Supplementary Information

Late-stage C–H amidation of pharmaceuticals enabled by earth-abundant Co(III)-catalysis

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1. General information

General reagent information
Anhydrous solvents were purchased from Sigma Aldrich, sparging with N_2 prior to use. Unless otherwise noted, all commercially available reagents were used as received. $Co_2(CO)_8$, 1,2,3,4-tetramethylcyclopentadiene, $AgSbF_6$, and PivOH were purchased from Strem Chemical Inc. or Sigma Aldrich. Reactions in sealed tubes were run in Biotage microwave vials (2–5 mL) with aluminium caps equipped with septa. Solids were either weighed by hand or – in the optimisation workflow – using a Mettler Toledo Quantos QB5 automated system. Solvents were either added by syringe or – in the optimisation workflow – using a Waters Andrew+ automated system. The dioxazolone reagents were typically stored at –20 °C under N_2 atmosphere; however, no decrease in purity was observed storing dioxazolone **4a** at room temperature under air for >1 year.

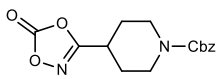
General safety considerations
Stoichiometric CO_2 gas is released as side-product during the reaction. Appropriate safety measure should be taken to mitigate pressure build-up. Keeping a 1:3 reaction volume to headspace ratio is recommended.

General purification information
Flash column chromatography purification on normal phase was performed on Biotage Selekt automated system with pre-packed silica gel columns (5–10 g SiO_2 Sfär HC Duo). Column chromatography purification on reverse phase was performed on Biotage Selekt automated system with pre-packed C18 columns (6-12 g Sfär C18 D – Duo 100 Å 30 µm) eluting with acidic (A: 0.1% HCO_2H in H_2O, B: MeCN) or basic mobile phase (A: 0.1% NH_3 in H_2O, B: MeCN). Purification by preparative reverse phase HPLC was performed on a Kromasil C8 column (10 µm, 250x50 ID mm) with a flow rate of 100 mL/min over 20 or 25 minutes, using acidic mobile phase (A: H_2O/MeCN/HCO_2H 95/5/0.2, B: MeCN), or on a XBridge C18 column (10 µm, 250x50 ID mm) with a flow rate of 100 mL/min over 20 or 25 minutes, using basic mobile phase (A: H_2O/MeCN 95/5, 10 mM NH_4HCO_3, B: MeCN). UV-triggered collection of fractions was performed at 254 nm wavelength. Purification by supercritical fluid chromatography SFC was performed on a BEH column (5 µm, 250x30 ID mm) using basic mobile phase (A: CO_2, B: MeOH/H_2O/NH_3 97/3/0.5), or on a DCPakB column (5 µm, 250x30 ID mm) using basic mobile phase (30% IPA/DEA 100/20mM in CO_2, 120 bar). Collection of fractions was performed at 230 or 254 nm wavelength.

General analytical information
Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution, phosphomolybdic acid solution, or ninhydrin solution in ethanol. Analytical LC-MS was performed on a Waters Acquity UPLC system with a HSS C18 column (1.8 µm, 50 × 2.1 mm) using an acidic mobile phase at pH 3 (A: H_2O, 10 mM HCO_2H, 1 mM NH_3; B: MeCN/H_2O 95/5), or with a BEH C18 column (1.7 µm, 50 × 2.1 mm) using a basic mobile phase at pH 10 (A: H_2O, 5 mM NH_4HCO_3, 50 mM NH_3; B: MeCN/H_2O 95/5). For SFC-MS analysis, a Waters Acquity UPC2 SFC-MS system with a BEH column (3.5 µm 3x100 mm; A: CO_2, B: MeOH/H_2O/NH_3 97/3/0.5), or a DCPakB column (3.0 µm 4.6x150 mm; 35% IPA/DEA 100/20mM in CO2, 120 bar) was used. All new compounds were characterized by NMR spectroscopy and high-resolution mass spectrometry (HRMS). Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{19}F, COSY, HSQC) were recorded on a Bruker Ultrashield 500 MHz spectrometer with a Bruker Cryo Platform. NMR data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet and br = broad]), coupling constant [in Hz] and integration. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) with the residual solvent resonance as internal reference ($CDCl_3$: δ = 7.26 ppm, DMSO-d_6: δ = 2.50 ppm, CD_3OD: δ = 3.31 ppm, CD_3NO_2: δ = 4.33 ppm). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million (ppm) with the solvent resonance as the internal reference ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, $^{13}CD_3OD$: δ = 49.0 ppm and $^{13}CD_3NO_2$: δ = 62.8 ppm). ^{19}F spectra were recorded with complete proton decoupling. HRMS data was recorded on a Waters Acquity UPLC System equipped with Acquity PDA and XEVO-QTOF mass spectrometer, or Agilent TOF LC-MS

with 1290 Infinity II LC System, using electronspray ionisation (ESI) in positive or negative mode. A linear gradient 5-90% (A: H_2O, 10 mM HCO_2H, 1 mM HCO_2NH_4, B: MeCN/H_2O 95/5, 10 mM HCO_2H, 1 mM HCO_2NH_4) was run with a flow of 1 mL/min for 2.5 min at 45 °C on a CSH C8 column (1.7 μm, 50x2.1 ID mm). Relative absorbance was recorded at 230 nm.

2. Dioxazolones and additional structures in SI



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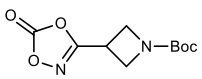

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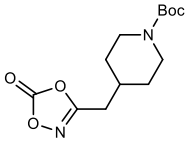

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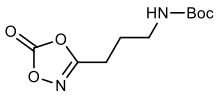

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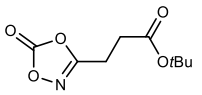

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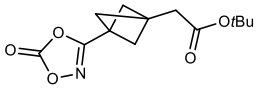

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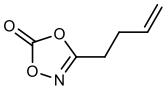

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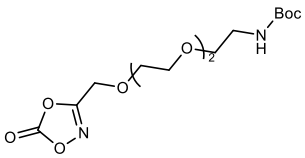

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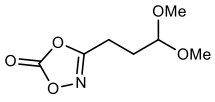

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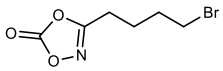

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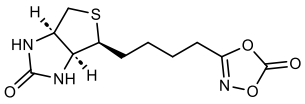

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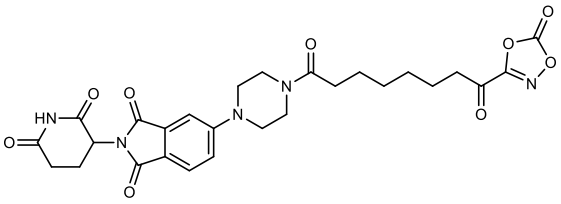

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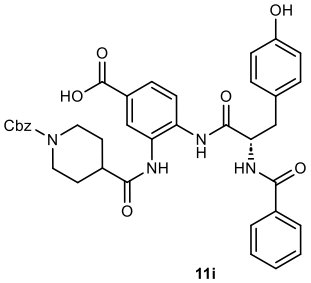

