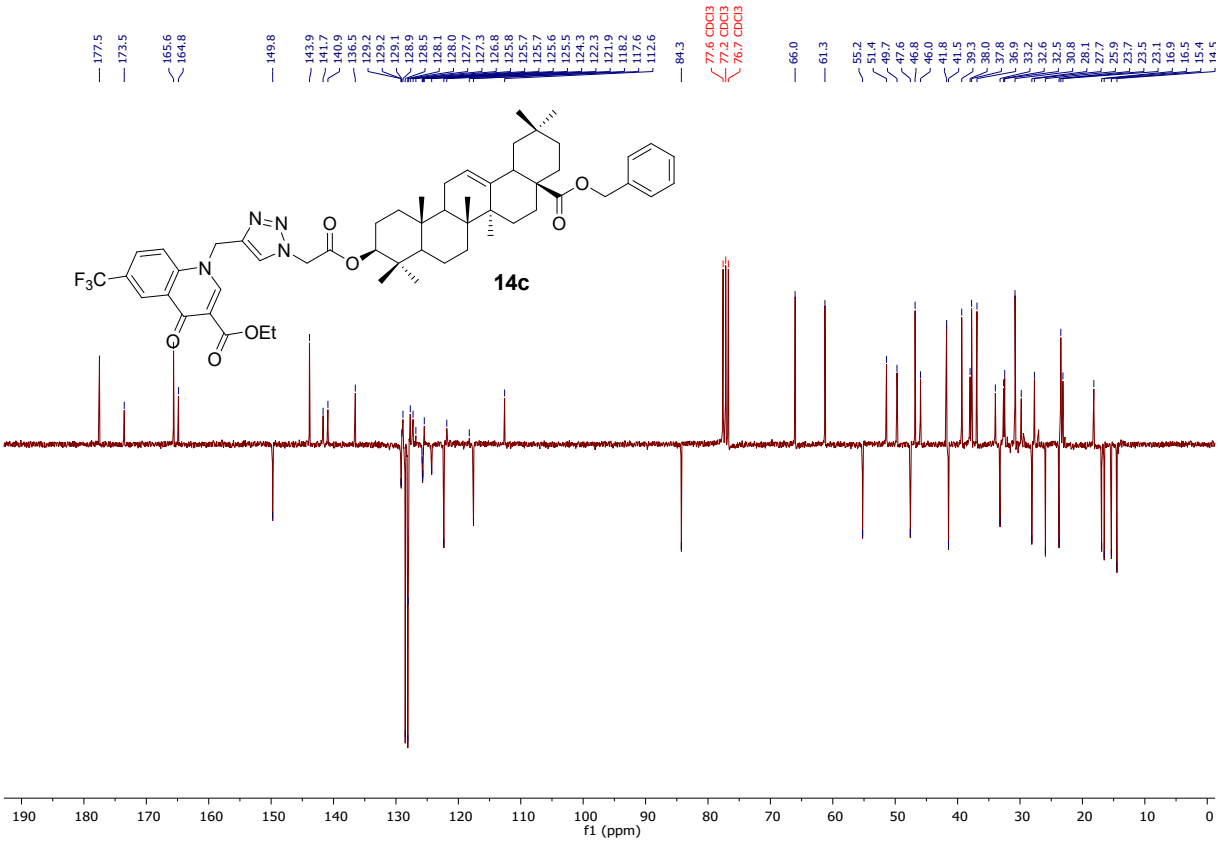
^{13}C NMR (75 MHz, $CDCl_3$)



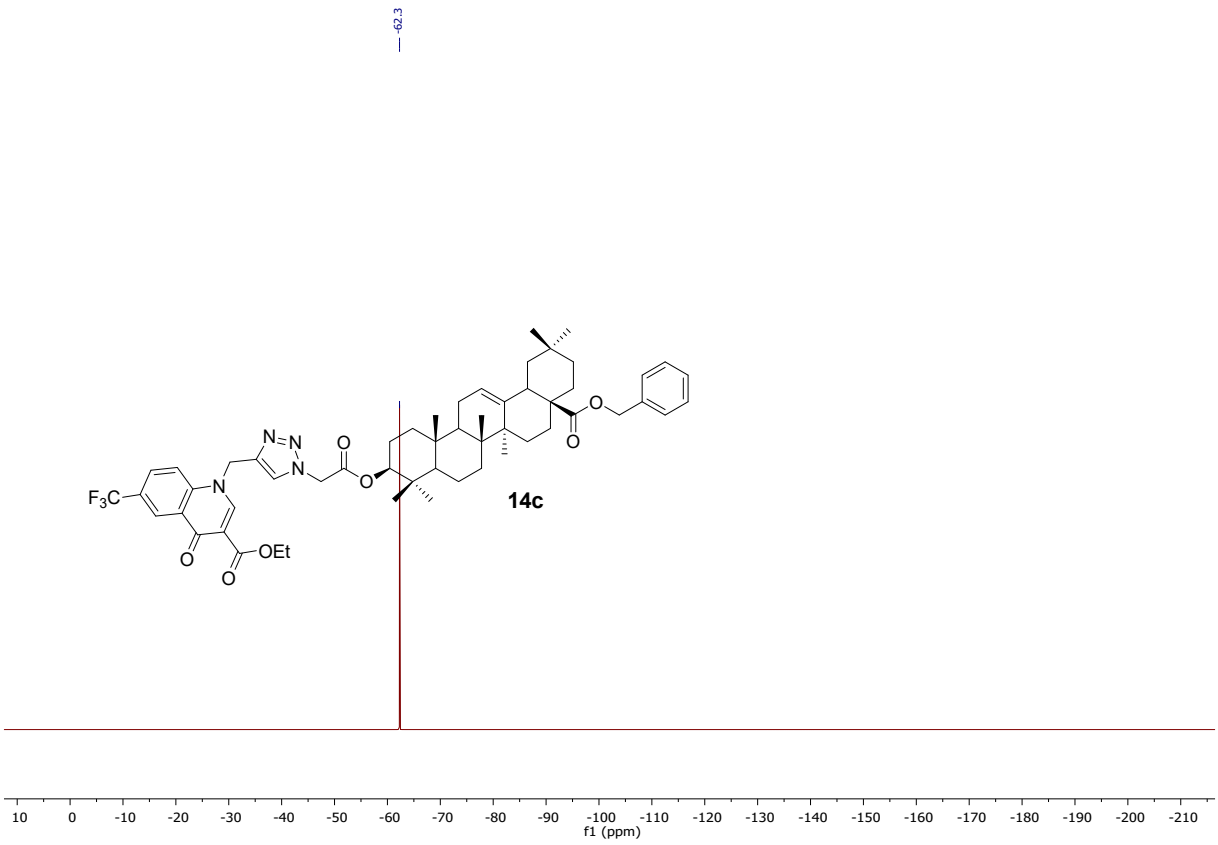
^{19}F NMR (282 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)



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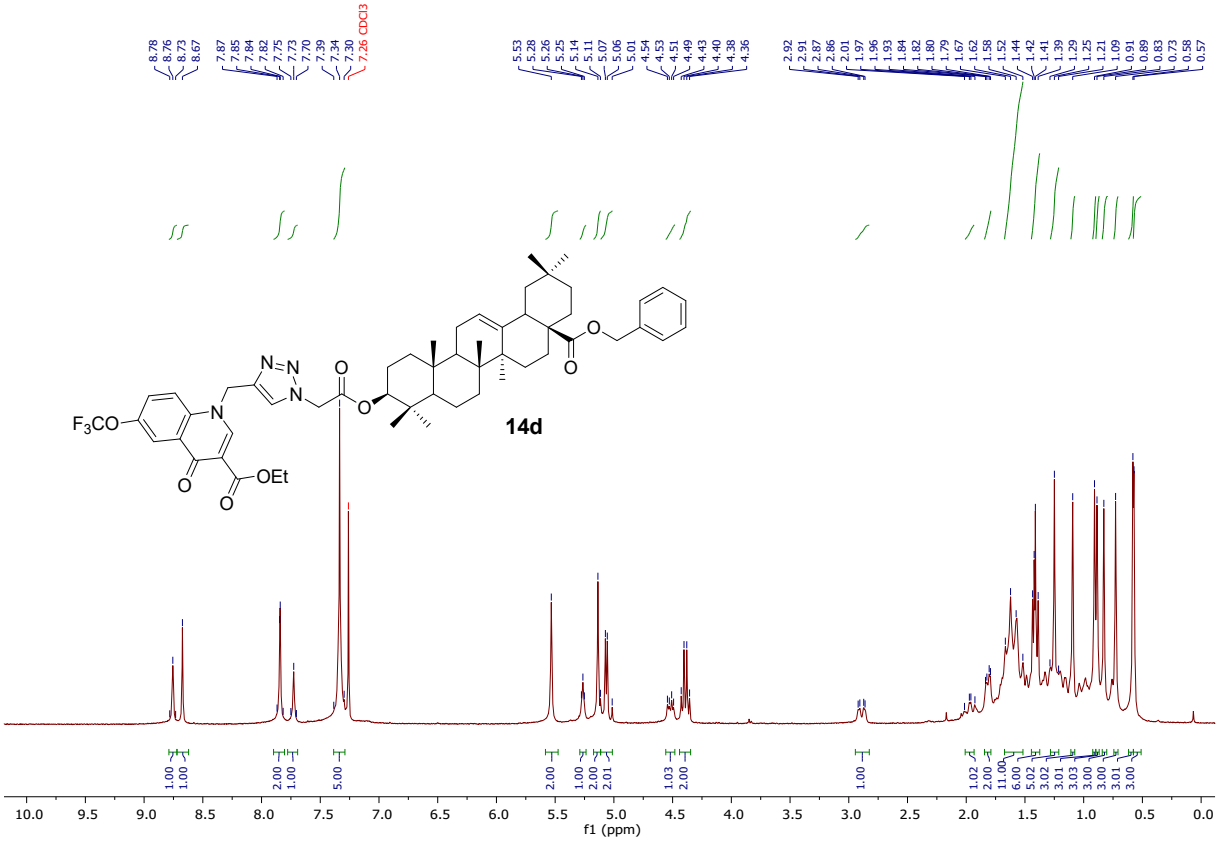

