Supporting Information

Identification and development of 2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one inhibitors targeting bromodomains within the Switch/Sucrose Non-Fermenting complex

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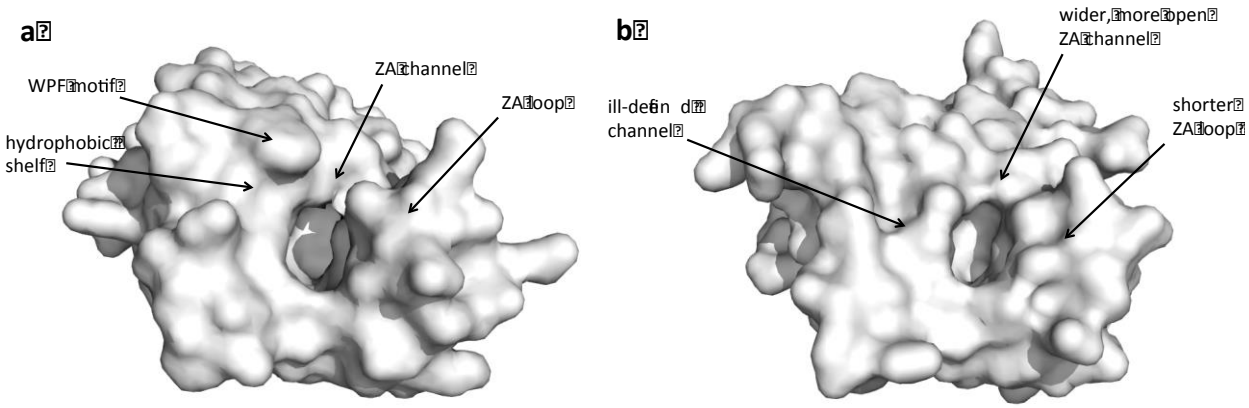
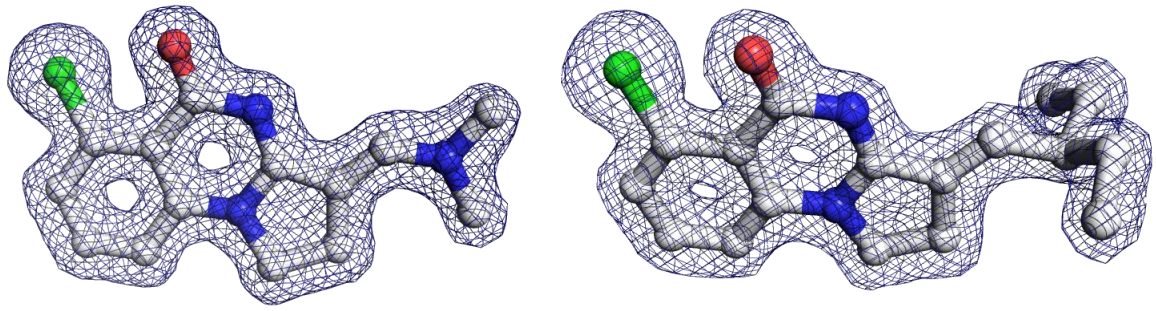
SUPPLEMENTARY FIGURES AND TABLES

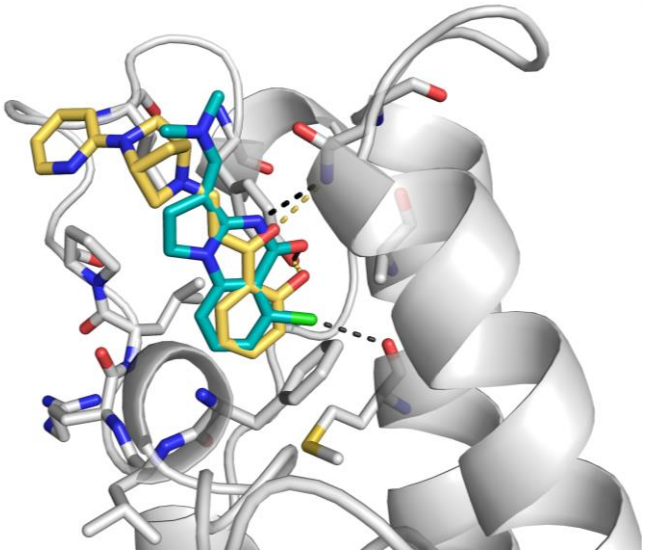
Supplementary Figure 1: Comparison of the surface view of the KAc binding sites of (a) BRD4(1) (PDB 3UW9) and (b) PB1(5) (PDB 3G0J).



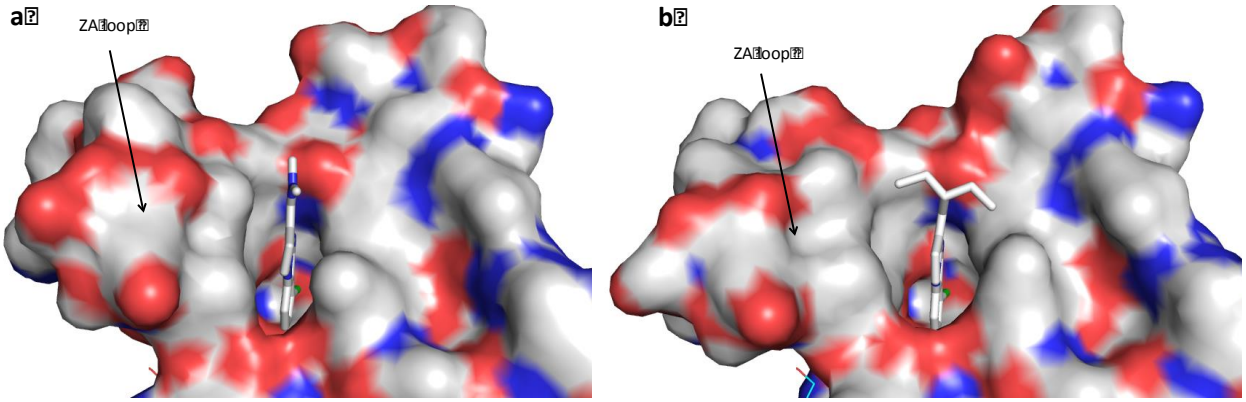
Supplementary Figure 2: Experimental electron density map (2Fo-Fc) contoured at 2s around (a) compound **18** and (b) compound **28**.



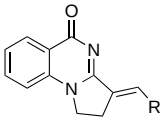
Supplementary Figure 3: Comparison of the binding modes of PFI-3 (yellow) with SMARCA2 (PDB 5DKD) and **18** (blue) with PB1(5) (PDB 5FH7). Hydrogen bonds are indicated by dotted yellow and black lines respectively.

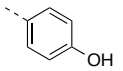
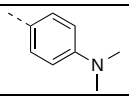
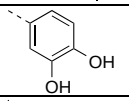
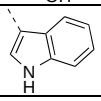


Supplementary Figure 4. Images of the crystal structures 5FH7 and 5FH8 showing the shift in the ZA loop from a surface perspective. (a) **18** with PB1(5). (b) **28** with PB1(5).



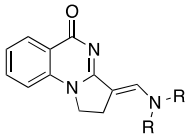
Supplementary Table 1. Influence of R side chain on binding of commercially available 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones to PB1(5) bromodomain as assessed by DSF.

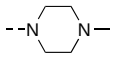
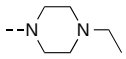
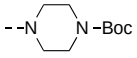
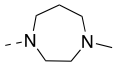


R	PB1(5) ΔT_m (°C)[a]
	2.0
	1.0
	0.5
	2.2
	0.2
	0.1
	3.7
	3.0

[a] Values shown are the average of a single replicate.

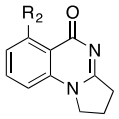
Supplementary Table 2. Selectivity of early stage analogues against non-SWI/SNF bromodomains.



Cpd	R	PB1(5) ΔT_m (°C) [a]	BRD9A ΔT_m (°C) [b]	BRPF1B ΔT_m (°C) [b]	CECR2A ΔT_m (°C) [b]
5		4.2 ± 0.6	0.2	0.1	0.1
9		4.3 ± 0.4	1.0	0.0	0.2
10		4.4 ± 0.6	0.2	0.0	0.1
11		1.1 ± 0.7	0.8	0.0	0.1
12		5.8 ± 0.1	0.5	0.2	0.3
13		5.0 ± 0.5	0.8	0.0	0.1
14		4.7 ± 0.6	0.7	0.2	0.1
15		3.5 ± 0.2	0.0	0.2	0.0

[a] Values shown are the average of three replicates and standard deviation. [b] Values are a single measurement.

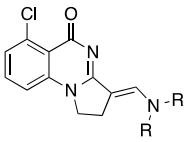
Supplementary Table 3: Binding of substituted core scaffolds.

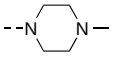


Cpd	R_2	PB1(5) ΔT_m (°C) [a]
4	H	0.0 ± 0.4
16c	Me	0.0 ± 0.6
17c	F	-0.1 ± 0.8
18c	Cl	2.6 ± 0.3
19c	Br	3.1 ± 0.3
20c	OMe	-0.6 ± 0.5
21c	OH	-0.1 ± 0.4

[a] Values shown are the average of three replicates and standard deviation.

Supplementary Table 4: Selectivity of chlorinated analogues against non SWI/SNF bromodomains

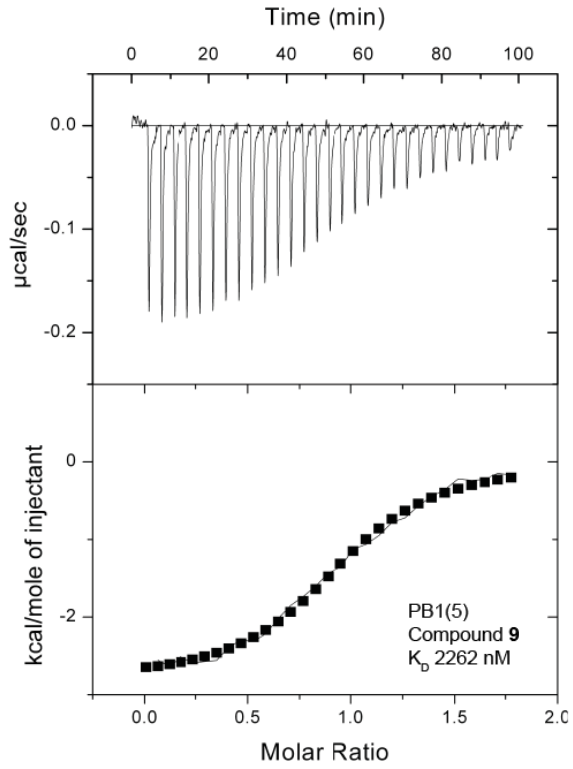


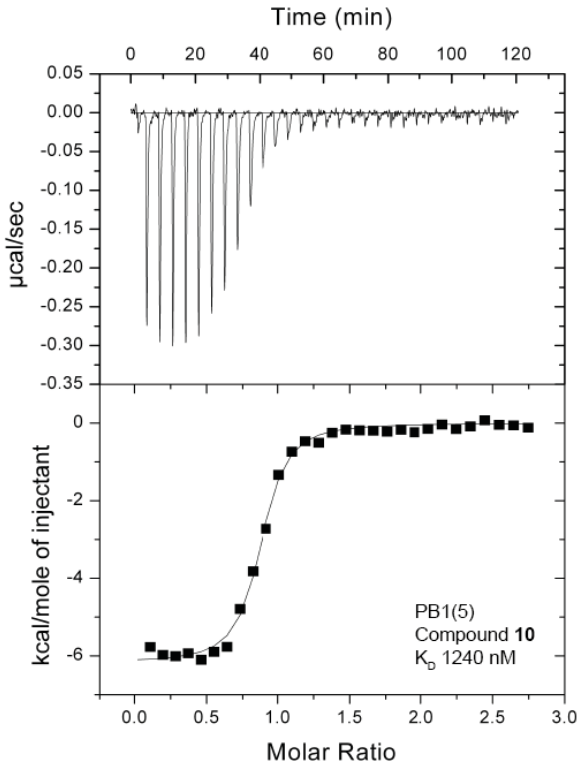
Cpd	R	PB1(5) ΔT_m (°C) [a]	BRD4(1) ΔT_m (°C) [b]	CREBBP ΔT_m (°C) [b]	PCAF ΔT_m (°C) [b]	TRIM33B ΔT_m (°C) [b]
18		8.4 ± 0.6	0.3	0.0	0.2	0.2
24		9.8 ± 0.4	1.0	0.0	0.9	-0.1
25		7.4 ± 1.2	0.4	0.1	0.8	0.9
26		10.2 ± 0.1	-0.1	0.1	0.4	0.4

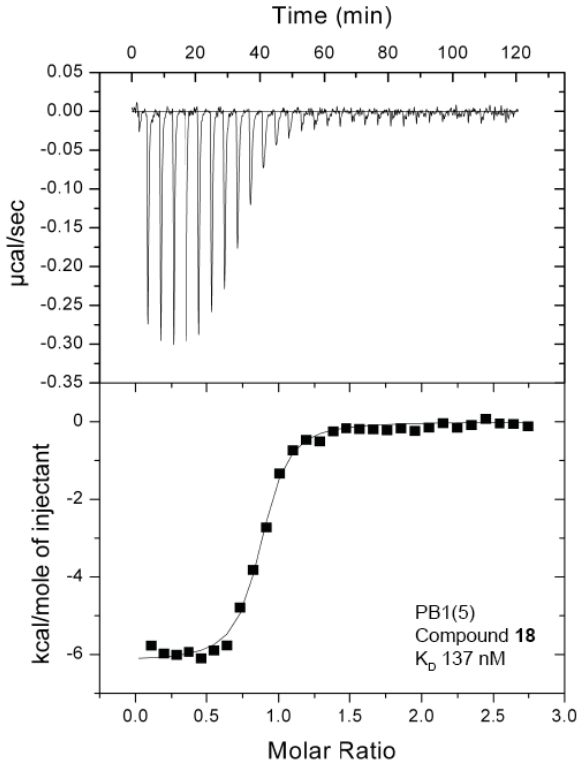
[a] Values shown are the average of three replicates and standard deviation. [b] Values are a single measurement.

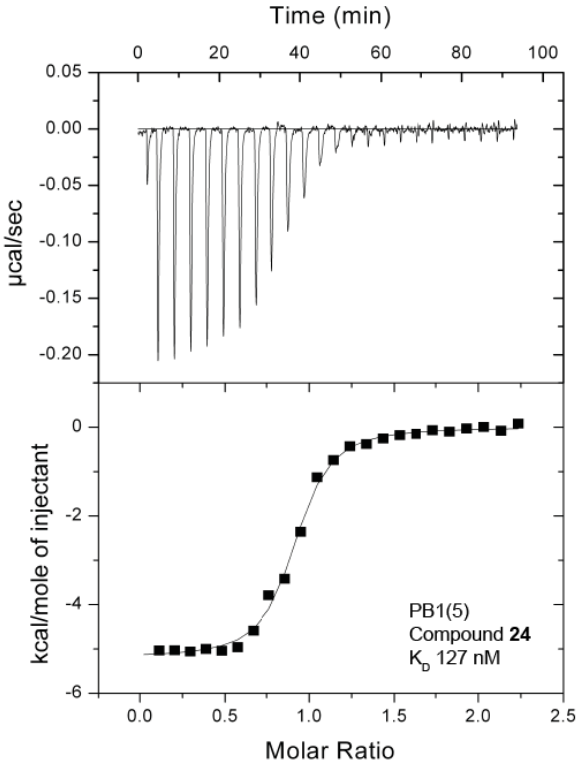
Supplementary Table 5: Summary of isothermal titration calorimetry data and traces.

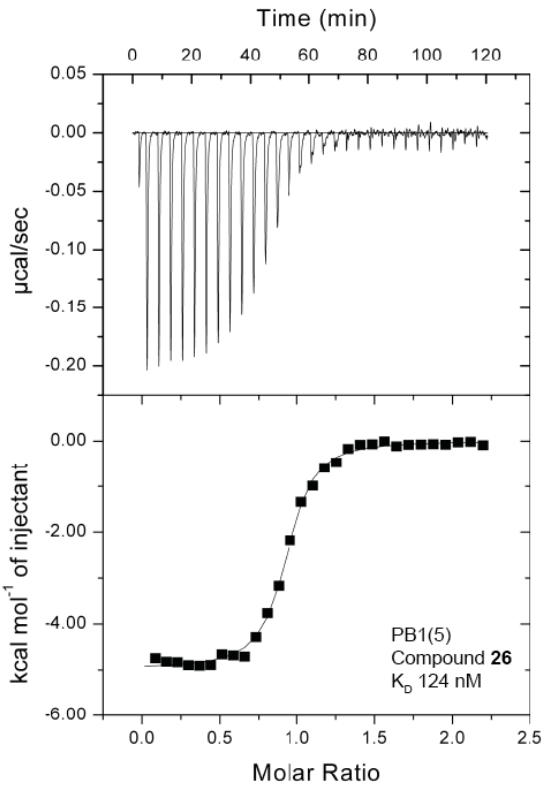
Cpd	Target	N	K×10^6 (M^{-1})	K_D (nM)	ΔH (kcal/mol)	TΔS (kcal/mol)	ΔG (kcal/mol)
9	PB1(5)	0.93	0.44 ± 0.02	2262 (2388-2149)	-2.860 ± 0.029	4.717	-7.577
10	PB1(5)	0.98	0.80 ± 0.08	1240 (1384 – 1132)	-2.652 ± 0.068	5.274	-7.926
18	PB1(5)	0.85	7.29 ± 0.91	137 (157-122)	-6.177 ± 0.069	3.018	-9.195
24	PB1(5)	0.89	7.86 ± 0.89	127 (143-114)	-5.200 ± 0.056	4.043	-9.243
26	PB1(5)	0.91	8.09 ± 0.66	124 (135-114)	-4.965 ± 0.034	4.307	-9.272
	SMARCA2B	1.09	3.81 ± 0.24	262 (280-198)	-3.302 ± 0.016	5.508	-8.810
	SMARCA4	0.91	2.40 ± 0.16	417 (446-391)	-3.727 ± 0.023	4.835	-4.838
27	PB1(5)	0.92	7.05 ± 0.68	142 (157-129)	-4.363 ± 0.035	4.835	-9.198
28	PB1(5)	0.93	6.22 ± 0.66	170 (189-154)	-6.748 ± 0.058	2.362	-9.110
	SMARCA4	0.65	0.49 ± 0.12	2033 (2660-1645)	-1.174 ± 0.058	6.446	-7.620

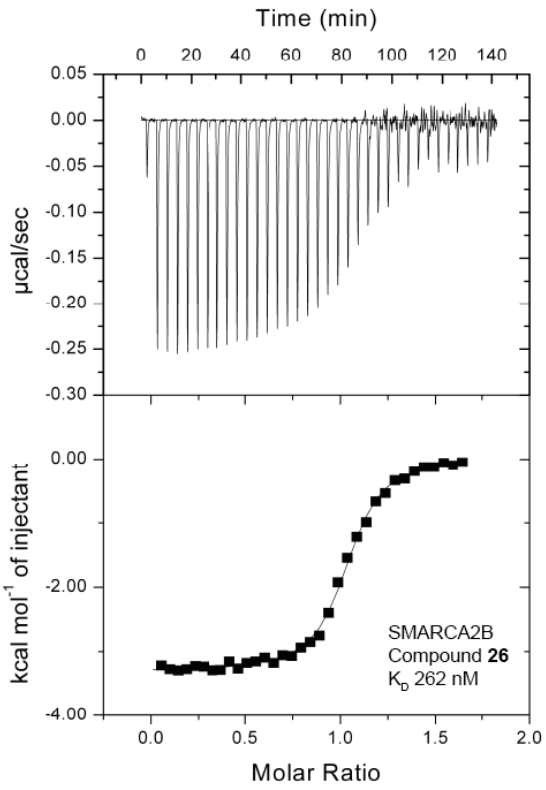

Time (min)
µcal/sec
kcal/mole of injectant
Molar Ratio
PB1(5)
Compound 9
K_D 2262 nM

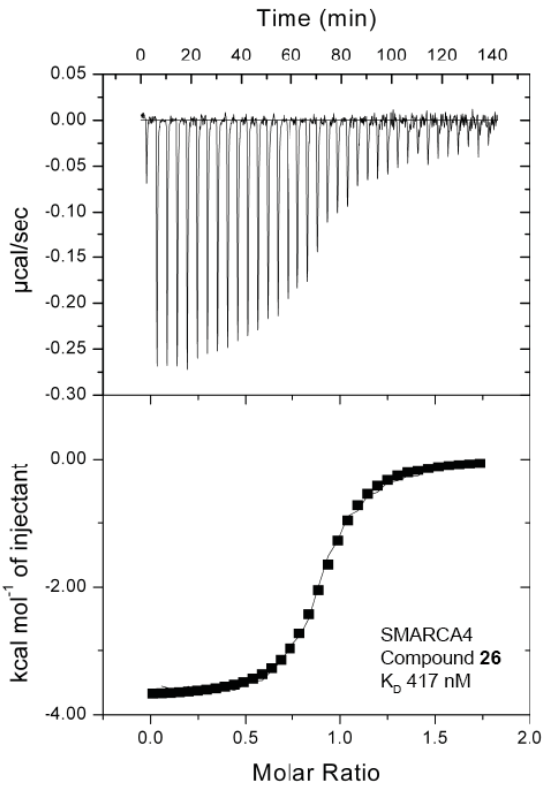

Time (min)
µcal/sec
kcal/mole of injectant
Molar Ratio
PB1(5)
Compound 10
K_D 1240 nM

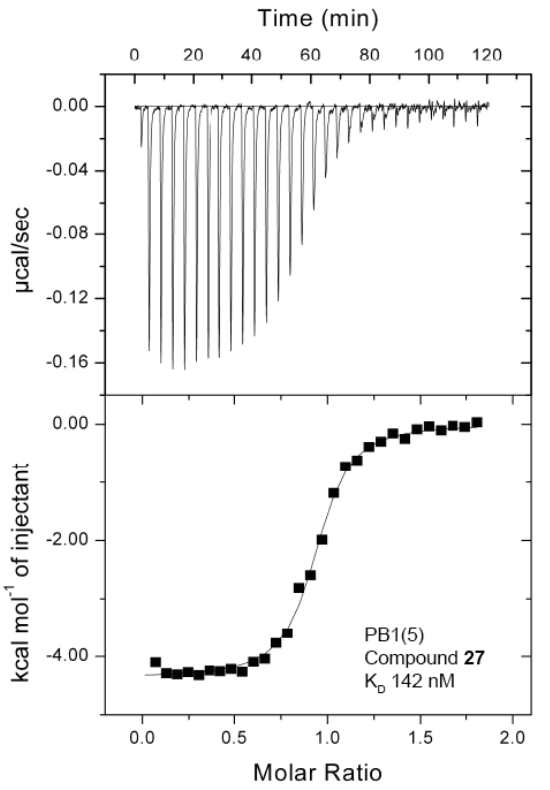

Time (min)
µcal/sec
kcal/mole of injectant
Molar Ratio
PB1(5)
Compound 18
K_D 137 nM

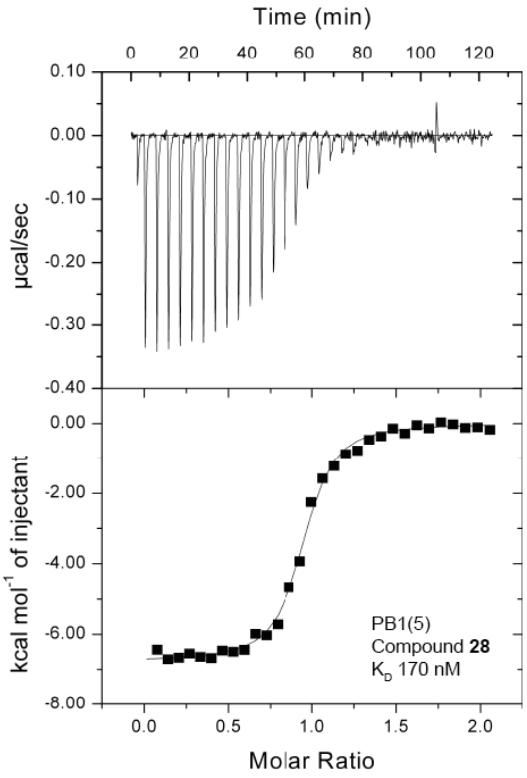

Time (min)
µcal/sec
kcal/mole of injectant
Molar Ratio
PB1(5)
Compound 24
K_D 127 nM

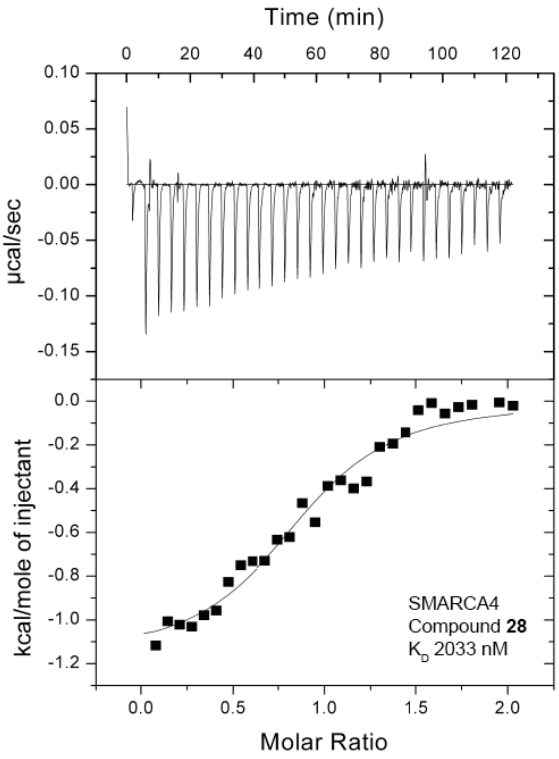

Time (min)
µcal/sec
kcal mol-1 of injectant
Molar Ratio
PB1(5)
Compound 26
KD 124 nM


Time (min)
µcal/sec
kcal mol-1 of injectant
Molar Ratio
SMARCA2B
Compound 26
KD 262 nM


Time (min)
µcal/sec
kcal mol-1 of injectant
Molar Ratio
SMARCA4
Compound 26
KD 417 nM


Time (min)
µcal/sec
kcal mol-1 of injectant
Molar Ratio
PB1(5)
Compound 27
KD 142 nM


Time (min)
µcal/sec
kcal mol-1 of injectant
Molar Ratio
PB1(5)
Compound 28
KD 170 nM


Time (min)
µcal/sec
kcal/mole of injectant
Molar Ratio
SMARCA4
Compound 28
KD 2033 nM

Supplementary Table 6: Data collection and refinement statistics

Data Collection			
PDB ID	**5FH6**	**5FH7**	**5FH8**
Protein/Ligand	PB1(5)/ **10**	PB1(5)/ **18**	PB1(5)/ **28**
Space group	P 1 2_1 1	P 2_1 2_1 2_1	P 1 2_1 1
Cell dimensions: a, b, c (Å) α, β, γ (deg)	41.87 136.42 56.75 90.00 92.33 90.00	41.98 59.21 138.90 90.00 90.00 90.00	41.98 59.21 138.90 90.00 90.00 90.00
Resolution* (Å)	29.73 (2.30)	59.21 (1.47)	64.55 (1.55)
Unique observations*	28108 (2581)	56934 (2939)	68763 (2902)
Completeness* (%)	99.3 (93.3)	95.2 (68.3)	90.6 (52.3)
Redundancy*	6.7 (6.2)	7.8 (2.8)	4.7 (3.4)
Rmerge*	0.086 (0.721)	0.052 (0.565)	0.053 (0.696)
I/ σI*	11.8 (2.2)	21.4 (2.1)	13.3 (1.5)
Refinement			
Resolution (Å)	2.30	1.45	1.55
R_{work} / R_{free} (%)	25.4 / 31.0	18.7 / 20.9	18.8 / 22.5
Number of atoms (protein/other/water)	3648 / 82 / 13	1940 / 46 / 212	3705 / 92 / 257
B-factors (Å^2) (protein/other/water)	79.02/70.17/66.73	23.71/21.81/32.51	29.38/21.85/32.79
r.m.s.d bonds (Å)	0.013	0.016	0.015
r.m.s.d angles (^{o})	1.750	1.649	1.632
Ramachadran Favoured (%)	97.21	100.00	100.00
Allowed (%)	2.32	0.00	0.00
Disallowed (%)	0.47	0.00	0.00

BIOLOGICAL EVALUATION

Protein Expression and Purification.

Proteins were cloned, expressed, and purified as previously described.[1]

DSF T_m Shift Assay.

Bromodomain DSF T_m assays were performed using a Mx3005p real-time PCR machine (Agilent) and low profile 96-well PCR plates (AB-0700, Life Technologies). Protein was buffered in 10 mM HEPES, pH 7.5, 500 mM NaCl and assayed at a concentration of 2 μM with 10 μM inhibitor concentration and 1:1000 SyproOrange (Invitrogen). Excitation and emission filters were set to 465 and 590 nm respectively. The temperature was raised by 3 °C per 1 min from 25–95 °C, and fluorescence readers were taken at each interval. Data analysis was carried out as described previously.[2]

AlphaScreen Displacement Assay.

AlphaScreen assays were based on a reported protocol, with minor variations.[3] In place of a biotinylated peptide, a biotinylated ligand was used at 25 nM final concentration.

Isothermal Calorimetry Experiments.

Calorimetric experiments were performed on a VP-ITC micro-calorimeter (MicroCal™, LLC Northampton, MA). Protein solutions were buffer exchanged by dialysis into buffer 20 mM Hepes pH 7.5, 150 mM NaCl, and 0.5 mM TCEP. All measurements were carried out at 293.15 K while stirring at 286 rpm. The micro syringe was loaded with protein solutions ranging from

113–262 μM, compound solutions were prepared at concentrations between 15–30 μM in 2 mL for the cell. All injections for PB1(5) were performed using an initial injection of 2 μl followed by 30 injections of 8 μl with a duration of 16 sec per injection and a spacing of 240 sec between injection. Injections for SMARCA2B and SMARCA4 were performed using an initial injection of 2 μl followed by 35 injections of 8 μl with a duration of 16 sec per injection and a spacing of 240 sec between injection.The data were analyzed with the MicroCal ORIGIN software package employing a single binding site model. The first data point was excluded from the analysis. Thermodynamic parameters were calculated ($\Delta G = \Delta H - T\Delta S = -RTlnK_B$ where ΔG, ΔH and ΔS are the changes in free energy, enthalpy and entropy of binding, respectively).

Fluorescence Recovery After Photobleaching (FRAP)

FRAP studies were performed essentially as described. In brief, U2OS cells were transfected (Fugene HD; Roche) with mammalian over-expression constructs encoding GFP fused to the N-terminus of full length wild-type or mutant SMARCA2 (1). The imaging system consisted of a Zeiss LSM 710 laser-scanning and control system (Zeiss) coupled to an inverted Zeiss Axio Observer.Z1 microscope equipped with a high-numerical-aperture (N. A. 1.3) 40 x oil immersion objective (Zeiss). Samples were placed in an incubator chamber in order to maintaining temperature and humidity. FRAP and GFP fluorescence imaging were both carried out with an argon-ion laser (488 nm) and with a PMT detector set to detect fluorescence between 500-550 nm. Once an initial scan had been taken, a region of interest corresponding to approximately 50 % of the entire GFP positive nucleus was empirically selected for bleaching. A time lapse series was then taken to record GFP recovery using 1% of the power used for bleaching. The image datasets and fluorescence recovery data were exported from ZEN 2009, the microscope control

software, into Origin to determine the average half-time for full recovery for 10-20 cells per treatment point. Data were analysed using one-way ANOVA with Tukey's multiple comparisons test.

X-RAY CRYSTALLOGRAPHY

Crystallization.

PB1 domain 5 construct (Uniprot identifier as PB1_HUMAN Q86U86-1 fragment 653-774) was used for crystallographic studies in complex with the inhibitors. Aliquots of the purified protein were set up for crystallization using a mosquito® crystallization robot (TTP Labtech). Coarse screens were typically setup onto Greiner 3-well plates using three different drop ratios of precipitant to protein per condition (200+100 nL, 150+150 nL and 100+200 nL). All crystallizations were carried out using the sitting drop vapour diffusion method at 277.15 K. PB1 bromodomain 5 crystals in complex with the compound **10** (5 mM final concentration) were obtained by mixing 200 nL of the protein (7.6 mg/ml) and 100 nL crystallization buffer (0.2 M lithium sulfate, 0.1 M bis-tris pH 6.5, 25% PEG3350); PB1 bromodomain 5 crystals in complex with the compound **18** (2.5 mM final concentration) were grown by mixing 100 nL of the protein (6.5 mg/ml) and 200 nL crystallization buffer (0.1 M magnesium formate, 15% PEG3350); PB1 bromodomain 5 crystals in complex of the compound **28** (2.5 mM final concentration) were grown by mixing 150 nL of the protein (6.5 mg/ml) and 150 nL crystallization buffer (10% MPD, 0.1 M bicine pH 9).

Data Collection and Structure Solution.

Complex crystals were cryo-protected using the well solution supplemented with additional 20 % ethylene glycol and was flash frozen in liquid nitrogen. Data was collected at Diamond Light Source beamline I03 at a wavelength of 0.9763 Å. Indexing and integration was carried out using XDS[4] and scaling was performed with XSCALE[4]. Initial phases were calculated by molecular replacement with PHASER[5] using the apo template structure 2OSS.pdb. Unique and initial solutions were improved in a total of 50 cycles of automated protein chain tracing starting from existing model and computed using ARP/wARP.[6] Further manual building with COOT[7] and refinement against maximum likelihood target using REFMAC5.[8] Thermal motions were analysed using TLSMD and hydrogen atoms were included in late refinement cycles. GRADE[9] was used to generate compound coordinates and cif files. All model validations were carried out using MolProbity[10] Data collection and refinement statistics are compiled in Supplemental Table 6. The models and structure factors have been deposited with PDB accession codes: 5FH6.pdb (**10**), 5FH7.pdb (**18**) and 5FH8.pdb (**28**).

GENERAL CHEMISTRY METHODS

All reactions were performed using oven-dried glassware (200 °C) under a dry argon atmosphere unless otherwise stated or aqueous reagents were employed. All solvents used in reactions were dried and distilled according to standard protocols. All reagents were used as supplied or purified using standard procedures as necessary.

Flash column chromatography (FCC) was performed using Sigma Aldrich silica gel pore size 60 Å, 230 – 400 mesh under air pressure. The solvents used for FCC were distilled before use. "Hexanes" refers to petroleum ether distillate (boiling point – 40-60 °C). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} pre-coated glass-backed plates and visualised by ultraviolet radiation (254 nm), potassium permanganate or ninhydrin as appropriate. Preparative TLC was performed using silica gel GF 500 micron UNIPLATES (Analtech).

^{1}H NMR spectra were recorded on Bruker Avance DPX-600 (600 MHz), Bruker DPX-400 (400 MHz) or Bruker DCH Cryoprobe (500 MHz). Chemical shifts are reported in ppm with the residual solvent peak as the internal standard ($CDCl_3$ – 7.26 ppm, d_6-DMSO – 2.50 ppm, CD_3OD – 3.31 ppm, D_2O – 4.79 ppm). ^{13}C NMR were recorded on Bruker Avance DPX-600 (150 MHz), Bruker DPX-400 (100 MHz) or Bruker DCH Cryoprobe (125 MHz), with complete proton decoupling. Chemical shifts are reported in ppm with the solvent response as the internal standard ($^{13}CDCl_3$ – 77.0 ppm, t; ^{13}C-d_6-DMSO – 39.5 ppm, septet; $^{13}CD_3OD$ – 49.0 ppm, q). All data are reported according to the following format: chemical shift δ/ppm (integration (^{1}H only), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent, m = multiplet, or combinations thereof. Unless otherwise stated, ^{13}C signals are singlets), coupling constants *J* Hz, assignment. ^{1}H NMR signals are reported to 2 decimal places and ^{13}C signals to 1

decimal place except when this would give multiple identical signals. In these cases, an additional decimal place is reported to differentiate signals. ^{1}H COSY, ^{13}C-DEPT, HSQC, HMBC, and NOESY have been used where appropriate to enable structural determination and full assignment of spectra to the greatest possible extent. Signals that could not be identified unambiguously are reported with all possible assignments e.g. H1/H2. Overlapping signals that could not be de-convoluted are reported with assignments in list format e.g. H1, H2, & H2.

High resolution mass spectrometry (HRMS) was performed on a Waters Micromass LCT Premier spectrometer using electrospray ionisiation and Micromass MS software, or on a ThermoFinnigan Orbitrap Classic using positive ion electrospray by the Mass Spectrometry Service, Department of Chemistry, University of Cambridge. Signals are reported to 4 decimal places and are within ± 5 ppm to theoretical values.

Infrared spectra were recorded as thin films on a Perkin-Elmer Spectrum One FTIR spectrometer and only selected peaks are reported (s = strong, m = medium, w = weak, br = broad, sh = shoulder).

Melting points were collected using a Stanford Research Systems Optimelt automated melting point system using a gradient of 1 °C per min and are reported as a range to the nearest degree.

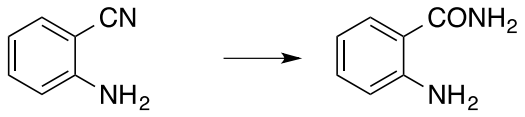
Purities of compounds were >95% as assessed by liquid chromatography mass spectrometry (LCMS) and additionally by high performance liquid chromatography (HPLC) for key compounds, unless otherwise stated. LCMS analysis was performed with an Alliance HT Waters 2795 separations module coupled to a Waters Micromass ZQ Quadrupole Mass Analyser with accuracy no greater than 0.4 Da. A gradient of 10 mM ammonium acetate containing 0.1% formic acid to 95% MeCN over 8 min was used. Analytical HPLC separation was carried out on

a Waters μBondapak™ column (C18, 3.9 × 150 mm) using a flow rate of 1 mL/min with detection at 310 nm. The method was as follows, with H_2O and 0.1 % formic acid as eluent A and MeOH and 0.1% formic acid as eluent B.

Time (min)	A (%)	B (%)
0	95	5
20	30	70
25	30	70
30	95	5

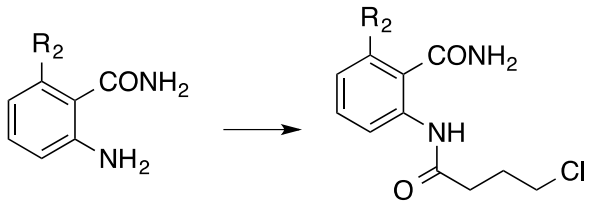
GENERAL SYNTHETIC PROCEDURES

General procedure A: microwave-assisted catalytic hydration of organonitrile intermediates A



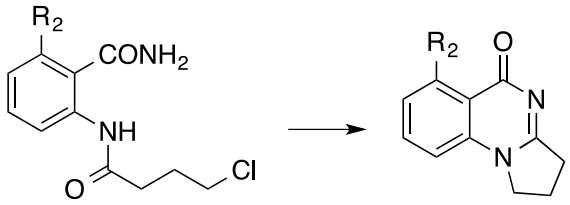
Adapted from a literature procedure,[11] the appropriate organonitrile (1.0 eq.) and K_2CO_3 (0.2 eq.) were added to a microwave tube with a stir-bar with deionized water (8.5 mL per mmol substrate). After irradiation under microwave at 150 °C for 30 minutes, the reaction mixture was cooled, extracted with EtOAc (3 × 20 mL), the combined phases dried over $MgSO_4$ and excess solvent removed *in vacuo*. The residue was purified by FCC, if required, to give the title compound.

General procedure B: synthesis of intermediates B



A solution of the appropriate substituted 2-aminobenzamide (1.0 eq) in THF (2.5 mL per mmol substrate) was cooled to 0 °C and triethylamine (2.0 eq) then the appropriate acid chloride (1.2 eq) in THF (2 mL per mmol substrate) were added to the stirred solution. The reaction was stirred at room temperature until completion as indicated by TLC, when the mixture was diluted with EtOAc and quenched with $NaHSO_4$ (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), combined organic phases dried over $MgSO_4$, excess solvent removed *in vacuo* and the residue purified by FCC to give the title compound.

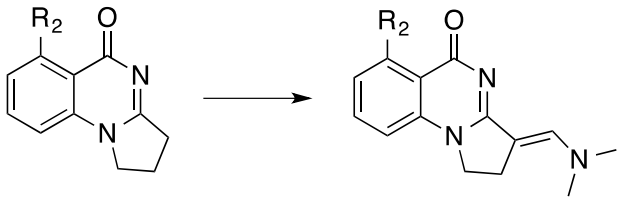
General procedure C: cyclisation to intermediates C



To a solution of the appropriate substrate (1.0 eq) in THF (10 mL per mmol substrate) was added ^{t}BuOK (2.0 eq). The reaction was stirred at room temperature until TLC indicated completion, then solvent was removed *in vacuo*, the resulting residue re-dissolved in CH_2Cl_2 (20 mL) and $NaHCO_3$ (15 mL), and the aqueous layer extracted with CH_2Cl_2 (5 × 20 mL). The combined

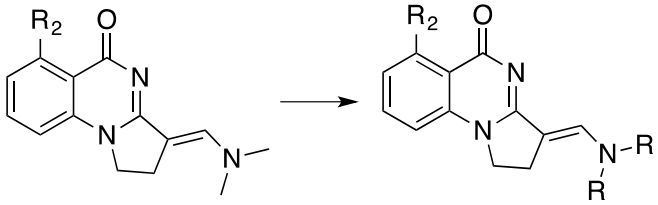
organic phases were dried over $MgSO_4$ and solvent removed *in vacuo*. The title compound was obtained after purification of the residue by FCC.

General procedure D: N,N dimethylformamide condensation



To a solution of the appropriate substrate (1.0 eq) in DMF was added phosphoryl trichloride (2.0 eq). The reaction was heated to 70 °C and followed by TLC until completion, when the solution was cooled to room temperature, diluted with CH_2Cl_2 and quenched using $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL), dried using Na_2SO_4 and solvent removed *in vacuo*. The residue was co-evaporated with toluene (3 × 5 mL), then purified by FCC to give the title compound.

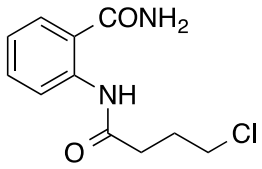
General procedure E: displacement reaction



To a solution of the appropriate dimethylamino substituted substrate (1.0 eq) in EtOH or 1:1 EtOH:CH_2Cl_2 for chlorinated substrates (2.5 mL per mmol substrate) was added DMAP (0.1 eq) and the appropriate amine (5.0 eq). The reaction was heated to 70 °C in a sealed tube for a minimum of 24 hours. When completion was indicated by TLC, the solvent was removed *in vacuo*, and purified by FCC to give the title compound.

COMPOUND CHARACTERIZATION DATA

2-(4-Chlorobutanamido)benzamide (**3**)

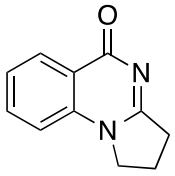


Anthranilamide (4.95 g, 36.4 mmol) and 4-chlorobutanoyl chloride (6.17 g, 43.7 mmol) were reacted according to general procedure B. Purification by FCC (gradient 50% EtOAc/hexanes to 5% MeOH/EtOAc) gave **3** (8.08 g, 33.6 mmol, 92%) as an off-white amorphous solid.

MP 117–119 °C, lit. 114–115 °C;[12] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 11.24 (1H, s, NH), 8.61 (1H, d, *J* 8.3 Hz), 7.54 (d, *J* 7.8 Hz), 7.49 (dt, *J* 8.1, 0.8 Hz), 7.08 (t, *J* 7.5 Hz), 6.32 (1H, br, NH), 5.88 (1H, br, NH), 3.65 (2H, t, *J* 6.4 Hz), 2.60 (2H, t, *J* 7.1 Hz), 2.20 (2H, quint., *J* 6.8 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.4. 170.8, 140.2, 133.5, 127.4, 122.9, 121.7, 118.7, 44.4, 35.2, 28.1; **FTIR** (neat, ν_{max} cm^{-1}) 3400 (s), 3270 (m), 3254 (w), 3221 (m), 1669 (s), 1667 (s), 1615 (m), 1591 (s), 1578 (s), 1519 (s), 757 (m); $\boldsymbol{R_f}$ 0.36 (50% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{11}H_{14}N_2O_2{}^{35}Cl$ $[M+H]^+$ 241.0744, found 241.0744; **LC/MS** $[M+H]^+$ found 241.5, purity 100%.

The data was in agreement with a reported example.[12]

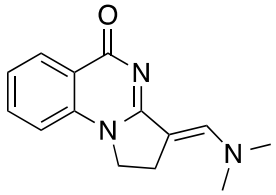
2,3-Dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **(4)**



3 (987 mg, 4.10 mmol) was cyclised according to general procedure C, and after FCC (3% MeOH/CH_2Cl_2) the title compound **4** (524 mg, 2.81 mmol, 69%) was obtained as a white amorphous solid.

MP 213–216 °C, lit. 217–218 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* 8.0, 1.1 Hz), 7.66 (1H, ddd, *J* 8.4, 7.3, 1.5 Hz), 7.40 (1H, ddd, *J* 8.1, 7.3, 0.9 Hz*)*, 7.17 (1H, d, *J* 8.2 Hz), 4.22 (2H, app t, *J* 7.4 Hz), 3.15 (2H, app t, *J* 7.8 Hz), 2.41–2.36 (2H, m,); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.3, 166.5, 138.8, 133.7, 128.9, 125.9, 118.9, 114.6, 48.8, 32.9, 18.7; **FTIR** (neat, ν_{max} cm^{-1}) 3059 (w), 2953 (w), 2925 (w), 2897 (w), 1634 (s), 1593 (s), 1533 (s), 1501 (s), 1461 (m), 1420 (m), 778 (m); ***R*$_f$** 0.17 (5% MeOH/$C1_2Cl_2$); **HRMS** (ESI+) calculated for $C_{11}H_{11}N_2O$ $[M+H]^+$ 187.0866, found 187.0870; **LC/MS** $[M+H]^+$ found 187.4, purity 100%.

(*E*)-3-((Dimethylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**5**)

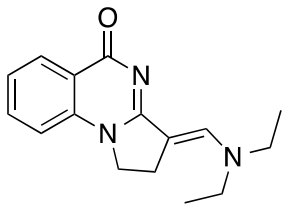


4 (372 mg, 2.00 mmol) was reacted according to general procedure D. Purification by FCC (4% MeOH/CH_2Cl_2) gave **5** (357 mg, 1.48 mmol, 74%) as a tan amorphous solid.

Decomposition 251–252 °C; **^{1}H NMR** (600 MHz, *d*$_6$-DMSO) δ 7.92 (1H, dd, *J* 7.8, 1.2 Hz), 7.64 (1H, ddd, *J* 7.8, 7.2, 1.2 Hz), 7.39 (1H, t, *J* 1.2 Hz), 7.27 (1H, dt, *J* 7.5, 0.6 Hz), 7.23 (1H, d, *J* 8.4 Hz), 4.10–4.08 (2H, m,), 3.21 (2H, t, *J* 7.8 Hz), 3.09 (6H, s); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.2, 163.9, 144.0, 139.5, 132.8, 127.1, 123.4, 118.8, 114.2, 94.4, 45.4, 40.1, 22.7; **FTIR**

(neat, ν_{max} cm^{-1}) 1646 (m), 1622 (m), 1598 (m), 1514 (s), 1495 (s), 1397 (m), 1373 (m), 1314 (m), 1109 (m), 776 (m); $\boldsymbol{R_f}$ 0.21 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1293, found 242.1295; **LC/MS** $[M+H]^+$ found 242.5, purity 100%. **HPLC** R_t 7.55 min, purity 96.0%.

(*E*)-3-((Diethylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **(6)**

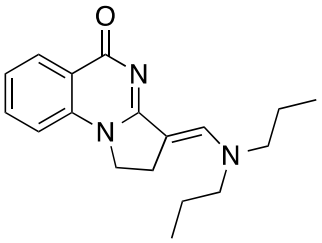


To a solution of **4** (81.0 mg, 0.435 mmol, 1.0 eq.) in CH_2Cl_2 (2.50 mL) was added *N,N*-dipropylformamide (242 µL, 2.18 mmol, 5.0 eq.) and $POCl_3$ (81.1 µL, 0.870 mmol, 2.0 eq.). The reaction mixture was refluxed for eight hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (3% MeOH/CH_2Cl_2) gave the title compound **6** (34.7 mg, 0.129 mmol, 30%) as a pale orange amorphous solid.

Decomposition 230 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* 7.9, 1.3 Hz), 7.72 (1H, t, *J* 1.6 Hz), 7.55 (1H, ddd, *J* 8.3, 7.4, 1.5 Hz), 7.26 (1H, m, H5), 6.97 (1H, d, *J* 8.1 Hz), 4.07 (2H, m), 3.35 (4H, q, *J* 7.3 Hz), 3.16 (2H, m), 1.22 (6H, t, *J* 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.3, 164.7, 143.5, 139.7, 132.9, 128.8, 123.9, 119.4, 113.0, 93.4, 46.8, 45.7, 23.6, 15.2, peak at 46.8 was broad in the ^{13}C NMR spectrum, but confirmed on the basis of a correlation in the

HSQC spectrum; **FTIR** (neat, ν_{max} cm^{-1}) 2970 (w), 2933 (w), 2893 (w), 1627 (m), 1587 (s), 1509 (s), 1487 (s), 1467 (s), 1404 (s); $\boldsymbol{R_f}$ 0.22 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{16}H_{20}N_3O$ $[M+H]^+$ 270.1606, found 270.1608.

(*E*)-3-((Dipropylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**7**)

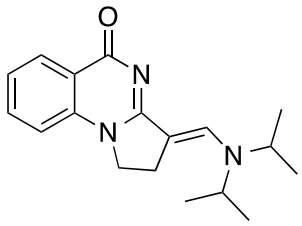


To a solution of **4** (40.0 mg, 0.215 mmol, 1.0 eq.), in CH_2Cl_2 (2.00 mL) was added *N,N*-dipropylformamide (160 µL, 1.08 mmol, 5.0 eq.) and $POCl_3$ (40.0 µL, 0.429 mmol, 2.0 eq.). The reaction mixture was refluxed for 48 hours, then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2) gave the title compound **7** (25.1 mg, 0.0844 mmol, 39%) as a pale orange amorphous solid.

Decomposition 90 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* 7.8, 1.1 Hz), 7.73 (1H, br s), 7.54 (1H, ddd, *J* 8.4, 7.4, 1.1 Hz), 7.25 (1H, t, *J* 7.6 Hz), 6.97 (1H, d, J 8.1 Hz), 4.07 (2H, app t, *J* 8.0 Hz), 3.23 (4H, t, *J* 7.7 Hz), 3.14 (2H, dt, *J* 7.7, 1.1 Hz), 1.63 (4H, sextet, *J* 7.4 Hz), 0.92 (6H, t, *J* 7.4 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.4, 164.8, 144.3, 139.8, 133.0, 128.8, 124.0, 119.5, 113.1, 93.2, 45.8, 23.7, 23.0, 11.1, N-*C*H- was not observed in the ^{13}C NMR spectrum; **FTIR** (neat, ν_{max} cm^{-1}) 2963 (m), 2937 (m), 2874 (w), 2194 (w), 1645 (m), 1615 (m), 1600 (m),

1598 (s), 1509 (s), 1487 (s), 1467 (s), 1404 (s); $\boldsymbol{R_f}$ 0.52 (10% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{18}H_{24}N_3O$ $[M+H]^+$ 298.1919, found 298.1916; **LC/MS** $[M+H]^+$ found 298.6, purity 100%.

