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Supporting Information

Aromatic Foldamer Helices as α -Helix Extended Surface Mimetics

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2. Figures and Schemes

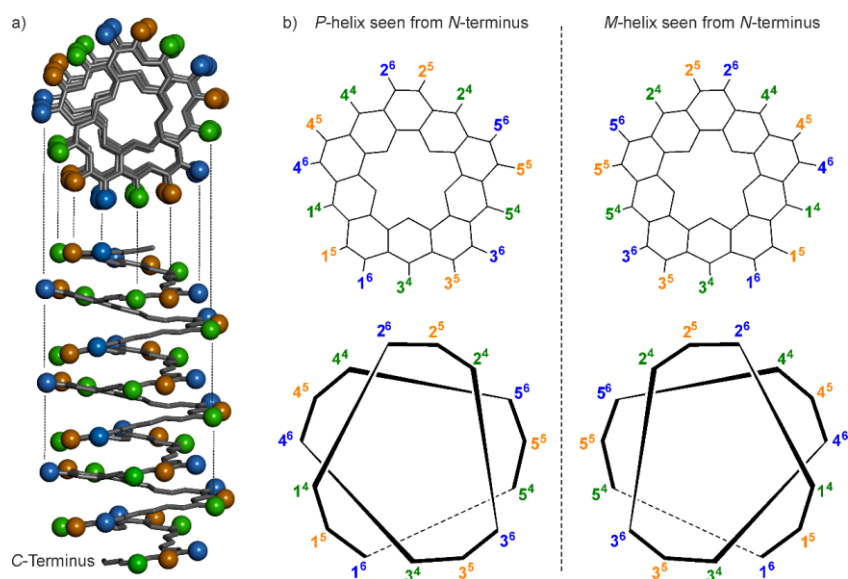


Figure S1. Schematic representations of an 8-amino-2-quinolinecarboxylic acid oligoamide helix showing the density of side chains in position 4 (green balls or letters), 5 (gold balls or numbers) and 6 (blue balls or numbers). Numbers indicate monomer position in the sequence, subscripted numbers indicate side chain position on a given quinoline monomer. Side chains in position 3 or 7 of quinoline rings are not considered here. a) Top view and side view of a molecular model showing the $C_{2.5}$ screw axis (2.5 units per turn). All atoms have been removed for clarity except the helix outer rim shown as grey tube and the first side chain atoms shown as colored spheres. b) Helix wheel representation indicating the side chain positions.

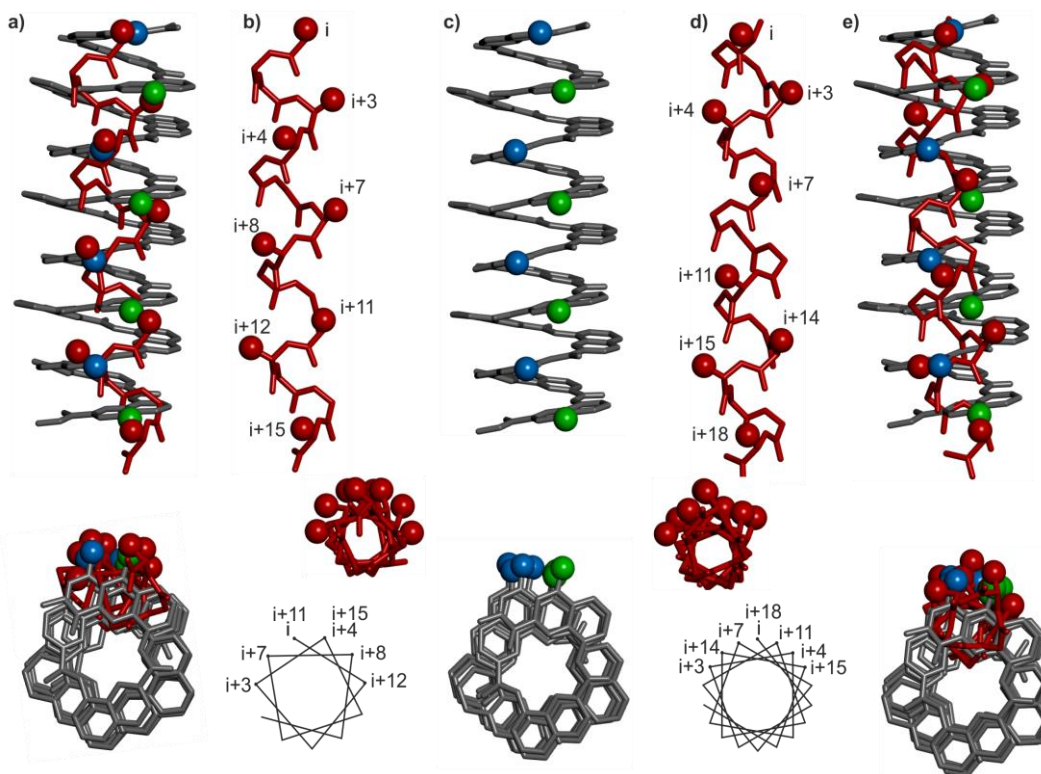


Figure S2. Overlay of eight side chains of a right-handed 8-amino-2-quinolinecarboxylic acid oligoamide helix (c) (blue spheres and green spheres depict the first exocyclic carbon of side chains in position 6 or 4 of a quinoline ring, respectively) with eight side chains (beta-carbons shown as red spheres) of a 3.66₁₃ α -helix or e) 3.6₁₃ α -helix. b) an ideal (computed) 3.66₁₃ α -helix (3 turns for 11 units). d) a 3.6₁₃ α -helix (5 turns for 18 units) from PDB # 4U5T.^[1] The RMSD is 1.50 Å in a) and 1.72 Å in e). Note that the peptide helix side chains involved are not all the same in a) and e).

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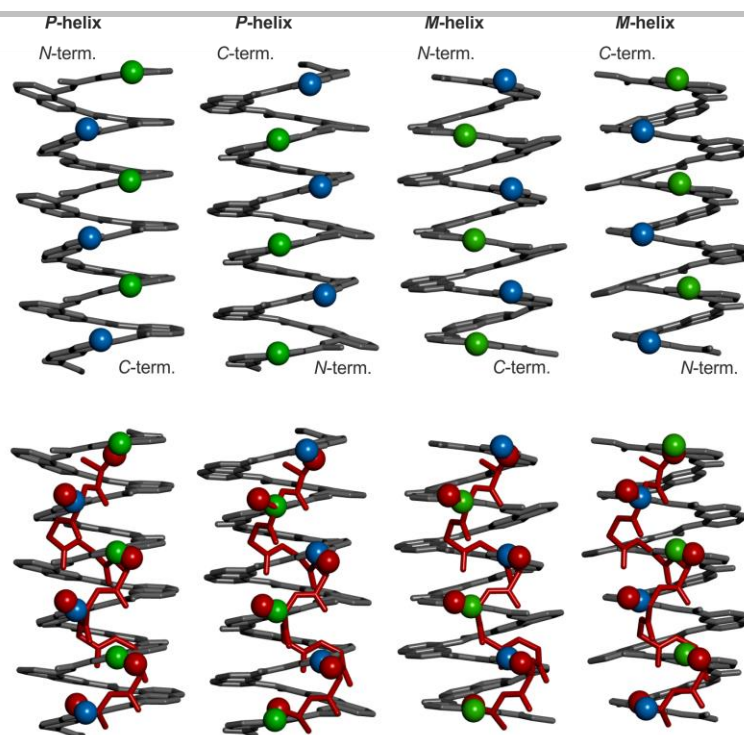


Figure S3. Top: Comparable but not identical side chain arrangements may be obtained through reverting the order of side chain on the sequence (reverting N-to-C polarity) or through inverting helix handedness. Note that the sequence length is not the same for the two structures at left and the two structures at right. Blue spheres and green spheres depict side chains in position 6 or 4 of a quinoline ring, respectively. Bottom: when overlaid with a 3.66_{13} α -helix, the four structures give comparable matches (RMSD = 1.5 Å), but the matches are different from side chain to side chain.

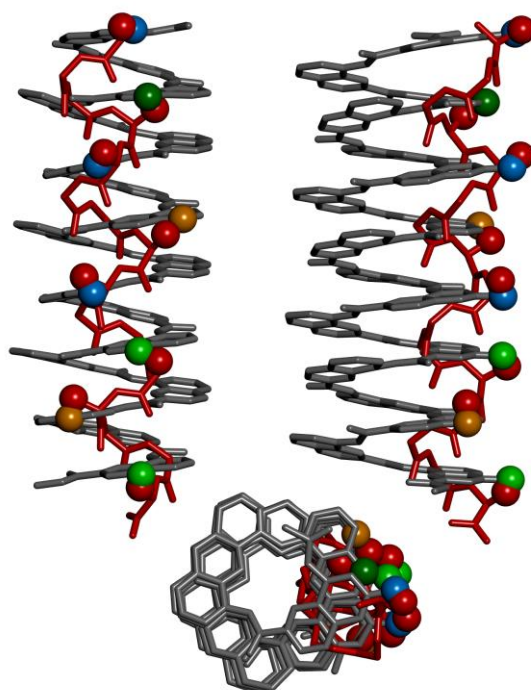


Figure S4. Overlay of eight side chains of a right-handed 8-amino-2-quinolinecarboxylic acid oligoamide helix with eight side chains of a 3.66_{13} α -helix (3 turns for 11 units). Red spheres indicate the β carbons of the α -helix. Blue spheres depict the first exocyclic carbon of side chains in position 6 of a quinoline ring. Light green spheres depict the first exocyclic carbon of side chains in position 4 of a quinoline ring. The dark green sphere depicts a C4 carbon atom of a quinoline ring. Gold spheres depict C5 carbon atoms of quinoline rings. The RMSD is 1.14 Å.

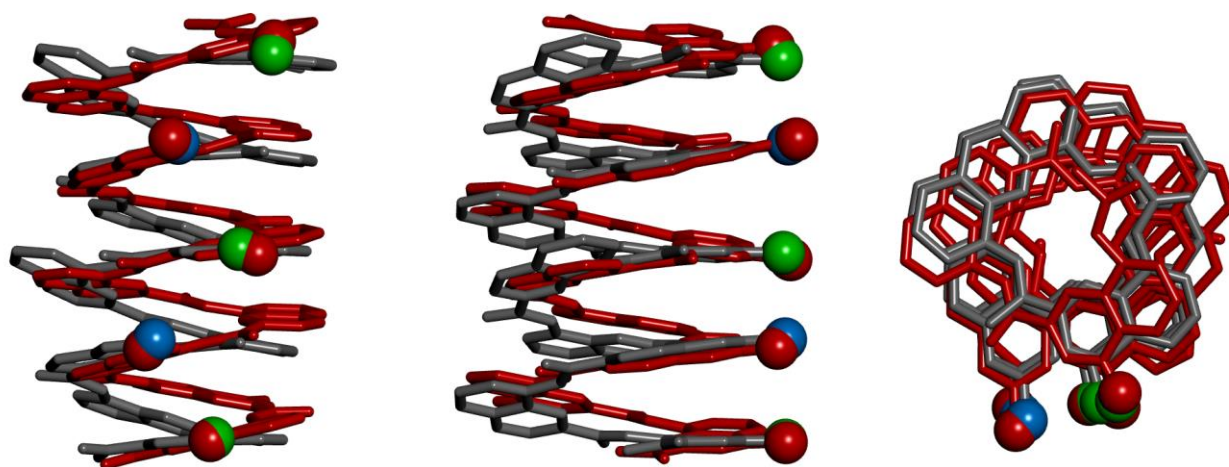


Figure S5. Overlay of five side chains of the crystal structure of **6** with the corresponding side chains of a molecular model. Only the first atom of each side chains have been overlaid, not the entire backbone. The RMSD is 0.40 Å, establishing the good prediction of side chain position by a simple molecular modelling tool, and the weak deviation of the structure of **6** from an ideal calculated helix.

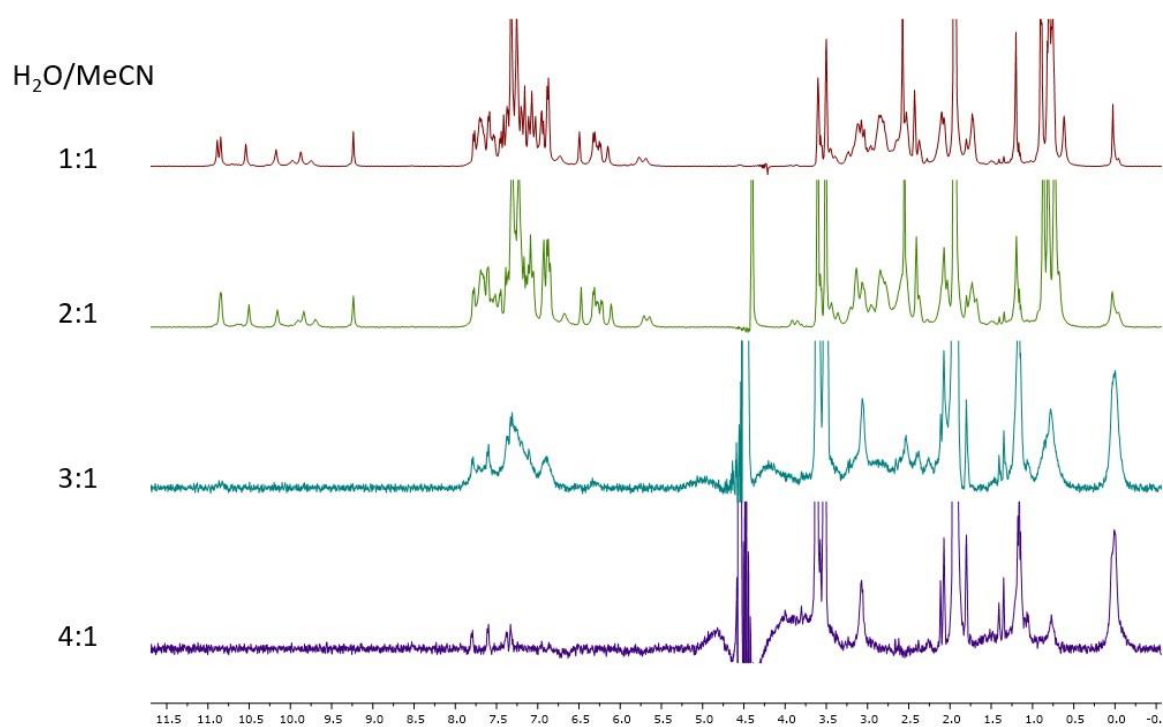
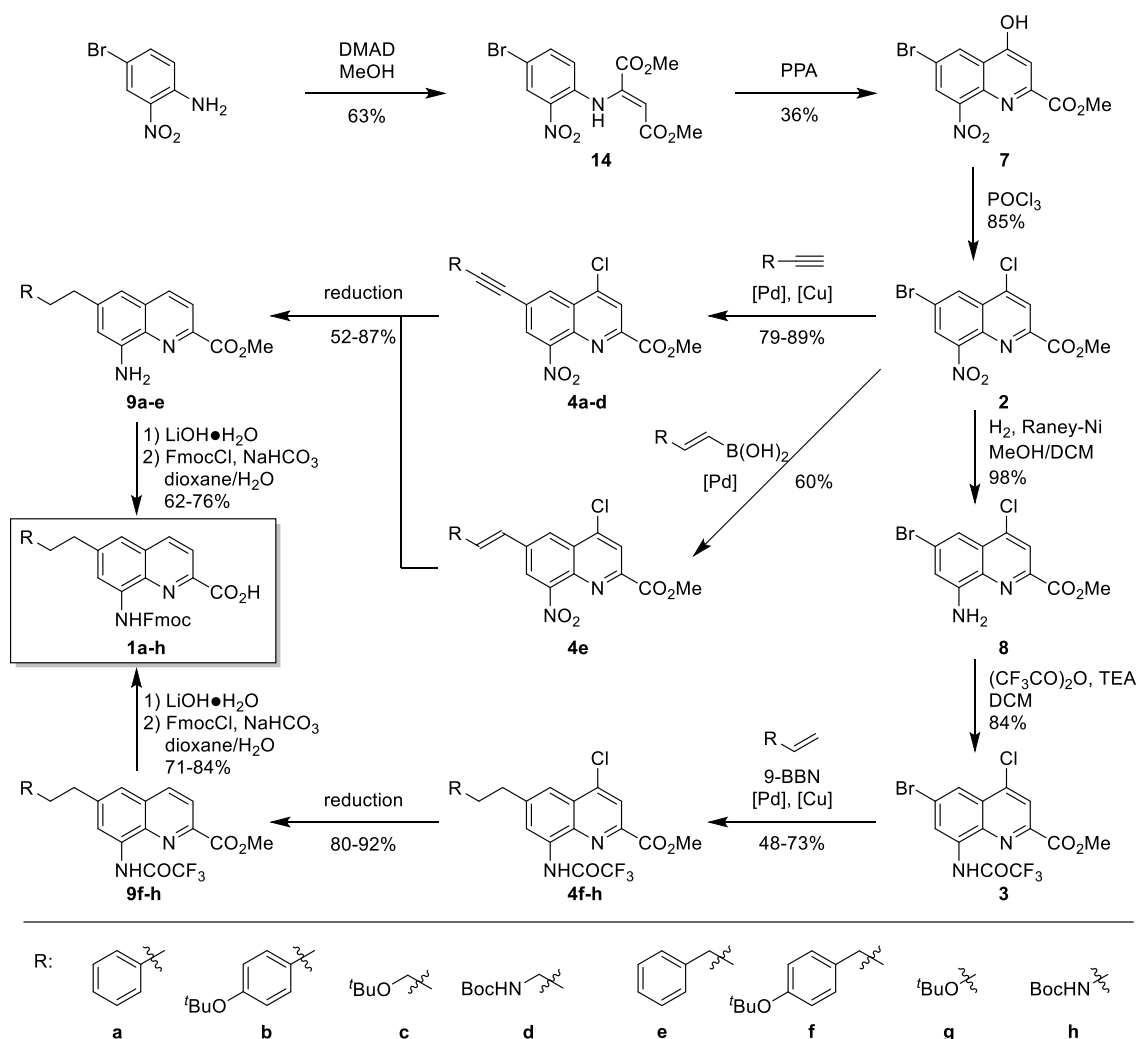


Figure S6. 500 MHz ^1H NMR spectrum of oligomer **6** (1mM, 25°C) in $\text{H}_2\text{O}/\text{CD}_3\text{CN}$ acetonitrile mixtures at different proportions.

3. Monomer synthesis strategy

One of the aims of this work was to elaborate a synthetic route to 6-substituted 8-amino-2-quinolinecarboxylate building blocks. A robust synthetic strategy was designed to allow the incorporation of a wide variety of side chains into position 6. The synthetic route relies on key intermediates **2** and **3** bearing two different halogen atoms at C-4 and C-6, which enables the selective functionalization of these positions. An efficient way to achieve this, was the use of sp^2 - sp^2 (Suzuki), sp^2 - sp^3 (Suzuki) or sp^2 - sp (Sonogashira) cross-coupling reactions, the choice of the conditions depending on the nature of side chain and availability of their synthons. It is important to note that the side chains could be introduced having a C-C triple, C-C double or C-C single bond followed by the reduction of the multiple bond at a later stage, therefore we had a wide range of potential coupling agents. The final form of the desired building blocks was obtained from the appropriate amino-esters **9a-h**, which were prepared by reduction of the corresponding intermediates **4a-h** already bearing the side chains (Scheme S1). This synthetic route also comprises the possibility of further functionalization at position 4 if the complexity of the system needs to be increased.

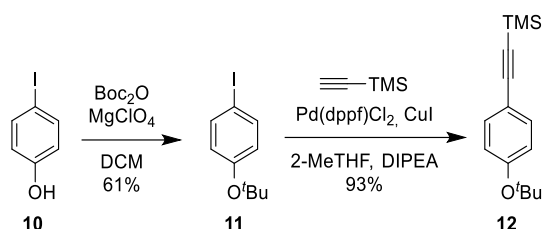


Scheme S1. General synthetic strategy of 6-substituted quinoline acid building blocks

In the first step of the building block synthesis a simple, chromatography free and scalable route was developed for the key intermediates **2** and **3**. The anilinfumarate adduct **14** was obtained from the Michael-addition of DMAD and 4-bromo-2-nitroaniline as described by Schmitt et al.^[2] Unfortunately the conditions (Ph_2O , 250°C , 15 min) reported by the same reference failed to give the cyclized product **7** in reasonable yields, therefore alternative reagents were tested. Out of cc. H_2SO_4 , MsOH , Eaton's reagent, Ph_2O , and PPA, the latter gave the most promising results. However even after optimization of the reaction conditions and the workup procedure, the ring closure step remained the bottleneck of the synthesis with a 36% yield. After the cyclization, **7** was subjected to nucleophilic chlorination at position 4 by POCl_3 at 100°C to give the key intermediate **2**. As the nitro function was found to be incompatible with certain sp^2 - sp^3 Suzuki couplings, it was reduced over Raney nickel and trifluoroacetylated to obtain a second key intermediate, **3**. Conditions of the nitro group's reduction had to be carefully chosen in order to avoid dehalogenation as a side reaction.

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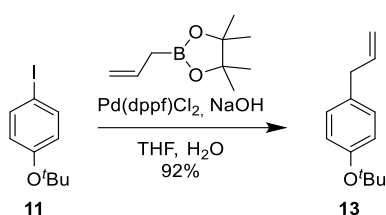
After obtaining the desired intermediates on a multigram scale we turned our attention to the introduction of the side chains. First we tested the Sonogashira reaction of the key intermediate **2** on the way to **4a-d** where acetylene synthons were easily accessible. Phenylacetylene, tert-butyl propargyl ether, and *N*-Boc-propargylamine were commercially available. For the synthesis of **4b** the TMS derivative **12** was utilized instead of 4-tert-butoxyphenylacetylene. MgClO₄ catalyzed etherification of **10** as described by Teresk^[3] and subsequent coupling with TMS-acetylene afforded **12** (Scheme S2), which was *in-situ* desilylated by H₂SiF₆ in the Sonogashira reaction with **2** to obtain **4b**.



Scheme S2. Preparation of side chain synthon for **1b**.

To reach satisfactory selectivity in the cross-coupling reactions between the chloro and bromo functions, the conditions, particularly the temperature, were optimized for each acetylene coupling. While **4a-d** were obtained in satisfactory yields, it was not the case for benzylacetylene. Thus, we decided to introduce a phenylpropenyl side chain in sp²-sp² Suzuki coupling. Utilizing the commercially available boronic acid we obtained **4e** with fair, 60% yield. The coupling reactions were followed by the reduction of **4a-e**, where simultaneously three functional groups were transformed: dehalogenation occurred at position 4, the alkyne/alkene linker part was saturated, and the nitro group was reduced to amine. Due to the complex nature of this reaction an extensive optimization/screening was required. To our delight, NH₄HCOO proved to be an excellent transfer hydrogenation agent and in most cases successfully suppressed side reactions. The reduction of **4a-e** furnished the amino-esters **9a-e** in fair to very good yields.

For certain side chains the acetylene or vinyl boronate synthons would have been difficult to obtain, therefore another approach was developed for the introduction of these moieties. The corresponding terminal alkenes were hydroborated with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF at room temperature to yield alkylboranes quantitatively. The resulting alkylborane solutions were directly utilized in a one-pot, sp²-sp³ Suzuki coupling with the key intermediate **3** to obtain **4f-h**. For the synthesis of **4f**, the terminal alkene synthon **13** was prepared in excellent yield through the Suzuki coupling of **11** with allyl pinacol boronate (Scheme S3). Conditions had to be optimized for each sp²-sp³ Suzuki coupling reactions in order to obtain good selectivity and suppress dehalogenation. Starting from **2** we obtained complex reaction mixtures, presumably due to the undesired side reaction of alkylboranes with the nitro group at position 8. The Suzuki coupling was followed in each case by dehalogenation at position 4 utilizing Pd/C, NH₄HCOO and hydrogen in methanol to furnish **9f-h** in 80-92% yields.



Scheme S3. Preparation of 1-allyl-4-tert-butoxy-benzene.

In the last step of the synthesis **9a-h** were subjected to alkaline hydrolysis of the methyl ester and subsequently the Fmoc protection of the aromatic amino group in a one-pot procedure to afford **1a-h** in 62-84% yield. In case of TFA protected amines (**9f-h**), the trifluoroacetamide was quickly hydrolyzed along with the methyl ester. The final products were purified by normal phase flash chromatography and preparative RP-HPLC to reach the desired purity (>99%) for solid phase foldamer synthesis.

4. Experimental Procedures

4.1. General experimental details

Reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying. Nitrogen gas dried on a column of Drierite[®] was used as inert atmosphere. The reactions were monitored using LC-MS and GC-MS instruments. **Analytical LC-MS:** Agilent HP1200 LC with Agilent 6140 quadrupole MS, operating in positive or negative ion electrospray ionisation mode. Molecular weight scan range was 100 to 1350 m/z. Parallel UV detection was done at 210 nm and 254 nm. Samples were supplied as a 1 mM solution in MeCN or in THF:water (1:1) with 5 μ L loop injection. LC-MS analyses were performed on two instruments, one of which was operated with basic, and the other with acidic eluents. Basic LC-MS: Gemini-NX, 3 μ m, C18, 50 mm \times 3.00 mm i.d. column at 23°C, at a flow rate of 1 mL min⁻¹ using 5 mM aq NH₄HCO₃ solution and MeCN as eluents. Acidic LC-MS: ZORBAX Eclipse XDB-C18, 1.8 μ m, 50 mm \times 4.6 mm i.d. column at 40°C, at a flow rate of 1 mL min⁻¹ using water and MeCN as eluents, both containing 0.02 V/V% formic acid. Combination **gas chromatography** and low resolution mass spectrometry were performed on Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using 15 m \times 0.25 mm column with 0.25 μ m HP-5MS coating and helium as carrier gas. Ion source: EI⁺, 70 eV, 230°C, quadrupole: 150°C, interface: 300°C. **Flash chromatography** was performed on ISCO CombiFlash Rf 200i or ISCO CombiFlash Torrent[®] with pre-packed silica-gel cartridges (RediSep[®]R_f Gold High Performance). **Preparative HPLC** purifications were performed on an ISCO CombiFlash EZ Prep system with a Gemini-NX[®] 10 μ m C18, 250 mm \times 50 mm column running at a flow rate of 118 mL min⁻¹ with UV diode array detection. **¹H NMR, ¹⁹F NMR and proton-decoupled ¹³C NMR** measurements were performed on Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer, using DMSO-d₆ or CDCl₃ as solvent. ¹H and ¹³C NMR data are in the form of delta values, given in part per million (ppm), using the residual peak of the solvent as internal standard (DMSO-d₆: 2.50 ppm (¹H) / 39.5 ppm (¹³C); CDCl₃: 7.26 ppm (¹H) / 77.0 ppm (¹³C)). Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sp (septet), m (multiplet), br s (broad singlet), dd (doublet of doublets), td (triplet of doublets), qd (quartet of doublets), dt (doublet of triplets). In some cases due to tautomers or amide rotamers two sets of signals appear in the spectra. **HRMS** were determined on a Shimadzu IT-TOF-MS, ion source temperature 200°C, ESI +/-, ionization voltage: (+/-)4.5 kV. Mass resolution: min. 10000.

For oligomers 5 and 6:

Low loading Wang resin was purchased from Novabiochem. 1-chloro-*N,N*,2-trimethylpropenylamine (Ghosez reagent) and anhydrous *N,N*-dimethylformamide (DMF) were purchased from Sigma Aldrich. *N,N*-diisopropylethylamine (DIEA) was distilled over calcium hydride. Analytical grade organic solvents were used for solid phase synthesis. Dry organic solvents for solid phase synthesis were dispensed from a solvent purification system that passes solvents through packed columns (THF, CH₂Cl₂: dry neutral alumina). Milli-Q water was delivered from a PureLab Prima 7/15/20 system. RP-HPLC quality acetonitrile (CH₃CN) and MilliQ water were used for RP-HPLC analysis and purification. ¹H NMR spectra were measured on a Bruker Avance II 300 MHz spectrometer using DMSO-d₆ as solvent. ¹H data are in the form of delta values, given in part per million (ppm), using the residual peak of the solvent as internal standard (DMSO-d₆: 2.50 ppm (¹H)). SPS was carried out manually at atmospheric pressure using a CEM Discover microwave oven and SPS station in the proprietary reactor vessels. The temperature of microwave-assisted reactions was controlled by an optical fiber probe internal to the reaction mixture. RP-HPLC analysis were performed using a Macherey-Nagel Nucleodur C18 HTEC column (4.6 \times 100 mm, 5 μ m) at 1.5 mL/min with running solvents: Milli-Q water containing 0.1% v/v TFA (solvent A), CH₃CN containing 0.1% v/v TFA (solvent B). Monitoring by UV detection was carried out at 214 nm, 254 nm and 300 nm using a diode array detector. Purification of oligomers was performed at 4 mL/min on a C18 column (10 mm \times 125 mm, 5 μ m) by semi-preparative RP-HPLC. The mobile phases were the same as for the analytical system. Monitoring by UV detection was carried out at 300 nm. High-resolution electrospray ionization time-of-flight (ESI-TOF) mass spectra were measured in the negative ion mode on a Thermo Exactive orbitrap.

4.2. Monomer synthesis

Preparation of 8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-6-phenethyl-quinoline-2-carboxylic acid (**1a**)

In a 500 mL round-bottom flask 846 mg compound **9a** (2.76 mmol) was dissolved in 84.6 mL 1,4-dioxane and a solution of 174 mg LiOH \cdot H₂O (1.50 equiv., 4.14 mmol) in 42.3 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (45 min), then it was quenched by the addition of 4.14 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 1.16 g NaHCO₃ (5.00 equiv., 13.8 mmol) was added and a solution of 1.07 g FmocCl (1.50 equiv., 4.14 mmol) in 25.4 mL 1,4-dioxane was added dropwise during a 60 minute period. Stirring at 0°C was continued for 2 h. 50 mL water was added and the pH adjusted to 4 by adding 1M aq HCl solution. The product was extracted with 100 mL DCM, the organic phase was washed with 2 \times 100 mL water, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (120 g silicagel column, DCM/MeOH, gradient elution: 0-2.0%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH₄HCO₃/MeCN, isocratic elution: 50%) to afford compound **1a** as a pale greenish-white solid (875 mg, 62%). HPLC-UV purity: 99.9%; ¹H NMR (500 MHz, DMSO-d₆): δ =13.53 (s, 1H), 10.48 (s, 1H), 8.48 (d, *J*=8.6 Hz, 1H), 8.40 (br s, 1H), 8.18 (d, *J*=8.5 Hz, 1H), 7.93 (d, *J*=7.5 Hz, 2H), 7.79 (d, *J*=7.5 Hz, 2H), 7.53 (d, *J*=1.2 Hz, 1H), 7.44 (t, *J*=7.4 Hz, 2H), 7.37 (td, *J*=7.4 Hz, *J*=1.1 Hz, 2H), 7.30-7.22 (m, 4H), 7.19-7.14 (m, 1H), 4.61 (d, *J*=6.9 Hz, 2H), 4.46 (t, *J*=7.0 Hz, 1H), 3.10-3.02 (m, 2H), 3.00-2.93 ppm (m, 2H); ¹³C NMR (125 MHz, DMSO-d₆): δ =165.4, 153.5, 144.7, 143.7, 143.3, 141.1, 140.8, 138.0, 135.6, 135.5, 129.3, 128.4, 128.3, 127.8, 127.2, 125.9,

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125.2, 120.8, 120.3, 119.6, 117.5, 66.4, 46.6, 37.7, 36.4 ppm; HRMS (ESI): m/z calcd for $C_{33}H_{27}N_2O_4$ [M+H]⁺: 515.1965; found: 515.1960.

Preparation of 6-[2-(4-tert-butoxyphenyl)ethyl]-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (1b)

In a 500 mL round-bottom flask 693 mg compound **9b** (1.83 mmol) was dissolved in 69.3 mL 1,4-dioxane and a solution of 115 mg LiOH·H₂O (1.50 equiv., 2.75 mmol) in 34.7 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (45 min), then it was quenched by the addition of 2.75 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 769 mg NaHCO₃ (5.00 equiv., 9.16 mmol) was added and a solution of 711 mg FmocCl (1.50 equiv., 2.75 mmol) in 20.8 mL 1,4-dioxane was added dropwise during a 60 min period. Stirring at 0°C was continued for 2 h. Then 50 mL water was added and the pH adjusted to 4 by adding 1M aq HCl solution. The product was extracted with 100 mL DCM, the organic phase was washed with 2x100 mL water, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (80 g silicagel column, DCM/MeOH, gradient elution: 0-50%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH₄HCO₃/MeCN, isocratic elution: 60%) to afford compound **1b** as a pale greenish-white solid (690 mg, 64%). HPLC-UV purity: 99.9%; ¹H NMR (500 MHz, DMSO-d₆): δ=13.53 (s, 1H), 10.46 (s, 1H), 8.47 (d, J = 8.6 Hz, 1H), 8.31 (br s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 1.0 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.37 (td, J = 7.4 Hz, J = 1.1 Hz, 2H), 7.14-7.09 (m, 2H), 6.86-6.82 (m, 2H), 4.60 (d, J = 6.8 Hz, 2H), 4.45 (t, J = 6.9 Hz, 1H), 3.06-3.00 (m, 2H), 2.95-2.88 (m, 2H), 1.23 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=165.4, 153.5, 153.0, 144.7, 143.7, 143.3, 140.8, 137.9, 135.7, 135.5, 135.4, 129.2, 128.8, 127.8, 127.2, 125.1, 123.7, 120.7, 120.3, 119.6, 117.6, 77.5, 66.4, 46.5, 37.8, 35.9, 28.5 ppm; HRMS (ESI): m/z calcd for $C_{37}H_{35}N_2O_5$ [M+H]⁺: 587.2540; found: 587.2535.

Preparation of 6-(3-tert-butoxypropyl)-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (1c)

In a 250 mL round-bottom flask 450 mg compound **9c** (1.42 mmol) was dissolved in 45.0 mL 1,4-dioxane and a solution of 89.5 mg LiOH·H₂O (1.50 equiv., 2.13 mmol) in 22.5 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (1 h), then it was quenched by the addition of 2.13 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 597 mg NaHCO₃ (5.00 equiv., 7.11 mmol) was added and a solution of 552 mg FmocCl (1.50 equiv., 2.13 mmol) in 13.5 mL 1,4-dioxane was added dropwise during a 60 min period. Stirring at 0°C was continued for 2 h. 25 mL water was added and the pH was adjusted to 4 by adding 1M aq HCl solution. The product was extracted with 50 mL DCM, the organic phase was washed with 50 mL water and 50 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-40%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH₄HCO₃/MeCN, isocratic elution: 50%) to afford compound **1c** as a pale greenish-white solid (570 mg, 76%). HPLC-UV purity: 99.2%; ¹H NMR (400 MHz, DMSO-d₆): δ=13.55 (s, 1H), 10.39 (s, 1H), 8.47 (d, J = 8.6 Hz, 1H), 8.31 (br s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.4 Hz, 2H), 7.77 (d, J = 7.4 Hz, 2H), 7.50 (d, J = 1.0 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.36 (td, J = 7.4 Hz, J = 1.0 Hz, 2H), 4.59 (d, J = 6.8 Hz, 2H), 4.44 (t, J = 6.9 Hz, 1H), 3.32 (t, J = 6.2 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 1.85-1.75 (m, 2H), 1.12 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆): δ=165.6, 153.5, 143.7, 143.6, 140.8, 137.7, 135.5, 135.3, 129.2, 127.8, 127.2, 125.1, 120.9, 120.3, 119.4, 117.3, 109.8, 72.0, 66.4, 59.9, 46.6, 32.6, 31.4, 27.4 ppm; HRMS (ESI): m/z calcd for $C_{32}H_{33}N_2O_5$ [M+H]⁺: 525.2384; found: 525.2378.

Preparation of 6-[3-(tert-butoxycarbonylamino)propyl]-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (1d)

In a 250 mL round-bottom flask 931 mg compound **9d** (2.59 mmol) was dissolved in 93.2 mL 1,4-dioxane and a solution of 163 mg LiOH·H₂O (1.50 equiv., 3.89 mmol) in 46.6 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (1 h), then it was quenched by the addition of 3.89 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 1.09 g NaHCO₃ (5.00 equiv., 13.0 mmol) was added and a solution of 1.01 g FmocCl (1.50 equiv., 3.89 mmol) in 27.9 mL 1,4-dioxane was introduced dropwise during a 60 min period. Stirring at 0°C was continued for 2 h. The pH of the reaction mixture was adjusted to 4 by adding 50 mL 5% aq citric acid solution. The product was extracted with 50 mL DCM, the organic phase was washed with 50 mL 5% aq citric acid solution and 50 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-30%) then reversed phase HPLC (EZ Prep system, eluent: 0.02% aq HCOOH/MeCN, gradient elution: 65-100%) to afford compound **1d** as a white solid (1.10 g, 75%). HPLC-UV purity: 99.5%; ¹H NMR (500 MHz, DMSO-d₆): δ=13.54 (s, 1H), 10.47 (s, 1H), 8.49 (d, J = 8.6 Hz, 1H), 8.31 (br s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.52 (s, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.37 (td, J = 7.4 Hz, J = 1.0 Hz, 2H), 6.93 (t, J = 5.5 Hz, 1H), 4.61 (d, J = 6.8 Hz, 2H), 4.45 (t, J = 6.9 Hz, 1H), 2.98 (q, J = 6.5 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 1.75 (quint, J = 7.2 Hz, 2H), 1.37 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=165.7, 155.8, 153.7, 145.2, 143.8, 143.7, 140.9, 138.0, 135.7, 135.6, 129.4, 127.9, 127.4, 125.3, 121.0, 120.4, 119.6, 117.5, 77.7, 66.5, 46.7, 39.6, 33.4, 31.0, 28.4 ppm; HRMS (ESI): m/z calcd for $C_{33}H_{34}N_3O_6$ [M+H]⁺: 568.2442; found: 568.2441.

Preparation of 8-(9H-fluoren-9-ylmethoxycarbonylamino)-6-(3-phenylpropyl)quinoline-2-carboxylic acid (1e)

In a 250 mL round-bottom flask 756 mg compound **9e** (2.36 mmol) was dissolved in 75.6 mL 1,4-dioxane and a solution of 149 mg LiOH·H₂O (1.50 equiv., 3.54 mmol) in 37.8 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (1 h), then it was quenched by the addition of 3.54 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 991 mg NaHCO₃ (5.00 equiv., 11.8 mmol) was added and a solution of 916 mg FmocCl (1.50 equiv., 3.54 mmol) in 22.7 mL 1,4-dioxane was introduced

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dropwise during a 60 min period. Stirring at 0°C was continued for 2 h. The pH of the reaction mixture was adjusted to 4 by adding 50 mL 5% aq citric acid solution. The product was extracted with 50 mL DCM, the organic phase was washed with 50 mL 5% aq citric acid solution and 50 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-20%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH₄HCO₃/MeCN, gradient elution: 45-55%) to afford compound **1e** as a pale greenish-white solid (865 mg, 69%). HPLC-UV purity: 99.6%; ¹H NMR (500 MHz, DMSO-*d*₆): δ=13.55 (s, 1H), 10.39 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.31 (br s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 1.1 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 2H), 7.30-7.20 (m, 4H), 7.17 (t, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.96 ppm (quint, *J* = 7.7 Hz, 2H) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ=165.6, 153.5, 145.7, 143.7, 143.5, 141.8, 140.8, 137.7, 135.5, 135.4, 129.2, 128.3, 128.3, 127.8, 127.2, 125.8, 125.1, 120.9, 120.3, 119.4, 117.2, 66.4, 46.6, 35.4, 34.7, 32.3 ppm; HRMS (ESI): *m/z* calcd for C₃₄H₂₉N₂O₄ [M+H]⁺: 529.2122; found: 529.2120.

Preparation of 6-[3-(4-*tert*-butoxyphenyl)propyl]-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (**1f**)

In a 500 mL round-bottom flask 960 mg compound **9f** (1.97 mmol) was dissolved in 96.0 mL 1,4-dioxane and a solution of 247 mg LiOH·H₂O (3.00 equiv., 5.90 mmol) in 48.0 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (12 h), then it was quenched by the addition of 3.93 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 826 mg NaHCO₃ (5.00 equiv., 9.83 mmol) was added and a solution of 763 mg FmocCl (1.50 equiv., 2.95 mmol) in 28.8 mL 1,4-dioxane was introduced dropwise during a 60 min period. Stirring at 0°C was continued for 2 h, then the reaction mixture was allowed to reach rt and stirred for further 12 h. The reaction mixture was diluted with 200 mL water, the pH was adjusted to 4 by adding 50 mL 5% aq citric acid solution. The product was extracted with 200 mL DCM, the organic phase was washed with 50 mL 5% aq citric acid solution and 100 mL saturated aq NaCl solution, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-40%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH₄HCO₃/MeCN, gradient elution: 55-65%) to afford compound **1f** as a pale greenish-white solid (990 mg, 84%). HPLC-UV purity: 99.9%; ¹H NMR (500 MHz, DMSO-*d*₆): δ=13.45 (s, 1H), 10.32 (s, 1H), 8.45 (d, *J* = 8.6 Hz, 1H), 8.28 (br s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.50 (s, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.35 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 2H), 7.14-7.08 (m, 2H), 6.88-6.83 (m, 2H), 4.59 (d, *J* = 6.7 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H), 1.94 (quint, *J* = 7.7 Hz, 2H), 1.24 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ=165.8, 153.4, 152.9, 146.2, 143.7, 143.3, 140.8, 137.5, 136.4, 135.5, 135.3, 129.1, 128.7, 127.8, 127.2, 125.1, 123.7, 121.0, 120.3, 119.3, 117.1, 77.5, 66.4, 46.5, 35.5, 34.0, 32.3, 28.5 ppm; HRMS (ESI): *m/z* calcd for C₃₈H₃₇N₂O₅ [M+H]⁺: 601.2697; found: 601.2690.

Preparation of 6-(2-*tert*-butoxyethyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (**1g**)

In a 500 mL round-bottom flask 1.26 g compound **9g** (3.16 mmol) was dissolved in 130 mL 1,4-dioxane and a solution of 332 mg LiOH·H₂O (2.50 equiv., 7.91 mmol) in 63.0 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (2 h), then it was quenched by the addition of 4.74 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 1.33 g NaHCO₃ (5.00 equiv., 15.8 mmol) was added and a solution of 1.23 g FmocCl (1.50 equiv., 4.74 mmol) in 37.8 mL 1,4-dioxane was introduced dropwise during a 60 min period. Stirring at 0°C was continued for 2 h, then the reaction mixture was allowed to reach rt and stirred for further 12 h. The pH of the reaction mixture was adjusted to 4 by adding 50 mL 5% aq citric acid solution. The product was extracted with 200 mL DCM, the organic phase was washed with 50 mL 5% aq citric acid solution and 100 mL brine, then dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-40%) then reversed phase HPLC (EZ Prep system, eluent: 0.1% aq TFA/MeCN, gradient elution: 75-95%) to afford compound **1g** as a pale greenish-white solid (1.30 g, 81%). HPLC-UV purity: 99.8%; ¹H NMR (500 MHz, DMSO-*d*₆): δ=13.53 (s, 1H), 10.46 (s, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 8.39 (br s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 2H), 4.61 (d, *J* = 7.0 Hz, 2H), 4.46 (t, *J* = 6.9 Hz, 1H), 3.60 (t, *J* = 6.7 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 1.09 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ=165.4, 153.5, 144.6, 143.7, 141.5, 140.8, 138.0, 135.6, 135.3, 129.2, 127.8, 127.2, 125.1, 120.7, 120.3, 120.2, 117.9, 72.4, 66.3, 61.6, 46.6, 37.3, 27.3 ppm; HRMS (ESI): *m/z* calcd for C₃₁H₃₁N₂O₅ [M+H]⁺: 511.2227; found: 511.2238.