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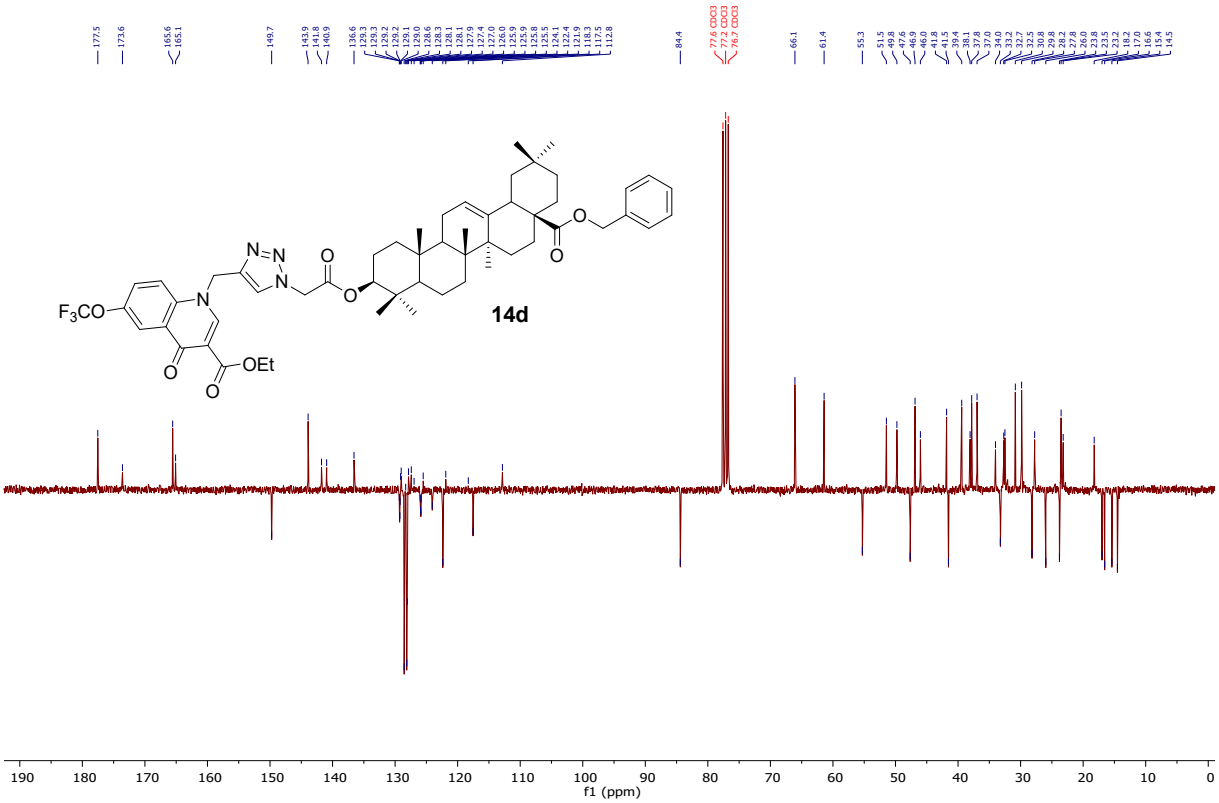

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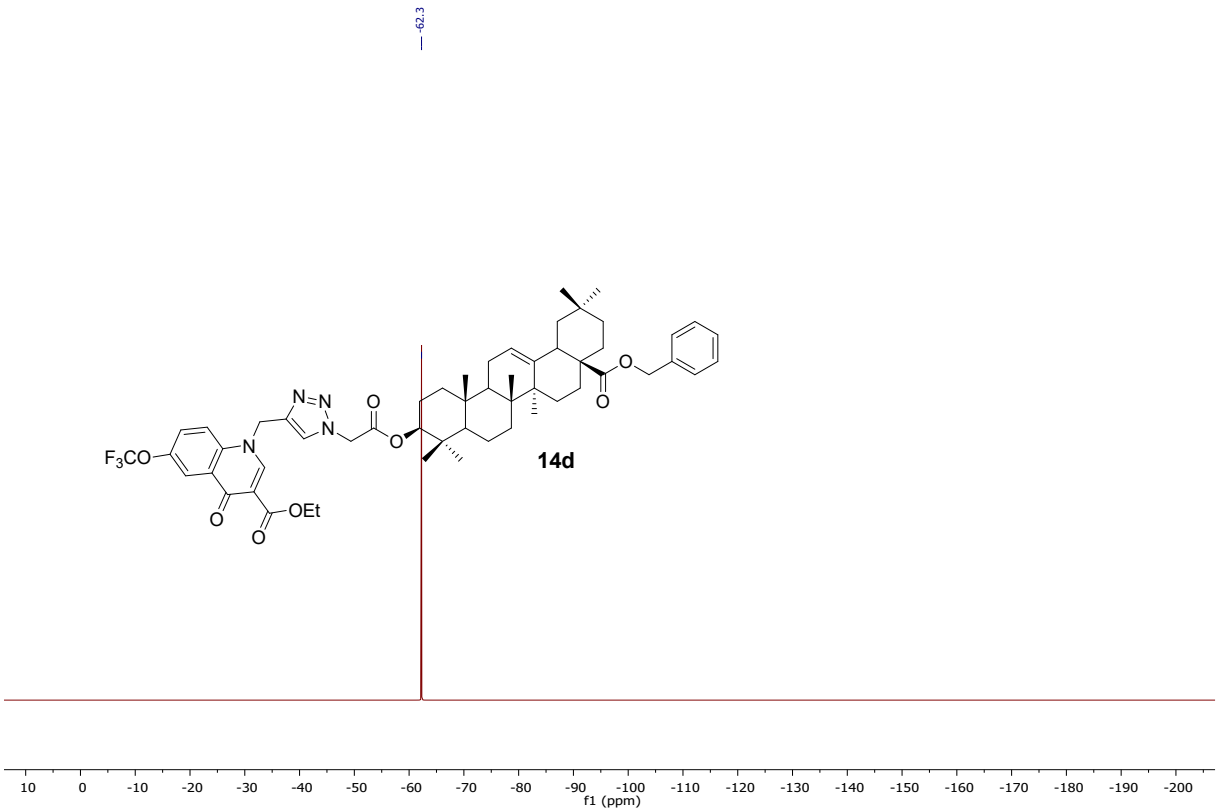

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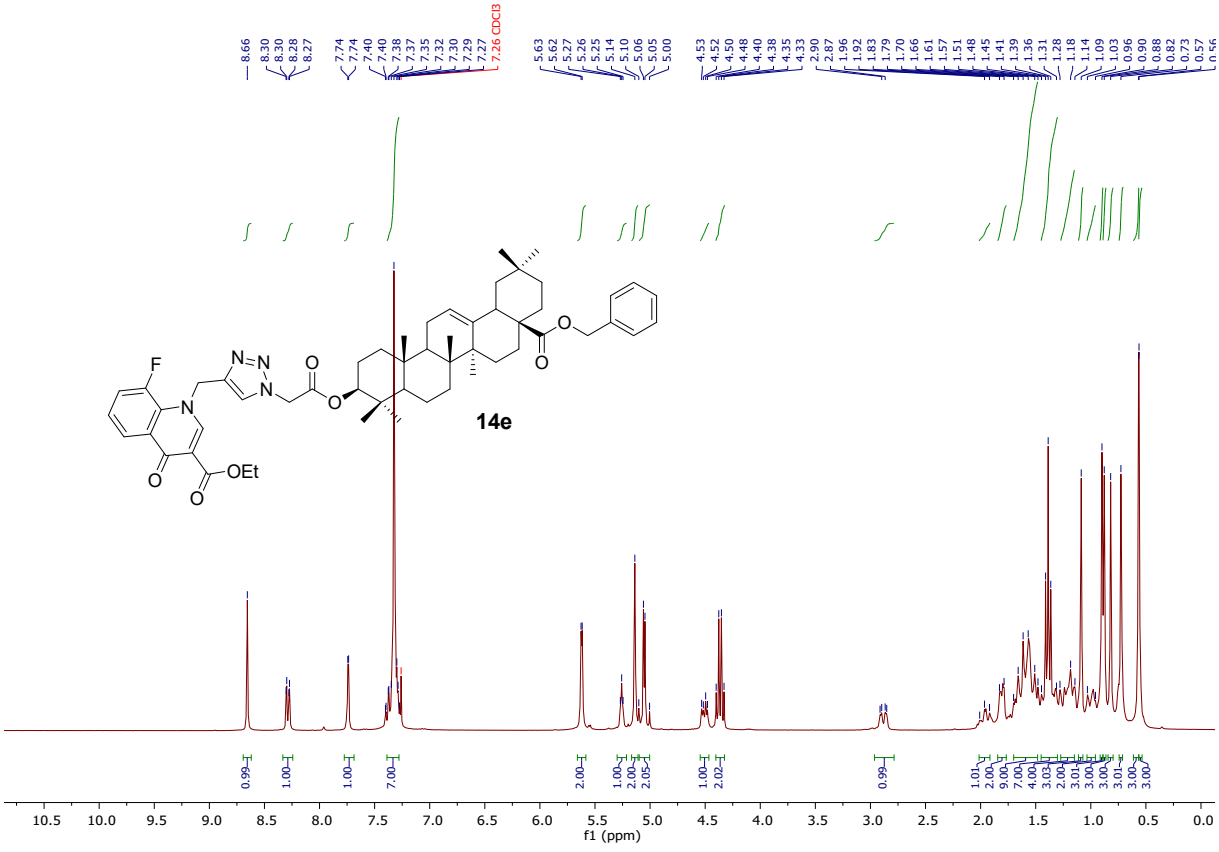

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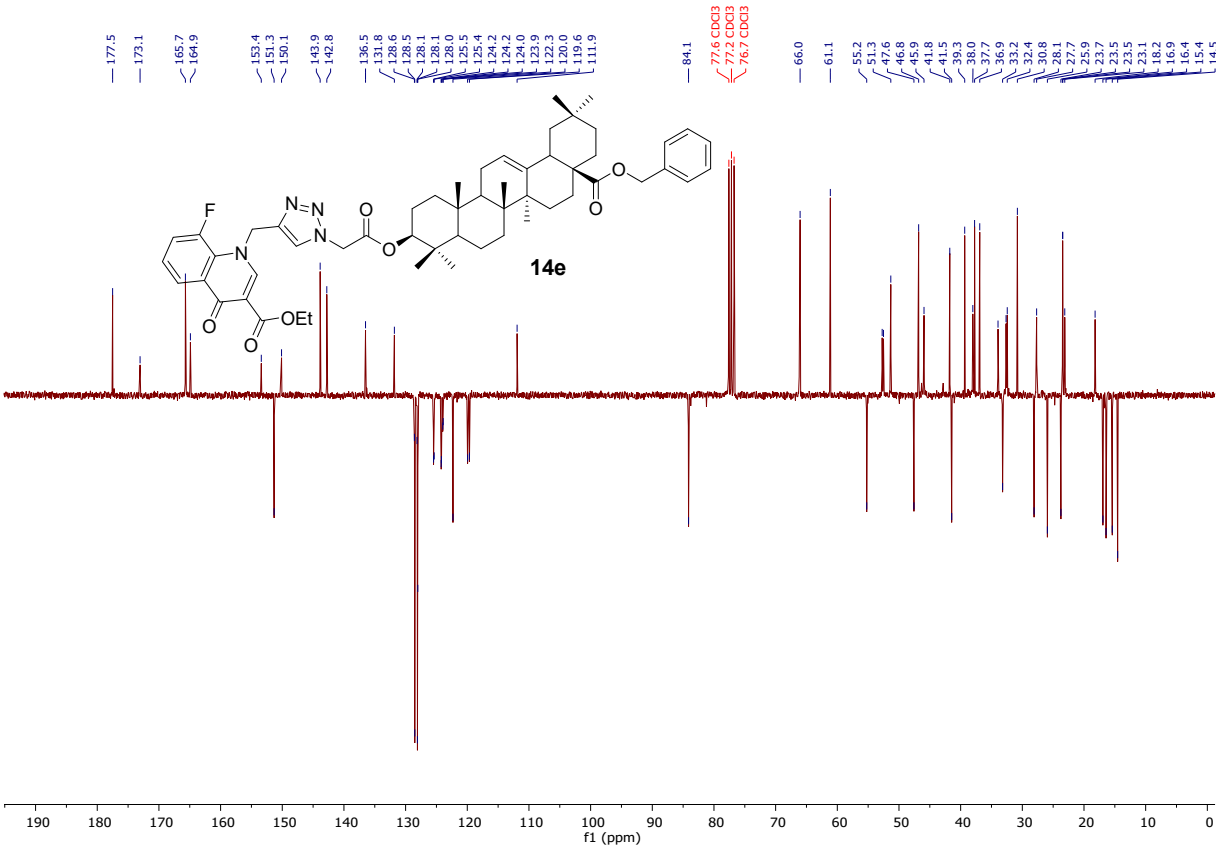

