Electronic Supporting Information

Synthesis of *β*- and *γ*-lactam fused dihydropyrazinones from Ugi adducts via sequential ring construction strategy

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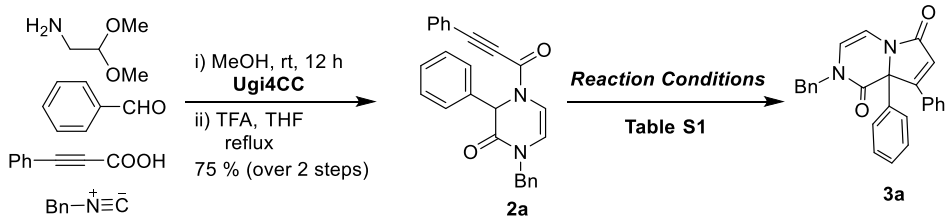
1. **General Information.** All the reagents and solvents were used as received from commercial sources without further purification. All air and moisture sensitive reactions were conducted under inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light, iodine, ninhydrin and *p*-anisaldehyde for visualization. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. ^{1}H–NMR and ^{13}C–NMR spectra were recorded in $CDCl_3$/DMSO-d_6 as solvent on 300/400/500 MHz (^{1}H), 75/100/125 MHz (^{13}C) spectrometer at ambient temperature. ^{19}F NMR spectra were recorded in $CDCl_3$ as solvent at 283 MHz and 376 MHz respectively. The coupling constant *J* is given in Hz. The chemical shifts (δ) are reported in ppm on scale downfield from TMS and using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 ppm and C: δ = 77.16 ppm) or TMS (δ = 0.00) as internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet. High-Resolution Mass Spectra (HRMS) were recorded on a Thermo Scientific Exactive "ORBITRAP" spectrometer using H_2O/MeOH mixed with 0.1% formic acid as mobile phase. Melting points have been recorded on Stuart SMP30 melting point apparatus and are uncorrected. 4-methoxy phenylpropiolic acid,[1] 4-methyl phenyl propiolic acid,[1] benzyl isocyanide,[2a] 1-bromo-2-(isocyanomethyl) benzene,[2b] and phenyl isocyanide[2c] were prepared and characterized as previously reported.

2. Optimization of the Reaction Conditions:

Table S1. Screening of bases for the cycloisomerization of dihydropyrazinone 2a to yield the *γ*-lactam fused dihydropyrazinones 3: In the first set of investigations, Ugi-4CR with aminoacetaldehyde dimethyl acetal, benzaldehyde, phenyl propiolic acid, benzyl isocyanide in methanol afforded Ugi adduct that was treated with TFA to furnish **2a** in 75% yield over 2 steps. **2a** was subsequently treated with different inorganic bases.

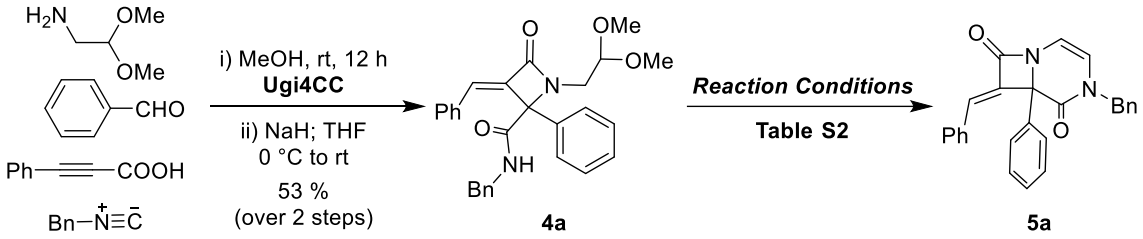


Entry	Base (equiv)	Solvent	T (°C) / *t* (h)	**3a (%** yield[b]**)**
1	K_2CO_3 (3.0)	CH_3CN	rt – reflux / 8	48
2	Cs_2CO_3 (3.0)	CH_3CN	rt – reflux / 8	44
3	NaOAc (3.0)	CH_3CN	rt – reflux / 16	0
4	Na_2CO_3 (3.0)	CH_3CN	rt – reflux / 16	0
5	NaH (3.0)	CH_3CN	0 °C – rt / 2	54
6	NaH (3.0)	THF	0 °C – rt / 2	60
7	NaH (1.5)	THF	0 °C – rt / 4	52
8	NaH (1.0)	THF	0 °C – rt / 4	48
9	Et_3N (3.0)	THF	rt – reflux / 16	0
10	DIPA (3.0)	THF	rt – reflux / 16	0
11	DBU (3.0)	THF	rt – reflux / 16	0

[a]**Reaction conditions:** Aminoacetaldehyde dimethyl acetal (0.475 mmol), benzaldehyde (0.475 mmol), phenyl propiolic acid (0.475 mmol) and benzyl isocyanide (0.475 mmol) in methanol (4.0 mL) at rt for 12 h, TFA (9.48 mmol) in THF (6.0 mL) 6 h, reflux; then base and 4.0 mL solvent. [b]Isolated yields.

Treatment with K_2CO_3 in acetonitrile under reflux afforded **3a** in 48% yield (entry 1, Table S1). Using Cs_2CO_3 as base did not improve the reaction yield and product **3a** was furnished in 44% yield (entry 2, Table S1). Bases NaOAc and Na_2CO_3 did not afford the desired product **3a** (entries 3 and 4, Table S1). However, using strong base such as NaH afforded **3a** in 54% yield (entry 5, Table S1). Solvent screening suggested that THF was more suitable for the transformation, improving the reaction yield to 60% (entry 6, Table S1). Lower concentrations of NaH did not improve the fate of the reaction (entries 7 and 8, Table S1). With organic bases like Et_3N, DIPA and DBU, the reaction did not proceed and no formation of **3a** was observed (entries 9–11, Table S1).

b) Table S2. Screening of acids for the formation of *β*-lactam fused dihydropyrazinones 5: Ugi-4CR was performed with aminoacetaldehyde dimethyl acetal, benzaldehyde, phenyl propiolic acid, benzyl isocyanide in methanol afforded the Ugi adduct, which on subsequent treatment with base furnished *β*-lactam **4a** with 53% yield over 2 steps (Table S2). *β*-lactam **4a** was further treated with various acids to obtain the suitable condition for the preparation of **5a**.



Entry	Acid (equiv)	Solvent	T / *t* (h)	**5a (%** yield[b]**)**
1	HCl (5.0)	THF	rt – reflux / 6	42
2	PTSA (5.0)	THF	rt – reflux / 6	74
3	H_2SO_4 (5.0)	THF	rt – reflux / 12	38
4	TFA (5.0)	THF	rt – reflux / 12	55
5	TFA (10.0)	THF	rt – reflux / 12	72
6	TFA (20.0)	THF	rt – reflux / 8	90
7	TFA (20.0)	CH_3CN	rt – reflux / 8	68
8	$BF_3.OEt_2$ (5.0)	THF	0 °C – reflux / 6	71
9	AgOTf (3.0)	THF	0 °C – reflux / 6	–[c]
10	$Sc(OTf)_3$ (3.0)	THF	0 °C – reflux / 6	–[c]

[a]**Reaction conditions:** Aminoacetaldehyde dimethyl acetal (0.475 mmol), benzaldehyde (0.475 mmol), phenyl propiolic acid (0.475 mmol) and benzyl isocyanide (0.475 mmol) in methanol (4.0 mL) at rt for 12 h, then NaH (9.48 mmol) in THF (4.0 mL), 0 °C to rt; then acid and 4.0 mL solvent. [b]Isolated yields. [c]Complex mixture.

Mild hydrochloric acid (5.0 equiv) in THF under reflux furnished desired product **5a** in 42% yield (entry 1, Table S2). Using PTSA as acid improved the reaction yield to 74% (entry 2, Table

S2). However, when H_2SO_4 was used, product **5a** was obtained albeit in poor yield (entry 3, Table S2). 5.0 equiv of trifluoroacetic acid in THF under reflux afforded product **5a** in 55% yield (entry 4, Table S2); increasing concentrations of TFA afforded **5a** in 72% and 90% yields respectively (entries 5 and 6, Table S2). However, changing solvent to CH_3CN lowered the reaction yield to 68% (entry 7, Table S2). In case of $BF_3.OEt_2$, reaction was also compatible and formed desired product **5a** with 71% yield (entry 8, Table S2). Screening of metal triflates *viz*. AgOTf and $Sc(OTf)_3$ did not favour the transformation and a complex mixture of undesired products was observed at reflux (entries 9 and 10, Table S2).

3. Crystallographic data for 3u and 5j

3.1. X-ray data for the compound 3u:

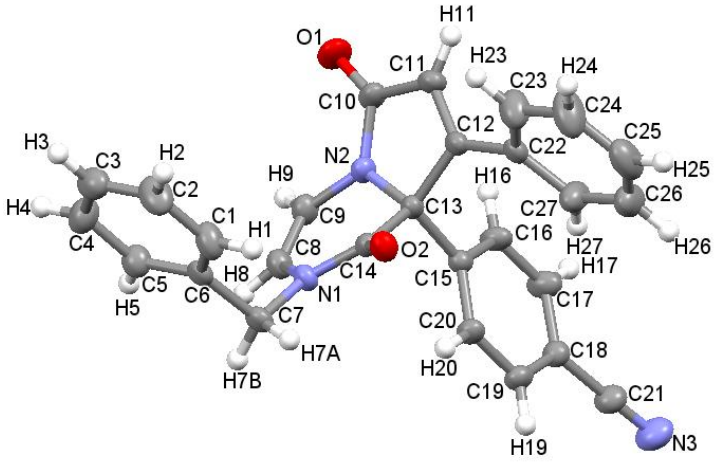


Figure S1: ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of the crystal structure of compound **3u** determined at 293 K.

Crystallization: Crystals of compound **3u** were grown from the solvent methanol by slow evaporation method.

Data Collection and Structure Refinement Details: A good quality colorless single crystal of size 0.49 x 0.19 x 0.15 mm, was selected under a polarizing microscope and was mounted on a glass fiber for data collection. Single crystal X-ray data for compound **3u** were collected on the RigakuKappa 3 circle diffractometer equipped with the AFC12goniometer and enhanced sensitivity (HG) Saturn724+ CCD detector in the 4x4 bin mode using the monochromated Mo-Kα radiation generated from the microfocus sealed tube MicroMax-003 X-ray generator equipped with specially designed confocal multilayer optics. Data collection was performed using ω-scans of 0.5^{o} steps at293(2)K. Cell determination, data collection and data reduction was performed using the RigakuCrystalClear-SM Expert 2.1 $b24^{3}$ software. Structure solution and

refinement were performed by using SHELXTL-NT[4]. Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method. The hydrogen atoms attached to carbon atoms were generated with idealized geometries and isotropically refined using a riding model.

Table S3: Crystal data and structure refinement details for compound **3u**.

Compound	**3u**
Empirical formula	$C_{27}\,H_{19}\,N_3\,O_2$
Formula weight	417.45
Crystal System	Monoclinic
Space group	$P2_1/n$
a (Å)	10.329(3)
b (Å)	19.409(5)
c (Å)	10.902(3)
α (°)	90.00
β(°)	98.698(5)
γ (°)	90.00
V (Å^3)	2160.4(10)
Z	4
D_c (g/cm^3)	1.283
F_{000}	872
μ(mm^{-1})	0.083
θ_{max} (°)	25.38
Total reflections	13313
Unique reflections	3718
Reflections [$I > 2\sigma(I)$]	2202
Parameters	290
R_{int}	0.1072

Goodness-of-fit	0.866
R [$F^2 > 2\sigma(F^2)$]	0.0599
wR (F^2, all data)	0.1463
CCDC No.	1922833

3.2. X-ray data for the compound 5j:

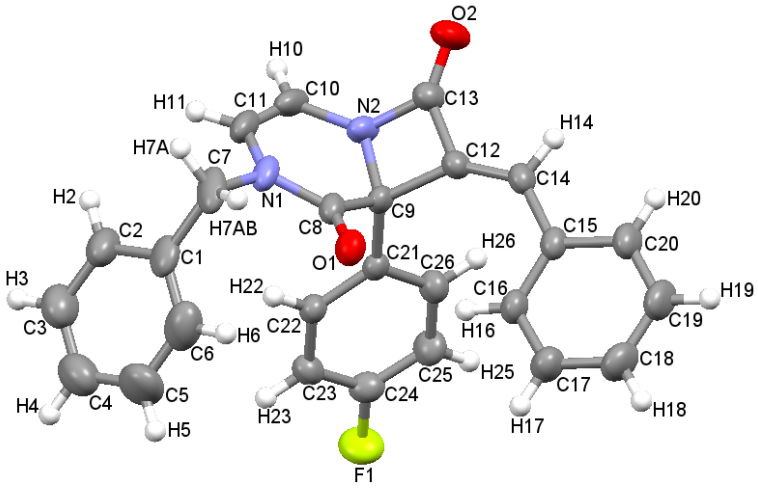


Figure S2: ORTEP diagram of **5j** compound with the atom-numbering. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. CCDC 1944108 contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://summary.ccdc.cam.ac.uk/structure-summary-form.

Crystallization: Crystals of compound **5j** were grown from the solvent methanol by slow evaporation method.

Data collection and Structure Refinement details: Single crystal X-ray data **5j** compound were collected at room temperature on a Bruker D8 QUEST equipped with a four-circle kappa diffractometer and Photon 100 detector. An I μs microfocus Mo source (λ=0.71073Å) supplied the multi-mirror monochromated incident beam. A combination of Phi and Omega scans were used to collect the necessary data and unit cell dimensions were determined using 9929 reflections for **5j** data. Integration and scaling of intensity data were accomplished using SAINT program.[5] The structures were solved by Direct Methods using SHELXS97[6] and refinement was carried out by full-matrix least-squares technique using SHELXL-2014/7.[6-7] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned

geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with U_{iso}(H) = 1.2U_{eq} (C) or 1.5U_{eq} for methyl atoms. The N bound H atoms were located from the difference Fourier map. CCDC 1944108 contain the supplementary crystallographic data for this paper which can be obtained free of charge athttps://summary.ccdc.cam.ac.uk/structure-summary-form.

Table S4. Crystal data and structure refinement details for compound **5j**.

Compound	**5j**
chemical formula	$C_{26}H_{19}FN_2O_2$
***Fw*; *F*(000)**	410.43; 856
***T* (K)**	293(2)
wavelength (Å)	0.71073
space group	P212121
***a* (Å)**	9.0888(9)
***b* (Å)**	10.5640(11)
***c* (Å)**	21.4630(19)
α (deg)	90
β(deg)	90
γ (deg)	90
Z	4
***V* (Å^3)**	2060.8(3)
ρ_{calcd} (g·cm^{-3})	1.323
μ (mm^{-1})	0.091
θ range (deg); completeness	2.434 − 24.998; 0.996
collectedreflections; R_σ	13121; 0.0222
unique reflections; R_{int}	13121; 0.0213
R1[a]; wR2[b] [I > 2σ(I)]	0.0410; 0.1305
R1; wR2 [all data]	0.0459; 0.1365

GOF	1.149
largest diff peak and hole	0.221 and -0.158

[a] $\mathbf{R_1=\Sigma(||F_o|-|F_c||)/\Sigma|F_o|}$

[b] $\mathbf{wR_2=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}}$

4. Mechanistic studies for the cycloisomerizations reaction using Density Functional Theory (DFT) calculations

Computational Methodology:

The geometries of all the reactants, intermediates, transition states, and products were optimized at the M06/6-31G(d) level of DFT on the Gaussian-09 program package.[8] Single point calculations were performed at various levels in the THF solvent using the IEF-PCM method, Table S5.[9] Frequency calculations were also performed at the same level of theory to confirm the obtained stationary points as a minima or a transition state structure. Water molecule was omitted during the optimization of transition states. The reaction path was validated, wherever necessary, by IRC calculations.[8-10]

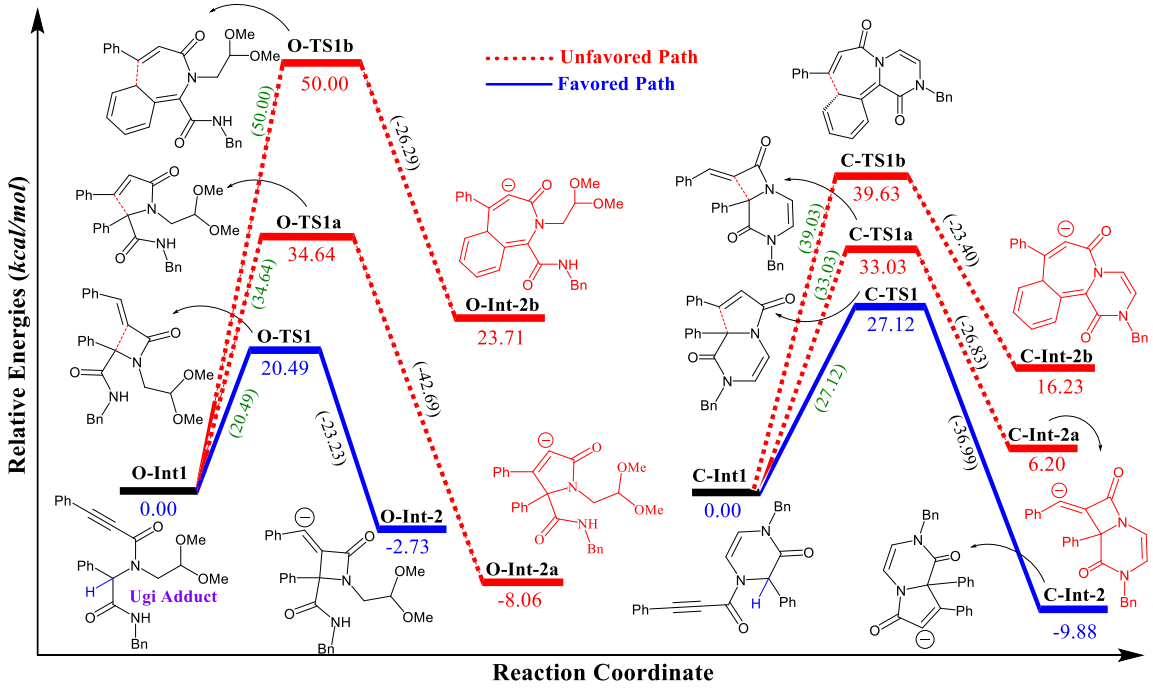


Figure S3. Energy profile diagram of the reactions: All the given energy values **(**kcal/mol**)** are calculated at the M06/6-31G **(**d**)** level of DFT. **"**Numbers in blue or red colours**"** depict the relative energies; **"**numbers in green colour**"** show the activation barrier; **"**numbers in black colour**"** show the stabilization energy**.**

The mode of cyclization (*4-exo-dig*/*5-endo-dig* or 6π-electrocyclization) in alkynamide derived **O-Int1** and **C-Int1** adducts is crucial for obtaining the *β*- and *γ*-lactam. DFT calculations were

performed using the M06 level to get more insight into the reaction mechanism. All the possible transition states and intermediates in both open and close systems are compared in Figure S3. The activation barrier for β and γ-lactam formation were compared. For the open system, **O-TS1** is favourable as the activation energy of **O-TS1** (20.49 kcal/mol) is much lower compared to **O-TS1a** (34.64 kcal/mol) and **O-TS1b** (50.00 kcal/mol). The activation energy of **O-TS1b** is very high and **O-Int-2b** is unstable compared to **O-Int-1**, which indicates that *β*-lactam is not forming via 6π-electrocyclization followed by the migration of bonds. In case of the cyclic system, the activation energy for **C-TS1** (27.12 kcal/mol) is lower compared to **C-TS1a** (33.03 kcal/mol) and **C-TS1b** (39.63 kcal/mol), which facilitates Michael addition in the cyclic system. The activation energy of **C-TS1b** is very high and **C-Int-2b** is unstable compared to **C-Int-1**, which indicates that 6π-electrocyclization is not favoured in this reaction. Formation of **O-Int-2** and **C-Int-2** through transition states **O-TS1** and **C-TS1**, respectively is a favourable reaction as clear from Figure S3. These calculations clearly show that the reaction in the closed system proceeds via the Michael addition pathway. However, the cyclization in *4-exo-dig* fashion is energetically favoured in the open system (Figure S3). The cycloisomerization via an aziridine type intermediate **8** is not favourable as all efforts to optimize those intermediates and transition states were futile. We performed single-point calculations at various DFT methods and basis sets, Table S5. Inclusion of solvent effect reduces the activation energy in all cases and the inclusion of polarization and diffuse functions in the basis set further reduces the overall activation energy. Interestingly, change in the DFT method has a minimal effect on the overall energetics. However, it is interesting to note that the level of the calculation does not affect the overall trend of the result, Table S5.

Table S5: Relative energy values for the reaction in the open/close system at various level of DFT

System	ΔE(1)	ΔE(2)	ΔE(3)	ΔE(4)	System	ΔE(1)	ΔE(2)	ΔE(3)	ΔE(4)
O-Int-1	0.00	0.00	0.00	0.00	C-Int-1	0.00	0.00	0.00	0.00
O-TS1	20.49	16.81	15.14	15.60	C-TS1	27.12	22.74	19.84	19.17
O-Int-2	-2.73	-4.65	-4.40	1.03	C-Int-2	-9.88	-15.18	-16.43	-12.11
O-Int-1	0.00	0.00	0.00	0.00	C-Int-1	0.00	0.00	0.00	0.00
O-TS1a	34.64	27.05	25.37	31.62	C-TS1a	33.03	28.49	24.82	22.52
O-Int-2a	-8.06	-13.76	-13.42	-9.60	C-Int-2a	6.20	2.66	0.40	4.09
O-Int-1	0.00	0.00	0.00	0.00	C-Int-1	0.00	0.00	0.00	0.00
O-TS1b	50.00	42.64	39.55	38.07	C-TS1b	39.63	34.07	29.61	30.53
O-Int-2b	23.71	19.90	20.22	22.28	C-Int-2b	16.23	13.18	11.87	14.51

ΔE(1) = M06/6-31G(d)[Gas]

ΔE(2) = M06/6-31G(d)[THF]//M06/6-31G(d)[Gas]

ΔE(3) = M06/6-31++G(d,p)[THF]//M06/6-31G(d)[Gas]

ΔE(4) = B3LYP/6-31++G(d,p)[THF]//M06/6-31G(d)[Gas]

All energies values are in kcal/mol. Gas indicates the calculation was performed in the gas phase. THF indicates that the calculation was performed in the solvent phase using the IEF-PCM method. Energy values from ΔE(1) were selected to draw Figure-1.

Table S5a: Optimized XYZ coordinates of O-Int-1

C	1.31564727	0.80615284	-2.04291054	H	0.97334673	0.37864008	2.87201579
C	0.15524933	1.09582161	-1.83136001	C	3.28651768	-0.89167771	3.84482088
C	2.64156287	0.29974220	-2.11891011	H	2.56700853	-2.16449831	2.26157799
C	3.74926433	1.15817140	-2.09251351	H	1.40308671	-1.95694912	3.57454633
C	2.84653778	-1.08958008	-2.13967164	C	3.63587809	1.00841178	2.24648587
C	5.03502448	0.63611906	-2.06099289	H	2.93022667	-0.19077072	0.60178978
H	3.58017834	2.23416242	-2.07373083	H	1.98885744	1.29043950	0.84721941
C	4.13629312	-1.60096351	-2.11913196	C	4.30875676	-0.12383934	3.01343356
H	1.97569854	-1.74612818	-2.15356735	H	3.76984723	-1.71460700	4.39289287
C	5.23316086	-0.74235836	-2.07187945	H	2.86561235	-0.21335646	4.60751018
H	5.89048552	1.30945842	-2.02540057	H	4.36981930	1.54815380	1.62889927
H	4.28721500	-2.67949787	-2.12694723	H	3.23110644	1.74124473	2.96608992
H	6.24328240	-1.14883265	-2.04393840	H	5.11716960	0.26048648	3.65409790
C	-1.24490180	1.47903483	-1.68721190	H	4.77900007	-0.81419331	2.29091665
O	-1.68120426	2.53332621	-2.15690057	N	0.43201828	-0.88548551	1.34672494
C	-1.29738848	-0.49786339	-0.31434231	H	0.78147915	-1.57329589	0.68297640
C	-3.41214848	0.72937884	-0.95391014	H	-3.90278777	-0.24751858	-1.06557700
C	-0.54072767	-0.02339644	0.80471079	H	-3.71990095	1.39220425	-1.76964733
N	-1.97581400	0.54137250	-1.03664429	C	-3.86504601	1.34374611	0.36054273
C	-1.29567653	-1.80438124	-0.91496685	H	-3.12062059	2.08074119	0.72133953
C	-1.67213716	-1.97550708	-2.27360612	O	-4.03719912	0.33621707	1.31531940
C	-0.95372424	-2.99815910	-0.22480256	O	-5.08798658	1.98385311	0.08033972
C	-1.66245519	-3.21507447	-2.89146641	C	-3.47969201	0.57928892	2.58747755
H	-1.96050099	-1.09708256	-2.85013007	H	-4.07551497	1.30551569	3.17005593
C	-0.94207859	-4.23319523	-0.85633633	H	-3.48922040	-0.37827506	3.12115037
H	-0.73838305	-2.94801533	0.84102812	H	-2.44231944	0.93096022	2.50079358
C	-1.28563693	-4.36616843	-2.20000278	C	-5.65517529	2.60174647	1.19607779
H	-1.94925490	-3.28158006	-3.94250439	H	-6.52191495	3.17710206	0.84991673
H	-0.67404353	-5.11721849	-0.27439740	H	-5.99338885	1.87093556	1.94777279
H	-1.27526228	-5.33922265	-2.68977824	H	-4.94297974	3.29457897	1.68185762
O	-0.66445846	1.11456628	1.30118369	O	0.47726471	3.81504339	-3.58652988
C	1.47435517	-0.31499051	2.17961988	H	-0.35932188	3.59255174	-3.13545982
C	2.15428081	-1.42481044	2.97342424	H	0.98832126	3.01133074	-3.42780390
C	2.50529190	0.47715223	1.37450633				

Table S5b: Optimized XYZ coordinates of O-TS1

C	1.10149413	-1.54408059	-1.47883575	C	2.97338196	1.92420221	1.52996604
C	-0.09625100	-1.21119704	-1.23729946	C	2.00489326	2.34678064	-0.75103563
C	2.39091727	-1.61254446	-0.89099357	H	1.13168147	2.96493250	1.11034988
C	3.50748463	-0.96901606	-1.47144361	C	3.92126455	3.10219328	1.34372600
C	2.61105463	-2.33859264	0.30464318	H	3.47805679	0.99940218	1.19296305
C	4.75544870	-1.01117996	-0.86781172	H	2.72465773	1.77766580	2.59160156
H	3.36443087	-0.43171312	-2.40892887	C	2.94777117	3.53062056	-0.92653877
C	3.86940931	-2.39264083	0.88548860	H	2.47343361	1.43497541	-1.15904974
H	1.76144741	-2.83916812	0.77093157	H	1.06145736	2.49595943	-1.29037150
C	4.95330398	-1.72411939	0.31527603	C	4.23333635	3.32685106	-0.13198631
H	5.59307321	-0.49199604	-1.33606551	H	4.84688098	2.93938523	1.91565846
H	4.00218106	-2.95123975	1.81258390	H	3.45493679	4.01499097	1.75501673
H	5.93657051	-1.76119878	0.78250152	H	3.17171016	3.68813067	-1.99187954
C	-1.50888281	-1.16764129	-1.68544266	H	2.45079876	4.45192485	-0.57355798
O	-2.03550146	-1.50565810	-2.72562390	H	4.91305627	4.18363037	-0.25719677
C	-1.01752662	-0.46816725	0.38156445	H	4.76079650	2.44002915	-0.52423867
C	-3.49883667	-0.47006831	-0.34440136	N	0.85619843	0.92442016	0.92614564
C	-0.43916084	0.88415318	0.43897979	H	1.35575916	0.03860076	0.87212082
N	-2.09106235	-0.64922771	-0.55293338	H	-3.80652670	-0.95417019	0.59773556
C	-0.95801508	-1.42597833	1.49124450	H	-4.02603847	-0.95661259	-1.17738688
C	-1.52920124	-2.70707420	1.33166396	C	-3.90621574	0.99062653	-0.31402945
C	-0.35489322	-1.15984731	2.73764936	H	-3.24025790	1.55998301	0.36339944
C	-1.47423645	-3.66141391	2.33651759	O	-5.25249896	1.11579541	0.13219784
H	-2.01024522	-2.95354059	0.38559896	O	-3.82020737	1.48363906	-1.59926735
C	-0.29813651	-2.12075474	3.73713413	C	-5.35016188	1.28765663	1.51379870
H	0.08506163	-0.18002304	2.91253236	H	-6.41327241	1.38912044	1.76233039
C	-0.85314065	-3.38476783	3.55197471	H	-4.94304410	0.43117348	2.08022389
H	-1.92148281	-4.64100531	2.16276161	H	-4.81724264	2.19455676	1.85357948
H	0.18192946	-1.87055495	4.68439598	C	-3.71008926	2.88402878	-1.63574741
H	-0.80550592	-4.13652734	4.33912864	H	-3.68623795	3.17909413	-2.69034585
O	-0.98907787	1.91186430	0.03221393	H	-4.57519198	3.36764860	-1.15214073
C	1.69016623	2.09517073	0.72430870	H	-2.78021925	3.20555050	-1.14399960

Table S5c: Optimized XYZ coordinates of O-TS1a

C	0.65213777	-2.21010062	-1.32759903	C	2.60851404	2.36114547	-0.37047042
C	-0.20912156	-2.59050291	-2.17738506	C	0.37815714	3.50135503	-0.14430094
C	1.97115511	-2.18788120	-0.75663218	H	1.58963541	2.76041878	1.45893457
C	2.34163236	-3.10526601	0.23693907	C	3.29700618	3.71941306	-0.43479316
C	2.89265162	-1.20234735	-1.14153837	H	2.35542611	2.01697921	-1.38343041
C	3.60298568	-3.04555553	0.81862367	H	3.26408358	1.59702519	0.07300845
H	1.61571421	-3.85372683	0.55395463	C	1.07180085	4.85781508	-0.21392359
C	4.14914727	-1.14416636	-0.55471955	H	0.07503081	3.16338291	-1.14628107
H	2.58378959	-0.47824447	-1.89436973	H	-0.53958993	3.55771231	0.45948706
C	4.51039145	-2.06615509	0.42682681	C	2.36585891	4.77767314	-1.01631556
H	3.87240199	-3.76187875	1.59478655	H	4.22274162	3.65311849	-1.02571192
H	4.85344250	-0.37093648	-0.86374760	H	3.59876012	4.02971563	0.58233311
H	5.49691668	-2.01699372	0.88799066	H	0.39655365	5.61193440	-0.64556781
C	-1.56618762	-2.03523585	-2.05799093	H	1.30927381	5.20408157	0.80897001
O	-2.54211081	-2.30139463	-2.74031587	H	2.86349197	5.75924320	-1.04823599
C	-0.53761564	-0.86095673	-0.13071132	H	2.12467535	4.50905257	-2.05849113
C	-2.96892018	-0.62258384	-0.64940428	N	0.70040897	1.12762345	0.60371724
C	0.13331483	0.41914290	-0.44884166	H	0.33334645	0.92512871	1.52422191
N	-1.65884188	-1.13089548	-0.96908890	H	-3.27418684	-0.92705034	0.36802354
C	-0.50269046	-1.55366879	1.14968433	H	-3.66574399	-1.08856087	-1.35727918
C	0.51573681	-1.39603069	2.12556553	C	-3.16150902	0.87868908	-0.75308117
C	-1.45052202	-2.57255385	1.42752547	H	-4.22980697	1.10149336	-0.48708069
C	0.53466771	-2.14139915	3.29756170	O	-2.90193214	1.27859648	-2.04275990
H	1.35342043	-0.73157497	1.92332209	O	-2.36074229	1.63534768	0.13208644
C	-1.42238416	-3.31148780	2.59835070	C	-3.03203937	2.65568364	-2.25519174
H	-2.20128078	-2.80504334	0.67437745	H	-2.98929957	2.81600330	-3.33755286
C	-0.43946538	-3.09740839	3.56496406	H	-4.00124169	3.03138535	-1.87462442
H	1.35091361	-1.98111262	4.00424138	H	-2.22504748	3.22354562	-1.77137976
H	-2.18056428	-4.08068854	2.75434798	C	-2.67525200	1.46281107	1.48064498
H	-0.42054802	-3.67811794	4.48660356	H	-3.76399630	1.55021403	1.66008283
O	0.23237528	0.84436180	-1.59966224	H	-2.33689293	0.48913619	1.87387051
C	1.31287867	2.43650164	0.43701737	H	-2.16578923	2.25913680	2.03798277

Table S5d: Optimized XYZ coordinates of O-TS1b

C	3.10953122	0.18075683	-0.09252438	C	-4.33161304	-1.62039503	-0.57953646
C	2.68953857	1.37274750	0.09412918	C	-3.01199356	-2.04969717	1.51487558
C	3.87551601	-0.83261781	0.61538599	H	-3.71321670	-0.13525860	0.85076466
C	3.59524618	-1.07961419	1.96700918	C	-5.60486210	-2.05325334	0.13948159
C	4.89153683	-1.57753245	0.00559968	H	-3.88968032	-2.49541288	-1.09175086
C	4.30620363	-2.03436729	2.68129517	H	-4.54750530	-0.87558769	-1.35934495
H	2.80200157	-0.49913236	2.43650781	C	-4.28592967	-2.47251203	2.23621019
C	5.60215000	-2.53488506	0.71925253	H	-2.52409980	-2.93754771	1.07277746
H	5.12327662	-1.38886932	-1.04167301	H	-2.29000610	-1.59874444	2.21022095
C	5.31244259	-2.77064227	2.05970246	C	-5.30179654	-3.04796868	1.25542030
H	4.07056297	-2.21013768	3.73121023	H	-6.32201060	-2.48118473	-0.57630704
H	6.39144107	-3.10126301	0.22423747	H	-6.09068931	-1.16346991	0.57519850
H	5.86747189	-3.52478093	2.61771229	H	-4.05947136	-3.19854965	3.03042041
C	1.79687656	2.21231039	-0.64063468	H	-4.72551821	-1.59163834	2.73497433
O	2.14305351	3.23966423	-1.22993865	H	-6.22725704	-3.33520680	1.77630350
C	0.04880589	0.43060720	-0.45428129	H	-4.89072589	-3.97139576	0.81175976
C	-0.49019277	2.66576408	-1.34305294	N	-2.11251949	-0.64704672	-0.31230652
C	-1.26146075	0.31750085	0.20708292	H	-1.71410529	-1.29762514	-0.98001169
N	0.45968771	1.77073944	-0.68394687	H	-1.24960799	2.04756340	-1.83869901
C	0.81122714	-0.68599328	-0.81641312	H	0.04910915	3.23986203	-2.10634518
C	2.05324498	-0.56948181	-1.57547960	C	-1.19038188	3.65969143	-0.42054174
C	0.54362122	-2.00644691	-0.30509997	H	-1.31076804	3.22534931	0.58993739
C	2.62495005	-1.75912875	-2.12764475	O	-2.47347339	3.99507493	-0.93593744
H	2.15383077	0.32318893	-2.19350560	O	-0.44615724	4.82717830	-0.36905941
C	1.24076530	-3.10800113	-0.72183785	C	-3.47842943	3.08640055	-0.58697656
H	-0.22546321	-2.13137673	0.45631901	H	-4.43368750	3.52295957	-0.90454231
C	2.27687442	-3.00605495	-1.68636472	H	-3.36020484	2.10599859	-1.08321537
H	3.42477624	-1.64161816	-2.86176581	H	-3.50298254	2.89374845	0.49825243
H	0.99396343	-4.08205235	-0.29677798	C	-0.89172079	5.72472875	0.60665082
H	2.78804759	-3.89874643	-2.04481410	H	-0.14930003	6.52768233	0.67212250
O	-1.67245417	1.07209791	1.09198872	H	-1.87160084	6.15848498	0.35342289
C	-3.30645696	-1.05204515	0.39350881	H	-0.97389899	5.23648214	1.59386424

Table S5e: Optimized XYZ coordinates of O-Int-2

C	-1.24366619	0.78909161	-2.43404916	H	-1.17990650	-2.18133818	2.00570619
C	-0.04644931	0.34933242	-2.06862207	C	-3.76996187	-1.73761206	2.97283993
C	-2.26793922	1.26878996	-1.55395953	H	-3.34039551	-0.03062600	1.72313652
C	-3.52567612	0.61648004	-1.51702863	H	-2.21986529	-0.21271467	3.08026285
C	-2.12925588	2.41563423	-0.73277410	C	-3.53682388	-3.30820255	1.03234149
C	-4.54330714	1.04041930	-0.67916857	H	-3.10530219	-1.65959159	-0.29712316
H	-3.67206537	-0.24141405	-2.17419517	H	-1.82722806	-2.88425467	-0.25054579
C	-3.16848937	2.85185002	0.08134300	C	-4.51764888	-2.55192416	1.92234608
H	-1.18103540	2.95576342	-0.74226771	H	-4.47459466	-1.18300522	3.60961292
C	-4.38143343	2.16760071	0.13177969	H	-3.22208704	-2.42783103	3.63850026
H	-5.48862380	0.49410030	-0.66774296	H	-4.07436674	-3.89275508	0.27191670
H	-3.01868136	3.73688405	0.70155729	H	-2.97938118	-4.03571075	1.64877494
H	-5.18924623	2.51134300	0.77667796	H	-5.22716316	-3.24308027	2.40186059
C	1.15351923	-0.14099489	-2.79327302	H	-5.11353728	-1.86526879	1.29636794
O	1.51816490	-0.32018341	-3.94134912	N	-0.92873856	-0.53906937	0.77836282
C	0.82688415	0.17109616	-0.72155467	H	-1.35279557	0.34045929	0.48669941
C	3.28157360	-0.49928445	-1.47123844	H	3.79643089	0.45855677	-1.27292133
C	0.21191883	-0.91812623	0.13529733	H	3.64564527	-0.88536460	-2.43145513
N	1.86683161	-0.33501461	-1.61614466	C	3.68450732	-1.44494989	-0.35905263
C	1.20277382	1.45938954	-0.02872514	H	3.04952992	-2.35016364	-0.34244874
C	1.69221119	2.51562764	-0.80856385	O	3.54548783	-0.75411575	0.85343031
C	1.12272216	1.65078500	1.35264515	O	5.02220762	-1.78833494	-0.62916667
C	2.06027492	3.72331429	-0.23307192	C	3.12992187	-1.49258839	1.97665951
H	1.76640811	2.38790347	-1.88820532	H	3.95721147	-2.05516651	2.44185967
C	1.48500529	2.86392501	1.93083210	H	2.75950444	-0.76486156	2.70943400
H	0.74705345	0.84731573	1.98451755	H	2.31120449	-2.17935982	1.72126791
C	1.95245872	3.90839705	1.14324642	C	5.58238001	-2.67335444	0.29378494
H	2.42910986	4.52985542	-0.86619083	H	6.51633201	-3.05549608	-0.13515602
H	1.40081134	2.98819171	3.01045387	H	5.81313804	-2.18112099	1.25213236
H	2.23295208	4.85906212	1.59569709	H	4.91166001	-3.52882036	0.49531972
O	0.65660142	-2.05990687	0.21582614	H	-1.27416399	0.62673022	-4.54052553
C	-1.81244107	-1.50736541	1.40325403	O	-0.92938870	0.42431418	-5.43661500
C	-2.78419008	-0.77544569	2.32154281	H	-0.03626199	0.12127757	-5.20522572
C	-2.55868547	-2.34845852	0.36782989				

Table S5f: Optimized XYZ coordinates of O-Int-2a

C	-2.08291291	0.36576824	-0.58554403	H	2.85513238	-0.70976512	-1.09770857
C	-2.57194266	1.60146823	-0.84998330	C	5.03495398	-1.73998354	0.28374891
C	-2.73633718	-0.89486114	-0.96913325	H	3.39659349	-1.87447303	1.67987971
C	-4.12125968	-0.89436710	-1.21831890	H	3.73563744	-0.21513154	1.14396675
C	-2.05289775	-2.10742902	-1.14775331	C	3.87556057	-3.28033919	-1.32723316
C	-4.78111610	-2.05230306	-1.59976830	H	2.18099016	-3.47358481	0.00573857
H	-4.66241333	0.04921949	-1.13357741	H	1.75761137	-2.83962585	-1.59371278
C	-2.71797619	-3.27001554	-1.52705160	C	4.94873650	-3.16650912	-0.24957240
H	-0.97039403	-2.14546068	-1.02888604	H	5.79911393	-1.66362853	1.07077006
C	-4.08906249	-3.25392940	-1.74882051	H	5.36098608	-1.07165593	-0.53220757
H	-5.85499049	-2.01605851	-1.78549658	H	3.80672588	-4.31297484	-1.69847661
H	-2.15092504	-4.19189263	-1.66229775	H	4.16666989	-2.65789230	-2.19072011
H	-4.61240986	-4.16323339	-2.04565652	H	5.92511494	-3.49223503	-0.63784809
C	-1.54589098	2.52977372	-0.32690949	H	4.69831221	-3.84732827	0.58272390
O	-1.50256016	3.75679302	-0.34931741	N	1.33366280	-0.94086092	0.26448157
C	-0.75853814	0.37684164	0.23790171	H	1.18868279	-0.97030235	1.26626669
C	0.66929585	2.45397569	0.78197351	H	1.16640253	1.83119333	1.54052184
C	0.43794290	-0.25139625	-0.50359869	H	0.34653918	3.38770316	1.26449371
N	-0.50199704	1.79902472	0.26961279	C	1.69115735	2.82062716	-0.30218074
C	-1.04839879	-0.16509074	1.63905948	H	1.18767902	2.79678242	-1.29230422
C	-1.07291093	-1.53485839	1.93740962	O	2.73169323	1.89424769	-0.27558559
C	-1.39784020	0.72179361	2.66444526	O	2.24982323	4.09664100	-0.09009980
C	-1.40435541	-1.99158075	3.20939447	C	3.51831332	1.94419695	-1.43861734
H	-0.84477916	-2.26207078	1.16138514	H	3.93496937	2.94993439	-1.59805751
C	-1.73010274	0.26729781	3.93436744	H	4.34473632	1.23396711	-1.30896251
H	-1.41943931	1.78824701	2.44632305	H	2.92616812	1.64682986	-2.32021328
C	-1.72912748	-1.09438592	4.21930387	C	1.47799613	5.11887423	-0.67764174
H	-1.41472723	-3.06376458	3.40420963	H	1.89220585	6.07417719	-0.33602599
H	-1.99547784	0.98784828	4.70775046	H	1.54051632	5.07589684	-1.78016054
H	-1.98673319	-1.45232387	5.21558714	H	0.41576619	5.04449108	-0.39939851
O	0.61268167	-0.07922623	-1.69952577	H	-4.28336047	2.08381627	-1.51327642
C	2.60747693	-1.38351077	-0.26147481	O	-5.27208871	2.26424719	-1.59280764
C	3.68562871	-1.26056502	0.80615142	H	-5.45535155	2.59215140	-0.70415338
C	2.52378274	-2.80746358	-0.80626415				

Table S5g: Optimized XYZ coordinates of O-Int-2b

C	-2.93922755	0.23738942	0.73376930	H	3.84020326	-0.48338469	-0.68512450
C	-2.52703184	1.50621179	0.65326796	C	5.77354219	-2.19611543	0.35472431
C	-3.94398043	-0.32069918	-0.20091281	H	4.03238375	-2.53018195	1.58360893
C	-4.00677649	0.19067497	-1.50740702	H	4.62241437	-0.86274874	1.63703461
C	-4.87833303	-1.30591779	0.14338380	C	4.54344668	-2.96991881	-1.69303948
C	-4.94262338	-0.26545137	-2.42346692	H	2.75447921	-3.33019012	-0.52994223
H	-3.29273941	0.96988535	-1.77145136	H	2.52114543	-2.18067532	-1.85946077
C	-5.81685406	-1.76974959	-0.77377376	C	5.54418152	-3.35534665	-0.60935619
H	-4.88375629	-1.70846557	1.15369936	H	6.48147691	-2.48236379	1.14566389
C	-5.85431069	-1.25700651	-2.06488490	H	6.23916801	-1.35933876	-0.19333200
H	-4.95905299	0.15295416	-3.43051233	H	4.36837576	-3.81237468	-2.37703168
H	-6.53306978	-2.53412139	-0.46922476	H	4.96922101	-2.15568626	-2.30402098
H	-6.58872453	-1.62072521	-2.78385499	H	6.49587270	-3.67808369	-1.05623511
C	-1.44127999	2.02697893	1.39277387	H	5.15121170	-4.21970326	-0.04655357
O	-1.44554061	2.96394255	2.20005674	N	2.21896821	-0.89188722	0.50318844
C	0.06299852	0.17025853	0.61608794	H	1.86512656	-1.38944723	1.31277684
C	0.98237530	2.39846345	1.13195302	H	1.91439965	1.83795488	1.27707739
C	1.34047981	-0.06625013	-0.14618308	H	0.80710512	3.02481117	2.01369133
N	-0.14396630	1.47914001	1.01232083	C	1.08376699	3.30777244	-0.08503570
C	-0.77861739	-0.89034913	0.86018207	H	0.98923764	2.70824802	-1.01339706
C	-2.05876998	-0.69709484	1.64604539	O	2.33120255	3.98987560	-0.10522118
C	-0.55609899	-2.18086196	0.24624916	O	0.06971525	4.22876095	0.01058913
C	-2.63724337	-1.98647142	2.12638198	C	3.35665909	3.24955231	-0.69821492
H	-1.84094721	-0.07650958	2.53010646	H	4.24092079	3.89628121	-0.74948043
C	-1.27219604	-3.27460490	0.59902834	H	3.62084965	2.34330253	-0.12266558
H	0.19952106	-2.26835561	-0.53516413	H	3.09168556	2.91713919	-1.71659530
C	-2.28606310	-3.18339346	1.62503411	C	-0.28297979	4.86250899	-1.19255648
H	-3.40919305	-1.91889519	2.89566501	H	-1.27647384	5.29010745	-1.02522632
H	-1.08241815	-4.23239843	0.11546896	H	0.44715031	5.63925694	-1.47195886
H	-2.76962621	-4.09584561	1.97646342	H	-0.34872159	4.12897827	-2.01431121
O	1.62272102	0.45841907	-1.21596340	H	-3.17341095	3.54143010	0.07408370
C	3.45293330	-1.34056448	-0.11012512	O	-3.09593579	4.48142076	0.33710114
C	4.46121864	-1.71898415	0.96657232	H	-2.51157242	4.36128334	1.10658002
C	3.22898225	-2.49895863	-1.08181837				

Table S5h: Optimized XYZ coordinates of C-Int-1

C	2.93763049	-1.37704532	-0.13827990	H	1.43319020	0.26473510	2.54079250
C	1.86677146	-1.61182407	0.37905251	C	2.79317467	3.02933739	1.10959923
C	4.19152733	-1.05476377	-0.72189382	H	2.07947142	3.92688747	-0.71656831
C	5.17595417	-2.04515957	-0.85637948	H	3.21995307	1.88834231	2.89071546

C	4.46020520	0.25827557	-1.13708378	H	3.59601924	3.75019655	1.26302993
C	6.40602801	-1.72694841	-1.41409901	O	-1.72837774	1.39748825	-1.02388568
H	4.95165901	-3.05023910	-0.49827648	C	-3.89422024	-0.12129754	-0.65891612
C	5.69606424	0.56362765	-1.69028552	C	-4.69716578	-1.36439271	-1.03013689
H	3.69088941	1.02077833	-1.00769235	C	-4.74300061	0.86451495	0.14381002
C	6.66786685	-0.42446920	-1.83388912	H	-3.59342415	0.39294524	-1.58327567
H	7.16787471	-2.49873045	-1.51764086	C	-5.96274383	-0.98176187	-1.79106929
H	5.90493106	1.58404826	-2.00876732	H	-4.98741450	-1.91752414	-0.11915510
H	7.63571688	-0.17637523	-2.26882750	H	-4.06606672	-2.04424191	-1.61990685
C	0.70254904	-2.00364031	1.13554891	C	-6.01576484	1.23493680	-0.60832110
O	0.69014532	-3.08729756	1.74594759	H	-5.00989367	0.41213732	1.11604072
C	-0.34615536	0.15724689	0.47539445	H	-4.12999922	1.75128188	0.35204472
C	-1.52138933	-1.51918892	1.79577117	C	-6.81591927	-0.00801125	-0.98448700
C	-1.52159038	0.44651112	-0.25362557	H	-6.54249092	-1.88034933	-2.04981753
C	-2.65562227	-1.18208995	1.17280733	H	-5.67971724	-0.50501378	-2.74522684
H	-1.45813130	-2.12120597	2.69483310	H	-6.63142551	1.92627337	-0.01373483
H	-3.62781782	-1.45160398	1.58426688	H	-5.74085283	1.77626302	-1.52968042
N	-0.31808976	-1.10821942	1.17775283	H	-7.72190289	0.26756525	-1.54531105
C	0.70352769	1.12735084	0.69396636	H	-7.15801780	-0.51077550	-0.06251524
C	0.92868757	2.19816526	-0.20530006	N	-2.64013624	-0.44672418	-0.00054394
C	1.56771430	1.06366468	1.81165673	O	2.85458479	-4.60770900	0.52938981
C	1.94520399	3.11960170	0.00654324	H	2.22913646	-4.20365953	1.16409531
H	0.27265056	2.28521657	-1.06641466	H	2.65603744	-4.09334347	-0.26286242
C	2.58185217	1.98628818	2.01090622				

Table S5i: Optimized XYZ coordinates of C-TS1

C	1.59295407	0.24677205	1.86923997	H	1.03752624	-0.94586544	-1.91981513
C	1.43655751	1.32910958	2.50878408	C	3.32910521	2.15419539	-1.82987284
C	2.31153094	-0.99316250	1.75008578	H	2.13716124	2.81238121	-0.17337055
C	3.48038637	-1.15750692	2.51389065	C	3.55495098	1.17150186	-2.79017414
C	1.88127438	-2.04795878	0.93595141	H	2.86897087	-0.72758473	-3.54347846
C	4.19640169	-2.34412499	2.46532342	H	3.97077828	3.03583343	-1.78931554
H	3.80173773	-0.32969520	3.14414035	H	4.37187111	1.26550406	-3.50569964
C	2.60860455	-3.23192699	0.89159496	O	-0.73834847	-1.19843273	-0.63729295
H	0.97098229	-1.92822407	0.34677694	C	-3.22898616	-0.28434377	-0.29668539
C	3.76347781	-3.38896821	1.65126541	C	-4.38735928	0.00255980	0.65380281
H	5.10039860	-2.45399445	3.06488727	C	-3.67312902	-0.19676580	-1.75624418
H	2.26264630	-4.04526604	0.25379985	H	-2.88322619	-1.31418776	-0.12508648
H	4.32580107	-4.32208952	1.61162215	C	-5.55520254	-0.93871191	0.37602536
C	0.51403601	2.36006775	2.04655817	H	-4.73341683	1.04284943	0.52822095
O	0.16269403	3.38057545	2.61612565	H	-4.03797442	-0.08690921	1.69196469
C	0.34286430	0.82562147	0.07368551	C	-4.85452148	-1.12031879	-2.02963475
C	-1.16988953	2.70183721	0.37170129	H	-3.95676036	0.84456248	-1.99128620
C	-0.78993472	-0.03268387	-0.21348024	H	-2.81502538	-0.45175940	-2.39224847
C	-2.20208523	1.94077395	-0.00145710	C	-6.01039573	-0.83571450	-1.07609332
H	-1.20243618	3.78544200	0.43263834	H	-6.39031515	-0.72426824	1.05913679
H	-3.14441767	2.35315957	-0.35752580	H	-5.24092409	-1.97641675	0.58123546
N	0.00586936	2.04207535	0.76168129	H	-5.18355130	-1.02964001	-3.07539812
C	1.43055855	0.91867260	-0.91732946	H	-4.52855864	-2.16584673	-1.89468579
C	1.68037538	-0.07069364	-1.88943886	H	-6.85013761	-1.52065476	-1.26743143
C	2.29474028	2.03040255	-0.91386652	H	-6.38843730	0.18524521	-1.26094275
C	2.71629630	0.06060918	-2.80417553	N	-2.06659618	0.54798508	-0.02371789

Table S5j: Optimized XYZ coordinates of C-TS1a

C	-2.62171000	0.63812300	0.98620700	C	-1.50526200	-4.32034200	-1.69532000
C	-1.57923400	0.00654600	1.32012400	H	-1.11231600	-5.42387100	0.11521700
C	-3.52689500	1.39497000	0.22704600	H	-1.77786800	-2.94069200	-3.32987800
C	-3.37259200	2.80143500	0.14595000	H	-1.87878300	-5.18340600	-2.24631400
C	-4.66247900	0.83696700	-0.40725700	O	0.71119800	0.44717700	-1.29721200
C	-4.28265600	3.58489400	-0.54190100	C	3.07725600	0.97391300	-0.22077500
H	-2.50288100	3.24739000	0.62730500	C	4.10141400	1.67697100	0.66832200
C	-5.58248500	1.63782200	-1.06631300	C	3.77028300	0.07748900	-1.24527200
H	-4.78597400	-0.24548200	-0.39071300	H	2.53709900	1.75845700	-0.77023800
C	-5.40411200	3.01751900	-1.14922400	C	5.11874500	2.45033800	-0.16930800
H	-4.11993200	4.66222800	-0.60084400	H	4.65415300	0.95094400	1.28676100
H	-6.45117100	1.17326400	-1.53531000	H	3.57901600	2.34696900	1.36644700
H	-6.12635600	3.64145600	-1.67500500	C	4.72129300	0.91001400	-2.09560600
C	-0.80913600	-0.37393800	2.52793800	H	4.35070000	-0.68969800	-0.70054100
O	-0.90870300	-0.09455100	3.70030900	H	3.01828500	-0.44120600	-1.85084900
C	-0.10673200	-0.89969700	0.49912300	C	5.78196900	1.55307700	-1.20994600
C	1.52081400	-1.19326700	2.35018300	H	5.87555000	2.89863900	0.49141600
C	0.86100500	-0.03119600	-0.17438900	H	4.61416000	3.28698100	-0.68124300
N	0.19520000	-1.13559000	1.90256100	H	5.16665000	0.31794800	-2.90741200
C	-0.53249700	-2.08324300	-0.27201200	H	4.13992900	1.71389700	-2.57887400
C	-0.60040700	-3.35135300	0.32499100	H	6.51110300	2.11996400	-1.80751500
C	-0.96876300	-1.96217500	-1.60261900	H	6.34827700	0.76083300	-0.68910600
C	-1.07684400	-4.45078000	-0.37681900	N	2.04647400	0.27544300	0.54858400
H	-0.28297800	-3.45766100	1.36137600	C	2.42518500	-0.50235300	1.65067600
C	-1.44403100	-3.06625500	-2.29891900	H	1.75331300	-1.74460200	3.25753000
H	-0.91731500	-0.98332900	-2.07461400	H	3.48289800	-0.52188700	1.90032600

Table S5k: Optimized XYZ coordinates of C-TS1b

C	0.86887390	-2.27956694	-1.24641205	C	1.92706861	-2.88423099	2.20964105
C	-0.05617939	-1.79526488	-1.97816617	H	0.65113791	-4.35326513	1.32127389
C	2.31158924	-2.46748383	-1.26646707	H	3.01336120	-1.14973459	2.93633981
C	2.90979905	-3.69964716	-0.98195615	H	2.53757472	-3.60191540	2.75756776
C	3.14074882	-1.37920424	-1.56929695	O	0.29591155	2.00628408	1.22695507
C	4.29165303	-3.84386404	-1.00879168	C	-1.87079960	3.48194843	0.69931736
H	2.27098751	-4.54817556	-0.74007007	C	-2.54319038	4.35800151	-0.35367083
C	4.52174280	-1.52186913	-1.59465259	C	-2.55092067	3.63859238	2.05974823
H	2.66881006	-0.41946775	-1.77615725	H	-0.82810378	3.81136020	0.81613402
C	5.10372196	-2.75580676	-1.31400495	C	-2.55069288	5.81720227	0.08869014
H	4.73890785	-4.81329981	-0.78822637	H	-3.58493348	4.02991323	-0.51308506
H	5.14930846	-0.66263864	-1.83123309	H	-2.02645784	4.23417670	-1.31576378
H	6.18792341	-2.86760369	-1.33101577	C	-2.57801513	5.09885107	2.49602692
C	-1.39760266	-1.39021341	-1.74392086	H	-3.58394932	3.25165953	1.99854049
O	-2.40092316	-1.78877992	-2.34857285	H	-2.01579764	3.01741373	2.79107266
C	-0.56255866	-0.00925523	0.24072351	C	-3.23931075	5.97893377	1.44035182
C	-2.81427311	0.17019164	-0.62460249	H	-3.03826857	6.44583751	-0.67101832
C	-0.58625812	1.39096595	0.61757980	H	-1.51013839	6.17514198	0.17163386
N	-1.54387003	-0.41306146	-0.72887729	H	-3.08959926	5.20483830	3.46413393
C	0.29882543	-0.94293667	0.85237946	H	-1.54135044	5.44348783	2.65152012
C	0.16363970	-2.37126495	0.60159167	H	-3.23305275	7.03380236	1.75362547
C	1.40670624	-0.56278029	1.67937515	H	-4.29963984	5.68743192	1.33950385
C	0.89205767	-3.29237841	1.41539110	N	-1.77196528	2.09208797	0.28678841
H	-0.81603769	-2.71436504	0.26939631	H	-3.64272959	-0.41452117	-1.00603109
C	2.18455666	-1.49410527	2.31585213	C	-2.91378708	1.40097997	-0.11999407
H	1.60508434	0.49480370	1.80883615	H	-3.87103995	1.89622796	0.02408847

Table S5l: Optimized XYZ coordinates of C-Int-2

C	1.82164114	-0.34766443	1.22066429	H	2.49316394	2.26159694	0.70864113
C	2.08465710	-0.01751452	2.51382719	C	1.79074769	3.16290141	-2.49714793
C	2.68678320	-1.20005380	0.38596090	H	0.29344375	2.22419230	-3.72809086
C	3.85130022	-1.75226279	0.95241660	H	3.20140683	3.88095890	-1.03217295
C	2.43579384	-1.48022847	-0.96505886	H	2.10289606	3.86779066	-3.26731641
C	4.71207591	-2.53671924	0.20020420	O	-0.50072696	-1.61553570	-0.21504550
H	4.06804304	-1.55065403	2.00222709	C	-2.99525868	-0.55362299	-0.21563842
C	3.30395281	-2.26330847	-1.71806804	C	-3.77016470	-1.21000647	0.92374144
H	1.53440758	-1.10000680	-1.43612268	C	-3.90595061	0.30951677	-1.08274424
C	4.45060897	-2.79790317	-1.14393422	H	-2.58187598	-1.35569719	-0.84497005
H	5.60365111	-2.95045453	0.67313015	C	-4.94212302	-2.02392237	0.38711132
H	3.07340870	-2.45834321	-2.76609517	H	-4.13941666	-0.42732452	1.60906160
H	5.13101095	-3.41371560	-1.73307667	H	-3.08017656	-1.84042468	1.50141119
C	1.02568635	0.92673034	2.91177626	C	-5.06262526	-0.52348427	-1.62636122
O	0.78862719	1.48490986	3.96923874	H	-4.32465391	1.14087107	-0.49083295
C	0.59318921	0.39597654	0.62317475	H	-3.31974550	0.76396103	-1.89542075
C	-1.02606819	1.81444620	1.80176843	C	-5.85055405	-1.16989764	-0.49127648
C	-0.59795275	-0.47133228	0.20179233	H	-5.51192962	-2.46979621	1.21499080
C	-2.00537348	1.36472918	1.00585374	H	-4.55175171	-2.86477401	-0.21095508
H	-1.13027953	2.65525554	2.48218813	H	-5.72096191	0.09957949	-2.24912881
H	-2.96230082	1.86374860	0.89666199	H	-4.66364553	-1.31388115	-2.28452685
N	0.18778660	1.17143362	1.77957198	H	-6.68020266	-1.77112376	-0.89156717
C	0.99115941	1.34373022	-0.51281217	H	-6.30705689	-0.37640917	0.12583630
C	0.38274989	1.34532439	-1.76705441	N	-1.82455029	0.17405159	0.26895804
C	2.00862651	2.26949743	-0.26746114	H	3.45212939	-0.58054125	3.71709537
C	0.78152162	2.24415139	-2.75369090	O	4.31781455	-0.79365078	4.18526699
H	-0.40662028	0.62593125	-1.99016456	H	4.86533196	-0.06480647	3.86912330
C	2.40384340	3.16974898	-1.24578670				

Table S5m: Optimized XYZ coordinates of C-Int-2a

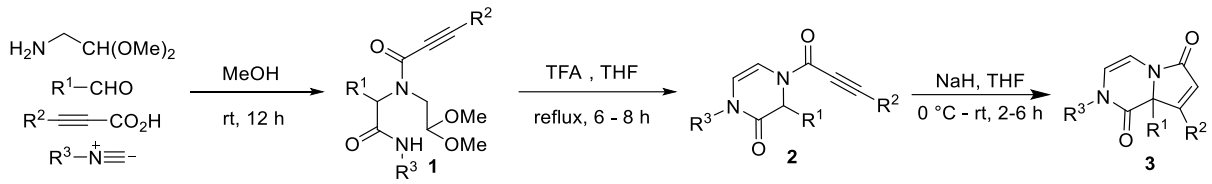
C	2.56542163	0.69250319	1.20925322	H	0.55292711	1.91085855	-2.78034053
C	1.47341432	1.19877292	0.64093667	C	1.65617286	-1.06294435	-4.00733234
C	2.99280763	-0.66996697	1.04174582	H	1.87351841	-2.86301666	-2.83654761
C	2.44827709	-1.74471286	1.77653873	H	1.34849831	0.87866309	-4.89002327
C	4.04576707	-0.97208560	0.14976747	H	2.01948365	-1.51632832	-4.92949891
C	2.90862162	-3.04212243	1.59799371	O	-0.63404318	-1.08605739	0.93594005
H	1.62794472	-1.54256970	2.46301715	C	-3.23154238	-0.37023909	0.51326992
C	4.48444073	-2.27311723	-0.03529824	C	-3.90162159	0.28913173	1.71553032
H	4.49229316	-0.15511264	-0.41801752	C	-4.24065187	-0.68238206	-0.58763116
C	3.92291623	-3.32799888	0.68562412	H	-2.78789419	-1.31772962	0.85054628
H	2.45190935	-3.84953157	2.17329460	C	-5.04285607	-0.57323478	2.24375525
H	5.28203637	-2.46952810	-0.75408945	H	-4.29240488	1.27896691	1.42184318
H	4.27649016	-4.34958158	0.54688554	H	-3.14380854	0.46555746	2.49165628
C	0.92055114	2.56943673	0.55189998	C	-5.37061929	-1.55203431	-0.04581239
O	1.09728504	3.67759745	1.00919877	H	-4.67480749	0.25234997	-0.98239339
C	0.31206832	0.74100737	-0.33143829	H	-3.72677546	-1.17197971	-1.42652837
C	-1.34663306	2.57888514	-0.67052841	C	-6.05233769	-0.88470796	1.14374267
C	-0.81207714	-0.06504954	0.29313825	H	-5.53443032	-0.07877458	3.09377053
C	-2.33430279	1.68836634	-0.51552347	H	-4.62992737	-1.52072380	2.62954227
H	-1.50887548	3.59319256	-1.02664432	H	-6.09970106	-1.76874205	-0.83994423
H	-3.36181352	1.90268215	-0.79573630	H	-4.95798747	-2.52399167	0.27362586
N	-0.05105963	2.16161252	-0.41159953	H	-6.86332683	-1.51939263	1.52994181
C	0.74252677	0.10841747	-1.63013111	H	-6.52183238	0.05641299	0.80772177
C	1.10861623	-1.24192506	-1.66255843	N	-2.09576810	0.41076482	0.02345156
C	0.83090920	0.85837257	-2.80335549	H	3.47913248	2.28208747	2.23811947
C	1.56743506	-1.81722081	-2.84030182	O	3.60300456	3.20330783	2.55805084
H	1.05259657	-1.83299451	-0.74916887	H	2.81730426	3.62038193	2.17143149
C	1.28371766	0.27661466	-3.98335732				

Table S5n: Optimized XYZ coordinates of C-Int-2b

C	-2.70856622	1.03745240	0.00808775	H	-2.13451731	-3.21169586	2.18667502
C	-2.04159219	1.93645042	-0.71534572	H	-3.70081461	-1.67984234	3.40525663
C	-3.78024086	0.18869852	-0.56427381	O	1.40899356	-1.68219227	-0.09024249
C	-4.98338528	-0.08826860	0.09500315	C	3.79835664	-0.48334091	-0.32994681
C	-3.61005651	-0.34053300	-1.85089821	C	4.70151700	0.15947463	-1.37734086
C	-5.97057287	-0.86697698	-0.50017413	C	4.54822875	-0.72324907	0.97891859
H	-5.15483756	0.32842664	1.08604651	H	3.46911583	-1.46101251	-0.70897660
C	-4.59075305	-1.12047743	-2.44825939	C	5.93810800	-0.70289758	-1.61068356
H	-2.67967839	-0.11220576	-2.36937151	H	5.02773104	1.15814330	-1.04147067
C	-5.77859870	-1.39219566	-1.77346447	H	4.13699588	0.31022133	-2.30809511
H	-6.90229970	-1.05704588	0.03388779	C	5.79949249	-1.56253180	0.74664655
H	-4.42645548	-1.52291108	-3.44824182	H	4.82915776	0.24860788	1.42188342
H	-6.55076260	-2.00430260	-2.23992088	H	3.86694704	-1.21492454	1.68714244
C	-0.88490554	2.59027600	-0.23864387	C	6.70035811	-0.93068304	-0.30910086
O	-0.67141678	3.81084219	-0.16944562	H	6.58948344	-0.23771644	-2.36452442
C	0.17478952	0.33142741	0.37458270	H	5.62799298	-1.67812975	-2.02282276
C	1.47700095	2.35029208	0.17957951	H	6.34761638	-1.70575656	1.68909193
C	1.38219853	-0.45874179	0.03397150	H	5.49787022	-2.56734202	0.40528886
N	0.24002576	1.71979387	0.08649889	H	7.58778538	-1.55615630	-0.48575235
C	-0.92111345	-0.23617602	0.99746597	H	7.06979325	0.04050667	0.06389831
C	-2.07264444	0.65211202	1.40407262	N	2.56480608	0.26351289	-0.10767240
C	-1.07783215	-1.65393957	1.22234295	H	1.43004866	3.42800424	0.27926477
C	-2.97783935	0.05480389	2.41939783	C	2.60659710	1.64429794	0.11066216
H	-1.68211902	1.60300612	1.79765916	H	3.58639374	2.09807132	0.21884295
C	-2.05923126	-2.13632364	2.02475911	O	-2.71270113	4.48342661	-2.11293129
H	-0.36938705	-2.32750645	0.75545206	H	-2.78959480	3.51357623	-2.02563669
C	-2.98977380	-1.26150595	2.69207495	H	-2.02288813	4.62720512	-1.44203925
H	-3.68199445	0.73218547	2.90608228				

5. Experimental procedures and characterization data:

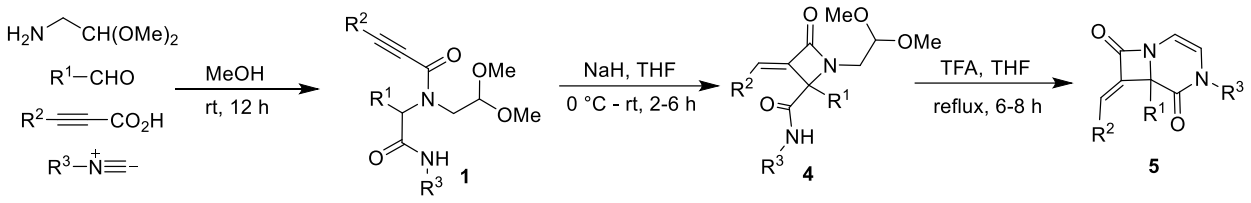
5.1. General procedure A for the synthesis of 3a-3aa:



Equimolar mixture of aminoacetaldehyde dimethyl acetal (0.475 mmol), aldehyde (0.475 mmol), acid (0.475 mmol) and isocyanide (0.475 mmol) were dissolved in methanol (4.0 mL) in an oven dried round bottom flask and stirred at room temperature for 12 h. After consumption of all the substrates (based on TLC), the solvent was removed under vacuum. The crude adduct **1** was dissolved in THF (6.0 mL), trifluoroacetic acid (9.51 mmol) was added to it at room temperature and the reaction mixture was refluxed for 6-8 h. After completion of the reaction (based on TLC), the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resultant crude mixture was then dissolved in dichloromethane and washed with saturated sodium bicarbonate solution (2.0 mL x 2). Aqueous layer was extracted with dichloromethane (10.0 mL x 2) and the combined organic layers were dried over anhydrous sodium sulfate, filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to afford desired product **2.**

Dihydropyrazinone **2** (0.127 mmol) was dissolved in anhydrous THF (4.0 mL), after complete dilution of starting material, sodium hydride (60% dispersion on mineral oil) (0.381 mmol) was added portion-wise at 0 °C and the reaction was kept at room temperature. After consumption of starting material (based on TLC), the reaction mixture was filtered through a celite pad, filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to afford desired product **3**.

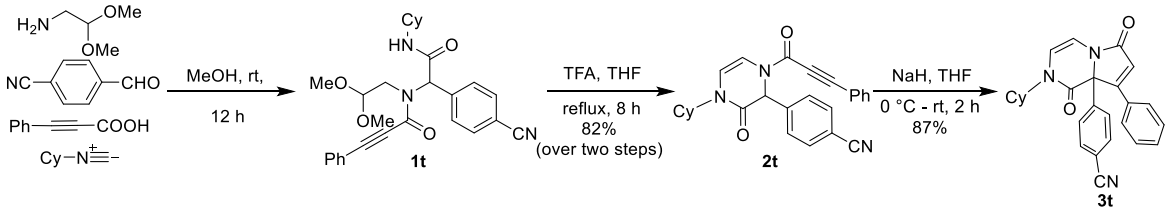
5.2. General procedure B for the synthesis of 5a-5aa:



Equimolar mixture of aminoacetaldehyde dimethyl acetal (0.475 mmol), aldehyde (0.475 mmol), acid (0.475 mmol) and isocyanide (0.475 mmol) was dissolved in methanol (4.0 mL). The resulting mixture was stirred at room temperature for 12 h. On completion of the reaction (based on TLC), methanol was removed *in vacuo*. The crude Ugi adduct **1** was dissolved in THF (6.0 mL), sodium hydride (60% dispersion on mineral oil) (1.43 mmol) was added portion-wise at 0 °C and the reaction was stirred at room temperature for 2-6 h. On completion of the reaction (based on TLC), the reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to afford desired product **4**.

β-lactam **4** (0.109 mmol) was then dissolved in THF (4.0 mL), after complete dilution of starting material, trifluoroacetic acid (2.18 mmol) was added at room temperature and the reaction was refluxed for 6-8 h. After completion of the reaction (based on TLC), the reaction mixture was cooled to rt and the solvent was evaporated under reduced pressure. The resultant crude mixture was then dissolved in dichloromethane and washed with saturated sodium bicarbonate solution (3.0 mL x 2). Aqueous layer was extracted with dichloromethane (10.0 mL x 2) and the combined organic layers were dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to afford desired product **5**.

5.3. Gram-Scale synthesis of compound 3t:

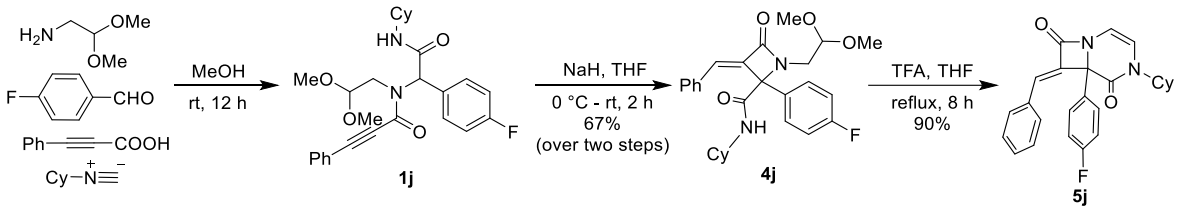


Equimolar mixture of aminoacetaldehyde dimethyl acetal (0.510 mL, 4.76 mmol), 4-cyanobenzldehyde (590.0 mg, 4.76 mmol), phenylpropiolic acid (695.0 mg, 4.76 mmol), and cyclohexyl isocyanide (0.592 mL, 0.475 mmol) were dissolved in methanol (15.0 mL) in an oven dried round bottom flask and stirred at room temperature for 12 h. After consumption of all the substrates, the solvent was removed under vacuum. The crude adduct **1t** was dissolved in THF (20.0 mL), trifluoroacetic acid (6.19 mL, 95.11 mmol) was added to it at room temperature and the reaction mixture was refluxed for 8 h. After completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resultant crude mixture was then dissolved in dichloromethane and washed with saturated sodium bicarbonate solution (10.0 mL x 2). Aqueous layer was extracted with dichloromethane (25.0 mL x 2) and the combined organic layers were dried over anhydrous sodium sulfate, filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford desired product **2t** as a grey solid (1.78 g, 82%)**.**

To a stirred solution of **2t** (1.78 g, 4.35 mmol) in anhydrous THF (20.0 mL), after dilution of reaction mixture then sodium hydride (312.0 mg, 13.04 mmol) was added portion-wise at 0 °C and the reaction was kept at room temperature for 2 h. After completion of the reaction (based on TLC), reaction mixture was filtered through a celite pad, filtrate was concentrated under reduced

pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to afford desired product **3t** as a yellow solid (1.32 g, 87%).

5.4. Gram-Scale synthesis of compound 5j:

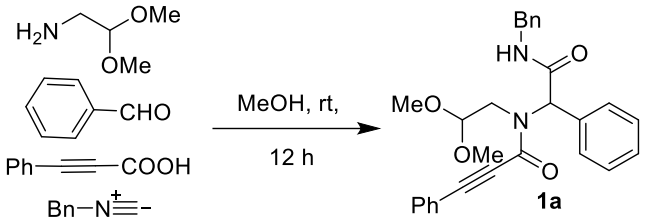


Equimolar mixture of aminoacetaldehyde dimethyl acetal (0.510 mL, 4.76 mmol), 4-fluorobenzaldehyde (0.513 mL, 4.76 mmol), phenylpropiolic acid (695.0 mg, 4.76 mmol), and cyclohexyl isocyanide (0.591 mL, 0.0475 mmol) was dissolved in methanol (15.0 mL). The resulting mixture was stirred at room temperature for 12 h. On completion of the reaction, methanol was removed *in vacuo*. The crude Ugi-adduct **1j** was dissolved in THF (20.0 mL), sodium hydride (570.0 mg, 14.27 mmol) was added portion-wise at 0 °C and the reaction was stirred at room temperature for 2 h. On completion of the reaction, the reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate/hexane) to afford desired product **4j** as a white solid (1.48 g, 67%).

To a stirred a solution of **4j** (1.48 g, 3.17 mmol) in THF (20.0 mL) was added trifluoroacetic acid (4.17 mL, 63.44 mmol) at room temperature and the reaction was refluxed for 8 h. After completion of the reaction (based on TLC), the reaction mixture was cooled to rt and the solvent was evaporated under reduced pressure. The resultant crude mixture was then dissolved in dichloromethane and washed with saturated sodium bicarbonate solution (6.0 mL x 2). Aqueous layer was extracted with dichloromethane (30.0 mL x 2) and the combined organic layers were

dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to afford desired product **5j** as a white solid (1.15 g, 90%).

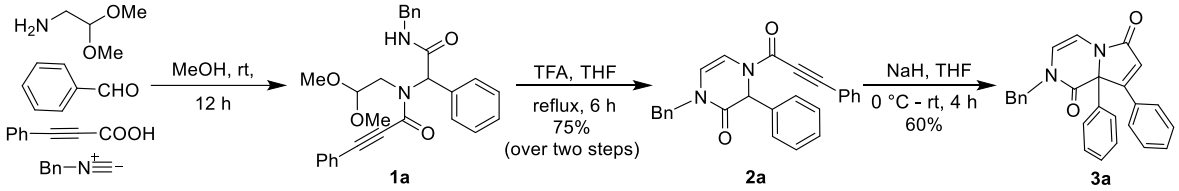
N-(2-(Benzylamino)-2-oxo-1-phenylethyl)-N-(2,2-dimethoxyethyl)-3-phenylpropiolamide (1a):



Equimolar mixture of aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.049 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol) were dissolved in methanol (4.0 mL) in an oven dried round bottom flask and stirred at room temperature for 12 h. After consumption of all the substrates, the solvent was removed under vacuum. The resultant crude mixture was then dissolved in dichloromethane and washed with saturated sodium bicarbonate solution (4.0 mL x 2). Aqueous layer was extracted with dichloromethane (4.0 mL x 2) and the combined organic layers were dried over anhydrous sodium sulfate, filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (25% ethyl acetate/hexane) to afford desired product **1a** as yellow oil (190.0 mg, 87%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.6); **^{1}H NMR (400 MHz, $CDCl_3$)*:*** δ 8.45 (t, *J* = 5.0 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.56 – 7.52 (m, 1.3H), 7.49 – 7.42 (m, 3H), 7.41 – 7.36 (m, 6.7H), 7.35 – 7.26 (m, 9.6H), 7.25 – 7.20 (m, 1.7H), 6.66 (t, *J* = 5.5 Hz, 0.6H), 6.32 (s, 1H), 5.77 (s, 0.6H), 4.89 (dd, *J* = 7.3, 3.9 Hz, 1H), 4.72 (dd, *J* = 14.7, 6.1 Hz, 1H), 4.55 (dd, *J* = 14.9, 5.8 Hz, 0.6H), 4.48 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.44 (d, *J* = 4.8 Hz, 0.6H), 4.31 (t, *J* = 5.2 Hz, 0.6H), 3.82 (dd, *J* = 15.2, 5.2 Hz, 0.6H), 3.70 (dd,

J = 15.3, 5.3 Hz, 0.6H), 3.34 (dd, *J* = 14.4, 3.9 Hz, 1H), 3.27 (s, 3H), 3.23 (s, 1.7H), 3.19 (s, 1.6H), 3.05 (s, 3H), 2.79 (dd, *J* = 14.4, 7.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.2, 168.9, 156.9, 156.2, 138.13, 134.6, 134.4, 133.2, 132.6, 130.8, 130.4, 129.9, 129.7, 129.2, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.2, 127.9, 127.6, 127.5, 120.4, 119.8, 103.5, 102.0, 93.1, 91.5, 82.0, 81.4, 68.2, 64.8, 55.8, 55.3, 55.0, 54.7, 50.7, 47.1, 44.0, 43.9; **HRMS (ESI)** m/z calcd for $C_{28}H_{29}N_2O_4$ $[M+H]^+$ 457.2127; found: 457.2128.

2-Benzyl-8,8a-diphenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3a):

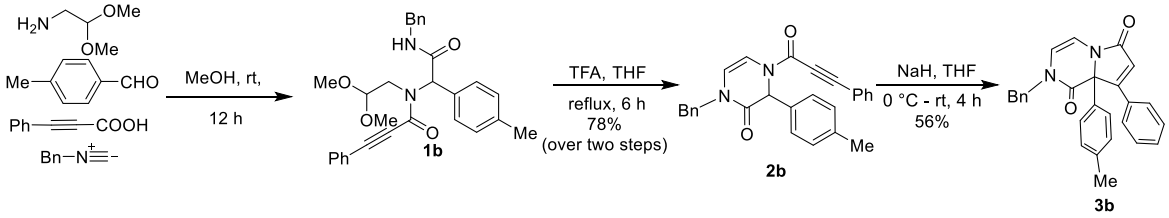


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.049 mL, 0.475 mmol), phenyl propiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC, followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2a** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid (140.0 mg, 75%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p**: 126-128 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.56 (dd, *J* = 8.2, 1.4 Hz, 2.33H), 7.48 – 7.36 (m, 14H), 7.35 – 7.31 (m, 8.46H), 7.29 (d, *J* = 1.8 Hz, 2H), 7.23 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.18 – 7.14 (m, 2H), 6.86 (dd, *J* = 6.2, 1.4 Hz, 1H), 6.77 (dd, *J* = 6.1, 1.4 Hz, 1H), 6.29 (s, 1H), 6.25 (s, 1H), 5.71 (dd, *J* = 9.4, 6.1 Hz, 2H), 4.78 (s, 2H), 4.74 (d, *J* = 2.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 164.3, 164.2, 163.4, 163.3, 161.8, 161.7, 152.4, 151.9, 135.9, 135.6, 132.8, 132.7, 131.9, 131.8 131.7, 131.6, 131.0, 130.9, 129.1, 129.0, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 119.7, 119.5, 116.2, 116.0, 115.7, 114.7, 113.6, 109.4, 107.8,

93.2, 93.0, 80.6, 80.3, 62.3, 58.1, 49.5, 49.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{21}N_2O_2$ $[M+H]^+$ 393.1603; found: 393.1587.

Using **2a** (50.0 mg, 0.127 mmol) and sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3a** as a yellow solid (30.0 mg, 60%); **m.p**: 194 -196 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.29 (dd, J = 12.8, 5.0 Hz, 11H), 7.23 (d, J = 2.0 Hz, 4H), 6.56 (s, 1H), 6.43 (d, J = 5.3 Hz, 1H), 5.83 (d, J = 5.3 Hz, 1H), 4.89 (d, J = 14.7 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.1, 162.7, 160.9, 135.8, 134.8, 132.2, 129.9, 129.4, 129.1, 129.0, 128.8, 128.4, 128.2, 128.1, 126.1, 122.0, 117.4, 106.9, 72.9, 50.1; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1066, 1675, 2922, 3394, 3740, 3840; **HRMS (ESI)** m/z calcd for $C_{26}H_{21}N_2O_2[M+H]^+$ 393.1603; found: 393.1601.

2-Benzyl-8-phenyl-8a-(p-tolyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3b):

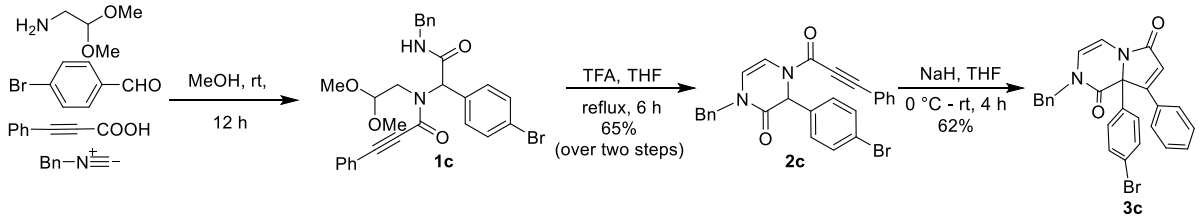


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-methyl benzaldehyde (0.056 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol) in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2b** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane)as a white oil, (152.0 mg, 78%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.55 (dd, J = 8.2, 1.5 Hz, 2H), 7.45 (ddd, J = 9.1, 6.9, 1.6 Hz, 4H), 7.39 – 7.28 (m, 13H), 7.26 – 7.22 (m, 3H), 7.16 (dt, J = 10.1, 5.5 Hz, 6H),

6.84 (dd, *J* = 6.2, 1.5 Hz, 1H), 6.75 (dd, *J* = 6.1, 1.4 Hz, 1H), 6.25 (s, 1H), 6.21 (s, 1H), 5.71 (dd, *J* = 9.1, 6.1 Hz, 2H), 4.77 (s, 2H), 4.73 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 163.7, 163.6, 152.5, 152.5, 152.0, 138.8, 138.6, 136.0, 135.8, 133.0, 132.9, 132.8, 132.7, 130.8, 130.8, 129.8, 129.6, 129.0, 128.7, 128.3, 128.2, 128.1, 128.0, 126.8, 126.1, 119.8, 120.0, 114.8, 113.8, 109.6, 108.0, 92.9, 92.8, 80.8, 80.5, 77.41, 77.2, 76.9, 62.7, 58.5, 49.5, 49.4, 21.2; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 699, 741, 961, 1358, 1432, 1511, 1649, 1657, 3024; **HRMS (ESI)** m/z calcd for $C_{27}H_{23}N_2O_2$ $[M+H]^+$: 407.1760 ; found: 407.1751.

Using **2b** (52.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3b** as a yellow solid, (29.0 mg, 56%); **m.p**: 163-166 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.36 – 7.30 (m, 5H), 7.29 – 7.21 (m, 5H), 7.14 – 7.04 (m, 4H), 6.55 (s, 1H), 6.42 (d, *J* = 5.4 Hz, 1H), 5.83 (d, *J* = 5.4 Hz, 1H), 4.81 (dd, *J* = 44.0, 14.7 Hz, 2H), 2.32 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.0, 162.8, 160.9, 139.3, 135.8, 132.3, 131.7, 129.8, 129.8, 129.0, 128.9, 128.4, 128.2, 128.1, 126.01, 121.8, 117.3, 106.8, 72.7, 50.0, 21.3; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1067, 1675, 2921, 3395, 3738, 3838; **HRMS (ESI)** m/z calcd for $C_{27}H_{23}N_2O_2$ $[M+H]^+$: 407.1760; found: 407.1752.

2-Benzyl-8a-(4-bromophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3c):

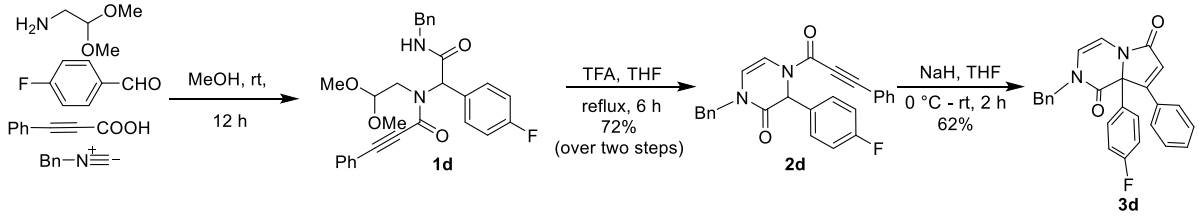


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-bromo benzaldehyde (88.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-

4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2c** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid, (145.0 mg, 65%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p:** 126-128 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58 – 7.37 (m, 13H), 7.37 – 7.27 (m, 10H), 7.24 – 7.13 (m, 5H), 6.85 (dd, *J* = 6.2, 1.5 Hz, 1H), 6.77 (dd, *J* = 6.1, 1.4 Hz, 1H), 6.22 (s, 1H), 6.19 (s, 1H), 5.72 (dd, *J* = 8.3, 6.1 Hz, 2H), 4.83 – 4.67 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.9, 162.8, 152.3, 151.9, 135.7, 135.5, 134.9, 134.7, 132.7, 132.6, 132.1, 132.0, 130.9, 130.8, 129.0, 128.9, 128.7, 128.5, 128.2, 128.15, 128.1, 127.8, 127.8, 123.0, 122.8, 119.5, 119.3, 114.6, 113.5, 109.3, 107.7, 93.2, 93.1, 80.4, 80.2, 62.3, 58.1, 49.5, 49.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}BrN_2O_2$ $[M+H]^+$ 471.0708; found: 471.0699.

Using **2c** (60.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3c** as a yellow solid, (37.0 mg, 62%); **m.p:** 172-175 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.44 – 7.26 (m, 11H), 7.24 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 6.43 (d, *J* = 5.4 Hz, 1H), 5.85 (d, *J* = 5.4 Hz, 1H), 4.90 (d, *J* = 14.7 Hz, 1H), 4.69 (d, *J* = 14.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.9, 162.2, 160.6, 135.6, 134.0, 132.7, 131.8, 130.11, 129.0, 128.9, 128.4, 128.2, 127.8, 123.4, 122.1, 117.4, 106.8, 72.3, 50.2; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 765, 1074, 1410, 1681, 2922, 3396, 3740, 3839; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}BrN_2O_2$ $[M+H]^+$ 471.0708; found: 471.0701.

***2-Benzyl-8a-(4-fluorophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3d)*:**

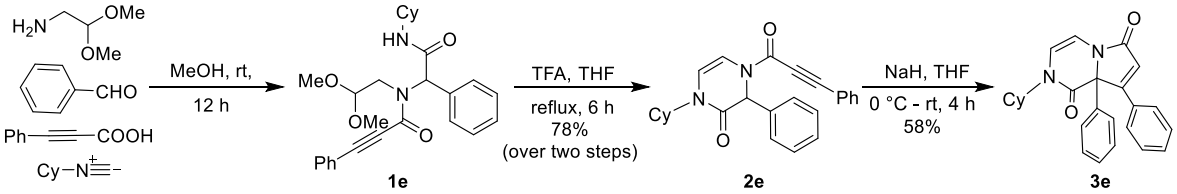


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.052 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0mL), compound **2d** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid (140.0 mg, 72%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p**: 112-115 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.55 (dd, J = 5.2, 3.2 Hz, 2H), 7.48 – 7.29 (m, 18H), 7.25 – 7.13 (m, 4H), 7.09 – 6.97 (m, 4H), 6.85 (dd, J = 6.2, 1.4 Hz, 1H), 6.77 (dd, J = 6.1, 1.3 Hz, 1H), 6.24 (s, 1H), 6.22 (s, 1H), 5.73 (dd, J = 8.2, 6.2 Hz, 2H), 4.85 – 4.64 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.4, 163.3, 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz), 162.9 (d, $J_{C\text{-}F}$ = 246.0 Hz), 152.4, 152.0, 135.8, 135.6, 132.8, 132.7 131.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 131.6 (d, $J_{C\text{-}F}$ = 3.75 Hz), 131.0, 130.9, 129.1, 129.0, 128.8, 128.7, 128.3, 128.2, 128.0 (d, $J_{C\text{-}F}$ = 8.25 Hz), 127.9, 119.6, 119.5, 116.0 (d, $J_{C\text{-}F}$ = 21.75 Hz), 115.8 (d, $J_{C\text{-}F}$ = 21.0 Hz), 114.7, 113.6, 109.4, 107.8, 93.2, 93.1, 80.6, 80.3, 62.3, 58.1, 49.5, 49.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}FN_2O_2$ $[M+H]^+$: 411.1509; found: 411.1499.

Using **2d** (52.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3d** as a yellow solid, (32.0 mg, 62%); **m.p**: 173-176 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.37 – 7.29 (m, 6H), 7.28 – 7.26 (m, 2H), 7.24 (dd, J = 3.1, 1.9 Hz, 2H), 7.20 – 7.13 (m, 2H), 6.98 (t, J = 8.6 Hz, 2H), 6.55 (s, 1H), 6.43 (d, J = 5.4 Hz, 1H), 5.85 (d, J = 5.4 Hz, 1H), 4.90 (d, J = 14.7 Hz, 1H), 4.71 (d, J = 14.7 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.9, 163.0 (d, $J_{C\text{-}F}$= 247.5 Hz), 162.5, 160.8, 135.7, 132.0, 130.5 (d, $J_{C\text{-}F}$= 3.75 Hz), 130.0, 129.0,

128.8, 128.3, 128.2, 128.1 (d $J_{C\text{-}F}$ = 9 Hz), 122.1, 117.4 , 116.2 (d $J_{C\text{-}F}$ = 21.7 Hz), 106.8, 72.3, 50.2; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}FN_2O_2$ $[M+H]^+$: 411.1509; found: 411.1494.

2-Cyclohexyl-8,8a-diphenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3e):

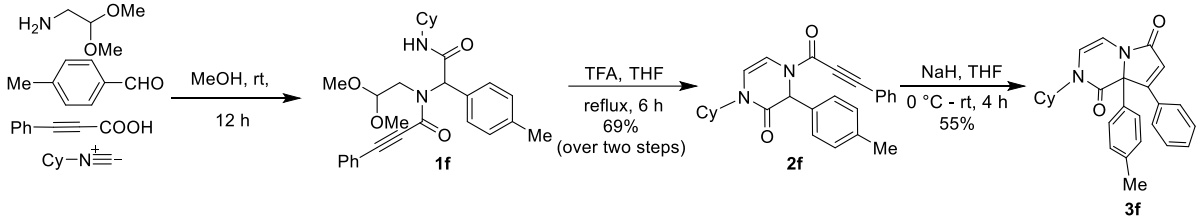


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.049 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), cyclohexyl isocyanide (0.06 mL, 0.475 mmol) in methanol (4.0 mL) to perform Ugi-4CC, followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL)**,** compound **2e** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil (155.0 mg, 78%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 – 7.56 (m, 2H), 7.49 – 7.40 (m, 8H), 7.39 – 7.35 (m, 6H), 7.34 – 7.30 (m, 4H), 6.83 (dd, J = 6.2, 1.2 Hz, 1H), 6.75 (dd, J = 6.1, 1.1 Hz, 1H), 6.22 (s, 1H), 6.16 (s, 1H), 5.87 (d, J = 6.3 Hz, 1H), 5.84 (d, J = 6.2 Hz, 1H), 4.50 – 4.39 (m, 2H), 1.84 (s, 6H), 1.72 – 1.62 (m, 5H), 1.49 – 1.41 (m, 4H), 1.39 (s, 3H), 1.14 (d, J = 3.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.9, 162.9, 152.4, 151.9, 136.1, 135.9, 132.8, 132.7, 130.8, 130.7, 129.0, 128.9, 128.7, 128.70, 128.5, 126.8, 126.2, 119.9, 119.7, 111.6, 110.7, 109.1, 107.7, 92.8, 92.7, 80.8, 80.6, 62.9, 58.6, 52.7, 52.5, 31.5, 31.4, 30.7, 30.5, 25.7, 25.7, 25.6, 25.6, 25.4, 25.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$: 385.1916; found: 385.1904.

Using **2e** (49.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.390 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl

acetate/hexane) to yield **3e** as a yellow solid (28.0 mg, 58%); **m.p**: 211-213 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.33 (m, 3H), 7.31 – 7.27 (m, 4H), 7.25 – 7.20 (m, 3H), 6.56 (s, 1H), 6.43 (d, J = 5.5 Hz, 1H), 5.90 (d, J = 5.5 Hz, 1H), 4.54 (dd, J = 14.4, 6.6 Hz, 1H), 1.90 – 1.76 (m, 5H), 1.41 (dd, J = 27.8, 11.7 Hz, 4H), 1.16 – 1.10 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.1, 162.2, 160.9, 134.9, 132.4, 129.8, 129.2, 129.0, 128.6, 128.0, 126.0, 121.9, 113.8, 106.6, 72.6, 53.3, 31.7, 30.9, 25.8 25.7, 25.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$: 385.1916 ; found: 385.1902.