Preparation of 6-[2-(*tert*-butoxycarbonylamino)ethyl]-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (**1h**)

In a 500 mL round-bottom flask 950 mg compound **9h** (2.15 mmol) was dissolved in 95.0 mL 1,4-dioxane and a solution of 271 mg LiOH·H₂O (3.00 equiv., 6.48 mmol) in 47.5 mL water was added. The reaction mixture was stirred at rt until the hydrolysis was complete (3 h), then it was quenched by the addition of 4.30 mL 1M aq HCl solution. The reaction mixture was cooled to 0°C, 904 mg NaHCO₃ (5.00 equiv., 10.8 mmol) was added and a solution of 835 mg FmocCl (1.50 equiv., 3.23 mmol) in 28.5 mL 1,4-dioxane was introduced dropwise during a 60 min period. Stirring at 0°C was continued for 2 h, then the reaction mixture was allowed to reach rt and stirred for further 12 h. The reaction mixture was diluted with 200 mL water, the pH was adjusted to 4 by adding 50 mL 5% aq citric acid solution. The product was extracted with 200 mL DCM, the organic phase was washed with 50 mL 5% aq citric acid solution and 100 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The crude product was purified by normal phase flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-10%) then reversed phase HPLC (EZ Prep system, eluent: 0.1% aq TFA/MeCN, gradient elution: 55-80%) to afford compound **1h** as a pale yellow solid (850 mg, 71%). HPLC-UV purity: 99.9%; ¹H NMR (500 MHz, DMSO-*d*₆): δ=13.54 (s, 1H), 10.48 (s, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 8.34 (br s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.94

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(d, $J = 7.5$ Hz, 2H), 7.78 (d, $J = 7.5$ Hz, 2H), 7.52 (s, 1H), 7.44 (t, $J = 7.3$ Hz, 2H), 7.37 (td, $J = 7.4$ Hz, $J = 1.1$ Hz, 2H), 6.96 (t, $J = 5.5$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 2H), 4.46 (t, $J = 6.8$ Hz, 1H), 3.23 (q, $J = 6.8$ Hz, 2H), 2.86 (t, $J = 7.1$ Hz, 2H), 1.33 ppm (s, 9H); ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 165.4, 155.5, 153.5, 144.8, 143.7, 141.3, 140.8, 138.0, 135.6, 135.5, 129.3, 127.8, 127.2, 125.2, 120.7, 120.3, 120.0, 117.7, 77.5, 66.4, 46.6, 41.2, 36.4, 28.2$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{32}\text{N}_3\text{O}_6$ $[\text{M}+\text{H}]^+$: 554.2286; found: 554.2288.

Preparation of Methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate (2)

A 100 mL pear-shaped flask fitted with a reflux condenser was filled with 11.0 g compound **7** (33.8 mmol) and 18.9 mL POCl_3 (6.00 equiv., 203 mmol). After stirring the reaction mixture at 100°C for 2 h, it was slowly poured into 500 mL ice-water mixture and stirred mechanically for 30 min. The crude product was filtered, washed with 2x50 mL cold water and dried in vacuo. The crude product was sonicated with 200 mL DCM, then filtered through a short pad of 30 g silicagel (conditioned in DCM), and eluted with 500 mL DCM. The filtrate was concentrated and dried in vacuo to give compound **2** as an orange powder (9.87 g, 85%). ^1H NMR (400 MHz, DMSO- d_6): $\delta = 8.85$ (d, $J = 2.0$ Hz, 1H), 8.67 (d, $J = 2.0$ Hz, 1H), 8.41 (s, 1H), 3.96 ppm (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 163.4, 149.6, 148.8, 142.5, 137.4, 129.4, 128.3, 128.2, 123.6, 122.2, 53.3$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_7\text{BrClN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 344.9272; found: 344.9265.

Preparation of Methyl 6-bromo-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (3)

3.64 g compound **8** (11.5 mmol) and 8.03 mL TEA (5.00 equiv., 57.6 mmol) were dissolved in 345 mL DCM, cooled to 0°C and a mixture of 4.80 mL trifluoroacetic anhydride (3.00 equiv., 34.6 mmol) and 20.0 mL DCM was added in 30 min dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h, then washed with 100 mL water, 100 mL 1M aq HCl solution, 50 mL saturated aq NaHCO_3 solution. The organic phase was dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuo. The residue was recrystallized from 200 mL EtOAc to afford compound **3** as an off-white, crystalline solid (3.99 g, 84%). ^1H NMR (400 MHz, CDCl_3): $\delta = 10.65$ (s, 1H), 8.98 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 4.08 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 163.9, 155.0$ (q, $J = 38.3$ Hz), 146.1, 143.5, 137.0, 133.9, 128.2, 125.3, 123.2, 122.6, 122.3, 115.4 (q, $J = 288.8$ Hz), 53.4 ppm; ^{19}F NMR (376 MHz, CDCl_3): $\delta = -75.8$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_8\text{BrClF}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 410.9353; found: 410.9356.

Preparation of Methyl 4-chloro-8-nitro-6-(2-phenylethynyl)quinoline-2-carboxylate (4a)

A 100 mL pear-shaped flask was filled with 1.40 g compound **2** (4.05 mmol), 23.1 mg CuI (3.00 mol%, 0.12 mmol) and 42.6 mg $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.50 mol%, 0.061 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N_2 , then 80.0 mL dry MeCN and 12.0 mL TEA (21.2 equiv, 86.1 mmol) were added. 620 mg phenylacetylene (1.50 equiv., 6.08 mmol) was dissolved in 7.50 mL dry MeCN and added to the reaction mixture via syringe pump (5.00 mL/h) at 20°C while stirring. (Note: Temperature has a key role in controlling selectivity, thus should be maintained at $20 \pm 3^\circ\text{C}$ for a reasonable yield.) After the addition of phenylacetylene, the reaction mixture was quenched by the addition of 100 mL DCM and washed with 2x80 mL 2M aq HCl solution. The combined aq phase was extracted with 20 mL DCM. The combined organic phase was washed with 40 mL brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, heptane/DCM, gradient elution: 0-100%) to afford compound **4a** as a yellow solid (1.32 g, 89%). ^1H NMR (400 MHz, CDCl_3): $\delta = 8.60$ (d, $J = 1.8$ Hz, 1H), 8.40 (s, 1H), 8.23 (d, $J = 1.7$ Hz, 1H), 7.64-7.59 (m, 2H), 7.45-7.39 (m, 3H), 4.06 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 164.3, 149.7, 148.8, 143.9, 138.9, 132.0, 130.3, 129.7, 128.6, 128.2, 127.9, 124.2, 123.4, 121.6, 95.2, 86.6, 53.6$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{12}\text{ClN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 367.0480; found: 367.0474.

Preparation of Methyl 6-[2-(4-tert-butoxyphenyl)ethynyl]-4-chloro-8-nitro-quinoline-2-carboxylate (4b)

A 250 mL pear-shaped flask was filled with 1.40 g compound **2** (4.05 mmol), 1.20 g compound **12** (1.20 equiv., 4.86 mmol), 23.1 mg CuI (3.00 mol%, 0.12 mmol) and 42.6 mg $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.50 mol%, 0.061 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N_2 , then 80.0 mL dry MeCN, 12.0 mL TEA (21.2 equiv, 86.1 mmol) and finally 590 μL H_2SiF_6 (0.50 equiv., 251 mg in 35 m/m% aq. solution) were added. The reaction mixture was stirred at 25°C for 22 h, then 100 mL DCM was added and the resulting solution washed with 3x100 mL 5% aq citric acid solution. Organic phase was dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, heptane/DCM, gradient elution: 70-100%) to afford compound **4b** as a yellow solid (1.41 g, 80%). ^1H NMR (400 MHz, CDCl_3): $\delta = 8.56$ (d, $J = 1.8$ Hz, 1H), 8.39 (s, 1H), 8.21 (d, $J = 1.8$ Hz, 1H), 7.54-7.48 (m, 2H), 7.05-7.00 (m, 2H), 4.05 (s, 3H), 1.40 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 164.3, 157.2, 149.5, 148.7, 143.8, 138.8, 133.0, 129.9, 128.2, 127.8, 124.5, 123.7, 123.4, 115.8, 95.4, 86.2, 79.6, 53.6, 28.9$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 439.1055; found: 439.1042.

Preparation of Methyl 6-(3-tert-butoxyprop-1-ynyl)-4-chloro-8-nitro-quinoline-2-carboxylate (4c)

A 100 mL pear-shaped flask was filled with 1.50 g compound **2** (4.34 mmol), 24.8 mg CuI (3.00 mol%, 0.13 mmol) and 45.7 mg $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.50 mol%, 0.065 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N_2 , then 87.0 mL dry MeCN, 12.8 mL TEA (21.2 equiv, 92.0 mmol) and 875 μL 2-methyl-2-prop-2-yloxy-propane (1.50 equiv., 6.51 mmol) were added. The reaction mixture was stirred at 40°C for 22 h, then 100 mL DCM was added and the resulting solution was washed with 3x100 mL 5% aq citric acid solution. The organic phase was dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, DCM/MeOH, gradient elution: 0-100%) to afford compound **4c** as an ivory solid (1.30 g, 79%). ^1H NMR (400 MHz, DMSO- d_6): $\delta = 8.60$ (d, $J = 1.7$ Hz, 1H), 8.46 (d, $J = 1.7$ Hz, 1H), 8.40 (s, 1H), 4.41 (s, 2H), 3.96 (s, 3H), 1.23 ppm (s, 9H); ^{13}C NMR (100 MHz, DMSO- d_6): $\delta = 163.4, 149.7, 148.7, 143.1, 137.9, 129.7, 127.4, 126.9, 123.4, 123.1, 93.8, 81.7, 74.2, 53.3, 50.5, 27.3$ ppm; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 377.0899; found: 377.0896.

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Preparation of Methyl 6-[3-(tert-butoxycarbonylamino)prop-1-ynyl]-4-chloro-8-nitro-quinoline-2-carboxylate (4d)

A 500 mL pear-shaped flask was filled with 1.50 g compound **2** (4.34 mmol), 808 mg tert-butyl *N*-prop-2-ynylcarbamate (1.20 equiv., 5.21 mmol), 82.7 mg CuI (10.0 mol%, 0.43 mmol) and 91.4 mg Pd(PPh₃)₂Cl₂ (3.00 mol%, 0.13 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then 21.7 mL dry THF, 4.34 mL DIPA (7.13 equiv, 31.0 mmol) and 434 μL P^tBu₃ (10.0 mol%, 0.43 mmol) were added. The reaction mixture was stirred at 25°C for 4 h, then 50 mL DCM was added and the resulting solution was washed with 2x20 mL 10% aq citric acid solution, 20 mL saturated aq NaHCO₃ solution and brine. The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g column, DCM/MeOH, gradient elution: 0-50%) to afford a brown solid, which was sonicated with 10 mL DIPE, filtered, washed with further 2x5 mL DIPE and dried in vacuo to afford compound **4d** as a beige solid (1.62 g, 89%). ¹H NMR (400 MHz, DMSO-*d*₆): δ=8.56 (d, *J* = 1.7 Hz, 1H), 8.45 (d, *J* = 1.7 Hz, 1H), 8.41 (s, 1H), 7.48 (t, *J* = 5.4 Hz, 1H), 4.10 (d, *J* = 5.6 Hz, 2H), 3.96 (s, 3H), 1.41 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ=163.4, 155.3, 149.7, 148.7, 143.1, 137.9, 129.7, 127.4, 126.9, 123.4, 123.2, 93.3, 79.2, 78.5, 53.3, 30.3, 28.2 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₁₉ClN₃O₆ [M+H]⁺: 420.0957; found: 420.0958.

Preparation of Methyl 4-chloro-8-nitro-6-[(*E*)-3-phenylprop-1-enyl]quinoline-2-carboxylate (4e)

A 100 mL pear-shaped flask was filled with 1.50 g compound **2** (4.34 mmol), 774 mg [(*E*)-3-phenylprop-1-enyl]boronic acid (1.10 equiv., 4.78 mmol), 30.5 mg Pd(AtaPhos)₂Cl₂ (1.00 mol%, 0.04 mmol) and 2.12 g Cs₂CO₃ (1.50 equiv., 6.51 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then 43.4 mL degassed toluene and 4.34 mL water were added. The reaction mixture was stirred at 80°C for 2 h, then 50 mL DCM was added, the organic phase separated, washed with 50 mL water and 50 mL brine. The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was recrystallized from 25 mL MeCN and further purified by flash chromatography (120 g column, heptane/EtOAc, gradient elution: 0-100%) to afford compound **4e** as a pale yellow solid (1.00 g, 60%). ¹H NMR (500 MHz, DMSO-*d*₆): δ=8.81 (d, *J* = 1.8 Hz, 1H), 8.35 (s, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 7.36-7.29 (m, 4H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.99 (td, *J* = 15.7 Hz, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 15.8 Hz, 1H), 3.95 (s, 3H), 3.64 ppm (d, *J* = 6.8 Hz, 2H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ=163.6, 149.1, 148.4, 143.0, 139.2, 138.5, 137.7, 136.3, 128.6, 128.6, 128.3, 127.7, 126.3, 123.6, 123.1, 122.2, 53.2, 38.7 ppm; HRMS (ESI): *m/z* calcd for C₂₀H₁₆ClN₂O₄ [M+H]⁺: 383.0793; found: 383.0798.

Preparation of Methyl 6-[3-(4-tert-butoxyphenyl)propyl]-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (4f)

Preparation of alkylboron-reagent: An oven-dried, 25 mL pear-shaped flask was filled with 1.20 g compound **13** (1.50 equiv., 6.31 mmol), closed with a rubber septum, evacuated and charged with dry N₂. 12.6 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.50 equiv., 6.31 mmol) was introduced at rt and the resulting mixture was stirred for 1 h. This solution was used in the next step. *Suzuki-coupling:* A 500 mL pear-shaped flask was filled with 1.73 g compound **3** (4.20 mmol), 64.3 mg Pd(dppf)Cl₂·CH₂Cl₂ (1.00 mol%, 0.04 mmol) and 2.43 g Cs₂CO₃ (3.00 equiv., 12.6 mmol), closed with a rubber septum, evacuated and charged with dry N₂. Through the septum 173 mL 2-MeTHF and 8.65 mL water and finally the solution of *alkylboron-reagent* were added. The mixture was stirred at 40°C for 3 h. After cooling to rt, the organic phase was separated and washed with 3x50 mL 15% aq NaCl solution, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, heptane/EtOAc, gradient elution: 0-25%) to afford compound **4f** as a white, fluffy solid (1.61 g, 73%). ¹H NMR (500 MHz, DMSO-*d*₆): δ=10.90 (s, 1H), 8.38 (d, *J* = 1.7 Hz, 1H), 8.28 (s, 1H), 7.89 (s, 1H), 7.14-7.10 (m, 2H), 6.89-6.84 (m, 2H), 3.99 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.01 (quint, *J* = 7.6 Hz, 2H), 1.26 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ=163.5, 154.4 (q, *J* = 37.8 Hz), 152.9, 145.6, 145.2, 142.5, 138.1, 136.0, 132.6, 128.5, 126.6, 123.4, 122.9, 121.8, 115.4 (q, *J* = 288.5 Hz), 77.3, 52.9, 35.2, 33.8, 31.9, 28.4 ppm; ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ=-74.5 ppm; HRMS (ESI): *m/z* calcd for C₂₆H₂₇ClF₃N₂O₄ [M+H]⁺: 523.1606; found: 523.1602.

Preparation of Methyl 6-(2-tert-butoxyethyl)-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (4g)

Preparation of alkylboron-reagent: An oven-dried, 50 mL pear-shaped flask was filled with 1.37 mL 2-methyl-2-vinyl-2-propoxypropane (2.00 equiv., 10.5 mmol), closed with a rubber septum, evacuated and charged with dry N₂. 20.9 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (2.00 equiv., 10.5 mmol) was introduced at rt and the resulting mixture was stirred for 30 min. This solution was used in the next step. *Suzuki-coupling:* A 100 mL pear-shaped flask was filled with 2.15 g compound **3** (5.22 mmol), 116 mg Pd(AtaPhos)₂Cl₂ (5.00 mol%, 0.26 mmol) and 3.02 g Cs₂CO₃ (3.00 equiv., 15.7 mmol), closed with a rubber septum, evacuated and charged with dry N₂. Through the septum 5.22 mL water and the *alkylboron-reagent* were added. The mixture was stirred at 40°C for 30 min. After cooling to rt, 50 mL DCM and 25 mL water were added, the organic phase was separated. The aqueous phase was extracted with 2x20 mL DCM, the combined organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, heptane/EtOAc, gradient elution: 0-35%) to afford compound **4g** as a white, crystalline solid (1.50 g, 66%). ¹H NMR (400 MHz, CDCl₃): δ=10.68 (s, 1H), 8.80 (d, *J* = 1.7 Hz, 1H), 8.31 (s, 1H), 7.95 (s, 1H), 4.07 (s, 3H), 3.72 (t, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 1.18 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ=164.3, 154.9 (q, *J* = 37.8 Hz), 145.2, 143.9, 143.4, 137.3, 132.7, 127.2, 122.3, 120.8, 119.4, 115.6 (q, *J* = 288.4 Hz), 73.2, 61.6, 53.2, 38.0, 27.5 ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ=-75.8 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₂₁ClF₃N₂O₄ [M+H]⁺: 433.1136; found: 433.1139.

Preparation of Methyl 6-[2-(tert-butoxycarbonylamino)ethyl]-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (4h)

Preparation of alkylboron-reagent: An oven-dried, 50 mL pear-shaped flask was filled with 995 mg tert-butyl *N*-vinylcarbamate (Prepared from *N*-vinyl formamide according to [4]) (1.30 equiv., 6.95 mmol), closed with a rubber septum, evacuated and charged with

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dry N₂. 21.4 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (2.00 equiv., 10.7 mmol) was introduced at 0°C, then the resulting mixture was allowed to reach rt and stirred for 1 h. This solution was used in the next step. *Suzuki-coupling*: A 500 mL pear-shaped flask was filled with 2.20 g compound **3** (5.35 mmol), 218 mg Pd(dppf)Cl₂·CH₂Cl₂ (5.00 mol%, 0.27 mmol) and 3.09 g Cs₂CO₃ (3.00 equiv., 16.0 mmol), closed with a rubber septum, evacuated and charged with dry N₂. Through the septum 220 mL 2-MeTHF and 5.35 mL water and finally the *alkylboron-reagent* were added. The mixture was stirred at 60°C for 5 h. After cooling to rt, 50 mL brine was added, the organic phase was separated and washed with 50 mL brine, then dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (220 g column, heptane/EtOAc, gradient elution: 0-100%) to afford a brown solid, which was sonicated with 30 mL DIPE, filtered, washed with further 2x10 mL DIPE and dried in vacuo to afford compound **4h** as a beige solid (1.23 g, 48%). ¹H NMR (500 MHz, DMSO-d₆): δ=10.99 (s, 1H), 8.36 (s, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 6.97 (t, *J* = 5.5 Hz, 1H), 3.98 (s, 3H), 3.28 (q, *J* = 6.4 Hz, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 1.31 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=163.7, 155.5, 154.5 (q, *J* = 36.9 Hz), 145.8, 142.9, 142.7, 138.3, 132.7, 126.6, 123.6, 122.0, 119.9, 115.6 (q, *J* = 288.5 Hz), 77.6, 53.1, 40.9, 36.0, 28.1 ppm; ¹⁹F NMR (376 MHz, DMSO-d₆): δ=-74.5 ppm; HRMS (ESI): *m/z* calcd for C₂₀H₂₂ClF₃N₃O₅ [M+H]⁺: 476.1194; found: 476.1188.

Preparation of Methyl 6-bromo-4-hydroxy-8-nitro-quinoline-2-carboxylate (7)

A 2 L, 3 necked round bottom flask fitted with a mechanical overhead stirrer was filled with 800 g polyphosphoric acid and heated to 130°C. During a 15 min period 208 g compound **14** (579 mmol, prepared as described by Schmitt^[2]) was added in portions. The reaction mixture instantly turned dark and a red-orange precipitate was observed. (Note: The reaction is slightly exothermic.) After stirring at 130°C for 3 h, the reaction mixture was slowly poured into 3 L warm water (40°C) in a 5 L beaker and stirred mechanically for 30 min. (Note: No significant heat evolution was observed, but dissolution of PPA was quicker at higher temperature.) The resulting slurry was cooled to 20°C by adding ca. 1.5 kg ice. The mixture was left to sit for 1 h, the supernatant liquid was decanted then the pH of the slurry was set to 7-8 by adding 25% NaOH solution (ca. 1.0 L) while stirring. Ice was added to keep the temperature below 30°C. The crude product was filtered on a G2 frit and washed with 200 mL cold water then dried. The crude product was stirred with 1L MeOH at rt for 1 h, then cooled to 0°C, left to crystallize for 1 h and filtered. Crystals were washed with 100 mL cold MeOH. The solid was stirred with 3.00 L MeOH at reflux temperature for 1 h, then cooled to 0°C, left to crystallize for 1 h and filtered cold. Crystals were washed with 50 mL cold MeOH and dried in vacuo to afford compound **7** as ochre solid (68.0 g, 36%). ¹H NMR (400 MHz, DMSO-d₆): δ=11.61 (br s, 1H), 8.74/7.79 (br s/d, *J* = 1.7 Hz, 1H), 8.56/7.72 (d/d, *J* = 2.2/8.7 Hz, 1H), 7.08/7.48 (br s/dd, *J* = 8.7 Hz, *J* = 1.9 Hz, 1H), 3.97/3.95 ppm (s/s, 3H) (Presence of tautomers!); ¹³C NMR (100 MHz, DMSO-d₆): δ=126.7, 123.0, 118.1, 112.8, 52.8 ppm; HRMS (ESI): *m/z* calcd for C₁₁H₈BrN₂O₅ [M+H]⁺: 326.9611; found: 326.9606.

Preparation of Methyl 8-amino-6-bromo-4-chloro-quinoline-2-carboxylate (8)

A 1 L glass pressure vessel was filled with 3.0 g Raney nickel (3.00 equiv., 35 mmol) under N₂ atmosphere, then washed with 3x50 mL water and 2x20 mL MeOH. 4.05 g compound **2** (11.7 mmol), 500 mL MeOH and 200 mL DCM were added to the vessel, and the atmosphere was changed to H₂ pressurized to 4 bar. The reaction mixture was stirred at rt for 24 h and filtered through a short pad of celite. The filtrate was concentrated in vacuo to afford compound **8** as an orange powder (3.64 g, 98%). ¹H NMR (500 MHz, DMSO-d₆): δ=8.15 (s, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.60 (s, 2H), 3.94 ppm (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆): δ=164.1, 148.5, 143.7, 140.7, 135.6, 128.4, 125.8, 122.1, 112.3, 110.0, 52.9 ppm; HRMS (ESI): *m/z* calcd for C₁₁H₉BrClN₂O₂ [M+H]⁺: 314.9530; found: 314.9538.

Preparation of Methyl 8-amino-6-phenethyl-quinoline-2-carboxylate (9a)

A 250 mL pear-shaped flask was filled with 1.18 g compound **4a** (3.20 mmol), and 256 mg Pd/C (10 m/m%, 7.50 mol%, 0.24 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 2.02 g NH₄HCOO (10 equiv., 32.0 mmol) in 125 mL dry MeOH was added. The reaction mixture was stirred for 2 h at rt, then at 50°C for 20 h. The catalyst was filtered off, washed with MeOH and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 50 mL DCM and washed with 2x25 mL water. The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g column, heptane/EtOAc, isocratic elution: 40%) to afford compound **9a** as a yellow powder (855 mg, 87%). ¹H NMR (400 MHz, DMSO-d₆): δ=8.24 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.28-7.23 (m, 4H), 7.20-7.15 (m, 1H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 6.02 (s, 2H), 3.93 (s, 3H), 2.95 ppm (s, 4H); ¹³C NMR (100 MHz, DMSO-d₆): δ=165.4, 145.8, 144.0, 143.2, 141.4, 136.5, 135.5, 129.7, 128.3, 128.3, 125.9, 120.9, 112.3, 110.3, 52.4, 37.7, 36.6 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₁₉N₂O₂ [M+H]⁺: 307.1441; found: 307.1443.

Preparation of Methyl 8-amino-6-[2-(4-tert-butoxyphenyl)ethyl]quinoline-2-carboxylate (9b)

A 250 mL pear-shaped flask was filled with 1.40 g compound **4b** (3.16 mmol), and 280 mg Pd/C (10 m/m%, 8.33 mol%, 0.26 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 1.99 g NH₄HCOO (10 equiv., 31.6 mmol) in 140 mL dry MeOH was added. The reaction mixture was stirred for 30 min at rt, then at 50°C for 30 h. The catalyst was filtered off, washed with MeOH and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 50 mL DCM and washed with 2x25 mL water. The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (220 g column, heptane/EtOAc, isocratic elution: 30%) to afford compound **9b** as a yellow powder (708 mg, 59%). ¹H NMR (400 MHz, DMSO-d₆): δ=8.23 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.18-7.12 (m, 2H), 6.96 (d, *J* = 1.7 Hz, 1H), 6.89-6.84 (m, 3H), 6.02 (s, 2H), 3.93 (s, 3H), 2.91 (m, 4H), 1.25 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆): δ=165.4, 153.0, 145.8, 144.1, 143.2, 136.5, 136.1, 135.5, 129.7, 128.8, 123.7, 120.9, 112.3, 110.3, 77.5, 52.4, 37.9, 36.0, 28.5 ppm; HRMS (ESI): *m/z* calcd for C₂₃H₂₇N₂O₃ [M+H]⁺: 379.2016; found: 379.2015.

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Preparation of Methyl 8-amino-6-(3-tert-butoxypropyl)quinoline-2-carboxylate (9c)

A 500 mL pear-shaped flask was filled with 1.19 g compound **4c** (3.15 mmol), and 240 mg Pd/C (10 m/m%, 7.15 mol%, 0.23 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 94.7 mg AcOH (0.50 equiv., 1.58 mmol) in 120 mL dry MeOH was added. The reaction mixture was stirred under 1 atm. H₂ at rt for 2 h. The catalyst was filtered off, washed with MeOH and the filtrate was treated with 6N NH₃ in MeOH then concentrated to dryness in vacuo. The residue was purified by flash chromatography (80 g column, heptane/EtOAc, gradient elution: 25-30%) to afford compound **9c** as an orange honey (518 mg 52%). ¹H NMR (400 MHz, DMSO-d₆): δ=8.24 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 1.6 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.01 (s, 2H), 3.93 (s, 3H), 3.32 (t, *J* = 6.3 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.84-1.74 (m, 2H), 1.13 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆): δ=165.4, 145.8, 144.5, 143.1, 136.4, 135.5, 129.8, 120.9, 112.2, 110.3, 72.0, 60.0, 52.4, 32.5, 31.5, 27.4 ppm; HRMS (ESI): *m/z* calcd for C₁₈H₂₅N₂O₃ [M+H]⁺: 317.1860; found: 317.1864.

Preparation of Methyl 8-amino-6-[3-(tert-butoxycarbonylamino)propyl]quinoline-2-carboxylate (9d)

A 500 mL pear-shaped flask was filled with 1.50 g compound **4d** (3.57 mmol), 150 mg Pd/C (10 m/m%, 4.0 mol%, 0.14 mmol) and 75.0 mg Pd(OH)₂/C (20 m/m%, 3.0 mol%, 0.11 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 2.25 g NH₄HCOO (10 equiv., 35.7 mmol) in 150 mL dry MeOH was added. The reaction mixture was stirred under 1 atm. H₂ at rt for 90 min. The catalyst was filtered off, washed with MeOH and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 40 mL DCM and washed with 2x40 mL water. The organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g column, heptane/EtOAc, gradient elution: 0-50%) to afford compound **9d** as a yellow powder (1.09 g 85%). ¹H NMR (500 MHz, DMSO-d₆): δ=8.23 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.90 (t, *J* = 5.5 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.02 (s, 2H), 3.93 (s, 3H), 2.97 (q, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.73 (quint, *J* = 7.4 Hz, 2H), 1.37 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=165.4, 155.6, 145.8, 144.4, 143.1, 136.4, 135.5, 129.8, 120.9, 112.2, 110.2, 77.4, 52.4, 39.7, 33.2, 30.9, 28.3 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₂₆N₃O₄ [M+H]⁺: 360.1918; found: 360.1914.

Preparation of Methyl 8-amino-6-(3-phenylpropyl)quinoline-2-carboxylate (9e)

A 500 mL pear-shaped flask was filled with 1.08 g compound **4e** (2.82 mmol), and 108 mg Pd/C (10 m/m%, 3.60 mol%, 0.10 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 1.78 g NH₄HCOO (10 equiv., 28.2 mmol) in 110 mL dry MeOH was added. The reaction mixture was stirred under 1 atm. H₂ at rt for 30 min. The catalyst was filtered off, washed with MeOH and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in 40 mL DCM and washed with 2x40 mL water, the organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (120 g column, heptane/EtOAc, gradient elution: 0-45%) to afford compound **9e** as a yellow powder (765 mg, 85%). ¹H NMR (500 MHz, DMSO-d₆): δ=8.26 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.31-7.20 (m, 4H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.01 (s, 2H), 3.93 (s, 3H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.95 ppm (quint, *J* = 7.7 Hz, 2H); ¹³C NMR (125 MHz, DMSO-d₆): δ=165.4, 145.9, 144.5, 143.2, 141.9, 136.5, 135.5, 129.8, 128.3, 128.3, 125.7, 120.9, 112.2, 110.2, 52.4, 35.3, 34.8, 32.3 ppm; HRMS (ESI): *m/z* calcd for C₂₀H₂₁N₂O₂ [M+H]⁺: 321.1598; found: 321.1592.

Preparation of Methyl 6-[3-(4-tert-butoxyphenyl)propyl]-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (9f)

A 500 mL pear-shaped flask was filled with 1.54 g compound **4f** (2.94 mmol), and 160 mg Pd/C (10 m/m%, 5.12 mol%, 0.15 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 1.85 g NH₄HCOO (10 equiv., 29.4 mmol) in 160 mL dry MeOH was added. The reaction mixture was stirred under 1 atm. H₂ at rt for 2 h. The catalyst was filtered off, washed with MeOH and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in 50 mL DCM and washed with 2x50 mL water, the organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (40 g column, heptane/EtOAc, gradient elution: 0-35%) to afford compound **9f** as a white solid (1.14 g, 80%). ¹H NMR (500 MHz, DMSO-d₆): δ=10.95 (s, 1H), 8.58 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 1.7 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 1.5 Hz, 1H), 7.14-7.10 (m, 2H), 6.89-6.84 (m, 2H), 3.97 (s, 3H), 2.86 (t, *J* = 7.7 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.99 (quint, *J* = 7.7 Hz, 2H), 1.25 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=164.7, 154.4 (q, *J* = 37.0 Hz), 152.9, 145.9, 143.4, 137.8, 137.4, 136.4, 132.1, 129.1, 128.7, 123.7, 123.3, 122.3, 122.0, 115.6 (q, *J* = 288.5 Hz), 77.5, 52.9, 35.1, 34.0, 32.2, 28.5 ppm; ¹⁹F NMR (376 MHz, DMSO-d₆): δ=-74.5 ppm; HRMS (ESI): *m/z* calcd for C₂₆H₂₆F₃N₂O₄ [M+H]⁺: 489.1996; found: 489.1984.

Preparation of Methyl 6-(2-tert-butoxyethyl)-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (9g)

A 500 mL pear-shaped flask was filled with 1.50 g compound **4g** (3.47 mmol), and 150 mg Pd/C (10 m/m%, 4.07 mol%, 0.14 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 2.19 g NH₄HCOO (10 equiv., 34.7 mmol) in 150 mL dry MeOH was added. The reaction mixture was stirred under 1 atm. H₂ at rt for 1 h. The catalyst was filtered off, washed with MeOH and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in 25 mL DCM and washed with 2x25 mL water, the organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (40 g column, heptane/EtOAc, gradient elution: 0-40%) to afford compound **9g** as an off-white solid (1.25 g, 90%). ¹H NMR (500 MHz, DMSO-d₆): δ=10.94 (s, 1H), 8.58 (d, *J* = 8.6 Hz, 1H), 8.38 (d, *J* = 1.7 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.98 (t, *J* = 6.6 Hz, 2H), 1.11 ppm (s, 9H); ¹³C NMR (125 MHz, DMSO-d₆): δ=164.7, 154.4 (q, *J* = 37.1 Hz), 146.0, 141.3, 137.8, 137.5, 131.8, 128.9, 124.2, 122.8, 121.9, 115.7 (q, *J* = 288.6 Hz), 72.5, 61.4, 52.9, 36.8, 27.3 ppm; ¹⁹F NMR (376 MHz, DMSO-d₆): δ=-74.5 ppm; HRMS (ESI): *m/z* calcd for C₁₉H₂₂F₃N₂O₄ [M+H]⁺: 399.1526; found: 399.1524.

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Preparation of Methyl 6-[2-(tert-butoxycarbonylamino)ethyl]-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (9h)

A 500 mL pear-shaped flask was filled with 1.21 g compound **4h** (2.55 mmol), and 125 mg Pd/C (10 m/m%, 4.61 mol%, 0.12 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then a solution of 1.61 g NH₄HCOO (10 equiv., 25.5 mmol) in 125 mL dry MeOH and 62.5 mL DCM were added. The reaction mixture was stirred under 1 atm. H₂ at rt for 2 h. The catalyst was filtered off, washed with MeOH and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in 50 mL DCM and washed with 2x50 mL water, the organic phase was dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g column, DCM/MeOH, gradient elution: 0-10%) to afford compound **9h** as a pale yellow solid (1.04 g, 92%). ¹H NMR (500 MHz, DMSO-d₆): δ=10.97 (s, 1H), 8.59 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 1.3 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 6.99 (t, *J* = 5.6 Hz, 1H), 3.97 (s, 3H), 3.27 (q, *J* = 6.7 Hz, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 1.33 ppm (s, 9H); ¹³C NMR (100 MHz, DMSO-d₆): δ=164.7, 155.5, 154.3 (q, *J* = 36.9 Hz), 145.9, 141.0, 137.9, 137.4, 132.0, 129.0, 123.9, 122.3, 122.0, 115.6 (q, *J* = 288.5 Hz), 77.6, 52.9, 41.0, 35.9, 28.2 ppm; ¹⁹F NMR (376 MHz, DMSO-d₆): δ=-74.6 ppm; HRMS (ESI): *m/z* calcd for C₂₀H₂₃F₃N₃O₅ [M+H]⁺: 442.1584; found: 442.1583.

Preparation of 1-tert-butoxy-4-iodo-benzene (11)

To a stirred solution of 6.50 g 4-iodophenol (29.5 mmol) (**10**) in 40.0 mL DCM, 1.30 g Mg(ClO₄)₂ (0.20 equiv., 5.90 mmol) was added. The flask was fitted with a dropping funnel and a gas bubbler and a solution of 13.0 g (Boc)₂O (2.00 equiv., 59.0 mmol) in 5.00 mL DCM was added dropwise while stirring at rt for 1.5 h. The reaction mixture was stirred for further 30 min, until the bubbling ceased. The reaction mixture was washed with 2x50 mL H₂O, 2x30 mL 2M aq NaOH solution, then dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to afford compound **11** as a colorless oil (5.05 g, 61%). ¹H NMR (400 MHz, DMSO-d₆): δ=7.63-7.58 (m, 2H), 6.83-6.79 (m, 2H), 1.28 ppm (s, 9H). ¹H-NMR spectrum was consistent with previous report.^[5] ¹³C NMR (100 MHz, DMSO-d₆): δ=150.0, 137.7, 126.2, 87.0, 78.5, 28.4 ppm; HRMS (EI): *m/z* calcd for C₁₀H₁₂O [M]⁺: 276.0011; found: 275.9997. GC-TOF

Preparation of 2-(4-tert-butoxyphenyl)ethynyl-trimethyl-silane (12)

A 50 mL pear-shaped flask was filled with 1.45 g compound **11** (5.25 mmol), 20.0 mg CuI (2.00 mol%, 0.11 mmol) and 29.8 mg Pd(dppf)Cl₂·DCM (1.00 mol%, 0.05 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then 30.0 mL 2-MeTHF and 1.83 mL DIPEA (2.00 equiv., 10.5 mmol) and finally 0.89 mL ethynyl(trimethyl)silane (1.20 equiv., 6.30 mmol) were added while stirring. The reaction mixture was stirred at rt for 2 h, then it was washed with 2x25 mL water, 2x25 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (40 g column, heptane/EtOAc, isocratic elution: 10%) to afford compound **12** as a colorless oil (1.21 g, 93%). ¹H NMR (400 MHz, DMSO-d₆): δ=7.38-7.34 (m, 2H), 6.97-6.93 (m, 2H), 1.30 (s, 9H), 0.21 ppm (s, 9H). ¹H-NMR spectrum was consistent with previous report.^[6] ¹³C NMR (100 MHz, DMSO-d₆): δ=155.9, 132.6, 123.3, 116.4, 105.2, 93.1, 78.8, 28.5, 0.0 ppm; HRMS (EI): *m/z* calcd for C₁₅H₂₂OSi [M]⁺: 246.1440; found: 246.1436. GC-TOF

Preparation of 1-allyl-4-tert-butoxy-benzene (13)

A 100 mL pear-shaped flask was filled with 4.14 g compound **11** (15.0 mmol) and 42.6 mg Pd(dppf)Cl₂·DCM (0.50 mol%, 0.08 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N₂, then 30.0 mL THF and 4.22 mL 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 equiv., 22.5 mmol) were added. The reaction mixture was stirred at 60°C while a solution of 2.40 g NaOH (4.00 equiv, 60.0 mmol) in 30.0 mL water was added dropwise in 30 min. After 1 h stirring, further 4.22 mL 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 equiv., 22.5 mmol) was added and the stirring continued for 1 h. The mixture was cooled to rt, the organic phase separated, washed with 20 mL 2M aq NaOH solution, 20 mL brine, dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g column, heptane/EtOAc, gradient elution: 0-10%) to afford compound **13** as a colorless oil (2.62 g, 92%). ¹H NMR (400 MHz, DMSO-d₆): δ=7.10-7.05 (m, 2H), 6.91-6.86 (m, 2H), 5.94 (ddt, *J* = 16.9 Hz, *J* = 10.1 Hz, *J* = 6.8 Hz, 1H), 5.10-4.99 (m, 2H), 3.31 (d, *J* = 6.8 Hz, 2H), 1.26 ppm (s, 9H). ¹H-NMR spectrum was consistent with previous report.^[7] ¹³C NMR (100 MHz, DMSO-d₆): δ=153.1, 137.8, 134.4, 128.9, 123.8, 115.6, 77.6, 38.8, 28.5 ppm; HRMS (EI): *m/z* calcd for C₁₃H₁₈O [M]⁺: 190.1358; found: 190.1348. GC-TOF

4.3. Oligomer synthesis

The Solid Phase Synthesis of the amine common precursor of oligomers **5** and **6** was carried out on a 22.0 μmol scale using reported methods (see above).^[8]

N-Terminal acetylation to give oligomer 5

The reaction was performed on a 7.00 μmol scale, as reported before.^[9] After Fmoc removal, the resin was swollen in THF (1.00 mL/50.0 mg resin). 7.32 μL DIEA (6.00 equiv., 42.0 μmol) was added. Acetyl chloride 1.50 μL (3.00 equiv., 21.0 μmol) was dissolved in dry THF and added to the resin. The solution was treated with microwaves (50 W, 60 °C, 15 min) and the process was repeated once. The resin was then washed thoroughly with DMF, CH₂Cl₂ and CH₂Cl₂/MeOH, 1:1, then dried and desiccated under vacuum.