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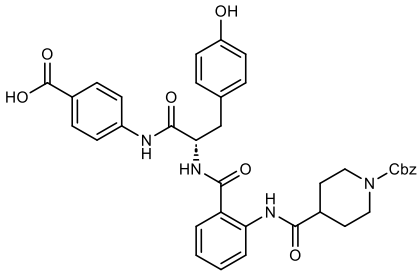

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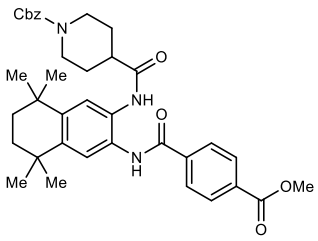

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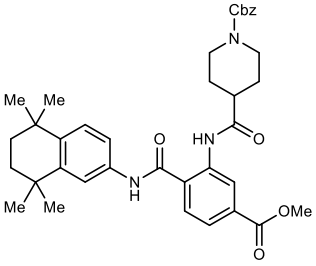

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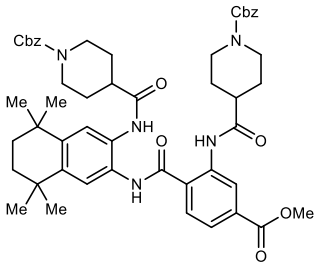


S1

3. Reaction optimisation through High Throughput Experimentation (HTE)

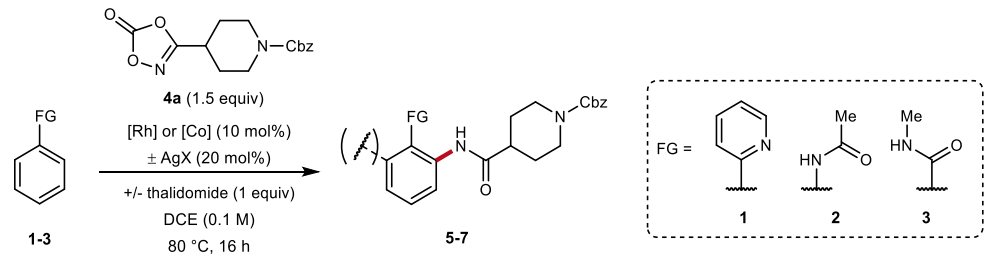
Selected optimisation data for the ruthenium-catalysed C–H amidation is shown below in Figures S1-S5. The reactions were analysed by LC-MS and the data shown is based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram, *i.e.* total conversion to product (mono + bis-functionalisation). For each screen, visualisation of the levels of mono-functionalisation is also provided, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram.

General procedure for reaction optimisation
The reactions were set-up using 96- or 24-wells Paradox plates with 1 mL glass vials equipped with stirrer bars on a 0.025 mmol substrate scale. In a glovebox under nitrogen, the vials were charged with all the solid substrates, additives and catalysts using a Mettler Toledo Quantos QB5 system for automated solid dispensing. Dioxazolone **4a** and any liquid reagent were then added as stock solutions in the required solvents for a total volume of 250 µl (0.1 M) using a Waters Andrew+ instrument for automated liquid dispensing. The plate was sealed with a teflon film, taken out of the glovebox and heated under stirring (600 rpm). After 15-18 hours the reaction mixtures were allowed to cool down, diluted with DMSO (500 µl) and stirred at room temperature for 5 min. A 50 µl aliquot was extracted from each vial, transferred to a 96-well Greiner_V plastic plate and diluted with further DMSO (50 µl). The solids were centrifuged with Eppendorf Centrifuge 5810 R (room temperature, atmospheric pressure, 3000 rpm, 15 min). A 25 µl aliquote was extracted from each well and transferred to a fresh 96-well Greiner_V plastic plate. The wells were finally diluted with further DMSO (75 µl) and analysed by LC-MS [Waters Acquity UPLC system, BEH C18 column (A: H_2O/MeCN/NH_3 = 95/5/0.2, B: MeCN)].

Identification of optimisation substrates
Throughout the optimisation process, compounds **5-8** were identified by comparison with the relevant LC-MS traces generated in our previous study.[1]

3.1 Catalyst, silver(I) salt and directing group screen

Cobalt and rhodium catalysts were evaluated in the C–H amidation of substrates **1-3** with dioxazolone **4a** (Figure S1). Unless otherwise noted, Ag(I) salts were added as halide scavengers to generate in situ the active cationic Co- or Rh-complexes. Where applicable, thalidomide was added as robustness probe. $Cp^*Co(MeCN)_3(SbF_6)_2$ proved superior to all other cobalt catalysts tested (row E). This provided 85-97% conversion for substrates **1** and **2** (with higher degree of mono-selectivity for 2-phenyl pyridine **1**), while lower reactivity was observed against benzamide **3** (columns 5, 6). On the other hand, rhodium-based catalysts performed well against the full substrate set, although benzanilide **3** was amidated with lower level of mono-selectivity (~7:3 mono:di, rows G, H). In both cases, addition of thalidomide did not have any detrimental effects.



Substrate		Catalyst		AgX		Thalidomide	
Columns		Rows		Rows		Columns	
1-2	1	**A**	$Cp^*Co(CO)I_2$	**A**	-	**1**	-
3-4	2	**B**	$Cp^*Co(CO)I_2$	**B**	$AgSbF_6$	**2**	+
5-6	3	**C**	$Cp^*Co(CO)I_2$	**C**	$AgNTf_2$	**3**	-
		D	$Cp^*Co(MeCN)_3(PF_6)_2$	**D**	-	**4**	+
		E	$Cp^*Co(MeCN)_3(SbF_6)_2$	**E**	-	**5**	-
		F	$Cp^*Co(PhH)(PF_6)_2$	**F**	-	**6**	+
		G	$[Cp^*RhCl_2]_2$ [a]	**G**	$AgSbF_6$		
		H	$[Cp^*RhCl_2]_2$ [a]	**H**	$AgNTf_2$		
		[a] 5 mol% pre-catalyst.					

