Supporting Information

A Facile and Light-Controllable Drug Combination for enhanced Photopharmacology

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1. Materials and Methods

1.1 Bacterial strain and growth conditions

The bacterial strains used in this study were *E. coli* BL21 (DE3) And *S. aureus* ATCC 23350. *E. coli* were grown in Luria Bertani (LB) medium (5 g/L yeast extract; 10 g/L tryptone; 5 g/L NaCl) at 37 °C and *S. aureus* were grown in Luria Bertani (LB) medium (5 g/L yeast extract; 10 g/L tryptone; 5 g/L NaCl) at 37 °C.

1.2 Solid medium

For bacterial patterning LB Agar (40 g/L Agar) was used. The required concentration of only 1A (5 μM), only 1B (100 μM) and a combination of 1A (5 μM) and 1B (100 μM) were dissolved in 12 mL LB Agar after which it was mixed and solidified in a plate. Subsequently, the plate was partly covered with a sterile thin cardboard and irradiated with λ = 532 nm for 30 minutes. The plate was then streaked with approximately 10^8 CFU/ml of *S. aureus* ATCC 23350 and incubated for 12 h (1A) or 36 h (1B, combination of 1A and 1B) at 37 °C.

1.3 Antibacterial activity and bacterial growth curves.

Overnight cultures of *E. coli* BL21 (DE3) and *S. aureus* ATCC 23350 were diluted to an OD_{600} of 0.1 and 100 µl of this cell suspension was added to 100 µl medium containing antibiotics at the corresponding concentration. Cells were grown in a microtiter plate at 37 °C, for *E. coli* and *S. aureus* and cell density (600 nm) was measured every 1 h for 12 h, with a 10 sec shaking step before each measurement, in a microplate reader (iMarks, BIO-RAD). The OD_{600} collected every hour will be subtracted from the OD_{600} at 0 h to get the corrected OD_{600}. MIC is the minimum concentration when bacteria are no longer growing over time and the cell suspension is transparent after OD_{600} test.

1.4 Drug combination and methodology of irradiation

Method of irradiation: in order to reduce the influence of blue light on bacterial growth and maintain the photo-stationary state of 1A and 1C, we decided to expose 10 s every 1 minute with illumination at λ = 405 nm rather than a long period of continuous illumination in 12 hours. The half-life of 1B is long enough, so 1B can be illuminated before adding to the cell suspension.

Drug combination: considering the effect of dilution, two drugs with corresponding concentrations were added directly into the cell suspension and mixed to reach their target concentration. The details are as follows:

The combination of 1A-*cis* and 1B-*trans*: Two drugs were directly added to the cell suspension without illumination;

The combination of 1A-*cis* and 1B-532 nm-PSS: After 1B was exposed to 532 nm light for 5 min, 1A and 1B were together added to the cell suspension;

The combination of 1A-405 nm-PSS and 1B-405 nm-PSS: After 1A and 1B were added to the cell suspension, the mixture was alternately illuminated at λ = 405 nm;

The combination of 1A-*cis* and 1B-*trans*: Two drugs were directly added to the cell suspension without illumination;

The combination of 1C-*cis* and 1B-532 nm-PSS: After 1B was exposed to 532 nm light for 5 min, 1C and 1B were together added to the cell suspension;

The combination of 1C-405 nm-PSS and 1B-405 nm-PSS: After 1A and 1B were added to the cell suspension, the mixture was alternately illuminated at λ = 405 nm.

Table S1 Photostationary States (PSS) and half-lives of 1B, 1C, commercial ciprofloxacin and sulfadiazine.

Compound	PSS thermally adapted	PSS irradiated[a]	Half-life in ACN/H_2O (1/1) at 25 °C
1B	4:96[b]	76:24[b] (25:75 [c])	47.2 h[d]
1C	100:0[b]	25:75[b]	37 s
Ciprofloxacin	N/A	N/A	N/A
Sulfadiazine	N/A	N/A	N/A

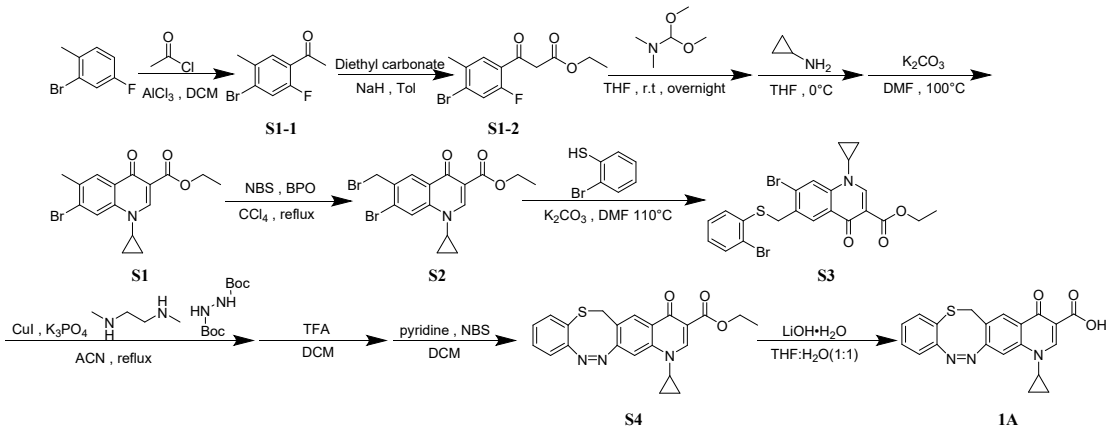
[a.] **1C** was irradiated with λ = 405 nm LED; **1B** was irradiated with λ = 532 nm laser for 3 min. [b.] The ratio is *cis*: *trans* content in the case of compounds **1B** and **1C**, respectively. [c.] The ratio is given in parentheses with illumination at λ = 405 nm LED. [d.] The half-life of **1B** was determined in DMSO at 25 °C.

Table S2 MIC values of 1B, 1C, commercial ciprofloxacin and sulfadiazine.

Compound	MIC thermally adapted on *E. coli* (μM)	MIC irradiated[a] on *E. coli* (μM)	MIC thermally adapted on *S. aureus* (μM)	MIC irradiated[a] on *S. aureus* (μM)
1B	200*	200*	200*	200*
1C	0.8	1	0.8	1
Ciprofloxacin	0.025	0.025	0.025	0.025
Sulfadiazine	4000*	4000*	4000*	4000*

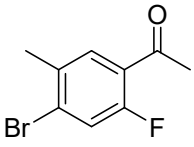
[a.] **1C** was irradiated with λ = 405 nm LED; **1B** was irradiated with λ = 532 nm laser for 3 min. * MIC values were determined up to limited solubility.

2. Synthesis procedure



Scheme. S1 Synthesis of 1A.

1-(4-bromo-2-fluoro-5-methylphenyl) ethan-1-one(**S1-1**)

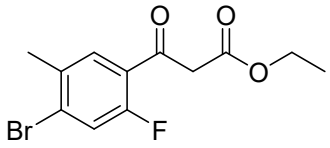


To an oven-dried flask under nitrogen was weighed $AlCl_3$ (7.76 g, 58.20 mmol). To this was added DCM (30 mL) and 2-brloro-4-fluorotoluene (5.00 g, 26.46 mmol). Acetyl chloride (2.82 mL, 39.68 mmol) was added dropwise over 30 min. After stirring for three hours at room temperature, the solution was cooled with an ice bath and the excess $AlCl_3$ was

destroyed by the slow addition of cold water. The aqueous and organic layers were separated. The water layer was extracted with DCM. The combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure followed by silica sol gel column chromatography (Petroleum/Ethyl acetate = 20/1) to furnish the product **S1-1** (4.93 g, 21.43 mmol, 81 %) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.8, 0.8 Hz, 1H), 7.36 (d, J = 10.1 Hz, 1H), 2.61 (d, J = 4.9 Hz, 3H), 2.39 (t, J = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.00 (d, J = 3.7 Hz), 159.79 (d, J = 256.5 Hz), 134.48 (d, J = 3.6 Hz), 131.55 (d, J = 2.8 Hz), 130.31 (d, J = 9.5 Hz), 124.32 (d, J = 13.0 Hz), 120.63 (d, J = 27.0 Hz), 31.40 (d, J = 7.8 Hz), 21.91. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.13. HRMS (ESI) calcd. for $C_9H_9BrFO^+$ 230.9815 [M+H$^+$], found 230.9821.

ethyl 3-(4-bromo-2-fluoro-5-methylphenyl)-3-oxopropanoate (**S1-2**)

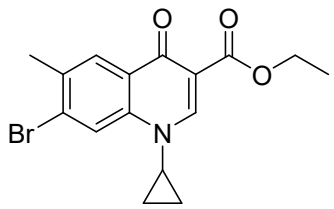


Added diethyl carbonate (4.85 g, 41.04 mmol) to a 150 mL reaction flask, sodium hydride (60 %, 2.05 g, 51.3 mmol), 50 mL of anhydrous toluene, Raised the temperature to reflux, then slowly added **S1-1** (4.72 g, 20.52 mmol) dropwise 20 mL of toluene solution. The dripping was completed in about 2 h, and the reaction was continued for 3h after the dripping was completed. After the reaction was completed, slowly cooled to room temperature, Adjusted the pH to neutral with dilute 5% HCl and removed the solvent. Then extracted the aqueous layer with DCM and the combined organic layers were washed with water, brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure followed by silica sol gel column chromatography (Petroleum/Ethyl acetate = 15/1) to furnish the product **S1-2** (6.86 g, 9.94 mmol, 47 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.8, 0.8 Hz, 1H), 7.37 (d, J = 10.5 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.94 (d, J = 3.5 Hz, 2H), 2.40 (t, J = 1.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.62, 189.58, 167.27, 167.25, 160.91, 158.37, 131.83, 131.80, 131.31, 131.21, 127.38, 127.28, 123.27, 123.14,

120.80, 120.52, 61.39, 49.77, 49.69, 21.96, 14.08. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.84. HRMS (ESI) calcd. for $C_{12}H_{13}BrFO_3^+$ 303.0027 [M+H$^+$], found 303.0021.

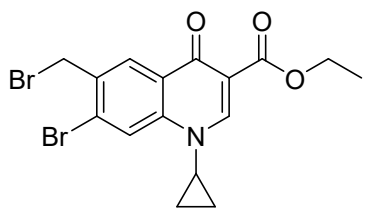
methyl 7-bromo-1-cyclopropyl-6-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (**S1**)



A solution of **S1-2** (6.06 g, 20 mmol) and N'N-dimethylformamide dimethyl acetal (3.01 g, 20 mmol) in 30 mL of THF was stirred overnight at room temperature. The mixture was concentrated under vacuum to give the mixture as a yellow oil. The oil was taken up in 90 mL of THF, cyclopropylamine (1.14 g, 20 mmol) was added, and then the mixture was stirred in an ice bath for 1 h. The mixture was concentrated under vacuum to give a yellow oil. This oil was combined with K_2CO_3 (3.75 g, 27.2 mmol) in 90 mL of DMF and heated for 1 h (steam bath). After this time the mixture was added to ice water and the precipitate filtered was dried and then recrystallized from DCM to give white solid **S1** (4.17 g, 11.95 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.28 (d, J = 1.0 Hz, 1H), 8.09 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.43 (tt, J = 7.2, 4.0 Hz, 1H), 2.56 – 2.43 (m, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.33 (tdd, J = 6.4, 5.4, 0.9 Hz, 2H), 1.19 – 1.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.82, 165.59, 148.53, 139.29, 135.41, 130.22, 128.81, 127.54, 120.08, 111.20, 60.94, 34.44, 22.56, 14.44, 8.15. HRMS (ESI) calcd. for $C_{16}H_{17}BrNO_3^+$ 350.0386 [M+H$^+$], found 350.0378.

ethyl 7-bromo-6-(bromomethyl)-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate **(S2)**

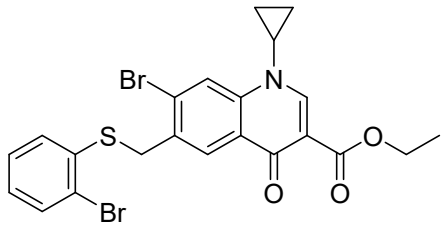


Compound **S1** (1.68 g, 5 mmol), tetrachloromethane (25 mL), benzoyl peroxide (0.12 g, 0.5 mmol) and NBS (1.07 g, 6 mmol) were added sequentially to a round-bottomed flask equipped with a reflux condenser. The reaction mixture was stirred for reflux overnight. After cooling

to 20 °C, the reaction mixture was quenched with water (40 mL), extracted with DCM (3 x 30 mL), washed with brine (20 mL) and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure followed by silica sol gel column chromatography (DCM/MeOH = 20/1) to furnish the product **S2** as a white solid (1.16 g, 2.7 mmol, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.47 (s, 1H), 8.13 (s, 1H), 4.67 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.44 (tt, J = 7.2, 3.9 Hz, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.35 (td, J = 6.4, 5.6, 2.7 Hz, 2H), 1.18 – 1.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.37, 165.13, 148.96, 140.95, 134.26, 130.07, 129.18, 127.82, 121.40, 111.87, 61.08, 34.56, 32.51, 14.41, 8.28. HRMS (ESI) calcd. for $C_{16}H_{16}Br_2NO_3^+$ 427.9491 [M+H$^+$], found 427.9485.

ethyl 7-bromo-6-(((2-bromophenyl) thio) methyl)-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (**S5**)

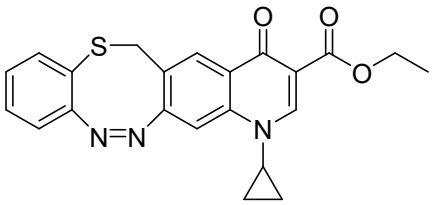


A 50 mL flask was charged with **S2** (0.86 g, 2 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) in DMF (3 mL). Then thiophenols (0.38 g, 2 mmol) was added at room temperature with constantly stirring, and this mixture was kept at 110 ℃ for 2 h. And then 30 mL of water was added to this reaction mixture, and the precipitated solids are washed several times with water and then dried. The dry precipitate filtered was washed with DCM (3 x 10 mL) to give **S3** as a white solid (0.69 g, 1.3 mmol, 65 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 1.0 Hz, 1H), 8.55 (s, 1H), 8.16 (s, 1H), 7.57 (dd, J = 7.9, 1.6 Hz, 1H), 7.28 (d, J = 1.6 Hz, 0H), 7.26 – 7.22 (m, 1H), 6.98 (dd, J = 8.3, 1.4 Hz, 1H), 6.87 (td, J = 7.7, 1.4 Hz, 1H), 5.24 (d, J = 0.9 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.46 (tt, J = 7.2, 3.9 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.38 – 1.34 (m, 2H), 1.16 (tdd, J = 5.4, 4.3, 2.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53, 165.58, 154.69, 148.92, 140.78, 133.66, 132.98, 128.59, 128.40, 127.74, 127.32, 122.64, 120.65, 113.85, 112.84, 111.83, 70.03, 61.11, 34.51, 14.46, 8.27. HRMS (ESI)

calcd. for $C_{22}H_{20}Br_2NO_3S^+$ 535.9525 [M+H$^+$], found 535.9535.

ethyl (Z)-1-cyclopropyl-4-oxo-1,6-dihydro-4H-benzo[2,3][1,4,5]thiadiazocino[7,6-g]quinoline-3-carboxylate (**S4**)

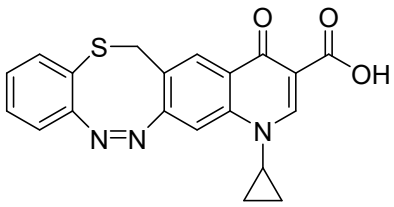


In a glovebox, **S3** (269 mg, 0.5 mmol), di-tert-butyl hydrazine-1,2-dicarboxylate (140 mg, 0.6 mmol), CuI (95 mg, 0.5 mmol), K_3PO_4 (319 mg, 1.5 mmol), acetonitrile (5 mL) and 1,2-dimethyl-ethylenediamine (9 mg, 0.1 mmol) were added sequentially to a pressure tube. The tube was capped with a crimp cap equipped with a PTFE septum, transferred out of the glovebox and stirred at 82 °C for 18 h. After cooling to 20 °C, the reaction mixture was quenched with water, extracted with DCM, washed with brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure and the crude residue (1 equiv) was treated with 10 mL of DCM and 5 mL of TFA. The reaction was stirred at r.t for 2 h. It was traced with TLC till the conversion was completed. Then it was neutralized with saturated $NaHCO_3$, the organic layer was separated and the water layer was extracted 3 x with 15 mL of DCM. The combined organic layers were dried over $MgSO_4$. After filtration, the organic phase was concentrated under reduced pressure. The resulting residue, DCM (10 mL) and pyridine (1.24 equiv) were added sequentially to a round-bottomed flask. NBS (1.2 equiv) was added portionwise over the course of 2 min under stirring and the reaction mixture was stirred at 20 °C for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to furnish the cyclic azobenzene product **S4** as a yellow solid (32 mg, 0.079 mmol, 16 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.23 (s, 1H), 7.16 – 7.11 (m, 2H), 7.09 (dd, J = 7.9, 1.2 Hz, 1H), 6.91 (td, J = 7.6, 1.4 Hz, 1H), 6.70 (dd, J = 7.8, 1.4 Hz, 1H), 4.40 – 4.29 (m, 2H), 4.13 (d, J = 11.6 Hz, 1H), 3.88 (d, J = 11.6 Hz, 1H), 3.34 (tt, J = 7.2, 3.9 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.32 – 1.19 (m, 2H), 1.07 (ddt, J = 10.5, 5.8, 4.2 Hz, 1H), 0.97 – 0.87 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.47, 165.42,

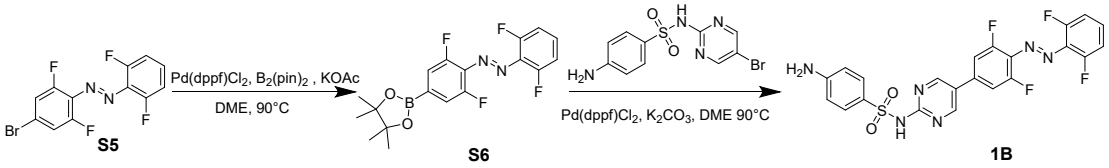
160.35, 157.98, 148.89, 140.27, 134.84, 129.37, 128.13, 127.67, 127.46, 123.05, 121.79, 118.71, 111.71, 104.79, 77.48, 77.36, 77.16, 76.84, 61.10, 34.68, 34.53, 14.52, 8.46, 8.10. HRMS (ESI) calcd. for $C_{22}H_{20}N_3O_3S^+$ 406.1220 [M+H$^+$], found 406.1213.

(Z)-1-cyclopropyl-4-oxo-1,6-dihydro-4H-benzo[2,3][1,4,5]thiadiazocino[7,6-g]quinoline-3-carboxylic acid (**1A**)



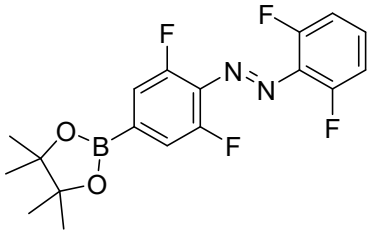
Ethanol (3 mL) and 2 M NaOH (3 mL) were added to the **S4** and stirred at reflux until total conversion, as indicated by TLC. The mixtures were acidified to pH 2-3 with diluted hydrochloric acid. The resultant precipitates were collected, washed and dried in vacuo to afford the product **1A** (72 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 14.77 (s, 1H), 8.67 (s, 1H), 8.30 (s, 1H), 7.74 (s, 1H), 7.28 (td, J = 7.6, 1.3 Hz, 1H), 7.14 (dd, J = 7.9, 1.2 Hz, 1H), 7.02 (td, J = 7.6, 1.4 Hz, 1H), 6.96 (dd, J = 7.9, 1.4 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 4.06 (d, J = 11.4 Hz, 1H), 3.71 (tt, J = 7.3, 4.0 Hz, 1H), 1.30 – 1.24 (m, 2H), 1.18 (ddd, J = 8.9, 4.6, 1.9 Hz, 1H), 0.90 – 0.79 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 177.60, 165.94, 161.21, 157.66, 149.92, 141.08, 134.30, 129.03, 128.37, 127.79, 124.71, 124.40, 121.04, 119.71, 108.07, 107.24, 36.46, 33.82, 8.11. HRMS (ESI) calcd. for $C_{20}H_{17}N_3O_3S^-$ 379.0991 [M+H$^-$], found 379.0998.



