Unprecedented linear products by mechanochemically activated Biginelli reaction using lawsone.

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1. MATERIALS AND METHODS

Our reagents and solvents were purchased from Sigma Aldrich, TCI, Alfa Aesar and Fluorochem and used as received without any further purification. Microwave irradiation reactions were performed in an apparatus Anton Paar Monowave 400. Mechanochemical reactions were performed by using a Retsch Mixer Mill MM400 with 10 mL zirconium oxide jar with 5.8 g of zirconium oxide balls (2 balls, 5 mm diameter each) and a Fritsch Planetary Micro Mill PULVERISETTE 7 with 20 mL zirconium oxide jar with 14.7 g of zirconium oxide balls (5 balls, 10 mm diameter each). Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck). The compounds and the reaction mixtures were visualized on the TLC plates by irradiation with UV light. For Flash Column Chromatography, a PuriFlash XS520Plus system was used in combination with PF-30SIHP-JP-F0040 columns. For semi-preparative HPLC a system of Autopurification Waters 2767 with a Photodiode Array Detector 2998 and a binary pump Waters 2545 was used in combination with a C18 column (XBridge 5µm 150mm x 19 mm). Water with 0.1% HCOOH and CH_3CN with 0.1% HCOOH were employed as solvents A and B with a flow rate of 20 mL/min. The elution was followed by UV detection at 260 nm. ^1H and ^{13}C NMR spectra for the reported compounds were recorded on a Bruker Avance I 300 MHz (300 MHz for ^1H and 75 MHz for ^{13}C), on a Bruker Avance III Nanobay 400 MHz (400.0 MHz for ^1H and 101 MHz for ^{13}C), and on a Bruker Avance 600 MHz (600 MHz for ^1H and 151 MHz for ^{13}C) equipped with a 5 mm triple resonance inverse Z-gradient probe (TBI ^1H, ^{31}P, BB). Chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hz, respectively. The NMR experiments were performed in $CDCl_3$ or DMSO-*d6* and MeOD-*d4* and referenced to the solvent signal. TMS was used as external reference for ^1H and ^{13}C NMR spectras while $CFCl_3$ for ^{19}F spectras. High resolution mass spectrometry (HRMS) analyses were carried out on an XevoG2QTof (Waters) using electrospray ionization (ESI). Melting points were determined using a Stuart SMP3 apparatus and the obtained values are not corrected.

2. EXPERIMENTAL PART

2.1 SYNTHESIS OF MICHAEL ADDUCT 8.

A mixture of lawsone (1.5 mmol), urea (1.5 mmol) and 4-chlorobenzaldehyde (1.5 mmol) in 2 mL ionic liquid $[HNMP]^+[HSO_4]^-$ media was stirred at 80 °C for 30 min, until it turned into a red solid. Then, iced water was added and the resulting suspension stayed under vigorous stirring for 10 min. The red solid was isolated by filtration and washed with excess of water. Afterwards, the crude product was purified by recrystallization in EtOH to afford 332 mg of **8** as a yellow-orange solid (yield 47%, mp 180−182 °C). *Rf* (Hex/AcOEt 1:1) = 0.12. ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.10 (dd, *J* = 7.6, 1.5 Hz, 4H), 7.76 (td, *J* = 7.6, 1.5 Hz, 2H), 7.70 (td, *J* = 7.6, 1.5 Hz, 2H), 7.23 (m, 4H), 6.15 (s, 1H), 3.49 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 184.5 (2 x C=O), 181.4 (2 x C=O), 154.6 (2 x C-OH), 137.1 (2 x C), 135.3 (2 x CH), 133.4 (2 x CH), 132.9 (2 x C), 132.6 (C-Cl), 129.8 (2 x CH), 129.6 (C), 128.5 (2 x CH), 127.4 (2 x CH), 126.5 (2 x CH), 122.3 (2 x C), 37.6 (CH). HRMS calcd for $C_{27}H_{14}O_6Cl^-$ $[M - H]^-$ = 469.0479; found 469.0481 with a consistent isotopic profile.

2.2 EXPERIMENTAL PROCEDURE FOR THE MECHANOCHEMICAL PREPARATION OF BIGINELLI-TYPE LINEAR LAWSONE DERIVATIVES.

Lawsone (1.0 equiv, 2.2 mmol), 4-substituted-benzaldehyde (1.0 equiv, 2.2 mmol), urea or *N*-alkylated urea (1.5 equiv, 3.3 mmol) and *p*-toluenesulfonic acid (pTSA) (0.2 equiv, 0.44 mmol) were added in a 20 mL zirconium oxide jar with 14.7 g of zirconium oxide balls (5 balls, 10 mm diameter each). The reaction was operated in a planetary ball milling Pulverisette 7 at 800 rpm (2 cycles x 40-60 min, 1 x pause 10 min). Afterwards, the reaction mixture was either scratched out of the jars either recovered by dissolving it in MeOH. If needed, the solvent was removed under vacuum. The collected residue was dissolved in dichloromethane. The organic phase was washed with water and brine. The organic layers were collected,

dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The obtained crude products were then purified by crystallization in dichloromethane/diethyl ether or dichloromethane/methanol. The products were isolated as solids after filtration and washing with Et_2O.

3-[(4'-chlorophenyl)methylurea]-2-hydroxynaphthalene-1,4-dione, **7**

The compound was synthesized by following the above-mentioned general procedure (2.2 mmol of lawsone scale). Ball milling for 2 cycles x 40 min. The crude product was purified by crystallization in DCM/Et_2O to yield 710 mg (90%) of the target product as a yellow solid (mp 137−139 °C). *Rf* (DCM/MeOH 9:1) = 0.11. ^{1}H NMR (400 MHz, DMSO) *δ* 8.03 – 7.99 (m, 1H), 7.94 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.83 – 7.78 (m, 1H), 7.36 – 7.29 (m, 4H), 6.81 (d, *J* = 9.8 Hz, 1H, NH), 6.40 (d, *J* = 9.8 Hz, 1H), 5.90 (bs, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO) *δ* 184.1 (C=O), 181.3 (C=O), 158.0 (NH-C=O), 155.8 (C-OH), 141.8 (C), 134.8 (CH), 133.4 (CH), 131.8 (C-Cl), 130.8 (C), 130.1 (C), 128.0 (2 x CH), 127.7 (2 x CH), 125.8 (CH), 125.7 (CH), 122.6 (C), 46.3 (CH). HRMS calcd for $C_{18}H_{12}N_2O_4Cl^-$ $[M - H]^-$ = 355.0486; found 355.0486 with consistent isotopic profile.

3-[(4'-fluorophenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **9**

The compound was synthesized by following the above-mentioned general procedure (1.5 mmol of lawsone scale). Ball milling for 2 cycles x 60 min. The crude product was purified by crystallization in DCM to yield 350 mg (63%) of the target product as a yellow solid (mp 172−174 °C). *Rf* (Hex/AcOEt 1:1) = 0.11. ^{1}H NMR (400 MHz, MeOD) *δ* 8.04 (tt, *J* = 7.4, 1.0 Hz, 2H), 7.77 (td, *J* = 7.5, 1.5 Hz, 1H), 7.73 (td, *J* = 7.5, 1.5 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.04 – 6.96 (m, 2H), 6.54 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) *δ* 186.0 (C=O), 182.7 (C=O), 163.2 (d, *J* = 244.4 Hz, C-F), 160.3 (NH-C=O), 156.9 (C-OH), 139.3 (d, *J* = 3.0 Hz, C), 135.7 (CH), 134.3 (CH), 133.8 (C), 131.5 (C), 129.2 (CH), 129.1 (CH), 127.1 (d, *J* = 25.3 Hz, 2 x CH), 123.9 (C), 115.8 (d, *J* = 22.2 Hz, 2 x CH), 49.0 (CH), 35.8 (CH_2), 15.7 (CH_3). ^{19}F NMR (376 MHz, MeOD) δ -118.61 (m, *J* = 9.5 Hz). HRMS calcd for $C_{20}H_{18}N_2O_4F^+$ $[M + H]^+$ = 369.1251; found 369.1245, for $C_{20}H_{17}N_2O_4NaF^+$ $[M + Na]^+$ = 391.1070; found 391.1064 with consistent isotopic profile.

3-[(4'-chlorophenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **10**

The compound was synthesized by following the above-mentioned general procedure (1.5 mmol of lawsone scale). Ball milling for 2 cycles x 40 min. The crude product was purified by crystallization in DCM/MeOH/Et_2O to yield 358 mg (62%) of the target product as a yellow solid (mp 168−170 °C). *Rf* (Hex/AcOEt 3:7) = 0.10. ^{1}H NMR (300 MHz, MeOD) *δ* 8.04 (td, *J* = 7.5, 2.2 Hz, 2H), 7.75 (dtd, *J* = 7.5, 1.7 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.31 – 7.19 (m, 2H), 6.55 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, MeOD) *δ* 186.0 (C=O), 182.6 (C=O), 160.2 (NH-C=O), 156.9 (C-OH), 142.1 (C), 135.8 (CH), 134.3 (CH), 133.7 (C), 133.5 (C-Cl), 131.5 (C), 129.3 (2 x CH), 128.9 (2 x CH), 127.2 (CH), 127.0 (CH), 123.7 (C), 48.9 (CH), 35.8 (CH_2), 15.7 (CH_3). HRMS calcd for $C_{20}H_{18}N_2O_4Cl^+$ $[M + H]^+$ = 385.0955; found 385.0949, for $C_{20}H_{17}N_2O_4NaCl^+$ $[M + Na]^+$ = 407.0775; found 407.0769 with consistent isotopic profile.

3-[(4'-bromophenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **11**

The compound was synthesized by following the above-mentioned general procedure (1.3 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM/Et_2O to yield 391 mg (70%) of the target product as a yellow solid (mp 187−189 °C). *Rf* (Hex/AcOEt 3:7) = 0.10. ^{1}H NMR (300 MHz, MeOD) *δ* 8.07 – 7.98 (m, 2H), 7.75 (dd, *J* = 7.5, 1.6 Hz, 2H), 7.46 – 7.38 (m, 2H), 7.35 – 7.28 (m, 2H), 6.53 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 184.2 (C=O),

181.3 (C=O), 157.2 (NH-C=O), 155.8 (C-OH), 142.3 (C), 134.8 (CH), 133.4 (CH), 131.7 (C), 130.8 (2 x CH), 130.1 (C), 128.1 (2 x CH), 125.8 (C), 125.7 (C), 122.5 (C-Br), 119.3 (C), 46.4 (CH), 34.1 (CH_2), 15.6 (CH_3). HRMS calcd for $C_{20}H_{18}N_2O_4Br^+$ $[M + H]^+$ = 429.0450; found 429.0446, for $C_{20}H_{17}N_2O_4NaBr^+$ $[M + Na]^+$ = 451.0269; found 451.0264 with consistent isotopic profile.

3-[(4'-iodophenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **12**

The compound was synthesized by following the above-mentioned general procedure (1.3 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM/Et_2O to yield 433 mg (70%) of the target product as a yellow solid (mp 186−188 °C). *Rf* (Hex/AcOEt 1:9) = 0.29. ^{1}H NMR (400 MHz, MeOD) δ 8.07 – 8.00 (m, 2H), 7.77 (td, *J* = 7.5, 1.6 Hz, 1H), 7.72 (td, *J* = 7.5, 1.6 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.22 – 7.14 (m, 2H), 6.52 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 185.9 (C=O), 182.6 (C=O), 160.2 (NH-C=O), 157.1 (C-OH), 143.3 (C), 138.4 (2 x CH), 135.8 (CH), 134.3 (CH), 133.8 (C), 131.6 (C), 129.5 (2 x CH), 127.2 (C), 127.0 (C), 123.6 (C), 92.5 (C-I), 49.1 (CH), 35.8 (CH_2), 15.7 (CH_3). HRMS calcd for $C_{20}H_{18}N_2O_4I^+$ $[M + H]^+$ = 477.0311; found 477.0315, for $C_{20}H_{17}N_2O_4NaI^+$ $[M + Na]^+$ = 499.0131; found 499.0133 with consistent isotopic profile.

3-[(4'-nitrophenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **13**

The compound was synthesized by following the above-mentioned general procedure (1.5 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM/Et_2O to yield 504 mg (85%) of the target product as a yellow-orange solid (mp 183−185 °C). *Rf* (Hex/AcOEt 3:7) = 0.09. ^{1}H NMR (400 MHz, MeOD) δ 8.19 – 8.13 (m, 2H), 8.06 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.02 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.66 – 7.61 (m, 2H), 6.67 (s, 1H), 3.17 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 185.8 (C=O), 182.5 (C=O), 160.1 (C), 157.5 (NH-C=O), 151.3 (C-OH), 148.2 (C), 135.8 (CH), 134.4 (CH), 133.7 (C), 131.6 (C), 128.3 (2 x CH), 127.2 (CH), 127.1 (CH), 124.4 (2 x CH), 123.0 (C), 49.1 (CH), 35.8 (CH_2), 15.7 (CH_3). HRMS calcd for $C_{20}H_{18}N_3O_6^+$ $[M + H]^+$ = 396.1196; found 396.1193, for $C_{20}H_{17}N_3O_6Na^+$ $[M + Na]^+$ = 418.1015; found 418.1009 with consistent isotopic profile.

3-[(4'-trifluoromethylphenyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **14**

The compound was synthesized by following the above-mentioned general procedure (1.0 mmol of lawsone scale). Ball milling for 1 cycle x 45 min. The crude product was purified by crystallization in DCM/MeOH/Et_2O to yield 376 mg (90%) of the target product as a yellow solid (mp 166−168 °C). *Rf* (Hex/AcOEt 1:1) = 0.08. ^{1}H NMR (400 MHz, DMSO) δ 8.04 – 7.99 (m, 1H), 7.96 – 7.91 (m, 1H), 7.82 (dtd, *J* = 17.8, 7.5, 1.5 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.55 – 7.48 (m, 2H), 6.75 (d, *J* = 9.7 Hz, 1H), 6.53 (m, 2H), 3.08 – 2.95 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 184.1 (C=O), 181.3 (C=O), 157.3 (NH-C=O), 156.0 (C-OH), 147.7 (C), 134.8 (CH), 133.4 (CH), 131.7 (C), 130.2 (C), 127.0 (d, *J* = 33.3 Hz, C), 126.6 (2 x CH), 125.9 (CH), 125.7 (CH), 124.9 (q, *J* = 3.9 Hz, 2 x CH), 124.4 (q, *J* = 272.7 Hz, CF_3), 122.3 (C), 46.7 (CH), 34.1 (CH_2), 15.5 (CH_3). ^{19}F NMR (282 MHz, DMSO) δ -60.69. HRMS calcd for $C_{21}H_{18}N_2O_4F_3^+$ $[M + H]^+$ = 419.1219; found 419.1219 with consistent isotopic profile.

3-[(4'-tolyl)methyl-(N'-ethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **15**

The compound was synthesized by following the above-mentioned general procedure (2.0 mmol of lawsone scale). Ball milling for 2 cycles x 60 min. The crude product was purified by crystallization in DCM to yield 510 mg (70%) of the target product as a yellow solid (mp 175−177 °C). *Rf* (AcOEt) = 0.21. ^{1}H NMR (300 MHz, MeOD) *δ* 8.02 (t, *J* = 7.5 Hz, 2H), 7.79 – 7.66 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.52 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) *δ* 186.1 (C=O), 182.7 (C=O), 160.4 (NH-C=O), 156.5 (C-OH), 140.1 (C), 137.5 (C), 135.7 (CH), 134.3 (CH), 133.8 (C), 131.5 (C), 129.9 (2 x CH), 127.2 (2 x CH), 127.2 (CH), 126.9 (CH), 124.4 (C), 49.3 (CH), 35.8 (CH_2), 21.0 ($PhCH_3$), 15.7 (CH_3). HRMS calcd for $C_{21}H_{21}N_2O_4^+$ [M + H]$^+$ = 365.1501; found 365.1499, for $C_{21}H_{20}N_2O_4Na^+$ [M + Na]$^+$ = 387.1321; found 387.1320 with consistent isotopic profile.

3-[(4'-fluorophenyl)methyl-(N'-butyl)-urea]-2-hydroxynaphthalene-1,4-dione, **16**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM to yield 450 mg (81%) of the target product as a yellow solid (mp 172−174 °C). *Rf* (Hex/AcOEt 3:7) = 0.12. ^{1}H NMR (400 MHz, MeOD) *δ* 8.04 (ddd, *J* = 8.9, 7.4, 1.8 Hz, 2H), 7.75 (dtd, *J* = 19.6, 7.4, 1.5 Hz, 2H), 7.42 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.03 – 6.95 (m, 2H), 6.54 (s, 1H), 3.12 (t, *J* = 7.0 Hz, 2H), 1.50 – 1.41 (m, 2H), 1.41 – 1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) *δ* 185.9 (C=O), 182.7 (C=O), 163.2 (d, *J* = 244.4 Hz, C-F), 160.4 (NH-C=O), 157.1 (C-OH), 139.3 (d, *J* = 3.0 Hz, C), 135.7 (CH), 134.3 (CH), 133.9 (C), 131.6 (C), 129.2 (CH), 129.1 (CH), 127.1 (d, *J* = 24.2 Hz, 2 x CH), 123.9 (C), 115.8 (d, *J* = 22.2 Hz, 2 x CH), 49.0 (CH), 40.7 (CH_2), 33.4 (CH_2), 21.0 (CH_2), 14.1 (CH_3). ^{19}F NMR (282 MHz, DMSO) δ -117.01. HRMS calcd for $C_{22}H_{22}N_2O_4F^+$ [M + H]$^+$ = 397.1564; found 397.1564, for $C_{22}H_{21}N_2O_4FNa^+$ [M + Na]$^+$ = 419.1383; found 419.1379 with consistent isotopic profile.

3-[(4'-chlorophenyl)methyl-(N'-butyl)-urea]-2-hydroxynaphthalene-1,4-dione, **17**

The compound was synthesized by following the above-mentioned general procedure (1.5 mmol of lawsone scale). Ball milling for 2 cycles x 45 min. The crude product was purified by crystallization in DCM/Et_2O to yield 526 mg (85%) of the target product as a yellow solid (mp 160−162 °C). *Rf* (Hex/AcOEt 3:7) = 0.16. ^{1}H NMR (400 MHz, MeOD) *δ* 8.09 – 7.98 (m, 2H), 7.77 (td, *J* = 7.5, 1.6 Hz, 1H), 7.72 (td, *J* = 7.5, 1.6 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.29 – 7.24 (m, 2H), 6.54 (s, 1H), 3.13 (t, *J* = 7.0 Hz, 2H), 1.49 – 1.41 (m, 2H), 1.40 – 1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 184.1 (C=O), 181.3 (C=O), 157.4 (NH-C=O), 155.9 (C-OH), 141.9 (C), 134.7 (CH), 133.4 (CH), 131.8 (C), 130.8 (C-Cl), 130.1 (C), 128.0 (2 x CH), 127.7 (2 x CH), 125.8 (CH), 125.7 (CH), 122.5 (C), 46.4 (CH_2), 39.7 (CH), 32.0 (CH_2), 19.5 (CH_2), 13.7 (CH_3). HRMS calcd for $C_{22}H_{22}N_2O_4Cl^+$ [M + H]$^+$ = 413.1268; found 413.1268, for $C_{22}H_{21}N_2O_4ClNa^+$ [M + Na]$^+$ = 435.1088; found 435.1085 with consistent isotopic profile.

3-[(4'-bromophenyl)methyl-(N'-butyl)-urea]-2-hydroxynaphthalene-1,4-dione, **18**

The compound was synthesized by following the above-mentioned general procedure (1.3 mmol of lawsone scale). Ball milling for 1 cycle x 60 min. The crude product was purified by crystallization in DCM/Et_2O to yield 564 mg (95%) of the target product as a yellow solid (mp 165−167 °C). *Rf* (Hex/AcOEt 3:7) = 0.11. ^{1}H NMR (400 MHz, MeOD) *δ* 8.08 – 8.00 (m, 2H), 7.78 (td, *J* = 7.5, 1.6 Hz, 1H), 7.73 (td, *J* = 7.5, 1.6 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.36 – 7.29 (m, 2H), 6.53 (s, 1H), 3.13 (t, *J* = 7.0 Hz, 2H), 1.51 – 1.41 (m, 2H), 1.39 – 1.27 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) *δ* 186.0 (C=O), 182.6 (C=O), 160.4 (NH-C=O), 156.9 (C-OH),

142.7 (C), 135.8 (CH), 134.3 (CH), 133.8 (C), 132.3 (2 x CH), 131.6 (C), 129.3 (2 x CH), 127.2 (CH), 127.0 (CH), 123.6 (C-Br), 121.4 (C), 49.1 (CH), 40.7 (CH_2), 33.4 (CH_2), 21.0 (CH_2), 14.1 (CH_3). HRMS calcd for $C_{22}H_{22}N_2O_4Br^+$ $[M + H]^+$ = 457.0763; found 457.0764, for $C_{22}H_{21}N_2O_4BrNa^+$ $[M + Na]^+$ = 479.0582; found 479.0586 with consistent isotopic profile.

3-[(4'-nitrophenyl)methyl-(N'-butyl)-urea]-2-hydroxynaphthalene-1,4-dione, **19**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 1 cycle x 50 min. The crude product was purified by crystallization in DCM/Et_2O to yield 534 mg (90%) of the target product as a yellow-orange solid (mp 175−177 °C). *Rf* (Hex/AcOEt 3:7) = 0.12. ^{1}H NMR (400 MHz, MeOD) δ 8.21 – 8.13 (m, 2H), 8.07 (dd, *J* = 7.1, 1.7 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.76 (dtd, *J* = 17.6, 7.5, 1.4 Hz, 2H), 7.68 – 7.58 (m, 2H), 6.67 (s, 1H), 3.14 (t, *J* = 7.0 Hz, 2H), 1.52 – 1.42 (m, 2H), 1.40 – 1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 185.7 (C=O), 182.6 (C=O), 160.3 (C), 157.7 (NH-C=O), 151.4 (C-OH), 148.2 (C), 135.8 (CH), 134.4 (CH), 133.8 (C), 131.6 (C), 128.3 (2 x CH), 127.2 (CH), 127.1 (CH), 124.4 (2 x CH), 123.0 (C), 49.2 (CH), 40.8 (CH_2), 33.4 (CH_2), 21.0 (CH_2), 14.1 (CH_3). HRMS calcd for $C_{22}H_{22}N_3O_6^+$ $[M + H]^+$ = 424.1509; found 424.1511, for $C_{22}H_{21}N_3O_6Na^+$ $[M + Na]^+$ = 446.1328; found 443.1328 with consistent isotopic profile.

3-[(4'-trifluoromethylphenyl)methyl-(N'-butyl)-urea]-2-hydroxynaphthalene-1,4-dione, **20**

The compound was synthesized by following the above-mentioned general procedure (2.0 mmol of lawsone scale). Ball milling for 2 cycles x 60 min. The crude product was purified by crystallization in cold Et_2O to yield 714 mg (80%) of the target product as a yellow solid (mp 156−158 °C). *Rf* (Hex/AcOEt 1:1) = 0.24. ^{1}H NMR (400 MHz, MeOD) δ 8.04 (ddd, *J* = 12.4, 7.4, 1.8 Hz, 2H), 7.81 – 7.70 (m, 2H), 7.58 (s, 4H), 6.64 (s, 1H), 3.14 (t, *J* = 7.0 Hz, 2H), 1.51 – 1.41 (m, 2H), 1.41 – 1.30 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 185.9 (C=O), 182.6 (C=O), 160.4 (NH-C=O), 157.2 (C-OH), 148.0 (C), 135.8 (CH), 134.4 (CH), 133.7 (C), 131.6 (C), 130.0 (d, *J* = 34.1 Hz, C), 127.8 (2 x CH), 127.3 (CH), 127.0 (CH), 126.1 (q, *J* = 4.0 Hz, 2 x CH), 125.7 (q, *J* = 271.7 Hz, CF_3), 123.4 (C), 49.2 (CH), 40.7 (CH_2), 33.4 (CH_2), 21.0 (CH_2), 14.1 (CH_3). ^{19}F NMR (282 MHz, MeOD) δ -63.87. HRMS calcd for $C_{23}H_{20}N_2O_4F_3^-$ $[M - H]^-$ = 445.1375; found 445.1377 with consistent isotopic profile.

3-[(4'-fluorophenyl)methyl-(N'-propargyl)-urea]-2-hydroxynaphthalene-1,4-dione, **21**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM to yield 440 mg (83%) of the target product as an olive-colored solid (mp 180−182 °C). *Rf* (Hex/AcOEt 3:7) = 0.18. ^{1}H NMR (400 MHz, MeOD) δ 8.04 (tt, *J* = 7.7, 1.2 Hz, 2H), 7.75 (dtd, *J* = 18.9, 7.5, 1.6 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.04 – 6.96 (m, 2H), 6.55 (s, 1H), 3.91 (t, *J* = 2.3 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 186.0 (C=O), 182.6 (C=O), 163.2 (d, *J* = 244.4 Hz, C-F), 159.7 (NH-C=O), 156.7 (C-OH), 139.0 (d, *J* = 3.0 Hz, C), 135.8 (CH), 134.3 (CH), 133.7 (C), 131.5 (C), 129.2 (CH), 129.1 (CH), 127.1 (d, *J* = 26.3 Hz, 2 x CH), 123.7 (C), 115.8 (d, *J* = 21.2 Hz, 2 x CH), 81.7 (C), 71.9 (CH), 49.1 (CH), 30.3 (CH_2). ^{19}F NMR (376 MHz, MeOD) δ -118.51. HRMS calcd for $C_{21}H_{16}N_2O_4F^+$ $[M + H]^+$ = 379.1094; found 379.1095 with consistent isotopic profile.

3-[(4'-chlorophenyl)methyl-(N'-propargyl)-urea]-2-hydroxynaphthalene-1,4-dione, **22**

The compound was synthesized by following the above-mentioned general procedure (1.5 mmol of lawsone scale). Ball milling for 2 cycles x 40 min. The crude product was purified by crystallization in DCM to yield 432 mg (73%) of the target product as a yellow solid (mp 180−182 °C). *Rf* (Hex/AcOEt 3:7) = 0.16. ^{1}H NMR (400 MHz, MeOD) δ 8.03 (ddd, *J* = 8.8, 7.5, 1.6 Hz, 2H), 7.74 (dtd, *J* = 18.7, 7.5, 1.6 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.31 – 7.22 (m, 2H), 6.55 (s, 1H), 3.91 (t, *J* = 2.3 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 185.9 (C=O), 182.5 (C=O), 159.7 (NH-C=O), 157.0 (C-OH), 141.9 (C), 135.8 (CH), 134.3 (CH), 133.7 (C), 133.6 (C-Cl), 131.5 (C), 129.3 (2 x CH), 128.9 (2 x CH), 127.2 (CH), 127.0 (CH), 123.5 (C), 81.7 (C), 71.9 (CH), 49.0 (CH), 30.3 (CH_2). HRMS calcd for $C_{21}H_{16}N_2O_4Cl^+$ $[M + H]^+$ = 395.0799; found 395.0798 with consistent isotopic profile.

3-[(4'-bromophenyl)methyl-(N'-propargyl)-urea]-2-hydroxynaphthalene-1,4-dione, **23**

The compound was synthesized by following the above-mentioned general procedure (2.0 mmol of lawsone scale). Ball milling for 2 cycles x 60 min. The crude product was purified by crystallization in DCM/Et_2O to yield 770 mg (88%) of the target product as a yellow solid (mp 176−178 °C). *Rf* (Hex/AcOEt 3:7) = 0.20. ^{1}H NMR (300 MHz, DMSO) δ 11.82 (bs, 1H), 8.03 – 7.99 (m, 1H), 7.98 – 7.91 (m, 1H), 7.82 (dtd, *J* = 7.5, 1.6 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.29 – 7.20 (m, 2H), 6.94 – 6.83 (m, 2H), 6.41 (d, *J* = 9.9 Hz, 1H), 3.81 (dt, *J* = 5.4, 2.7 Hz, 2H), 3.06 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 185.9 (C=O), 182.5 (C=O), 159.7 (NH-C=O), 156.9 (C-OH), 142.4 (C), 135.8 (CH), 134.4 (CH), 133.7 (C), 132.3 (2 x CH), 131.5 (C), 129.3 (2 x CH), 127.3 (CH), 127.0 (CH), 123.4 (C), 121.5 (C-Br), 81.7 (C), 71.9 (CH), 49.1 (CH) 30.3 (CH_2). HRMS calcd for $C_{21}H_{16}N_2O_4Br^+$ $[M + H]^+$ = 439.0293; found 439.0288 with consistent isotopic profile.

3-[(4'-nitrophenyl)methyl-(N'-propargyl)-urea]-2-hydroxynaphthalene-1,4-dione, **24**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 2 cycles x 40 min. The crude product was purified by crystallization in DCM/Et_2O to yield 398 mg (70%) of the target product as a brownish solid (mp 170−172 °C). *Rf* (Hex/AcOEt 3:7) = 0.14. ^{1}H NMR (400 MHz, MeOD) δ 11.88 (bs, 1H), 8.22 – 8.12 (m, 2H), 8.09 – 8.05 (m, 1H), 8.05 – 7.99 (m, 1H), 7.81 – 7.71 (m, 2H), 7.65 – 7.60 (m, 2H), 6.68 (s, 1H), 3.93 (dd, *J* = 3.7, 2.5 Hz, 2H), 2.55 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 185.8 (C=O), 182.4 (C=O), 159.6 (NH-C=O C), 157.2 (C-OH), 151.0 (C), 148.2 (C), 135.8 (CH), 134.5 (CH), 133.6 (C), 131.6 (C), 128.3 (2 x CH), 127.3 (CH), 127.1 (CH), 124.4 (2 x CH), 122.8 (C), 81.6 (C), 72.0 (CH), 49.2 (CH), 30.3 (CH_2). HRMS calcd for $C_{21}H_{16}N_3O_6^+$ $[M + H]^+$ = 406.1039; found 406.1037 with consistent isotopic profile.

3-[(4'-trifluoromethylphenyl)methyl-(N'-propargyl)-urea]-2-hydroxynaphthalene-1,4-dione, **25**

The compound was synthesized by following the above-mentioned general procedure (1.0 mmol of lawsone scale). Ball milling for 2 cycles x 40 min. The crude product was purified by crystallization in DCM to yield 351 mg (82%) of the target product as a yellow solid (mp 169−171 °C). *Rf* (Hex/AcOEt 7:3) = 0.06. ^{1}H NMR (400 MHz, DMSO) δ 8.03 – 8.00 (m, 1H), 7.95 – 7.92 (m, 1H), 7.82 (dtd, *J* = 18.3, 7.5, 1.6 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (dd, *J* = 8.0, 0.9 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 1H), 6.92 (t, *J* = 5.6 Hz, 1H), 6.52 (d, *J* = 9.2 Hz, 1H), 3.85 – 3.80 (m, 2H), 3.07 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 184.0 (C=O), 181.3 (C=O), 156.9 (NH-C=O), 156.3 (C-OH), 147.4 (C), 134.7 (CH), 133.4 (CH), 131.8 (C), 130.2 (C), 127.1 (d, *J* = 39.4 Hz, C), 126.5 (2 x CH), 125.9 (CH), 125.7 (CH), 125.0 (q, *J* = 3.0 Hz, 2 x CH), 124.4 (q, *J* = 231.7 Hz, CF_3), 121.9 (C), 82.2 (C),

72.8 (CH), 46.8 (CH), 28.8 (CH_2). ^{19}F NMR (376 MHz, DMSO) δ -60.73. HRMS calcd for $C_{22}H_{14}N_2O_4F_3^-$ $[M - H]^-$ = 427.0906; found 427.0902 with consistent isotopic profile.

3-[(4'-chlorophenyl)methyl-(N-2-hydroxyethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **26**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM/MeOH/Et_2O to yield 449 mg (80%) of the target product as a yellow-orange solid (mp 85-87 °C). *Rf* (Hex/AcOEt 3:7) = 0.08. ^1H NMR (300 MHz, MeOD) *δ* 8.05 – 7.95 (m, 2H), 7.72 (dtd, *J* = 7.5, 1.6 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.30 – 7.23 (m, 2H), 6.56 (s, 1H), 3.58 (t, *J* = 5.6 Hz, 2H), 3.26 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) *δ* 185.9 (C=O), 182.5 (C=O), 160.5 (NH-C=O), 156.8 (C-OH), 142.0 (C), 135.8 (CH), 134.3 (CH), 133.7 (C), 133.5 (C-Cl), 131.5 (C), 129.2 (2 x CH), 128.9 (2 x CH), 127.2 (CH), 127.0 (CH), 123.7 (C), 62.6 (CH_2), 49.0 (CH), 43.5 (CH_2). HRMS calcd for $C_{20}H_{16}N_2O_5Cl^-$ $[M - H]^-$ = 399.0748; found 399.0750 with consistent isotopic profile.

3-[(4'-nitrophenyl)methyl-(N-2-hydroxyethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **27**

The compound was synthesized by following the above-mentioned general procedure (1.4 mmol of lawsone scale). Ball milling for 2 cycles x 50 min. The crude product was purified by crystallization in DCM/MeOH/Et_2O to yield 472 mg (82%) of the target product as a yellow solid (mp 184−186 °C). *Rf* (Hex/AcOEt 3:7) = 0.08. ^1H NMR (400 MHz, DMSO) *δ* 8.16 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.89 – 7.77 (m, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 9.4 Hz, 1H), 6.69 (bs, 1H), 6.55 (d, *J* = 9.4 Hz, 1H), 3.42 – 3.33 (m, 2H), 3.09 (t, *J* = 5.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) *δ* 183.9 (C=O), 181.2 (C=O), 157.5 (NH-C=O), 156.2 (C-OH), 151.0 (C), 146.1 (C), 134.8 (CH), 133.4 (CH), 131.7 (C), 130.1 (C), 127.0 (2 x CH), 125.9 (C), 125.7 (C), 123.3 (2 x CH), 121.9 (C), 60.7 (CH_2), 46.7 (CH), 42.3 (CH_2). HRMS calcd for $C_{20}H_{18}N_3O_7^+$ $[M + H]^+$ = 412.1145; found 412.1141 with consistent isotopic profile.

3-[(4'-trifluoromethylphenyl)methyl-(N-2-hydroxyethyl)-urea]-2-hydroxynaphthalene-1,4-dione, **28**

The compound was synthesized by following the above-mentioned general procedure (2.0 mmol of lawsone scale). Ball milling for 2 cycles x 60 min. The crude product was purified by crystallization in DCM to yield 690 mg (80%) of the target product as a yellow solid (mp 167−169 °C). *Rf* (AcOEt) = 0.05. ^1H NMR (300 MHz, DMSO) *δ* 11.82 (bs, 1H), 8.06 – 7.99 (m, 1H), 7.94 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.83 (dtd, *J* = 7.4, 1.6 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.69 (t, *J* = 6.1 Hz, 1H), 6.52 (d, *J* = 9.0 Hz, 1H), 3.48 – 3.25 (m, 2H), 3.09 (m, 2H). ^{13}C NMR (75 MHz, DMSO) *δ* 184.0 (C=O), 181.3 (C=O), 157.5 (NH-C=O), 156.1 (C-OH), 147.8 (C), 134.7 (CH), 13.4 (CH), 131.8 (C), 130.2 (C), 127.0 (d, *J* = 31.5 Hz, C), 126.6 (2 x CH), 125.9 (CH), 125.7 (CH), 125.0 (q, *J* = 3.8 Hz, 2 x CH), 124.8 (q, *J* = 272.1 Hz, CF_3), 122.3 (C), 60.7 (CH_2), 46.7 (CH), 42.2 (CH_2). HRMS calcd for $C_{21}H_{16}N_2O_5F_3^-$ $[M - H]^-$ = 433.1011; found 433.1020 with consistent isotopic profile.

2.3 SYNTHESIS OF MICHAEL ADDUCT 29.

Compound **9** (1.3 mmol) was added in 3 mL ionic liquid $[HNMP]^+[HSO_4]^-$ media and was stirred at 80 °C for 60 min, until it turned into a brown solid. Then, iced water was added and the resulting suspension stayed under vigorous stirring for 10 min. The red solid was isolated by filtration and washed with excess of water. Afterwards, the crude product was purified by recrystallization in EtOH and washed with cold (0°C) Et_2O to

afford 238 mg of **29** as an orange solid (yield 40%, mp 202−204 °C). *Rf* (Hex/AcOEt 1:1) = 0.11. ^{1}H NMR (400 MHz, DMSO) δ 8.00 – 7.96 (m, 2H), 7.94 – 7.91 (m, 2H), 7.80 (dtd, *J* = 18.9, 7.4, 1.5 Hz, 4H), 7.29 – 7.22 (m, 2H), 7.04 – 6.95 (m, 2H), 5.98 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 183.5 (2 x C), 181.3 (2 x C), 160.5 (d, *J* = 243.8 Hz, C-F), 156.6 (2 x C), 137.0 (d, *J* = 3.1 Hz, C), 134.6 (2 x CH), 133.1 (2 x CH), 132.2 (2 x C), 129.9 (2 x C), 129.8 (d, *J* = 8.2 Hz, 2 x CH), 126.0 (2 x CH), 125.6 (2 x CH), 123.0 (2 x C), 114.2 (d, *J* = 21.4 Hz, 2 x CH), 36.94 (CH). HRMS calcd for $C_{27}H_{15}O_6F^-$ [M - H]$^-$ = 453.0774; found 453.0781 with consistent isotopic profile.

2.4 CYCLIZATION: SYNTHESIS OF LAWSONE CARBAMATE 31.

Et_3N (1.75 mmol, 2.2 equiv) was added dropwise in a suspension of linear Biginelli compound **9** (0.80 mmol, 1 equiv) in 10 mL anhydrous DCM under inert argon atmosphere. To the providing red solution, a solution of *para*-nitrophenyl chloroformate (0.9 mmol, 1.1 equiv) in 5 mL anhydrous DCM was added dropwise. Bubbling was observed during the addition at this step. The reaction stayed under stirring at rt, overnight under inert argon atmosphere. The end of the reaction was controlled by TLC. The solvent was then removed under pressure and the residue was dissolved in AcOEt. The organic phase was then washed successively with 5% aqueous solution of citric acid, water and brine. The organic phase was collected, dehydrated by Na_2SO_4, filtered and condensated until dry. The crude product was first purified by PuriFlash column chromatography by using Hex/AcOEt (8:2) followed by Hex/AcOEt (7:3) as isocratic systems of eluents. The product was obtained pure after a second semi-prep HPLC purification (the byproduct *p*-nitrophenol has the same *Rf* and was 90% pure after the first attempt) by using a C18 column and a gradient system of 0.1% $HCOOH.H_2O$/ 0.1% $HCOOH.CH_3CN$ as eluent at 20% yield as yellow oil.

N-Ethyl-4-(P-fluorophenyl)-2,9,10-trioxo-3,4-dihydro-10H,9H,2H-1-oxa-3-azaanthracene-3-carboxamide, **31**

Rf (Hex/AcOEt 8:2) = 0.20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (t, *J* = 5.6 Hz, 1H), 8.20 – 8.13 (m, 1H), 8.08 – 8.01 (m, 1H), 7.81 – 7.73 (m, 2H), 7.49 – 7.40 (m, 2H), 7.08 – 6.98 (m, 2H), 6.84 (s, 1H), 3.42 – 3.22 (m, 2H), 1.17 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9 (C=O), 176.3 (C=O), 163.0 (d, *J* = 248.0 Hz, C-F), 151.3 (NH-C=O), 148.5 (N-(C=O)-O), 147.5 (C-O), 135.0 (CH), 134.6 (CH), 134.0 (C), 131.3 (C), 130.7 (C), 129.5 (d, *J* = 8.0 Hz, 2 x CH), 127.1 (CH), 127.0 (CH), 123.3 (C), 116.3 (d, *J* = 21.0 Hz, 2 x CH), 52.6 (CH), 36.3 (CH_2), 14.7 (CH_3). HRMS calcd for $C_{21}H_{15}N_2O_5F^-$ [M - H]$^-$ = 394.0965; found 399.0969 with consistent isotopic profile.

3. ^{1}H, ^{13}C AND MS SPECTRAS OF BIGINELLI LINEAR LAWSONE DERIVATIVES.