2-Cyclohexyl-8-phenyl-8a-(p-tolyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3f):

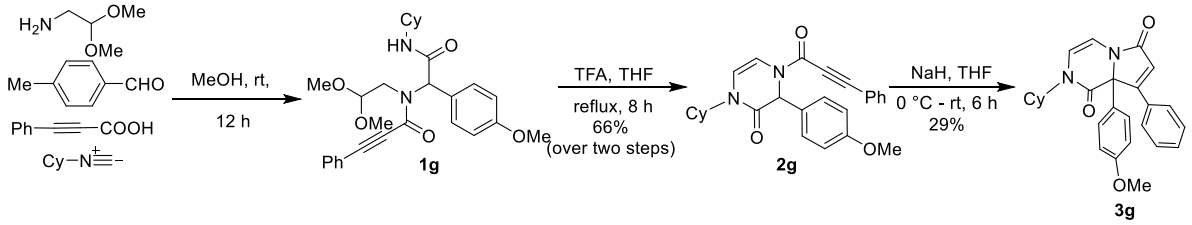


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-methyl benzaldehyde (0.056 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.058 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2f** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow oil, (131.0 mg, 69%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60 – 7.54 (m, 2H), 7.52 – 7.45 (m, 3H), 7.44 – 7.40 (m, 2H), 7.40 – 7.34 (m, 3H), 7.33 – 7.26 (m, 3H), 7.24 (s, 1H), 7.13 (t, J = 7.7 Hz, 4H), 6.81 (dd, J = 6.3, 1.4 Hz, 1H), 6.73 (dd, J = 6.2, 1.3 Hz, 1H), 6.18 (s, 1H), 6.12 (s, 1H), 5.84 (dd, J = 9.2, 6.3 Hz, 2H), 4.54 – 4.35 (m, 2H), 2.31 (d, J = 3.5 Hz, 6H), 1.83 (m, 6H), 1.74 – 1.59 (m, 7H), 1.40 (dd, J = 17.4, 6.3 Hz, 7H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 163.1, 163.1,

152.4, 151.9, 138.6, 138.4, 133.2, 133.1, 132.8, 132.7, 130.8, 130.7, 129.7, 129.6, 128.7, 128.7, 126.8, 126.1, 119.9, 119.8, 111.7, 110.7, 109.1, 107.7, 92.7, 92.6, 80.8, 80.6, 62.7, 58.4, 52.7, 52.5, 31.6, 31.5, 30.8, 30.6, 25.7, 25.7, 25.6, 25.6, 25.5, 25.4, 21.2, 21.1; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_2$ $[M+H]^+$: 399.2073 ; found: 399.2062.

Using **2f** (51.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3f** as a yellow solid (28.0 mg, 55%); **m.p**: 163-166 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.34 – 7.27 (m, 3H), 7.26 – 7.20 (m, 2H), 7.19 – 7.07 (m, 4H), 6.63 (s, 1H), 6.44 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 5.5 Hz, 1H), 4.64 – 4.41 (m, 1H), 2.33 (s, 3H), 1.90 – 1.64 (m, 6H), 1.49 – 1.35 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.4, 162.4, 161.1, 139.3, 132.5, 131.8, 129.8, 128.7, 128.1, 126.0, 121.8, 114.0, 106.6, 72.6, 53.4, 31.8, 31.0, 25.9, 25.8, 25.4, 21.3; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_2[M+H]^+$: 399.2073; found: 399.2062.

2-Cyclohexyl-8a-(4-methoxyphenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3g):

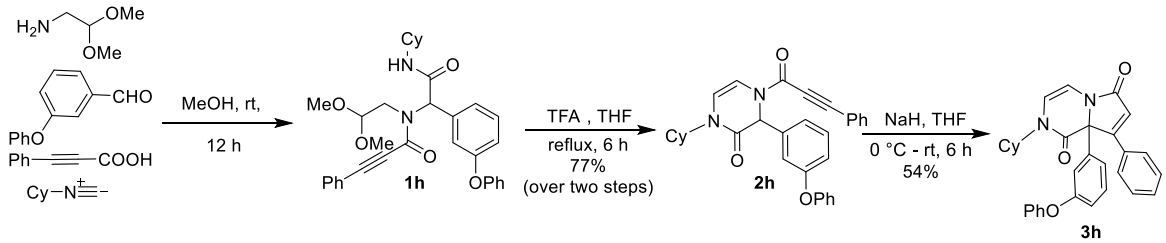


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-methoxy benzaldehyde (0.045 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2g** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow oil, (130.0 mg, 66%). Two rotamers were present on NMR

timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 – 7.55 (m, 2H), 7.52 – 7.48 (m, 2H), 7.46 – 7.39 (m, 3H), 7.37 (d, *J* = 9.2 Hz, 3H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 3H), 6.84 – 6.79 (m, 2H), 6.73 (dd, *J* = 6.1, 1.1 Hz, 1H), 6.17 (s, 1H), 6.10 (s, 1H), 5.85 (dd, *J* = 12.0, 6.3 Hz, 2H), 4.53 – 4.38 (m, 2H), 3.77 (d, *J* = 3.1 Hz, 6H), 1.85 (d, *J* = 9.7 Hz, 6H), 1.68 (dd, *J* = 23.8, 13.9 Hz, 5H), 1.46 – 1.35 (m, 8H), 1.15 – 1.11 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 163.2, 163.1, 159.9, 159.8, 152.3, 151.9, 132.8, 132.6, 130.7, 130.7, 128.7, 128.7, 128.4, 128.3, 128.2, 127.5, 119.9, 119.7, 114.4, 114.2, 111.6, 110.6, 109.0, 107.6, 92.7, 92.6, 80.9, 80.6, 62.4, 58.0, 55.3, 52.7, 52.5, 31.5, 31.4, 30.8, 30.6, 25.7, 25.6, 25.6, 25.4, 25.7; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_3$ $[M+H]^+$: 415.2022; found: 415.2017.

Using **2g** (52.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3g** as a yellow solid (15.0 mg, 29%); **m.p:**153-156 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32 – 7.27 (m, 3H), 7.26 – 7.21 (m, 2H), 7.18 – 7.12 (m, 2H), 6.87 – 6.82 (m, 2H), 6.54 (s, 1H), 6.43 (d, *J* = 5.5 Hz, 1H), 5.91 (d, *J* = 5.6 Hz, 1H), 4.53 (dd, *J* = 15.5, 7.5 Hz, 1H), 3.79 (s, 3H), 1.92 – 1.74 (m, 5H), 1.69 (d, *J* = 13.6 Hz, 1H), 1.49 – 1.41 (m, 2H), 1.35 (d, *J* = 6.5 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.2, 162.4, 161.0, 160.1, 132.5, 129.8, 128.7, 128.0, 127.4, 126.4, 121.7, 114.4, 113.8, 106.6, 72.3, 55.4, 53.3, 31.7, 31.0, 25.8, 25.7, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_3$ $[M+H]^+$: 415.2022; found: 415.2016.

2-Cyclohexyl-8a-(3-phenoxyphenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3h):

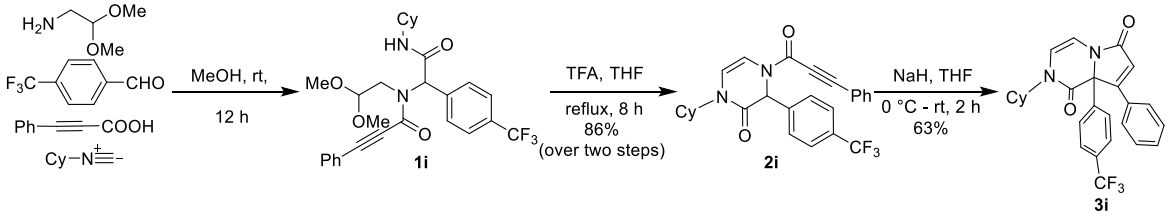


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 3-phenoxybenzaldehyde (0.083 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0mL),compound **2h** was prepared and purified and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid, (175.0 mg, 77%). Two rotamers were present on NMR timescale (R^1: R^2 = 1 : 1); **m.p**: 126-129 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.50 – 7.40 (m, 5H), 7.39 – 7.32 (m, 5H), 7.31 – 7.27 (m, 3H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.17 – 7.05 (m, 5H), 7.01 – 6.90 (m, 7H), 6.78 (dd, *J* = 6.3, 1.4 Hz, 1H), 6.72 (dd, *J* = 6.2, 1.3 Hz, 1H), 6.19 (s, 1H), 6.11 (s, 1H), 5.84 (d, *J* = 6.3 Hz, 1H), 5.79 (d, *J* = 6.2 Hz, 1H), 4.41 (d, *J* = 10.7 Hz, 2H), 1.82 (s, 6H), 1.72 – 1.57 (m, 6H), 1.37 (d, *J* = 8.6 Hz, 6H), 1.16 – 1.06 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.6, 162.5, 158.0, 157.8, 156.8, 156.7, 152.3, 151.9, 138.2, 137.8, 132.8, 132.7, 130.8, 130.7, 130.4, 130.2, 129.9, 128.8, 123.7, 123.6, 122.1, 121.0, 119.9, 119.6, 119.4, 119.3, 118.9, 118.6, 116.8, 116.7, 111.6, 110.7, 109.0, 107.6, 92.9, 80.8, 80.5, 62.7, 58.3, 52.8, 52.6, 31.5, 31.4, 30.7, 30.6, 25.7, 25.6, 25.4, 25.3; **HRMS (ESI)** m/z calcd for $C_{31}H_{29}N_2O_3$ $[M+H]^+$: 477.2178; found: 477.2163.

Using **2h** (61.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3h** as a yellow solid, (33.0 mg, 54%); **m.p**: 153-156 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.27 (m, 8H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.97 (dd, *J* = 8.0, 2.1 Hz, 2H), 6.92 – 6.89 (m, 2H), 6.56 (s, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 5.90 (d, *J* = 5.5 Hz, 1H), 4.48 – 4.38 (m, 1H), 1.84 – 1.64 (m, 5H), 1.37 – 1.31 (m, 4H), 1.13 – 1.07 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.1, 161.9, 160.6, 157.9, 156.9, 137.2, 132.3, 130.5, 129.9, 129.8,

128.9, 128.1, 123.8, 122.0, 120.7, 119.60, 119.1, 116.9, 113.9, 106.7, 72.4, 53.5, 31.7, 30.9, 25.8, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{31}H_{29}N_2O_3$ $[M+H]^+$: 477.2178; found: 477.2165.

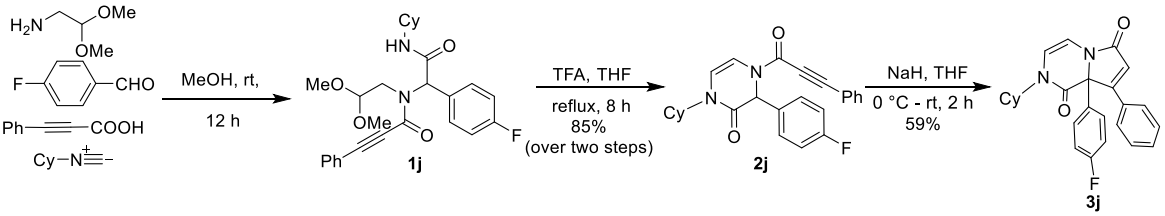
2-Cyclohexyl-8-phenyl-8a-(4-(trifluoromethyl)phenyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3i):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), trifluoromethyl benzaldehyde (0.045 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC, followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2i** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid (76.0 mg, 86%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.83); **m.p:** 150-152 °C; **^{1}H NMR (300 MHz, $CDCl_3$):**δ 7.66 – 7.41 (m, 15H), 7.37 (ddd, *J* = 8.6, 7.5, 1.6 Hz, 3H), 6.87 (dd, *J* = 6.3, 1.3 Hz, 0.85H), 6.80 (dd, *J*= 6.2,1.2 Hz, 1H), 6.24 (s, 1H), 6.22 (s, 0.83H), 5.86 (dd, *J* = 7.9, 6.3 Hz, 2H), 4.52 – 4.34 (m, 2H), 1.85 (d, *J* = 7.2 Hz, 6H), 1.75 – 1.62 (m, 4H), 1.47 – 1.34 (m, 8H), 1.18 – 1.08 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 162.3, 162.1, 152.3, 152.0, 140.0, 139.8, 132.8, 132.7, 131.1, 131.0, 130.9, 130.6, 128.8, 127.3, 126.6, 126.0 (d, J_{C-F} = 3.70 Hz), 125.9 (d, J_{C-F} = 2.50 Hz), 125.1, 125.0, 122.9, 122.9, 119.7, 119.4, 111.6, 110.5, 109.0, 107.6, 93.3, 93.1, 80.5, 80.3, 62.6, 58.4, 53.0, 52.7, 31.5, 31.4, 30.7, 30.5, 25.7, 25.6, 25.4, 25.3; **^{19}F NMR (283 MHz, $CDCl_3$):**δ -62.7; **HRMS (ESI)** m/z calcd for $C_{26}H_{24}F_3N_2O_2$ $[M+H]^+$: 453.1790; found: 453.1780.

Using **2i** (58.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3i** as a yellow solid, (36.0 mg, 63%); **m.p**: 145-148 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (d, J = 8.3 Hz, 2H), 7.40 – 7.27 (m, 7H), 6.59 (s, 1H), 6.45 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 5.5 Hz, 1H), 4.52 (dd, J = 11.3, 8.0 Hz, 1H), 1.92 – 1.76 (m, 5H), 1.41 (dd, J = 25.1, 10.2 Hz, 4H), 1.13 (dd, J = 12.3, 3.1 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.0, 161.6, 160.5, 139.4, 131.9, 131.6, 131.3, 130.1, 128.8, 128.2, 126.6, 126.1 (dd, $J_{C\text{-}F}$ = 11.2 Hz), 124.8, 122.6, 122.4, 113.8, 106.6, 72.3, 53.6, 31.7, 31.0, 25.8, 25.7, 25.3; **^{19}F NMR (283 MHz, $CDCl_3$):** δ -62.8; **HRMS (ESI)** m/z calcd for $C_{26}H_{24}F_3N_2O_2$ $[M+H]^+$: 453.1790; found: 453.1778.

2-Cyclohexyl-8a-(4-fluorophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3j):

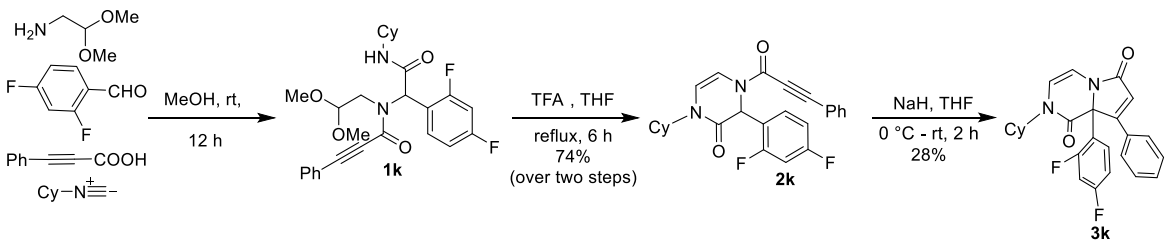


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.052 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2j** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (160.0 mg, 85%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61 – 7.55 (m, 2.4H), 7.51 – 7.43 (m, 4H), 7.43 – 7.32 (m, 9H), 7.08 – 6.96 (m, 4.5H), 6.83 (dd, J = 6.3, 1.4 Hz, 1H), 6.75 (dd, J = 6.2, 1.3 Hz, 1H), 6.18 (s, 1H), 6.13 (s, 1H), 5.86 (dd, J = 8.3, 6.3 Hz, 2H), 4.52 – 4.35 (m, 2H),

1.85 (d, J = 7.8 Hz, 6H), 1.77 – 1.65 (m, 4H), 1.47 – 1.35 (m, 8H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 162.9 (d, $J_{C\text{-}F}$ = 246 Hz), 162.8, 162.7, 152.4, 152.0, 132.8, 132.7, 132.1, 132.0, 130.9, 130.8, 128.9, 128.8, 128.0 (d, $J_{C\text{-}F}$ = 8.75 Hz), 119.8, 119.6, 116.1 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22.5 Hz), 111.5, 110.6, 109.0, 107.6, 93.0, 92.9, 80.7, 80.5, 62.4, 58.0, 52.9, 52.6, 31.6,31.5, 30.8, 30.6, 25.7, 25.6, 25.5, 25.4; **HRMS (ESI)** m/z calcd for $C_{25}H_{24}FN_2O_2$ $[M+H]^+$: 403.1822; found: 403.1813.

Using **2j** (51.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3j** as a yellow solid, (30.0 mg, 59%); **m.p**: 181-185 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30 (dd, J = 7.6, 4.0 Hz, 3H), 7.26 – 7.18 (m, 4H), 7.02 (t, J = 8.5 Hz, 2H), 6.55 (s, 1H), 6.43 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 5.5 Hz, 1H), 4.55 – 4.48 (m, 1H), 1.91 – 1.75 (m, 6H), 1.71 (s, 1H), 1.47 (d, J = 5.8 Hz, 1H), 1.40 – 1.36 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.1, 163.0 (d, $J_{C\text{-}F}$ = 248.2 Hz), 162.1, 160.9, 132.3, 130.7 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.9, 128.7, 128.2, 128.1, 128.0, 122.1, 116.2 (d $J_{C\text{-}F}$ = 21.7 Hz), 113.8, 106.6, 72.2, 53.5, 31.7, 31.0, 25.8, 25.7, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1068, 1672, 2923, 3396, 3739, 3840; **HRMS (ESI)** m/z calcd for $C_{25}H_{24}FN_2O_2$ $[M+H]^+$: 403.1822; found: 403.1821.

2-Cyclohexyl-8a-(2,4-difluorophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3k):

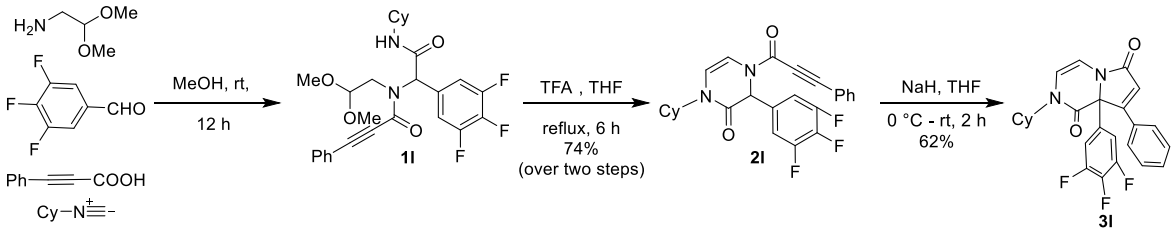


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 2,4-difluorobenzaldehyde (0.045 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2k** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow oil, (148.0 mg, 74%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 – 7.54 (m, 4H), 7.50 – 7.47 (m, 1H), 7.46 – 7.43 (m, 2H), 7.38 (td, *J* = 7.4, 1.9 Hz, 5H), 6.93 (d, *J* = 6.4 Hz, 1H), 6.81 (ddd, *J* = 12.5, 10.9, 5.5 Hz, 5H), 6.42 (s, 1H), 6.22 (s, 1H), 5.92 (d, *J* = 6.5 Hz, 1H), 5.85 (d, *J* = 6.4 Hz, 1H), 4.52 – 4.34 (m, 2H), 1.88 – 1.79 (m, 6H), 1.70 (dd, *J* = 26.9, 11.6 Hz, 4H), 1.49 – 1.35 (m, 8H), 1.19 – 1.10 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 164.0 (t, $J_{C\text{-}F}$ = 25, 12.5 Hz), 162.2, 162.1,162.0 (t, $J_{C\text{-}F}$ = 23.7, 11.2Hz), 160.8, 160.2 (dd, $J_{C\text{-}F}$ = 262 Hz), 159.7 (dd, $J_{C\text{-}F}$ = 262 Hz), 132.8, 132.5,131.1 (dd, $J_{C\text{-}F}$ = 15Hz), 130.8, 130.7, 128.7, 128.6,128.5 (dd, $J_{C\text{-}F}$ = 13.7 Hz), 122.1 (dd, $J_{C\text{-}F}$ = 18.7, 11.2 Hz), 121.1 (dd, $J_{C\text{-}F}$ = 18.7, 12.5 Hz) , 119.6, 119.5, 112.2 (dd, $J_{C\text{-}F}$ = 25, 17.5Hz), 111.5 (dd, $J_{C\text{-}F}$ = 25, 17.5 Hz), 110.6, 109.5, 109.0, 107.6, 104.3 (dd, $J_{C\text{-}F}$ = 25, 17.5Hz), 104.2 (dd, $J_{C\text{-}F}$ = 25, 17.5 Hz), 93.3, 92.7, 80.3, 80.3, 56.1, 54.2, 52.8, 52.6, 31.1, 31.1, 30.5, 30.4, 25.6, 25.5, 25.4, 25.3, 25.2; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -108.13 (d, *J* = 8.5 Hz), -109.05 (d,*J* = 8.4 Hz), -110.87 (d,*J* = 8.3 Hz), -111.12 (d,*J* = 8.5 Hz); **HRMS (ESI)** m/z calcd for $C_{25}H_{23}F_2N_2O_2$ $[M+H]^+$: 421.1728 ; found: 421.1722.

Using **2k** (53.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3k** as a yellow solid (15.0 mg, 28%); **m.p:**187-189 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.5 – 7.4 (m, 2H), 7.3 (m, 2H), 7.2 (d, *J* = 1.3 Hz, 1H), 7.1 (td, *J* = 8.9, 6.1 Hz,

1H), 6.9 – 6.8 (m, 1H), 6.7 (ddd, *J* = 11.3, 8.6, 2.6 Hz, 1H), 6.6 (s, 1H), 6.4 (d, *J* = 5.4 Hz, 1H), 6.0 (d, *J* = 5.4 Hz, 1H), 4.5 (ddd, *J* = 11.8, 8.1, 3.7 Hz, 1H), 1.9 – 1.74 (m, 5H), 1.70 (d, *J* = 13.1 Hz, 1H), 1.5 – 1.4 (m, 2H), 1.4 – 1.3 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.1, 163.5 (d, $J_{C\text{-}F}$ = 243 Hz), 161.3, 161.5(d, $J_{C\text{-}F}$ = 235 Hz) , 158.9 (t, $J_{C\text{-}F}$ = 20.0, 10.0 Hz), 131.9, 130.1, 130.0 (dd, $J_{C\text{-}F}$ = 13.7, 6.2 Hz), 128.6, 128.4, 122.3 (dd, $J_{C\text{-}F}$ = 13.7, 6.2 Hz), 114.3, 112.0, 111.8, 106.9, 105.7 (t, $J_{C\text{-}F}$ = 51.2, 25.0 Hz), 70.0, 53.9, 31.8, 30.8, 25.9, 25.8, 25.4; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -107.50 (d, *J* = 9.7 Hz), -108.57 (d, *J* = 9.8 Hz); **HRMS (ESI)** m/z calcd for $C_{25}H_{23}F_2N_2O_2$ $[M+H]^+$: 421.1728; found: 421.1723.

2-Cyclohexyl-8-phenyl-8a-(3,4,5-trifluorophenyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3l):

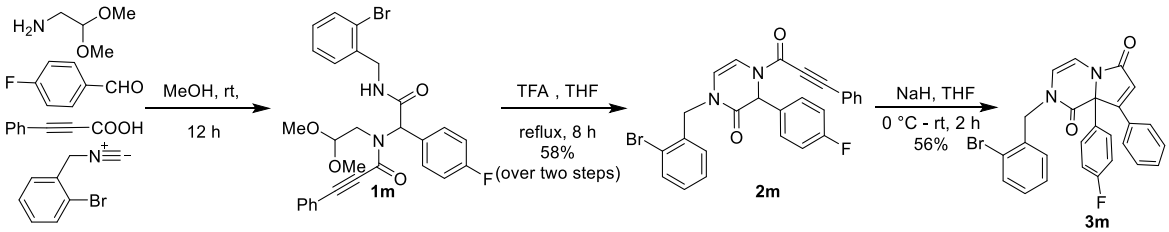


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 3,4,5-trifluorobenzaldehyde (0.047 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2l** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid, (148.0 mg, 74%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.84); **m.p:**176-178 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.62 – 7.58 (m, 2H), 7.55 – 7.32 (m, 8H), 7.04 (dd, *J*= 14.7, 7.9 Hz, 4H), 6.81 (ddd, *J* = 18.2, 6.2, 1.2 Hz, 2H), 6.11 (s, 1H), 6.09 (s, 1H), 5.86 (dd, *J*= 9.2, 6.3 Hz, 2H), 4.41 (dd, *J* = 10.2, 5.1 Hz, 2H),

1.88 – 1.67 (m, 10H), 1.37 (dd, J = 15.6, 6.9 Hz, 10H); **^{13}C NMR (125 MHz, CDCl$_3$):** δ 161.7, 161.6, 151.4 (d, $J_{C\text{-}F}$ = 248 Hz), 151.3 (dd, $J_{C\text{-}F}$ = 248 Hz), 151.2 (d, $J_{C\text{-}F}$ = 248 Hz), 151.1 (dd, $J_{C\text{-}F}$ = 248 Hz), 141.9 (m, $J_{C\text{-}F}$ = 30 Hz), 139.9 (m, $J_{C\text{-}F}$ = 25 Hz), 132.7, 132.4(q, $J_{C\text{-}F}$ = 17.5 Hz), 132.1 (q, $J_{C\text{-}F}$ = 17.5 Hz), 133.1, 131.0, 128.8, 128.7, 119.5, 119.2, 111.4, 111.3 (dd, $J_{C\text{-}F}$ = 22.5, 11.2 Hz), 110.6 (q, $J_{C\text{-}F}$ = 22.5, 11.2 Hz), 110.4, 108.8, 107.3, 93.7, 93.3, 80.2, 80.1, 61.8, 57.6, 53.1, 52.9, 31.4, 31.3, 30.7,30.5, 29.8, 25.6, 25.5, 25.3, 25.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{22}F_3N_2O_2$ $[M+H]^+$: 439.1633; found: 439.1620.

Using **2l** (56.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3l** as a yellow oil (35.0 mg, 62%); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.38 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 6.94 – 6.83 (m, 2H), 6.57 (s, 1H), 6.46 (d, J = 5.6 Hz, 1H), 5.94 (d, J = 5.6 Hz, 1H), 4.50 (tt, J = 11.6, 3.7 Hz, 1H), 1.92 – 1.69 (m, 5H), 1.54 – 1.35 (m, 4H), 1.18 – 1.07 (m, 1H); **^{13}C NMR (125 MHz, CDCl$_3$):** δ 168.6, 160.9, 160.1, 151.4 (dd, $J_{C\text{-}F}$ = 250 Hz), 151.3 (dd, $J_{C\text{-}F}$ = 251 Hz), 139.8 (dt, $J_{C\text{-}F}$ = 253 Hz), 131.8 (q, $J_{C\text{-}F}$ = 16.2, 3.7 Hz),131.5, 130.1, 128.7, 128.2, 122.4, 113.7, 110.7(dd, $J_{C\text{-}F}$ = 22.5, 12.5 Hz), 106.5, 71.5, 53.7, 31.5, 30.8, 25.7, 25.6, 25.2; **^{19}F NMR (377 MHz, CDCl$_3$):** δ -131.38, -131.43, -157.40, -157.45, -157.50; **HRMS (ESI)** m/z calcd for $C_{25}H_{22}F_3N_2O_2$ $[M+H]^+$: 439.1633; found**:**439**.**1620**.**

2-(2-Bromobenzyl)-8a-(4-fluorophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3m):

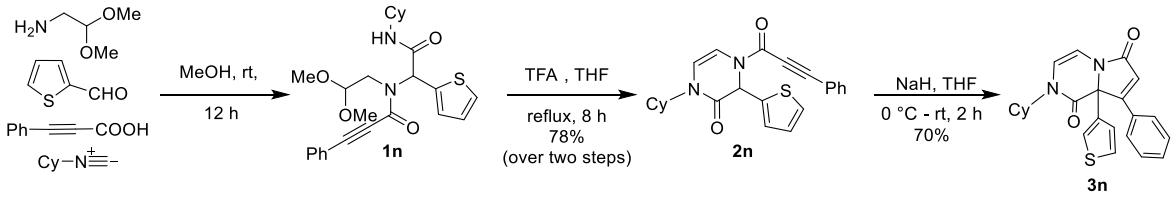


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and 2-bromo benzyl isocyanide (92.0 mg, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2m** was prepared and purified and purified by silica gel column chromatography (30% ethyl acetate/hexane) as a yellow oil, (135.0 mg, 58%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.84); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60 – 7.54 (m, 4H), 7.43 (ddd, *J* = 19.7, 9.9, 4.4 Hz, 12H), 7.24 (dd, *J* = 4.4, 1.3 Hz, 1H), 7.17 (dt, *J* = 7.8, 4.7 Hz, 4H), 7.10 – 7.00 (m, 5H), 6.89 (dd, *J* = 6.2, 1.4 Hz, 1H), 6.81 (dd, *J* = 6.1, 1.3 Hz, 1H), 6.26 (s, 1H), 6.25 (s, 1H), 5.77 (dd, *J* = 6.2, 1.7 Hz, 2H), 4.88 (dd, *J* = 16.9, 5.4 Hz, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.4, 163.3, 163.1 (d, $J_{C\text{-}F}$ = 246.7 Hz), 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz), 152.4, 152.0, 135.0, 134.7, 133.3, 133.2, 132.8, 132.7, 131.6 (d, $J_{C\text{-}F}$ = 3.75 Hz), 131.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 131.0, 130.9, 130.0, 129.8, 129.7, 129.4, 128.8, 128.7, 128.2, 128.1, 128.0, 123.7, 123.5, 119.6, 119.4, 116.0 (d, $J_{C\text{-}F}$ = 21.75 Hz), 115.8 (d, $J_{C\text{-}F}$ = 21.75 Hz), 114.7, 113.7, 109.5, 107.9, 93.3, 93.1, 80.5, 80.3, 62.3, 58.1, 49.5, 49.2; **HRMS (ESI)** m/z calcd for $C_{26}H_{19}BrFN_2O_2$ $[M+H]^+$: 489.0614; found: 489.0601.

Using **2m** (62.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3m** as a yellow solid, (35.0 mg, 56%); **m.p**: 185-188 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.25 – 7.15 (m, 5H), 7.05 – 6.98 (m, 2H), 6.55 (s, 1H), 6.47 (d, *J* = 5.4 Hz, 1H), 5.90 (d, *J* = 5.4 Hz, 1H), 4.93 (s, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.9, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 162.7, 161.0, 134.8, 133.2, 131.9, 130.4 (d, $J_{C\text{-}F}$ = 3.75 Hz), 130.0, 129.8 (d $J_{C\text{-}F}$ = 8.2 Hz), 128.9, 128.2, 128.1, 128.0, 123.6, 122.1,

117.6, 116.2 (d $J_{C\text{-}F}$ = 21.7 Hz), 107.0, 72.5, 50.1; **HRMS (ESI)** m/z calcd for $C_{26}H_{19}BrFN_2O_2$ $[M+H]^+$: 489.0614; found: 489.0601.

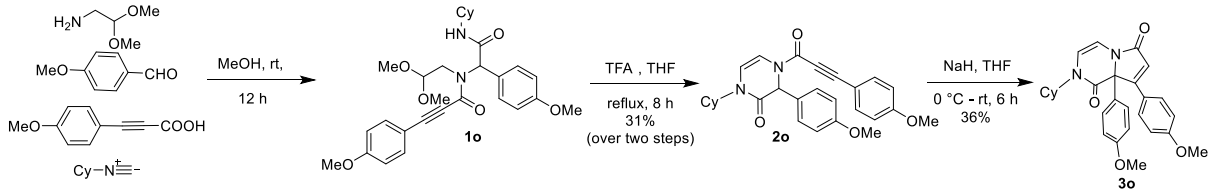
2-Cyclohexyl-8-phenyl-8a-(thiophen-3-yl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3n):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 2-thiophenecarboxaldehyde (0.045 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2n** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid, (146.0 mg, 78%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p:** 120-123 °C; **^{1}H NMR (400 MHz, $CDCl_3$):**δ 7.60 – 7.56 (m, 4H), 7.49 – 7.44 (m, 2H), 7.41 – 7.36 (m, 4H), 7.27 – 7.25 (m, 1H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 2H), 6.94 (ddd, *J* = 6.8, 5.1, 3.6 Hz, 2H), 6.72 (dd, *J* = 6.3, 1.4 Hz, 1H), 6.67 (dd, *J* = 6.1, 1.3 Hz, 1H), 6.43 (s, 1H), 6.36 (s, 1H), 5.95 (d, *J* = 6.3 Hz, 1H), 5.89 (d, *J* = 6.2 Hz, 1H), 4.50 – 4.42 (m, 2H), 1.87 – 1.69 (m, 12H), 1.43 (dd, *J* = 10.7, 7.1 Hz, 6H), 1.20 – 1.11 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.1, 162.0, 151.8, 151.7, 138.1, 137.3, 132.9, 132.7, 130.9, 130.8, 128.7, 128.7, 126.9, 126.8, 126.7, 126.3, 126.1, 126.0, 119.7, 119.6, 111.8, 110.9, 108.6, 107.1, 93.0, 92.9, 80.6, 80.4, 59.1, 54.4, 52.9, 52.7, 31.5, 31.4, 30.6, 30.5, 25.8, 25.7, 25.6, 25.4, 25.3; **HRMS (ESI)** m/z calcd for $C_{23}H_{23}N_2O_2S[M+H]^+$: 391.1480; found: 391.1476.

Using **2n** (50.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3n** as a yellow solid (35.0 mg, 70%); **m.p:** 246-248 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.43 – 7.24 (m, 6H), 7.08 – 6.87 (m, 2H), 6.58 (s, 1H), 6.44 (d, J = 5.3 Hz, 1H), 5.99 (d, J = 5.3 Hz, 1H), 4.50 (t, J = 11.5 Hz, 1H), 1.93 – 1.65 (m, 6H), 1.39 (dd, J = 17.8, 5.9 Hz, 3H), 1.13 (d, J = 11.2 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.1, 161.2, 160.2, 139.4, 132.0, 130.0, 128.8, 128.1, 127.2, 126.9, 121.6, 113.6, 106.3, 77.5, 77.1, 76.7, 69.4, 53.1, 31.6, 30.95, 25.80, 25.74, 25.4; **HRMS (ESI)** m/z calcd for $C_{23}H_{23}N_2O_2S$ $[M+H]^+$: 391.1480; found: 391.1454.

2-Cyclohexyl-8,8a-bis(4-methoxyphenyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3o):

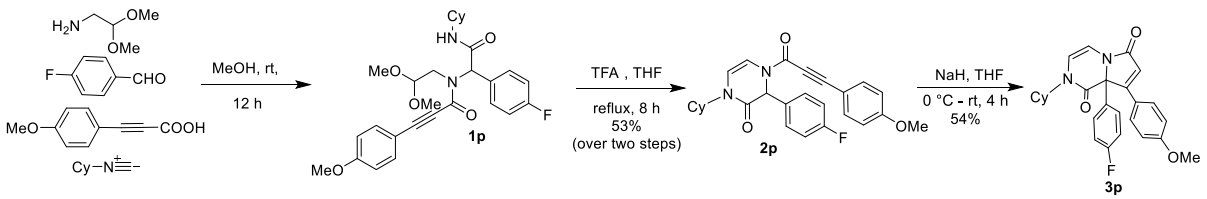


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.051 mL, 0.475 mmol), 4-methoxy benzaldehyde (0.048 mL, 0.475 mmol), 3-(4-Methoxyphenyl) propiolic acid (84.0 mg, 0.475 mmol),and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2o** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow oil, (65.0 mg, 31%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54 – 7.49 (m, 2H), 7.47 – 7.42 (m, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 6.90 (s, 1H), 6.88 (d, J = 3.1 Hz, 2H), 6.87 – 6.85 (m, 2H), 6.85 – 6.84 (m, 2H), 6.82 (d, J = 3.3 Hz, 1H), 6.81 (dd, J = 6.2, 1.2 Hz, 1H), 6.72 (dd, J = 6.1, 1.1 Hz, 1H), 6.16 (s, 1H), 6.10 (s, 1H), 5.83 (dd,J = 13.3, 6.2

Hz, 2H), 4.52 – 4.36 (m, 2H), 3.83 (d, *J* = 5.5 Hz, 6H), 3.77 (d, *J* = 4.1 Hz, 6H), 1.84 (d, *J* = 11.0 Hz, 6H), 1.76 – 1.66 (m, 5H), 1.41 (dt, *J* = 7.9, 4.2 Hz, 9H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 163.3, 163.2, 161.7, 161.6, 159.9, 159.8, 152.7, 152.2, 134.8, 134.6, 128.5, 128.5, 128.3, 127.5,114.5, 114.4, 114.3,114.1, 111.8, 111.6, 111.4, 110.4, 109.3, 107.8, 93.6, 93.5, 80.4, 80.1, 62.4, 58.0,55.5, 55.4, 52.7, 52.5, 31.7, 31.6, 31.5, 30.9, 30.6, 29.8, 29.7, 25.7, 25.6, 25.5, 25.4; **HRMS (ESI)** m/z calcd for $C_{27}H_{29}N_2O_4$ $[M+H]^+$: 445.2127; found: 445.2115.

Using **2o** (57.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3o** as a yellow oil (20.0 mg, 36%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.38 – 7.32 (m, 2H), 7.17 – 7.11 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.52 (s, 1H), 6.41 (d, *J* = 5.5 Hz, 1H), 5.91 (d, *J* = 5.5 Hz, 1H), 4.61 – 4.49 (m, 1H), 3.77 (d, *J* = 5.3 Hz, 6H), 1.86 (d, *J* = 7.4 Hz, 2H), 1.77 – 1.67 (m, 3H), 1.50 – 1.44 (m, 2H), 1.37 – 1.31 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.8, 162.4, 161.1, 160.6, 160.1, 130.6, 127.4, 126.8, 124.6, 119.0, 114.4, 113.8, 113.6, 106.7, 72.2, 55.4, 53.5, 31.8, 31.0, 29.8, 25.9, 25.8, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 764, 1068, 1406, 1675, 2922, 3412, 3740, 3840; **HRMS (ESI)** m/z calcd for $C_{27}H_{29}N_2O_4$ $[M+H]^+$: 445.2127; found: 445.2125.

2-Cyclohexyl-8a-(4-fluorophenyl)-8-(4-methoxyphenyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3p):



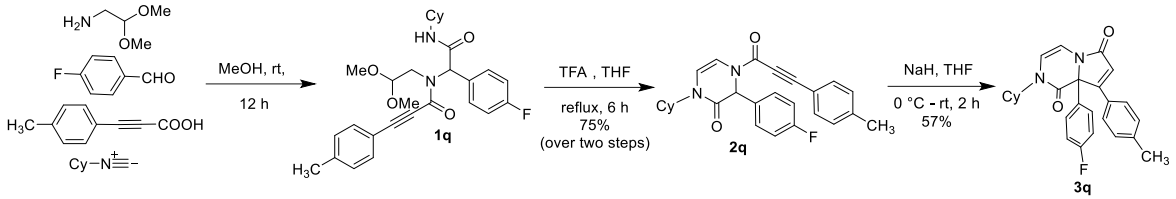
According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), 3-(4-Methoxyphenyl) propiolic acid

(84.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL) refluxed up to 8 h, compound **2p** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid (109.0 mg, 53%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p:** 125-127 °C; **^{1}H NMR (300 MHz,$CDCl_3$):** δ 7.53 (d, J = 8.7 Hz, 2H), 7.44 – 7.32 (m, 6H), 7.02 (d, J = 9.6 Hz, 4H), 6.91 – 6.81 (m, 5H), 6.75 (d, J = 5.8 Hz, 1H), 6.18 (s, 1H), 6.13 (s, 1H), 5.84 (t, J = 6.8 Hz, 2H), 4.45 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 1.84 (s, 6H), 1.70 (s, 4H), 1.40 (m, J = 8.4 Hz, 8H), 1.15 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.5-161.2 (d, $J_{C\text{-}F}$ = 245.2 Hz), 162.9, 162.8, 161.8, 161.7, 152.6, 152.2, 134.7, 134.6, 132.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 132.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 128.8 (d, $J_{C\text{-}F}$ = 8.25 Hz), 128.0 (d, $J_{C\text{-}F}$ = 8.25 Hz), 116.0 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.8 (d, $J_{C\text{-}F}$ = 21.75 Hz), 114.5,111.6,111.3, 110.3, 109.2, 107.7, 93.8, 93.8, 80.2, 80.0, 62.3, 57.9, 55.5, 52.8, 52.6, 31.6, 31.4, 30.8, 30.6, 25.7, 25.6, 25.5, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_3$ $[M+H]^+$: 433.1927 ; found: 433.1924.

Using **2p** (56.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3p** as a yellow oil, (30.0 mg, 54%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.37 – 7.32 (m, 2H), 7.21 (ddd, J = 8.1, 5.1, 2.6 Hz, 2H), 7.06 – 6.96 (m, 2H), 6.82 – 6.72 (m, 2H), 6.50 (s, 1H), 6.41 (d, J = 5.5 Hz, 1H), 5.90 (d, J = 5.5 Hz, 1H), 4.59 – 4.48 (m, 1H), 3.77 (s, 3H), 1.93 – 1.66 (m, 6H), 1.54 – 1.43 (m, 3H), 1.35 (d, J = 5.1 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.4, 161.2 (d, $J_{C\text{-}F}$ = 138.0 Hz), 161.1, 131.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.6, 128.0 (d $J_{C\text{-}F}$ = 8.2 Hz), 124.4, 119.5, 116.2 (d $J_{C\text{-}F}$ = 21.7 Hz), 113.7, 113.6, 106.8, 71.9, 55.4, 53.6, 31.8,

31.0, 25.9, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_3$ $[M+H]^+$: 433.1927 ; found: 433.1918.

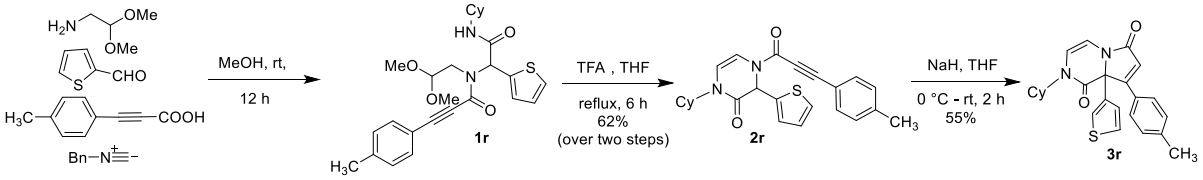
2-Cyclohexyl-8a-(4-fluorophenyl)-8-(p-tolyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3q):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), 4-methyl phenylpropiolic acid (76.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2q** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (150.0 mg, 75%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.47 (d, J = 8.0 Hz, 2H), 7.42 – 7.30 (m, 6H), 7.18 (t, J = 8.4 Hz, 4H), 7.01 (q, J = 8.7 Hz, 4H), 6.83 (d, J = 5.1 Hz, 1H), 6.75 (d, J= 5.1 Hz, 1H), 6.18 (s, 1H), 6.13 (s, 1H), 5.85 (dd, J = 8.1, 6.3 Hz, 2H), 4.52 – 4.36 (m, 2H), 2.38 (d, J = 5.1 Hz, 6H), 1.85 (d, J = 7.5 Hz, 6H), 1.75 – 1.59 (m, 6H), 1.40 (dd, J = 16.0, 7.8 Hz, 7H), 1.16–1.10 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 163.1 (d, $J_{C\text{-}F}$ = 246.0 Hz), 163.0 (d, $J_{C\text{-}F}$ = 245.0 Hz), 162.9, 162.8, 152.5, 152.1, 141.7, 141.5, 132.8, 132.7, 132.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 132.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.6, 128.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 128.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 116.7, 116.5, 116.0 (d, $J_{C\text{-}F}$ = 22.0 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22.0 Hz), 111.4, 110.4, 109.1, 107.6, 93.6, 93.5, 80.4, 80.1, 62.3, 58.0, 52.8, 52.6, 31.6, 31.4, 30.8, 30.6, 25.7, 25.6, 25.6, 25.4, 25.3, 21.8; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_2$ $[M+H]^+$: 417.1978; found: 417.1969.

Using **2q** (53.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol), THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3q** as a yellow liquid, (30.0 mg, 57%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ7.24 – 7.19 (m, 4H), 7.07 – 6.98 (m, 4H), 6.53 (s, 1H), 6.42 (d, J = 5.5 Hz, 1H), 5.90 (d, J = 5.5 Hz, 1H), 4.51 (t, J = 9.9 Hz, 1H), 2.30 (s, 3H), 1.91 – 1.71 (m, 5H), 1.62 (d, J = 29.7 Hz, 3H), 1.38 (d, J = 11.0 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.3, 163.0 (d, $J_{C\text{-}F}$ = 248.0 Hz), 162.1, 160.8, 140.4, 131.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.3, 128.9, 128.7, 128.1 (d $J_{C\text{-}F}$ = 9 Hz), 121.0, 116.2 (d $J_{C\text{-}F}$ = 22 Hz), 113.7, 106.7, 72.0, 53.6, 31.7, 31.0, 25.9, 25.8, 25.4, 21.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_2$ $[M+H]^+$: 417.1978; found: 417.1969.

2-Cyclohexyl-8a-(thiophen-3-yl)-8-(p-tolyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3r):

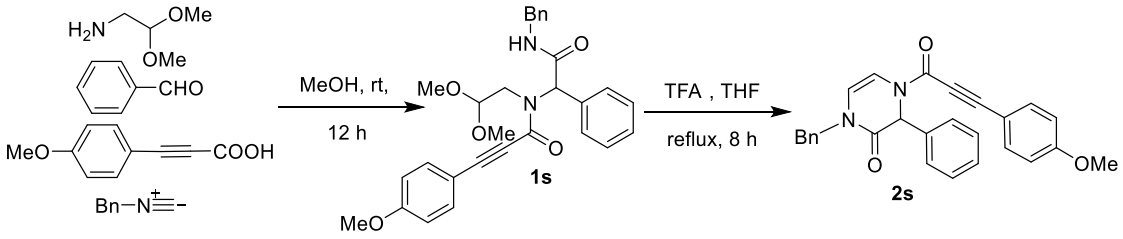


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 2-thiophenecarboxaldehyde (0.045 mL, 0.475 mmol), 4-methoxy phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.060 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol)in THF (6.0 mL),compound **2r** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid, (125.0 mg, 62%). Two rotamers were present on NMR time-scale (R^1: R^2 = 1 : 1); **m.p:** 175-177 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 – 7.47 (m, 4H), 7.36 (d, J = 1.8 Hz, 1H), 7.34 (t, J = 2.2 Hz, 2H), 7.31 (d, J = 2.2 Hz, 2H), 7.30 – 7.27 (m, 3H), 7.25 – 7.21 (m, 3H), 7.07 (ddd, J = 3.4, 2.3, 1.1 Hz, 2H), 6.95 (ddd,J = 8.6, 5.1, 3.6 Hz,

2H), 6.91 – 6.86 (m, 4H), 6.74 (dd, *J* = 6.1, 1.5 Hz, 1H), 6.68 (dd, *J* = 6.0, 1.4 Hz, 1H), 6.50 (s, 1H), 6.44 (s, 1H), 5.79 (d, *J* = 6.1 Hz, 1H), 5.74 (d, *J* = 6.0 Hz, 1H), 4.87 (d, *J* = 4.1 Hz, 1H), 4.83 (d, *J* = 4.2 Hz, 1H), 4.72 (dd, *J* = 14.8, 9.5 Hz, 2H), 3.84 (d, *J* = 4.6 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 162.7, 162.7, 161.8, 161.7, 152.3, 152.1, 138.1, 137.3, 135.8, 135.6,134.91, 134.7, 129.0, 128.4, 128.3, 128.2, 127.1, 126.9, 126.7, 126.4, 126.1, 114.7, 114.6, 114.5, 113.7, 111.5,111.4, 109.3, 107.7, 94.1, 94.0, 80.1, 79.8, 59.2, 55.6, 55.5, 54.6, 49.6, 49.4; **HRMS (ESI)** m/z calcd for $C_{25}H_{21}N_2O_3S$ $[M+H]^+$: 429.1273; found: 429.1266.

Using **2r** (55.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3r** as a yellow solid (30.0 mg, 55%); **m.p:**102-104 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 7.5 – 7.5 (m, 2H), 7.4 – 7.3 (m, 3H), 7.3 – 7.3 (m, 3H), 6.9 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.9 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.8 – 6.8 (m, 2H), 6.6 (s, 1H), 6.4 (d, *J* = 5.4 Hz, 1H), 5.9 (d, *J* = 5.4 Hz, 1H), 4.9 (d, *J* = 14.6 Hz, 1H), 4.7 (d, *J* = 14.6 Hz, 1H), 3.8 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** *δ* 168.8, 161.7, 161.5, 159.9, 139.4, 135.7, 131.0, 129.0, 128.6, 128.3, 127.3, 127.3, 126.8, 123.9, 118.8, 117.1, 113.7, 106.6, 69.5, 55.4, 50.4; **HRMS (ESI)** m/z calcd for $C_{25}H_{21}N_2O_3S$ $[M+H]^+$: 429.1273; found: 429.1271.

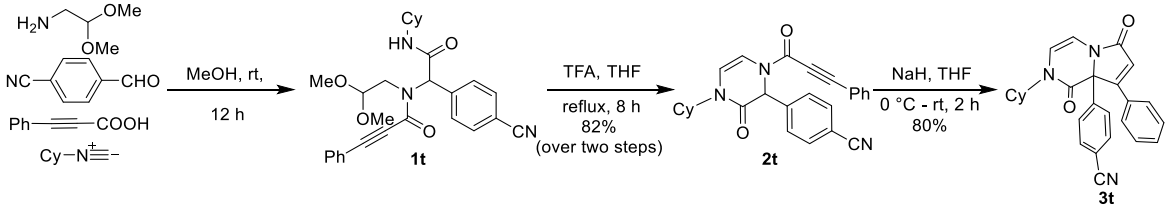
1-Benzyl-4-(3-(4-methoxyphenyl)propioloyl)-3-phenyl-3,4-dihydropyrazin-2(1H)-one (2s):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),benzaldehyde (0.048 mL, 0.475 mmol), 4-methoxy phenylpropiolic acid (70 mg, 0.475

mmol), and benzyl isocyanide (0.060 mL, 0.475 mmol),in methanol (4 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2s** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil (65 mg, 33%).Two rotamers were present on NMR timescale (R^1: R^2 = 1 : 1); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 – 7.49 (m, 2H), 7.46 – 7.41 (m, 4H), 7.40 – 7.35 (m, 6H), 7.32 (dd, *J* = 5.1, 2.8 Hz, 5H), 7.28 (s, 2H), 7.24 – 7.21 (m, 2H), 7.15 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.90 – 6.84 (m, 6H), 6.78 (dd, *J* = 6.0, 1.3 Hz, 1H), 6.29 (s, 1H), 6.25 (s, 1H), 5.71 (d, *J*= 6.2 Hz, 1H), 5.68 (d, *J* = 6.1 Hz, 1H), 4.77 (s, 2H), 4.73 (d, *J* = 2.9 Hz,2H), 3.83 (s, 3H), 3.82 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 163.6, 163.5, 161.7, 161.7, 152.8, 152.2, 136.0, 136.1, 135.8, 135.7, 134.7, 134.6, 129.0, 128.99, 128.97, 128.90, 128.86, 128.6, 128.2, 128.1, 128.1, 127.9, 126.8, 126.2, 114.6, 114.5, 114.4, 113.6, 111.6, 111.4, 109.8, 108.16, 93.8, 80.2, 79.9, 62.9, 58.6, 55.5, 49.5, 49.4; **HRMS (ESI)** m/z calcd for $C_{27}H_{23}N_2O_3$ $[M+H]^+$: 423.1709; found: 429.423.1701.

4-(2-Cyclohexyl-1,6-dioxo-8-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3t):

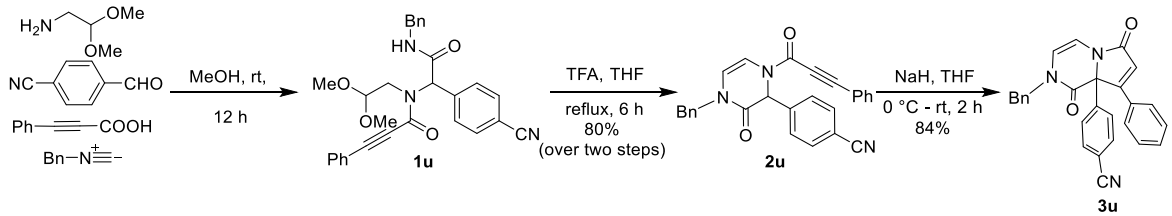


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-cyano benzaldehyde (63.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2t** was prepared and purified by silica gel column chromatography (15%

ethyl acetate/hexane) as a grey solid, (160.0 mg, 82%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.7); **m.p:** 191-193 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 – 7.58 (m, 6H), 7.56 – 7.33 (m, 11H), 6.87 (dd, *J* = 6.3, 1.3 Hz, 0.7H), 6.81 (dd, *J* = 6.2, 1.1 Hz, 1H), 6.22 (s, 1H), 6.21 (s, 0.7H), 5.87 (d, *J* = 6.4 Hz, 0.7H), 5.84 (d, *J* = 6.3 Hz, 1H), 4.41 (dt, *J* = 13.4, 11.2 Hz,2H), 1.72 (ddd, *J*= 46.8, 33.4, 14.7 Hz, 11H), 1.41 (dq, *J* = 19.5, 9.6 Hz, 8H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.8, 161.7, 152.2, 151.9, 141.16, 141.0, 132.8, 132.7, 132.7, 132.6, 131.1, 131.0, 128.8, 127.6,126.9, 119.5, 119.2, 118.5, 118.3, 112.8, 112.5, 111.45, 110.5, 109.0, 107.5, 93.5, 80.1, 62.6, 58.4, 53.1, 52.8, 31.4, 31.3, 30.7, 30.5, 25.6, 25.5, 25.3, 25.2; **HRMS (ESI)** m/z calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$: 410.1869; found: 410.1861.

Using **2t** (52.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3t** as a yellow solid, (42.0 mg, 80%); **m.p**: 164-166 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.29 – 7.23 (m, 4H), 6.59 (s, 1H), 6.46 (d, *J* = 5.5 Hz, 1H), 5.91 (d, *J* = 5.6 Hz, 1H), 4.58 – 4.46 (m, 1H), 1.91 – 1.69 (m, 5H), 1.45 (ddd, *J* = 33.2, 18.6, 7.3 Hz, 4H), 1.13 (dd, *J* = 17.1, 8.1 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.9, 161.4, 160.3, 140.7, 132.9, 131.8, 130.2, 128.8, 128.3, 127.0, 122.7, 118.1, 113.9, 113.4, 106.7, 72.3, 53.8, 31.7, 31.0, 25.8, 25.8, 25.3; **HRMS (ESI)** m/z calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$: 410.1869; found: 410.1862.

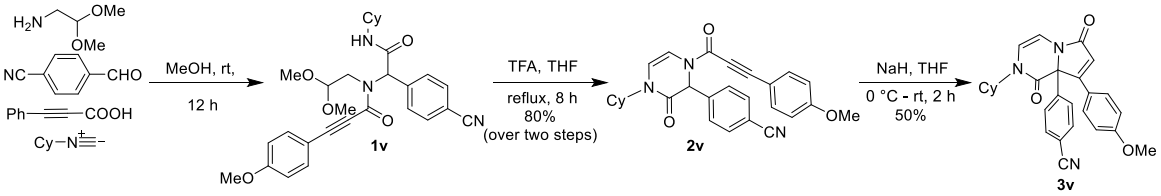
4-(2-Benzyl-1,6-dioxo-8-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3u):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-cyanobenzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0mL), compound **2u** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid, (180.0 mg, 80%). Two rotamers were present on NMR timescale (R^1: R^2 = 1 : 1); **m.p**: 108-110 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 – 7.62 (m, 4H), 7.59 – 7.54 (m, 4H), 7.53 – 7.28 (m, 17H), 7.21 (dd, *J* = 7.2, 2.2 Hz, 2H), 7.14 (dd,*J* = 6.7, 2.8 Hz, 1H), 6.89 (dd, *J* = 6.2, 1.4 Hz, 1H), 6.81 (dd, *J* = 6.1, 1.3 Hz, 1H), 6.29 (s, 2H), 5.73 (dd, *J* = 11.6, 6.2 Hz, 2H), 4.81 – 4.66 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.3, 162.2, 152.2, 151.9, 140.9, 140.7, 135.6, 135.3, 132.8, 132.7, 132.7, 131.1, 131.0, 129.0, 128.8, 128.3, 128.3, 128.1, 127.9, 127.6, 126.9, 119.4, 119.1, 118.4, 118.2, 114.7, 113.6, 112.9, 112.6, 109.3, 107.7, 93.7, 93.5, 80.2, 80.0, 62.5, 58.5, 49.7, 49.6; **HRMS (ESI)** m/z calcd for $C_{27}H_{20}N_3O_2$ $[M+H]^+$ 418.1556; found: 418.1551.

Using **2u** (50.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (25% ethyl acetate/hexane) to yield **3u** as a yellow solid, (45.0 mg, 84%); **m.p**: 213-215 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.30 (ddd, *J* = 14.8, 11.0, 5.6 Hz, 12H), 6.58 (s, 1H), 6.45 (d, *J* = 5.4 Hz, 1H), 5.87 (d, *J* = 5.4 Hz, 1H), 4.93 (d, *J* = 14.7 Hz, 1H), 4.68 (d, *J* = 14.7 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.8, 161.7, 160.3, 140.4, 135.5, 132.8, 131.5, 130.3, 129.1, 128.9, 128.5, 128.4, 127.0, 122.7, 118.0, 117.4, 113.4, 106.8, 72.4, 50.4; **HRMS (ESI)** m/z calcd for $C_{27}H_{20}N_3O_2$ $[M+H]^+$: 418.1556; found: 418.1534.

4-(2-Cyclohexyl-8-(4-methoxyphenyl)-1,6-dioxo-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3v):

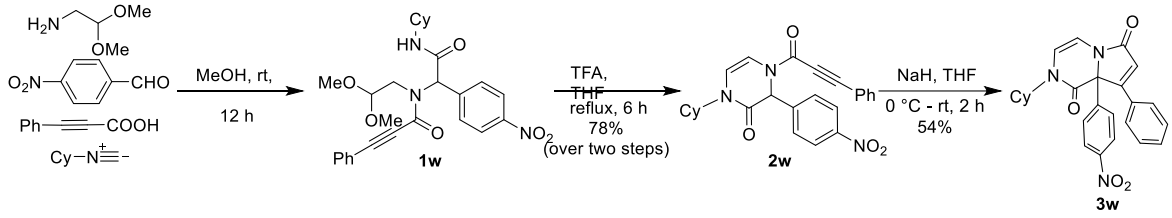


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-cyano benzaldehyde (63.0 mg, 0.475 mmol), 4-methoxy phenylpropiolic acid (84.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2v** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (170.0 mg, 80%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.75); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.64 (dd, J = 14.7, 8.5 Hz, 4H), 7.56 – 7.48 (m, 6H), 7.38 (d, J = 8.9 Hz, 2H), 6.92 – 6.85 (m, 5H), 6.80 (dd, J = 6.2, 1.2 Hz, 1H), 6.22 (s, 1H), 6.21 (s, 0.77H), 5.87 – 5.80 (m, 2H), 4.44 – 4.36 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 1.84 (d,J = 6.2 Hz, 7.50H), 1.68 (d,J = 5.5 Hz, 5H), 1.58 (s, 1H), 1.34 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.8, 161.7, 161.7, 152.4, 152.2, 141.1, 141.0, 134.6, 132.7, 132.6, 127.5, 126.8, 118.4, 118.3, 114.5, 114.0, 112.7, 112.4, 111.2, 111.1, 110.9, 110.1, 109.1, 107.6, 94.4, 94.2, 79.8, 79.6, 62.5, 58.3, 55.4, 52.9, 52.7, 31.9, 31.4, 31.2, 30.6, 30.4, 25.6, 25.5, 25.3, 25.2; **HRMS (ESI)** m/z calcd for $C_{27}H_{26}N_3O_3$ $[M+H]^+$: 440.1974; found: 440.1962.

Using **2v (**56.0 mg, 0.127 mmol), sodium hydride (10.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3v** as a yellow solid, (28.0 mg, 50%); **m.p:**92-94 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.62 (d, J = 8.4 Hz, 2H), 7.39 – 7.32 (m, 4H), 6.78 (d, J = 8.9 Hz, 2H), 6.54 (s,

1H), 6.42 (d, *J* = 5.5 Hz, 1H), 5.90 (d, *J* = 5.5 Hz, 1H), 4.54 (s, 1H), 3.77 (s, 3H), 1.93 – 1.80 (m, 3H), 1.71 (d, *J* = 12.7 Hz, 1H), 1.60 (s, 1H), 1.48 (s, 1H), 1.36 (dd, *J* = 21.0, 10.3 Hz, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.1, 161.2, 159.6, 141.1, 132.7, 130.6, 126.8, 123.7, 119.9, 117.9, 113.7, 113.4, 113.2, 106.7, 72.0, 55.3, 53.7, 31.6, 30.9, 25.7, 25.6, 25.2; **HRMS (ESI)** m/z calcd for $C_{27}H_{26}N_3O_3$ $[M+H]^+$: 440.1974 ; found: 440.1966.

2-Cyclohexyl-8a-(4-nitrophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3w):

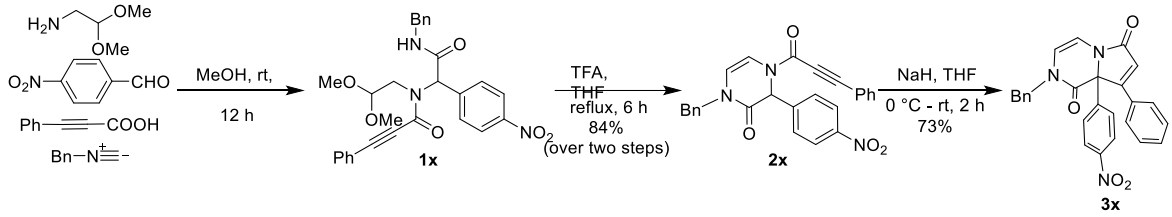


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-nitro benzaldehyde (72.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL),compound **2w** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid, (160.0 mg, 78%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.75); **m.p**: 186-188 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.25 – 8.17 (m, 4H), 7.62 – 7.55 (m, 6H), 7.50 – 7.34 (m, 7.84H), 6.91 – 6.88 (m, 0.80H), 6.85 – 6.81 (m, 1.19H), 6.27 (s, 1.09H), 6.26 (s, 0.72H), 5.88 (d, *J* = 6.4 Hz, 0.77H), 5.87 – 5.85 (m, 1.12H), 4.48 – 4.35 (m, 2H), 1.86 (d, *J* = 5.4 Hz, 6H), 1.71 (d, *J* = 17.0 Hz, 4H), 1.40 (dt, *J* = 26.8, 9.7 Hz, 9H), 1.13 (d, *J* = 9.4 Hz, 2.83H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.8, 161.7, 152.2, 152.0, 148.3, 148.1, 143.0, 142.9, 132.8, 131.1, 131.0, 128.9, 127.8, 127.2, 124.3, 124.1, 119.6, 119.2, 111.5, 110.5, 109.0, 107.6, 93.7, 93.5, 80.3, 80.1, 77.5, 77.1, 76.8, 62.6, 58.4, 53.2,

52.9,31.5, 31.4, 30.7, 30.5, 25.7, 25.6, 25.4, 25.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$: 430.1767; found: 430.1754.

Using **2w** (55.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3w** as a yellow solid (29.0 mg, 54%); **m.p**: 133-135 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.21 – 8.15 (m, 2H), 7.47 – 7.41 (m, 2H), 7.37 – 7.29 (m, 3H), 7.28 (s, 1H), 7.26 – 7.23 (m, 1H), 6.60 (s, 1H), 6.47 (d, J = 5.6 Hz, 1H), 5.92 (d, J = 5.6 Hz, 1H), 4.58 – 4.48 (m, 1H), 1.81 (dd, J = 44.9, 18.9 Hz, 5H), 1.40 (dt, J = 20.5, 7.7 Hz, 4H), 1.17 – 1.09 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.9, 161.4, 160.3, 148.4, 142.6, 131.7, 130.3, 128.8, 128.3, 127.3, 124.3, 122.8, 113.9, 106.7, 72.2, 53.8, 31.7, 31.0, 25.8, 25.7, 25.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$: 430.1767; found: 430.1764.

2-Benzyl-8a-(4-nitrophenyl)-8-phenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3x):

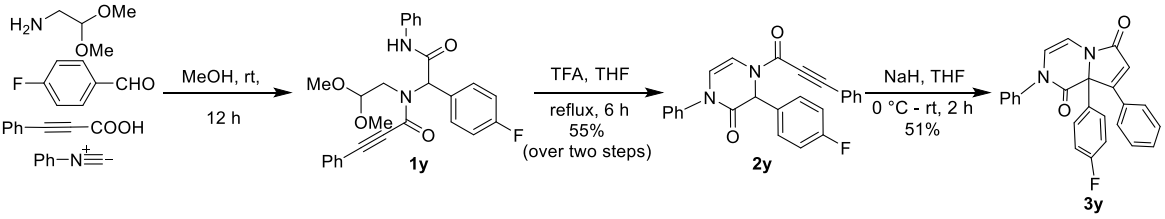


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-nitro benzaldehyde (72.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol)in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2x** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow solid, (175.0 mg, 84%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.65); **m.p**: 120-122 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.21 (dd,J = 12.3, 8.8 Hz, 3H), 7.58 (ddd, J = 10.2, 6.8, 5.6 Hz, 5H), 7.53 – 7.26 (m, 12H), 7.22 (dd, J = 7.1,

2.4 Hz, 2H), 7.15 (dd, *J* = 6.7, 2.9 Hz, 1H), 6.91 (dd, *J* = 6.2, 1.4 Hz, 0.67H), 6.83 (dd, *J* = 6.1, 1.3 Hz,1H), 6.33 (s, 1.62H), 5.75 (dd, *J* = 8.1, 6.2 Hz, 1.69H), 4.75 (dd, *J* = 11.4, 6.2 Hz, 3.55H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.3, 162.1, 152.2, 152.0, 148.1, 142.8, 142.6, 135.5, 135.3, 132.8, 131.2, 131.1, 129.1, 129.2, 128.8, 128.9, 128.4, 128.3, 128.20, 127.9, 127.8, 127.2, 124.3, 124.1, 119.4, 119.1, 114.7, 113.5, 109.3, 107.9, 93.8, 93.6, 80.2, 80.0, 62.5, 58.4, 49.8, 49.7; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 958, 1068, 1346, 1522, 1640, 1679, 2213, 3062; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}N_3O_4$ $[M+H]^+$: 438.1454; found: 438.1447.

Using **2x** (56.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **3x** as a yellow solid (41.0 mg, 73%); **m.p**: 198-201 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.15 – 8.08 (m, 2H), 7.37 – 7.33 (m, 7H), 7.32 – 7.26 (m, 4H), 7.24 (dd, *J* = 4.9, 2.7 Hz, 1H), 6.60 (s, 1H), 6.47 (d, *J* = 5.4 Hz, 1H), 5.88 (d, *J* = 5.4 Hz, 1H), 4.95 (d, *J* = 14.6 Hz, 1H), 4.69 (d, *J* = 14.6 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.8, 161.7, 160.2, 148.4, 142.3, 135.4, 131.4, 130.3, 129.1, 128.9, 128.5, 128.4, 127.3, 124.2, 122.7, 117.5, 106.8, 72.3, 50.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}N_3O_4$ $[M+H]^+$: 438.1454; found: 438.1444.

3-(4-Fluorophenyl)-1-phenyl-4-(3-phenylpropioloyl)-3,4-dihydropyrazin-2(1H)-one (3y):

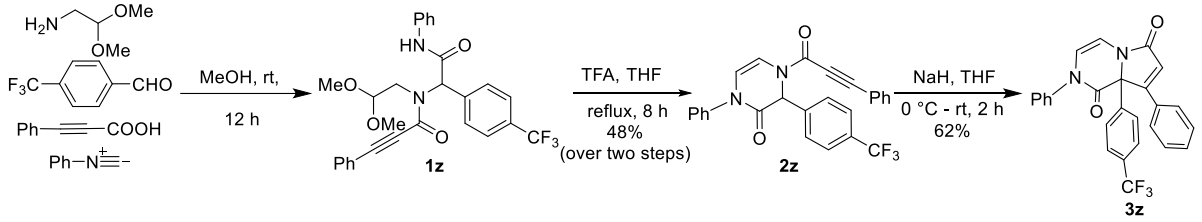


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0

mL),compound **3y** was prepared and purified and purified by silica gel column chromatography (20% ethyl acetate/hexane)as a yellow solid, (105.0 mg, 55%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **m.p**: 137-140 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.64 – 7.59 (m, 2H), 7.54 – 7.28 (m, 20H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.23 (t, *J* = 1.9 Hz, 1H), 7.15 – 7.03 (m, 4H), 6.96 (dd, *J* = 6.2, 1.5 Hz, 1H), 6.92 – 6.84 (m, 1H), 6.35 (s, 1H), 6.29 (s, 1H), 6.01 (dd,*J* = 6.1, 3.2 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.7 (d, $J_{C\text{-}F}$ = 246.7 Hz), 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz), 162.7, 162.7, 152.4, 152.0, 139.2, 139.1, 132.8, 132.8, 131.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 131.3 (d, $J_{C\text{-}F}$ = 3 Hz), 131.1, 131.0, 129.5, 129.5, 128.9, 128.8, 128.7, 128.2, 128.1, 128.0, 127.9,125.9,119.7, 119.4, 116.5, 116.2 (d, $J_{C\text{-}F}$ = 21.7 Hz), 116.0 (d, $J_{C\text{-}F}$ = 21.7 Hz), 115.6, 109.4, 107.8, 93.4, 93.2, 80.5, 80.3, 62.7, 58.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 692, 716, 976, 1364, 1417, 1508, 1638, 1689, 2213, 3013; **HRMS (ESI)** m/z calcd for $C_{25}H_{18}FN_2O_2$ $[M+H]^+$: 397.1352; found: 397.1351.

Using **2y** (51.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3y** as a yellow solid, (26.0 mg, 51%); **m.p**: 146-148 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48 – 7.29 (m, 10H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 3.8 Hz, 2H), 6.04 (d, *J* = 4.9 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.0, 161.6 (d, $J_{C\text{-}F}$ = 85.5 Hz), 161.5, 139.3, 132.0, 130.5 (d, $J_{C\text{-}F}$ = 3.75 Hz), 130.0, 129.6, 128.9, 128.3, 128.2, 128.0 (d $J_{C\text{-}F}$ = 8.2 Hz), 126.3, 122.2, 118.8, 116.4 (d $J_{C\text{-}F}$ = 21.7 Hz), 106.8, 72.7; **HRMS (ESI)** m/z calcd for $C_{25}H_{18}FN_2O_2$ $[M+H]^+$: 397.1352; found: 397.1349.

2,8-Diphenyl-8a-(4-(trifluoromethyl)phenyl)pyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3z):

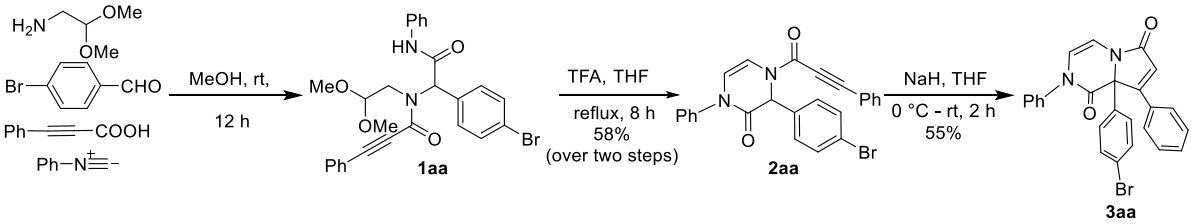


According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-trifluoromethyl benzaldehyde (0.058 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL)**,**compound **2z** was prepared and purified and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil(101.0 mg, 48%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.81); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72 – 7.60 (m,10H), 7.50 – 7.41 (m, 9H), 7.40 – 7.34 (m, 4H), 7.33 – 7.27 (m, 3H), 7.23 (d, J = 0.5 Hz, 1H), 7.00 (dd, J = 6.2, 1.5 Hz, 0.87H), 6.93 (dd, J = 6.0, 1.4 Hz, 1H), 6.42 (s, 1H), 6.38 (s, 0.81H), 6.01 (dd, J = 6.1, 2.8 Hz, 1.84H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.2, 162.1, 152.4, 152.1, 139.4, 139.2, 139.1, 139.0, 132.9, 132.8, 131.1, 131.0, 129.6, 129.5, 128.9, 128.8, 128.3, 128.1, 127.2, 126.6, 126.3 (q, J_{C-F} = 11.0, 4.0 Hz), 126.1 (q, J_{C-F} = 11.0, 4.0 Hz), 126.0, 125.9, 125.9, 119.6, 119.3, 116.6, 115.6, 109.4, 107.9, 93.7, 93.6, 80.3, 80.2, 63.0, 58.8; **^{19}F NMR (377 MHz, $CDCl_3$):** δ -62.76; **HRMS (ESI)** m/z calcd for $C_{26}H_{18}F_3N_2O_2$ $[M+H]^+$: 447.1320 ; found: 447.1314.

Using **2z** (57.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3z** as a yellow solid (35.0 mg, 62%); **m.p**: 154-158 °C;**^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66 (d, J = 8.4 Hz, 2H), 7.54 – 7.43 (m, 4H), 7.39 – 7.27 (m, 7H), 7.22 (dd, J= 6.8, 1.7 Hz, 1H), 6.61 (s, 1H), 6.58 (d, J = 5.4 Hz, 1H), 6.03 (d, J = 5.4 Hz, 1H); **^{13}C NMR (125**

MHz, $CDCl_3$): δ 168.9, 161.8, 160.7, 139.2, 139.1, 131.8, 131.7, 131.6, 130.1, 129.6, 129.0, 128.4, 128.3, 126.6, 126.3 (dd, $J_{C\text{-}F}$ = 11.2, 3.7 Hz), 126.2, 122.6, 118.8, 106.8, 72.8; **^{19}F NMR (283 MHz, $CDCl_3$):** δ -62.8; **HRMS (ESI)** m/z calcd for $C_{26}H_{18}F_3N_2O_2$ $[M+H]^+$: 447.1320; found: 447.1316.

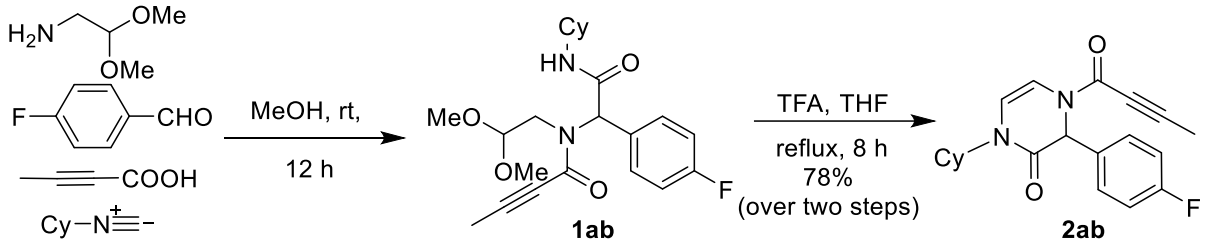
8a-(4-Bromophenyl)-2,8-diphenylpyrrolo[1,2-a]pyrazine-1,6(2H,8aH)-dione (3aa):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-bromo benzaldehyde (88.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.727 mL, 9.51 mmol) in THF (6.0 mL), compound **2aa** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a brown oil, (127.0 mg, 58%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.88); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.64 – 7.59 (m, 2H), 7.57 – 7.45 (m, 8H), 7.44 – 7.37 (m, 10H), 7.36 – 7.27 (m, 6H), 7.26 – 7.21 (m, 2H), 6.96 (dd, J = 6.2, 1.5 Hz, 1H), 6.89 (dd, J = 6.0, 1.4 Hz, 1H), 6.32 (s, 1H), 6.27 (s, 1H), 5.99 (dd, J = 6.1, 2.9 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.4, 162.4, 152.4, 152.0, 139.1, 139.1, 134.5, 134.4, 132.9, 132.8, 132.4, 132.2, 131.1, 131.0, 129.5, 129.5, 128.9, 128.8, 128.5, 128.2, 128.1, 127.8, 125.9, 123.3,123.0,119.7, 119.4, 116.5, 115.6, 109.4, 107.85, 93.5, 93.3, 80.4, 80.3, 62.8, 58.5; **HRMS (ESI)** m/z calcd for $C_{25}H_{18}BrN_2O_2$ $[M+H]^+$: 457.0552 ; found: 457.0540.

Using **2aa** (58.0 mg, 0.127 mmol), sodium hydride (9.0 mg, 0.381 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **3aa** as a yellow solid (32.0 mg, 55%); **m.p:** 77-79 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.55 – 7.52 (m, 2H), 7.46 – 7.42 (m, 2H), 7.35 – 7.34 (m, 1H), 7.34 – 7.31 (m, 3H), 7.30 (s, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.21 (m, 3H), 6.57 (s, 1H), 6.56 (d, J = 5.4 Hz, 1H), 6.03 (d, J = 5.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 168.9, 162.0, 160.8, 139.2, 134.0, 132.5, 131.8, 130.0, 129.6, 128.9, 128.3, 128.2, 127.8, 126.3, 123.6, 122.3, 118.8, 106.7, 72.7; **HRMS (ESI)** m/z calcd for $C_{25}H_{18}BrN_2O_2$ $[M+H]^+$: 457.0552; found: 457.0546.

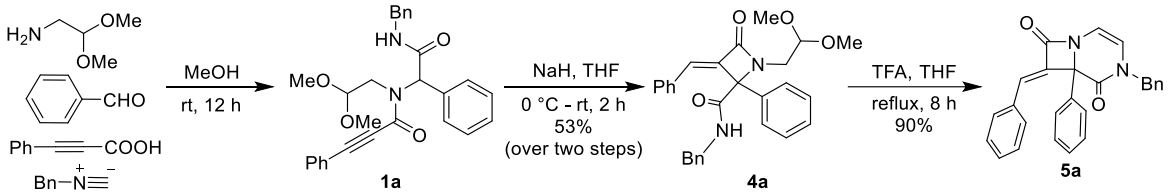
4-(but-2-ynoyl)-1-cyclohexyl-3-(4-fluorophenyl)-3,4-dihydropyrazin-2(1H)-one (2ab):



According to general procedure A using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.052 mL, 0.475 mmol), 2-butynoic acid (40.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.060 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC followed by the second step with trifluoroacetic acid (0.830 mL, 9.51 mmol) in THF (6.0 mL), compound **2ab** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (180 mg, 78%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.35 – 7.27 (m, 4H), 7.08 – 6.95 (m, 4H), 6.74 (dd, J = 6.3, 1.5 Hz, 1H), 6.65 (dd, J = 6.2, 1.3 Hz, 1H), 6.11 (s, 1H), 6.05 (s, 1H), 5.81 (d, J = 6.3 Hz, 1H), 5.78 (d, J = 6.2 Hz, 1H), 4.42 (dd, J = 11.4, 3.5 Hz, 2H), 2.06 (s, 3H), 2.00 (s, 3H), 1.87 – 1.65 (m, 9H), 1.39 (dd, J = 22.7, 13.5 Hz, 9H), 1.04 – 1.21 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4 (d, J = 246 Hz), 164.3, 161.2 (d, J = 246 Hz), 152.3, 151.9, 131.92 (d, J = 3

Hz), 131.8 (d, *J* = 3.0 Hz), 128.6 (d, *J* = 8.25 Hz), 127.9 (d, *J* = 8.25 Hz), 115.8 (d, *J* = 13.5 Hz), 115.6 (d, *J* = 13.5 Hz), 111.5, 110.1, 109.2, 107.5, 77.4, 72.4, 72.3, 62.0, 57.7, 52.7, 52.4, 31.4, 31.3, 30.6, 30.5, 29.7, 25.6, 25.5, 25.3, 25.2, 4.2, 4.1; **HRMS (ESI)** m/z calcd for $C_{20}H_{22}FN_2O_2$ $[M+H]^+$: 341.1665; found: 341.1647.

(E)-4-Benzyl-7-benzylidene-6-phenyl-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5a):

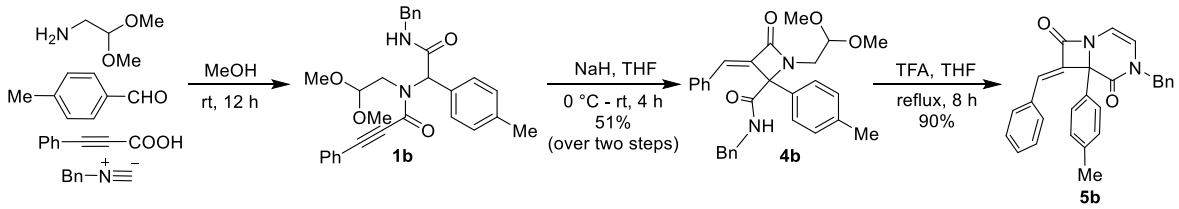


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.048 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL,0.475 mmol) in methanol (4.0 mL) to perform Ugi-4CC, product **1a** was obtained; followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4a** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid (115.0 mg, 53%); **m.p:** 121-125 °C; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 8.28 (t, *J* = 5.1 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.40 – 7.35 (m, 5H), 7.29 (dt, *J* = 2.6, 1.6 Hz, 4H), 7.27 – 7.21 (m, 5H), 4.64 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.54 – 4.48 (m, 2H), 3.43 (dd, *J* = 14.6, 4.6 Hz, 1H), 3.25 (s, 3H), 3.14 (s, 3H), 2.70 (dd, *J* = 14.6, 6.3 Hz, 1H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 168.8, 167.2, 138.3, 138.0, 133.9, 131.7, 131.7, 130.3, 129.2, 129.2, 128.7, 128.6, 128.4, 128.1, 127.7, 127.6, 101.4, 76.4, 55.4, 53.7, 44.1, 43.2; **HRMS (ESI)** m/z calcd for $C_{28}H_{29}N_2O_4$ $[M+H]^+$ 457.2127; found: 457.2128.

Using **4a** (50.0 mg, 0.109 mmol) and trifluoroacetic acid (0.14 mL, 2.19 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15 % ethyl acetate/hexane) to yield **5a** as a yellow solid (39.0 mg, 90%); **m.p:** 151-153 °C; **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 7.68 (dd, J = 8.0, 1.4 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.31 (m, 6H), 7.31 – 7.26 (m, 4H), 7.23 (d, J = 6.7 Hz, 2H), 6.20 (d, J = 5.2 Hz, 1H), 5.93 (d, J = 5.2 Hz, 1H), 5.02 (d, J = 14.8 Hz, 1H), 4.77 (d, J = 14.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.6, 163.6, 139.8, 135.9, 135.1, 131.4, 131.3, 130.5, 129.6, 129.4, 129.1, 129.0, 128.4, 128.3, 128.2, 126.7, 120.7, 106.9, 68.3, 50.2; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1062, 1386, 1664, 2921, 3402; **HRMS (ESI)** m/z calcd for $C_{26}H_{21}N_2O_2[M+H]^+$ 393.1603; found: 393.1593.

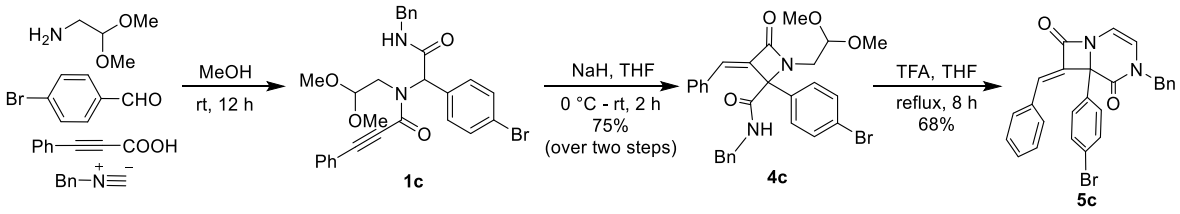
(E)-4-Benzyl-7-benzylidene-6-(p-tolyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5b):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.051 mL, 0.475 mmol), *p*-tolualdehyde (0.056 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC,product **1b** was obtained, followed by the second step with sodium hydride (34.0 mg, 1.43 mmol), in THF (6.0mL), compound **4b** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid (113.0 mg, 51%); **m.p**: 115-117 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.25 (t,J = 5.2 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.31 – 7.25 (m, 10H), 7.20-7.25 (t,J = 9Hz,3H) , 4.64 (dd,J = 6.3, 4.6 Hz, 1H), 4.53 – 4.48 (m, 2H), 3.45 – 3.37 (m, 1H), 3.25 (s, 3H), 3.14 (s, 3H), 2.69 (dd,J = 14.6, 6.4 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.9, 167.4, 139.2, 138.4, 138.1, 131.8, 131.7, 130.8, 130.3, 129.9, 128.7, 128.6, 128.3, 128.2, 127.6, 127.5, 101.4, 76.3, 55.4, 53.6, 44.1, 43.2, 29.8, 21.3; **HRMS (ESI)** m/z calcd for $C_{29}H_{31}N_2O_4[M+H]^+$ 471.2284; found: 471.2267.

Using **4b** (51.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.19 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford **5b** as a yellow solid; (40.0 mg, 90%); **m.p**: 220-222 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.69 (dd, J = 7.6, 1.8 Hz, 2H), 7.40 – 7.27 (m, 8H), 7.26 – 7.20 (m, 3H), 7.13 (d, J = 8.1 Hz, 2H), 6.18 (d, J = 5.2 Hz, 1H), 5.92 (d, J = 5.2 Hz, 1H), 5.01 (d, J = 14.8 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 2.31 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.7, 163.9, 140.0, 139.5, 136.1, 132.1, 131.6, 131.5, 130.5, 129.8, 129.5, 129.1, 128.5, 128.3, 128.2, 126.8, 120.7, 106.9, 68.3, 50.3, 21.4; **HRMS (ESI)** m/z calcd for $C_{27}H_{23}N_2O_2$ $[M+H]^+$ 407.1760; found: 407.1747.

(E)-4-Benzyl-7-benzylidene-6-(4-bromophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5c):

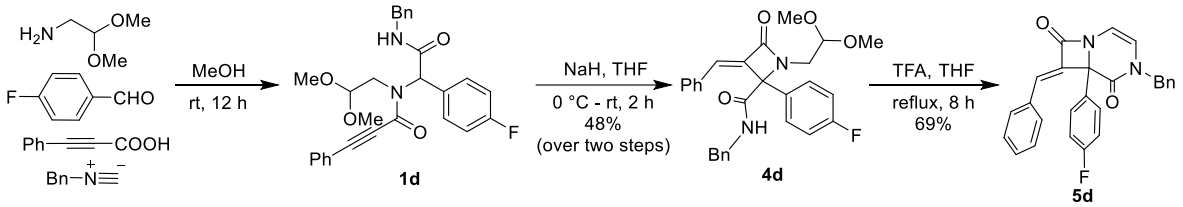


According to general procedure B using aminoacetaldehyde dimethyl acetal(0.052 mL, 0.475 mmol), 4-bromo benzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL,0.475 mmol), was dissolved in methanol (4.0 mL) to perform Ugi-4CC,product **1c** was obtained, followed by the second step with sodium hydride (33.0mg, 1.43 mmol) in THF (6.0 mL),compound **4c** was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) as a transparent oil (190.0 mg, 75%);Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.5); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.27 (t, J = 5.3 Hz, 1H), 7.63 (dd, J = 7.6, 1.9 Hz, 2H), 7.56 – 7.45 (m, 3H), 7.38 – 7.19 (m,

15H), 4.63 (dd,*J* = 6.0, 4.4 Hz, 1H), 4.54 – 4.51 (m, 0.5H), 4.49 (d, *J* = 5.6 Hz, 1.6H), 3.90 (dd, *J* = 15.0, 3.3 Hz, 0.4H), 3.46 (dd, *J* = 14.6, 4.4 Hz, 1H), 3.39 (s, 1H), 3.37 (s, 1H), 3.26 (s, 3H), 3.16 (s, 3H), 2.82 (dd, *J* = 15.0, 6.6 Hz, 0.4H), 2.67 (dd, *J* = 14.6, 6.1 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.3, 170.8, 168.4, 167.0, 138.0, 137.9, 135.9, 134.8, 134.7, 133.0,132.4,132.3, 131.7, 131.5, 130.6, 130.3, 128.9, 128.8, 128.7, 128.6, 128.2, 128.0, 127.7, 124.1, 123.6, 101.8, 101.4, 86.7, 75.8, 55.6, 55.5, 55.0, 53.9, 44.2, 43.3, 42.9, 41.8; **HRMS (ESI)** m/z calcd for $C_{28}H_{28}BrN_2O_4$ $[M+H]^+$ 535.1232; found: 535.1221.

Using **4c** (59.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **5c** as a yellow solid (35.0 mg, 68%); **m.p:** 210-215 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.73 – 7.67 (m, 2H), 7.46 – 7.41 (m, 2H), 7.37 – 7.24 (m, 11H), 6.18 (d, *J* = 5.2 Hz, 1H), 5.93 (d, *J* = 5.2 Hz, 1H), 5.02 (d, *J* = 14.8 Hz, 1H), 4.71 (d, *J* = 14.8 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.3, 163.2, 139.5, 135.8, 134.3, 132.2, 131.3, 131.2, 130.7, 130.0, 129.1, 128.6, 128.5, 128.4, 128.2, 123.7, 120.7, 106.8, 67.8, 50.3; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}BrN_2O_2$ $[M+H]^+$ 471.0708; found: 471.0700.

(E)-4-Benzyl-7-benzylidene-6-(4-fluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5d):

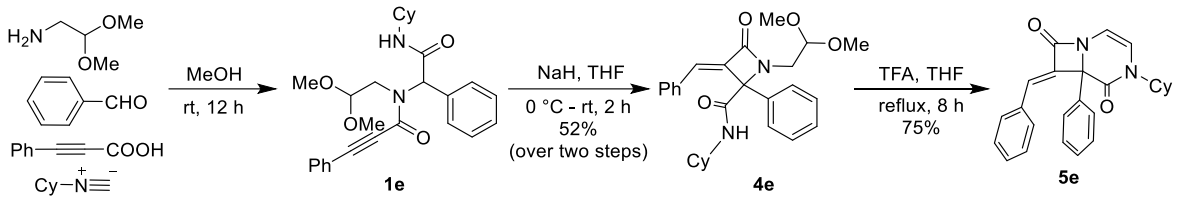


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.058 mL,0.475 mmol), was dissolved in methanol (4.0 mL) to

perform Ugi-4CC, product **1d** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4d** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil (108.0 mg, 48%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 – 7.32 (m, 5H), 7.22 – 7.18 (m, 4H), 7.11 – 7.04 (m, 4H), 6.92 (dd, *J* = 6.7, 2.8 Hz, 2H), 5.41 (s, 1H), 5.17 (d, *J* = 14.9 Hz, 1H), 4.46 (dd, *J* = 6.9, 3.8 Hz, 1H), 4.18 (dd, *J* = 13.9, 3.8 Hz, 1H), 3.95 (d, *J* = 14.9 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.93 (dd, *J* = 13.9, 6.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 166.3, 163.6, 163.0 (d, $J_{C\text{-}F}$ = 246 Hz), 136.3, 133.6, 130.9 (d, $J_{C\text{-}F}$ = 2 Hz) , 129.7, 129.3, 129.2, 128.8, 128.5, 127.8, 127.7, 123.4, 116.3 (d, $J_{C\text{-}F}$ = 22 Hz), 103.1, 65.9, 56.2, 54.4, 48.0, 47.6; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1063, 1634, 2922, 3394, 3740, 3839; **HRMS (ESI)** m/z calcd for $C_{28}H_{28}FN_2O_4[M+H]^+$ 475.2033; found: 475.201.

Using **4d** (52.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5d** as a yellow solid (31.0 mg, 69%); **m.p**: 150-152 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72 – 7.66 (m, 2H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.39 (s, 1H), 7.37 – 7.32 (m, 4H), 7.29 (dt, *J* = 5.2, 1.6 Hz, 4H), 7.25 – 7.18 (m, 1H), 7.04 (dd, *J* = 7.2, 4.3 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.19 (d, *J* = 5.2 Hz, 1H), 5.95 (d, *J* = 5.2 Hz, 1H), 5.03 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 5.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.5, 163.5, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 139.8, 135.9, 131.3, 130.9 (d, $J_{C\text{-}F}$= 3.75 Hz), 130.7, 129.9, 129.1, 128.9, 128.7, 128.5, 128.4, 128.2, 120.8, 116.3 (d, $J_{C\text{-}F}$ = 22 Hz), 106.9, 67.8, 50.3; **HRMS (ESI)** m/z calcd for $C_{26}H_{20}FN_2O_2$ $[M+H]^+$ 411.1509; found: 411.1504.

(E)-7-Benzylidene-4-cyclohexyl-6-phenyl-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5e):

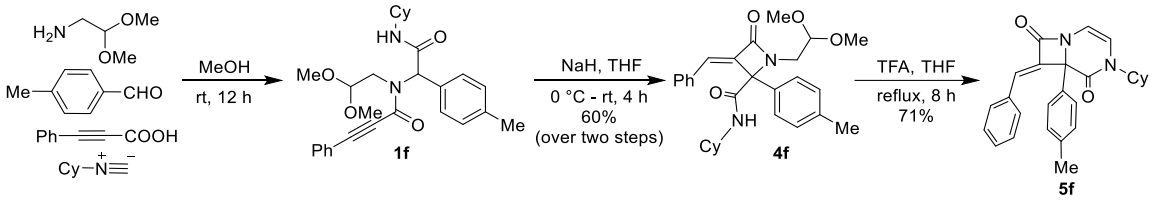


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.049 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolved in methanol (4.0 mL) to perform Ugi-4CC, product **1e** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4e** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid (112.0 mg, 52%); **m.p:** 123-126°C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 – 7.58 (m, 3H), 7.41 – 7.33 (m, 5H), 7.27 – 7.22 (m, 3H), 7.18 (s, 1H), 4.76 (dd, J = 6.2, 5.0 Hz, 1H), 3.83 (ddd, J = 11.0, 7.1, 3.6 Hz, 1H), 3.49 – 3.42 (m, 4H), 3.38 (s, 3H), 2.75 (dd, J = 14.6, 6.2 Hz, 1H), 2.03 (dd, J = 9.9, 2.0 Hz, 1H), 1.83 (dd, J = 10.7, 1.6 Hz, 1H), 1.75 – 1.62 (m, 4H), 1.41 – 1.29 (m, 2H), 1.19 – 1.12 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.7, 167.3, 138.5, 134.1, 131.8, 131.6, 130.2, 129.1, 128.5, 128.3, 127.3, 101.3, 76.1, 55.6, 53.4, 48.9, 43.1, 33.2, 32.7, 25.6, 25.1, 25.1; **HRMS (ESI)** m/z calcd for $C_{27}H_{33}N_2O_4$ $[M+H]^+$ 449.2440; found: 449.2433.

Using **4e** (49.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5e** as a yellow solid (32.0 mg, 75%); **m.p:** 165-167 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.65 (dd, J= 7.8, 1.4 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.37 – 7.31 (m, 3H), 7.28 – 7.21 (m, 4H), 6.21 (d, J = 5.4 Hz, 1H), 6.03 (d, J = 5.4 Hz, 1H), 4.80 – 4.58 (m, 1H), 1.93 – 1.80 (m, 4H), 1.71 (d, J = 13.1 Hz, 1H), 1.44 (dt, J = 21.3, 9.9 Hz, 4H), 1.19 – 1.08 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.8, 163.2, 140.0, 135.4, 131.6, 131.4, 130.4, 129.4, 129.3, 129.1,

128.4, 126.7, 117.0, 106.7, 68.0, 53.4, 31.9, 31.3, 25.8, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1064, 1665, 2923, 3404, 3699, 3783; **HRMS (ESI)** m/z calcd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$ 385.1916; found: 385.1911.