Scheme. S2 Synthesis of **1B**.

(E)-1-(2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)-2-(2,6-difluorophenyl) diazene (**S6**)

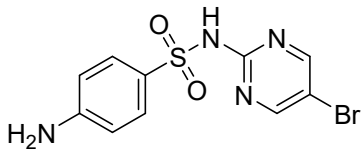


S5(333 mg, 1 mmol), which was prepared from the previous literature [1], potassium acetate (294 mg,

3 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-1,3,2-dioxaborolane (762 mg, 3 mmol), and $Pd(dppf)Cl_2$ (44 mg, 0.06 mmol) were dissolved in deoxygenated 1,4-dioxane (6 mL). The mixture was heated to 80 °C and stirred overnight under N_2. After removal of the solvent under reduced pressure, the residue was extracted with DCM and water. The combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (Petroleum/Ethyl acetate = 10/1) to furnish the red product **T2** (274 mg, 0.72 mmol, 72 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.69-7.62 (m, 1H), 7.46-7.35 (m, 4H), 1.32 (s, 12H) ppm.

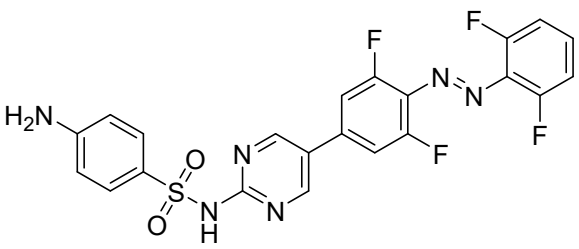
4-amino-N-(5-bromopyrimidin-2-yl) benzenesulfonamide



4-acetamidobenzenesulfonyl chloride (1.402 g, 6 mmol) was treated with 2-Amino-5-bromopyrimidine (0.870 g, 5 mmol) in 5 mL pyridine at 40 ℃ for 2 h. Then, 30 mL of 1 M hydrochloric acid was added and a lot of precipitation was precipitated for filtration. The crude solid was washed with water and directly used in the next step. All the intermediates were dissolved in 20% NaOH solution and the reaction mixtures were heated to reflux in an oil bath for 2 h. Then the reaction solution was quenched with 1 M hydrochloric acid to pH 7.4, resulting yellow solid. The precipitation was obtained and washed with water, then dried overnight in a vacuum desiccator, and recrystallized from DCM as a white solid (0.592 g, 1.8 mmol, 36 %).

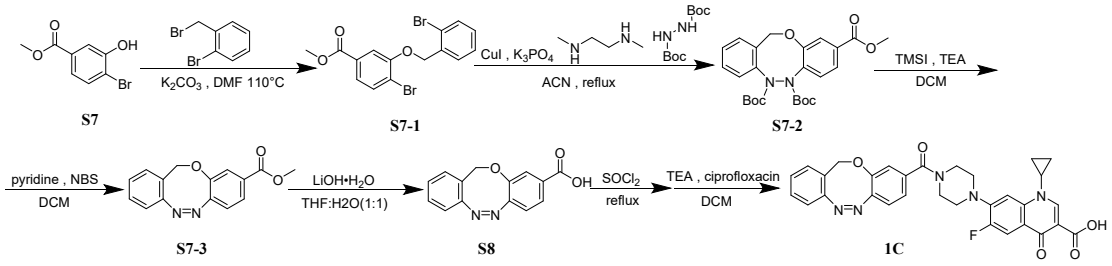
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.64 (s, 2H), 7.67-7.55 (m, 2H), 6.62 – 6.51 (m, 2H), 6.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.07, 156.23, 153.71, 130.34, 124.71, 112.66, 112.52, 55.38. HRMS (ESI) calcd. for $C_{10}H_{10}BrN_4O_2S^+$ 328.9702 [M+H^+], found 328.9697.

(E)-4-amino-N-(5-(4-((2,6-difluorophenyl) diazenyl)-3,5-difluorophenyl)-pyrimi-din-2-yl) benzenesulfonamide (**1B**)



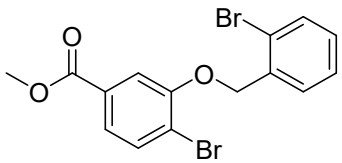
S6 (228 mg, 0.6 mmol), 4-amino-N-(5-bromopyrimidin-2-yl) benzene-sulfonamide (165 mg, 0.5 mmol), $Pd(dppf)Cl_2$ (22 mg, 0.03 mmol), and potassium carbonate (207 mg, 1.5 mmol) were dissolved in deoxygenated 1,4-dioxane (3 mL). The reaction mixture was heated to 90 °C and stirred overnight under N_2. After removal of the solvent under reduced pressure, the residue was extracted with DCM and water. The combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (DCM/MeOH = 20/1) to furnish the red product **1B** (103 mg, 0.205 mmol, 41 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 9.02 (s, 2H), 7.91 – 7.79 (m, 2H), 7.71 – 7.55 (m, 3H), 7.46 – 7.30 (m, 2H), 6.66 – 6.53 (m, 2H), 6.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.00, 156.20, 156.13, 156.08, 155.54, 155.50, 153.55, 153.50, 152.96, 152.74, 138.58, 130.34, 129.43, 129.07, 124.20, 123.36, 112.92, 112.72, 112.69, 111.75, 110.13, 109.92.^{19}F NMR (376 MHz, DMSO-d_6) δ -120.28, -121.70. HRMS (ESI) calcd. for $C_{22}H_{15}F_4N_6O_2S^+$ 503.0908 [M+H$^+$], found 503.0905.



Scheme. S3 Synthesis of **1C**.

methyl 4-bromo-3-((2-bromobenzyl) oxy) benzoate (**S7-1**)

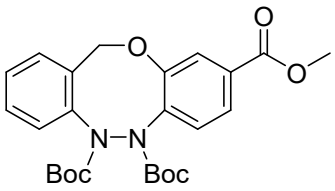


A 50 mL flask was charged with 1-bromo-2-(bromomethyl) benzene (2.50 g, 10 mmol) and K_2CO_3 (1.66 g, 12 mmol) in DMF (10 mL). Then methyl 4-bromo-3-hydroxybenzoate (2.30 g, 10 mmol) was added portionwise at room temperature with constantly stirring, and this mixture was kept at 110 ℃ for 2 h. After

cooling to 20 °C, the reaction mixture was quenched with water, extracted with EA, washed with brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (Petroleum/Ethyl acetate = 20/1) to give **S7-1** as a white solid (3.66 g, 9.2 mmol, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 1H), 7.67 – 7.62 (m, 2H), 7.57 (ddd, J = 16.7, 8.1, 1.6 Hz, 2H), 7.37 (td, J = 7.6, 1.3 Hz, 1H), 7.20 (td, J = 7.7, 1.7 Hz, 1H), 5.23 (s, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.30, 154.74, 135.43, 133.47, 132.57, 130.66, 129.39, 128.70, 127.70, 123.41, 121.93, 118.17, 113.94, 70.19, 52.43. HRMS (ESI) calcd. for $C_{15}H_{13}Br_2O_3^+$ 398.9226 [M+H$^+$], found 398.9234.

5,6-di-tert-butyl 9-methyl 6H-dibenzo[*b,f*][1,4,5]oxadiazocine-5,6,9(12H)-tricarboxylate (**S7-2**)

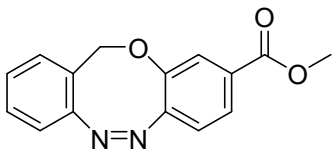


In a glovebox, **S7-1** (832 mg, 2 mmol), di-tert-butyl hydrazine-1,2-dicarboxylate (558 mg, 2.4 mmol), CuI (380 mg, 2 mmol), K_3PO_4 (1.27 g, 6 mmol), acetonitrile (10 mL) and 1,2-dimethylethylenediamine (35 mg, 0.4 mmol) were added sequentially to a pressure tube. The tube was capped with a crimp cap equipped with a PTFE septum, transferred out of the glovebox and stirred at 82 °C for 18 h. After cooling to 20 °C, the reaction mixture was quenched with water, extracted with DCM, washed with brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (Petroleum/Ethyl acetate = 5/1) to furnish **S7-2** product as a white solid (351 mg, 0.72 mmol, 36 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.52 (m, 4H), 7.37 – 7.29 (m, 1H), 7.22 – 7.06 (m, 2H), 5.22 (d, J = 14.4 Hz, 1H), 5.06 (d, J = 14.3 Hz, 1H), 3.90 (s, 3H), 1.36 (d, J = 6.0 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.43, 153.33, 152.45, 151.88, 138.49, 134.82, 129.94, 128.74, 128.24, 128.20, 128.09, 126.13, 125.39, 122.82, 122.27, 83.34, 82.95, 74.04, 52.30, 28.19, 28.14. HRMS (ESI) calcd. for $C_{25}H_{31}N_2O_7^+$

471.2126 [M+H$^+$], found 472.2122.

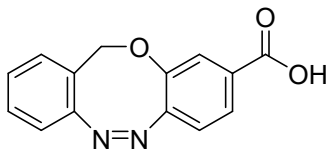
methyl (Z)-12H-dibenzo[*b,f*][1,4,5]oxadiazocine-9-carboxylate (**S7-3**)



In a glovebox, **S7-2** (243 mg, 0.5 mmol), DCM (10 mL) and trimethylsilyl iodide (200 mg, 1 mmol) were added sequentially to a round-bottomed flask equipped with a magnetic stirring bar. The reaction mixture was stirred at 20 °C for 10 min before it was treated with triethylamine (101 mg, 1 mmol). The flask was capped, transferred out of the glovebox where the reaction mixture was quenched with water (5 mL / mmol), extracted with DCM, washed with brine and dried over Na_2SO_4. After filtration, the organic phase was concentrated under reduced pressure. The resulting residue, DCM (10 mL) and pyridine (49 mg, 0.64 mmol) were added sequentially to a round-bottomed flask. NBS (107 mg, 0.6 mmol) was added portionwise over the course of 1 min under stirring and the reaction mixture was stirred at 20 °C for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to furnish the cyclic azobenzene product **S7-3** as a yellow solid (68 mg,0.24 mmol, 48 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H), 7.15 (td, J = 7.6, 1.3 Hz, 1H), 7.08 (dd, J = 7.9, 1.3 Hz, 1H), 6.93 (td, J = 7.6, 1.4 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.70 (dd, J = 7.9, 1.4 Hz, 1H), 4.09 (d, J = 11.7 Hz, 1H), 3.84 (s, 3H), 3.72 (d, J = 11.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.88, 160.78, 157.65, 133.99, 130.92, 129.75, 129.33, 128.06, 127.38, 124.77, 121.56, 119.10, 117.22, 52.28, 34.73. HRMS (ESI) calcd. for $C_{15}H_{13}N_2O_3^+$ 269.0921 [M+H$^+$], found 269.0916.

(Z)-12H-dibenzo[*b,f*][1,4,5]thiadiazocine-2-carboxylic acid (**S8**)

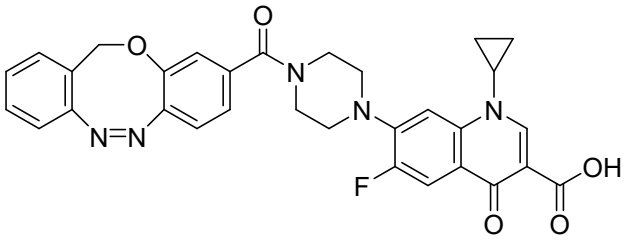


A mixture of **S7-3**(30 mg, 0.06 mmol) in THF/H_2O (1/1), LiOH (15 mg, 0.6 mmol) was stirred vigorous at room temperature over 30 min and was traced with TLC till the conversion was completed. The mixture was then evaporated to remove organic solution in vacuum and was basified with 1 M aq. HCl to adjust the pH

around 2 and extracted twice with DCM. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (DCM/MeOH = 16/1) to furnish the product **S8** (23 mg, 0.05 mmol, 81 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.53 (dd, J = 8.2, 1.7 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.40 (d, J = 1.6 Hz, 1H), 7.32 (td, J = 7.5, 1.2 Hz, 1H), 7.26 (dd, J = 7.7, 1.2 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 5.01 (s, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 166.01, 156.19, 149.14, 142.97, 131.69, 130.51, 130.07, 128.76, 123.44, 122.25, 122.09, 121.02, 119.78, 71.25, 39.52. HRMS (ESI) calcd. for $C_{14}H_{14}N_2O_3^-$ 255.0775 [M+H$^-$], found 255.0782.

(Z)-7-(4-(12H-dibenzo[*b*,*f*][1,4,5]oxadiazocine-9-carbonyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1C**)



Compound **S8** (565 mg, 2.5 mmol) was suspended in $SOCl_2$ (10 mL). The resulting mixture was stirred for 2 h under reflux. Next, the mixture was concentrated in vacuo and the resulting residue was redissolved in DCM (5 mL). This solution was added dropwise to an ice-cooled solution of ciprofloxacin (331 mg, 1 mmol) and TEA (111 mg, 1.1 mmol) in DCM (20 mL) and stirred for 1h on ice. Next, the mixture was stirred for an additional 16 h at room temperature. The volatiles were evaporated and the crude product was purified by flash chromatography (DCM/MeOH = 97/3) resulting in a yellow solid (410 mg, 0.76 mmol, 76 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 14.90 (s, 1H), 8.77 (s, 1H), 8.04 (d, J = 12.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.00 (q, J = 8.1 Hz, 2H), 6.93 (s, 1H), 4.93 (s, 2H), 3.96 (s, 2H), 3.66 (s, 2H), 3.54 (s, 1H), 3.31 (d, J = 57.8 Hz, 4H), 1.40 (d, J = 6.8 Hz, 2H), 1.20 (d, J = 3.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.26, 169.21, 167.01, 157.18, 147.80, 146.28,

143.44, 139.10, 135.74, 130.88, 130.34, 129.02, 123.71, 120.63, 120.47, 120.26, 112.95, 108.44, 105.39, 70.83, 35.46, 29.84, 8.44. ^{19}F NMR (565 MHz, $CDCl_3$) δ -121.11. HRMS (ESI) calcd. for $C_{31}H_{27}FN_5O_5^-$ 568.2002 [M+H$^-$], found 568.1994.

Reference

1 Mutruc D, Goulet-Hanssens A, Fairman S, Wahl S, Zimathies A, Knie C, Hecht S, *Angew Chem Int Ed*, 2019, 58: 12862.

3. Photostationary states of 1A、1B and 1C

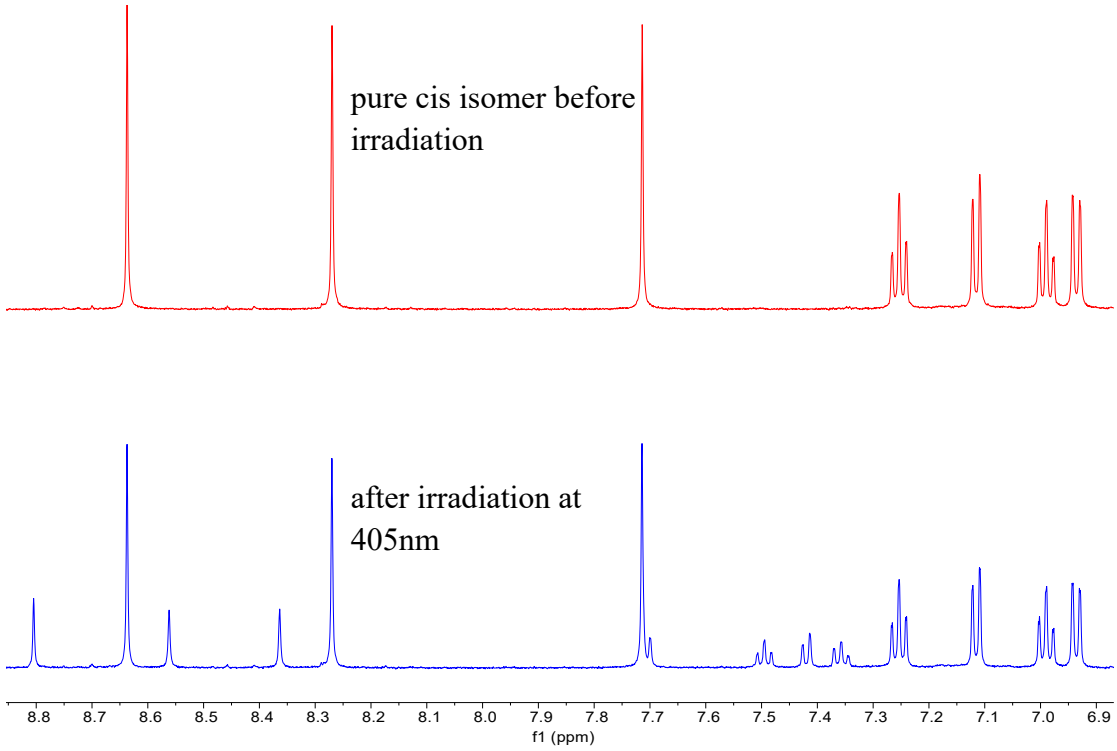


Fig. S1 Aromatic regions of the ^{1}NMR spectra of **1A** before (red) and after irradiation (blue).

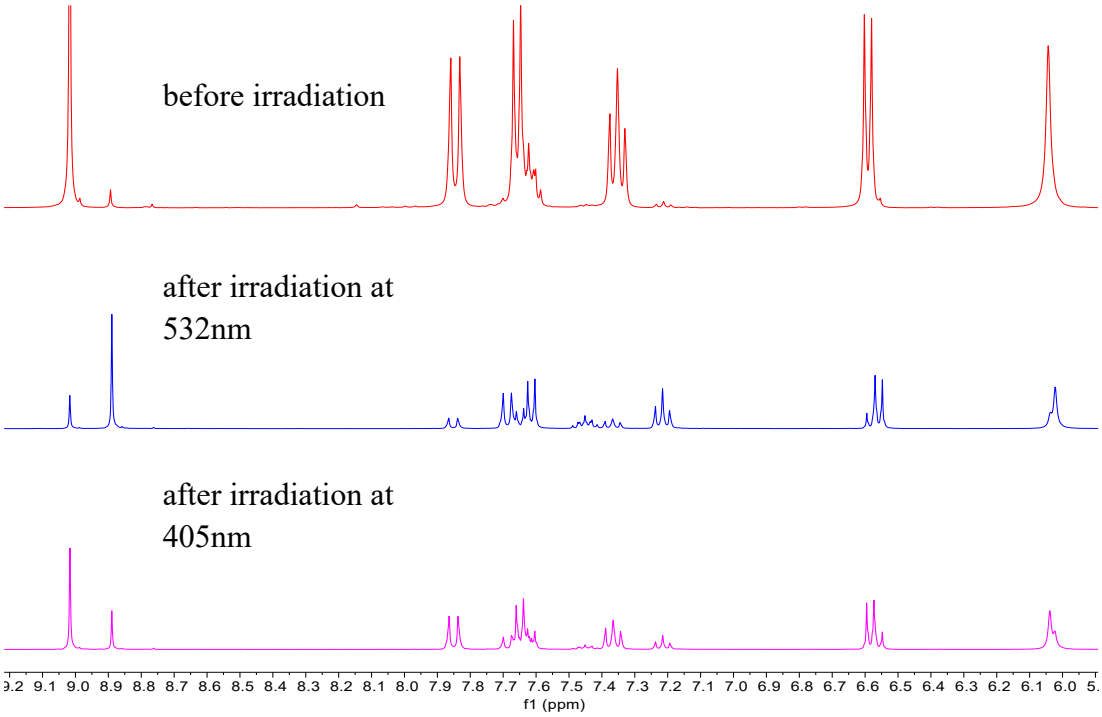


Fig. S2 Aromatic regions of the ^{1}NMR spectra of **1B** before (red) and after irradiation at 532nm(blue) and after irradiation at 405nm(pink).