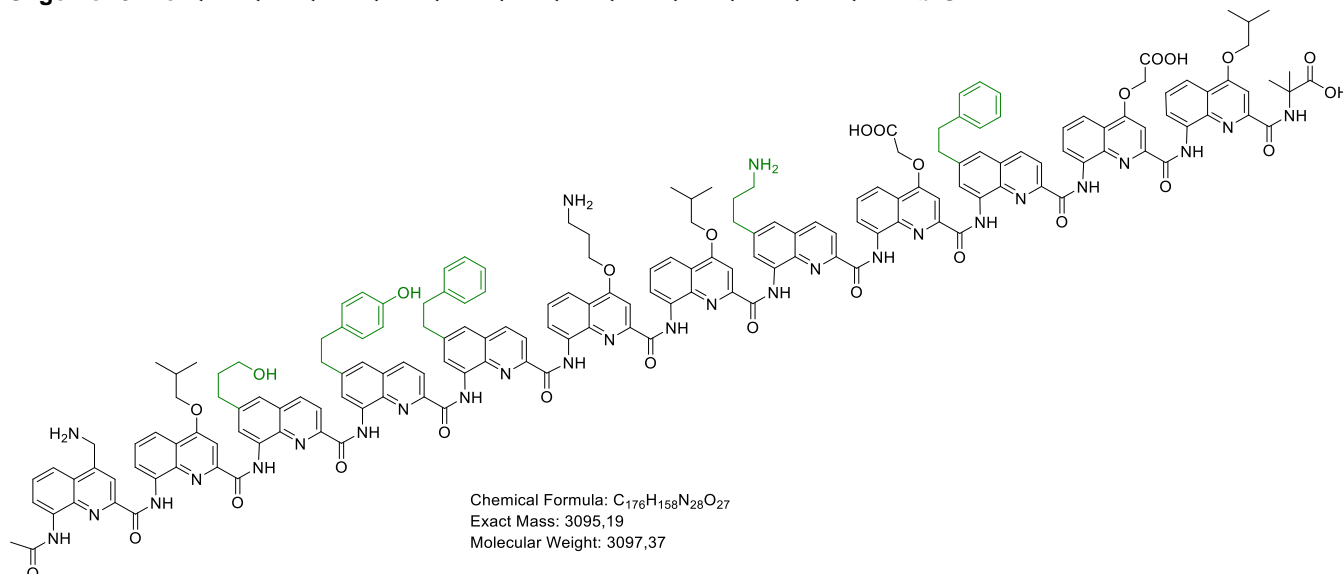
N-Terminal acylation to give oligomer 6

The reaction was carried out on a 7.00 μmol scale. After Fmoc removal, the resin was swollen in dry THF (1.00 mL/50.0 mg resin) to which 8.04 μL 2,4,6-Collidine (8.70 equiv., 60.9 μmol) was added. 2.15 μL 2-[2-(2-Methoxyethoxy)ethoxy]acetic acid (2.00 equiv., 14.0

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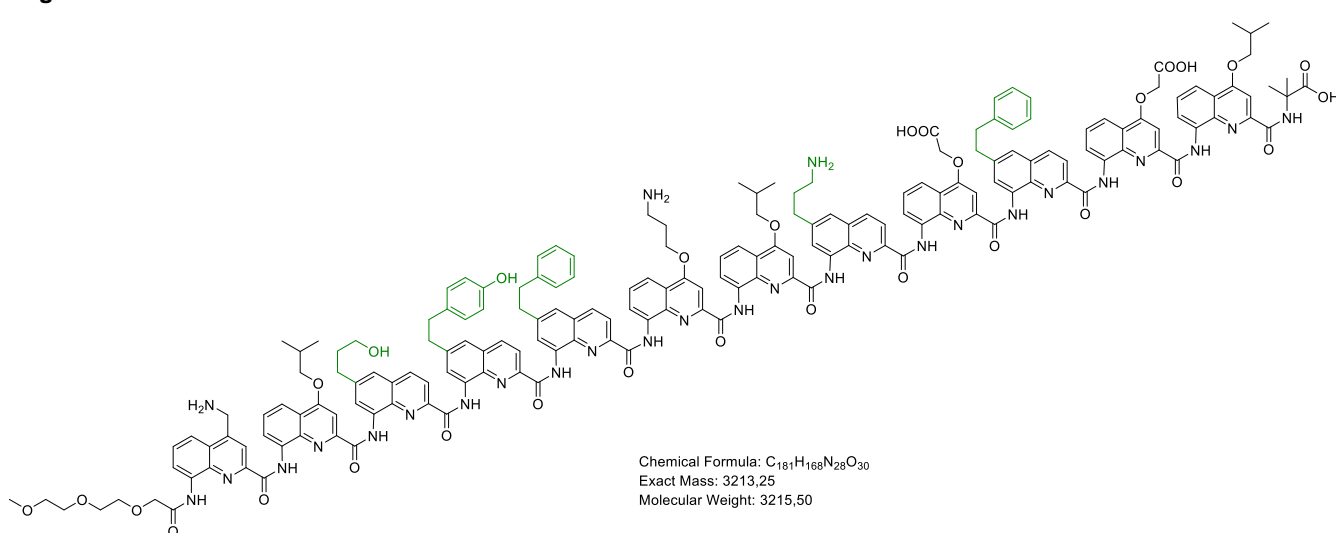
μmol) and 20.2 mg PPh_3 (11.0 equiv., 77.0 μmol) were dissolved in 1.00 mL dry THF followed by the addition of 6.11 μL trichloroacetonitrile (TCAN, 8.70 equiv., 60.9 μmol) and the solution was quickly transferred to the resin. The solution was treated with microwaves (50 W, 50 $^\circ\text{C}$, 15 min), the resin was filtered off and washed with dry THF and dry DMF. The process was repeated once. The resin was then washed thoroughly with DMF, CH_2Cl_2 and $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 1:1, then dried and desiccated under vacuum.

Oligomer 5: Ac-Q^{Dap}-Q^{Leu}-Q^{6Hpr}-Q^{6Tyr}-Q^{6Phe}-Q^{Orn}-Q^{Leu}-Q^{6Apr}-Q^{Asp}-Q^{6Phe}-Q^{Asp}-Q^{Leu}-Aib-OH



Crude compound was obtained in 66% purity. The compound was purified through HPLC purification; Gradient: 5-100% Solvent B in solvent A in 22.9 min ($t_r = 14.0$ min). Purified Yield = 40%. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 13.76$ -13.16 (br s, 1H, COOH), 12.01-11.88 (br s, 1H, OH), 11.01 (s, 1H, NH^α), 10.81 (s, 2H, 2 x NH^α), 10.69 (s, 1H, NH^α), 10.54 (s, 1H, NH^α), 10.44 (s, 1H, NH^α), 10.32 (s, 1H, NH^α), 10.29-10.21 (br s, 1H, OH), 10.07 (s, 1H, NH^α), 9.94 (s, 1H, NH^α), 9.81 (s, 1H, NH^α), 9.40 (s, 1H, NH^α), 8.52 (s, 1H, NH^α), 8.46-6.83 (m, 59H), 6.66 (s, 1H), 6.47-6.20 (m, 6H), 5.95 (s, 1H), 5.89 (s, 1H), 5.79 (s, 1H), 4.91-4.50 (m, 6H), 4.21-0.76 ppm (m, 66H). HRMS (ESI⁻): m/z calcd for $\text{C}_{176}\text{H}_{156}\text{N}_{28}\text{O}_{27}$ [$\text{M}-2\text{H}$]²⁻: 1546.5853 found 1546.5898.

Oligomer 6: X-Q^{Dap}-Q^{Leu}-Q^{6Hpr}-Q^{6Tyr}-Q^{6Phe}-Q^{Orn}-Q^{Leu}-Q^{6Apr}-Q^{Asp}-Q^{6Phe}-Q^{Asp}-Q^{Leu}-Aib-OH



Crude compound was obtained in 94% purity. The compound was purified through HPLC purification; Gradient: 5-100% Solvent B in solvent A in 22.9 min ($t_r = 13.6$ min). Purified Yield = 60%. ^1H NMR (300 MHz, DMSO-d_6): $\delta = 13.84$ -13.16 (br s, 1H, COOH), 12.07-11.88 (br s, 1H, OH), 10.90 (s, 1H, NH^α), 10.89-10.77 (br s, 1H, OH), 10.76 (s, H, NH^α), 10.69 (s, H, NH^α), 10.52 (s, 1H, NH^α), 10.44 (s, 1H, NH^α), 10.31 (s, 1H, NH^α), 10.26 (s, 1H, NH^α), 10.08 (s, 1H, NH^α), 9.94 (s, 1H, NH^α), 9.81 (s, 1H, NH^α), 9.39 (s, 1H, NH^α), 9.18 (s, 1H, NH^α), 8.48-6.84 (m, 59H), 6.65 (s, 1H), 6.49-6.20 (m, 6H), 5.94 (s, 1H), 5.89 (s, 1H), 5.80 (s, 1H), 4.92-4.48 (m, 6H), 4.22-0.77 ppm (m, 76H). HRMS (ESI⁻): m/z calcd for $\text{C}_{181}\text{H}_{166}\text{N}_{28}\text{O}_{30}$ [$\text{M}-2\text{H}$]²⁻: 1605.6168 found 1605.6233.

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5. X-ray crystallography of oligomer 6

Oligomer **6** was dissolved in a water and acetonitrile (50:50) mixture to a concentration of 1 mM. X-ray quality crystals were obtained by the hanging drop vapor diffusion method at 293 K. The drop was set up using a 1 μ L solution of oligomer **6** and 2 μ L of crystallization reagent 35% vol/vol 2-methyl-2,4-pentanediol, 100 mM TRIS buffer (pH 7.0) and 200 mM sodium chloride; equilibrated against 400 μ L of crystallization reagent in reservoir. A single crystal was fished from the drop using a MiTeGen microloop and flash-cooled directly into liquid nitrogen. Synchrotron data was collected at beamline P13^[10] operated by EMBL Hamburg, at the Petra III storage ring (DESY, Hamburg, Germany) using 0.827 Å wavelength. During data collection, the crystal was cooled to 100(2) K. To achieve maximum completeness of the data, rotation passes of 360° were measured at two different regions of same crystal using a mini-kappa goniostat. The crystal was exposed for 0.04s and 0.1° oscillation per frame. Data were processed with CrysAlis PRO^[11] software. Structure was solved with the ShelXT^[12] structure solution program using Intrinsic Phasing and using Olex2^[13] was refined with the ShelXL^[12] refinement package using Least Squares minimization. Only non-H atoms of the backbones were refined with anisotropic displacement parameters. No H-atoms were introduced to the refinement, nor were some atoms of side chains localized. Missing atoms were taken into account in SFAC and UNIT calculation. DFIX, AFIX, FLAT, EADP and DELU instructions were employed to model geometry of the molecules and temperature parameters.

The SQUEEZE procedure from the Platon Suite was introduced to remove unmodeled electron density from the channels formed between foldamer molecules. For search and analysis of solvent accessible voids in the structures default parameters were used: grid 0.20 Å, probe radius 1.2 Å and NStep 6. Calculated total potential solvent accessible void volumes and electron counts per unit cell were 7808 Å³ and 1570.

The final cif file was checked using IUCR's checkcif algorithm. Due to the characteristics of the crystals, i.e. large volume fractions of disordered solvent molecules, weak diffraction intensity, incompleteness of the data and moderate resolution, a number of A - level and B - level alerts remain in the check cif file. These alerts are inherent to the data and refinement procedures and do not reflect errors. Rather, they illustrate the limited practicality of the checkcif tool for medium size molecule crystallography. They are explicitly listed below and have been divided into two groups. The first group illustrates weak quality of the data and refinement statistics if compared to that expected for small molecule structures from highly diffracting crystals. The second group is connected to decisions made during refinement and explained below.

Group 1 alerts:

THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less than 0.550

Calculated sin(theta_max)/wavelength = 0.5000.

PLAT023_ALERT_3_A Resolution (too) Low [sin(theta)/Lambda < 0.6].. 0.50 Ang-1

PLAT082_ALERT_2_A High R1 Value 0.34 Report

PLAT084_ALERT_3_A High wR2 Value (i.e. > 0.25) 0.71 Report

PLAT934_ALERT_3_A Number of (lobs-lcalc)/Sigma(W) > 10 Outliers .. 67 Check

PLAT340_ALERT_3_B Low Bond Precision on C-C Bonds 0.01353 Ang.

PLAT910_ALERT_3_B Missing # of FCF Reflection(s) Below Theta(Min). 11 Note

PLAT241_ALERT_2_A High 'MainMol' Ueq as Compared to Neighbors of

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of

Group 2 alerts:

PLAT201_ALERT_2_A Isotropic non-H Atoms in Main Residue(s)

PLAT202_ALERT_3_A Isotropic non-H Atoms in Anion/Solvent

As mentioned above not all atoms were refined with ADP.

PLAT097_ALERT_2_B Large Reported Max. (Positive) Residual Density 1.00 eA-3

High electron density was observed in the proximity of dummy O atom and was not introduced to the refinement.

PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?)

Dummy O atoms were introduced into refinement.

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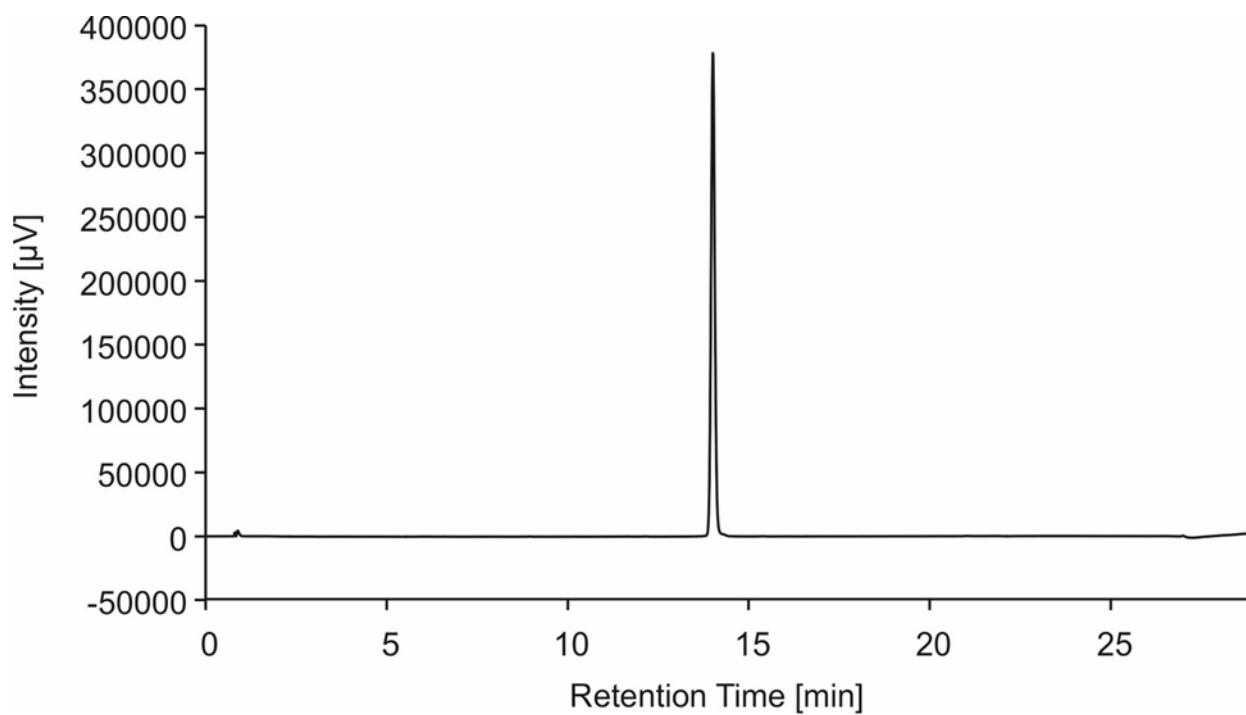
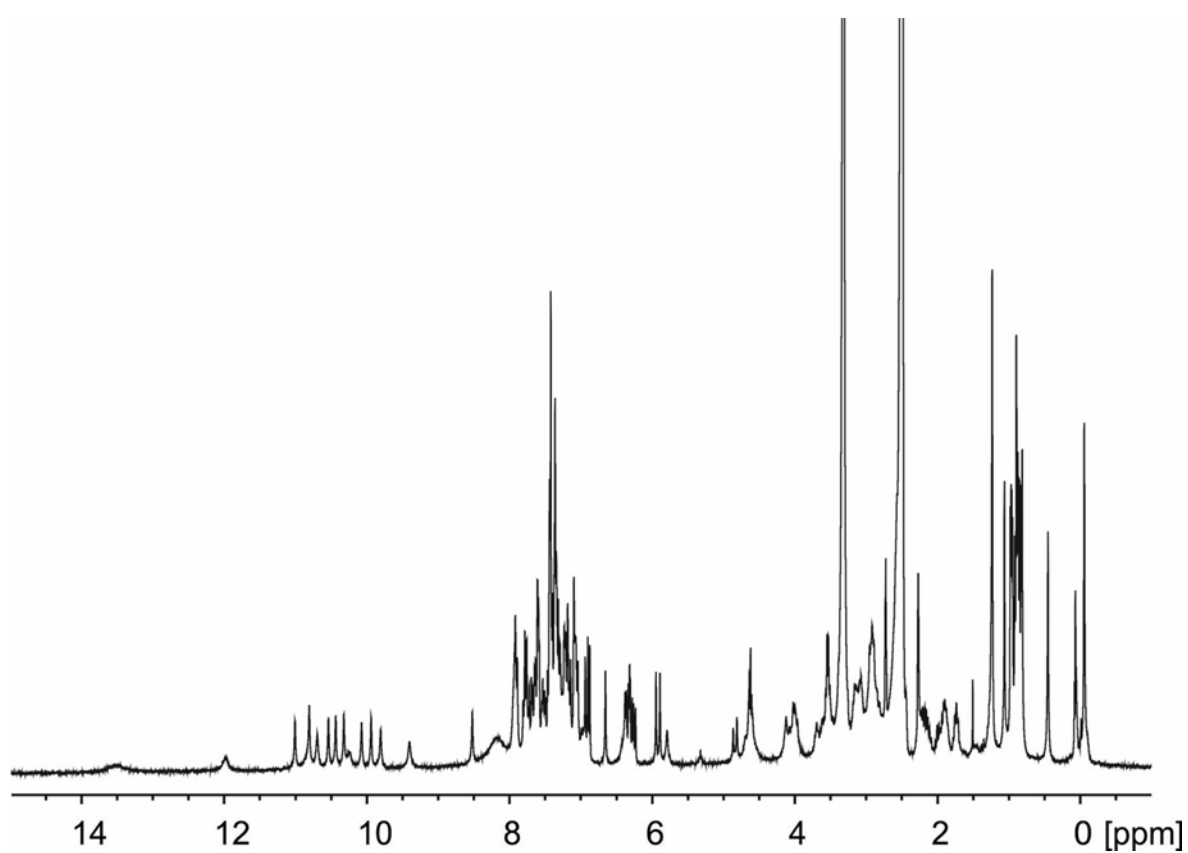
Table S1. Crystal data and refinement details for oligomer **6**.

Identification code	6
Chemical formula	$C_{181}H_{168}N_{28}O_{30} \cdot O_{10}^{[a]}$
Formula weight	3375.42
Temperature	100(2)
Wavelength	0.827 Å
Crystal system	Triclinic
Space group	<i>P</i> -1
Unit cell dimensions	$a=24.3711$ (4), $\alpha=90.869$ (1) $b=29.8647$ (5), $\beta=109.130$ (2) $c=30.6603$ (5), $\gamma=92.469$ (1)
Volume	21054 (1)
Z	4
Density (calculated)	1.065
Absorption coefficient	1.11
Absorption correction	Multi-scan
Crystal size	0.10 × 0.06 × 0.02
Index ranges	$h = -24 \rightarrow 24$, $k = -29 \rightarrow 29$, $l = -30 \rightarrow 30$
Completeness to theta = 24.22°	97.3
Reflections collected	172651
Reflections observed [$I > 2\sigma(I)$]	21626
R_{int}	0.062
Data/parameters/restraints	42903/2250/329
Goodness-of-fit on F^2	2.36
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.2707$, $wR2 = 0.6074$
R indices (all data)	$R1 = 0.3046$, $wR2 = 0.6491$
Largest diff. peak and hole	0.94, -0.41
CCDC #	2014258

[a] Unrecognized electron density near foldamer core was introduced to the refinement as a dummy oxygen atoms.

SUPPORTING INFORMATION

6. NMR spectra and chromatograms



SUPPORTING INFORMATION

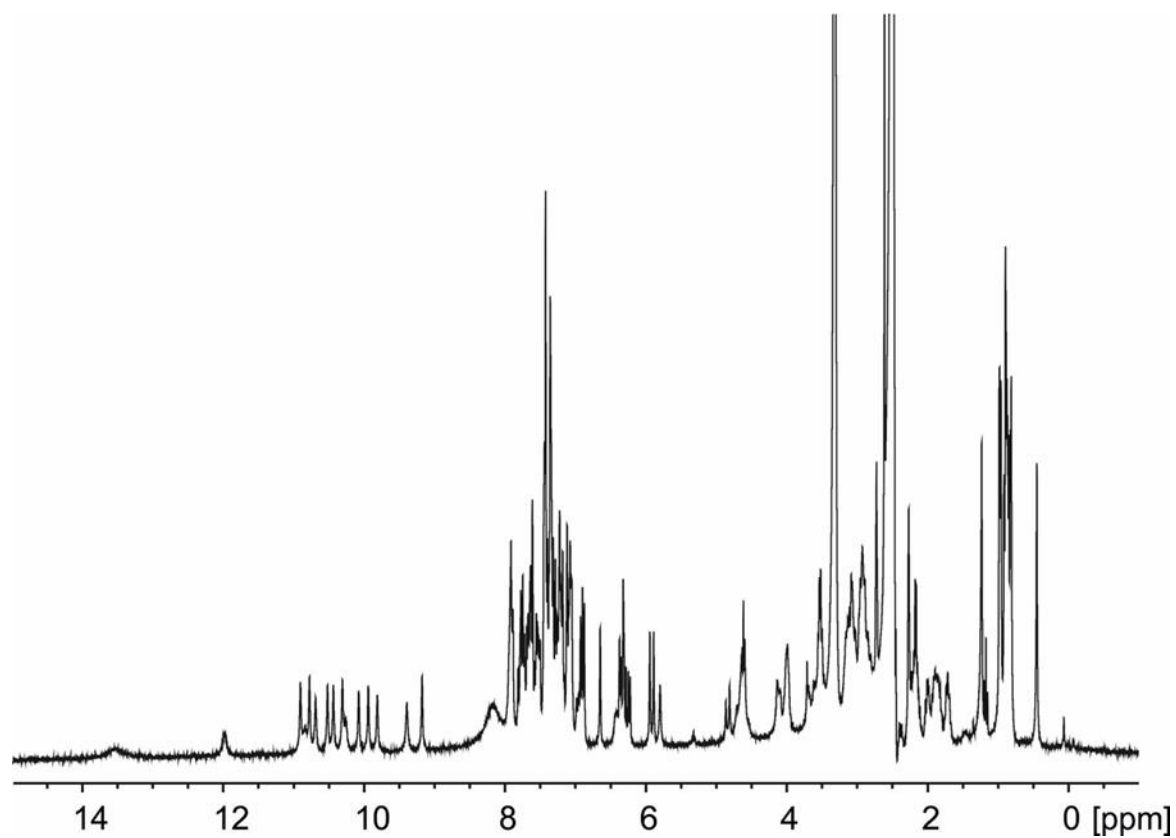


Figure S9. ^1H NMR (300 MHz, DMSO-d_6) of oligomer 6.

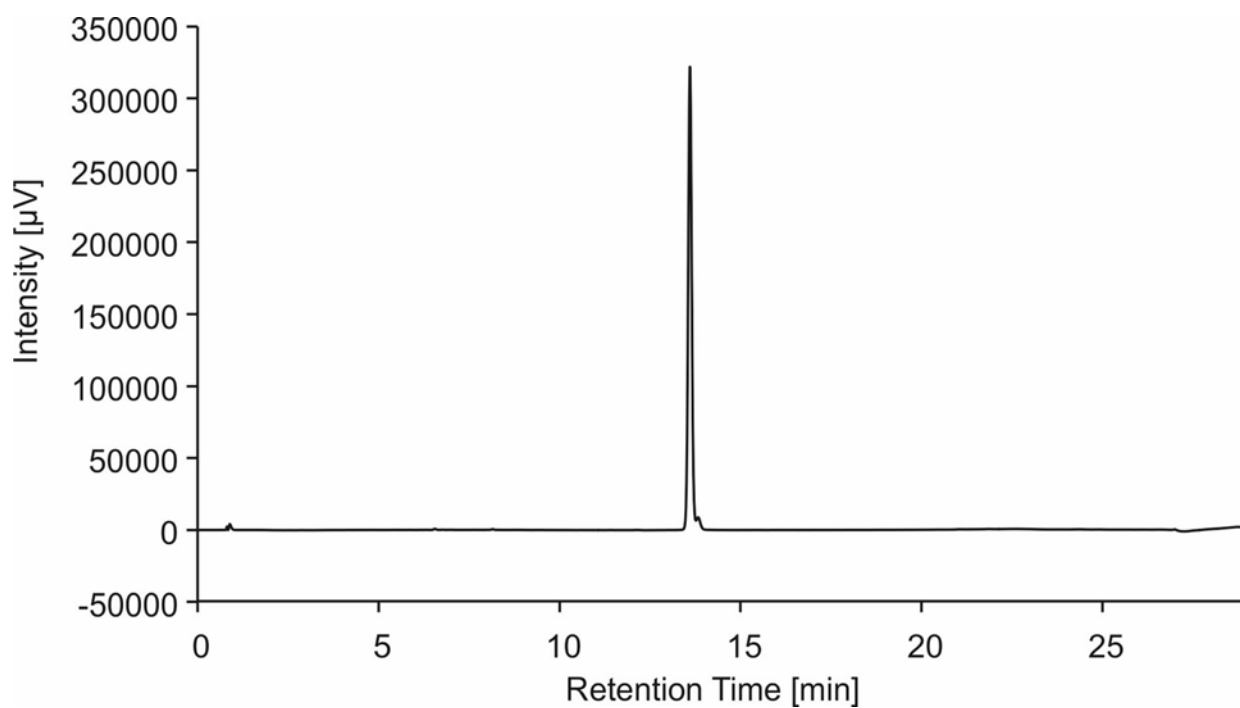
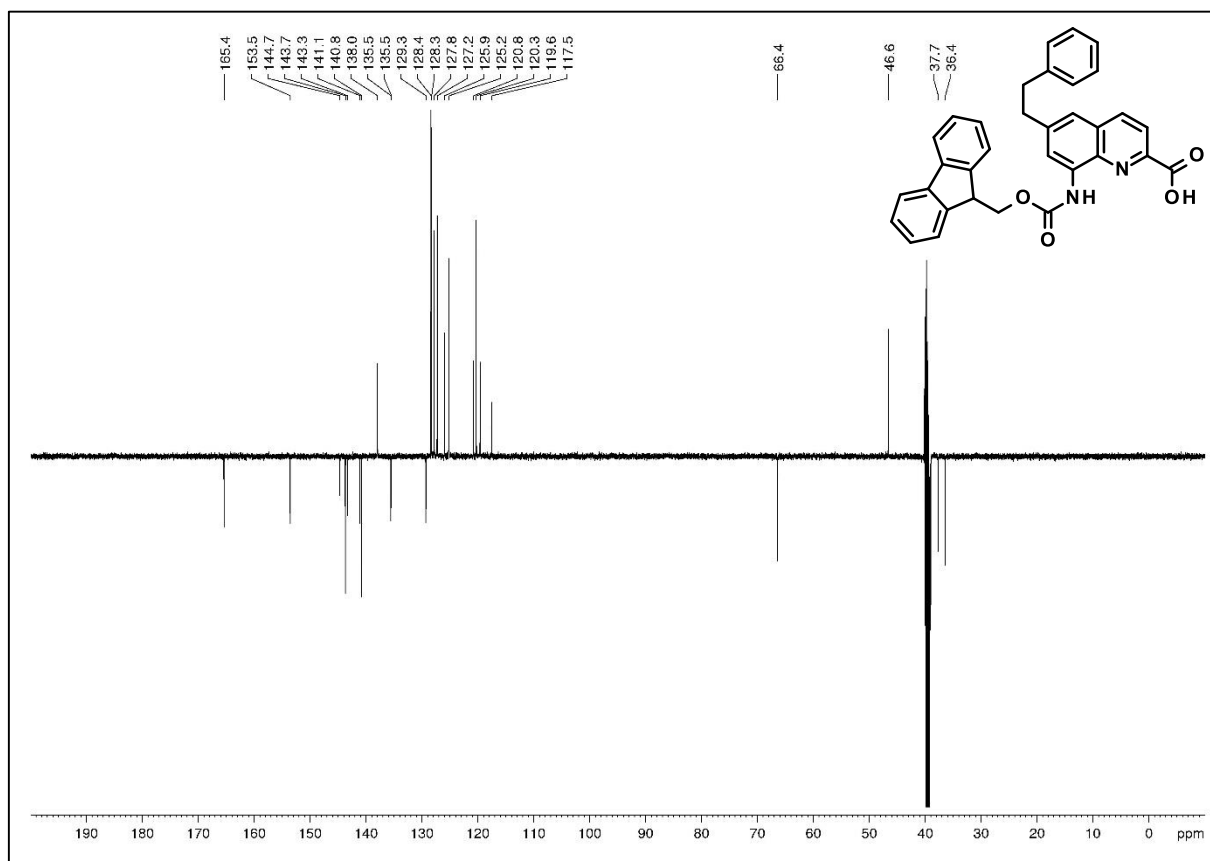
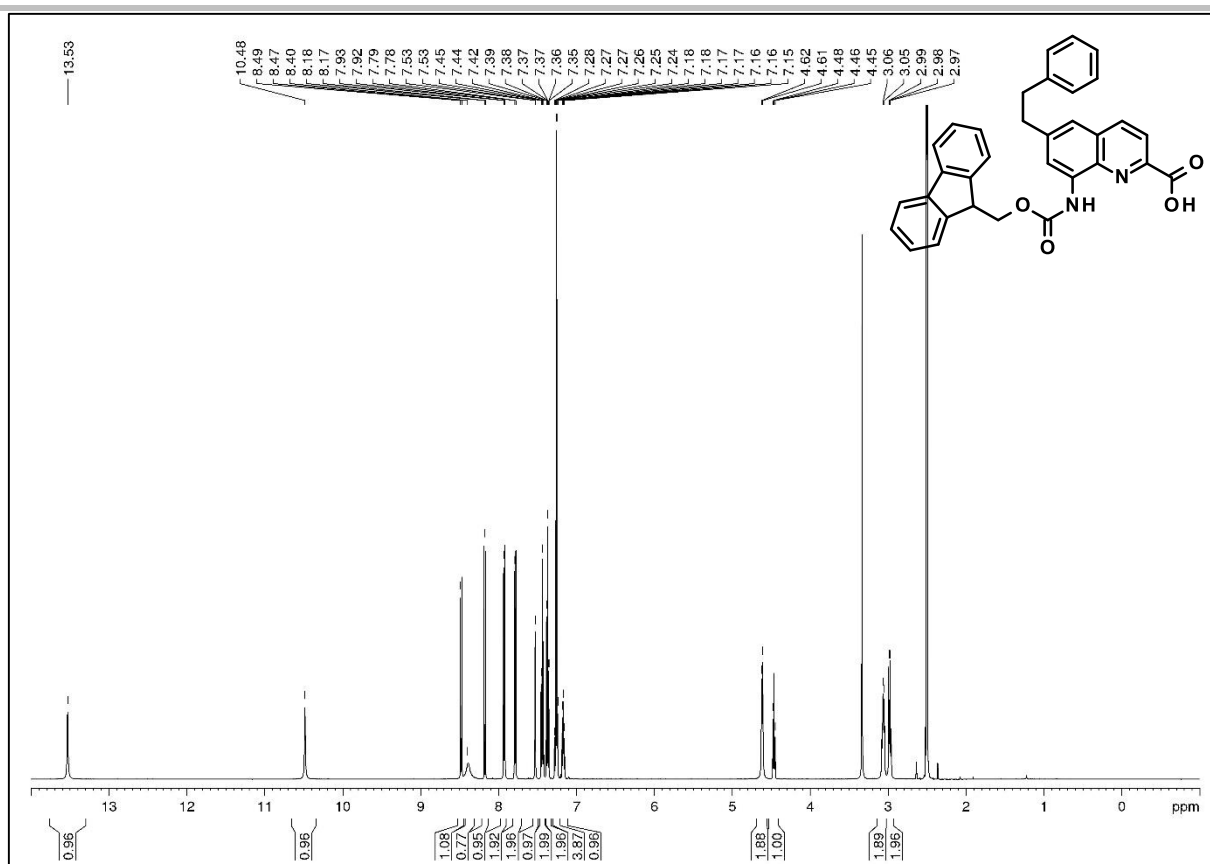


Figure S10. ^1H NMR (300 MHz) of purified oligomer 6.

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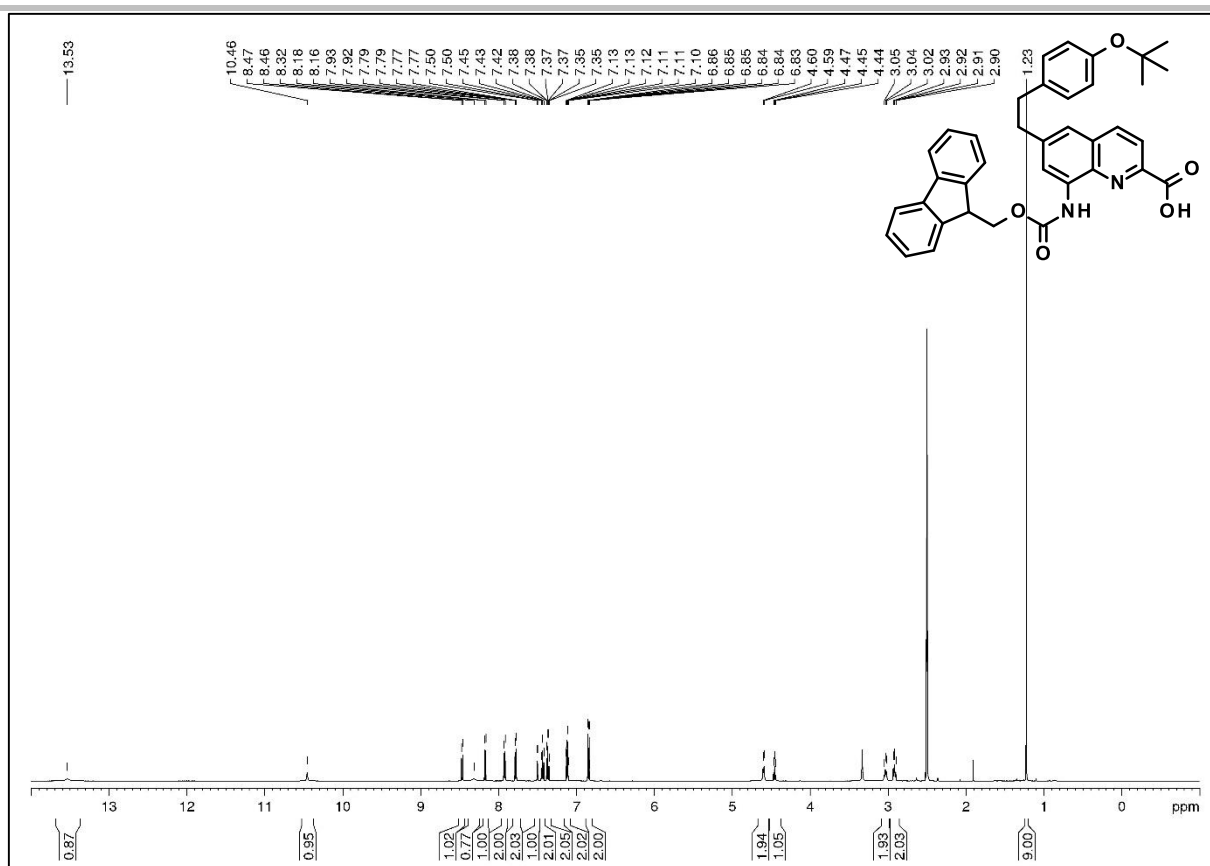


Figure S13. ^1H NMR (500 MHz, DMSO-d_6) of compound **1b**.

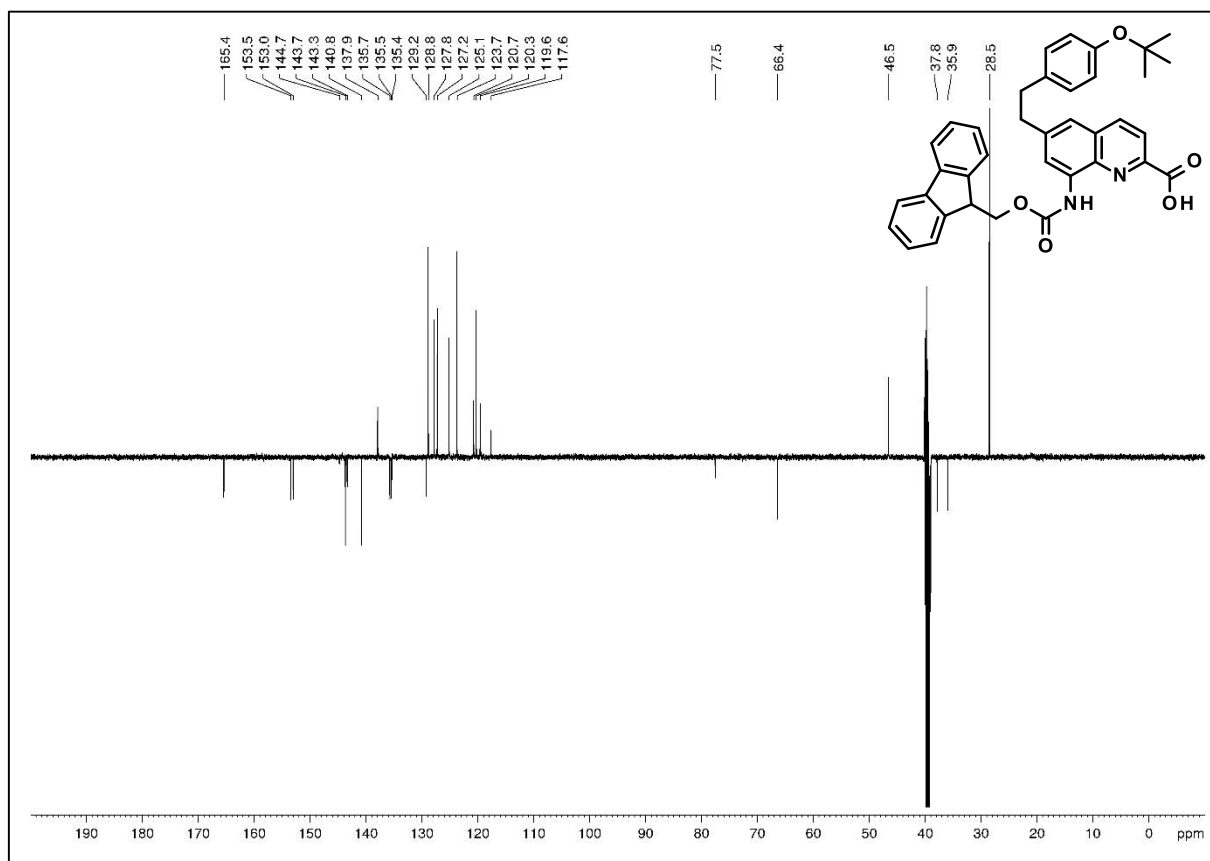
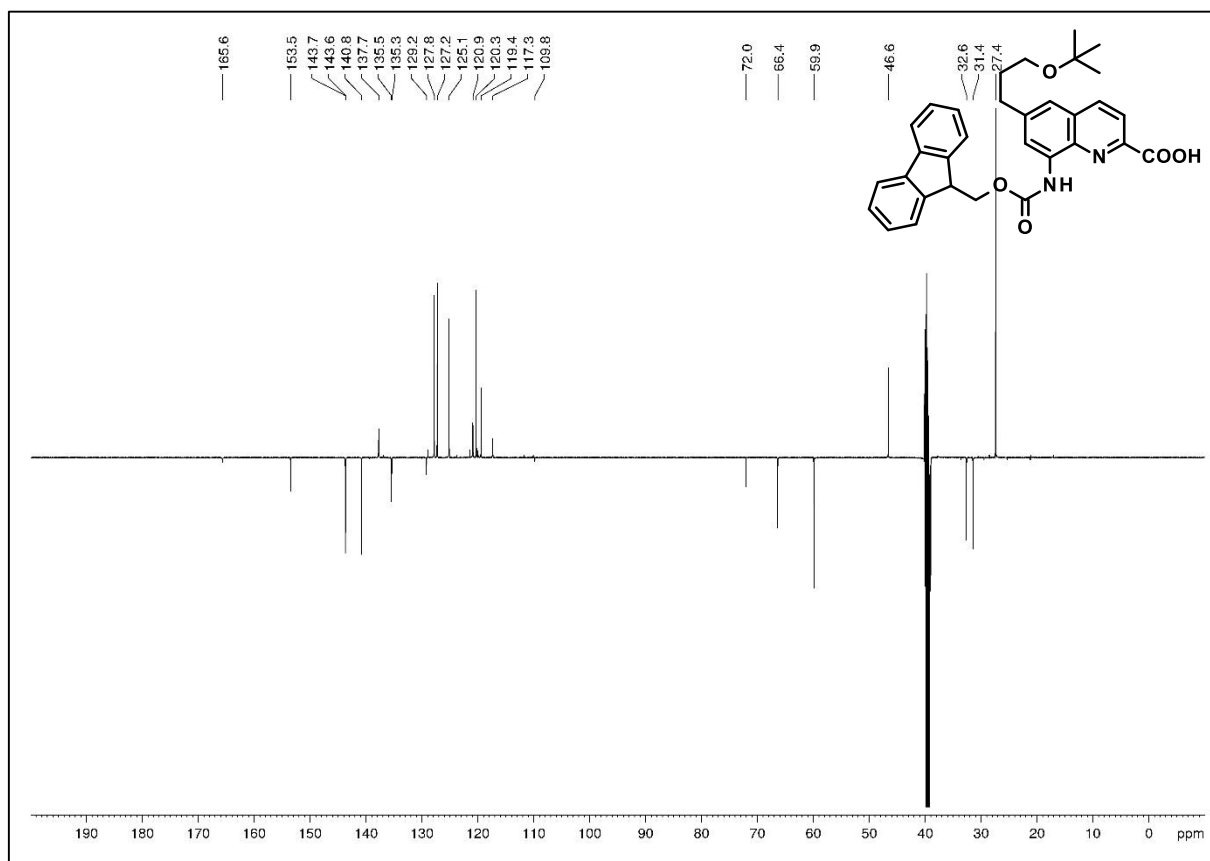
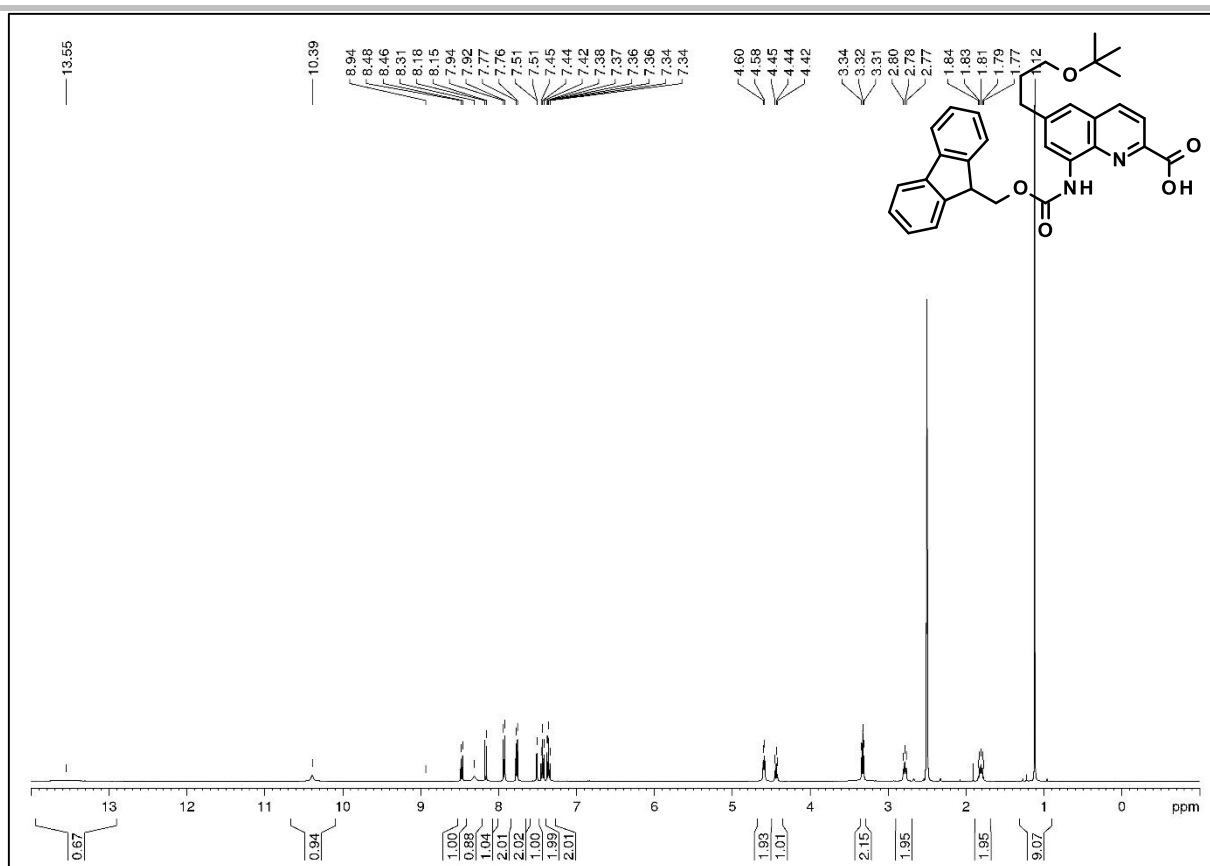


Figure S14. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **1b**.