(*E*)-3-((Diisopropylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**8**)

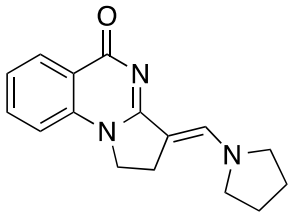


To a solution of **4** (40.0 mg, 0.215 mmol, 1.0 eq.), in CH_2Cl_2 (2.00 mL) was added *N,N*-diisopropylformamide (156 μL, 1.07 mmol, 5.0 eq.) and $POCl_3$ (40.0 μL, 0.429 mmol, 2.0 eq.). The reaction mixture was refluxed for 24 hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 8% MeOH/CH_2Cl_2) gave the title compound **8** (10.2 mg, 0.0344 mmol, 16%) as a tan amorphous solid.

MP 74–78 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.27 (1H, dd, *J* 7.8, 1.2 Hz), 7.84 (1H, br s), 7.55 (1H, ddd, *J* 8.2, 7.4, 1.5 Hz), 7.27–7.25 (1H, m), 6.98 (1H, d, *J* 8.1 Hz), 4.09–4.07 (2H, m), 3.93 (2H, br), 3.16 (2H, dt, *J* 8.1, 1.4 Hz), 1.29 (12H, d, *J* 6.6 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.2, 164.7, 139.72, 139.67, 133.0, 128.9, 123.9, 119.4, 112.9, 93.4, 45.7, 24.8, 22.8, N-<u>C</u>H- was not observed in the ^{13}C NMR spectrum; **FTIR** (neat, ν_{max} cm^{-1}) 3448 (br), 2979 (w), 2937 (w), 1635 (m), 1588 (s), 1508 (s), 1492 (s), 1441 (m), 1411 (s), 1360 (m), 1270 (s); $\boldsymbol{R_f}$ 0.37 (10%

MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{18}H_{23}N_3ONa$ $[M+Na]^+$ 320.1739, found 320.1739.; **LC/MS** $[M+H]^+$ found 298.6, purity 100%.

(*E*)-3-(Pyrrolidin-1-ylmethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**9**)

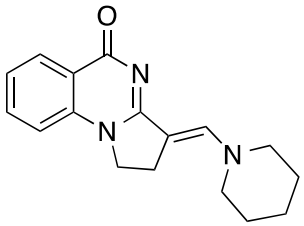


To a solution of **4** (21.5 mg, 0.115 mmol, 1.0 eq.) in CH_2Cl_2 (500 μL) was added 1-formylpyrrolidine (110 μL, 1.15 mmol, 10.0 eq.) and $POCl_3$ (21.5 μL, 0.230 mmol, 2.3 eq.). The reaction mixture was refluxed for four hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by FCC (8% MeOH/CH_2Cl_2) gave the title compound **9** (18.0 mg, 0.0673 mmol, 58%) as a tan amorphous solid.

MP 232–235 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (1H, dd, *J* 7.9, 1.3 Hz,), 7.65 (1H, s br,), 7.59 (1H, ddd, *J* 8.3, 7.4, 1.5 Hz), 7.32 (1H, ddd, *J* 8.0, 7.3, 1.0 Hz), 7.02 (1H, d, *J* 8.2 Hz), 4.14–4.11 (2H, m), 3.76–3.74 (4H, m), 3.00–3.48 (4H, m), 3.17 (2H, app dt, *J* 7.9, 1.6 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 164.4, 143.0, 139.5, 133.1, 128.9, 124.5, 119.5, 113.3, 95.6, 66.8, 50.4, 45.9, 24.0; **FTIR** (neat, ν_{max} cm^{-1}) 3213 (w, br), 2960 (w) 2874 (w), 1642 (m), 1604 (m), 1588 (s), 1512 (s), 1491 (s), 1400 (m), 1370 (s), 1292 (m); R_f 0.28 (5% MeOH/CH_2Cl_2); **HRMS**

(ESI+) calculated for $C_{16}H_{18}N_3O$ $[M+H]^+$ 268.1450, found 268.1459; **LC/MS** $[M+H]^+$ found 268.5, purity 100%.

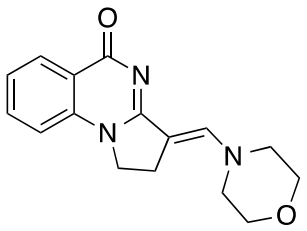
(*E*)-3-(Piperidin-1-ylmethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**10**)



To a solution of **4** (59.0 mg, 0.317 mmol, 1.0 eq.) in CH_2Cl_2 (1.00 mL) was added 1-formylpiperazine (107 μL, 0.951 mmol, 3.0 eq.) and $POCl_3$ (59.1 μL, 0.634 mmol, 2.0 eq.). The reaction mixture was refluxed for 28 hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave the title compound **10** (28.9 mg, 0.103 mmol, 32%) as a tan amorphous solid.

^{1}H NMR (600 MHz, d_6-DMSO) δ 7.93 (1H, dd, *J* 7.8, 1.2 Hz), 7.64 (1H, ddd, *J* 8.4, 7.8, 1.2 Hz), 7.40 (1H, s), 7.27 (1H, dt, *J* 7.8, 0.6 Hz), 7.23 (1H, d, *J* 8.4 Hz), 4.11 (2H, app t, *J* 7.8 Hz), 3.47–3.45 (4H, m), 3.11 (2H, app t, *J* 7.8 Hz), 1.63–1.57 (6H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 164.1, 142.4, 139.5, 132.9, 127.2, 123.4, 118.8, 114.2, 93.9, 50.9, 45.5, 26.1, 23.6, 23.2; **FTIR** (neat, ν_{max} cm^{-1}) 2934 (m), 2853 (m), 1643 (m), 1600 (sh), 1587 (s), 1510 (s), 1486 (s), 1439 (m), 1402 (s); R_f 0.30 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{17}H_{20}N_3O$ $[M+H]^+$ 282.1606, found 282.1615. **LC/MS** $[M+H]^+$ found 282.3, purity 100%.

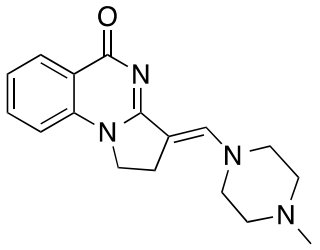
(*E*)-3-(Morpholinomethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**11**)



To a solution of **4** (50.0 mg, 0.269 mmol, 1.0 eq.) in CH_2Cl_2 (1.35 mL) was added morpohline-4-carbaldehyde (310 mg, 2.69 mmol, 10.0 eq.) and $POCl_3$ (50.1 μL, 0.538 mmol, 2.0 eq.). The reaction mixture was refluxed for three hours, diluted with CH_2Cl_2 (10 mL) cooled to room temperature, and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave the title compound **11** (26.7 mg, 0.0942 mmol, 35%) as a tan amorphous solid.

Decomposition 275 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.29 (1H, dd, *J* 7.9, 1.3 Hz), 7.65 (1H, s), 7.59 (1H, ddd, *J* 8.3, 7.4, 1.6 Hz), 7.32 (1H, ddd, *J* 8.0, 7.5, 0.9 Hz), 7.03 (1H, d, *J* 8.2 Hz), 4.14–4.11 (2H, m), 3.76–3.75 (4H, m), 3.51–3.48 (4H, m), 3.50 (2H, d, *J* 4.8 Hz), 3.18 (2H, ddd, *J* 8.3, 6.7, 1.7 Hz,); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 164.4, 143.0, 139.5, 133.2, 128.9, 124.5, 119.4, 113.3, 95.6, 66.7, 50.4, 45.0, 24.0; **FTIR** (neat, ν_{max} cm^{-1}) 2961 (w), 2925 (w), 2887 (w), 1634 (s), 1600 (s), 1594 (s), 1525 (s), 1510 (s), 1110 (s), 760 (m); ***R*$_f$** 0.25 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{16}H_{18}N_3O_2$ $[M+H]^+$ 284.1399, found 284.1396;

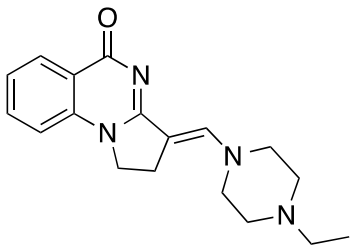
(*E*)-3-((4-Methylpiperazin-1-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**12**)



5 (21.0 mg, 0.0870 mmol) was reacted with 1-methylpiperazine according to general procedure E. Purification by FCC (10% MeOH/DCM) gave the product **12** (10.0 mg, 0.0337 mmol, 39%) as a pale brown amorphous solid.

Decomposition 97 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* 7.9, 1.2 Hz), 7.59 (1H, t, *J* 1.6 Hz), 7.55 (1H, dt, *J* 7.6, 1.4 Hz), 7.27 (1H, t, *J* 7.6 Hz), 6.98 (1H, d, *J* 8.1 Hz), 4.07 (2H, app t, *J* 8.0 Hz), 3.48–3.47 (4H, m), 3.12 (2H, app dt, *J* 8.1, 1.4 Hz,), 2.45 (4H, app t, *J* 4.9 Hz), 2.31 (3H, s,); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.3, 164.6, 143.0, 139.6, 133.1, 128.7, 124.2, 119.4, 113.2, 94.8, 54.9, 50.1, 46.2, 45.9, 23.9; **FTIR** (neat, ν_{max} cm^{-1}) 3405 (br), 2922 (w), 2850 (w), 2795 (w), 1645 (m), 1590 (s), 1514 (s), 1490 (s), 1438 (m), 1405 (s); $\boldsymbol{R_f}$ 0.35 (10% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{17}H_{21}N_4O$ $[M+H]^+$ 297.1715, found 297.1718; **LC/MS** $[M+H]^+$ found 297.6, purity 100%.

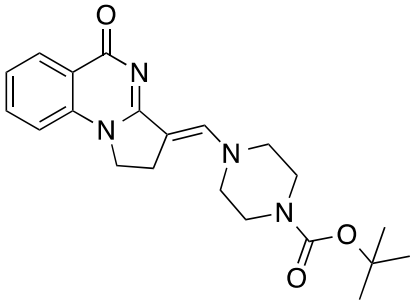
(*E*)-3-((4-Ethylpiperazin-1-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**13**)



5 (50.0 mg, 0.207 mmol) was reacted with 1-ethylpiperazine according to general procedure E. Purification by FCC (5% MeOH/DCM) gave the product **13** (39.6 mg, 0.128 mmol, 62%) as a pale brown amorphous solid.

MP 165–168 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.27 (1H, dd, *J* 7.9, 1.3 Hz), 7.65 (1H, s), 7.57 (1H, dd, *J* 8.4, 7.4, 1.5 Hz), 7.29 (1H, dt, *J* 7.8, 0.6 Hz), 7.00 (1H, d, *J* 7.8 Hz), 4.10 (2H, app t, *J* 7.8 Hz), 3.52 (4H, app t, *J* 5.0 Hz), 3.16 (2H, dt, *J* 7.8, 1.2 Hz), 2.51 (4H, app t, *J* 4.8 Hz), 2.46 (2H, q, *J* 7.2 Hz), 1.10 (3H, t, *J* 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.3, 164.6, 143.1, 139.6, 133.1, 128.9, 124.7, 119.5, 113.1, 94.6, 52.8, 52.4, 50.3, 45.9, 24.0, 12.0; **FTIR** (neat, ν_{max} cm^{-1}) 2970 (w), 2901 (w), 2819 (w), 1645 (m), 1613 (m), 1598 (m), 1588 (m), 1509 (s), 1491 (s); R_f 0.30 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{18}H_{23}N_4O$ $[M+H]^+$ 311.1861, found 311.1866; **LC/MS** $[M+H]^+$ found 311.6, purity 81%, decomposed on column 16% found 187.4.

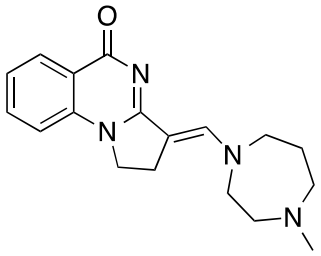
Tert-Butyl-(*E*)-4-((5-oxo-1,2-dihydropyrrolo[1,2-*a*]quinazolin-3(5*H*)-ylidene)methyl)piperazine-1-carboxylate (**14**)



5 (21.0 mg, 0.0870 mmol) was reacted with 1-boc-piperazine according to general procedure E. Purification by FCC (5% MeOH/CH_2Cl_2) gave the product **14** (20.0 mg, 0.0522 mmol, 58%) as a pale brown amorphous solid.

Decomposition 140 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.24 (1H, dd, *J* 7.4, 1.2 Hz), 7.57 (1H, m), 7.54 (1H, ddd, *J* 8.4, 7.4, 1.4 Hz), 7.27 (1H, dt, *J* 7.9, 0.6 Hz), 6.97 (1H, d, *J* 8.1 Hz), 4.07 (2H, app t, *J* 7.9 Hz), 3.48–3.46 (4H, m), 3.39 (4H, br), 3.10 (2H, dt, *J* 7.8, 1.4 Hz), 1.46 (9H, s); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.2, 164.3, 154.5, 142.5, 139.5, 133.0, 128.6, 124.2, 119.4, 113.4, 95.8, 80.6, 45.8, 28.4, 24.0, Note: -N-$\underline{C}H_2$-$\underline{C}H_2$-N- were very broad in the ^{13}C NMR and could not be reliably assigned; **FTIR** (neat, ν_{max} cm^{-1}) 2974 (w), 2918 (w), 1688 (m), 1644 (m), 1605 (m), 1591 (s), 1518 (s), 1494 (m), 1405 (s); $\boldsymbol{R_f}$ 0.25 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{21}H_{27}N_4O_3$ $[M+H]^+$ 383.2078, found 383.2070; **LC/MS** $[M+H]^+$ found 383.7, purity 98%.

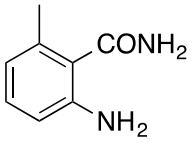
(*E*)-3-((4-Methyl-1,4-diazepan-1-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**15**)



5 (21.0 mg, 0.0870 mmol) was reacted with 1-methylhomopiperazine according to general procedure E. Purification by FCC (5% MeOH/CH_2Cl_2) gave the product **15** (13.2 mg, 0.0425 mmol, 49%) as a pale brown amorphous solid.

MP 92–94 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* 7.9, 1.4 Hz), 7.73 (1H, t, *J* 1.5 Hz), 7.56 (1H, ddd, *J* 8.3, 7.3, 1.5 Hz), 7.28 (1H, ddd, *J* 8.1, 7.5, 1.0 Hz), 6.99 (1H, d, *J* 8.0 Hz), 4.10–4.06 (2H, m), 3.61 (2H, t, *J* 6.3 Hz), 3.58–3.56 (2H, m), 3.20 (2H, m), 2.66–2.64 (2H, m), 2.60–2.58 (2H, m), 2.38 (3H, s), 1.94–1.90 (2H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 164.6, 144.5, 139.7, 133.0, 128.8, 124.1, 119.5, 113.1, 94.1, 59.1, 57.0, 54.1, 51.7, 46.9, 45.8, 28.5, 23.9; **FTIR** 2939 (w), 2913 (w), 2857 (w), 2810 (w), 1641 (m), 1602 (m), 1587 (s), 1506 (s), 1496 (s); R_f 0.32 (10% MeOH/CH_2Cl_2 + 1% NH_4OH); **HRMS** (ESI+) calculated for $C_{18}H_{23}N_4O$ $[M+H]^+$ 311.1872, found 311.1884; **LC/MS** $[M+H]^+$ found 311.6, purity 100%.

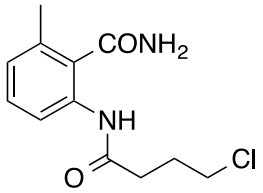
2-Amino-6-methylbenzamide (**16a**)



2-Amino-6-methylbenzonitrile (264 mg, 2.00 mmol) was hydrolysed according to general procedure A. After separation from remaining starting material (93.0 mg, 0.704 mmol, 35%) by FCC (50% EtOAc/hexanes to 100% EtOAc) the title compound **16a** (168 mg, 1.12 mmol, 56%) was obtained as a crystalline, white solid.

MP 139–141 °C, lit. 138–139 °C;[13] **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.62 (1H, br, NH), 7.42 (1H, br, NH), 6.91 (1H, t, *J* 7.8 Hz), 6.51 (1H, d, *J* 7.8 Hz), 6.39 (1H, d, *J* 7.4 Hz), 4.90 (2H, br, NH), 2.21 (3H, s); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 170.5, 145.4, 134.2, 128.7, 123.0, 117.9, 112.7, 19.9; **FTIR** (neat, ν_{max} cm^{-1}) 3453 (s), 3353 (m), 3165 (m, br), 1652 (s), 1618 (s), 1596 (s), 1461 (m), 1399 (m); R_f 0.42 (EtOAc); **HRMS** (ESI+) calculated for $C_8H_{11}N_2O$ $[M+H]^+$ 151.0866, found 151.0873.

2-(4-Chlorobutanamido)-6-methylbenzamide (**16b**)

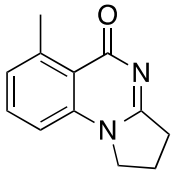


16a (118 mg, 0.781 mmol) was reacted with 4-chlorobutanoyl chloride according to general procedure B. Purification by FCC (75% EtOAc/hexanes to 100% EtOAc) gave the title compound **16b** (120 mg, 0.471 mmol, 60%) as a white amorphous solid.

Decomposition 176–179 °C; **^{1}H NMR** (600 MHz, d_6-DMSO) δ 9.20 (1H, s, NH), 7.68 (1H, s, NH), 7.61 (1H, s, NH), 7.47 (1H, d, *J* 7.9 Hz), 7.23 (1H, t, *J* 7.8 Hz), 7.03 (1H, d, *J* 7.5 Hz), 3.68 (2H, t, *J* 6.6 Hz), 2.45 (2H, t, *J* 7.1 Hz), 2.30 (3H, s), 2.00 (2H, quintet, *J* 6.8 Hz); **^{13}C NMR** (150

MHz, d_6-DMSO) δ 170.4, 169.1, 134.5, 134.2, 132.0, 128.2, 126.4, 122.2, 44.8, 33.2, 28.2, 19.5; **FTIR** (neat, ν_{max} cm^{-1}) 3409 (m), 3288 (s), 3193 (m), 2966 (w), 2926 (w), 1656 (s), 1607 (m), 1520 (s); $\boldsymbol{R_f}$ 0.44 (75% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{12}H_{15}N_2O_2{}^{35}ClNa$ $[M+Na]^+$ 277.0714, found 277.0718.

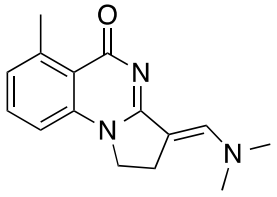
6-Methyl-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**16c**)



16b (85.0 mg, 0.334 mmol) was cyclised according to general procedure C. Purification by FCC (5% MeOH/CH_2Cl_2) gave **16c** (60.2 mg, 0.300 mmol, 91%) as a white amorphous solid.

Decomposition 215–217 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (1H, t, *J* 7.9 Hz), 7.19 (1H, d, *J* 7.5 Hz), 7.00 (1H, d, *J* 8.2 Hz), 4.17 (2H, t, *J* 7.3 Hz), 3.14 (2H, t, *J* 8.1 Hz), 2.89 (3H, s), 2.41–2.35 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.9, 165.2, 143.3, 140.1, 132.6, 128.8, 117.6, 112.3, 49.1, 32.6, 23.3, 18.8; **FTIR** (neat, ν_{max} cm^{-1}) 2925 (w), 1641 (w), 1626 (w), 1599 (s), 1543 (m), 1500 (m), 1427 (w); $\boldsymbol{R_f}$ 0.31 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{12}H_{13}N_2O$ $[M+H]^+$ 201.1022, found 201.1028; **LC/MS** $[M+H]^+$ found 201.4, purity 100%.

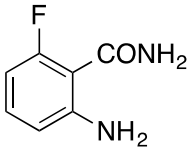
(*E*)-3-((Dimethylamino)methylene)-6-methyl-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**16**)



16c (15.0 mg, 0.075 mmol) was reacted according to general procedure D. Purification by preparative TLC (5% MeOH/CH_2Cl_2) gave **16** (14.3 mg, 0.056 mmol, 75%) as a yellow amorphous solid.

Decomposition 215–219 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 7.47 (1H, t, *J* 7.8 Hz), 7.33 (1H, t, *J* 1.6 Hz), 7.06–7.02 (2H, m), 4.06–4.02 (2H, m), 3.20 (2H, t, *J* 7.8 Hz), 3.08 (6H, s), 2.71 (3H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 169.4, 162.8, 143.5, 140.8, 140.4, 131.9, 126.5, 117.1, 112.2, 94.1, 45.9, 41.7, 22.8, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2924 (w), 1648 (s), 1629 (m), 1613 (m), 1588 (s), 1524 (s), 1493 (s), 1400 (m), 1374 (m); $\boldsymbol{R_f}$ 0.25 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{15}H_{18}N_3O$ $[M+H]^+$ 256.1444, found 256.1435; **LC/MS** $[M+H]^+$ found 256.6, purity 100%.

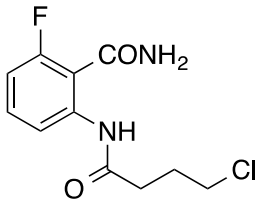
2-Amino-6-fluorobenzamide (**17a**)



According to general procedure A, 2-amino-6-fluorobenzonitrile was hydrolysed to give **17a** (290 mg, 1.88 mmol, 94%) as a yellow amorphous solid, without the need for further purification.

MP 119–120 °C, lit. 120–122 °C;[14] **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.53 (1H, br, NH), 7.50 (1H, br, NH), 7.07 (1H, dt, *J* 8.0, 6.8 Hz), 6.51 (1H, d, *J* 8.0 Hz), 6.30 (1H, dd, *J* 10.9, 8.4 Hz), 6.15 (2H, br, NH); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 166.7, 160.8 (d, *J* 244.3 Hz), 150.5 (d, *J* 6.3 Hz), 131.3 (d, *J* 11.7 Hz), 111.6 (d, *J* 2.3 Hz), 106.0 (d, *J* 17.8 Hz), 101.6 (d, *J* 24.0 Hz); **FTIR** (neat, ν_{max} cm^{-1}) 3489 (m), 3421 (s), 3382 (s), 3182 (s, br), 2924 (m), 2853 (w), 1643 (m), 1620 (s), 1581 (s), 1549 (m), 1456 (m), 1404 (s), 1295 (m); ***R*$_f$** 0.32 (40% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_7H_8N_2OF$ $[M+H]^+$ 155.0615, found 155.0614.

2-(4-Chlorobutanamido)-6-fluorobenzamide (**17b**)

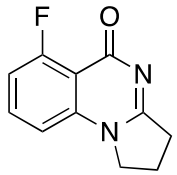


17a (250 mg, 1.62 mmol) was reacted with 4-chlorobutanoyl chloride according to general procedure B. Purification by FCC (gradient 30% EtOAc/hexanes to 40% EtOAc/hexanes) gave the title compound **17b** (392 mg, 1.52 mmol, 94%) as a white amorphous solid.

MP 99–101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.73 (1H, NH), 8.49 (1H, d, *J* 8.4 Hz), 7.42 (1H, dt, *J* 8.3, 6.9 Hz), 6.83 (1H, ddd, *J* 12.6, 8.4, 0.6 Hz), 6.83 (1H, br, NH), 6.28 (1H, br, NH), 3.63 (2H, t, *J* 6.4 Hz), 2.60 (2H, t, *J* 7.2 Hz), 2.19 (2H, quint., *J* 6.8 Hz,); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 167.9, 161.4 (d, *J* 246.9 Hz), 142.4 (d, *J* 4.3 Hz), 133.9 (d, *J* 12.2 Hz), 117.5 (d, *J* 3.1 Hz), 110.3 (d, *J* 25.6 Hz), 107.1 (d, *J* 13.3 Hz), 44.4, 35.3, 28.1; **FTIR** (neat, ν_{max} cm^{-1}) 3423 (m), 3204 (m, br), 1702 (m), 1649 (s), 1617 (s), 1591 (s), 1518 (s), 1459 (m), 1388 (s),

1239 (s), 808 (m); R_f 0.32 (40% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{11}H_{13}N_2O_2F^{35}Cl$ $[M+H]^+$ 259.0650, found 259.0647.

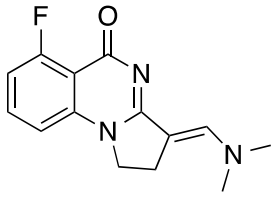
6-Fluoro-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**17c**)



17b (383 mg, 1.48 mmol) was cyclised according to general procedure C. Purification by FCC (5% MeOH/CH_2Cl_2) gave **17c** (220 mg, 1.08 mmol, 73%) as a white amorphous solid.

Decomposition 207–209 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (1H, dt, *J* 8.3 Hz, 5.2 Hz), 6.95 (2H, dd, *J* 10.3, 8.5 Hz), 6.93 (1H, d, *J* 8.3 Hz), 4.18 (2H, app t, *J* 7.4 Hz), 3.10 (2H, t, *J* 8.1 Hz), 2.38 (2H, app quint., *J* 7.8 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.2 (*J* 3.8 Hz), 166.4, 162.0 (*J* 264.4 Hz), 140.6 (*J* 3.2 Hz), 134.3 (*J* 10.8 Hz), 112.8 (*J* 21.8 Hz), 110.5 (*J* 4.6 Hz), 108.3 (*J* 10.5 Hz), 49.4, 32.7, 18.6; **FTIR** (neat, ν_{max} cm^{-1}) 3380 (br, w), 1652 (m), 1607 (s), 1549 (m), 1500 (m), 818 (m); R_f 0.26 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{11}H_{10}N_2OF$ $[M+H]^+$ 205.0772, found 205.0766; **LC/MS** $[M+H]^+$ found 205.4, purity 100%.

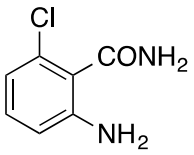
(*E*)-3-((Dimethylamino)methylene)-6-fluoro-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**17**)



17c (50.0 mg, 0.245 mmol) was reacted according to general procedure D. Purification by FCC (2% MeOH/CH_2Cl_2) gave **17** (57.6 mg, 0.222 mmol, 91%) as a yellow amorphous solid.

Decomposition 247–248 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (1H, t, *J* 1.5 Hz), 7.48 (1H, dt, *J* 8.3, 5.2 Hz), 6.92 (1H, ddd, *J* 10.6, 8.3, 0.6 Hz), 6.75 (1H, d, *J* 8.3 Hz), 4.04 (2H, app t, *J* 8.0 Hz), 3.25 (2H, app dt, *J* 7.9, 1.4 Hz), 3.09 (6H, s); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.5 (d, *J* 3.6 Hz), 164.2, 162.4 (d, *J* 261.9 Hz), 145.5, 141.7 (d, *J* 3.6 Hz), 133.5 (d, *J* 11.1 Hz), 111.5 (d, *J* 22.7), 108.8 (d, *J* 4.1 Hz), 108.6 (d, *J* 10.1 Hz), 93.8, 46.4, 42.4, 23.5; **FTIR** (neat, ν_{max} cm^{-1}) 2952 (w), 2893 (w), 1648 (m), 1594 (s), 1576 (s), 1520 (s), 1473 (s), 1397 (m); ***R*$_f$** 0.26 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{14}H_{15}N_3OF$ $[M+H]^+$ 260.1199, found 260.1203; **LC/MS** $[M+H]^+$ found 260.5, purity 100%; **HPLC** R_t 7.53 min, purity 98.6%.

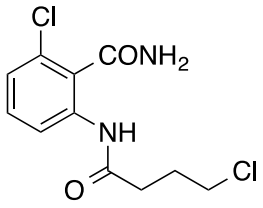
2-Amino-6-chlorobenzamide (**18a**)



According to general procedure A, 2-amino-6-chlorobenzonitrile (305 mg, 2.00 mmol) was hydrolysed to give **18a** (335 mg, 1.96 mmol, 98%) as an off-white crystalline solid, without the need for further purification.

MP 133–134 °C, lit. 130–131 °C;[15] **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.81 (1H, br, NH), 7.58 (1H, br, NH), 7.01 (1H, t, *J* 8.0 Hz), 6.63 (1H, dd, *J* 8.2, 0.7 Hz), 6.57 (1H, dd, *J* 7.9, 0.7 Hz), 5.21 (2H, NH); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 167.5, 147.0, 130.0, 129.8, 121.7, 116.1, 113.6; **FTIR** (neat, ν_{max} cm^{-1}) 3472 (s), 3430 (m), 3326 (s, br), 1630 (s, br), 1606 (s), 1570 (m), 1469 (m), 1447 (m), 1388 (m); ***R*$_f$** 0.36 (67% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_7H_7N_2O^{35}ClNa$ $[M+Na]^+$ 193.0139, found 193.0148.

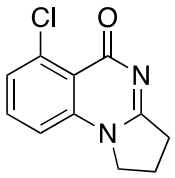
2-(4-Chlorobutanamido)-6-chlorobenzamide (**18b**)



18a (325 mg, 1.91 mmol) was reacted with 4-chlorobutanoyl chloride according to general procedure B. Purification by FCC (33% EtOAc/hexanes to 66% EtOAc/hexanes) gave the title compound **18b** (485 mg, 1.77 mmol, 93%) as a white amorphous solid.

MP 251–253 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.35 (1H, br, NH), 8.23 (1H, d, *J* 8.3 Hz), 7.35 (1H, t, *J* 8.2 Hz), 7.17 (1H, dd, *J* 8.0, 0.6 Hz), 6.29 (1H, br, NH), 6.10 (1H, br, NH), 3.64 (2H, t, *J* 6.3 Hz), 2.57 (2H, t, *J* 7.2 Hz), 2.20–2.16 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.7, 168.2, 138.3, 131.8, 130.6, 125.7, 121.4, 110.1, 44.4, 34.6, 27.9; **FTIR** (neat, ν_{max} cm^{-1}) 3369 (m), 3287 (s), 3188 (m), 1662 (s), 1612 (m), 1594 (m), 1514 s), 1444 (m); ***R*$_f$** 0.23 (33% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{11}H_{13}N_2O_2Cl_2$ $[M+H]^+$ 275.0354, found 275.0349.

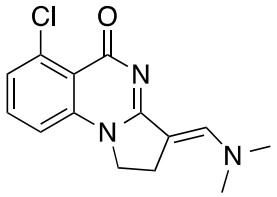
6-Chloro-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**18c**)



18b (965 mg, 3.51 mmol) was cyclised according to general procedure C. Purification by FCC (5% MeOH/CH_2Cl_2) gave **18c** (743 mg, 3.37 mmol, 96%) as a white, amorphous solid.

Decomposition 232–238 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (1H, t, *J* 8.1 Hz), 7.25 (1H, d, *J* 8.1 Hz), 7.01 (1H, d, *J* 8.4 Hz), 4.16 (2H, t, *J* 7.2 Hz), 3.08 (2H, t, *J* 8.1 Hz), 2.36 (2H, app quint., *J* 7.8 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.8, 165.8, 141.0, 136.1, 133.1, 128.6, 115.6, 113.7, 49.6, 32.7, 18.6; **FTIR** (neat, ν_{max} cm^{-1}) 1648 (m), 1605 (s), 1588 (s), 1544 (m), 1486 (m), 1412 (m), 1100 (w), 1053 (m); $\boldsymbol{R_f}$ 0.29 (4% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{11}H_{10}N_2O^{35}Cl$ $[M+H]^+$ 221.0482, found 221.0490; **LC/MS** $[M+H]^+$ found 221.4, purity 100%.

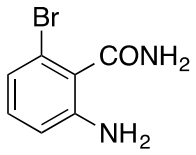
(*E*)-6-Chloro-3-((dimethylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**18**)



18c (400 mg, 1.81 mmol) was reacted according to general procedure D. Purification by FCC (2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave **18** (387 mg, 1.40 mmol, 78%) as a yellow amorphous solid.

Decomposition 248-250 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 7.55 (1H, t, *J* 8.1 Hz), 7.37 (1H, t, *J* 1.6 Hz), 7.25 (1H, dd, *J* 7.8, 1.0 Hz), 7.17 (1H, dd, *J* 8.2, 1.0 Hz), 4.07–4.04 (2H, m), 3.19 (2H, dt, *J* 7.9, 1.4 Hz), 3.10 (6H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 165.9, 163.0, 144.3, 142.0, 133.6, 132.7, 126.1, 115.2, 113.6, 93.8, 46.2, 41.8, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2895 (w), 1648 (m), 1624 (m), 1613 (m), 1594 (s), 1578 (s), 1518 (s), 1475 (s); ***R*$_f$** 0.28 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{14}H_{15}N_3O^{35}Cl$ $[M+H]^+$ 276.0904, found 276.0904. **LC/MS** $[M+H]^+$ found 276.5, purity 100%; **HPLC** R_t 8.26 min, purity 100%.

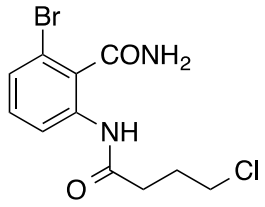
2-Amino-6-bromobenzamide (**19a**)



According to general procedure A, 2-amino-6-bromobenzonitrile (195 mg, 1.00 mmol) was hydrolysed. Purification by FCC (gradient 50% EtOAc/hexanes to 100% EtOAc) gave the title compound **19a** (184 mg, 0.856 mmol, 86%) as a crystalline, white solid.

MP 150–153 °C; **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.80 (1H, s, br, NH), 7.55 (1H, s, br, NH), 6.93 (1H, t, *J* 7.8 Hz), 6.73 (1H, dd, *J* 7.8, 0.6 Hz), 6.66 (1H, dd, *J* 8.4, 0.6 Hz), 5.15 (2H, s, br, NH); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 168.3, 146.8, 130.1, 124.0, 119.3, 119.2, 114.1; **FTIR** (neat, ν_{max} cm^{-1}) 3469 (s), 3324 (s), 1634 (s), 1606 (m), 1562 (m), 1465 (w), 1446 (m), 1387 (w); ***R*$_f$** 0.32 (67% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_7H_8N_2O^{79}Br$ $[M+H]^+$ 214.9820, found 214.9828.

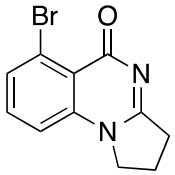
2-Bromo-6-(4-chlorobutanamido)benzamide (**19b**)



19a (161 mg, 0.749 mmol) was reacted with 4-chlorobutanoyl chloride according to general procedure B. Purification by FCC (50% EtOAc/hexanes) gave the title compound **19b** (186 mg, 0.582 mmol, 78%) as a white amorphous solid.

Decomposition 254 °C; **^{1}H NMR** (600 MHz, d_6-DMSO) δ 9.31 (1H, NH), 7.85 (1H, NH), 7.70 (1H, NH), 7.61 (1H, d, *J* 7.3 Hz), 7.43 (1H, d, *J* 8.0 Hz), 7.27 (1H, t, *J* 8.1 Hz), 3.67 (2H, t, *J* 6.7 Hz), 2.47 (2H, t, *J* 7.1 Hz), 2.00 (2H, quint., *J* 7.0 Hz); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 170.8, 167.0, 135.7, 134.1, 129.7, 128.8, 124.8, 118.8, 44.8, 33.0, 28.2; **FTIR** (neat, ν_{max} cm^{-1}) 3341 (m), 3289 (s), 3182 (m), 1662 (s), 1610 (m), 1520 (m), 1444 (m), 1385 (m); $\boldsymbol{R_f}$ 0.35 (33% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{11}H_{12}N_2O_2{}^{79}Br^{35}ClNa$ $[M+Na]^+$ 340.9663, found 340.9656.

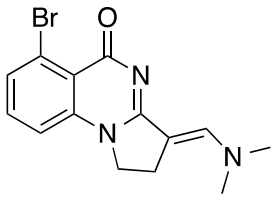
6-Bromo-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**19c**)



19b (160 mg, 0.500 mmol) was cyclised according to general procedure C. Purification by FCC (5% MeOH/CH_2Cl_2) gave **19** (112 mg, 0.442 mmol, 88%) as a white amorphous solid.

Decomposition 226–229 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* 7.8 Hz), 7.35 (1H, t, *J* 7.8 Hz), 7.08 (1H, d, *J* 8.4 Hz), 4.18 (2H, app t, *J* 7.4 Hz), 3.11 (2H, t, *J* 8.0 Hz), 2.38 (2H, app quint., *J* 7.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.8, 165.7, 140.6, 133.2, 132.3, 123.7, 116.3, 114.5, 49.6, 32.7, 18.5; **FTIR** (neat, ν_{max} cm^{-1}) 1646 (m), 1605 (s), 1584 (s), 1544 (m), 1488 (s), 1409 (m), 1052 (m); $\boldsymbol{R_f}$ 0.27 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{11}H_{10}N_2O^{79}Br$ $[M+H]^+$ 264.9971, found 264.9966; **LC/MS** $[M+H]^+$ found 267.4, purity 100%.

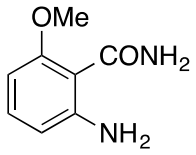
(*E*)-6-Bromo-3-((dimethylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**19**)



19c (40.0 mg, 0.151 mmol) was reacted according to general procedure D. Purification by FCC (6% MeOH/CH_2Cl_2) gave **19** (15.8 mg, 0.0493 mmol, 33%) as a yellow amorphous solid.

Decomposition 160–162 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 7.50–7.45 (2H, m), 7.41 (1H, t, *J* 1.4 Hz) 7.23 (1H, dd, *J* 7.5, 1.9 Hz), 4.09–4.06 (2H, m), 3.21–3.18 (2H, m), 3.11 (6H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 165.5, 162.5, 144.6, 141.8, 133.2, 129.9, 121.9, 116.0, 114.3, 93.6, 46.3, 41.8, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2927 (w), 2901 (w), 1645 (m), 1593 (s), 1574 (s), 1516 (s), 1473 (s), 1396 (m), 1378 (s), 1107 (m), 1064 (m), 723 (s); $\boldsymbol{R_f}$ 0.32 (6% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{14}H_{15}N_3O^{79}Br$ $[M+H]^+$ 320.0395, found 320.0398; **LC/MS** $[M+H]^+$ found 320.5, purity 94%.

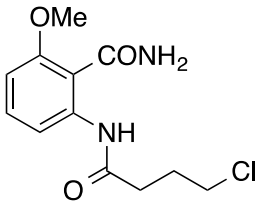
2-Amino-6-methoxybenzamide (**20a**)



2-Amino-6-methoxybenzonitrile (445 mg, 3.00 mmol, 1.0 eq.) was hydrolysed according to general procedure A to give **20a** (395 mg, 2.38 mmol, 79%) as a white crystalline solid.

MP 150–151 °C, lit. 151–152 °C;[16] **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.20 (1H, t, *J* 8.3 Hz), 6.35 (1H, dd, *J* 8.4, 0.6 Hz), 6.21 (1H, dd, *J* 8.1, 0.6 Hz), 5.99 (2H, br, NH), 3.78 (3H, s); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 161.5, 153.0, 134.4, 115.7, 107.5, 97.6, 83.8, 55.8; **FTIR** (neat, ν_{max} cm^{-1}) 3468 (m), 3425 (s), 3349 (m), 3165 (s), 1635 (s), 1607 (s), 1575 (s), 1548 (m), 1457 (m), 1394 (m); $\boldsymbol{R_f}$ 0.27 (33% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_8H_{10}N_2O_2Na$ $[M+Na]^+$ 189.0634, found 189.0631.

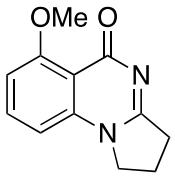
2-(4-Chlorobutanamido)-6-methoxybenzamide (**20b**)



According to general procedure B, **20a** (340 mg, 2.05 mmol) was reacted with 4-chlorobutanoyl chloride. Purification by FCC (50% EtOAc/hexanes) gave the product **20b** (440 mg, 1.62 mmol, 79%) as a white amorphous powder.

MP 108–109 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 12.26 (1H, NH), 8.34 (1H, dd, *J* 8.4, 0.8 Hz), 7.89 (1H, br, NH), 7.40 (1H, t, *J* 8.4 Hz), 6.70 (1H, dd, *J* 8.4, 0.7 Hz), 6.18 (1H, br, NH), 3.95 (3H, s), 3.64 (2H, t, *J* 6.4 Hz), 2.59 (2H, t, *J* 7.2 Hz), 2.18 (2H, quint., *J* 7.8 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.9, 170.2, 158.4, 142.7, 133.2, 114.4, 107.4, 106.0, 56.4, 44.5, 35.4, 28.2; **FTIR** (neat, ν_{max} cm^{-1}) 3404 (s), 3322 (m), 3204 (s), 2968 (w), 2921 (w), 2947 (w), 2845 (w), 1693 (m), 1643 (m), 1609 (s), 1597 (s), 1508 (m), 1467 (s), 1255 (s); ***R*$_f$** 0.35 (50% EtOAc/hexanes); **HRMS** (ESI+) calculated for $C_{12}H_{15}N_2O_3{}^{35}ClNa$ $[M+H]^+$ 293.0663, found 293.0658.

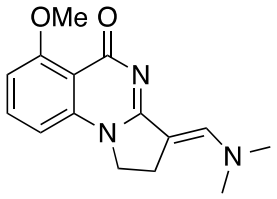
6-Methoxy-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**20c**)



According to general procedure C, **20b** (30.0 mg, 0.11 mmol) was cyclised and purification by FCC (4% MeOH/CH_2Cl_2) gave **20c** (19.4 mg, 0.09 mmol, 81%) as a white amorphous solid.

Decomposition 192–194 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (1H, t, *J* 8.3 Hz), 6.81 (1H, d, *J* 8.5 Hz), 6.68 (1H, d, *J* 8.3 Hz), 4.13 (2H, t, *J* 7.3 Hz), 3.94 (3H, s), 3.08 (2H, t, *J* 8.1 Hz), 2.34 (2H, app quint., *J* 7.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.7, 165.0, 161.0, 141.1, 134.1, 108.6, 107.3, 106.3, 56.4, 49.3, 32.5, 18.7; **FTIR** (neat, ν_{max} cm^{-1}) 3067 (w), 2944 (w), 2841 (w), 1646 (m), 1635 (m), 1599 (s,), 1552 (m), 1498 (m), 1259 (m); ***R*$_f$** 0.33 (8% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.0972, found 217.0969; **LC/MS** $[M+H]^+$ found 217.5, purity 100%.

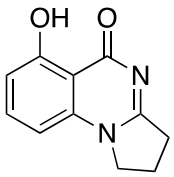
(*E*)-3-((Dimethylamino)methylene)-6-methoxy-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**20**)



20c (49.8 mg, 0.23 mmol) was reacted according to general procedure D. Purification by FCC (8% MeOH/CH_2Cl_2) gave the product **20** (32.1 mg, 0.12 mmol, 51%) as a yellow amorphous solid.

Decomposition 219–222 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 7.53 (1H, t, *J* 8.3 Hz), 7.30 (1H, t, *J* 1.6 Hz), 6.82 (1H, d, *J* 8.2 Hz), 6.74 (1H, dd, *J* 8.2, 0.8 Hz), 4.01 (2H, app t, *J* 7.9 Hz), 3.79 (3H, s), 3.18 (2H, app t, *J* 7.4 Hz), 3.07 (6H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 166.6, 162.4, 159.8, 143.4, 141.8, 133.4, 108.1, 106.4, 106.1, 93.9, 55.7, 46.0, 41.7, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2922 (w), 2893 (w), 1651 (m), 1630 (m), 1622 (m), 1585 (s), 1524 (s), 1486 (s), 1397 (m), 1375 (m), 1284 (m), 1257 (m); $\boldsymbol{R_f}$ 0.32 (8% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{15}H_{18}N_3O_2$ $[M+H]^+$ 272.1394, found 272.1385; **LC/MS** $[M+H]^+$ found 272.6, purity 100%.

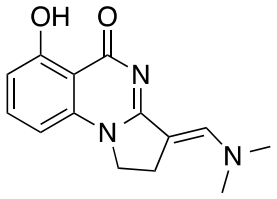
6-Hydroxy-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**21c**)



To a stirred solution of **20c** (17.0 mg, 0.078 mmol, 1.0 eq.) in CH_2Cl_2 (800 µL) at -20 °C was added BBr_3 (100 µL, 1.04 mmol, 13.2 eq.) drop-wise. After stirring at room temperature for 24 hours CH_2Cl_2 (10 mL) and $NaHCO_3$ (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and excess solvent removed *in vacuo*. Unreacted starting material (8.0 mg, 0.037 mmol, 47%) was removed by FCC (5% MeOH/CH_2Cl_2), giving the product **21c** (7.9 mg, 0.039 mmol, 50%) as a white amorphous solid.

MP 209–210 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 13.26 (1H, s, OH), 7.53 (1H, t, *J* 8.2 Hz, H6), 6.83 (1H, dd, *J* 8.3, 0.7 Hz, H5), 6.57 (1H, dd, *J* 8.2, 0.7 Hz, H7), 4.20 (2H, app t, *J* 7.4 Hz, H9), 3.18 (2H, t, *J* 8.0 Hz, H11), 2.43–2.38 (2H, m, H10); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.4 (C4), 167.2 (C1), 161.9 (C2), 139.2 (C8), 136.8 (C6), 112.7 (C5), 105.5 (C3), 103.6 (C7), 49.5 (C9), 33.0 (C11), 18.6 (C10); **FTIR** (neat, ν_{max} cm^{-1}) 2964 (w), 2897 (w), 2743 (w), 1627 (s), 1597 (s), 1497 (s), 1450 (s), 1242 (s); R_f 0.41 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{11}H_{11}N_2O_2$ $[M+H]^+$ 203.0815, found 203.0823; **LC/MS** $[M+H]^+$ found 201.4, purity 100%.

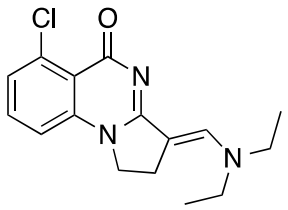
(*E*)-3-((Dimethylamino)methylene)-6-hydroxy-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**21**)



To a stirred solution of (*E*)-3-((dimethylamino)methylene)-6-methoxy-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one **20** (6.4 mg, 0.0240 mmol, 1.0 eq.) in CH_2Cl_2 (500 μL) at -20 °C was added BBr_3 (23 μL, 1.240 mmol, 10.0 eq.) drop-wise. After stirring at room temperature for 2 hours, CH_2Cl_2 (10 mL) and $NaHCO_3$ (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, excess solvent removed *in vacuo*, and purification by FCC (5% MeOH/CH_2Cl_2) gave **21** (5.9 mg, 0.0229 mmol, 96%) as a pale yellow amorphous solid.

MP 211–214 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 14.30 (1H, s, OH), 7.49 (1H, t, *J* 8.2 Hz), 7.46 (1H, t, *J* 1.5 Hz), 6.60 – 6.58 (2H, m), 4.09 – 4.06 (2H, m), 3.22 (2H, dt, *J* 8.0, 1.2 Hz), 3.12 (6H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 174.0, 164.5, 160.9, 145.3, 140.0, 135.0, 109.8, 104.3, 103.1, 94.4, 46.1, 42.3, 22.7; **FTIR** (neat, ν_{max} cm^{-1}) 3579 (w), 2917 (w), 1646 (m), 1625 (m), 1597 (s), 1541 (m), 1479 (s) 1419 (m), 1405 (s), 1281 (s), 1115 (m); ***R*$_f$** 0.29 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{14}H_{16}N_3O_2$ $[M+H]^+$ 258.1243, found 258.1244; **LC/MS** $[M+H]^+$ found 258.5, purity 100%.

(*E*)-6-Chloro-3-((diethylamino)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**22**)

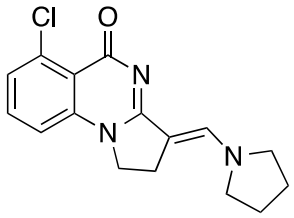


To a solution of **18c** (50.0 mg, 0.226 mmol, 1.0 eq.) in CH_2Cl_2 (1.50 mL) was added diethylformamide (126 μL, 1.13 mmol, 5.0 eq.) and $POCl_3$ (42.1 μL, 0.452 mmol, 2.0 eq.). The

reaction mixture was refluxed for 48 hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (5% MeOH/CH_2Cl_2) gave the title compound **22** (45.5 mg, 0.150 mmol, 66%) as a tan amorphous solid.

Decomposition 221 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (1H, t, *J* 1.4 Hz), 7.32 (1H, t, *J* 8.1 Hz), 7.17 (1H, dd, *J* 7.9, 0.8 Hz), 6.81 (1H, dd, *J* 8.4, 0.7 Hz), 3.99 (2H, app t, *J* 7.9 Hz), 3.32 (4H, q, *J* 7.2 Hz), 3.10 (2H, dt, *J* 8.0, 1.3 Hz), 1.20 (6H, t, *J* 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.9, 163.6, 143.7, 142.0, 135.7, 132.2, 126.7, 116.1, 112.1, 92.8, 46.9, 46.3, 23.4, 15.1; **FTIR** (neat, ν_{max} cm^{-1}) 3076 (w), 2973 (w), 2933 (w), 2877 (w), 1644 (m), 1629 (m), 1617 (m), 1590 (s), 1574 (s), 1509 (s); ***R*$_f$** 0.28 (3% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{16}H_{19}N_3O^{35}Cl$ $[M+H]^+$ 304.1217, found 304.1227; **LC/MS** $[M+H]^+$ found 304.6, purity 100%.

(*E*)-6-Chloro-3-(pyrrolidin-1-ylmethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**23**)

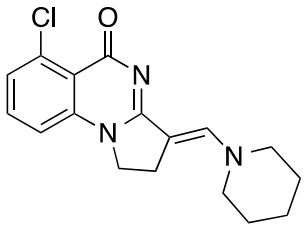


To a solution of **18c** (40.0 mg, 0.181 mmol, 1.0 eq.) in CH_2Cl_2 (1.00 mL) was added 1-formylpyrrolidine (86.0 μL, 0.902 mmol, 5.0 eq.) and $POCl_3$ (33.8 μL, 0.362 mmol, 2.0 eq.). The reaction mixture was refluxed for 24 hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with

CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 8% MeOH/CH_2Cl_2) gave the title compound **23** (34.2 mg, 0.113 mmol, 63%) as a tan amorphous solid.

Decomposition 265 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.39 (1H, t, *J* 8.1 Hz), 7.24 (1H, dd, *J* 8.0, 1.1 Hz), 6.86 (1H, dd, *J* 8.2, 1.0 Hz), 4.02 (2H, app t, *J* 8.0 Hz), 3.59 – 3.56 (4H, m), 3.26 (2H, t, *J* 7.9 Hz), 1.95 – 1.91 (4H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.9, 163.2, 142.1, 141.7, 136.1, 132.2, 126.9, 116.3, 112.0, 94.4, 50.6, 46.5, 25.6, 23.2; **FTIR** (neat, ν_{max} cm^{-1}) 2968 (w), 2869 (w), 1638 (m), 1591 (s), 1578 (s), 1522 (s), 1477 (s), 1401 (m), 1371 (m), 1290 (m); $\boldsymbol{R_f}$ 0.45 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{16}H_{17}N_3O^{35}Cl$ $[M+H]^+$ 302.1060, found 302.1054; **LC/MS** $[M+H]^+$ found 301.5, purity 100%.