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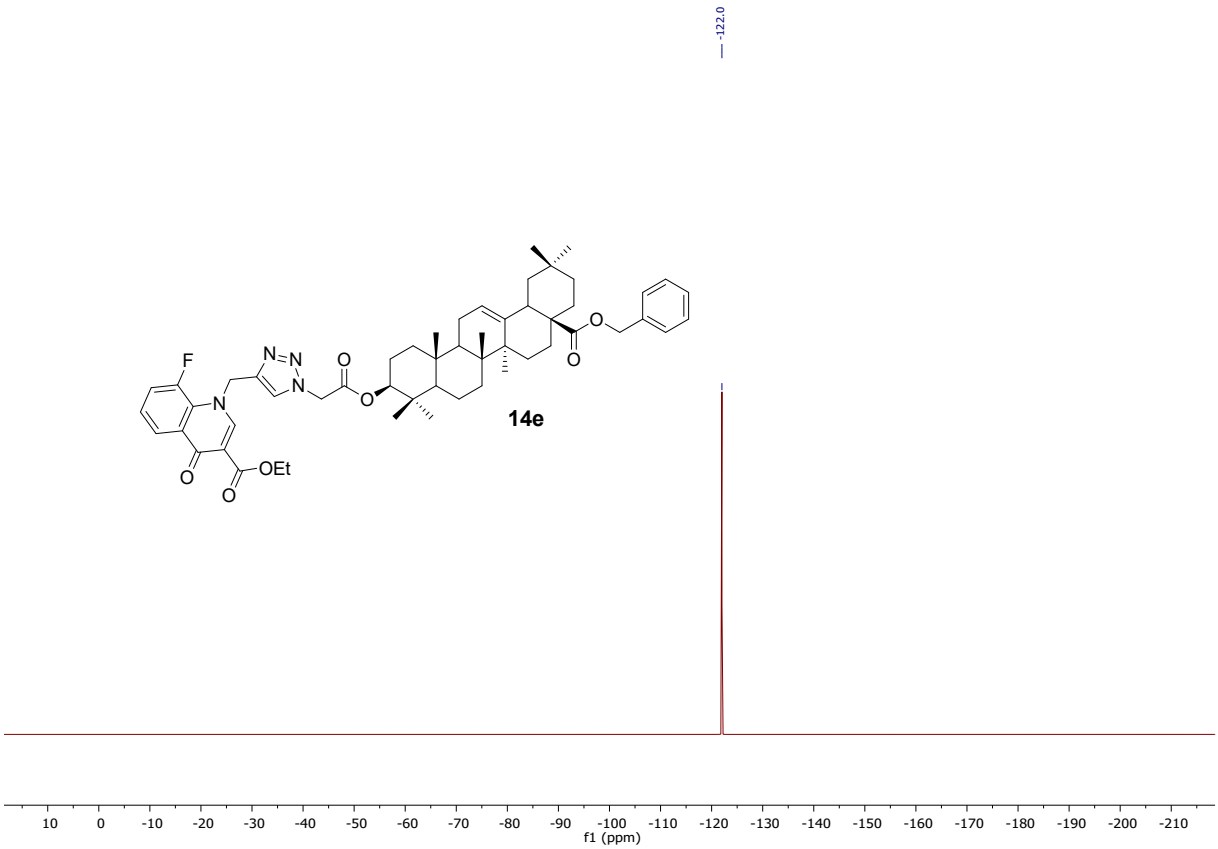

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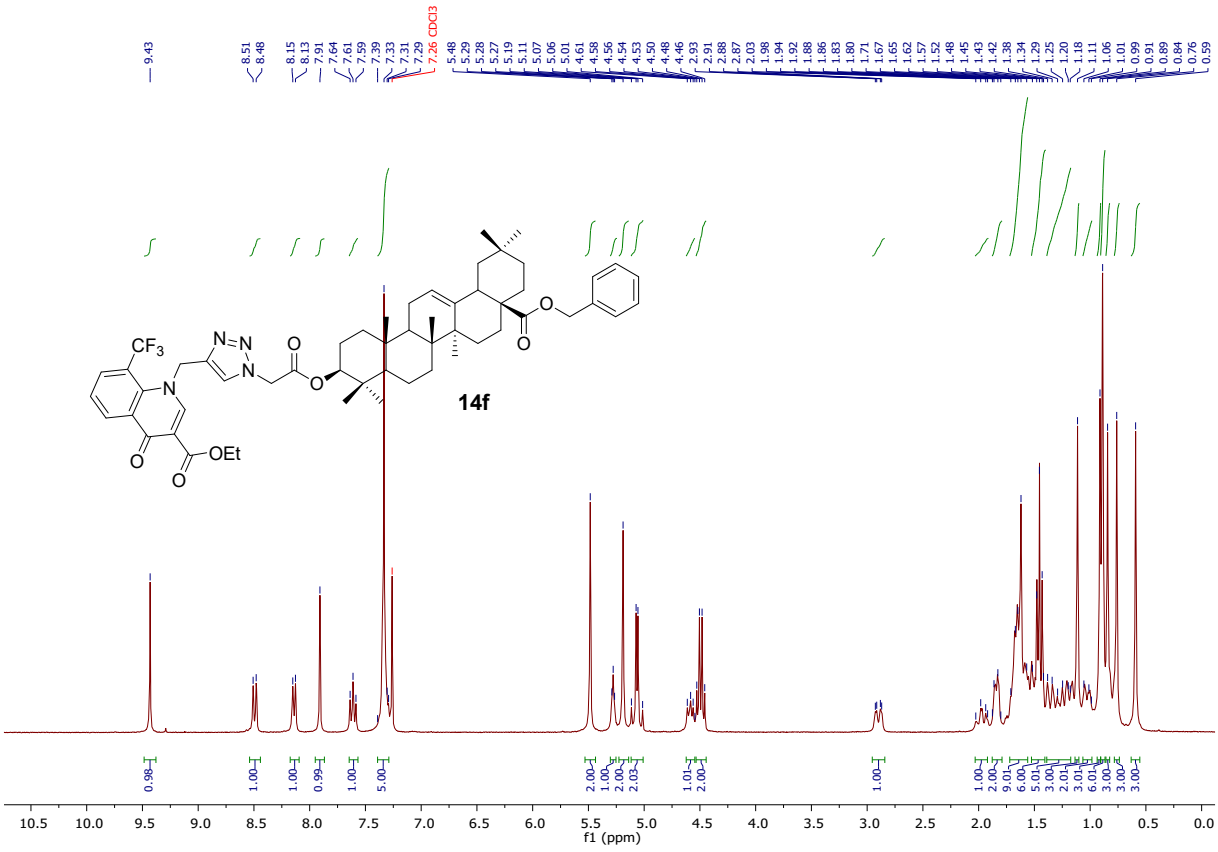

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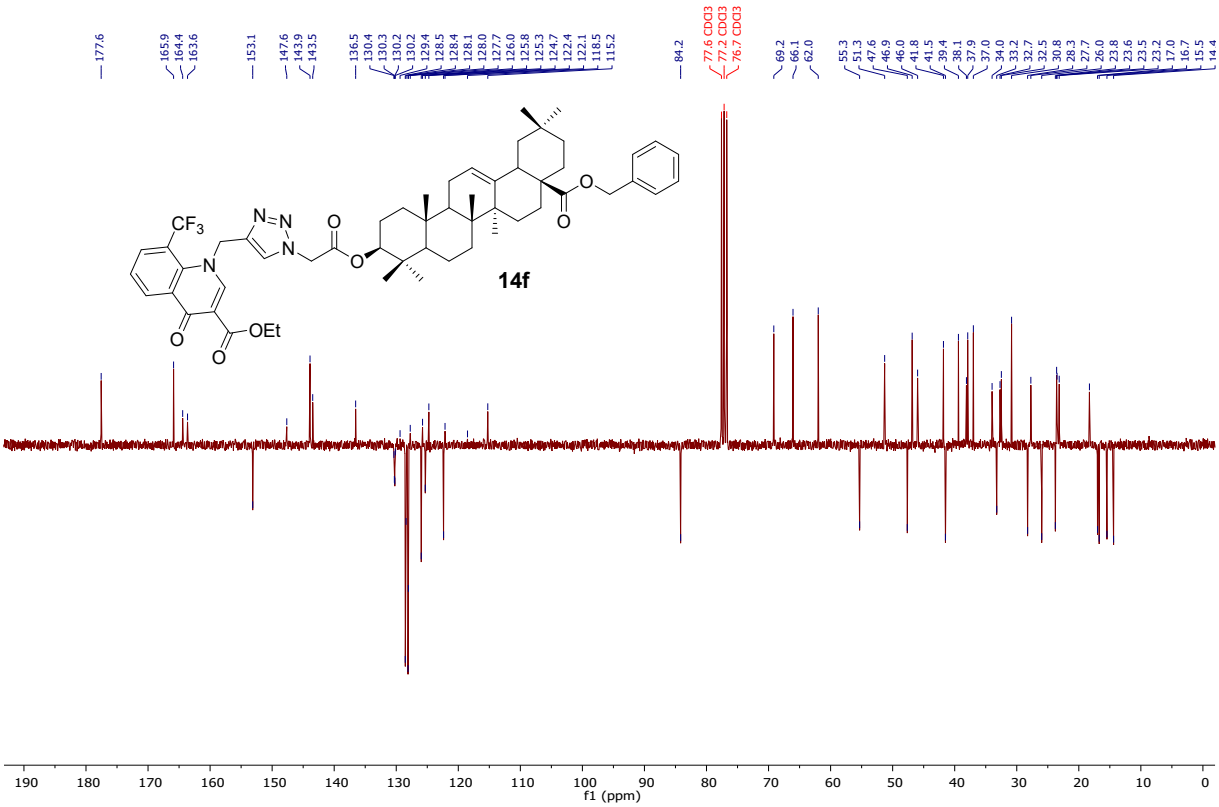

