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Supplementary Material

Synthesis and binding testing of *N*1-alkylamino-substituted 2-aminobenzimidazole analogs targeting the hepatitis C virus internal ribosome entry site

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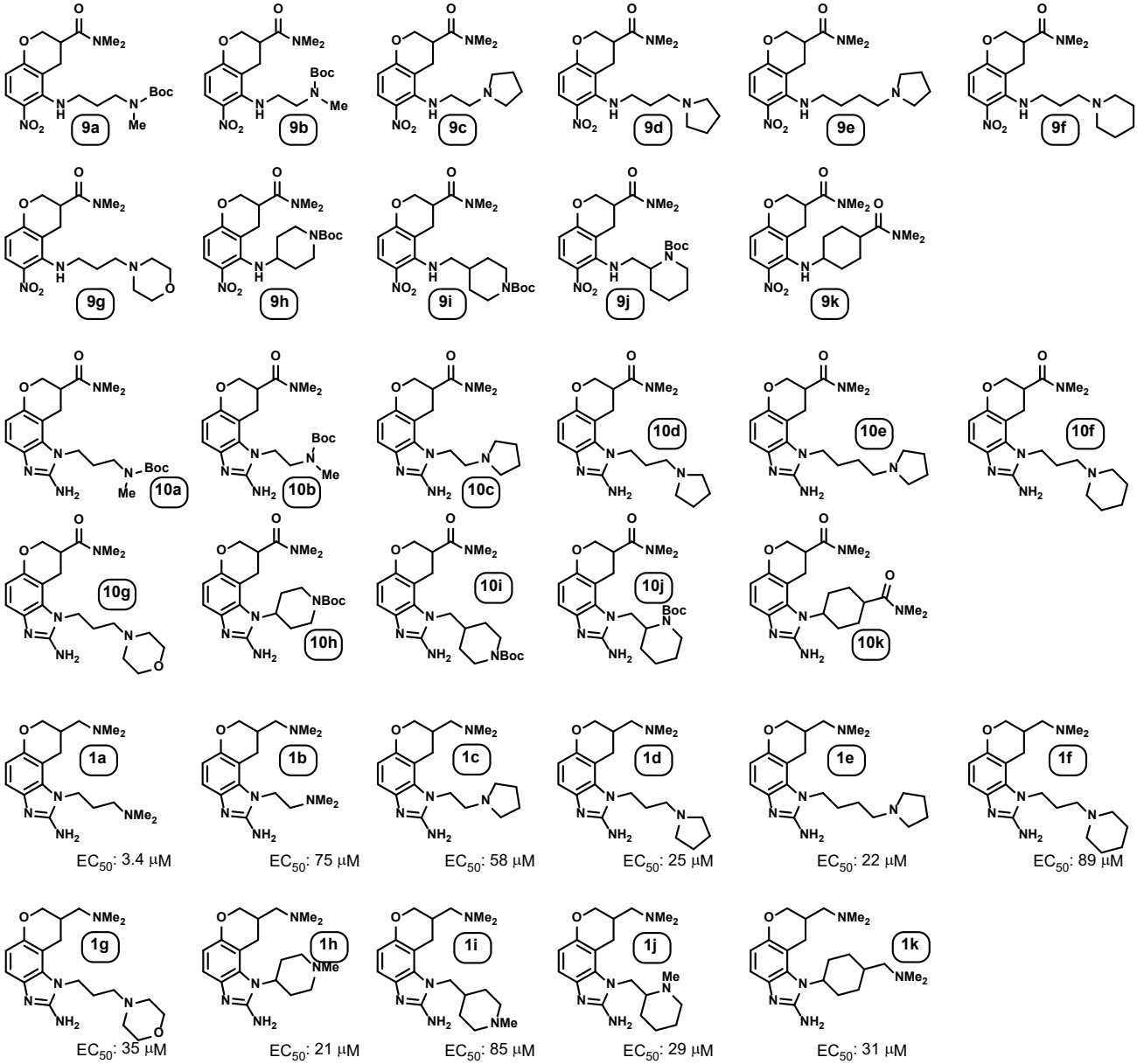

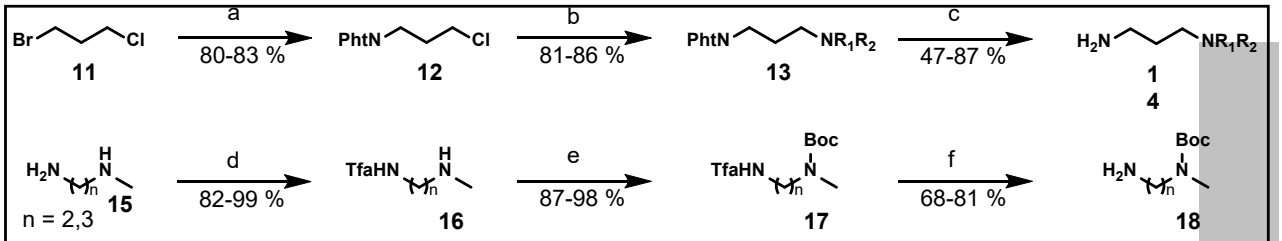

Figure 1.) Reagents and conditions: (a) Phtalimide, K_2CO_3, DMF, r.t.; (b) Sec-Amine, NaI, acetone, reflux; (c) N_2H_4, MeOH, reflux; (d) F_3CCO_2Et, CH_3CN 0 C to r.t.; (e) Boc_2O, CH_2Cl_2, r.t.; (f) K_2CO_3, MeOH, H_2O, reflux. Pht = Phtaloyl; Tfa = Trifluoroacetyl.

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Experimental

***N*-(3-Chloropropyl)phtalimide** (**12**) was prepared according to a procedure reported by Nagarapu *et al.*[1] Phthalimide (3.30 g, 22.4 mmol) was dissolved in anhydrous DMF (50 mL) under argon and slowly added to a stirred solution of 1-bromo-3-chloropropane (**11**) (5.30 g, 33.7 mmol) and finely divided anhydrous K_2CO_3 (6.20 g, 44.9 mmol) in anhydrous DMF (25 mL). The reaction was stirred under argon at ambient temperature for 16 h. The reaction was then treated with ice water (50 mL) and the mixture stirred for 15 minutes. The mixture was transferred to a separation funnel and the aqueous phase was extracted three times with dichloromethane (3 × 25 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was extracted with diethyl ether (50 mL). The organic extract was washed with water (5 × 25 mL) and brine (2 × 25 mL). The organic phase was then evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (silica gel, 0-30% EtOAc in hexanes) to provide the pure as a white crystalline solid (80% yield).

Tertiary propyl amines (**13**) were prepared according to a general procedure. Thus, ***N*-(3-morpholin-4'-yl-propyl)phtalimide** was obtained according to a protocol reported by Contreras *et al*.[2] To a solution of compound **12** (1.5 g, 6.7 mmol) in acetone (50 mL) was added morpholine (1.26 g, 14.4 mmol) and sodium iodide (3.02 g, 20.1 mmol). The reaction mixture was heated under reflux for 24 h. The reaction mixture was cooled to ambient temperature and the acetone was removed under reduced pressure. Water (50 mL) was added and the mixture transferred to a separation funnel. The aqueous phase was extracted three times with diethyl ether (3 × 25 mL) and the combined organic phases were dried over anhydrous with sodium sulfate. After filtration the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (silica gel, 100 % EtOAc) to provide ***N*-(3-morpholin-4'-yl-propyl)phtalimide** as a light beige oil (86% yield).

Primary propyl amines (**14**) were prepared according to a general phthalimide deprotection procedure with hydrazine. Thus, **3-morpholin-4'-yl-propylamine** was obtained from a protocol reported by Lukinavičius *et al*.[3] Hydrazine (0.36 g, 11 mmol) was added dropwise to compound **13** (1.54 g, 5.63 mmol) dissolved in methanol (35 mL). The reaction mixture was then heated on reflux for three hours. After the reaction mixture was cooled to ambient temperature the methanol was removed under reduced pressure. A mixture of ethanol and water (1:1, 35 mL) was added followed by the addition of 1M aqueous HCl and the pH adjusted to ~ 1. The white precipitate was collected via filtration and was washed with water (4 × 20 mL). The solid was then dissolved in 1M aqueous NaOH and transferred to a separation funnel. The aqueous phase was extracted with dichloromethane (3 × 25 mL) and the combined organic phases were dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and the crude product was obtained as a colorless oil (82% yield). This product was then used in the next step without further purification.

***N*-Boc-*N*-methyl-1,3-trimethylenediamine** (**18**, n=3).[4,5] Ethyl trifluoroacetate (5.32 g, 37.4 mmol) was slowly added to a solution of ***N*-methyl-1,3-trimethylenediamine** (**15**) (3.00 g, 34.0 mmol) in acetonitrile (15 mL) at 0 °C. The ice-water bath was removed and the reaction mixture was refluxed for 2 h and then stirred at ambient temperature for 20 h. The solvent was then removed under reduced pressure and subsequently azeotrope dried with benzene (2 × 20 mL) to provide ***N*-Trifluoroacetyl-*N*'-methyl-1,3-trimethylenediamine** (**16**) (6.26 g, 99%) as a colorless oil. To a

solution of the product obtained (**16**) (6,26 g) in dichloromethane (20 mL) at 0 °C was dropwise added a solution of di-*tert*-butyl dicarbonate (8.15 g, 37.4 mmol) in dichloromethane (25 mL). Caution! CO_2 formation! Once the formation of carbon dioxide ceased the ice-water bath was removed and the reaction mixture was stirred over night at ambient temperature. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to provide ***N*-trifluoroacetyl-*N*'-methyl-*N*'-*tert*-butoxycarbonyl-1,3-trimethylenediamine** (**17**) (8.23 g, 85%) as a colorless oil. To a solution of **17** (500 mg, 1.76 mmol) in methanol (10 mL), water was added (4 mL) followed by adding a solution of potassium carbonate (486 mg, 3.52 mmol) in water (10 mL) and the reaction mixture was stirred for 20 h at ambient temperature. The methanol was removed under reduced pressure and the remaining aqueous phase diluted with brine (50 mL). The mixture was transferred to a separation funnel, extracted with dichloromethane (2 × 25 mL) and the combined organic phases were dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under reduced pressure and product **18** was obtained as a colorless oil (290 mg, 88%). This product and was then used in the next step without further purification.

Preparation of compounds 4-8:

5-Chloro-*2H*-chromene-3-carboxaldehyde (**4**).[6] A mixture of 6-chlorosalicylaldehyde **3** (16.5 g, 0.105 mol), DABCO (5.90 g, 0.053 mol), acrolein (10.5 mL, 0.158 mol), and dioxane (36 mL) was placed in a sealed vial and heated with stirring at 95 °C for 140 minutes. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with 10% aqueous HCl and then brine, dried with anhydrous Na_2SO_4, and evaporated. Chromatography on silica using a gradient of 25–50% CH_2Cl_2 in hexanes gave 14.8 g (72%) of **4** as light yellow crystals. An analytical sample was recrystallized from EtOAc/hexanes: m.p. 65.5–66 °C. ^{1}H NMR (DMSO-d_6) δ 9.69 (s, C*H*O, 1H), 7.77 (s, C*H*=CCHO, 1H), 7.34 (dd, *J*=8.0, 8.0 Hz, Ar*H*, 1H), 7.13 (d, *J*=8.0 Hz, Ar*H*, 1H), 6.88 (d, *J*=8.0 Hz, Ar*H*, 1H), 4.94 (s, OCH_2, 2H). ^{13}C NMR ($CDCl_3$) δ 189.7, 157.1, 137.0, 133.8, 133.0, 132.3, 122.6, 119.2, 115.3, 63.0. HRMS $(M+H)^+$: calc. for $C_{10}H_8O_2Cl$, 195.0207; found, 195.0204.

5-Chloro-*2H*-chromene-3-carboxylic acid (**5**).[6] To absolute ethanol (195 mL) in a round-bottomed flask was added a solution of sodium hydroxide (12.2 g, 305 mmol) in water (97 mL). A solution of silver nitrate (27.2 g, 160 mmol) in water (97 mL) was then added dropwise with vigorous stirring. To the resulting suspension of Ag_2O was added aldehyde **4** (14.8 g), and the mixture was heated and stirred at 85 °C for 75 minutes. The mixture was cooled to room temperature and the clear supernatant was decanted. The solid was washed with a 1:1 ethanol/water solution (3 × 20 mL), and the washings were combined with the decanted supernatant. Dilution with an excess of 1M aq. HCl gave a voluminous white precipitate which dissolved upon extraction with CH_2Cl_2. The resulting CH_2Cl_2 solution was dried with Na_2SO_4, filtered, and evaporated to give 15.5 g (97%) of **5** as cream-colored fluffy crystals. An analytical sample was recrystallized from EtOAc/hexanes: m.p. 192.5–193 °C. ^{1}H- NMR (DMSO-d_6) δ 13.10 (bs, CO_2H, 1H), 7.54 (m, C*H*=CCHO, 1H), 7.28 (dd, Ar*H*, *J* = 8.2, 8.2 Hz, 1H), 7.09 (dd, Ar*H*, *J* = 8.2, 1.1 Hz, 1H), 6.87 (ddd, Ar*H*, *J* = 8.2, 1.1, 1.1 Hz, 1H), 4.92 (s, OCH_2, 2H**)**. ^{13}C NMR ($CDCl_3$) δ 168.7, 156.6, 133.8, 132.3, 132.1, 122.7, 122.5, 119.4, 115.1, 64.0. HRMS $(M–H)^–$: calc. for $C_{10}H_6O_3Cl$, 209.0011; found, 209.0012.

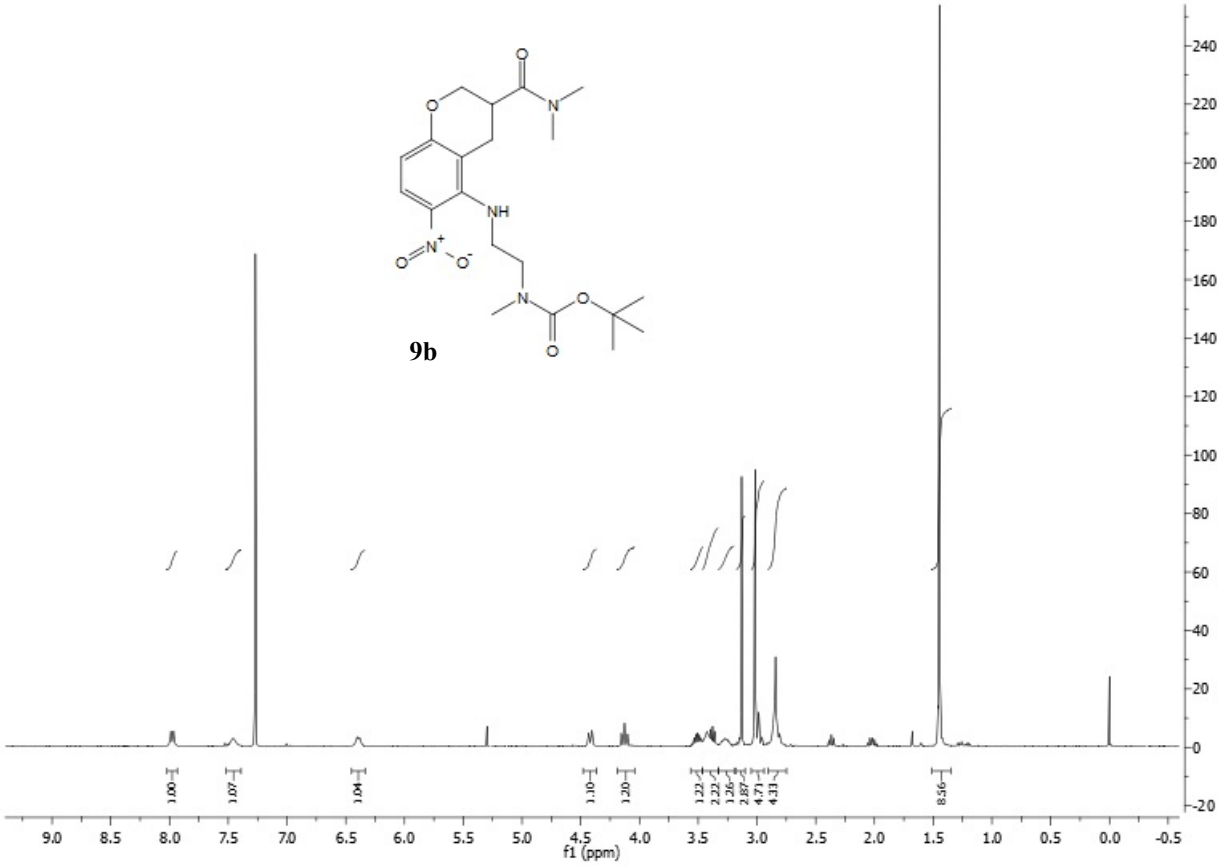
5-Chlorochroman-3-carboxylic acid (**6**). To a solution of **5** (7.50 g) in 10% aqueous NaOH (193 mL) was added 3% sodium amalgam (103 g). The mixture was stirred overnight at room

temperature. The supernatant was decanted from the liquid mercury, and the mercury was washed twice with small portions of 10% aq. NaOH. The washings were combined with the supernatant, acidified to a pH of 2 with conc. HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried with Na_2SO_4, filtered, and evaporated to give 7.51 g (99%) of **6** as a white crystalline solid. An analytical sample was recrystallized from EtOAc/hexanes: m.p. 129.5–130 °C. ^{1}H NMR (DMSO-d_6) δ 12.70 (bs, CO_2H, 1H), 7.10 (dd, *J*=8.0, 8.0 Hz, Ar*H*, 1H), 6.99 (dd, *J*=8.0, 1.2 Hz, Ar*H*, 1H), 6.75 (dd, *J*=8.0, 1.2 Hz, Ar*H*, 1H), 4.28 (dd, *J*=10.8, 4.3 Hz, OCH_2CH, 1H), 4.16 (dd, *J*=10.8, 7.0 Hz, OCH_2CH, 1H), 3.05 (m, C*H*CO_2H, 1H), 2.90 (d, *J*=6.6 Hz, ArCH_2CH, 2H). ^{13}C NMR ($CDCl_3$) δ 178.3, 155.2, 134.6, 127.8, 121.7, 119.0, 115.4, 65.8, 38.2, 25.4. HRMS $(M–H)^-$: calc. for $C_{10}H_8O_3Cl$, 211.0167; found, 211.0166.

5-Chloro-*N,N*-dimethylchroman-3-carboxamide (**7**). A mixture of **6** (1.50 g, 7.06 mmol), dimethylamine hydrochloride (1.44 g, 17.6 mmol), HOBt (1.43 g, 10.6 mmol), *N*-methylmorpholine (3.88 mL, 35.3 mmol), and EDC hydrochloride (2.03 g, 10.6 mmol) in dichloromethane (65 mL) was stirred at room temperature for 50 hours. The reaction mixture was diluted with additional CH_2Cl_2, and an equal volume of saturated aq. $NaHCO_3$ was added. The CH_2Cl_2 phase was separated, and the aqueous phase was washed 3 × with CH_2Cl_2. The CH_2Cl_2 phases were combined, dried with Na_2SO_4, and evaporated. Chromatography on silica (25–75% EtOAc in hexanes) gave 1.56 g (92%) of **7** as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.12 (dd, *J*=8.2, 8.0 Hz, Ar-*H*, 1H), 7.01 (dd, *J*=8.0, 1.1 Hz, Ar-*H*, 1H), 6.79 (dd, *J*=8.2, 1.1 Hz, Ar-*H*, 1H), 4.31 (m, OCH_2CH, 1H), 3.84 (dd, *J*=10.8, 10.8 Hz, OCH_2CH, 1H), 3.37–3.30 (m, *partly hidden*, C*H*$CONMe_2$, 1H), 3.11 (s, NCH_3, 3H), 2.89 (dd, *partly hidden*, *J*=16.8, 5.7 Hz, ArCH_2CH, 1H), 2.86 (s, NCH_3, 3H), 2.79 (dd, *J*=16.8, 10.2 Hz, ArCH_2CH, 1H). ^{13}C NMR ($CDCl_3$) δ 171.7, 155.3, 134.6, 127.6, 121.3, 119.9, 115.2, 67.0, 37.2, 35.6, 35.4, 26.9. HRMS $(M+H)^+$: calc. for $C_{12}H_{15}NO_2Cl$, 240.0786; found, 240.0792.

5-Chloro-3-(*N,N*-dimethylcarboxamide)-6-nitrochroman (**8**). Substrate **7** (5.36 g, 22.4 mmol) was dissolved in anhydrous dichloroacetic acid (270 mL) in a 500 mL round bottomed fitted with an egg-shaped stir-bar. The resulting solution was stirred at +20 °C and finely divided powder of sodium nitrate (5.70 g, 67.1 mmol) was added. Anhydrous trifluoroacetic acid (624 μL, 8.16 mmol) was added via a micro syringe, the reaction flask was capped with a stopper and mixture was stirred for 20 hours at +20 °C. The stopper was removed and the resulting dark crude reaction mixture was then slowly poured into a rapidly stirred solution of sodium carbonate (10%, 4L) (Caution CO_2 liberated). After rapid stirring for 15 minutes, the crude reaction mixture was transferred to a 5L separation funnel and the aqueous phase was extracted with ether (3 × 350 mL). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The resulting crude material was purified on silica (100% Et_2O) gave 4.07 g (64%) of the nitrated product **8** as a yellow oil. ^{1}H NMR spectroscopy showed 1:5 ratio of the *para*- and *ortho*-substituted nitrated isomers. The major isomer is the essential ortho-substituted product **8**. A small sample of regioisomers were separated and characterized below. **Major isomer:** ^{1}H NMR (DMSO-d_6) δ 7.86 (d, *J*=9.0 Hz, Ar-*H*, 1H), 7.00 (d, *J*=9.0 Hz, Ar-*H*, 1H), 4.39 (m, OCH_2CH, 1H), 4.01 (dd, *J*=11.0, 8.8 Hz, OCH_2CH, 1H), 3.40 (m, C*H*CO_2H, 1H), 3.10 (s, NCH_3, 3H), 2.88 (dd, *J*=17.0, 5.3 Hz, ArCH_2CH, 1H), 2.85 (s, NCH_3, 3H), 2.84 (dd, *partly hidden*, *J*=17.0, 9.2 Hz, ArCH_2CH, 1H). ^{13}C NMR ($CDCl_3$) δ 170.8, 158.2, 141.6, 128.7, 124.9, 122.1, 115.4, 67.4, 37.3, 35.7, 34.7, 27.3. **Minor isomer:** The undesired minor *para*-isomer (eluted just before compound **8**) was isolated as **5-Chloro-3-(*N,N*-dimethylcarboxamide)-8-nitrochroman** as a pale yellow oil, ^{1}H NMR (DMSO-d_6) δ 7.79 (d, *J*=8.8 Hz, Ar-*H*, 1H), 7.21 (d, *J*=8.8 Hz, Ar-*H*, 1H), 4.48 (m, OCH_2CH, 1H), 4.06 (dd,

J=10.9, 9.1 Hz, OC*H*$_2$CH, 1H), 3.46 (m, C*H*CO$_2$H, 1H), 3.11 (s, NC*H*$_3$, 3H), 2.95 (dd, *J*=17.0, 5.8 Hz, ArC*H*$_2$CH, 1H), 2.86 (s, NC*H*$_3$, 3H), 2.86 (dd, *partly hidden*, *J*=16.7, 10.0 Hz, ArC*H*$_2$CH, 1H). ^{13}C NMR (CDCl$_3$) δ 170.5, 149.3, 139.8, 137.6, 124.0, 123.1, 120.6, 67.8, 37.2, 35.7, 34.4, 27.2.



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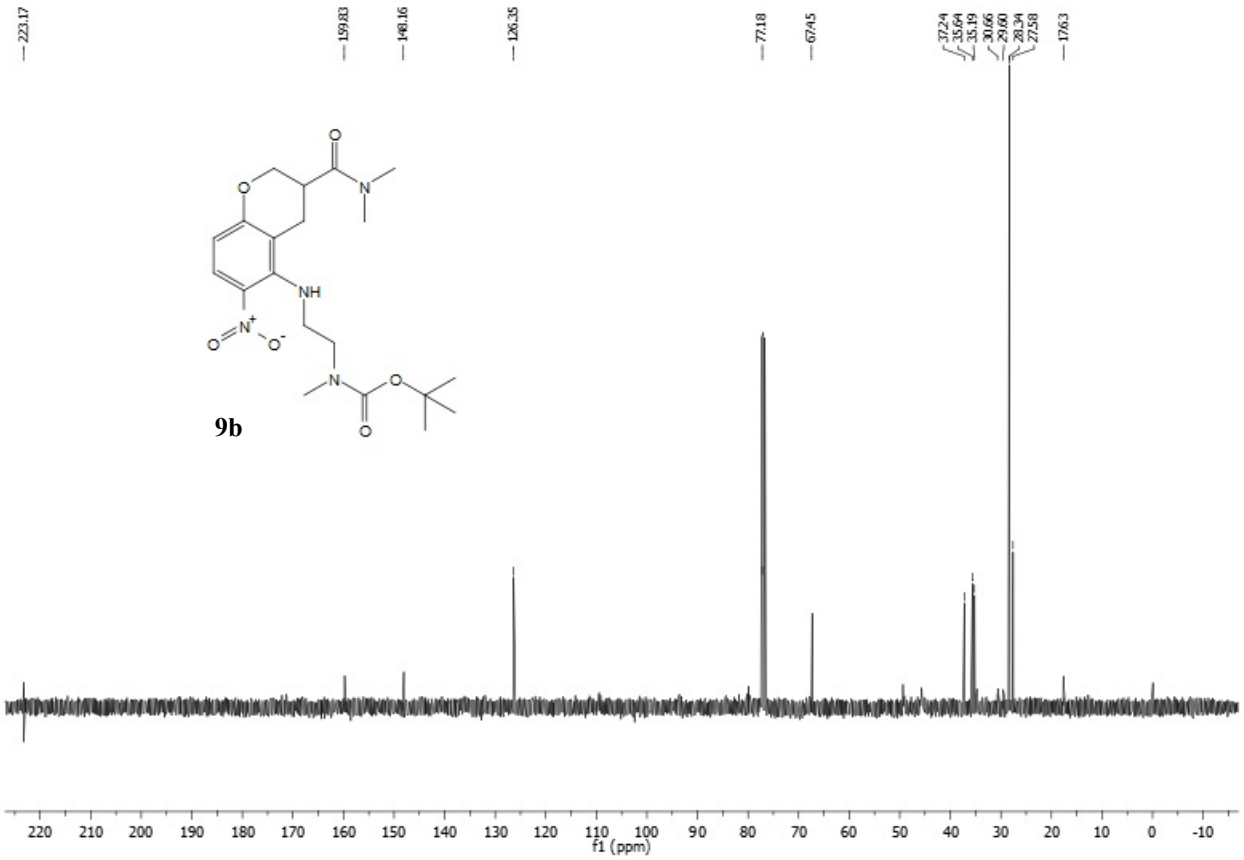

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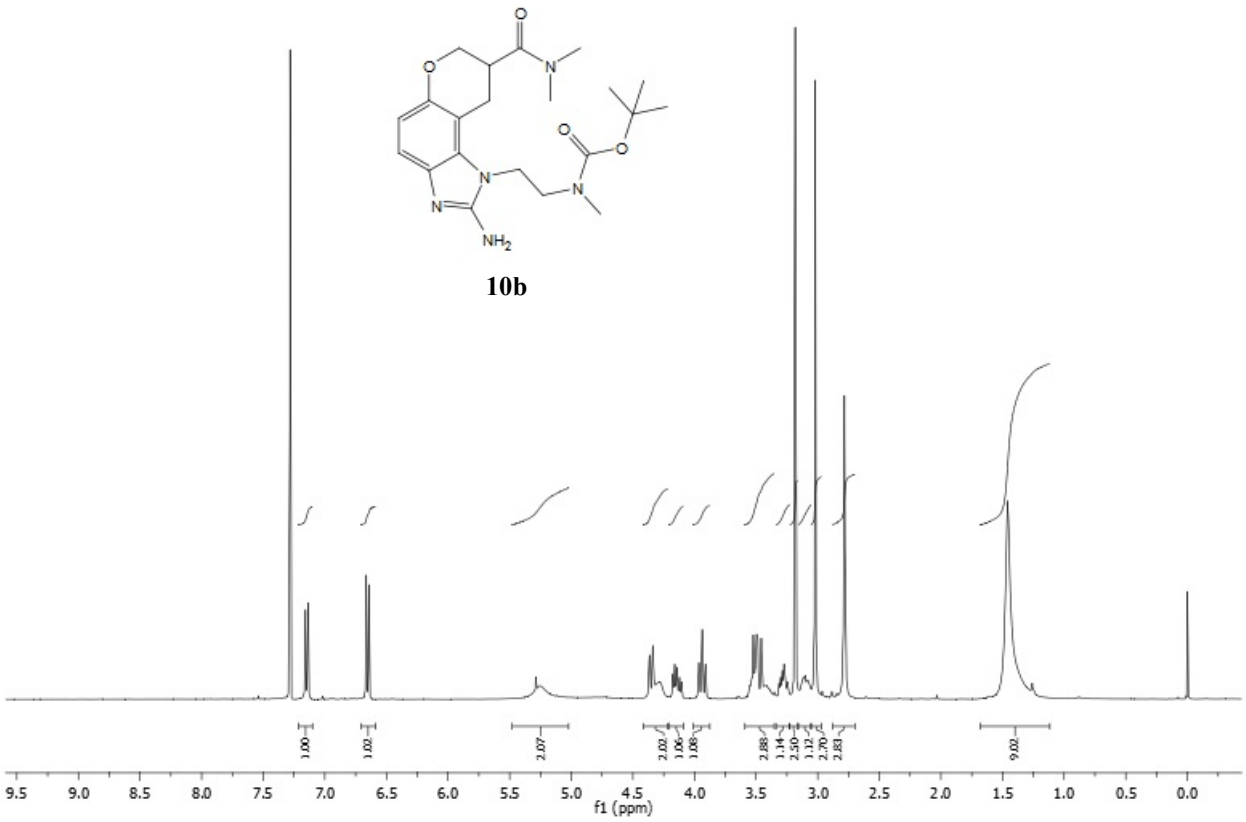

