Development of aromatic foldamer building blocks bearing multiple biogenic side chains

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Table of Contents

1 Picture of the Purepep® Chorus synthesizer (Protein Technologies)

The synthesizer is composed of six reaction vessels in total, meaning with the *in situ* protocols one can perform up to three SPFS in parallel. Each reaction vessel can be heated up independently. Heating is performed by induction. For a detailed procedure and explanation of the use of this instrument please refer to the *Chem. Eur. J.* 2023, e202300898

2 General information

All reagents obtained from commercial sources were used without further purification unless otherwise stated. Anhydrous solvents were obtained from commercial sources and used without further drying. TG R Wang resin was purchased from CEM. Peptide grade *N*,*N*-dimethylformamide (DMF) was purchased from Carlo Erba and peptide grade *N*-methyl-2-pyrrolidone was purchased from Iris. Anhydrous triethylamine (TEA) and *N*,*N*-diisopropylethylamine (DIPEA) were obtained via distillation over CaH_2 prior to use. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM) and toluene were obtained via an MBRAUN SPS-800 solvent purification system. Anhydrous acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF) were purchased from Fischer Scientific. Nitrogen gas dried on a column of

Drierite® was used as inert atmosphere. In hydrogenation reactions H_2 pressure was provided with a balloon. The reactions were monitored using LC-MS and GC-MS instruments or by thin layer chromatography (TLC) on Merck silica gel 60-F254 plates and observed under UV light. 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 with 2 µL loop injection, unless stated otherwise. 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 µm, C18, 50 mm × 3.00 mm i.d. column at 23°C, at a flow rate of 1 mL min^{-1} using 5 mM aq. NH_4HCO_3 solution and MeCN as eluents. Acidic LC-MS: ZORBAX Eclipse XDB-C18, 1.8 µm, 50 mm × 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 0.07 *V/V*% TFA. Combination gas chromatography and low-resolution mass spectrometry were performed on Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using 15 m × 0.25 mm column with 0.25 µm 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 (Redi*Sep*®*R*$_f$ Gold High Performance). Preparative RP-HPLC purifications were performed on an ISCO CombiFlash EZ Prep system with a Gemini-NX® 10 µm C18, 250 mm × 50 mm column running at a flow rate of 118 mL min^{-1} with UV diode array detection or performed on a Thermo Fisher Scientific Ultimate 3000 HPLC System using Macherey-Nagel Nucleodur C8 Gravity columns (4 × 100 mm, 5 µm and 10 × 250 mm, 5 µm) and Macherey-Nagel Nucleodur C8 Gravity columns (4 × 50 mm, 5 µm and 10 × 100 mm, 5 µm).In the latter case, solvent mixture composed of H_2O+0.1% TFA in A and 0.1%TFA+MeCN in B. For RP-HPLC analyses, a flow rate of 1.0 mL/min was applied; semi-preparative RP-HPLC purification were performed at a flow rate of 5.0 mL/min. UV absorbance was monitored at 300 nm if not stated otherwise. ^{1}H NMR, and proton-decoupled ^{13}C/DEPTQ NMR measurements were performed on Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer, using DMSO-d_6 or $CDCl_3$ as solvent. ^{1}H and ^{13}C/DEPTQ 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-d_6: 2.50 ppm (^{1}H) / 39.5 ppm (^{13}C/DEPTQ), $CDCl_3$: 7.26 ppm (^{1}H) / 77.2 ppm (^{13}C/DEPTQ), DMF-d_7 8.03 ppm (^{1}H)). Measurements were performed at 298 K unless stated otherwise. NMR spectra of the oligomers were recorded in DMF-d_7. The raw data were evaluated using Mnova version 14.0.0 from Mestrelab Research or Bruker Topspin 3.2 in case of all small molecules, while Mnova version 14.0.0 from Mestrelab Research for the evaluation of the prepared foldamer. Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplets), quintet (quint), sextet (sext), septet (sp). In some cases, due to tautomers or amide rotamers two sets of signals appear in the spectra, which are represented in a format like „6.98/6.64 (t/br s, *J* = 5.4 Hz for triplet signal, 1H)" meaning that the singlet signal at 6.98 ppm and the triplet signal with *J* = 5.4 Hz coupling at 6.64 ppm corresponds to the same proton, and together give an integral of 1. LC-HRMS were determined on an Agilent 1290 Infinity II - Agilent 6545 LC-QTOF, ion source temperature 200°C, ESI +/-, ionization voltage: +/-4.5 kV. InfinityLab Poroshell 120 SB-C18, 2.1 mm, 1.9 µm column. Mass resolution: min. 10000. LC-HRMS spectra for some quinoline monomeres were recorded on a Thermo Scientific Dionex UltiMate 3000 equipped with a Nucleodur C18 gravity column (2 x 50 mm, 1.8 µm) with a flow of 0.33 mL min-1. 0.1% of formic acid in water (solvent A) and 0.1% of formic acid in acetonitrile (solvent B) were used as mobile phase for the ionization of the quinoline monomers and the oligomer. Elution was monitored by UV detection at 214, 254 and 300 nm with a diode array detector. The LC system was coupled to a micrOTOF II mass spectrometer by Bruker Daltonics and molecules were ionized by ESI. GC-HRMS were determined on Agilent 7890B gas chromatograph and AccuTOF GCX mass spectrometer using 15 m × 0.25 mm column with 0.25 µm HP-5MS coating and helium as carrier gas. Ion source: FI, 37V, interface: 320°C. Chemical names were generated by BioviaDraw 2021.

3 Experimental data

3.1 Analytical data of the newly synthesized compounds in this work

General procedure A for hydrogenation

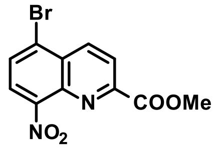
To a pear-shaped flask and **methyl 8-nitro-quinoline-2-carboxylate** (1.0 equiv.) and Pd/C (10% mol%, 0.1 g/g). were measured, the flask was closed with a rubber septum, evacuated, and charged with dry N_2. Then methanol (100 ml/g, dry, N_2 flushed), dichloromethane (100 mL/g, dry, N_2 flushed) and *N*,*N*-diethylethanamine (10 ml/g) were added. The headspace of the flask was evacuated then backfilled with H_2 gas (1 bar). The reaction mixture was stirred at RT for 1-48 h until full conversion was observed. Catalyst was filtered on a celite pad, washed with DCM, the organic phase dried over Na_2SO_4 and the filtrate was concentrated in *vacuo*. The crude product was purified by normal phase flash chromatography (eluent: DCM/MeOH) to afford **methyl 8-amino-quinoline-2-carboxylate**.

General procedure B for the hydrolysis and Fmoc-protection steps

To a pear-shaped flask **methyl 8-amino-quinoline-2-carboxylate** (1.0 equiv.) was measured and dissolved in 1,4-dioxane (100 mL/g). A solution of $LiOH \cdot H_2O$ (1.5 equiv.) in water (50 mL/g) was added and the reaction mixture was stirred at room temperature until hydrolysis was complete (usually 1 h). Hydrolysis was quenched by addition of 1M aq. HCl solution (1.5 equiv.). The reaction mixture was cooled to 0°C, $NaHCO_3$ (5 equiv.) was added (pH set to ~7-8), and a solution of FmocCl (1.5 equiv.) in 1,4-dioxane (30 mL/g) was introduced dropwise during a 1 h period. Stirring at 0°C was continued for 1h-18h until complete conversion was observed. The reaction mixture was diluted with water, pH was adjusted to 3-4 by the addition of 5% citric acid solution. DCM was added, the organic layer separated and washed with 5% citric acid solution. Organic phase was dried over Na_2SO_4 filtered and the filtrate was concentrated. The crude product was purified by normal phase flash chromatography (eluent: heptane/DCM/MeOH), then was further purified with RP-HPLC purification in (MeCN/25mM aq NH_4HCOO buffer) to afford **8-(9H-fluoren-9-ylmethoxycarbonylamino)-2-carboxylic acid** derivatives.

3.2 Synthetic procedure and analytical data of the newly synthesized compounds in this work

Methyl 5-bromo-8-nitro-quinoline-2-carboxylate (2)

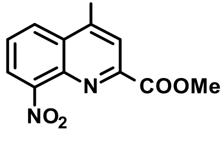


20.8 g **5-bromo-8-nitroquinoline-2-carboxylic acid** (prepared according to [1], 1.0 equiv., 70 mmol) is dissolved in 250 mL of MeOH, then 5 mL of concentrated H_2SO_4 was added and the mixture was heated up to reflux using an oil bath and left stirring overnight. After reaction completion, mixture was cooled down to room temperature, the precipitate was filtered and washed with cold MeOH. The reaction yielded product **2** as a brown solid (16.6 g, 76%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ= 8.86 (d, *J* = 8.8 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.36 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 3.97 (s, 3H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$): δ = 164.1, 150.1, 147.9, 138.3, 137.7, 131.7, 128.4, 124.8, 124.1, 53.1.

HRMS (ESI) *m/z* calcd for $C_{11}H_7BrN_2O_4$: $[M+Na]^+$: 332.9481; found: 332.9483.

Methyl 4-ethoxy-8-nitro-quinoline-2-carboxylate (5a)

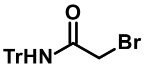


5.00 g **methyl 4-hydroxy-8-nitro-quinoline-2-carboxylate (1)** (prepared according to [2], 1.0 equiv., 20.1 mmol) and 5.55 g K_2CO_3 (2 equiv., 40.2 mmol) were suspended in 100 mL anhydrous DMF under N_2 atmosphere. 2.30 mL **ethyl iodide** (1.4 equiv., 28.6 mmol) was then added and the mixture was heated up to 70°C by a heating block and stirred overnight. Then the mixture was cooled to RT and 500 mL of cold H_2O was added. The precipitate was filtered and washed with 3x100 mL of cold H_2O. The resulting solid was then dried *in vacuo* at 50°C for 2 days. Without further purification, **5a** was obtained as a beige solid (5.23 g, 94%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.45 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.34 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.83 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.67 (s, 1H), 4.47 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H).

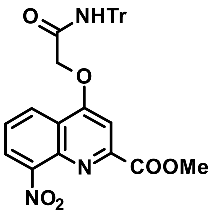
$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-*d*$_6$): δ = 164.9, 162.2, 151.0, 148.3, 138.8, 127.0, 125.5, 124.4, 122.2, 102.6, 65.5, 53.0, 14.1.
HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{13}H_{12}N_2O_5$: 299.0638; found: 299.0638.

2-bromo-*N*-trityl-acetamide (S1)



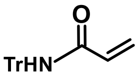
To a 250 mL pear-shaped flask 2.000 g **2-bromoacetamide** (1.0 equiv., 14.497 mmol) and 7.547 g **triphenylmethanol** (2 equiv., 28.994 mmol) were measured were measured, the flask was closed with a rubber septum, evacuated and charged with dry N_2., then 43.49 mL acetic acid (3 mL/mmol), 2.74 mL acetyl acetate (2 equiv., 28.994 mmol) and 0.074 mL sulfuric acid (0.1 equiv., 1.450 mmol). The reaction mixture was heated to 50°C by a heating block and stirred at this temperature for 30 minutes. After 30 minutes, precipitation was observed. The reaction mixture was cooled to 0°C, the formed precipitate was filtered, washed with 10 mL cold water and 10 mL cold Et_2O. The solid was dried *in vacuo* to afford **S1** (2.814 g, 51%) as a white solid.
^1H NMR (500 MHz, dmso-*d*$_6$) δ 9.07 (s, 1H), 7.33-7.27 (m, 6H), 7.25-7.20 (m, 3H), 7.19-7.15 (m, 6H), 4.03 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, dmso-*d*$_6$) δ 165.5, 144.3, 128.4, 127.6, 126.6, 69.4, 30.6.
HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{21}H_{18}BrNO$: 402.0469; found: 402.0465.

Methyl 8-nitro-4-[2-oxo-2-(tritylamino)ethoxy]quinoline-2-carboxylate (5b)



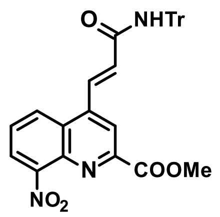
To a 250 mL pear-shaped flask 2.000 g **methyl 4-hydroxy-8-nitro-quinoline-2-carboxylate (1)** (prepared according to [2], 1.0 equiv., 8.058 mmol), 3.800 g **2-bromo-*N*-trityl-acetamide** (1.25 equiv., 9.992 mmol) and 7.877 g Cs_2CO_3 (3 equiv., 24.1749 mmol,) were measured the flask was closed with a rubber septum, evacuated and charged with dry N2., then 40 mL *N*,*N*-dimethylformamide was added and the reaction mixture heated to 50°C by a heating block and stirred for 1 hour. Then 100 mL DCM was added to the reaction mixture, was washed with 20 mL water and 20 mL brine, the organic phase dried over Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (220 g silicagel column, DCM/MeOH, gradient elution: 0-100%) to afford **5b** (3.846 g, 78%) as a beige solid.
^1H NMR (500 MHz, dmso-*d*$_6$) δ 9.14 (s, 1H), 8.42 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H), 8.34 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.31-7.17 (m, 15H), 5.29 (s, 2H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, dmso-*d*$_6$) δ 165.8, 164.8, 162.0, 150.5, 148.2, 144.4, 138.8, 128.5, 127.6, 127.2, 126.6, 125.6, 124.5, 122.1, 103.1, 69.5, 67.4, 53.2.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{32}H_{25}N_3O_6$: 548.1816; found: 548.1815.

N-tritylprop-2-enamide (S2)



To a 250 mL pear-shaped flask 2.000 g **prop-2-enamide** (1.0 equiv., 28.14 mmol) and 14.650 g **triphenylmethanol** (2 equiv., 56.27 mmol) were measured, the flask was closed with a rubber septum, evacuated and charged with dry N_2., then 84.41 mL acetic acid (3 mL/mmol), 5.32 mL acetyl acetate (2 equiv., 56.27 mmol) and 0.1434 mL sulfuric acid (0.1 equiv., 2.814 mmol). The reaction mixture was heated to 50°C by a heating block and stirred at this temperature for 1 hour. Then the reaction mixture was poured onto 500 g ice, precipitation was observed. The formed precipitate was filtered, washed with 10 mL cold water and taken up in 300 mL EtOAc and was washed with 3 x 100 mL water, the organic phase dried over Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography (220 g silicagel column, heptane/EtOAc, gradient elution: 0-100%) to afford **S2**(6.929 g, 79%) as a white solid.
^1H NMR (500 MHz, dmso-*d*$_6$) δ 8.88 (s, 1H),), 7.32-7.25 (m, 6H), 7.24-7.16 (m, 9H), 6.67 (dd, *J* = 16.6 Hz, 10.1 Hz, 1H), 5.96 (dd, *J* = 17.1 Hz, 2.3 Hz, 1H), 5.54 (dd, *J* = 10.1 Hz, 2.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, dmso-*d*$_6$) δ 164.2, 144.7, 132.3, 128.5, 127.5, 126.4, 125.4, 69.4.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{22}H_{19}NO$: 314.1539; found: 314.1540.

Methyl 8-nitro-4-[(E)-3-oxo-3-(tritylamino)prop-1-enyl]quinoline-2-carboxylate (5c)

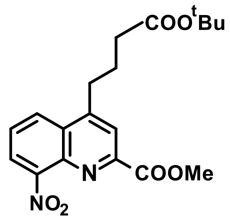


To a 250 mL pear-shaped flask 3.500 g **methyl 4-bromo-8-nitro-quinoline-2-carboxylate (4)** (prepared according to [2], 1.0 equiv., 11.25 mmol), 126 mg diacetoxypalladium (0.05 equiv., 0.5625 mmol), 685 mg tris-*o*-tolylphosphane (0.2 equiv., 2.250 mmol) and 5.289 g ***N*-tritylprop-2-enamide** (1.5 equiv., 16.88 mmol) were measured, the flask was closed with a rubber septum, evacuated, and charged with dry N_2. Then 22.5 mL *N*,*N*-dimethylformamide (2 mL/mmol) and 22.5 mL *N*-ethyl-*N*-*iso*propyl-propan-2-amine (2 mL/mmol, 129.2 mmol) were added and the reaction mixture was heated to 100°C by a heating block and stirred for 1 h. Reaction mixture was partitioned between 250 mL EtOAc and 100 mL water. Organic phase was washed with 30 mL water and 30 mL brine, dried over Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography (220 g silicagel column, DCM/MeOH, gradient elution: 0-20%) to afford **5c** (2.987 g, 42 %) as a yellow solid.

^1H NMR (500 MHz, dmso-d_6) δ 9.24 (s, 1H), 8.59 (dd, J = 1.1 Hz, 8.8 Hz, 1H), 8.44 (s, 1H), 8.39 (dd, J = 1.1 Hz, 7.6 Hz, 1H), 8.07 (d, J = 15.5 Hz, 1H), 7.90 (dd, J = 7.6 Hz, 8.6 Hz, 1H), 7.66 (d, J = 15.5 Hz, 1H), 7.37-7.29 (m, 6H), 7.29-7.22 (m, 9H), 3.98 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, dmso-d_6) δ 164.5, 163.3, 149.1, 148.8, 144.5, 142.8, 138.5, 131.9, 131.3, 128.6, 128.4, 127.73, 127.67, 127.1, 126.6, 124.2, 118.7, 69.8, 53.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{25}N_3O_5$: 544.1867; found: 544.1869.

Methyl 4-(4-*tert*-butoxy-4-oxo-butyl)-8-nitro-quinoline-2-carboxylate (5d)



Preparation of alkylboron-reagent:

An oven-dried, 250 mL pear-shaped flask was filled with 738 mg ***tert*-butyl but-3-enoate** (1.2 equiv, 12.85 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 27.8 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.3 equiv., 13.92 mmol) was added at RT, then the resulting mixture was stirred for 12 h. This solution was used in the next step.

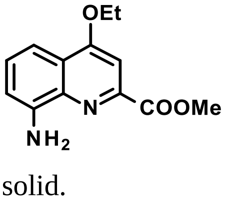
Suzuki-coupling:

A 500 mL pear-shaped flask was filled with 3.330 g **methyl 4-bromo-8-nitro-quinoline-2-carboxylate (4)** (prepared according to [2], 1.0 equiv., 10.70 mmol), 379 mg $Pd(AtaPhos)_2Cl_2$ (5.00 mol%, 0.535 mmol) and 10.460 g Cs_2CO_3 (3.00 equiv., 32.11 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 0.193 mL (1 equiv., 10.70 mmol) water and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 30 min. After cooling to RT, the reaction mixture was filtered through a celite pad and was washed with 300 mL EtOAc. The filtrate was washed with 2x50 mL water and 50 mL brine, the organic phase was separated and dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. [SAFETY NOTE: Crude product should be handled under inert gas, as borane residues might be present, causing sudden heating, fuming and fire hazard upon exposition to air.] The crude product was purified by flash chromatography (220 g silicagel column, heptane/DCM, gradient elution: 0-100%) to afford **5d** as a brown, crystalline solid (1206 mg, 27%).

^1H NMR (500 MHz, DMSO-d_6) δ= 8.54 (dd, J = 8.7 Hz, 1.1 Hz, 1H), 8.36 (dd, J = 8.7 Hz, 1.1 Hz, 1H), 8.12 (s, 1H), 7.92 (dd, J = 9.0, 7.6 Hz), 3.95 (s, 3H), 2.66 (t, J = 7.4 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 1.91 (quint, J = 7.4 Hz, 2H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=171.9, 164.7, 150.8, 149.1, 149.0, 138.0, 128.6, 127.9, 127.8, 123.7, 122.3, 79.8, 53.0, 34.0, 30.8, 27.7, 25.3 ppm.

HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_6$ $[M+H]^+$: 373.1394; found: 373.1397.

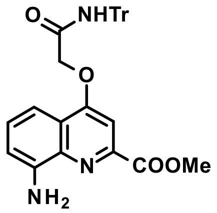
Methyl 8-amino-4-ethoxy-quinoline-2-carboxylate (6a)



5.230 g **5a** (1.0 equiv., 18.9 mmol) was dissolved in a mixture of 175 mL THF and 175 mL EtOAc. The mixture was bubbled with N_2 for 15 min before 523 mg Pd/C (0.1 equiv., 10 m/m%) was added to the mixture. The mixture was then stirred at room temperature under H_2 atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc and the filtrate was concentrated *in vacuo*. Without further purification, **6a** (4.62 g, 99%) was obtained as a yellow solid.

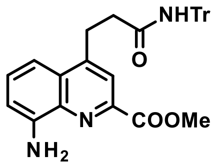
^{1}H NMR (500 MHz, DMSO-d6): δ = 7.44 (s, 1H), 7.35 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.25 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.92 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.01 (s, 2H), 4.32 (q, *J* = 6.9 Hz, 2H), 3.93 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d6): δ = 165.6, 161.6, 146.0, 145.1, 137.2, 129.0, 122.2, 109.8, 107.0, 100.6, 64.3, 52.5, 14.3.
HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{13}H_{14}N_2O_3$: 269.0897; found: 269.0896.

Methyl 8-amino-4-[2-oxo-2-(tritylamino)ethoxy]quinoline-2-carboxylate (6b)



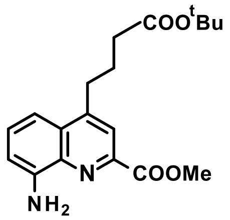
Using **General Procedure A** 3.470 g compound **5b** (1.0 equiv., 6.337 mmol), **6b** (3.379 g, 97%) was obtained as yellow solid.
^{1}H NMR (500 MHz, dmso-d_6) δ 9.05 (s, 1H), 7.46 (s,H), 7.38-7.14 (m, 15H), 6.91 (dd, *J* = 7.6 Hz, 1.1 Hz), 6.02 (s, 2H), 5.13(s, 2H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 166.3, 165.5, 161.2, 146.0, 144.7, 144.4, 137.2, 129.1, 128.5, 127.6, 126.6, 122.1, 109.8, 107.0, 101.1, 69.5, 66.9, 52.7.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{32}H_{27}N_3O_4$: 518.2074; found: 518.2080.

Methyl 8-amino-4-[3-oxo-3-(tritylamino)propyl]quinoline-2-carboxylate (6c)



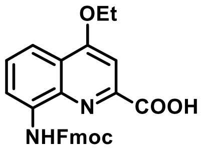
Using **General Procedure A** 2.800 g compound **5c** (1.0 equiv., 5.151 mmol), **6c** (2.405 g, 83%) was obtained as yellow solid
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 7.94 (s, 1H), 7.44 (dd, *J* = 7.8 Hz, 8.3 Hz, 1H), 7.24-7.14 (m, 10H), 7.13-7.09 (m, 6H), 6.93 (dd, *J* = 1.1 Hz, 7.6 Hz, 1H), 6.12 (s, 2H), 3.95 (s, 3H), 3.22 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ= 170.7, 165.5, 148.4, 146.8, 144.8, 143.3, 136.4, 130.1, 128.9, 128.5, 127.4, 126.3, 119.8, 109.2, 109.0, 69.3, 52.5, 34.8, 27.0 ppm.
HRMS (ESI) *m/z* calcd for $C_{33}H_{29}N_3O_3$ [M+H]$^+$: 516.2282; found: 516.2281.

Methyl 8-amino-4-(4-*tert*-butoxy-4-oxo-butyl)quinoline-2-carboxylate (6d)



Using **General Procedure A** 1.200 g compound **5d** (1.0 equiv., 3.205 mmol), **6d** (1.090 g, 87%) was obtained as yellow solid.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H), 6.93 (dd, *J* = 7.6 Hz, 1.1 Hz), 6.11 (s, 2H), 3.94 (s, 3H), 3.05 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.88 (quint, *J* = 7.4 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ= 172.0, 165.5, 148.7, 146.8, 143.3, 136.5, 130.1, 128.8, 120.5, 109.2, 109.0, 79.7, 52.5, 34.2, 31.0, 27.7, 25.0 ppm.
HRMS (ESI) *m/z* calcd for $C_{19}H_{24}N_2O_4$ [M+H]$^+$: 345.1809; found: 345.1816.

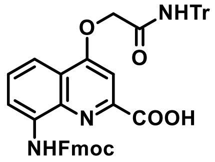
4-ethoxy-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (7a)



4.62 g **6a** (1.0 equiv., 18.8 mmol) was dissolved in 500 mL 1,4-dioxane. A solution of 1.19 g LiOH · H_2O (1.5 equiv., 28.3 mmol) in 375 mL water was added and the reaction mixture was stirred at room temperature for 1 hour. Hydrolysis was quenched by addition of 28.3 mL 1 M aq. hydrogen chloride solution (1.5 equiv., 28.3 mmol). The reaction mixture was cooled to 0°C, 7.87 g $NaHCO_3$ (5 equiv., 93.7 mmol) was added (pH was set to 7-8), and a solution of 7.28 g FmocCl (1.5 equiv., 28.3 mmol) in 200 mL 1,4-dioxane was introduced dropwise during a 1 h period. After reaction completion, 5% citric acid solution was added until pH 4 was reached. Mixture was then extracted with DCM (3×200mL). Organic layers were combined and dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to room temperature it was let at -25°C overnight. The suspension was filtered and washed with cold MeOH to afford **7a** as an off-white solid. (5.45 g, 64%).
HPLC-UV purity: 97.9%.
^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.50 (b s, 1H), 10.44 (s, 1H), 8.34 (b s, 1H), 7.93 (dt, *J* = 7.6, 1.0 Hz, 2H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.78 (dd, *J* = 7.4, 0.6 Hz, 2H), 7.62 (s, 2H), 7.44 (tt, *J* = 7.5, 0.9 Hz, 2H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.44 (quint, *J* = 7.1 Hz, 3H), 2.53 (s, 1H), 1.50 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.5, 162.6, 153.5, 146.7,

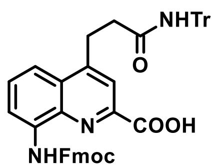
143.7, 140.8, 137.5, 135.7, 128.4, 127.8, 127.2, 125.2, 121.8, 120.2, 116.5, 114.6, 100.4, 66.4, 64.9, 46.6, 14.2.
HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{27}H_{23}N_2O_5$: 455.1601; found: 455.1596.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[2-oxo-2-(tritylamino)ethoxy]quinoline-2-carboxylic acid (7b)



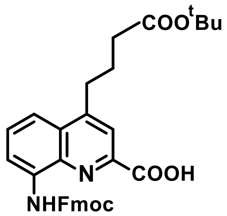
Using General Procedure B 3.200 g **6b** (1.0 equiv., 5.812 mmol), **7b** (1.184 g, 28%) was obtained as an off-white solid.
HPLC-UV purity: 98.8%.
^{1}H NMR (500 MHz, dmso-*d₆*) δ 10.26 (bs, 1H), 9.10 (s, 1H), 8.31 (bs, 1H), 7.93 (d, *J* = 7.8, 2H), 7.77 (d, *J* = 7.8 Hz, 3H), 7.65 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (td, *J* = 7.4, 1.1 Hz, 2H), 7.31-7.17 (m, 15H), 5.21 (s, 1H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, dmso-*d₆*) δ 166.1, 165.9, 161.9, 153.4, 144.4, 143.7, 140.8, 137.6, 135.4, 128.6, 127.9, 127.8, 127.6, 127.2, 126.6, 125.1, 121.4, 120.3, 116.0, 114.6, 109.8, 101.3, 69.5, 67.1, 66.4, 46.6.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{46}H_{35}N_3O_6$: 726.2599; found: 726.2603.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-4-[3-oxo-3-(tritylamino)propyl]quinoline-2-carboxylic acid (7c)



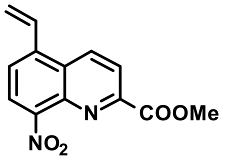
Using **General Procedure B** 2.300 g **6c** (1.0 equiv., 4.104 mmol), **7c** (1.391 g, 45%) was obtained as an off-white solid.
HPLC-UV purity: 96.5%.
^{1}H NMR (500 MHz, dmso-*d₆*) δ 10.34 (bs, 1H), 8.78 (s, 1H), 8.31 (bs, 1H), 8.10 (s, 1H), 7.93 (d, *J* = 7.6, 2H), 7.79 (d, *J* = 7.6, 1H), 7.77 (dd, *J* = 0.6 Hz, 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 1.1 Hz, 7.4 Hz, 2H), 7.24-7.19 (m, 6H), 7.19-7.14 (m, 3H), 7.13-7.08 (m, 6H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 6.6 Hz, 1H), 3.30 (t, *J* = 7.1 Hz, 2H), 2.84 (t, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, dmso-*d₆*) δ 170.6, 165.7, 153.5, 150.2, 144.8, 143.7, 140.8, 136.7, 136.2, 129.2, 128.5, 128.4, 127.8, 127.4, 127.2, 126.3, 125.2, 120.3, 119.8, 117.0, 115.8, 69.3, 66.4, 46.6, 34.8, 26.9.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{47}H_{37}N_3O_5$: 724.2806; found: 724.2805.

4-(4-*tert*-butoxy-4-oxo-butyl)-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (7d)



Using General Procedure B 2.900 g **6d** (1.0 equiv., 7.747 mmol), **7d** (2.079 g, 49%) was obtained as an off-white solid.
HPLC-UV purity: 99.5%.
^{1}H NMR (500 MHz, dmso-*d₆*) δ 10.27 (bs, 1H), 8.29 (bs, 1H), 8.02 (s, 1H), 7.92 (d, *J* = 7.6, 2H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.74 (d, , *J* = 7.6 Hz 2H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (dt, *J* = 7.6, 1.1 Hz, 2H), 4.57 (d, *J* = 6.6 Hz, 2H), 4.40 (t, *J* = 6.6 Hz, 1H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.88 (quint, *J* = 7.4 Hz, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, dmso-*d₆*) δ 171.9, 166.2, 153.3, 149.8, 143.7, 140.8, 136.8, 136.0, 128.6, 127.9, 127.8, 127.2, 125.1, 120.8, 120.3, 116.9, 115.3, 79.7, 66.4, 46.5, 34.1, 30.9, 27.8, 25.2.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{32}N_2O_6$: 553.2333; found: 553.2333.

Methyl 8-nitro-5-vinyl-quinoline-2-carboxylate (8a)

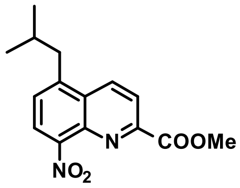


1.00 g **methyl 5-bromo-8-nitroquinoline-2-carboxylate (2)** (1.0 equiv., 3.20 mmol), 0.515 g potassium trifluoro(vinyl)borate (1.2 equiv., 3.84 mmol), 35.9 mg $Pd(OAc)_2$ (0.05 equiv., 0.160 mmol), 131.4 mg SPhos (0.1 equiv., 0.320 mmol) and 1.33 g K_2CO_3 (3.0 equiv., 9.6 mmol) were added in a sealed tube. The combined solids were flushed 3 times with N_2. 8.5 mL toluene and 2.0 mL degassed water were then added and the reaction mixture was heated to 85°C using an oil bath for 18 h. Then H_2O was added and mixture was extracted with DCM. Organic layers were combined and dried over $MgSO_4$, filtered and and the filtrate was concentrated *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to RT, it was let to stir at -25°C overnight. The suspension was filtered and washed with cold MeOH to afford **8a** as a brown solid (0.390 g, 47%).

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 9.03 (d, *J* = 8.9 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 17.2, 11.1 Hz, 1H), 6.14 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.75 (dd, *J* = 11.0, 0.9 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 164.6, 149.3, 147.6, 139.2, 138.1, 135.1, 131.3, 126.9, 124.4, 124.3, 122.6, 122.0, 53.1, 48.7.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{13}H_{10}N_2O_4$: 281.0533; found: 281.0531.

Methyl 5-*iso*butyl-8-nitro-quinoline-2-carboxylate (8b)

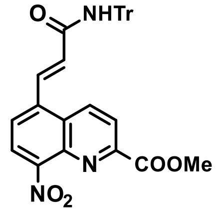


1.87 g **methyl 5-bromo-8-nitroquinoline-2-carboxylate (2)** (1.0 equiv., 6.00 mmol), 253 mg $Pd(PPh_3)_2Cl_2$ (0.06 equiv., 0.36 mmol), 2.93 g Cs_2CO_3 (1.5 equiv., 9.0 mmol), 857 mg ***iso*butylboronic acid** (1.4 equiv., 8.4 mmol) were added in a flask and flushed three times with N_2, then 150 mL dry toluene was added. The mixture was heated up to 80°C using an oil bath and stirred under N_2 overnight. Full conversion was observed, then the mixture was diluted with 300 mL EtOAc, washed with 2x150 mL aq. citric acid 5% and 2x150mL H_2O. The combined aqueous phase were extracted with 3x150 mL EtOAc. Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in iPr_2O and sonicated for 1h. After going back to RT it was stirred at -25°C overnight. The suspension was filtered and washed with cold $^{i}Pr_2O$ to obtain **8b** as a brown solid (1.34 g, 78%).

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 8.92 (d, *J* = 8.9 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 3.96 (s, 3H), 3.05 (d, *J* = 7.2 Hz, 2H), 1.95 (h, *J* = 6.7 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 164.6, 148.9, 146.9, 143.5, 138.2, 135.5, 128.2, 128.1, 123.9, 122.2, 53.0, 40.5, 29.7, 22.3.

HRMS (ESI): *m/z* [M+Na]$^+$ for $C_{15}H_{16}N_2O_4$: 311.1002; found: 311.1002.

Methyl 8-nitro-5-[(E)-3-oxo-3-(tritylamino)prop-1-enyl]quinoline-2-carboxylate (8c)

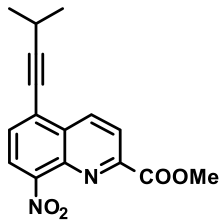


To a 250 mL pear-shaped flask 6.000 g **methyl 5-bromo-8-nitro-quinoline-2-carboxylate (2)** (1.0 equiv., 19.29 mmol), 217 mg diacetoxypalladium (0.05 equiv., 0.9644 mmol), 1.174 g tris-*o*-tolylphosphane (0.2 equiv., 3.857 mmol) and 9.067 g ***N*-tritylprop-2-enamide** (1.5 equiv., 28.93 mmol) were measured, the flask was closed with a rubber septum, evacuated, and charged with dry N_2. Then 38.6 mL N,N-dimethylformamide (2 mL/mmol) and 38.6 mL *N*-ethyl-*N*-*iso*propyl-propan-2-amine (2 mL/mmol) were added and the reaction mixture was heated to 100°C by a heating block and stirred for 2 h. Reaction mixture was partitioned between 500 mL EtOAc and 150 mL water. Organic phase was washed with 50 mL water and 50 mL brine, dried over Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography (330 g silicagel column, DCM/MeOH, gradient elution: 0-100%) to afford **8c** (7.260 g, 69%) as a yellow solid.

^{1}H NMR (500 MHz, dmso-*d$_6$*) δ 9.14 (s, 1H), 9.00 (d, *J* = 9.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 15.6 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.36-7.20 (m, 15H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, dmso-*d$_6$)* δ 164.4, 163.7, 149.4, 148.1, 144.6, 138.1, 136.9, 135.1, 132.4, 130.0, 128.6, 127.6, 127.4, 126.6, 125.6, 124.2, 122.8, 69.7, 53.1.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{33}H_{25}N_3O_5$: 544.1867; found: 544.1871.

Methyl 5-(3-methylbut-1-ynyl)-8-nitro-quinoline-2-carboxylate (8d)

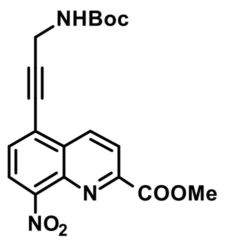


2.50 g **methyl 5-bromo-8-nitroquinoline-2-carboxylate (2)** (1.0 equiv., 8.00 mmol), 337 mg $Pd(PPh_3)_2Cl_2$ (0.06 equiv., 0.480 mmol), 46 mg CuI (0.03 equiv., 0.240 mmol) were added in a flask and flushed 3 times with N_2. To the flask 150 mL of dry MeCN was added followed by 35 mL Et_3N (30 equiv., 240 mmol) and 1.2 mL **3-methylbut-1-yne** (1.4 equiv., 11.3 mmol). The mixture was heated up to 70°C using an oil bath and left stirring under N_2 overnight. After reaction completion, mixture was diluted with 300 mL of DCM, washed with 3x250 mL of 5% aq. citric acid solution. The combined aqueous phase were extracted with 3x200 mL of DCM. Organic layers were combined and dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crude product was suspended in MeCN and sonicated for 1h. After going back to RT it was let at -25°C overnight. The suspension was filtered and washed with cold MeCN to afford **8d** as a off white solid (2.06 g, 86%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.88 (d, *J* = 8.7 Hz, 1H), 8.36 (t, *J* = 9.0 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 3.97 (s, 3H), 3.04 (hept, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ =164.4, 149.7, 147.3, 137.8, 136.5, 131.0, 129.4, 125.1, 124.3, 123.4, 105.9, 75.3, 53.1, 22.5, 20.8.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{16}H_{14}N_2O_4$: 321.0846; found: 321.0845.

Methyl 5-[3-(*tert*-butoxycarbonylamino)prop-1-ynyl]-8-nitro-quinoline-2-carboxylate (8e)

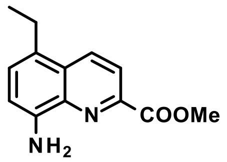


2.00 g **methyl 5-bromo-8-nitroquinoline-2-carboxylate (2) (**1.0 equiv., 6.40 mmol), 140 mg Pd(PPh$_3$)$_2$Cl$_2$ (0.03 equiv., 0.19 mmol), 125 mg CuI (0.1 equiv., 0.64 mmol), 200 mg P(oTol)$_3$ (0.1 equiv., 0.64 mmol) and 1.20 g ***N*-Boc-propargylamine** (1.2 equiv., 7.68 mmol) were added to a flask and flushed 3 times with N$_2$. 50 mL dry DMF was added followed by 8.40 mL DIPEA (7.1 equiv., 45.44 mmol). The mixture was stirred under N$_2$ atmosphere overnight at RT. Full conversion was observed, then the mixture was diluted with 100 mL DCM, washed with 2x50 mL aq. citric acid 5% and 50 mL sat. aq. NaHCO$_3$ solution. The combined aqueous phase was extracted with 3x200 mL DCM. Organic layers were combined and dried over MgSO$_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in iPr$_2$O and sonicated for 1h. After going back to RT it was let at -25°C overnight. The suspension was filtered and washed with cold ^{i}Pr$_2$O to obtain **8e** as a off white solid (1.50 g, 61%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.94 (d, *J* = 8.7 Hz, 1H), 8.38 (d, *J* = 7.8 Hz, 1H), 8.34 (d, *J* = 8.7 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 5.4 Hz, 1H), 4.18 (d, J = 5.5 Hz, 2H), 3.97 (s, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$): δ = 164.4, 155.5, 149.9, 147.7, 137.7, 136.5, 131.3, 129.5, 124.3, 123.4, 97.3, 78.6, 77.0, 53.1, 30.6, 28.2.

HRMS (ESI): m/z [M+Na]$^+$ for $C_{19}H_{19}N_3O_6$: 408.1166; found: 408.1169.

Methyl 8-amino-5-vinyl-quinoline-2-carboxylate (9a)

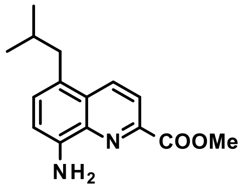


0.390 g **8a** (1.0 equiv., 1.50 mmol) was dissolved in a mixture of 25 mL THF and 25 mL EtOAc. The mixture was bubbled with N$_2$ for 15 min before 40 mg Pd/C (0.1 equiv., 10 *m/m%*) was added to the mixture. The mixture was then stirred at RT under H$_2$ atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc and solvents were removed *in vacuo*. Without further purification, the **9a** was obtained as a yellow oily solid (0.341g, 99%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.51 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.91 (s, 2H), 3.95 (s, 3H), 2.91 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ = 165.4, 144.4, 143.4, 137.0, 133.6, 129.0, 127.8, 125.7, 120.5, 109.1, 52.5, 23.9, 15.5.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{13}H_{14}N_2O_2$: 253.0947; found: 253.0947.

Methyl 8-amino-5-isobutyl-quinoline-2-carboxylate (9b)

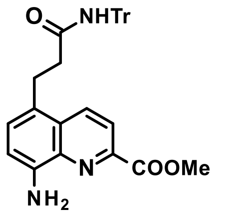


1.34 g **8b** (1.0 equiv., 4.65 mmol) was dissolved in a mixture of 50 mL THF and 50 mL EtOAc. The mixture was bubbled with N$_2$ for 15 min before 135 mg Pd/C (0.1 equiv. 10% *m/m%*) was added to the mixture. The mixture was then stirred at RT under H$_2$ atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc and solvents were removed *in vacuo*. Without further purification, **9b** was obtained as a yellow solid (1.19 g, 99%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.49 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.93 (s, 2H), 3.95 (s, 3H), 2.74 (d, *J* = 7.2 Hz, 2H), 1.82 (h, *J* = 6.8 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d*$_6$): δ = 165.4, 144.5, 143.3, 136.9, 133.9, 130.9, 128.2, 123.1, 120.3, 108.9, 52.5, 40.2, 29.5, 22.4.

HRMS (ESI): *m/z* [M+Na]$^+$ for $C_{15}H_{18}N_2O_2$: 281.1260; found: 281.1260.

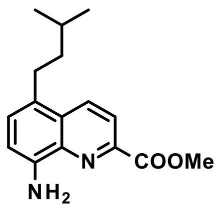
Methyl 8-amino-4-[3-oxo-3-(tritylamino)propyl]quinoline-2-carboxylate (9c)



Using **General Procedure A** 7.200 g compound **8c** (1.0 equiv., 13.25 mmol), **9c** (5.686 g, 67%) was obtained as yellow solid.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.58 (s, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.30-7.14 (m, 10H), 7.12-7.04 (m, 6H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 2H), 3.95 (s, 3H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ= 171.2, 165.4, 144.8, 144.7, 143.3, 136.9, 133.8, 130.2, 128.5, 128.0, 127.4, 126.3, 123.1, 120.5, 108.9, 69.2, 52.5, 37.1, 26.6 ppm. HRMS (ESI) *m/z* calcd for $C_{33}H_{29}N_3O_3$ [M+H]$^+$: 516.2282; found: 516.2283.

Methyl 8-amino-5-isopentyl-quinoline-2-carboxylate (9d)

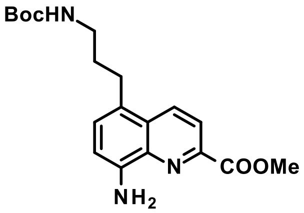


2.06 g **8d** (1.0 equiv., 6.90 mmol) was dissolved in a mixture of 62.5 mL THF and 62.5 mL EtOAc. The mixture was bubbled with N_2 for 15 min before 210 mg Pd/C (0.1 equiv., 10 *m*/*m%*) was added to the mixture. The mixture was then stirred at RT under H_2 atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc and solvents were removed *in vacuo*. Without further purification **9d** (1.86 g, 99%) was obtained as a yellow solid.

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 8.47 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.90 (s, 2H), 3.95 (s, 3H), 2.91 – 2.84 (m, 2H), 1.62 (hept, *J* = 6.6 Hz, 1H), 1.50 – 1.42 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 165.3, 144.4, 143.4, 137.0, 133.6, 129.7, 127.8, 124.4, 120.4, 109.0, 52.5, 40.2, 28.8, 27.4, 22.5.

HRMS (ESI): *m/z* [M+Na]$^+$ for $C_{16}H_{20}N_2O_2$: 295.1417; found: 295.1417.

Methyl 8-amino-5-[3-(*tert*-butoxycarbonylamino)propyl]quinoline-2-carboxylate (9e)

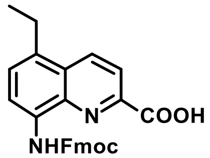


1.50 g **8e** (1.0 equiv., 3.90 mmol) was dissolved in a mixture of 50 mL THF and 50 mL EtOAc. The mixture was bubbled with N_2 for 15 min before 150 mg Pd/C (0.1 equiv.,10 *m/m*%) was added to the mixture. The mixture was then stirred at RT under H_2 atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc and solvents were removed *in vacuo*. Without further purification, **9e** was obtained as a yellow solid (1.39 g, 99%).

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 8.49 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 5.7 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.92 (s, 2H), 3.95 (s, 3H), 2.97 (q, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 7.7 Hz, 2H), 1.68 (quint, *J* = 7.2 Hz, 2H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 165.4, 155.7, 144.5, 143.4, 137.0, 133.6, 130.0, 127.9, 123.7, 120.4, 109.0, 77.4, 52.5, 30.9, 28.3, 28.2.

HRMS (ESI): *m/z* [M+Na]$^+$ for $C_{19}H_{25}N_3O_4$: 382.1737; found: 382.1737.

5-ethyl-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (10a)



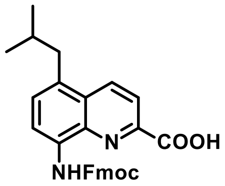
0.348 g **9a** (1.0 equiv., 1.48 mmol) was dissolved in 50 mL 1,4-dioxane and mixed with aqueous solution of 95.0 mg LiOH · H_2O (1.5 equiv., 2.25 mmol) in 30 mL H_2O. After 1 h full conversion was observed, the mixture was quenched with 2.3 mL of 1 M HCl (2.25 mmol) aqueous solution. The mixture was then cooled to 0 °C and 0.630 g $NaHCO_3$ (5.0 equiv., 7.5 mmol) was added (pH was set to 7-8. A solution of 0.580 g Fmoc-Cl (1.5 equiv., 2.25 mmol) in 20 mL 1,4-dioxane was added dropwise to the reaction mixture within 1h. After reaction completion, 5% aq. citric acid solution was added until pH 4 was reached. Then the mixture was extracted with DCM (3×50mL). Organic layers were combined and dried over $MgSO_4$, filtered and the filtrate was concentrated *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back RT it was stirred at -25°C overnight. The suspension was filtered and washed with cold MeOH to afford **10a** as an off-white solid (0.530 g, 82%).

HPLC-UV purity: 98.9%.

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 13.61 (b s, 1H), 10.38 (b s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.29 (b s, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz,

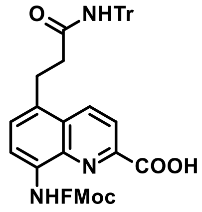
1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 3.05 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.4, 153.5, 143.7, 140.8, 137.1, 135.0, 133.9, 133.7, 127.9, 127.8, 127.6, 127.2, 125.2, 120.4, 120.3, 116.2, 66.3, 46.6, 24.1, 15.2.
HRMS (ESI): *m/z* [M+H]$^+$ calcd. for $C_{27}H_{22}N_2O_4$: 439.1652; found: 439.1650.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-5-isobutyl-quinoline-2-carboxylic acid (10b)



1.19 g **9b** (1.0 equiv., 4.60 mmol) was dissolved in 150 mL 1,4-dioxane and 290 mg $LiOH \cdot H_2O$ (1.5 equiv., 6.90 mmol) in 100 mL H_2O was added. After 1h full conversion was observed, the mixture was quenched with 6.9 mL of 1 M HCl aqueous solution. The mixture was then cooled to 0 °C and 1.93 g $NaHCO_3$ (5.0 equiv., 23.0 mmol) was added (pH was set to 7-8). A solution of 1.78 g FmocCl (1.5 equiv., 6.9 mmol) in 60 mL 1,4-dioxane was added dropwise to the reaction mixture within 1h. After reaction completion, 5% aq. citric acid solution was added until pH 4 was reached. Mixture was then extracted with DCM (3×150mL). Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to rt it was stirred at -25°C overnight. The suspension was filtered and washed with cold MeOH. The reaction yielded product **10b** as an off-white solid (1.63 g, 76%).
HPLC-UV purity: 99.6%.
^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.60 (s, 1H), 10.40 (s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.28 (b s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 6.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 2.89 (d, *J* = 7.2 Hz, 2H), 1.89 (h, *J* = 6.8 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.4, 153.5, 143.7, 140.8, 137.1, 135.4, 134.0, 131.2, 129.9, 128.0, 127.8, 127.2, 125.1, 120.2, 115.9, 66.3, 46.6, 29.5, 22.3.
HRMS (ESI): *m/z* [M+H]$^+$ for $C_{29}H_{26}N_2O_4$: 467.1965; found: 467.1961.

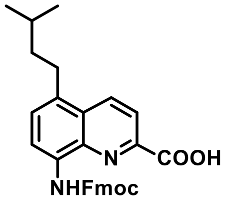
8-(9H-fluoren-9-ylmethoxycarbonylamino)-5-[3-oxo-3-(tritylamino)propyl]quinoline-2-carboxylic acid (10c)



Using **General Procedure B** 5.600 g **9c** (1.0 equiv., 9.558 mmol) **10c** (5.820 g, 77%) was obtained as an off-white solid.
HPLC-UV purity: 95.7%.
^{1}H NMR (500 MHz, dmso-d_6) δ 10.11 (bs, 1H), 8.61 (bs, 1H), 8.58 (d, *J* = 15.4 Hz, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.24 (bs, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (dd, *J* = 0.6 Hz, 7.5 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.36 (dt, *J* = 1.1 Hz, 7.4 Hz, 2H), 7.26-7.14 (m, 9H), 7.11-7.05 (m, 6H), 4.59 (d, *J* = 6.8 Hz, 2H), 4.42 (t, *J* = 6.8 Hz, 1H), 3.18 (t, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 171.0, 153.3, 144.9, 143.7, 140.8, 137.4, 137.0, 134.1, 131.0, 128.9, 128.5, 127.8, 127.4, 127.2, 126.3, 125.1, 121.4, 121.0, 120.3, 120.1, 115.0, 69.2, 66.3, 63.8, 46.6, 36.7, 26.7.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{47}H_{37}N_3O_5$: 724.2806; found: 724.2804.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-5-isopentyl-quinoline-2-carboxylic acid (10d)



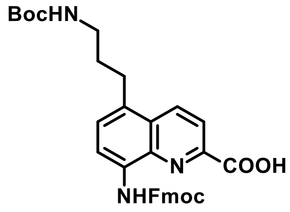
1.86 g **9d** (1.0 equiv., 6.83 mmol) was dissolved in 175 mL 1,4-dioxane and mixed with aqueous solution of 430 mg $LiOH \cdot H_2O$ (1.5 equiv., 10.25 mmol) in 150 mL H_2O. After 1 h, full conversion was observed, the mixture was quenched with 10.3 mL of 1 M HCl aqueous solution. The mixture was then cooled to 0°C and 2.87 g $NaHCO_3$ (5.0 equiv., 34.2 mmol) was added (pH was set to 7-8). A solution of 2.65 g FmocCl (1.5 equiv., 10.25 mmol) in 75 mL 1,4-dioxane was added dropwise to the reaction mixture within 1h. After reaction completion, 5% aq. citric acid solution was added until pH 4 was reached. Mixture was then extracted with DCM (3×100 mL). Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to RT it was let at -25°C overnight. The suspension was filtered and washed with cold MeOH to afford **10d** as an off-white solid (3.02 g, 92%).

HPLC-UV purity: 99.2%.

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 13.55 (b s, 1H), 10.38 (s, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 4.60 (d, *J* = 6.9 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H), 3.04 – 2.97 (m, 2H), 1.63 (hept, *J* = 6.6 Hz, 1H), 1.55 – 1.47 (m, 2H), 0.95 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 165.4, 153.5, 145.0, 143.7, 140.8, 137.1, 135.0, 133.9, 132.5, 128.7, 127.8, 127.6, 127.2, 125.1, 120.4, 120.2, 116.1, 66.3, 46.6, 29.0, 27.5, 22.4.

HRMS (ESI): *m/z* $[M+H]^+$ for $C_{30}H_{28}N_2O_4$: 481.2122; found: 481.2116.

5-[3-(*tert*-butoxycarbonylamino)propyl]-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (10e)



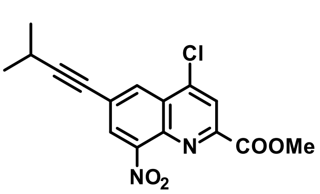
1.39 g **9e** (1.0 equiv., 3.86 mmol) was dissolved in 100 mL 1,4-dioxane and 245 mg LiOH · H_2O (1.5 equiv., 5.79 mmol) in 75 mL H_2O was added. After 1 h full conversion was observed, the mixture was quenched with 6 mL of 1 M HCl aqueous solution. The mixture was then cooled to 0 °C and 1.62 g $NaHCO_3$ (5.0 equiv., 19.3 mmol) was added (pH was set to 7-8). A solution of 1.50 g FmocCl (1.5 equiv., 5.79 mmol) in 50 mL 1,4-dioxane was added dropwise to the reaction mixture within 1 h. After reaction completion, 5% aq. citric acid solution was added until pH 4 was reached. Mixture was then extracted with DCM (3×100mL). Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to RT it was stirred at -25°C overnight. The suspension was filtered and washed with cold MeOH to obtain **10e** as an off-white solid (1.58 g, 72%).

HPLC-UV purity: 98.1%.

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 13.62 (s, 1H), 10.43 (s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.29 (b s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.94 (dt, *J* = 7.5, 0.9 Hz, 2H), 7.79 (dd, *J* = 7.4, 1.1 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.37 (td, *J* = 7.4, 1.2 Hz, 2H), 6.96 (t, *J* = 5.5 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.46 (t, *J* = 6.8 Hz, 1H), 3.00 (q, *J* = 7.9 Hz, 4H), 1.74 (quint, *J* = 7.1 Hz, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-*d$_6$*): δ = 165.4, 155.7, 153.5, 144.9, 143.7, 140.8, 137.1, 135.1, 134.1, 131.8, 129.0, 128.2, 127.8, 127.7, 127.3, 125.2, 120.34, 120.29, 116.1, 77.5, 66.3, 46.6, 30.7, 28.4, 28.3.

HRMS (ESI): *m/z* $[M+H]^+$ for $C_{33}H_{33}N_3O_6$: 568.2442; found: 568.2437.

Methyl 4-chloro-6-(3-methylbut-1-ynyl)-8-nitro-quinoline-2-carboxylate (11a)

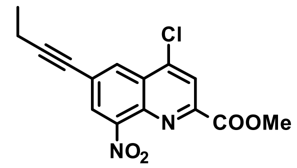


A 1 L pear-shaped flask was filled with 12.00 g compound **methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate (3)** (prepared according to [2], 1.0 equiv., 25.70 mmol), 489 mg CuI (0.1 equiv., 2.57 mmol) and 902 mg $Pd(PPh_3)_2Cl_2$ (0.05 equiv., 1.29 mmol). The flask was closed with a rubber septum, evacuated and charged with dry N_2, then 385 mL THF (15 mL/mmol methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate), 51 mL TEA (2 mL/mmol methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate) and 3.15 mL 3-methylbut-1-yne (1.20 equiv., 30.84 mmol) were added. The reaction mixture was stirred at RT for 24 h, then diluted with 500 mL DCM, washed with 2x100 mL 1 M aq. HCl solution and 100 mL sat. aq. $NaHCO_3$ solution. The combined aq phase was extracted with 2x100 mL DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (220 g column, DCM/MeOH as eluents) to afford 7.157 g **11a** as a beige solid (85% purity, 18.29 mmol, 71%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=8.53 (d, *J* = 1.7 Hz, 1H), 8.40 (s, 1H), 8.39 (s, 1H), 3.96 (s, 3H), 2.93 (hept, *J* = 6.9 Hz, 1H), 1.28 ppm (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=163.5, 149.4, 148.7, 143.0, 137.6, 129.2, 127.4, 127.2, 124.1, 123.4, 102.0, 77.7, 53.3, 22.3, 20.6 ppm.

HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClN_2O_4$ $[M+H]^+$: 333.0642; found: 333.0638.

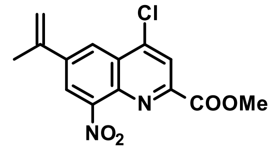
Methyl 6-but-1-ynyl-4-chloro-8-nitro-quinoline-2-carboxylate (11b)



3.46 g **methyl 6-bromo-4-chloro-8-nitroquinoline-2-carboxylate (3)** (prepared according to [2], 1.0 equiv., 10.0 mmol), 211 mg $Pd(PPh_3)_2Cl_2$ (0.03 equiv., 0.30 mmol) and 115 mg CuI (0.06 equiv., 0.60 mmol) were added in a flask and flushed 3 times with N_2. 200 mL of dry THF was added followed by 30.0 mL Et_3N (21.2 equiv., 212 mmol), 1.96 mL **but-1-yn-1-yltrimethylsilane** (1.20 equiv., 12.0 mmol) and 620 mg H_2SiF_6 (0.5 equiv., in 35 *m/m*% aq. solution). The mixture was heated up to 60°C using an oil bathf and was stirred under N_2 for 6h. After reaction completion, mixture was diluted with 300 mL of DCM, washed with 2x200mL of citric acid 5%. The combined aqueous phase were extracted with 3x300mL of DCM. Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in $^iPr_2O$ and sonicated for 1h. After going back to room temperature it was stirred at -25°C overnight. The suspension was filtered and washed with cold $^iPr_2O$. The reaction yielded product **11b** (2.20 g, 69%) as a yellowish solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.55 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 1.7 Hz, 1H), 8.40 (s, 1H), 3.96 (s, 3H), 2.56 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ = 163.5, 149.4, 148.7, 143.0, 137.7, 129.3, 127.4, 127.2, 124.2, 123.4, 98.4, 77.9, 53.3, 13.3, 12.6.
HRMS (ESI): *m/z* $[M+Na]^+$ for $C_{15}H_{11}ClN_2O_4$: 341.0300; found: 341.0299.

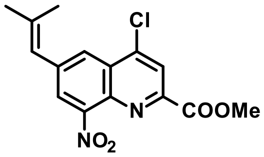
Methyl 4-chloro-6-*iso*propenyl-8-nitro-quinoline-2-carboxylate (11c)



To a 250 mL pear-shaped flask 3.000 g **methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate (3)** (prepared according to [2], 1.0 equiv., 6.425 mmol), 6.280 g Cs_2CO_3 (3 equiv., 19.27 mmol,), 262 mg cyclopenta-1,3-dien-1-yl(diphenyl)phosphane;dichloromethane;dichloropalladium;iron(2+) (0.05 equiv., 0.3212 mmol) and 1.509 mL **2-*iso*propenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane** (1.25 equiv., 1349 mg, 8.031 mmol) were measured. The flask was closed with a rubber septum, evacuated and charged with dry N_2. Then 45 mL 2-methyltetrahydrofuran and 4.5 mL water were added. The reaction mixture was heated to 60°C by a heating block and stirred at this temperature for 6 hours. Full conversion was observed, presence of disubstituted by-product was detected. Then 100 mL EtOAc and 50 ml water were added to the reaction mixture, the phases were separated. The organic phase was washed with 2x20 mL water. The combined aqueous phase was extracted with 20 mL EtOAc. Then the combined organic phase dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (220 g silicagel column, DCM/MeOH, gradient elution: 0-40%) to **11c** as a yellow solid (1.333 g, 62%).

^{1}H NMR (400 MHz, dmso-d_6) δ 8.82 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H) 5.94 (s, 1H), 5.52 (s, 1H), 3.96 (s, 3H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, dmso-d_6) δ 163.6, 148.9, 143.5, 141.0, 140.0, 137.9, 127.3, 123.2, 122.7, 122.1, 122.0, 118.5, 53.2, 21.0.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}ClN_2O_4$: 307.0480; found: 307.0472.

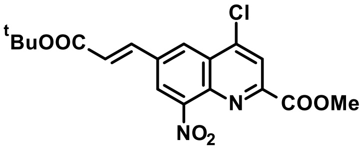
Methyl 4-chloro-6-(2-methylprop-1-enyl)-8-nitro-quinoline-2-carboxylate (11d)



To a 1 L pear-shaped flask 13.000 g **methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate (3)** (prepared according to [2], 1.0 equiv., 27.841 mmol), 27.214 g Cs_2CO_3 (3 equiv., 83.524 mmol,), 1.137 g cyclopenta-1,3-dien-1-yl(diphenyl)phosphane;dichloromethane;dichloropalladium;iron(2+) (0.05 equiv., 1.3921 mmol) and 6.084 g **4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane** (1.2 equiv., 33.410 mmol) were measured. The flask was closed with a rubber septum, evacuated, and charged with dry N_2. Then 418 mL 2-methyltetrahydrofuran and 42 mL water were added. The reaction mixture was heated to 60°C by a heating block and stirred at this temperature for 26 hours. Then the reaction mixture was filtered on a celite pad, 500 mL EtOAc and 100 ml water were added, the phases were separated. The organic phase was washed with 2x150 mL water. Combined aqueous phase was extracted with 100 mL EtOAc. Then the combined organic phase dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (220 g silicagel column, DCM/MeOH, gradient elution: 0-15%) to afford **11d** as a yellow solid (3.620 g, 28%).

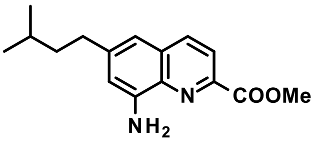
^{1}H NMR (500 MHz, dmso-d_6) δ 8.40 (d, J = 1.5 Hz, 1H), 8.34 (s, 1H), 8.22 (d, J = 1.5 Hz, 1H), 6.56 (bs, 1H), 3.95 (s, 3H), 1.99 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 164.1, 149.0, 148.9, 143.4, 142.2, 140.0, 137.4, 127.6, 126.5, 125.4, 123.3, 123.1, 53.7, 27.6, 20.0.
HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{15}H_{13}ClN_2O_4$: 321.0637; found: 321.0640.

Methyl 6-[(E)-3-*tert*-butoxy-3-oxo-prop-1-enyl]-4-chloro-8-nitro-quinoline-2-carboxylate (11e)



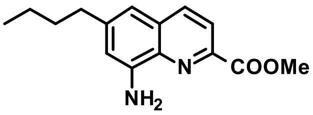
To a 500 mL pear-shaped 7.000 g flask **methyl 6-bromo-4-chloro-8-nitro-quinoline-2-carboxylate (3)** (prepared according to [2], 1.0 equiv., 20.26 mmol) and 1.113 g (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one;palladium;triphenylphosphane (0.06 equiv., 1.216 mmol) were measured. The flask was closed with a rubber septum, evacuated, and charged with dry N_2. Then 101 mL *N*,*N*-dimethylformamide (dry, degassed), 41 mL *N*-ethyl-*N*-*iso*propyl-propan-2-amine (11.5 equiv., 232.6 mmol), 0.590 mL **tri*tert*-butylphosphane** (0.12 equiv., 2.431 mmol) and 3.56 mL tert-butyl prop-2-enoate (1.2 equiv, 24.31 mmol) were added. The reaction mixture was heated to 100°C by a heating block and stirred at this temperature for 30 min. 300 mL EtOAc and 100 mL water were added to the reaction mixture and the phases were separated. Organic phase was washed with 50 mL water and 50 mL brine. Then the combined organic phase dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (220 g silicagel column, heptane/DCM, gradient elution: 30-100%) to afford **11e** as an off-white solid (4.568 g, 57%).
^{1}H NMR (500 MHz, dmso-d_6) δ 8.99 (d, J = 1.7 Hz, 1H), 8.75 (d, J = 1.7 Hz, 1H), 8.39 (s, 1H), 7.91 (d , J = 16.1 Hz, 1H), 6.95 (d , J = 16.1 Hz, 1H), 3.96 (s, 3H), .1.51 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 164.9, 163.5, 149.6, 149.1, 144.0, 140.5, 138.9, 135.5, 128.1, 127.6, 125.1, 123.4, 122.8, 80.6, 53.3, 27.8.
HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{18}H_{17}ClN_2O_6$: 393.0848; found: 393.0844.

Methyl 8-amino-6-*iso*pentyl-quinoline-2-carboxylate (12a)



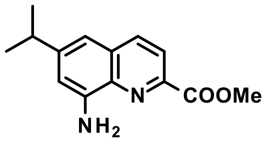
Using **General Procedure A** 6.500 g compound **11a** (1.0 equiv., 16.61 mmol), **12a** (88% purity, 3.328 g, 65%) was obtained as brown solid.
^{1}H NMR (400 MHz, dmso-d_6) δ 8.24 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 6.00 (s, 2H), 3.93 (s , 3H), 2.64 (t, 2H), 1.61-1.49 (m, 3 H), 0.92 (d, J = 6.3 Hz, 6H) ^{13}C{^{1}H} NMR (100 MHz, dmso-d_6) δ165.4, 145.8, 145.1, 143.1, 136.4, 135.5, 129.8, 120.9, 112.1, 110.3, 52.4, 33.7, 27.2, 22.4.
HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{16}H_{20}N_2O_2$: 273.1598; found: 273.1594.

Methyl 8-amino-6-butyl-quinoline-2-carboxylate (12b)



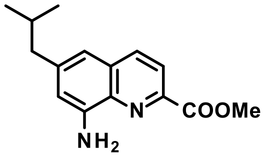
2.20 g **11b** (1.0 equiv., 6.90 mmol) was dissolved in a mixture of 200 mL THF and 200 mL EtOAc. The mixture was bubbled with N_2 for 15 min before 220 mg Pd/C (0.1 g/g., 10% *m*/*m*%), 440 mg $Pd(OH)_2/C$ (0.2 g/g, 20% *m*/*m*%) and 4.365 g NH_4COOH (10.0 equiv., 69.0 mmol) were added to the mixture. The mixture was then stirred at rt under H_2 atmosphere overnight. The reaction mixture was filtered through celite, washed with EtOAc. The filtrate was then washed with 2x200 mL water. The combined aqueous phase were extracted with 3x300 mL of DCM. Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Without further purification, the **12b** was obtained as a yellow solid (1.78 g, 99%).
^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.25 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 1.3 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 6.00 (s, 2H), 3.93 (s, 3H), 2.64 (t, J = 7.4 Hz, 2H), 1.66-1.57 (m, 2H), 1.34(sext, 2H), 0.91 (t, J = 7.4 Hz, 3H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.4, 145.8, 144.9, 143.1, 136.4, 135.5, 129.8, 120.9, 112.2, 110.3, 52.5, 35.5, 32.7, 21.9, 13.8.
HRMS (ESI): m/z [M+Na]$^+$ for $C_{15}H_{18}N_2O_2$: 281.1260; found: 281.1260.

Methyl 8-amino-6-*iso*propyl-quinoline-2-carboxylate (12c)



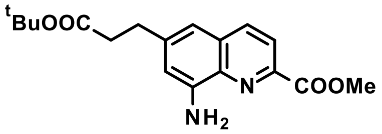
Using **General Procedure A** 1.333 g compound **11c** (1.0 equiv., 3.991 mmol), **12c** (556 mg, 46%) was obtained as brown solid.
^{1}H NMR (500 MHz, dmso-d_6) δ 8.27 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 5.99 (bs, 2H), 3.93 (s, 3H), 2.94 (sp, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H) ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 165.4, 150.8, 145.9, 143.2, 136.6, 135.7, 129.8, 120.9, 110.1, 108.7, 52.4, 34.0, 23.6.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}N_2O_2$: 245.1284; found: 245.1275.

Methyl 8-amino-6-*iso*butyl-quinoline-2-carboxylate (12d)



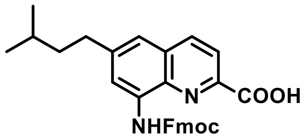
Using **General Procedure A** 330 mg **11d** (1.0 equiv., 0.8952 mmol), **12d** (178 mg, 77%) was obtained as yellow solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 2H), 6.93 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 5.09 (bs, 2H), 4.03 (s , 3H), 2.55 (d, *J* = 7.3 Hz, 2H), 1.97 (sp, *J* = 6.6 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.3, 144.7, 144.3, 144.1, 136.8, 136.4, 130.2, 121.4, 115.2, 52.8, 46.2, 30.1, 25.0, 22.7.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}N_2O_2$: 259.1441; found: 259.1430.

Methyl 8-amino-6-(3-*tert*-butoxy-3-oxo-propyl) quinoline-2-carboxylate (12e)



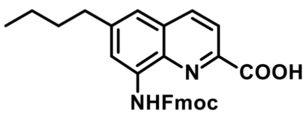
Using **General Procedure A** 4.500 g compound **11e** (1.0 equiv., 11.46 mmol), **12e** (3.159 g, 83%) was obtained as yellow solid.
^{1}H NMR (500 MHz, dmso-d_6) δ 8.25 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 6.81 (d, *J* = 1.7 Hz, 1H), 6.03 (bs, 2H), 3.93 (s , 3H), 2.88 (tr, *J* = 7.5 Hz, 2H), 2.57 (tr, *J* = 7.5 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, dmso-d_6) δ 171.5, 165.4, 145.8, 143.3, 143.1, 136.5, 135.6, 129.7, 121.0, 112 2, 110.1, 79.7, 52.5, 35 9, 31.1, 27.7.
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{22}N_2O_4$: 331.1652; found: 331.1649.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-6-*iso*pentyl-quinoline-2-carboxylic acid (13a)



Using **General Procedure B** 3.328 g **12a** (1.0 equiv., 10.76 mmol), **13a** (3.354 g, 65%) was obtained as pale yellow crystals.
HPLC-UV purity: 97.8%.
^{1}H NMR (500 MHz, dmso-d_6) δ 10.32 (bs, 1H), 8.45 (d, *J* = 8.6 Hz, 1H), 8.30 (bs, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 1.0 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (td, *J* = 7.4, 1.0 Hz, 2H), 4.58 (d, *J* = 6.9 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 1H), 2.75 (t, *J* = 8.0 Hz, 2 H), 1.64-1.50 (m, 3H), 0.93(d, J = 6.4 Hz, 6H) ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 165.8, 153.4, 143.7, 140.8, 137.5, 135.5, 135.3, 129.1, 127.8, 127.2, 125.1, 121.0, 120.3, 119.2, 117.1, 66.4, 46.6, 33.8, 27.2, 22.4. HR-MS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_2O_4$: 481.2122; found: 481.2127.

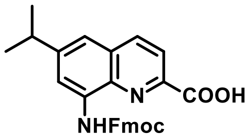
6-butyl-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (13b)



1.78 g **12b** (1.0 equiv., 6.85 mmol) was dissolved in 200 mL 1,4-dioxane and mixed with aqueous solution of 432 mg $LiOH \cdot H_2O$ (1.5 equiv., 10.3 mmol) in 150 mL H_2O. After 1h full conversion was observed, the mixture was quenched with 10.3 mL of 1 M HCl aqueous solution. The mixture was then cooled to 0 °C and 2.88 g $NaHCO_3$ (5.0 equiv., 34.3 mmol) was added. A solution of 2.65 g FmocCl (1.5 equiv., 10.3 mmol) in 75 mL 1,4-dioxane was added dropwise to the reaction mixture within 1h. After full conversion was observed, 5% aq. citric acid solution was added until pH 4 was reached. Mixture was then extracted with 3×200mL DCM. Organic layers were combined and dried over $MgSO_4$, filtered and solvent was removed *in vacuo*. Crude product was suspended in MeOH and sonicated for 1h. After going back to room temperature it was stirred at -25°C overnight. The suspension was filtered and washed with cold MeOH. The reaction yielded **13b** as an off-white solid (2.08 g, 65%).

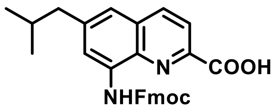
HPLC-UV purity: 96.9%.
^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.53 (b s, 1H), 10.44 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.32 (b s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (dt, *J* = 7.4, 1.0 Hz, 2H), 4.61 (d, *J* = 6.7 Hz, 2H), 4.45 (t, *J* = 6.9 Hz, 1H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.64 (m, *J* = 6.8 Hz, 2H), 1.35 (sext, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.5, 153.5, 144.1, 143.7, 140.8, 137.8, 135.5, 135.4, 129.3, 127.8, 127.2, 125.1, 120.8, 120.3, 119.3, 117.4, 66.4, 46.6, 40.4, 35.6, 32.7, 21.8, 13.8.
HRMS (ESI): *m/z* [M+H]$^+$ for $C_{29}H_{26}N_2O_4$: 467.1965; found: 467.1961.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-6-*iso*propyl-quinoline-2-carboxylic acid (13c)



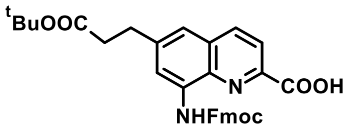
Using **General Procedure B** 950 mg **12c** (1.0 equiv., 3.111 mmol), **13c** (333 mg, 24%) was obtained as off-white crystals.
HPLC-UV purity: 98.8%.
^{1}H NMR (500 MHz, dmso-d_6) δ 10.14 (bs, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.32 (bs, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 1.1 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (td, *J* = 7.5, 1.1 Hz, 2H), 4.59 (d, *J* = 6.6 Hz, 2H), 4.43 (t, *J* = 6.6 Hz, 1H), 3.04 (quint, *J* = 6.9 Hz, 1 H), 1.28 (d, *J* = 6.9 Hz, 6H) ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 165.5, 153.6, 149.9, 144.7, 143.7, 140.8, 138.0, 135.7, 135.6, 129.4, 127.8, 127.2, 125.2, 120.7, 120.3, 117.2, 115.9, 66.4, 46.6, 34.1, 23.5.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{28}H_{24}N_2O_4$: 453.1809; found: 453.1810.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-6-*iso*butyl-quinoline-2-carboxylic acid (13d)



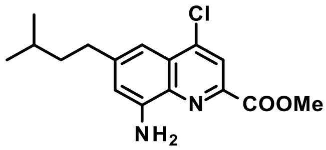
Using **General Procedure B** 2.100 g **12d** (1.0 equiv., 7.154 mmol), **13d** (1.985 g, 57%) was obtained as an off-white solid.
HPLC-UV purity: 98.8%.
^{1}H NMR (500 MHz, dmso-d_6) δ 10.41(s, 1H) 8.48 (d, *J* = 8.6 Hz, 1H), 8.30 (bs, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 1.1 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (td, *J* = 7.4, 1.1 Hz, 2H), 4.59 (d, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 6.6 Hz, 1H), 2.66-2.60 (m, 2H) , 1.94 (sp, *J* = 6.5 Hz, 1 H), 0.90 (d, *J* = 6.5 Hz, 6H) ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 165.4, 153.6, 144.6, 143.7, 143.1, 140.8, 137.9, 135.5, 135.4, 129.2, 127.8, 127.2, 125.2, 120.7, 120.3, 120.2, 117.9, 66.4, 46.6, 45.2, 29.6, 22.2.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{29}H_{26}N_2O_4$: 467.1965; found: 467.1968.

6-(3-*tert*-butoxy-3-oxo-propyl)-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (13e)



Using **General Procedure B** 4.100 g **12e** (1.0 equiv., 11.29 mmol), **13e** (1.595 g, 26%) was obtained as an off-white solid.
HPLC-UV purity: 99.5%.
^{1}H NMR (500 MHz, dmso-d_6) δ 10.18 (bs, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.24 (bs, 1 H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (dd, *J* = 0.6 Hz, 7.5 Hz, 2H), 7.49 (d, *J* = 0.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (td, *J* = 7.4, 1.1 Hz, 2H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 6.6 Hz, 1H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, dmso-d_6) δ 171.7, 166.7, 153.7, 144.1, 142.0, 141.2, 137.7, 136.0, 135.6, 129.4, 129.2, 128.2, 127.7, 125.6, 121.8, 120.7, 119.8, 117.1, 80.3, 66.8, 47.0, 36.4, 31.6, 28.2.
HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{32}H_{30}N_2O_6$: 539.2177; found: 539.2177.

Methyl 8-amino-4-chloro-6-isopentyl-quinoline-2-carboxylate (15a)



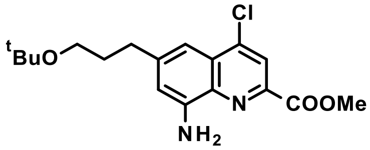
A 2 L pear-shaped flask was filled with 1.10 g Raney nickel (1.94 equiv., 11.8 mmol) under N_2 atmosphere, then washed with 3x20 mL water and 2x20 mL MeOH. 2.02 g compound **11a** (6.06 mmol) and 403 mL MeOH were added and the atmosphere was changed to H_2 (1 bar). The reaction mixture was stirred at RT for 1 week and then filtered through a short pad of celite. The filtrate was concentrated *in vacuo* and the obtained residue was purified by flash chromatography (40 g silicagel column, heptane/EtOAc, gradient elution: 20-50%) to afford compound

15a as an orange crystalline solid (1.53 g, 82%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=8.10 (s, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.91 (d, *J* = 1.7 Hz, 1H), 6.22 (s, 2H), 3.94 (s, 3H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.62-1.50 (m, 3H), 0.93 ppm (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=164.4, 147.0, 146.7, 142.5, 141.1, 135.9, 127.4, 121.0, 111.2, 107.6, 52.7, 40.0, 34.0, 27.2, 22.4 ppm.

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}ClN_2O_2$ [M+H]$^+$: 307.1213; found: 307.1209.

Methyl 8-amino-6-(3-*tert*-butoxypropyl)-4-chloro-quinoline-2-carboxylate (15b)

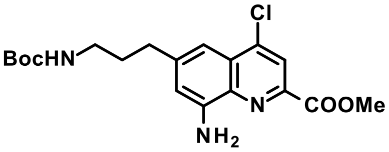


A 2 L pear-shaped flask was filled with 720 mg Raney nickel (2.20 equiv., 8.38 mmol) under N_2 atmosphere, then washed with 3x20 mL water and 2x20 mL MeOH. 1.44 g **14a** (prepared according to [2], 1.0 equiv., 3.81 mmol) and 1.12 L MeOH were added and the atmosphere was changed to H_2 (1 bar). The reaction mixture was stirred at RT for 27 h and then filtered through a short pad of celite. The filtrate was concentrated *in vacuo* and the obtained residue was purified by flash chromatography (40 g silicagel column, heptane/EtOAc, gradient elution: 35-60%) to afford compound **15b** as an orange crystalline solid (1.19 g, 89%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=8.10 (s, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 6.23 (s, 2H), 3.94 (s, 3H), 3.32 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 1.80 (quint, *J* = 6.7 Hz, 2H), 1.13 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=164.4, 146.7, 146.4, 142.5, 141.1, 135.9, 127.3, 121.0, 111.3, 107.9, 72.0, 59.8, 52.7, 32.7, 31.4, 27.4 ppm.

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}ClN_2O_3$ [M+H]$^+$: 351.1475; found: 351.1476.

Methyl 8-amino-6-[3-(*tert*-butoxycarbonylamino)propyl]-4-chloro-quinoline-2-carboxylate (15c)

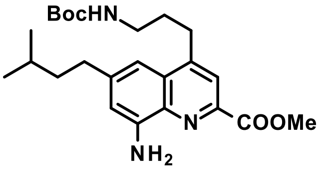


A 2 L pear-shaped flask was filled with 490 mg Raney nickel (2.45 equiv., 5.72 mmol) under N_2 atmosphere, then washed with 3x20 mL water and 2x20 mL MeOH. 980 mg **14b** (prepared according to [2], 1.0 equiv., 2.33 mmol), 49.0 mL DCM and 392 mL MeOH were added and the atmosphere was changed to H_2 (1 bar). The reaction mixture was stirred at RT for 24 h and then filtered through a short pad of celite. The filtrate was concentrated *in vacuo* and the obtained residue was purified by flash chromatography (40 g silicagel column, heptane/EtOAc, gradient elution: 20-60%) to afford compound **15c** as an orange crystalline solid (695 mg, 76%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=8.10 (s, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 6.91 (t, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.24 (s, 2H), 3.94 (s, 3H), 2.97 (q, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.74 (quint, *J* = 7.4 Hz, 2H), 1.38 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=164.4, 155.6, 146.7, 146.3, 142.6, 141.1, 135.9, 127.4, 121.0, 111.2, 107.8, 77.4, 52.7, 39.6, 33.4, 31.0, 28.3 ppm.

HRMS (ESI) *m/z* calcd for $C_{19}H_{25}ClN_3O_4$ [M+H]$^+$: 394.1534; found: 394.1528.

Methyl 8-amino-4-[3-(*tert*-butoxycarbonylamino)propyl]-6-isopentyl-quinoline-2-carboxylate (16a)



Preparation of alkylboron-reagent:

An oven-dried, 25 mL pear-shaped flask was filled with 738 mg ***tert*-butyl *N*-allylcarbamate** (2.00 equiv, 4.69 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 8.21 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.75 equiv., 4.11 mmol) was added at RT, then the resulting mixture was stirred for 1 h. This solution was used in the next step.

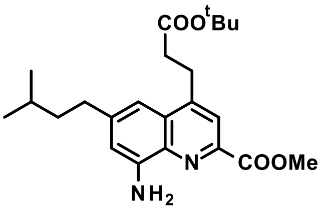
Suzuki-coupling:

A 25 mL pear-shaped flask was filled with 720 mg compound **15a** (1.0 equiv., 2.35 mmol), 83.1 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.12 mmol) and 2.29 g Cs_2CO_3 (3.00 equiv., 7.04 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 2.35 mL (1mL/mmol) water and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 20 h. After cooling to RT, the organic phase was separated and dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. [SAFETY NOTE: Crude product should be handled under inert gas, as borane residues might be present, causing sudden heating, fuming and fire hazard upon exposition to air.] The residue was triturated with 50 mL heptane, filtered, and the crystals were washed with 3x5 mL heptane. The resulting solid was purified by flash chromatography (120 g silicagel column, DCM/EtOAc, gradient elution: 0-25%) to afford compound **16a** as a pale yellow, crystalline solid (890 mg, 88%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=7.87 (s, 1H), 7.03 (s, 1H), 6.98/6.64 (t/br s, *J* = 5.4 Hz for triplet signal, 1H), 6.80 (d, *J* = 1.3 Hz, 1H), 6.01 (s, 2H), 3.92 (s, 3H), 3.05-2.99 (m, 4H) 2.66 (t, *J* = 7.9 Hz, 2H), 1.78 (quint, *J* = 7.3 Hz, 2H), 1.58 (hept, *J* = 6.2 Hz, 1H), 1.55-1.50 (m, 2H), 1.38/1.32 (s/s, 9H), 0.93 ppm (d, *J* = 6.4 Hz, 6H). (Amide rotamers present at room temperature.) ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=165.6, 155.7, 148.2, 146.4, 144.8, 142.5, 135.5, 128.8, 120.2, 109.9, 108.3, 77.5, 52.4, 40.2, 39.7, 34.1, 29.6, 29.1, 28.2, 27.3, 22.4 ppm.

HRMS (ESI) *m/z* calcd for $C_{24}H_{36}N_3O_4$ [M+H]$^+$: 430.2706; found: 430.2704.

Methyl 8-amino-4-(3-*tert*-butoxy-3-oxo-propyl)-6-isopentyl-quinoline-2-carboxylate (16b)



Preparation of alkylboron-reagent:

An oven-dried, 50 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 1.60 mL ***tert*-butyl acrylate** (5.00 equiv., 10.9 mmol), and 21.8 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (5.00 equiv., 10.9 mmol) were added at RT, then the resulting mixture was stirred for 2 h. This solution was used in the next step.

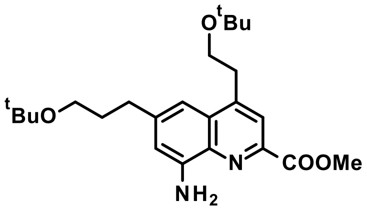
Suzuki-coupling:

A 50 mL pear-shaped flask was filled with 670 mg compound **15a** (1.0 equiv., 2.18 mmol), 77.3 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.11 mmol) and 2.14 g Cs_2CO_3 (3.00 equiv., 6.55 mmol), closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 2.18 mL water (1 mL/mmol) and the *alkylboron-reagent* were added. The mixture was heated to 65°C by a heating block and stirred for 2 h. After cooling to RT, the reaction mixture was washed with 2x25 mL brine, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (80 g silicagel column, heptane/EtOAc, gradient elution: 0-50%) then reversed phase HPLC (EZ Prep system, eluent: 0.1% aq. TFA/MeCN, gradient elution: 70-100%) to afford compound **16b** as a yellow solid (390 mg, 45%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ=7.86 (s, 1H), 7.04 (d, *J* = 1.1 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.03 (s, 2H), 3.92 (s, 3H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.0 Hz, 2H), 1.62-1.50 (m, 3H), 1.36 (s, 9H), 0.94 ppm (d, *J* = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.3, 165.5, 146.6, 146.5, 145.1, 142.4, 135.4, 128.7, 120.0, 110.0, 108.0, 80.0, 52.4, 40.1, 34.2, 34.1, 27.6, 27.2, 26.9, 22.4 ppm.

HRMS (ESI) *m/z* calcd for $C_{23}H_{33}N_2O_4$ [M+H]$^+$: 401.2440; found: 401.2435.

Methyl 8-amino-4-(2-*tert*-butoxyethyl)-6-(3-*tert*-butoxypropyl)quinoline-2-carboxylate (16c)



Preparation of alkylboron-reagent:

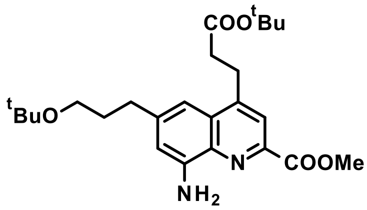
An oven-dried, 25 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 1.21 mL **2-methyl-2-vinyloxy-propane** (3.50 equiv., 9.18 mmol), and 15.7 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (3.00 equiv., 7.87 mmol) were added at RT, then the resulting mixture was stirred for 30 min. This solution was used in the next step.

Suzuki-coupling:

A 50 mL pear-shaped flask was filled with 920 mg compound **15b** (1.0 equiv., 2.62 mmol), 92.9 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.13 mmol) and 2.56 g Cs_2CO_3 (3.00 equiv., 7.87 mmol), closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 2.62 mL water (1 mL/mmol) and the *alkylboron-reagent* were added. The mixture was was heated to 65°C by a heating block and stirred for 20 h. After cooling to RT, the reaction mixture was filtered through a short pad of celite. The filtrate was washed with 2x15 mL brine, and the aqueous phase back-extracted with 2x10 mL THF. The combined 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 silicagel column, DCM/EtOAc, gradient elution: 0-40%) to afford compound **16c** as a yellow honey (682 mg, 62%).

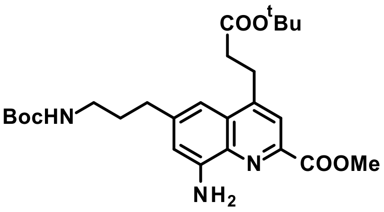
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=7.94 (s, 1H), 7.05 (s, 1H), 6.80 (d, *J* = 1.4 Hz, 1H), 6.01 (s, 2H), 3.92 (s, 3H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.33 (t, *J* = 6.3 Hz, 2H), 3.18 (t, *J* = 6.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 1.80 (quint, *J* = 7.0 Hz, 2H), 1.13 (s, 9H), 1.08 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=165.6, 146.3, 145.8, 144.2, 142.4, 135.5, 129.1, 121.0, 109.9, 108.5, 72.5, 72.0, 60.3, 60.0, 52.4, 32.9, 32.9, 31.6, 27.4, 27.2 ppm.
HRMS (ESI) *m/z* calcd for $C_{24}H_{37}N_2O_4$ $[M+H]^+$: 417.2753; found: 417.2749.

Methyl 8-amino-4-(3-*tert*-butoxy-3-oxo-propyl)-6-(3-*tert*-butoxypropyl)quinoline-2-carboxylate (16d)



Preparation of alkylboron-reagent:
An oven-dried, 50 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 5.30 mL ***tert*-butyl acrylate** (10.0 equiv., 36.2 mmol), and 36.2 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (5.00 equiv., 18.1 mmol) were added at RT, then the resulting mixture was stirred for 20 h. This solution was used in the next step.
Suzuki-coupling:
A 100 mL pear-shaped flask was filled with 1.27 g compound **15b** (1.0 equiv., 3.62 mmol), 128 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.18 mmol) and 3.54 g Cs_2CO_3 (3.00 equiv., 10.9 mmol), closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 3.62 mL water (1 mL/mmol) and the *alkylboron-reagent* were added. The mixture was was heated to 65°C by a heating block and stirred for 20 h. After cooling to RT, the reaction mixture was washed with 2x25 mL brine, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (330 g silicagel column, heptane/EtOAc/MeOH 89/10/1 as eluent) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH_4HCO_3/MeCN, gradient elution: 50-80%) to afford compound **16d** as a yellow solid (596 mg, 37%).
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=7.86 (s, 1H), 7.03 (d, *J* = 1.1 Hz, 1H), 6.82 (d, *J* = 1.4 Hz, 1H), 6.04 (s, 2H), 3.92 (s, 3H), 3.33 (t, *J* = 6.3 Hz, 2H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.72-2.66 (m, 4H), 1.80 (quint, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.13 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.2, 165.5, 146.7, 146.5, 144.5, 142.4, 135.5, 128.6, 120.1, 110.0, 108.2, 80.0, 72.0, 60.0, 52.4, 34.2, 32.9, 31.5, 27.6, 27.4, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{25}H_{37}N_2O_5$ $[M+H]^+$: 445.2702; found: 445.2706.