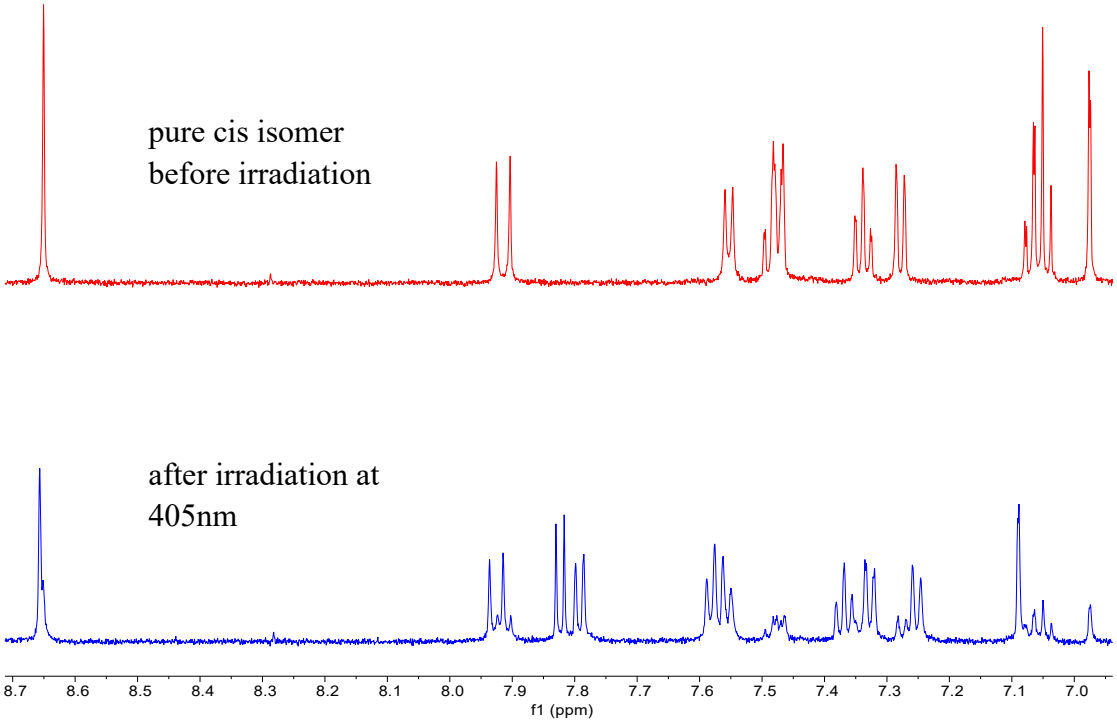


Fig. S3 Aromatic regions of the ^{1}NMR spectra of **1C** before (red) and after irradiation (blue).

4. MIC determination

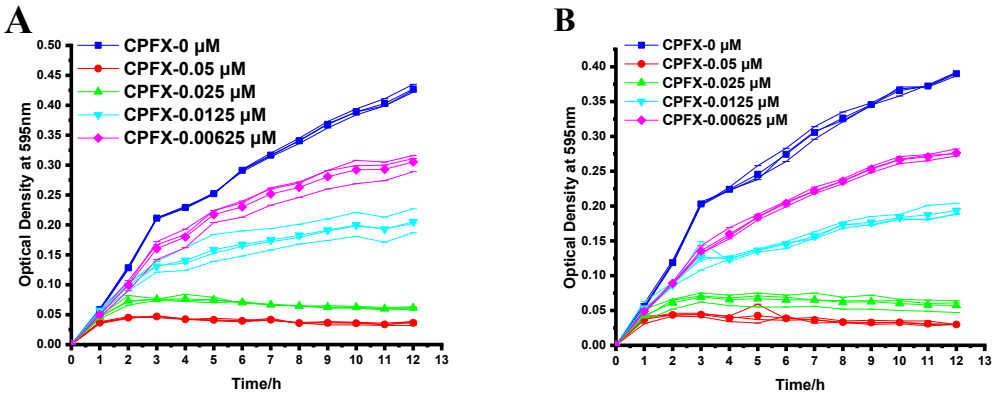


Fig. S4 Bacterial growth curves of *E. coli* BL21 (DE3) at increasing concentrations of **ciprofloxacin (CPFX)**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

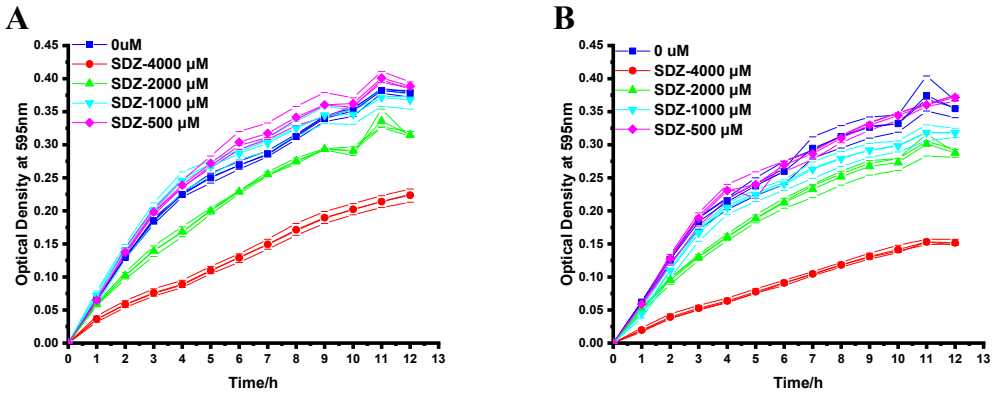


Fig. S5 Bacterial growth curves of *E. coli* BL21 (DE3) at increasing concentrations of **sulfadiazine (SDZ)**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

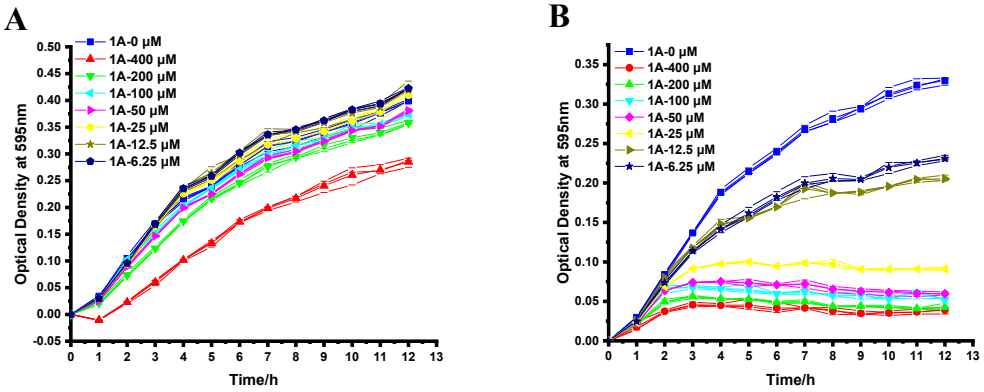


Fig. S6 Bacterial growth curves of *E. coli* BL21 (DE3) at increasing concentrations of **1A**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

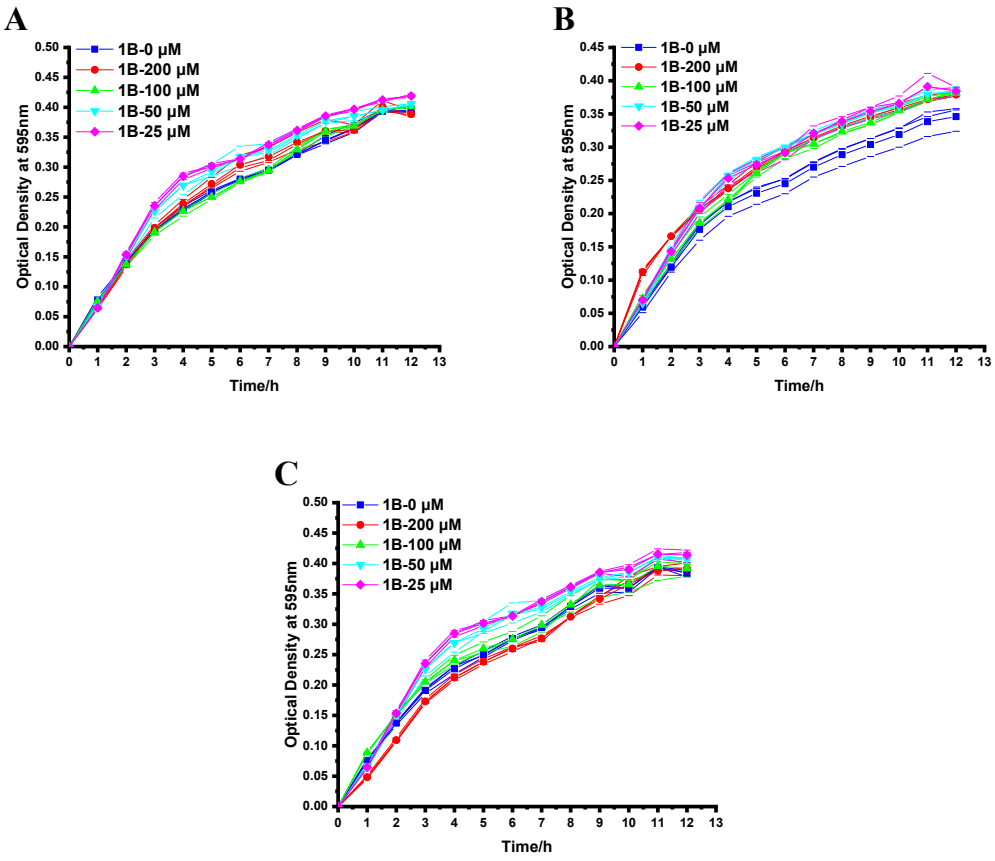


Fig. S7 Bacterial growth curves of *E. coli* BL21 (DE3) at increasing concentrations of **1B**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. C) λ = 532 nm-light irradiated. The measurement is the average of three results.

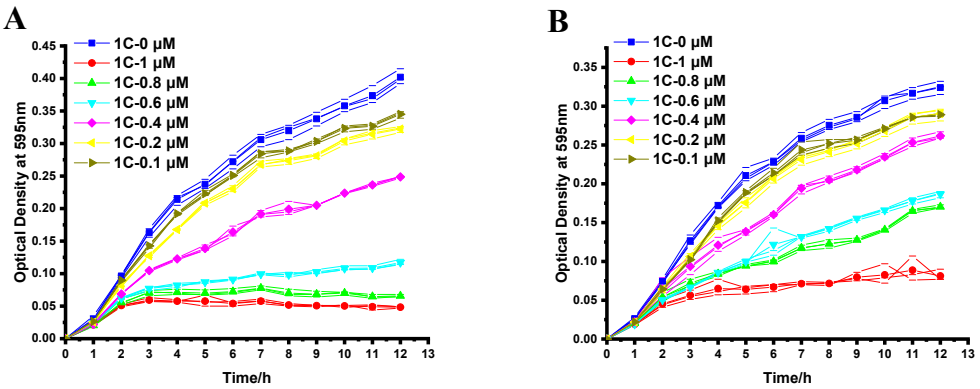


Fig. S8 Bacterial growth curves of *E. coli* BL21 (DE3) at increasing concentrations of **1C**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

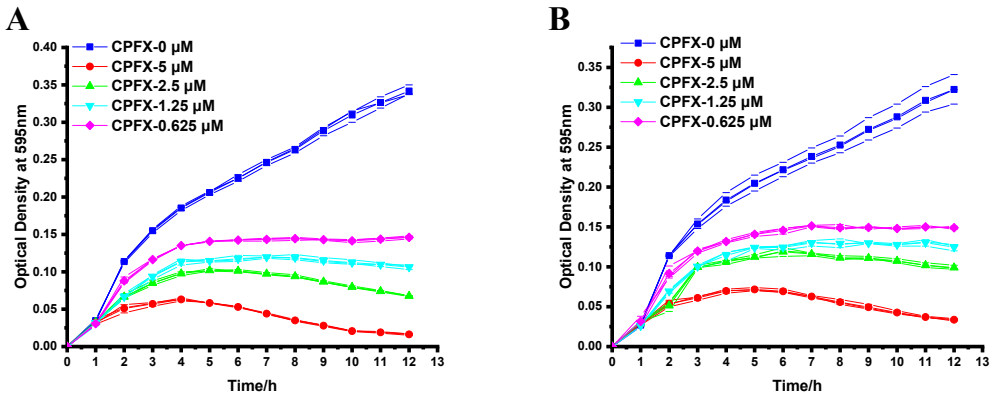


Fig. S9 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **ciprofloxacin (CPFX)**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. The measurement is the average of three results.

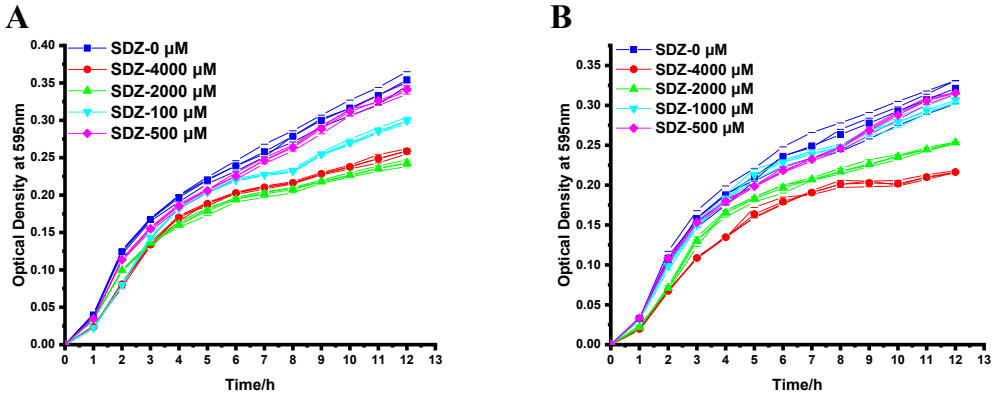


Fig. S10 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **sulfadiazine (SDZ)**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. The measurement is the average of three results.

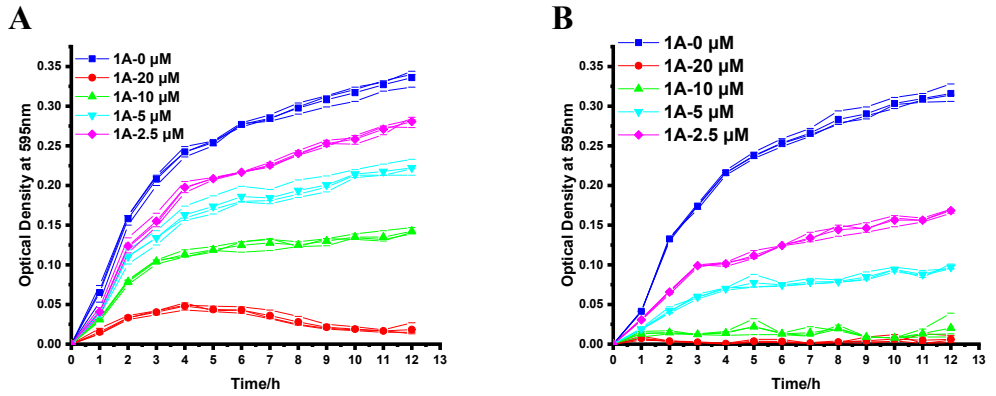


Fig. S11 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **1A**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated.

The measurement is the average of three results.

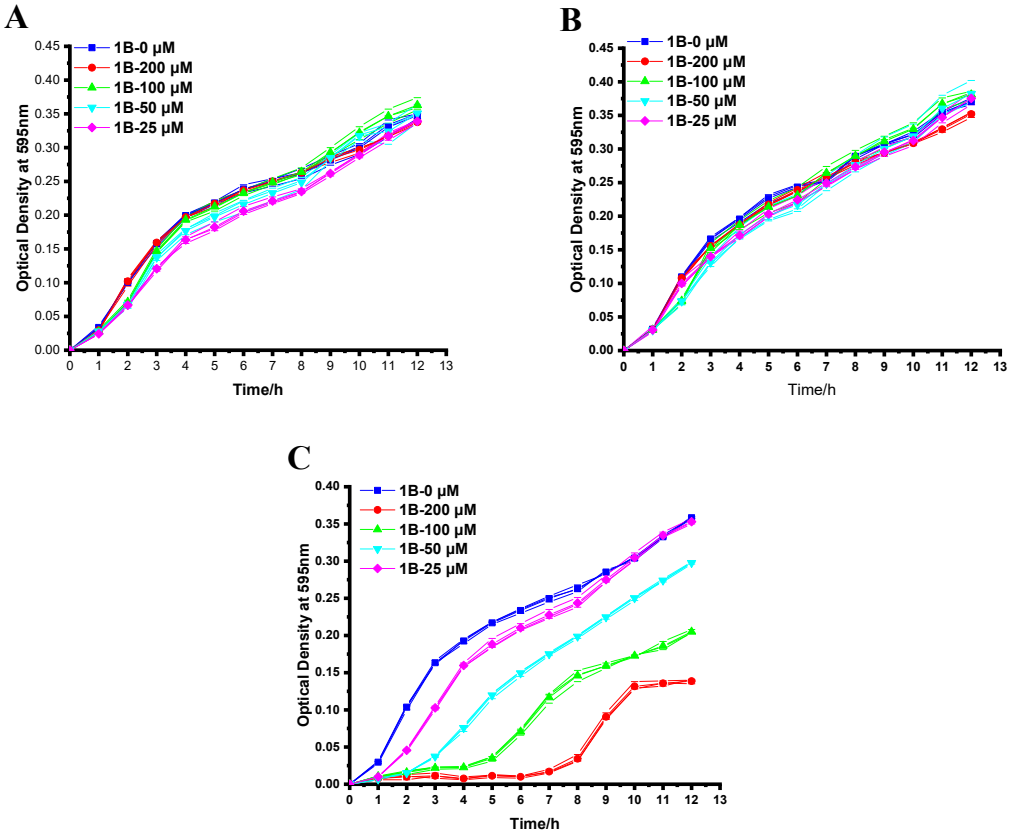


Fig. S12 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **1B**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. C) λ = 532 nm-light irradiated. The measurement is the average of three results.

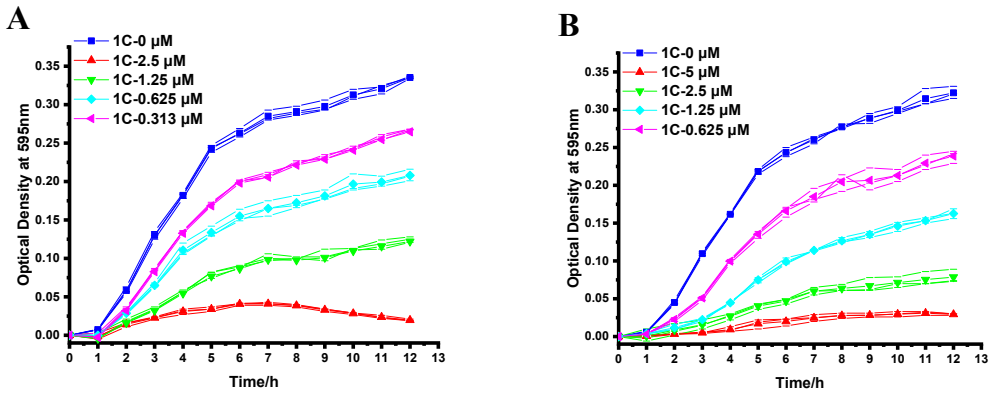


Fig. S13 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **1C**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. The measurement is the average of three results.