(E)-7-Benzylidene-4-cyclohexyl-6-(p-tolyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5f):

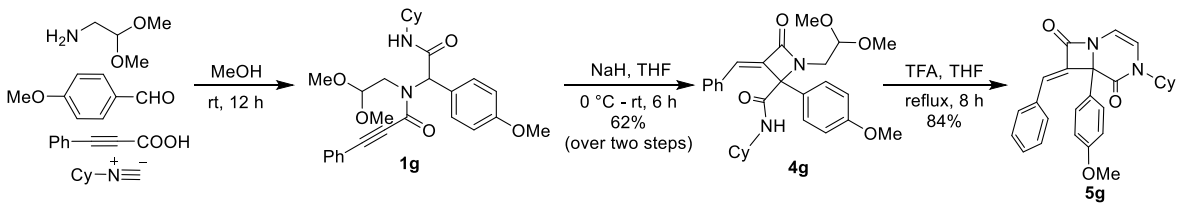


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), *p*-tolualdehyde (0.056 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol) was dissolved in methanol (4.0 mL) to perform Ugi-4CC, product **1f** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4f** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid (133.0 mg, 60%); **m.p:** 155-157 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.63 (dd, J = 7.6, 1.7 Hz, 3H), 7.24 (dd, J = 4.6, 2.3 Hz, 5H), 7.15 (d, J = 8.4 Hz, 3H), 4.75 (dd, J = 6.0, 5.2 Hz, 1H), 3.82 (tdt, J = 11.5, 7.9, 3.9 Hz, 1H), 3.47 – 3.37 (m, 7H), 2.73 (dd, J = 14.6, 6.3 Hz, 1H), 2.33 (s, 3H), 2.02 (d, J = 12.4 Hz, 1H), 1.82 (d, J = 12.3 Hz, 1H), 1.70 (dd, J = 19.0, 9.3 Hz, 2H), 1.42 – 1.04 (m, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.8, 167.3, 138.1, 138.7, 131.9, 131.5, 131.0, 130.0, 129.8, 128.5, 128.2, 127.1, 101.2, 75.9,55.5, 53.2, 48.8, 43.0, 33.1, 32.6, 25.6, 25.0, 25.0, 21.2;**HRMS (ESI)** m/z calcd for $C_{28}H_{34}N_2NaO_4$ $[M+Na]^+$ 485.2416; found: 485.2413.

Using **4f** (51.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5f** as a yellow solid, (30.0 mg, 71%); **m.p**: 180-182 °C; **^{1}H NMR (400**

MHz, $CDCl_3$): δ 7.68 – 7.64 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.31 – 7.26 (m, 1H), 7.25 – 7.21 (m, 3H), 7.15 (d, J = 8.1 Hz, 2H), 6.20 (d, J = 5.4 Hz, 1H), 6.02 (d, J = 5.4 Hz, 1H), 4.67 (t, J = 9.2 Hz, 1H), 2.31 (s, 3H), 1.86 (dd, J = 19.3, 7.7 Hz, 4H), 1.70 (d, J = 12.9 Hz, 1H), 1.49 – 1.35 (m, 4H), 1.19 – 1.08 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.8, 163.3, 140.1, 139.3, 132.2, 131.6, 131.4, 130.3, 129.8, 129.0, 128.4, 126.6, 116.9, 106.5, 67.8, 53.3, 31.8, 31.3, 25.8, 25.4, 21.3; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1055, 1634, 2923, 3400, 3739, 3839; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_2$ $[M+H]^+$ 399.2073; found: 399.2066.

(E)-7-Benzylidene-4-cyclohexyl-6-(4-methoxyphenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5g):

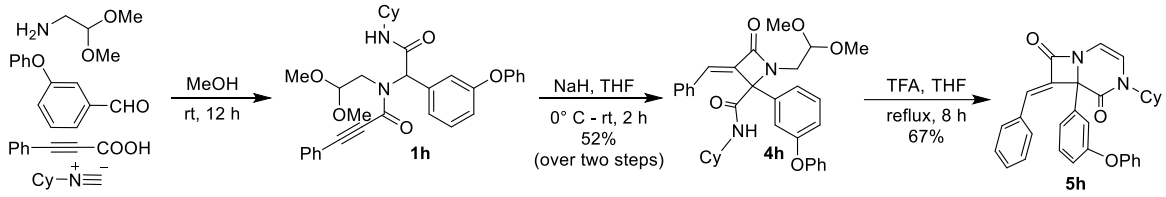


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-methoxybenzaldehyde (0.057 mL, 0.475 mmol), phenylpropiolic acid (69.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL, 0.475 mmol), in methanol (4.0 mL), perform Ugi-4CC product **1g** was obtained, followed by the second step with sodium hydride (34.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4g** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a transparent oil (142.0 mg, 62%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.68 – 7.54 (m, 3H), 7.32 – 7.27 (m, 2H), 7.27 – 7.20 (m, 3H), 7.16 (s, 1H), 6.87 (d, J = 8.9 Hz, 2H), 4.74 (dd, J = 6.1, 5.1 Hz, 1H), 3.86 – 3.78 (m, 4H), 3.49 – 3.41 (m, 4H), 3.37 (d, J = 7.3 Hz, 3H), 2.74 (dd, J = 14.6, 6.2 Hz, 1H), 2.04 (s, 1H), 1.82 (d, J = 12.2 Hz, 1H), 1.71 – 1.59 (m, 4H), 1.38 – 1.28 (m, 2H), 1.19 – 1.10 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.9, 167.4, 160.1, 139.0, 132.0, 131.6, 130.1, 129.8, 128.6, 127.2, 126.0, 114.5, 101.4, 75.9, 55.6, 55.4, 53.4, 49.0, 43.1,

33.2, 32.7, 25.7, 25.137; **HRMS (ESI)** m/z calcd for $C_{28}H_{35}N_2O_5$ $[M+H]^+$ 479.2546; found: 479.2545.

Using **4g** (52.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford **5g** as a yellow solid (37.0 mg, 84%); **m.p**: 195-197 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66 (dd, *J*= 7.8, 1.7 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 6.7, 4.4 Hz, 4H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.20 (d, *J* = 5.4 Hz, 1H), 6.03 (d, *J* = 5.4 Hz, 1H), 4.67 (s, 1H), 3.77 (s, 3H), 1.84 (d, *J* = 7.0 Hz, 4H), 1.71 (d, *J* = 12.9 Hz, 1H), 1.60 (s, 1H), 1.50 – 1.34 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 163.4, 160.3, 140.1, 131.7, 131.5, 130.4, 129.1, 128.4, 128.2, 127.1, 117.0, 114.5, 106.6, 67.7, 55.4, 53.3, 31.9, 31.4, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{27}N_2O_3$ $[M+H]^+$: 415.2022; found: 415.2018.

(E)-7-Benzylidene-4-cyclohexyl-6-(3-phenoxyphenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5h):

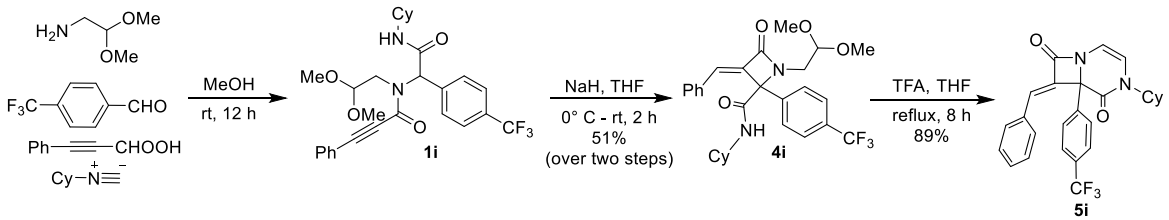


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 3-Phenoxybenzaldehyde (0.082 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC,product **1h** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4h** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (134.0 mg, 52%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.65 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.36 – 7.25 (m, 5H), 7.19 (dd, *J* = 10.7, 5.2

Hz, 2H), 7.14 – 7.08 (m, 2H), 7.06 – 6.97 (m, 3H), 6.89 – 6.79 (m, 2H), 4.76 (dd, *J* = 5.9, 5.1 Hz,1H), 3.79 (ddd, *J* = 11.0, 7.1, 3.6 Hz, 1H), 3.51 – 3.32 (m, 7H), 2.77 (dd, *J* = 14.6, 6.2 Hz, 1H), 1.97 (d, *J* = 11.8 Hz, 1H), 1.86 – 1.62 (m, 4H), 1.38 – 1.27 (m, 2H), 1.18 – 1.06 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** *δ* 167.5, 167.1, 157.9, 156.6, 138.2, 136.0, 131.8, 131.7, 130.5,130.3, 129.8, 128.6, 127.5, 123.5, 123.2, 119.4, 119.0, 118.5, 101.3, 75.9, 55.6, 53.4, 49.0, 43.2, 33.1, 32.6, 25.6, 25.1; **HRMS (ESI)** m/z calcd for $C_{33}H_{37}N_2O_5$ $[M+H]^+$ 541.2702; found: 541.2697.

Using **4h** (59.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5h** as a yellow solid, (35.0 mg, 67%); **m.p:** 150-152 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** *δ* 7.68 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.34 – 7.22 (m, 7H), 7.18 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.97 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.20 (d, *J* = 5.4 Hz, 1H), 6.01 (d, *J* = 5.4 Hz, 1H), 4.59 (dt, *J* = 15.0, 7.6 Hz, 1H), 1.81 (d, *J* = 6.9 Hz, 3H), 1.69 – 1.61 (m, 2H), 1.43 – 1.30 (m, 4H), 1.17 – 1.05 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** *δ*165.6, 163.0, 157.9, 156.7, 139.6, 137.2, 131.5, 131.4, 130.5, 130.5, 129.9, 129.5, 128.4, 123.7, 121.4, 119.7, 119.1, 117.0, 116.9, 106.6, 67.7, 53.4, 31.8, 31.2, 25.8, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 760, 1068, 1252, 1395, 1668, 1760, 2924, 3394, 3701, 3783; **HRMS (ESI)** m/z calcd for $C_{31}H_{29}N_2O_3$ $[M+H]^+$ 477.2178; found: 477.2178.

(E)-7-Benzylidene-4-cyclohexyl-6-(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5i):

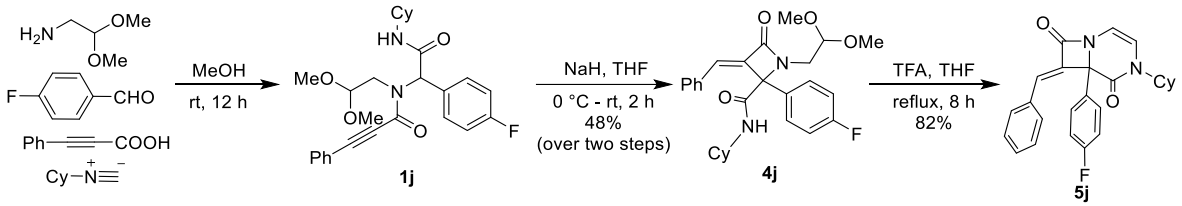


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-(trifluoromethyl)benzaldehyde (0.065 mL, 0.475 mmol), phenylpropiolic acid (70 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol),was dissolve in methanol (4.0mL) to perform Ugi-4CC product **1i** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4i** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid, (125.0 mg, 51%); **m.p:** 127-130 °C; **^{1}H NMR (300 MHz, $CDCl_3$):**δ 7.70 (d,*J* = 7.2 Hz, 1H), 7.62 (d,*J*= 7.7 Hz, 4H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.25 (dd, *J* = 11.2, 8.0 Hz, 4H), 4.76 (t, *J* = 5.1 Hz, 1H), 3.88 – 3.74 (m, 1H), 3.53 – 3.45 (m, 4H), 3.39 (s, 3H), 2.71 (dd, *J*= 14.6, 5.8 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.83 – 1.64 (m, 4H), 1.31 (d, *J*= 14.7 Hz, 2H), 1.22 – 1.08 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):**δ 167.2, 166.9, 138.2, 138.0, 131.6, 131.5, 131.4, 131.0, 130.5, 129.1, 128.7,128.0,126.1 (dd, J_{C-F} = 10.5 Hz), 125.7, 122.1, 101.4, 75.5, 55.8, 53.8, 49.2, 43.3, 33.2, 32.7, 25.6, 25.1, 25.0; **^{19}F NMR (283 MHz, $CDCl_3$):**δ -62.8; **HRMS (ESI)** m/z calcd for $C_{28}H_{32}F_3N_2O_4$ $[M+H]^+$ 517.2314; found: 517.2302.

Using **4i** (56.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5i** as a yellow solid (44.0 mg, 89%); **m.p**: 85-87 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 – 7.64 (m, 2H), 7.60 (s, 4H), 7.33 – 7.26 (m, 3H), 7.26 – 7.23 (m, 1H), 6.23 (d, *J* = 5.4 Hz, 1H), 6.04 (d, *J* = 5.4 Hz, 1H), 4.73 – 4.62 (m, 1H), 1.90 – 1.80 (m, 4H), 1.72 (d, *J* = 13.1 Hz, 1H), 1.49 – 1.38 (m, 4H), 1.15 (dd, *J* = 8.3, 3.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.4, 162.6, 139.5, 131.3, 131.2, 131.1, 130.7, 130.0, 128.5, 127.2, 126.0 (dd, J_{C-F} = 11.0 Hz), 117.0, 106.6, 67.6, 53.6, 31.8, 31.3, 29.8, 25.8, 25.3; **^{19}F NMR (283 MHz, $CDCl_3$):**δ -

62.8; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1067, 1634, 2352, 2923, 3395, 3739, 3837; **HRMS (ESI)** m/z calcd for $C_{26}H_{24}F_3N_2O_2$ $[M+H]^+$ 453.1790; found: 453.1783.

(E)-7-Benzylidene-4-cyclohexyl-6-(4-fluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5j):

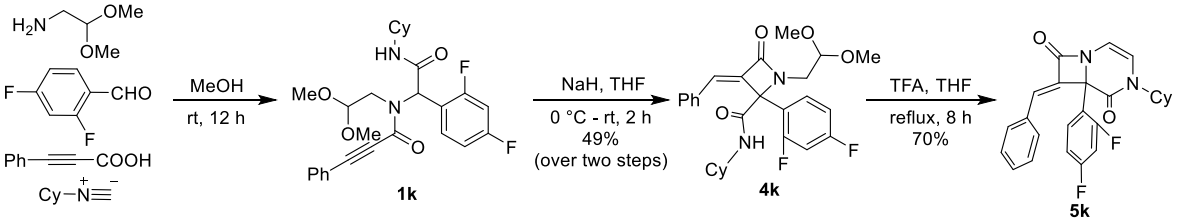


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluoro benzaldehyde (0.048 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.058 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC product **1j** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4j** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid (108.0 mg, 48%); **m.p**: 115-118 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.70 – 7.59 (m, 3H), 7.39 – 7.33 (m, 2H), 7.30 – 7.27 (m, 1H), 7.26 – 7.22 (m, 2H), 7.18 (d, J = 5.3 Hz, 1H), 7.08 – 7.02 (m, 2H), 4.75 (dd, J = 5.9, 4.9 Hz,1H), 3.86 – 3.75 (m, 1H), 3.49 – 3.33 (m, 7H), 2.72 (dd, J = 14.6, 6.0 Hz, 1H), 1.76 (dd,J = 44.5, 7.9 Hz, 4H), 1.41 – 1.26 (m, 3H), 1.24 – 1.09 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 167.6, 167.1, 163.0 (d, $J_{C\text{-}F}$ = 247 Hz), 138.6, 131.7, 131.6, 130.5 (d, $J_{C\text{-}F}$ = 7.5 Hz), 130.3, 130.0 (d, $J_{C\text{-}F}$ = 3.75 Hz), 123.0, 128.6, 127.5, 116.1 (d, $J_{C\text{-}F}$ = 21.2 Hz), 101.40, 75.5, 55.7, 53.6, 49.1, 43.1, 33.2, 32.7, 25.6, 25.1, 25.1; **HRMS (ESI)** m/z calcd for $C_{27}H_{31}FN_2NaO_4$ $[M+Na]^+$ 489.2166; found: 489.2168.

Using **4j** (51.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl

acetate/hexane) to yield **5j** as a white solid (36.0 mg, 82%); **m.p**: 98-100 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, J = 7.2 Hz, 2H), 7.43 (dd, J = 8.1, 5.3 Hz, 2H), 7.31 – 7.22 (m, 4H), 7.03 (t, J = 8.5 Hz, 2H), 6.21 (d, J = 5.2 Hz, 1H), 6.04 (d, J = 5.3 Hz, 1H), 4.68 (d, J = 8.5 Hz, 1H), 1.92 – 1.80 (m, 4H), 1.71 (d, J = 12.9 Hz, 1H), 1.53 – 1.37 (m, 4H), 1.14 (d, J = 9.7 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 165.6, 164.2, 163.0 (d $J_{C\text{-}F}$ = 247.5 MHz), 140.0, 131.4, 131.3, 131.2 (d $J_{C\text{-}F}$ = 2.5 MHz), 130.5, 129.5, 128.7 (d $J_{C\text{-}F}$ = 7.5 Hz), 128.5, 117.0, 116.1 (d $J_{C\text{-}F}$ = 21.2 Hz), 106.6, 67.5, 53.5, 31.8, 31.3, 25.8, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 761, 1068, 1403, 1665, 1758, 2924, 3426, 3697, 3783, 3920; **HRMS (ESI)** m/z calcd for $C_{25}H_{24}FN_2O_2$ $[M+H]^+$ 403.1822; found: 403.1817.

(E)-7-Benzylidene-4-cyclohexyl-6-(2,4-difluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5k):

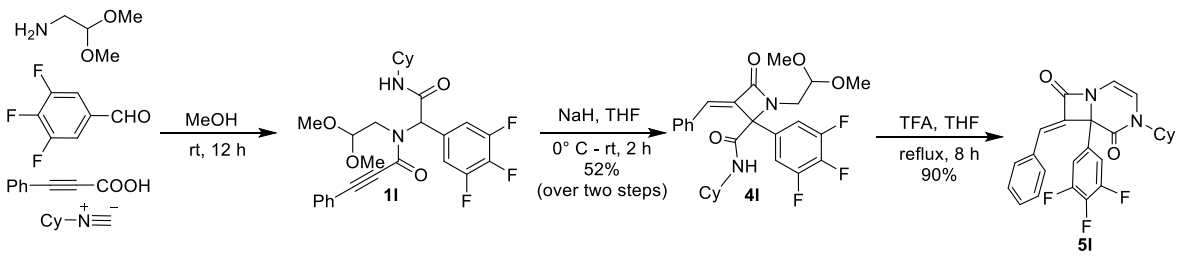


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 2,4-difluorobenzaldehyde (0.052 mL, 0.475 mmol), phenylpropiolic acid (69.0 mg, 0.475 mmol) and cyclohexyl isocyanide (0.059 mL, 0.475 mmol) in methanol (4.0 mL) to perform Ugi-4CC product **1k** was obtained, followed by the second step with 60% sodium hydride (34.0mg, 1.43 mmol) in THF (6.0 mL),compound **4k** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white oil (112.0 mg, 49%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.71 (dt, J = 8.3, 3.8 Hz, 3H), 7.35 – 7.27 (m, 3H), 7.26 – 7.19 (m, 2H), 6.91 (ddd, J = 11.0, 8.6, 2.5 Hz, 1H), 6.78 (tdd, J = 8.8, 2.5, 0.9 Hz, 1H), 4.95 (t, J = 5.9 Hz, 1H), 3.82 – 3.68 (m, 1H), 3.61 (dd, J = 14.7, 6.4 Hz, 1H), 3.50 (s, 3H), 3.43 (s, 3H), 2.90 (ddd, J = 14.6,

5.9, 1.6 Hz, 1H), 2.05 (t, J = 6.0 Hz, 1H), 1.78 – 1.59 (m, 4H), 1.37 – 1.11 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.2, 166.3, 163.5 (dd, J_{C-F} = 249.7 MHz), 161.5 (dd, J_{C-F} = 248.2 MHz), 136.4, 132.1, 131.8 (dd, J_{C-F} =5.2, 4.5 MHz), 131.6, 130.6, 128.8, 128.4, 117.9 (dd, J_{C-F} = 18 MHz), 112.2 (dd, J_{C-F} = 24.7 MHz) , 104.9 (t, J_{C-F} = 51 MHz), 100.1 (dd, J_{C-F} = 2.2 MHz), 100.1, 73.5, 55.9, 51.6, 49.2, 42.8, 32.7, 32.6, 25.7, 25.1, 25.0; **HRMS (ESI)** m/z calcd for $C_{27}H_{30}F_2N_2NaO_4$ $[M+Na]^+$ 507.2071; found: 507.2069.

Using **4k** (53.0 mg, 0.10 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford **5k** (32.0 mg, 70%) as a yellow solid; **m.p**: 196-198 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66 (dd, J = 8.0, 1.5 Hz, 2H), 7.41 – 7.22 (m, 5H), 6.90 – 6.72 (m, 2H), 6.19 (d, J = 5.3 Hz, 1H), 6.09 (d, J = 5.3 Hz, 1H), 4.71 – 4.54 (m, 1H), 1.93 – 1.75 (m, 4H), 1.75 – 1.51 (m, 2H), 1.42 (ddd, J = 21.3, 10.8, 1.9 Hz, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 163.5 (dd, J_{C-F} = 251 Hz), 163.2, 162.0 (dd, J_{C-F} = 254 Hz), 138.8, 131.4, 131.3, 131.0 (dd, J_{C-F} = 15 Hz), 130.7, 129.7, 128.6, 119.1, 119.0, 118.9, 118.9, 117.9, 112.0 (dd, J_{C-F} = 24.7 Hz), 107.2, 105.4 (t, J_{C-F} = 51 Hz), 65.8, 53.5, 31.8, 30.7, 25.8, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{25}H_{23}F_2N_2O_2$ $[M+H]^+$ 421.1728; found: 421.1714.

(E)-7-Benzylidene-4-cyclohexyl-6-(3,4,5-trifluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5l):

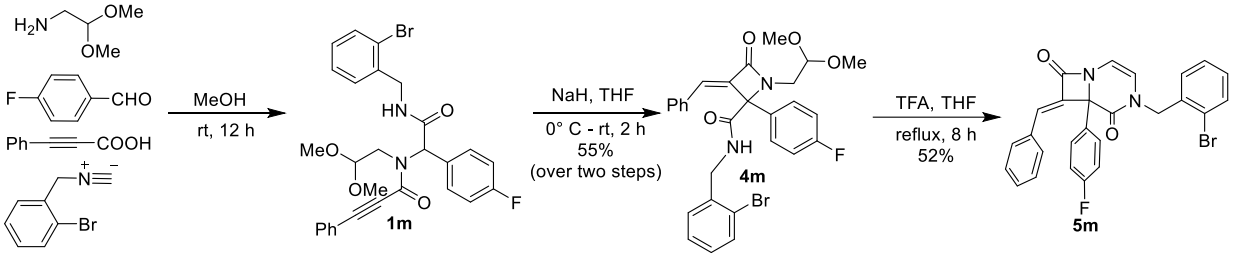


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 3,4,5-trifluorobenzaldehyde (0.054 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to product **1l** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4l** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a brown solid (125.0 mg, 52%); **m.p:** 126-130 °C;**^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72 – 7.53 (m, 3H), 7.32 (dd, J = 12.0, 6.8 Hz, 3H), 7.18 (s, 1H), 7.06 (dd, J = 8.5, 6.4 Hz, 2H), 4.78 – 4.71 (m, 1H), 3.78 (ddd, J = 10.9, 9.2, 5.8 Hz, 1H), 3.60 – 3.45 (m, 4H), 3.41 (s, 3H), 2.72 (dd, J = 14.6, 5.6 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.84 – 1.62 (m, 4H), 1.40 – 1.34 (m, 1H), 1.22 – 1.06 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 165.1, 162.0, 151.6, (dd, $J_{C\text{-}F}$ = 250 Hz), 151.4 (dd, $J_{C\text{-}F}$ = 250 Hz), 140.1 (dt, $J_{C\text{-}F}$ = 252.5 Hz), 139.3, 132.0 (q, $J_{C\text{-}F}$ = 18.7, 5.0 Hz), 131.2, 131.0, 130.9, 130.4, 128.6, 117.0, 111. (dd, $J_{C\text{-}F}$ = 22.5, 11.2 Hz), 106.7, 67.0, 53.8, 31.8, 31.3, 29.8, 25.8, 25.3; **^{19}F NMR (283 MHz, $CDCl_3$):** δ -131.9 (d, J = 19.8 Hz), -157.9 (t, J = 39.6 Hz); **HRMS (ESI)** m/z calcd for $C_{27}H_{30}F_3N_2O_4$ $[M+H]^+$ 503.2158; found: 503.2141.

Using **4l** (55.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5l** as a yellow solid, (43.0 mg, 90%); **m.p:** 118-120 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (d, J = 6.8 Hz, 2H), 7.38 – 7.26 (m, 4H), 7.12 (dd, J = 8.1, 6.4 Hz, 2H), 6.23 (d, J = 5.4 Hz, 1H), 6.04 (d, J = 5.4 Hz, 1H), 4.69 – 4.59 (m, 1H), 1.85 (ddd, J = 22.0, 13.8, 5.3 Hz, 4H), 1.72 (d, J = 12.8 Hz, 1H), 1.48 – 1.36 (m, 4H), 1.14 (dd, J = 5.9, 2.9 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.1, 162.1, 151.6 (dd, $J_{C\text{-}F}$ = 250 Hz), 151.4 (dd, $J_{C\text{-}F}$ = 250 Hz), 153.3, 153.2, 153.2, 153.1, 149.9, 149.9, 149.8, 149.8, 139.3, 132.0 (t, $J_{C\text{-}F}$ = 9.7, 5.2 Hz), 131.2,

131.0, 130.9, 130.4, 128.7, 117.0, 111.3 (dd, $J_{C\text{-}F}$ = 22.5, 8.2 Hz), 106.7, 67.0, 53.8, 31.8, 31.3, 25.8, 25.3, 22.8; **^{19}F NMR (283 MHz, $CDCl_3$):** δ -132.3 (d, J = 22.6 Hz), -158.4 (t, J = 42.4 Hz); **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1048, 1360, 1528, 1668, 1756, 2926, 3391, 3740, 3841; **HRMS (ESI)** m/z calcd for $C_{25}H_{22}F_3N_2O_2$ $[M+H]^+$ 439.1633; found: 439.1626.

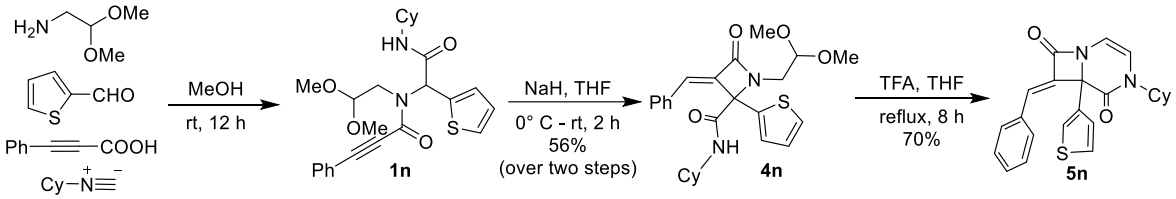
(E)-7-Benzylidene-4-(2-bromobenzyl)-6-(4-fluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5m):



According to general procedure B using aminoacetaldehyde dimethyl acetal(0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and 2-bromobenzyl isocyanide (94.0 mg,0.475 mmol), was dissolve in methanol (4.0mL) to perform Ugi-4CC,product **1m** was obtained followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4m** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid, (145.0 mg, 55%), **m.p**: 118-120°C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 (ddd, J = 13.7, 8.0, 3.3 Hz, 3H), 7.32 – 7.29 (m, 3H), 7.17 (s, 1H), 7.10 – 7.01 (m, 6H), 6.63 (dd, J= 7.3, 1.8 Hz, 1H), 5.46 (s, 1H), 5.15 (d, J = 15.5 Hz, 1H), 4.58 (dd, J = 6.9, 3.6 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.39 (d, J = 11.3 Hz, 6H), 2.93 (dd, J = 14.0, 6.9 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.4, 163.6, 163.0 (d, $J_{C\text{-}F}$ = 246.7 Hz), 134.5, 133.5, 133.1, 130.9 (d, $J_{C\text{-}F}$ = 3 Hz), 130.2, 129.6, 129.4, 129.3, 129.1, 128.7, 127.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.1, 123.4, 123.2, 116.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 103.1, 65.8, 55.8, 54.4, 49.2, 47.3; **HRMS (ESI)** m/z calcd for $C_{28}H_{27}BrFN_2O_4$ $[M+H]^+$ 553.1138; found: 553.1131.

Using **4m** (59.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF(4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5m** as a yellow solid(30.0 mg, 52%); **m.p**: 105-108°C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72 – 7.65 (m, 2H), 7.59 (dd, J = 7.9, 1.0 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.33 – 7.26 (m, 4H), 7.22 (dd, J = 13.0, 4.8 Hz, 3H), 7.07 – 6.99 (m, 2H), 6.23 (d, J = 5.2 Hz, 1H), 5.98 (d, J = 5.2 Hz, 1H), 5.01 (q, J = 15.6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.4, 163.6, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 139.8, 134.9, 133.3, 131.3, 130.7, 130.6, 130.0,129.8, 129.7, 128.8 (d, $J_{C\text{-}F}$ = 9 Hz), 128.5, 128.1, 123.6, 120.9, 116.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 107.1, 67.9, 50.3; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1057, 1757, 2923, 3398, 3780, 3924; **HRMS (ESI)** m/z calcd for $C_{26}H_{19}BrFN_2O_2$ $[M+H]^+$ 489.0614; found: 489.0610.

(E)-7-Benzylidene-4-cyclohexyl-6-(thiophen-2-yl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5n):

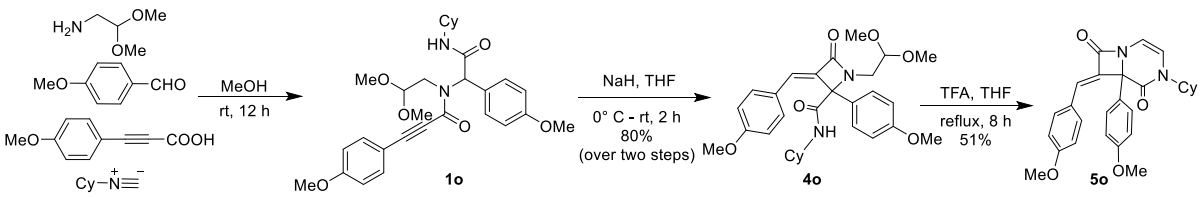


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),2-thiophenecarboxaldehyde(0.045 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC, product **1n** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4n** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow solid, (120 mg,56%); **m.p:** 125-127°C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.63 (dd, J = 6.5, 3.2 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.33 (dd, J= 5.1, 1.2 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.19 (dd, J = 3.6, 1.2 Hz, 1H), 7.08

(s, 1H), 6.99 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.76 (dd, *J* = 6.1, 5.2 Hz, 1H), 3.85 – 3.72 (m, 1H), 3.55 (dd, *J* = 14.6, 5.1 Hz, 1H), 3.42 (d, *J* = 22.7 Hz, 6H), 2.89 (dd, *J* = 14.6, 6.2 Hz, 1H), 1.99 (d, *J*= 12.3 Hz, 1H), 1.86 – 1.65 (m, 3H), 1.34 (ddd, *J* = 16.8, 13.3, 8.2 Hz, 3H), 1.18 – 0.99 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.8, 166.7, 140.5, 137.1, 131.7, 131.6, 130.3, 128.8, 128.6, 127.8, 127.2, 126.9, 101.1, 72.2, 55.5, 53.1, 49.1, 43.0, 32.9, 32.6, 25.6, 25.0, 24.9; **HRMS (ESI)** m/z calcd for $C_{25}H_{30}N_2NaO_4S[M+Na]^+$ 477.1824; found: 477.1797.

Using **4n** (49.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5n** as a yellow solid(30.0 mg, 70%); **m.p:** 221-223 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.78 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.33 – 7.25 (m, 5H), 7.11 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.95 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.22 (d, *J* = 5.4 Hz, 1H), 6.07 (d, *J* = 5.4 Hz, 1H), 4.64 (dd, *J* = 14.0, 5.7 Hz, 1H), 1.86 (t, *J* = 11.6 Hz, 4H), 1.71 (d, *J* = 12.6 Hz, 1H), 1.45 (ddd, *J* = 18.8, 14.2, 5.9 Hz, 4H), 1.22 – 1.07 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 162.5, 139.7, 139.2, 131.7, 131.4, 130.6, 129.9, 128.4, 127.6, 127.3, 127.2, 116.6, 106.3, 65.1, 53.6, 31.8, 31.2, 25.8, 25.4; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 760, 1065, 1403, 1669, 1760, 2926, 3394; **HRMS (ESI)** m/z calcd for $C_{23}H_{23}N_2O_2S[M+H]^+$ 391.1480; found: 391.1468.

(E)-4-Benzyl-7-(4-methoxybenzylidene)-6-(4-methoxyphenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5o):



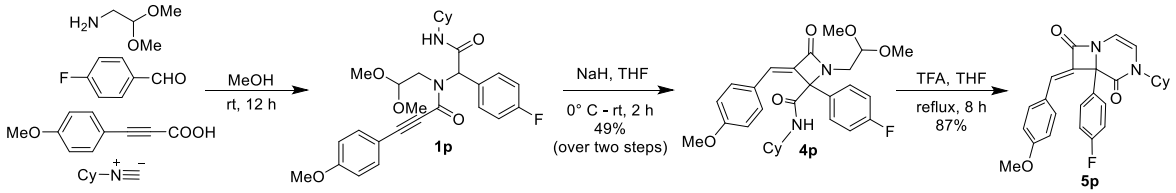
According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-methoxybenzaldehyde (0.057 mL, 0.475 mmol), 4-methoxy phenylpropiolic acid (83.0

mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL, 0.475 mmol),in methanol (4.0 mL) to perform Ugi-4CC, product **1o** was obtained, followed by the second step with sodium hydride (34.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4o** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white oil (194.0 mg, 80%). Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.75); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.71 (d, J = 7.9 Hz, 0.82H), 7.61 (d, J = 8.8 Hz, 1.67H), 7.35 – 7.24 (m, 4.21H), 7.11 (s, 0.84H), 6.97 – 6.82 (m, 4.02H), 6.76 (d, J = 8.8 Hz, 1.69H), 5.22 (s, 1H), 4.74 (dd, J = 6.0, 5.1 Hz, 0.77H), 4.53 (dd, J = 6.6, 3.5 Hz, 1H), 3.91 (ddd, J = 18.5, 13.7, 6.0 Hz, 2.76H), 3.80 (d, J = 3.3 Hz, 5.64H), 3.75 (s, 2.24H), 3.47 (s, 2.46H), 3.42 – 3.34 (m, 9.25H), 2.87 (dd, J = 14.9, 6.7 Hz, 1.12H), 2.69 (dd, J = 14.6, 6.2 Hz, 0.87H), 2.21 – 1.98 (m, 3.35H), 1.84 (s, 2.84H), 1.76 – 1.60 (m, 5.70H), 1.43 – 1.26 (m, 5H), 1.14 (ddd, J = 11.3, 10.8, 7.1 Hz, 3.34H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.6, 168.2, 167.9, 161.2, 160.5, 160.0, 156.1, 136.0, 133.5, 129.8, 127.8, 127.5, 127.0, 126.1,124.7,114.5, 114.4, 114.0, 101.9, 101.4, 86.0, 75.8, 55.6, 55.4, 55.3, 55.1, 54.6, 53.3, 51.9, 48.9, 42.9, 41.6, 33.3, 32.7, 29.6, 29.5, 26.0, 25.9, 25.7, 25.1; **HRMS (ESI)**: calcd for $C_{29}H_{37}N_2O_6$ $[M+H]^+$ 509.2652; found: 509.2642.

Using **4o** (55.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford **5o** as a yellow oil (25.0 mg, 51%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.62 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 6.86 (d, J = 8.9 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 6.18 (d, J = 5.4 Hz, 1H), 6.01 (d, J = 5.4 Hz, 1H), 4.67 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 1.86 (t, J = 12.3 Hz, 4H), 1.71 (d, J = 13.2 Hz, 2H), 1.48 (d, J = 8.1 Hz, 2H), 1.44 – 1.37 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.4, 163.8, 161.5, 160.3, 137.5, 133.4, 128.9,

128.2, 127.4, 124.4, 116.6, 114.5, 114.0, 106.8, 67.6, 55.4, 53.3, 31.9, 31.4, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{27}H_{29}N_2O_4$ $[M+H]^+$ 445.2127; found: 445.2120.

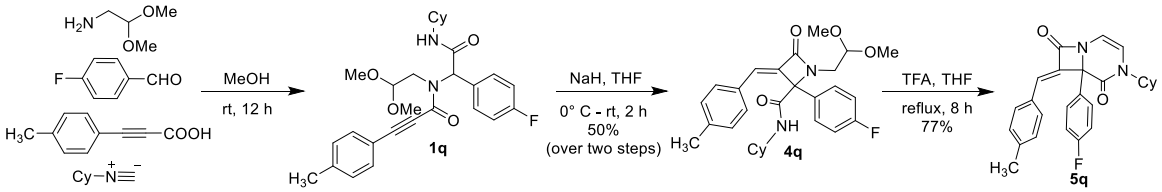
(E)-4-Cyclohexyl-6-(4-fluorophenyl)-7-(4-methylbenzylidene)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5p):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), 3-(4-Methoxyphenyl)-propiolic acid (84.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4 mL) to perform Ugi-4CC, product **1p** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4p** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (115.0 mg, 49%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.74 (d,J = 7.8 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.38 – 7.31 (m, 2H), 7.13 (s, 1H), 7.08 – 7.00 (m, 2H), 6.81 – 6.73 (m, 2H), 4.74 (dd,J = 5.9, 4.9 Hz, 1H), 3.88 – 3.74 (m, 4H), 3.49 – 3.38 (m, 7H), 2.67 (dd,J = 14.6, 6.1 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.85 – 1.65 (m, 4H), 1.38 – 1.28 (m, 3H), 1.15 (dd,J = 9.6, 2.2 Hz, 2H);**^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.9, 167.6, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 161.4,135.6,133.5,130.6 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.0 (d, $J_{C\text{-}F}$ = 3.75 Hz), 127.3, 124.4, 116.1 (d, $J_{C\text{-}F}$ = 21Hz), 114.1, 101.4, 75.4, 55.7, 55.3, 53.5, 49.0, 43.0, 33.2, 32.7, 25.6, 25.1, 25.0; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1061, 1608, 2922, 3398, 3782, 3923; **HRMS (ESI)** m/z calcd for $C_{28}H_{34}FN_2O_5$ $[M+H]^+$497.2452; found: 497.2443. Using **4p** (54.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl

acetate/hexane) to yield **5p** as a yellow oil (41.0 mg, 87%); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66 – 7.57 (m, 2H), 7.47 – 7.36 (m, 2H), 7.21 (s, 1H), 7.09 – 6.94 (m, 2H), 6.82 – 6.71 (m, 2H), 6.19 (d, J = 5.4 Hz, 1H), 6.02 (d, J = 5.4 Hz, 1H), 4.73 – 4.60 (m, 1H), 3.77 (s, 3H), 1.87 (dd, J = 23.3, 10.7 Hz, 4H), 1.71 (d, J = 12.6 Hz, 1H), 1.48 (d, J = 10.8 Hz, 1H), 1.37 (dd, J = 21.2, 11.2 Hz, 3H), 1.16 – 1.12 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.2, 163.4,163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 161.6, 137.2, 133.3, 131.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.2, 128.8 (d $J_{C\text{-}F}$ = 8.2 Hz),124.1, 116.7, 116.1 (d $J_{C\text{-}F}$ = 21.7 Hz), 114.0, 106.9, 67.3, 55.4, 53.4, 31.8, 31.3, 29.7, 25.8, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_3$ $[M+H]^+$ 433.1927; found: 433.1943.

(E)-4-Cyclohexyl-6-(4-fluorophenyl)-7-(4-methylbenzylidene)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5q):

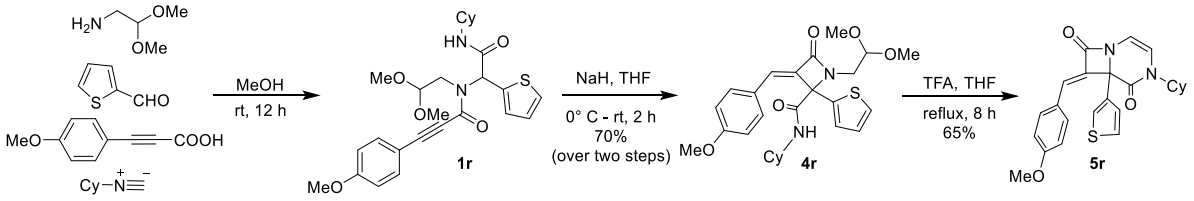


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.051 mL, 0.475 mmol), 3-(4-methylphenyl) propiolic acid (76.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC,product **1q** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4q** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white solid (114 mg,50%); **m.p:** 99-101 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.36 (dd, J = 8.7, 5.3 Hz, 2H), 7.07 (dd, J = 24.5, 16.1 Hz, 5H), 4.74 (t, J = 5.4 Hz, 1H), 3.90 – 3.74 (m, 1H), 3.48 (s, 3H), 3.44 – 3.32 (m, 4H), 2.71 (dd, J = 14.6, 6.0 Hz, 1H), 2.28 (s, 3H), 2.02 (d, J = 11.0 Hz, 1H), 1.84 – 1.65 (m, 4H), 1.44 – 1.30 (m, 2H), 1.22 – 1.06 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 167.3, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 140.9, 137.4, 131.6, 130.5 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.1(d, $J_{C\text{-}F}$ = 3.0 Hz), 129.4, 128.9, 127.5, 116.1 (d, $J_{C\text{-}F}$ = 21.7 Hz), 101.4,75.4,55.7, 53.5, 49.0, 43.1, 33.2, 32.7, 25.6, 25.1, 25.1, 21.56; **HRMS (ESI)** m/z calcd for $C_{28}H_{34}FN_2O_4$ $[M+H]^+$ 481.2503; found: 481.2501.

Using **4q** (53.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5q** as a yellow solid (35.0 mg, 77%); m.p: 71-73 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.54 (d, J = 8.1 Hz, 2H), 7.46 – 7.39 (m, 2H), 7.22 (s, 1H), 7.08 – 6.99 (m, 4H), 6.19 (d, J = 5.4 Hz, 1H), 6.03 (d, J = 5.4 Hz, 1H), 4.67 (t, J = 9.7 Hz, 1H), 2.29 (s, 3H), 1.93 – 1.81 (m, 4H), 1.71 (d, J = 12.0 Hz, 1H), 1.44 (dd, J = 22.0, 9.2 Hz, 4H), 1.20 – 1.12 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 163.2, 163.0 (d, $J_{C\text{-}F}$= 247.5 Hz), 141.1, 138.8, 131.4, 129.5, 129.3, 128.8 (d $J_{C\text{-}F}$ = 8.2 Hz), 128.6, 116.8, 116.1 (d $J_{C\text{-}F}$ = 21 Hz), 106.7, 67.4, 60.5, 53.4, 31.8, 31.3, 25.8, 25.4, 21.6; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 1066, 1399, 1663, 1756, 2924, 3416, 3740, 348; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_2$ $[M+H]^+$417.1978; found: 417.1971.

(E)-4-Benzyl-7-(4-methoxybenzylidene)-6-(thiophen-2-yl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5r):

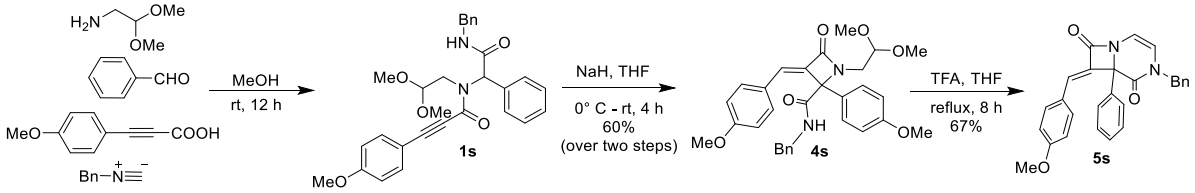


According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), thiophene-2-carbaldehyde (0.045 mL, 0.475 mmol),3-(4-Methoxyphenyl)-propiolic acid (83.0 mg, 0.475 mmol) and benzyl isocyanide (0.057 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC product **1r** was obtained, followed by the second step with sodium hydride

(34.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4r** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a brown oil (164.0 mg, 70%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.11 (t, J = 5.3 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.33 (dd, J = 5.1, 1.2 Hz, 1H), 7.27 – 7.21 (m, 5H), 7.20 (dd, J = 3.6, 1.2 Hz, 1H), 7.07 (s, 1H), 7.00 (dd, J = 5.1, 3.6 Hz, 1H), 6.84 – 6.74 (m, 2H), 4.63 (dd, J = 6.3, 4.7 Hz, 1H), 4.49 (d, J = 5.6 Hz, 2H), 3.76 (s, 3H), 3.52 (dd, J = 14.6, 4.7 Hz, 1H), 3.26 (s, 3H), 3.15 (s, 3H), 2.82 (dd, J = 14.6, 6.3 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.2, 167.3, 161.4, 137.9, 137.4, 137.1, 133.6, 128.9, 128.7, 128.1,127.7,127.6, 127.3, 127.1, 124.3, 114.1, 101.2, 72.3, 55.4, 55.3, 53.4, 44.2, 43.0; **HRMS (ESI)** m/z calcd for $C_{27}H_{29}N_2O_5S$ $[M+H]^+$ 493.1797; found: 493.1788.

Using **4r** (53.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to afford as a yellow oil **5r** (30.0 mg, 65%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.80 – 7.74 (m, 2H), 7.40 – 7.30 (m, 6H), 7.22 (s, 1H), 7.10 (dd, J = 3.6, 1.2 Hz, 1H), 6.95 (dd, J = 5.1, 3.6 Hz, 1H), 6.82 (d, J = 8.9 Hz, 2H), 6.18 (d, J = 5.2 Hz, 1H), 5.94 (d, J = 5.3 Hz, 1H), 5.03 (d, J = 14.8 Hz, 1H), 4.70 (d, J = 14.8 Hz, 1H), 3.78 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.3, 163.4, 161.8, 139.5, 137.0, 135.8, 133.7, 129.9, 129.1, 128.3, 127.6, 127.4, 127.2, 124.1, 120.0, 114.1, 106.9, 65.2, 55.4, 50.3; **HRMS (ESI)** m/z calcd for $C_{25}H_{21}N_2O_3S$ $[M+H]^+$429.1273; found: 429.1267.

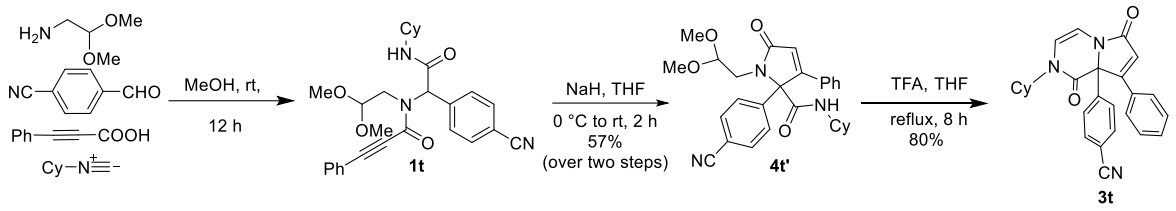
(E)-4-Benzyl-7-(4-methoxybenzylidene)-6-phenyl-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5s):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), benzaldehyde (0.048 mL, 0.475 mmol), 3-(4-Methoxyphenyl)-propiolic acid (83.0 mg, 0.475 mmol), and benzyl isocyanide (0.057 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC, product **1s** was obtained, followed by the second step with sodium hydride (34.0mg,1.43 mmol) in THF (6.0mL), compound **4s** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white oil (135.0 mg, 60%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.33 (t, J = 5.3 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.36 (d, J= 1.9 Hz, 5H), 7.31 – 7.27 (m, 5H), 7.18 (s, 1H), 6.84 – 6.69 (m, 2H), 4.63 (dd, J = 6.3, 4.6 Hz, 1H), 4.52 (dd, J = 5.6, 3.2 Hz, 2H), 3.74 (s, 3H), 3.44 – 3.38 (m, 1H), 3.25 (s, 3H), 3.14 (s, 3H), 2.66 (dd, J = 14.6, 6.4 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.1, 167.7, 161.4, 138.1, 135.5, 134.0, 133.6, 129.2, 128.7, 128.5, 128.2, 127.6, 127.5, 124.5, 114.1, 101.4, 76.3, 55.4, 55.4, 53.6, 44.1, 43.2; **HRMS (ESI)** m/z calcd for $C_{29}H_{30}N_2NaO_5$ $[M+Na]^+$509.2052; found: 509.2046.

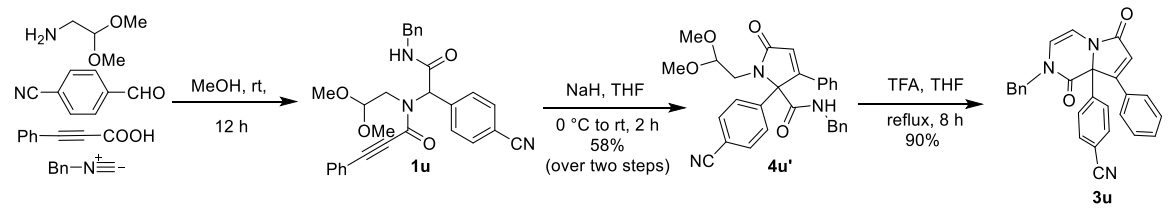
Using **4s** (52.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL),compound **4s** was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) as a yellow oil (30.0 mg, 67%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.64 (d, J = 8.9 Hz, 2H), 7.45 (ddd, J = 4.4, 2.4, 1.4 Hz, 2H), 7.38 – 7.28 (m, 8H), 7.22 (s, 1H), 6.79 – 6.73 (m, 2H), 6.17 (d, J = 5.2 Hz, 1H), 5.91 (d, J = 5.2 Hz, 1H), 5.02 (d, J = 14.8 Hz, 1H), 4.76 (d, J = 14.8 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.1, 164.1, 161.6, 137.2, 136.0, 135.4, 133.3, 129.4, 129.3, 129.2, 129.1, 128.3, 126.8, 124.2, 120.4, 114.0, 107.1, 68.2, 55.4, 50.2; **HRMS (ESI)** m/z calcd for $C_{27}H_{23}N_2O_3$ $[M+H]^+$ 423.1709; found: 423.1702.

4-(2-Cyclohexyl-1,6-dioxo-8-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3t):



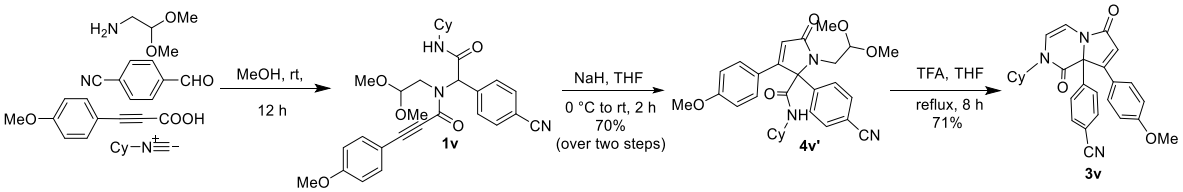
According to general procedure B using aminoacetaldehyde dimethyl acetal(0.052 mL, 0.475 mmol), 4-cyano benzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC, product **1t** was obtained, followed by the second step with sodium hydride (33.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4t'** was prepared and purified by silica gel column chromatography (25% ethyl acetate/hexane) as a white oil (130.0 mg, 57%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.70 (dd, J = 15.1, 8.1 Hz, 3H), 7.51 (d, J = 8.6 Hz, 2H), 7.32 (dd, J = 9.5, 5.6 Hz, 3H), 7.24 – 7.21 (m, 1H), 6.60 (s, 1H), 5.19 (dd, J = 7.3, 4.3 Hz, 1H), 3.67 (ddd, J = 18.7, 9.4, 5.8 Hz, 1H), 3.52 (s, 3H), 3.40 (s, 3H), 3.15 – 3.08 (m, 1H), 2.60 (dd, J = 14.2, 7.3 Hz, 1H),2.06 – 1.89 (m, 2H), 1.74 – 1.63 (m, 4H), 1.32 (dd, J = 23.4, 11.3 Hz, 3H), 1.21 – 1.16 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 172.80, 164.83, 161.39, 141.32, 132.83, 130.56, 130.43, 129.15, 129.01, 128.25, 122.38, 118.23, 112.91, 101.91, 78.67, 77.58, 77.16, 76.74, 56.57, 55.06, 49.37, 45.16, 34.06, 32.93, 32.62, 25.75, 25.58, 25.15, 25.10, 25.05; **HRMS (ESI)** m/z calcd for $C_{28}H_{31}N_3NaO_4$ $[M+Na]^+$ 496.2212; found: 496.2200.

4-(2-Benzyl-1,6-dioxo-8-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3u):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-cyanobenzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and benzyl isocyanide (0.054 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC,product **1u,** was obtained, followed by the second step with Sodium hydride (33.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4u'** was prepared and purified by silica gel column chromatography (25% ethyl acetate/hexane) as a white solid (133.0 mg, 58%); **m.p**: 153-157 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.30 (t, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 6.9 Hz, 3H), 7.27 (m, 3H), 7.25 – 7.23 (m, 1H), 7.16 (d, J = 6.8 Hz, 2H), 6.62 (s, 1H), 5.04 (dd, J = 6.6, 4.1 Hz, 1H), 4.48 (dd, J = 14.6, 6.3 Hz, 1H), 4.27 (dd, J = 14.5, 4.5 Hz, 1H), 3.33 (s, 3H), 3.17 (d, J = 10.7 Hz, 4H), 2.56 (dd, J = 14.2, 7.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.9, 160.7, 144.3, 132.8, 130.5, 129.9, 128.8, 127.8, 127.0, 119.2, 112.8, 102.3, 92.2, 56.1, 55.3, 41.4; **HRMS (ESI)** m/z calcd for $C_{29}H_{27}N_3NaO_4$ $[M+Na]^+$ 504.1899; found: 504.1887.

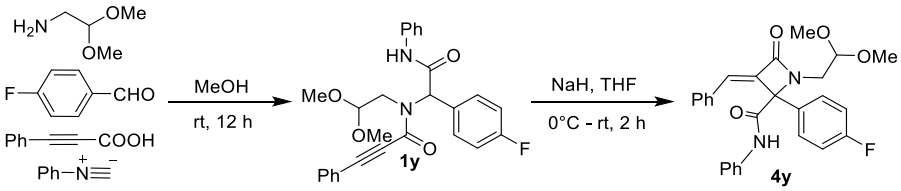
4-(2-Cyclohexyl-8-(4-methoxyphenyl)-1,6-dioxo-1,2-dihydropyrrolo[1,2-a]pyrazin-8a(6H)-yl)benzonitrile (3v):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-cyano benzaldehyde (62.0 mg, 0.475 mmol), 3-(4-Methoxyphenyl)propiolic acid (70.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC,product **1v** was obtained, followed by the second step with sodium hydride (33.0 mg, 1.43 mmol) in THF (6.0 mL),compound **4v'** was prepared and purified by

silica gel column chromatography (50% ethyl acetate/hexane) as a light pink solid (130.0 mg, 70%); **m.p:** 164-169 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72 (d,*J* = 7.8 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.53 – 7.47 (m, 2H), 7.35 – 7.28 (m, 2H), 6.80 – 6.71 (m, 2H), 6.51 (s, 1H), 5.17 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.76 (s, 3H), 3.72 – 3.61 (m, 1H), 3.51 (s, 3H), 3.39 (s, 3H), 3.11 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.59 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.02 (d, *J* = 11.8 Hz, 1H), 1.75 – 1.55 (m, 4H), 1.36 – 1.04 (m, 5H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.1, 165.2, 161.4, 160.9, 141.6, 132.8, 130.8, 129.2, 122.7, 119.9, 118.2, 113.7, 112.8, 101.9, 78.5, 56.5, 55.3, 55.0, 49.3, 45.0, 32.9, 32.6, 25.6, 25.2, 25.1; **HRMS (ESI)** m/z calcd for $C_{29}H_{33}N_3NaO_5$ $[M+Na]^+$ 526.2318; found: 526.2313.

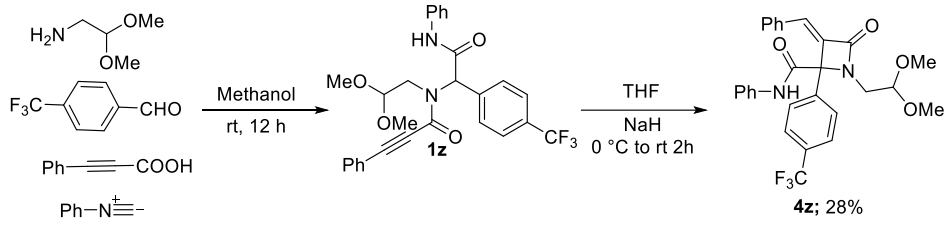
(E)-3-Benzylidene-1-(2,2-dimethoxyethyl)-2-(4-fluorophenyl)-4-oxo-N-phenylazetidine-2-carboxamide (4y):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol),4-fluorobenzaldehyde (0.048 mL, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol), in methanol (4.0 mL) to perform Ugi-4CC, product **1y** was obtained, followed by the second step with sodium hydride (34.0 mg, 1.43 mmol) in THF (6.0 mL), titled compound **4y** was purified by silica gel column chromatography (20% ethyl acetate/hexane) as a white oil(45.0 mg, 21%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.58 (s, 1H), 7.67 – 7.59 (m, 4H), 7.48 – 7.39 (m, 2H), 7.35 – 7.28 (m, 4H), 7.26 (d, *J* = 5.9 Hz,2H),7.14 – 7.01 (m, 3H), 4.74 (t, *J* = 4.7 Hz, 1H), 3.67 (dd, *J* = 14.8, 4.6 Hz, 1H), 3.55 (s, 3H), 3.40 (s, 3H), 2.75 (dd, *J* = 14.8, 4.8 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.3, 166.9,

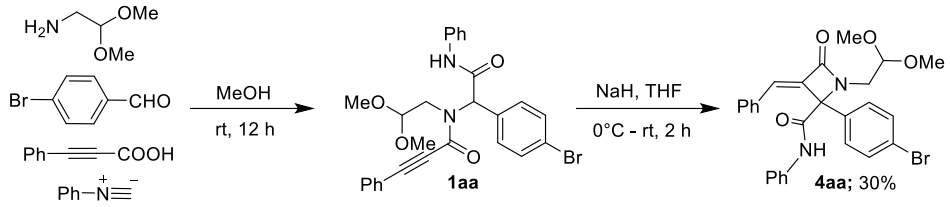
163.0 (d, $J_{C\text{-}F}$ = 247 Hz) , 138.0, 131.8, 131.5, 131.0, 130.9, 130.5, 129.1, 129.0, 128.7,128.4, 124.7,120.1, 116.2 (d, $J_{C\text{-}F}$ = 21.7 Hz), 101.7, 76.3, 55.8, 54.1, 42.6; **HRMS (ESI)** m/z calcd for $C_{27}H_{26}FN_2O_4[M+H]^+$461.1877; found: 461.1868.

(E)-3-Benzylidene-1-(2,2-dimethoxyethyl)-4-oxo-N-phenyl-2-(4-(trifluoromethyl)phenyl)-azetidine-2-carboxamide (4z) :



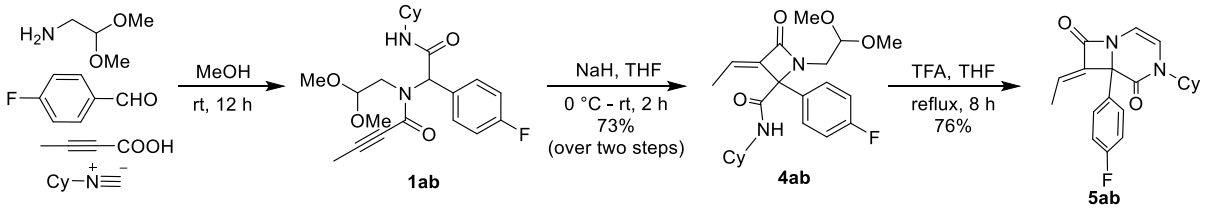
According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-triflоromethyl benzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol), was dissolve in methanol (4.0 mL) to perform Ugi-4CC, product **1z** was obtained, followed by the second step with sodium hydride (33 mg, 1.43 mmol) in THF (6.0 mL),compound **4z** was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) as a yellow oil (70.0 mg, 28%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.60 (s, 1H), 7.61 (ddd, J = 11.6, 7.1, 5.5 Hz, 8H), 7.35 – 7.27 (m, 6H), 7.14 – 7.08 (m, 1H), 4.74 (t, J = 4.5 Hz, 1H), 3.70 (dd, J = 14.8, 4.4 Hz, 1H), 3.57 (s, 3H), 3.40 (s, 3H), 2.73 (dd, J = 14.8, 4.5 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.1, 166.7, 138.0, 137.4, 131.8, 131.4, 130.7, 129.5, 129.1, 128.8, 126.1 (q, $J_{C\text{-}F}$ = 11.2, 3.7 Hz), 124.8, 120.1, 101.8, 76.4, 56.0, 54.4, 42.7; **HRMS (ESI)** m/z calcd for $C_{28}H_{26}F_3N_2O_4$ $[M+H]^+$ 511.1845; found: 511.1837.

(E)-3-Benzylidene-2-(4-bromophenyl)-1-(2,2-dimethoxyethyl)-4-oxo-N-phenylazetidine-2-carboxamide (4aa):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-bromo benzaldehyde (62.0 mg, 0.475 mmol), phenylpropiolic acid (70.0 mg, 0.475 mmol), and phenyl isocyanide (0.050 mL, 0.475 mmol),was dissolve in methanol (4.0 mL) to perform Ugi-4CC product **1aa** was obtained, followed by the second step with sodium hydride (33.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4aa** was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) as a white oil (65.0 mg, 30%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.58 (s, 1H), 7.61 (t,*J* = 6.7 Hz, 4H), 7.51 (d,*J* = 8.5 Hz, 2H), 7.36 – 7.26 (m, 8H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.73 (t, *J* = 4.6 Hz, 1H), 3.68 (dd, *J* = 14.8, 4.5 Hz, 1H), 3.54 (s, 3H), 3.39 (s, 3H), 2.74 (dd, *J* = 14.8, 4.7 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.2, 166.7, 138.0, 137.7, 132.3, 132.3, 131.8, 131.4, 130.6, 130.6, 129.0, 128.7, 128.5, 124.7, 123.6, 120.0, 101.7, 76.4, 55.9, 54.2, 42.6; **HRMS (ESI)** m/z calcd for $C_{27}H_{25}BrN_2NaO_4$ $[M+Na]^+$ 543.0895; found:543.0892.

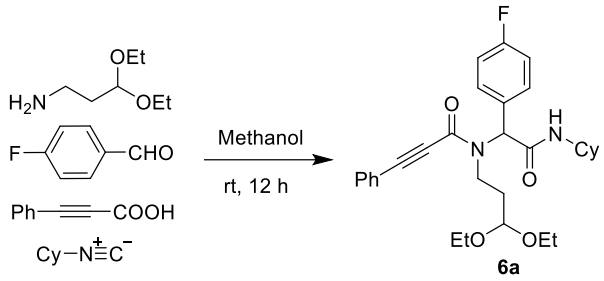
(E)-4-cyclohexyl-7-ethylidene-6-(4-fluorophenyl)-1,4-diazabicyclo[4.2.0]oct-2-ene-5,8-dione (5ab):



According to general procedure B using aminoacetaldehyde dimethyl acetal (0.052 mL, 0.475 mmol), 4-fluorobenzaldehyde (0.053 mL, 0.475 mmol), 2-butynoic acid (40.0 mg, 0.475 mmol), and cyclohexyl isocyanide (0.059 mL,0.475 mmol), was dissolve in methanol (4 mL) to perform Ugi-4CC, product **1ab** was obtained, followed by the second step with sodium hydride (35.0 mg, 1.43 mmol) in THF (6.0 mL), compound **4ab** was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) as a yellow oil, (140.0 mg, 73%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.93 (d, J = 7.5 Hz, 1H), 7.19 – 7.10 (m, 2H), 7.02 (t, J = 8.7 Hz, 2H), 6.00 (d, J = 1.5 Hz, 1H), 5.20 (dd, J = 7.7, 4.1 Hz, 1H), 3.77 (dtd, J = 11.2, 7.5, 4.0 Hz, 1H), 3.50 (s, 3H), 3.39 (s, 3H), 3.05 (dd, J = 14.2, 4.1 Hz, 1H), 2.55 (dd, J = 14.2, 7.7 Hz, 1H), 2.03 (t, J = 6.7 Hz, 4H), 1.86 (d, J = 12.3 Hz, 1H), 1.80 – 1.63 (m, 3H), 1.43 – 1.31 (m, 2H), 1.29 – 1.23 (m, 1H), 1.21 – 1.15 (m, 1H), 1.14 – 1.07 (m, 1H); **13C NMR (75 MHz, $CDCl_3$):** δ 174.3, 166.1, , 162.8, 162.7 (d, J = 246 Hz), 131.1(d, J = 3 Hz), 129.9 (d, J = 8.25 Hz), 123.0, 116.0 (d, J = 21.7 Hz), 102.2, 79.6, 56.7, 54.9, 49.2, 45.6, 33.1, 32.9, 25.7, 25.3, 14.9; **HRMS (ESI)** m/z calcd for $C_{22}H_{29}FN_2NaO_4$ $[M+Na]^+$ 427.2009; found: 427.1999.

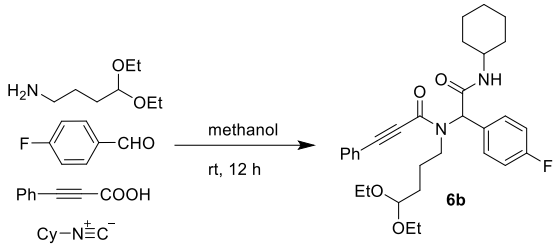
Using **4ab** (44.0 mg, 0.109 mmol), trifluoroacetic acid (0.14 mL, 2.18 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (15% ethyl acetate/hexane) to yield **5ab** as a yellow oil (28 mg, 76%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.26 – 7.18 (m, 2H), 7.08 – 6.99 (m, 2H), 6.49 (d, J = 5.6 Hz, 1H), 5.89 (q, J = 1.5 Hz, 1H), 5.78 (d, J = 5.6 Hz, 1H), 4.41 (tt, J = 11.0, 3.4 Hz, 1H), 2.18 (d, J = 1.5 Hz, 3H), 1.90 – 1.74 (m, 3H), 1.72 – 1.60 (m, 3H), 1.49 – 1.37 (m, 2H), 1.32 (dd, J = 10.7, 6.0 Hz, 2H); **13C NMR (75 MHz, $CDCl_3$):** δ 170.2, 163.0 (d, J = 246 Hz), 162.8, 162.3, 130.7, (d, J = 3.0 Hz), 127.2, (d, J = 8.25 Hz), 121.6, 116.1, (d, J = 21.75 Hz), 113.3, 106.9, 72.3, 53.2, 31.5, 30.9, 25.8, 25.4, 15.5; **HRMS (ESI)** m/z calcd for $C_{20}H_{22}FN_2O_2$ $[M+H]^+$ 341.1665; found: 341.1653.

N-(2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)-N-(3,3-diethoxypropyl)-3-phenylpropiolamide (6a):



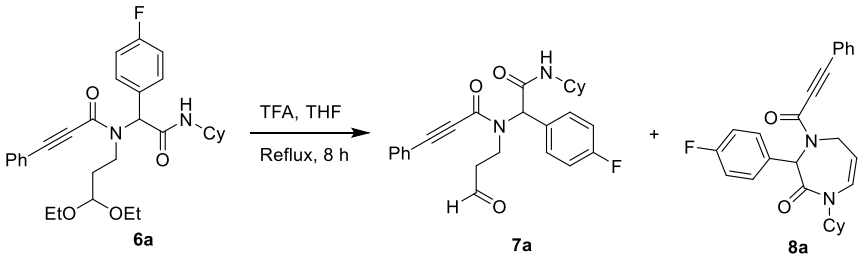
Equimolar mixture of 1-amino-3,3-diethoxypropane(0.475 mmol), 4-fluorobenzaldehyde (0.475 mmol), phenylpropiolic acid (0.475 mmol), and cyclohexyl isocyanide (0.475 mmol), was dissolved in methanol (6 mL). The resulting mixture was stirred at room temperature for 12 h. On completion of the reaction (based on TLC), the solvent was removed under vacuum and the crude was purified by silica gel column chromatography(15% ethyl acetate/hexane)to afford **6a** as white solid (284.0 mg,82%); **m.p:**120-122°C; Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.2); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60 – 7.52 (m, 2.41H), 7.48 – 7.32 (m, 6.13H), 7.08 (ddd, J = 13.1, 5.6, 3.2 Hz, 2.42H), 6.18 (d, J = 8.2 Hz, 0.2H), 6.14 (s, 0.26H), 5.99 (d, J = 8.0 Hz, 0.87H), 5.88 (s, 1H), 4.46 – 4.40 (m, 0.23H), 4.36 (t, J = 5.3 Hz, 1H), 3.85 – 3.78 (m, 0.86H), 3.77 – 3.69 (m, 1.89H), 3.58 – 3.47 (m, 2H), 3.45 – 3.30 (m, 3H), 2.04 (s, 0.78H), 1.98 – 1.79 (m, 3H), 1.58 (dd, J = 10.4, 5.1 Hz, 4H), 1.36 (td, J = 12.1, 2.3 Hz, 4.1H), 1.22 – 1.04 (m, 11.58H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.9, 167.8, 162.9 (d, $J_{C\text{-}F}$ = 246.7 Hz), 155.7, 155.4, 155.0, 132.7, 132.7, 131.6, 131.5, 131.4, 130.7(d, $J_{C\text{-}F}$= 3 Hz), 130.6, 130.4, 128.8, 128.6, 120.4, 120.1, 116.1 (d, $J_{C\text{-}F}$ = 21.7 Hz), 116.0 (d, $J_{C\text{-}F}$ =21.0 Hz), 115.8, 101.8, 101.2, 91.9, 91.0, 81.8, 81.5, 66.2, 61.9, 61.7, 61.6, 61.4, 61.2, 49.1, 48.8, 44.1, 40.4, 33.9, 33.1, 33.0, 32.9, 32.8, 32.0, 25.6, 25.5, 25.0, 24.95, 24.9, 24.8, 15.4, 15.3; **HRMS (ESI)** m/z calcd for $C_{30}H_{38}FN_2O_4$ $[M+H]^+$509.2816; found: 509.2806.

N-(2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)-N-(4,4-diethoxybutyl)-3-phenylpropiolamide (6b):



Equimolar mixture of 4,4-diethoxybutan-1-amine (0.475 mmol), 4-fluorobenzaldehyde (0.475 mmol), phenylpropiolic acid (0.475 mmol), and cyclohexyl isocyanide (0.475 mmol), was dissolved in methanol (6 mL). The resulting mixture was stirred at room temperature for 12 h. On completion of the reaction (based on TLC), the solvent was removed under vacuum and the crude was purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **6b** as white oil (257.0 mg, 79%); Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.2); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58 – 7.50 (m, 2.4H), 7.50 – 7.31 (m, 6H), 7.12 – 7.01 (m, 2.4H), 6.15 (s, 0.2H), 6.00 (d, J = 8.0 Hz, 0.9H), 5.91 (s, 1H), 5.74 (d, J = 8.0 Hz, 0.2H), 4.31 (t, J = 5.5 Hz, 0.9H), 4.27 (d, J = 5.6 Hz, 0.2H), 3.86 – 3.73 (m, 1.2H), 3.66 (td, J = 10.4, 5.7 Hz, 1.6H), 3.51 (ddq, J = 14.3, 9.3, 7.0 Hz, 2.6H), 3.42 – 3.29 (m, 2.4H), 1.91 (dd, J = 8.2, 3.8 Hz, 2.5H), 1.71 – 1.56 (m, 4.4H), 1.51 – 1.42 (m, 2.1H), 1.33 (dd, J = 13.7, 8.2 Hz, 3.6H), 1.19 (dd, J = 9.7, 4.7 Hz, 2.1H), 1.10 (td, J = 7.0, 2.5 Hz, 8.7H) ; **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.9, 167.6, 163.0 (d, $J_{C\text{-}F}$ = 246.7 Hz), 155.7, 132.6, 131.5, 131.3 (d, $J_{C\text{-}F}$ = 7.5 Hz), 130.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 130.5, 130.4, 128.8, 128.7, 120.4, 116.0 (d, $J_{C\text{-}F}$ = 21.7 Hz) , 115.9 (d, $J_{C\text{-}F}$ = 21.0 Hz), 102.4, 102.4, 91.7, 91.0, 81.8, 81.5, 65.8, 61.2, 61.1, 60.9, 48.9, 48.8, 48.2, 44.6, 33.1, 33.0, 32.9, 32.8, 32.0, 31.3, 29.5, 25.6, 25.5, 24.9, 24.8, 23.4, 22.8, 15.3, 14.2; **HRMS (ESI)** m/z calcd for $C_{31}H_{39}FN_2NaO_4$ $[M+Na]^+$545.2792; found: 545.2782.

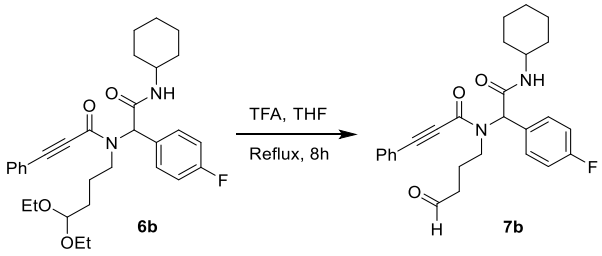
1-Cyclohexyl-3-(4-fluorophenyl)-4-(3-phenylpropioloyl)-1,3,4,5-tetrahydro-2H-1,4-diazepin-2-one (7a) *and* ***N-(2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)-N-(3-oxopropyl)-3-phenyl propiolamide (8a):***



Ugi adduct **6a** (100 mg, 0.196 mmol) on treatment with trifluoroacetic acid (0.256 mL, 3.93 mmol)in THF (4.0 mL) under reflux conditions, a mixture of compounds **7a** and **8a** were obtained, which were purified by silica gel column chromatography; **7a*:*** isolated in 20*%* ethyl acetate/hexane as a white solid (72 mg, 84%); **m.p**: 210-212 °C; Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.5); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.67 (s, 1H), 9.62 (s, 0.4H), 7.52 (dt, *J* = 8.4, 4.3 Hz, 3H), 7.46 – 7.33 (m, 7.2H), 7.16 – 7.04 (m, 3H), 6.15 (s, 0.5H), 6.02 (s, 1H), 5.83 (d, *J* = 7.7 Hz, 1H), 5.74 (d, *J* = 7.6 Hz, 0.5H), 4.00 (ddd, *J* = 15.1, 9.4, 5.5 Hz, 1H), 3.90 – 3.74 (m, 2.4H), 3.70 – 3.49 (m, 1H), 2.98 (ddd, *J* = 18.2, 9.4, 5.5 Hz, 1H), 2.88 – 2.70 (m, 0.5H), 2.58 (ddd, *J* = 18.4, 9.3, 5.6 Hz, 1H), 2.47 – 2.32 (m, 0.5H), 1.92 (d, *J* = 11.9 Hz, 3H), 1.74 – 1.57 (m, 6H), 1.40 – 1.31 (m, 2.5H), 1.20 – 1.08 (m, 4.4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.5, 199.9, 167.7, 167.3, 163.0 (d, $J_{C\text{-}F}$ = 247.5 Hz), 155.6, 155.3, 132.7, 132.6, 131.3 (d, $J_{C\text{-}F}$ = 8.25 Hz), 131.2 (d, $J_{C\text{-}F}$ = 7.5 Hz), 130.7, 130.6 (d, $J_{C\text{-}F}$ = 3.75 Hz),130.4 (d, $J_{C\text{-}F}$ = 3.75 Hz), 128.8, 128.8, 120.0, 119.9, 116.5 (d, $J_{C\text{-}F}$ = 21.7 Hz), 116.4 (d, $J_{C\text{-}F}$ = 21 Hz), 92.0, 91.8, 81.4, 81.2, 80.7, 65.9, 60.6, 49.1, 49.0, 44.6, 42.5, 40.7, 38.5, 33.1, 33.0, 32.9, 32.8, 25.5, 25.4, 24.9, 24.8; **HRMS (ESI)** m/z calcd for $C_{26}H_{28}FN_2O_3$ $[M+H]^+$ 435.2084; found: 435.2082.

8a: isolated in 12% ethyl acetate/hexane as a white solid(9 mg,12%); **m.p**: 165-167 °C; Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.5); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.46 – 7.35 (m, 3H), 7.35 – 7.28 (m, 2H), 7.17 – 6.97 (m, 6.4H), 6.58 (s, 1H), 6.52 (s, 0.5H), 5.86 (dd, *J* = 9.1, 1.5 Hz, 0.5H), 5.78 (dd, *J* = 9.3, 2.2 Hz, 1H), 5.19 (dt, *J* = 9.1, 5.4 Hz, 0.5H), 5.11 (ddd, *J* = 9.3, 5.8, 4.8 Hz, 1H), 4.56 – 4.41 (m, 2.5H), 4.37 (dd, *J* = 4.7, 2.4 Hz, 0.5H), 4.20 (dd, *J* = 16.3, 5.5 Hz, 0.5H), 3.98 (dd, *J* = 17.1, 6.0 Hz, 1H), 1.82 (d, *J* = 10.9 Hz, 5.5H), 1.69 (d, *J* = 15.8 Hz, 3.5H), 1.46 – 1.34 (m, 5H), 1.17 – 1.04 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.0, 168.5, 162.5 (d, $J_{C\text{-}F}$ = 246 Hz), 154.9, 154.1, 132.9, 132.6, 130.6, 130.2 (d, $J_{C\text{-}F}$ = 3 Hz), 128.7, 128.6, 128.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.9, 127.6 (d, $J_{C\text{-}F}$ = 7.5 Hz), 127.2, 120.2, 120.0, 115.8 (d, $J_{C\text{-}F}$ = 21.7 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.7 Hz), 113.0, 112.1, 92.2, 91.6, 81.2, 80.8, 67.9, 63.2, 54.7, 54.6, 44.3, 39.7, 31.8, 31.7, 29.6, 29.5, 25.9, 25.6, 25.5; **HRMS (ESI)** m/z calcd for $C_{26}H_{26}FN_2O_2[M+H]^+$417.1978; found: 417.1978.

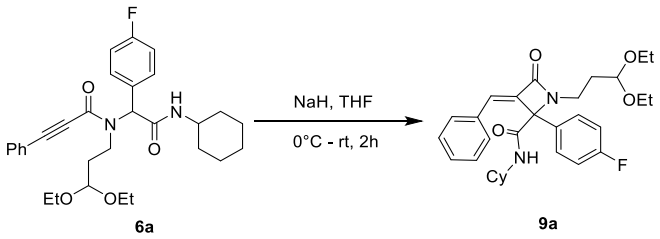
N-(2-(Cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)-N-(4-oxobutyl)-3-phenylpropiolamide (7b):



Using Ugi adduct **6b** (100 mg, 0.191 mmol) and trifluoroacetic acid (0.249 mL, 3.83 mmol) in THF (4.0 mL) under reflux conditions, the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **7b** (66 mg, 76%) as a white solid; **m.p**: 180-182°C; Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.3); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.66 (t, *J* = 1.1 Hz, 0.9H), 9.61 (t, *J* = 1.2 Hz, 0.2H), 7.55 (ddd, *J* =

9.3, 5.3, 1.5 Hz, 2.5H), 7.49 – 7.33 (m, 6.3H), 7.08 (dd, *J* = 11.9, 5.3 Hz, 2.5H), 6.13 (s, 0.2H), 5.92 (d, *J* = 8.0 Hz, 0.9H), 5.82 (s, 1H), 5.75 (s, 0.0.2H), 3.93 – 3.72 (m, 1.3H), 3.67 (t, *J* = 7.6 Hz, 2H), 3.46 (ddd, *J* = 14.9, 9.6, 5.6 Hz, 0.3H), 3.34 – 3.22 (m, 0.3H), 2.42 (dt, *J* = 7.0, 3.7 Hz, 2H), 2.31 (t, *J* = 6.9 Hz, 0.6H), 1.92 (dt, *J* = 17.5, 6.9 Hz, 3.6H), 1.71 – 1.53 (m, 5H), 1.44 – 1.28 (m, 3H), 1.12 (ddd, *J* = 17.2, 9.6, 5.9 Hz, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 201.6, 201.1, 167.8, 167.5, 162.9 (d,$J_{C\text{-}F}$ = 247.5 Hz), 155.7, 155.4, 132.7, 132.6, 131.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 131.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.6 (d, $J_{C\text{-}F}$ = 3 Hz), 130.5, 128.8, 120.2, 116.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 116.1 (d, $J_{C\text{-}F}$ = 21.0 Hz), 91.9, 91.4, 81.7, 81.4, 65.8, 61.3, 49.0, 48.9, 47.2, 43.8, 41.5, 41.0, 33.1, 33.0, 32.9, 32.8, 25.5, 25.4, 24.9, 24.8, 22.2, 20.8; **HRMS (ESI)** m/z calcd for $C_{27}H_{30}FN_2O_3$ $[M+H]^+$449.2240; found: 449.2238.

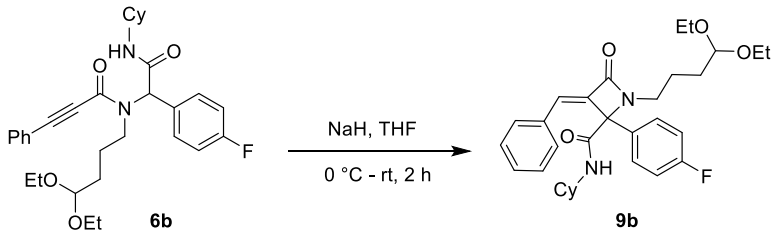
(E)-3-Benzylidene-N-cyclohexyl-1-(3,3-diethoxypropyl)-2-(4-fluorophenyl)-4-oxoazetidine-2-carboxamide (9a):



According to general procedure A using Ugi adduct (100 mg, 0.196 mmol), sodium hydride (14 mg, 0.589 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **9a** as a transparent oil (72 mg, 72%); Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 1); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.41 (ddd, *J* = 9.1, 6.1, 3.6 Hz, 6.1H), 7.27 (dd, *J* = 4.6, 2.7 Hz, 3.56H), 7.14 (s, 1H), 7.07 (td, *J* = 8.7, 6.6 Hz, 4.45H), 6.98 – 6.80 (m,1.83H), 6.65 (t, *J* = 8.7 Hz, 0.4H), 5.53 (s, 1H), 4.67 (dd, *J* = 6.1, 4.0 Hz, 1H), 4.55 (t, *J* = 5.4 Hz, 1.1H), 4.01 – 3.89 (m, 1.2H), 3.83 – 3.36 (m,

12H), 3.05 (dt, *J* = 14.6, 6.3 Hz, 1H), 2.92 (dt, *J* = 14.7, 5.6 Hz, 1H), 2.19 – 2.07 (m, 2H), 2.05 – 1.95 (m, 2.34H), 1.94 – 1.79 (m, 5.77H), 1.58 (d, *J* = 11.3 Hz, 4H), 1.36 – 1.28 (m, 4.63H), 1.23 – 1.14 (m, 15.6H), 1.11 – 0.98 (m, 3.3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.6, 166.3, 155.7, 139.9, 132.0, 131.9, 131.8, 131.0, 130.7, 130.6, 130.5, 130.4, 130.2, 128.9, 128.2, 128.1, 128.0, 125.9, 125.6, 116.3, 116.1, 116.0, 115.9, 102.3, 101.9, 86.4, 74.9, 63.0, 62.6, 61.7, 60.9, 51.8, 49.1, 37.7, 35.7, 32.9, 32.5, 32.3, 32.1, 29.7, 29.5, 25.9, 25.5, 25.1, 25.0, 24.9, 15.5, 15.4, 15.3; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 622, 691, 815, 1237, 1509, 1666, 1714, 2213, 2930; **HRMS (ESI)** m/z calcd for $C_{30}H_{37}FN_2NaO_4[M+H]^+$531.2635; found: 531.2622.

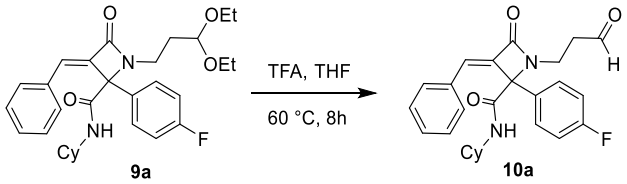
(E)-3-Benzylidene-N-cyclohexyl-1-(4,4-diethoxybutyl)-2-(4-fluorophenyl)-4-oxoazetidine-2-carboxamide (9b):



According to general procedure A using Ugi adduct (100 mg, 0.191 mmol), sodium hydride (14 mg, 0.573 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to afford **9b** as a transparent oil (68.0 mg, 68%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.53 – 7.45 (m, 2H), 7.33 – 7.23 (m, 5H), 7.14 (s, 1H), 7.07 (dd, *J* = 11.9, 5.2 Hz, 2H), 6.09 (d, *J* = 8.0 Hz, 1H), 4.36 (t, *J* = 5.0 Hz, 1H), 3.78 (ddd, *J* = 14.3, 10.2, 4.0 Hz, 1H), 3.56 (dq, *J* = 9.1, 7.1 Hz, 2H), 3.47 – 3.29 (m, 3H), 3.22 (dd, *J* = 9.8, 4.2 Hz, 1H), 1.82 (d, *J* = 9.5 Hz, 1H), 1.75 – 1.66 (m, 2H), 1.59 – 1.47 (m, 7H), 1.30 (m, 3H), 1.15 (t, *J* = 7.0 Hz, 7H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.2, 165.8, 163.1 (d, J_{C-F} = 247.5 Hz), 140.6, 132.1, 131.0(d, J_{C-F} = 3.75 Hz), 130.6, 130.5 (d, J_{C-F} = 8.25 Hz), 130.2, 129.1, 125.5,

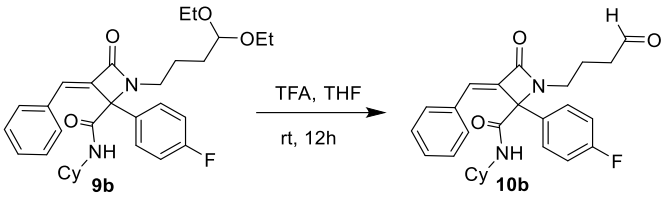
116.2 (d, $J_{C\text{-}F}$ = 21.7 Hz), 102.4, 74.3, 61.3, 61.2, 48.7, 41.8, 32.7, 32.5, 31.4, 31.0, 29.8, 25.43, 24.6,24.5, 24.1, 15.4; **HRMS (ESI)** m/z calcd for $C_{31}H_{39}FN_2NaO_4$ $[M+Na]^+$545.2792; found: 545.2786.

(E)-3-Benzylidene-N-cyclohexyl-2-(4-fluorophenyl)-4-oxo-1-(3-oxopropyl)azetidine-2-carboxamide (10a):



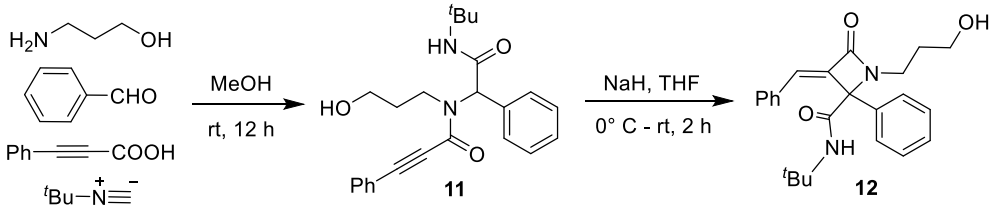
According to general procedure B using *β*-lactam **9a**(100.0 mg, 0.196 mmol), trifluoroacetic acid (0.256 mL, 3.93 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **10a** as a yellow solid (64.0mg, 75%); **m.p**: 90-92 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.78 (s, 1H), 7.47 – 7.39 (m, 4H), 7.32 – 7.27 (m, 2H), 7.14 – 7.05 (m, 4H), 3.87 – 3.78 (m, 2H), 3.47 – 3.23 (m, 3H), 2.77 – 2.65 (m, 1H), 1.90 (d, J = 13.8 Hz, 1H), 1.79 (d, J = 11.3 Hz, 2H), 1.74 – 1.49 (m, 7H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 200.5, 167.0, 166.0, 163.1 (d, $J_{C\text{-}F}$ = 248.2 Hz), 139.6, 131.9, 130.9, 130.5(d, $J_{C\text{-}F}$ = 3.0 Hz), 130.4, 130.3(d, $J_{C\text{-}F}$ = 8.2 Hz), 129.0, 126.3, 116.5 (d, $J_{C\text{-}F}$ = 21.7 Hz),116.3(d, $J_{C\text{-}F}$ = 21 Hz), 92.2, 74.8, 60.5, 49.1, 41.2, 35.9, 32.9, 32.4, 25.5, 24.9, 24.8; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 665, 689, 745, 1236, 1509, 1604, 166, 1716, 2856, 2933, 3012; **HRMS (ESI)** m/z calcd for $C_{26}H_{28}FN_2O_3$ $[M+H]^+$435.2084; found: 435.2080.

(E)-3-Benzylidene-N-cyclohexyl-2-(4-fluorophenyl)-4-oxo-1-(4-oxobutyl)azetidine-2-carboxamide (10b):



According to general procedure B using *β*-lactam **9b** (100.0 mg, 0.191 mmol), trifluoroacetic acid (0.249 mL, 3.83 mmol) in THF (4.0 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **10b** as a transparent oil (43.0 mg, 50%); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 9.68 (t, J = 1.1 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.35 – 7.24 (m, 5H), 7.11 (dd, J = 16.6, 8.1 Hz, 3H), 6.16 (d, J = 7.7 Hz, 1H), 3.77 (ddd, J = 10.3, 3.9, 2.0 Hz, 1H), 3.42 – 3.16 (m, 2H), 2.58 – 2.30 (m, 2H), 1.83 (ddt, J = 23.5, 16.3, 9.7 Hz, 5H), 1.51 (d, J = 9.4 Hz, 3H), 1.33 – 1.22 (m, 3H), 1.12 – 1.00 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 201.3, 167.1, 165.8, 163.2 (d, $J_{C\text{-}F}$ = 248.2 Hz) , 140.6, 132.0, 131.1 (d, $J_{C\text{-}F}$ = 3 Hz), 130.5, 130.4, 130.3, 129.1, 125.6, 116.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 74.4, 48.7, 41.6, 41.4, 32.6,32.4,25.4, 24.5, 24.4, 21.1; **HRMS (ESI)** m/z calcd for $C_{27}H_{30}FN_2O_3[M+H]^+$449.2240; found: 449.2233.

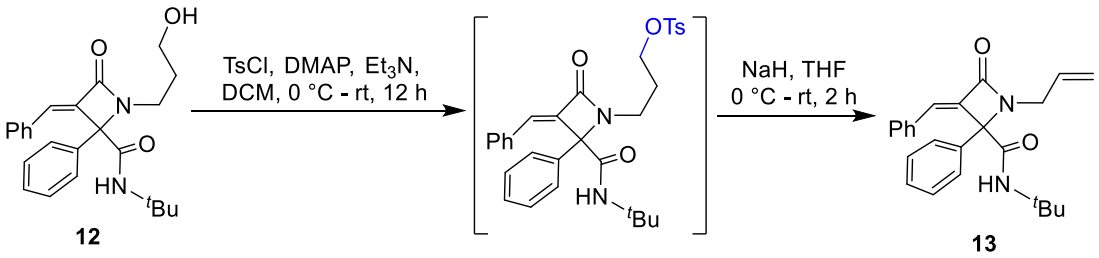
(E)-3-Benzylidene-N-(tert-butyl)-1-(3-hydroxypropyl)-4-oxo-2-phenylazetidine-2-carboxamide (12):



According to general procedure B using 3-aminopropan-1-ol (0.051 mL, 0.665 mmol), benzaldehyde (0.067 mL, 0.665 mmol), phenylpropiolic acid (97mg, 0.665 mmol), and *tert*-butyl isocyanide (0.075mL,0.665 mmol)in methanol (6 mL) to perform Ugi-4CC afforded compound

11, followed by the second step with sodium hydride (78 mg,2.0 mmol) in THF (10 mL), the titled compound was prepared and purified by silica gel column chromatography (20% ethyl acetate/hexane) to yield **12** as a transparent oil (210 mg,80%); **^{1}H NMR (400 MHz,CDCl$_3$):** δ 7.51 (dd, J = 8.0, 1.7 Hz, 2H), 7.46 – 7.40 (m, 3H), 7.30 – 7.21 (m, 5H), 7.14 (s, 1H), 5.98 (s, 1H), 3.69 – 3.56 (m, 2H), 3.49 (dt, J = 14.4, 5.8 Hz, 1H), 3.37 – 3.30 (m, 1H), 1.80 – 1.72 (m, 2H), 1.14 (s, 9H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 167.9, 166.4, 141.3, 135.8, 132.4, 130.1, 130.1, 129.4, 129.3, 129.2, 128.1, 124.7, 75.2, 59.2, 52.1, 38.6, 30.9, 28.3; **HRMS (ESI)** m/z calcd for $C_{24}H_{29}N_2O_3[M+H]^+$ 393.2178; found: 393.2173.