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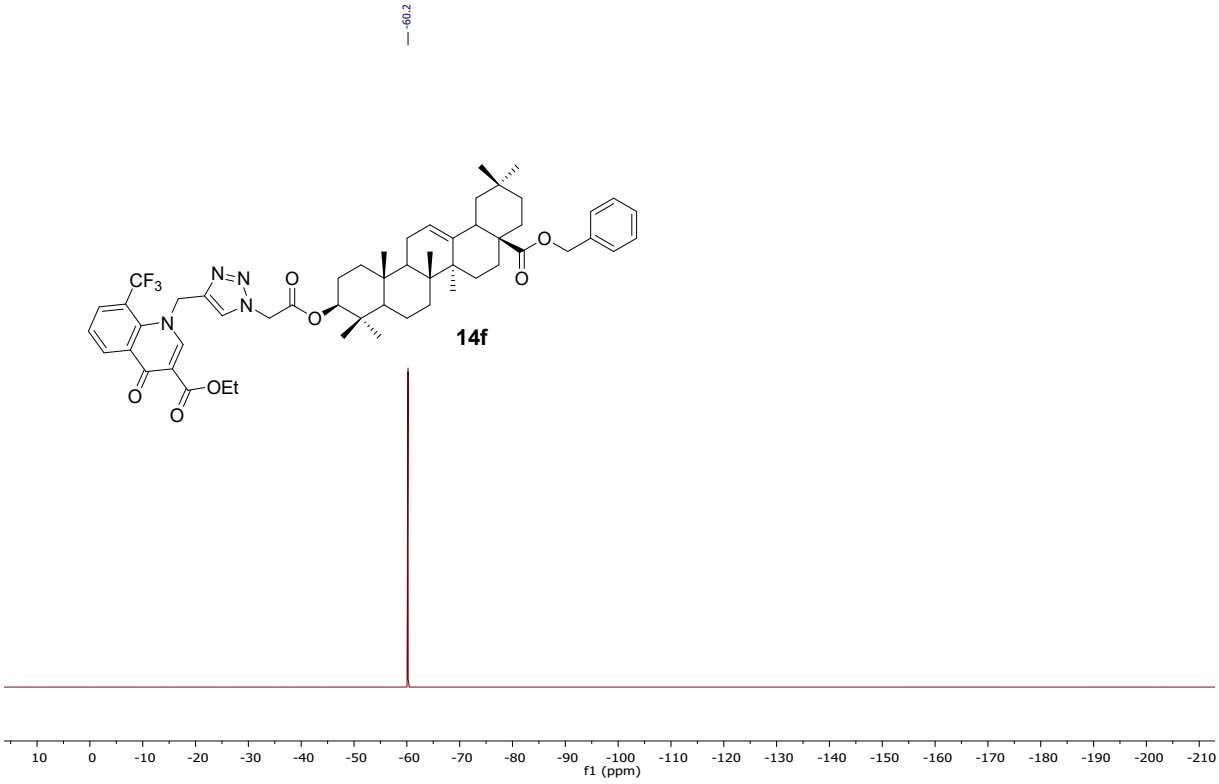

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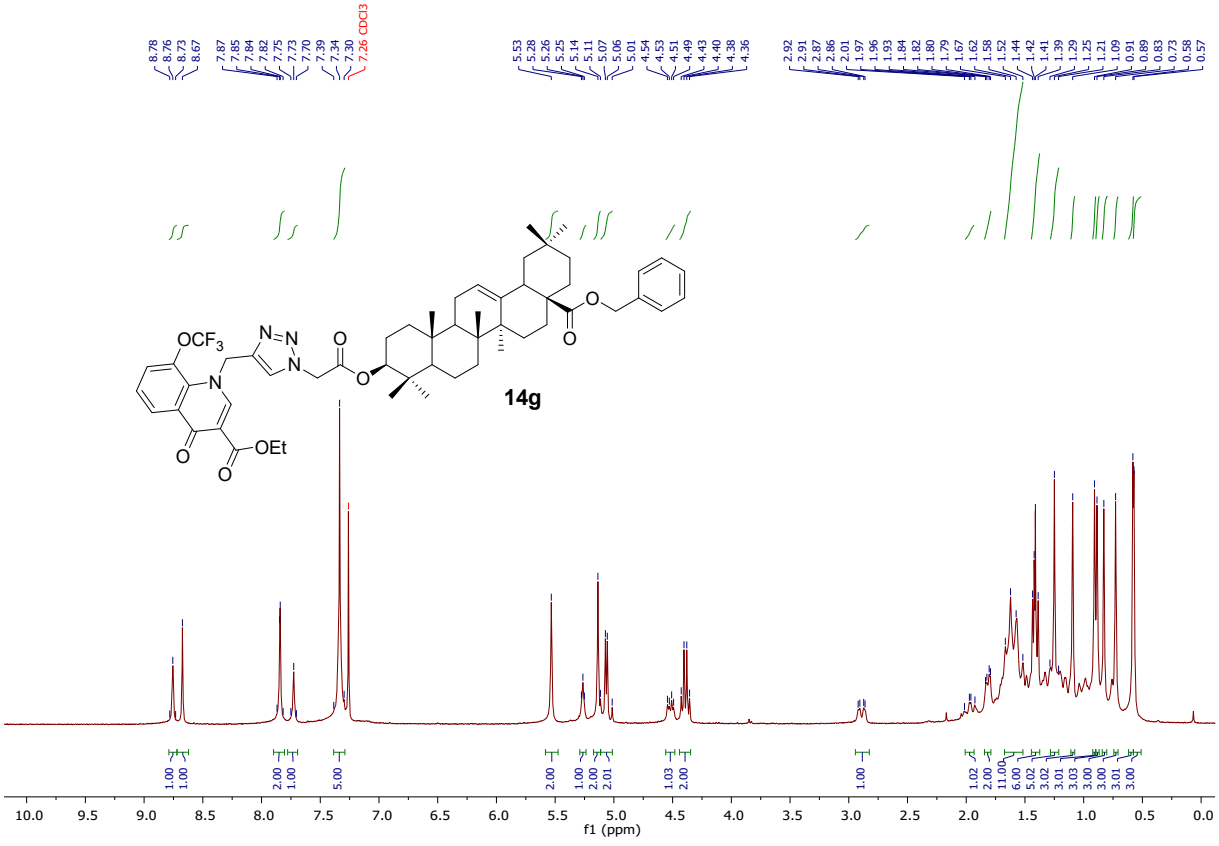

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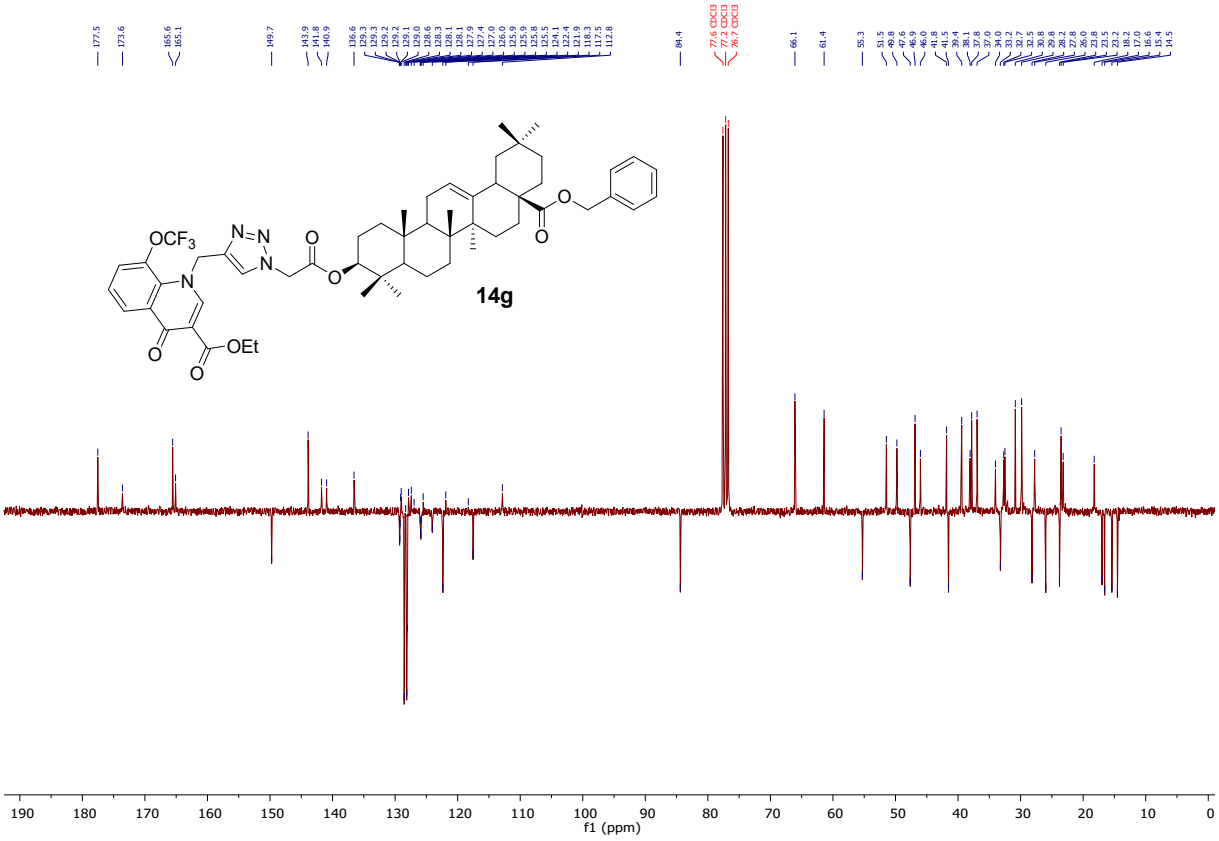