(*E*)-6-Chloro-3-(piperidin-1-ylmethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**24**)

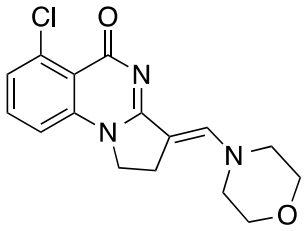


To a solution of **18c** (38.1 mg, 0.173 mmol, 1.0 eq.), in CH_2Cl_2 (900 μL) was added 1-formylpiperazine (34.0 μL, 0.364 mmol, 2.1 eq.) and $POCl_3$ (20.0 μL, 0.215 mmol, 2.2 eq.). The reaction mixture was refluxed for 24 hours before being cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in*

vacuo. Purification by FCC (2% MeOH/CH_2Cl_2) gave the title compound **24** (25.2 mg, 0.0798 mmol, 46%) as an off-white amorphous solid.

MP 182–185 °C; **^{1}H NMR** (600 MHz, d_6-DMSO) δ 7.54 (1H, t, *J* 7.8 Hz), 7.37 (1H, s), 7.25 (1H, d, *J* 7.8 Hz), 7.16 (1H, d, *J* 8.4 Hz), 4.07 (2H, app t, *J* 7.8 Hz), 3.48–3.45 (4H, m), 3.09 (2H, app t, *J* 7.8 Hz), 1.59 (6H, m); **^{13}C NMR** (150 MHz, d_6-DMSO) δ 165.9, 163.2, 142.6, 141.9, 133.6, 132.7, 126.1, 115.2, 113.5, 93.2, 50.6, 46.2, 26.1, 23.6, 23.1; **FTIR** (neat, ν_{max} cm^{-1}) 2938 (w), 2854 (w), 1635 (s), 1592 (s), 1577 (s), 1517 (s), 1484 (m), 1461 (m), 1404 (s), 1206 (m); ***R*$_f$** 0.35 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{17}H_{19}N_3O^{35}Cl$ $[M+H]^+$ 316.1217 found 316.1229; **LC/MS** $[M+H]^+$ found 316.6, purity 98%.

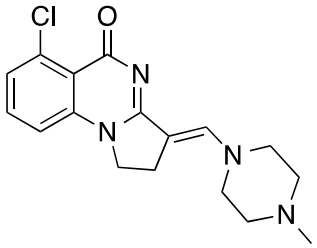
(*E*)-6-Chloro-3-(morpholinomethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**25**)



To a solution of **18c** (46.1 mg, 0.173 mmol, 1.0 eq.), in CH_2Cl_2 (1.50 mL) was added morpohline-4-carbaldehyde (75.0 μL, 0.364 mmol, 2.1 eq.) and $POCl_3$ (60.0 μL, 0.215 mmol, 2.2 eq.). The reaction mixture was refluxed for 24 hours, then cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 7% MeOH/CH_2Cl_2) gave the title compound **25** (34.7 mg, 0.11 mmol, 75%) as an off-white amorphous solid.

Decomposition 270 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (1H, br, s), 7.42 (1H, t, *J* 8.1 Hz), 7.29 (1H, dd, *J* 7.9, 0.7 Hz), 6.90 (1H, dd, *J* 8.2, 0.7 Hz), 4.09–4.06 (2H, m), 3.76–3.74 (2H, m), 3.51–3.49 (4H, m), 3.15 (2H, app dt, *J* 8.6, 1.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.9, 163.4, 143.3, 141.8, 136.3, 132.4, 127.4, 116.4, 112.2, 94.7, 66.8, 50.4, 46.6, 23.8; **FTIR** (neat, ν_{max} cm^{-1}) 2962 (w), 2901 (w), 2857 (w), 1649 (m), 1629 (m), 1595 (s), 1579 (s), 1527 (s), 1109 (s); $\boldsymbol{R_f}$ 0.32 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{16}H_{17}N_3O_2{}^{35}Cl$ $[M+H]^+$ 318.1009, found 318.1011; **LC/MS** $[M+H]^+$ found 318.5, purity 97%.

(*E*)-6-Chloro-3-((4-methylpiperazin-1-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**26**)

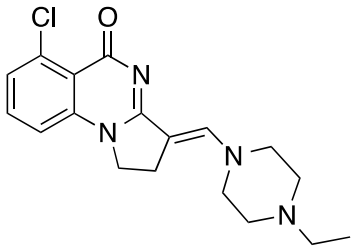


18 (46.2 mg, 0.168 mmol) was reacted with 1-methylpiperazine according to general procedure E. Purification by FCC (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH) gave the product **26** (41.0 mg, 0.124 mmol, 74%) as a yellow amorphous solid.

Decomposition 249–252 °C; **^{1}H NMR** (500 MHz, d_6-DMSO) δ 7.57 (1H, t, *J* 8.0 Hz), 7.38 (1H, t, *J* 1.5 Hz), 7.28 (1H, dd, *J* 7.9, 1.0 Hz), 7.20 (1H, dd, *J* 8.3, 1.0 Hz), 4.10–4.07 (2H, m), 3.50 (4H, app t, *J* 5.0 Hz), 3.112–3.08 (2H, m), 2.41 (4H, t, *J* 4.7 Hz), 2.23 (3H, s); **^{13}C NMR** (125 MHz, d_6-DMSO) δ 165.9, 163.0, 142.3, 141.9, 133.6, 132.8, 126.3, 115.2, 113.7, 94.5, 54.6, 49.5, 46.3, 45.5, 23.0; **FTIR** (neat, ν_{max} cm^{-1}) 2944 (w), 2914 (w), 2843 (w), 2795 (w), 1644 (m),

1638 (m), 1593 (s), 1575 (s), 1527 (s), 1486 (m), 1404 (s); $\boldsymbol{R_f}$ 0.35 (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH); **HRMS** (ESI+) calculated for $C_{17}H_{20}N_4O^{35}Cl$ $[M+H]^+$ 331.1326, found 331.1342; **LC/MS** $[M+H]^+$ found 331.6, purity 100%; **HPLC** R_t 5.28 min, purity 100%.

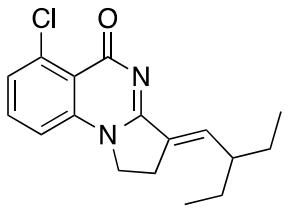
(*E*)-6-Chloro-3-((4-ethylpiperazin-1-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**27**)



18 (52.1 mg, 0.189 mmol) was reacted with 1-ethylpiperazine according to general procedure E. Purification by FCC (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH) gave the product **27** (38.2 mg, 0.111 mmol, 59%) as a yellow amorphous solid.

Decomposition 223 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (1H, s, br), 7.39 (1H, t, *J* 8.0 Hz), 7.26 (1H, m), 6.87 (1H, dd, *J* 8.2, 0.6 Hz), 4.05 (2H, app t, *J* 8.0 Hz), 3.51 (4H, app t, *J* 5.0 Hz), 3.14 (2H, t, *J* 7.8 Hz), 2.50 (4H, app t, *J* 4.8 Hz), 2.44 (2H, q, *J* 7.2 Hz), 1.21 (3H, t, *J* 7.2 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.0, 163.6, 143.3, 141.9, 136.1, 132.3, 127.2, 116.4, 112.1, 93.8, 52.8, 52.4, 50.3, 46.5, 23.8, 12.0; **FTIR** (neat, ν_{max} cm^{-1}) 2968 (w), 2933 (w), 2813 (w), 1645 (m), 1633 (m), 1593 (s), 1577 (s), 1514 (s), 1485 (m), 1404 (m); $\boldsymbol{R_f}$ 0.42 (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH); **HRMS** (ESI+) calculated for $C_{18}H_{22}N_4O^{35}Cl$ $[M+H]^+$ 345.1475, found 345.1482; **LC/MS** $[M+H]^+$ found 345.6, purity 100%; **HPLC** R_t 5.79 min, purity 100%.

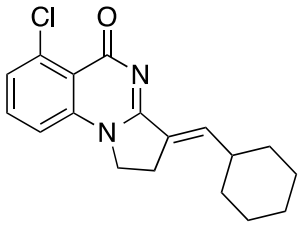
(*E*)-6-Chloro-3-(2-ethylbutylidene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**28**)



To a solution of **18c** (50.0 mg, 0.227 mmol) in CH_2Cl_2 (920 μL) ^tBuOK (30.5 mg, 0.272 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then 2-ethylbutyraldehyde (30.8 μL, 0.250 mmol, 1.1 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. Purification by FCC (4% MeOH/CH_2Cl_2) gave the product **28** (27.6 mg, 0.0911 mmol, 40%) as a white amorphous solid.

Decomposition 184–187 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (1H, t, *J* 8.1 Hz), 7.34 (1H, dd, *J* 7.9 Hz), 7.06 (1H, dd, *J* 8.3 Hz), 6.88 (1H, dt, *J* 10.8, 0.9 Hz), 4.16 (2H, t, *J* 7.3 Hz), 3.01 (2H, dt, *J* 7.3, 2.7 Hz), 2.19–2.13 (1H, m), 1.60–1.53 (2H, m), 1.42–1.34 (2H, m), 0.87 (6H, t, *J* 7.4 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.2, 159.3, 142.8, 141.2, 136.2, 132.9, 130.9, 128.7, 116.7, 113.3, 46.4, 44.4, 27.7, 23.0, 12.1; **FTIR** (neat, ν_{max} cm^{-1}) 2963 (m), 2927 (m), 2877 (m,), 2861 (m), 1645 (s), 1601 (s), 1584 (s), 1543 (m), 1483 (s); $\boldsymbol{R_f}$ 0.29 (4% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{17}H_{20}N_2O^{35}Cl$ $[M+H]^+$ 303.1259, found 303.1254; **LC/MS** $[M+H]^+$ found 303.1, purity 100%; **HPLC** R_t 9.08 min, purity 97%.

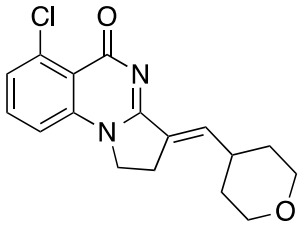
(*E*)-6-Chloro-3-(cyclohexylmethylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**29**)



To a solution of **18c** (50.0 mg, 0.227 mmol, 1.0 eq.) in CH_2Cl_2 (920 μL) ^tBuOK (30.5 mg, 0.272 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then cyclohexanecarboxcarbaldehyde (30.2 μL, 0.250 mmol, 1.1 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2) gave the product **29** (45.5 mg, 0.150 mmol, 66%) as an off-white amorphous solid.

Decomposition 221 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (1H, t, *J* 8.1 Hz), 7.38 (1H, dd, *J* 7.0, 0.6 Hz), 7.06 (1H, dd, *J* 8.2, 0.5 Hz), 6.98 (1H, dt, *J* 9.9, 2.6 Hz), 4.16 (2H, t, *J* 7.3 Hz), 3.03 (2H, dt, *J* 7.3, 2.6 Hz), 2.32–2.26 (1H, m), 1.79–1.77 (2H, m), 1.71–1.69 (2H, m), 1.34–1.23 (6H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.2, 159.8, 143.1, 141.2, 136.4, 132.9, 128.87, 128.85, 116.8, 113.2, 46.5, 39.4, 31.8, 25.9, 25.6, 22.5; **FTIR** (neat, ν_{max} cm^{-1}) 2922 (s), 2851 (m), 2206 (w), 1642 (m), 1602 (m), 1587 (s), 1534 (m), 1495 (m), 1471 (m), 725 (m); $\boldsymbol{R_f}$ 0.28 (3% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{18}H_{20}N_2O^{35}Cl$ $[M+H]^+$ 315.1264, found 315.1272; **LC/MS** $[M+H]^+$ found 315.6, purity 97%.

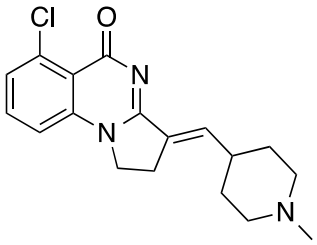
(*E*)-6-Chloro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**30**)



To a solution of **18c** (50.0 mg, 0.227 mmol) in CH_2Cl_2 (920 μL) ^tBuOK (30.5 mg, 0.272 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then tetrahydro-2*H*-pyrane-4-carbaldehyde (0.250 mmol, 1.1 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. Purification by preparative TLC (5% MeOH/CH_2Cl_2) gave the product **30** (48.4 mg, 0.153 mmol, 67%) as an off-white amorphous solid.

Decomposition 211–214 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 (1H, t, *J* 8.1 Hz), 7.41 (1H, dd, *J* 7.8, 0.7 Hz), 7.08 (1H, dd, *J* 8.3, 0.7 Hz), 6.98 (1H, dt, *J* 9.7, 2.8 Hz), 4.19 (2H, t, *J* 7.3 Hz), 4.01 (2H, dt, *J* 11.5, 3.4 Hz), 3.50–3.45 (2H, m), 3.06 (2H, dt, *J* 7.3, 2.8 Hz), 2.59–2.53 (1H, m), 1.66–1.62 (4H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.1, 159.5, 141.2, 140.5, 136.6, 133.0, 130.0, 129.1, 116.9, 113.2, 67.3, 46.5, 36.6, 31.3, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2931 (m), 2832 (m), 1645 (m), 1602 (s), 1585 (s), 1543 (m), 1488 (s); $\boldsymbol{R_f}$ 0.33 (5% MeOH/CH_2Cl_2); **HRMS** (ESI+) calculated for $C_{17}H_{18}N_2O_2{}^{35}Cl$ $[M+H]^+$ 317.1052, found 317.1056.

(*E*)-6-Chloro-3-((1-methylpiperidin-4-yl)methylene)-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**31**)



To a solution of **18c** (61.0 mg, 0.276 mmol, 1.0 eq.) in CH_2Cl_2 (920 μL) ^tBuOK (30.5 mg, 0.272 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then 1-methylpiperidine carbaldehyde (0.304 mmol, 1.1 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. was reacted with. Purification by preparative TLC (5% MeOH/CH_2Cl_2) gave the product **31** (14.0 mg, 0.0510 mmol, 45%) as an off-white amorphous solid.

Decomposition 206–208 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (1H, t, *J* 8.1 Hz), 7.37 (1H, dd, *J* 7.9, 0.8 Hz), 7.06 (1H, dd, *J* 8.3, 0.8 Hz), 6.99 (1H, dt, *J* 9.8, 2.6 Hz), 4.17 (2H, app t, *J* 7.4 Hz), 3.04 (2H, dt, *J* 7.3, 2.8 Hz), 2.87 (2H, br d, *J* 11.6 Hz), 2.29 (3H, s), 2.29–2.25 (1H, m), 2.01 (2H, t, *J* 11.2), 1.71 (2H, dd, *J* 13.6, 2.5 Hz), 1.65–1.58 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 168.1, 159.5, 141.4, 141.2, 136.4, 133.0, 129.9, 128.9, 116.7, 113.2, 55.2, 46.7, 46.5, 31.1, 22.6; **FTIR** (neat, ν_{max} cm^{-1}) 2927 (w), 2781 (w), 2652 (w), 1645 (w), 1588 (s), 1541 (m), 1489 (s), 1416 (w); $\boldsymbol{R_f}$ 0.18 (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH); **HRMS** (ESI+) calculated for $C_{18}H_{21}N_3O^{35}Cl$ $[M+H]^+$ 330.1373, found 330.1375; **LC/MS** $[M+H]^+$ found 330.6, purity 98%.

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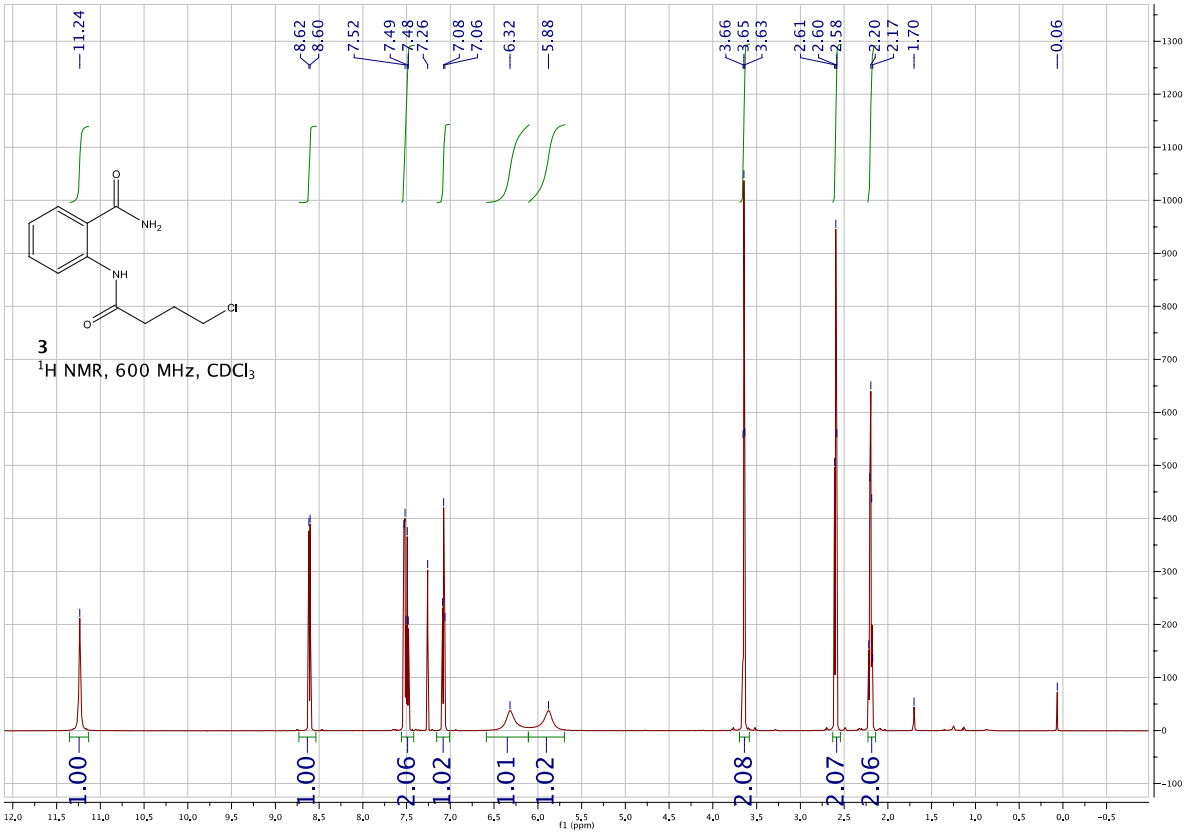
NMR SPECTRA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3.63
2.61
2.60
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2.20
2.17
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1.00
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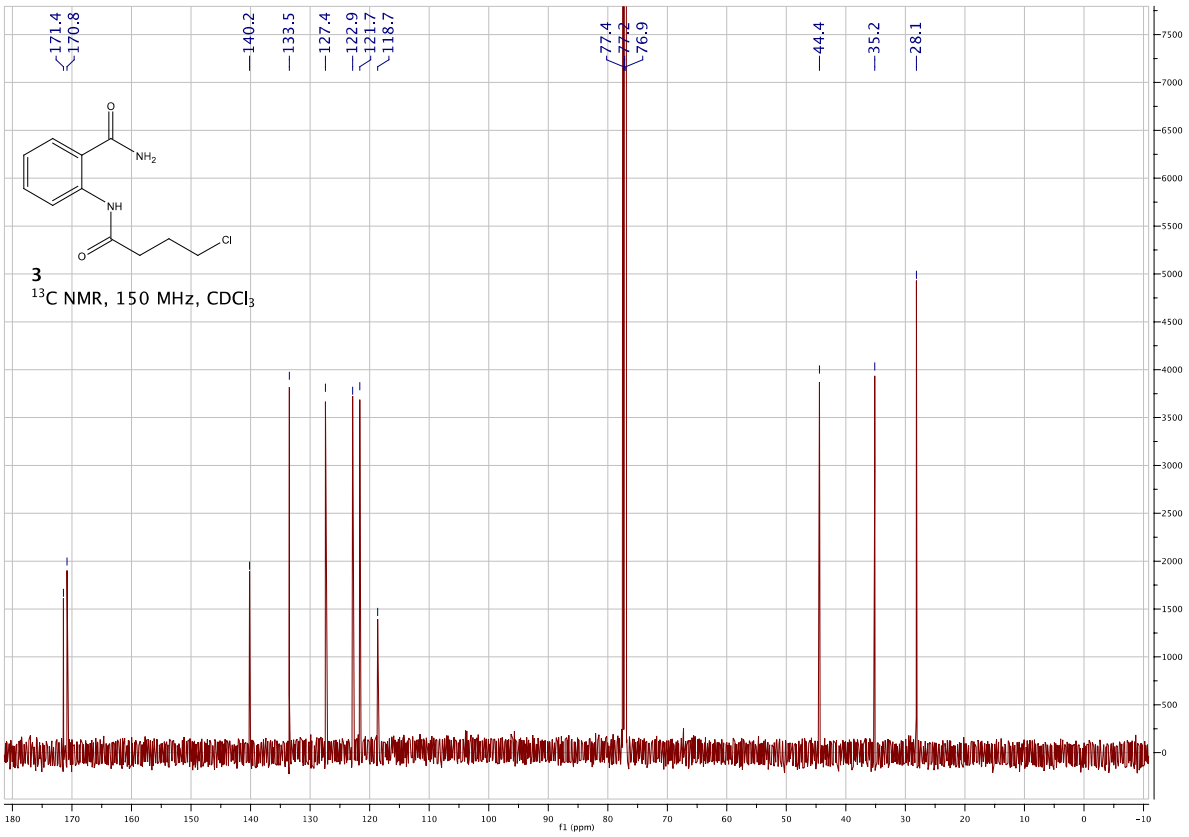
2.06
f1 (ppm)
3
1H NMR, 600 MHz, CDCl3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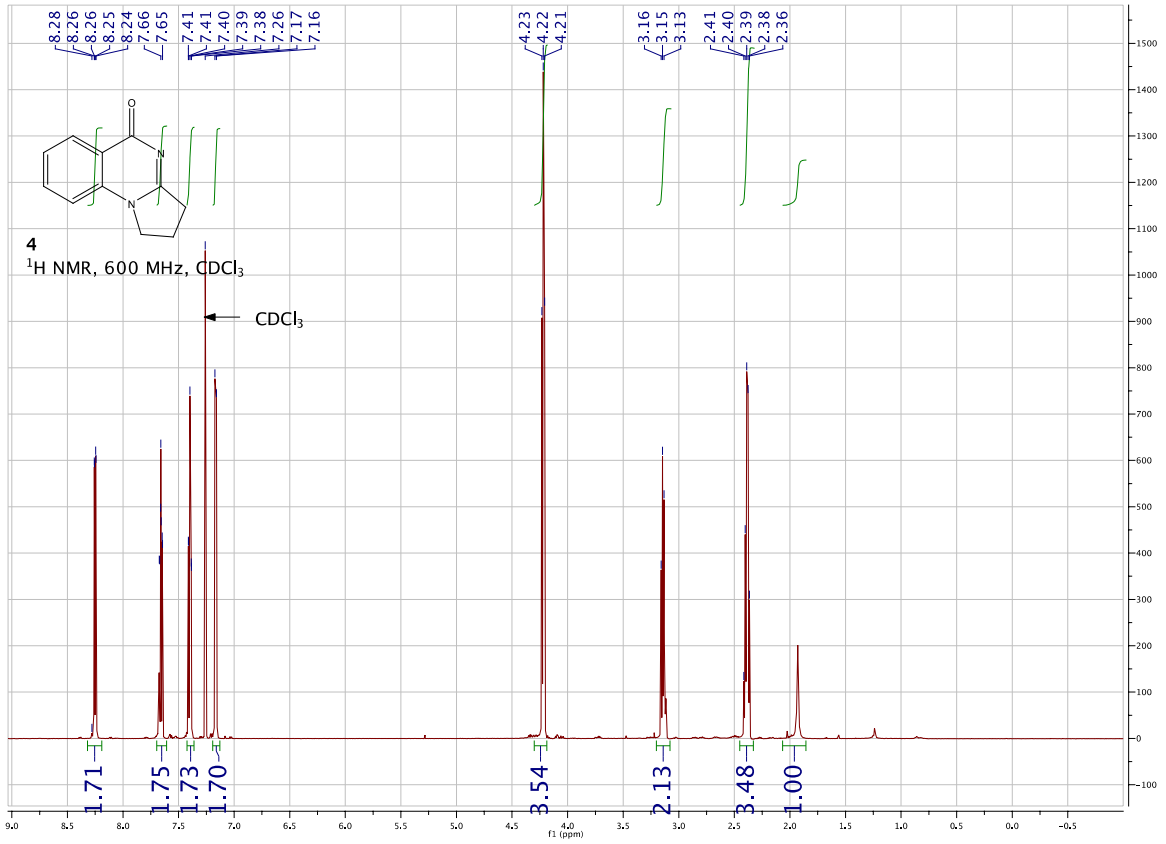
28.1
f1 (ppm)
3
13C NMR, 150 MHz, CDCl3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7.17
7.16
4.23
4.22
4.21
3.16
3.15
3.13
2.41
2.40
2.39
2.38
2.36
4
1H NMR, 600 MHz, CDCl3
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2.13
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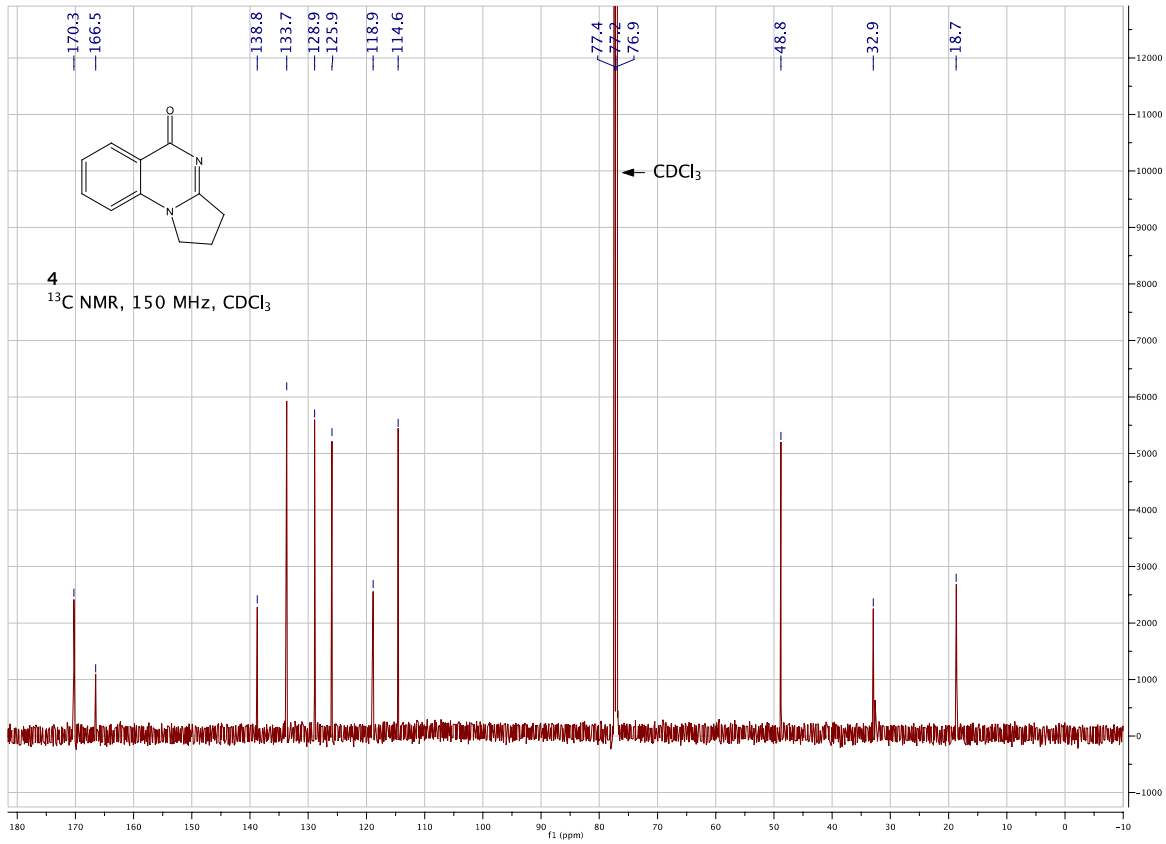
1.00
f1 (ppm)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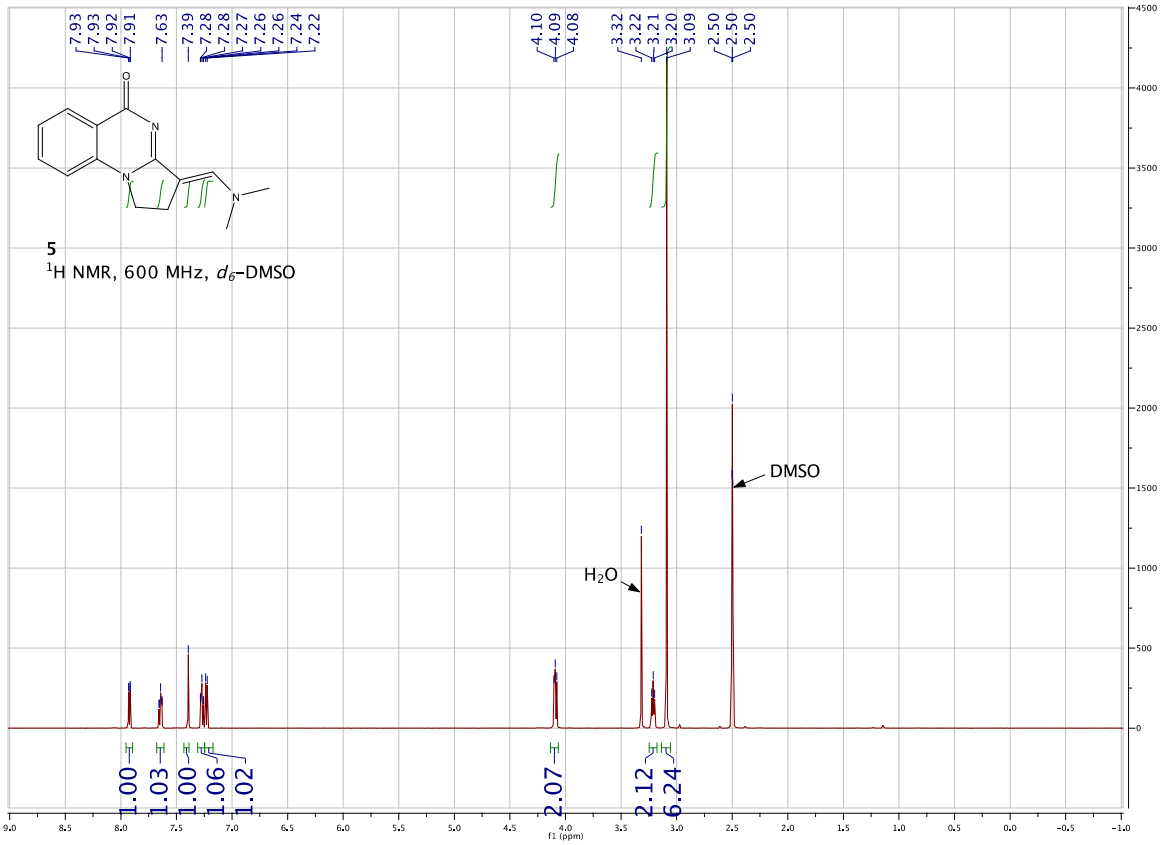
18.7
CDCl3
4
13C NMR, 150 MHz, CDCl3
f1 (ppm)



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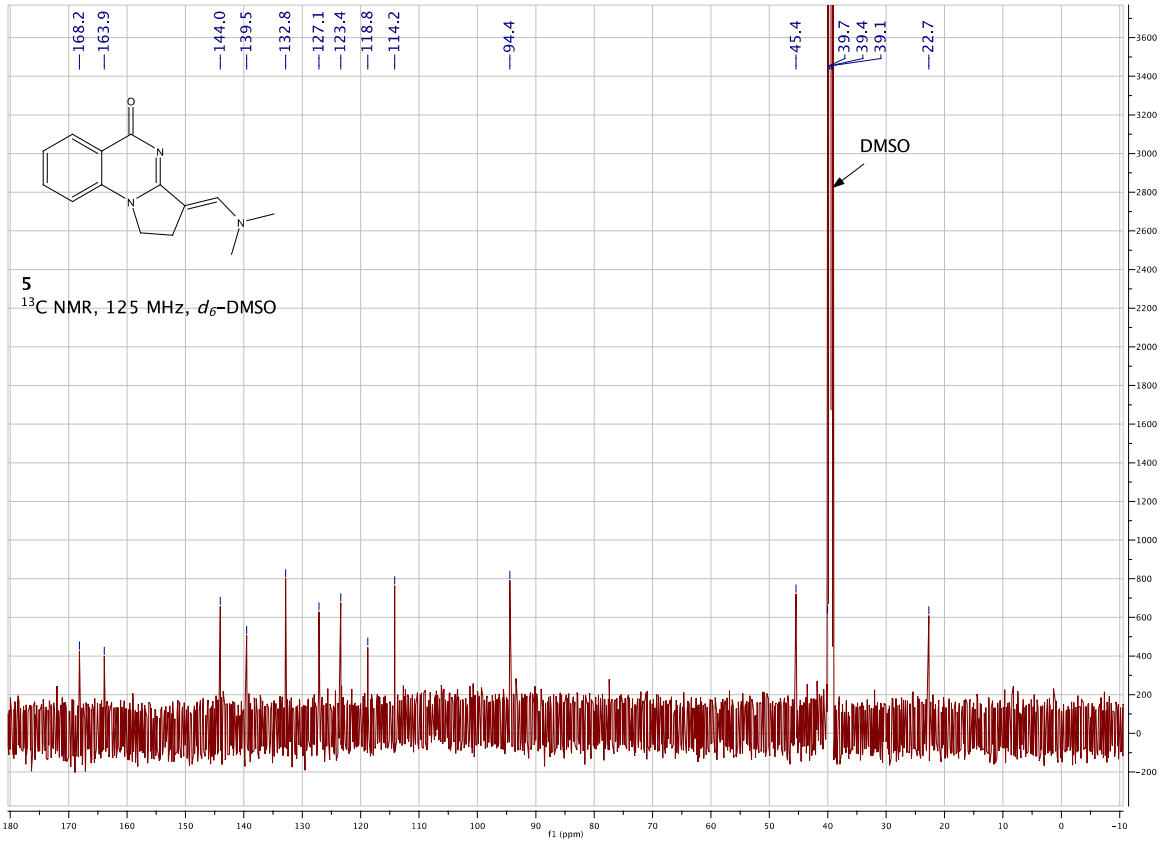