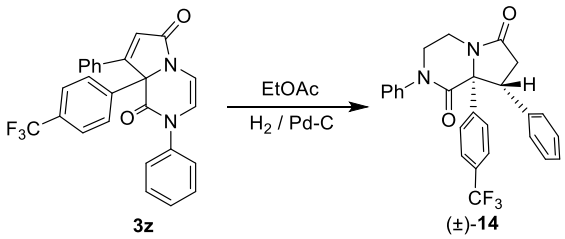
(E)-1-Allyl-3-benzylidene-N-(tert-butyl)-4-oxo-2-phenylazetidine-2-carboxamide (13):



4-Methylbenzenesulfonyl chloride (204.0 mg, 1.07 mmol), 4-Dimethylaminopyridine (0.008 mL, 0.107 mmol), triethylamine (0.076 mL, 1.07 mmol) was dissolved in DCM (5.0 mL) and added in the mixture of β-lactam **12** (210.0 mg, 0.535 mmol) in anhydrous DCM (10.0 mL) at 0 °C. After completion of reaction, solvent was removed under reduced pressure. Crude product was dissolved in anhydrous THF (10.0 mL) followed by the addition of sodium hydride (64.0 mg, 1.61 mmol), the titled compound was prepared and purified by silica gel column chromatography (30% ethyl acetate/hexane) to yield **13** as a transparent oil (125.0 mg, 62%); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.49 – 7.45 (m, 2H), 7.39 (dtd, J = 7.1, 4.6, 2.4 Hz, 3H), 7.36 – 7.32 (m, 2H), 7.28 – 7.24 (m, 3H), 7.17 (s, 1H), 6.07 (s, 1H), 5.76 (ddt, J = 16.8, 10.1, 6.4 Hz, 1H), 5.20 – 5.06 (m, 2H), 4.04 (ddt, J = 15.7, 6.1, 1.4 Hz, 1H), 3.69 (ddt, J = 15.7, 6.7, 1.2 Hz, 1H), 1.20 (s, 9H);

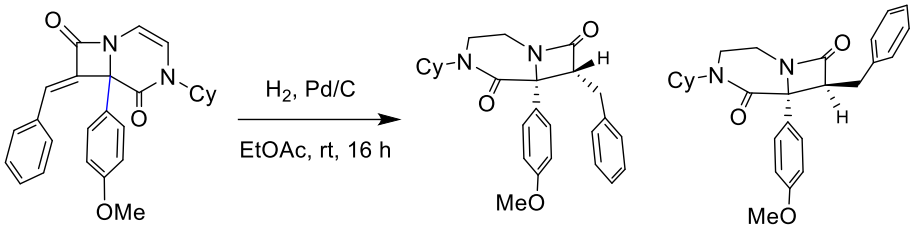
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 165.7, 140.9, 135.2, 132.5, 132.4, 130.6, 130.1, 129.2,129.1,129.0, 128.6, 125.5, 118.7, 75.5, 52.0, 44.3, 28.4; **HRMS (ESI)** m/z calcd for $C_{24}H_{27}N_2O_2[M+H]^+$375.2073; found: 375.2068.

Reduction of 3z through hydrogenation*:*



2,8-Diphenyl-8a-(4-(trifluoromethyl)phenyl)tetrahydropyrrolo[1,2-a]pyrazine-1,6(2H,7H)-dione **(14):** To a stirred solution of γ-lactam fused dihydropyrazinone **3z** (50.0 mg, 0.11 mmol) in ethyl acetate after complete dilution of starting material, then added 10% Pd/C (60.0 mg, 0.56 mmol) at room temperature. The reaction mixture was vigorously stirred under hydrogen (balloon pressure) atmosphere for 16 h. After the completion of reaction, the reaction mixture was filtered over celite and concentrated under vacuum. The crude was purified by silica gel column chromatography (20% ethyl acetate/hexane) to afford **14** (35.0 mg, 70%) as a white solid; **m.p**: 165-167 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.47 – 7.37 (m, 4H), 7.32 – 7.27 (m, 1H), 7.22 – 7.09 (m, 4H), 7.09 – 6.98 (m, 3H), 6.94 – 6.89 (m, 2H), 4.54 (dd, J = 11.0, 9.3 Hz, 1H), 4.11 (ddd, J = 12.8, 10.4, 6.1 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.69 – 3.60 (m, 1H), 3.46 (ddd, J = 13.3, 10.3, 5.0 Hz, 1H), 2.95 – 2.78 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.9, 169.7, 141.4, 139.9, 136.3, 130.7 (q, $J_{C\text{-}F}$ = 33.0, 98.0 Hz), 129.7, 129.5, 127.8, 127.5, 127.4, 126.3, 125.6 (q, $J_{C\text{-}F}$ = 10.0, 3.0 Hz), 125.5, 125.2, 122.5, 72.7, 47.5, 47.0, 38.8, 36.2; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 658, 697, 846, 1070, 1124, 1166, 1324, 1395, 1493, 1685, 1691, 2856, 2729, 3007; **HRMS (ESI)** m/z calcd for $C_{26}H_{22}F_3N_2O_3$ $[M+H]^+$ 451.1633; found: 451.1645.

Reduction of 5g through hydrogenation*:*



(±)-**5g** (±)-(6,7-*syn*)-**15** (±)-(6,7-*anti*)-**15**

To a stirred solution of *β*-lactam fused dihydropyrazinone **5g** (50.0 mg, 0.120 mmol) in ethyl acetate, after complete dilution of starting material, then added 10% Pd/C (64.0 mg, 0.60 mmol) at room temperature. The reaction mixture was vigorously stirred under hydrogen (balloon pressure) atmosphere for 16 h. After the completion of reaction, the reaction mixture was filtered over celite and concentrated under vacuum. The crude was purified by silica gel column chromatography to afford (±)-**(**6,7-*syn***)-15** and *(±)*-**(**6,7-*anti***)-15.**

***7-Benzyl-4-cyclohexyl-6-(4-methoxyphenyl)-1,4-diazabicyclo[4.2.0]octane-5,8-dione [*(±)-(6,7-*syn*)-15*]*:** isolated in 20% ethyl acetate/hexane as a white solid (26.0 mg, 52%); **m.p**: 165-167 °C; **^{1}H NMR (300 MHz, $CDCl_3$):** *δ* 7.51 – 7.44 (m, 2H), 7.36 – 7.30 (m, 2H), 7.26 (dd,*J* = 6.1, 2.5 Hz, 2H), 7.16 (t,*J* = 7.2 Hz, 1H), 6.91 – 6.84 (m,2H), 4.59 – 4.46 (m, 1H), 3.85 – 3.75 (m, 4H), 3.52 – 3.30 (m, 4H), 3.11 – 2.90 (m, 2H), 1.79 – 1.57 (m, 6H), 1.43 – 1.37 (m, 2H), 1.17 (dd,*J* = 12.3, 3.6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** *δ* 172.9, 168.1, 159.7, 139.3, 130.6, 129.1, 128.4, 126.6, 126.3, 114.4, 65.2, 63.1, 55.4,52.4, 39.6, 38.3, 32.6, 30.3, 30.2, 25.7, 25.6, 25.5; **IR ($CHCl_3$) ν_{max} (cm^{-1})** = 695, 747, 828, 1032, 1175, 1246, 1345, 1509, 1650, 1753, 2854, 2927, 3005; **HRMS (ESI)** m/z calcd for $C_{26}H_{31}N_2O_3$ $[M+H]^+$419.2335; found: 419.2323;

***7-Benzyl-4-cyclohexyl-6-(4-methoxyphenyl)-1,4-diazabicyclo[4.2.0]octane-5,8-dione [*(±)-(6,7-*anti*)-15]*:** isolated in 20% ethyl acetate/hexane as a transparent oil **(**6.0 mg, 12**%)**; **^{1}H NMR (300 MHz, $CDCl_3$):** *δ* 7.37 – 7.29 (m, 2H), 7.20 – 7.07 (m, 3H), 7.06 – 6.95 (m, 2H), 6.89 – 6.78

(m, 2H), 4.43 (tt, *J* = 11.8, 3.6 Hz, 1H), 4.15 (dd, *J* = 8.5, 7.3 Hz, 1H), 3.80 (s, 3H), 3.65 (td, *J* = 12.1, 5.5 Hz, 1H), 3.47 – 3.31 (m, 2H), 2.99 (ddd, *J* = 17.7, 13.2, 4.8 Hz, 1H), 2.78 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.52 – 2.40 (m, 1H), 1.81 – 1.63 (m, 4H),1.55 – 1.27 (m,4H), 1.14 – 0.98 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 172.9, 170.4, 159.9, 137.8,128.6, 128.2, 127.8, 126.2, 126.1, 114.1, 65.0, 59.2, 55.4, 52.3, 41.5, 37.9, 32.0, 30.7, 30.0, 25.6, 25.4; **HRMS (ESI)** m/z calcd for $C_{26}H_{31}N_2O_3$ $[M+H]^+$419.2335; found: 419.2339.

6. References:

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Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, Jr, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. Fox and D. Gaussian, Inc., Wallingford CT, 2013.

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7. Copies of ^{1}H, ^{13}C and ^{19}F NMR Spectra:

Figure S7: ^{1}H and ^{13}C NMR of compound **1a** (rotamer 1:0.6)

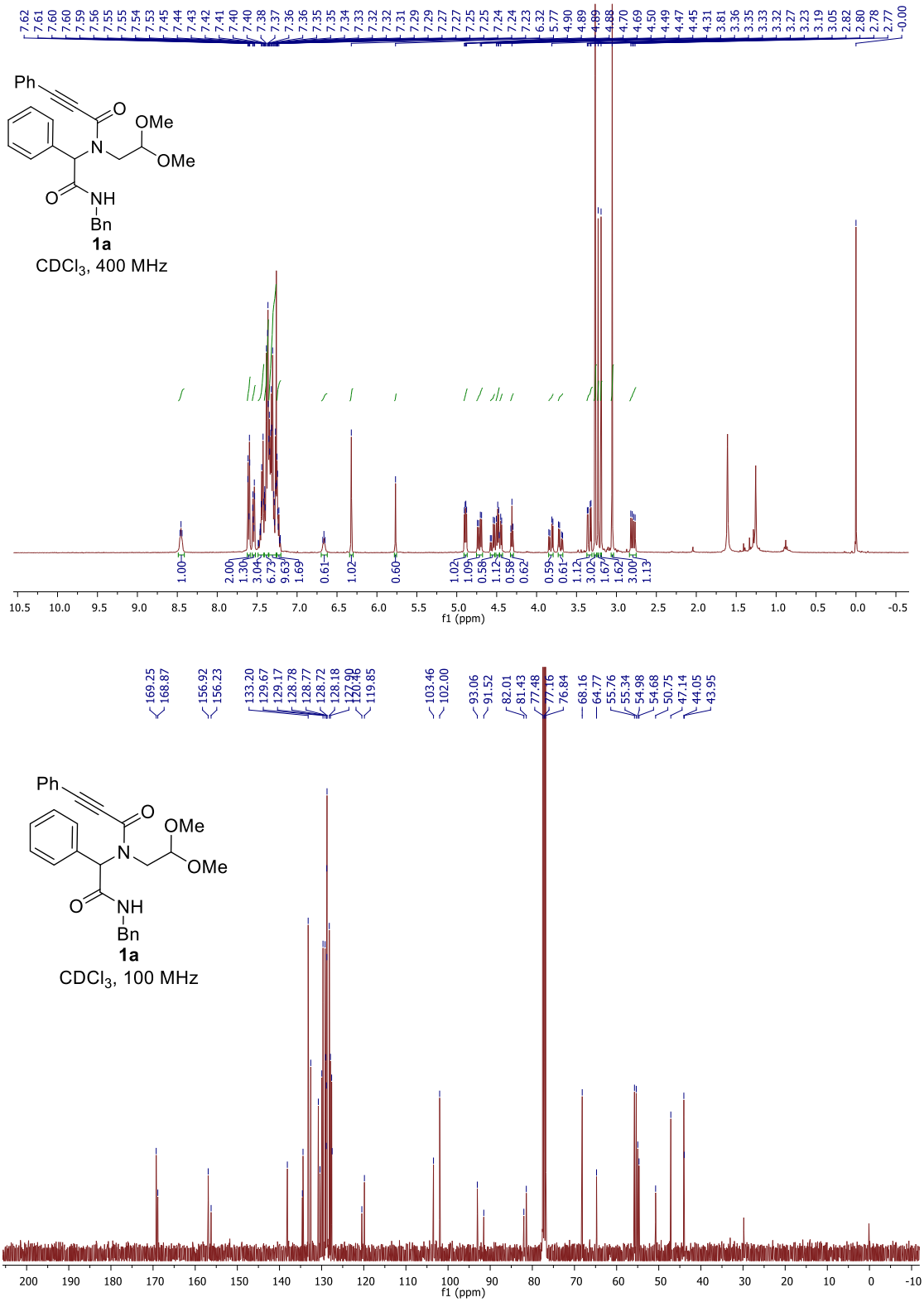


Figure S8: ^{1}H and ^{13}C NMR of compound **2a** (rotamer 1:1)

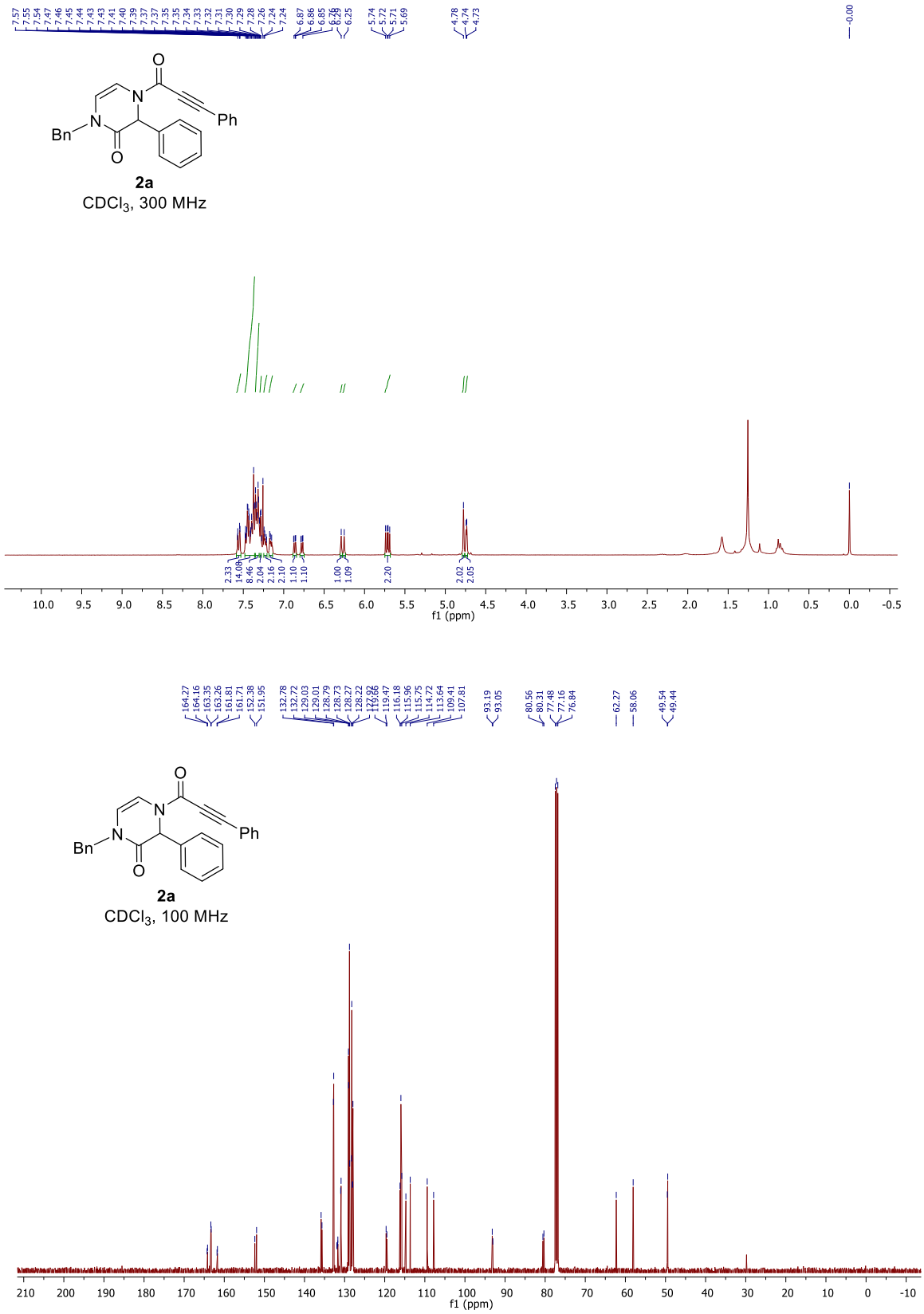


Figure S9: ^{1}H and ^{13}C NMR of compound **2b** (rotamer 1:1)

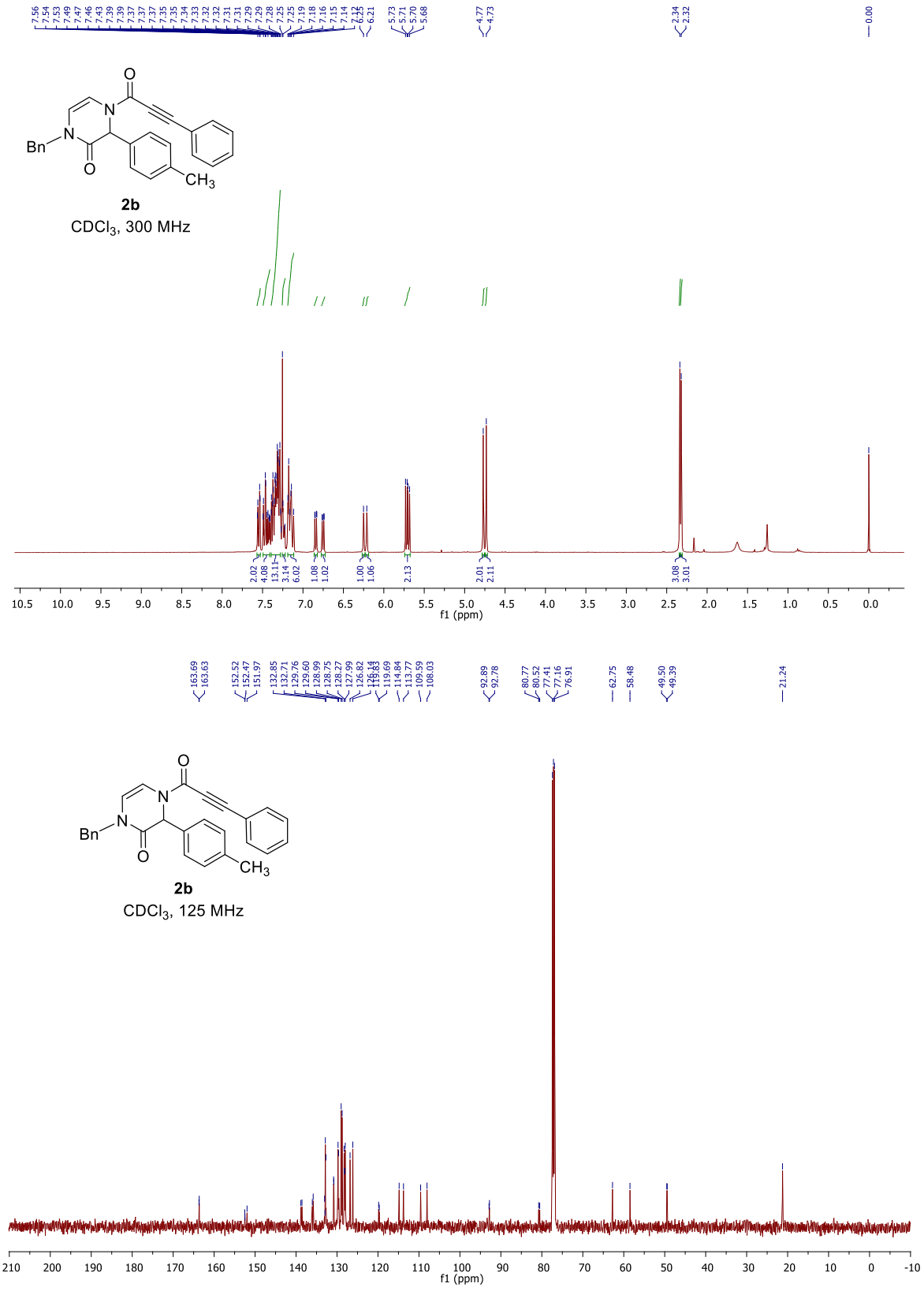


Figure S10: ^{1}H and ^{13}C NMR of compound **2c** (rotamer 1:1)

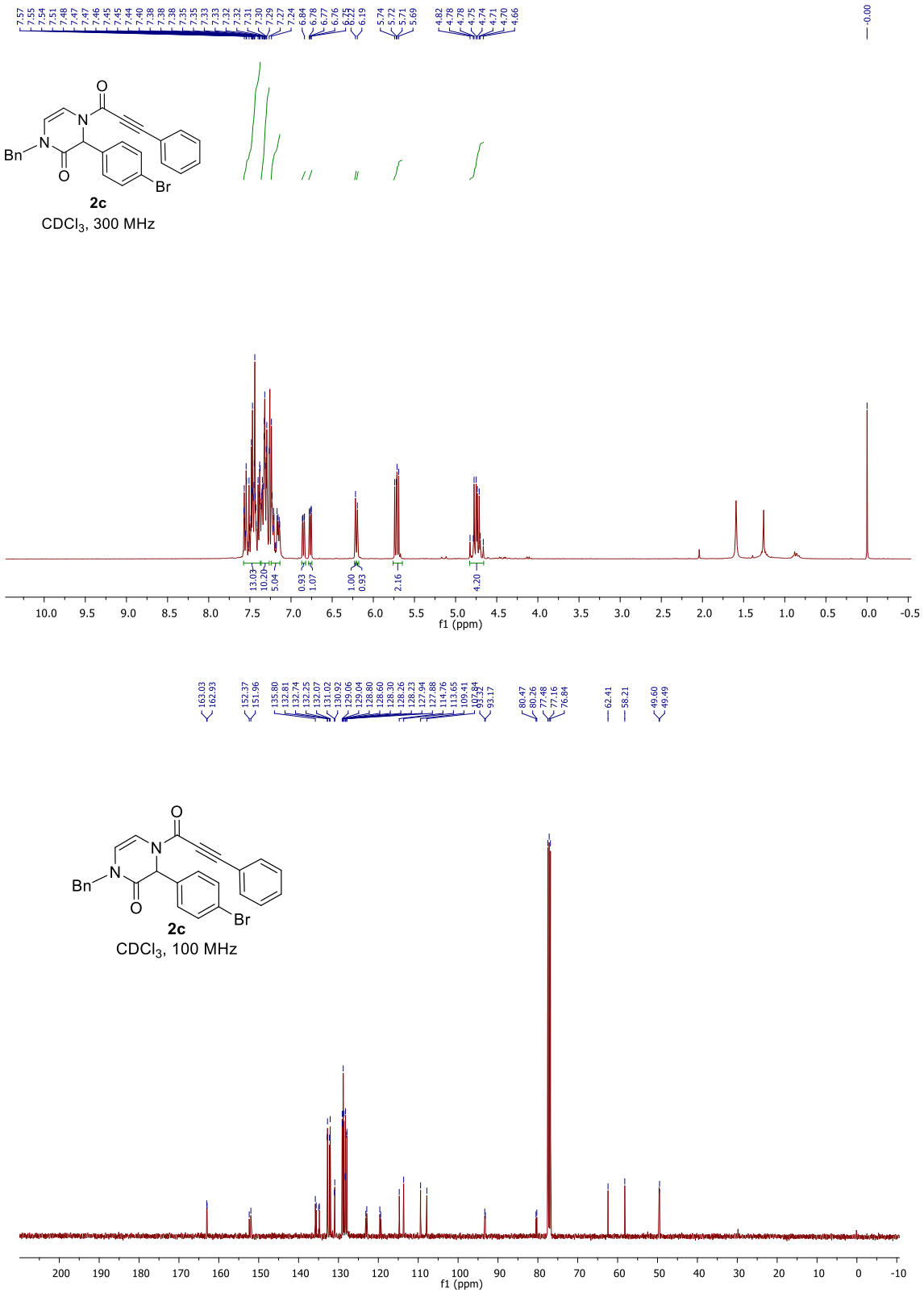


Figure S11: ^{1}H and ^{13}C NMR of compound **2d** (rotamer 1:1)

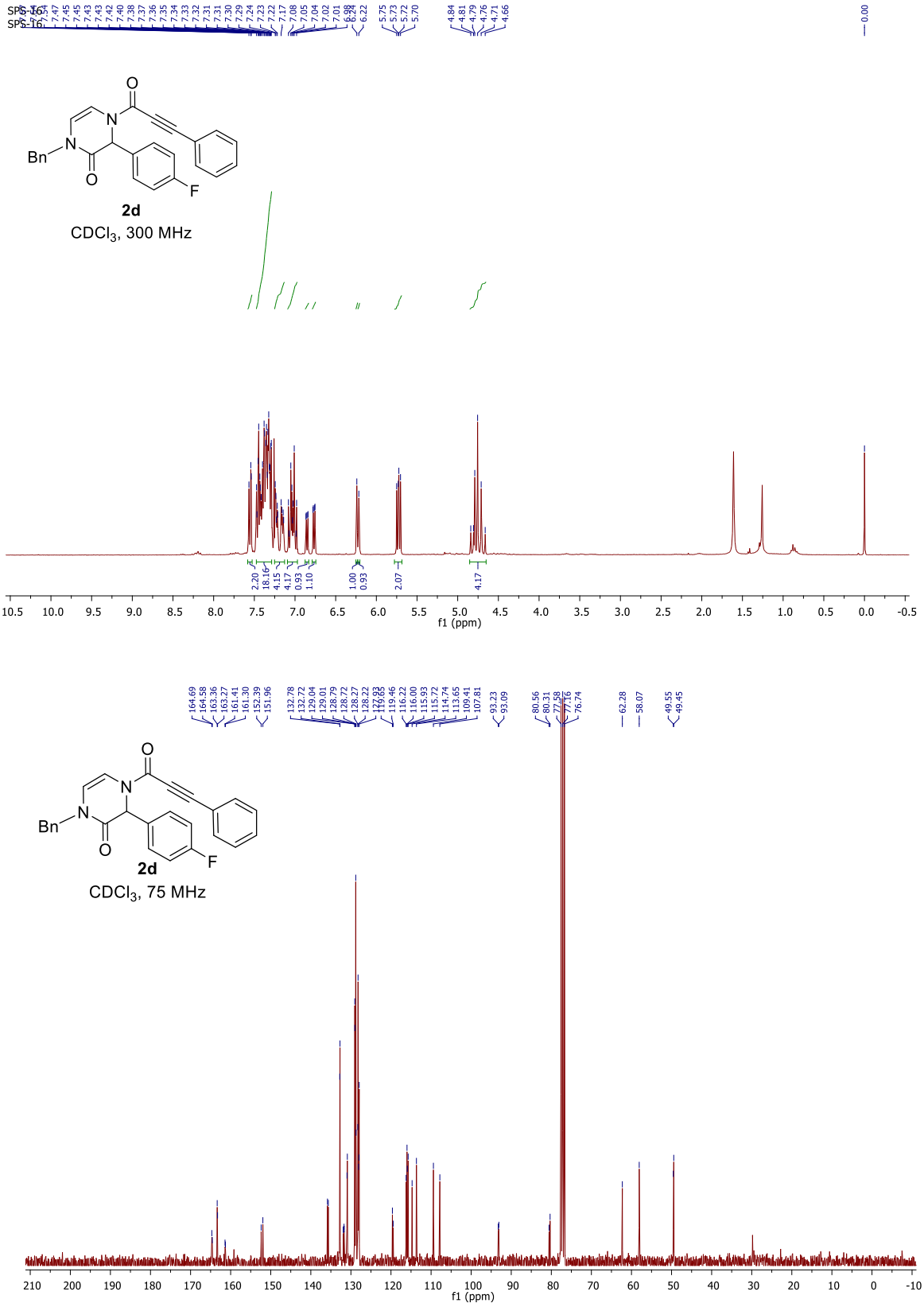


Figure S12: ^{1}H and ^{13}C NMR of compound **2e** (rotamer 1:1)

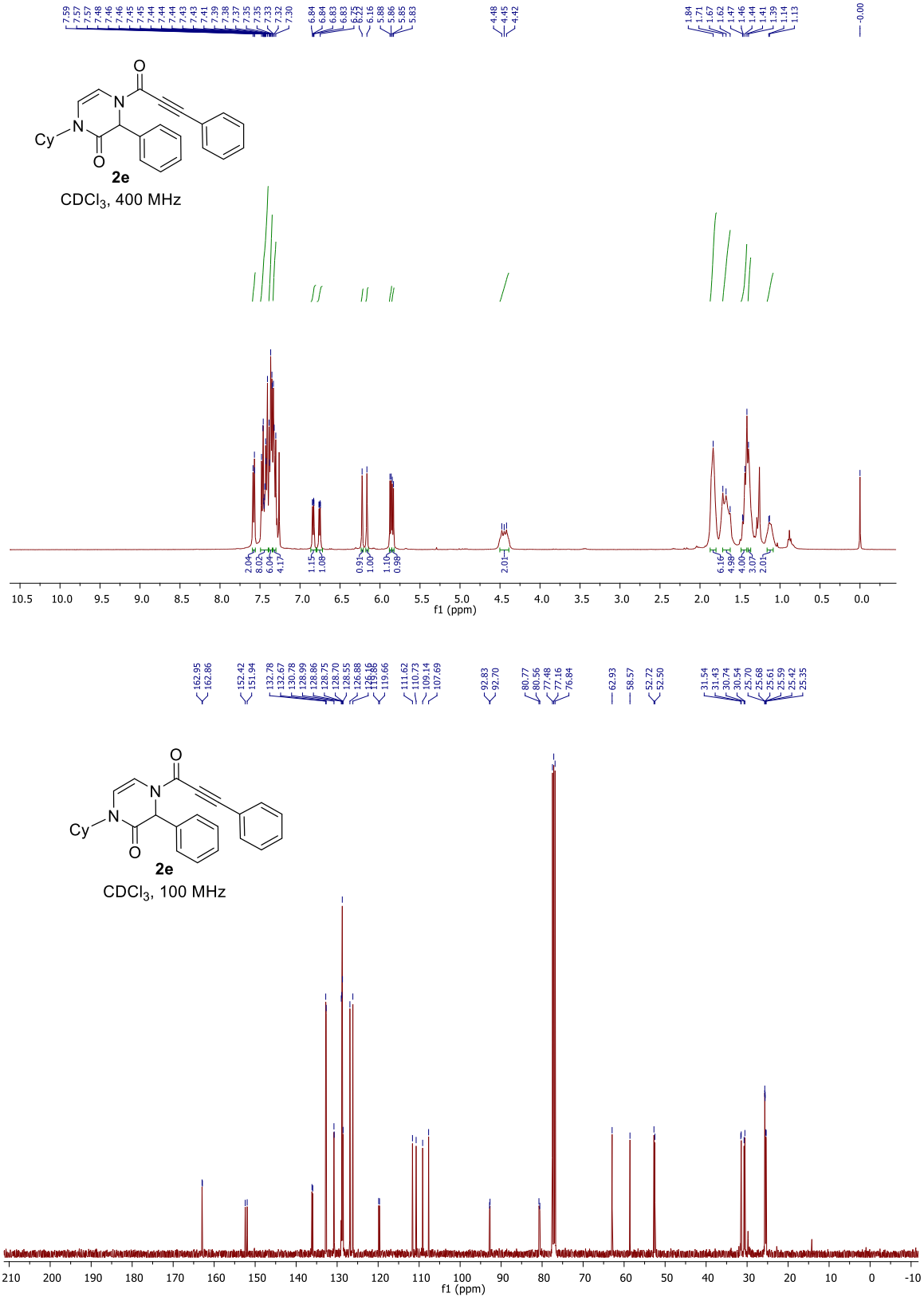


Figure S13: ^{1}H and ^{13}C NMR of compound **2f** (rotamer 1:1)

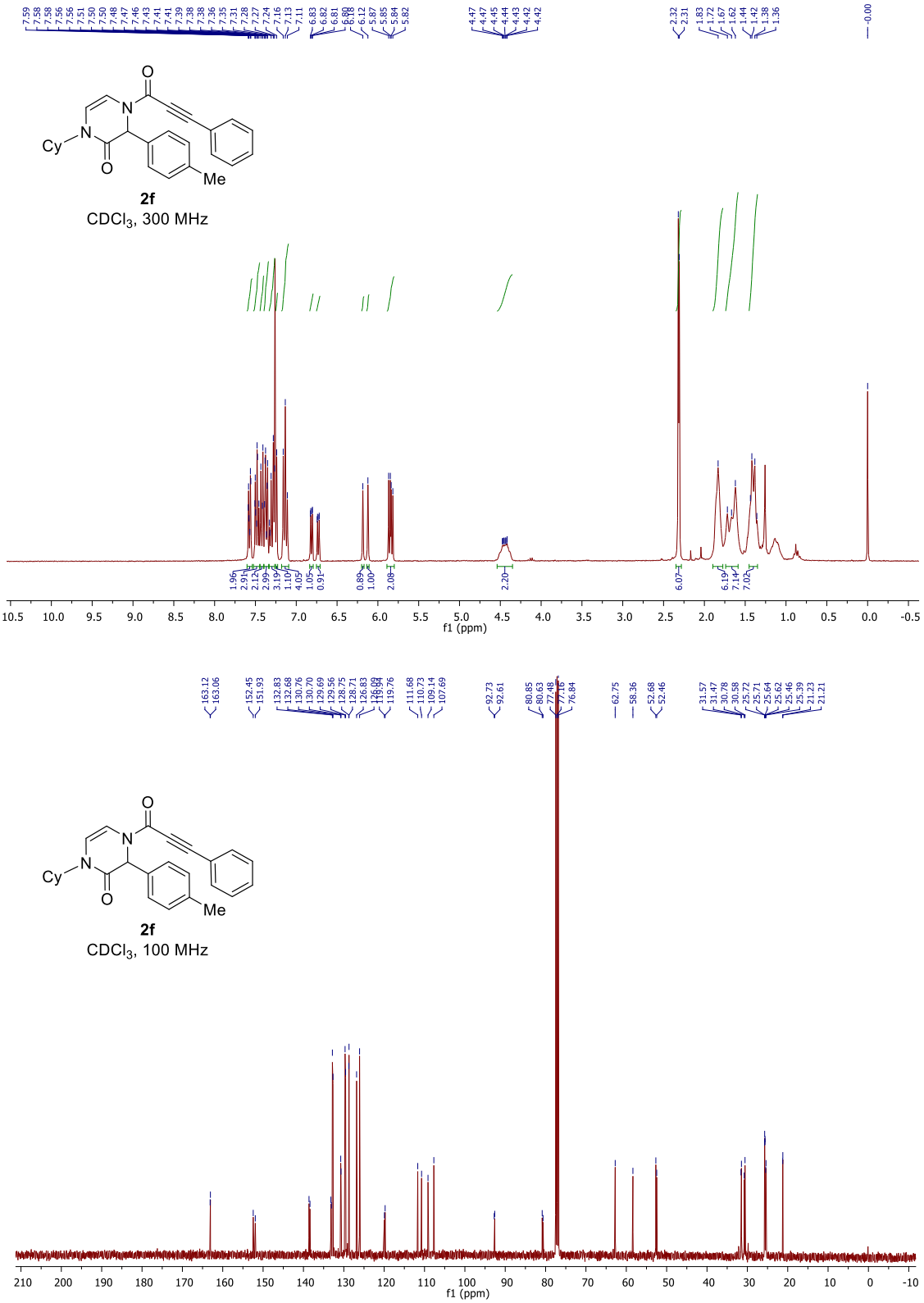


Figure S14: ^{1}H and ^{13}C NMR of compound **2g** (rotamer 1:1)

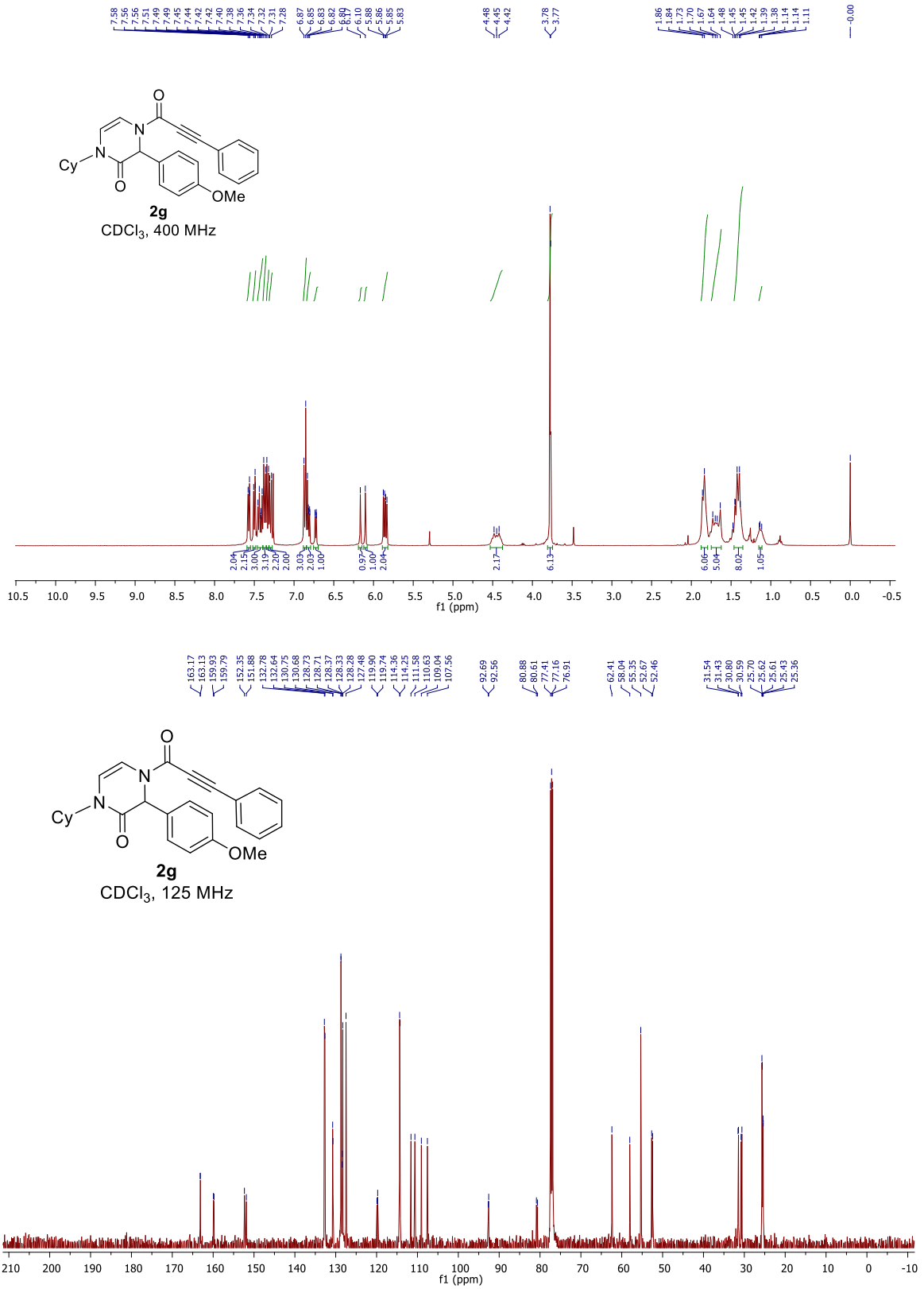


Figure S15: ^{1}H and ^{13}C NMR of compound **2h** (rotamer 1:1)

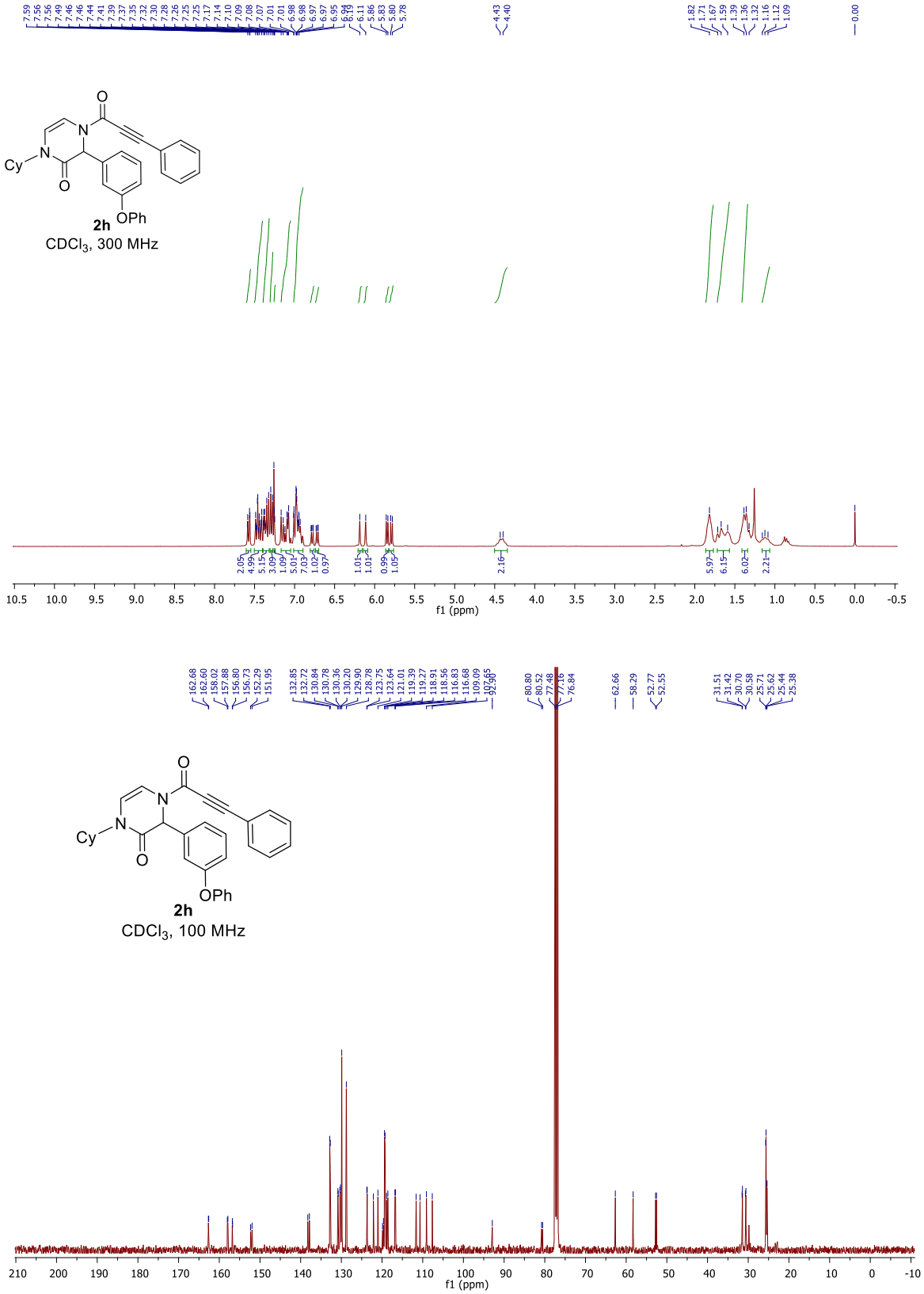
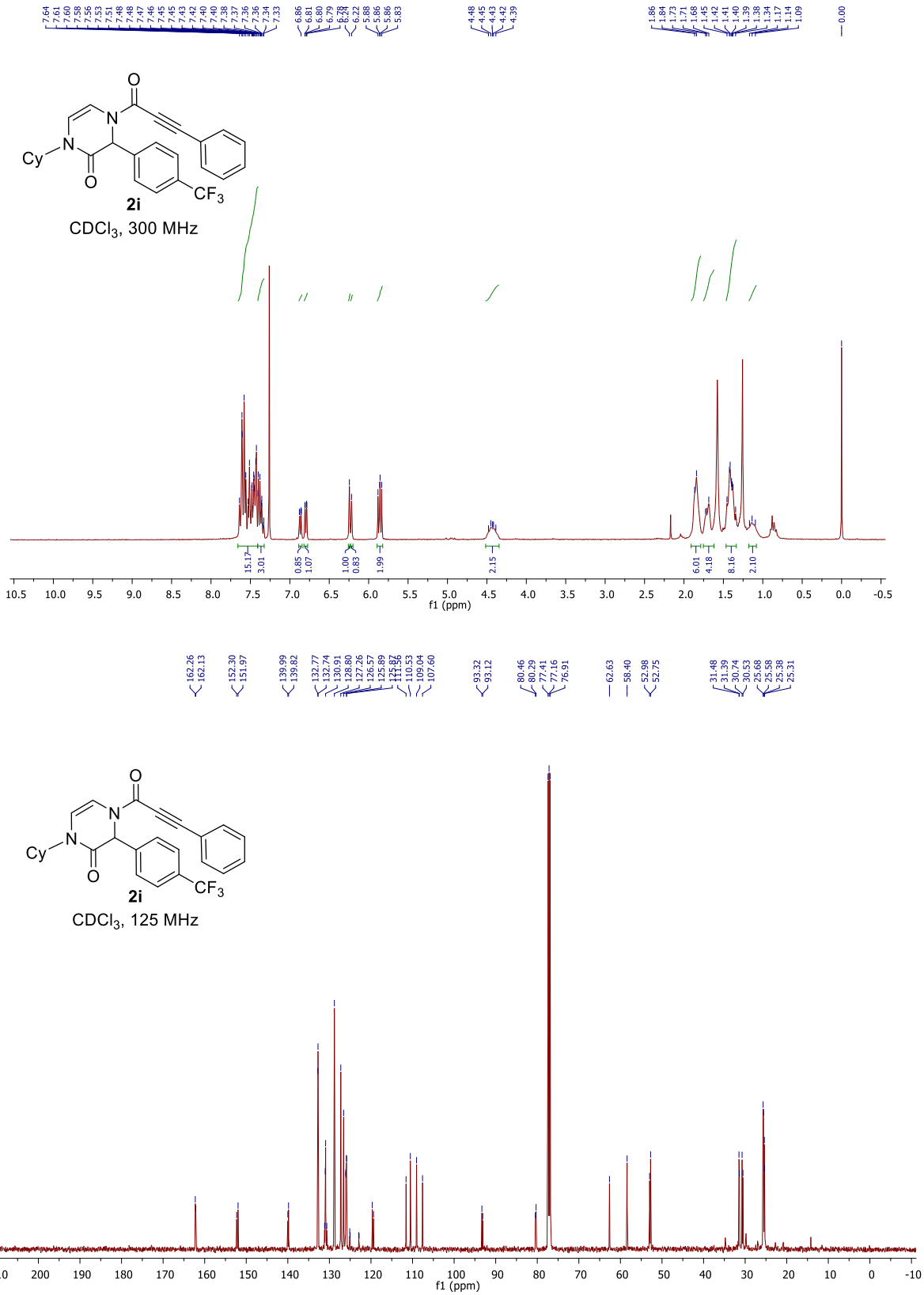
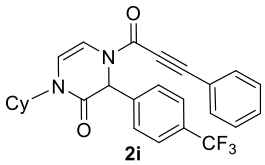


Figure S16: ^{1}H, ^{13}C and ^{19}F NMR of compound **2i**(rotamer 1:0.8)





2i

$CDCl_3$, 283 MHz

Figure S17: ^{1}H and ^{13}C NMR of compound **2j** (rotamer 1:1)

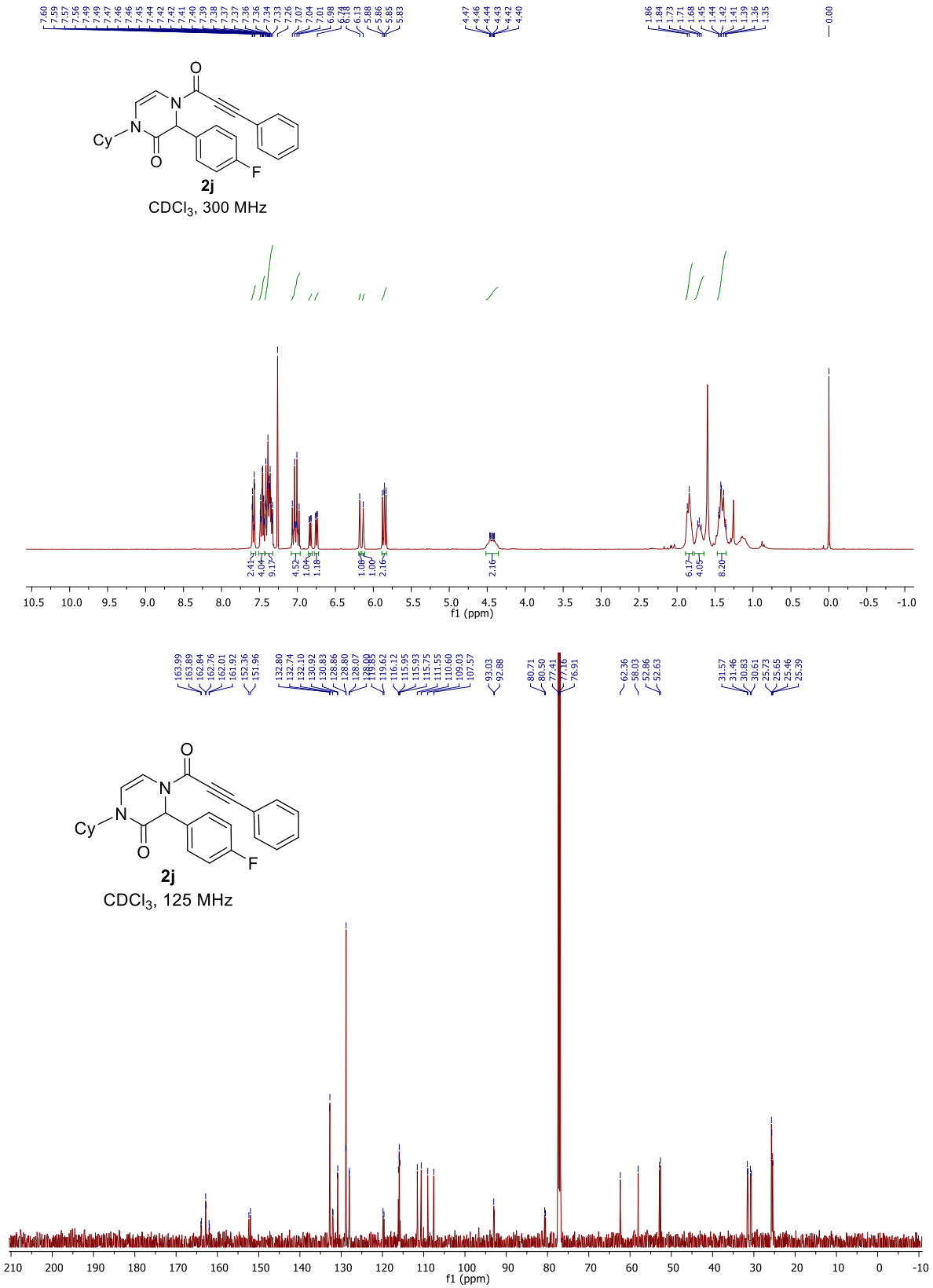
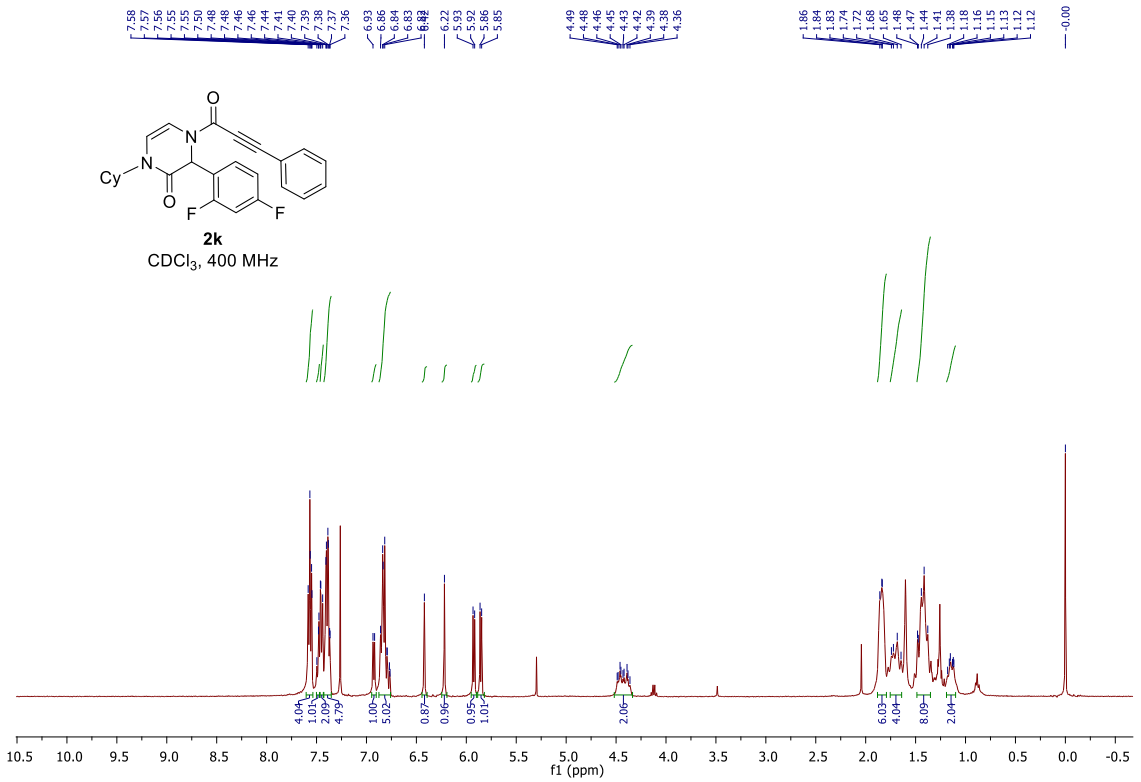
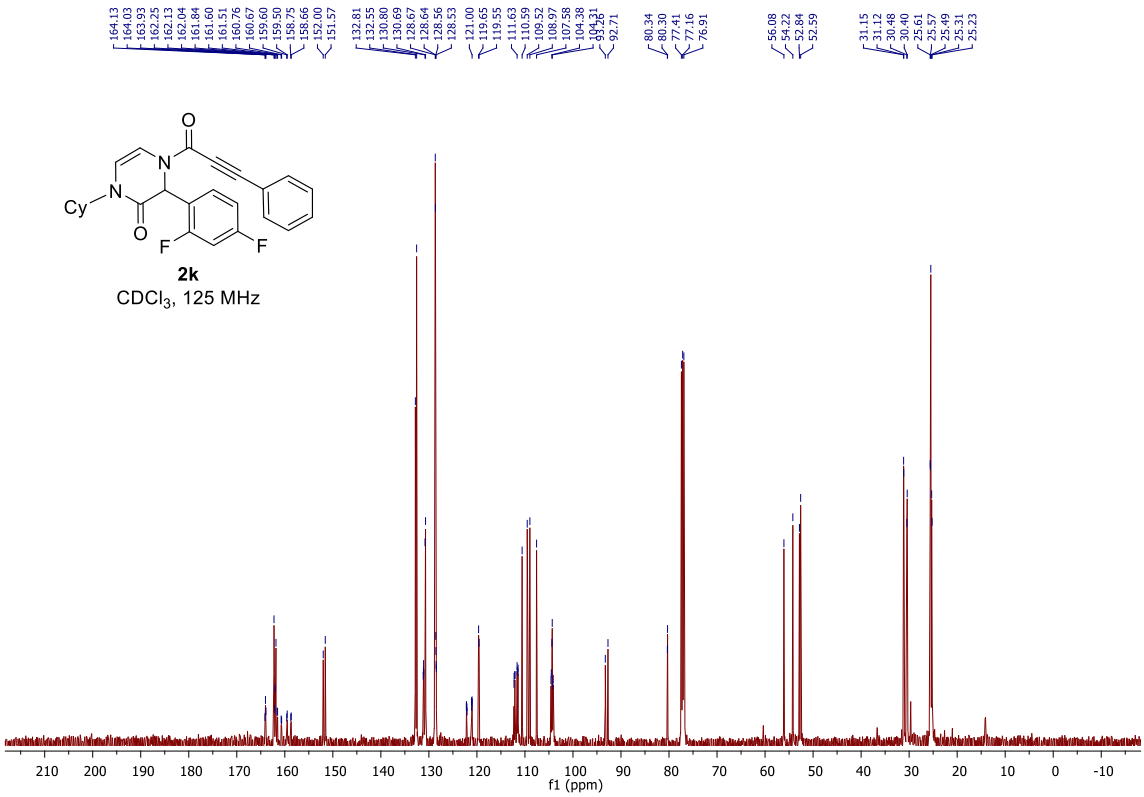
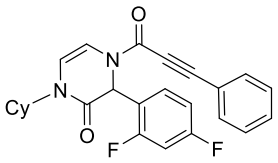


Figure S18: ^{1}H,^{13}C and ^{19}F NMR of compound **2k** (rotamer 1:1)







2k

$CDCl_3$, 377 MHz

Figure S19: ^{1}H, ^{13}C and ^{19}F NMR of compound **2l** (rotamer 1:0.8)

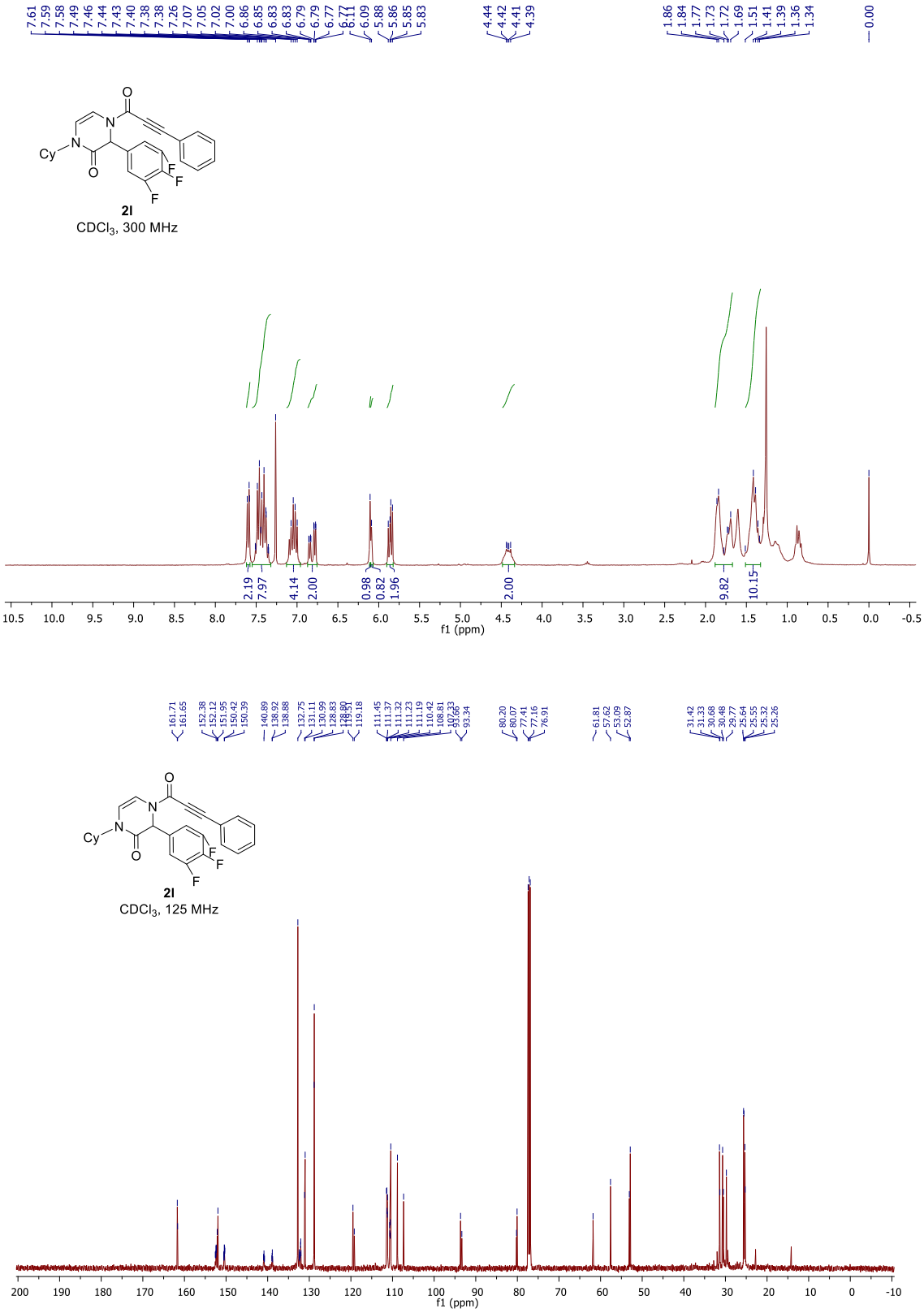


Figure S20: ^{1}H and ^{13}C NMR of compound **2m** (rotamer 1:0.8)

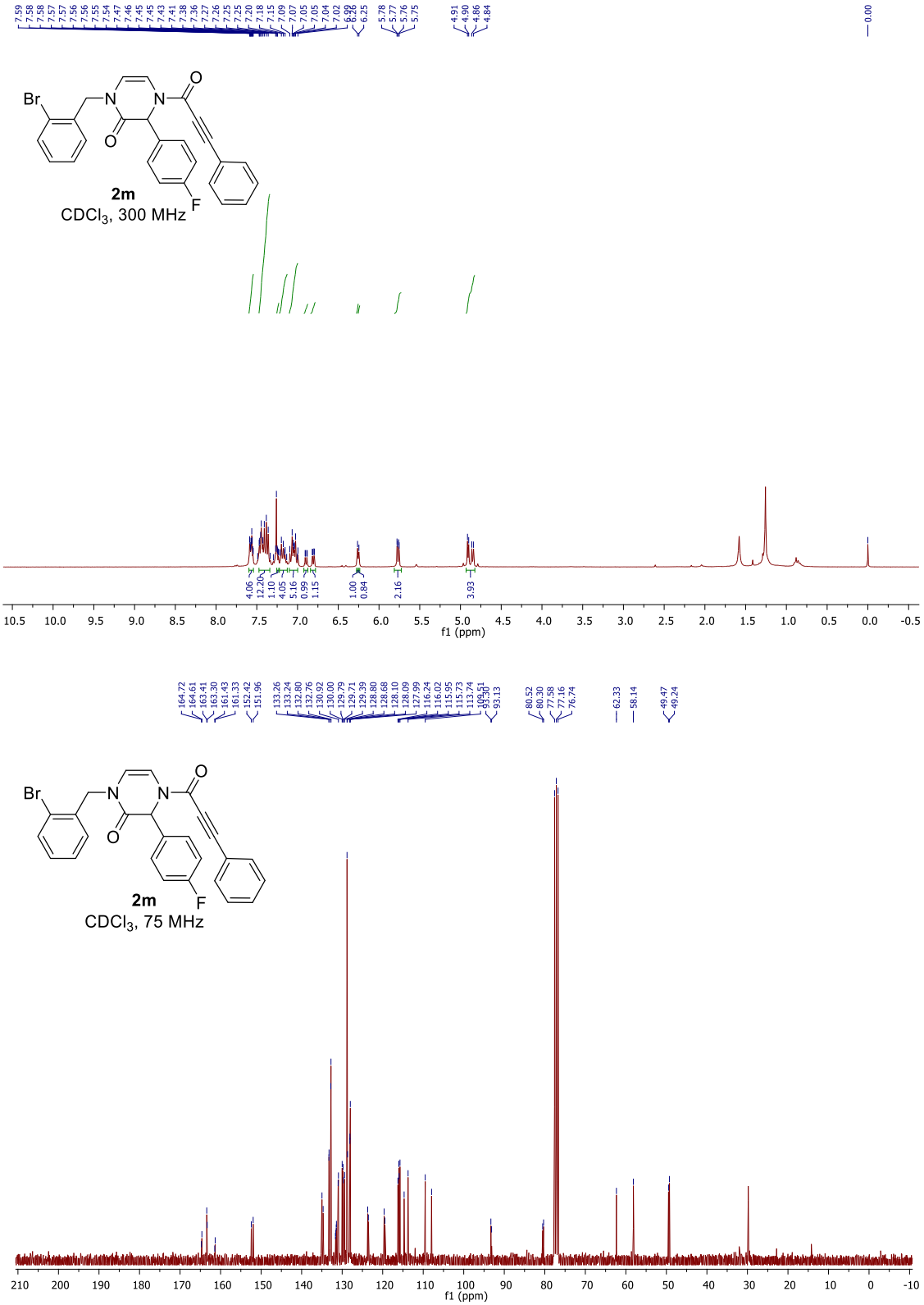


Figure S21: ^{1}H and ^{13}C NMR of compound **2n** (rotamer 1:1)

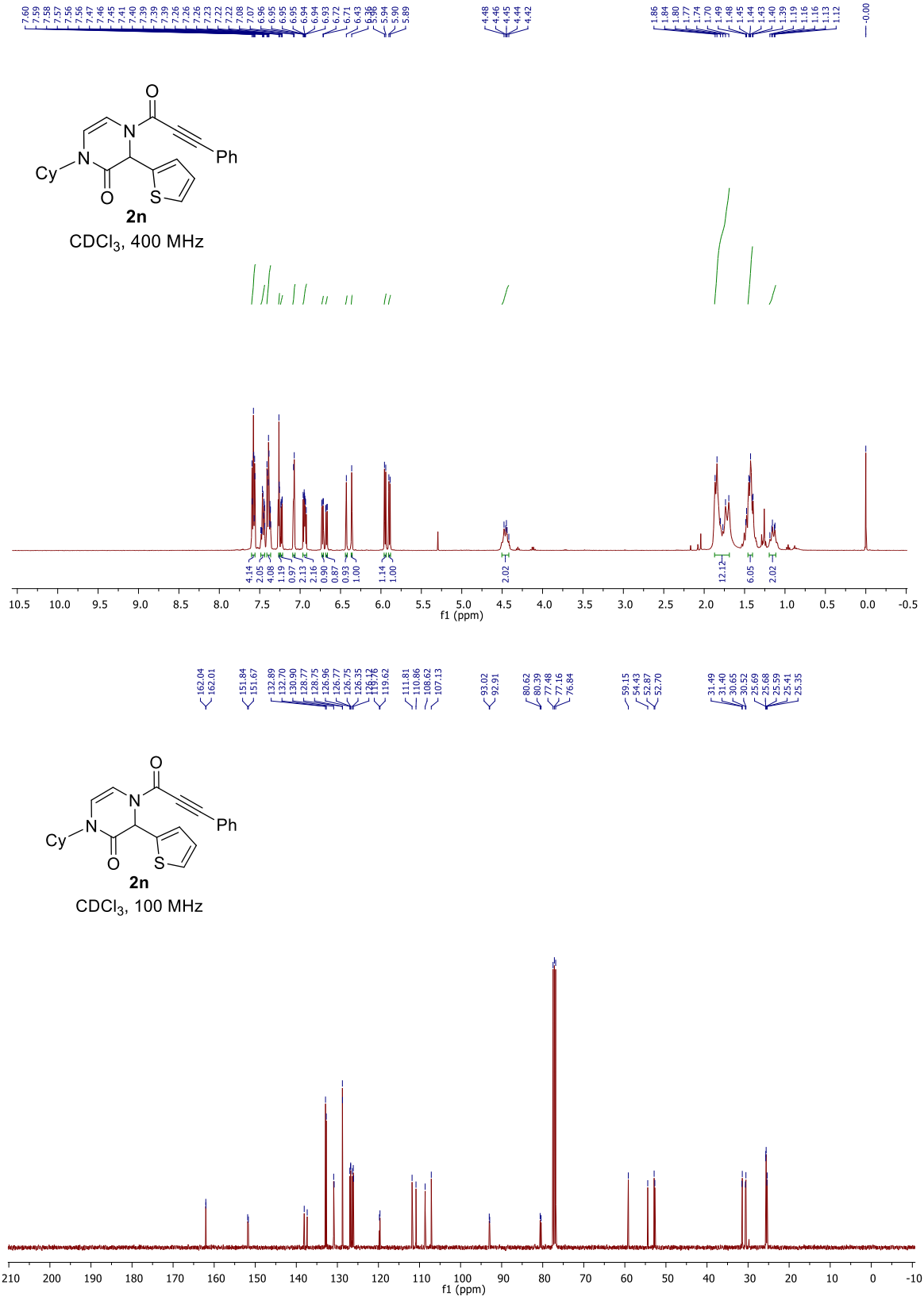


Figure S22: ^{1}H and ^{13}C NMR of compound **2p** (rotamer 1:1)

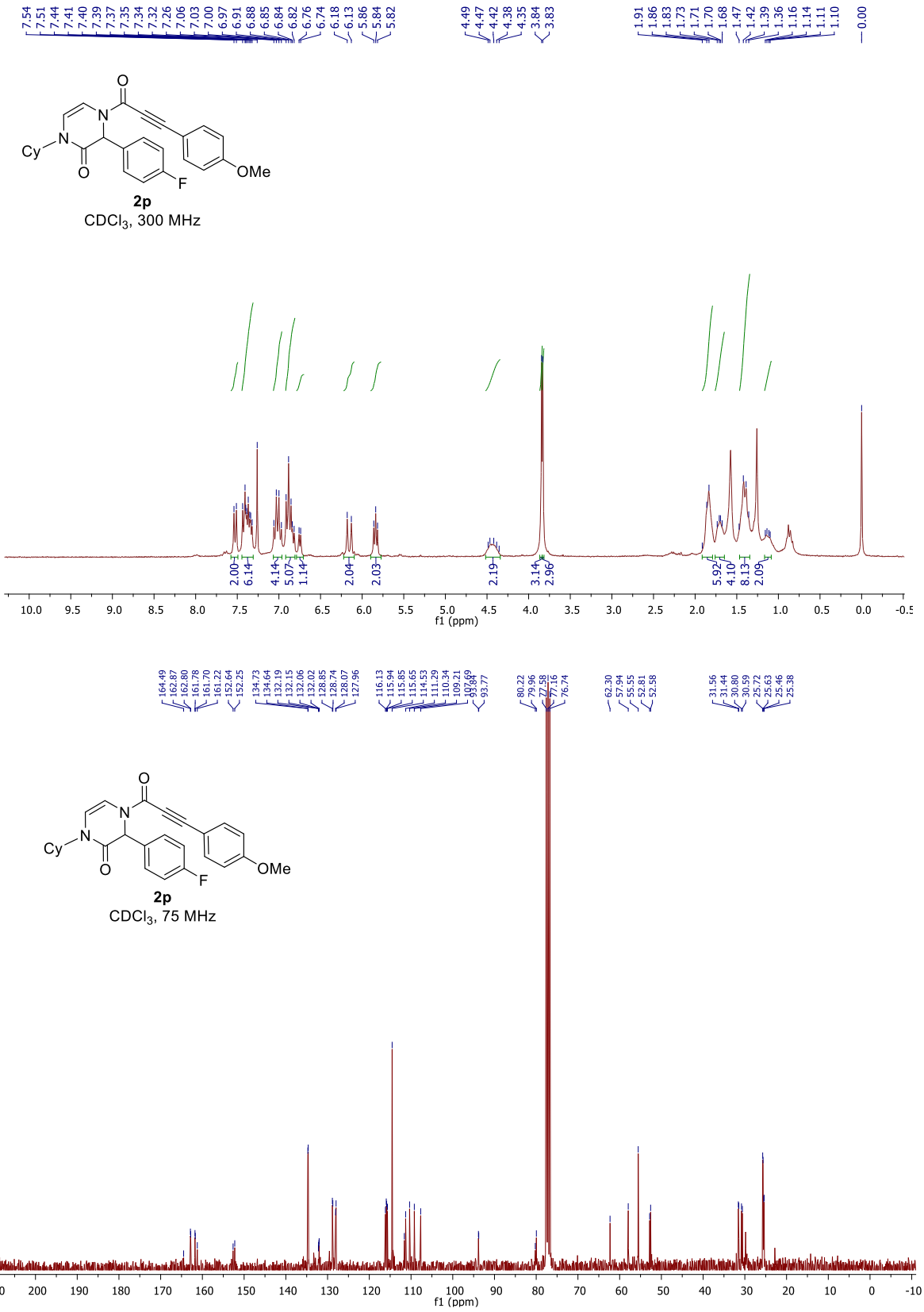


Figure S23: ^{1}H and ^{13}C NMR of compound **2q** (rotamer 1:1)

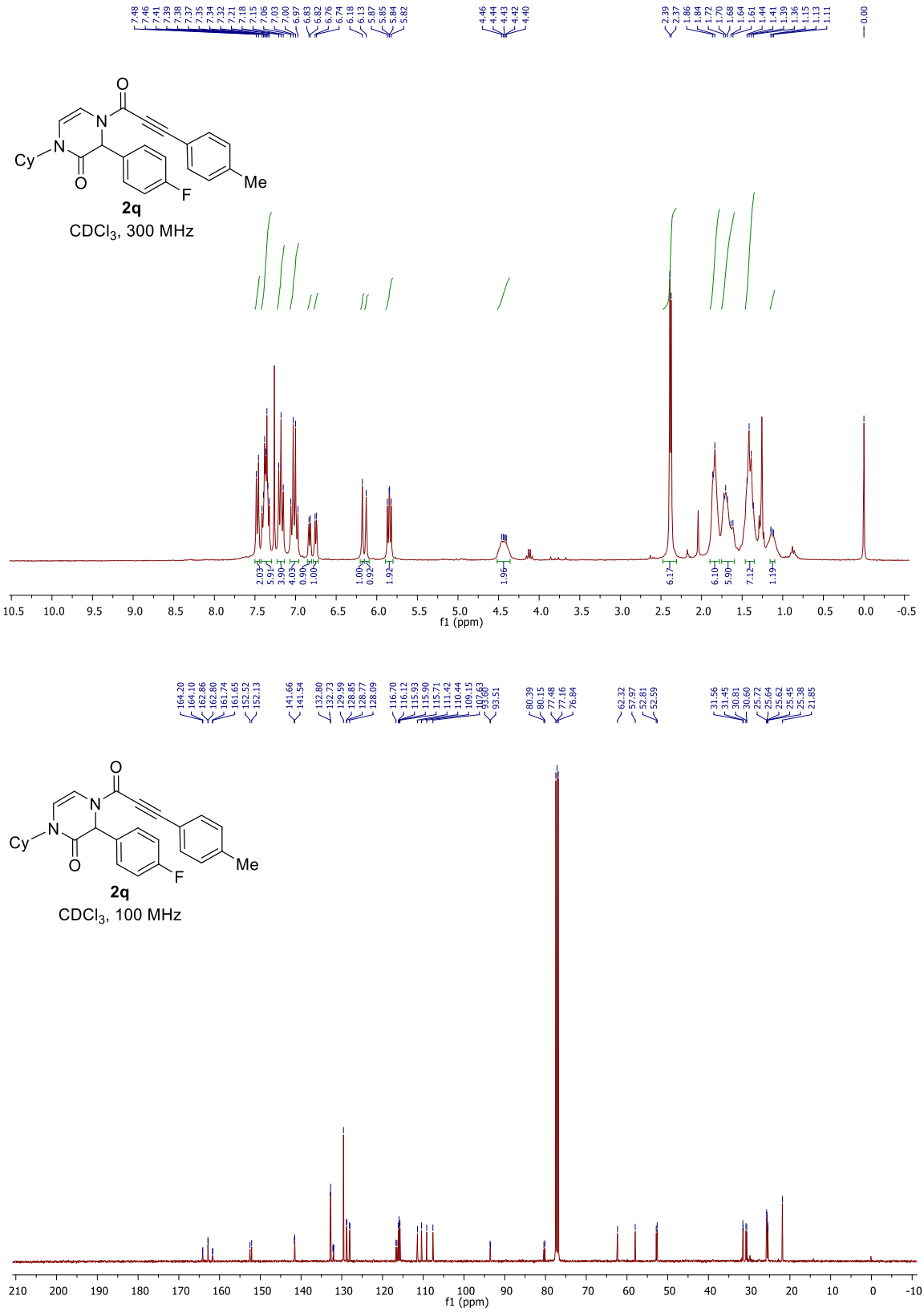
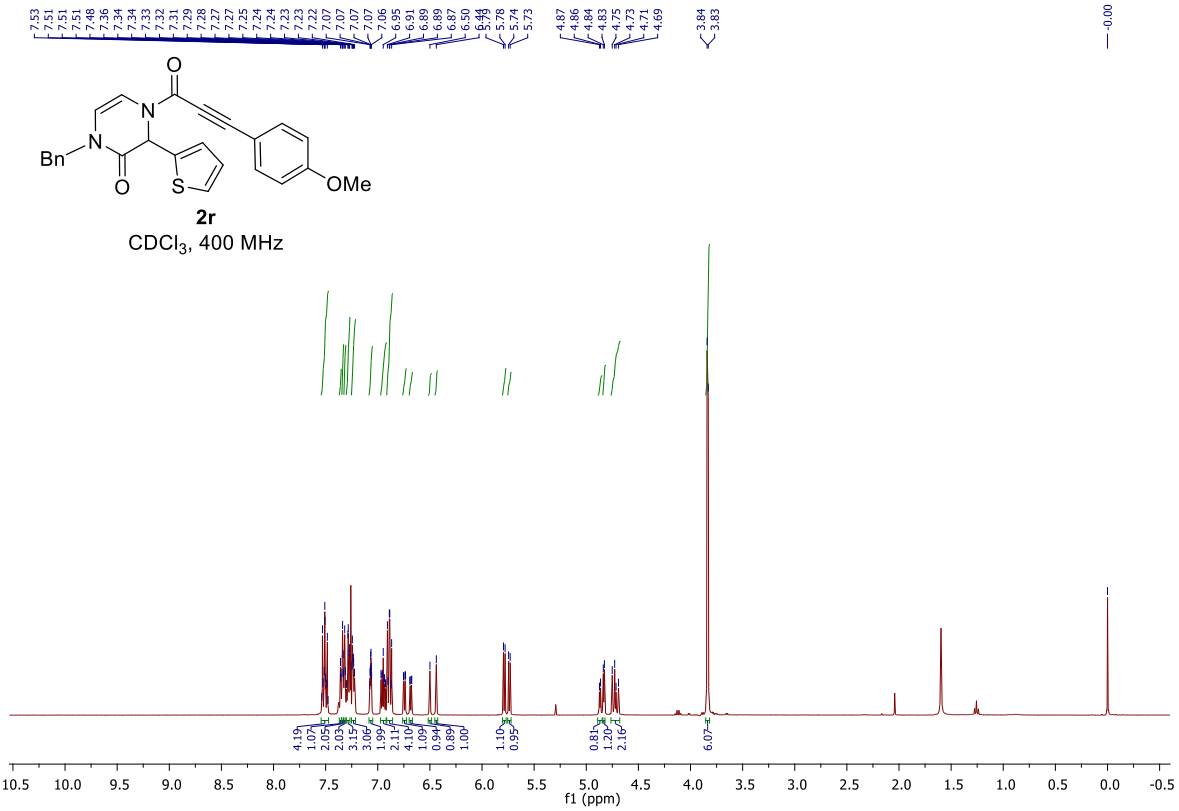


Figure S24: ^{1}H and ^{13}C NMR of compound **2r** (rotamer 1:1)



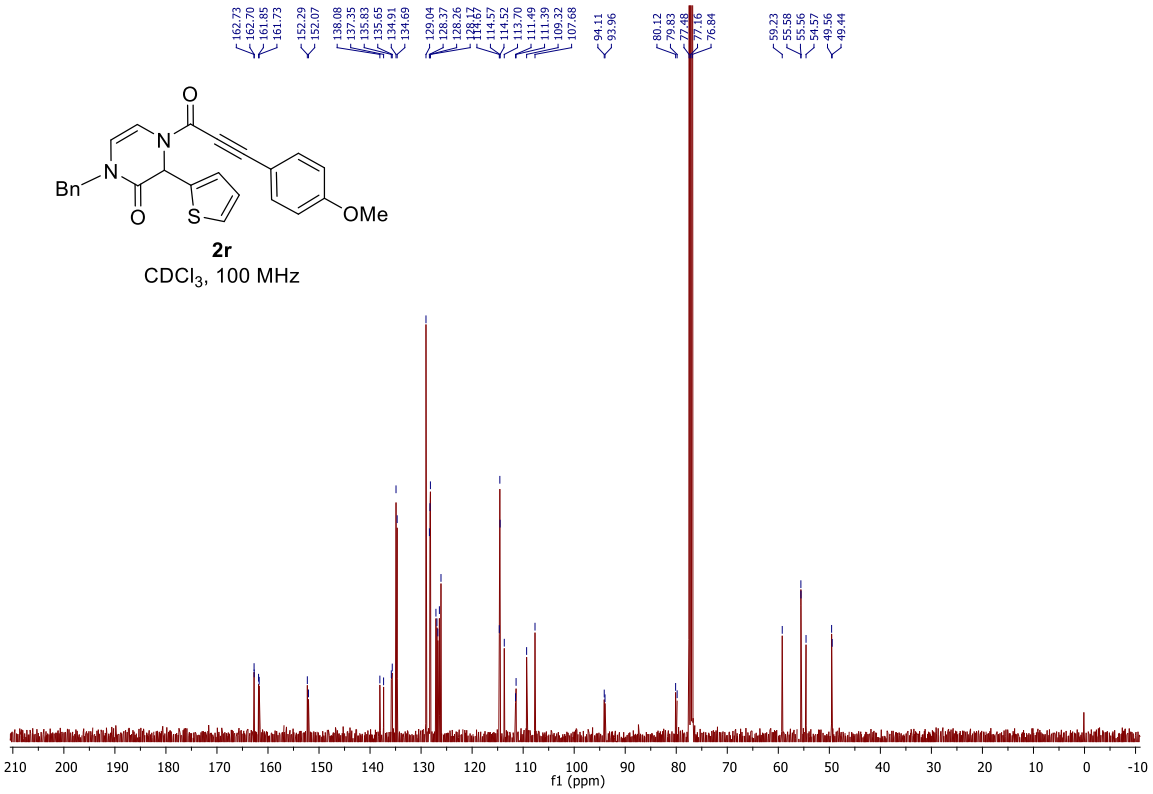


Figure S25: ^{1}H and ^{13}C NMR of compound **2s** (rotamer 1:1)

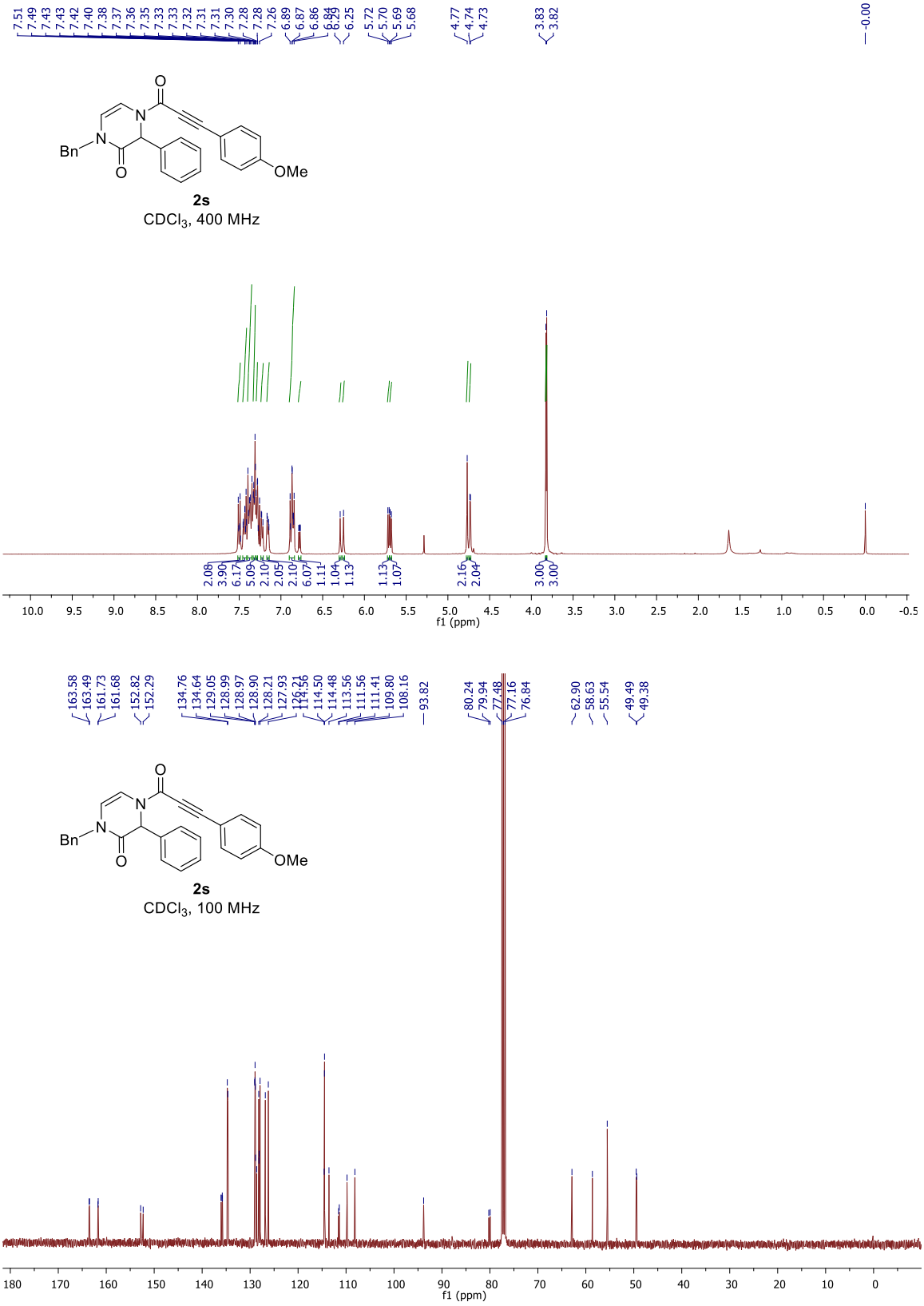


Figure S26: ^{1}H and ^{13}C NMR of compound **2u** (rotamer 1:0.8)

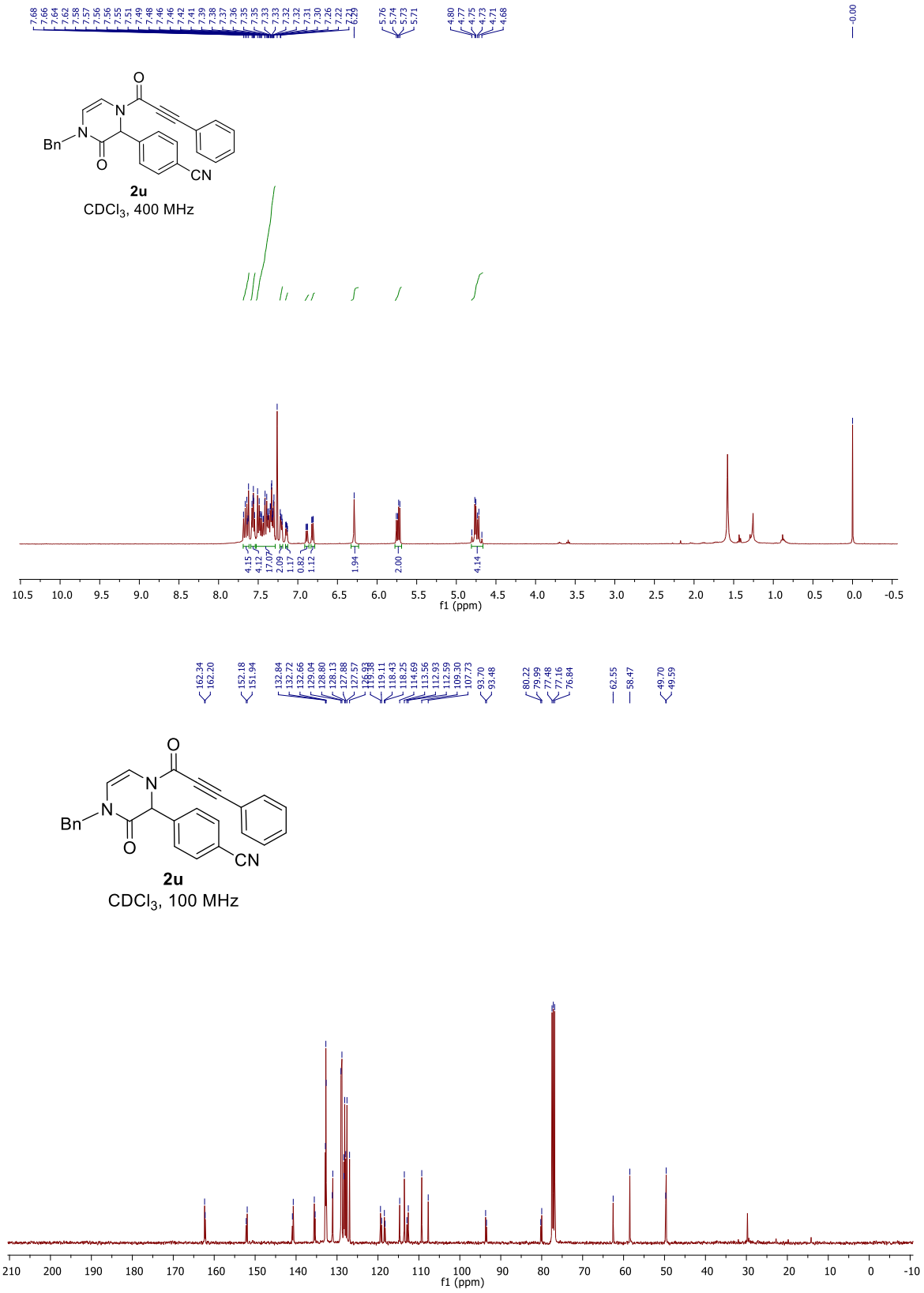


Figure S27: ^{1}H and ^{13}C NMR of compound **2x** (rotamer 1:0.6)

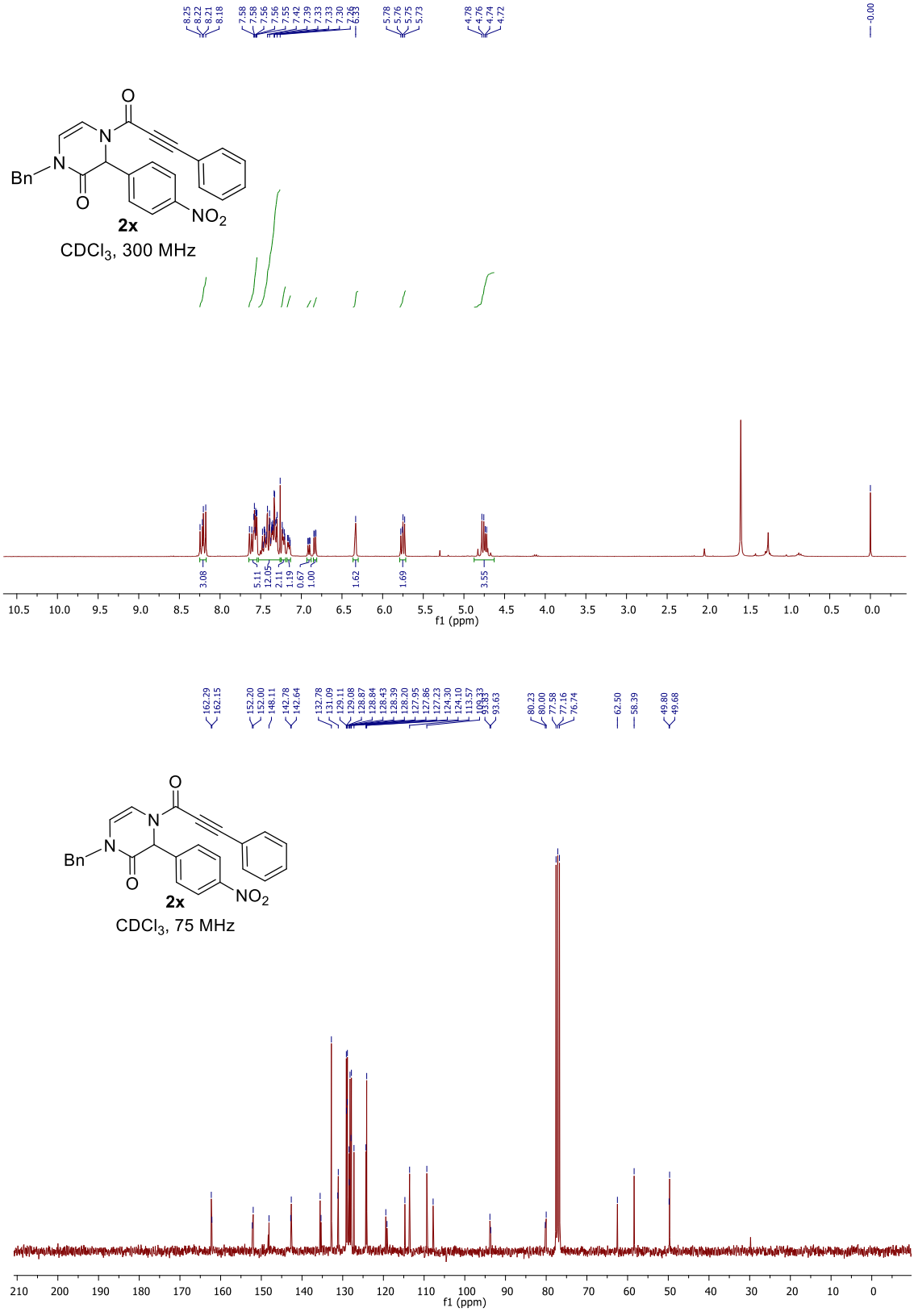


Figure S28: ^{1}H and ^{13}C NMR of compound **2y** (rotamer 1:1)

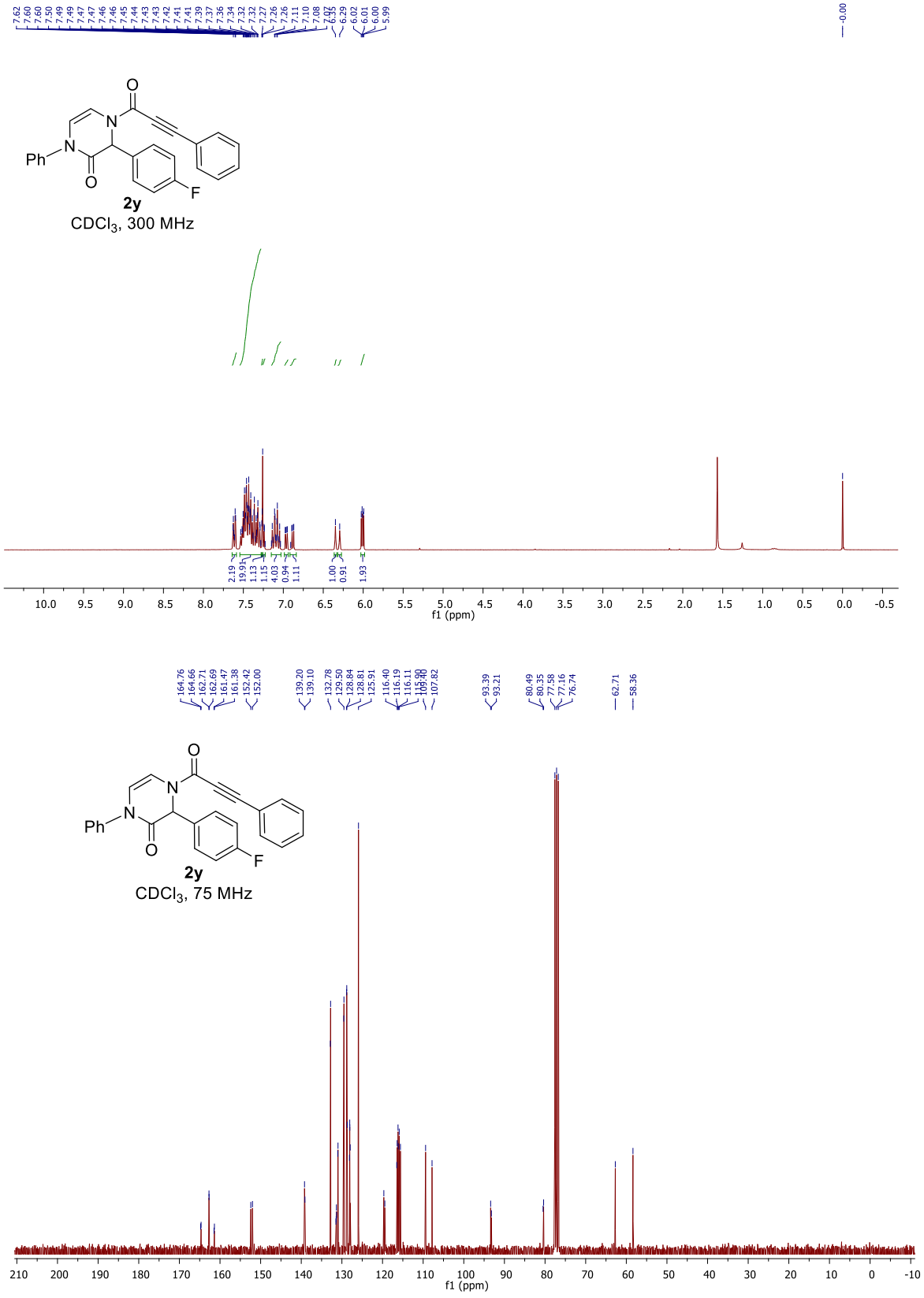


Figure S29: ^{1}H and ^{13}C NMR of compound **2ab** (rotamer 1:1)