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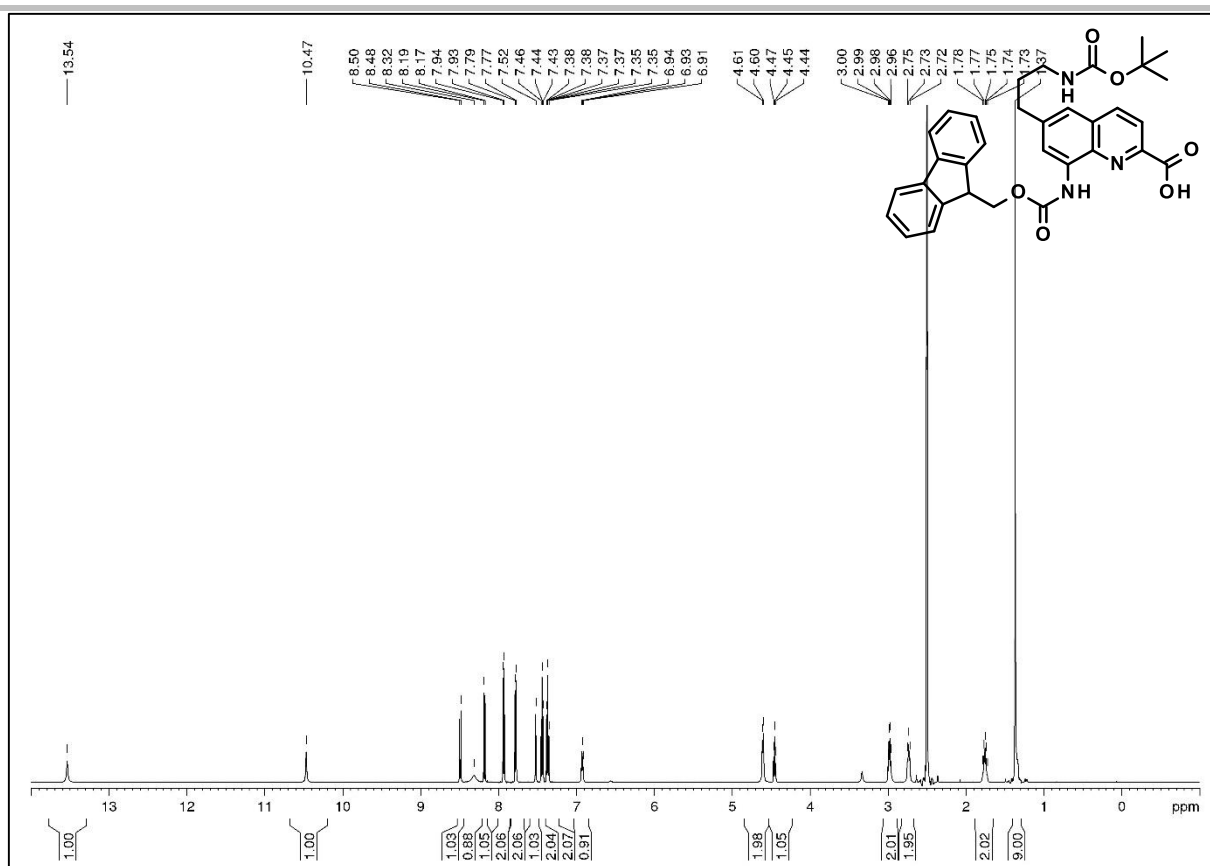


Figure S17. ^1H NMR (500 MHz, DMSO-d_6) of compound **1d**.

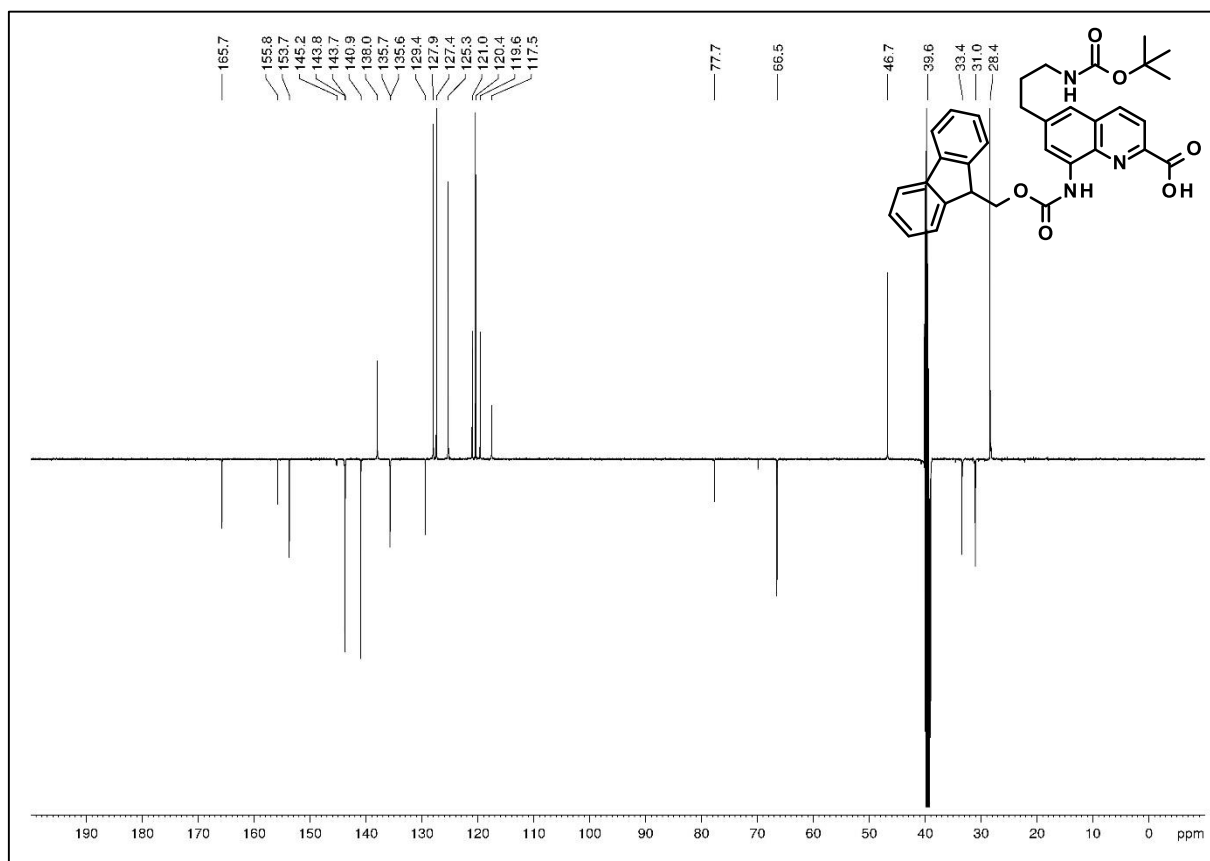


Figure S18. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **1d**.

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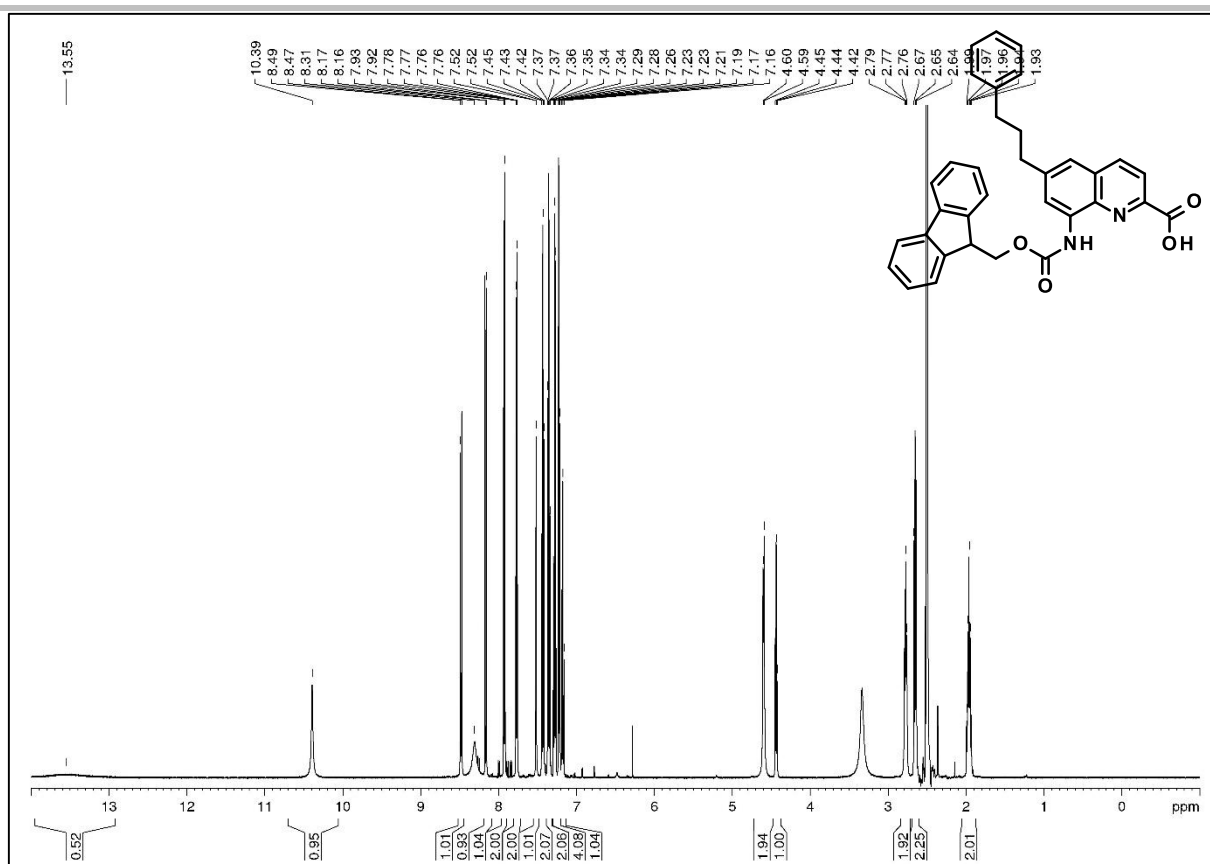


Figure S19. ^1H NMR (500 MHz, DMSO-d_6) of compound **1e**.

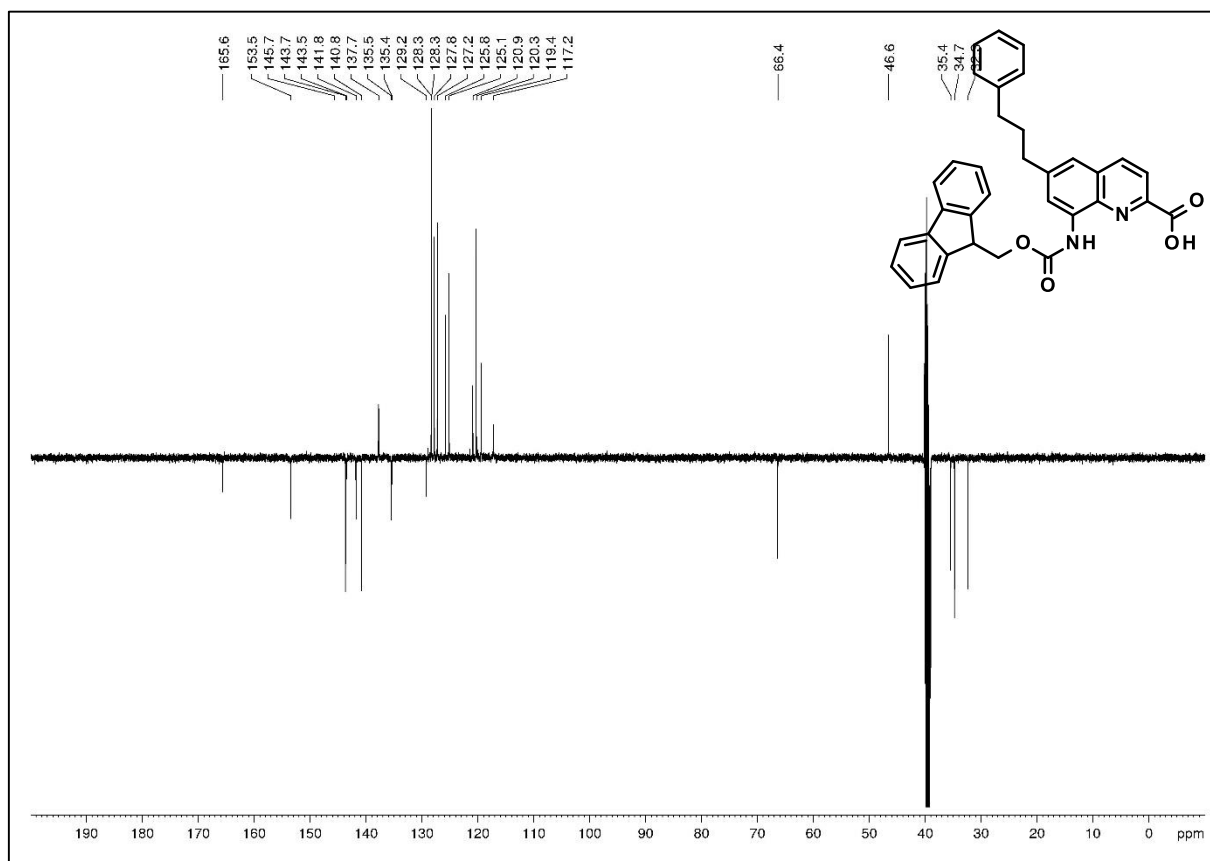
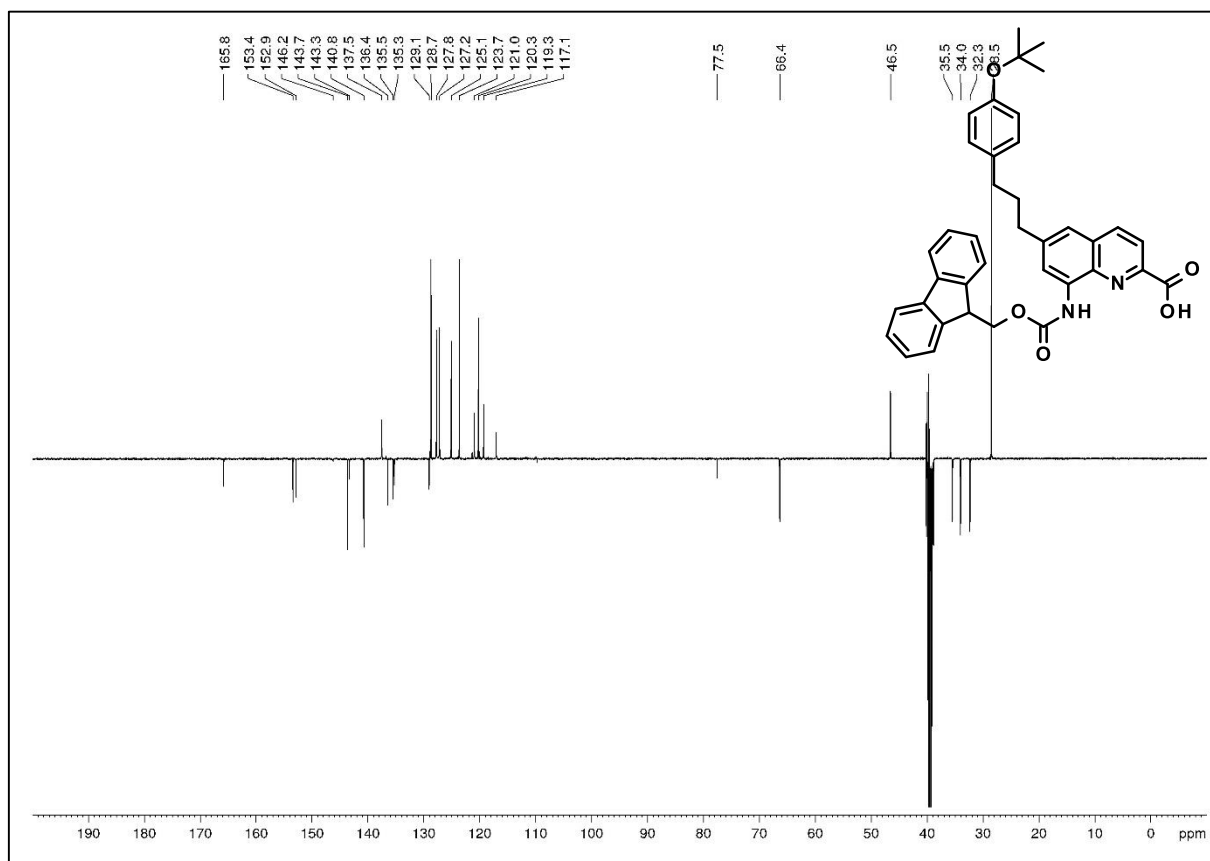
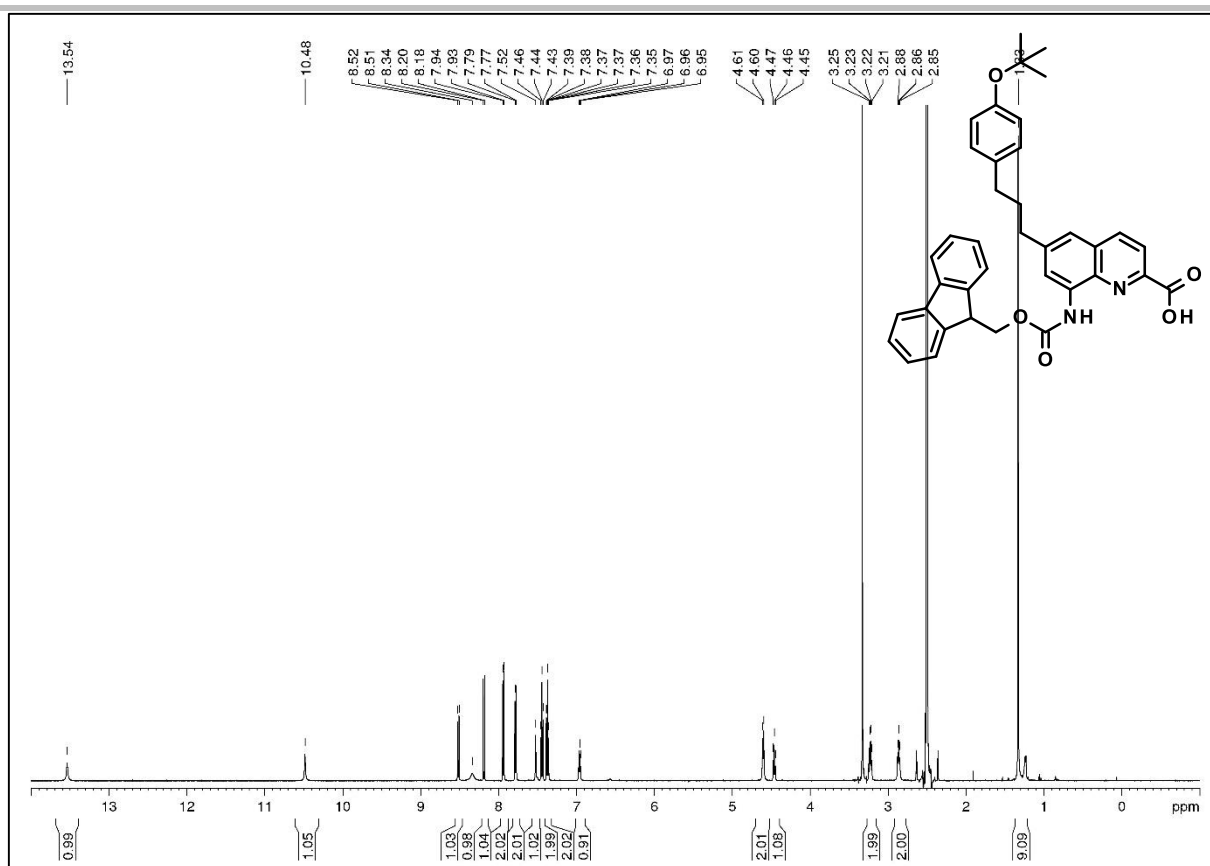


Figure S20. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **1e**.

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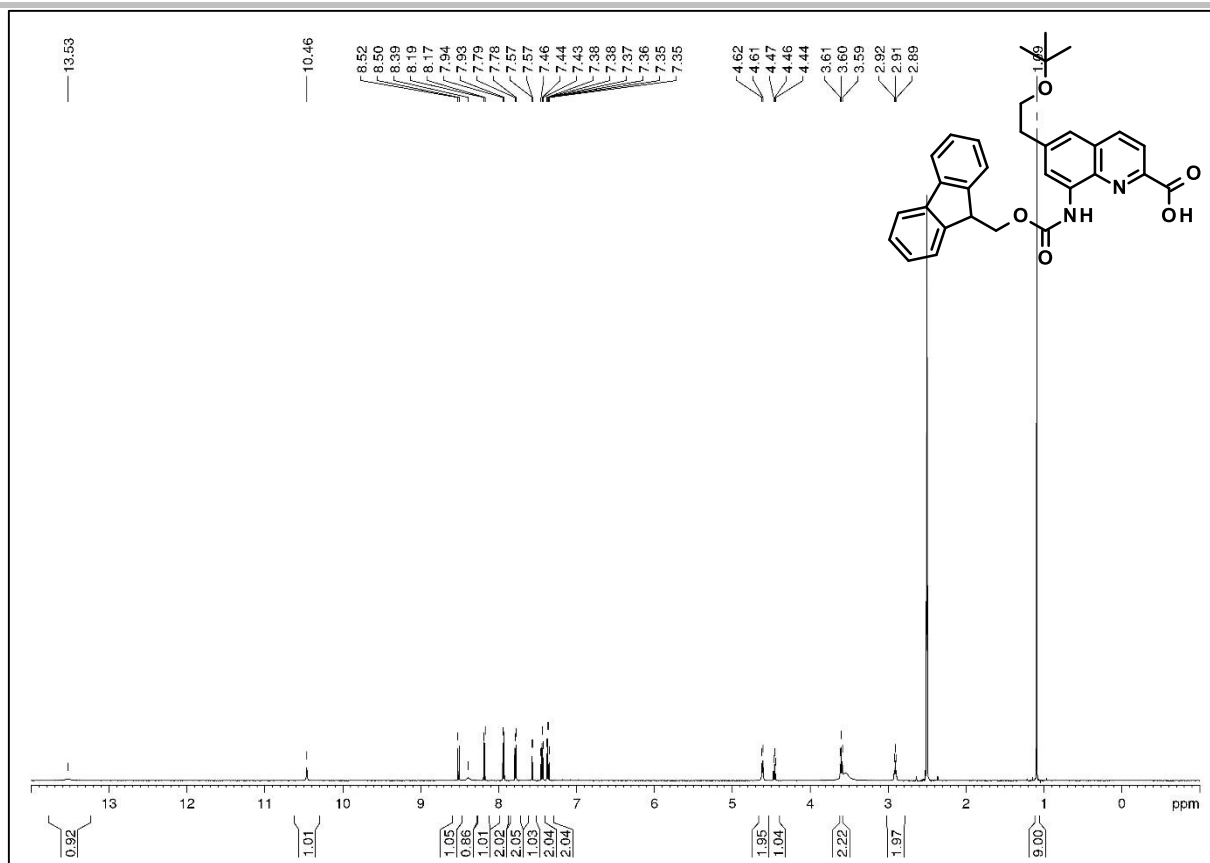


Figure S23. ^1H NMR (500 MHz, DMSO-d_6) of compound **1g**.

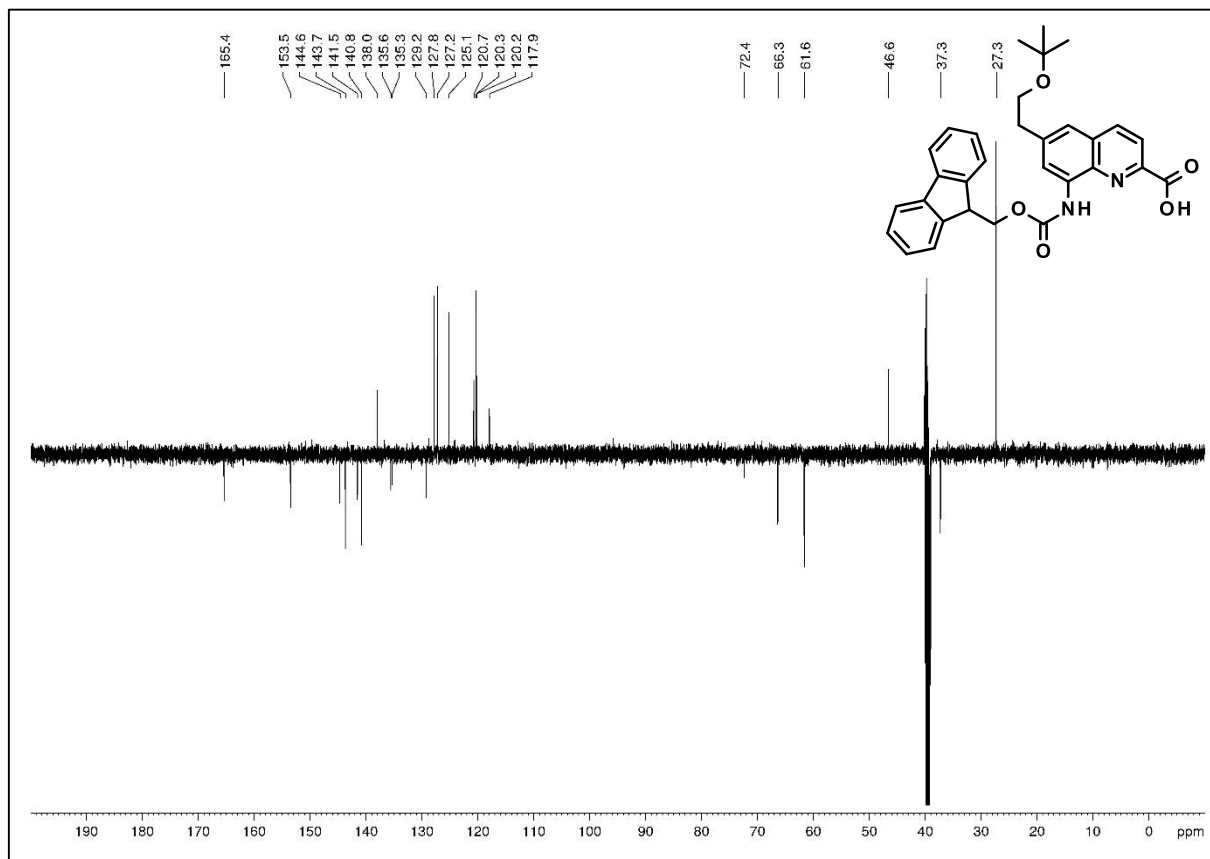
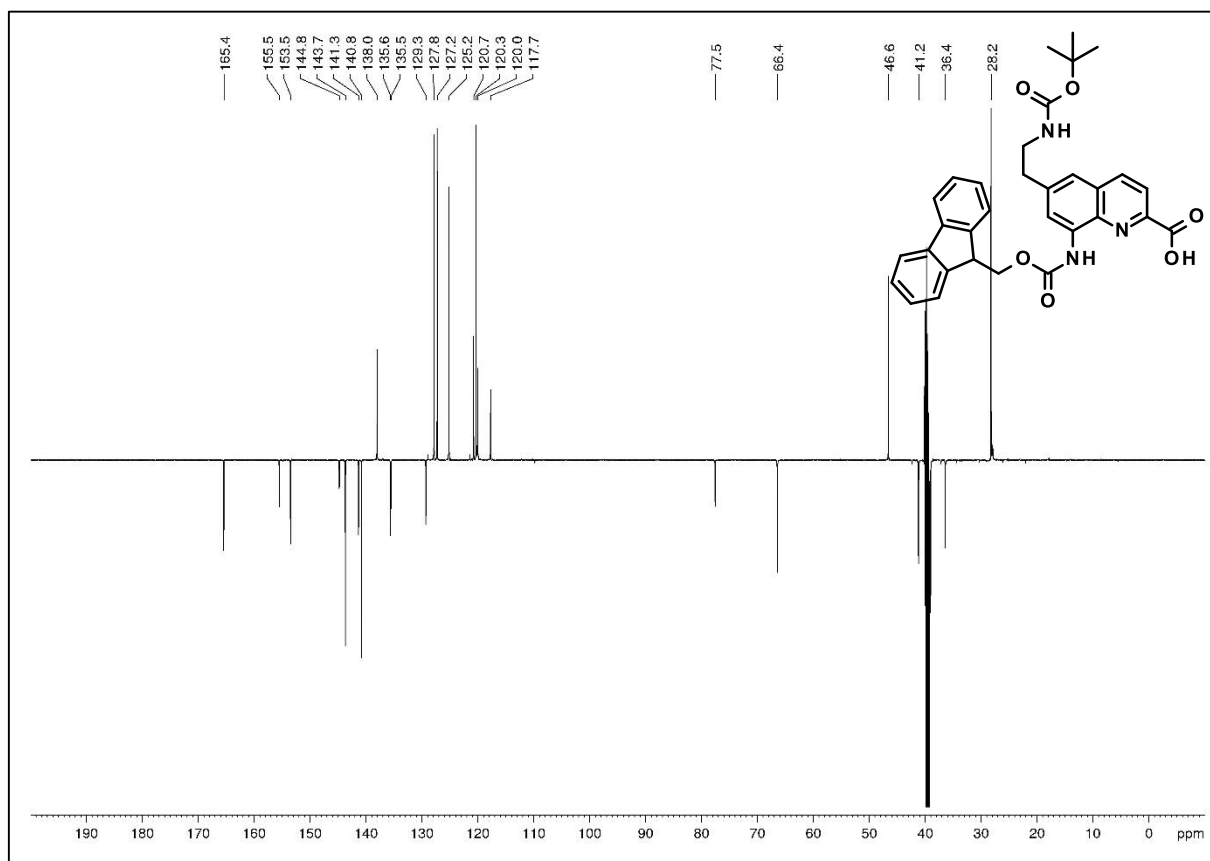
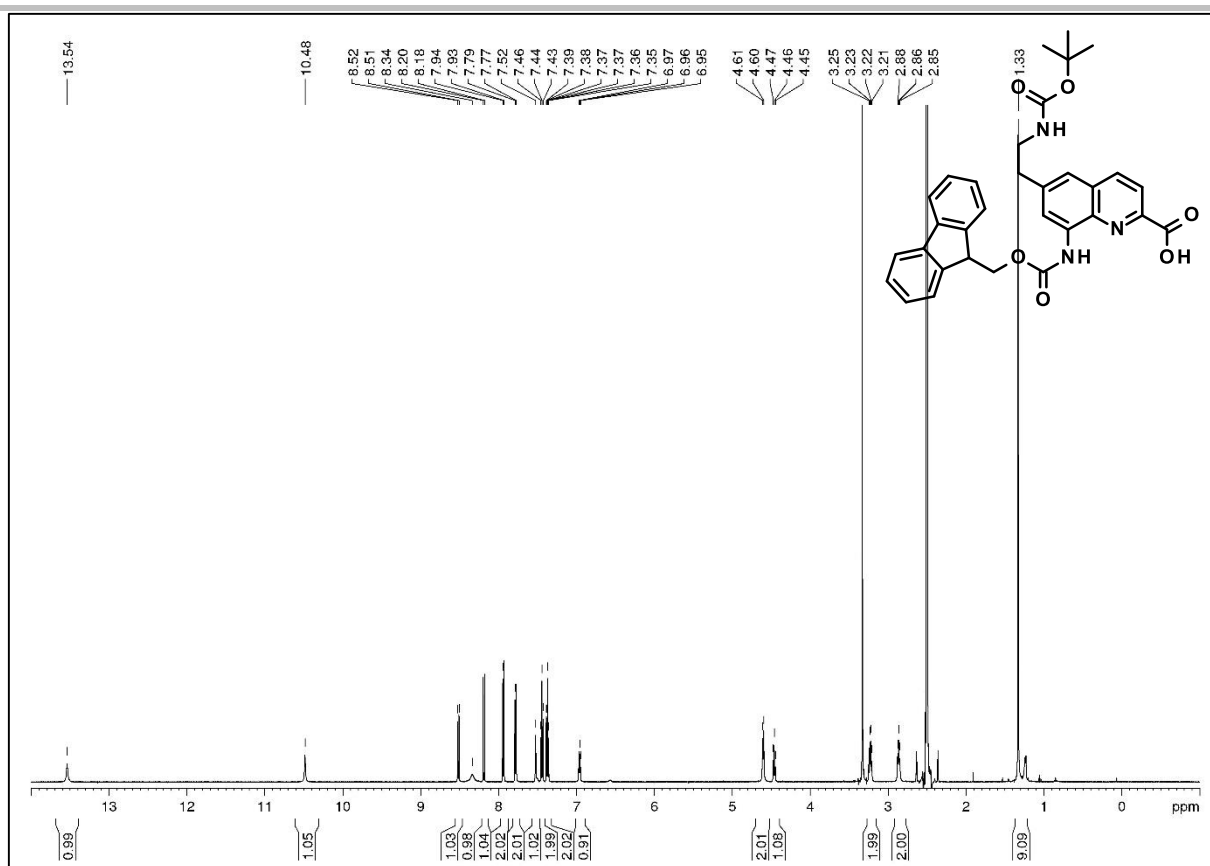


Figure S24. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **1g**.

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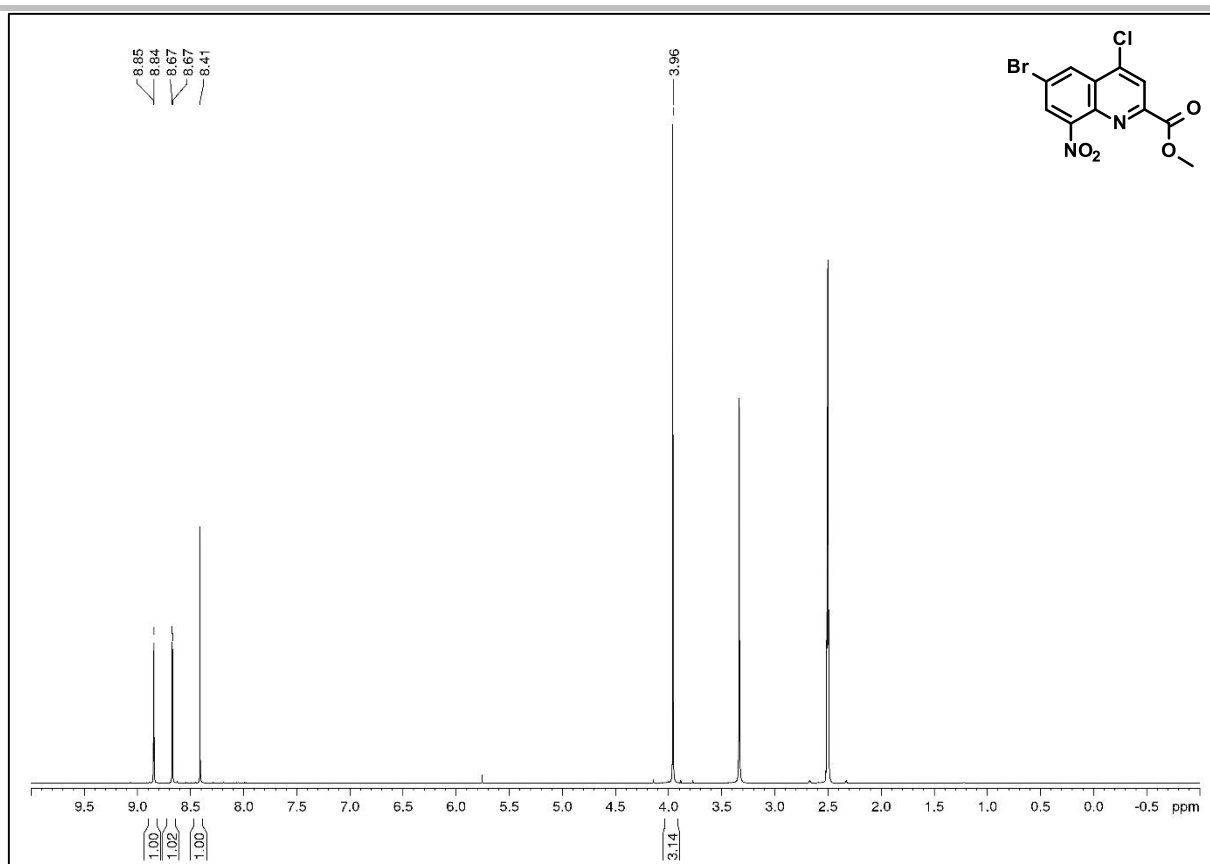


Figure S27. ¹H NMR (400 MHz, DMSO-d₆) of compound 2.

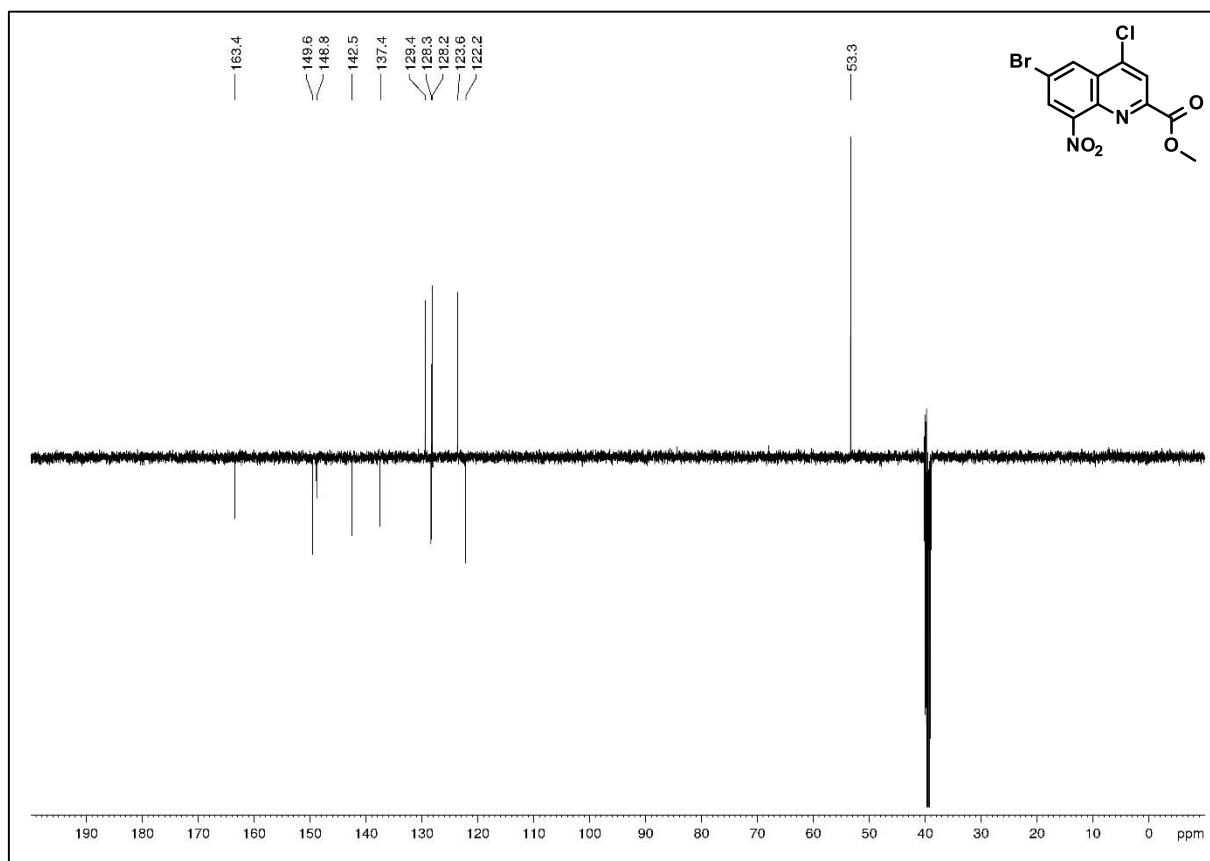
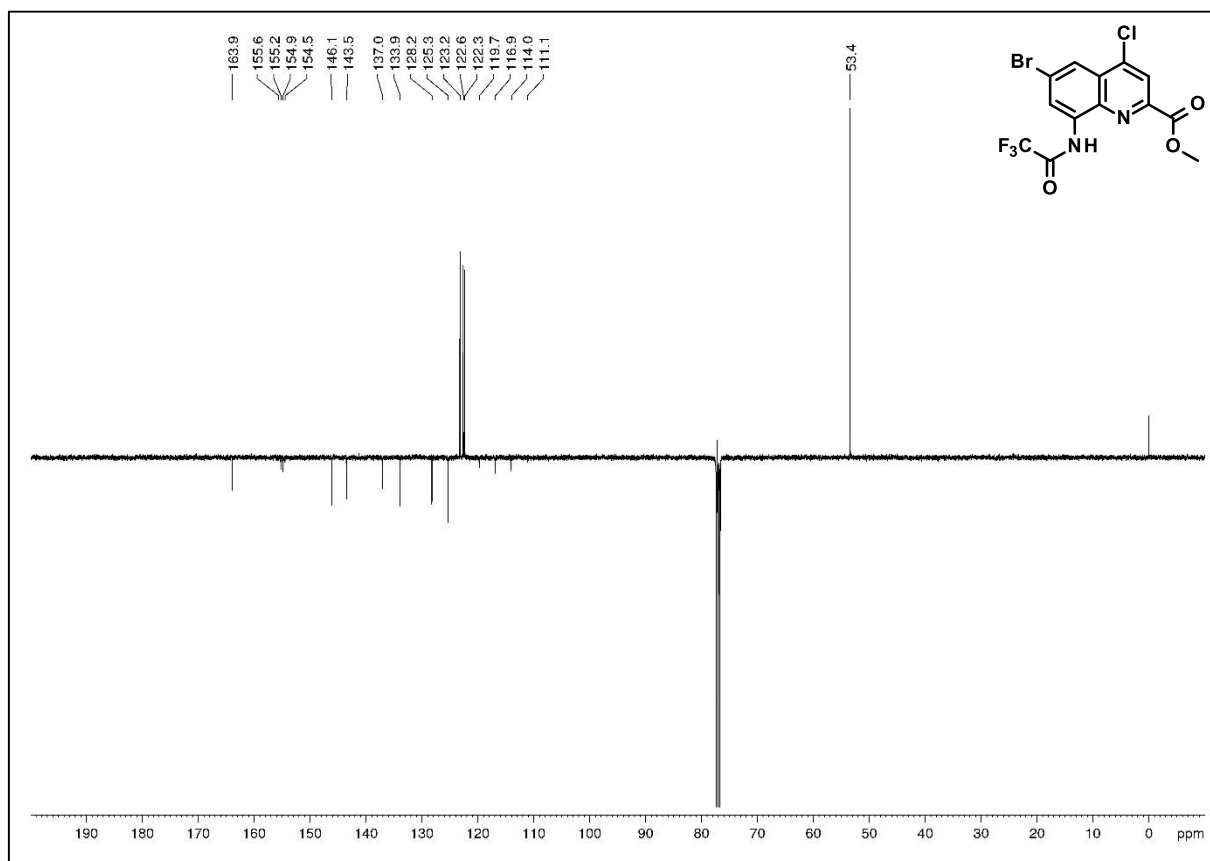
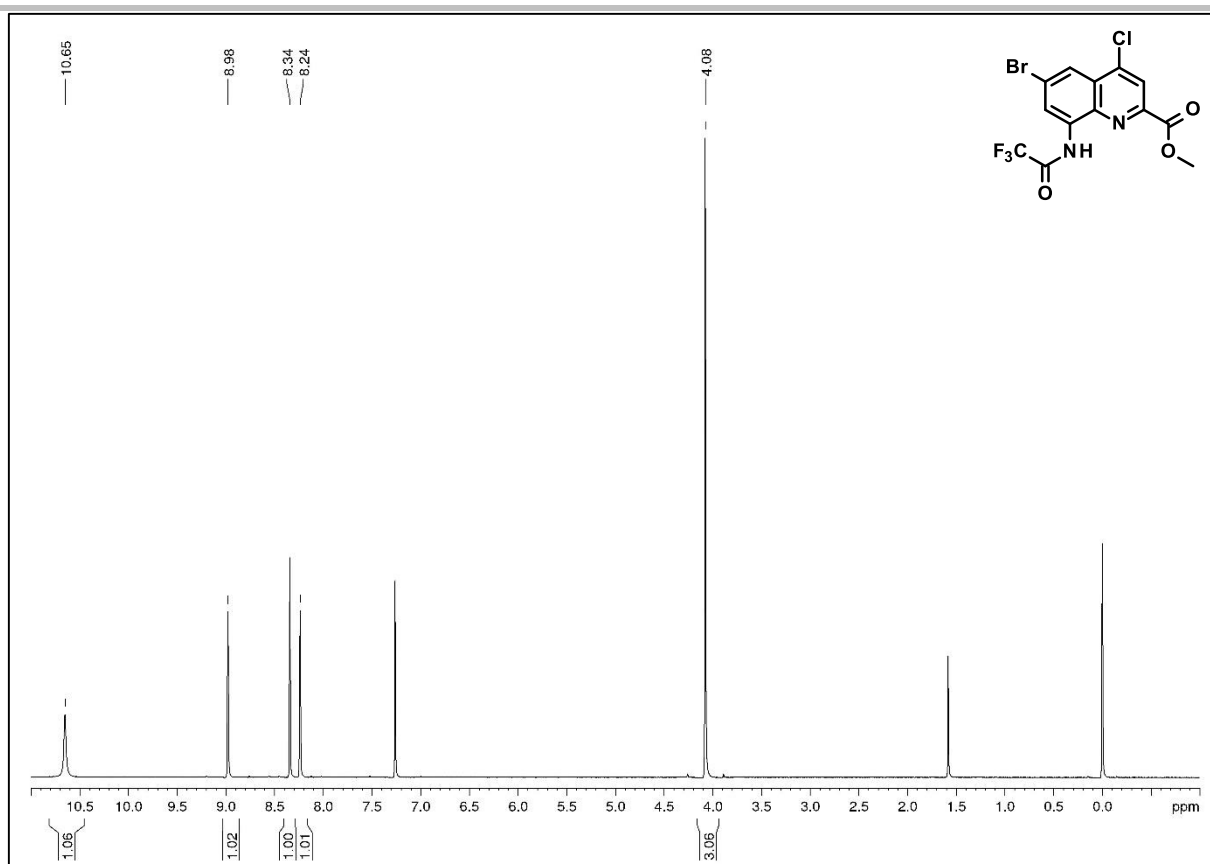


Figure S28. DEPTQ ¹³C NMR (100 MHz, DMSO-d₆) of compound 2.