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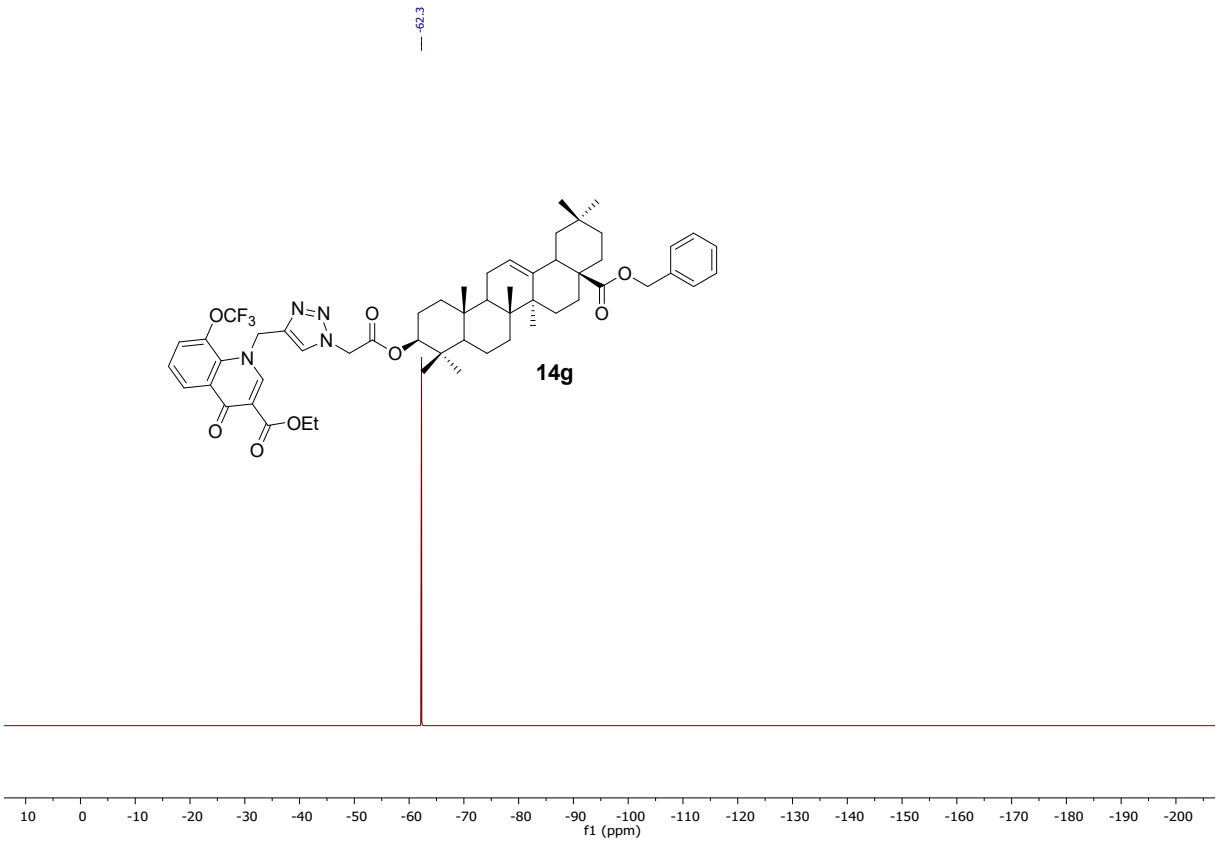

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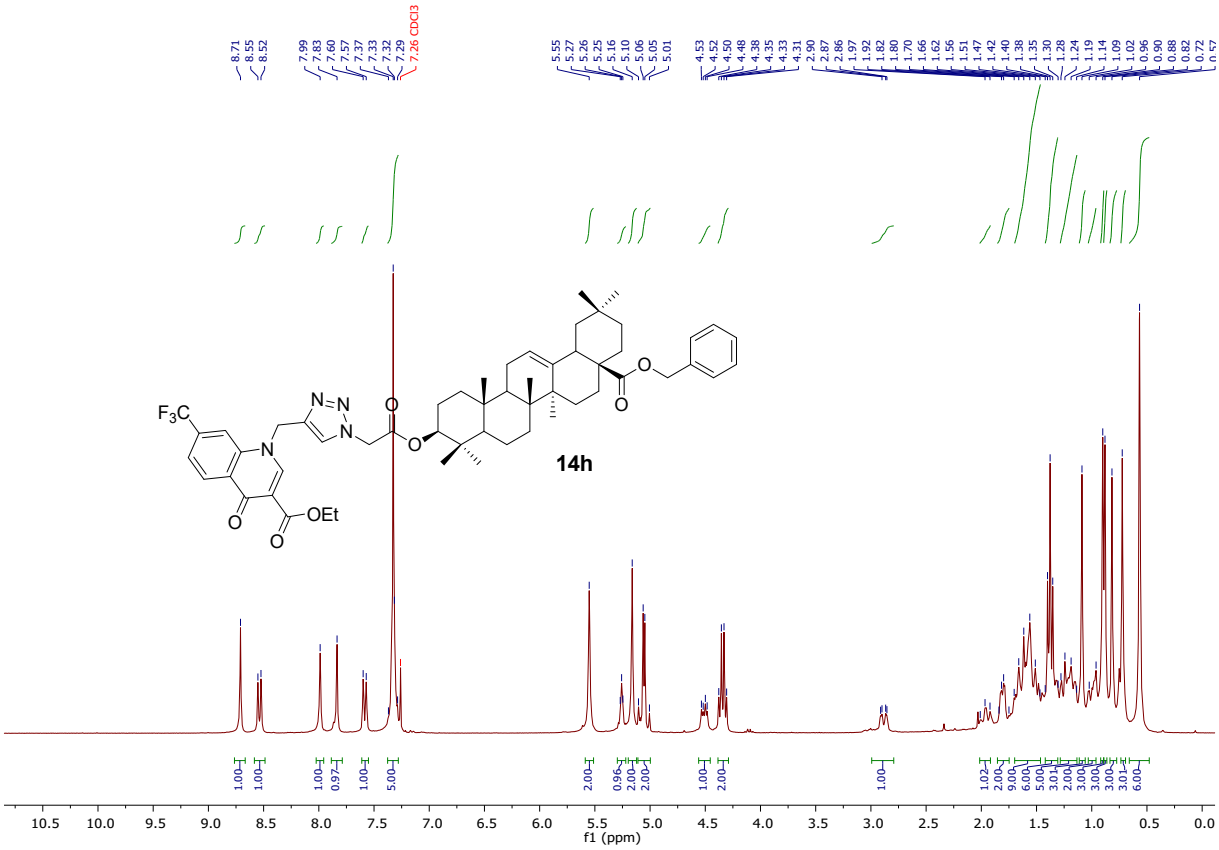

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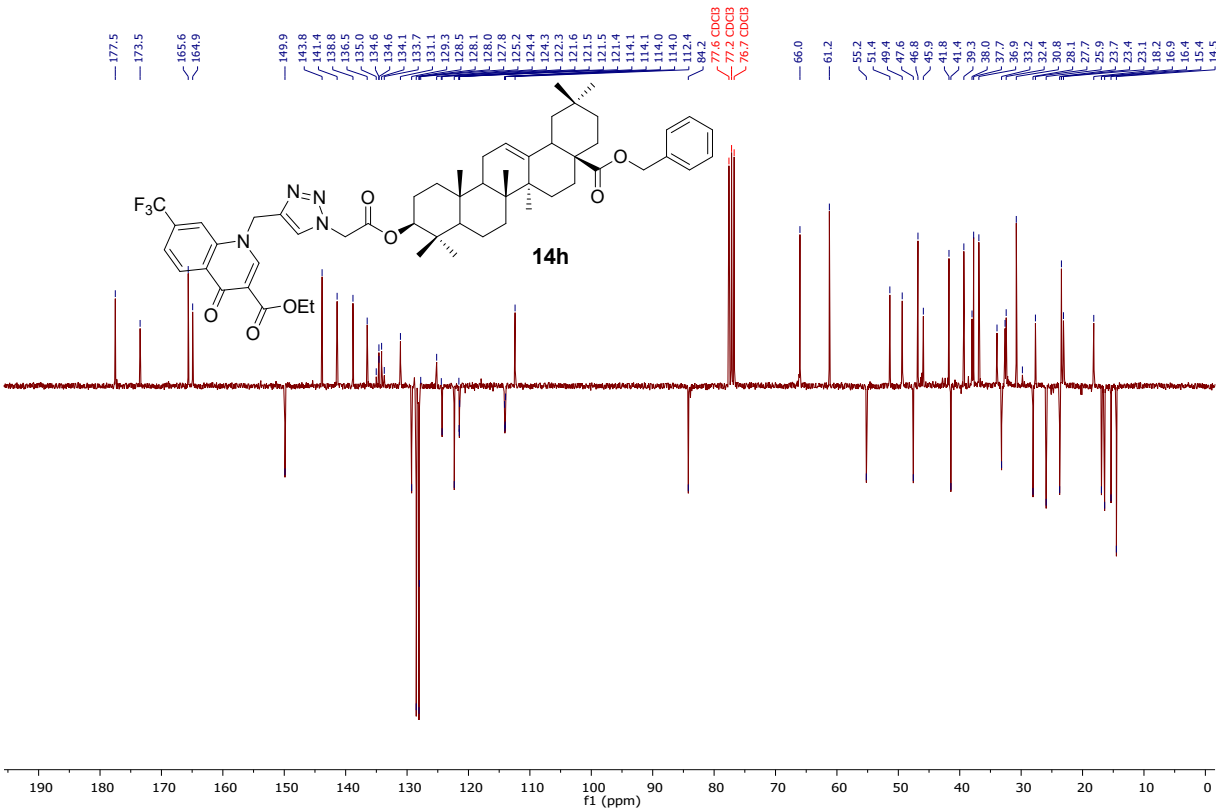