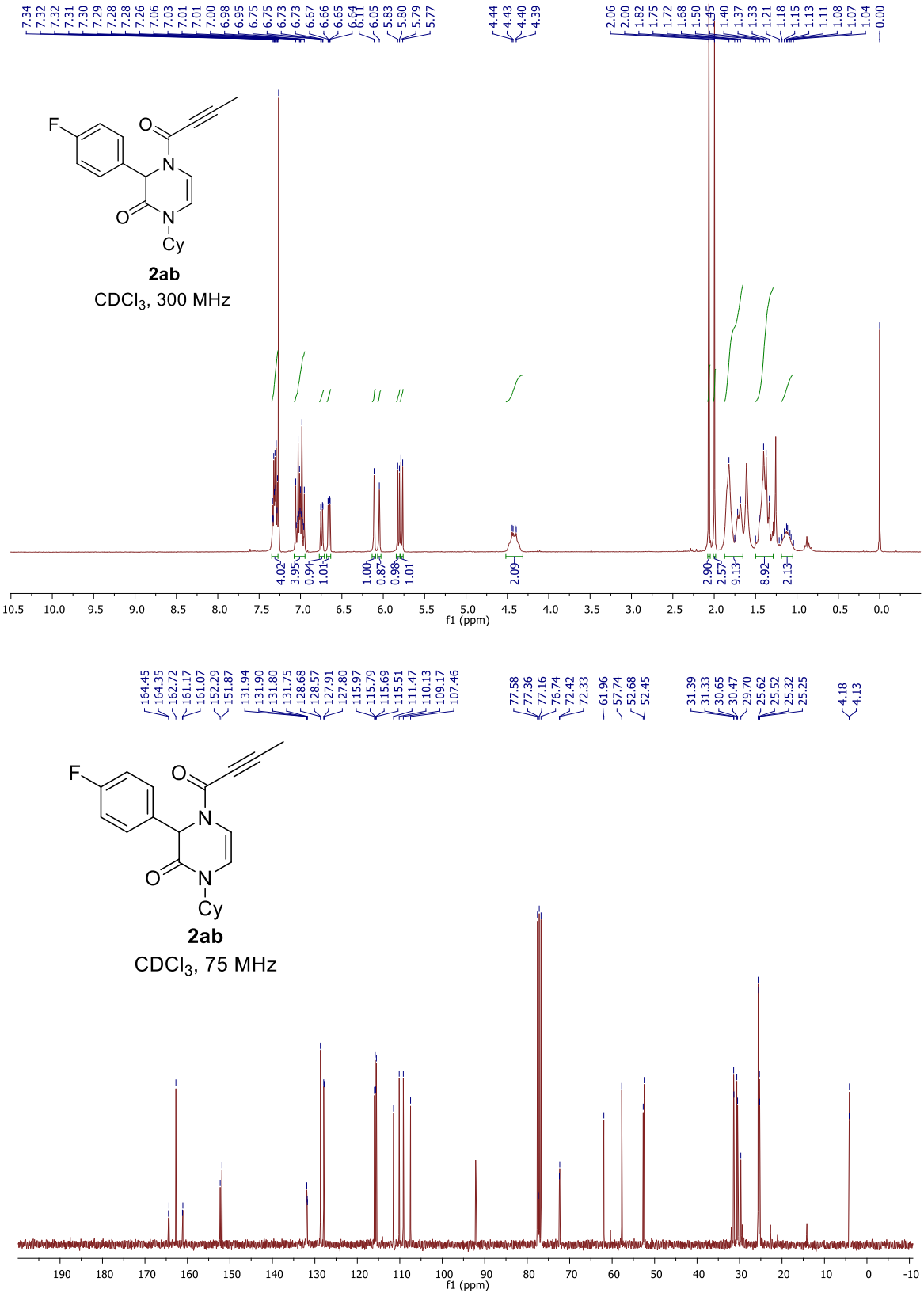


Figure S30: ^{1}H and ^{13}C NMR of compound **3a**

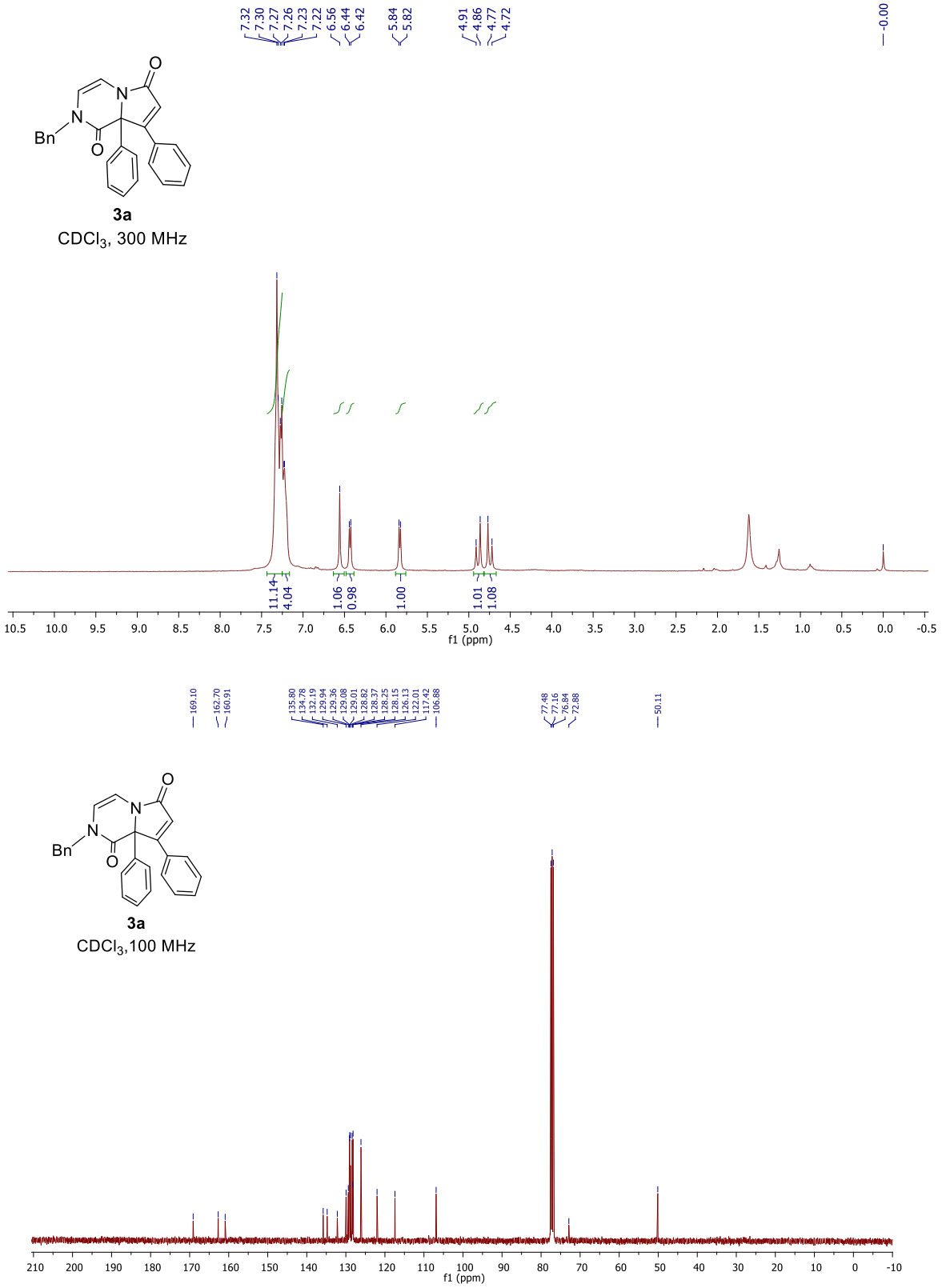


Figure S31: ^{1}H and ^{13}C NMR of compound **3b**

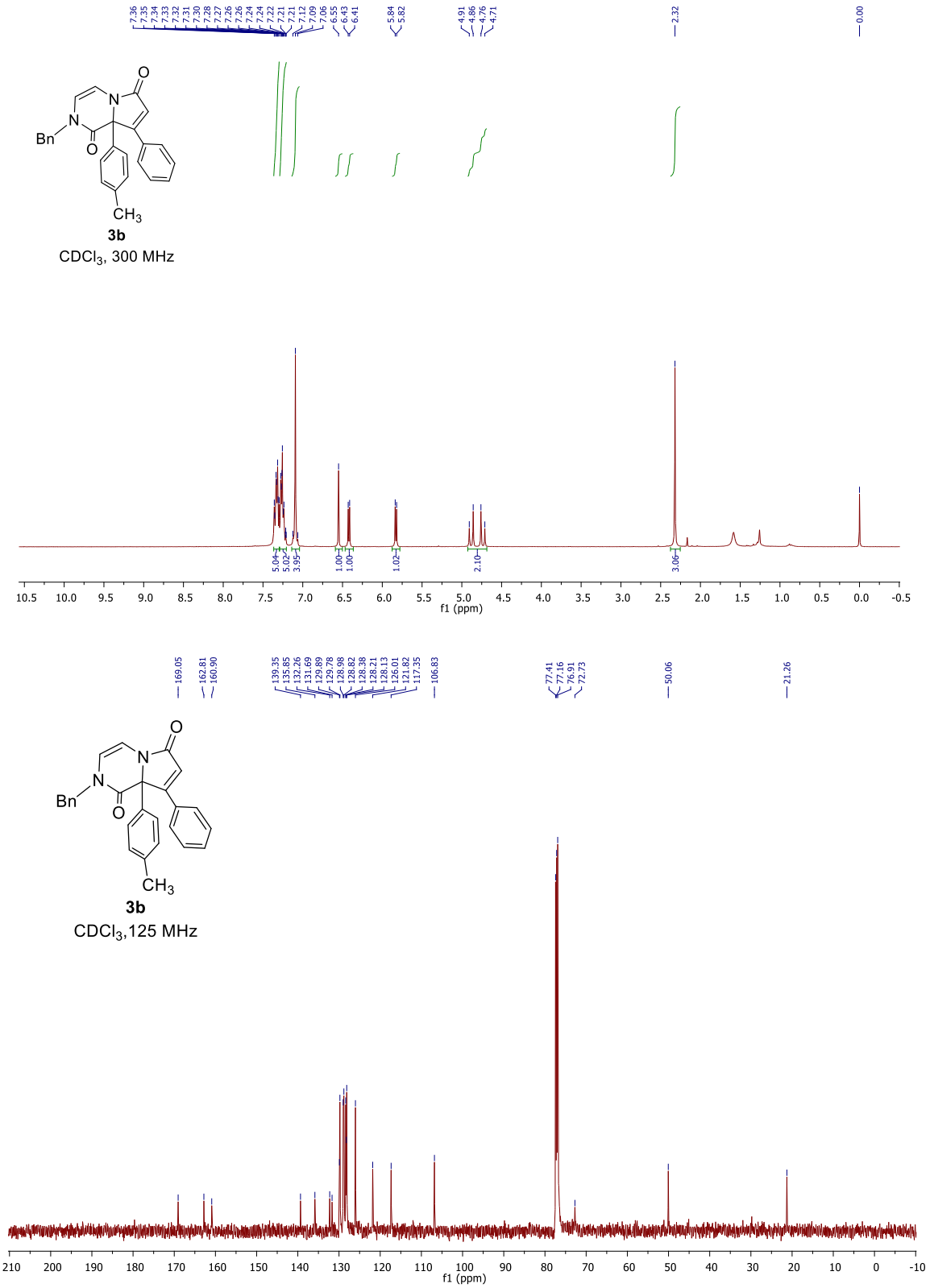


Figure S32: ^{1}H and ^{13}C NMR of compound **3c**

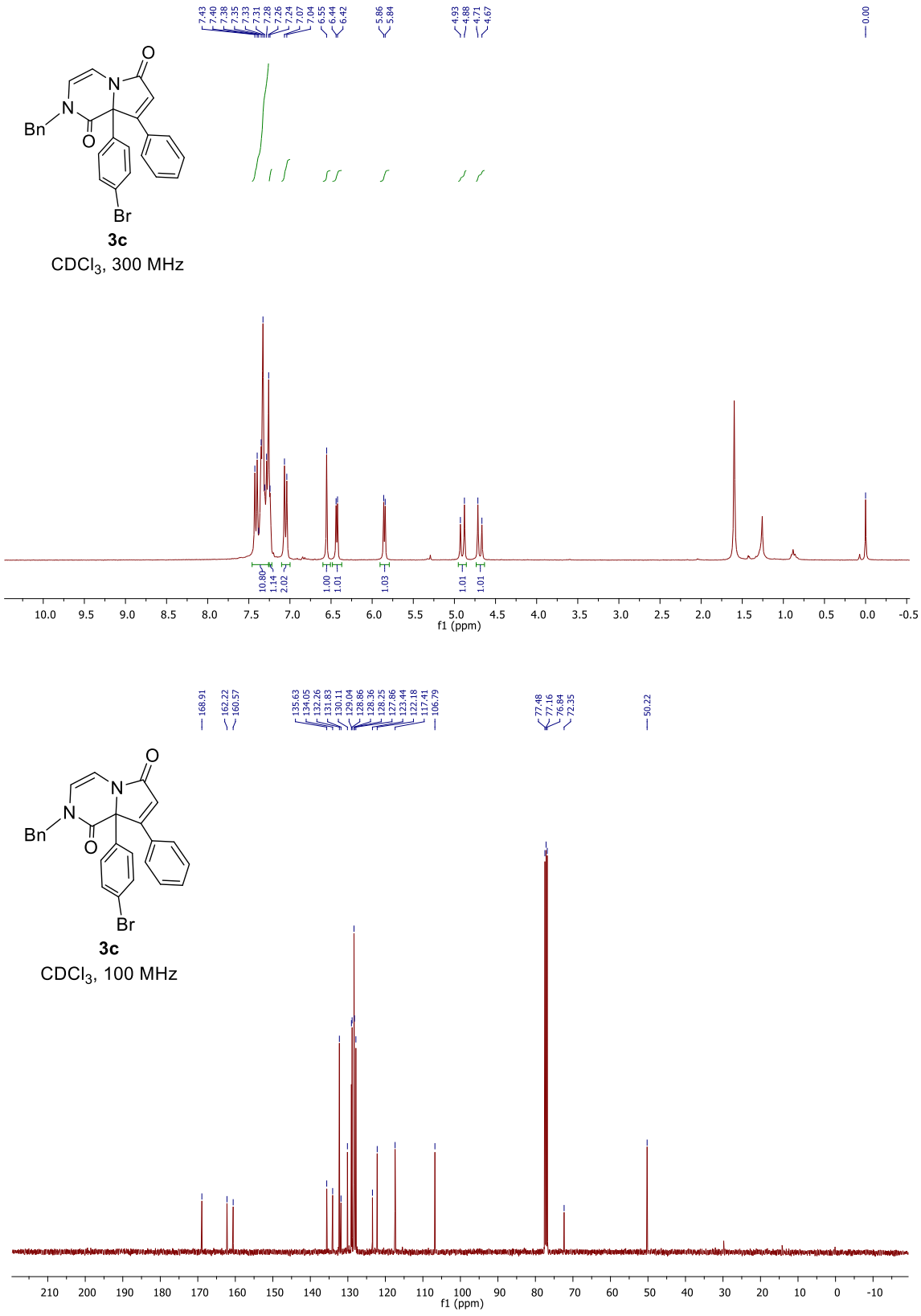


Figure S33: ^{1}H and ^{13}C NMR of compound **3d**

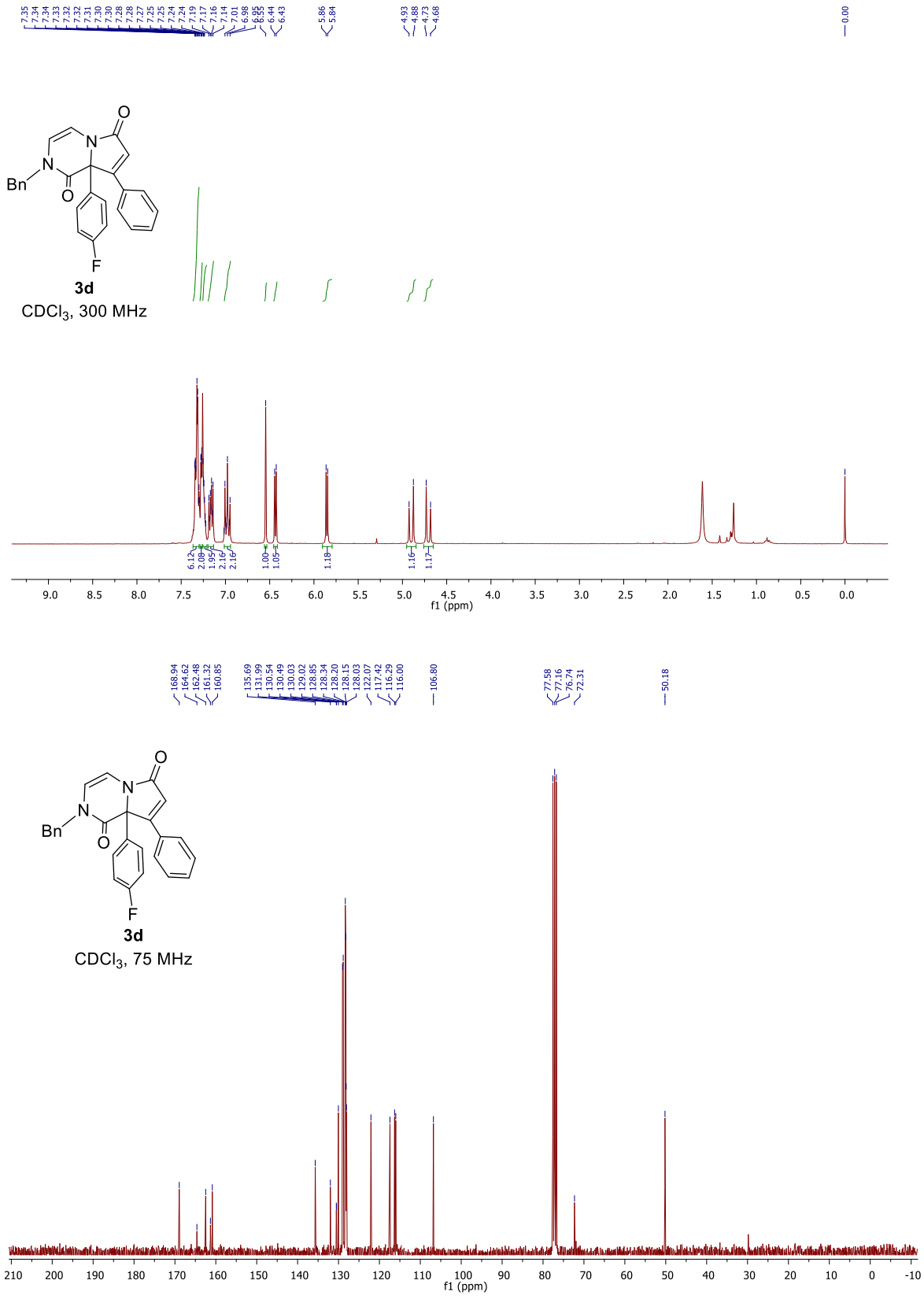


Figure S34: ^{1}H and ^{13}C NMR of compound **3e**

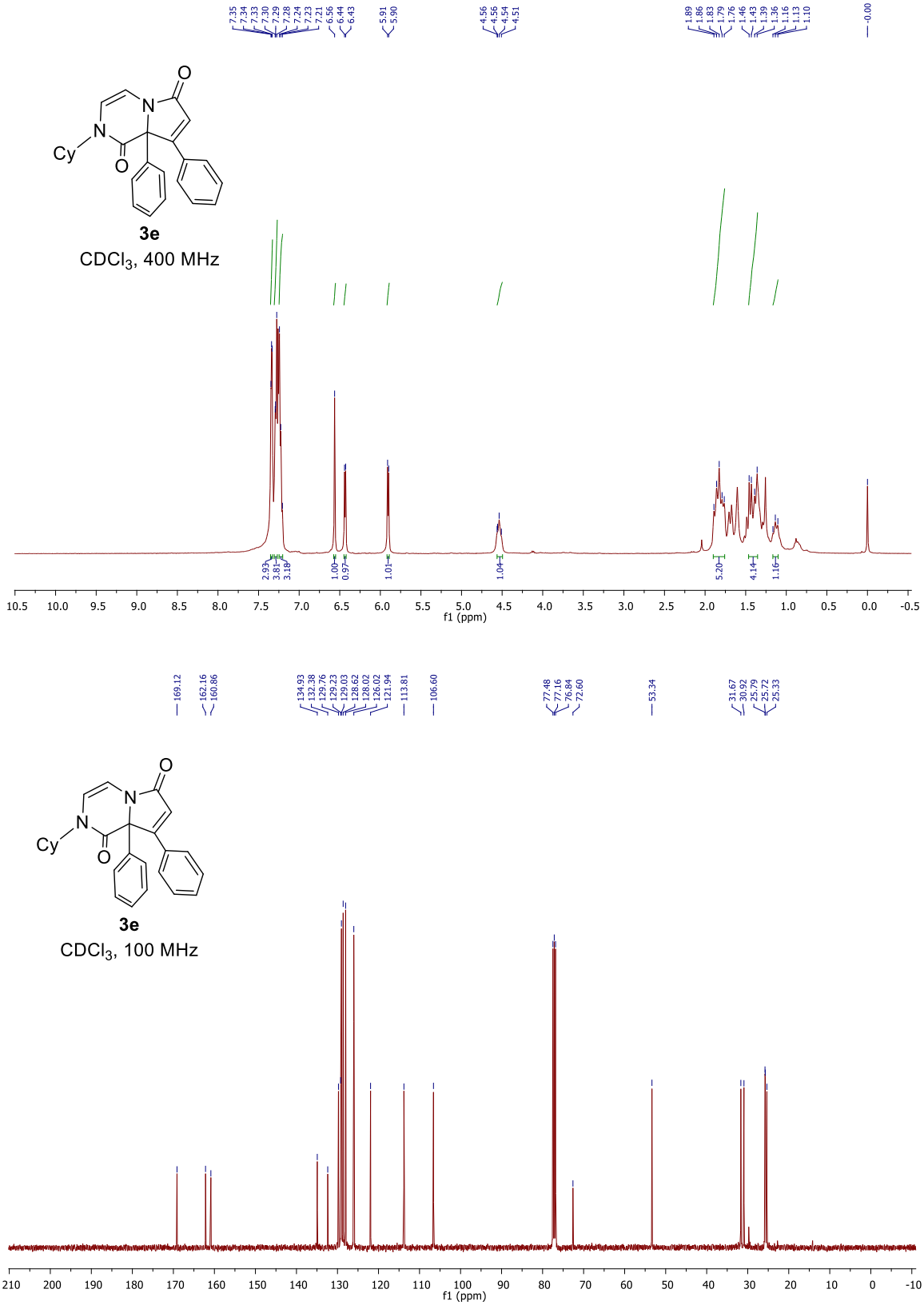


Figure S35: ^{1}H and ^{13}C NMR of compound **3f**

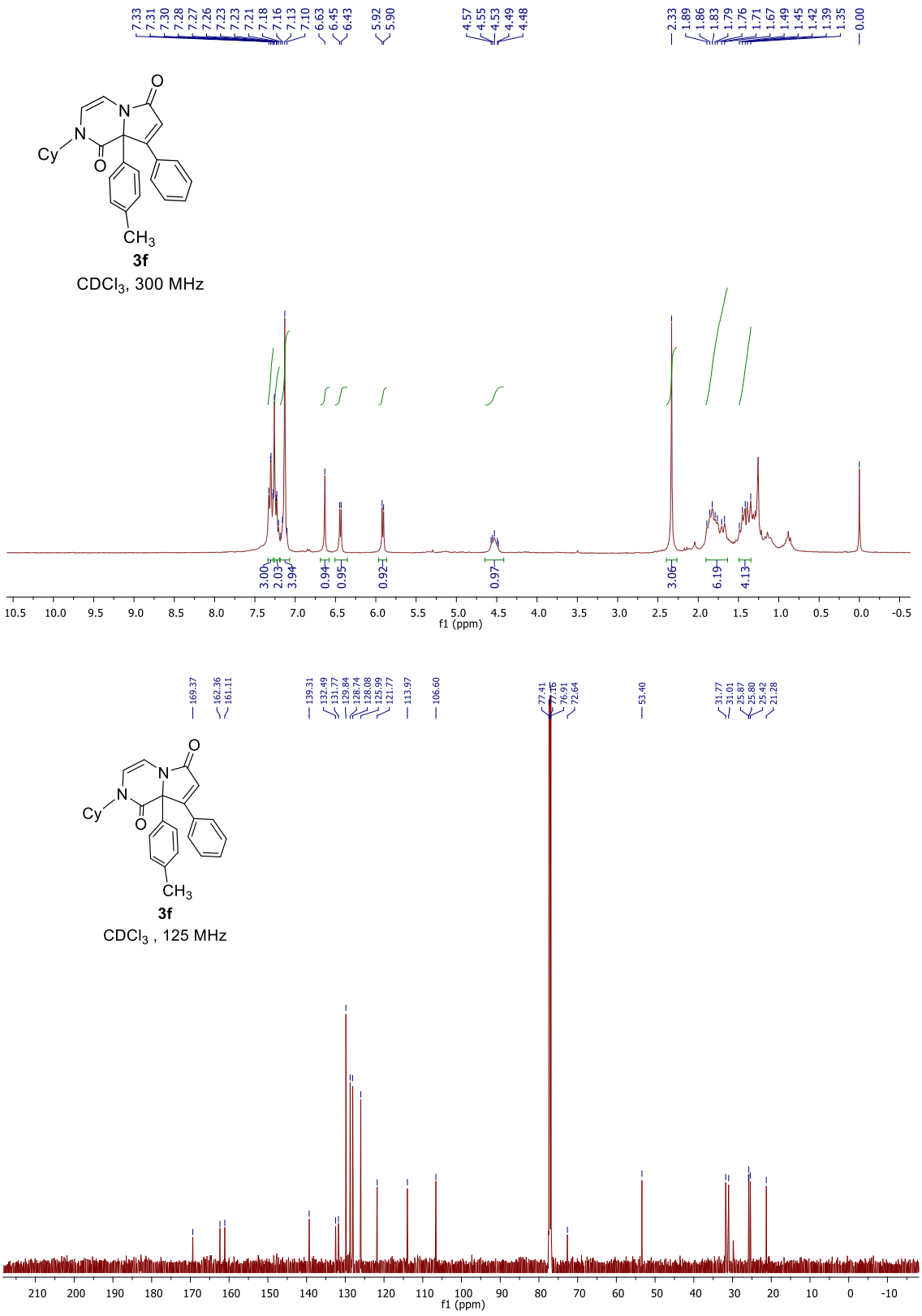


Figure S36: ^{1}H and ^{13}C NMR of compound **3g**

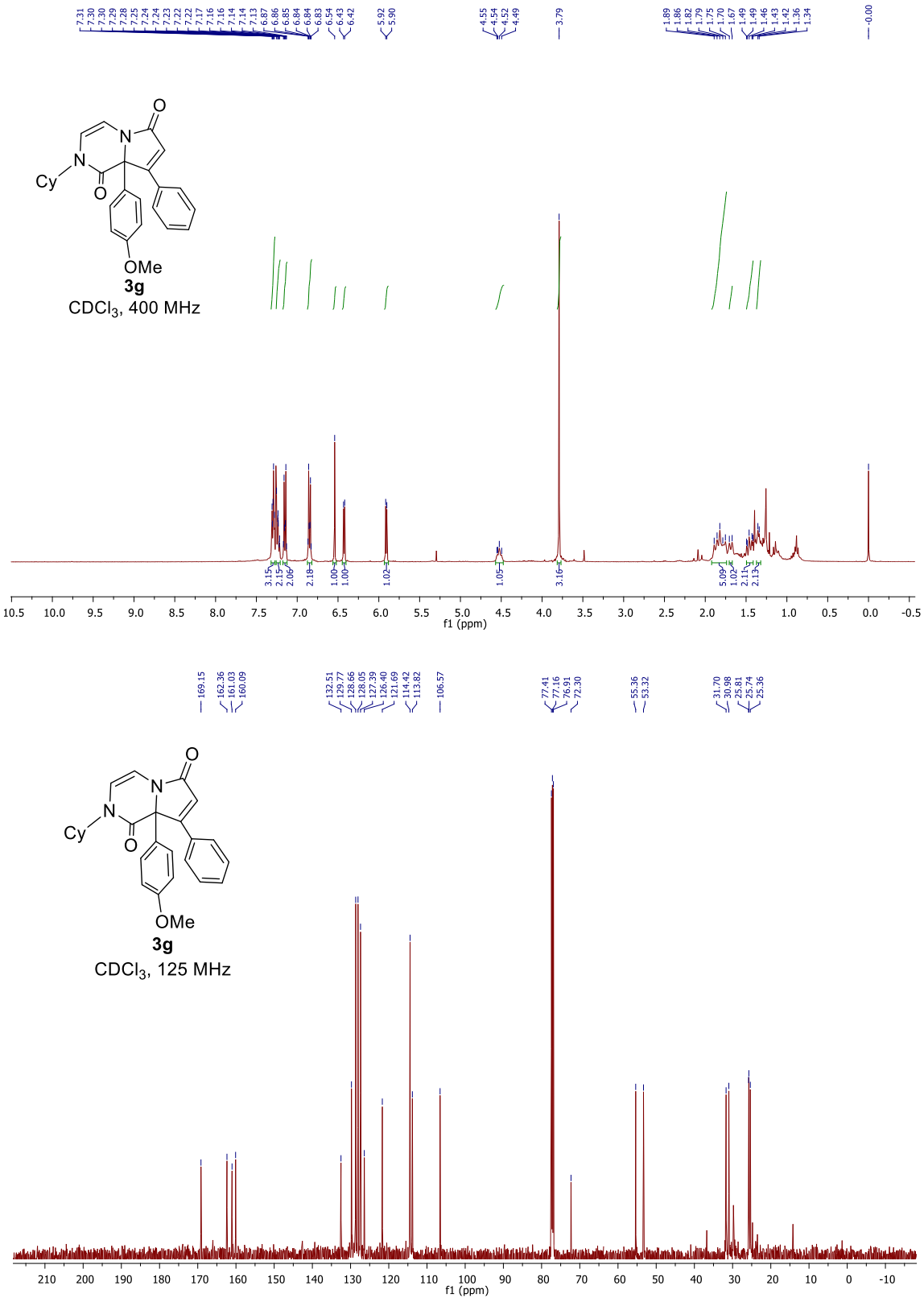


Figure S37: ^{1}H and ^{13}C NMR of compound **3h**

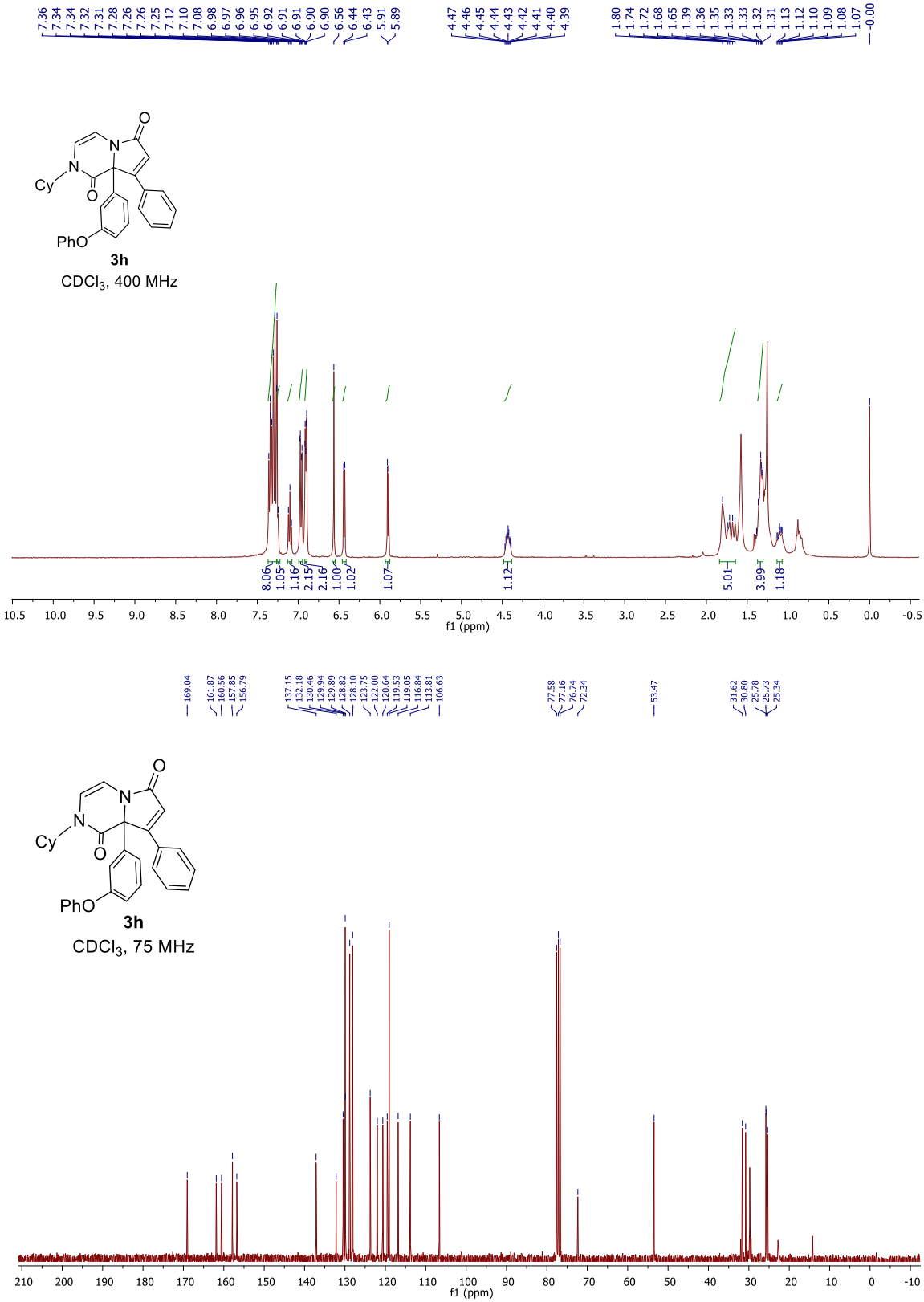
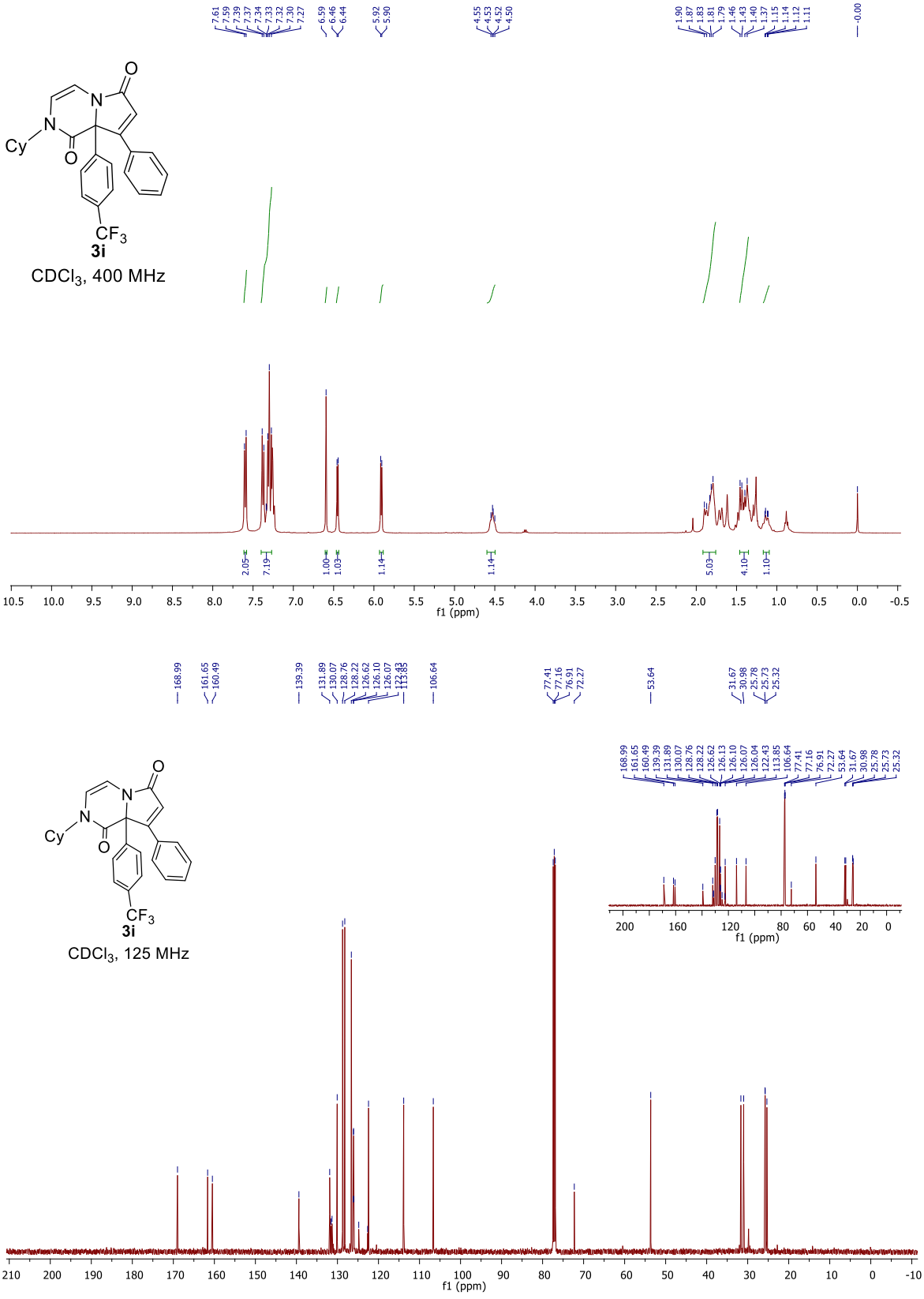
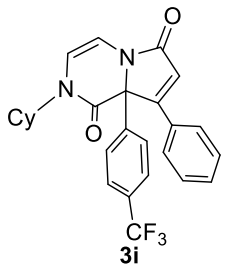


Figure S38: ^{1}H,^{13}C and ^{19}F NMR of compound **3i**





3i

$CDCl_3$, 283 MHz

Figure S39: ^{1}H and ^{13}C NMR of compound **3j**

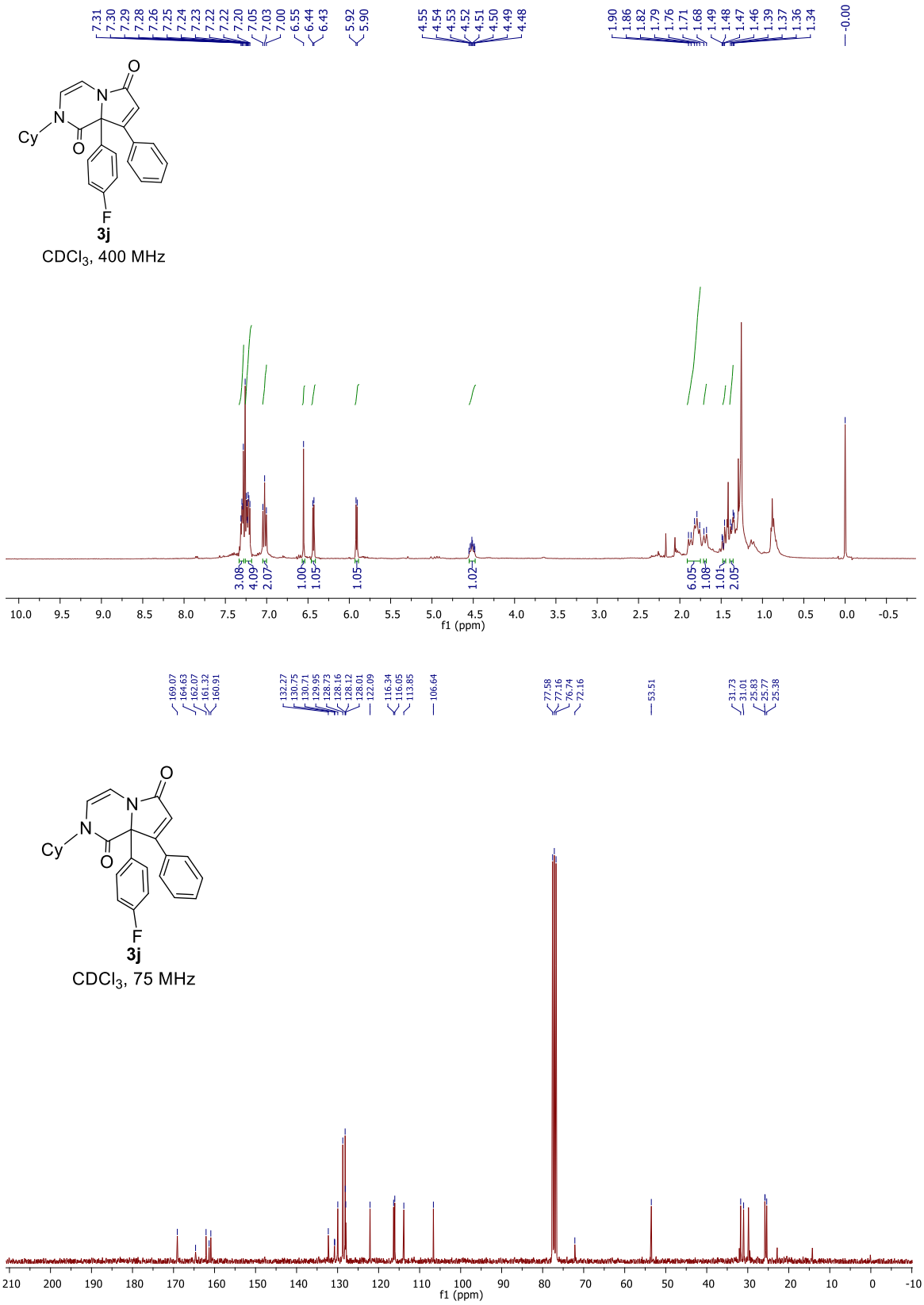
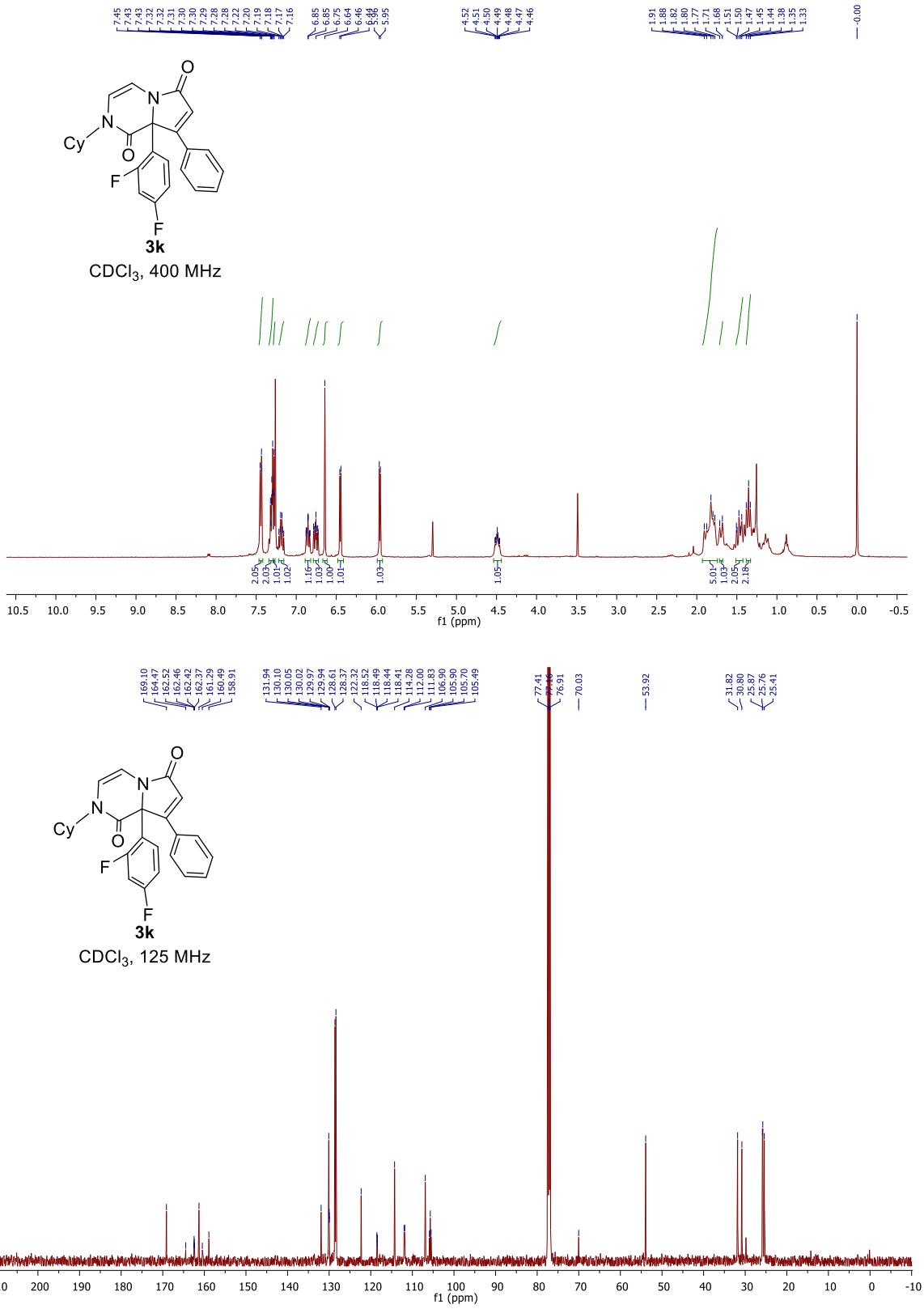
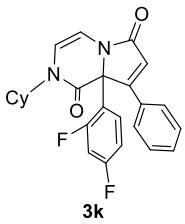


Figure S40: ^{1}H,^{13}C and ^{19}F NMR of compound **3k**

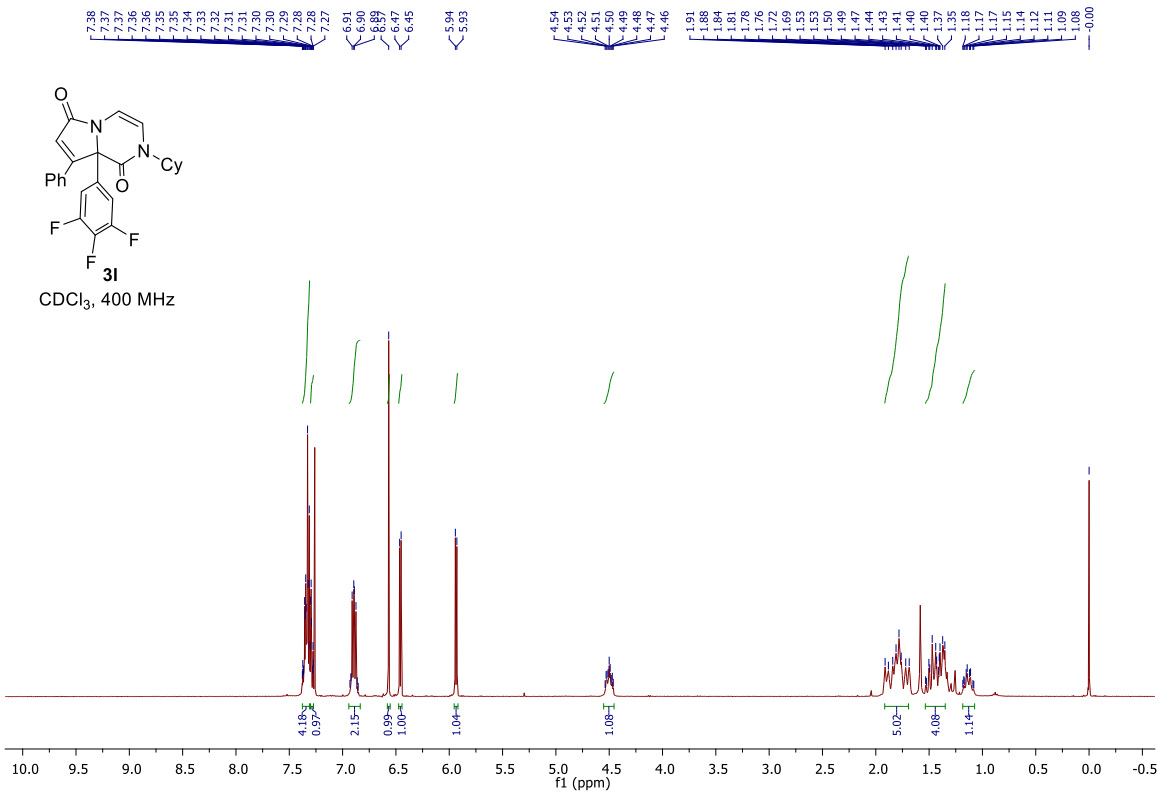


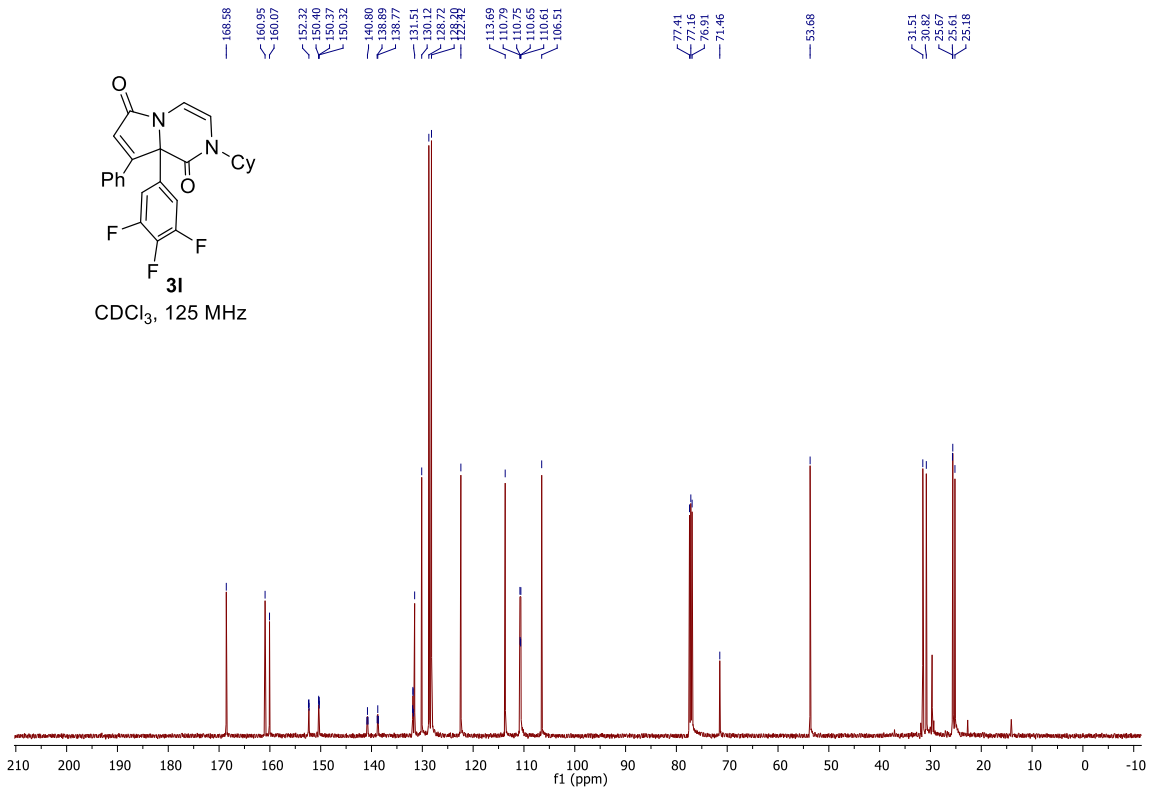


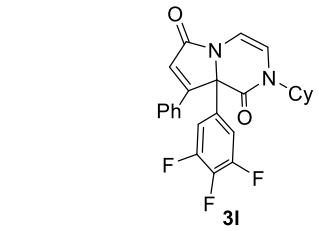
3k

$CDCl_3$, 377 MHz

Figure S41: ^{1}H,^{13}C and ^{19}F NMR of compound **3l**







3l

$CDCl_3$, 377 MHz

Figure S42: ^{1}H and ^{13}C NMR of compound **3m**

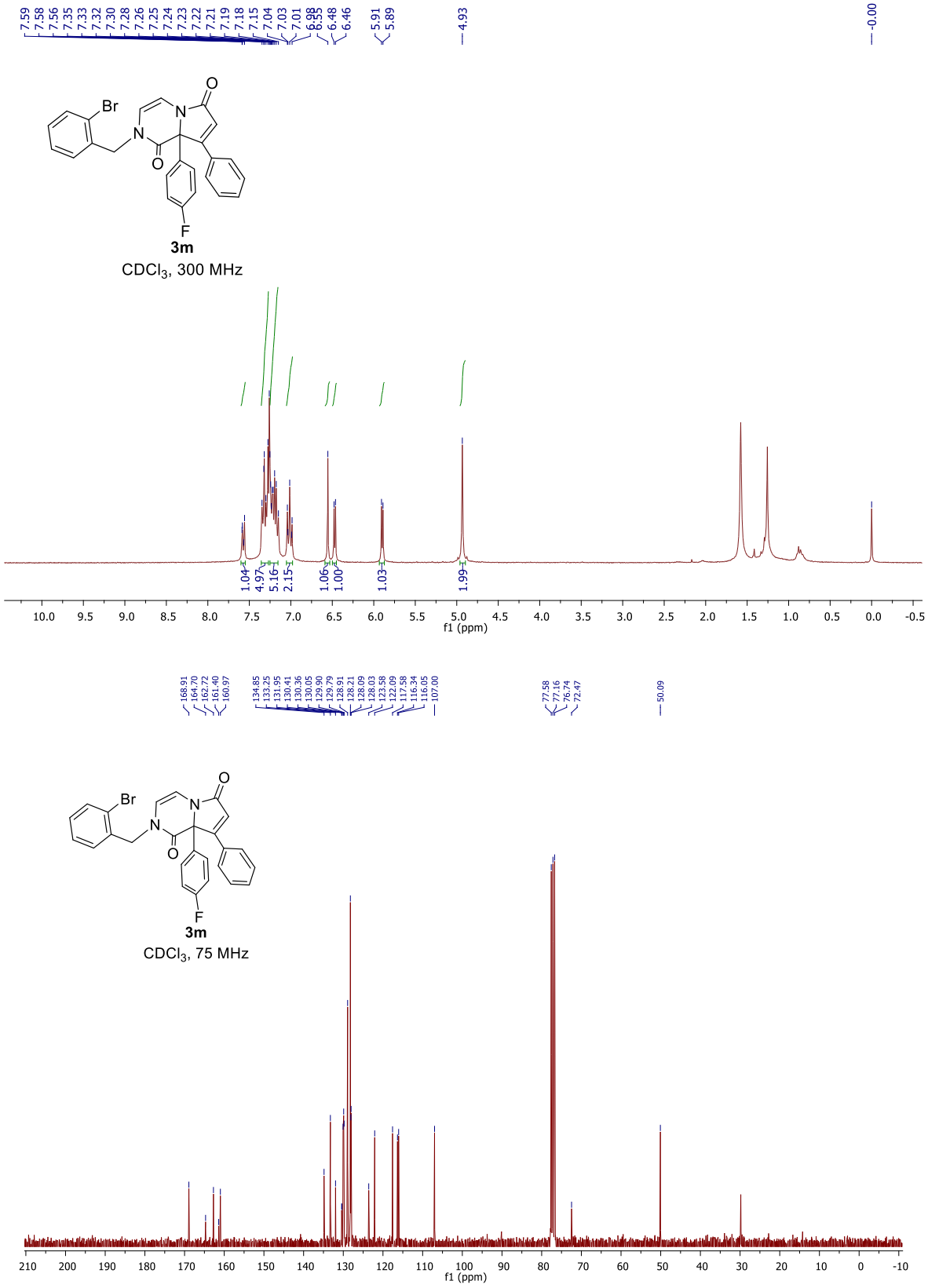


Figure S43: ^{1}H and ^{13}C NMR of compound **3n**

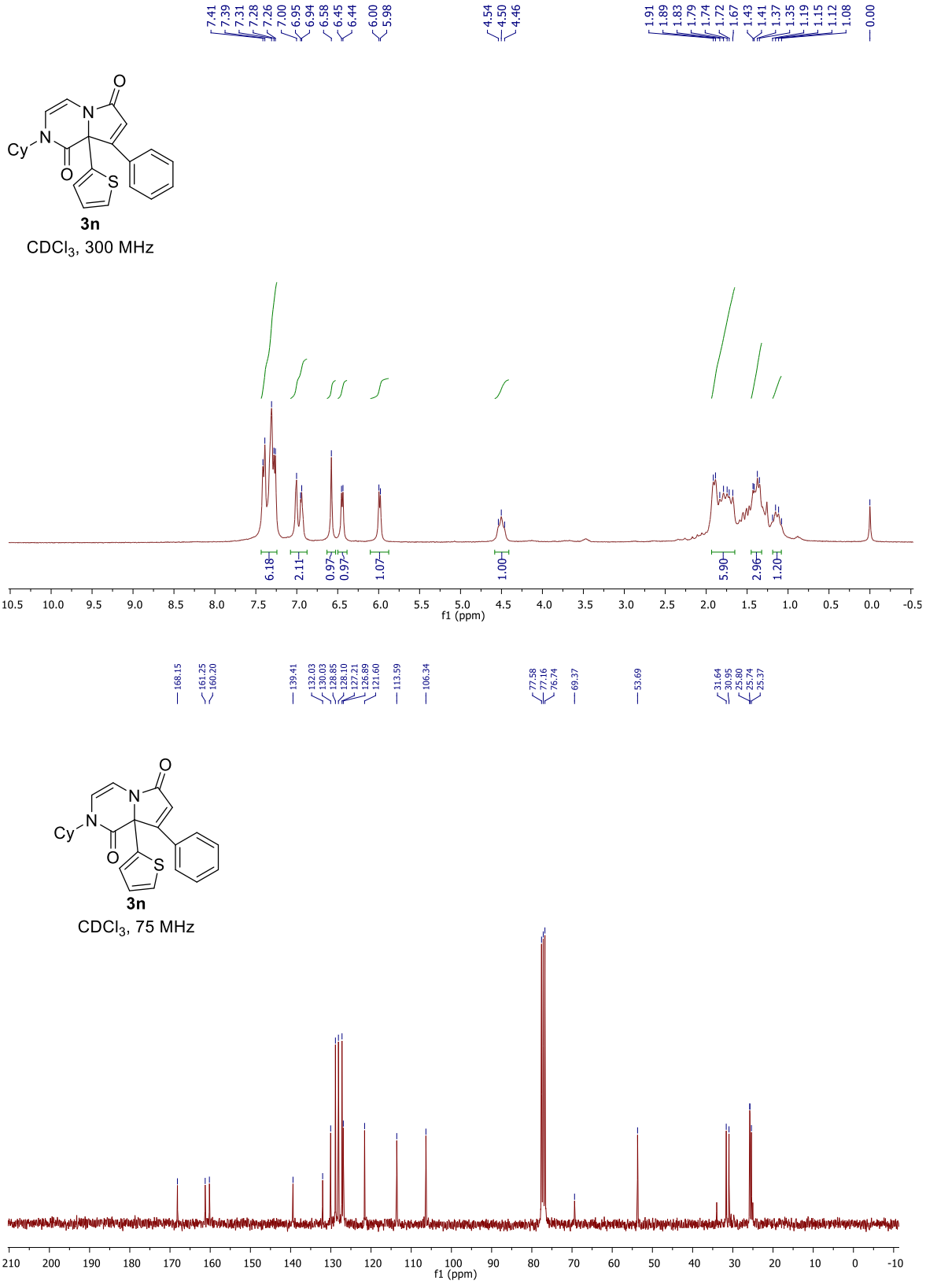


Figure S44: ^{1}H and ^{13}C NMR of compound **3o**

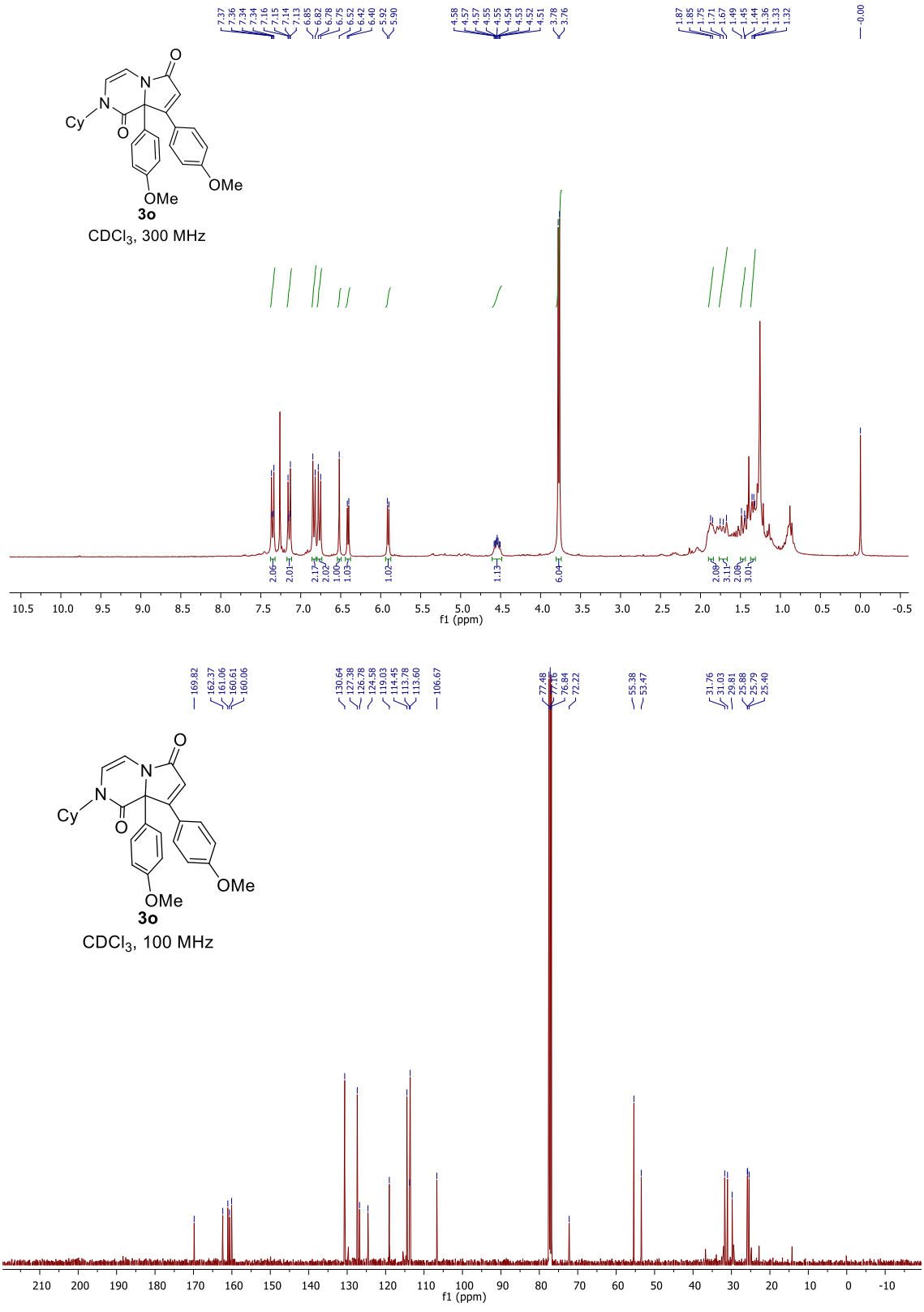


Figure S45: ^{1}H and ^{13}C NMR of compound **3p**

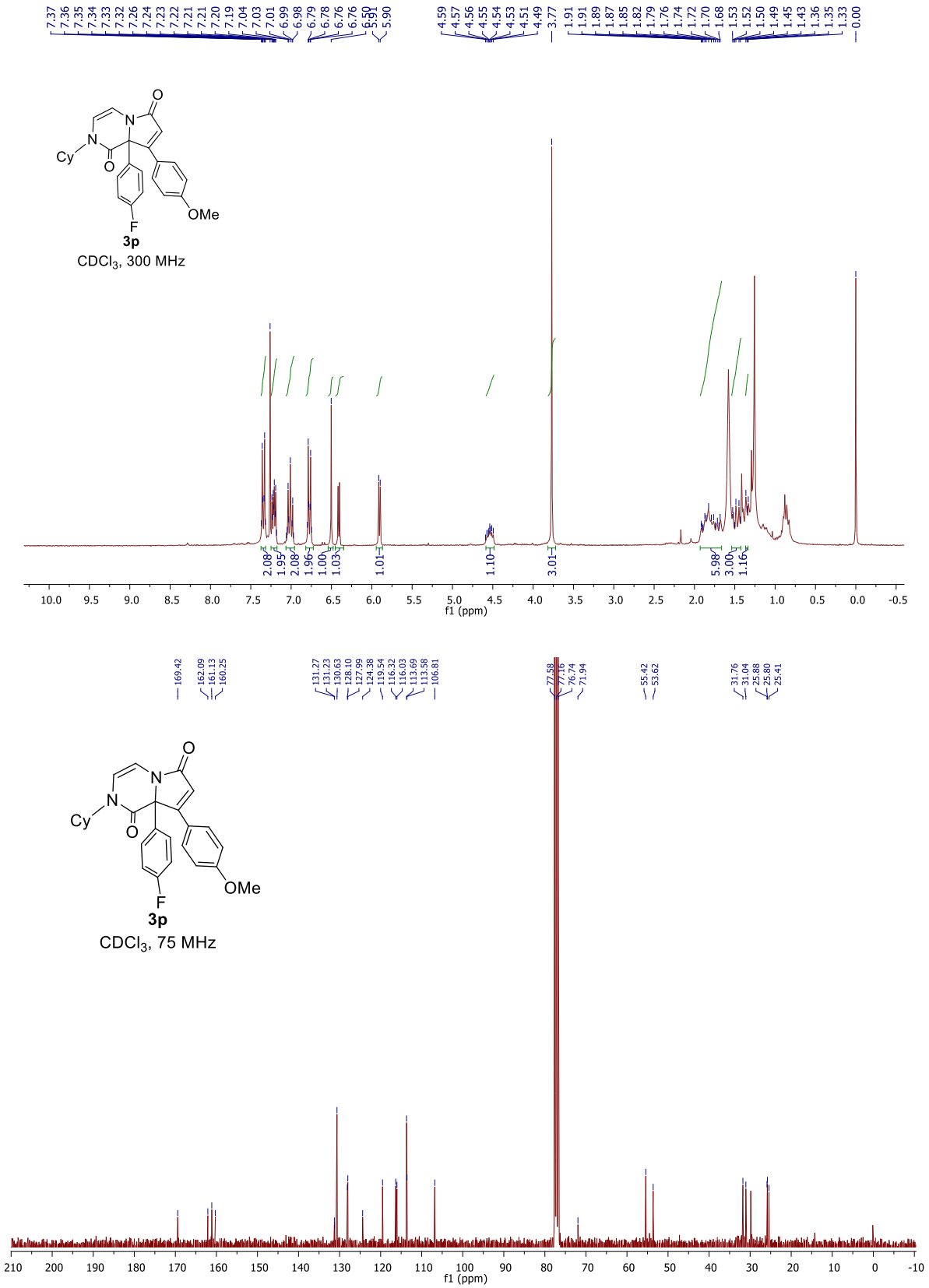


Figure S46: ^{1}H and ^{13}C NMR of compound **3q**

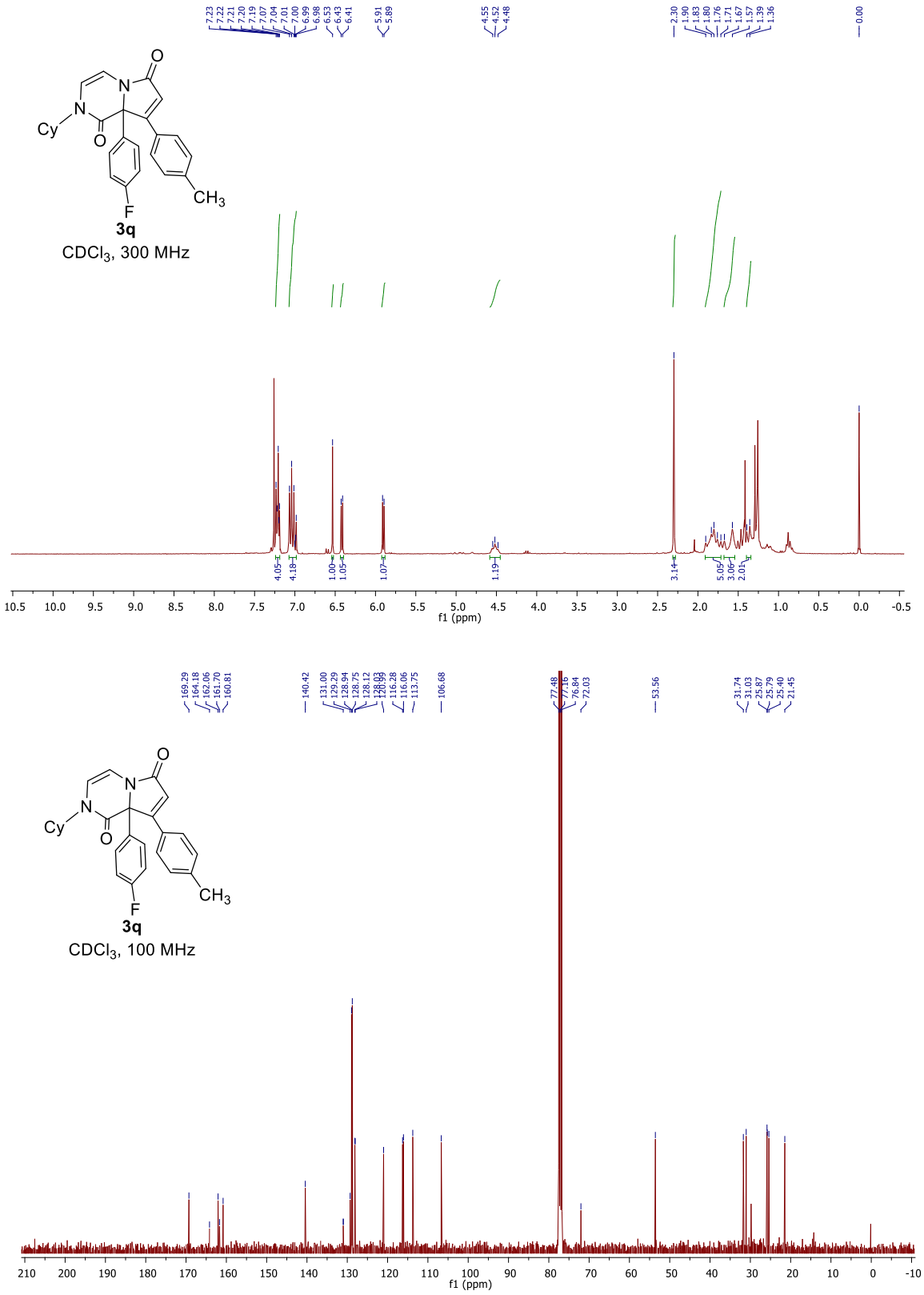


Figure S47: ^{1}H and ^{13}C NMR of compound **3r**

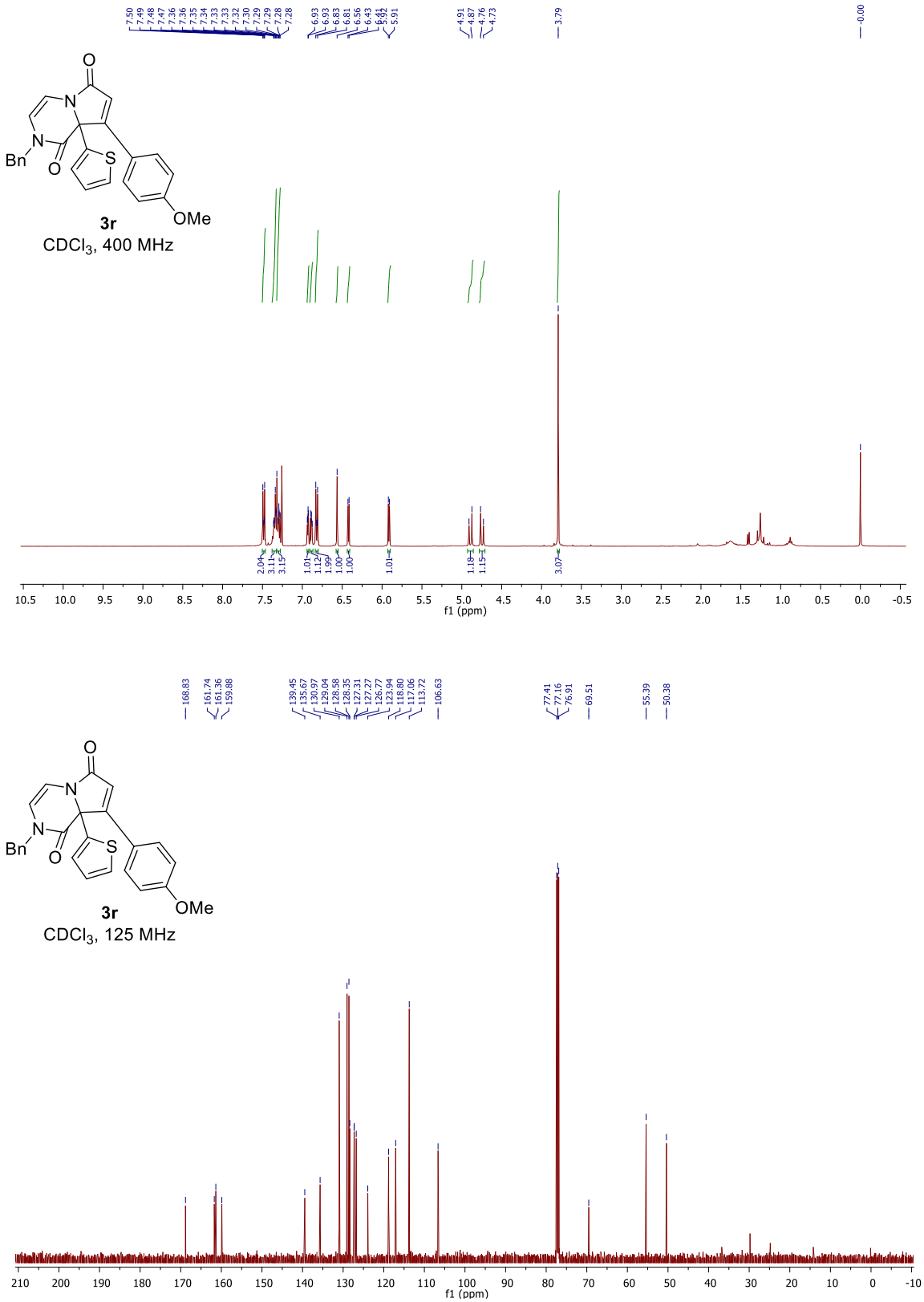


Figure S48: ^{1}H and ^{13}C NMR of compound **3t**

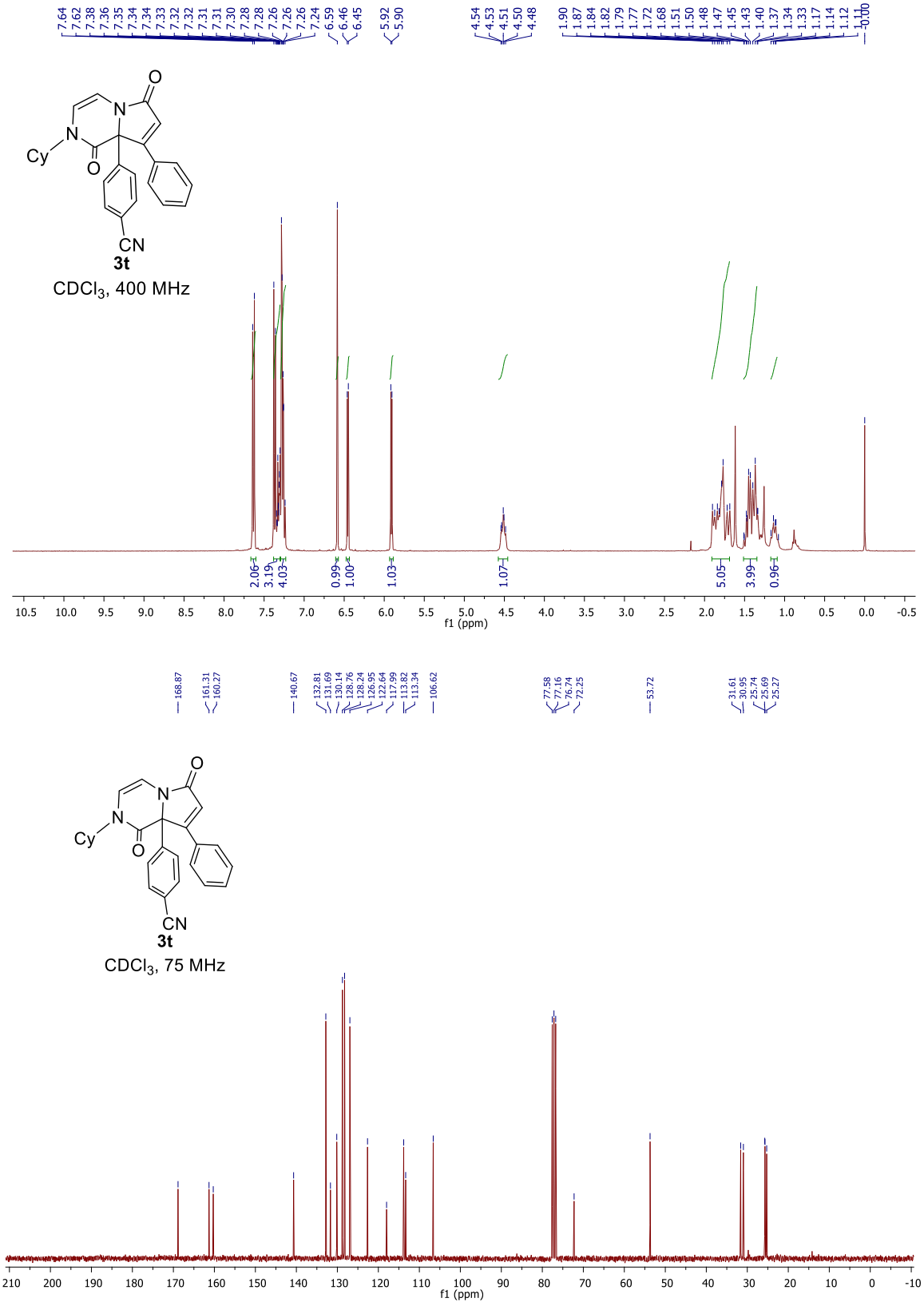


Figure S49: ^{1}H and ^{13}C NMR of compound **3u**

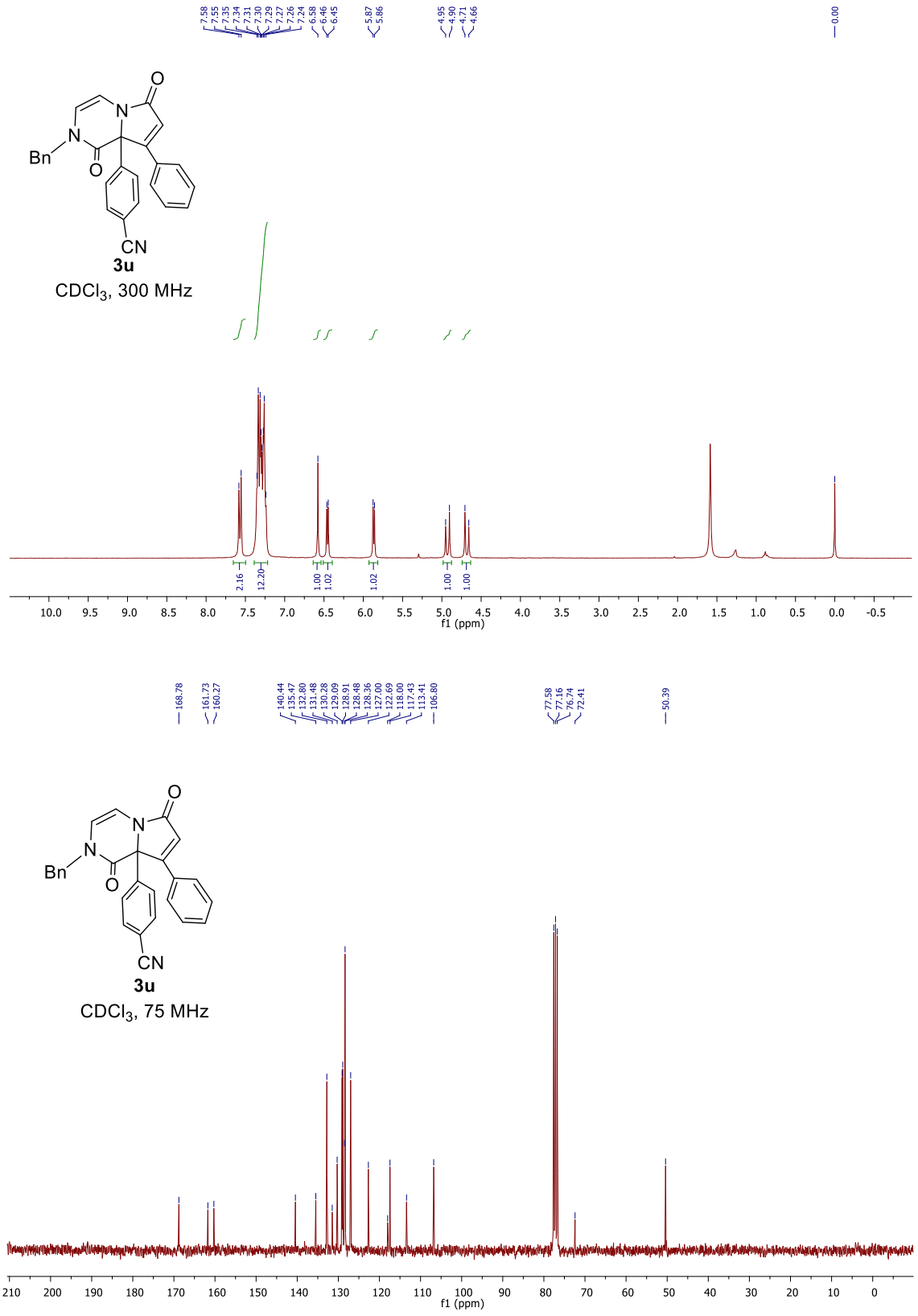


Figure S50: ^{1}H and ^{13}C NMR of compound **3v**

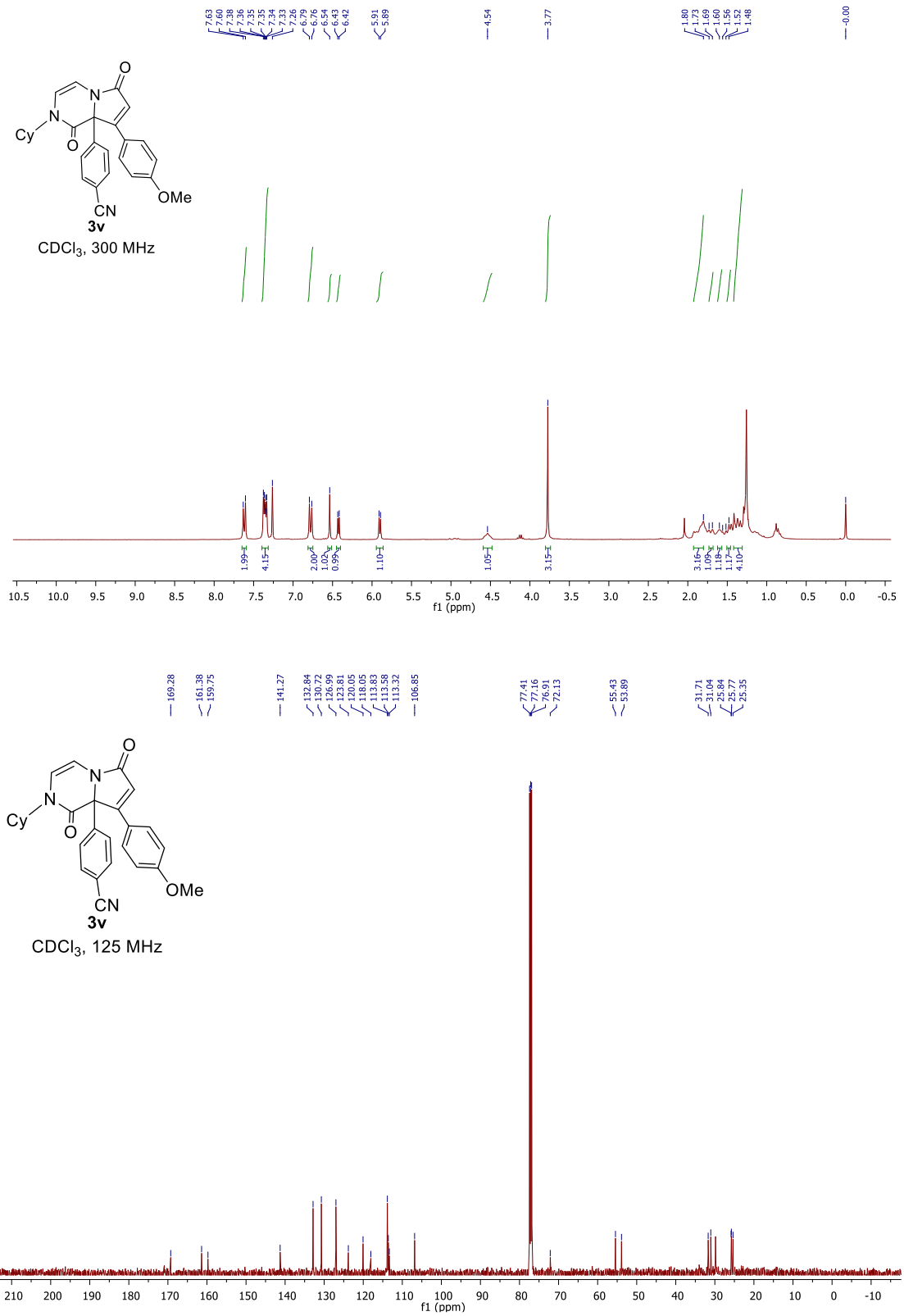


Figure S51: ^{1}H and ^{13}C NMR of compound **3w**

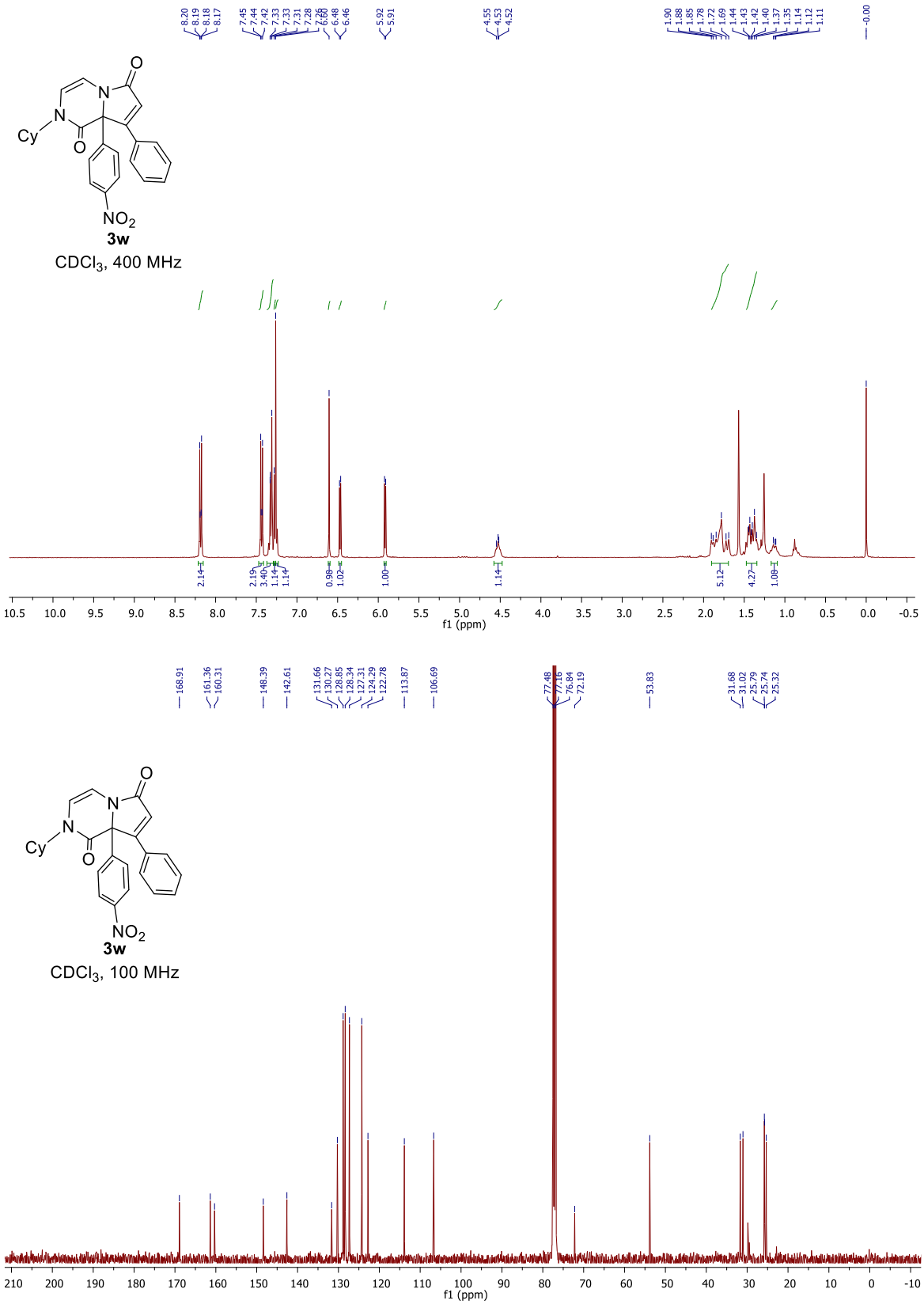


Figure S52: ^{1}H and ^{13}C NMR of compound **3x**

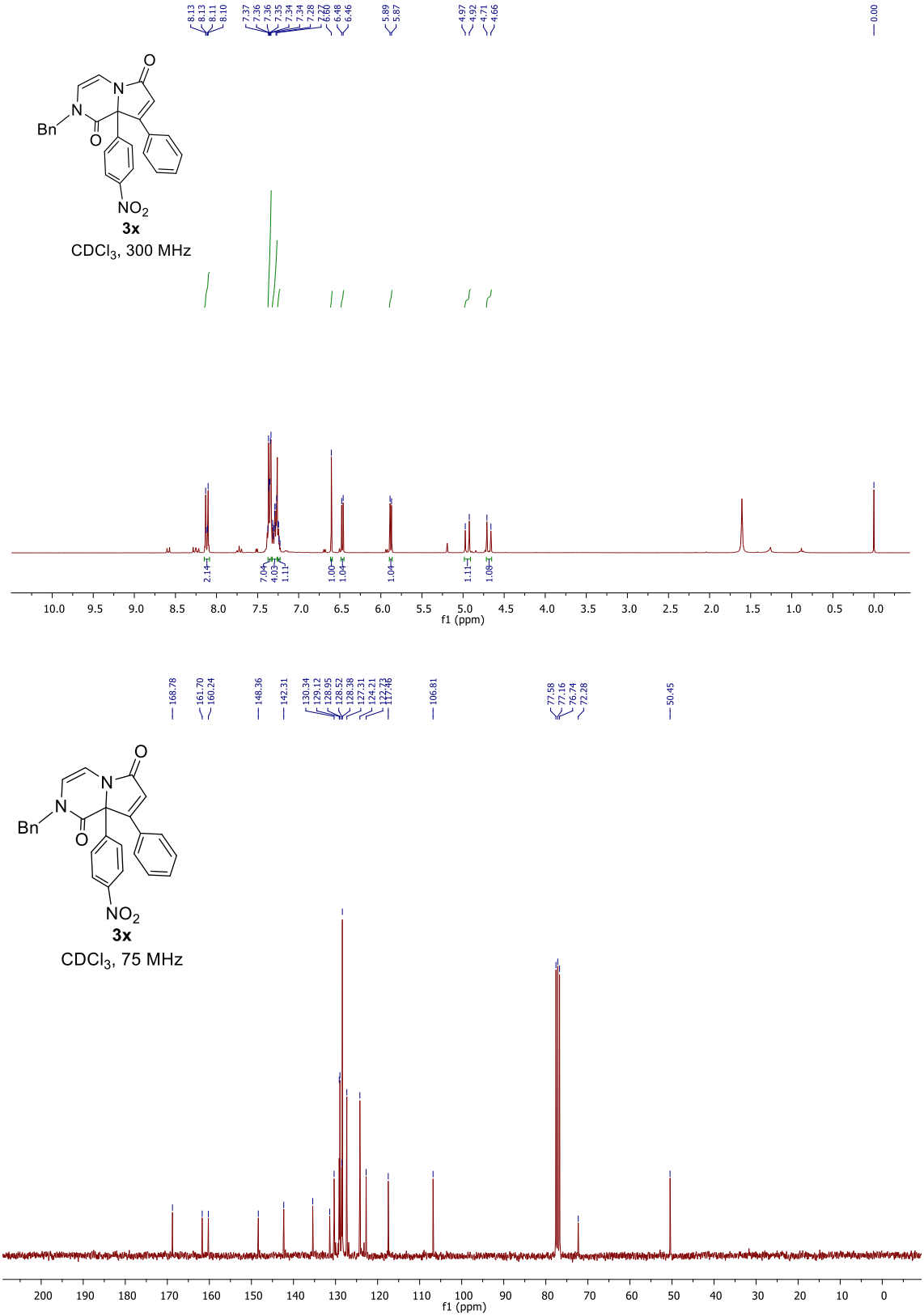


Figure S53: ^{1}H and ^{13}C NMR of compound **3y**

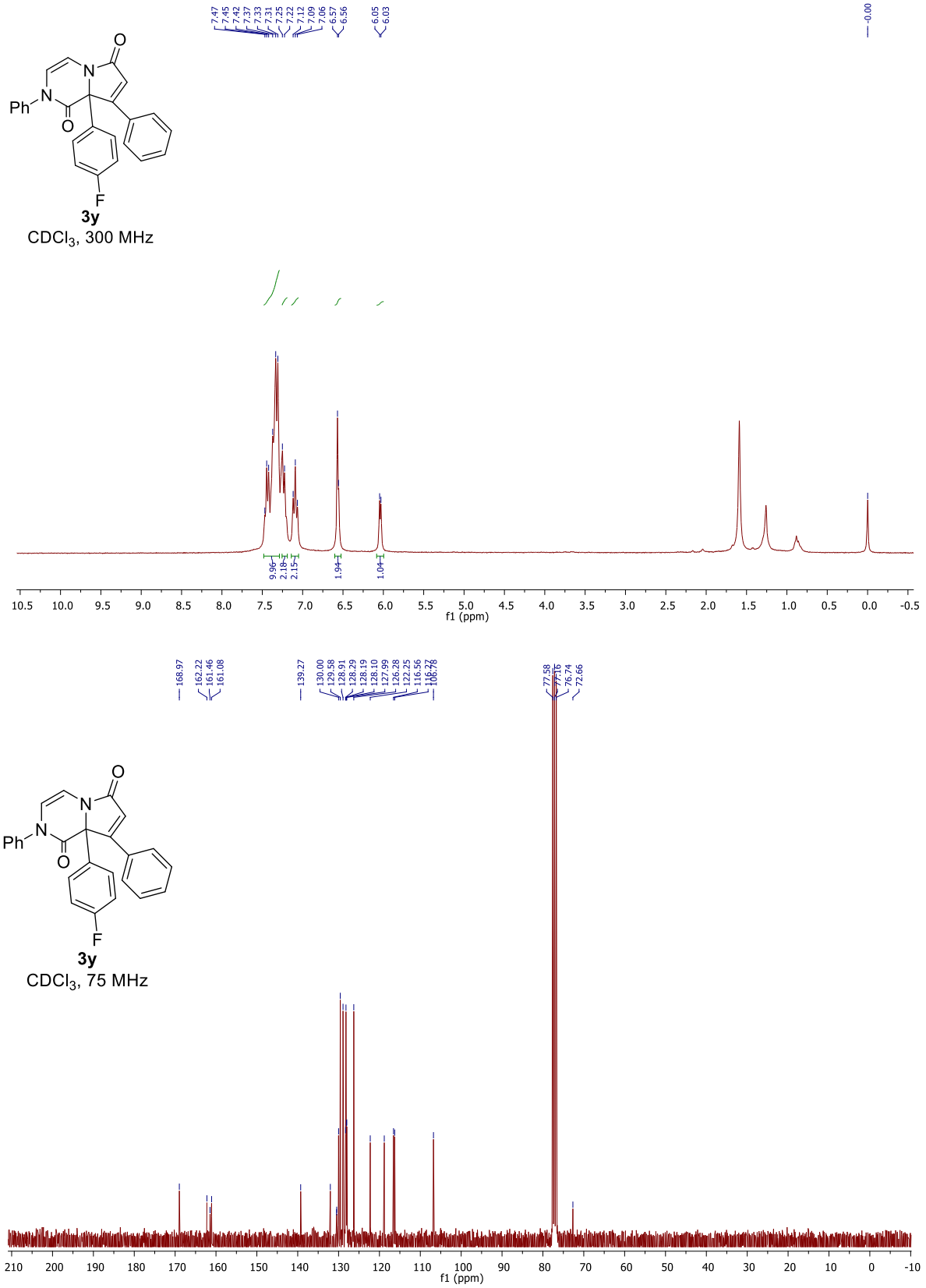
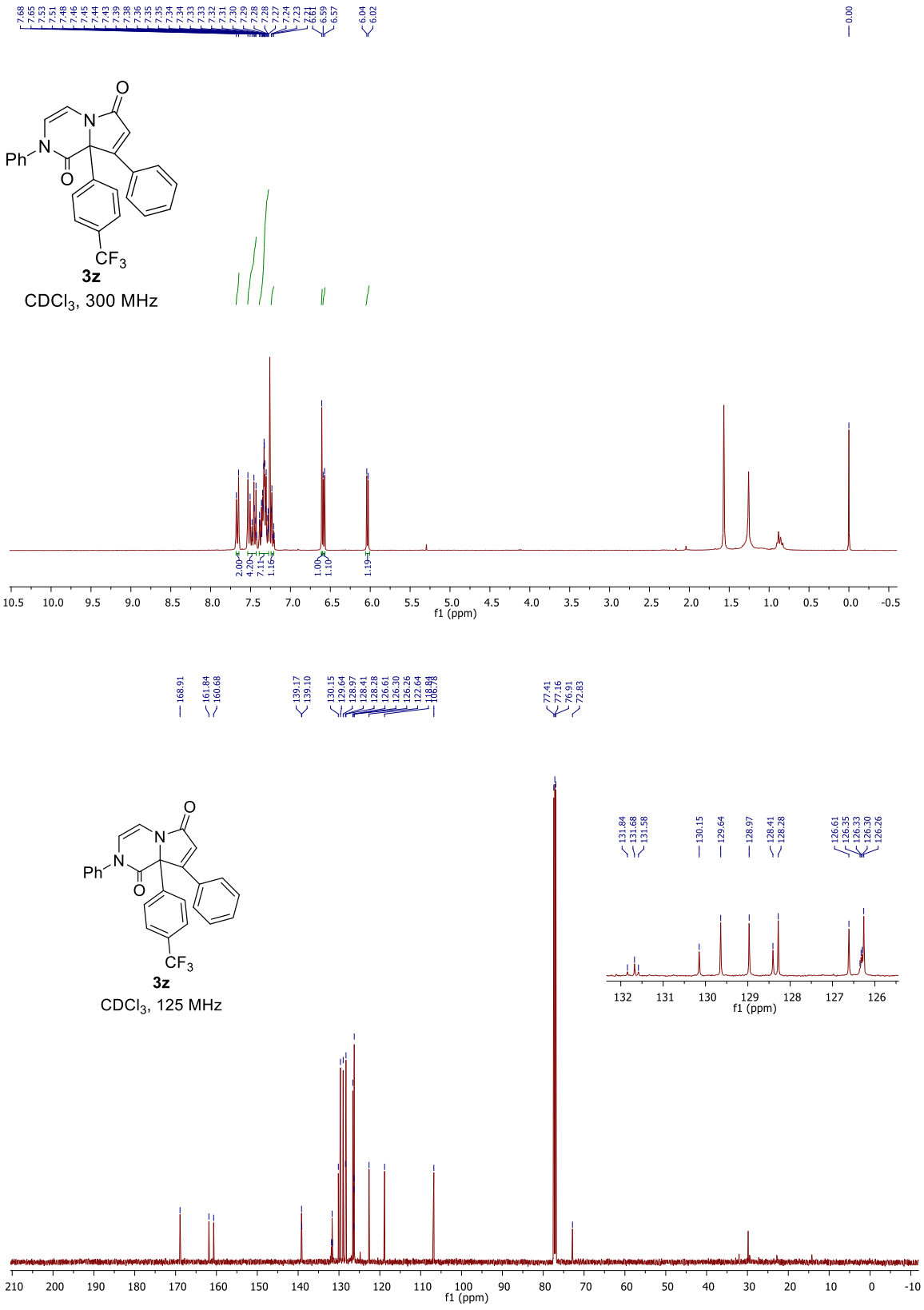
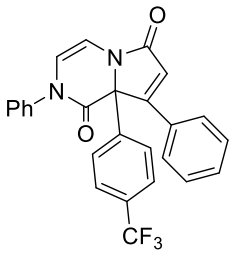