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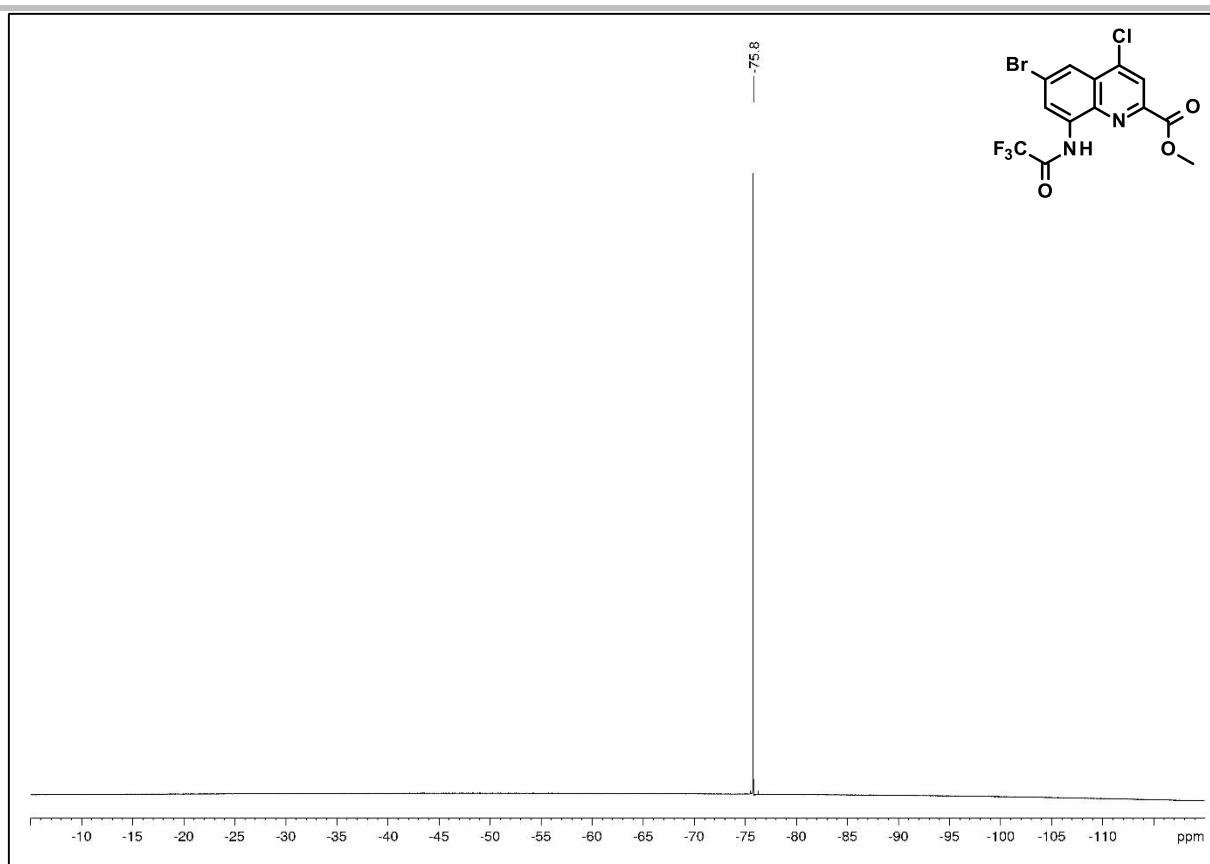


Figure S31. ^{19}F NMR (376 MHz, CDCl_3) of compound 3.

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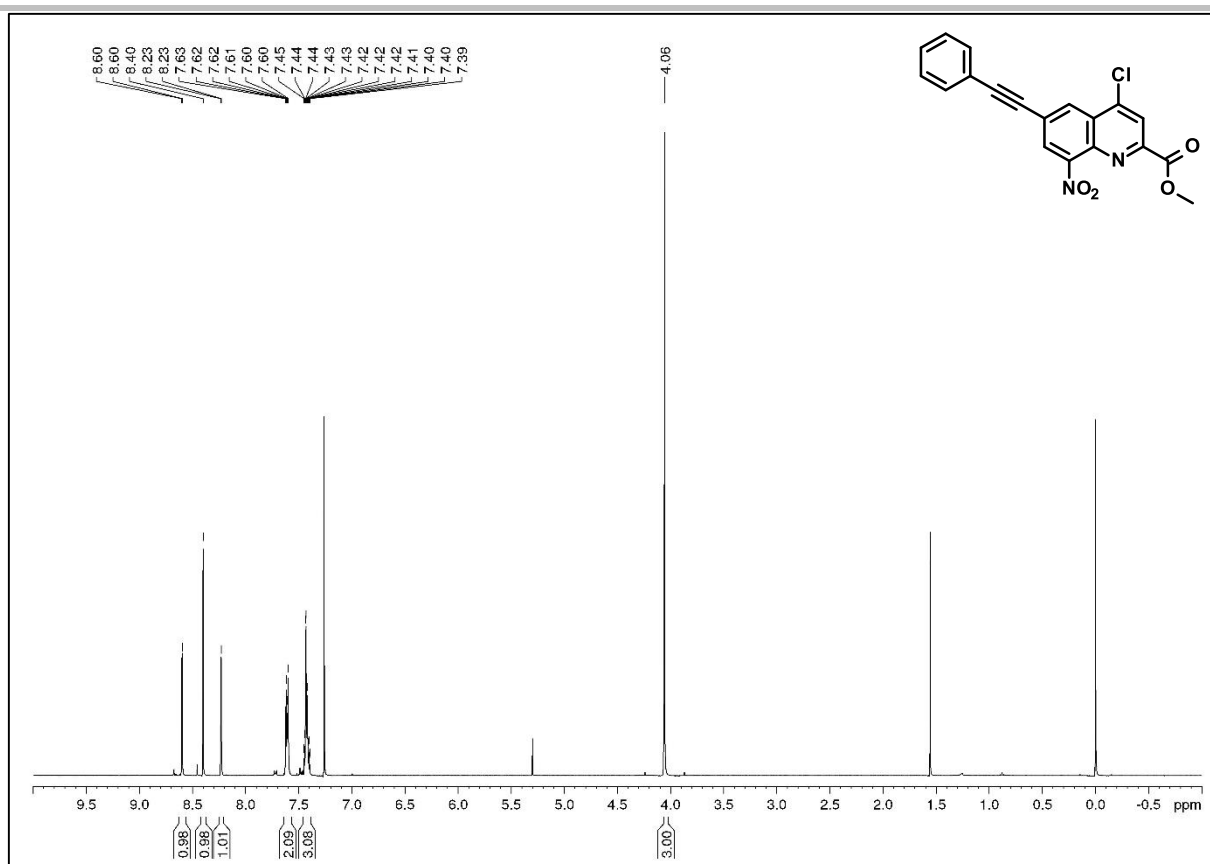


Figure S32. ¹H NMR (400 MHz, CDCl₃) of compound 4a.

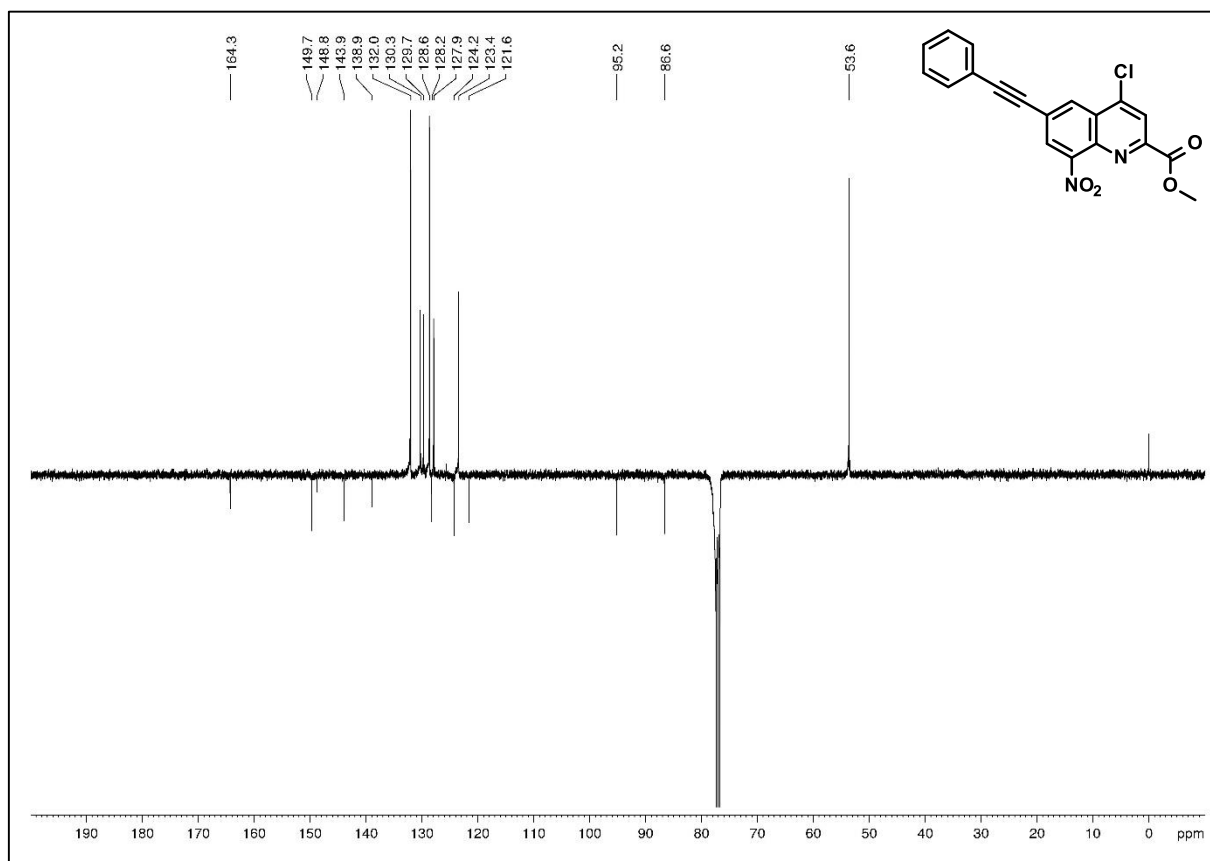


Figure S33. DEPTQ ¹³C NMR (100 MHz, CDCl₃) of compound 4a.

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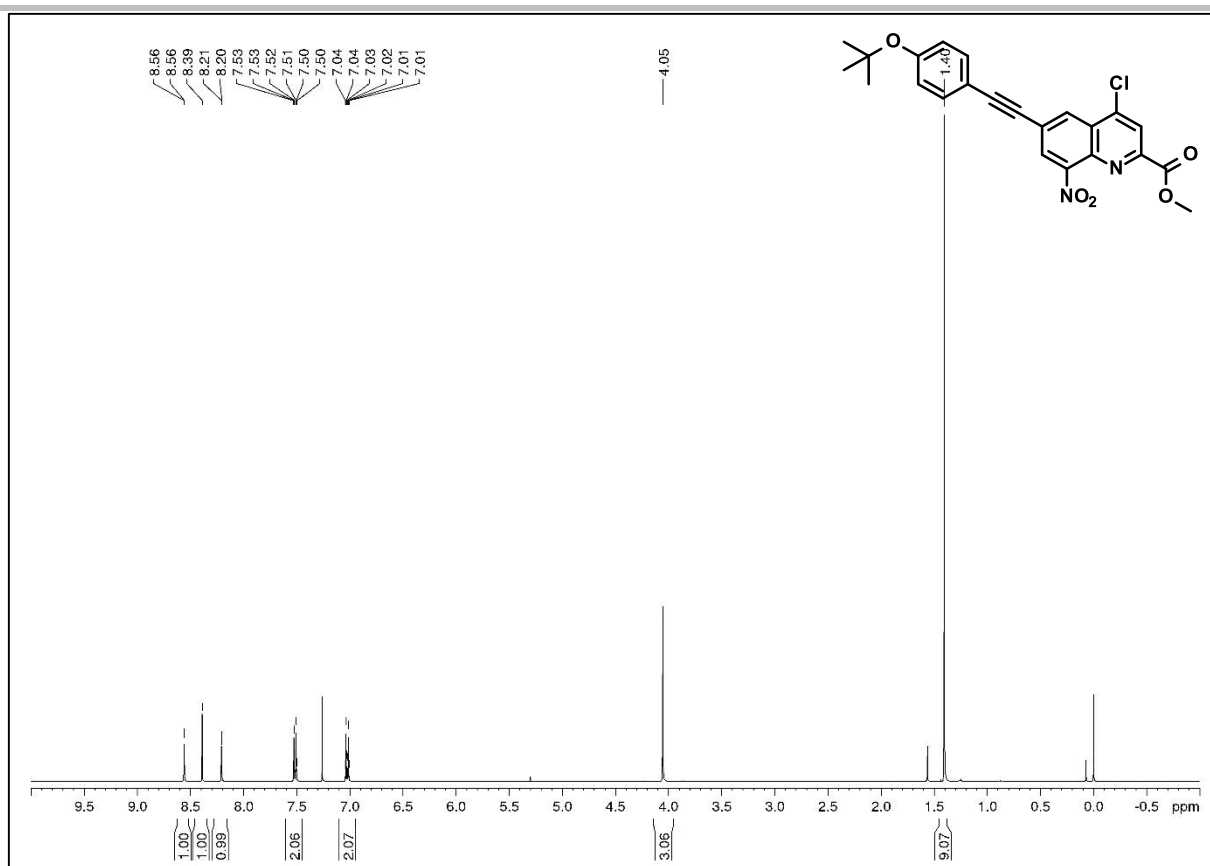


Figure S34. ^1H NMR (400 MHz, CDCl_3) of compound **4b**.

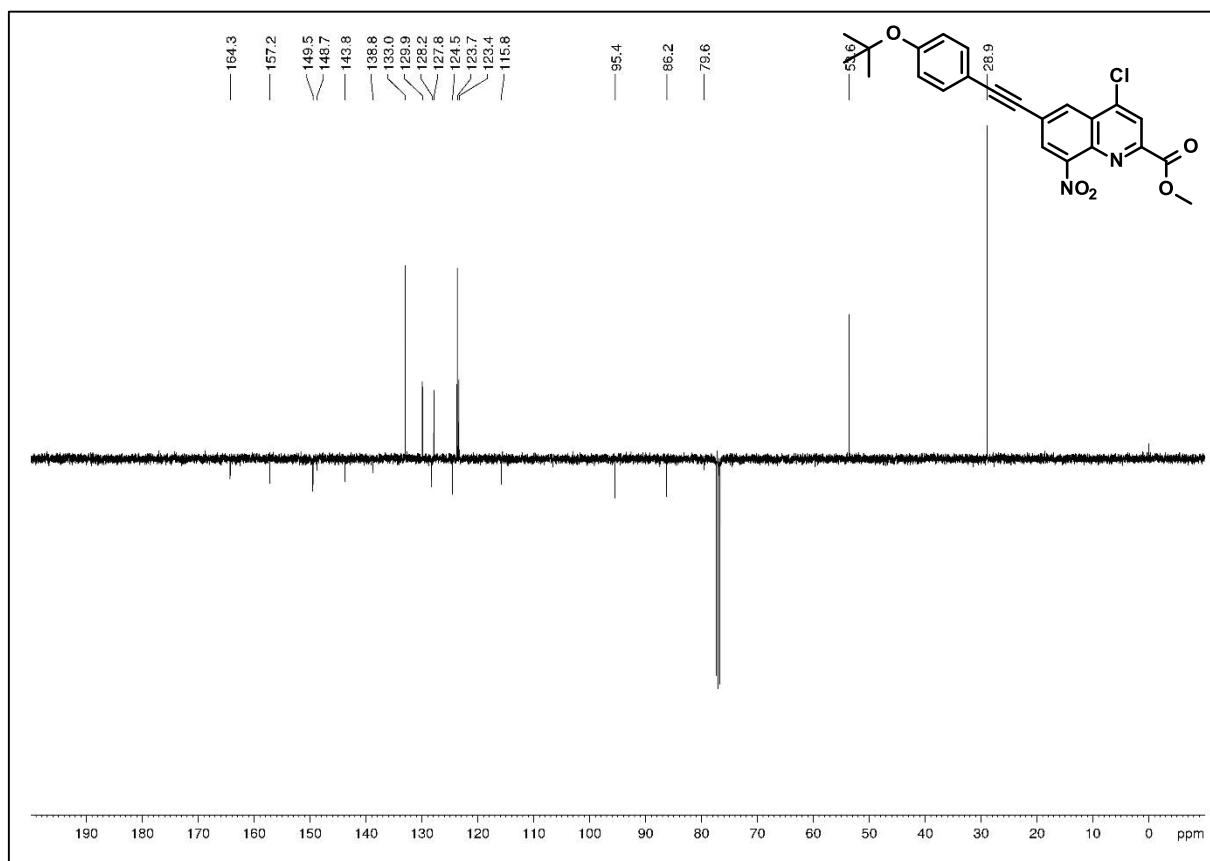


Figure S35. DEPTQ ^{13}C NMR (100 MHz, CDCl_3) of compound **4b**.

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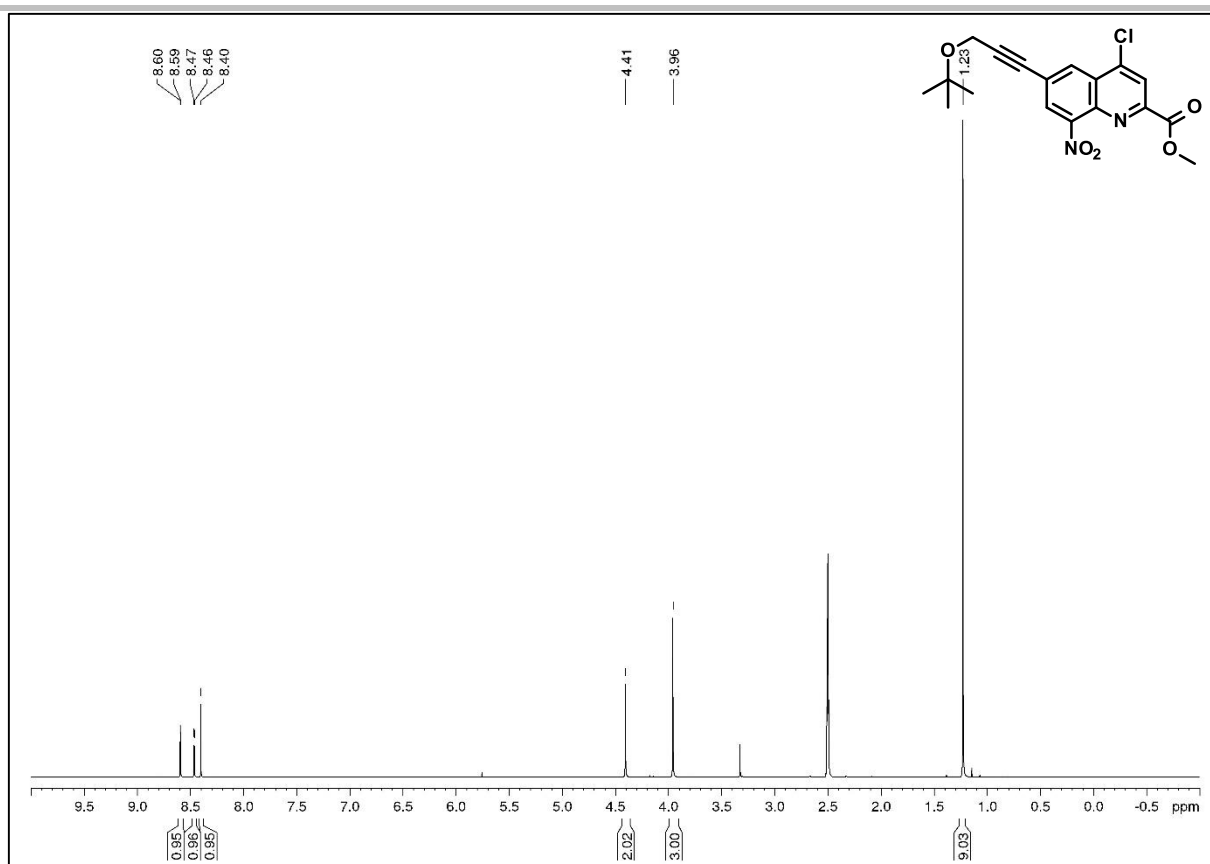


Figure S36. ¹H NMR (400 MHz, DMSO-d₆) of compound 4c.

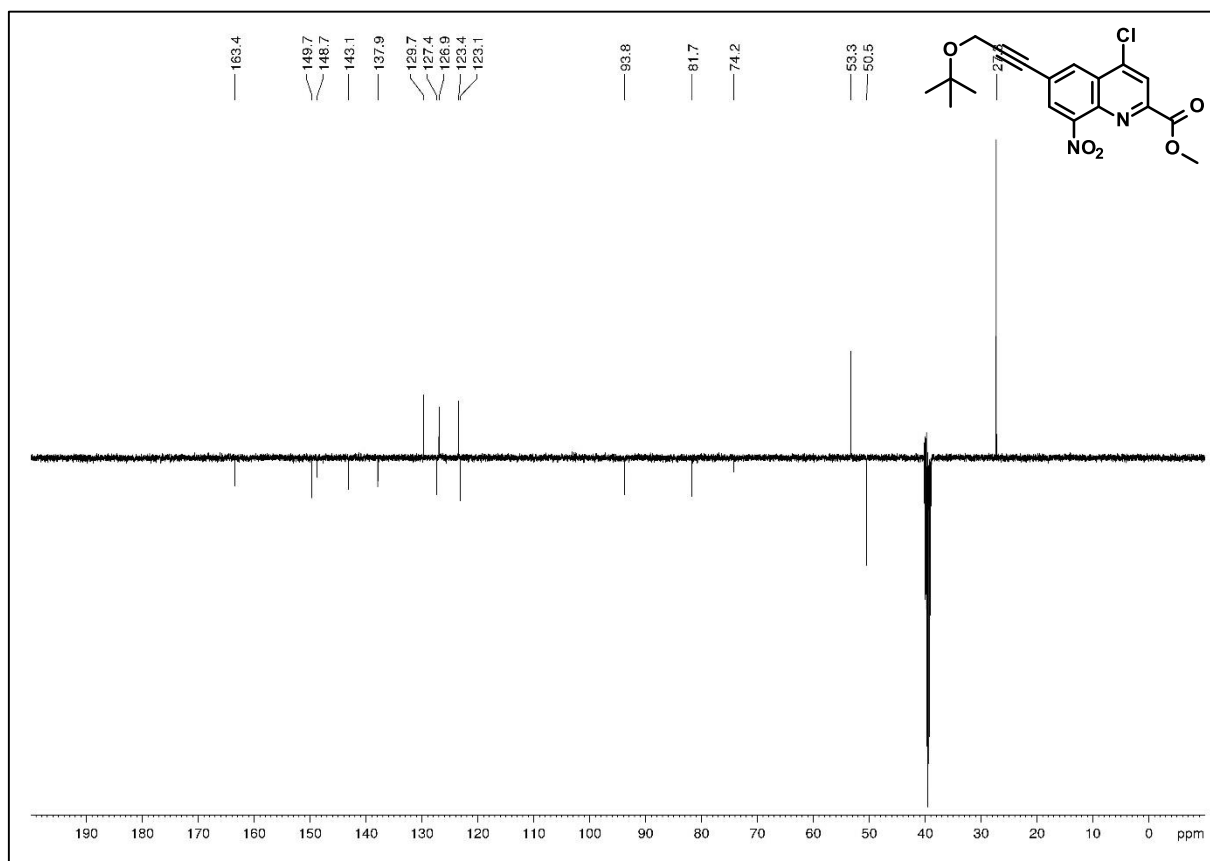


Figure S37. DEPT ¹³C NMR (100 MHz, DMSO-d₆) of compound 4c.

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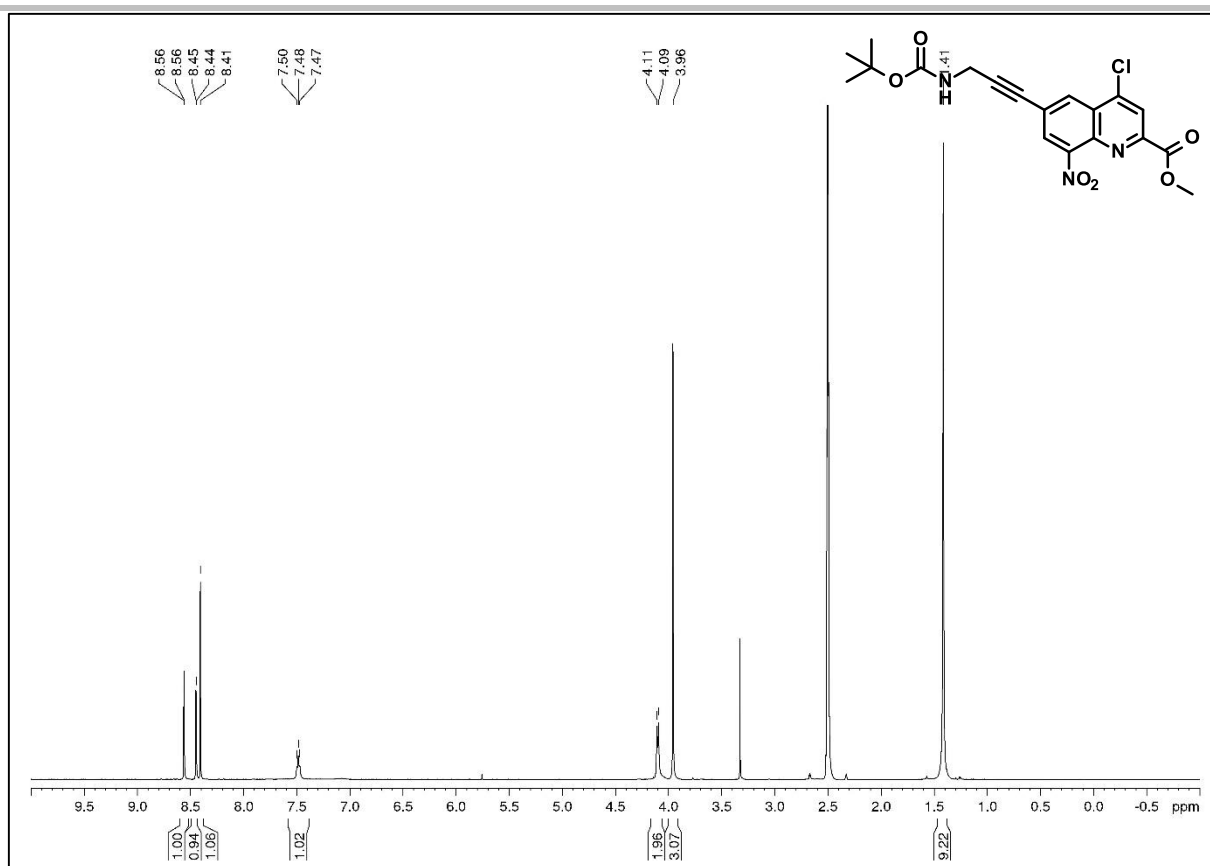


Figure S38. ¹H NMR (400 MHz, DMSO-d₆) of compound 4d.

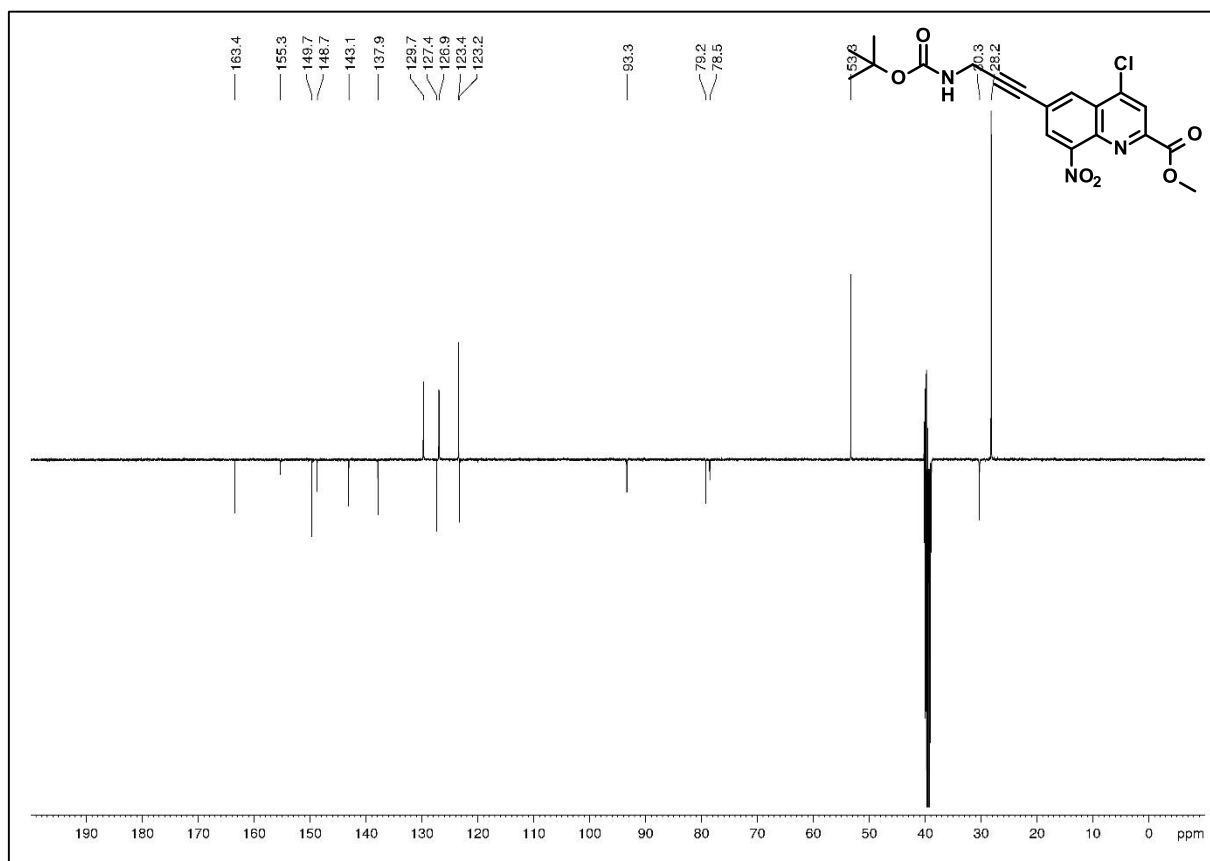


Figure S39. DEPTQ ¹³C NMR (100 MHz, DMSO-d₆) of compound 4d.

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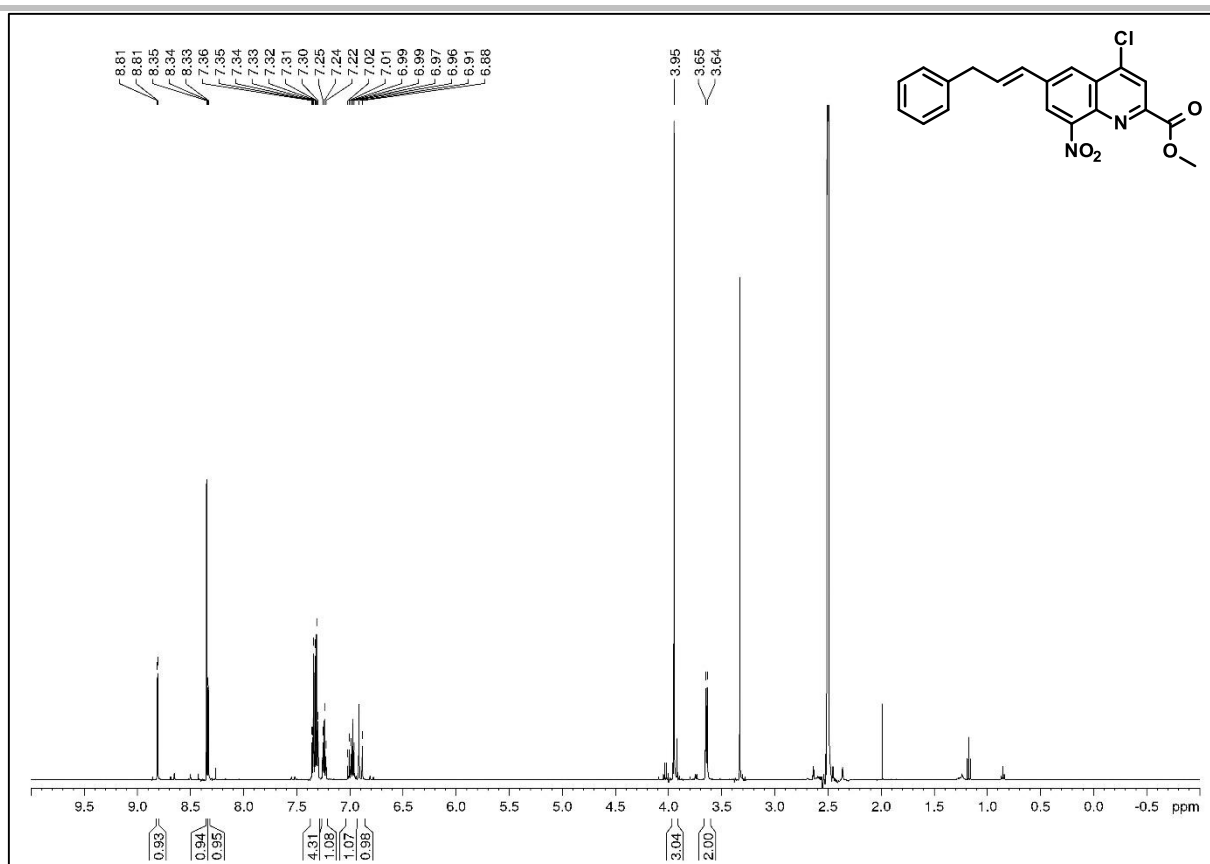


Figure S40. ^1H NMR (500 MHz, DMSO-d_6) of compound **4e**.

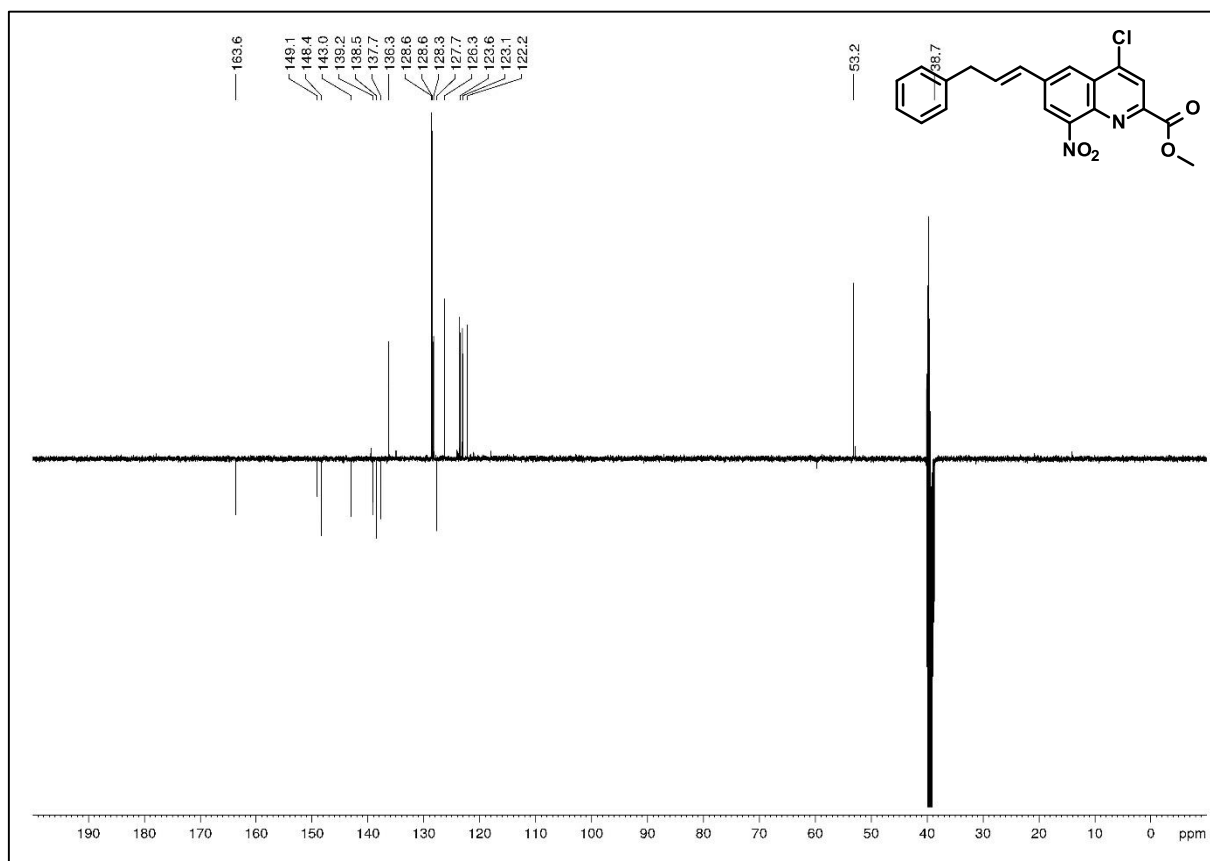


Figure S41. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **4e**.