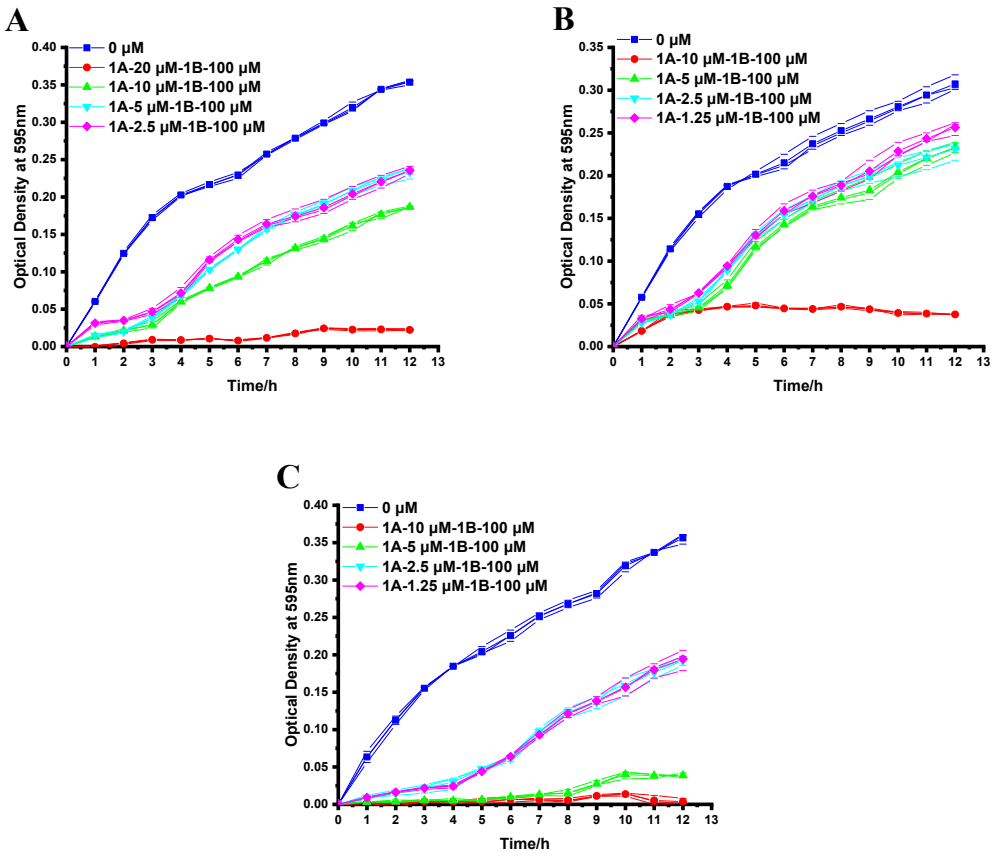
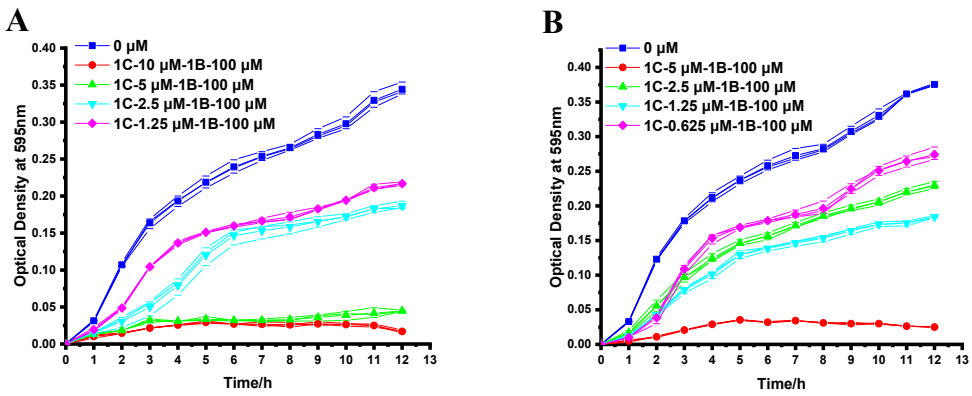


Fig. S14 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **1A with 100 μM 1B**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. C) λ = 532 nm-light irradiated. The measurement is the average of three results.



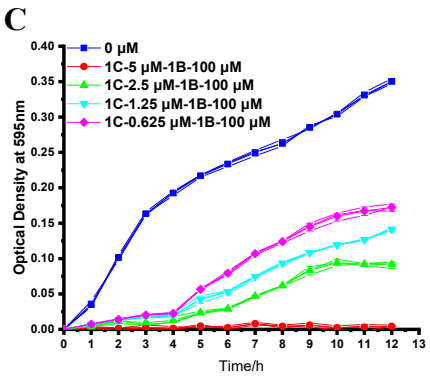


Fig. S15 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of **1C with 100 μM 1B**. A) Thermally-adapted sample B) λ = 405 nm-light irradiated. C) λ = 532 nm-light irradiated. The measurement is the average of three results.

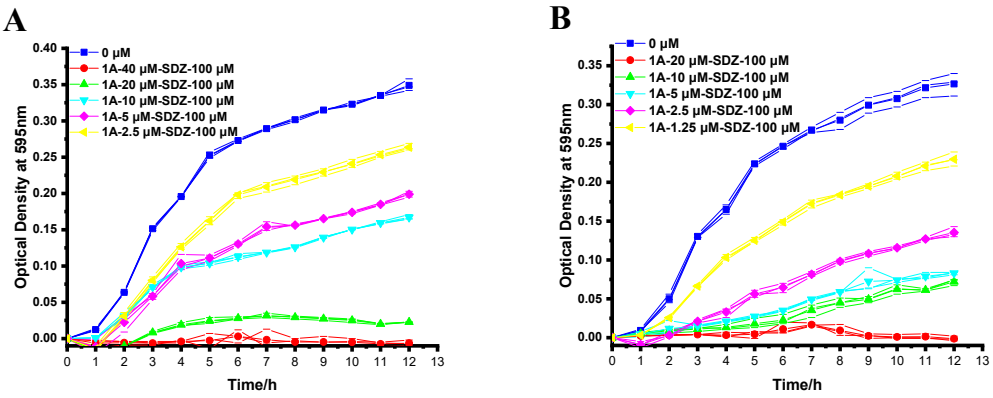


Fig. S16 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of combination **1A with 100 μM sulfadiazine (SDZ)**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

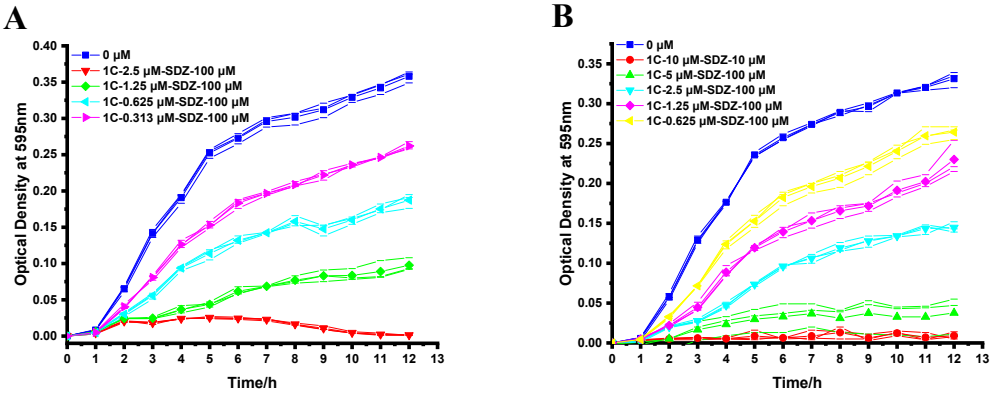


Fig. S17 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of combination **1C with 100 μM sulfadiazine (SDZ)**. A) Thermally-adapted sample. B) λ = 405 nm-light irradiated. The measurement is the average of three results.

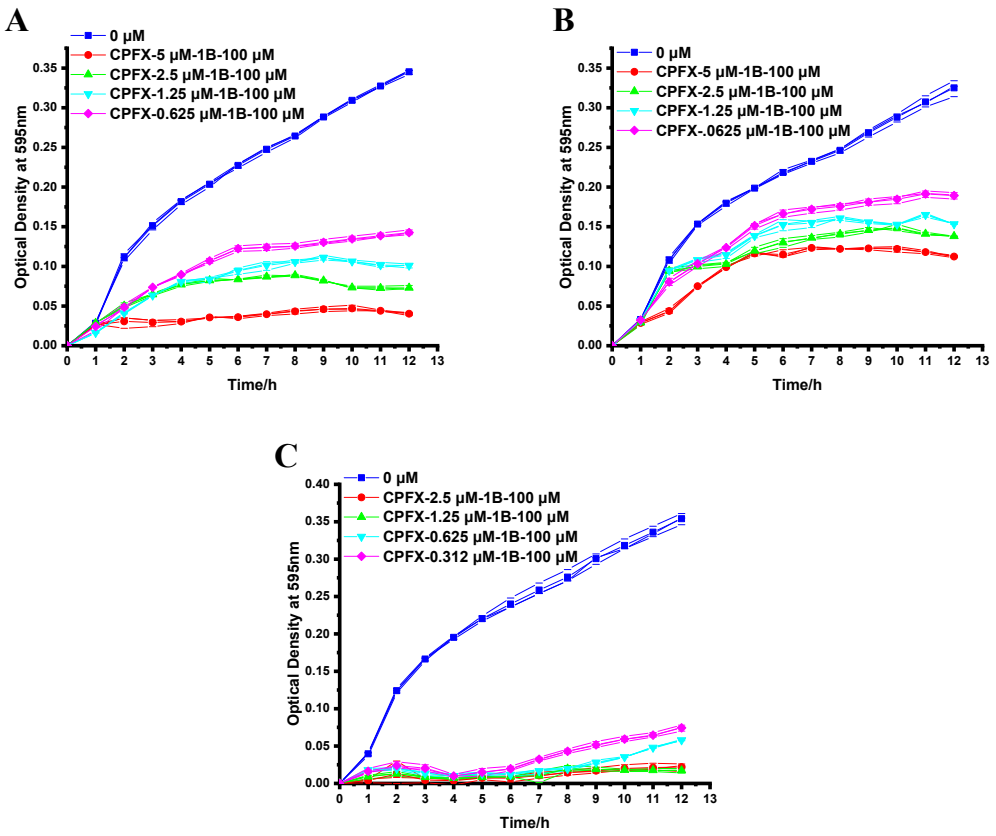
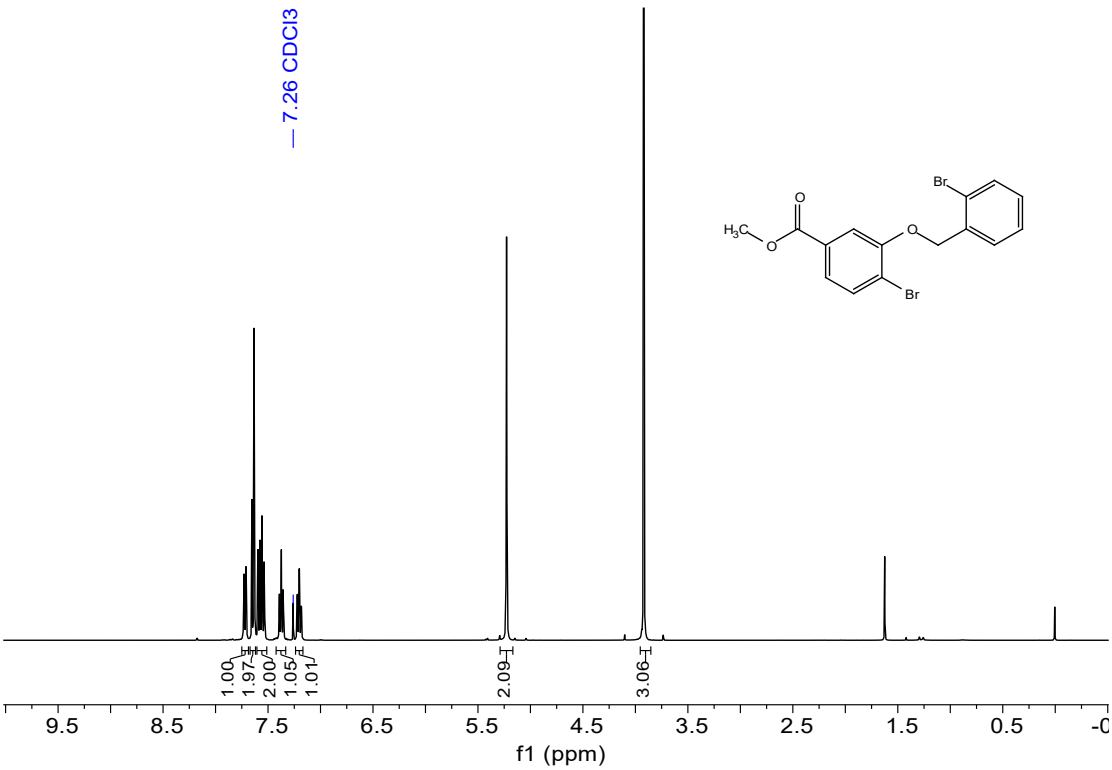


Fig. S18 Bacterial growth curves of *S. aureus* ATCC 23350 at increasing concentrations of combination **Ciprofloxacin (CPFX) with 100 μM 1B**. A) Thermally-adapted sample. B) λ = 532 nm-light irradiated. The measurement is the average of three results.

5. NMR spectra of compounds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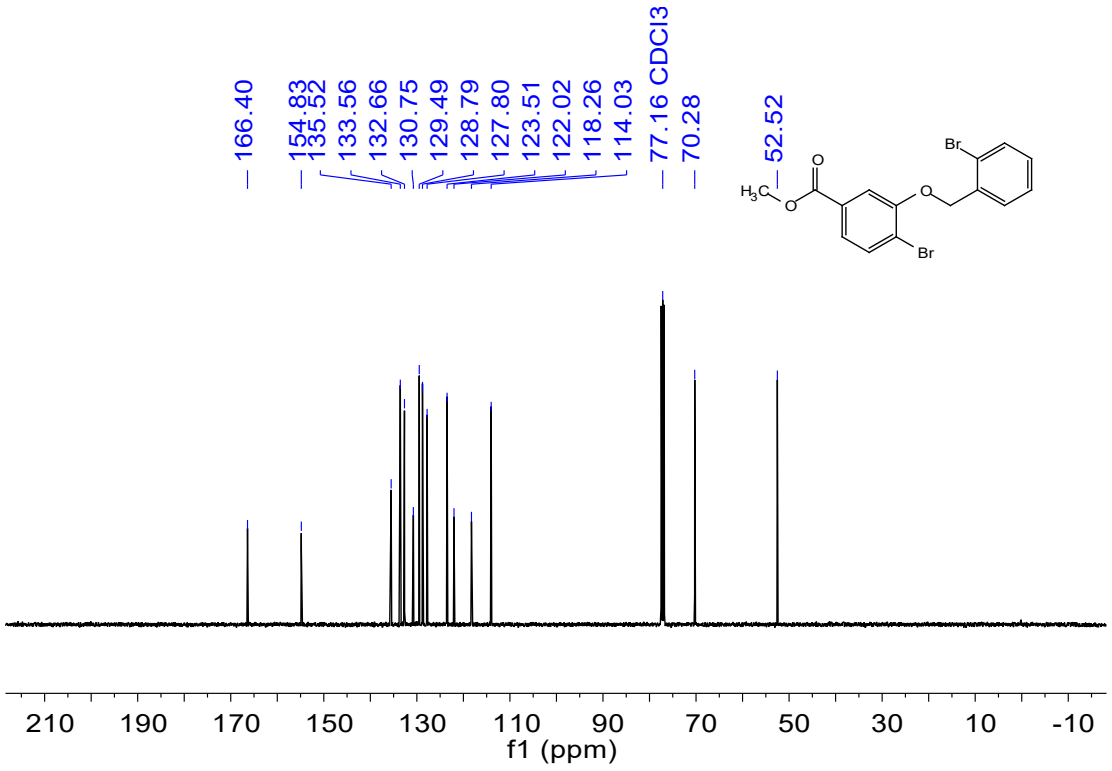
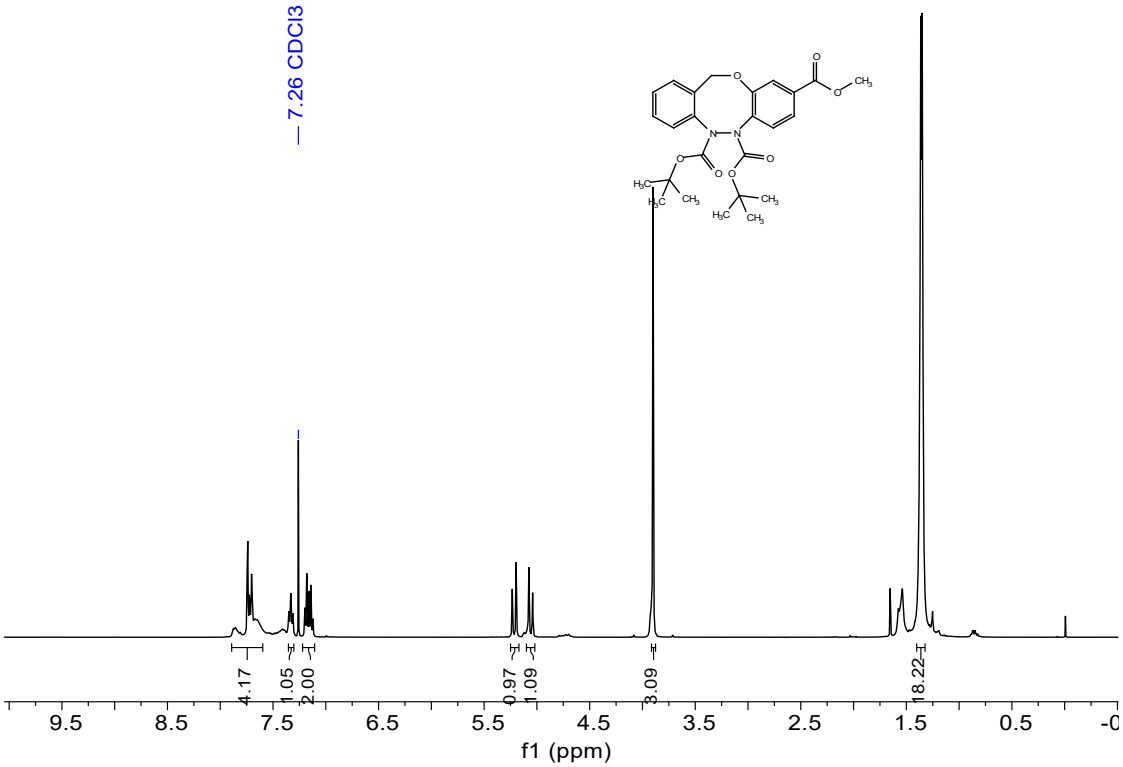
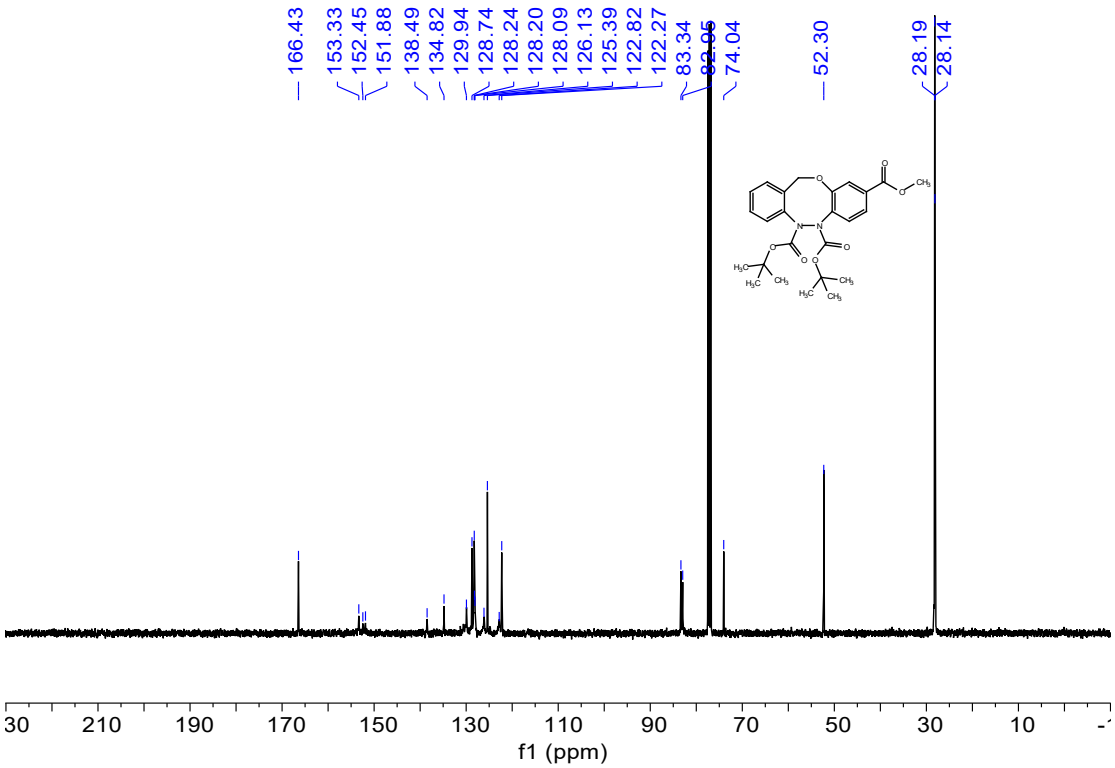
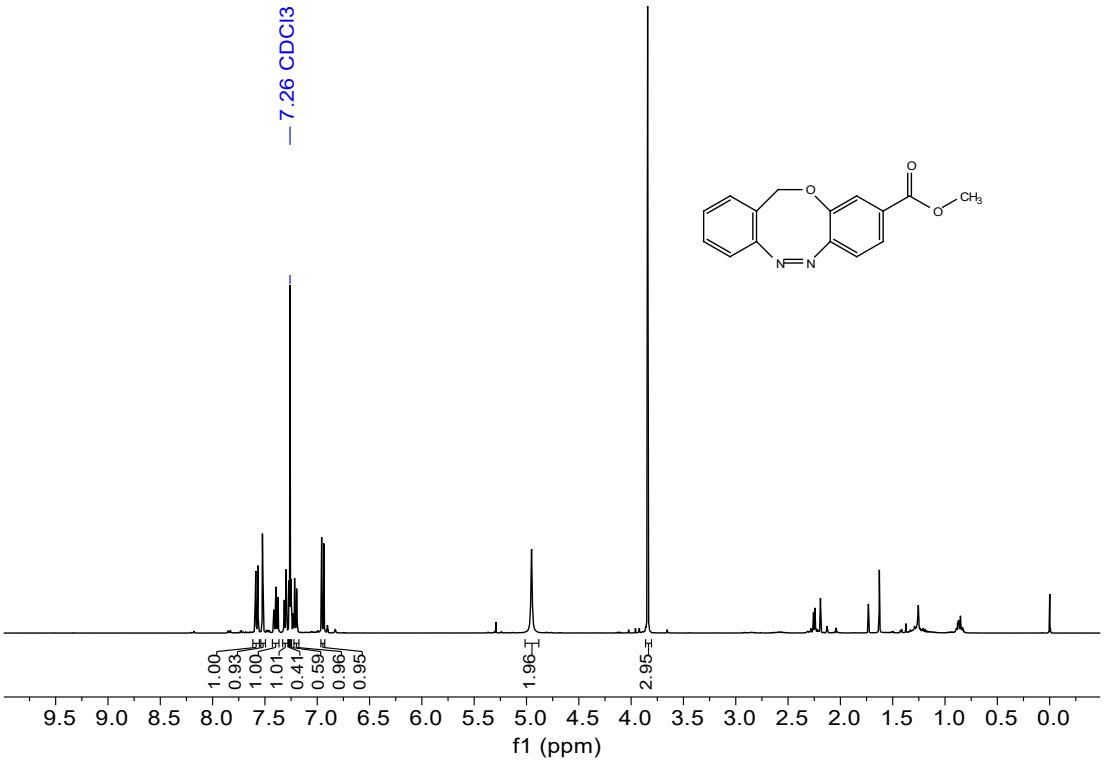
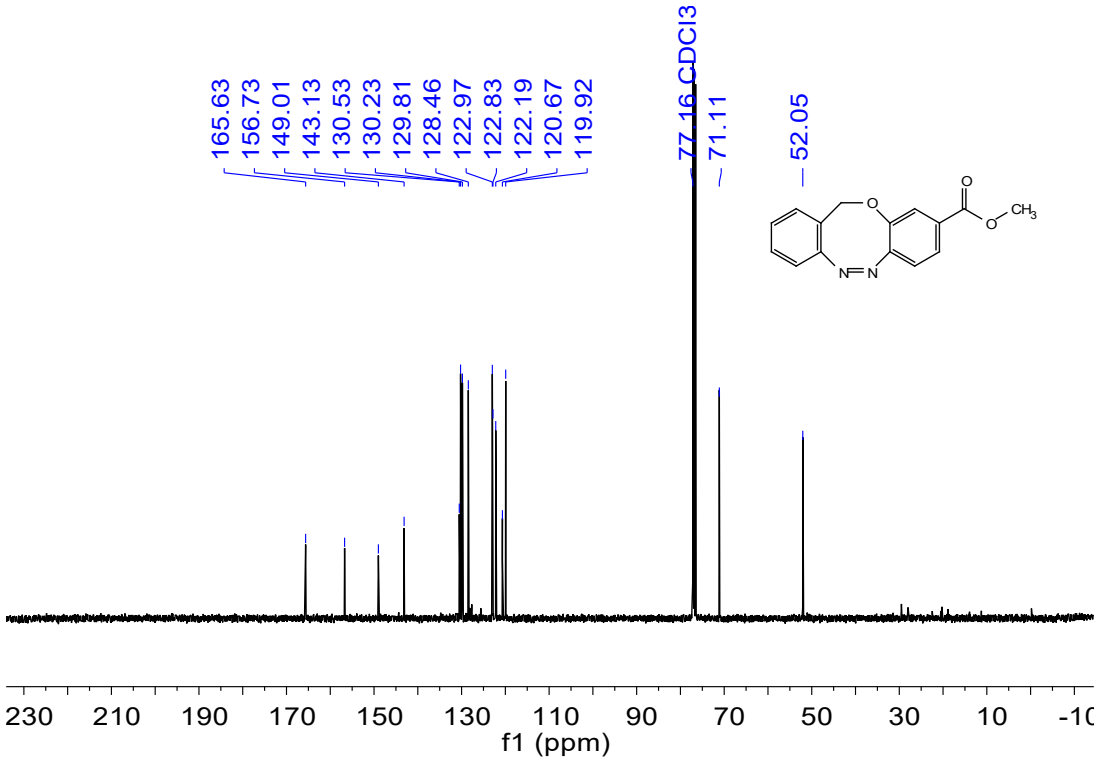
Br