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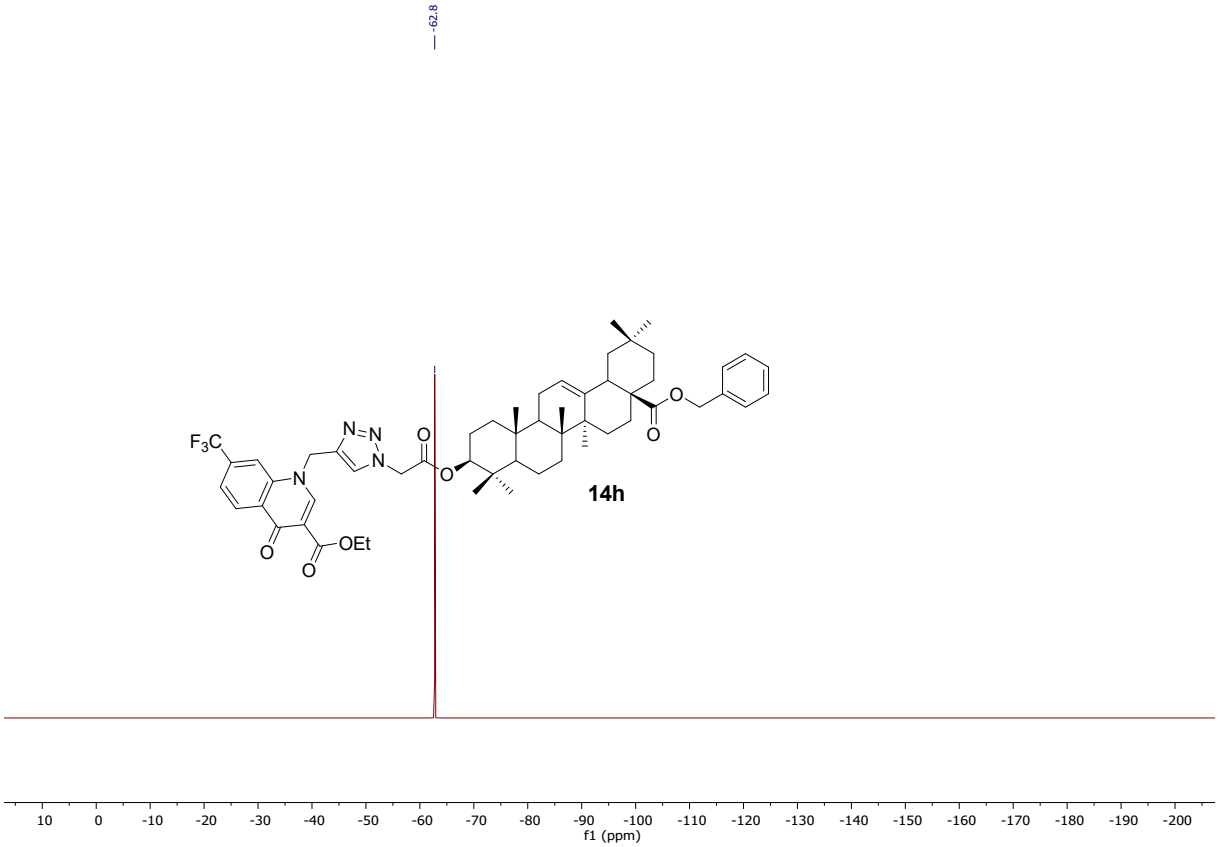

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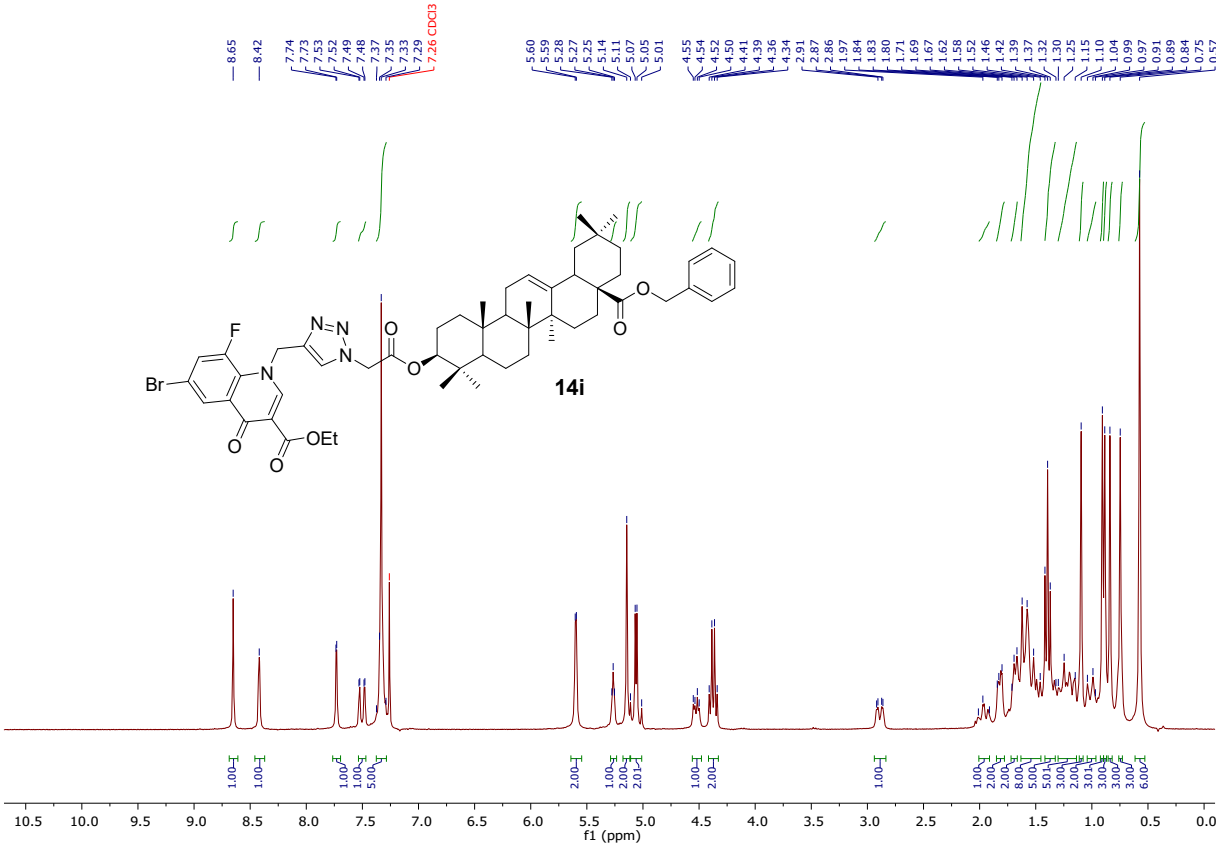

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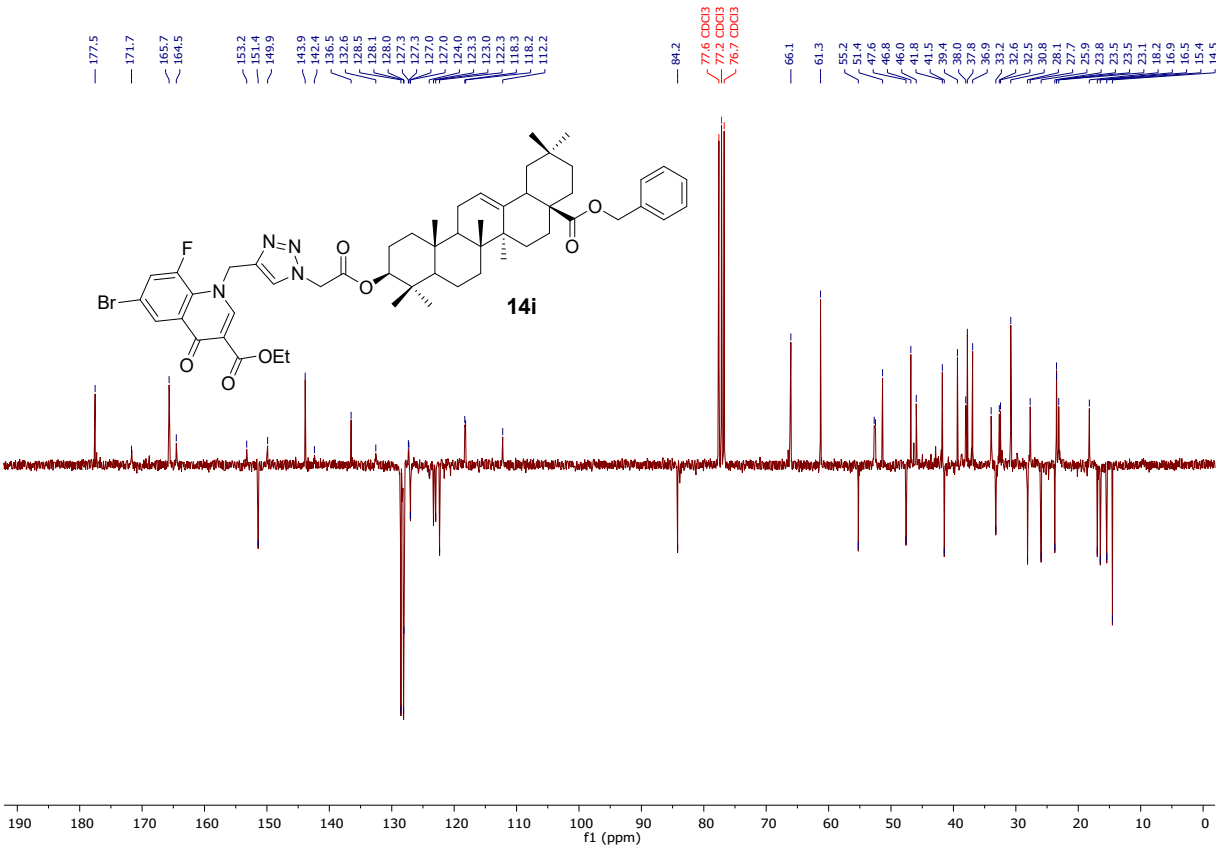

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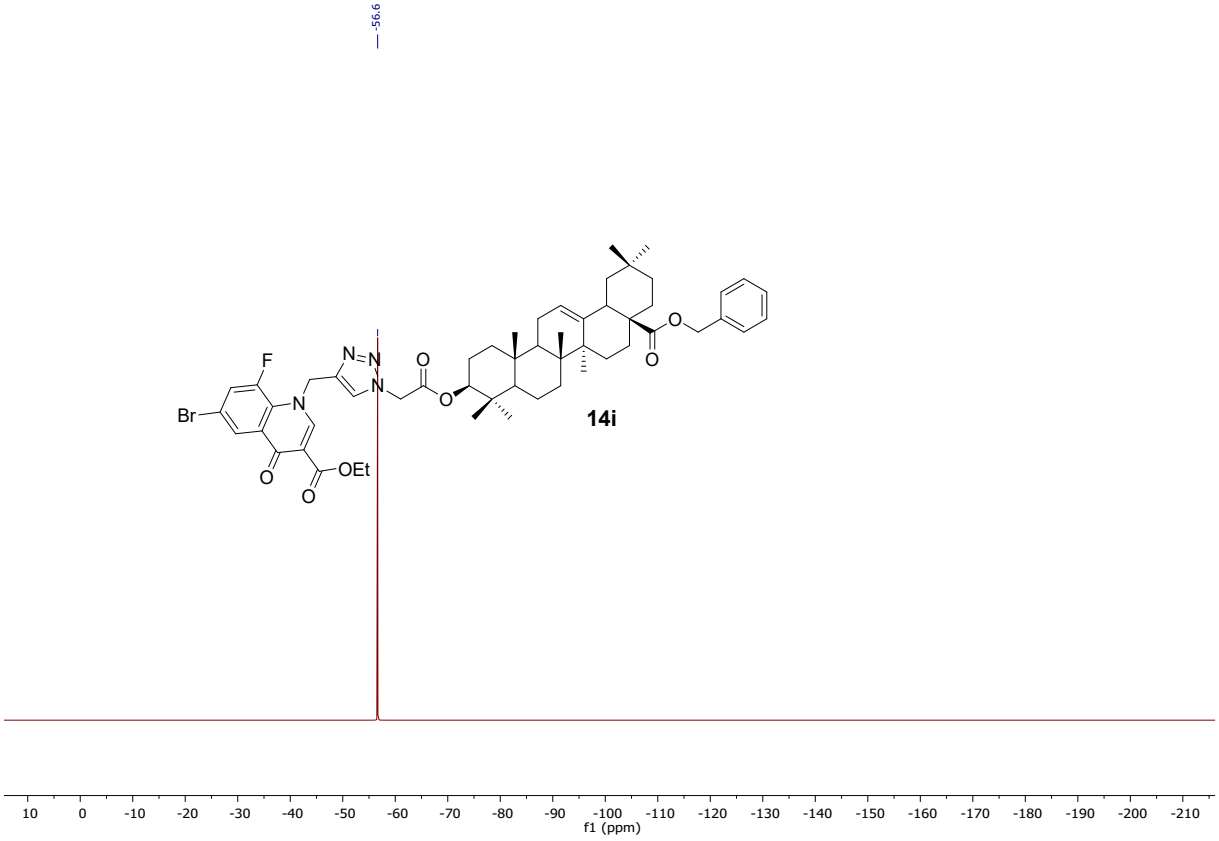