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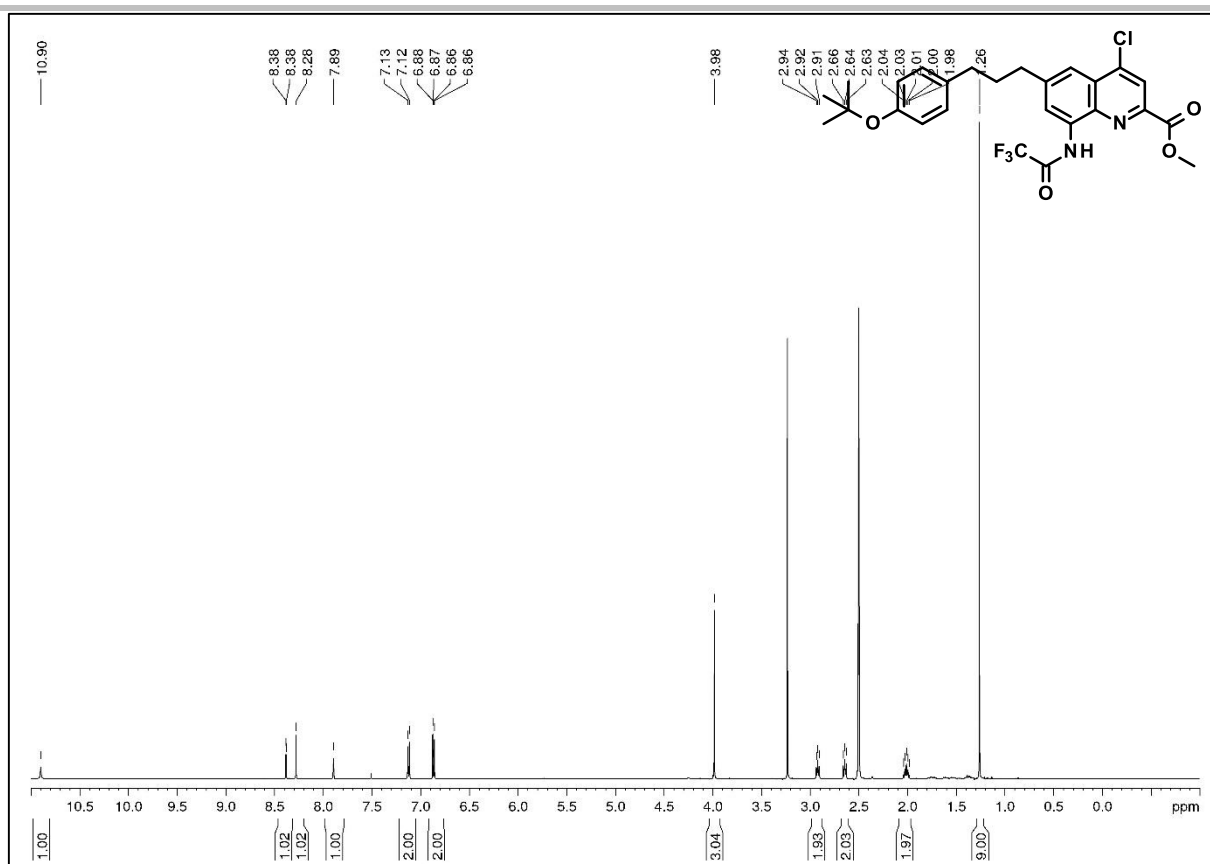


Figure S42. ¹H NMR (500 MHz, DMSO-d₆) of compound 4f.

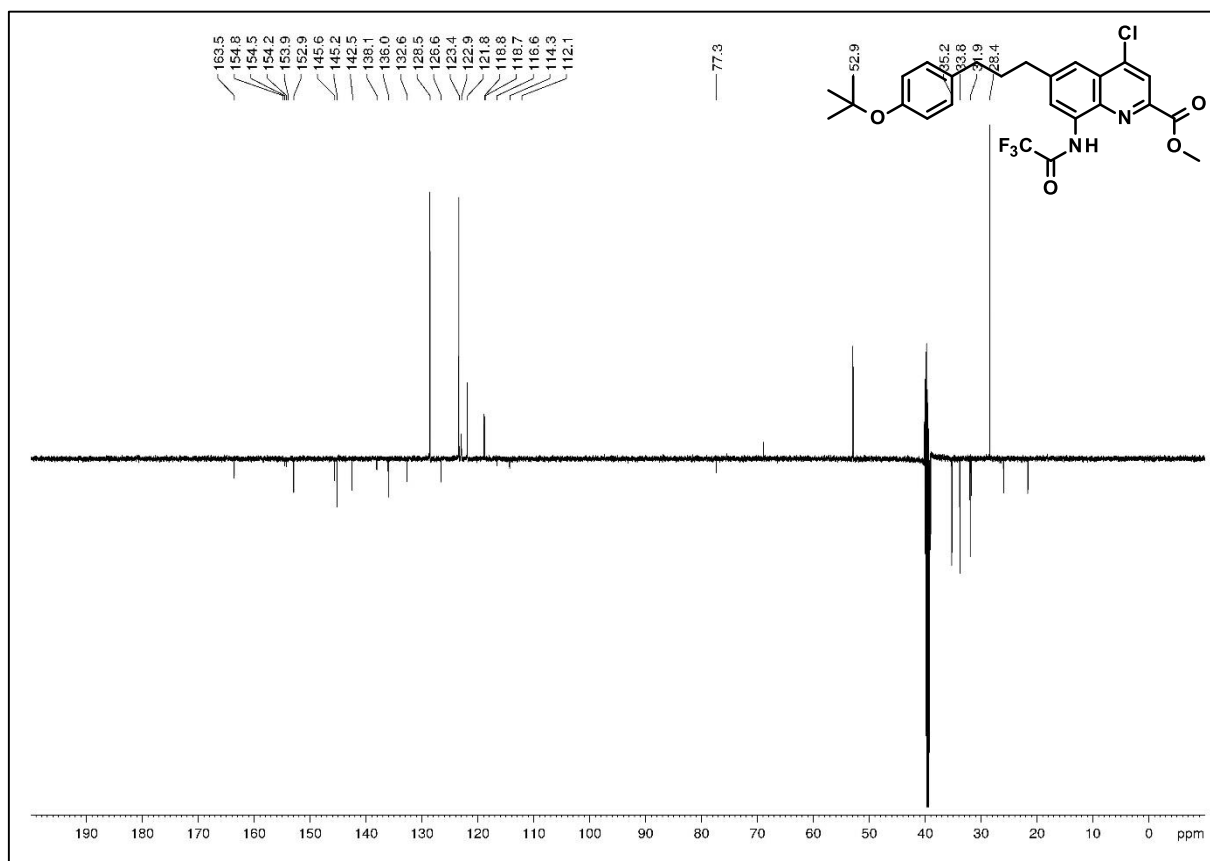


Figure S43. DEPTQ ¹³C NMR (125 MHz, DMSO-d₆) of compound 4f.

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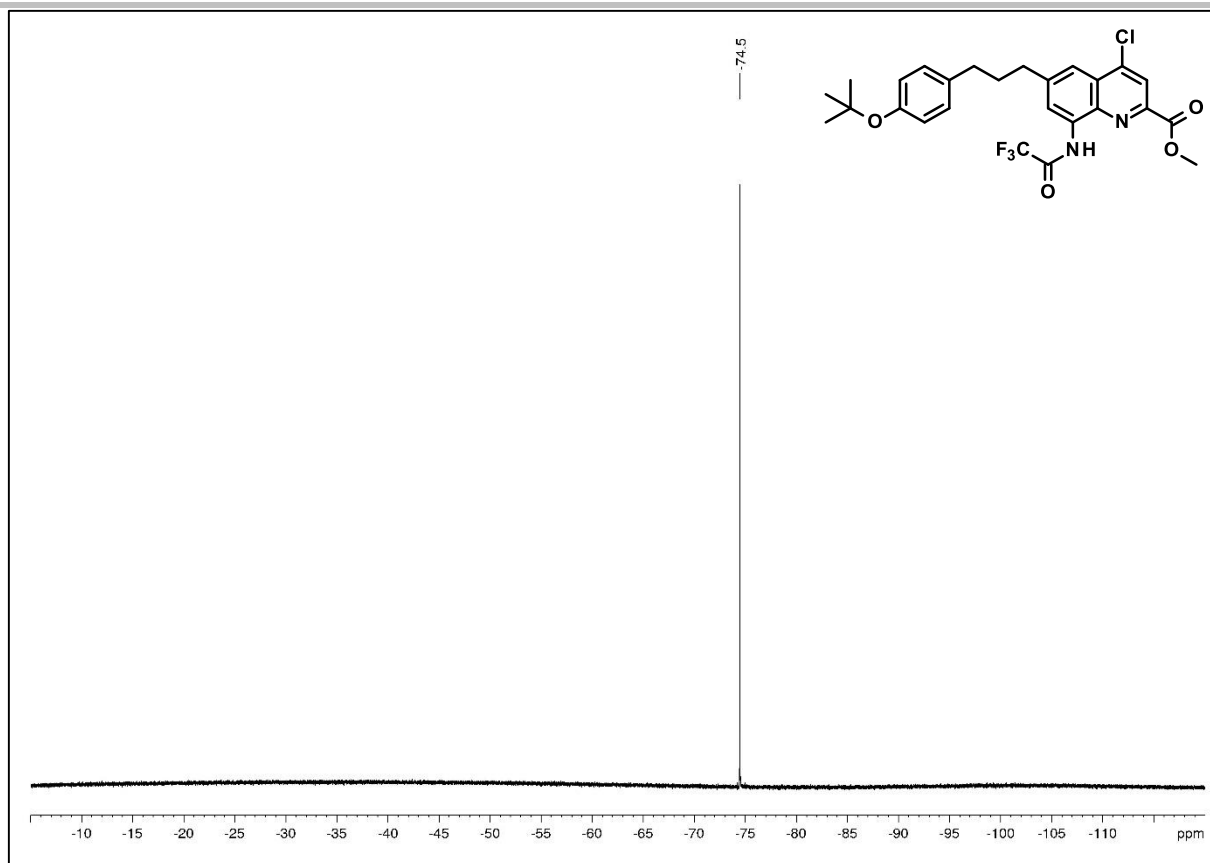


Figure S44. ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) of compound **4f**.

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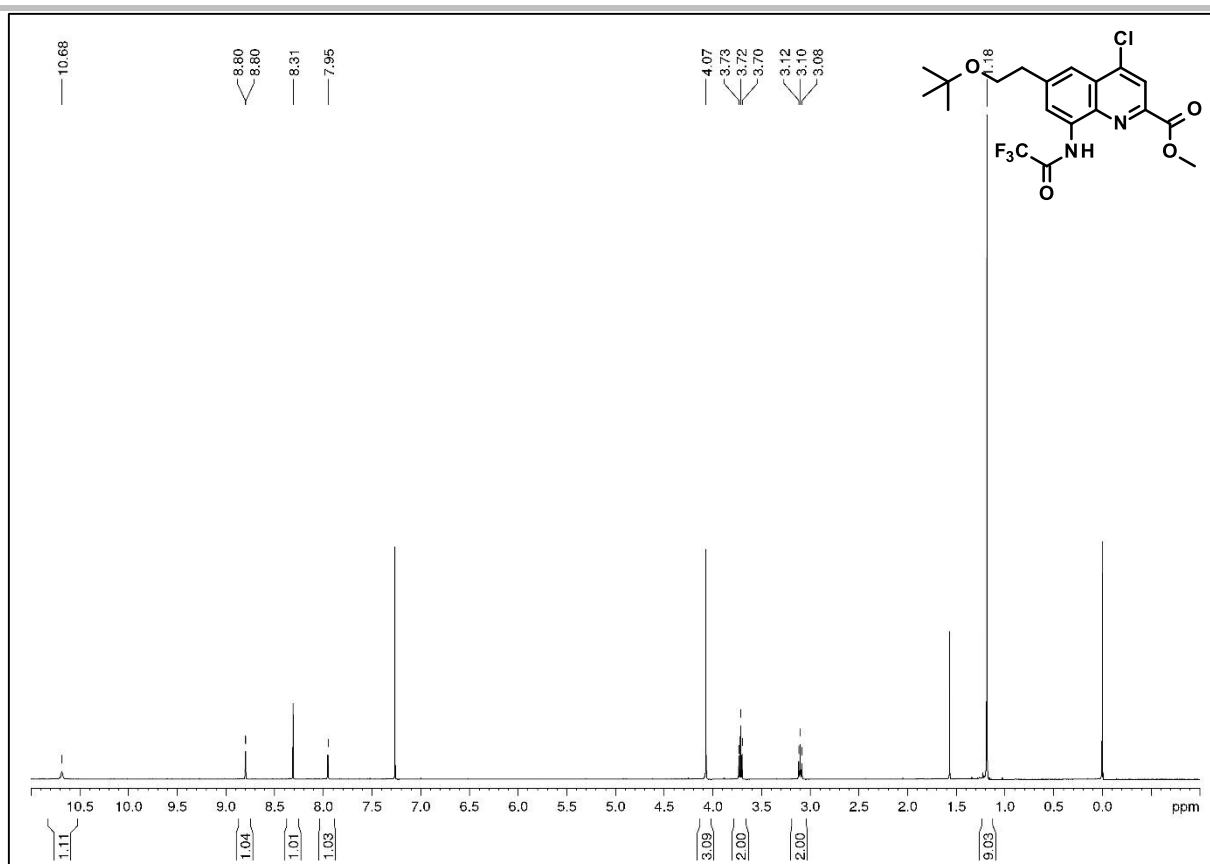


Figure S45. ¹H NMR (400 MHz, CDCl₃) of compound 4g.

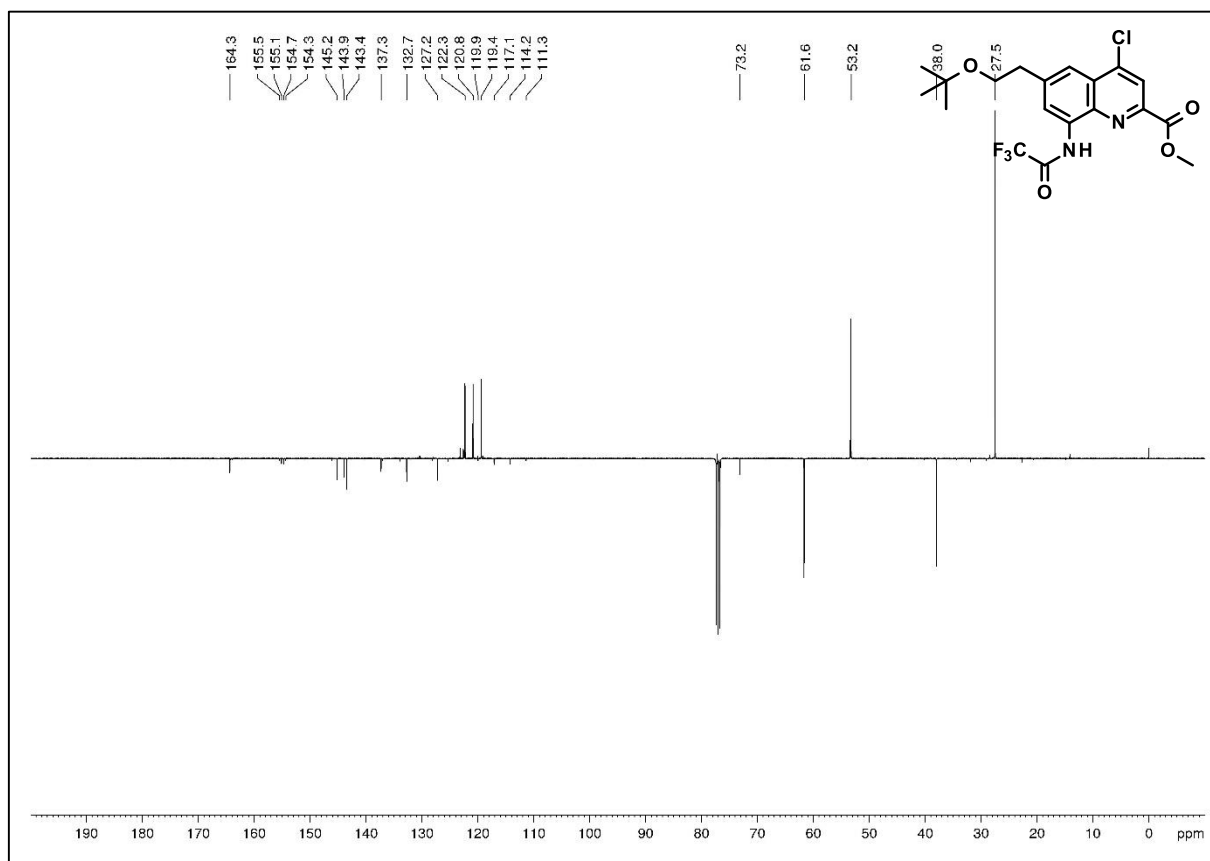


Figure S46. DEPTQ ¹³C NMR (100 MHz, CDCl₃) of compound 4g.

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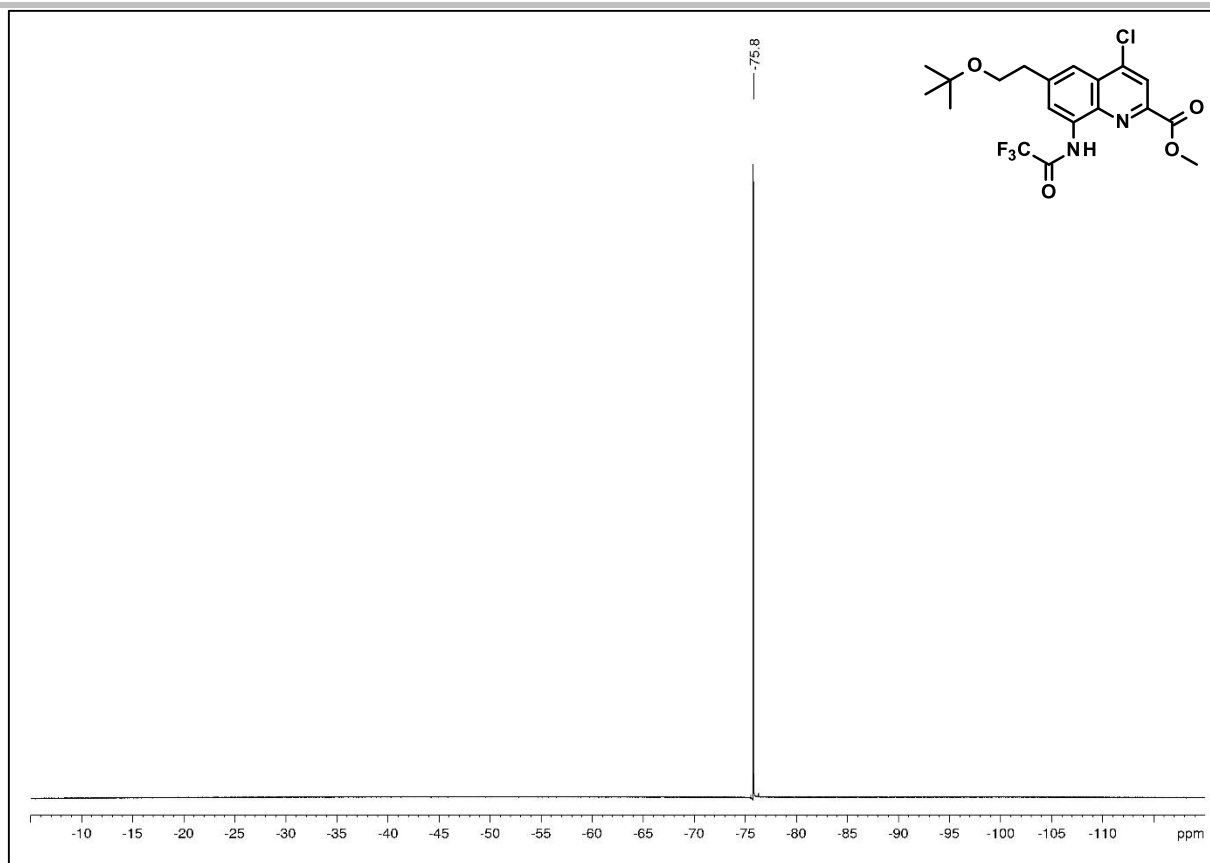


Figure S47. ^{19}F NMR (376 MHz, CDCl_3) of compound **4g**.

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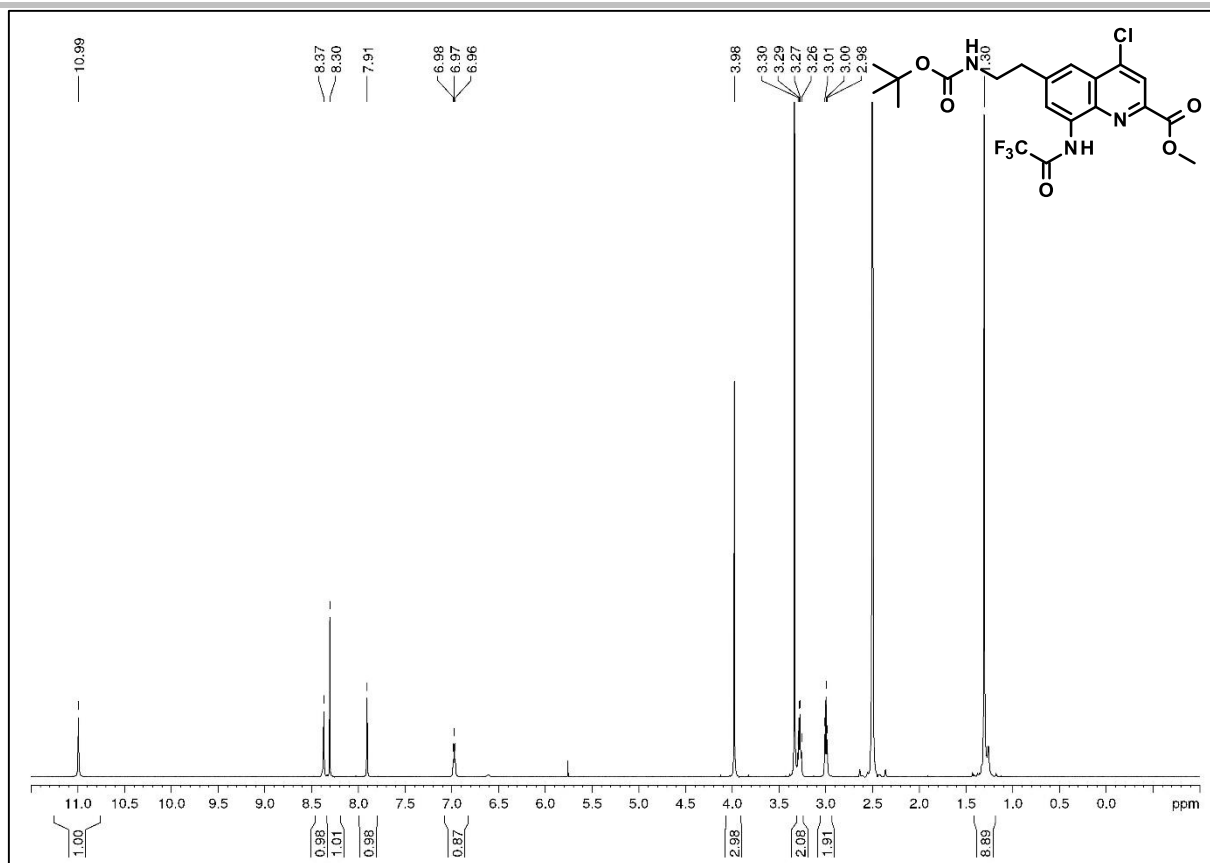


Figure S48. ^1H NMR (500 MHz, DMSO-d_6) of compound **4h**.

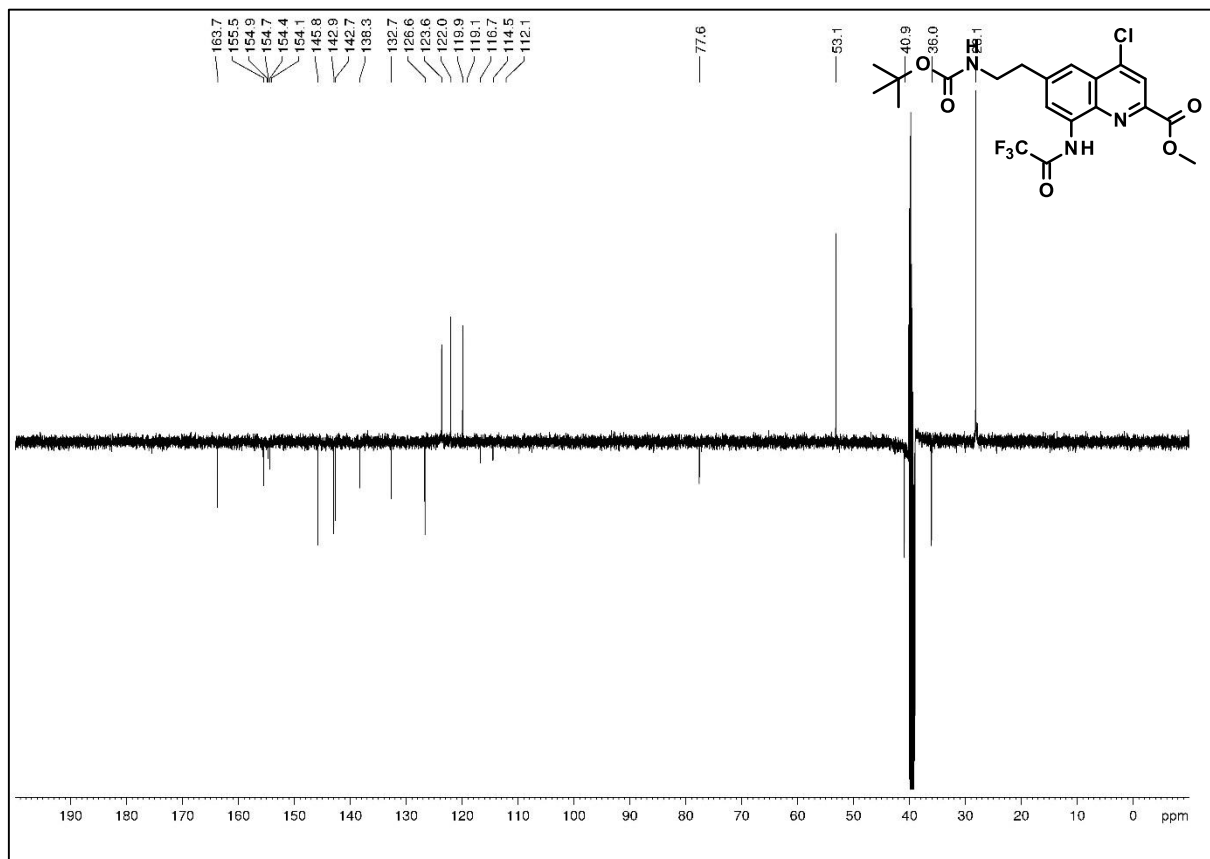


Figure S49. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **4h**.

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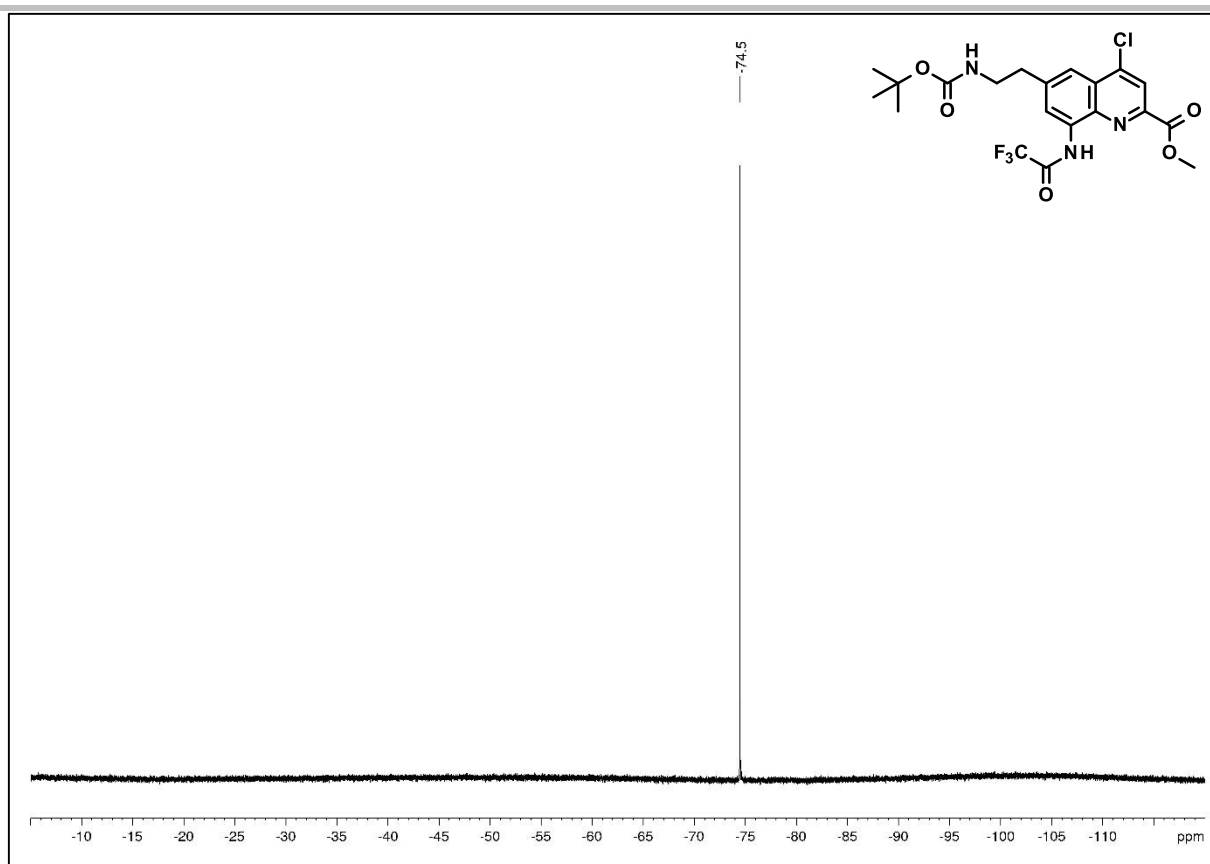


Figure S50. ^{19}F NMR (376 MHz, DMSO-d_6) of compound 4h.

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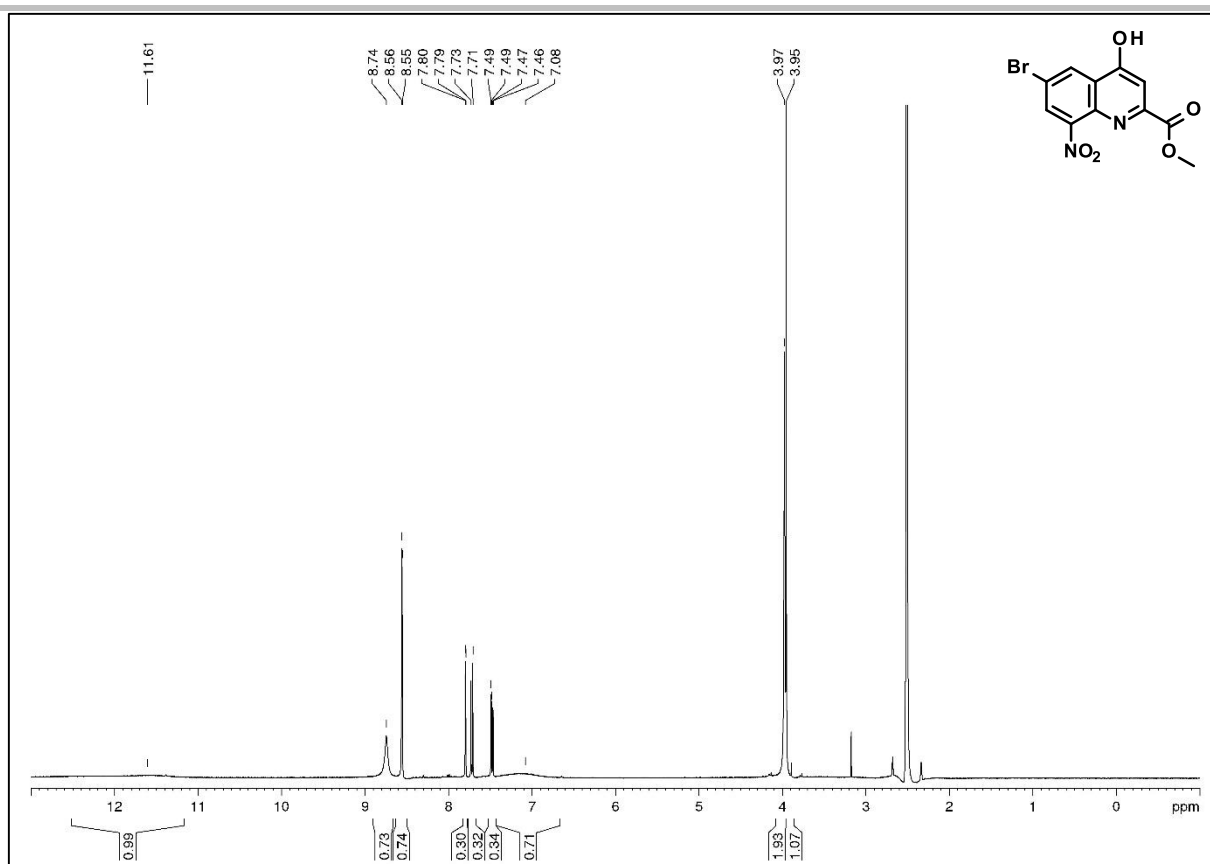


Figure S51. ^1H NMR (400 MHz, DMSO-d_6) of compound 7.

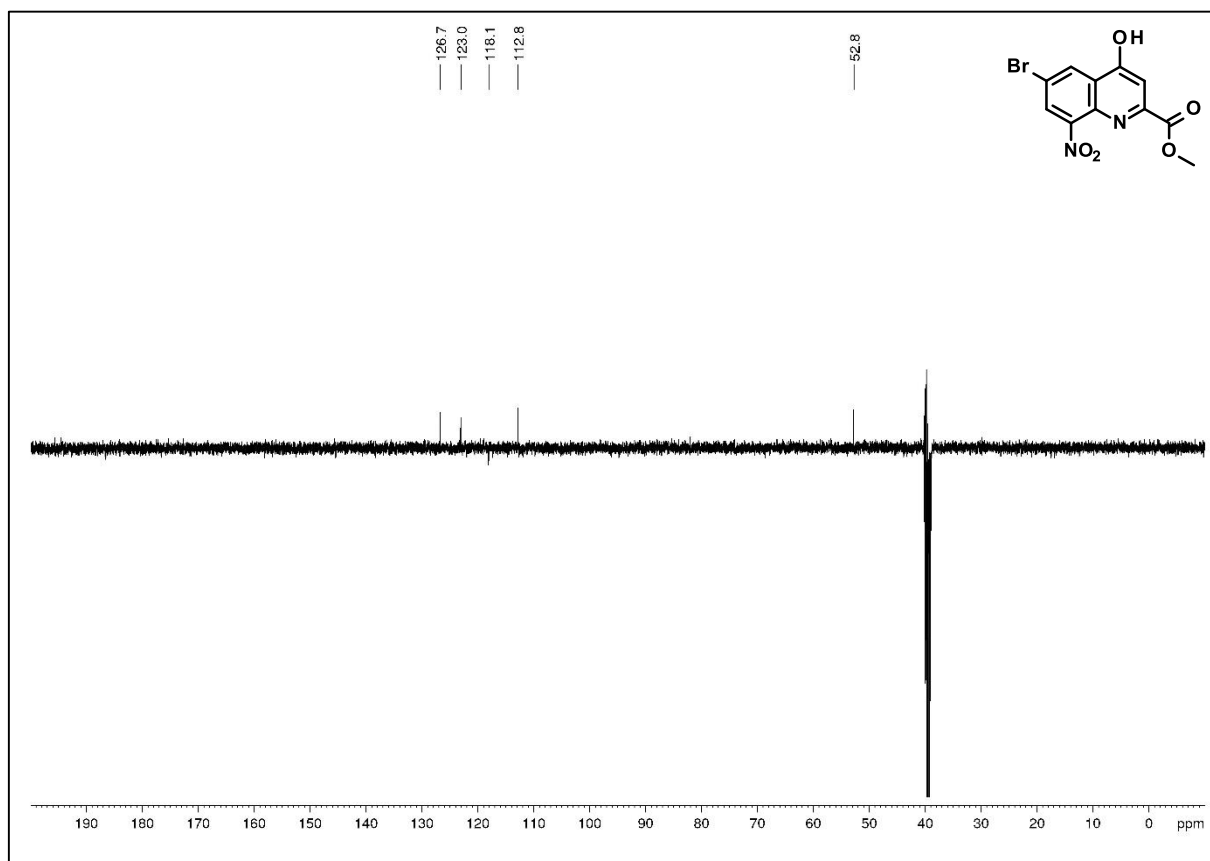


Figure S52. DEPT ^{13}C NMR (100 MHz, DMSO-d_6) of compound 7.

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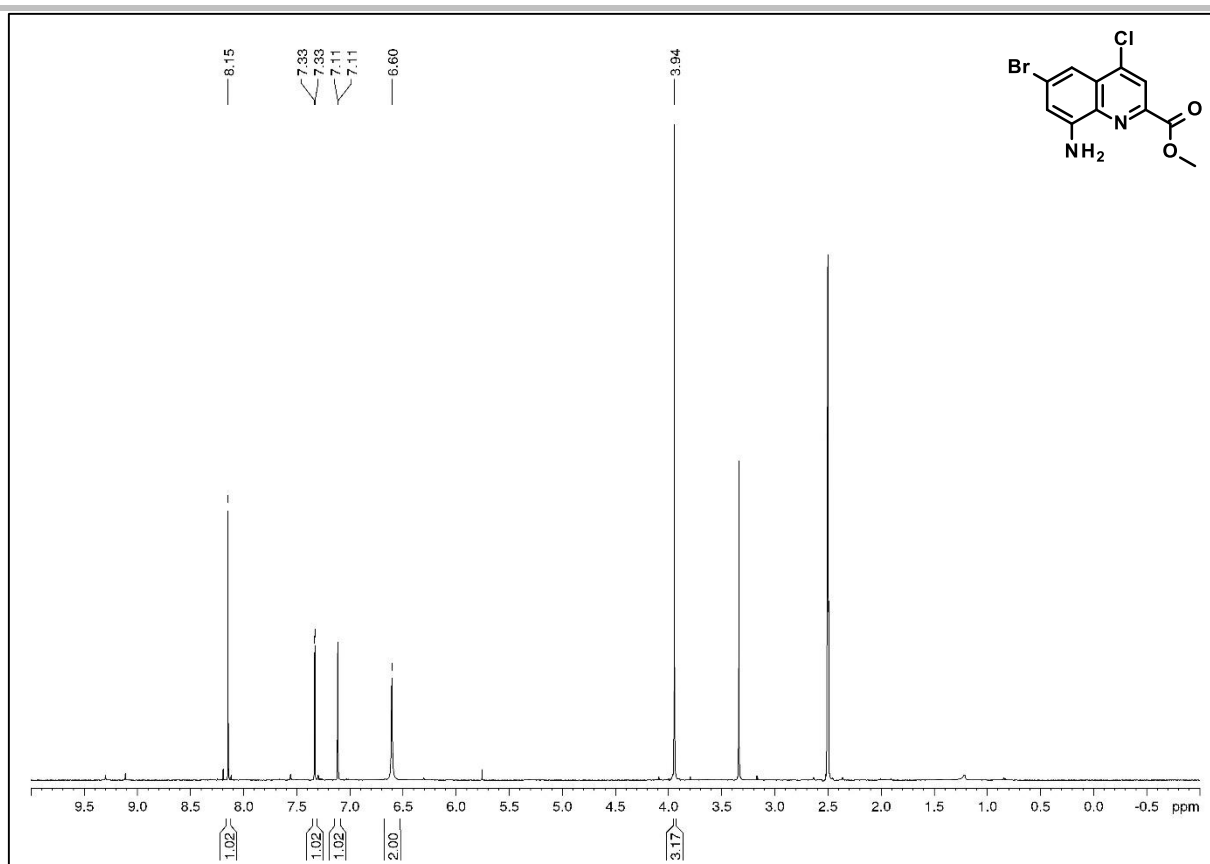


Figure S53. ¹H NMR (500 MHz, DMSO-d₆) of compound 8.

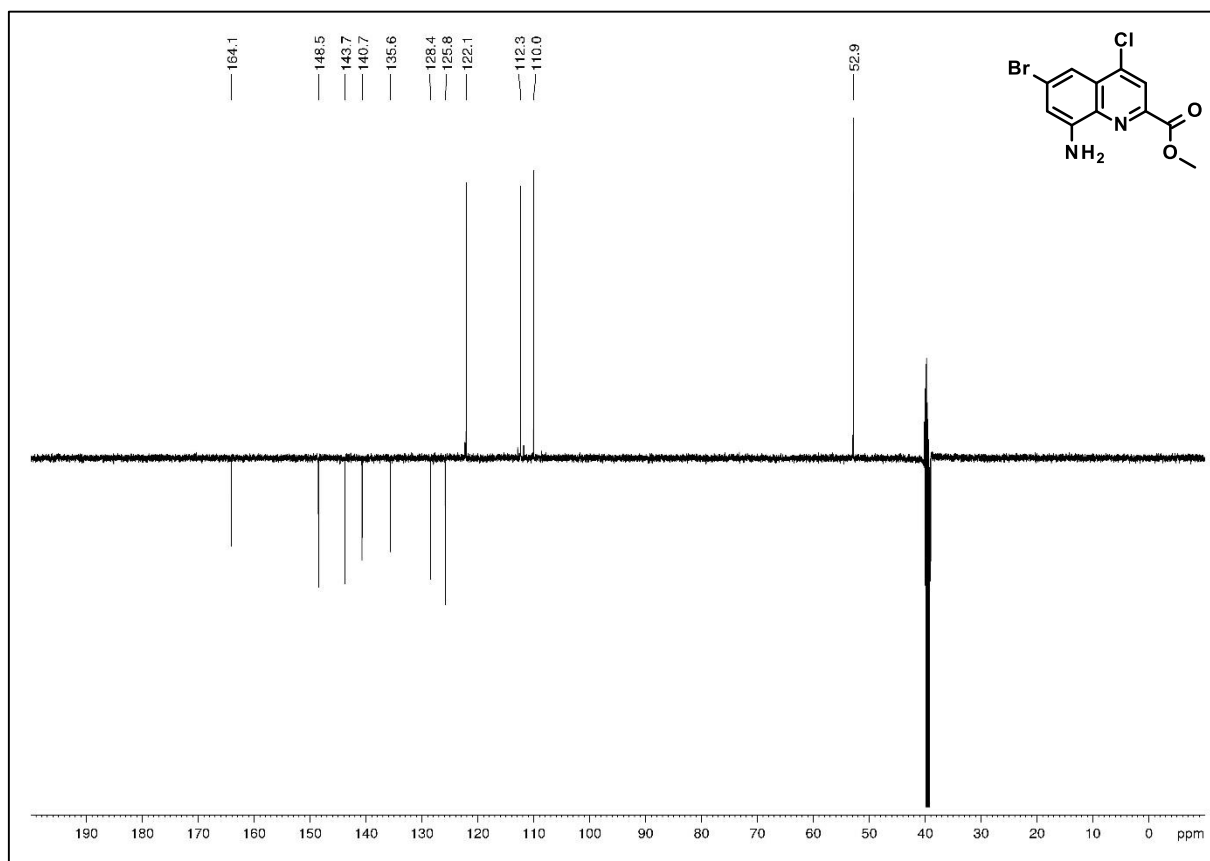


Figure S54. DEPTQ ¹³C NMR (125 MHz, DMSO-d₆) of compound 8.