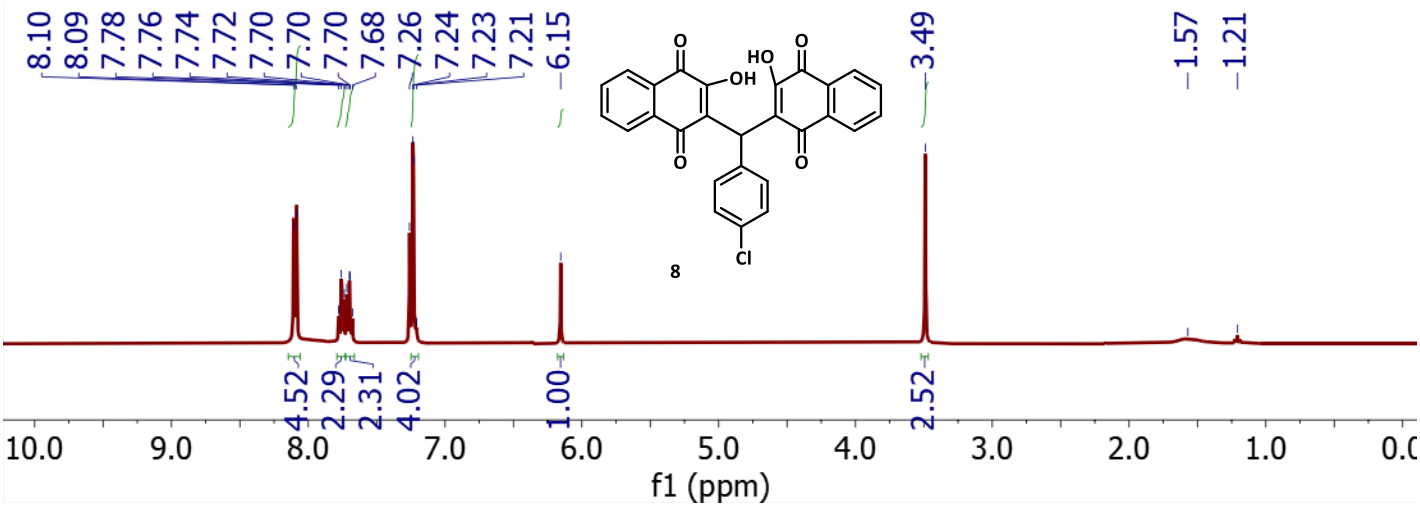


Figure S1: ^{1}H NMR (400 MHz, $CDCl_3$) of compound **8**

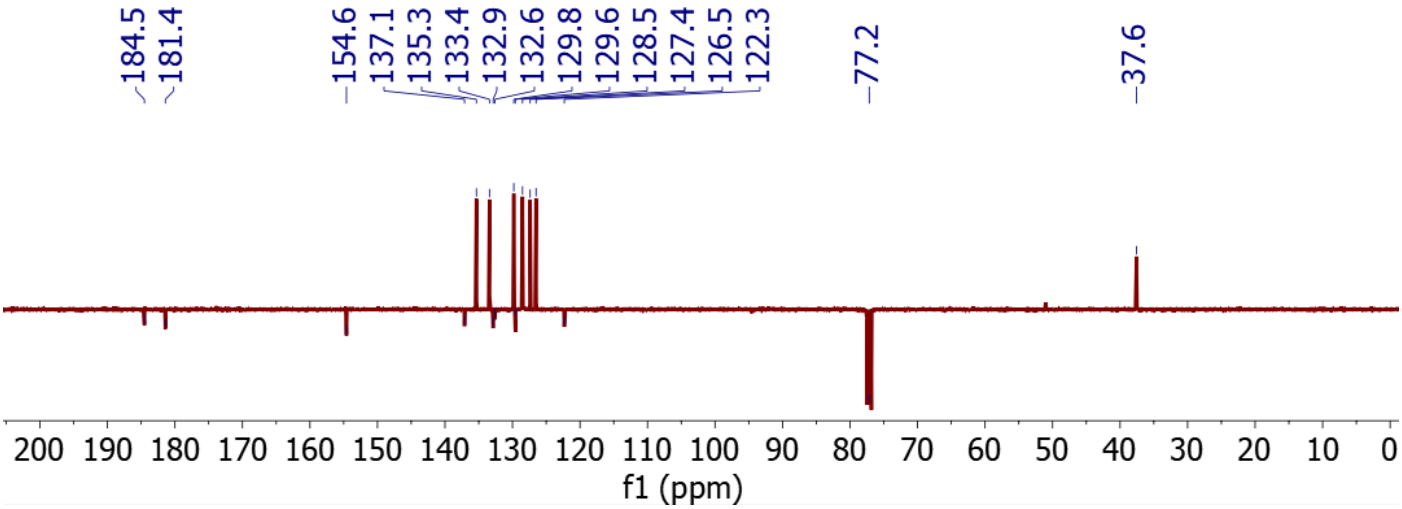


Figure S2: ^{13}C NMR (101 MHz, $CDCl_3$) of compound **8**

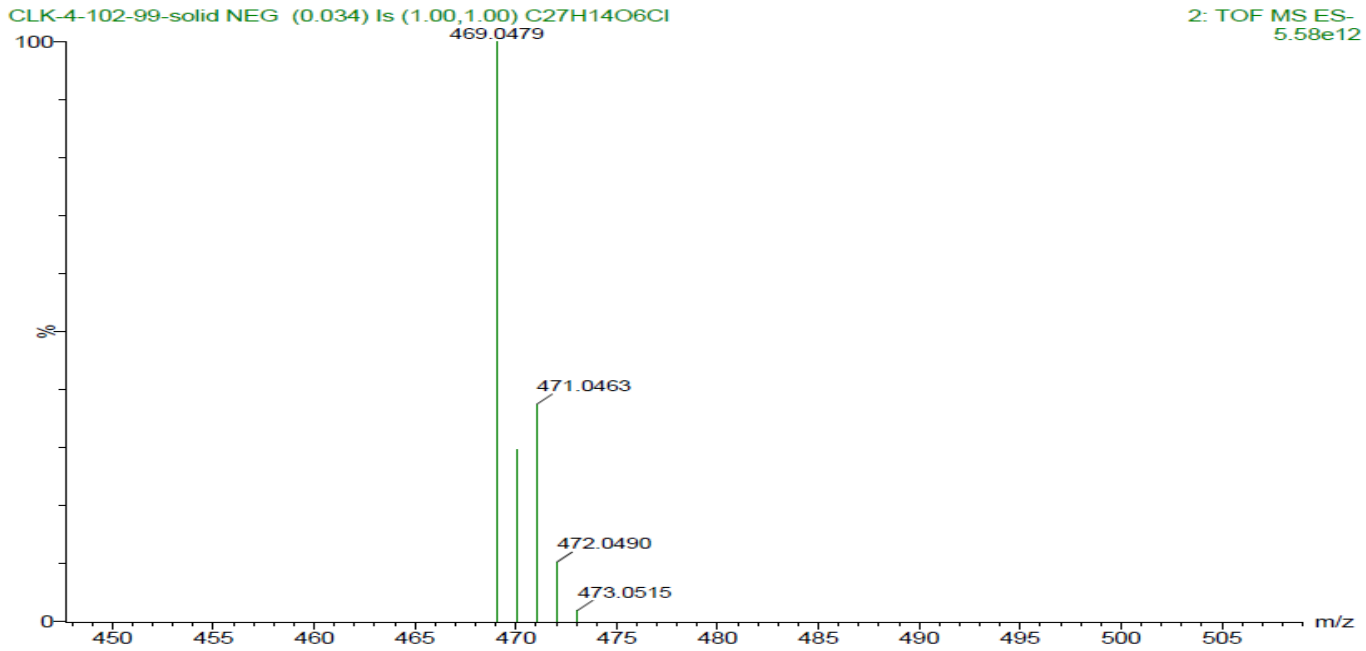


Figure S3: HRMS of compound **8**

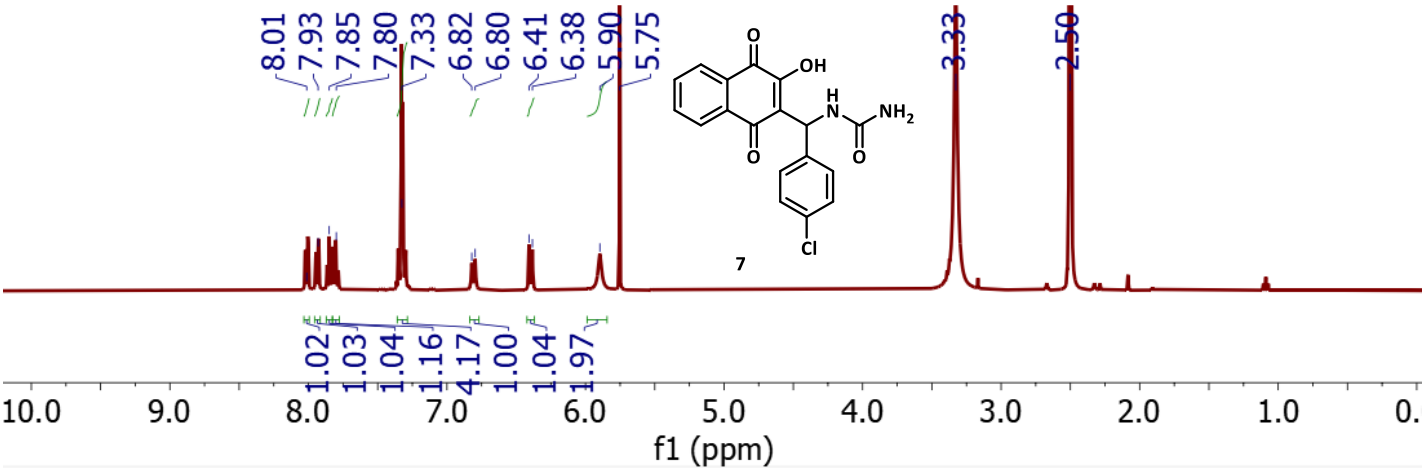


Figure S4: ^{1}H NMR (400 MHz, DMSO-d6) of compound **7**

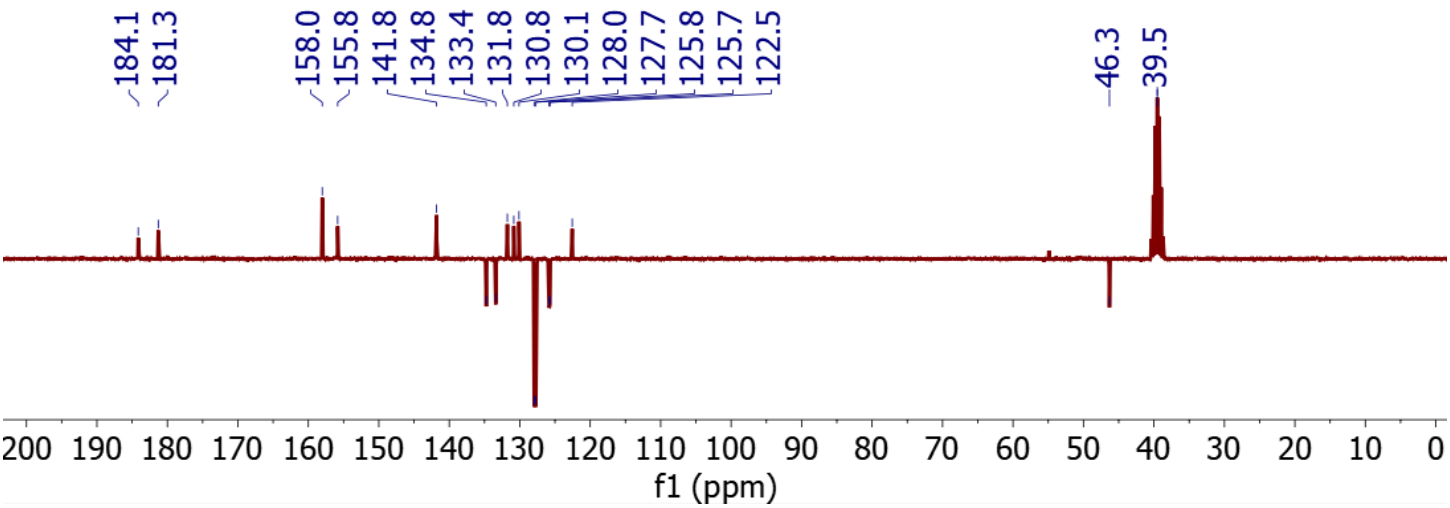


Figure S5: ^{13}C NMR (75 MHz, DMSO-d6) of compound **7**

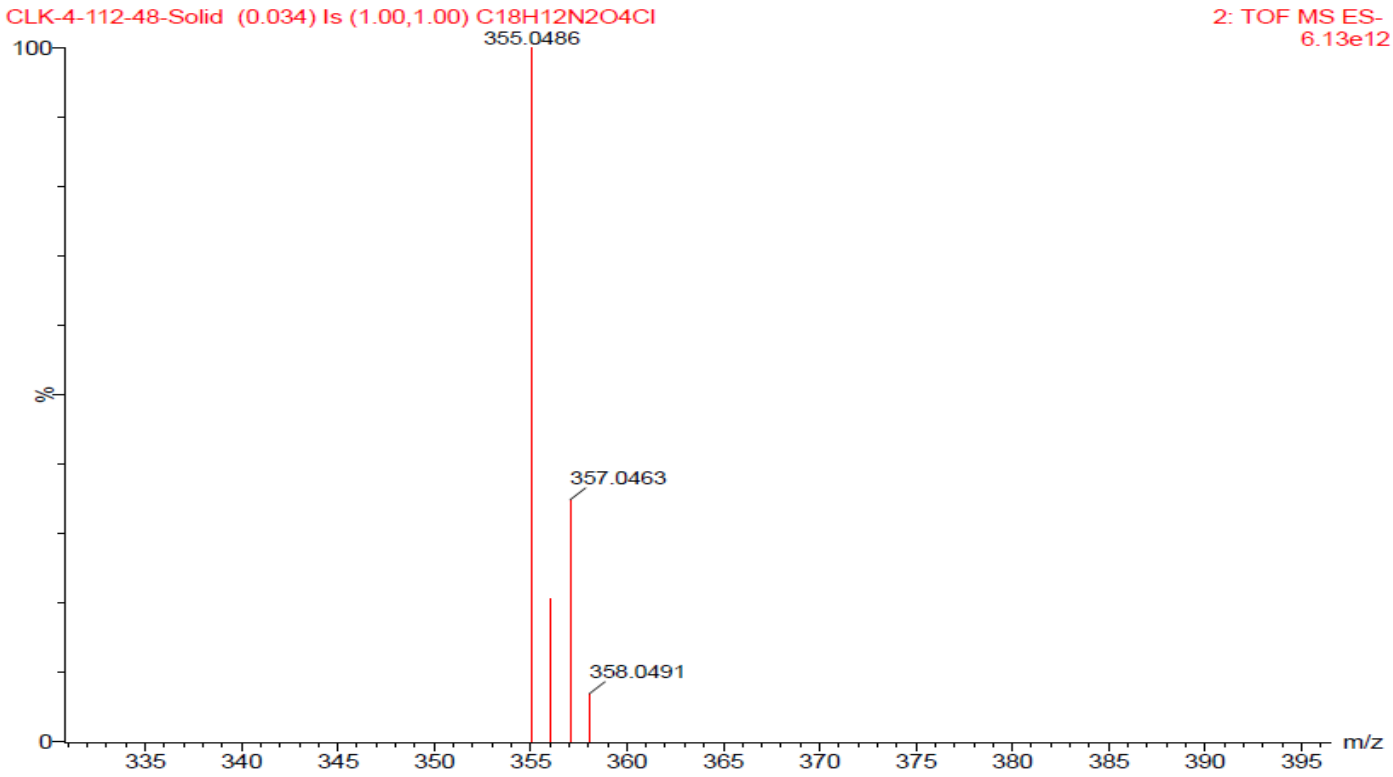
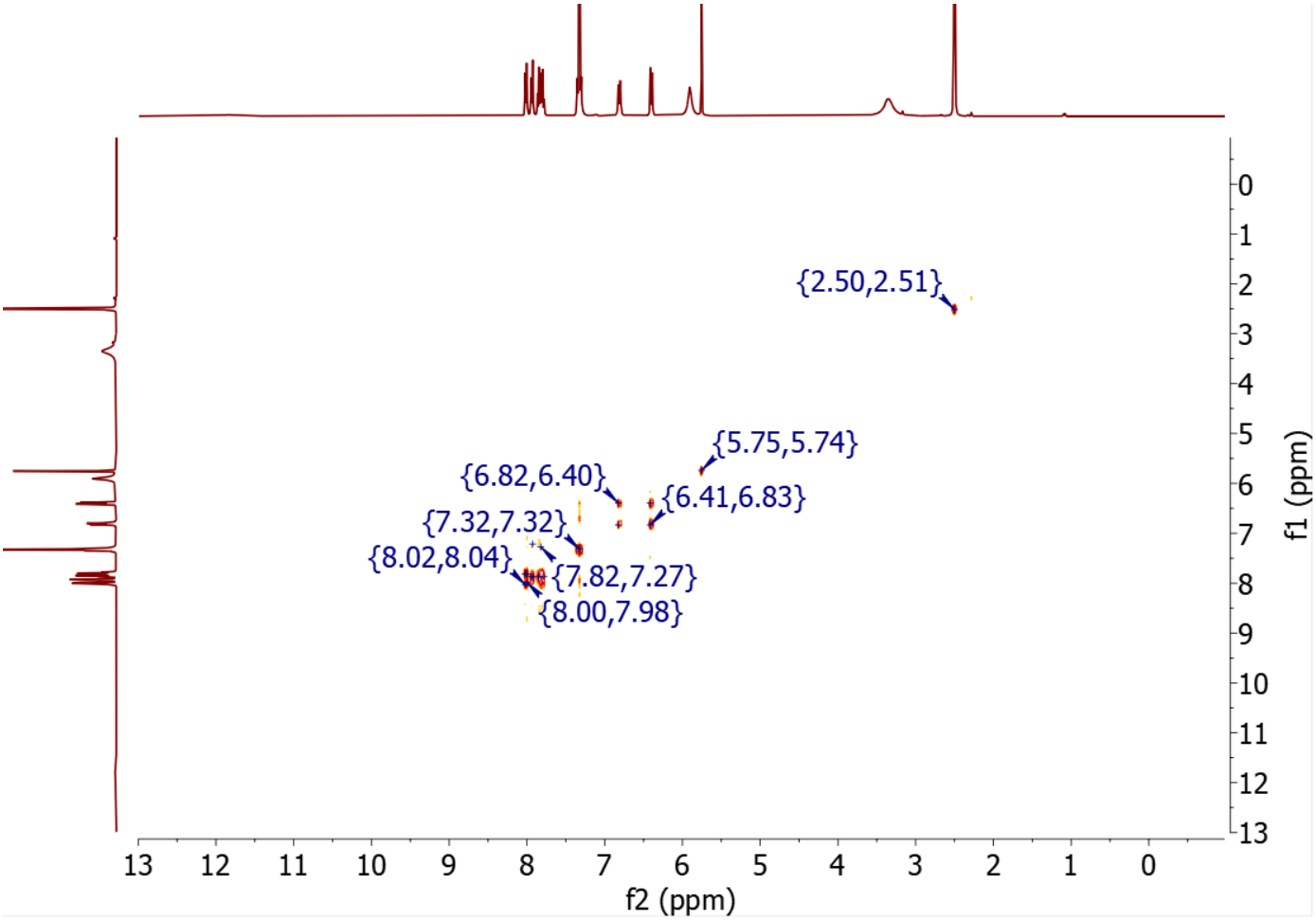


Figure S6: HRMS of compound **7**



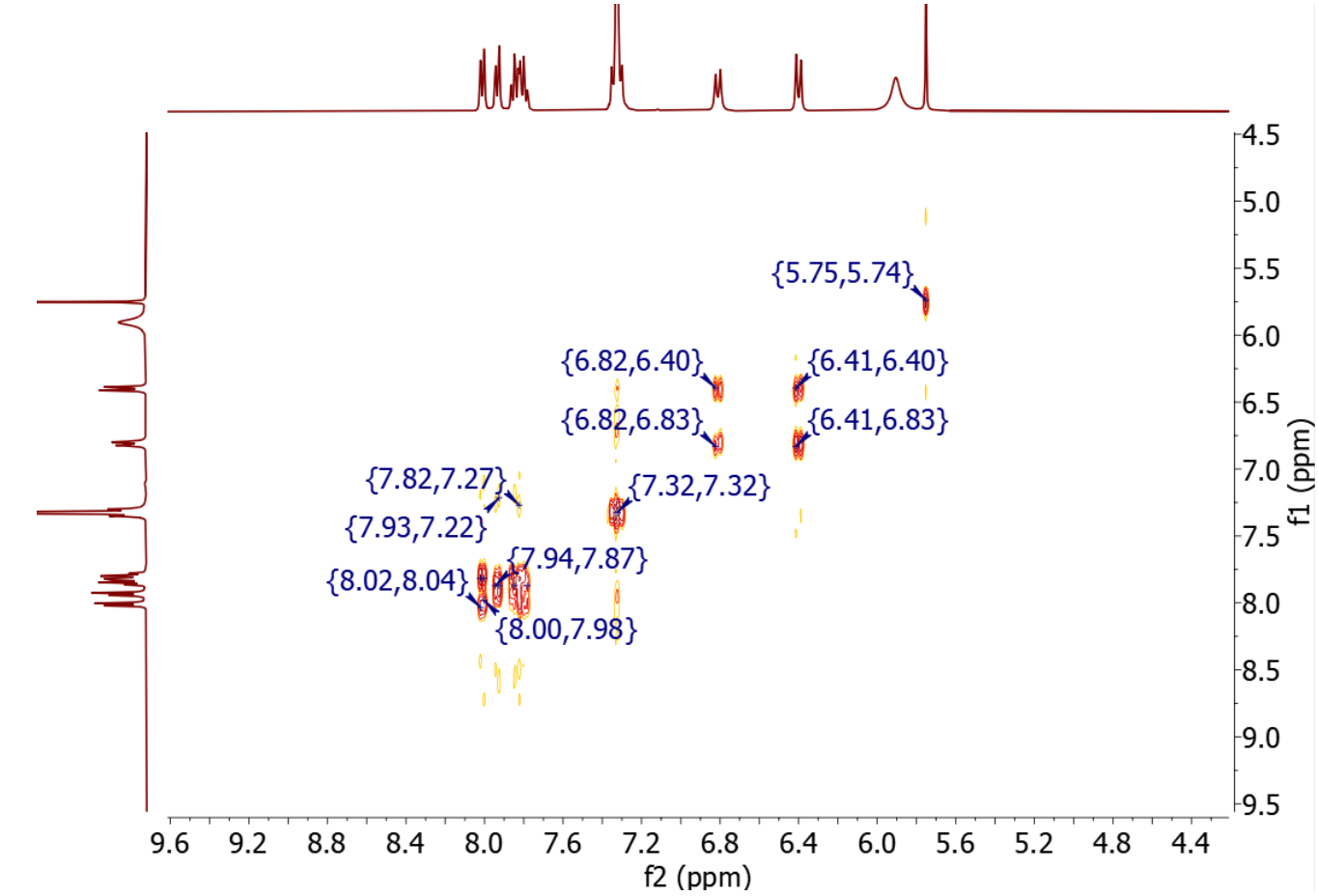


Figure S7: 2D COSY NMR (400 MHz, DMSO-d6) of compound **7**

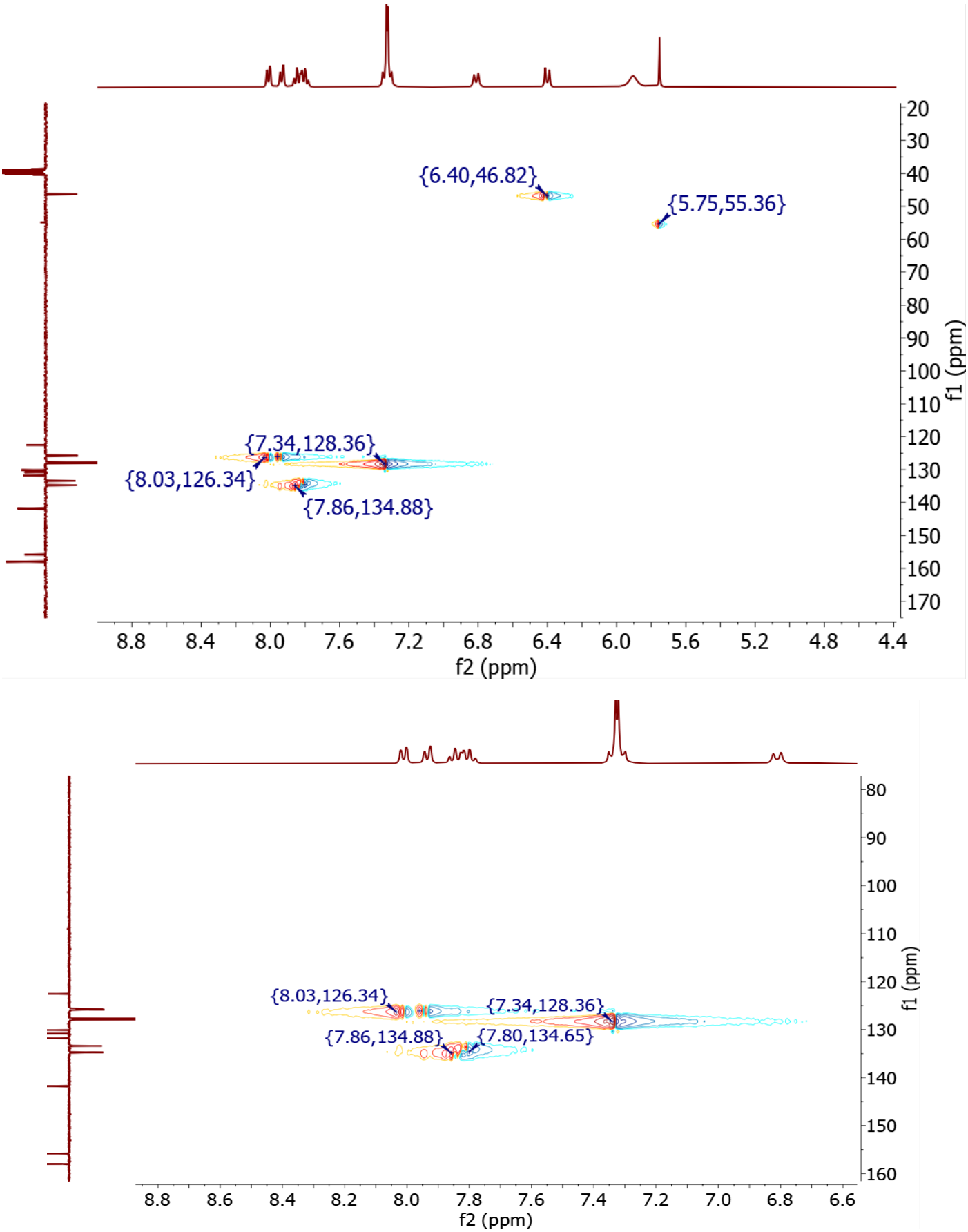
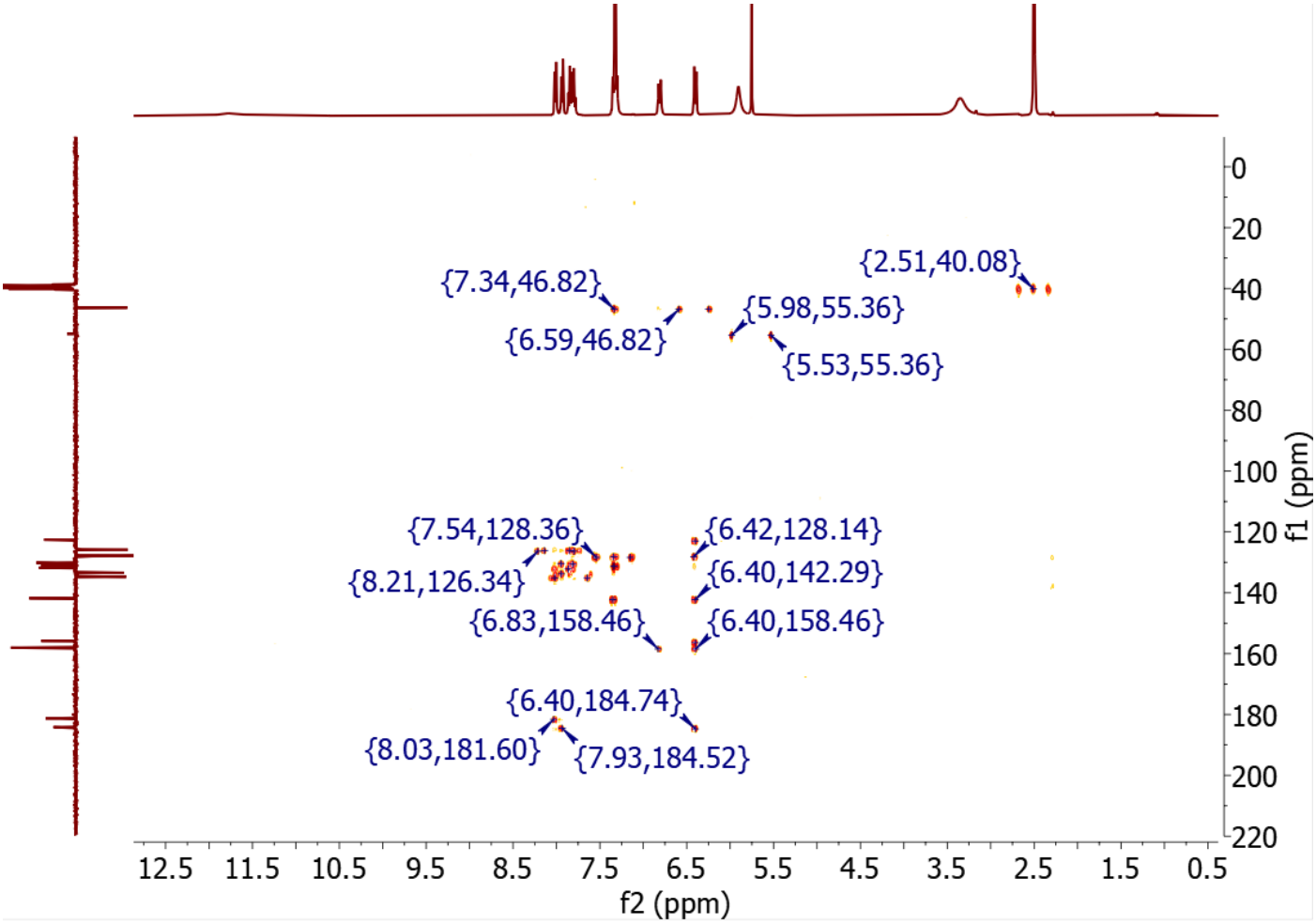


Figure S8: 2D HSQC NMR (400 MHz, DMSO-d6) of compound **7**



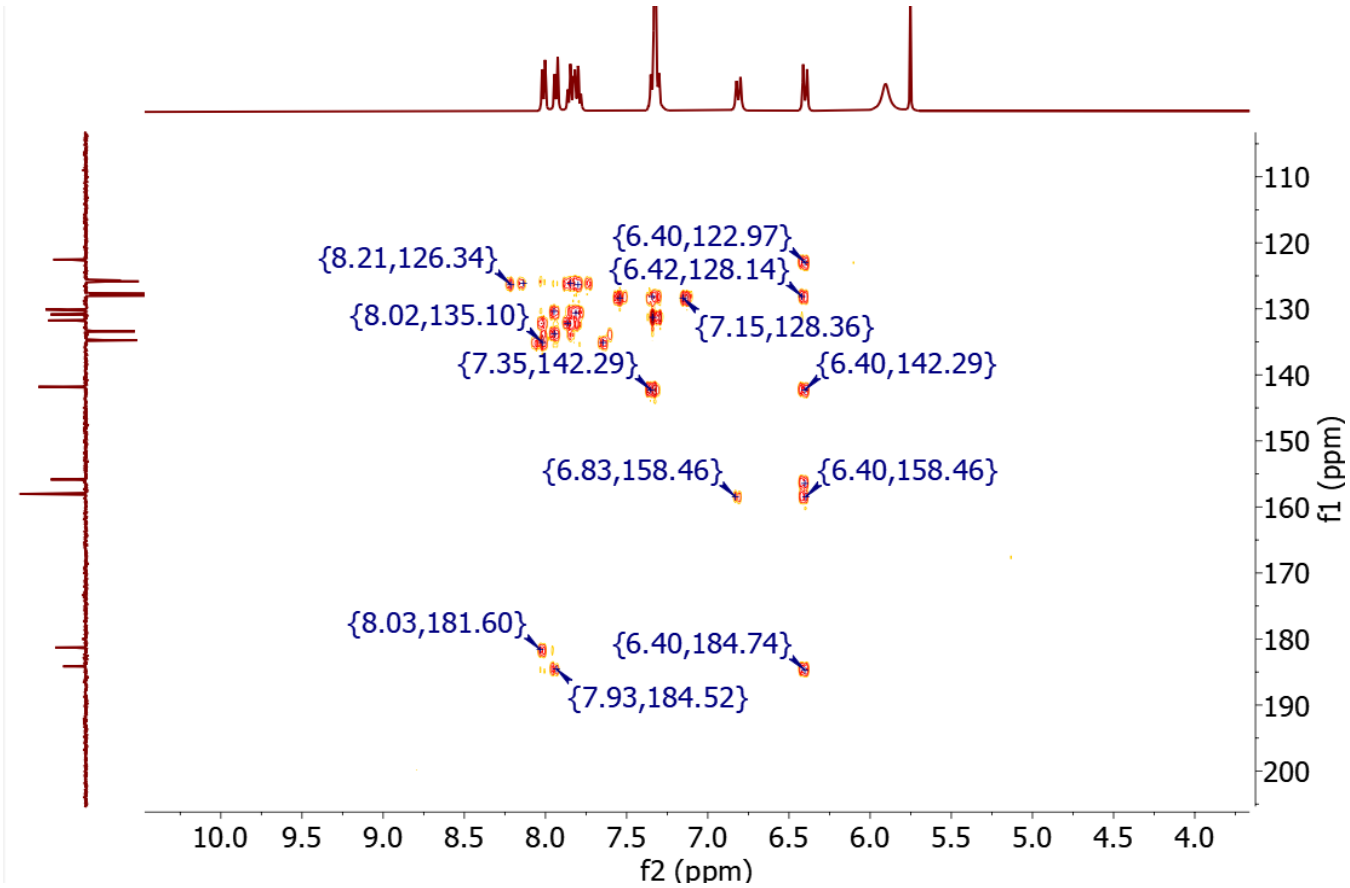
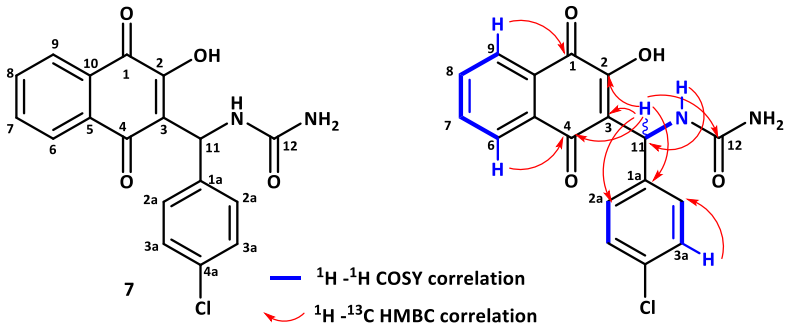


Figure S9: 2D HMBC NMR (400 MHz, DMSO-d6) of compound **7**

Table S1. ^{1}H and ^{13}C NMR data assignments of compound **7** in DMSO-d6 at 298K.