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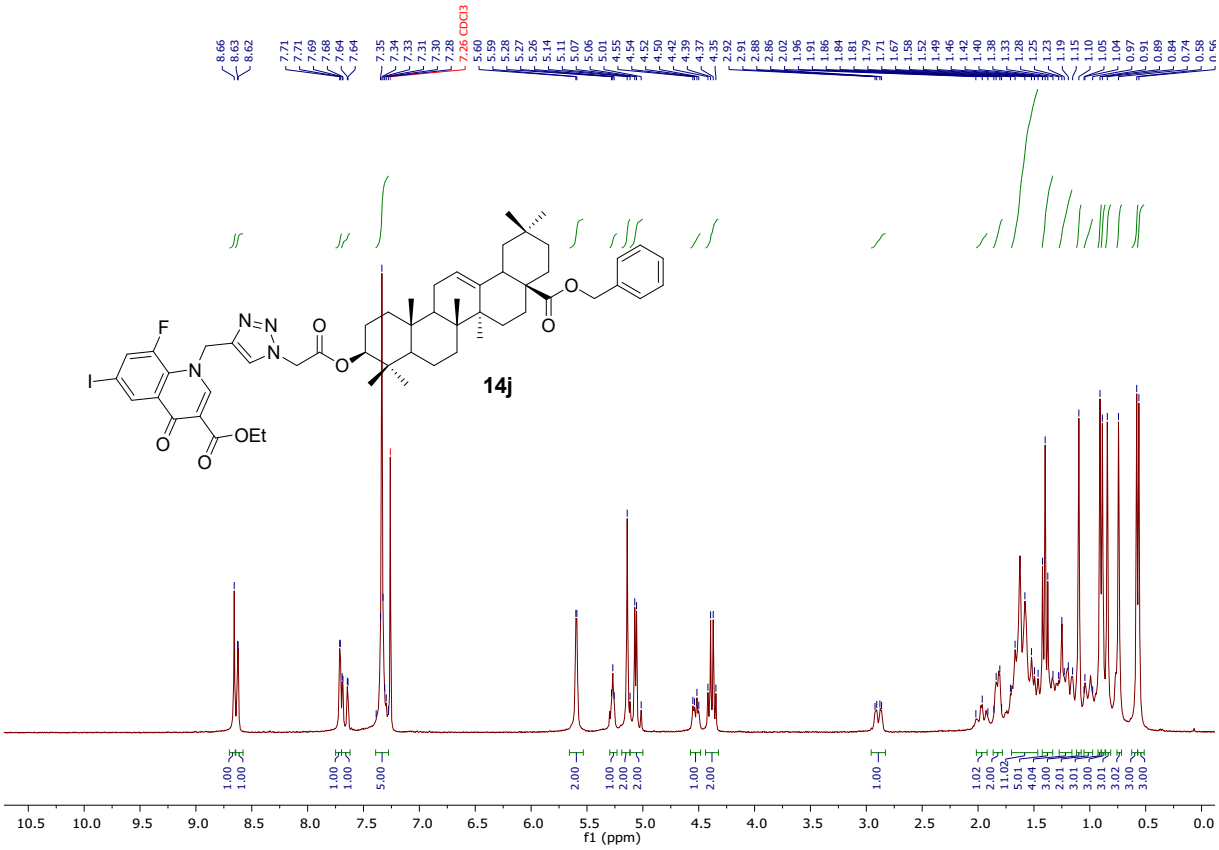

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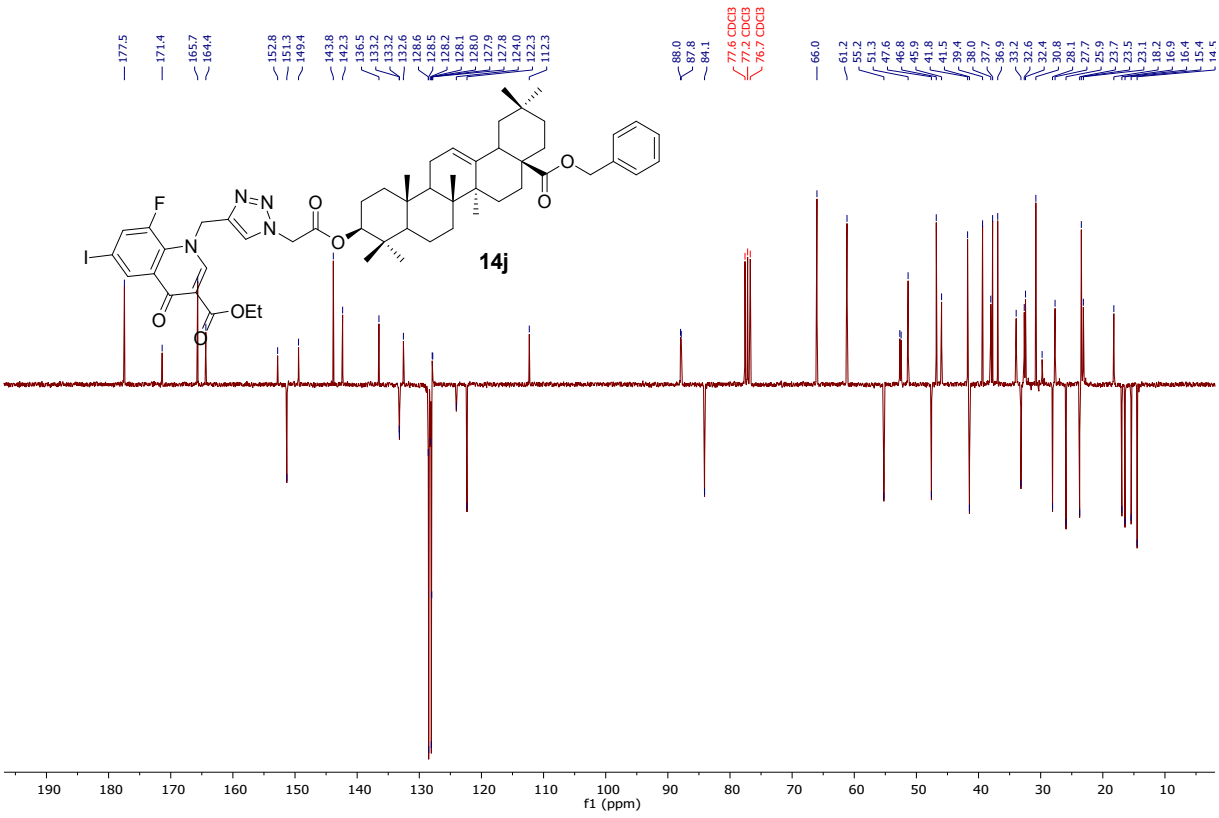

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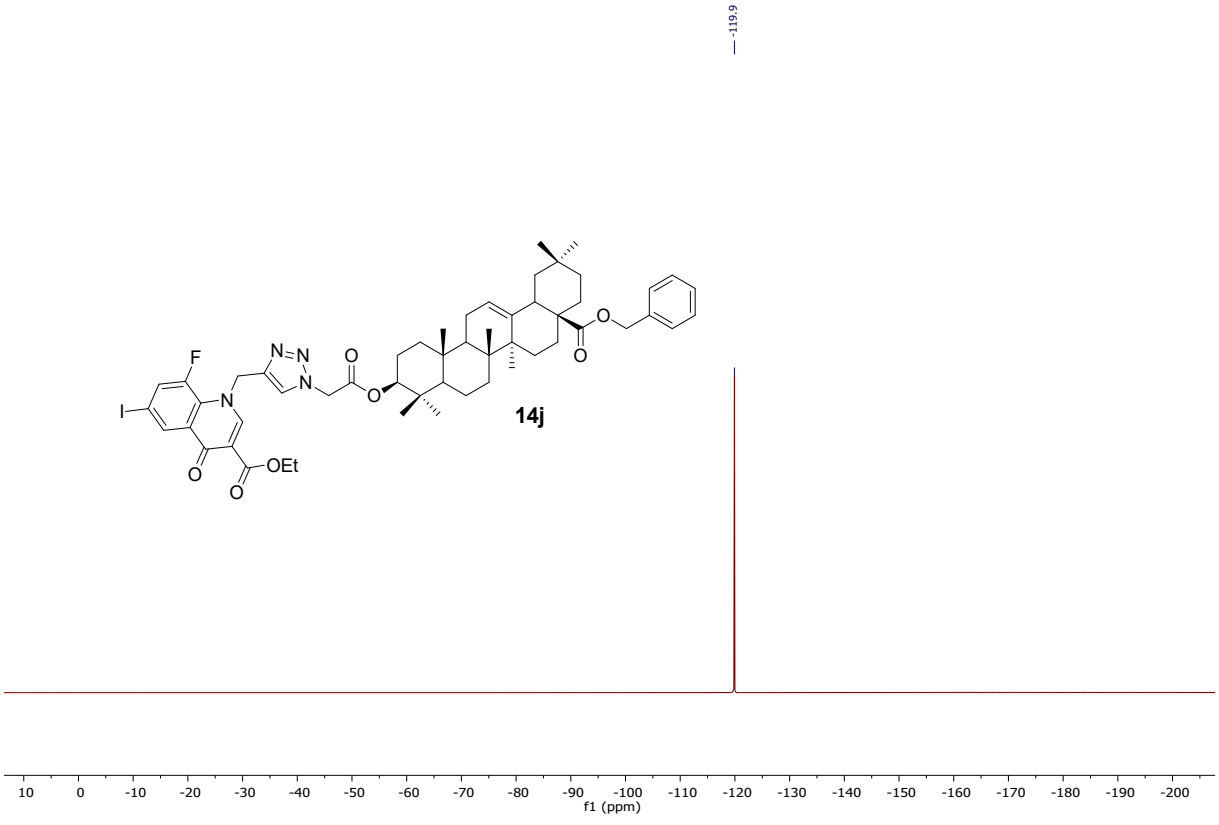