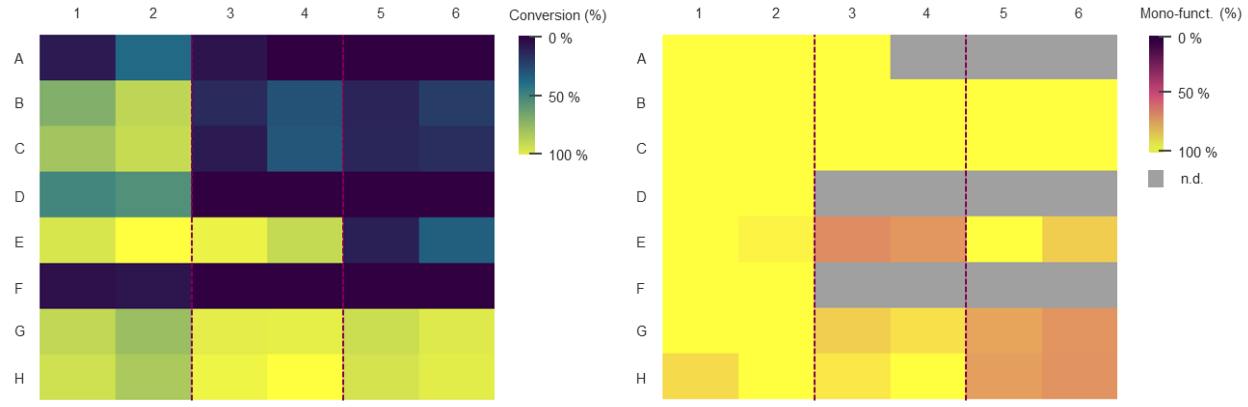
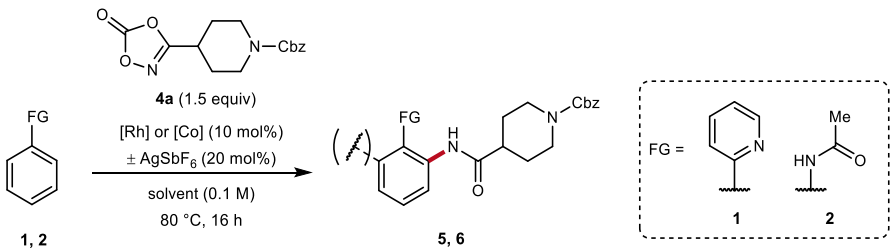


Figure S1. Evaluation of cobalt and rhodium catalysts against substrates **1-3**. Left: Heat map for conversion (%) determined by LC-MS, based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram. Right: Heat map for mono-functionalisation (%) determined by LC-MS, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram. n. d. = Not determined due to low conversion (< 10%).

3.2 Solvent screen

Different solvents were evaluated in the cobalt- and rhodium-catalysed C–H amidation of substrates **1-2** with dioxazolone **4a** (Figure S2). Unless otherwise noted, Ag(I) salts were added as halide scavengers to generate in situ the active cationic Co- or Rh-complexes. The rhodium-catalysed C–H amidation of 2-phenyl pyridine **1** showed broad tolerance to different solvents (rows C, D), while higher solvent dependence was observed for anilide **2** (rows G, H). DME and DCE were the best solvents for the C–H amidation of **1** when using $Cp^*Co(MeCN)_3(SbF_6)_2$ (wells B2, B10), while TFT led to 62% conversion of **2** (well F5). Interestingly, EtOAc (column 4) was identified as an attractive greener alternative providing 65% to 42% conversion under cobalt catalysis, and 100% to 60% conversion under rhodium catalysis for **1** and **2** respectively (wells B4, F4, D4, H4).



Substrate		Catalyst		AgSbF$_6$		Solvent	
Rows		Rows		Rows		Columns	
A-D	1	**A, E**	Cp*Co(CO)I$_2$	**A, E**	+	**1**	2-MeTHF
E-H	2	**B, F**	Cp*Co(MeCN)$_3$(SbF$_6$)$_2$	**B, F**	-	**2**	DME
		C, G	[Cp*RhCl$_2$]$_2$ [a]	**C, G**	+	**3**	CPME
		D, H	Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$	**D, H**	-	**4**	EtOAc
			[a] 5 mol% pre-catalyst.			**5**	TFT
						6	toluene
						7	DMSO
						8	DMAc
						9	t-AmylOH
						10	DCE
						11	HFIP
						12	TFE

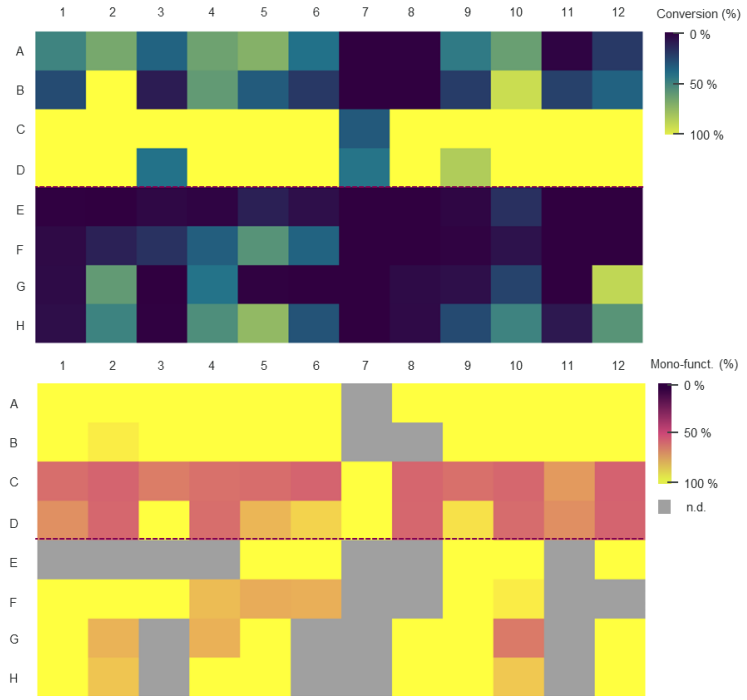
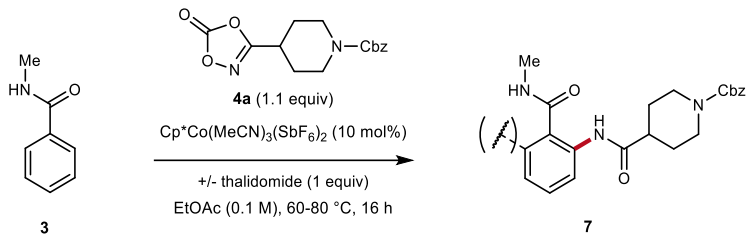


Figure S2. Evaluation of cobalt and rhodium catalysts in different solvents against substrates **1-2**. Left: Heat map for conversion (%) determined by LC-MS, based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram. Right: Heat map for mono-functionalisation (%) determined by LC-MS, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram. n. d. = Not determined due to low conversion (< 10%). TFT = trifluorotoluene.

3.3 Catalyst loading and temperature evaluation

As the most challenging substrate in the Co-catalysed C–H amidation (*cf* Figure S1), benzamide **3** was reacted with dioxazolone **4a** using increasing amounts of cobalt catalyst at both 60 °C and 80 °C (Figure S3). While 5 mol% of catalyst did not provide satisfactory conversion (column 1), no significant improvement in reaction performance was found increasing the catalyst loading above 10 mol%. Interestingly, when using 10 mol% catalyst loading, the reaction temperature could be lowered to 60 °C without any reduction in conversion. Again, addition of thalidomide as robustness probe did not have any detrimental effects.