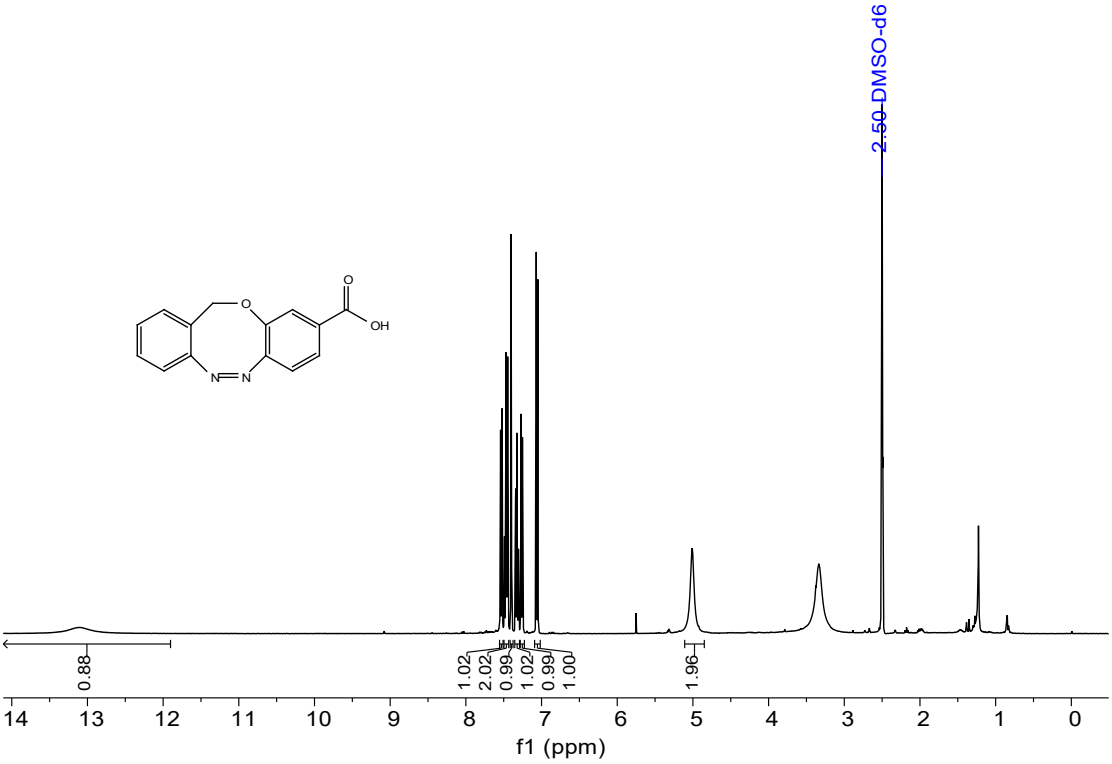

166.40
154.83
135.52
133.56
132.66
130.75
129.49
128.79
127.80
123.51
122.02
118.26
114.03
77.16 CDCl3
70.28
52.52
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)
Br
O
H3C
O
O
Br

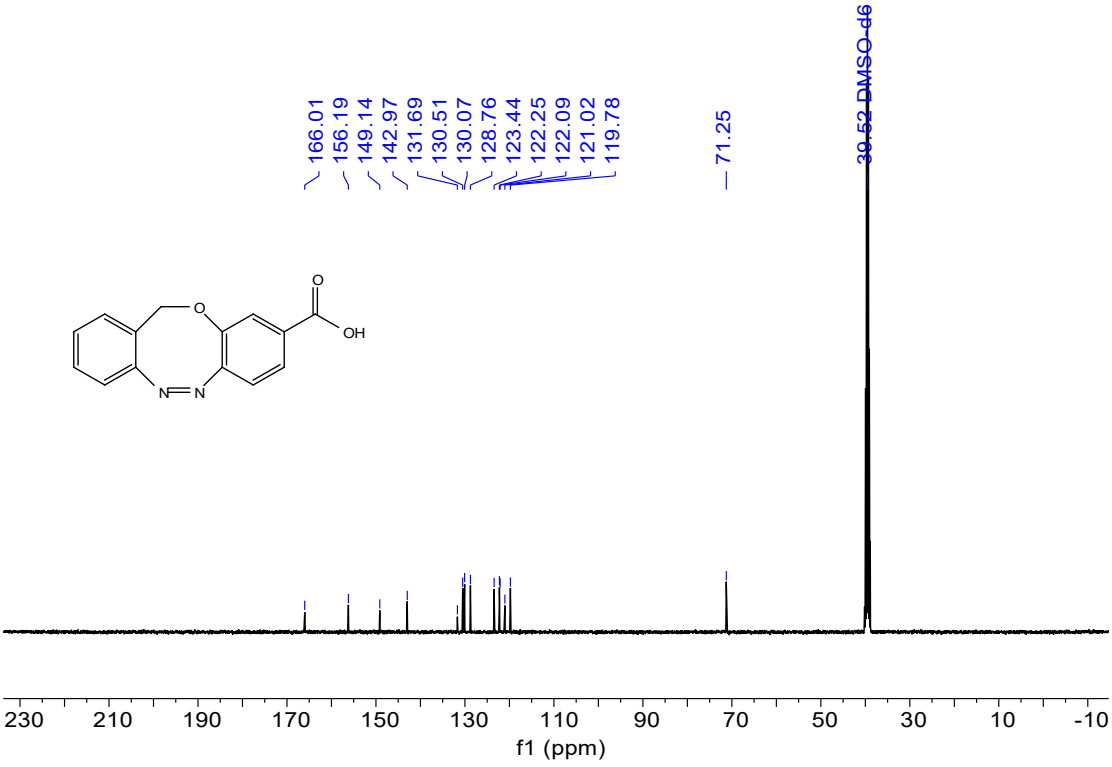

7.26 CDCl3
4.17
1.05
2.00
0.97
1.09
3.09
18.22
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

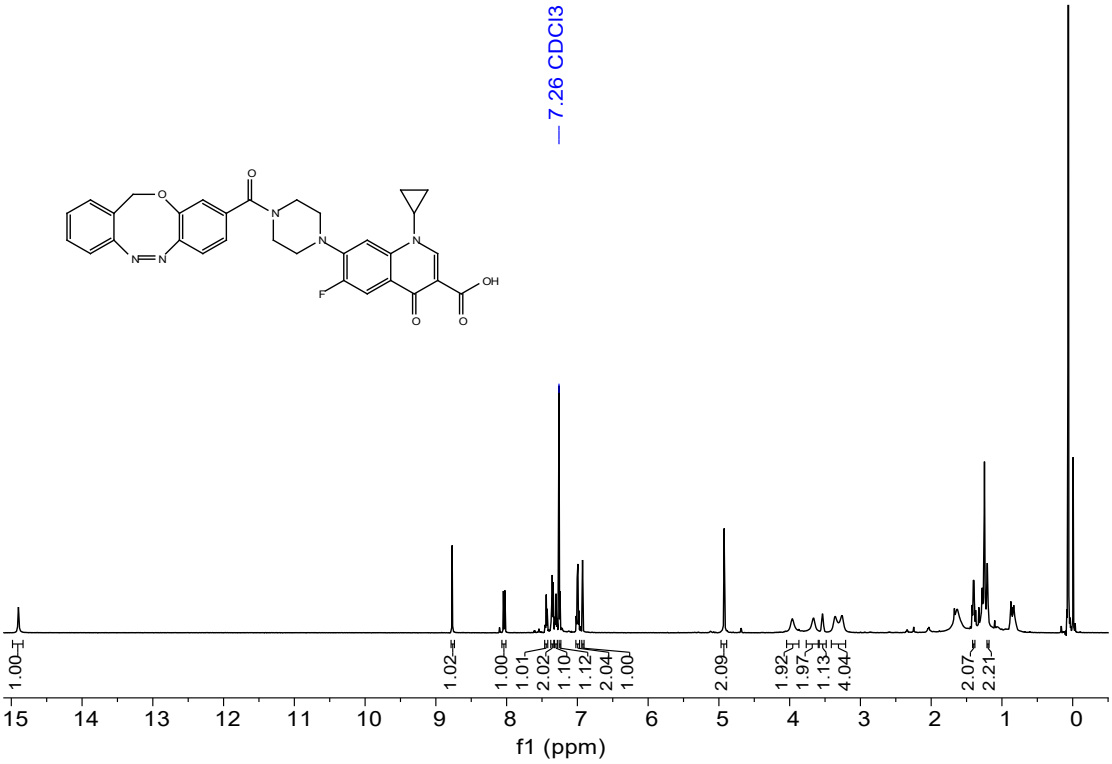

166.43
153.33
152.45
151.88
138.49
134.82
129.94
128.74
128.24
128.20
128.09
126.13
125.39
122.82
122.27
83.34
82.06
74.04
52.30
28.19
28.14
210
190
170
150
130
110
90
70
50
30
10
f1 (ppm)

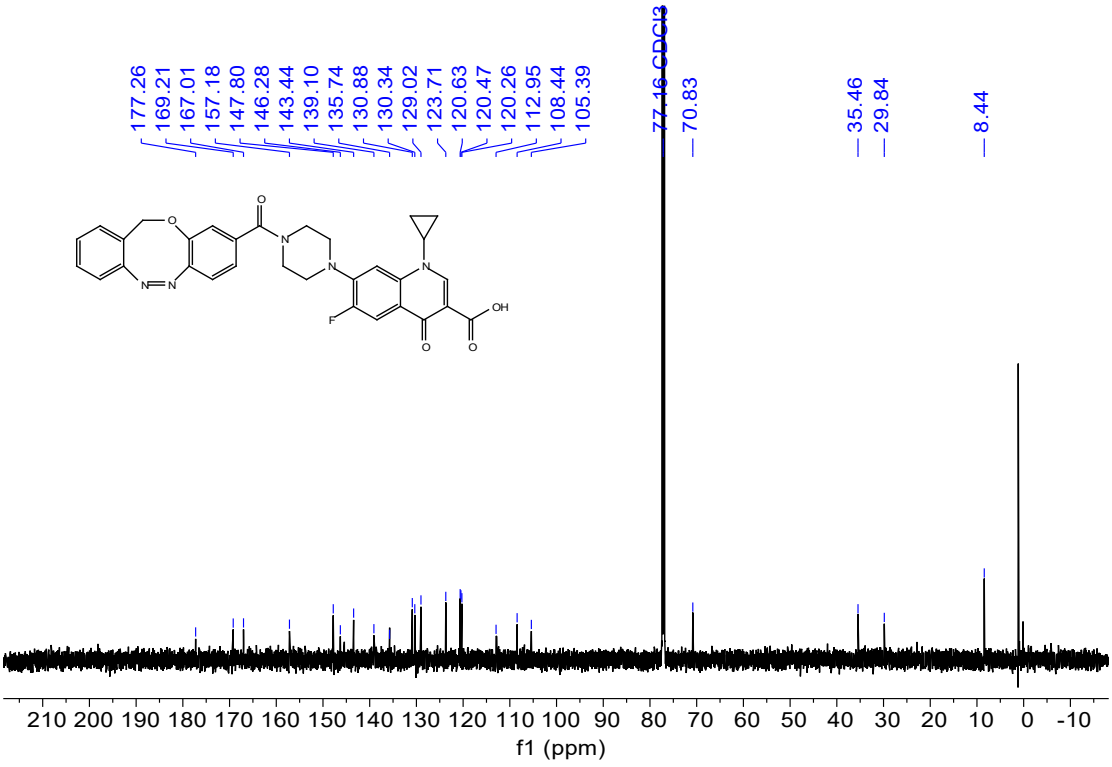

7.26 CDCl3
1.00
0.93
1.00
1.01
0.41
0.59
0.96
0.95
1.96
2.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

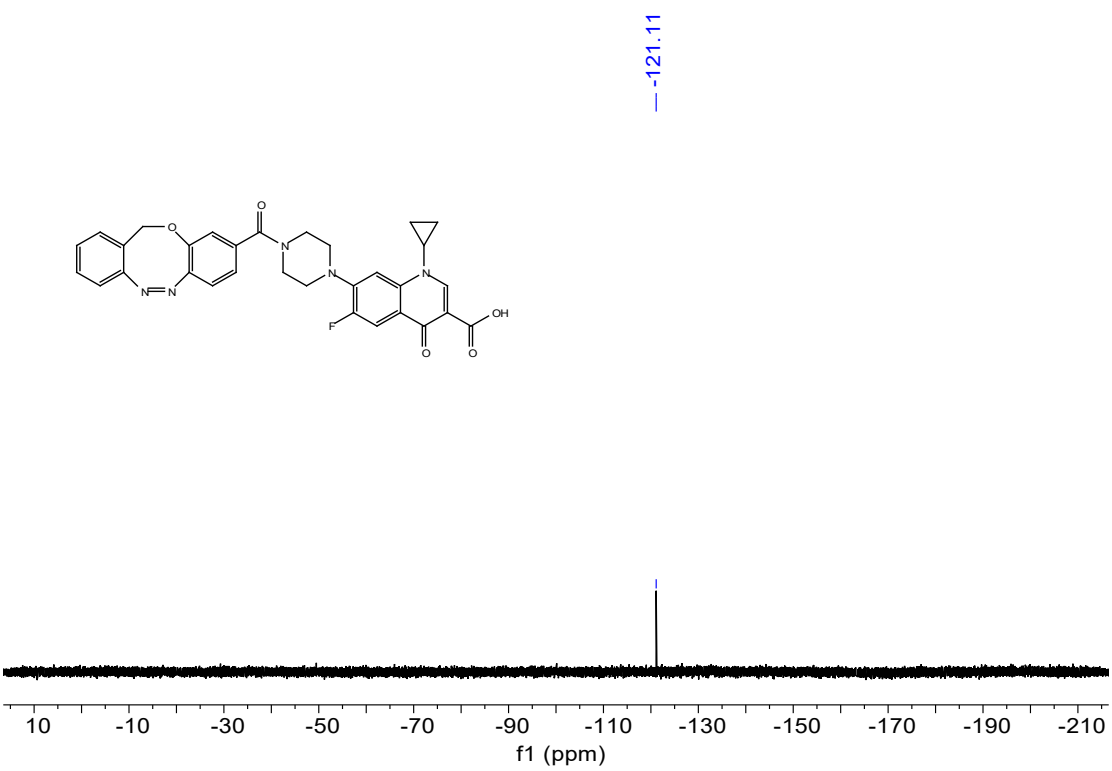

165.63
156.73
149.01
143.13
130.53
130.23
129.81
128.46
122.97
122.83
122.19
120.67
119.92
77.16 CDCl3
71.11
52.05
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