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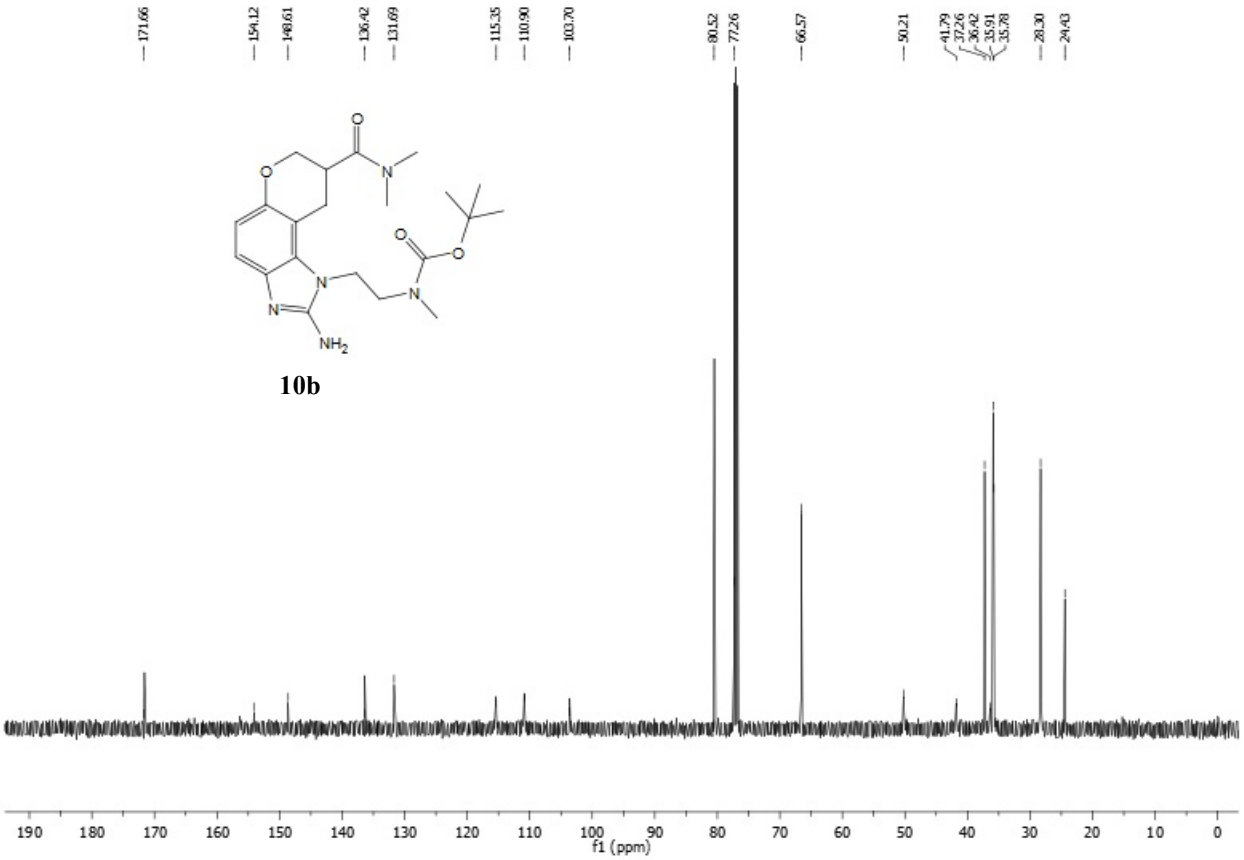

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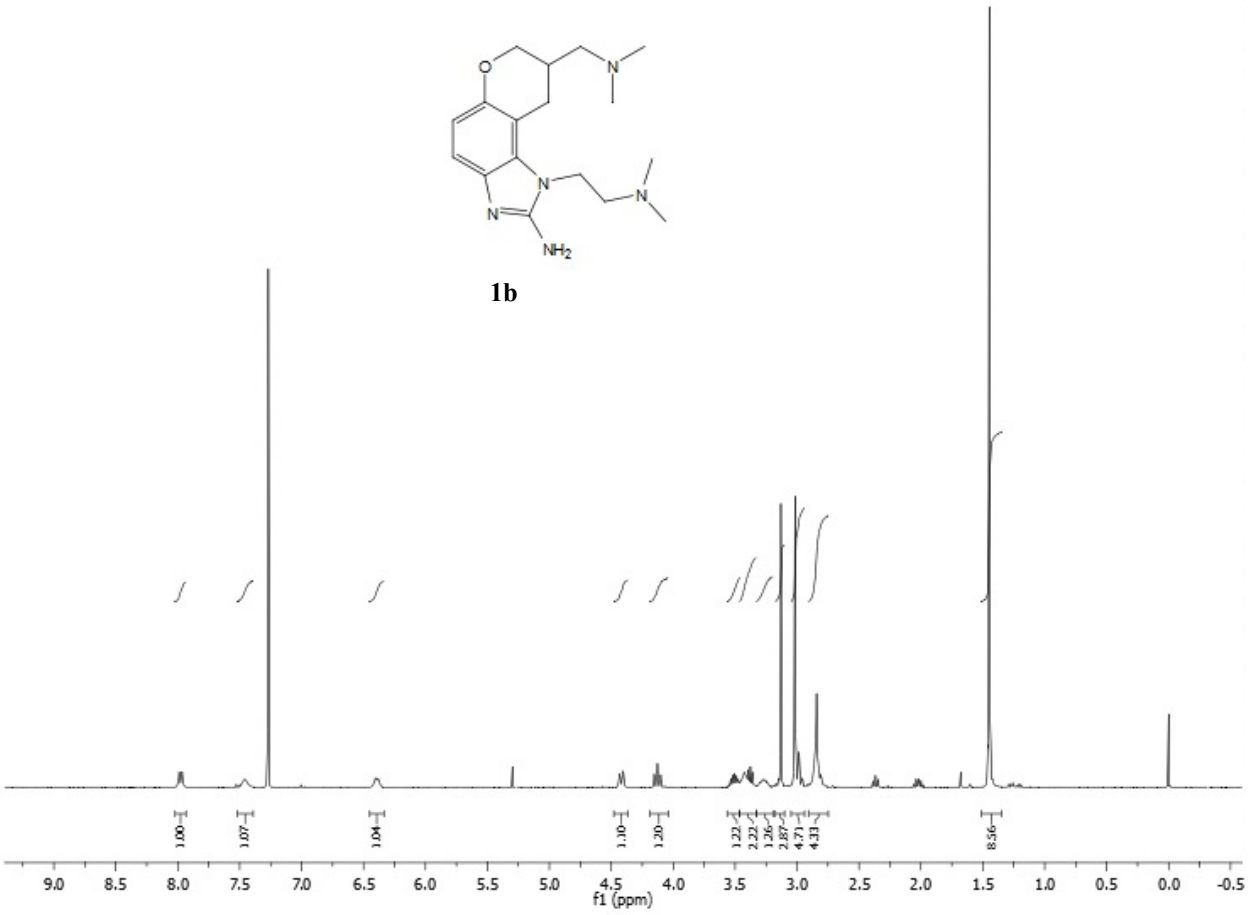

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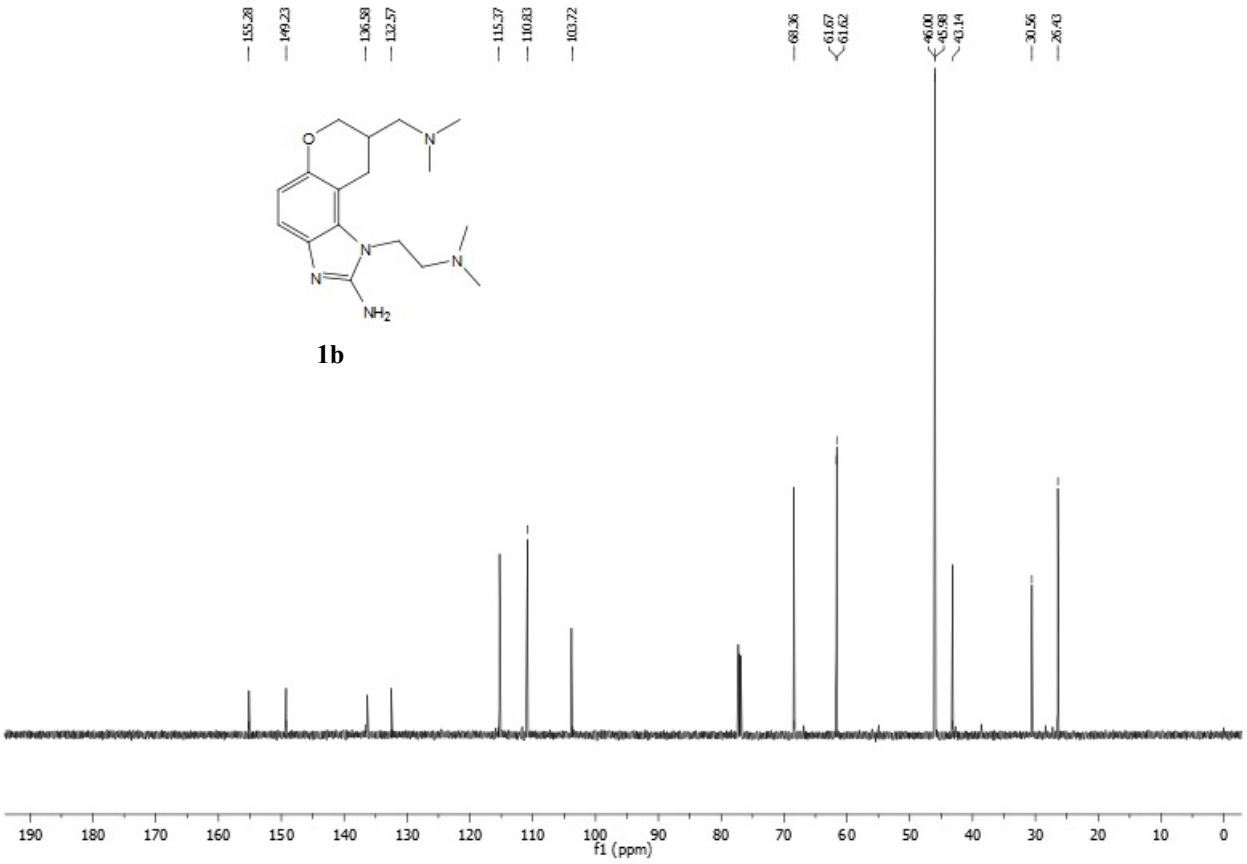

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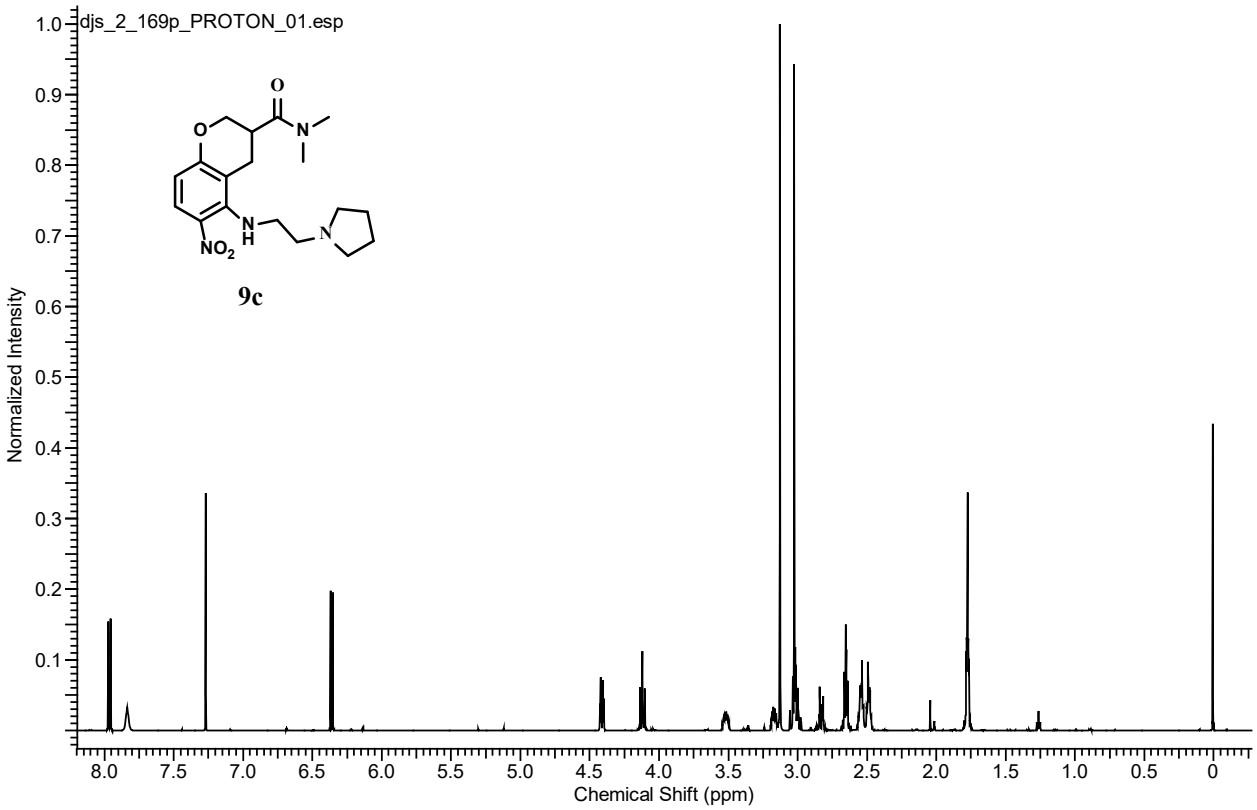

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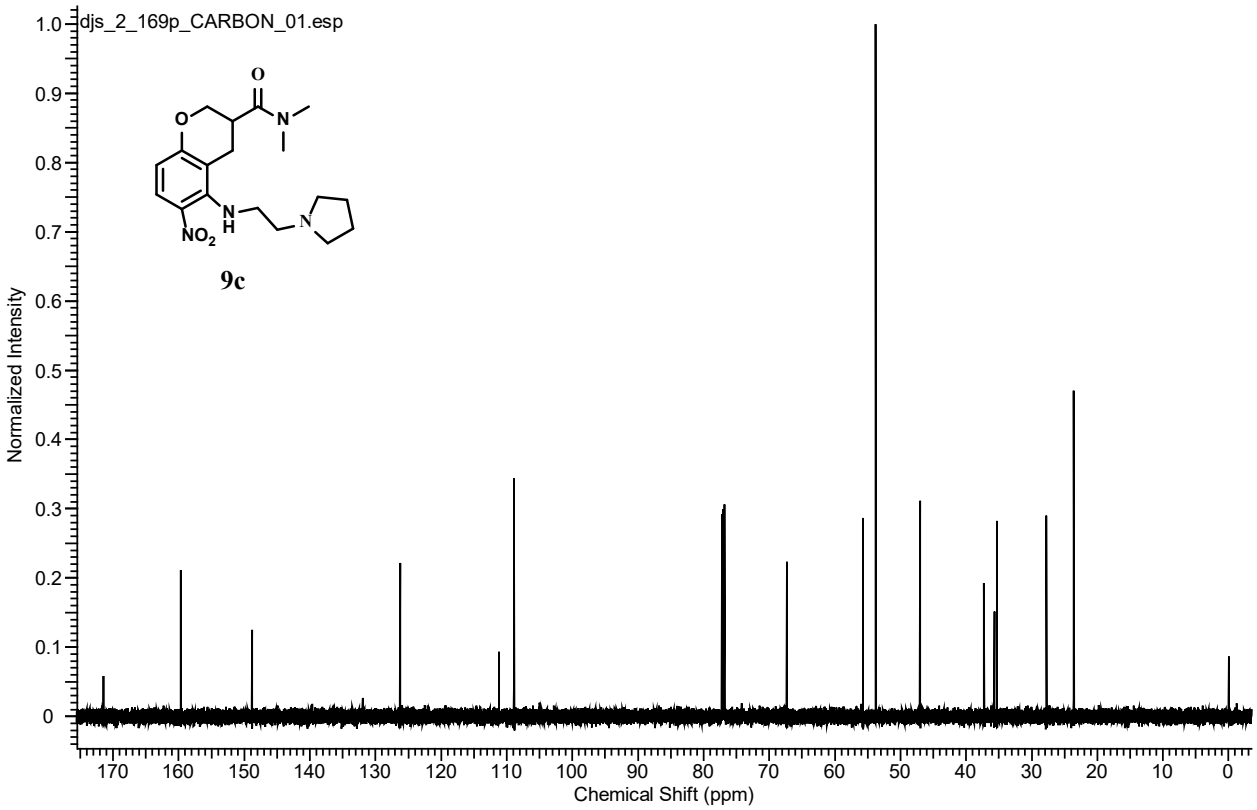

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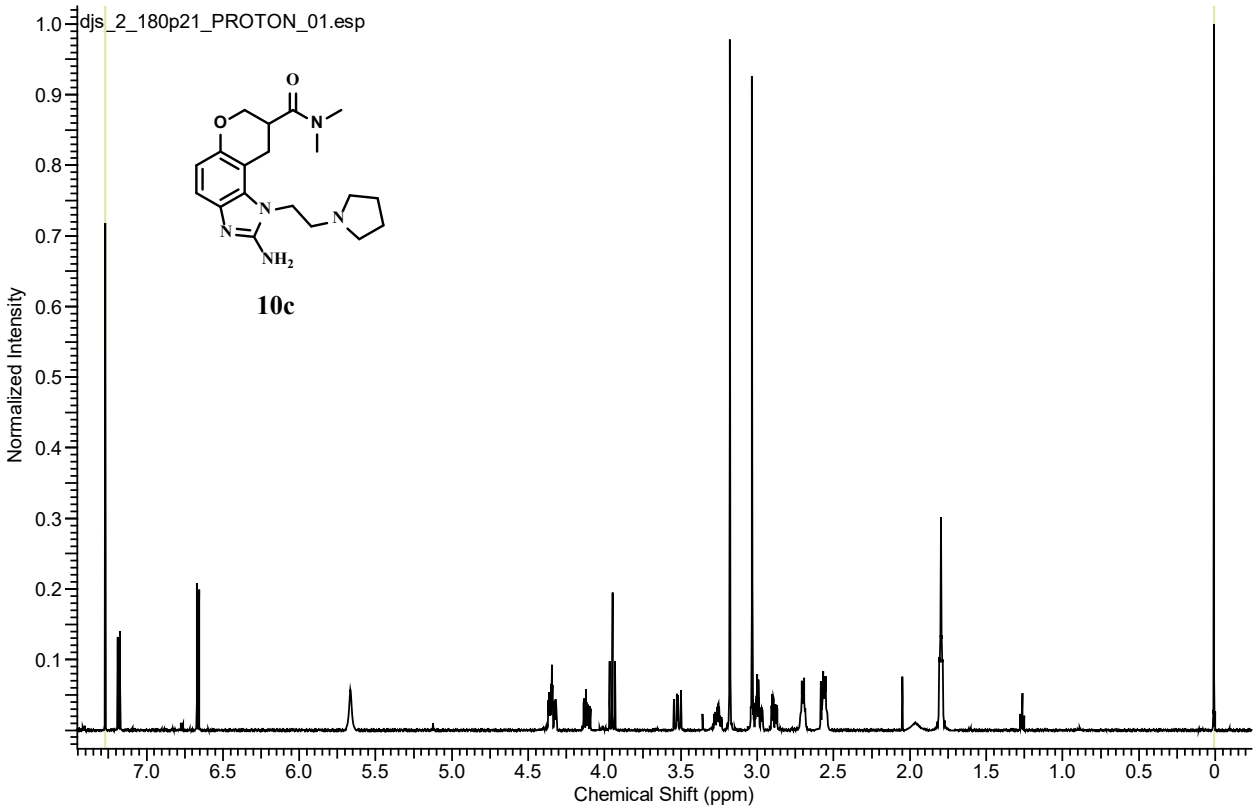

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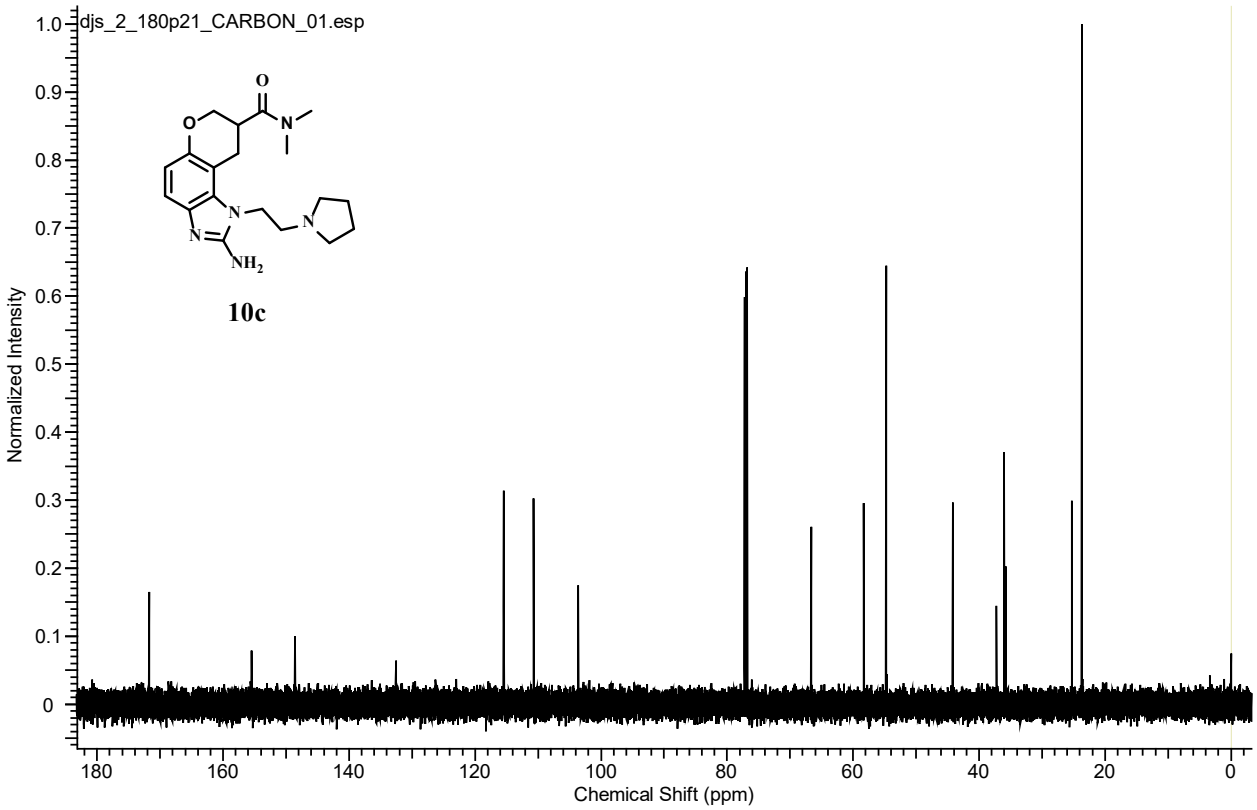

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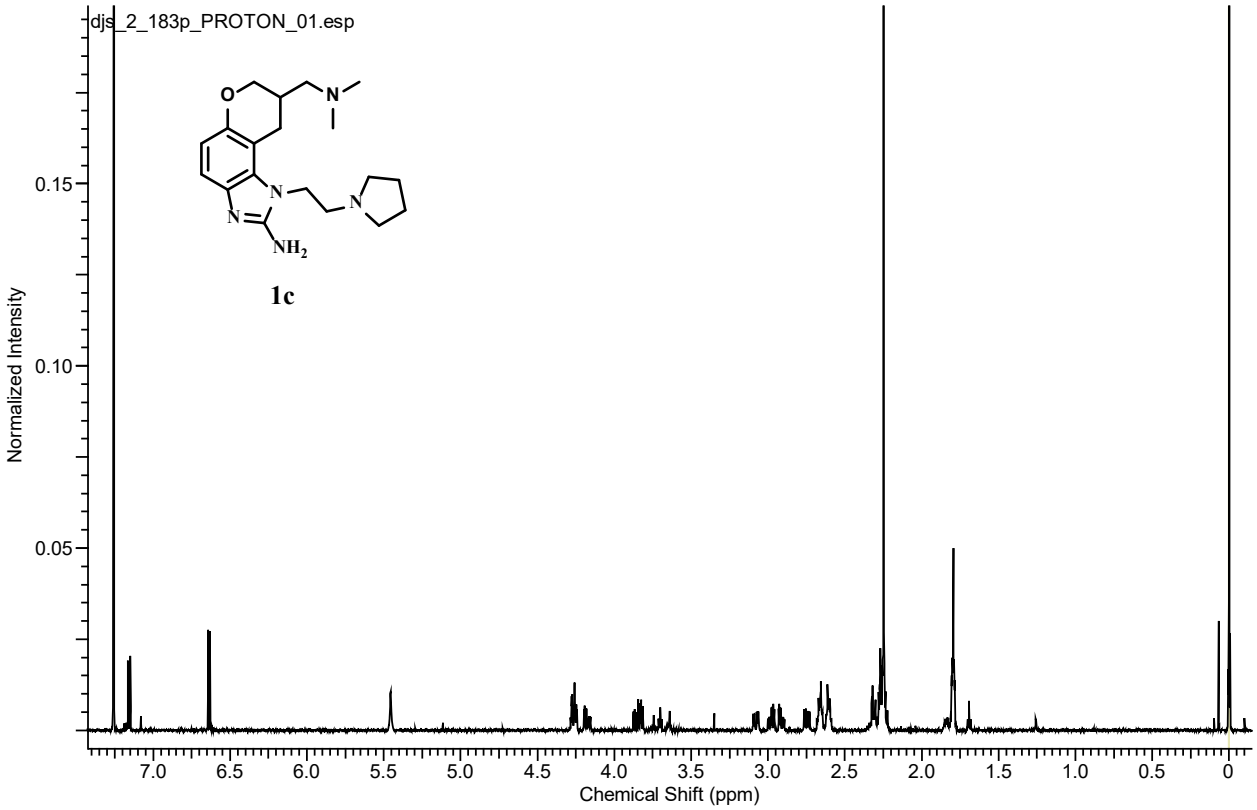

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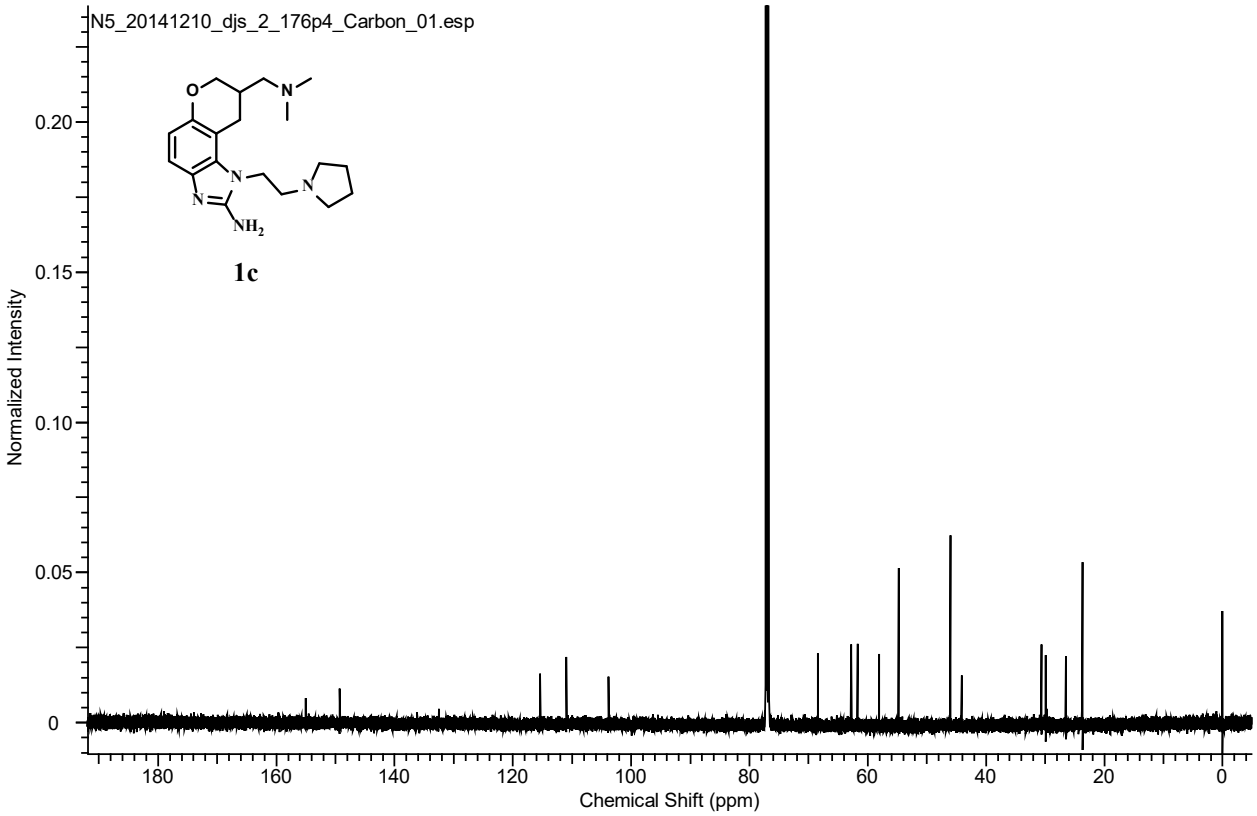