Thalidomide		Catalyst loading	
Rows		Columns	
A	-	**1**	5 mol%
B	+	**2**	10 mol%
		3	20 mol%
		4	50 mol%
		5	100 mol%

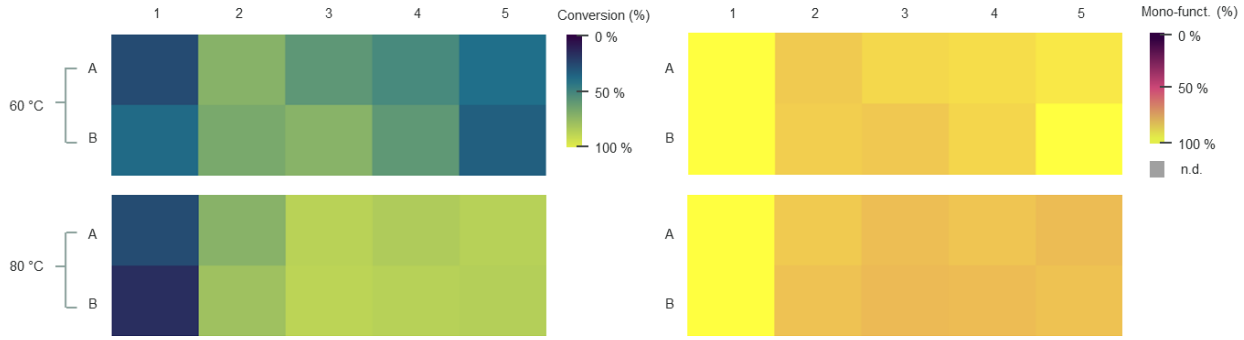
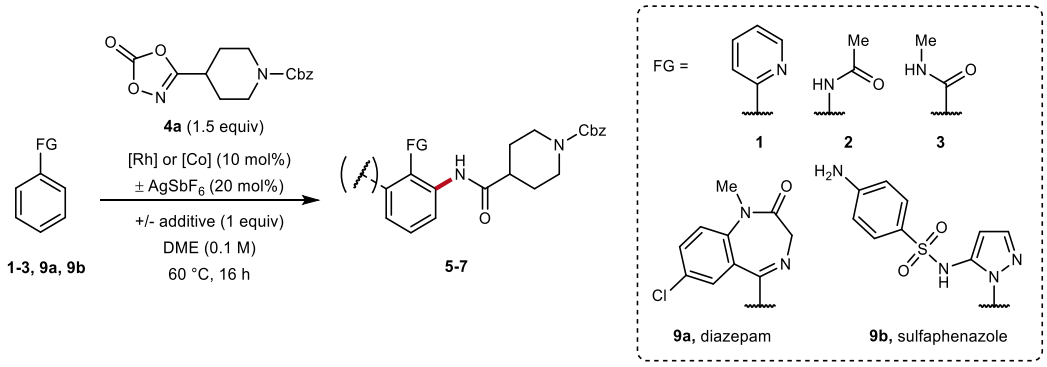
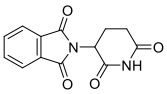
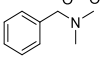
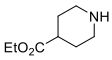
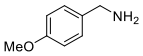
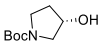
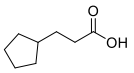


Figure S3. Evaluation of cobalt catalyst loading for the C–H amidation of benzamide **3**. Left: Heat map for conversion (%) determined by LC-MS, based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram. Right: Heat map for mono-functionalisation (%) determined by LC-MS, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram. n. d. = Not determined due to low conversion (< 10%).

3.4 Compatibility screen

To assess the tolerance of the reaction to different polar functionalities that are often found in complex biologically active molecules, the reaction of substrates **1-3**, **9a** and **9b** with dioxazolone **4a** was evaluated in the presence of different additives (Figure S4). Overall, substrates bearing more Lewis basic directing groups such as **1**, **9a** and **9b** were tolerant to a broader range of additives, compared to the weaker directing groups in **2** and **3**.[2] The reaction was generally not compatible with 1°, 2° (and to a lower extent 3°) nucleophilic amines which are known to react with the dioxazolone coupling partner (rows C–E).[3] Unprotected alcohols were better tolerated under rhodium catalysis (row F), while the cyclic sulphide used in row H was exclusively tolerated when using cobalt catalysis. Interestingly, in the presence of an aliphatic carboxylic acid, improved conversion of **1** and **2** was observed for the Co-catalysed C–H amidation suggesting a beneficial effect of such acidic additives (row G, *vide infra*).



Substrate		Catalyst		$AgSbF_6$		Additive	
Columns		Columns		Columns		Rows	
1, 6	1	**1-5**	$Cp^*Co(MeCN)_3(SbF_6)_2$	**1-5**	-	**A**	none
2, 7	2	**6-10**	$[Cp^*RhCl_2]_2$ [a]	**6-10**	+	**B**	
3, 8	3		[a] 5 mol% pre-catalyst.			**C**	
4, 9	9a					**D**	
5, 10	9b					**E**	
						F	
						G	
						H	

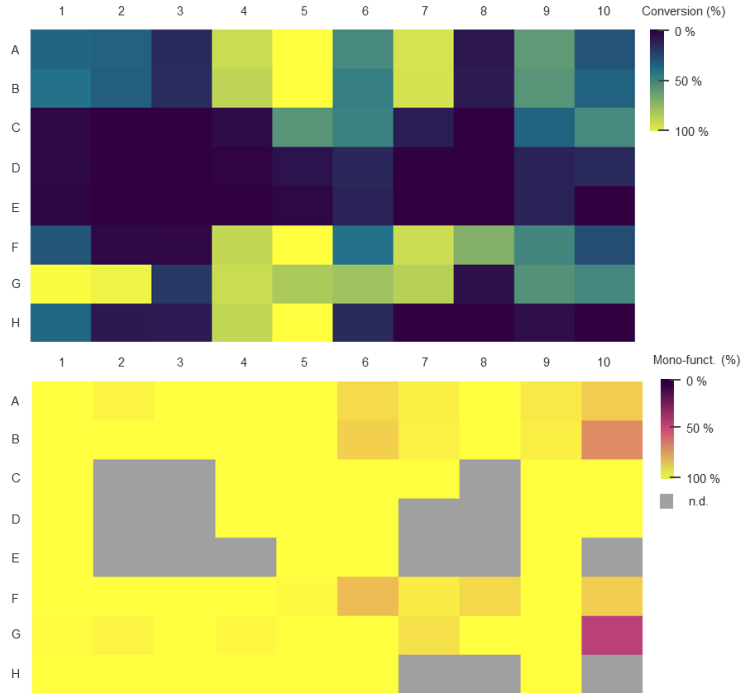
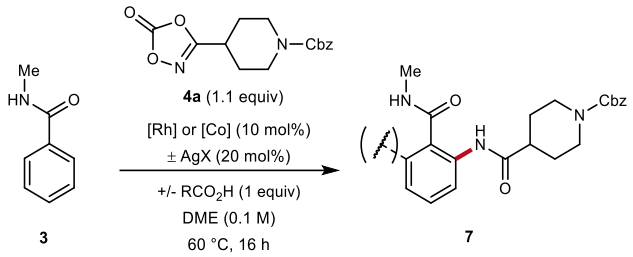


Figure S4. Functional group compatibility of cobalt- and rhodium-catalysed C–H amidation. Left: Heat map for conversion (%) determined by LC-MS, based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram. Right: Heat map for mono-functionalisation (%) determined by LC-MS, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram. n. d. = Not determined due to low conversion (< 10%).