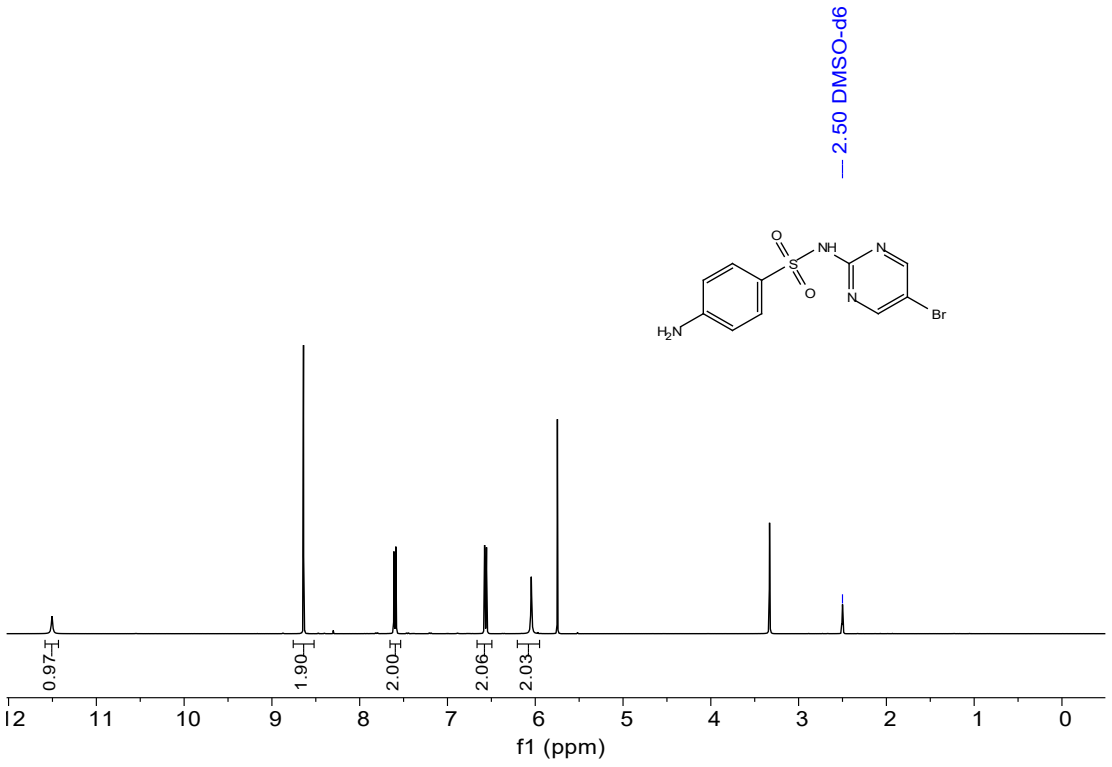

2.50 DMSO-d6
O
OH
N=N
0.88
1.02
2.02
0.99
1.02
0.99
1.00
1.96
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

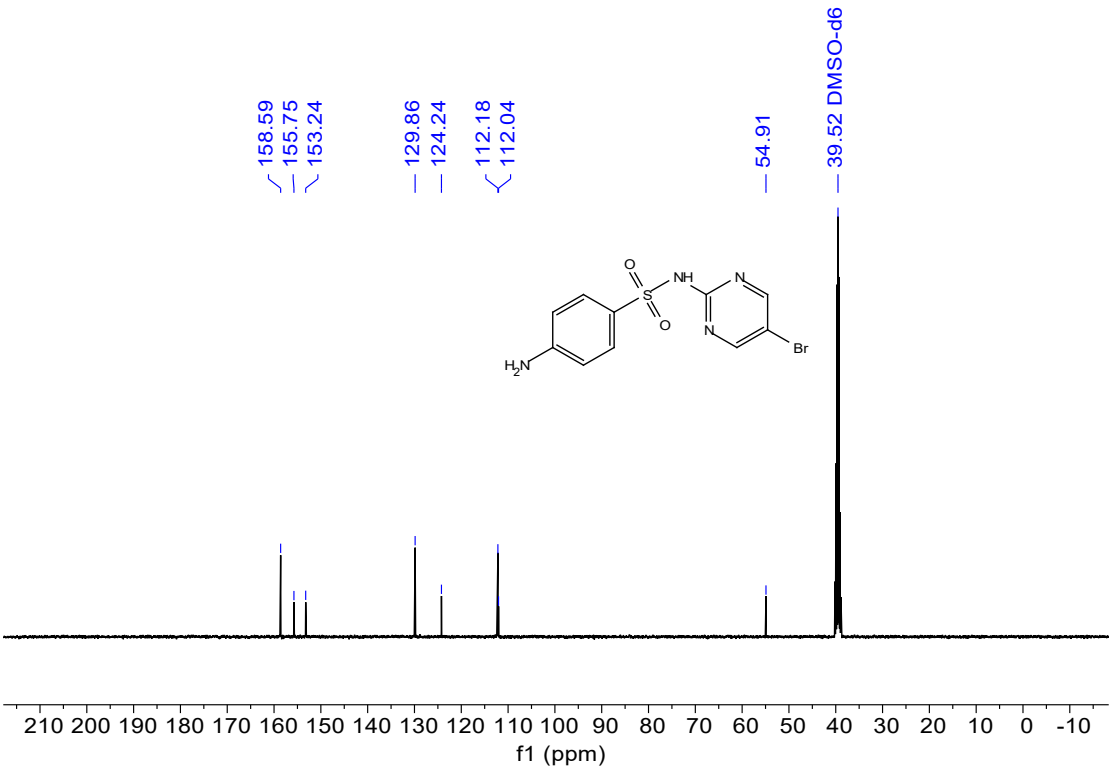

166.01
156.19
149.14
142.97
131.69
130.51
130.07
128.76
123.44
122.25
122.09
121.02
119.78
71.25
39.52 DMSO-d6
O
OH
N=N
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

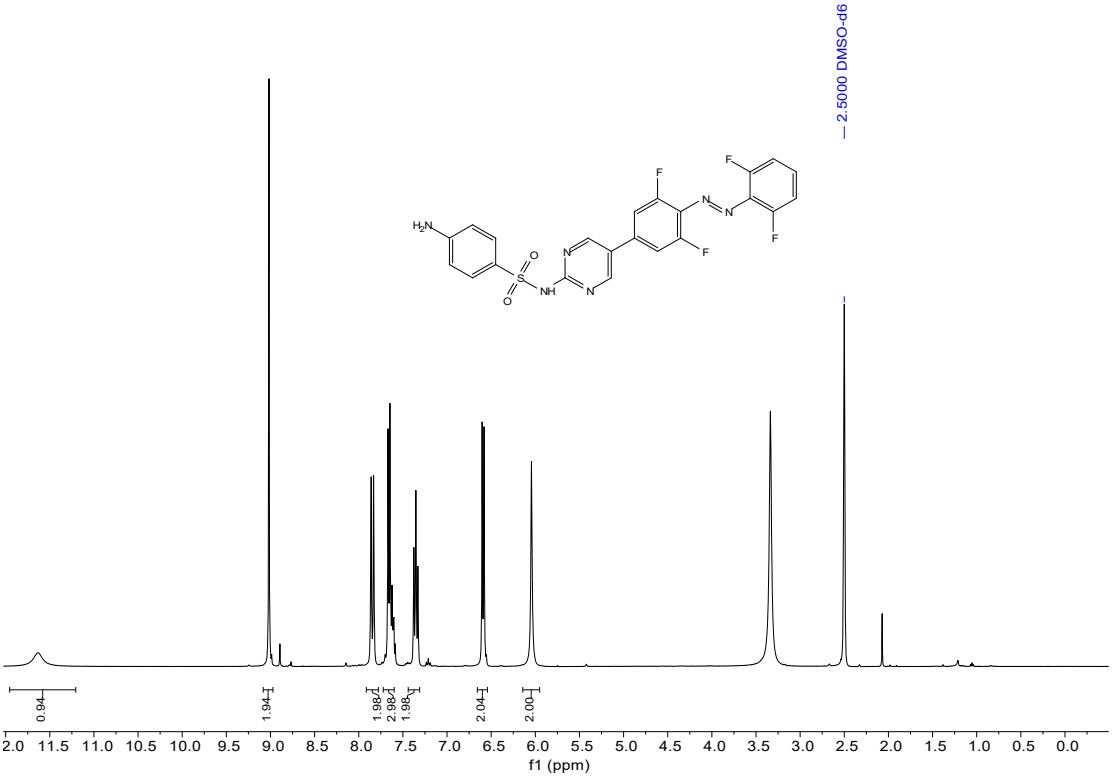

7.26 CDCl3
1.00
1.02
1.00
1.01
2.02
1.10
1.12
2.04
1.00
2.09
1.92
1.97
1.13
4.04
2.07
2.21
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

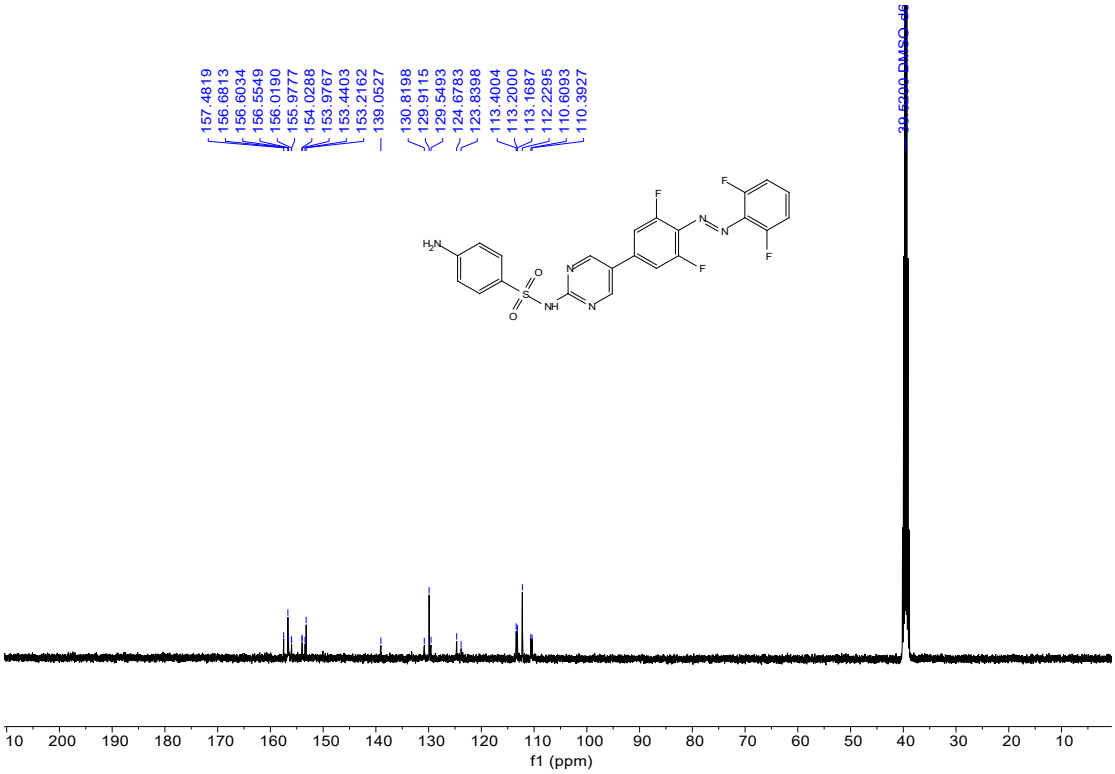

177.26
169.21
167.01
157.18
147.80
146.28
143.44
139.10
135.74
130.88
130.34
129.02
123.71
120.63
120.47
120.26
112.95
108.44
105.39
77.16 CDCl3
70.83
35.46
29.84
8.44
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

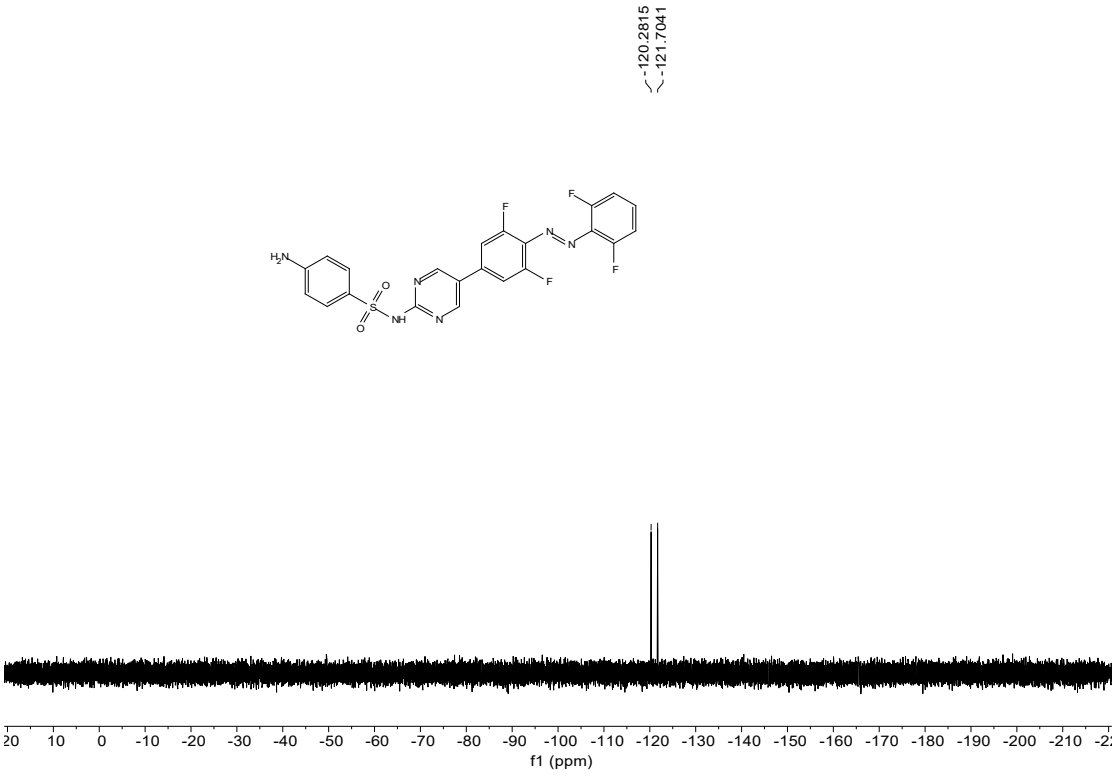

-121.11
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
f1 (ppm)

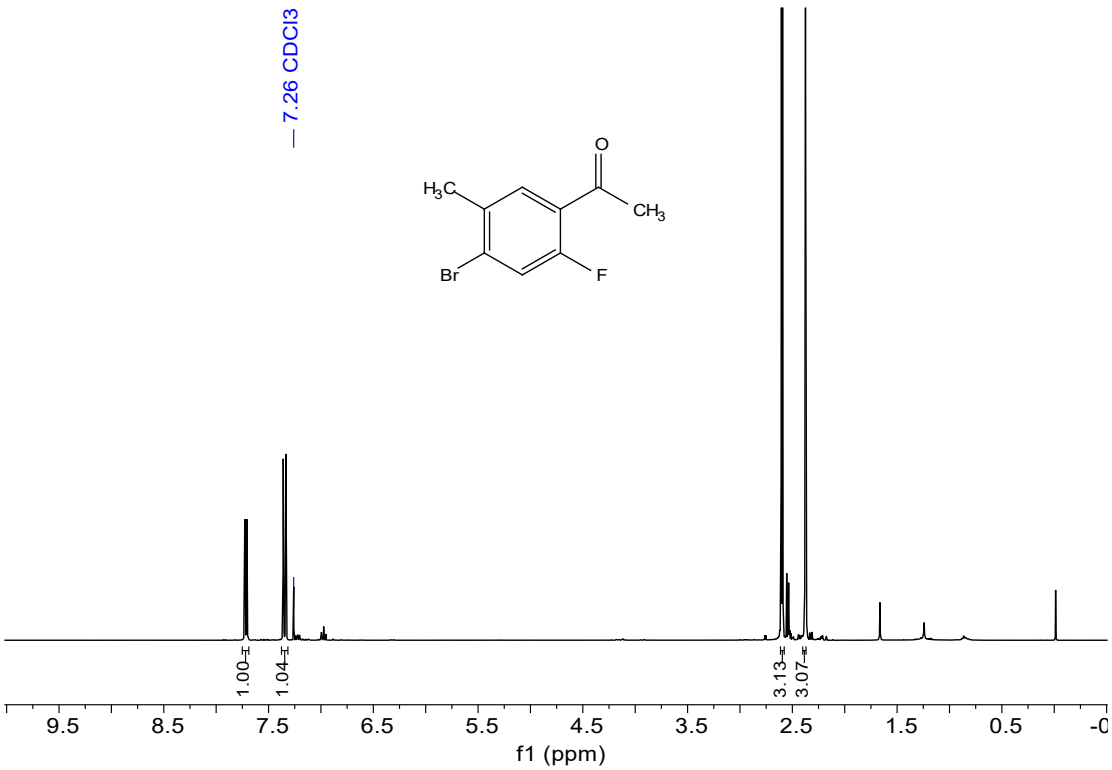

2.50 DMSO-d6
0.97
1.00
2.00
2.00
2.03
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

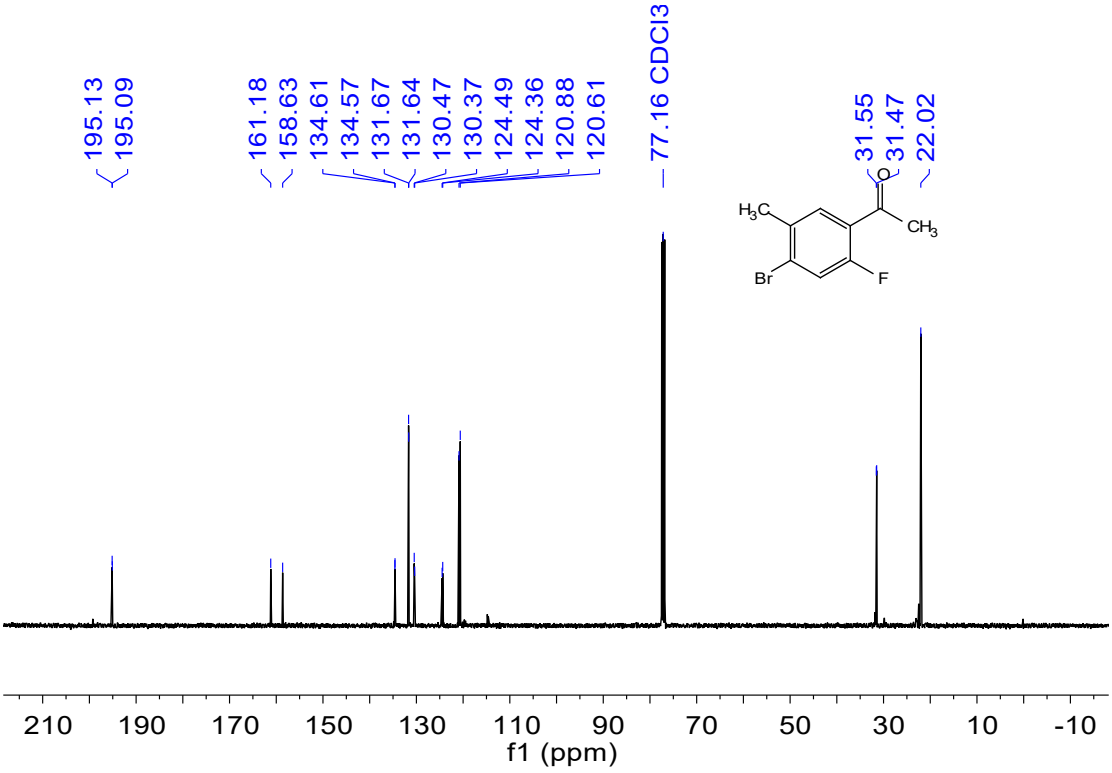

158.59
155.75
153.24
129.86
124.24
112.18
112.04
54.91
39.52 DMSO-d6
O
S
O
NH
N
N
Br
H2N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