$^{1}H/^{13}C$ numbering	d^{1}H (ppm) in DMSO-d6	d^{13}C (ppm) in DMSO-d6
C-1		181.3
C-2		155.8
C-3		122.6
C-4		184.1
C-5		130.8
CH-6	7.80 (m)	125.8
CH-7	8.03 (m)	134.8
CH-8	7.90 (m)	133.4
CH-9	7.94 (dd)	125.7
C-10		130.1
CH-11	6.40 (d)	46.3
C-12		158.0
NH	6.82 (d)	
NH_2	5.88 (bs)	
C-1a		141.8
CH-2a	7.32 (m)	127.7
CH-3a	7.32 (m)	128.0
C-4a		131.8

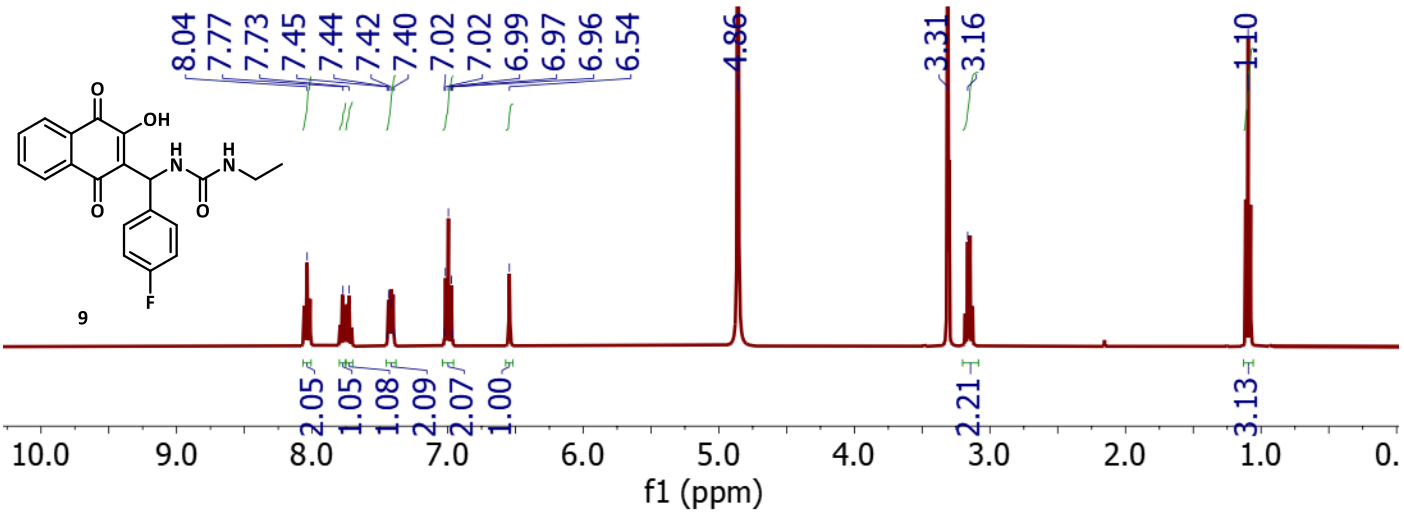


Figure S10: ^{1}H NMR (400 MHz, MeOD) of compound **9**

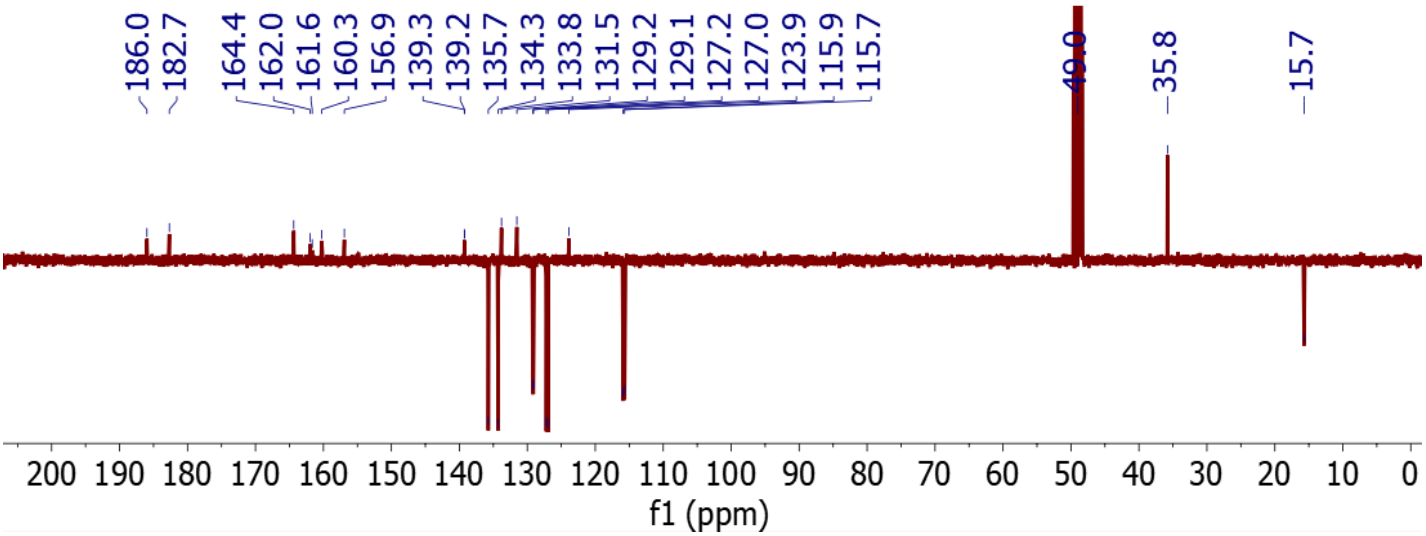


Figure S11: ^{13}C NMR (101 MHz, MeOD) of compound **9**

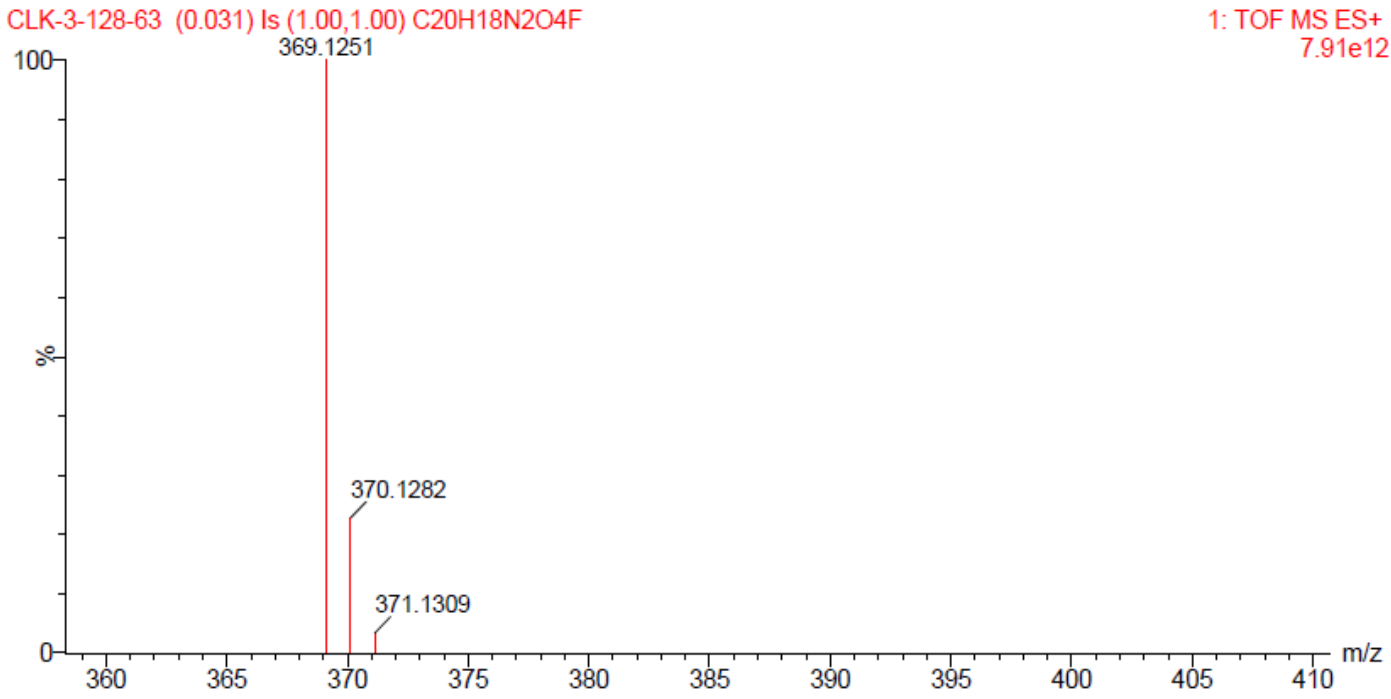


Figure S12: HRMS of compound **9**

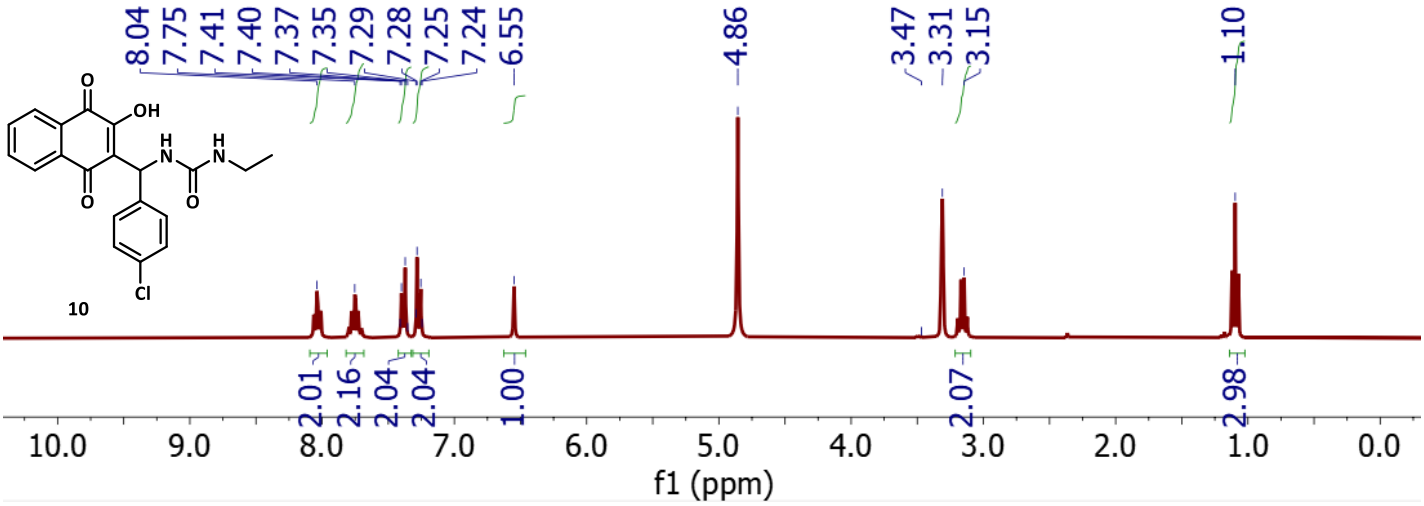


Figure S13: ^{1}H NMR (300 MHz, MeOD) of compound **10**

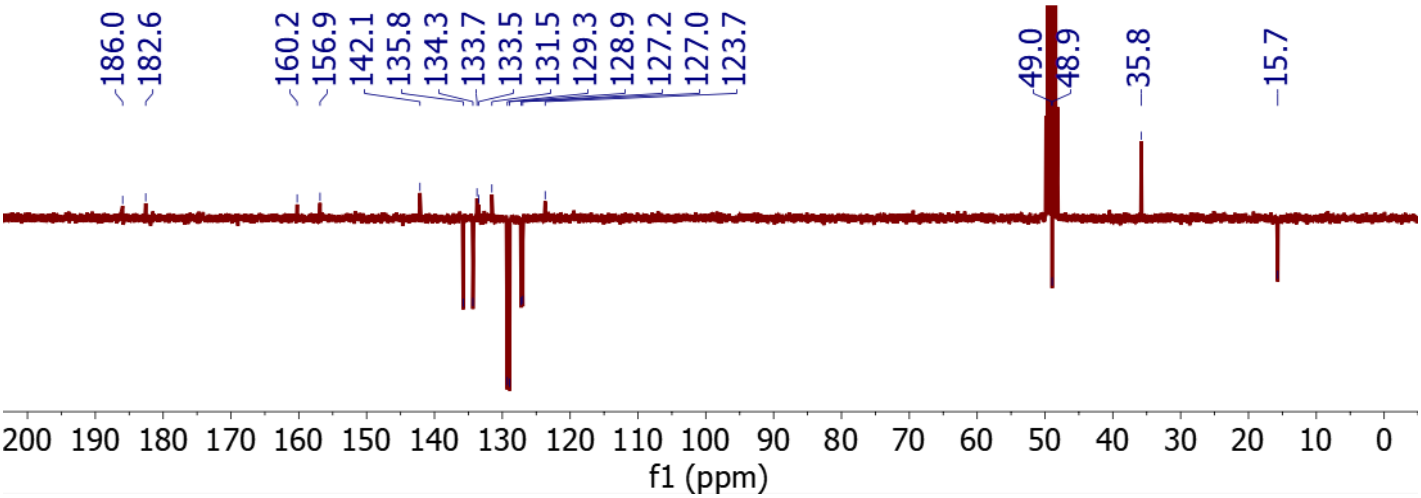


Figure S14: ^{13}C NMR (75 MHz, MeOD) of compound **10**

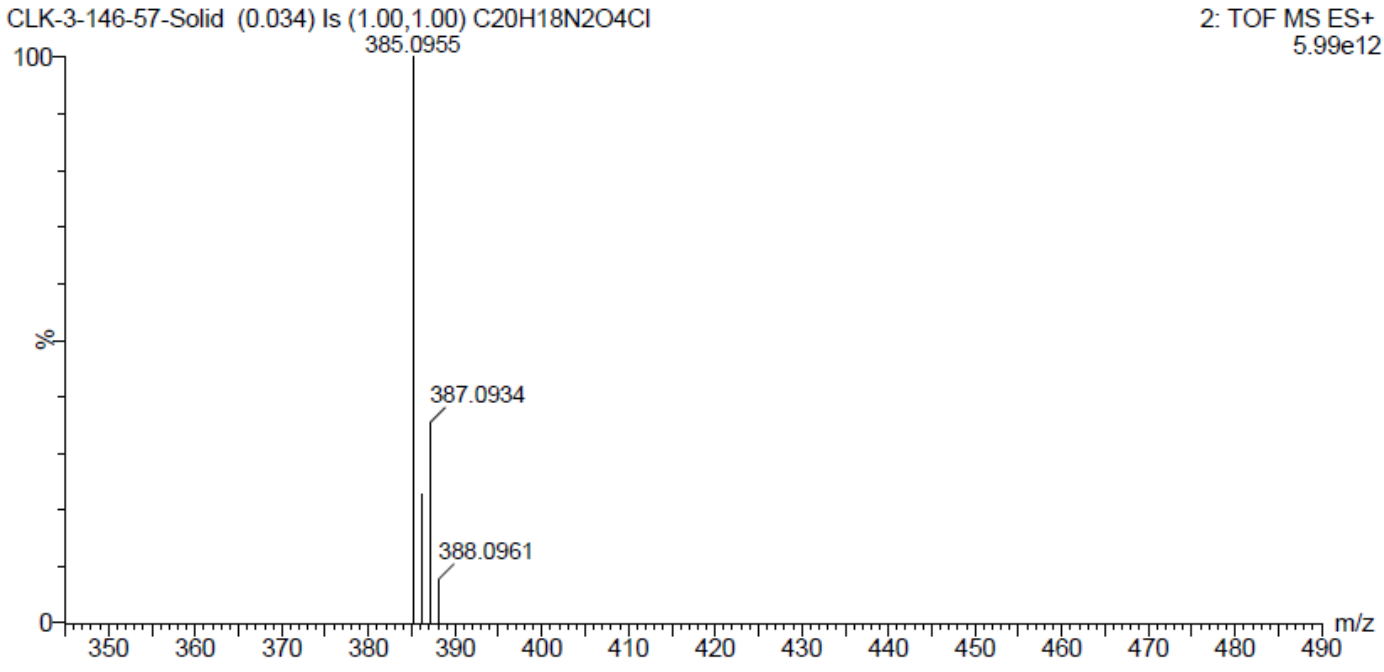


Figure S15: HRMS of compound **10**

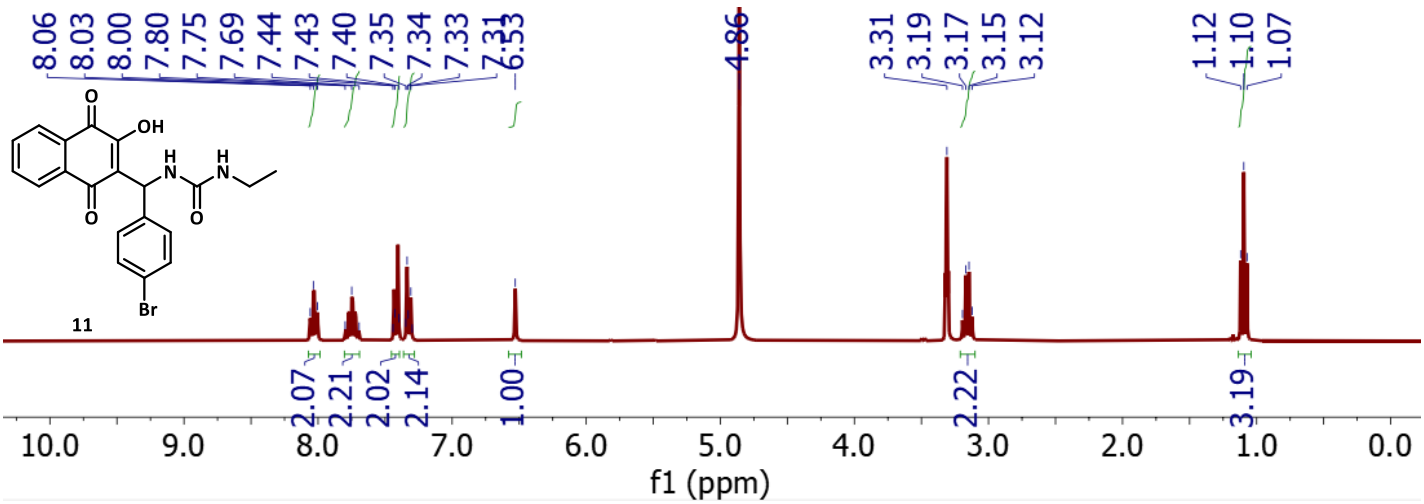


Figure S16: ^{1}H NMR (300 MHz, MeOD) of compound **11**

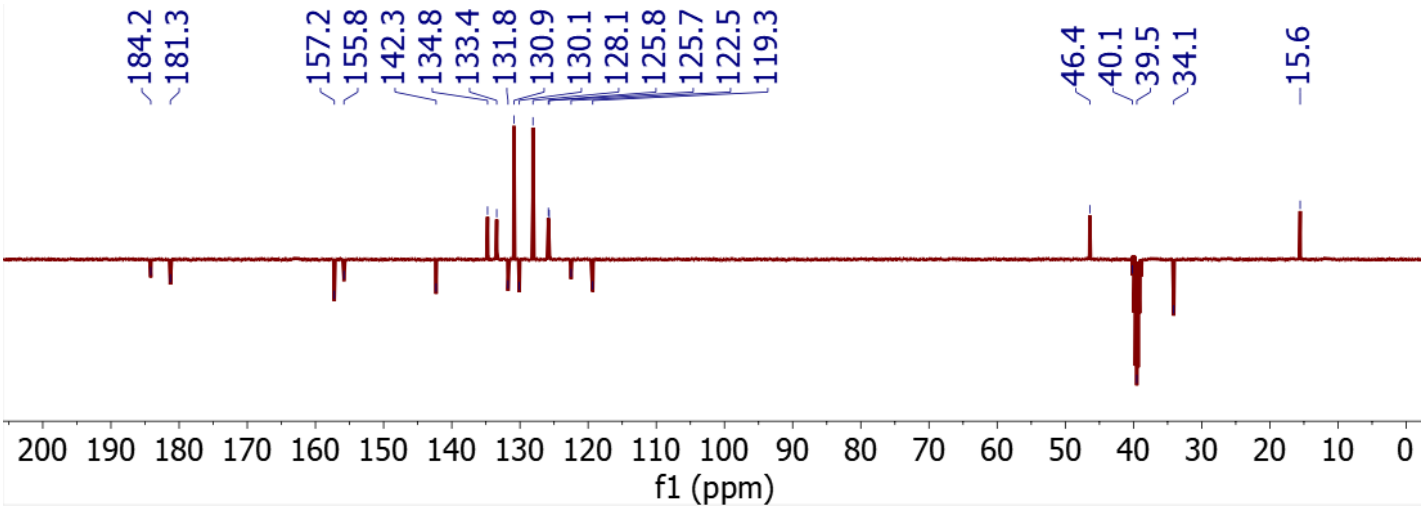


Figure S17: ^{13}C NMR (101 MHz, DMSO-d6) of compound **11**

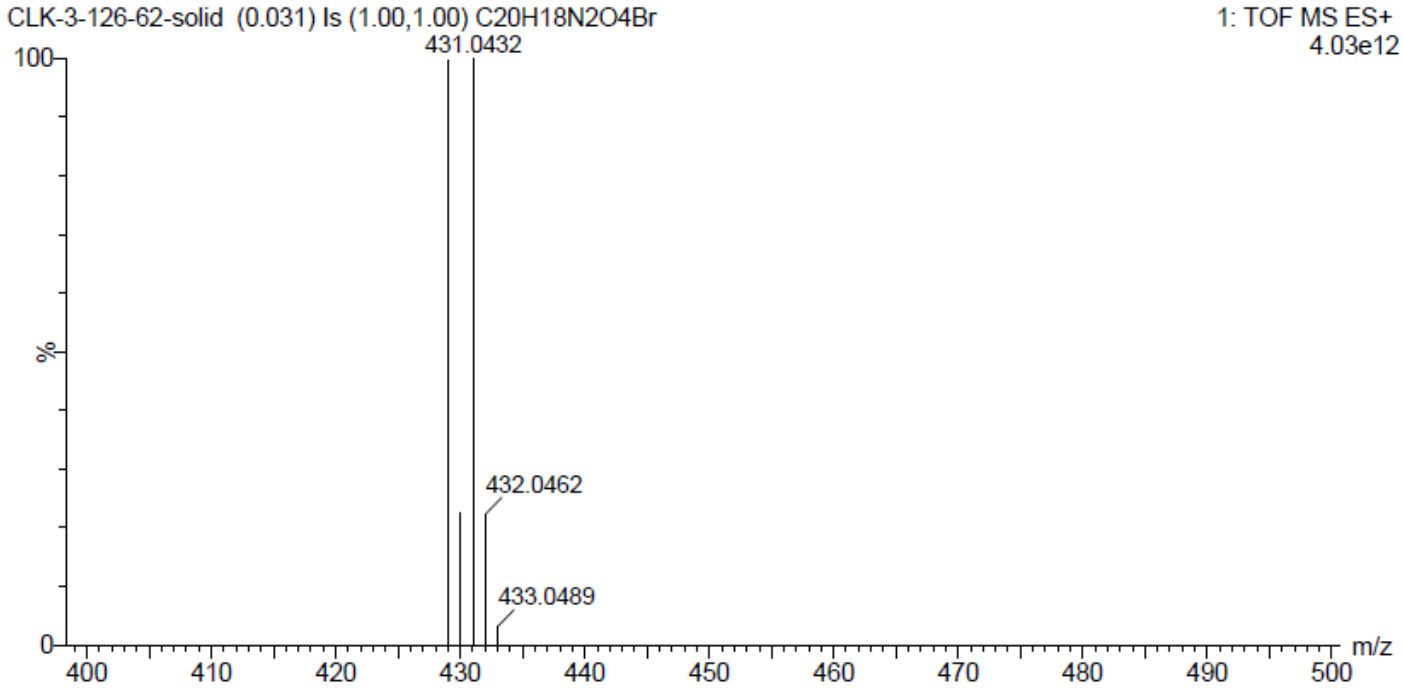


Figure S18: HRMS of compound **11**

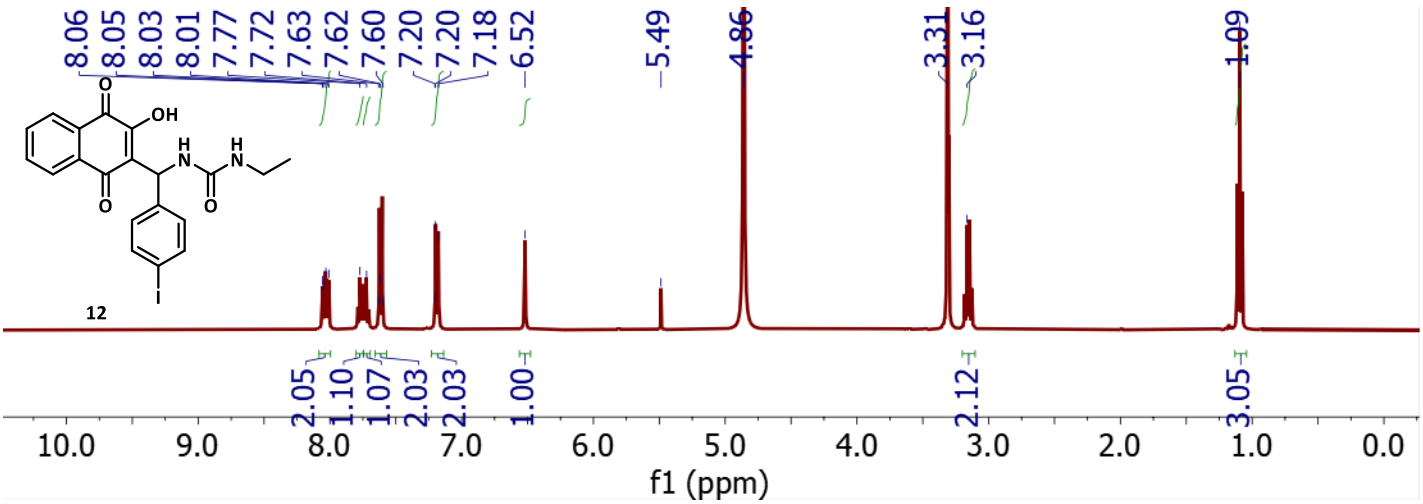


Figure S19: ^{1}H NMR (400 MHz, MeOD) of compound **12**

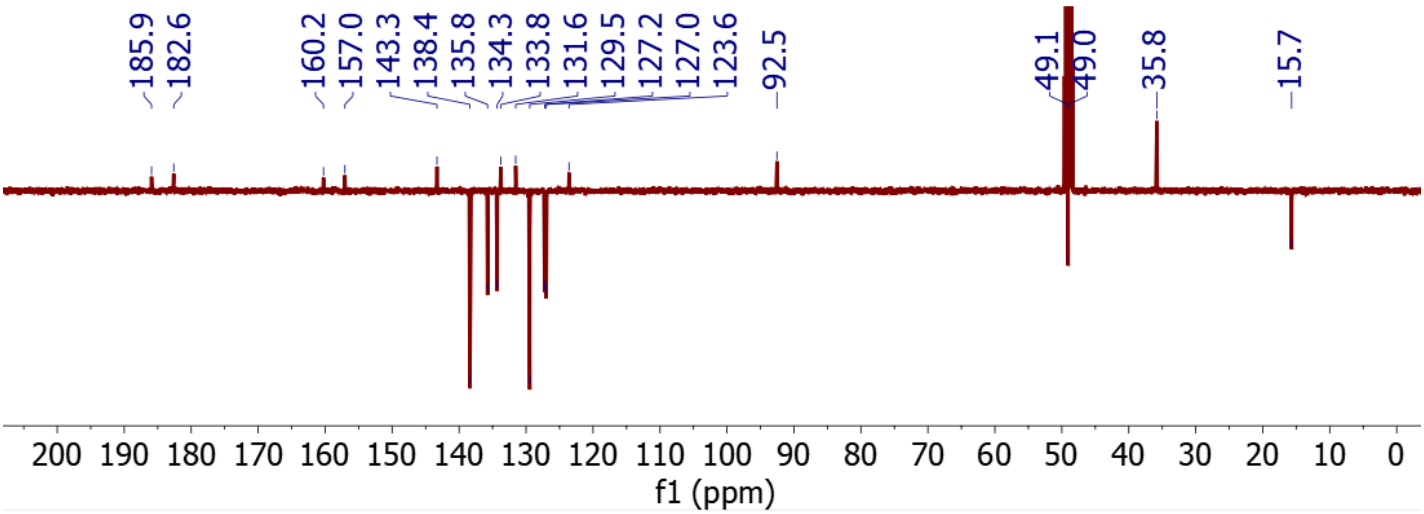


Figure S20: ^{13}C NMR (101 MHz, MeOD) of compound **12**

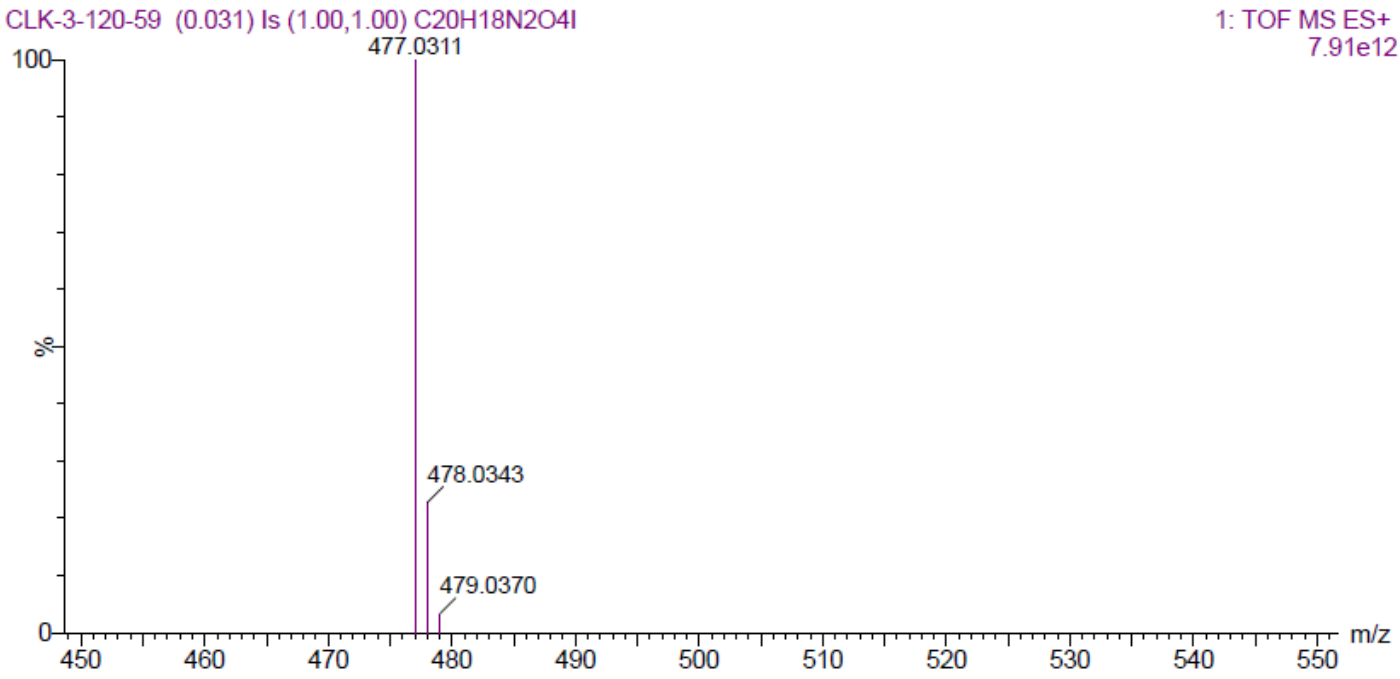


Figure S21: HRMS of compound **12**

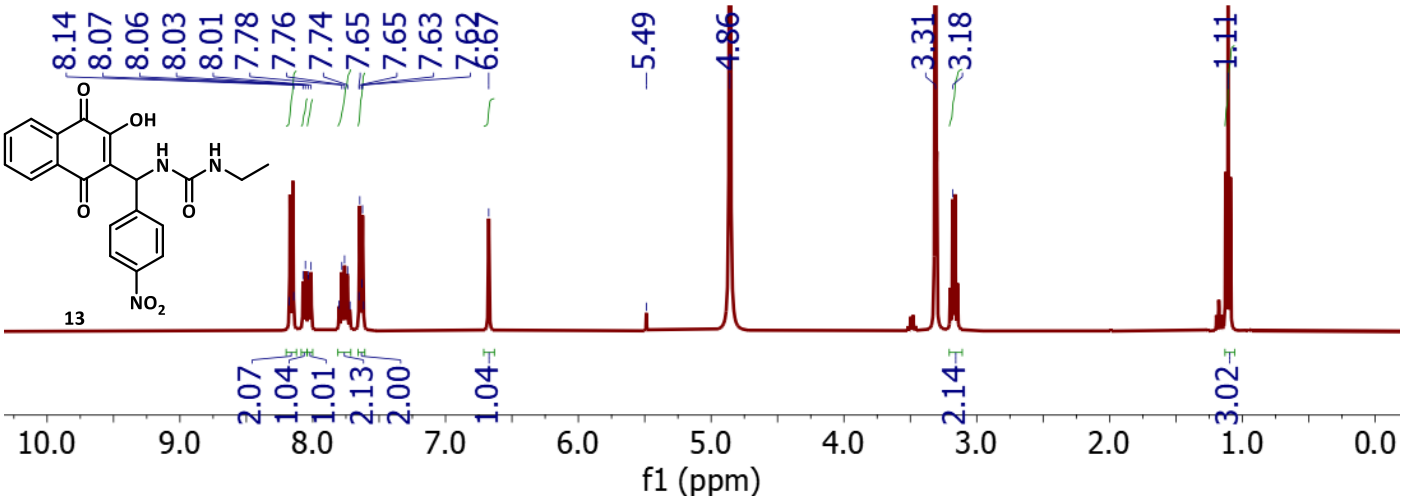


Figure S22: ^{1}H NMR (400 MHz, MeOD) of compound **13**

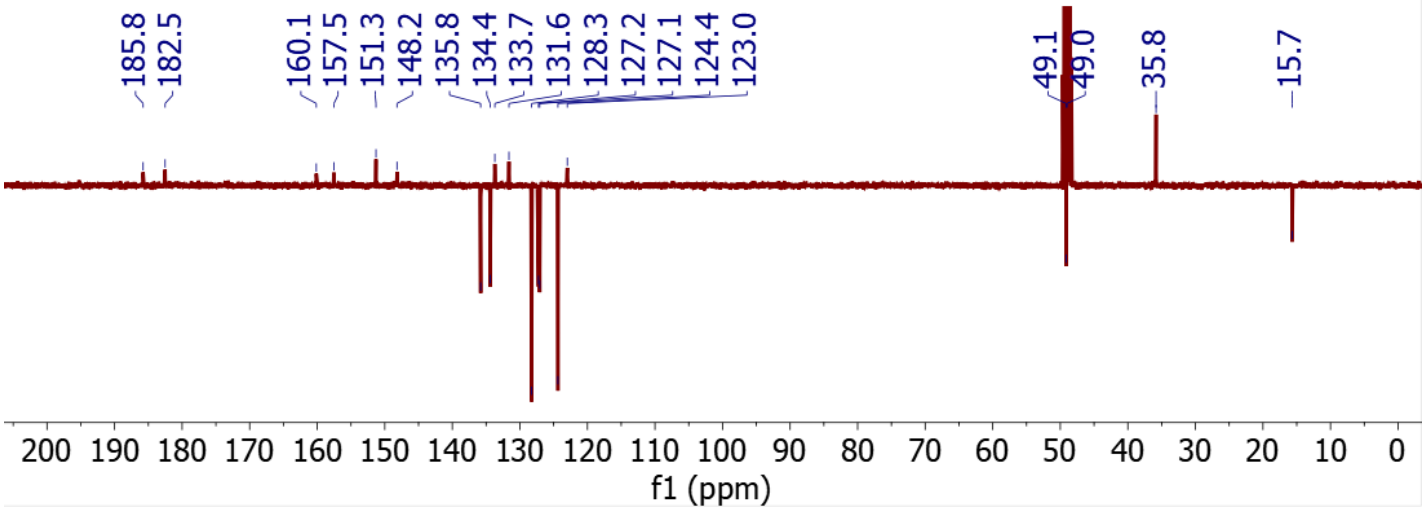


Figure S23: ^{13}C NMR (101 MHz, MeOD) of compound **13**

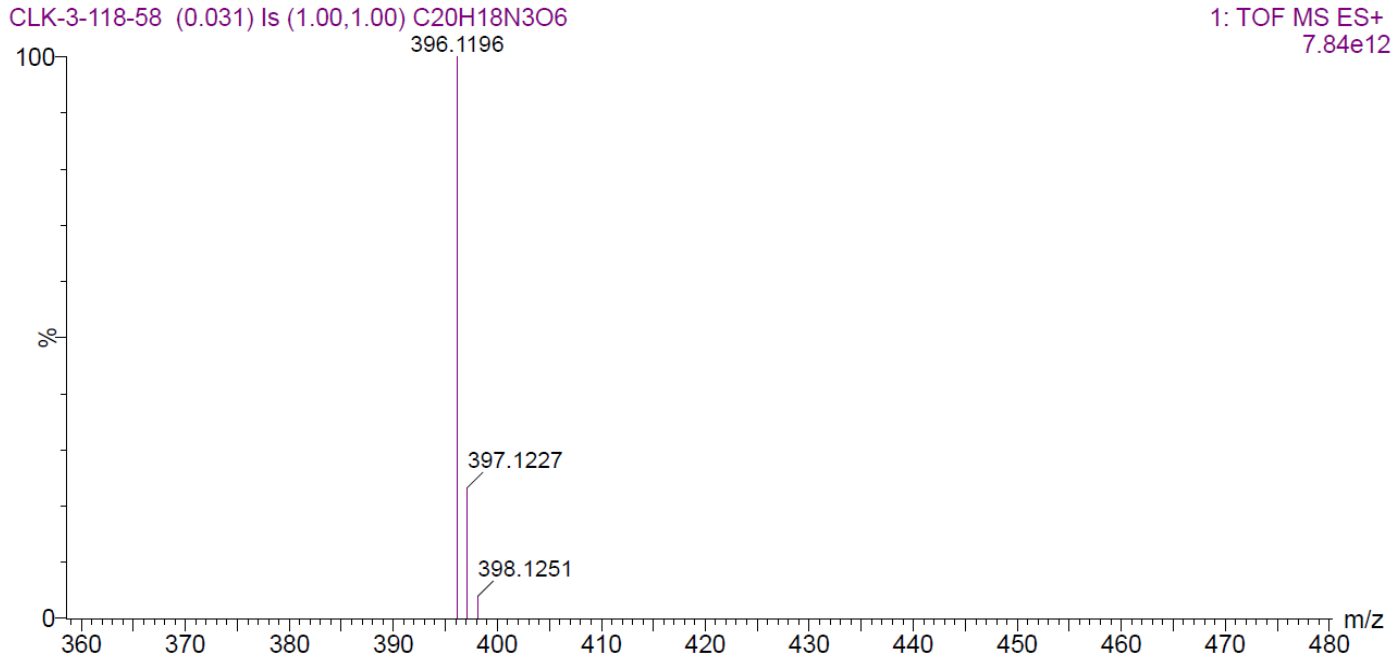


Figure S24: HRMS of compound **13**

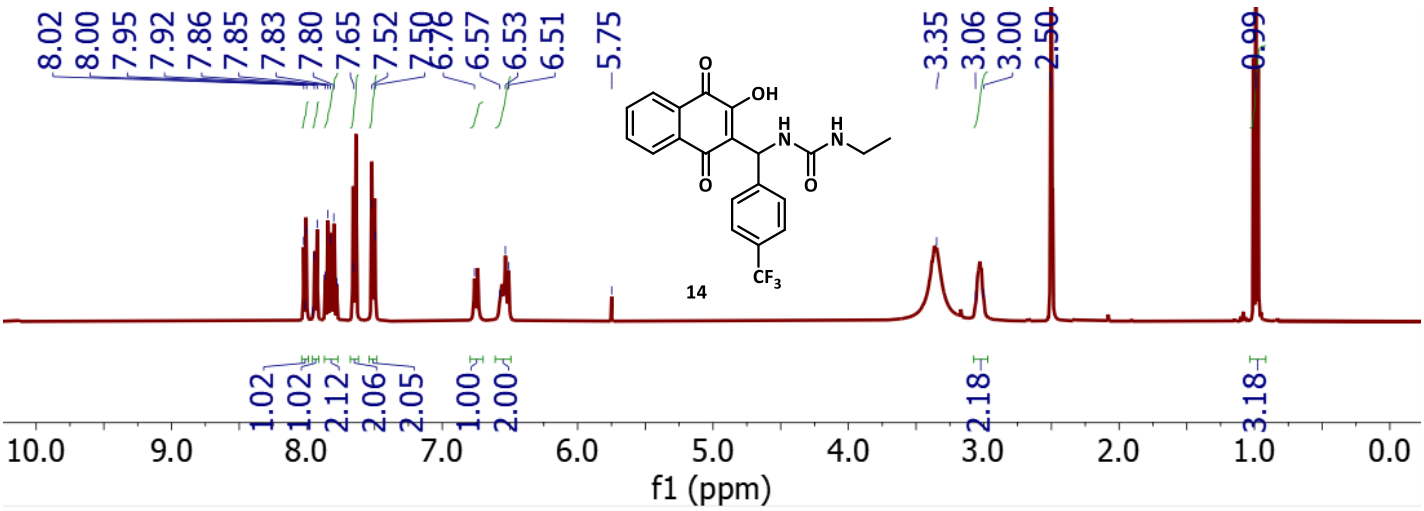


Figure S25: ^{1}H NMR (400 MHz, DMSO-d6) of compound **14**

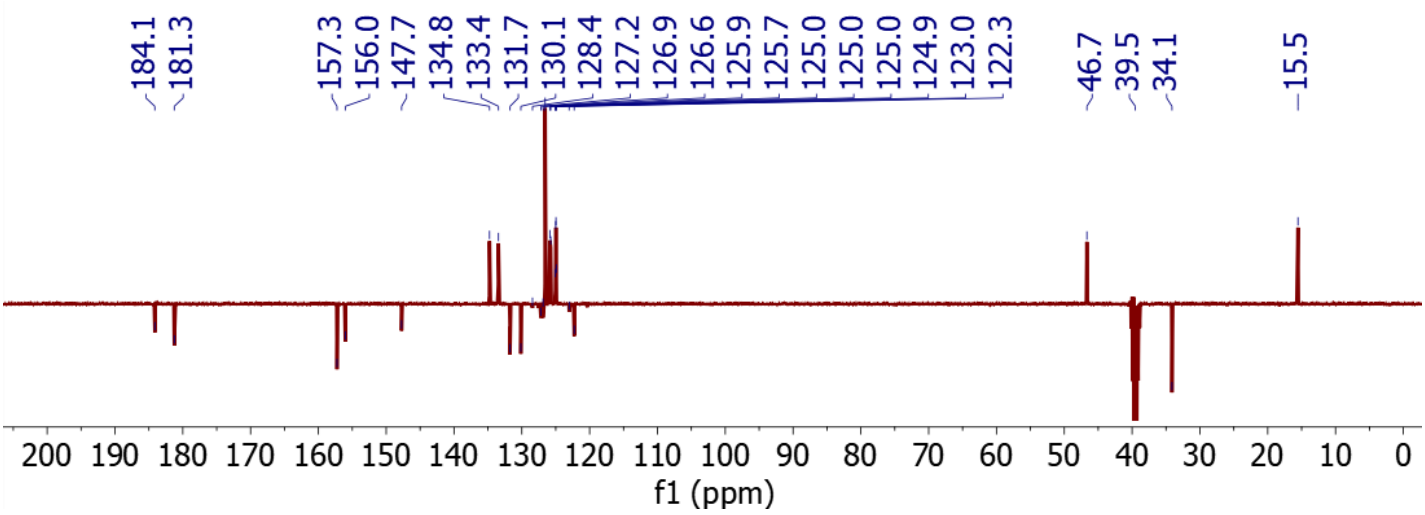


Figure S26: ^{13}C NMR (101 MHz, DMSO-d6) of compound **14**

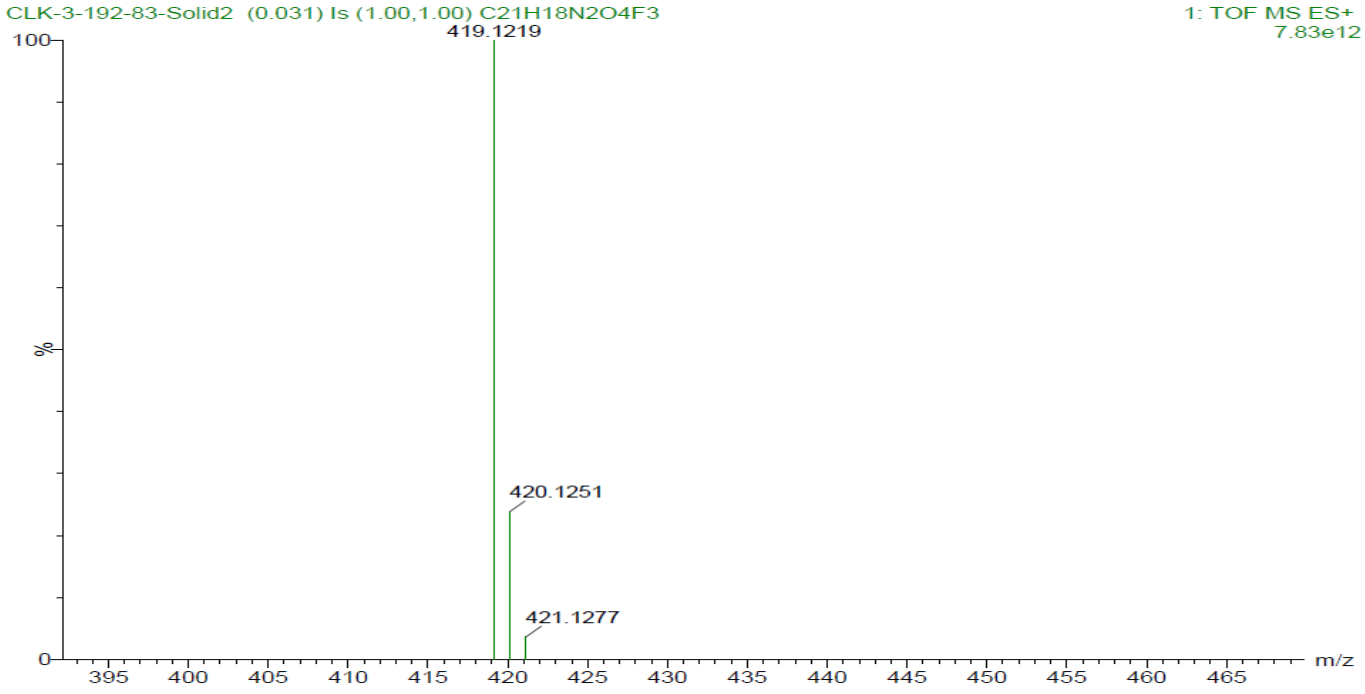


Figure S27: HRMS of compound **14**

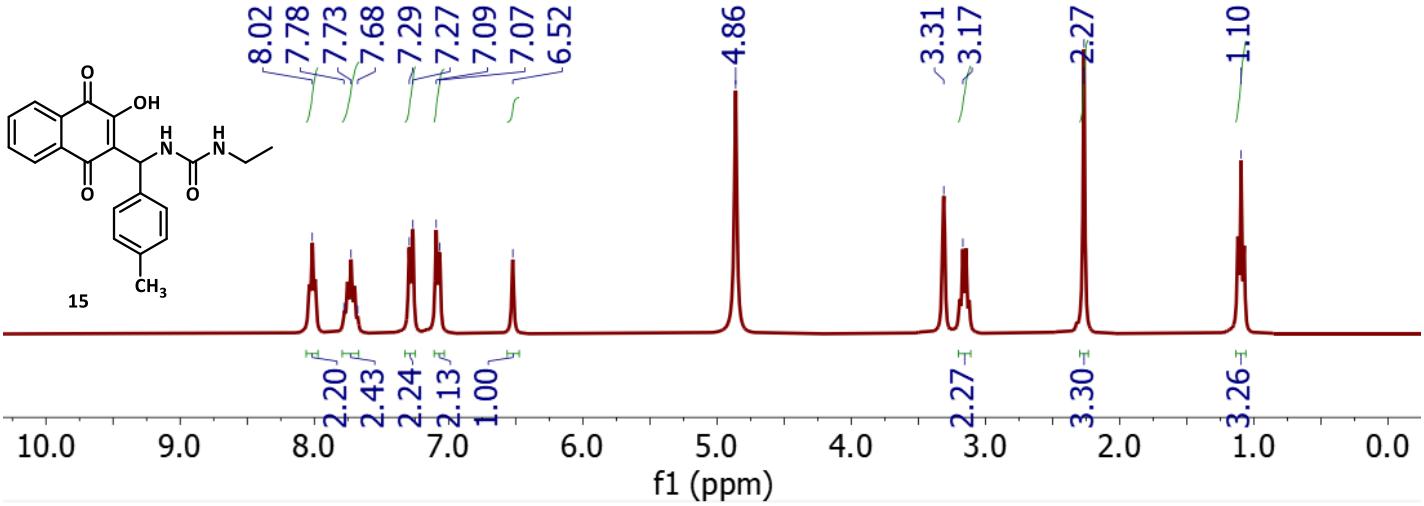


Figure S28: ^{1}H NMR (300 MHz, MeOD) of compound **15**

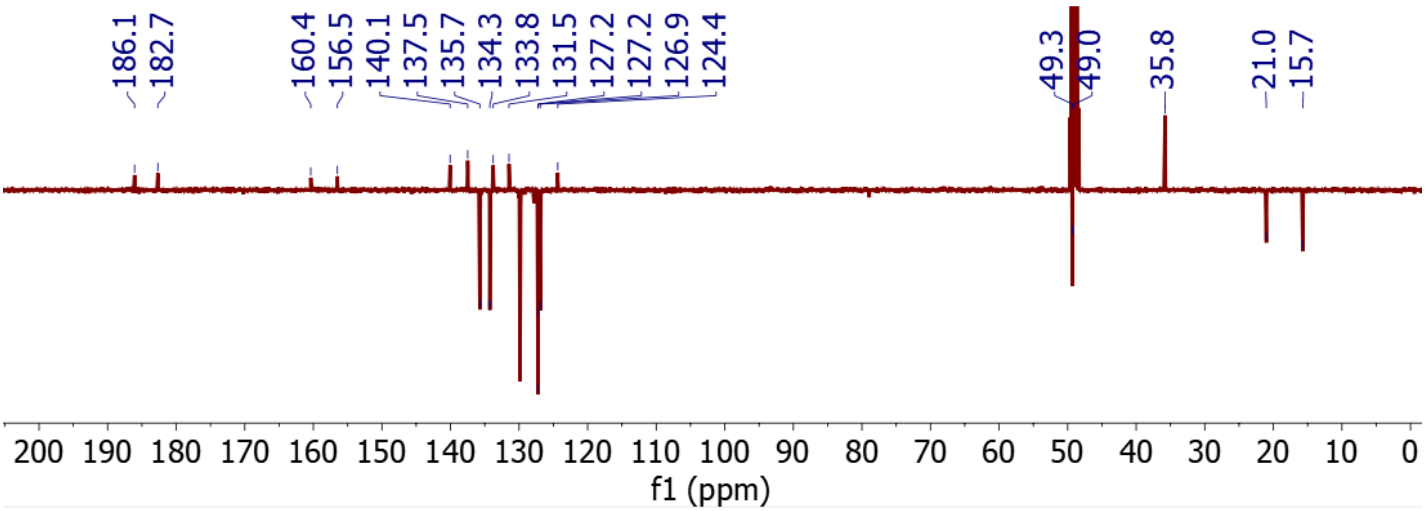


Figure S29: ^{13}C NMR (101 MHz, MeOD) of compound **15**

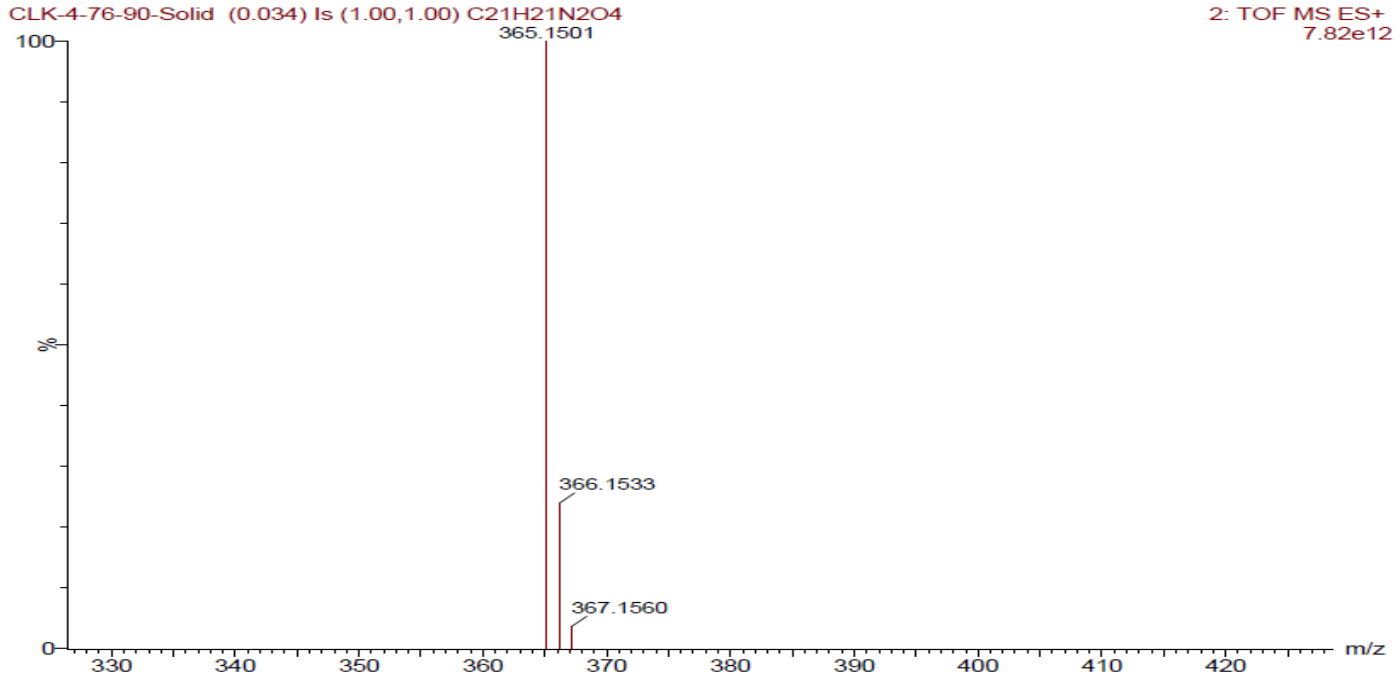


Figure S30: HRMS of compound **15**

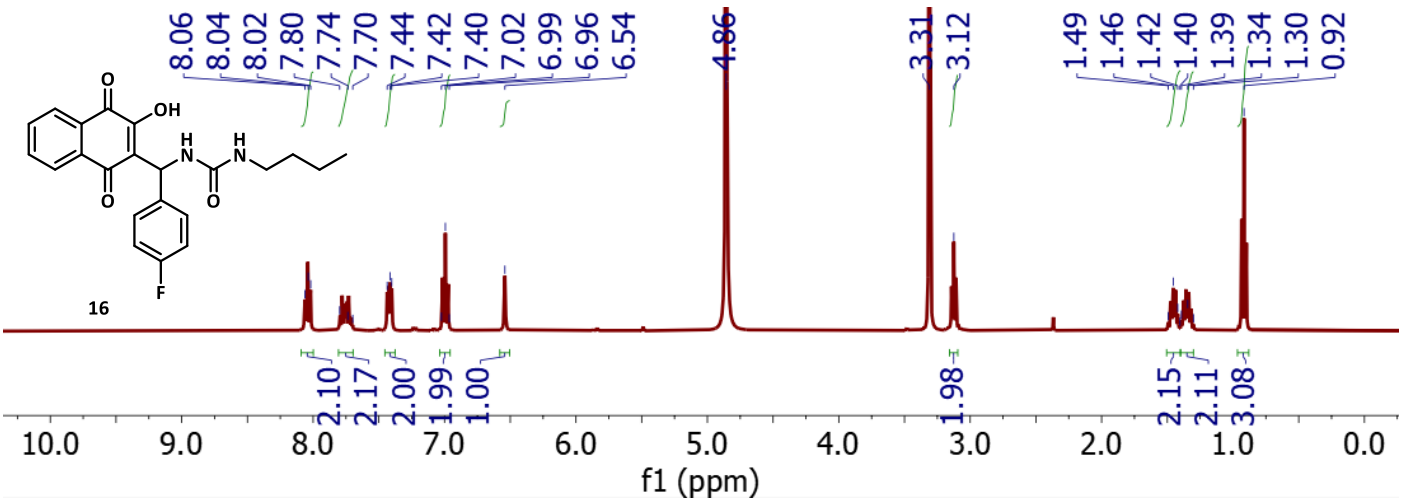


Figure S31: ^{1}H NMR (400 MHz, MeOD) of compound **16**

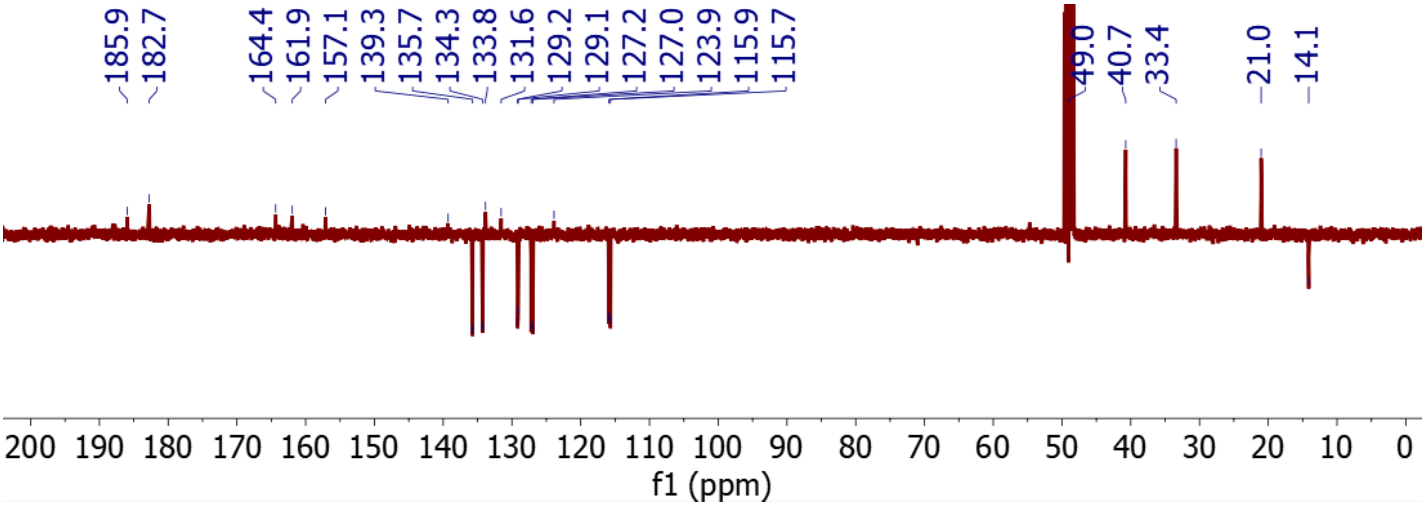


Figure S32: ^{13}C NMR (101 MHz, MeOD) of compound **16**

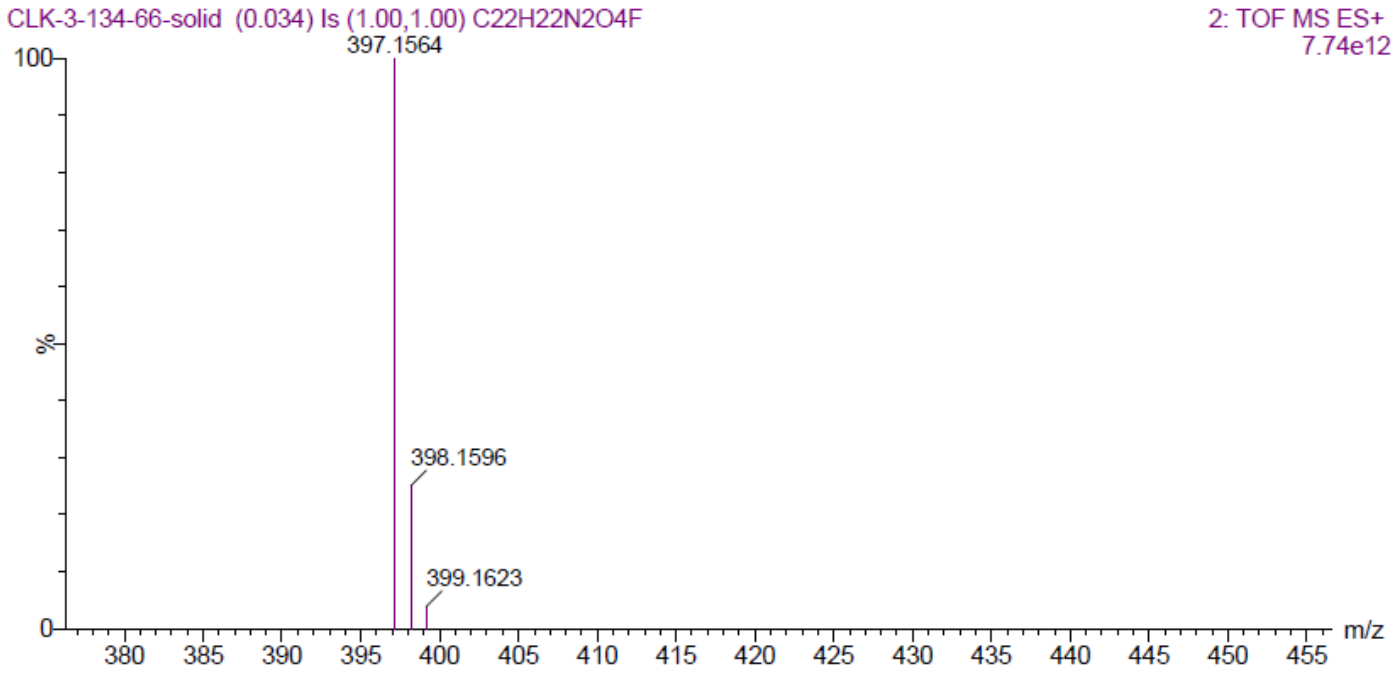


Figure S33: HRMS of compound **16**

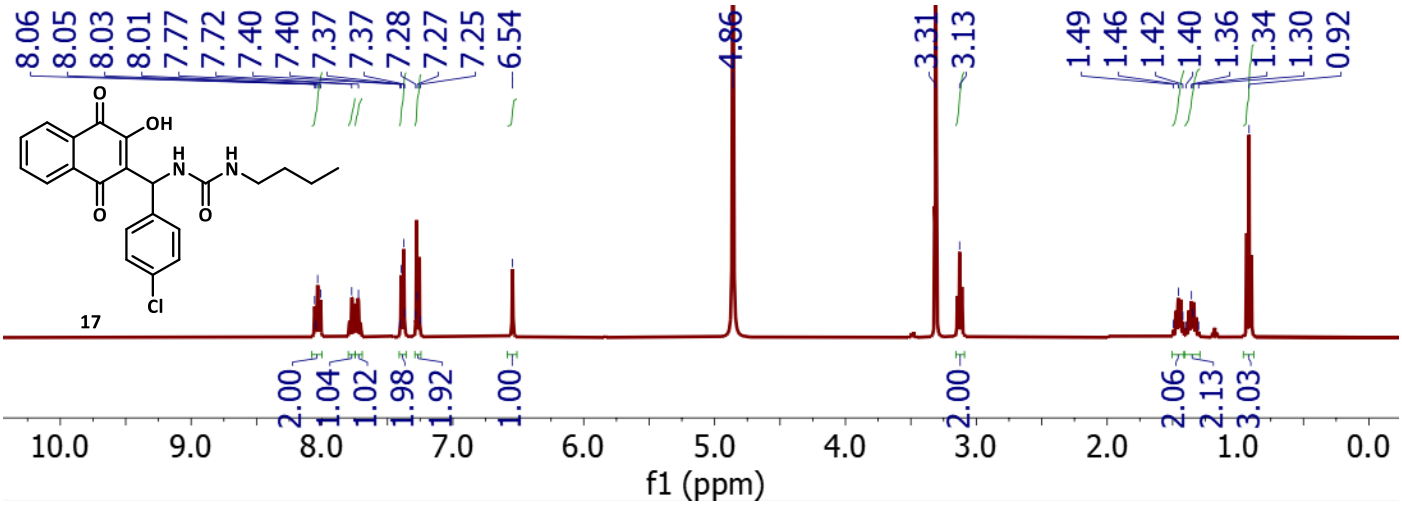


Figure S34: ^{1}H NMR (400 MHz, MeOD) of compound **17**

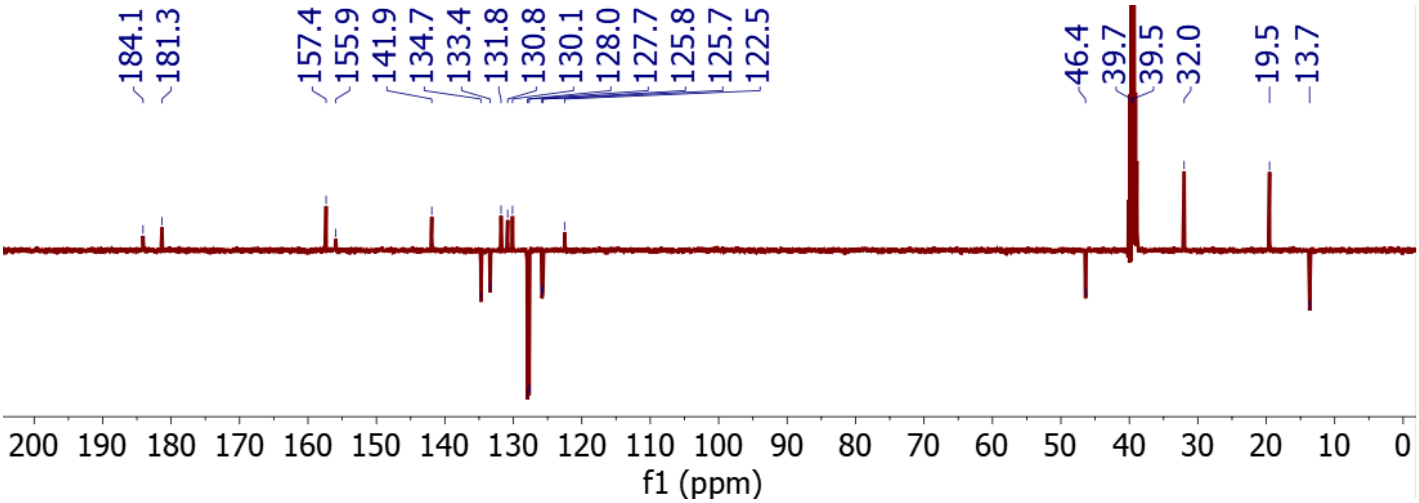


Figure S35: ^{13}C NMR (101 MHz, DMSO-d6) of compound **17**

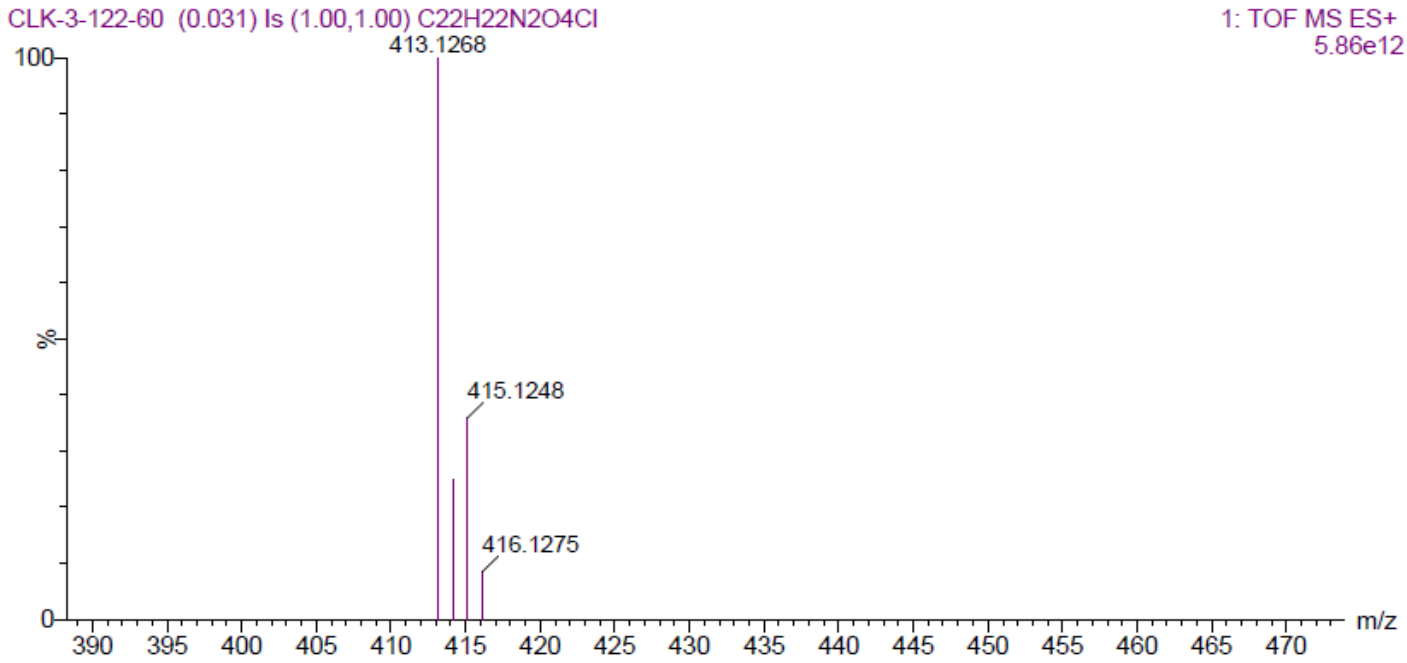


Figure S36: HRMS of compound **17**

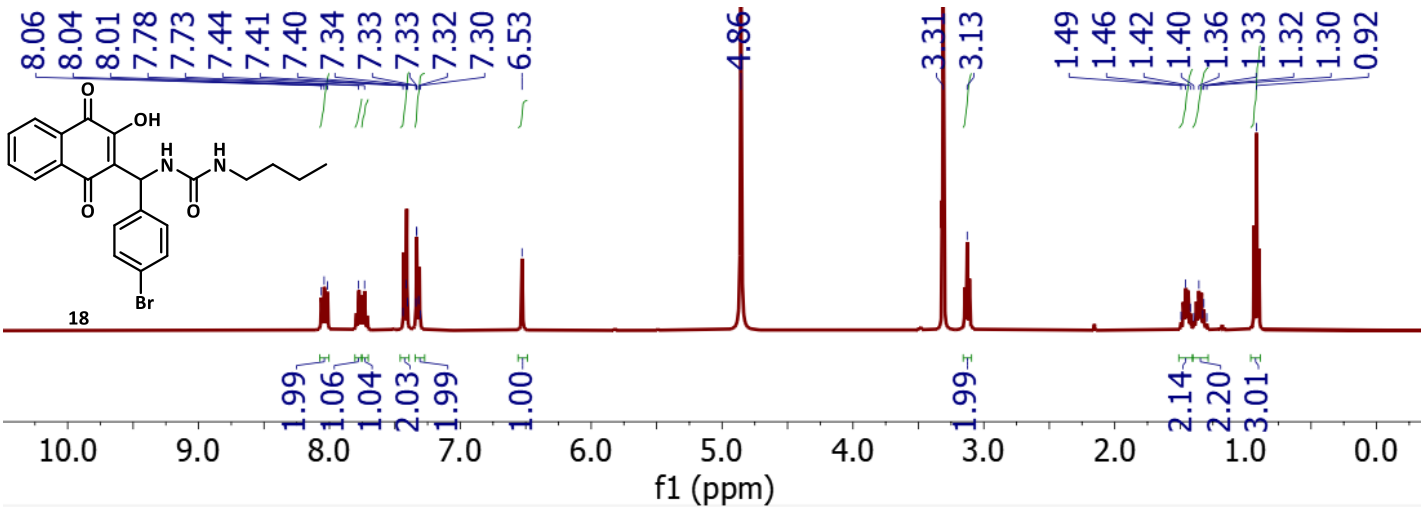


Figure S37: ^{1}H NMR (400 MHz, MeOD) of compound **18**

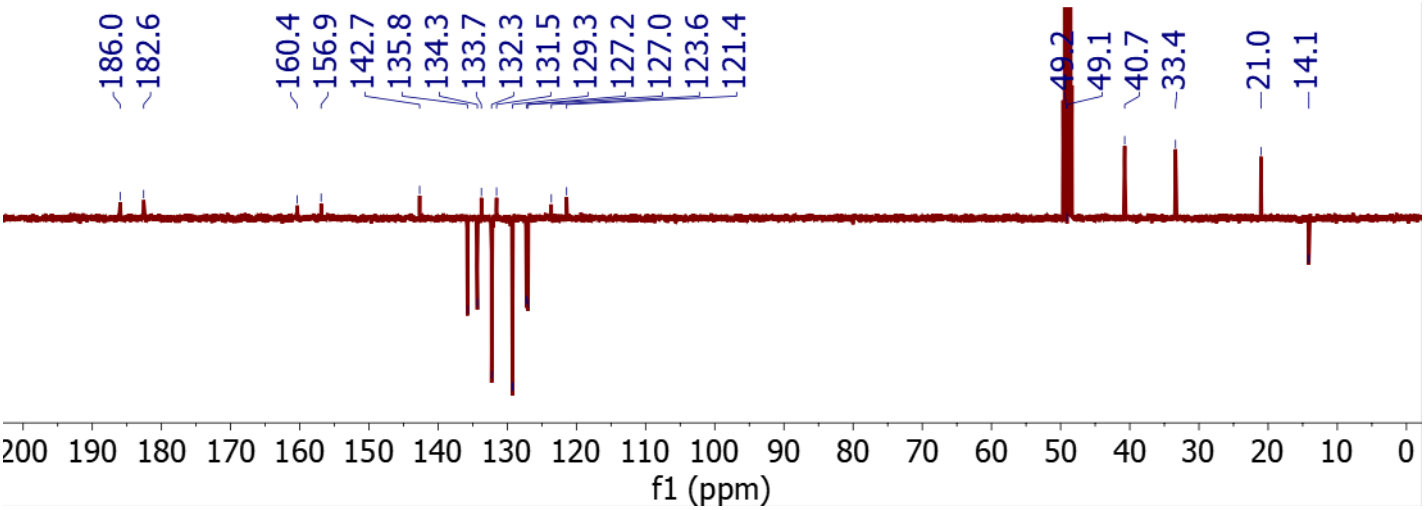


Figure S38: ^{13}C NMR (101 MHz, MeOD) of compound **18**

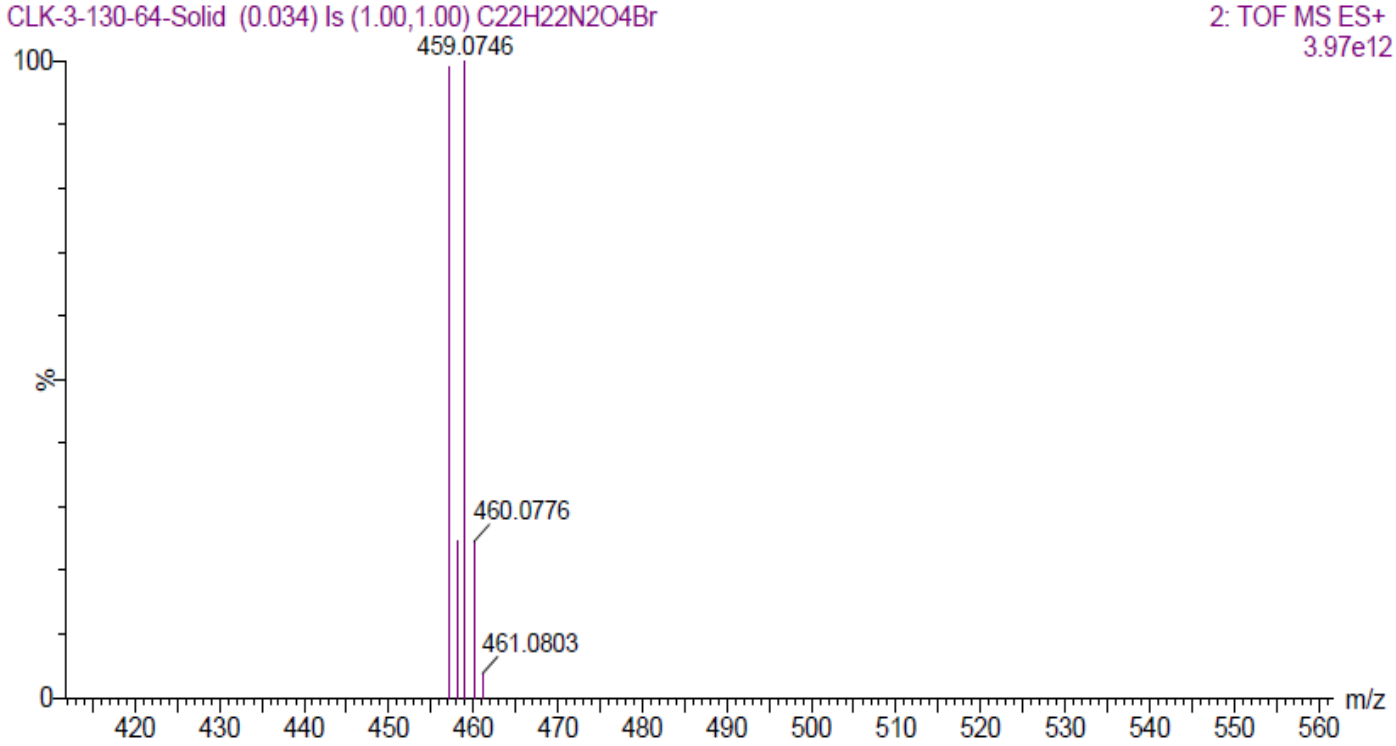


Figure S39: HRMS of compound **18**

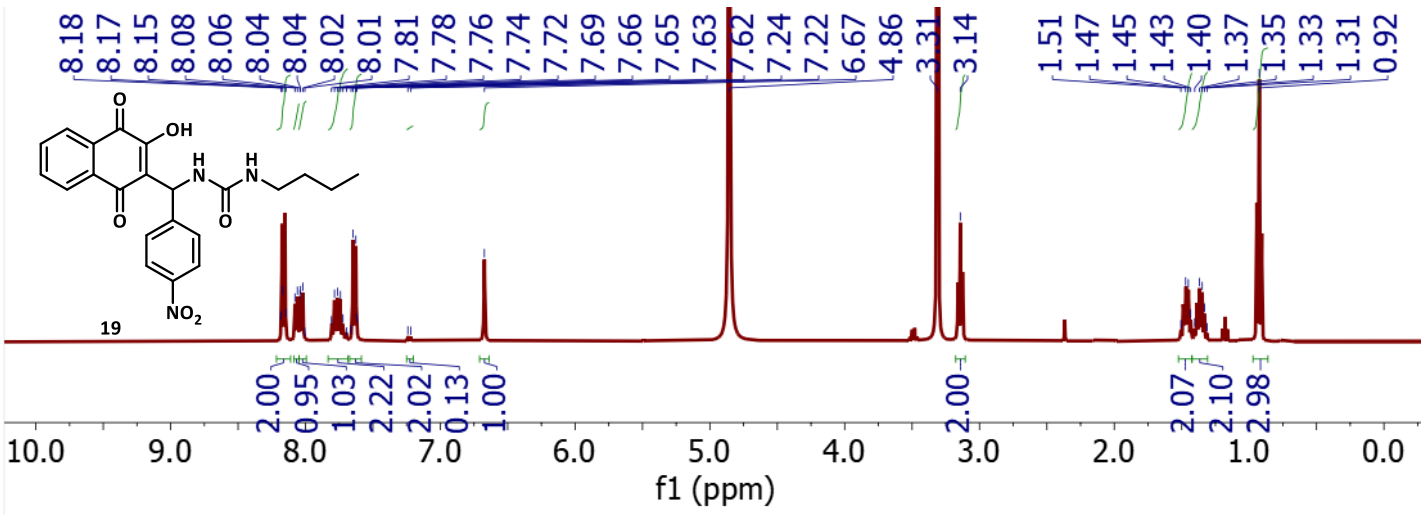


Figure S40: ^{1}H NMR (400 MHz, MeOD) of compound **19**

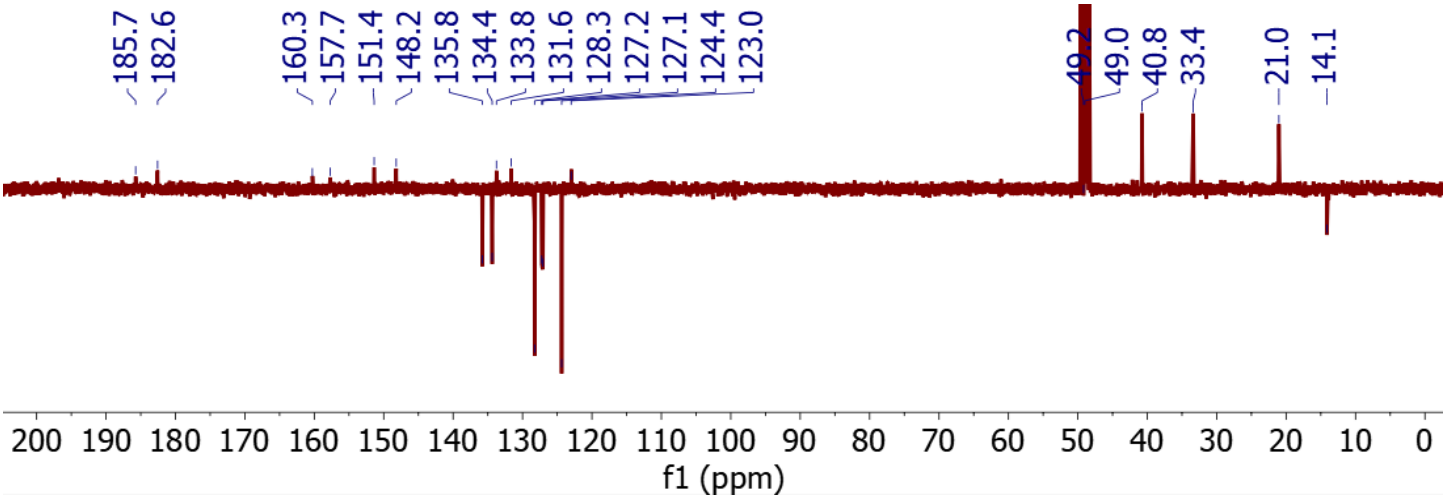


Figure S41: ^{13}C NMR (101 MHz, MeOD) of compound **19**

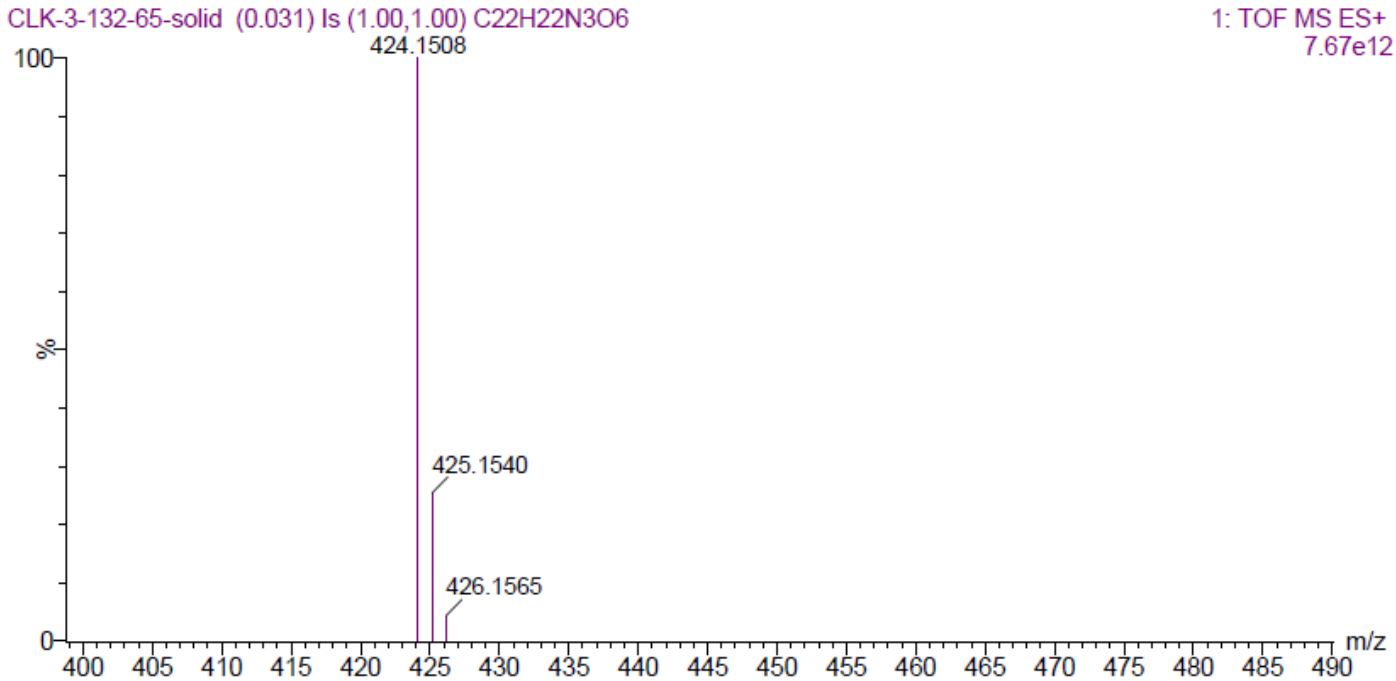


Figure S42: HRMS of compound **19**