3.5 Additive screen

As the most challenging substrate in the Co-catalysed C–H amidation (*cf* Figure S1), benzamide **3** was reacted with dioxazolone **4a** in the presence of different additives to increase conversion (Figure S5). Catalytic amounts of bulky carboxylic acids such as $MesCO_2H$ and PivOH significantly improved conversion in the cobalt-catalysed C–H amidation of **3** (wells B1, C1), versus the control conditions (well H1). On the other hand, the addition carboxylate salt PivOK completely shut down catalysis (row D). Increasing the additive loading to 1.0 or 2.0 equiv did not improve efficiency further. In contrast to cobalt, when using $[Cp^*RhCl_2]_2/AgSbF_6$, additive addition did not affect conversion while reduced mono-selectivity (wells C4, H4).



Catalyst		$AgSbF_6$		Additive		Add. equiv	
Columns		Columns		Rows		Columns	
1-3	$Cp^*Co(MeCN)_3(SbF_6)_2$	**1-3**	-	**A**	$PhCO_2H$	**1,4**	0.5
4-6	$[Cp^*RhCl_2]_2$ [a]	**4-6**	+	**B**	$MesCO_2H$	**2,5**	1.0
	[a] 5 mol% pre-catalyst.			**C**	PivOH	**3,6**	2.0
				D	PivOK		
				E	N-Ac-Gly-OH		
				F	CSA		
				G	$(PhO)_2PO_2H$		
				H	-		

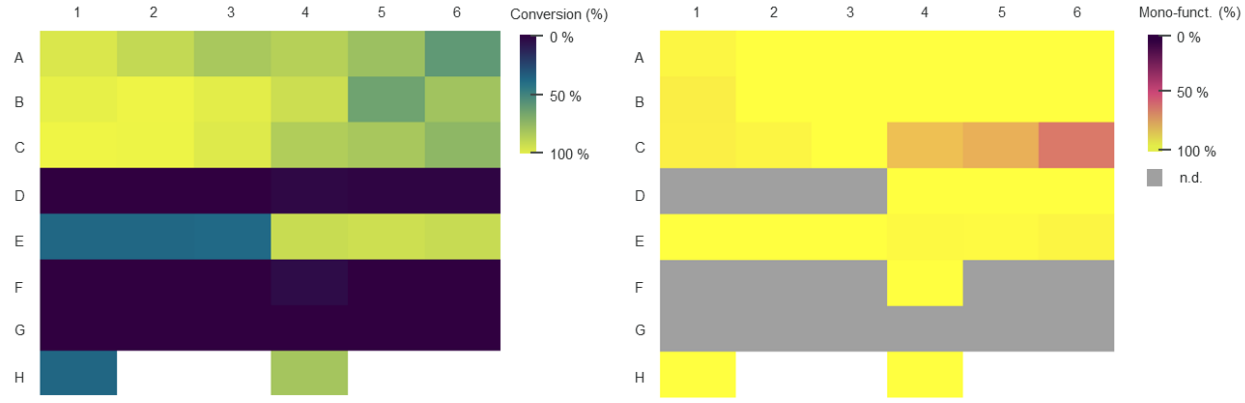
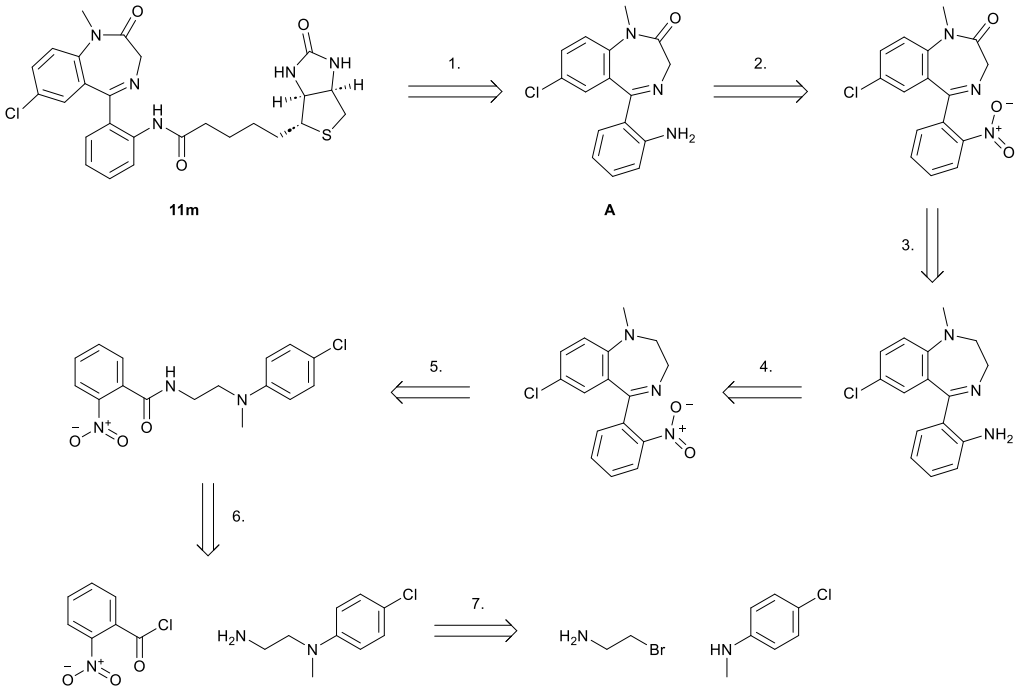