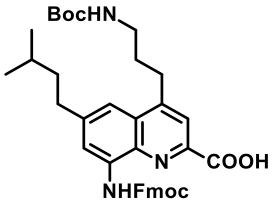
Methyl 8-amino-6-[3-(*tert*-butoxycarbonylamino)propyl]-4-(3-*tert*-butoxy-3-oxo-propyl)quinoline-2-carboxylate (16e)



Preparation of alkylboron-reagent:
An oven-dried, 50 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 21.6 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (5.00 equiv., 10.8 mmol) and 1.58 mL ***tert*-butyl acrylate** (5.00 equiv., 10.8 mmol) were added at RT, then the resulting mixture was stirred for 2 h. This solution was used in the next step.
Suzuki-coupling:
A 50 mL pear-shaped flask was filled with 850 mg compound **15c** (1.0 equiv., 2.16 mmol), 45.5 mg 4-[bis(1-adamantyl)phosphanyl]-*N,N*-dimethyl-aniline (5.00 mol%, 0.11 mmol, prepared according to [2]), 24.7 mg $Pd_2(dba)_3$ (1.25 mol%, 0.03 mmol) and 2.11 g Cs_2CO_3 (3.00 equiv., 6.47 mmol), closed with a rubber septum, evacuated and charged with dry N$_2$. Through the septum 5.00 mL THF was added and the mixture was stirred at RT for 5 min, then 2.18 mL water (1 mL/mmol) and the *alkylboron-reagent* were added. The mixture was heated to 65°C by a heating block and stirred for 1.5 h. After cooling to RT, the reaction mixture was washed with 2x25 mL brine, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (80 g silicagel column, heptane/EtOAc, gradient elution: 30-60%) then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH_4HCO_3/MeCN, gradient elution: 70-90%) to afford compound **16e** as a yellow solid (626 mg, 59%).
^{1}H NMR (400 MHz, DMSO-d$_6$) δ=7.87 (s, 1H), 7.05 (s, 1H), 6.90 (t, *J* = 5.4 Hz, 1H), 6.80 (s, 1H), 6.05

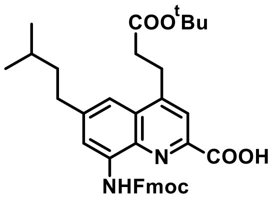
(s, 2H), 3.92 (s, 3H), 3.26 (t, *J* = 7.1 Hz, 2H), 2.97 (q, *J* = 6.5 Hz, 2H), 2.72-2.60 (m, 4H), 1.74 (quint, *J* = 7.3 Hz, 2H), 1.38 (s, 9H), 1.36 ppm (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d$_6$) δ=171.3, 165.4, 155.6, 146.7, 146.5, 144.4, 142.4, 135.5, 128.7, 120.1, 110.0, 108.3, 80.0, 77.4, 52.4, 39.4, 34.1, 33.5, 31.1, 28.3, 27.6, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{26}H_{38}N_3O_6$ $[M+H]^+$: 488.2761; found: 488.2760.

4-[3-(*tert*-butoxycarbonylamino)propyl]-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-6-*iso*pentyl-quinoline-2-carboxylic acid (17a)



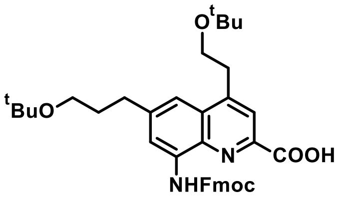
Using **General Procedure B** 865 mg compound **16a** (1.0 equiv., 2.01 mmol), **17a** (1.05 g, 82%) was obtained as pale yellow solid.
HPLC-UV purity: 98.8%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.53 (br s, 1H), 10.39 (br s, 1H), 8.32 (br s, 1H), 8.04 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 6.99/6.65 (t/br s, *J* = 5.4 Hz for triplet signal, 1H), 4.58 (d, *J* = 6.9 Hz, 2H), 4.44 (t, *J* = 7.0 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 2H), 3.04 (q, *J* = 6.2 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 1.80 (quint, *J* = 7.2 Hz, 2H), 1.59 (hept, *J* = 6.5 Hz, 1H), 1.57-1.51 (m, 2H), 1.38/1.32 (s/s, 9H), 0.94 ppm (d, *J* = 6.5 Hz, 6H). (Amide rotamers present at room temperature.) $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d$_6$) δ=166.1, 155.7, 153.4, 149.7, 145.5, 143.7, 143.7, 140.7, 135.9, 135.6, 128.1, 127.8, 127.2, 125.1, 120.3, 120.2, 116.6, 115.3, 77.5, 66.4, 46.5, 40.1, 39.7, 34.2, 29.7, 29.0, 28.2, 27.3, 22.4 ppm.
HRMS (ESI) *m/z* calcd for $C_{38}H_{44}N_3O_6$ $[M+H]^+$: 638.3230; found: 638.3229.

4-(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-6-*iso*pentyl-quinoline-2-carboxylic acid (17b)



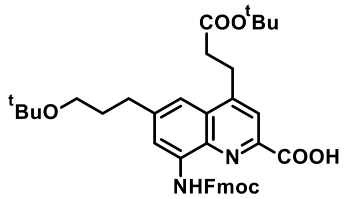
Using **General Procedure B** 390 mg compound **16b** (1.0 equiv., 0.97 mmol), **17b** (400 mg, 67%) was obtained as pale yellow solid.
HPLC-UV purity: 99.6%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.52 (br s, 1H), 10.48 (br s, 1H), 8.35 (br s, 1H), 8.05 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.64 (s, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.36 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 2H), 4.59 (d, *J* = 7.1 Hz, 2H), 4.45 (t, *J* = 7.0 Hz, 1H), 3.37 (t, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.1 Hz, 2H), 1.62-1.50 (m, 3H), 1.35 (s, 9H), 0.94 ppm (d, *J* = 6.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d$_6$) δ=171.1, 165.5, 153.5, 148.6, 144.4, 143.7, 140.8, 136.1, 135.5, 128.3, 127.8, 127.2, 125.2, 120.3, 119.9, 117.1, 115.3, 80.1, 66.4, 46.6, 40.0, 34.2, 34.1, 27.6, 27.3, 26.9, 22.4 ppm.
HRMS (ESI) *m/z* calcd for $C_{37}H_{41}N_2O_6$ $[M+H]^+$: 609.2965; found: 609.2963.

4-(2-*tert*-butoxyethyl)-6-(3-*tert*-butoxypropyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (17c)



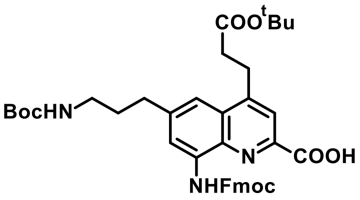
Using **General Procedure B** 658 mg compound **16c** (1.0 equiv., 1.58 mmol), **17c** (798 mg, 81%) was obtained as pale yellow solid.
HPLC-UV purity: 99.2%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.58 (br s, 1H), 10.37 (br s, 1H), 8.30 (br s, 1H), 8.09 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 2H), 4.58 (d, *J* = 6.8 Hz, 2H), 4.43 (t, *J* = 6.9 Hz, 1H), 3.68 (t, *J* = 6.5 Hz, 2H), 3.33 (t, *J* = 6.2 Hz, 2H), 3.28 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 1.82 (quint, *J* = 6.9 Hz, 2H), 1.12 (s, 9H), 1.06 ppm (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d$_6$) δ=166.0, 153.4, 147.5, 145.1, 143.7, 143.1, 140.7, 135.8, 135.6, 128.5, 127.8, 127.2, 125.1, 121.0, 120.2, 116.8, 115.8, 72.5, 72.0, 66.4, 60.4, 59.9, 46.5, 32.9, 32.8, 31.5, 27.4, 27.2 ppm.
HRMS (ESI) *m/z* calcd for $C_{38}H_{45}N_2O_6$ $[M+H]^+$: 625.3278; found: 625.3279.

4-(3-*tert*-butoxy-3-oxo-propyl)-6-(3-*tert*-butoxypropyl)-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (17d)



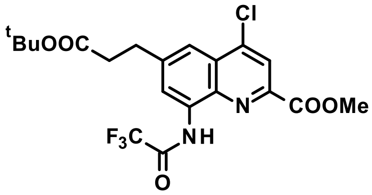
Using **General Procedure B** 575 mg compound **16d** (1.0 equiv., 1.29 mmol), **17d** (559 mg, 66%) was obtained as pale yellow solid.
HPLC-UV purity: 98.4%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.58 (br s, 1H), 10.40 (br s, 1H), 8.32 (br s, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.61 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 4.59 (d, *J* = 6.8 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 3.33 (t, *J* = 6.2 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.82 (quint, *J* = 6.8 Hz, 2H), 1.35 (s, 9H), 1.12 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.1, 165.8, 153.4, 148.3, 144.9, 143.7, 143.6, 140.8, 136.0, 135.6, 128.0, 127.8, 127.2, 125.1, 120.2, 120.0, 116.9, 115.3, 80.1, 72.0, 66.4, 59.8, 46.5, 34.3, 32.9, 31.5, 27.6, 27.4, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{39}H_{45}N_2O_7$ [M+H]$^+$: 653.3227; found: 653.3226.

6-[3-(*tert*-butoxycarbonylamino)propyl]-4-(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (17e)



Using **General Procedure B** 800 mg compound **16e** 25 (1.0 equiv., 1.641 mmol), **17e** (960 mg, 84%) was obtained as pale yellow solid.
HPLC-UV purity: 97.5%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.52 (br s, 1H), 10.48 (br s, 1H), 8.32 (br s, 1H), 8.05 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (dd, *J* = 7.4 Hz, *J* = 0.6 Hz, 2H), 7.66 (s, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.37 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 2H), 6.93/6.58 (t/s, *J* = 6.8 Hz for triplet signal, 1H), 4.60 (d, *J* = 6.8 Hz, 2H), 4.46 (t, *J* = 6.9 Hz, 1H), 3.38 (t, *J* = 6.9 Hz, 2H), 2.98 (q, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 2.72 (t, *J* = 7.1 Hz, 2H), 1.76 (quint, *J* = 7.1 Hz, 2H), 1.37 (s, 9H), 1.35 ppm (s, 9H). (Amide rotamers present at room temperature.) ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.1, 165.5, 155.6, 153.5, 148.7, 143.9, 143.7, 140.8, 136.1, 135.6, 128.3, 127.8, 127.2, 125.2, 120.3, 120.0, 117.1, 115.6, 80.1, 77.4, 66.3, 46.6, 39.2, 34.2, 33.5, 31.1, 28.3, 27.6, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{40}H_{46}N_3O_8$ [M+H]$^+$: 696.3285; found: 696.3292.

Methyl 6-(3-*tert*-butoxy-3-oxo-propyl)-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (19b)

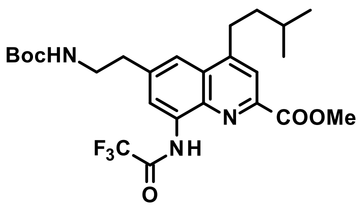


Preparation of alkylboron-reagent:
An oven-dried, 250 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 137 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (5.00 equiv., 68.3 mmol) and 20.0 mL ***tert*-butyl acrylate** (10.0 equiv., 137 mmol) were added at RT, then the resulting mixture was stirred for 12 h. This solution was used in the next step.

Suzuki-coupling:
A 250 mL pear-shaped flask was filled with 5.62 g **18** (prepared according to [2], 1.0 equiv., 13.7 mmol), 483 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.68 mmol) and 13.3 g Cs_2CO_3 (3.00 equiv., 41.0 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 13.7 mL water (1 mL/mmol) and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 30 min. After cooling to RT, the reaction mixture was washed with 2x25 mL brine, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was was triturated with 90 mL pentane, filtered and washed with 3x10 mL pentane. The obtained solid was purified by flash chromatography (40 g silicagel column, DCM as eluent), then the resulting solid was triturated again with 15 mL pentane, filtered and dried in vacuo to afford **19b** as a white solid (4.52 g, 72%).
^{1}H NMR (400 MHz, DMSO-d$_6$) δ=11.05 (s, 1H), 8.38 (d, *J* = 1.7 Hz, 1H), 8.32 (s, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 3.98 (s, 3H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H), 1.35 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ= 171.2, 163.8, 154.7 (q, *J* = 37.4 Hz), 146.1, 144.0, 142.7, 138.7, 132.9, 126.7, 123.9, 122.1, 119.5, 115.6 (q, *J* = 288.4 Hz), 80.0, 53.1, 35.5, 30.9, 27.7 ppm. ^{19}F NMR (376 MHz,

DMSO-d_6) δ=-74.5 ppm.
HRMS (ESI) *m/z* calcd for $C_{20}H_{21}ClF_3N_2O_5$ $[M+H]^+$: 461.1091; found: 461.1090.

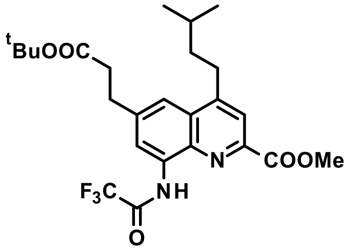
Methyl 6-[2-(*tert*-butoxycarbonylamino)ethyl]-4-*iso*pentyl-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (20a)



Preparation of alkylboron-reagent:
An oven-dried, 25 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 4.04 mL 1.50 M solution of **3-methylbut-1-ene** in THF (3.0 equiv., 6.05 mmol), and 6.05 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.5 equiv., 3.03 mmol) were added at RT, then the resulting mixture was stirred for 12 h. This solution was used in the next step.

Suzuki-coupling:
A 50 mL pear-shaped flask was filled with 960 mg compound **methyl 6-[2-(*tert*-butoxycarbonylamino)ethyl]-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (19a)** (prepared according to [2], 1.0 equiv., 2.02 mmol), 71.4 mg $Pd(AtaPhos)_2Cl_2$ (5.00 mol%, 0.10 mmol) and 1.32 g Cs_2CO_3 (2.00 equiv., 4.04 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 2.02 mL (1 mL/mmol) water and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 1 h. After cooling to RT, 15 mL EtOAc was added, the organic phase was separated and washed with 2x5 mL brine. The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (40 g silicagel column, heptane/EtOAc, gradient elution: 0-60%), then the resulting solid was triturated with 20 mL heptane, filtered and dried *in vacuo* to afford compound **20a** as an off-white, crystalline solid (770 mg, 75%).
^{1}H NMR (500 MHz, DMSO-d_6) δ=11.00 (s, 1H), 8.37/8.34 (s/s, 1H), 8.06 (s, 1H), 7.87/7.81 (s, 1H), 6.96/6.60 (t/br s, J = 5.6 Hz for triplet signal, 1H), 3.96 (s, 3H), 3.29 (q, J = 6.4 Hz, 2H), 3.17 (t, J = 8.0 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H), 1.70 (hept, J = 6.5 Hz, 1H), 1.60 (q, J = 7.6 Hz, 2H), 1.31/1.25 (s, 9H), 1.00 (d, J = 6.5 Hz, 6H). (Amide rotamers present at room temperature.) $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=164.7, 155.5, 154.1 (q, J = 36.8 Hz), 151.2, 145.2, 140.7, 137.1, 132.4, 127.9, 121.1, 121.0, 119.9, 115.6 (q, J = 288.5 Hz), 77.5, 52.8, 41.0, 38.6, 36.2, 29.3, 28.1, 27.7, 22.3 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ=-74.7 ppm.
HRMS (ESI) *m/z* calcd for $C_{25}H_{33}F_3N_3O_5$ $[M+H]^+$: 512.2372; found: 512.2369.

Methyl 6-(3-*tert*-butoxy-3-oxo-propyl)-4-*iso*pentyl-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (20b)

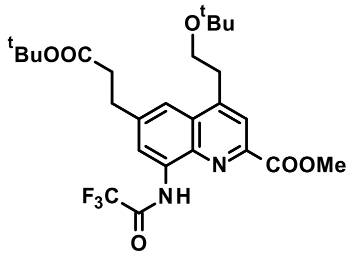


Preparation of alkylboron-reagent:
An oven-dried, 25 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 1.25 mL 1.50M solution of **3-methylbut-1-ene** in THF (3.00 equiv., 2.28 mmol), and 2.28 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.50 equiv., 1.14 mmol) were added at RT, then the resulting mixture was stirred for 12 h. This solution was used in the next step.

Suzuki-coupling:
A 25 mL pear-shaped flask was filled with 350 mg **19b** (1.0 equiv., 0.76 mmol), 26.9 mg $Pd(AtaPhos)_2Cl_2$ (5.00 mol%, 0.04 mmol) and 495 mg Cs_2CO_3 (2.00 equiv., 1.52 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 0.76 mL (1mL/mmol) water and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 1 h. After cooling to RT, the organic phase was separated and washed with 2x2 mL brine. The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (12 g silicagel column, heptane/EtOAc, gradient elution: 0-40%), then reversed phase HPLC (EZ Prep system, eluent: 25mM aq NH_4HCO_3/MeCN, gradient elution: 80-100%) to afford **20b** as an off-white, crystalline solid (317 mg, 84%).
^{1}H NMR (500 MHz, DMSO-d_6) δ=10.95 (s, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.02 (s, 1H), 7.87 (s, 1H), 3.96 (s, 3H), 3.16-3.10 (m, 2H), 3.08 (t, J = 7.3 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 1.70 (hept, J = 6.6 Hz, 1H), 1.62-1.53 (m, 2H), 1.34 (s, 9H), 0.99 ppm (d, J = 6.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-

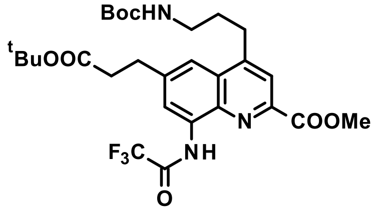
d_6) δ=171.3, 164.7, 154.2 (q, *J* = 36.9 Hz), 151.2, 145.4, 141.8, 137.2, 132.5, 127.9, 121.1, 121.1, 119.4, 115.6 (q, *J* = 288.5 Hz), 79.9, 52.8, 38.7, 35.7, 31.1, 29.3, 27.7, 27.7, 22.3 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ=-74.7 ppm.
HRMS (ESI) *m/z* calcd for $C_{25}H_{32}F_3N_2O_5$ $[M+H]^+$: 497.2260; found: 497.2258.

Methyl 4-(2-*tert*-butoxyethyl)-6-(3-*tert*-butoxy-3-oxo-propyl)-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (20c)



Preparation of alkylboron-reagent:
An oven-dried, 25 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 713 µL **2-methyl-2-vinyloxy-propane** (2.00 equiv., 5.43 mmol), and 10.9 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (2.00 equiv., 5.43 mmol) were added at RT, then the resulting mixture was stirred for 30 min. This solution was used in the next step.
Suzuki-coupling:
A 25 mL pear-shaped flask was filled with 1.25 g compound **19b** (1.0 equiv., 2.71 mmol), 96.0 mg $Pd(AtaPhos)_2Cl_2$ (5.00 mol%, 0.14 mmol) and 2.65 g Cs_2CO_3 (3.00 equiv., 8.14 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 2.71 mL (1mL/mmol) water and the *alkylboron-reagent* were added. The mixture was stirred atheated to 50°C by a heating block and stirred for 30 min. After cooling to RT, the organic phase was separated and washed with 2x5 mL brine. The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g silicagel column, heptane/EtOAc, gradient elution: 0-30%), then reversed phase HPLC (EZ Prep system, eluent: 0.1% aq TFA/MeCN, gradient elution: 90-100%) to afford **20c** as an off-white, crystalline solid (1.14 g, 80%).
^{1}H NMR (400 MHz, DMSO-d_6) δ=11.00 (s, 1H), 8.35 (d, *J* = 1.3 Hz, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 3.97 (s, 3H), 3.71 (t, *J* = 6.4 Hz, 2H), 3.34 (t, *J* = 5.2 Hz, 2H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 1.35 (s, 9H), 1.05 ppm (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ=171.3, 164.8, 154.3 (q, *J* = 36.9 Hz), 148.5, 145.2, 141.6, 137.4, 132.6, 128.5, 122.2, 121.3, 120.0, 115.7 (q, *J* = 291.5 Hz), 79.9, 72.5, 60.4, 52.9, 35.8, 32.5, 31.1, 27.7, 27.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ=-74.6 ppm.
HRMS (ESI) *m/z* calcd for $C_{26}H_{34}F_3N_2O_6$ $[M+H]^+$: 527.2369; found: 527.2369.

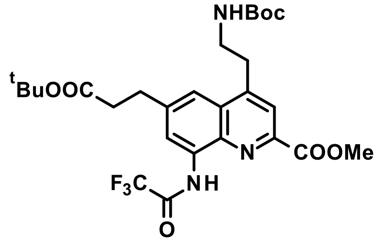
Methyl 4-[3-(*tert*-butoxycarbonylamino)propyl]-6-(3-tert-butoxy-3-oxo-propyl)-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (20d)



Preparation of alkylboron-reagent:
An oven-dried, 25 mL pear-shaped flask was filled with 880 mg ***tert*-butyl N-allylcarbamate** (3.00 equiv, 5.60 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 5.60 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (1.50 equiv., 2.80 mmol) was added at RT, then the resulting mixture was stirred for 1 h. This solution was used in the next step.
Suzuki-coupling:
A 25 mL pear-shaped flask was filled with 860 mg compound **19b** (1.0 equiv., 1.87 mmol), 66.1 mg $Pd(AtaPhos)_2Cl_2$ (5.00 mol%, 0.09 mmol) and 1.22 g Cs_2CO_3 (2.00 equiv., 3.73 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 1.87 mL (1mL/mmol) water and the *alkylboron-reagent* were added. The mixture was stirred atheated to 50°C by a heating block and stirred for 1 h. After cooling to RT, 10 mL DCM was added, the organic phase was separated and washed with 2x10 mL brine. The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. [SAFETY NOTE: Crude product should be handled under inert gas, as borane residues might be present, causing sudden heating, fuming and fire hazard upon exposition to air.] The residue was triturated with 25 mL pentane, filtered, and the crystals were washed with 3x5 mL pentane. The resulting solid was purified by flash chromatography (40 g silicagel column, DCM/MeOH, gradient elution: 0-5%) to afford **20d** as an off-white, crystalline solid (977 mg, 90%).
^{1}H NMR (500 MHz, DMSO-d_6) δ=10.99 (s, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 6.99 (t, *J* = 5.4 Hz, 1H), 3.96 (s, 3H), 3.16 (t, *J* = 7.7 Hz, 2H), 3.09 (t, *J* = 7.5 Hz, 2H), 3.04 (q, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.82 (quint, *J* = 7.3 Hz, 2H), 1.39 (s, 9H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR

(100 MHz, DMSO-d$_6$) δ=171.3, 164.8, 155.7, 154.3 (q, *J* = 36.8 Hz), 150.6, 145.5, 141.9, 137.4, 132.6, 128.1, 121.5, 121.3, 119.6, 115.6 (q, *J* = 289.8 Hz), 79.9, 77.5, 52.8, 39.6, 35.8, 31.1, 29.8, 28.8, 28.3, 27.7 ppm. ^{19}F NMR (376 MHz, DMSO-d$_6$) δ=-74.6 ppm.
HRMS (ESI) *m/z* calcd for $C_{28}H_{37}F_3N_3O_7$ [M+H]$^+$: 584.2584; found: 584.2583.

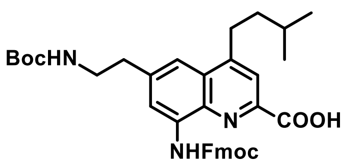
Methyl 4-[2-(*tert*-butoxycarbonylamino)ethyl]-6-(3-*tert*-butoxy-3-oxo-propyl)-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (20e)



Preparation of alkylboron-reagent:
An oven-dried, 25 mL pear-shaped flask was filled with 699 mg **tert-butyl *N*-vinylcarbamate** (Prepared from *N*-vinyl formamide according to [2].) (1.50 equiv., 4.88 mmol), closed with a rubber septum, evacuated and charged with dry N_2. 13.0 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (2.00 equiv., 6.51 mmol) was added at RT, then the resulting mixture was stirred for 1 h. This solution was used in the next step.

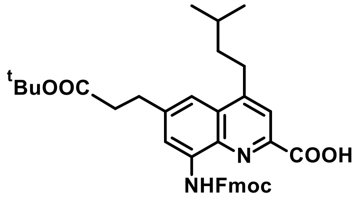
Suzuki-coupling:
A 25 mL pear-shaped flask was filled with 1.50 g **19b** (1.0 equiv., 3.26 mmol), 115 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.16 mmol) and 3.18 g Cs_2CO_3 (3.00 equiv., 9.77 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 3.26 mL (1mL/mmol) water and the *alkylboron-reagent* were added. The mixture was heated to 50°C by a heating block and stirred for 3 h. After cooling to RT, the organic phase was separated and washed with 2x5 mL brine. 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 silicagel column, heptane/EtOAc, gradient elution: 0-60%). The obtained solid was triturated with 15 mL DIPE, filtered, washed with furter 2x2 mL DIPE and dried in vacuo to afford **20e** as an off-white, crystalline solid (800 mg, 43%).
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=10.98 (s, 1H), 8.35 (d, *J* = 1.1 Hz, 1H), 8.04 (s, 1H), 8.01/7.93 (s/s, 1H), 7.01/6.60 (t/s, *J* = 5.2 Hz for triplet signal, 1H), 3.96 (s, 3H), 3.32-3.23 (m, 4H), 3.09 (t, *J* = 7.7 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.37 (s, 9H), 1.30/1.09 ppm (s/s, 9H). (Amide rotamers present at room temperature.) ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.3, 164.7, 155.5, 154.3 (q, *J* = 36.8 Hz), 148.2, 145.2, 141.8, 137.4, 132.5, 128.4, 122.3, 121.2, 119.7, 115.6 (q, *J* = 288.5 Hz), 79.9, 77.6, 52.8, 40.2, 35.6, 32.1, 31.1, 28.1, 27.7 ppm. ^{19}F NMR (376 MHz, DMSO-d$_6$) δ=-74.6 ppm.
HRMS (ESI) *m/z* calcd for $C_{27}H_{35}F_3N_3O_7$ [M+H]$^+$: 570.2427; found: 570.2419.

6-[2-(*tert*-butoxycarbonylamino)ethyl]-8-(9H-fluoren-9-ylmethoxycarbonylamino)-4-*iso*pentyl-quinoline-2-carboxylic acid (21a)



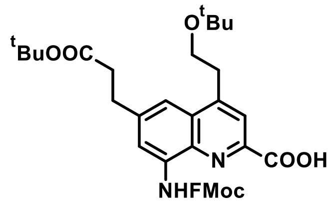
Using **General Procedure B** 730 mg compound **20a** (1.0 equiv., 1.43 mmol), **21a** (625 mg, 70%) was obtained as pale yellow solid.
HPLC-UV purity: 98.3%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.58 (br s, 1H), 10.38 (br s, 1H), 8.30 (br s, 1H), 8.03 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.59/7.55 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 6.93/6.56 (t/br s, *J* = 5.5 Hz for triplet signal, 1H), 4.59 (d, *J* = 6.7 Hz, 2H), 4.44 (t, *J* = 6.9 Hz, 1H), 3.24 (q, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 8.0 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.68 (hept, *J* = 6.5 Hz, 1H), 1.59 (q, *J* = 8.1 Hz, 2H), 1.32/1.23 (s, 9H), 0.99 ppm (d, *J* = 6.6 Hz, 6H). (Amide rotamers present at room temperature.) ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=165.8, 155.5, 153.4, 150.7, 144.8, 143.7, 140.8, 140.7, 136.0, 135.8, 128.2, 127.8, 127.2, 125.1, 120.3, 119.9, 117.2, 116.0, 77.5, 66.4, 46.5, 41.1, 38.5, 36.5, 29.4, 28.2, 27.6, 22.3 ppm.
HRMS (ESI) *m/z* calcd for $C_{37}H_{42}N_3O_6$ [M+H]$^+$: 624.3074; found: 624.3070.

6-(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-*iso*pentyl-quinoline-2-carboxylic acid (21b)



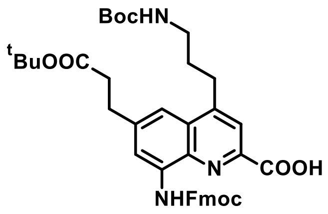
Using **General Procedure B** 800 mg **20b** (1.0 equiv., 1.61 mmol), **21b** (587 mg, 60%) was obtained as pale yellow solid.
HPLC-UV purity: 99.8%.
^{1}H NMR (500 MHz, DMSO-d_6) δ=13.53 (br s, 1H), 10.46 (br s, 1H), 8.29 (br s, 1H), 8.04 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.63 (s, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.36 (td, J = 7.4 Hz, J = 1.0 Hz, 2H), 4.61 (d, J = 6.6 Hz, 2H), 4.45 (t, J = 6.9 Hz, 1H), 3.12 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 9.7 Hz, 2H), 1.68 (hept, J = 6.6 Hz, 1H), 1.62-1.55 (m, 2H), 1.34 (s, 9H), 0.99 ppm (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ=171.3, 165.6, 153.5, 150.9, 144.4, 143.7, 142.0, 140.8, 136.0, 135.7, 128.2, 127.8, 127.2, 125.1, 120.3, 120.0, 116.9, 115.5, 79.8, 66.4, 46.6, 38.6, 35.8, 31.4, 29.5, 27.7, 27.6, 22.3 ppm.
HRMS (ESI) *m/z* calcd for $C_{37}H_{41}N_2O_6$ [M+H]$^+$: 609.2965; found: 609.2963.

4-(2-*tert*-butoxyethyl)-6-(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (21c)



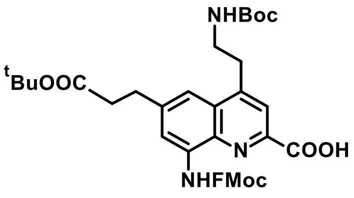
Using **General Procedure B** 1.11 g **20c** (1.0 equiv., 2.11 mmol), **21c** (825 mg, 61%) was obtained as pale yellow solid.
HPLC-UV purity: 99.8%.
^{1}H NMR (500 MHz, DMSO-d_6) δ=13.51 (br s, 1H), 10.46 (br s, 1H), 8.29 (br s, 1H), 8.11 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.68 (s, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.37 (td, J = 7.5 Hz, J = 1.0 Hz, 2H), 4.61 (d, J = 6.5 Hz, 2H), 4.46 (t, J = 6.9 Hz, 1H), 3.70 (t, J = 6.5 Hz, 2H), 3.29 (t, J = 6.5 Hz, 2H), 3.00 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 1.34 (s, 9H), 1.07 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ=171.3, 165.6, 153.5, 148.1, 144.0, 143.7, 142.0, 140.8, 135.9, 135.7, 128.7, 127.8, 127.2, 125.1, 120.9, 120.3, 117.0, 115.9, 79.8, 72.5, 66.4, 60.3, 46.6, 35.9, 32.7, 31.4, 27.7, 27.2 ppm.
HRMS (ESI) *m/z* calcd for $C_{38}H_{43}N_2O_7$ [M+H]$^+$: 639.3070; found: 639.3065.

4-[3-(*tert*-butoxycarbonylamino)propyl]-6-(3-tert-butoxy-3-oxo-propyl)-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (21d)



Using **General Procedure B** 942 mg **20d** (1.0 equiv., 1.43 mmol), **21d** (700 mg, 62%) was obtained as pale yellow solid.
HPLC-UV purity: 99.8%.
^{1}H NMR (500 MHz, DMSO-d_6) δ=13.53 (br s, 1H), 10.34 (br s, 1H), 8.26 (br s, 1H), 8.04 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H), 7.63 (s, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 6.98 (t, J = 5.4 Hz, 1H), 4.60 (d, J = 6.6 Hz, 2H), 4.44 (t, J = 6.8 Hz, 1H), 3.10 (t, J = 7.7 Hz, 2H), 3.03 (q, J = 6.4 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.80 (quint, J = 7.2 Hz, 2H),1.38 (s, 9H), 1.35 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ=171.3, 166.0, 155.7, 153.3, 149.8, 143.7, 141.6, 140.7, 135.9, 135.7, 128.0, 127.8, 127.2, 125.1, 120.5, 120.2, 116.5, 115.5, 79.8, 77.5, 66.4, 46.5, 39.7, 36.0, 31.5, 29.7, 29.0, 28.3, 27.7 ppm.
HRMS (ESI) *m/z* calcd for $C_{40}H_{46}N_3O_8$ [M+H]$^+$: 696.3285; found: 696.3280.

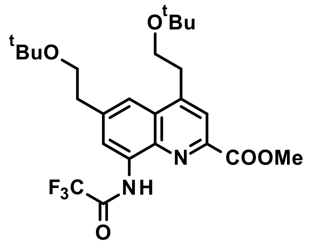
4-[2-(*tert*-butoxycarbonylamino)ethyl]-6-(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (21e)



Using **General Procedure B** 780 mg compound **20e** (1.0 equiv., 1.37 mmol), **21e** (760 mg, 81%) was obtained as pale yellow solid.
HPLC-UV purity: 97.9%.
^{1}H NMR (500 MHz, DMSO-d_6) δ=13.50 (br s, 1H), 10.46 (br s, 1H), 8.29 (br s, 1H), 8.02 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.78 (dd, J = 7.5 Hz, J = 0.5 Hz, 2H), 7.74/7.68 (s/s, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.36 (td, J = 7.4 Hz, J = 1.0 Hz, 2H), 6.97/6.57 (t/s, J = 5.6 Hz for triplet

signal, 1H), 4.61 (d, *J* = 6.6 Hz, 2H), 4.46 (t, *J* = 6.9 Hz, 1H), 3.33-3.18 (m, 4H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.36 (s, 9H), 1.30/1.07 ppm (s/s, 9H). (Amide rotamers present at room temperature.) $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=171.3, 165.5, 155.5, 153.5, 148.0, 144.0, 143.7, 142.1, 140.8, 136.0, 135.8, 128.7, 127.8, 127.2, 125.1, 121.2, 120.3, 116.9, 115.7, 79.8, 77.6, 66.3, 46.6, 40.2, 35.8, 32.3, 31.4, 28.1, 27.7 ppm.
HRMS (ESI) *m/z* calcd for $C_{39}H_{44}N_3O_8$ $[M+H]^+$: 682.3128; found: 682.3126.

Methyl 4,6-bis(2-*tert*-butoxyethyl)-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (22b)



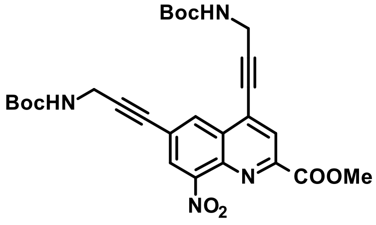
Preparation of alkylboron-reagent:

An oven-dried, 50 mL pear-shaped flask was closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 1.37 mL **2-methyl-2-vinyloxy-propane** (2.00 equiv., 10.5 mmol), and 20.9 mL 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (2.00 equiv., 10.5 mmol) were added at RT, then 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 **methyl 6-bromo-4-chloro-8-[(2,2,2-trifluoroacetyl)amino]quinoline-2-carboxylate (18)** (1.0 equiv., 5.22 mmol, prepared according to [2]), 116 mg Pd(AtaPhos)$_2$Cl$_2$ (5.00 mol%, 0.26 mmol) and 3.02 g Cs_2CO_3 (3.00 equiv., 15.7 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 5.22 mL water and the *alkylboron-reagent* were added. The mixture was heated to 40°C by a heating block and stirred 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 Na_2SO_4, 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 **22b** as a yellow solid (643 mg, 25%).
^1H NMR (500 MHz, DMSO-d_6) δ=10.95 (s, 1H), 8.40 (d, *J* = 1.6 Hz, 1H), 8.12 (s, 1H), 7.96 (d, *J* = 1.5 Hz, 1H), 3.96 (s, 3H), 3.70 (t, *J* = 6.4 Hz, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 3.32 (t, *J* = 6.4 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H), 1.11 (s, 9H), 1.04 ppm (s,9H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=164.8, 154.2 (q, *J* = 36.7 Hz), 148.4, 145.0, 140.8, 137.2, 132.1, 128.4, 122.1, 121.6, 120.5, 115.7 (q, *J* = 287.1 Hz), 72.5, 72.4, 61.4, 60.5, 52.8, 37.0, 32.6, 27.3, 27.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ=-74.6 ppm.
HRMS (ESI) *m/z* calcd for $C_{25}H_{34}F_3N_2O_5$ $[M+H]^+$: 499.2420; found: 499.2410.

Methyl 4,6-bis[3-(tert-butoxycarbonylamino)prop-1-ynyl]-8-nitro-quinoline-2-carboxylate (24a)

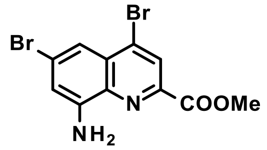


415 mg **methyl 4,6-dibromo-8-nitro-quinoline-2-carboxylate (23)** (prepared according to [3], 1.0 equiv., 1.00 mmol), 466 mg ***tert*-butyl *N*-prop-2-ynylcarbamate** (3.0 equiv., 3.00 mmol), 39 mg copper(I)-iodide (0.2 equiv., 0.20 mmol) were measured into a 50 mL flask. The flask was evacuated then back-filled with N_2 (repeated 3x), then 7.5 mL 1,4-dioxane (dry, degassed) and 2.00 mL *N-iso*propylpropan-2-amine (14.3 equiv., 14.3 mmol) were added at rt while stirring. The reaction mixture was heated to 80°C by a heating block and 35.4 mg dichloropalladium, 4-di*tert*-butylphosphanyl-*N*,*N*-dimethyl-aniline (1:2) (0.05 equiv., 0.05 mmol) was added at this temperature. After 10 min, full conversion was observed and 25 mL DCM was added, the resulting solution was washed with 2x10 mL 5% aq. citric acid solution and 15 mL sat. aq. $NaHCO_3$ solution. Combined aqueous phase was extracted with 2x10 mL DCM. Combined organic phase dried over Na_2SO_4, was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (40 g silicagel column, heptane/DCM, gradient elution: 0-80%) to afford **24a** as an off-white solid (323 mg, 90%).
^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (s, 1H), 8.27 (s, 1H), 8.03 (s, 1H), 5.18 (b s, 1H), 5.04 (b s, 1H), 4.34 (d, *J* = 4.9 Hz, 2H), 4.23 (d, *J* = 4.9 Hz, 2H)) 4.02 (s, 3H), 1.49 (s, 9H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR

(125 MHz, $CDCl_3$): δ = 164.9, 155.6, 149.8, 148.7, 138.7, 132.7, 131.2, 129.4, 127.8, 126.0, 123.1, 99.4, 91.5, 80.7, 77.4, 53.7, 31.6, 31.3, 28.6.

HRMS (ESI): *m/z* $[M+H]^+$ for $C_{27}H_{30}N_4O_8$: 539.2136; found: 539.2137.

Methyl 8-amino-4,6-dibromo-quinoline-2-carboxylate (25)

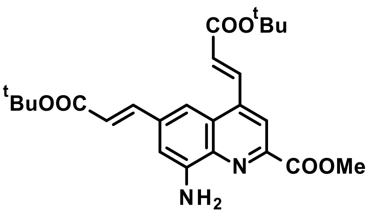


A 2 L pear-shaped flask was filled with 6.74 g Raney nickel (3.14 equiv., 78.7 mmol) under N_2 atmosphere, then washed with 3x20 mL water and 2x20 mL MeOH. 9.77 g compound **methyl 4,6-dibromo-8-nitro-quinoline-2-carboxylate (23)** (prepared according to [3],1.0 equiv., 25.1 mmol) and 1.12 L MeOH were added and the atmosphere was changed to H_2 (1 bar). The reaction mixture was stirred at RT for 18 h and then filtered through a short pad of celite. The filtrate was concentrated *in vacuo* and the obtained residue was purified by flash chromatography (330 g silicagel column, DCM/MeOH, gradient elution: 0-5%) to afford **25** as a yellow solid (6.41 g, 71%).

^1H NMR (500 MHz, DMSO-d_6) δ=8.33 (s, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.61 (s, 2H), 3.94 ppm (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=163.9, 148.5, 143.6, 135.3, 132.3, 130.0, 126.0, 125.8, 112.6, 112.3, 52.8 ppm.

HRMS (ESI) *m/z* calcd for $C_{11}H_9Br_2N_2O_2$ $[M+H]^+$: 358.9031; found: 358.9017.

Methyl 8-amino-4,6-bis[(*E*)-3-*tert*-butoxy-3-oxo-prop-1-enyl]quinoline-2-carboxylate (26)

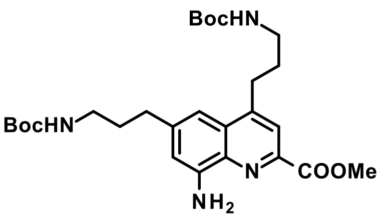


A 25 mL pear-shaped flask was filled with 1.41 g compound **25** (1.0 equiv., 3.92 mmol), 22.0 mg $Pd(OAc)_2$ (2.5 mol%, 0.10 mmol) and 119 mg tris-*o*-tolylphosphane (10.0 mol%, 0.39 mmol), closed with a rubber septum, evacuated and charged with dry N_2. Through the septum 3.92 mL DMF (1 mL/mmol), 3.92 mL DIPEA (1 mL/mmol) and 1.72 mL ***tert*-butyl acrylate** (3.0 equiv., 11.8 mmol) were added. The mixture was heated to 100°C by a heating block and stirred for 1 h. After cooling to RT, 20 mL EtOAc and 20 mL water were added, the organic phase was separated. The organic phase was washed with 20 mL water and 20 mL brine then it was dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (80 g silicagel column, heptane/EtOAc, gradient elution: 0-60%) to afford compound **26** as an orange solid (1.32 g, 74%).

^1H NMR (500 MHz, DMSO-d_6) δ=8.28 (d, *J* = 15.7 Hz, 1H), 8.27 (s, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.65 (d, *J* = 1.2 Hz, 1H), 7.24 (d, *J* = 1.4 Hz, 1H), 6.81 (d, *J* = 15.8 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.21 (s, 2H), 3.96 (s, 3H), 1.53 (s, 9H), 1.51 ppm (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ=165.3, 164.9, 164.7, 146.8, 144.3, 143.8, 140.9, 138.1, 137.6, 136.0, 127.5, 127.0, 121.5, 118.8, 111.3, 106.2, 80.7, 80.2, 52.7, 27.8, 27.8 ppm.

HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_2O_6$ $[M+H]^+$: 455.2182; found: 455.2181.

Methyl 8-amino-4,6-bis[3-(tert-butoxycarbonylamino)propyl]quinoline-2-carboxylate (27a)

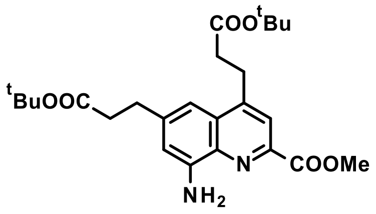


Using **General Procedure A** 90 mg compound **24a** (1.0 equiv., 0.465 mmol), **27a** was obtained as a pale yellow solid (112 mg, 50%).

^1H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.88 (s, 1H), 7.05 (s, 1H), 6.97 (t, *J* = 5.5 Hz, 1H), 6.89 (t, *J* = 5.5 Hz, 1H), 6.79 (d, *J* = 1.4 Hz, 1H), 6.03 (b s, 2H), 3.92 (s, 3H), 3.09-2.89 (m, 6H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.83-1.68 (m, 4H), 1.381 (s, 9H), 1.378 (s, 9H).$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-*d*$_6$): δ = 165.6, 155.7, 155.6, 148.3, 146.5, 144.1, 142.6, 135.6, 128.8, 120.3, 109.9, 108.5, 77.5, 77.4, 52.4, 33.6, 31.1, 29.5, 29.0, 28.3.

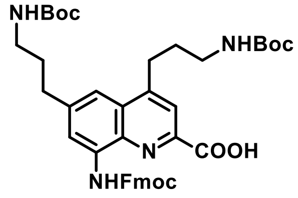
HRMS (ESI): *m/z* $[M+H]^+$ for $C_{27}H_{30}N_4O_8$: 517.3021; found: 517.3022.

Methyl 8-amino-4,6-bis(3-*tert*-butoxy-3-oxo-propyl)quinoline-2-carboxylate (27c)



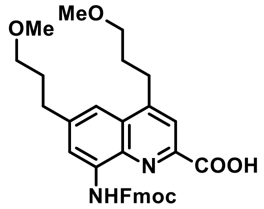
Using **General Procedure A** 1.300 g compound **26** (1.0 equiv., 2.85 mmol), **27c** was obtained as a yellow solid (1.270 g, 97%).
^{1}H NMR (400 MHz, DMSO-d$_6$) δ=7.87 (s, 1H), 7.06 (d, *J* = 1.4 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.06 (s, 2H), 3.92 (s, 3H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H),1.36 (s, 9H), 1.36 ppm (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ=171.5, 171.2, 165.4, 146.8, 146.5, 143.1, 142.6, 135.5, 128.6, 120.1, 109.9, 108.0, 80.0, 79.7, 52.4, 36.0, 34.1, 31.4, 27.7, 27.6, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{25}H_{35}N_2O_6$ $[M+H]^+$: 459.2495; found: 459.2502.

4,6-bis[3-(tert-butoxycarbonylamino)propyl]-8-(9H-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (28a)



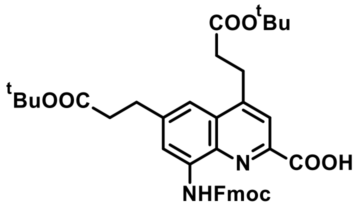
Using **General Procedure B** 160 mg compound **27a** (1.0 equiv., 0.167 mmol), **28a** was obtained as a pale yellow solid (59 mg, 68%).
HPLC-UV purity: 98.2%.
^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.22 (s, 1H), 8.24 (s, 1H), 8.02 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (dt, *J* = 1.0, 7.4 Hz, 2H), 6.97 (t, *J* = 5.1 Hz, 1H), 6.92 (t, *J* = 5.1 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 2H), 4.41 (t, *J* = 6.8 Hz, 1H), 3.13-2.92 (m, 6H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.86-1.70 (m, 4H), 1.38 (s, 9H), 1.37 (s, 9H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 166.3, 155.7, 155.6, 153.3, 149.4, 143.7, 142.5, 140.8, 135.8, 135.6, 127.9, 127.8, 127.24, 127.15, 126.8, 125.2, 125.1, 120.6, 120.3, 119.9, 116.4, 115.6, 77.50, 77.46, 66.4, 46.6, 33.6, 31.2, 29.7, 29.0, 28.3.
HRMS (ESI): *m/z* $[M+H]^+$ for $C_{41}H_{48}N_4O_8$: 725.3545; found: 726.3546.

8-(9H-fluoren-9-ylmethoxycarbonylamino)-4,6-bis(3-methoxypropyl)quinoline-2-carboxylic acid (28b)



Using **General Procedure B** 188 mg compound **methyl 8-amino-4,6-bis(3-methoxypropyl)quinoline-2-carboxylate (27b)** (prepared according to [3], 1.0 equiv., 0.543 mmol), **28b** was obtained as a pale yellow solid (97 mg, 30%).
HPLC-UV purity: 93.1%
^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.53 (b s, 1H), 10.45 (s, 1H), 8.31 (b s, 1H), 8.04 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.78 (dd, *J* = 0.6, 7.3 Hz, 1H), 7.63 (d, *J* = 0.7 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 (dt, *J* = 1.2, 7.5 Hz, 2H), 4.60 (d, *J* = 6.7 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.36 (t, *J* = 6.3 Hz, 2H), 3.26 (s, 3H), 3.25 (s, 3H), 3.20-3.14 (m, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.97-1.83 (m, 4H).^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ = 165.7, 153.5, 143.7, 140.8, 136.1, 135.7, 128.4, 127.8, 127.2, 125.2, 120.3, 117.0, 115.6, 71.0, 70.9, 66.4, 57.9, 46.6, 32.8, 30.7, 29.4, 28.3.
HRMS (ESI): *m/z* $[M+H]^+$ for $C_{33}H_{34}N_2O_6$: 555.2490; found: 555.2495.

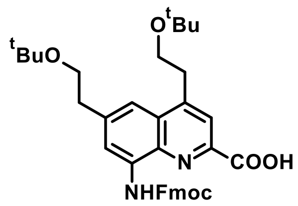
4,6-bis(3-*tert*-butoxy-3-oxo-propyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (28c)



Using **General Procedure B** 1.240 g compound **27c** (1.0 equiv., 2.70 mmol), **28c** (1.300 g, 72%) was obtained as pale yellow solid.
HPLC-UV purity: 99.9%.
^{1}H NMR (500 MHz, DMSO-d$_6$) δ=13.53 (br s, 1H), 10.30 (br s, 1H), 8.25 (br s, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.63 (s, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.36 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 2H), 4.60 (d, *J* = 6.2 Hz, 2H), 4.44 (t, *J* = 6.9 Hz, 1H), 3.34 (t, *J* = 7.0 Hz, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 7.2 Hz,

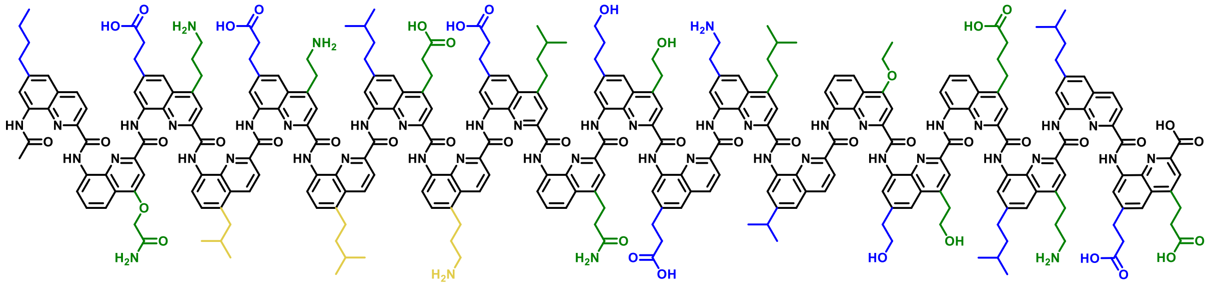
2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.36 (s, 9H), 1.35 ppm (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d$_6$) δ=171.3, 171.1, 166.1, 153.3, 148.1, 146.3, 143.7, 141.8, 140.7, 135.9, 135.6, 127.8, 127.7, 127.2, 125.1, 120.3, 120.2, 116.5, 115.3, 80.0, 79.8, 66.4, 46.5, 35.9, 34.2, 31.4, 27.7, 27.6, 26.9 ppm.
HRMS (ESI) *m/z* calcd for $C_{39}H_{43}N_2O_8$ $[M+H]^+$: 667.3019; found: 667.3003.

4,6-bis(2-*tert*-butoxyethyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (28d)



Using **General Procedure B** 624 mg **22b** (1.0 equiv., 1.25 mmol), **4,6-bis(2-*tert*-butoxyethyl)-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-quinoline-2-carboxylic acid (28d)** (380 mg, 50%) was obtained as pale yellow solid.
HPLC-UV purity: 99.9%.
^1H NMR (500 MHz, DMSO-d$_6$) δ=13.51 (br s, 1H), 10.45 (br s, 1H), 8.35 (br s, 1H), 8.11 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.71 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 2H), 4.60 (d, *J* = 6.9 Hz, 2H), 4.45 (t, *J* = 7.0 Hz, 1H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 1.09 (s, 9H), 1.06 ppm (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d$_6$) δ=165.6, 153.5, 148.0, 143.9, 143.7, 141.1, 140.8, 135.7, 135.6, 128.6, 127.8, 127.2, 125.1, 120.9, 120.3, 117.5, 116.6, 72.5, 72.3, 66.3, 61.6, 60.4, 46.6, 37.5, 32.8, 27.3, 27.2 ppm.
HRMS (ESI) *m/z* calcd for $C_{37}H_{43}N_2O_6$ $[M+H]^+$: 611.3121; found: 611.3098.

Oligomer 29



Oligomer **29** was synthesized on TG-R Wang resin (0.19mmol.g^{-1}, 15µmol scale) according to the standard method [4]. Loading of the first monomer: **28c** 0.16mmol.g^{-1} (85%). Unreacted amines were capped using Ac_2O/DCM (1:1) for 2h at room temperature. The final acetyl group was added using the general acetylation method [5]. After purification by semi-preparative HPLC (C8, 20-80B, 50°C, A: H_2O+0.1%TFA, B: MeCN+0.1%TFA), the title compound was obtained as a yellow powder (8.1 mg, 1.54µmol, 10.3%; HPLC purity >95%).
^{1}H NMR (500 MHz, *d*$_7$-DMF): δ = 12.58 (s, 14H), 11.77 (s, 2H), 11.08 (s, 1H), 11.01 (s, 1H), 10.81 (s, 1H), 10.56 (s, 2H), 10.45 (s, 1H), 10.33 (s, 2H), 10.21 (s, 1H), 10.04 (d, *J* = 15.8 Hz, 2H), 9.95 (d, *J* = 7.1 Hz, 5H), 9.84 (s, 1H), 9.65 (s, 1H), 9.41 (s, 1H), 8.57 (s, 8H), 8.42 (s, 11H), 8.36 (s, 1H), 8.27 (s, 5H), 7.93 (d, *J* = 3.4 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.79 – 7.69 (m, 5H), 7.61 (t, *J* = 6.7 Hz, 5H), 7.48 (d, *J* = 7.9 Hz, 3H), 7.46 – 7.39 (m, 4H), 7.38 (s, 1H), 7.37 – 7.31 (m, 3H), 7.30 (d, *J* = 6.9 Hz, 3H), 7.26 (s, 1H), 7.23 (s, 1H), 7.15 (d, *J* = 5.0 Hz, 2H), 7.12 (t, *J* = 3.7 Hz, 2H), 7.08 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 6.98 (t, *J* = 7.4 Hz, 4H), 6.93 (s, 1H), 6.91 (s, 3H), 6.90 – 6.88 (m, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.85 (d, *J* = 4.9 Hz, 4H), 6.82 (s, 2H), 6.80 (d, *J* = 4.7 Hz, 2H), 6.77 (s, 1H), 6.75 (t, *J* = 3.7 Hz, 2H), 6.62 (d, *J* = 7.3 Hz, 1H), 6.51 (s, 1H), 6.49 (s, 1H), 6.46 (s, 1H), 6.45 (s, 1H), 6.40 (t, *J* = 3.8 Hz, 3H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 6.26 (s, 1H), 6.22 (s, 1H), 6.19 (d, *J* = 8.1 Hz, 1H), 6.16 (d, *J* = 6.0 Hz, 2H), 6.04 (d, *J* = 8.1 Hz, 1H), 5.97 (s, 1H), 5.73 (s, 1H), 4.93 (d, *J* = 3.5 Hz, 2H), 4.84 (s, 1H), 4.45 (s, 1H), 4.39 (s, 1H), 4.09 (s, 3H), 3.86 (s, 2H), 3.74 (s, 2H), 3.31 (s, 5H), 3.25 (s, 6H), 3.12 (s, 4H), 2.99 (s, 1H), 2.67 – 2.49 (m, 36H), 2.45 – 2.34 (m, 3H), 2.15 (t, *J* = 7.4 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.89 – 1.67 (m, 5H), 1.54 (dt, *J* = 21.5, 6.7 Hz, 4H), 1.44 (s, 1H), 1.36 (t, *J* = 8.2 Hz, 5H), 1.32 (d, *J* = 3.9 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 13H), 1.21 – 1.11 (m, 41H), 1.11 – 1.03 (m, 19H), 0.88 (t, *J* = 6.8 Hz, 2H), 0.79 (t, *J* = 7.5 Hz, 4H).
HRMS (ESI) *m/z* calcd for $C_{297}H_{301}N_{47}O_{46}$ $[M+3H]^{3+}$: 1755.7656; found: 1755.8044.

3.3 NMR data of newly synthesized compounds

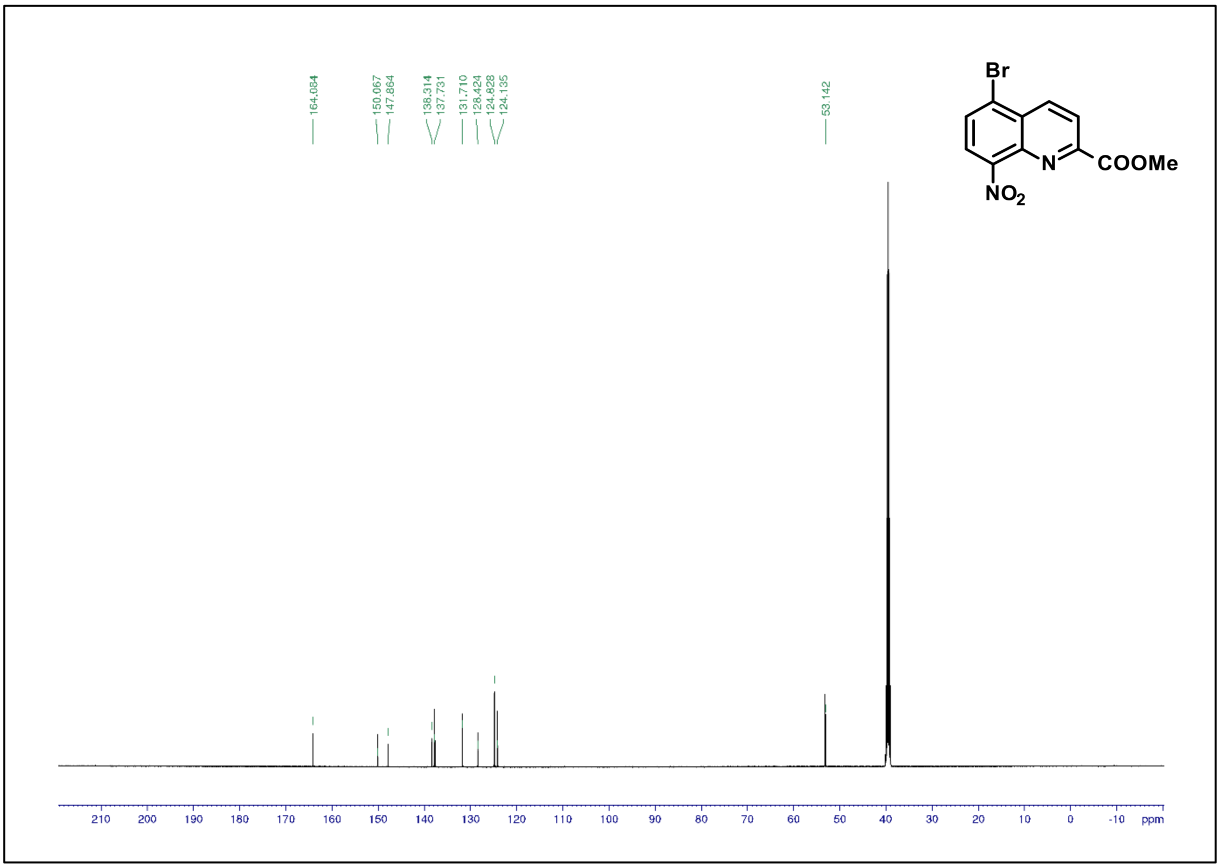


Figure S1. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **2**.

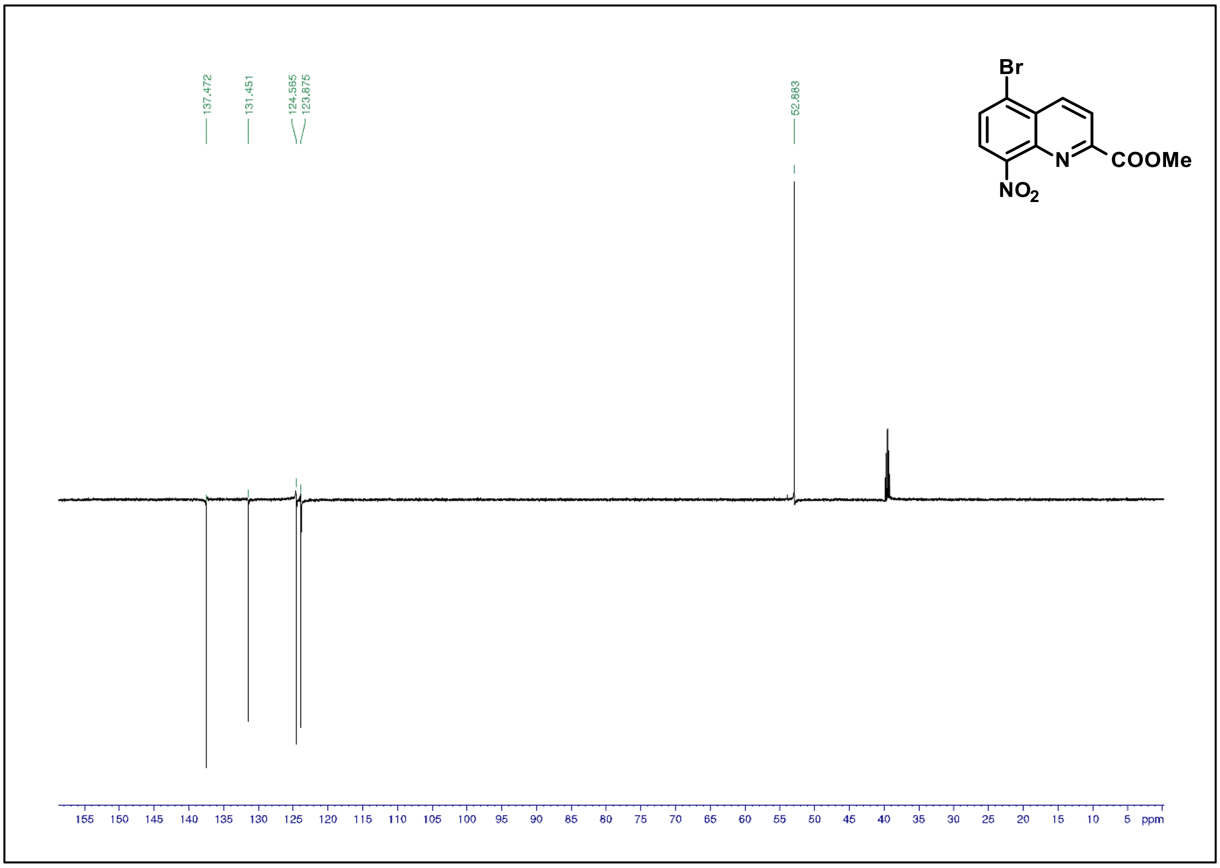


Figure S2. ^{13}C{^{1}H}NMR (125 MHz, DMSO-d$_6$) of compound **2**.

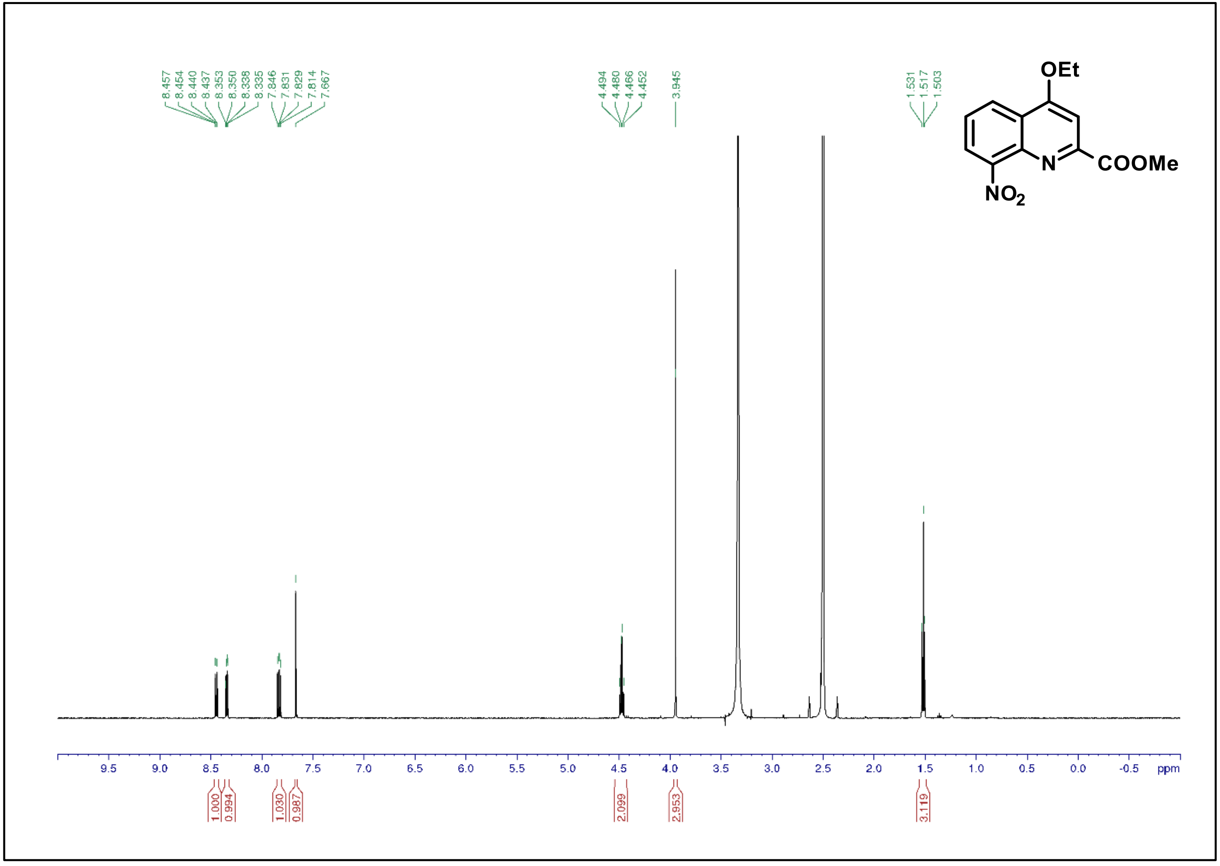


Figure S3. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **5a**.

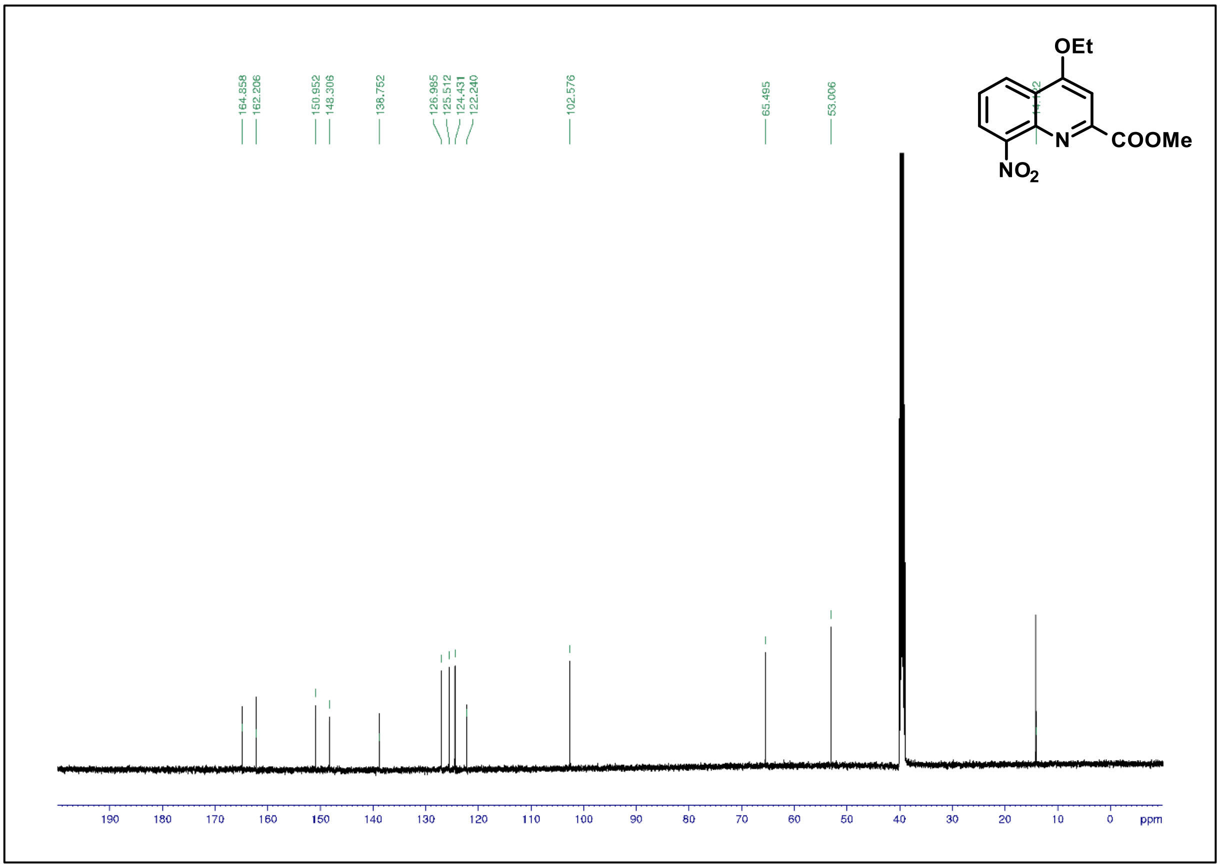


Figure S4. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **5a**.

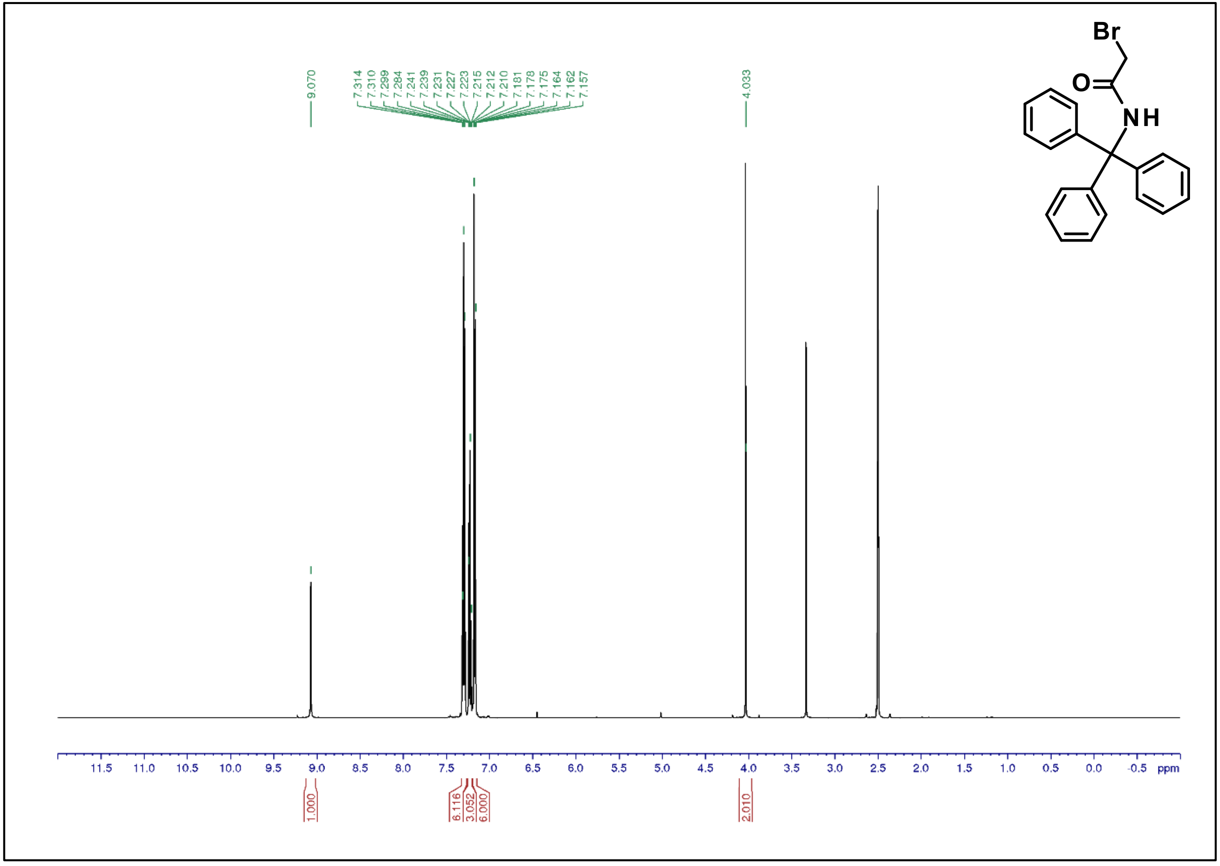


Figure S5. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **S1**.

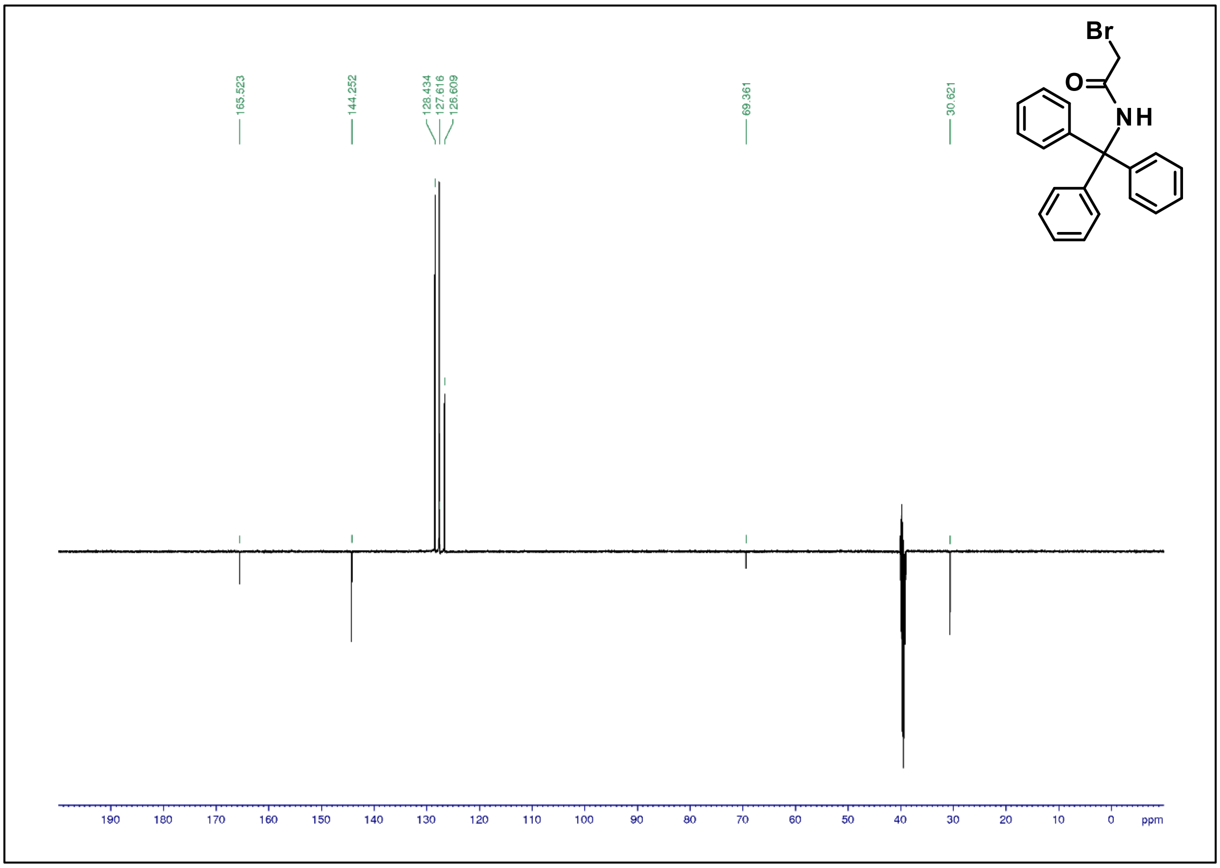


Figure S6. $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) of compound **S1**.

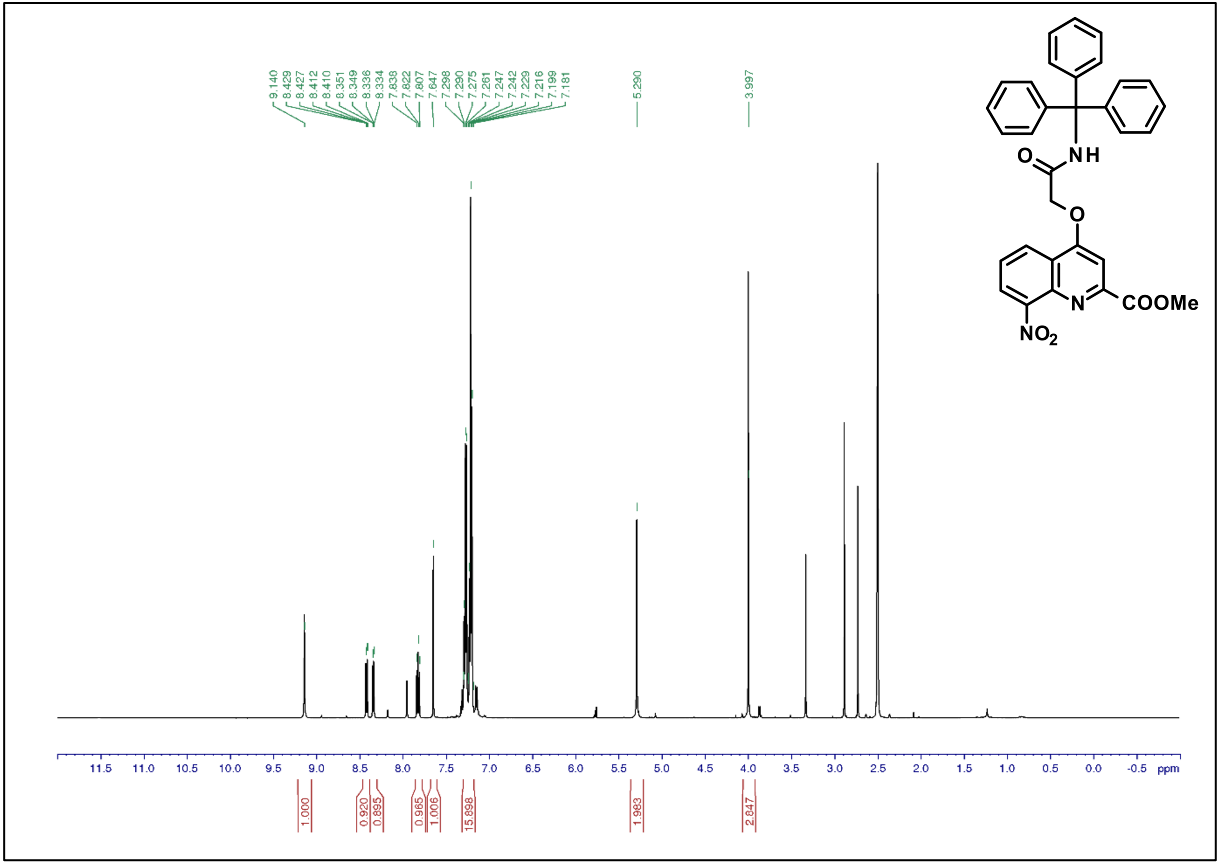


Figure S7. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **5b**.

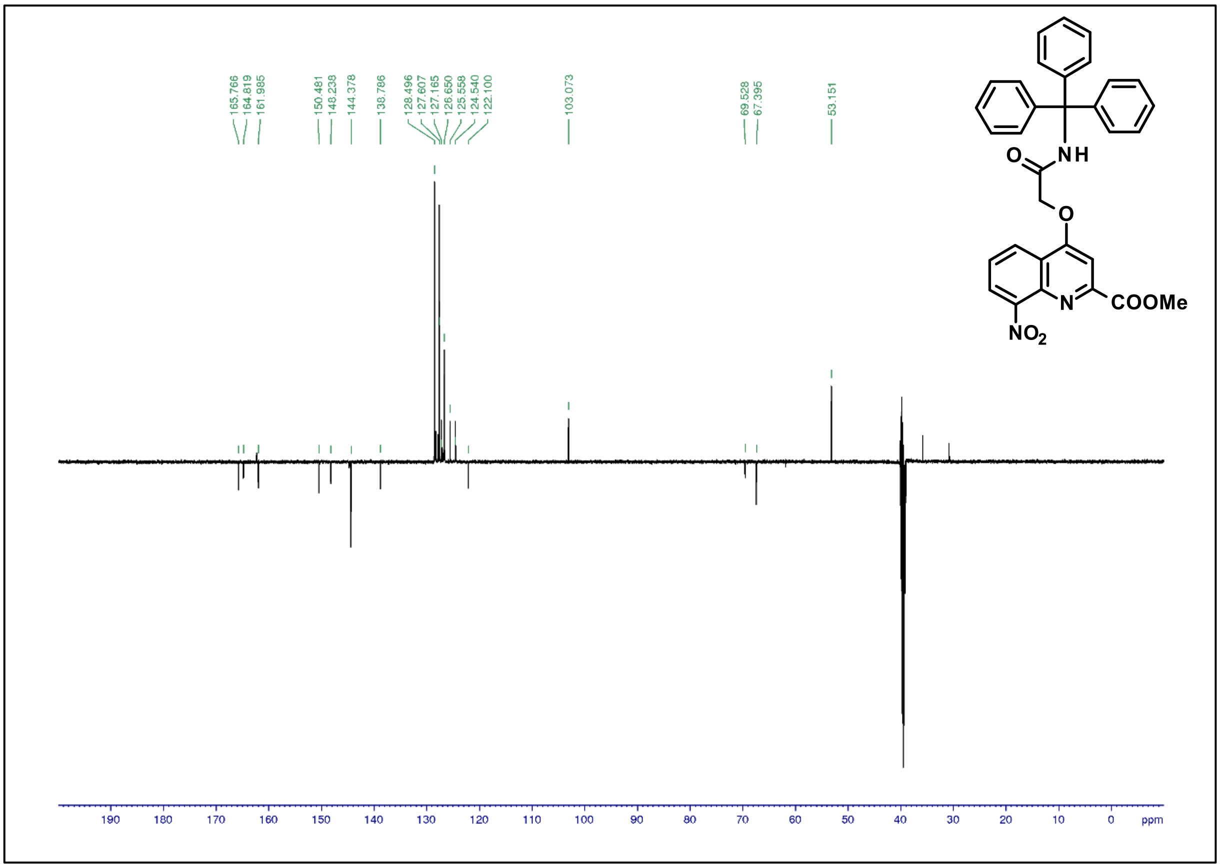


Figure S8. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **5b**.

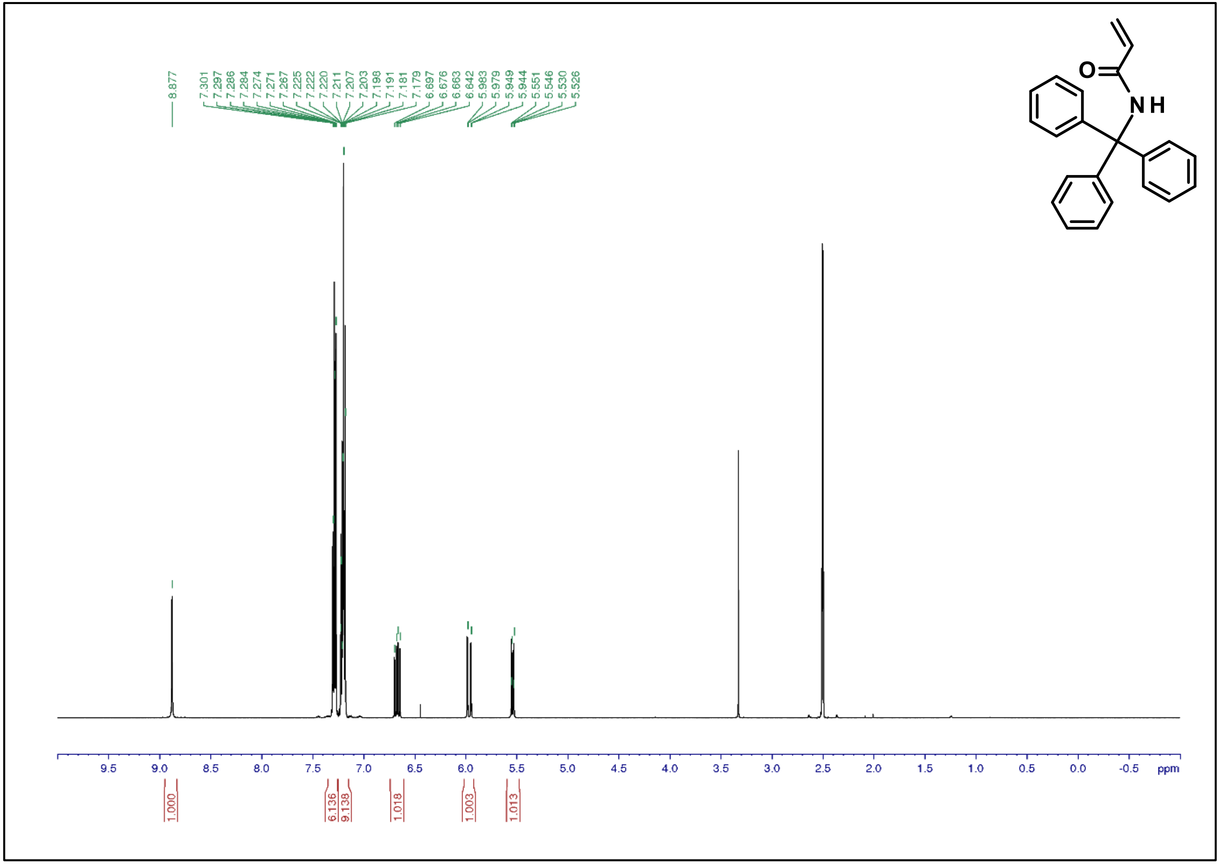


Figure S9. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **S2**.

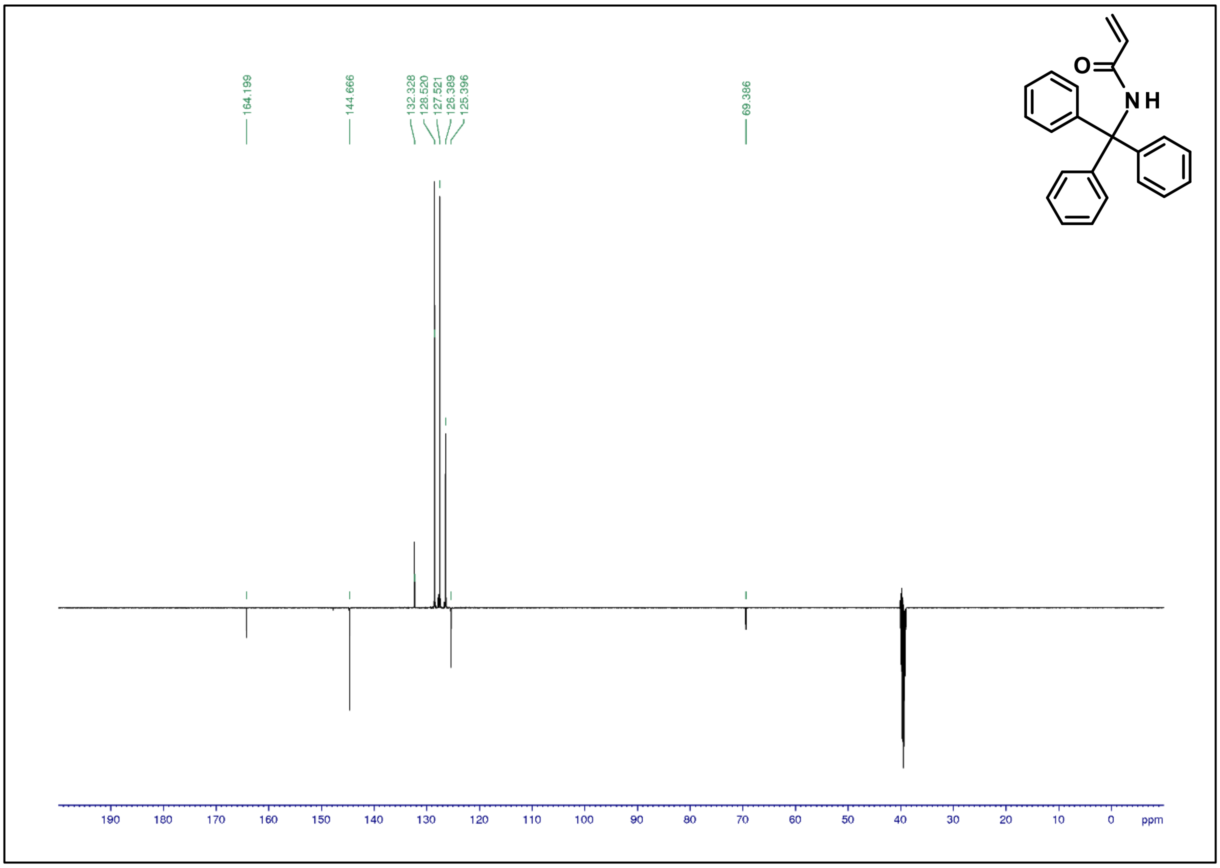


Figure S10. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound S**2**.