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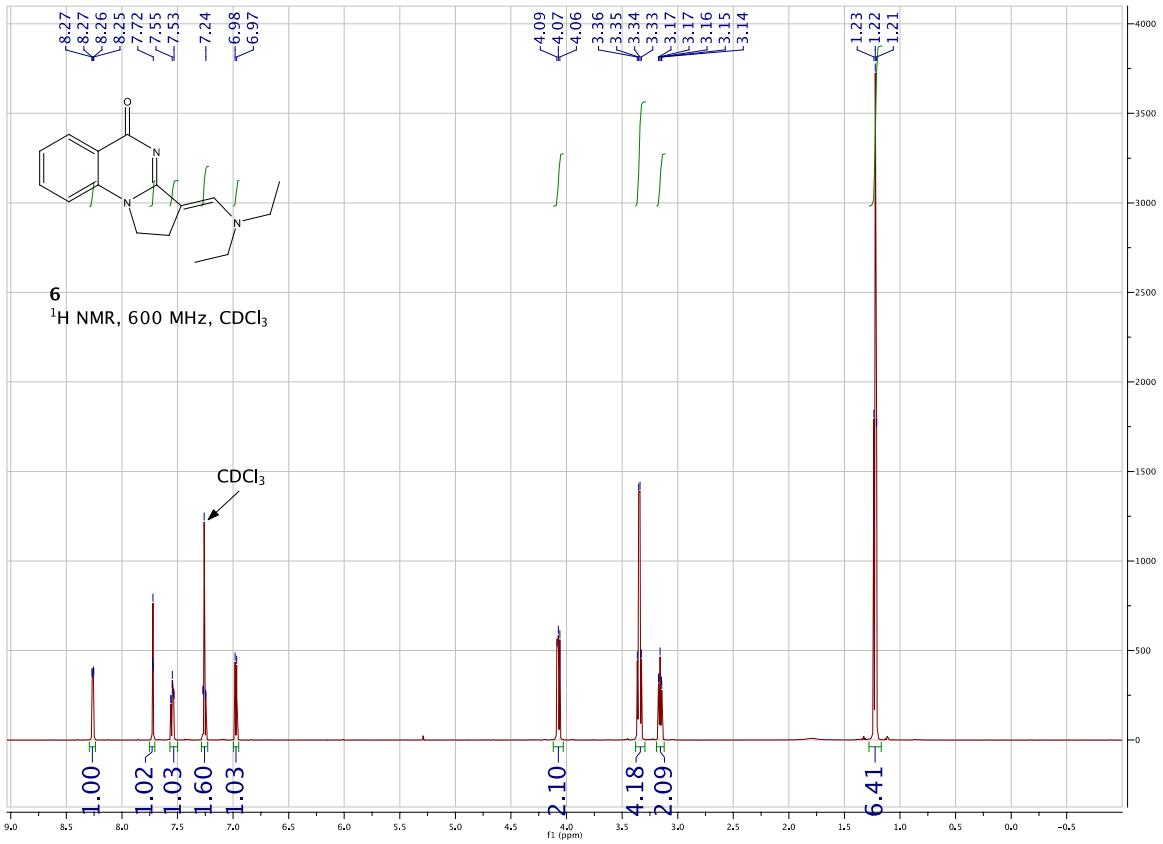
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4.06
3.36
3.35
3.34
3.33
3.17
3.17
3.16
3.15
3.14
1.23
1.22
1.21
6
^{1}H NMR, 600 MHz, $CDCl_3$
$CDCl_3$
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1.60
1.03
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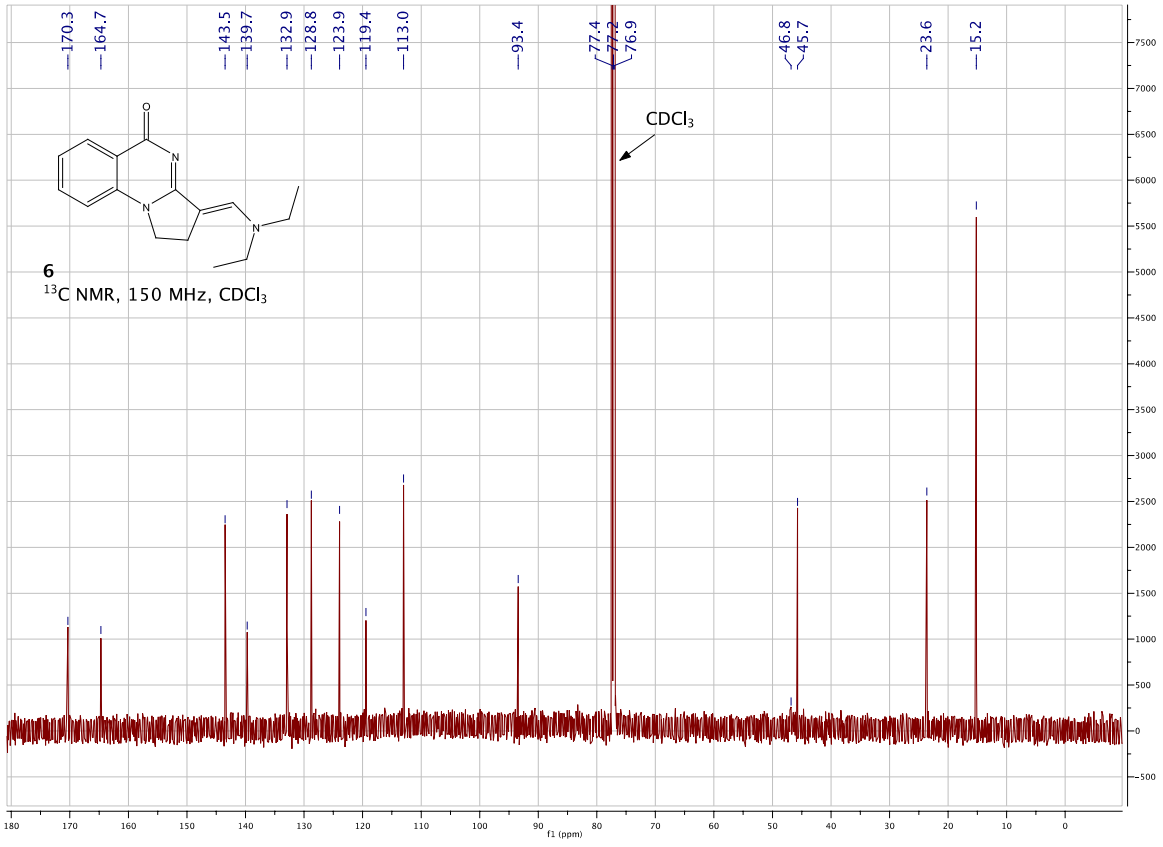
6.41
f1 (ppm)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23.6
15.2
6
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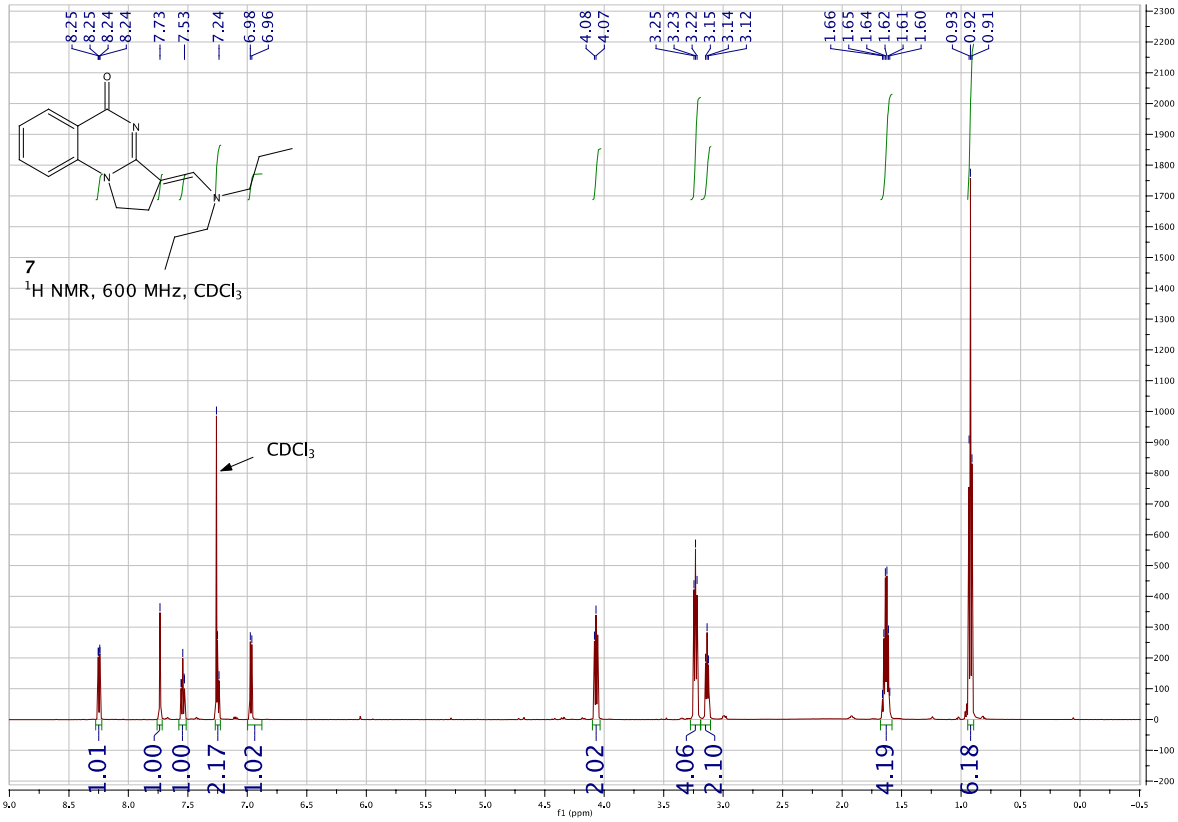
$CDCl_3$
f1 (ppm)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3.14
3.12
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1.65
1.64
1.62
1.61
1.60
0.93
0.92
0.91
7
1H NMR, 600 MHz, CDCl3
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2.02
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2.10
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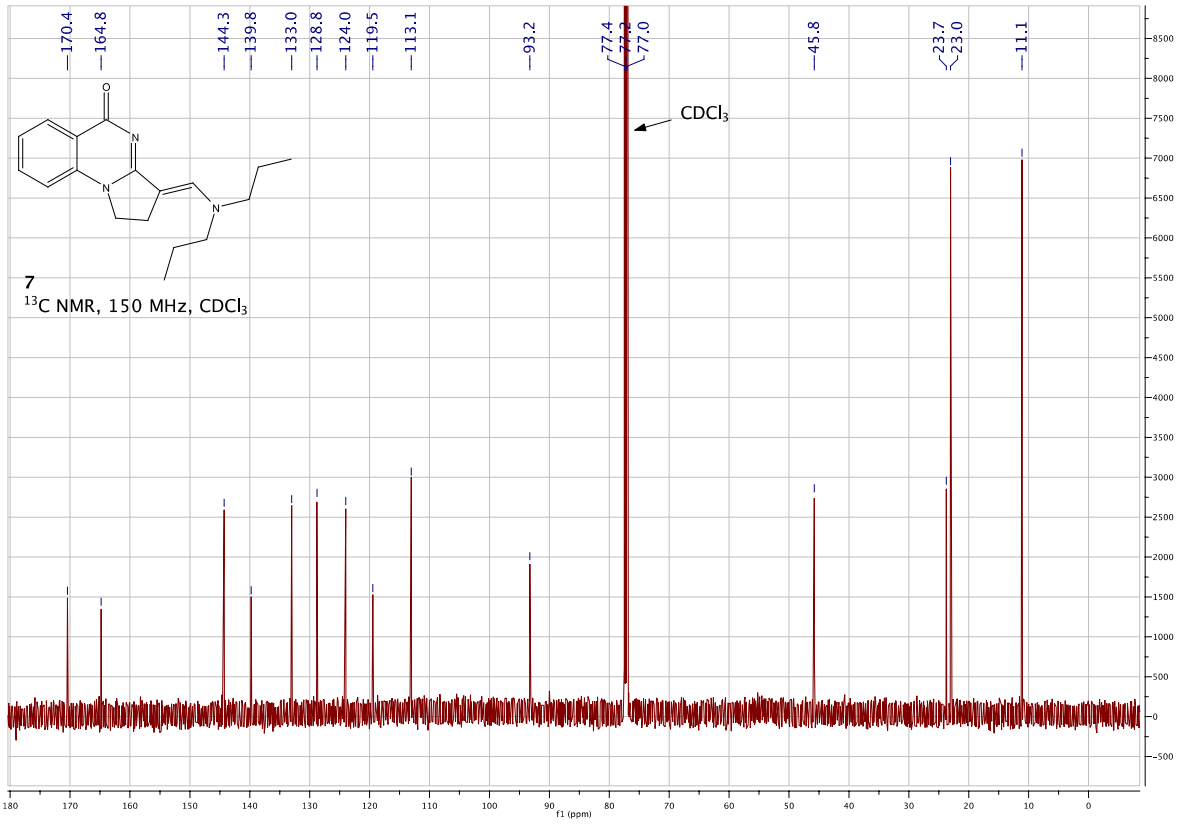
6.18
f1 (ppm)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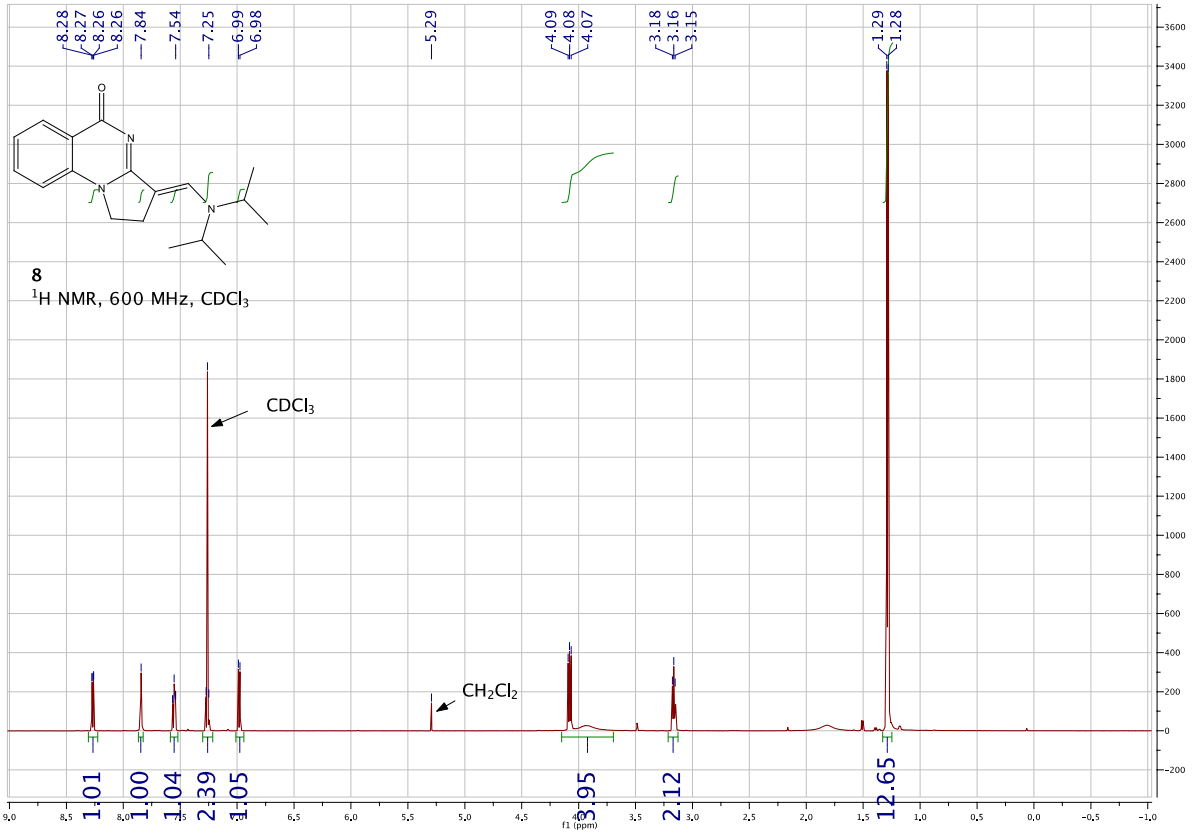
7
13C NMR, 150 MHz, CDCl3
CDCl3
f1 (ppm)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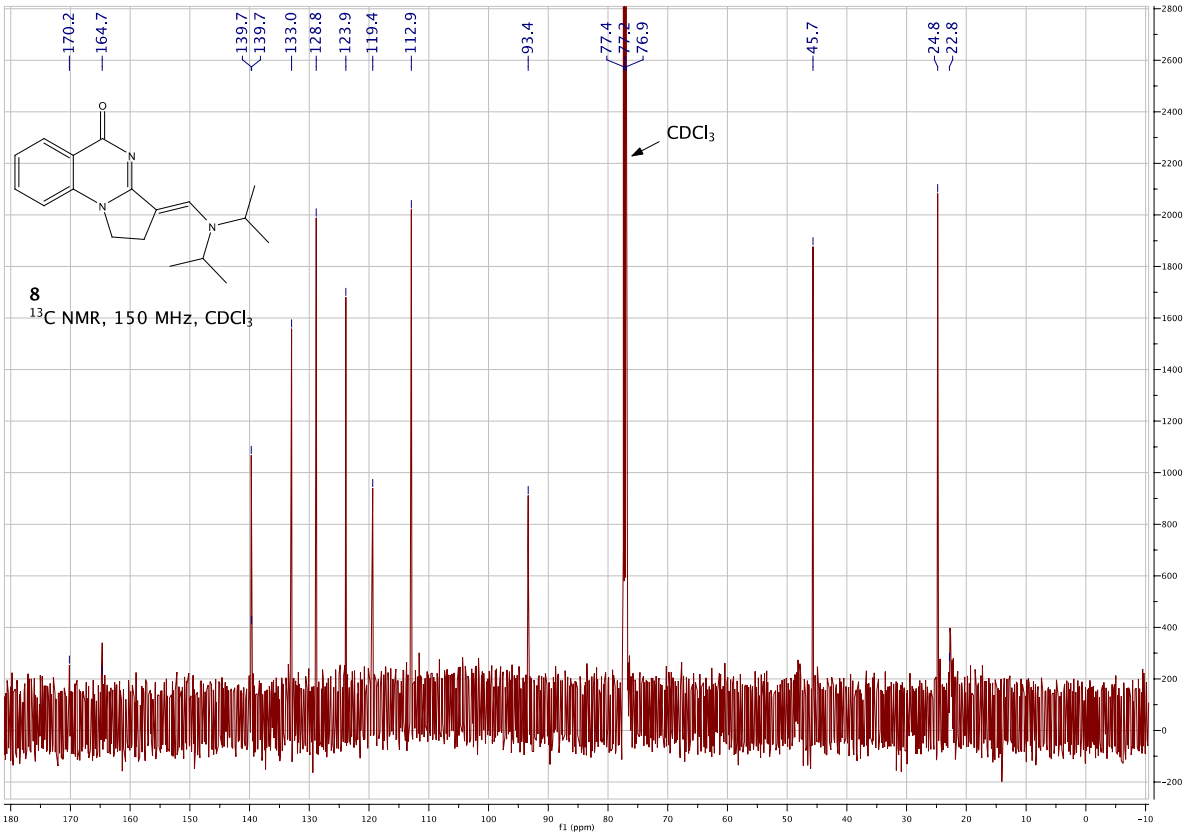
f1 (ppm)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8
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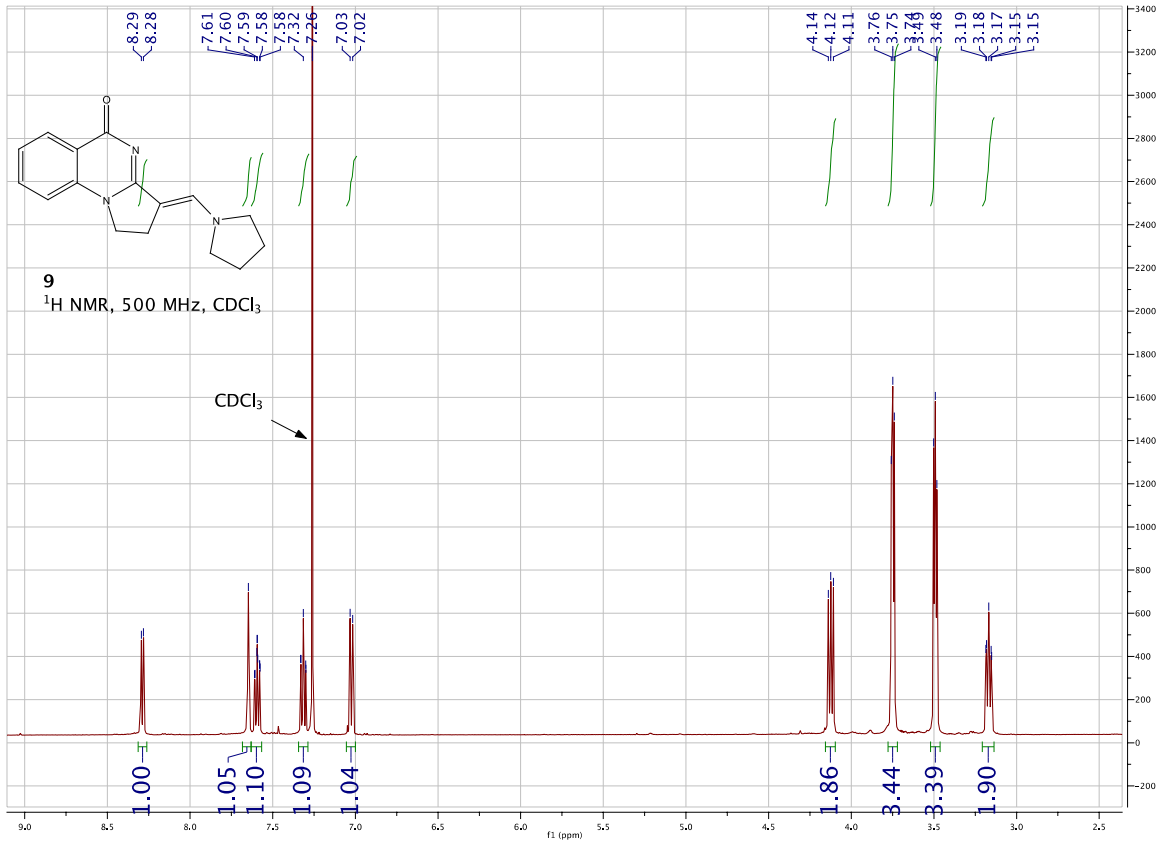
$CDCl_3$
f1 (ppm)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4.12
4.11
3.76
3.75
3.48
3.19
3.18
3.17
3.15
3.15
9
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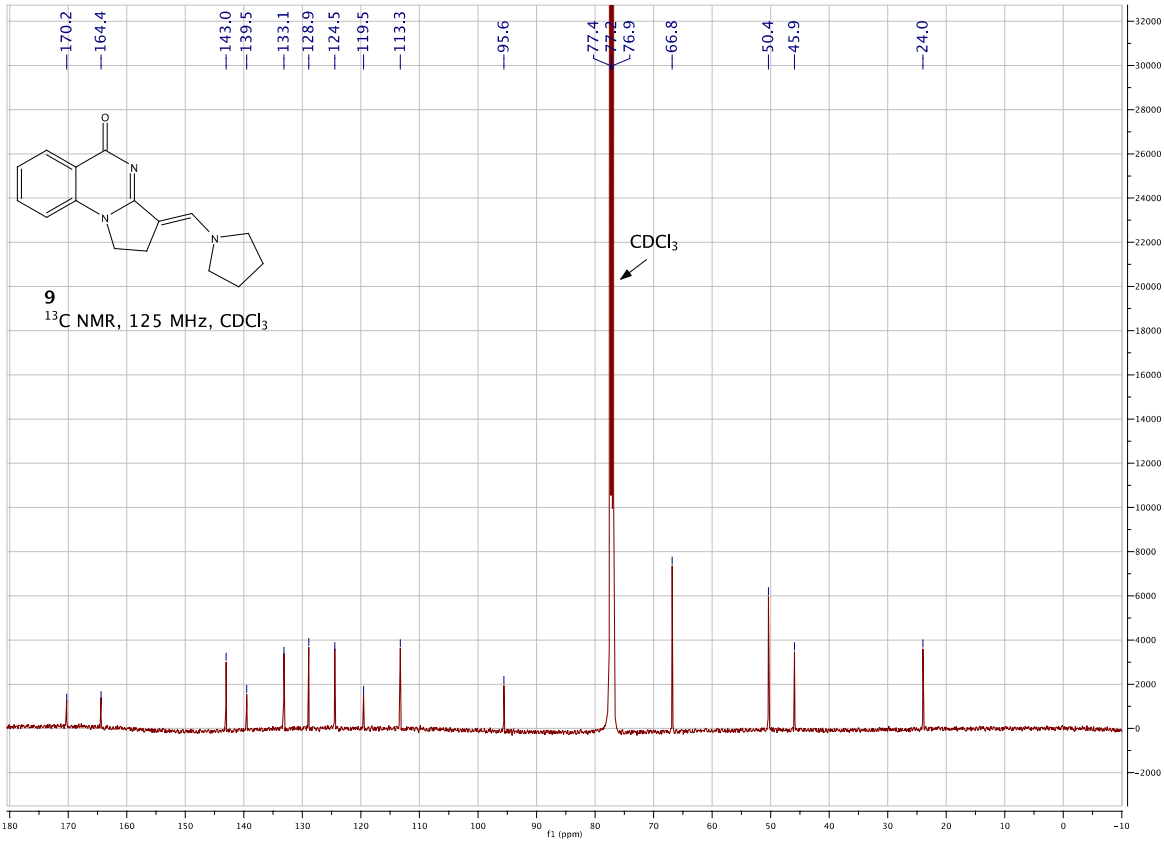
f1 (ppm)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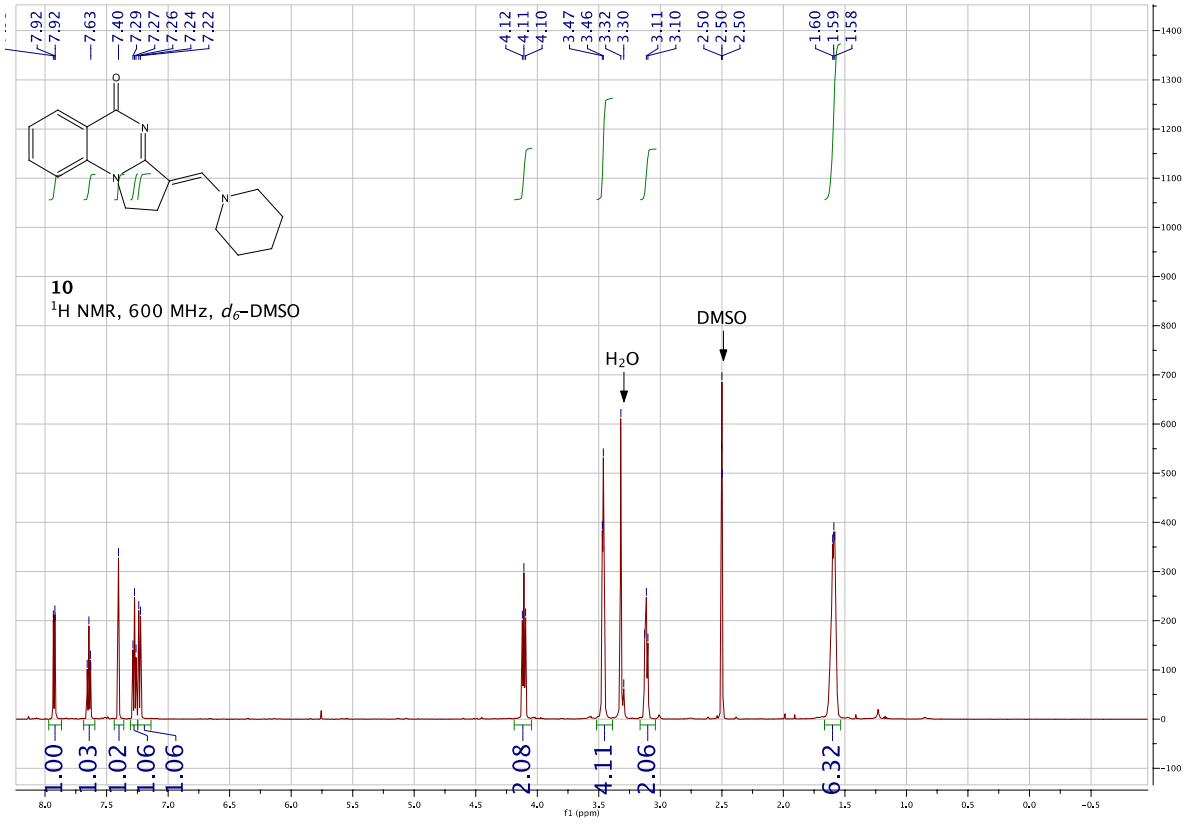
CDCl3
f1 (ppm)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10
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2.08
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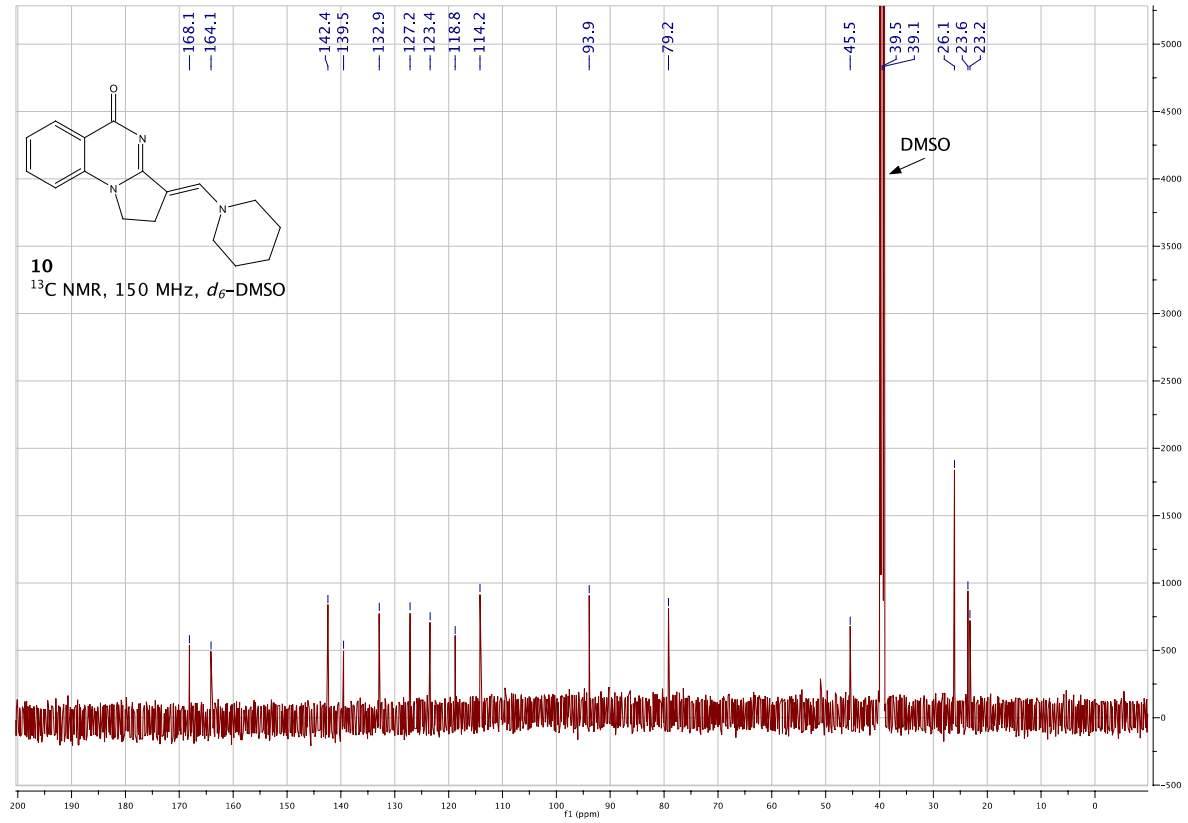
6.32
f1 (ppm)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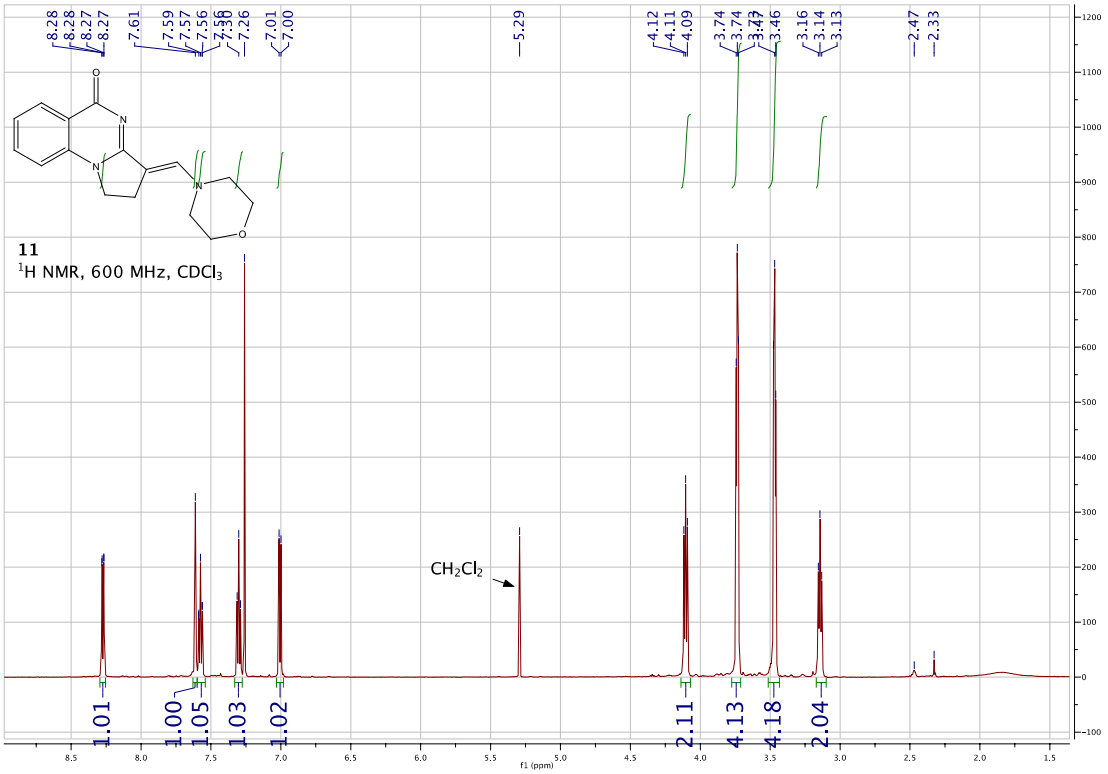
DMSO
f1 (ppm)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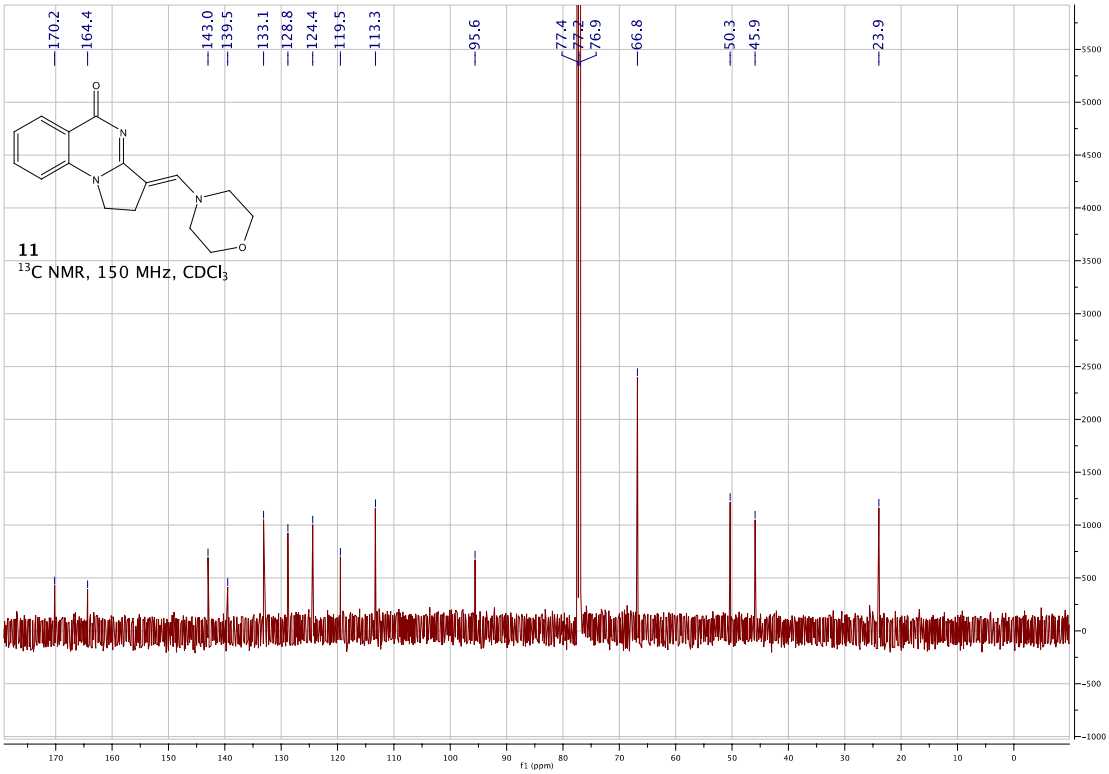
7.56
7.56
7.26
7.01
7.00
5.29
4.12
4.11
4.09
3.74
3.74
3.47
3.46
3.16
3.14
3.13
2.47
2.33
11
1H NMR, 600 MHz, CDCl3
CH2Cl2
1.01
1.00
1.05
1.03
1.02
2.11
4.13
4.18
2.04
f1 (ppm)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139.5
133.1
128.8
124.4
119.5
113.3
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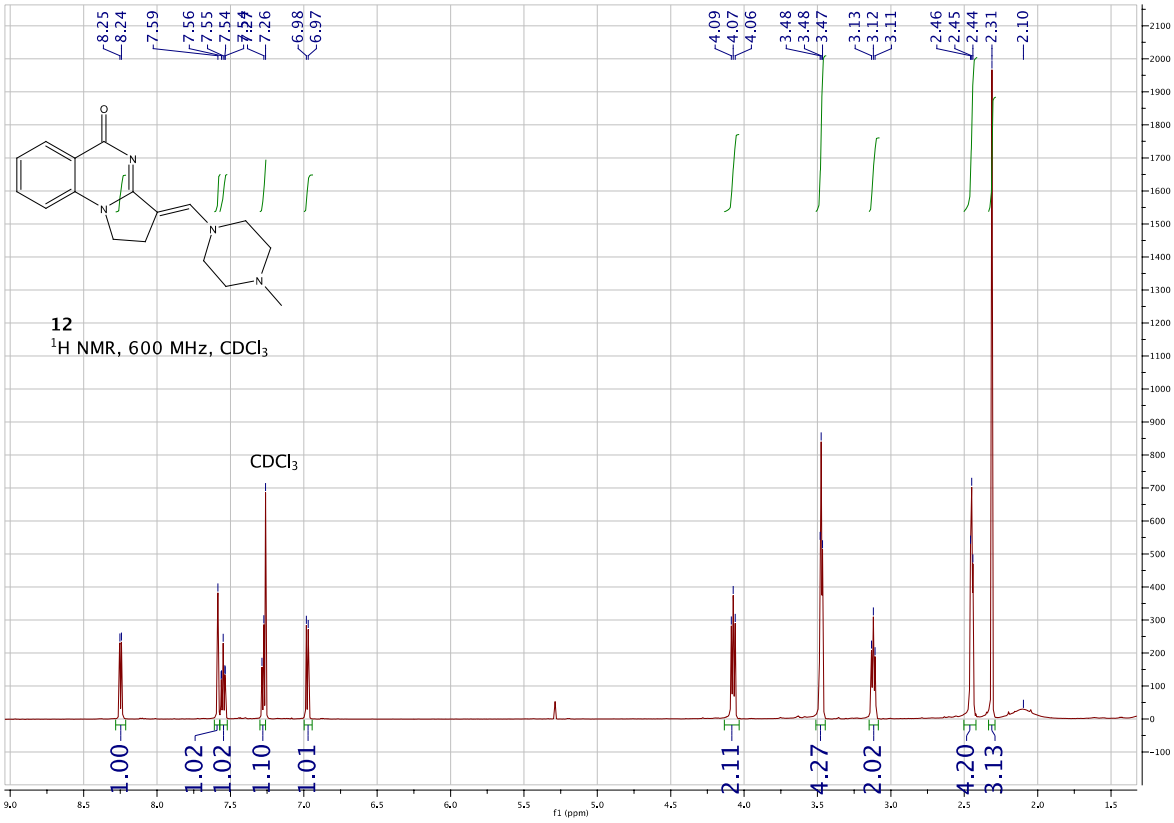
77.2
76.9
66.8
50.3
45.9
23.9
11
13C NMR, 150 MHz, CDCl3
f1 (ppm)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8.24
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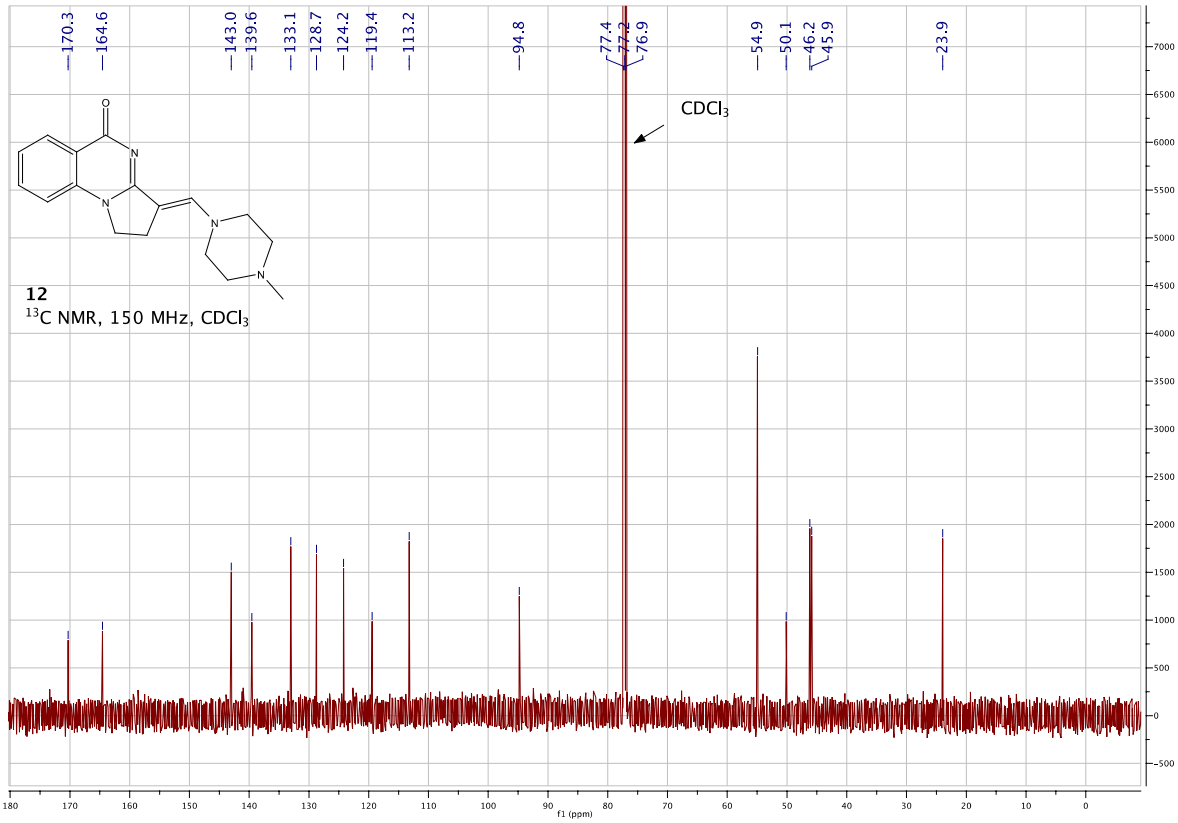
7.55
7.54
7.26
6.98
6.97
4.09
4.07
4.06
3.48
3.48
3.47
3.13
3.12
3.11
2.46
2.45
2.44
2.31
2.10
12
1H NMR, 600 MHz, CDCl3
CDCl3
1.00
1.02
1.02
1.10
1.01
2.11
4.27
2.02
4.20
3.13
f1 (ppm)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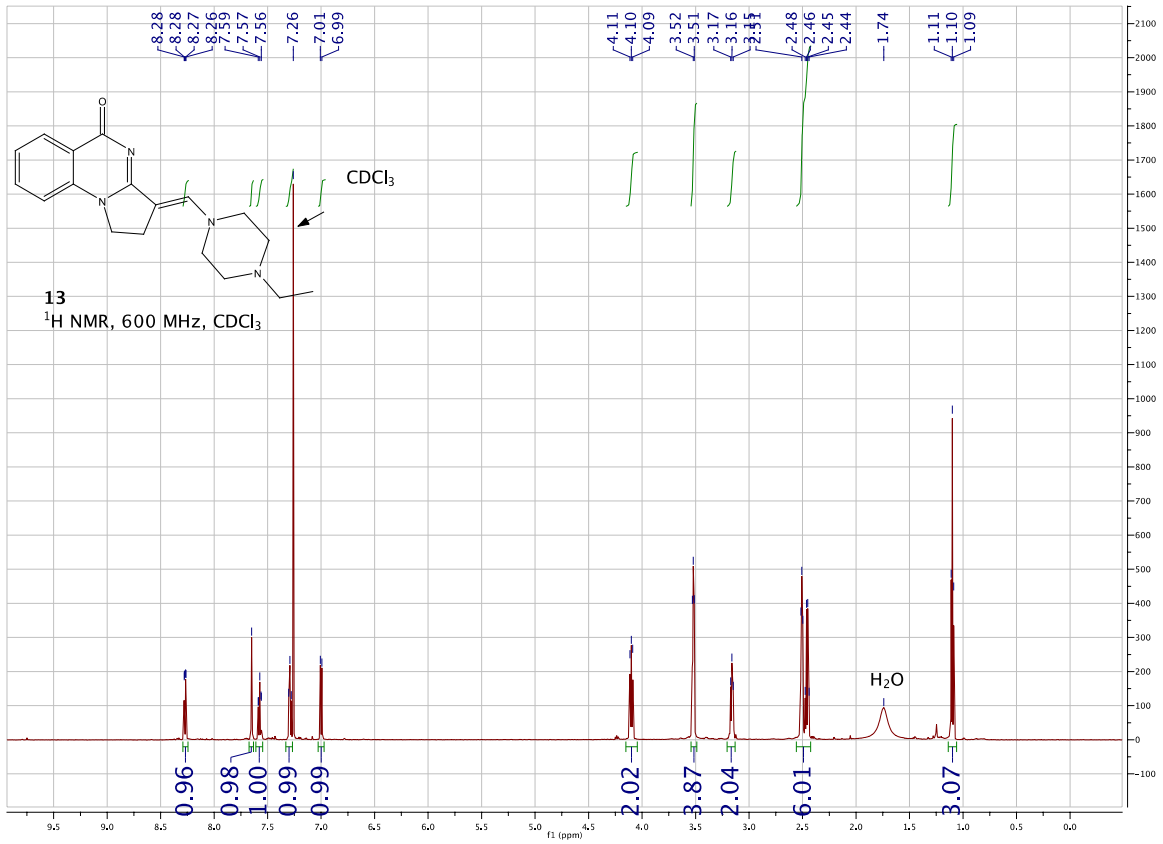
164.6
143.0
139.6
133.1
128.7
124.2
119.4
113.2
94.8
77.4
77.2
76.9
54.9
50.1
46.2
45.9
23.9
CDCl3
12
13C NMR, 150 MHz, CDCl3
f1 (ppm)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8.28
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8.26
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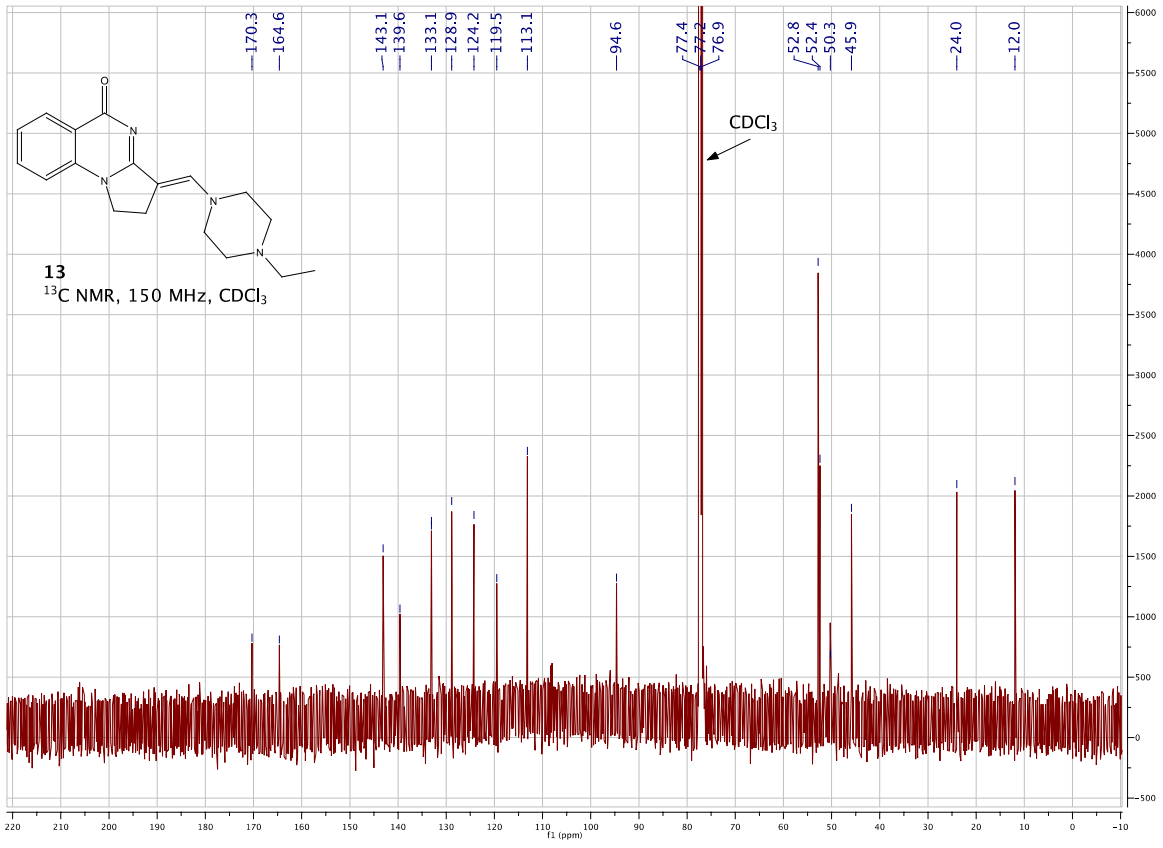
7.57
7.56
7.26
7.01
6.99
4.11
4.10
4.09
3.52
3.51
3.17
3.16
2.48
2.46
2.45
2.44
1.74
1.11
1.10
1.09
CDCl3
13
1H NMR, 600 MHz, CDCl3
H2O
0.96
0.98
1.00
0.99
0.99
2.02
3.87
2.04
6.01
3.07
f1 (ppm)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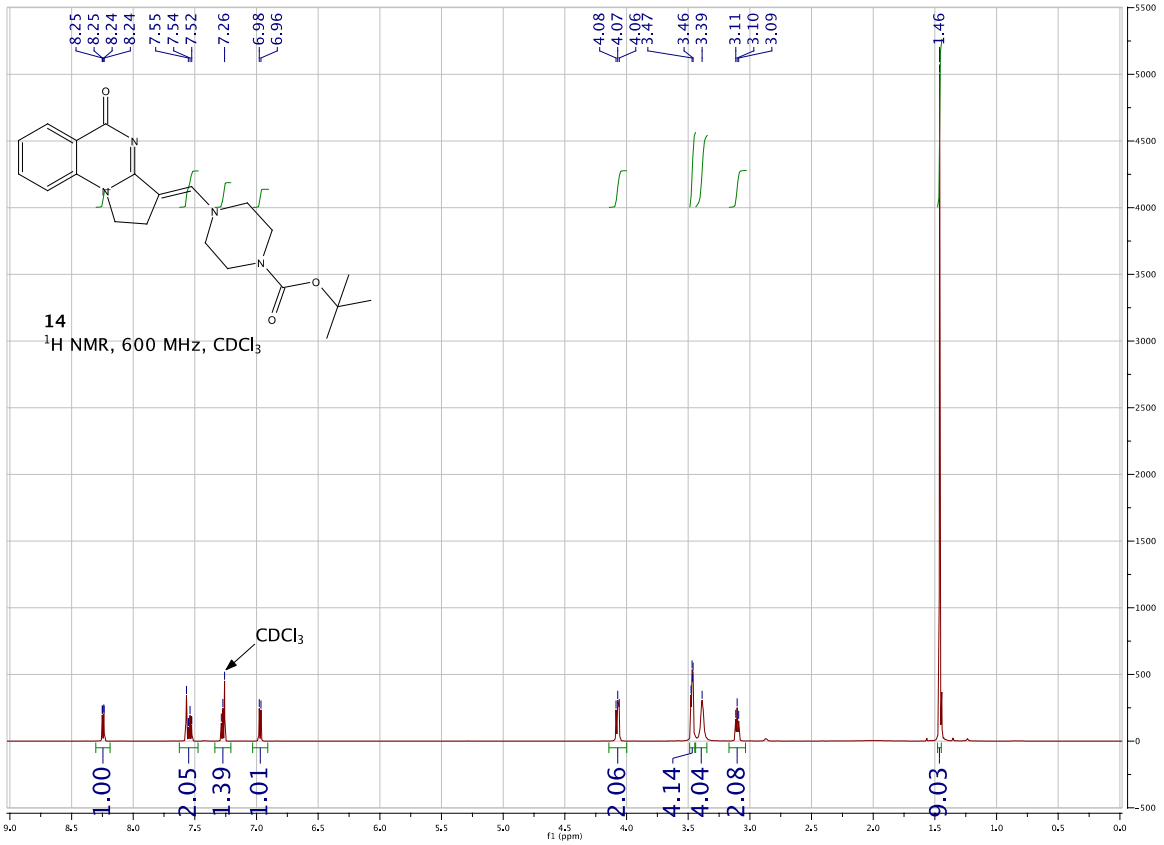
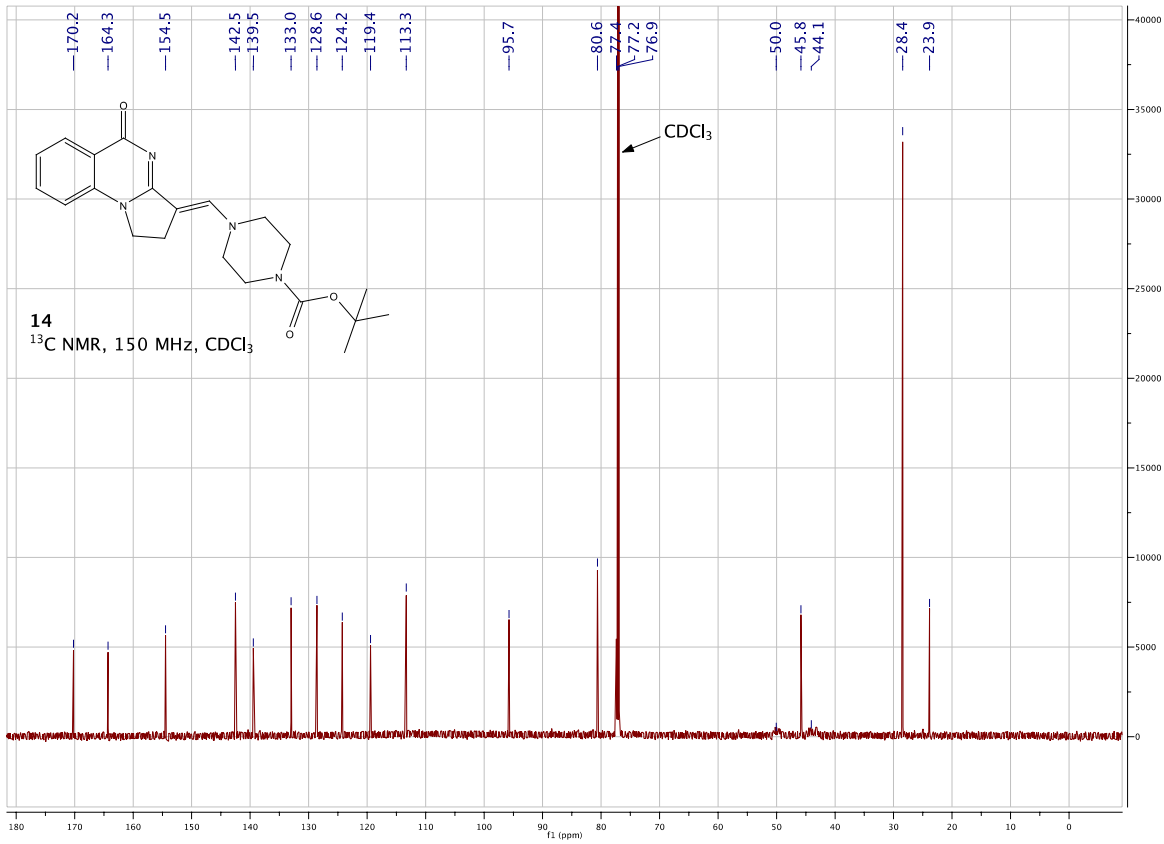
164.6
143.1
139.6
133.1
128.9
124.2
119.5
113.1
94.6
77.4
76.9
52.8
52.4
50.3
45.9
24.0
12.0
CDCl3
13
13C NMR, 150 MHz, CDCl3
f1 (ppm)


8.25
8.25
8.24
8.24
7.55
7.54
7.52
7.26
6.98
6.96
4.08
4.07
4.06
3.47
3.46
3.39
3.11
3.10
3.09
1.46
14
1H NMR, 600 MHz, CDCl3
CDCl3
1.00
2.05
1.39
1.01
2.06
4.14
4.04
2.08
9.03
f1 (ppm)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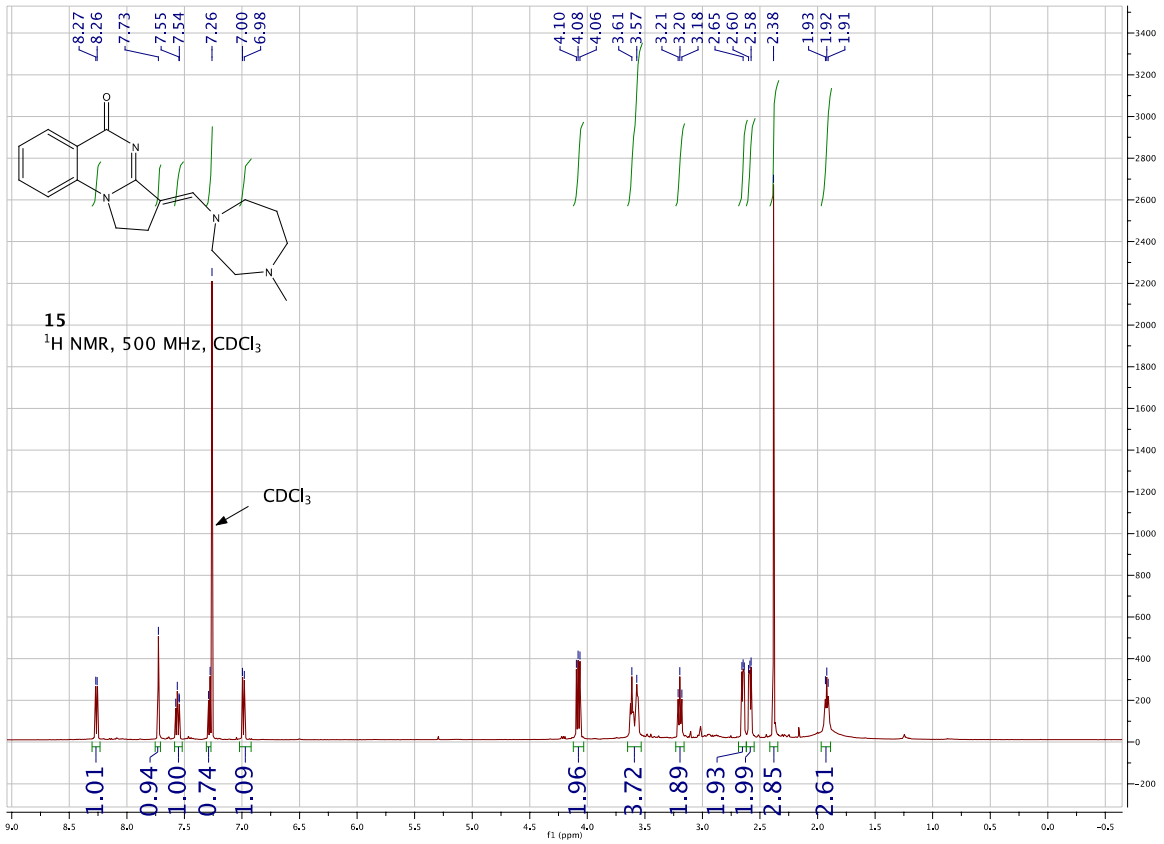
164.3
154.5
142.5
139.5
133.0
128.6
124.2
119.4
113.3
95.7
80.6
77.4
77.2
76.9
50.0
45.8
44.1
28.4
23.9
CDCl3
14
13C NMR, 150 MHz, CDCl3
f1 (ppm)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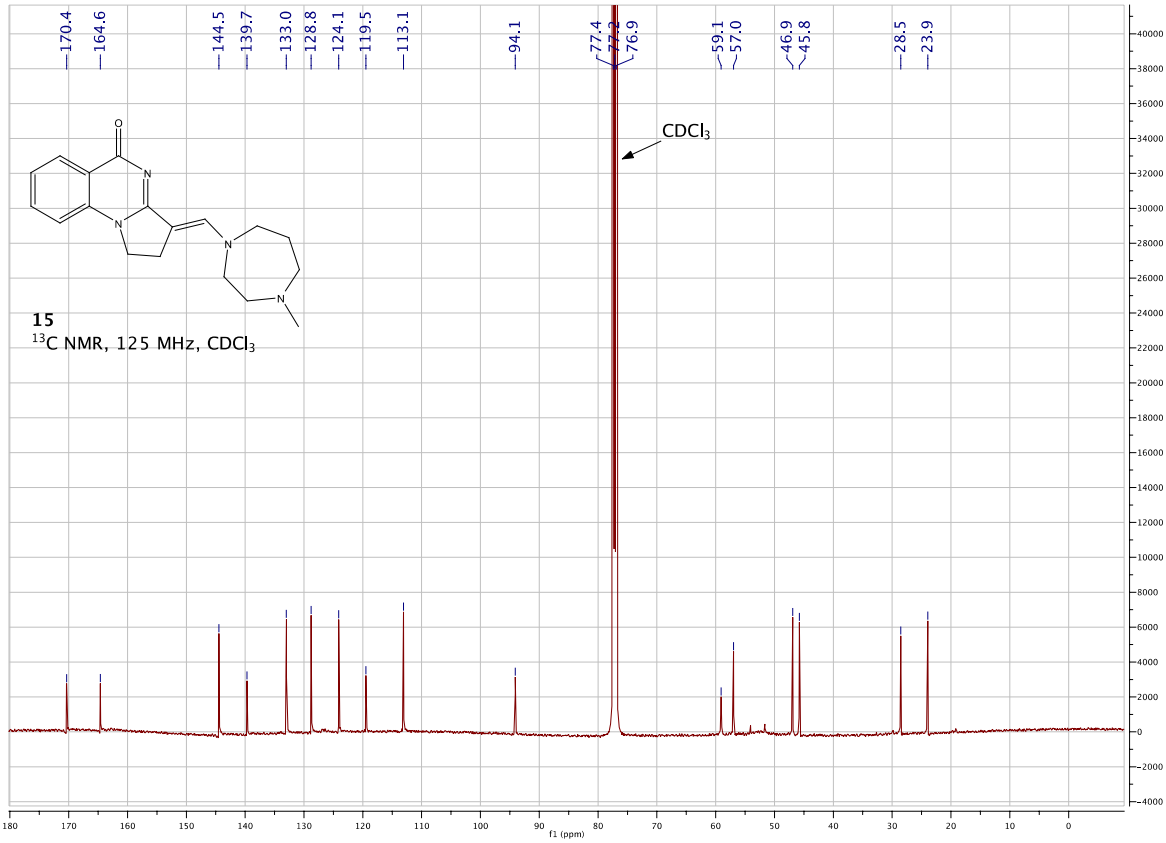
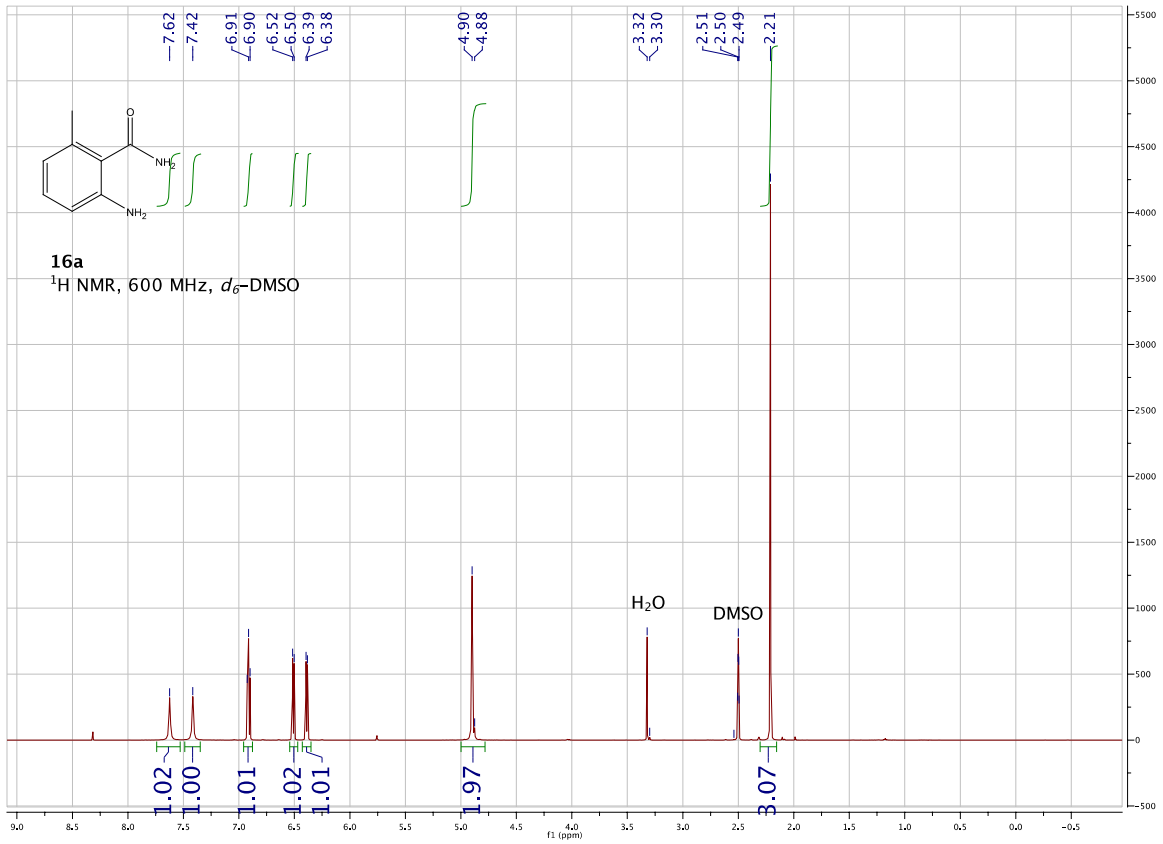
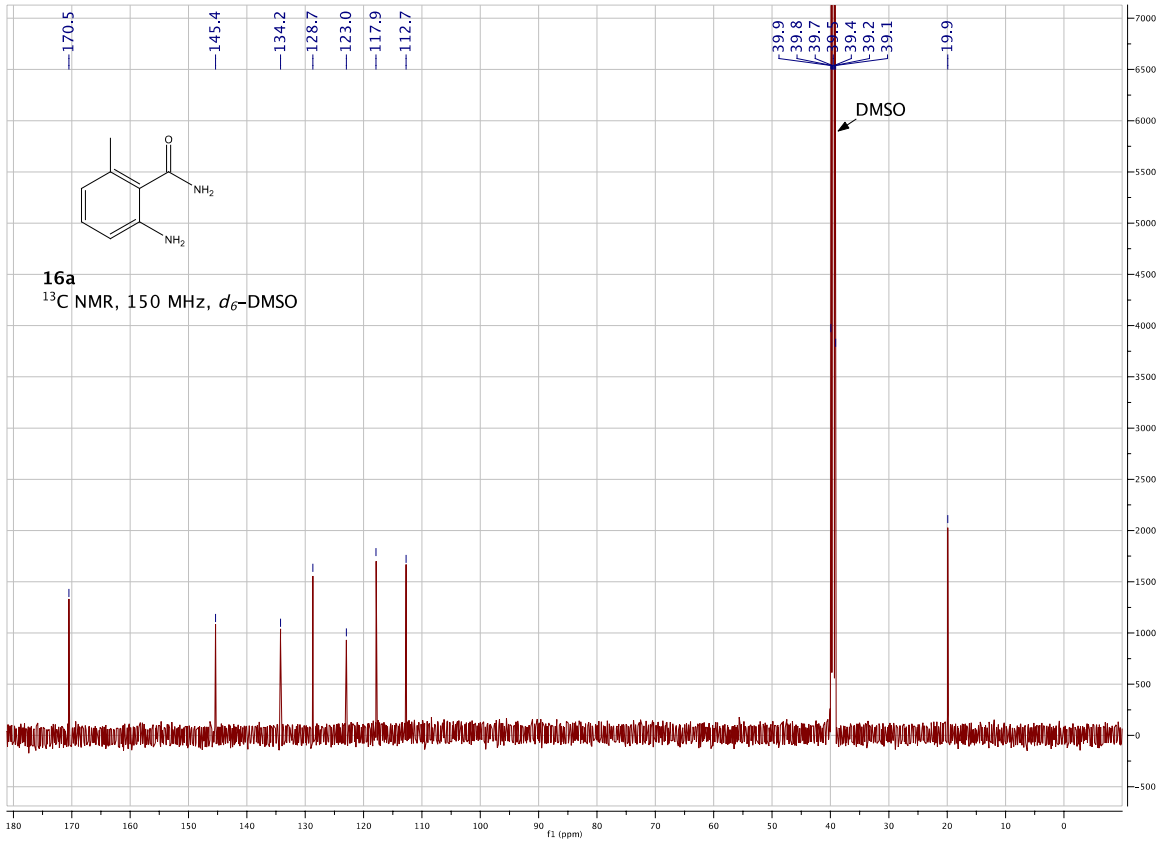
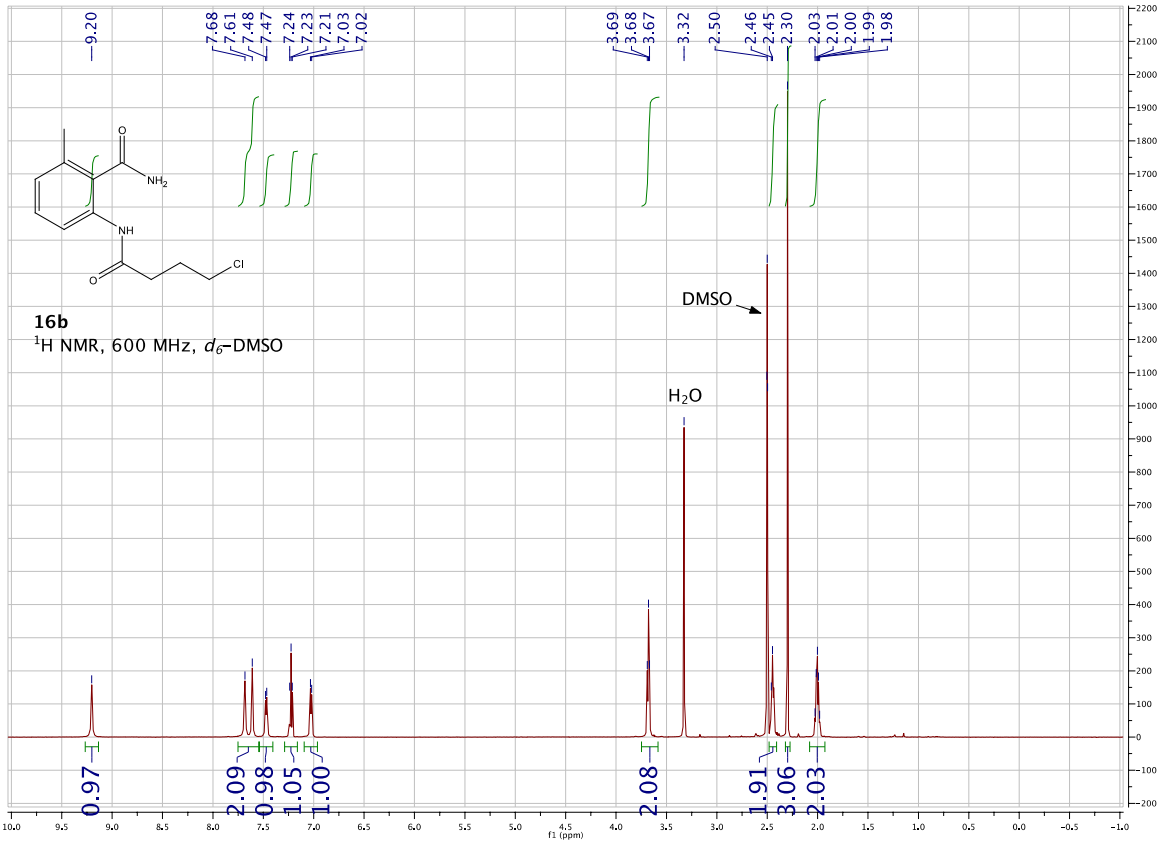
8.26
7.73
7.55
7.54
7.26
7.00
6.98
4.10
4.08
4.06
3.61
3.57
3.21
3.20
3.18
2.65
2.60
2.58
2.38
1.93
1.92
1.91
15
1H NMR, 500 MHz, CDCl3
CDCl3
1.01
0.94
1.00
0.74
1.09
1.96
3.72
1.89
1.93
1.99
2.85
2.61
f1 (ppm)