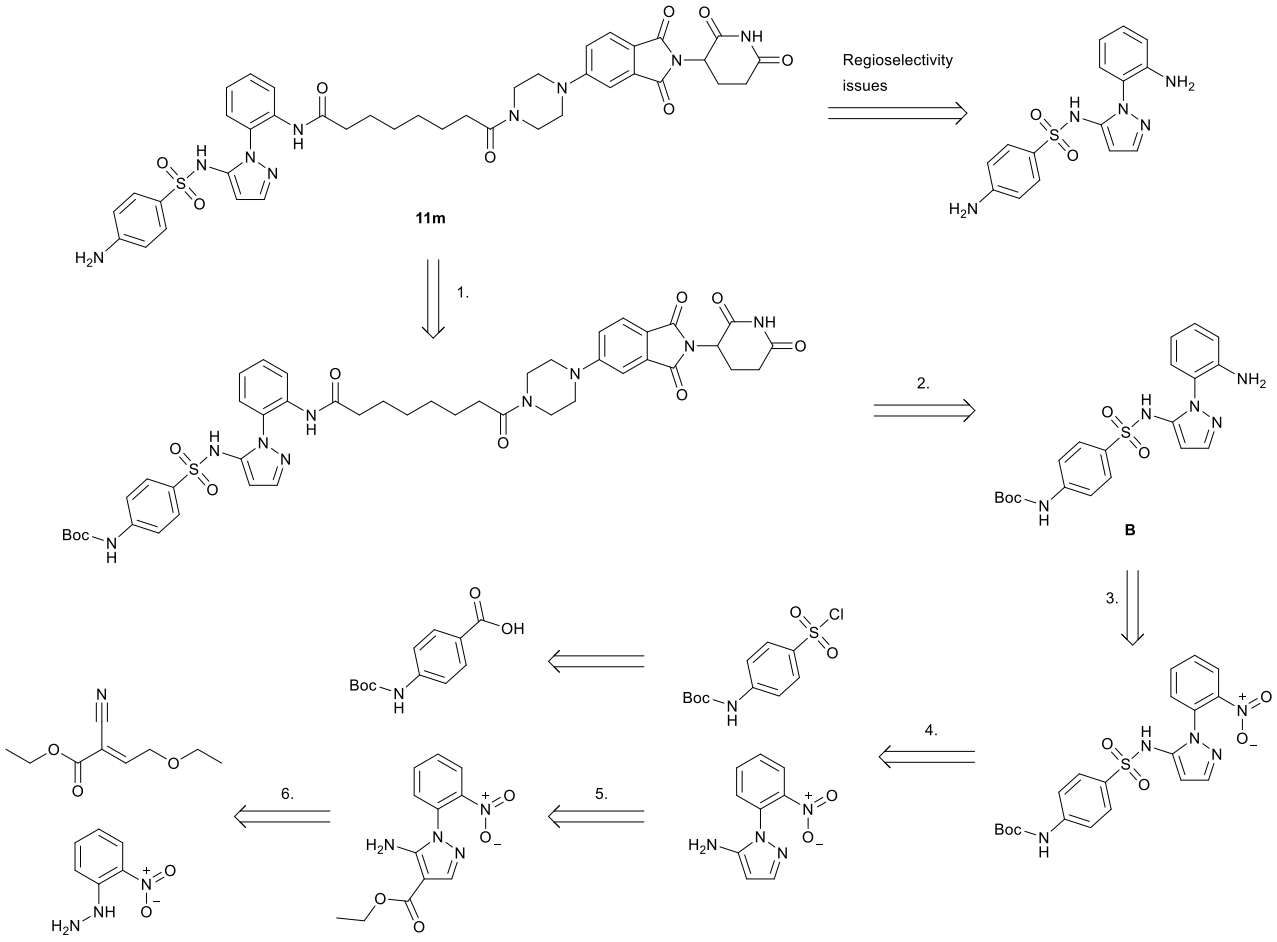
Figure S5. Evaluation of acidic additives for the C–H amidation of benzamide **3** with cobalt and rhodium catalysts. Left: Heat map for conversion (%) determined by LC-MS, based on the relative intensities of the product peak(s) *versus* substrate peak in the UV chromatogram. Right: Heat map for mono-functionalisation (%) determined by LC-MS, based on the relative intensity of the mono-functionalised product peak *versus* bis-functionalisation peak in the UV chromatogram. n. d. = Not determined due to low conversion (< 10%). $MesCO_2H$ = 2,4,6-trimethylbenzoic acid. CSA = camphorsulfonic acid.

4. Proposed *de Novo* syntheses for PMI predictions (*cf* Scheme 3)

Diazepam derivative **11m**: No known synthetic route. Proposed *de novo* route based on the reported synthesis of diazepam and 5-(2-aminophenyl)-7-chloro-1-methyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one intermediate **A**.[4,5]

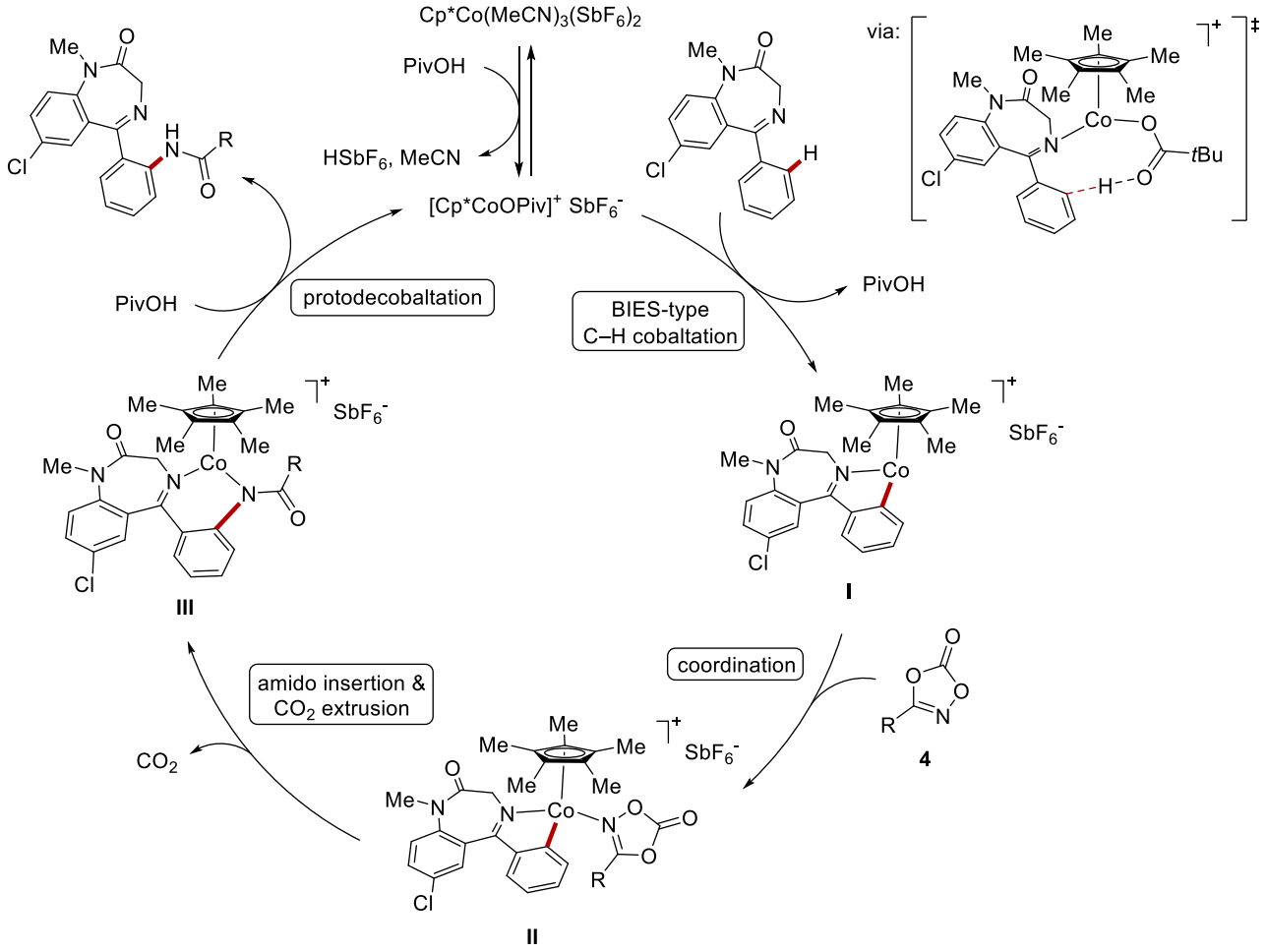


Sulfaphenazole derivative **11n**: No known synthetic route of either **11n** or key intermediate **B**. Proposed route based on reported synthesis of sulfaphenazole and ethyl 5-amino-1-(2-nitrophenyl)-1*H*-pyrazole-4-carboxylate synthesis.[6,7]