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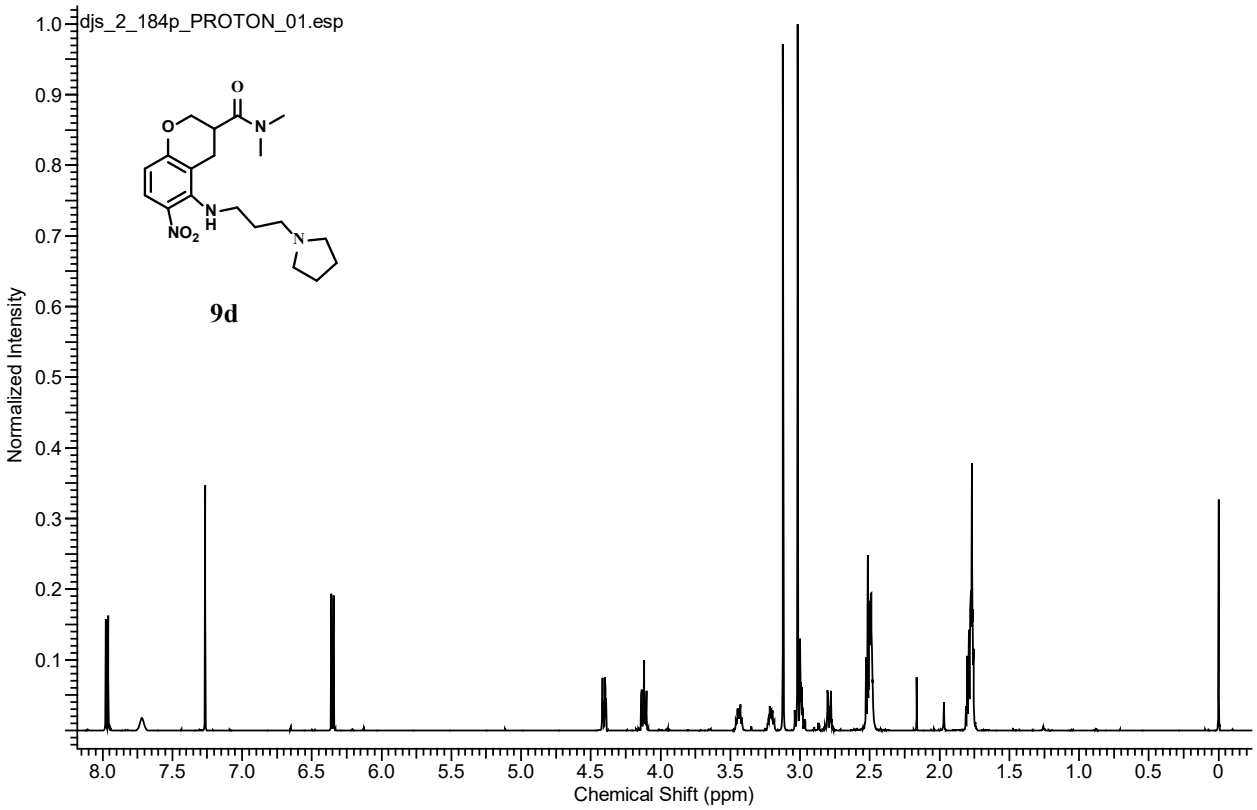

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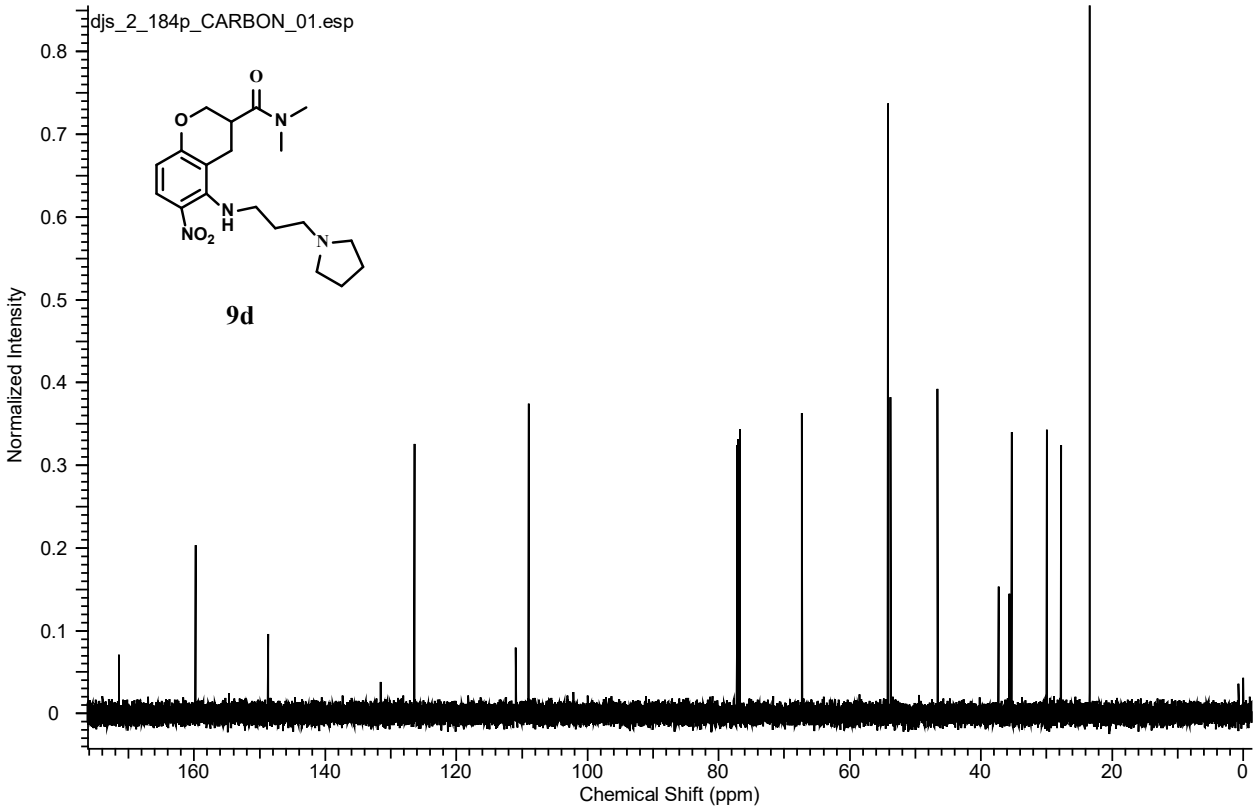

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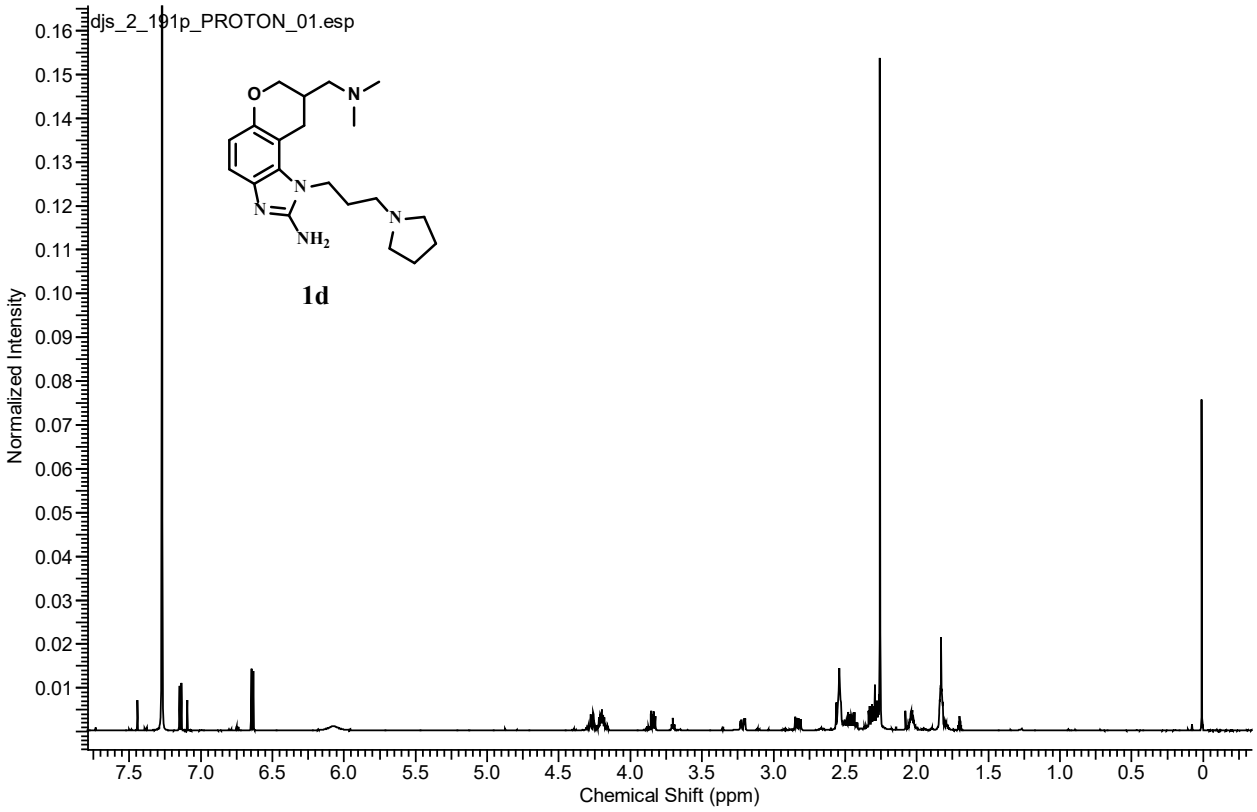

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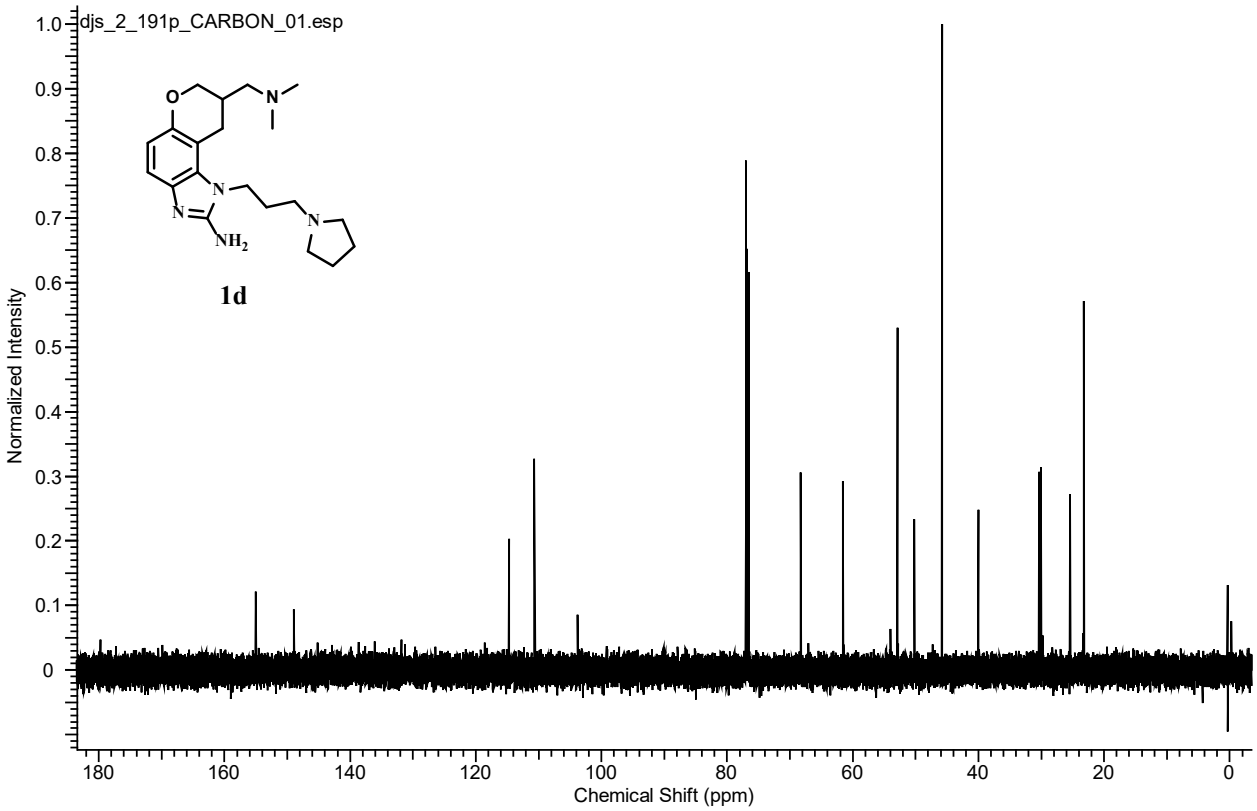

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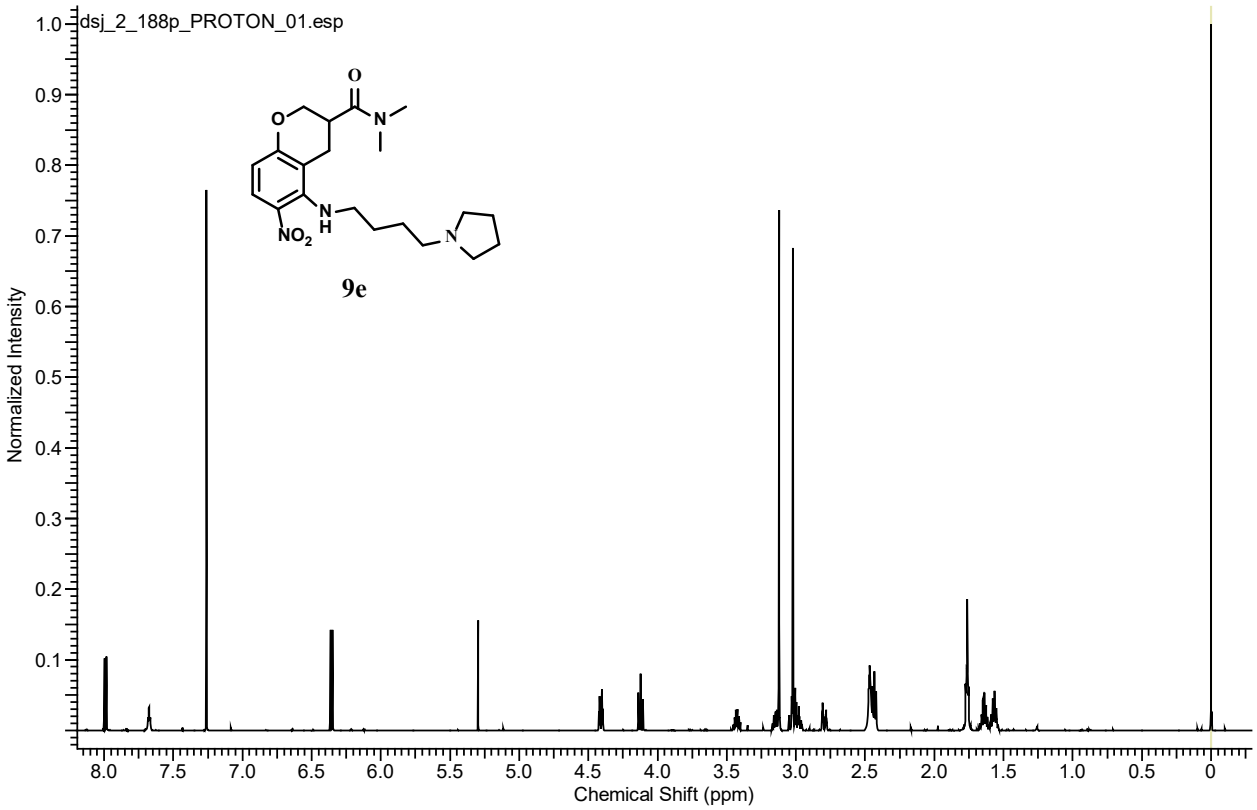

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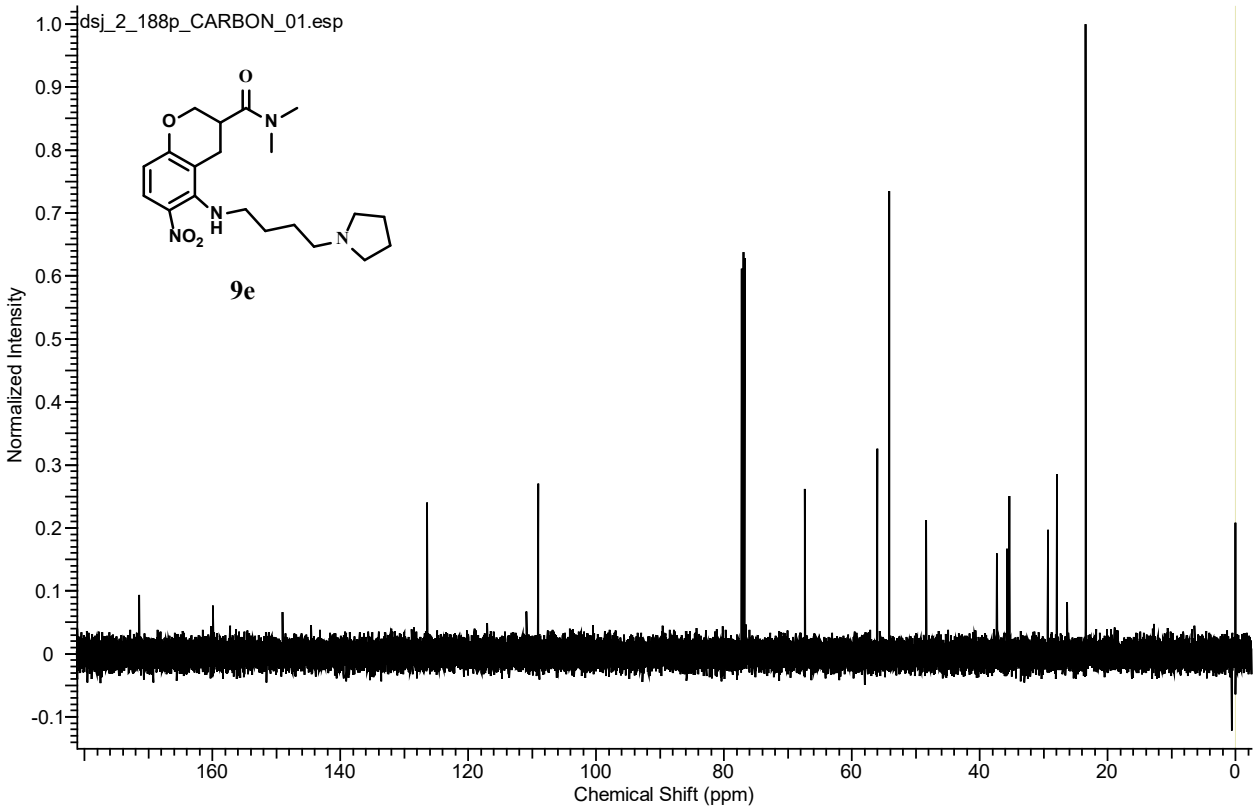

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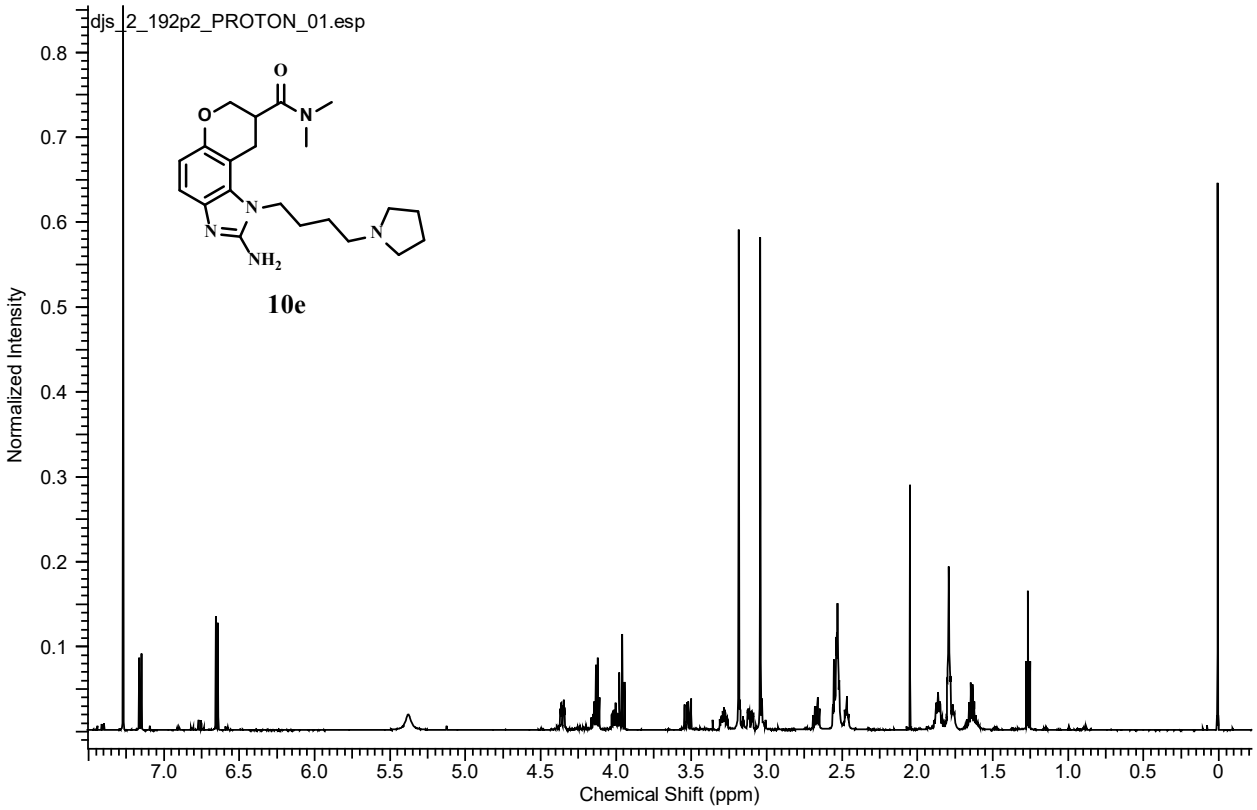

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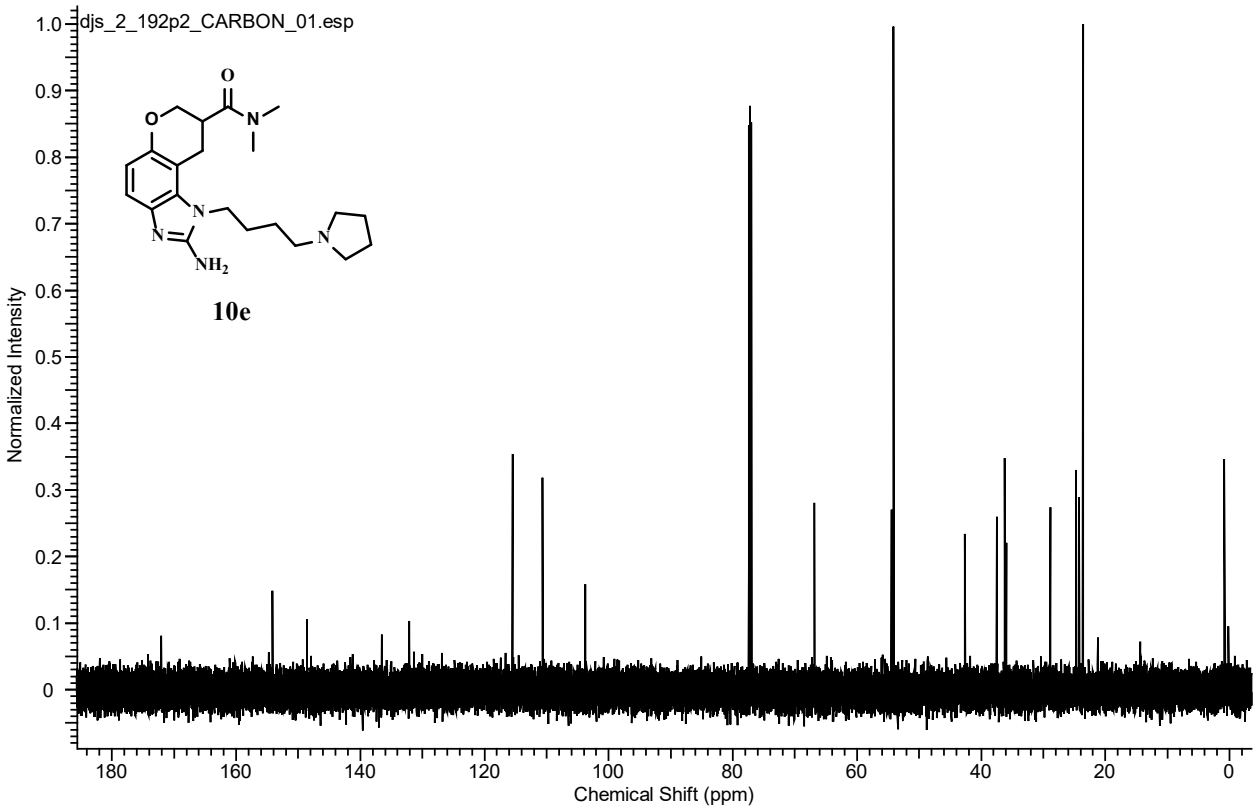

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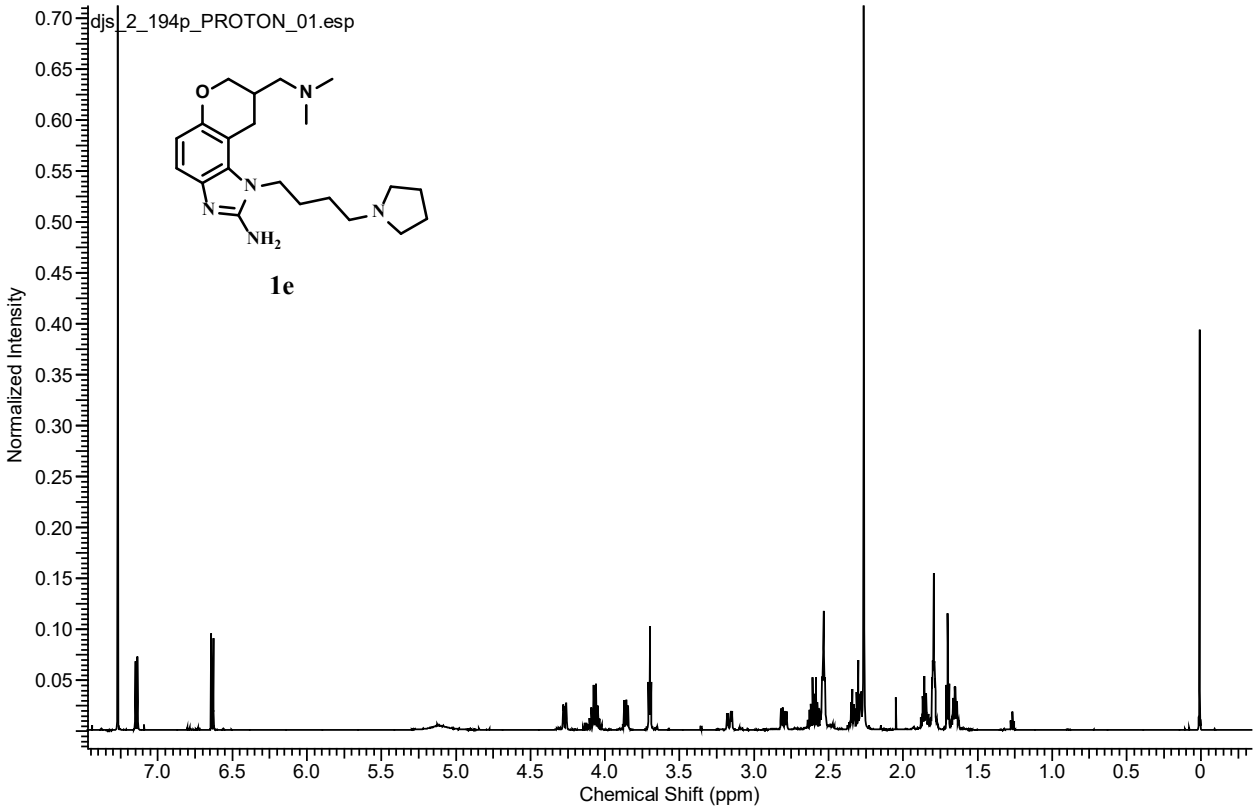