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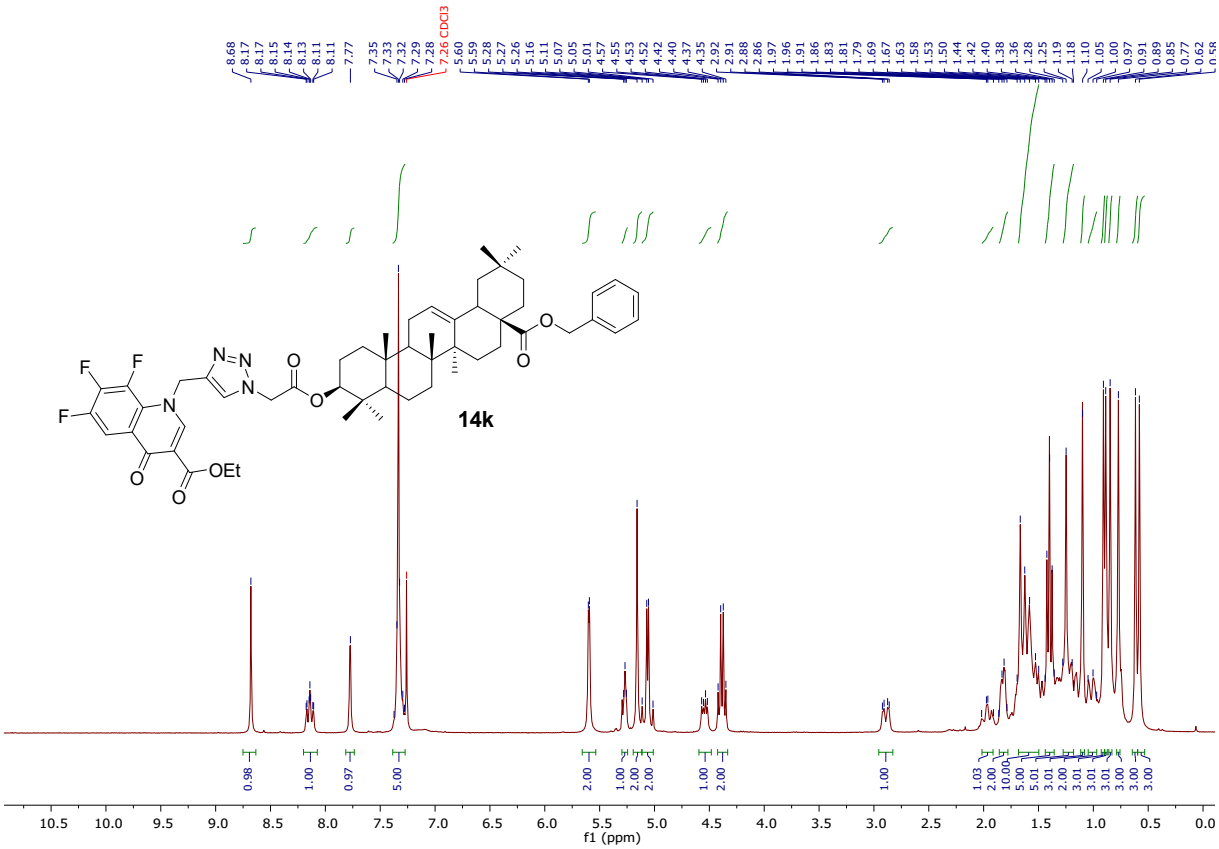

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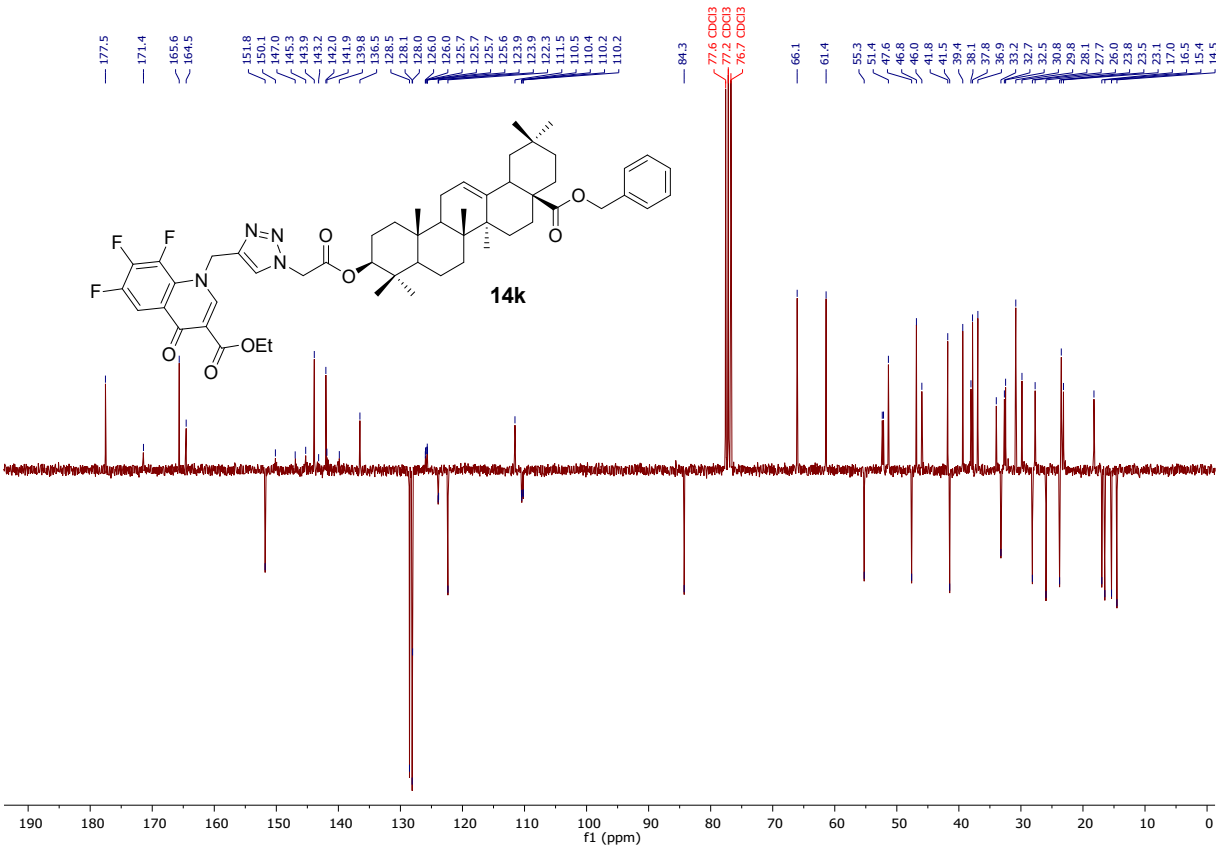

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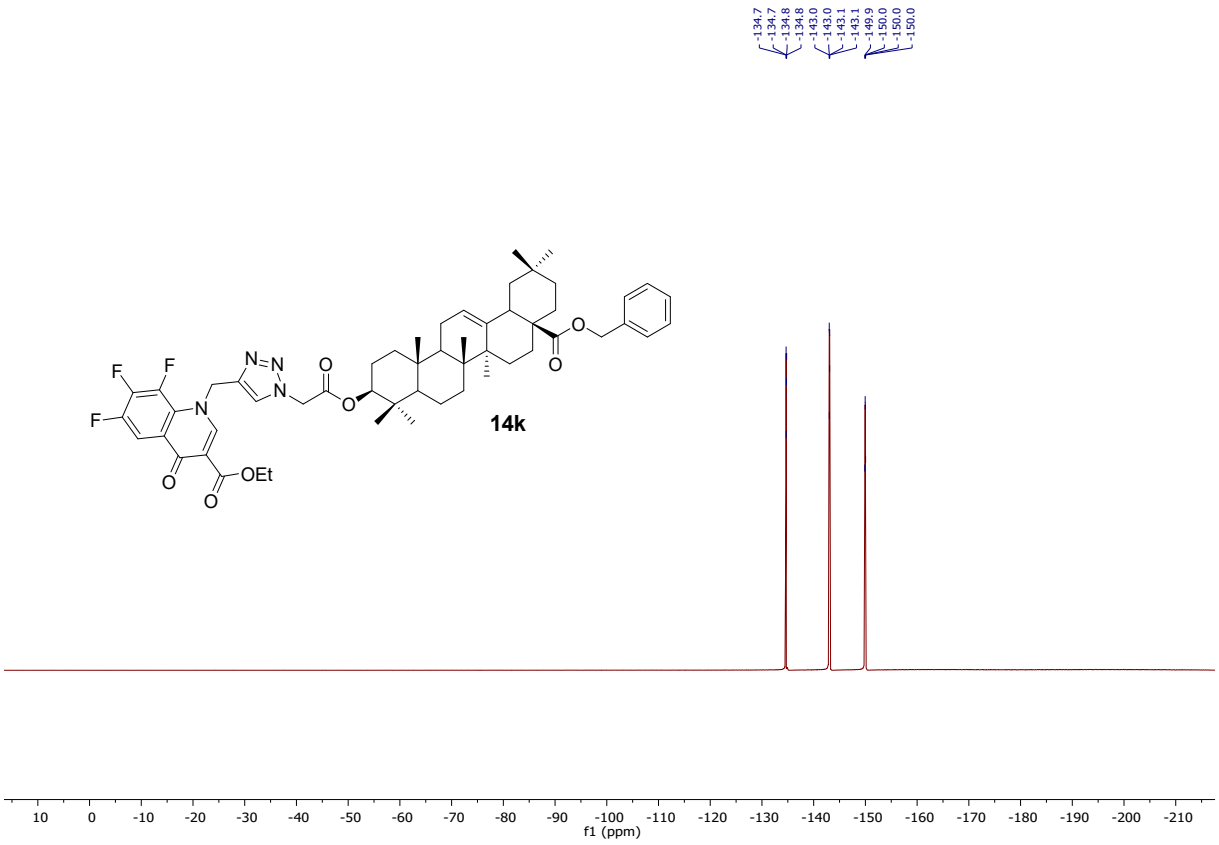

^{19}F NMR (282 MHz, $CDCl_3$)