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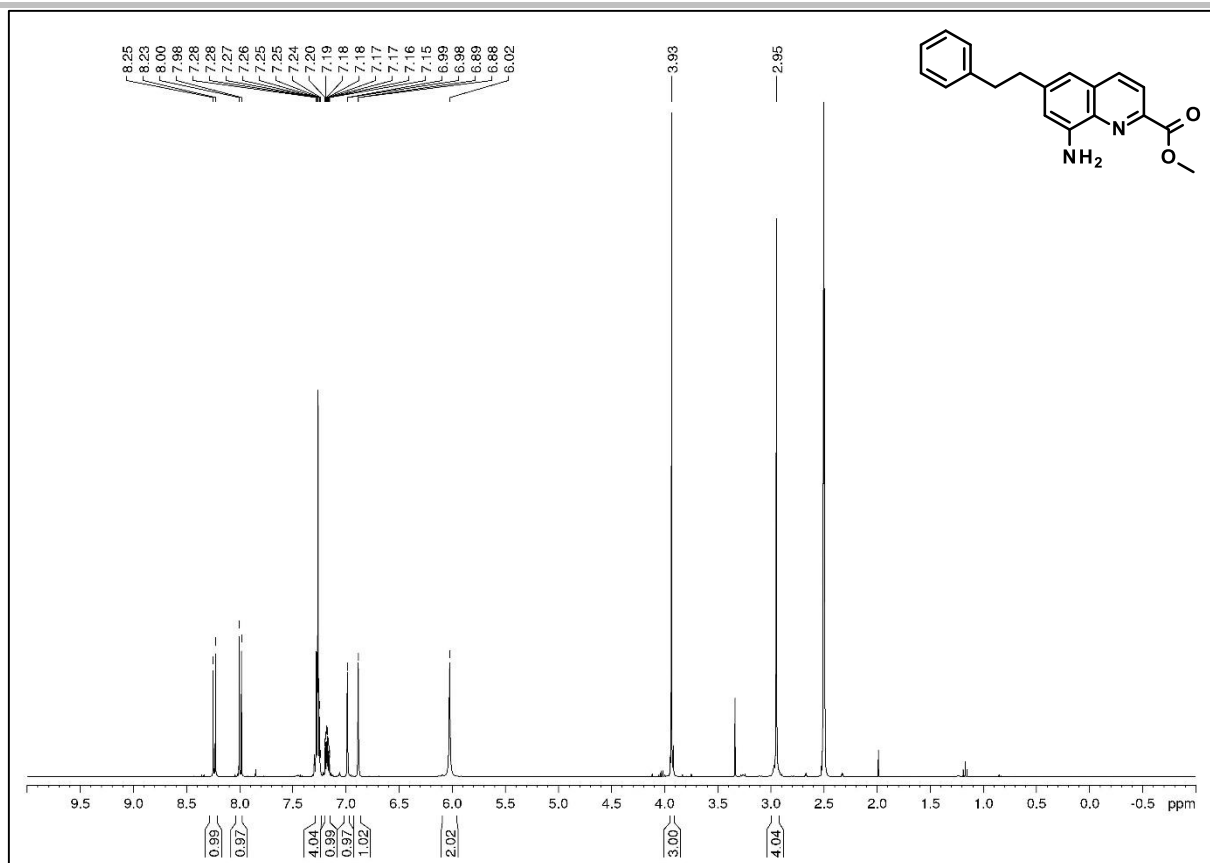


Figure S55. ¹H NMR (400 MHz, DMSO-d₆) of compound 9a.

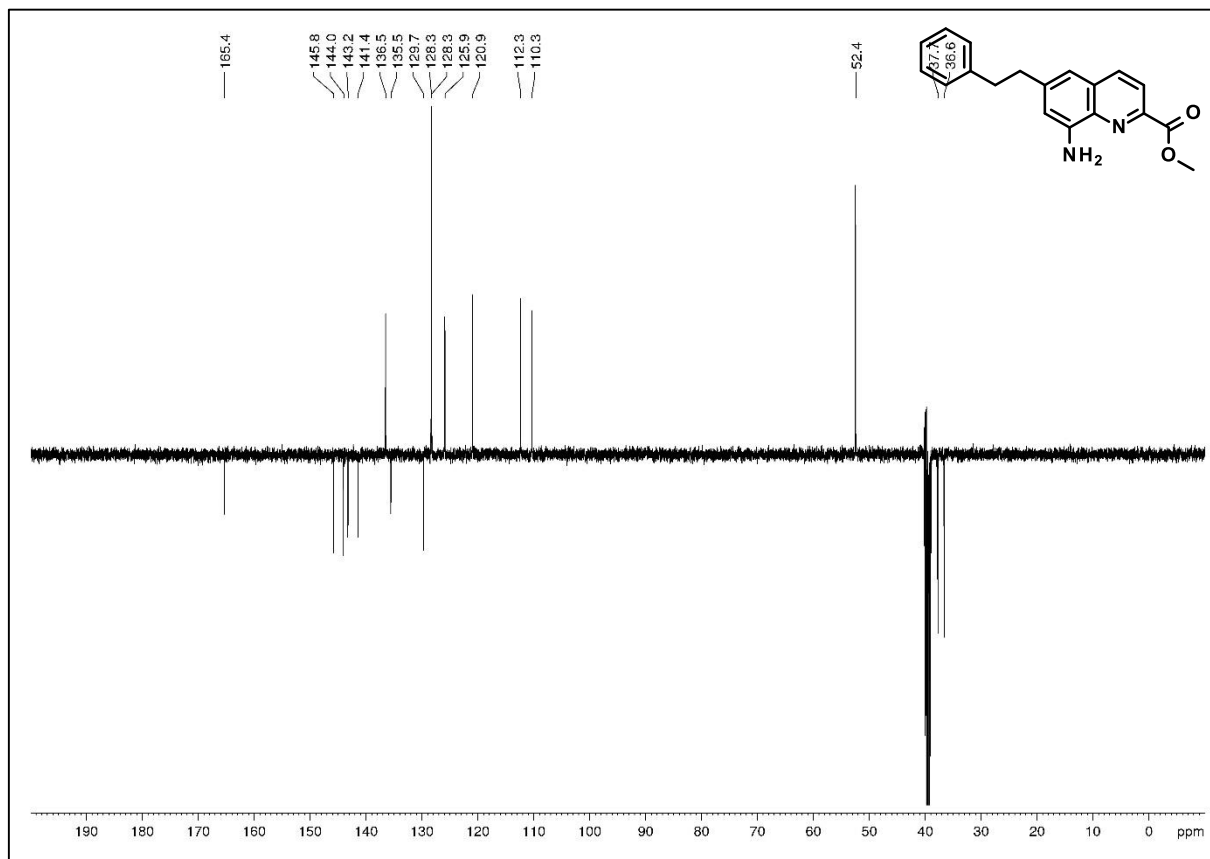


Figure S56. DEPTQ ¹³C NMR (100 MHz, DMSO-d₆) of compound 9a.

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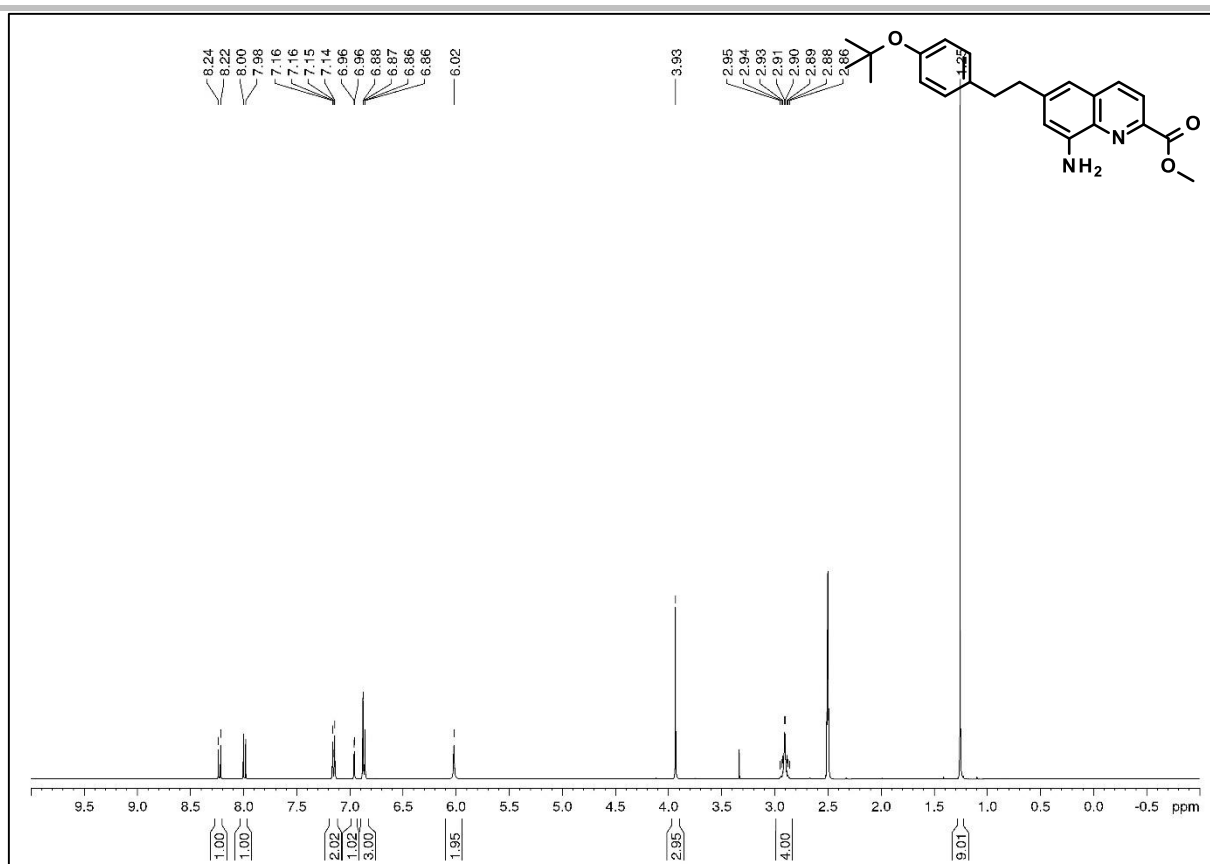


Figure S57. ^1H NMR (400 MHz, DMSO-d_6) of compound **9b**.

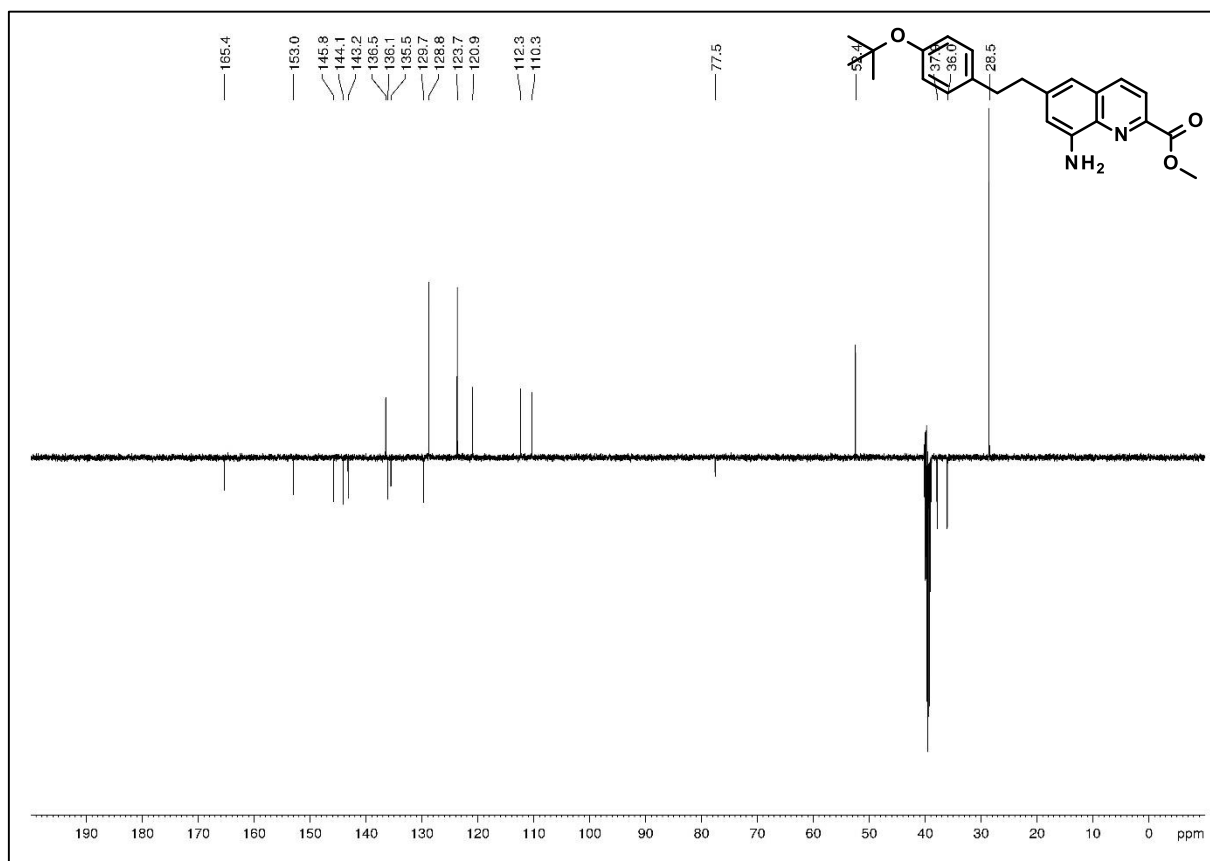


Figure S58. DEPTQ ^{13}C NMR (100 MHz, DMSO-d_6) of compound **9b**.

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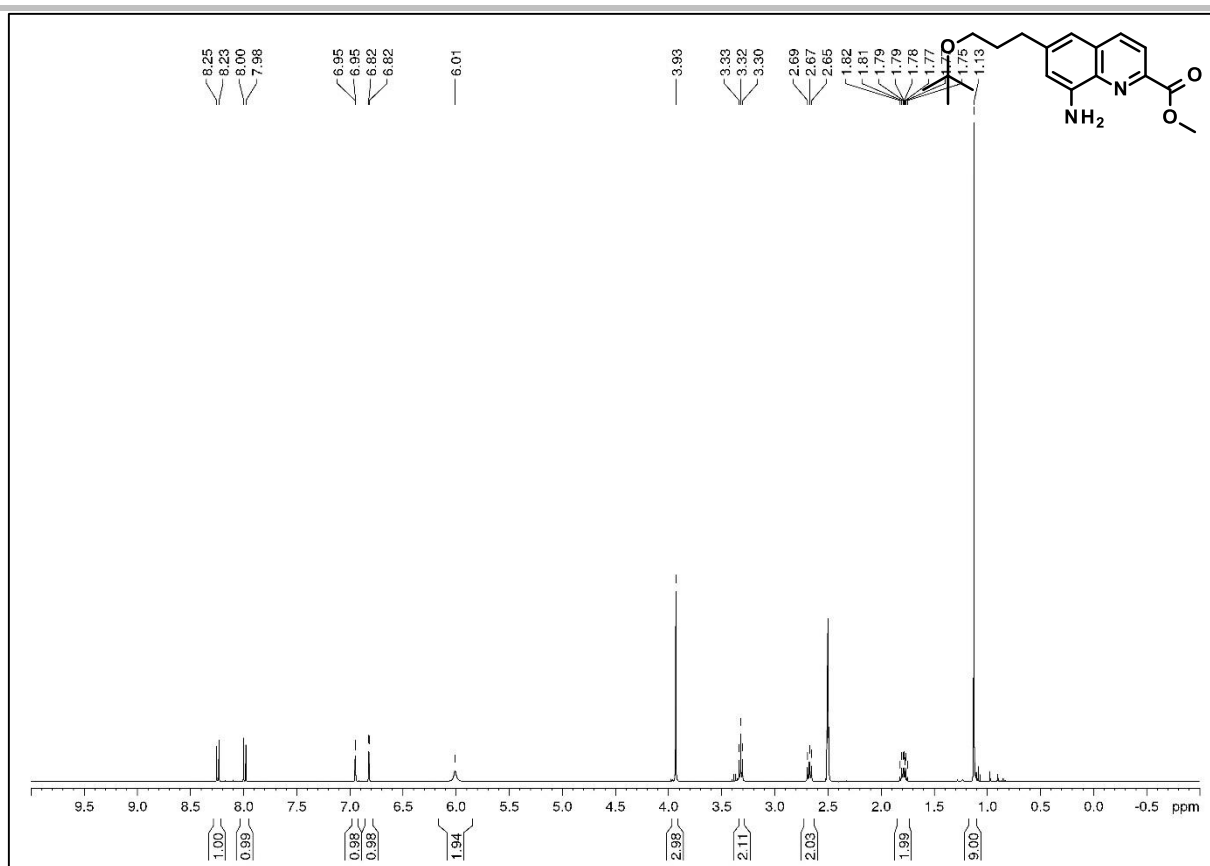


Figure S59. ^1H NMR (400 MHz, DMSO-d_6) of compound **9c**.

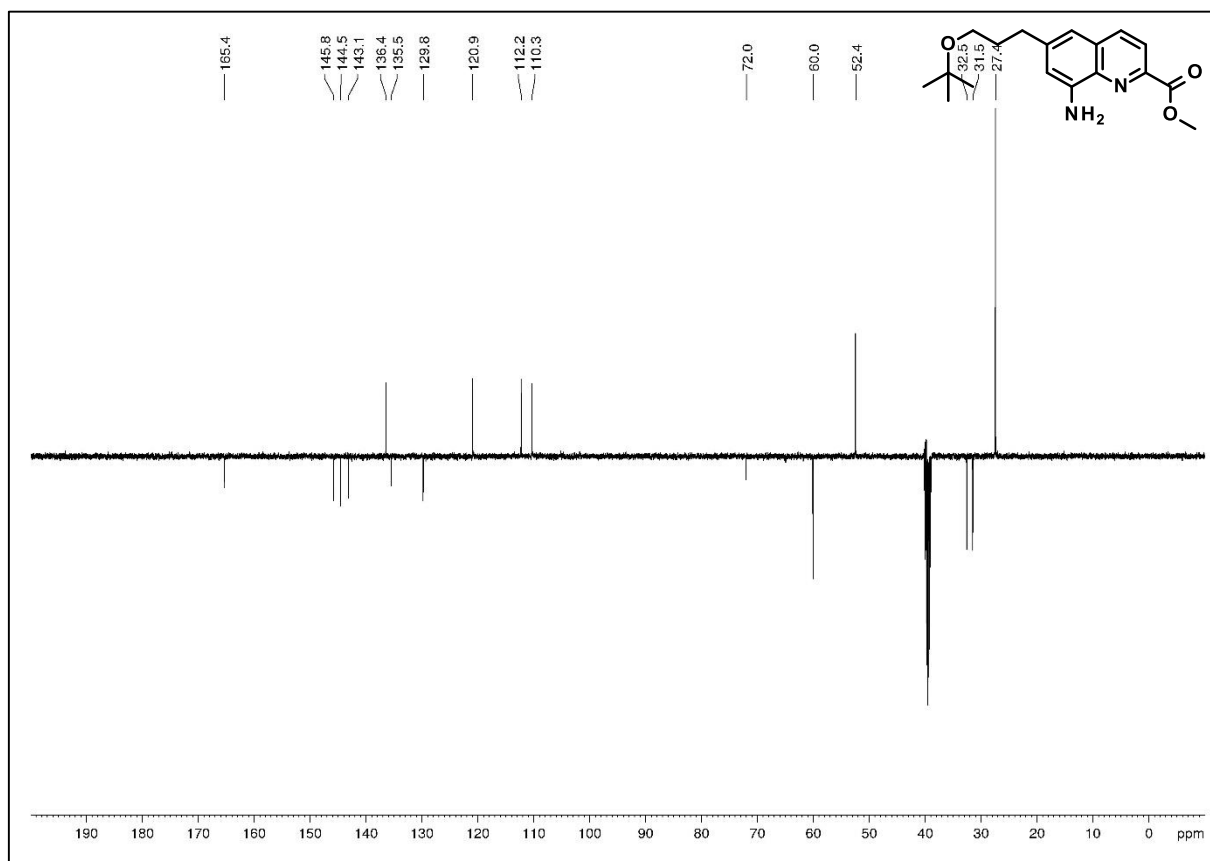


Figure S60. DEPTQ ^{13}C NMR (100 MHz, DMSO-d_6) of compound **9c**.

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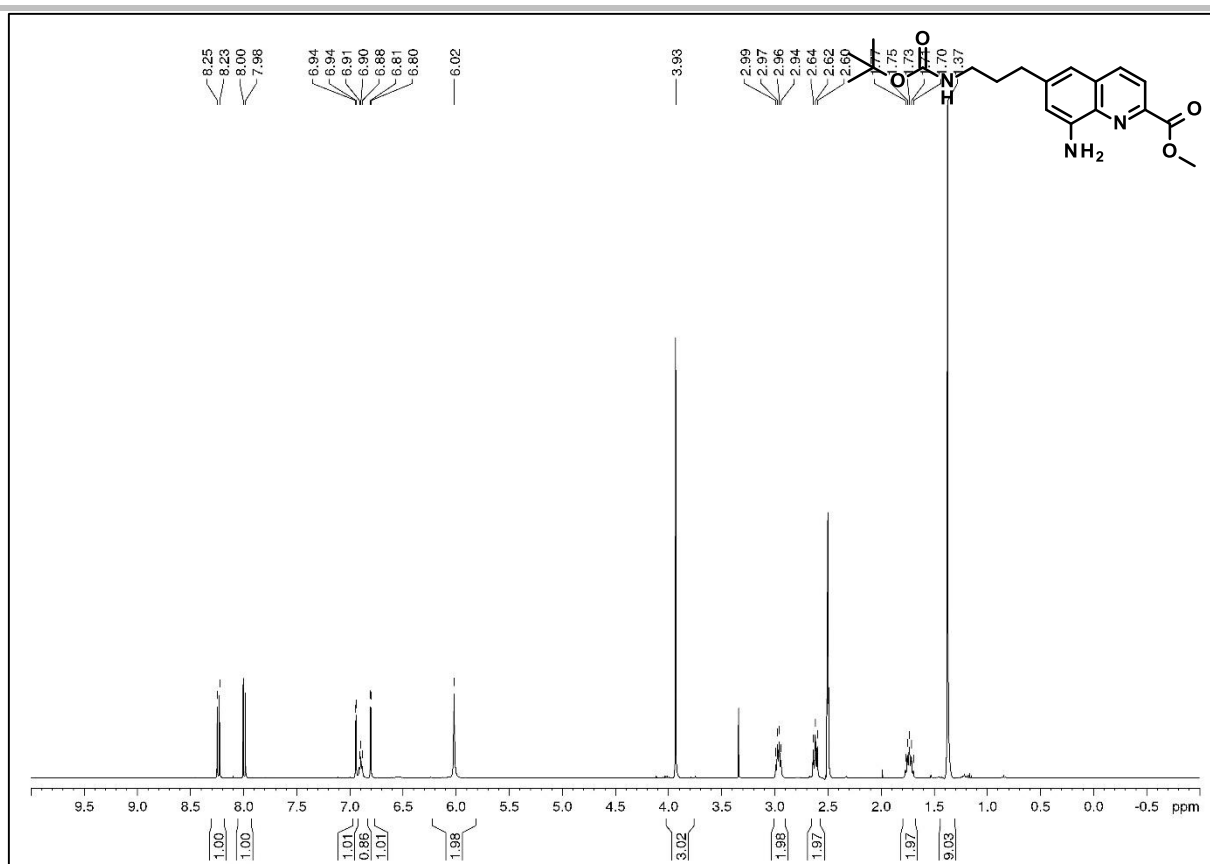


Figure S61. ^1H NMR (500 MHz, DMSO-d_6) of compound **9d**.

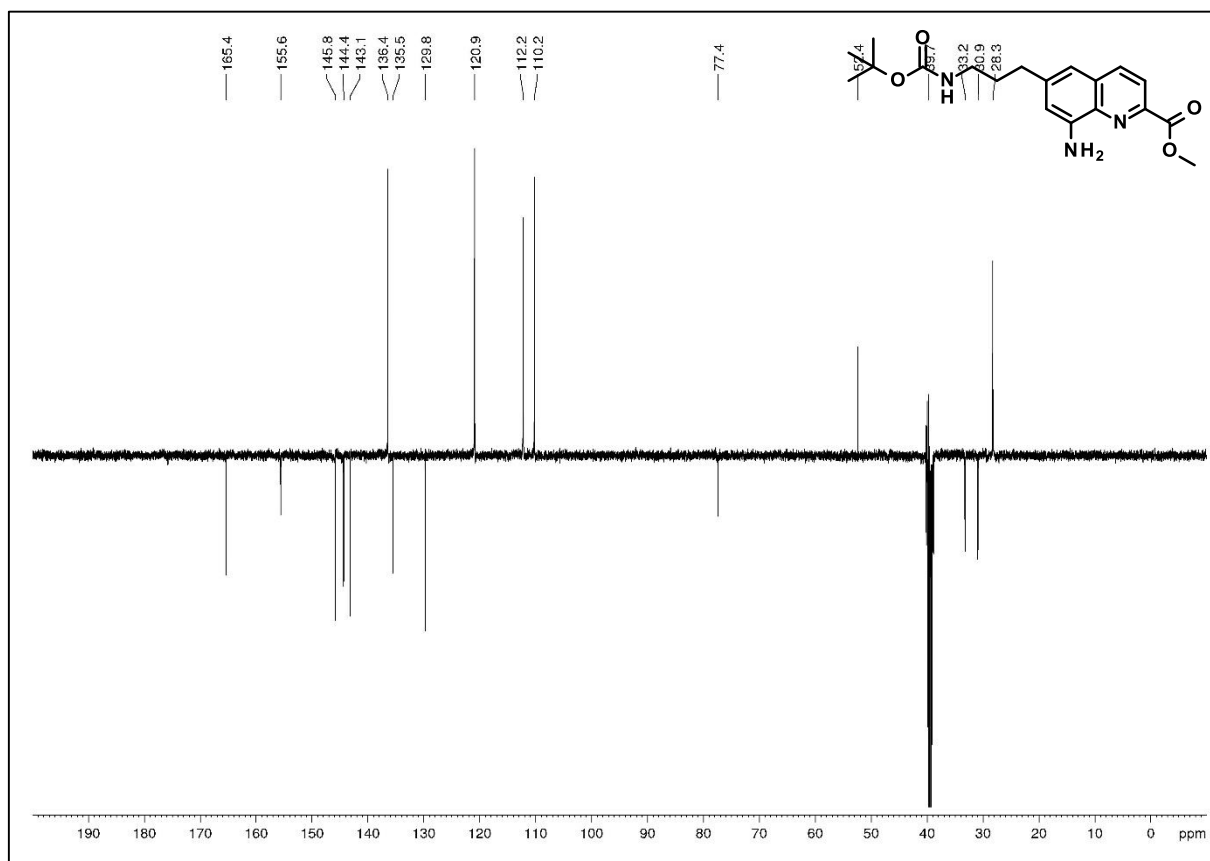


Figure S62. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **9d**.

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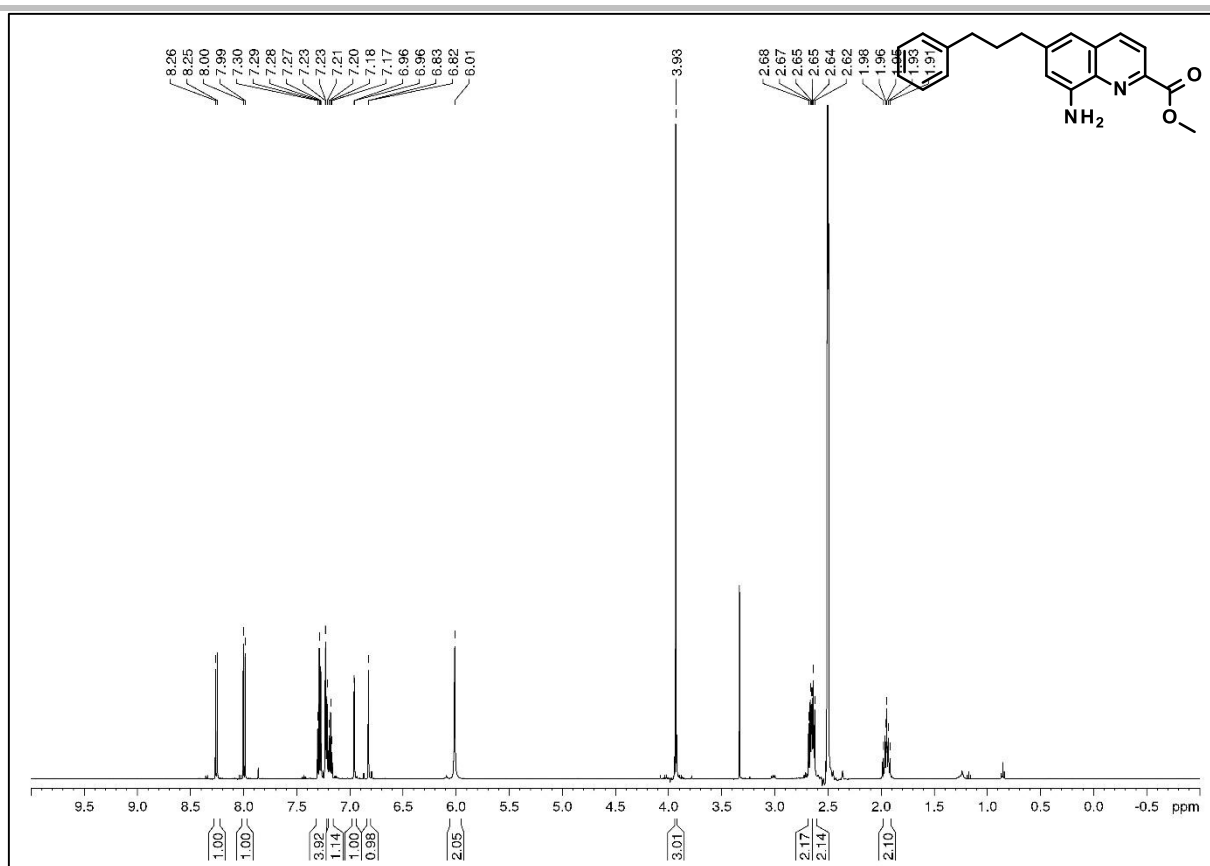


Figure S63. ^1H NMR (500 MHz, DMSO-d_6) of compound **9e**.

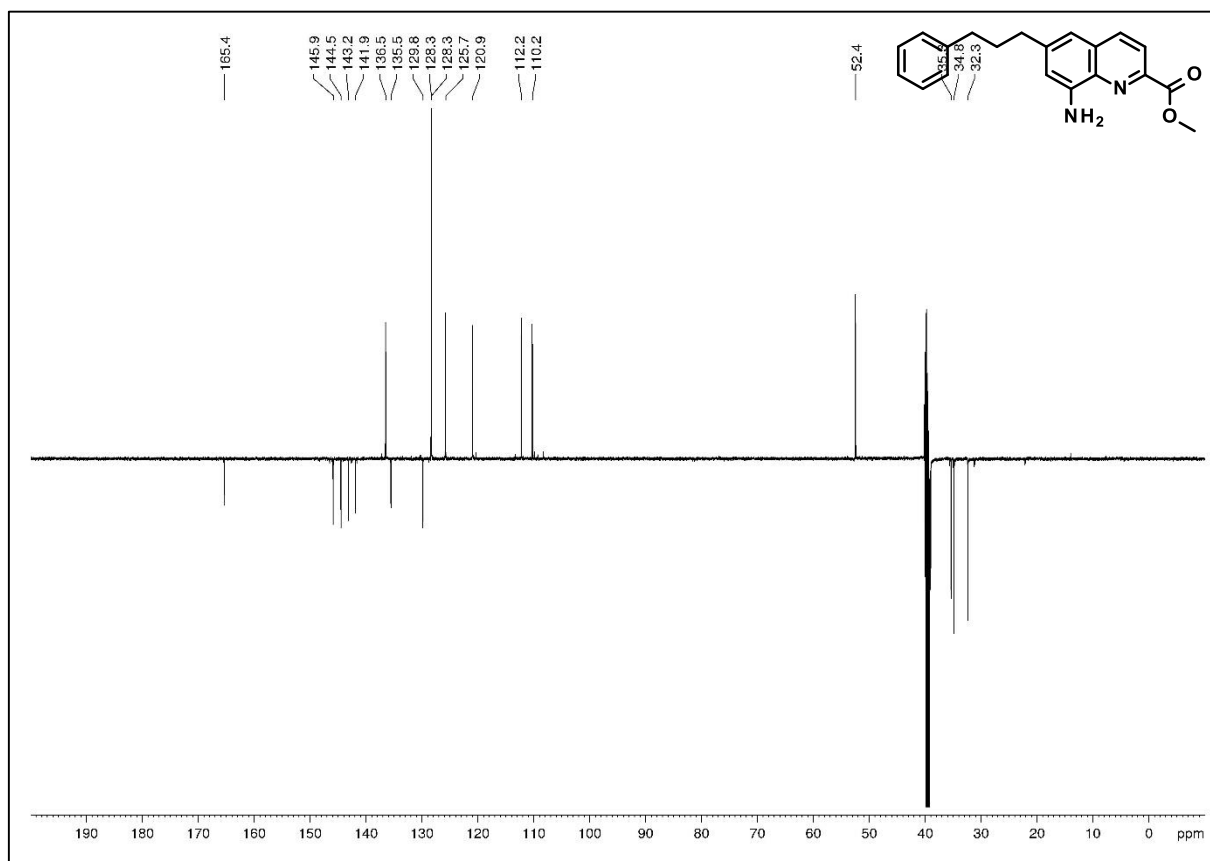


Figure S64. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **9e**.

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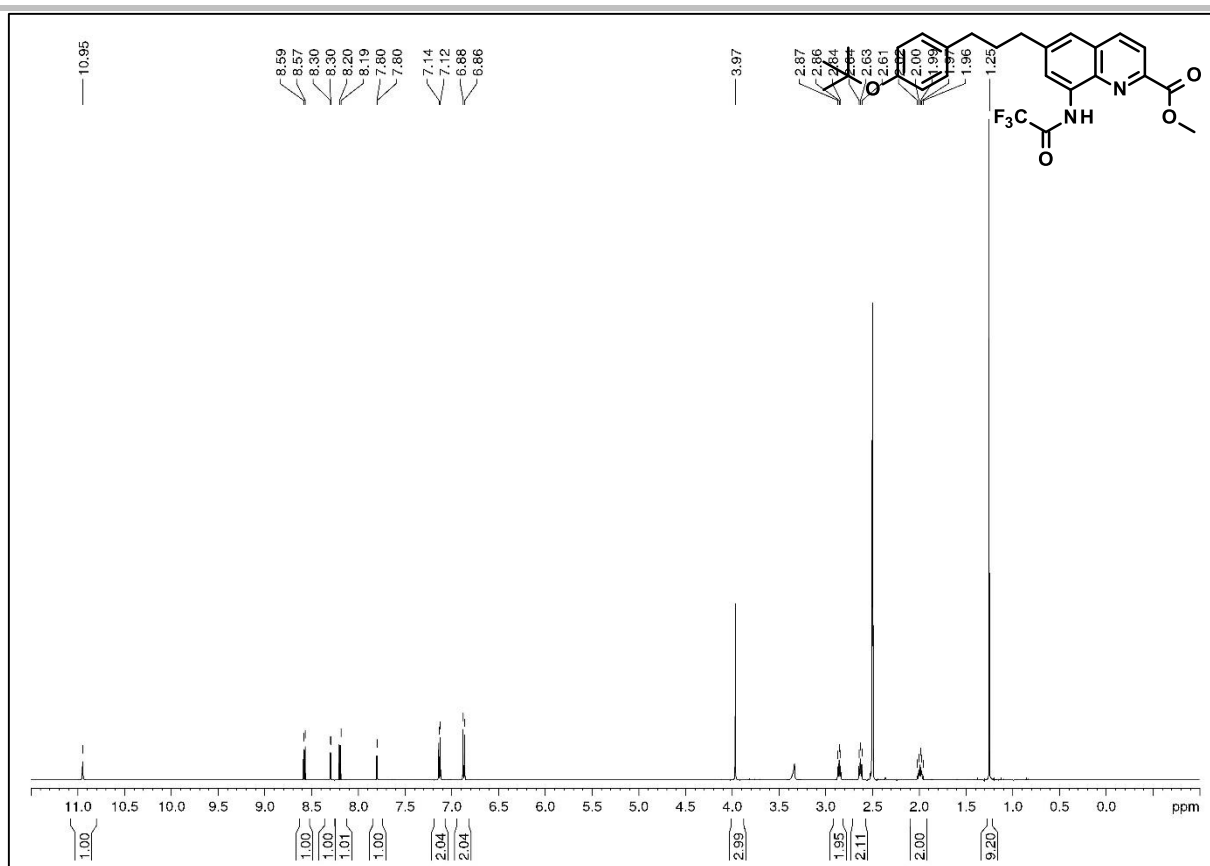


Figure S65. ¹H NMR (500 MHz, DMSO-d₆) of compound 9f.

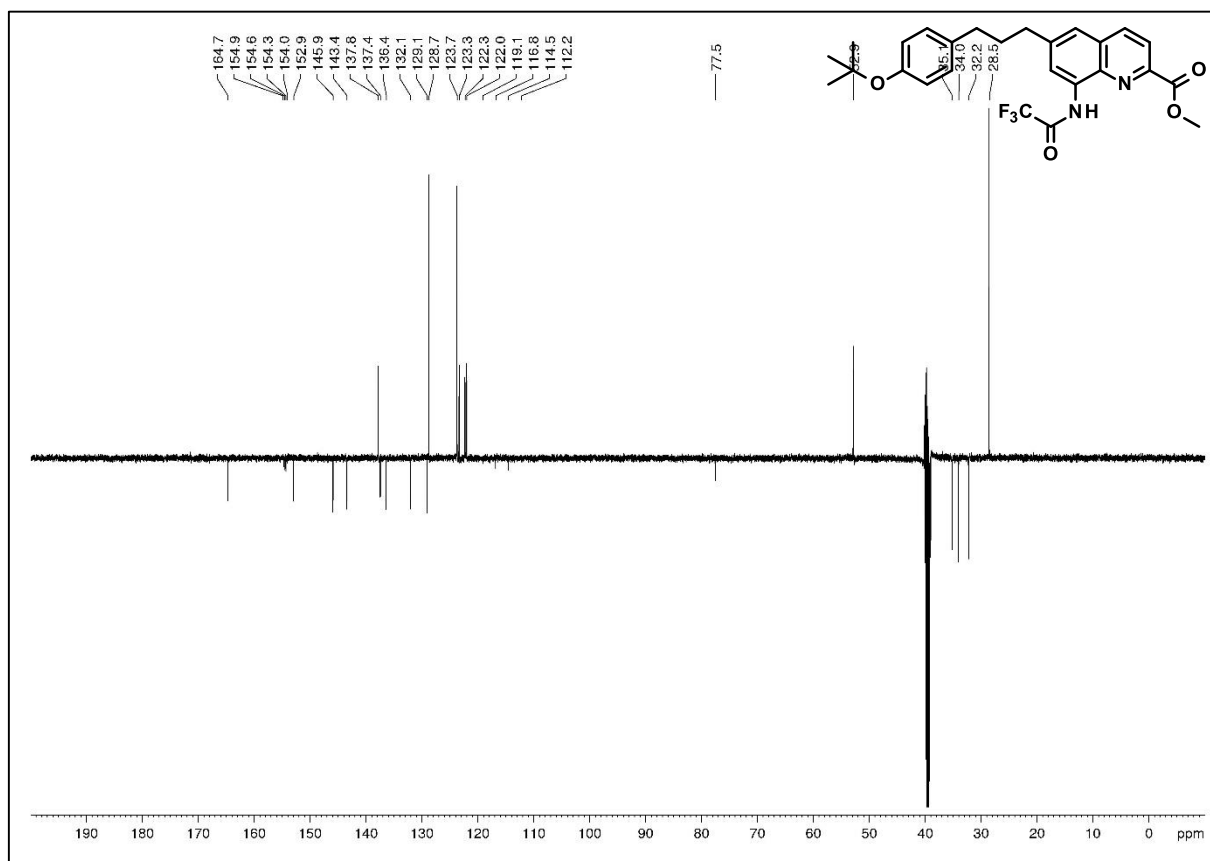


Figure S66. DEPTQ ¹³C NMR (125 MHz, DMSO-d₆) of compound 9f.

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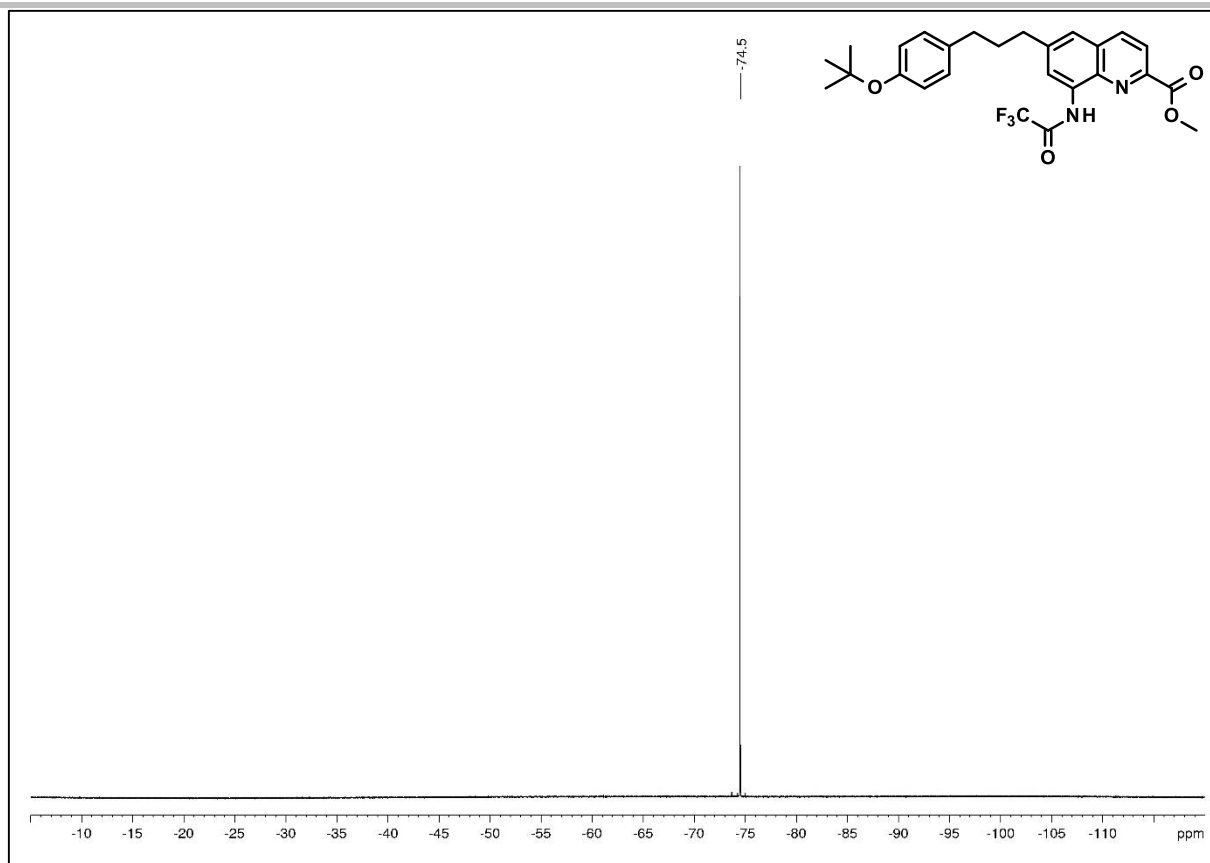


Figure S67. ^{19}F NMR (376 MHz, DMSO-d_6) of compound **9f**.