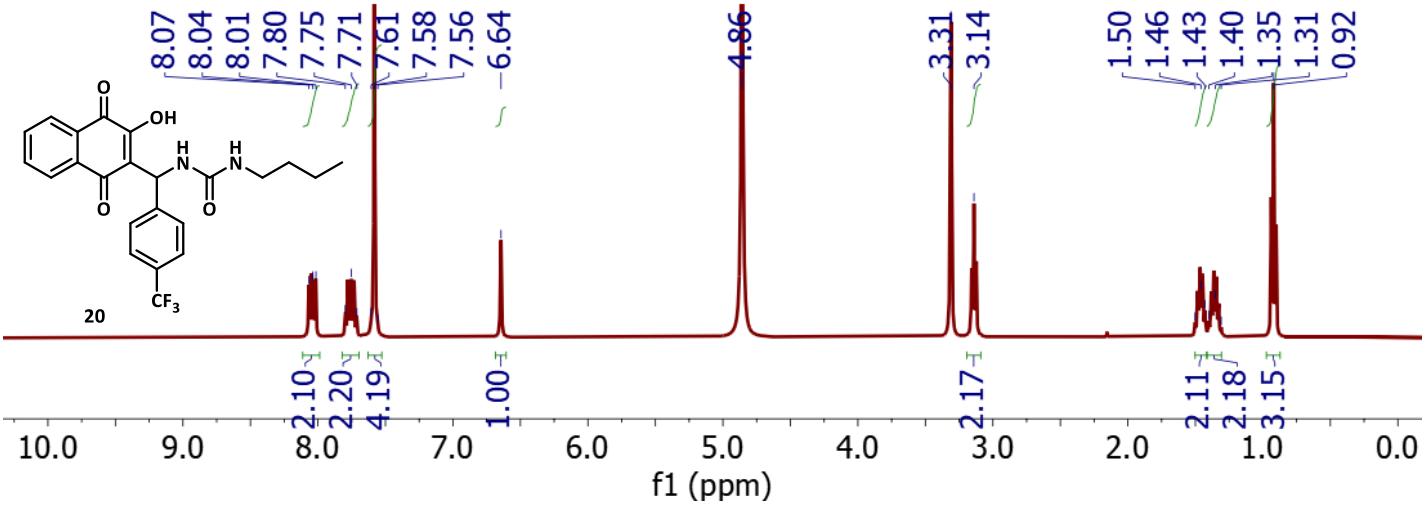


Figure S43: ^{1}H NMR (400 MHz, MeOD) of compound **20**

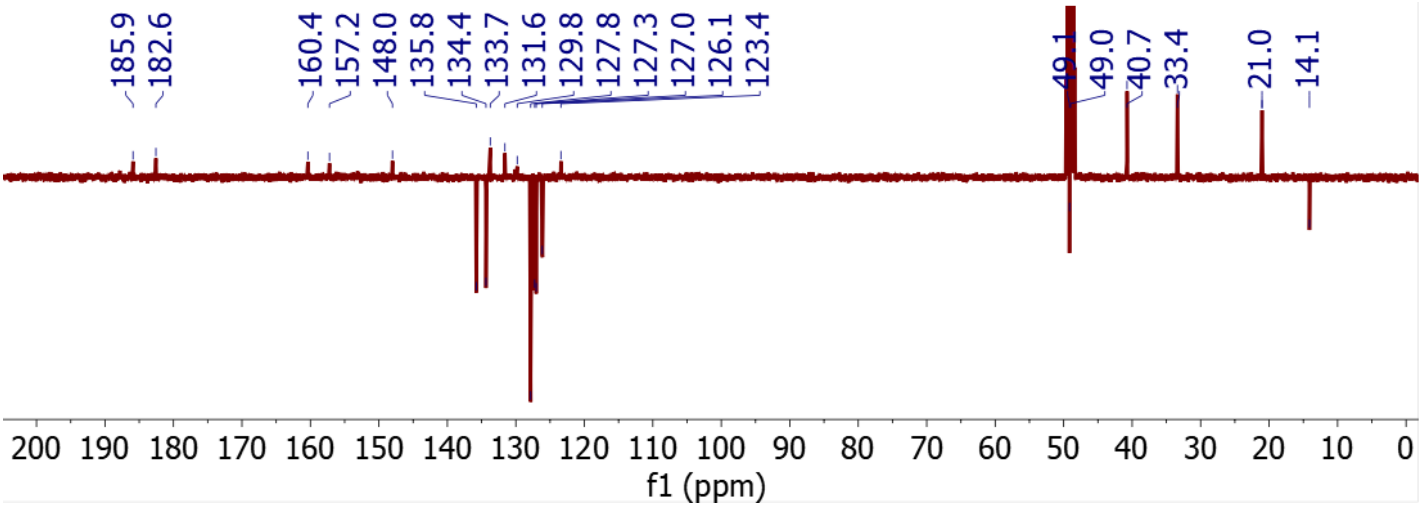


Figure S44: ^{13}C NMR (101 MHz, MeOD) of compound **20**

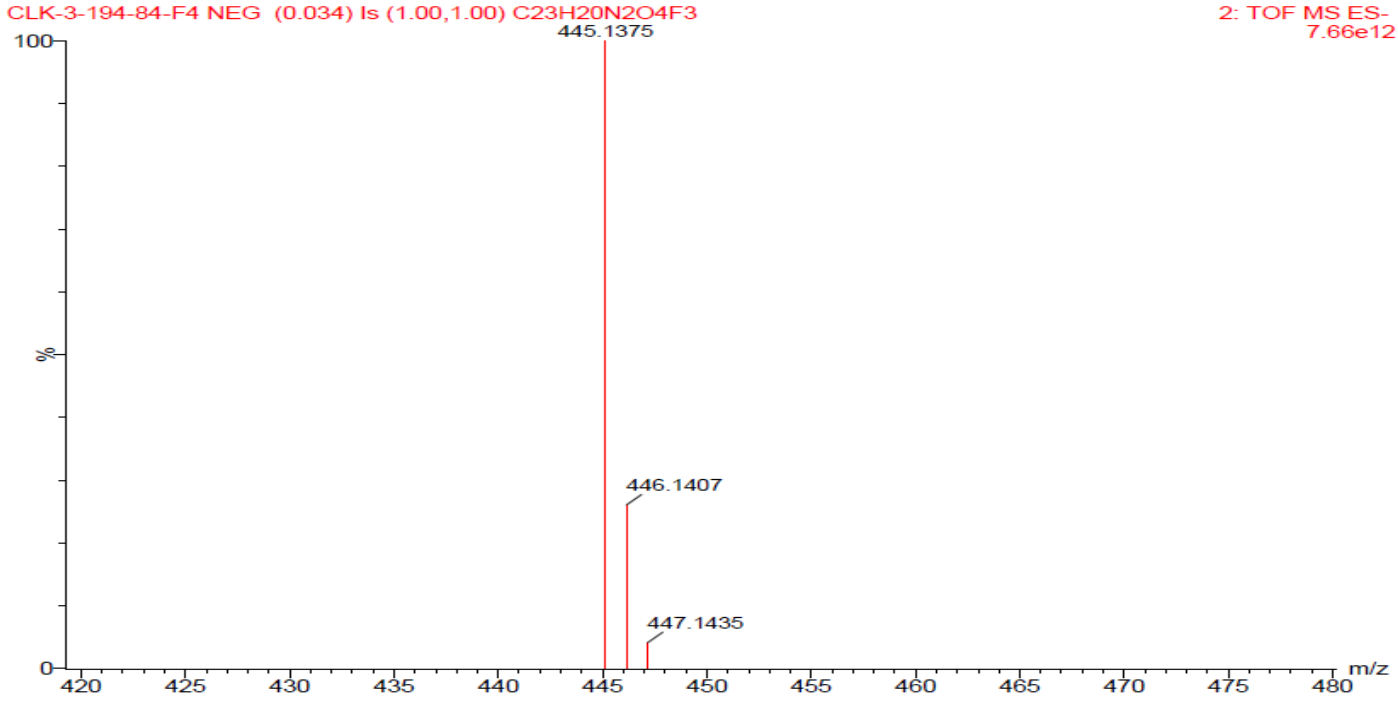


Figure S45: HRMS of compound **20**

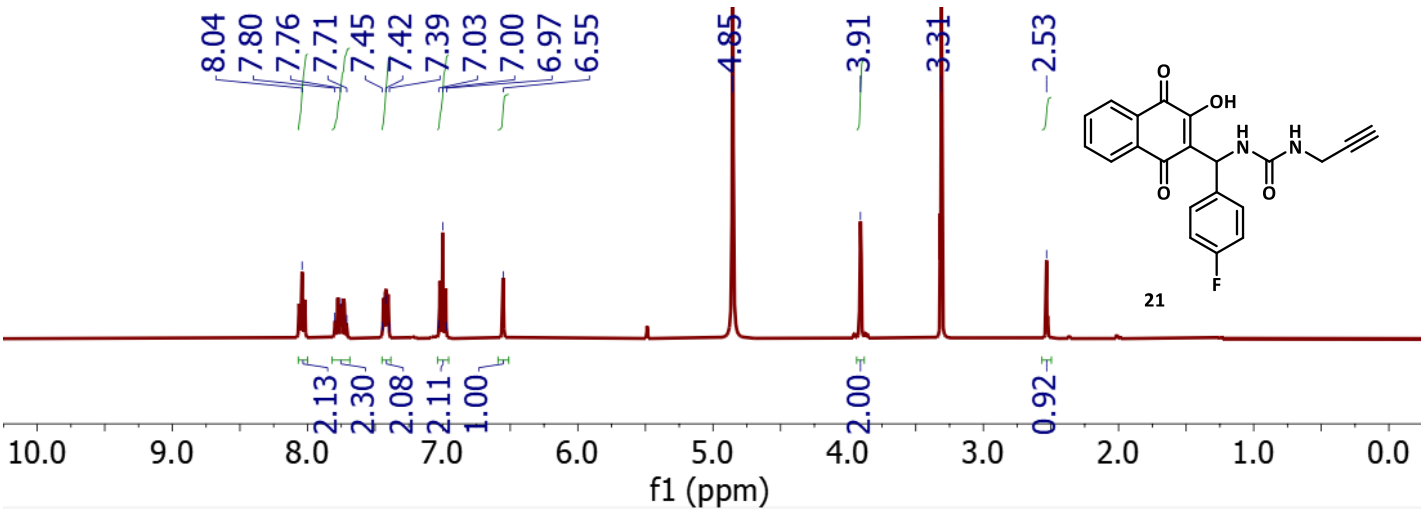


Figure S46: ^{1}H NMR (400 MHz, MeOD) of compound **21**

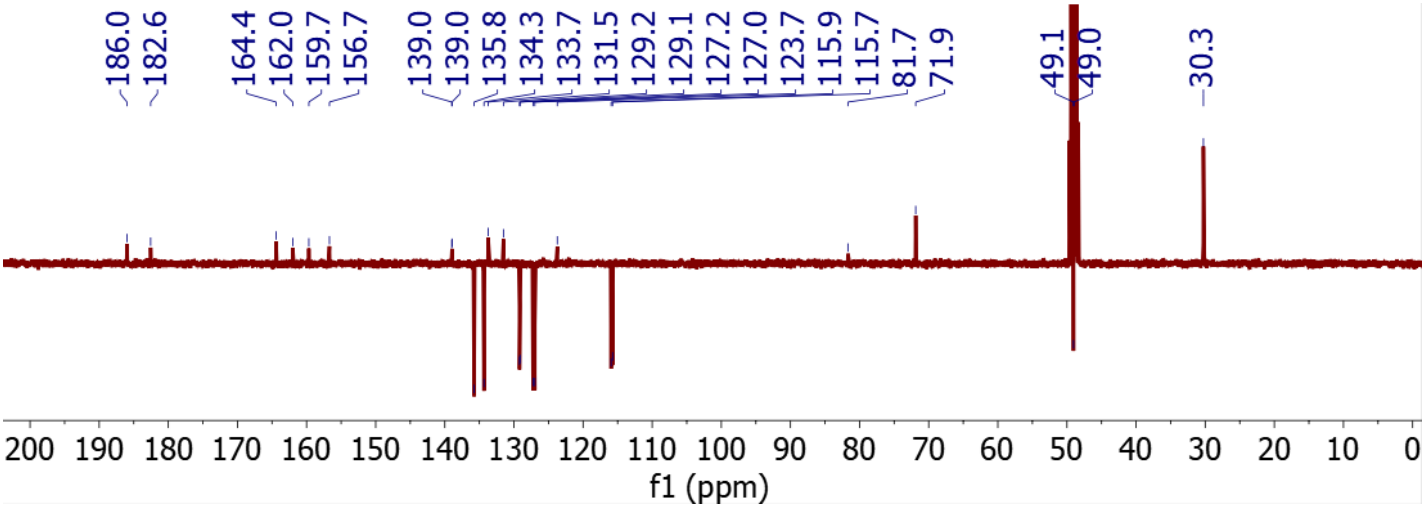


Figure S47: ^{13}C NMR (101 MHz, MeOD) of compound **21**

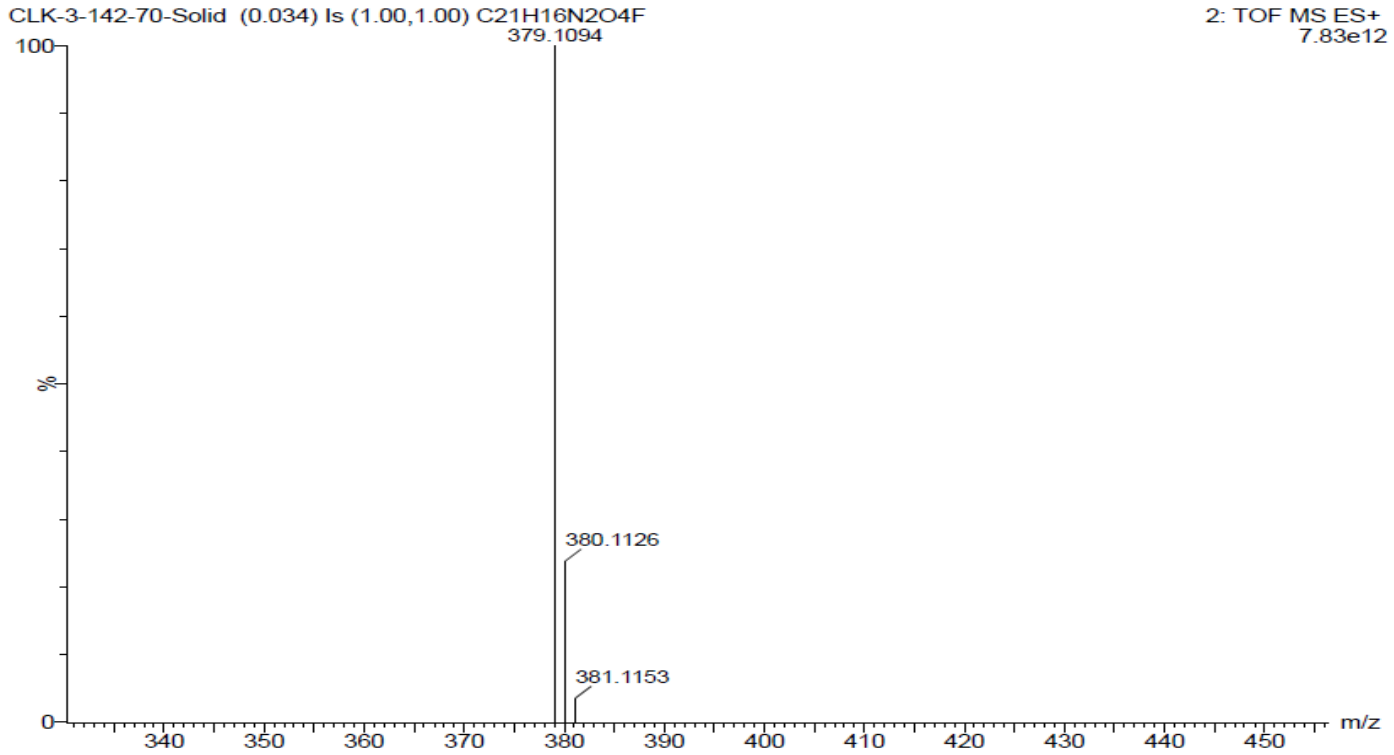


Figure S48: HRMS of compound **21**

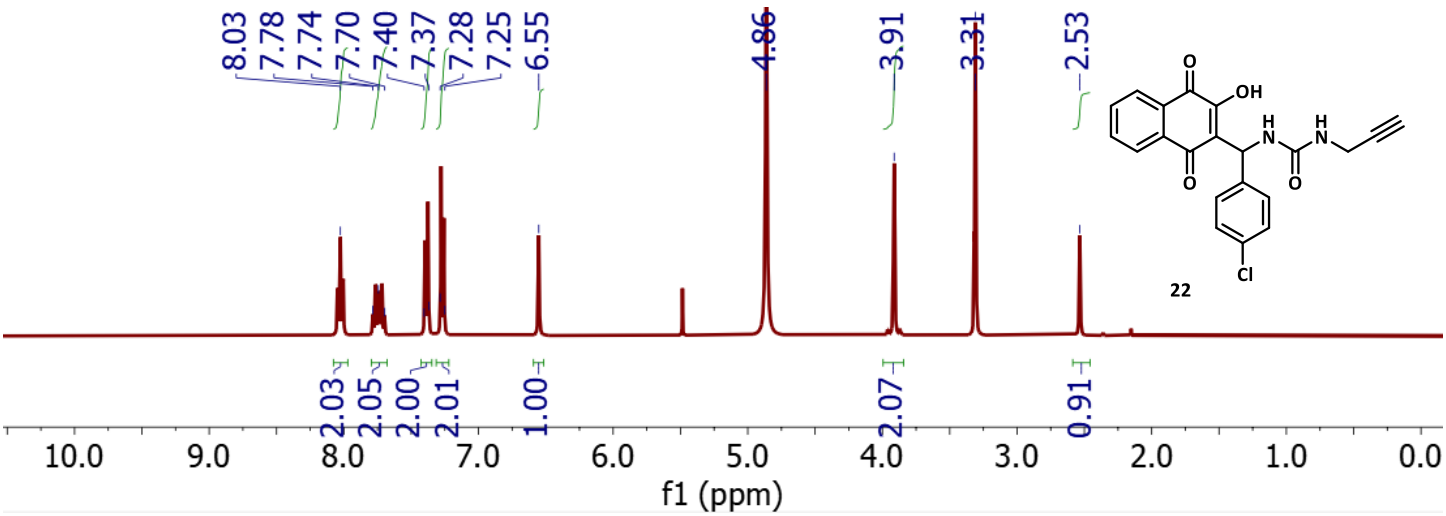


Figure S49: ^{1}H NMR (400 MHz, MeOD) of compound **22**

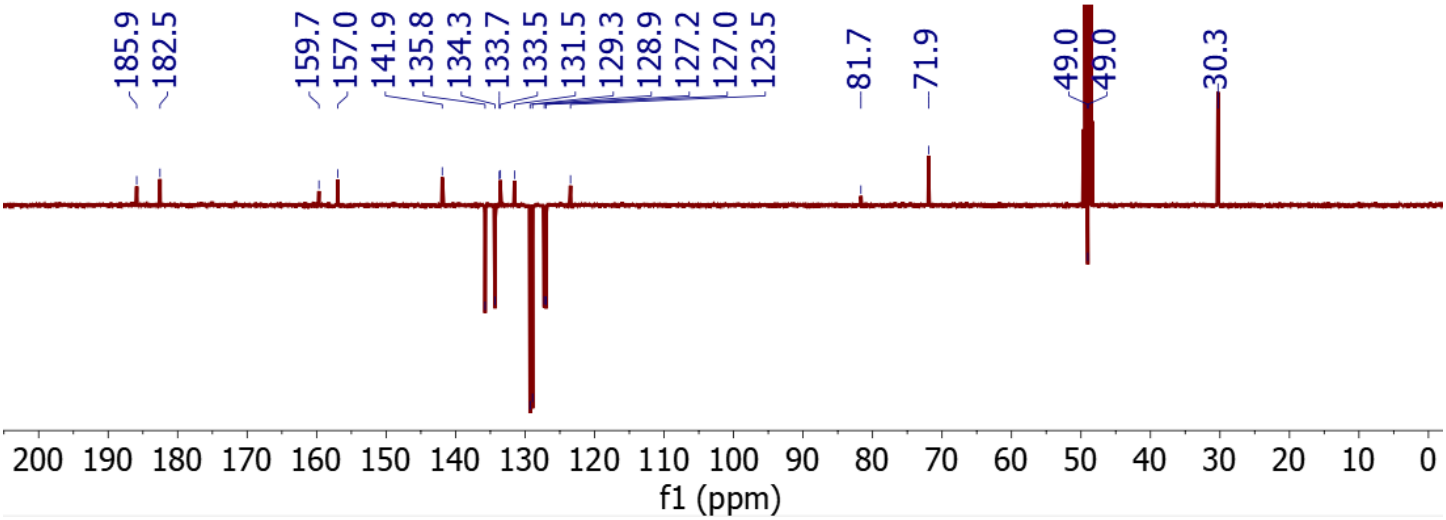


Figure S50: ^{13}C NMR (101 MHz, MeOD) of compound **22**

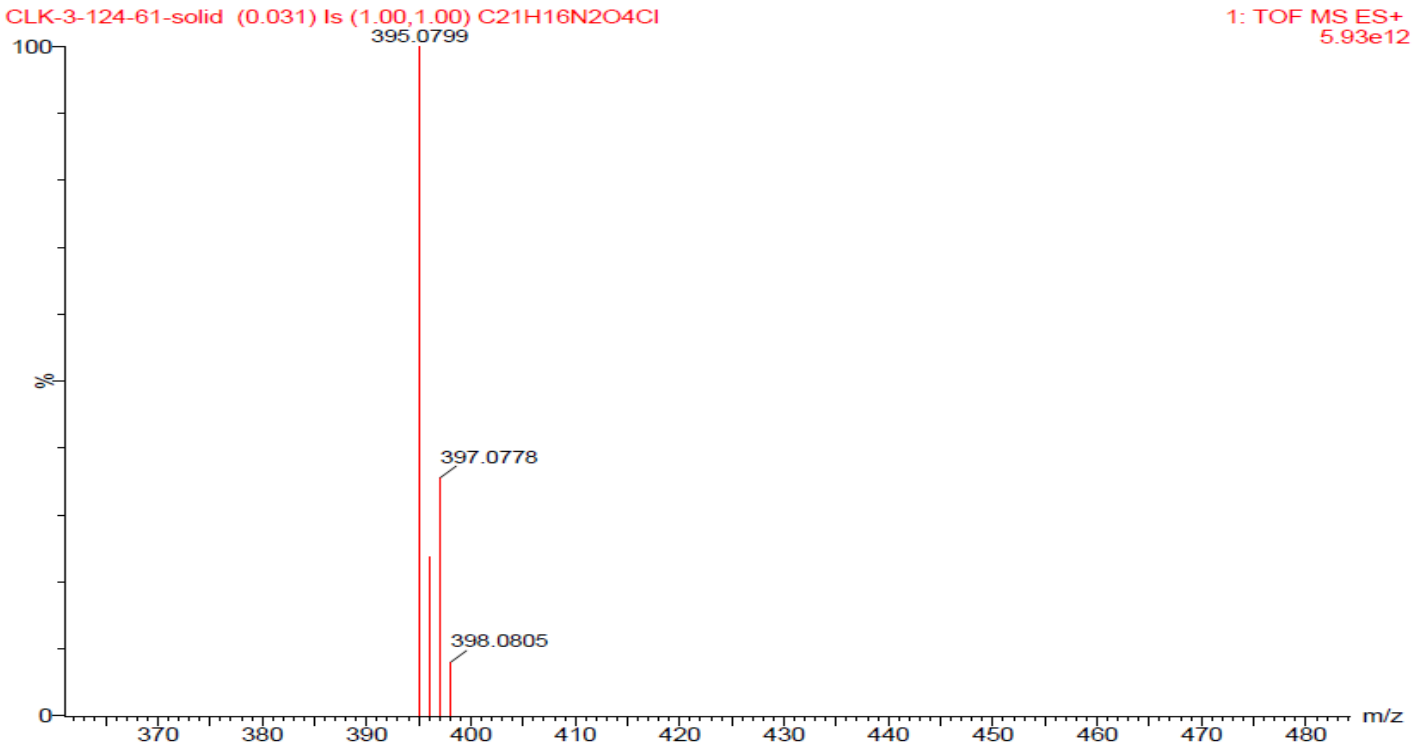


Figure S51: HRMS of compound **22**

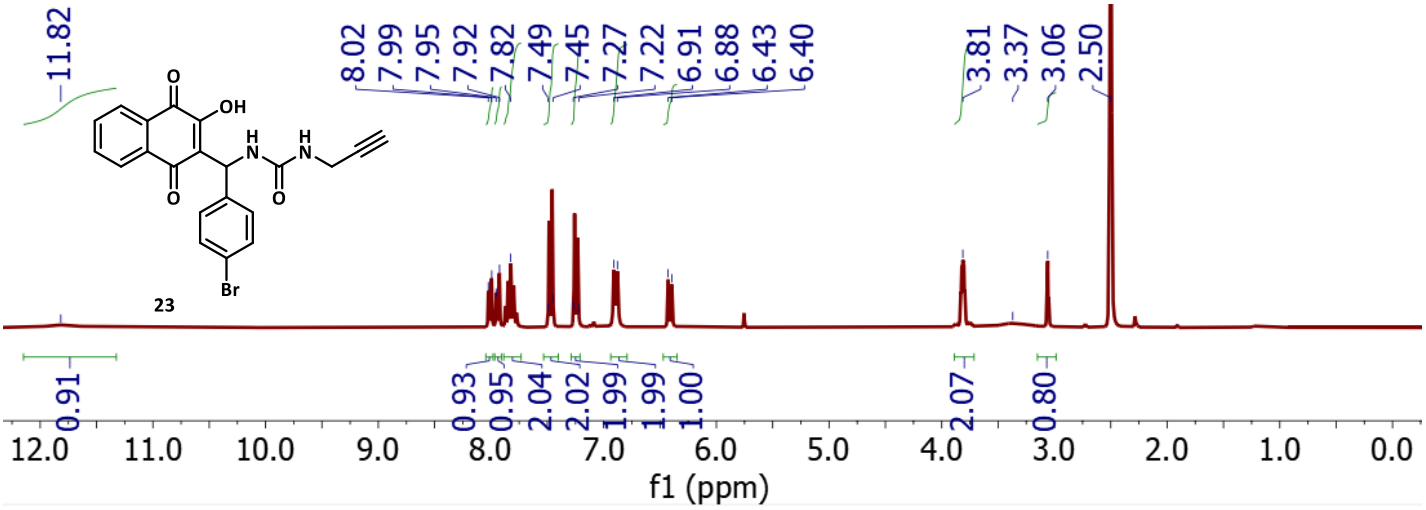


Figure S52: ^{1}H NMR (300 MHz, DMSO-d6) of compound **23**

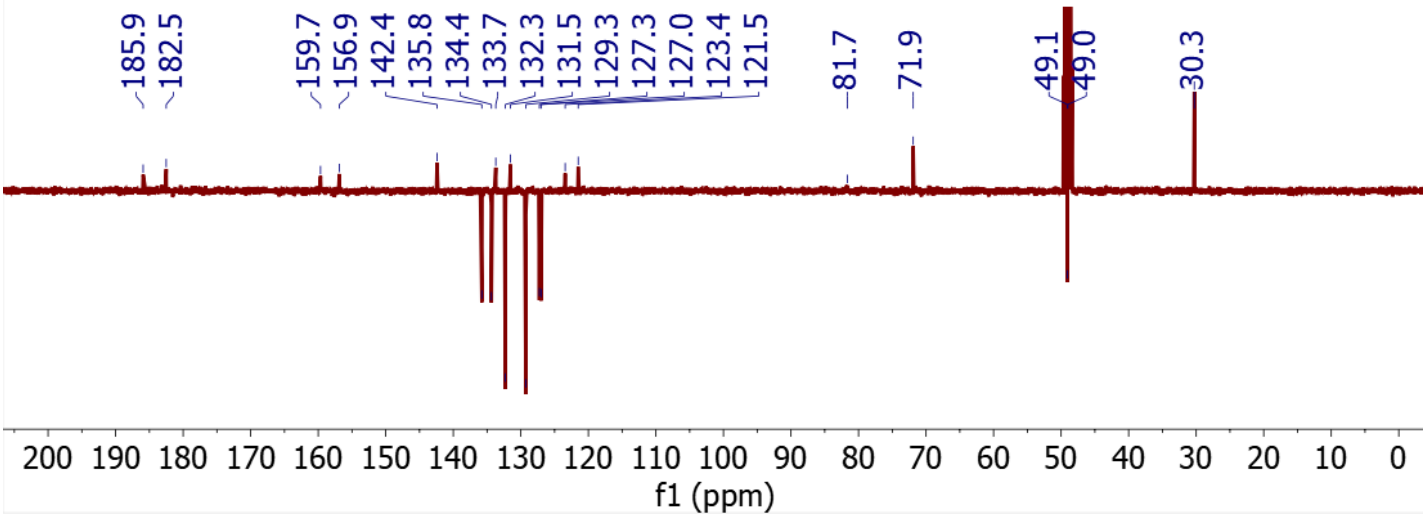


Figure S53: ^{13}C NMR (101 MHz, MeOD) of compound **23**

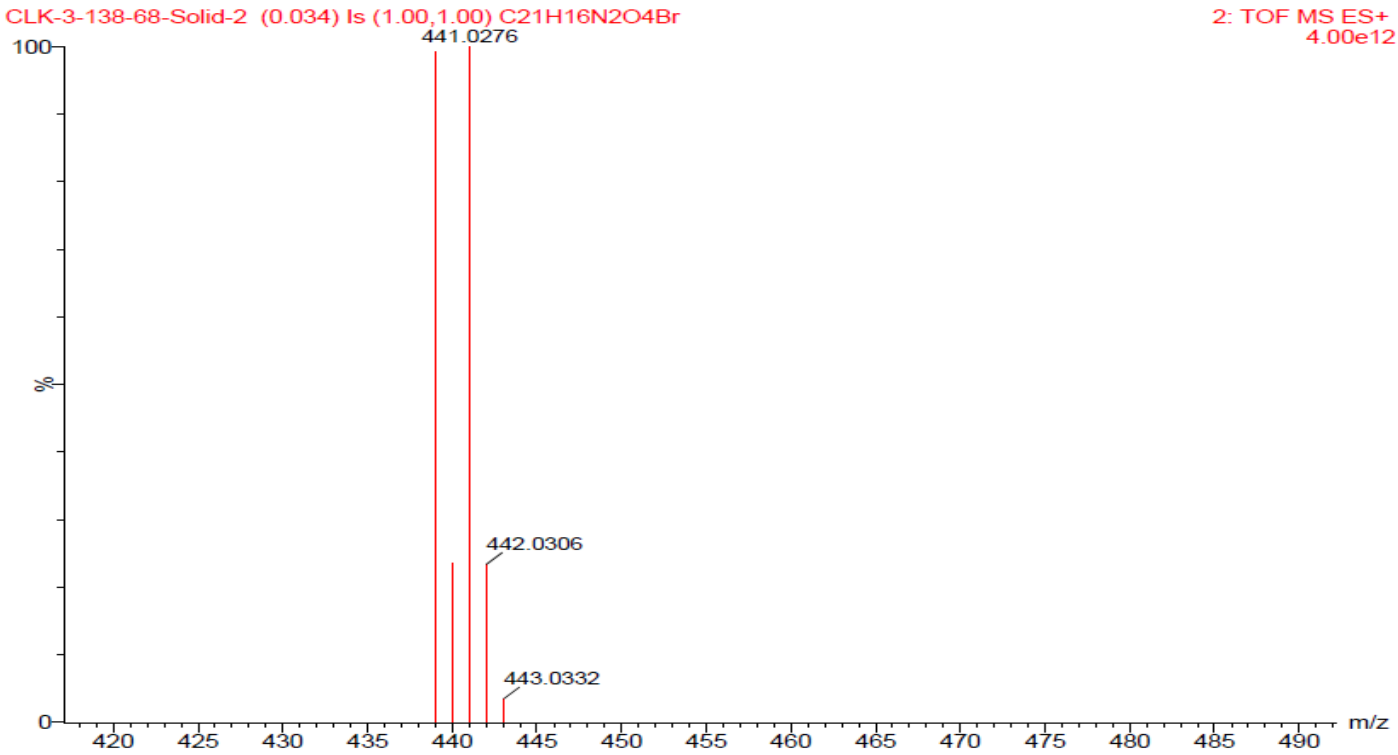


Figure S54: HRMS of compound **23**

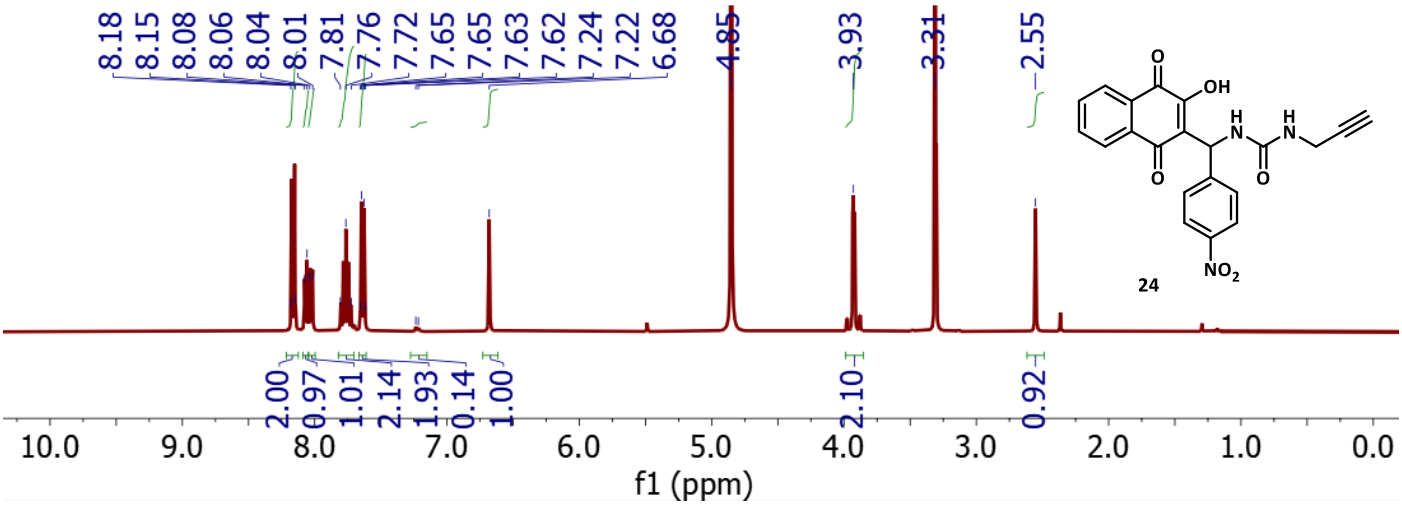


Figure S55: ^{1}H NMR (400 MHz, MeOD) of compound **24**

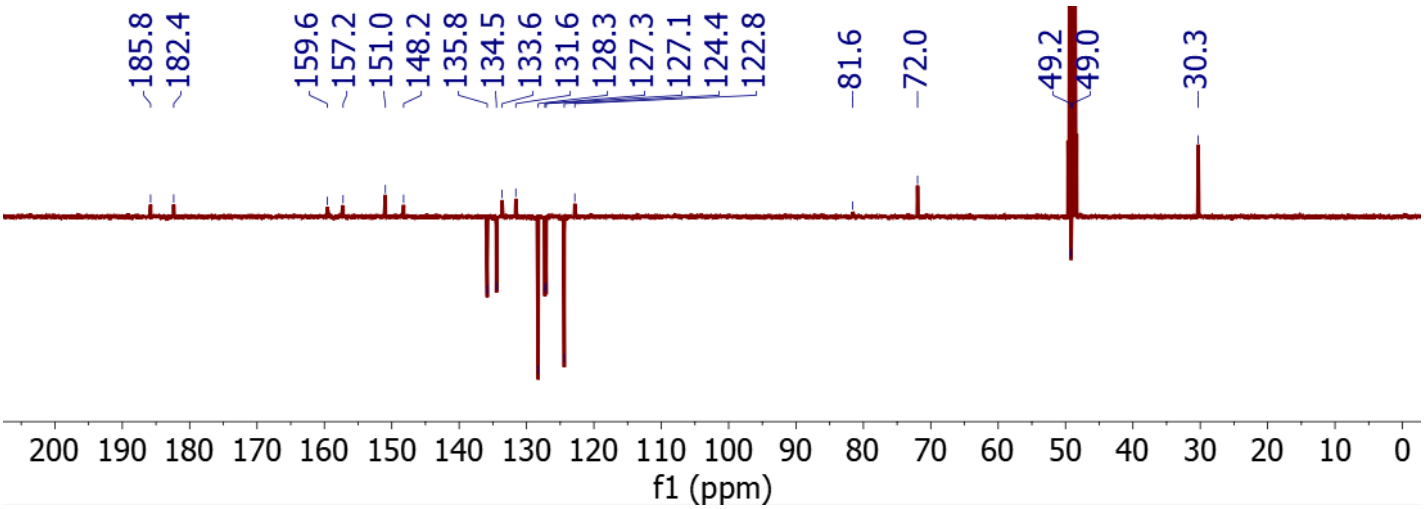


Figure S56: ^{13}C NMR (101 MHz, MeOD) of compound **24**

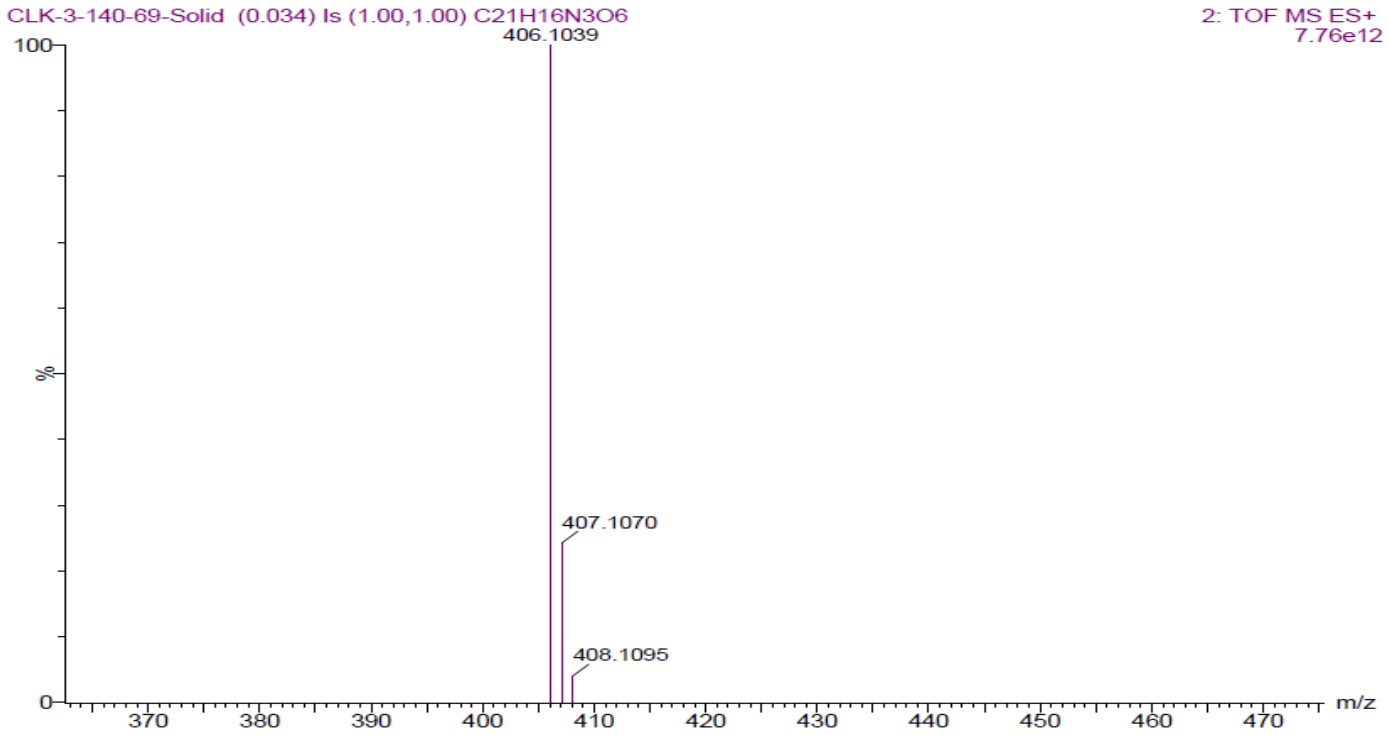


Figure S57: HRMS of compound **24**

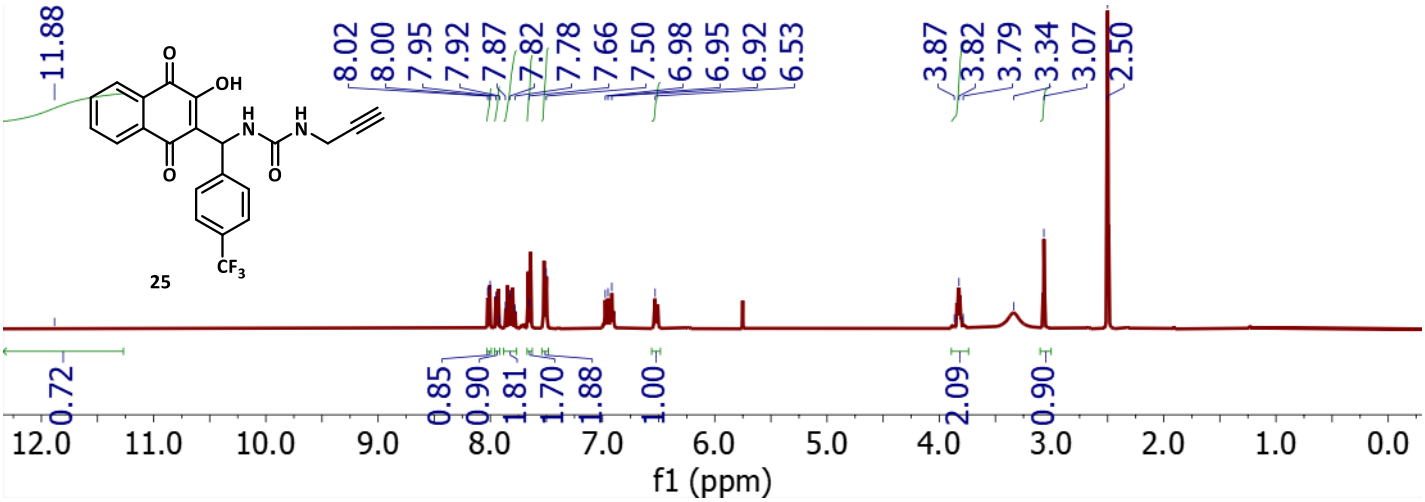


Figure S58: ^{1}H NMR (400 MHz, DMSO-d6) of compound **25**

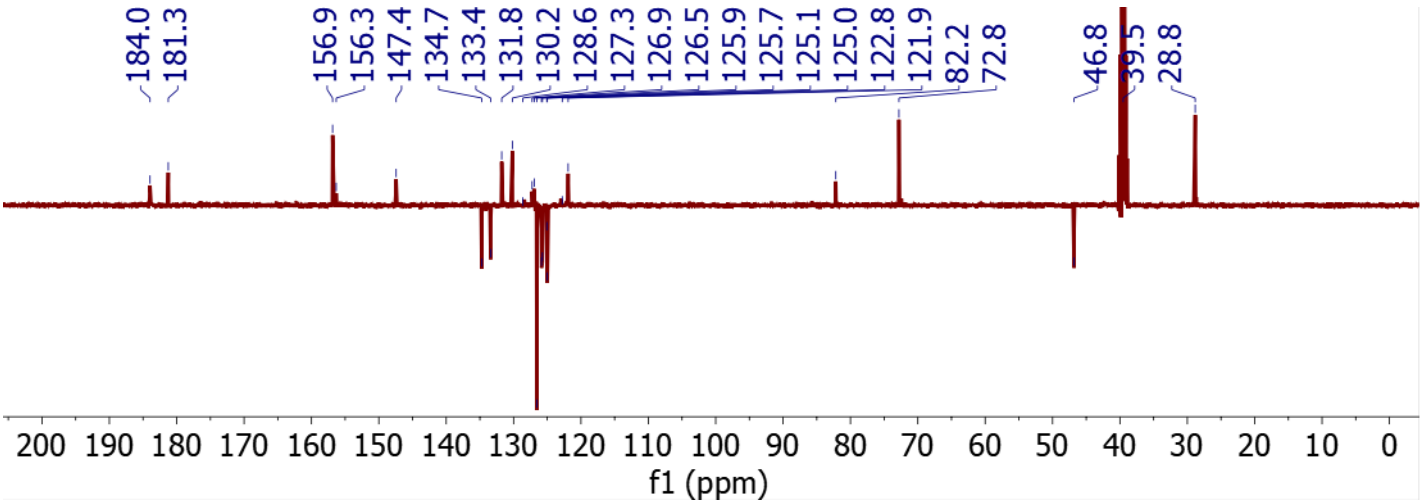


Figure S59: ^{13}C NMR (101 MHz, DMSO-d6) of compound **25**

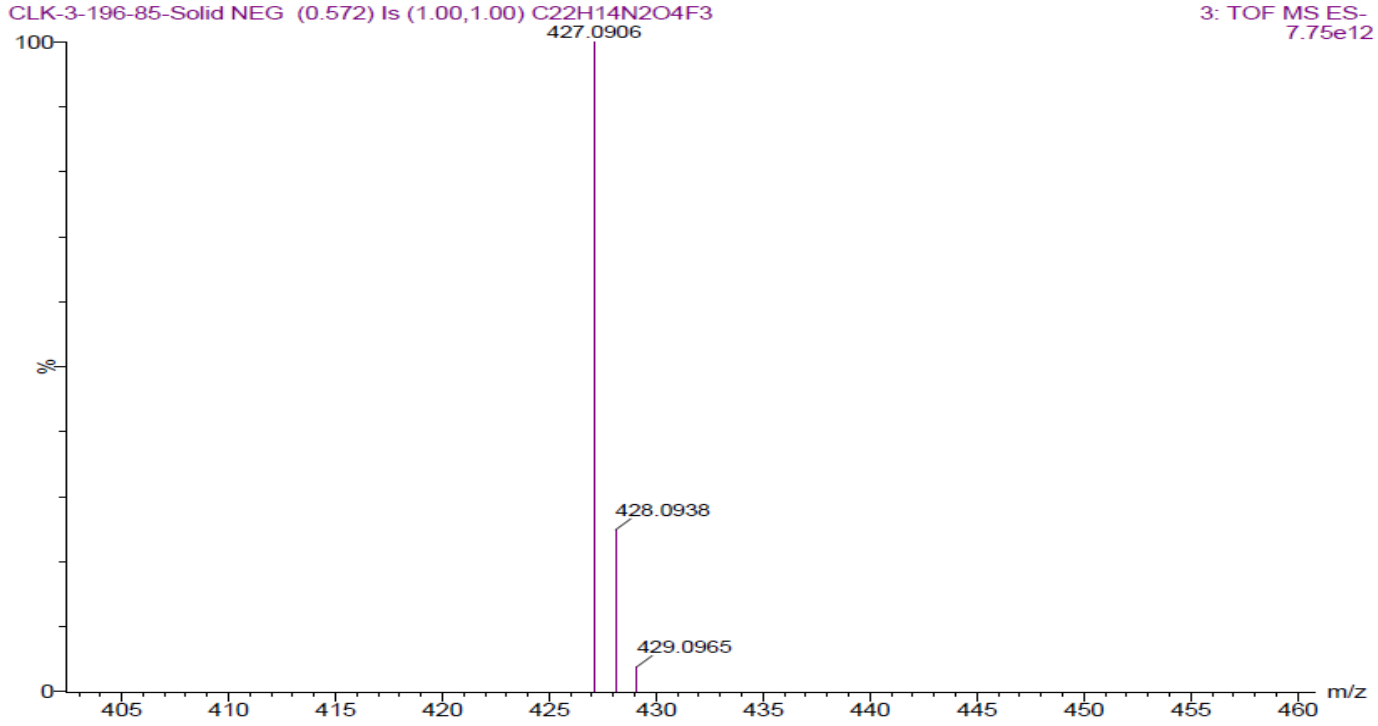


Figure S60: HRMS of compound **25**

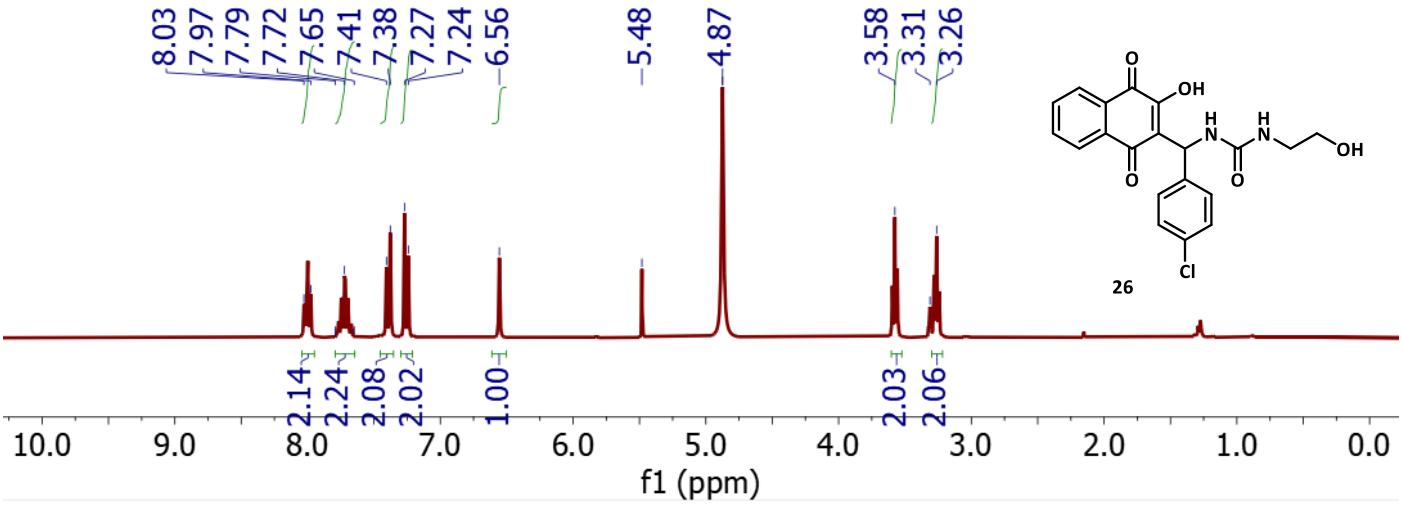


Figure S61: ^{1}H NMR (300 MHz, MeOD) of compound **26**

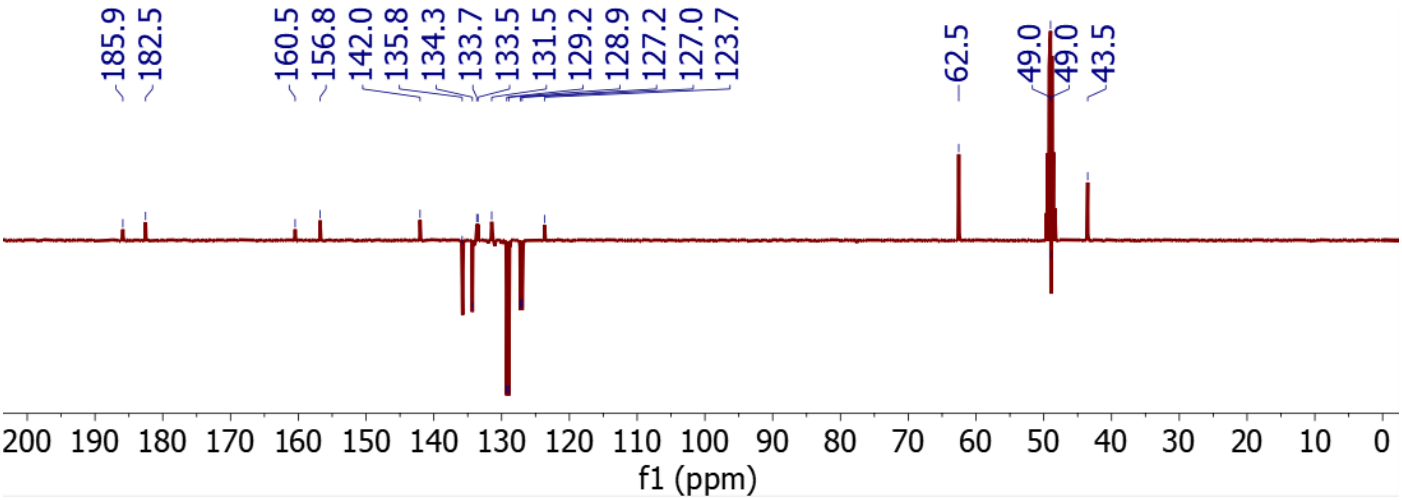


Figure S62: ^{13}C NMR (101 MHz, MeOD) of compound **26**

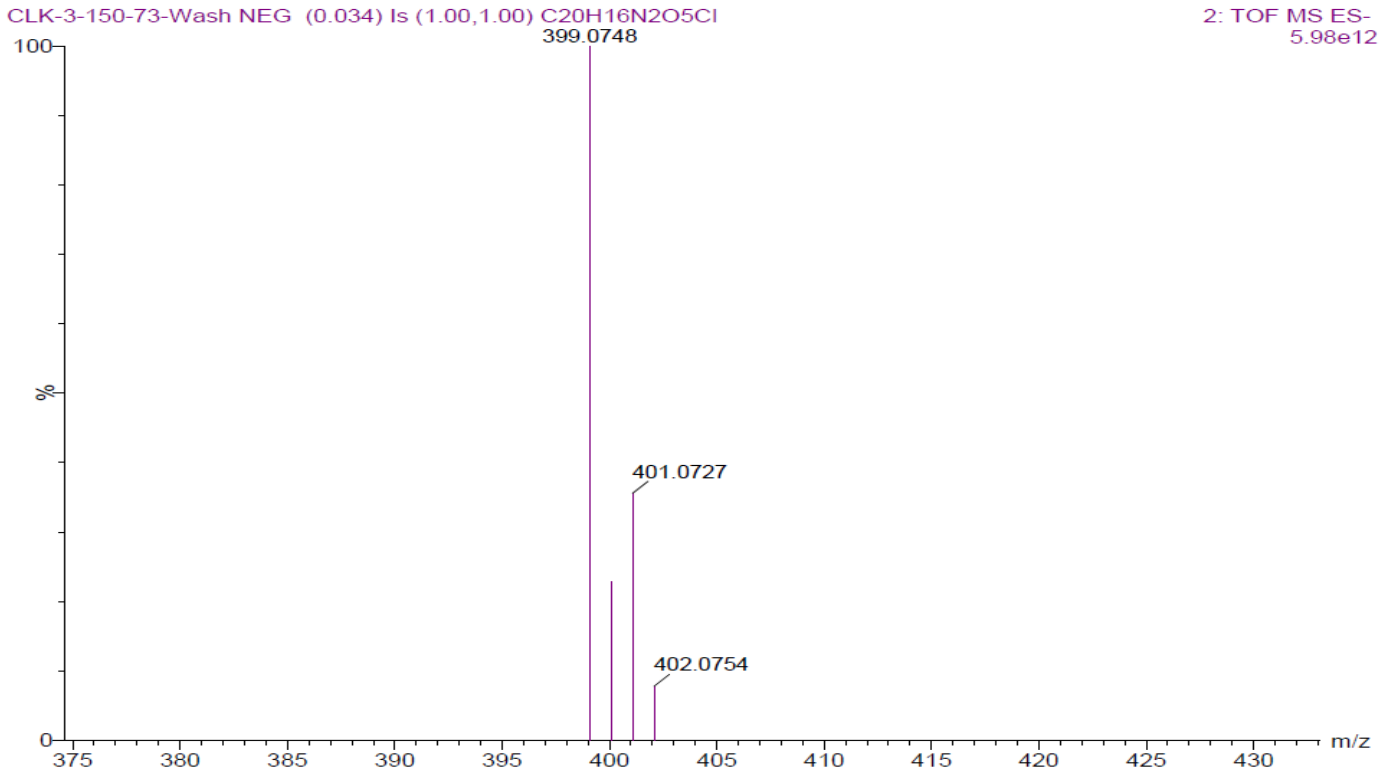


Figure S63: HRMS of compound **26**

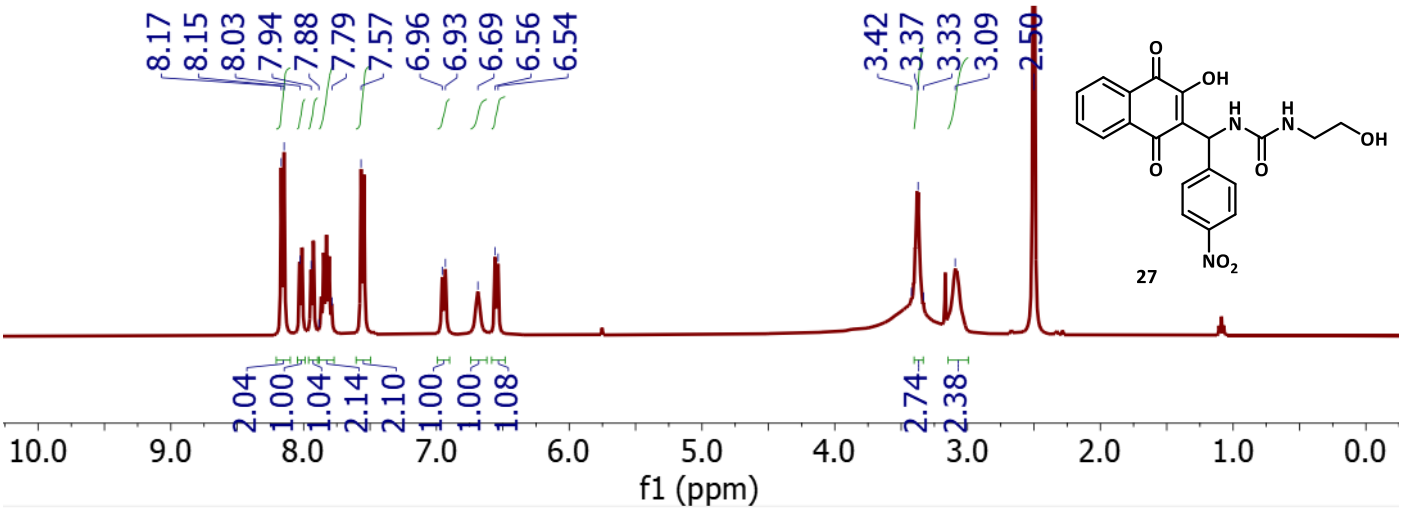


Figure S64: ^{1}H NMR (400 MHz, DMSO-d6) of compound **27**

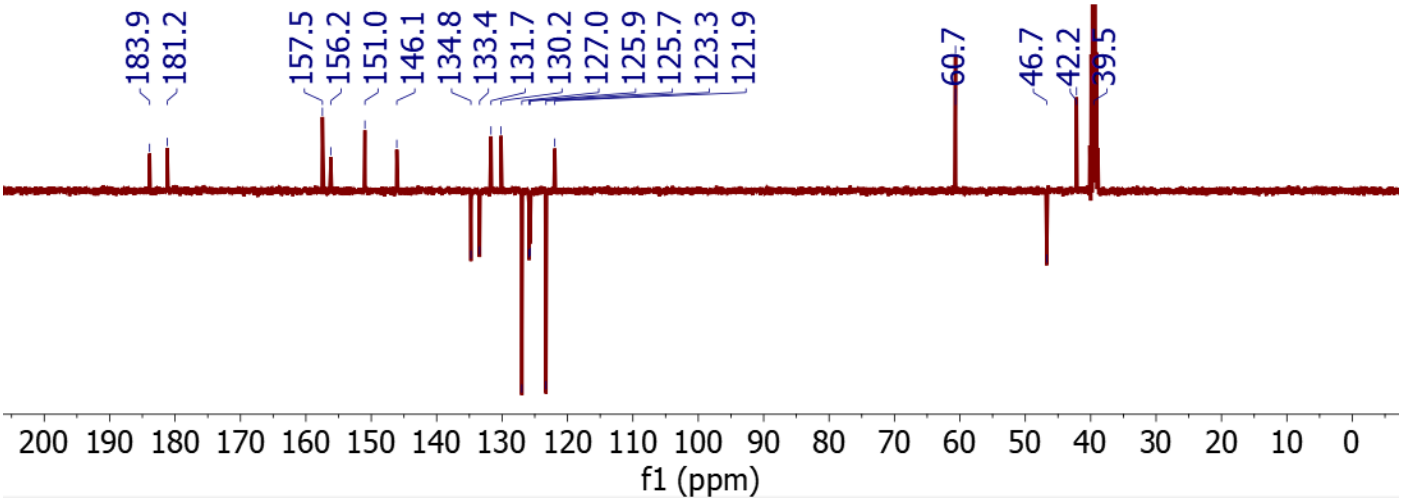


Figure S65: ^{13}C NMR (101 MHz, DMSO-d6) of compound **27**

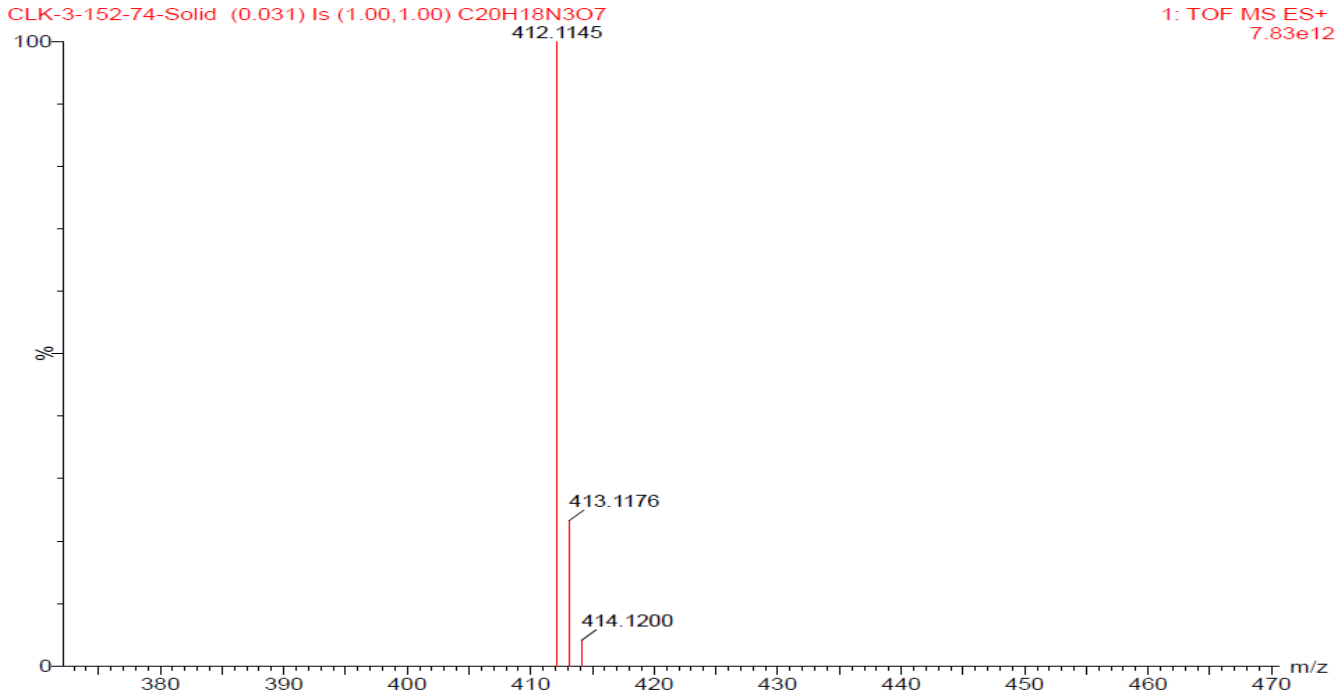


Figure S66: HRMS of compound **27**

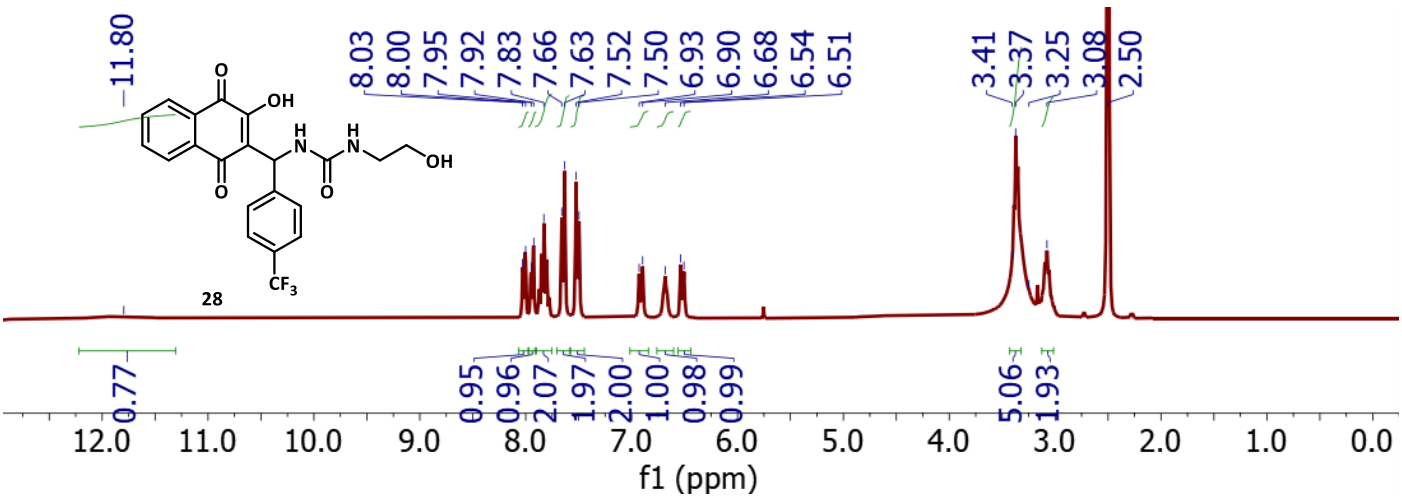


Figure S67: ^{1}H NMR (300 MHz, DMSO-d6) of compound **28**

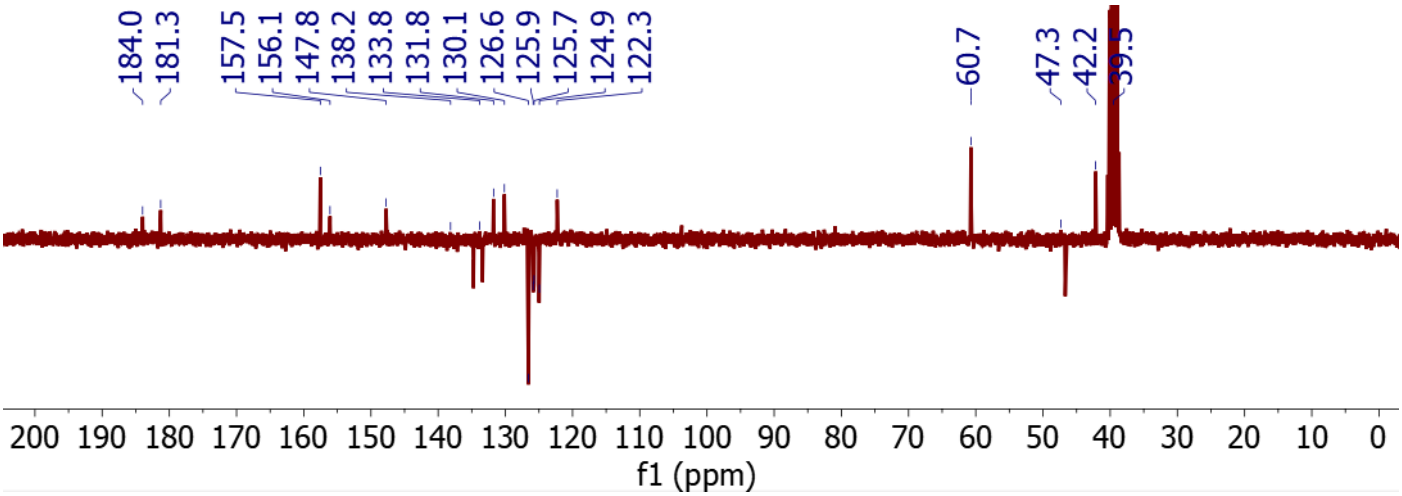


Figure S68: ^{13}C NMR (75 MHz, DMSO-d6) of compound **28**

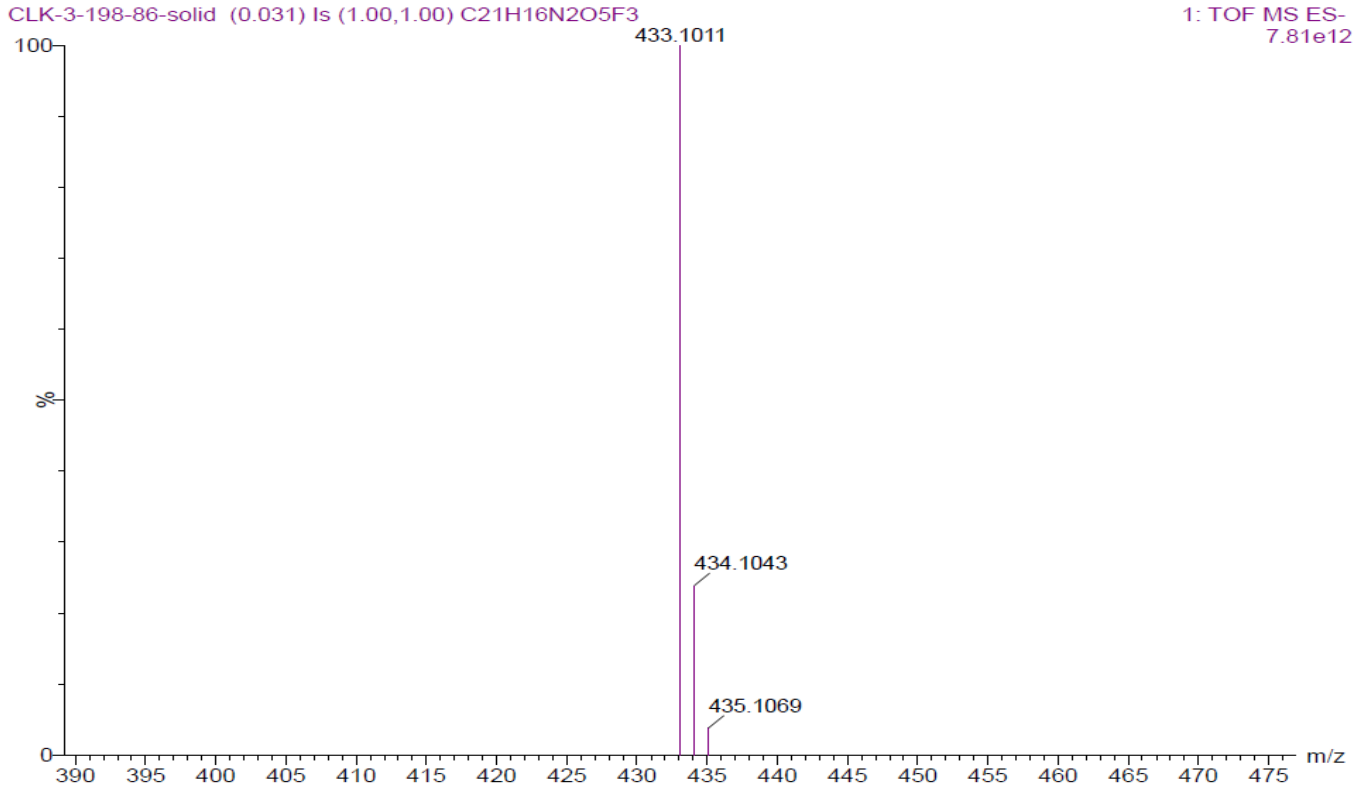


Figure S69: HRMS of compound **28**

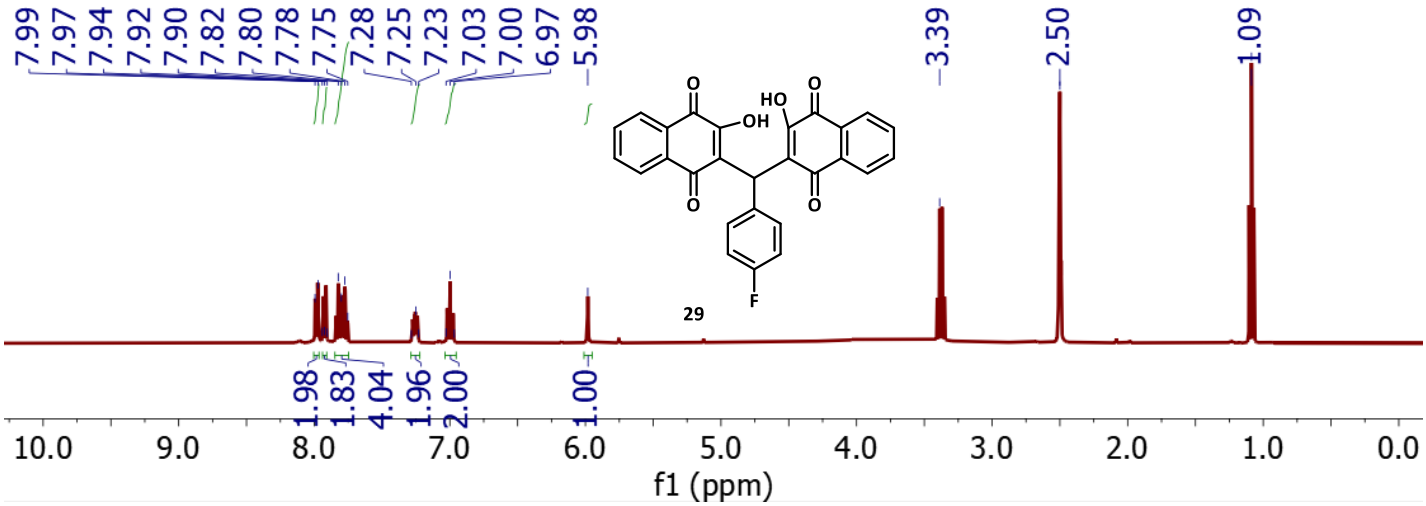


Figure S70: ^{1}H NMR (400 MHz, DMSO-d6) of compound **29**

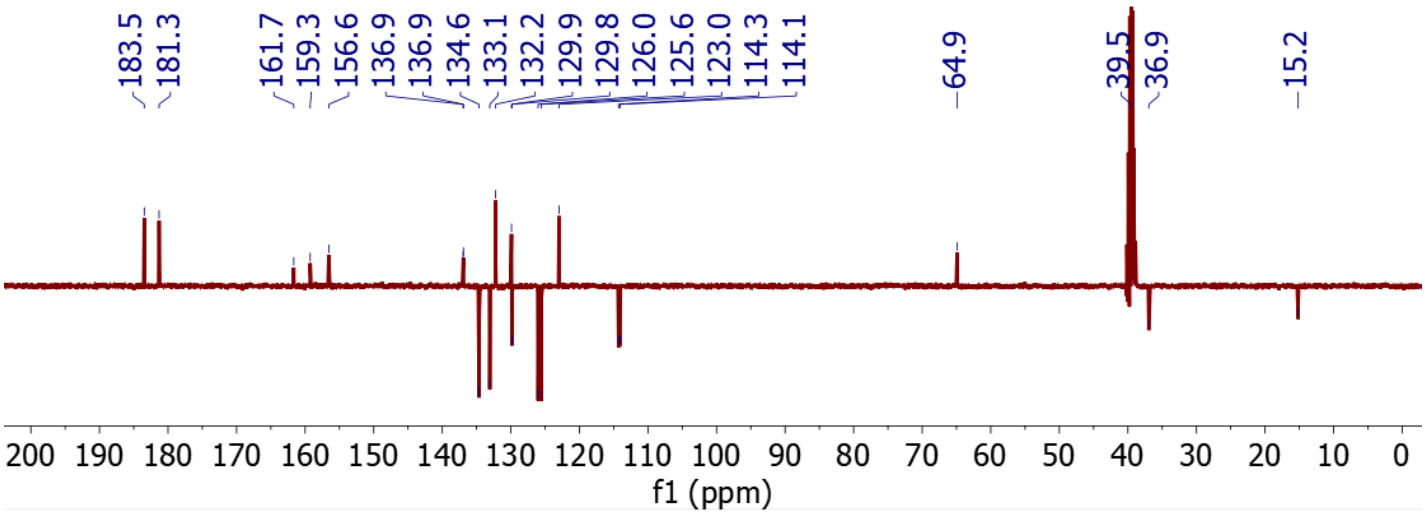


Figure S71: ^{13}C NMR (101 MHz, DMSO-d6) of compound **29**

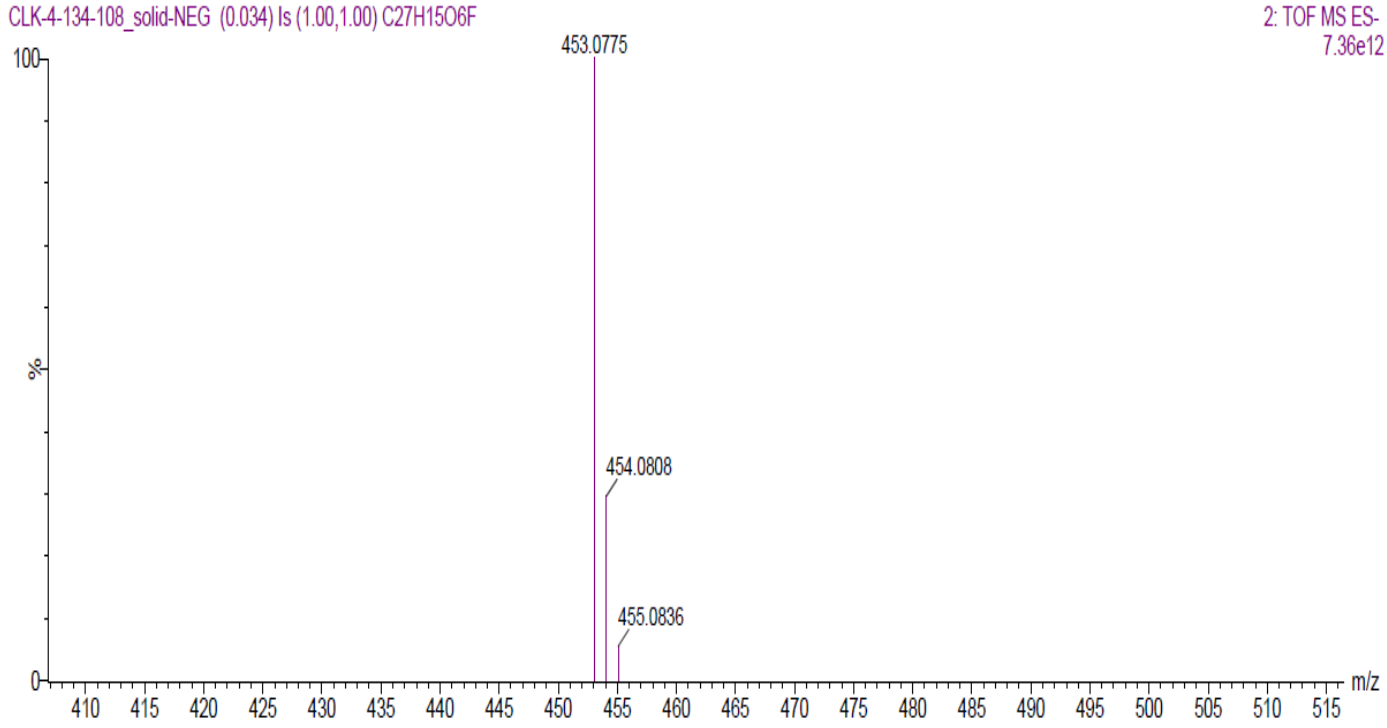


Figure S72: HRMS of compound **29**

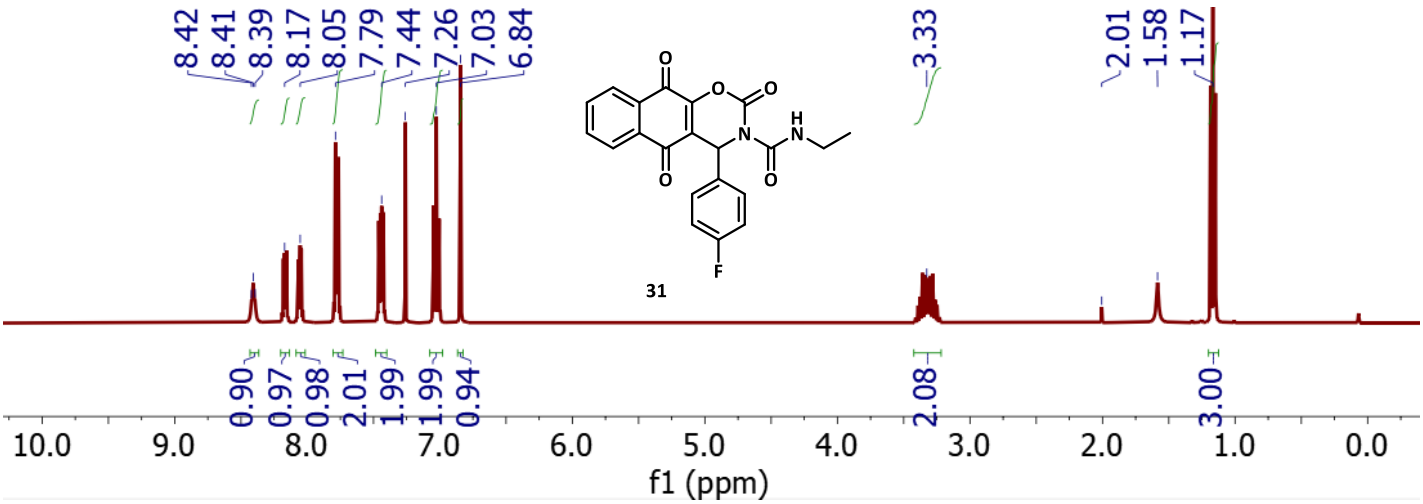


Figure S73: ^{1}H NMR (400 MHz, $CDCl_3$) of compound **31**

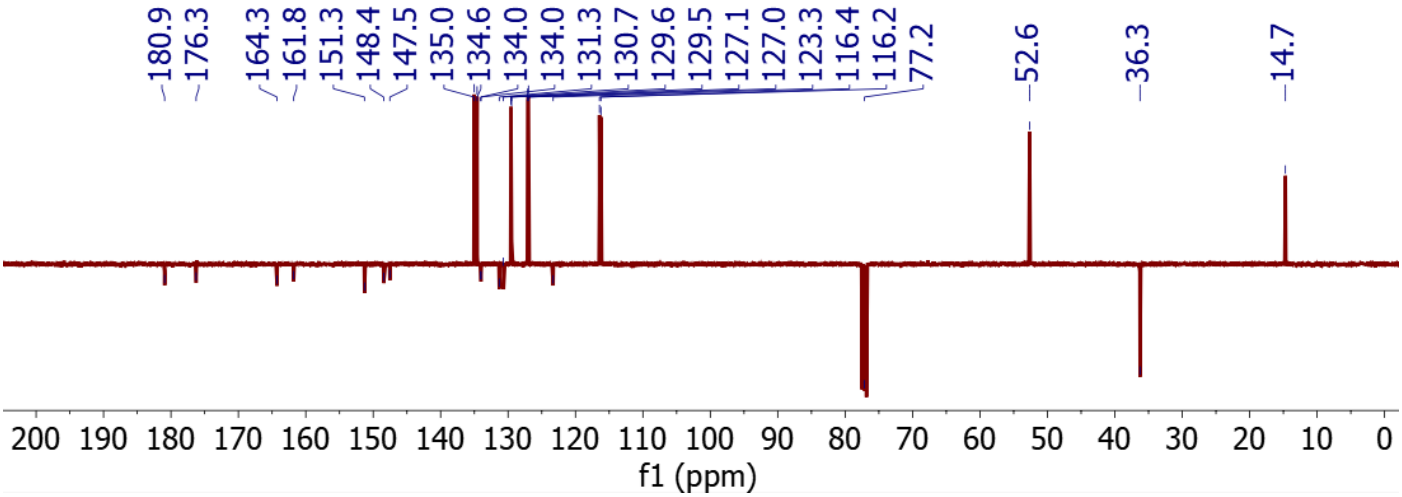


Figure S74: ^{13}C NMR (101 MHz, $CDCl_3$) of compound **31**

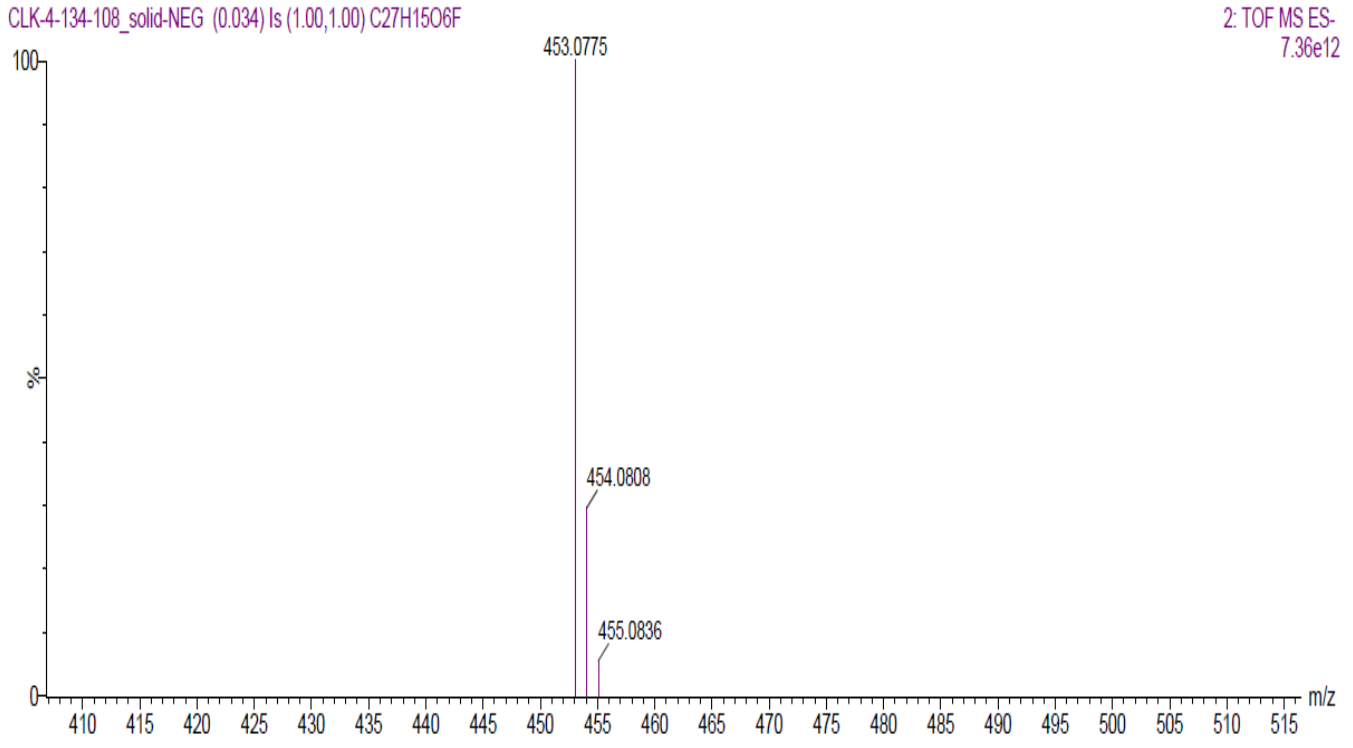


Figure S75: HRMS of compound **31**

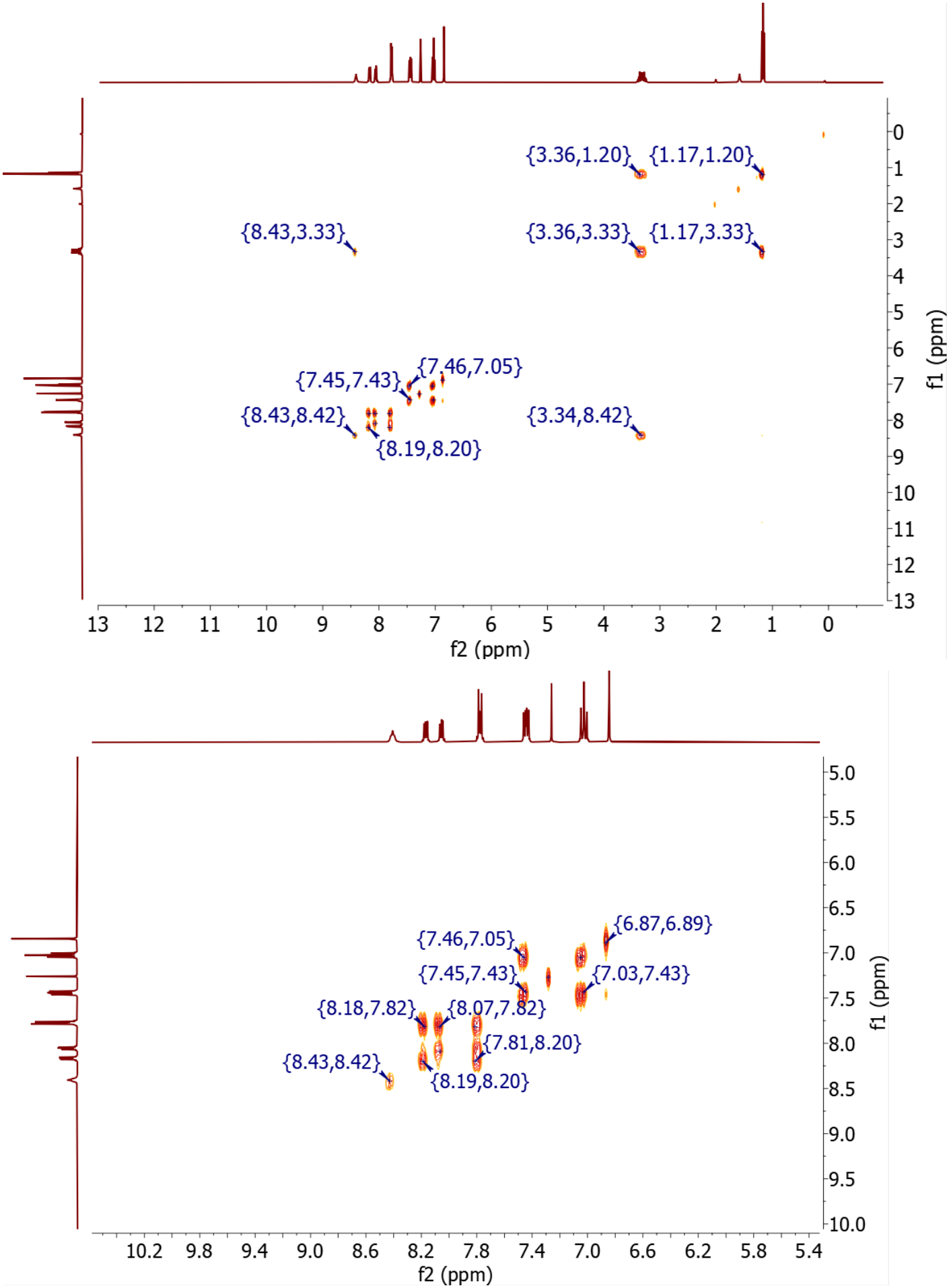


Figure S76: 2D COSY NMR (400 MHz, $CDCl_3$) of compound **31**

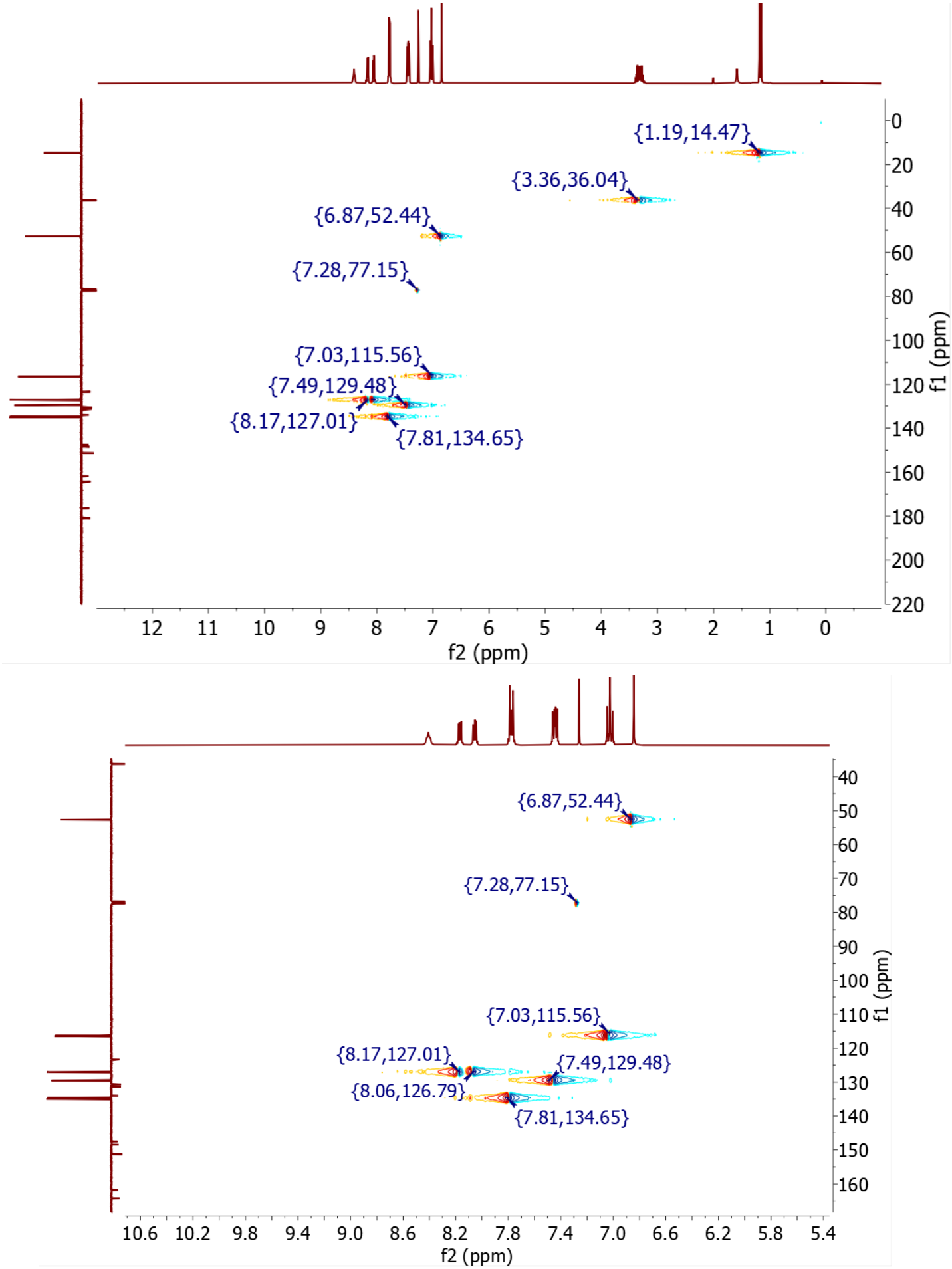


Figure S77: 2D HSQC NMR (400 MHz, $CDCl_3$) of compound **31**

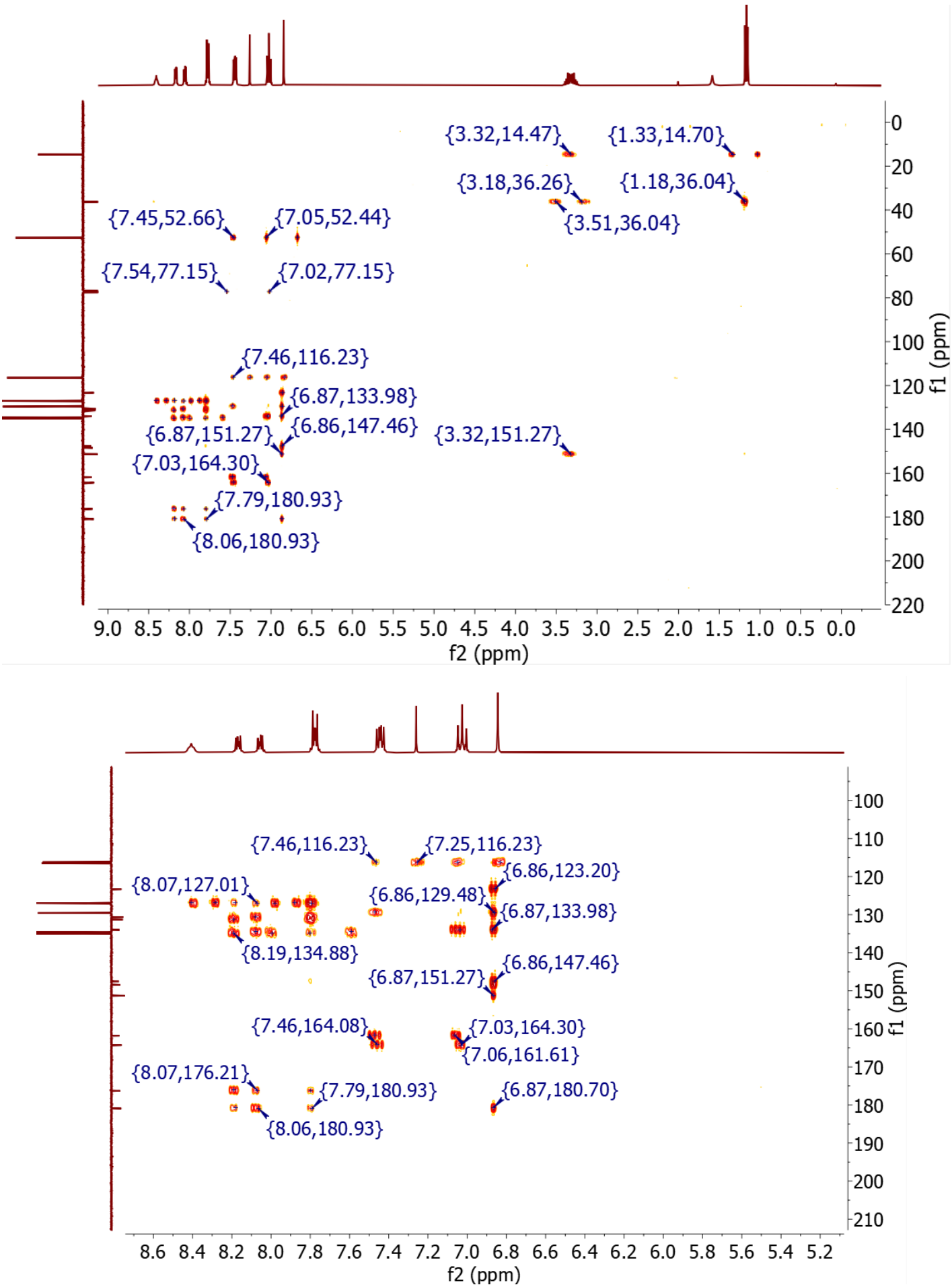
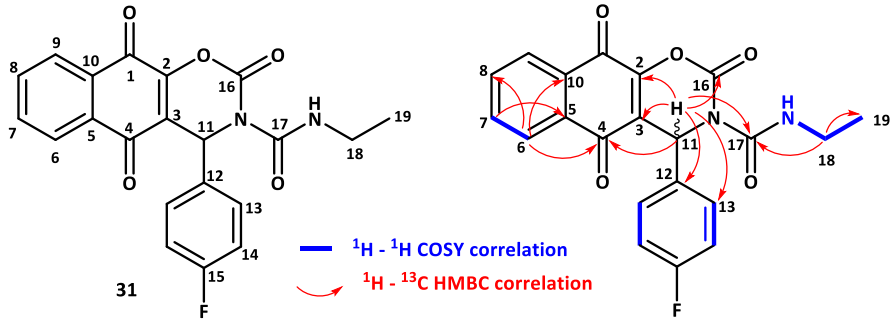