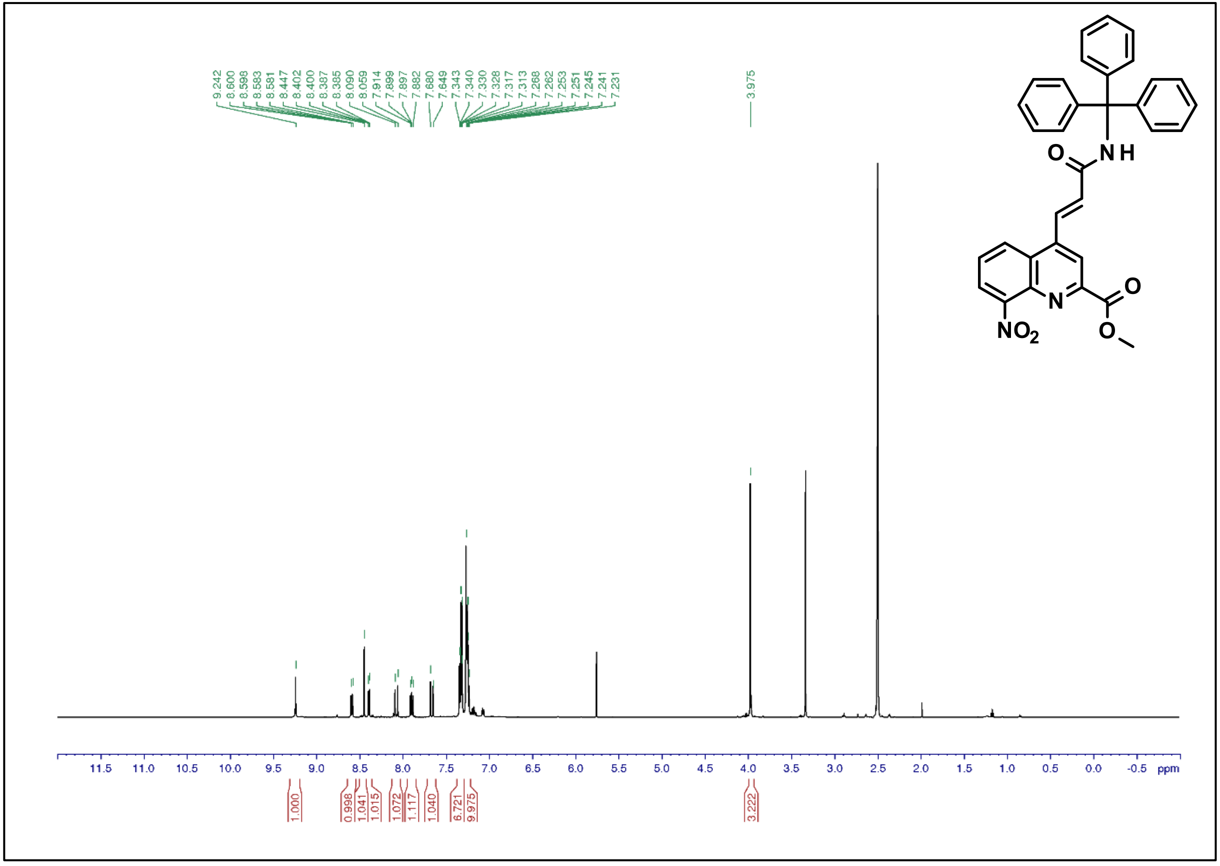


Figure S11. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **5c**.

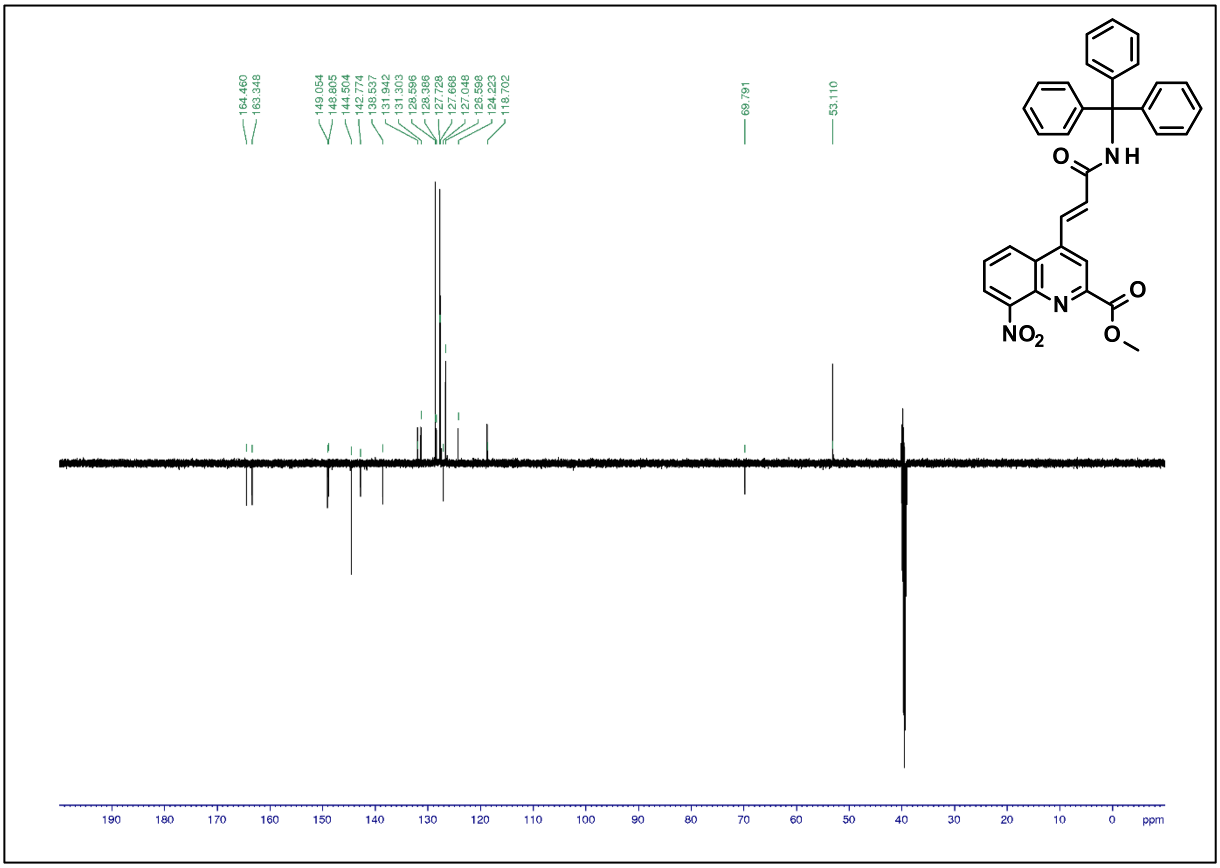


Figure S12. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **5c**.

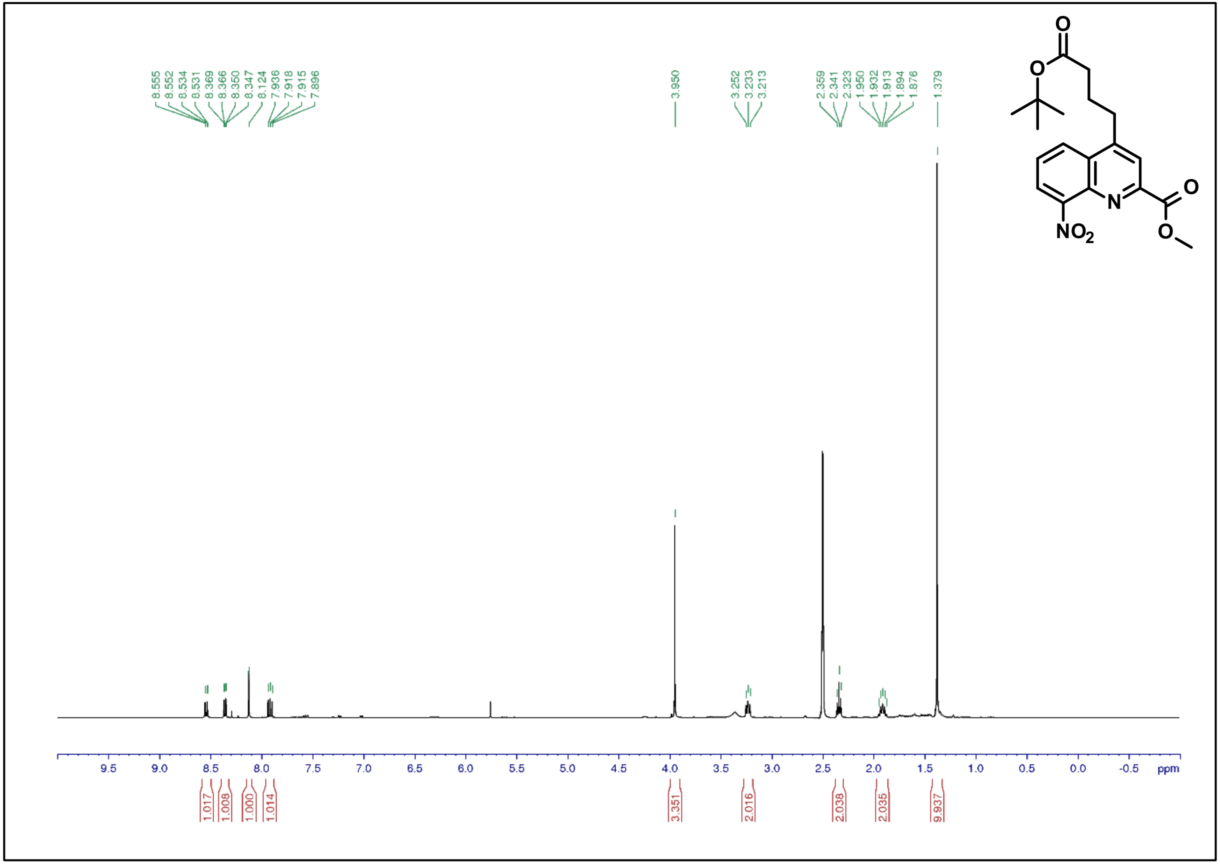


Figure S13. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **5d**.

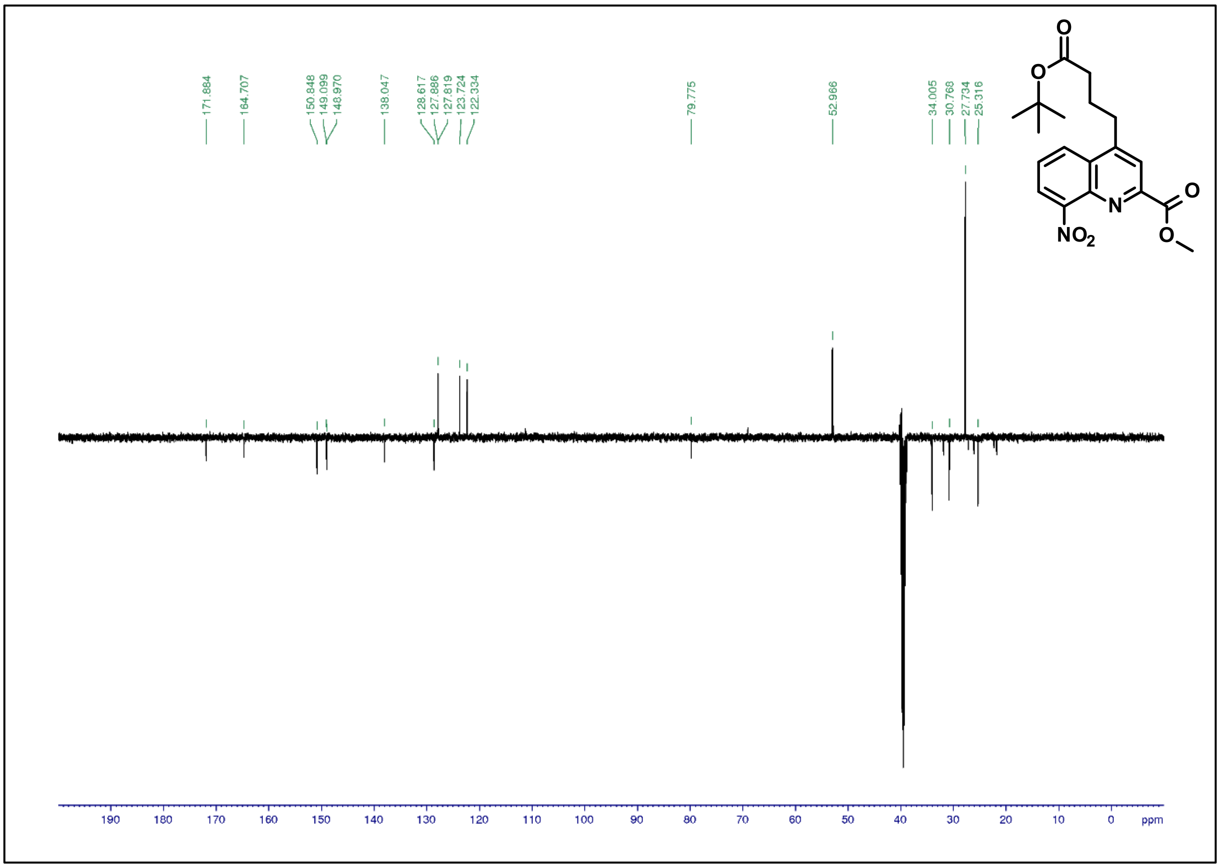


Figure S14. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **5d**.

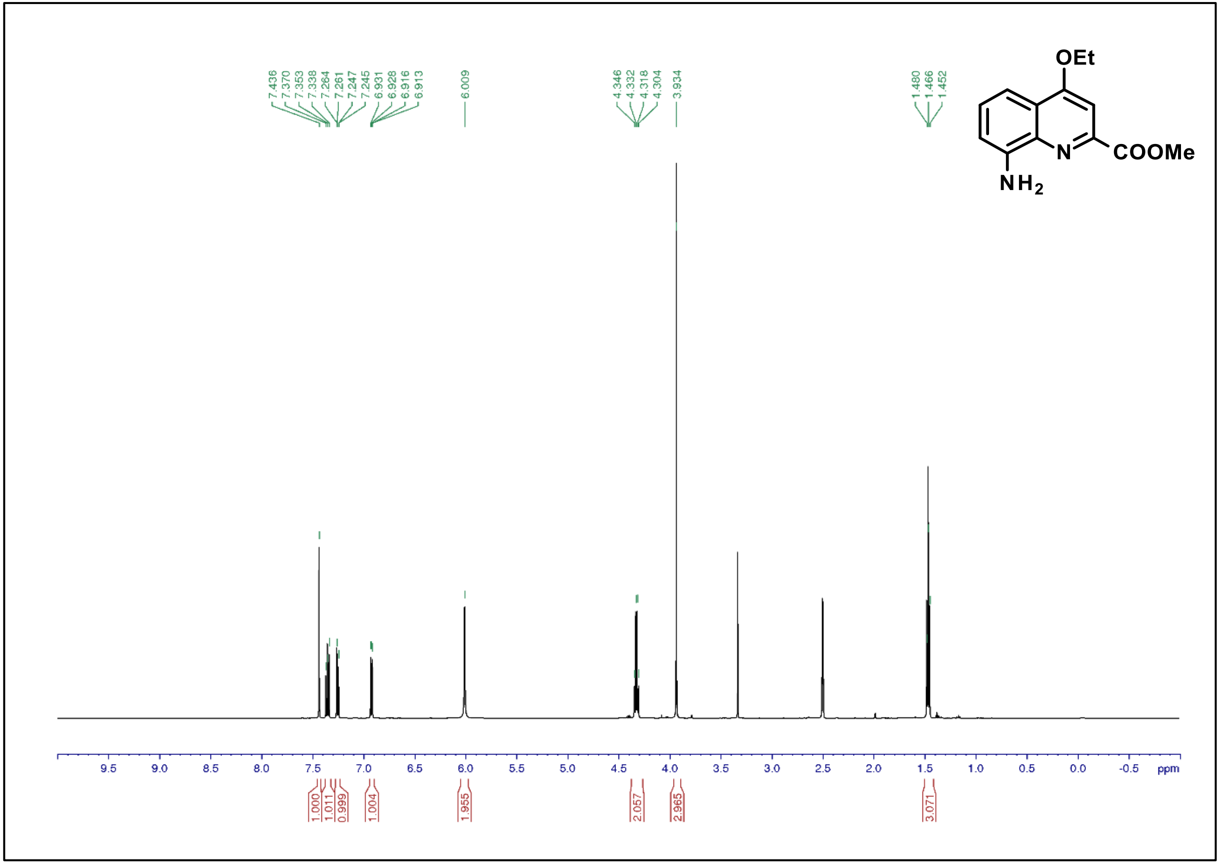


Figure S15. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **6a**.

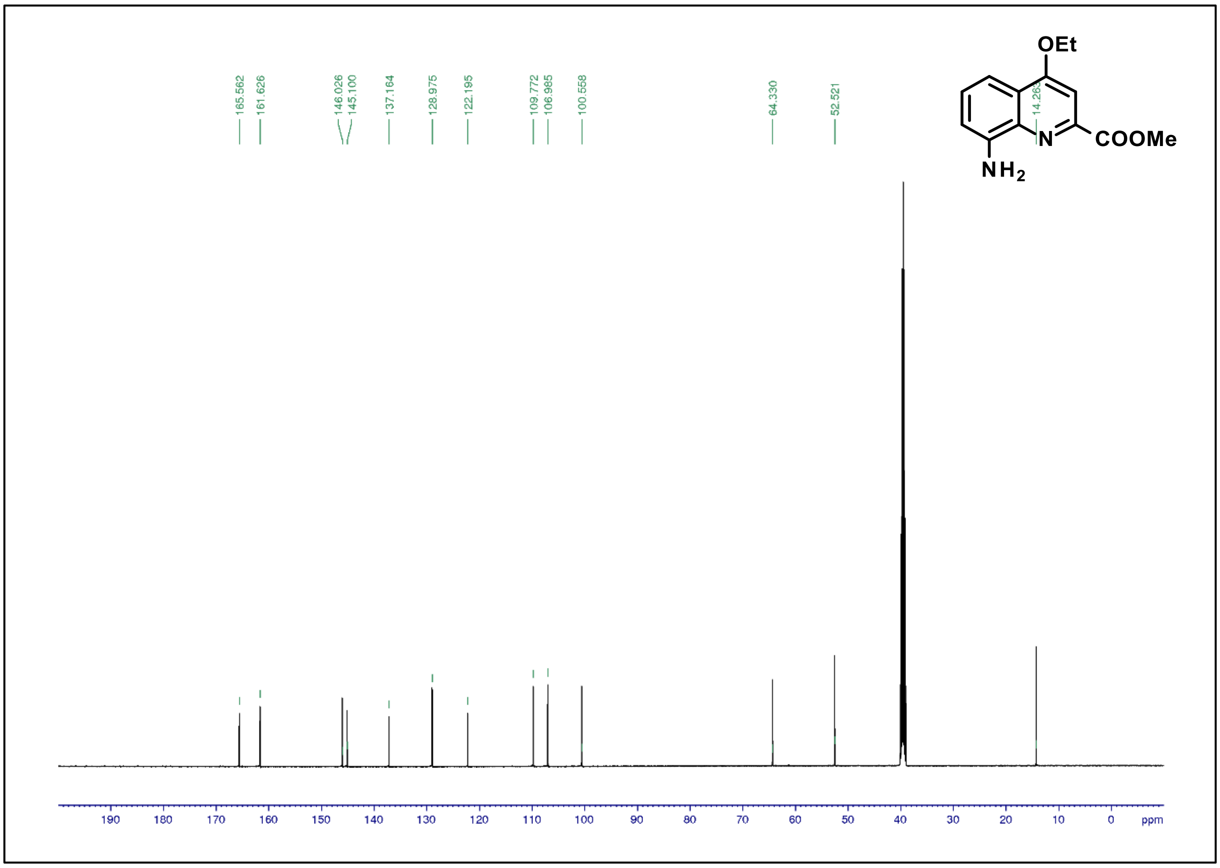


Figure S16. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **6a**.

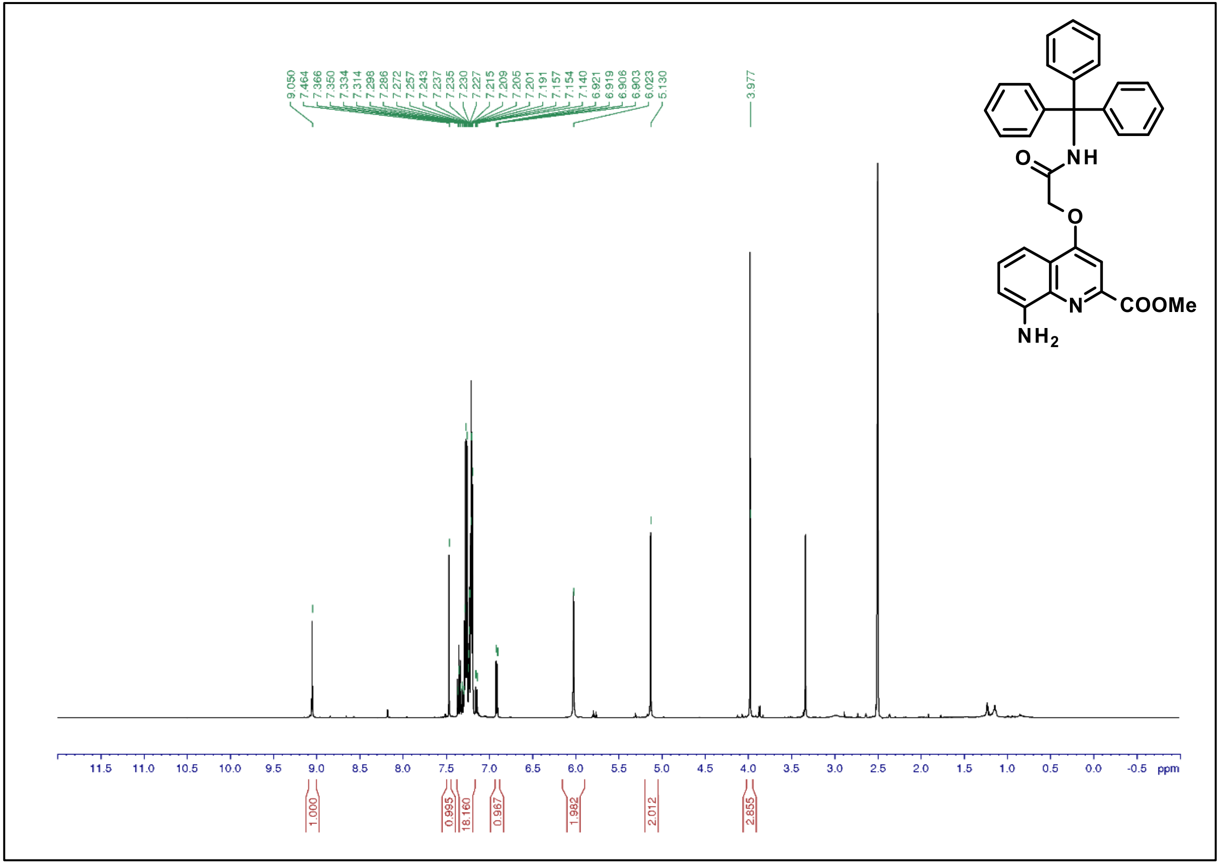


Figure S17. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **6b**.

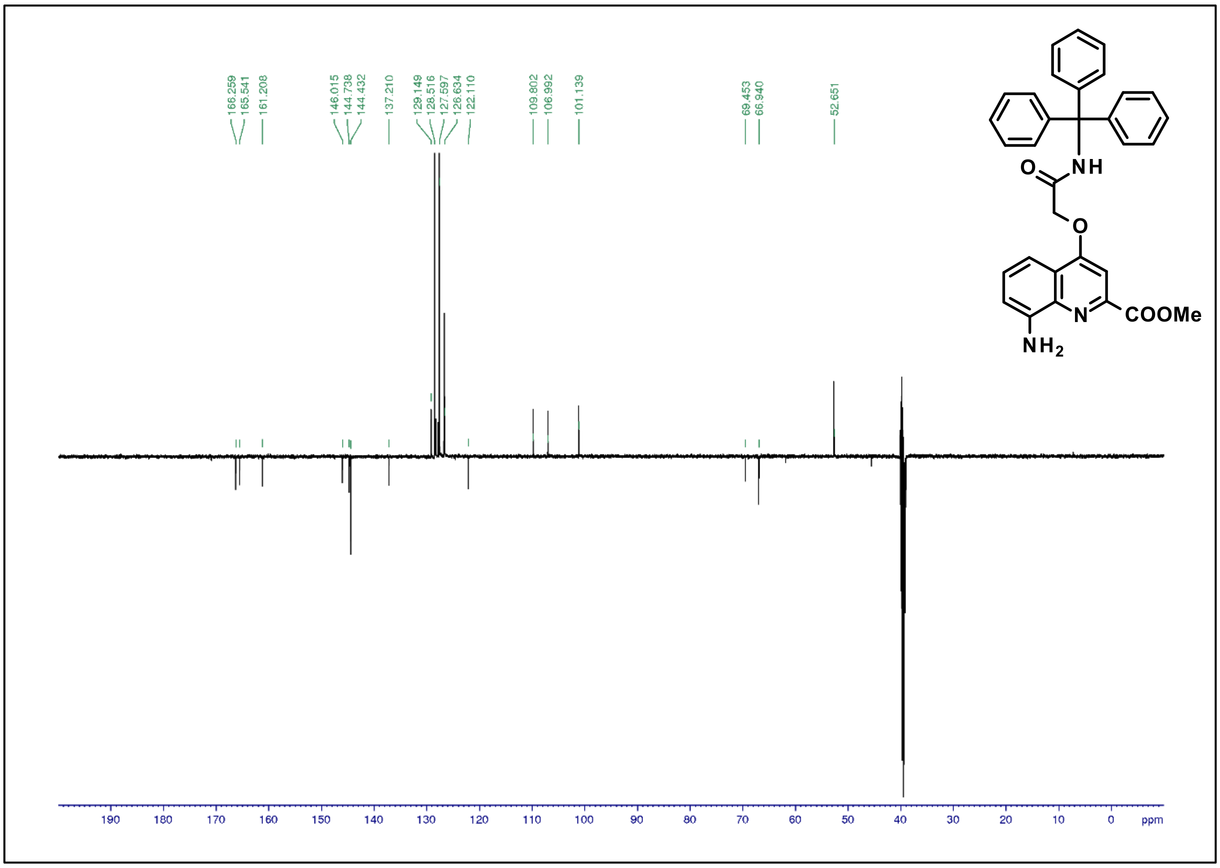


Figure S18. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **6b**.

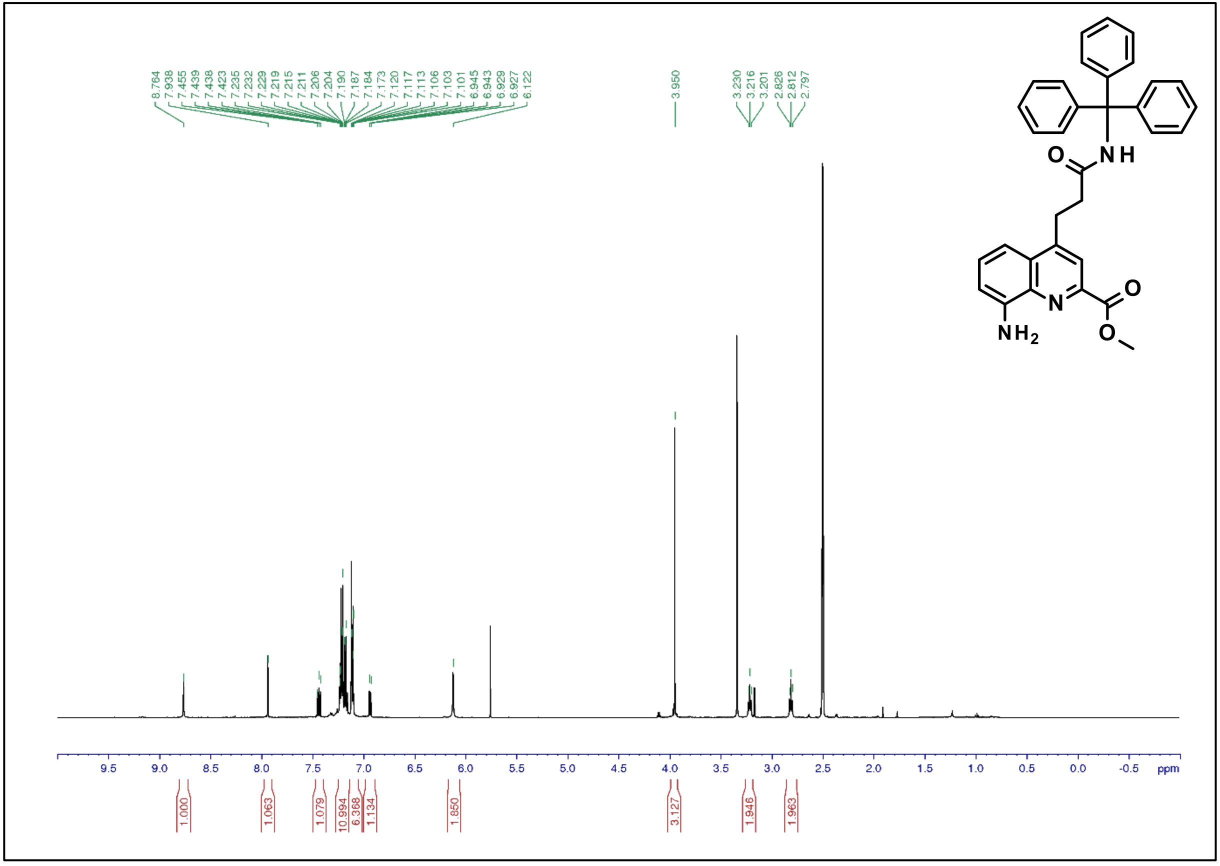


Figure S19. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **6c**.

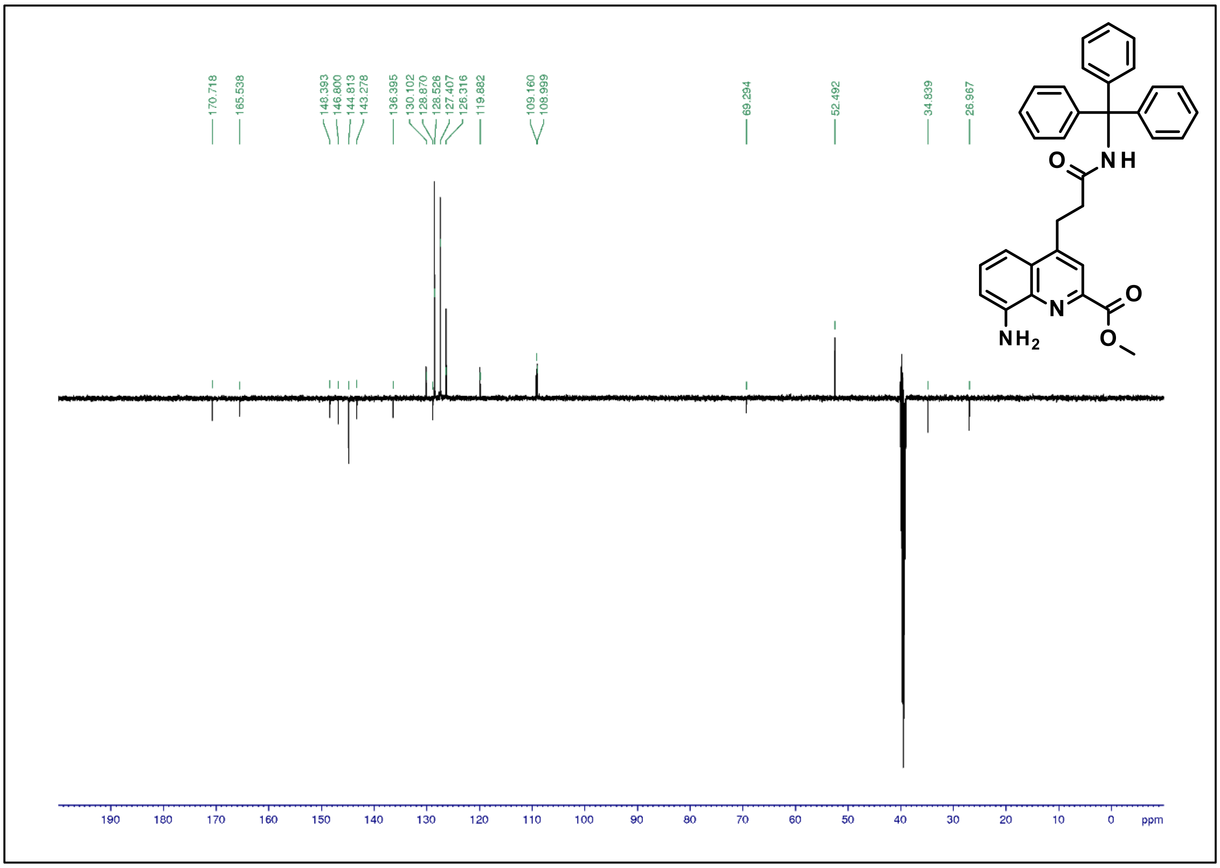


Figure S20. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **6c**.

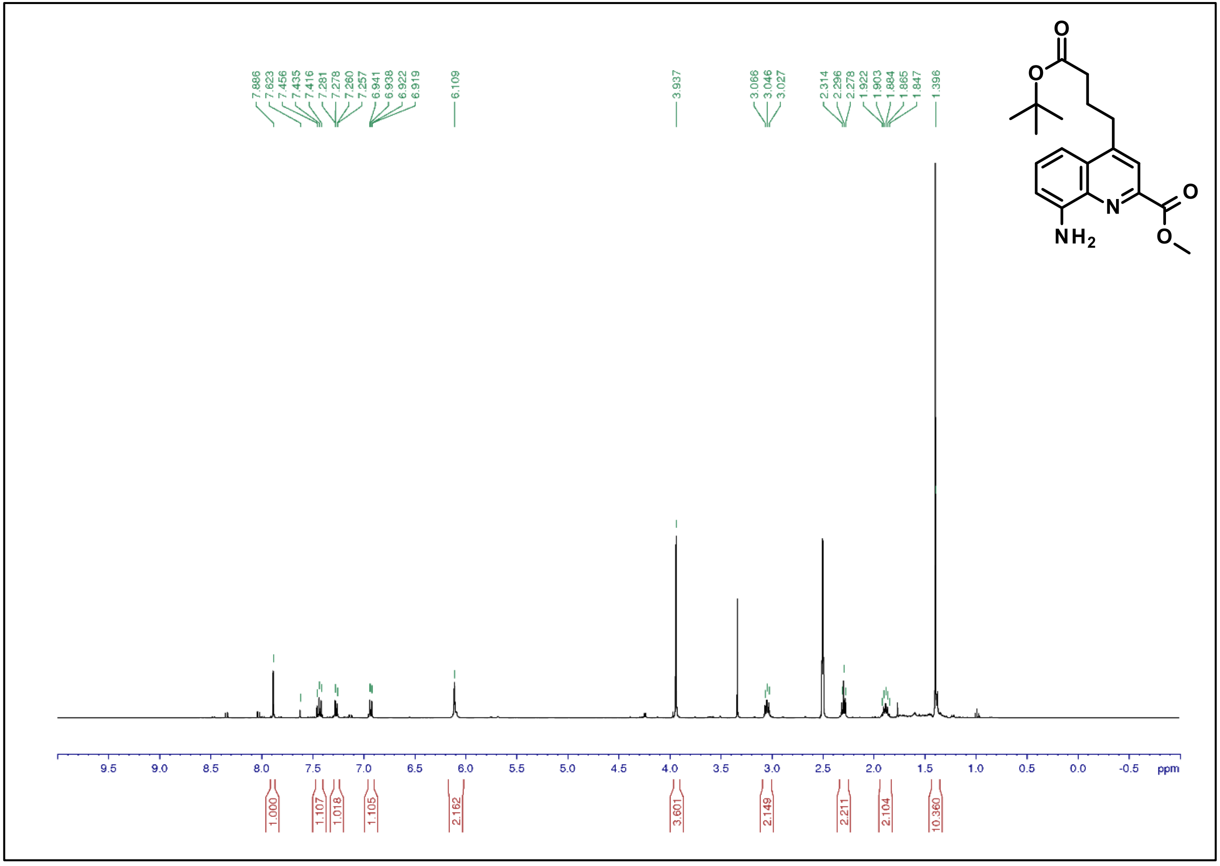


Figure S22. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **6d**.

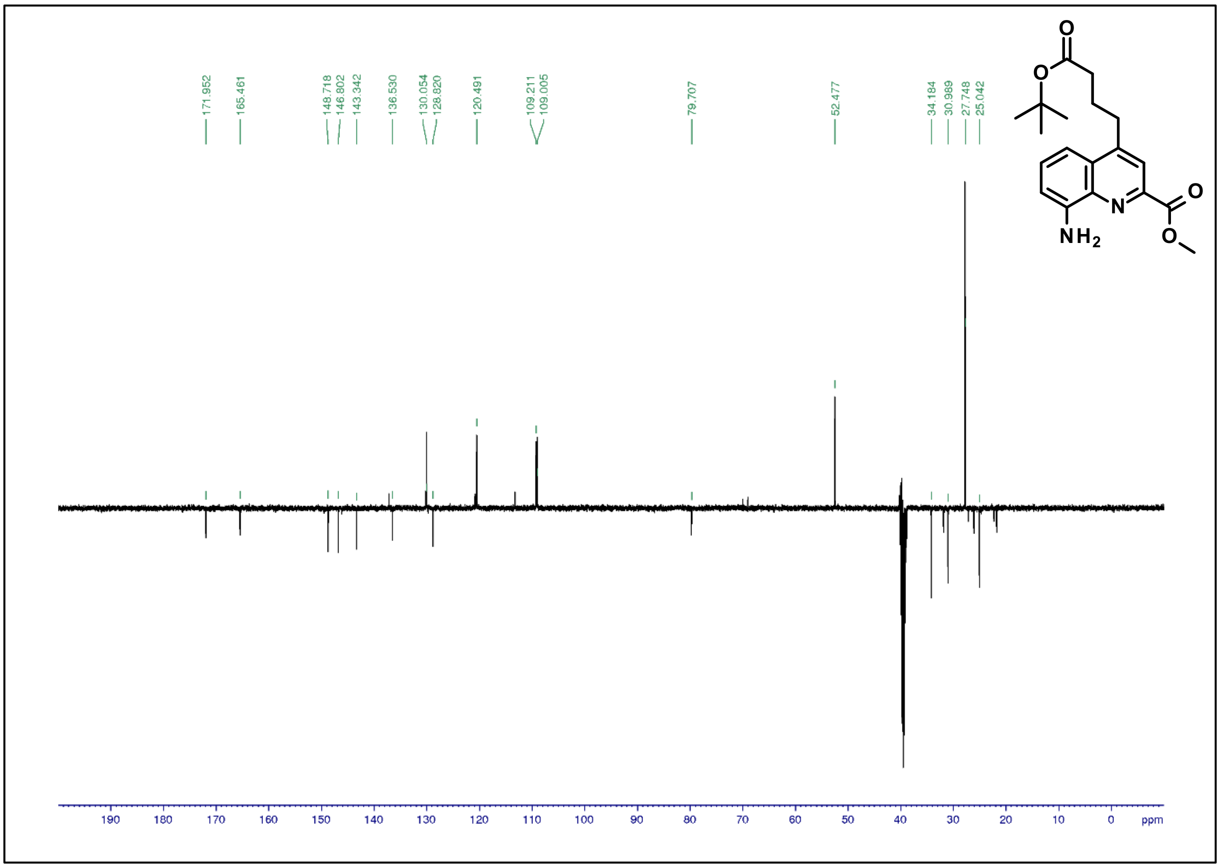


Figure S22. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **6d**.

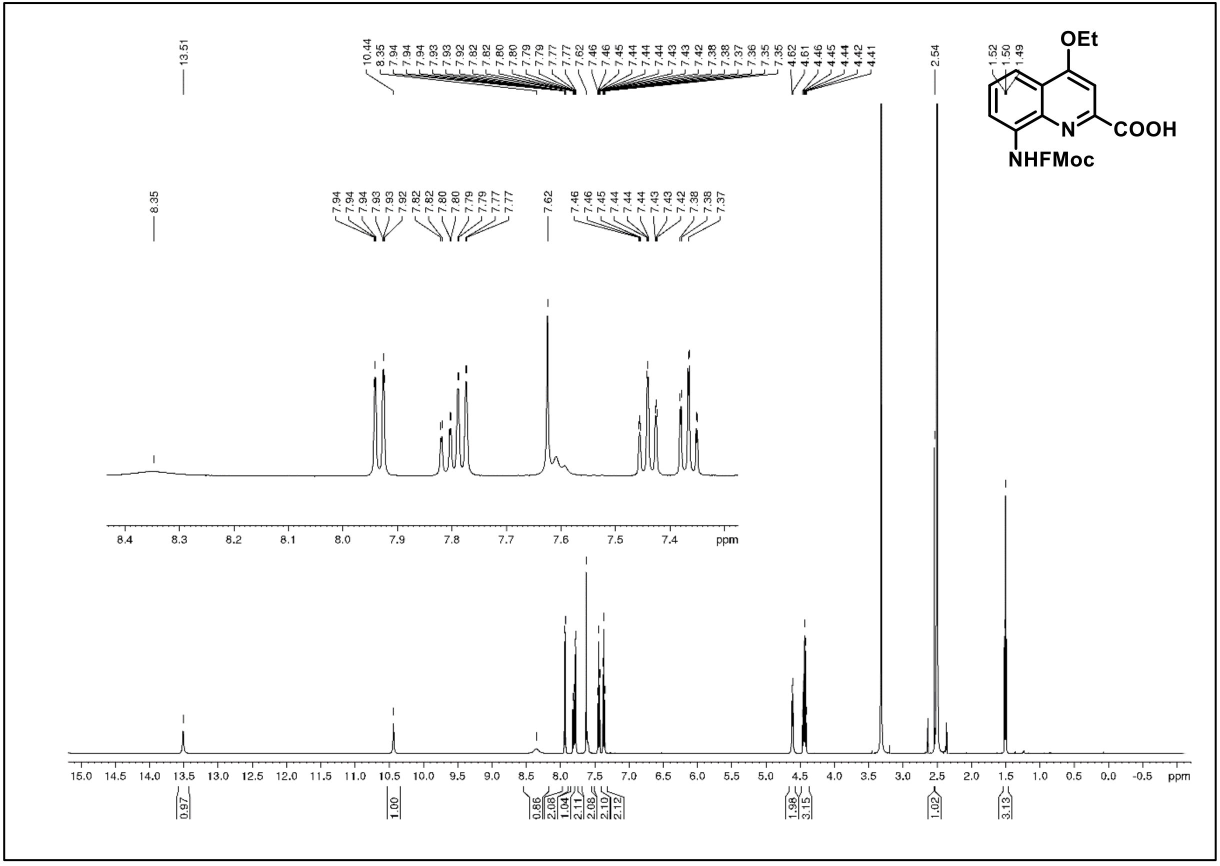


Figure S23. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **7a**.

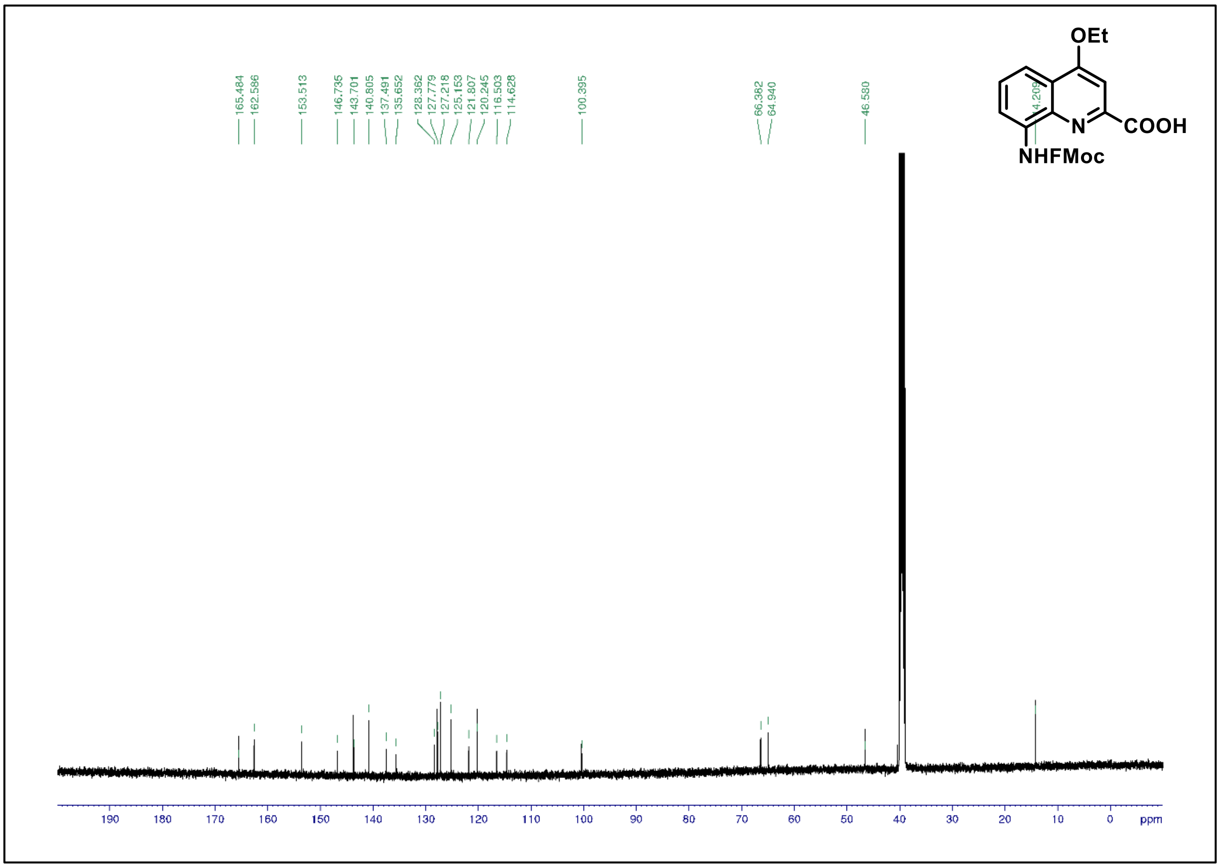


Figure S24. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **7a**.

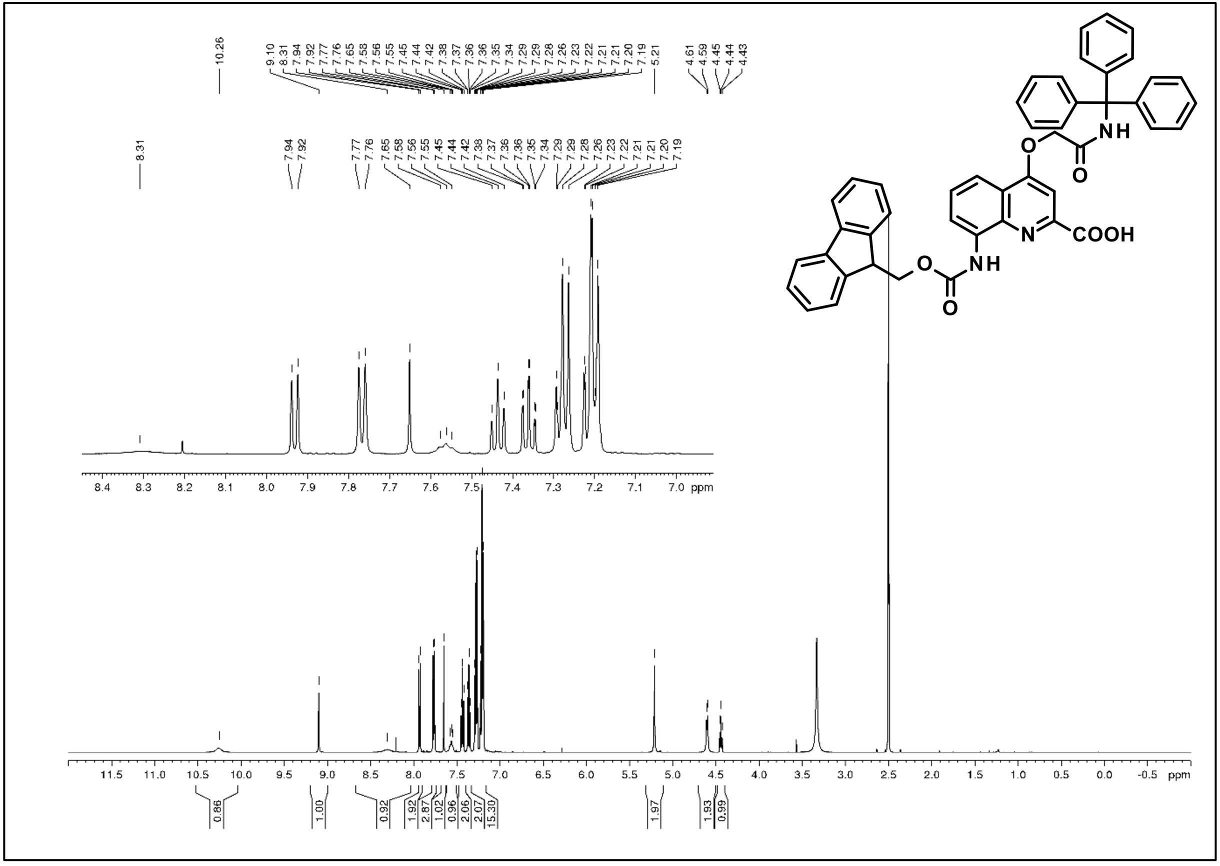


Figure S25. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **7b**.

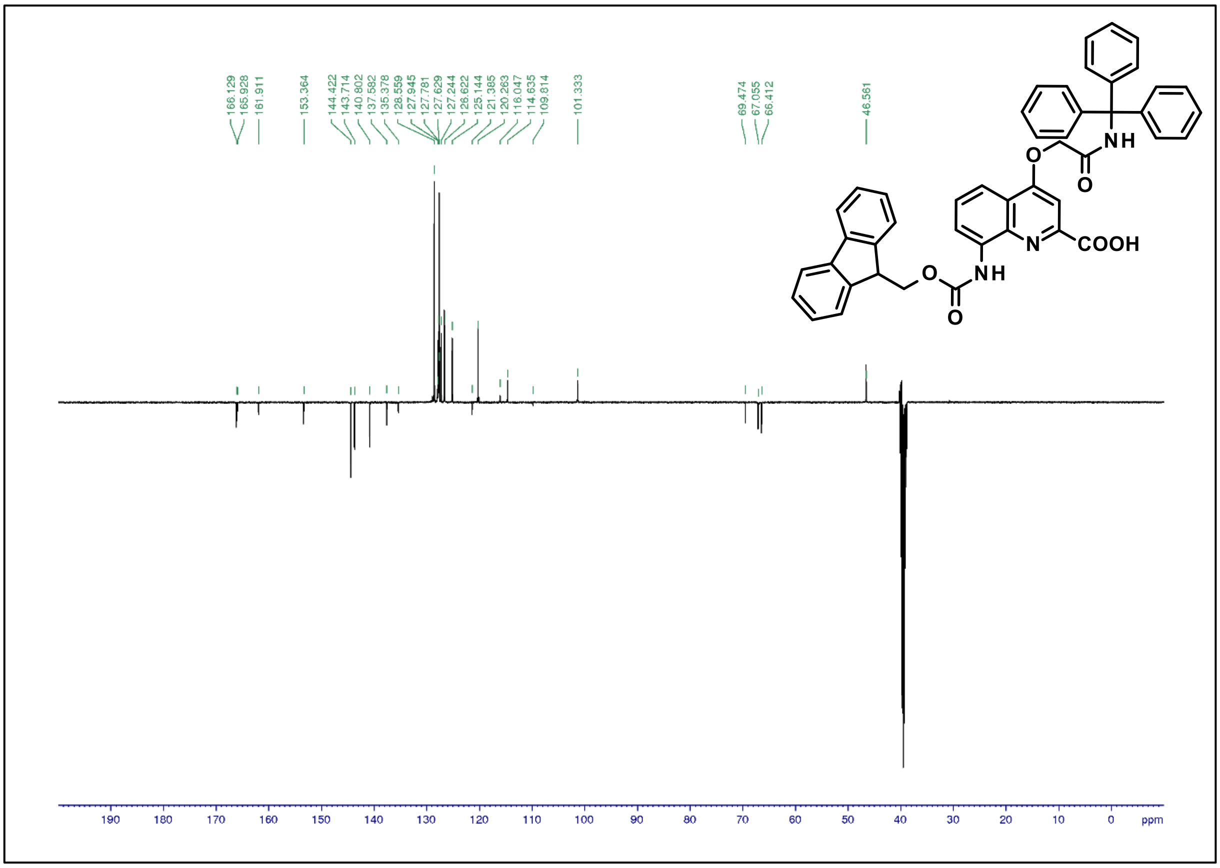


Figure S26. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **7b**.

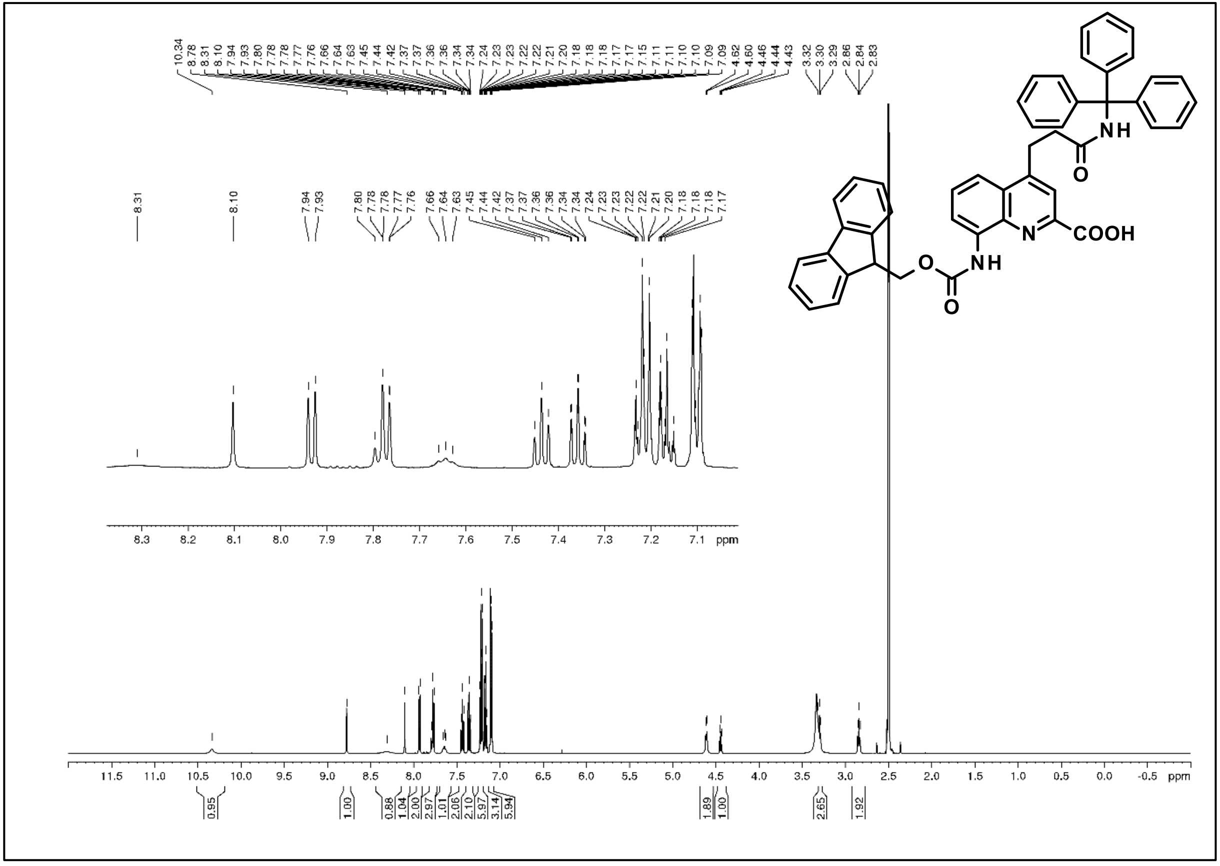


Figure S27. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **7c**.

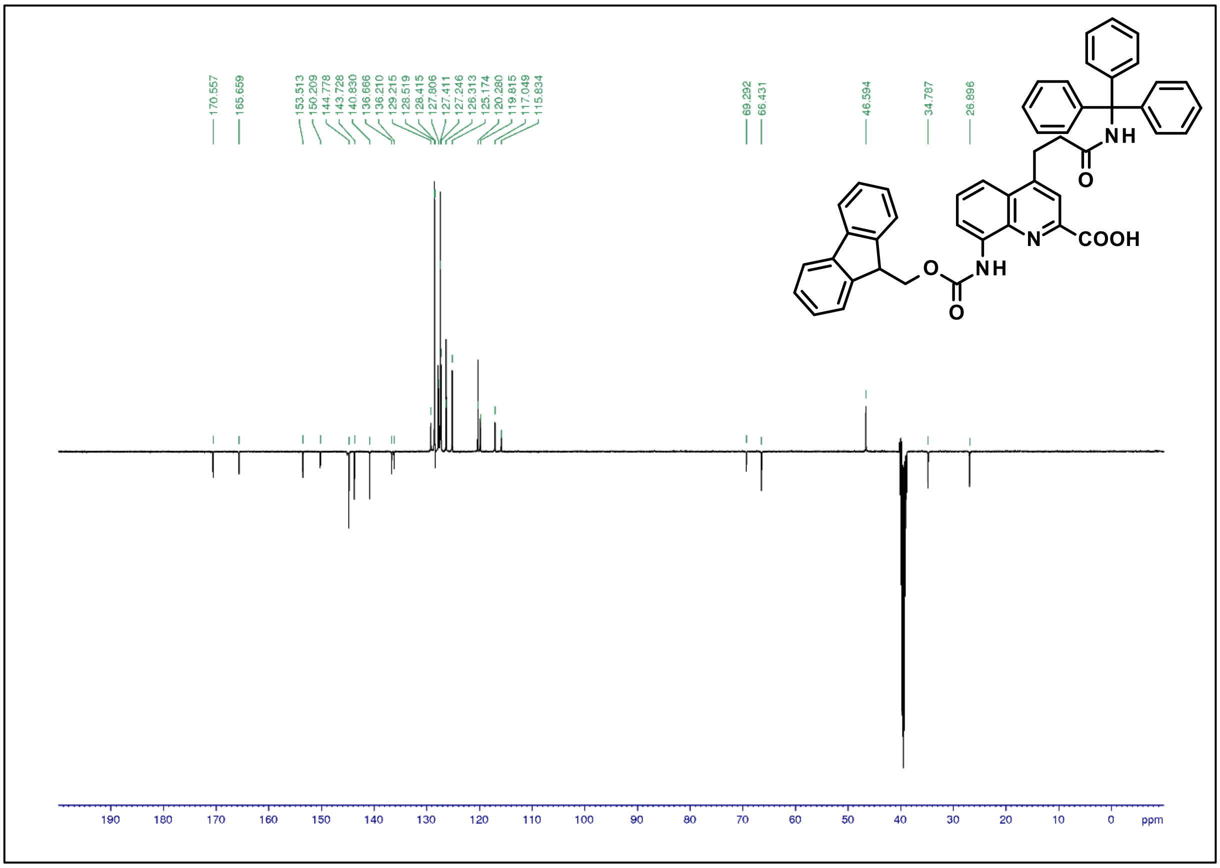


Figure S28. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **7c**.

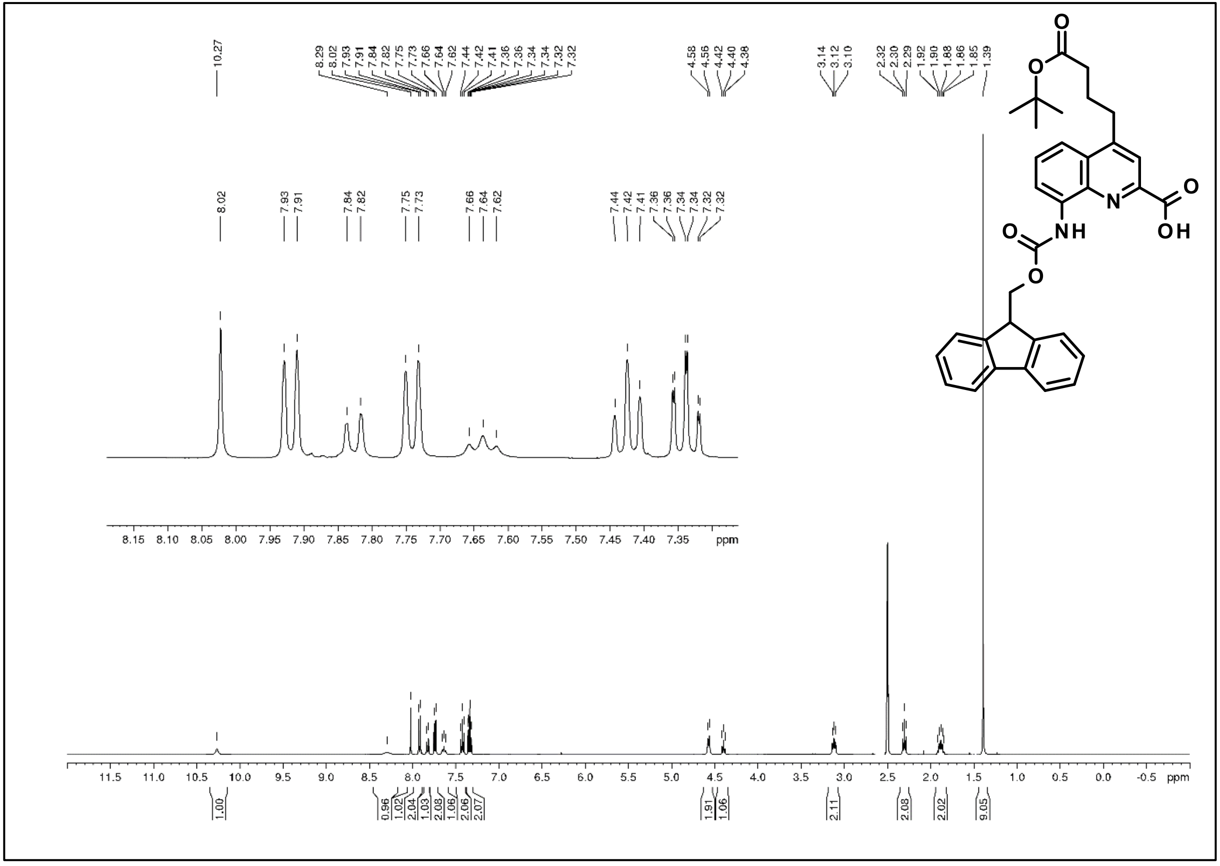


Figure S29. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **7d**.

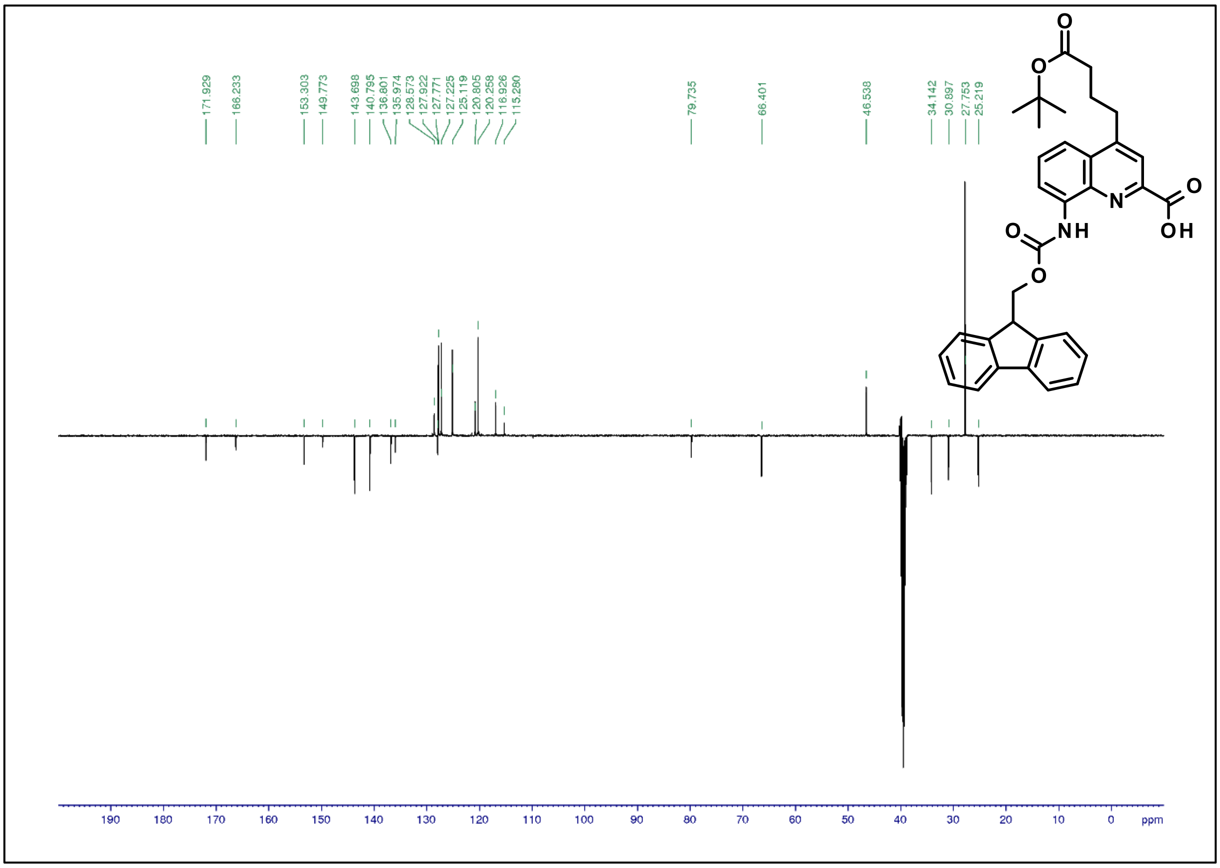


Figure S30. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **7d**.

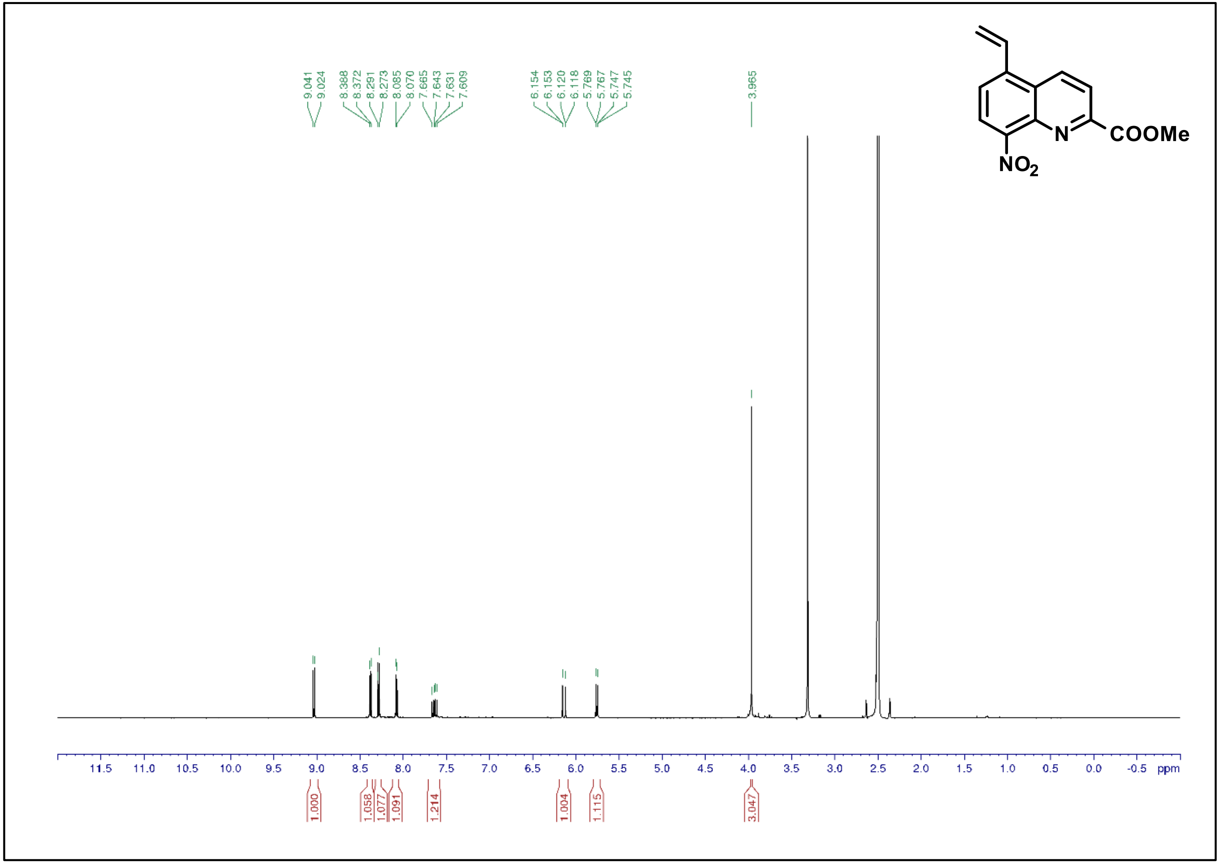


Figure S31. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **8a**.

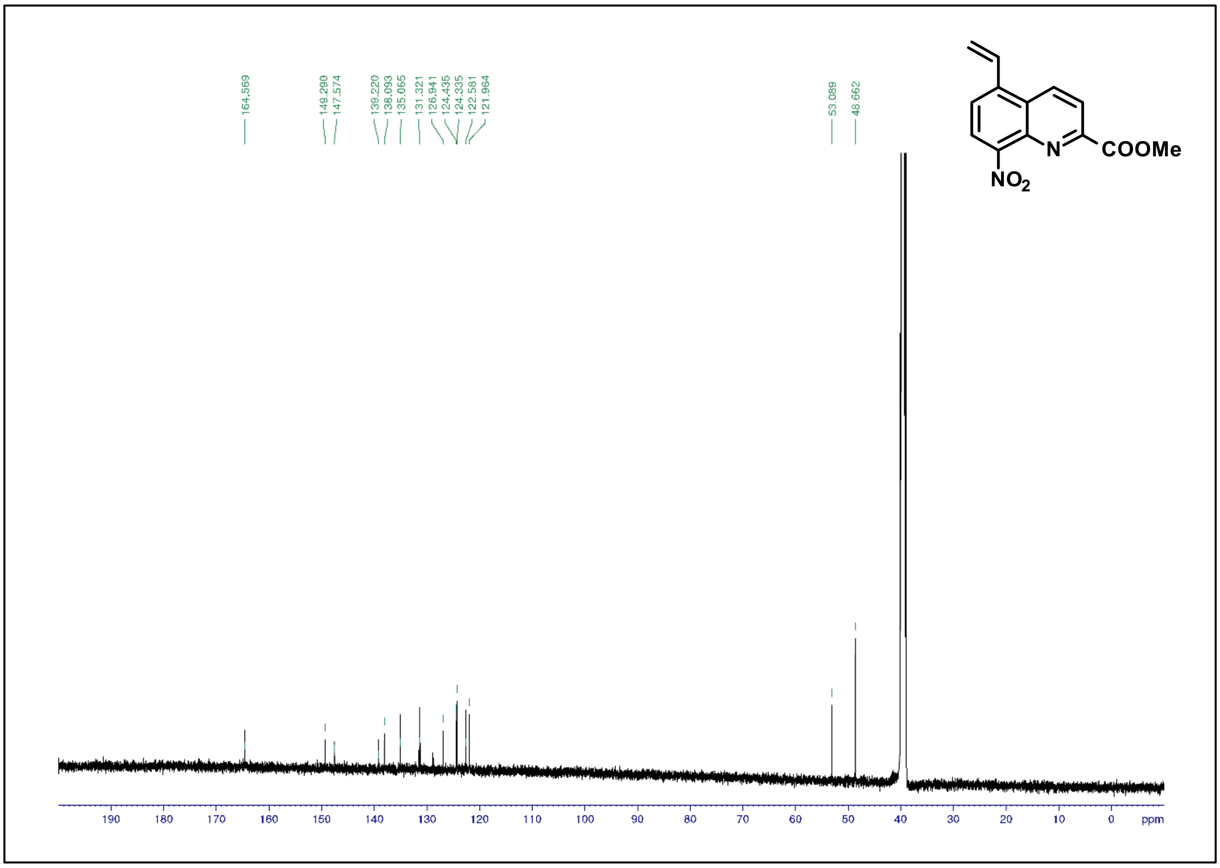


Figure S32. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **8a**.

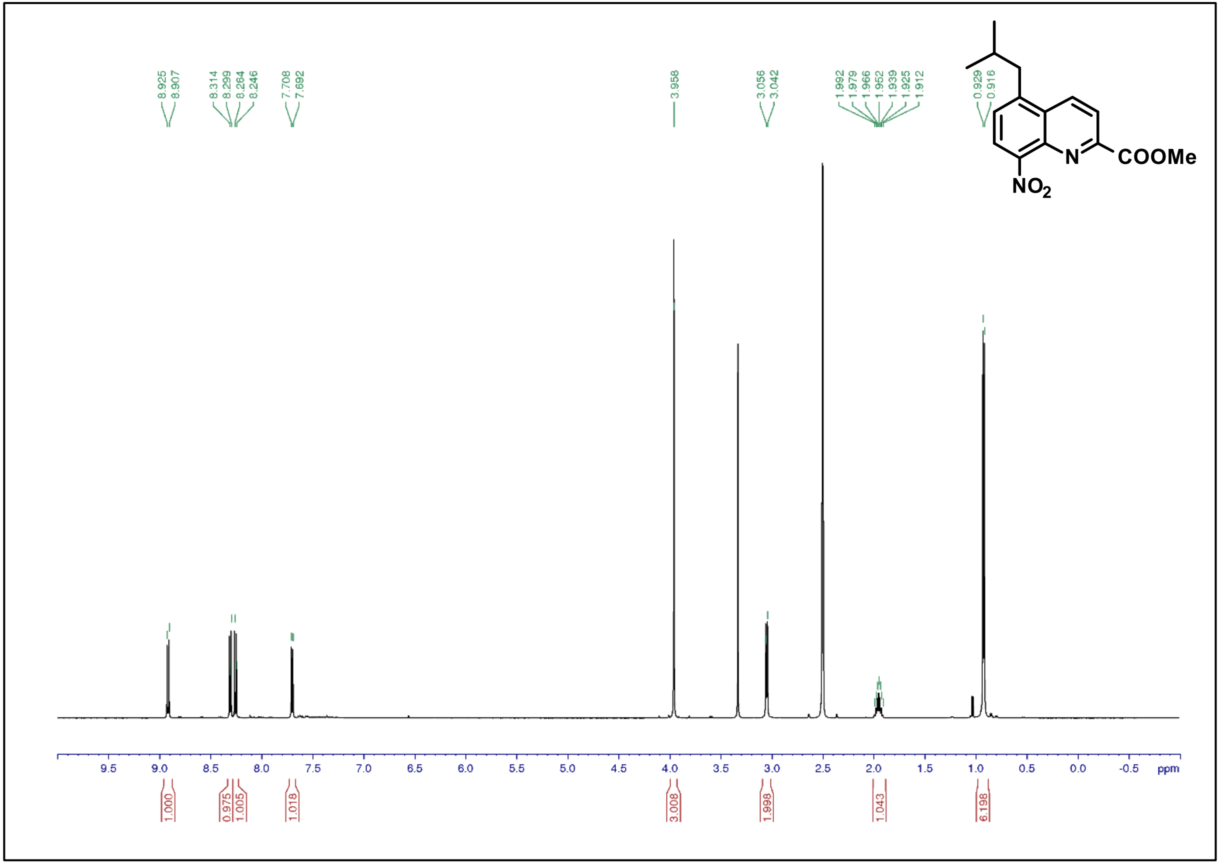


Figure S33. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **8b**.

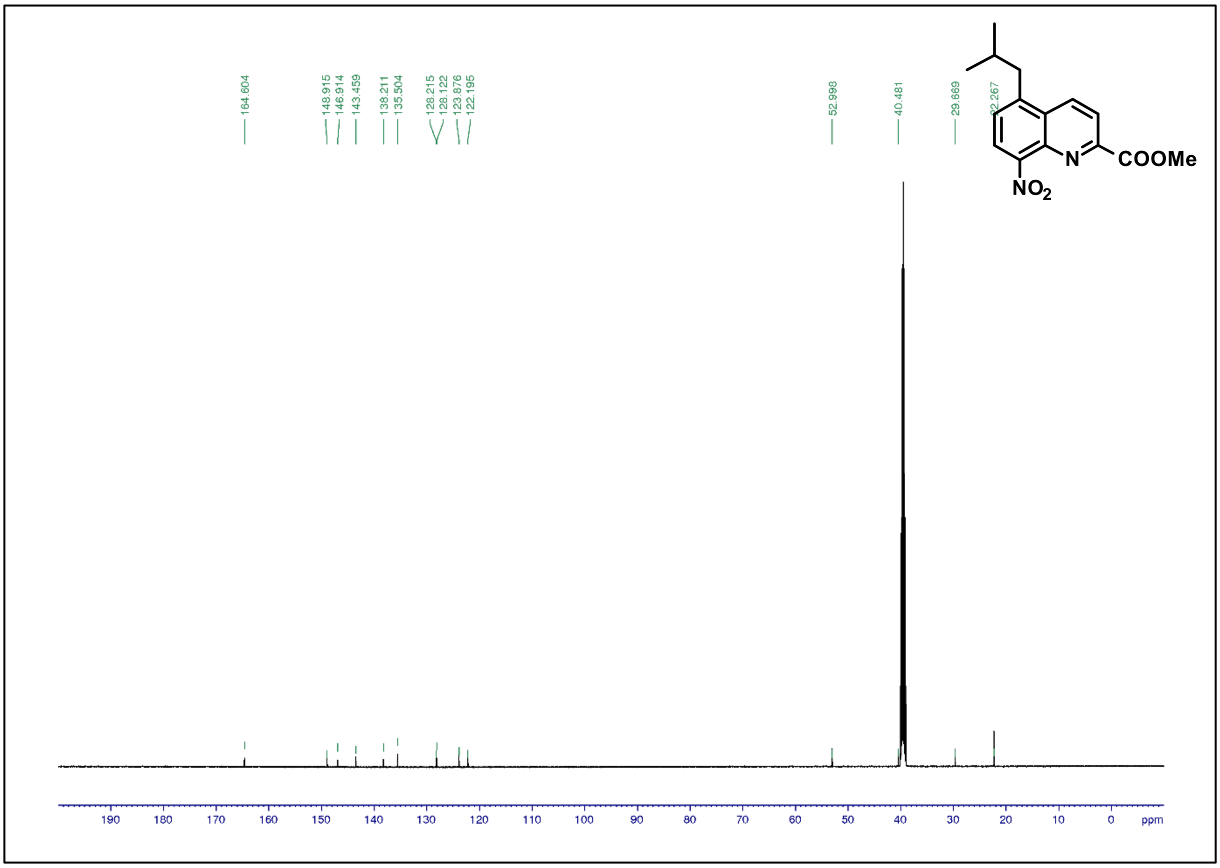


Figure S34. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **8b**.

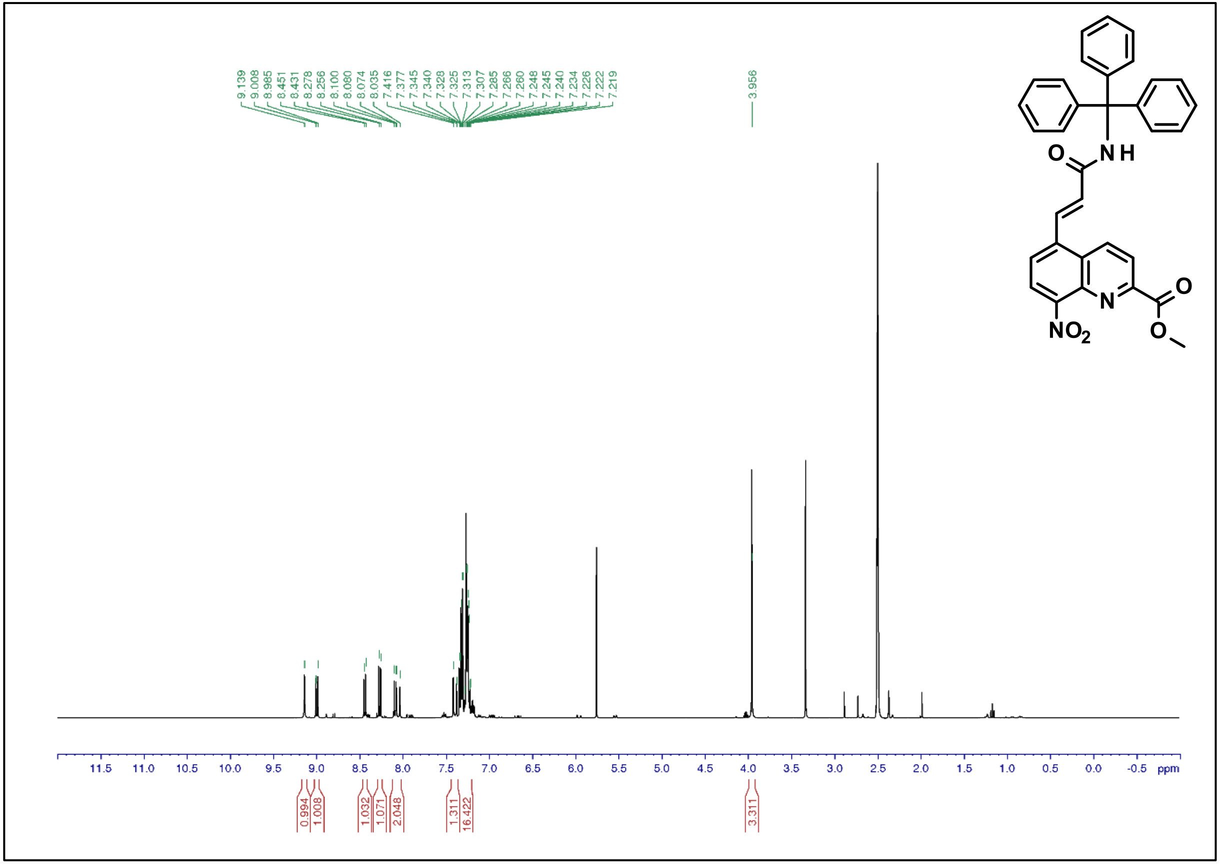


Figure S35. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **8c**.

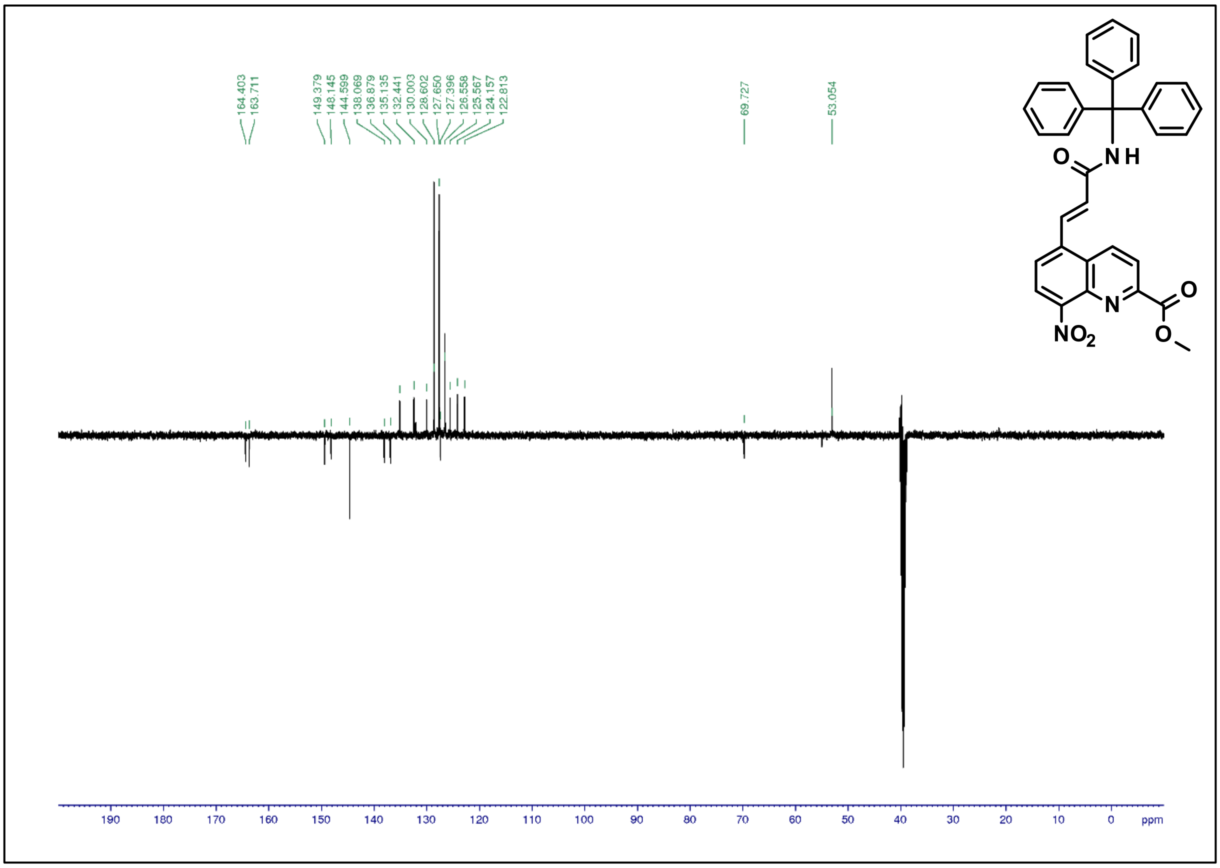


Figure S36. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **8c**.