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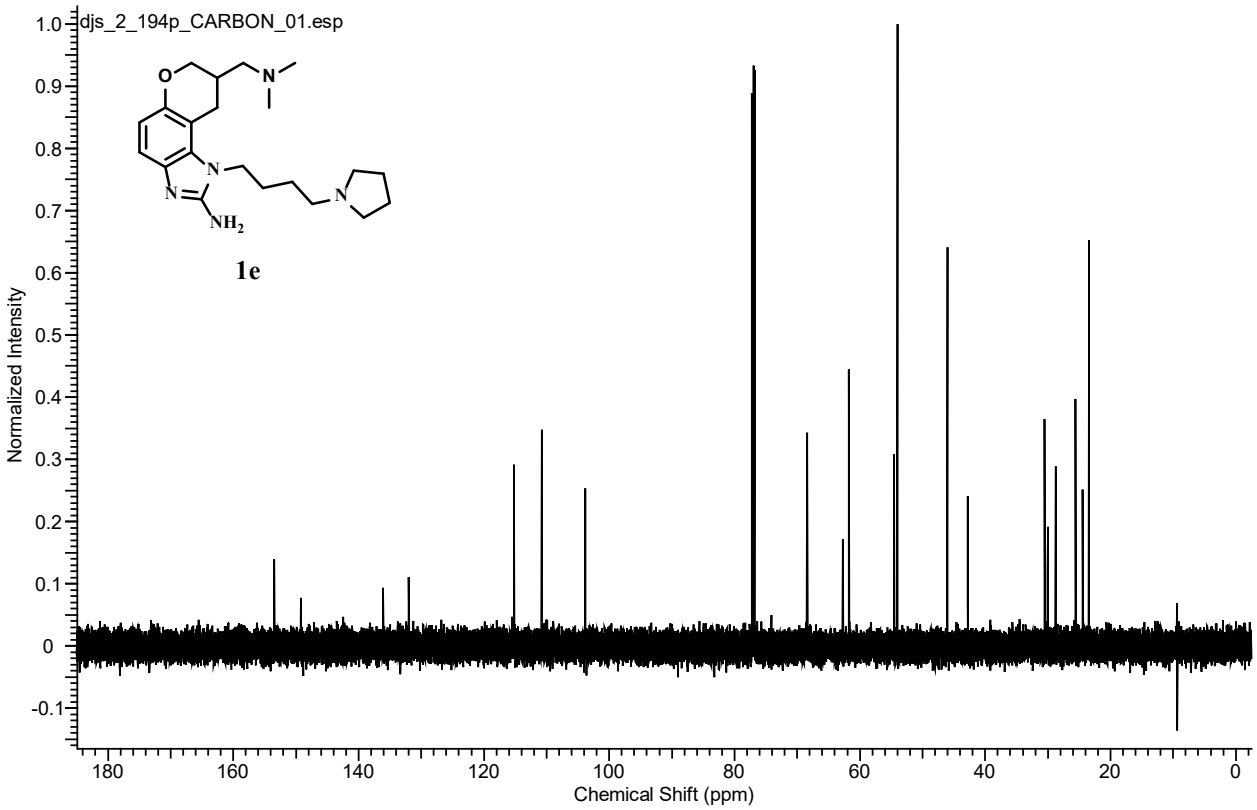

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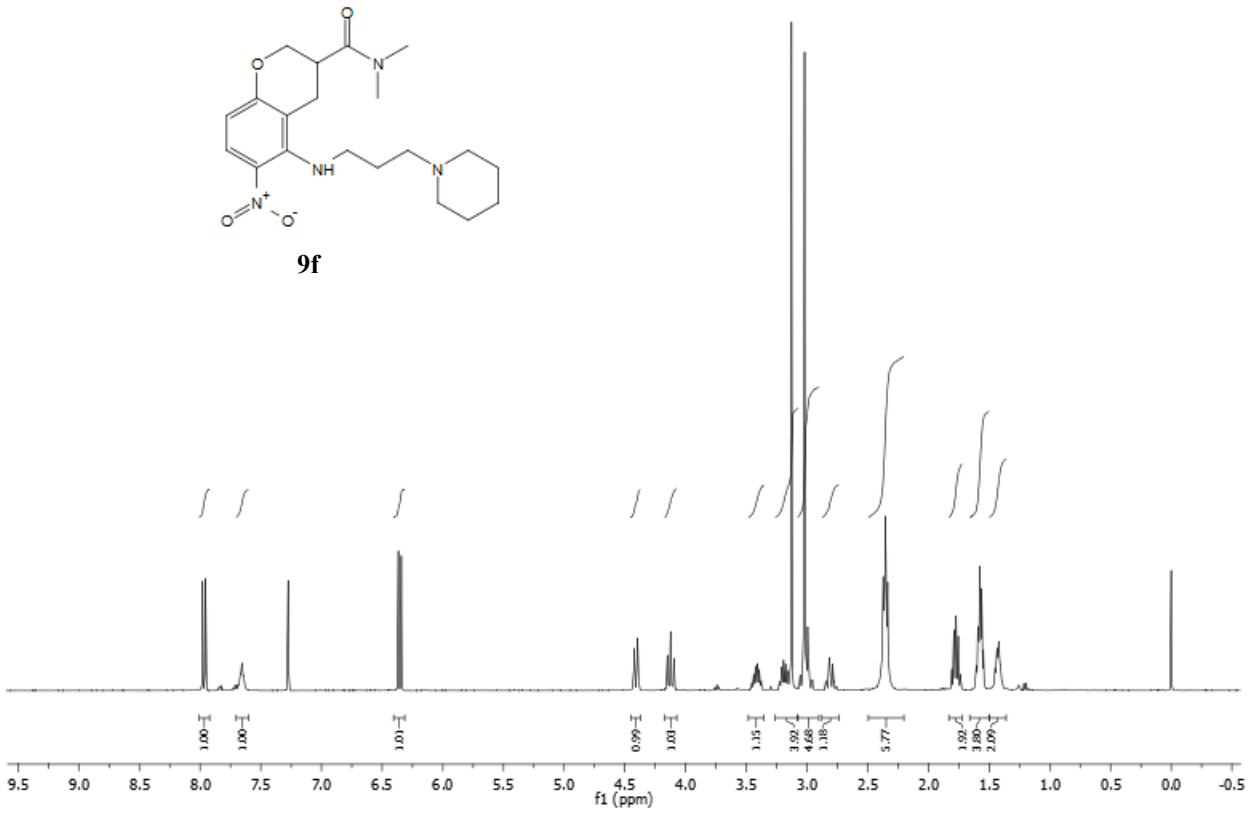

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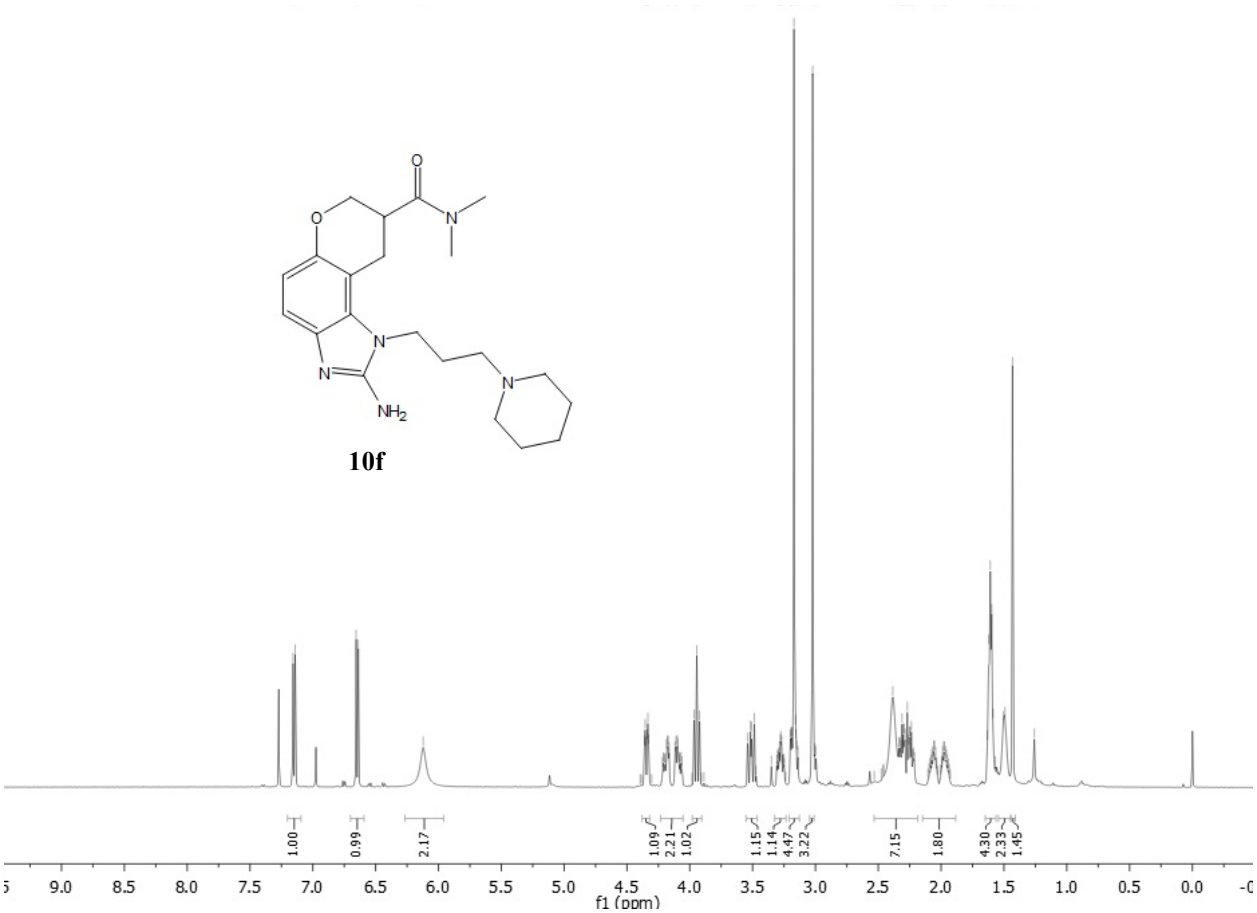

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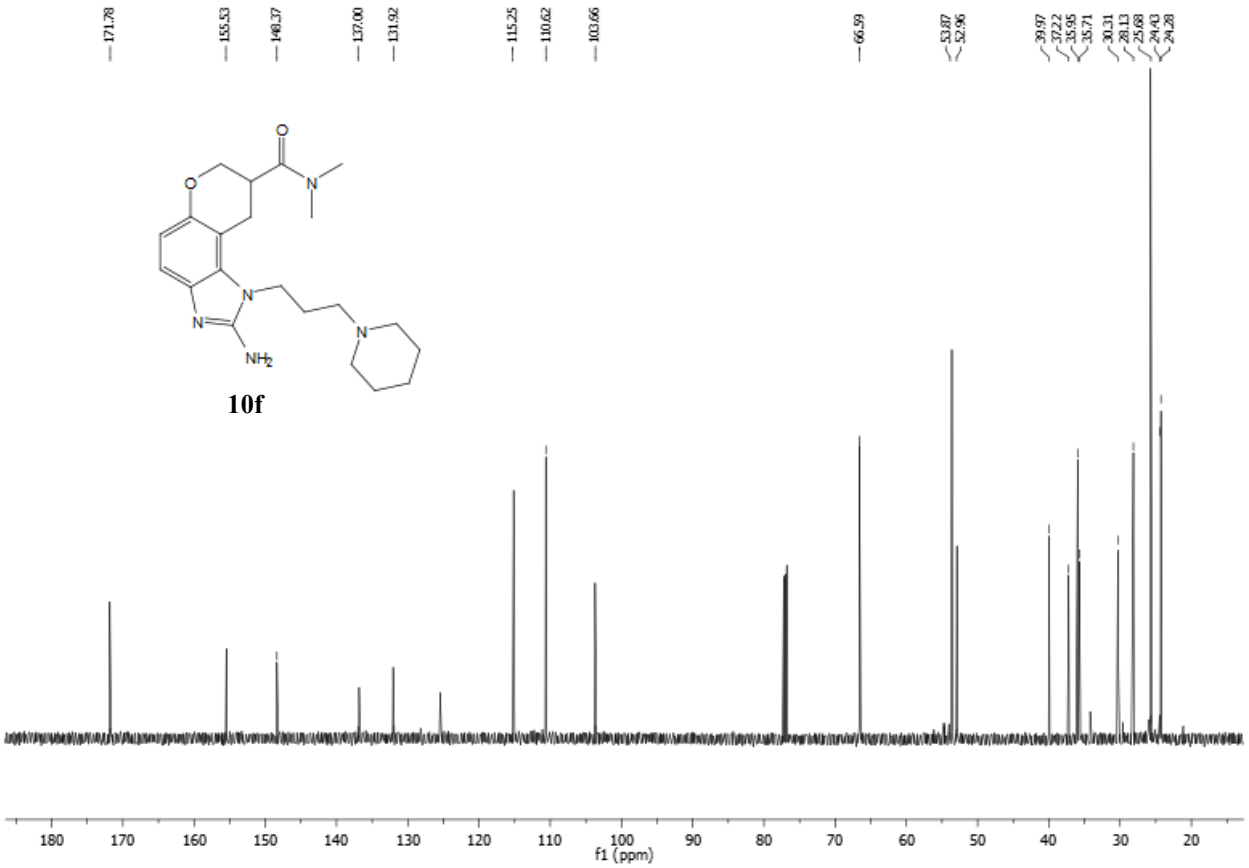

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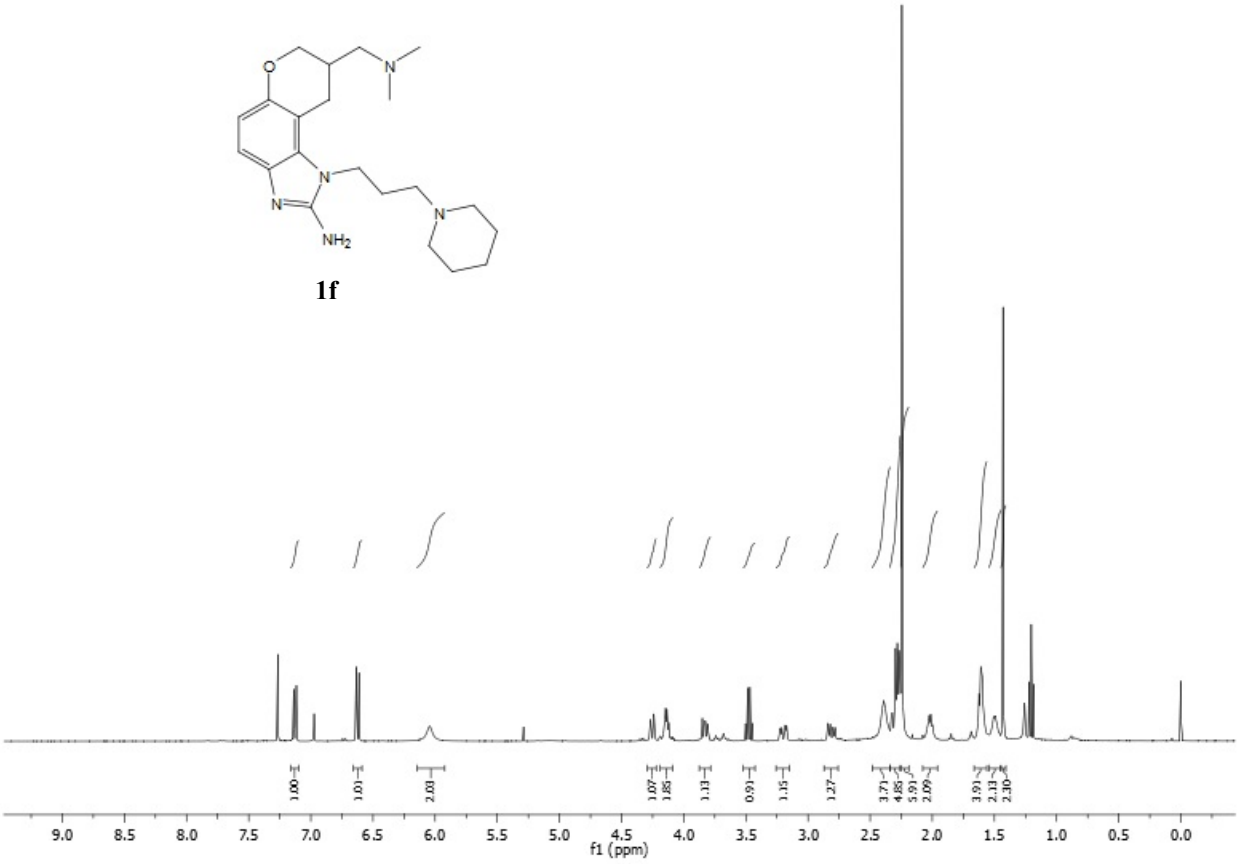

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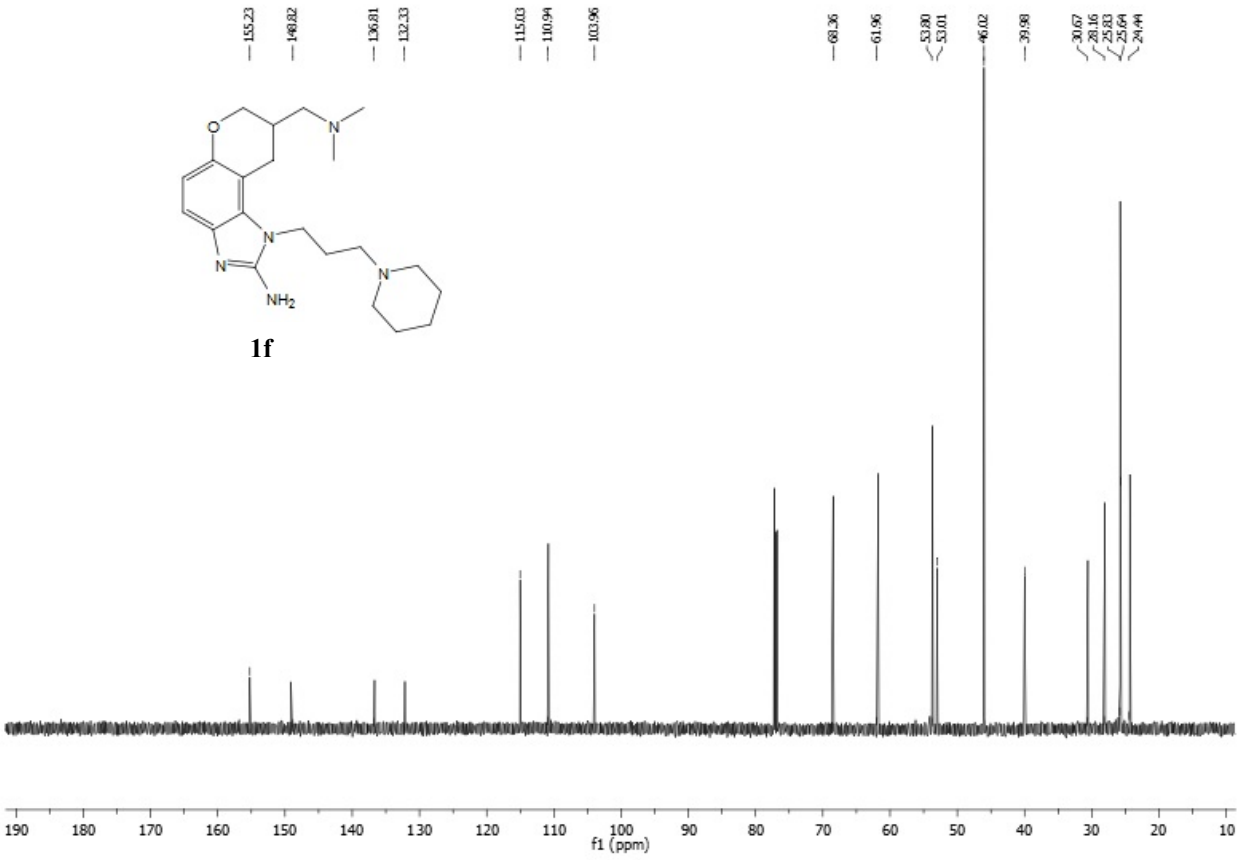

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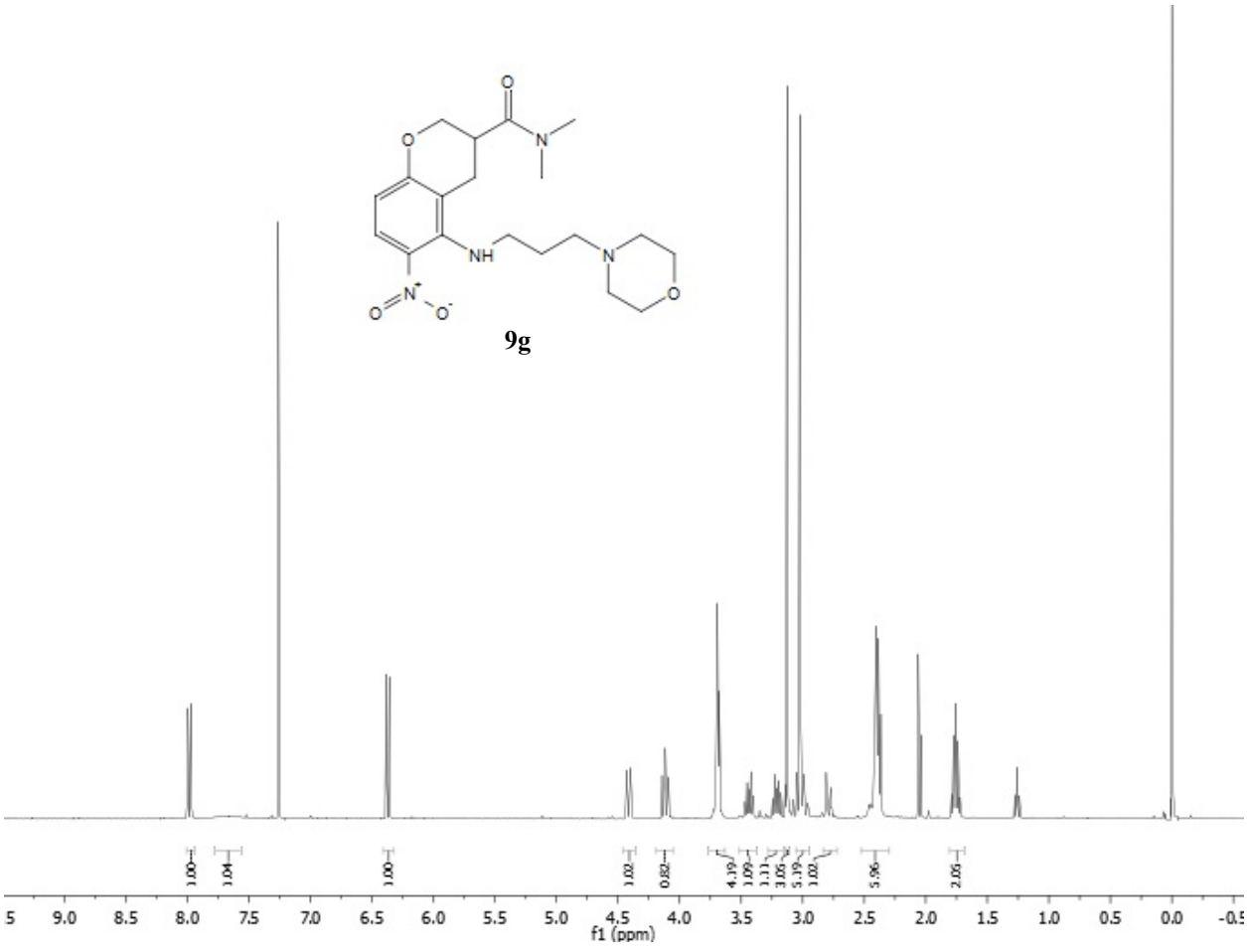

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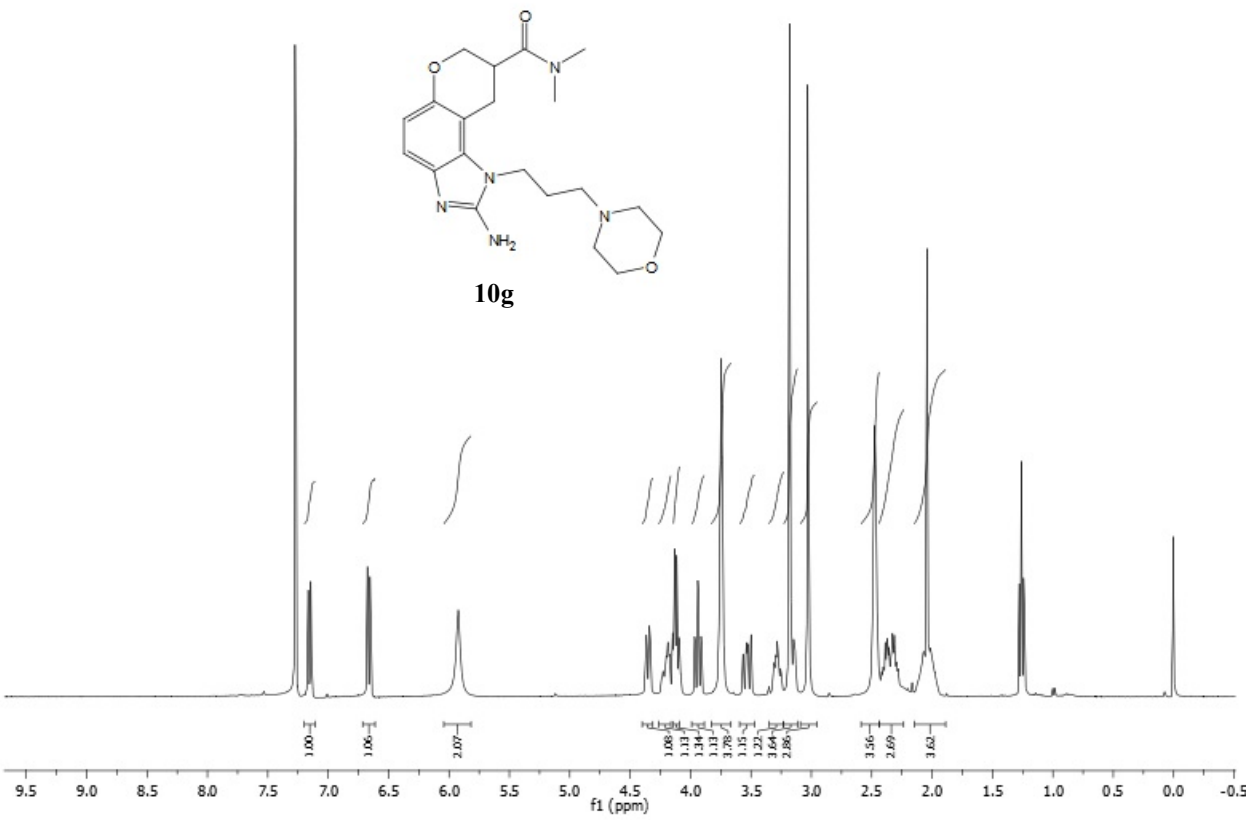