Figure S78: 2D HMBC NMR (400 MHz, $CDCl_3$) of compound **31**

Table S2. ^{1}H and ^{13}C NMR data assignments of compound **31** in $CDCl_3$ at 298K.



$^{1}H/^{13}C$ numbering	$d^{1}H$ (ppm) in $CDCl_3$	$d^{13}C$(ppm) in $CDCl_3$
C-1		176.3
C-2		147.6
C-3		123.3
C-4		180.9
C-5		131.3
CH-6	8.05 (m)	127.0
CH-7	7.79 (m)	135.0
CH-8	7.90 (m)	134.6
CH-9	8.17 (m)	127.1
C-10		131.3
CH-11	6.84 (s)	52.6
C-12		134.0
CH-13	7.44 (m)	129.5 (d)
CH-14	7.03 (m)	116.3 (d)
C-15		163.0 (d)
C-16		148.5
C-17		151.3
NH	8.41 (t)	
CH-18	a= 3.33 (m) b=3.37 (m)	36.3
CH-19	1.17 (t)	14.7

4. CRYSTALLOGRAPHIC DATA FOR COMPOUND 22

Table S3: Crystallographic data for compound **22**

$C_{21}H_{15}ClN_2O_4$	F(000) = 408
M_r = 394.80	
Triclinic, P-1	D_x = 1.412 Mg m^{-3}
Hall symbol: -P 1	
a = 9.5285 (15) Å	Mo Kα radiation, λ = 0.71073 Å
b = 10.8463 (17) Å	Cell parameters from 9921 reflections
c = 10.9208 (16) Å	θ = 2.5–36.9°
α = 94.939 (9)°	μ = 0.24 mm^{-1}
β = 113.931 (8)°	T = 100 K
γ = 110.838 (8)°	Block, yellow
V = 928.4 (3) $Å^3$	0.18 × 0.10 × 0.04 mm
Z = 2	

Table S4: Data collection

Bruker Kappa APEX II diffractometer	3423 reflections with $I > 2\sigma(I)$
Radiation source: fine-focus sealed tube	R_{int} = 0.056
Graphite monochromator	θ_{max} = 26.4°, θ_{min} = 2.1°
ω–ϕ scans	h = −11 11
Absorption correction: multi-scan [c.f. r.h. blessing, acta cryst. (1995), a51, 33-38]	k = −13 13
T_{min} = 0.715, T_{max} = 0.743	l = −13 13
39871 measured reflections	Standard reflections: 0
3787 independent reflections	

Table S5: Refinement

Refinement on F^2	
Least-squares matrix: full	Hydrogen site location: mixed
$R[F^2 > 2\sigma(F^2)] = 0.035$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.094$	$w = 1/[\sigma^2(F_o^2) + (0.0353P)^2 + 0.7665P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.04$	$(\Delta/\sigma)_{max} = 0.001$
3787 reflections	$\Delta\rho_{max} = 0.37$ e Å^{-3}
259 parameters	$\Delta\rho_{min} = -0.36$ e Å^{-3}
0 restraints	Extinction correction: none

Table S6: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.3609 (2)	0.02555 (15)	0.66677 (17)	0.0198 (3)
C1A	0.23661 (17)	0.41456 (14)	0.67006 (15)	0.0144 (3)
C2	0.26302 (18)	0.11018 (14)	0.63711 (15)	0.0146 (3)
C2A	0.28821 (18)	0.39958 (15)	0.80487 (15)	0.0170 (3)
H2A	0.311460	0.323348	0.824861	0.020*
C2B	0.2024 (2)	0.52667 (16)	0.64309 (16)	0.0221 (3)
H2B	0.165706	0.537336	0.551427	0.026*
C3	0.31583 (18)	0.22860 (14)	0.60102 (14)	0.0143 (3)
C3A	0.30604 (19)	0.49471 (16)	0.91028 (16)	0.0200 (3)
H3A	0.340146	0.483567	1.001701	0.024*

C3B	0.2207 (2)	0.62329 (17)	0.74746 (18)	0.0255 (4)
H3B	0.197475	0.699683	0.728155	0.031*
C4	0.48788 (18)	0.28985 (14)	0.61690 (14)	0.0152 (3)
C4A	0.2734 (2)	0.60568 (16)	0.88002 (16)	0.0214 (3)
C5	0.58968 (18)	0.20848 (15)	0.64490 (14)	0.0162 (3)
C6	0.74895 (19)	0.26095 (16)	0.65075 (16)	0.0219 (3)
H6	0.793074	0.348431	0.635773	0.026*
C7	0.8434 (2)	0.18490 (18)	0.67863 (18)	0.0263 (4)
H7	0.951875	0.220730	0.681819	0.032*
C8	0.7817 (2)	0.05743 (18)	0.70184 (17)	0.0244 (3)
H8	0.847850	0.006794	0.721574	0.029*
C9	0.6228 (2)	0.00428 (16)	0.69611 (16)	0.0206 (3)
H9	0.579389	−0.083127	0.711441	0.025*
C10	0.52745 (18)	0.07983 (15)	0.66773 (15)	0.0163 (3)
C11	0.20248 (18)	0.30243 (14)	0.55341 (14)	0.0143 (3)
H11	0.083392	0.232258	0.519429	0.017*
C12	0.11935 (18)	0.26723 (14)	0.30524 (15)	0.0149 (3)
C13	0.0812 (2)	0.23991 (16)	0.06734 (16)	0.0220 (3)
H13A	0.052177	0.295479	0.002098	0.026*
H13B	−0.025638	0.160747	0.046118	0.026*