Figure S54: ^{1}H, ^{13}C and ^{19}F NMR of compound **3z**





3z

$CDCl_3$, 283 MHz

Figure S55: ^{1}H and ^{13}C NMR of compound **3aa**

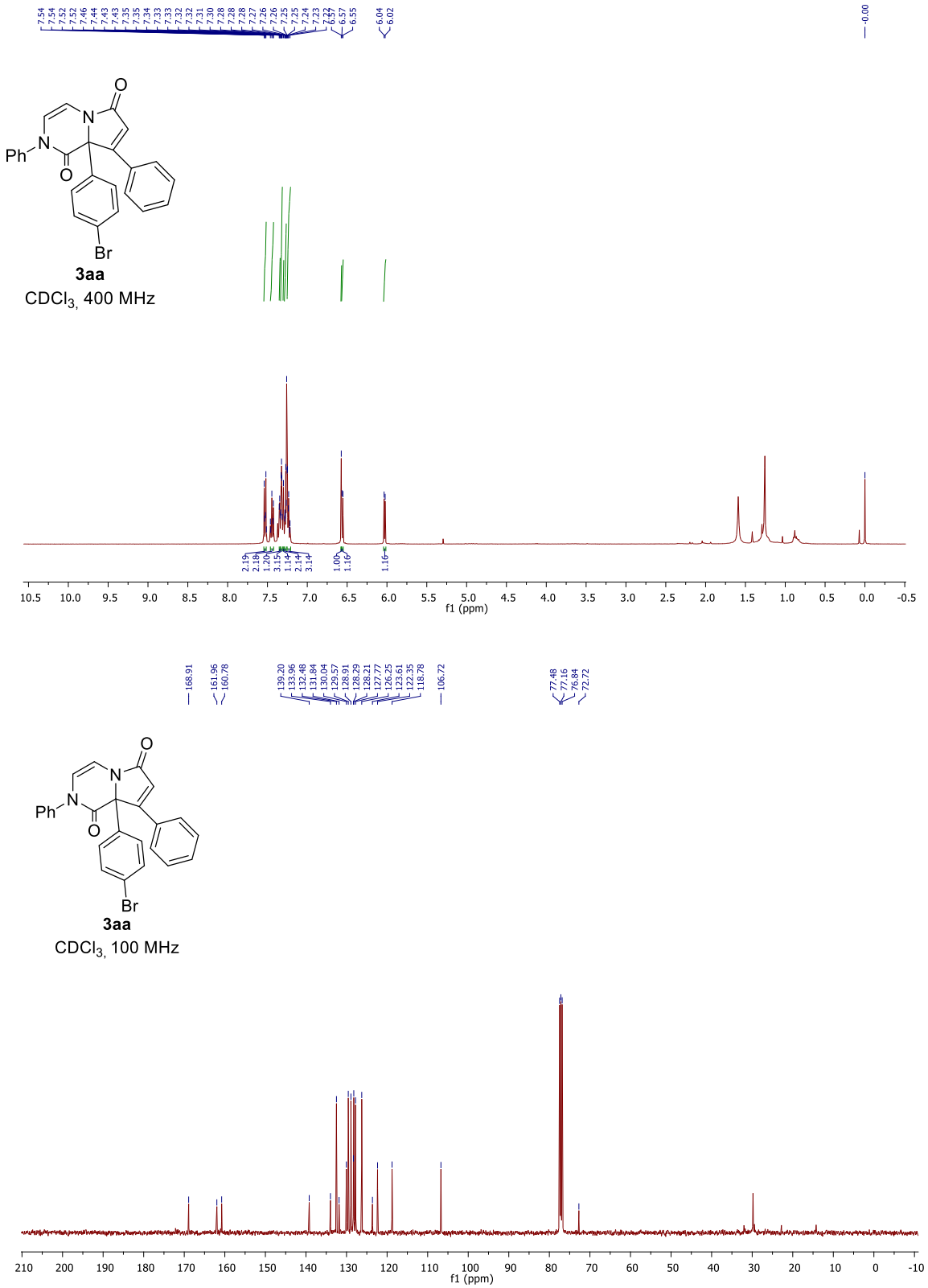


Figure S56: ^{1}H and ^{13}C NMR of compound **4a**

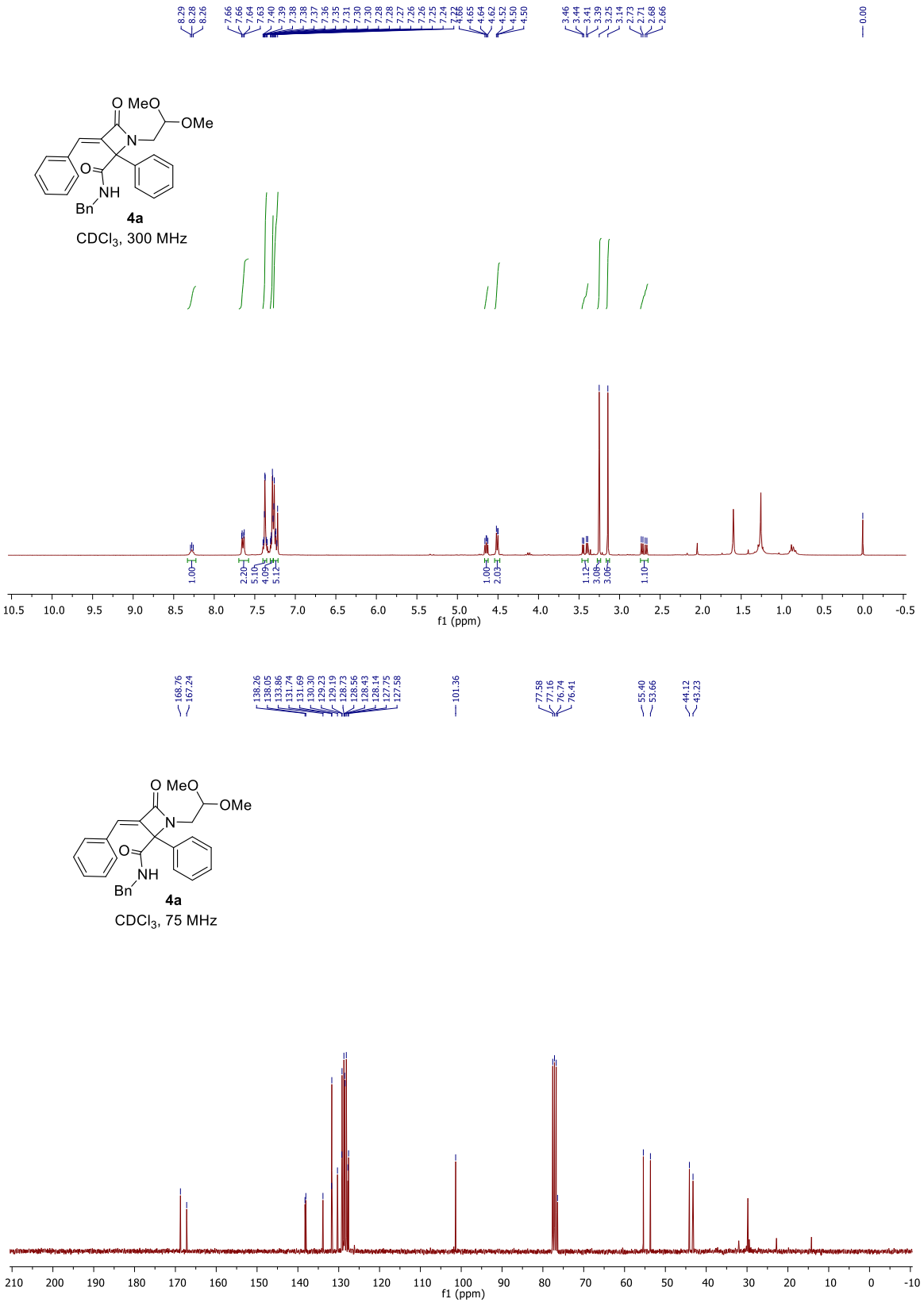


Figure S57: ^{1}H and ^{13}C NMR of compound **4b**

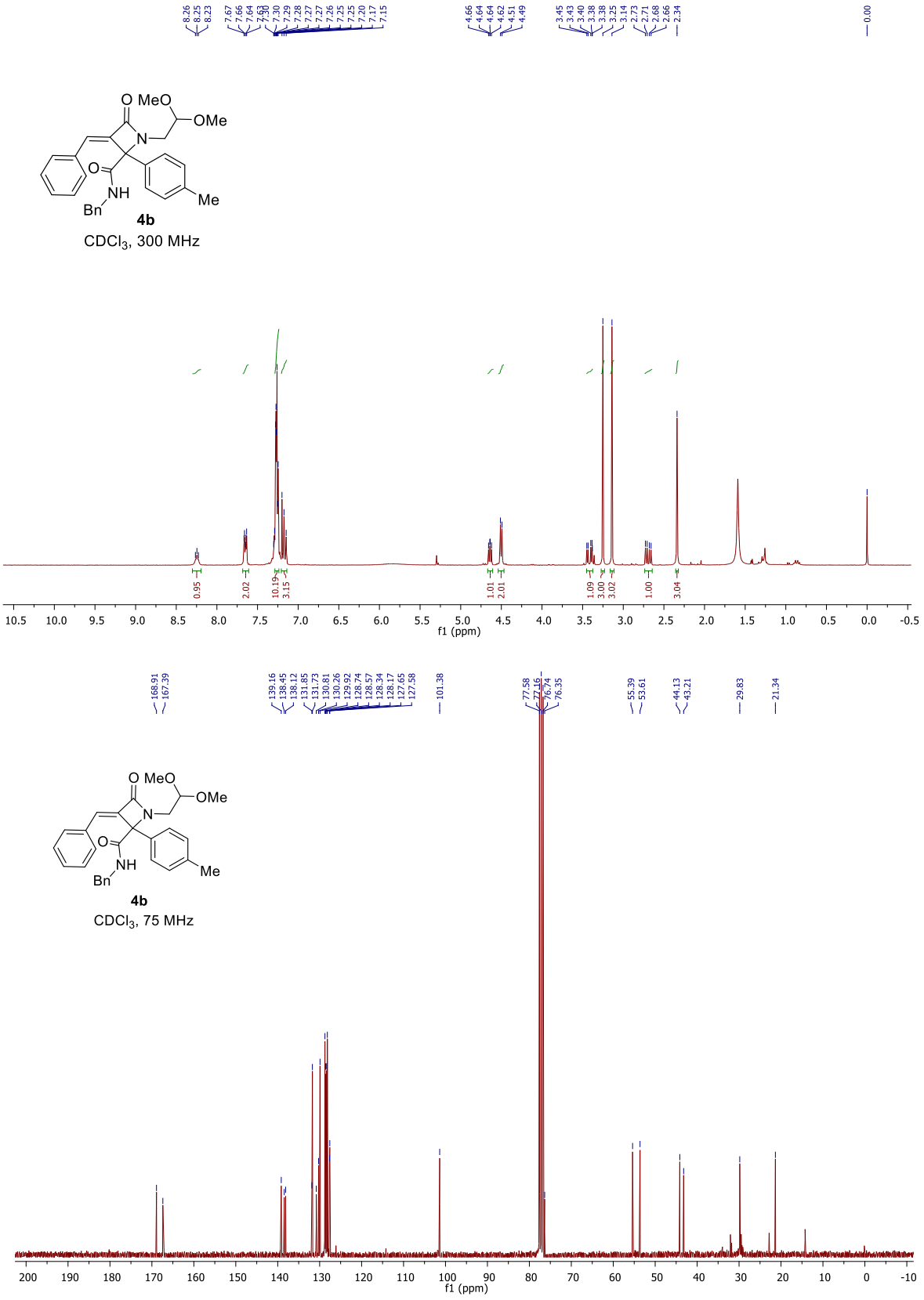


Figure S58: ^{1}H and ^{13}C NMR of compound **4c**(rotamer 1:0.4)

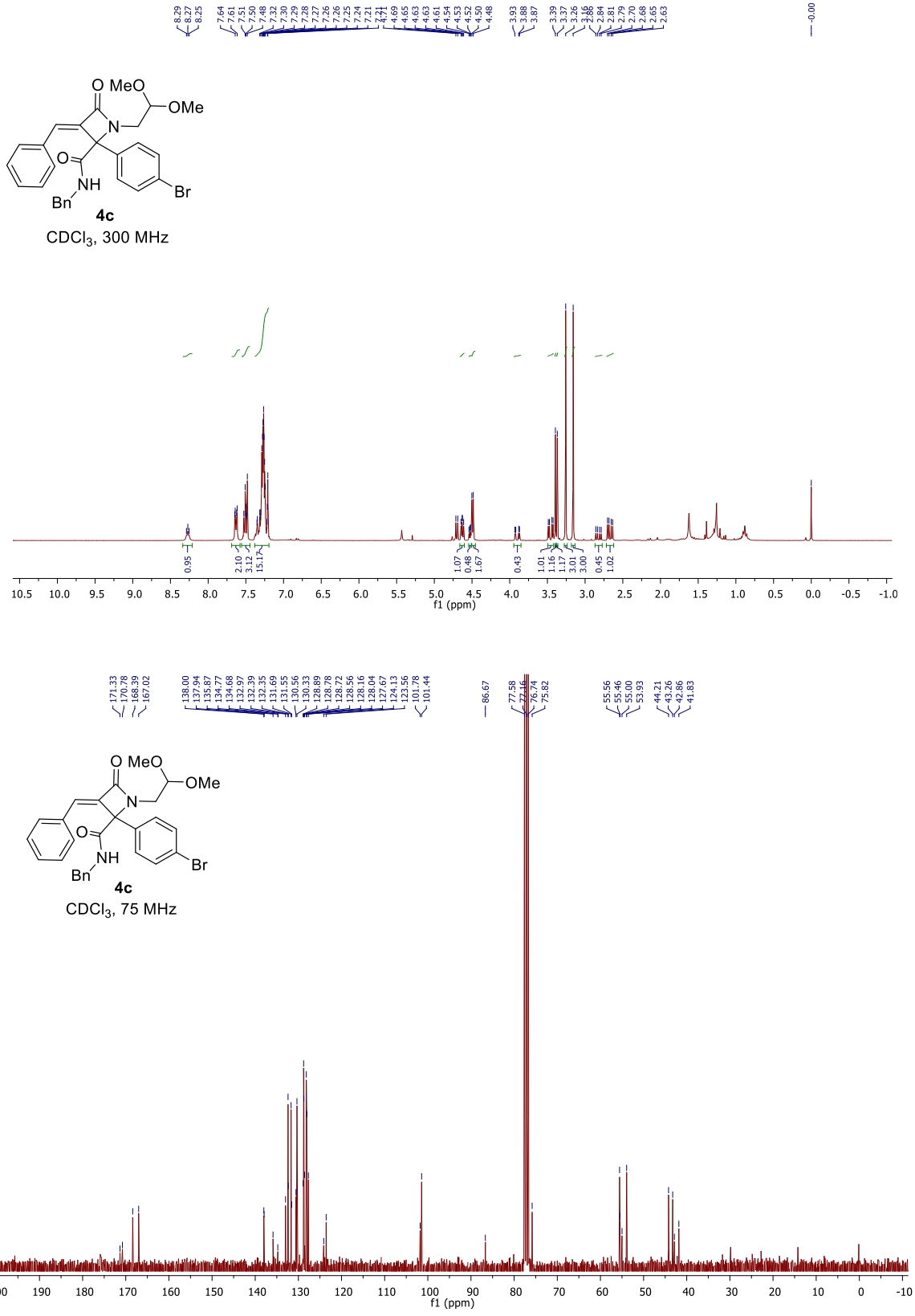


Figure S59: ^{1}H and ^{13}C NMR of compound **4d**

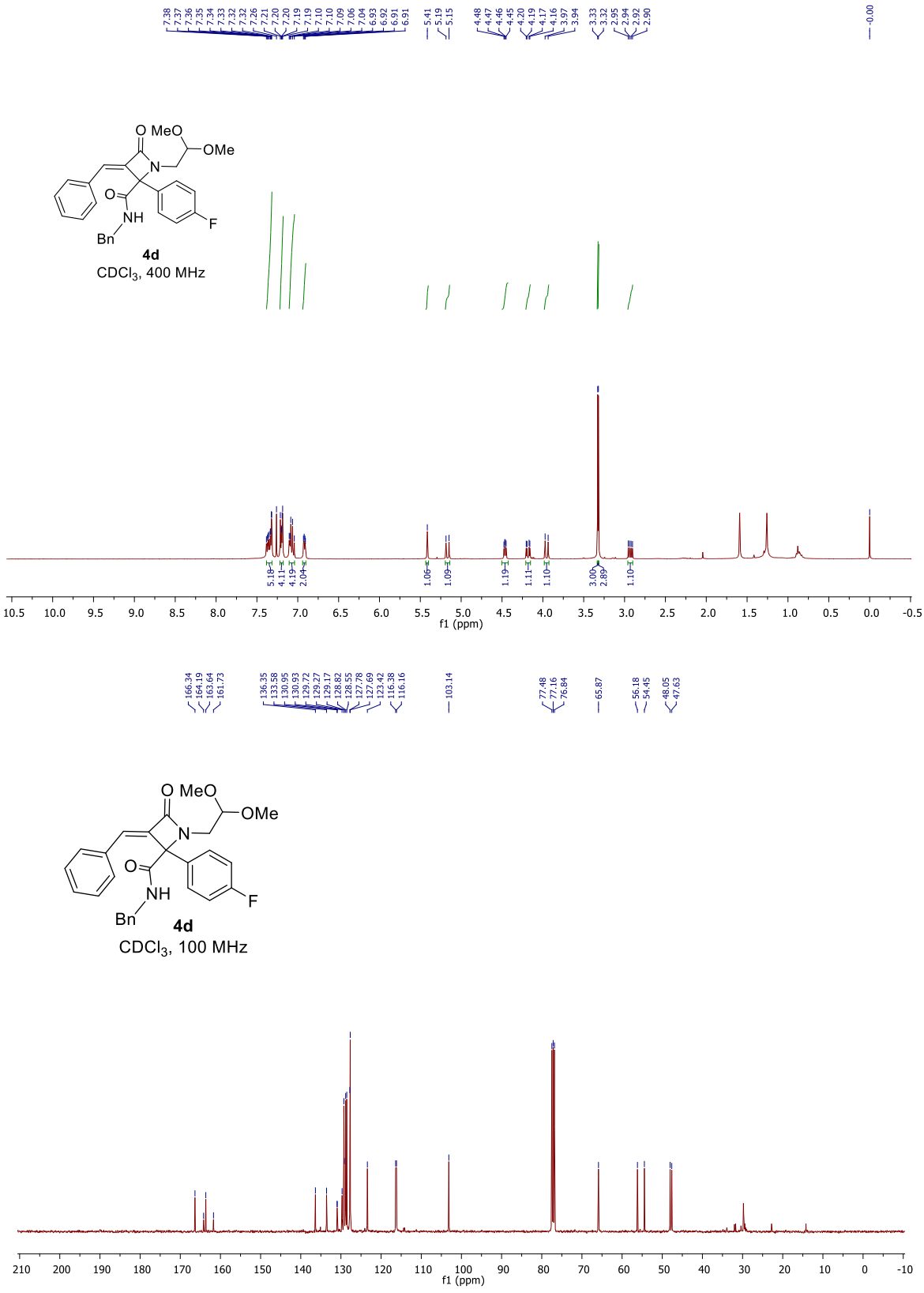


Figure S60: ^{1}H and ^{13}C NMR of compound **4e**

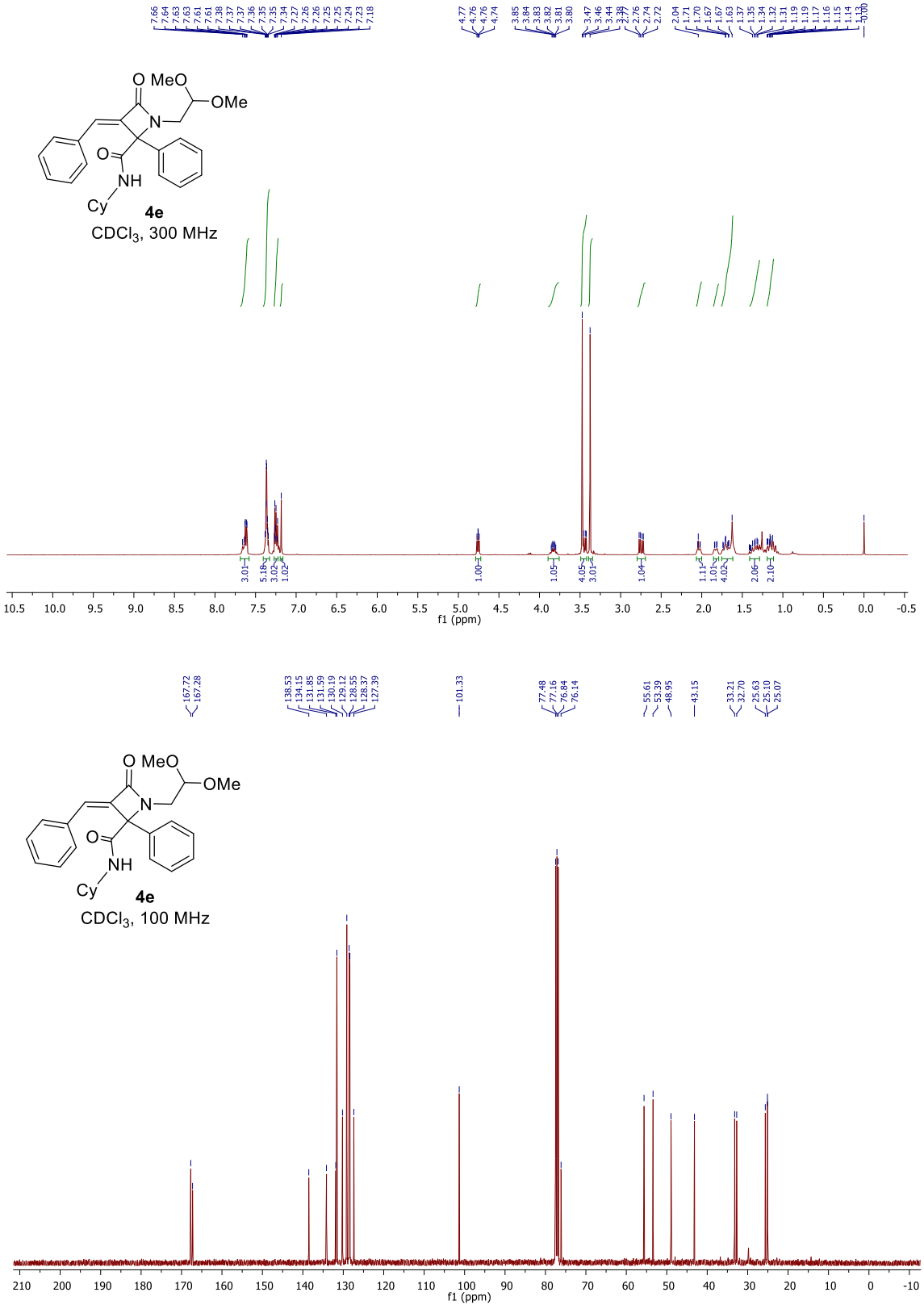


Figure S61: ^{1}H and ^{13}C NMR of compound **4f**

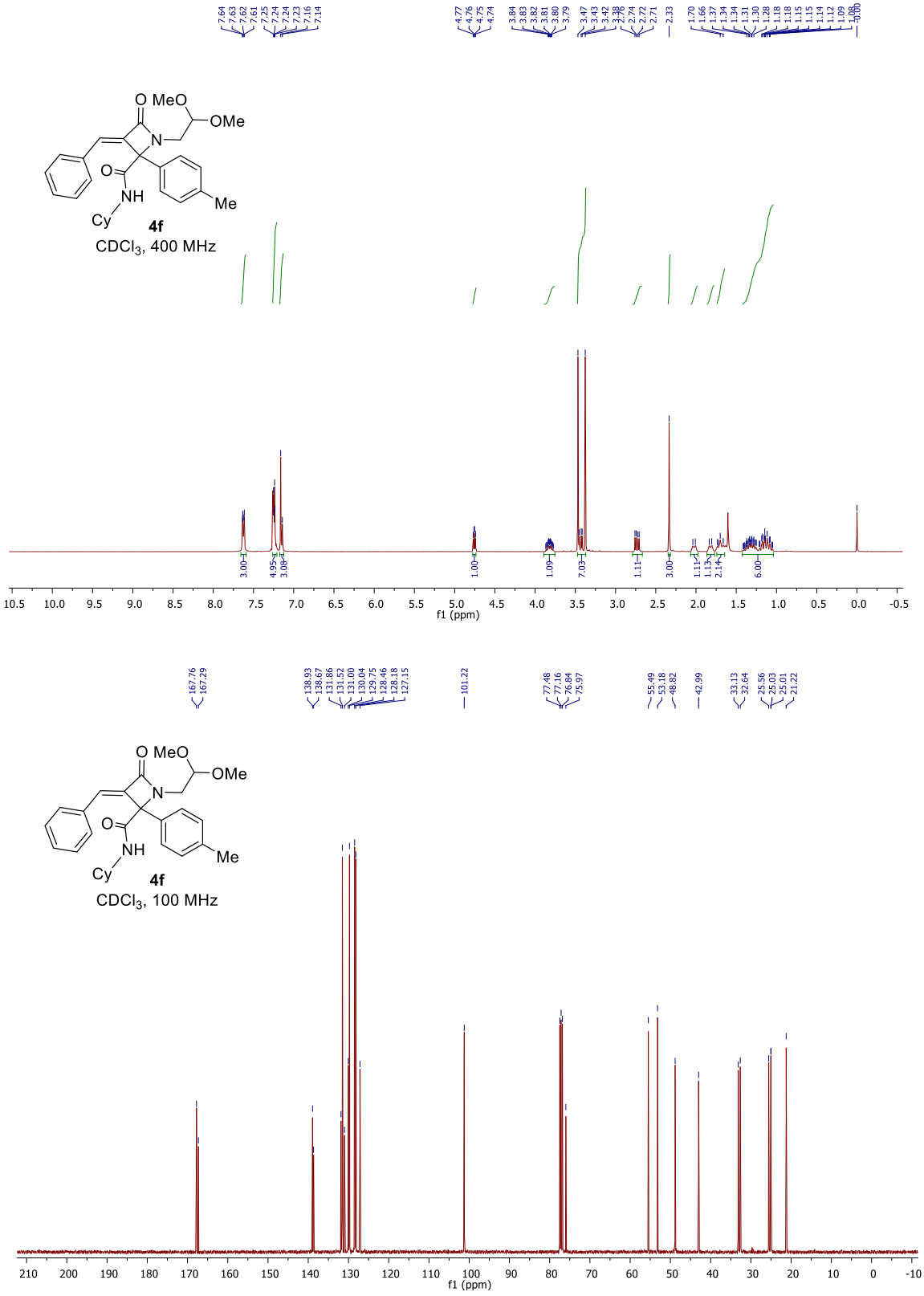


Figure S62: ^{1}H and ^{13}C NMR of compound **4g**

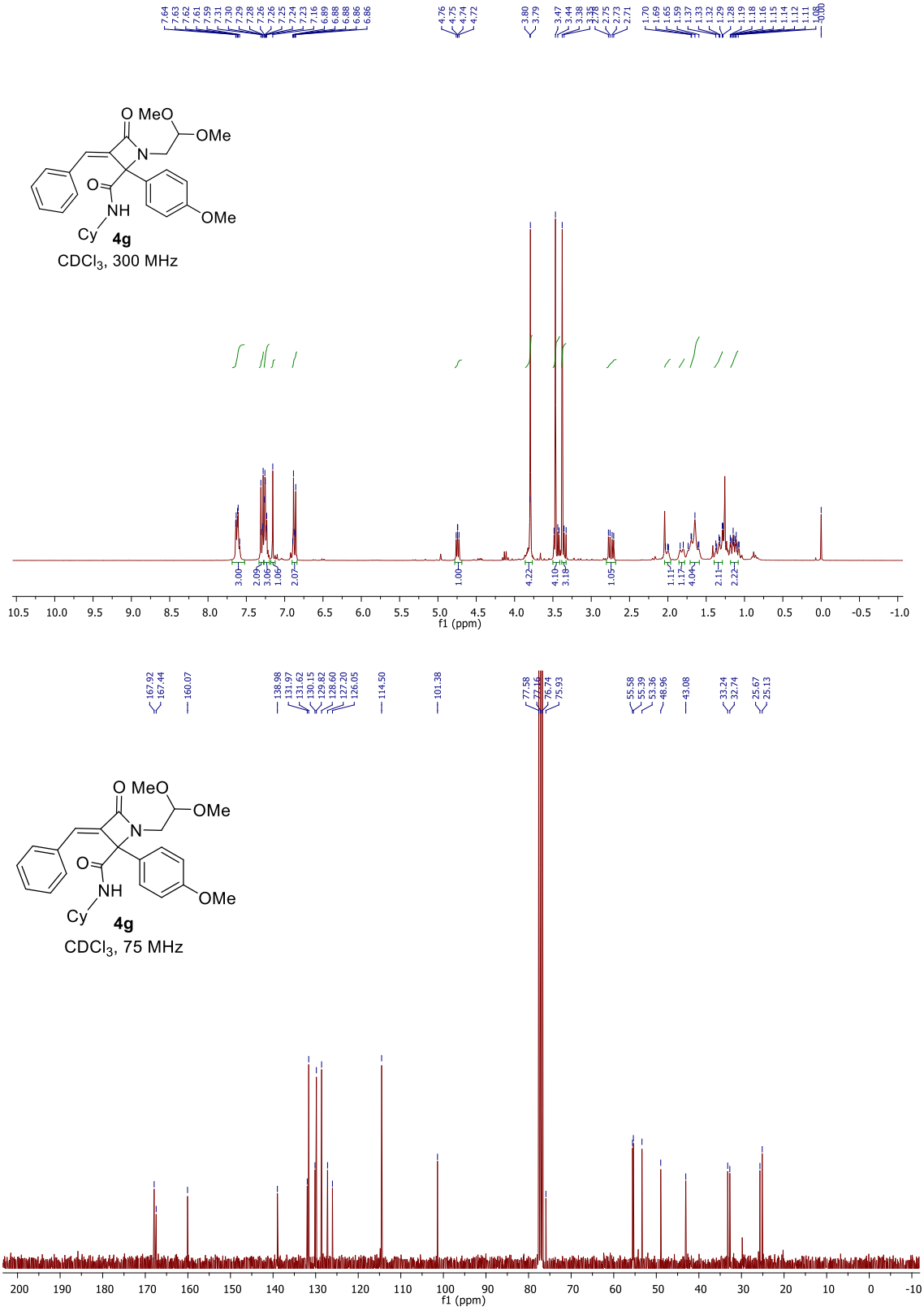


Figure S63: ^{1}H and ^{13}C NMR of compound **4h**

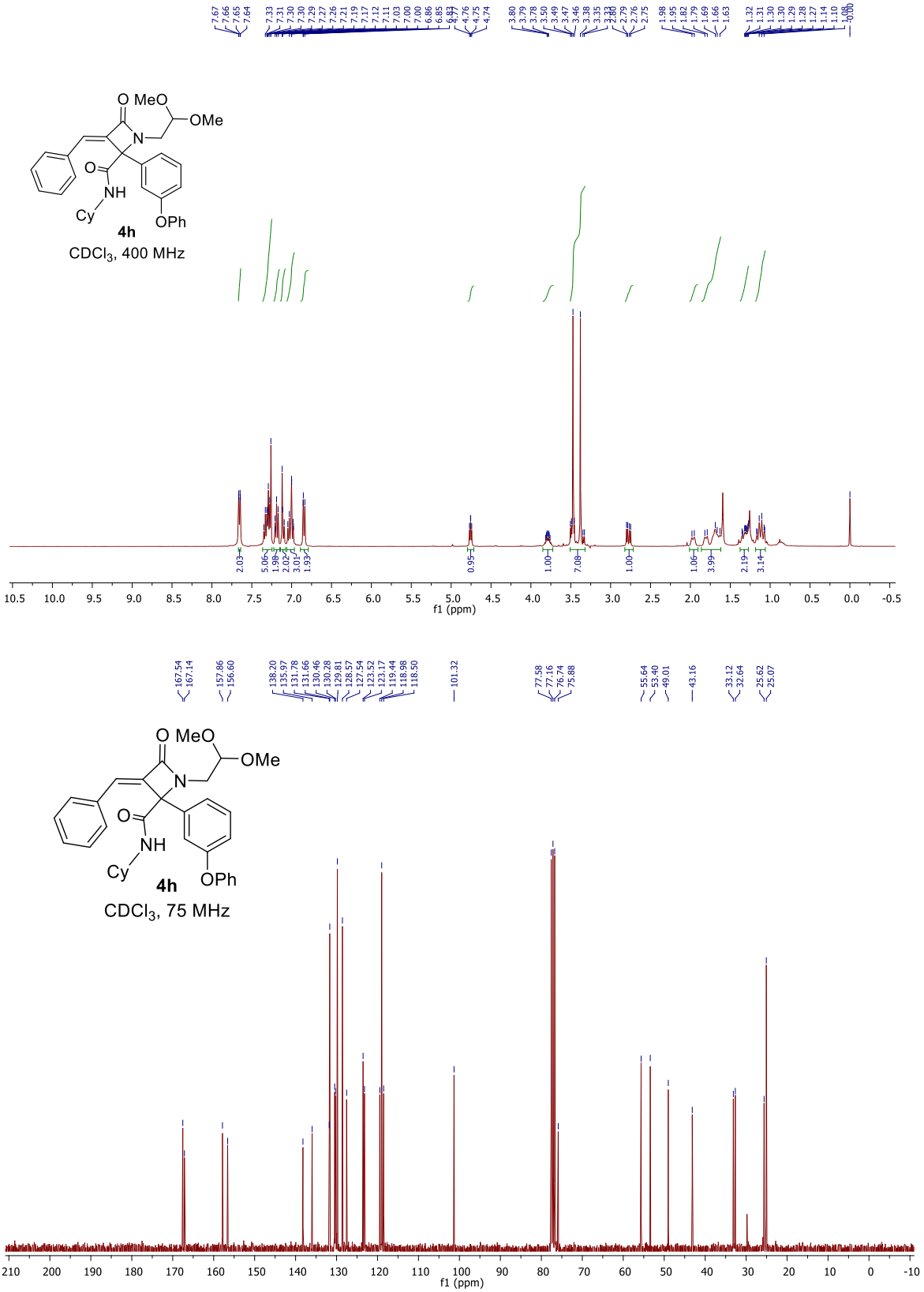
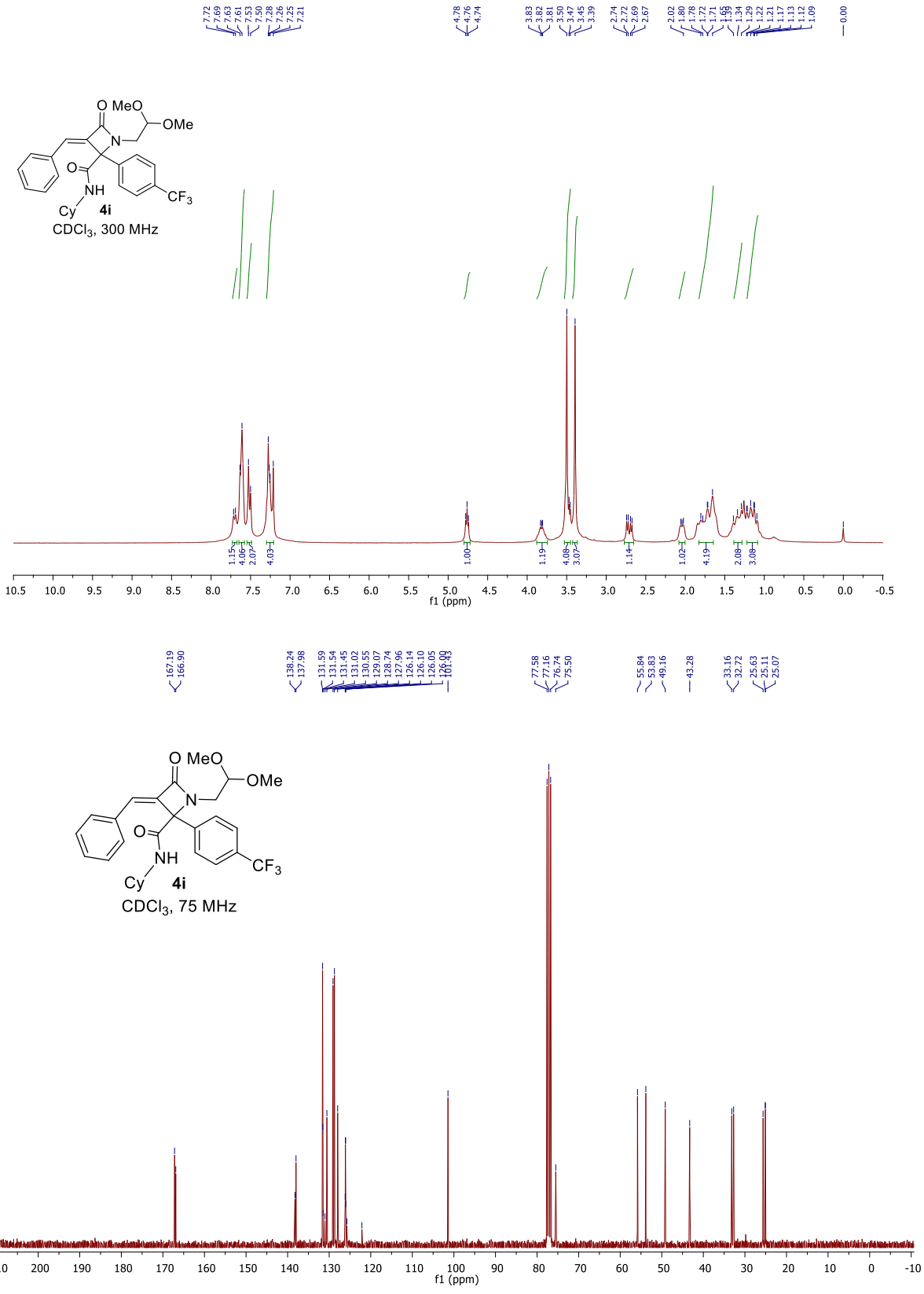
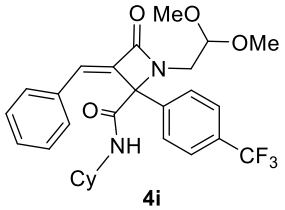


Figure S64: ^{1}H, ^{13}C and ^{19}F NMR of compound **4i**





4i

$CDCl_3$, 283 MHz

Figure S65: ^{1}H, ^{13}C and ^{19}F NMR of compound **4j**

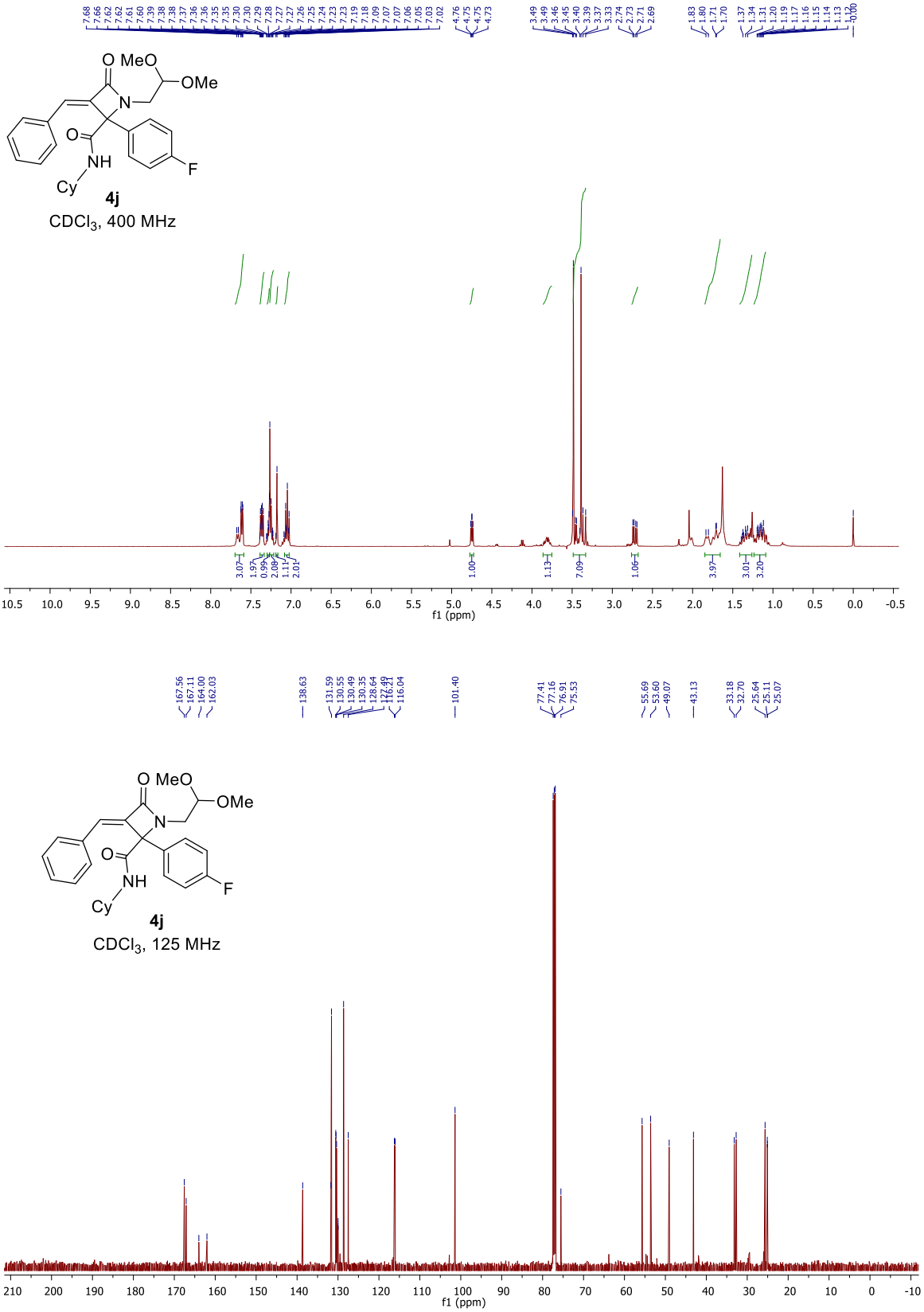


Figure S66: ^{1}H and ^{13}C NMR of compound **4k**

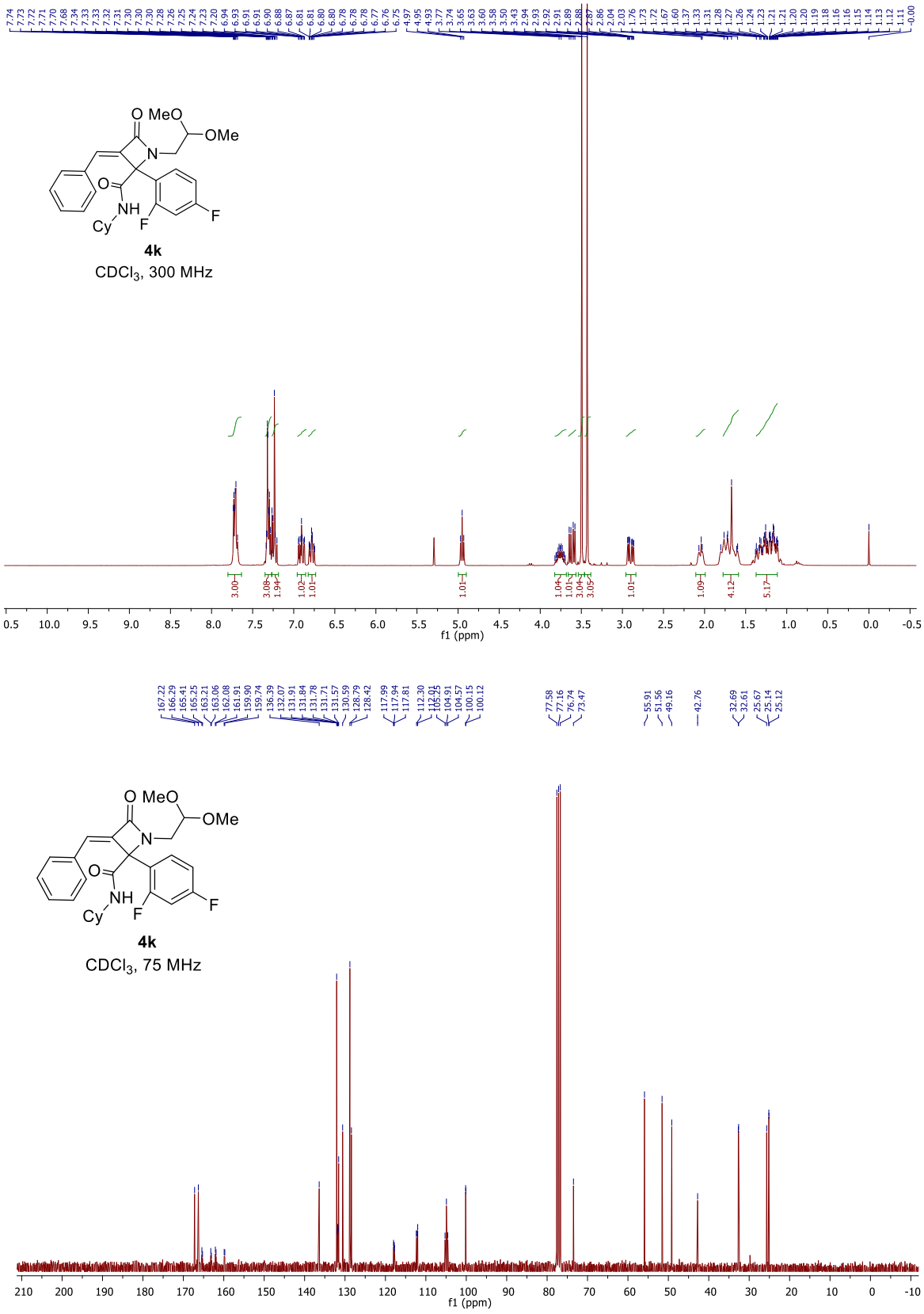
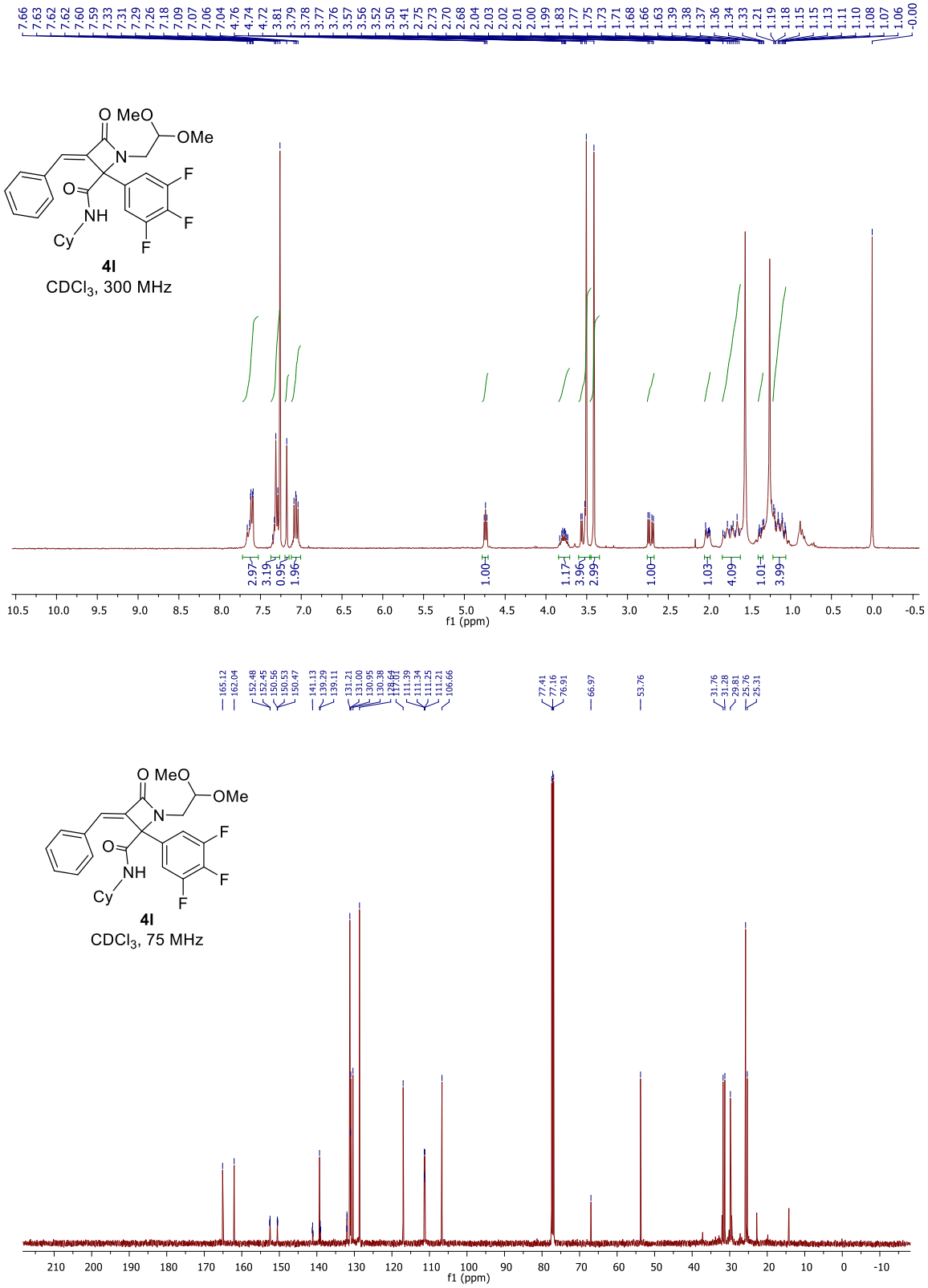
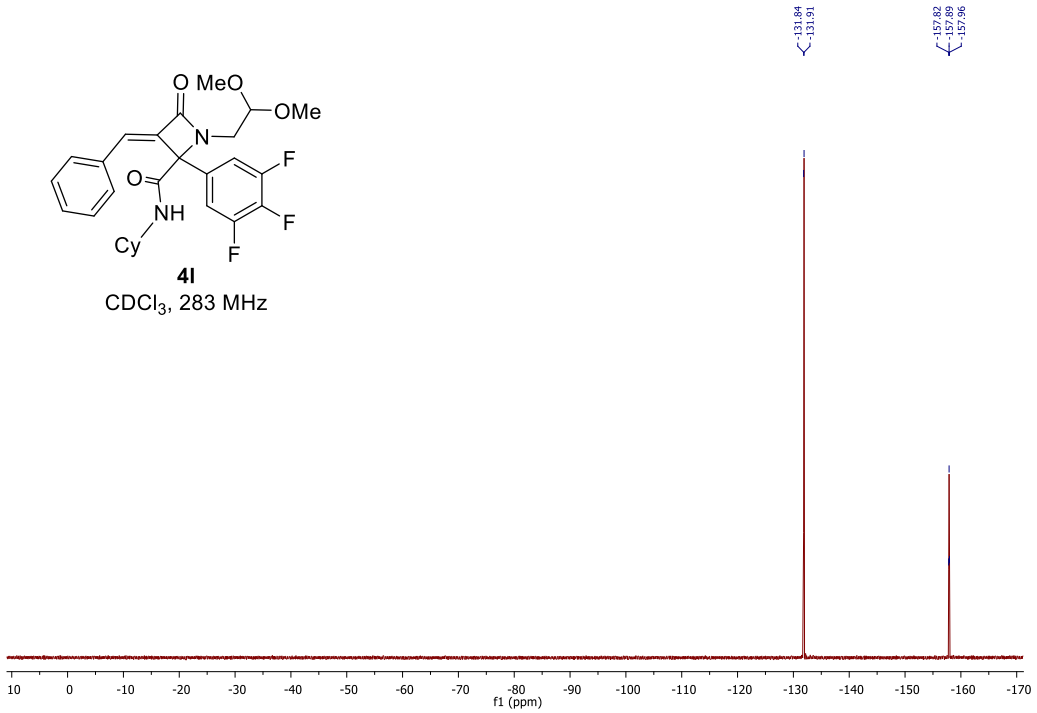


Figure S67: ^{1}H, ^{13}C and ^{19}F NMR of compound **4l**





4l

$CDCl_3$, 283 MHz

Figure S68: ^{1}H and ^{13}C NMR of compound **4m**

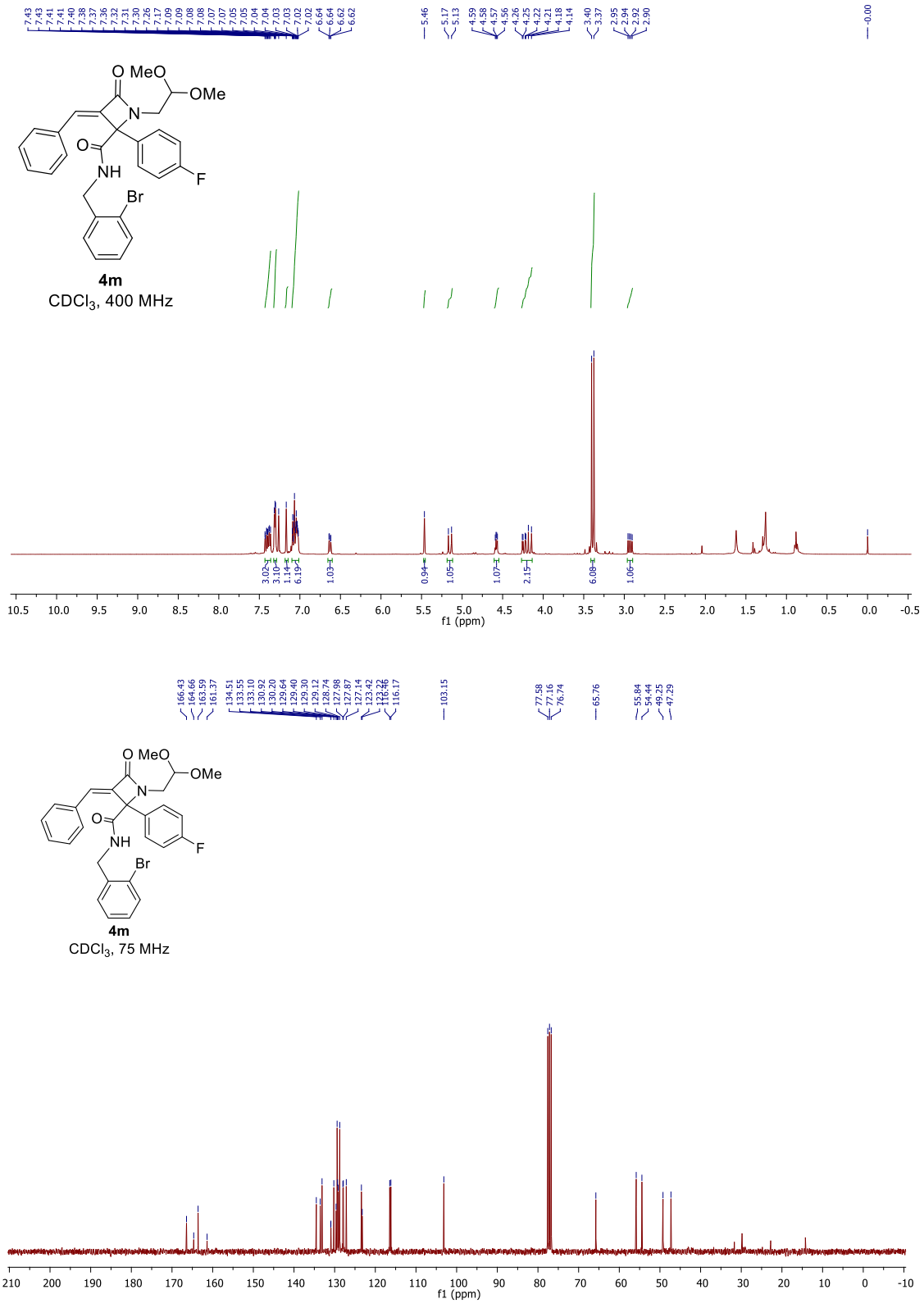


Figure S69: ^{1}H and ^{13}C NMR of compound **4n**

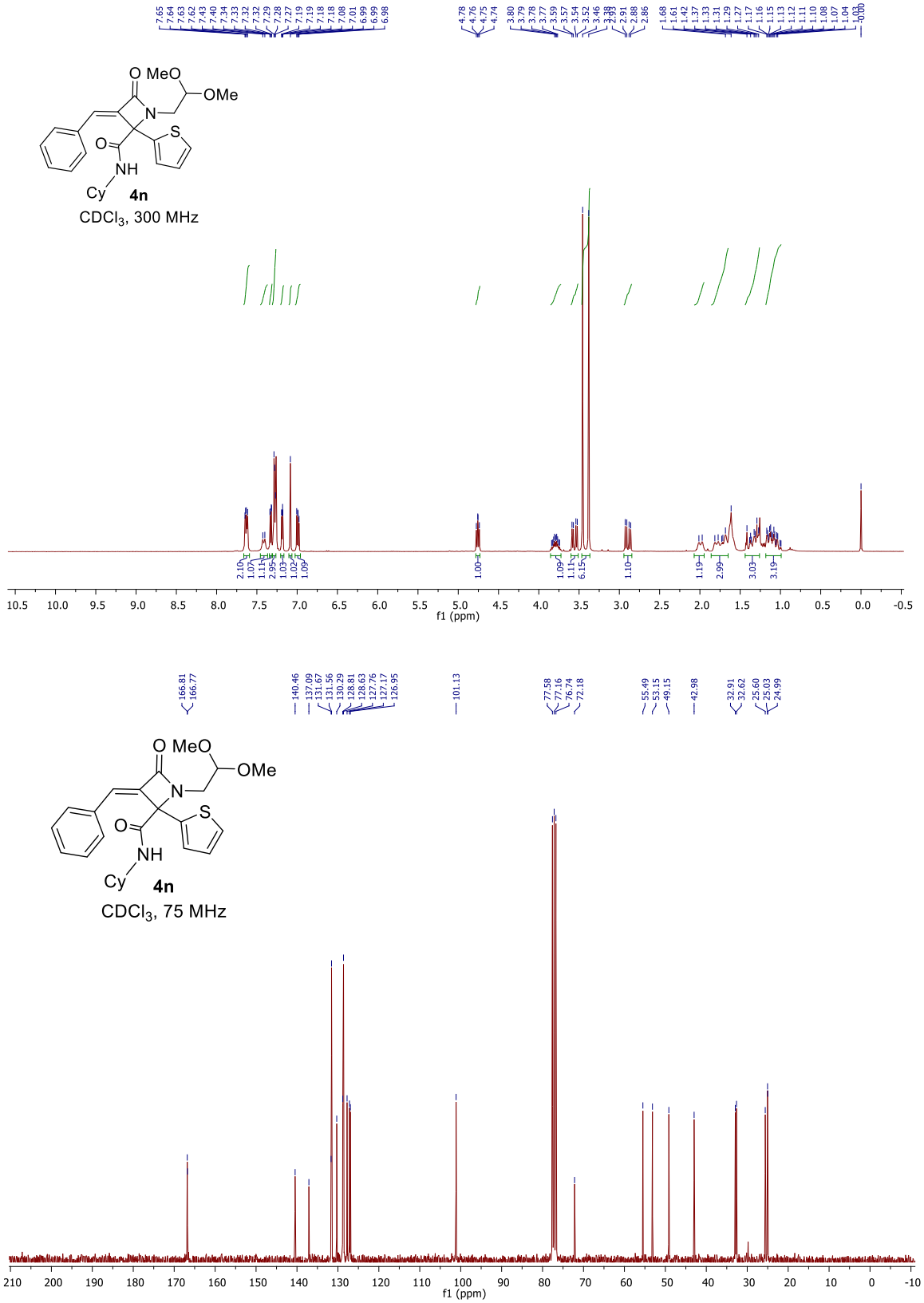


Figure S70: ^{1}H and ^{13}C NMR of compound **4o**(rotamer 1:0.8)

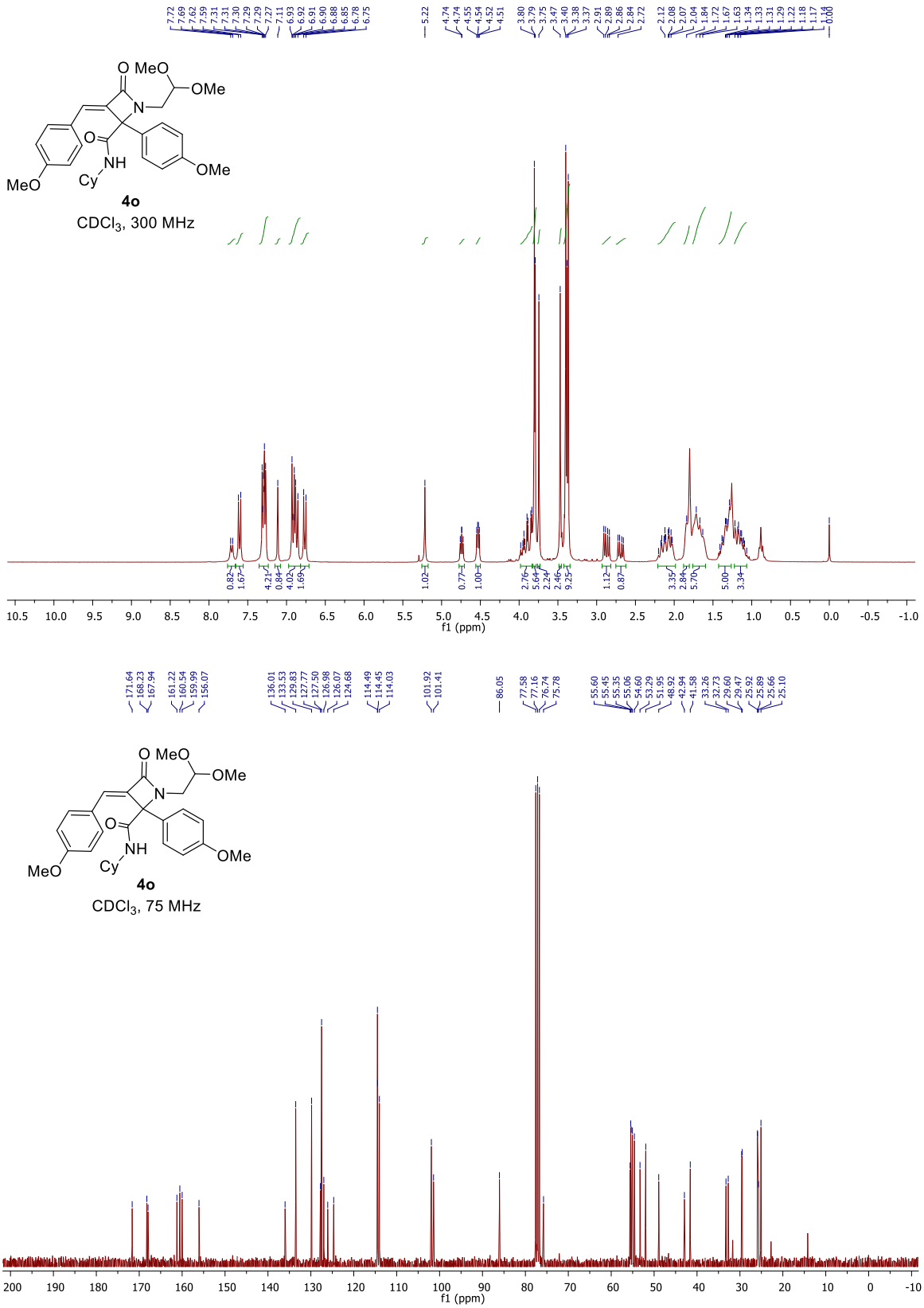


Figure S71: ^{1}H and ^{13}C NMR of compound **4p**

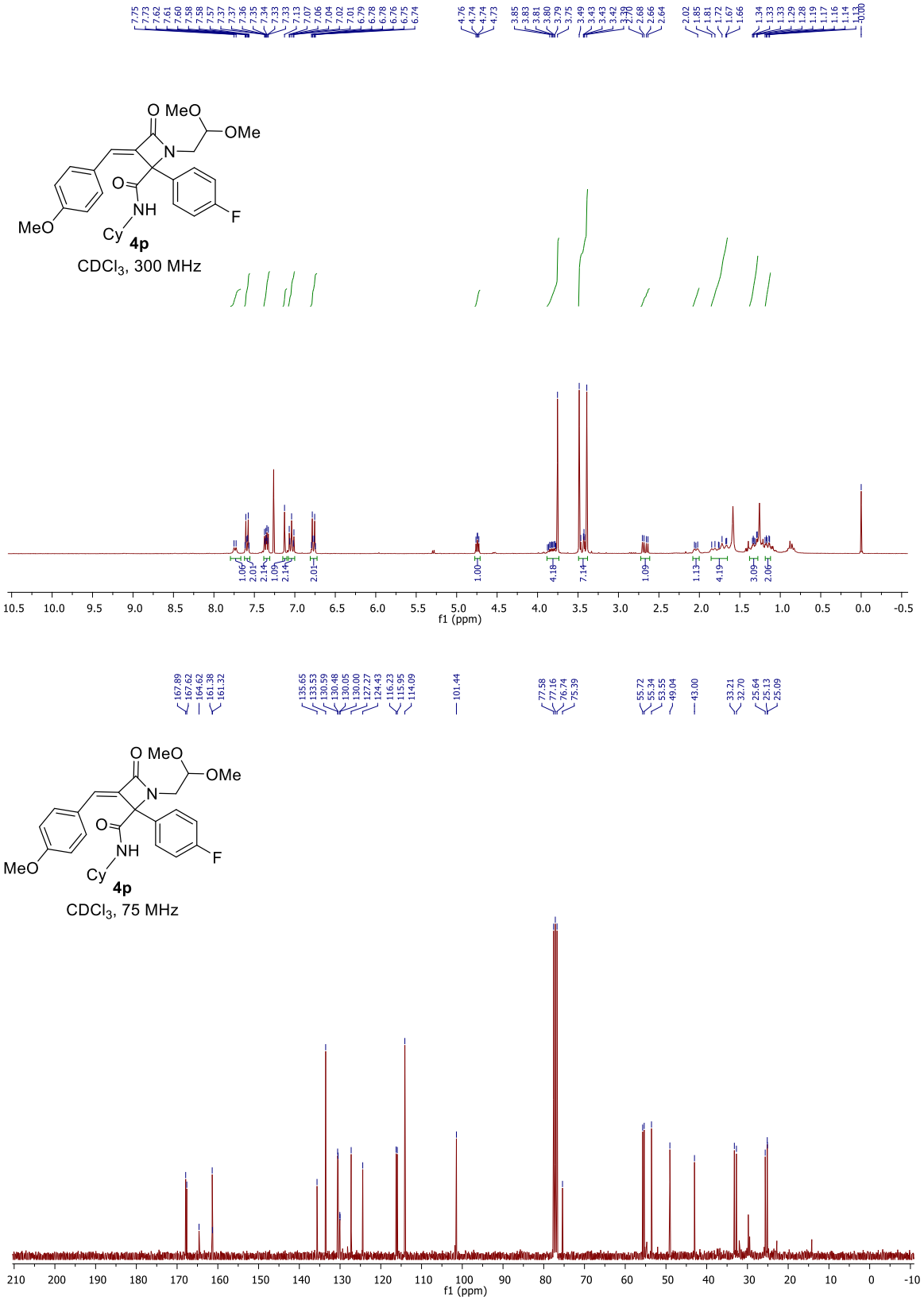


Figure S72: ^{1}H and ^{13}C NMR of compound **4q**

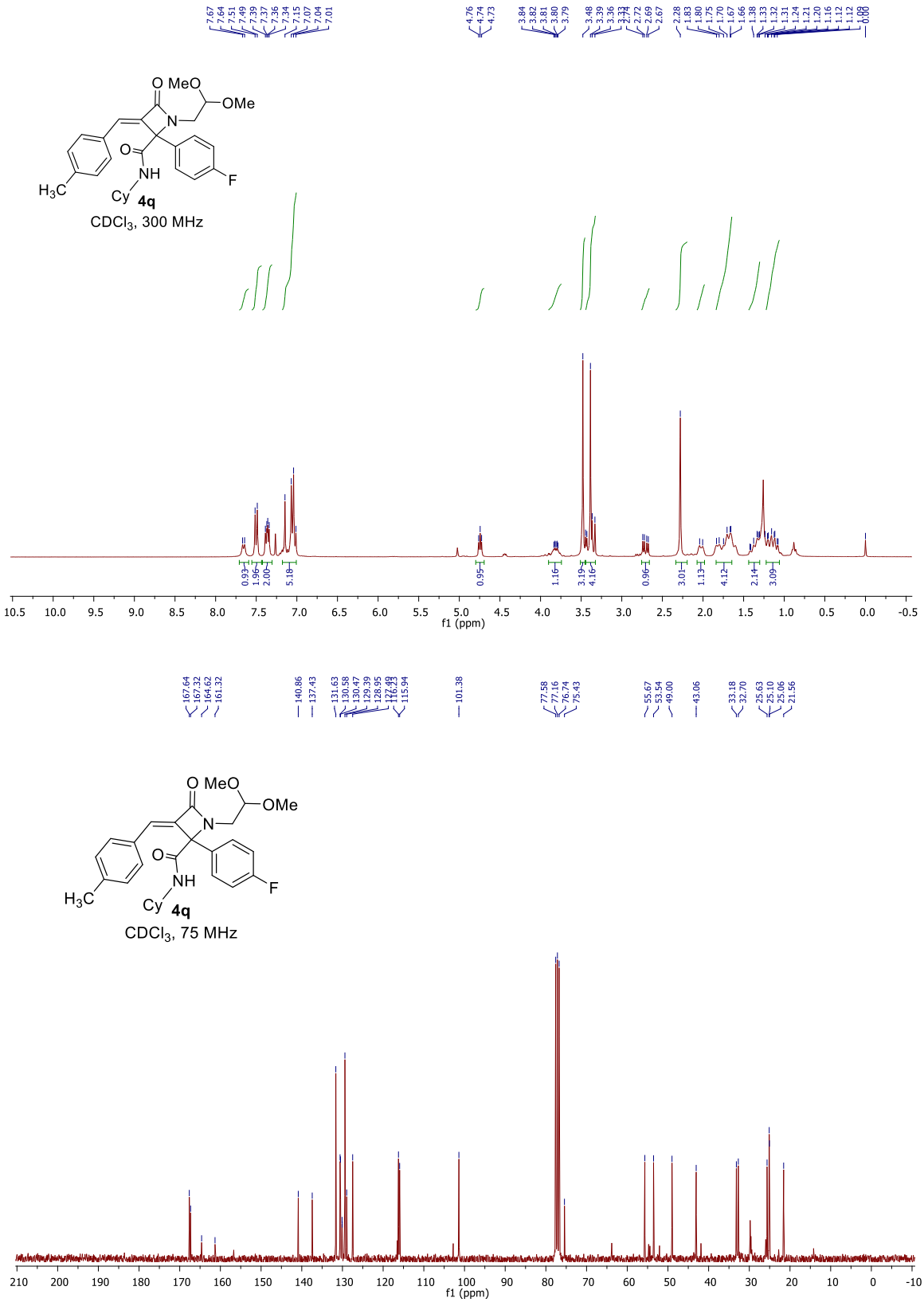
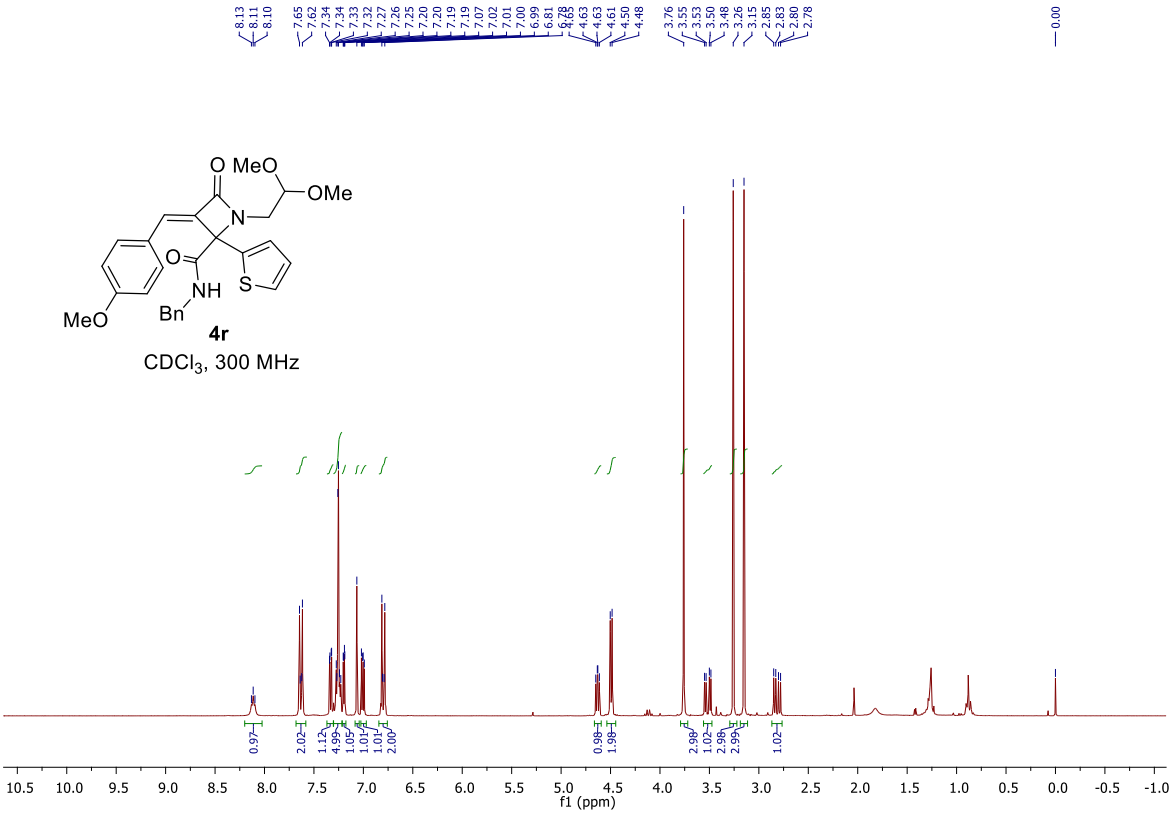


