Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Developing ciprofloxacin analogues against plant DNA gyrase: A novel herbicide mode of action

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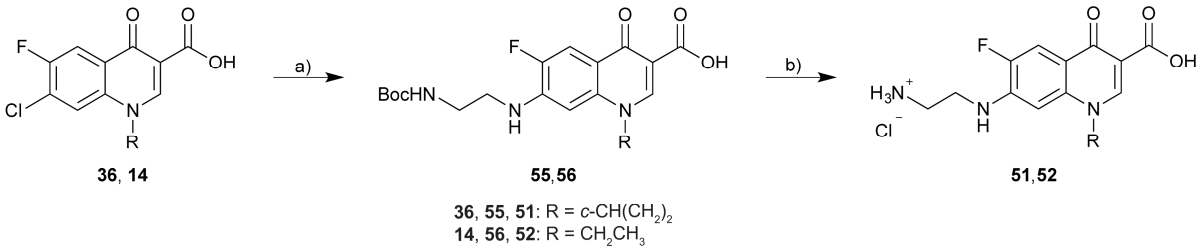
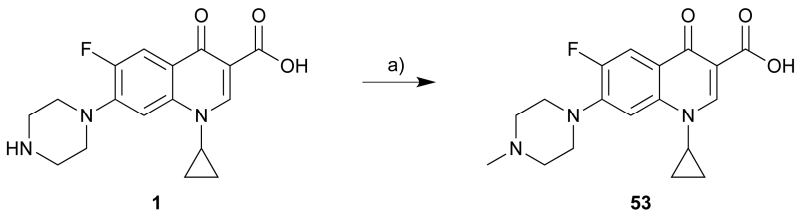


36, **14** **55**,**56** **51**,**52**

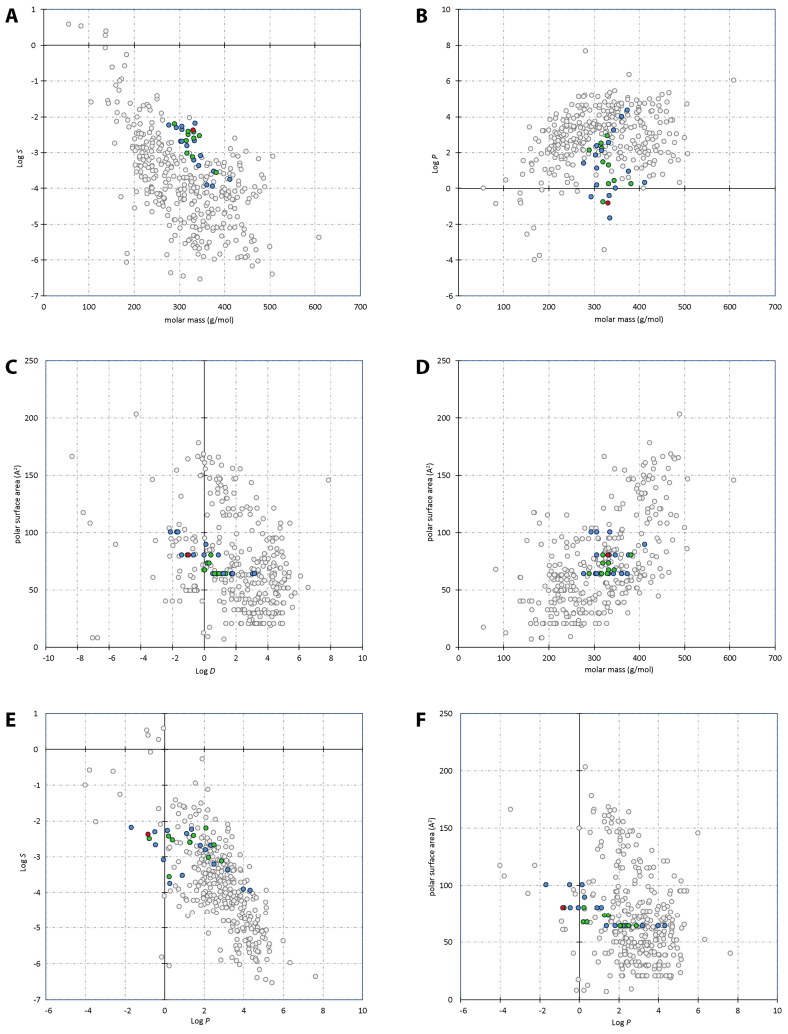
36, **55**, **51**: R = *c*-$CH(CH_2)_2$
14, **56**, **52**: R = CH_2CH_3

Supporting Scheme 1. a) *tert*-Butyl *N*-(2-aminoethyl)carbamate[1] DMSO; b) 3M HCl, EtOH.

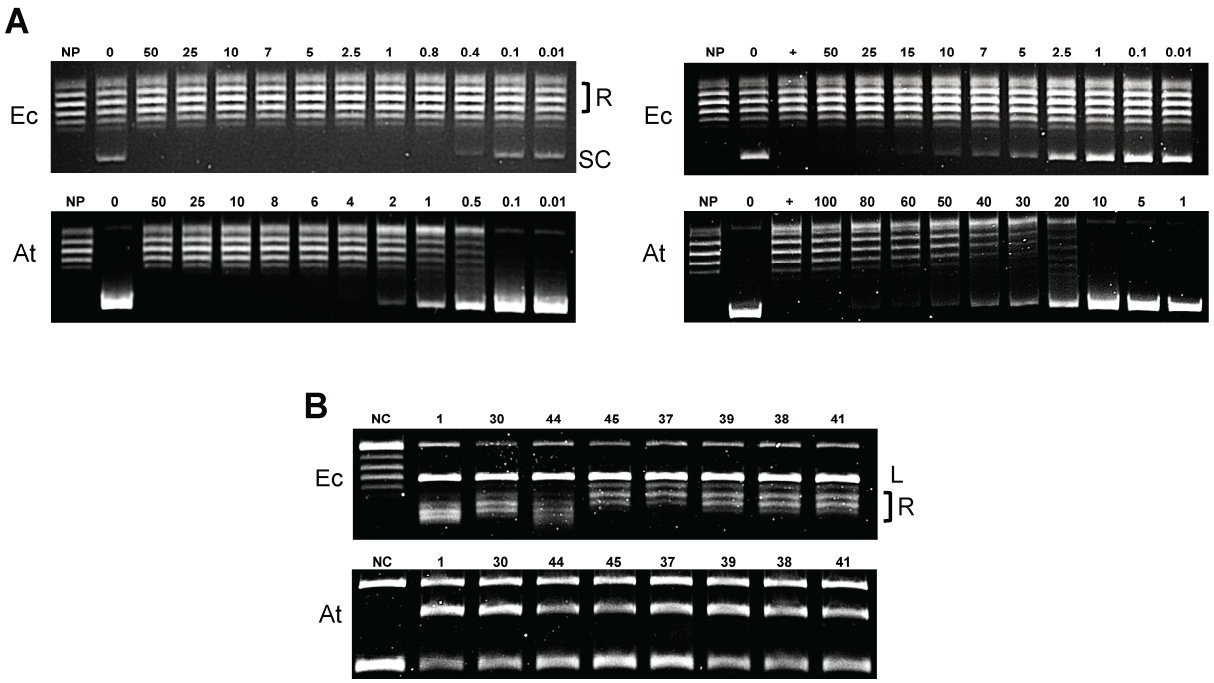


1 **53**

Supporting Scheme 2. a) 85% aq. HCOOH, 41% aq. CH_2O.



Supporting Figure 1. Cluster analysis of physicochemical properties of ciprofloxacin and prepared analogues versus known herbicides. Representative charts (**A**–**F**) were extracted using an interactive database containing the physicochemical properties of commercial herbicides.[2] New data points (i.e. ciprofloxacin and synthesised compounds) were added to the database and plotted on graphs comparing two chemical properties (**A**) molar mass *vs* aqueous solubility (Log *S*) (**B**) molar mass *vs* lipophilicity (Log *P*), (**C**) distribution coefficient (Log *D*) *vs* polar surface area (Å^2), (**D**) molar mass *vs* polar surface area (Å^2), (**E**) lipophilicity (Log *P*) *vs* aqueous solubility (Log *S*) and (**F**) lipophilicity (Log *P*) *vs* polar surface area (Å^2). The red dot is ciprofloxacin, the green dots and blue dots represent the analogues, with the green and blue dots representing the analogues with or without reasonable herbicidal activity, respectively.



Supporting Figure 2. Gyrase supercoiling inhibition and DNA cleavage assays. (A) Representative supercoiling inhibition assays for ciprofloxacin **1** (left) and compound **44** (right); compound concentrations (μM) are specified above each gel. (B) Gyrase cleavage assays with 100 μM of each indicated compound. Top gels: *E. coli* gyrase (Ec); bottom gels: *A. thaliana* gyrase (At). R: relaxed topoisomers, SC: supercoiled DNA, L: linear DNA, NP: no protein control, +: 50 μM ciprofloxacin (positive control) and NC: no compound. *Note*: partially relaxed DNA species can be seen in the *E. coli* gyrase assay as, under these conditions, some ATP-independent DNA relaxation can occur.

Supporting Table 1. Overview of compounds displaying herbicidal potency against *A. thaliana* Col-0 with an IC_{50} value greater than 25 mg/L. Minimum inhibitory concentrations (MICs) against *E. coli* B. IC_{50} values against recombinant *A. thaliana* and *E. coli* gyrase. Errors represent standard error of the mean.

	IC_{50}[a]	MIC[a]	DNA Gyrase IC_{50}[b]	
Compound	*A. thaliana*	*E. coli*	*A. thaliana*	*E. coli*
28	>50	0.5	6.60 ± 0.20	2.85 ± 0.25
29	>50	0.25	74.7 ± 3.3	9.26 ± 1.95
31	>200	2	25.9 ± 1.95	4.35 ± 0.56
32	>200	64	>100	>100
33	>25	1	20.6 ± 1.55	2.1 ± 0.53
34	>100	128	>100	>100
35	>200	4	10.6 ± 1.39	2.70 ± 0.60
40	>25	2	4.6 ± 0.1	0.83 ± 0.073
42	>25	1	5.1 ± 0.38	4.35 ± 0.21
43	>200	>128	>100	>100
46	>100	32	9.25 ± 1.3	1.56 ± 0.088
47	>100	16	14.9 ± 1.1	2.43 ± 0.16
48	>25	2	29.9 ± 5.8	16.1 ± 2.6
49	>200	8	21.8 ± 2.05	10.7 ± 1.48
50	>200	>128	>100	>100
51	>100	1	4.75 ± 0.15	1.52 ± 0.11
52	>100	32	19.0 ± 2.25	11.9±0.95
53	>25	0.0078	3.75 ± 0.15	0.55±0.11
54	>25	0.0625	5.80 ± 1.08	0.79±0.14

[a]mg/L. [b]μM

Supporting Table 2. MIC values (mg/L) obtained for susceptibility assays against *P. aeruginosa* (ATCC 19429) and *S. aureus* (ATCC 25923).

Compound	*P. aeruginosa*	*S. aureus*
1	0.125	0.5
28	4	8
29	2	8
30	1	2
31	16	16
32	>128	>128
33	2	2
34	>128	64
35	64	64
37	32	0.25
38	8	0.125
39	>128	0.0625
40	>128	0.25
41	8	0.125
42	32	0.5
43	>128	8
44	>128	0.5
45	16	0.5
46	>128	0.25
47	>128	0.5
48	64	0.5
49	>128	4
50	>128	8
51	4	16
52	64	>128
53	1	0.25
54	2	0.5

Experimental

General

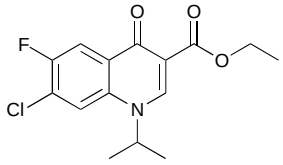
All reactions were performed with a $CaCl_2$ guard tube or under a nitrogen gas atmosphere where appropriate, in oven-dried glassware (125 ºC) with magnetic stirring, unless otherwise indicated. CH_2Cl_2 was distilled prior to use.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance IIIHD 500 (500 MHz for ^1H and 125.8 MHz for ^{13}C) or Bruker Avance IIIHD 600 spectrometer (600 MHz for ^1H and 150.9 MHz for ^{13}C). Solvents used for NMR were: deuteriochloroform ($CDCl_3$) with $CHCl_3$ (^1H, δ 7.26 ppm) or $CDCl_3$ (^{13}C, δ 77.16 ppm), deuteriodimethylsulfoxide $(CD_3)_2SO$ with $CD_3S(O)CD_2H$ (^1H, δ 2.50 ppm) or $(CD_3)_2SO$ (^{13}C, δ 39.52 ppm), deuteriotrifluoroacetic acid (CF_3COOD) with CF_3COOH (^1H, δ 11.50 ppm) or CF_3COOD (^{13}C, δ 164.2 & 116.6 ppm) or deuteriomethanol (CD_3OD) with CD_2HOD (^1H, δ 3.31 ppm) or CD_3OD (^{13}C, δ 49.00 ppm) used as an internal standard.[3] The chemical shift (in ppm) is stated in the bottom right corner of each spectrum.

High resolution mass spectra (HR-MS) were obtained on a Waters LCT Premier XE spectrometer, run in W-mode, using the electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) method with CH_3CN:0.1% HCOOH (9:1) as a matrix. Infrared spectra were obtained on a PerkinElmer spectrum one FTIR spectrometer fitted with a PerkinElmer Universal ATR sampling accessory. Samples were analysed as neat samples and recorded in wave numbers (cm^{-1}). Melting points (m.p.) were determined on a Gallenkamp melting point apparatus. Flash chromatography was performed on Merck silica gel using the specified solvents. Thin layer chromatography (TLC) was effected on Merck silica gel 60 F254 aluminium-backed plates that were visualised using a UV lamp. The chloride **36** and Pefloxacin **54** were purchased from Sigma.

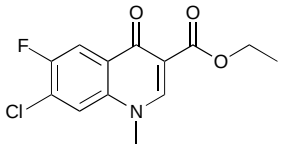
General procedure for the preparation of the ethyl 1-alkyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate esters **4-11**.

Potassium carbonate (5 eq) and the appropriate alkyl halide (5 eq) were added to a solution of **2**[4] in DMF (20 ml). The resulting mixture for each reaction was stirred at 90 ºC until the starting material was consumed, as indicated by TLC. The solution was then cooled and concentrated and the resultant residue was diluted with water (30 ml) and extracted with $CHCl_3$ (3 x 20 ml), and the combined organic extracts washed with water (30 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated. The resultant residue was purified by flash chromatography to yield the corresponding ethyl esters **4-11**.



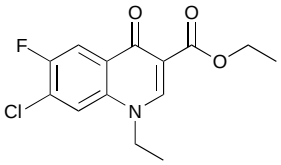
Ethyl 7-chloro-6-fluoro-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **4**

Using **2** (102 mg, 0.378 mmol), K_2CO_3 (261 mg, 1.89 mmol), 2-bromopropane (0.18 ml, 1.9 mmol), the reaction did not reach completion after 17 h so a further 5 eq of 2-bromopropane (0.18 ml, 1.9 mmol) was added. The reaction had not reached completion after a further 6 h, so it was cooled and after which the general procedure and flash chromatography (EtOAc:hexane 3:2) yielded the title compound **4** as a white solid (19.5 mg, 17%). $R_f = 0.39$ (EtOAc/hexane 7:3). The ^1H NMR spectrum of the compound was consistent with that found in the literature.[5] ^1H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.28 (d, $J = 9.1$ Hz, 1H), 7.66 (d, $J = 5.7$ Hz, 1H), 4.78 (sept, $J = 6.6$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 1.62 (d, $J = 6.6$ Hz, 6H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 172.6 (d, $J = 2.0$ Hz), 165.9, 155.5 (d, $J = 251$ Hz), 144.4, 136.0 (d, $J = 2.0$ Hz), 129.9 (d, $J = 5.8$ Hz), 127.2 (d, $J = 20$ Hz), 117.8, 114.6 (d, $J = 23$ Hz), 111.1, 61.3, 52.1, 22.2, 14.5.



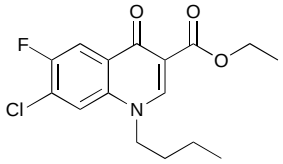
Ethyl 7-chloro-6-fluoro-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **5**

Using **2** (528 mg, 1.96 mmol), K_2CO_3 (1.35 g, 9.80 mmol), iodomethane (0.61 ml, 9.80 mmol), reacting for 3 h and flash chromatography (EtOAc:hexane 1:1), the title compound **5** was obtained as a yellow solid (509 mg, 92%). $R_f = 0.60$ (CH_3OH:$CHCl_3$ 1:9). The ^1H NMR spectrum of the compound was consistent with that found in the literature.[5] ^1H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.26 (d, $J = 9.0$ Hz, 1H), 7.52 (d, $J = 5.7$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.87 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.0 (d, $J = 2.0$ Hz), 165.35, 155.9 (d, $J = 251$ Hz), 150.1, 136.5 (d, $J = 2.0$ Hz), 129.1 (d, $J = 5.8$ Hz), 127.3 (d, $J = 21$ Hz,), 118.3, 114.3 (d, $J = 23$ Hz), 110.9, 61.2, 41.8, 14.5.



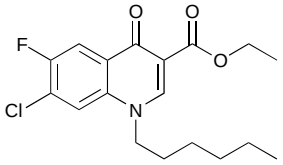
Ethyl 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **6**

Using **2** (500 mg, 1.85 mmol), K_2CO_3 (1.28 g, 9.26 mmol), iodoethane (0.75 ml, 9.2 mmol), reacting for 3.5 h and flash chromatography (EtOAc:hexane 4:1), the title compound **6** was obtained as a white solid (435 mg, 79%). $R_f = 0.64$ (CH_3OH:$CHCl_3$ 1:9). The ^1H and ^{13}C NMR spectra of the compound were consistent with those found in the literature.[6]



Ethyl 1-butyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **7**

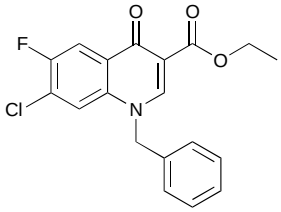
Using **2** (497 mg, 1.84 mmol), K_2CO_3 (1.27 g, 9.19 mmol), 1-iodobutane (1.05 ml, 9.22 mmol), reacting for 2 h and flash chromatography (EtOAc:hexane 1:1), the title compound **7** was obtained as a white solid (439 mg, 73%). $R_f = 0.66$ (CH_3OH:$CHCl_3$ 1:9). The ^1H NMR spectrum of the compound was consistent with that found in the literature.[5] ^1H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.24 (d, $J = 9.1$ Hz, 1H), 7.50 (d, $J = 5.7$ Hz, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 4.14 (t, $J = 7.6$ Hz, 2H) 1.87 (quint, $J = 7.6$ Hz, 2H), 1.49-1.38 (m, 5H), 1.01 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 172.8 (d, $J = 2.1$ Hz), 165.6, 155.6 (d, $J = 251$ Hz), 149.4, 135.6 (d, $J = 2.1$ Hz), 129.7 (d, $J = 6.1$ Hz), 127.3 (d, $J = 21$ Hz), 118.3, 114.5 (d, $J = 23$ Hz), 110.9, 61.3, 54.3, 30.9, 20.0, 14.5, 13.7.



Ethyl 7-chloro-6-fluoro-1-hexyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **8**

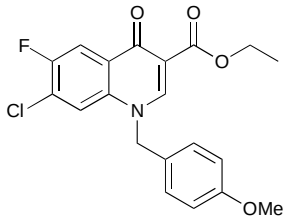
Using **2** (518 mg, 1.92 mmol), K_2CO_3 (1.33 g, 9.62 mmol), 1-bromohexane (1.34 ml, 9.58 mmol), reacting for 6 h and flash chromatography (EtOAc:hexane 9:11) the title compound **8** was obtained as a white solid (611 mg, 90%). m.p. 72-74 ºC. $R_f = 0.44$ (CH_3OH:$CHCl_3$ 1:9). ^1H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.26 (d, $J = 9.1$ Hz, 1H), 7.50 (d, $J = 5.7$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.13 (t, $J = 7.5$ Hz, 2H) 1.89 (quint, $J = 7.5$ Hz, 2H), 1.44-1.38 (m, 9H), 0.90 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.0, 165.8, 155.7 (d, $J = 251$ Hz), 149.5, 135.7, 129.8 (d, $J = 6.2$ Hz), 127.4 (d, $J = 21$ Hz), 118.3, 114.7 (d, $J = 23$ Hz), 111.0, 61.4, 54.7, 31.4, 28.9, 26.4, 22.7, 14.6, 13.7;

FTIR (ATR): υ = 1717, 1628, 1609, 1547 cm^{-1}; HR-MS (ESI): *m/z* 354.1273; $[M+H]^+$ requires 354.1272.[1]



Ethyl 1-benzyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **9**

Using **2** (505 mg, 1.87 mmol), K_2CO_3 (1.29 g, 9.33 mmol), benzyl bromide (1.11 ml, 9.33 mmol), reacting for 4.5 h and flash chromatography (EtOAc:hexane 1:1), the title compound **9** was obtained as a white solid (627 mg, 93%). R_f = 0.32 (EtOAc:hexane 1:1). The ^1H NMR spectrum of the compound was consistent with that found in the literature.[5] ^1H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.23 (d, *J* = 9.1 Hz, 1H), 7.43-7.13 (m, 6H), 5.36 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.0 (d, *J* = 2.0 Hz), 165.4, 155.7 (d, *J* = 251 Hz), 150.0, 135.9 (d, *J* = 2.1 Hz), 133.5, 129.7, 129.6 (d, *J* = 5.9 Hz), 129.1, 127.3 (d, *J* = 21 Hz), 126.2, 119.1, 114.3 (d, *J* = 23 Hz), 111.2, 61.3, 57.9, 14.5.

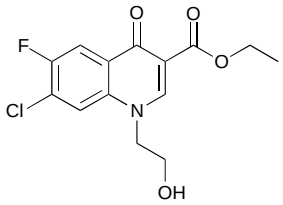


Ethyl 7-chloro-6-fluoro-1-(4-methoxybenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **10**

Using **2** (499 mg, 1.85 mmol), K_2CO_3 (1.28 g, 9.26 mmol), 4-methoxybenzyl chloride (1.26 ml, 9.28 mmol), reacting for 2.5 h and flash chromatography (EtOAc:hexane 1:1), the title compound **10** was obtained as a white solid (634 mg, 88%). m.p. 187-190 ºC. R_f = 0.23 (EtOAc:hexane 1:1). ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.22 (d, *J* = 9.1 Hz, 1H),

[1] Where appropriate for all mass spectra containing a chlorine atom the ^{35}Cl analysis is shown.

7.45 (d, J = 5.7 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.28 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 173.0 (d, J = 2.1 Hz), 165.5, 160.2, 155.6 (d, J = 251 Hz), 149.8, 135.9 (d, J = 2.1 Hz), 129.6 (d, J = 5.9 Hz), 127.9, 127.2 (d, J = 21 Hz), 125.2, 119.1, 115.1, 114.3 (d, J = 23 Hz), 111.1, 61.3, 57.5, 55.5, 14.5; FTIR (ATR): υ = 1715, 1677, 1646, 1609, 1548, 1513 cm^{-1}; HR-MS (ESI): *m/z* 390.0907; $[M+H]^+$ requires 390.0908.



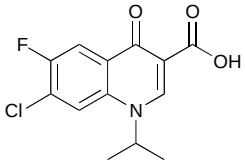
Ethyl 7-chloro-6-fluoro-1-(2-hydroxy-ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **11**

Using **2** (507 mg, 1.88 mmol), K_2CO_3 (1.30 g, 9.41 mmol), 2-bromoethanol (0.67 ml, 9.5 mmol), reacting for 5.5 h and flash chromatography (EtOAc:hexane 9:1), the title compound **11** was obtained as a yellow solid (313 mg, 53%). R_f = 0.34 (EtOAc). The ^{1}H NMR spectrum of the compound was consistent with that found in the literature.[5] ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.58 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 5.73 (*br* s, 1H), 4.30-4.20 (m, 6H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.9, 164.0, 155.4 (d, J = 251 Hz), 151.0, 135.8, 128.5 (d, J = 5.6 Hz), 127.5 (d, J = 21 Hz), 118.5, 112.7 (d, J = 23 Hz), 109.3, 61.1, 59.5, 57.7, 14.4.

General procedure for the preparation of the 1-alkyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **12-19**.

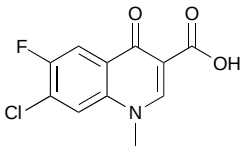
Ethanol (5 ml) and 2 M NaOH (5 eq) were added to the appropriate ethyl ester **4-11** and stirred at reflux until total conversion, as indicated by TLC. The mixtures were acidified to

pH 4-5 with glacial acetic acid. The resultant precipitates were collected, washed (water 20 ml) and dried *in vacuo* to afford the acids **12-19**.



7-Chloro-6-fluoro-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **12**

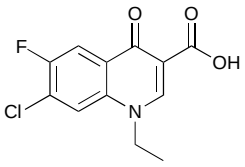
Using **4** (221 mg, 0.709 mmol), NaOH (2 M, 1.8 ml, 3.6 mmol), EtOH (5 ml) and reacting for 0.5 h, the title compound **12** was yielded as a white solid (161 mg, 80%). m.p. 218-220 ºC. R_f = 0.14 (CH_3OH:$CHCl_3$ 1:24). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 14.79 (*br* s, 1H), 8.87 (s, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 5.30 (sept, *J* = 6.6 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.2 (d, *J* = 2.5 Hz), 165.6, 154.9 (d, *J* = 249 Hz), 144.9, 136.8, 127.5 (d, *J* = 20 Hz), 126.2 (d, *J* = 6.6 Hz), 120.8, 112.0 (d, *J* = 23 Hz), 108.0, 53.3, 21.4; FTIR (ATR): *v* = 2623, 1725, 1610, 1557, 1543, 1505 cm^{-1}; HR-MS (ESI): *m/z* 284.0491; $[M+H]^+$ requires 284.0490.



7-Chloro-6-fluoro-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **13**

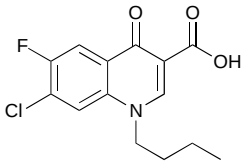
Using **5** (485 mg, 1.71 mmol), NaOH (2 M, 4.3 ml, 8.6 mmol), EtOH (5 ml) and reacting for 1.5 h, the title compound **13** was obtained as a white solid (387 mg, 89%). m.p. >300 ºC [lit.[7] >300 ºC]. R_f = 0.69 (CH_3OH:$CHCl_3$ 1:9). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 14.80 (*br* s, 1H), 9.06 (s, 1H), 8.34 (d, *J* = 6.1 Hz, 1H), 8.20 (d, *J* = 9.1 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.6 (d, *J* = 2.6 Hz), 165.6, 155.0 (d, *J* = 249 Hz), 150.7, 137.5, 127.1 (d, *J* = 20 Hz), 125.6 (d, *J* = 6.8 Hz), 121.5, 111.7 (d, *J* = 23 Hz), 107.7, 42.1; FTIR

(ATR): υ = 2503, 1706, 1615, 1568, 1518 cm^{-1}; HR-MS (ESI): *m/z* 256.0175; $[M+H]^+$ requires 256.0177.



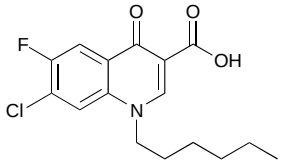
7-Chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **14**

Using **6** (383 mg, 1.29 mmol), NaOH (2 M, 3.2 ml, 6.4 mmol), EtOH (5 ml) and reacting for 2.5 h, the title compound **14** was obtained as a white solid (318 mg, 91%). R_f = 0.62 (CH_3OH:$CHCl_3$ 1:9). The ^1H and ^{13}C NMR spectra of the compound were consistent with those found in the literature.[6]



1-Butyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **15**

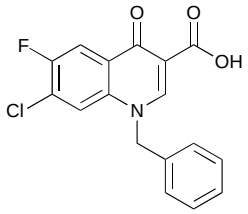
Using **7** (376 mg, 1.15 mmol), NaOH (2 M, 2.9 ml, 5.8 mmol), EtOH (5 ml) and reacting for 3 h, the title compound **15** was obtained as a white solid (302 mg, 88%). R_f = 0.58 (CH_3OH:$CHCl_3$ 1:19). The ^1H and ^{13}C NMR spectra of the compound were consistent with those found in the literature.[8]



7-Chloro-6-fluoro-1-hexyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **16**

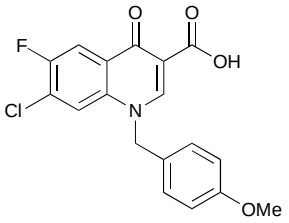
Using **8** (570 mg, 1.61 mmol), NaOH (2 M, 4.0 ml, 8.0 mmol), EtOH (5 ml) and reacting for 1.5 h, the title compound **16** was obtained as a white solid (430 mg, 82%). m.p. 162-164 ºC. R_f = 0.62 (CH_3OH:$CHCl_3$ 1:19). ^1H NMR (500 MHz, $(CD_3)_2SO$): δ 14.71 (*br* s, 1H), 8.94 (s,

1H), 8.36 (d, J = 5.9 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 4.51 (t, J = 7.3 Hz, 2H) 1.74 (quint, J = 7.3 Hz, 2H), 1.36-1.21 (m, 6H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 175.9, 165.7, 154.6 (d, J = 248 Hz), 149.7, 136.4, 126.8 (d, J = 20 Hz), 126.6 (d, J = 6.5 Hz), 120.8, 112.0 (d, J = 22 Hz), 110.5, 53.6, 30.7, 28.7, 25.3, 22.0, 13.8; FTIR (ATR): υ = 2623, 1725, 1610, 1556, 1543, 1505 cm^{-1}; HR-MS (ESI): *m/z* 326.0954; $[M+H]^+$ requires 326.0959.



1-Benzyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **17**

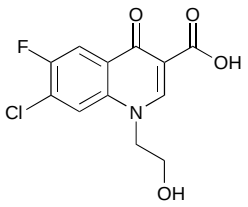
Using **9** (598 mg, 1.66 mmol), NaOH (2 M, 4.2 ml, 8.4 mmol), EtOH (5 ml) and reacting for 1 h, the title compound **17** was obtained as a white solid (496 mg, 90%). R_f = 0.45 (CH_3OH:$CHCl_3$ 1:19). The ^{1}H NMR spectrum of the compound was consistent with that found in the literature.[9] ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 14.69 (*br* s, 1H), 9.24 (s, 1H), 8.24-8.20 (m, 2H), 7.40-7.27 (m, 5H), 5.89 (s, 2H); ^{13}C NMR (150.9 MHz, $(CD_3)_2SO$): δ 176.7, 165.5, 154.9 (d, J = 250 Hz), 150.6, 136.6, 135.0, 129.0, 128.2, 127.0 (d, J = 20 Hz), 126.7, 126.3 (d, J = 6.6 Hz), 121.4, 112.2 (d, J = 23 Hz), 108.5, 56.4.



7-Chloro-6-fluoro-1-(4-methoxybenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **18**

Using **10** (597 mg, 1.53 mmol), NaOH (2 M, 3.8 ml, 7.6 mmol), EtOH (5 ml) and reacting for 0.5 h, the title compound **18** was obtained as a white solid (540 mg, 98%). m.p. 237-239 ºC. R_f = 0.44 (CH_3OH:$CHCl_3$ 1:19). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 14.58 (*br* s, 1H),

9.16 (s, 1H), 8.27 (d, J = 6.0 Hz, 1H), 8.19 (d, J = 9.1 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 5.77 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.4, 165.5, 159.2, 154.8 (d, J = 249 Hz), 150.1, 136.6, 128.6, 126.8 (d, J = 20 Hz), 126.7, 126.5 (d, J = 6.7 Hz), 121.3, 114.4, 112.1 (d, J = 23 Hz), 109.2, 55.9, 55.1; FTIR (ATR): υ = 2611, 1712, 1609, 1566, 1543, 1513 cm^{-1}; HR-MS (ESI): *m/z* 362.0598; $[M+H]^+$ requires 362.0595.



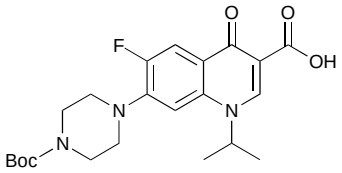
7-Chloro-6-fluoro-1-(2-hydroxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **19**

Using **11** (266 mg, 0.848 mmol), NaOH (2 M, 2.1 ml, 4.2 mmol), EtOH (5 ml) and reacting for 0.5 h, the title compound **19** was obtained as a white solid (204 mg, 84%). R_f = 0.14 (CH_3OH:$CHCl_3$ 1:19). The ^{1}H NMR spectrum of the compound was consistent with that found in the literature.[10] ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 14.80 (*br* s, 1H), 8.92 (s, 1H), 8.48 (d, J = 6.1 Hz, 1H), 8.22 (d, J = 9.1 Hz, 1H), 5.02 (d, J = 5.6 Hz, 1H), 4.65 (t, J = 5.0 Hz, 2H), 3.75 (q, J = 5.3 Hz, 2H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.6, 165.6, 154.9 (d, J = 249 Hz), 150.9, 136.7, 127.2 (d, J = 20 Hz), 126.0 (d, J = 6.7 Hz), 121.4, 111.9 (d, J = 23 Hz), 107.3, 58.7, 56.2.

General procedure for the preparation of the 1-alkyl-7-(4-(tert-butoxycarbonyl) piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **20-27.**

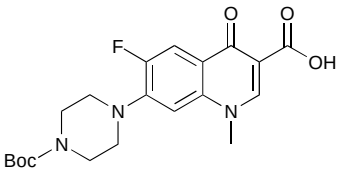
Piperazine (5 eq) was added to a solution of the appropriate acid **12-19** in DMSO (2 ml) and stirred at 140 ºC, to form a dark solution, until complete conversion of the starting material, as indicated by TLC. The solutions were then cooled and concentrated and the resultant residues were treated with 1 M NaOH (10 eq), THF (10 ml) and Boc_2O (3.5 eq). The

mixtures were then allowed to stir at room temperature overnight. The THF was then removed by evaporation *in vacuo* and the resulting mixtures neutralised with saturated NH_4Cl solution. The mixtures were then extracted with $CHCl_3$ (5 x 20 ml), and the combined organic extracts were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated. The resultant residues were then purified by flash chromatography to yield the carbamates **20**-**22**, or by preparative TLC to yield the carbamates **23**-**27**.



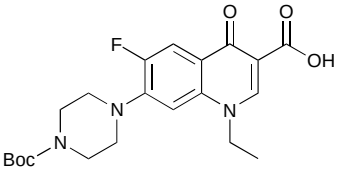
7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-6-fluoro-1-isopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **20**

Using **12** (144 mg, 0.508 mmol), piperazine (219 mg, 2.54 mmol), DMSO (2 ml), reacting for 35 min, and Boc_2O (389 mg, 1.78 mmol), NaOH (1 M, 5.1 ml, 5.1 mmol), THF (10 ml) and flash chromatography (CH_3OH:$CHCl_3$ 1:49) the title compound **20** was obtained as a pale yellow solid (101 mg, 46%). m.p. 240-242 ºC. R_f = 0.27 (CH_3OH:$CHCl_3$ 1:49). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.09 (*br* s, 1H), 8.76 (s, 1H), 8.03 (d, J = 13 Hz, 1H), 6.97 (d, J = 6.9 Hz, 1H), 4.90 (sept, J = 6.6 Hz, 1H), 3.65 (t, J = 5.2 Hz, 4H), 3.26 (t, J = 5.2 Hz, 4H), 1.65 (d, J = 6.6 Hz, 6H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 176.7 (d, J = 2.4 Hz), 167.3, 154.6, 153.5 (d, J = 252 Hz), 146.0 (d, J = 10 Hz), 143.0, 137.7, 121.1 (d, J = 7.7 Hz), 113.0 (d, J = 23 Hz), 108.5, 104.0 (d, J = 3.0 Hz), 80.4, 52.7, 50.0, 43.5, 28.5, 22.3; FTIR (ATR): υ = 1724, 1687, 1629, 1625 cm^{-1}; HR-MS (ESI): *m/z* 434.2090; $[M+H]^+$ requires 434.2091.



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-6-fluoro-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **21**

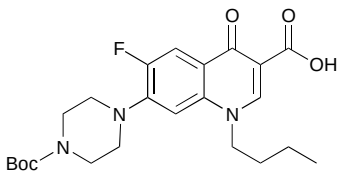
Using **13** (179 mg, 0.700 mmol), piperazine (301 mg, 3.49 mmol), DMSO (2 ml), reacting for 20 min, and Boc_2O (535 mg, 2.45 mmol), NaOH (1 M, 7.0 ml, 7.0 mmol), THF (10 ml) and flash chromatography (CH_3OH:$CHCl_3$ 3:97) the title compound **21** was obtained as a white solid (116 mg, 41%). m.p. 254-257 ºC. R_f = 0.22 (CH_3OH:$CHCl_3$ 3:97). ^1H NMR (600 MHz, $CDCl_3$): δ 14.98 (*br* s, 1H), 8.60 (s, 1H), 8.00 (d, *J* = 13 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 1H), 3.95 (s, 3H), 3.66 (t, *J* = 4.9 Hz, 4H), 3.29 (t, *J* = 4.9 Hz, 4H), 1.49 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 177.2, 167.1, 154.7, 153.7 (d, *J* = 252 Hz), 148.5, 146.2 (d, *J* = 10 Hz), 138.3, 120.5 (d, *J* = 8.0 Hz), 112.9 (d, *J* = 24 Hz), 108.4, 104.2 (d, *J* = 3.0 Hz), 80.5, 49.9, 43.4, 42.2, 28.5; FTIR (ATR): *v* = 1700, 1627 cm^{-1}; HR-MS (ESI): *m/z* 406.1779; $[M+H]^+$ requires 406.1778.



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **22**

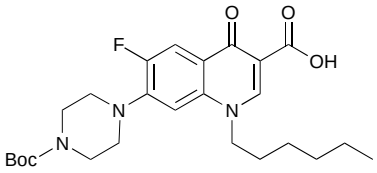
Using **14** (198 mg, 0.734 mmol), piperazine (316 mg, 3.67 mmol), DMSO (2 ml), reacting for 3.5 h, and Boc_2O (560 mg, 2.57 mmol), NaOH (1 M, 7.3 ml, 7.3 mmol), THF (10 ml) and flash chromatography (CH_3OH:$CHCl_3$ 1:49) the title compound **22** was obtained as a pale yellow solid (126 mg, 41%). R_f = 0.38 (CH_3OH:$CHCl_3$ 1:19). The ^1H NMR spectrum of the compound was consistent with that found in the literature.[11] ^1H NMR (500 MHz, $CDCl_3$): δ

15.02 (*br* s, 1H), 8.66 (s, 1H), 8.05 (d, J = 13 Hz, 1H), 6.84 (d, J = 6.8 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 5.0 Hz, 4H), 3.27 (t, J = 5.0 Hz, 4H), 1.58 (t, J = 7.1 Hz, 3H) 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.1 (d, J = 2.5 Hz), 167.2, 154.7, 153.6 (d, J = 251 Hz), 147.3, 146.1 (d, J = 11 Hz), 137.2, 121.0 (d, J = 7.8 Hz), 113.0 (d, J = 23 Hz), 108.6, 104.2 (d, J = 3.2 Hz), 80.5, 50.0, 49.9, 43.5, 28.5, 14.6.



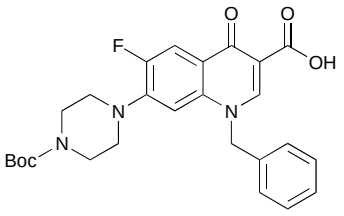
7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-1-butyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **23**

Using **15** (184 mg, 0.618 mmol), piperazine (266 mg, 3.09 mmol), DMSO (2 ml), reacting for 35 min, and Boc_2O (472 mg, 2.16 mmol), NaOH (1 M, 6.2 ml, 6.2 mmol), THF (10 ml) and preparative TLC (CH_3OH:$CHCl_3$ 1:24), the title compound **23** was obtained as a pale yellow solid (92.0 mg, 33%). m.p. >200 ºC (decomposed). R_f = 0.41 (CH_3OH:$CHCl_3$ 1:19). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.01 (*br* s, 1H), 8.62 (s, 1H), 8.05 (d, J = 13 Hz, 1H), 6.82 (d, J = 6.7 Hz, 1H), 4.24 (t, J = 7.3 Hz, 2H), 3.66 (t, J = 4.8 Hz, 4H), 3.26 (t, J = 4.8 Hz, 4H), 1.89 (quint, J = 7.3 Hz, 2H), 1.49 (s, 9H), 1.49-1.40 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.1 (d, J = 2.5 Hz), 167.2, 154.7, 153.6 (d, J = 252 Hz), 147.8, 146.1 (d, J = 11 Hz), 137.3, 121.1 (d, J = 7.7 Hz), 113.1 (d, J = 23 Hz), 108.4, 104.3 (d, J = 3.1 Hz), 80.5, 54.8, 49.9, 43.3, 30.9, 28.5, 20.1, 13.7; FTIR (ATR): υ = 1717, 1694, 1623, 1549 cm^{-1}; HR-MS (ESI): *m/z* 448.2248; $[M+H]^+$ requires 448.2248.