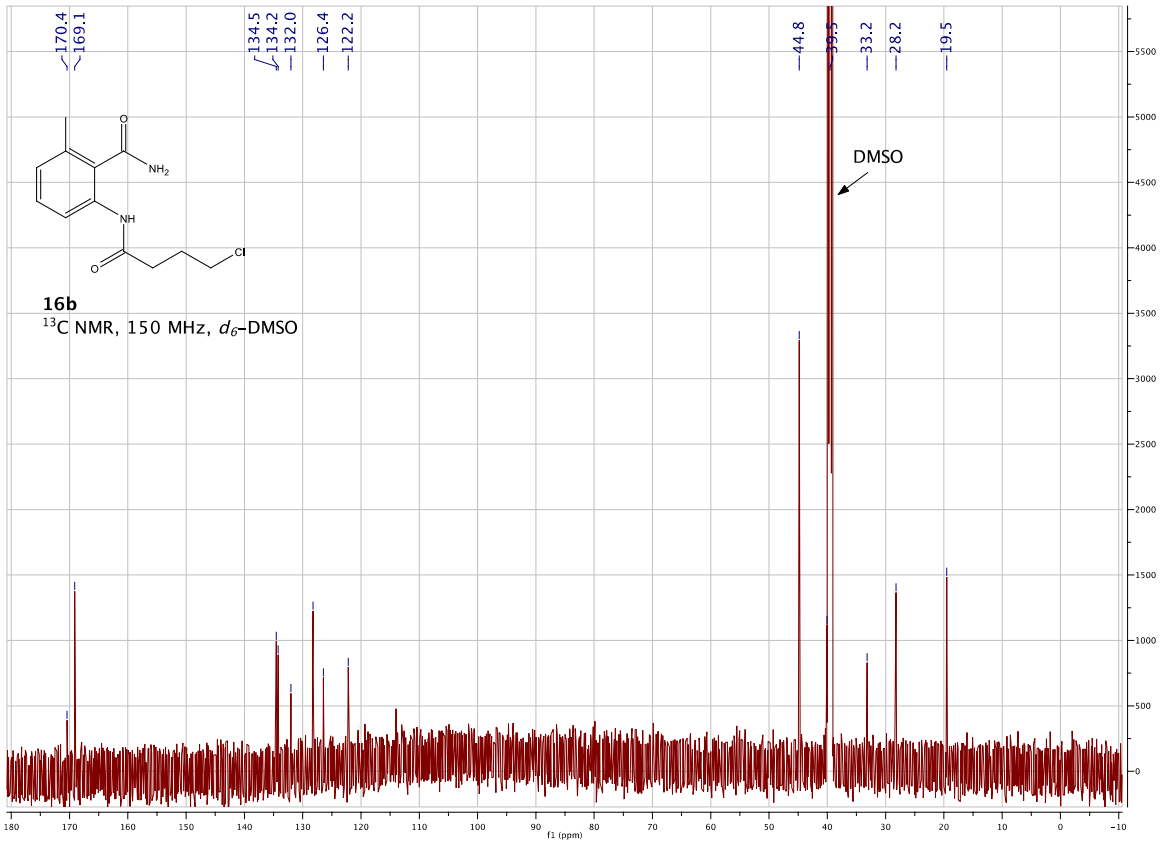

170.4
164.6
144.5
139.7
133.0
128.8
124.1
119.5
113.1
94.1
77.4
77.2
76.9
59.1
57.0
46.9
45.8
28.5
23.9
CDCl3
15
13C NMR, 125 MHz, CDCl3
f1 (ppm)


7.62
7.42
6.91
6.90
6.52
6.50
6.39
6.38
4.90
4.88
3.32
3.30
2.51
2.50
2.49
2.21
NH2
NH2
16a
1H NMR, 600 MHz, d6-DMSO
H2O
DMSO
1.02
1.00
1.01
1.02
1.01
1.97
3.07
f1 (ppm)

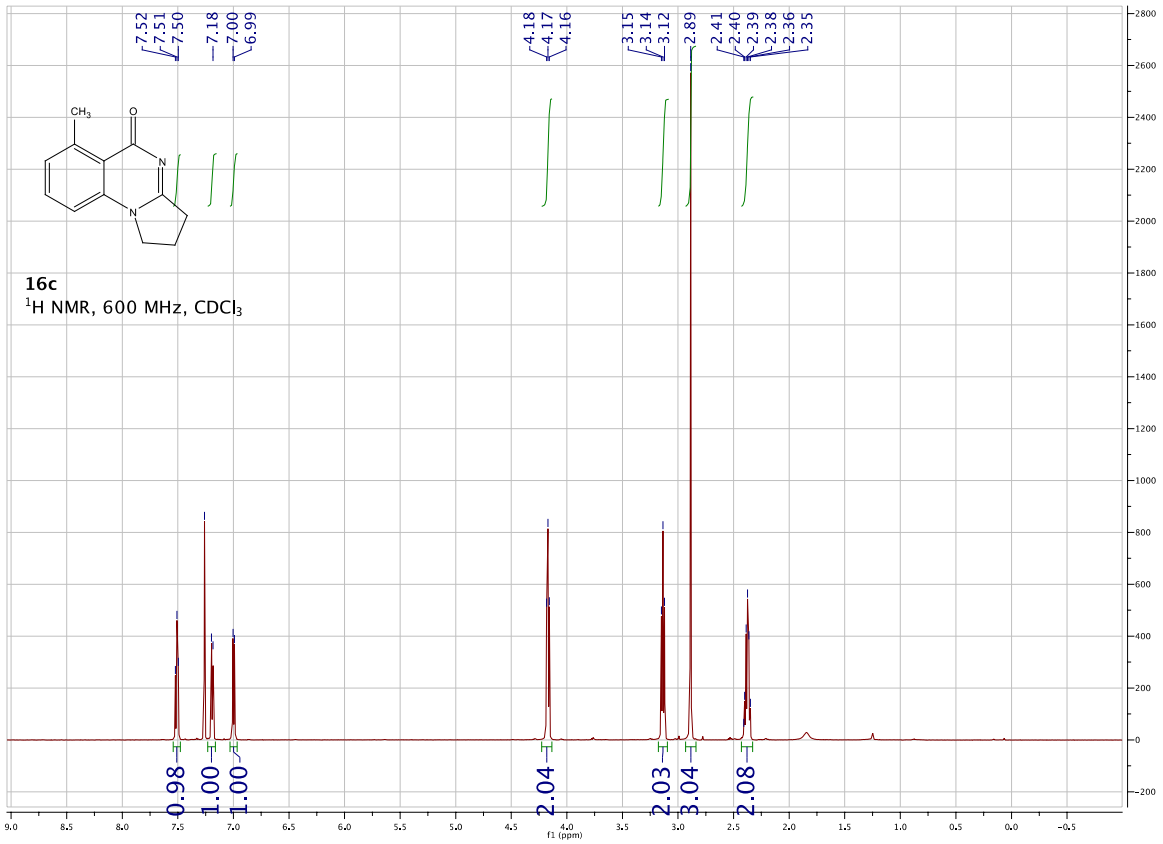

170.5
145.4
134.2
128.7
123.0
117.9
112.7
39.9
39.8
39.7
39.5
39.4
39.2
39.1
19.9
DMSO
NH2
NH2
16a
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)

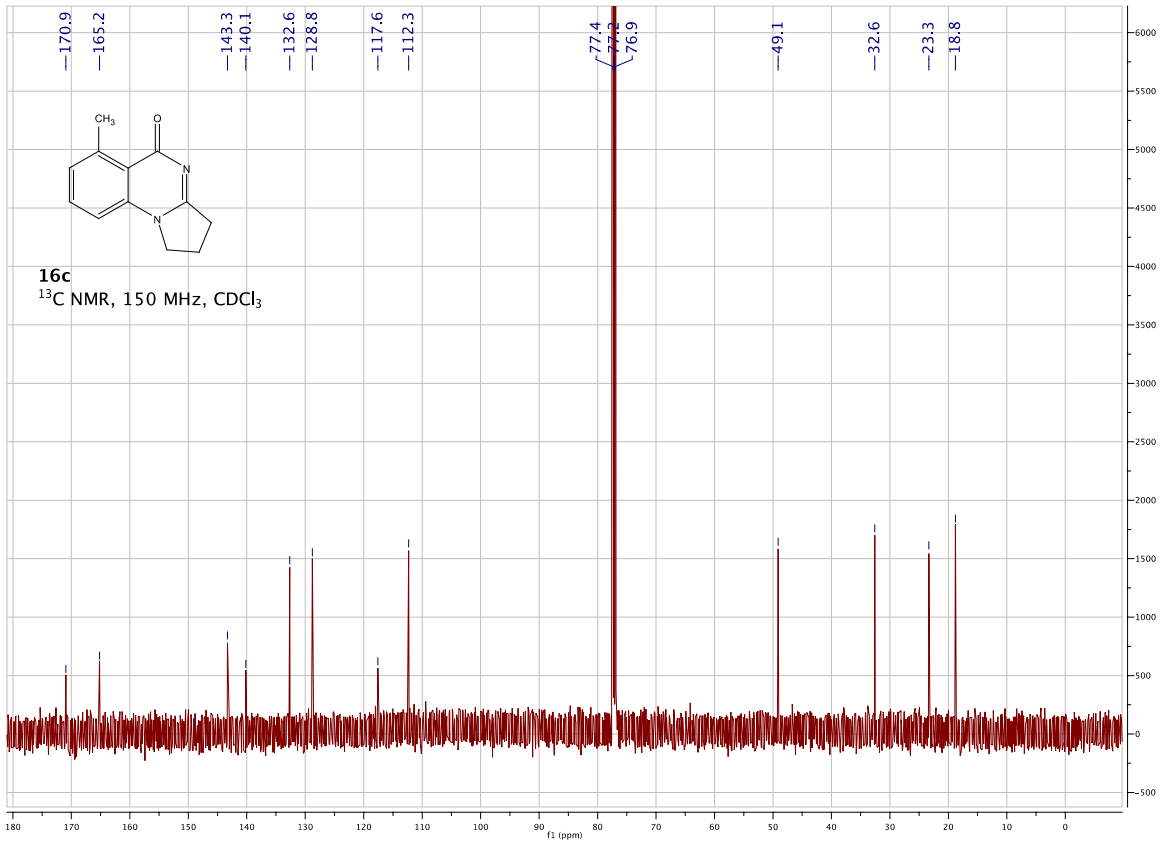


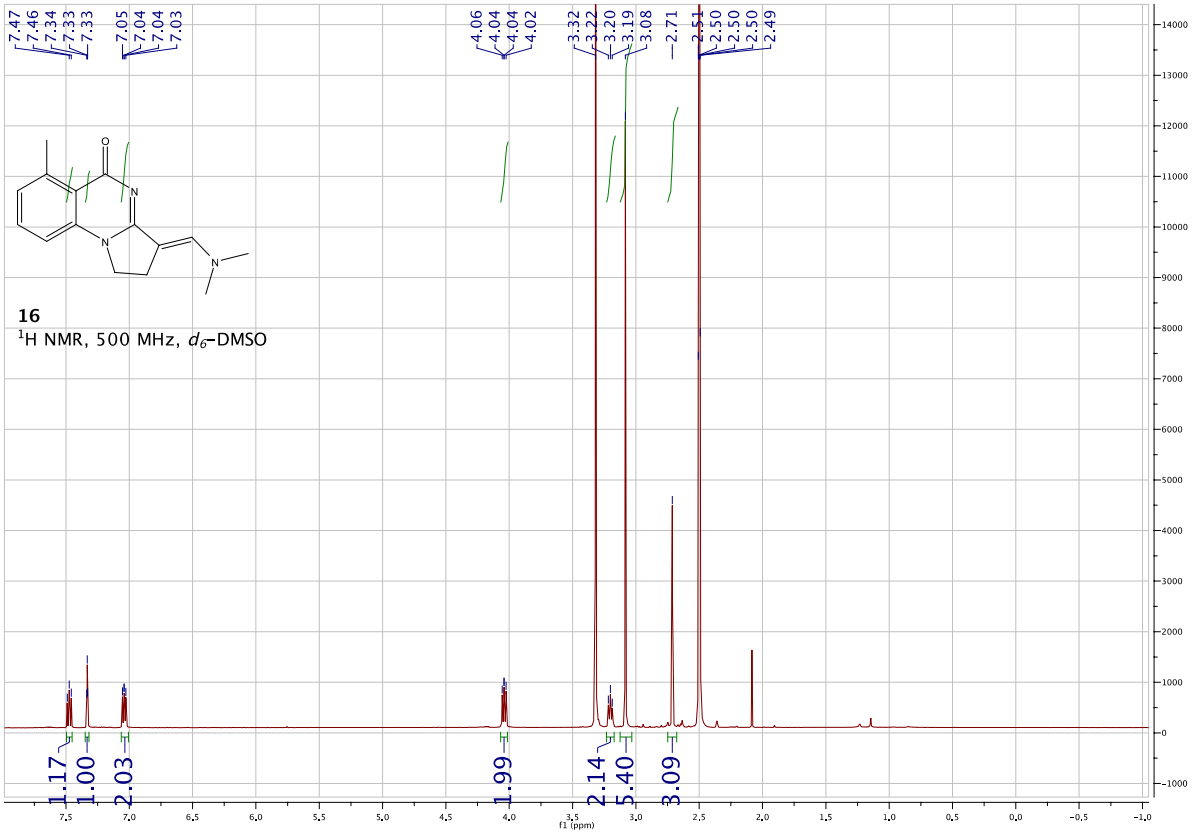
16b
^{1}H NMR, 600 MHz, d_6–DMSO



16b
^{13}C NMR, 150 MHz, d_6–DMSO

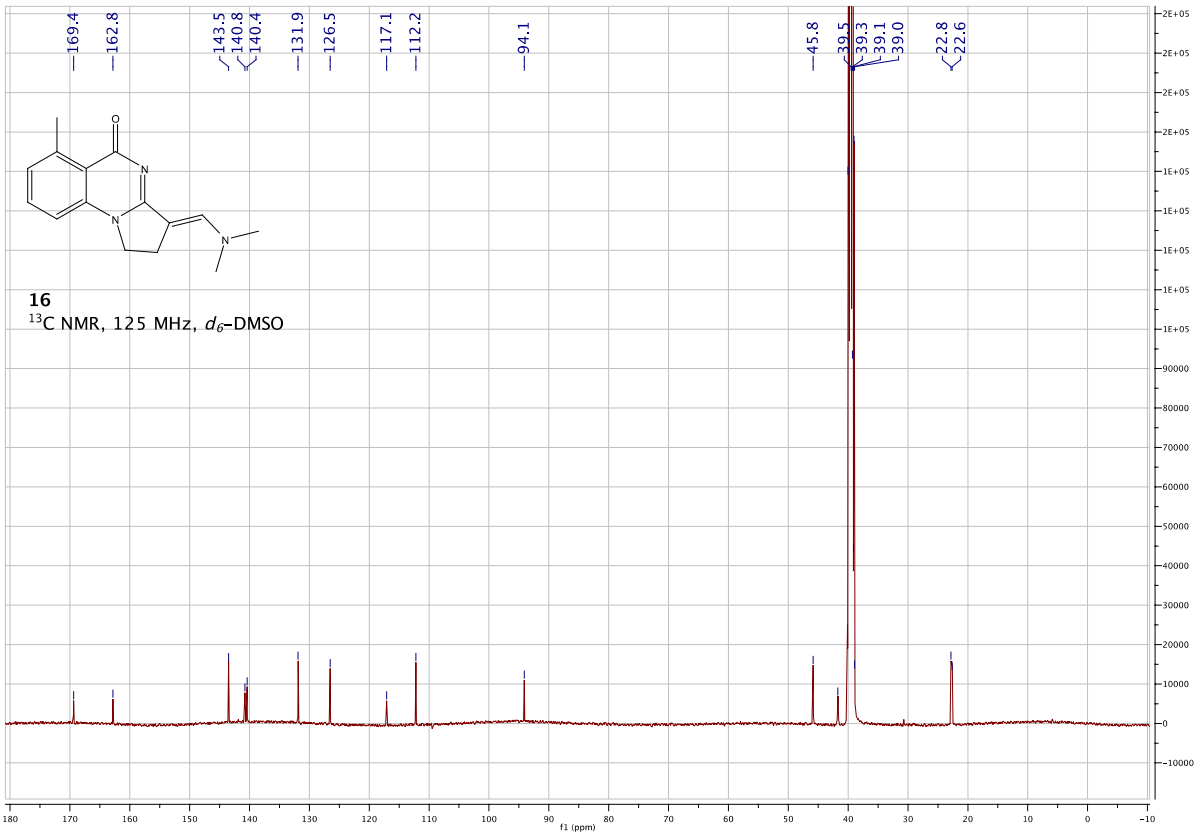

7.52
7.51
7.50
7.18
7.00
6.99
4.18
4.17
4.16
3.15
3.14
3.12
2.89
2.41
2.40
2.39
2.38
2.36
2.35
CH3
O
N
N
16c
1H NMR, 600 MHz, CDCl3
0.98
1.00
1.00
2.04
2.03
3.04
2.08
f1 (ppm)


170.9
165.2
143.3
140.1
132.6
128.8
117.6
112.3
77.4
77.2
76.9
49.1
32.6
23.3
18.8
CH3
O
N
N
16c
13C NMR, 150 MHz, CDCl3
f1 (ppm)



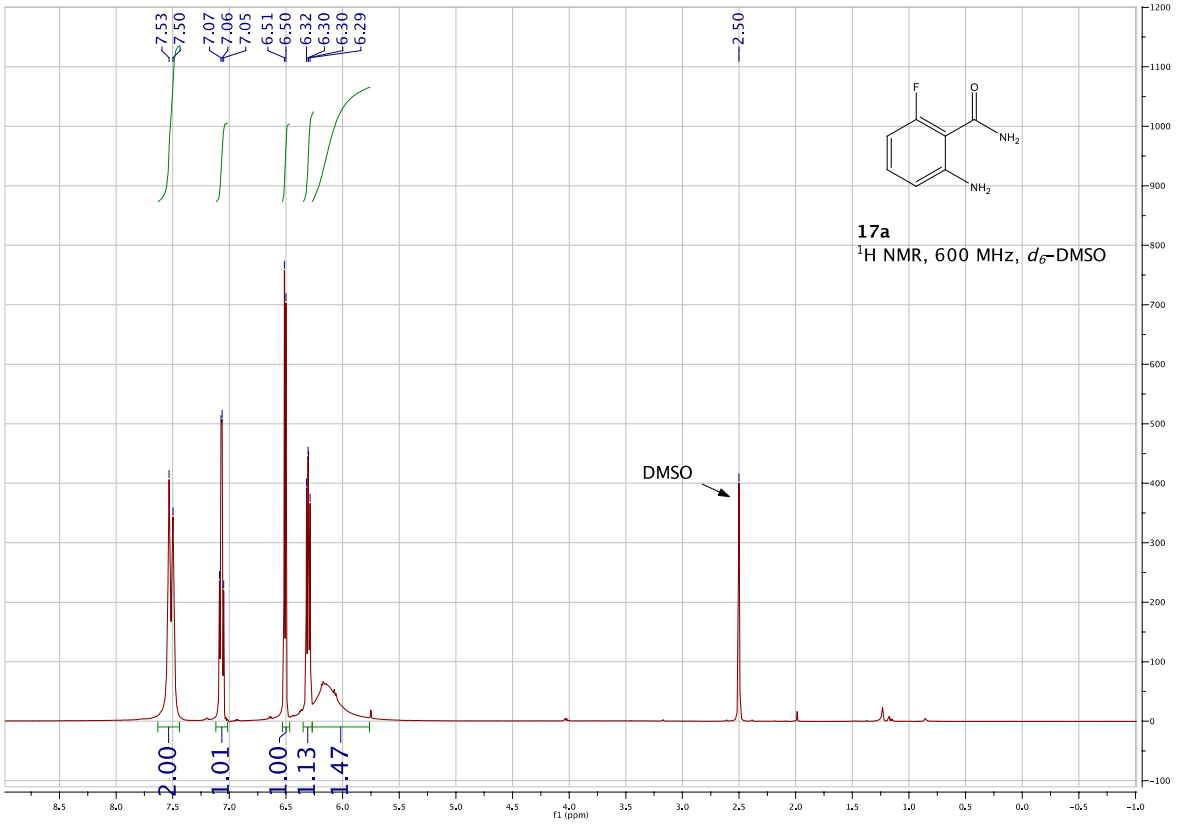
16

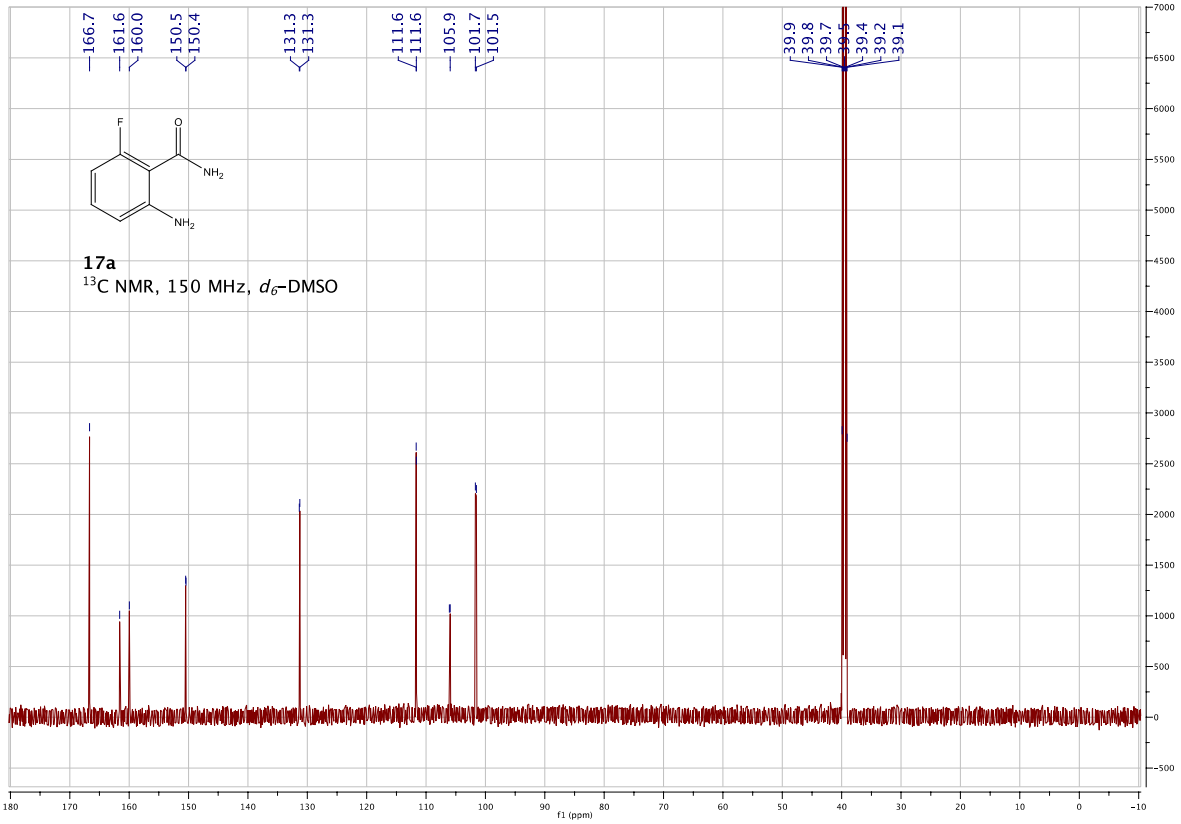
^{1}H NMR, 500 MHz, d_6–DMSO



16

^{13}C NMR, 125 MHz, d_6–DMSO


7.53
7.50
7.07
7.06
7.05
6.51
6.50
6.32
6.30
6.30
6.29
2.50
F
O
NH2
NH2
17a
1H NMR, 600 MHz, d6-DMSO
DMSO
2.00
1.01
1.00
1.13
1.47
f1 (ppm)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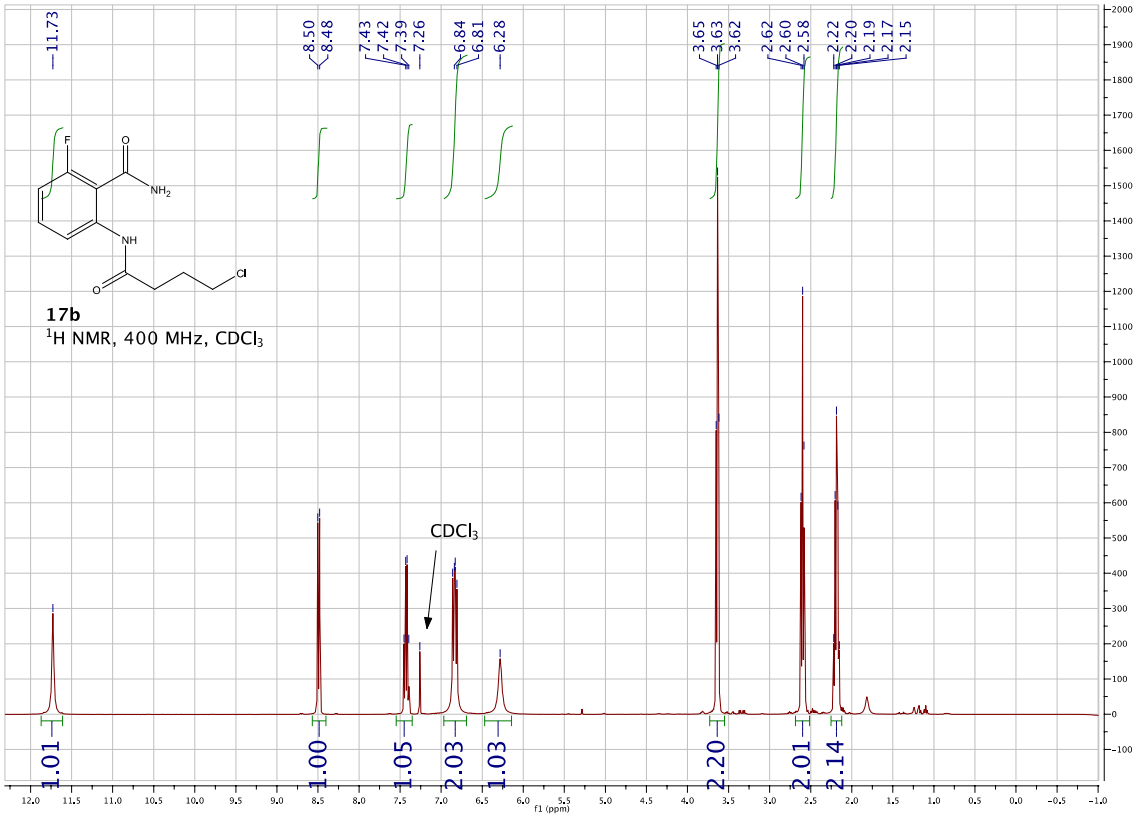
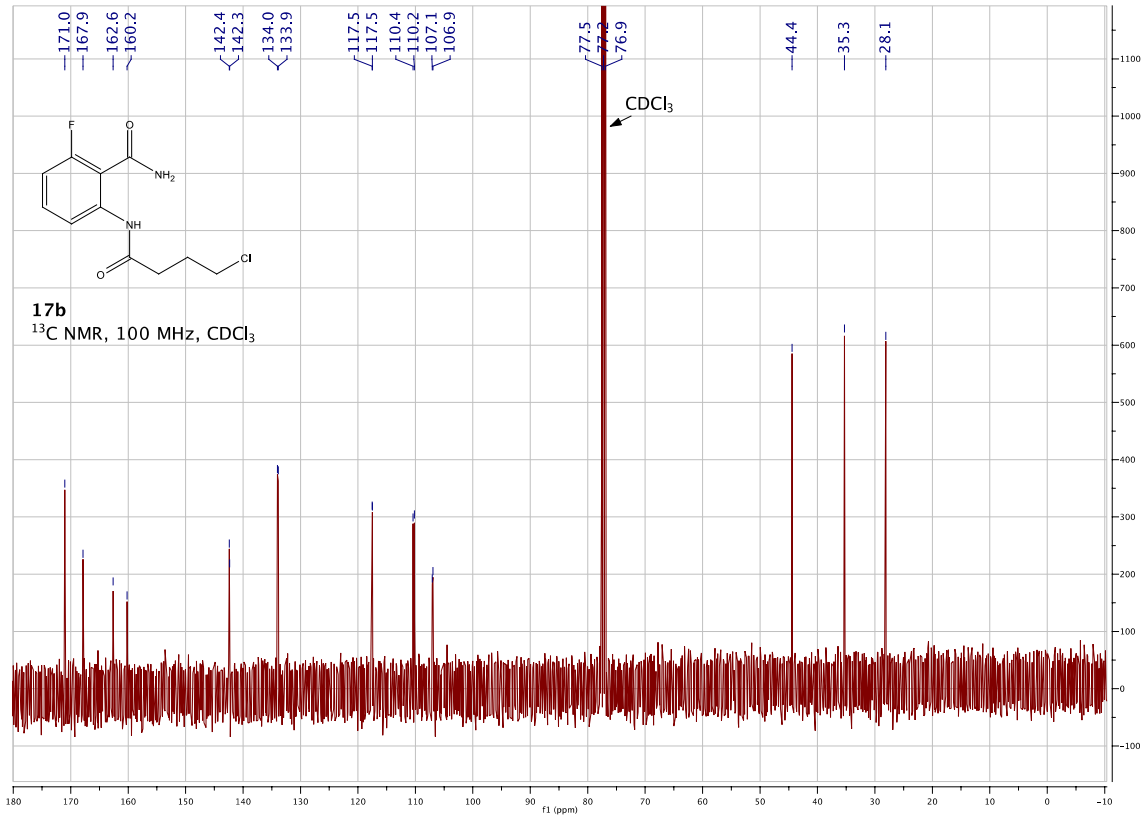
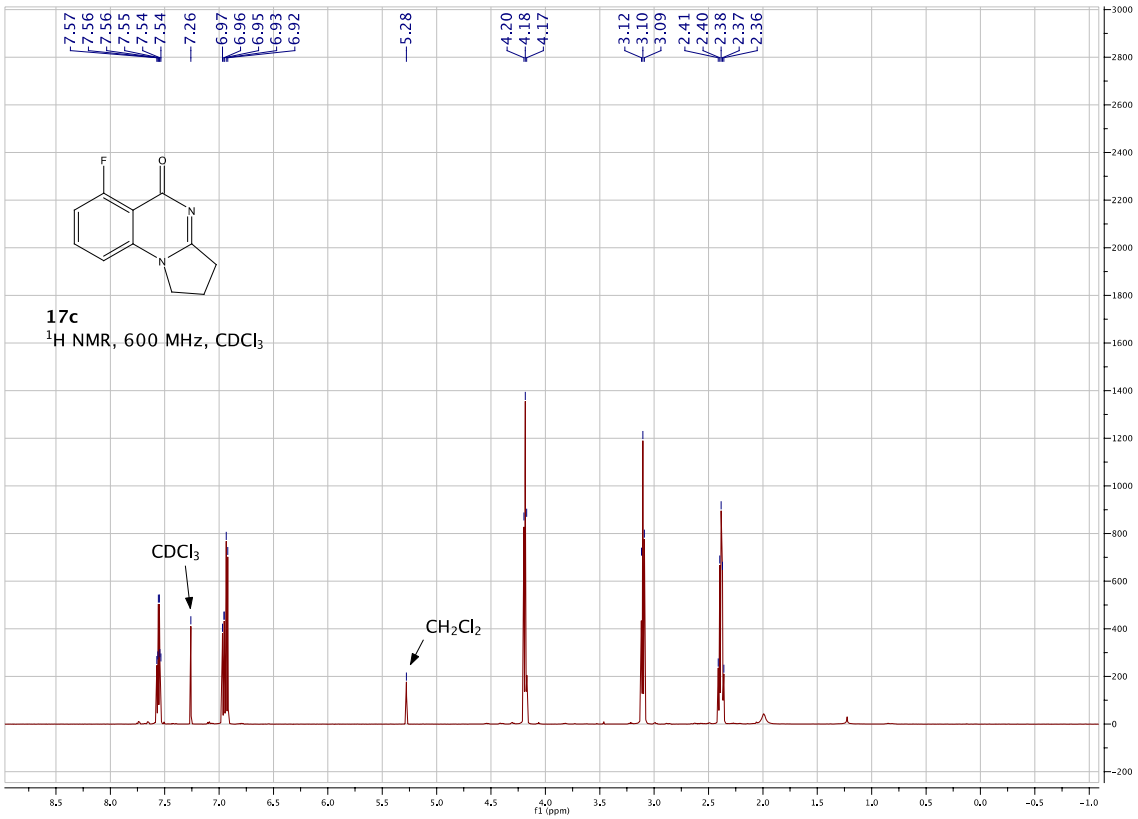
161.6
160.0
150.5
150.4
131.3
131.3
111.6
111.6
105.9
101.7
101.5
39.9
39.8
39.7
39.4
39.2
39.1
F
O
NH2
NH2
17a
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)