C14	0.1942 (2)	0.18894 (17)	0.04345 (17)	0.0265 (4)
C15	0.2841 (3)	0.1478 (2)	0.0222 (2)	0.0393 (5)
H15	0.349 (3)	0.109 (2)	0.004 (2)	0.047*
N1	0.20678 (15)	0.35434 (12)	0.43586 (12)	0.0153 (3)
N2	0.15434 (17)	0.32243 (13)	0.20854 (13)	0.0228 (3)

O1	0.01213 (13)	0.14886 (10)	0.27472 (11)	0.0189 (2)
O2	0.54967 (13)	0.40855 (10)	0.61017 (11)	0.0204 (2)
O3	0.12003 (13)	0.06443 (10)	0.64617 (11)	0.0175 (2)
O4	0.29957 (18)	−0.08393 (13)	0.68741 (18)	0.0427 (4)
Cl1	0.30280 (6)	0.72832 (5)	1.01386 (4)	0.03234 (13)
H1	0.299320	0.424210	0.454280	0.016 (4)*
H2	0.240808	0.402761	0.236869	0.027 (5)*
H3	0.097110	−0.008350	0.666970	0.049 (7)*

Table S7: Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0230 (8)	0.0160 (7)	0.0266 (8)	0.0095 (6)	0.0154 (7)	0.0098 (6)
C1A	0.0137 (6)	0.0130 (6)	0.0157 (7)	0.0041 (5)	0.0076 (6)	0.0040 (5)
C2	0.0138 (6)	0.0144 (7)	0.0150 (7)	0.0047 (5)	0.0075 (6)	0.0034 (5)
C2A	0.0172 (7)	0.0186 (7)	0.0169 (7)	0.0086 (6)	0.0084 (6)	0.0066 (6)
C2B	0.0327 (9)	0.0198 (7)	0.0178 (7)	0.0136 (7)	0.0129 (7)	0.0085 (6)
C3	0.0166 (7)	0.0128 (7)	0.0140 (7)	0.0056 (6)	0.0081 (6)	0.0036 (5)
C3A	0.0184 (7)	0.0271 (8)	0.0148 (7)	0.0102 (6)	0.0078 (6)	0.0049 (6)
C3B	0.0379 (9)	0.0193 (8)	0.0271 (8)	0.0168 (7)	0.0179 (7)	0.0089 (7)
C4	0.0176 (7)	0.0142 (7)	0.0112 (6)	0.0038 (6)	0.0072 (6)	0.0028 (5)
C4A	0.0212 (8)	0.0215 (8)	0.0194 (7)	0.0075 (6)	0.0103 (6)	−0.0011 (6)
C5	0.0159 (7)	0.0176 (7)	0.0120 (6)	0.0042 (6)	0.0069 (6)	0.0017 (5)
C6	0.0181 (7)	0.0227 (8)	0.0211 (8)	0.0043 (6)	0.0099 (6)	0.0041 (6)
C7	0.0162 (7)	0.0340 (9)	0.0264 (8)	0.0082 (7)	0.0111 (7)	0.0033 (7)
C8	0.0216 (8)	0.0331 (9)	0.0204 (8)	0.0167 (7)	0.0079 (6)	0.0032 (7)

C9	0.0226 (8)	0.0214 (8)	0.0184 (7)	0.0109 (6)	0.0092 (6)	0.0042 (6)
C10	0.0174 (7)	0.0168 (7)	0.0149 (7)	0.0067 (6)	0.0086 (6)	0.0028 (5)
C11	0.0169 (7)	0.0132 (6)	0.0136 (7)	0.0056 (5)	0.0081 (6)	0.0054 (5)
C12	0.0159 (7)	0.0143 (7)	0.0167 (7)	0.0076 (6)	0.0084 (6)	0.0056 (5)
C13	0.0244 (8)	0.0228 (8)	0.0154 (7)	0.0055 (6)	0.0100 (6)	0.0053 (6)
C14	0.0326 (9)	0.0263 (8)	0.0190 (8)	0.0084 (7)	0.0137 (7)	0.0097 (6)
C15	0.0527 (12)	0.0508 (12)	0.0378 (11)	0.0323 (11)	0.0311 (10)	0.0232 (9)
N1	0.0178 (6)	0.0118 (6)	0.0151 (6)	0.0032 (5)	0.0091 (5)	0.0052 (5)
N2	0.0269 (7)	0.0155 (6)	0.0168 (6)	−0.0018 (5)	0.0115 (6)	0.0028 (5)
O1	0.0197 (5)	0.0148 (5)	0.0192 (5)	0.0022 (4)	0.0108 (4)	0.0048 (4)
O2	0.0193 (5)	0.0143 (5)	0.0240 (6)	0.0022 (4)	0.0109 (5)	0.0071 (4)
O3	0.0168 (5)	0.0146 (5)	0.0260 (6)	0.0065 (4)	0.0136 (4)	0.0105 (4)
O4	0.0432 (8)	0.0293 (7)	0.0906 (12)	0.0251 (6)	0.0499 (8)	0.0403 (7)
Cl1	0.0392 (3)	0.0333 (2)	0.0249 (2)	0.01861 (19)	0.01478 (19)	−0.00284 (17)

Table S8: Geometric parameters (Å, °)

C1—O4	1.2090 (19)	C6—C7	1.390 (2)
C1—C10	1.478 (2)	C6—H6	0.9500
C1—C2	1.494 (2)	C7—C8	1.387 (3)
C1A—C2B	1.392 (2)	C7—H7	0.9500
C1A—C2A	1.395 (2)	C8—C9	1.387 (2)
C1A—C11	1.5243 (19)	C8—H8	0.9500
C2—O3	1.3226 (17)	C9—C10	1.393 (2)
C2—C3	1.359 (2)	C9—H9	0.9500
C2A—C3A	1.389 (2)	C11—N1	1.4551 (17)
C2A—H2A	0.9500	C11—H11	1.0000

C2B—C3B	1.390 (2)	C12—O1	1.2329 (17)
C2B—H2B	0.9500	C12—N2	1.3554 (19)
C3—C4	1.461 (2)	C12—N1	1.3658 (19)
C3—C11	1.520 (2)	C13—N2	1.453 (2)
C3A—C4A	1.381 (2)	C13—C14	1.469 (2)
C3A—H3A	0.9500	C13—H13A	0.9900
C3B—C4A	1.382 (2)	C13—H13B	0.9900
C3B—H3B	0.9500	C14—C15	1.185 (3)
C4—O2	1.2336 (18)	C15—H15	0.93 (2)
C4—C5	1.493 (2)	N1—H1	0.8641 (12)
C4A—Cl1	1.7471 (16)	N2—O3	5.8051 (18)
C5—C6	1.390 (2)	N2—H2	0.8774 (13)