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-6-fluoro-1-hexyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **24**

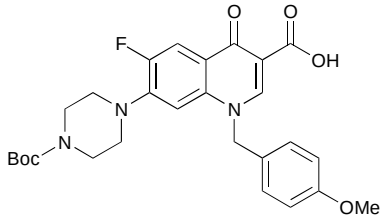
Using **16** (210 mg, 0.645 mmol), piperazine (278 mg, 3.23 mmol), DMSO (2 ml), reacting for 25 min, and Boc_2O (493 mg, 2.26 mmol), NaOH (1 M, 6.4 ml, 6.4 mmol), THF (10 ml) and preparative TLC (CH_3OH:$CHCl_3$ 1:19), the title compound **24** was obtained as a pale yellow solid (70.8 mg, 23%). m.p. 180-182 ºC. $R_f = 0.31$ (CH_3OH:$CHCl_3$ 1:49). ^1H NMR (500 MHz, $CDCl_3$): δ 15.01 (*br* s, 1H), 8.64 (s, 1H), 8.10 (d, $J = 13$ Hz, 1H), 6.82 (d, $J = 6.8$ Hz, 1H), 4.23 (t, $J = 7.4$ Hz, 2H), 3.67 (t, $J = 5.0$ Hz, 4H), 3.25 (t, $J = 5.0$ Hz, 4H), 1.91 (quint, $J = 7.4$ Hz, 2H), 1.50 (s, 9H), 1.45-1.31 (m, 6H), 0.91 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.1 (d, $J = 2.4$ Hz), 167.2, 154.7, 153.6 (d, $J = 252$ Hz), 147.8, 146.0 (d, $J = 11$ Hz), 137.3, 121.0 (d, $J = 7.8$ Hz), 113.0 (d, $J = 23$ Hz), 108.3, 104.3 (d, $J = 2.9$ Hz), 80.5, 55.1, 49.9, 43.4, 31.3, 28.9, 28.5, 26.4, 22.5, 14.0; FTIR (ATR): υ = 1701, 1622, 1545, 1501 cm^{-1}; HR-MS (ESI): *m/z* 476.2561; $[M+H]^+$ requires 476.2561.



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-1-benzyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **25**

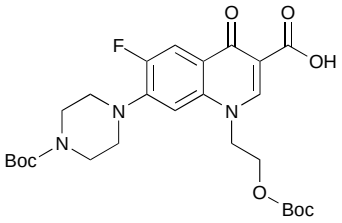
Using **17** (213 mg, 0.642 mmol), piperazine (277 mg, 3.21 mmol), DMSO (2 ml), reacting for 35 min, and Boc_2O (491 mg, 2.25 mmol), NaOH (1 M, 6.4 ml, 6.4 mmol), THF (10 ml) and preparative TLC (CH_3OH:$CHCl_3$ 1:24) the title compound **25** was obtained as a pale yellow solid (98.3 mg, 32%). m.p. 220-222 ºC. $R_f = 0.35$ (CH_3OH:$CHCl_3$ 1:19). ^1H NMR

(500 MHz, $CDCl_3$): δ 14.98 (*br* s, 1H), 8.82 (s, 1H), 8.05 (d, *J* = 13 Hz, 1H), 7.43-7.35 (m, 3H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.72 (d, *J* = 6.9 Hz, 1H), 5.43 (s, 2H), 3.54 (t, *J* = 4.9 Hz, 4H), 3.08-3.00 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.4 (d, *J* = 2.5 Hz), 167.2, 154.7, 153.5 (d, *J* = 252 Hz), 148.6, 145.7 (d, *J* = 10 Hz), 137.6, 133.6, 129.8, 129.3, 126.3, 121.0 (d, *J* = 7.8 Hz), 112.8 (d, *J* = 23 Hz), 108.6, 105.7 (d, *J* = 3.3 Hz), 80.5, 59.0, 49.6, 43.4, 28.5; FTIR (ATR): *v* = 1723, 1696, 1625, 1530, 1504 cm^{-1}; HR-MS (ESI): *m/z* 482.2092; $[M+H]^+$ requires 482.2091.



7-(4-(*tert*-Butoxycarbonyl)piprazin-1-yl)-6-fluoro-1-(4-methoxybenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **26**

Using **18** (233 mg, 0.644 mmol), piperazine (276 mg, 3.22 mmol), DMSO (2 ml), reacting for 25 min, and Boc_2O (491 mg, 2.25 mmol), NaOH (1 M, 6.4 ml, 6.4 mmol), THF (10 ml) and preparative TLC (CH_3OH:$CHCl_3$ 1:19) the title compound **26** was obtained as a pale yellow solid (70.2 mg, 21%). m.p. 195-196 ºC. R_f = 0.26 (CH_3OH:$CHCl_3$ 1:49). ^1H NMR (500 MHz, $CDCl_3$): δ 15.00 (*br* s, 1H), 8.79 (s, 1H), 8.05 (d, *J* = 13 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 6.9 Hz, 1H), 5.36 (s, 2H), 3.80 (s, 3H), 3.57 (t, *J* = 4.8 Hz, 4H), 3.12-3.04 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.2, 167.1, 160.1, 154.6, 153.4 (d, *J* = 252 Hz), 148.3, 145.7 (d, *J* = 10 Hz), 137.4, 128.0, 125.3, 120.7 (d, *J* = 7.6 Hz), 115.0, 112.5 (d, *J* = 23 Hz), 108.2, 105.7, 80.4, 58.5, 55.4, 49.6, 43.2, 28.5; FTIR (ATR): *v* = 1723, 1697, 1623, 1586, 1515, 1502 cm^{-1}; HR-MS (ESI): *m/z* 512.2197; $[M+H]^+$ requires 512.2197.

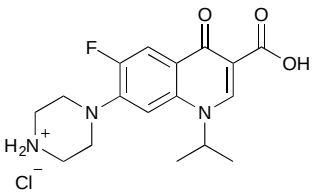


1-(2-((*tert*-Butoxycarbonyl)oxy)ethyl)-7-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **27**

Using **19** (145 mg, 0.508 mmol), piperazine (219 mg, 2.54 mmol), DMSO (2 ml), reacting for 35 min, and Boc_2O (389 mg, 1.78 mmol), NaOH (1 M, 5.1 ml, 5.1 mmol), THF (10 ml) and preparative TLC (CH_3OH:$CHCl_3$ 1:24) the title compound **27** was obtained as a pale yellow solid (60.8 mg, 22%). m.p. 180-182 ºC. R_f = 0.27 (CH_3OH:$CHCl_3$ 3:97). ^{1}H NMR (500 MHz, $CDCl_3$): δ 14.94 (*br* s, 1H), 8.62 (s, 1H), 7.97 (d, *J* = 13 Hz, 1H), 7.08 (d, *J* = 6.7 Hz, 1H), 5.56-4.49 (m, 2H), 4.49-4.43 (m, 2H), 3.67-3.60 (m, 4H), 3.35-3.28 (m, 4H), 1.48 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 177.1, 167.0, 154.6, 153.5 (d, *J* = 252 Hz), 153.0, 148.4, 146.1 (d, *J* = 9.9 Hz), 137.7, 120.4, 112.7 (d, *J* = 24 Hz), 108.5, 104.8, 83.7, 80.3, 63.4, 53.1, 49.8, 43.5, 28.5, 27.6; FTIR (ATR): υ = 1723, 1697, 1623, 1586, 1515, 1502 cm^{-1}; HR-MS (ESI): *m/z* 536.2410; $[M+H]^+$ requires 536.2408.

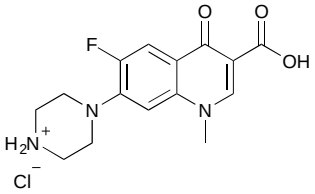
General procedure for the preparation of the 1-alkyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochlorides **28**-**33** and **35**.

Ethanol (4 ml per 0.2 mmol of carbamate) and 3 M HCl (30 eq) were added to the appropriate carbamate **20**-**27**, and the resulting solutions were stirred at reflux until complete consumption of the starting material**,** as indicated by TLC. The solutions were then concentrated to yield the hydrochlorides **28**-**33** and **35**.



6-Fluoro-1-isopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **28**

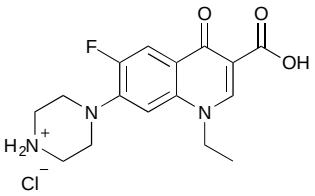
Using **20** (66.9 mg, 0.154 mmol), HCl (3 M, 1.5 ml, 4.5 mmol), EtOH (3.1 ml) and reacting for 3 h, the title compound **28** was obtained as a pale yellow solid (55.5 mg, 97%). m.p. 248-250 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 9.56 (*br* s, 2H), 8.78 (s, 1H), 7.96 (d, J = 13 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 5.36 (sept, J = 6.5 Hz, 1H), 3.60-3.55 (m, 4H), 3.32-3.25 (m, 4H), 1.55 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 175.8 (d, J = 2.0 Hz), 166.1, 152.7 (d, J = 249 Hz), 144.5 (d, J = 10 Hz), 143.9, 137.7, 120.1 (d, J = 7.6 Hz), 111.4 (d, J = 23 Hz), 107.2, 106.3 (d, J = 2.5 Hz), 52.6, 46.5, 42.5, 21.5; FTIR (ATR): υ = 3382, 2718, 1709, 1627, 1610, 1504 cm^{-1}; HR-MS (ESI): *m/z* 412.1705; $[M+DMSO]^+$ requires 412.1706.



6-Fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **29**

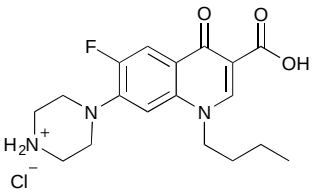
Using **21** (98.5 mg, 0.243 mmol), HCl (3 M, 2.4 ml, 7.2 mmol), EtOH (4.9 ml) and reacting for 3 h, the title compound **29** was obtained as a white solid (81.3 mg, 98%). m.p. >300 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.28 (*br* s, 1H), 9.46 (*br* s, 2H), 8.95 (s, 1H), 7.94 (d, J = 13 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 4.09 (s, 3H), 3.60-3.53 (m, 4H), 3.32-3.27 (m, 4H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.3, 166.1, 152.8 (d, J = 249 Hz), 149.7, 144.2 (d, J = 10 Hz), 138.4, 119.6 (d, J = 7.7 Hz), 111.1 (d, J = 23 Hz), 106.9 (d, J = 2.7 Hz), 106.8,

46.4, 42.5, 42.0; FTIR (ATR): υ = 3381, 2718, 1704, 1626 cm^{-1}; HR-MS (ESI): *m/z* 384.1395; $[M+DMSO]^+$ requires 384.1393.



1-Ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **30**

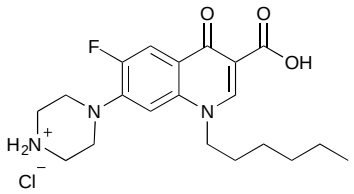
Using **22** (107 mg, 0.255 mmol), HCl (3 M, 2.8 ml, 7.6 mmol), EtOH (5.1 ml) and reacting for 3 h, the title compound **30** was obtained as a yellow solid (73.3 mg, 81%). m.p. >250 ºC (decomposed). ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 15.27 (*br* s, 1H), 9.46 (*br* s, 2H), 8.97 (s, 1H), 7.95 (d, J = 13 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 4.62 (q, J = 7.1 Hz, 2H), 3.57 (t, J = 5.0 Hz, 4H), 3.32-3.26 (m, 4H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150.9 MHz, $(CD_3)_2SO$): δ 176.2 (d, J = 2.0 Hz), 166.0, 152.7 (d, J = 249 Hz), 148.7, 144.4 (d, J = 10 Hz), 137.1, 120.0 (d, J = 7.6 Hz), 111.4 (d, J = 23 Hz), 107.2, 106.5 (d, J = 1.9 Hz), 49.1, 46.5, 42.5, 14.5; FTIR (ATR): υ = 3365, 2711, 1702, 1626, 1515 cm^{-1}; HR-MS (ESI): *m/z* 398.1557; $[M+DMSO]^+$ requires 398.1550.



1-Butyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **31**

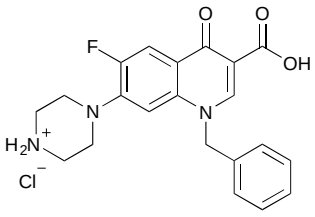
Using **23** (67.9 mg, 0.152 mmol), HCl (3 M, 1.5 ml, 4.5 mmol), EtOH (3.0 ml) and reacting for 3.5 h, the title compound **31** was obtained as a yellow solid (58.1 mg, 100%). m.p. 196-198 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.25 (*br* s, 1H), 9.15 (*br* s, 2H), 8.96 (s, 1H), 7.98

(d, J = 13 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 4.61 (q, J = 7.4 Hz, 2H), 3.58-3.51 (m, 4H), 3.35-3.28 (m, 4H), 1.78 (quint, J = 7.4 Hz, 2H), 1.33 (sext, J = 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.1 (d, J = 2.2 Hz), 166.0, 152.7 (d, J = 249 Hz), 149.0, 144.4 (d, J = 10 Hz), 137.3, 120.0 (d, J = 7.7 Hz), 111.3 (d, J = 23 Hz), 106.9, 106.6 (d, J = 2.8 Hz), 53.4, 46.4, 42.5, 30.4, 19.1, 13.5; FTIR (ATR): υ = 3383, 2725, 1709, 1626 cm^{-1}; HR-MS (ESI): *m/z* 426.1861; $[M+DMSO]^+$ requires 426.1863.



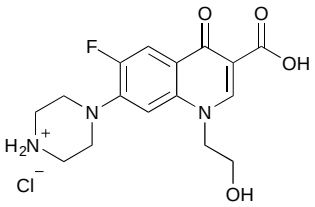
6-Fluoro-1-hexyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **32**

Using **24** (42.7 mg, 0.0898 mmol), HCl (3 M, 0.90 ml, 2.7 mmol), EtOH (1.8 ml) and reacting for 3.5 h, the title compound **32** was obtained as a yellow solid (36.0 mg, 97%). m.p. 190-192 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 9.60 (*br* s, 2H), 8.95 (s, 1H), 7.94 (d, J = 13 Hz, 1H), 7.24 (d, J = 7.0 Hz, 1H), 4.59 (q, J = 7.1 Hz, 2H), 3.59-3.53 (m, 4H), 3.32-3.24 (m, 4H), 1.82-1.72 (m, 2H), 1.34-1.21 (m, 6H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.2, 166.0, 152.8 (d, J = 249 Hz), 149.0, 144.4 (d, J = 10 Hz), 137.3, 120.0 (d, J = 7.4 Hz), 111.4 (d, J = 23 Hz), 106.9, 106.6, 53.6, 46.4, 42.5, 30.7, 28.3, 25.4, 22.0, 13.8; FTIR (ATR): υ = 3383, 2719, 1710, 1626, 1515 cm^{-1}; HR-MS (ESI): *m/z* 454.2168; $[M+DMSO]^+$ requires 454.2176.



1-Benzyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **33**

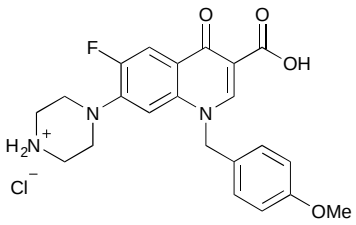
Using **25** (76.3 mg, 0.160 mmol), HCl (3 M, 1.6 ml, 4.8 mmol), EtOH (3.2 ml) and reacting for 3 h, the title compound **33** was obtained as a pale yellow solid (57.1 mg, 85%). The ^{1}H NMR spectrum of the compound was consistent with that found in the literature.[12] ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 15.14 (*br* s, 1H), 9.29 (*br* s, 2H), 9.22 (s, 1H), 7.96 (d, *J* = 13 Hz, 1H), 7.41-7.32 (m, 5H), 7.20 (d, *J* = 7.3, 1H), 5.90 (s, 2H), 3.41-3.35 (m, 4H), 3.26-3.20 (m, 4H); ^{13}C NMR (150.9 MHz, $(CD_3)_2SO$): δ 176.4, 166.0, 152.6 (d, *J* = 250 Hz), 149.7, 144.0 (d, *J* = 10 Hz), 137.5, 135.3, 129.1, 128.3, 127.0, 120.2 (d, *J* = 7.5 Hz), 111.5 (d, *J* = 23 Hz), 107.4, 107.3 (d, *J* = 3.0 Hz), 56.6, 46.3, 42.4.



6-Fluoro-1-(2-hydroxyethyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **35**

Using **27** (37.8 mg, 0.0706 mmol), HCl (3 M, 0.7 ml, 2.1 mmol), EtOH (1.4 ml) and reacting for 3 h, the title compound **35** was obtained as a pale yellow solid (24.5 mg, 93%). m.p. >300 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.29 (*br* s, 1H), 9.48 (*br* s, 2H), 8.82 (s, 1H), 7.97 (d, *J* = 13 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 4.70-4.63 (m, 2H), 3.81-3.75 (m, 2H), 3.60-3.53 (m, 4H), 3.32-3.25 (m, 4H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.3, 166.2, 152.7 (d, *J* = 249 Hz), 150.0, 144.2 (d, *J* = 10 Hz), 137.6, 119.9 (d, *J* = 7.7 Hz), 111.3 (d,

J = 23 Hz), 106.9 (d, *J* = 2.5 Hz), 106.5, 58.5, 56.1, 46.5, 42.5; FTIR (ATR): υ = 3364, 2765, 1727, 1626 cm^{-1}; HR-MS (ESI): *m/z* 414.1497; $[M+DMSO]^+$ requires 414.1499.



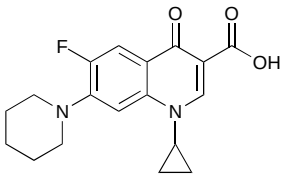
6-Fluoro-1-(4-methoxybenzyl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **34**

Ethanol (0.9 ml) and HCl (3 M, 0.46 ml, 1.4 mmol) were added to the carbamate **26** (23.7 mg, 0.0463 mmol), and the resulting solution was stirred at 50 ºC until complete consumption of the starting material, as indicated by TLC. The solution was then concentrated to obtain the title compound **34** as a pale yellow solid (18.7 mg, 90%). m.p. 260-262 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.20 (*br* s, 1H), 9.47 (*br* s, 2H), 9.16 (s, 1H), 7.94 (d, *J* = 13 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 7.1, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.79 (s, 2H), 3.72 (s, 3H), 3.47-3.40 (m, 4H), 3.27-3.20 (m, 4H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.4, 166.0, 159.1, 152.6 (d, *J* = 250 Hz), 149.3, 143.9 (d, *J* = 10 Hz), 137.4, 128.8, 126.9, 120.1 (d, *J* = 7.6 Hz), 114.4, 111.4 (d, *J* = 23 Hz), 107.3 (d, *J* = 2.5 Hz), 107.2, 56.1, 55.1, 46.3, 42.4. FTIR (ATR): υ = 3308, 2737, 1707, 1626, 1611, 1515 cm^{-1}; HR-MS (ESI): *m/z* 490.1815; $[M+DMSO]^+$ requires 490.1812.

General procedure for the preparation of the 1-alkyl-7-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **37-50**

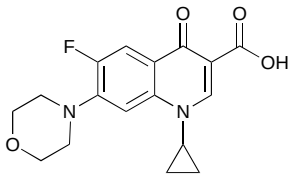
The appropriate amine (5 eq) was added to a solution of the relevant acid **36** or **14** in DMSO (2 ml) and stirred at 140 ºC, until the starting material was consumed, as indicated by TLC. The solution was then cooled and concentrated. The residue was then diluted with $1x10^{-4}$ M

HCl (20 ml) and extracted with $CHCl_3$ (3 x 30 ml), and the combined organic extracts were washed with $1x10^{-4}$ M HCl solution (30 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated. The resultant residue was then purified by flash chromatography to yield the fluorides **37**-**50**.



1-Cyclopropyl-6-fluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **37**

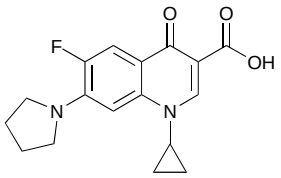
Using **36** (255 mg, 0.905 mmol), piperidine (0.44 ml, 4.5 mmol), DMSO (2 ml), reacting for 45 min and flash chromatography (EtOAc:hexane 4:1), the title compound **37** was obtained as a white solid (184 mg, 61%). $R_f = 0.32$ (EtOAc:hexane 4:1). The ^1H NMR spectra of the compound was consistent with that found in the literature.[13] ^1H NMR (600 MHz, $CDCl_3$): δ 15.12 (*br* s, 1H), 8.75 (s, 1H), 7.98 (d, J = 13 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 3.53 (tt, J = 11, 3.7 Hz, 1H), 3.30 (t, J = 5.5 Hz, 4H), 1.80 (appt quint, J = 5.5 Hz, 4H), 1.69 (appt quint, J = 5.4 Hz, 2H), 1.38 (q, J = 7.0 Hz, 2H), 1.20 (q, J = 5.5 Hz, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 177.3 (d, J = 2.1 Hz), 167.4, 153.9 (d, J = 252 Hz), 147.4, 146.9 (d, J = 10 Hz), 139.3, 119.4 (d, J = 7.8 Hz), 112.4 (d, J = 24 Hz), 108.2, 104.7 (d, J = 3.1 Hz), 51.4, 35.4, 25.9, 24.2, 8.4.



1-Cyclopropyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **38**

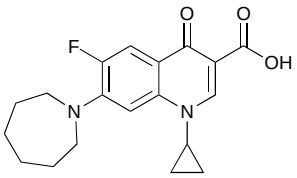
Using **36** (259 mg, 0.920 mmol), morpholine (0.40 ml, 4.6 mmol), DMSO (2 ml), reacting for 45 min and flash chromatography (EtOAc:hexane:AcOH 9:1:0.1 to CH_3OH:$CHCl_3$ 1:19), the title compound **38** was obtained as a white solid (260 mg, 85%). $R_f = 0.23$ (EtOAc:hexane

9:1). The ^{1}H NMR spectra of the compound was consistent with that found in the literature.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 14.95 (*br* s, 1H), 8.76 (s, 1H), 8.02 (d, *J* = 13 Hz, 1H), 7.36 (d, *J* = 7.1 Hz, 1H), 3.80 (t, *J* = 3.9 Hz, 4H), 3.54 (tt, *J* = 11, 3.7 Hz, 1H), 3.33 (t, *J* = 4.7 Hz, 4H), 1.40 (q, *J* = 6.8 Hz, 2H), 1.24-1.18 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.3 (d, *J* = 2.5 Hz), 167.1, 153.8 (d, *J* = 251 Hz), 147.6, 145.9 (d, *J* = 10 Hz), 139.2, 120.2 (d, *J* = 7.9 Hz), 112.8 (d, *J* = 23 Hz), 108.4, 104.7 (d, *J* = 3.4 Hz), 66.7, 50.2, 35.4, 8.4.



1-Cyclopropyl-6-fluoro-4-oxo-7-(pyrrolidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **39**

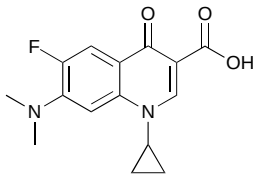
Using **36** (236 mg, 0.838 mmol), pyrrolidine (0.35 ml, 4.2 mmol), DMSO (2 ml), reacting for 0.75 h and flash chromatography (EtOAc:hexane 9:1 to CH_3OH:$CHCl_3$ 1:49), the title compound **39** was obtained as a white solid (154 mg, 58%). R_f = 0.54 (EtOAc). The ^{1}H NMR spectra of the compound was consistent with that found in the literature.[14] ^{1}H NMR (600 MHz, ($CDCl_3$): δ 15.42 (*br* s, 1H), 8.66 (s, 1H), 7.89 (d, *J* = 14 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 3.66-3.59 (m, 4H), 3.47 (sept, *J* = 3.7 Hz, 1H), 2.12-2.02 (m, 4H), 1.37-1.30 (m, 2H), 1.20-1.14 (m, 2H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 176.8, 167.7, 150.6 (d, *J* = 248 Hz), 146.9, 142.4 (d, *J* = 12 Hz), 140.0, 115.5 (d, *J* = 7.0 Hz), 112.0 (d, *J* = 23 Hz), 107.7, 99.2 (d, *J* = 5.8 Hz), 50.2, 35.2, 25.6, 8.2.



7-(Azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **40**

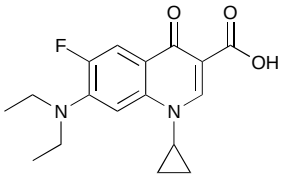
Using **36** (242 mg, 0.859 mmol), hexamethyleneimine (0.48 ml, 4.3 mmol), DMSO (2 ml), reacting for 0.75 h and flash chromatography (EtOAc:hexane 7:3), the title compound **40** was

obtained as a white solid (171 mg, 58%). m.p. 208-209 ºC. R_f = 0.56 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.32 (*br* s, 1H), 8.69 (s, 1H), 7.92 (d, *J* = 15 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 3.64-3.58 (m, 4H), 3.47 (tt, *J* = 11, 3.7 Hz, 1H), 1.95-1.87 (m, 4H), 1.68-1.62 (m, 4H), 1.37-1.31 (m, 2H), 1.21-1.15 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 176.9 (d, *J* = 2.8 Hz), 167.6, 151.6 (249 Hz), 147.1, 144.7 (d, *J* = 9.9 Hz), 139.8, 116.4 (d, *J* = 7.7 Hz), 112.8 (d, *J* = 25 Hz), 107.8, 100.7 (d, *J* = 5.0 Hz), 52.3, 35.2, 28.6, 27.1, 8.3; FTIR (ATR): *v* = 2522, 1713, 1624, 1505 cm^{-1}; HR-MS (APCI): *m/z* 345.1608; $[M+H]^+$ requires 345.1614.



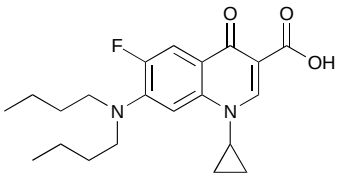
1-Cyclopropyl-7-dimethylamino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **41**

Using **36** (253 mg, 0.898 mmol), dimethylamine gas, DMSO (2 ml), reacting for 0.75 h and flash chromatography (EtOAc:AcOH 99:1), the title compound **41** was obtained as a white solid (106 mg, 41%). m.p. 232-234 ºC [lit.[7] 224-226 ºC]. R_f = 0.31 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.22 (*br* s, 1H), 8.72 (s, 1H), 7.96 (d, *J* = 14 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 3.54-3.48 (m, 1H), 3.15 (s, 6H), 1.39-1.34 (m, 2H), 1.22-1.17 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.1 (d, *J* = 2.8 Hz), 167.5, 152.4 (d, *J* = 250 Hz), 147.3, 145.7 (d, *J* = 10 Hz), 139.5, 117.7 (d, 7.6 Hz), 112.6 (d, *J* = 24 Hz), 108.0, 102.0 (d, *J* = 4.4 Hz), 42.4, 35.3, 8.3; FTIR (ATR): *v* = 3329, 2851, 1727, 1623, 1506 cm^{-1}; HR-MS (APCI): *m/z* 291.1140; $[M+H]^+$ requires 291.1145.



1-Cyclopropyl-7-diethylamino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **42**

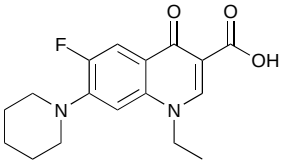
Using **36** (267 mg, 0.95 mmol), diethylamine (4.9 ml, 4.7 mmol), DMSO (2 ml), reacting for 20 h and flash chromatography (EtOAc:hexane:AcOH 7:3:0.1), the title compound **42** was obtained as a pale yellow solid (96 mg, 32%). m.p. 135-137 ºC. $R_f = 0.39$ (EtOAc:hexane 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.29 (*br* s, 1H), 8.67 (s, 1H), 7.90 (d, $J = 15$ Hz, 1H), 7.14 (d, $J = 7.5$ Hz), 3.54-3.48 (m, 4H), 3.50-3.46 (m, 1H), 1.35 (q, $J = 6.8$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 6H), 1.21-1.15 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 176.9 (d, $J = 2.8$ Hz), 167.6, 151.9 (d, $J = 249$), 147.2, 143.5 (d, $J = 10$ Hz), 139.7, 116.7 (d, $J = 7.2$ Hz), 112.8 (d, $J = 25$ Hz), 107.7, 101.5, 46.7, 35.2, 13.0, 8.3; FTIR (ATR): $\upsilon = 2567, 1715, 1626, 1509$ cm^{-1}; HR-MS (APCI): *m/z* 319.1451; $[M+H]^+$ requires 319.1458.



1-Cyclopropyl-7-dibutylamino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **43**

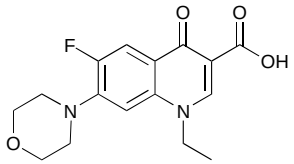
Using **36** (258 mg, 0.916 mmol), dibutylamine (0.78 ml, 4.6 mmol), DMSO (2 ml), reacting for 18 h and flash chromatography (EtOAc:hexane 3:2), the title compound **43** was obtained as a yellow solid (110 mg, 32%). m.p. 135-138 ºC. $R_f = 0.45$ (EtOAc:hexane 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.30 (*br* s, 1H), 8.70 (s, 1H), 7.93 (d, $J = 15$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 3.50-3.45 (m, 1H), 3.43 (t, $J = 7.5$ Hz, 4H), 1.66 (quint, $J = 7.5$ Hz, 4H), 1.39 (sext, $J = 7.5$ Hz, 4H), 1.36-1.29 (m, 2H), 1.22-1.16 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 176.9, 167.6, 151.9 (d, $J = 249$ Hz), 147.2, 143.6 (d, $J = 9.8$ Hz), 139.7, 116.7 (d, $J = 7.5$ Hz), 112.9 (d, $J = 25$ Hz), 107.8, 101.7 (d, $J = 4.9$ Hz),

53.0, 35.2, 29.9, 20.4, 14.1, 8.3; FTIR (ATR): υ = 2613, 1727, 1627, 1507 cm^{-1}; HR-MS (APCI): *m/z* 375.2083; $[M+H]^+$ requires 375.8084.



1-Ethyl-6-fluoro-4-oxo-7-(piperidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **44**

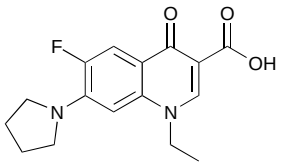
Using **14** (138 mg, 0.512 mmol), piperidine (0.25 ml, 2.5 mmol), DMSO (2 ml), reacting for 45 min and flash chromatography (EtOAc:hexane:AcOH 9:1:0.2), the title compound **44** was obtained as a white solid (60.6 mg, 37%). m.p. 192-194 ºC [lit.[4] 208-209 ºC]. R_f = 0.25 (EtOAc:hexane:AcOH 9:1:0.2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.21 (*br* s, 1H), 8.61 (s, 1H), 7.92 (d, *J* = 13 Hz, 1H), 6.80 (d, *J* = 7.0 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 5.7 Hz, 4H), 1.81-1.74 (m, 4H), 1.70-1.63 (m, 2H), 1.57 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.0 (d, *J* = 2.4 Hz), 167.4, 153.7 (d, *J* = 252 Hz), 147.1 (d, *J* = 10 Hz), 147.0, 137.3, 119.8 (d, *J* = 7.8 Hz), 112.4 (d, *J* = 24 Hz), 108.1, 103.7 (d, *J* = 3.6 Hz), 51.3, 49.8, 25.9, 24.1, 14.5; FTIR (ATR): υ = 2496, 1732, 1614, 1520 cm^{-1}; HR-MS (ESI): *m/z* 319.1447; $[M+H]^+$ requires 319.1458.



1-Ethyl-6-fluoro-7-morpholino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **45**

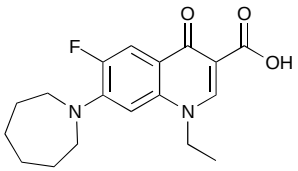
Using **14** (148 mg, 0.549 mmol), morpholine (0.24 ml, 2.7 mmol), DMSO (2 ml), reacting for 45 min and flash chromatography (EtOAc:AcOH 99:1 to CH_3OH:$CHCl_3$ 1:19), the title compound **45** was obtained as a white solid (103 mg, 59%). m.p. 248-250 ºC [lit.[4] 256-257 ºC]. R_f = 0.30 (CH_3OH:$CHCl_3$ 1:19). ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 15.32 (*br* s, 1H), 8.95 (s, 1H), 7.92 (d, *J* = 13 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 2H), 3.80

(t, J = 4.6 Hz, 4H), 3.31 (t, J = 4.6 Hz, 4H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150.9 MHz, $(CD_3)_2SO$): δ 176.2, 166.1, 152.9 (d, J = 250 Hz), 148.6, 145.4 (d, J = 10 Hz), 137.2, 119.4 (d, J = 7.6 Hz), 111.2 (d, J = 23 Hz), 107.1, 105.8 (d, J = 3.4 Hz), 65.9, 49.8, 49.1, 14.4; FTIR (ATR): υ = 2501, 1728, 1614, 1520 cm^{-1}; HR-MS (ESI): *m/z* 321.1251; $[M+H]^+$ requires 321.1251.



1-Ethyl-6-fluoro-4-oxo-7-(pyrrolidin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **46**

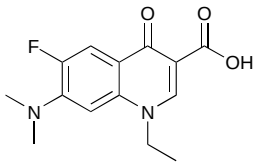
Using **14** (164 mg, 0.608 mmol), pyrrolidine (0.25 ml, 3.0 mmol), DMSO (2 ml), reacting for 1 h and flash chromatography (EtOAc:AcOH 99:1 to CH_3OH:$CHCl_3$ 1:19), the title compound **46** was obtained as a yellow solid (74.7 mg, 40%). m.p. >250 ºC (decomposed) [lit.[4] >300 ºC]. R_f = 0.33 (CH_3OH:$CHCl_3$ 1:24). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.68 (*br* s, 1H), 8.84 (s, 1H), 7.80 (d, J = 14 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 4.51 (q, J = 6.9 Hz, 2H), 3.63-3.56 (m, 4H), 2.53-2.48 (m, 4H), 1.40 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$/CD_3OD): δ 176.6, 168.4, 150.5 (d, J = 249 Hz), 146.8, 142.6 (d, J = 12 Hz), 138.1, 116.1 (d, J = 6.9 Hz), 112.2 (d, J = 23 Hz), 107.4, 98.1 (d, J = 6.0 Hz), 40.2, 49.7, 25.9, 14.2; FTIR (ATR): υ = 2580, 1706, 1602, 1506 cm^{-1}; HR-MS (ESI): *m/z* 305.1299; $[M+H]^+$ requires 305.1301.



7-(Azepan-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **47**

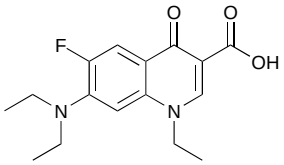
Using **14** (141 mg, 0.523 mmol), hexamethyleneimine (0.29 ml, 2.6 mmol), DMSO (2 ml), reacting for 1.5 h and flash chromatography (EtOAc:hexane:AcOH 1:1:0.02 to EtOAc:AcOH

99:1), the title compound **47** was obtained as a white solid (74.1 mg, 43%). m.p. 188-190 ºC. R_f = 0.39 (CH_3OH:$CHCl_3$ 1:24). ^1H NMR (600 MHz, $CDCl_3$): δ 15.42 (*br* s, 1H), 8.50 (s, 1H), 7.80 (d, *J* = 15 Hz, 1H), 6.54 (d, *J* = 7.3 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.55 (t, *J* = 5.7 Hz, 4H), 1.90-1.85 (m, 4H), 1.64-1.59 (m, 4H), 1.53 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 176.5 (d, *J* = 2.3 Hz), 167.6, 151.3 (d, *J* = 249 Hz), 146.6, 144.9 (d, *J* = 9.9 Hz), 137.7, 116.7 (d, *J* = 4.5 Hz), 112.5 (d, *J* = 25 Hz), 107.6, 99.6 (d, *J* = 4.9 Hz), 52.1, 49.7, 28.5, 27.1, 14.3; FTIR (ATR): *υ* = 2495, 1708, 1626, 1505 cm^{-1}; HR-MS (ESI): *m/z* 333.1610; $[M+H]^+$ requires 333.1614.



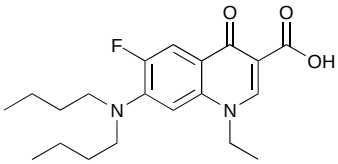
7-Dimethylamino-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **48**

Using **14** (197 mg, 0.731 mmol), dimethylamine gas, DMSO (2 ml), reacting for 0.75 h and flash chromatography (MeOH:EtOAc 1:24), the title compound **48** was obtained as a white solid (94.1 mg, 44%). m.p. >250 ºC [lit.[4] 259-261 ºC]. R_f = 0.30 (CH_3OH:EtOAc 1:24). ^1H NMR (500 MHz, $CDCl_3$): δ 15.29 (*br* s, 1H), 8.61 (s, 1H), 7.99 (d, *J* = 14 Hz, 1H), 6.59 (d, *J* = 7.3 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 3.14 (s, 6H), 1.58 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 177.0 (d, *J* = 2.8 Hz), 167.7, 152.4 (d, *J* = 250 Hz), 147.0, 145.9 (d, *J* = 10 Hz), 137.7, 118.5 (d, *J* = 7.6 Hz), 113.0 (d, *J* = 24 Hz), 108.3, 101.0 (d, *J* = 4.4 Hz), 49.9, 42.5, 14.6; FTIR (ATR): *υ* = 3329, 2466, 1708, 1630, 1519 cm^{-1}; HR-MS (APCI): *m/z* 279.1141; $[M+H]^+$ requires 279.1145.



7-Diethylamino-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **49**

Using **14** (160 mg, 0.593 mmol), diethylamine (0.31 ml, 3.0 mmol), DMSO (2 ml), reacting for 16 h and flash chromatography (CH_3OH:$CHCl_3$ 1:49), the title compound **49** was obtained as a pale yellow solid (63.9 mg, 35%). m.p. 158-161 ºC. R_f = 0.33 (CH_3OH:$CHCl_3$ 1:19). ^{1}H NMR (600 MHz, $CDCl_3$): δ 15.35 (*br* s, 1H), 8.60 (s, 1H), 7.98 (d, *J* = 15 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 4H), 1.57 (t, *J* = 7.3 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 175.8 (d, *J* = 2.8 Hz), 166.3, 151.3 (d, *J* = 247 Hz), 148.2, 143.0 (d, *J* = 10 Hz), 137.6, 116.3 (d, *J* = 7.6 Hz), 111.5 (d, *J* = 24 Hz), 106.6, 102.2 (d, *J* = 4.8 Hz), 48.9, 45.8, 14.2, 12.8; FTIR (ATR): *v* = 2471, 1707, 1625, 1511 cm^{-1}; HR-MS (ESI): *m/z* 307.1451; $[M+H]^+$ requires 307.1458.



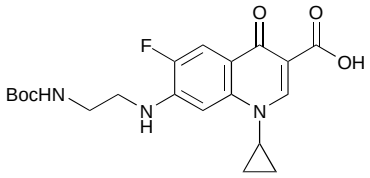
7-Dibutylamino-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **50**

Using **14** (161 mg, 0.597 mmol), dibutylamine (0.51 ml, 3.0 mmol), DMSO (2 ml), reacting for 21 h and flash chromatography (EtOAc:hexane 9:11), the title compound **50** was obtained as a yellow solid (60.6 mg, 28%). m.p. 112-114 ºC. R_f = 0.50 (EtOAc:hexane 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.35 (s, 1H), 8.61 (s, 1H), 7.99 (d, *J* = 15 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 3.41 (t, *J* = 7.5 Hz, 4H), 1.65 (quint, *J* = 7.5 Hz, 4H), 1.57 (t, *J* = 7.3 Hz, 3H), 1.38 (sext, *J* = 7.5 Hz, 4H), 0.97 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 176.9 (d, *J* = 2.7 Hz), 167.8, 151.9 (d, *J* = 249 Hz), 147.0, 143.8 (d, *J* = 10 Hz),

137.7, 117.6 (d, J = 7.7 Hz), 113.3 (d, J = 25 Hz), 108.0, 100.7 (d, J = 4.9 Hz), 52.9, 49.8, 29.9, 20.4, 14.5, 14.0; FTIR (ATR): υ = 2542, 1718, 1624, 1509 cm^{-1}; HR-MS (APCI): *m/z* 363.2079; $[M+H]^+$ requires 363.2084.