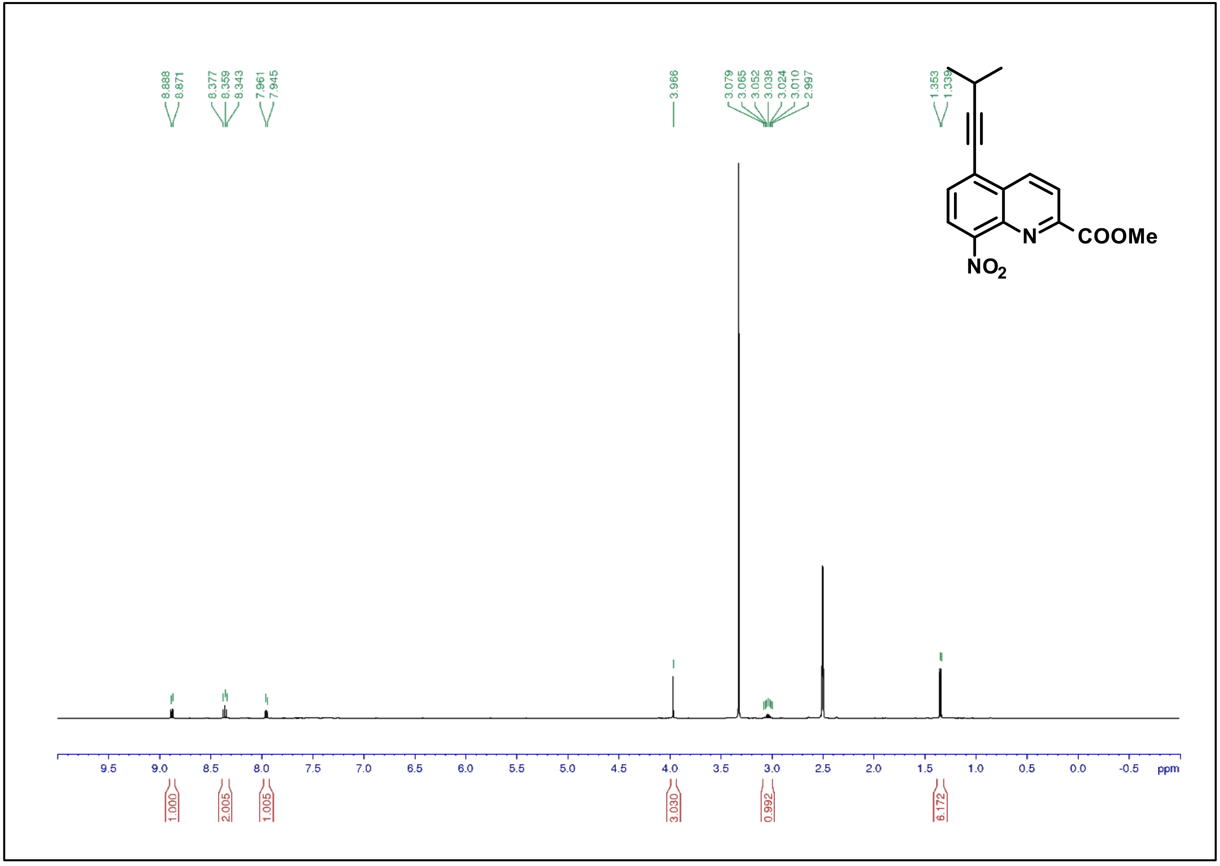


Figure S37. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **8d**.

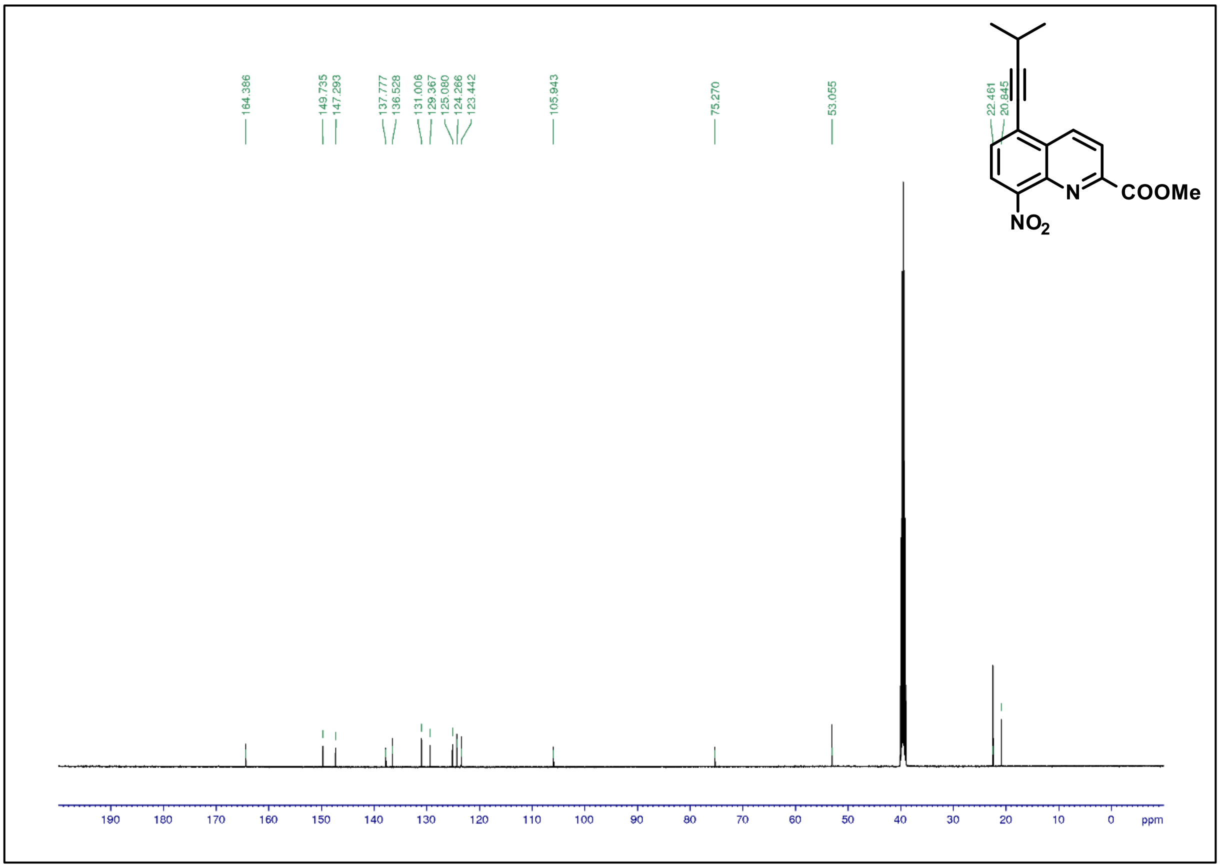


Figure S38. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **8d**.

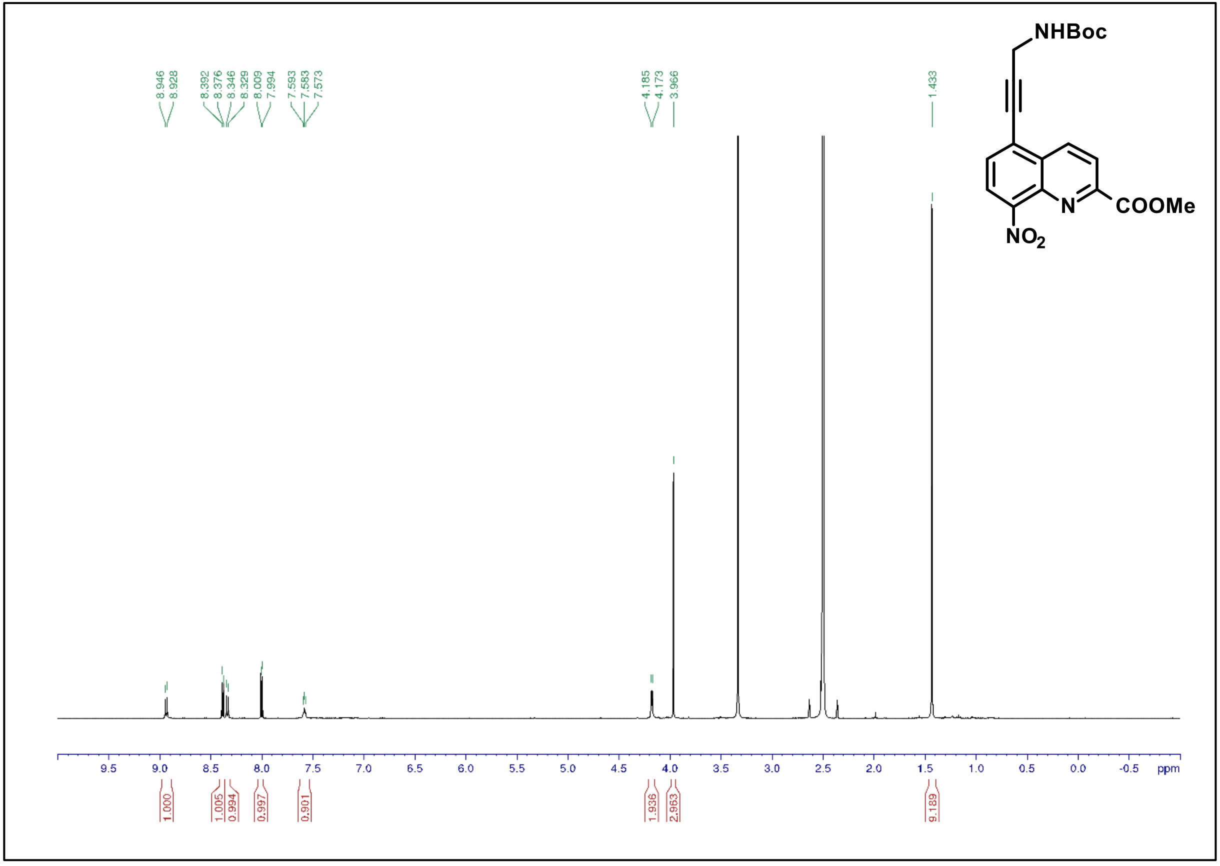


Figure S39. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **8e**.

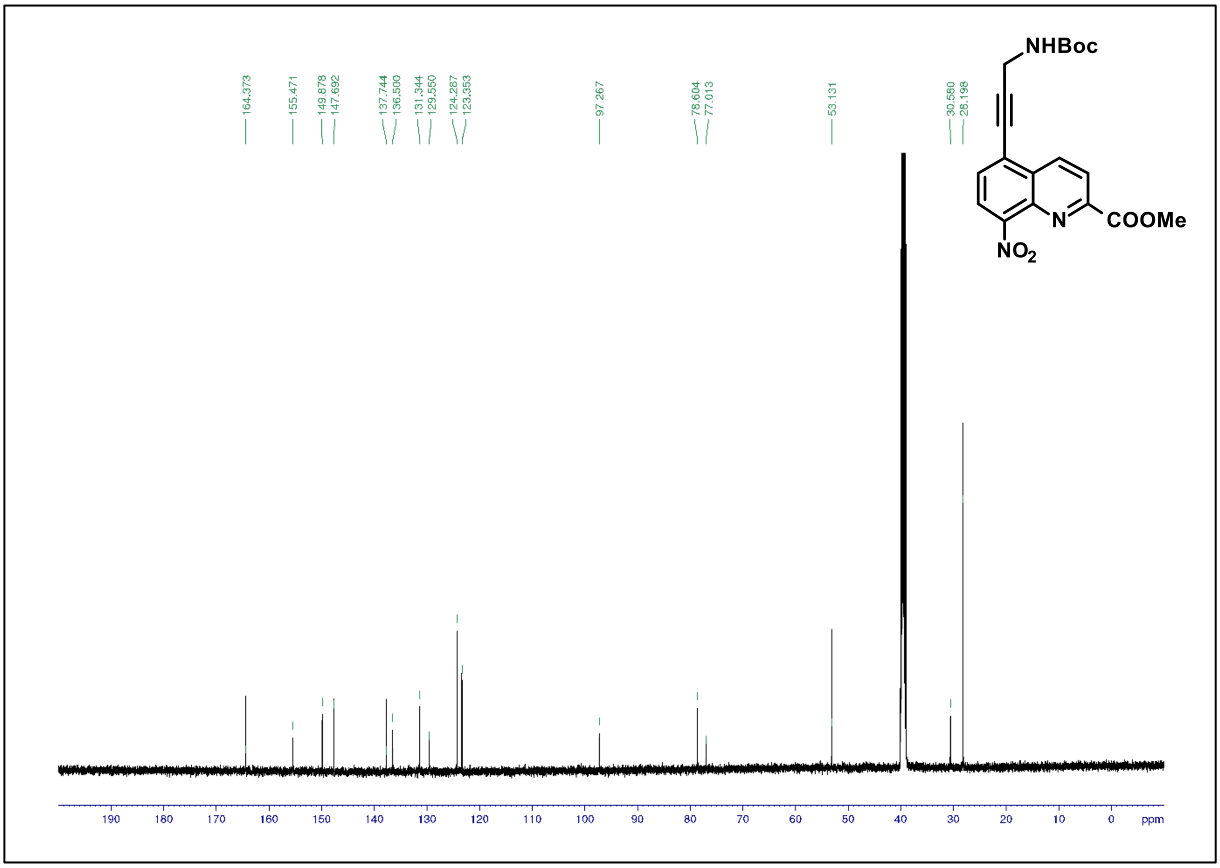


Figure S40. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) of compound **8e**.

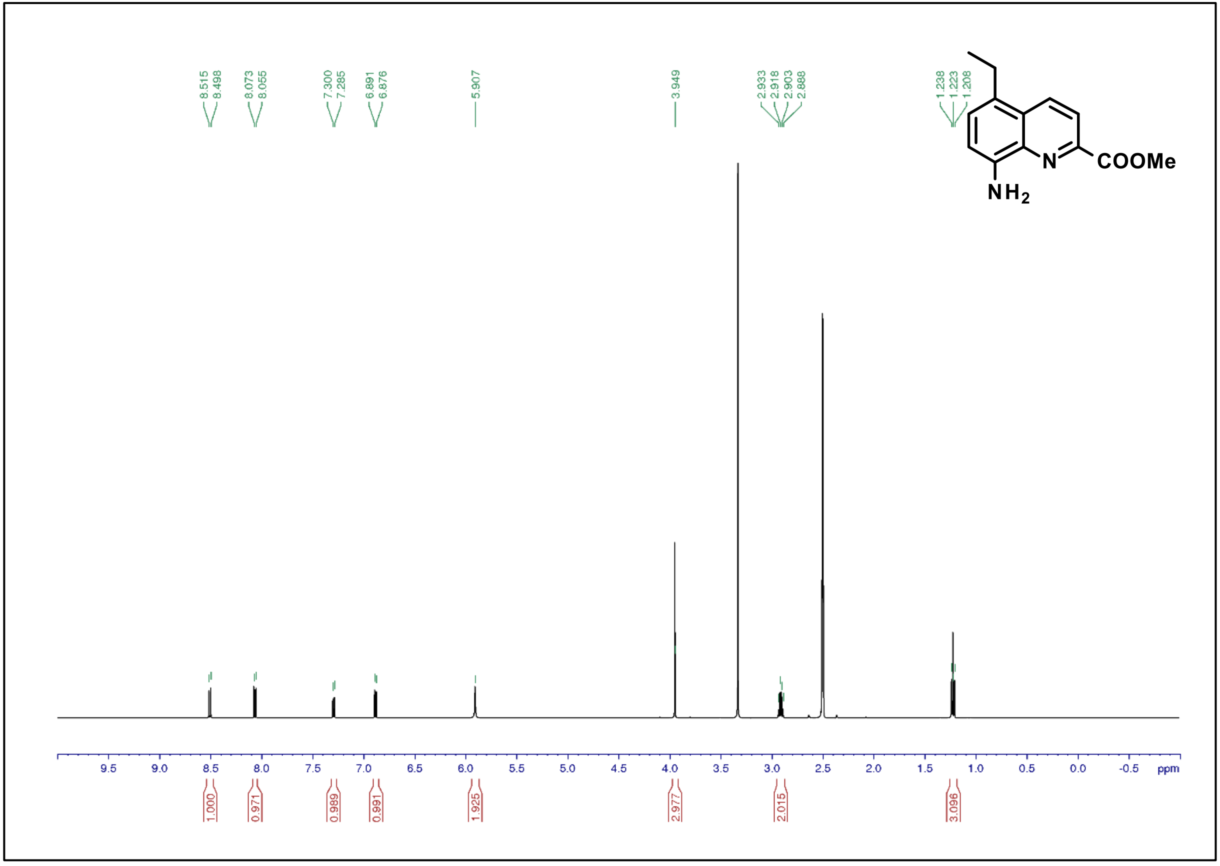


Figure S41. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **9a**.

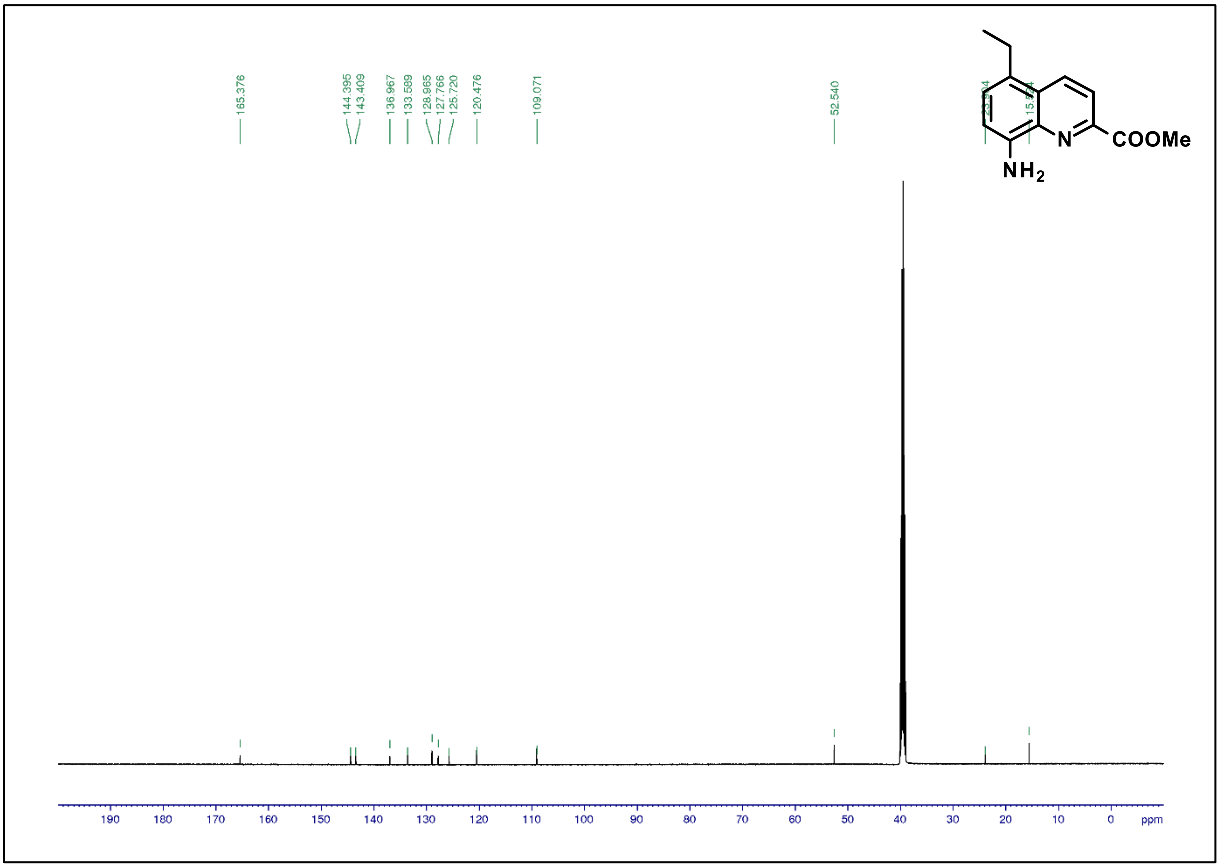


Figure S42. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **9a**.

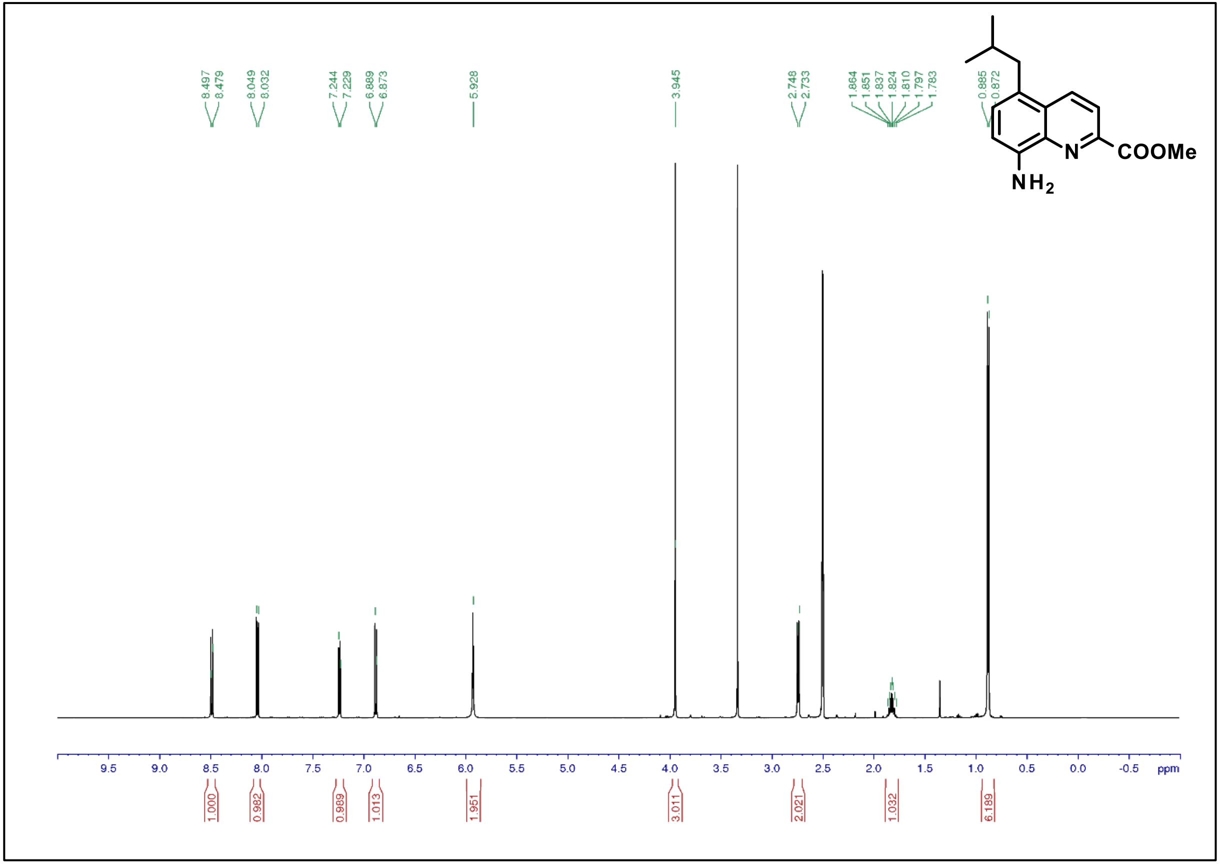


Figure S43. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **9b**.

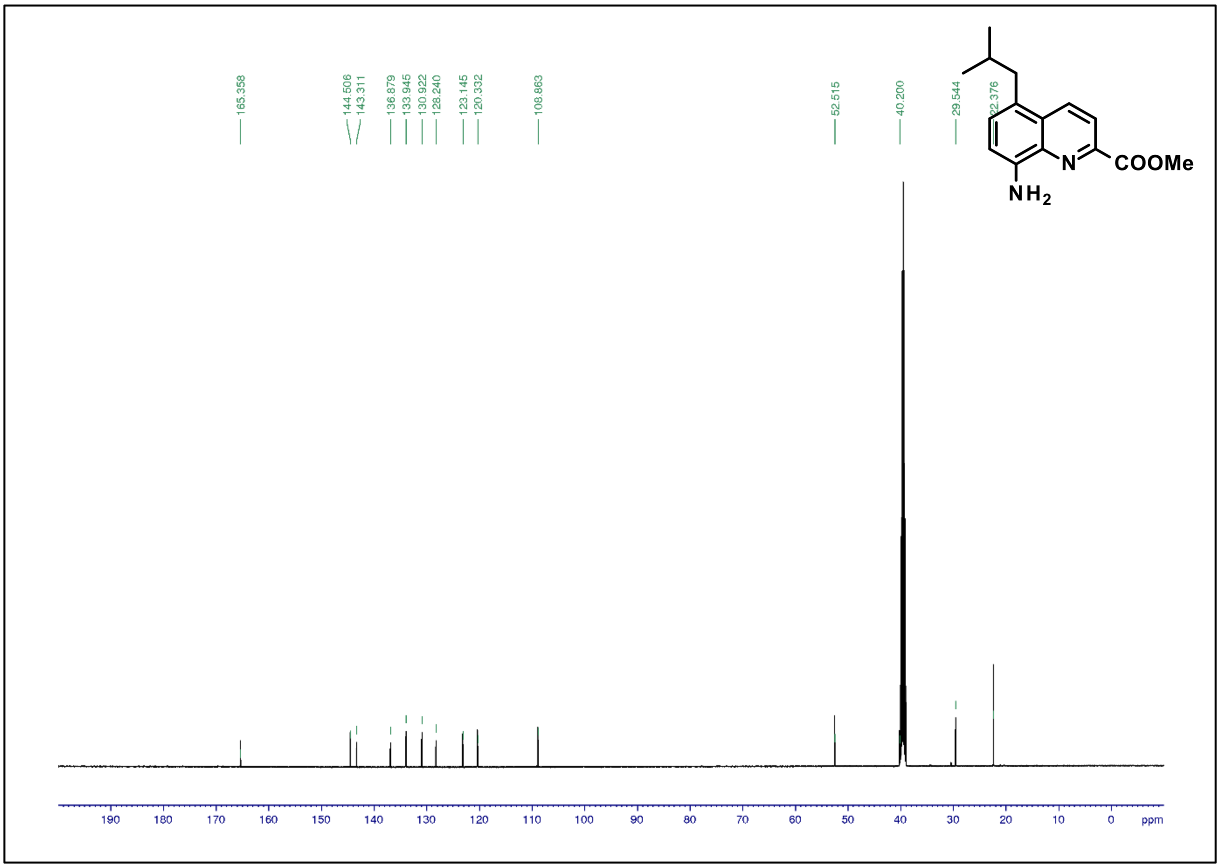


Figure S44. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **9b**.

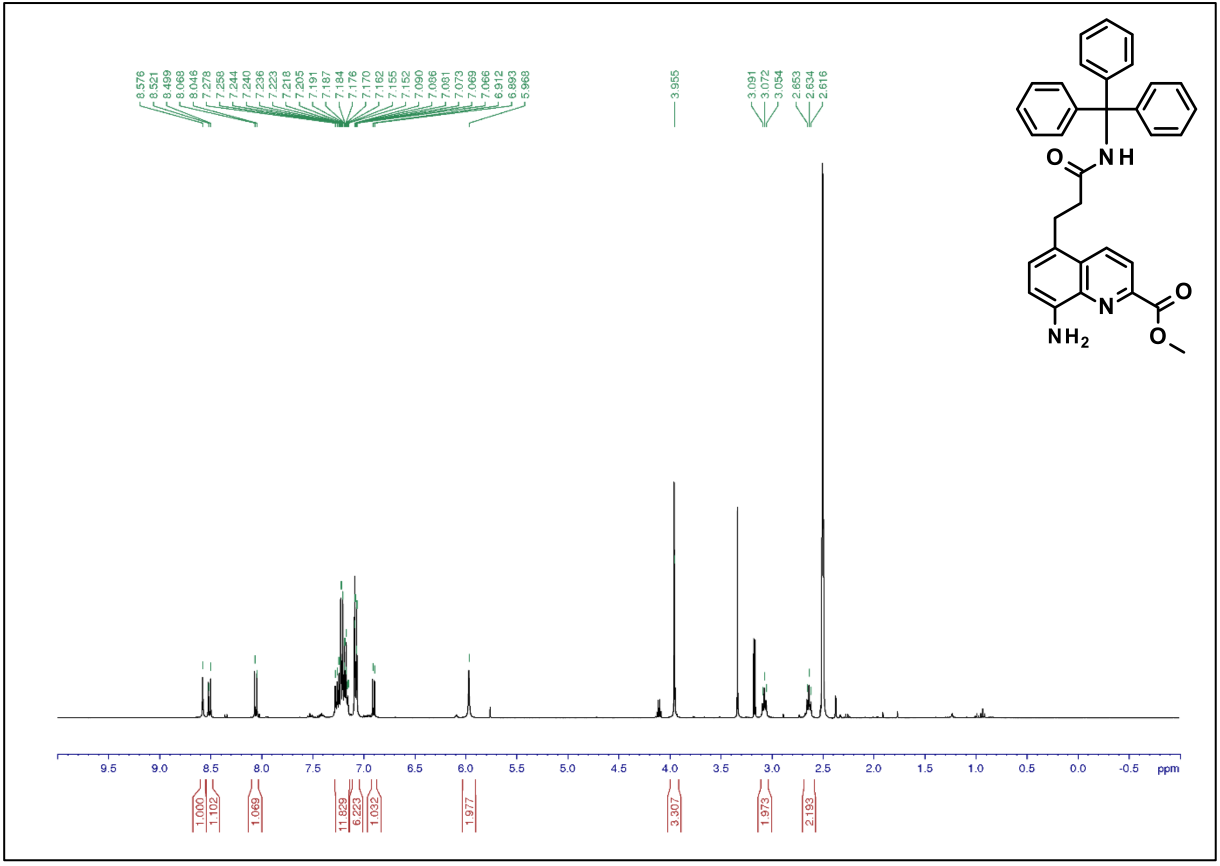


Figure S45. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **9c**.

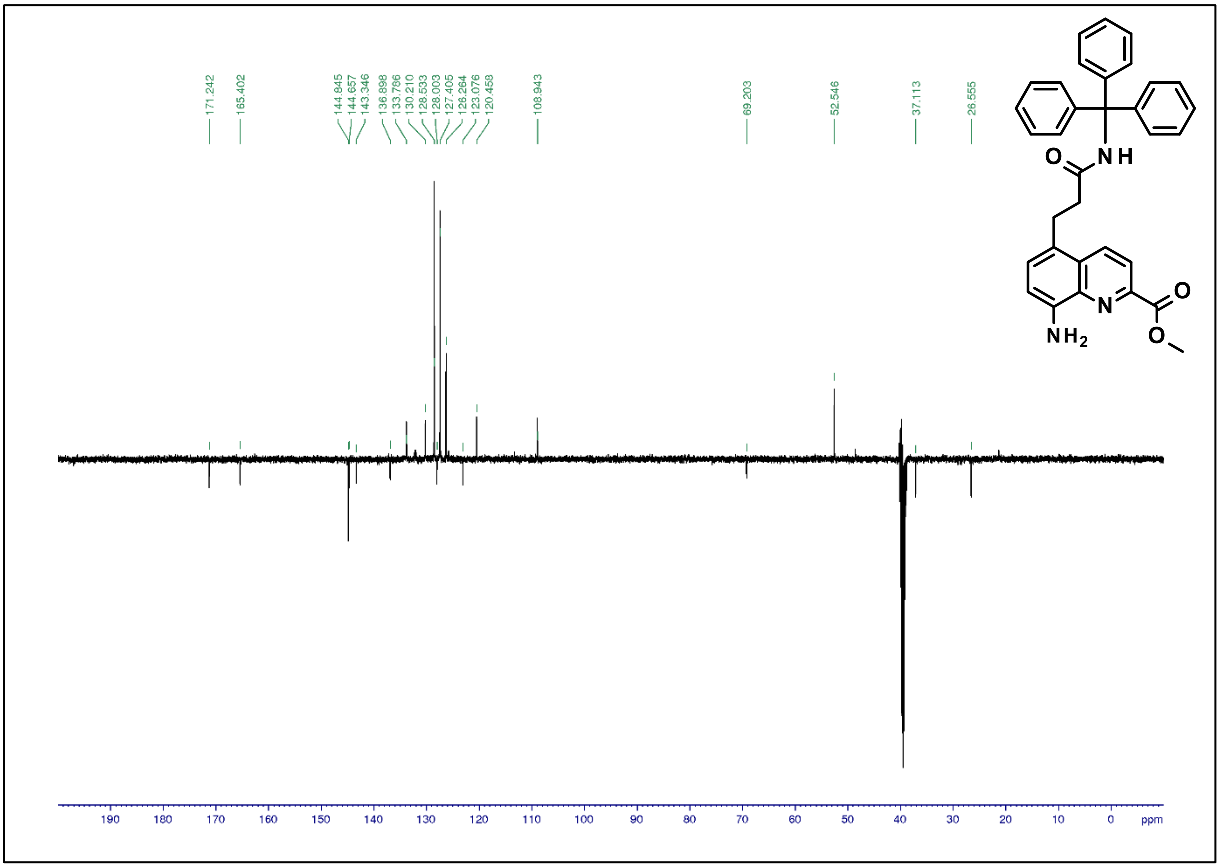


Figure S46. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **9c**.

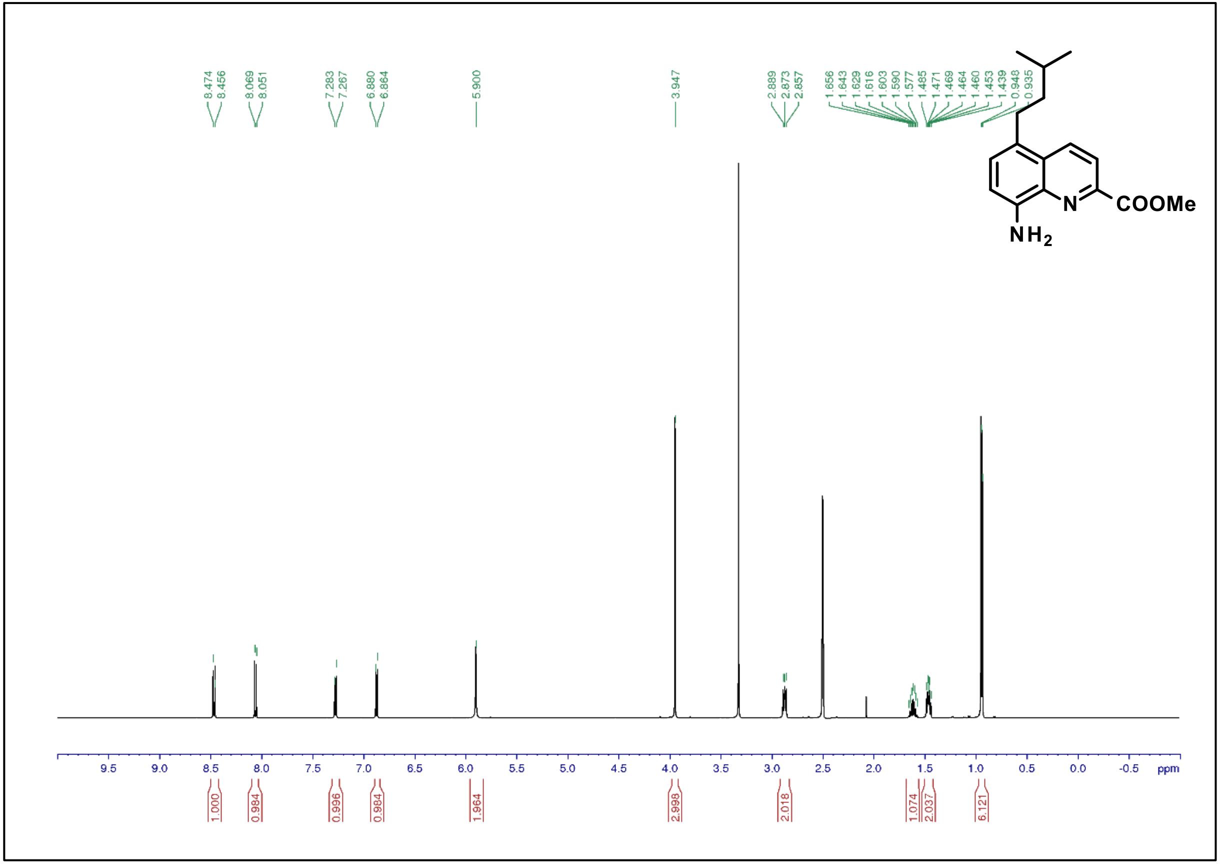


Figure S47. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **9d**.

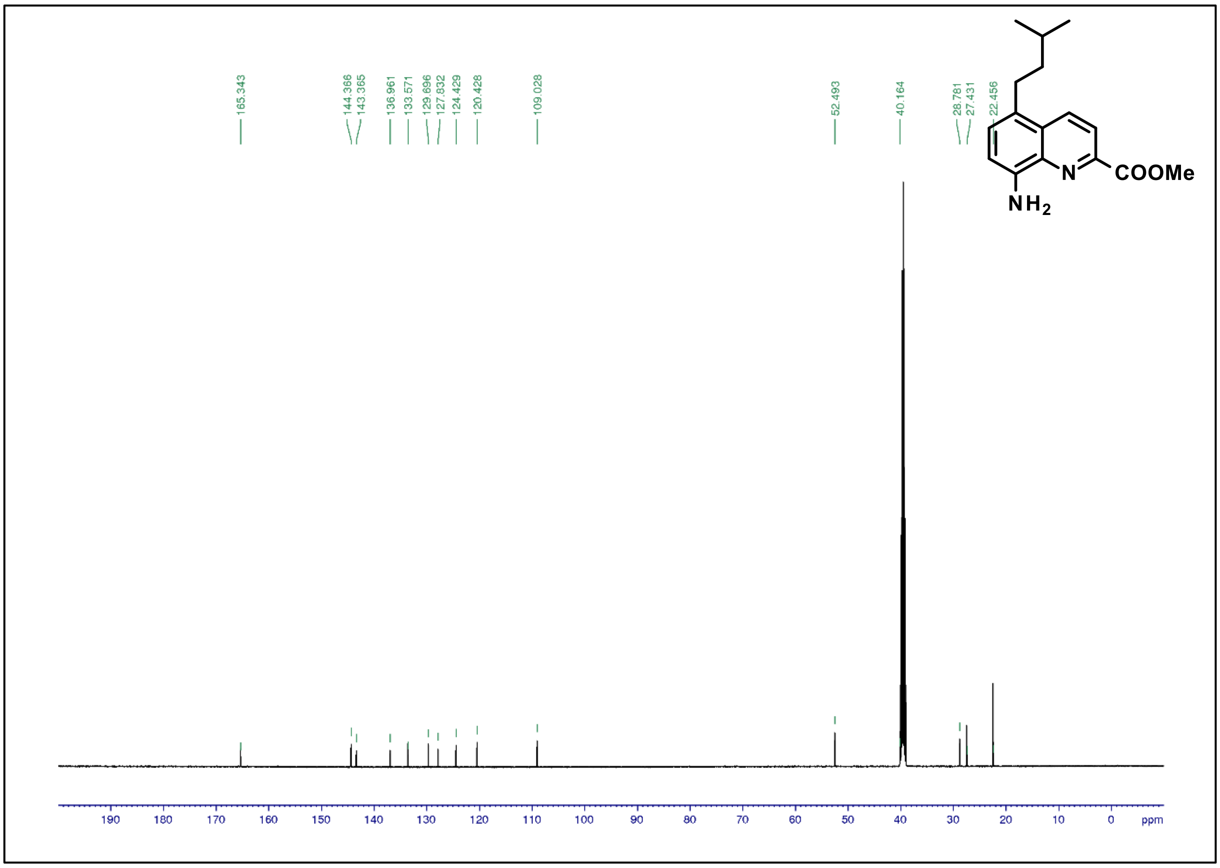


Figure S48. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **9d**.

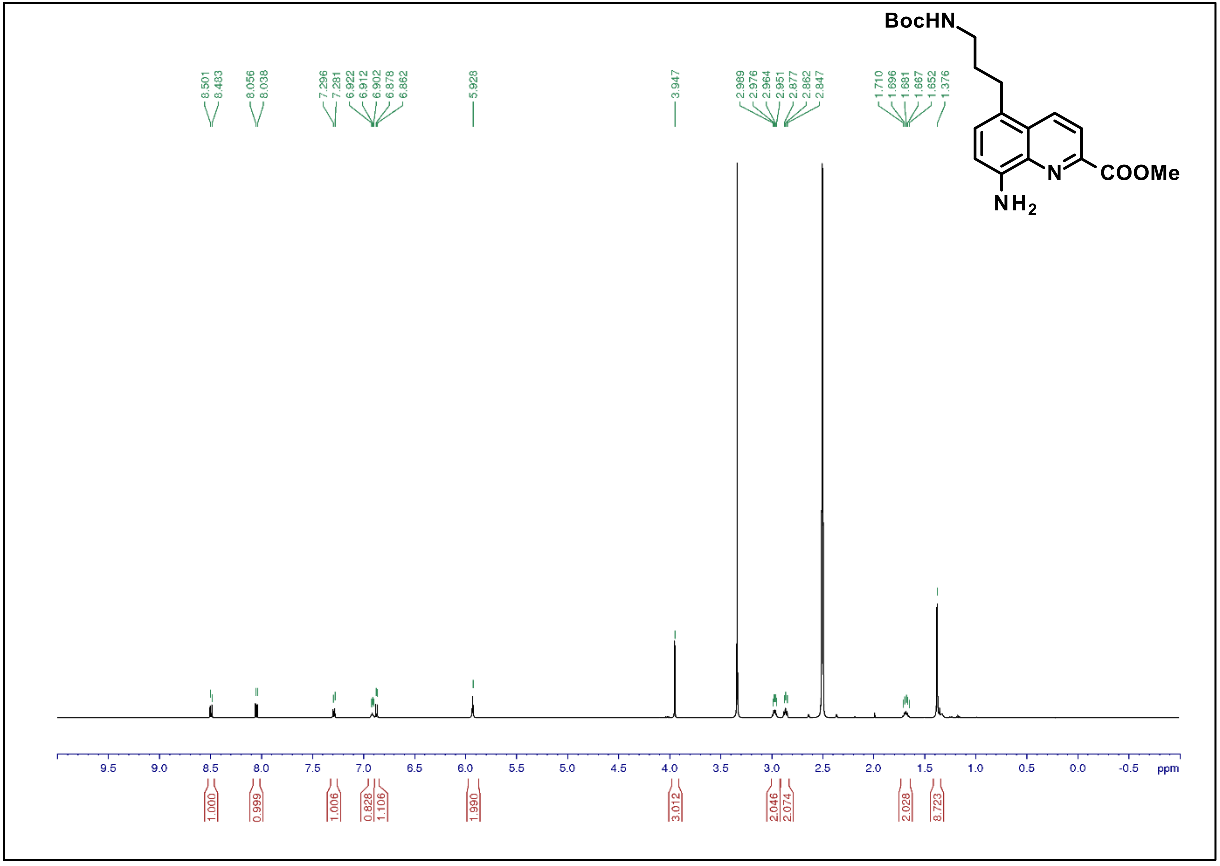


Figure S49. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **9e**.

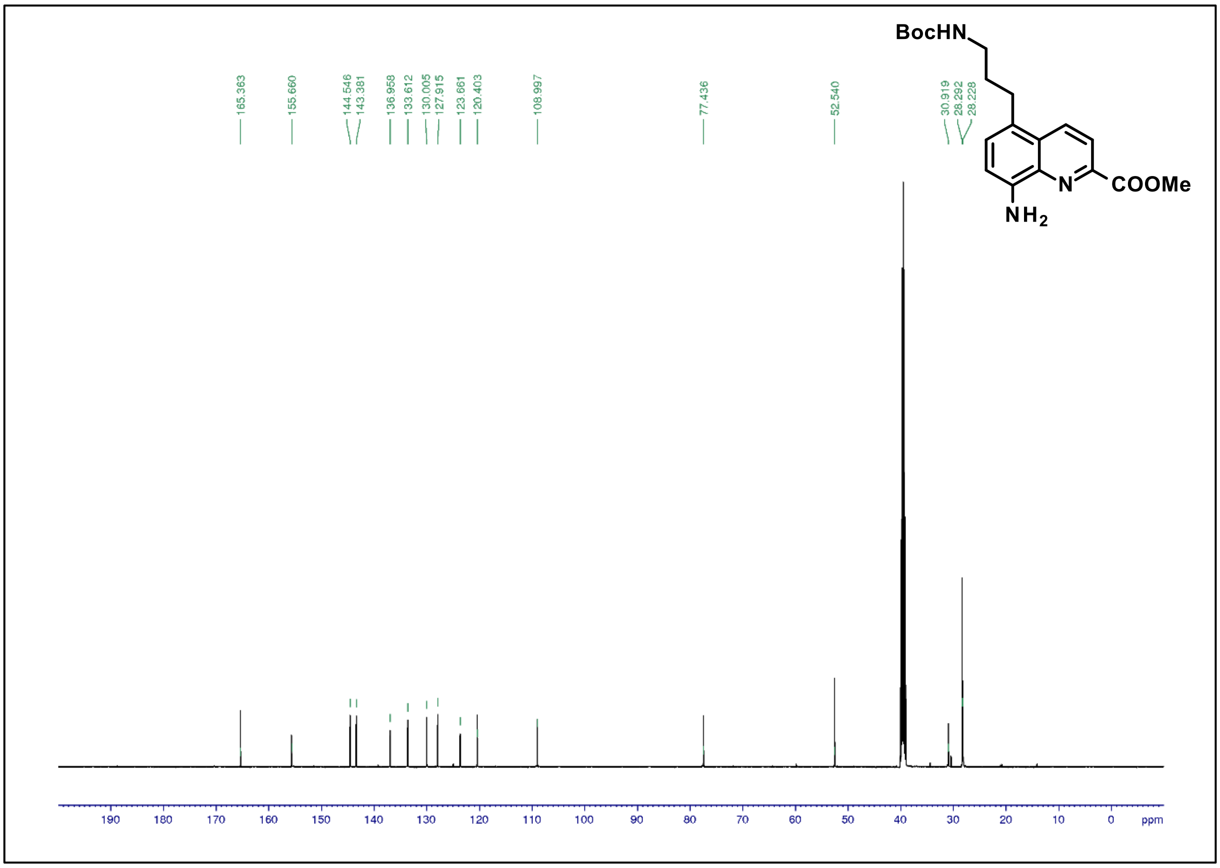


Figure S50. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) of compound **9e**.

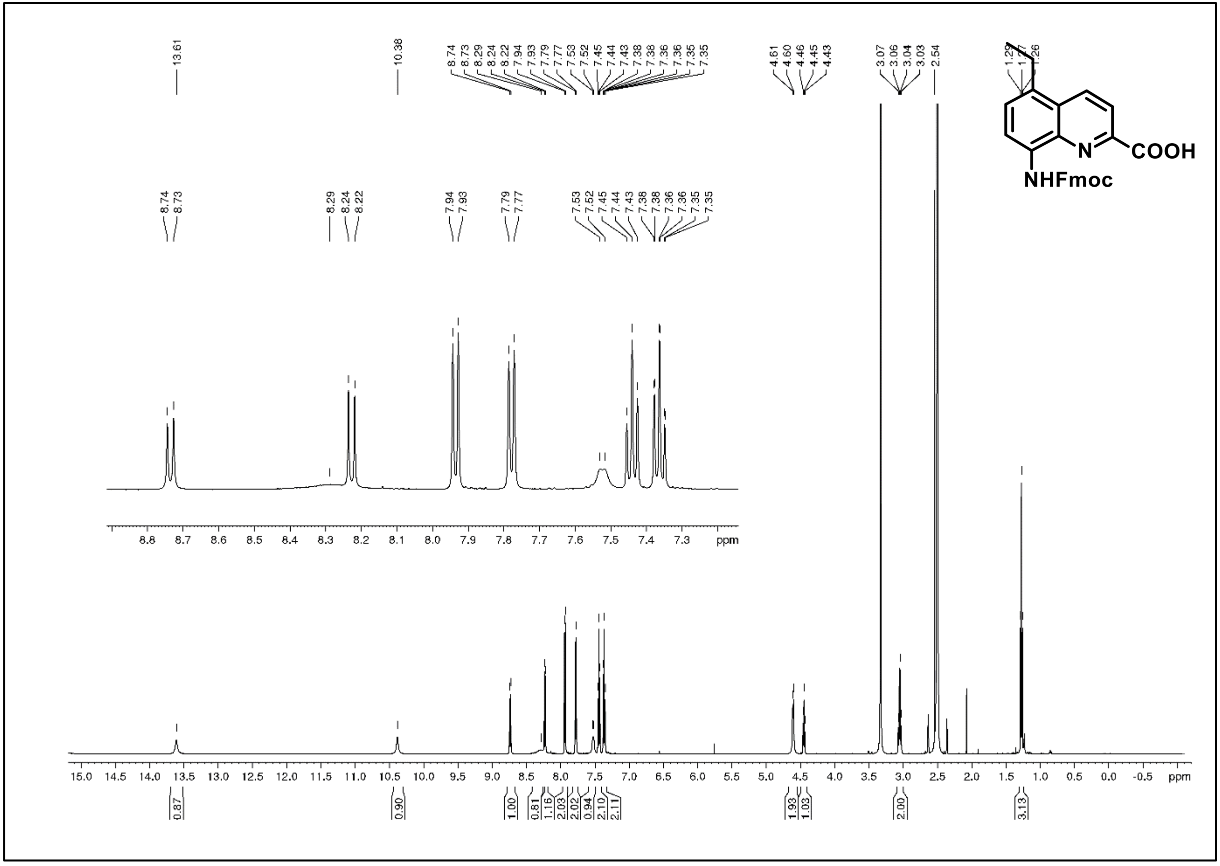


Figure S51. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **10a**.

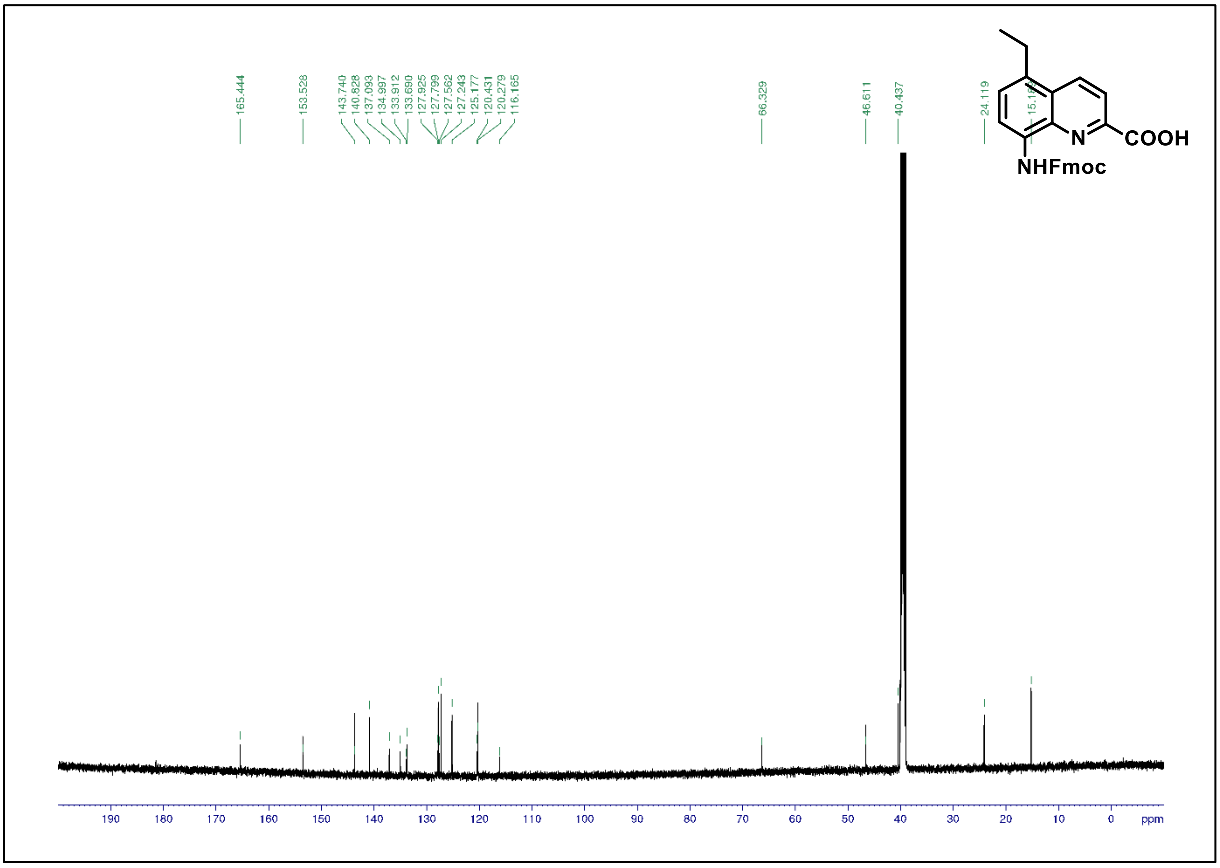


Figure S52. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **10a**.

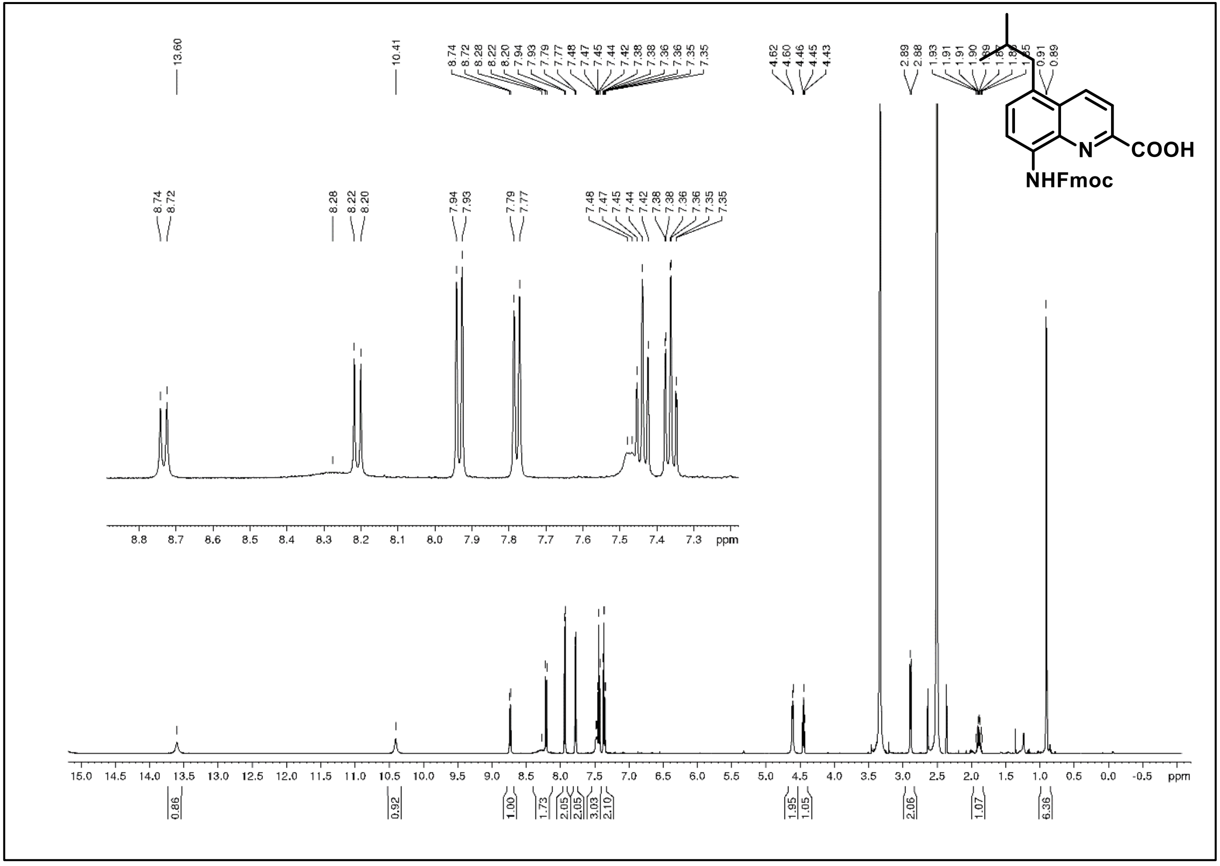


Figure S53. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **10b**.

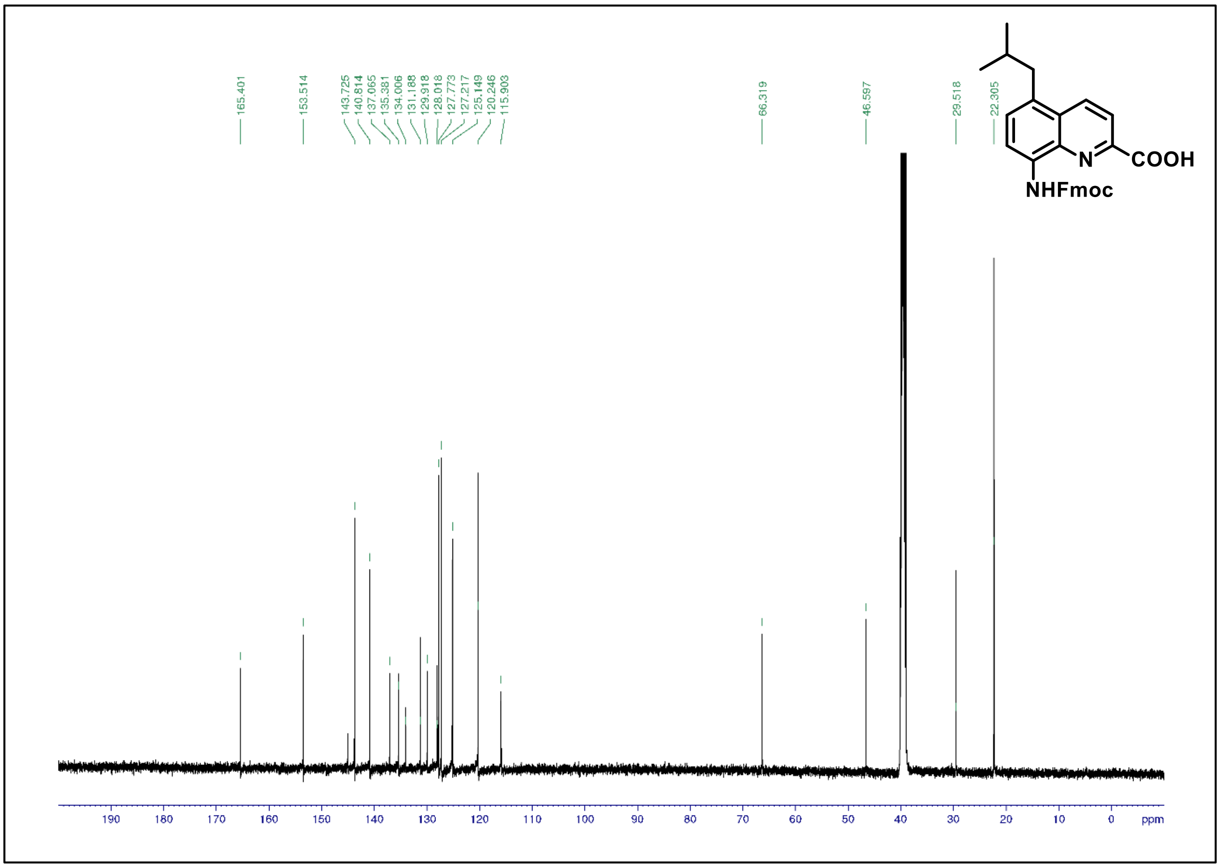


Figure S54. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **10b**.

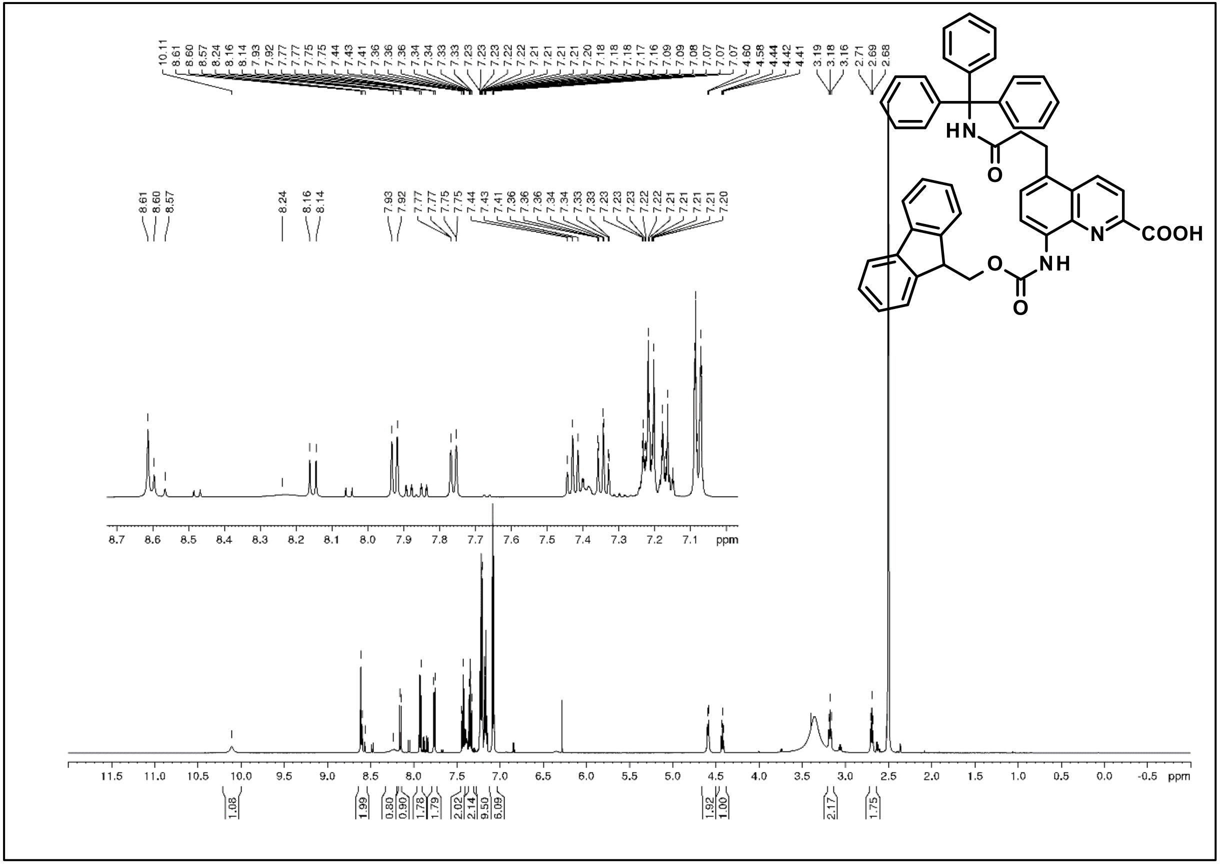


Figure S55. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **10c**.

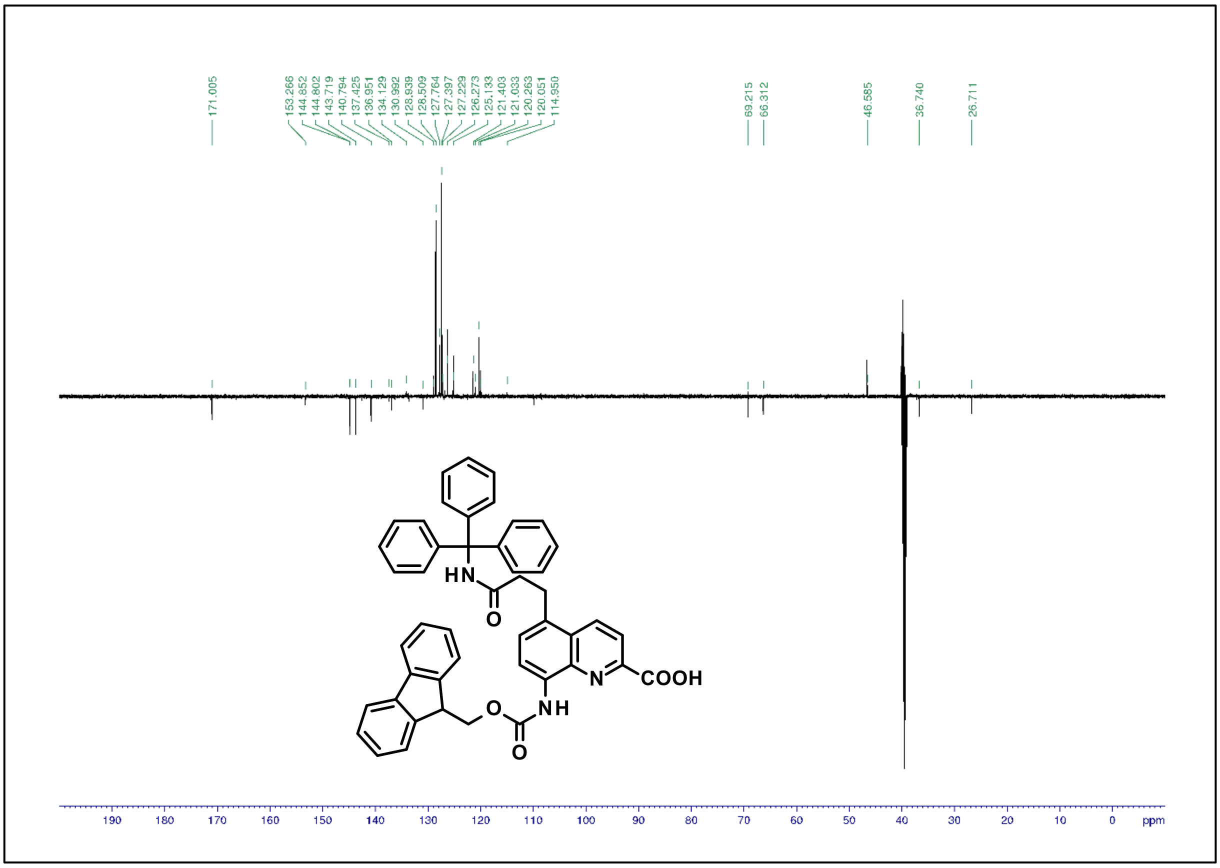


Figure S56. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **10c**.

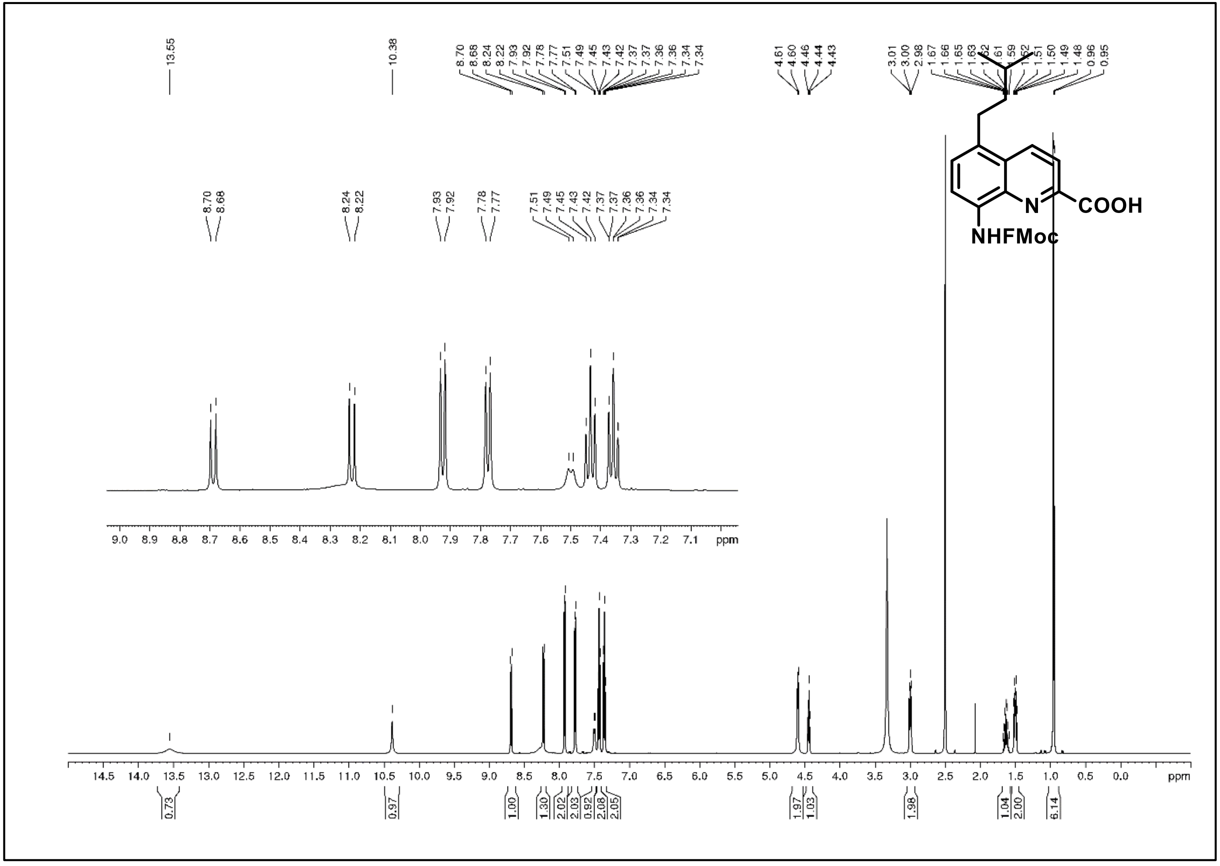


Figure S57. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **10d**.

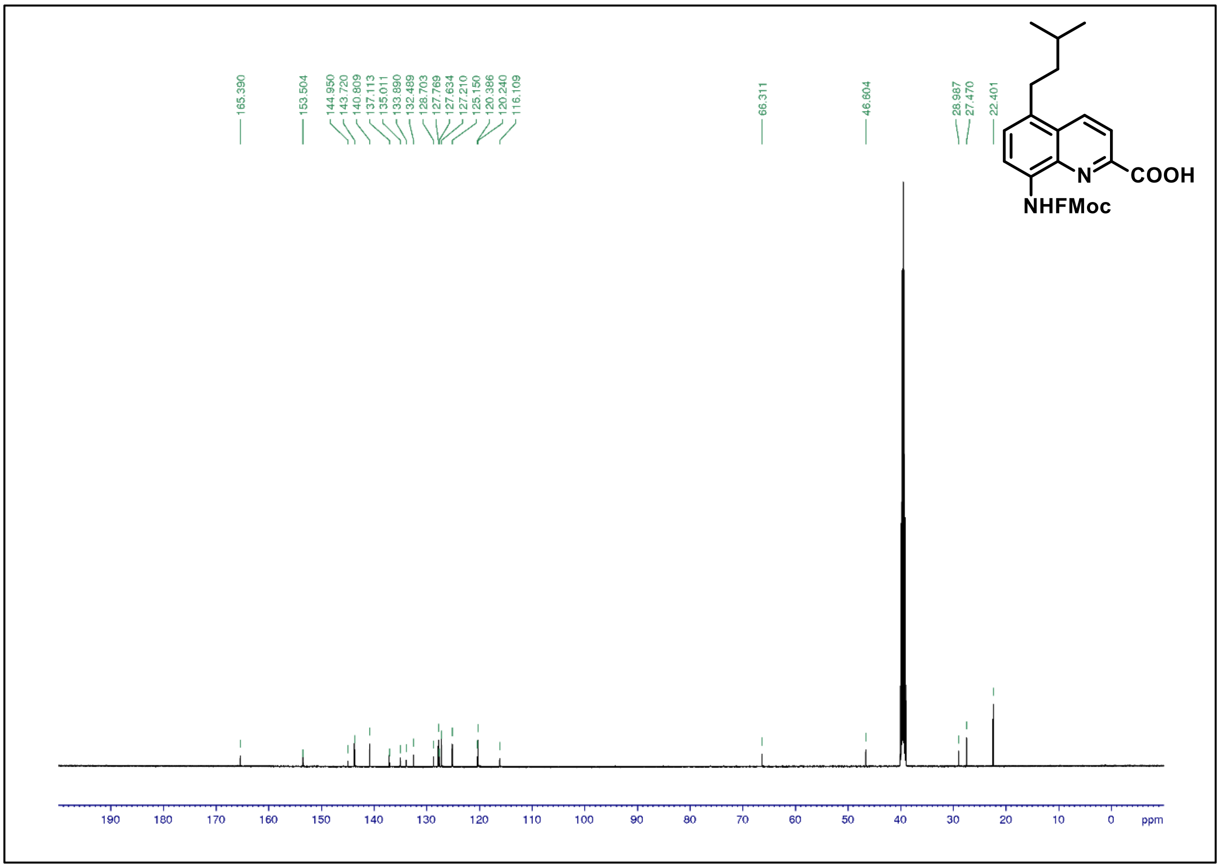


Figure S58. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **10d**.

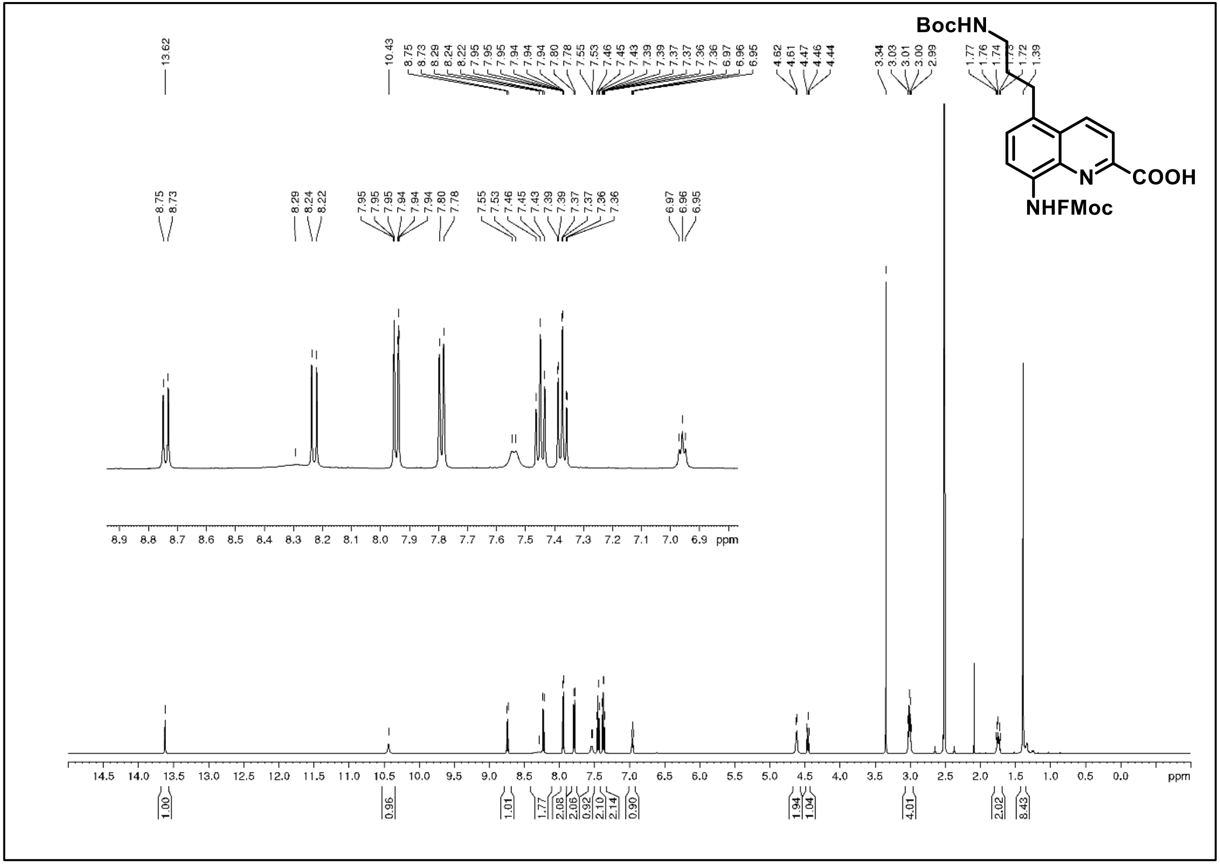


Figure S59. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **10e**.

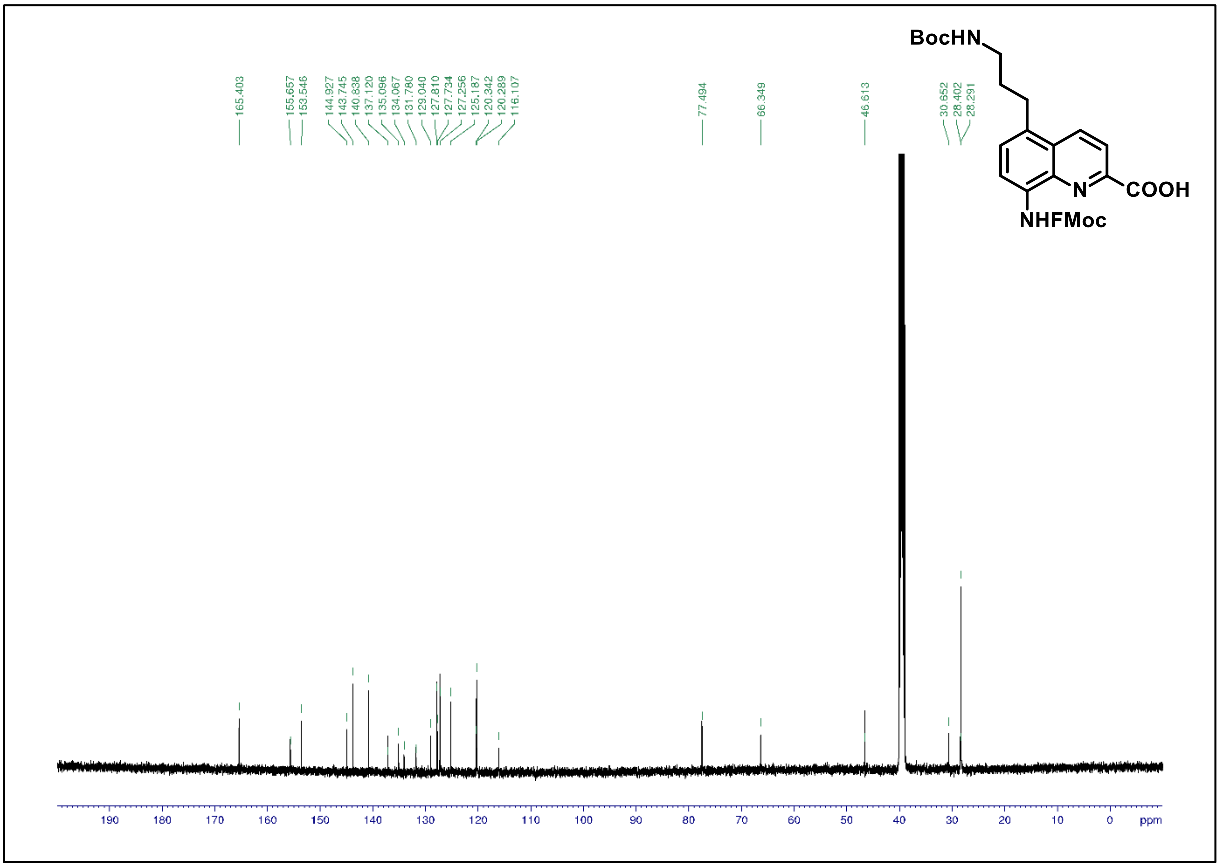


Figure S60. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **10e**.

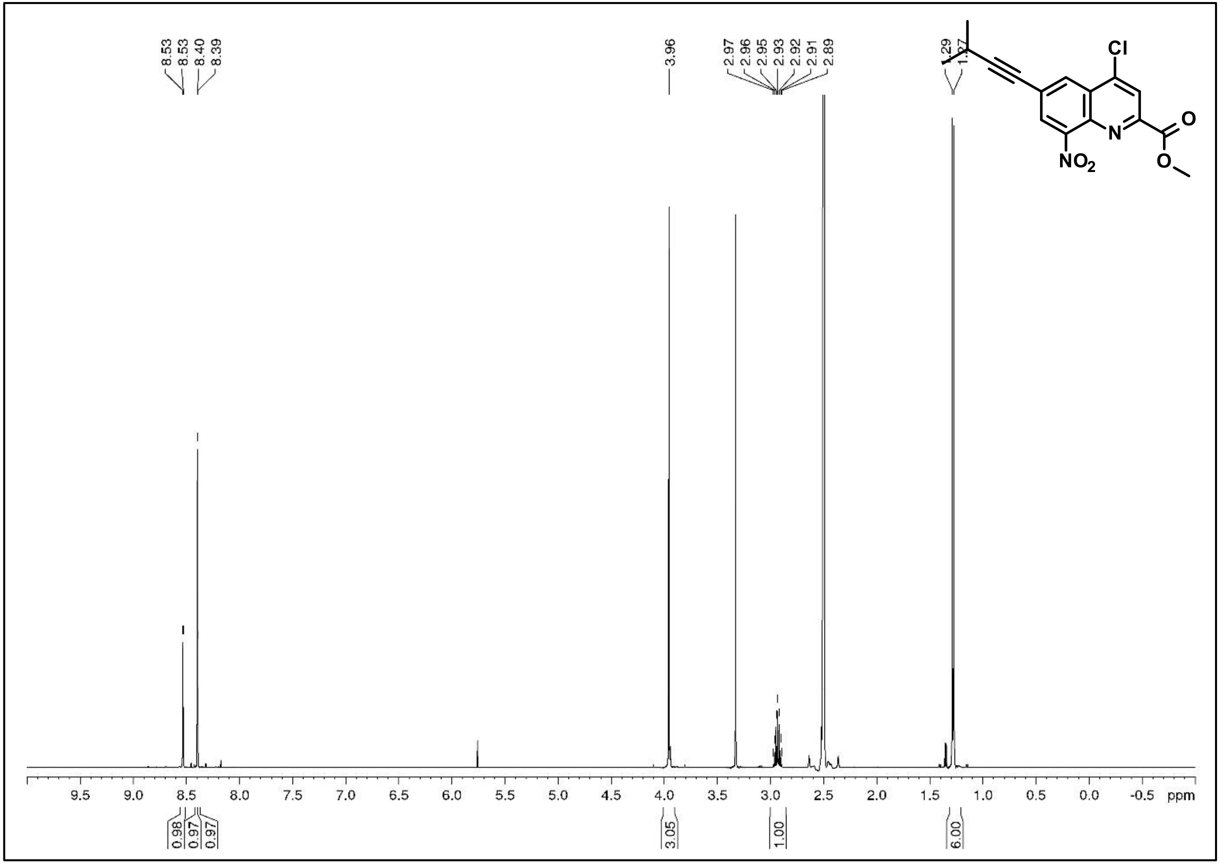


Figure S61. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **11a**.

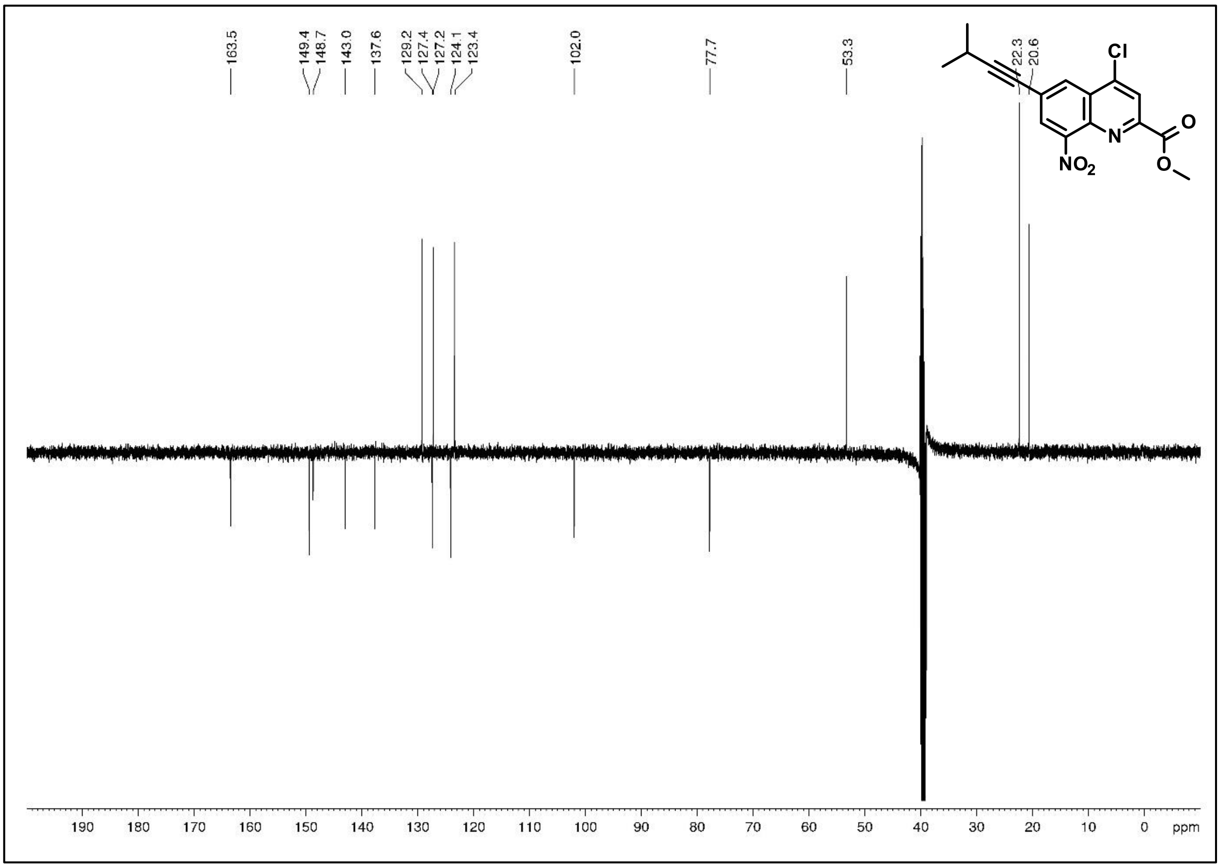


Figure S62. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **11a**.

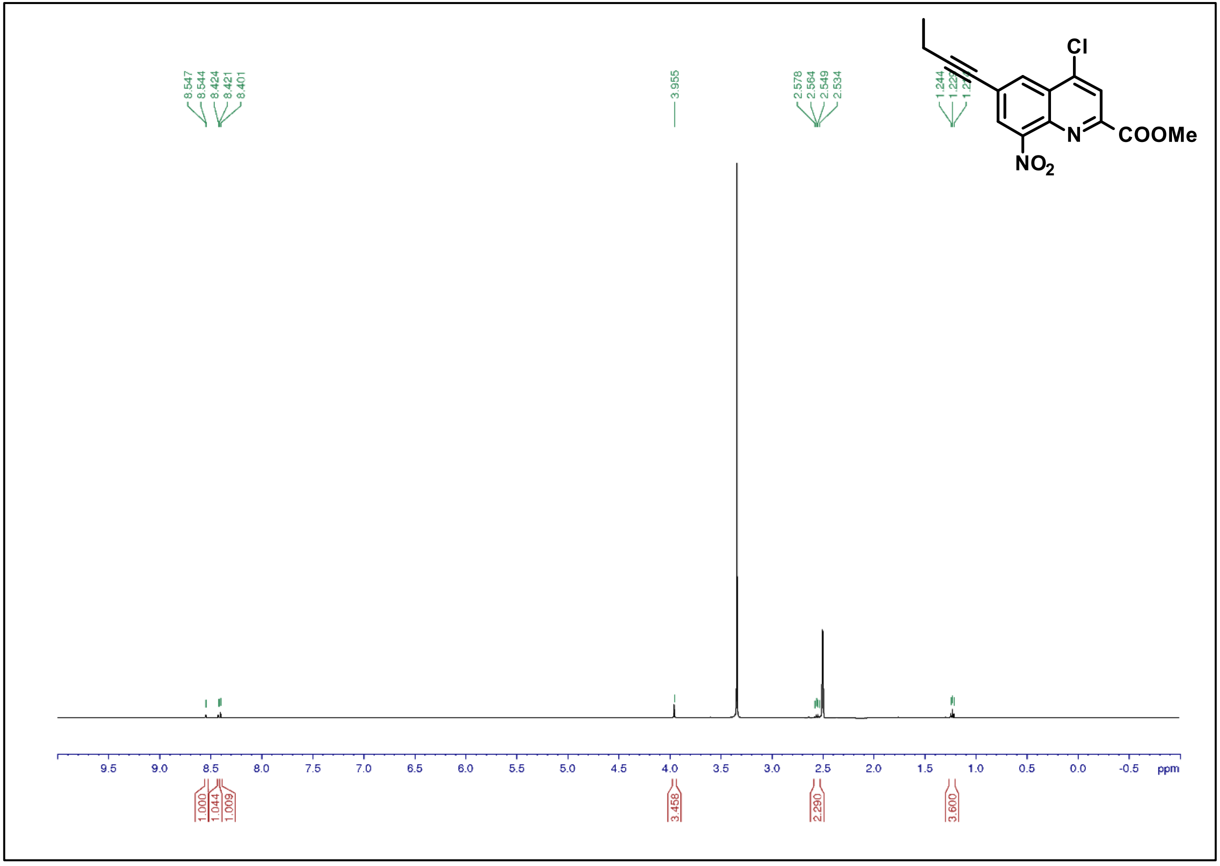


Figure S63. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **11b**.