17b
^{1}H NMR, 400 MHz, $CDCl_3$



17b
^{13}C NMR, 100 MHz, $CDCl_3$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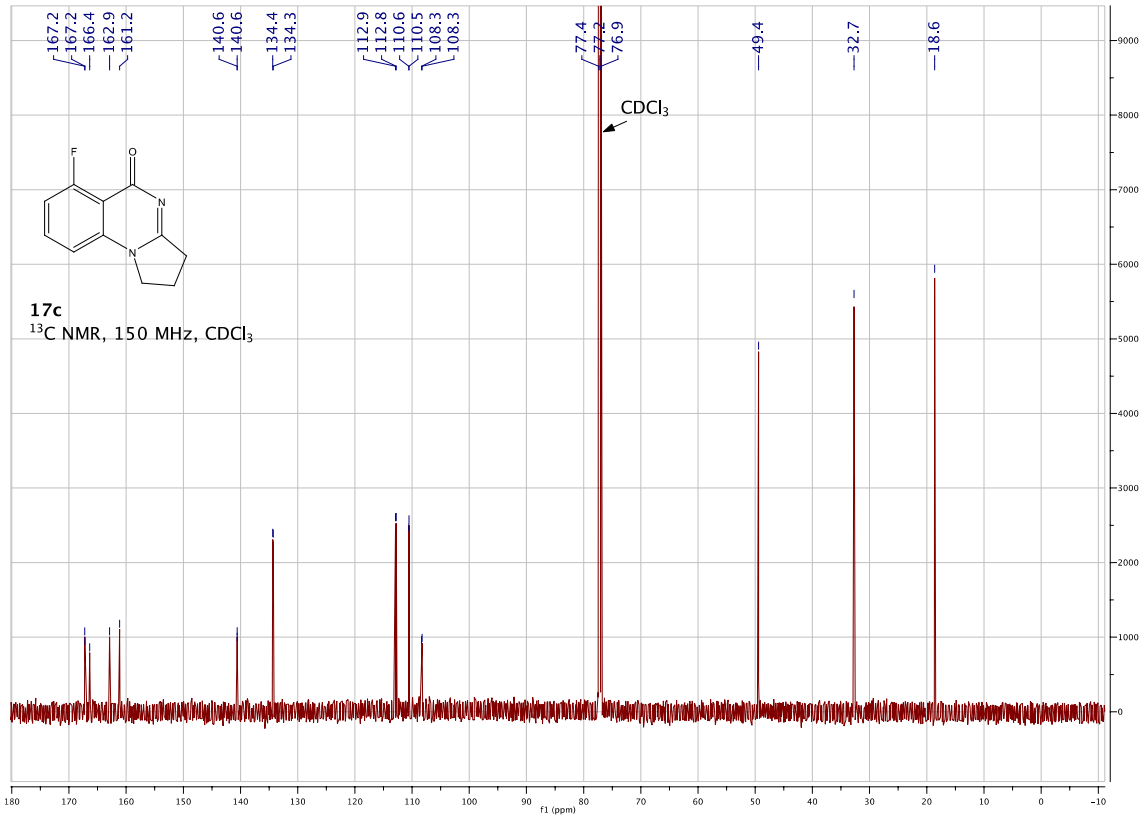
7.56
7.56
7.55
7.54
7.54
7.26
6.97
6.96
6.95
6.93
6.92
5.28
4.20
4.18
4.17
3.12
3.10
3.09
2.41
2.40
2.38
2.37
2.36
F
O
N
N
17c
1H NMR, 600 MHz, CDCl3
CDCl3
CH2Cl2
f1 (ppm)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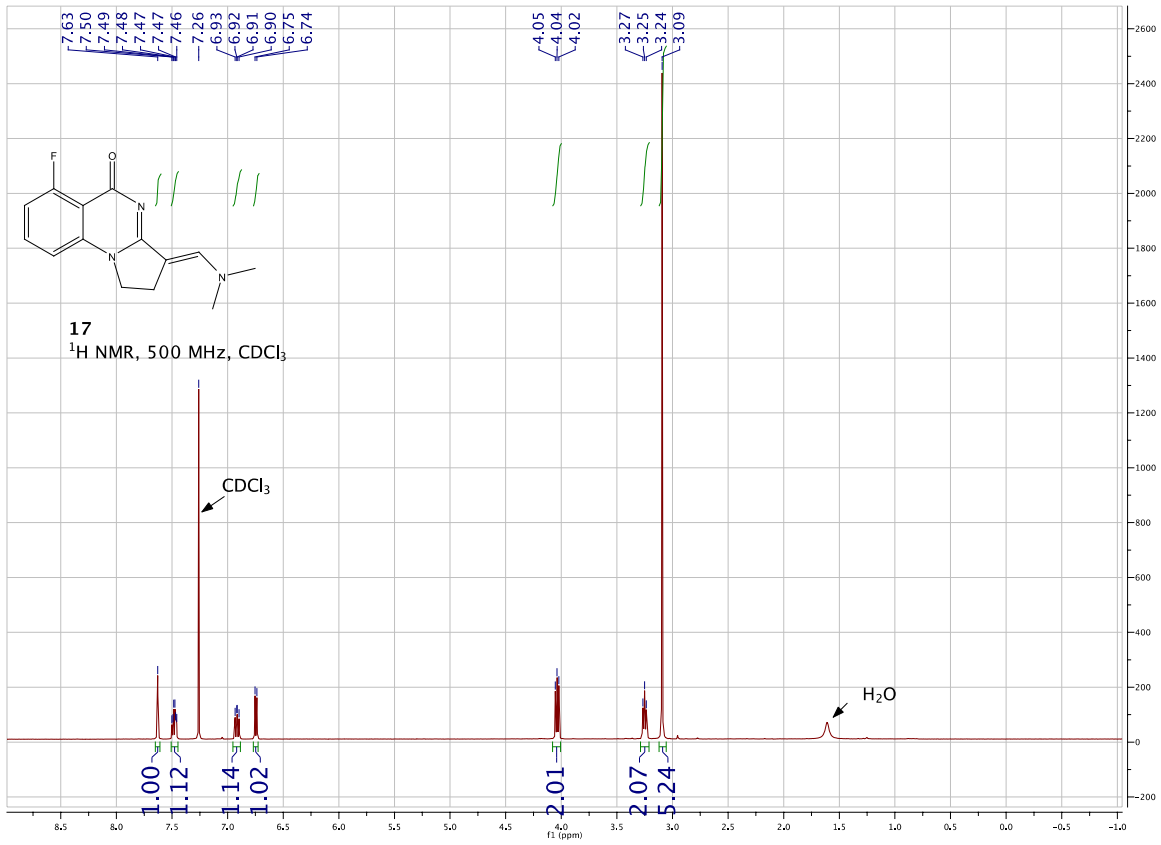
167.2
166.4
162.9
161.2
140.6
140.6
134.4
134.3
112.9
112.8
110.6
110.5
108.3
108.3
77.4
77.2
76.9
49.4
32.7
18.6
CDCl3
F
O
N
N
17c
13C NMR, 150 MHz, CDCl3
f1 (ppm)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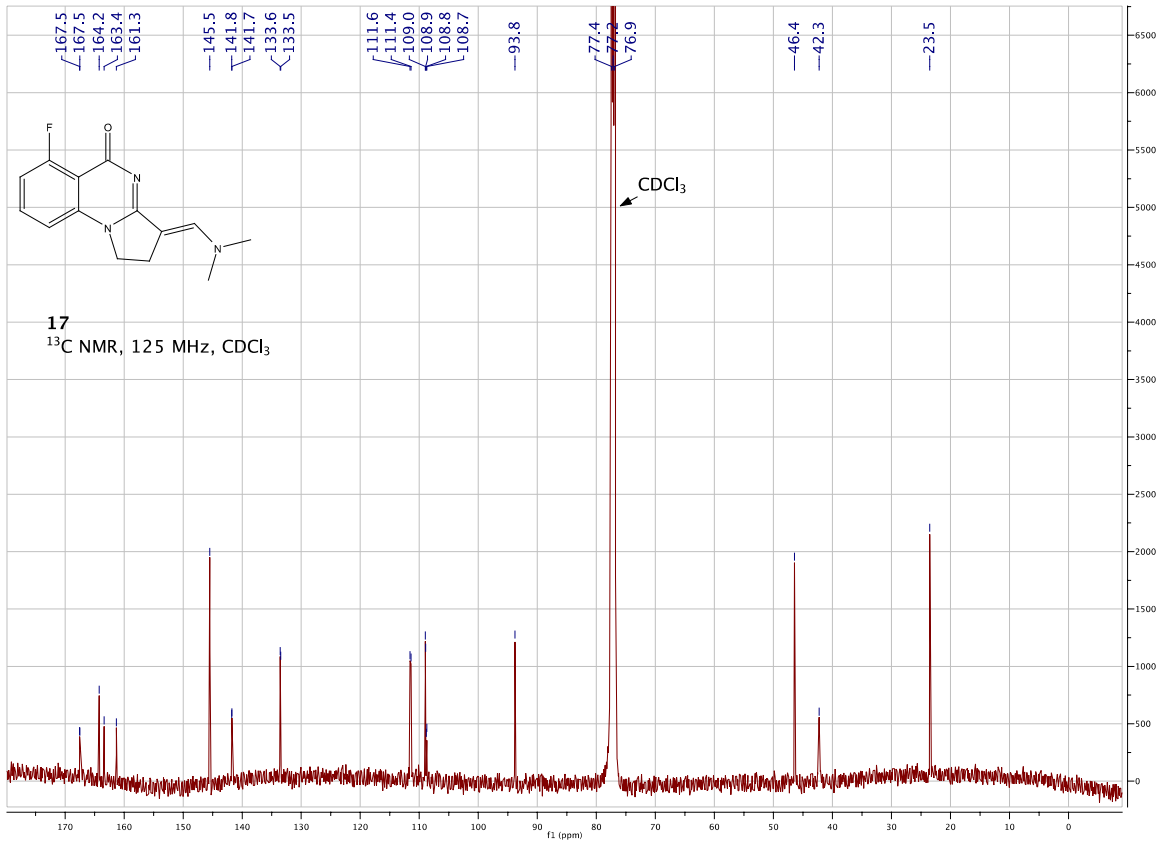
7.50
7.49
7.48
7.47
7.47
7.46
7.26
6.93
6.92
6.91
6.90
6.75
6.74
4.05
4.04
4.02
3.27
3.25
3.24
3.09
F
O
N
N
N
17
1H NMR, 500 MHz, CDCl3
CDCl3
H2O
1.00
1.12
1.14
1.02
2.01
2.07
5.24
f1 (ppm)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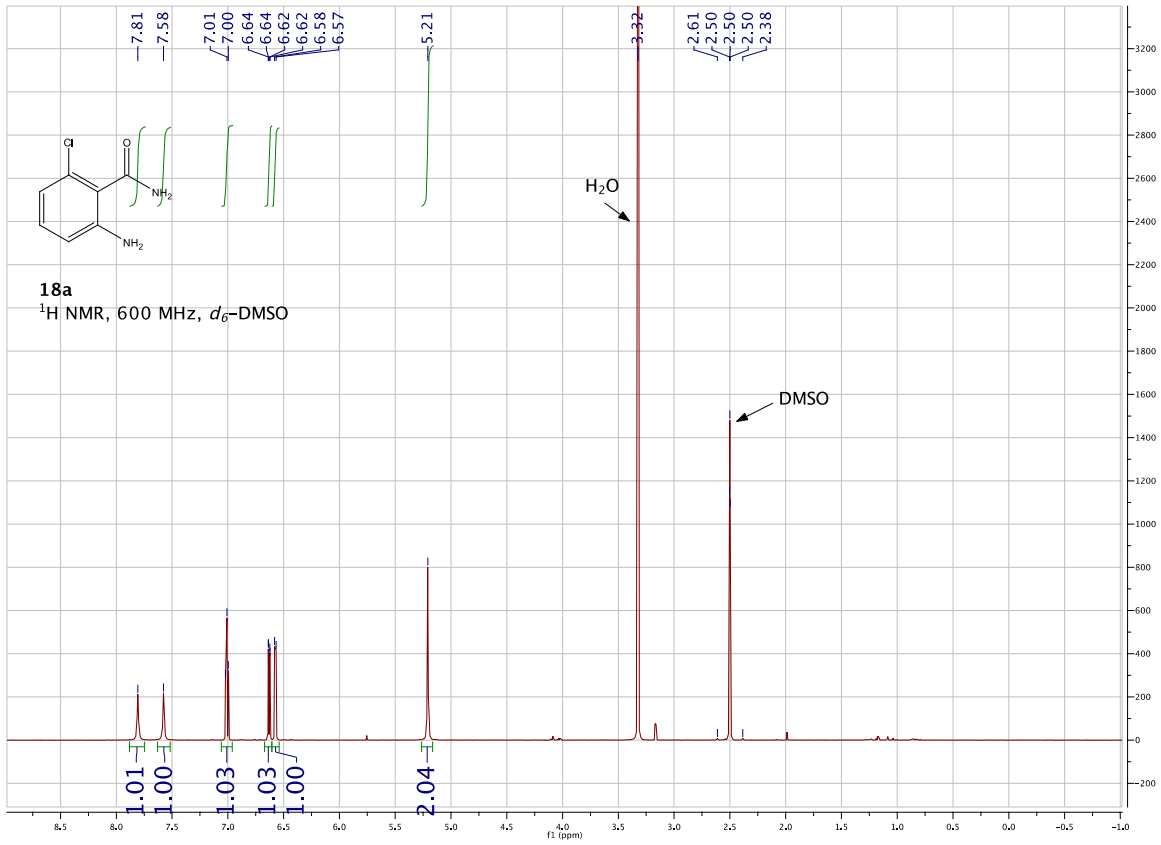
167.5
164.2
163.4
161.3
145.5
141.8
141.7
133.6
133.5
111.6
111.4
109.0
108.9
108.8
108.7
93.8
77.4
77.2
76.9
46.4
42.3
23.5
F
O
N
N
N
17
13C NMR, 125 MHz, CDCl3
CDCl3
f1 (ppm)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7.58
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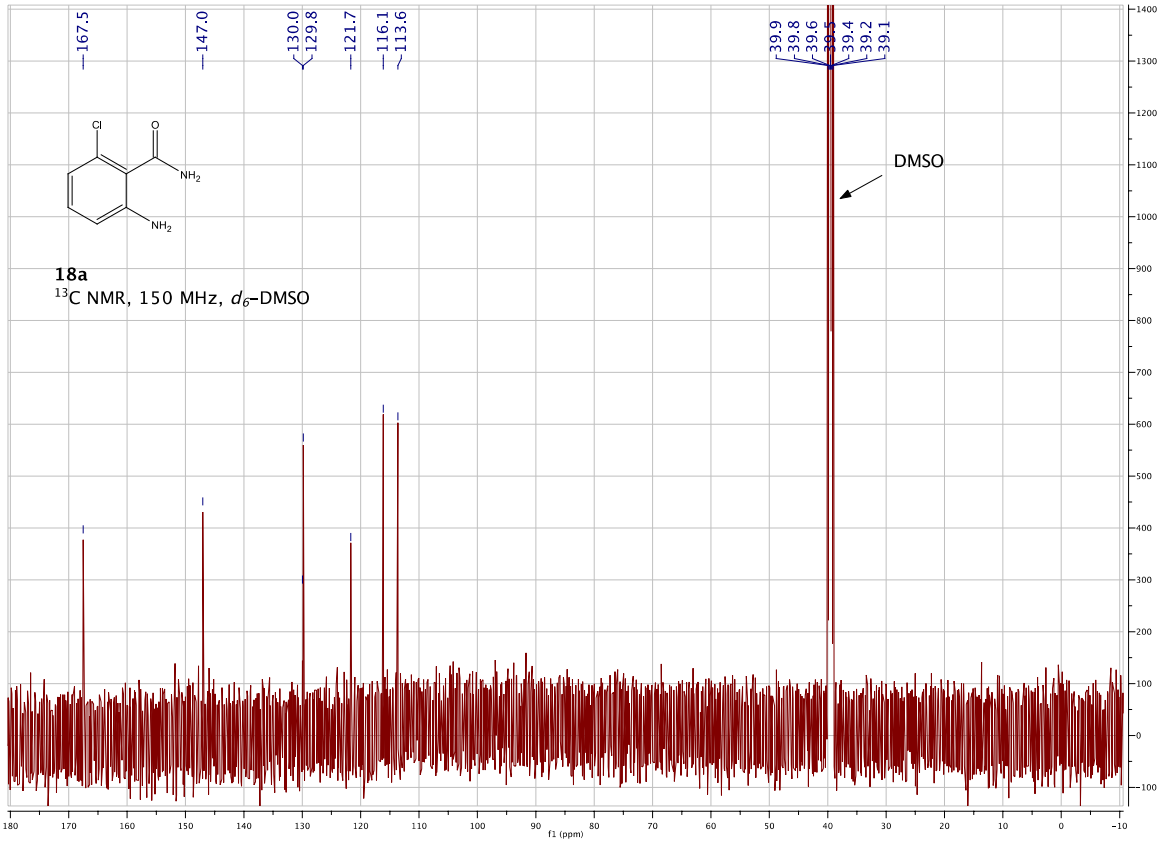
7.00
6.64
6.64
6.62
6.62
6.58
6.57
5.21
3.32
2.61
2.50
2.50
2.50
2.38
H2O
DMSO
1.01
1.00
1.03
1.03
1.00
2.04
Cl
O
NH2
NH2
18a
1H NMR, 600 MHz, d6-DMSO
f1 (ppm)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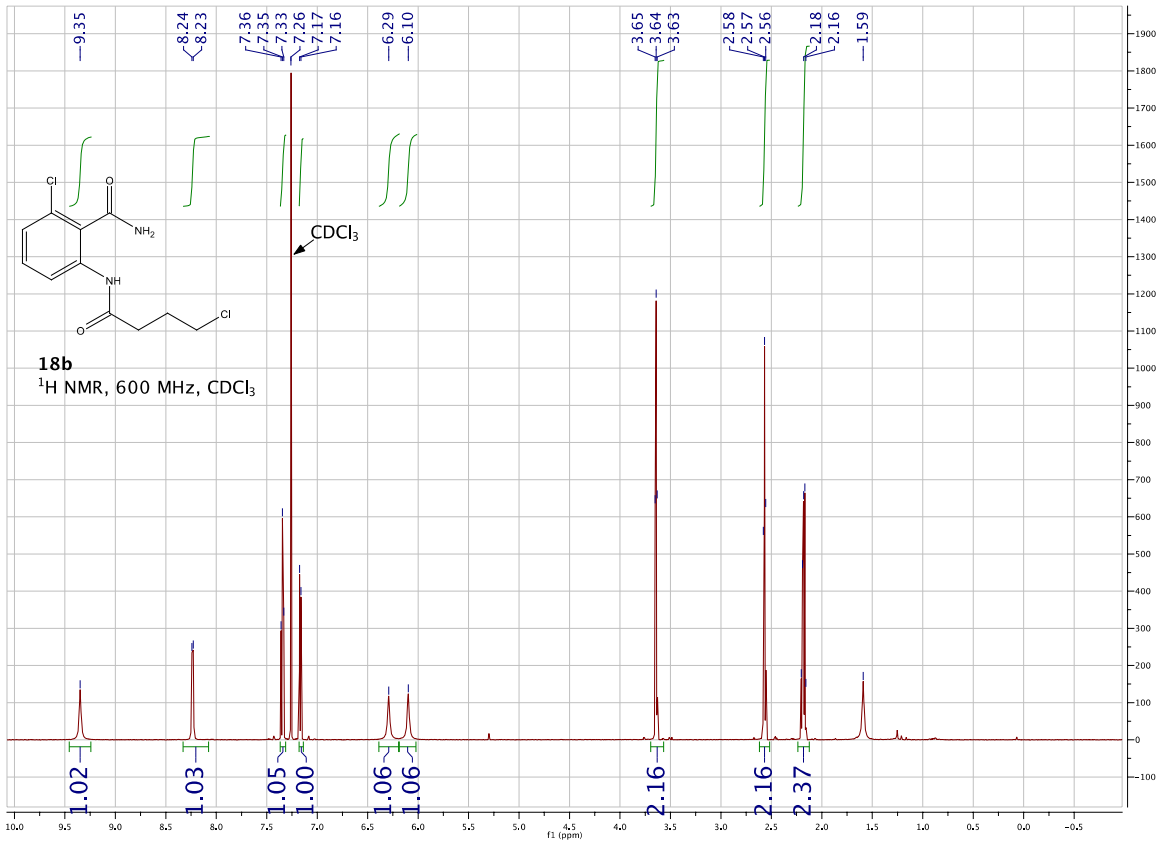
147.0
130.0
129.8
121.7
116.1
113.6
39.9
39.8
39.6
39.5
39.4
39.2
39.1
DMSO
Cl
O
NH2
NH2
18a
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)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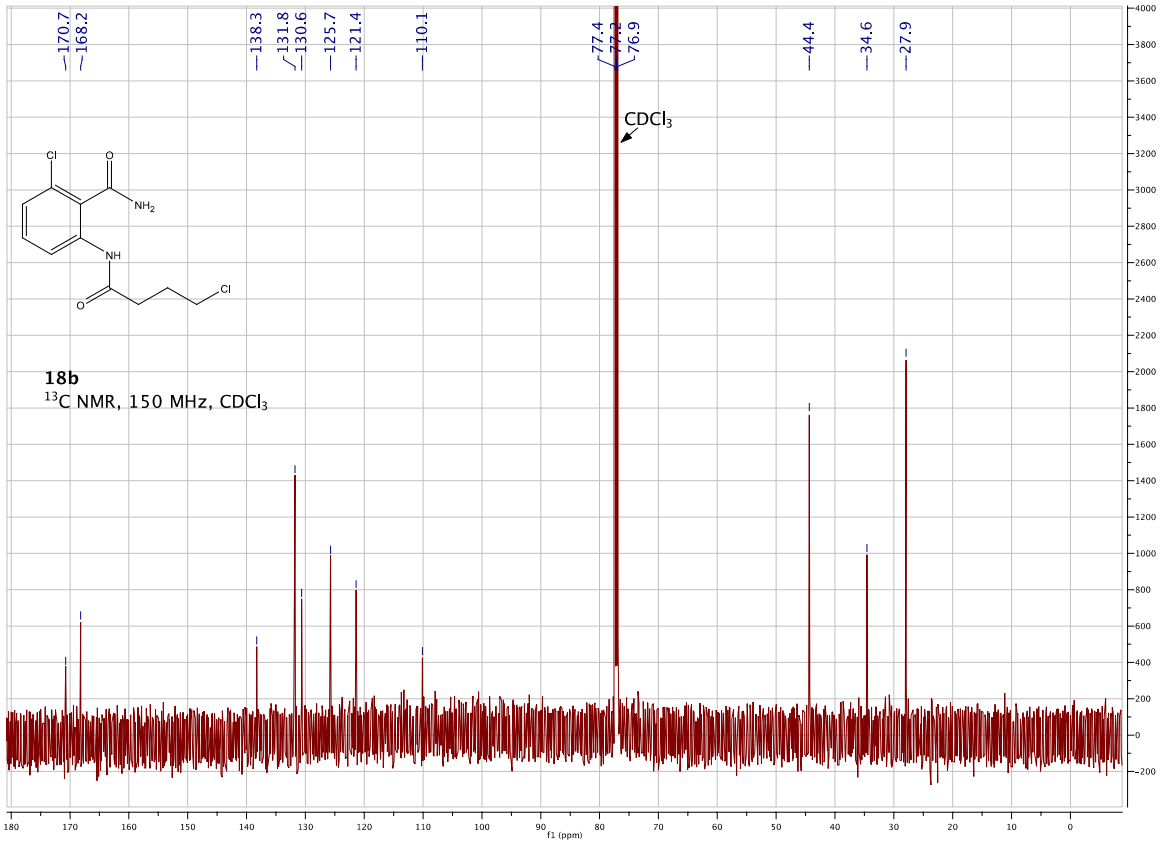
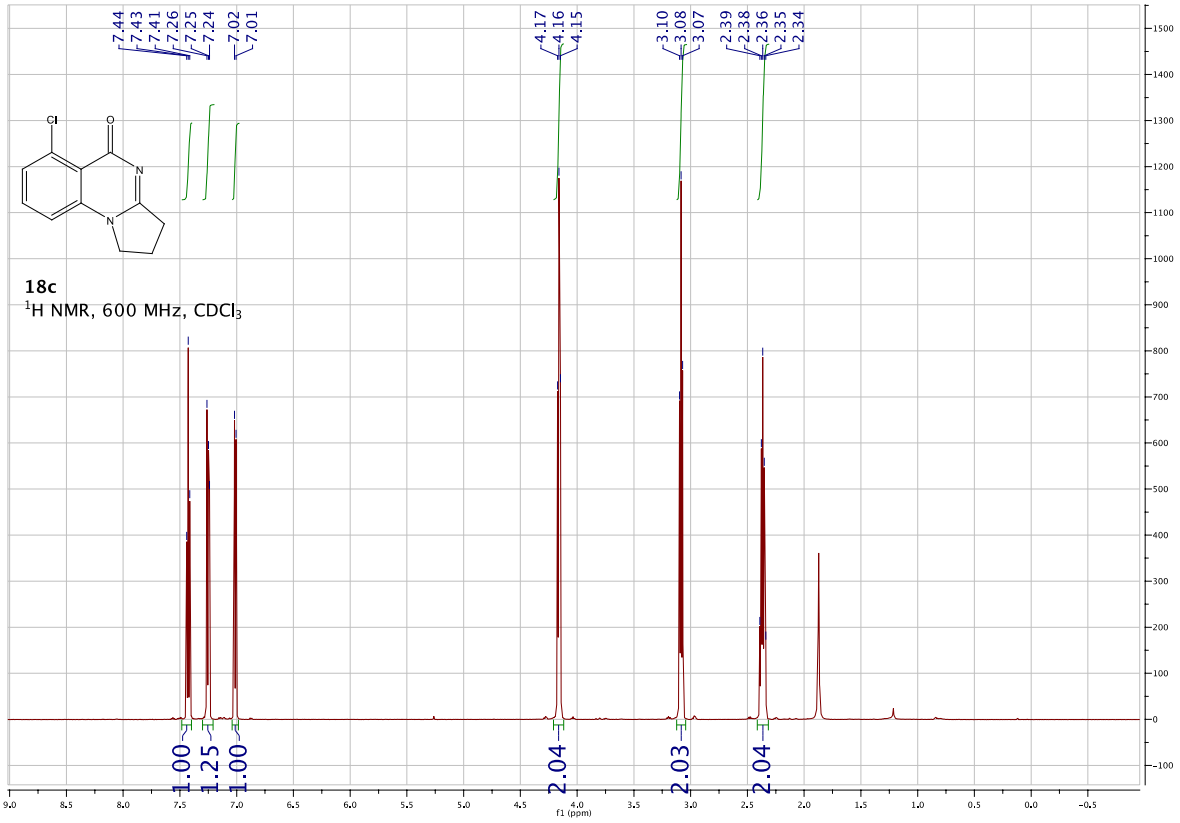
8.24
8.23
7.36
7.35
7.33
7.26
7.17
7.16
6.29
6.10
3.65
3.64
3.63
2.58
2.57
2.56
2.18
2.16
1.59
CDCl3
18b
1H NMR, 600 MHz, CDCl3
1.02
1.03
1.05
1.00
1.06
1.06
2.16
2.16
2.37
f1 (ppm)


170.7
168.2
138.3
131.8
130.6
125.7
121.4
110.1
77.4
76.9
44.4
34.6
27.9
CDCl3
18b
13C NMR, 150 MHz, CDCl3
f1 (ppm)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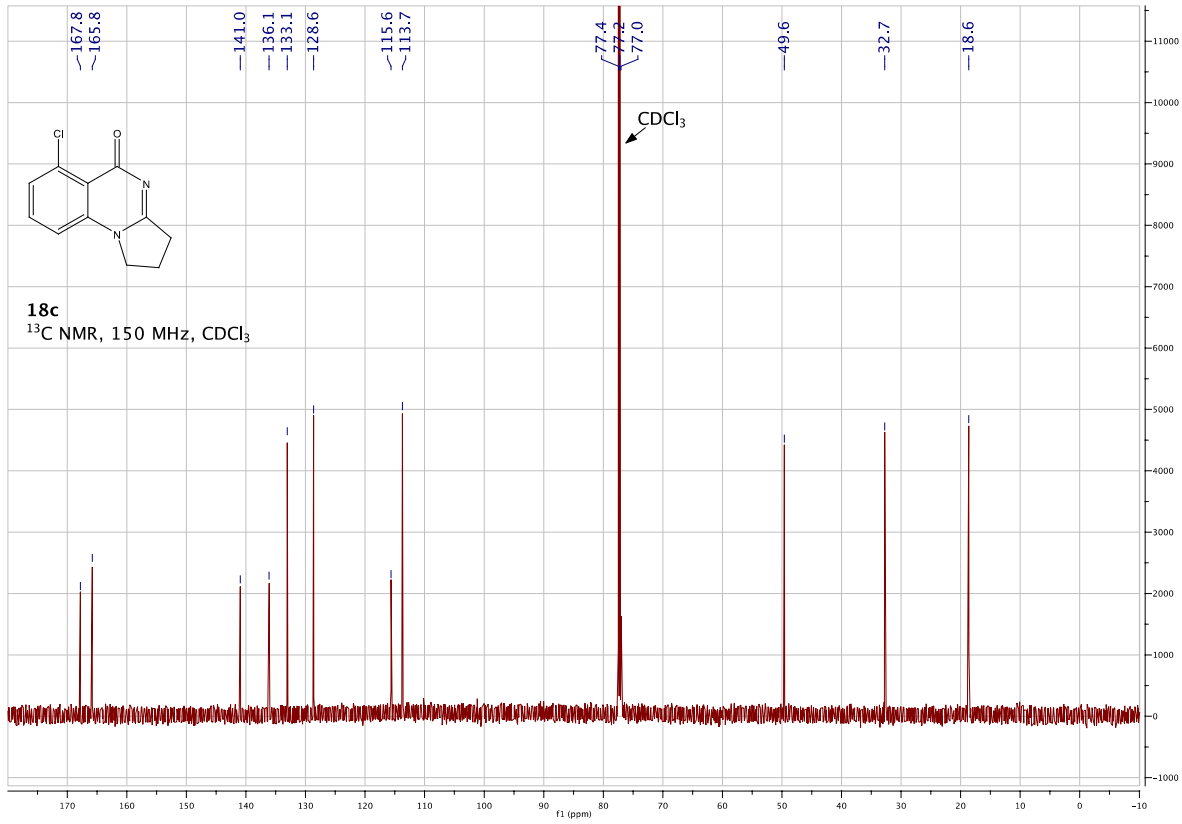
7.24
7.02
7.01
4.17
4.16
4.15
3.10
3.08
3.07
2.39
2.38
2.36
2.35
2.34
Cl
O
N
N
18c
1H NMR, 600 MHz, CDCl3
1.00
1.25
1.00
2.04
2.03
2.04
f1 (ppm)


167.8
165.8
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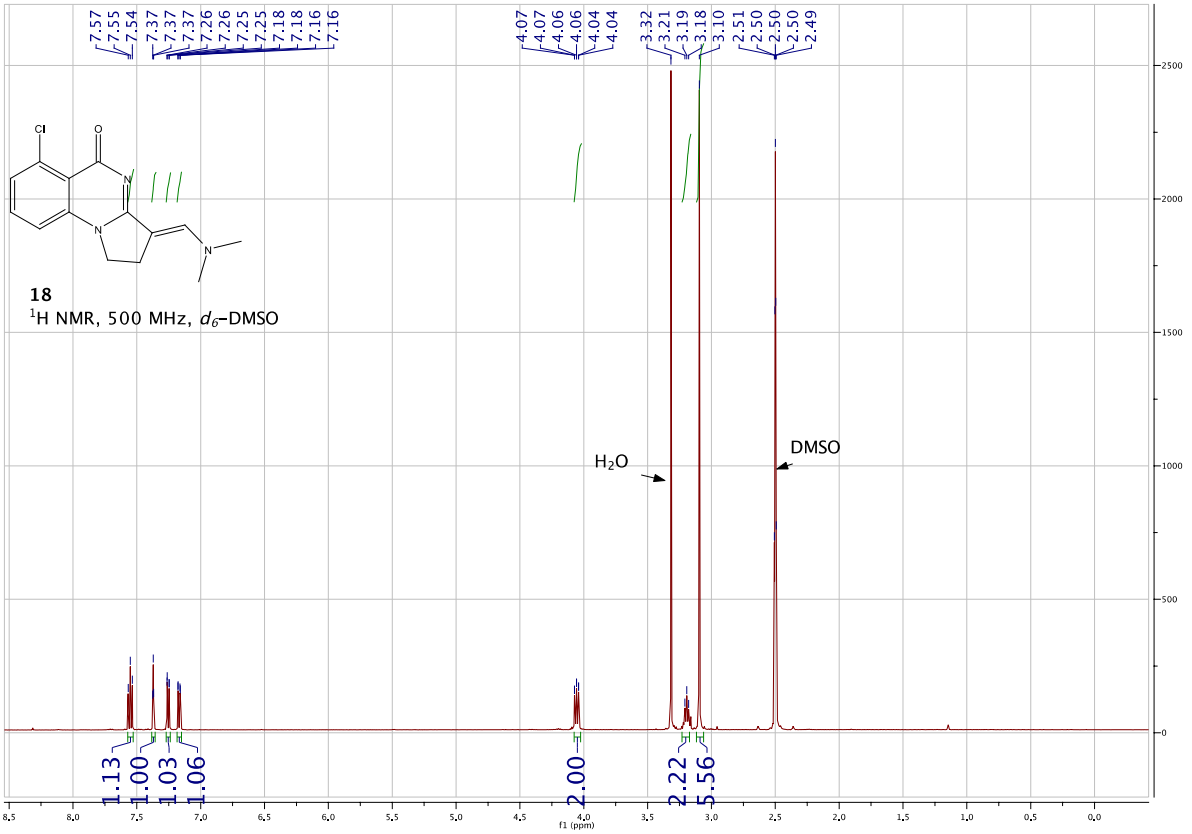
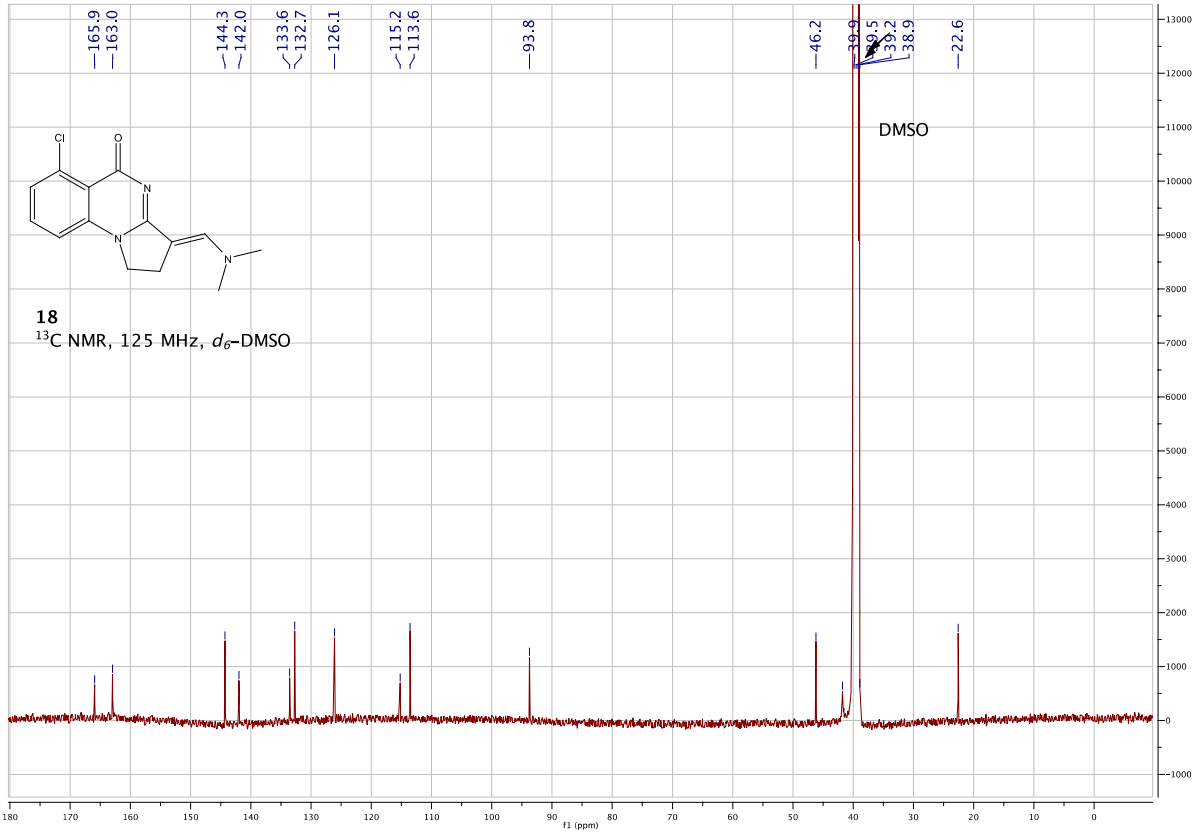
136.1
133.1
128.6
115.6
113.7
77.4
77.2
77.0
49.6
32.7
18.6
CDCl3
Cl
O
N
N
18c
13C NMR, 150 MHz, CDCl3
f1 (ppm)


7.57
7.55
7.54
7.37
7.37
7.37
7.37
7.26
7.26
7.25
7.25
7.18
7.18
7.16
7.16
4.07
4.07
4.06
4.06
4.04
4.04
3.32
3.21
3.19
3.18
3.10
2.51
2.50
2.50
2.50
2.49
Cl
O
N
N
N
18
^{1}H NMR, 500 MHz, d_6–DMSO
H_2O
DMSO
1.13
1.00
1.03
1.06
2.00
2.22
5.56
f1 (ppm)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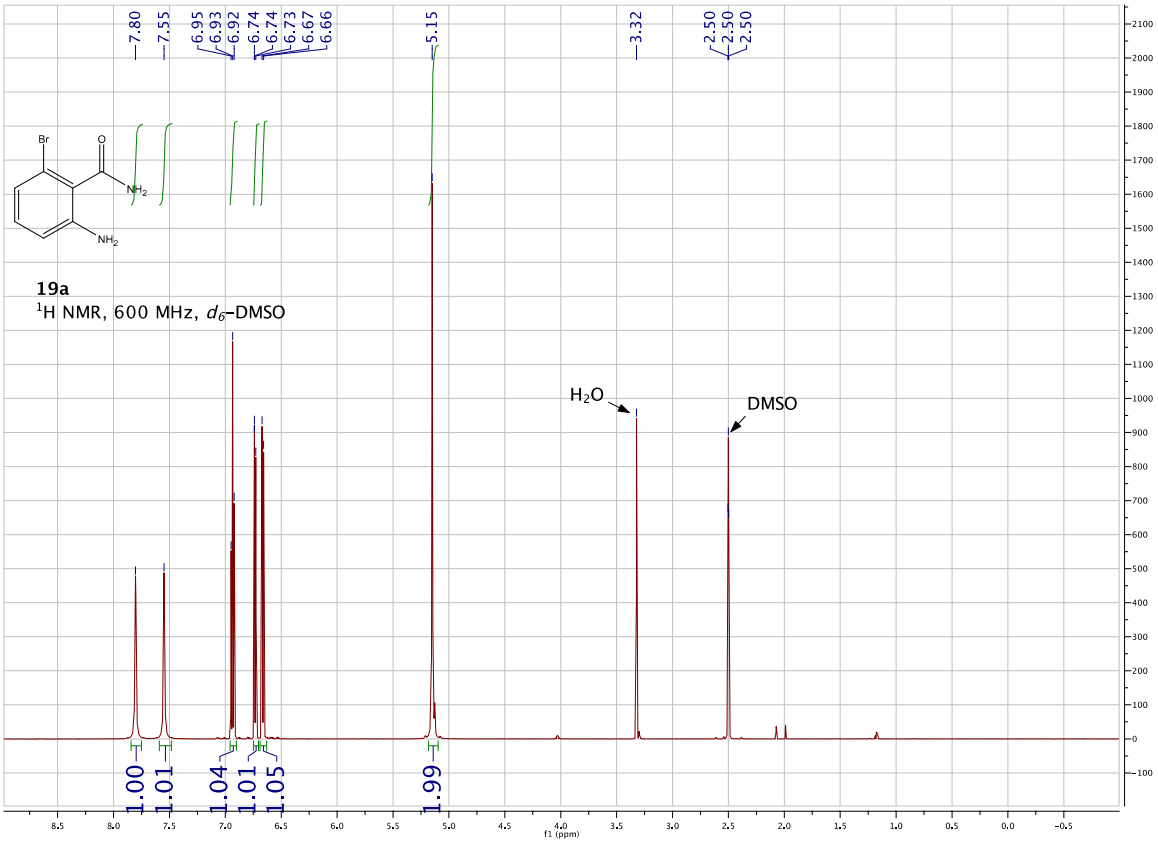
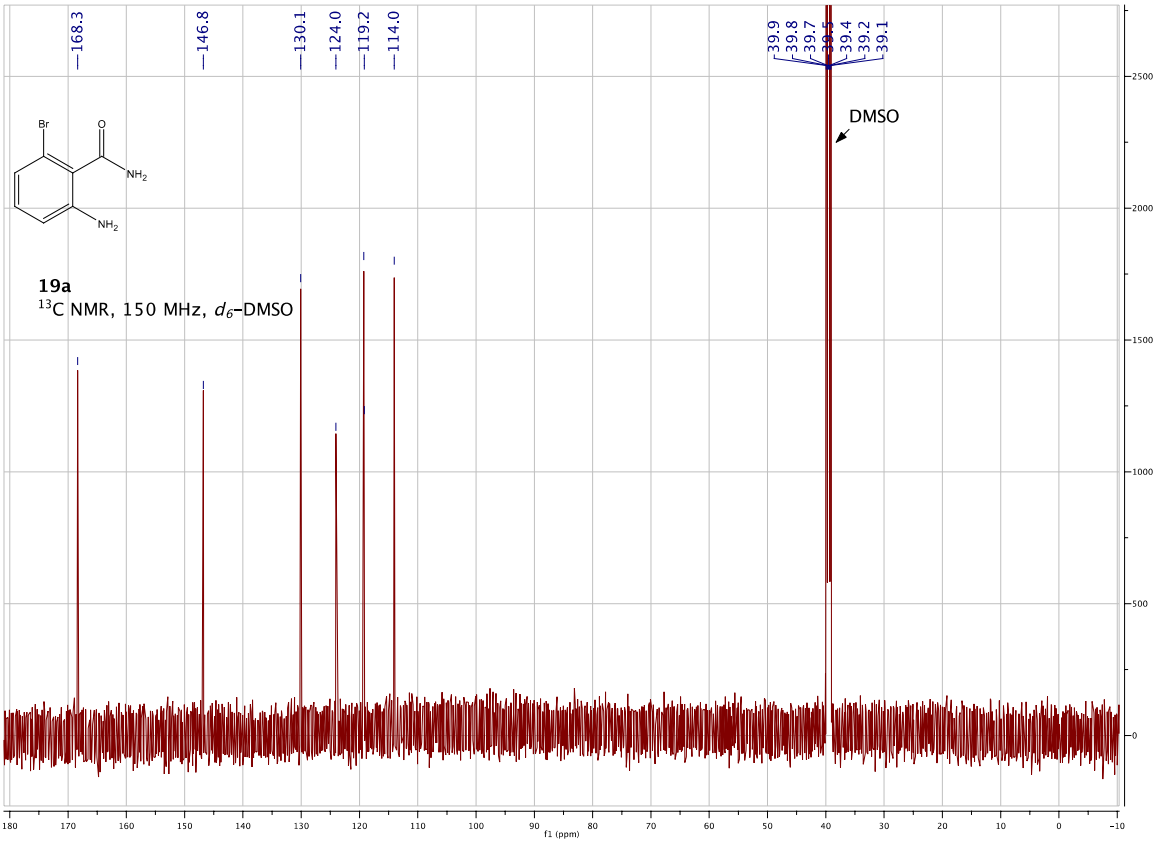
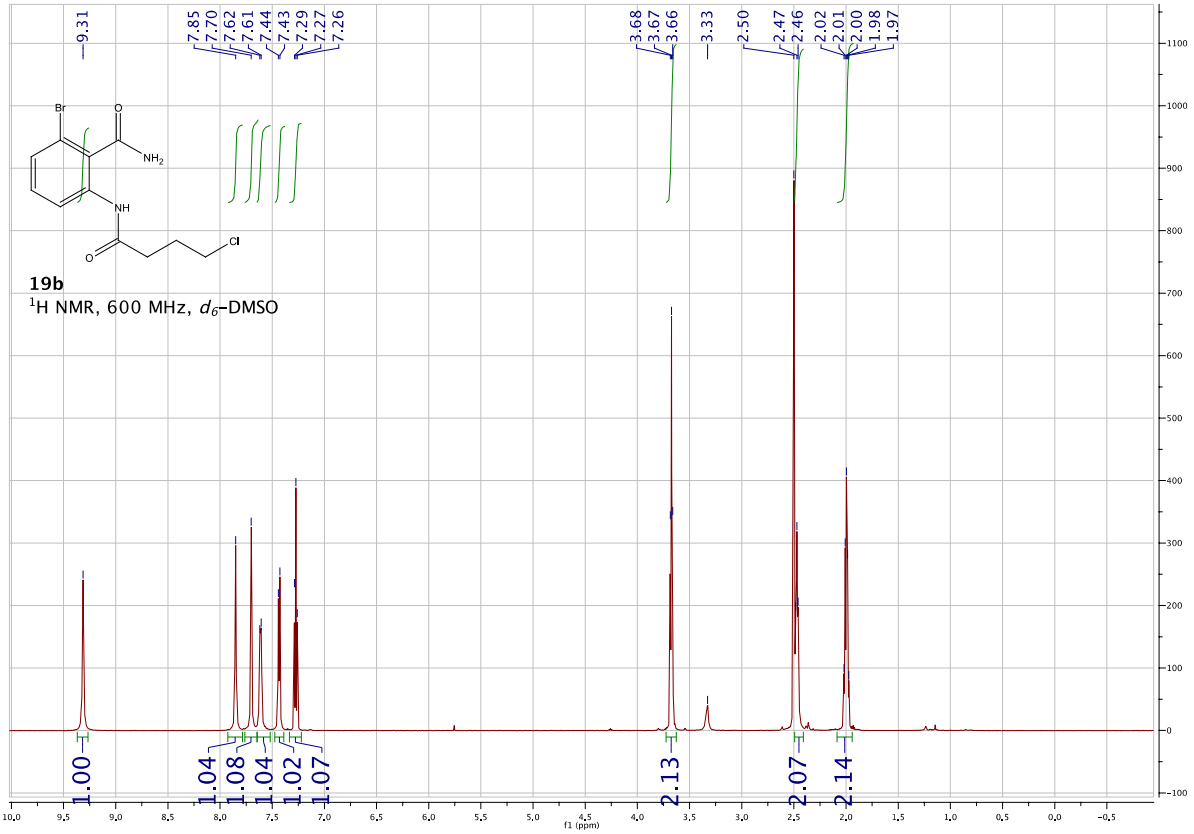
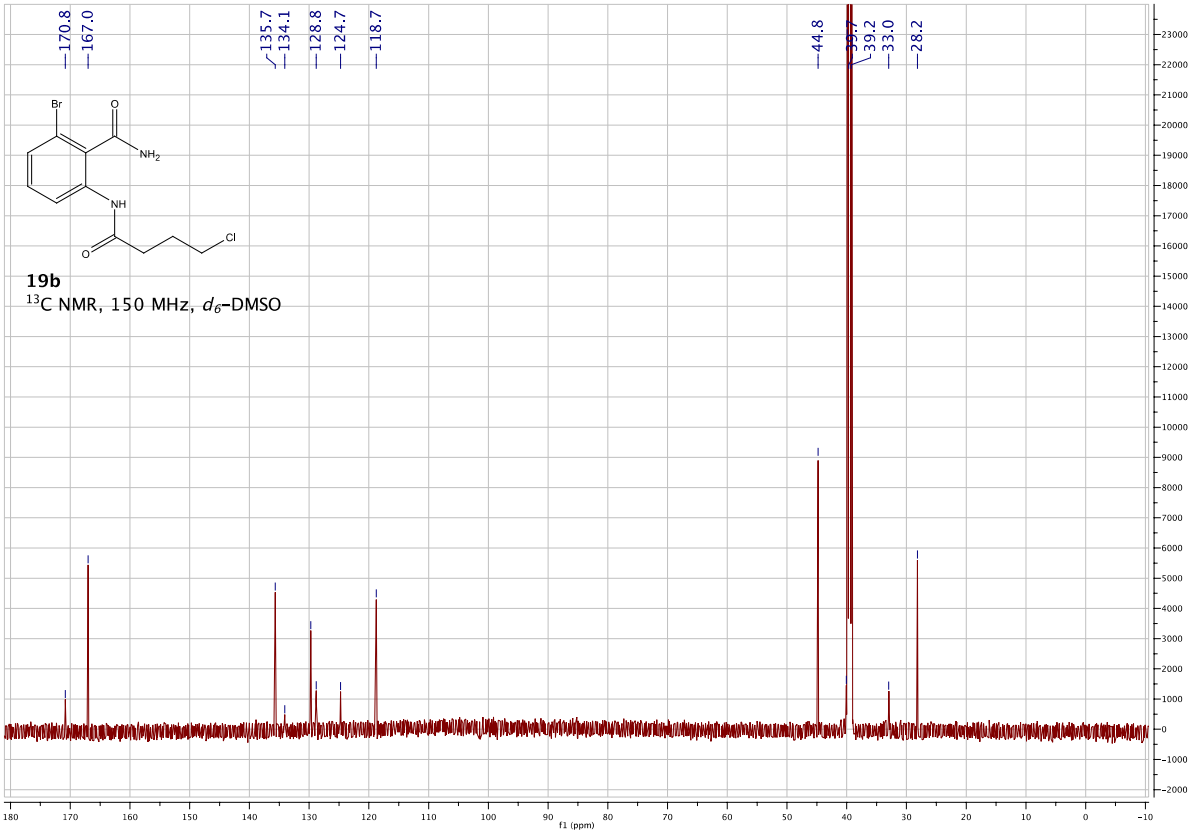
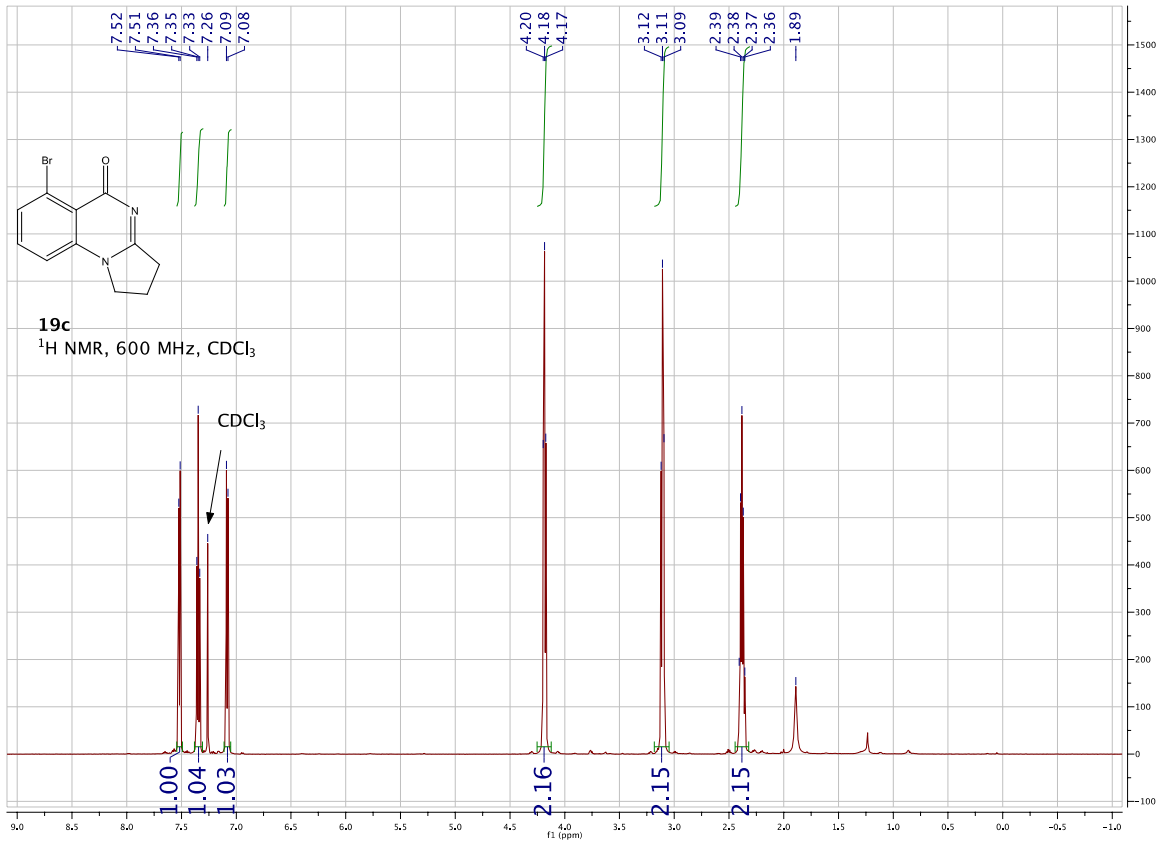
163.0
144.3
142.0
133.6
132.7
126.1
115.2
113.6
93.8
46.2
39.9
39.5
39.2
38.9
22.6
DMSO
Cl
O
N
N
N
18
^{13}C NMR, 125 MHz, d_6–DMSO
f1 (ppm)

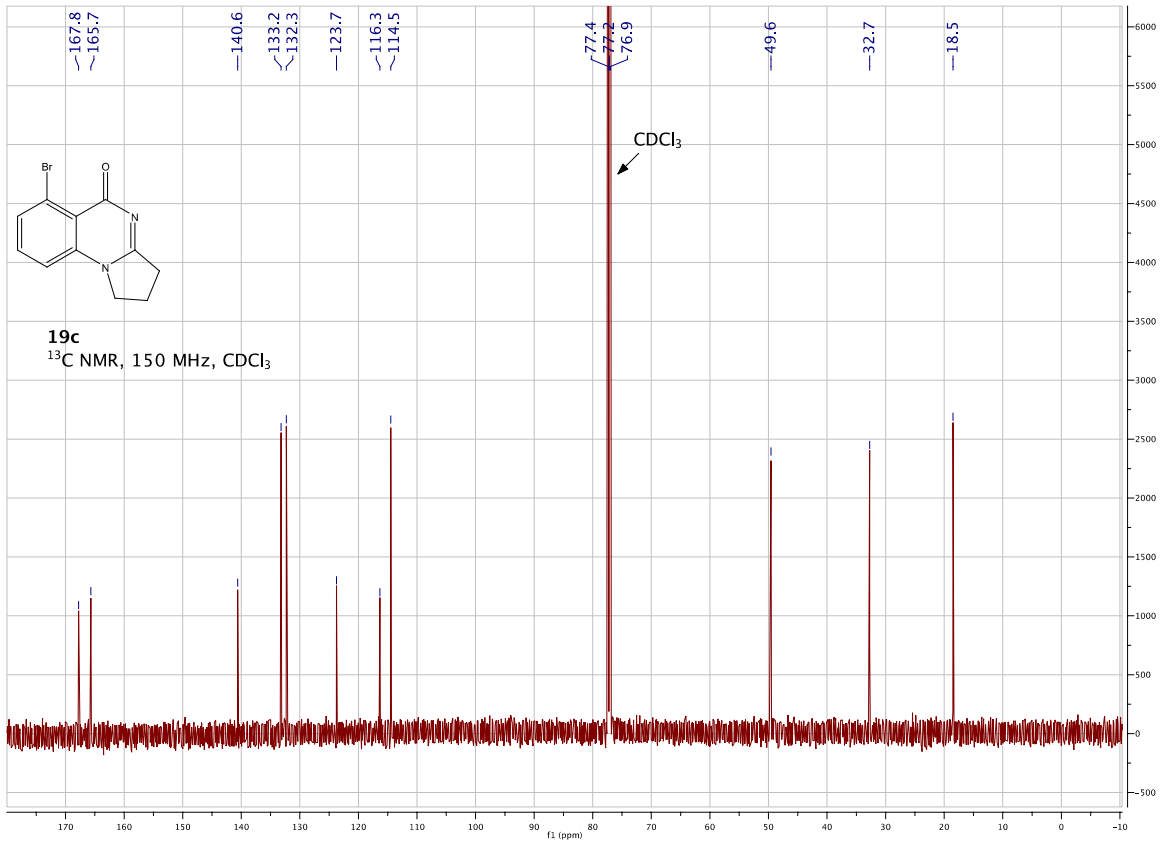

7.80
7.55
6.95
6.93
6.92
6.74
6.74
6.73
6.67
6.66
5.15
3.32
2.50
2.50
2.50
Br
O
NH2
NH2
19a
1H NMR, 600 MHz, d6-DMSO
H2O
DMSO
1.00
1.01
1.04
1.01
1.05
1.99
f1 (ppm)

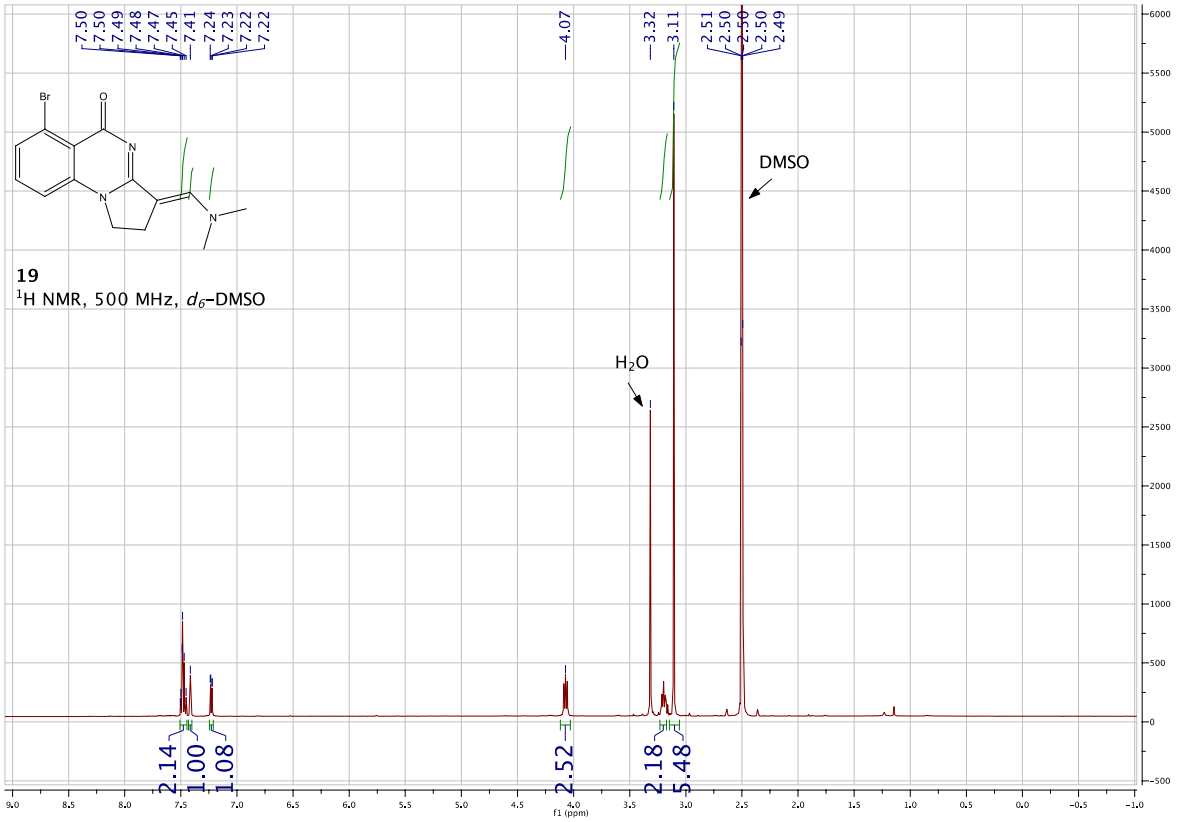

168.3
146.8
130.1
124.0
119.2
114.0
39.9
39.8
39.7
39.5
39.4
39.2
39.1
DMSO
Br
O
NH2
NH2
19a
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)

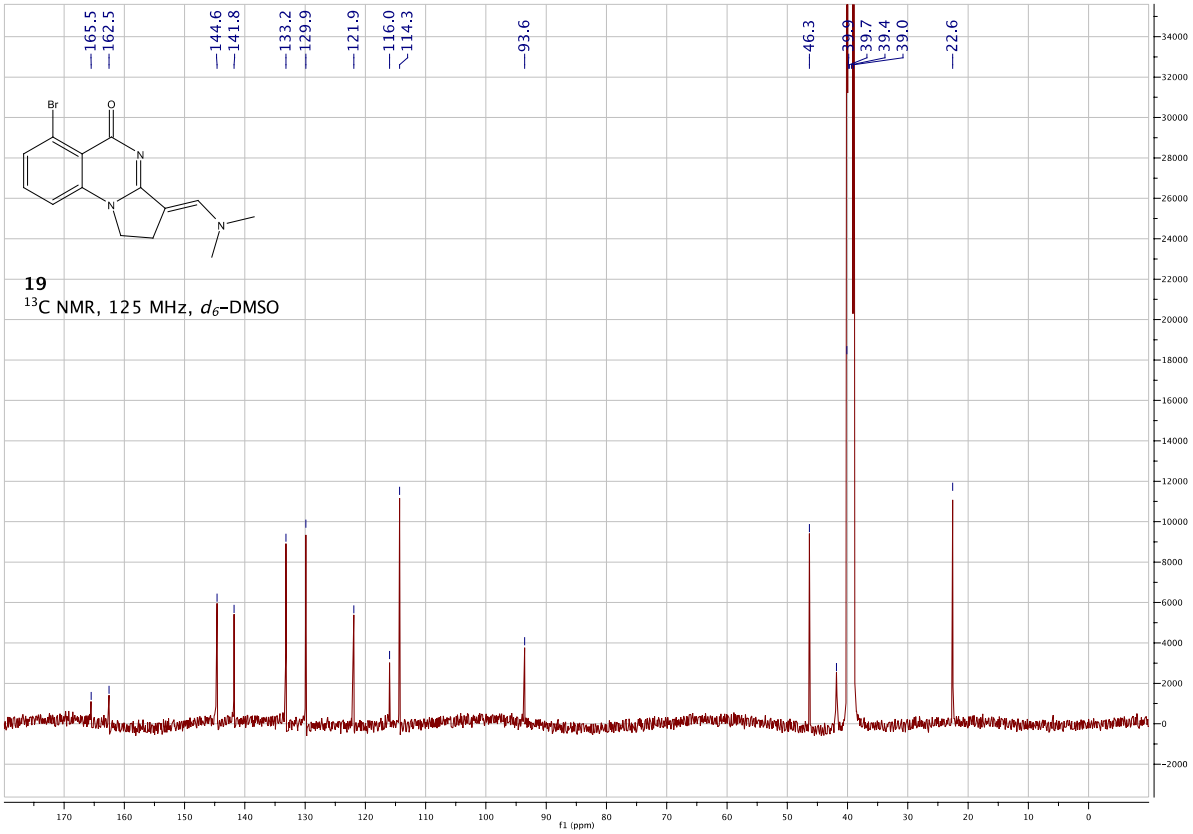

9.31
7.85
7.70
7.62
7.61
7.44
7.43
7.29
7.27
7.26
3.68
3.67
3.66
3.33
2.50
2.47
2.46
2.02
2.01
2.00
1.98
1.97
Br
O
NH2
NH
O
Cl
19b
1H NMR, 600 MHz, d6-DMSO
1.00
1.04
1.08
1.04
1.02
1.07
2.13
2.07
2.14
f1 (ppm)