General procedure for the preparation of the 7-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-1-alkyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **55**, **56**.

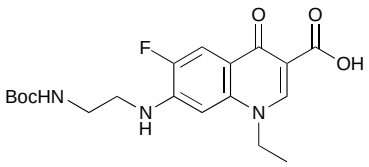
tert-Butyl *N*-(2-aminoethyl)carbamate[1] (5 eq) was added to a solution of the appropriate acid **36** and **14** in DMSO (2 ml) and stirred at 140 ºC, to form a dark solution, until complete conversion of the starting material, as indicated by TLC. The solutions were then cooled and concentrated and the resultant residues were diluted with saturated NH_4Cl solution. The mixtures were then extracted with $CHCl_3$ (3 x 30 ml), and the combined organic extracts were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated. The resultant residues were then purified by flash chromatography to yield the carbamates **55** and **56**.



7-((2-((*tert*-Butoxycarbonyl)amino)ethyl)amino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **55**

Using **36** (303 mg, 1.08 mmol), *tert*-butyl *N*-(2-aminoethyl)carbamate[1] (865 mg, 5.4 mmol), DMSO (2 ml), reacting for 2 h and flash chromatography (EtOAc:hexane 9:1), the title compound **55** was obtained as a pale yellow solid (126 mg, 29%). m.p. 212-215 ºC. R_f = 0.27 (EtOAc:hexane 9:1). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.63 (*br* s, 1H), 8.57 (s, 1H), 7.79 (d, J = 12 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.13-7.04 (m, 2H), 3.78-3.71 (m, 1H), 3.46-3.39

(m, 2H), 3.24-3.17 (m, 1H), 1.36 (s, 9H), 1.36-1.30 (m, 2H), 1.18-1.10 (m, 2H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 176.0 (d, J = 2.7 Hz), 166.4, 156.0, 149.9 (d, J = 246 Hz), 147.0, 142.6 (d, J = 14 Hz), 140.6, 113.9 (d, J = 6.7 Hz), 108.8 (d, J = 20 Hz), 106.3, 96.5, 78.0, 42.4, 38.1, 36.0, 28.2, 7.6; FTIR (ATR): υ = 3343, 1709, 1631, 1525 cm^{-1}; HR-MS (APCI): *m/z* 4061772; $[M+H]^+$ requires 406.1778.



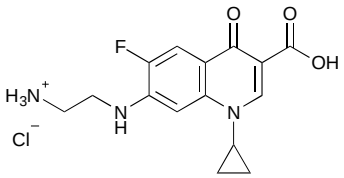
7-((2-((*tert*-Butoxycarbonyl)amino)ethyl)amino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **56**

Using **14** (213 mg, 0.790 mmol), *tert*-butyl *N*-(2-aminoethyl)carbamate[1] (633 mg, 3.95 mmol), DMSO (2 ml), reacting for 3 h and flash chromatography (EtOAc:hexane 9:1), the title compound **56** was obtained as a pale yellow solid (86.9 mg, 28%). R_f = 0.27 (EtOAc:hexane 9:1). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 15.80 (*br* s, 1H), 8.84 (s, 1H), 7.81 (d, J = 12 Hz, 1H), 7.12-7.00 (m, 3H), 4.62-4.48 (m, 2H), 3.37-3.28 (m, 2H), 3.22-3.12 (m, 2H), 1.45-1.39 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 175.9, 166.8, 156.4, 149.9 (d, J = 246 Hz), 147.8, 143.0 (d, J = 14 Hz), 138.7, 114.6 (d, J = 6.5 Hz), 109.1 (d, J = 20 Hz), 106.7, 96.0, 78.3, 49.2, 42.3, 38.2, 28.3, 14.6; HR-MS (APCI): *m/z* 394.1772; $[M+H]^+$ requires 394.1778.

General procedure for the deprotection of **51** and **52**.

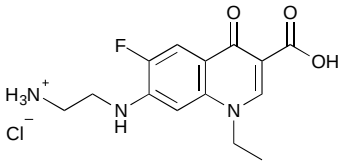
Ethanol (4 ml per 0.2 mmol of carbamate) and 3 M HCl (30 eq) were added to the appropriate carbamate **55** and **56**, and the resulting solutions were stirred at reflux until complete consumption of the starting material**,** as indicated by TLC. The solutions were then

allowed to cool. The resultant precipitate was then collected and washed with ethanol to yield the hydrochlorides **51** and **52**.



7-((2-Aminoethyl)amino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **51**

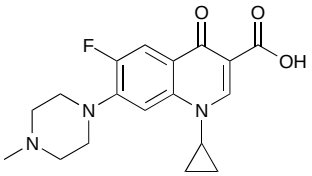
Using **55** (107 mg, 0.264 mmol), HCl (3 M, 2.6 ml, 7.9 mmol), EtOH (5.2 ml) and reacting for 1.5 h, the title compound **51** was obtained as a white solid (52.4 mg, 58%). m.p. >250 ºC. ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 8.60 (s, 1H), 7.83 (d, J = 12 Hz, 1H), 7.22 (d, J = 7.3 Hz), 7.17-7.11 (m, 1H), 3.83-3.77 (m, 1H), 3.64-3.58 (m, 2H), 3.10 (t, J = 6.3 Hz), 1.39-1.33 (m, 2H), 1.17-1.11 (m, 2H); ^{13}C NMR (150.9 MHz, $(CD_3)_2SO$): δ 176.1, 166.3, 150.1 (d, J = 246 Hz), 147.2, 142.2 (d, J = 14 Hz), 140.5, 114.4 (d, J = 6.7 Hz), 109.0 (d, J = 20 Hz), 106.3, 96.9 (d, J = 3.8 Hz), 40.1, 37.3, 36.1, 7.7; FTIR (ATR): υ = 3329, 2826, 1705, 1632, 1585, 1526 cm^{-1}; HR-MS (APCI): *m/z* 306.1252; $[M+H]^+$ requires 306.1254.



7-((2-Aminoethyl)amino)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **52**

Using **56** (82.9 mg, 0.211 mmol), HCl (3 M, 2.1 ml, 6.3 mmol), EtOH (4.2 ml) and reacting for 1.5 h, the title compound **52** was obtained as a white solid (35.5 mg, 51%). m.p. >250 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 8.86 (s, 1H), 7.85 (d, J = 12 Hz, 1H), 7.13-7.05 (m, 1H), 6.95-6.89 (m, 1H), 4.64-4.54 (m, 2H), 3.67-3.59 (m, 2H), 3.09-3.02 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.8 MHz, $(CD_3)_2SO$): δ 175.9, 166.5, 149.9 (d, J = 246 Hz), 147.8, 142.5, 138.5, 115.0 (d, J = 6.7 Hz), 109.2 (d, J = 20 Hz), 106.7, 96.2 (d, J = 3.7 Hz),

49.1, 37.5, 14.5; FTIR (ATR): υ = 3339, 2822, 1690, 1628, 1561, 1528 cm^{-1}; HR-MS (APCI): *m/z* 294.1248; $[M+H]^+$ requires 294.1254.



1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **53**

An aqueous solution of 85% formic acid (1 ml), 41% formaldehyde (1 ml), and 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **1** (99.2 mg, 0.299 mmol) was stirred at reflux, until complete consumption of the starting material, as indicated by TLC (5 h). The solution was then cooled and concentrated, and the resultant residue was dissolved in water, neutralised with 1 M NaOH, and extracted with DCM (3 x 20 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was then purified by flash chromatography (MeOH:$CHCl_3$ 1:9) to yield the title compound **53** as a white solid (47.3 mg, 46%). R_f = 0.33 (MeOH:$CHCl_3$ 1:9). The ^1H and ^{13}C NMR spectra of the compound were consistent with those found in the literature.[15]

Herbicidal Activity

Approximately 30 seeds of *Arabidopsis thaliana* (WT Col-0) were sown per pot (6x6 cm) of soil (Seedling Substrate Plus+, Bord Na Móna), and stored for four days at 4 °C in a dark room to synchronise germination. At day zero, the seeds were placed in growing conditions at 22 °C, 60% relative humidity in 16 h light/8 h dark conditions, for 16 or 20 days. The post-emergence treatments were done three and six days after germination. Compounds were dissolved in DMSO, at 10 g/L for compounds **1**, **28**-**35**, **37**-**43**, **51** and **53**, and 40 g/L for

compounds **30**, **44**-**50**, **52** and **54**, and diluted to the required concentration with a 0.2% surfactant solution, where the DMSO concentration does not exceed 2%. The surfactant used was Brushwet (SST Australia). A 2% DMSO solution, without the active ingredient, was used as the negative control, and ciprofloxacin (Sigma Aldrich, Cat# 17850) as a positive control. Seedlings were treated with 500 μL of 0, 3.125, 6.25, 12.5, 25, 50, 100 or 200 mg/L and 0, 12.5, 25, 50, 100, 200, 400 or 800 mg/L solution of the active ingredient using a pipette, for the treatments of **1**, **28**-**35**, **37**-**43**, **51** and **53**, and **30**, **44**-**50**, **52** and **54**, respectively, with each conducted in triplicate. Pictures were taken at day 16 or 20 using a Nikon D80 SLR in manual mode (shutter speed: 250, aperture: F5), fitted with 18-135 mm lens and fixed on to a camera stand set a 75 cm. The images were then analysed for growth, and health of the *A. thaliana* plants, using ImageJ according to the methods of Corral *et al.*[16] Assays against the *ATGYRA* mutant were performed using a similar methodology to the initial WT *A. thaliana* screenings. Compounds **1**, **30**, **37**-**39**, **41**, **44** and **45** were applied to WT seedlings at concentrations of 0, 12.5, 25 and 50 mg/L, and to *gyra*-3 seedlings at concentrations of 0, 50, 100, 200, 400, 800 mg/L.

Antibacterial Activity

The Minimum Inhibitory Concentrations (MIC) were determined via the Broth Microdilution Method, as per the Clinical and Laboratory Standards Institute Approved Standards.[17] Compounds dissolved in Mueller Hinton broth with 4% DMSO, were added to 96-well plates with a 2-fold serial dilution. The bacteria were grown to exponential growth phase in Mueller Hinton broth, and 100 μL was added to the respective wells, at a concentration of 5×10^5 CFU/ml, with a final DMSO concentration of 2%. Plates were then incubated at 37 ºC for 18 h. MICs were recorded by visual inspection and confirmed by absorbance measured at 600 nm with each compound tested in triplicate.

Enzyme assays

A. thaliana DNA gyrase protein was produced as described previously;[18] *Escherichia coli* gyrase was a gift from Lesley Mitchell and made as described previously.[19] Supercoiling assays were performed as described previously[19] except that the assay buffers were as follows: *A. thaliana* gyrase: 40 mM HEPES·KOH (pH 7.6), 10 mM magnesium acetate, 10 mM DTT, 2 mM ATP, 700 mM potassium glutamate and 0.05 mg/mL albumin; *E. coli* gyrase: 35 mM Tris·HCl (pH 7.5), 24 mM KCl, 4 mM $MgCl_2$, 2 mM DTT, 1.8 mM spermidine, 1 mM ATP, 6.5% w/v glycerol and 0.1 mg/mL albumin. All samples were incubated at 37°C for 30 mins, after which the reaction was stopped by adding 30 μL of 40% sucrose, 100 mM Tris·HCl (pH 8), 100 mM EDTA, 0.5 mg/ml bromophenol blue and 30 μL of chloroform/isoamylalcohol (24:1). The amount of enzyme used was adjusted such that in the inhibited controls less than full supercoiling was achieved. DNA cleavage assays were carried out as described for supercoiling, except that ATP was omitted and supercoiled rather than relaxed DNA was used, and after 60 mins at 37°C, SDS and proteinase K were added to final concentrations of 0.2% and 1 mg/mL respectively and the incubation continued for a further 30 mins before stopping the reactions as described above. For cleavage assays the amount of enzyme used was adjusted to yield an easily-visible linear band in the presence of ciprofloxacin.

Samples were analysed on 1% w/v agarose gels in 40 mM Tris acetate (pH 8), at 80 V for 2-3 h. Gel images were captured using a Syngene documentation system. Image J was used to analyse gel images and data were input into GraphPad Prism 7 in order to determine plots and consequently, IC_{50} values for supercoiling assays. The IC_{50} values are defined here by the concentration of compound required to inhibit the gyrase supercoiling activity by 50% with errors given as standard error in the mean of triplicate measurements. Ciprofloxacin **1** and analogues **28**-**35** and **37**-**54** were dissolved in DMSO for the analysis.

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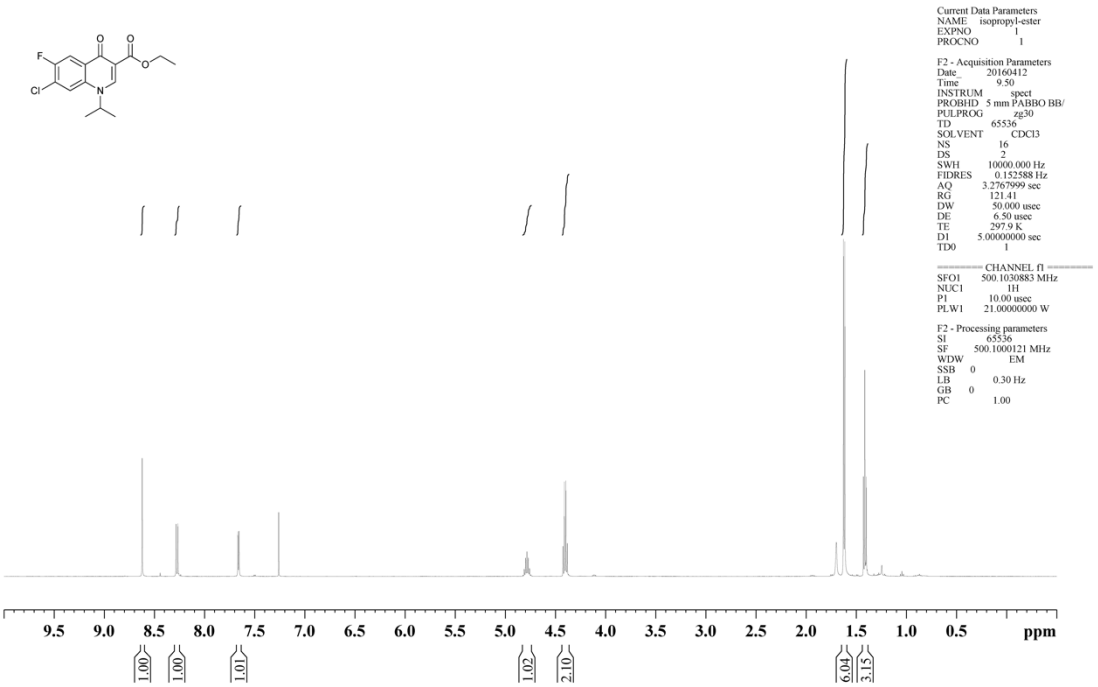
^{1}H NMR spectrum of **4**



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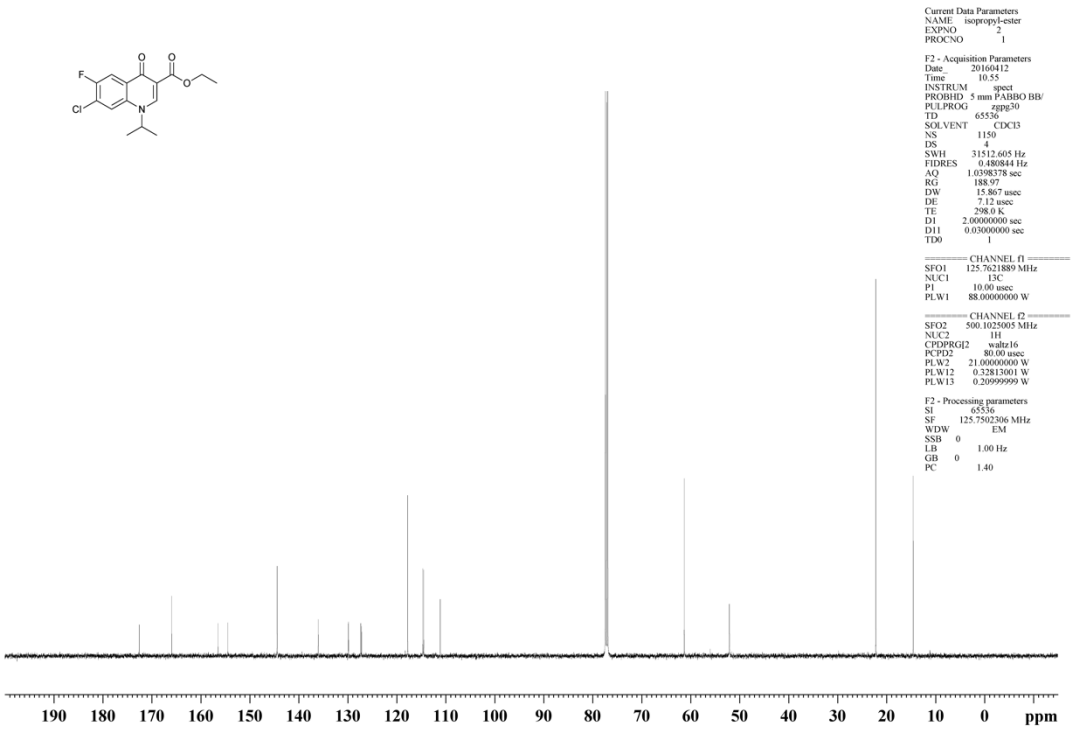

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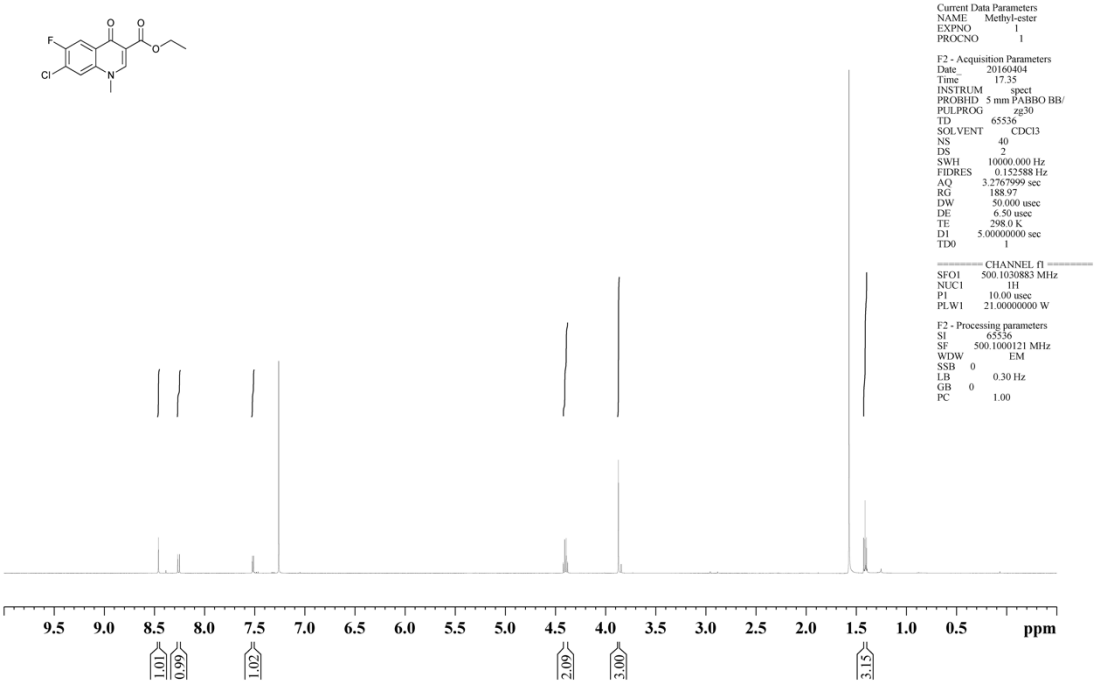

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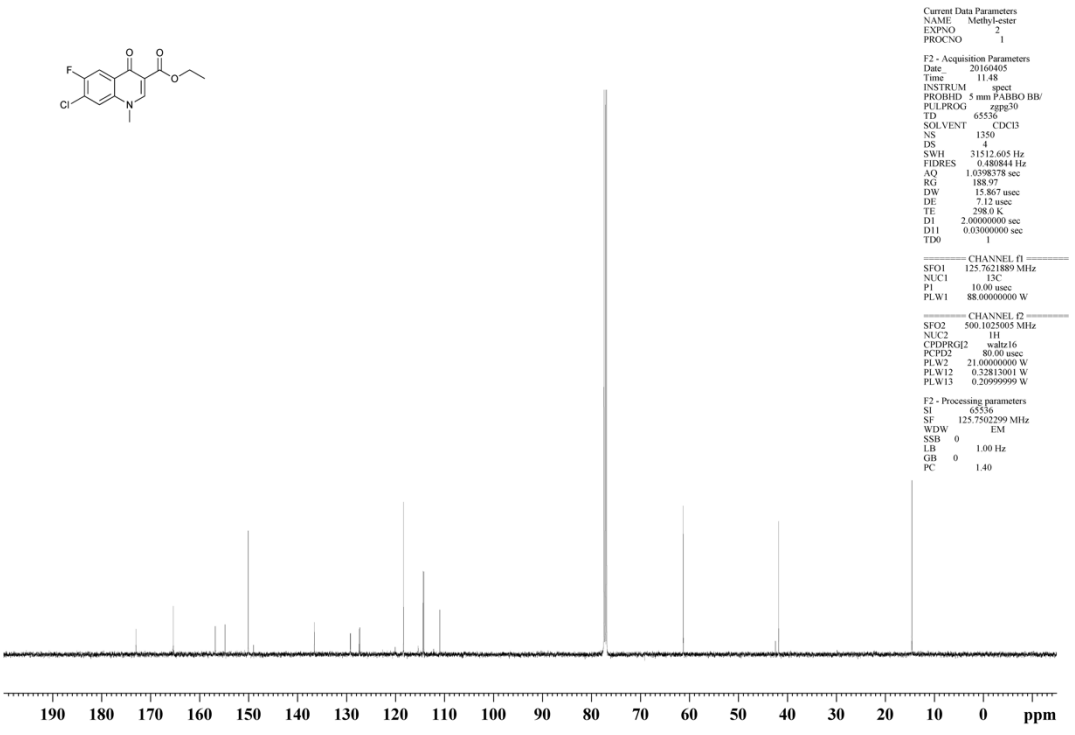

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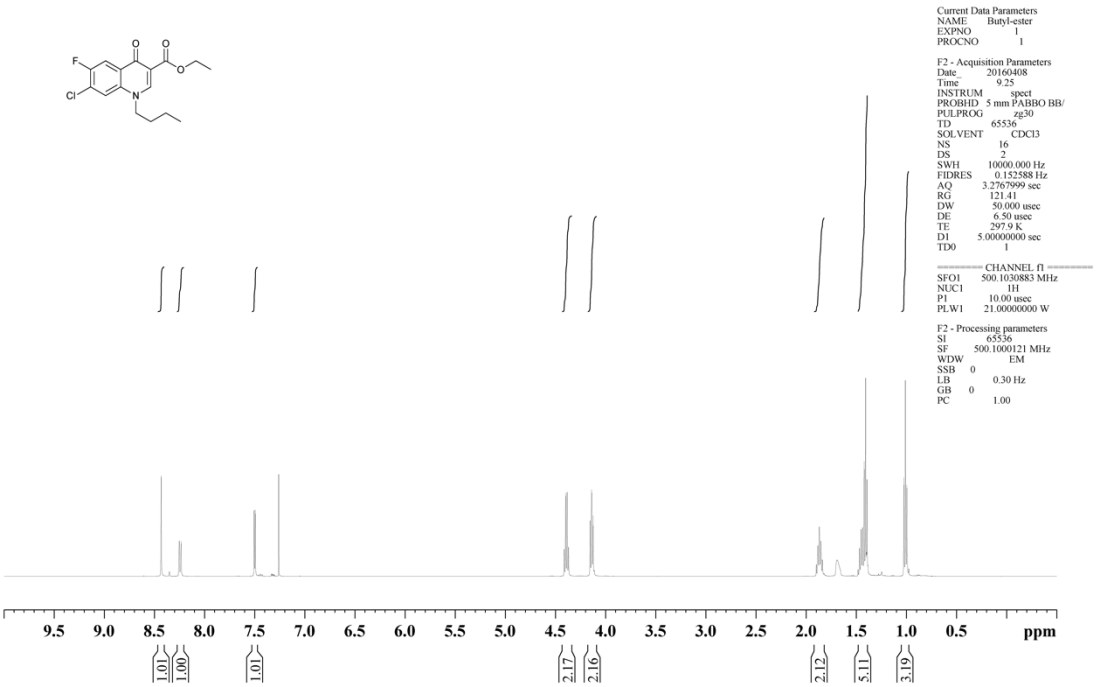

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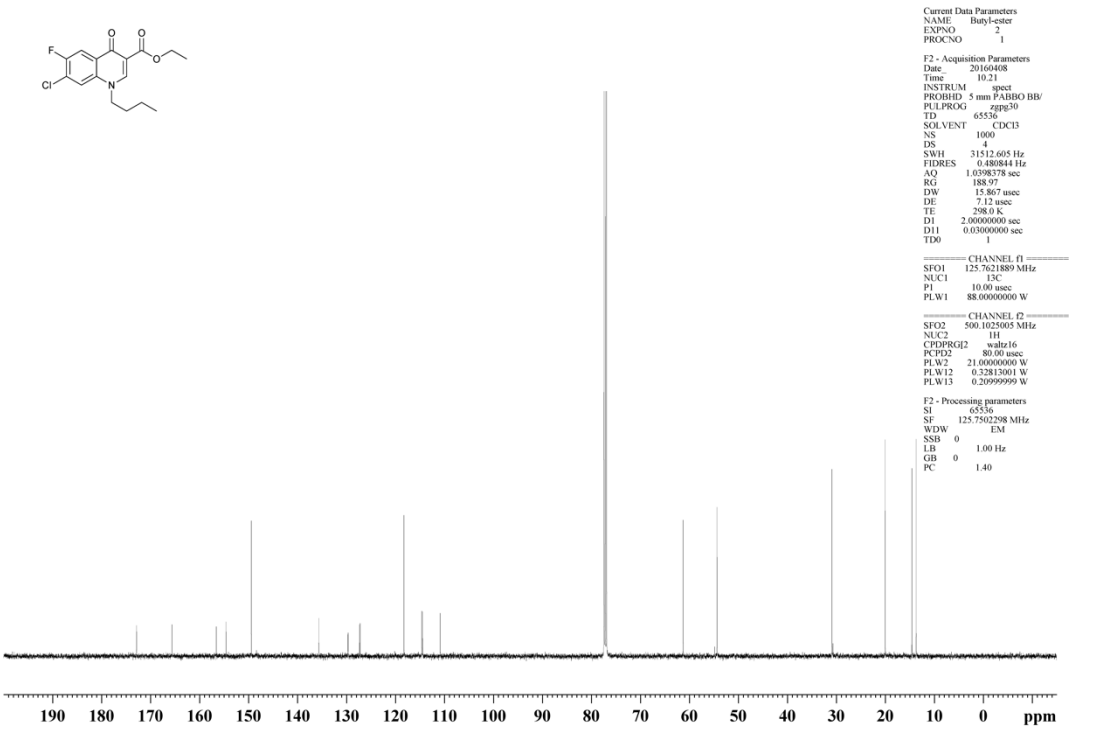

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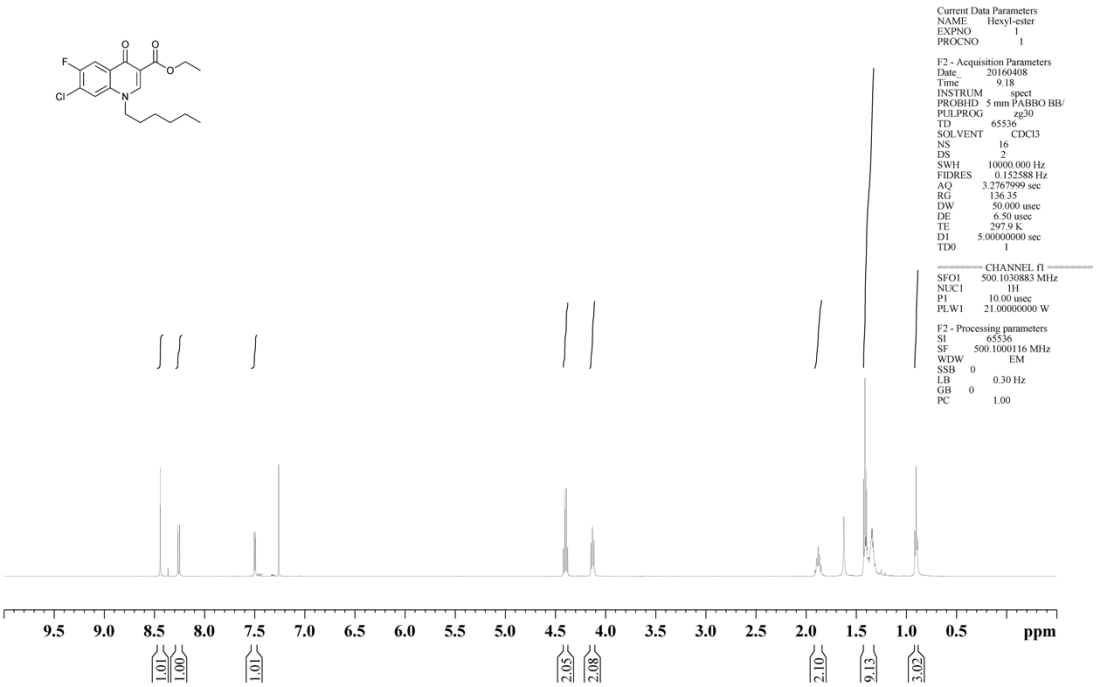

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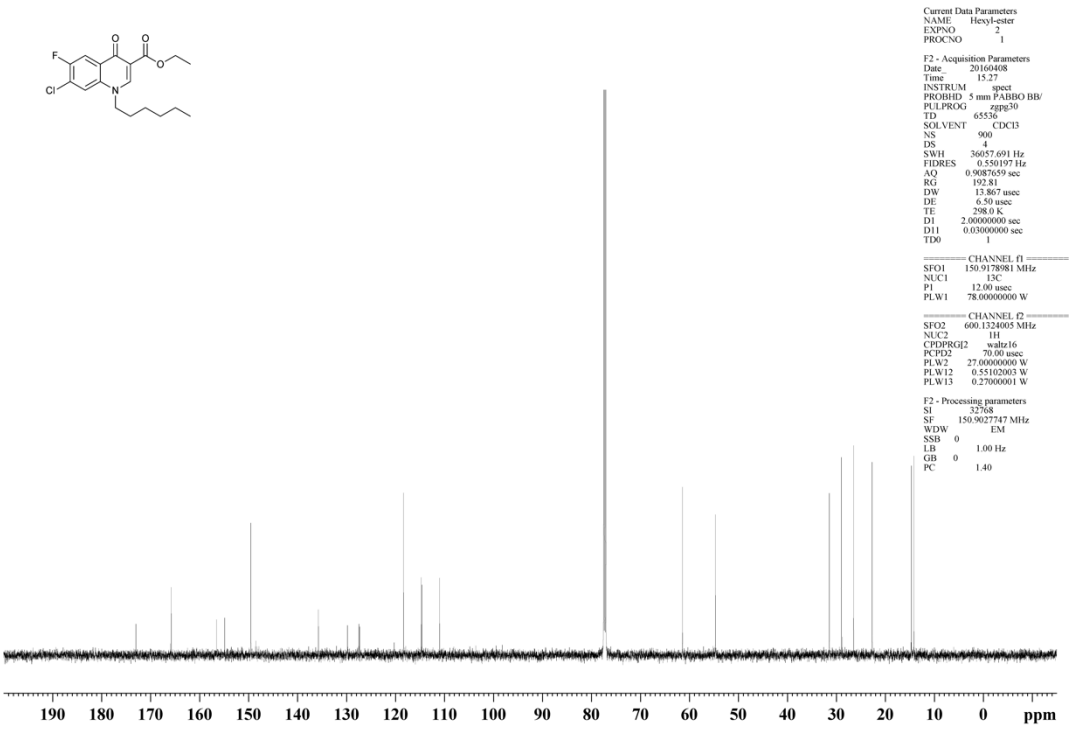

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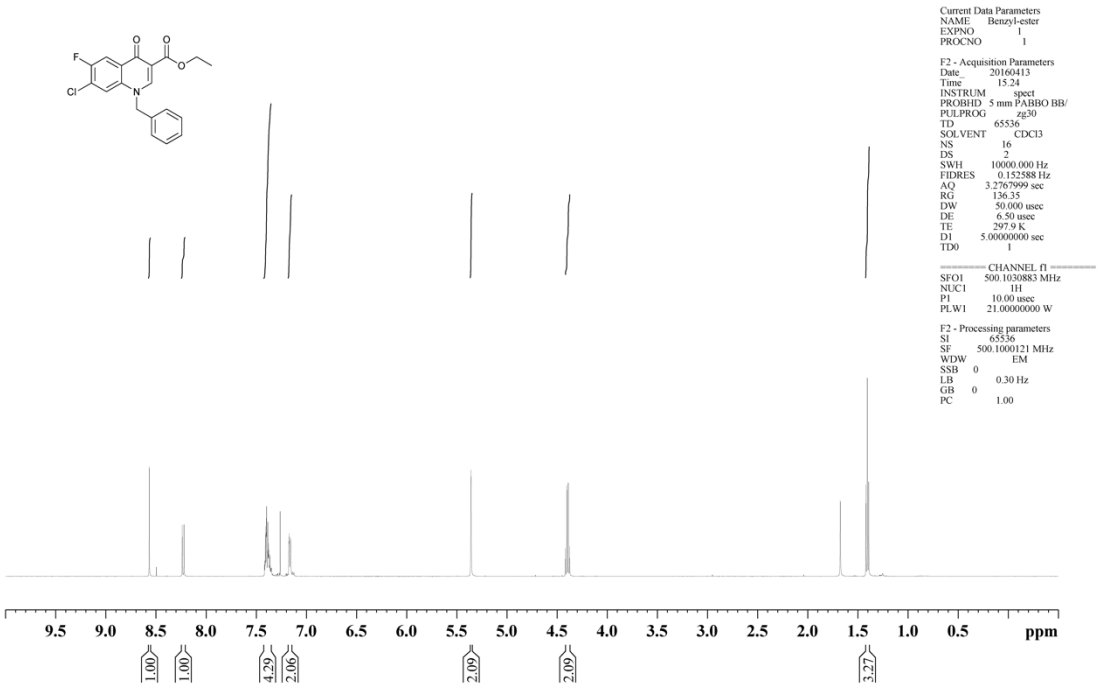

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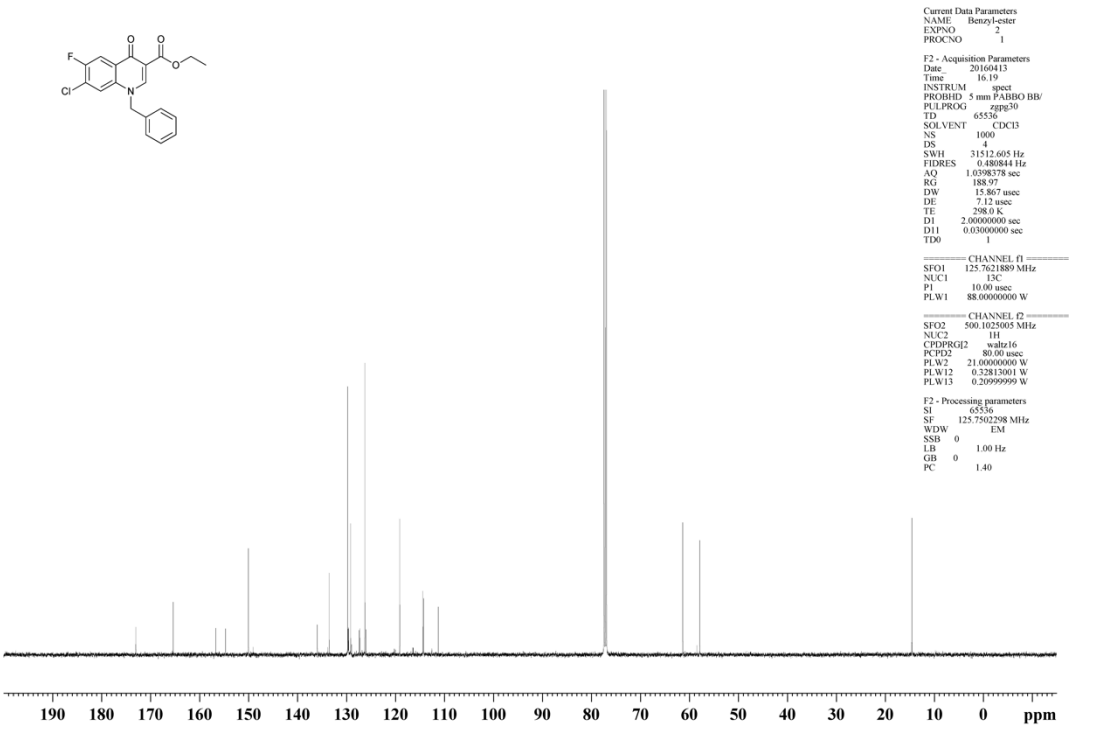

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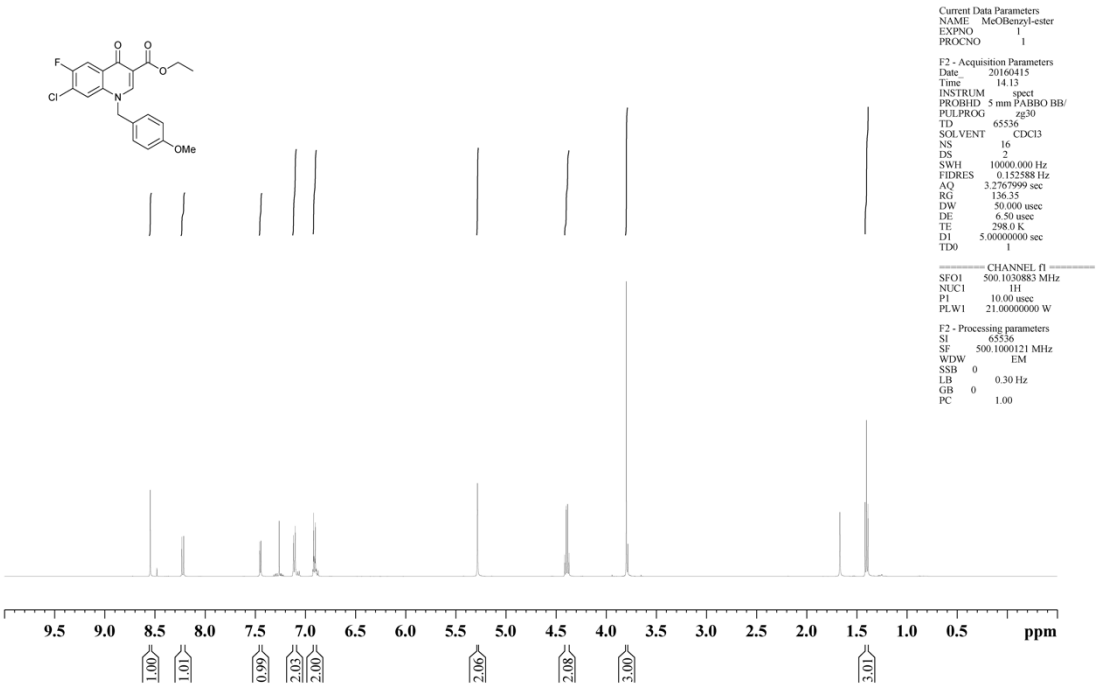