Figure S73: ^{1}H and ^{13}C NMR of compound **4r**



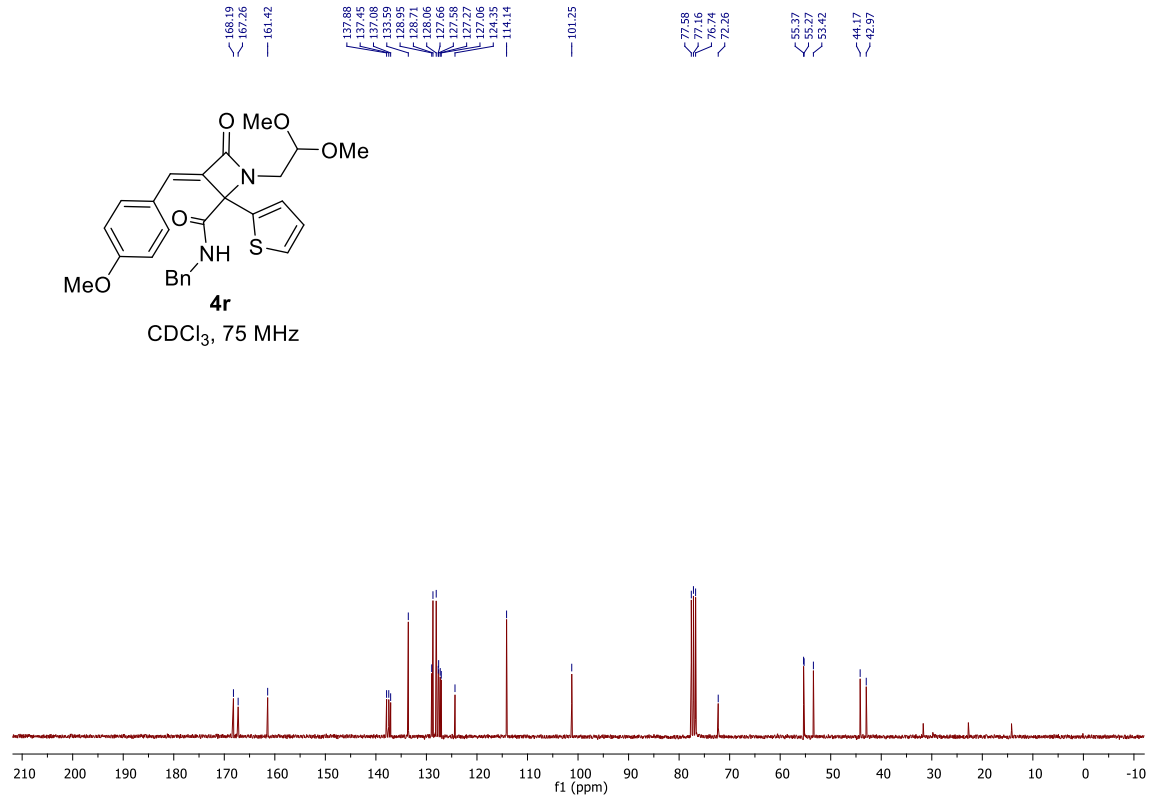


Figure S74: ^{1}H and ^{13}C NMR of compound **4s**

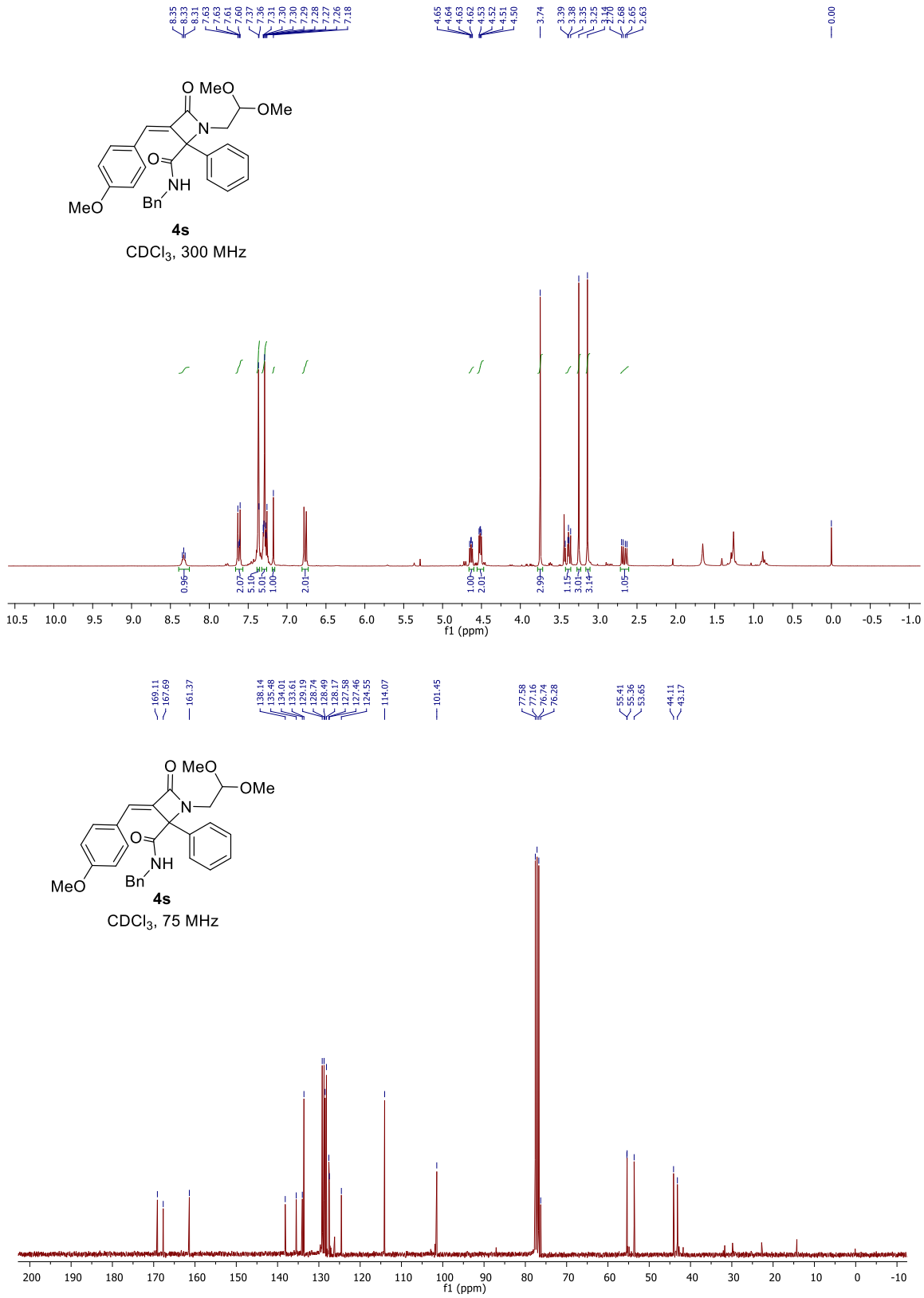


Figure S75: ^{1}H and ^{13}C NMR of compound **4t'**

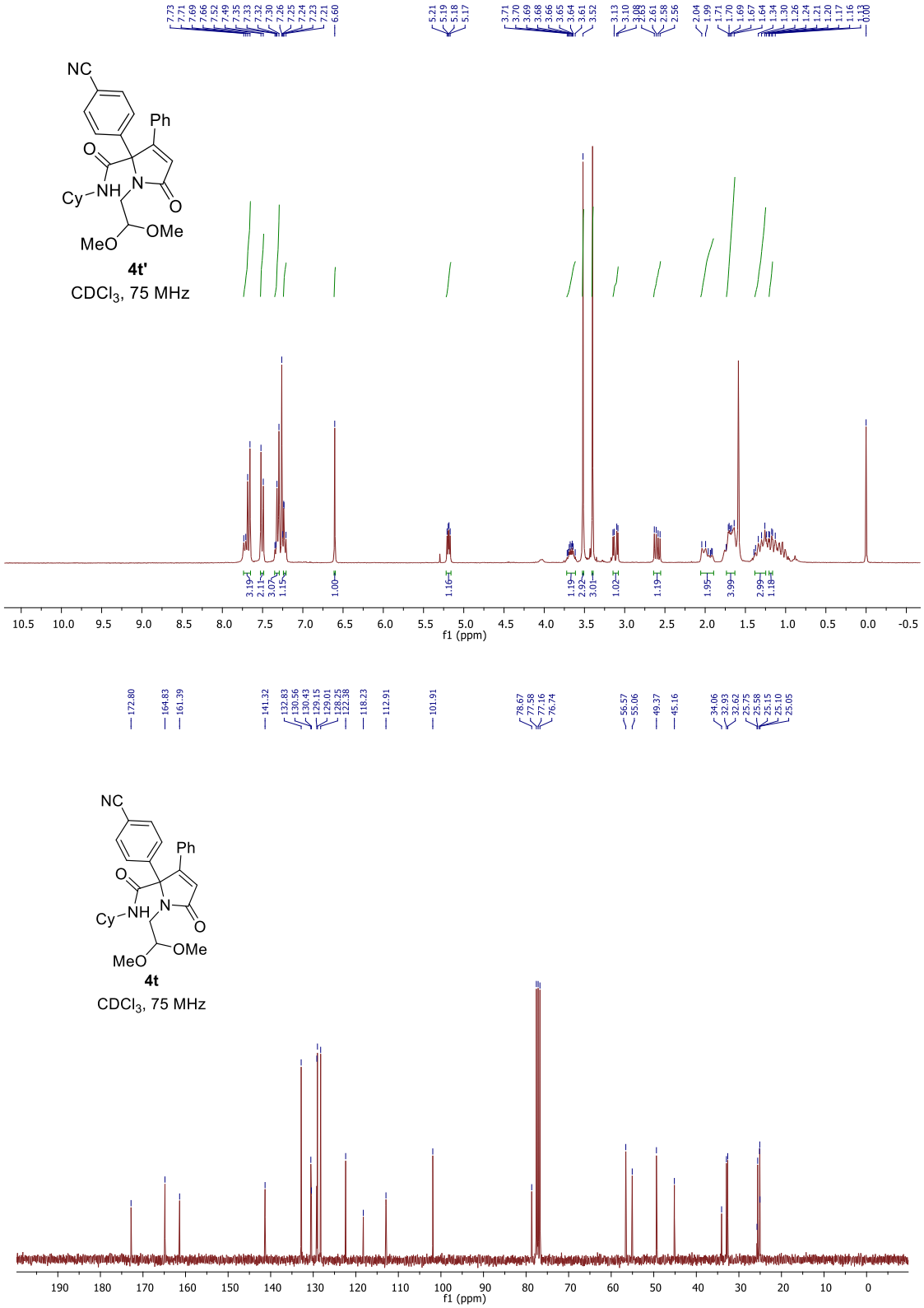


Figure S76: ^{1}H and ^{13}C NMR of compound **4u'**

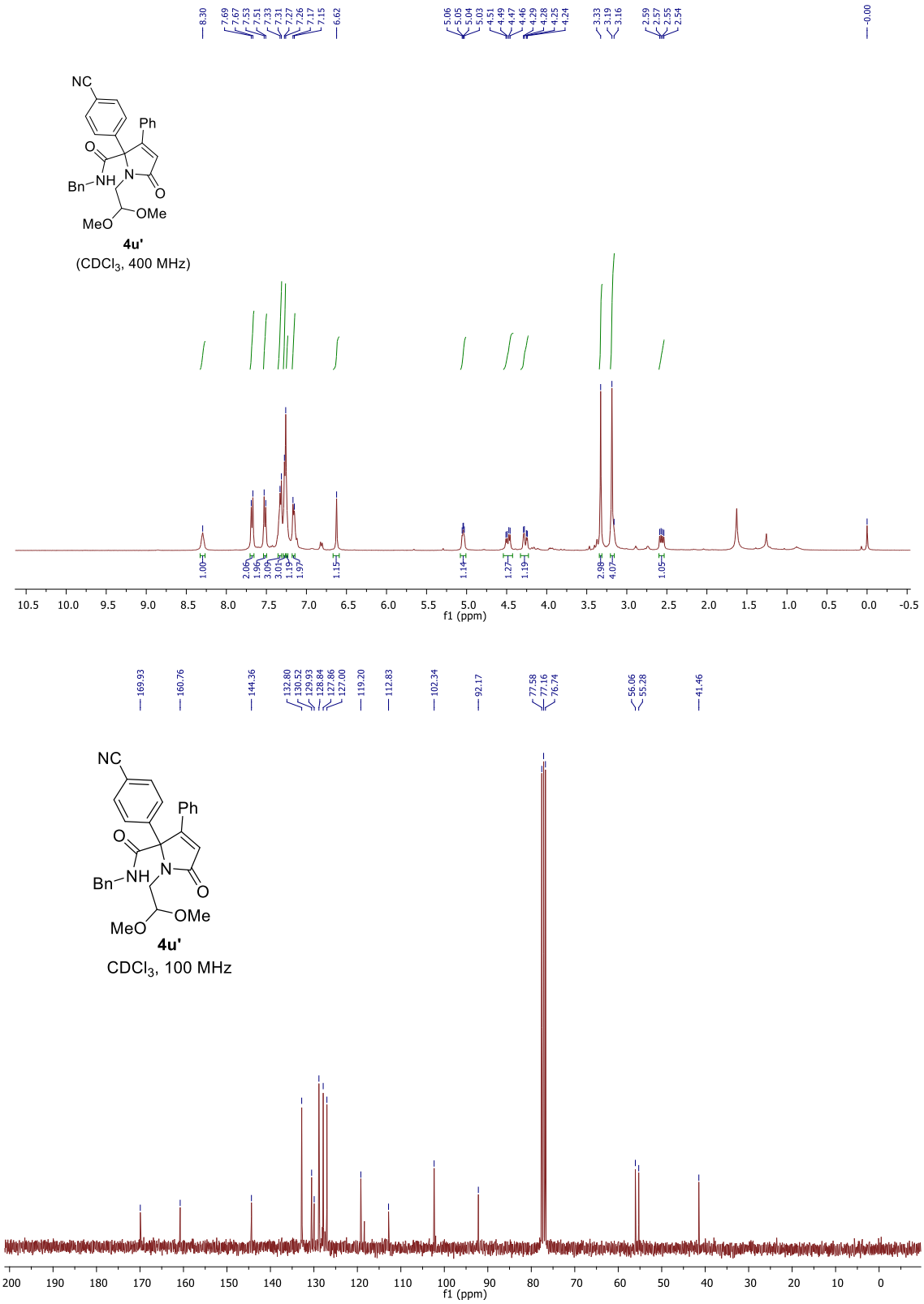


Figure S77: ^{1}H and ^{13}C NMR of compound **4v'**

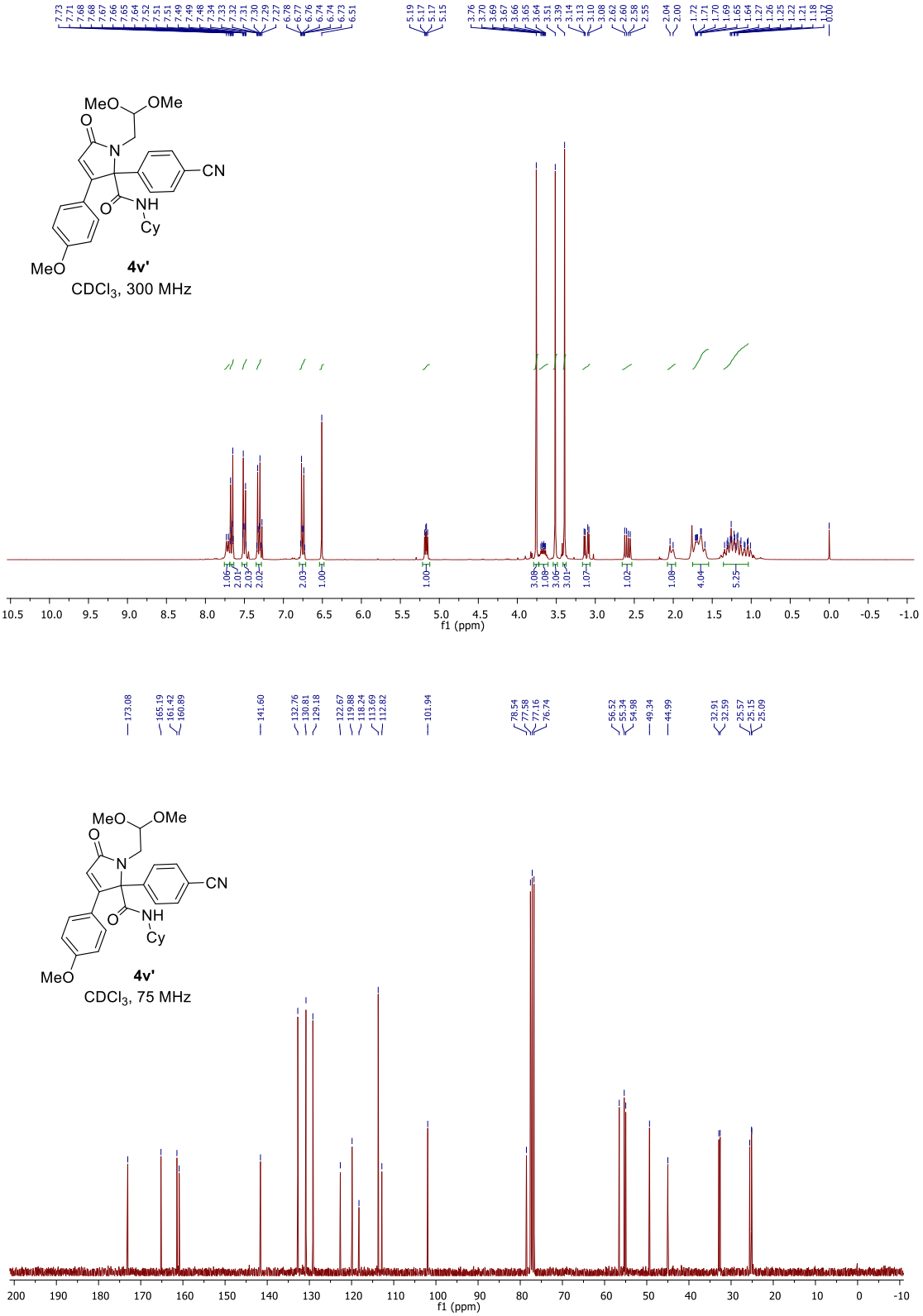


Figure S78: ^{1}H and ^{13}C NMR of compound **4y**

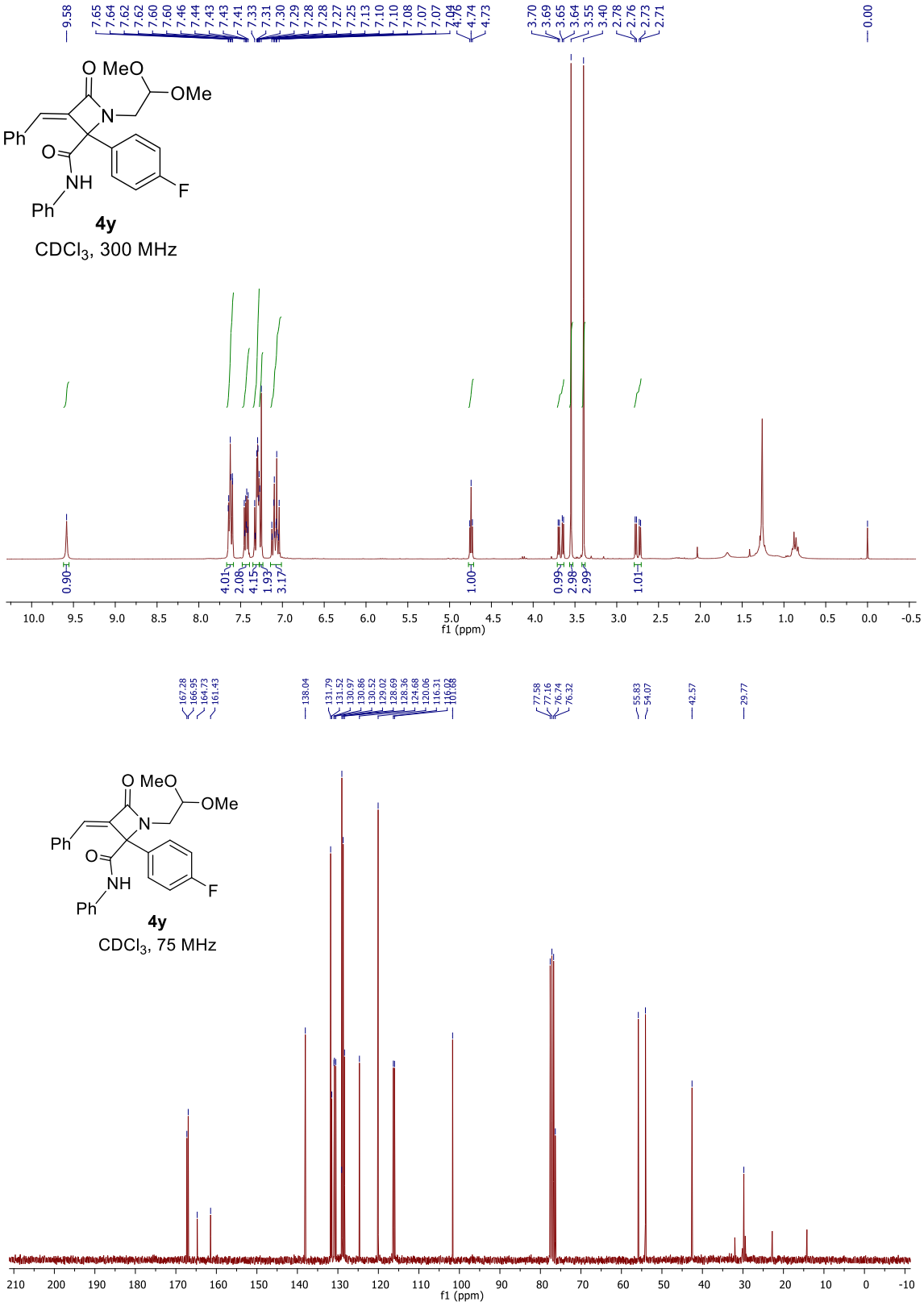


Figure S79: ^{1}H and ^{13}C NMR of compound **4z**

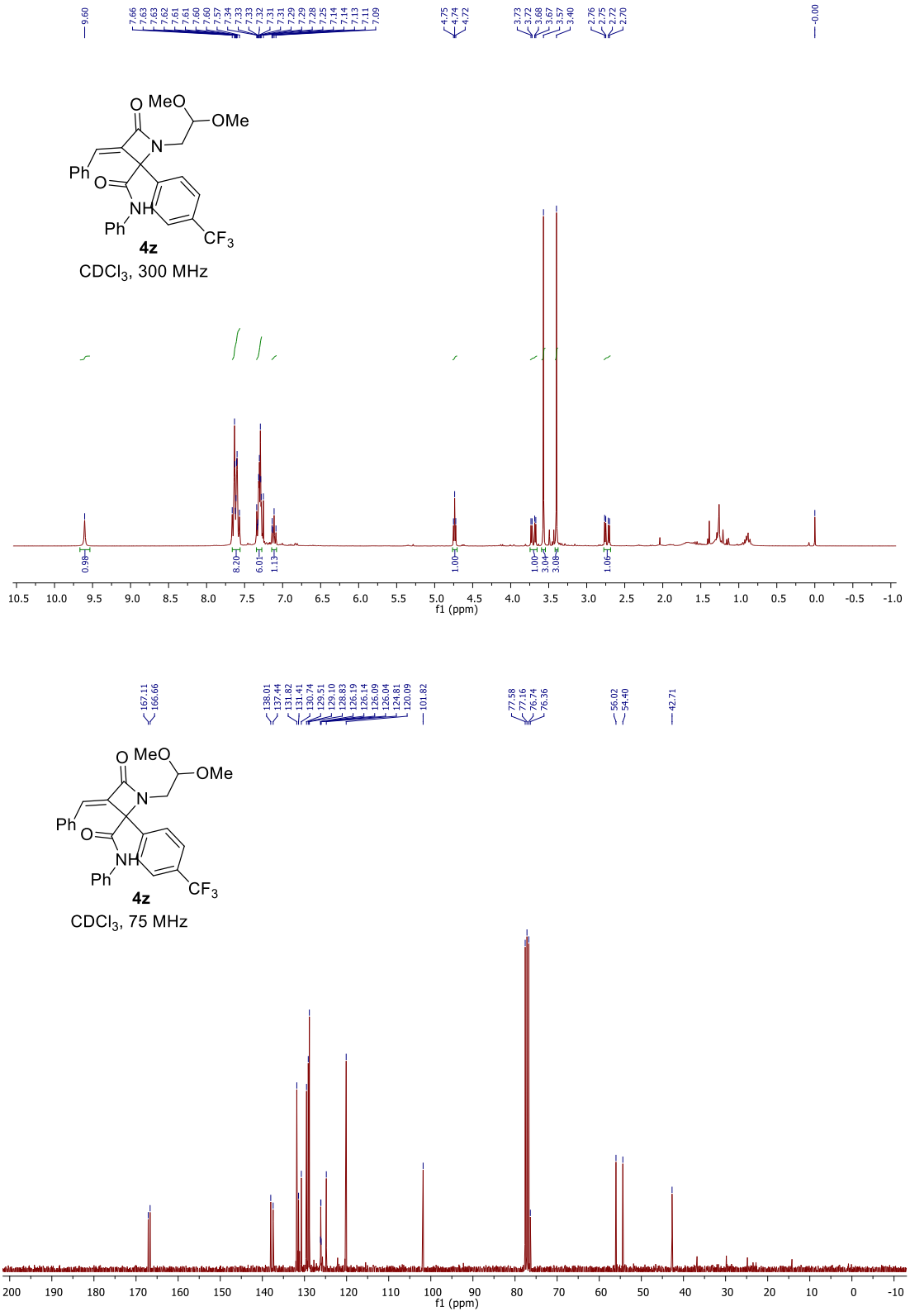


Figure S80: ^{1}H and ^{13}C NMR of compound **4aa**

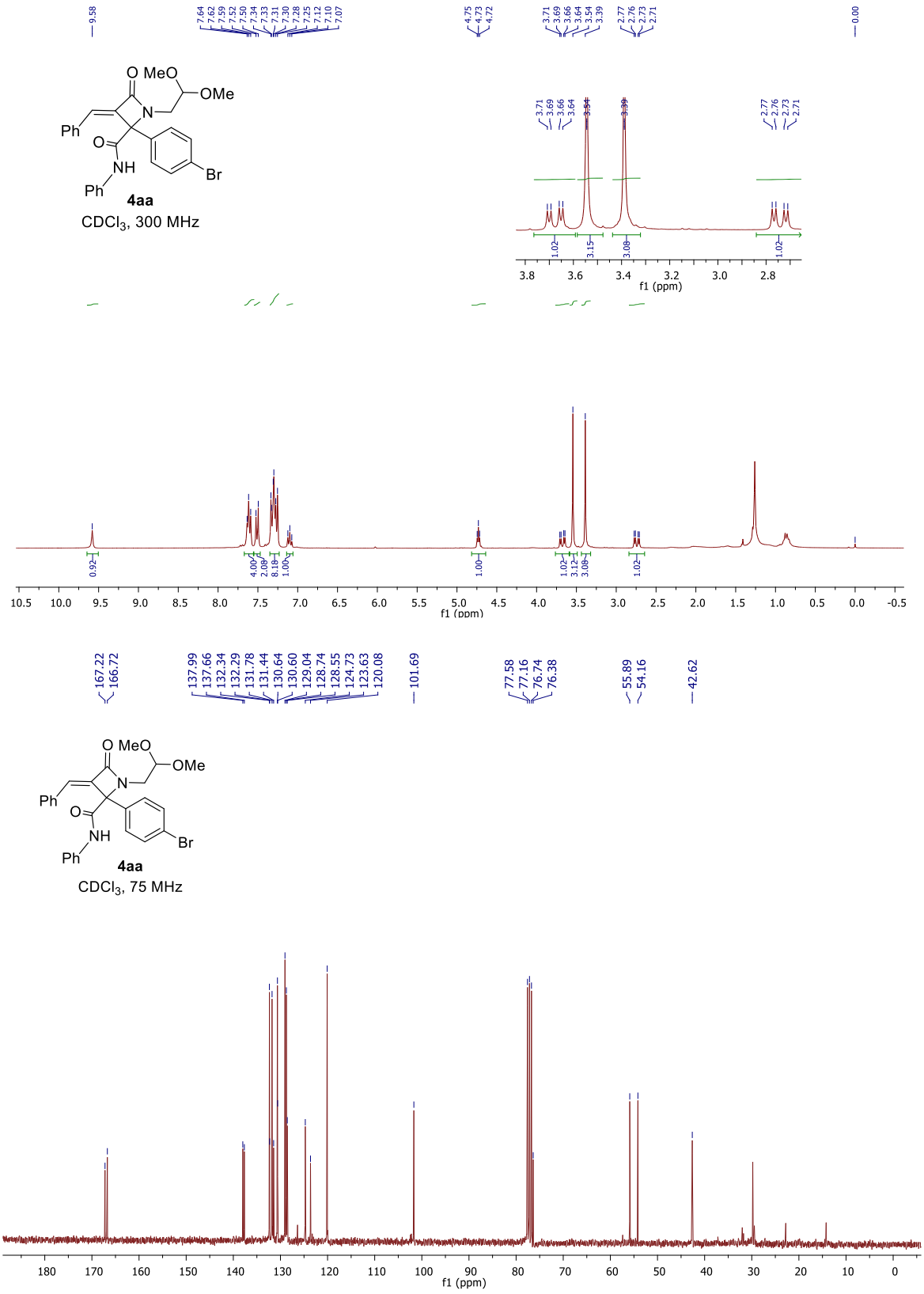


Figure S81: ^{1}H and ^{13}C NMR of compound **4ab**

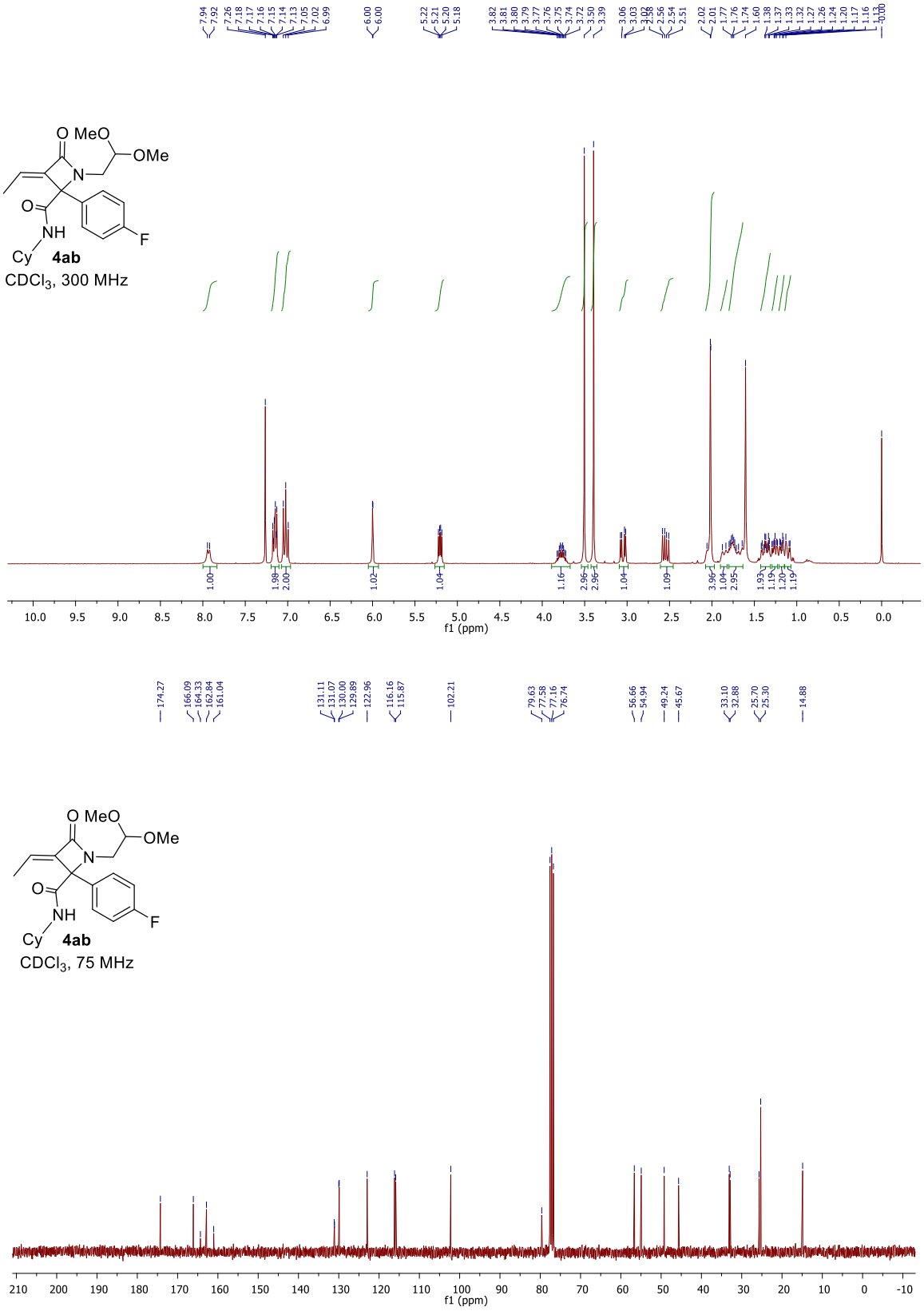


Figure S82: ^{1}H and ^{13}C NMR of compound **5a**

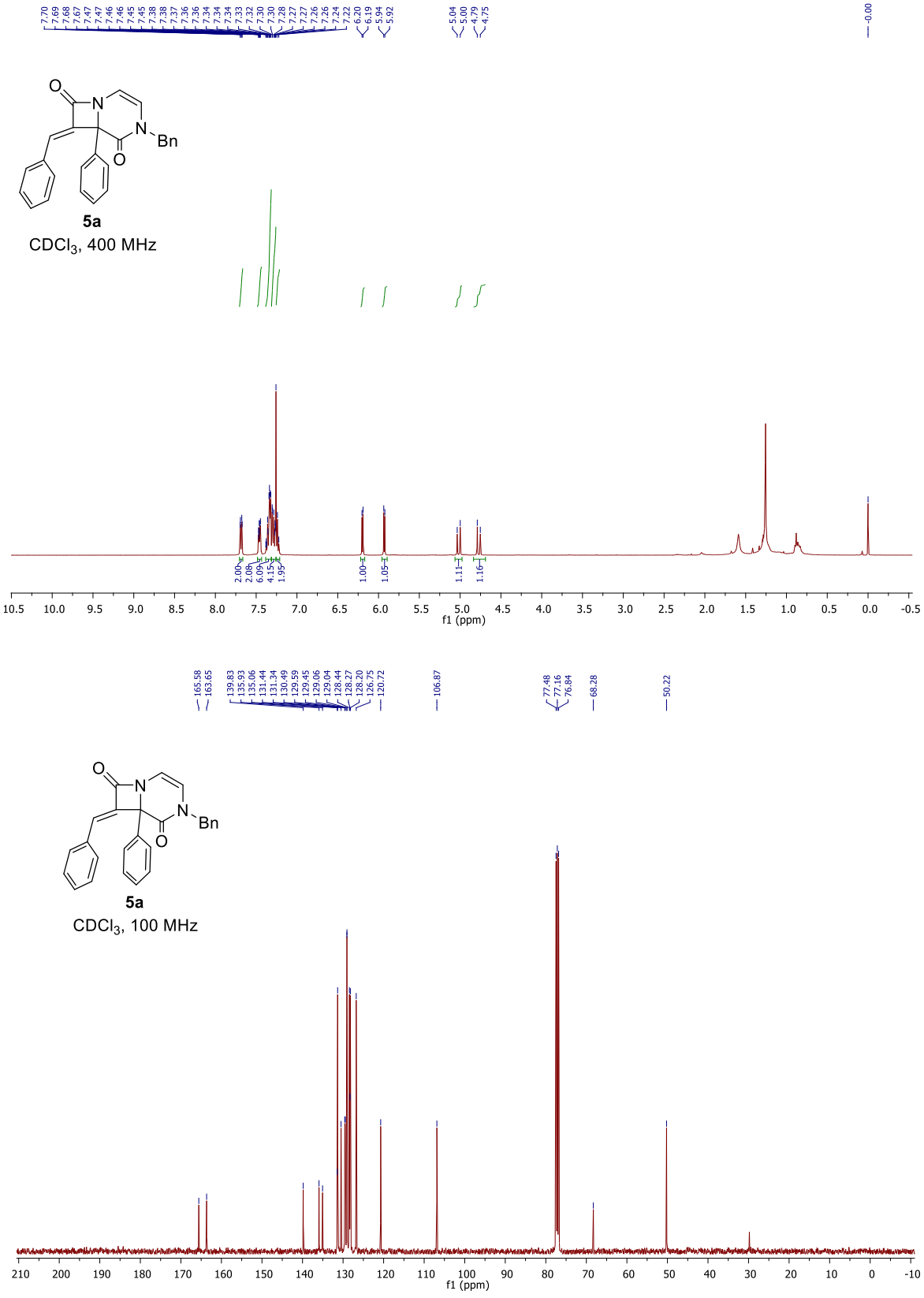
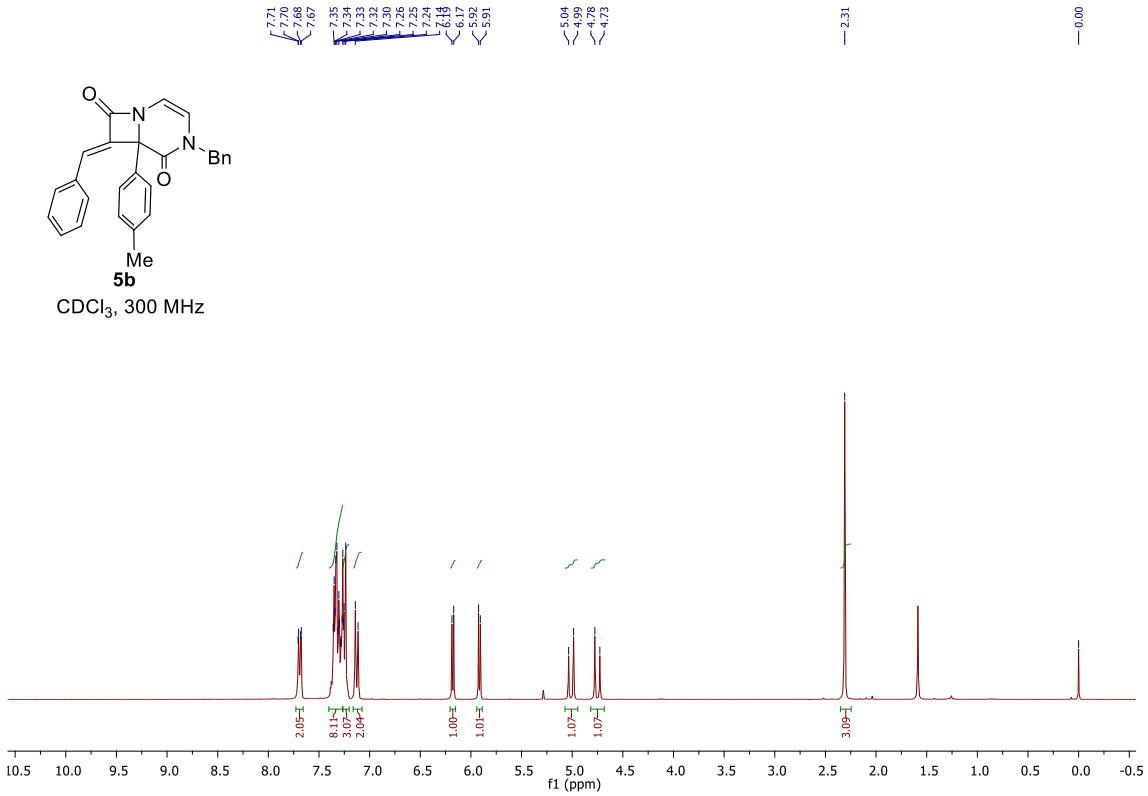


Figure S83: ^{1}H and ^{13}C NMR of compound **5b**



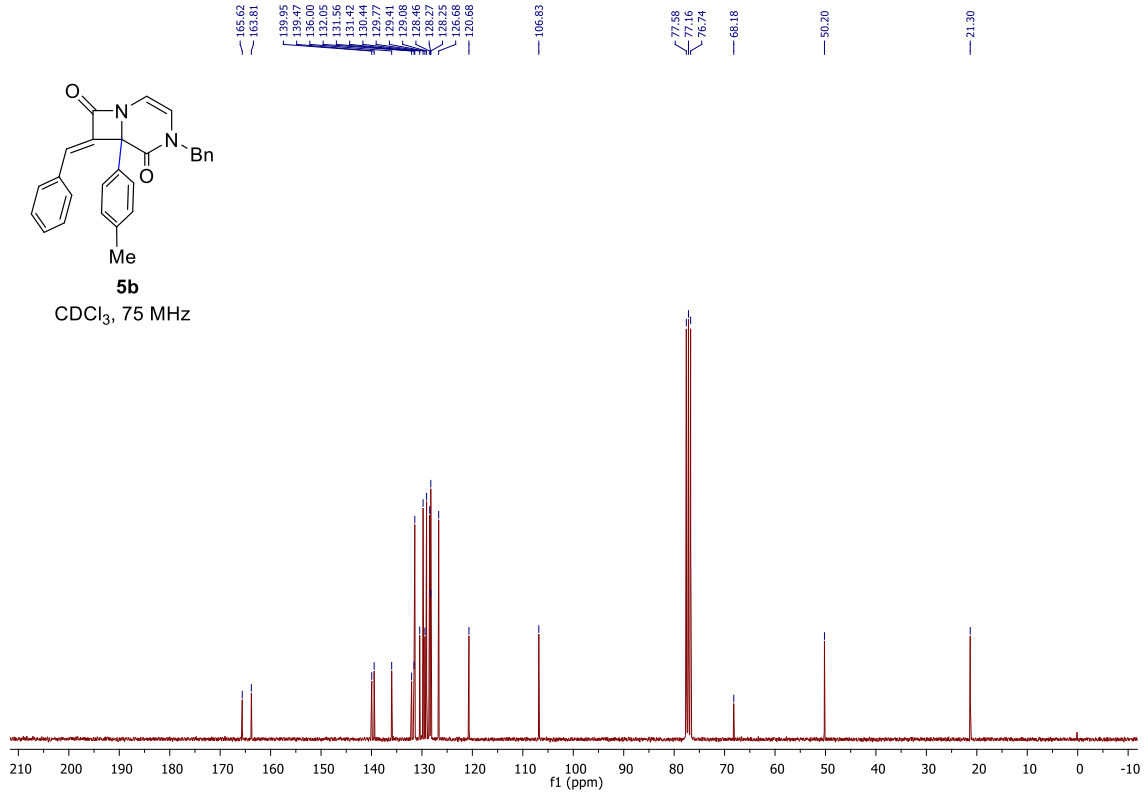


Figure S84: ^{1}H and ^{13}C NMR of compound **5c**

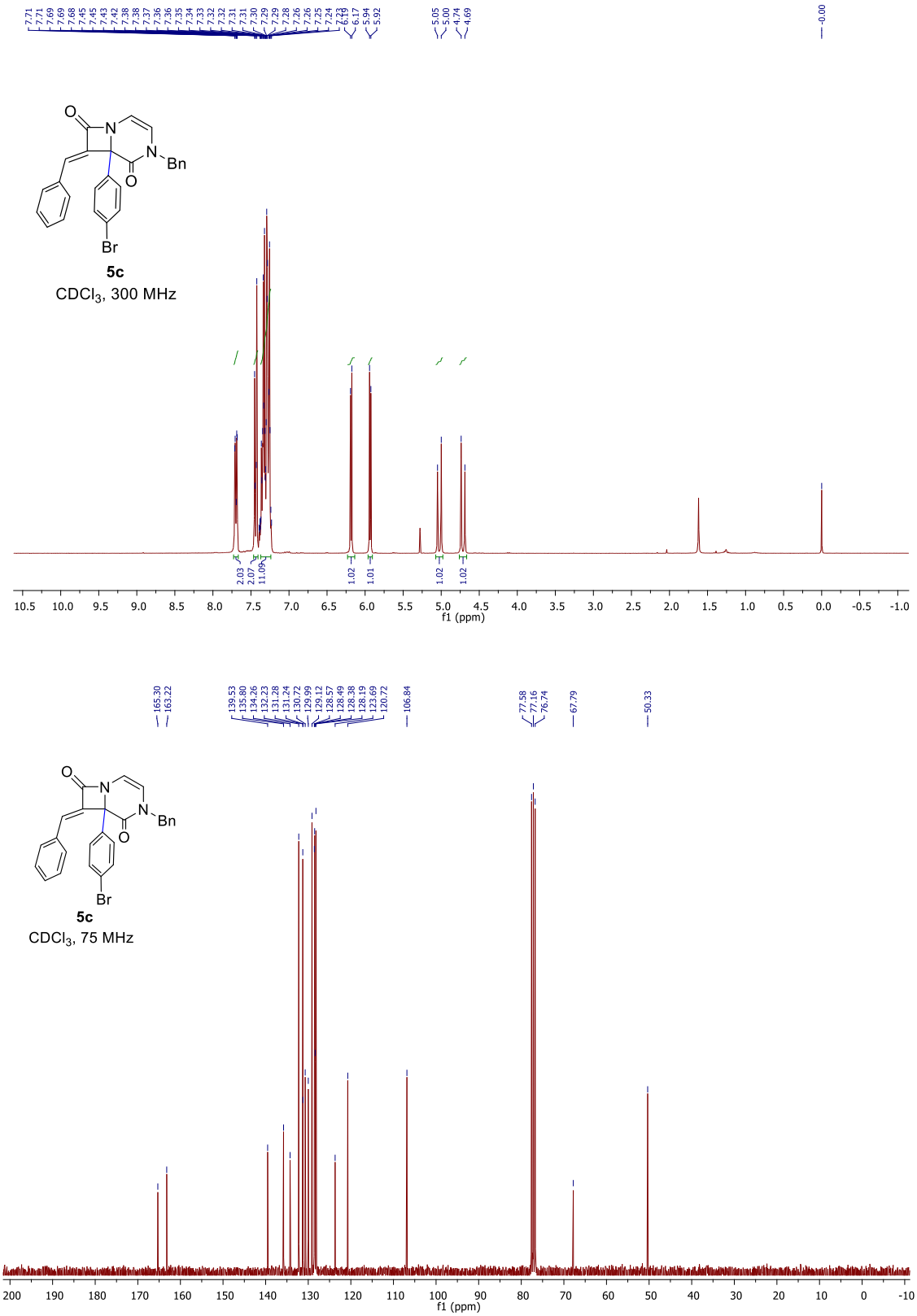


Figure S85: ^{1}H and ^{13}C NMR of compound **5d**

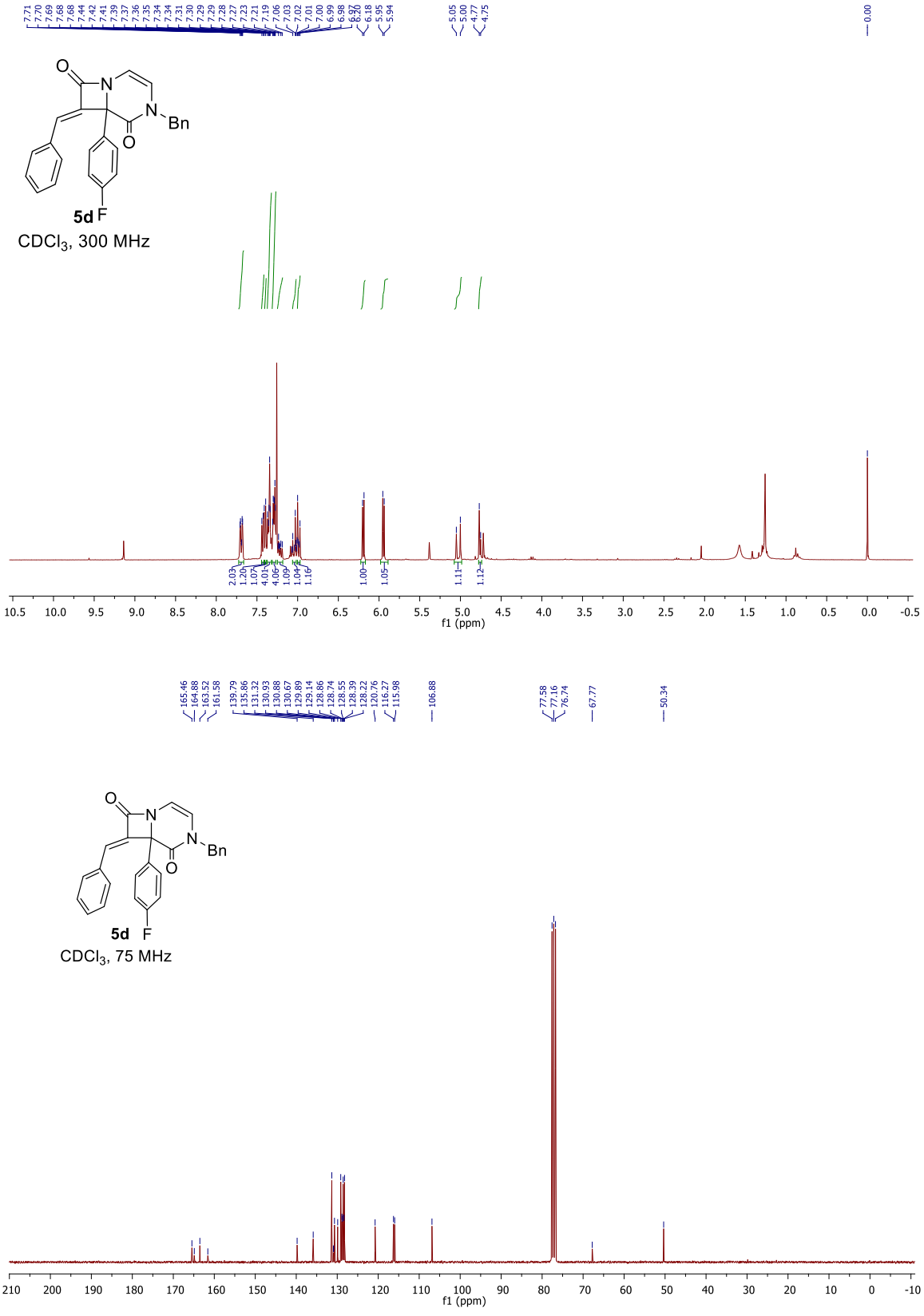


Figure S86: ^{1}H and ^{13}C NMR of compound **5e**

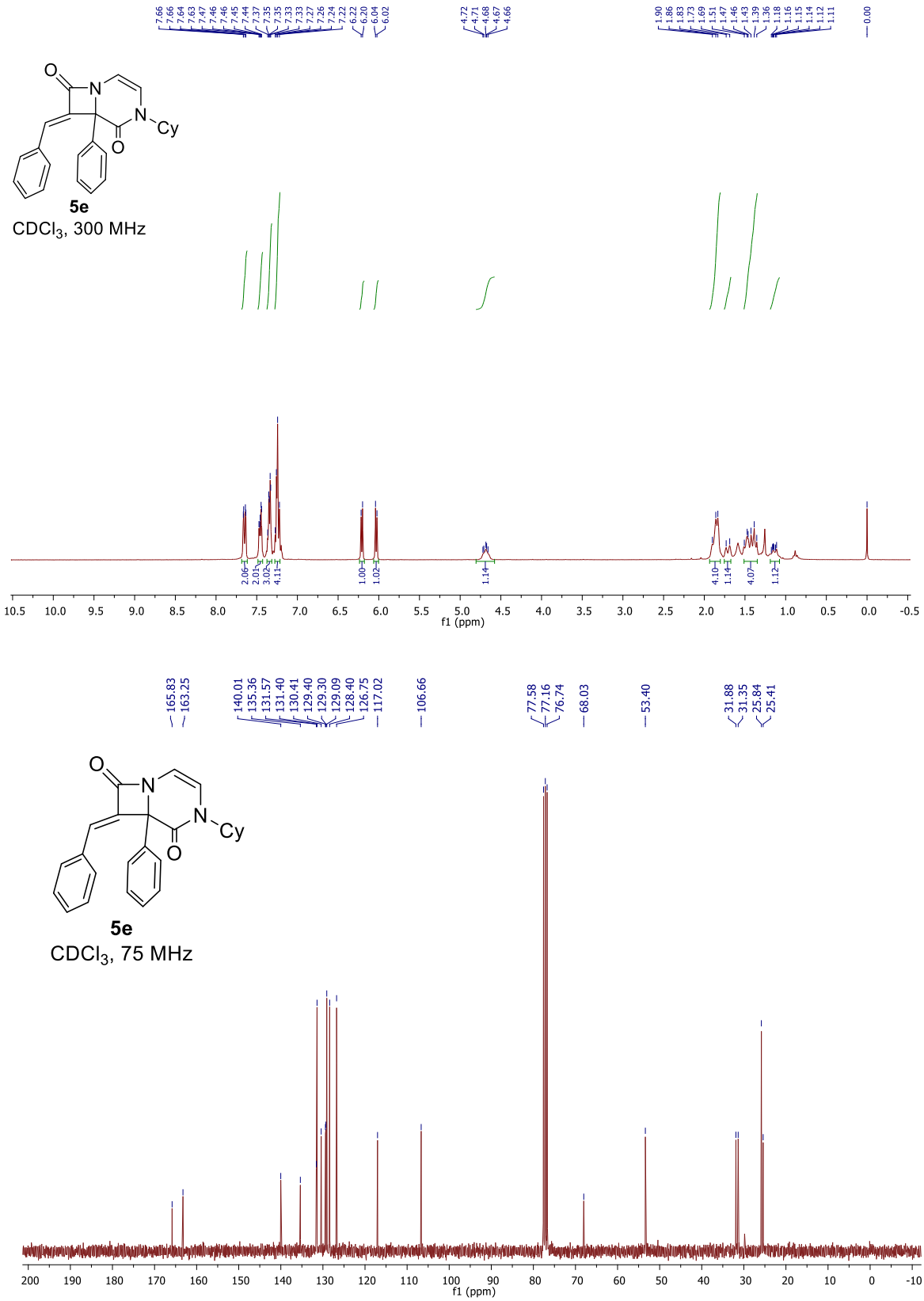


Figure S87: ^{1}H and ^{13}C NMR of compound **5f**

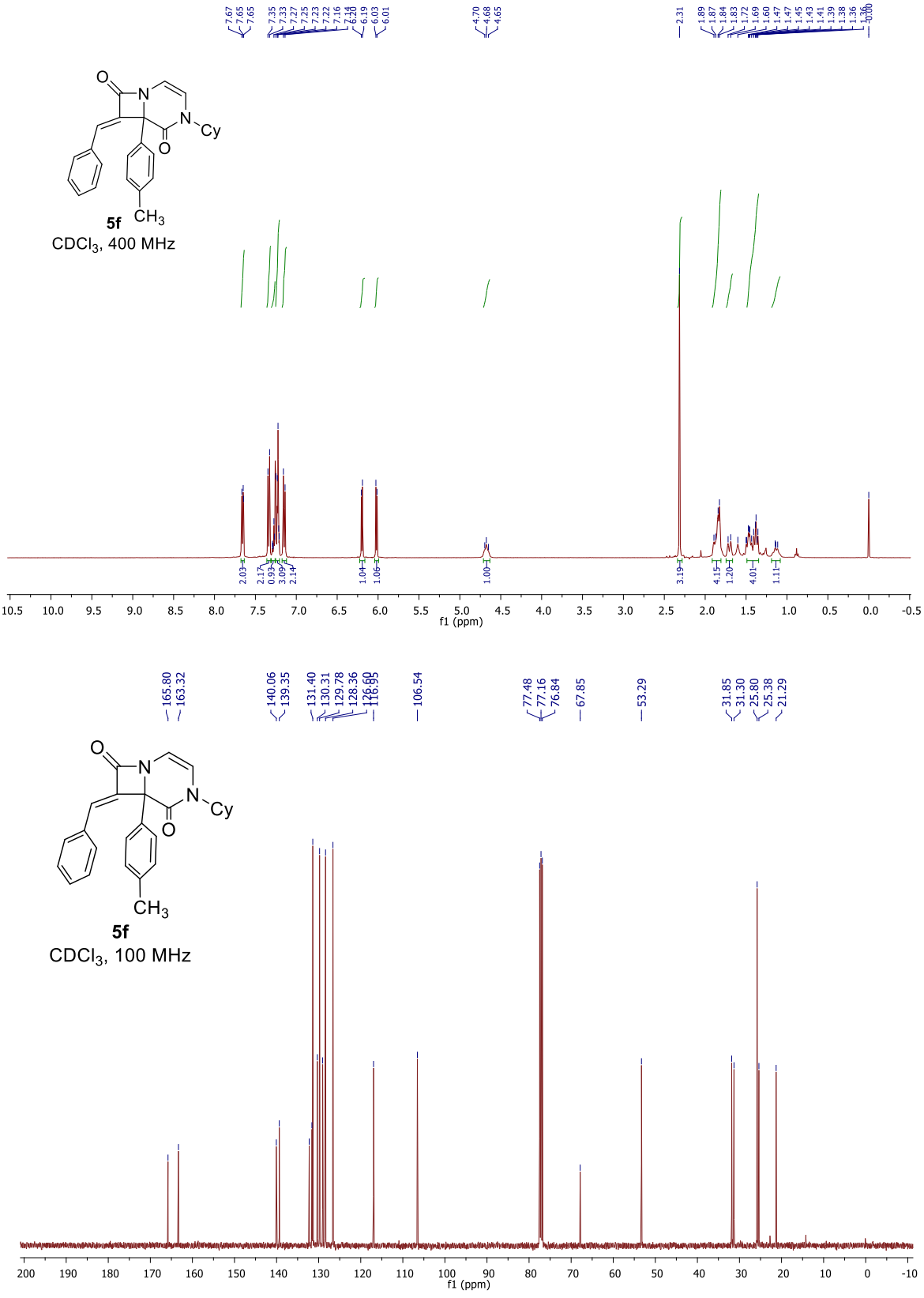


Figure S88: ^{1}H and ^{13}C NMR of compound **5g**

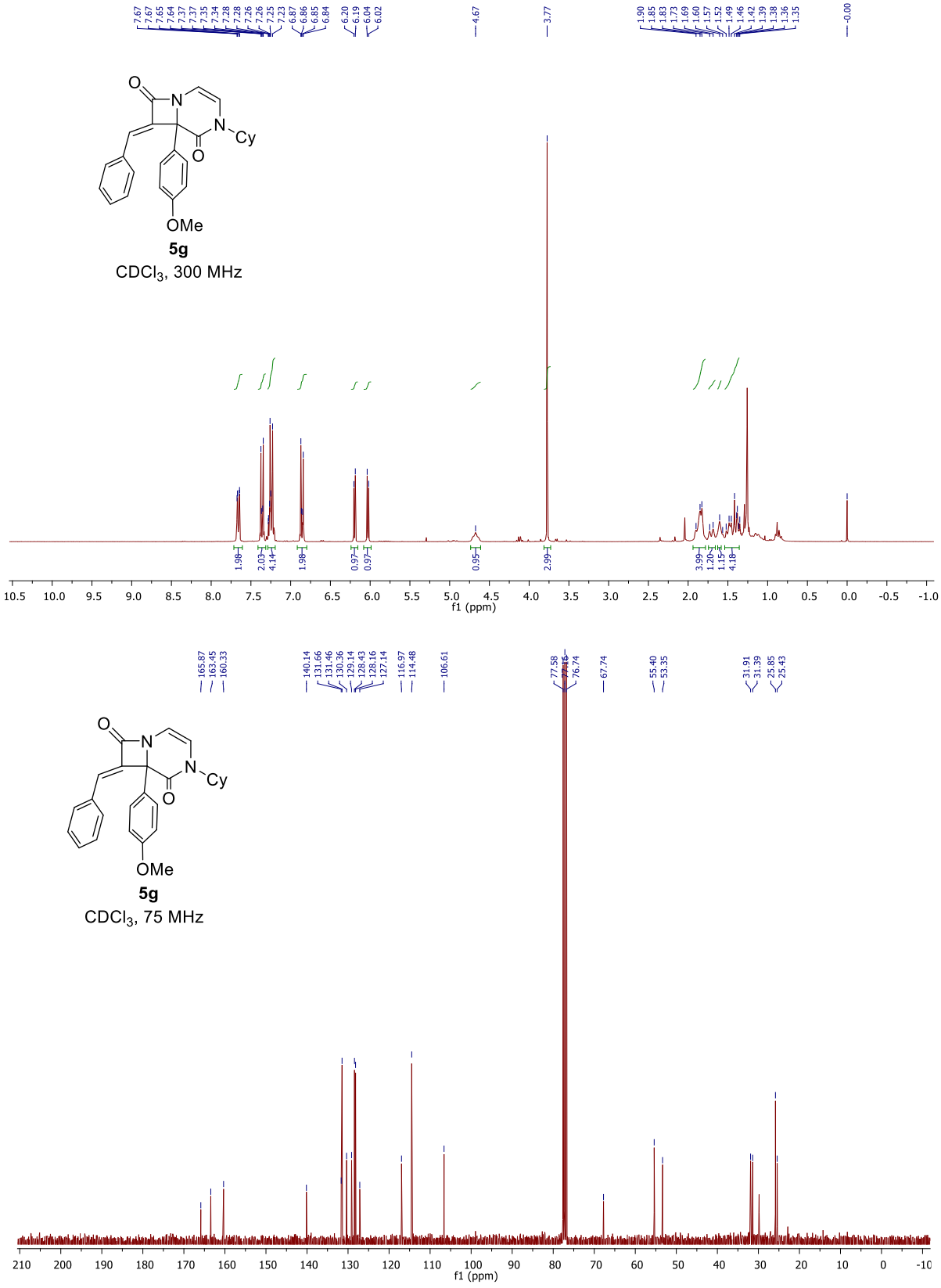


Figure S89: ^{1}H and ^{13}C NMR of compound **5h**

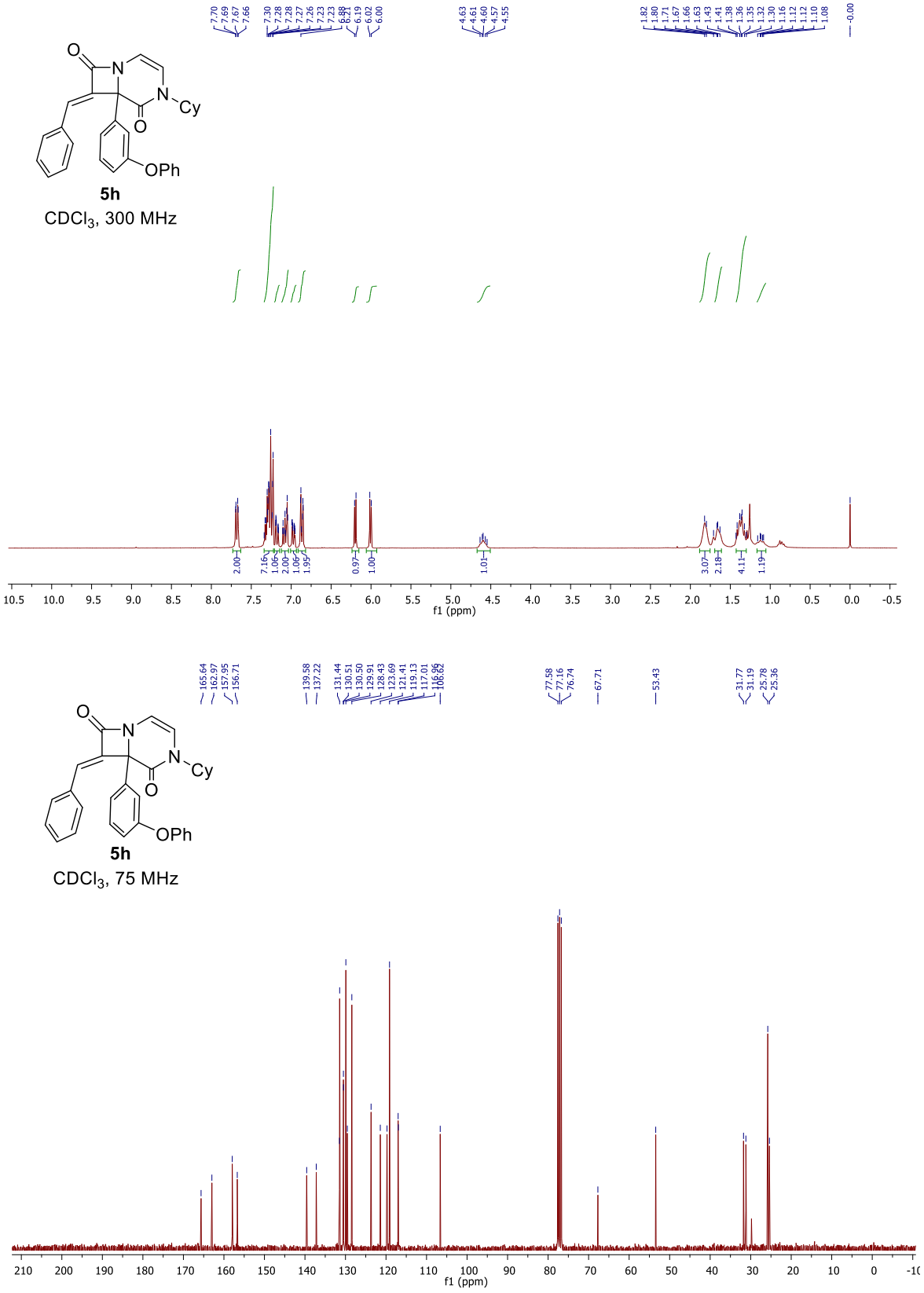
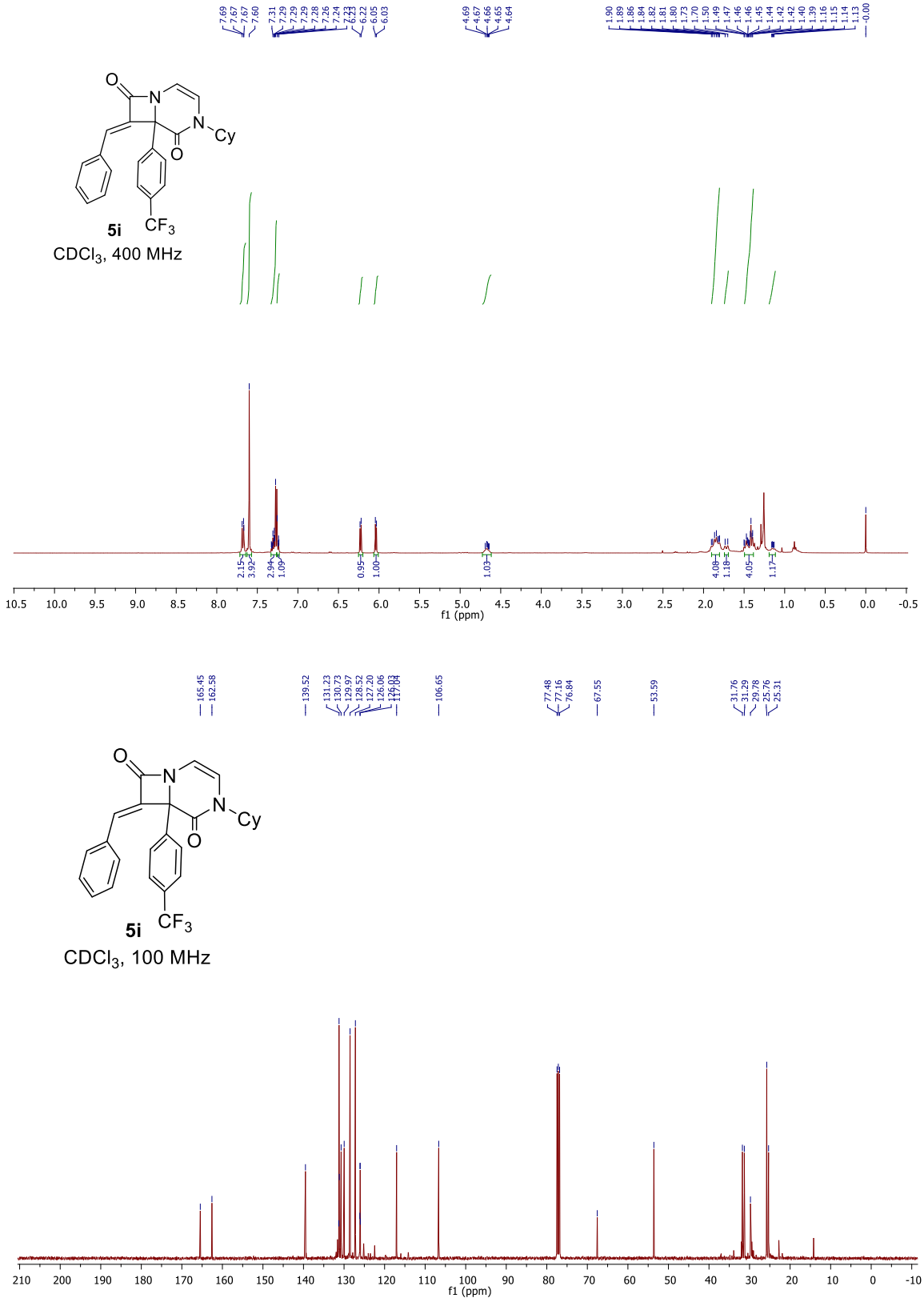
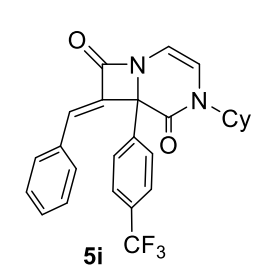


Figure S90: ^{1}H,^{13}C and ^{19}F NMR of compound **5i**





5i

$CDCl_3$, 283 MHz

Figure S91: ^{1}H and ^{13}C NMR of compound **5j**

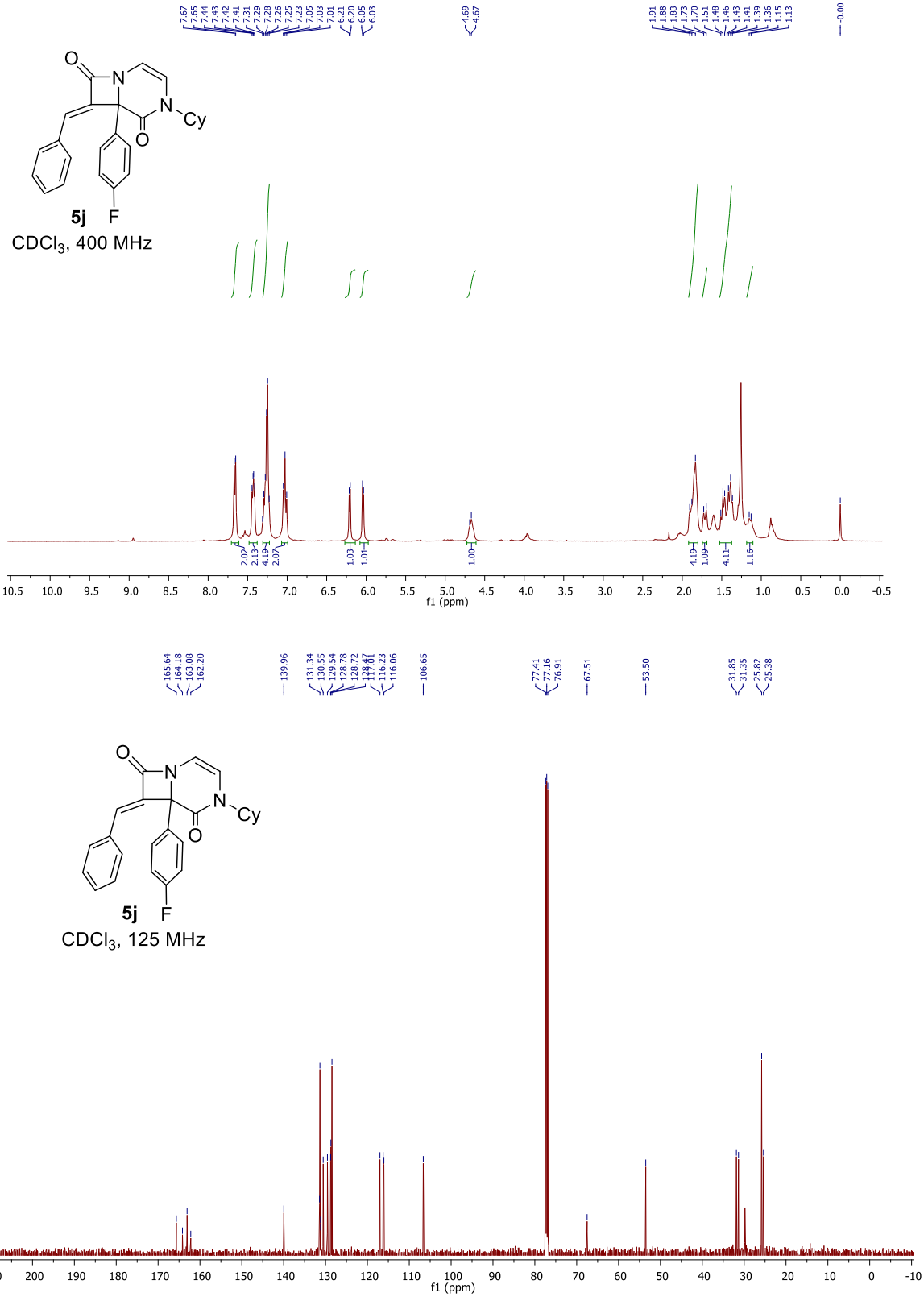


Figure S92: ^{1}H and ^{13}C NMR of compound **5k**

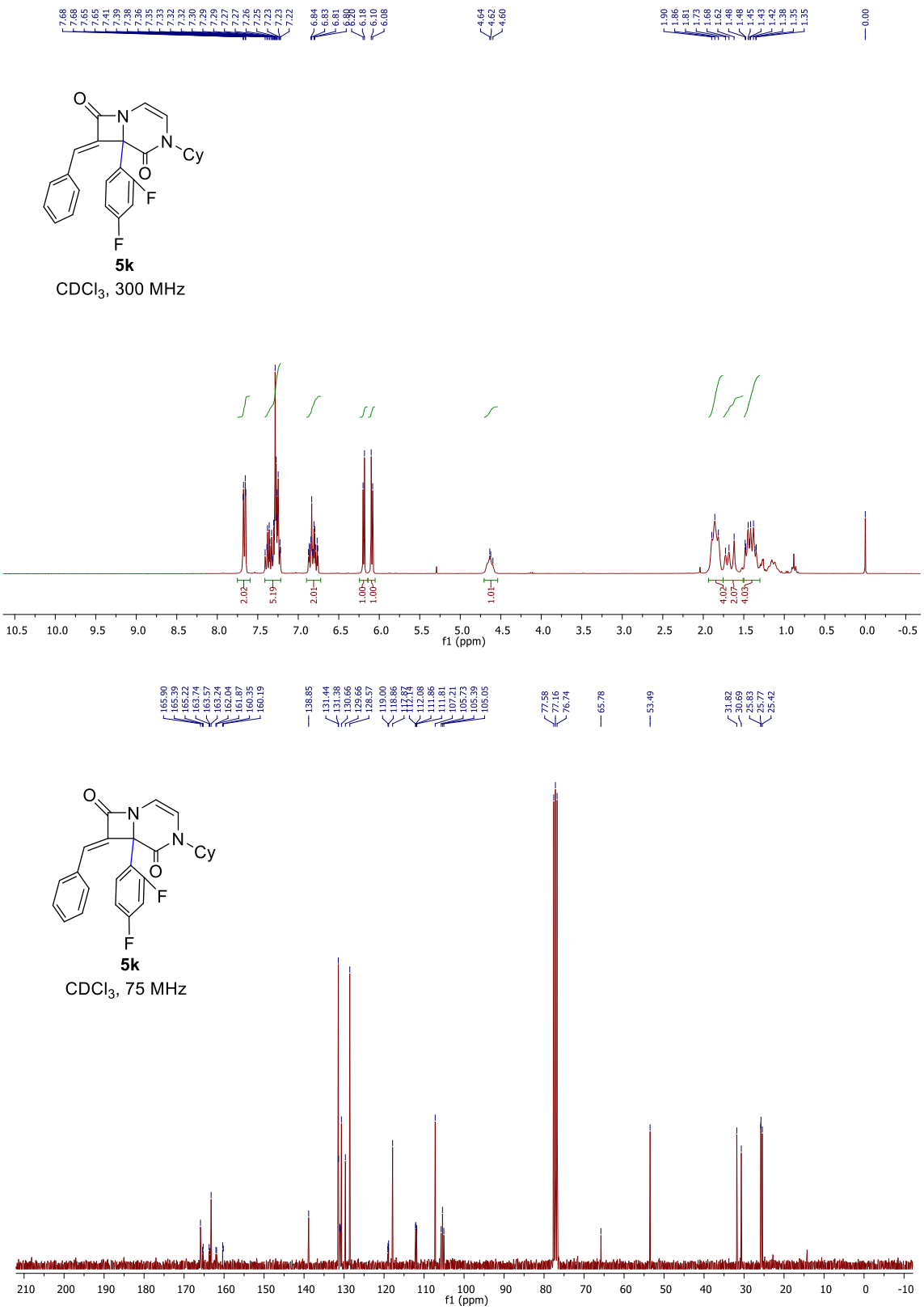
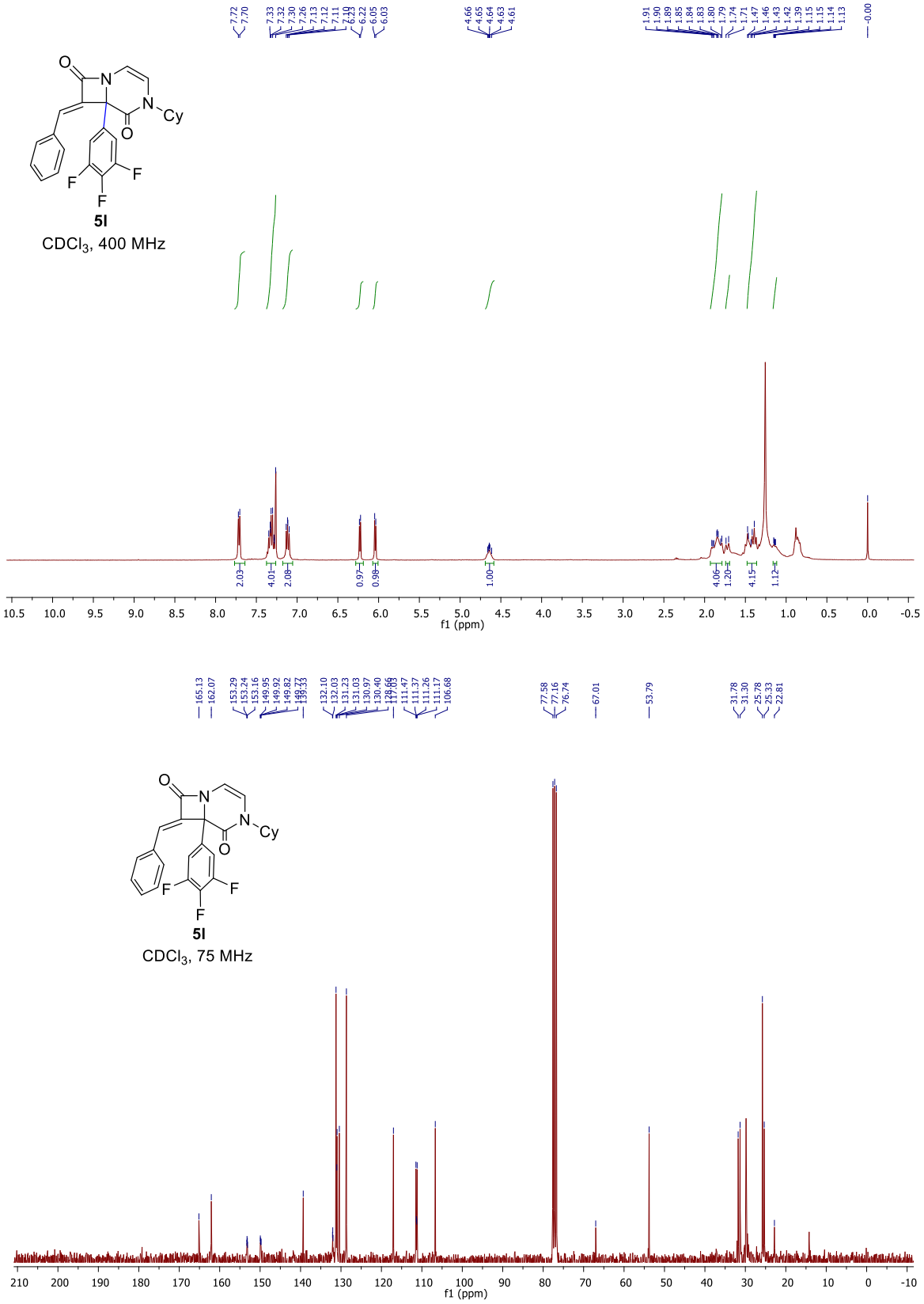
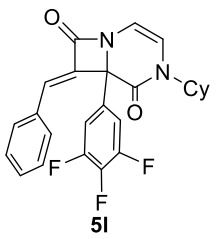


Figure S93: ^{1}H,^{13}C and ^{19}F NMR of compound **5l**





5l

$CDCl_3$, 283 MHz

Figure S94: ^{1}H and ^{13}C NMR of compound **5m**

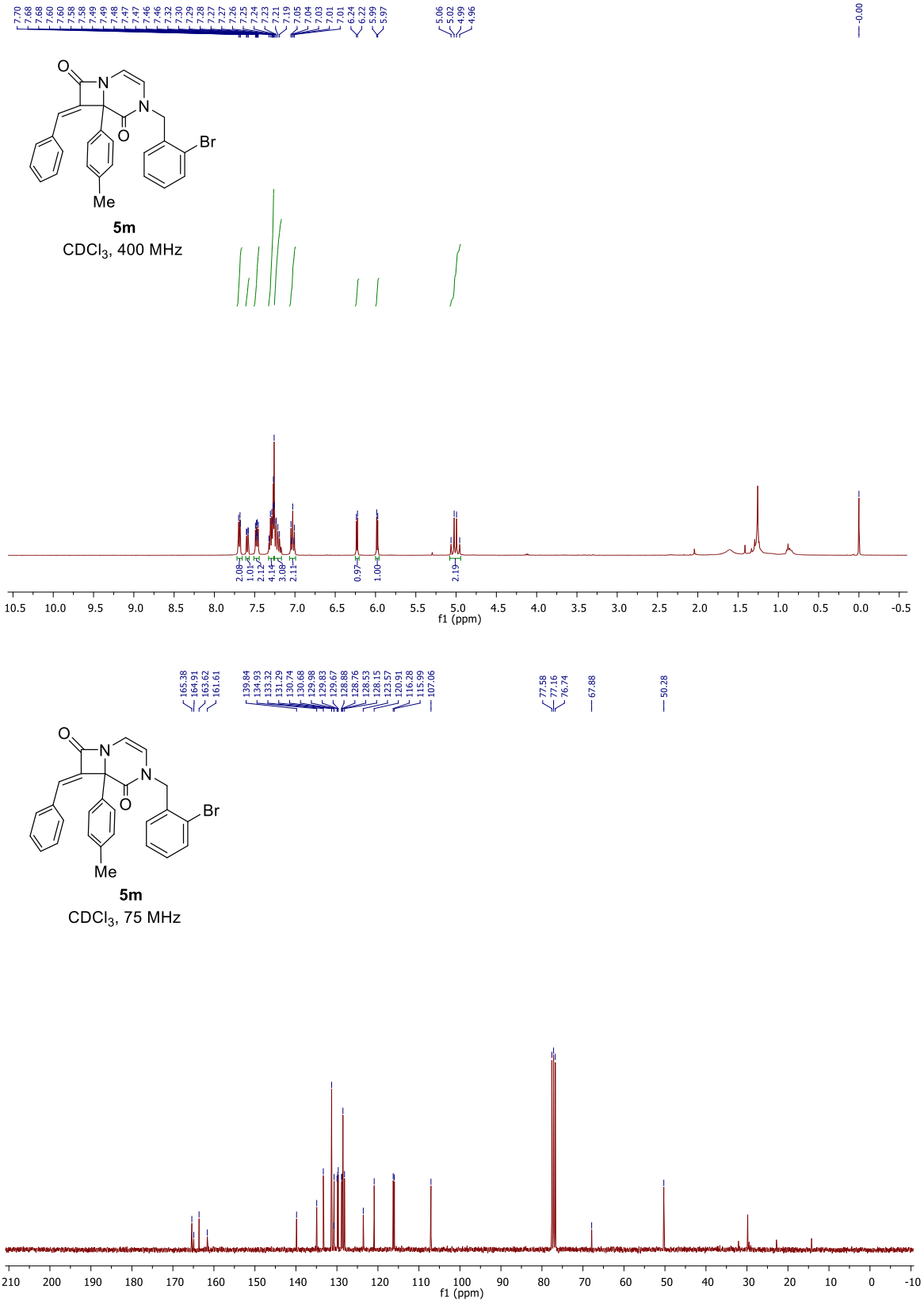


Figure S95: ^{1}H and ^{13}C NMR of compound **5n**

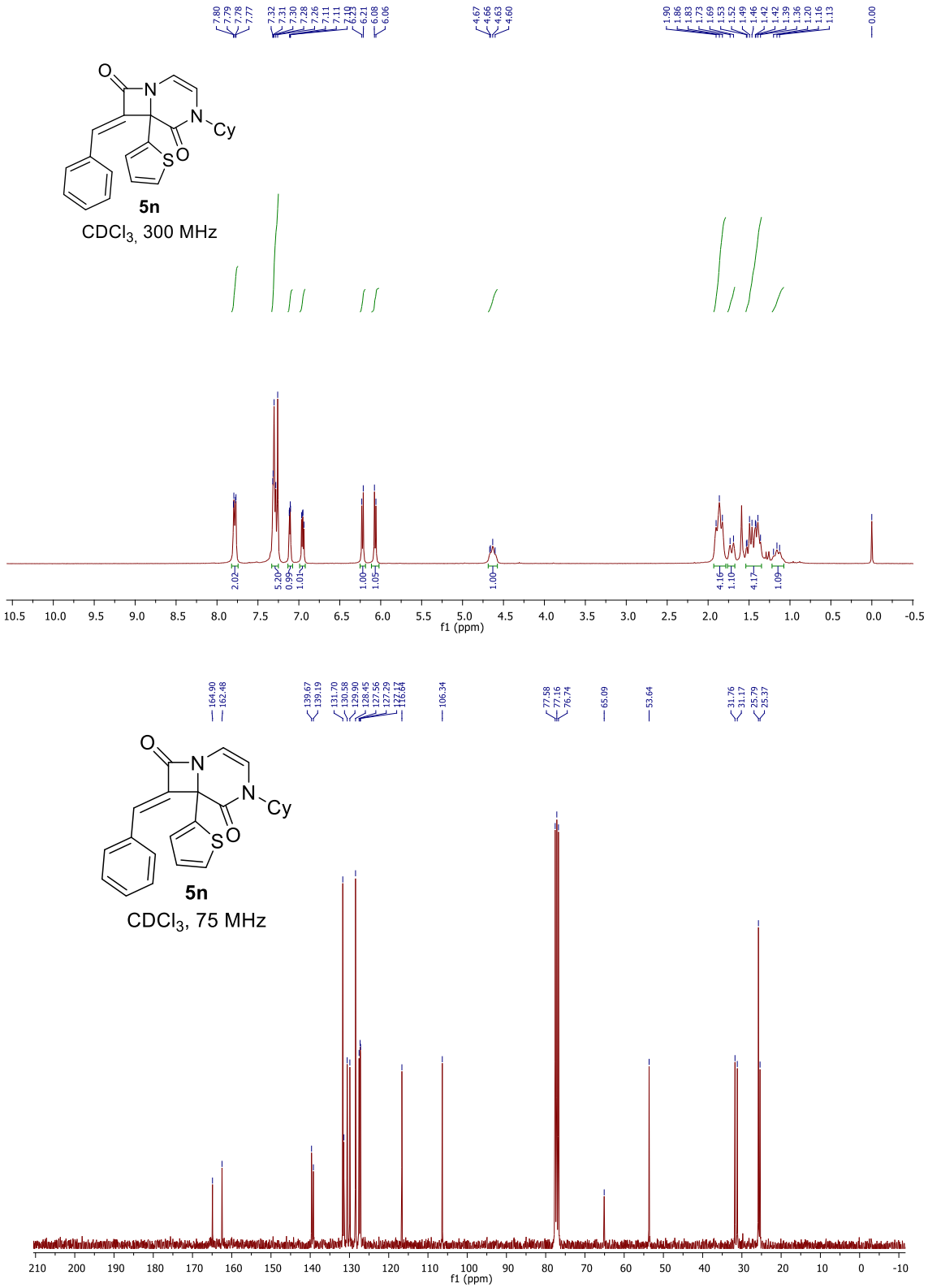


Figure S96: ^{1}H and ^{13}C NMR of compound **5o**

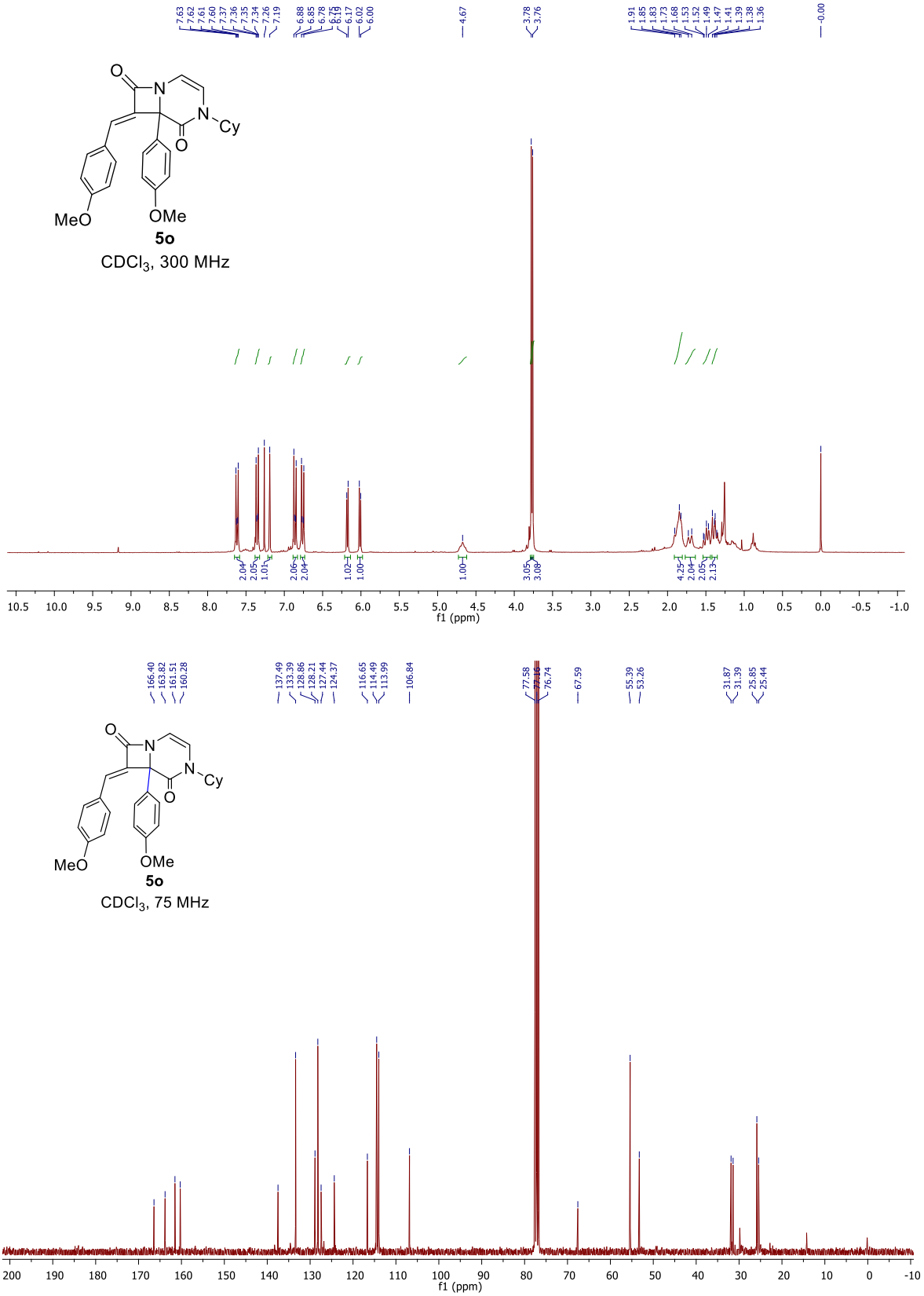


Figure S97: ^{1}H and ^{13}C NMR of compound **5p**

Figure S98: ^{1}H and ^{13}C NMR of compound **5q**

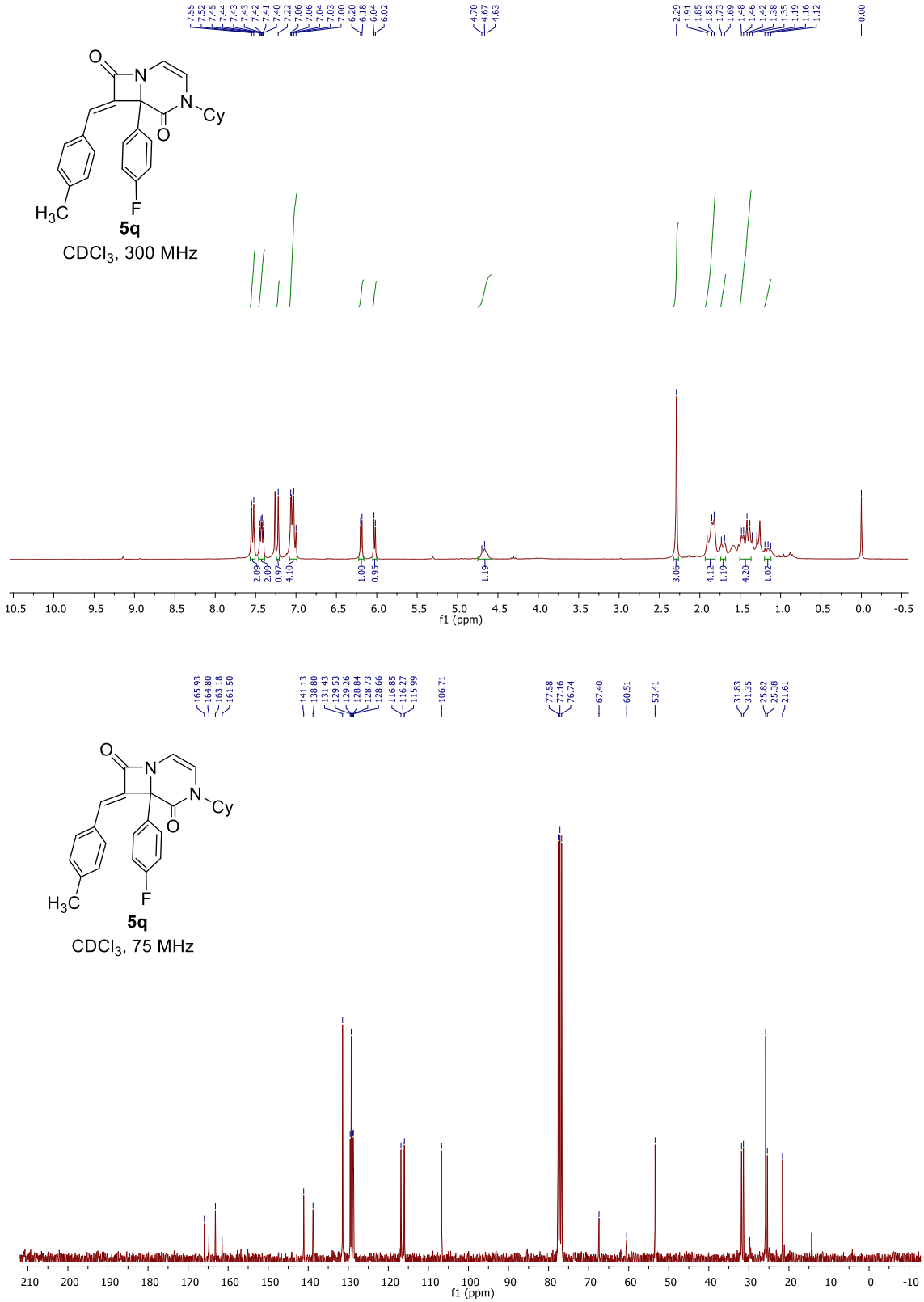


Figure S99: ^{1}H and ^{13}C NMR of compound **5r**

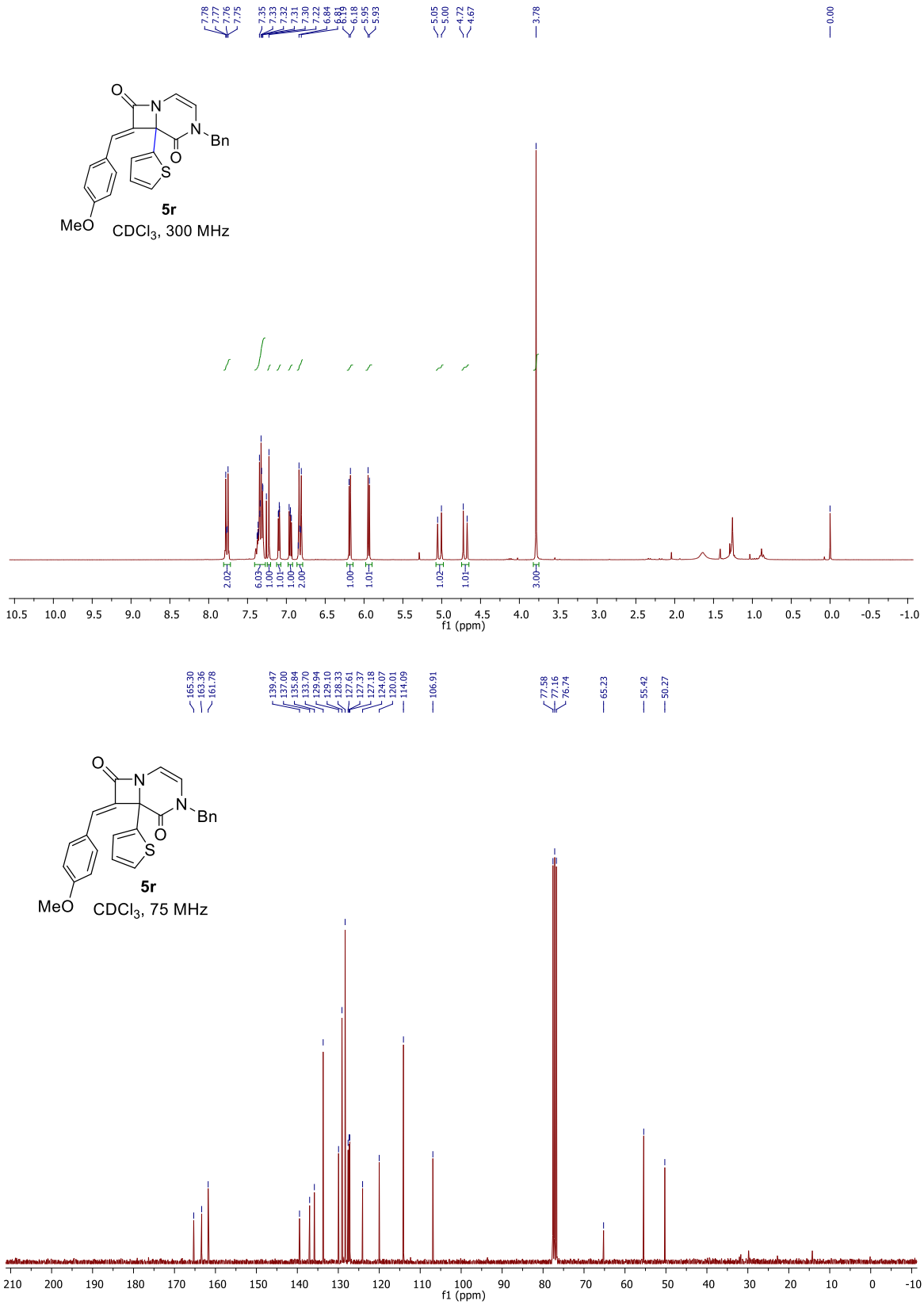


Figure S100: ^{1}H and ^{13}C NMR of compound **5s**

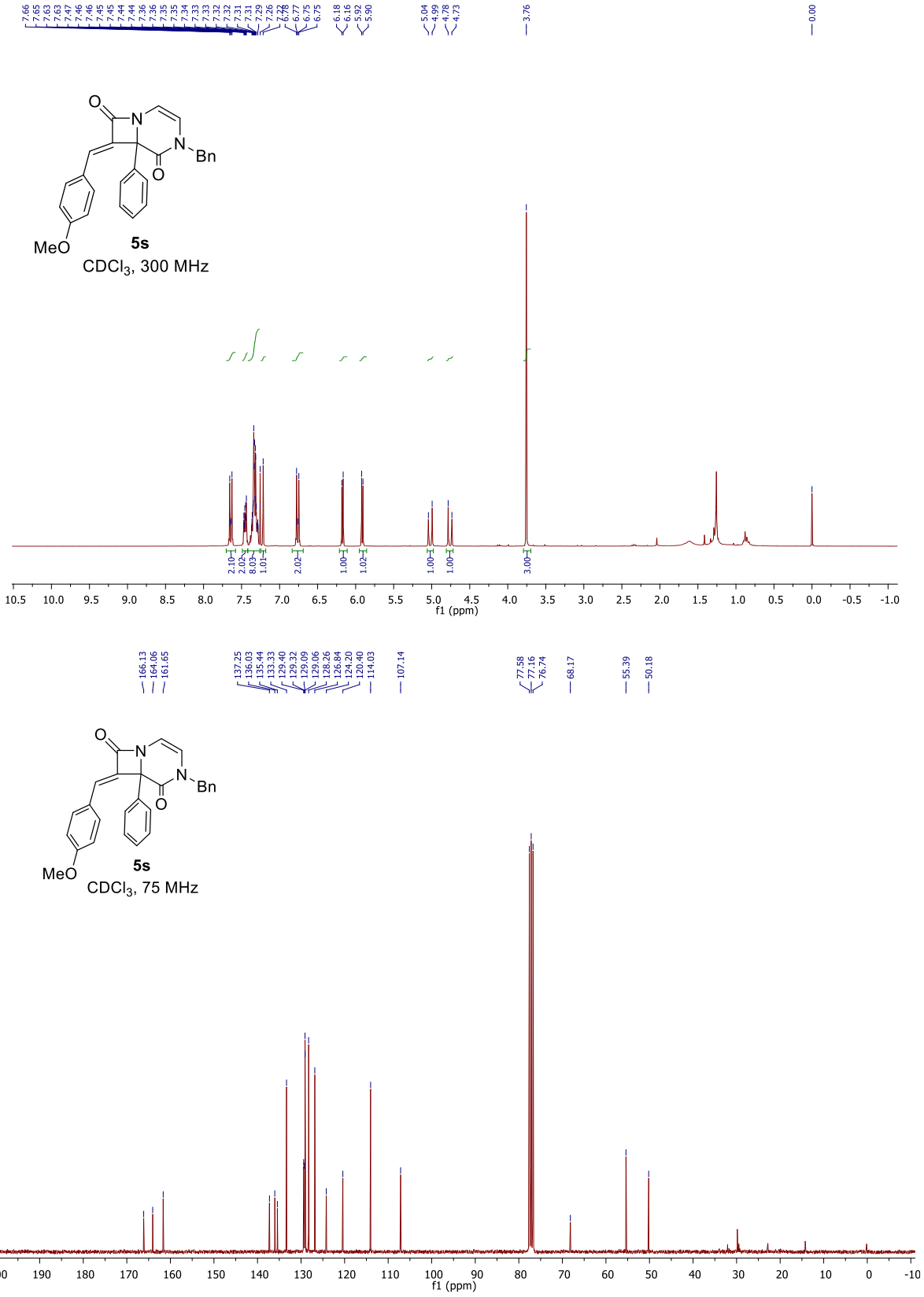


Figure S101: ^{1}H and ^{13}C NMR of compound **5ab**

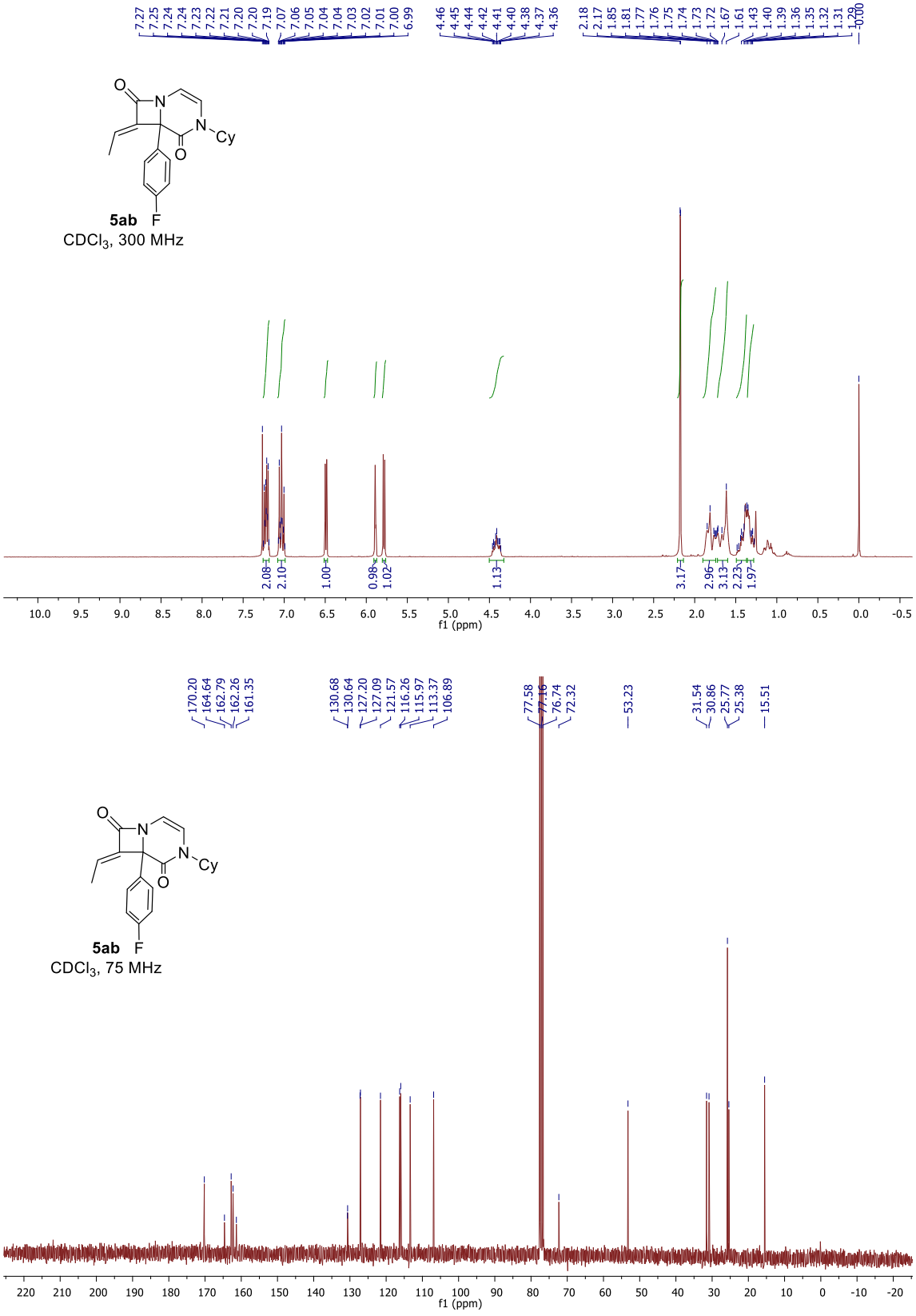


Figure S102: ^{1}H and ^{13}C NMR of compound **6a** (rotamers 1:0.2)