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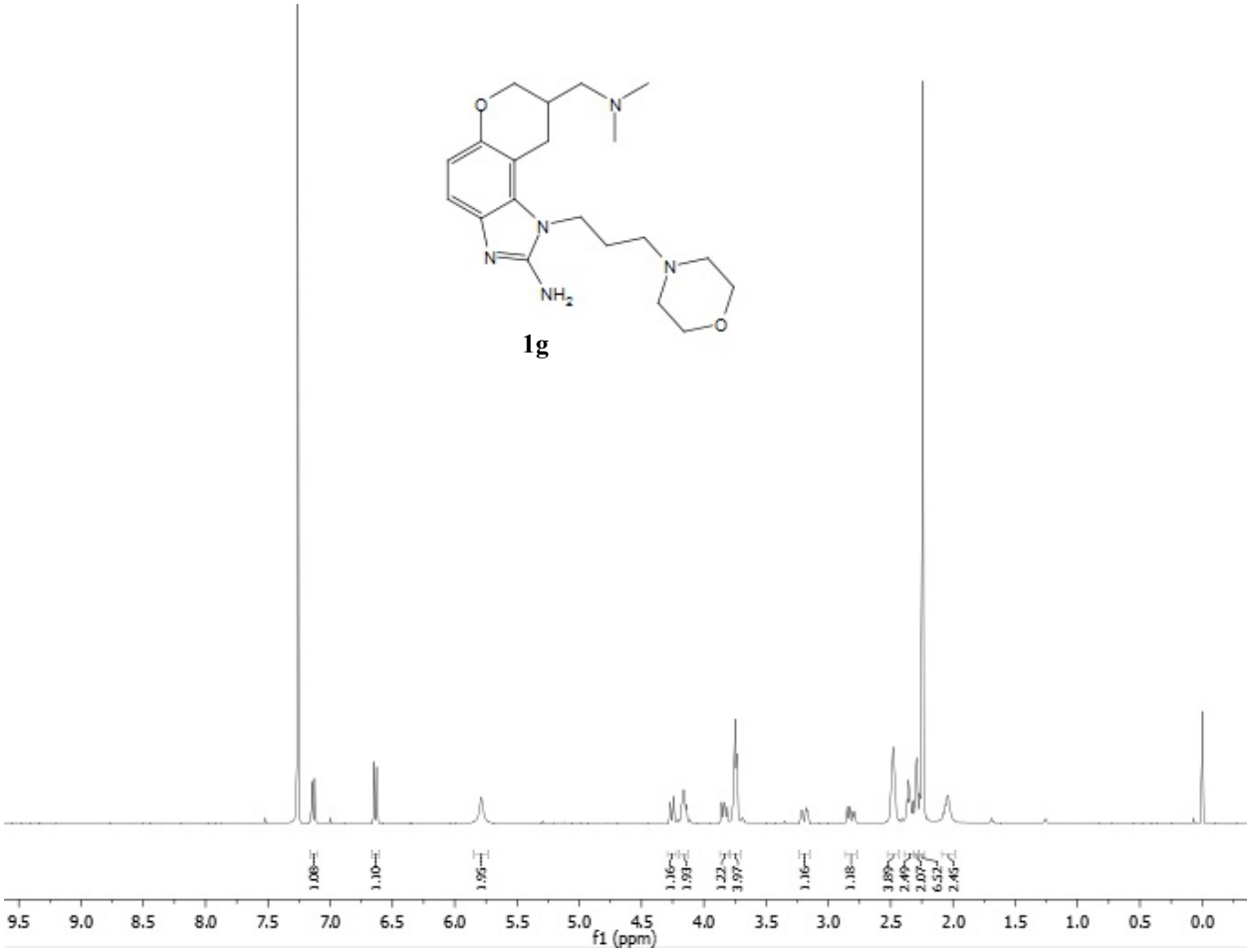

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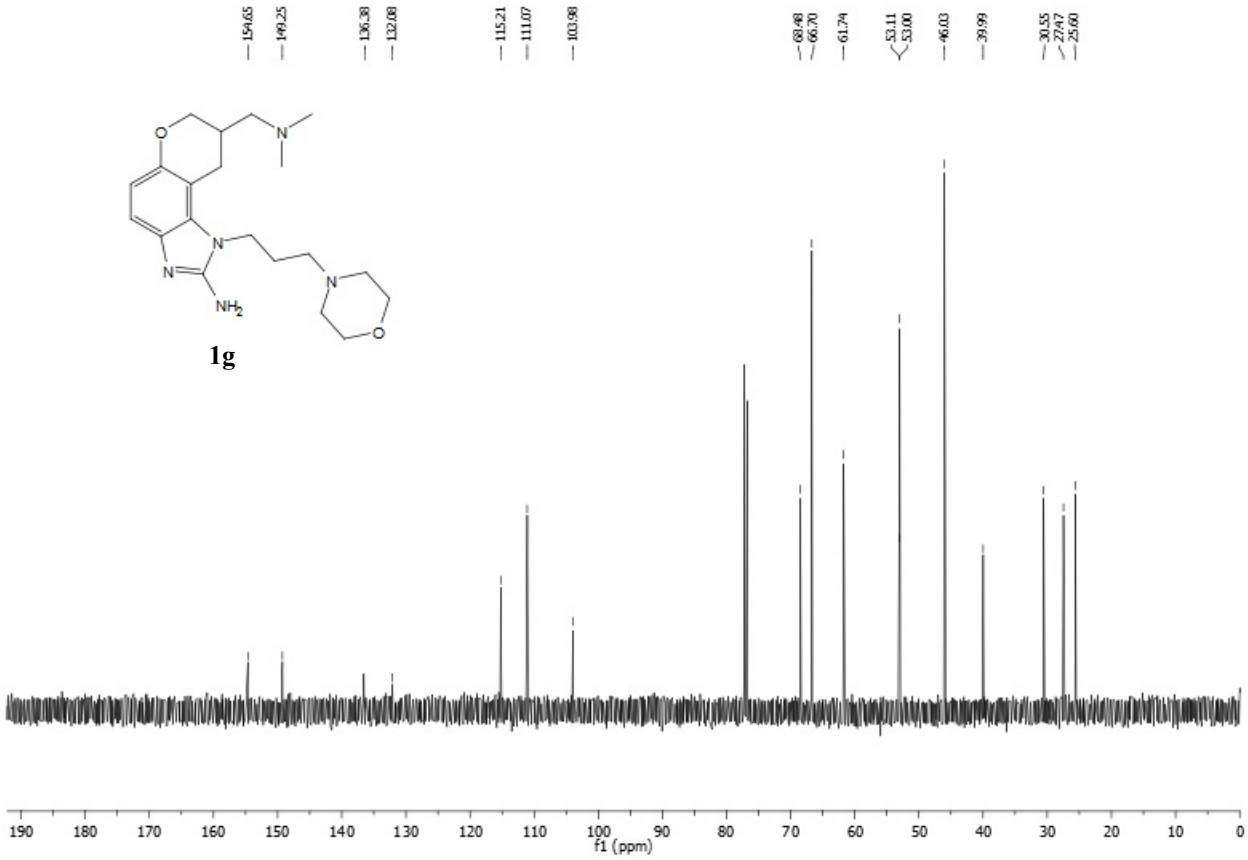

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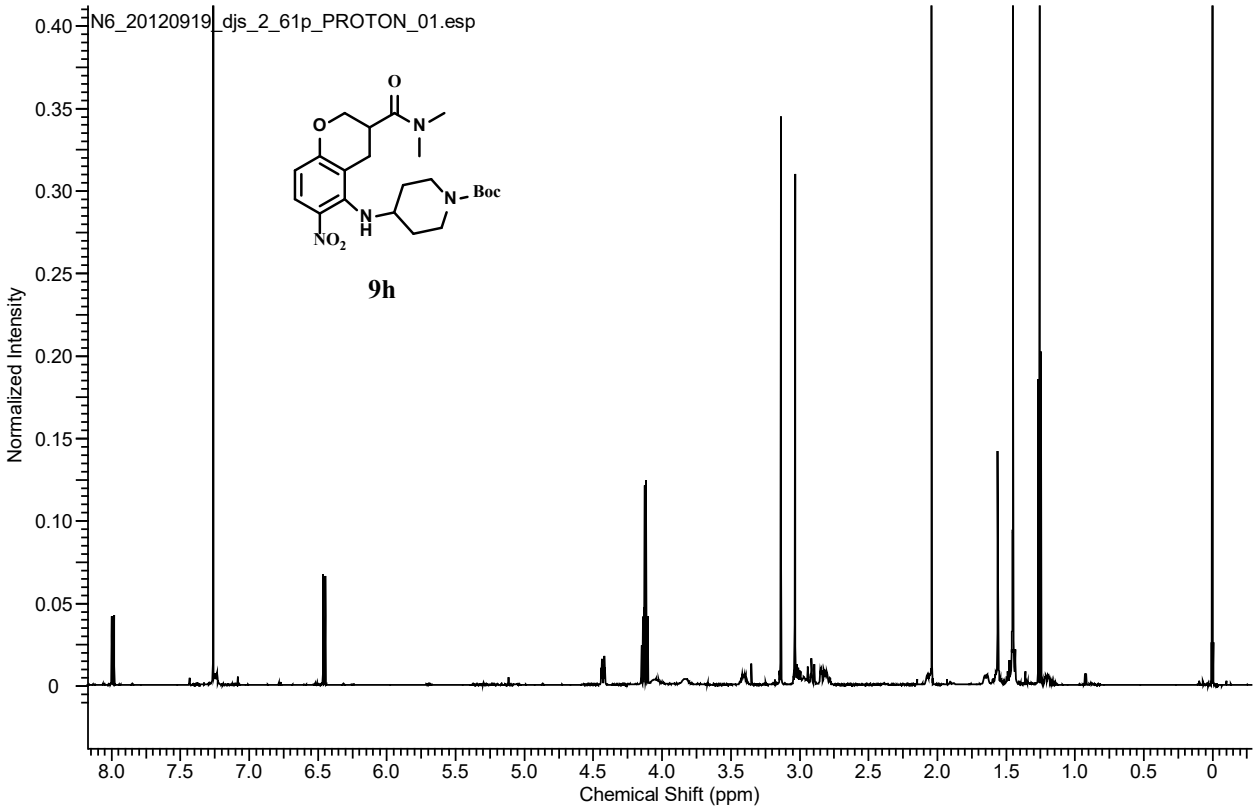

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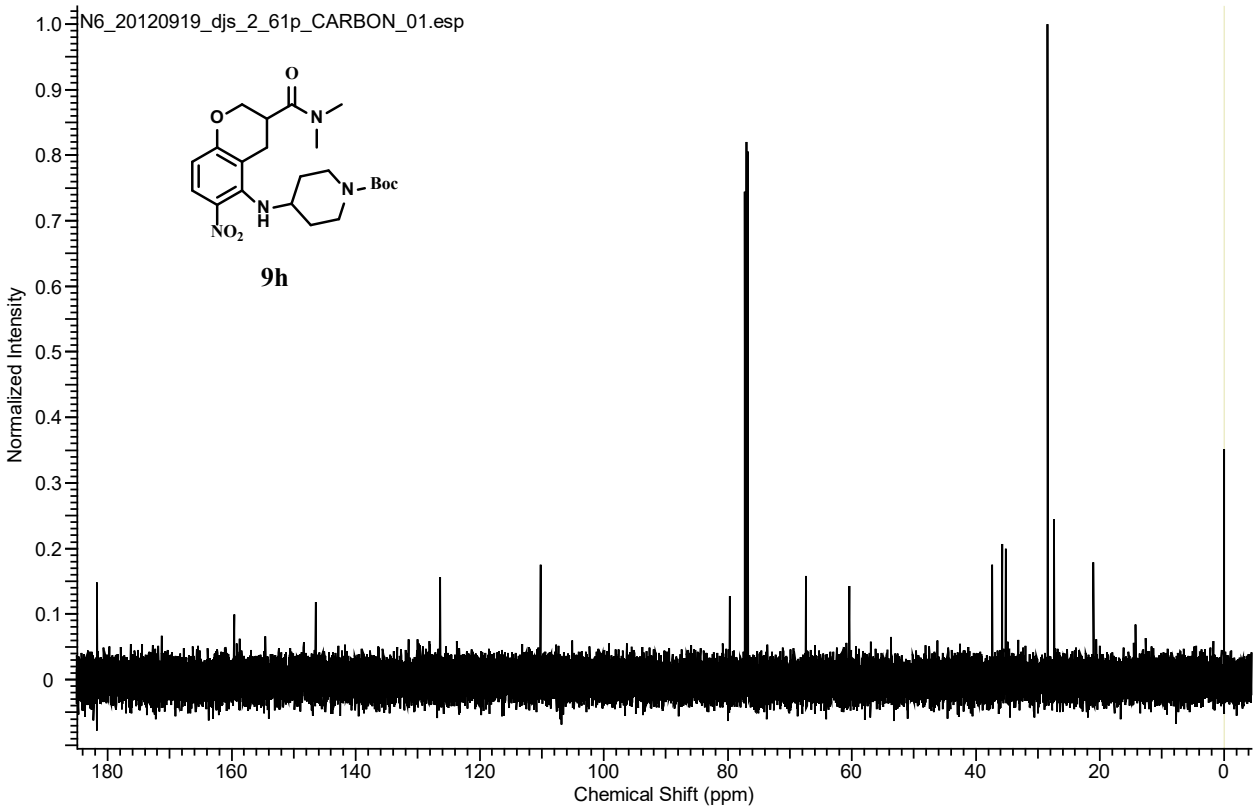

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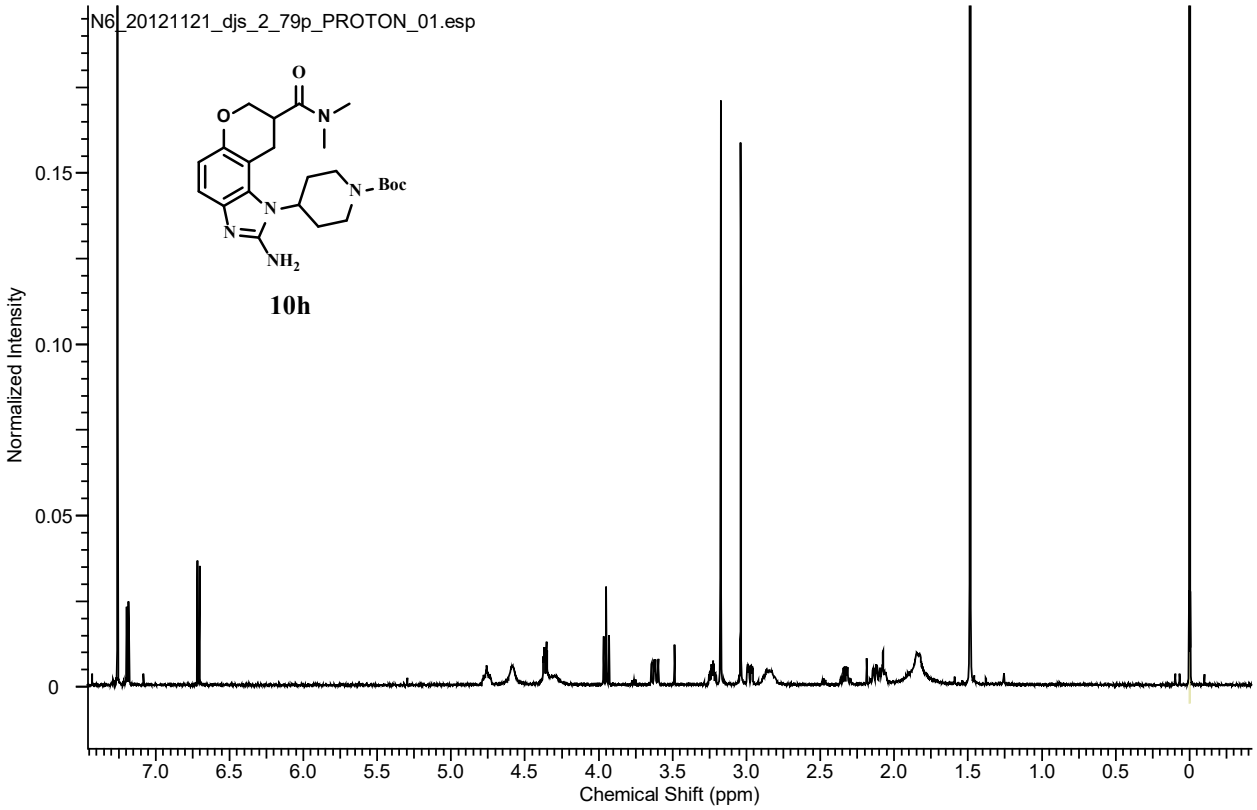

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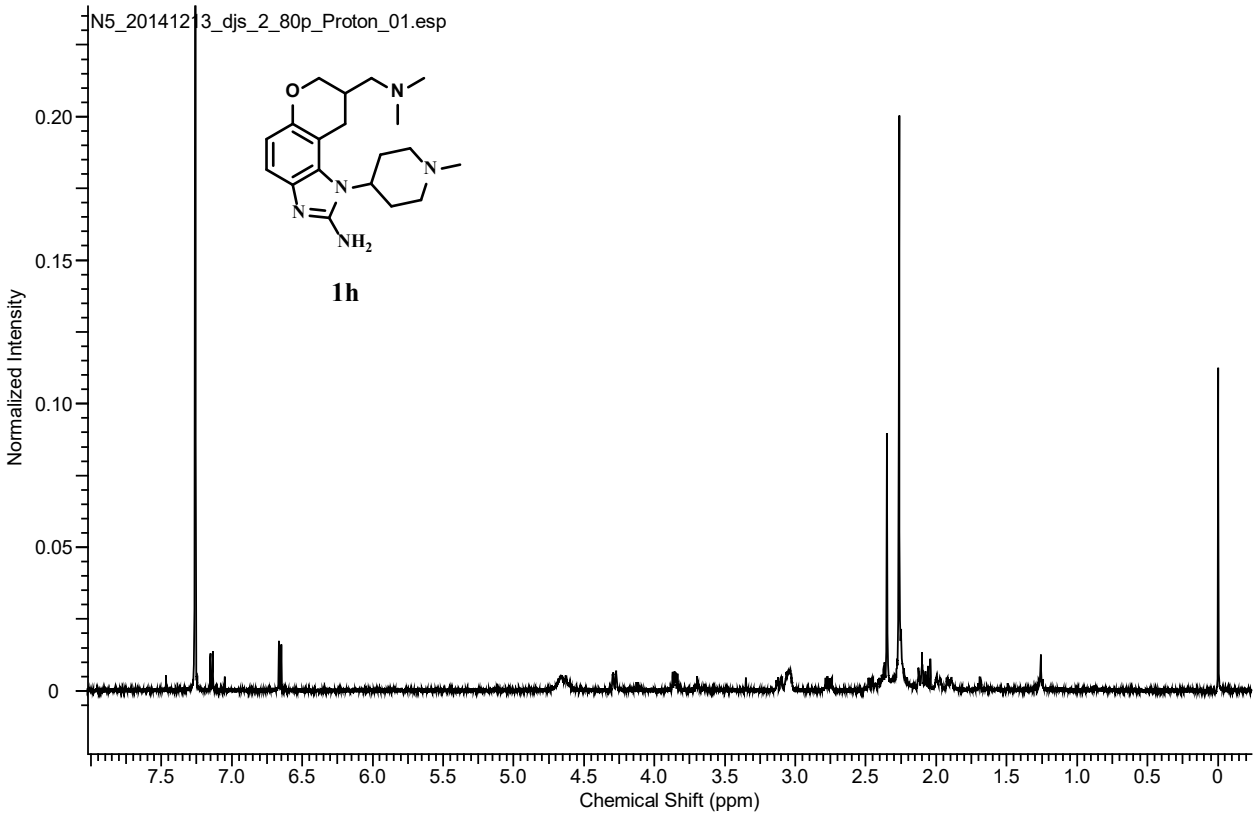

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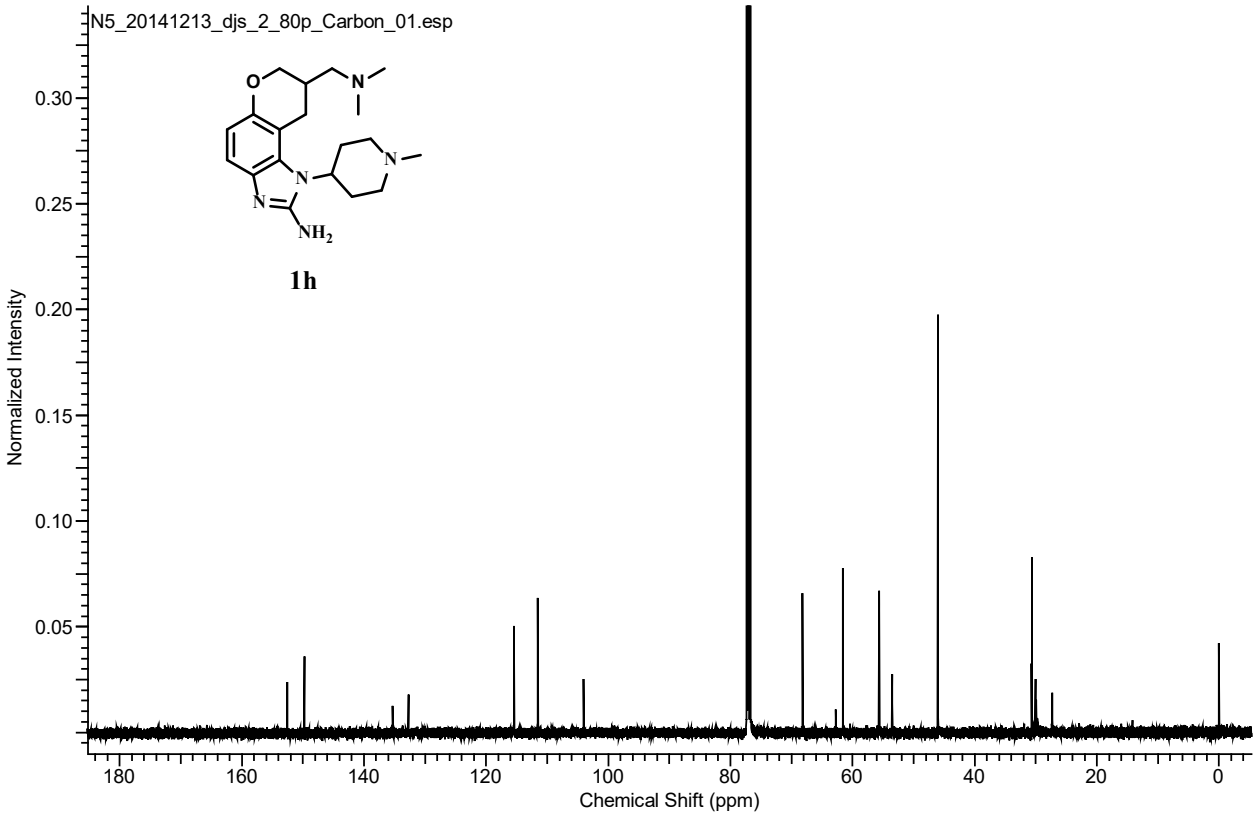

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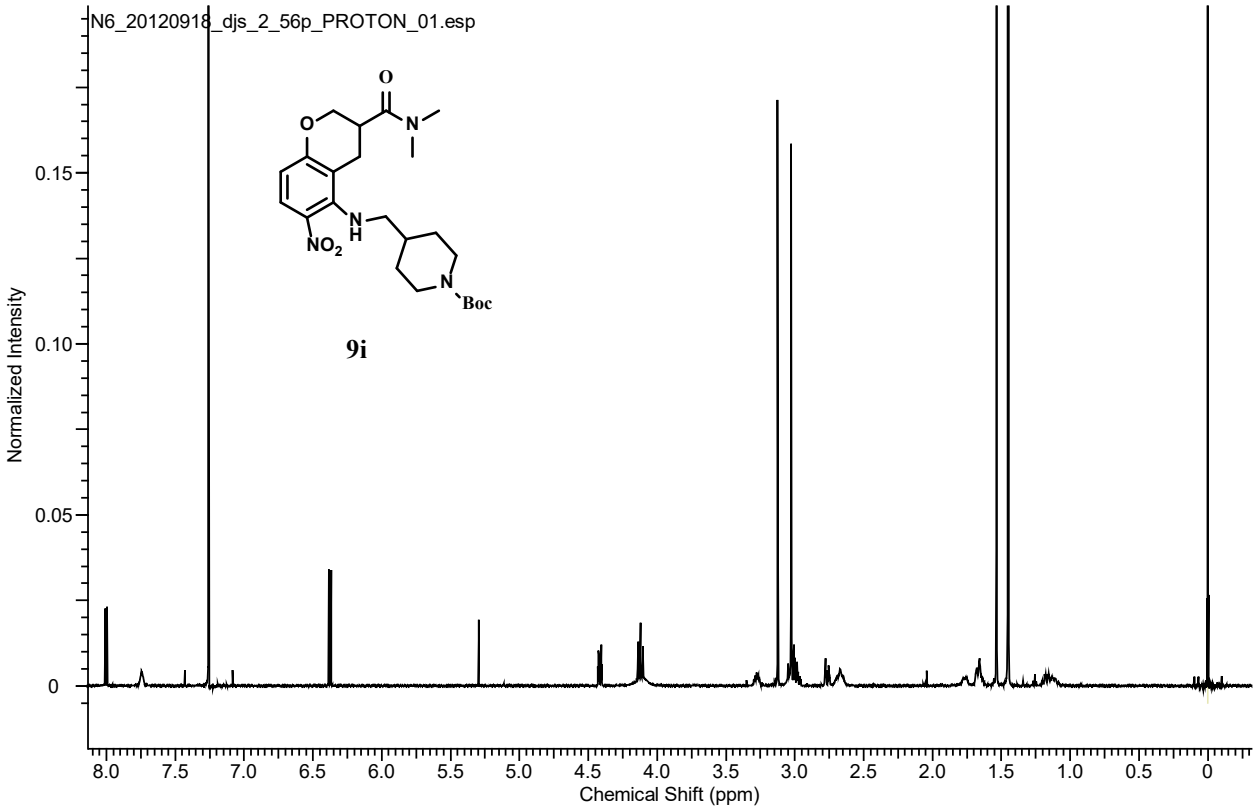

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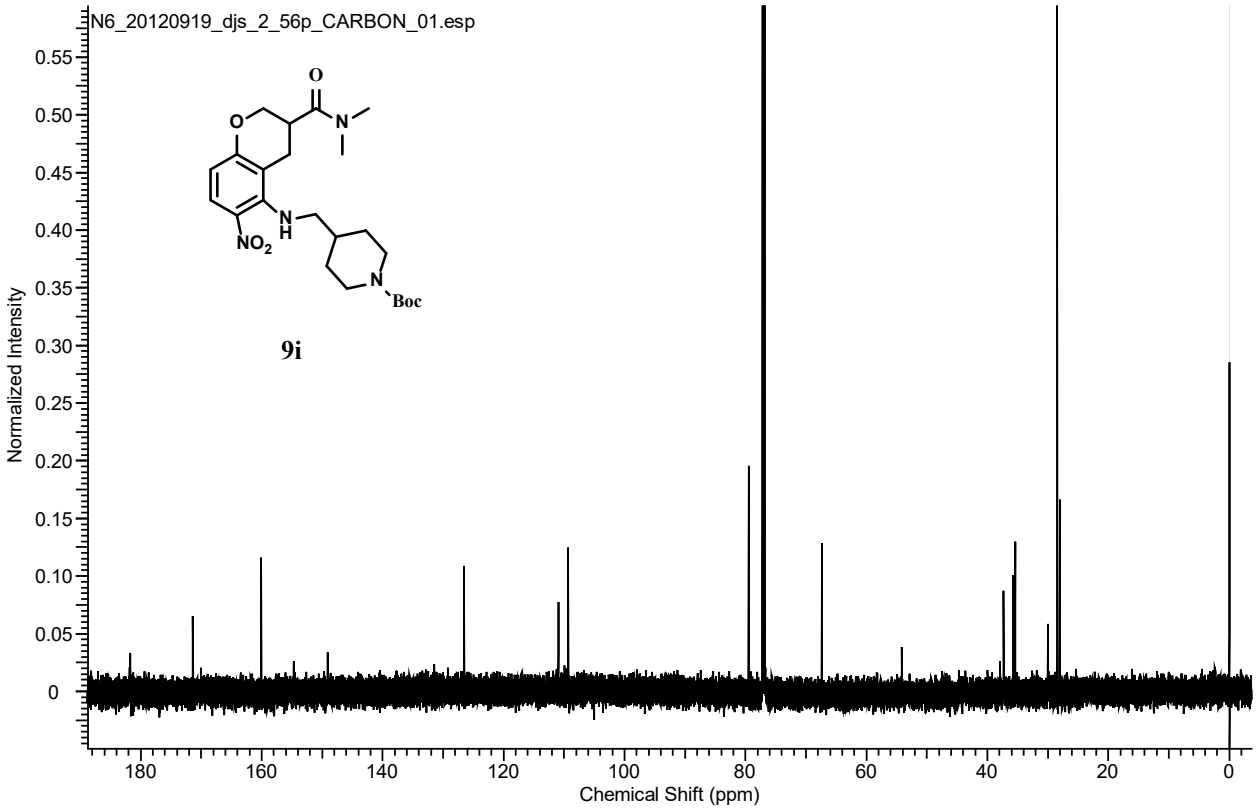