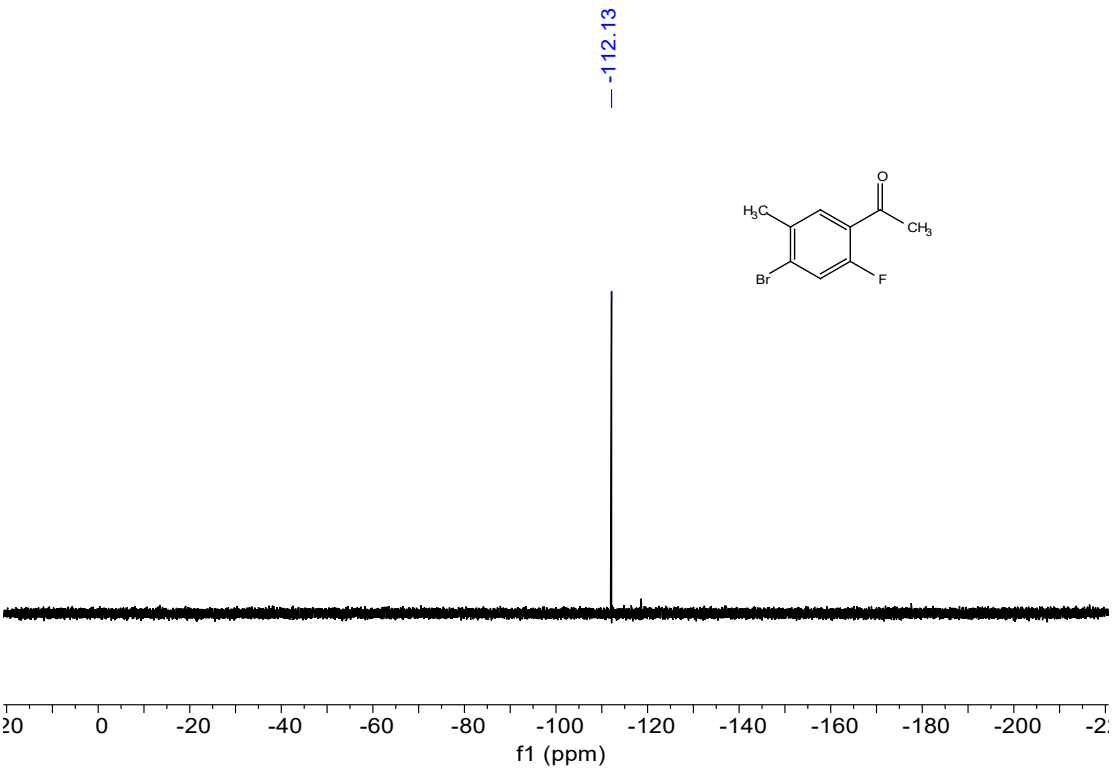

2.5000 DMSO-d6
F
F
F
F
N
N
H2N
O
S
O
NH
N
N
0.94
1.94
1.98
2.98
1.91
2.04
2.00
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

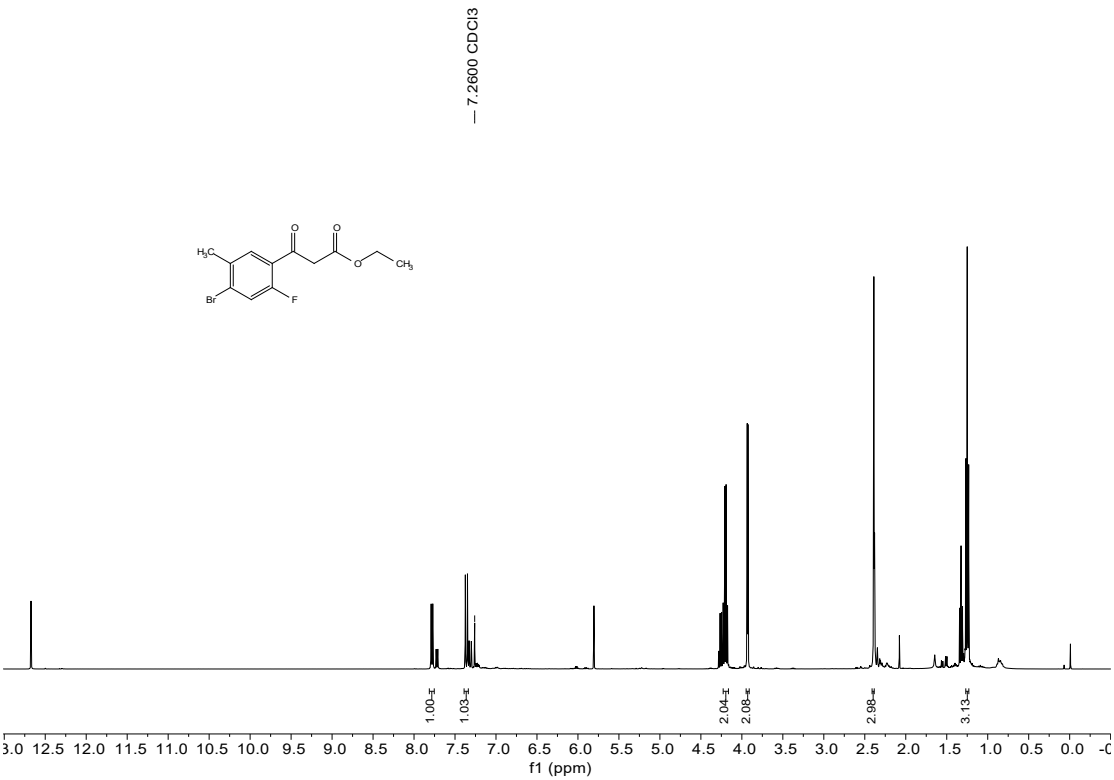

157.4819
156.6813
156.6034
156.5549
156.0190
155.9777
154.0288
153.9767
153.4403
153.2162
139.0527
130.8198
129.9115
129.5493
124.6783
123.8398
113.4004
113.2000
113.1687
112.2295
110.6093
110.3927
39.5200 DMSO-d6
f1 (ppm)

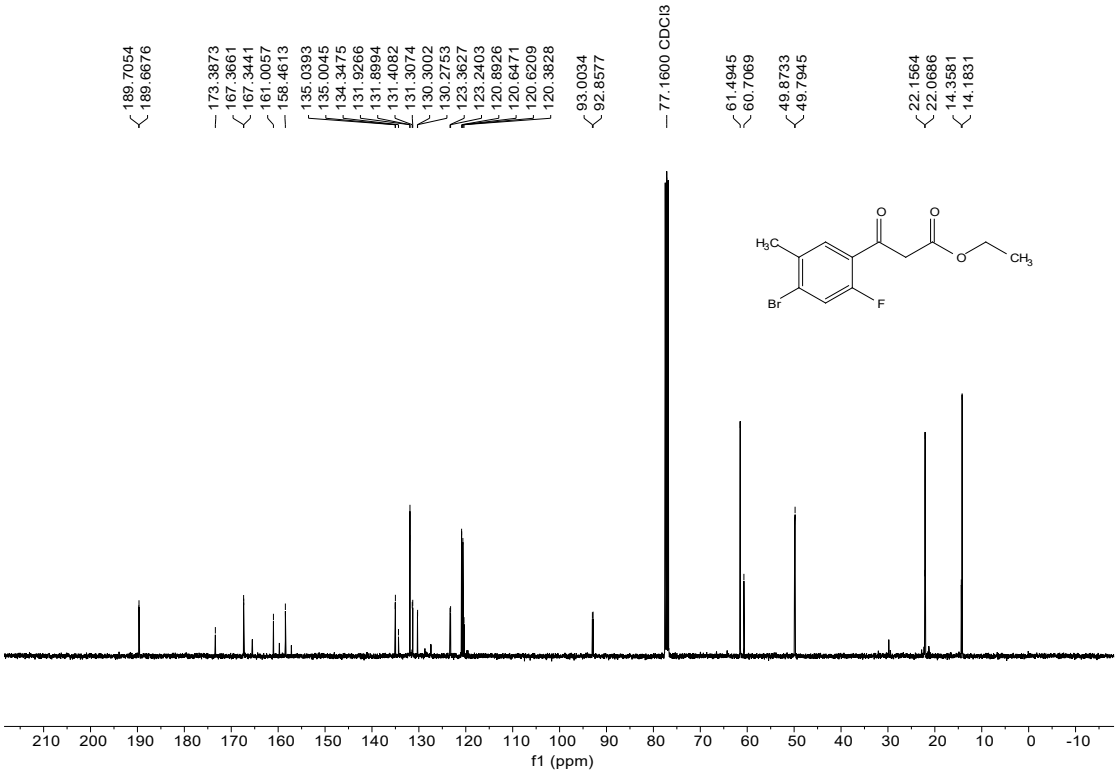

-120.2815
-121.7041
f1 (ppm)

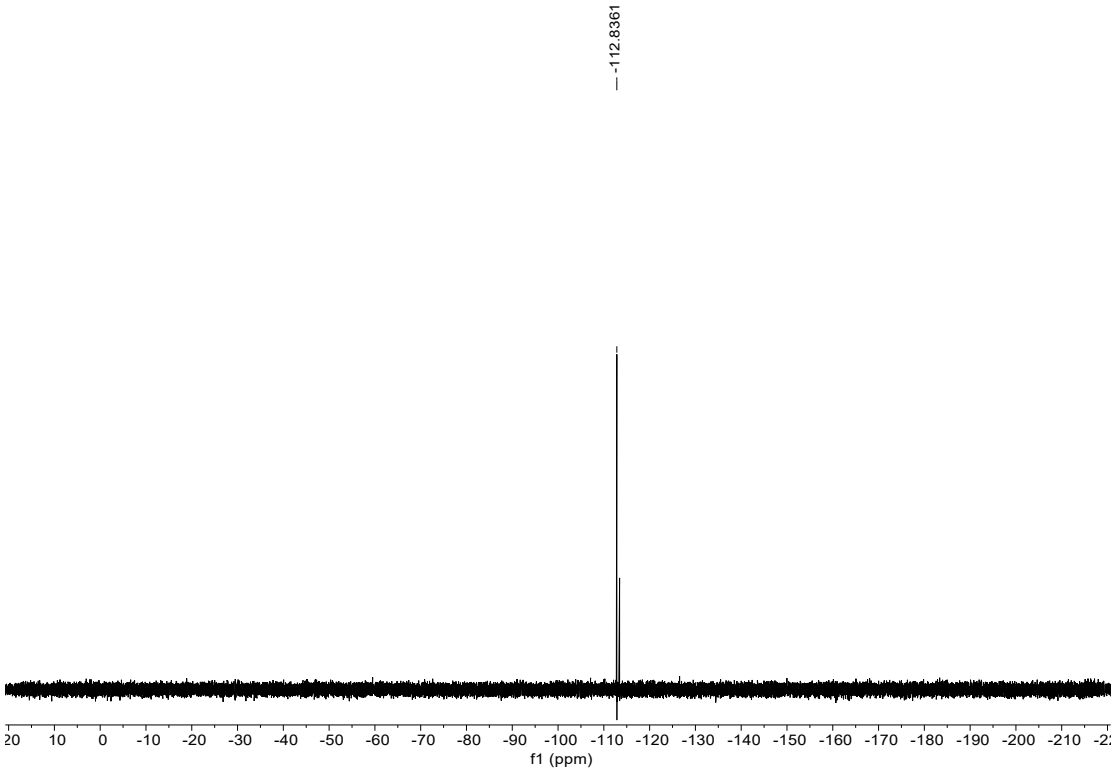

7.26 CDCl3
O
H3C
CH3
Br
F
1.00
1.04
3.13
3.07
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

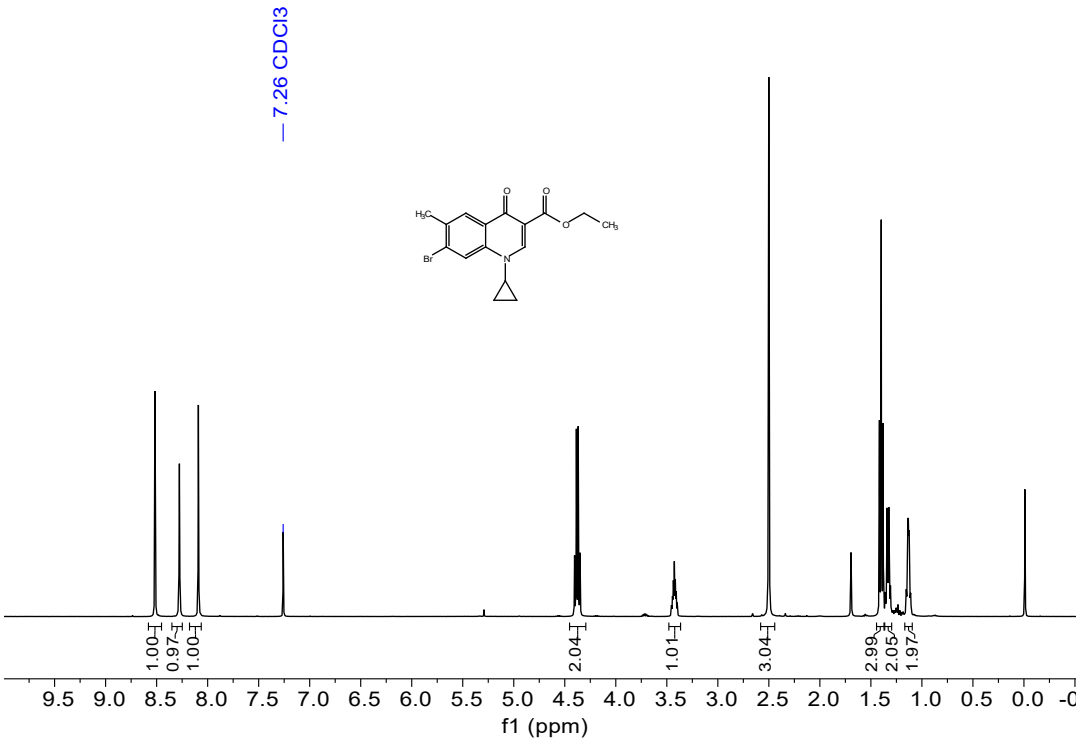

195.13
195.09
161.18
158.63
134.61
134.57
131.67
131.64
130.47
130.37
124.49
124.36
120.88
120.61
77.16 CDCl3
31.55
31.47
22.02
O
H3C
CH3
Br
F
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

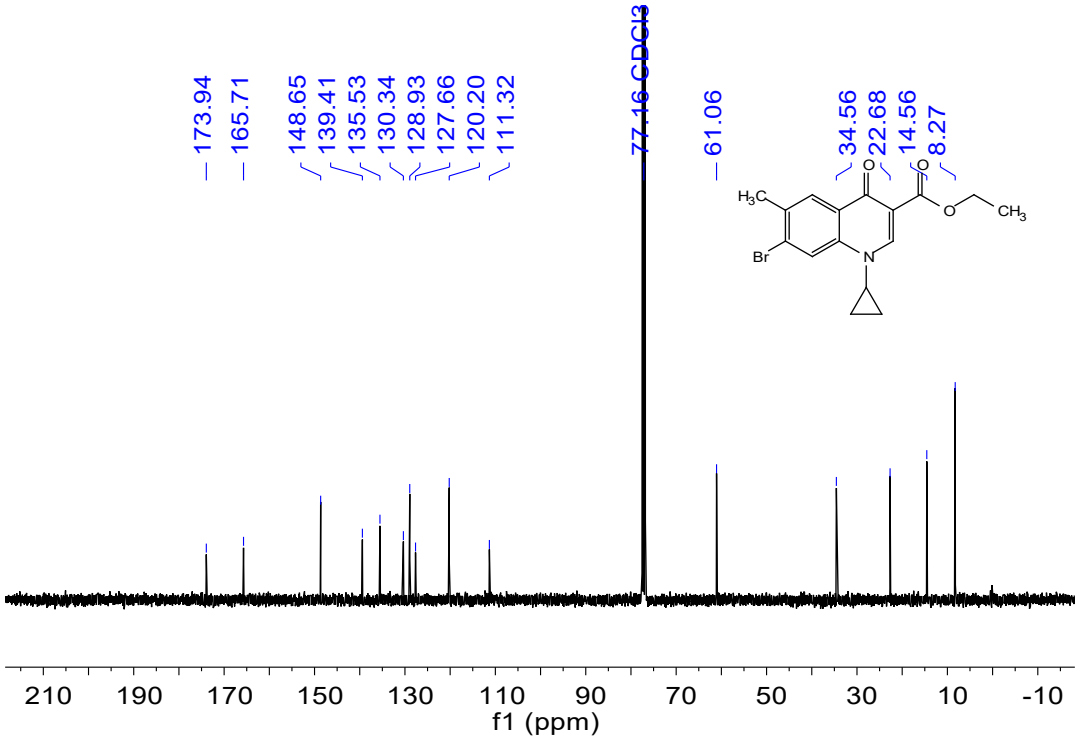

-112.13
O
H3C
CH3
Br
F
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
f1 (ppm)

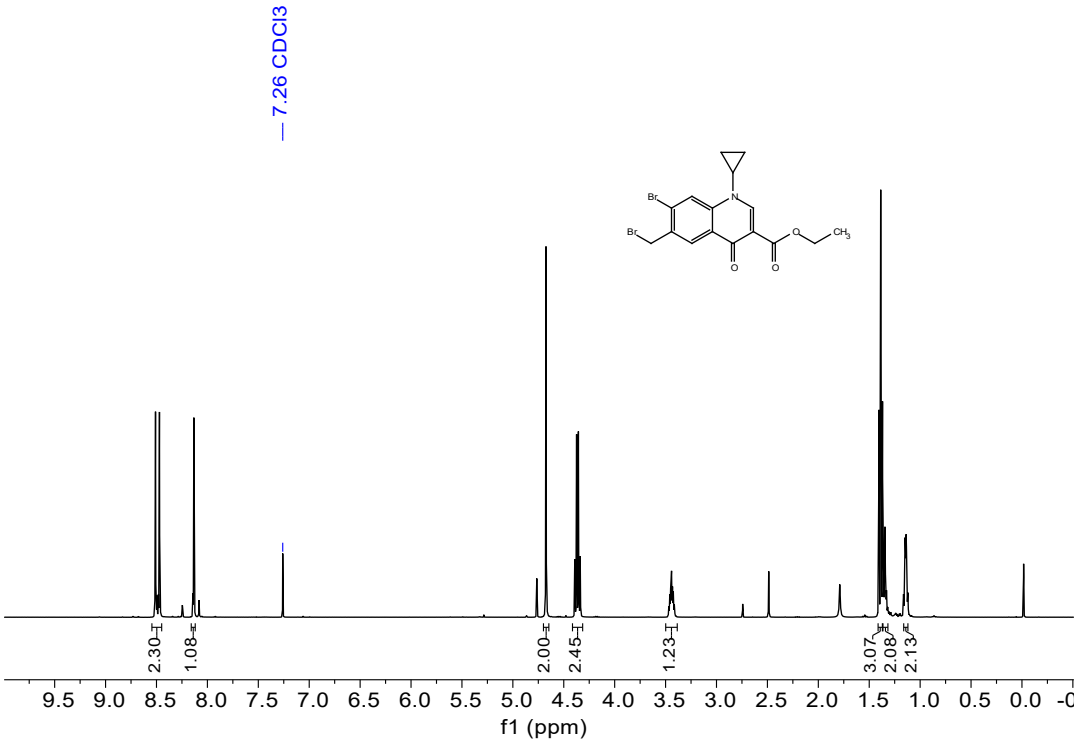

7.2600 CDCl3
O
O
H3C
O
CH3
Br
F
1.00
1.03
2.04
2.08
2.98
3.13
f1 (ppm)

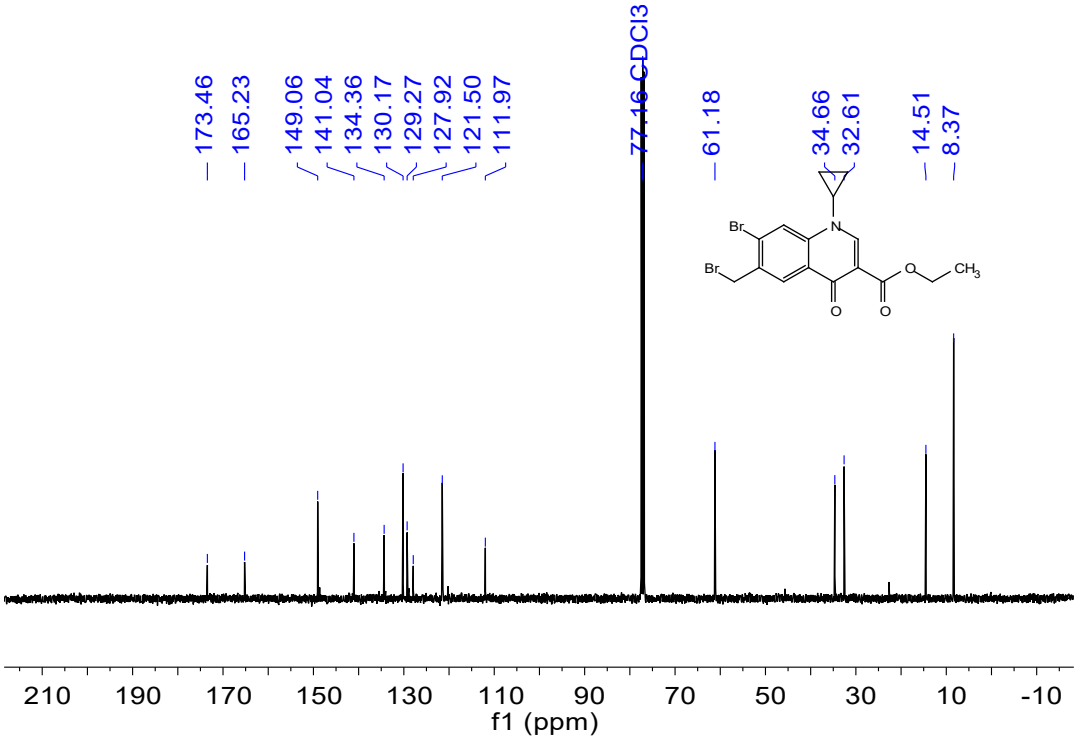

189.7054
189.6676
173.3873
167.3661
167.3441
161.0057
158.4613
135.0393
135.0045
134.3475
131.9266
131.8994
131.4082
131.3074
130.3002
130.2753
123.3627
123.2403
120.8926
120.6471
120.6209
120.3828
93.0034
92.8577
77.1600 CDCl3
61.4945
60.7069
49.8733
49.7945
22.1564
22.0686
14.3581
14.1831
O
O
O
H3C
CH3
Br
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