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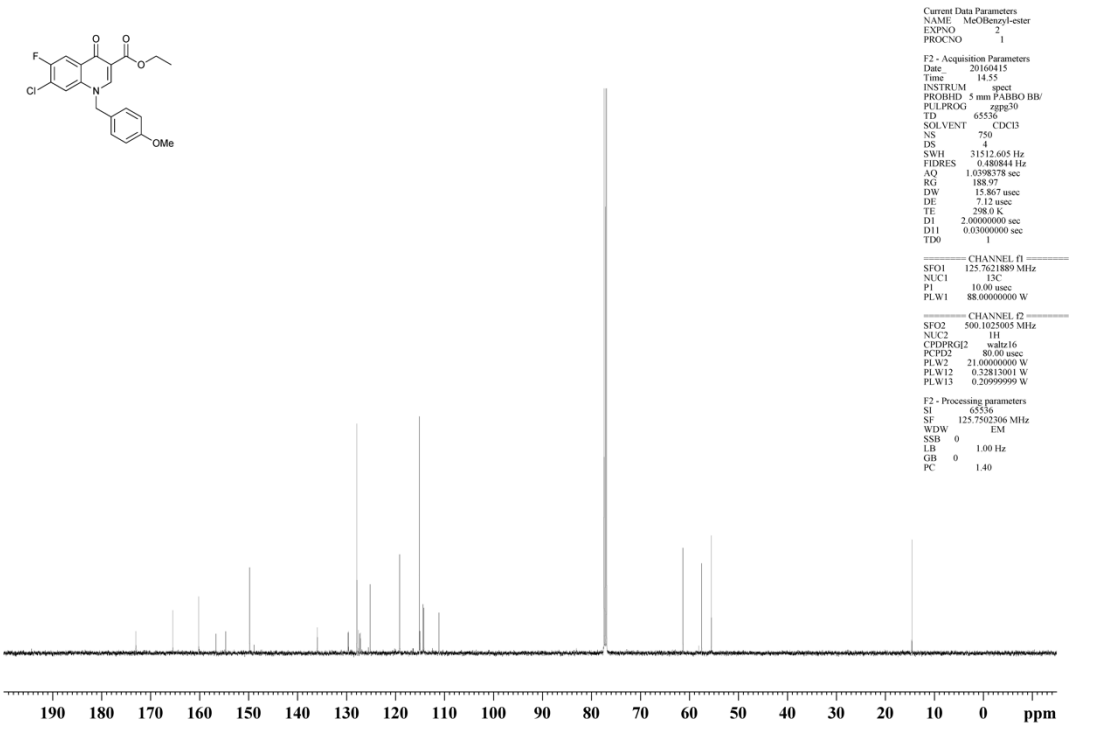

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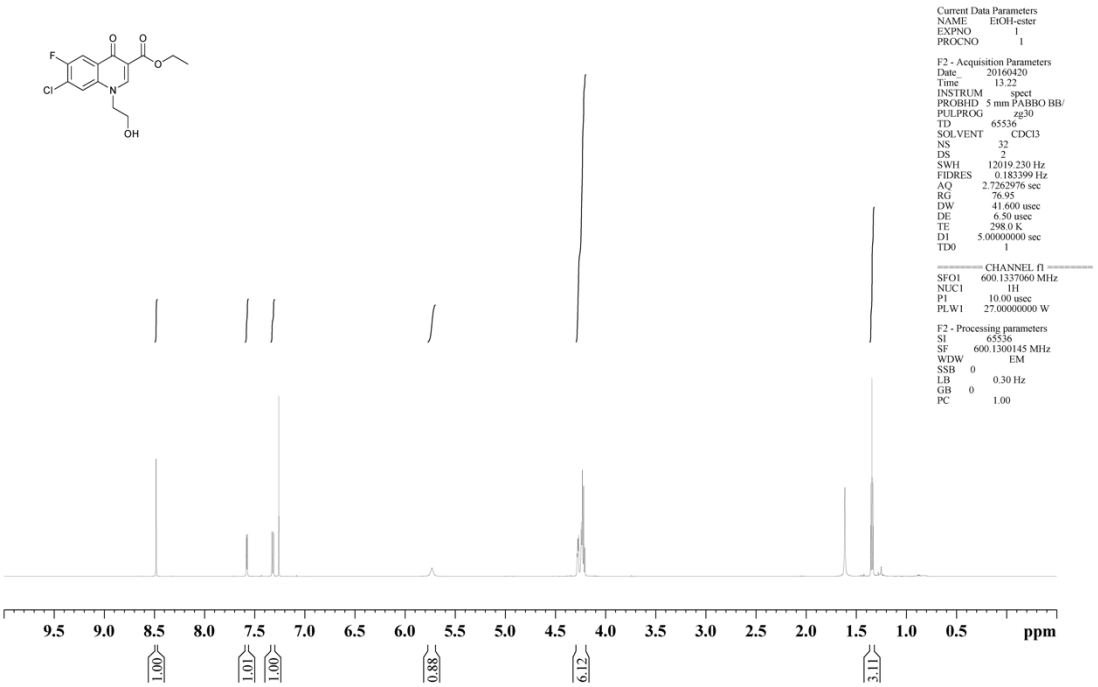

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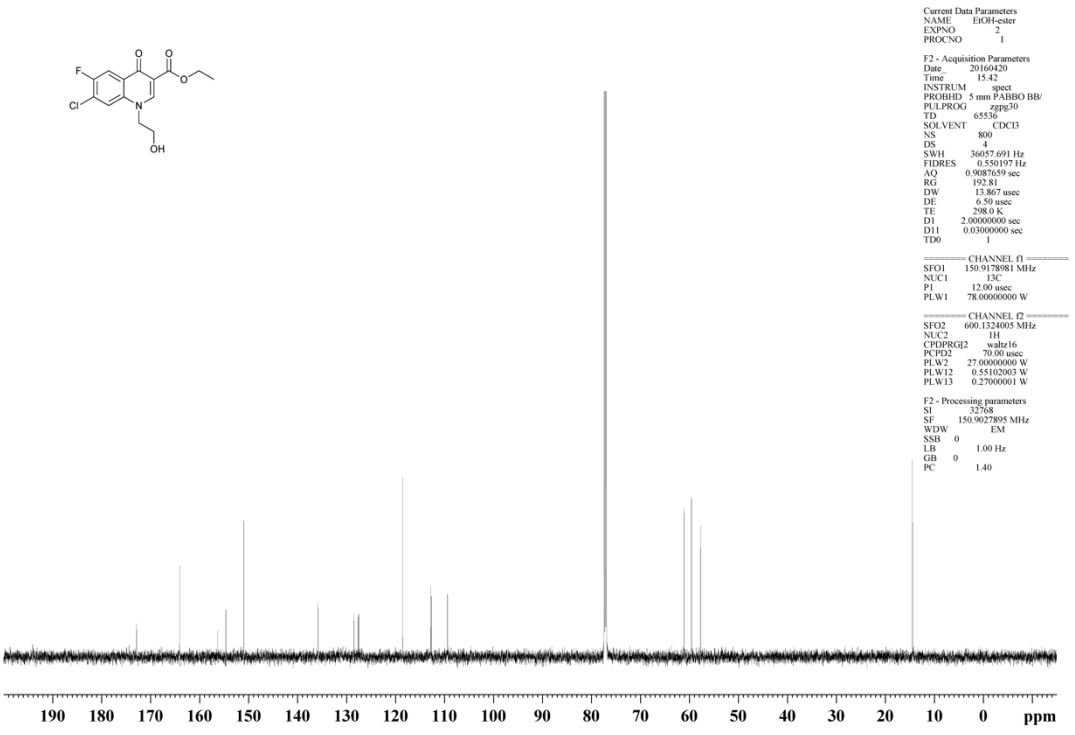

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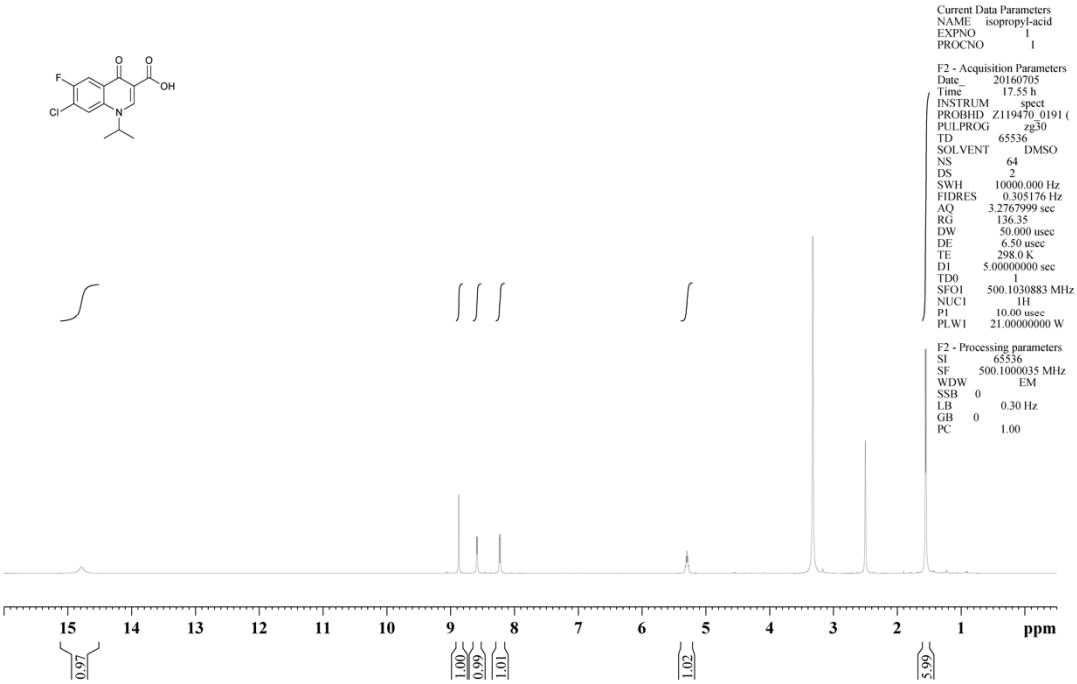

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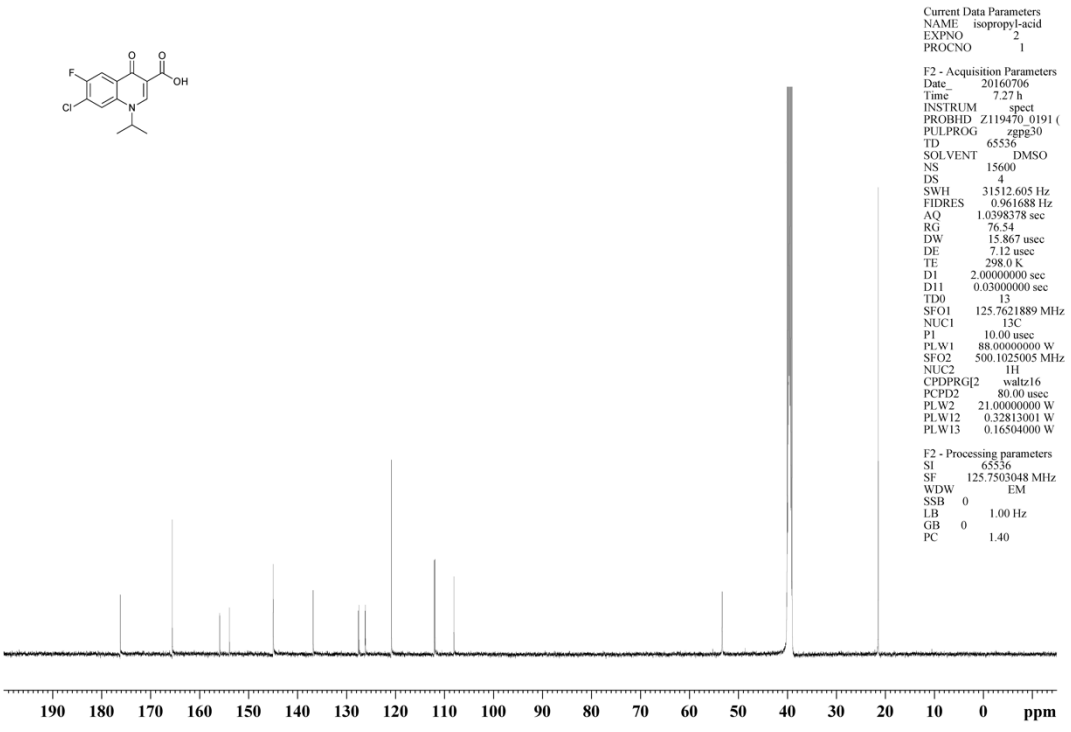

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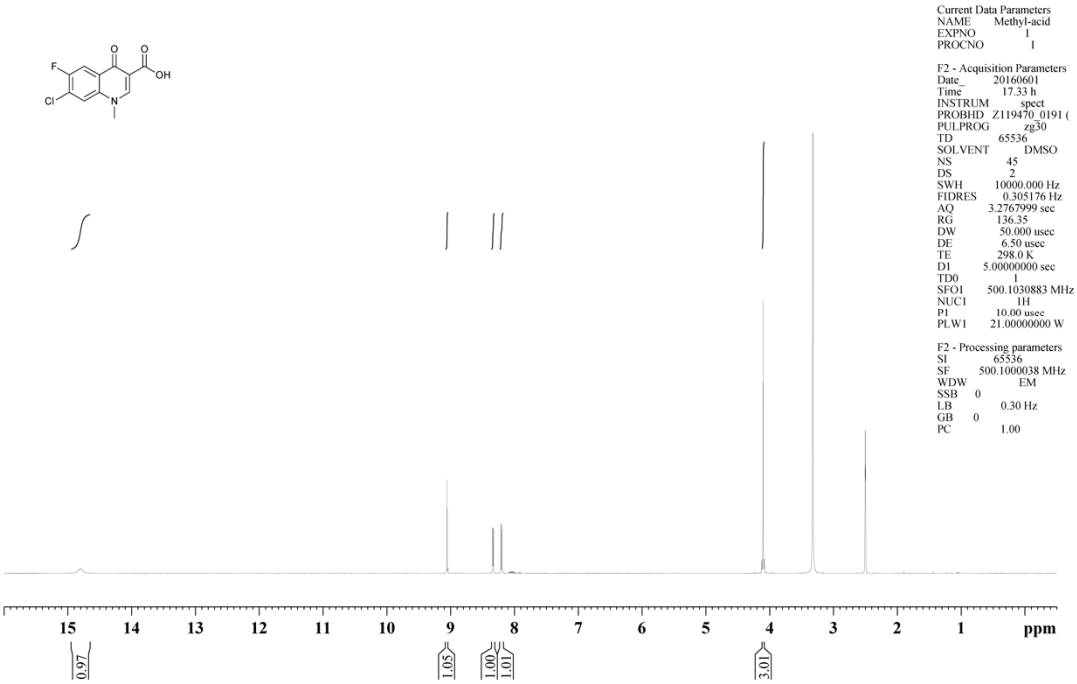

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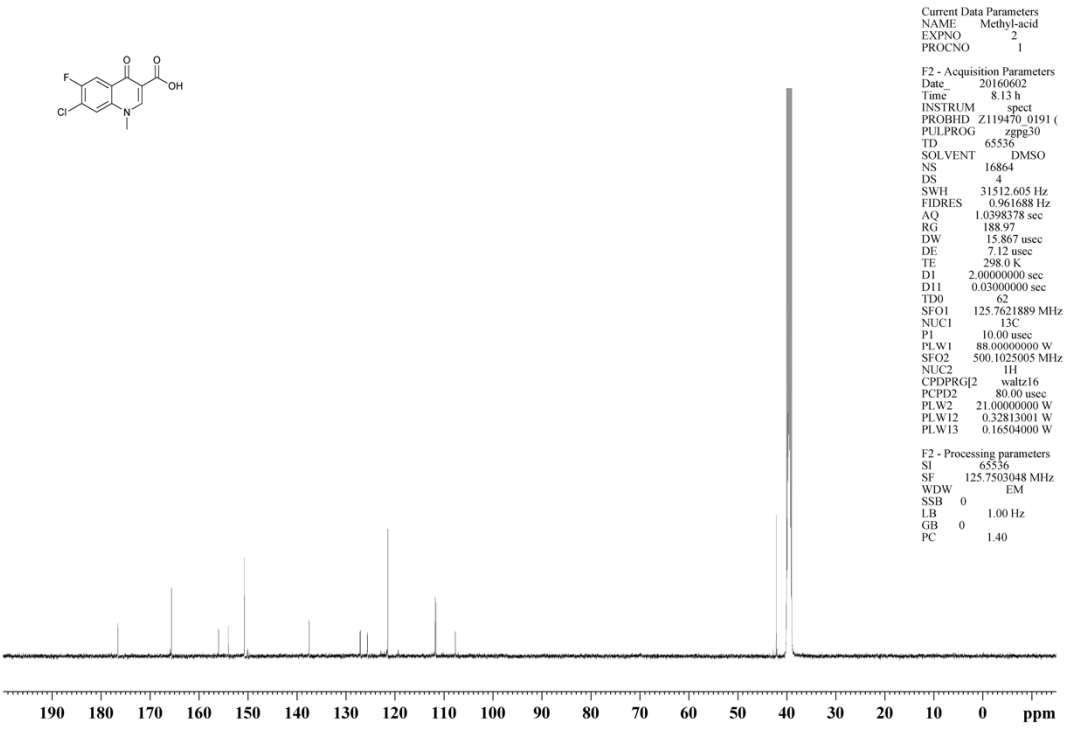

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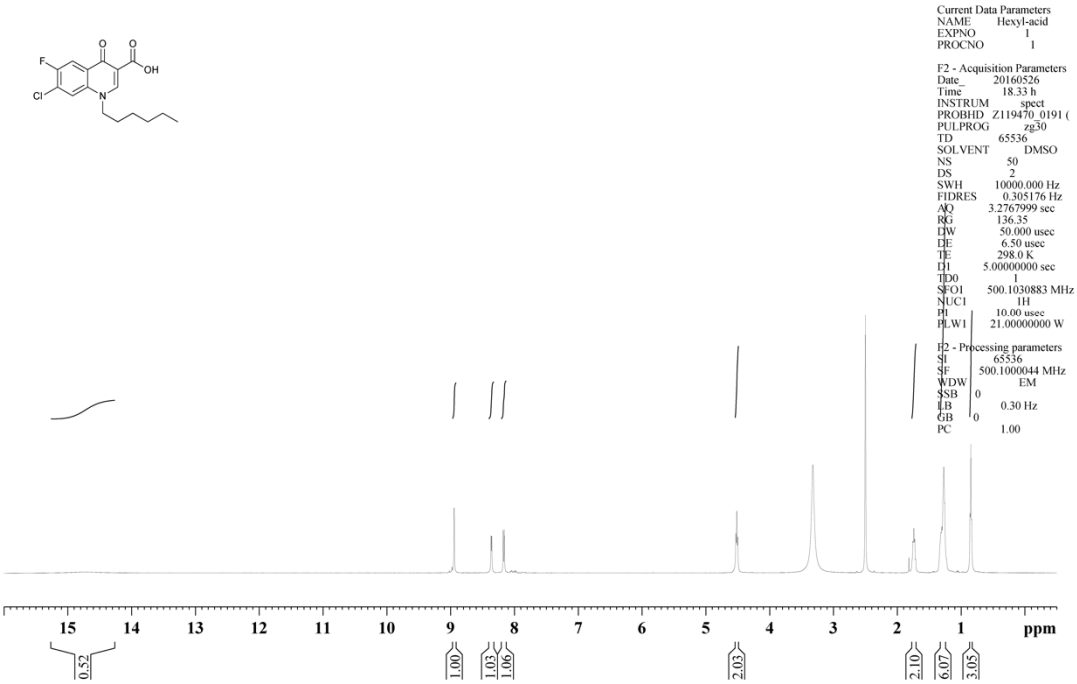

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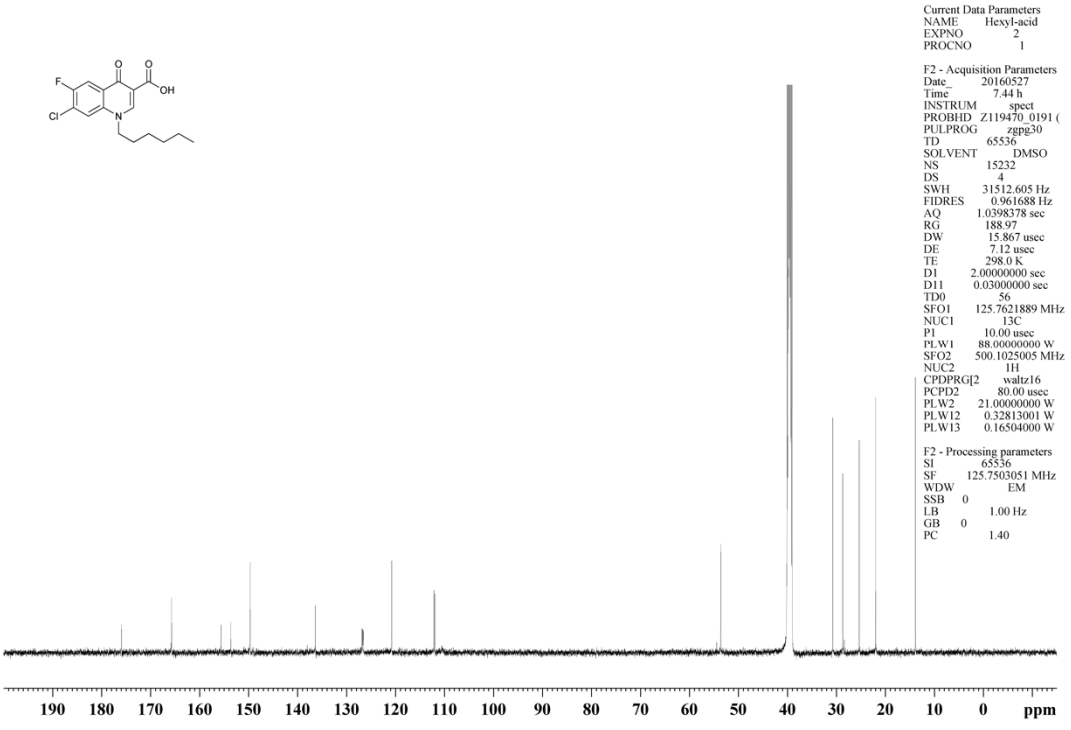

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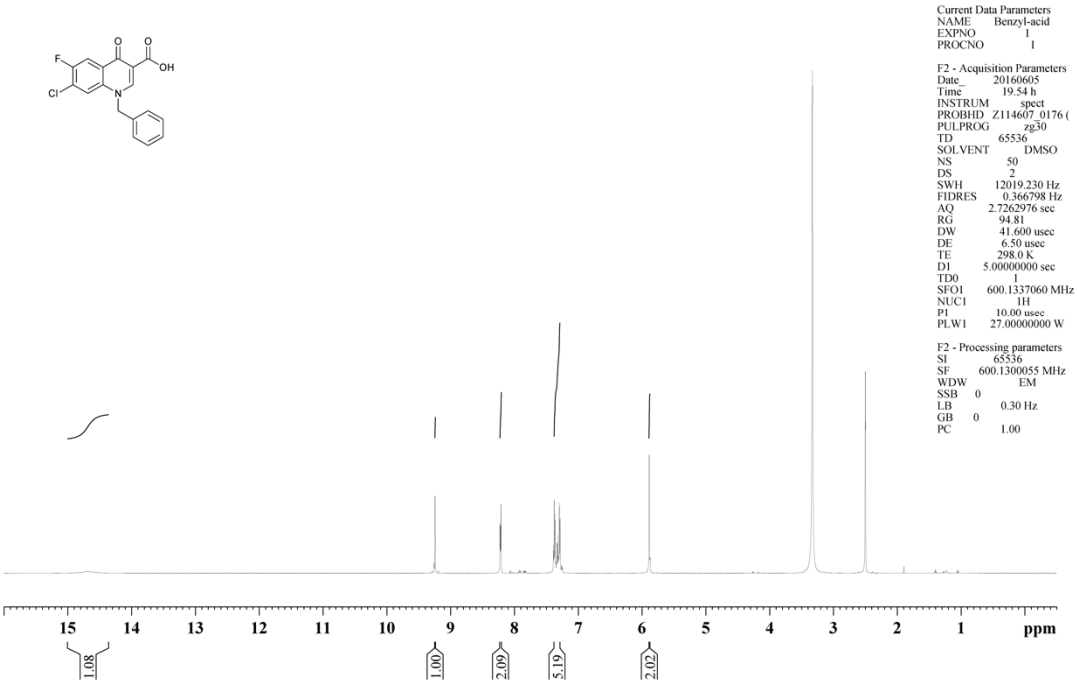

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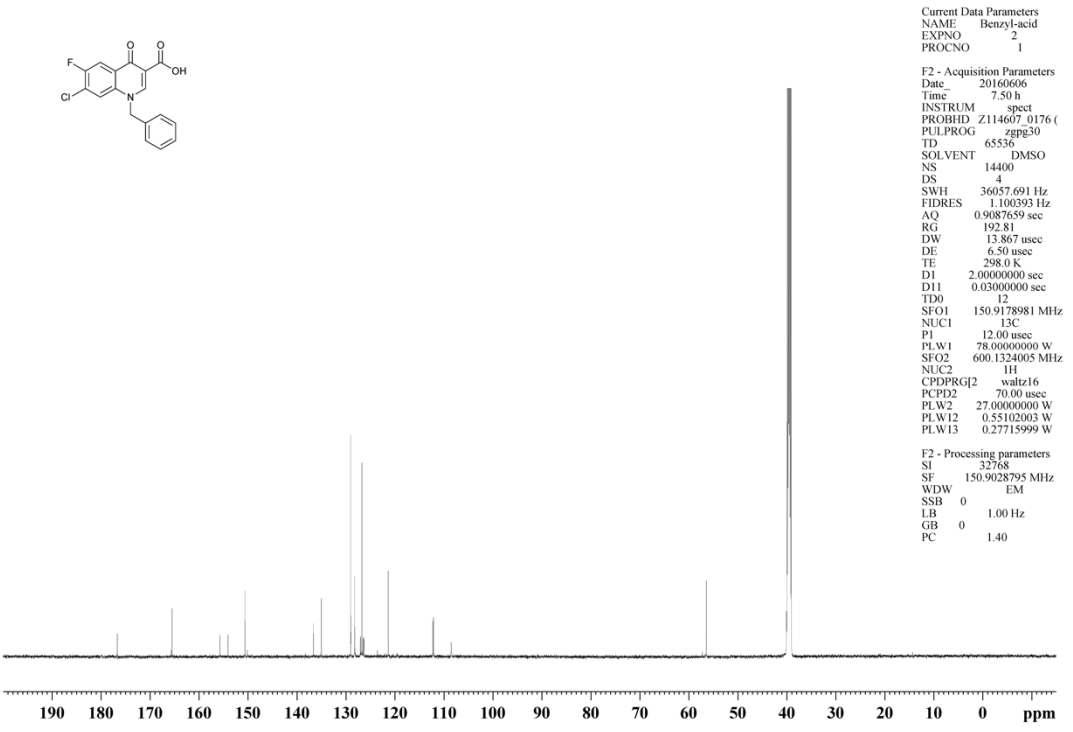

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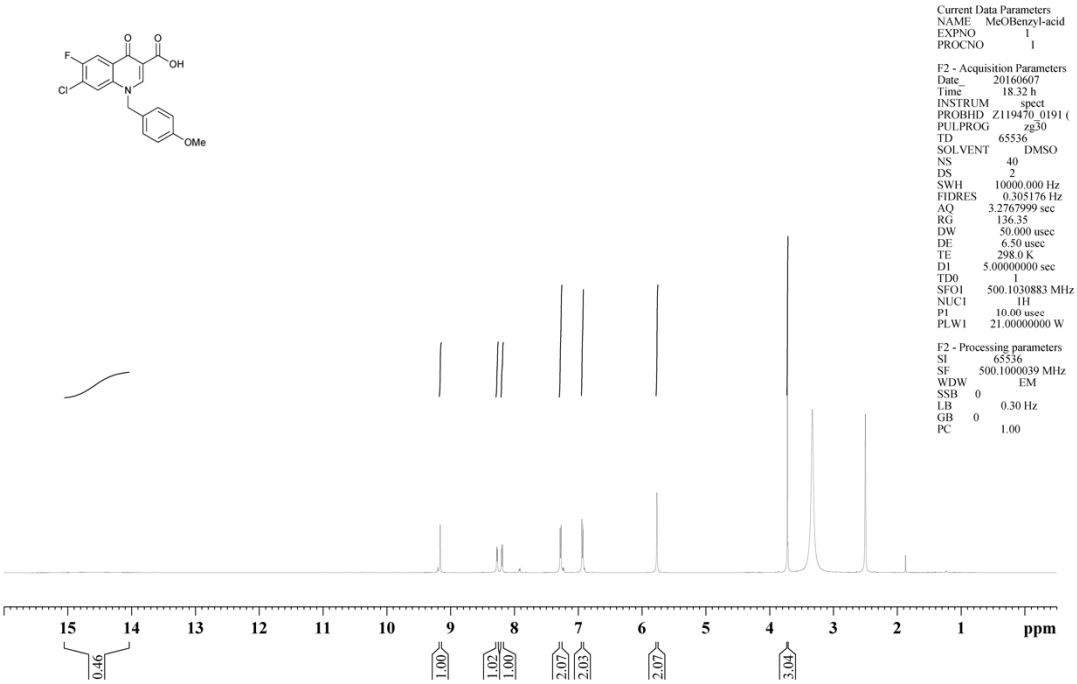

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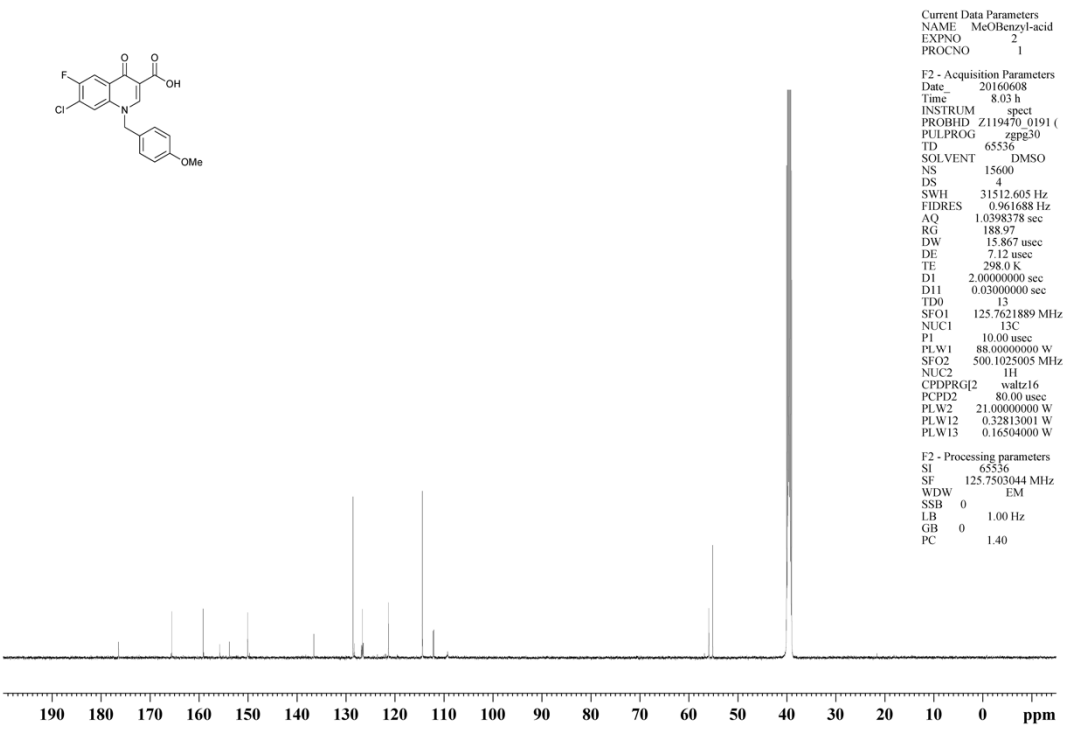

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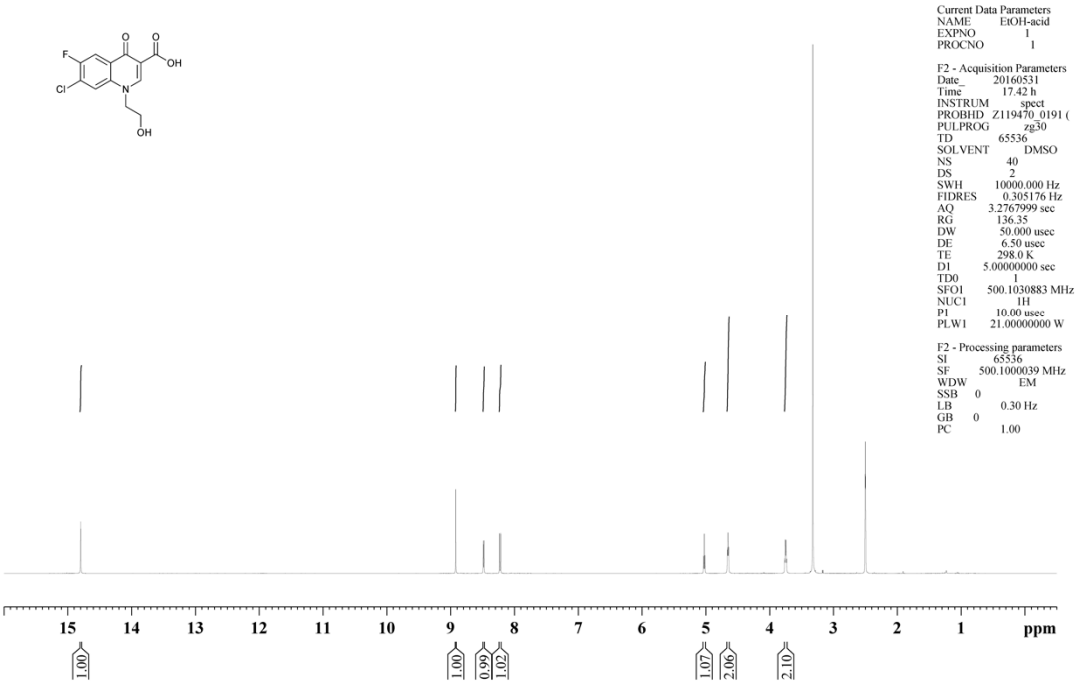

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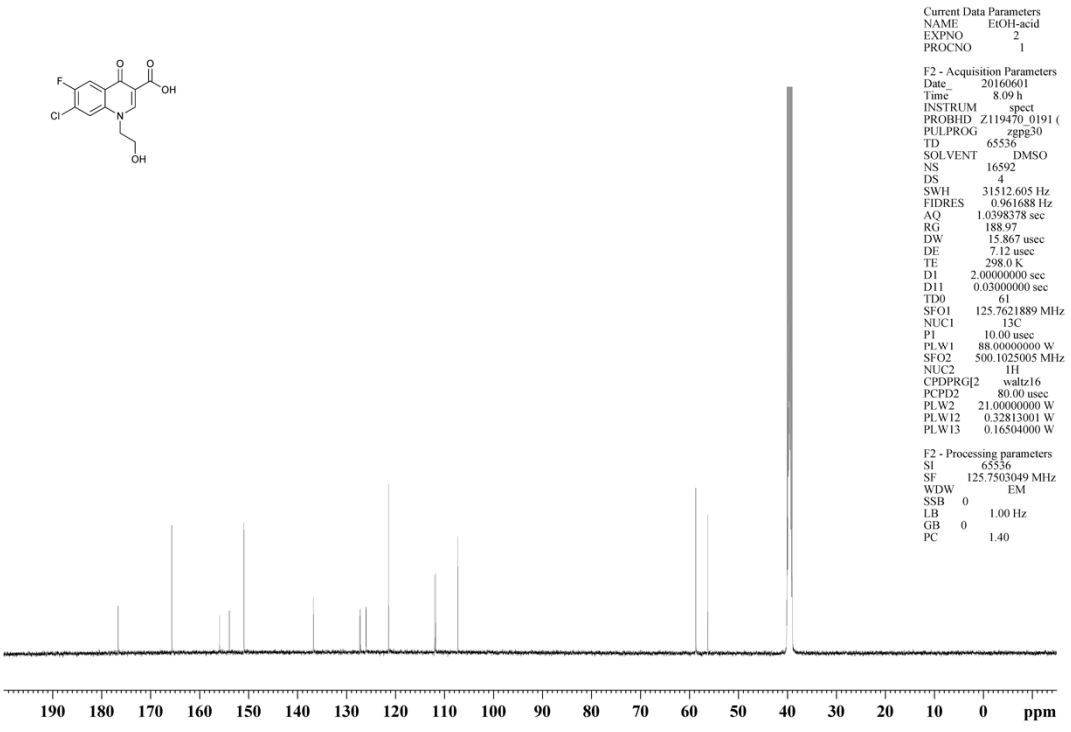

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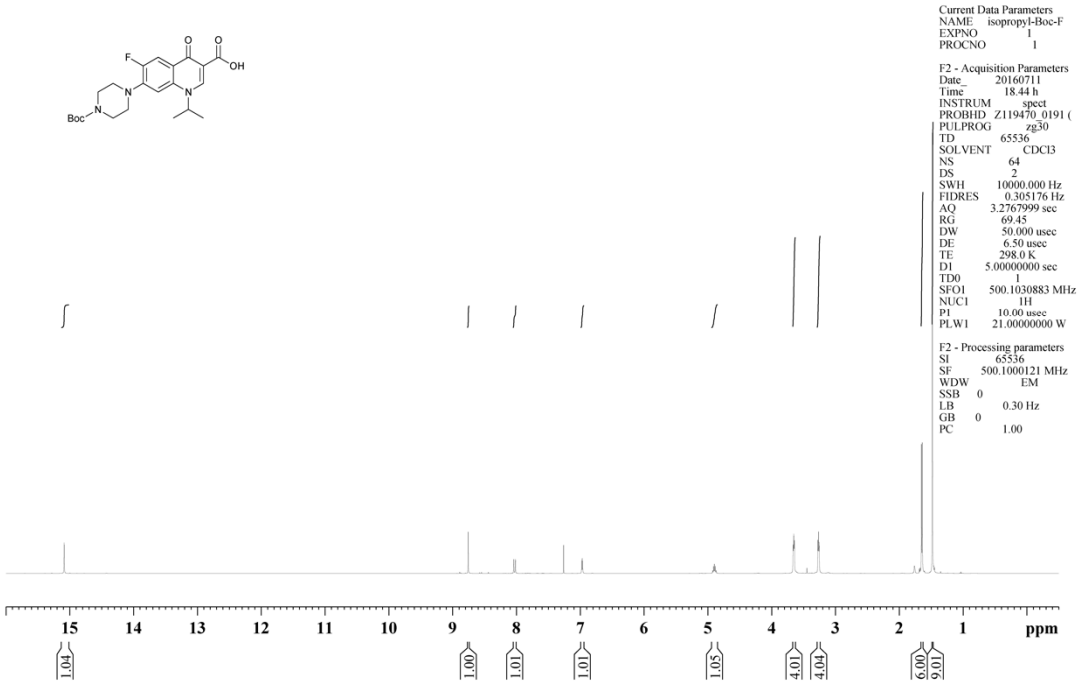

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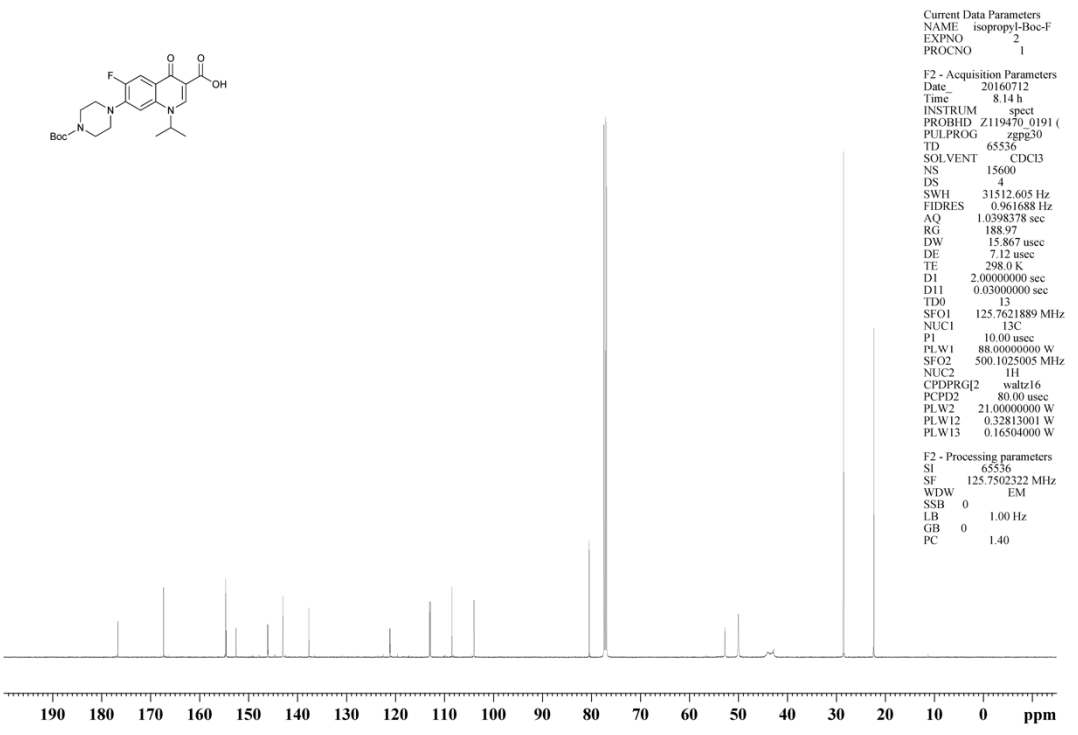