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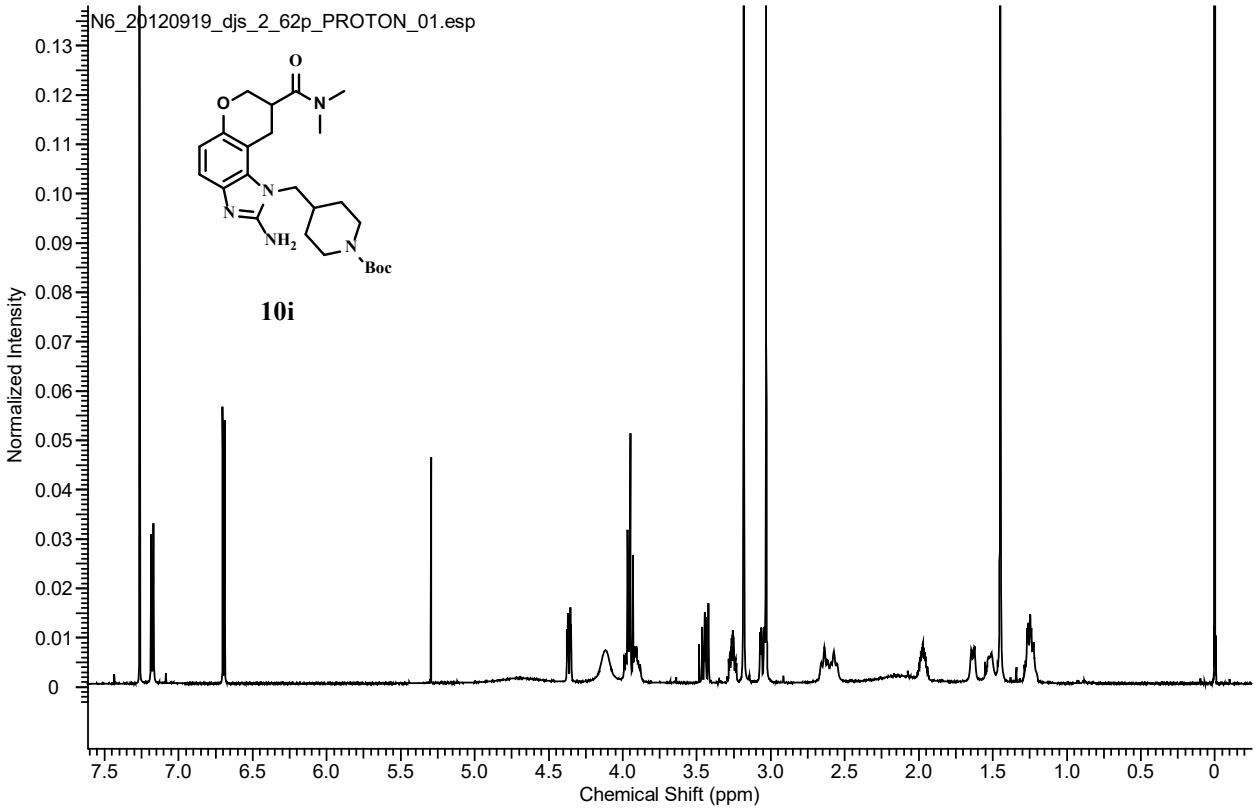

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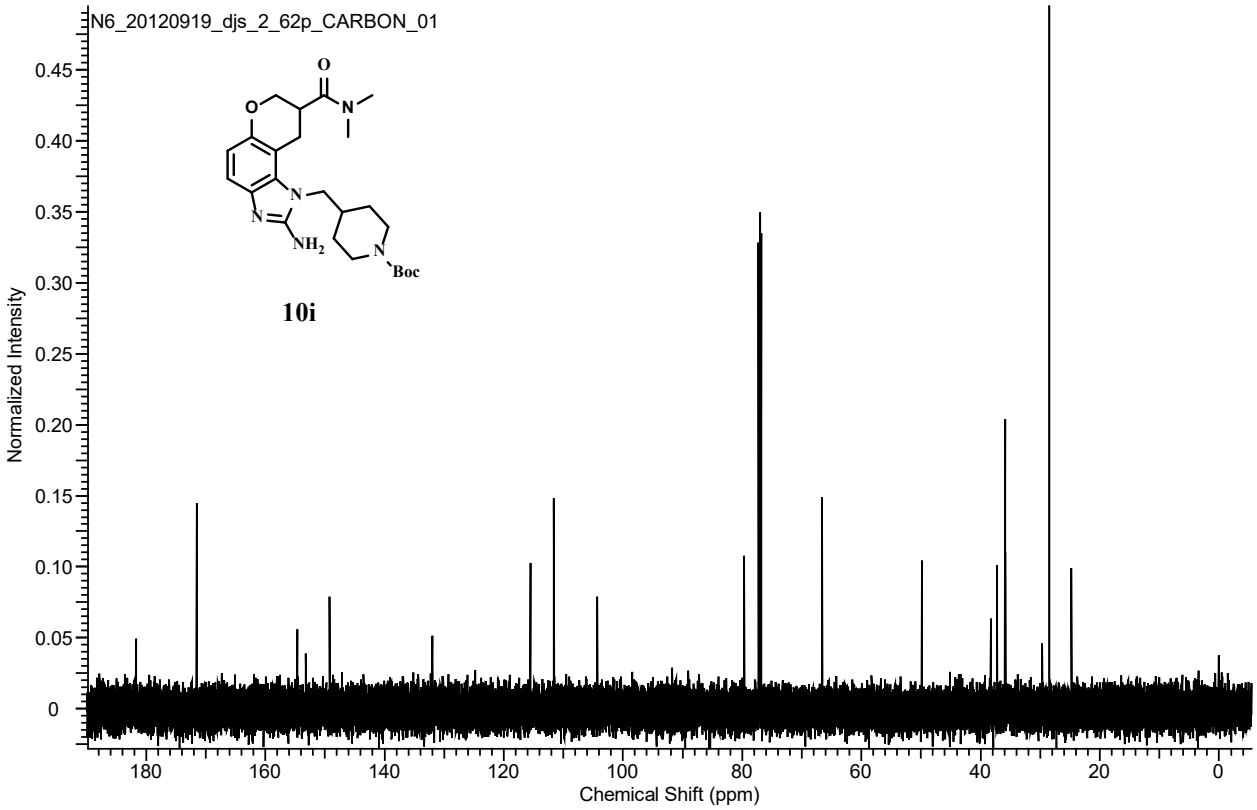

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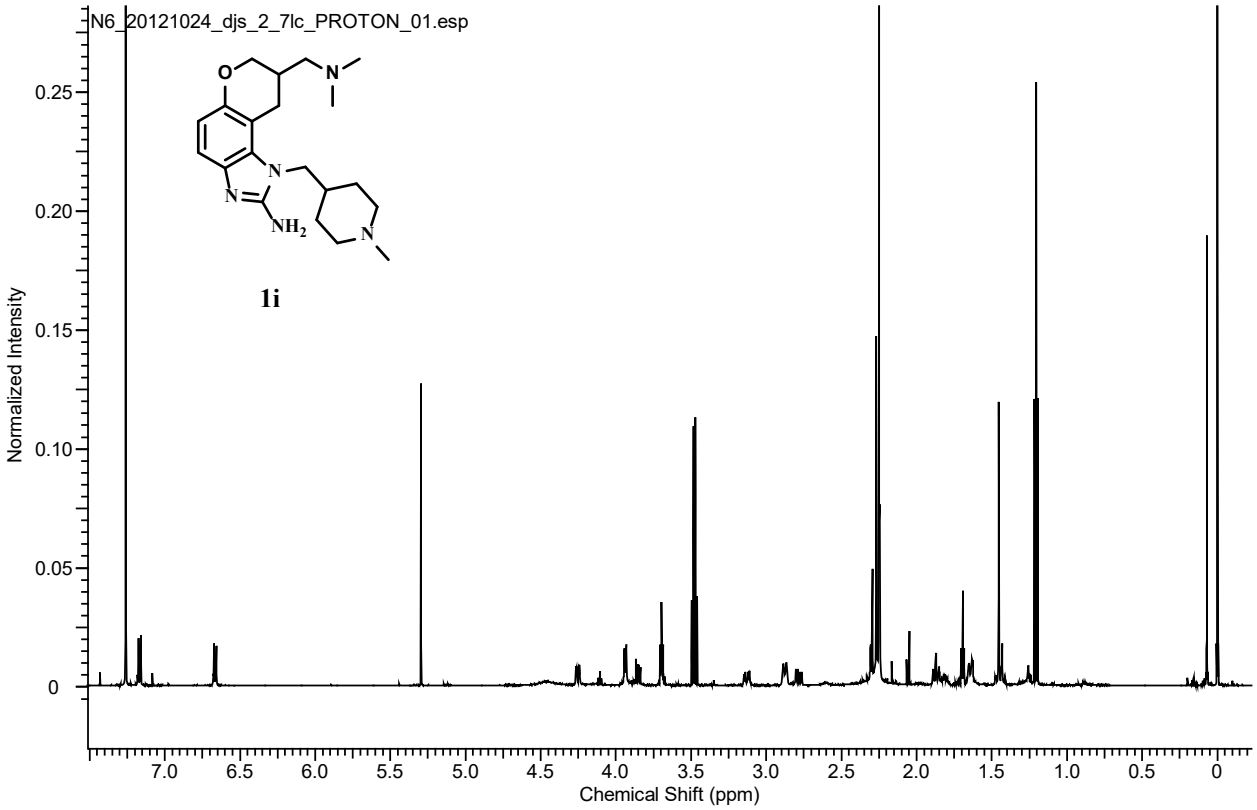

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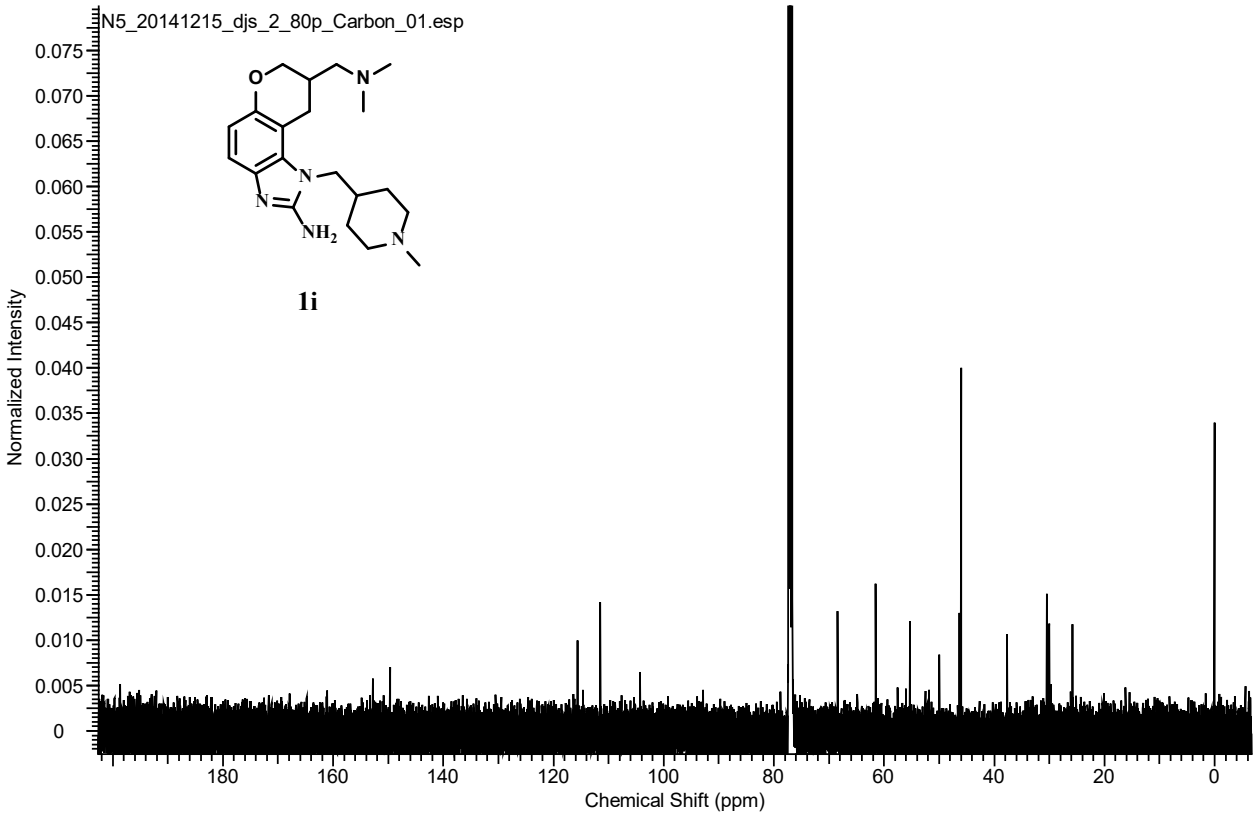

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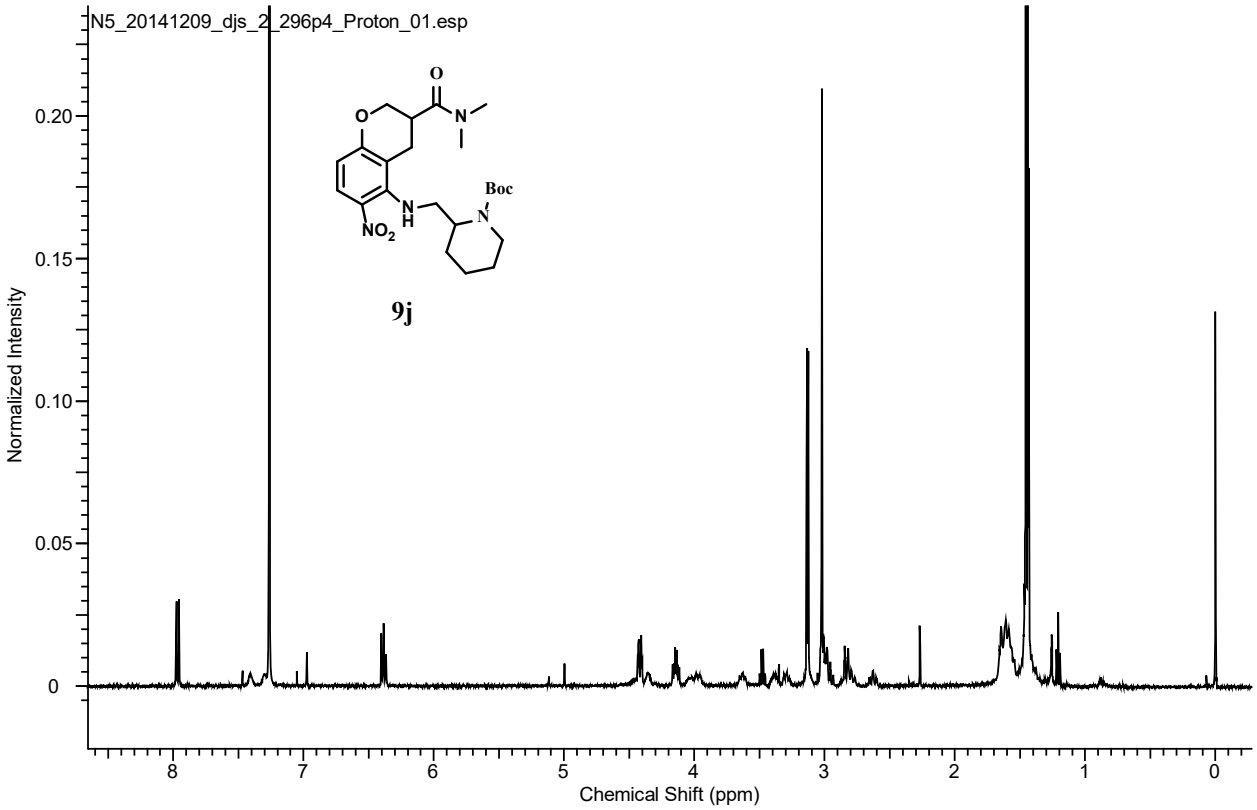

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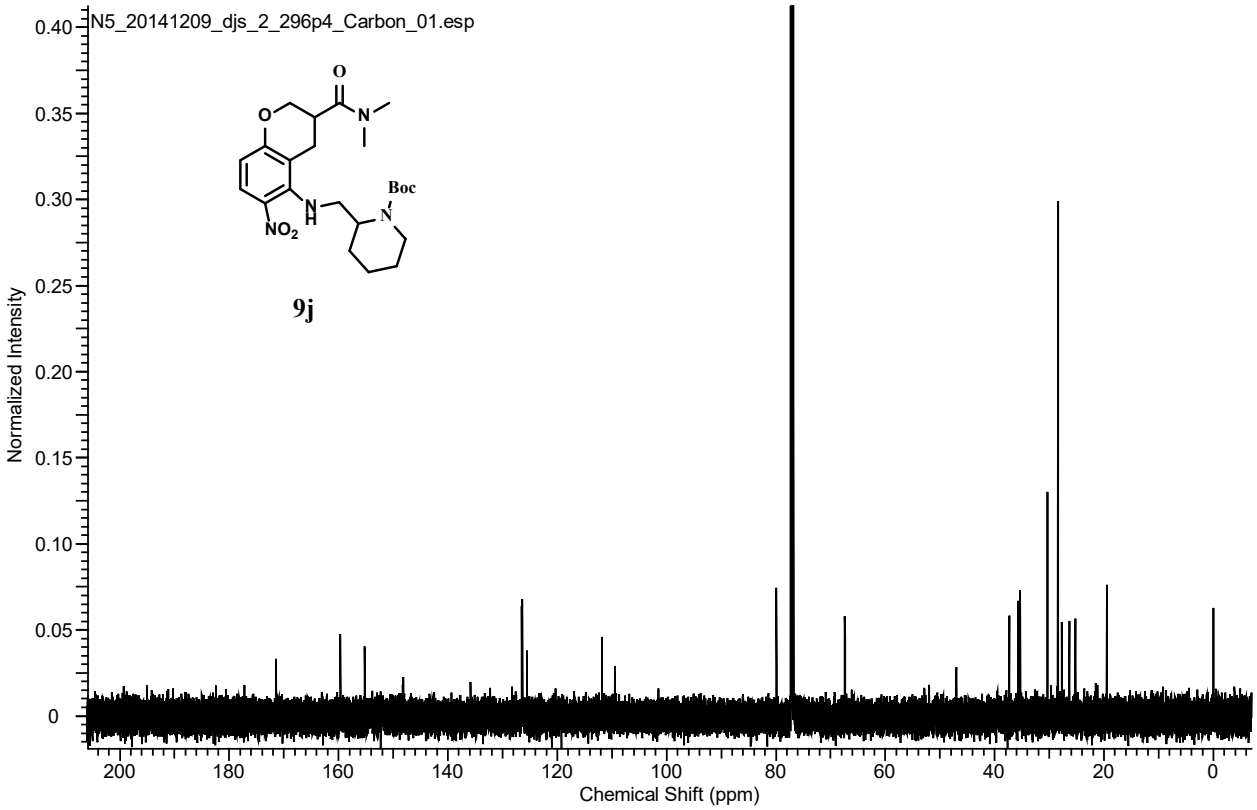

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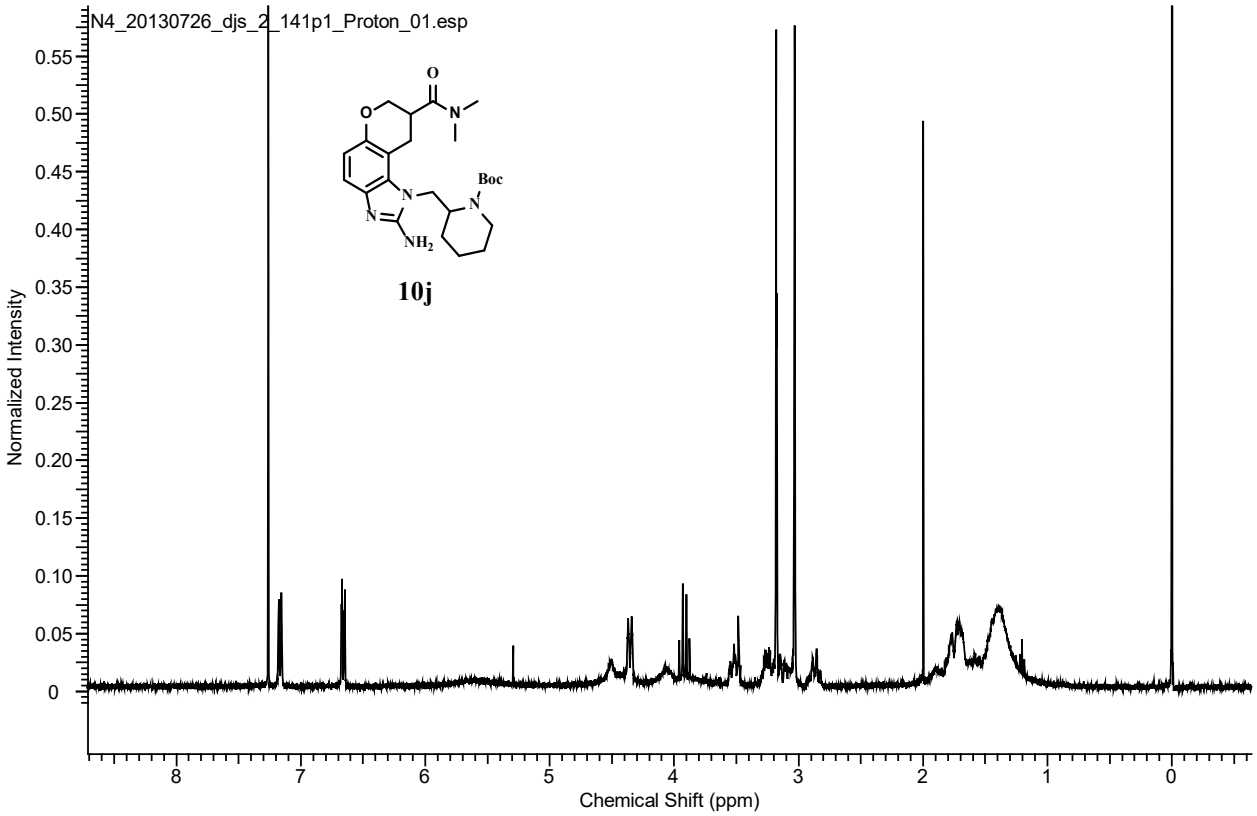

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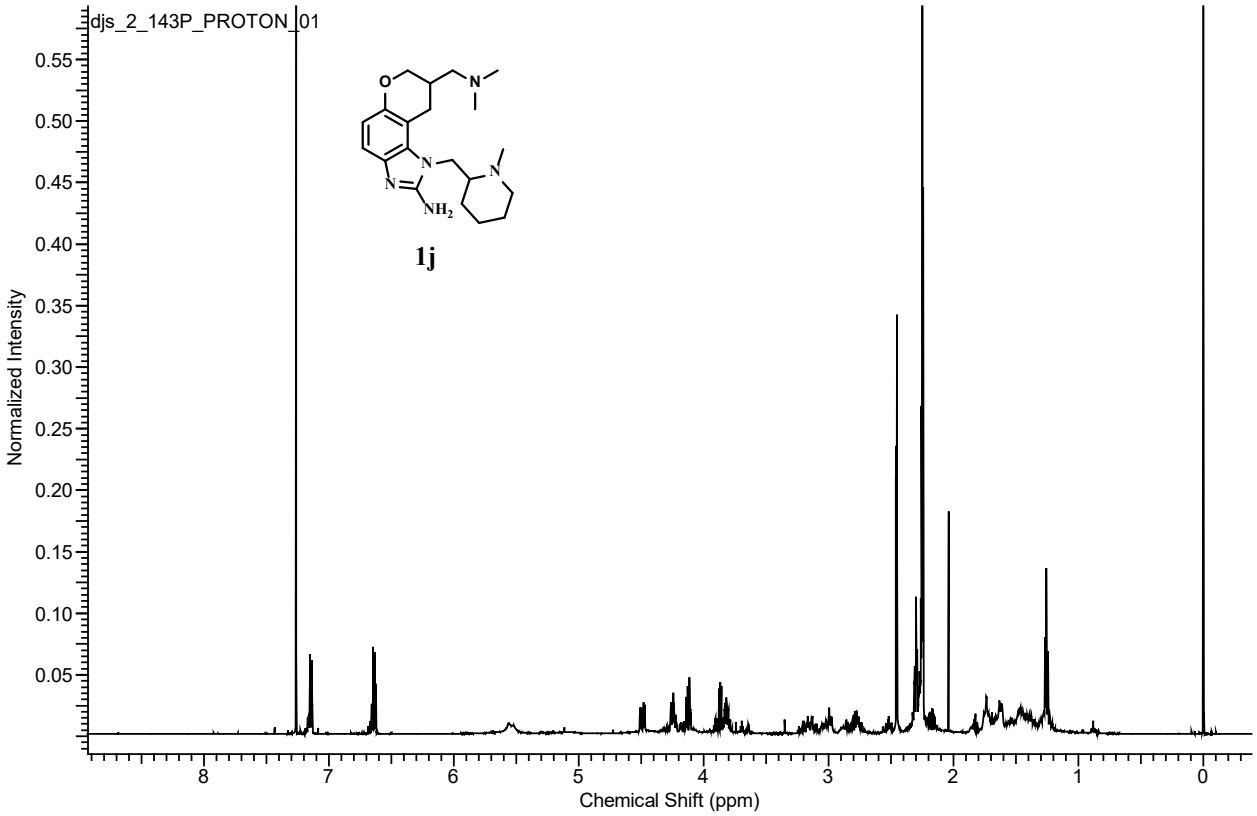

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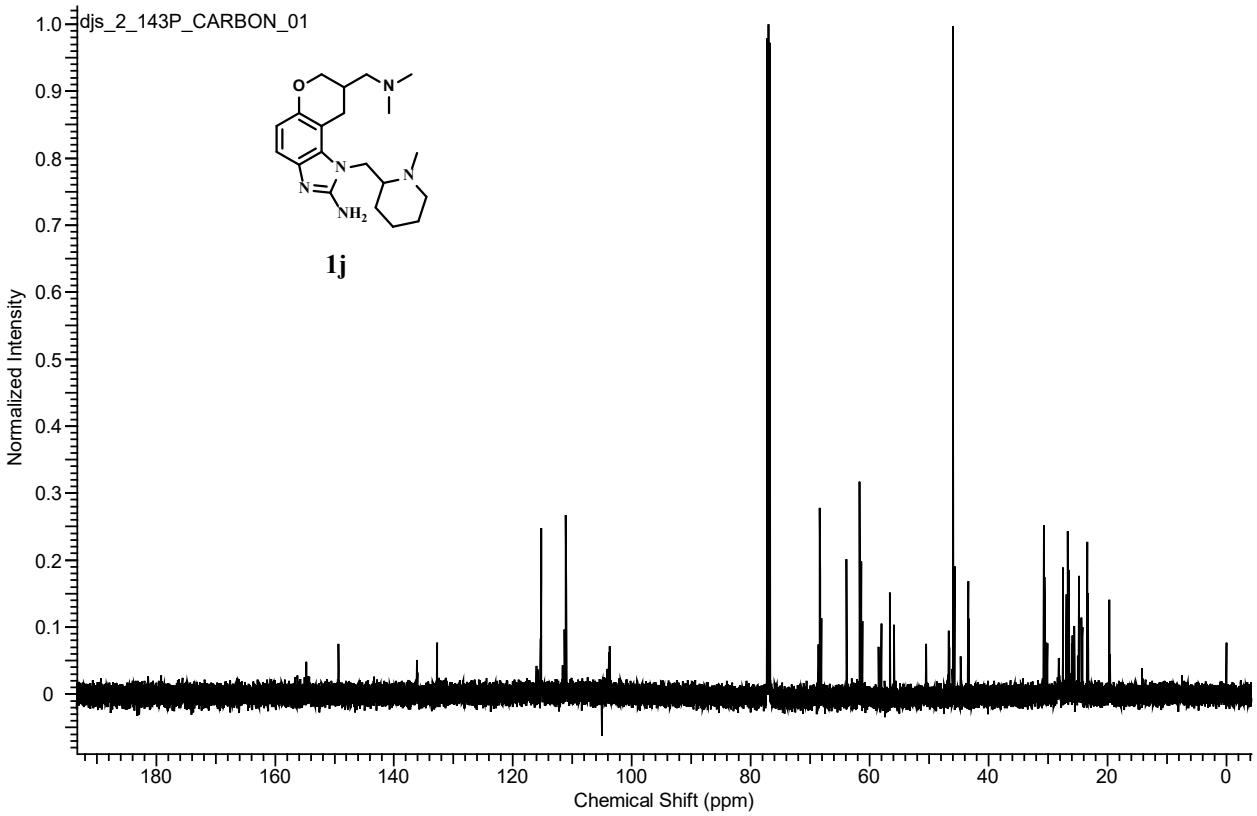