6. Proposed catalytic cycle

The catalytic cycle below was proposed based on DFT calculations for the key C–H activation elementary step (*vide infra*), and previous studies on Co-catalysed C–H amidation.[8,9] This plausibly proceeds via an initial pivalate-assisted C–H activation to form cobaltacycle **I**, followed by dioxazolone coordination and CO_2 extrusion leading to amido-inserted species **II**. Final protodecobaltation by PivOH regenerates the active cobalt(III) species and forms the desired amidated product.



7. Computational studies

Calculations were performed using the Gaussian 16, Revision A.03 package.[10] All structures were optimized at the TPSS[11] level of theory in combination with Grimme's D3 dispersion corrections with the Becke-Johnson[12,13] damping scheme in combination with a def2-SVP[14,15] basis set. Analytical frequency calculations were carried out at the same level of theory to identify the stationary points either as intermediates (no imaginary frequencies) or transition states (only one imaginary frequency), as well as to provide thermal and non-thermal corrections to the free energy at 60 °C and 1 atm. The electronic energy was then refined through ωB97X-D[16] single-point calculations on the optimized geometries using the def2-TZVPP[14,15] basis set. Solvent effects were included in both optimization and single-point calculations using the implicit solvation model SMD.[17] In the latter parameters for EtOAc, the experimental solvent of choice, were included as implemented in Gaussian 16. Unless otherwise stated, the energies herein provided are based on Gibbs free energies with the def2-SVP basis set for which the electronic energies were improved at the ωB97X-D/def2-TZVPP level of theory.

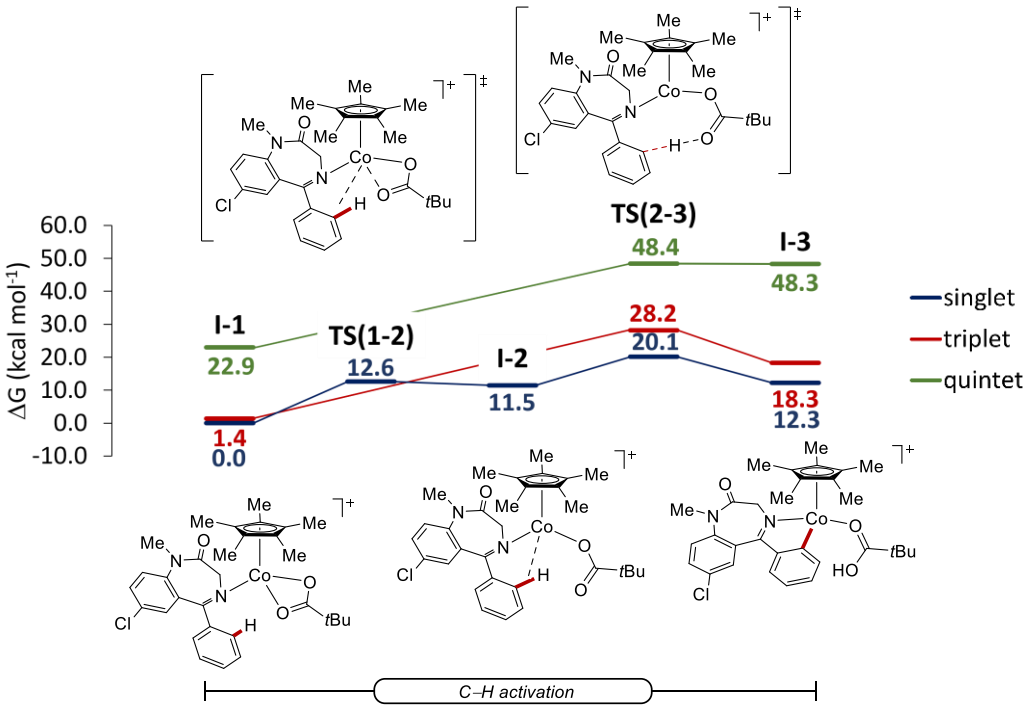


Figure S6. Computed relative Gibbs free energies (Δ*G*) in kcal mol^{-1} at ωB97X-D/def2-TZVPP+SMD(EtOAc)//TPSS-D3(BJ)/def2-SVP level of theory for the C–H activation elementary step.

Table S1. Calculated electronic energies at the ωB97X-D/def2-TZVPP+SMD(EtOAc) level of theory and Gibbs free energies for all structures in the present study (all in Hartree).[a]

Structure	Electronic energy	Total Gibbs Free Energy
I-1^1	-3381.875218	-3381.259618
I-1^3	-3381.870286	-3381.349229
I-1^5	-3381.846768	-3381.314918
TS(1-2)^1	-3381.857900	-3381.331411
I-2^1	-3381.859382	-3381.333202
TS(2-3)^1	-3381.841741	-3381.319430
TS(2-3)^3	-3381.823548	-3381.306525
TS(2-3)^5	-3381.800587	-3381.274338
I-3^1	-3381.858500	-3381.331947
I-3^3	-3381.842403	-3381.322283
I-3^5	-3381.804165	-3381.274515

[a] Superscripts correspond to the respective spin state pathway.