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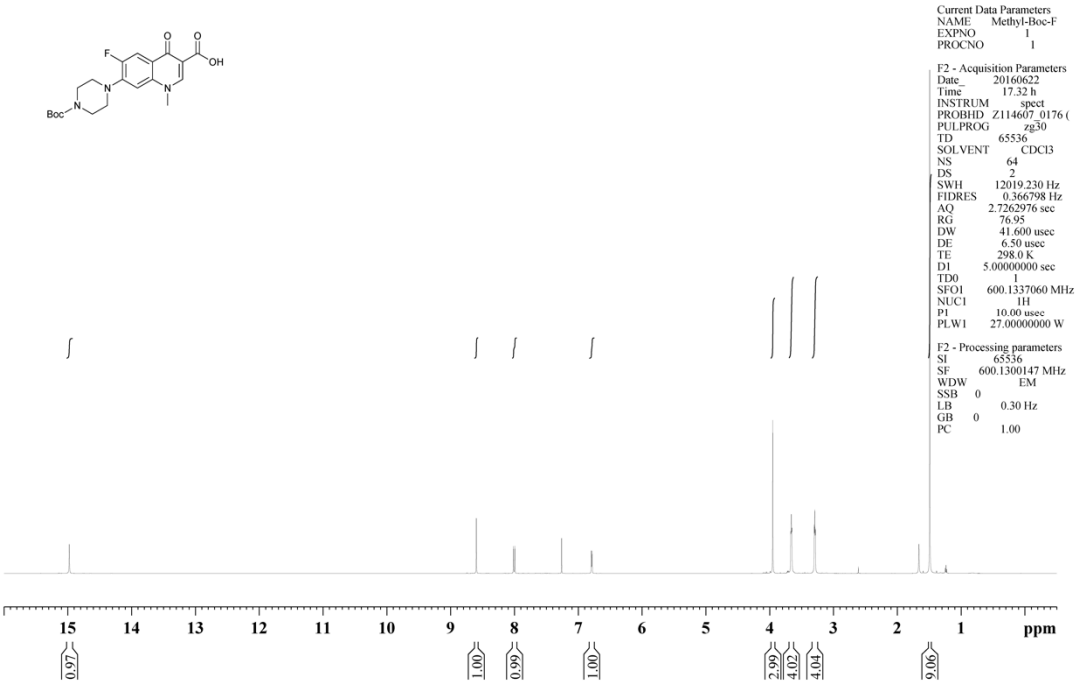
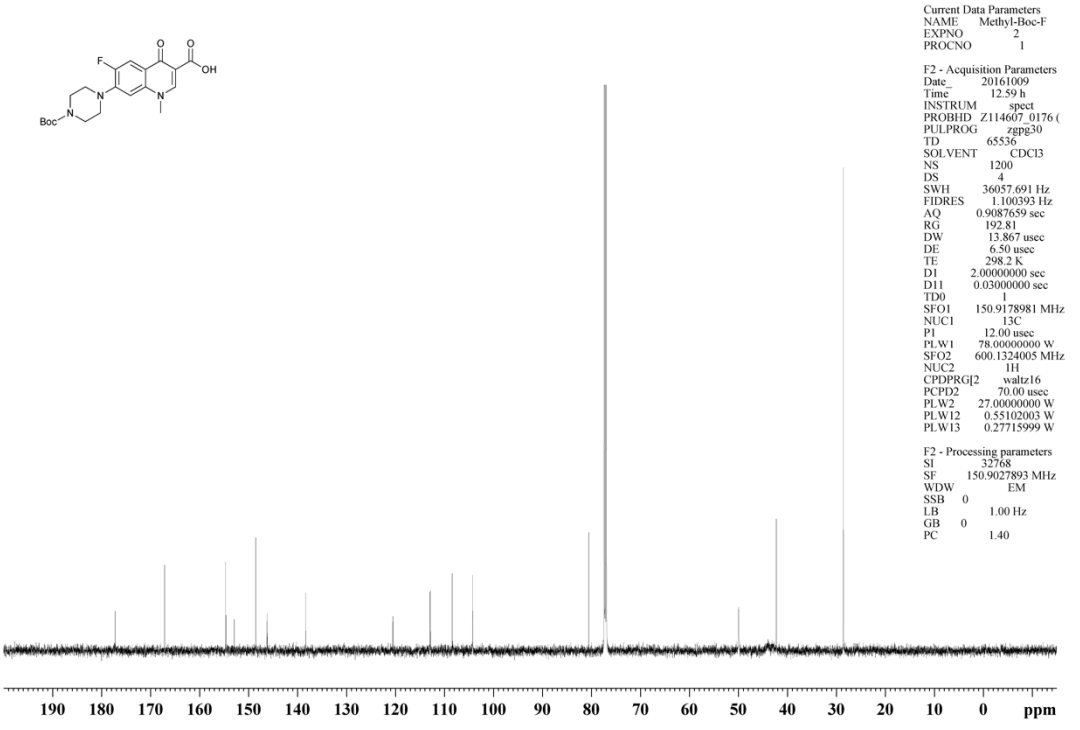
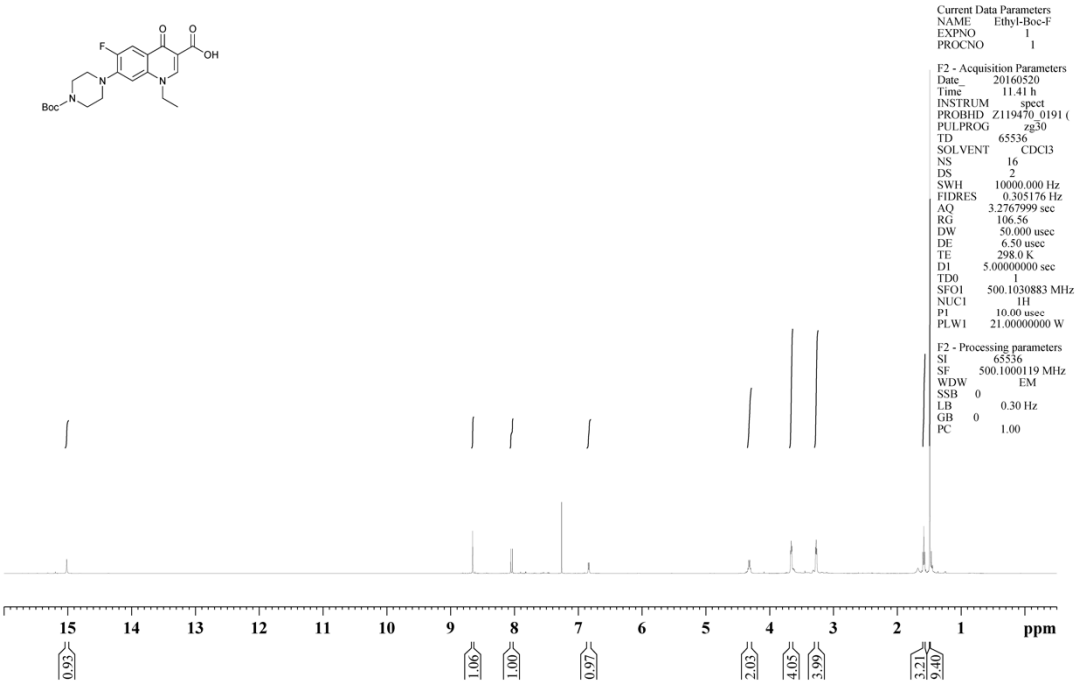