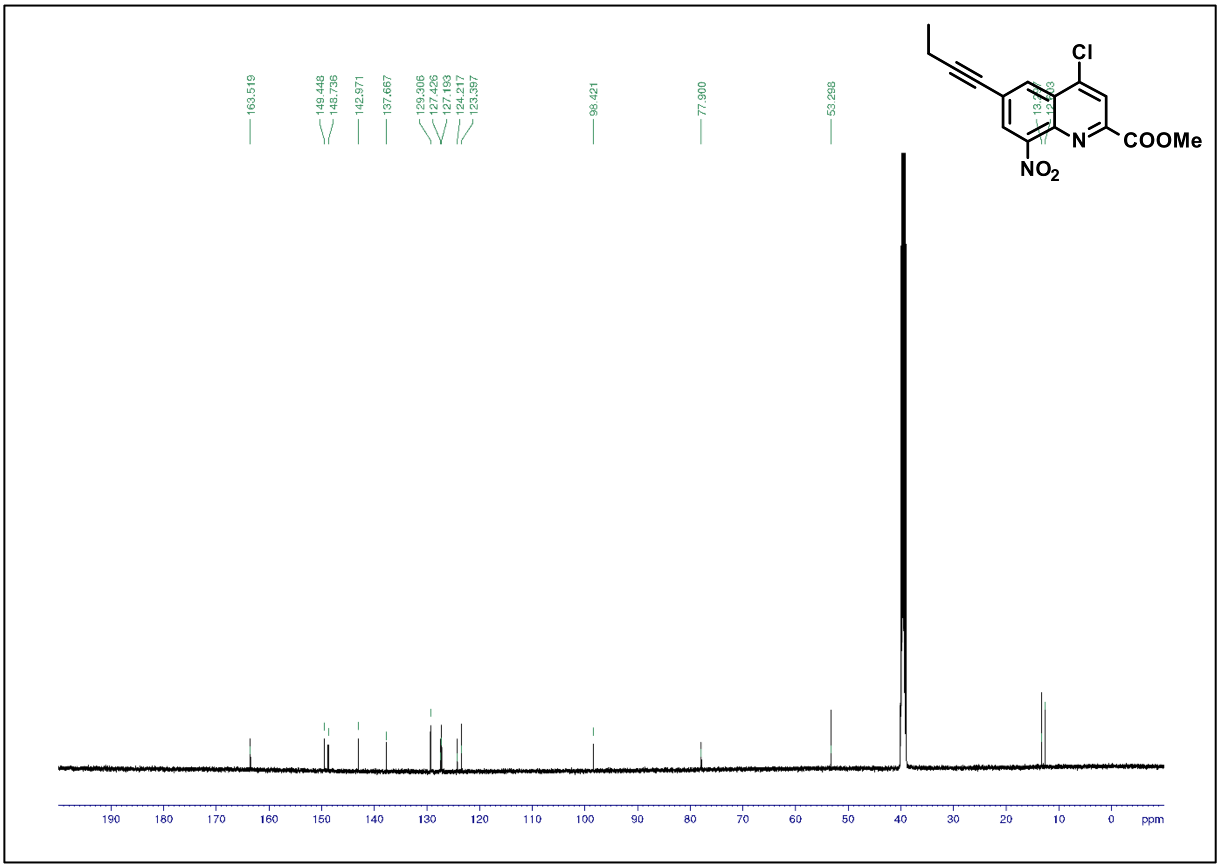


Figure S64. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **11b**.

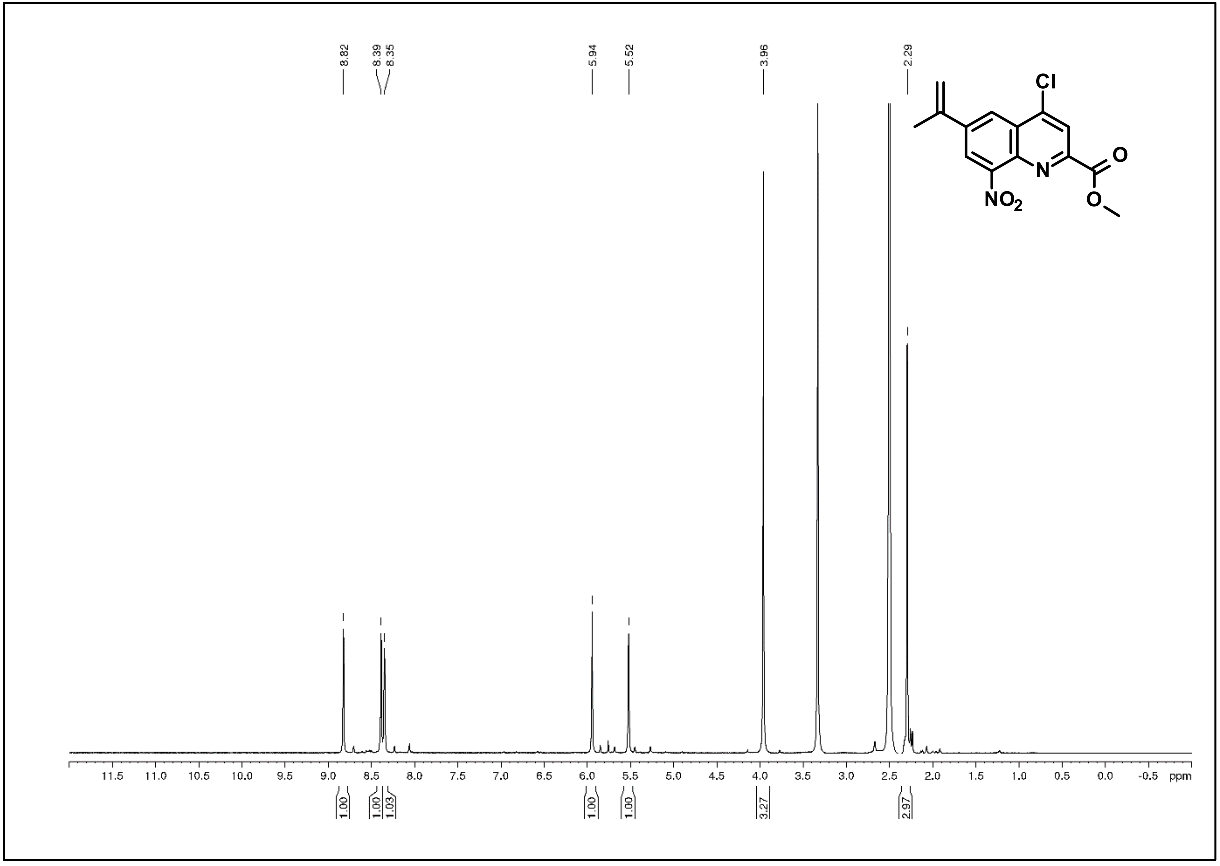


Figure S65. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **11c**.

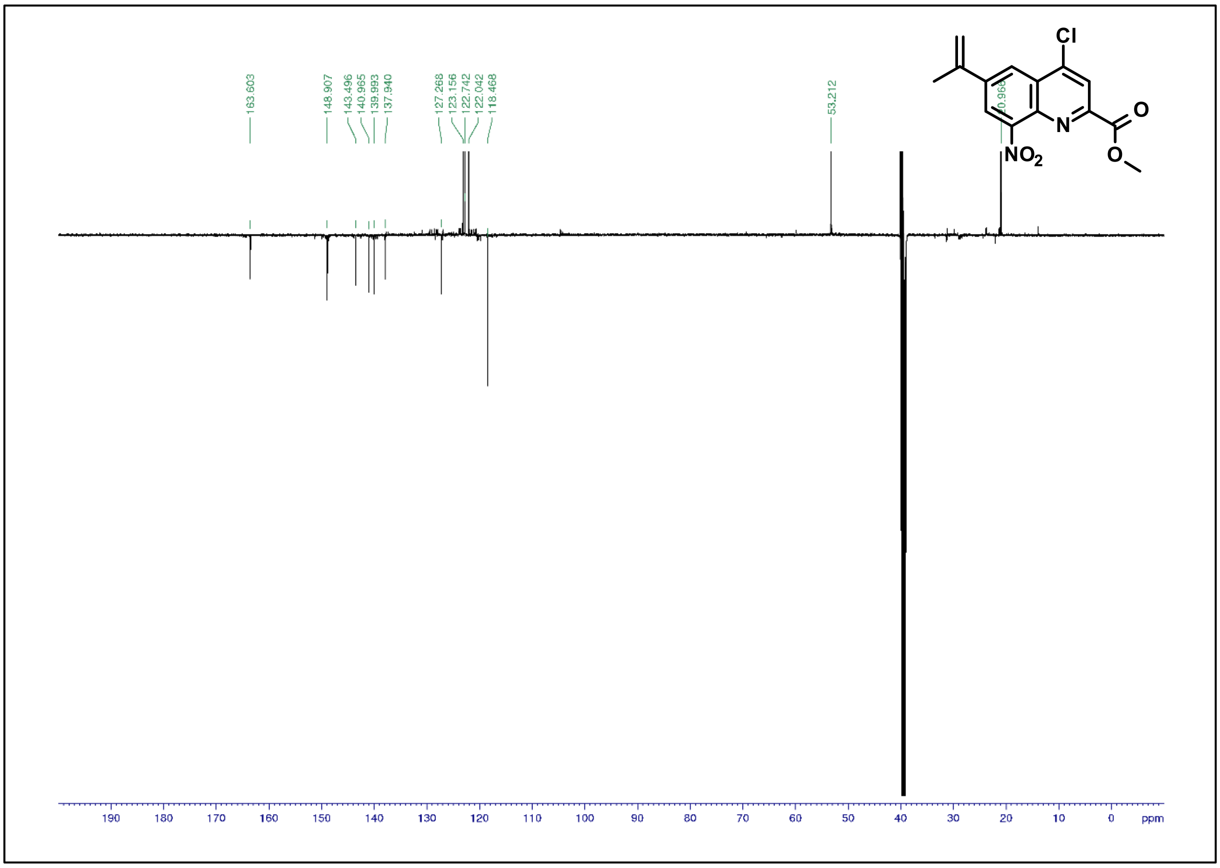


Figure S66. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) of compound **11c**.

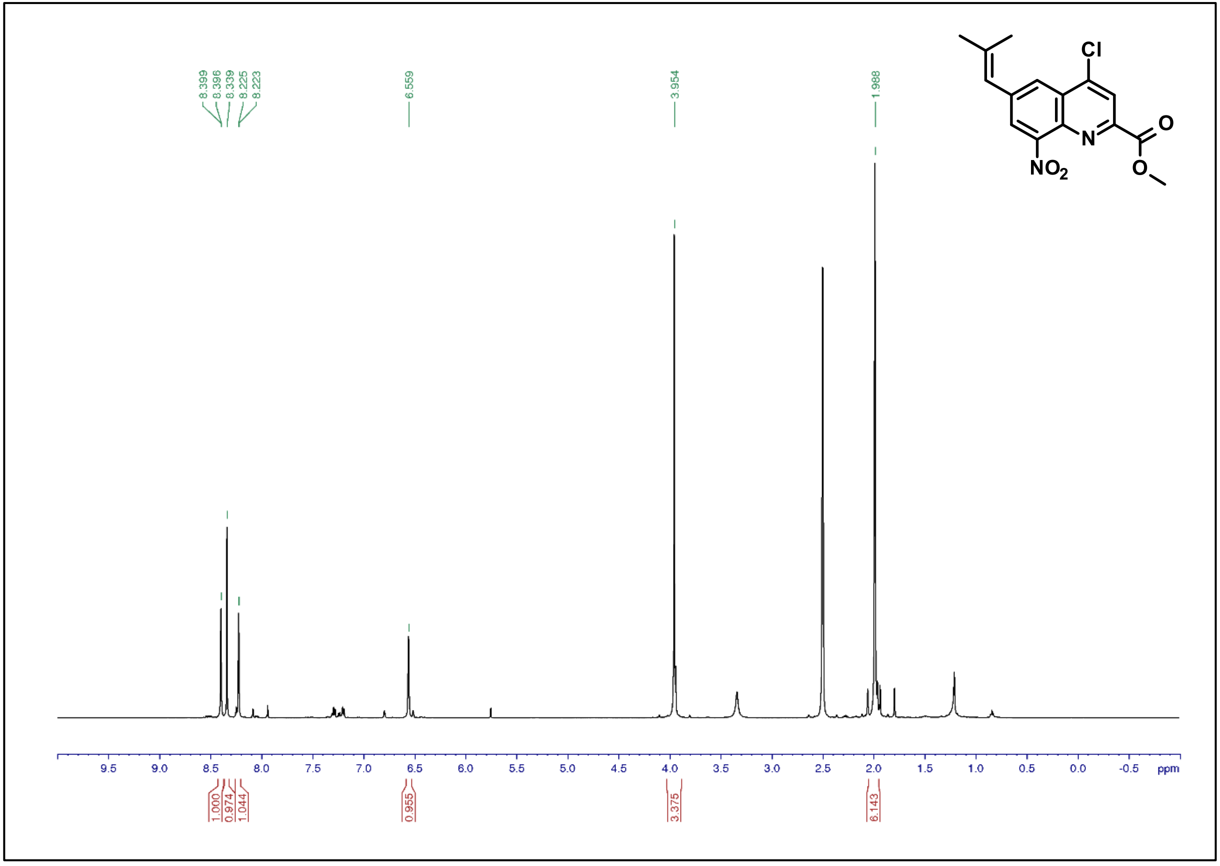


Figure S67. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **11d**.

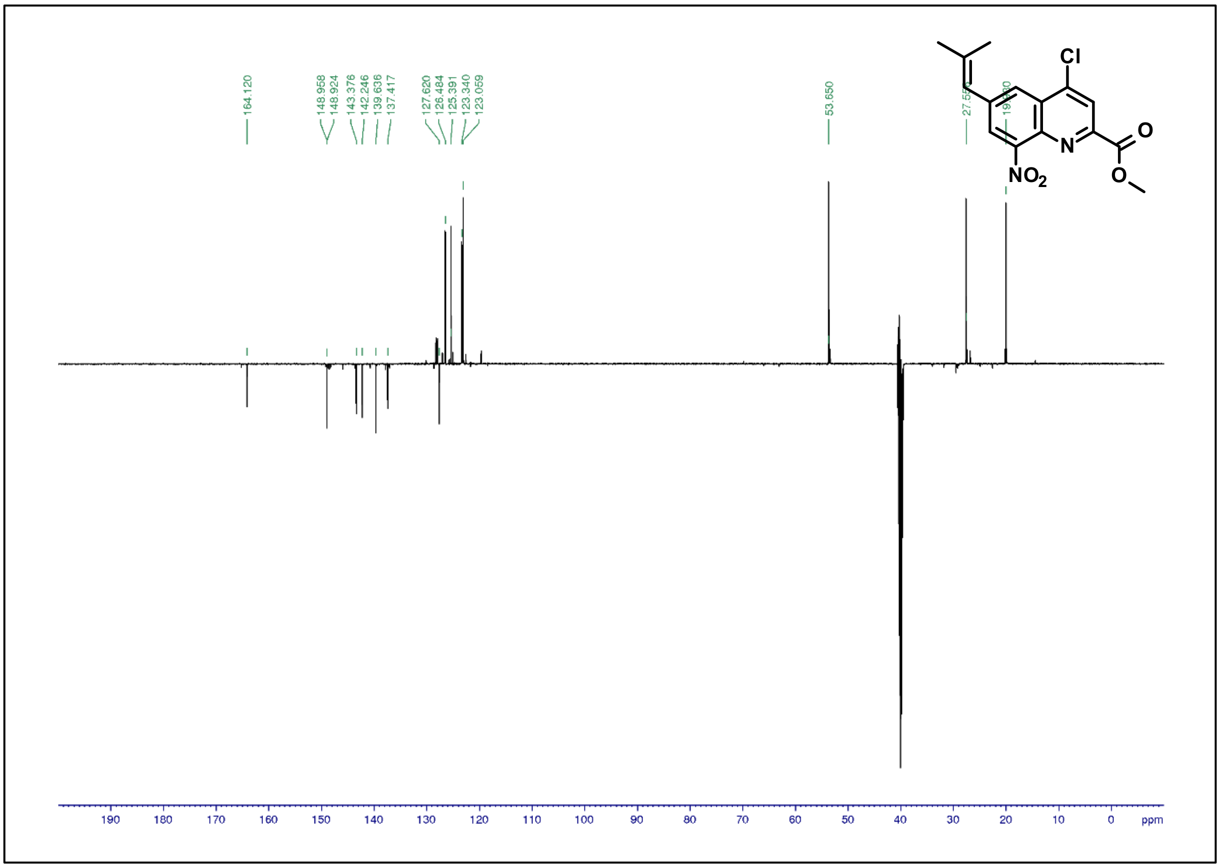


Figure S68. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **11d**.

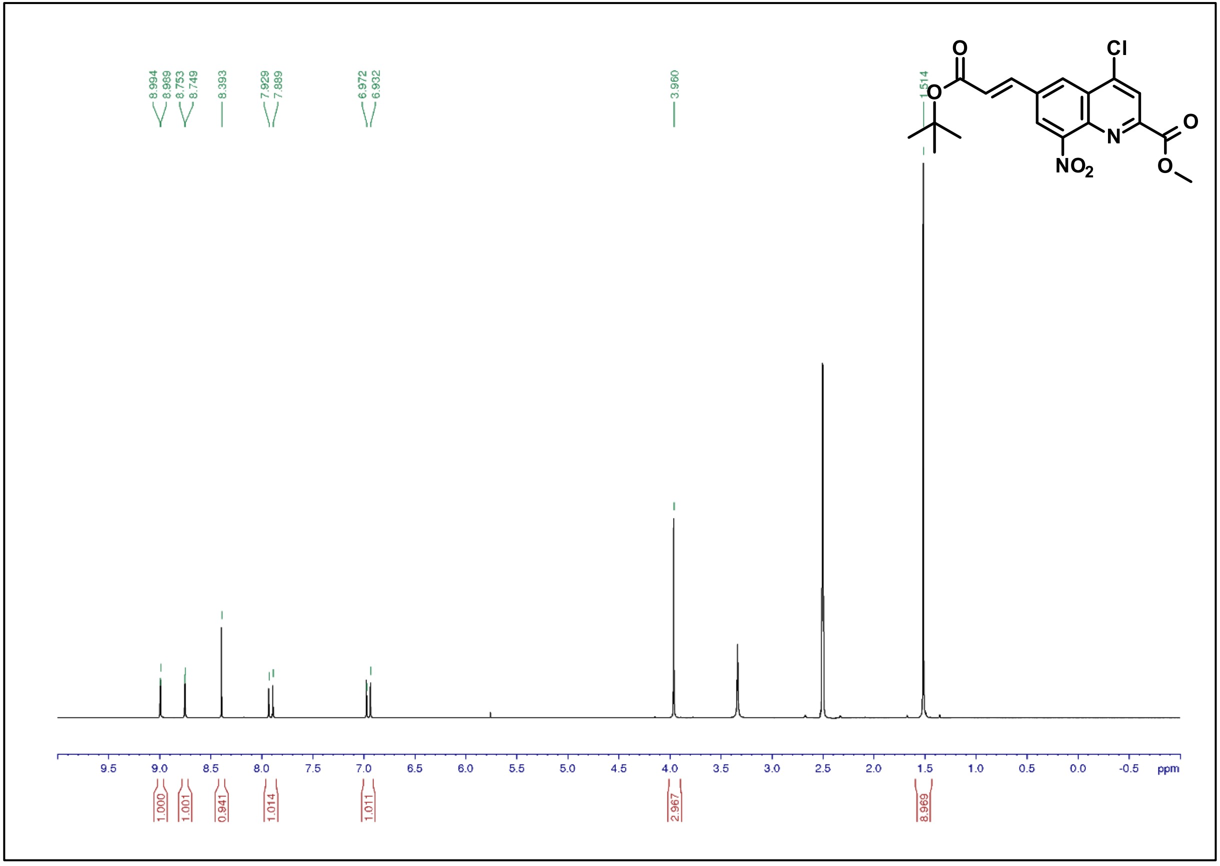


Figure S69. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **11e**.

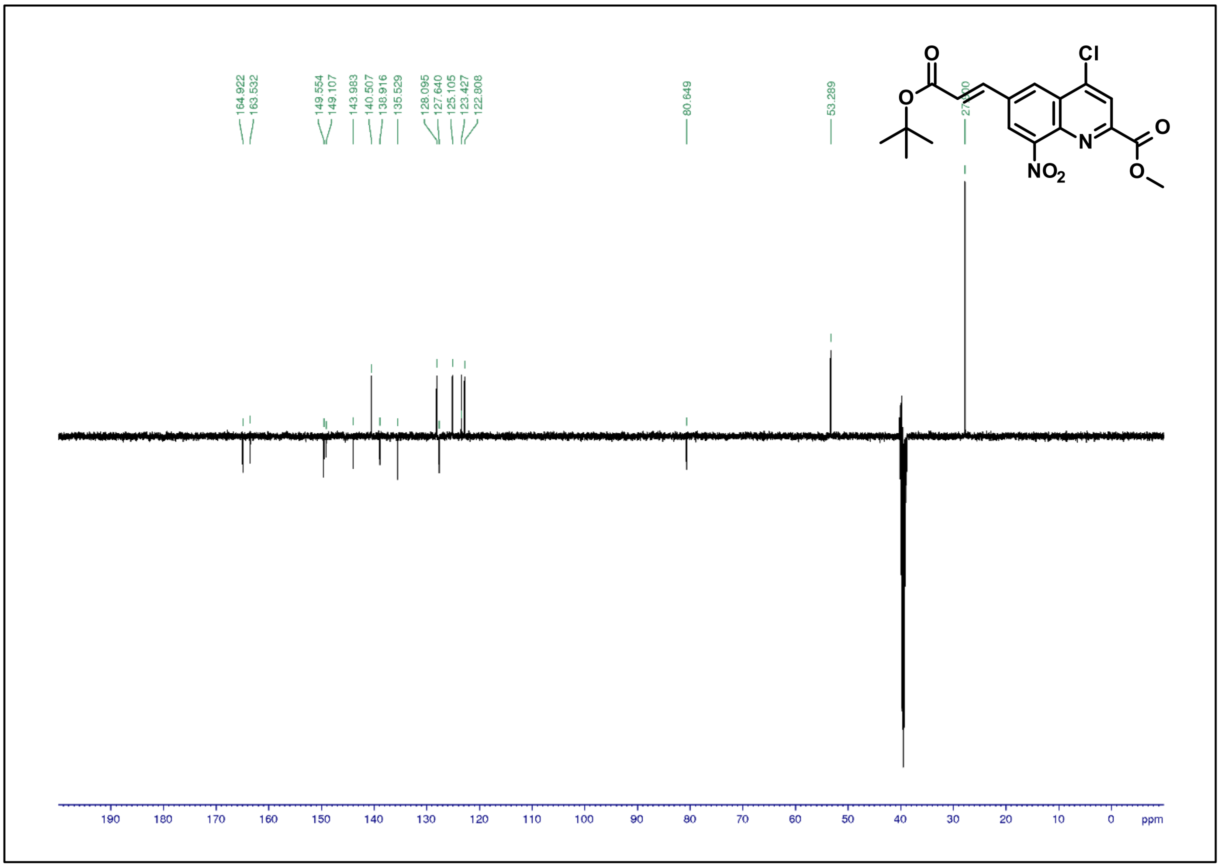


Figure S70. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **11e**.

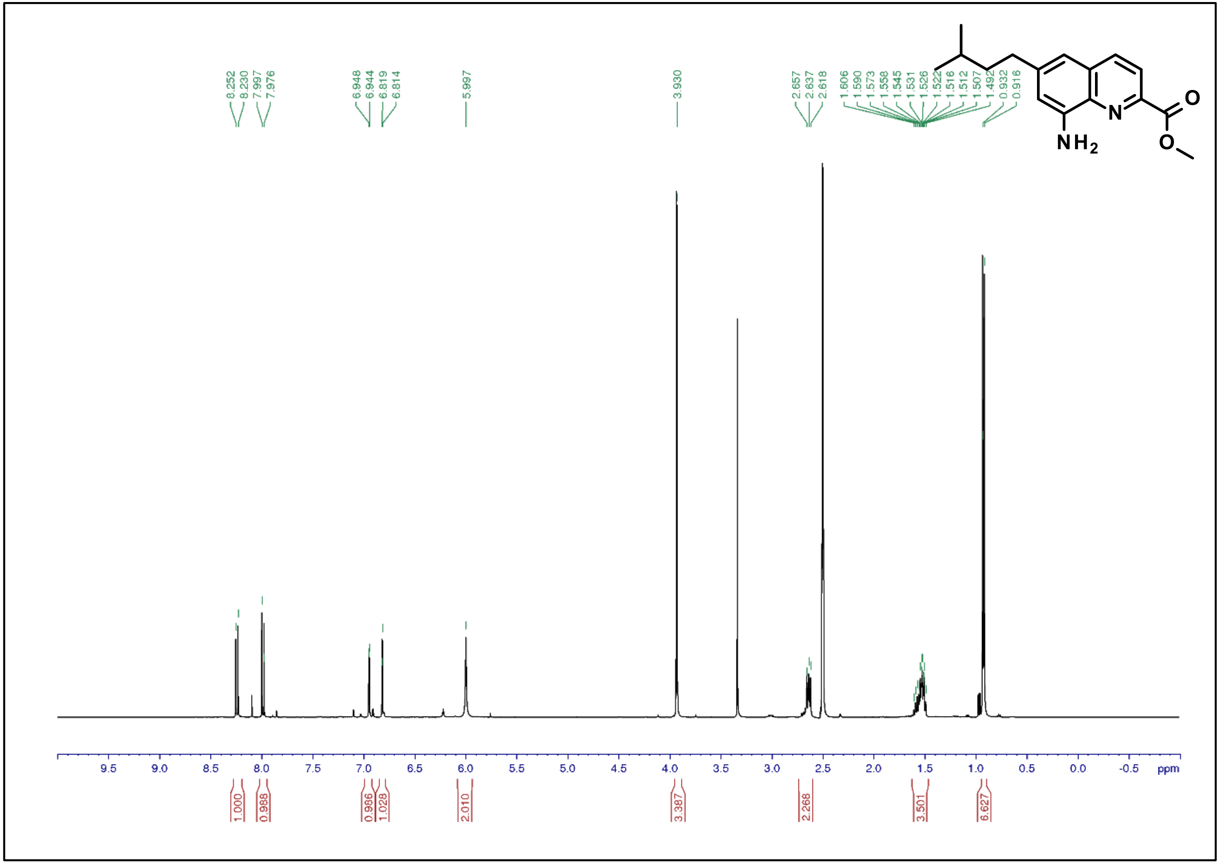


Figure S71. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **12a**.

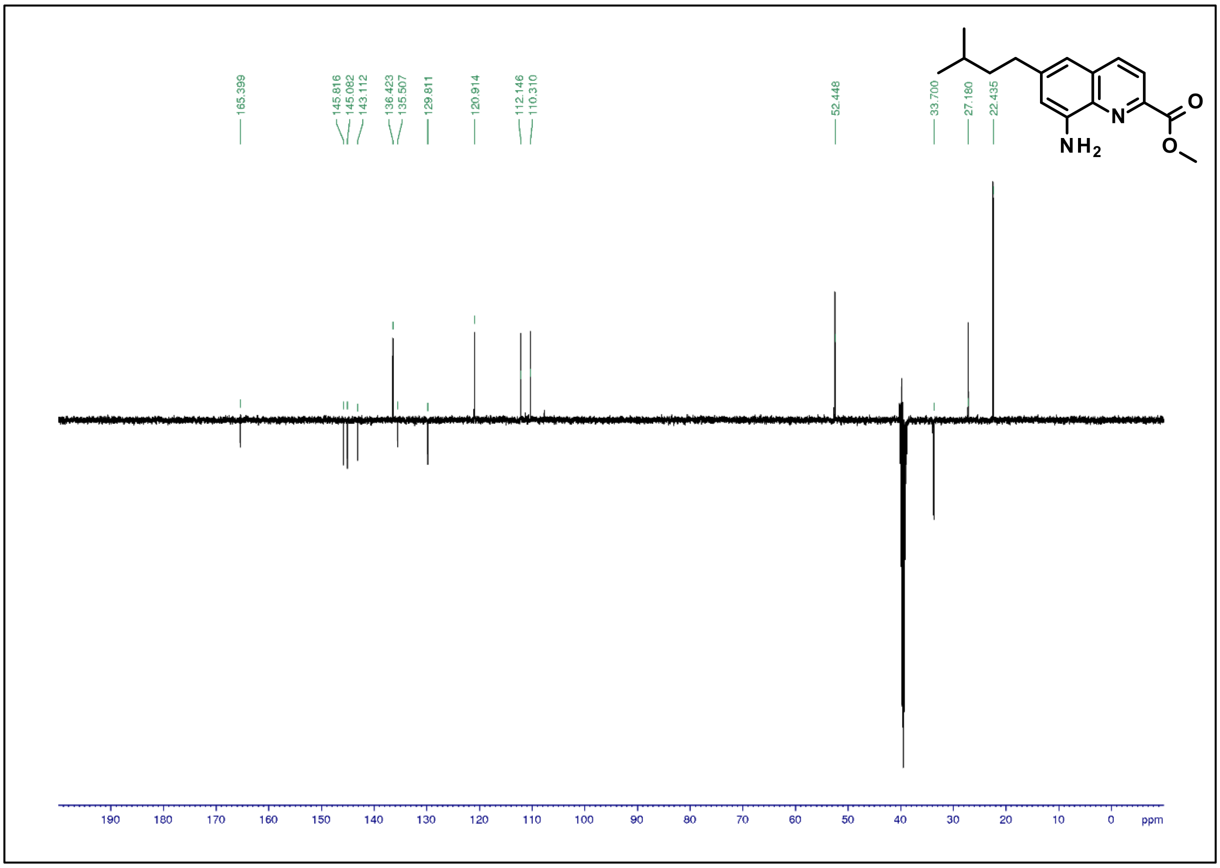


Figure S72. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **12a**.

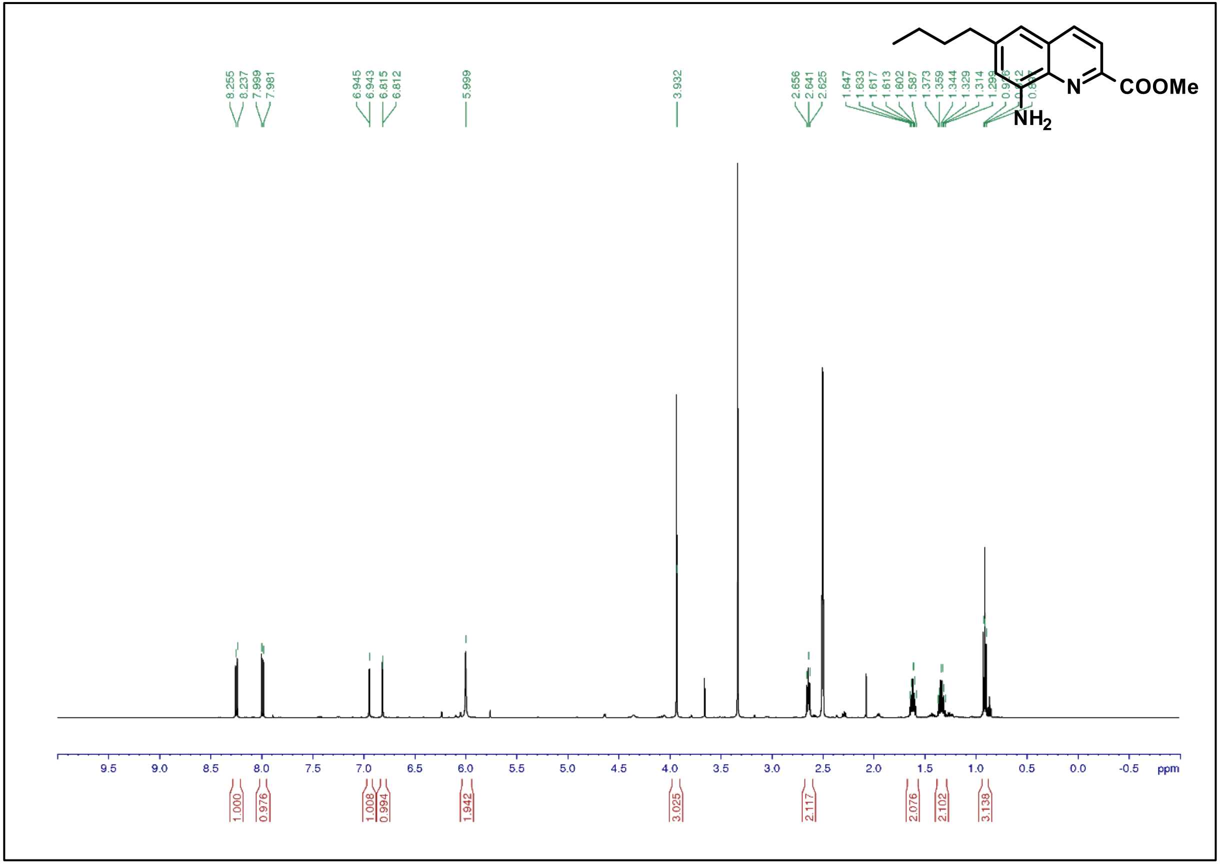


Figure S73. ${}^{1}H$ NMR (500 MHz, DMSO-d_6) of compound **12b**.

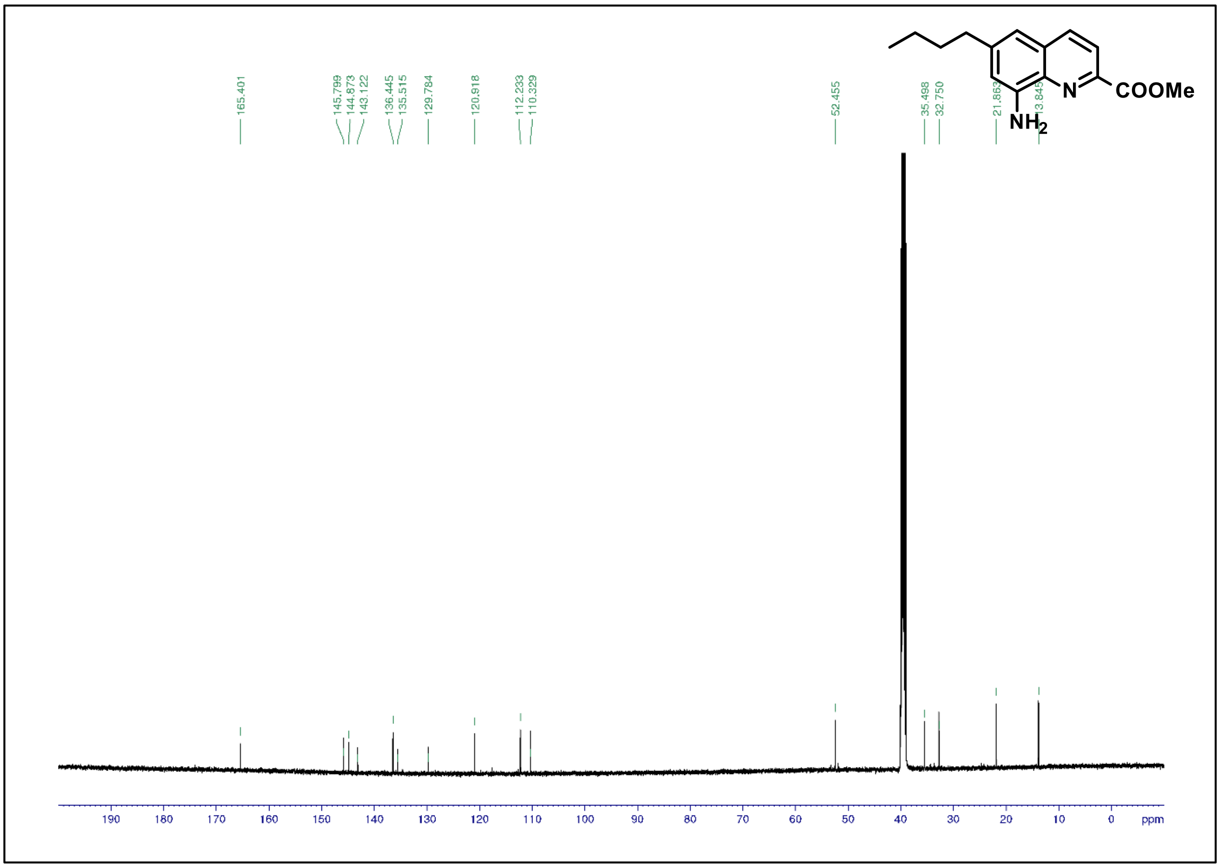


Figure S74. ${}^{13}C\{{}^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **12b**.

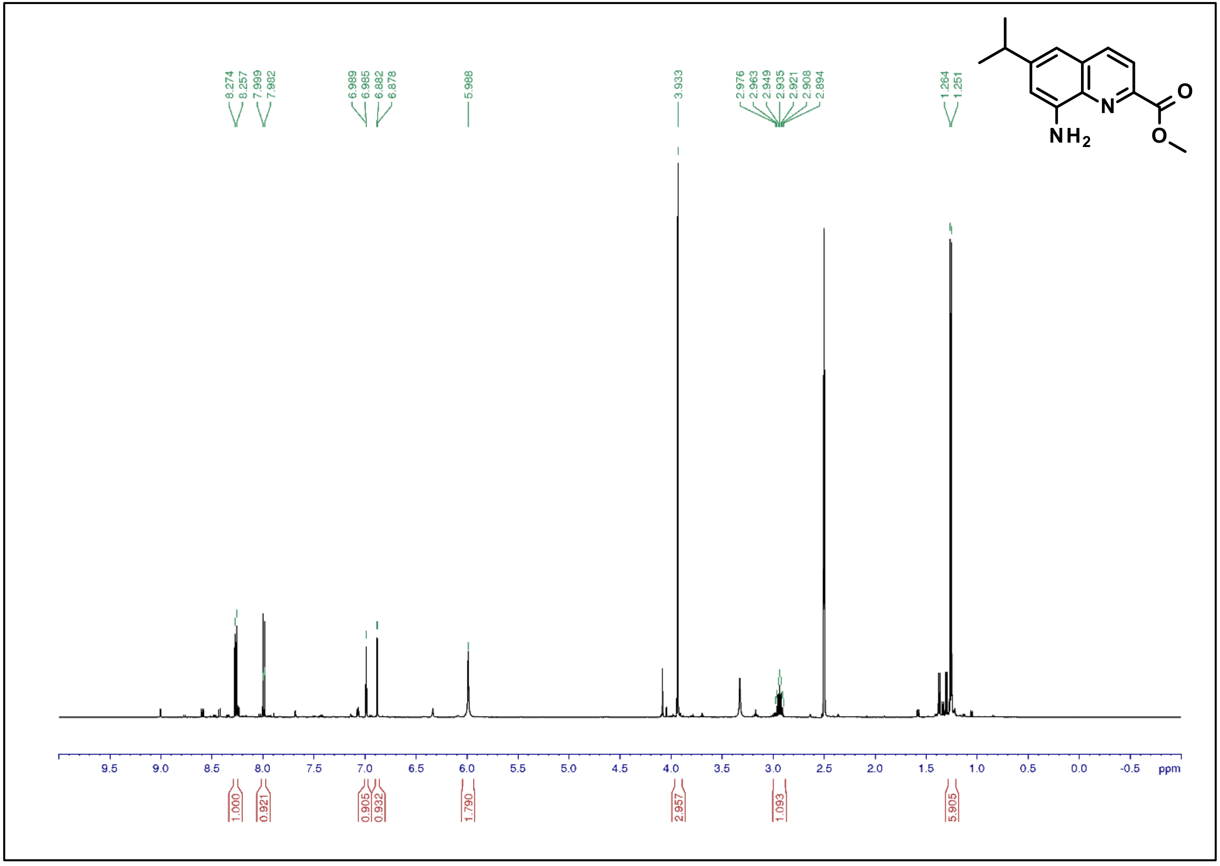


Figure S75. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **12c**.

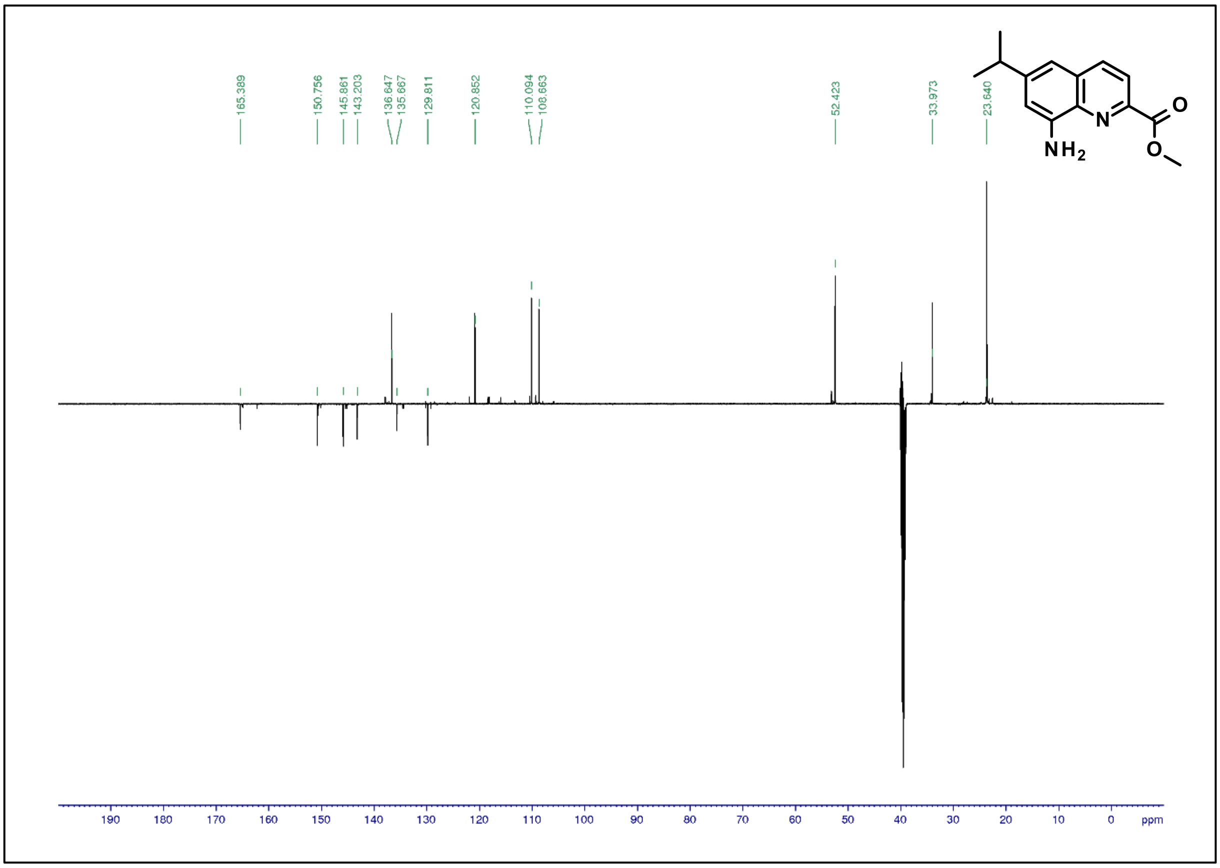


Figure S76. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **12c**.

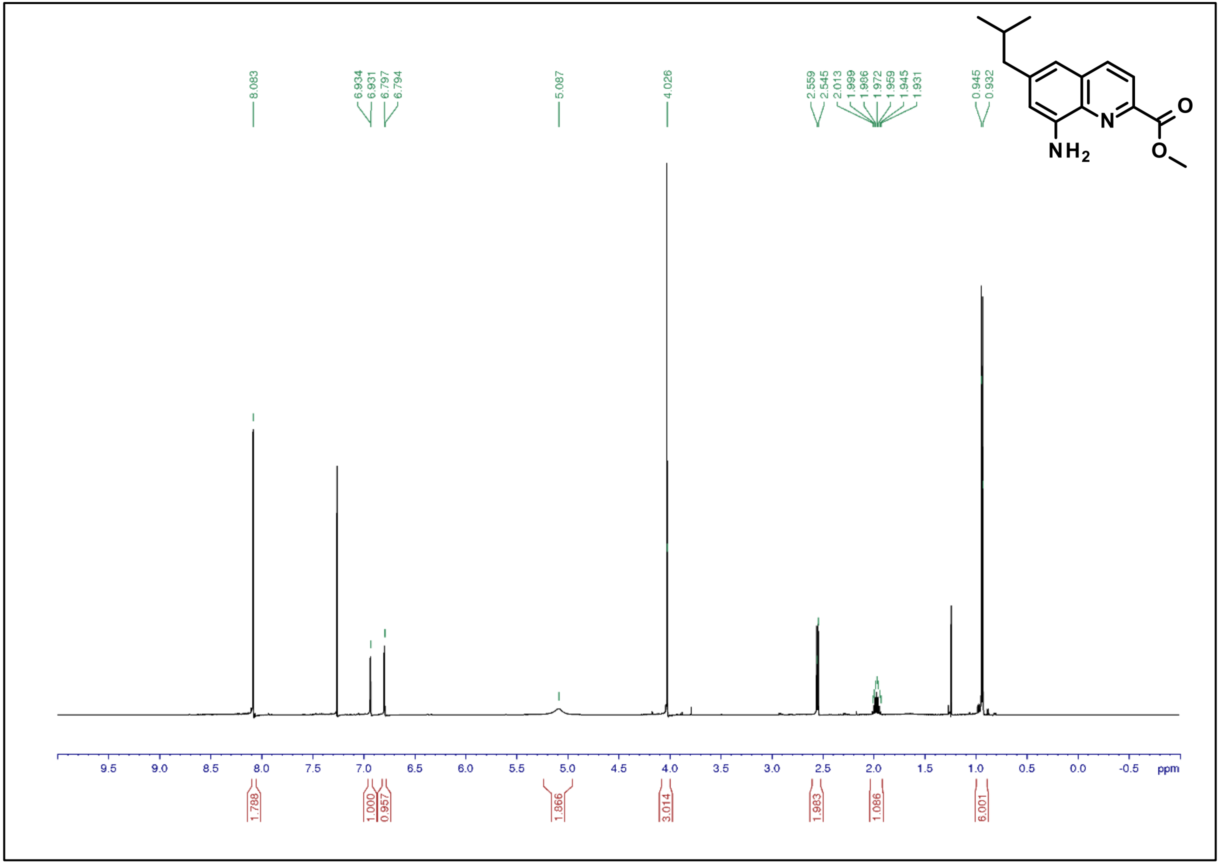


Figure S77. ^{1}H NMR (500 MHz, CDCl$_3$) of compound **12d**.

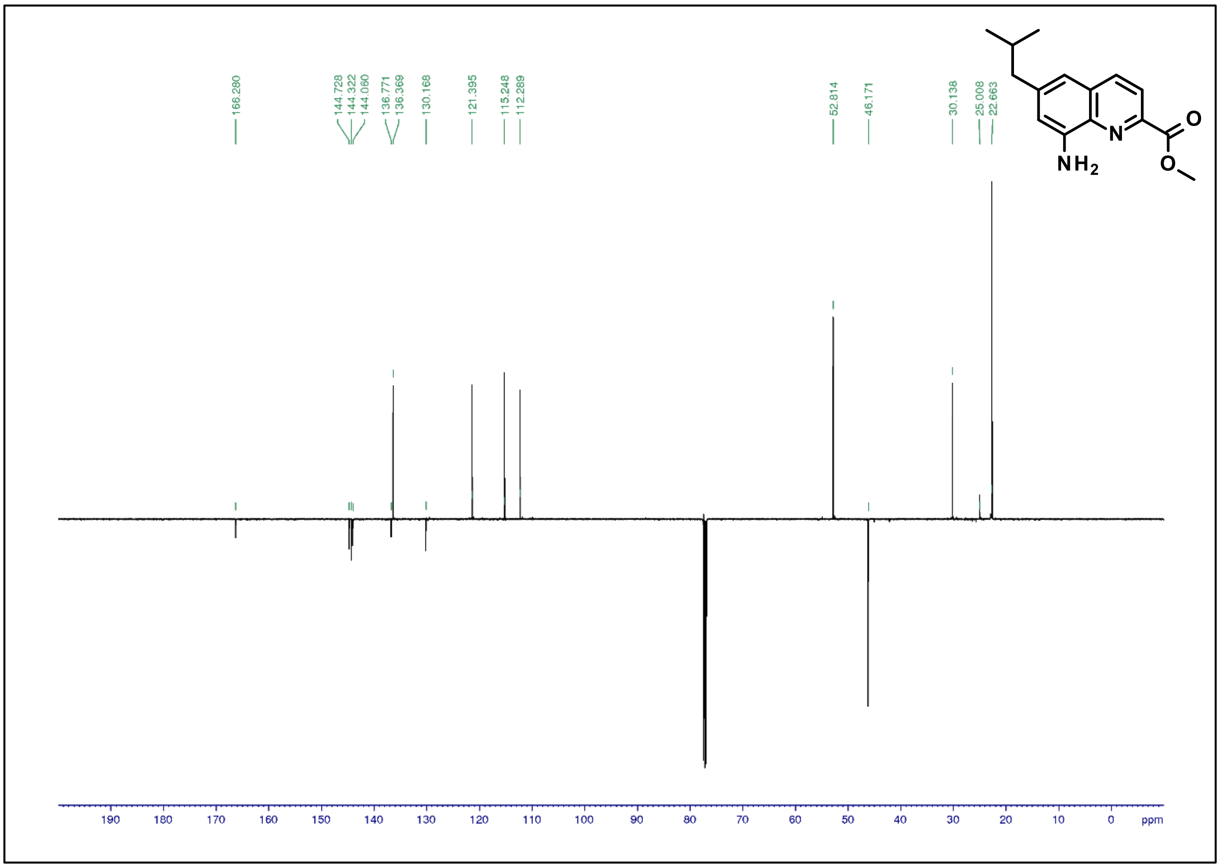


Figure S78. ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) of compound **12d**.

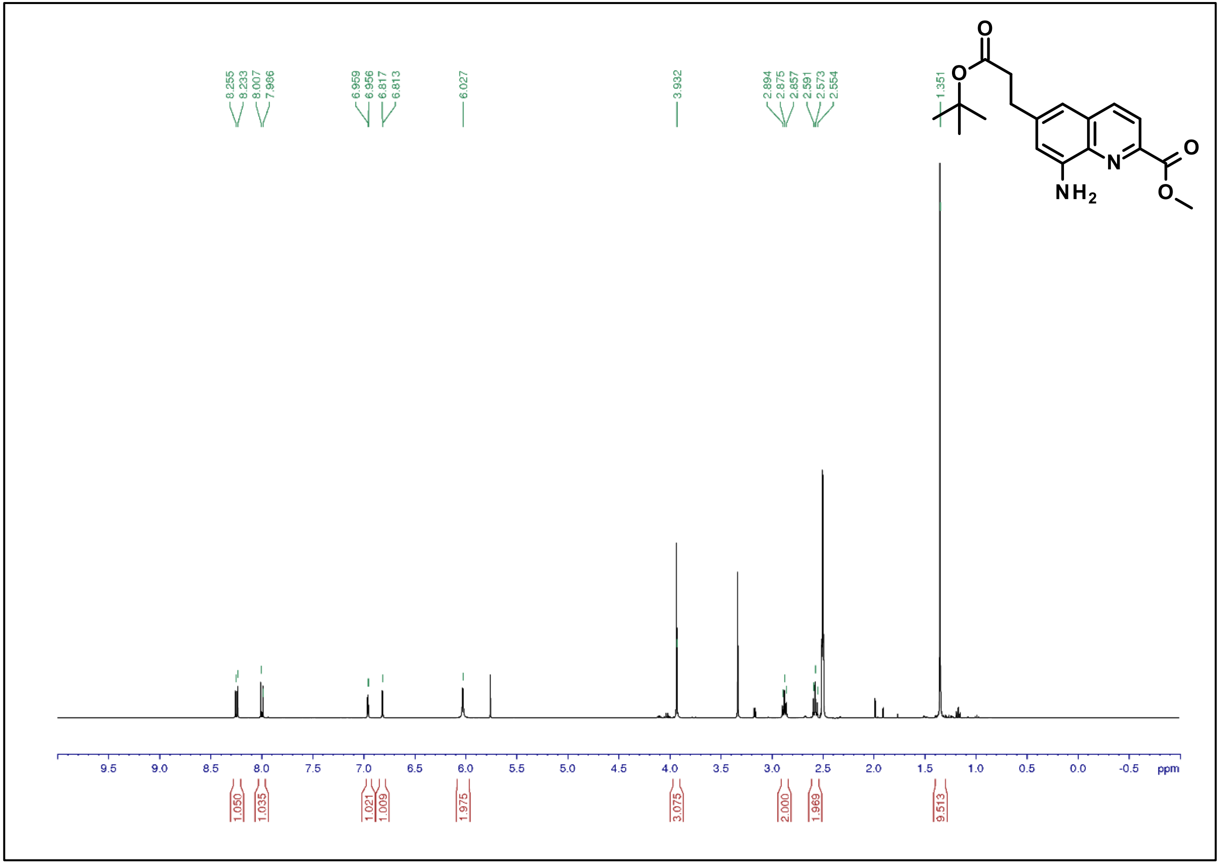


Figure S79. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **12e**.

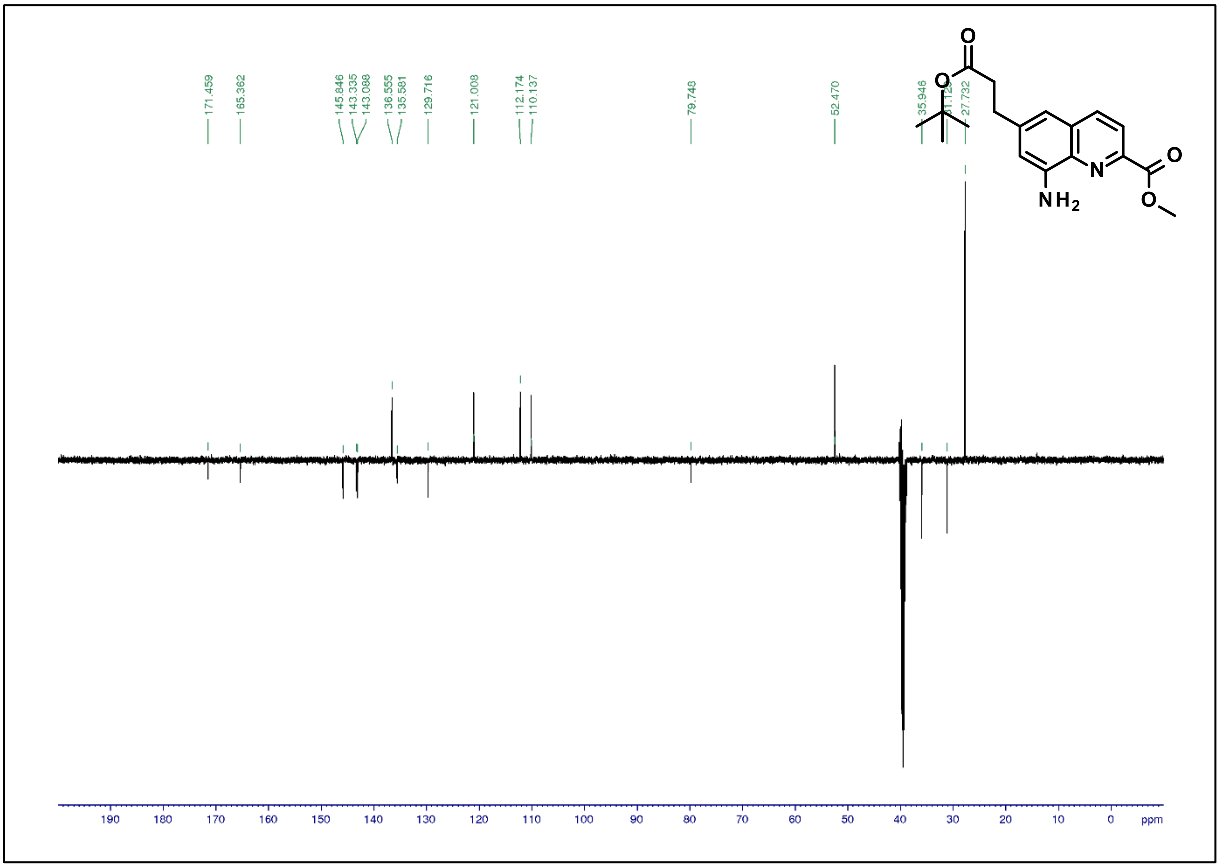


Figure S80. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **12e**.

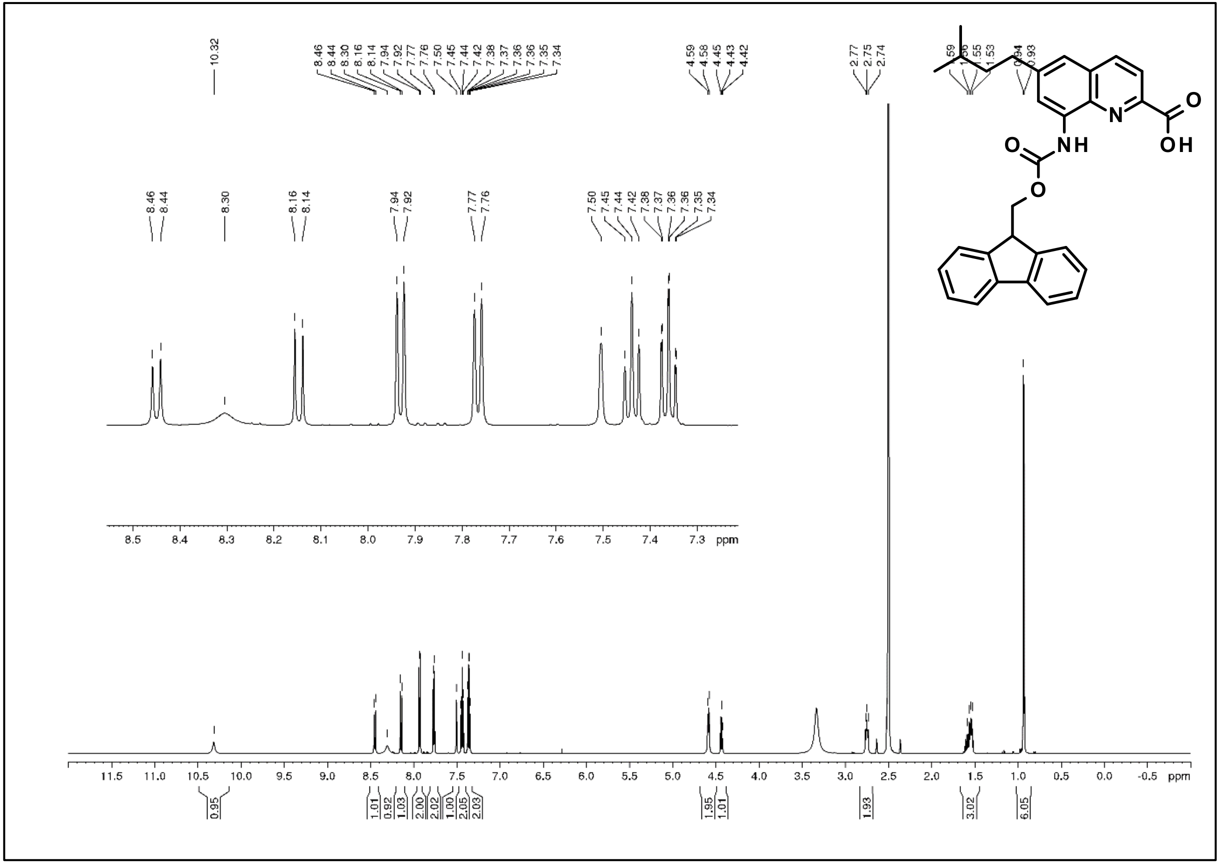


Figure S81. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13a**.

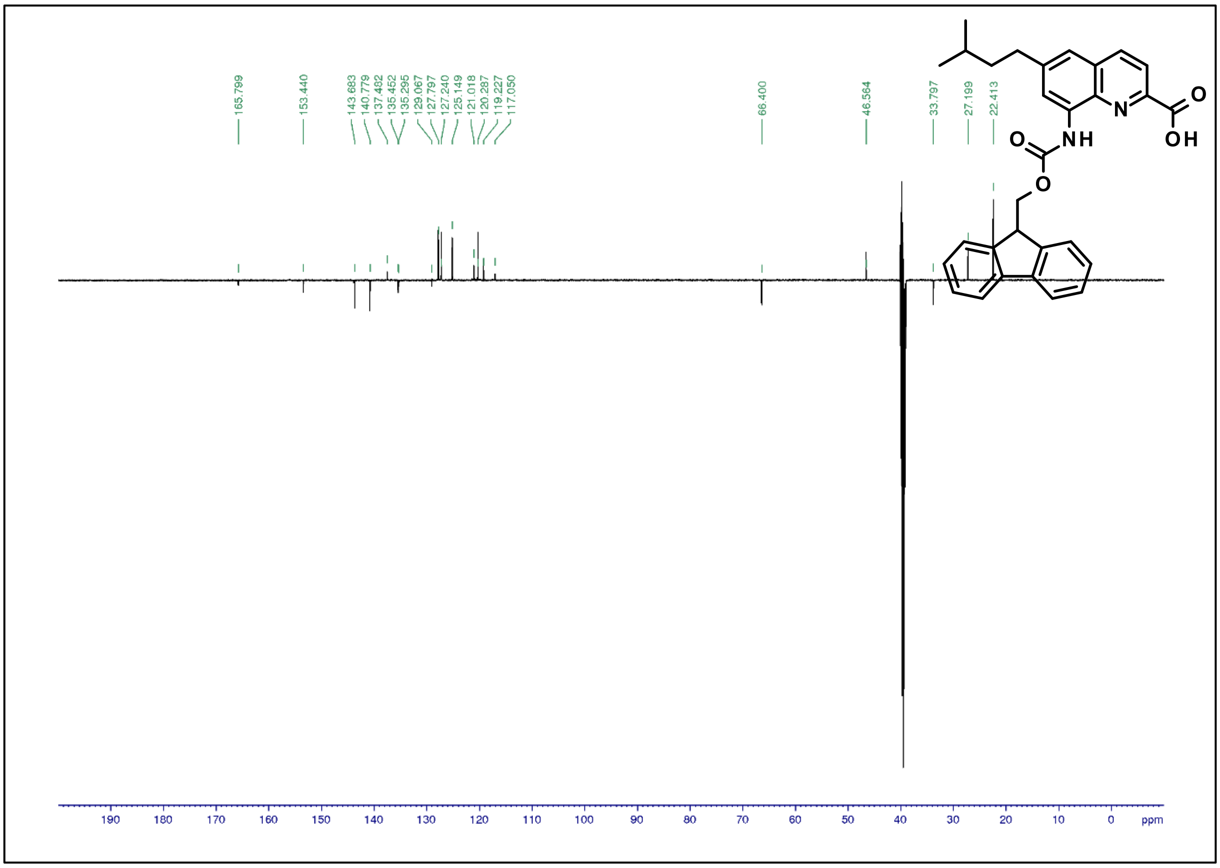


Figure S82. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13a**.

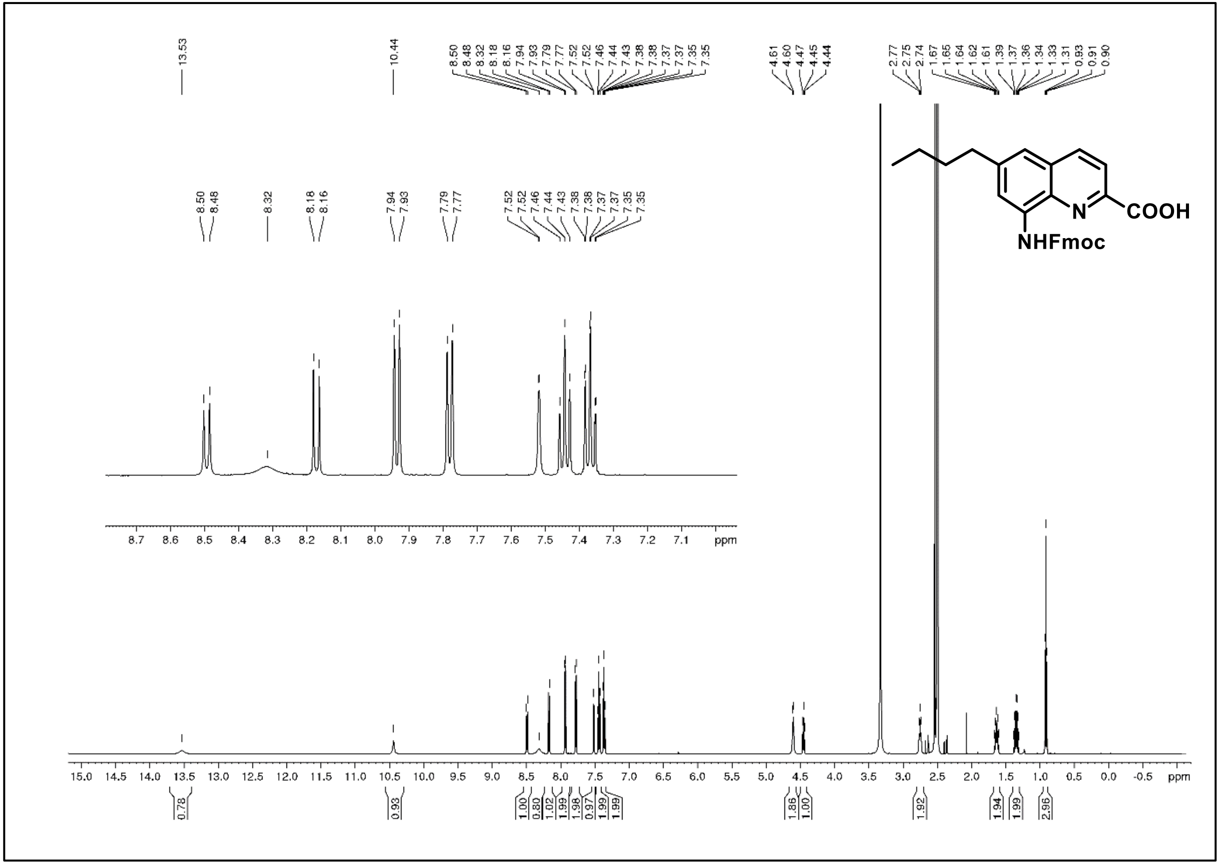


Figure S83. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13b**.

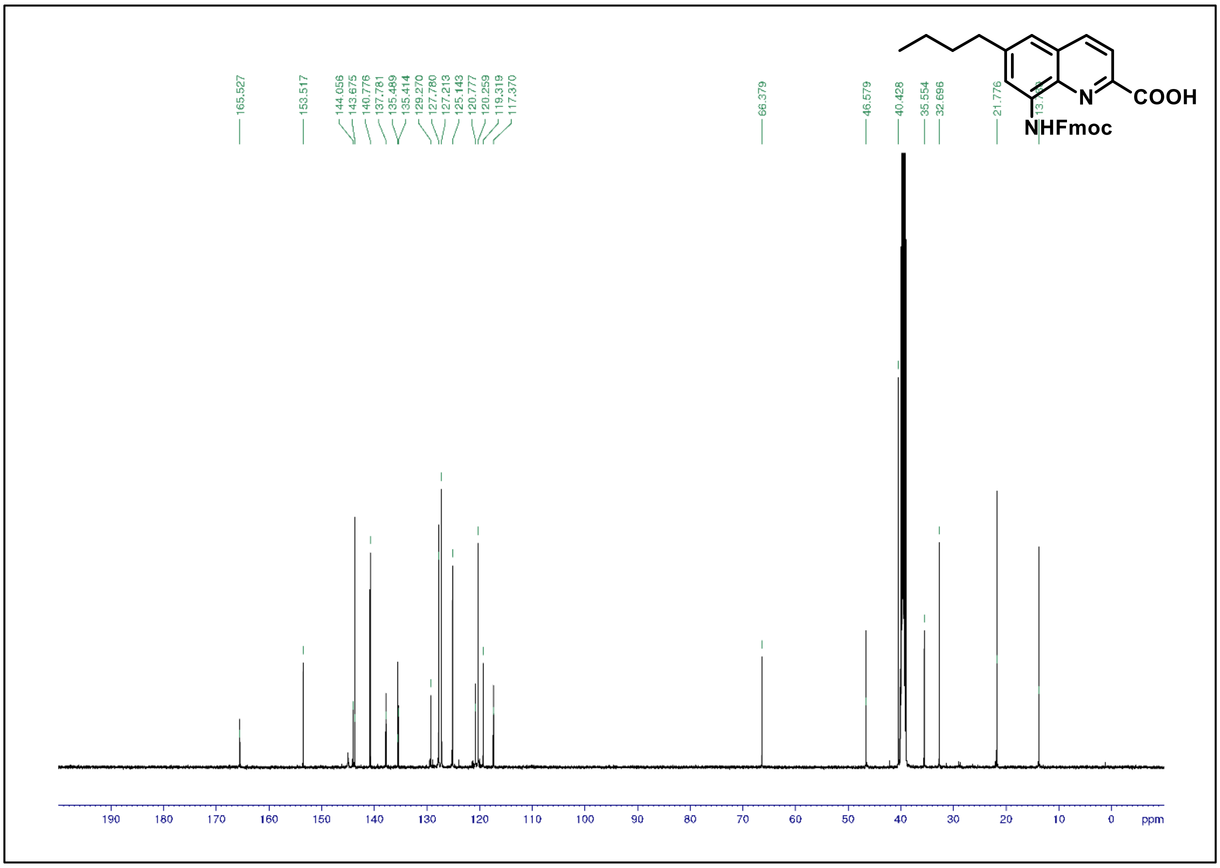


Figure S84. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13b**.

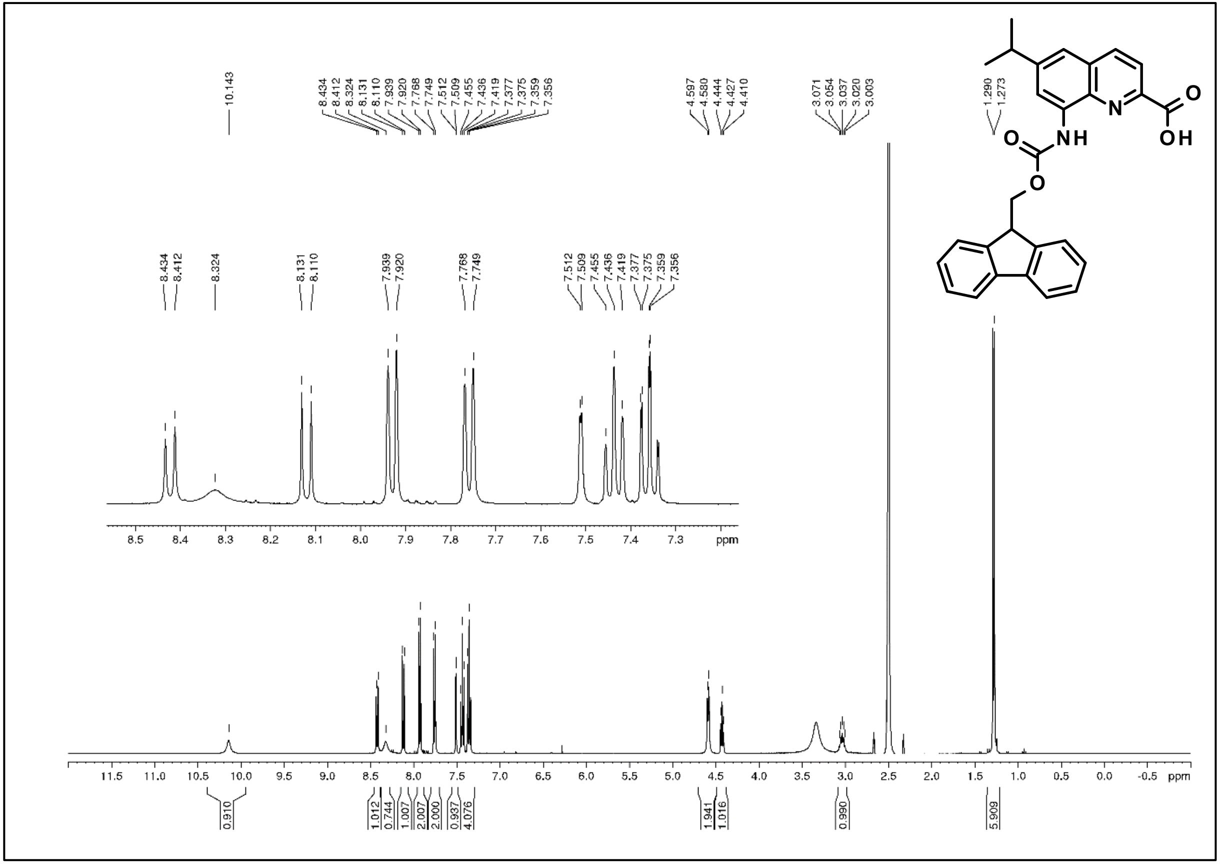


Figure S85. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13c**.

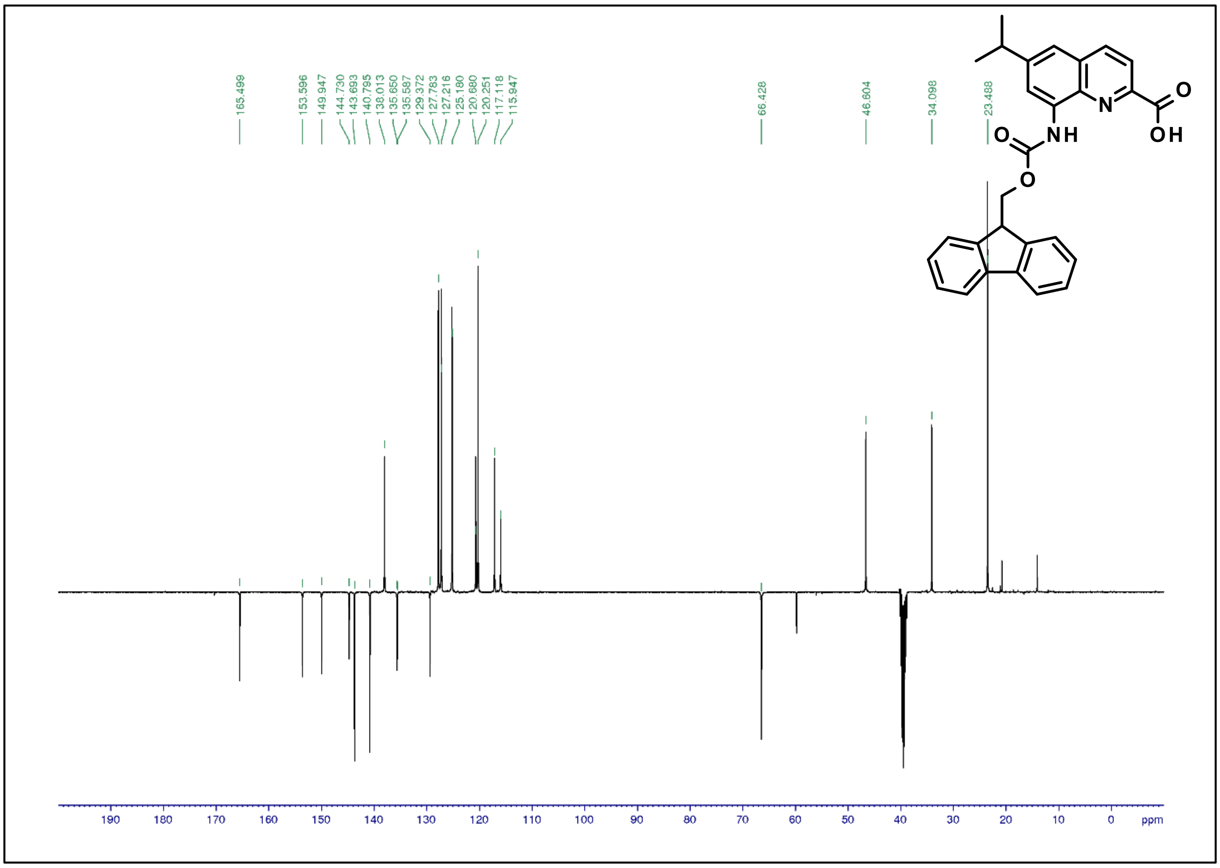


Figure S86. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13c**.

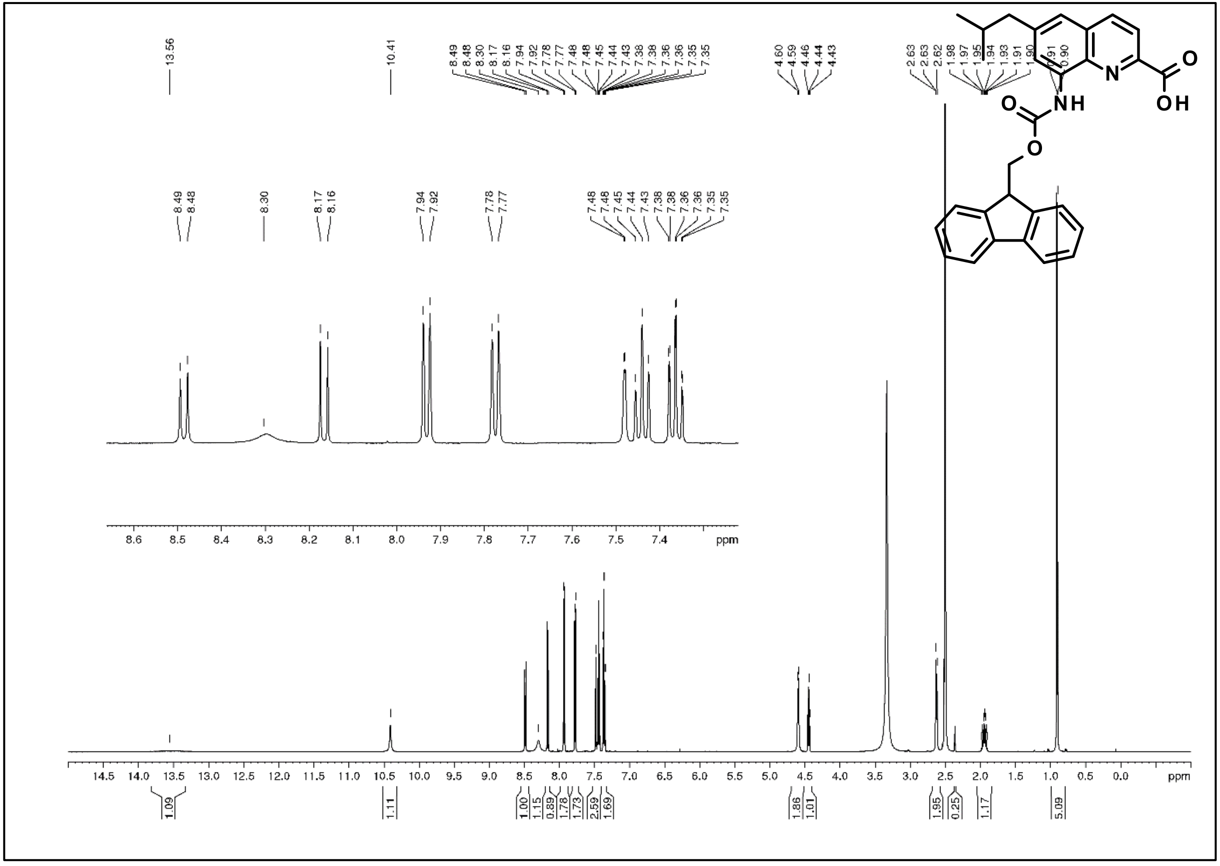


Figure S87. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13d**.

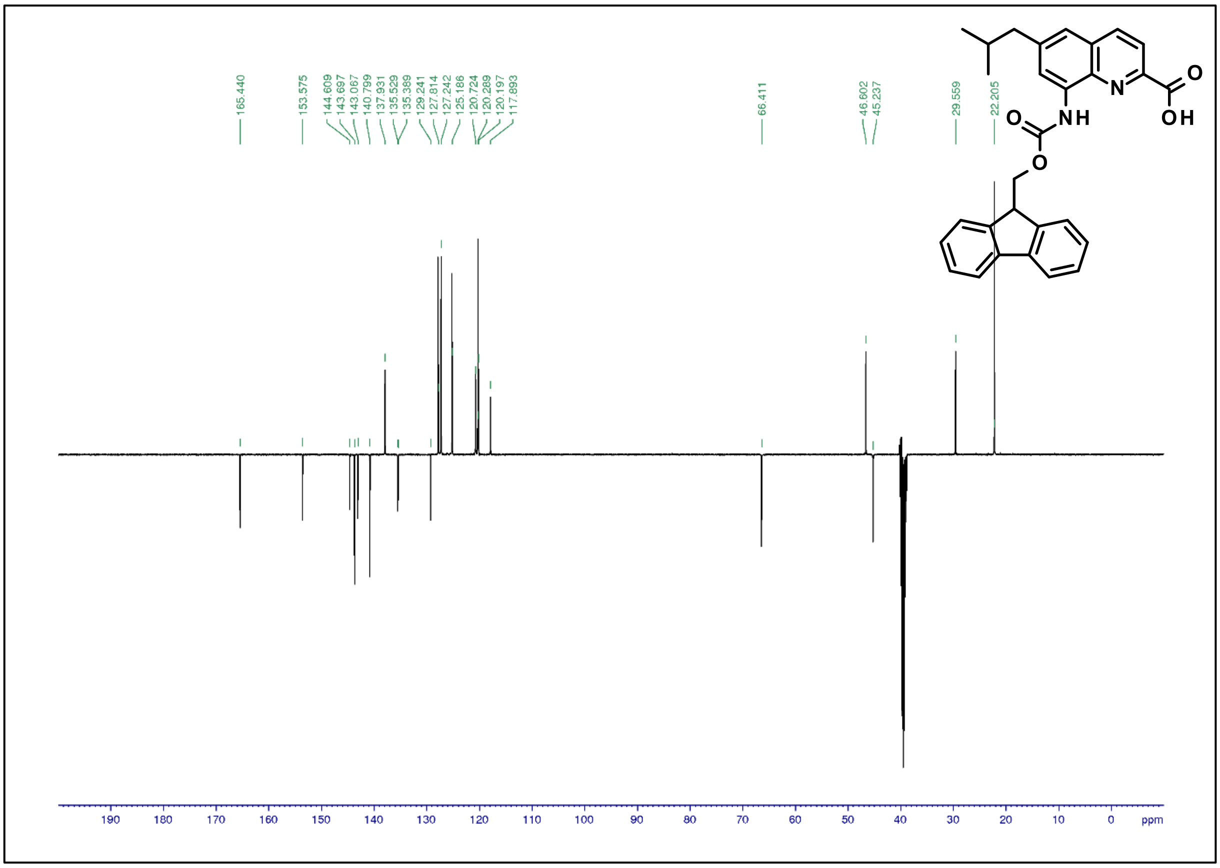


Figure S88. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13d**.

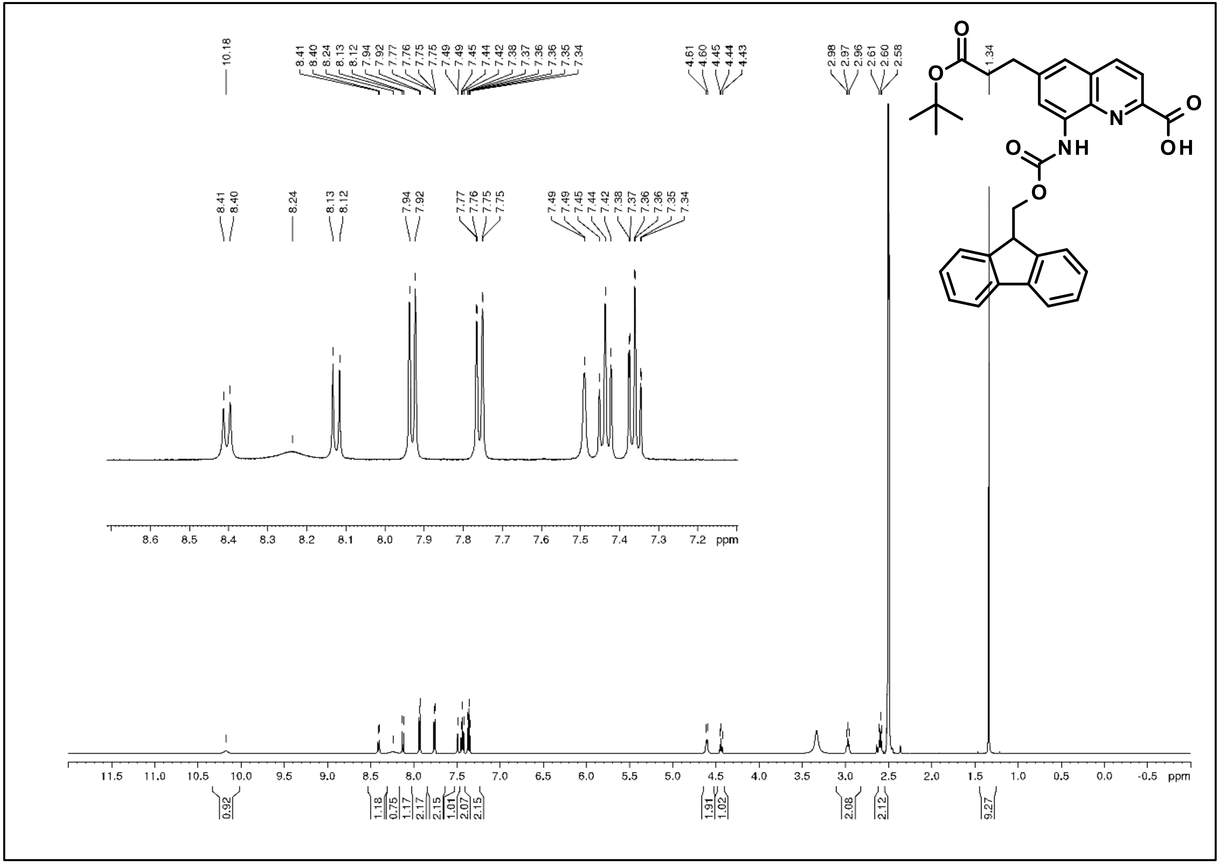


Figure S89. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13e**.