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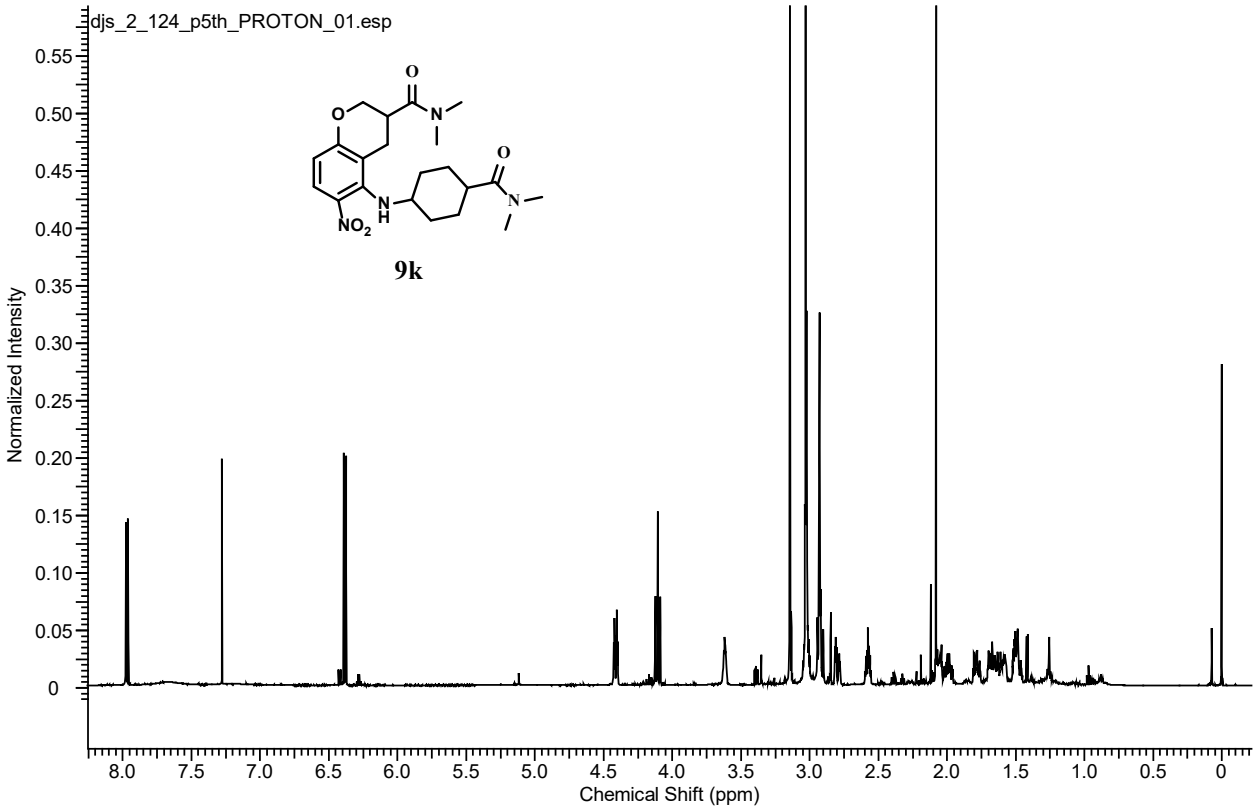

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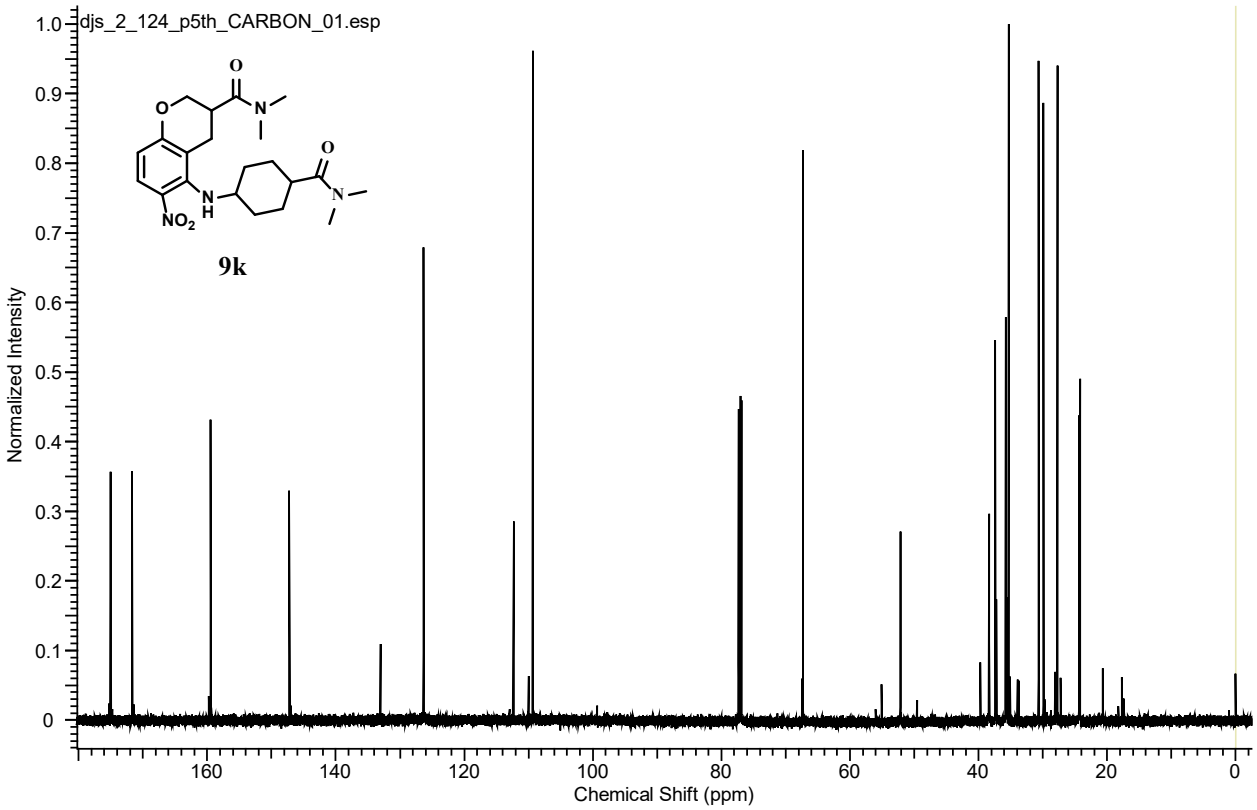

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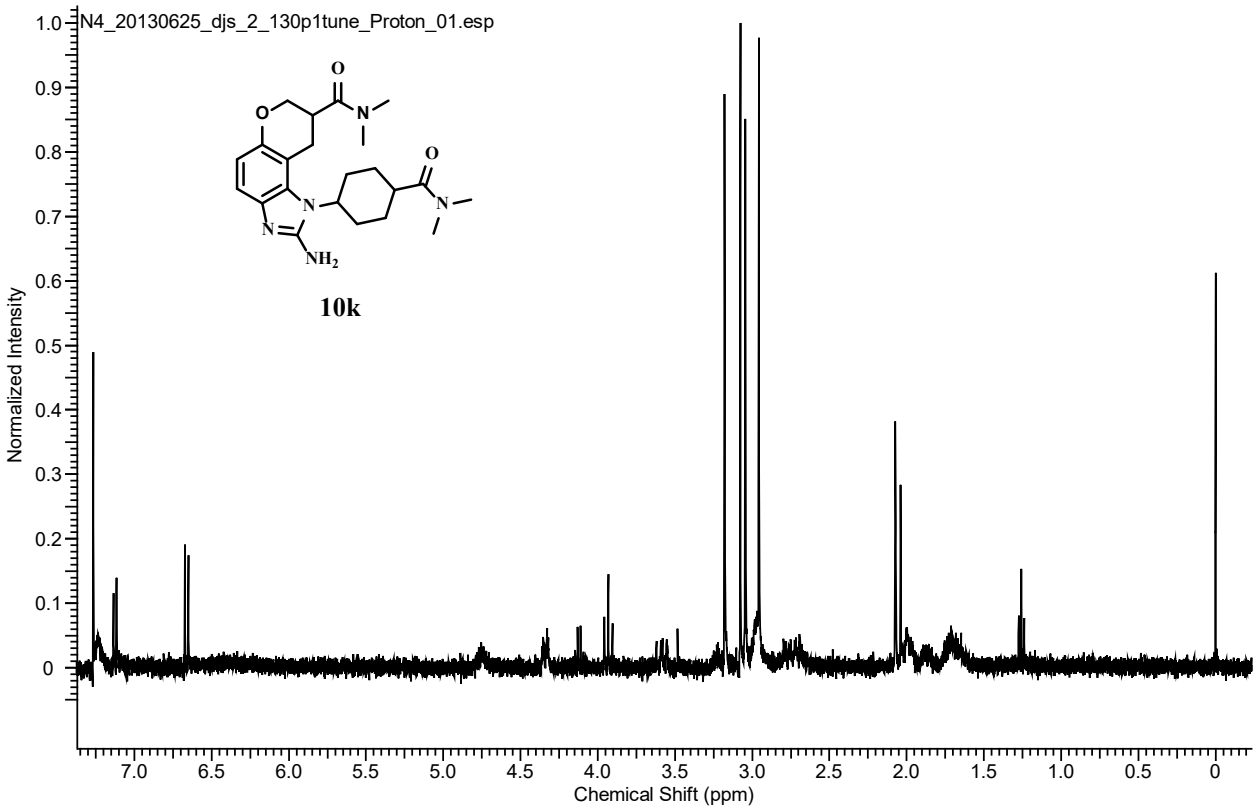

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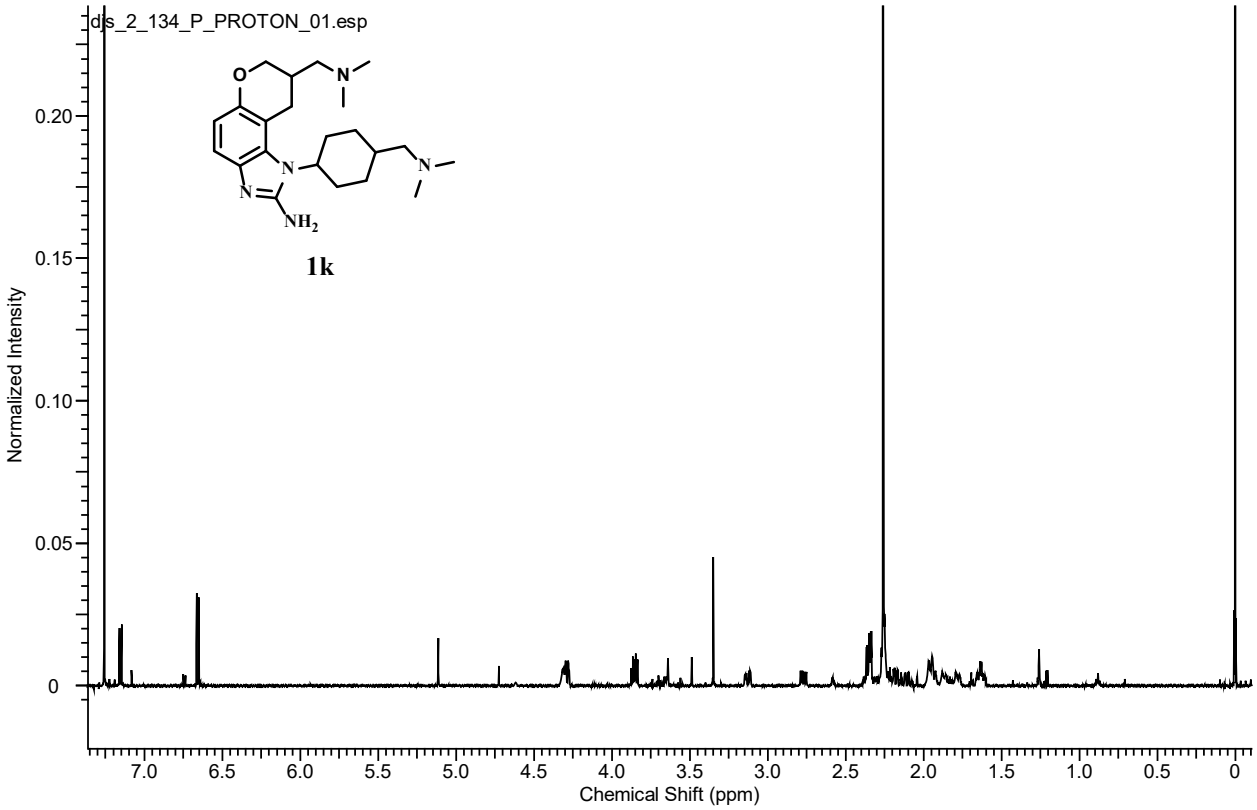

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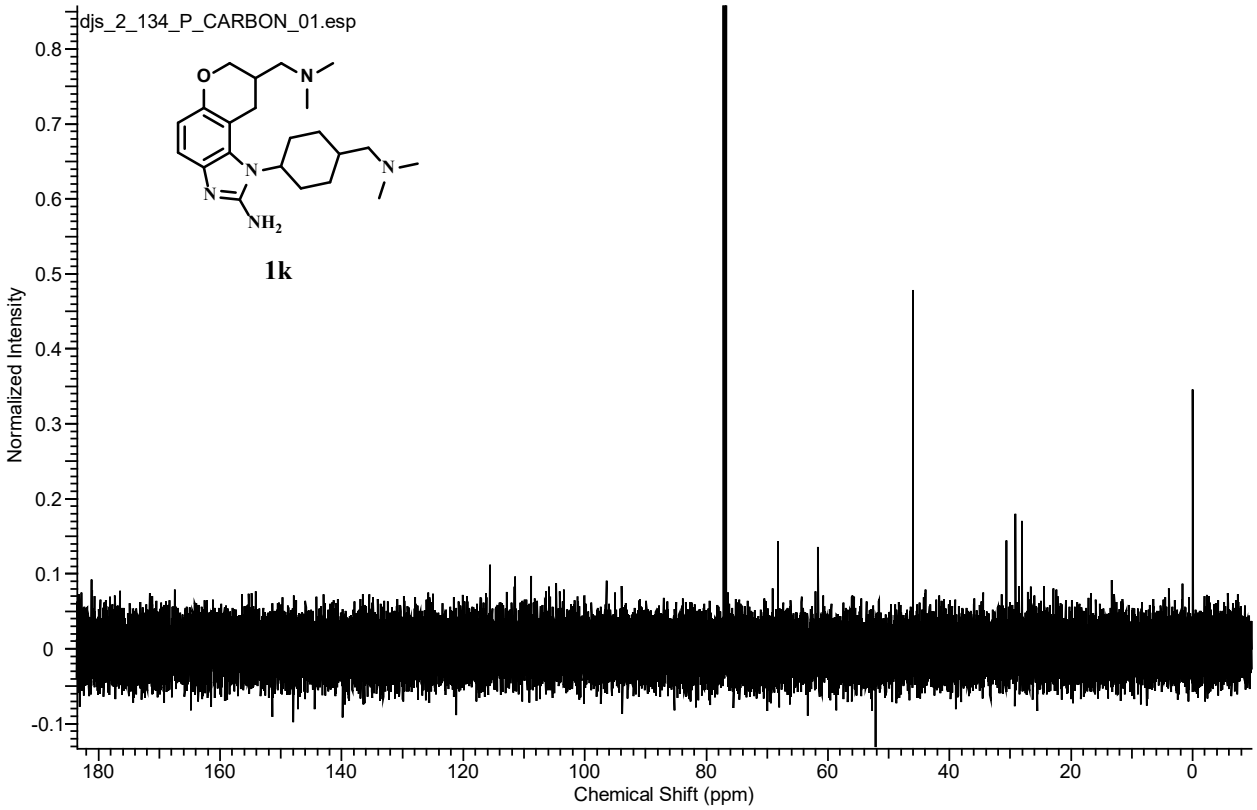


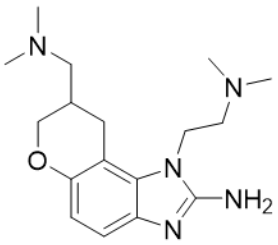
Supplementary Material

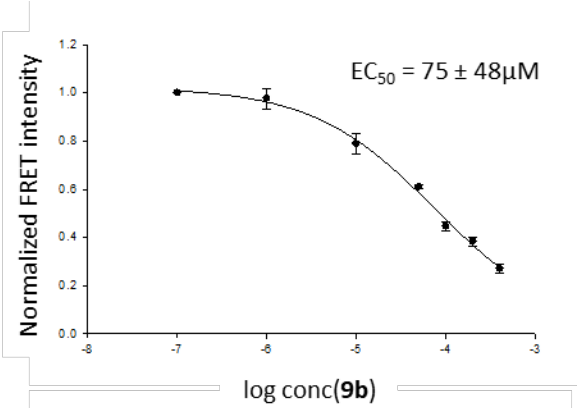
FRET Compound Screening Experiments and EC50 d

HCV IRES IIa RNA constructs were obtained by annealing terminally Cy3/Cy5 dye-conjugated oligonucleotides from commercial custom synthesis, purified by HPLC (Integrated DNA Technologies). Oligonucleotide stock solutions were prepared by dissolving lyophilized nucleic acid in 10 mM sodium cacodylate buffer, pH 6.5. Annealing of RNA target constructs was performed by heating oligonucleotide mixtures in cacodylate buffer with 2 mM $MgCl_2$ added, to 65°C for 5 min followed by cooling on ice. FRET measurements were performed in 96-well plates, at 120 µL well filling volume, on a Spectra Max Gemini monochromator plate reader (Molecular Devices) at 25°C at a final RNA concentration of 100 nM in 10 mM sodium cacodylate buffer, pH 6.5, containing 2 mM $MgCl_2$. Ligand induced FRET changes were monitored for terminally Cy3/Cy5-labelled IIa RNA target construct in the presence of increasing ligand concentration. To measure FRET signal, the Cy3 label was excited at 520 nm and transferred fluorescence was read as Cy5 emission at 670 nm. For each compound, FRET signal at each concentration was ***tested in triplicate***. Data sets were analyzed and FRET calculated as described previously.[7] Binding selectivity for the HCV IIa RNA was tested, as described previously,[8] by repeating titrations and EC_{50} determination in the presence of an unlabeled competitor RNA (wheat germ total tRNA, Sigma) at a 20x excess (2 µM) over target. HCV target EC_{50} shift in the presence of competitor RNA was not observed for the 2-aminobenzimdazole analogs, indicating selectivity for the IIa RNA.

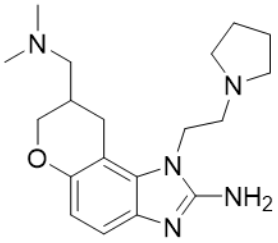
FRET compound titration curves used for EC_{50} determination of compound binding at the IIa RNA target. Error bars represent ±1σ calculated from triplicate measurements.

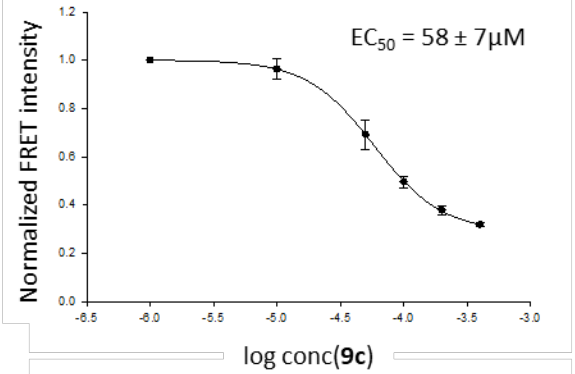
1b



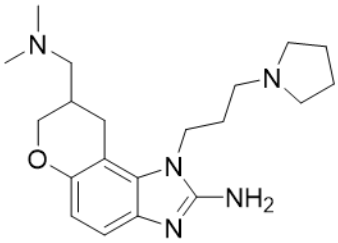

EC50 = 75 ± 48µM
Normalized FRET intensity
log conc(9b)

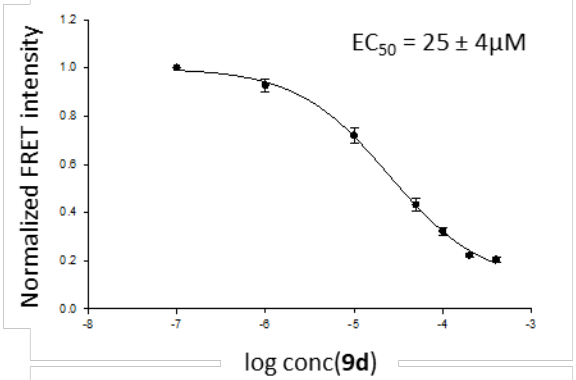
1c



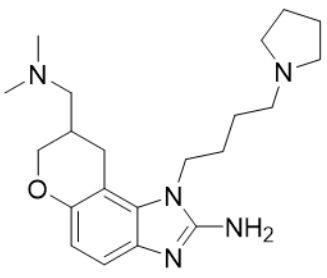

EC50 = 58 ± 7µM
Normalized FRET intensity
log conc(9c)

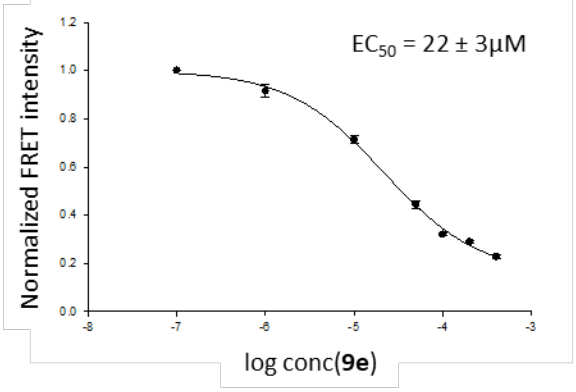
1d




EC50 = 25 ± 4µM
Normalized FRET intensity
log conc(9d)

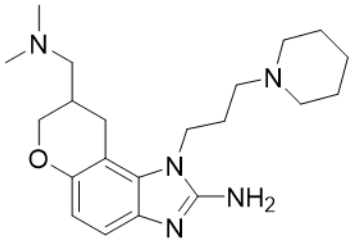
1e

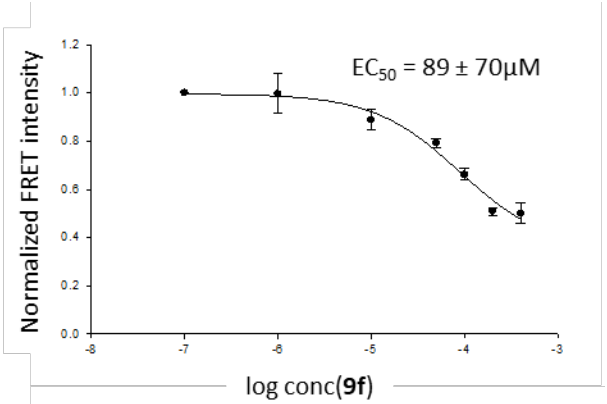



EC50 = 22 ± 3µM
Normalized FRET intensity
log conc(9e)

Supplementary Material

1f





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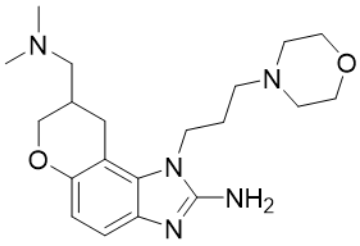

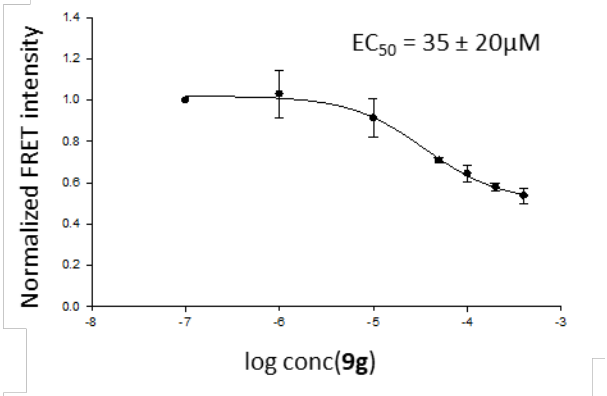

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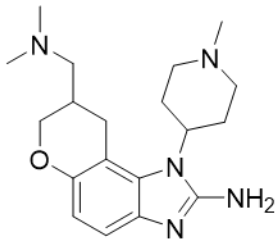

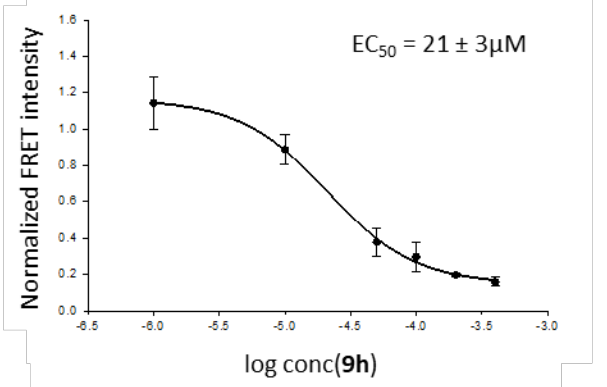

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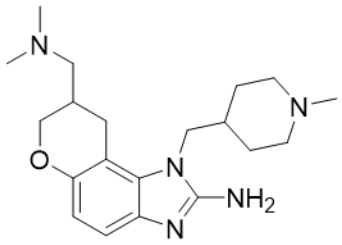

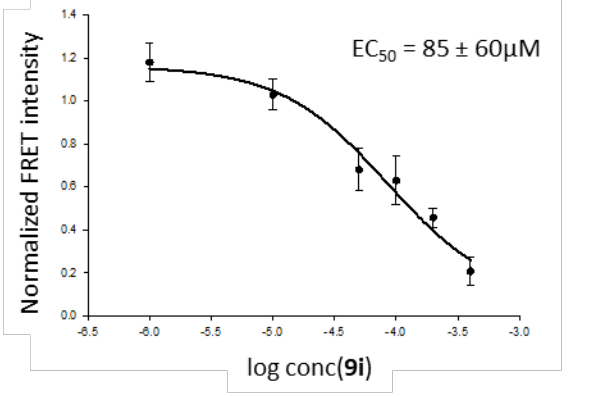

Supplementary Material

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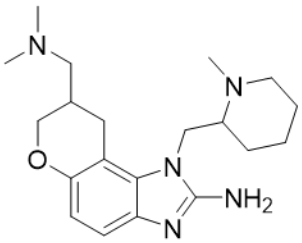

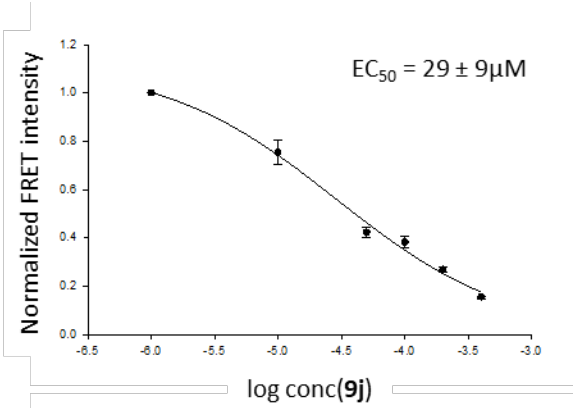

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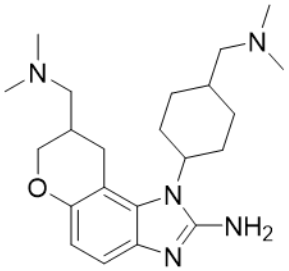
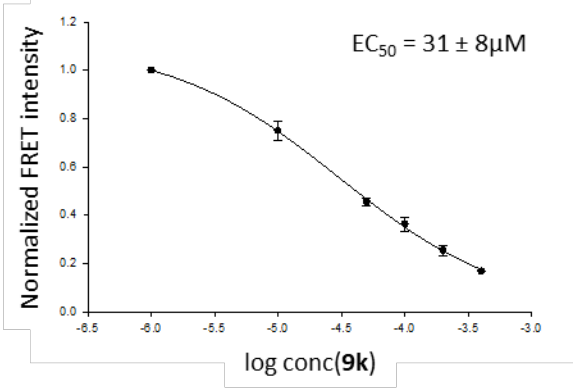




Supplementary Material

In silico docking and quantitative structure activity relationship (QSAR) methodology. The x-ray crystal structure of inhibitor **1a** in complex with the IRES of HCV RNA (PDB: 3TZR) was used for these studies.[9] Compounds **1a**-**1g** were drawn using Chemdraw (Cambridgesoft, Inc.) and then imported into MOE (Chemical Computing Group). The two-dimensional structures were converted to three dimensions and minimized using the MMFF94x gas phase potential.[10] The bound x-ray conformation of **1a** from 3TZR was used to define the binding pocket in the IRES. Docking experiments were performed with the Dock function in MOE by using the Amber12:EHT forcefield[11] with parameterized solvation and the default Dock parameters and fitness functions. In order to verify that poses resulting from *in silico* docking represent correctly bound conformations, each pose was visually inspected and compared to the experimentally determined binding modes and conformations of **1a**. The docking score output for each of the top scoring poses were exported to Molegro Data Modeller (Molegro, APS.) for QSAR analysis. Feature selection was performed and artificial neural net (ANN) models were generated using default settings. The top scoring backpropagation trained ANN had 5-4-1 architecture (R^2= 0.99). To test the generalizability of these models on held-out samples, leave-one-out (LOO) cross validation was performed (R^2= 0.78).

Figure S5. Docked poses of: a). **1a** with **< 1.0 Å** rmsd from bound x-ray conformation; b). **1b**; c). **1c**; d). **1d**; e). **1e**; f). **1f**; g). **1g**.