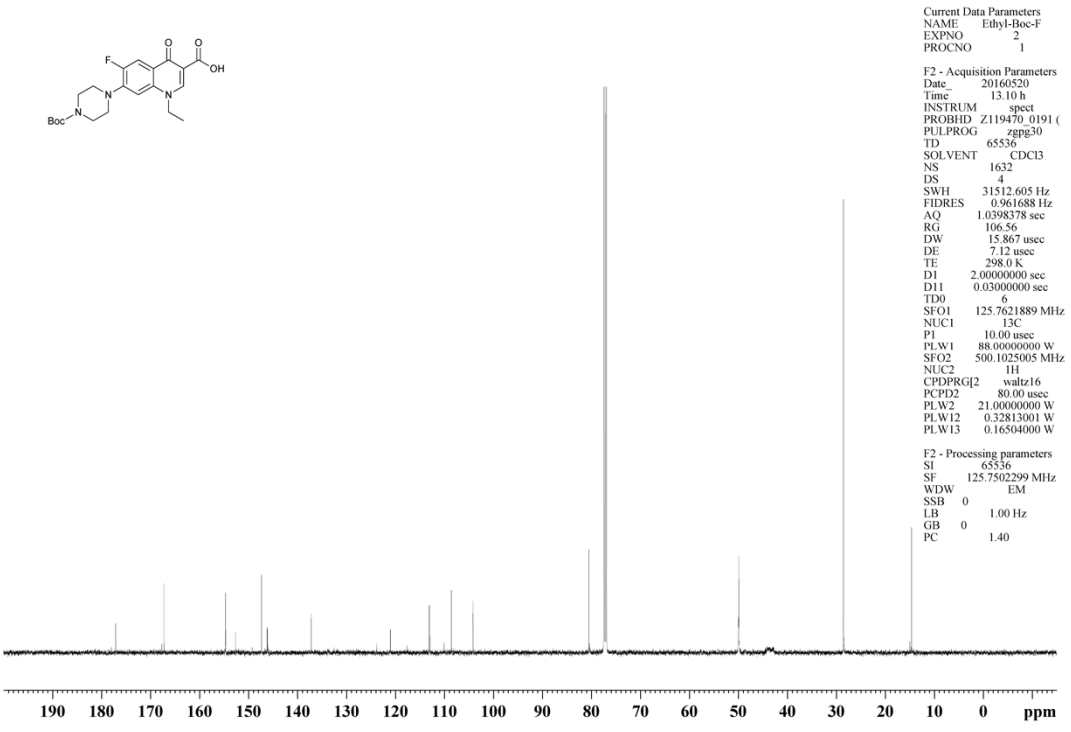
^{13}C NMR spectrum of **21**



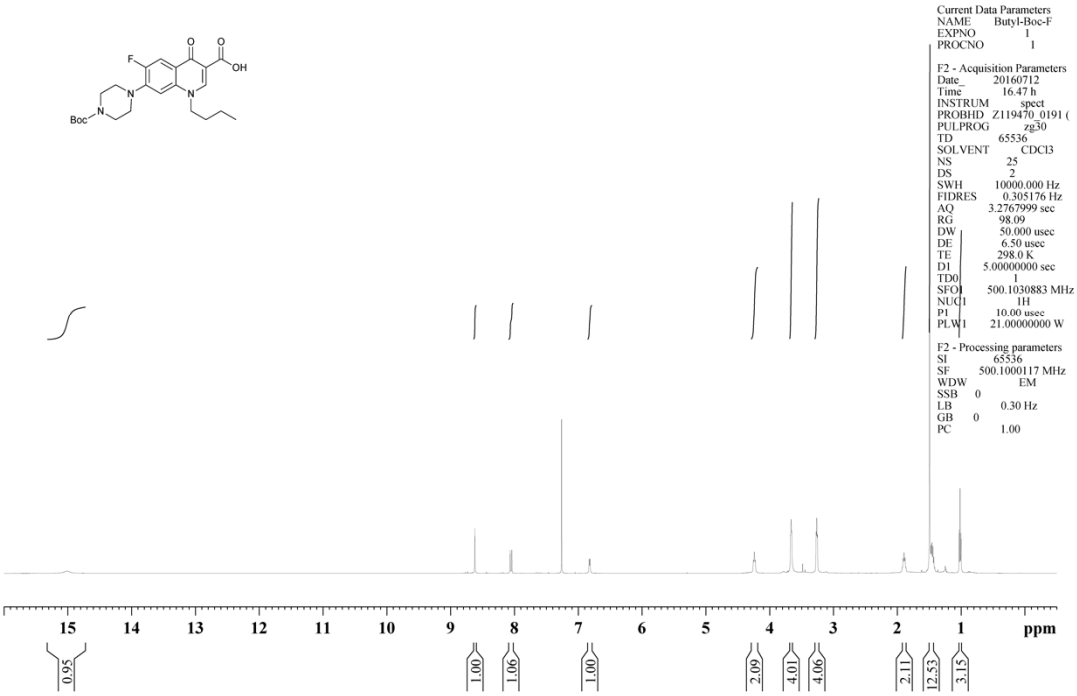
^{1}H NMR spectrum of **22**



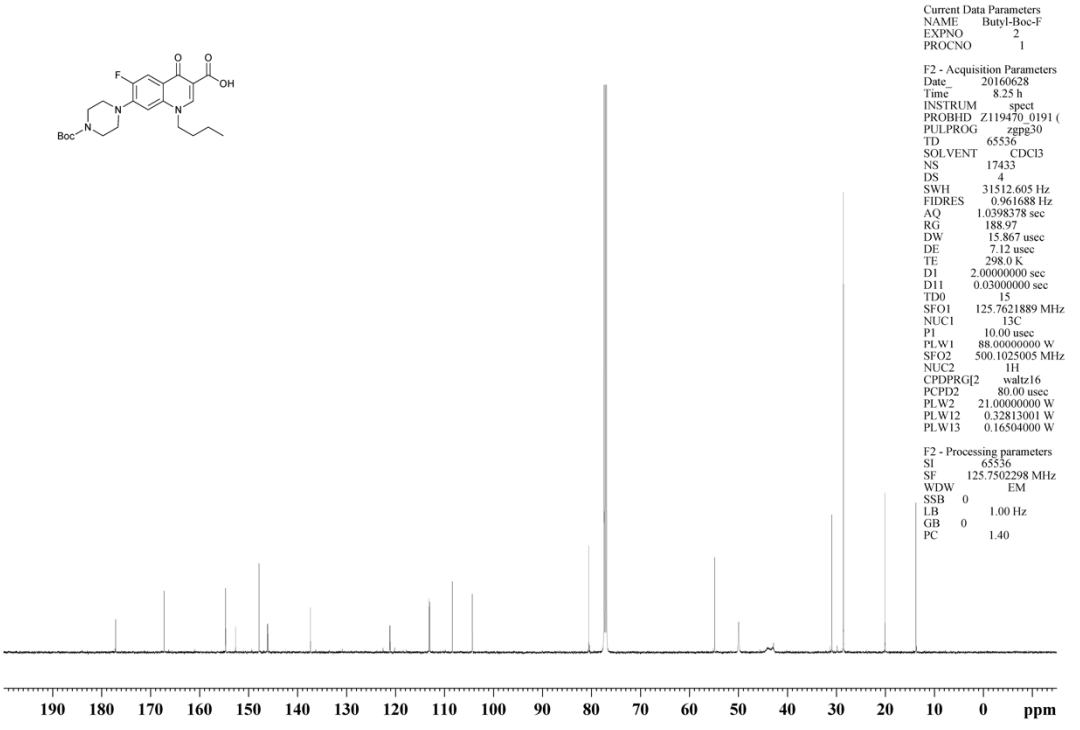
^{13}C NMR spectrum of **22**



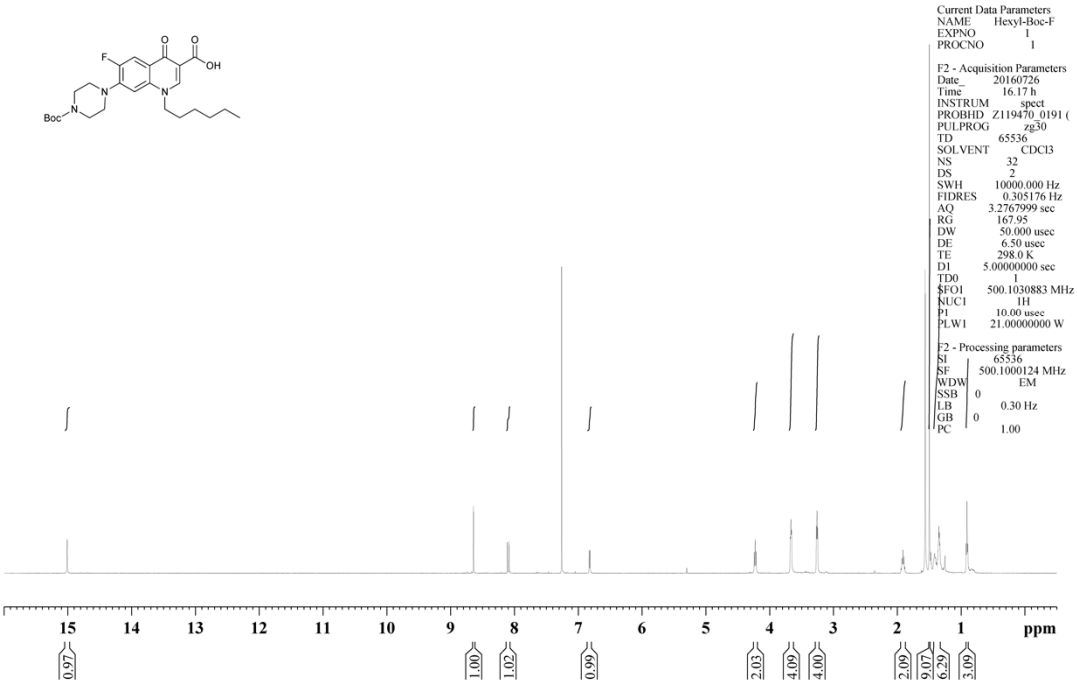
^{1}H NMR spectrum of **23**



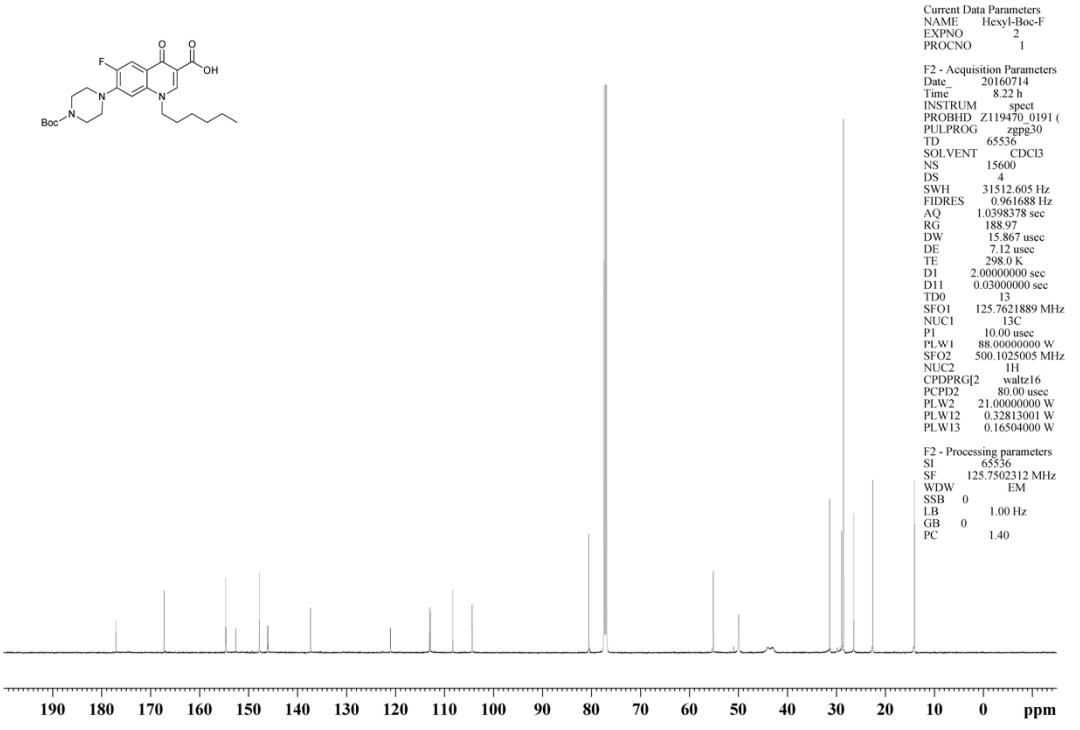
^{13}C NMR spectrum of **23**



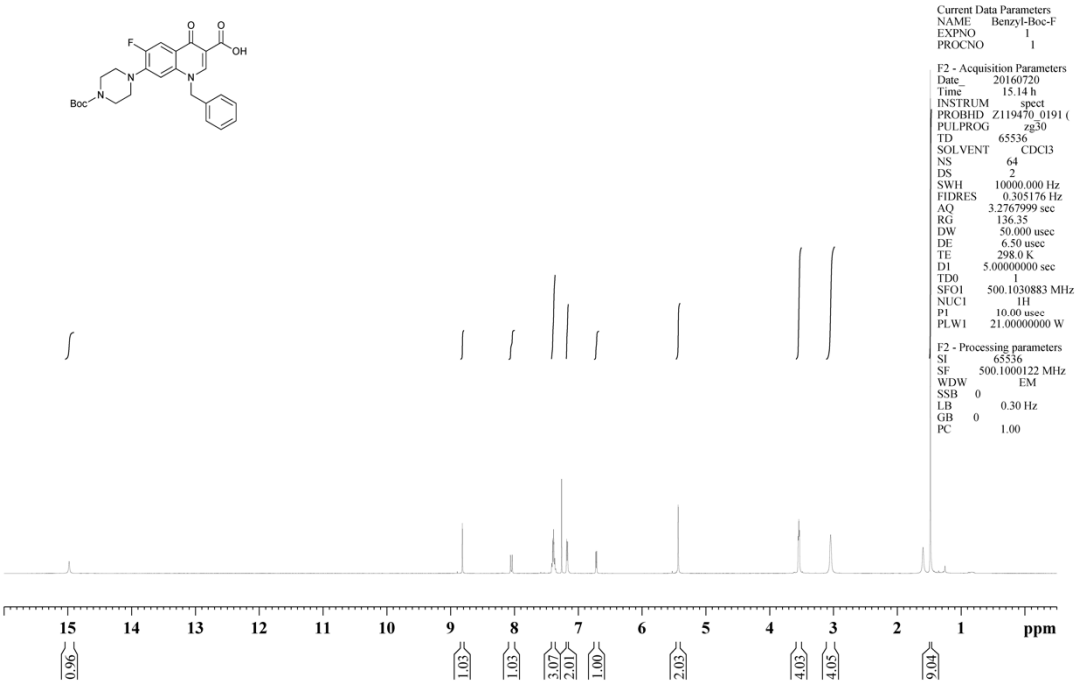
^{1}H NMR spectrum of **24**



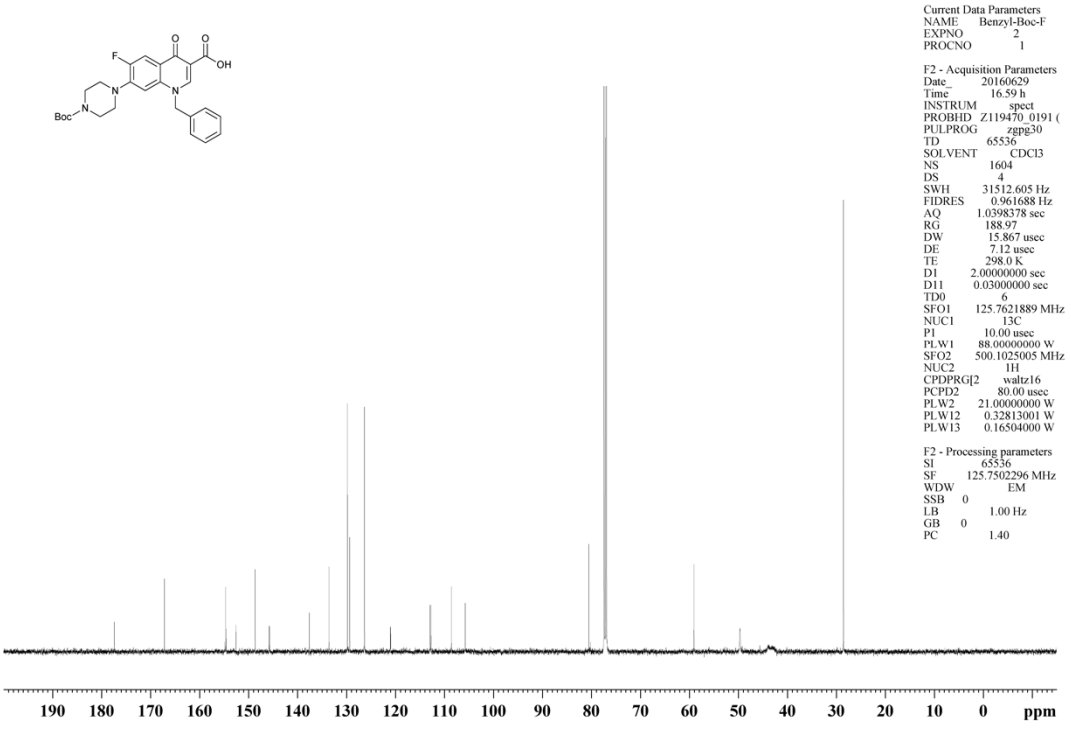
^{13}C NMR spectrum of **24**



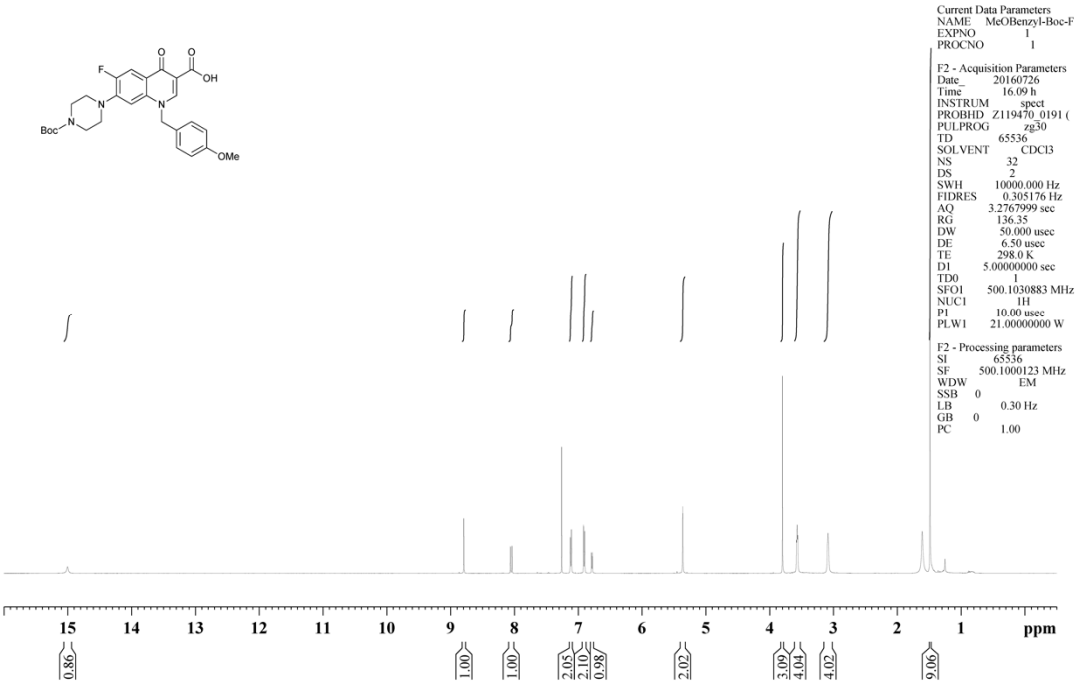
^{1}H NMR spectrum of **25**



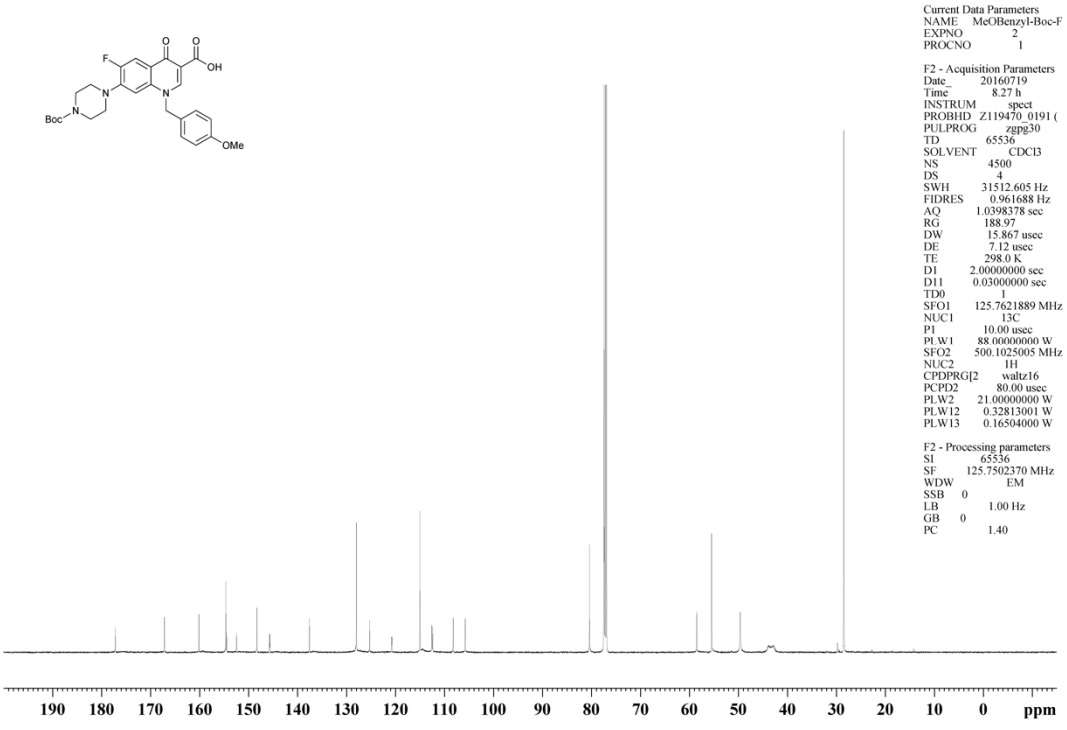
^{13}C NMR spectrum of **25**



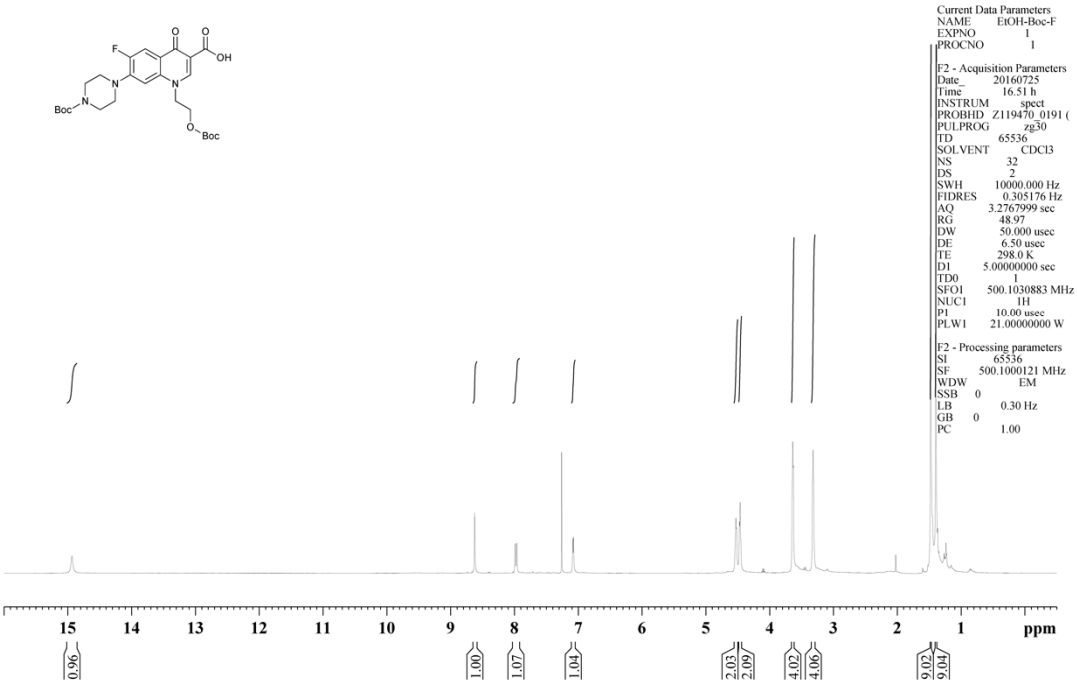
^{1}H NMR spectrum of **26**



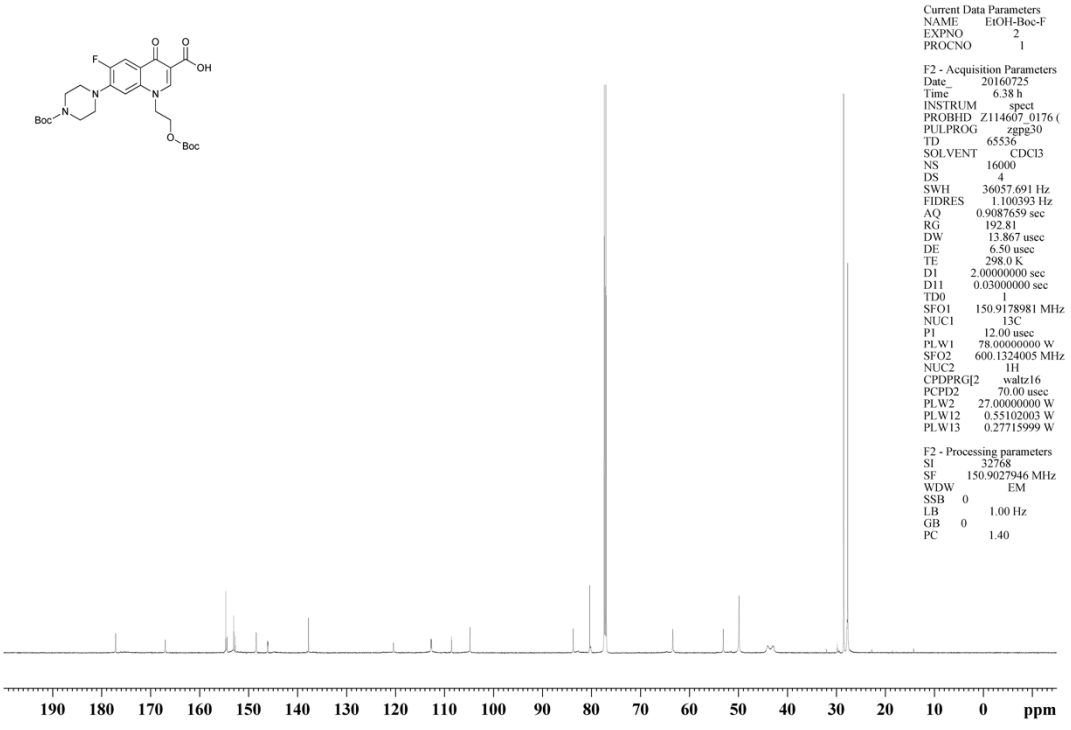
^{13}C NMR spectrum of **26**



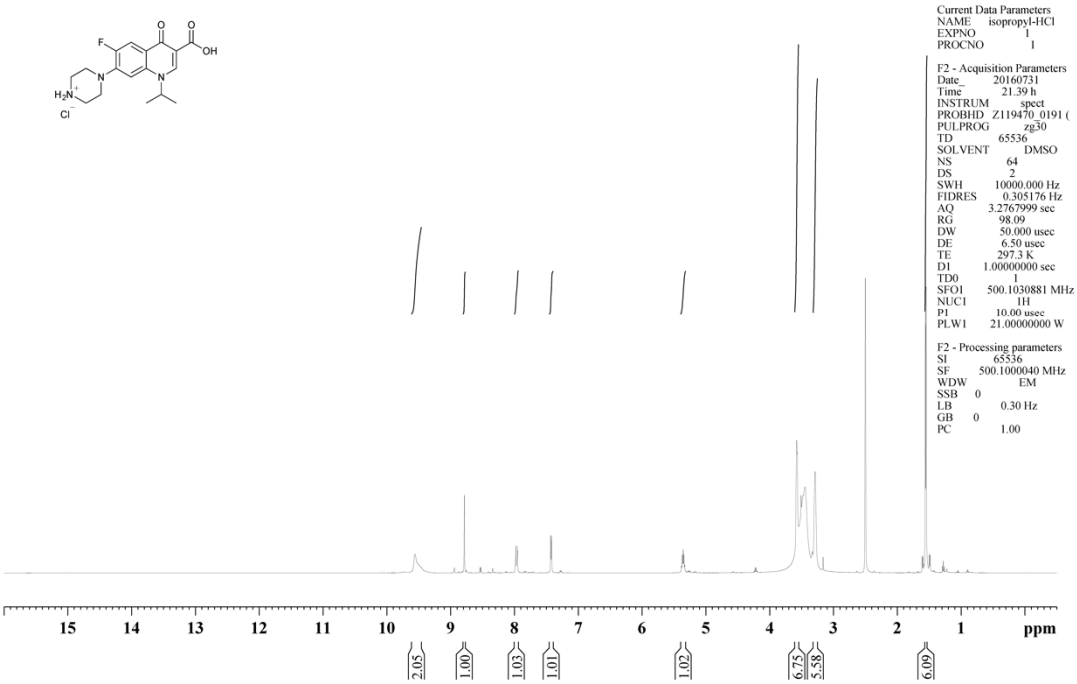
^{1}H NMR spectrum of **27**



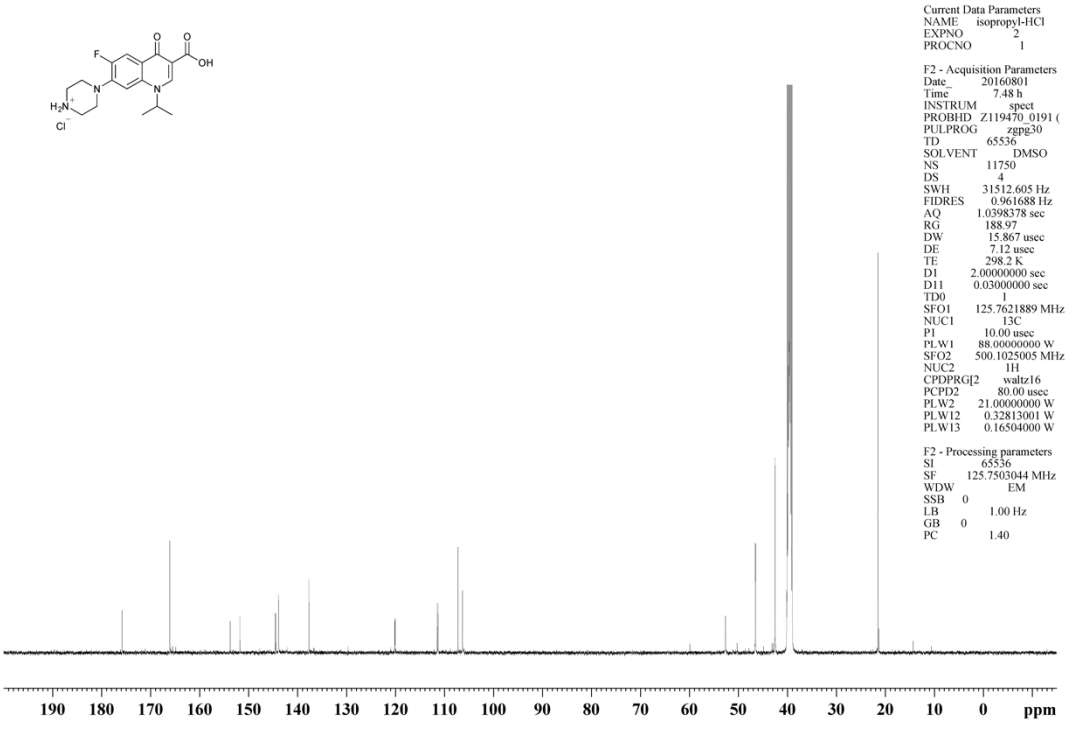
^{13}C NMR spectrum of **27**



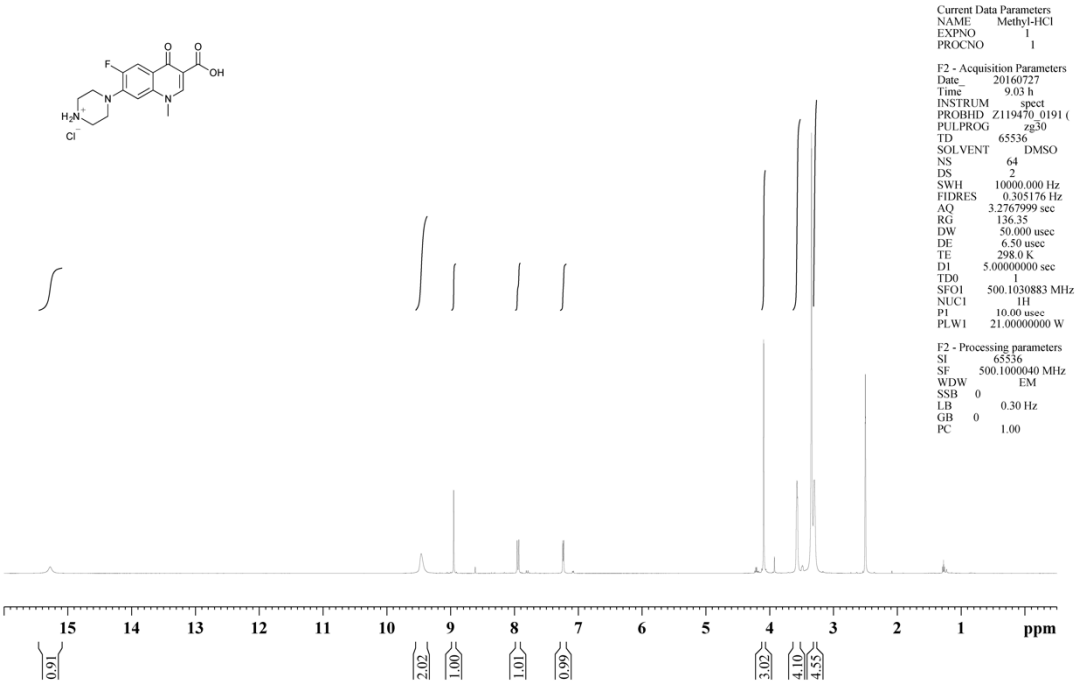
^{1}H NMR spectrum of **28**



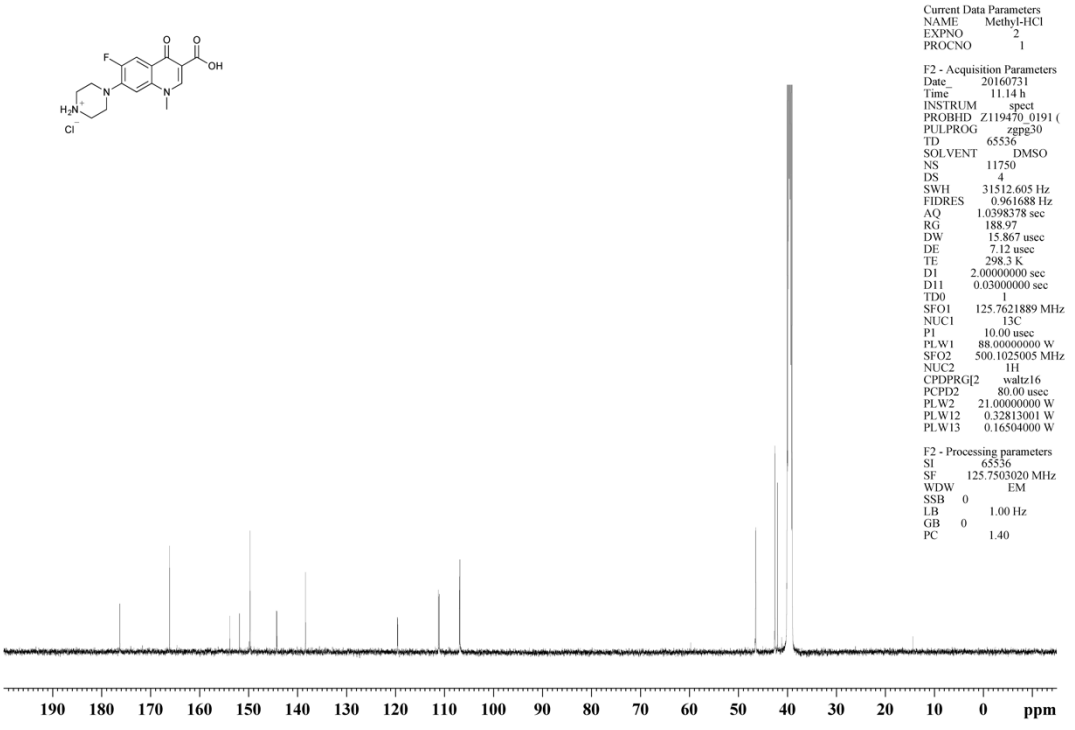
^{13}C NMR spectrum of **28**



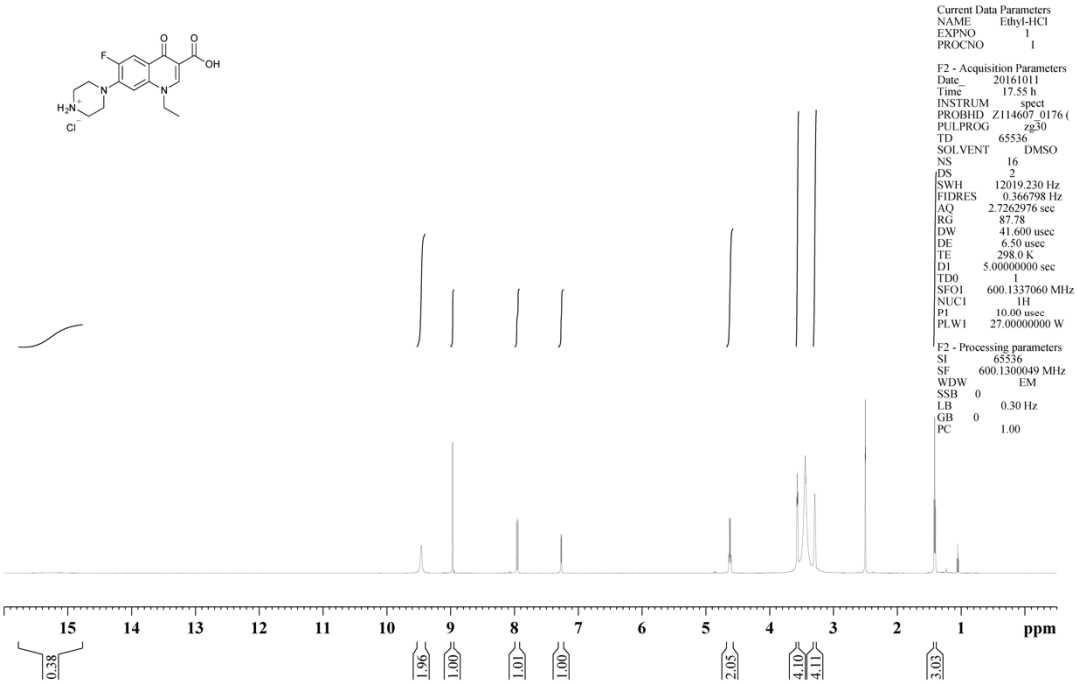
^{1}H NMR spectrum of **29**



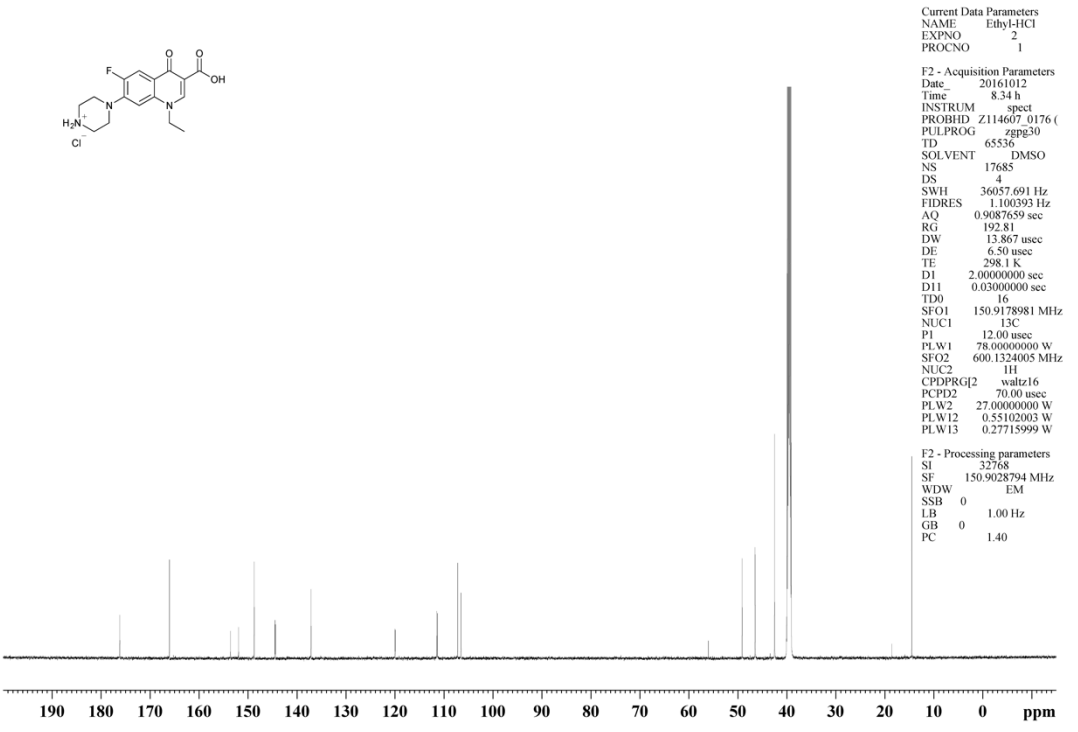
^{13}C NMR spectrum of **29**



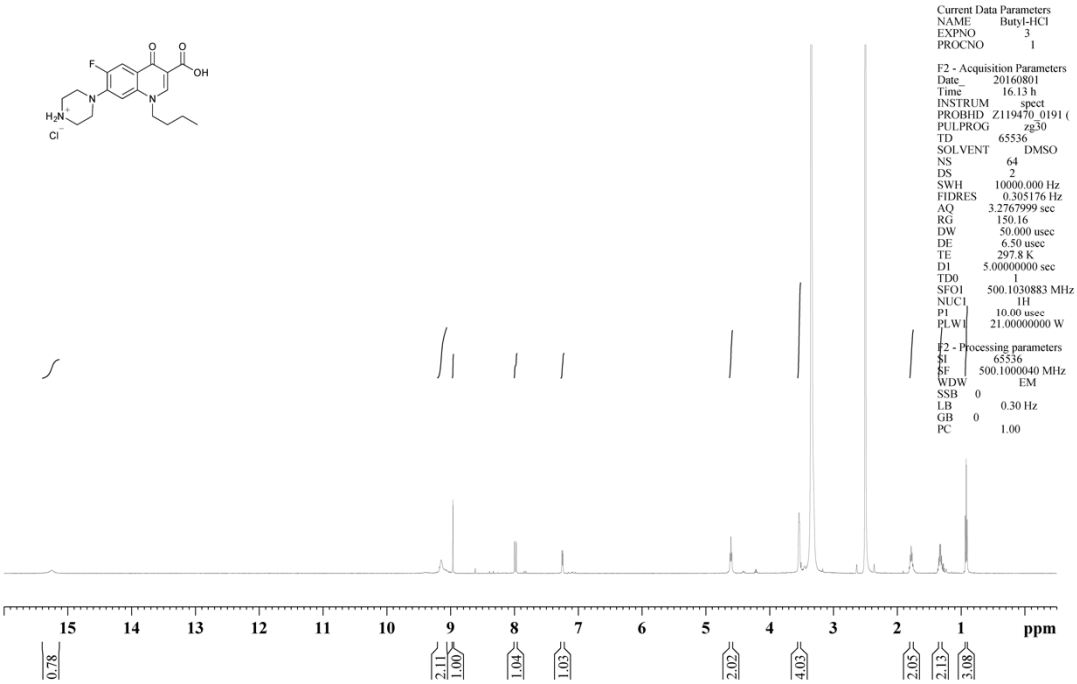
^{1}H NMR spectrum of **30**



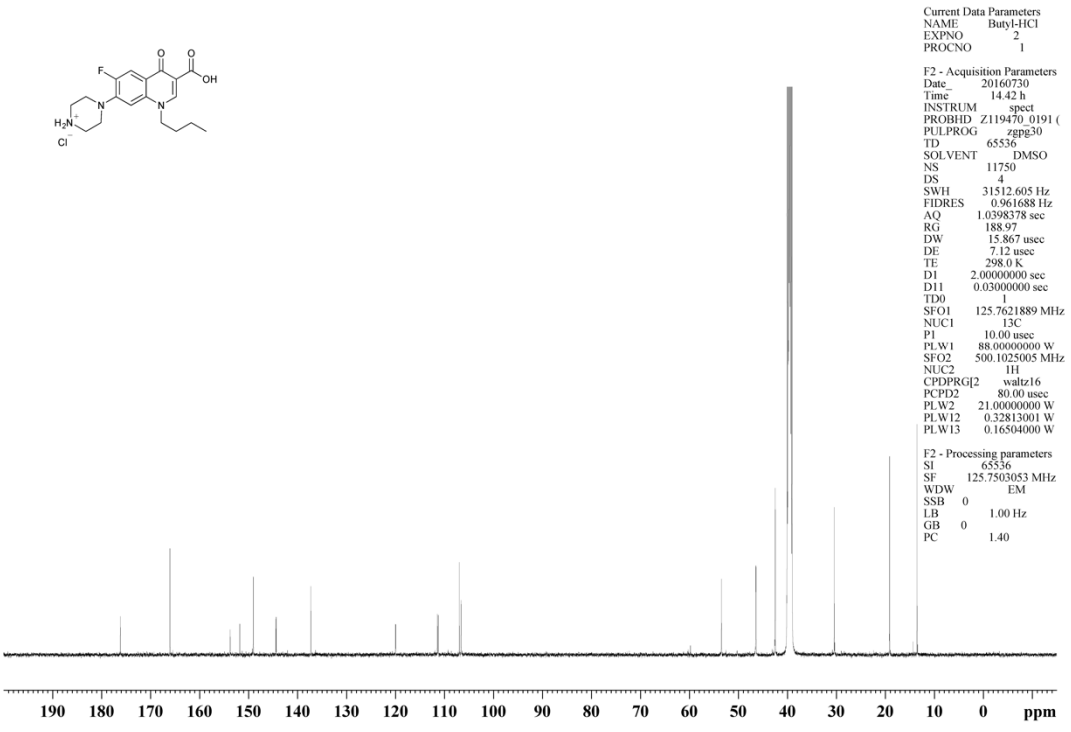
^{13}C NMR spectrum of **30**



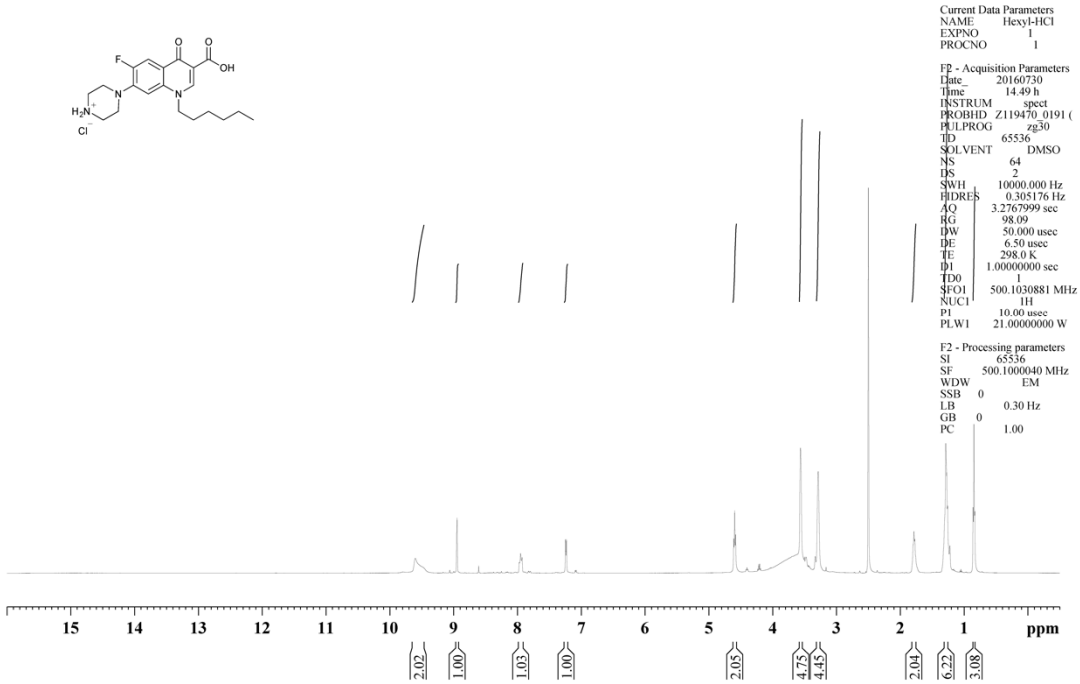
^{1}H NMR spectrum of **31**



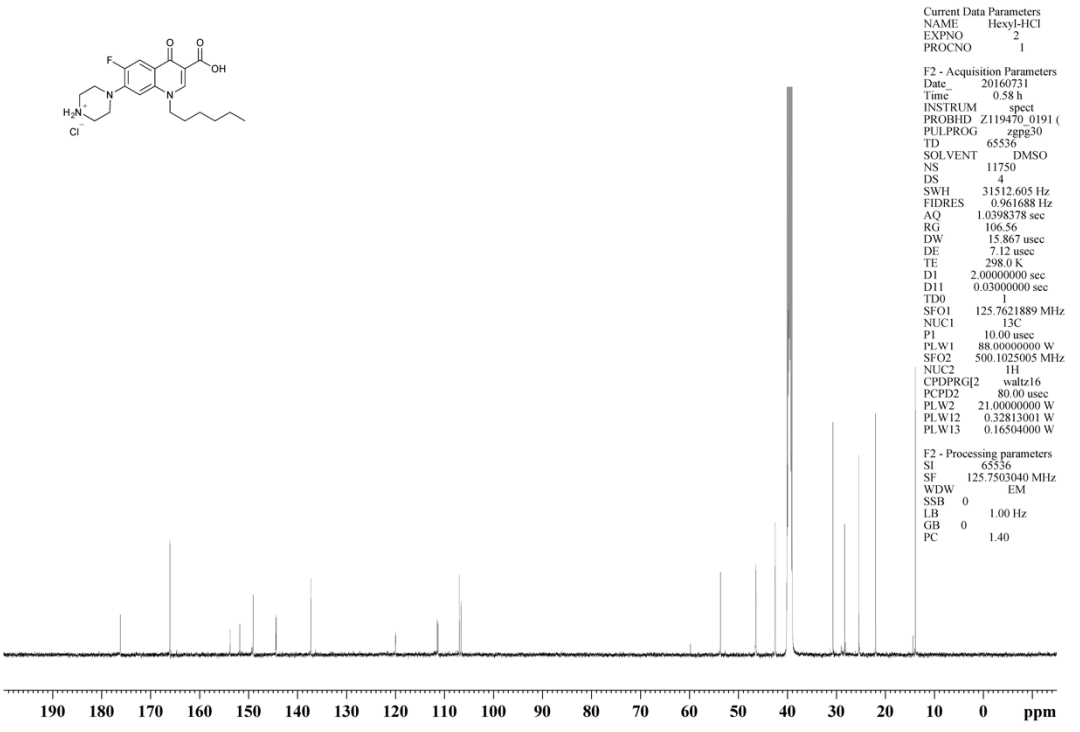
^{13}C NMR spectrum of **31**