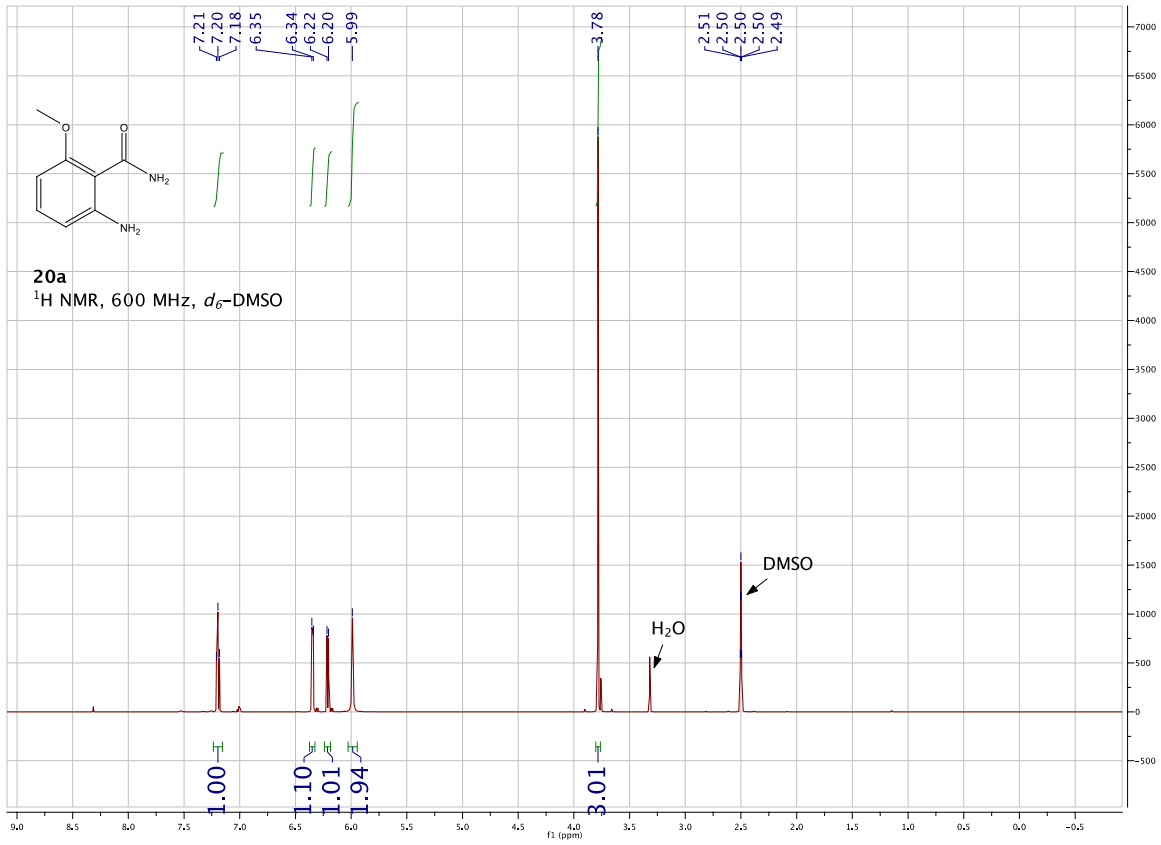

170.8
167.0
135.7
134.1
128.8
124.7
118.7
44.8
39.7
39.2
33.0
28.2
Br
O
NH2
NH
O
Cl
19b
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)

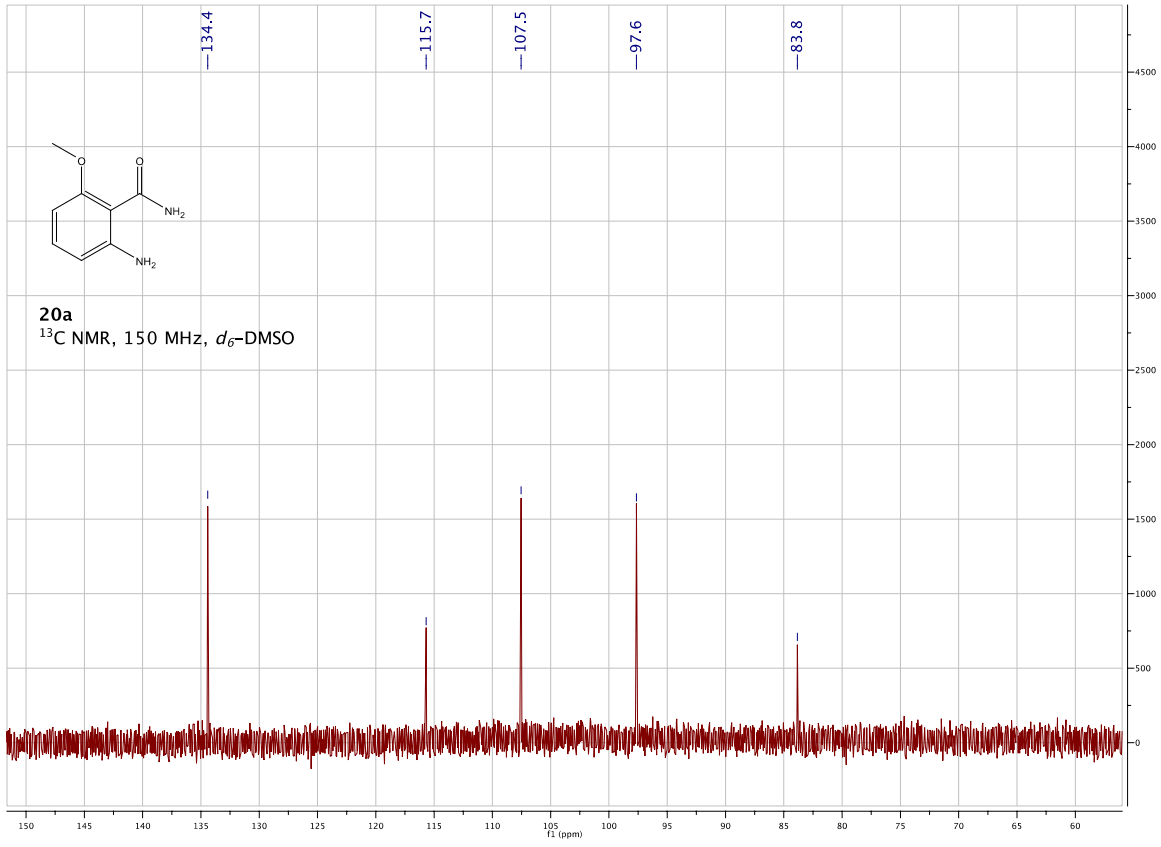

7.52
7.51
7.36
7.35
7.33
7.26
7.09
7.08
4.20
4.18
4.17
3.12
3.11
3.09
2.39
2.38
2.37
2.36
1.89
Br
O
N
N
19c
1H NMR, 600 MHz, CDCl3
CDCl3
1.00
1.04
1.03
2.16
2.15
2.15
f1 (ppm)

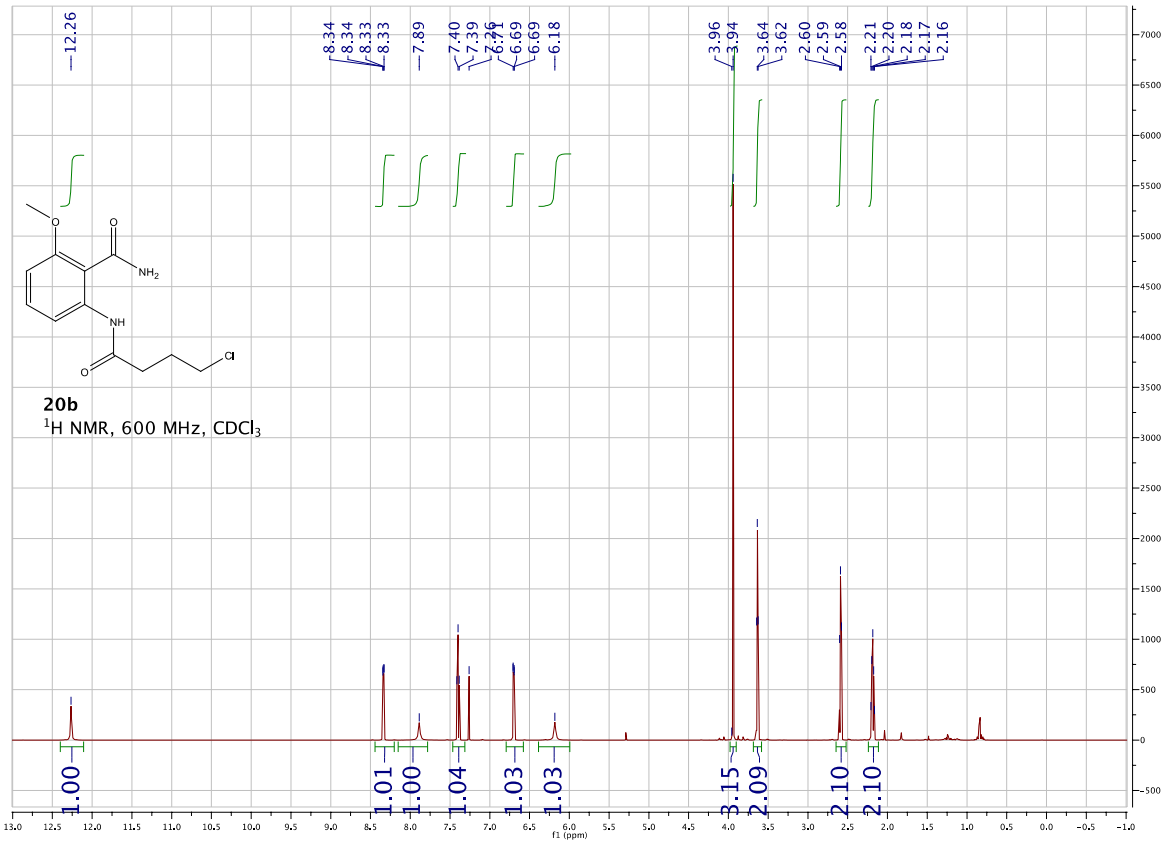

167.8
165.7
140.6
133.2
132.3
123.7
116.3
114.5
77.4
77.2
76.9
49.6
32.7
18.5
Br
O
N
N
19c
13C NMR, 150 MHz, CDCl3
CDCl3
f1 (ppm)


7.50
7.50
7.49
7.48
7.47
7.45
7.41
7.24
7.23
7.22
7.22
4.07
3.32
3.11
2.51
2.50
2.50
2.50
2.49
Br
O
N
N
N
DMSO
H2O
19
1H NMR, 500 MHz, d6-DMSO
2.14
1.00
1.08
2.52
2.18
5.48
f1 (ppm)


165.5
162.5
144.6
141.8
133.2
129.9
121.9
116.0
114.3
93.6
46.3
39.9
39.7
39.4
39.0
22.6
Br
O
N
N
N
19
13C NMR, 125 MHz, d6-DMSO
f1 (ppm)

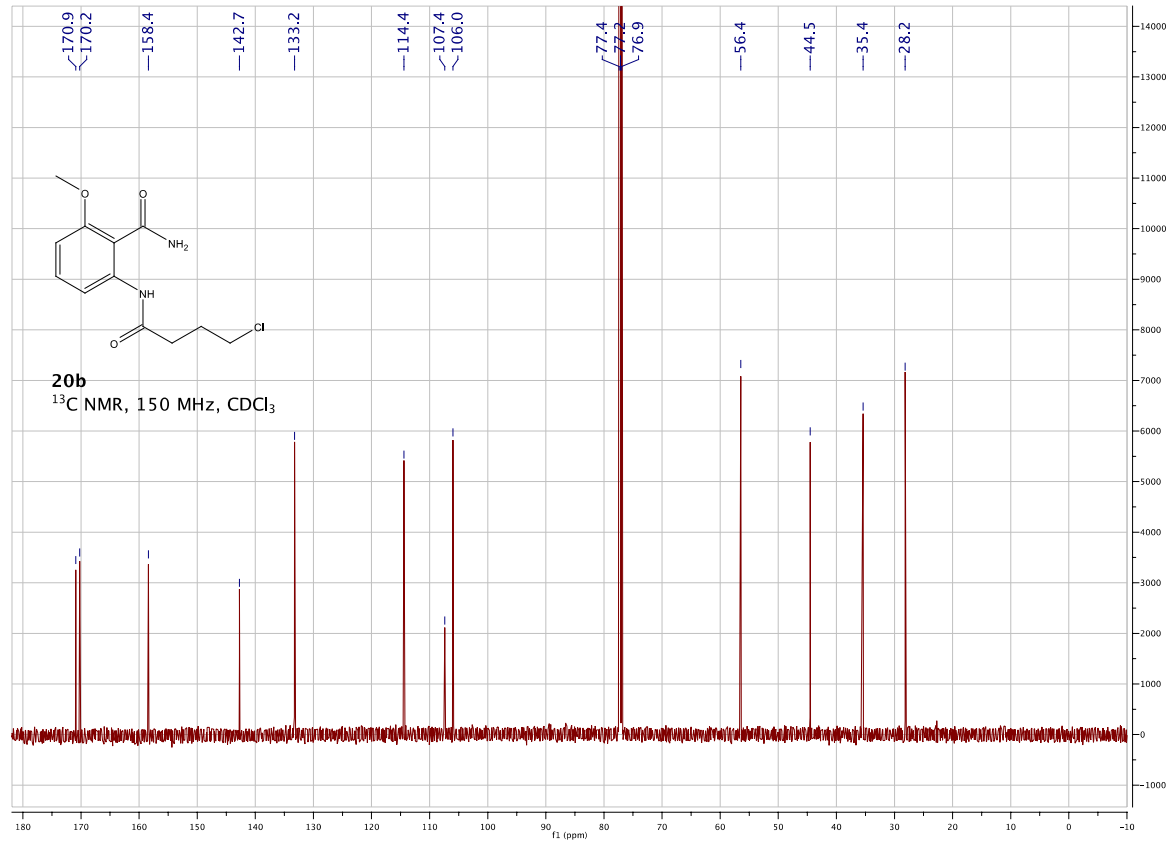

7.21
7.20
7.18
6.35
6.34
6.22
6.20
5.99
3.78
2.51
2.50
2.50
2.50
2.49
O
O
NH2
NH2
20a
1H NMR, 600 MHz, d6-DMSO
DMSO
H2O
1.00
1.10
1.01
1.94
3.01
f1 (ppm)


134.4
115.7
107.5
97.6
83.8
O
O
NH2
NH2
20a
13C NMR, 150 MHz, d6-DMSO
f1 (ppm)



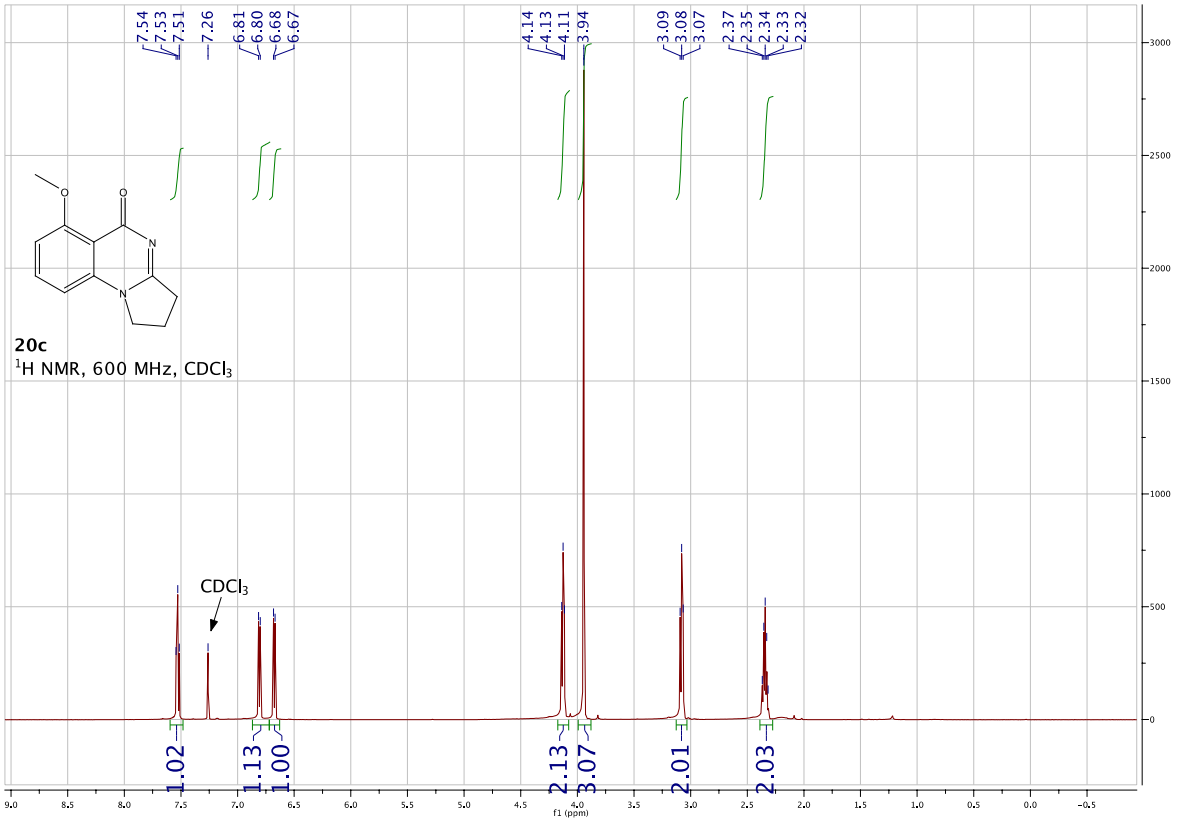
20b

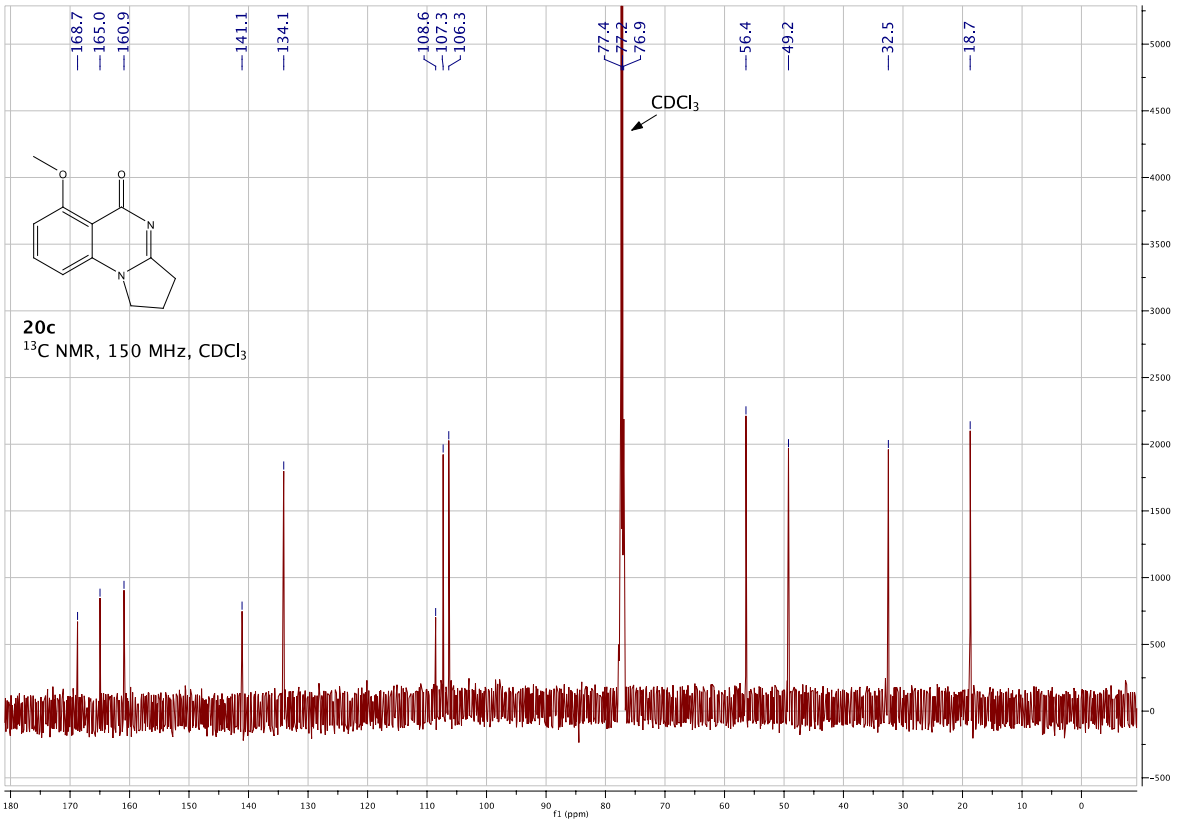
^{1}H NMR, 600 MHz, $CDCl_3$

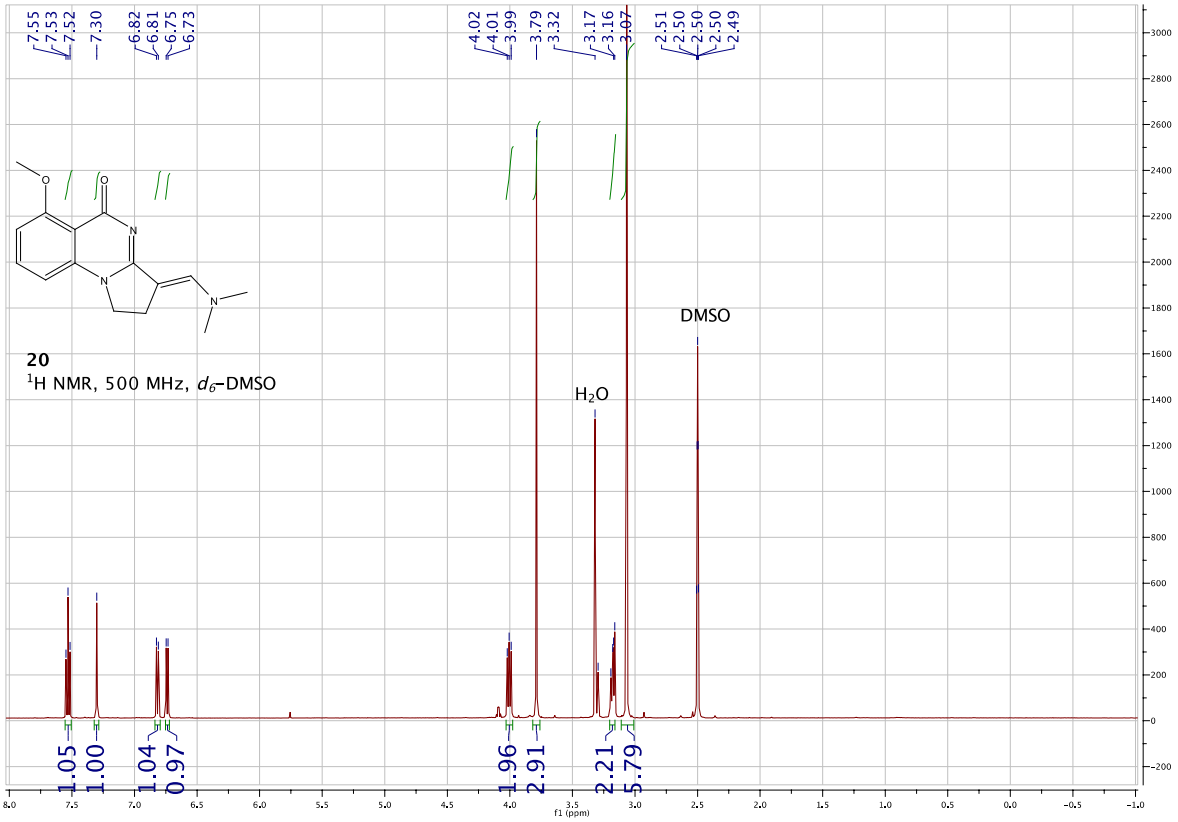


20b

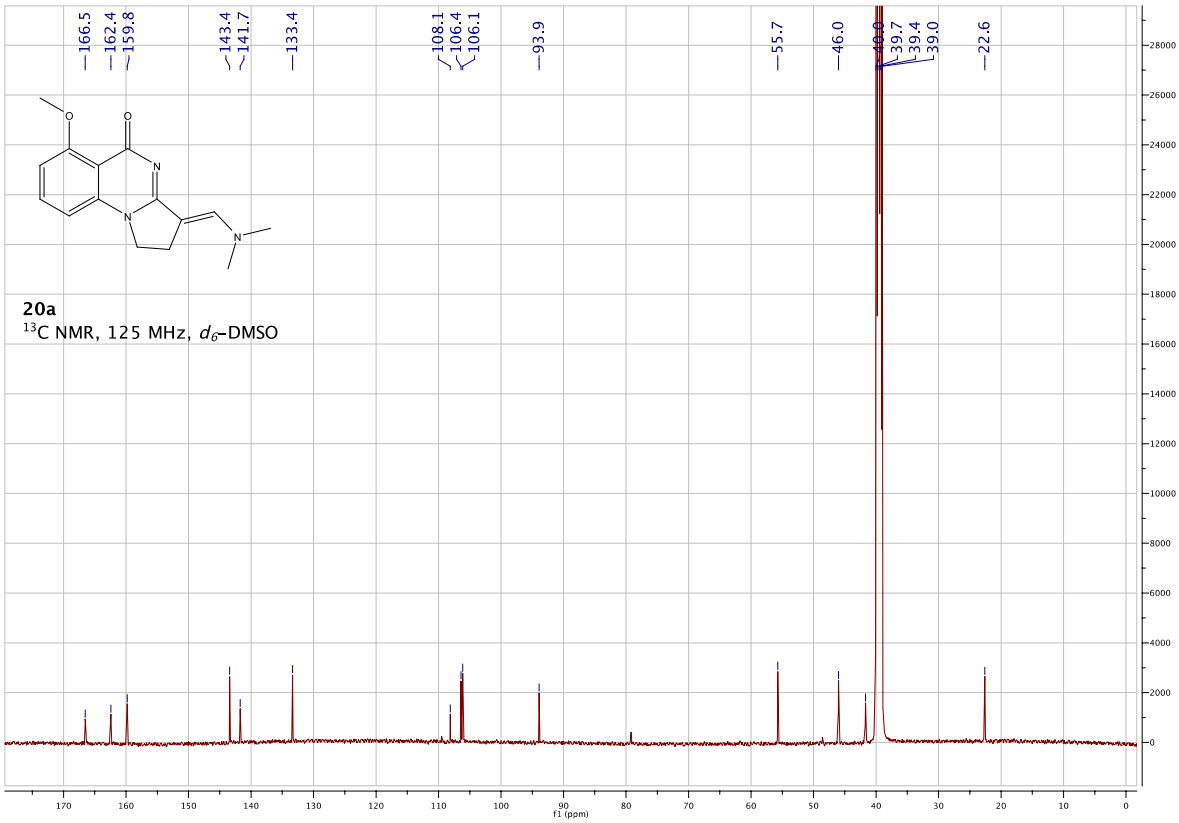
^{13}C NMR, 150 MHz, $CDCl_3$


7.54
7.53
7.51
7.26
6.81
6.80
6.68
6.67
4.14
4.13
4.11
3.94
3.09
3.08
3.07
2.37
2.35
2.34
2.33
2.32
20c
1H NMR, 600 MHz, CDCl3
CDCl3
1.02
1.13
1.00
2.13
3.07
2.01
2.03
f1 (ppm)

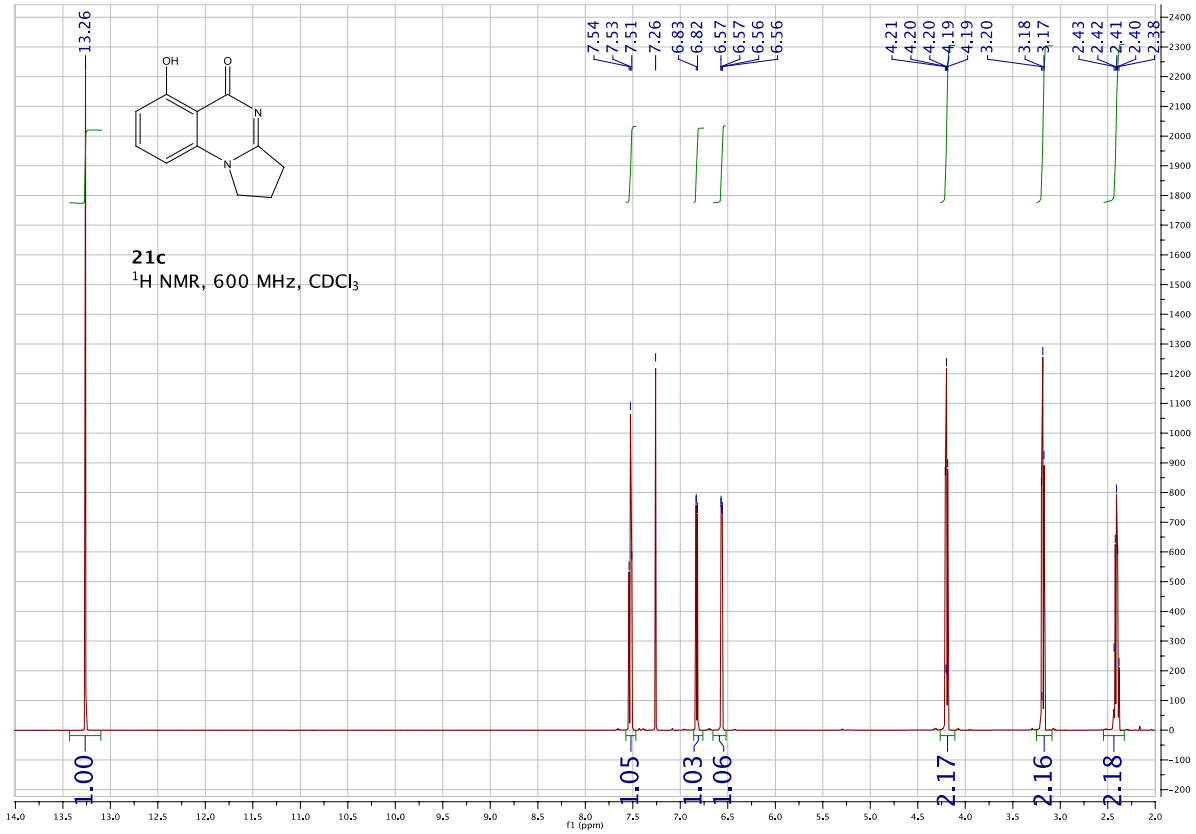

168.7
165.0
160.9
141.1
134.1
108.6
107.3
106.3
77.4
77.2
76.9
56.4
49.2
32.5
18.7
CDCl3
20c
13C NMR, 150 MHz, CDCl3
f1 (ppm)

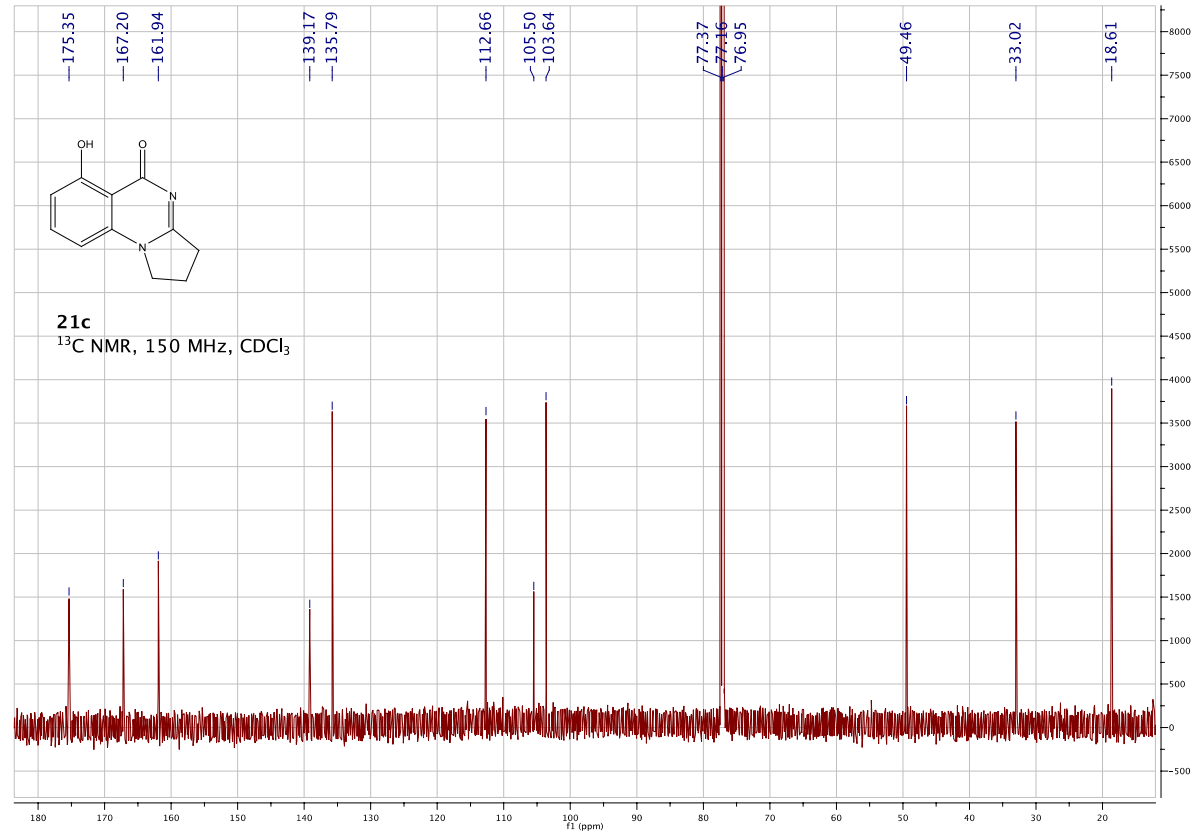


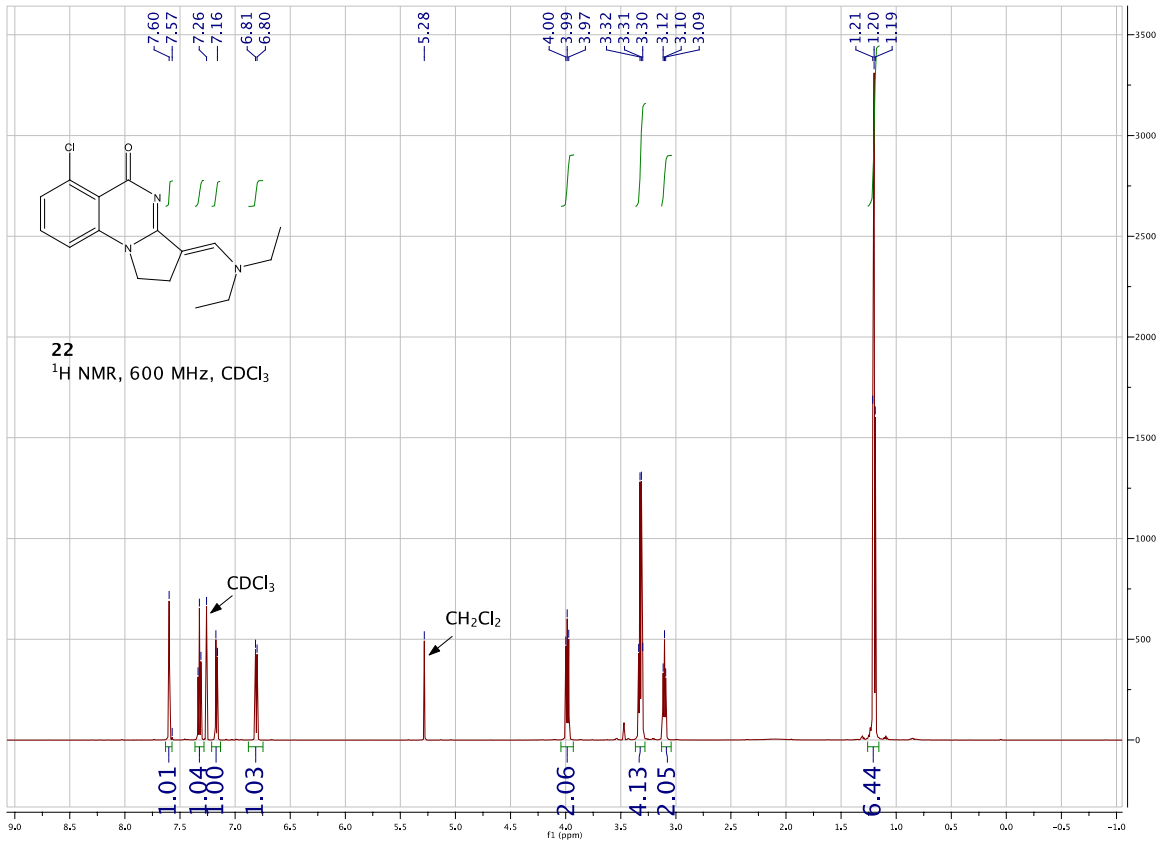
20
^{1}H NMR, 500 MHz, d_6-DMSO

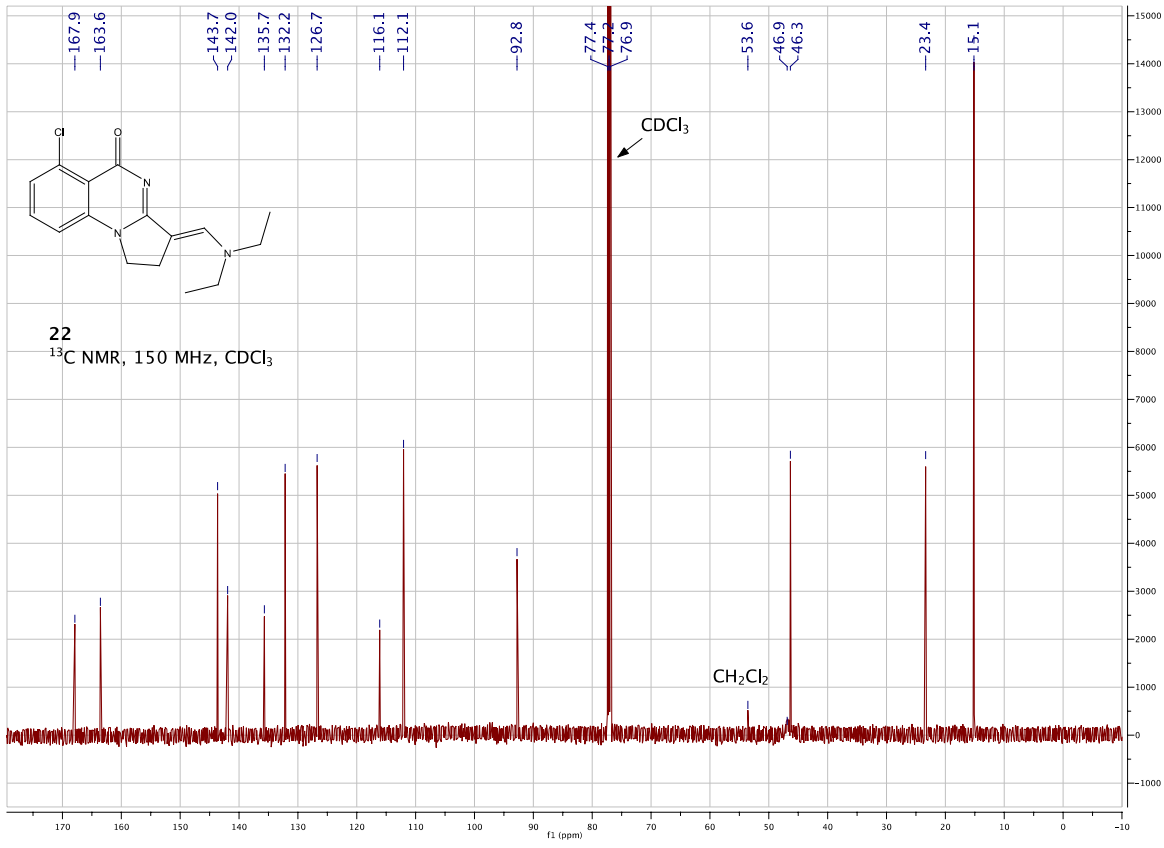


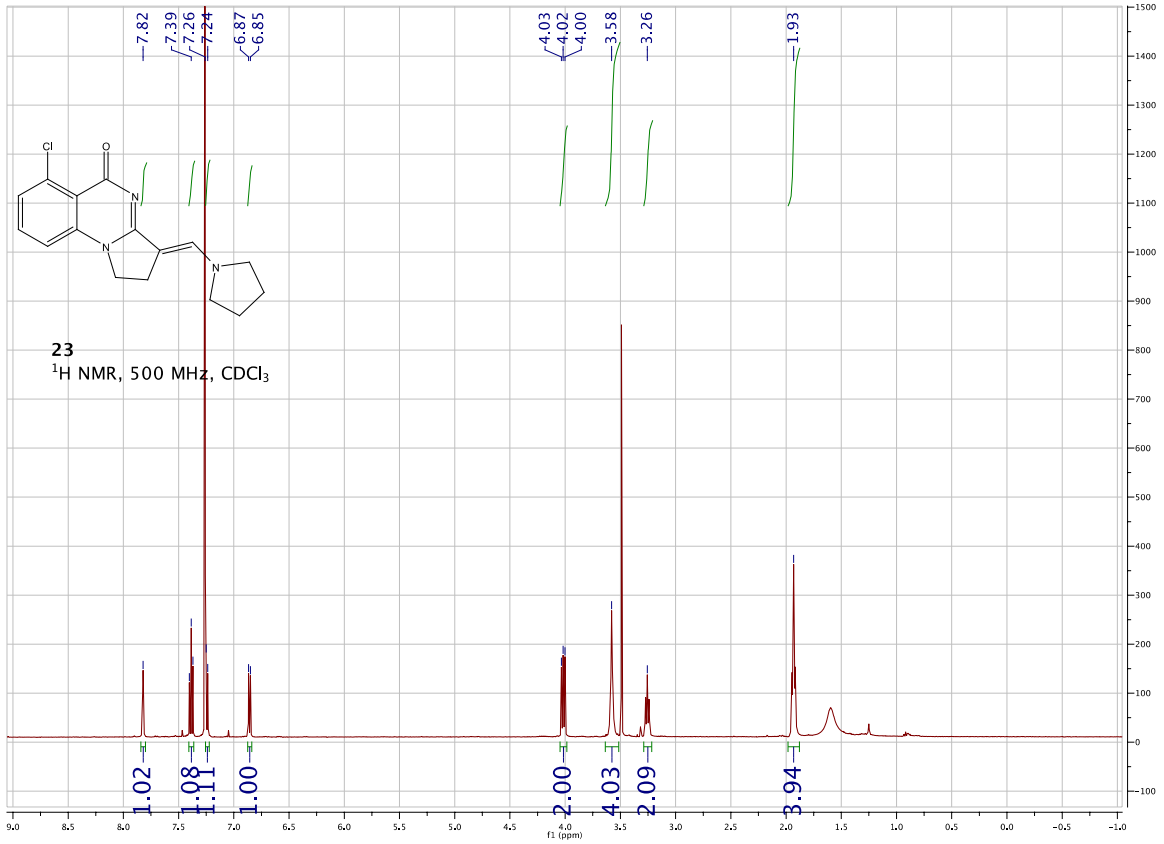
20a
^{13}C NMR, 125 MHz, d_6-DMSO

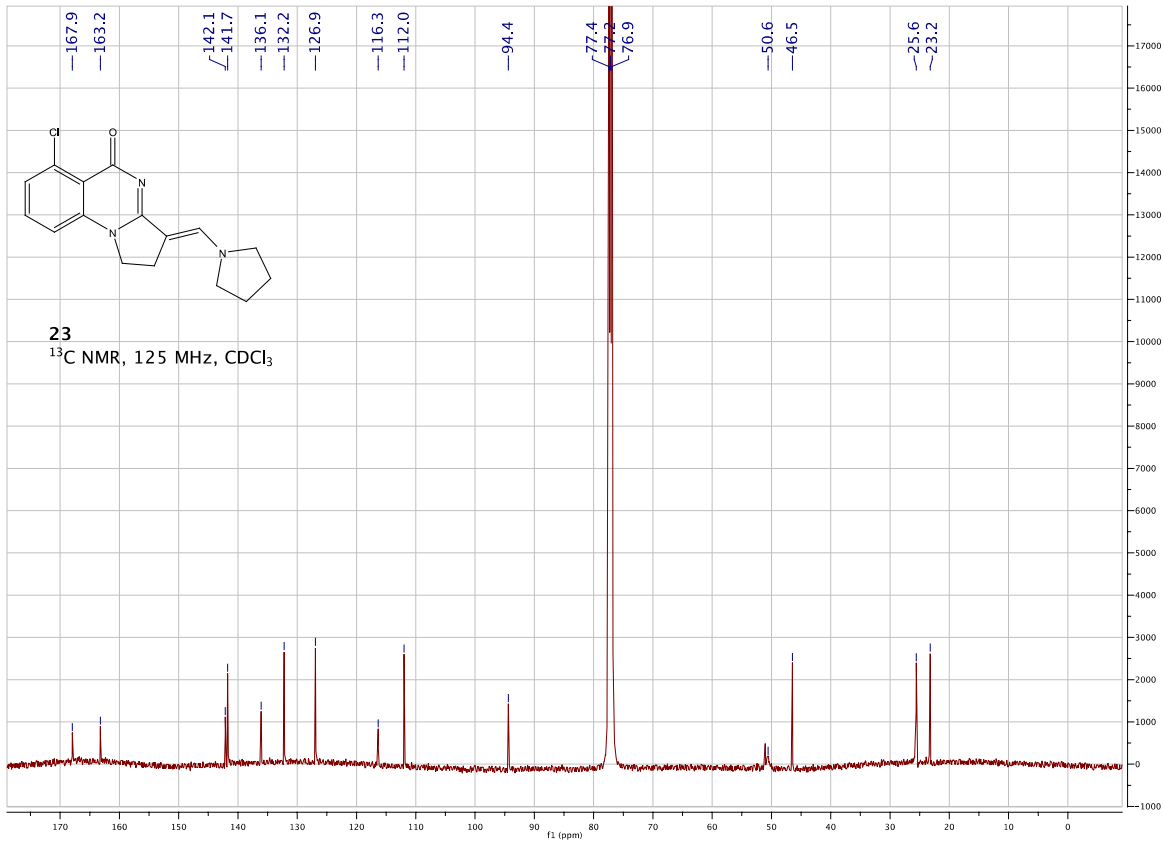

13.26
7.54
7.53
7.51
7.26
6.83
6.82
6.57
6.57
6.56
6.56
4.21
4.20
4.20
4.19
4.19
3.20
3.18
3.17
2.43
2.42
2.41
2.40
2.38
OH
O
N
N
21c
1H NMR, 600 MHz, CDCl3
1.00
1.05
1.03
1.06
2.17
2.16
2.18
f1 (ppm)

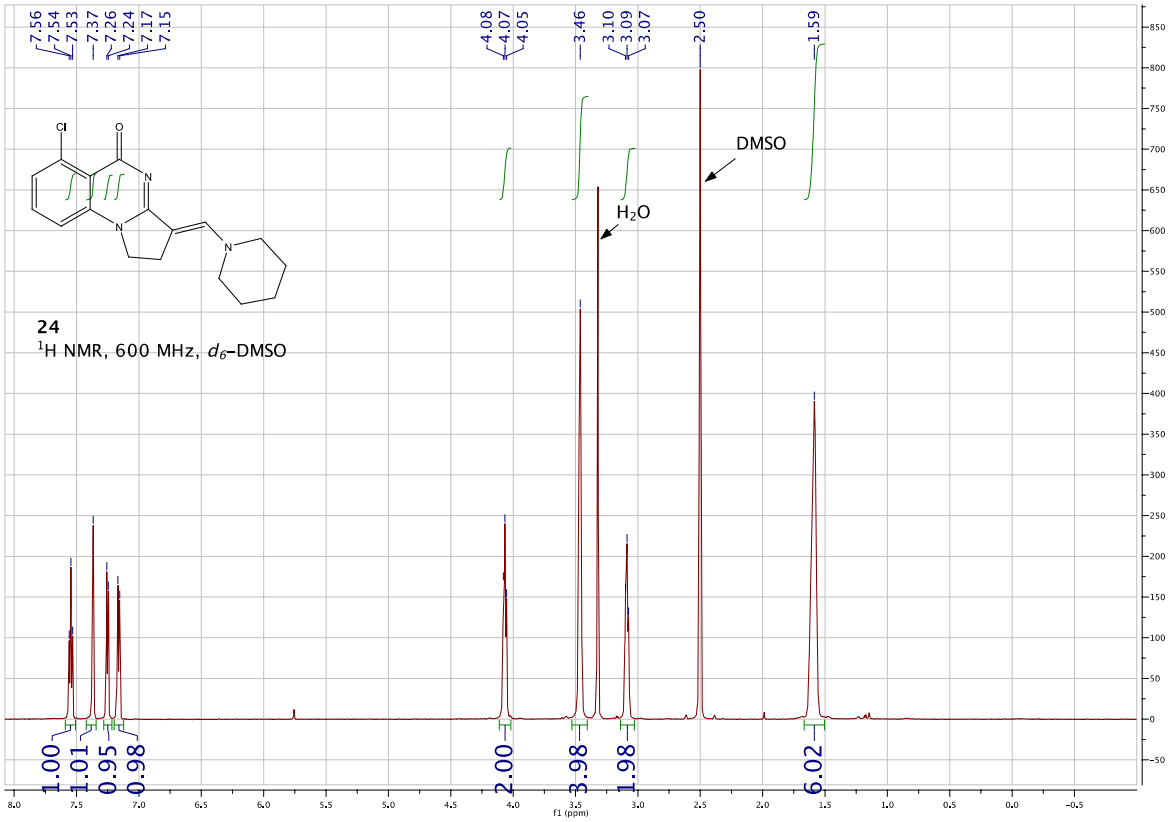

175.35
167.20
161.94
139.17
135.79
112.66
105.50
103.64
77.37
77.16
76.95
49.46
33.02
18.61
OH
O
N
N
21c
13C NMR, 150 MHz, CDCl3
f1 (ppm)


7.60
7.57
7.26
7.16
6.81
6.80
5.28
4.00
3.99
3.97
3.32
3.31
3.30
3.12
3.10
3.09
1.21
1.20
1.19
Cl
O
N
N
N
22
1H NMR, 600 MHz, CDCl3
CDCl3
CH2Cl2
1.01
1.04
1.00
1.03
2.06
4.13
2.05
6.44
f1 (ppm)


167.9
163.6
143.7
142.0
135.7
132.2
126.7
116.1
112.1
92.8
77.4
77.2
76.9
53.6
46.9
46.3
23.4
15.1
Cl
O
N
N
N
22
13C NMR, 150 MHz, CDCl3
CDCl3
CH2Cl2
f1 (ppm)


7.82
7.39
7.26
7.24
6.87
6.85
4.03
4.02
4.00
3.58
3.26
1.93
Cl
O
N
N
N
23
^{1}H NMR, 500 MHz, $CDCl_3$
1.02
1.08
1.11
1.00
2.00
4.03
2.09
3.94
f1 (ppm)