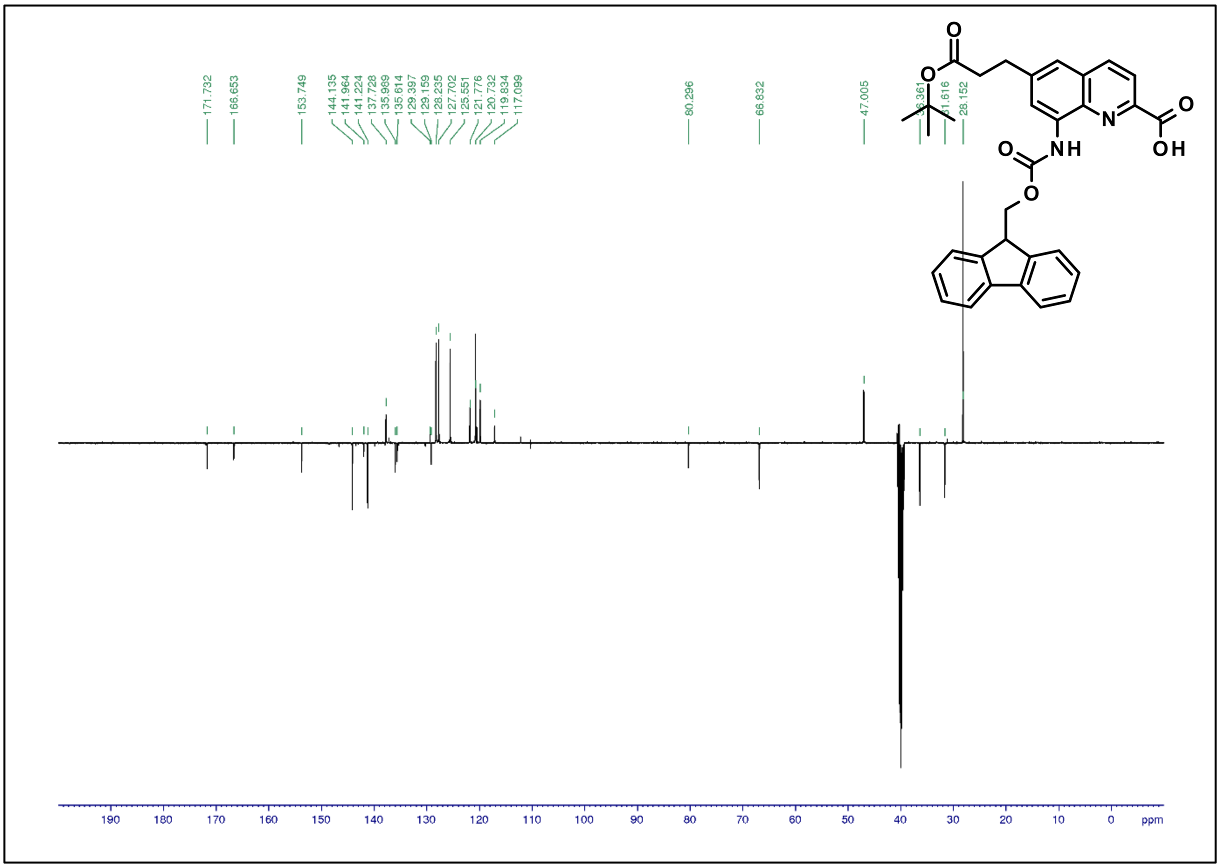


Figure S90. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13e**.

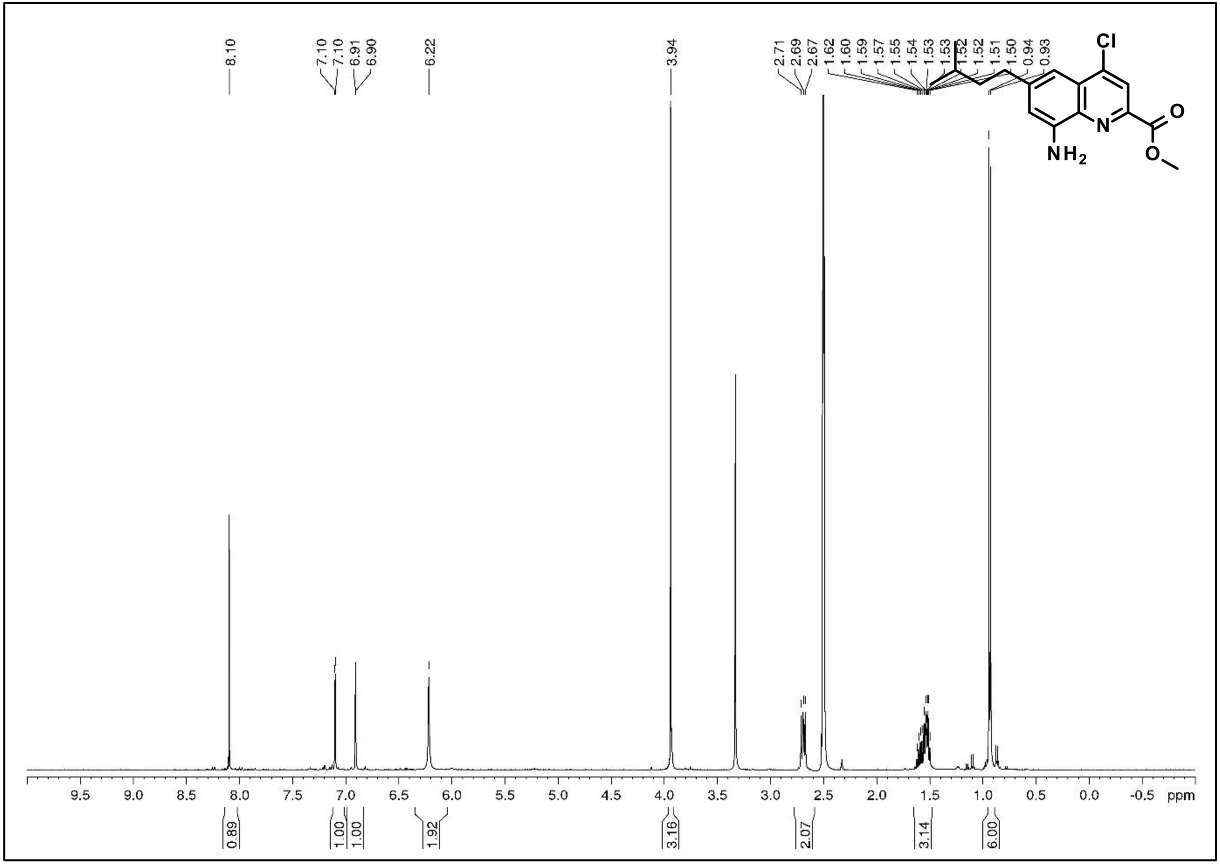


Figure S91. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **13f**.

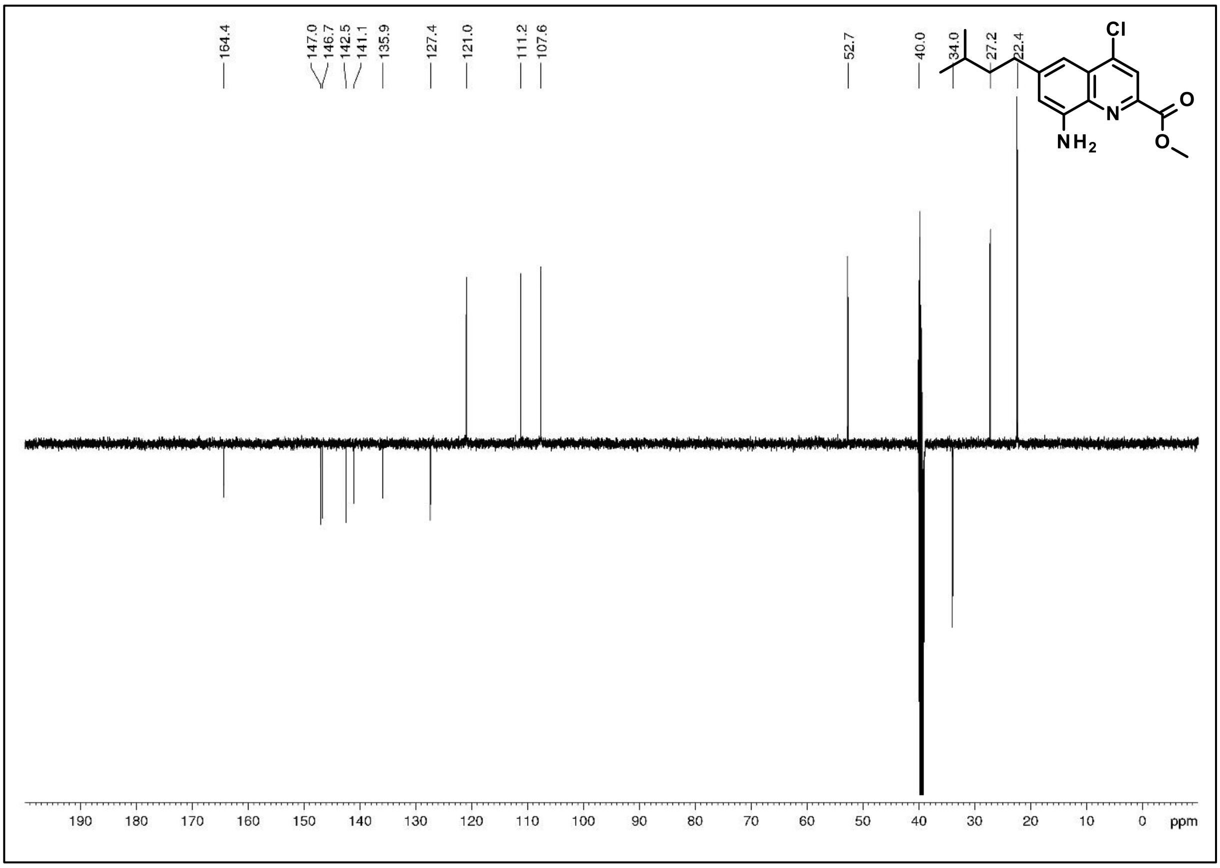


Figure S92. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **13f**.

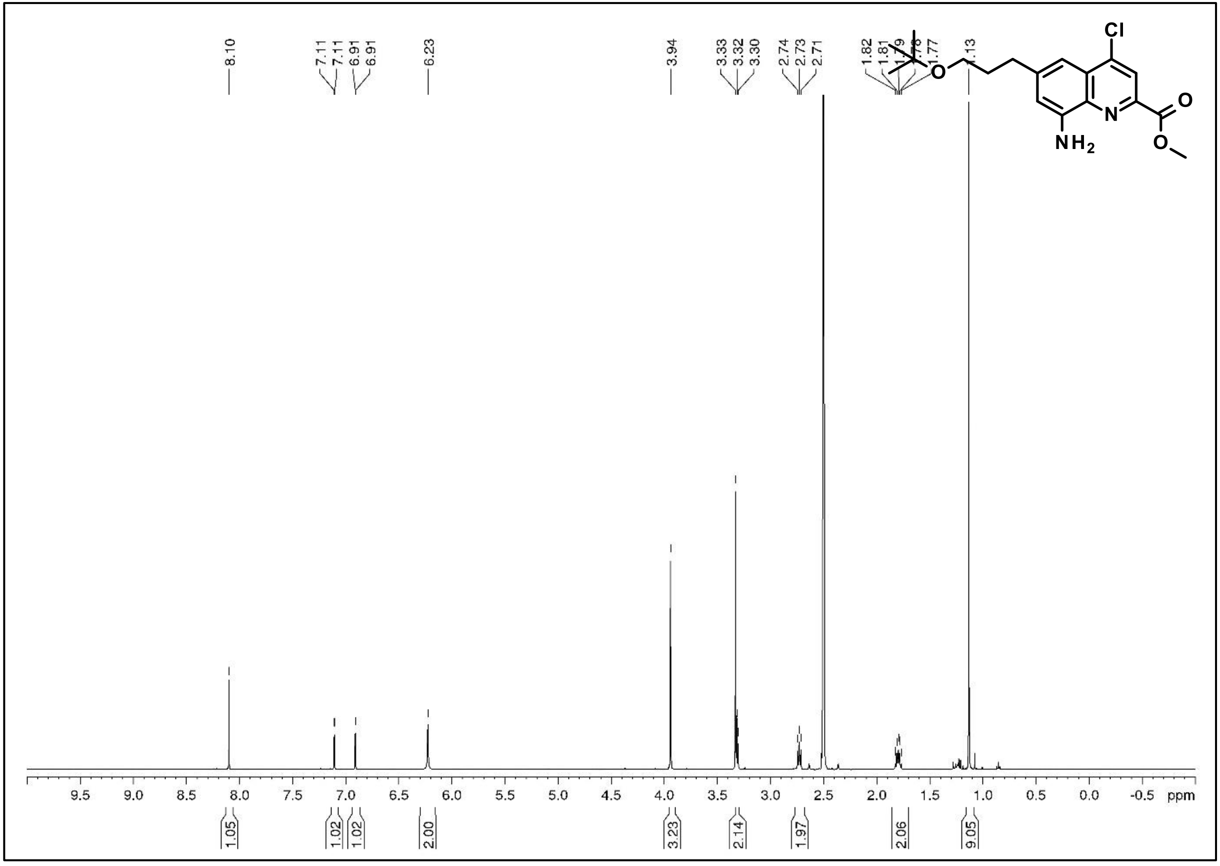


Figure S93. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **15b**.

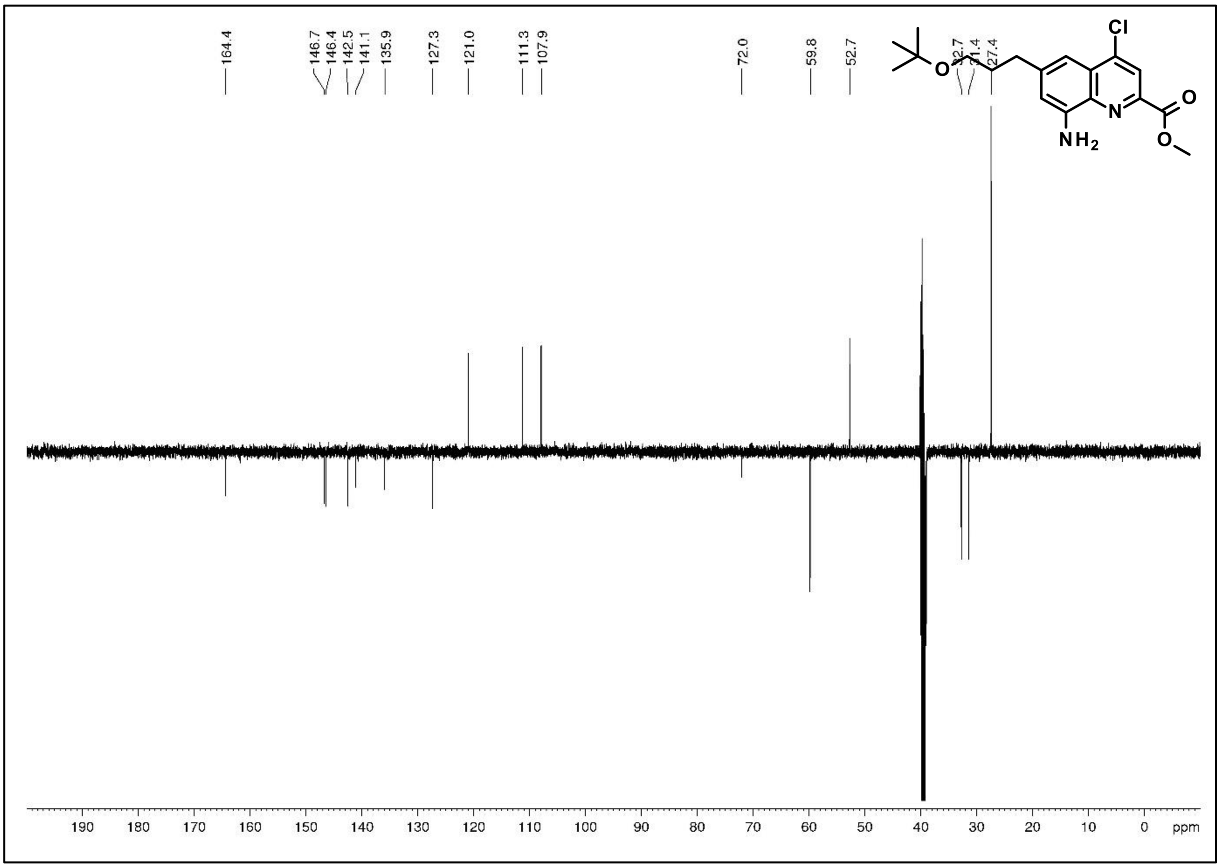


Figure S94. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **15b**.

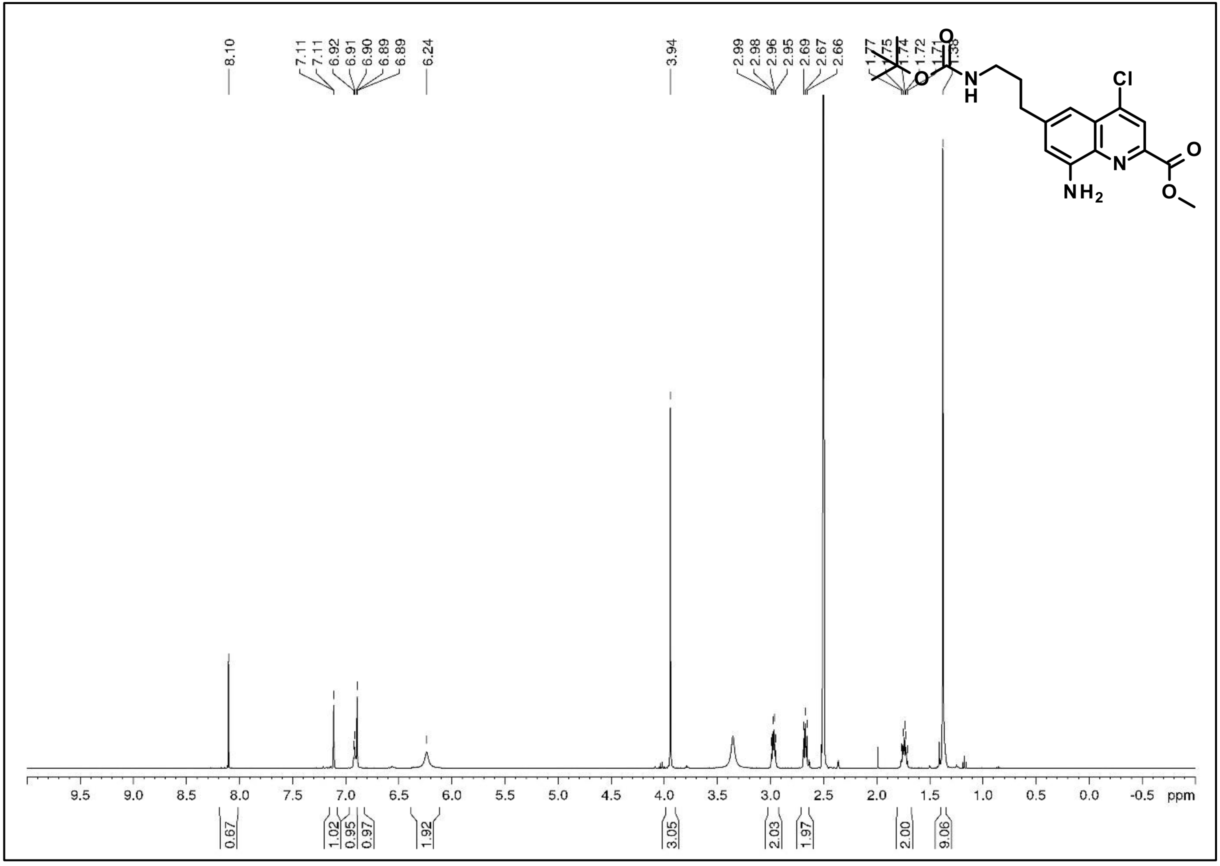


Figure S95. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **15c**.

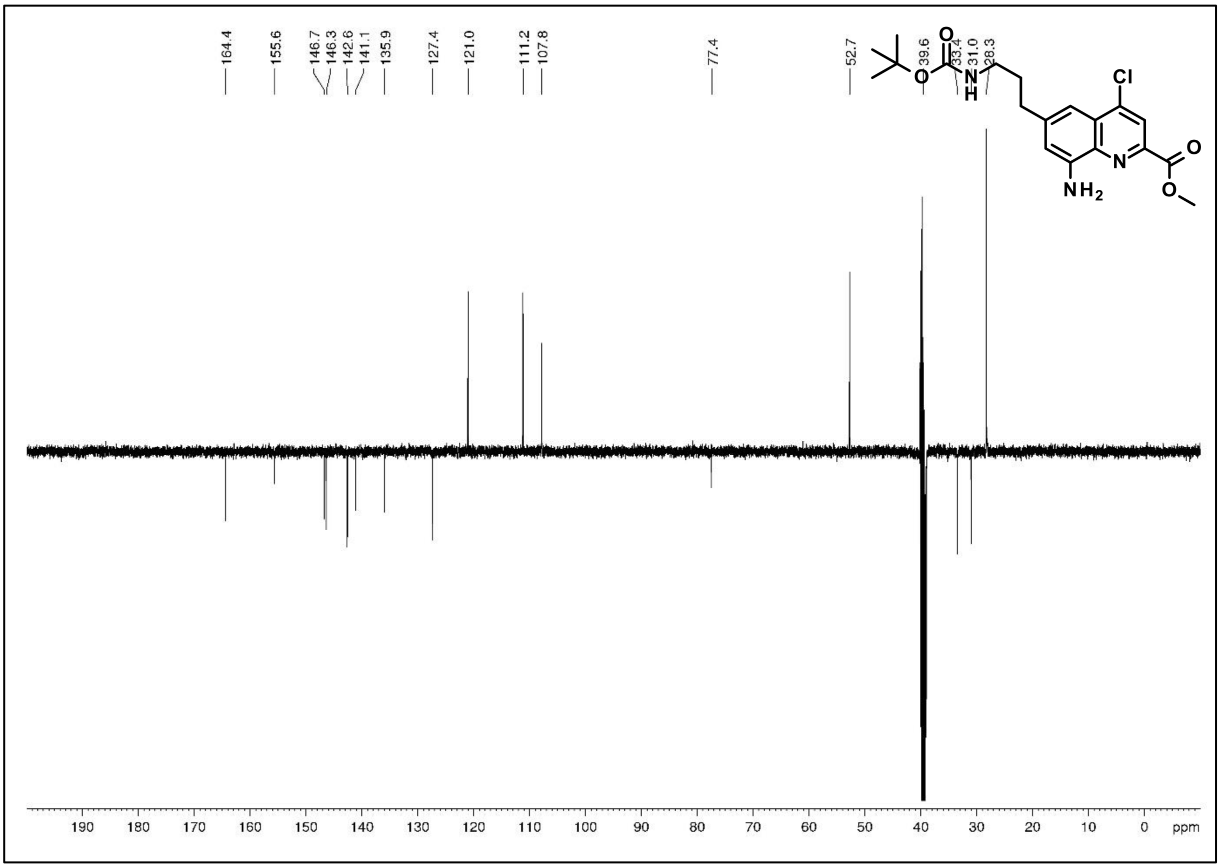


Figure S96. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **15c**.

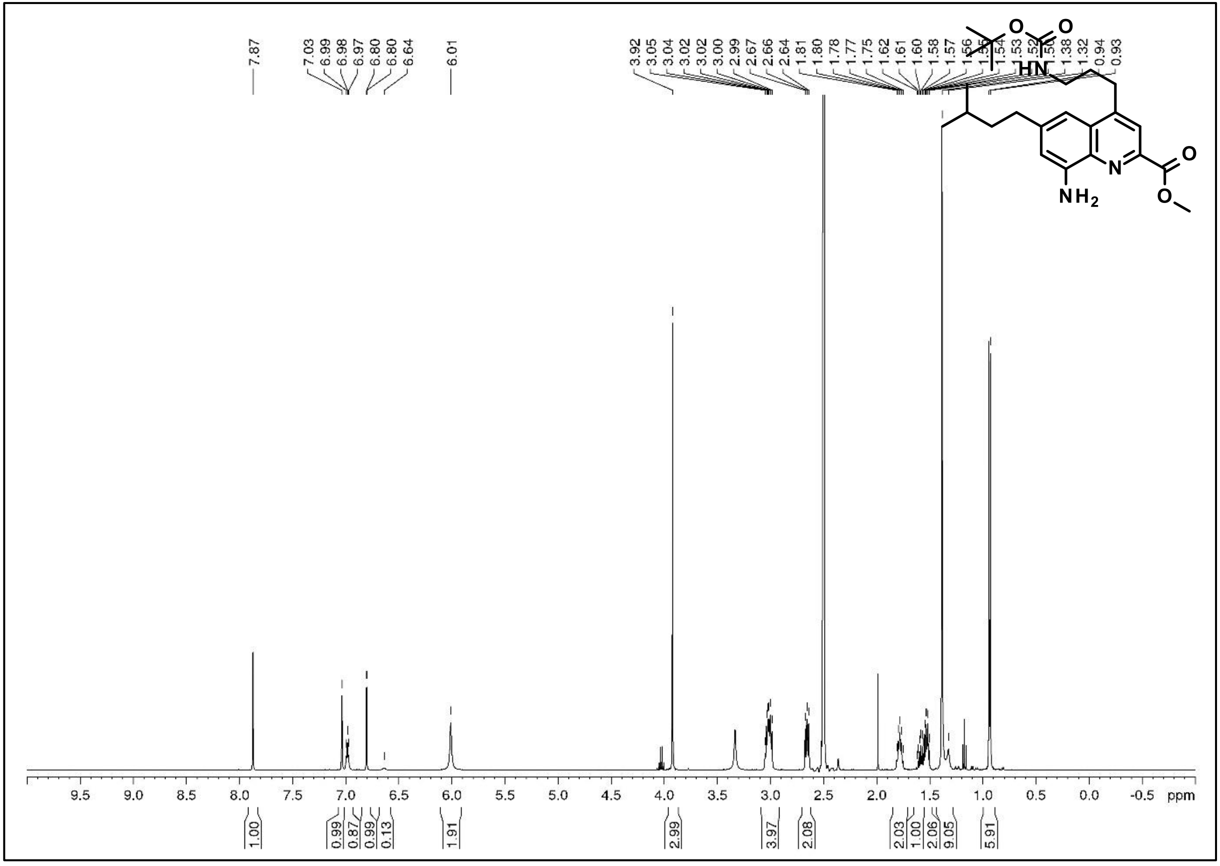


Figure S97. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **16a**.

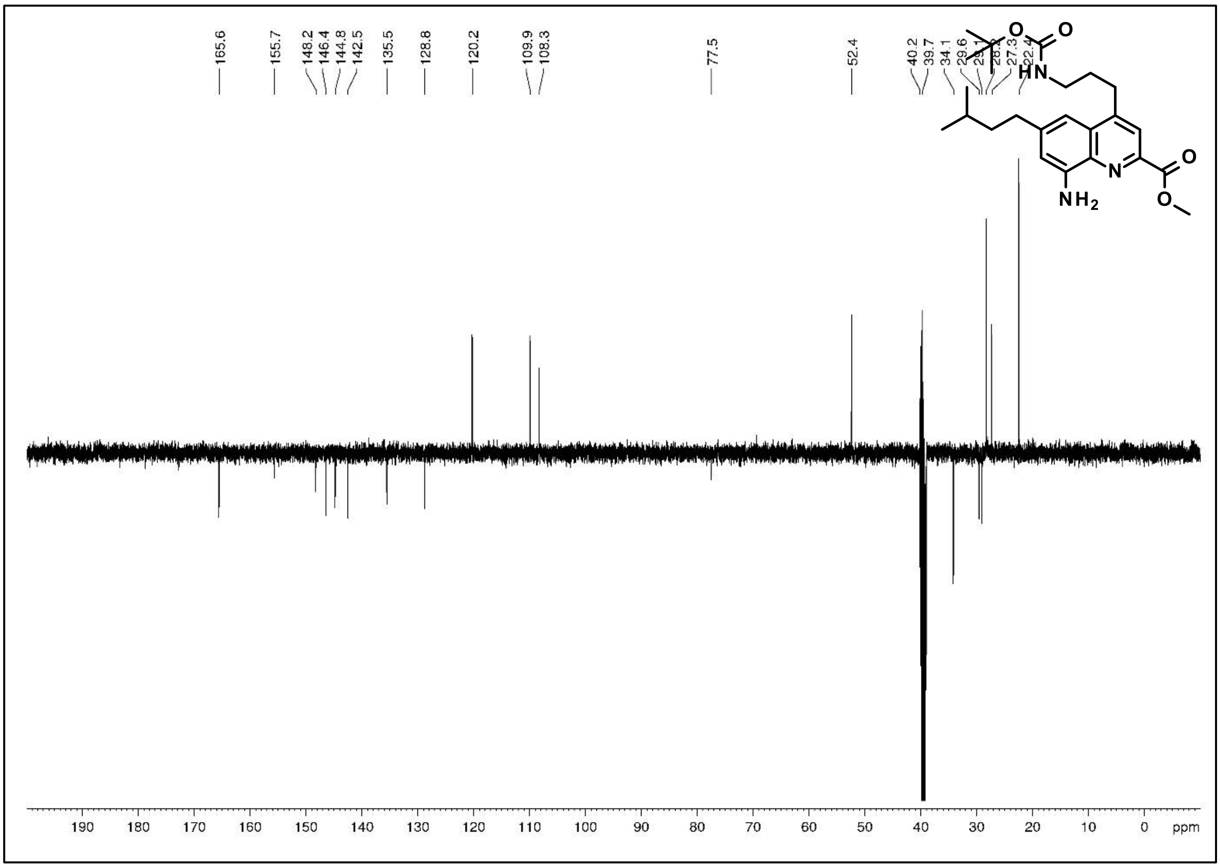


Figure S98. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **16a**.

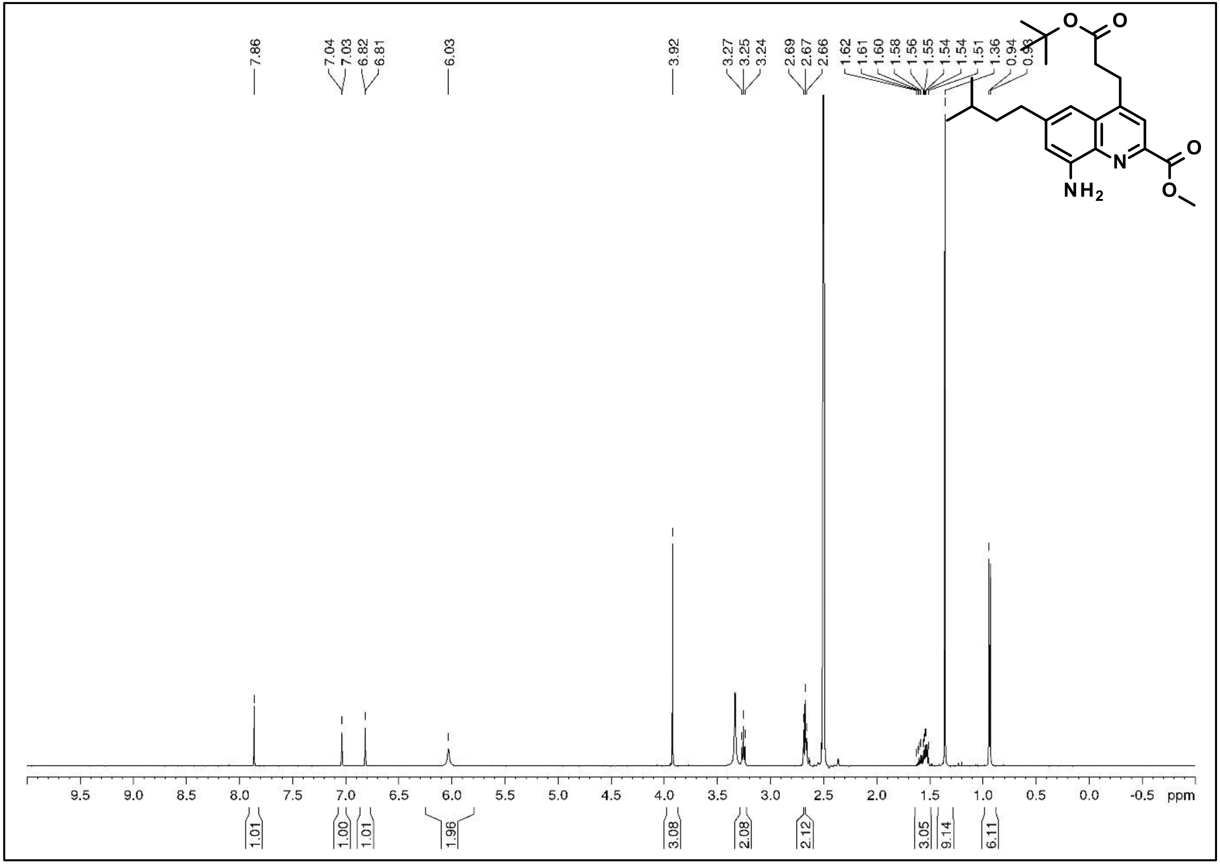


Figure S99. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **16b**.

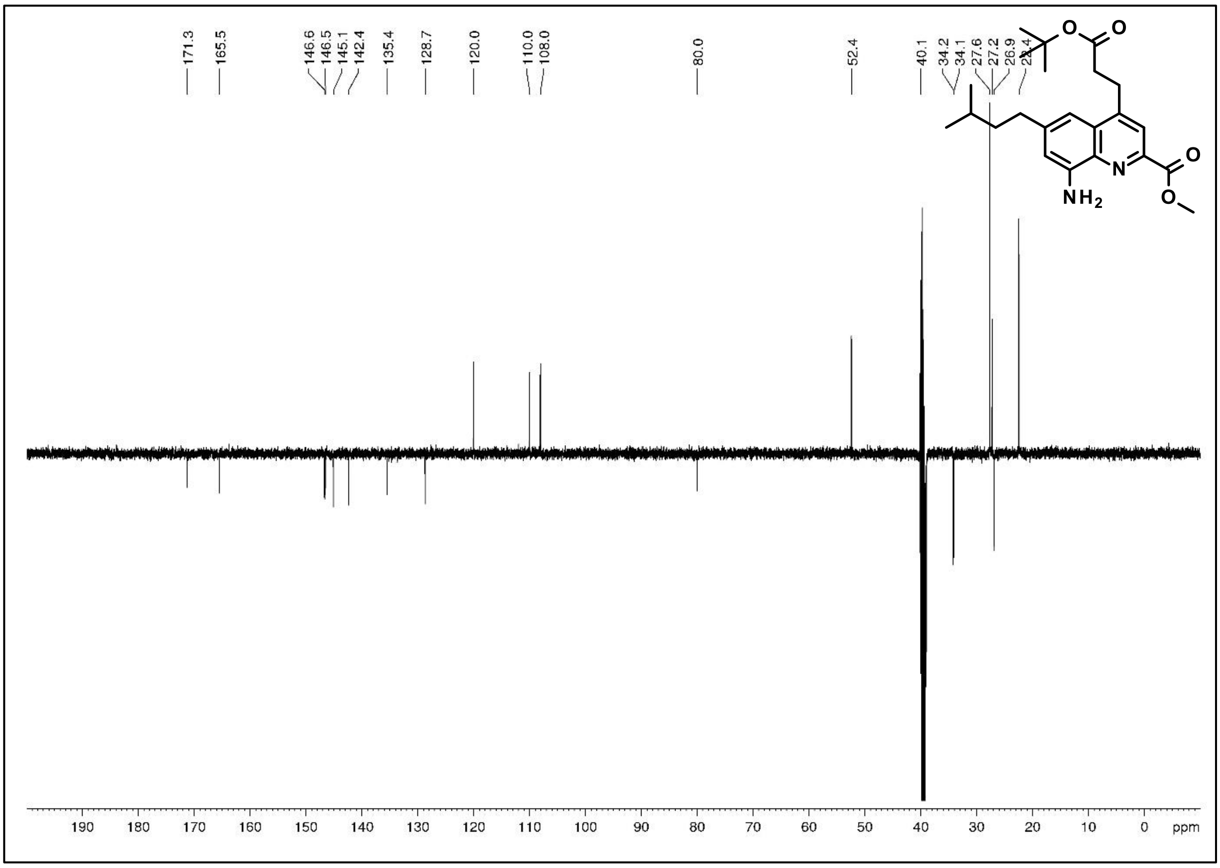


Figure S100. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **16b**.

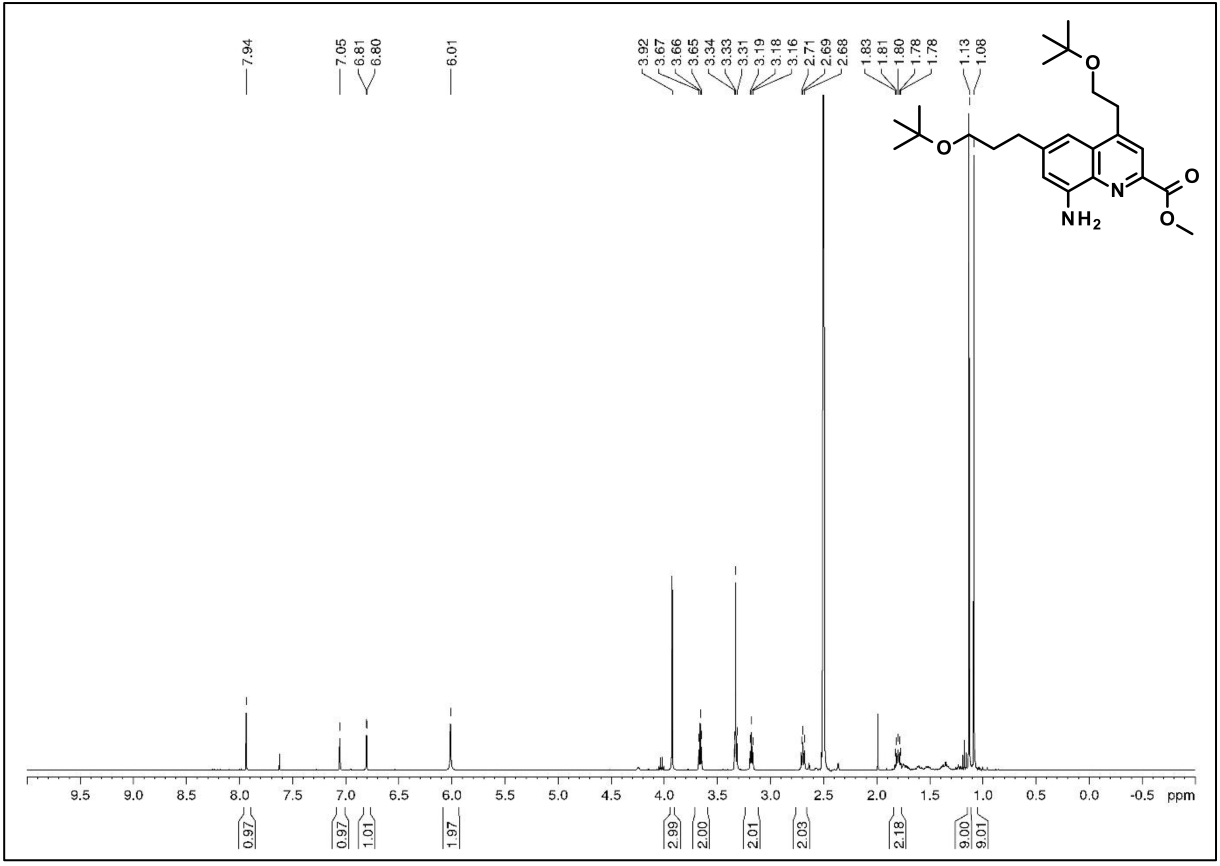


Figure S101. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **16c**.

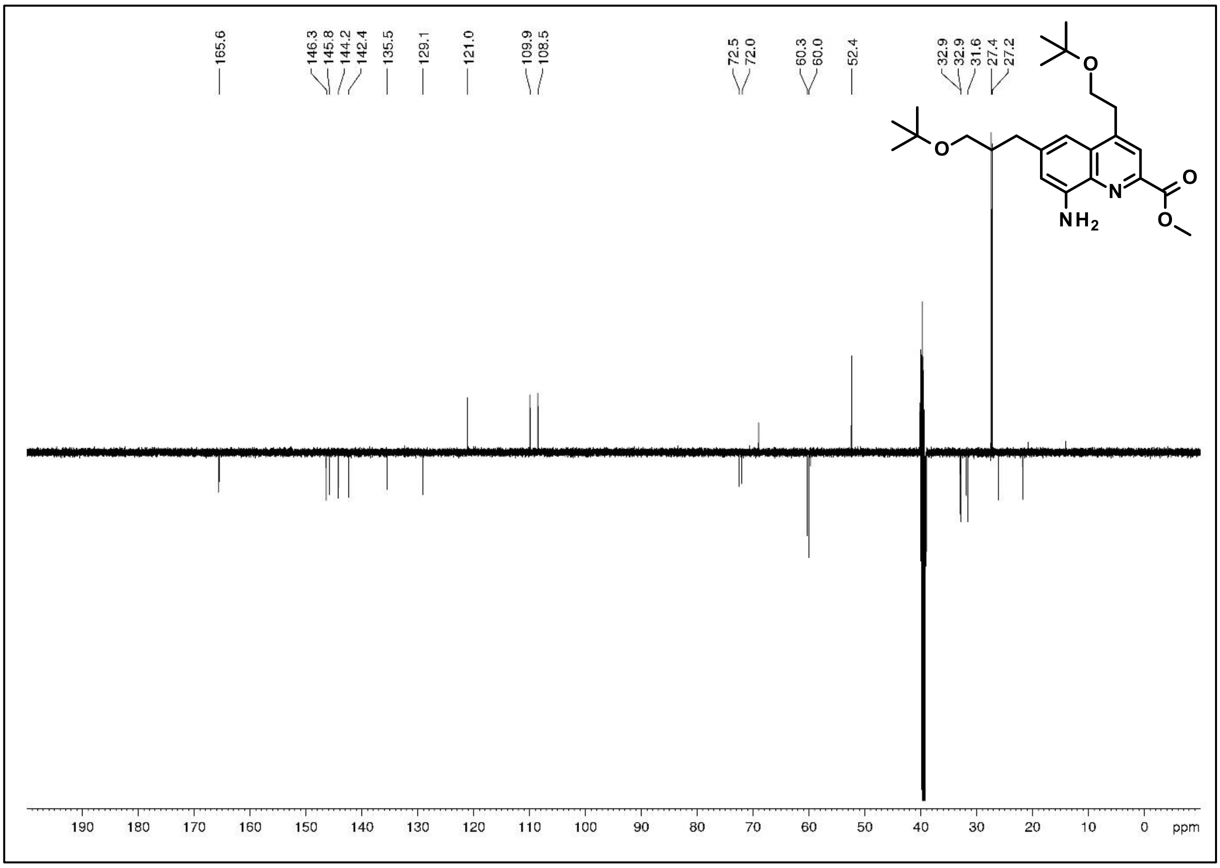


Figure S102. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **16c**.

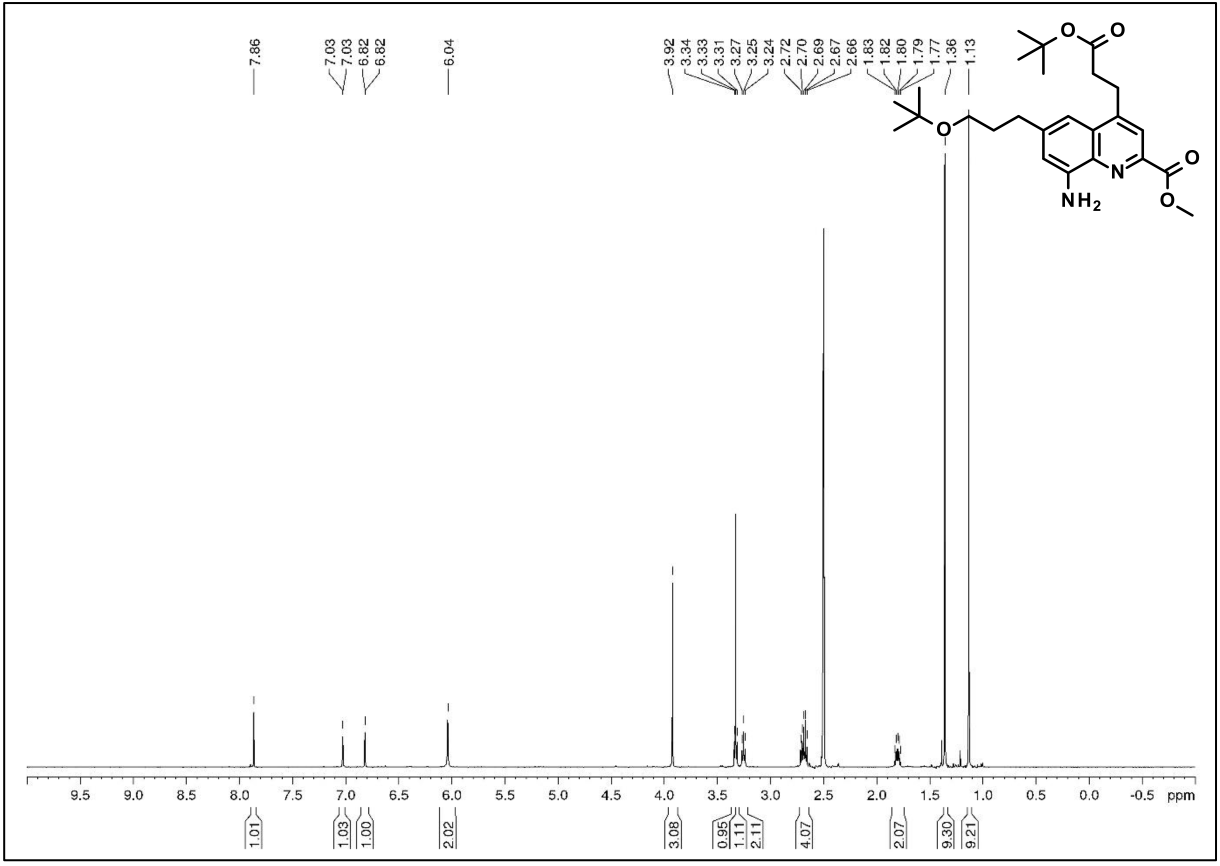


Figure S103. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **16d**.

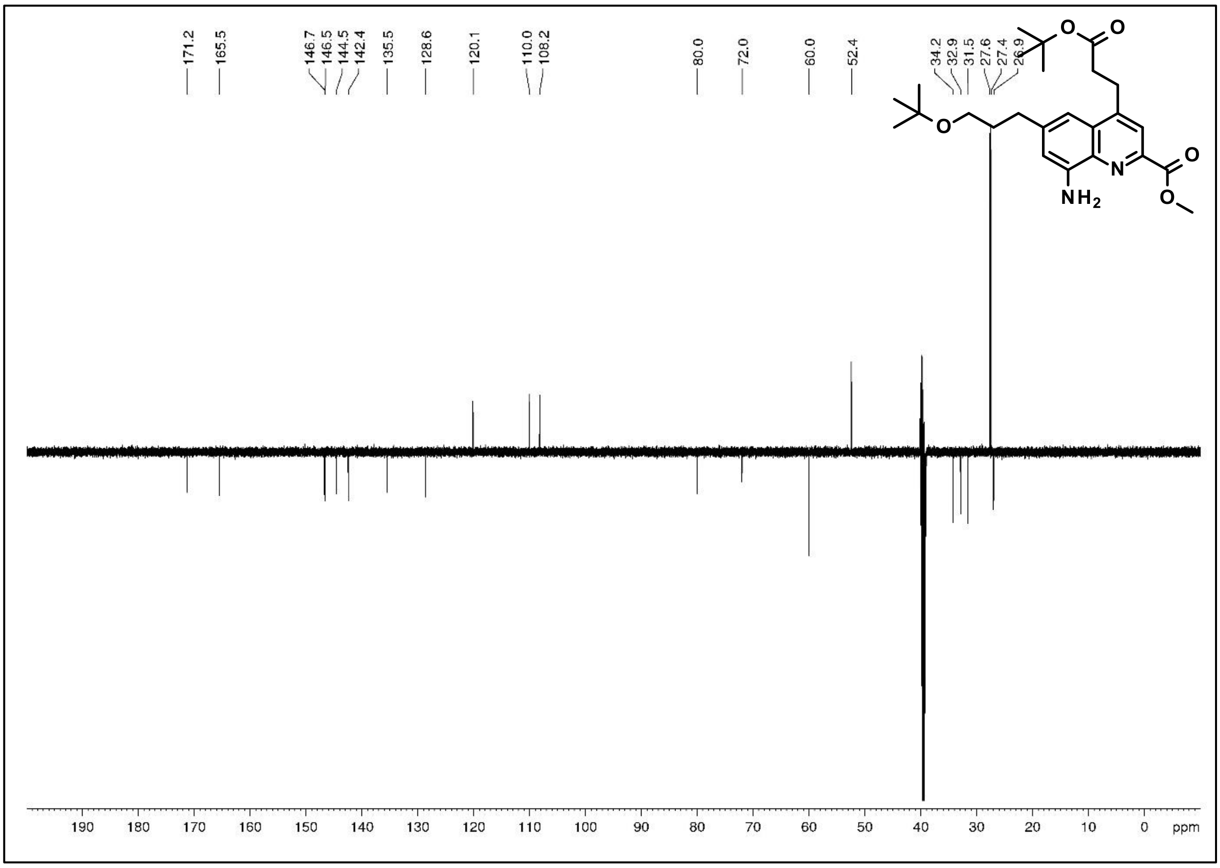


Figure S104. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **16d**.

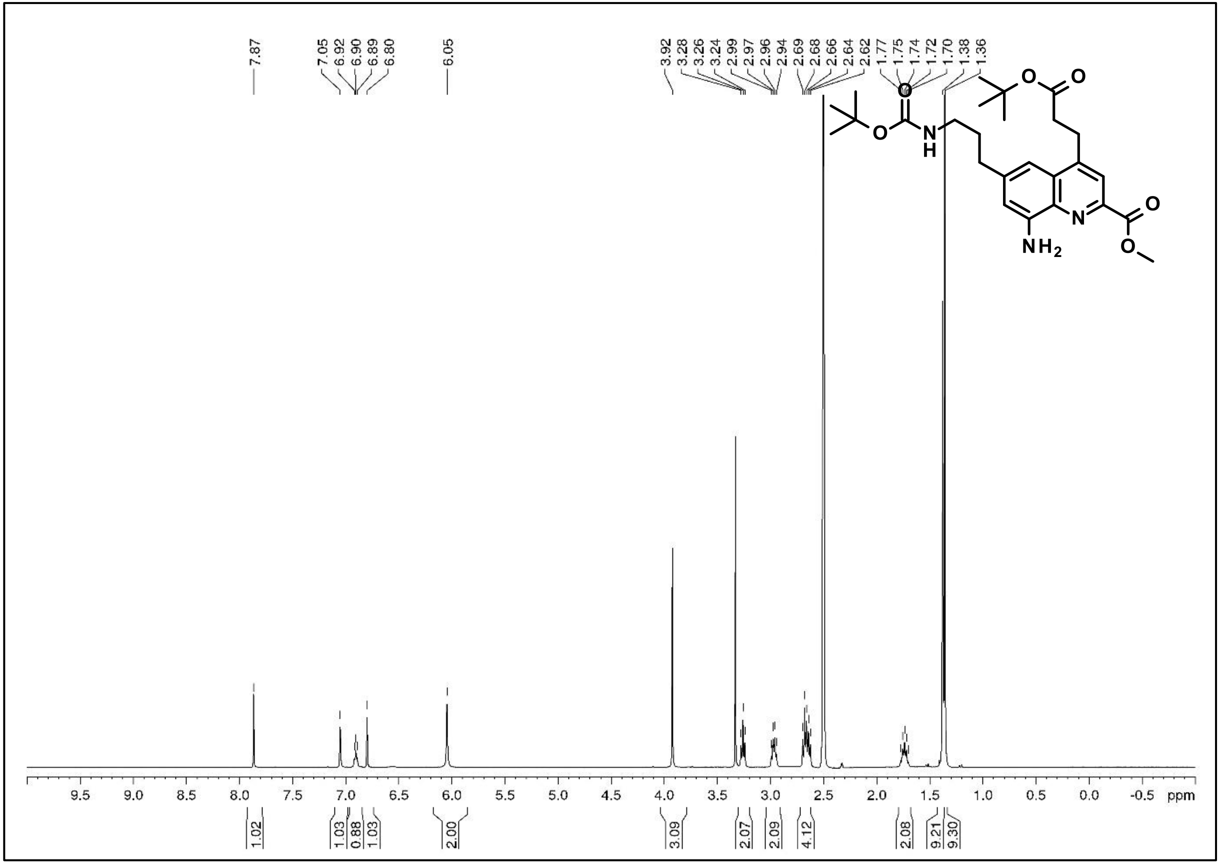


Figure S105. ^{1}H NMR (400 MHz, DMSO-d$_6$) of compound **16e**.

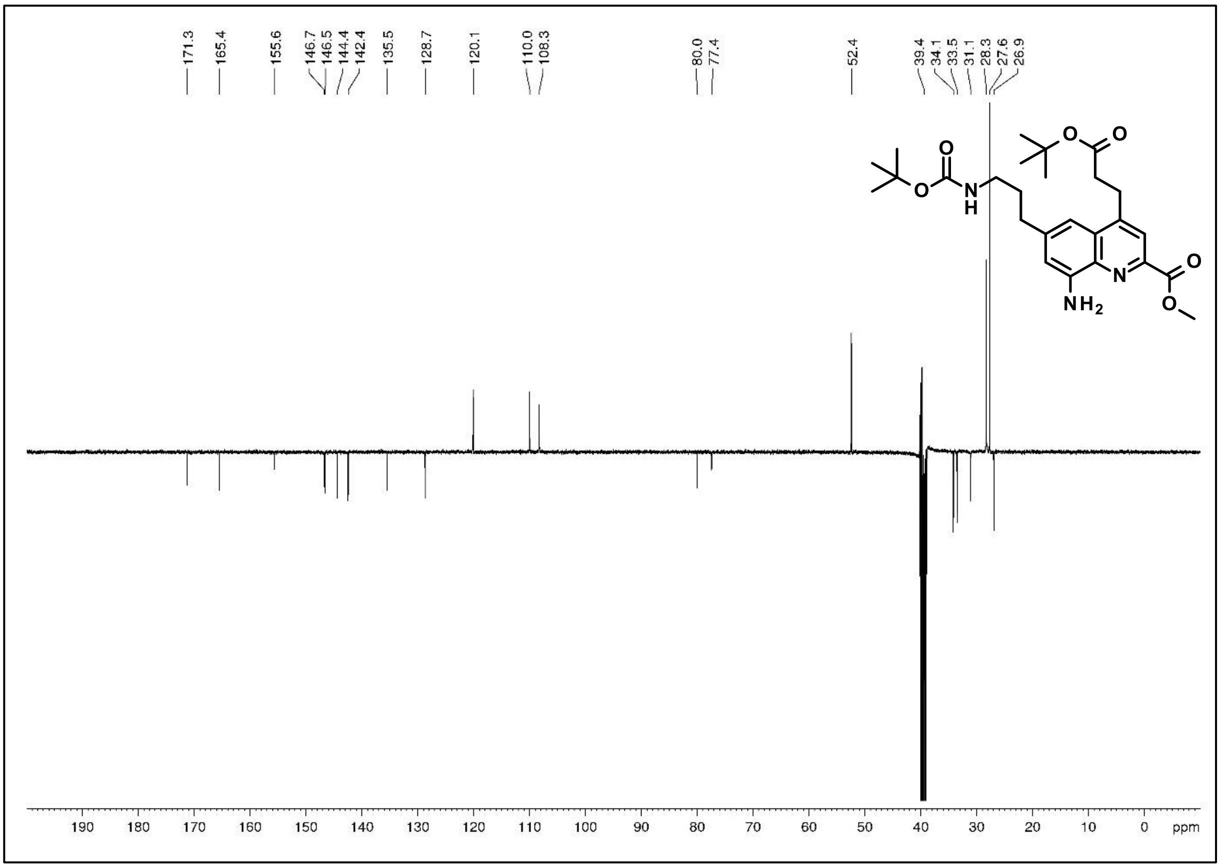


Figure S106. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **16e**.

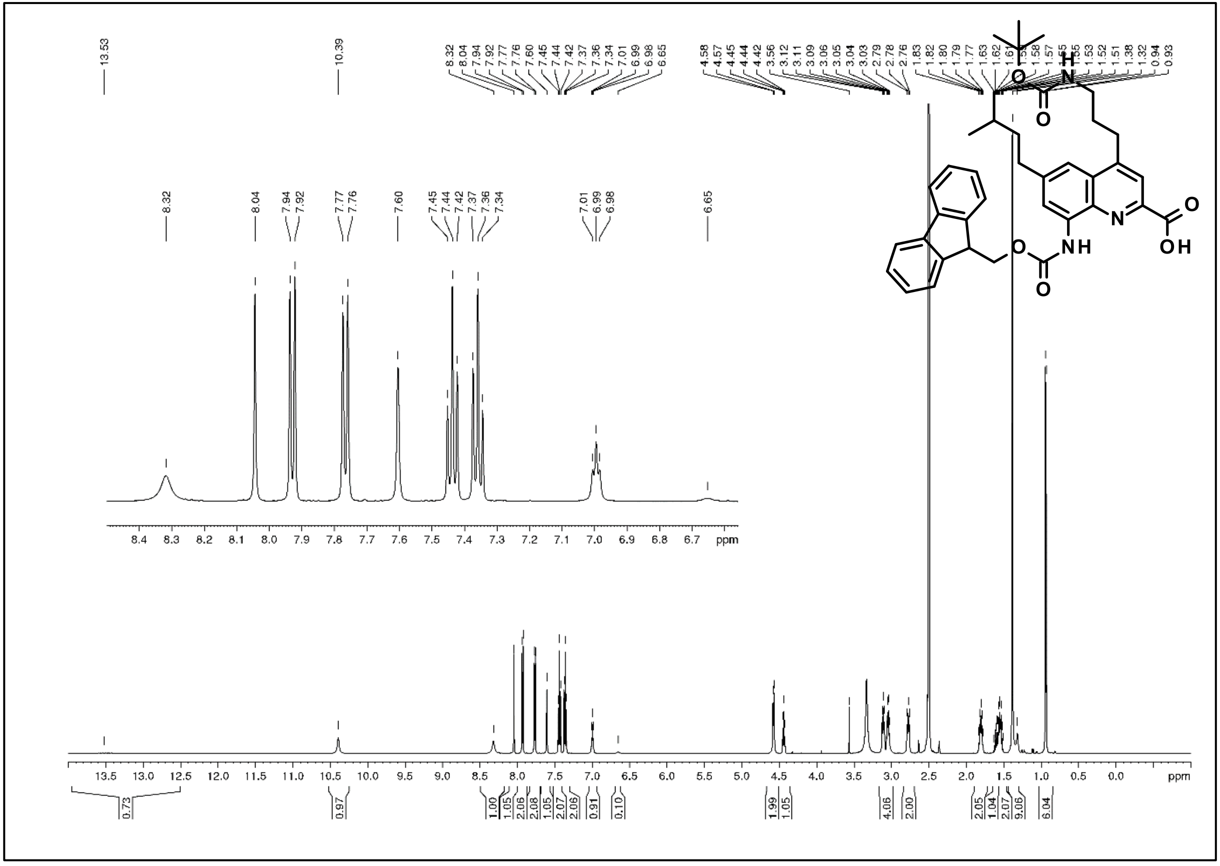


Figure S107. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **17a**.

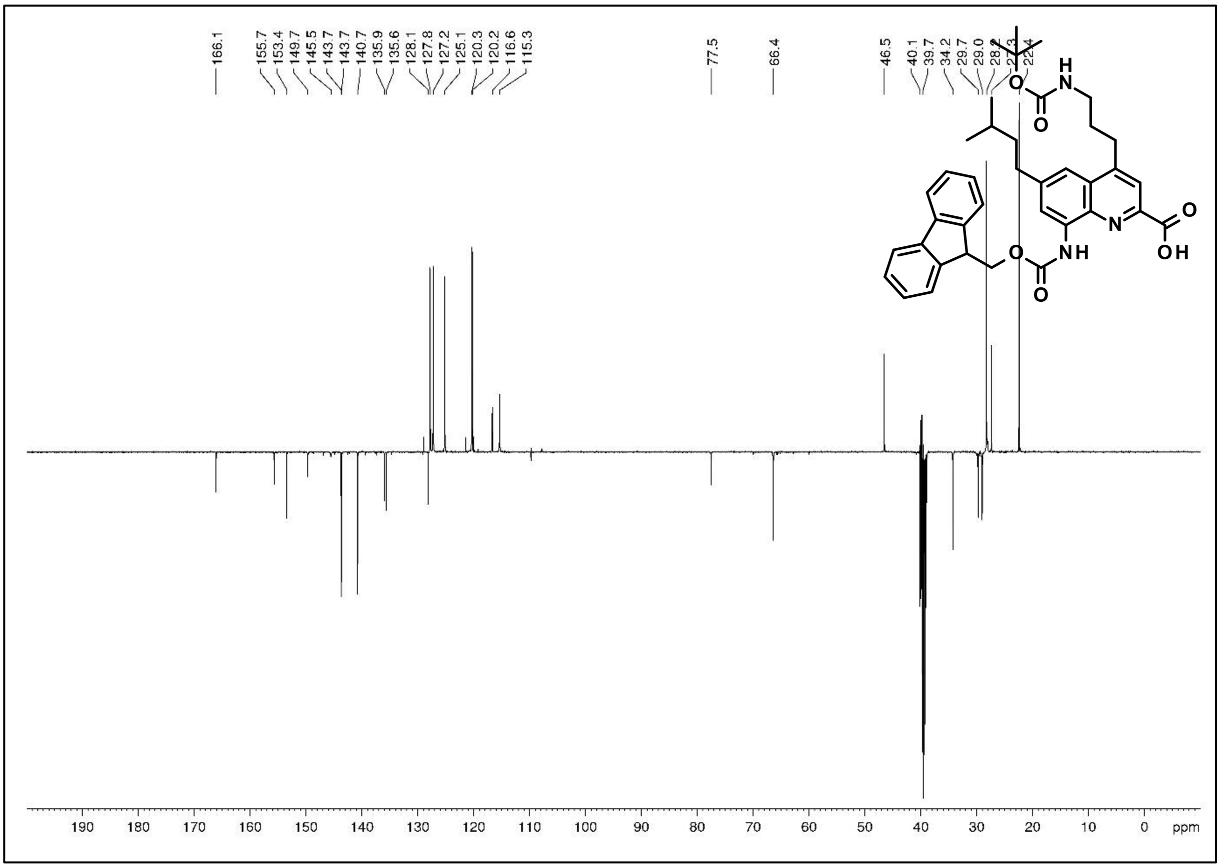


Figure S108. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **17a**.

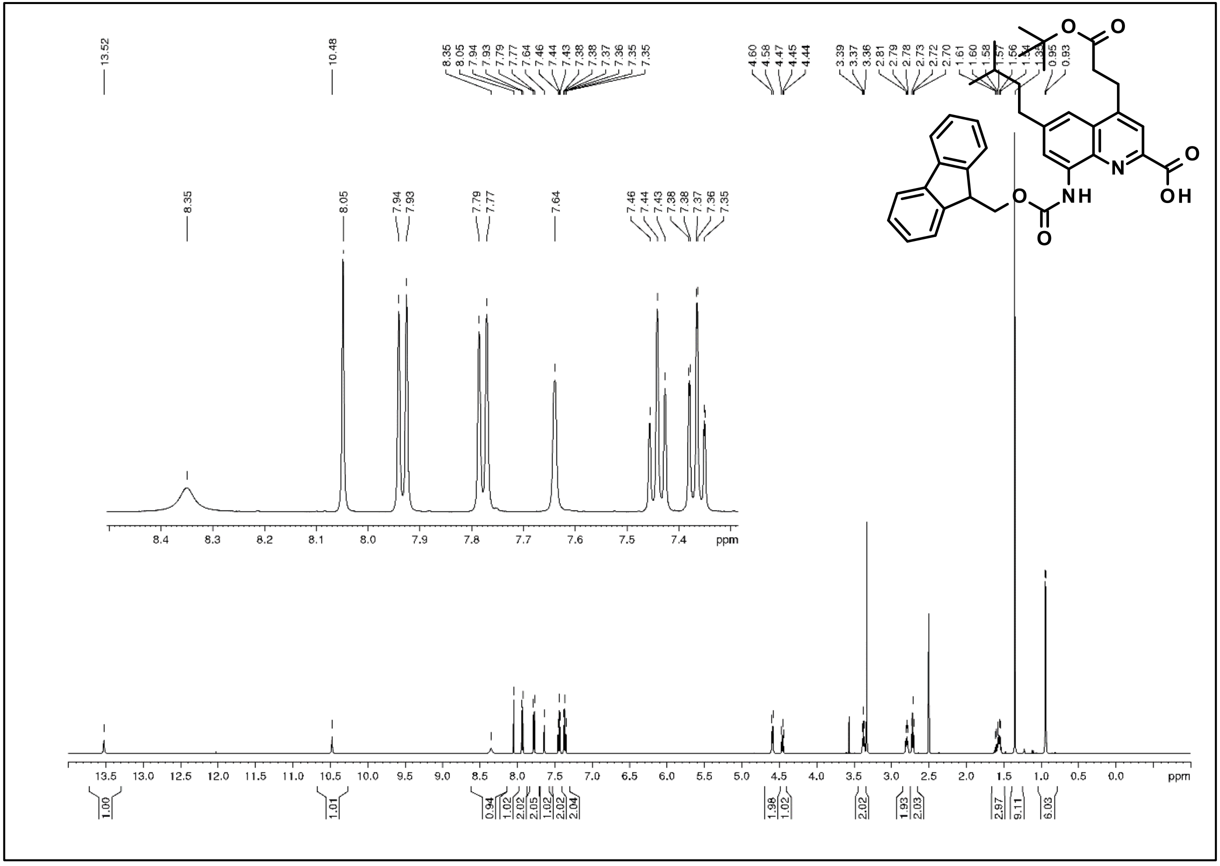


Figure S109. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **17b**.

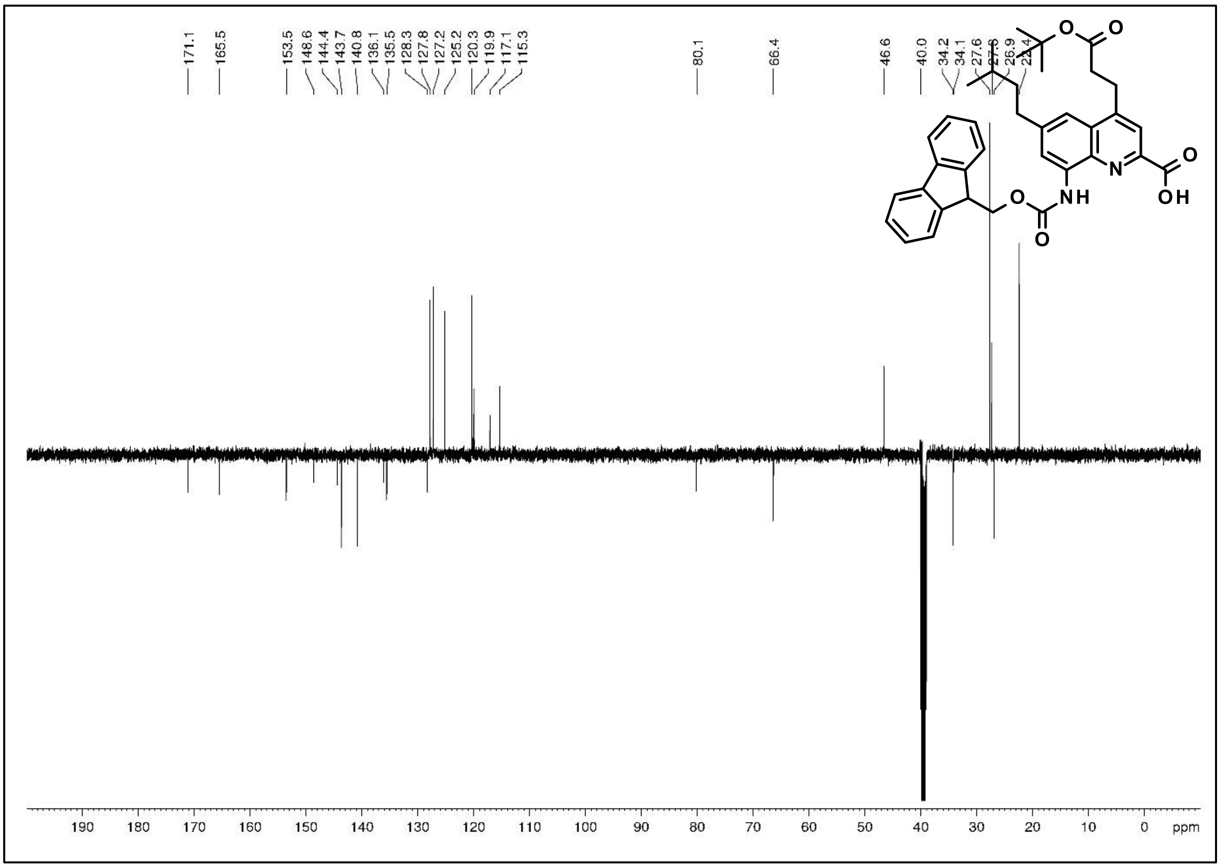


Figure S110. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **17b**.

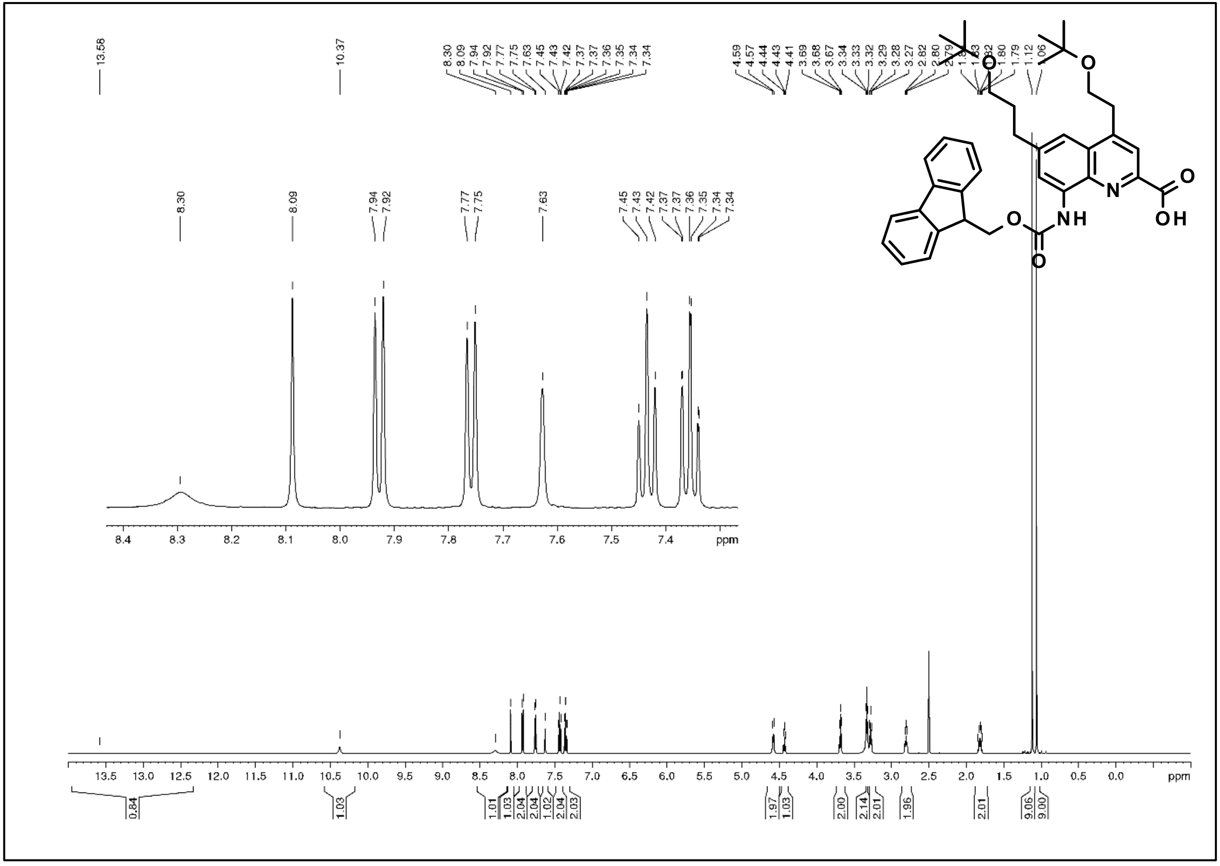


Figure S111. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **17c**.

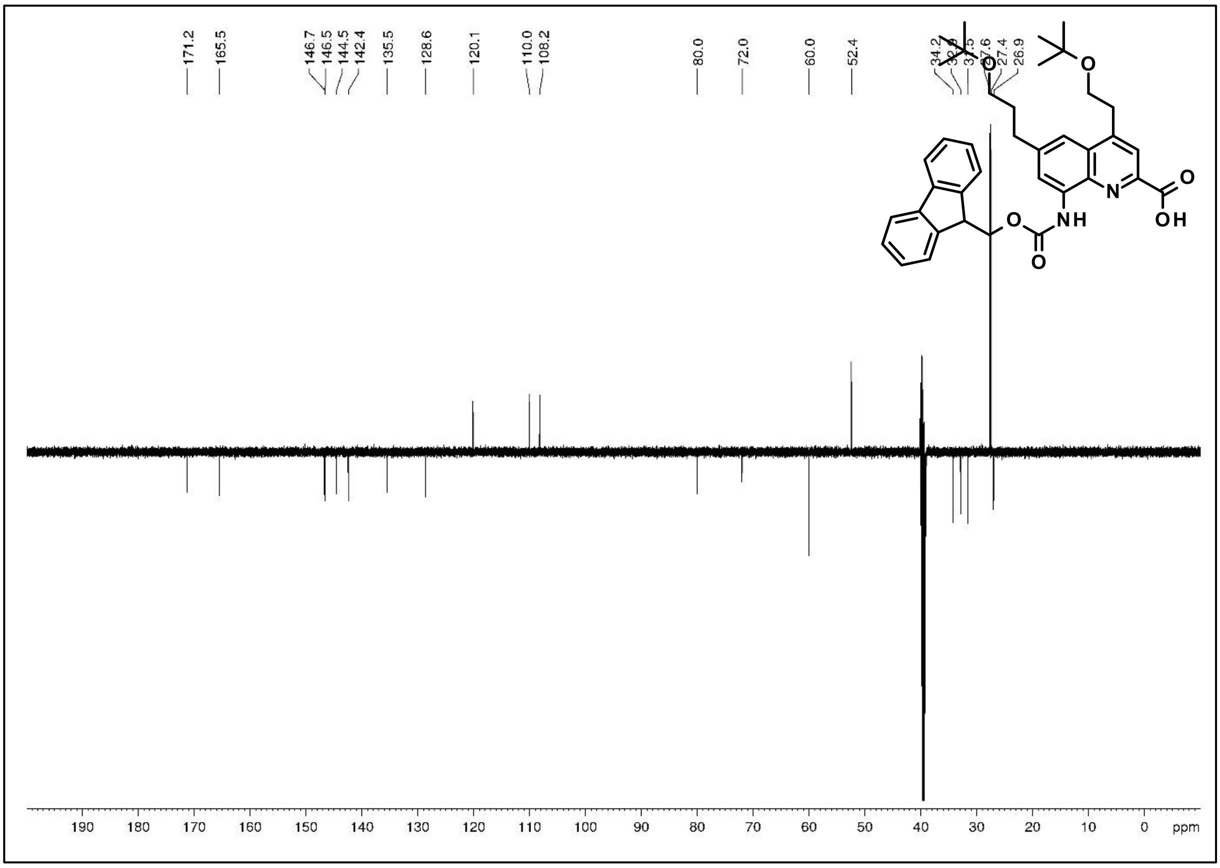


Figure S112. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **17c**.

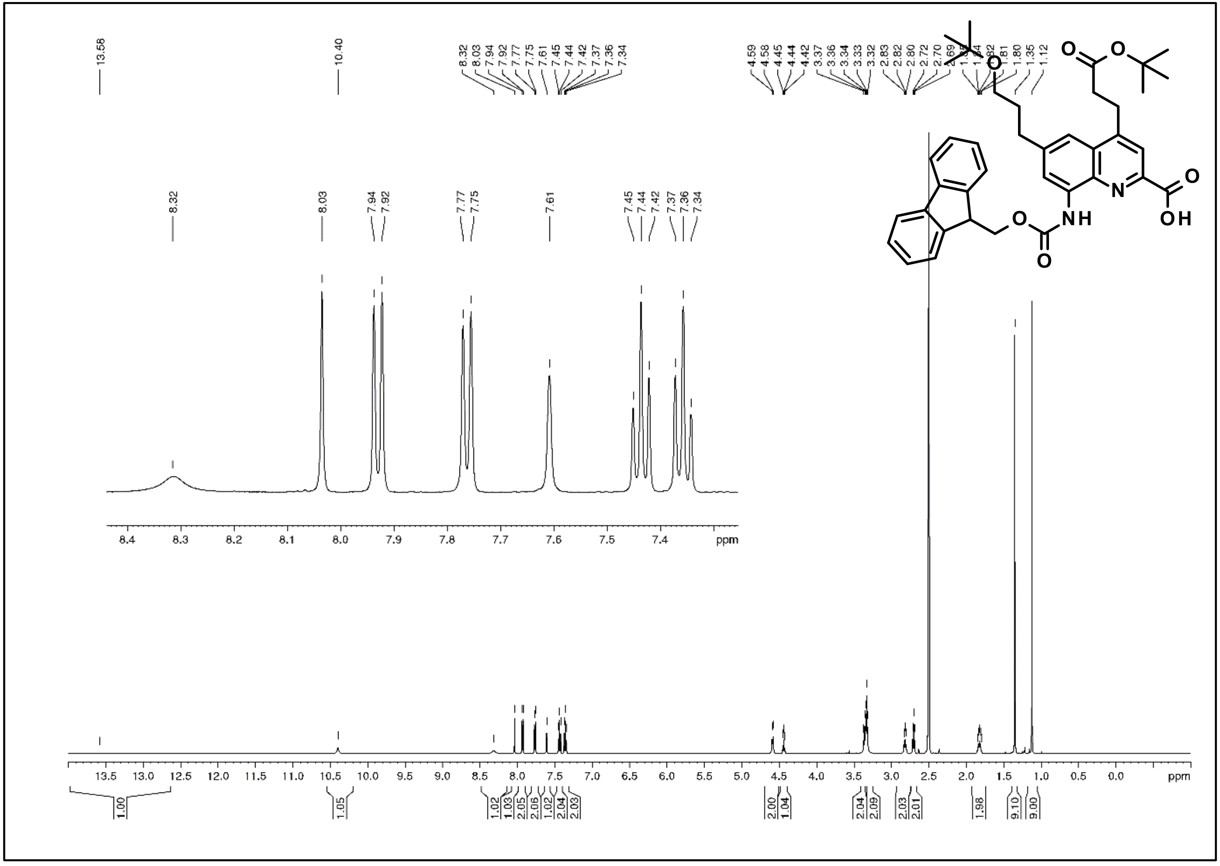


Figure S113. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **17d**.

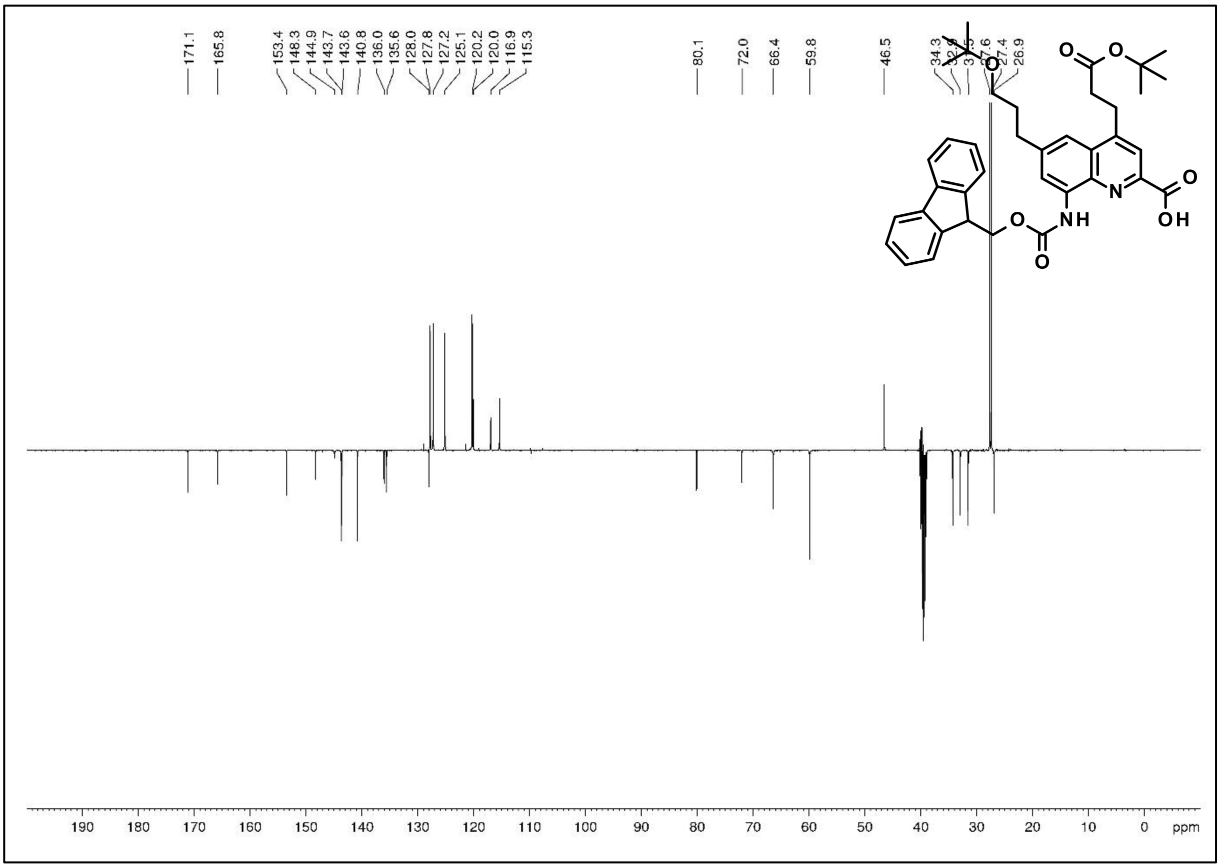


Figure S114. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **17d**.

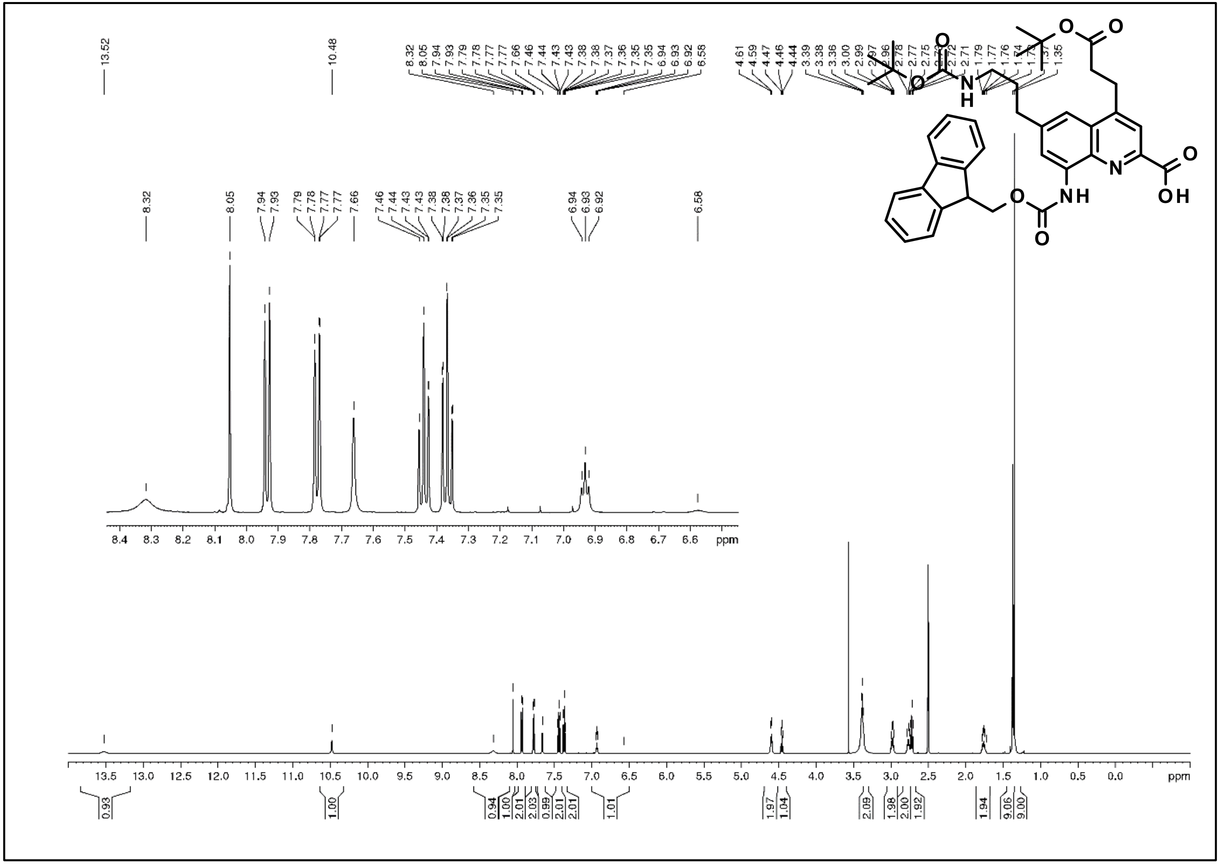


Figure S115. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **17e**.

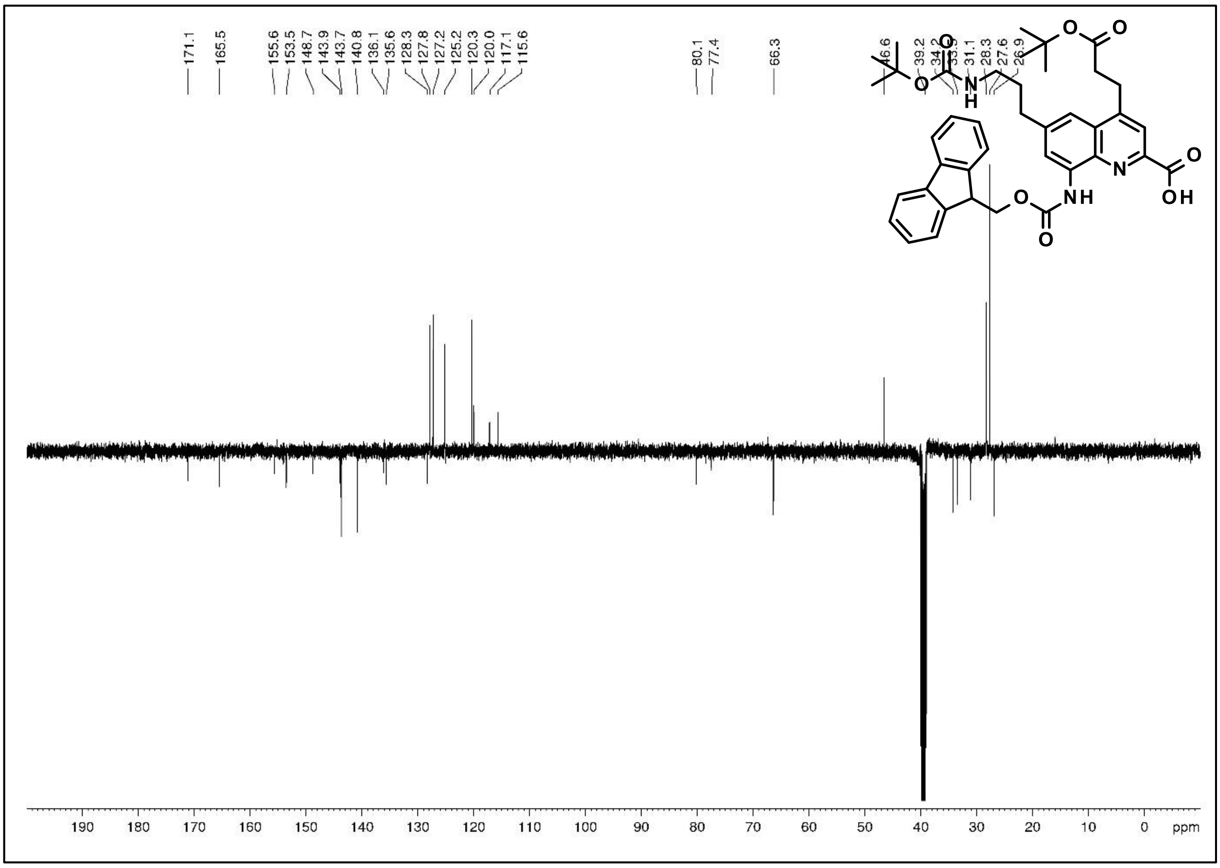


Figure S116. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **17e**.