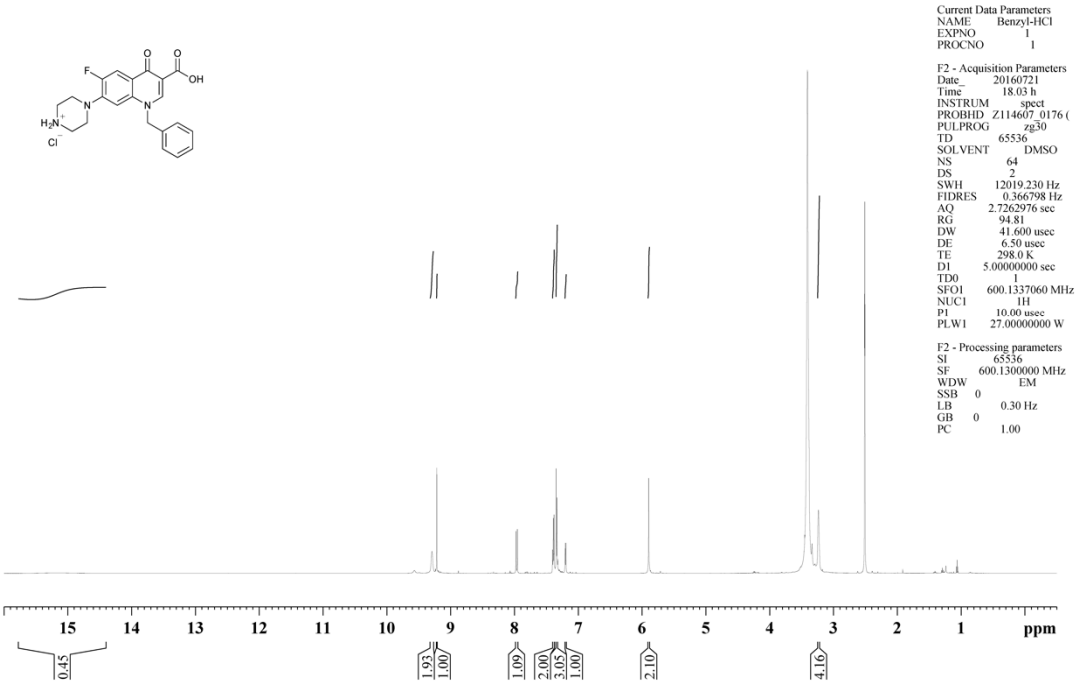
^{1}H NMR spectrum of **32**



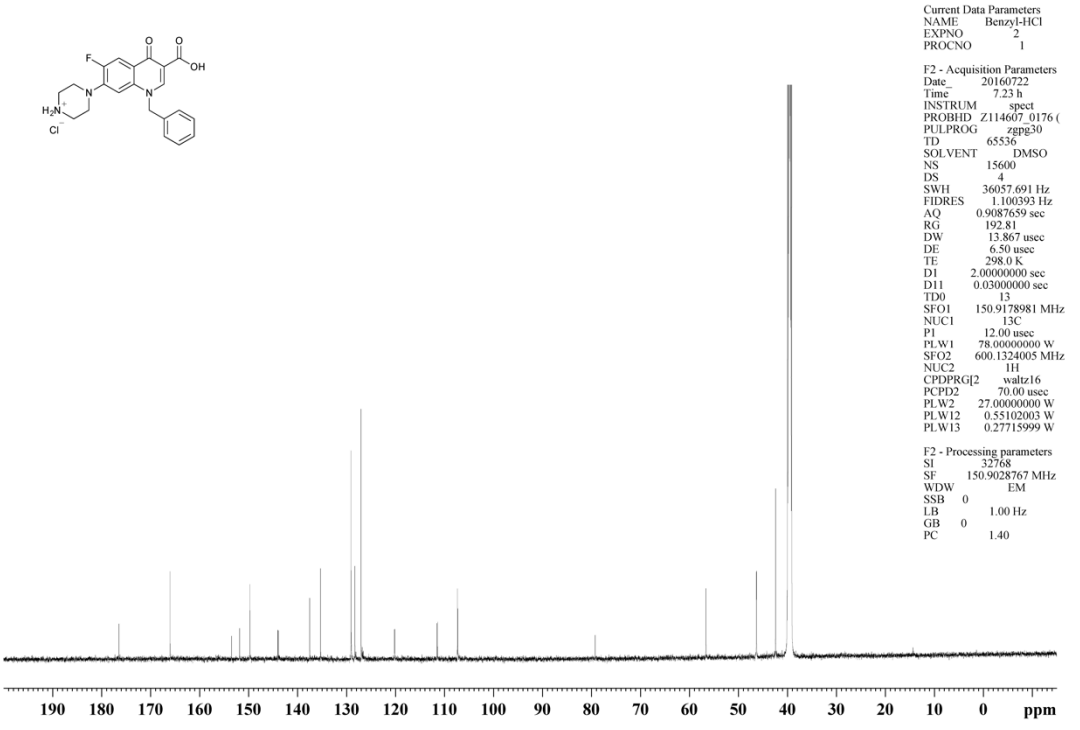
^{13}C NMR spectrum of **32**



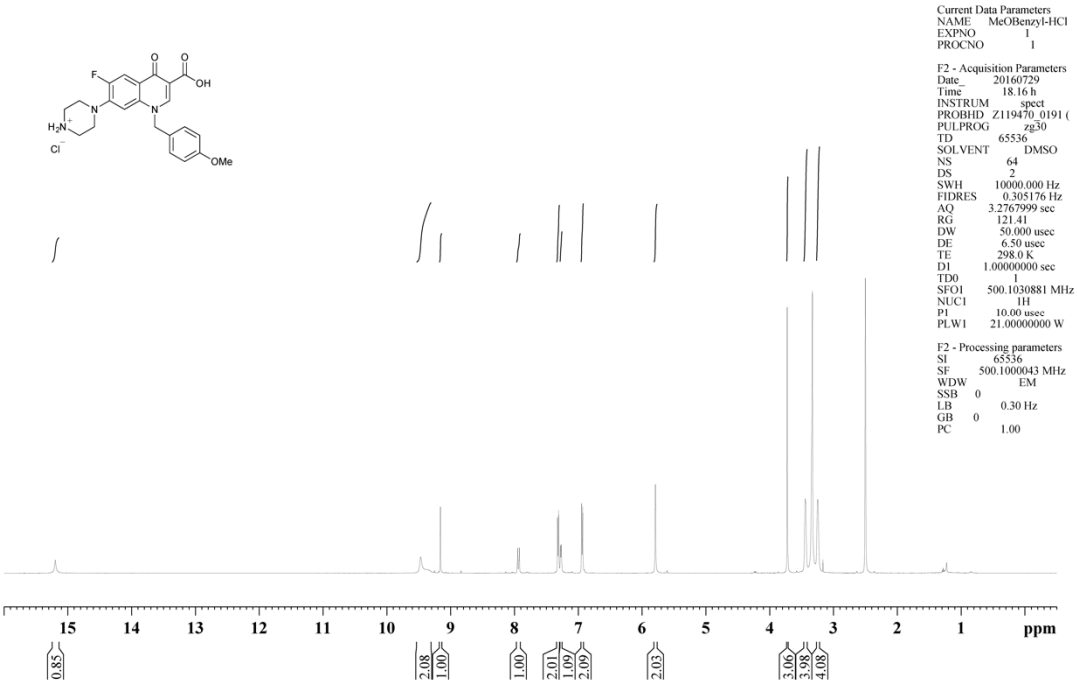
^{1}H NMR spectrum of **33**



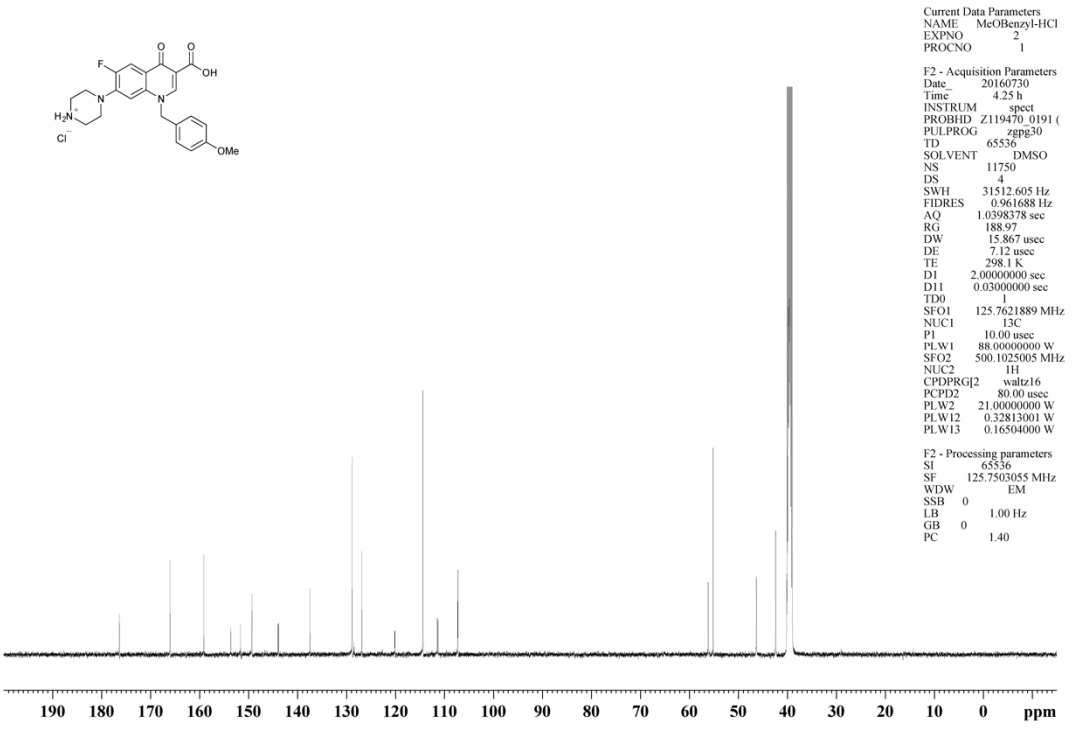
^{13}C NMR spectrum of **33**



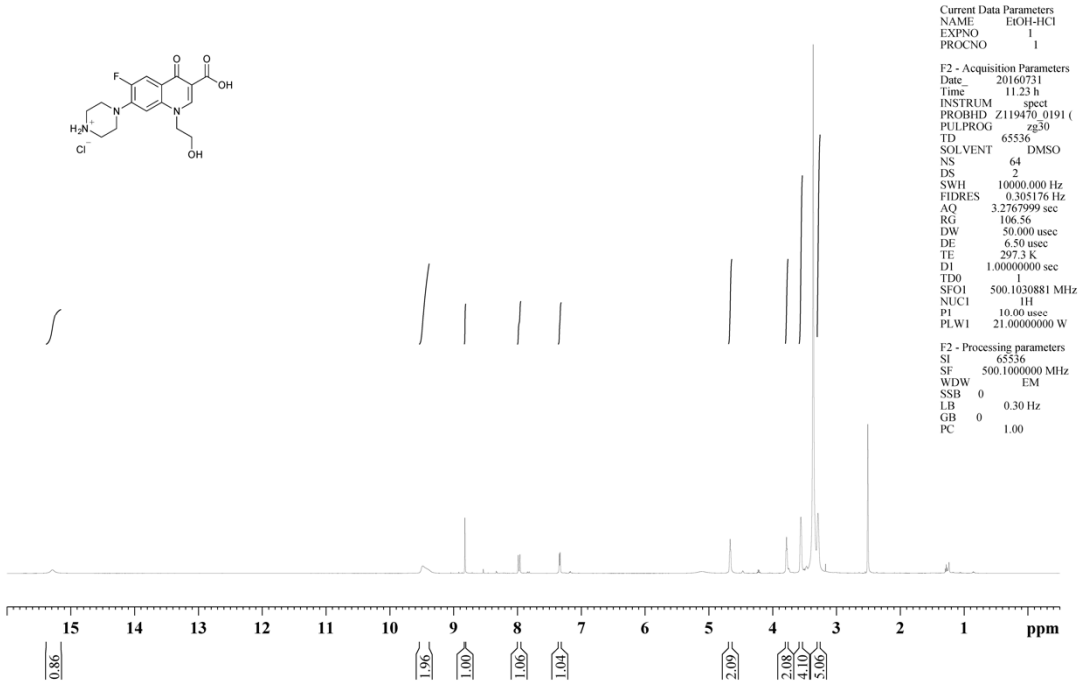
^{1}H NMR spectrum of **34**



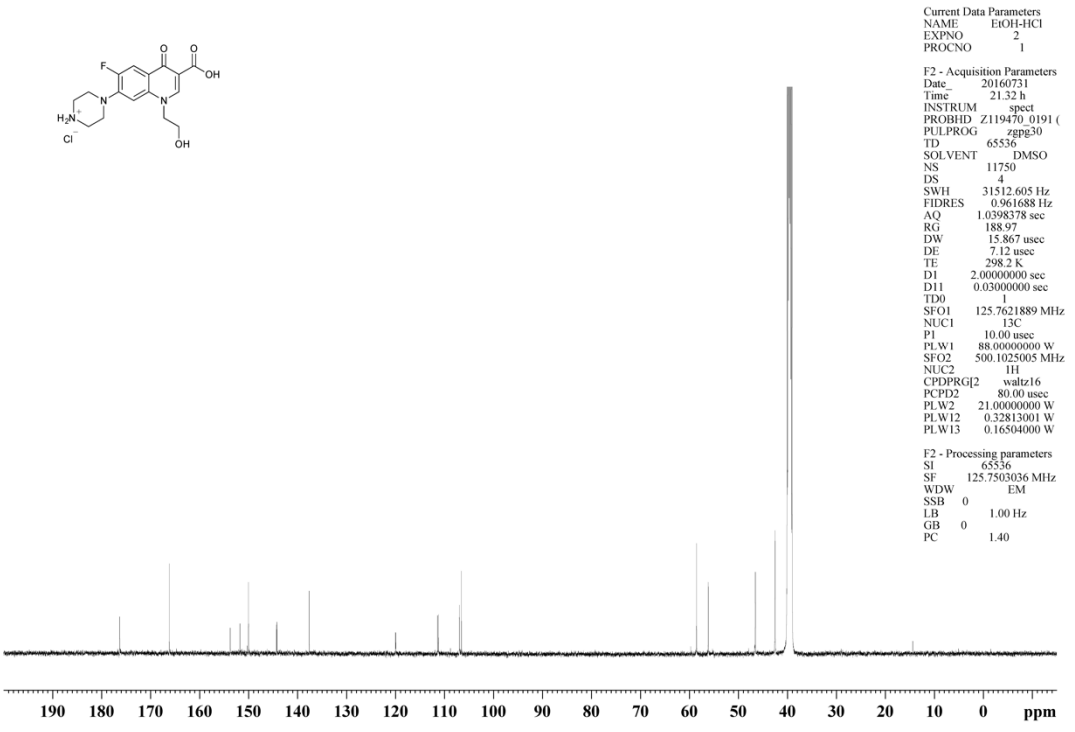
^{13}C NMR spectrum of **34**



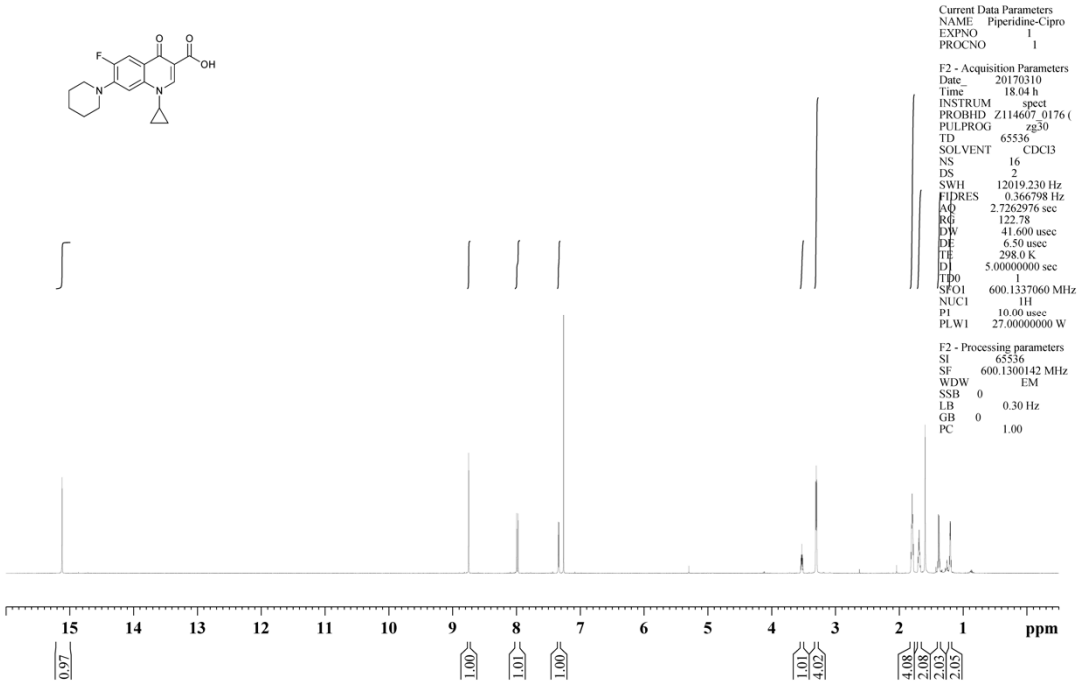
^{1}H NMR spectrum of **35**



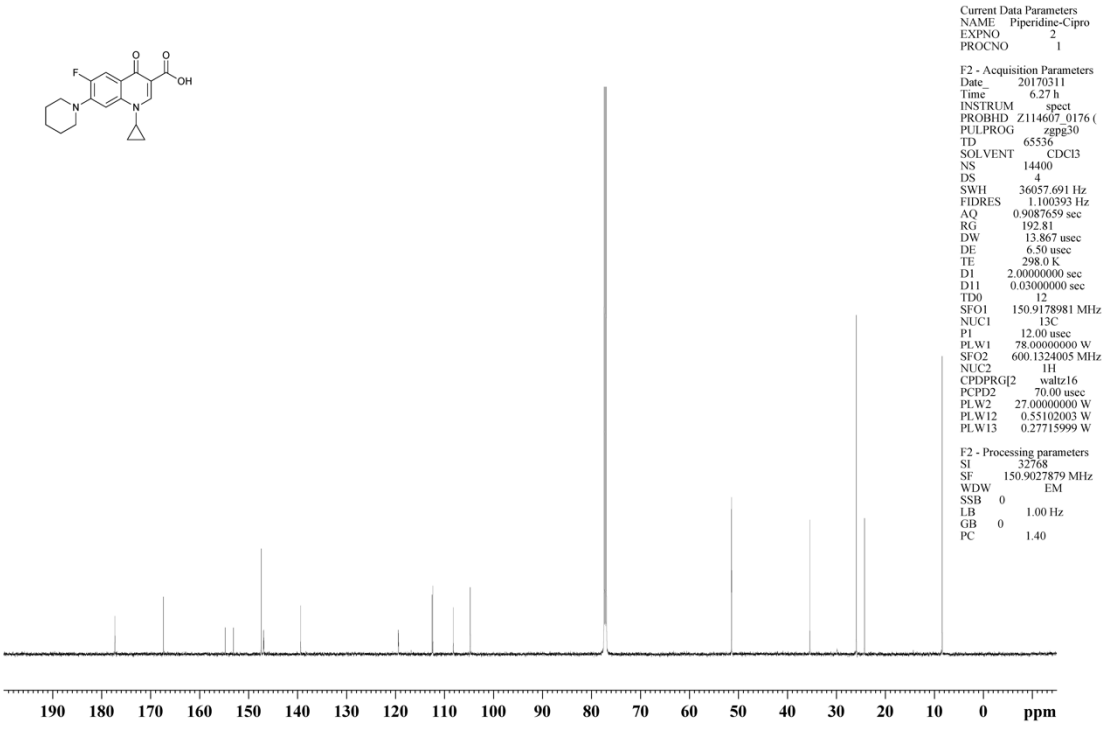
^{13}C NMR spectrum of **35**



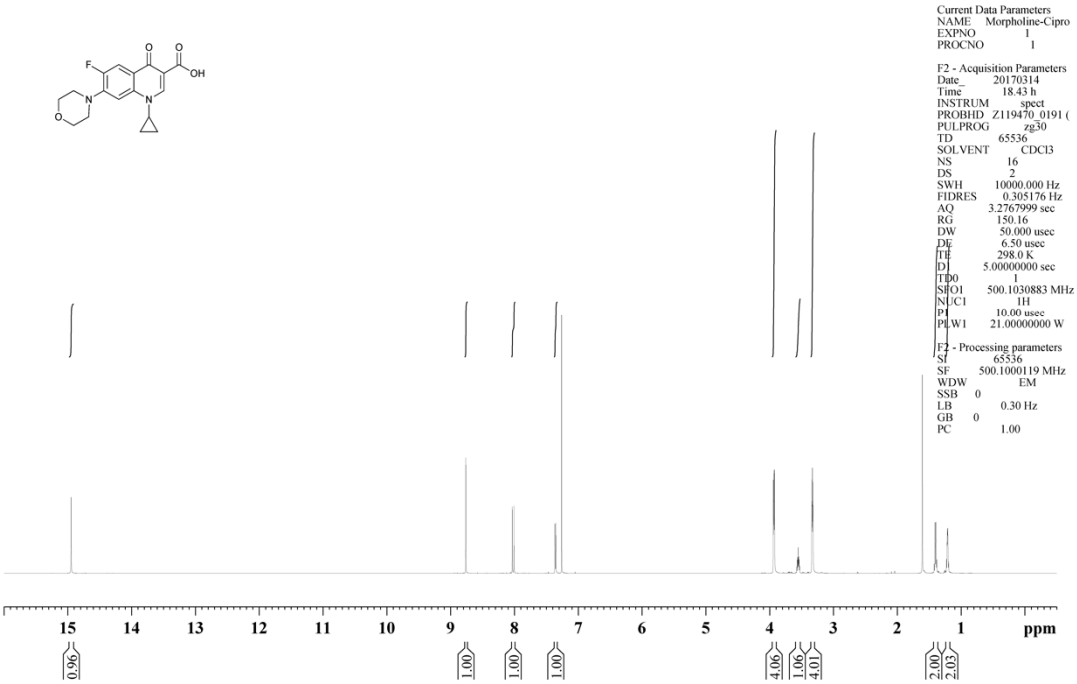
^{1}H NMR spectrum of **37**



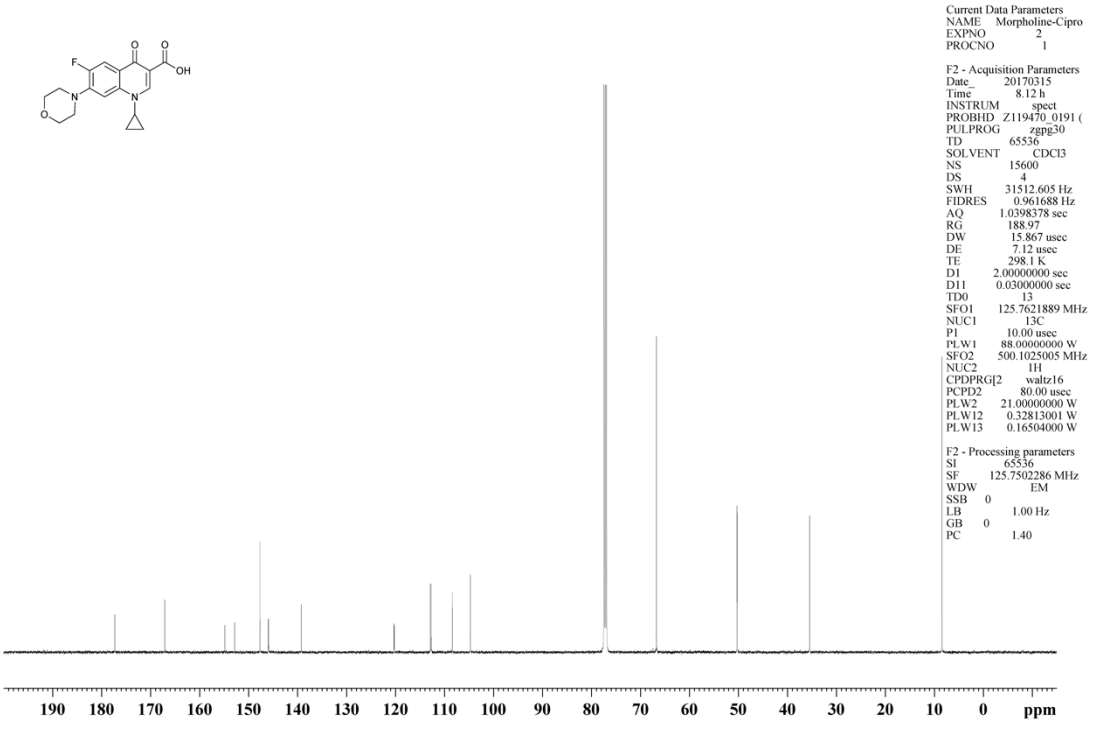
^{13}C NMR spectrum of **37**



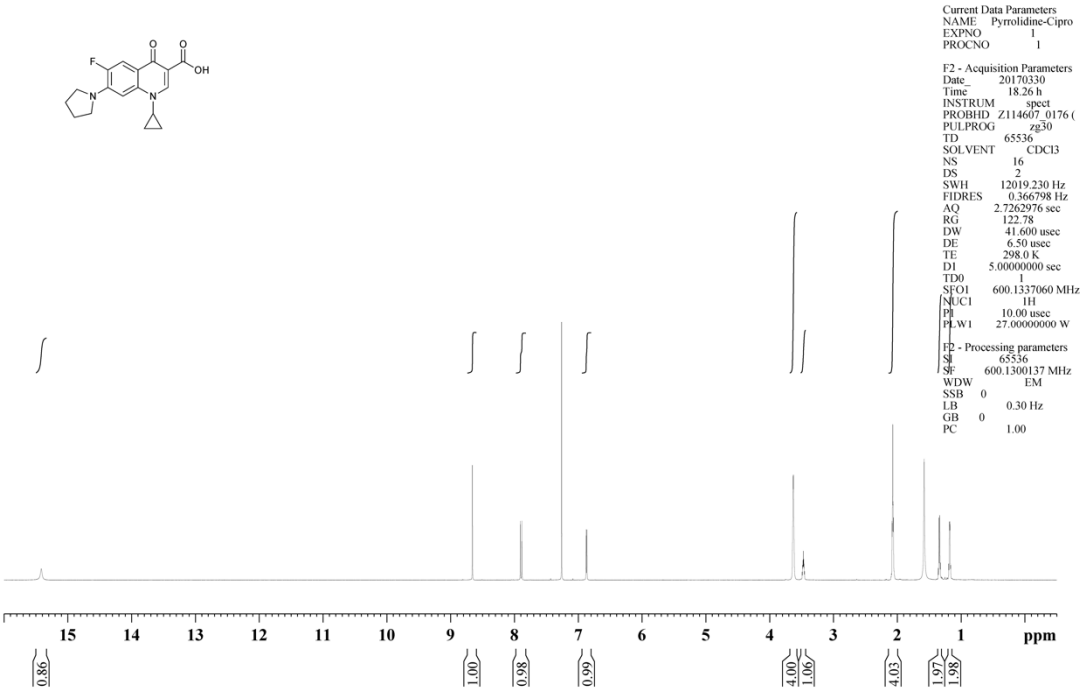
^{1}H NMR spectrum of **38**



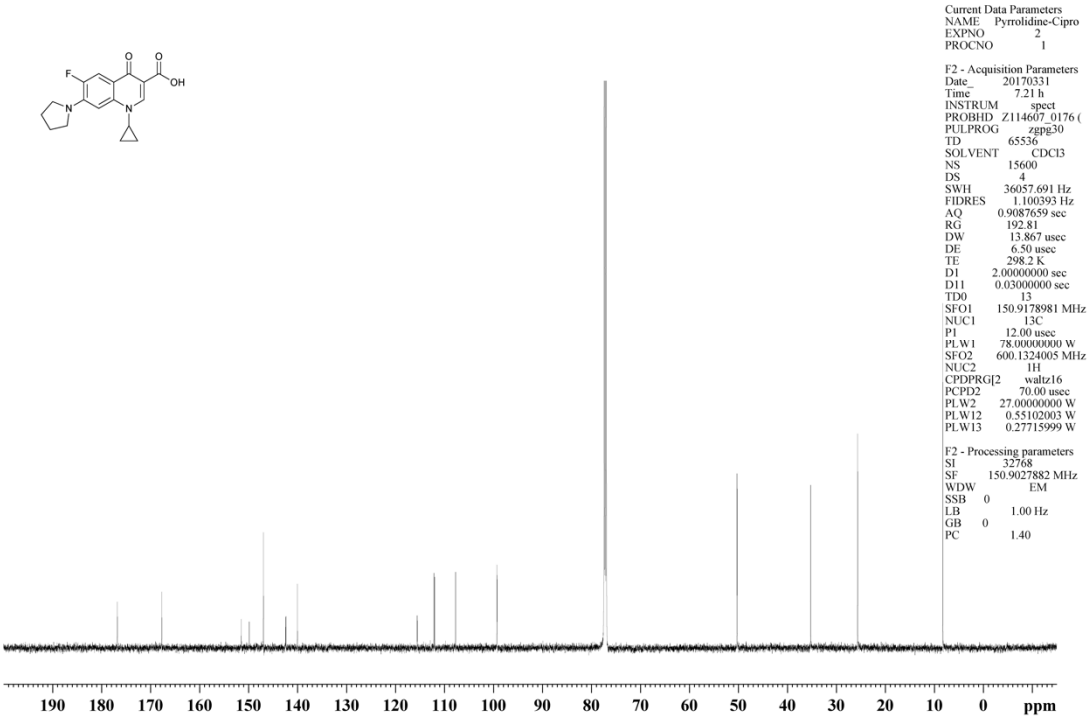
^{13}C NMR spectrum of **38**



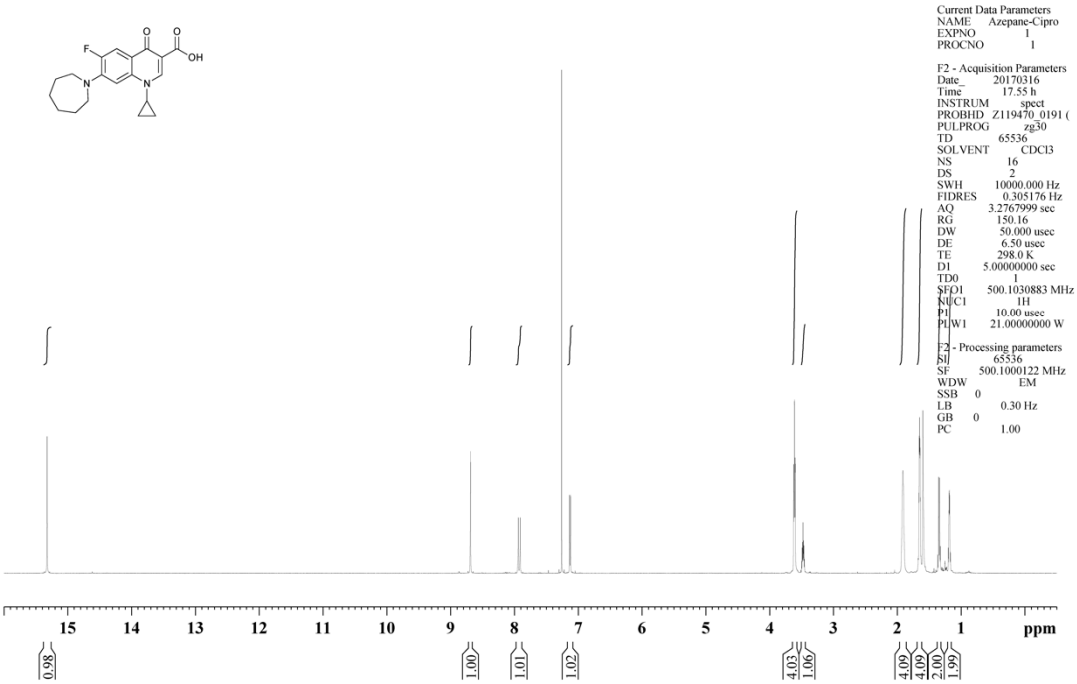
^{1}H NMR spectrum of **39**



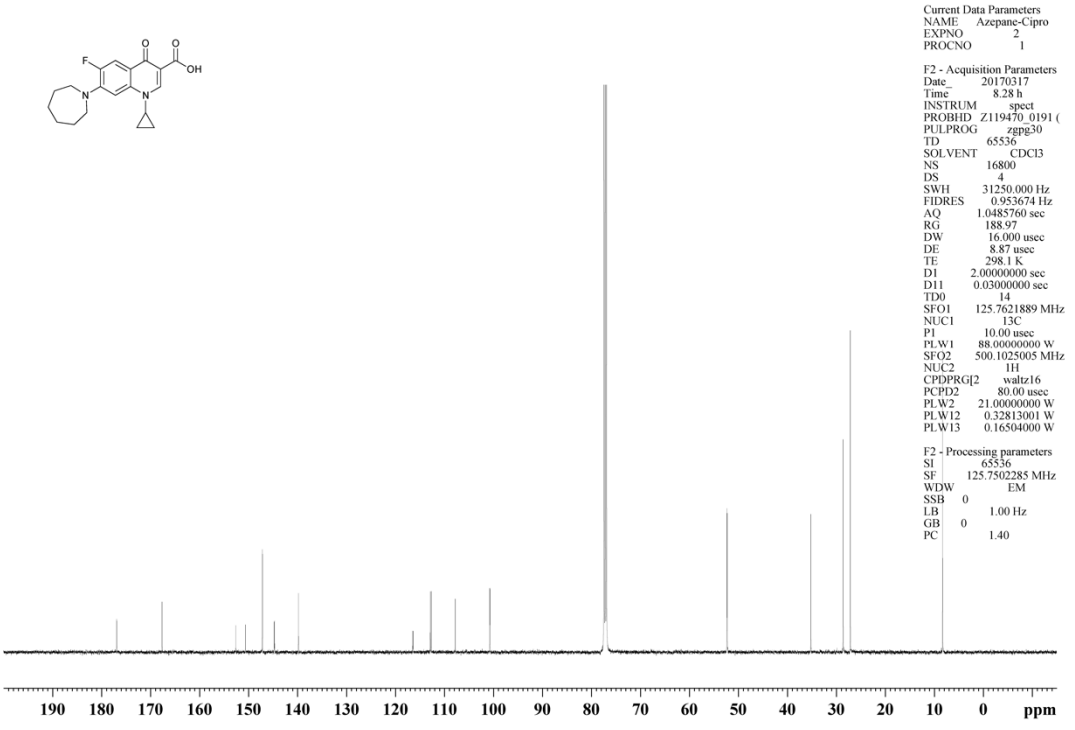
^{13}C NMR spectrum of **39**



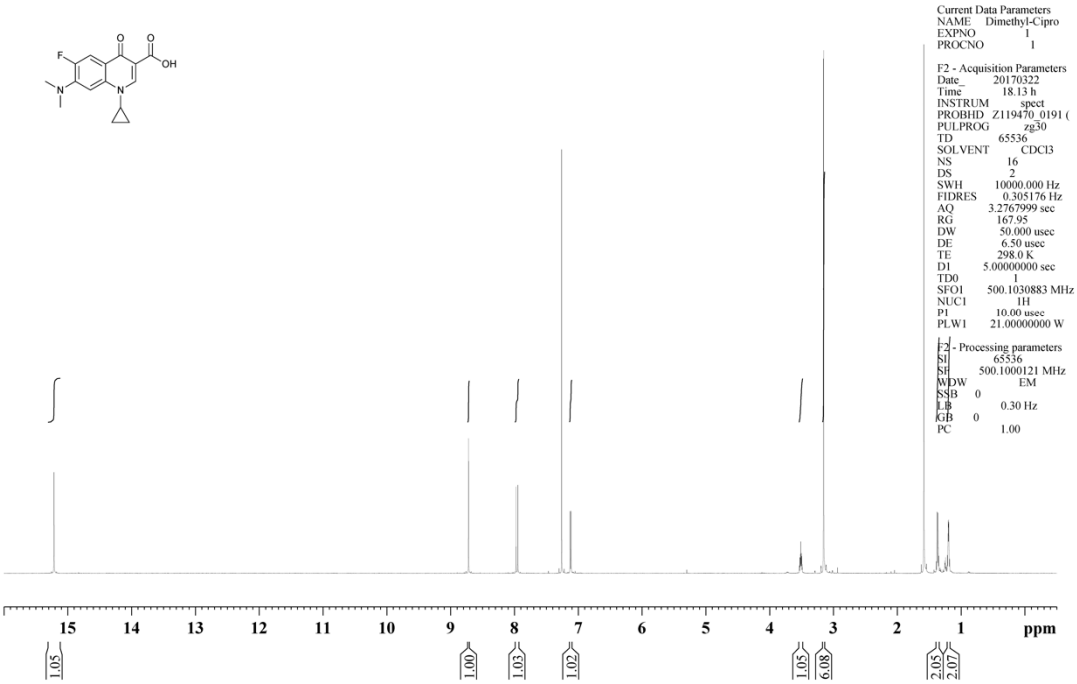
^{1}H NMR spectrum of **40**



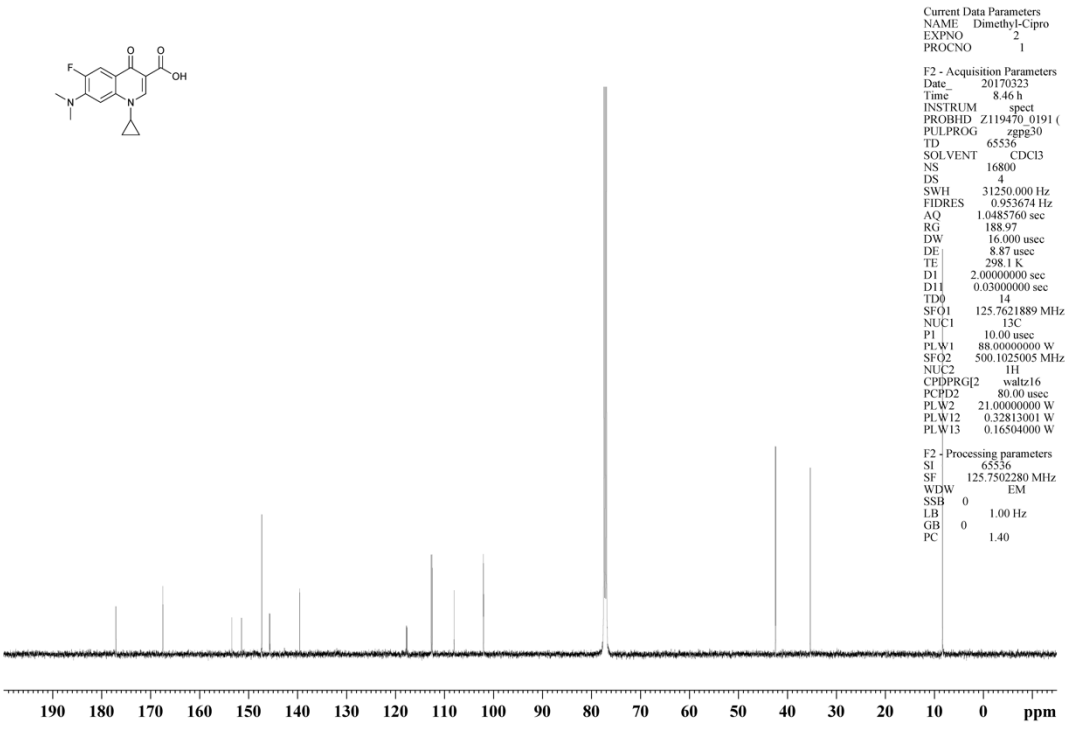
^{13}C NMR spectrum of **40**



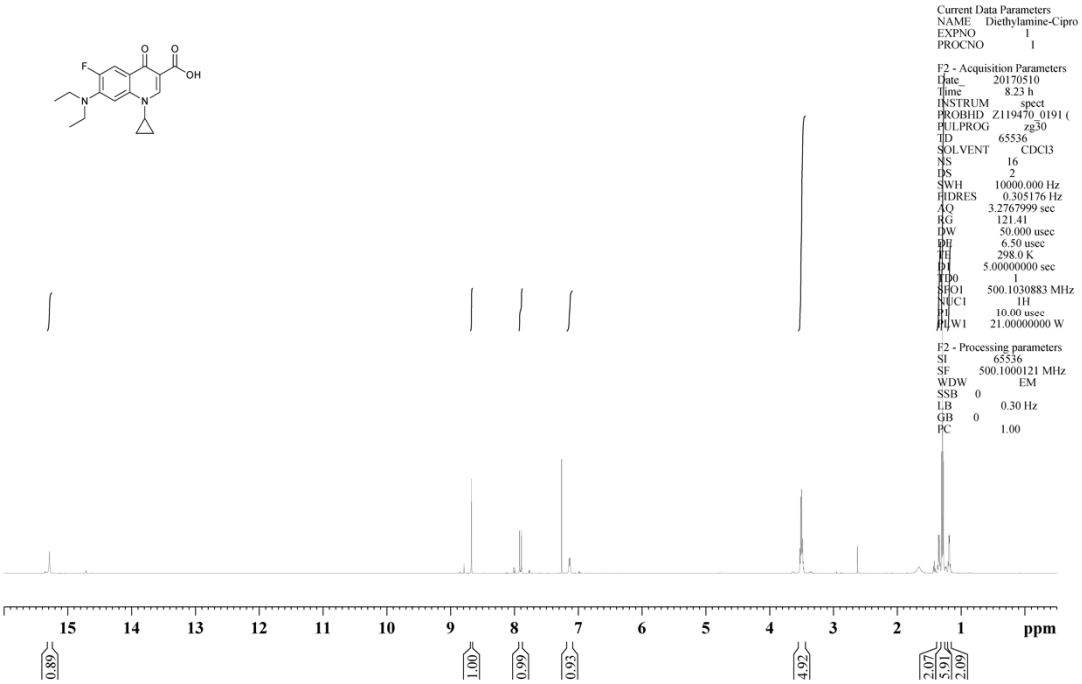
^{1}H NMR spectrum of **41**



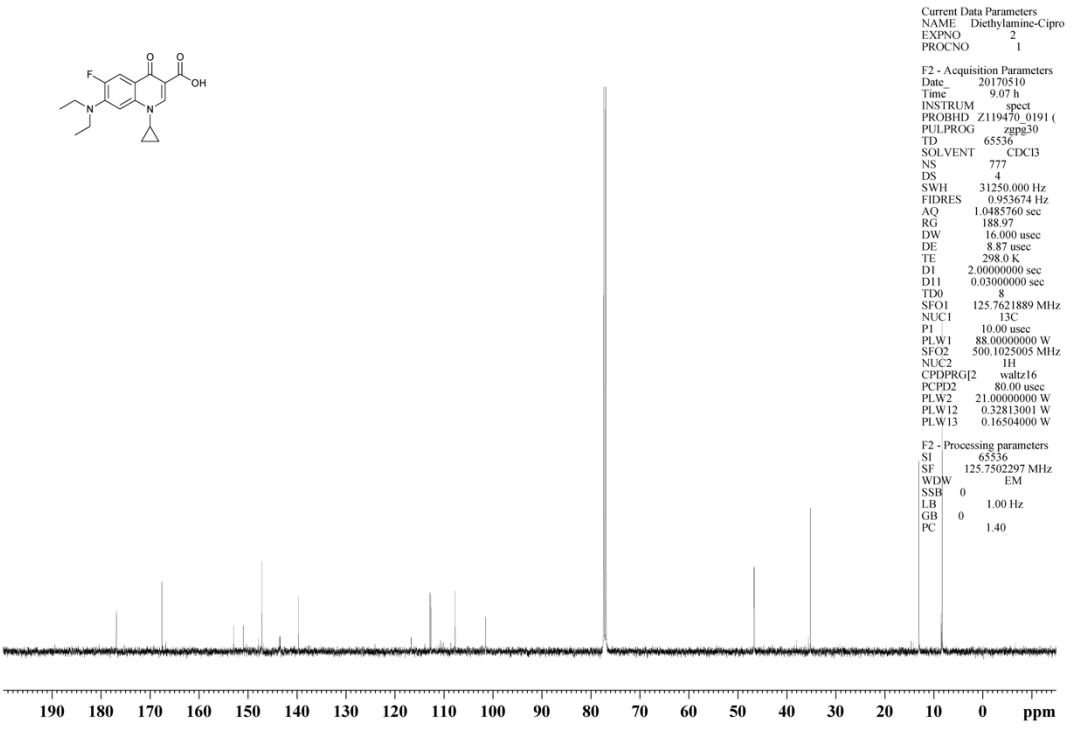
^{13}C NMR spectrum of **41**



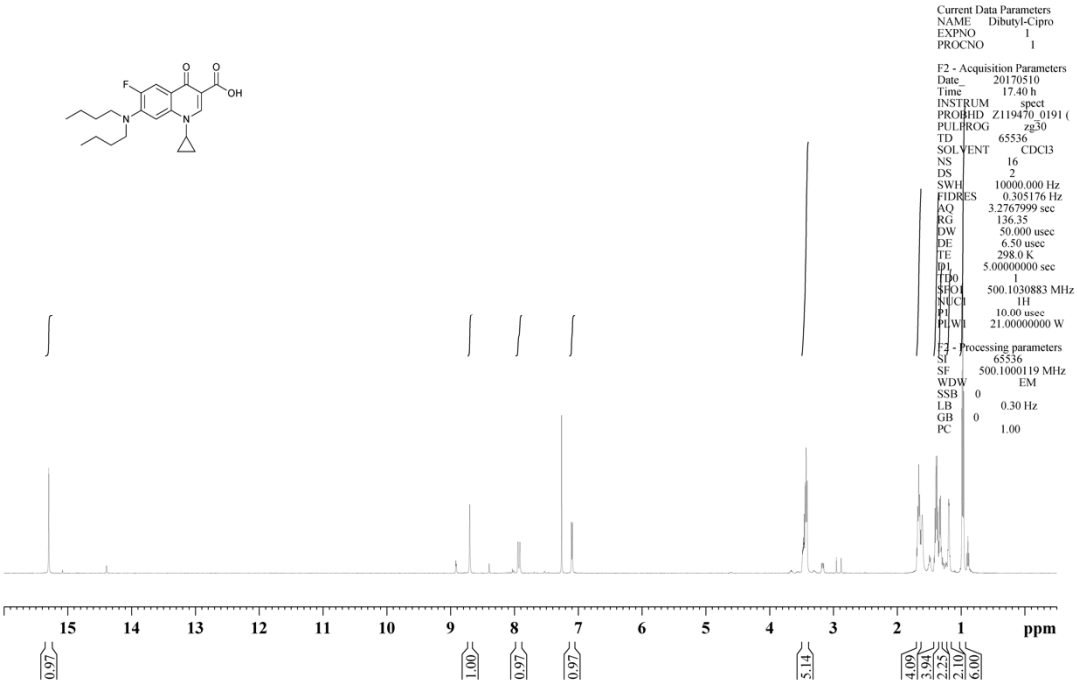
^{1}H NMR spectrum of **42**



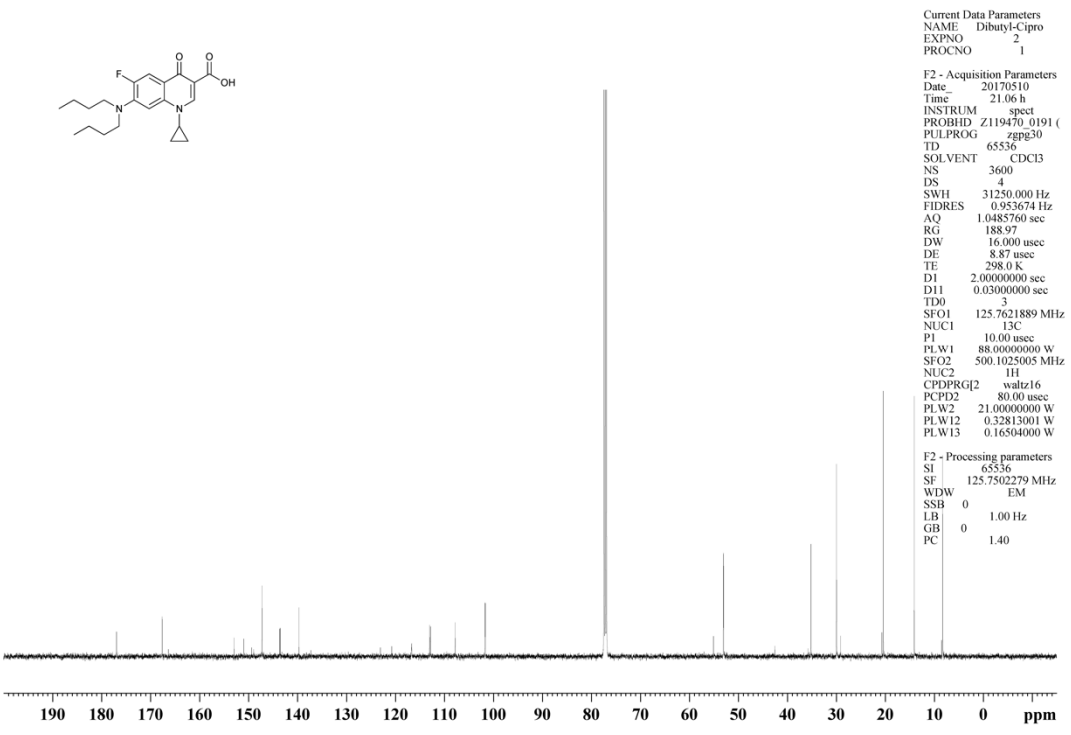
^{13}C NMR spectrum of **42**



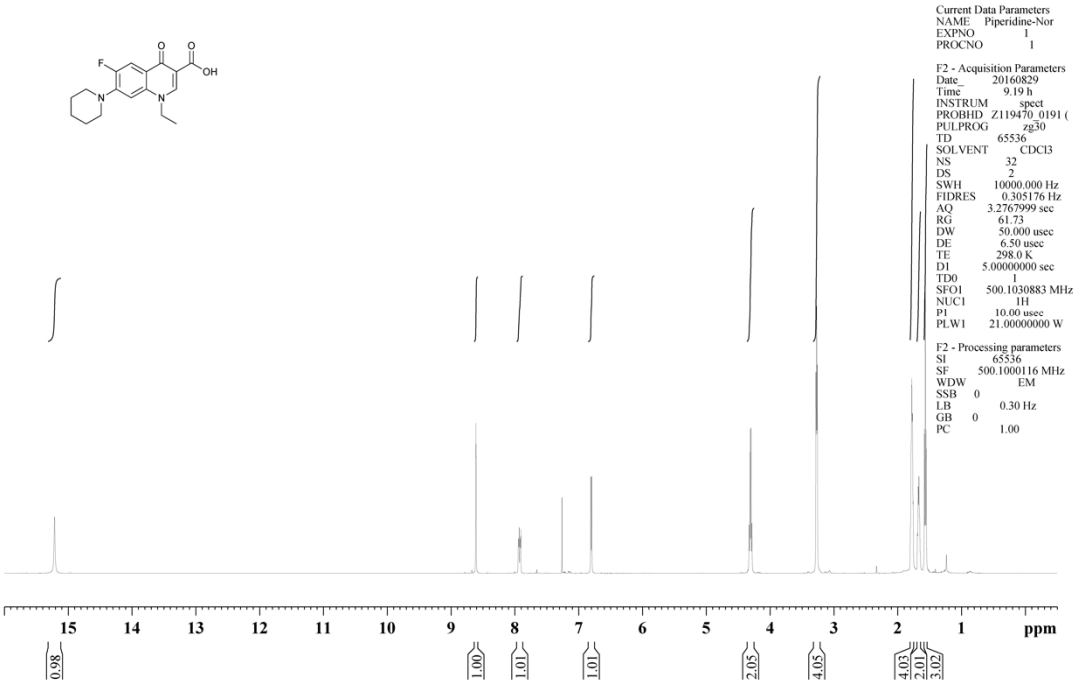
^{1}H NMR spectrum of **43**