C5—C10	1.397 (2)	O3—H3	0.8191 (10)
O4—C1—C10	123.43 (14)	C9—C8—C7	119.70 (15)
O4—C1—C2	118.54 (14)	C9—C8—H8	120.2
C10—C1—C2	118.02 (13)	C7—C8—H8	120.2
C2B—C1A—C2A	118.54 (13)	C8—C9—C10	119.57 (15)
C2B—C1A—C11	121.32 (13)	C8—C9—H9	120.2
C2A—C1A—C11	119.88 (12)	C10—C9—H9	120.2
O3—C2—C3	120.66 (13)	C9—C10—C5	120.85 (14)
O3—C2—C1	117.10 (12)	C9—C10—C1	119.60 (13)
C3—C2—C1	122.23 (13)	C5—C10—C1	119.51 (13)
C3A—C2A—C1A	120.86 (14)	N1—C11—C3	112.29 (12)
C3A—C2A—H2A	119.6	N1—C11—C1A	111.12 (11)
C1A—C2A—H2A	119.6	C3—C11—C1A	113.62 (11)

C3B—C2B—C1A	121.37 (14)	N1—C11—H11	106.4
C3B—C2B—H2B	119.3	C3—C11—H11	106.4
C1A—C2B—H2B	119.3	C1A—C11—H11	106.4
C2—C3—C4	119.32 (13)	O1—C12—N2	121.76 (13)
C2—C3—C11	120.83 (13)	O1—C12—N1	123.41 (13)
C4—C3—C11	119.73 (12)	N2—C12—N1	114.79 (12)
C4A—C3A—C2A	118.94 (14)	N2—C13—C14	113.73 (14)
C4A—C3A—H3A	120.5	N2—C13—H13A	108.8
C2A—C3A—H3A	120.5	C14—C13—H13A	108.8
C4A—C3B—C2B	118.47 (14)	N2—C13—H13B	108.8
C4A—C3B—H3B	120.8	C14—C13—H13B	108.8
C2B—C3B—H3B	120.8	H13A—C13—H13B	107.7
O2—C4—C3	120.34 (13)	C15—C14—C13	179.05 (18)
O2—C4—C5	120.36 (13)	C14—C15—H15	176.0 (15)
C3—C4—C5	119.28 (12)	C12—N1—C11	120.22 (12)
C3A—C4A—C3B	121.82 (14)	C12—N1—H1	116.63 (13)
C3A—C4A—Cl1	118.92 (12)	C11—N1—H1	115.77 (12)
C3B—C4A—Cl1	119.25 (12)	C12—N2—C13	121.29 (12)
C6—C5—C10	119.20 (14)	C12—N2—O3	11.26 (8)
C6—C5—C4	120.27 (13)	C13—N2—O3	120.59 (9)
C10—C5—C4	120.52 (13)	C12—N2—H2	118.38 (13)
C5—C6—C7	119.73 (15)	C13—N2—H2	118.60 (13)
C5—C6—H6	120.1	O3—N2—H2	114.94 (9)
C7—C6—H6	120.1	C2—O3—N2	60.54 (8)
C8—C7—C6	120.95 (15)	C2—O3—H3	114.04 (11)

C8—C7—H7	119.5	N2—O3—H3	144.89 (9)
C6—C7—H7	119.5		

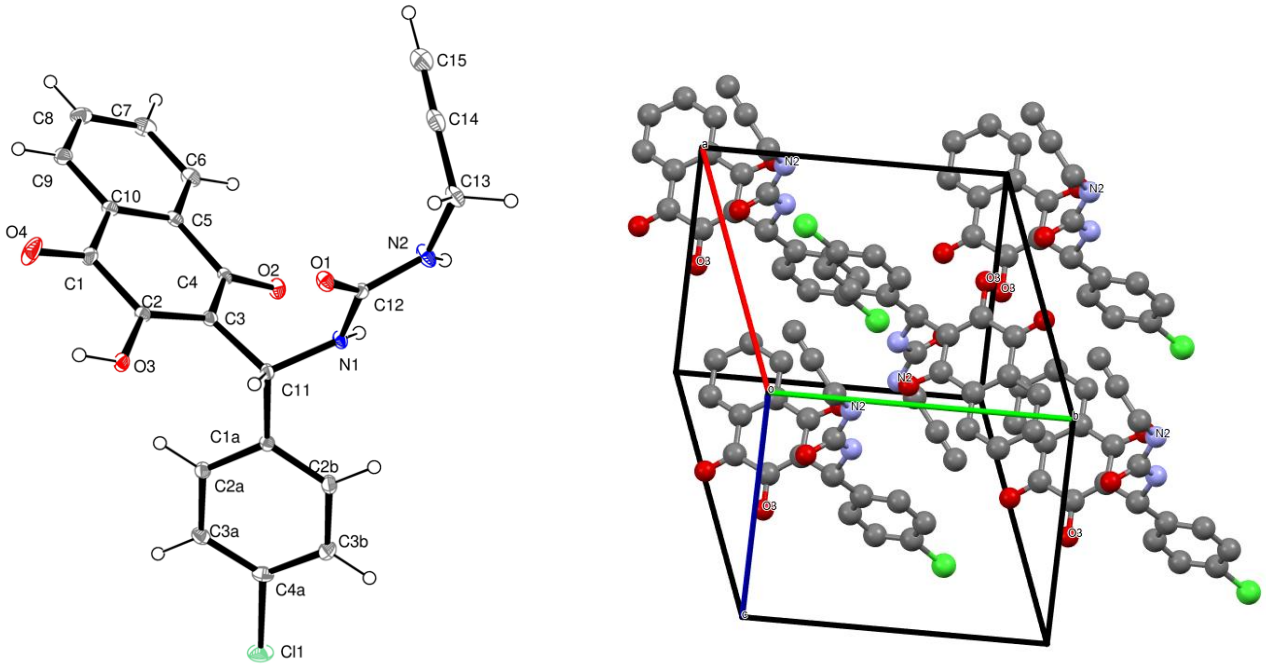


Figure S79: Crystallographic structure and crystal lattice of compound **22**

5. DFT CALCULATIONS

Calculations were performed with the Gaussian 16 suite of programs [1] using the density functional method B3LYP with dispersion (D3). [2, 3] All other atoms have been described with a 6-31+G(d,p) basis set with diffuse function for heavy atoms. Geometry optimisations were carried out without any symmetry restrictions. Frequency calculations were undertaken to confirm the nature of the stationary points, yielding one imaginary frequency for transition states (TS) and all of them positive for *minima*. The connectivity of the transition states and their adjacent *minima* was confirmed by intrinsic reaction coordinate (IRC) calculations.[4,5]

Solvent effects were taken into account using the conductor-like polarizable continuum model (CPCM).[6] Single-point calculations on the gas-phase optimized geometries were performed to estimate the change in energy in the presence of the solvent, ethanol. The triple-zeta quality 6-311++G(d,p) basis set was used to account for the solvent effects. The Gibbs free energy values provided in the text are Gibbs energy in solution, Gsol, which was calculated by adding the thermochemistry corrections, G-E, to the refined single point energies, Esol, i.e., Gsol = Esol + G – E. The sums of the electronic and thermal free energies (G) for reactants and transition states were obtained by the standard procedure in the framework of the harmonic approximation. The ΔG# of the reactions was calculated from the differences in the G values of the transition states and the reactants.

5.1 CYCLIZATION PATHWAY

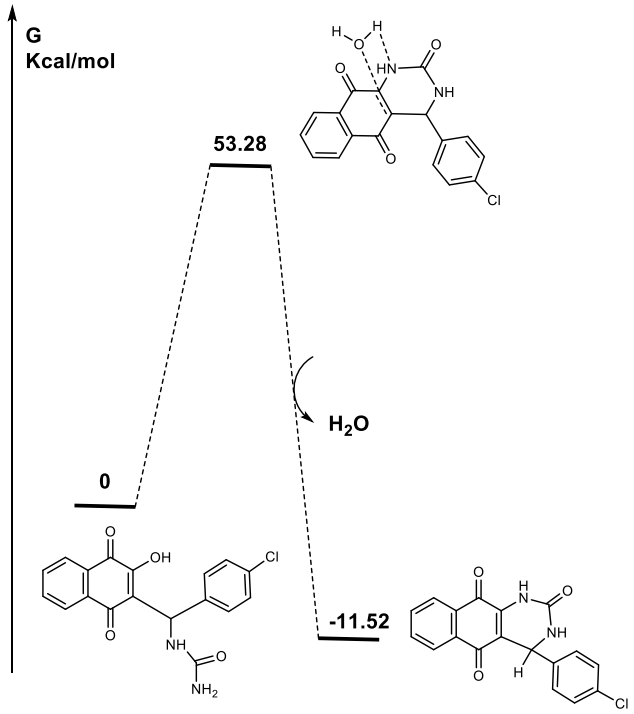
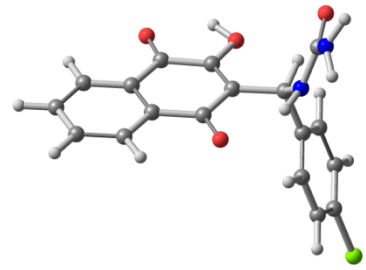


Figure S80: Cyclization pathway of Biginelli-linear to DHPM.