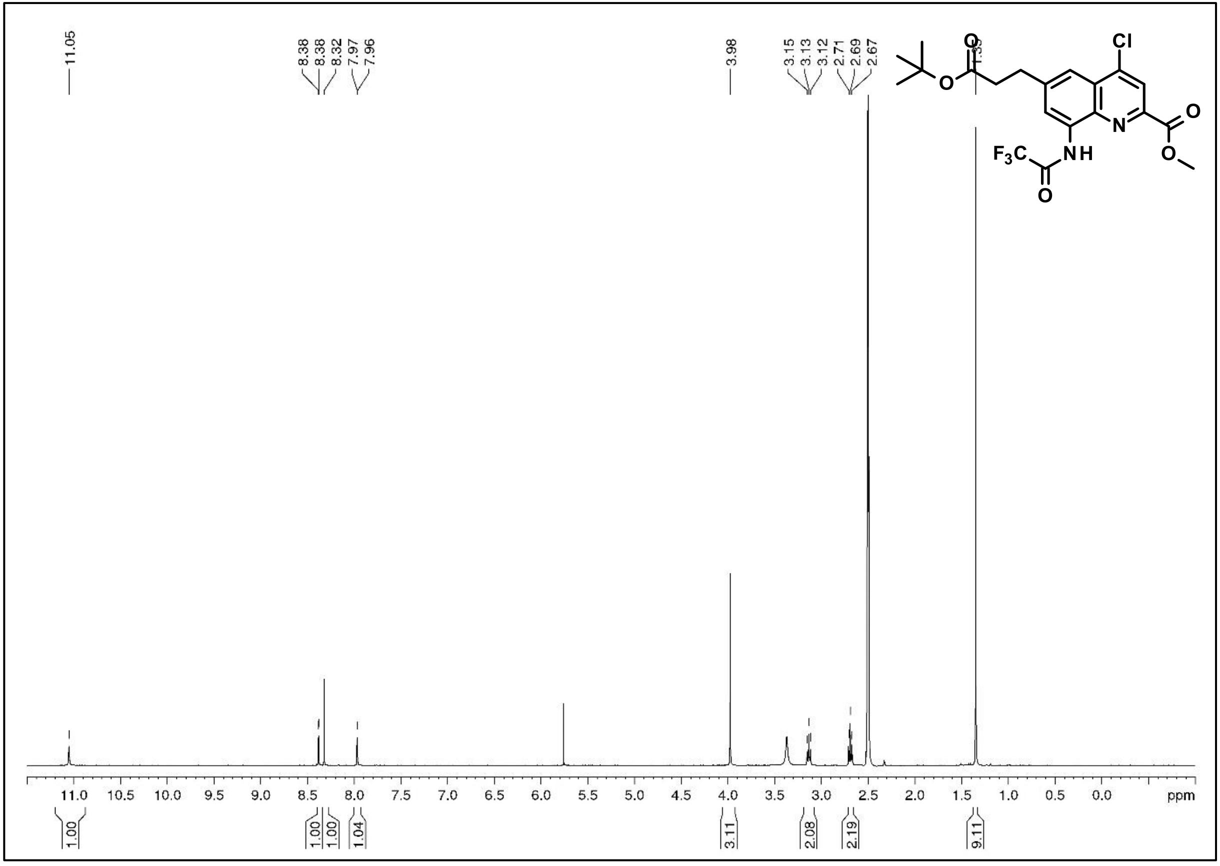


Figure S117. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **19b**.

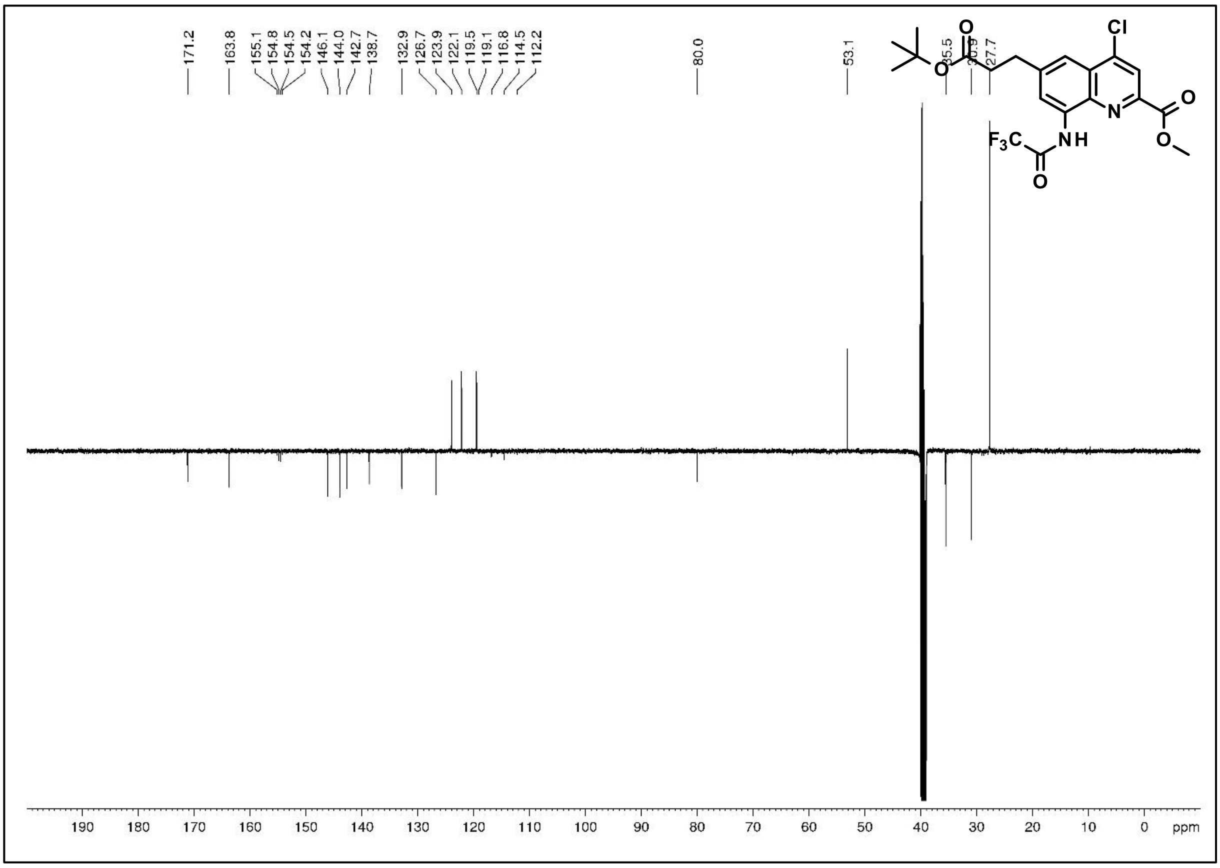


Figure S118. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **19b**.

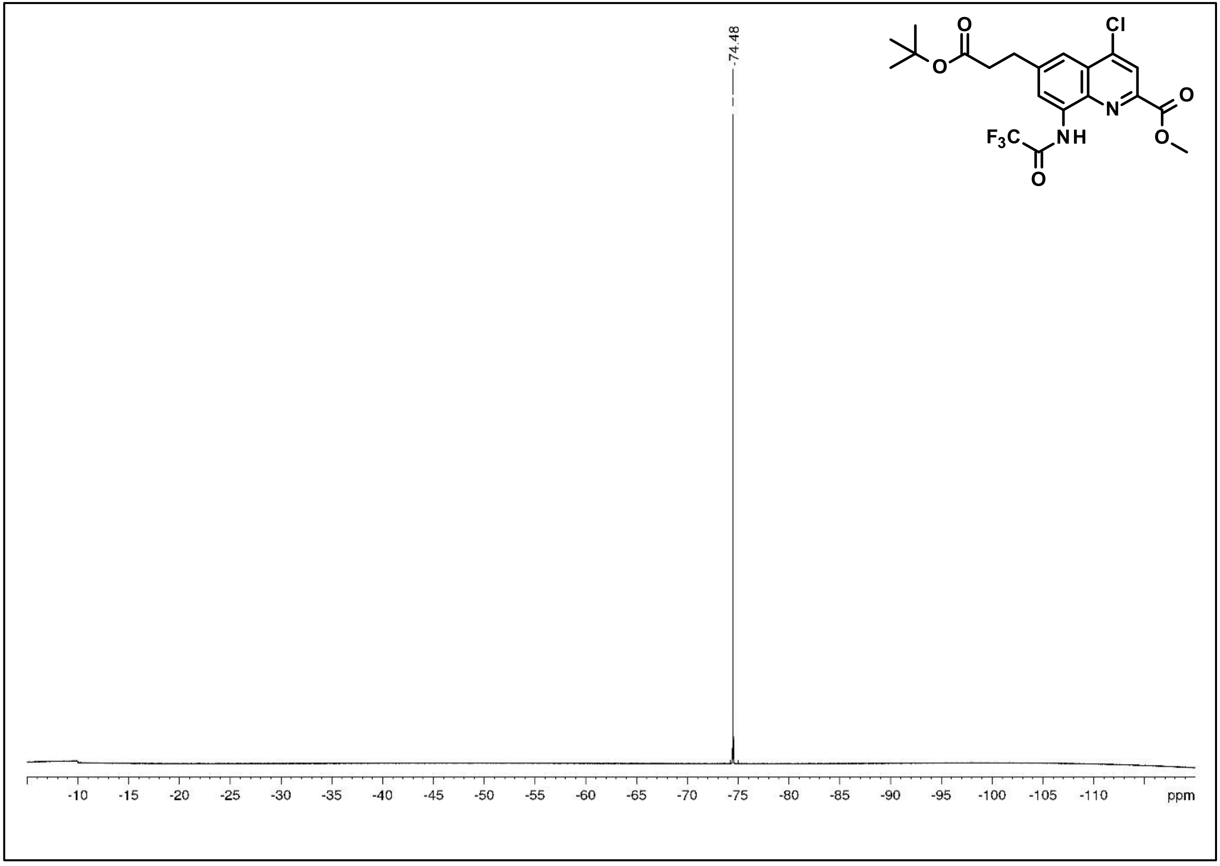


Figure S119. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **19b**.

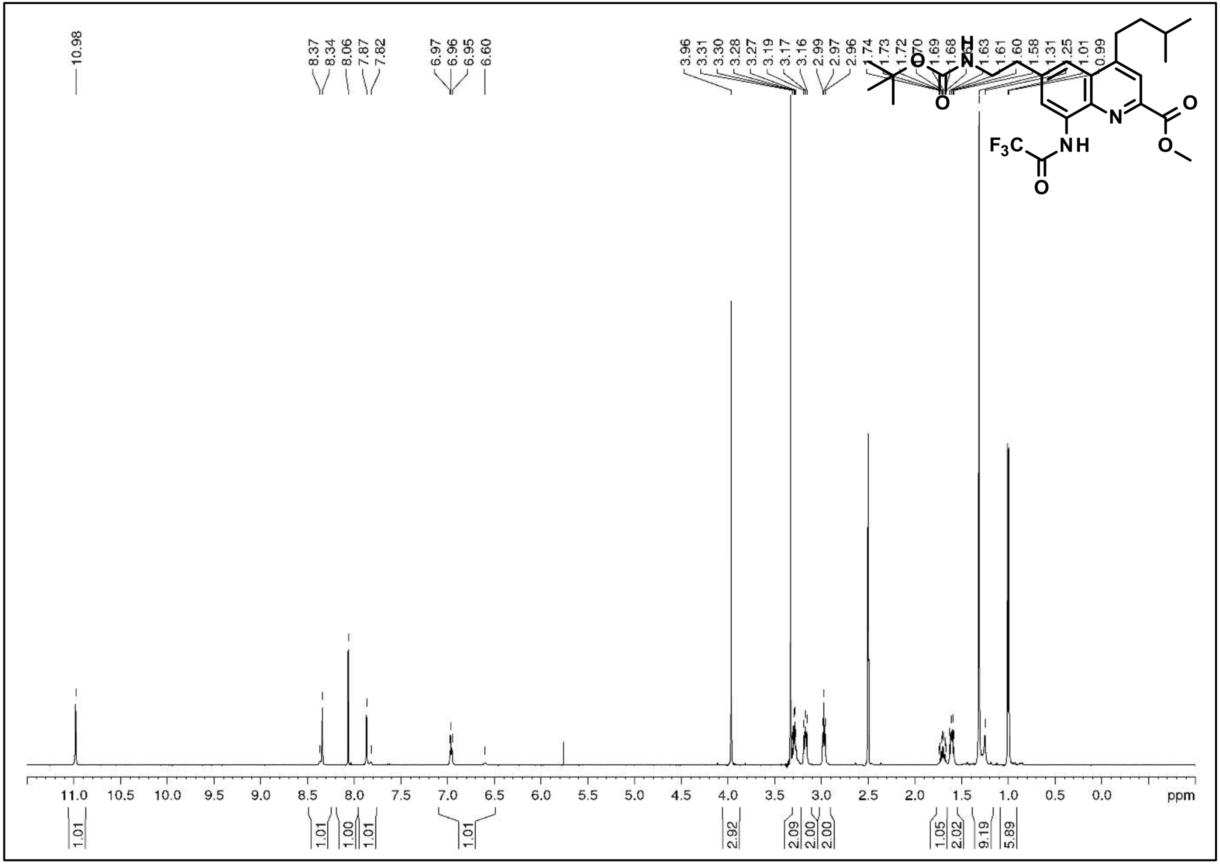


Figure S120. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **20a**.

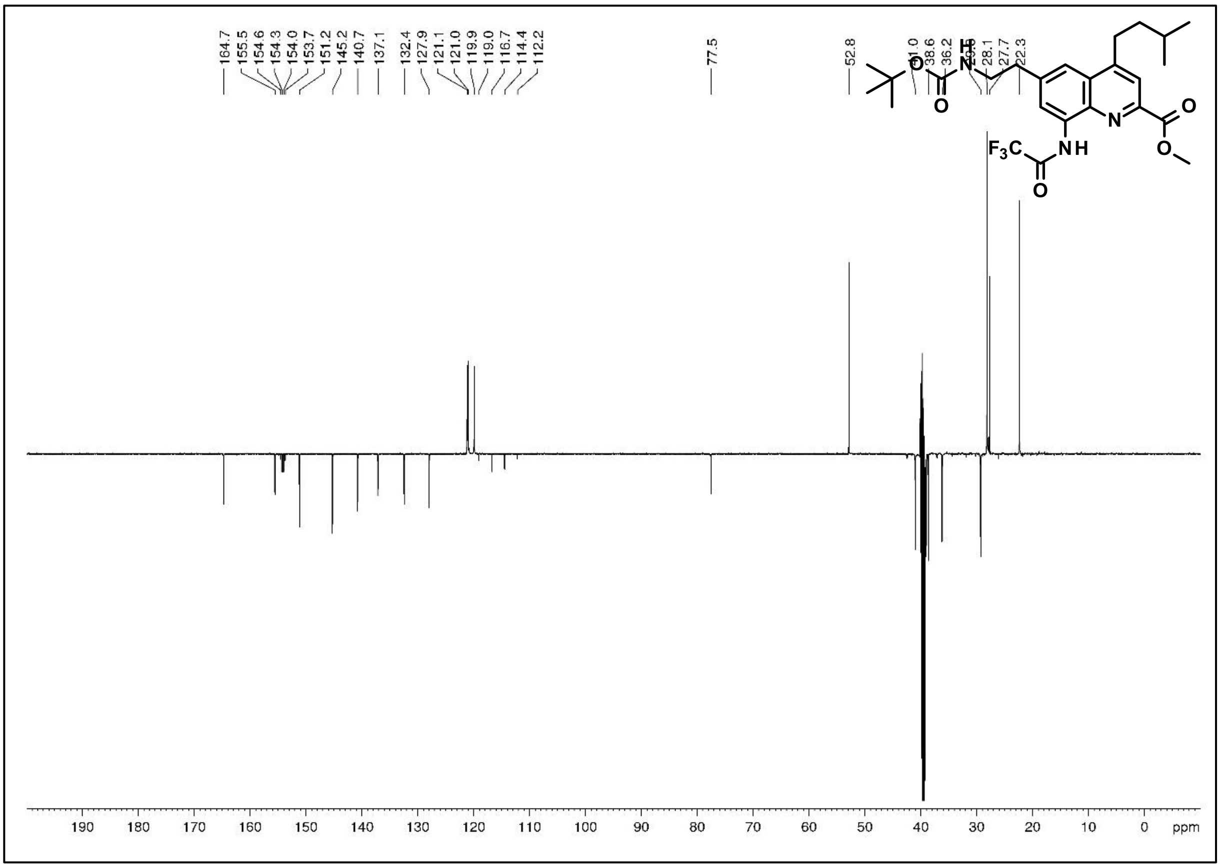


Figure S121. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **20a**.

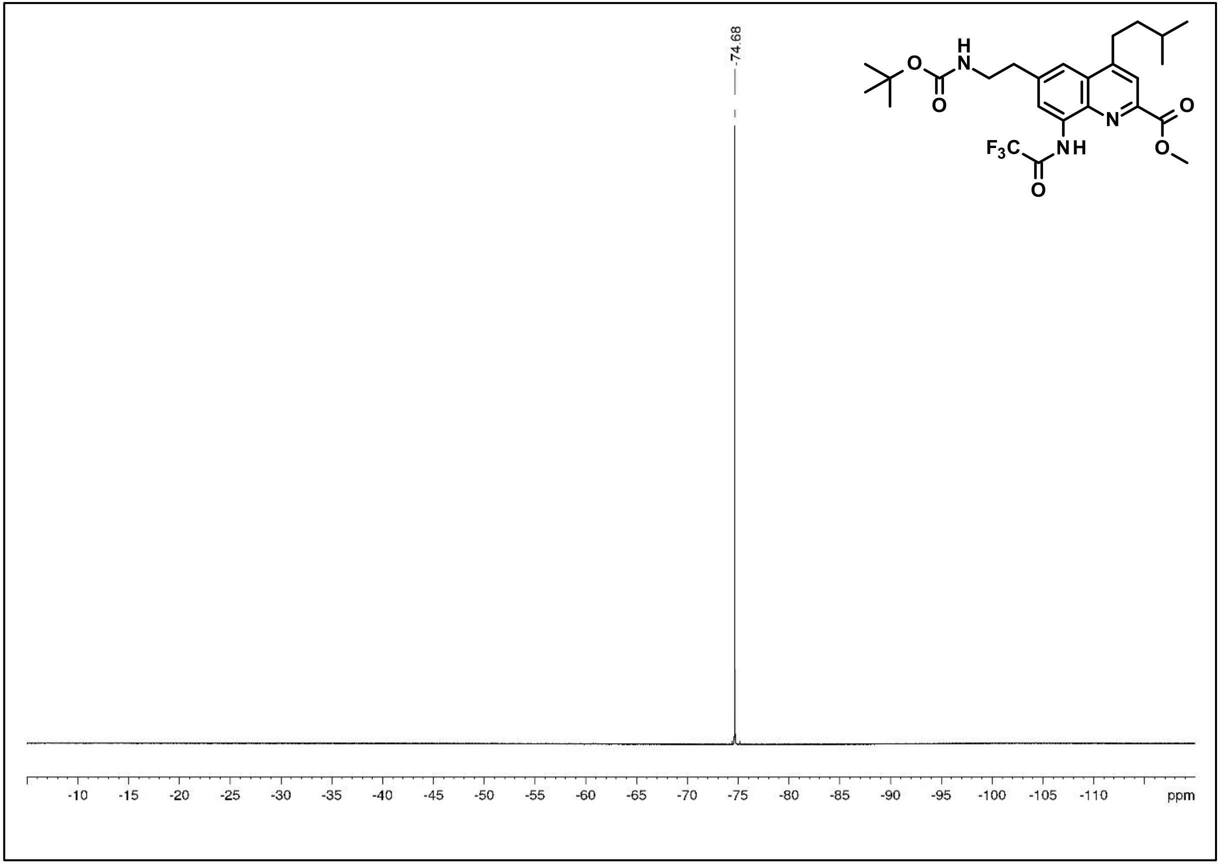


Figure S122. ^{19}F NMR (376 MHz, DMSO-d_6) of compound **20a**.

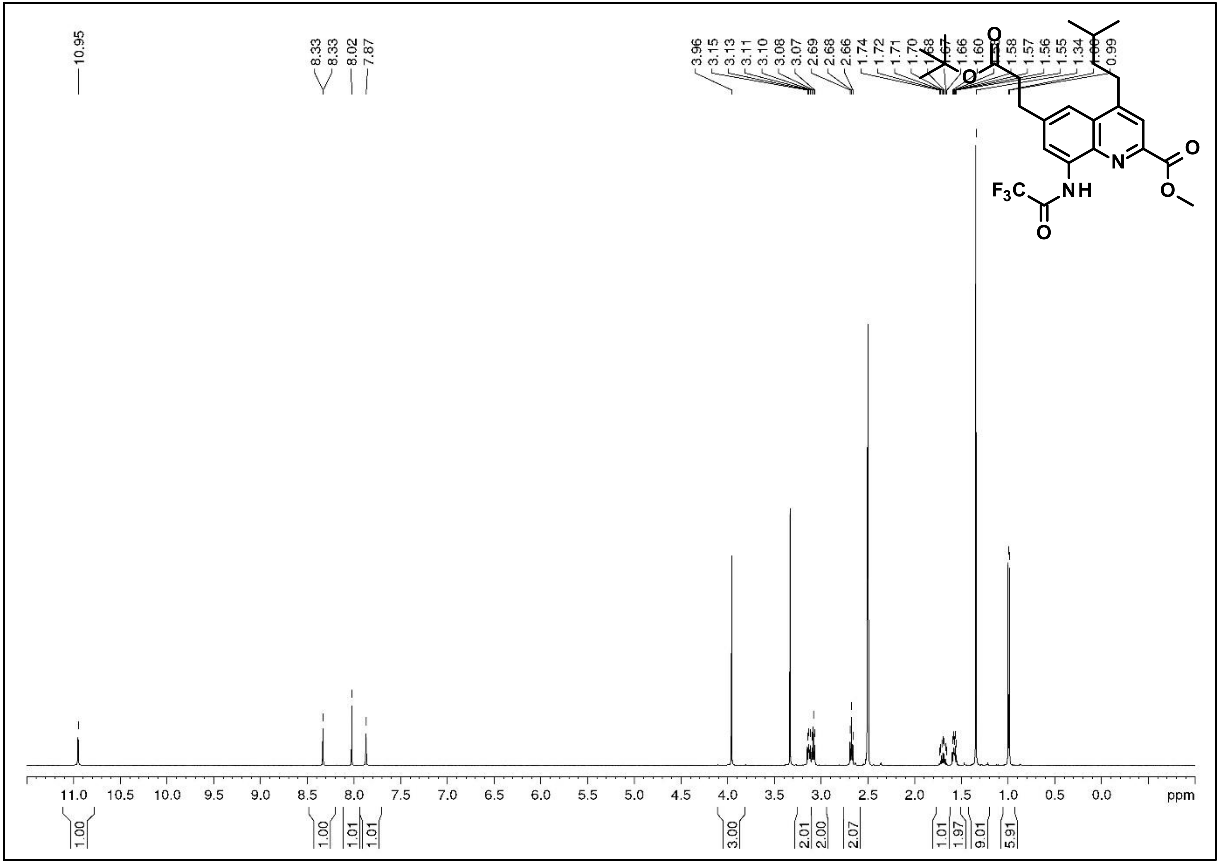


Figure S123. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **20b**.

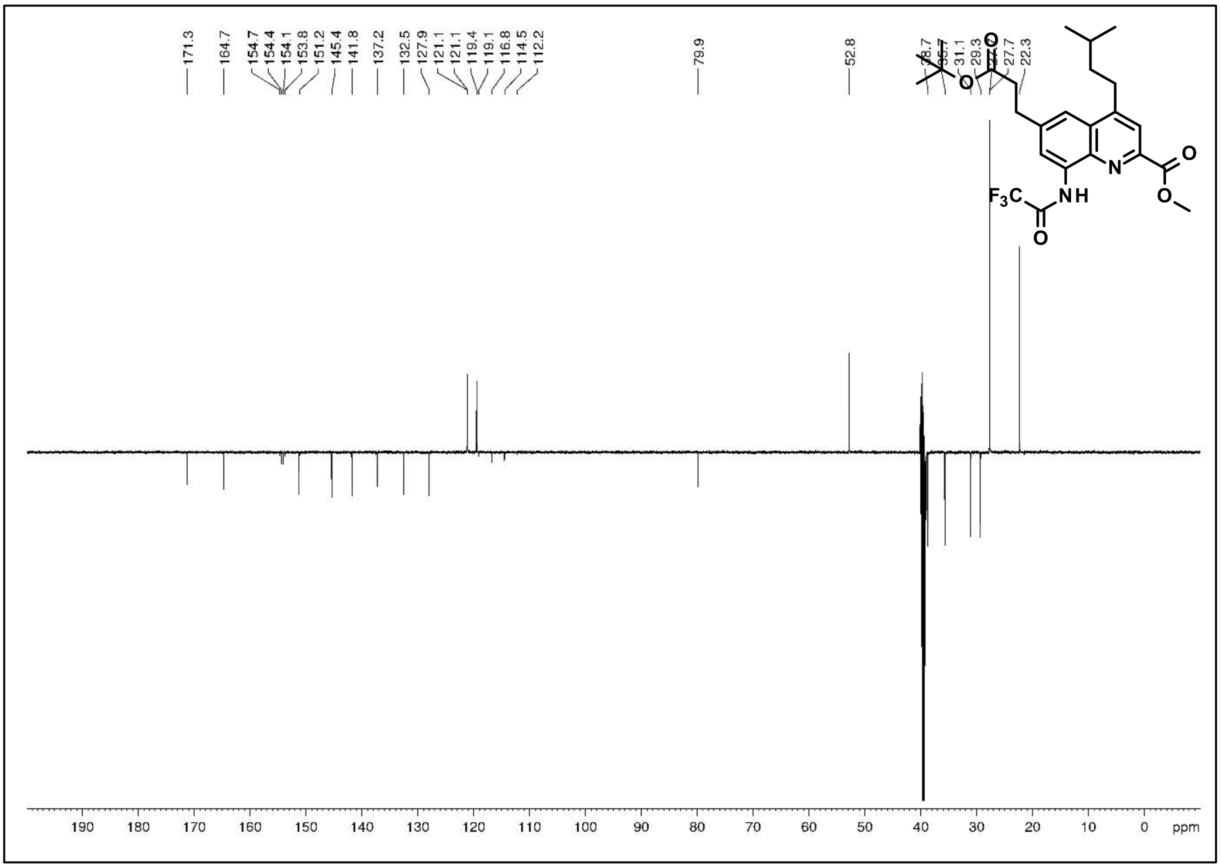


Figure S124. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **20b**.

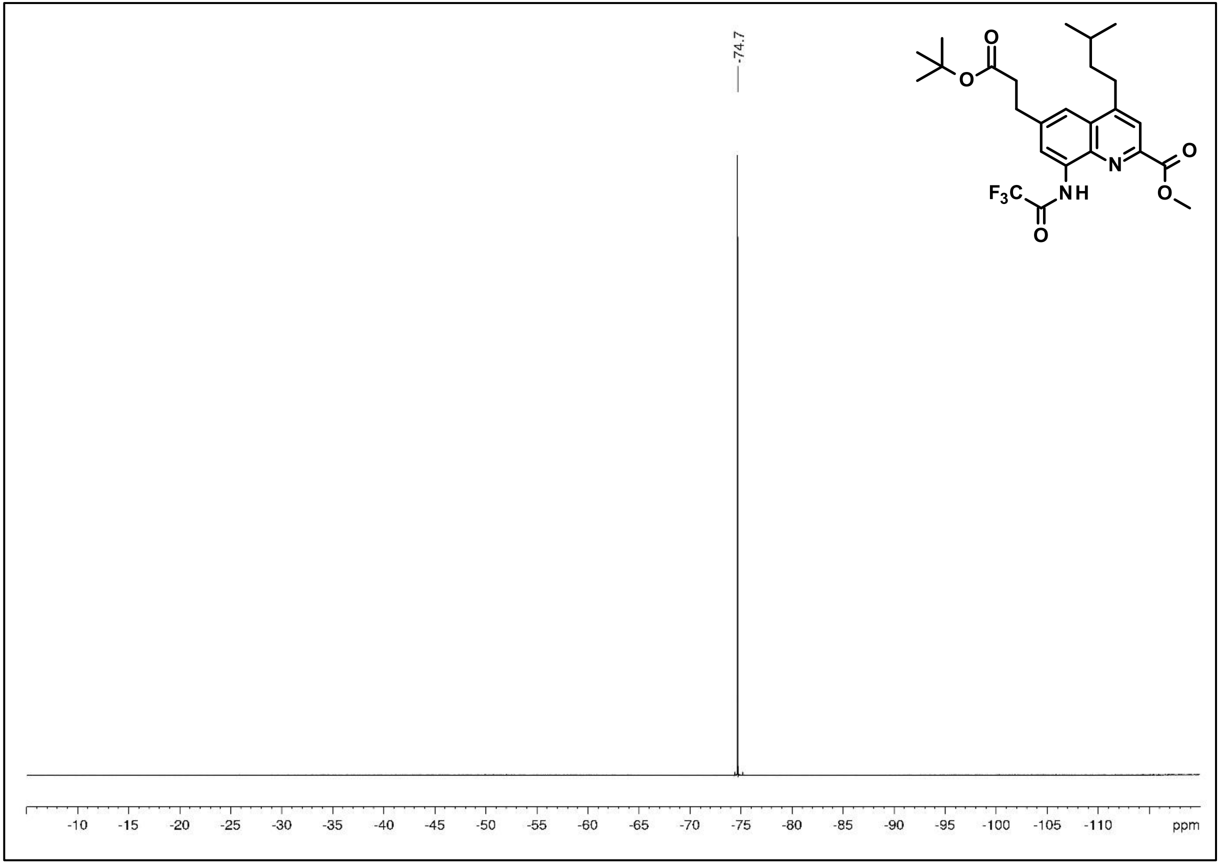


Figure S125. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **20b**.

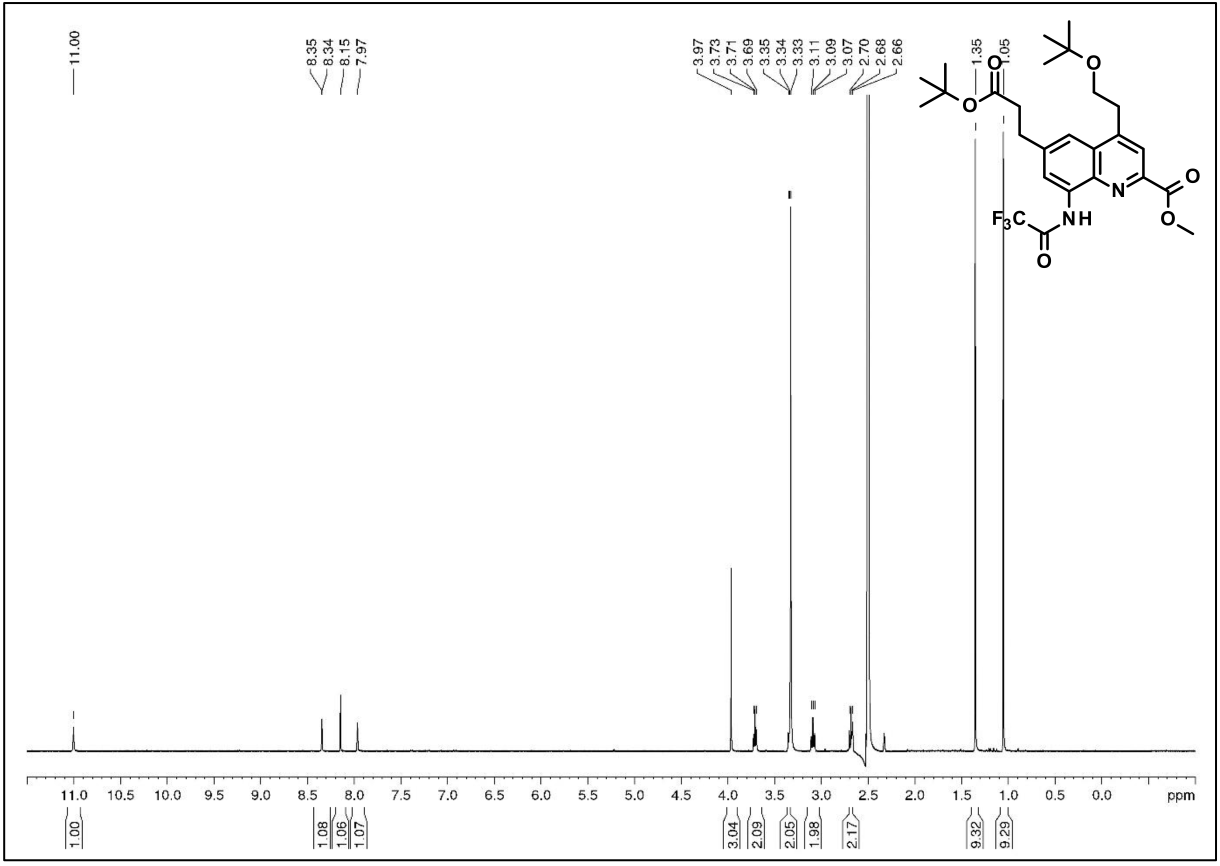


Figure S126. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **20c**.

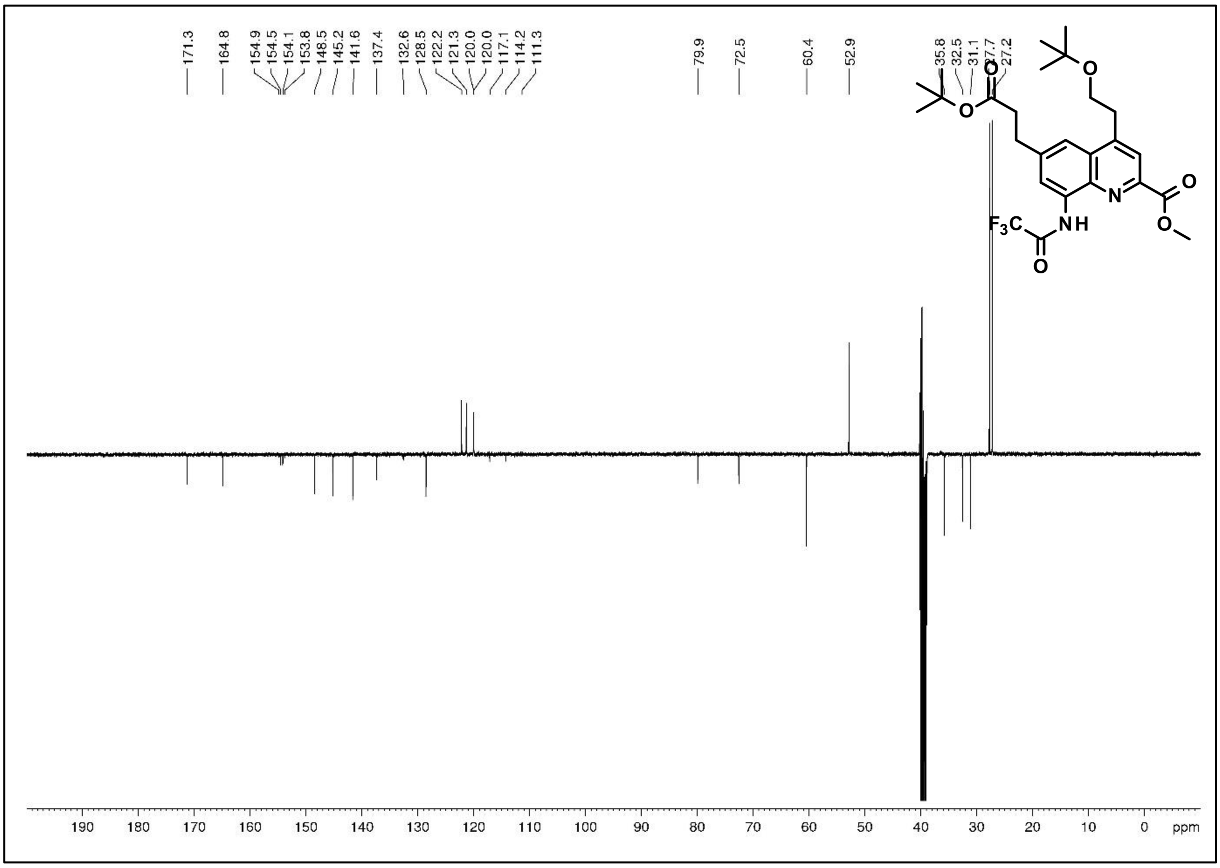


Figure S127. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) of compound **20c**.

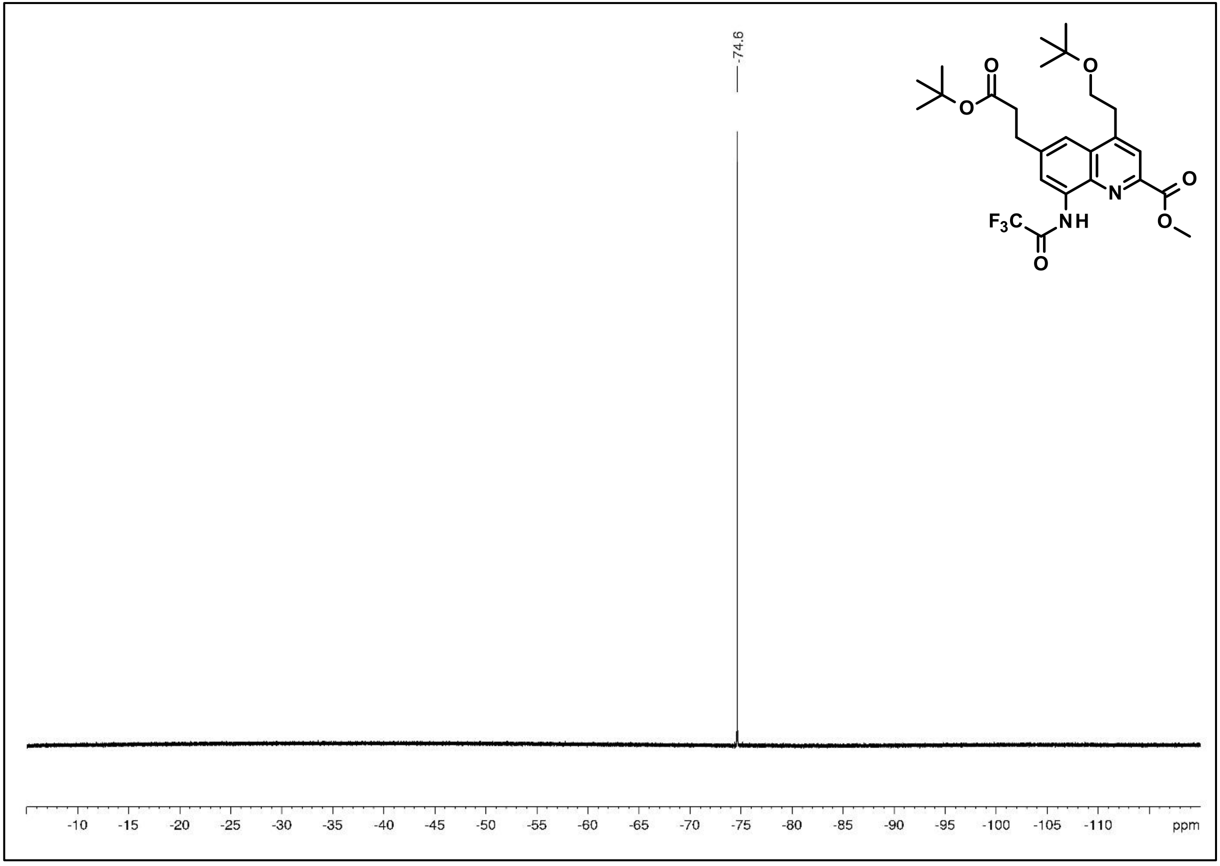


Figure S128. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **20c**.

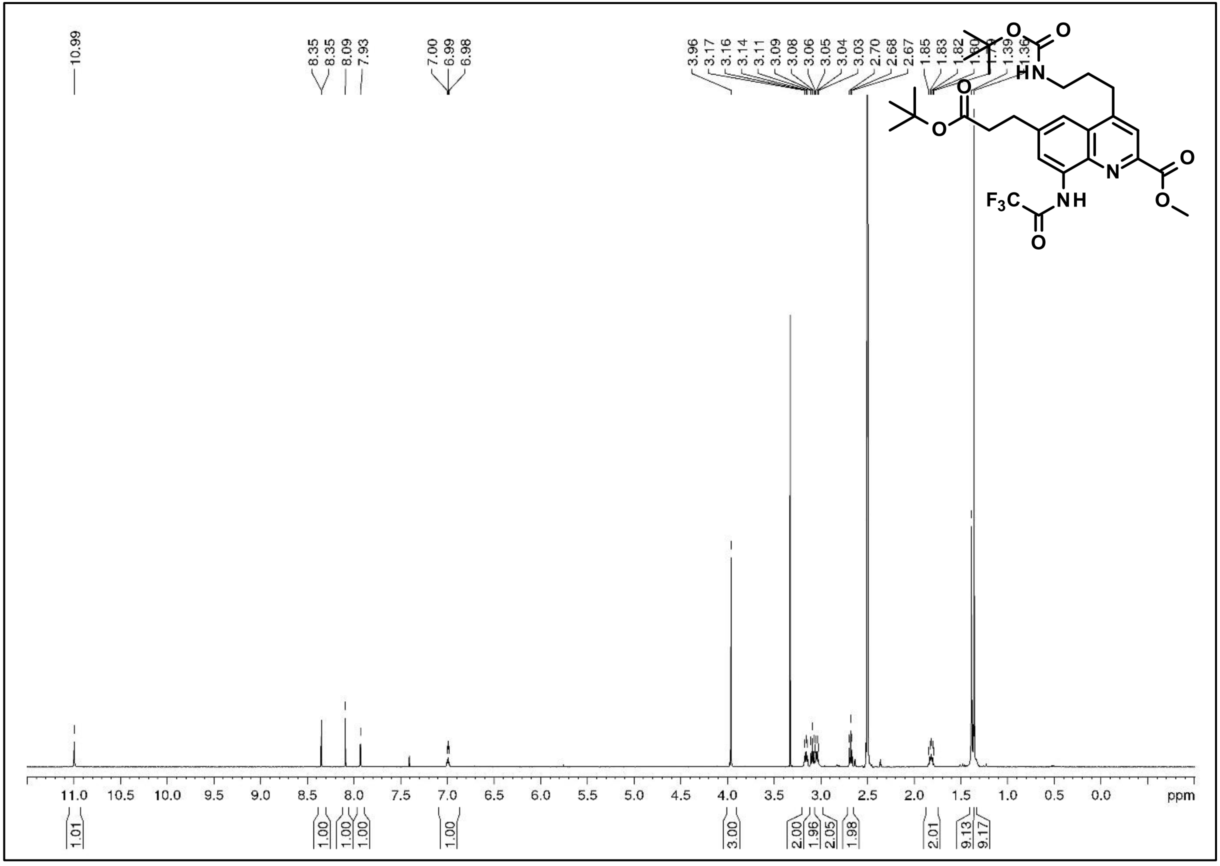


Figure S129. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **20d**.

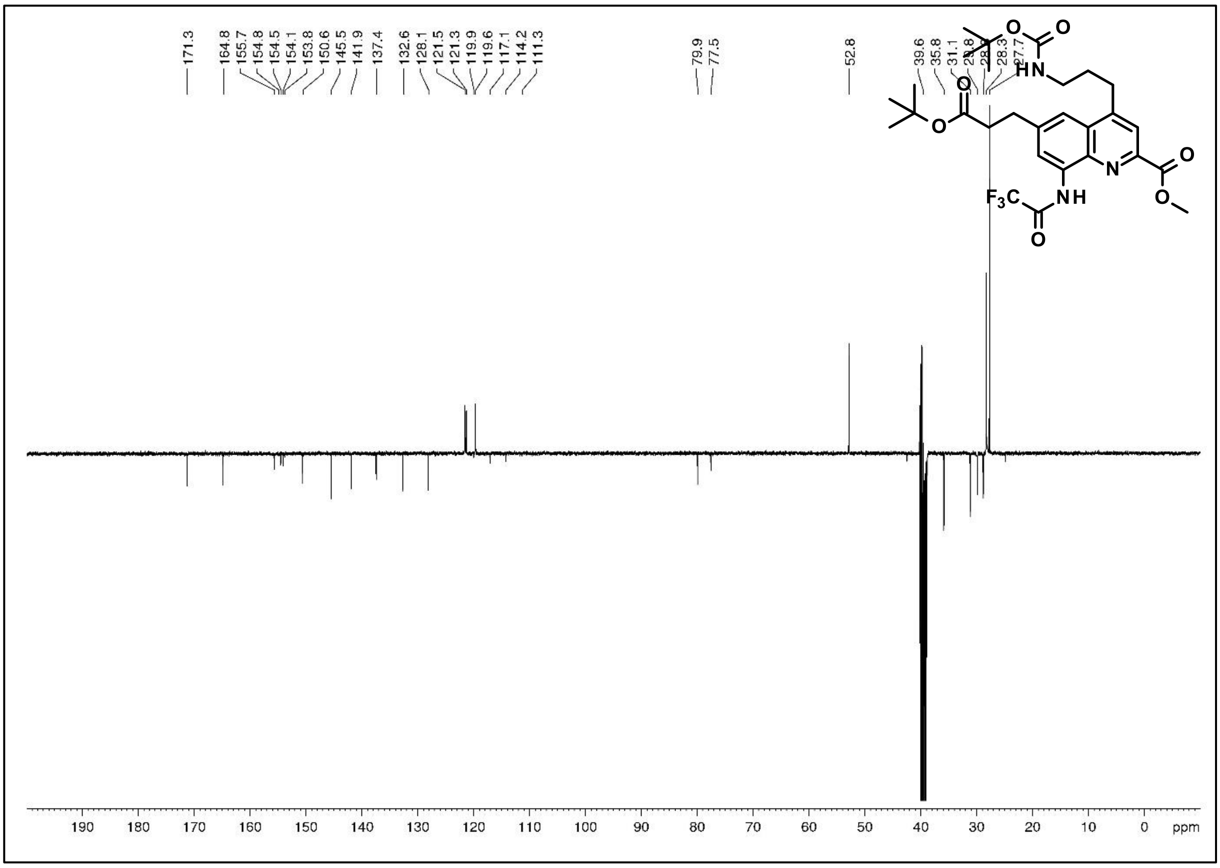


Figure S130. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) of compound **20d**.

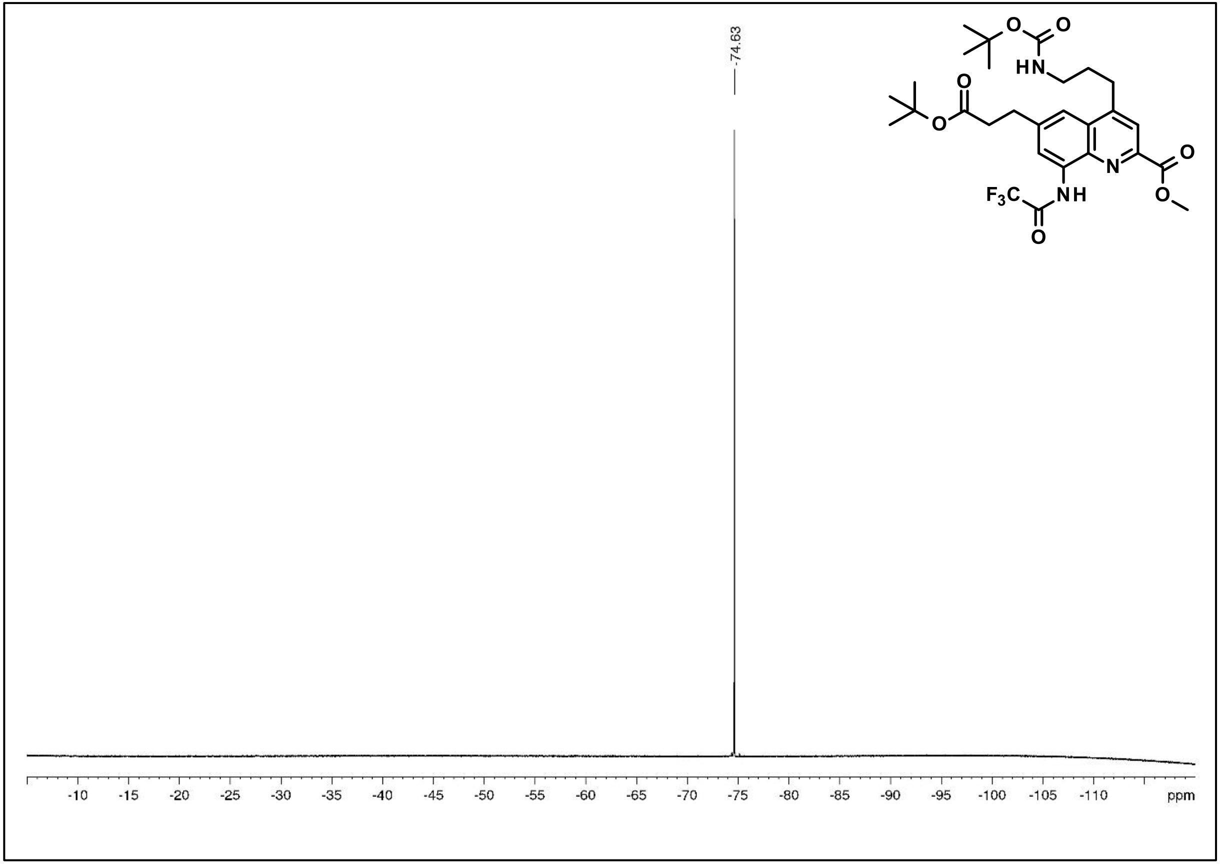


Figure S131. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **20d**.

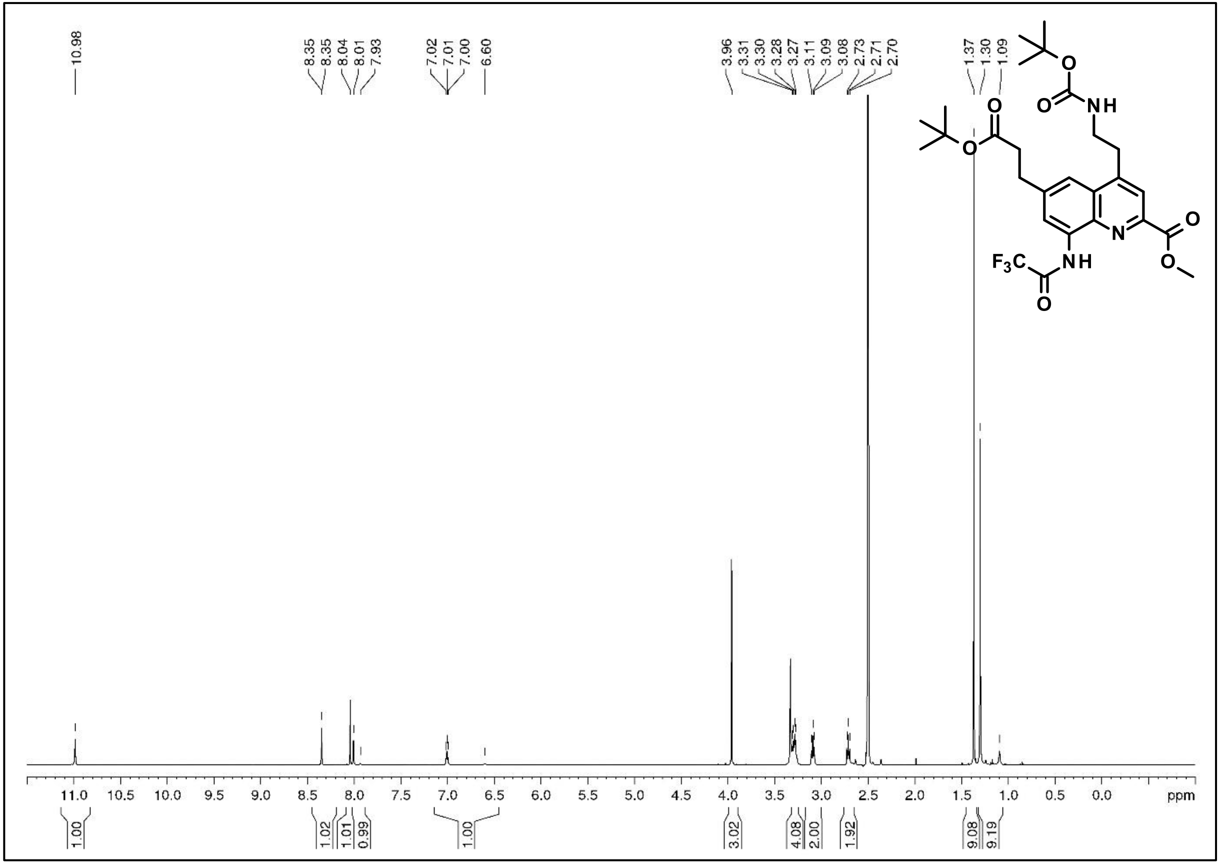


Figure S132. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **20e**.

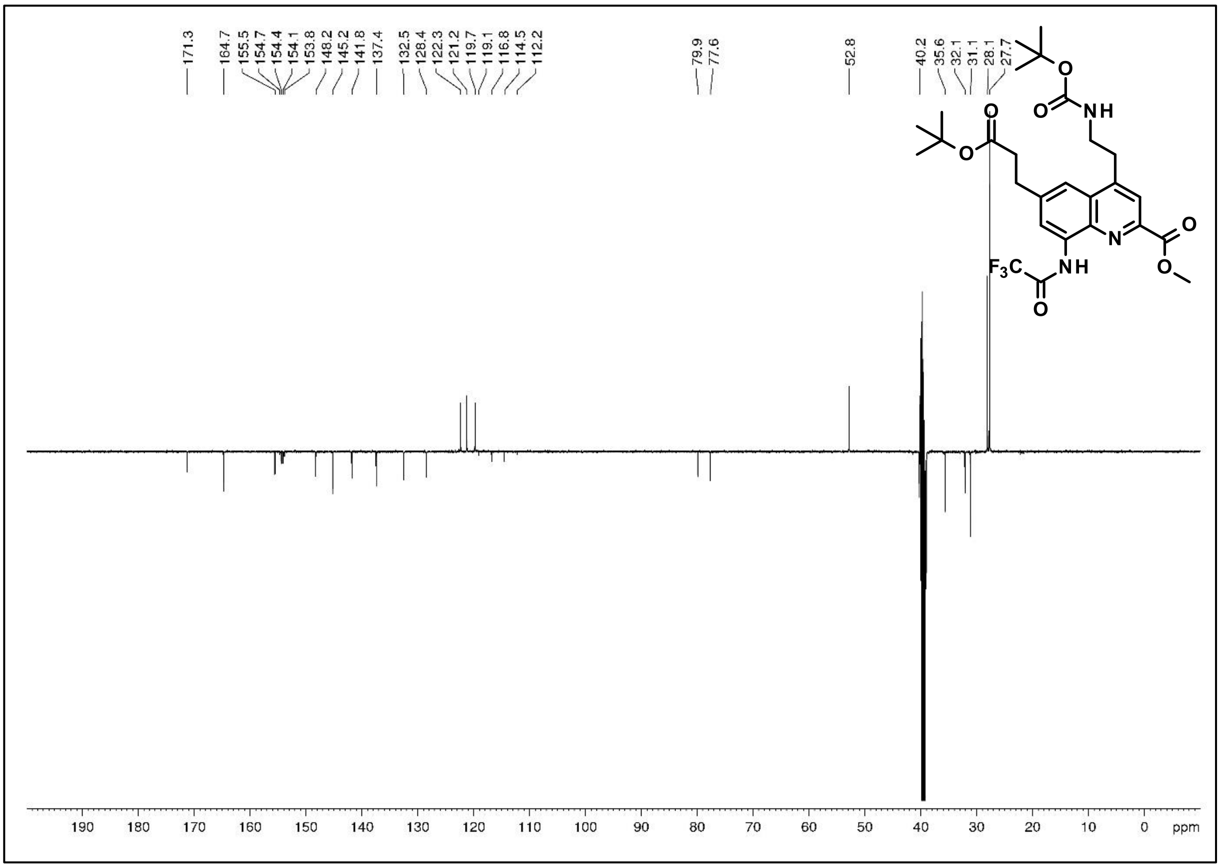


Figure S133. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) of compound **20e**.

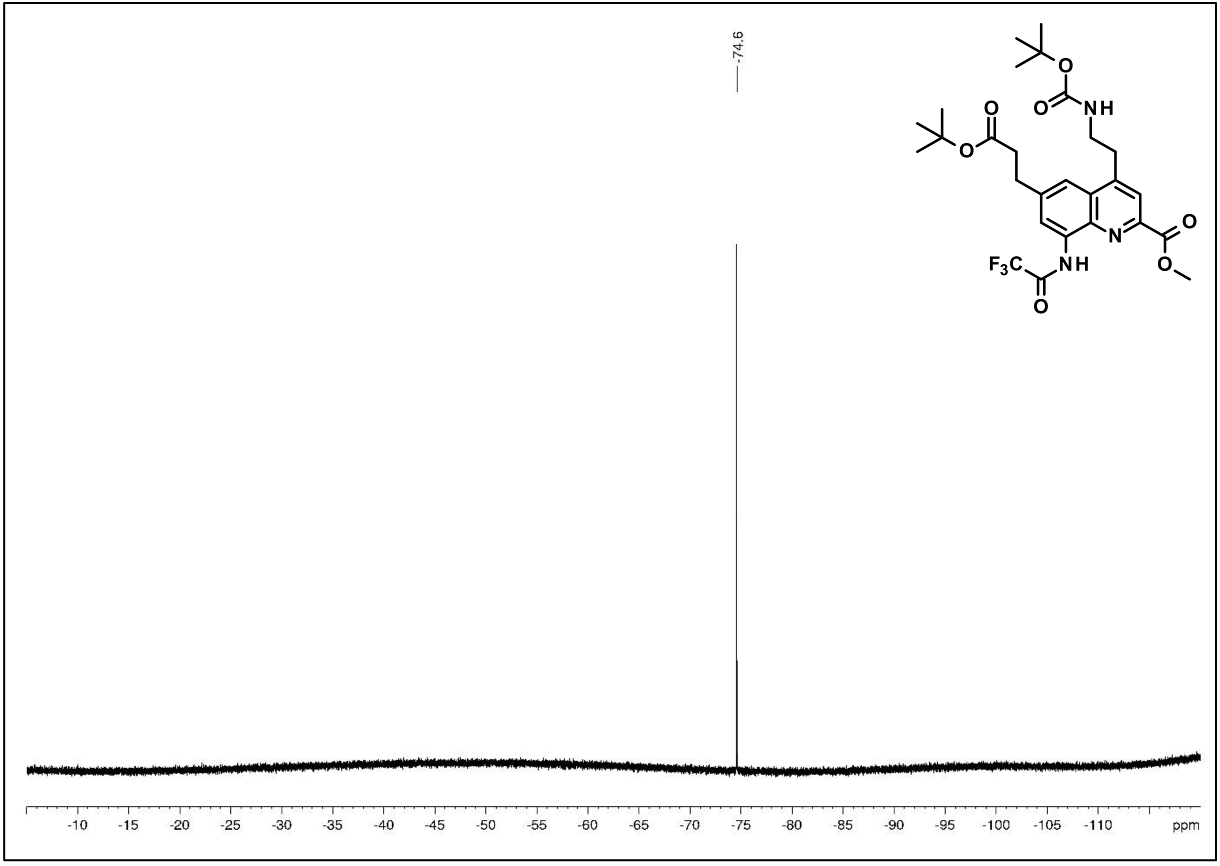


Figure S134. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **20e.**

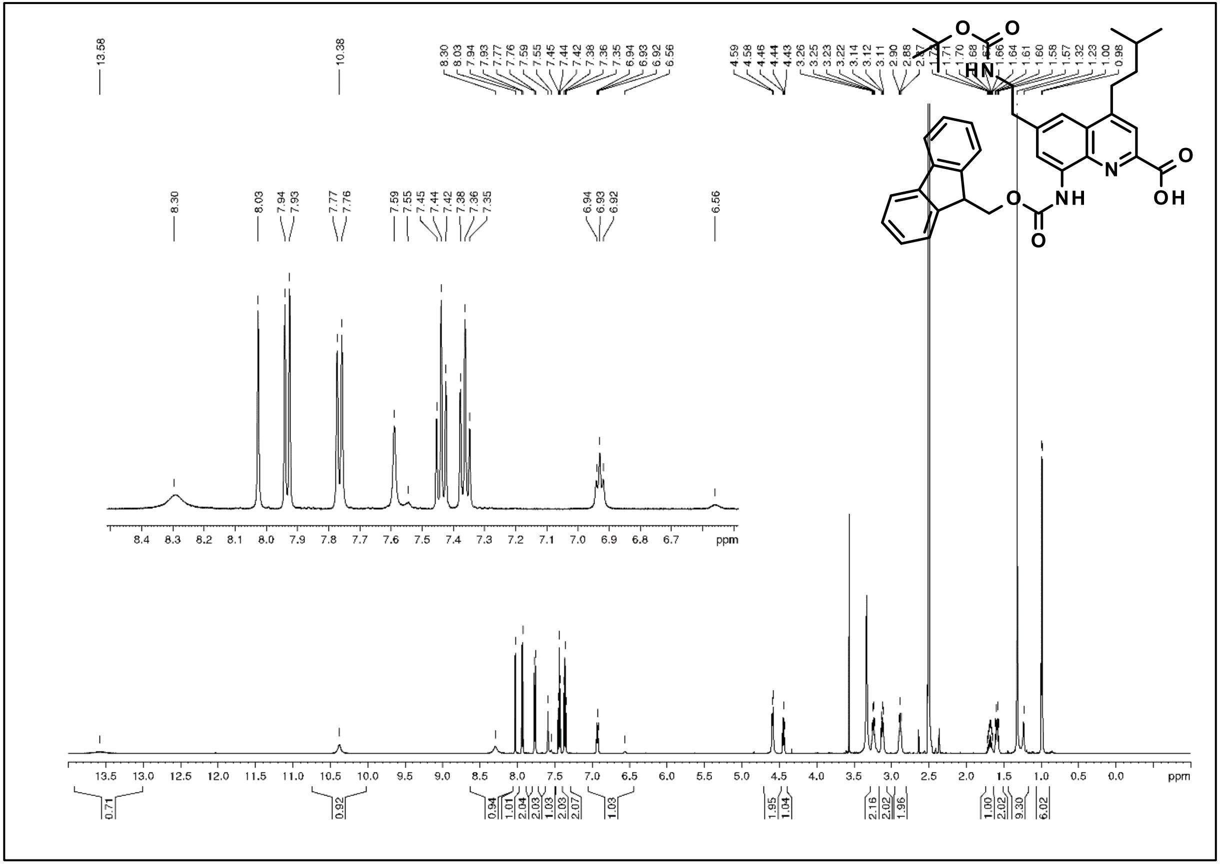


Figure S135. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **21a**.

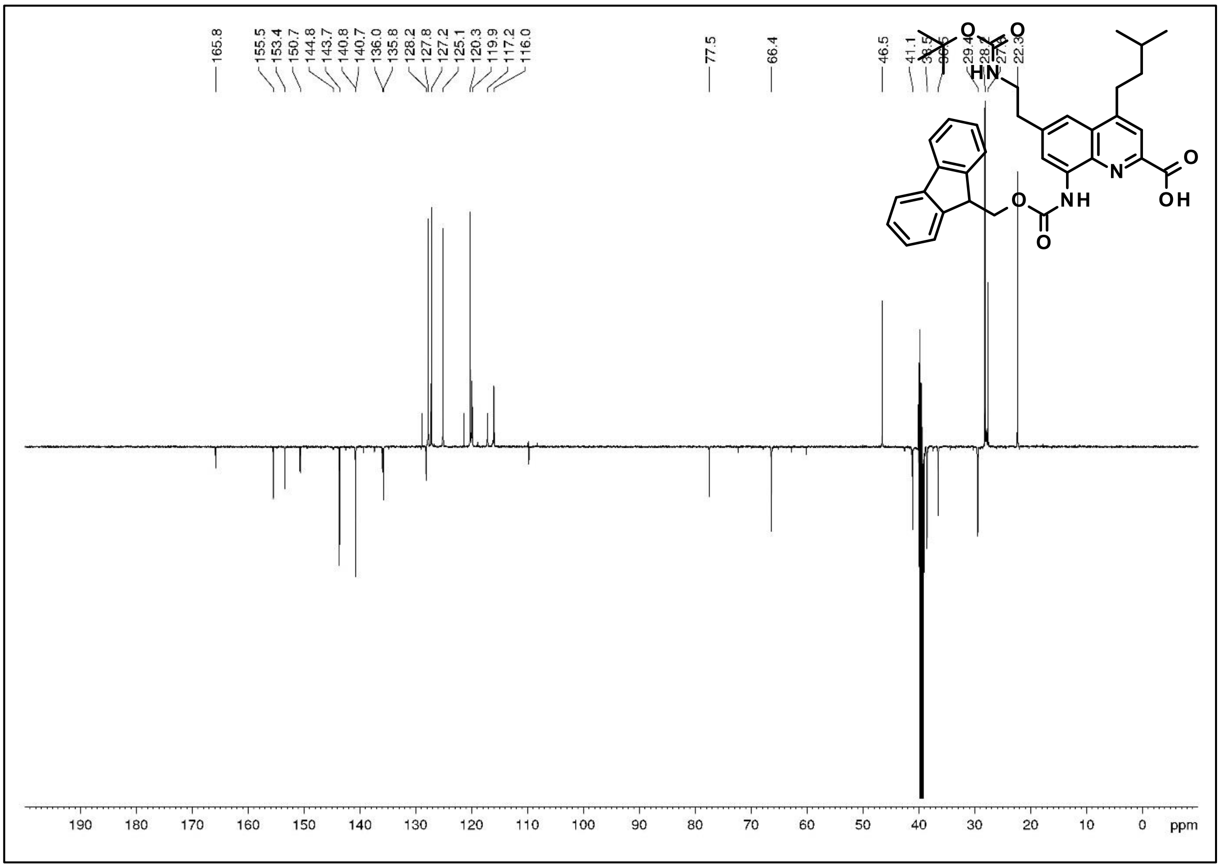


Figure S136. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **21a**.

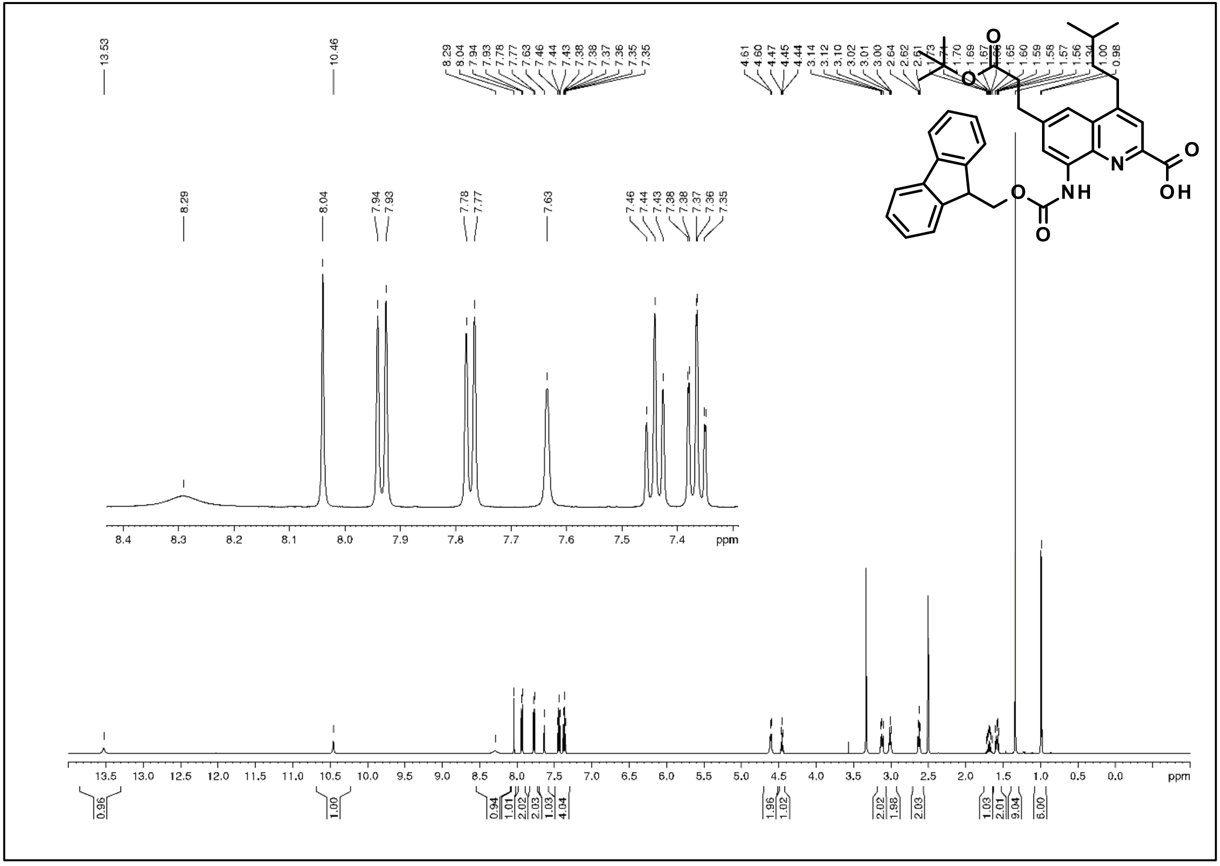


Figure S137. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **21b**.

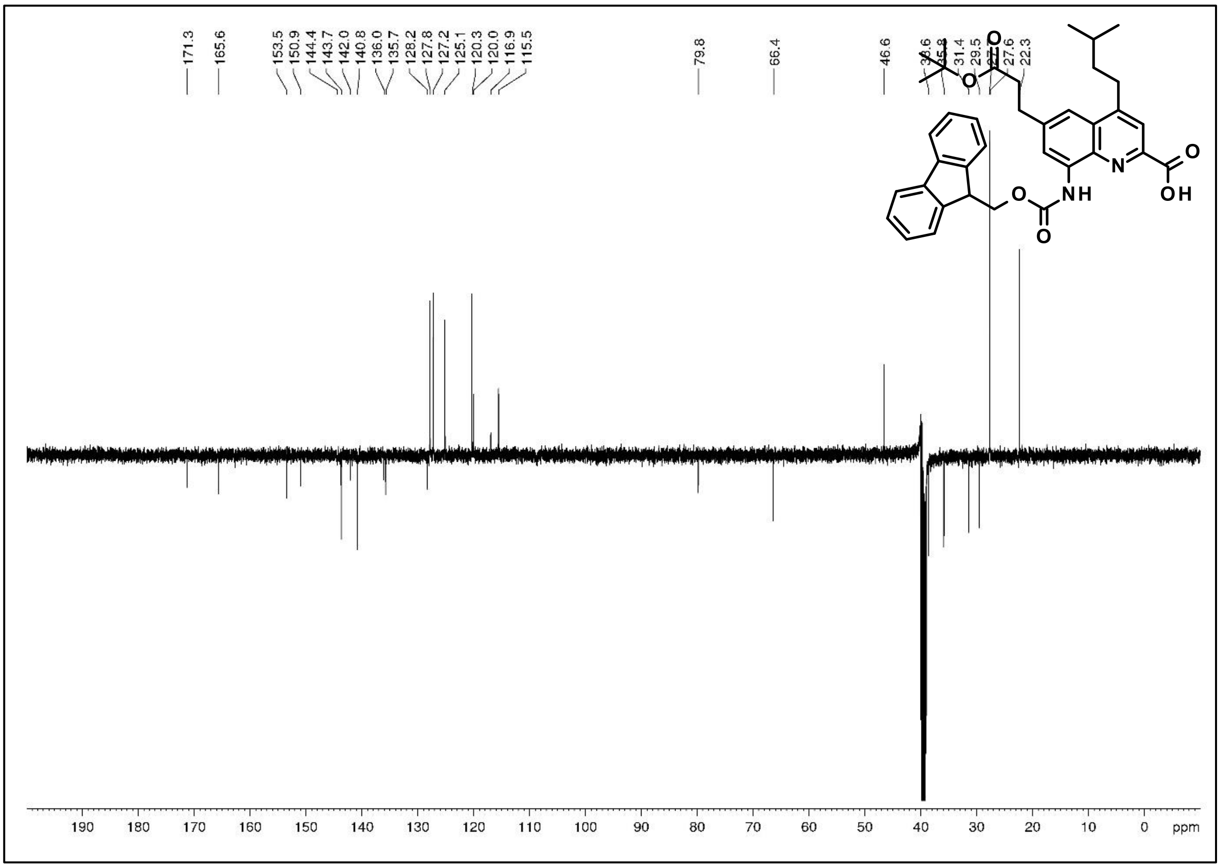


Figure S138. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **21b**.

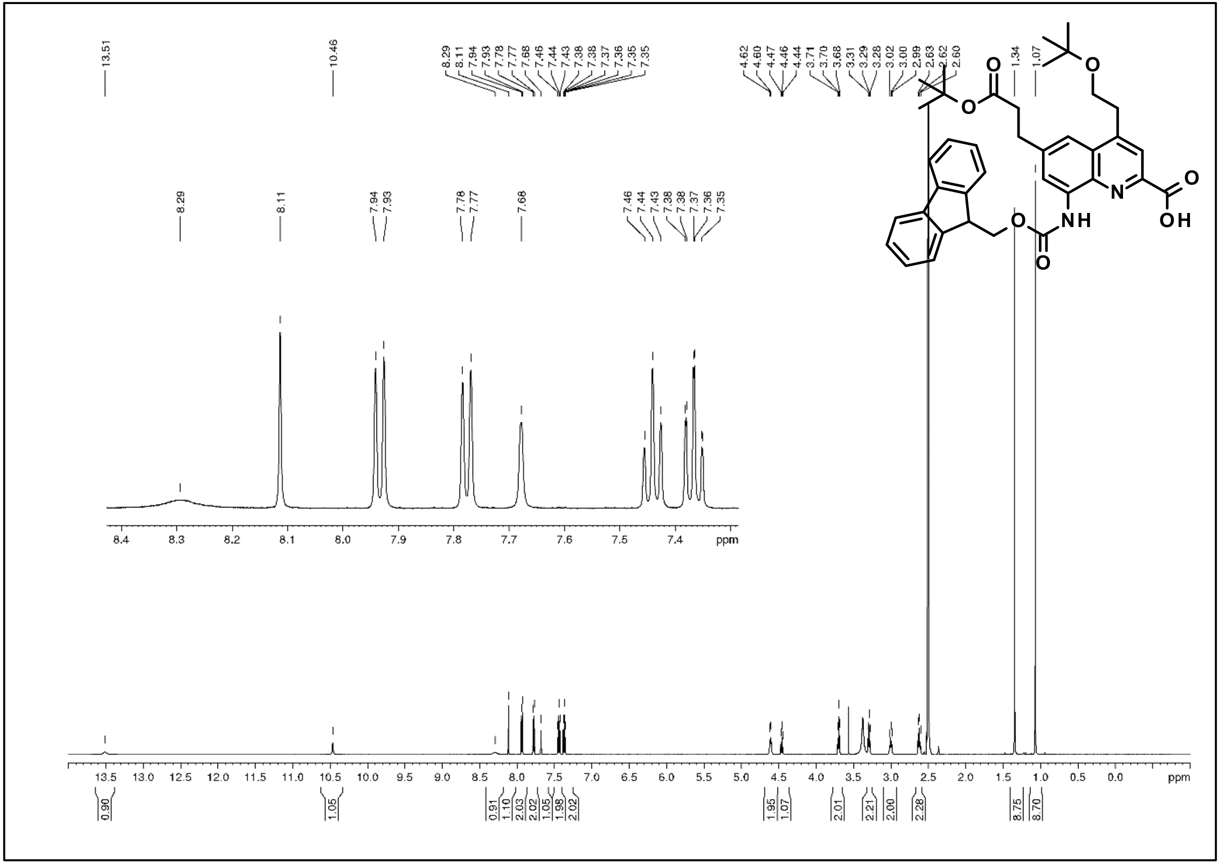


Figure S139. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **21c**.

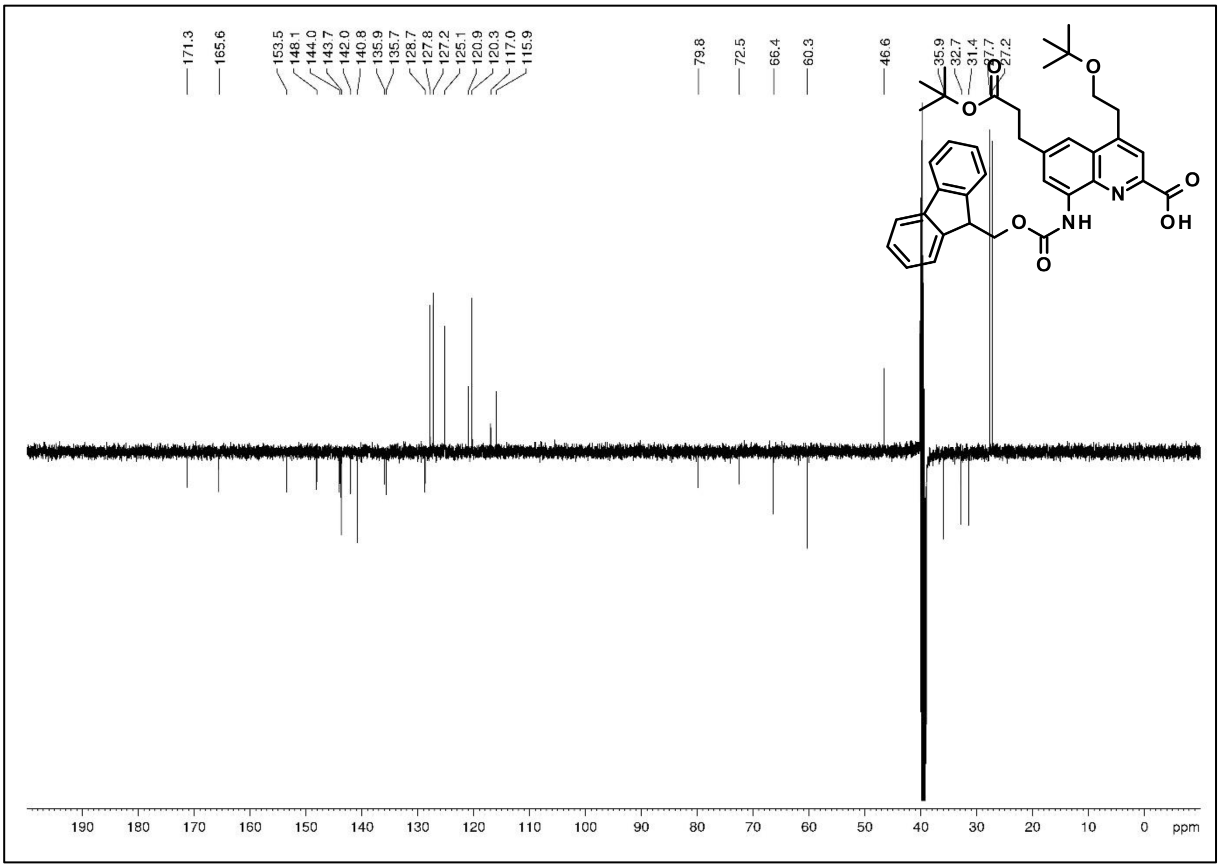


Figure S140. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **21c**.

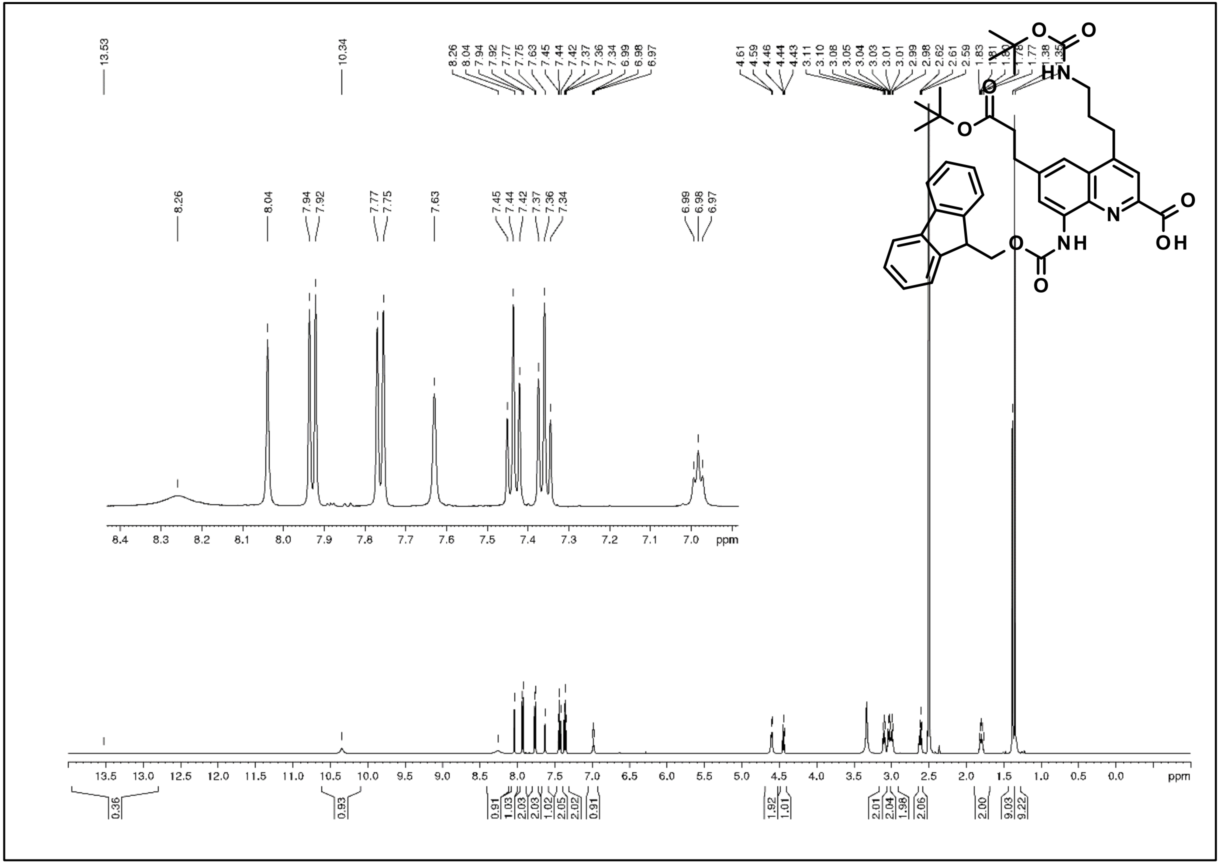


Figure S141. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **21d**.

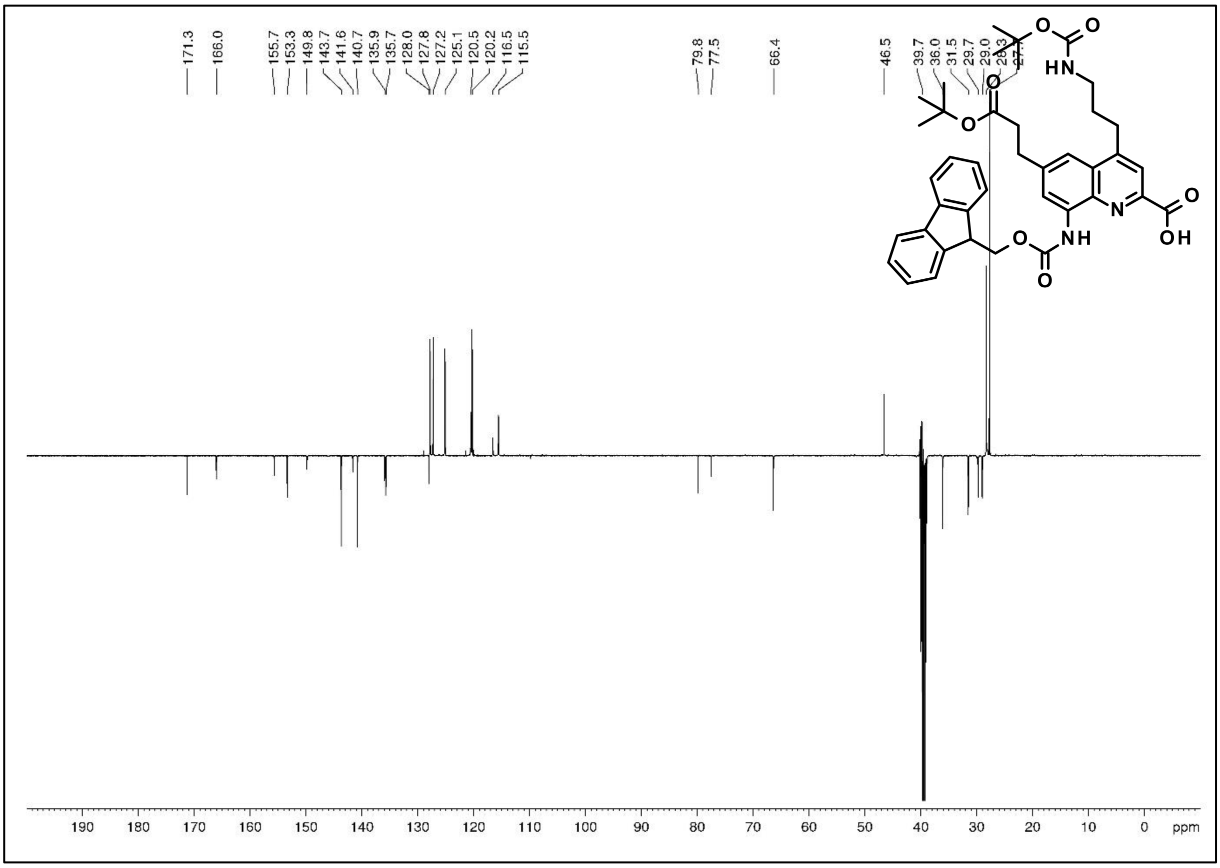


Figure S142. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **21d**.