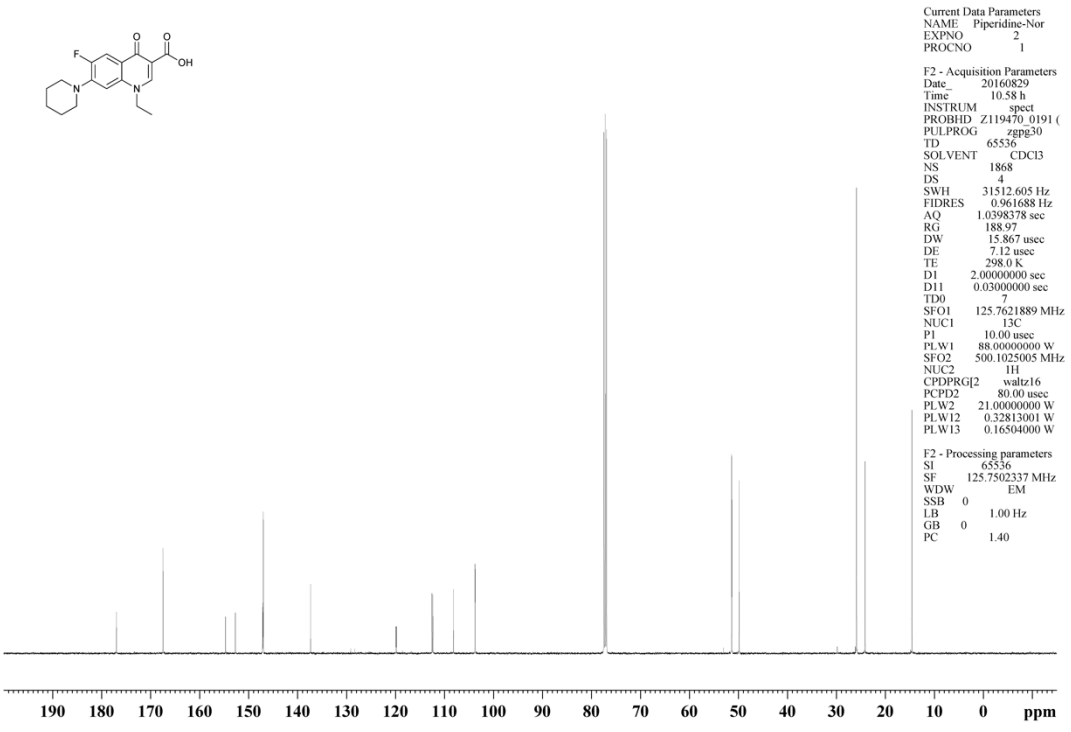
^{13}C NMR spectrum of **43**



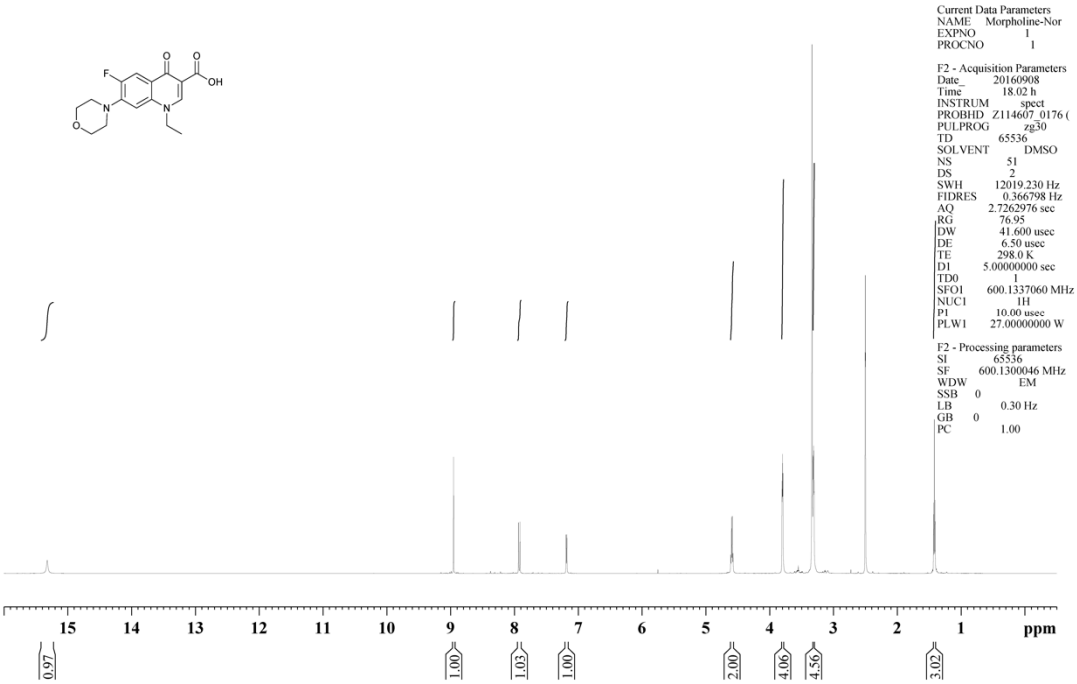
^{1}H NMR spectrum of **44**



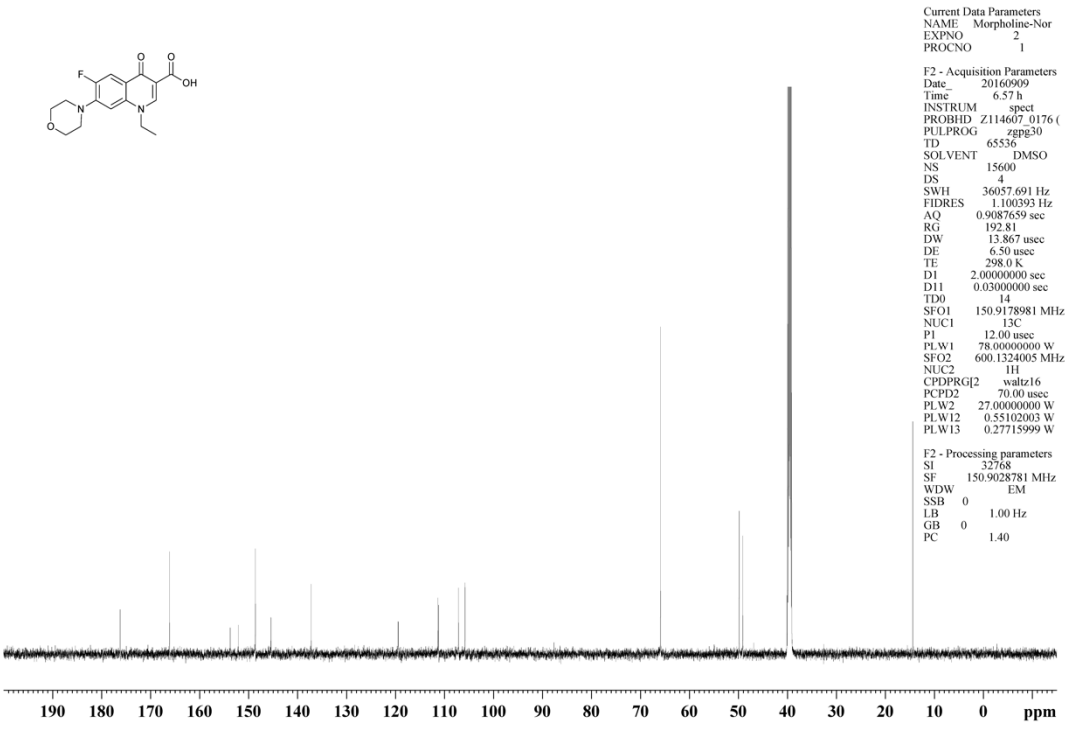
^{13}C NMR spectrum of **44**



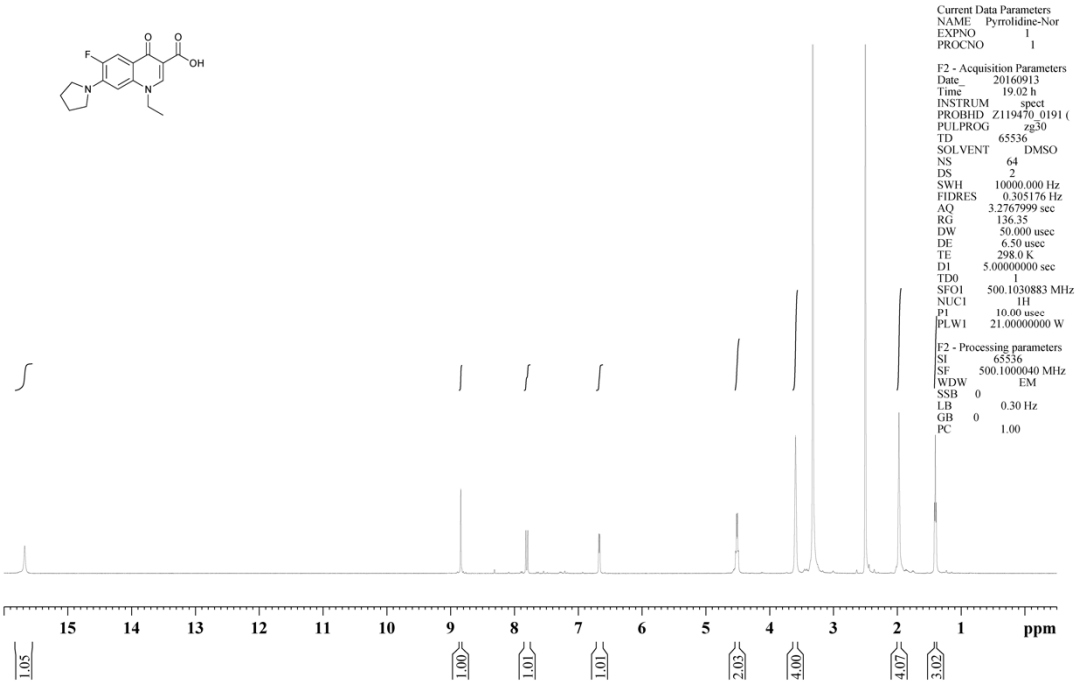
^{1}H NMR spectrum of **45**



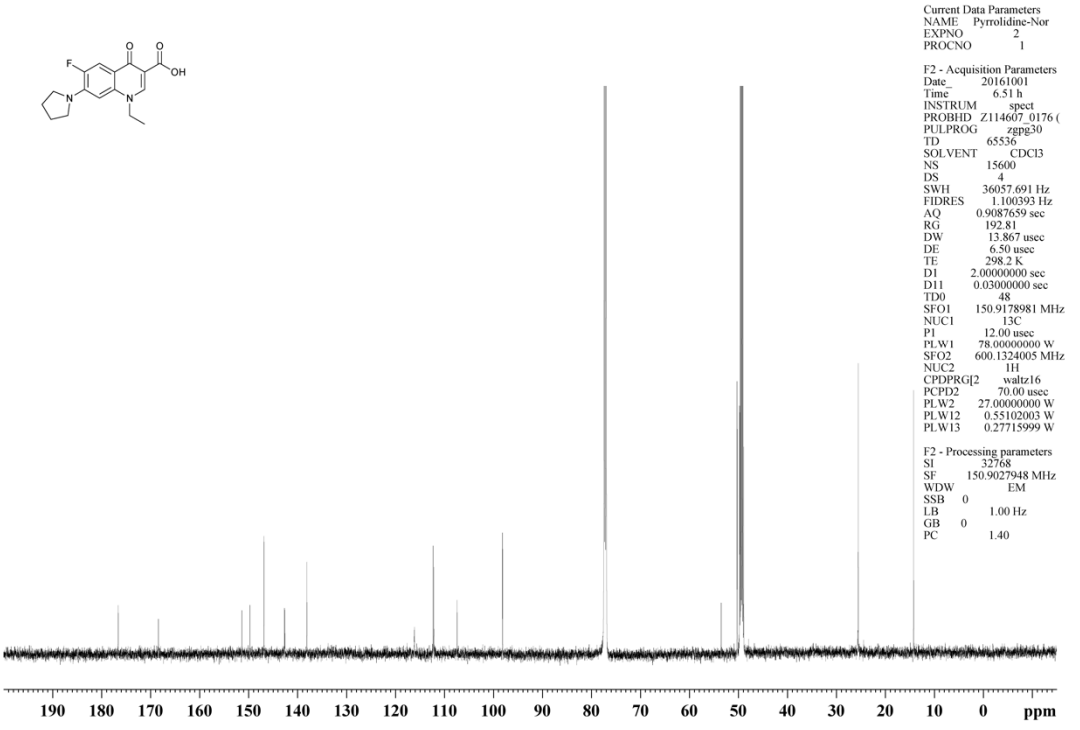
^{13}C NMR spectrum of **45**



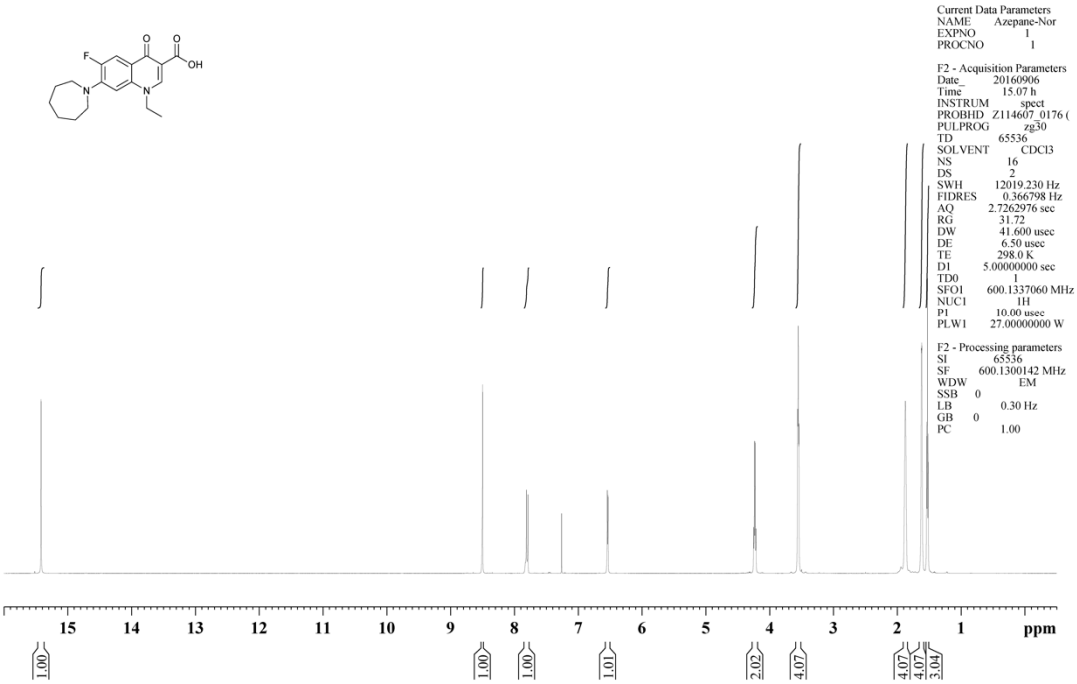
^{1}H NMR spectrum of **46**



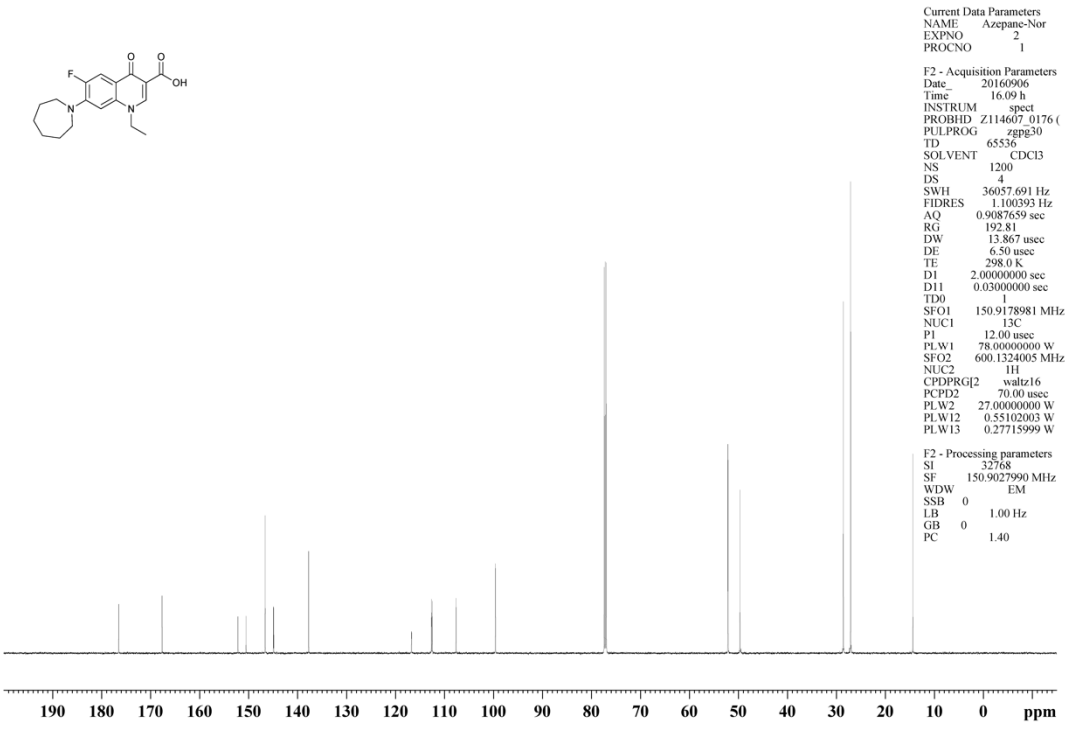
^{13}C NMR spectrum of **46**



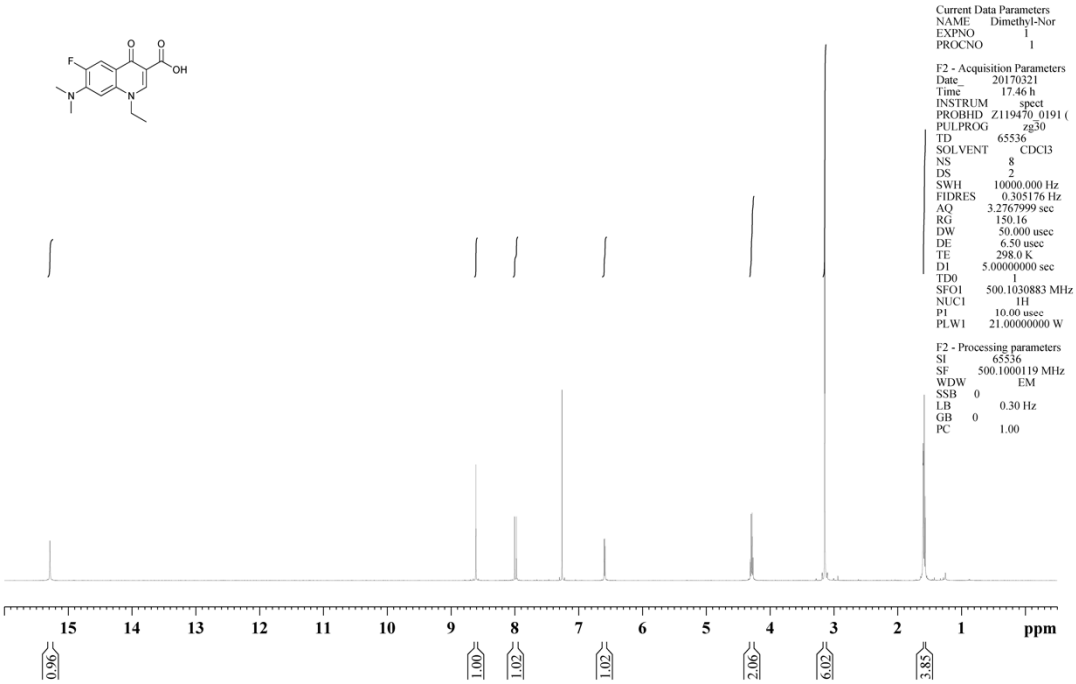
^{1}H NMR spectrum of **47**



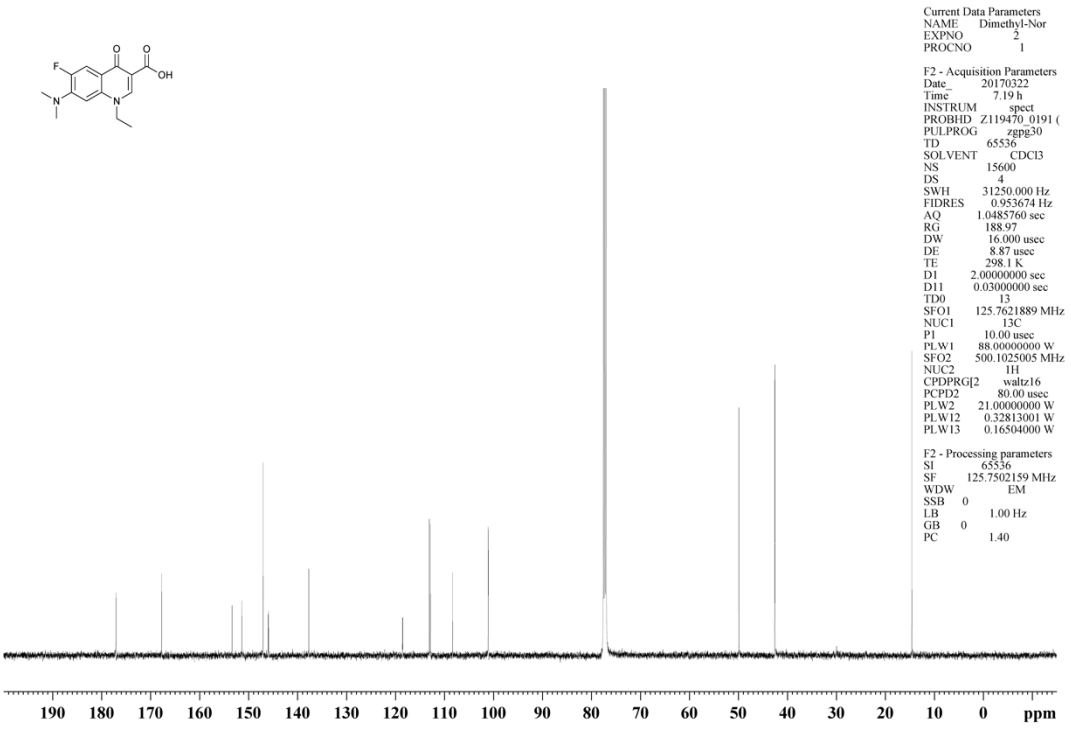
^{13}C NMR spectrum of **47**



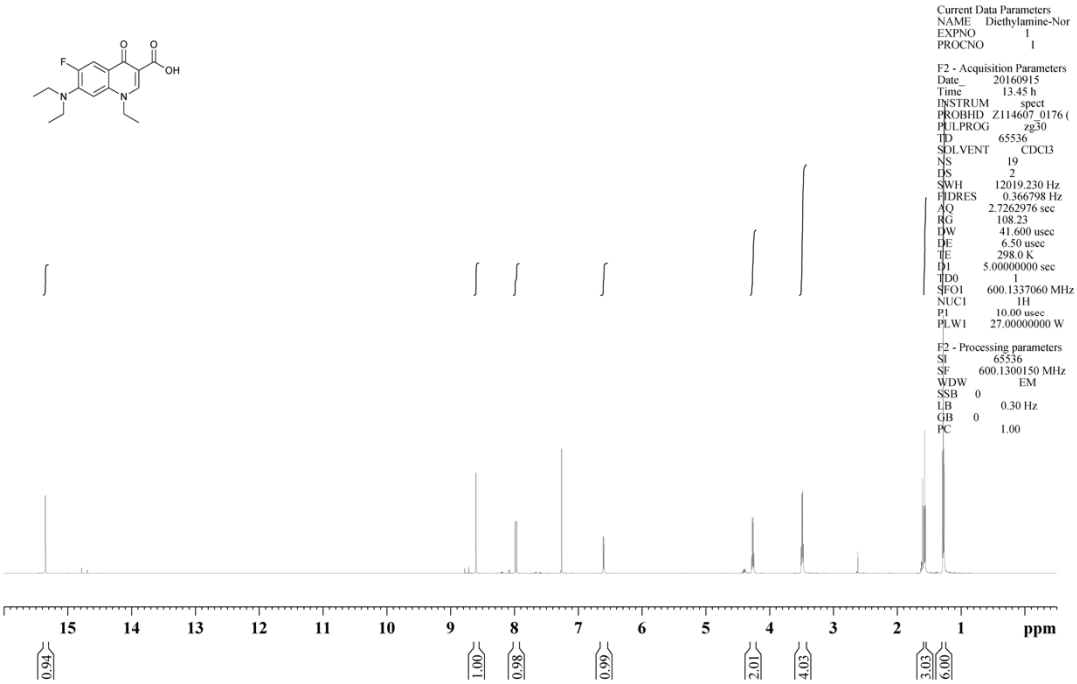
^{1}H NMR spectrum of **48**



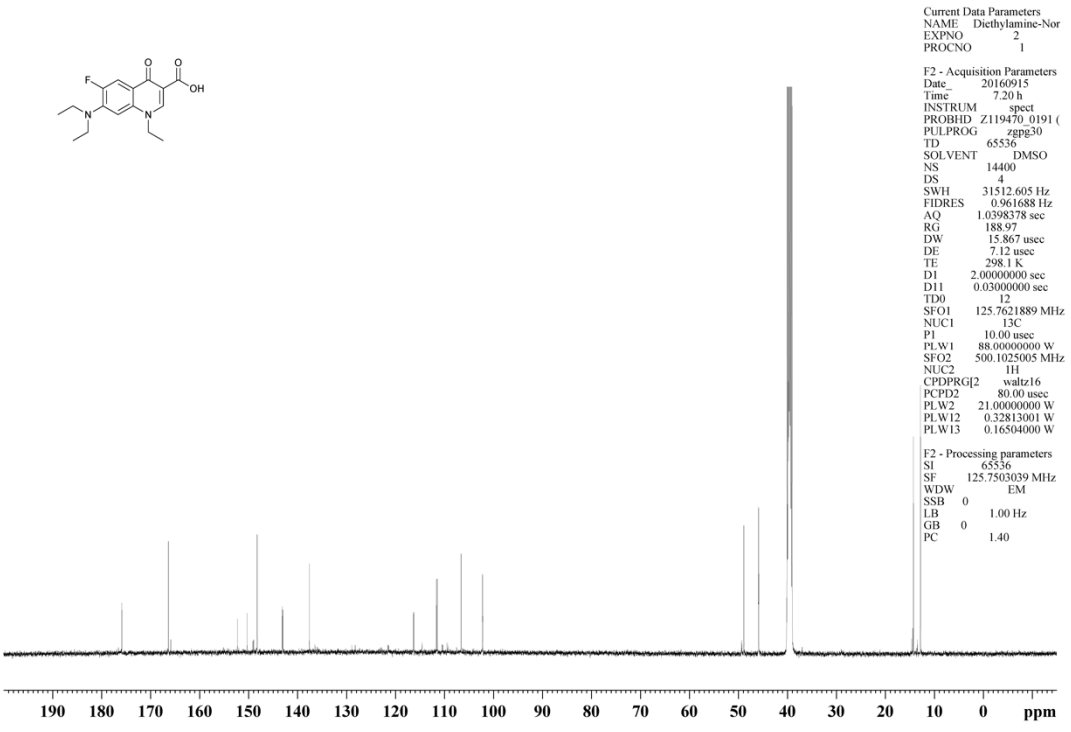
^{13}C NMR spectrum of **48**



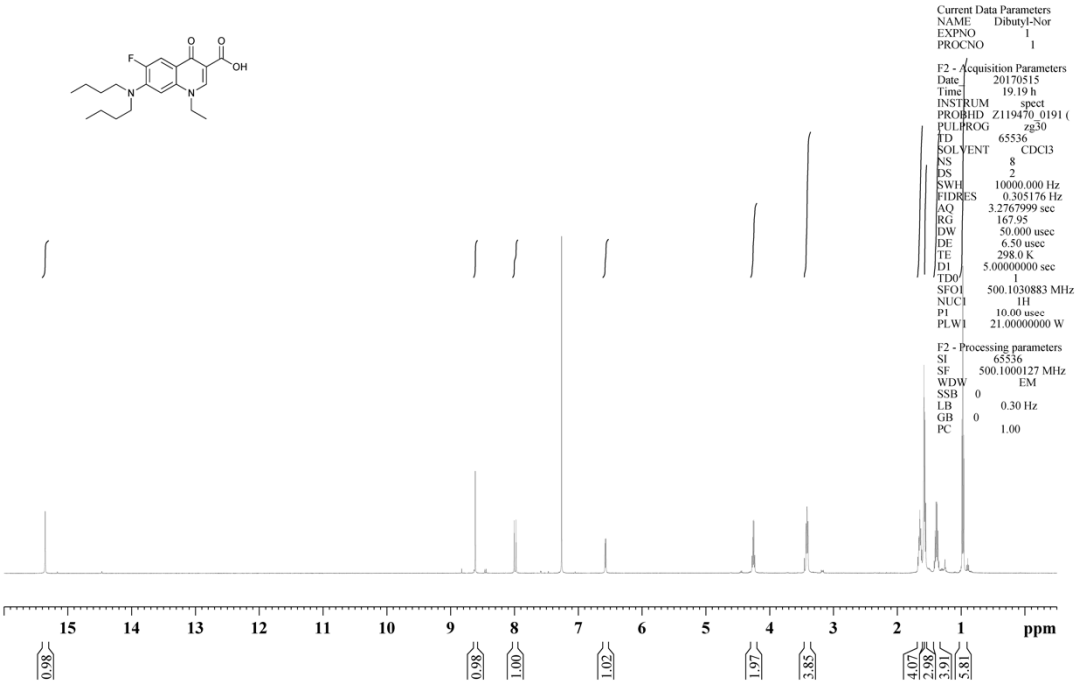
^{1}H NMR spectrum of **49**



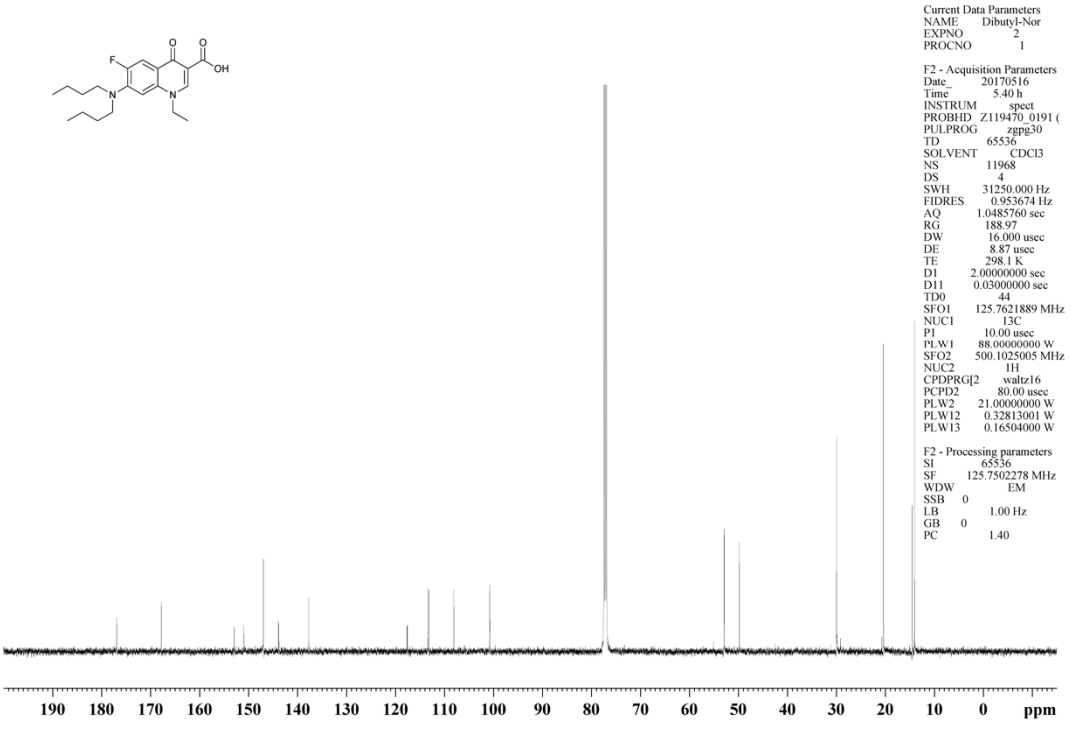
^{13}C NMR spectrum of **49**



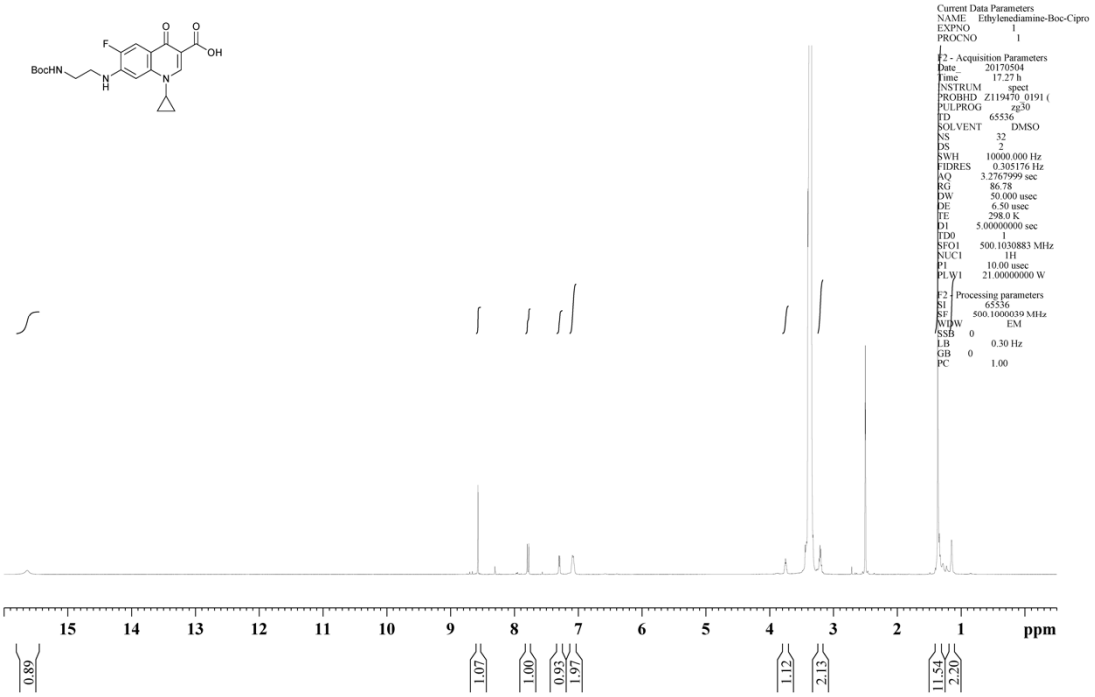
^{1}H NMR spectrum of **50**



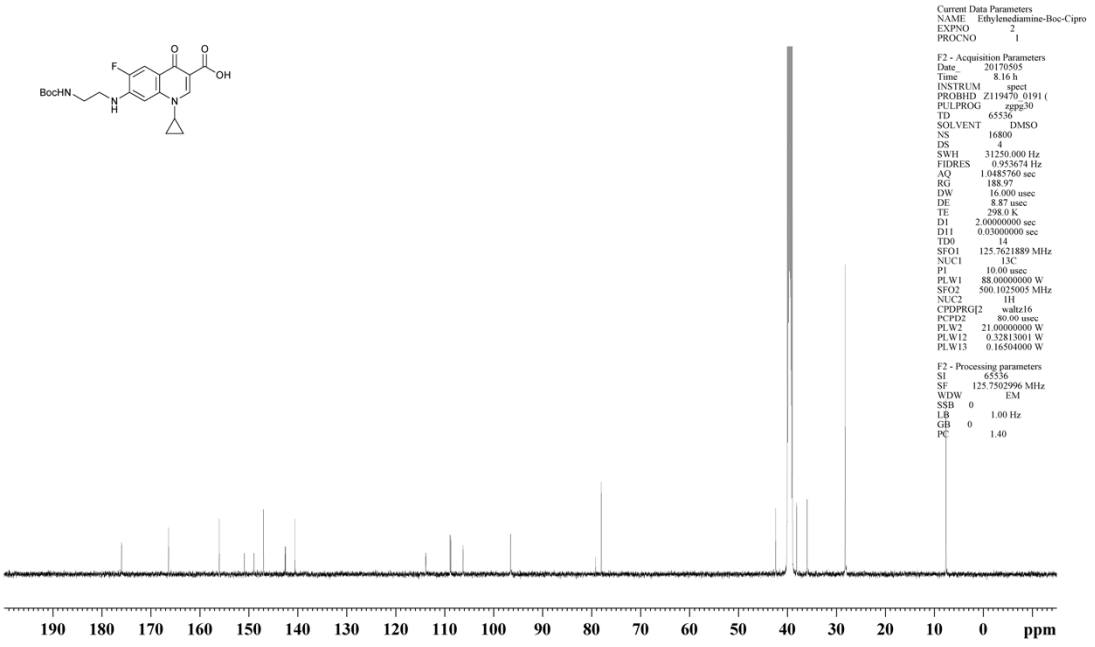
^{13}C NMR spectrum of **50**



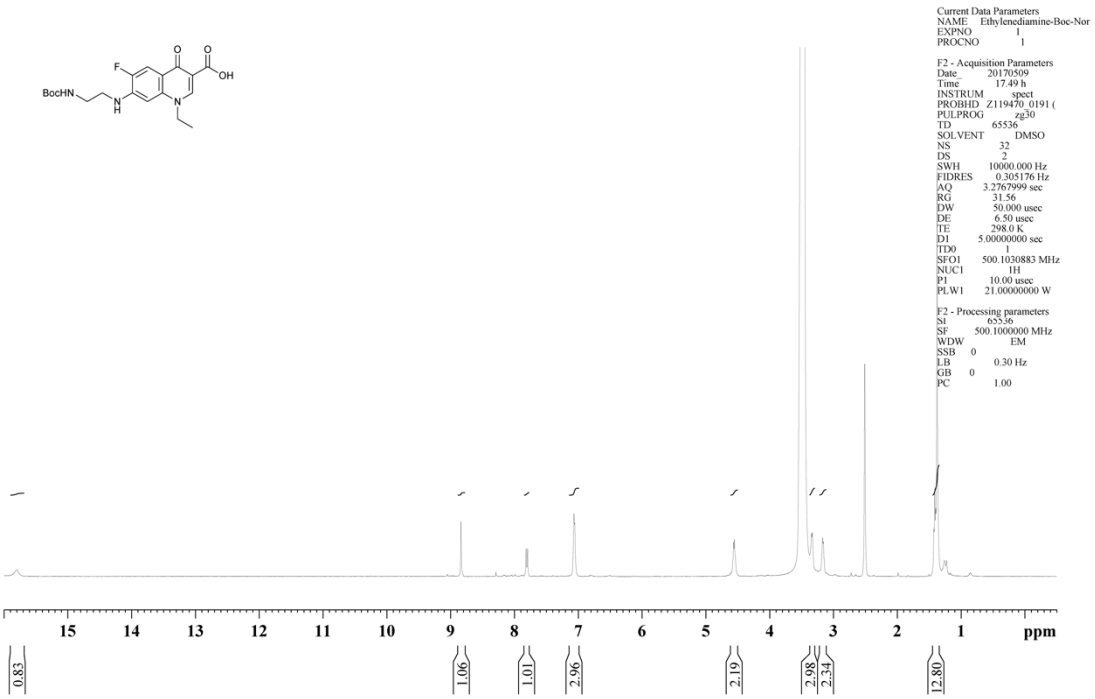
^{1}H NMR spectrum of **55**



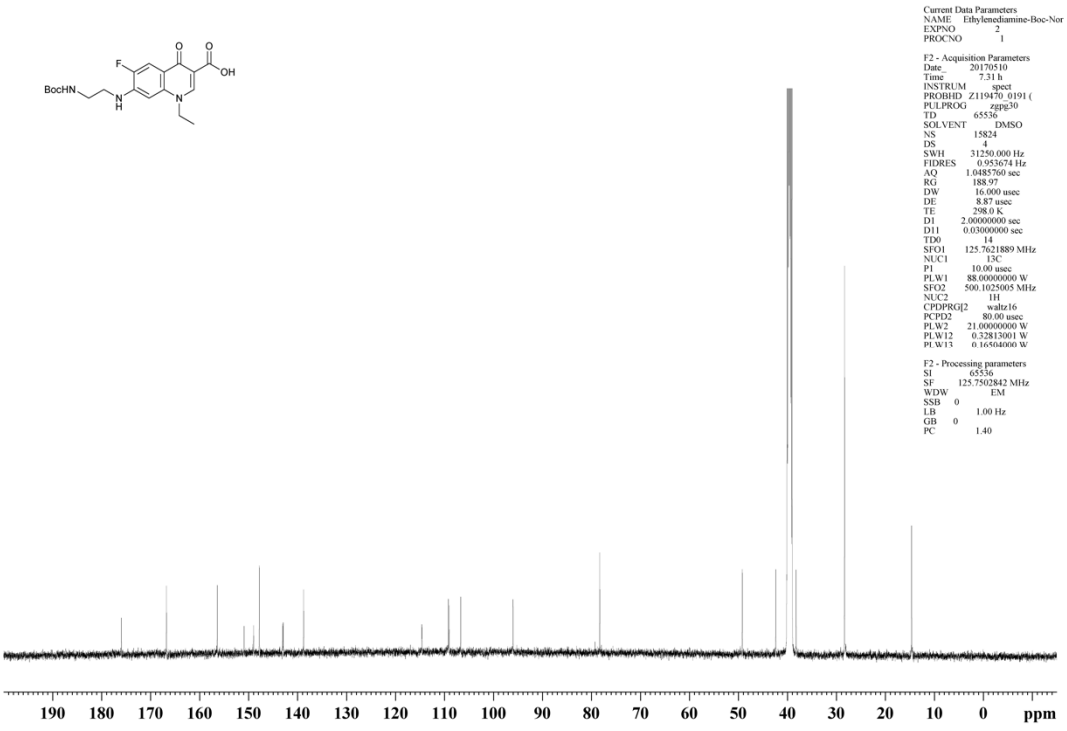
^{13}C NMR spectrum of **55**



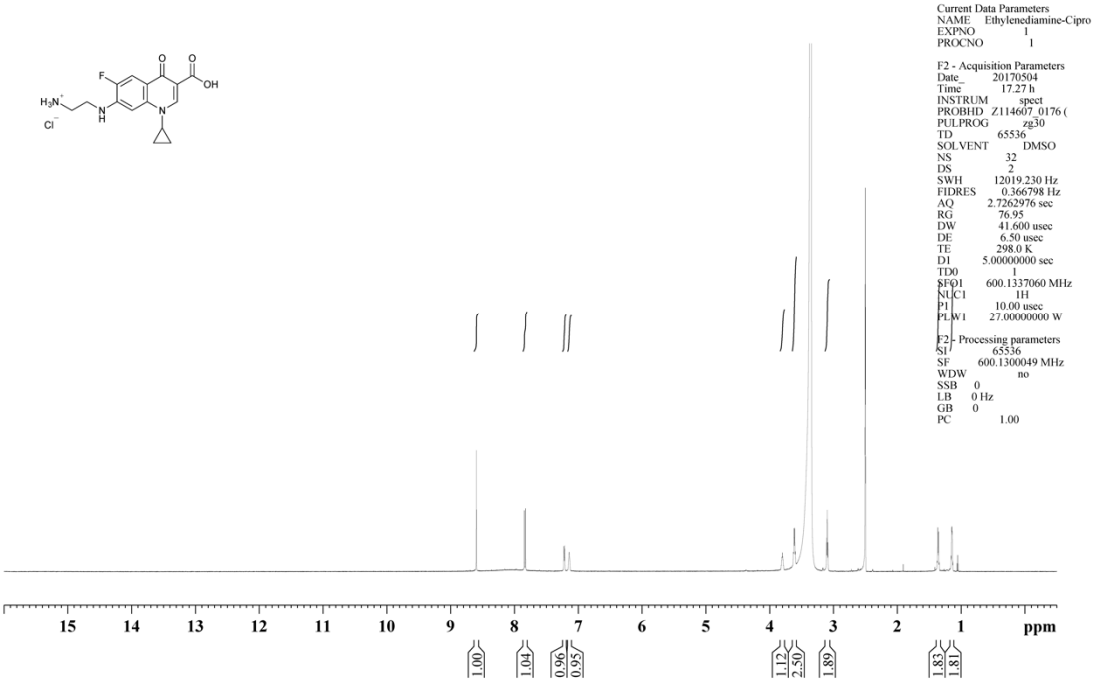
^{1}H NMR spectrum of **56**



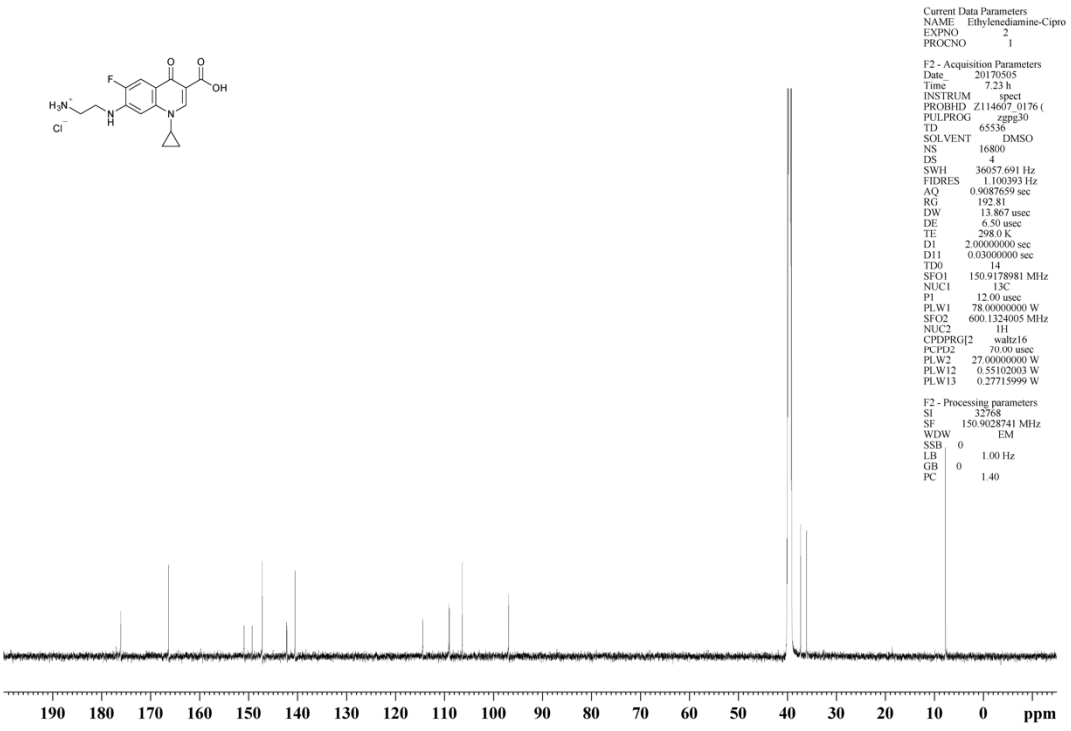
^{13}C NMR spectrum of **56**



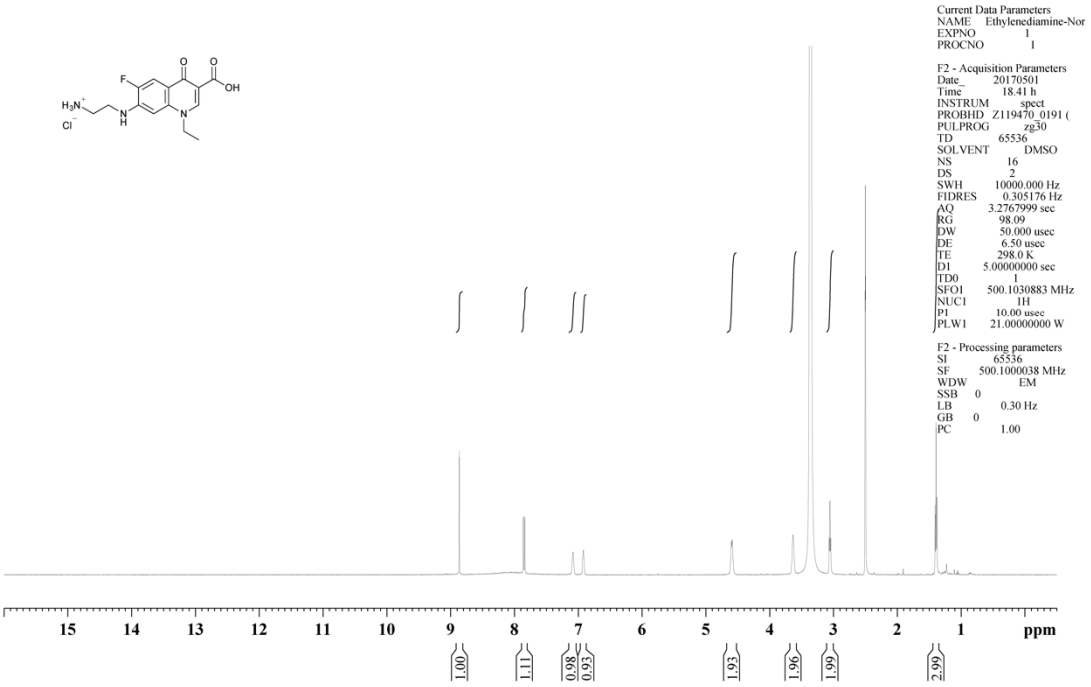
^{1}H NMR spectrum of **51**



^{13}C NMR spectrum of **51**



^{1}H NMR spectrum of **52**



^{13}C NMR spectrum of **52**