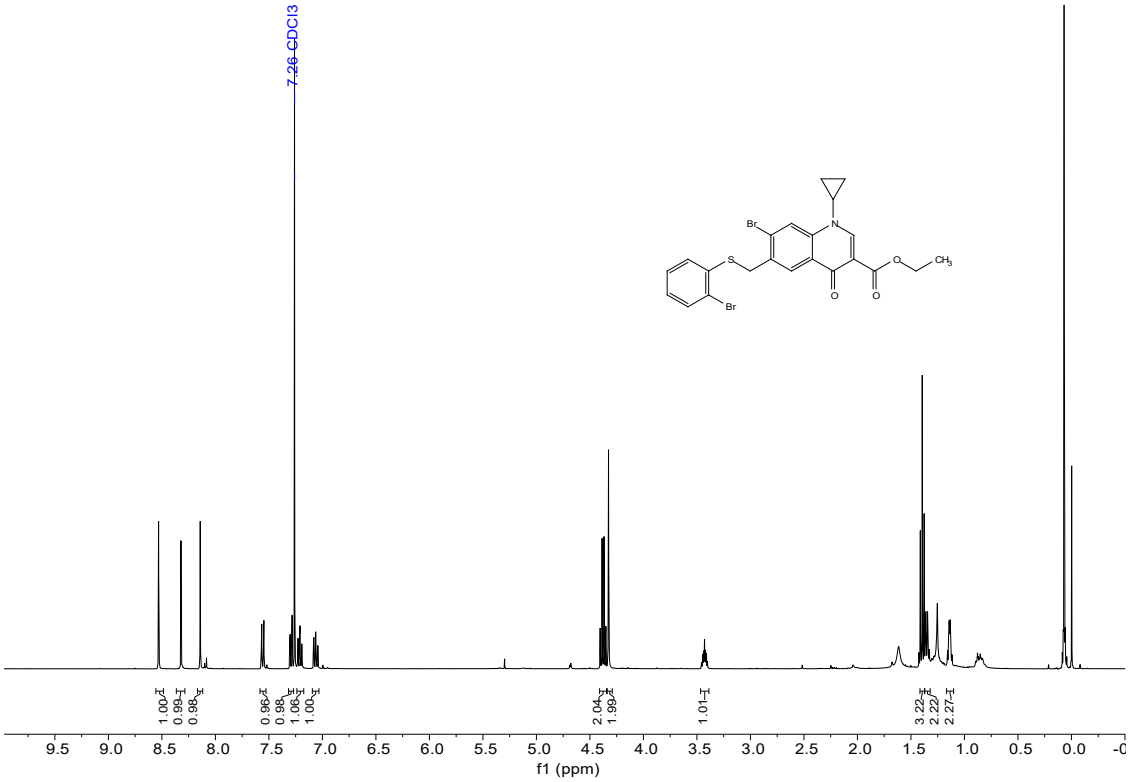

-112.8361
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -2
f1 (ppm)

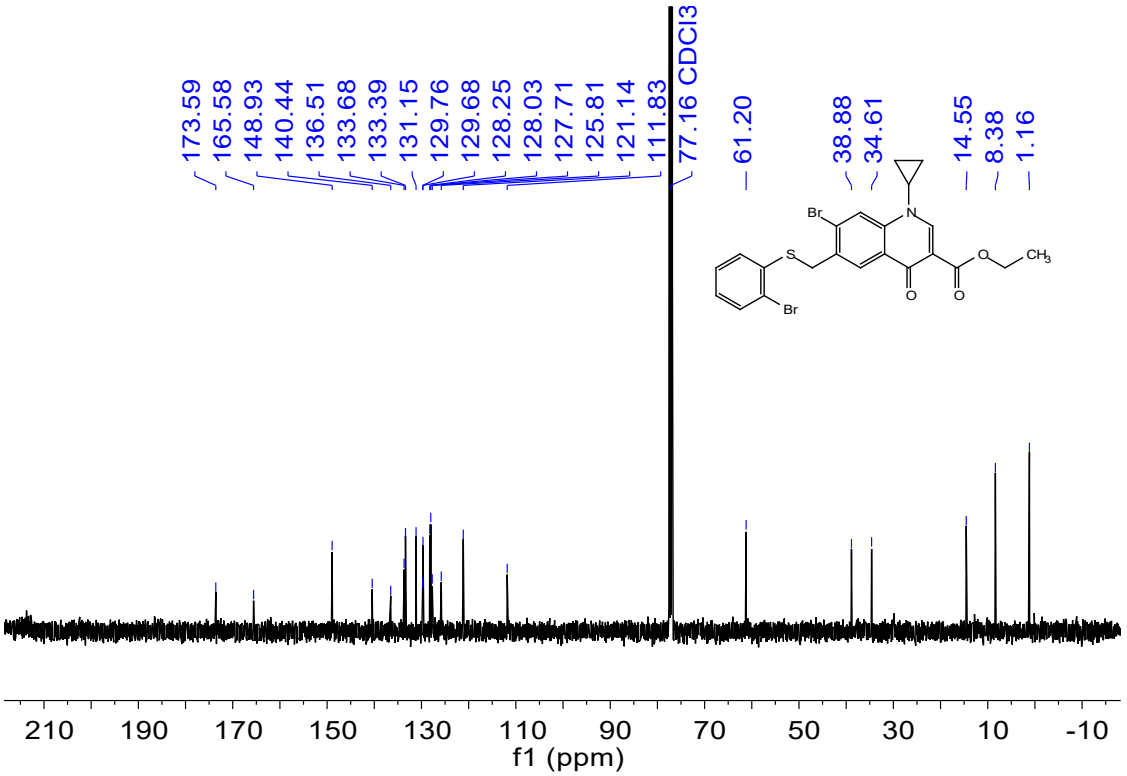

7.26 CDCl3
1.00
0.97
1.00
2.04
1.01
3.04
2.99
2.05
1.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

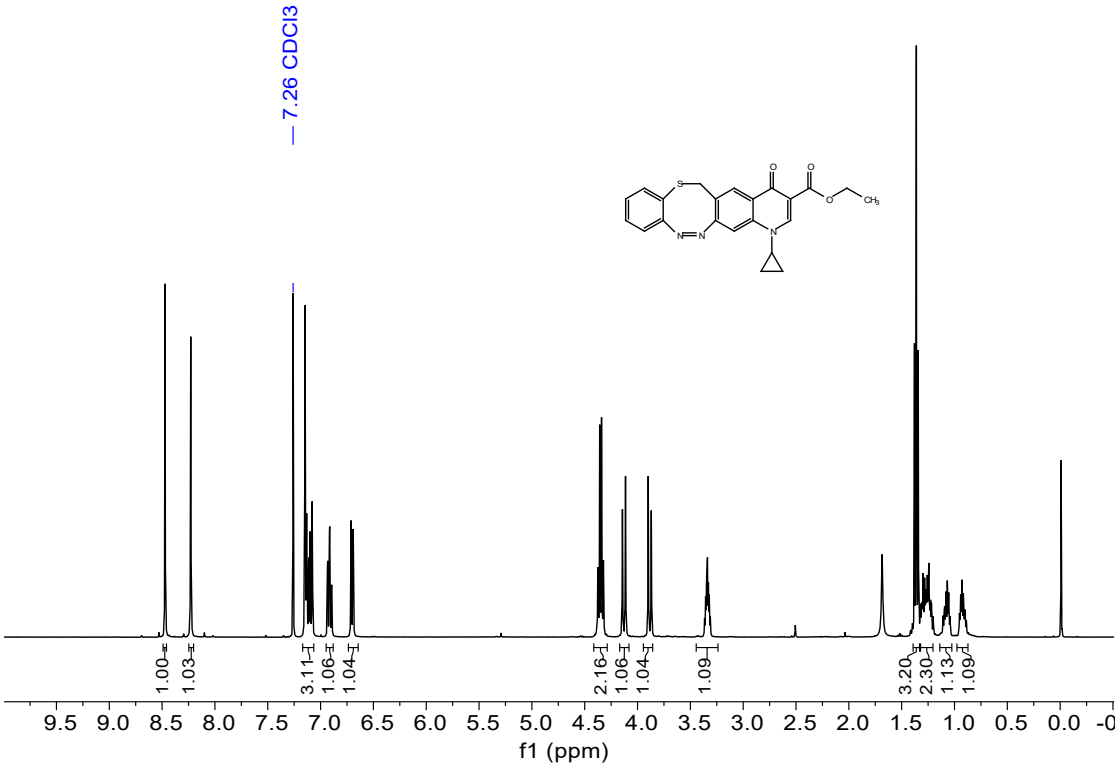

173.94
165.71
148.65
139.41
135.53
130.34
128.93
127.66
120.20
111.32
77.16 CDCl3
61.06
34.56
22.68
14.56
8.27
210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

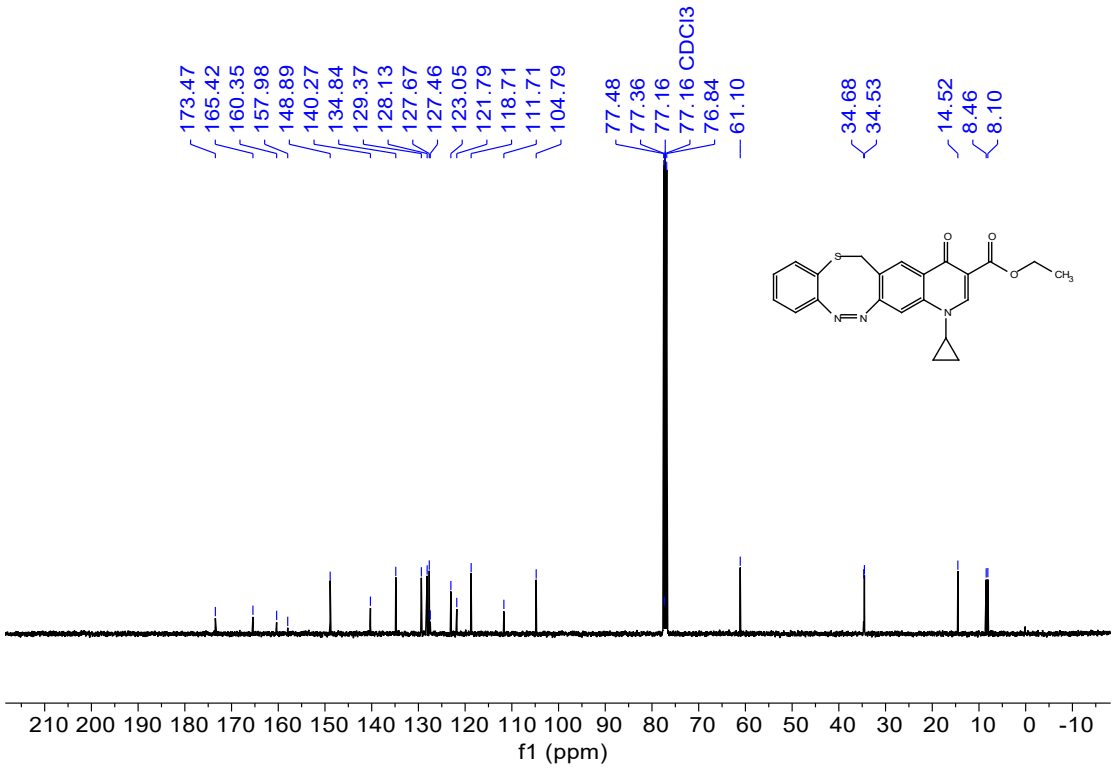

7.26 CDCl3
Br
Br
N
O
O
O
CH3
2.30
1.08
2.00
2.45
1.23
3.07
2.08
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

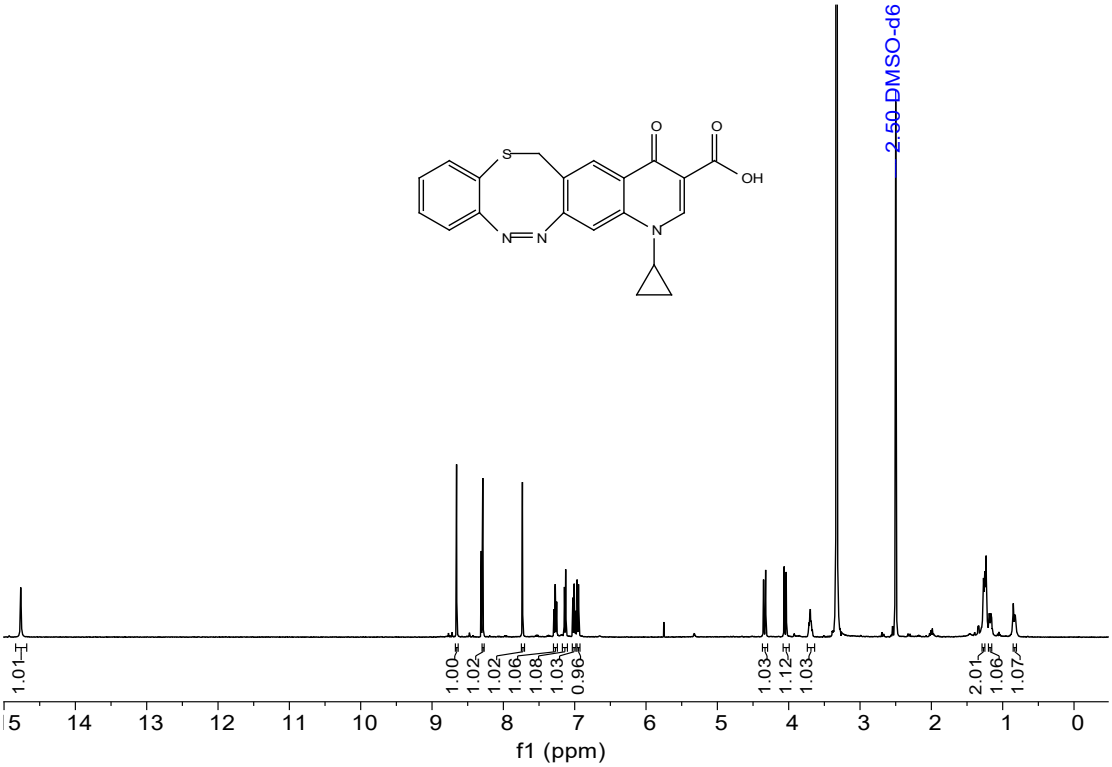

173.46
165.23
149.06
141.04
134.36
130.17
129.27
127.92
121.50
111.97
77.16 CDCl3
61.18
34.66
32.61
14.51
8.37
Br
Br
N
O
O
O
CH3
210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

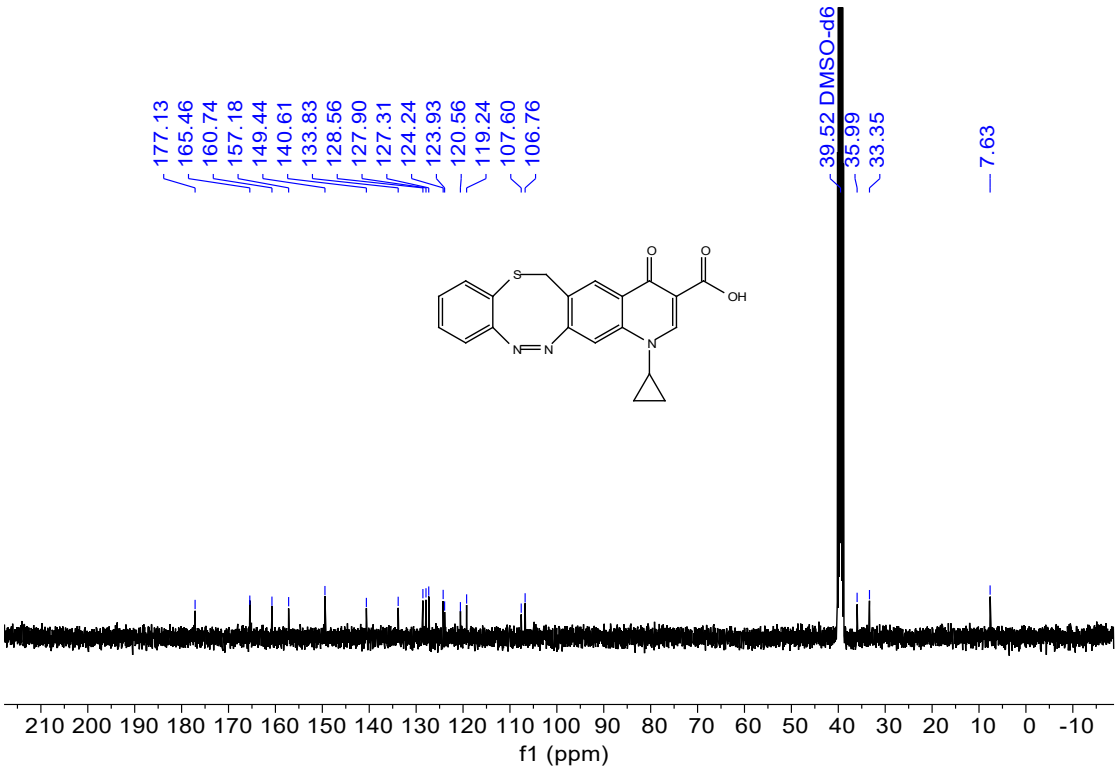

7.26 CDCl3
1.00
0.99
0.98
0.96
0.98
1.06
1.00
2.04
1.99
1.01
3.22
2.22
2.27
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


173.59
165.58
148.93
140.44
136.51
133.68
133.39
131.15
129.76
129.68
128.25
128.03
127.71
125.81
121.14
111.83
77.16 CDCl3
61.20
38.88
34.61
14.55
8.38
1.16
210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)


7.26 CDCl3
1.00
1.03
3.11
1.06
1.04
2.16
1.06
1.04
1.09
3.20
2.30
1.13
1.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


173.47
165.42
160.35
157.98
148.89
140.27
134.84
129.37
128.13
127.67
127.46
123.05
121.79
118.71
111.71
104.79
77.48
77.36
77.16
77.16 CDCl3
76.84
61.10
34.68
34.53
14.52
8.46
8.10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


2.50 DMSO-d6
1.01
1.00
1.02
1.02
1.06
1.08
1.03
0.96
1.03
1.12
1.03
2.01
1.06
1.07
f1 (ppm)


177.13
165.46
160.74
157.18
149.44
140.61
133.83
128.56
127.90
127.31
124.24
123.93
120.56
119.24
107.60
106.76
39.52 DMSO-d6
35.99
33.35
7.63
f1 (ppm)