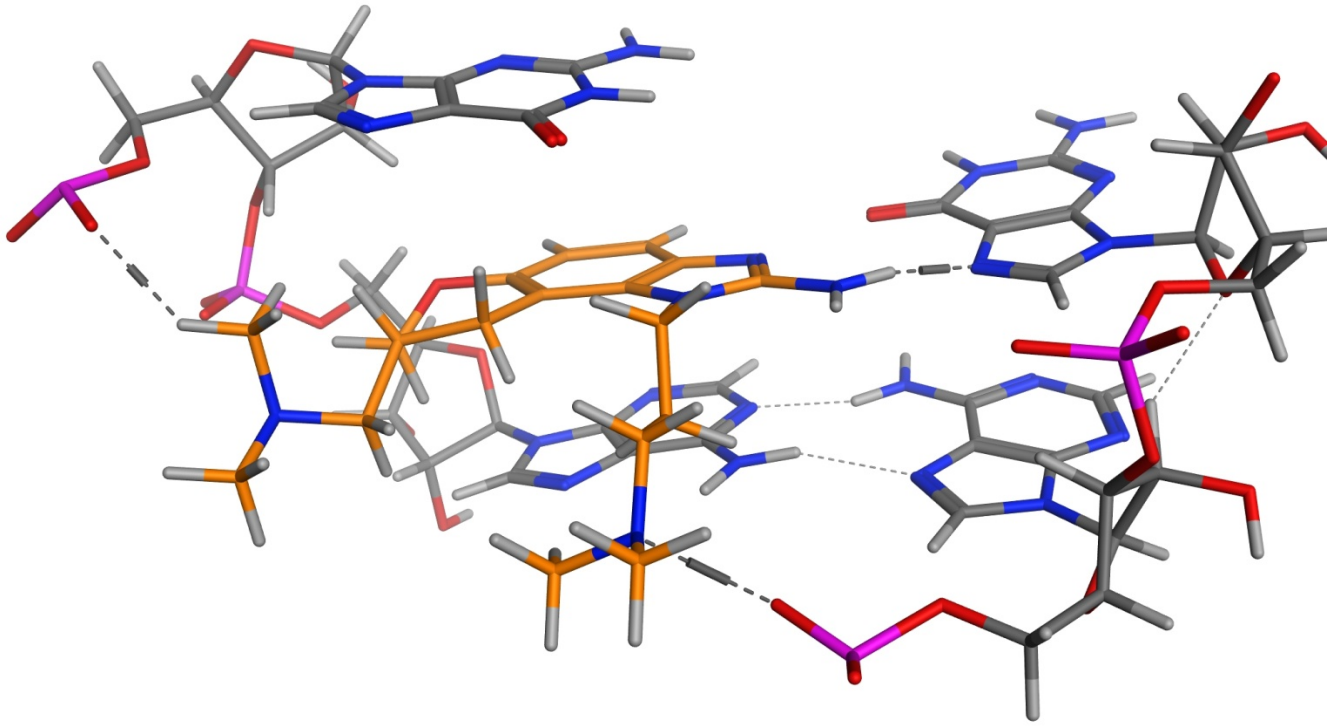


Figure S5a. **1a** 3.4 μM

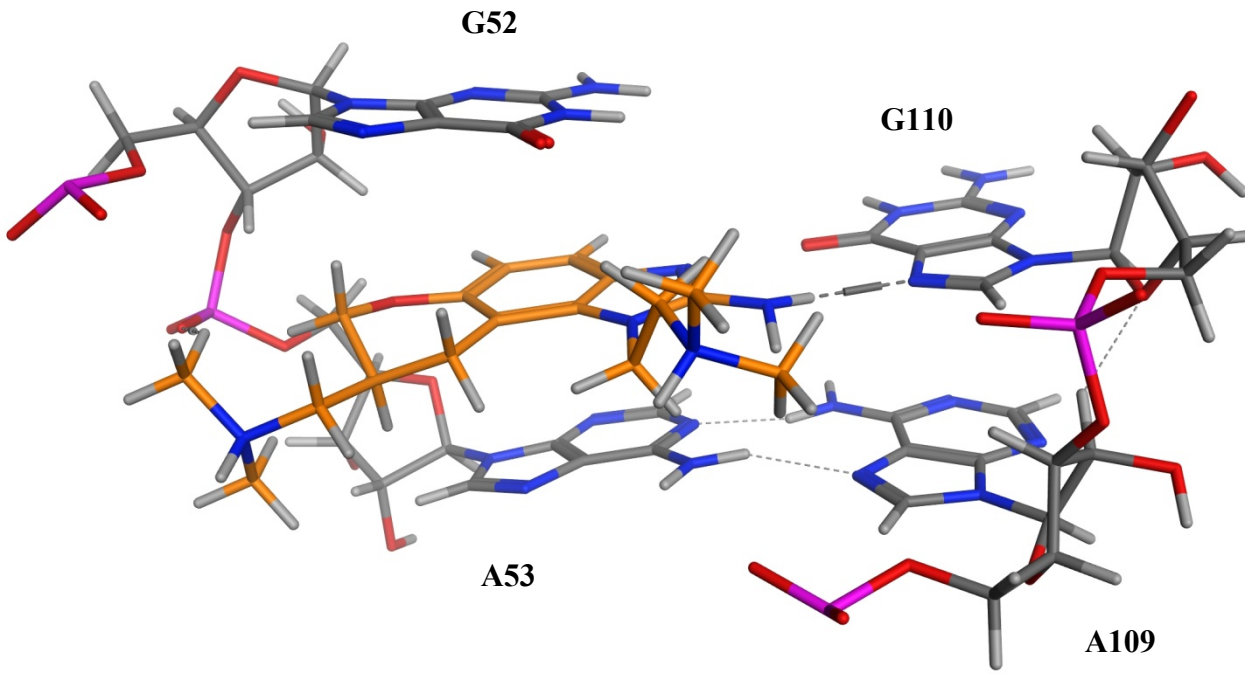


Figure S5b. **1b** 75 μM

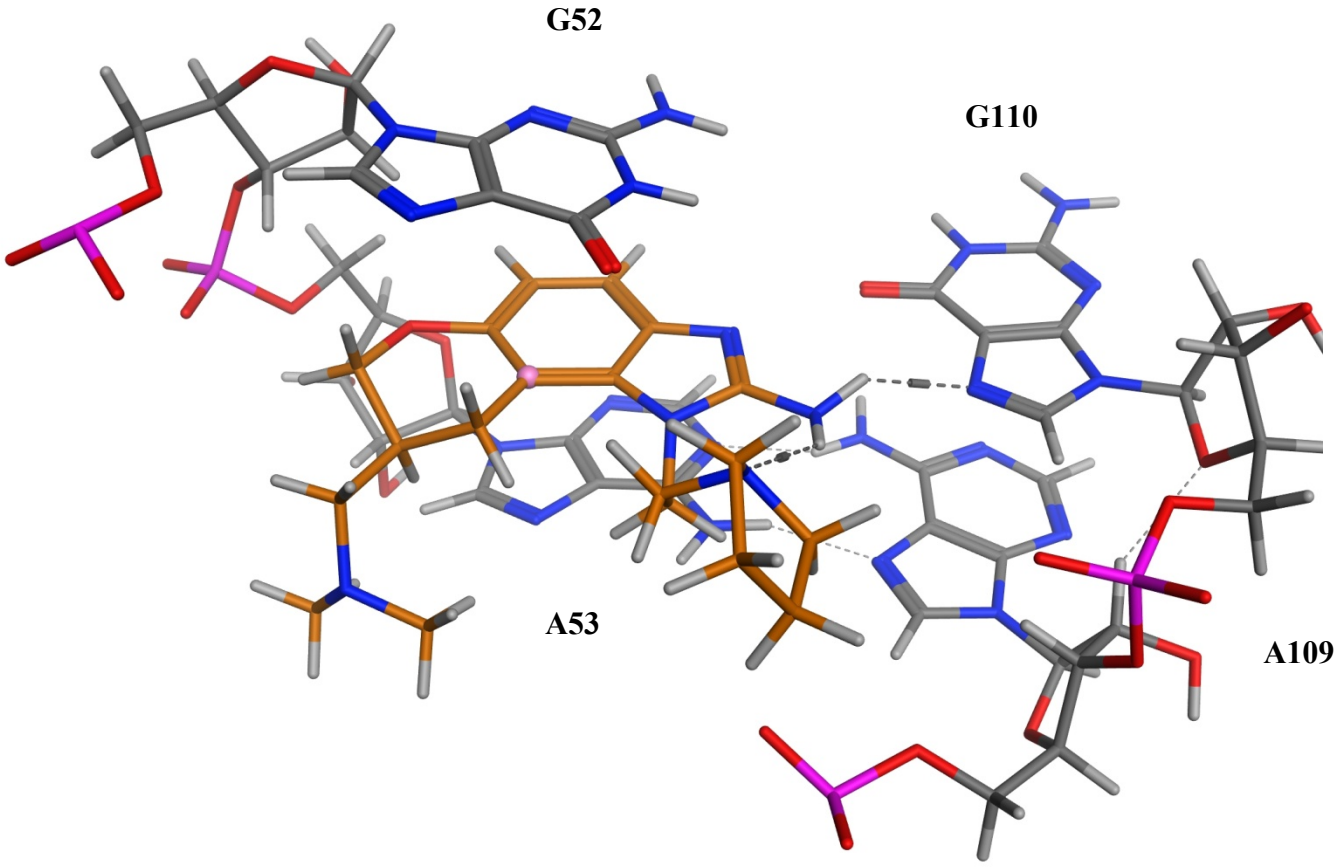


Figure S5c. **1c** 58 μM

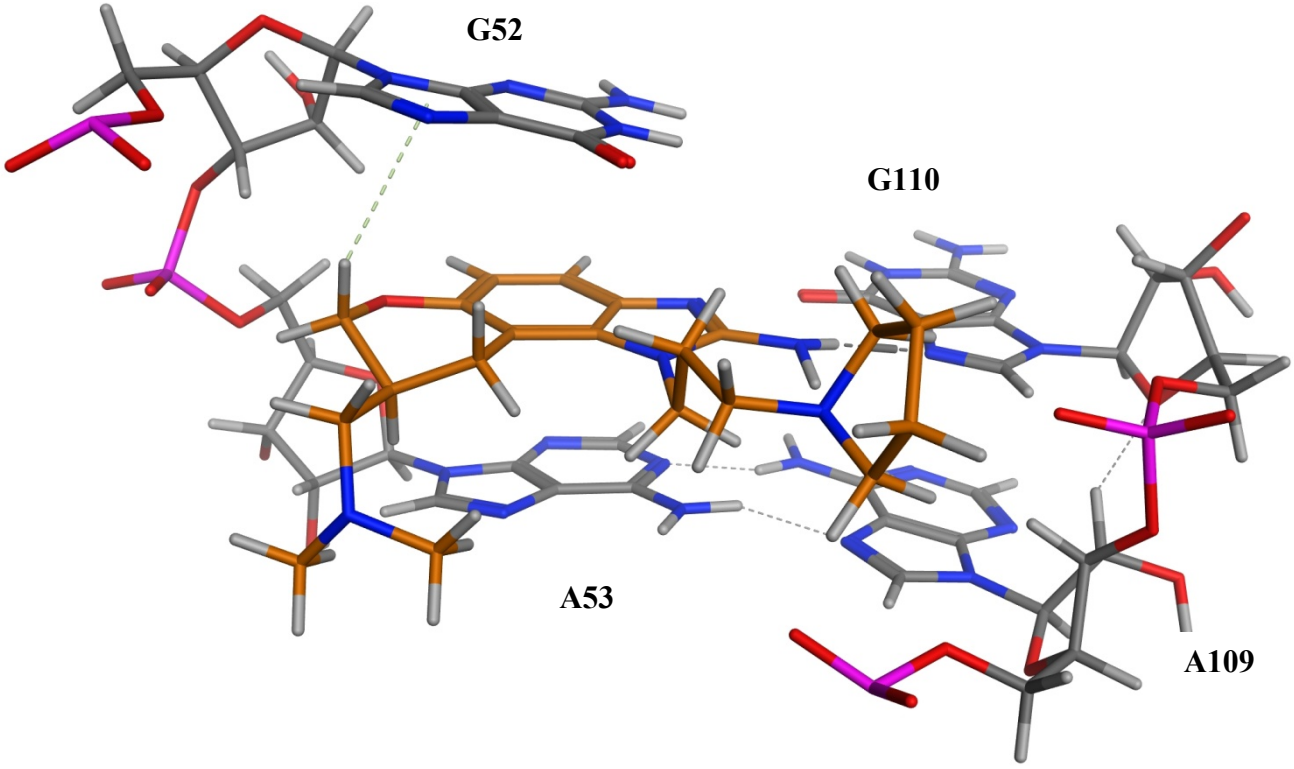


Figure S5d. **1d** 25 μM

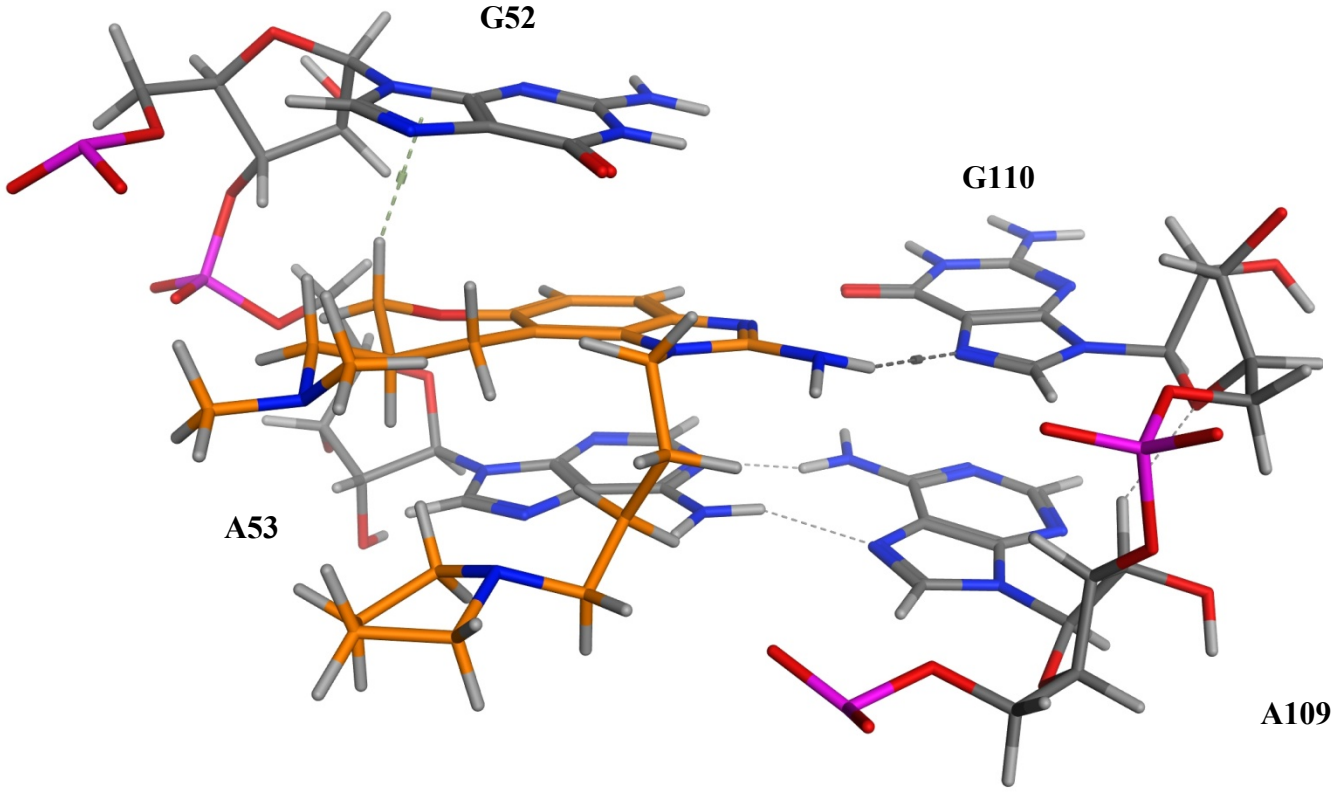


Figure S5e. **1e** 22 µM

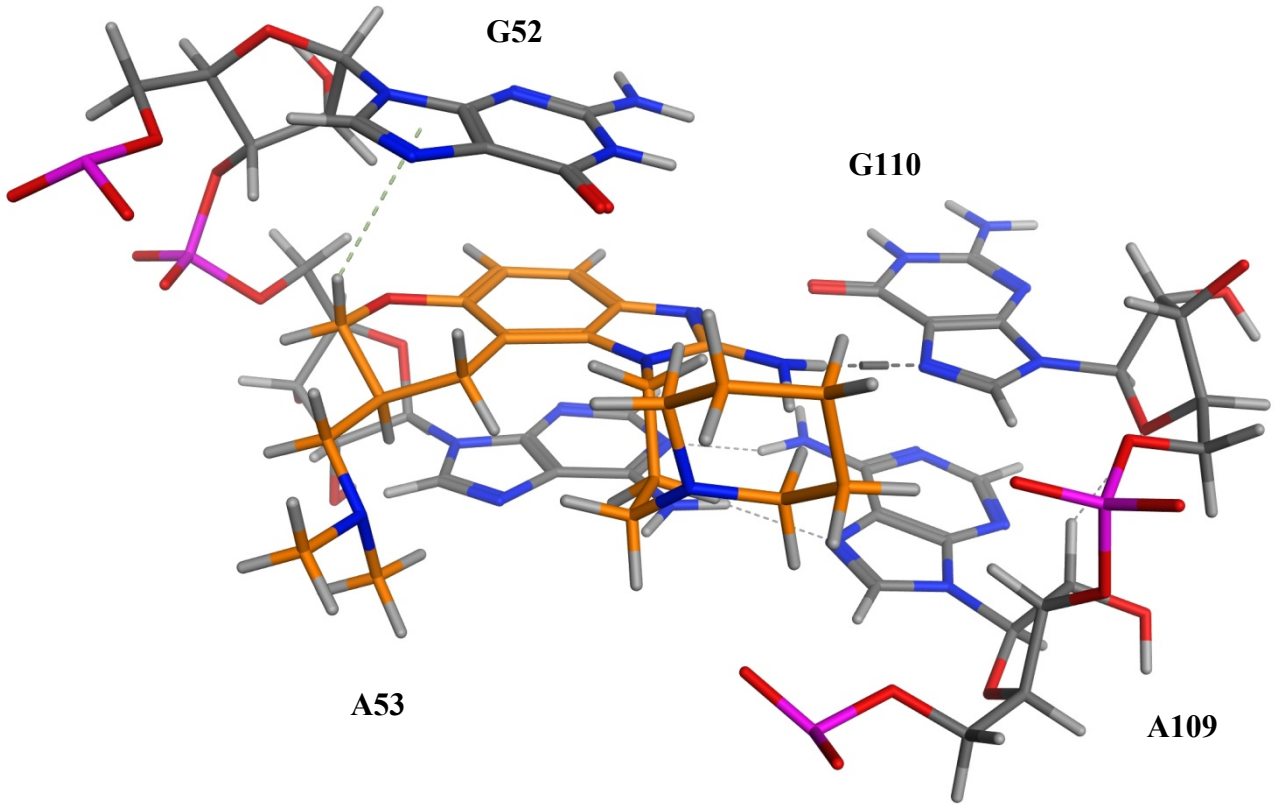


Figure S5f. **1f** 89 μM

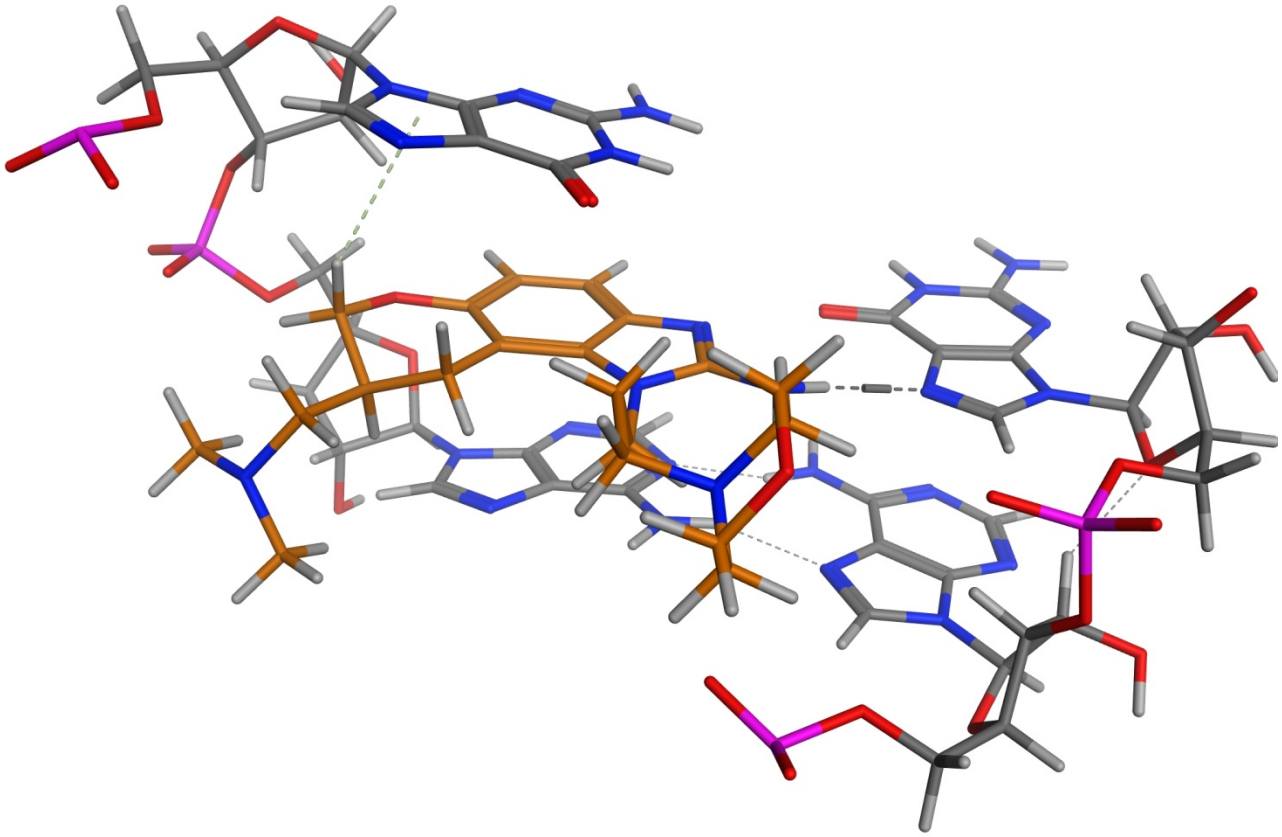
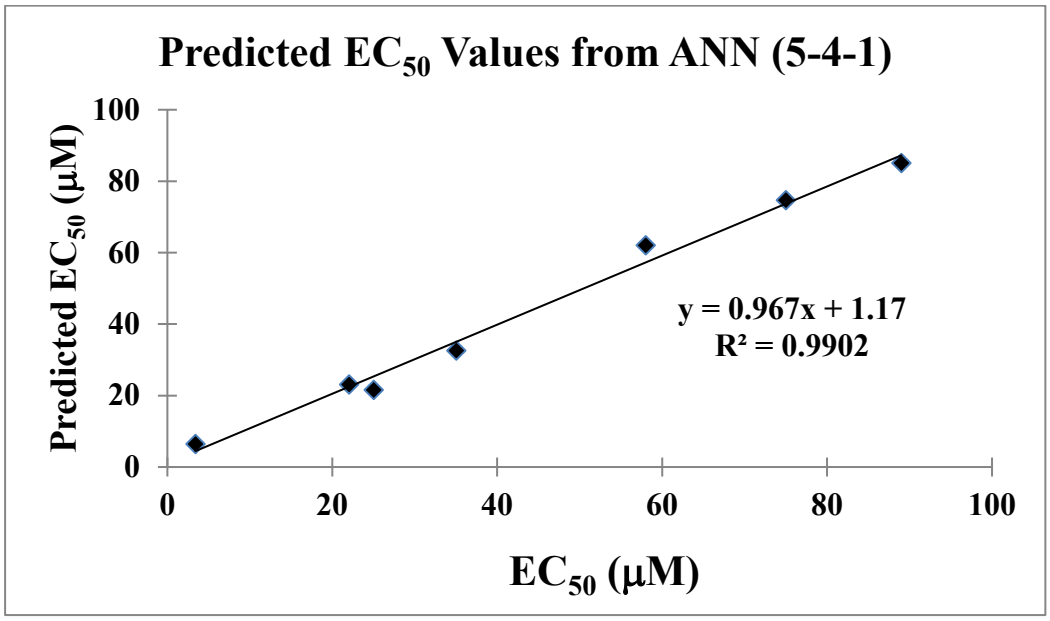


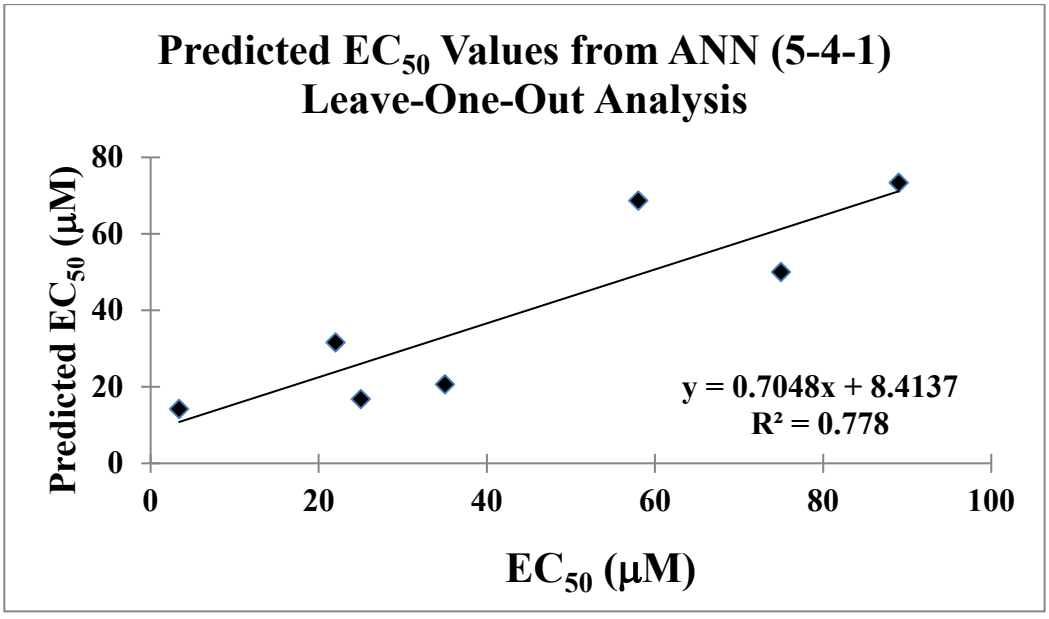
Figure S5g. **1g** 35 μM

Figure S6. a). Correlation of 5-4-1 artificial neural net (ANN) generated from 5 output scores from MOE docking. b). Correlation of 5-4-1 artificial neural net (ANN) with Leave-One-Out analysis generated from same 5 output scores from MOE docking.

A).



B).



Supplementary Material

References:

[1] J. Nagarapu, H. K. Mateti, R. Gaikwad, M. S. Bantu, S. Rani, N. J. P. Subhashini, *J. Biorg. Med. Chem. Lett.* **2011**, *21*, 4138-4140.

[2] J. M. Contreras, Y. M. Rival, S. Chayer, J. J. Bourguignon, C. G. Wermuth, *J. Med. Chem*., **1999**, *42*, 730-741.

[3] G. Lukinavičius, V. Lapiené, Z. Staševskij, C. Dalhoff, E. Weinhold, S. Klimašauskas, *J. Am. Chem. Soc*, **2007**, *129*, 2758-2759.

[4] Y. Liu, T. M. Reineke, *Biomacromolecules*, **2010**, *11*, 316-325.

[5] D. L. Boger, D. Yohannes, *J. Org. Chem*., **1989**, *54*, 2498-2502.

[6] M. A. Parker, T. Hermann, E. Satkiewicz, B. M. Bergdahl, *Molecules*, **2011**, *16*, 281-290.

[7] S. Zhou, K. D. Rynearson, K. Ding, N. D. Brunn, T. Hermann, *Bioorg. Med. Chem.* **2013**, *21*, 6139-6144.

[8] J. Parsons, M. P. Castaldi, S. Dutta, S. M. Dibrov, D. L. Wyles, T. Hermann, *Nat. Chem. Biol.,* **2009**, *5*, 823-825.

[9] S. M. Dibrov, K. Ding, N. Brunn, M. Parker, B. M. Bergdahl, D. L. Wyles, T. Hermann, *Proc. Natl. Acad. Sci. U. S. A*., **2012**, *109*, 5223-5228.

[10] T.A., Halgren, *J. Comp. Chem.,* **1996**, *17*, 490-512.

[11] P. R. Gerber, K. Müller, *J. Comput. Aided Mol. Des.*, **1995**, *3*, 251–68.