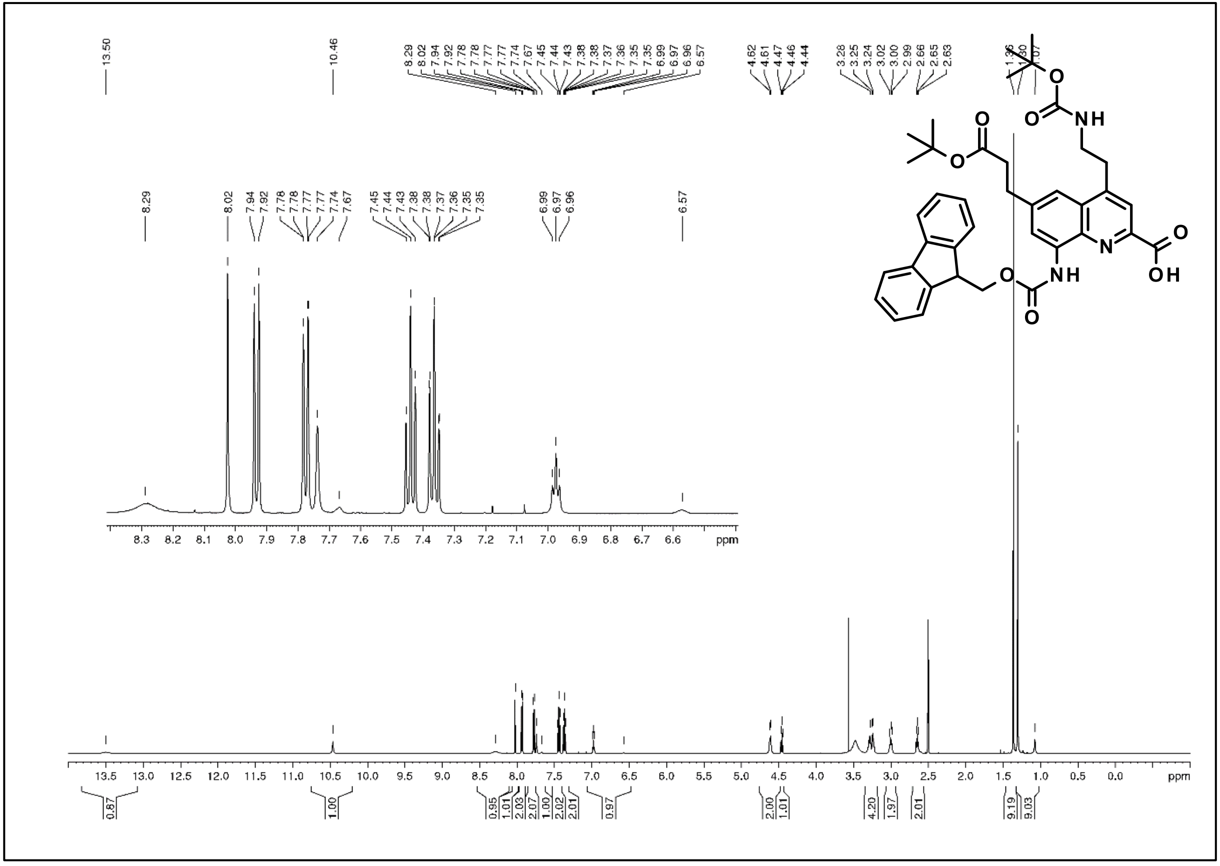


Figure S143. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **21e**.

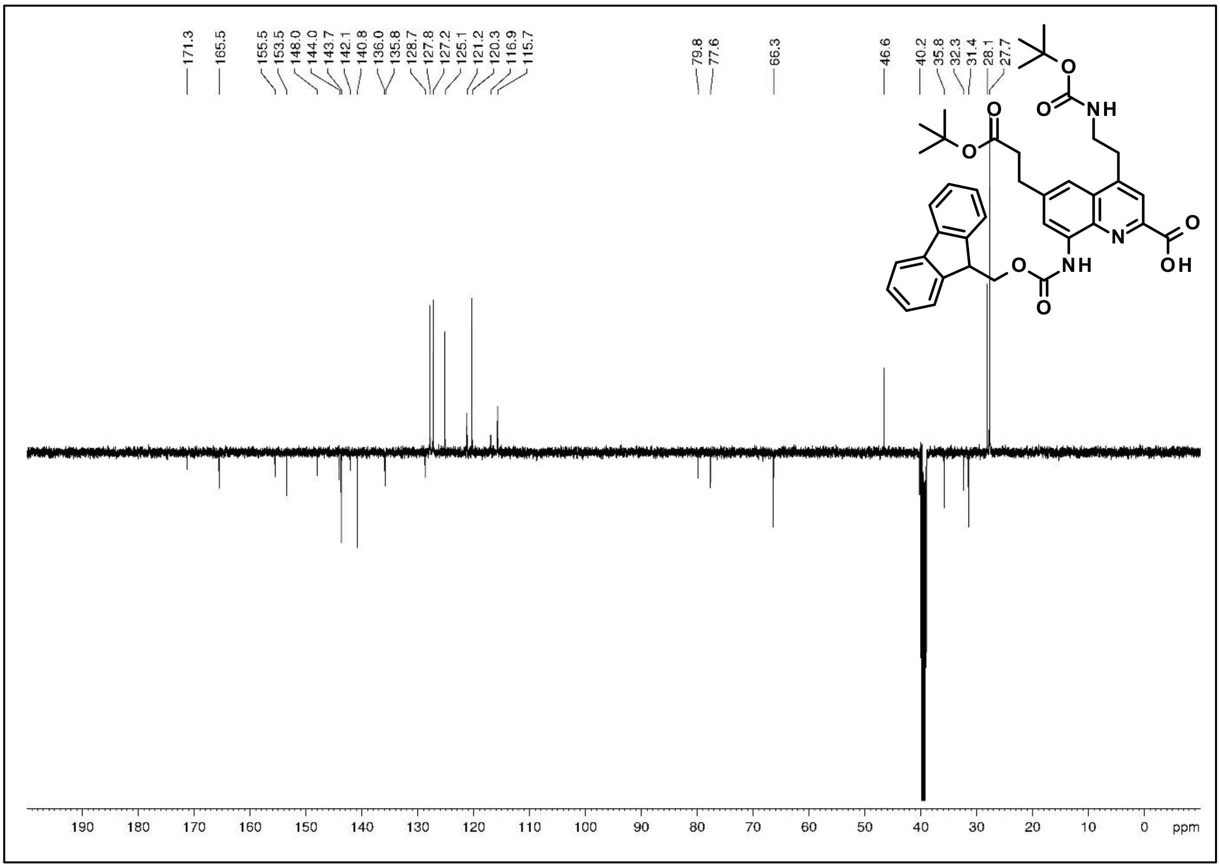


Figure S144. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **21e**.

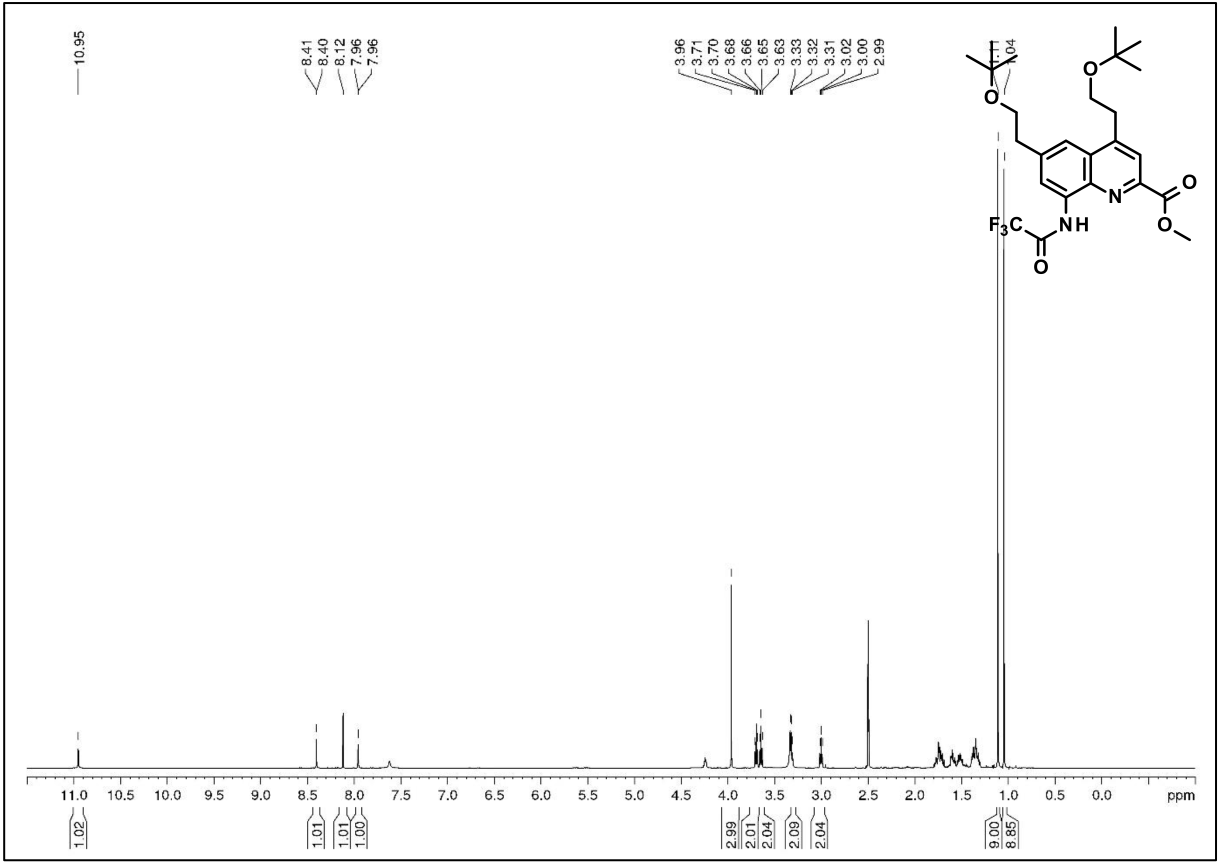


Figure S145. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **22b**.

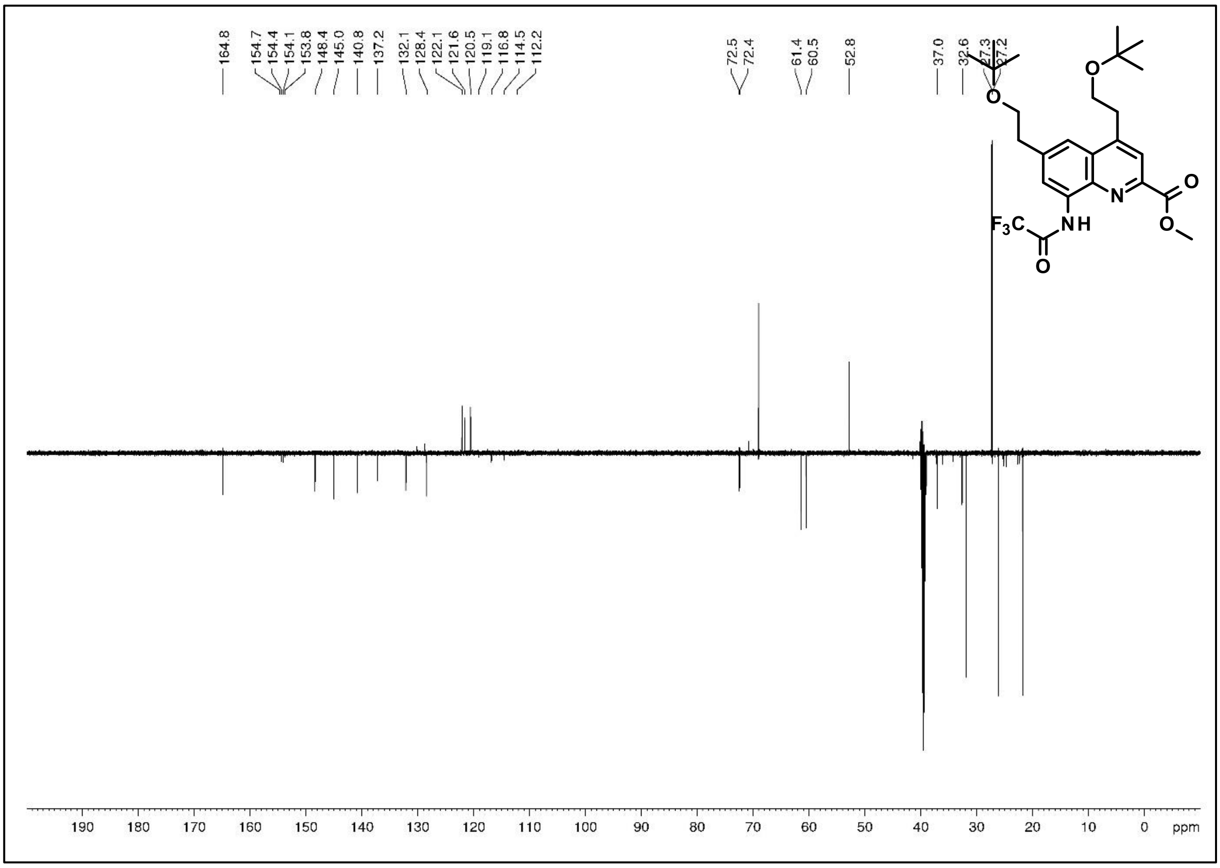


Figure S146. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **22b**.

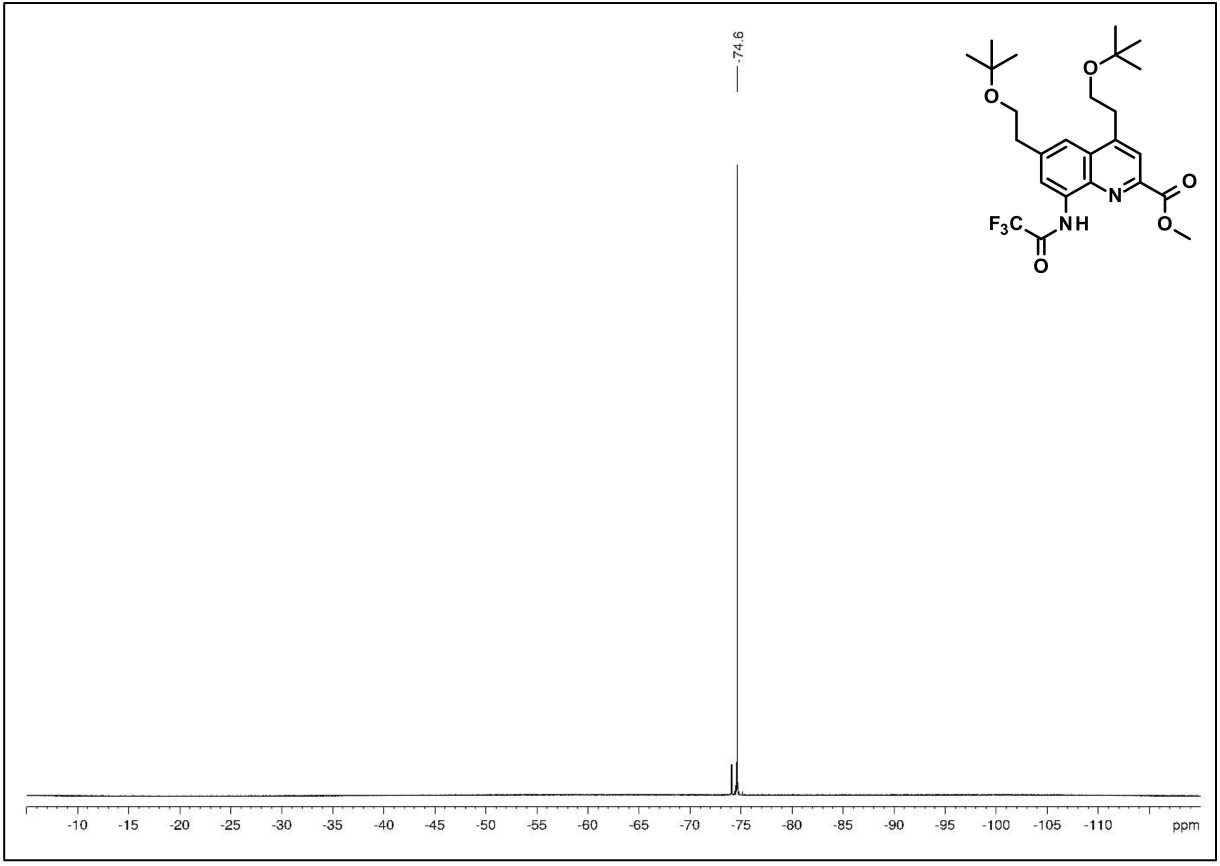


Figure S147. ^{19}F NMR (376 MHz, DMSO-d$_6$) of compound **22b**.

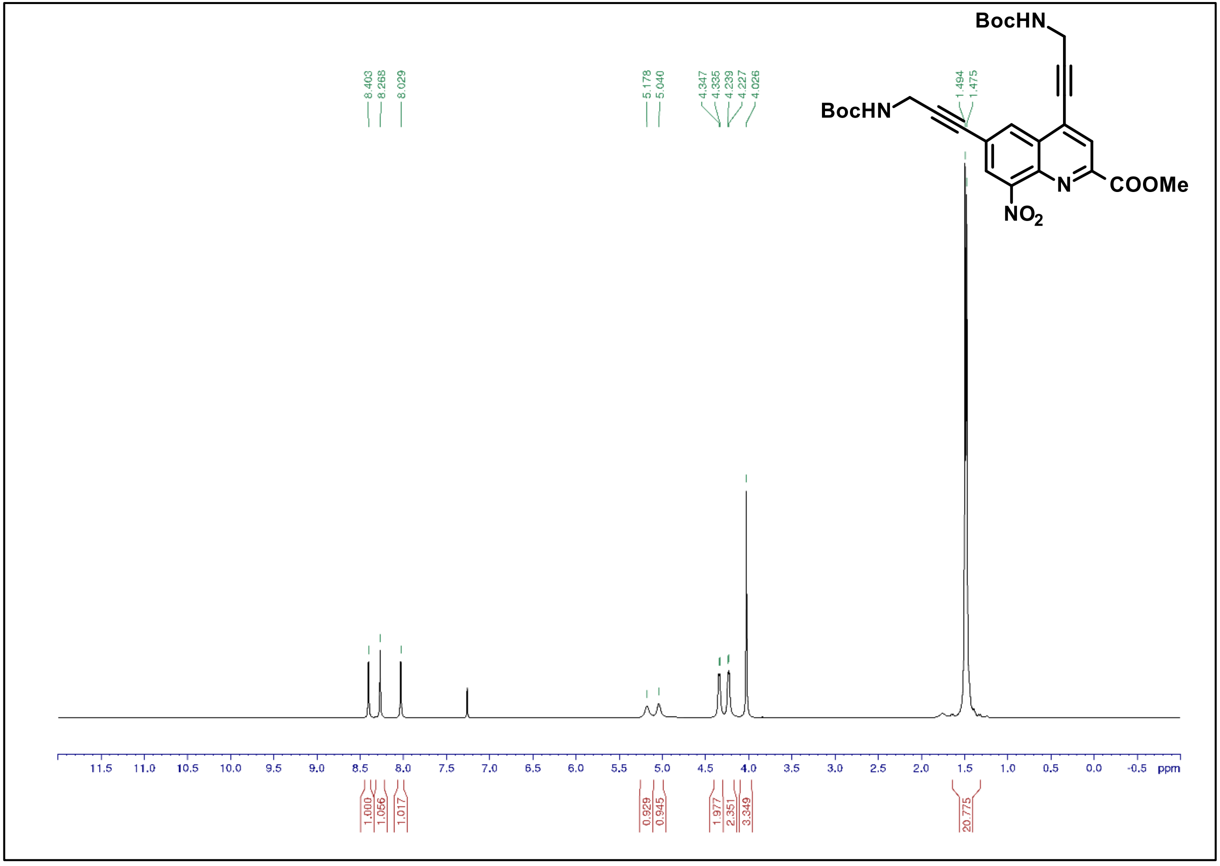


Figure S148. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **24a**.

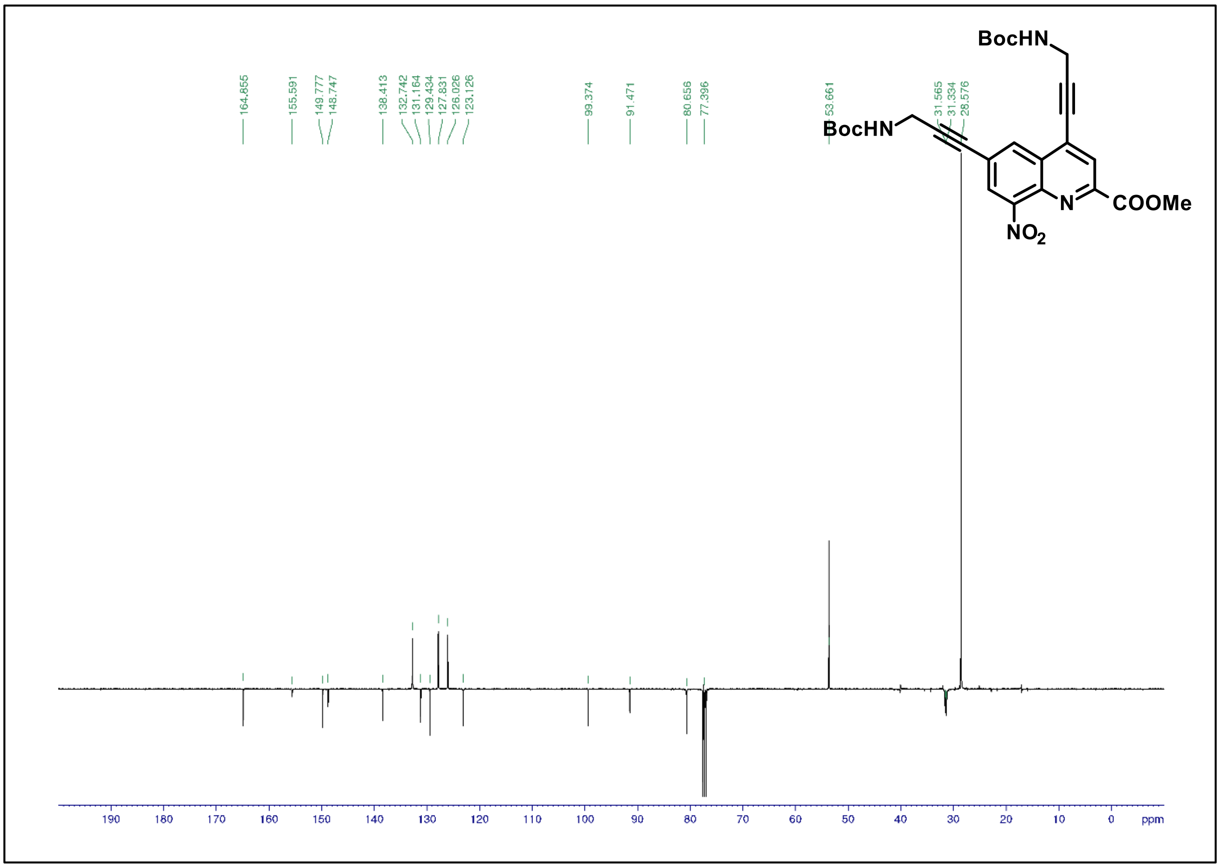


Figure S149. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) of compound **24a**.

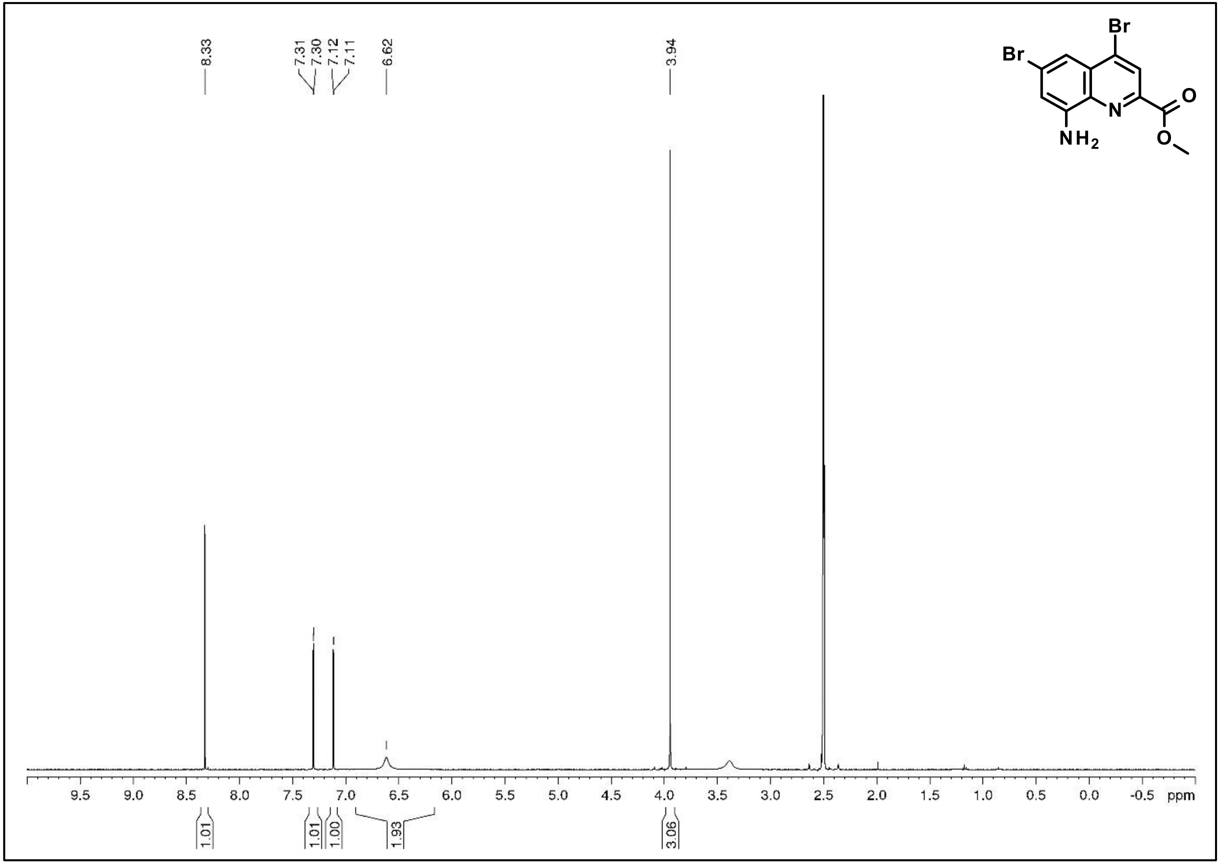


Figure S150. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **25**.

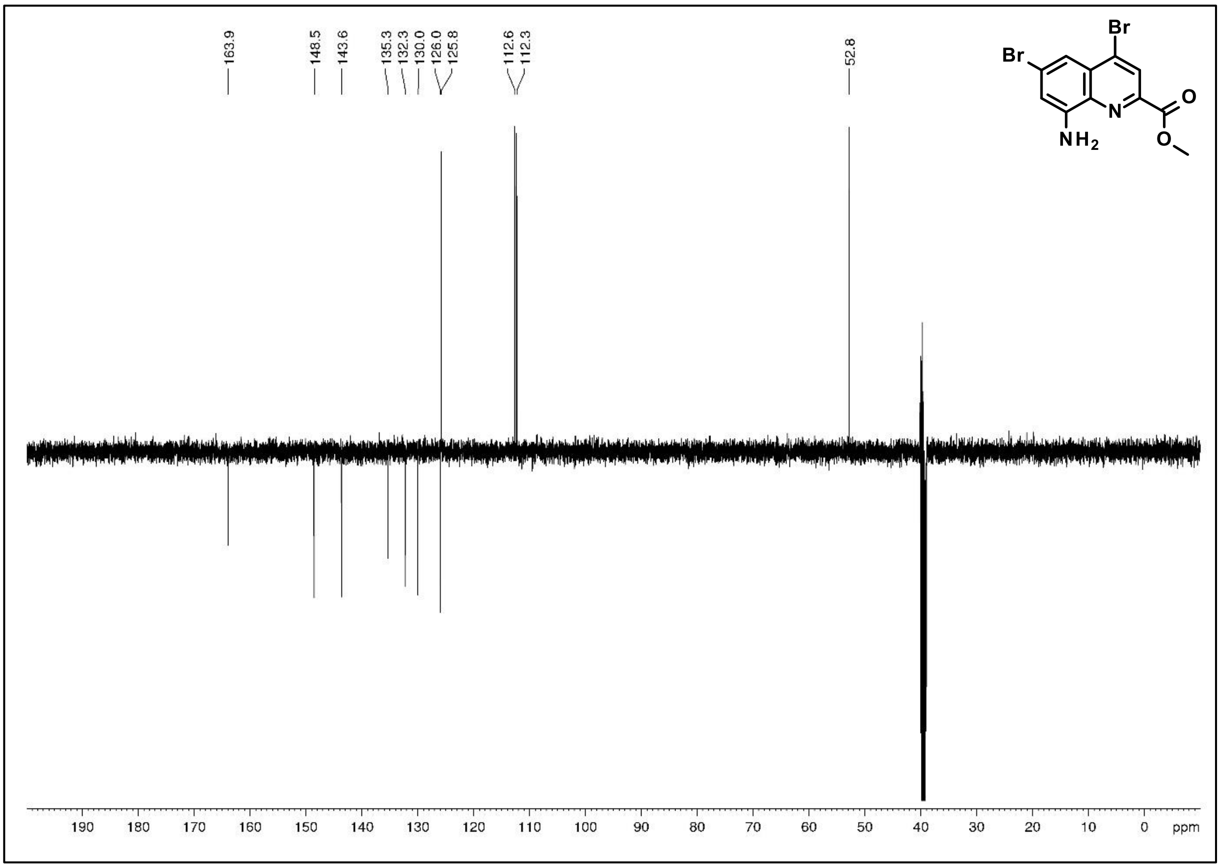


Figure S151. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **25**.

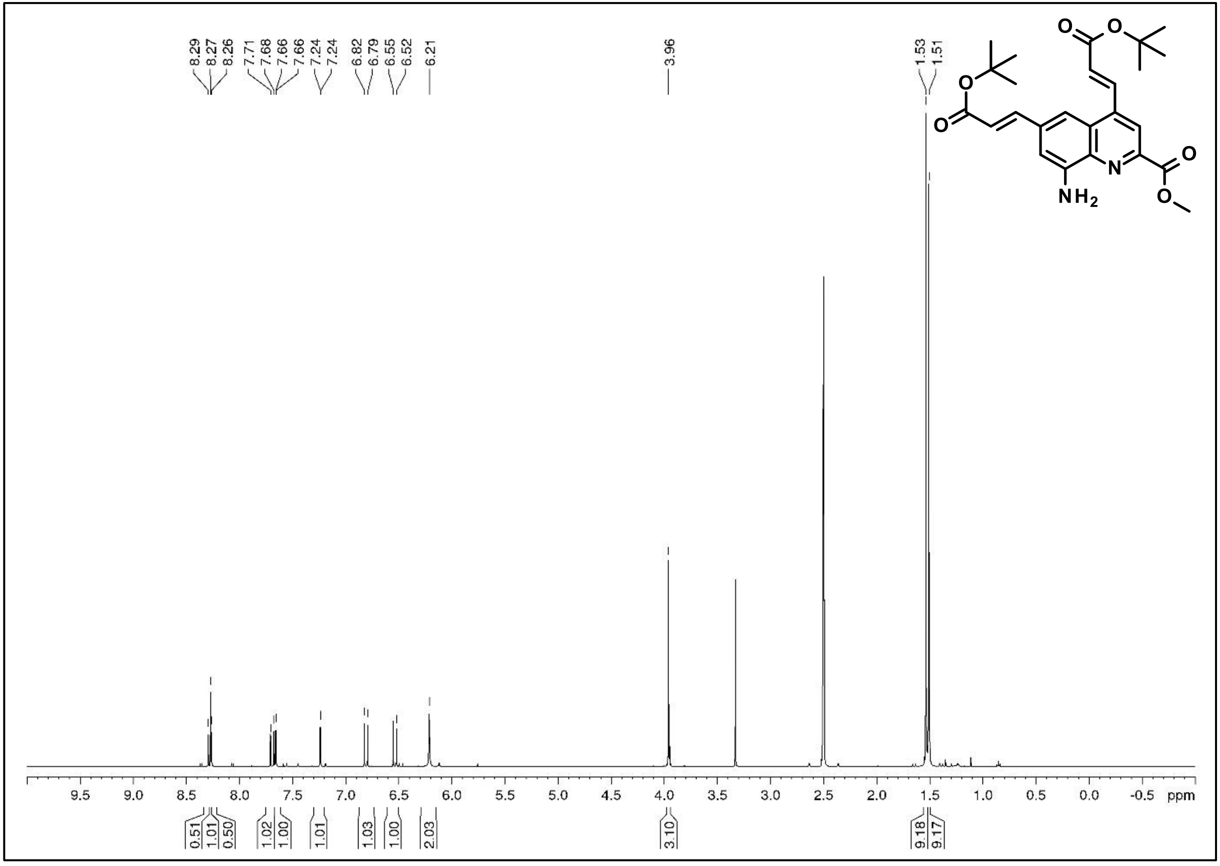


Figure S152. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **26**.

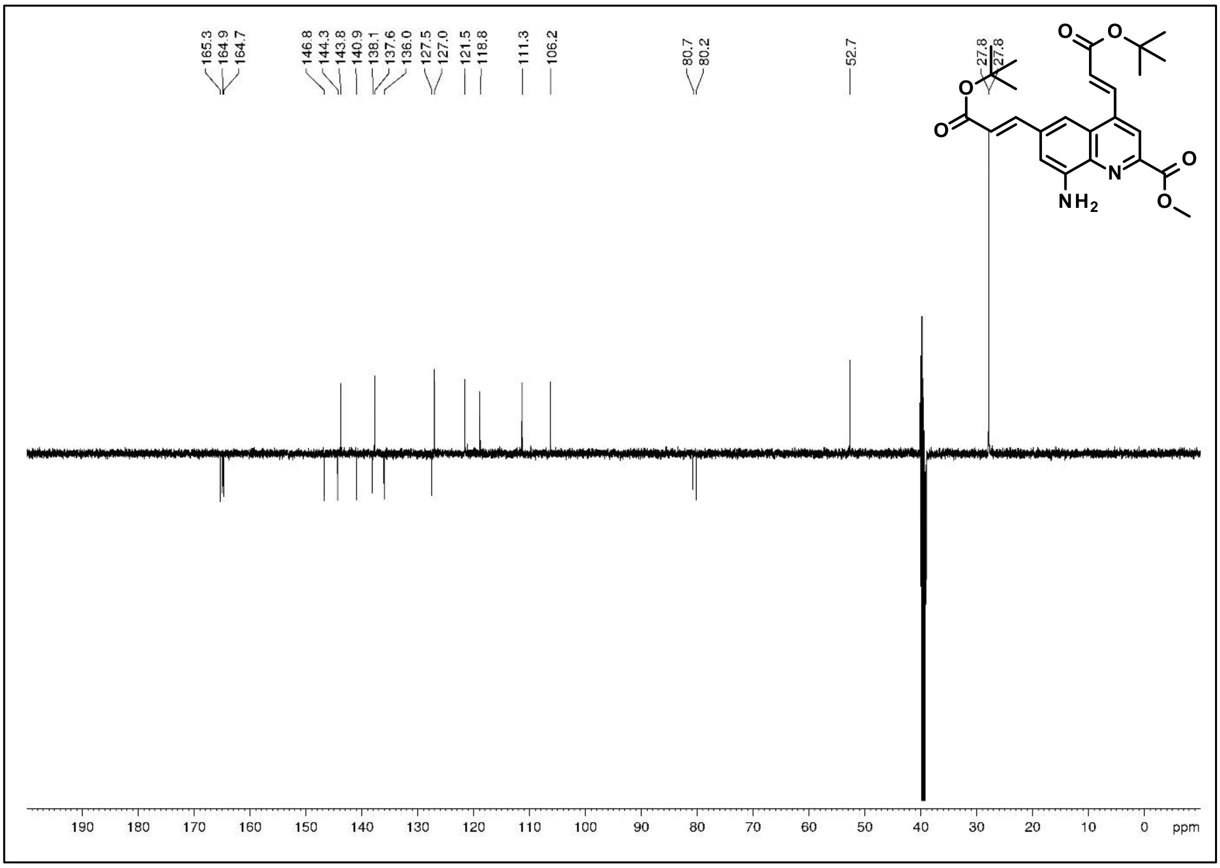


Figure S153. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) of compound **26**.

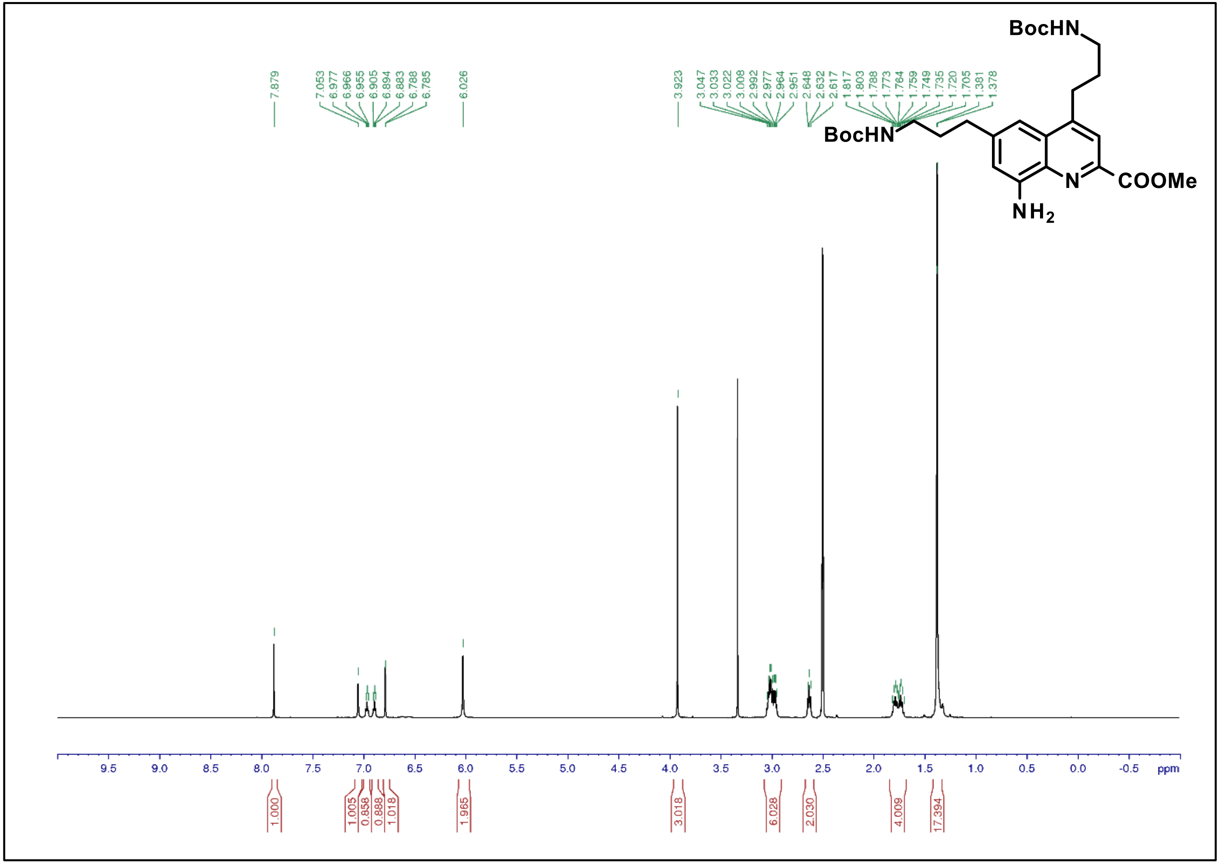


Figure S154. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **27a**.

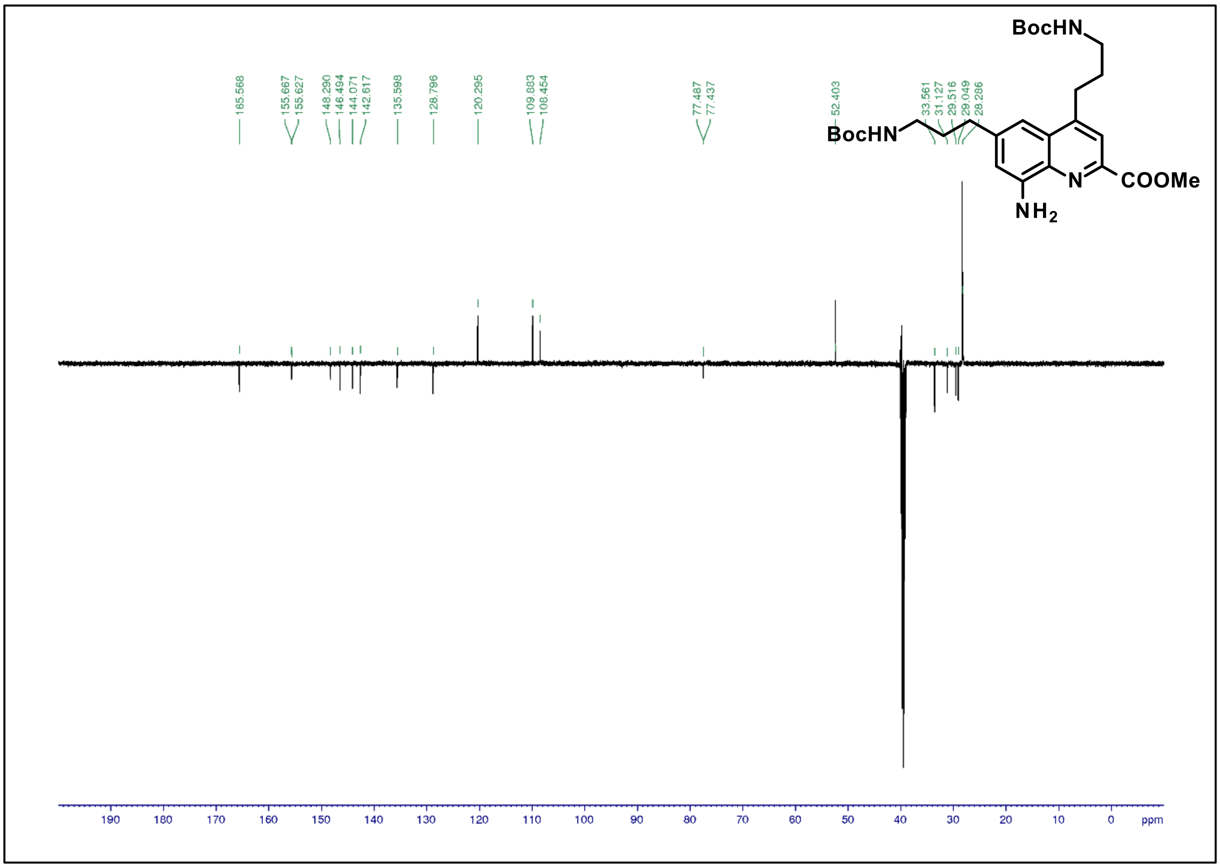


Figure S155. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d$_6$) of compound **27a**.

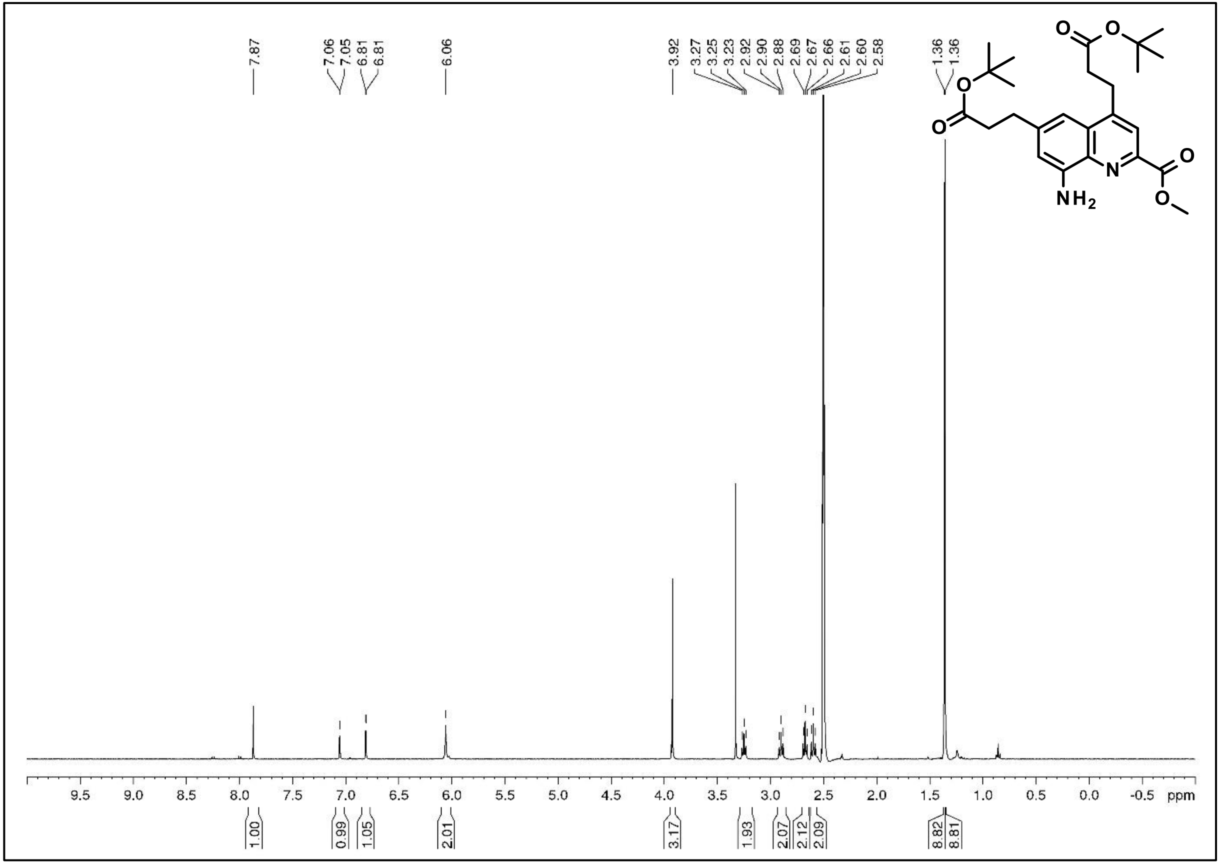


Figure S156. ^{1}H NMR (400 MHz, DMSO-d$_6$) of compound **27c**.

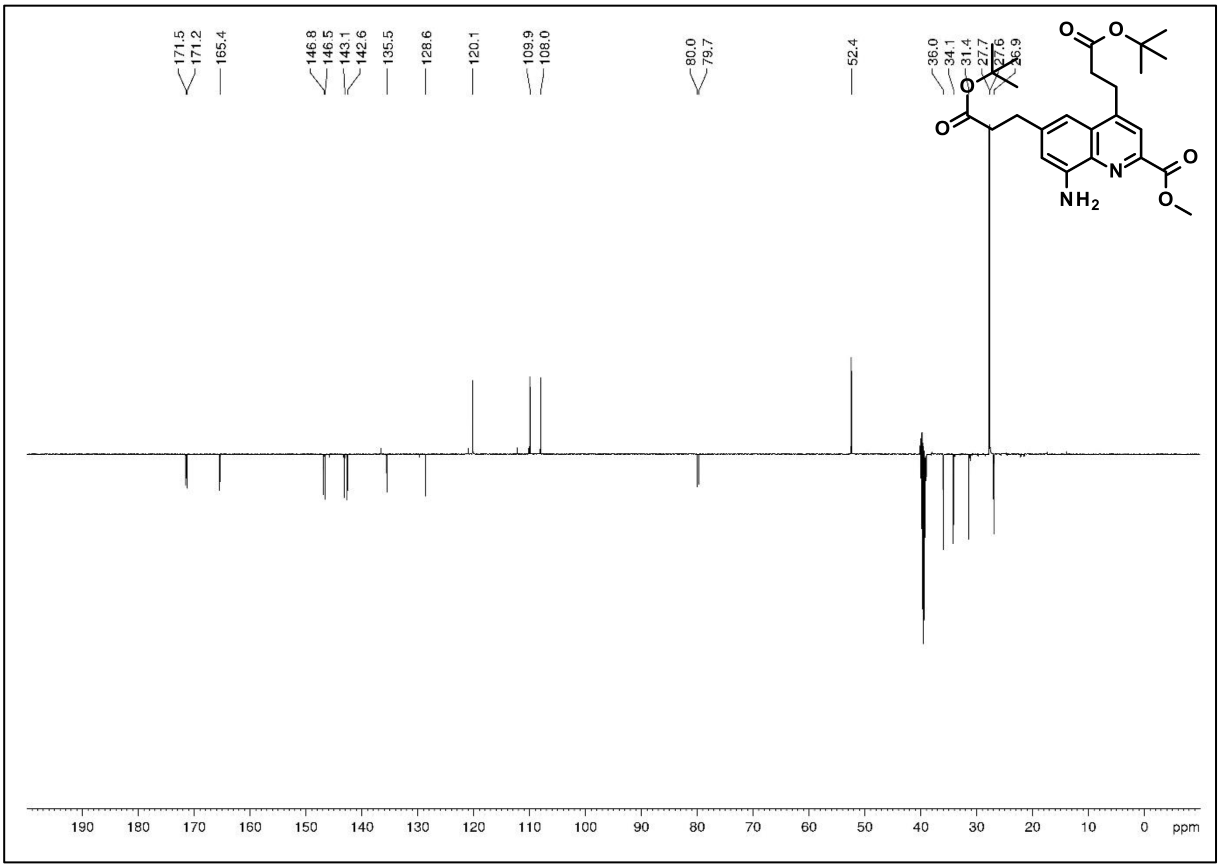


Figure S157. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **27c**.

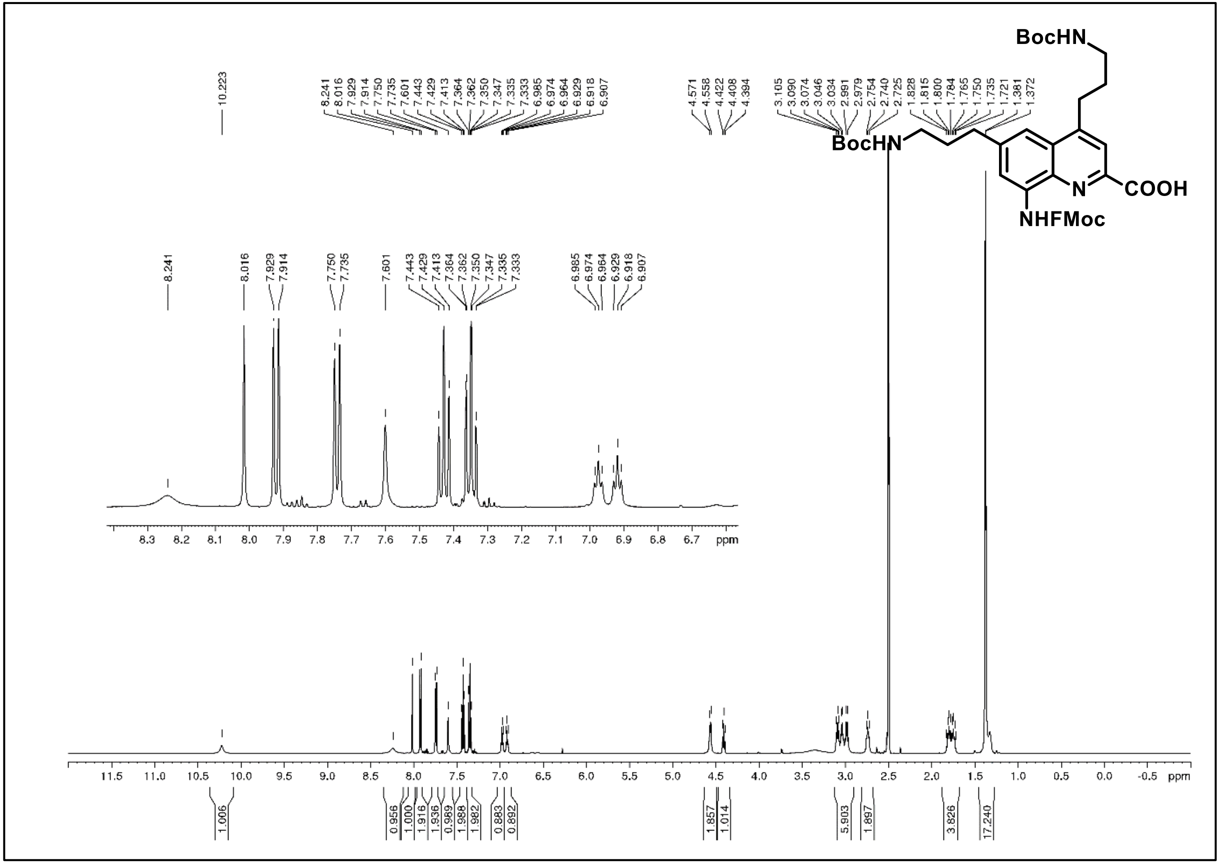


Figure S158. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **28a**.

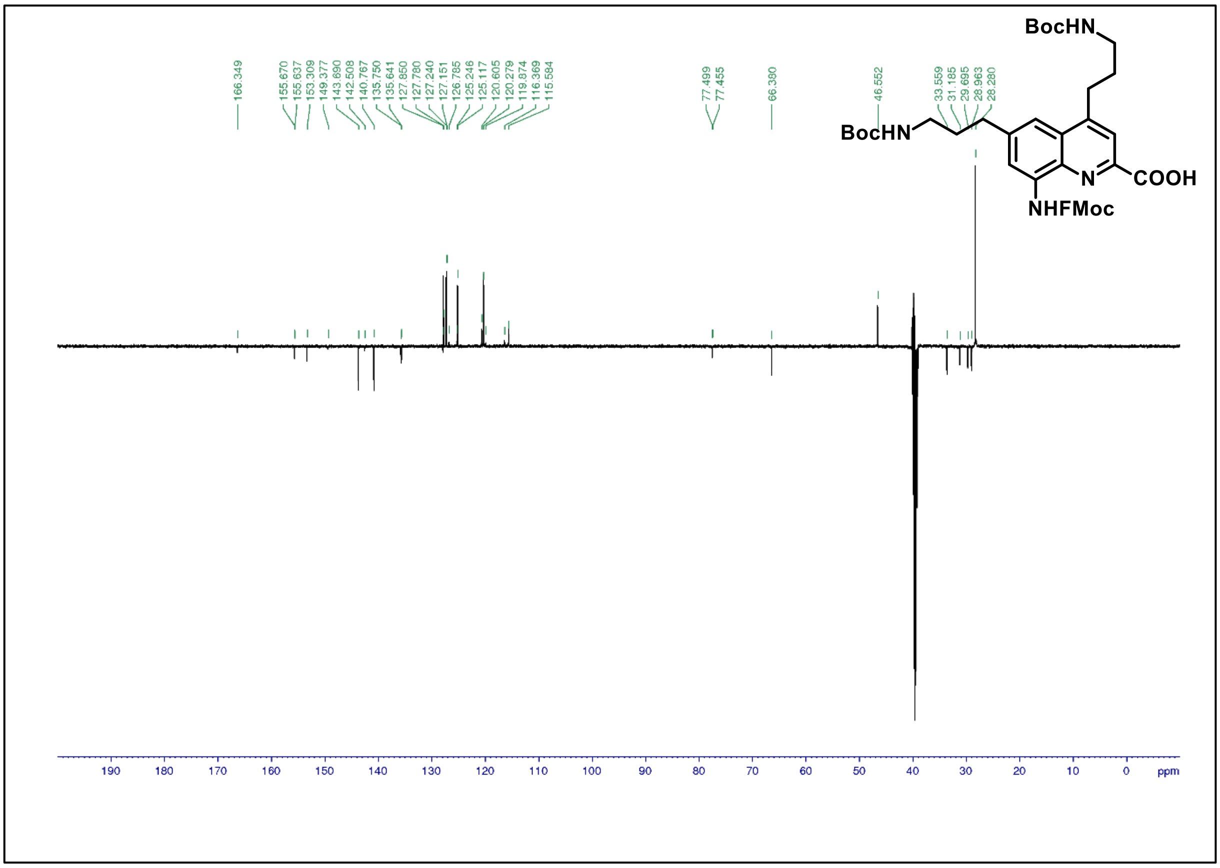


Figure S159. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **28a**.

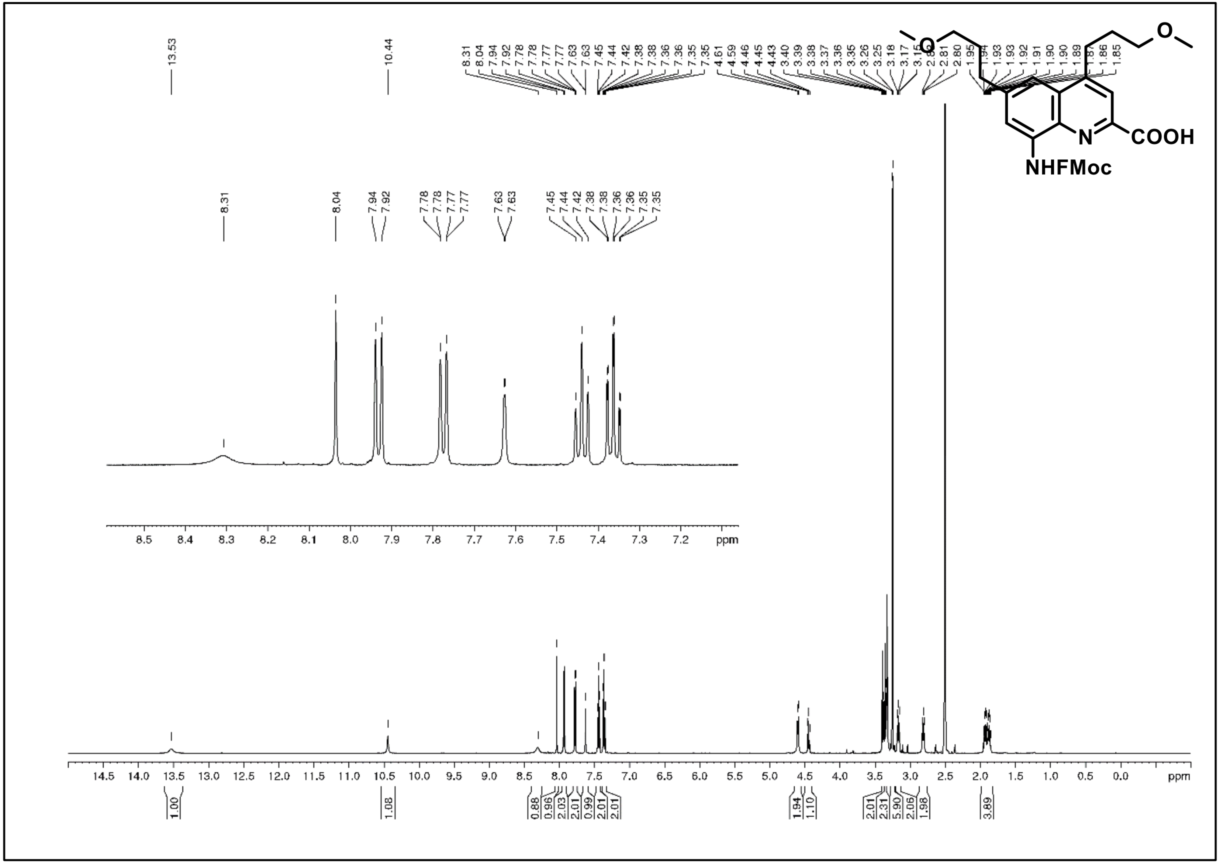


Figure S160. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **28b**.

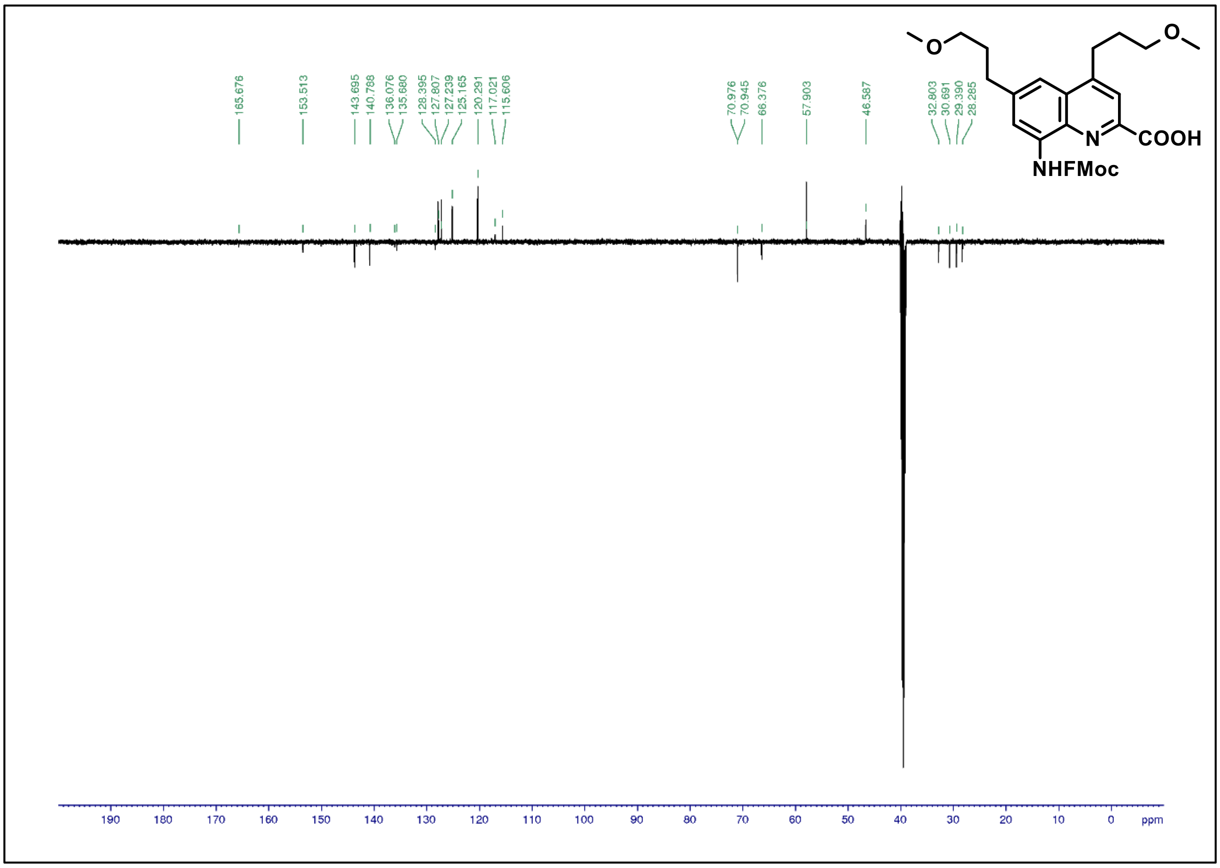


Figure S161. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **28b**.

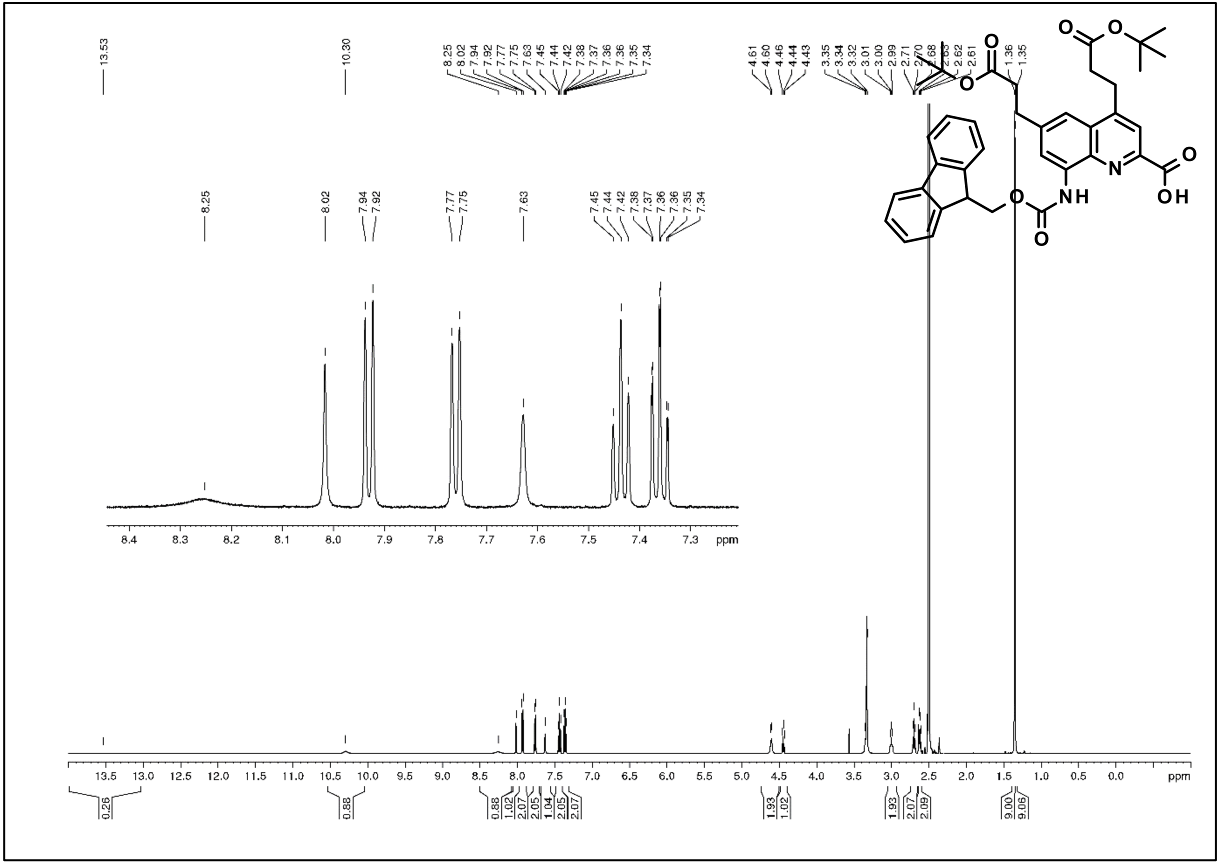


Figure S162. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **28c**.

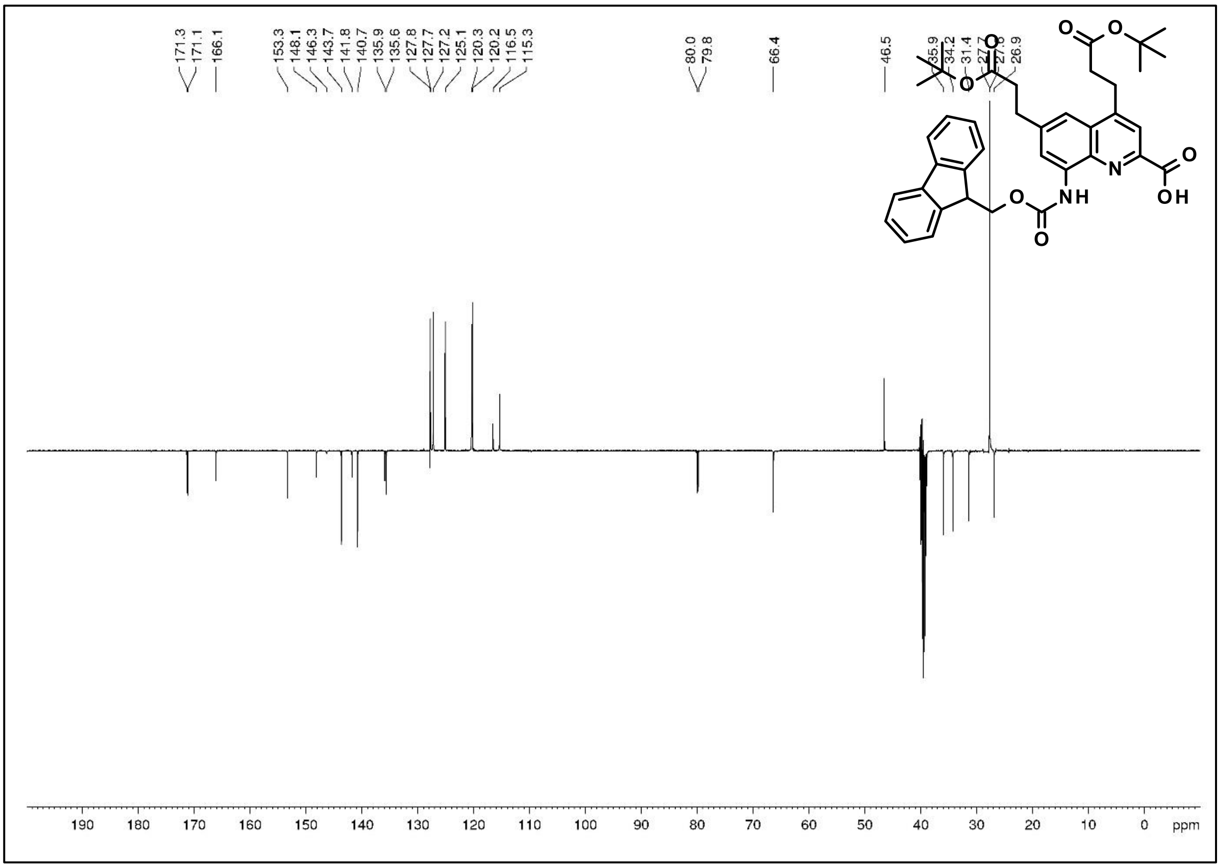


Figure S163. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of compound **28c**.

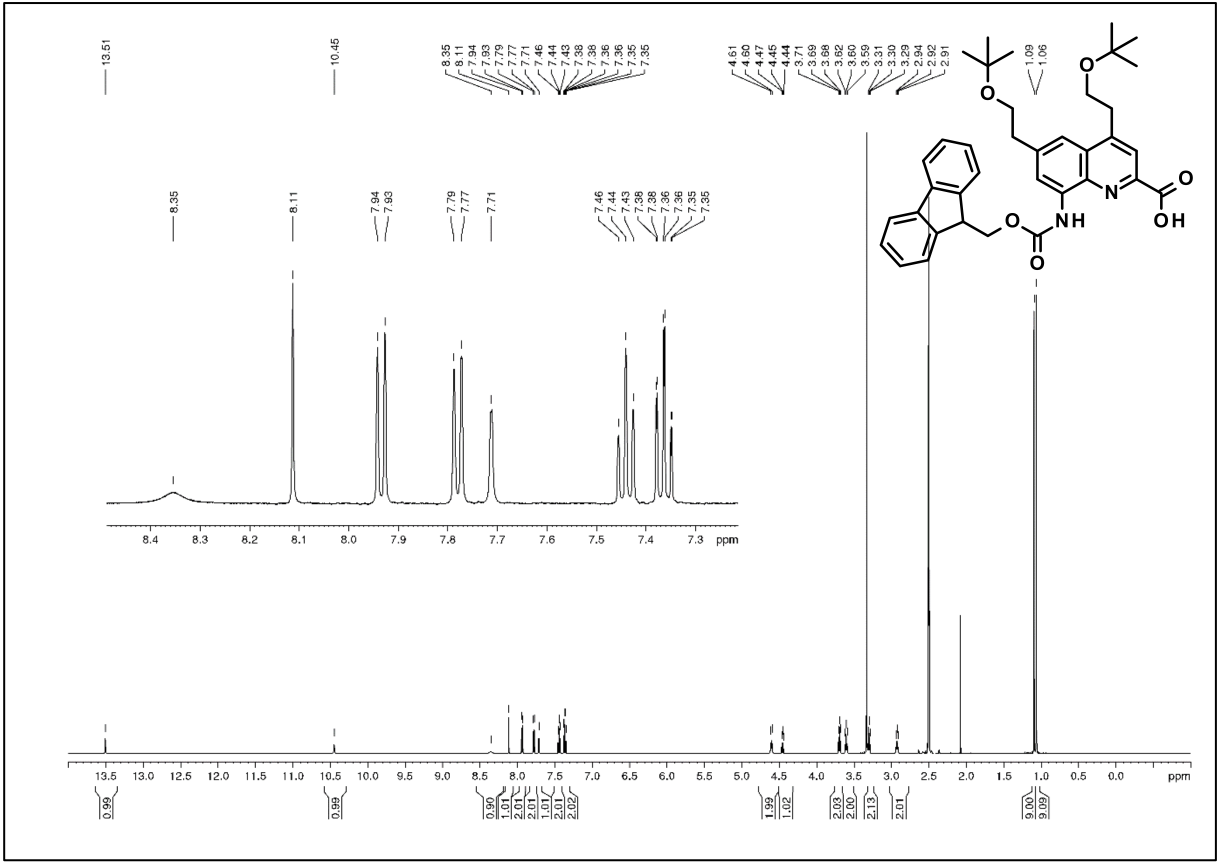


Figure S164. ^{1}H NMR (500 MHz, DMSO-d$_6$) of compound **28d**.

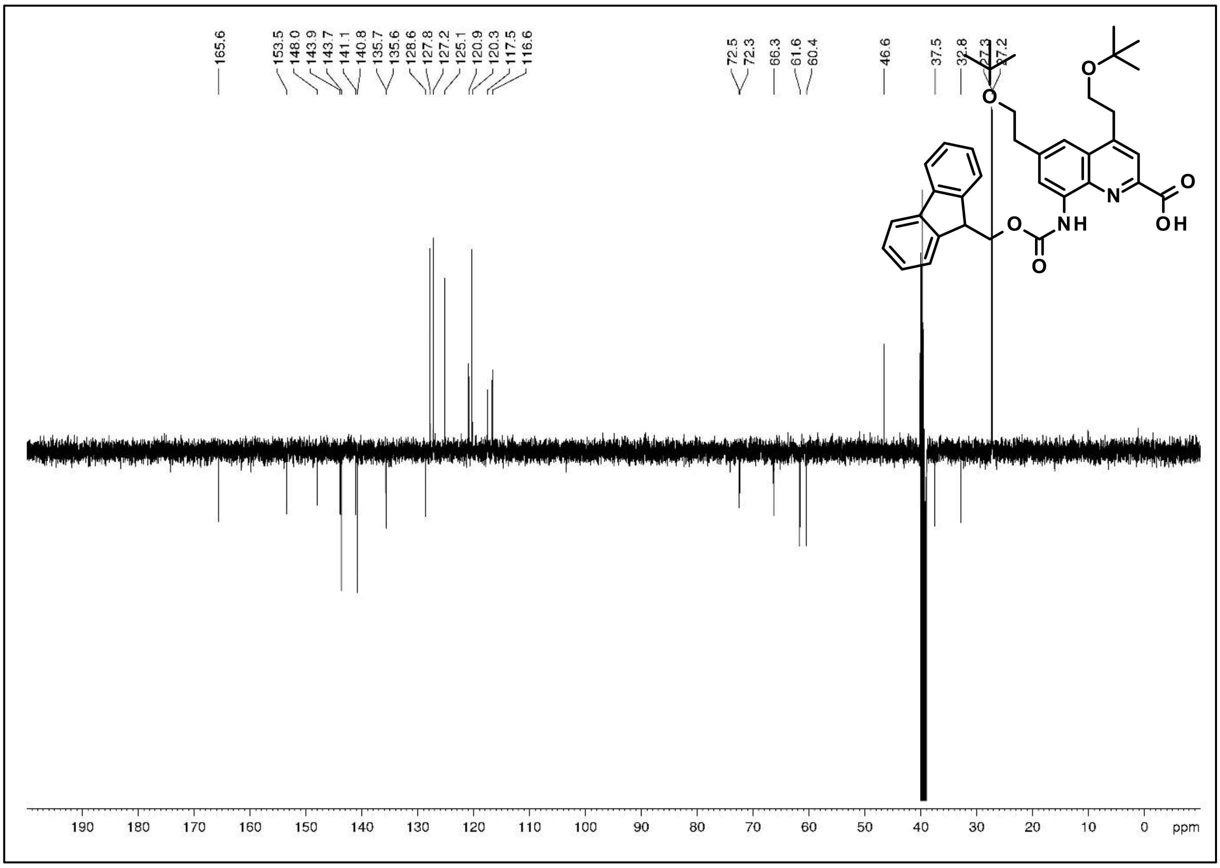


Figure S165. ^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) of compound **28d**.

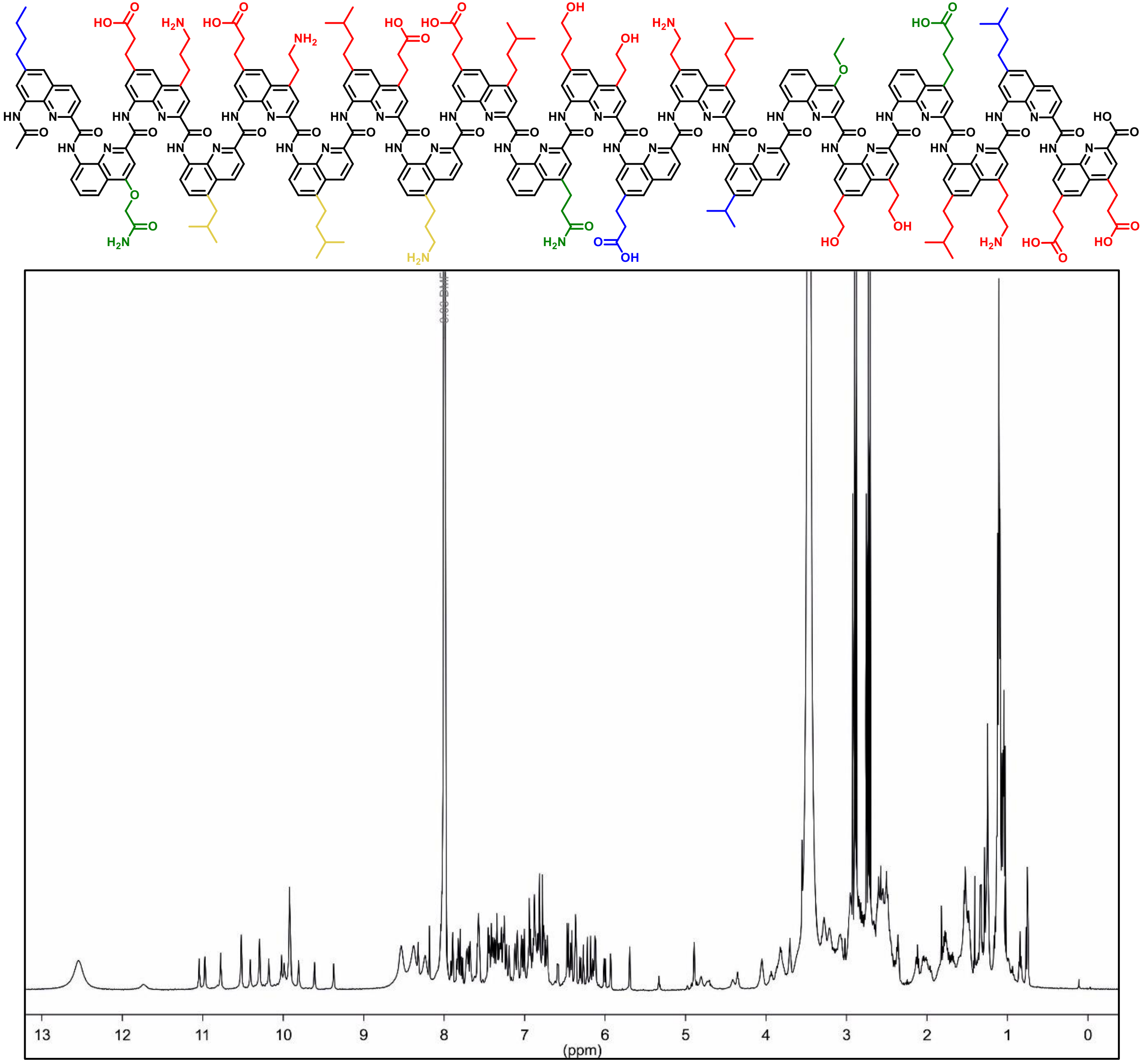
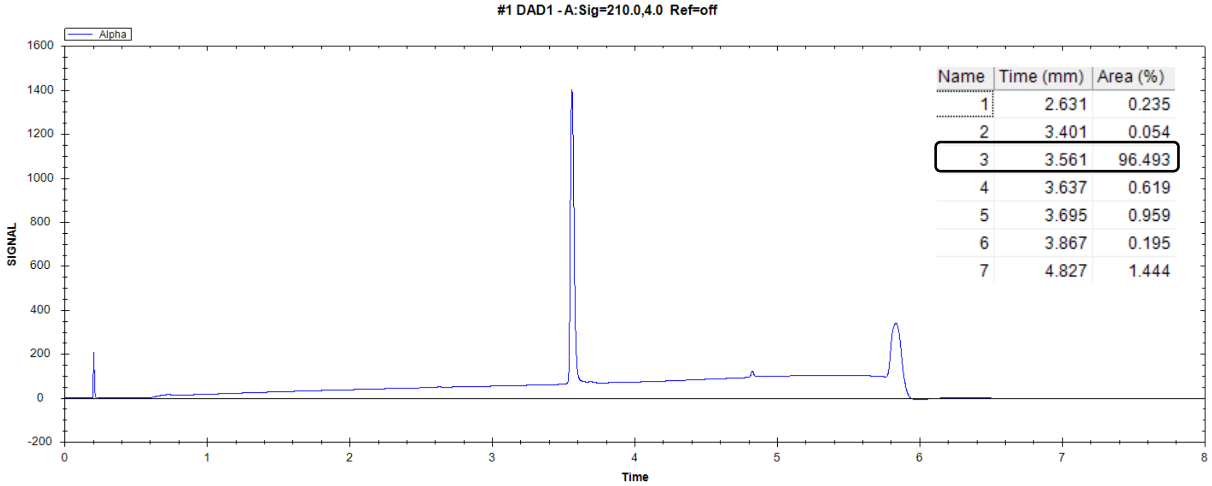


Figure S166. ^{1}H NMR (500 MHz, DMF-d$_7$) of compound **29**.

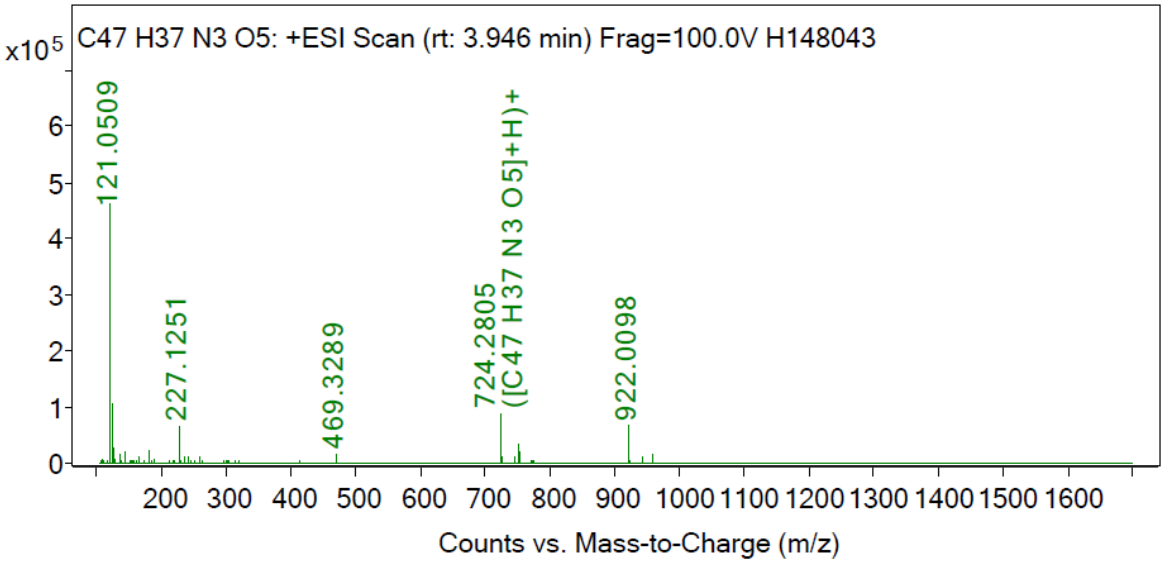
3.4 UV and MS spectra of newly synthesized compounds

A representative example of UV chromatogram and MS spectrum of final intermediate **7c** is shown below:

General conditions: LC-HRMS were determined on an Agilent 1290 Infinity II - Agilent 6545 LC-QTOF, ion source temperature 200°C, ESI +/-, ionization voltage: +/-4.5 kV. InfinityLab Poroshell 120 SB-C18, 2.1 mm, 1.9 µm column. Mass resolution: min. 10000.



Name	Time (mm)	Area (%)
1	2.631	0.235
2	3.401	0.054
3	3.561	96.493
4	3.637	0.619
5	3.695	0.959
6	3.867	0.195
7	4.827	1.444



3.5 The cumulative yields of advanced intermediates and final building blocks

Quinoline precursor (side chain position)	Advanced intermediate	Cumulated yield (steps)	Final Fmoc-acid monomer	Cumulated yield (steps)	Yield limiting transformation
1 (4)	**6a**	93%(2)	**7a**	60% (3)	Fmoc installation
1 (4)	**6b**	75%(2)	**7b**	21%(3)	Fmoc installation
4 (4)	**6c**	35%(2)	**7c**	16%(3)	Heck coupling
4 (4)	**6d**	23%(2)	**7d**	12%(3)	Suzuki coupling
2 (5)	**9a**	47%(2)	**10a**	39% (3)	Suzuki coupling
2 (5)	**9b**	77%(2)	**10b**	59% (3)	Suzuki coupling/Fmoc installation
2 (5)	**9c**	46%(2)	**10c**	36%(3)	Reduction
2 (5)	**9d**	85%(2)	**10d**	78% (3)	Sonogashira coupling
2 (5)	**9e**	60%(2)	**10e**	43% (3)	Sonogashira coupling
3 (6)	**12a**	46%(2)	**13a**	30%(3)	Reduction/ Fmoc installation
3 (6)	**12b**	68%(2)	**13b**	44% (3)	Fmoc installation
3 (6)	**12c**	26%(2)	**13c**	6%(3)	Fmoc installation
3 (6)	**12d**	22%(2)	**13d**	12%(3)	Suzuki coupling
3 (6)	**12e**	47%(2)	**13e**	12%(3)	Fmoc installation
3 (4,6)	**16a**	51%(3)	**17a**	42% (4)	Sonogashira coupling
3 (4,6)	**16b**	31%(3)	**17b**	21% (4)	Suzuki coupling
3 (4,6)	**16c**	42%(3)	**17c**	34% (4)	Suzuki coupling
3 (4,6)	**16d**	26%(3)	**17d**	17% (4)	Suzuki coupling
3 (4,6)	**16e**	40%(3)	**17e**	34% (4)	Suzuki coupling

The cumulative yields of advanced intermediates and final building blocks (continued)

Quinoline precursor (side chain position)	Advanced intermediate	Cumulated yield (steps)	Final Fmoc-acid monomer	Cumulated yield (steps)	Yield limiting transformation
18 (4,6)	**20a**	36%(2)	**21a**	25% (3)	Suzuki coupling
18 (4,6)	**20b**	60%(2)	**21b**	36% (3)	Fmoc installation
18 (4,6)	**20c**	58%(2)	**21c**	35% (3)	Fmoc installation
18 (4,6)	**20d**	65%(2)	**21d**	40% (3)	Fmoc installation
18 (4,6)	**20e**	31%(2)	**21e**	25% (3)	Suzuki coupling
18 (4,6)	**22b**	25%(1)	**28d**	13%(2)	Suzuki coupling
23 (4,6)	**27a**	45%(2)	**28a**	31%(3)	Reduction
23 (4,6)	**27b**	80%(2)	**28b**	24%(3)	Fmoc installation
23 (4,6)	**27c**	51%(3)	**28c**	37%(4)	NO_2 reduction

3.6 Literature:

[1] Hu, X., Dawson, S. J., Mandal, P. K., de Hatten, X., Baptiste, B. and Huc, I. Optimizing side chains for crystal growth from water: a case study of aromatic amide foldamers. *Chem. Sci*. **2017**, 8, 3741-3749. https://doi.org/10.1039/C7SC00430C
[2] Zwillinger, M.; Reddy, P. S.; Wicher, B.; Mandal, P. K.; Csékei, M.; Fischer, L.; Kotschy, A.; Huc, I. Aromatic Foldamer Helices as α-Helix Extended Surface Mimetics. *Chem. Eur. J.* **2020**, *26* (72), 17366–17370. https://doi.org/10.1002/chem.202004064.
[3] Sőregi, P., Zwillinger, M., Vágó, L., Csékei, M., Kotschy, A. High density information storage through isotope ratio encoding. *Chem. Sci*. **2024**. https://doi.org/10.1039/D4SC03519D
[4] Baptiste, B., Douat-Casassus, C., Laxmi-Reddy, K., Godde, F., Huc, I., Solid Phase Synthesis of Aromatic Oligoamides: Application to Helical Water-Soluble Foldamer. *J. Org. Chem*. **2010**, *75*, 7175-7185. https://doi.org/10.1021/jo101360h
[5] Corvaglia, V., Sanchez, F., Menke, F. S., Douat, C., Huc, I. Optimization and Automation of Helical Aromatic Oligoamide Foldamer Solid-Phase Synthesis. *Chem. Eur. J.* 2023, 29, e202300898. https://doi.org/10.1002/chem.202300898