167.9
163.2
142.1
141.7
136.1
132.2
126.9
116.3
112.0
94.4
77.4
77.2
76.9
50.6
46.5
25.6
23.2
Cl
O
N
N
N
23
^{13}C NMR, 125 MHz, $CDCl_3$
f1 (ppm)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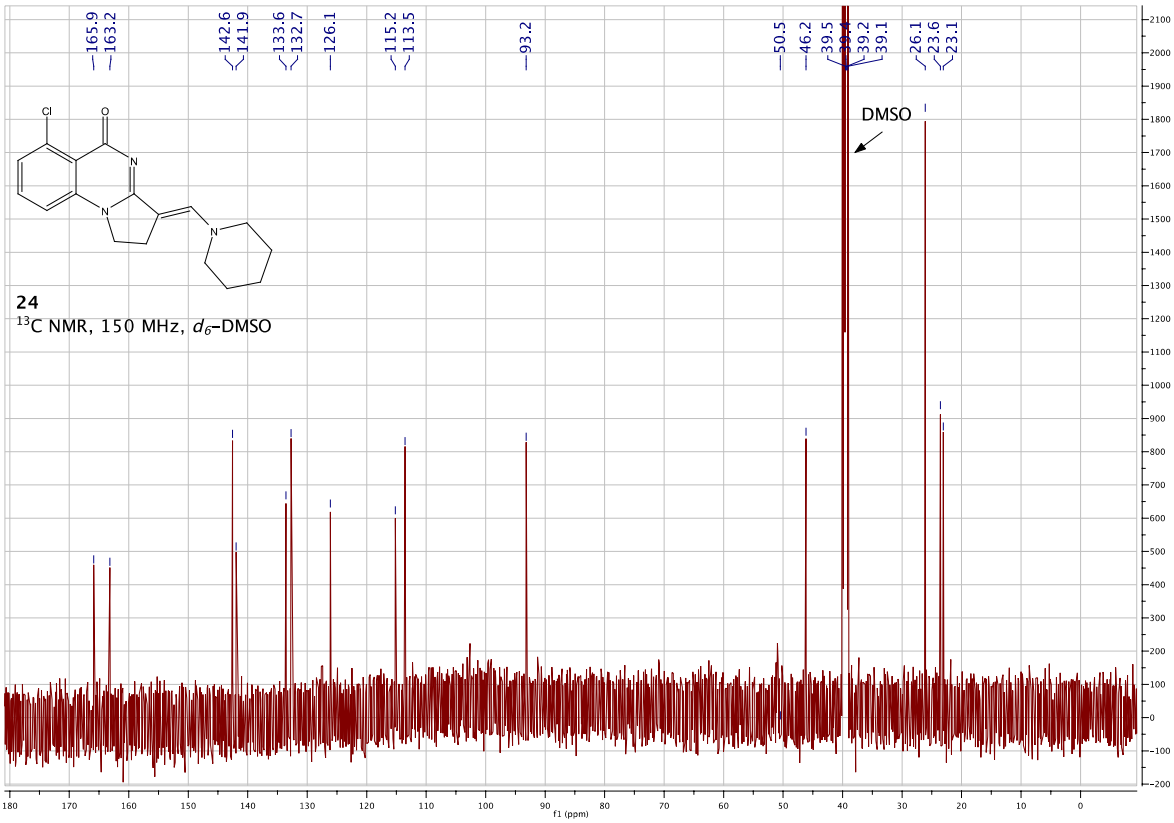
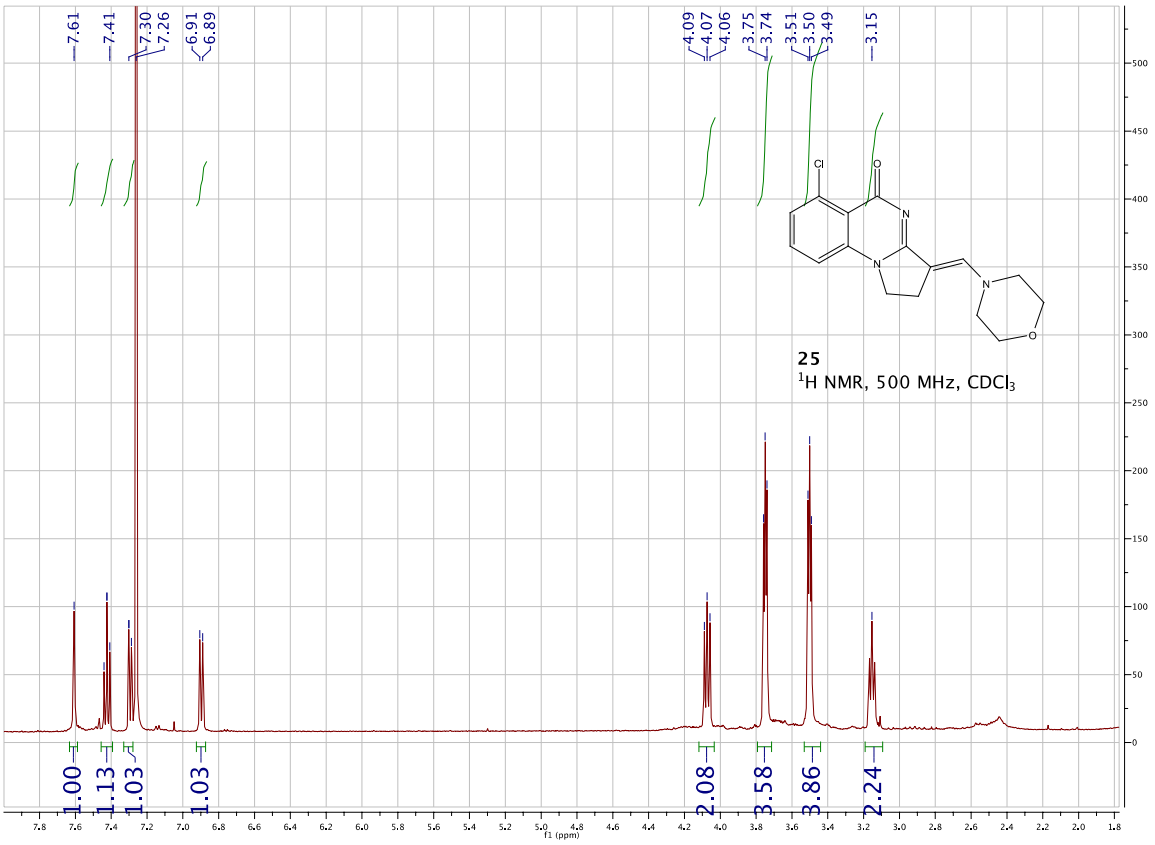
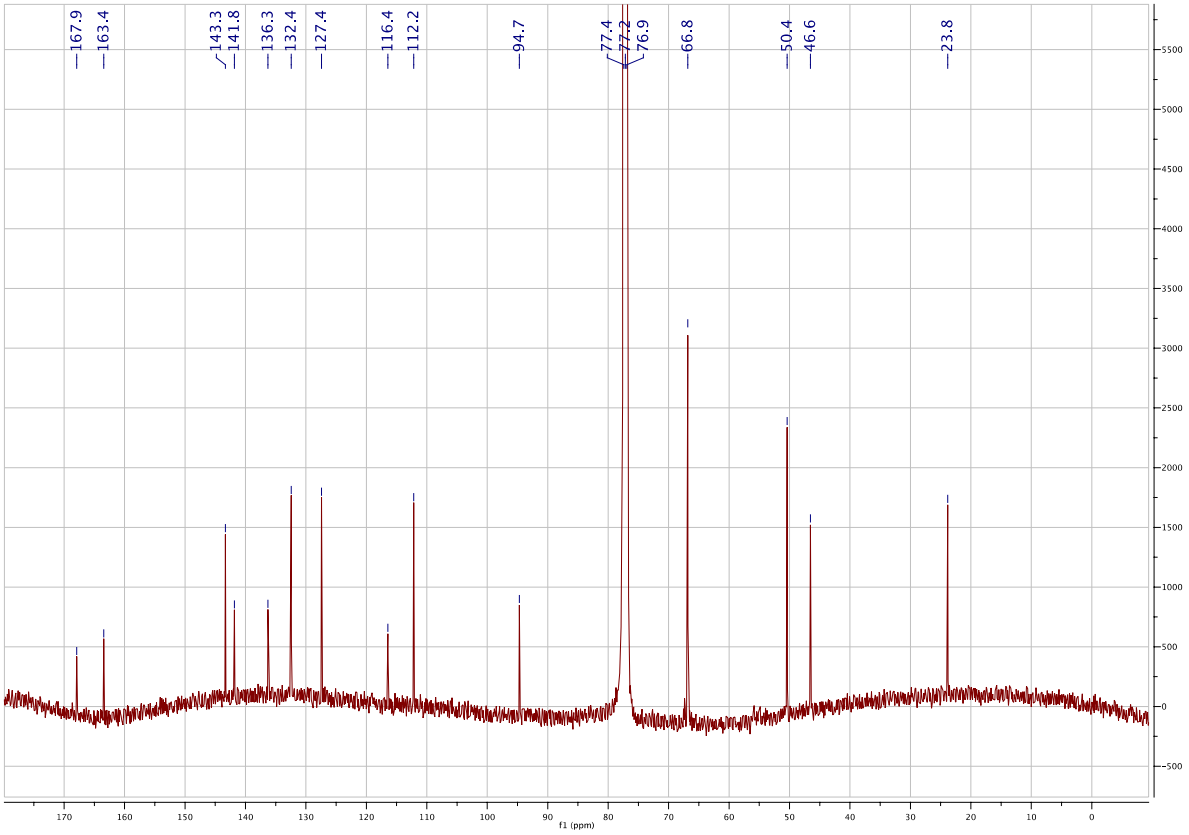
7.54
7.53
7.37
7.26
7.24
7.17
7.15
4.08
4.07
4.05
3.46
3.10
3.09
3.07
2.50
1.59
DMSO
H2O
Cl
O
N
N
N
24
1H NMR, 600 MHz, d6–DMSO
1.00
1.01
0.95
0.98
2.00
3.98
1.98
6.02
f1 (ppm)


165.9
163.2
142.6
141.9
133.6
132.7
126.1
115.2
113.5
93.2
50.5
46.2
39.5
39.4
39.2
39.1
26.1
23.6
23.1
DMSO
Cl
O
N
N
N
24
13C NMR, 150 MHz, d6–DMSO
f1 (ppm)


7.61
7.41
7.30
7.26
6.91
6.89
4.09
4.07
4.06
3.75
3.74
3.51
3.50
3.49
3.15
Cl
O
N
N
N
O
25
^{1}H NMR, 500 MHz, $CDCl_3$
1.00
1.13
1.03
1.03
2.08
3.58
3.86
2.24
f1 (ppm)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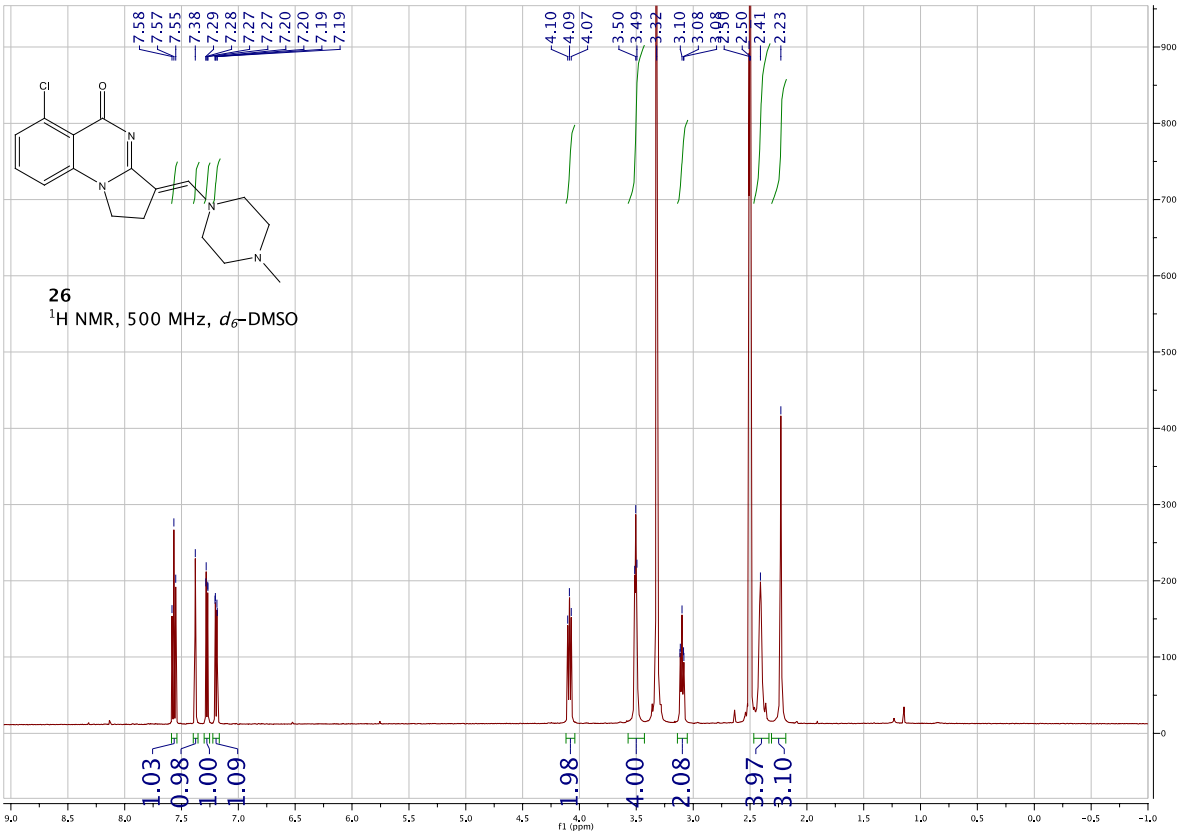
163.4
143.3
141.8
136.3
132.4
127.4
116.4
112.2
94.7
77.4
77.2
76.9
66.8
50.4
46.6
23.8
f1 (ppm)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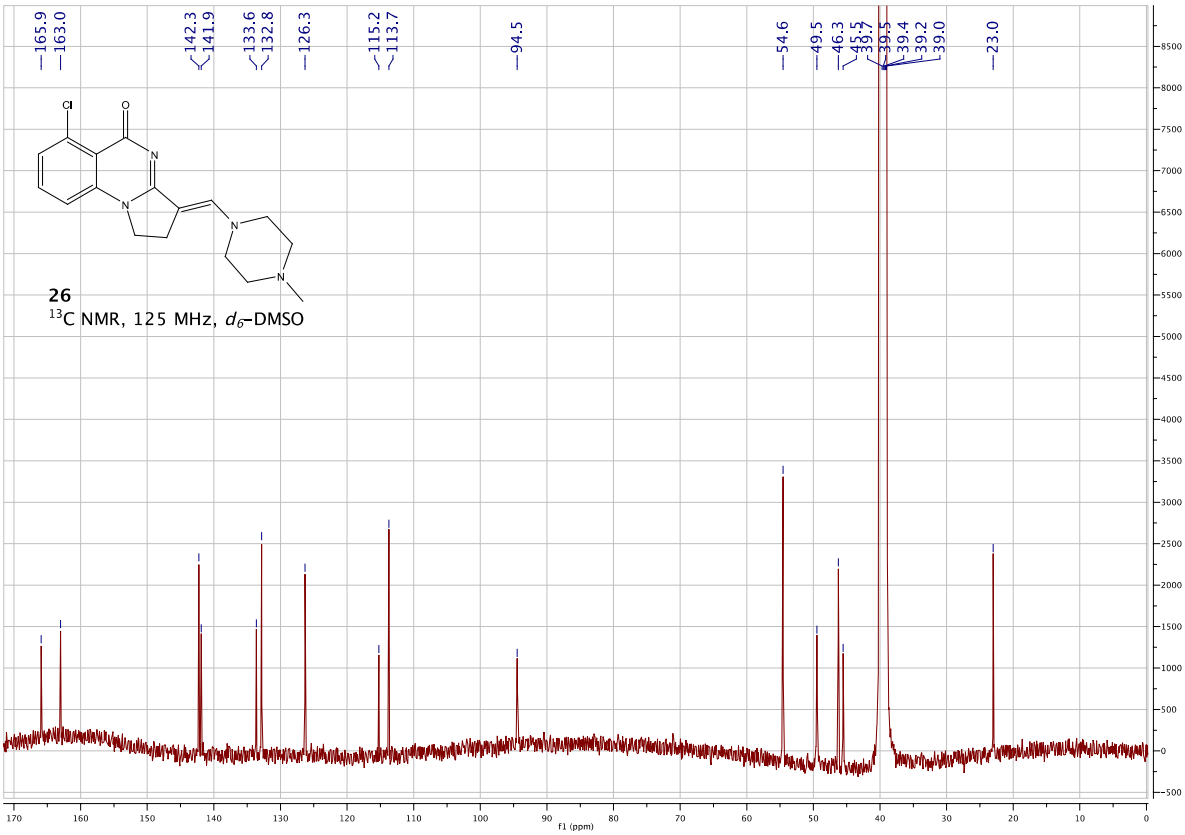
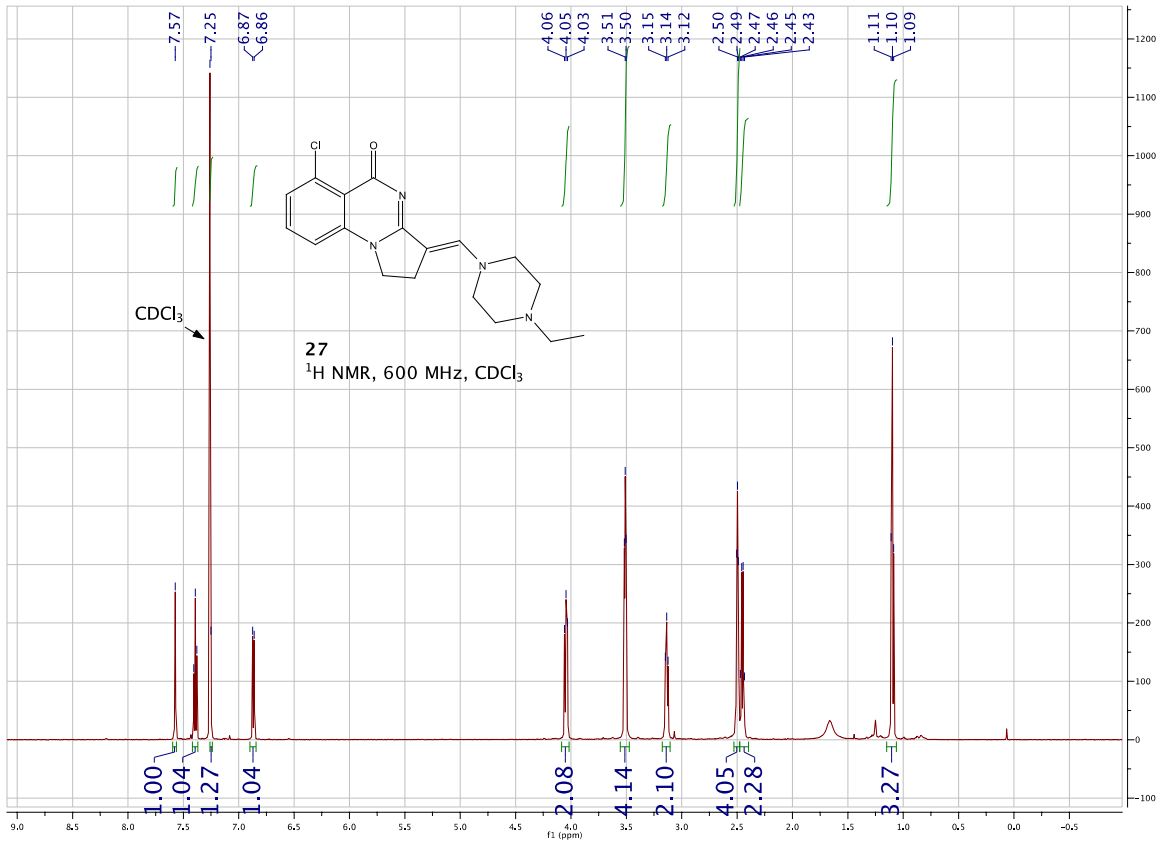
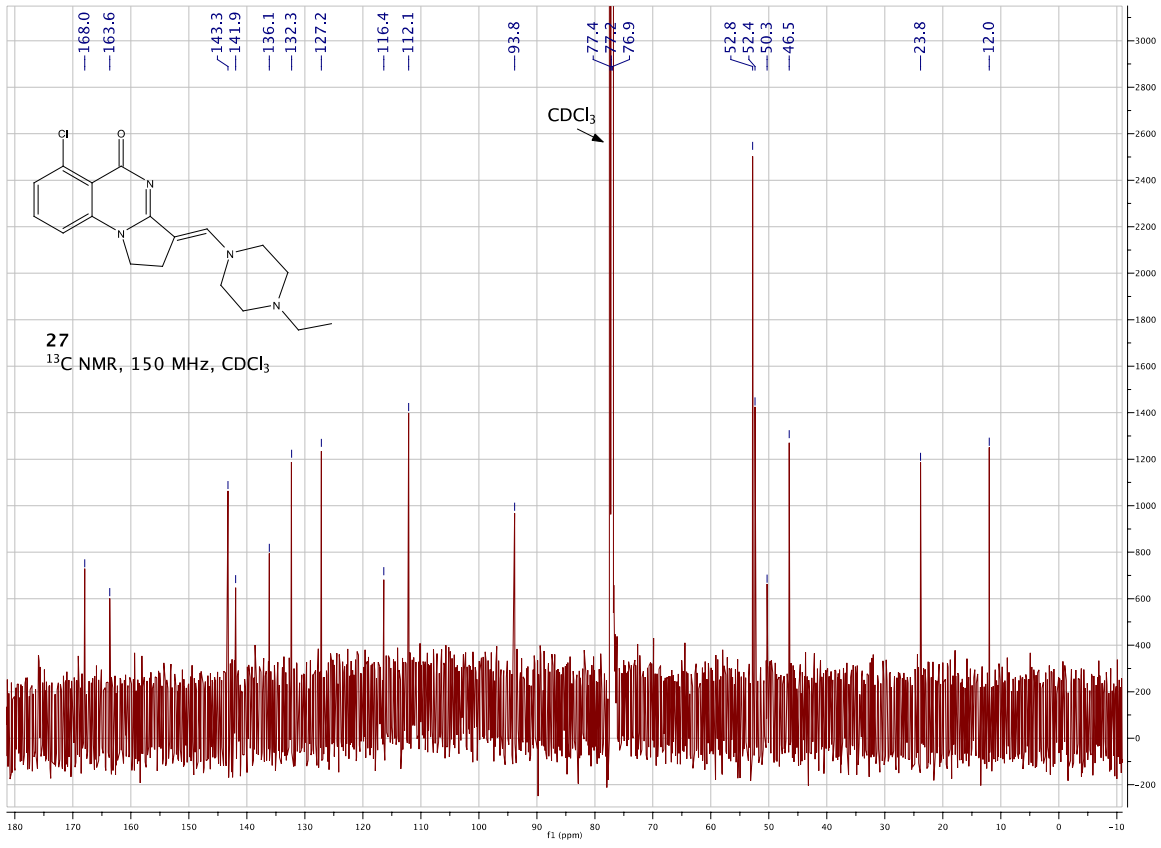
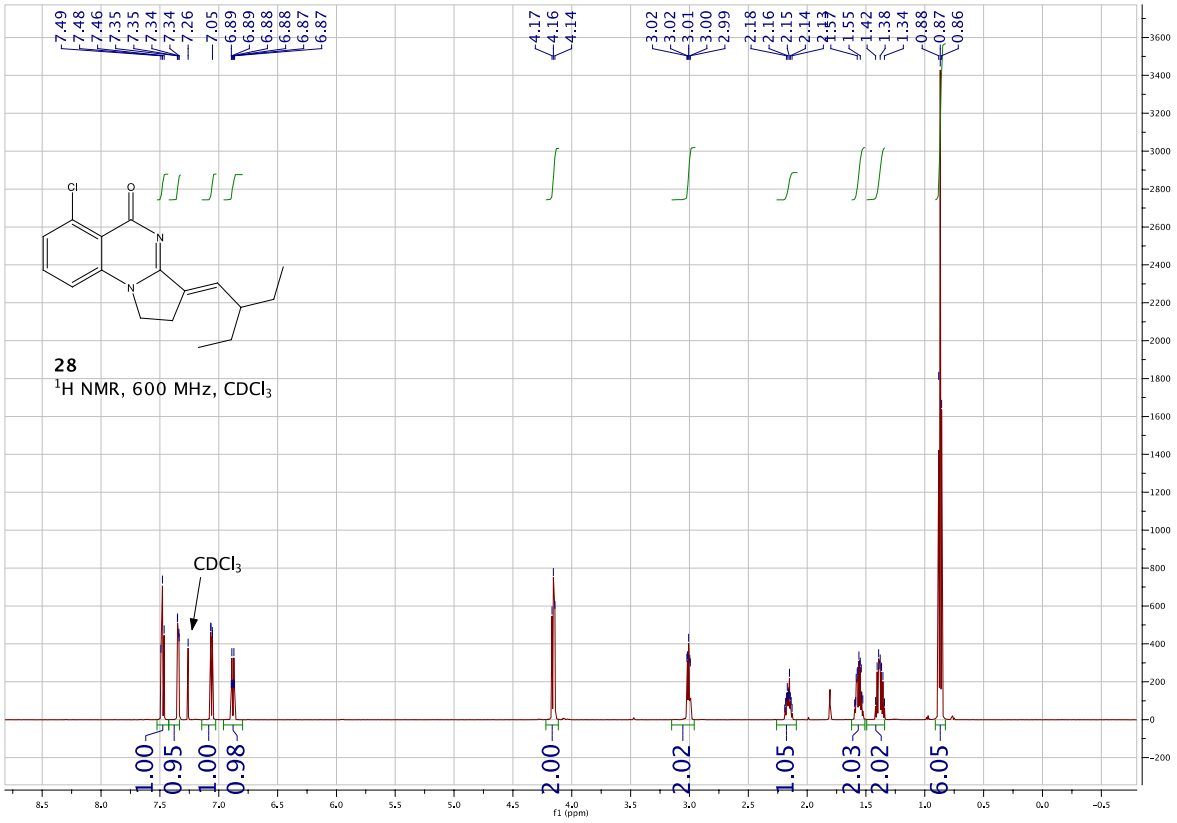
7.57
7.55
7.38
7.29
7.28
7.27
7.27
7.20
7.20
7.19
7.19
4.10
4.09
4.07
3.50
3.49
3.32
3.10
3.08
2.50
2.41
2.23
1.03
0.98
1.00
1.09
1.98
4.00
2.08
3.97
3.10
f1 (ppm)
26
^{1}H NMR, 500 MHz, d_6–DMSO


165.9
163.0
142.3
141.9
133.6
132.8
126.3
115.2
113.7
94.5
54.6
49.5
46.3
45.5
39.5
39.4
39.2
39.0
23.0
f1 (ppm)
26
^{13}C NMR, 125 MHz, d_6–DMSO


7.57
7.25
6.87
6.86
4.06
4.05
4.03
3.51
3.50
3.15
3.14
3.12
2.50
2.49
2.47
2.46
2.45
2.43
1.11
1.10
1.09
CDCl3
27
1H NMR, 600 MHz, CDCl3
1.00
1.04
1.27
1.04
2.08
4.14
2.10
4.05
2.28
3.27
f1 (ppm)


168.0
163.6
143.3
141.9
136.1
132.3
127.2
116.4
112.1
93.8
77.4
77.2
76.9
52.8
52.4
50.3
46.5
23.8
12.0
CDCl3
27
13C NMR, 150 MHz, CDCl3
f1 (ppm)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7.48
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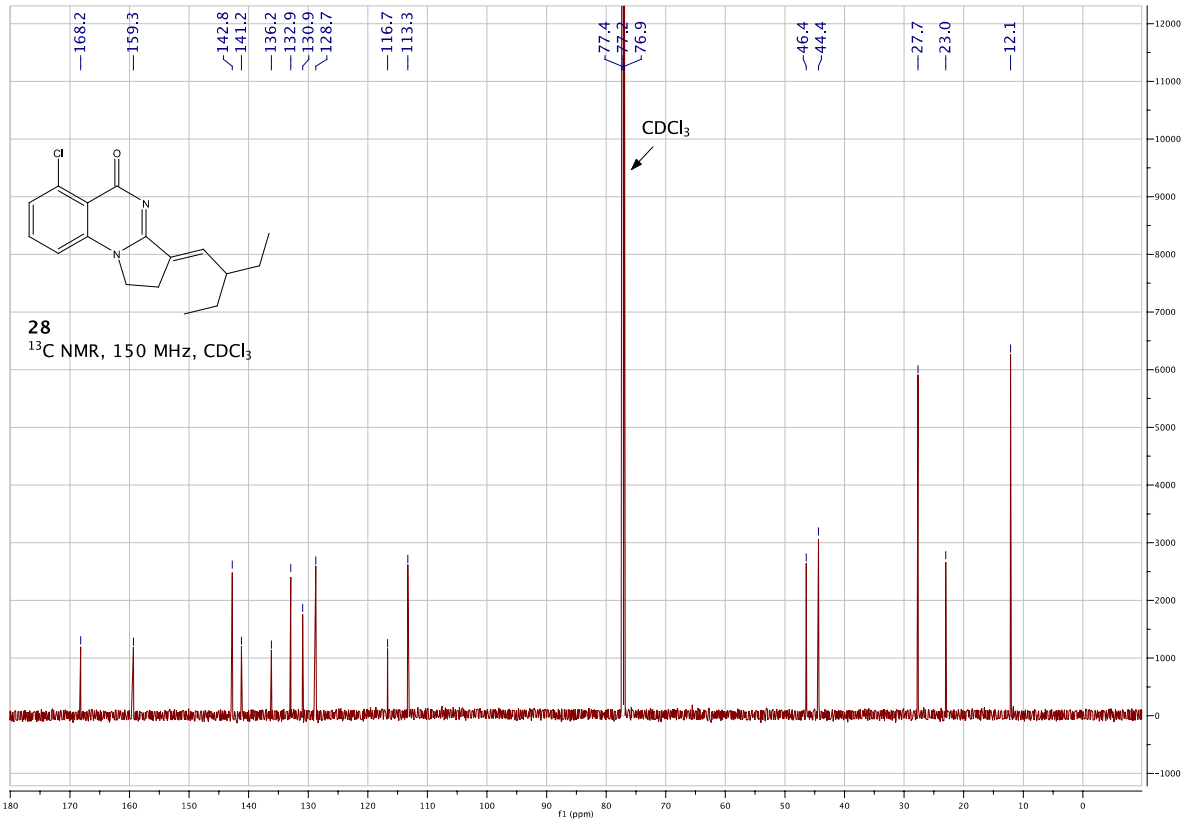
7.35
7.34
7.34
7.26
7.05
6.89
6.89
6.88
6.88
6.87
6.87
4.17
4.16
4.14
3.02
3.02
3.01
3.00
2.99
2.18
2.16
2.15
2.14
1.55
1.42
1.38
1.34
0.88
0.87
0.86
Cl
O
N
N
28
^{1}H NMR, 600 MHz, $CDCl_3$
$CDCl_3$
1.00
0.95
1.00
0.98
2.00
2.02
1.05
2.03
2.02
6.05
f1 (ppm)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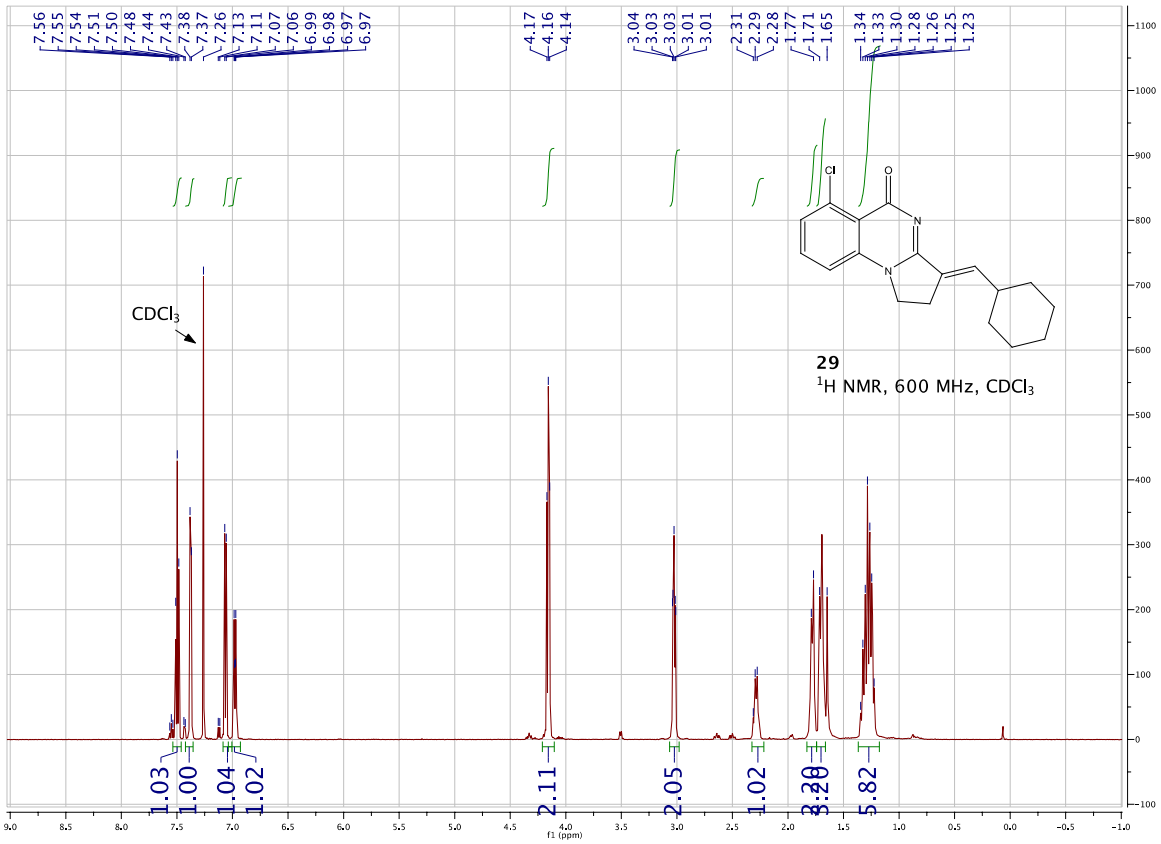
159.3
142.8
141.2
136.2
132.9
130.9
128.7
116.7
113.3
77.4
77.2
76.9
46.4
44.4
27.7
23.0
12.1
$CDCl_3$
Cl
O
N
N
28
^{13}C NMR, 150 MHz, $CDCl_3$
f1 (ppm)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7.54
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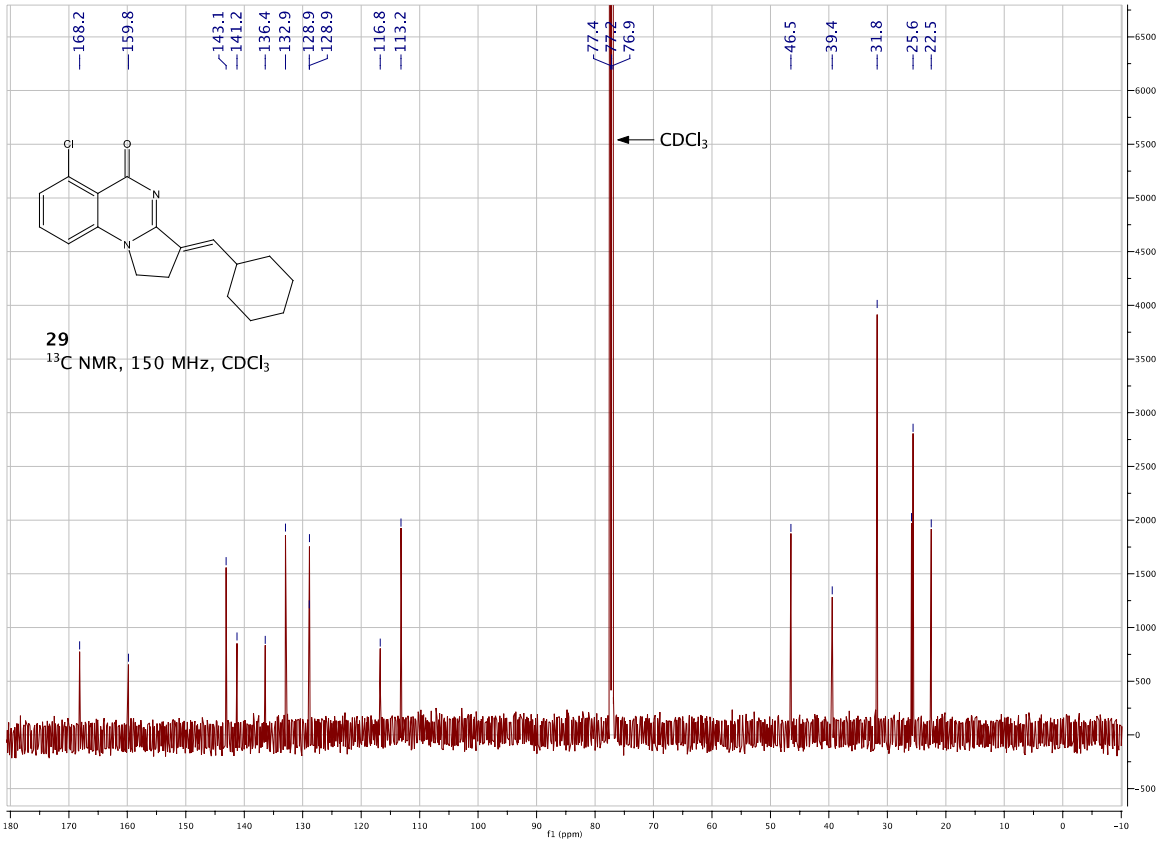
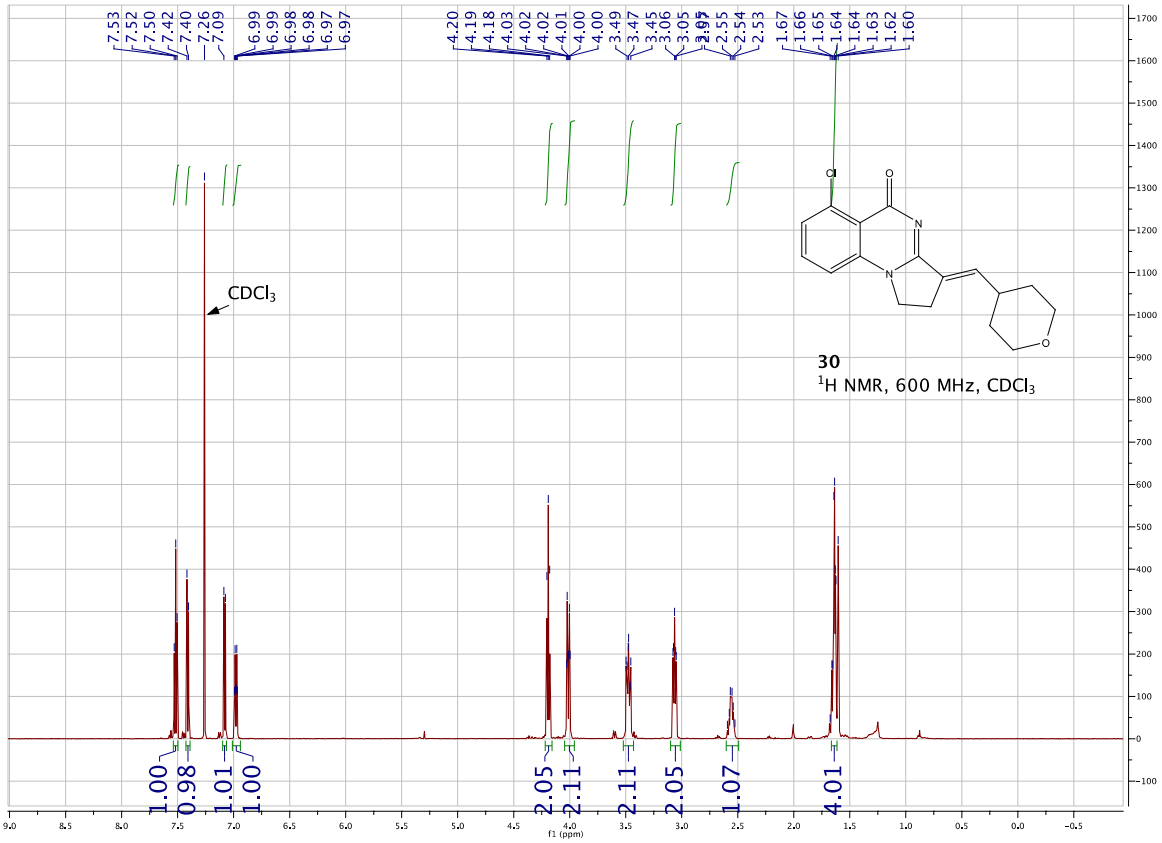
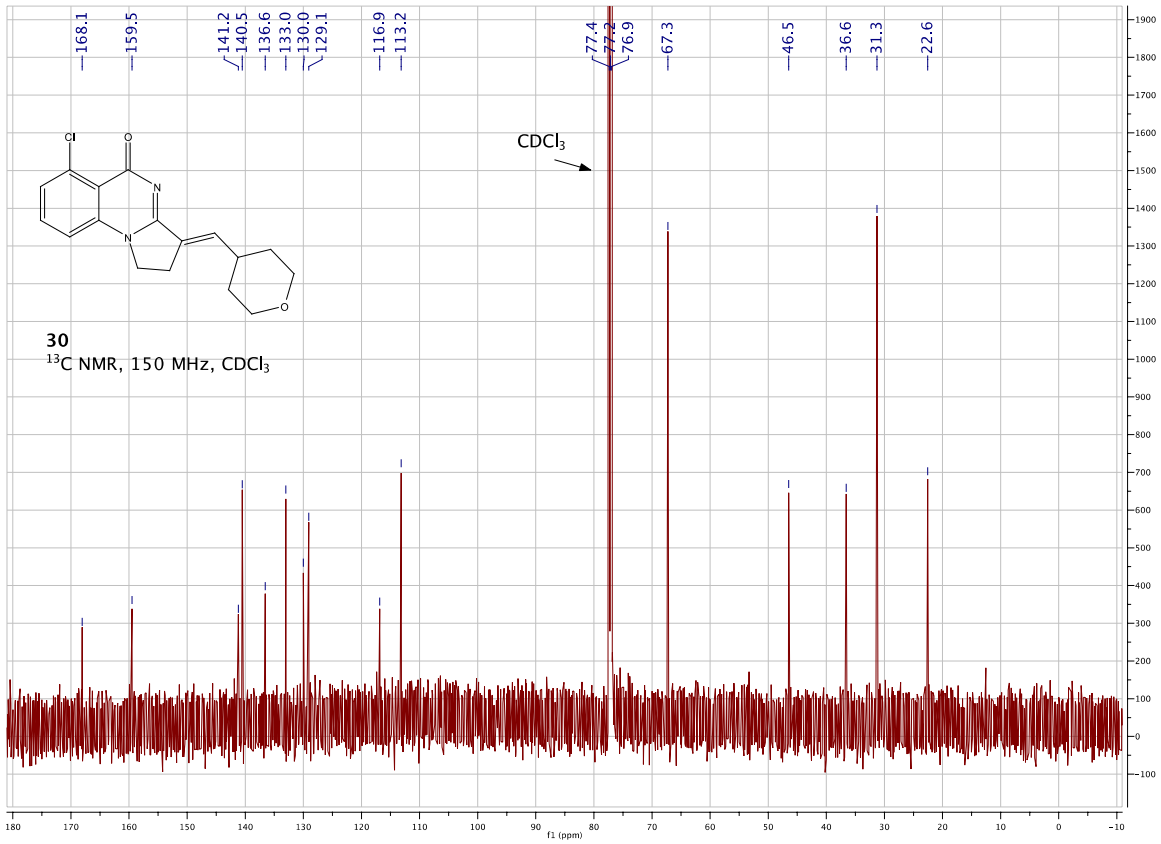
7.50
7.48
7.44
7.43
7.38
7.37
7.26
7.13
7.11
7.07
7.06
6.99
6.98
6.97
6.97
4.17
4.16
4.14
3.04
3.03
3.03
3.01
3.01
2.31
2.29
2.28
1.77
1.71
1.65
1.34
1.33
1.30
1.28
1.26
1.25
1.23
CDCl3
29
1H NMR, 600 MHz, CDCl3
1.03
1.00
1.04
1.02
2.11
2.05
1.02
3.20
5.82
f1 (ppm)

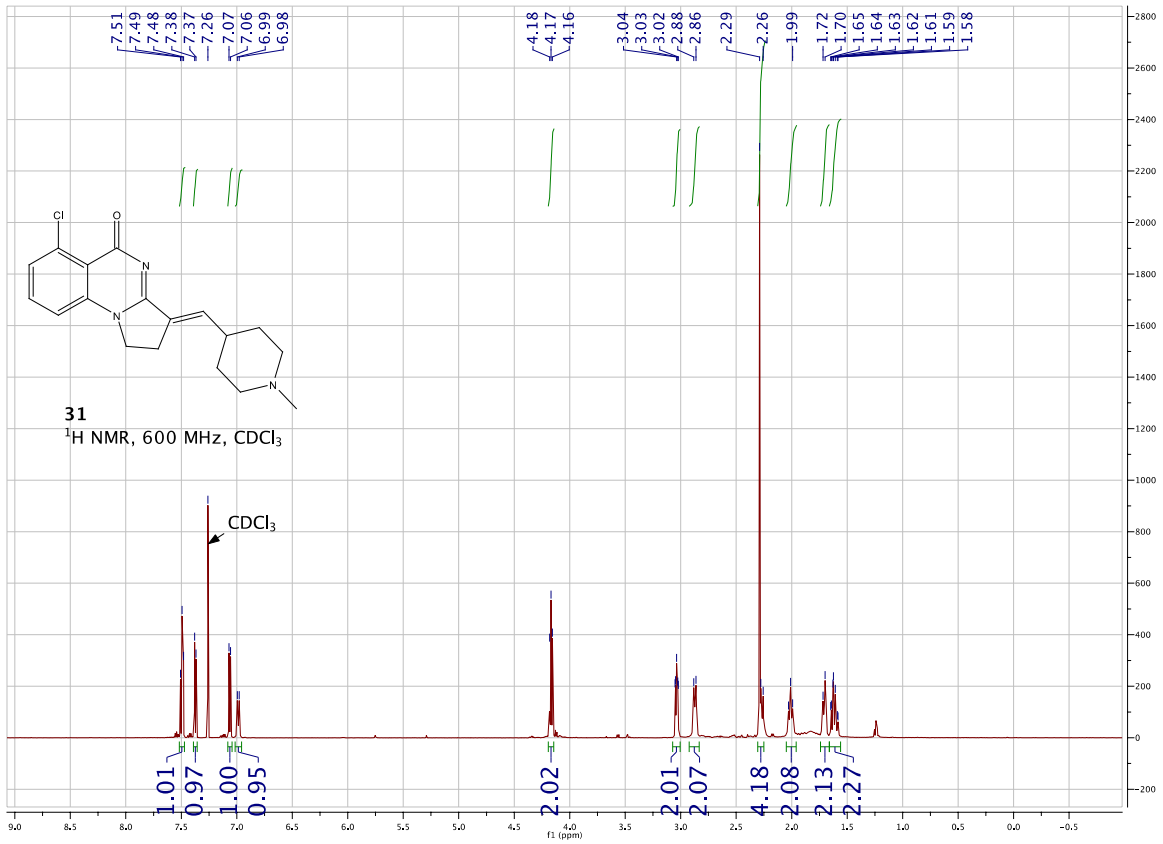

168.2
159.8
143.1
141.2
136.4
132.9
128.9
128.9
116.8
113.2
77.4
76.9
46.5
39.4
31.8
25.6
22.5
CDCl3
29
13C NMR, 150 MHz, CDCl3
f1 (ppm)

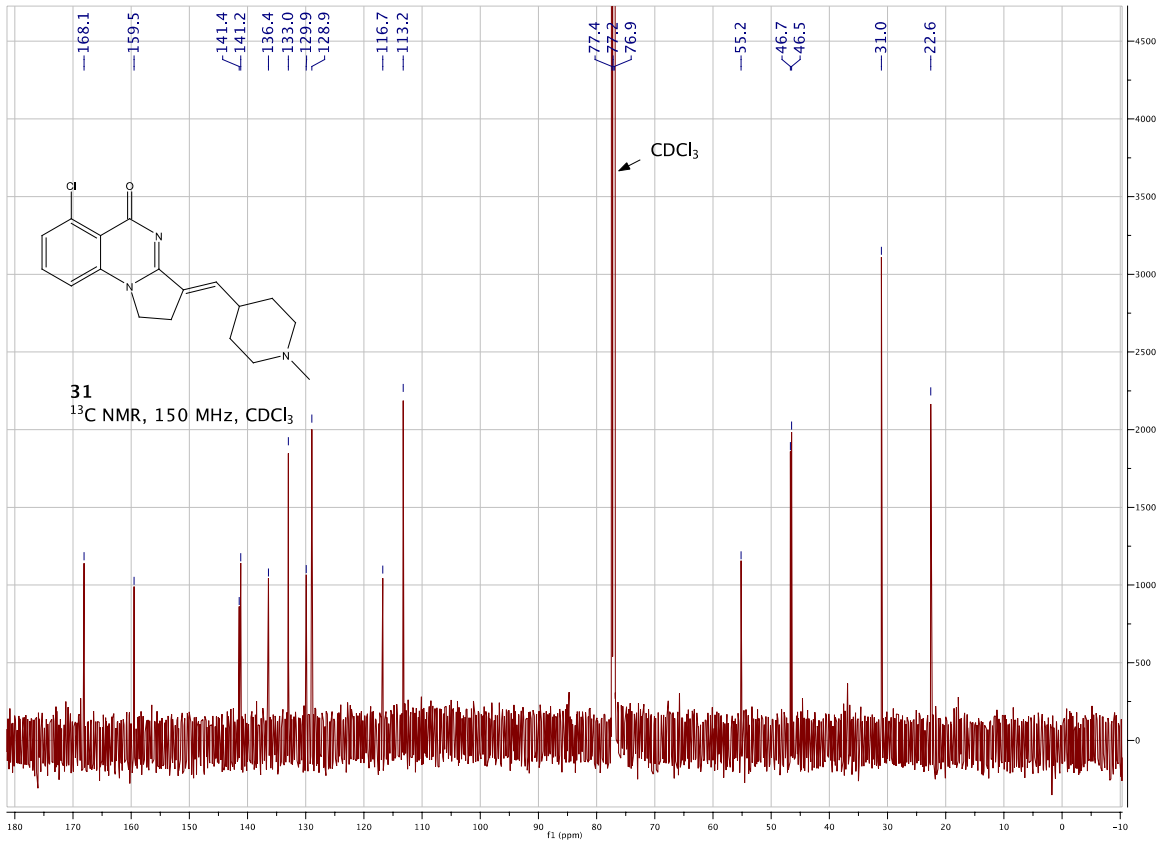


30
^{1}H NMR, 600 MHz, $CDCl_3$



30
^{13}C NMR, 150 MHz, $CDCl_3$


7.51
7.49
7.48
7.38
7.37
7.26
7.07
7.06
6.99
6.98
4.18
4.17
4.16
3.04
3.03
3.02
2.88
2.86
2.29
2.26
1.99
1.72
1.70
1.65
1.64
1.63
1.62
1.61
1.59
1.58
Cl
O
N
N
N
31
1H NMR, 600 MHz, CDCl3
CDCl3
1.01
0.97
1.00
0.95
2.02
2.01
2.07
4.18
2.08
2.13
2.27
f1 (ppm)


168.1
159.5
141.4
141.2
136.4
133.0
129.9
128.9
116.7
113.2
77.4
77.2
76.9
55.2
46.7
46.5
31.0
22.6
Cl
O
N
N
N
31
13C NMR, 150 MHz, CDCl3
CDCl3
f1 (ppm)