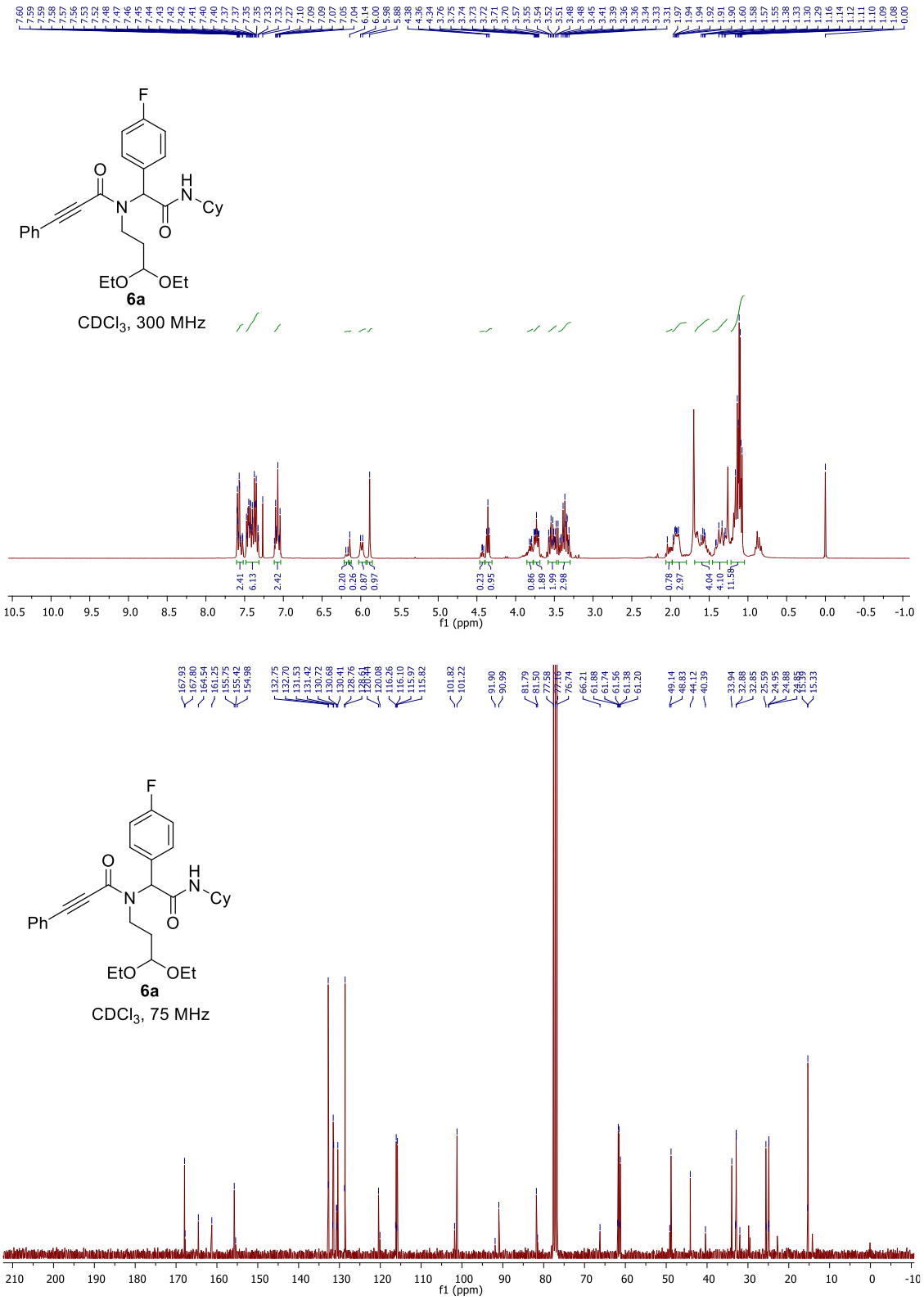


Figure S103: ^{1}H and ^{13}C NMR of compound **6b** (rotamers 1:0.2)

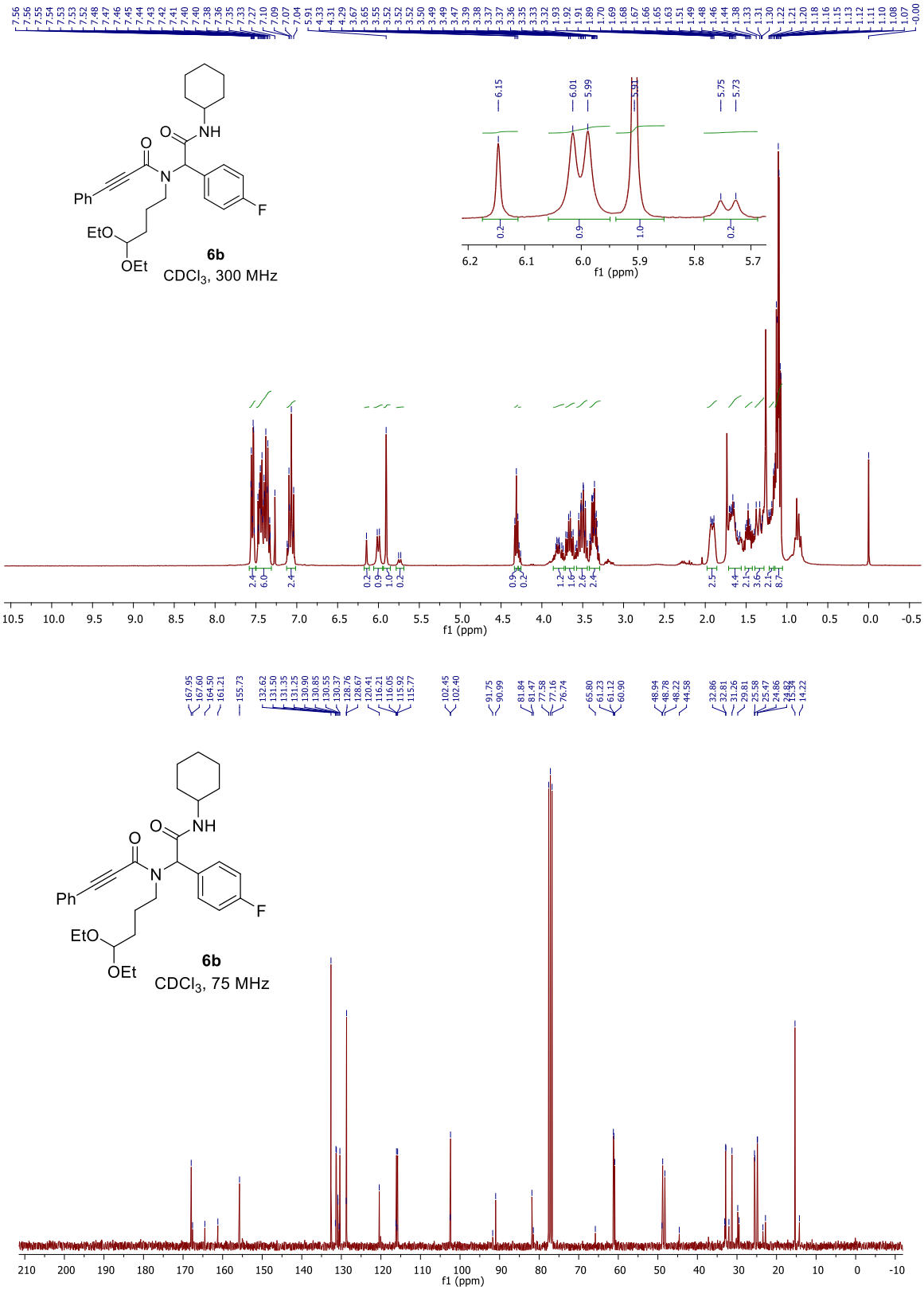


Figure S104: ^{1}H and ^{13}C NMR of compound **7a**(rotamers 1:0.5)

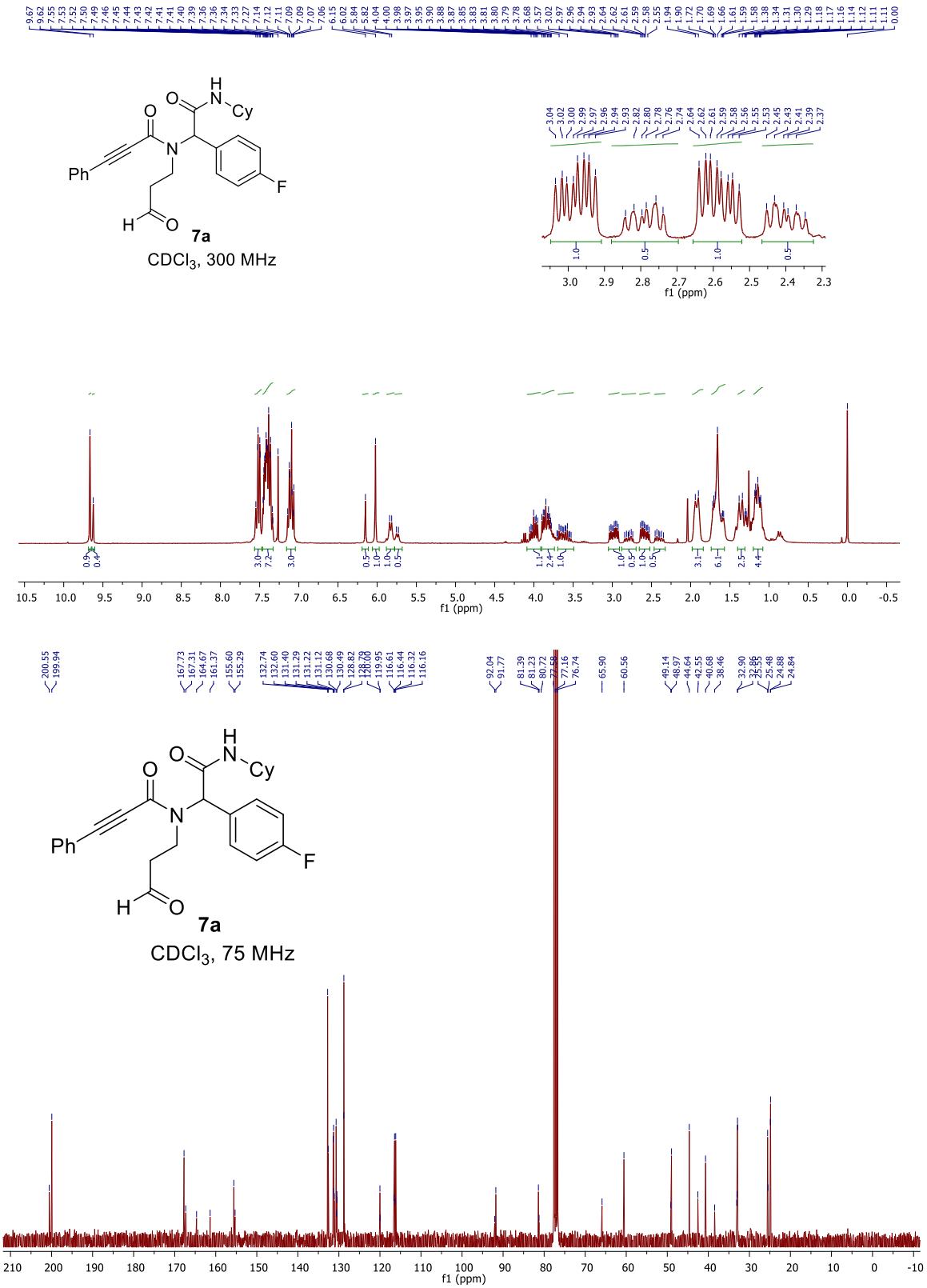


Figure S105: ^{1}H and ^{13}C NMR of compound **7b**(rotamers 1:0.3)

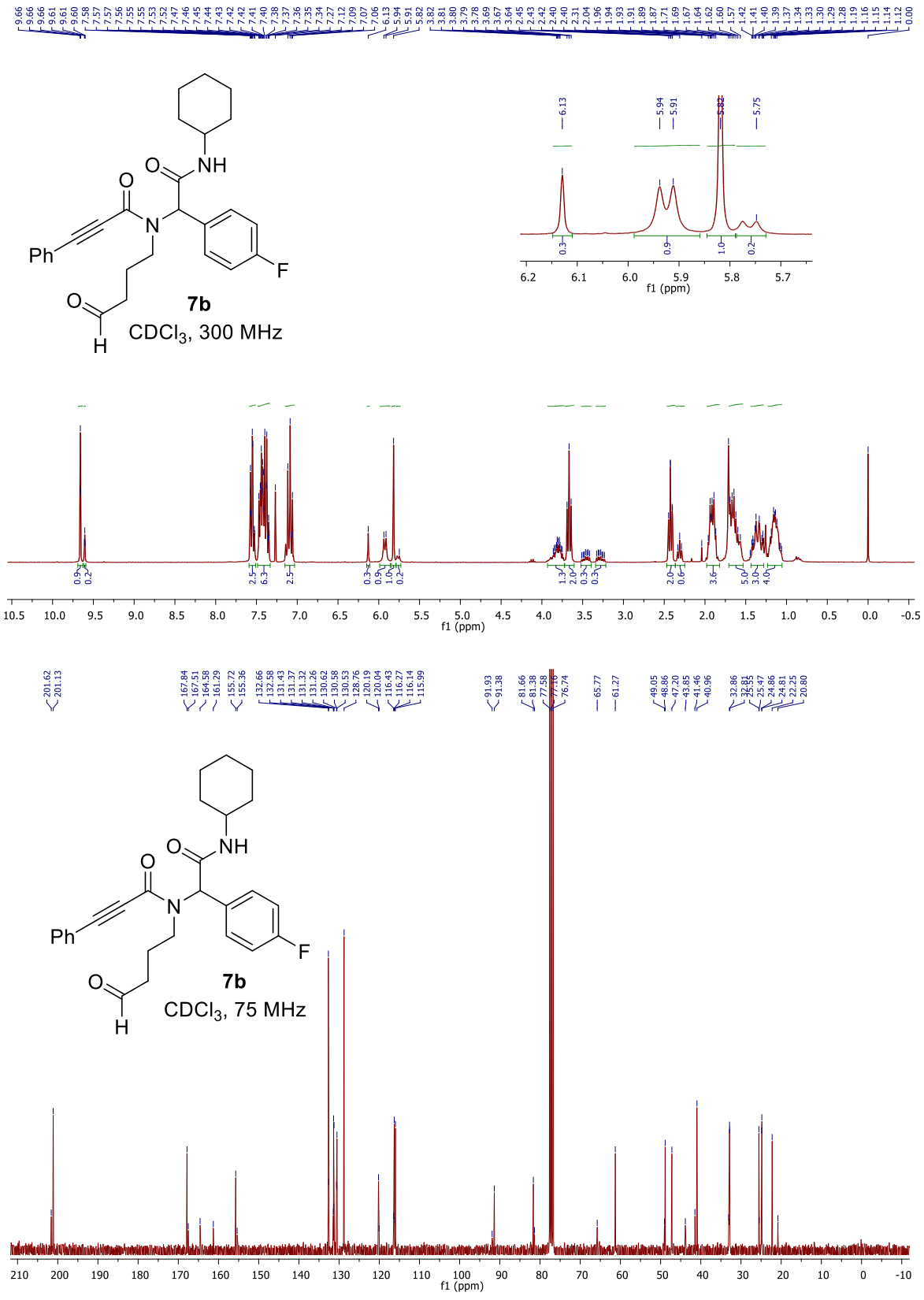


Figure S106: ^{1}H and ^{13}C NMR of compound **8a**(rotamers 1:0.5)

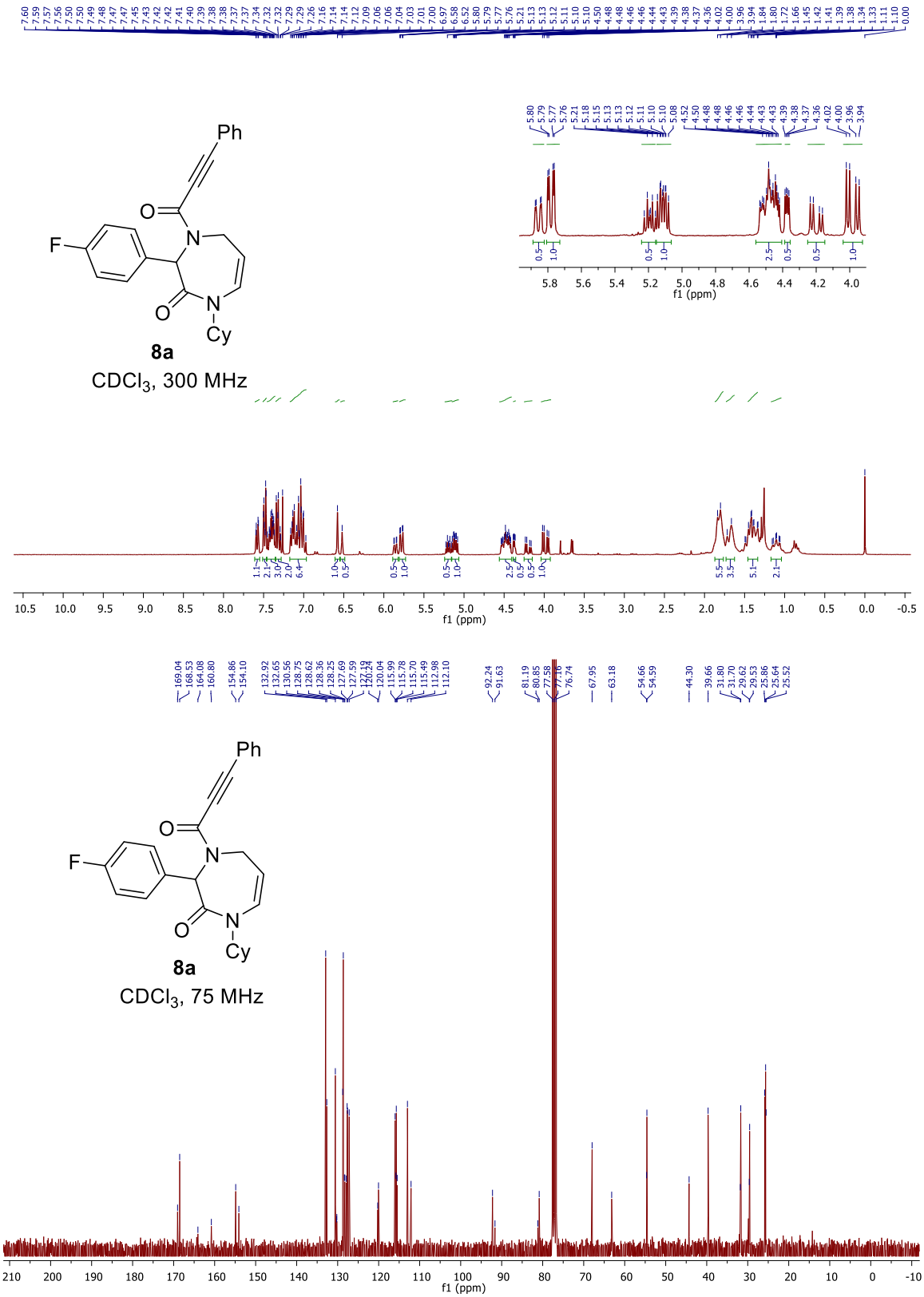


Figure S107: ^{1}H and ^{13}C NMR of compound **9a** (rotamers 1:1)

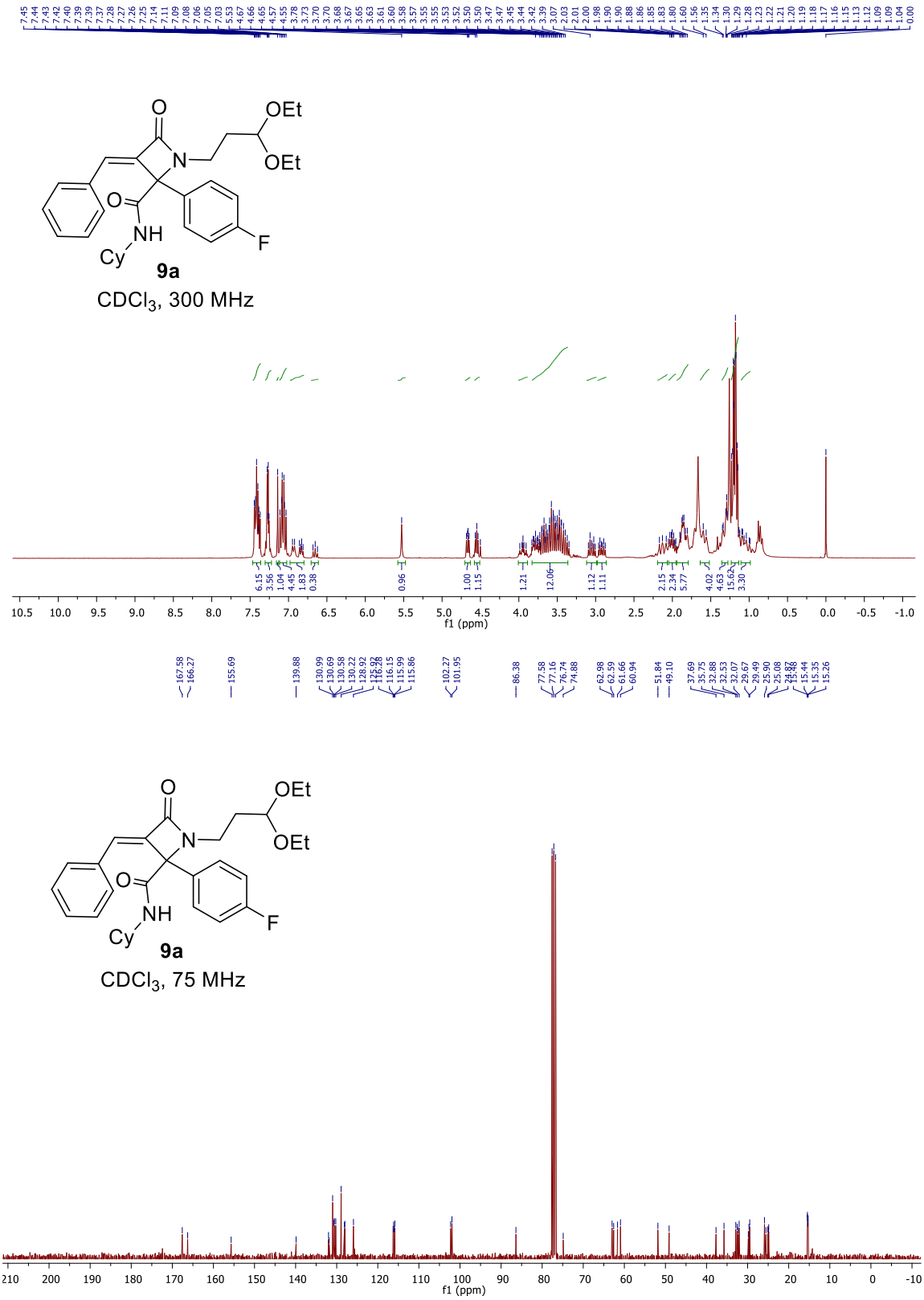


Figure S108: ^{1}H and ^{13}C NMR of compound **9b**

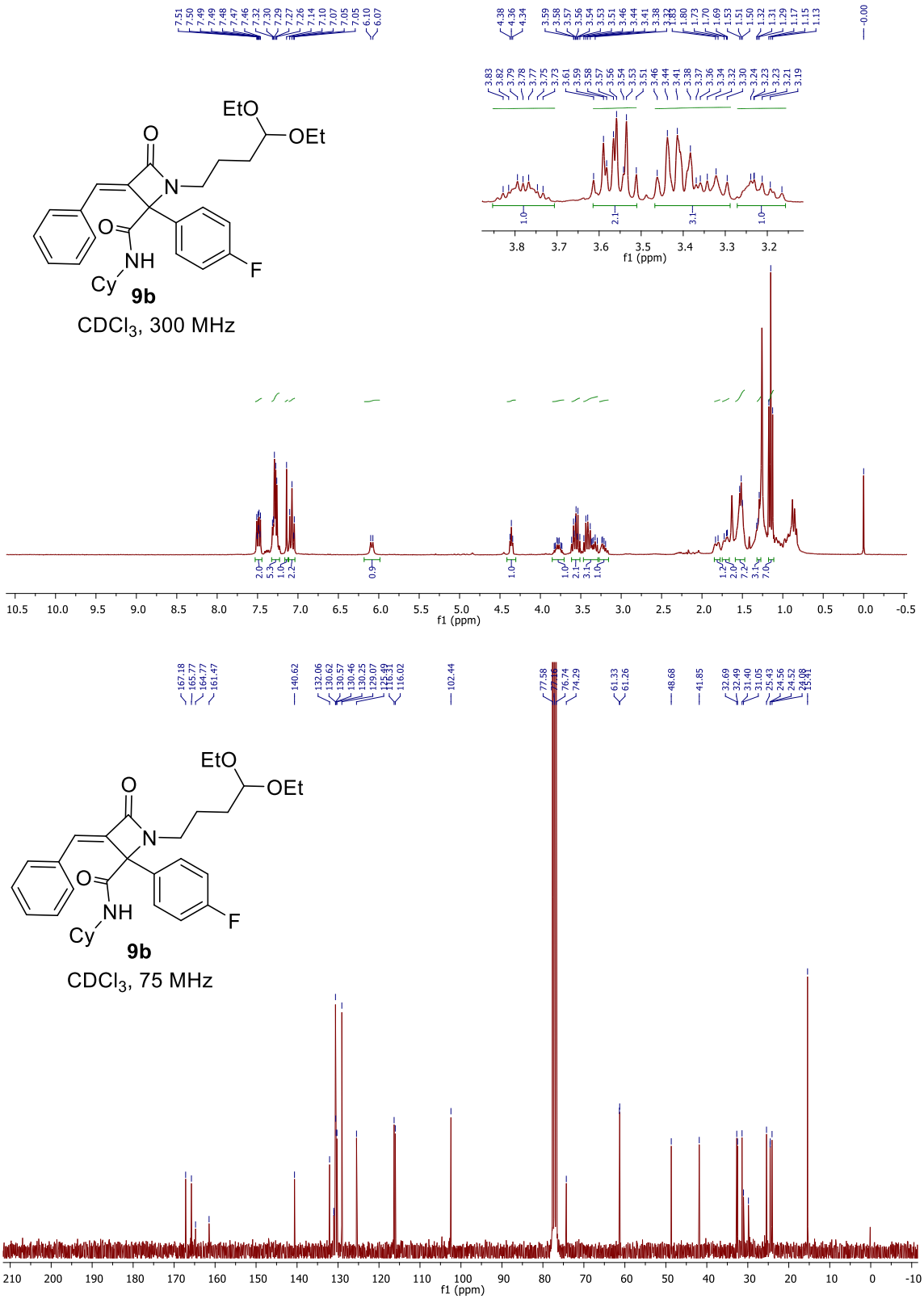


Figure S109: ^{1}H and $^{13}CNMR$ of compound **10a**

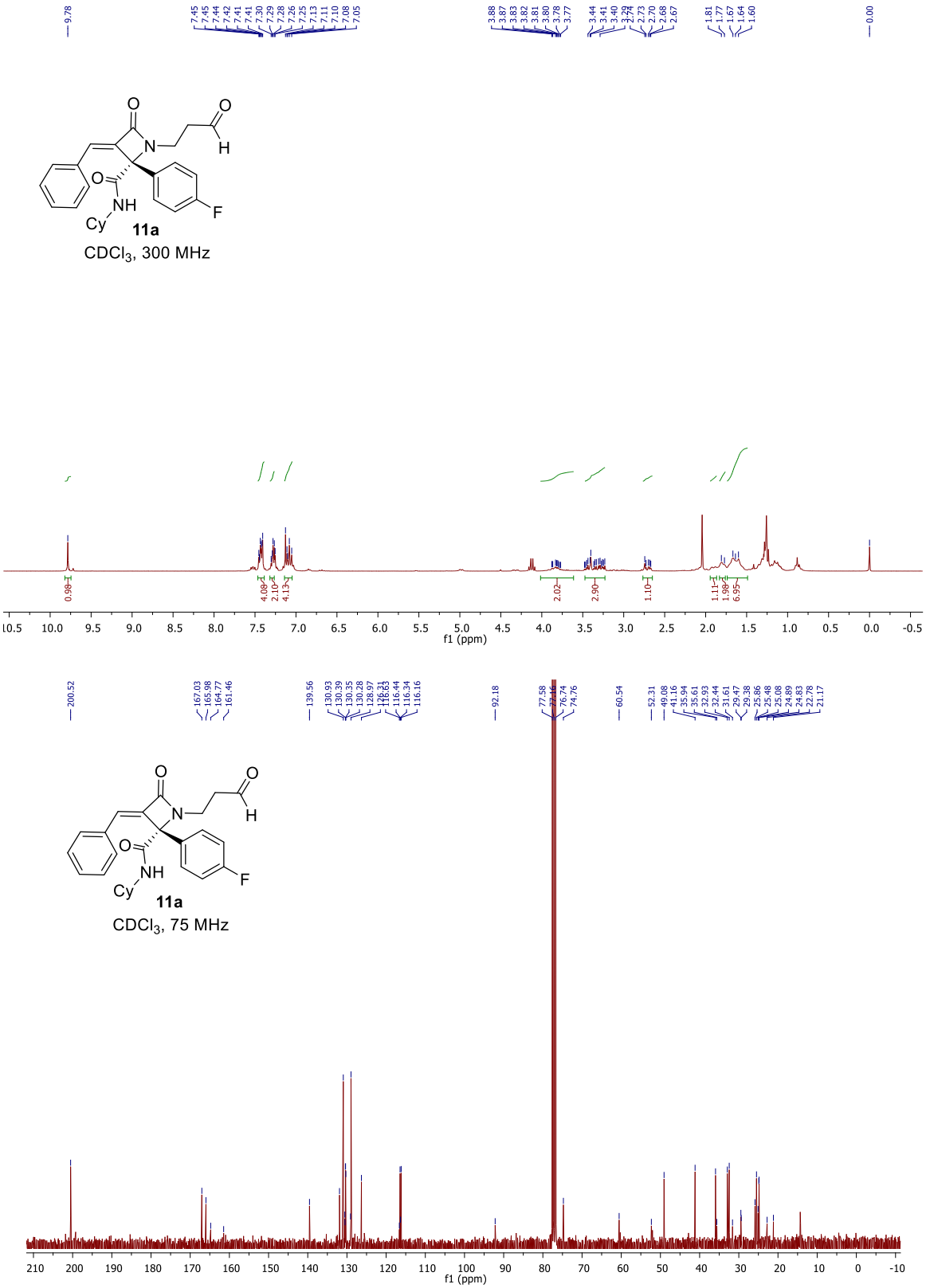


Figure S110: ^{1}H and ^{13}C NMR of compound **10b**

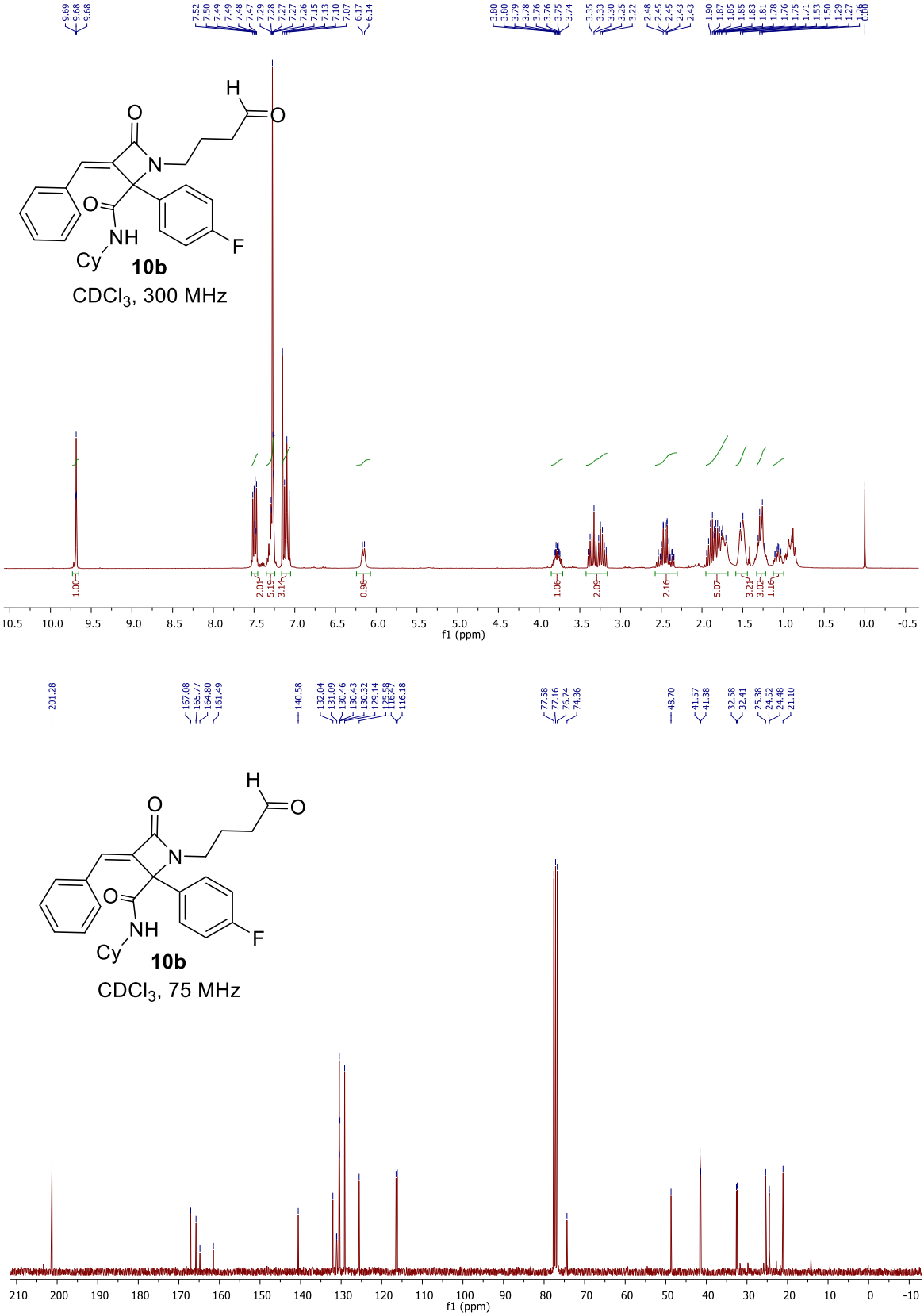


Figure S111: ^{1}H and ^{13}C NMR of compound **12**

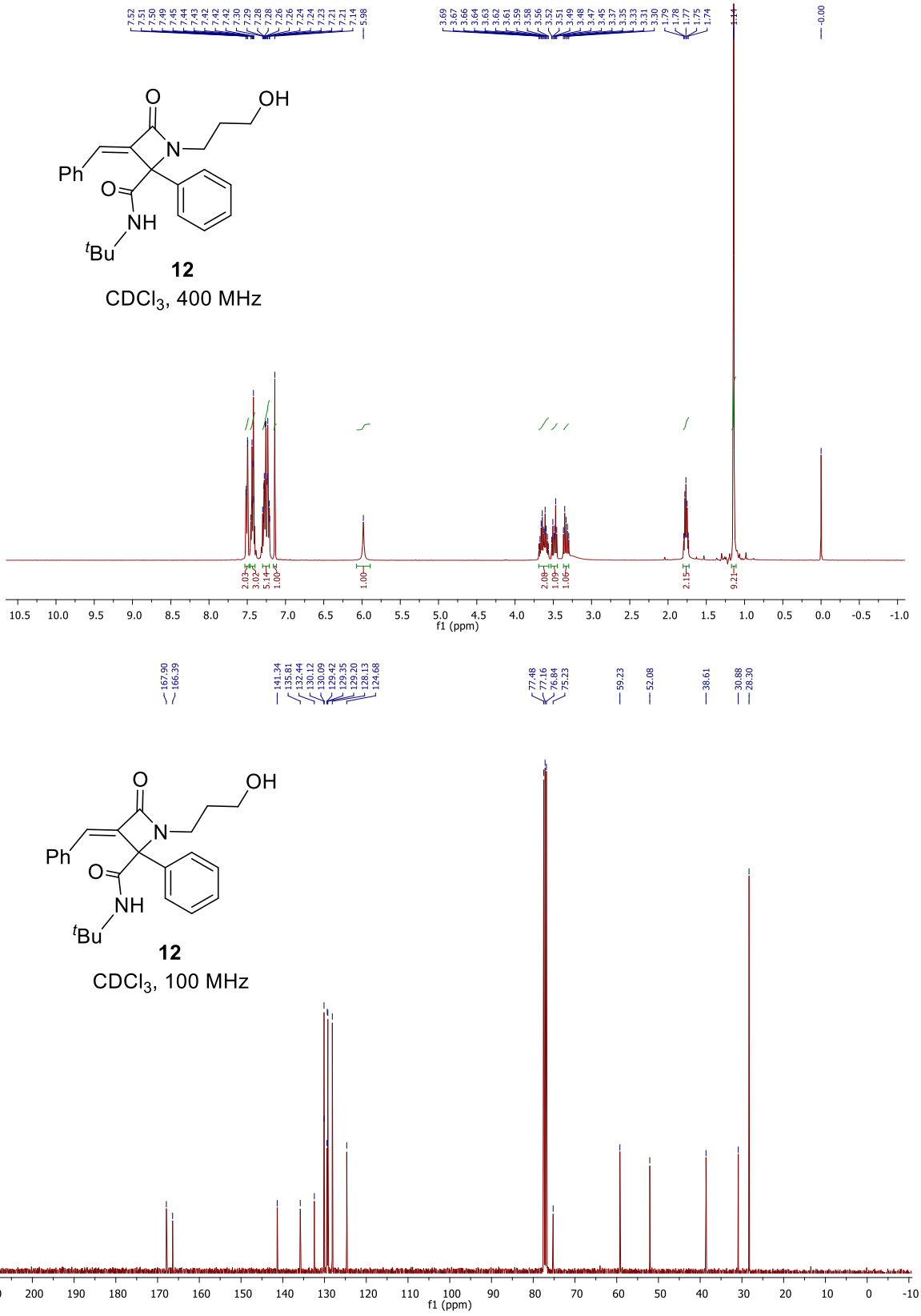


Figure S112: ^{1}H and ^{13}C NMR of compound **13**

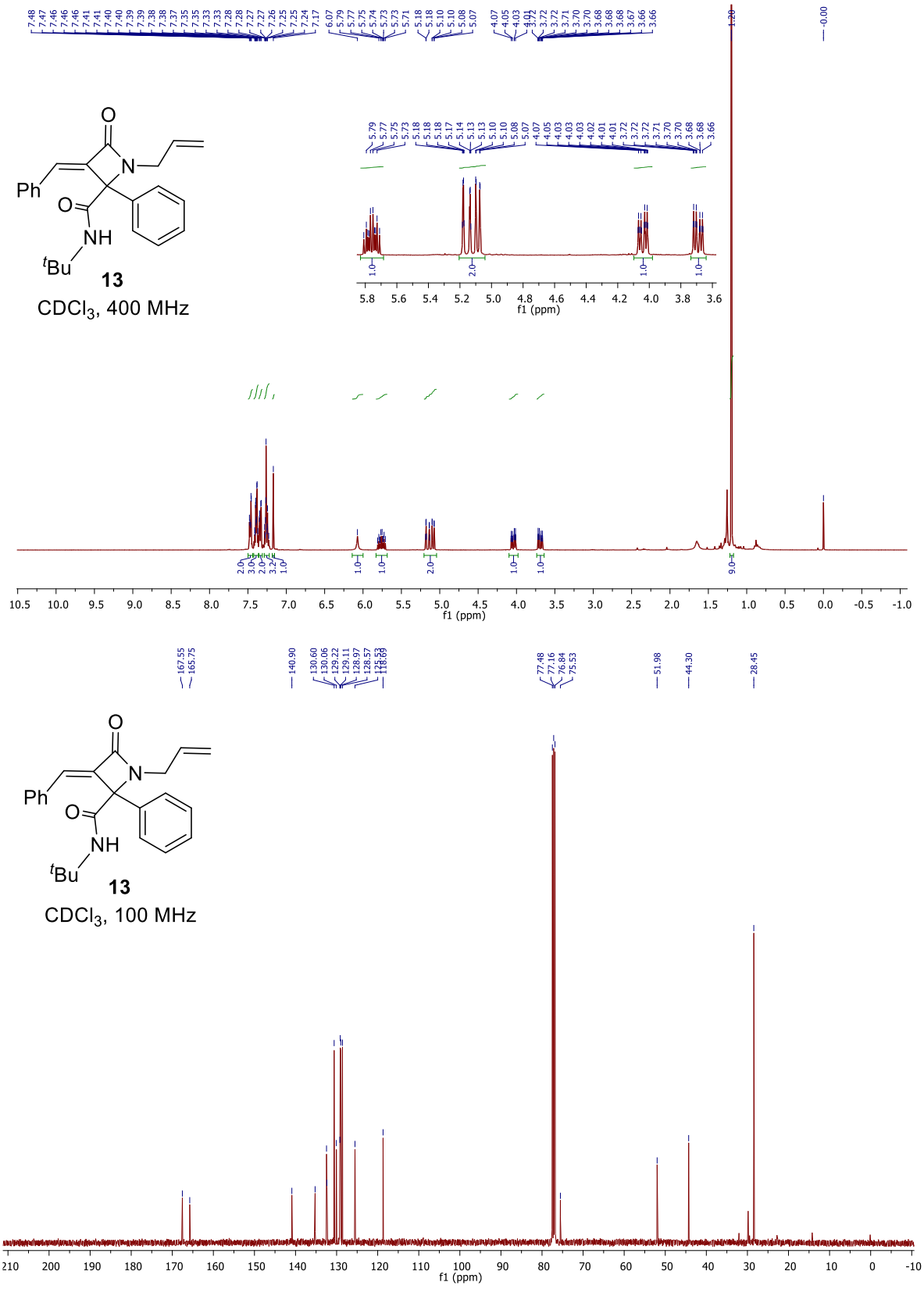
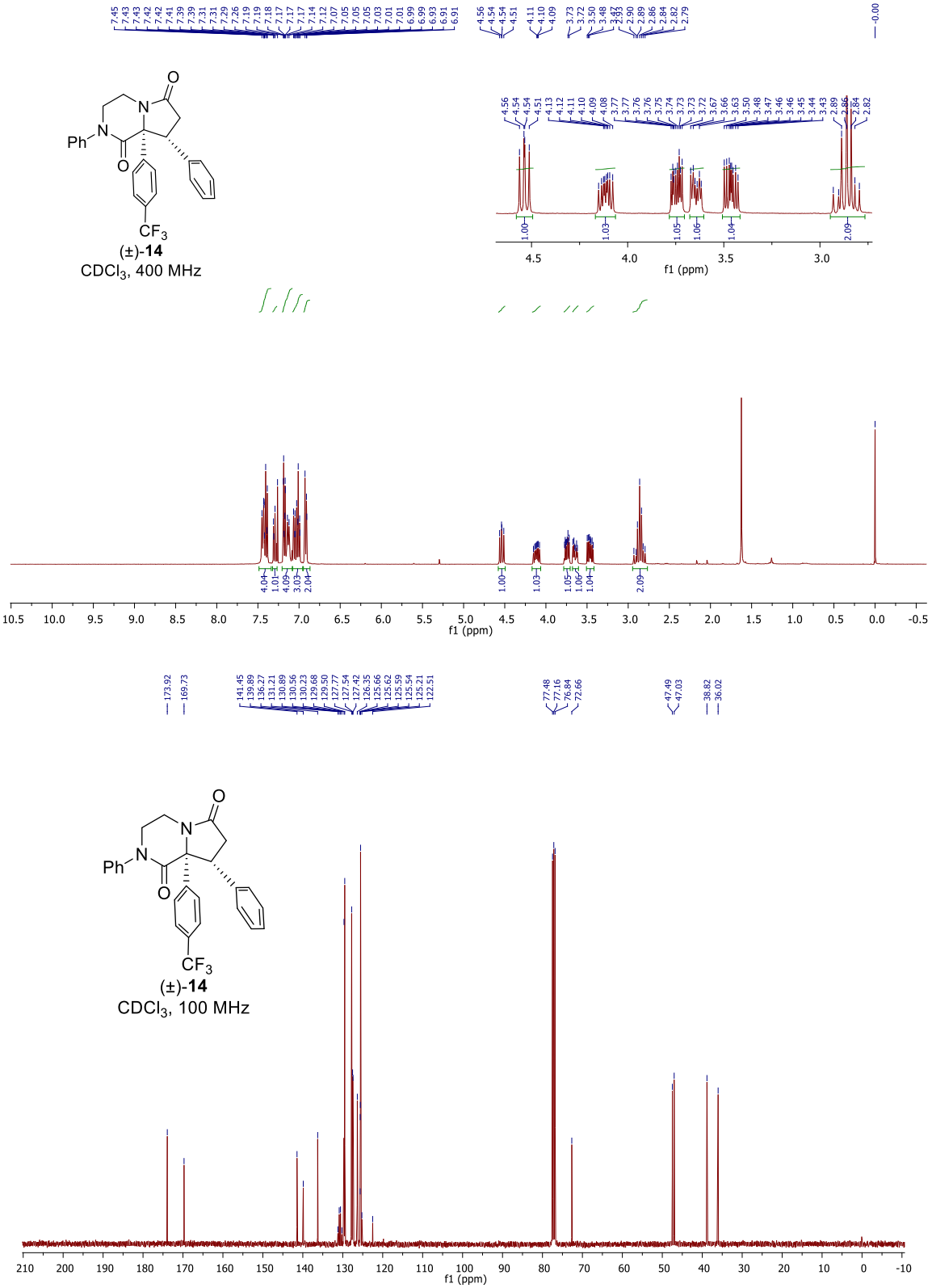


Figure S113: ^{1}H ,^{13}C NMR, DEPT-135 of compound **(±)-14**



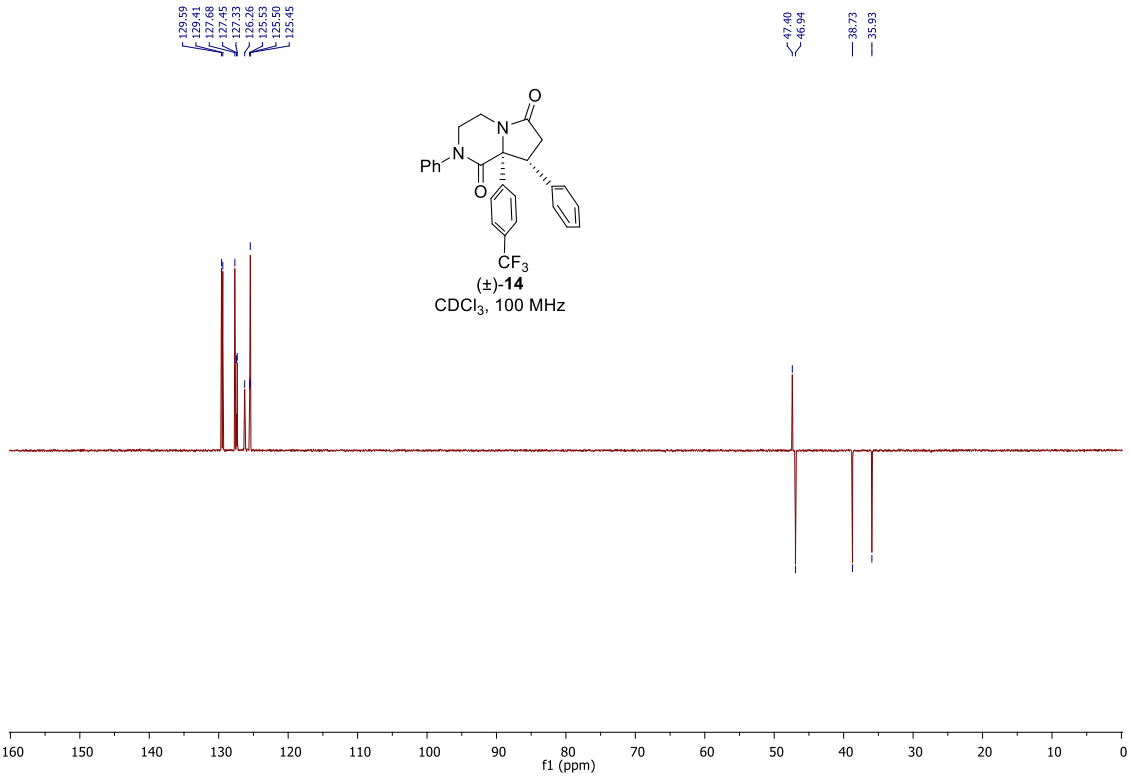

129.59
129.41
127.68
127.45
127.33
126.26
125.53
125.50
125.45
47.40
46.94
38.73
35.93
O
N
Ph
N
O
CF3
(±)-14
CDCl3, 100 MHz
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Figure S114: ^{1}H-^{1}H COSY spectrum of compound **(±)-14**

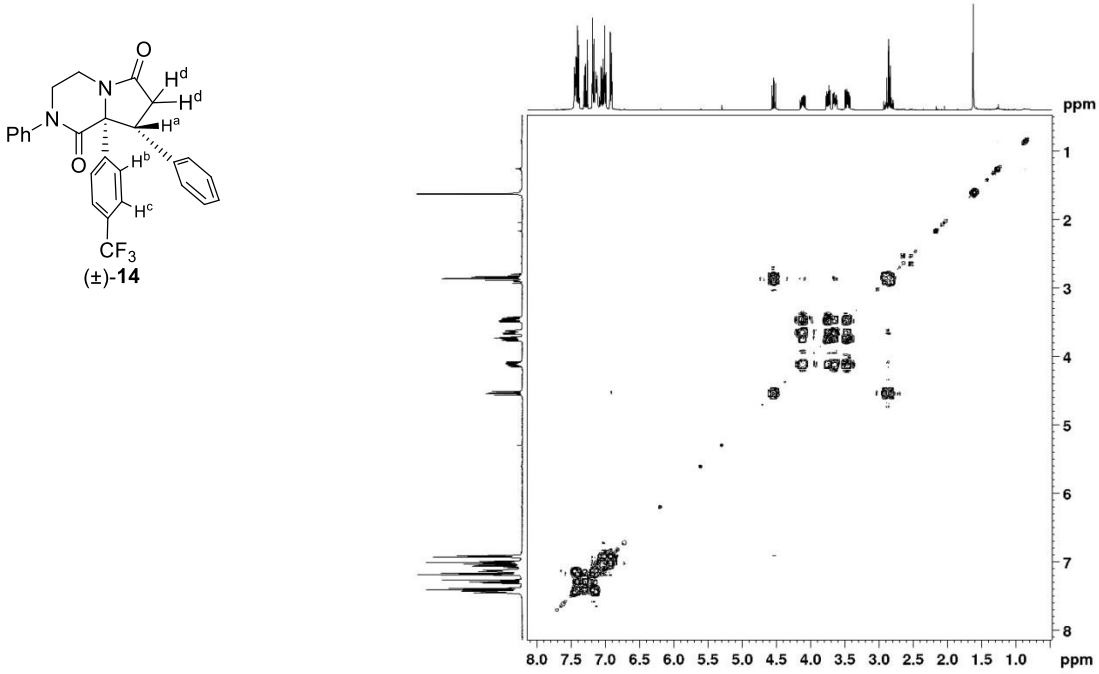


Figure S115: Expansions of ^{1}H-^{1}H COSY spectrum of compound **(±)-14**

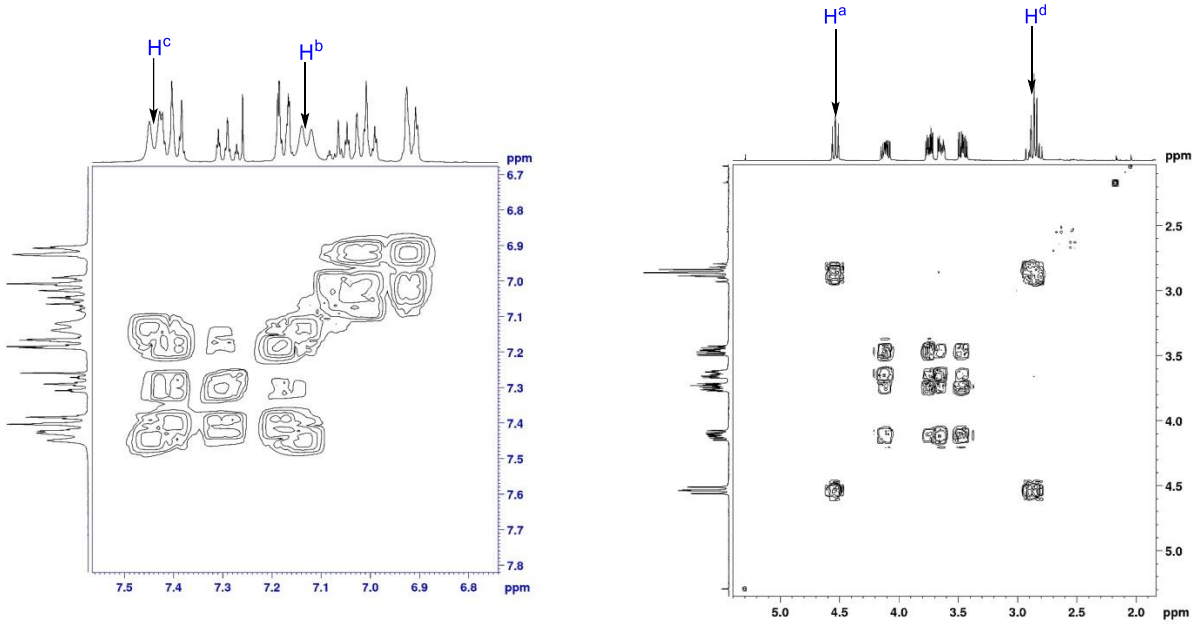


Figure S116: ^{1}H-^{13}C HMQC spectrumof compound **(±)-14**

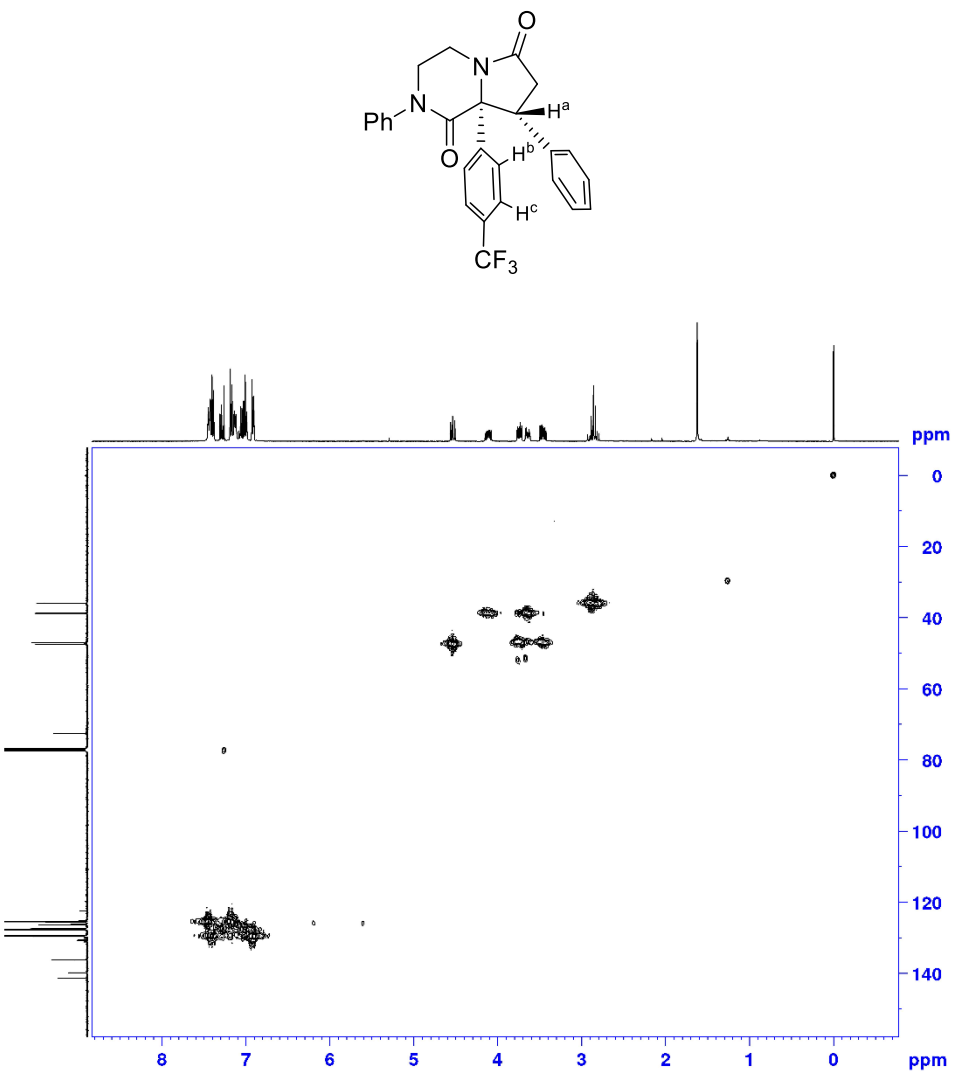


Figure S117: ^{1}H-^{1}H NOESY spectrum of compound **(±)-14**

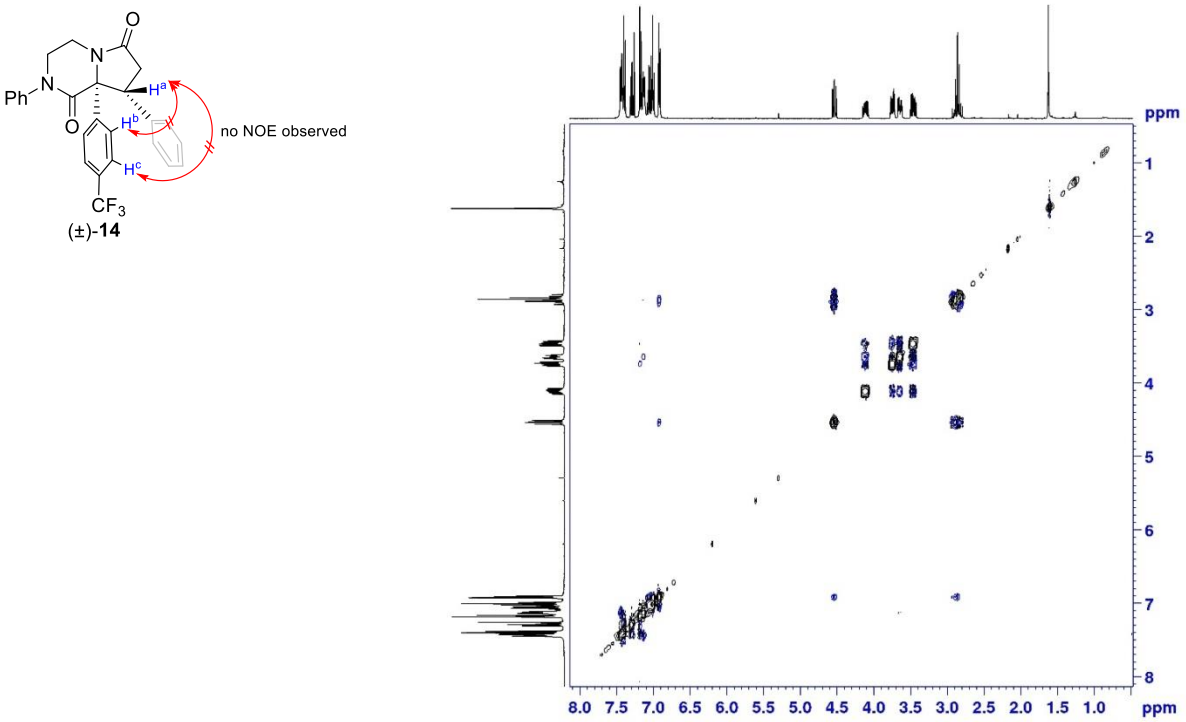


Figure S118: Expansions of NOESY spectrum of compound **(±)-14**

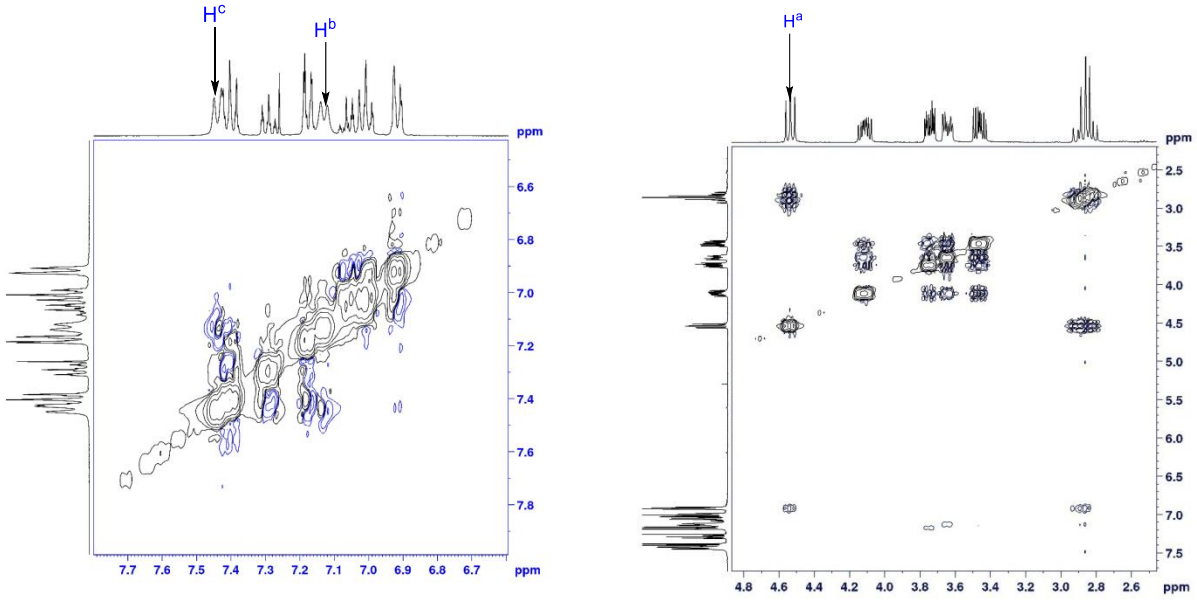
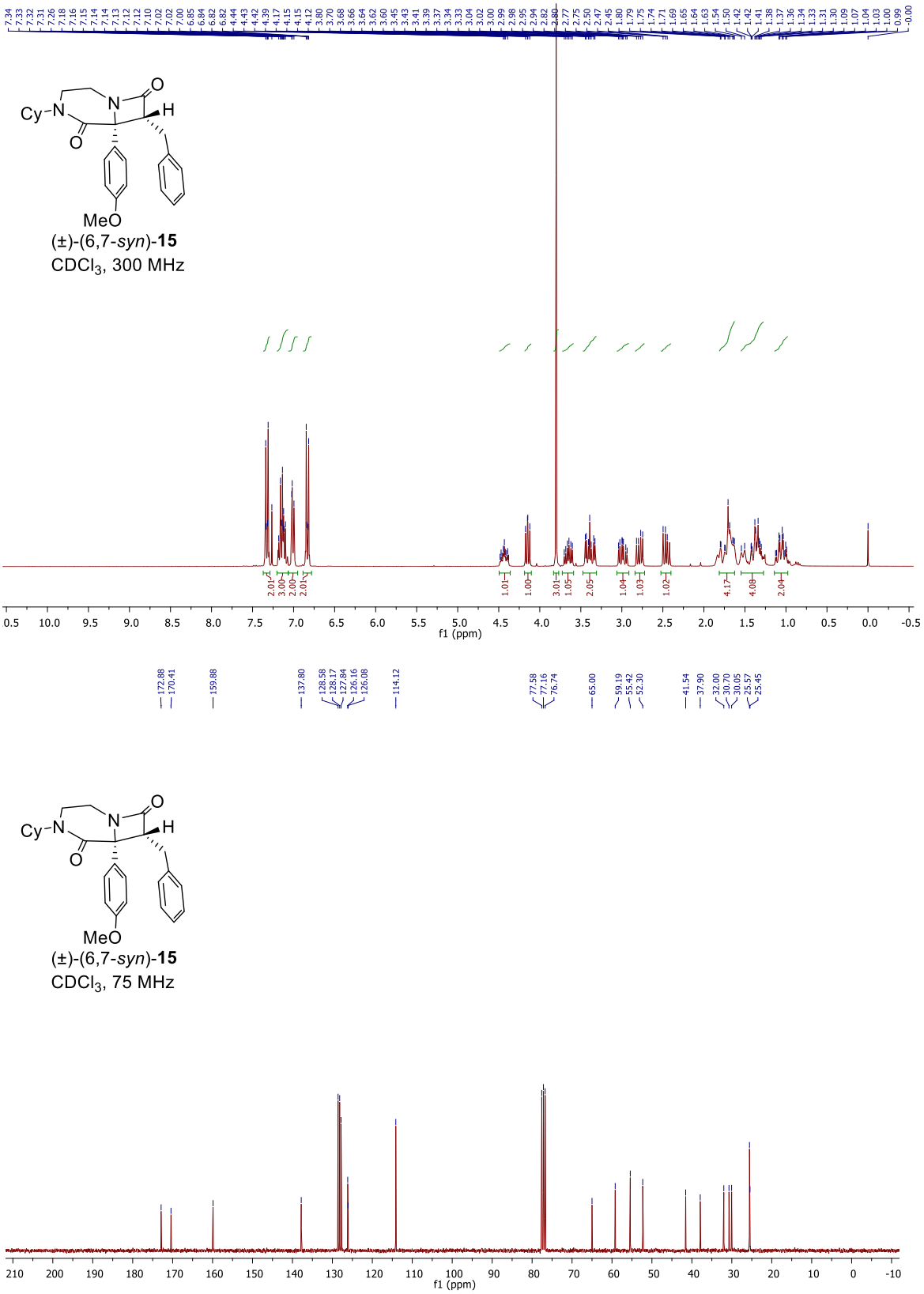


Figure S119: ^{1}H, ^{13}C NMR, DEPT-135 of compound **(±)-(**6,7-*syn***)-15**



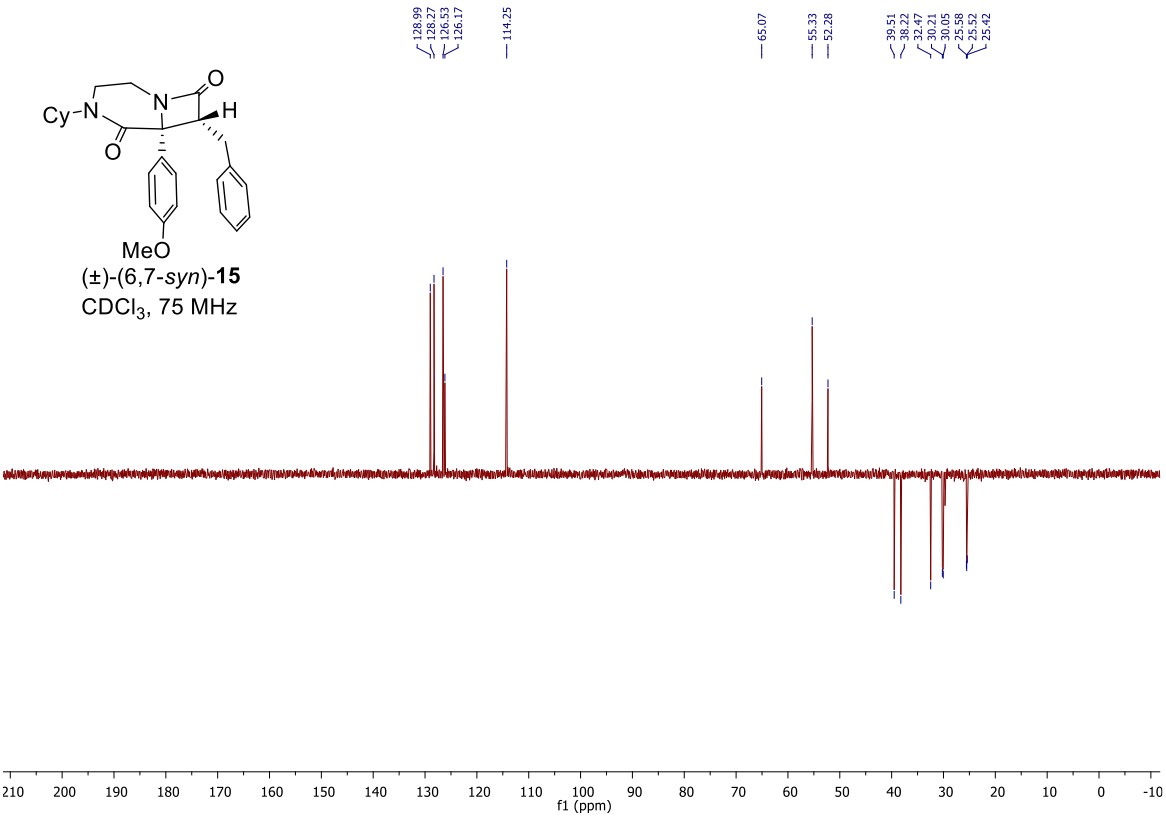
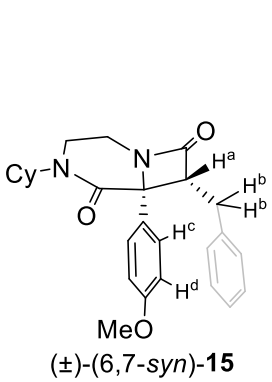

128.99
128.27
126.53
126.17
114.25
65.07
55.33
52.28
39.51
38.22
32.47
30.21
30.05
25.58
25.52
25.42
Cy–N
N
O
O
H
MeO
(±)-(6,7-*syn*)-**15**
$CDCl_3$, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Figure S120: ^{1}H-^{1}H COSY spectrum of compound **(±)-(**6,7-*syn*)**-15**



(±)-(6,7-*syn*)-**15**

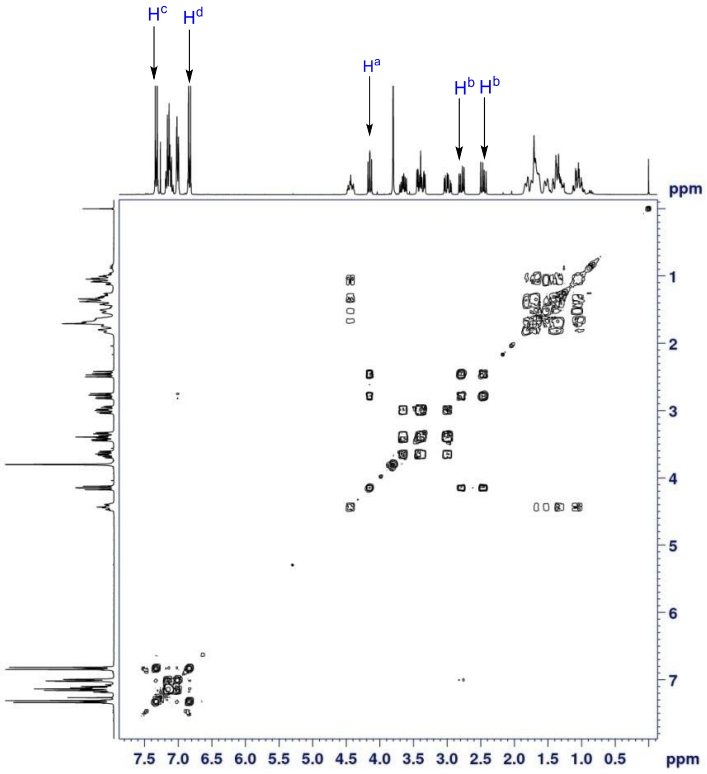


Figure S121: Expansion of ^{1}H-^{1}H COSY spectrum of compound **(±)-(6,7-syn)-15**

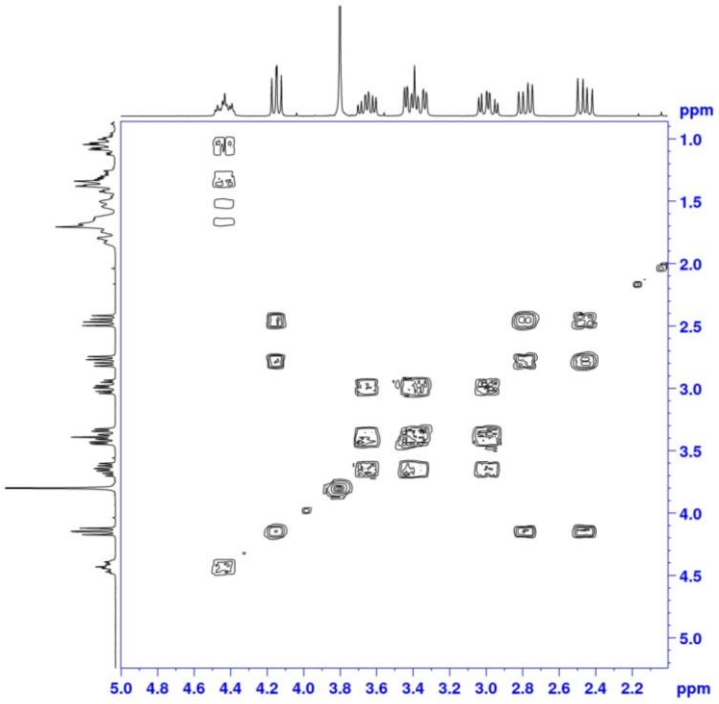
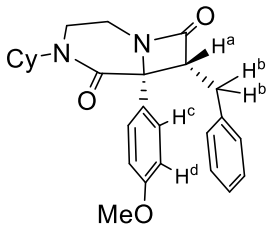


Figure S122: ^{1}H-^{13}C HMQC spectrum of compound **(±)-(6,7-syn)-15**



(±)-(6,7-*syn*)-**15**

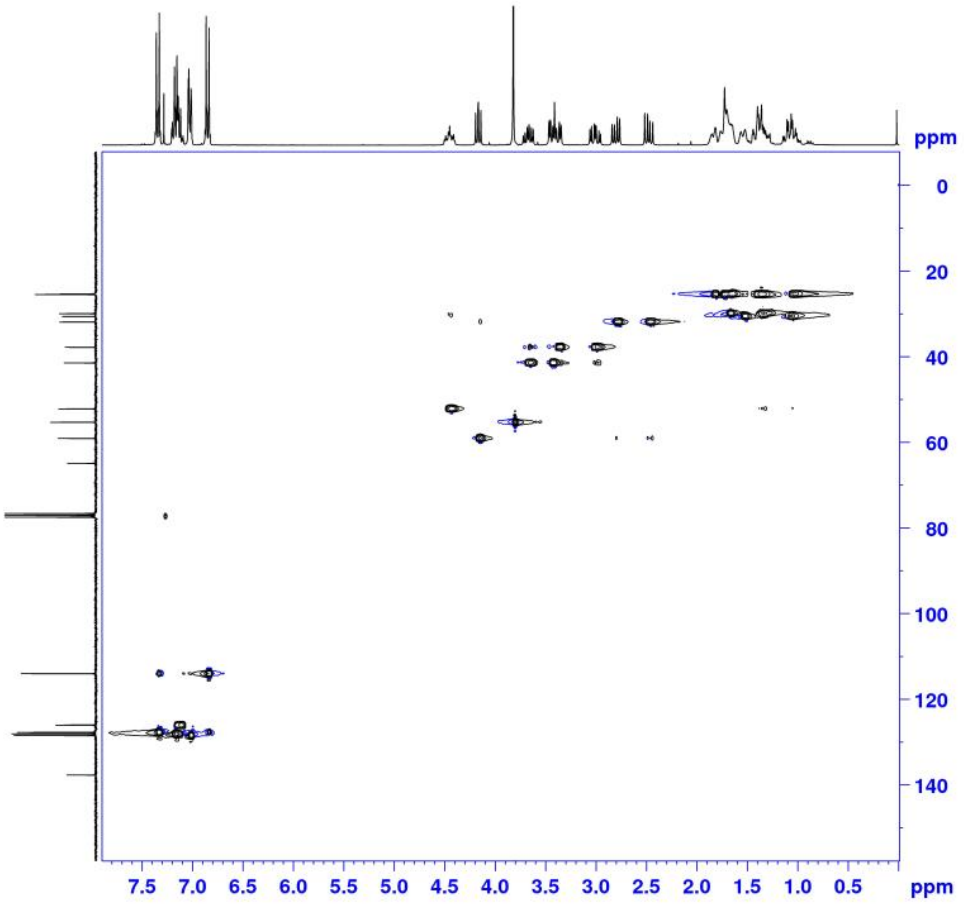


Figure S123: ^{1}H-^{1}H NOESY spectrumof compound **(±)-(6,7-syn)-15**

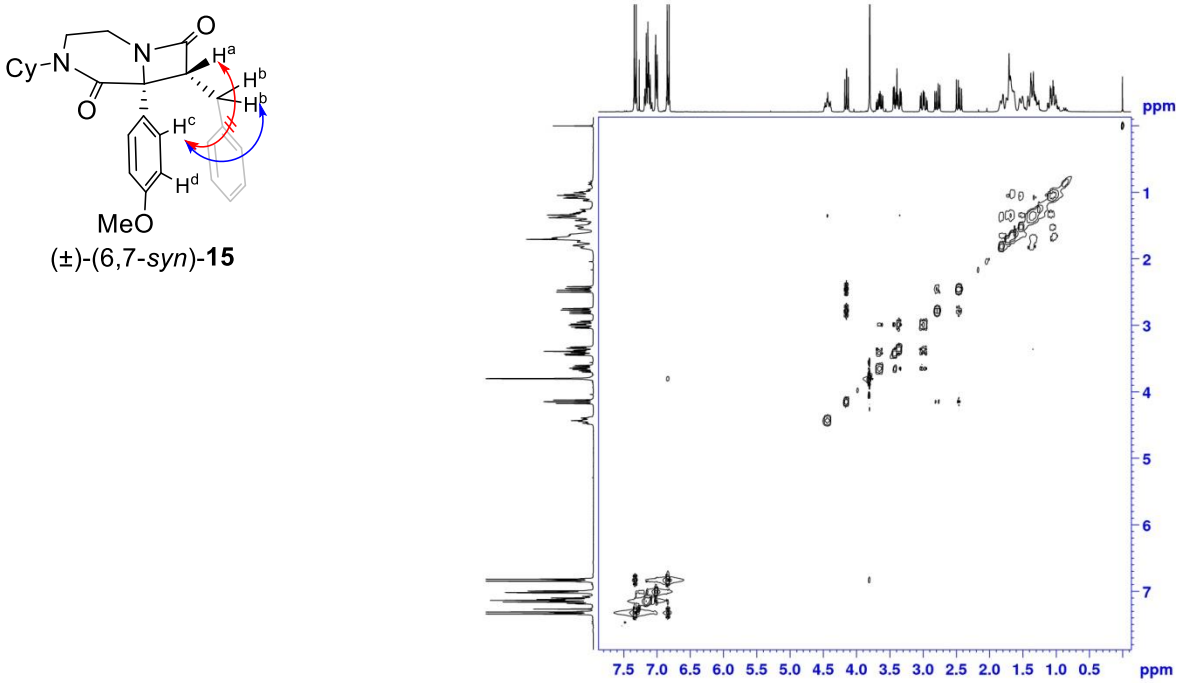


Figure S124: Expansion of NOESY spectrum of compound **(±)-(6,7-syn)-15**

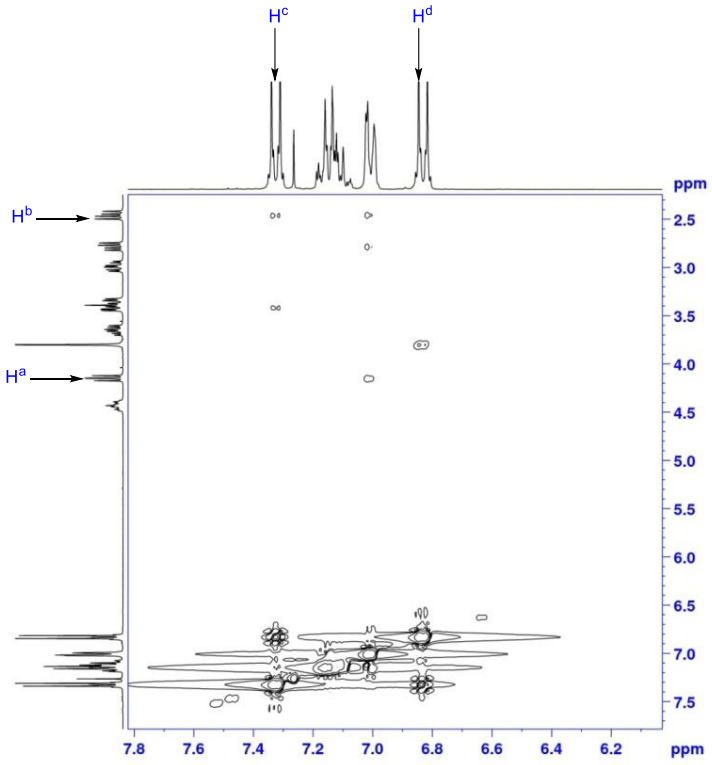
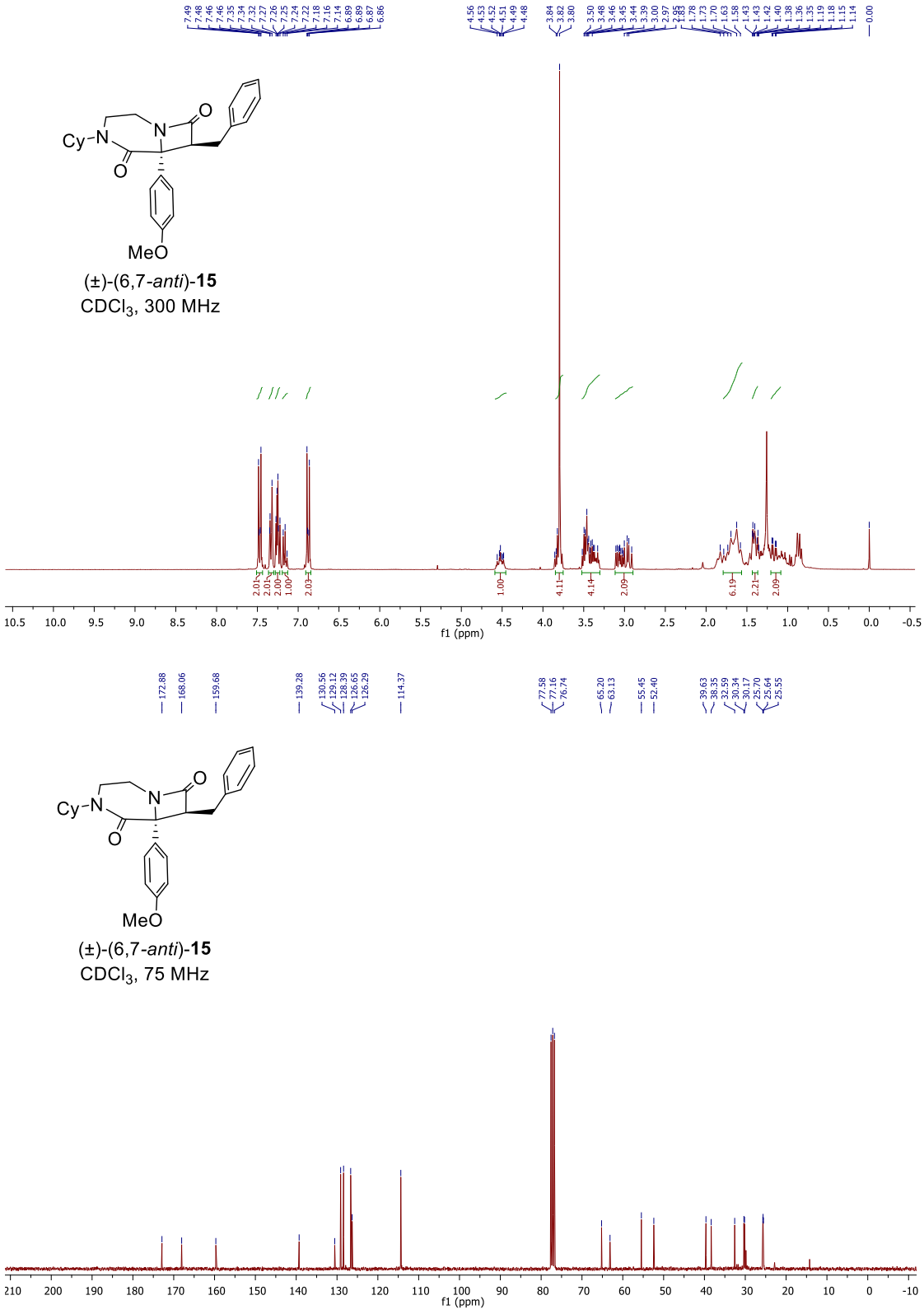


Figure S125: ^{1}H, ^{13}C NMR, DEPT-135 of compound **(±)-(**6,7-*anti***)-15**



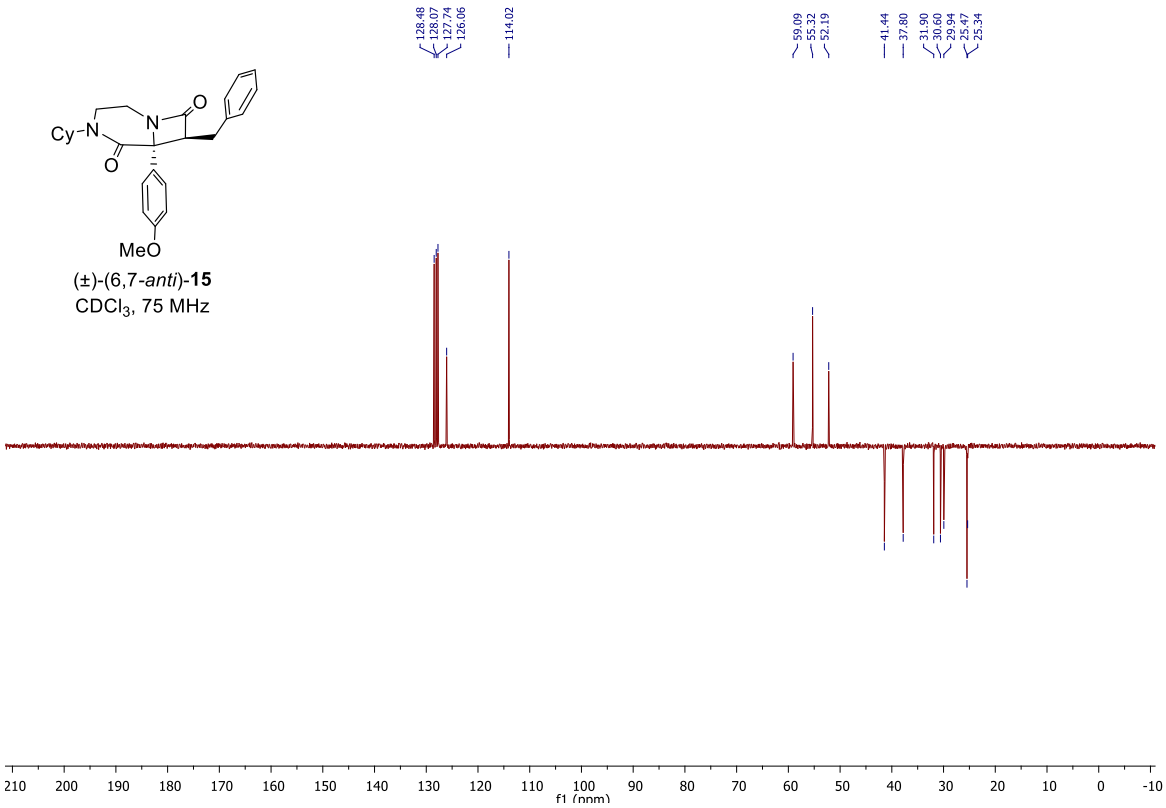
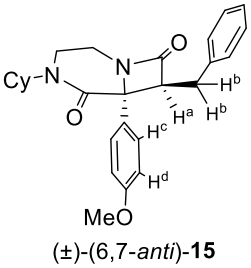

128.48
128.07
127.74
126.06
114.02
59.09
55.32
52.19
41.44
37.80
31.90
30.60
29.94
25.47
25.34
Cy–N
N
O
O
MeO
(±)-(6,7-anti)-15
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Figure S126: ^{1}H-^{1}H COSY spectrum of compound **(±)-(**6,7-*anti*)**-15**



(±)-(6,7-*anti*)-**15**

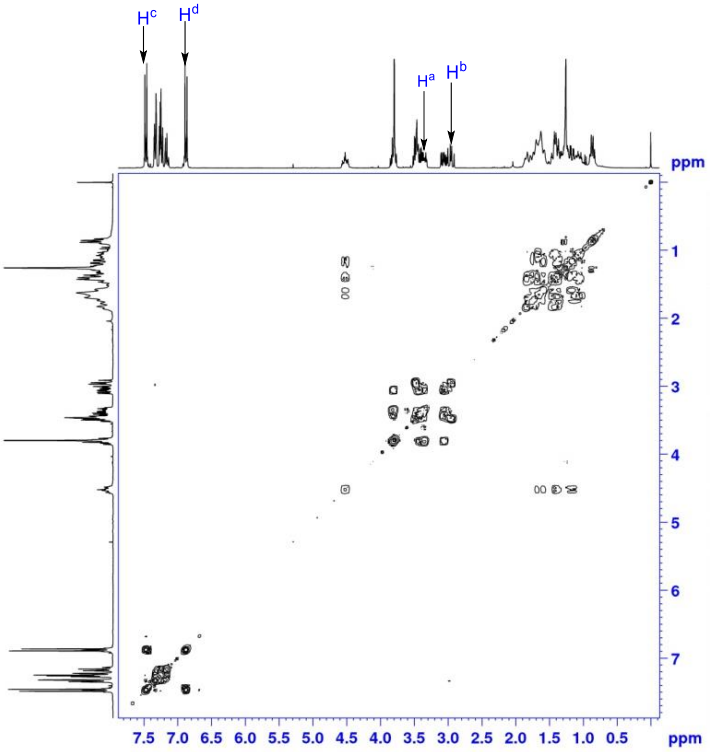


Figure S127: Expansion of COSY spectrum of compound **(±)-(6,7-anti)-15**

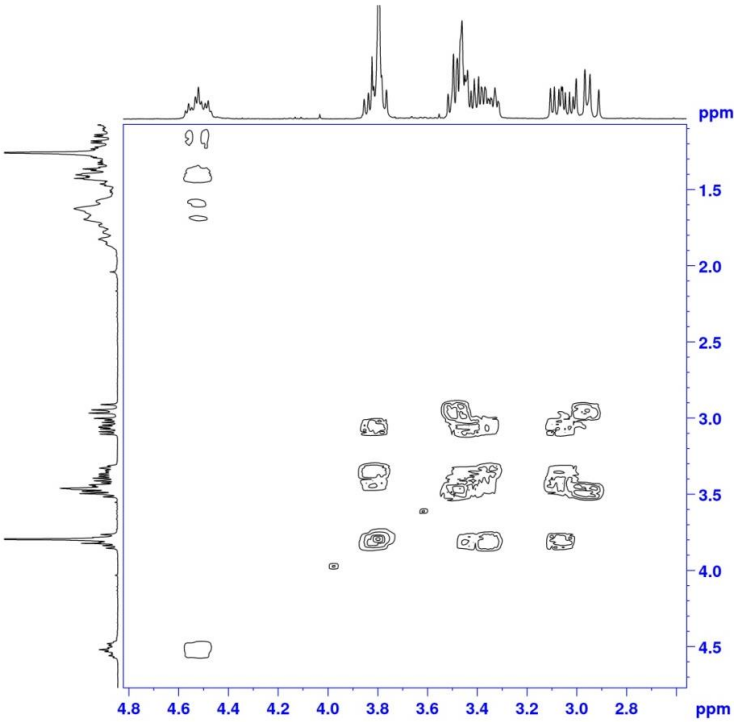


Figure S128: ^{1}H-^{1}H NOESY spectrum of compound **(±)-(**6,7-*anti*)**-15**

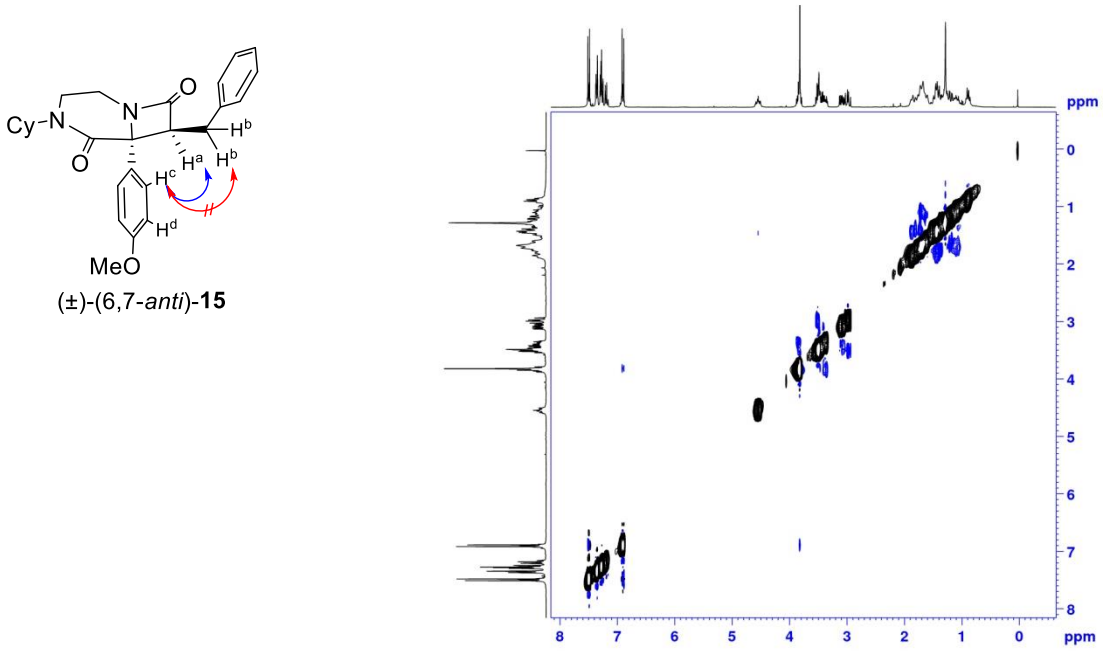


Figure S129: Expansion of NOESY spectrum of compound **(±)-(**6,7-*anti*)**-15**