Sum of electronic and thermal Free Energies= -1564.308665 au

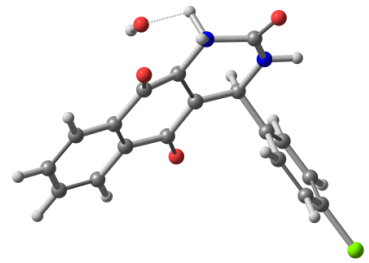


C	-8.194218000000	-2.621556000000	6.256976000000
C	-6.923060000000	-2.047491000000	6.271151000000
C	-6.708906000000	-0.825401000000	5.626854000000
C	-7.765141000000	-0.171977000000	4.964581000000
C	-9.033711000000	-0.752938000000	4.956767000000
C	-9.246264000000	-1.974222000000	5.601030000000
H	-8.365389000000	-3.570042000000	6.755705000000
H	-6.090786000000	-2.528470000000	6.773315000000
C	-5.376036000000	-0.203104000000	5.635811000000
C	-7.548737000000	1.137426000000	4.269426000000
H	-9.837815000000	-0.237663000000	4.443742000000
H	-10.235056000000	-2.421924000000	5.591512000000
C	-6.204975000000	1.732742000000	4.261766000000
C	-5.203212000000	1.102617000000	4.930119000000
C	-5.949320000000	3.065333000000	3.569118000000

H	-4.880587000000	3.116144000000	3.357052000000
O	-4.387337000000	-0.686645000000	6.187611000000
O	-8.501254000000	1.695474000000	3.712635000000
O	-3.967264000000	1.609017000000	5.015132000000
H	-3.435027000000	0.957055000000	5.516636000000
N	-6.601723000000	3.151300000000	2.271488000000
H	-7.577971000000	2.884516000000	2.259507000000
C	-5.857659000000	2.954816000000	1.126664000000
N	-6.618162000000	2.841668000000	-0.027620000000
H	-7.522462000000	3.291876000000	-0.057602000000
H	-6.074424000000	2.914202000000	-0.875705000000
O	-4.632464000000	2.869459000000	1.113984000000
C	-6.304584000000	4.218093000000	4.500362000000
C	-7.625142000000	4.646207000000	4.683625000000
C	-5.284786000000	4.847523000000	5.222701000000
C	-7.923320000000	5.687674000000	5.561733000000
H	-8.431004000000	4.160044000000	4.145287000000
C	-5.566411000000	5.889318000000	6.108046000000
H	-4.257276000000	4.522679000000	5.090943000000
C	-6.888070000000	6.300022000000	6.268150000000
H	-8.946194000000	6.019682000000	5.699563000000
H	-4.772061000000	6.378886000000	6.659987000000
Cl	-7.258296000000	7.613657000000	7.377026000000

TS

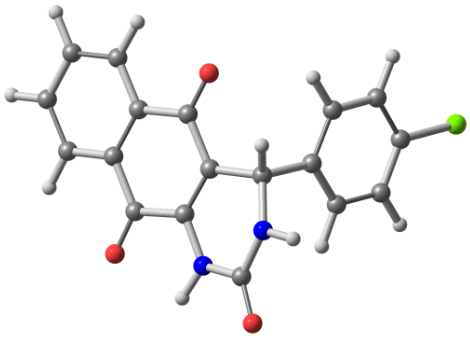
Sum of electronic and thermal Free Energies= -1564.222159 au



C	-8.504638000000	-2.631285000000	4.879914000000
C	-7.272037000000	-2.232164000000	4.366439000000
C	-6.838865000000	-0.915861000000	4.553209000000
C	-7.647311000000	0.018305000000	5.232391000000
C	-8.884975000000	-0.391167000000	5.733023000000
C	-9.308009000000	-1.710313000000	5.562490000000
H	-8.839596000000	-3.655577000000	4.751293000000
H	-6.630263000000	-2.924179000000	3.832046000000
C	-5.544553000000	-0.474393000000	4.008015000000
C	-7.229274000000	1.454043000000	5.396459000000
H	-9.500240000000	0.340723000000	6.244598000000
H	-10.269581000000	-2.022070000000	5.958672000000
C	-5.937955000000	1.843180000000	4.864152000000
C	-5.058573000000	0.843779000000	4.513150000000
C	-5.503206000000	3.280255000000	4.989375000000
H	-5.299507000000	3.529171000000	6.039332000000
O	-4.893318000000	-1.072003000000	3.155580000000
O	-7.967854000000	2.254953000000	5.982950000000
O	-3.990396000000	-0.001454000000	5.902562000000
H	-4.405449000000	0.184781000000	6.756422000000
N	-4.246897000000	3.503030000000	4.226703000000
H	-4.042199000000	4.466473000000	3.988294000000
C	-3.485940000000	2.623466000000	3.563490000000
N	-3.758234000000	1.205207000000	3.920925000000
H	-3.153199000000	0.881426000000	4.730627000000
H	-3.578874000000	0.581704000000	3.116788000000
O	-2.584837000000	2.847072000000	2.782758000000
C	-6.532410000000	4.269276000000	4.461868000000
C	-6.952794000000	5.340606000000	5.250390000000

C	-7.036032000000	4.136974000000	3.163827000000
C	-7.868478000000	6.272671000000	4.760008000000
H	-6.584620000000	5.438367000000	6.267387000000
C	-7.949982000000	5.057718000000	2.656968000000
H	-6.722087000000	3.299969000000	2.547000000000
C	-8.358623000000	6.120670000000	3.464515000000
H	-8.203424000000	7.099194000000	5.376025000000
H	-8.345530000000	4.953782000000	1.653093000000
Cl	-9.511766000000	7.285258000000	2.835161000000

Sum of electronic and thermal Free Energies= -1487.895400 au



C	-9.222482000000	-2.137917000000	4.887640000000
C	-8.342576000000	-1.613822000000	3.941020000000
C	-7.498929000000	-0.553564000000	4.287429000000
C	-7.535078000000	-0.014382000000	5.589061000000
C	-8.416777000000	-0.546956000000	6.530559000000
C	-9.258515000000	-1.604789000000	6.180218000000
H	-9.877880000000	-2.960416000000	4.619822000000
H	-8.293558000000	-2.012185000000	2.933495000000
C	-6.560745000000	-0.007168000000	3.283461000000
C	-6.643971000000	1.123713000000	5.978432000000
H	-8.429626000000	-0.119974000000	7.527207000000
H	-9.943731000000	-2.013867000000	6.916030000000
C	-5.765244000000	1.684137000000	4.953469000000
C	-5.698554000000	1.135818000000	3.711981000000
C	-4.927010000000	2.903231000000	5.269569000000
H	-4.555173000000	2.804427000000	6.293117000000
O	-6.460407000000	-0.437527000000	2.138740000000
O	-6.650272000000	1.569710000000	7.127952000000
N	-3.771308000000	2.919639000000	4.367144000000
H	-3.051891000000	3.607074000000	4.547918000000
C	-3.770381000000	2.470519000000	3.073190000000
N	-4.827636000000	1.606021000000	2.767325000000

H	-4.806784000000	1.147773000000	1.863097000000
O	-2.915681000000	2.751079000000	2.244507000000
C	-5.772334000000	4.175161000000	5.189059000000
C	-6.428585000000	4.644413000000	6.333175000000
C	-5.933388000000	4.866831000000	3.982762000000
C	-7.235618000000	5.780477000000	6.278941000000
H	-6.323263000000	4.103894000000	7.267847000000
C	-6.736636000000	6.005542000000	3.913481000000
H	-5.424960000000	4.533011000000	3.084650000000
C	-7.382807000000	6.451730000000	5.065403000000
H	-7.741646000000	6.142746000000	7.166602000000
H	-6.856139000000	6.541475000000	2.978816000000
Cl	-8.393540000000	7.885855000000	4.987820000000

5.2 KNOEVENAGEL PATHWAY

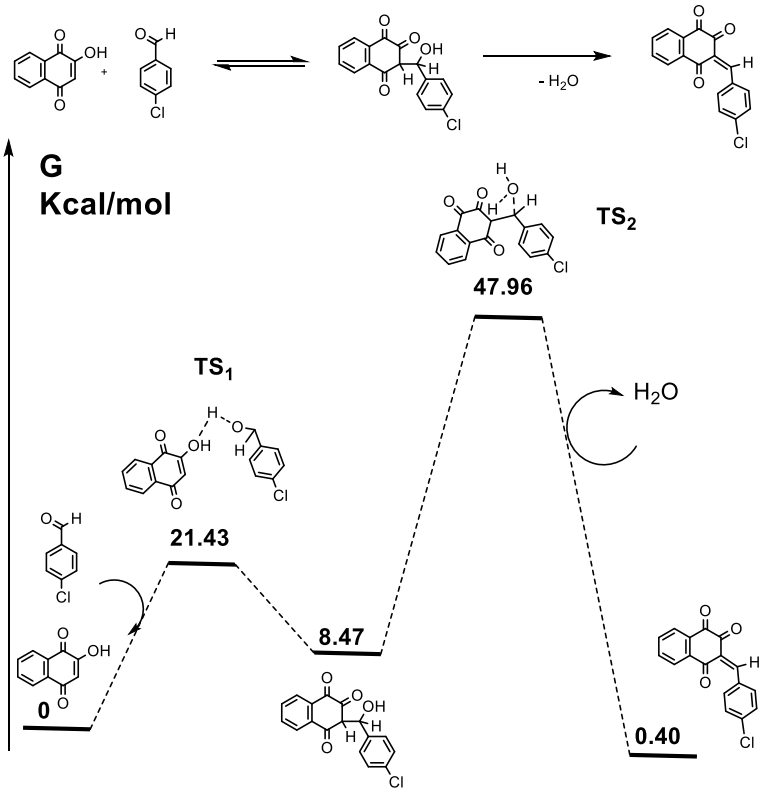
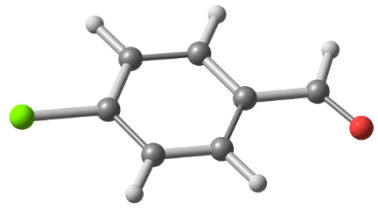


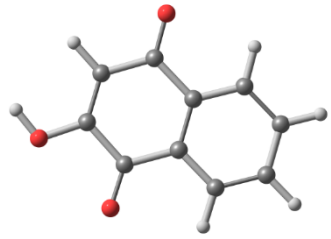
Figure S81: Knoevenagel pathway between lawsone and 4-chlorobenzaldehyde.

Sum of electronic and thermal Free Energies= -805.152331 au



C	-6.000385000000	4.997664000000	3.770735000000
C	-5.819501000000	3.605746000000	3.797086000000
C	-6.932781000000	5.559797000000	2.888982000000
C	-6.560241000000	2.786356000000	2.953778000000
H	-5.093627000000	3.185762000000	4.485530000000
C	-7.682536000000	4.750481000000	2.037659000000
H	-7.072800000000	6.637509000000	2.868646000000
C	-7.486234000000	3.369283000000	2.080838000000
H	-6.430575000000	1.710199000000	2.963837000000
H	-8.406169000000	5.175928000000	1.352121000000
C	-5.216993000000	5.877013000000	4.664079000000
O	-4.384522000000	5.487969000000	5.463986000000
H	-5.437774000000	6.960994000000	4.562665000000
Cl	-8.421084000000	2.339291000000	1.017010000000

Thermal Free Energies= -610.313048 au

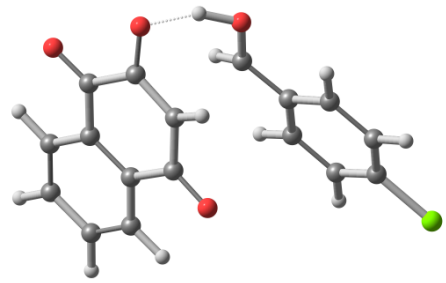


C	-8.086854000000	-1.054923000000	9.007834000000
C	-6.890241000000	-0.573793000000	8.478807000000
C	-6.782748000000	0.770628000000	8.106070000000
C	-7.882552000000	1.634588000000	8.265819000000
C	-9.078440000000	1.145727000000	8.796561000000
C	-9.180092000000	-0.195615000000	9.166542000000
H	-8.169145000000	-2.097986000000	9.296635000000
H	-6.029973000000	-1.220780000000	8.346638000000
C	-5.497750000000	1.263785000000	7.543888000000
C	-7.781289000000	3.073083000000	7.871705000000
H	-9.911808000000	1.830351000000	8.910172000000
H	-10.110830000000	-0.572730000000	9.578783000000
C	-5.442312000000	2.717790000000	7.161532000000
O	-4.521719000000	0.546063000000	7.389931000000

O	-8.731581000000	3.842860000000	8.003914000000
O	-4.248436000000	3.083830000000	6.662216000000
H	-4.258797000000	4.023965000000	6.430862000000
C	-6.506392000000	3.539197000000	7.319737000000
H	-6.464600000000	4.589643000000	7.042961000000

TS1

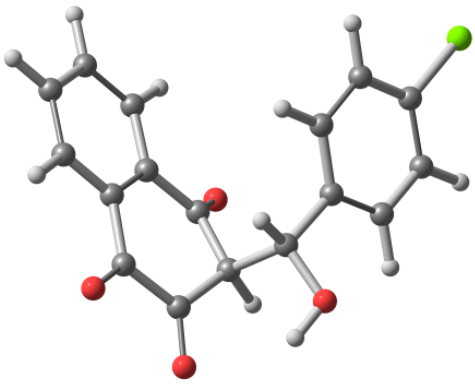
Sum of electronic and thermal Free Energies= -1415.431218 au



C	-8.674039000000	0.302234000000	8.940743000000
C	-7.550482000000	1.083364000000	9.200726000000
C	-6.743459000000	1.527216000000	8.144753000000
C	-7.067736000000	1.176432000000	6.818592000000
C	-8.194987000000	0.388270000000	6.567295000000
C	-8.996421000000	-0.045035000000	7.622791000000
H	-9.298641000000	-0.037673000000	9.760906000000
H	-7.279387000000	1.364378000000	10.212653000000
C	-5.562148000000	2.379901000000	8.450170000000
C	-6.207360000000	1.610497000000	5.672129000000
H	-8.415661000000	0.121481000000	5.539405000000
H	-9.870258000000	-0.657273000000	7.421916000000
C	-4.752380000000	2.921076000000	7.263234000000
O	-5.235640000000	2.666143000000	9.589266000000
O	-6.465826000000	1.250038000000	4.519139000000
O	-3.883363000000	3.808526000000	7.495122000000
H	-4.175604000000	4.833598000000	6.506089000000
C	-6.451207000000	4.546418000000	4.245139000000
C	-7.788763000000	4.120278000000	4.166834000000
C	-5.729552000000	4.795750000000	3.063040000000
C	-8.406461000000	3.956495000000	2.933501000000
H	-8.341316000000	3.906235000000	5.076822000000
C	-6.338754000000	4.634363000000	1.827268000000
H	-4.696610000000	5.117807000000	3.130363000000

C	-7.673819000000	4.215495000000	1.773504000000
H	-9.434774000000	3.622581000000	2.864891000000
H	-5.794819000000	4.824870000000	0.909540000000
O	-4.662771000000	5.245905000000	5.661895000000
C	-5.109149000000	2.517509000000	5.954696000000
H	-4.419353000000	2.701137000000	5.139353000000
C	-5.833360000000	4.692252000000	5.543659000000
H	-6.483173000000	4.660249000000	6.420096000000
Cl	-8.439207000000	4.009764000000	0.216776000000

Sum of electronic and thermal Free Energies= -1415.451884 au

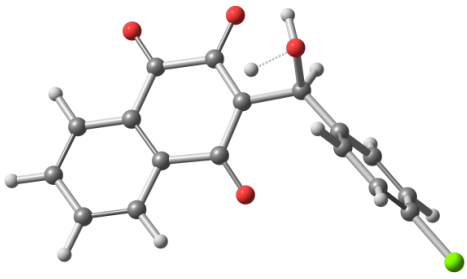


C	-8.169548000000	1.247043000000	9.716146000000
C	-6.851009000000	1.687589000000	9.765530000000
C	-6.065179000000	1.687351000000	8.603145000000
C	-6.615104000000	1.222543000000	7.388864000000
C	-7.937660000000	0.765256000000	7.352766000000
C	-8.713304000000	0.784853000000	8.508850000000
H	-8.777003000000	1.256651000000	10.615521000000
H	-6.405346000000	2.034715000000	10.691335000000
C	-4.652971000000	2.138083000000	8.694834000000
C	-5.807161000000	1.199084000000	6.138096000000
H	-8.334387000000	0.406864000000	6.409266000000
H	-9.741673000000	0.439055000000	8.475539000000
C	-3.822308000000	2.153935000000	7.383662000000
O	-4.135224000000	2.507184000000	9.732496000000
O	-6.117578000000	0.510680000000	5.180659000000
O	-2.621180000000	2.330876000000	7.421373000000
H	-3.095888000000	4.128355000000	5.992195000000
C	-6.010801000000	3.690619000000	4.670405000000
C	-5.639851000000	3.542061000000	3.330494000000
C	-7.360770000000	3.852560000000	4.993367000000
C	-6.603490000000	3.550475000000	2.324289000000

H	-4.591997000000	3.429737000000	3.075527000000
C	-8.338431000000	3.856964000000	3.997937000000
H	-7.658801000000	3.978070000000	6.030633000000
C	-7.947176000000	3.702766000000	2.669436000000
H	-6.319770000000	3.437496000000	1.284258000000
H	-9.385460000000	3.985937000000	4.247005000000
C	-4.981985000000	3.612155000000	5.769352000000
O	-3.822247000000	4.316794000000	5.377653000000
H	-5.413787000000	4.050076000000	6.681317000000
C	-4.589809000000	2.102691000000	6.085548000000
H	-3.940606000000	1.771933000000	5.272231000000
Cl	-9.166662000000	3.708370000000	1.406191000000

TS2

Sum of electronic and thermal Free Energies= -1415.388951 au

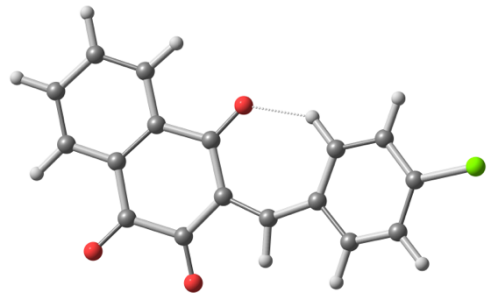


C	-7.804373000000	-0.242563000000	10.319820000000
C	-6.711196000000	0.617923000000	10.307105000000
C	-6.433283000000	1.386896000000	9.167476000000
C	-7.267538000000	1.293650000000	8.035758000000
C	-8.369738000000	0.432104000000	8.062366000000
C	-8.634549000000	-0.334794000000	9.194949000000
H	-8.014498000000	-0.839571000000	11.201674000000
H	-6.056674000000	0.713587000000	11.166586000000
C	-5.261650000000	2.294954000000	9.186903000000
C	-7.036594000000	2.114130000000	6.799697000000
H	-9.005455000000	0.385218000000	7.185285000000
H	-9.489327000000	-1.004041000000	9.205518000000
C	-4.937450000000	3.070167000000	7.892140000000
O	-4.553650000000	2.446820000000	10.166279000000
O	-7.887969000000	2.135789000000	5.913328000000
O	-3.941805000000	3.802753000000	7.866688000000
H	-3.461526000000	3.581401000000	5.856066000000

C	-6.304123000000	3.951349000000	4.385237000000
C	-6.282477000000	2.989124000000	3.370446000000
C	-7.160185000000	5.049580000000	4.269351000000
C	-7.114791000000	3.111537000000	2.262239000000
H	-5.617373000000	2.135840000000	3.441972000000
C	-8.011436000000	5.178235000000	3.172215000000
H	-7.176798000000	5.808687000000	5.046284000000
C	-7.979704000000	4.203839000000	2.177192000000
H	-7.100841000000	2.367225000000	1.474539000000
H	-8.681807000000	6.025440000000	3.086159000000
C	-5.445559000000	3.842725000000	5.602046000000
O	-4.094988000000	3.193910000000	5.210630000000
H	-5.196520000000	4.826027000000	6.004707000000
C	-5.760515000000	2.841685000000	6.705274000000
H	-4.633337000000	2.317279000000	5.916746000000
Cl	-9.037072000000	4.357783000000	0.784709000000

Knoevenagel intermediate

Sum of electronic and thermal Free Energies= -1339.033096 au



C	-7.218876000000	1.305988000000	11.240269000000
C	-6.038304000000	1.791169000000	10.688765000000
C	-5.875488000000	1.829643000000	9.296322000000
C	-6.906535000000	1.376845000000	8.451151000000
C	-8.091680000000	0.888963000000	9.019062000000
C	-8.247143000000	0.853736000000	10.401675000000
H	-7.342978000000	1.276649000000	12.318201000000
H	-5.224747000000	2.145673000000	11.312043000000
C	-4.605297000000	2.342196000000	8.738629000000
C	-6.803058000000	1.398489000000	6.956736000000
H	-8.875638000000	0.544446000000	8.354812000000
H	-9.169264000000	0.474275000000	10.830810000000
C	-4.413957000000	2.295183000000	7.203964000000

O	-3.712564000000	2.793137000000	9.432826000000
O	-7.740312000000	0.945219000000	6.298052000000
O	-3.309624000000	2.563983000000	6.761942000000
C	-6.086376000000	2.136544000000	3.746177000000
C	-5.392970000000	2.666609000000	2.627861000000
C	-7.378036000000	1.604533000000	3.525382000000
C	-5.950751000000	2.681829000000	1.357829000000
H	-4.397213000000	3.075885000000	2.769064000000
C	-7.944480000000	1.615243000000	2.256239000000
H	-7.918134000000	1.181085000000	4.358466000000
C	-7.232107000000	2.153351000000	1.181990000000
H	-5.407916000000	3.092755000000	0.514674000000
H	-8.934527000000	1.203896000000	2.096112000000
C	-5.363576000000	2.210041000000	4.999695000000
H	-4.361808000000	2.613444000000	4.856809000000
C	-5.581758000000	1.950284000000	6.332976000000
Cl	-7.951209000000	2.160894000000	-0.411008000000

5.3 MICHAEL PATHWAY

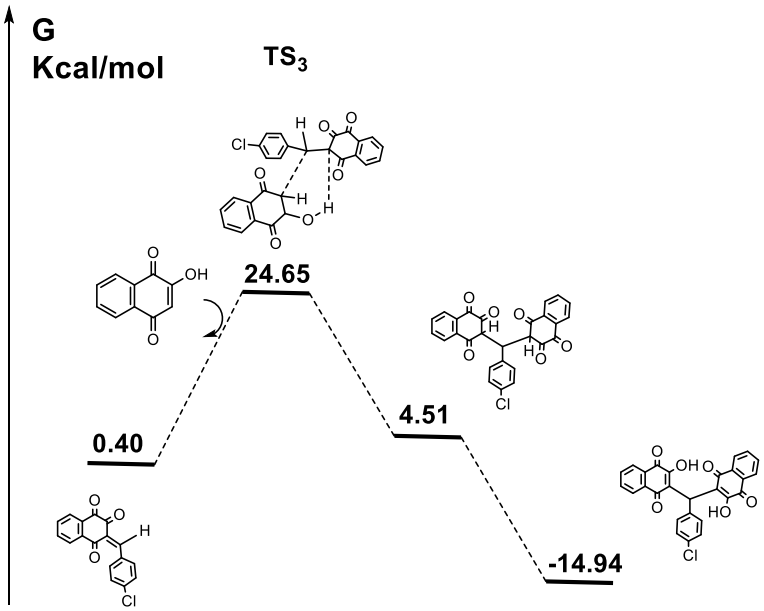
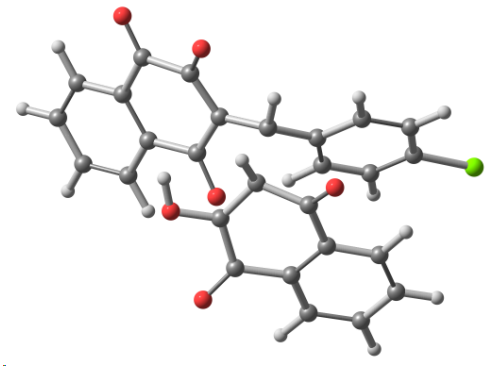


Figure S82: Michael reaction pathway starting from Knoevenagel intermediate to Michael product formation.

TS3

Sum of electronic and thermal Free Energies= -1949.306861 au



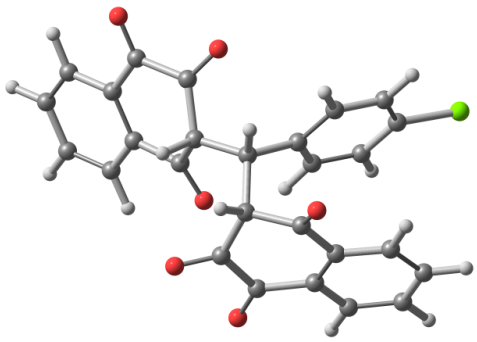
C	-5.372914000000	-2.202274000000	7.845453000000
C	-5.304293000000	-0.896498000000	8.327791000000
C	-4.932492000000	0.148101000000	7.473487000000
C	-4.631021000000	-0.121440000000	6.123848000000
C	-4.689883000000	-1.434780000000	5.649494000000
C	-5.062242000000	-2.470244000000	6.507199000000
H	-5.661177000000	-3.011056000000	8.509511000000
H	-5.525595000000	-0.663691000000	9.363851000000
C	-4.821400000000	1.529603000000	8.008738000000
C	-4.260172000000	0.976962000000	5.192078000000
H	-4.439374000000	-1.623176000000	4.611703000000
H	-5.109074000000	-3.488356000000	6.133239000000
C	-4.294523000000	2.633121000000	7.055958000000
O	-5.113026000000	1.818107000000	9.155473000000
O	-3.858928000000	0.697209000000	4.026466000000
O	-3.942776000000	3.712331000000	7.531025000000
C	-4.702271000000	3.728805000000	3.484722000000
C	-5.291160000000	2.788614000000	2.621416000000
C	-4.827096000000	5.092488000000	3.161935000000
C	-5.957013000000	3.195140000000	1.468859000000
H	-5.195237000000	1.733835000000	2.830323000000
C	-5.486955000000	5.512957000000	2.010407000000
H	-4.382789000000	5.838149000000	3.812958000000
C	-6.036977000000	4.553208000000	1.162715000000
H	-6.394106000000	2.461036000000	0.801935000000
H	-5.565783000000	6.567052000000	1.770878000000
C	-3.931358000000	3.411651000000	4.727906000000
H	-3.790577000000	4.322229000000	5.307883000000
C	-4.260019000000	2.325815000000	5.633826000000
C	-2.093347000000	1.881363000000	1.642929000000

C	-2.204559000000	3.285589000000	1.696988000000
C	-2.567431000000	4.003987000000	0.554545000000
C	-2.859305000000	3.324616000000	-0.625678000000
C	-2.756450000000	1.928490000000	-0.678799000000
C	-2.356057000000	1.209183000000	0.445510000000
H	-2.641328000000	5.083182000000	0.618534000000
H	-3.170876000000	3.879465000000	-1.504671000000
H	-2.984455000000	1.404303000000	-1.601440000000
H	-2.250129000000	0.130295000000	0.419339000000
C	-1.648233000000	1.106365000000	2.827985000000
C	-1.957208000000	4.006485000000	2.970865000000
O	-1.183362000000	-0.018573000000	2.772921000000
O	-1.690310000000	5.196634000000	3.028780000000
C	-1.764849000000	1.832327000000	4.135867000000
O	-1.363929000000	1.168284000000	5.197060000000
H	-1.449625000000	1.708514000000	6.000241000000
C	-2.127234000000	3.206248000000	4.232738000000
H	-1.690600000000	3.715556000000	5.092707000000
Cl	-6.828885000000	5.059668000000	-0.317841000000

Keto-Michael

Sum of electronic and thermal Free Energies= -1949.338949 au

C	-6.007754000000	-1.092893000000	8.725885000000
C	-5.731226000000	0.267276000000	8.822650000000
C	-5.130053000000	0.939287000000	7.749278000000
C	-4.816358000000	0.233694000000	6.568272000000
C	-5.104278000000	-1.134347000000	6.477933000000
C	-5.694148000000	-1.793661000000	7.552875000000
H	-6.468313000000	-1.611805000000	9.560486000000
H	-5.972944000000	0.832057000000	9.716374000000
C	-4.874033000000	2.394520000000	7.864807000000

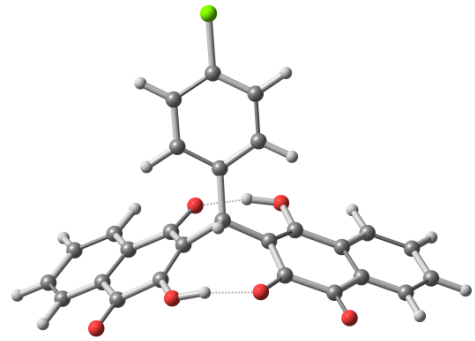


C	-4.171923000000	0.897689000000	5.404606000000
H	-4.848688000000	-1.658320000000	5.563736000000
H	-5.909591000000	-2.854979000000	7.481741000000
C	-4.316735000000	3.109255000000	6.612808000000
O	-5.078515000000	3.036937000000	8.877993000000
O	-4.128782000000	0.351522000000	4.314425000000
O	-4.493585000000	4.295158000000	6.457757000000
C	-4.094458000000	3.501779000000	3.412191000000
C	-4.215051000000	4.881315000000	3.185381000000
C	-4.867233000000	2.640166000000	2.619675000000
C	-5.048649000000	5.393237000000	2.192841000000
H	-3.635025000000	5.572334000000	3.787927000000
C	-5.709264000000	3.134018000000	1.623908000000
H	-4.798467000000	1.571047000000	2.751469000000
C	-5.784705000000	4.507659000000	1.409211000000
H	-5.120156000000	6.462084000000	2.027432000000
H	-6.285821000000	2.452911000000	1.008605000000
C	-3.035740000000	3.062750000000	4.420756000000
H	-2.682675000000	3.998684000000	4.858259000000
C	-3.501020000000	2.249532000000	5.645378000000
C	-2.321164000000	1.374847000000	1.111508000000
C	-1.981904000000	2.738473000000	1.242002000000
C	-2.210404000000	3.619053000000	0.178578000000
C	-2.792914000000	3.155378000000	-0.997085000000
C	-3.123730000000	1.799905000000	-1.132003000000
C	-2.875186000000	0.912589000000	-0.089698000000
H	-1.948865000000	4.663338000000	0.305857000000
H	-2.995651000000	3.846443000000	-1.809011000000
H	-3.576103000000	1.442029000000	-2.051530000000
H	-3.114616000000	-0.141769000000	-0.175008000000
C	-2.093294000000	0.403061000000	2.212962000000
C	-1.429798000000	3.278714000000	2.512702000000
O	-2.239435000000	-0.797204000000	2.080863000000
O	-0.844414000000	4.348236000000	2.571961000000

C	-1.634496000000	0.980113000000	3.570459000000
O	-1.160346000000	0.253851000000	4.420171000000
H	-2.601375000000	1.973925000000	6.227279000000
C	-1.705755000000	2.482559000000	3.783143000000
H	-0.910444000000	2.713874000000	4.497624000000
Cl	-6.813574000000	5.129468000000	0.128388000000

Enol-Michael

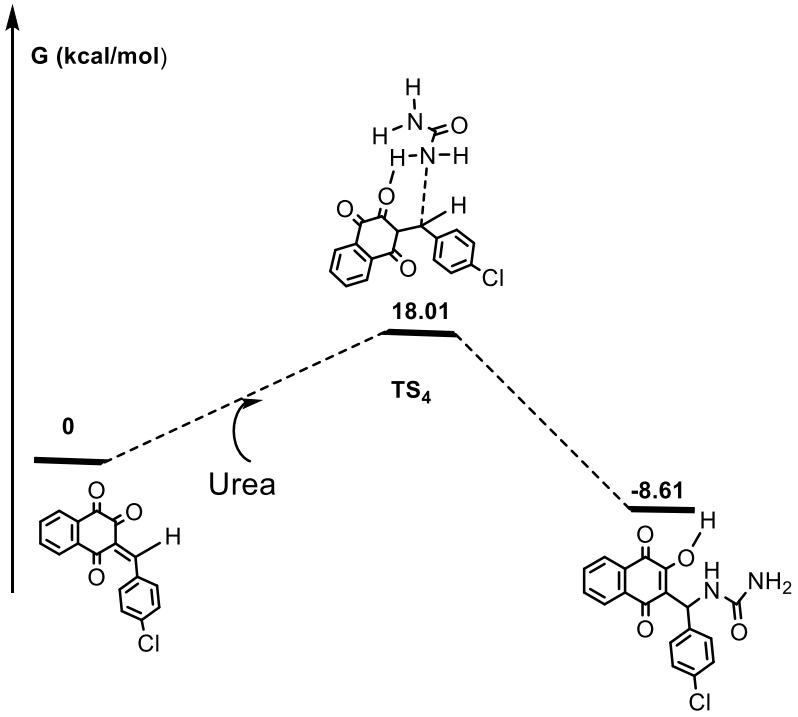
Sum of electronic and thermal Free Energies= -1949.369959 au



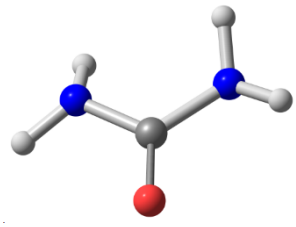
C	-4.227826000000	-2.134657000000	8.611394000000
C	-3.608053000000	-0.900996000000	8.813798000000
C	-3.488179000000	-0.001378000000	7.751675000000
C	-3.987647000000	-0.339098000000	6.482242000000
C	-4.600754000000	-1.579012000000	6.282421000000
C	-4.723758000000	-2.472294000000	7.347742000000
H	-4.321973000000	-2.833614000000	9.436376000000
H	-3.209467000000	-0.619366000000	9.782240000000
C	-2.817365000000	1.306121000000	7.965143000000
C	-3.863553000000	0.615170000000	5.350803000000
H	-4.975890000000	-1.822591000000	5.295033000000
H	-5.205346000000	-3.432564000000	7.192693000000
C	-2.743448000000	2.248665000000	6.783844000000
O	-2.353175000000	1.636904000000	9.043227000000
O	-4.220998000000	0.248042000000	4.212712000000
O	-2.094244000000	3.363829000000	7.059116000000
C	-4.831300000000	3.129406000000	3.857994000000
C	-5.972029000000	2.869597000000	4.627926000000
C	-5.010627000000	3.632890000000	2.565641000000
C	-7.253785000000	3.075573000000	4.121499000000
H	-5.867900000000	2.500766000000	5.643214000000

C	-6.285774000000	3.845808000000	2.040027000000
H	-4.150071000000	3.868559000000	1.949984000000
C	-7.401047000000	3.559584000000	2.822733000000
H	-8.127460000000	2.864285000000	4.727483000000
H	-6.409275000000	4.229806000000	1.033830000000
C	-3.435994000000	2.999365000000	4.480274000000
H	-3.293803000000	3.959081000000	4.987425000000
C	-3.347487000000	1.954379000000	5.584607000000
C	-0.076767000000	3.117885000000	1.552568000000
C	-1.132445000000	2.199711000000	1.384918000000
C	-1.155776000000	1.381521000000	0.250156000000
C	-0.144099000000	1.485293000000	-0.707573000000
C	0.900264000000	2.398224000000	-0.539703000000
C	0.932769000000	3.213281000000	0.592313000000
H	-1.965617000000	0.673558000000	0.125261000000
H	-0.172689000000	0.848409000000	-1.586054000000
H	1.685866000000	2.472068000000	-1.284723000000
H	1.733290000000	3.927152000000	0.753404000000
C	-0.032912000000	3.978979000000	2.757469000000
C	-2.210330000000	2.108712000000	2.390915000000
O	0.834183000000	4.811015000000	2.949100000000
O	-3.113134000000	1.185635000000	2.116159000000
C	-1.156716000000	3.794273000000	3.799710000000
O	-1.048280000000	4.413551000000	4.871311000000
H	-1.796516000000	3.854347000000	6.237353000000
C	-2.275708000000	2.940496000000	3.494820000000
H	-3.680219000000	0.938635000000	2.916418000000
Cl	-9.011472000000	3.815062000000	2.168876000000

5.4 UREA ADDITION TO KNOEVENAGEL INTERMEDIATE TOWARDS BIGINELLI-LINEAR



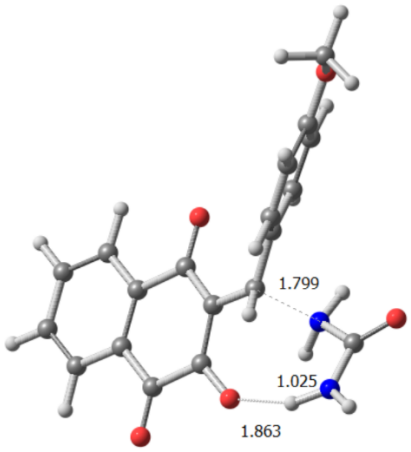
Thermal Free Energies= -225.261842 au



N	-4.595143000000	0.924114000000	-0.395423000000
H	-4.018256000000	1.743943000000	-0.269204000000
H	-4.113321000000	0.041430000000	-0.300679000000
N	-6.448335000000	2.174423000000	0.258031000000
H	-6.164807000000	2.900147000000	-0.385232000000
H	-7.436139000000	2.148228000000	0.467359000000
C	-5.872514000000	0.919192000000	0.142088000000
O	-6.444152000000	-0.107598000000	0.485590000000

TS 4

Thermal Free Energies= -1219.164899 au



C	-8.209976000000	-2.805175000000	7.310745000000
C	-6.926077000000	-2.434697000000	6.919699000000
C	-6.702928000000	-1.175602000000	6.346966000000
C	-7.773363000000	-0.282572000000	6.162495000000
C	-9.060361000000	-0.665371000000	6.553239000000
C	-9.277490000000	-1.917695000000	7.126747000000
H	-8.382311000000	-3.780298000000	7.755783000000
H	-6.080286000000	-3.101834000000	7.046538000000
C	-5.331583000000	-0.797322000000	5.930281000000
C	-7.586069000000	1.079749000000	5.548564000000
H	-9.872208000000	0.036349000000	6.398750000000
H	-10.279628000000	-2.205014000000	7.430610000000
C	-6.231374000000	1.500005000000	5.242488000000
C	-5.133686000000	0.596299000000	5.317941000000
C	-5.837850000000	2.850623000000	4.831380000000
H	-4.857455000000	3.071882000000	5.250746000000
O	-4.374244000000	-1.542516000000	6.061300000000
O	-8.589446000000	1.774720000000	5.341337000000
O	-3.986807000000	0.878592000000	4.883232000000
H	-5.021094000000	1.686429000000	3.080634000000
N	-5.253724000000	2.679977000000	3.138112000000
H	-6.023172000000	2.934490000000	2.520243000000
C	-4.091845000000	3.524665000000	2.826369000000
N	-2.981858000000	3.062646000000	3.427441000000
H	-3.039049000000	2.244424000000	4.041818000000
H	-2.125629000000	3.581486000000	3.307239000000
O	-4.230068000000	4.514583000000	2.135254000000
C	-6.674693000000	4.075004000000	4.821898000000
C	-6.168710000000	5.209021000000	5.467255000000

C	-7.892491000000	4.195460000000	4.124732000000
C	-6.858462000000	6.422661000000	5.470243000000
H	-5.217542000000	5.146935000000	5.988799000000
C	-8.574996000000	5.398889000000	4.093745000000
H	-8.319065000000	3.332089000000	3.630810000000
C	-8.068779000000	6.519660000000	4.774700000000
H	-6.439822000000	7.271603000000	5.995202000000
H	-9.514082000000	5.496750000000	3.560478000000
O	-8.821655000000	7.648815000000	4.694076000000
C	-8.359157000000	8.820699000000	5.357525000000
H	-9.109293000000	9.587009000000	5.162573000000
H	-8.275401000000	8.656365000000	6.438466000000
H	-7.390956000000	9.145391000000	4.958102000000

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