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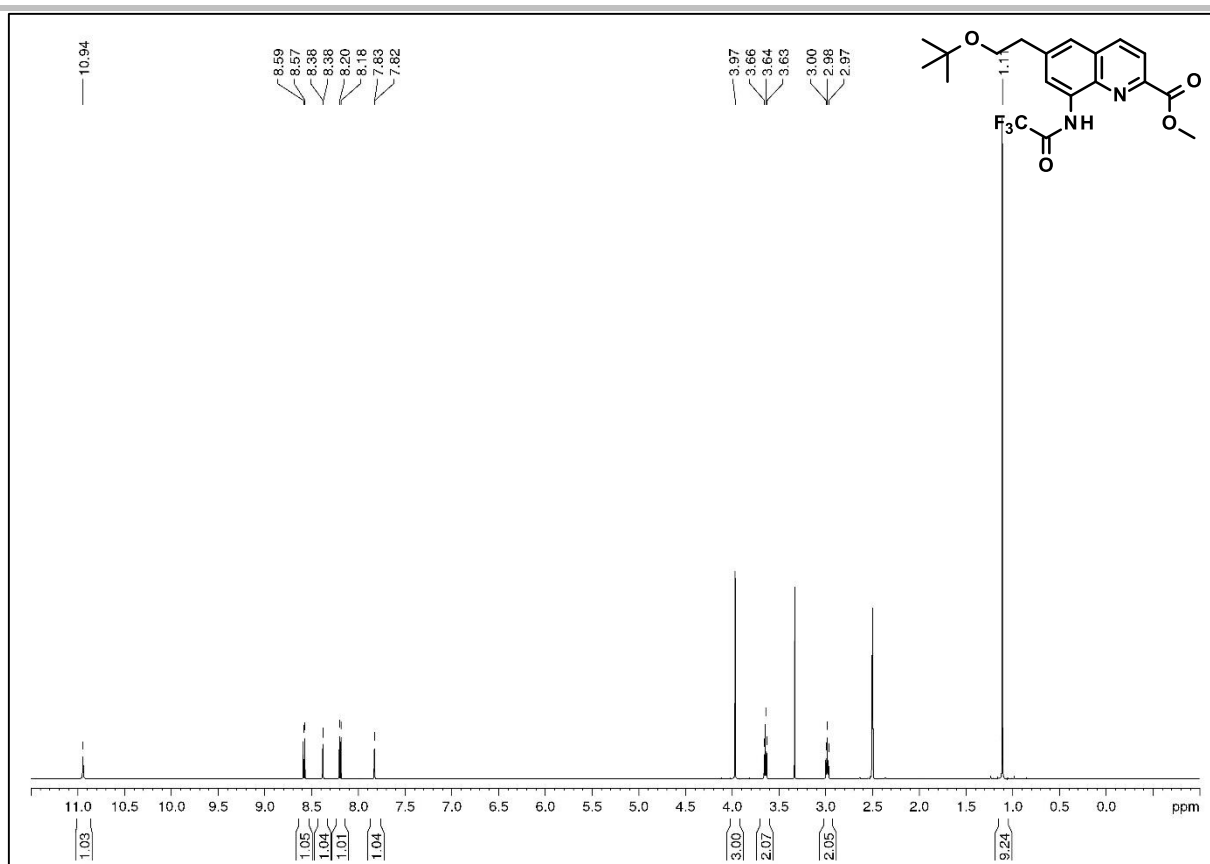


Figure S68. ^1H NMR (500 MHz, DMSO-d_6) of compound **9g**.

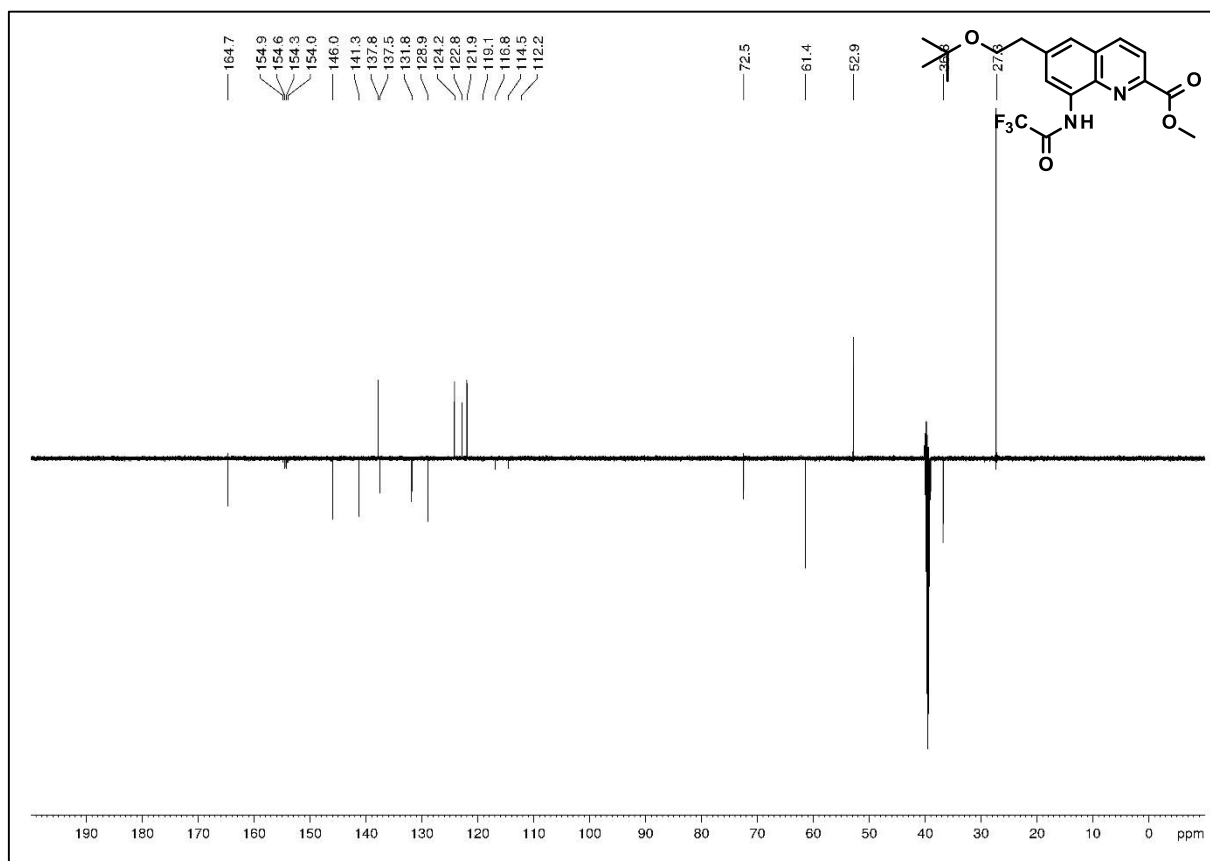


Figure S69. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **9g**.

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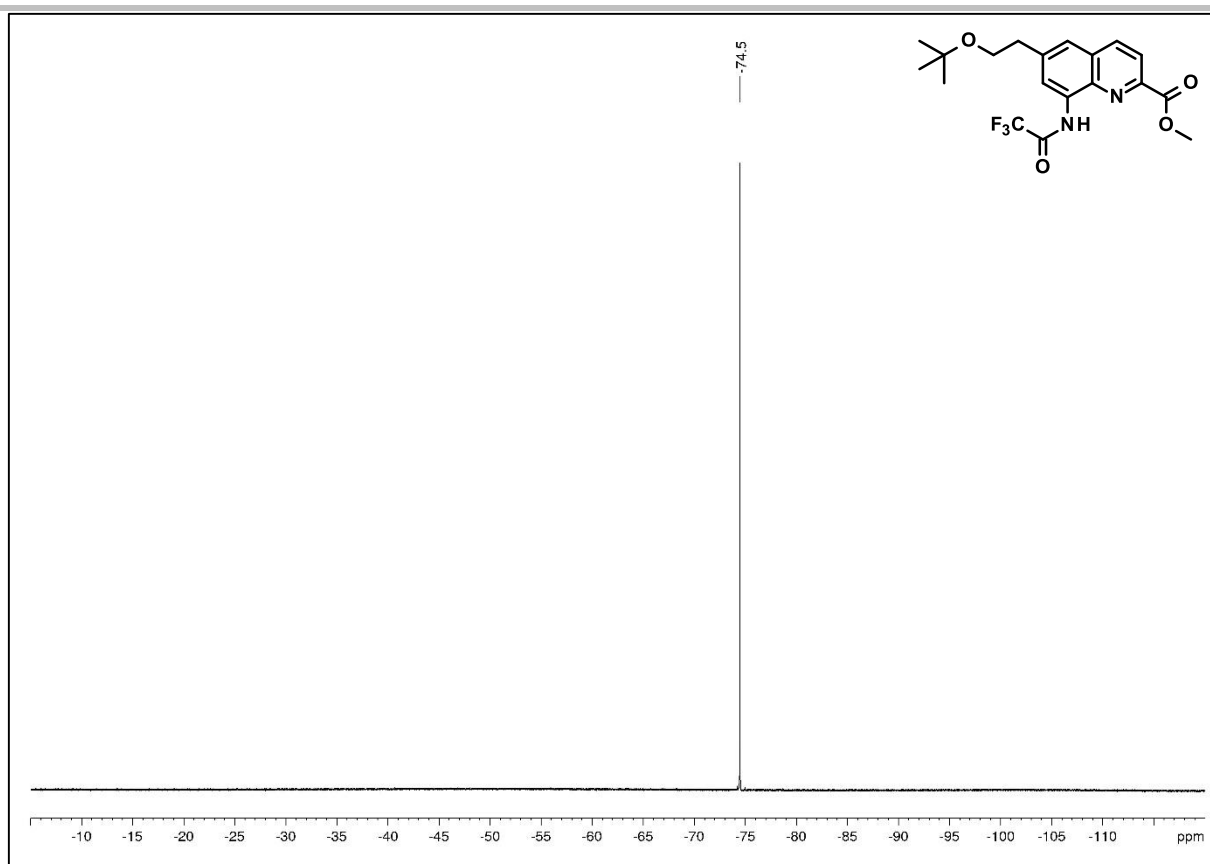


Figure S70. ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) of compound **9g**.

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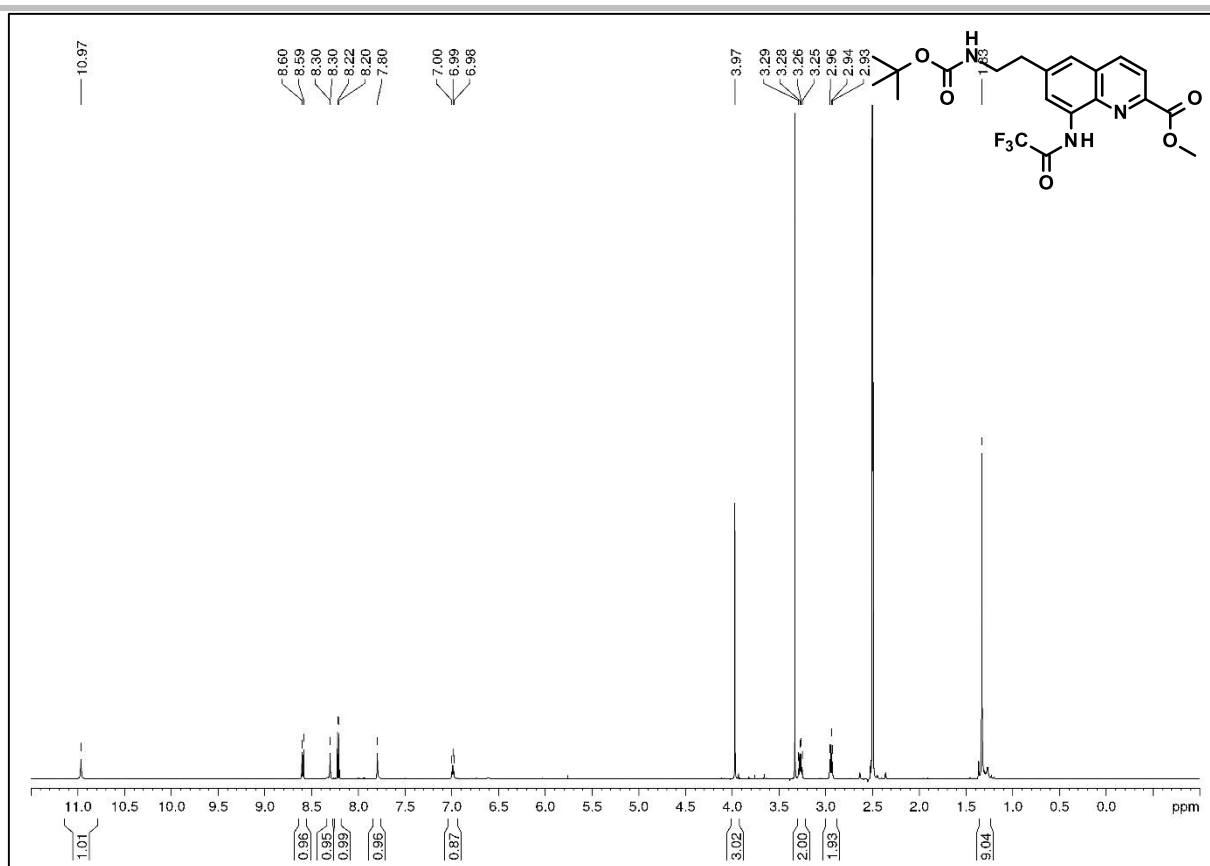


Figure S71. ^1H NMR (500 MHz, DMSO-d_6) of compound **9h**.

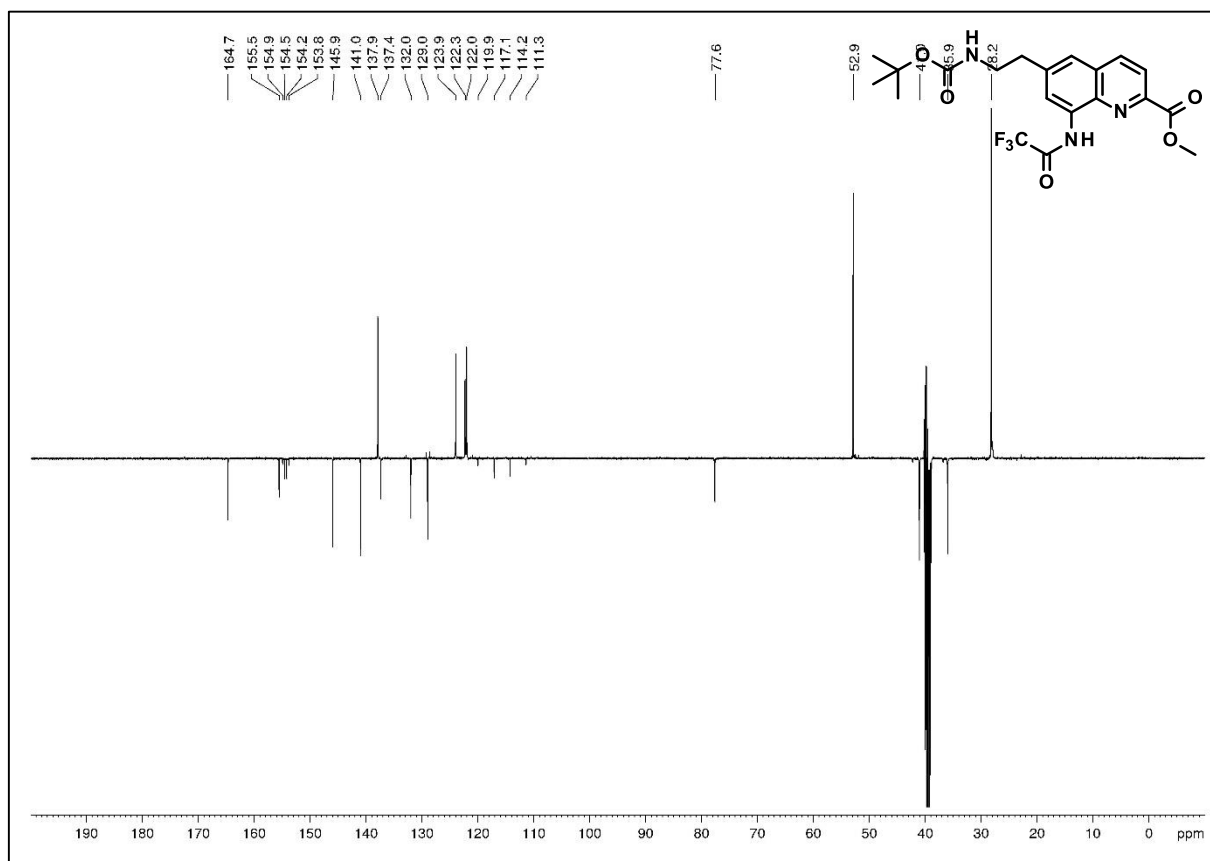


Figure S72. DEPTQ ^{13}C NMR (125 MHz, DMSO-d_6) of compound **9h**.

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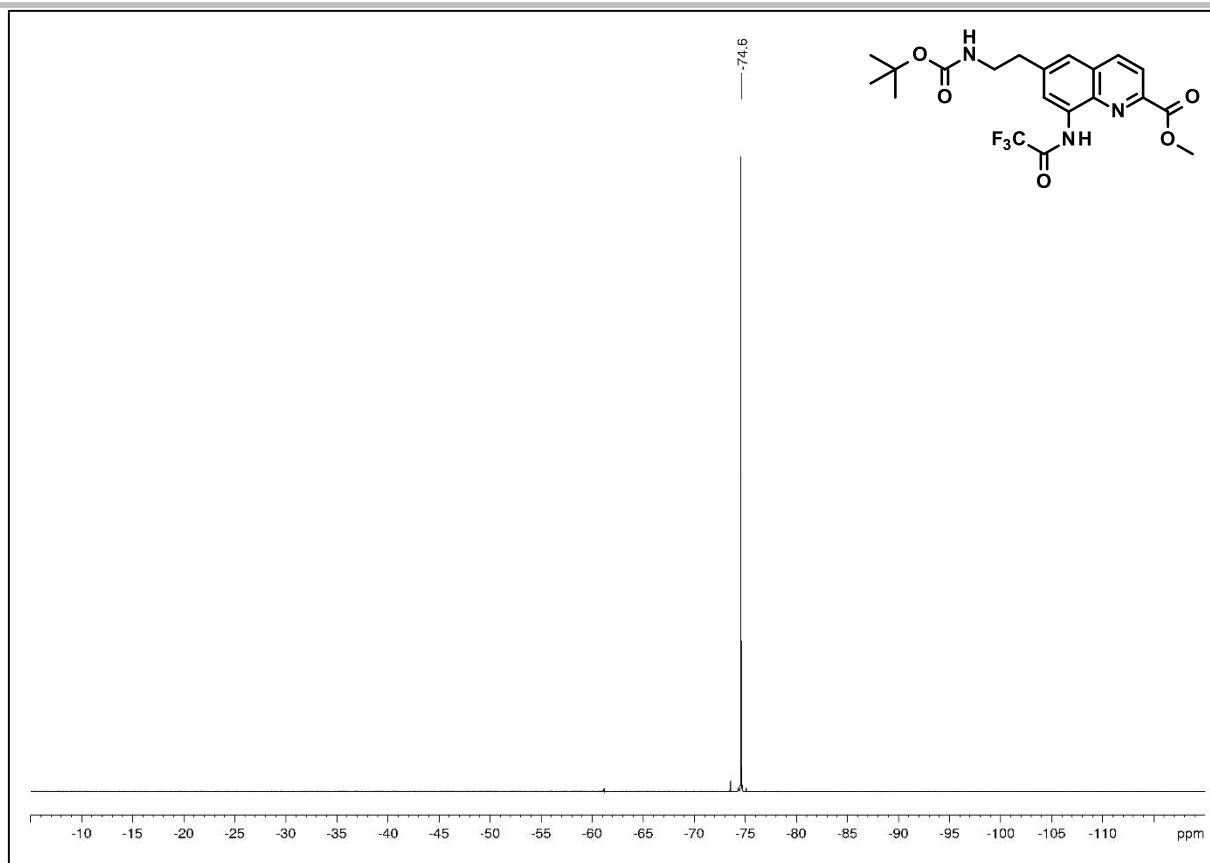
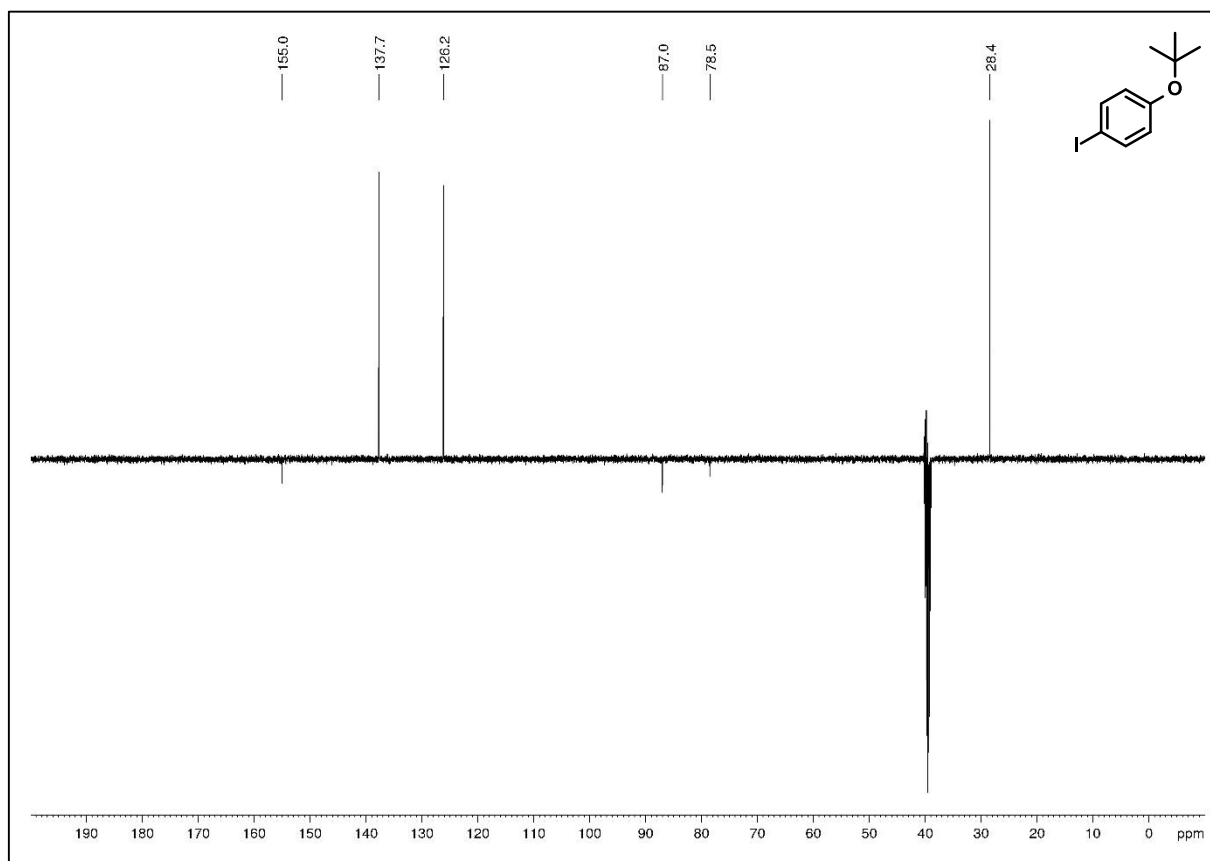
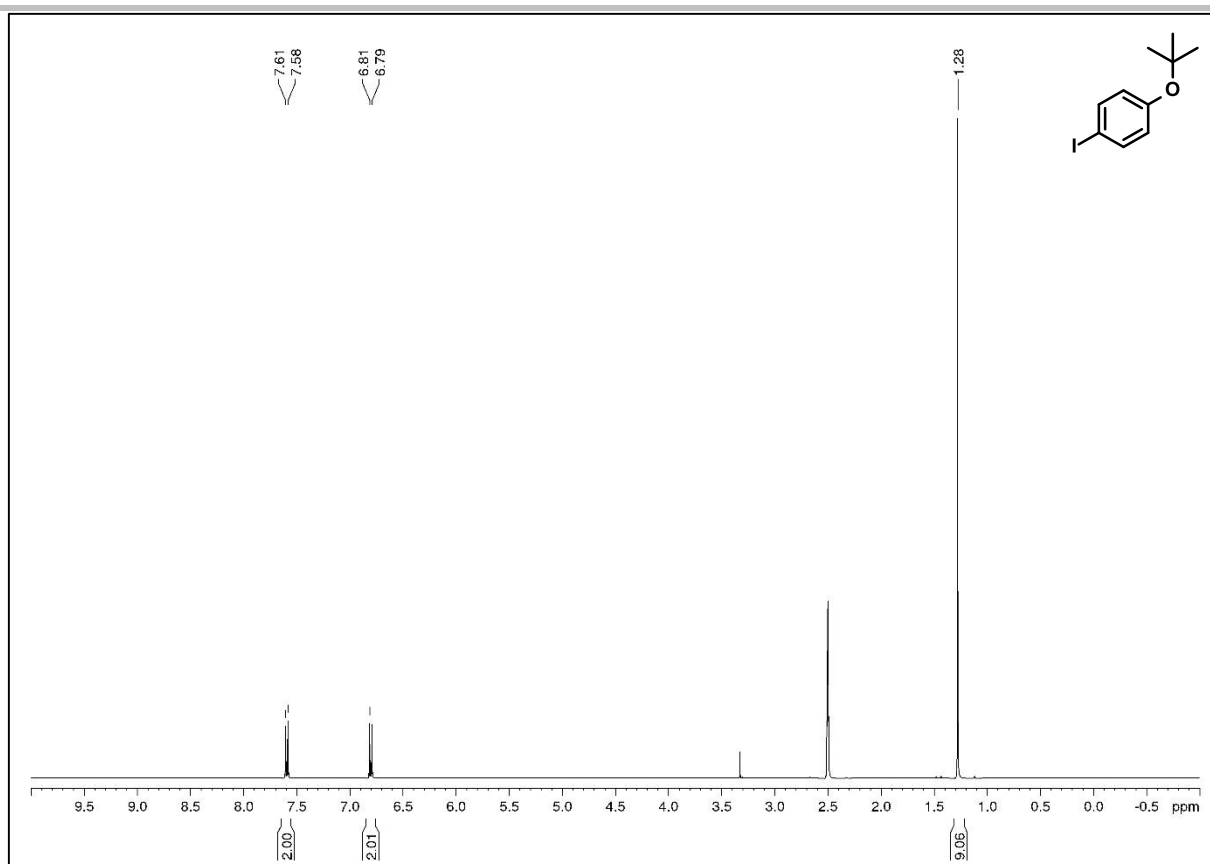


Figure S73. ^{19}F NMR (376 MHz, DMSO-d_6) of compound **9h**.

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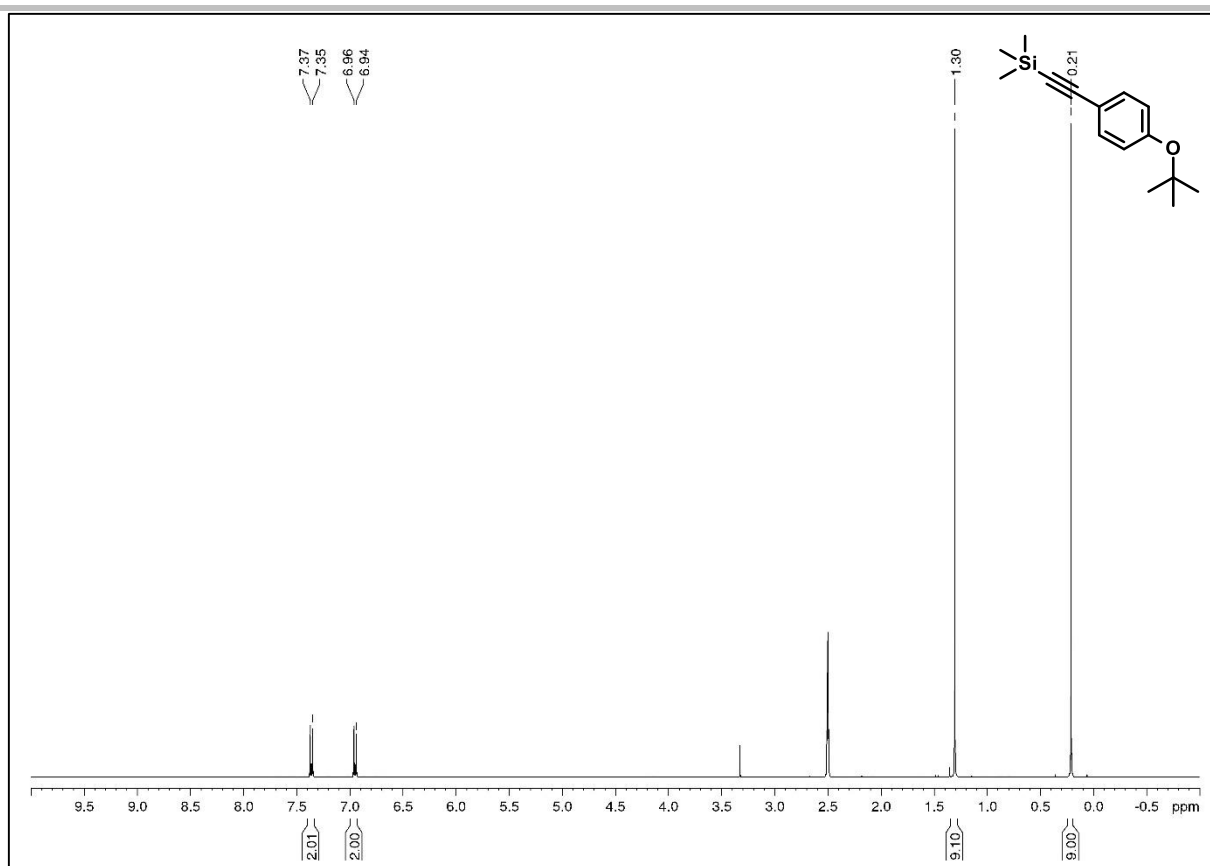


Figure S76. ^1H NMR (400 MHz, DMSO-d_6) of compound 12.

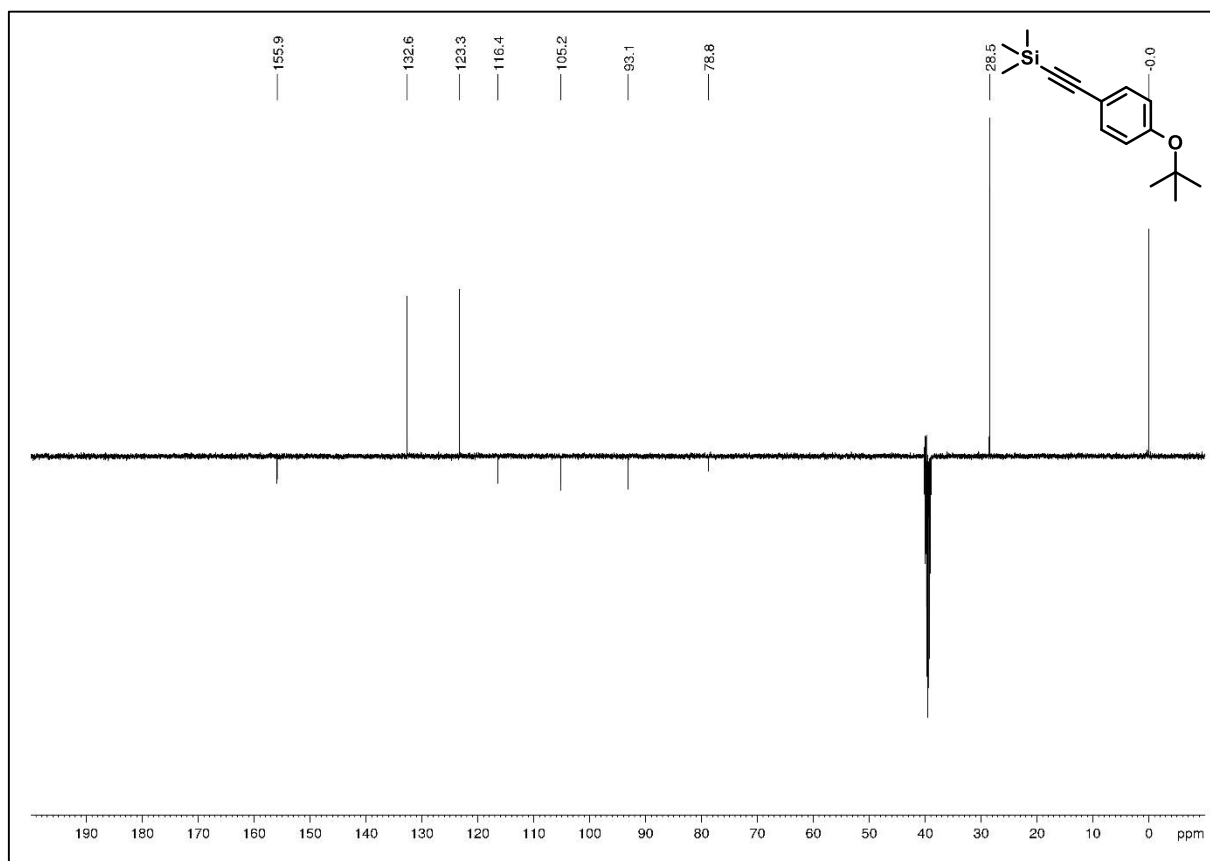


Figure S77. DEPTQ ^{13}C NMR (100 MHz, DMSO-d_6) of compound 12.

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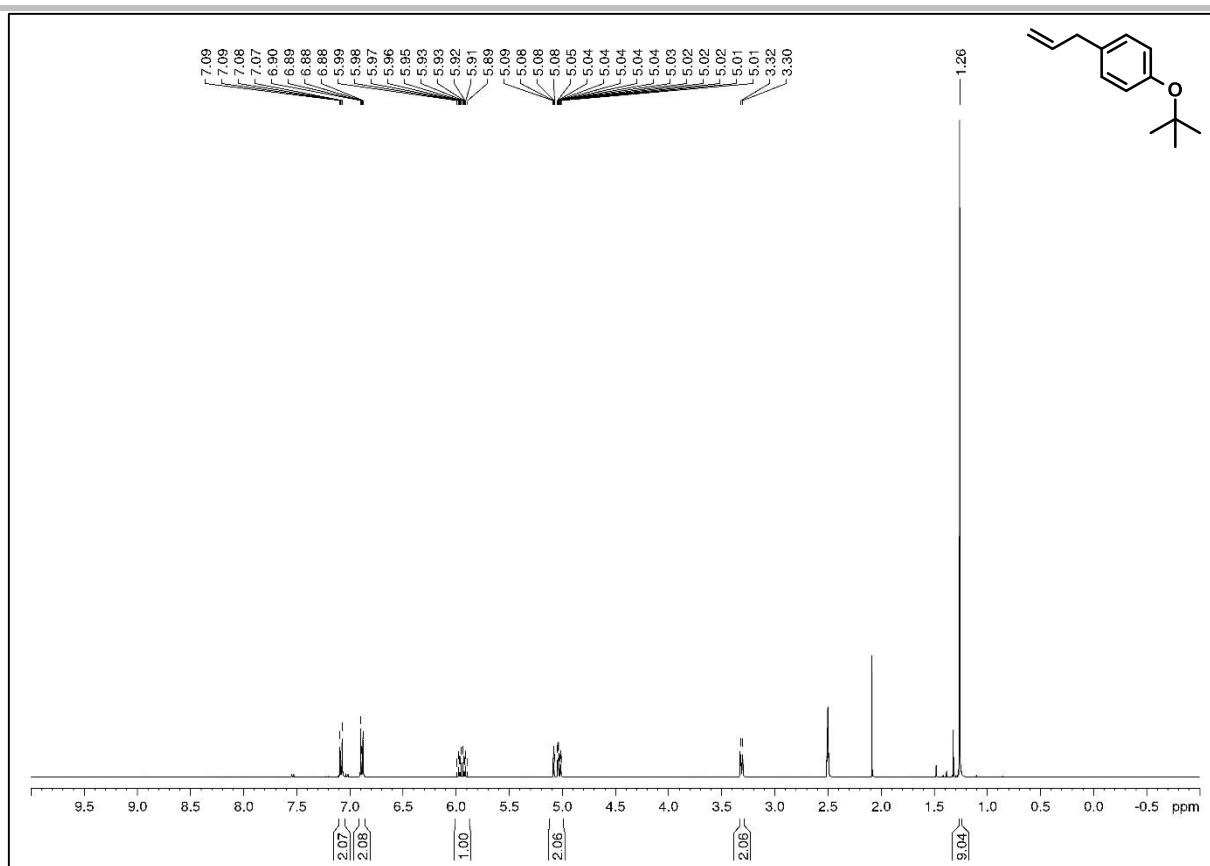


Figure S78. ^1H NMR (400 MHz, DMSO-d_6) of compound **13**.

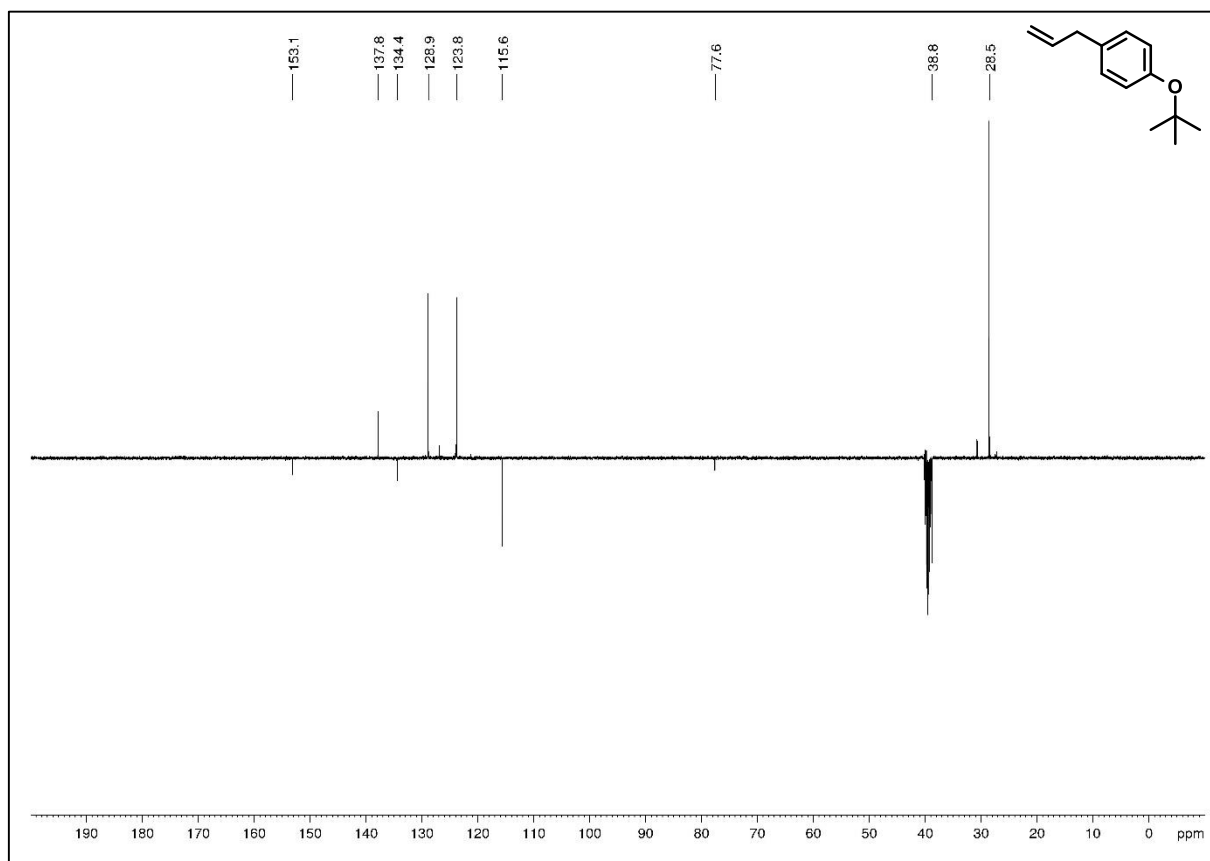


Figure S79. DEPTQ ^{13}C NMR (100 MHz, DMSO-d_6) of compound **13**.

SUPPORTING INFORMATION

References

- [1] J. Zhao, J. R. Stagno, L. Varticovski, E. Nimako, V. Rishi, K. McKinnon, R. Akee, R. H. Shoemaker, X. Ji, C. Vinson, *Mol. Pharmacol.* **2012**, *82*, 814–823.
- [2] M. Schmitt, E. Klotz, J.-P. Macher, J.-J. Bourguignon, WO/2003/010146, **2003**.
- [3] G. M. Teresk, PhD thesis, The University of Texas at Austin (USA), **2008**.
- [4] A. F. Kassir, S. S. Ragab, T. A. M. Nguyen, F. Chamay-Pouget, R. Guillot, M.-C. Scherrmann, T. Boddaert, D. J. Aitken, *J. Org. Chem.* **2016**, *81*, 9983–9991.
- [5] J. P. Davidson, O. Lubman, T. Rose, G. Waksman, S. F. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 205–215.
- [6] H. Moser, Q. Lu, P. A. Patten, D. Wang, R. Kasar, S. Kaldor, B. D. Patterson, WO/2008/154642, **2008**.
- [7] A. P. H. J. Schenning, J.-D. Arndt, M. Ito, A. Stoddart, M. Schreiber, P. Siemsen, R. E. Martin, C. Boudon, J.-P. Gisselbrecht, M. Gross, et al., *Helv. Chim. Acta* **2001**, *84*, 296–334.
- [8] S. J. Dawson, X. Hu, S. Claerhout, I. Huc, in *Methods Enzymol.*, **2016**, pp. 279–301.
- [9] M. Vallade, P. Sai Reddy, L. Fischer, I. Huc, *European J. Org. Chem.* **2018**, *2018*, 5489–5498.
- [10] M. Cianci, G. Bourenkov, G. Pompidor, I. Karpics, J. Kallio, I. Bento, M. Roessle, F. Cipriani, S. Fiedler, T. R. Schneider, *J. Synchrotron Radiat.* **2017**, *24*, 323–332.
- [11] Rigaku Oxford Diffraction, **2019**, CrysAlisPro Software system, version 1.171.40.57a, Rigaku Corporation, Wroclaw, Poland.
- [12] G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Adv.* **2015**, *71*, 3–8.
- [13] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339–341.