Cartesian coordinates of the optimized structures

I-1^1
Lowest frequency = 2.3633 cm^{-1}
Charge = 1, Multiplicity = 1

75

Co	-1.696366	0.216324	-0.295680
C	-1.622109	1.570362	-1.861395
C	-2.755677	1.798288	-1.010134
C	-1.699706	0.216402	-2.373604
C	-3.556460	0.580953	-0.998202
C	-2.899804	-0.380927	-1.845359
C	-0.571544	2.561800	-2.251060
H	0.436934	2.118265	-2.206281
H	-0.592894	3.453350	-1.610803
H	-0.748431	2.873464	-3.297342
C	-3.041004	3.039848	-0.228525
H	-2.110808	3.568216	0.034105
H	-3.676486	3.719026	-0.827700
H	-3.580557	2.802476	0.701528
C	-0.819218	-0.353718	-3.438987
H	0.179819	0.103871	-3.428658
H	-1.274981	-0.143455	-4.425765
H	-0.701879	-1.443223	-3.346953
C	-4.834982	0.372602	-0.248521
H	-4.982166	-0.689687	0.003276
H	-5.692194	0.692054	-0.869916
H	-4.852511	0.958332	0.683119
C	-3.350618	-1.786498	-2.082131
H	-2.524329	-2.413943	-2.448149
H	-4.154494	-1.795004	-2.841431
H	-3.747071	-2.236858	-1.158524
O	-2.295822	0.471740	1.600341
C	-2.292462	-0.799320	1.773609
O	-1.996814	-1.487736	0.733541
C	-2.551611	-1.432661	3.126146
C	-1.183223	-1.443473	3.862576
H	-0.434487	-2.026262	3.298872
H	-1.307682	-1.907508	4.855591
H	-0.803525	-0.417384	4.005258
C	-3.567448	-0.575083	3.908580
H	-3.714162	-1.002740	4.914470
H	-4.545505	-0.555456	3.397570
H	-3.211499	0.462277	4.015098
C	-3.064889	-2.873525	2.936949
H	-4.028497	-2.883988	2.399171
H	-3.217151	-3.342806	3.923315
H	-2.344708	-3.481993	2.366463
C	1.227904	-1.311401	-1.106338
C	2.166812	-1.354886	-2.163390
C	0.325113	-2.382238	-0.941869
C	2.176349	-2.429220	-3.058700
H	2.881411	-0.534704	-2.286228
C	0.357107	-3.467277	-1.827283
H	-0.379001	-2.375775	-0.107963
C	1.272781	-3.490708	-2.890756
H	2.896226	-2.444649	-3.882770
H	-0.330384	-4.305957	-1.676959
H	1.293108	-4.340915	-3.579962
C	1.270018	-0.178193	-0.150296
C	2.618345	0.219611	0.320032
C	3.044801	1.574163	0.463798
C	0.369308	1.443820	1.328203
C	0.883959	2.731509	0.697965
H	1.083686	1.077797	2.089177
H	-0.592428	1.659596	1.802192
N	0.180277	0.414245	0.286134
O	0.198841	3.742352	0.597033
C	2.744309	3.914862	-0.340951
H	3.213784	4.533143	0.443931
H	3.486722	3.664270	-1.112546
H	1.911710	4.486301	-0.772962
C	4.390139	1.830247	0.810423
C	3.546708	-0.820615	0.568953
N	2.186513	2.669920	0.213309
C	4.859260	-0.537787	0.942589
C	5.291800	0.795760	1.051017
H	4.732181	2.862515	0.912130
H	3.227308	-1.860071	0.466624

H	6.324868	1.014041	1.333521
Cl	5.968296	-1.840208	1.260906

I-1[3]
Lowest frequency = 12.5219 cm^{-1}
Charge = 1, Multiplicity = 3

75			
Co	1.509339	0.001451	-0.354406
C	1.446103	-0.937677	-2.310299
C	2.547071	-1.497222	-1.563056
C	1.680151	0.481671	-2.520594
C	3.389870	-0.403557	-1.196079
C	2.845860	0.828684	-1.790711
C	0.325631	-1.702048	-2.942559
H	-0.640587	-1.185520	-2.813818
H	0.244530	-2.718575	-2.534340
H	0.511813	-1.775693	-4.030759
C	2.730165	-2.934241	-1.183638
H	1.762237	-3.436016	-1.024429
H	3.271537	-3.474104	-1.983000
H	3.315362	-3.020816	-0.255317
C	0.863631	1.358521	-3.415743
H	-0.208294	1.114013	-3.361035
H	1.182505	1.210824	-4.465202
H	0.987019	2.423708	-3.172603
C	4.673350	-0.476193	-0.432859
H	4.819107	0.420685	0.189811
H	5.520564	-0.528807	-1.142691
H	4.710179	-1.366568	0.211529
C	3.478708	2.178545	-1.661373
H	2.830751	2.967088	-2.072894
H	4.441590	2.205629	-2.203638
H	3.682475	2.409424	-0.601809
O	2.246228	-1.109126	1.478994
C	2.499037	0.044210	1.923354
O	2.259058	1.047644	1.135487
C	3.018251	0.298922	3.332342
C	1.771549	0.647855	4.190063
H	1.270473	1.554146	3.809331
H	2.083924	0.834749	5.231622
H	1.047650	-0.185465	4.191390
C	3.695882	-0.974227	3.872042
H	4.028084	-0.805705	4.910341
H	4.579603	-1.239780	3.266793
H	3.002065	-1.829941	3.857397
C	3.998951	1.489673	3.324596
H	4.892585	1.263799	2.716842
H	4.333333	1.701161	4.354336
H	3.520493	2.394625	2.916712
C	-1.208219	1.562420	-0.629665
C	-2.137202	2.048091	-1.578211
C	-0.123269	2.379687	-0.239678
C	-1.968145	3.317558	-2.139590
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C	0.033983	3.654909	-0.800844
H	0.545629	2.056073	0.564064
C	-0.883815	4.123801	-1.751084
H	-2.685665	3.684328	-2.879964
H	0.861132	4.291271	-0.471301
H	-0.766673	5.123845	-2.180500
C	-1.376508	0.221658	-0.029867
C	-2.737674	-0.216026	0.332456
C	-3.222957	-1.541895	0.119301
C	-0.507279	-1.798943	0.888914
C	-1.113141	-2.810720	-0.079265
H	-1.175563	-1.653614	1.758556
H	0.462961	-2.175306	1.226167
N	-0.310877	-0.515458	0.198686
O	-0.486297	-3.766931	-0.517734
C	-3.065028	-3.560156	-1.331159
H	-3.544306	-4.361517	-0.742396
H	-3.813941	-3.062716	-1.964362
H	-2.274636	-4.013037	-1.944869
C	-4.572263	-1.825771	0.426660
C	-3.611989	0.760036	0.869992
N	-2.428241	-2.557255	-0.459465
C	-4.931532	0.442586	1.187195
C	-5.420786	-0.855649	0.955939
H	-4.960535	-2.833259	0.261828
H	-3.243820	1.773594	1.044619
H	-6.457613	-1.099723	1.201221
Cl	-5.976101	1.657981	1.863060

I-1[5]
Lowest frequency = 15.3474 cm^{-1}
Charge = 1, Multiplicity = 5

75			
Co	1.475377	0.180676	-0.242606
C	1.238051	-1.020118	-2.435828
C	2.380632	-1.500509	-1.713440
C	1.385857	0.397419	-2.616439
C	3.261326	-0.371054	-1.470740
C	2.633533	0.808230	-2.001815
C	0.097474	-1.831235	-2.968204
H	-0.875953	-1.418010	-2.646515
H	0.153986	-2.876319	-2.634161
H	0.103063	-1.818150	-4.074037
C	2.655734	-2.908616	-1.294715
H	1.726558	-3.487009	-1.175914
H	3.289121	-3.415823	-2.048145
H	3.197136	-2.927752	-0.335145
C	0.480371	1.268321	-3.425727
H	-0.546172	0.872567	-3.458777
H	0.849683	1.317946	-4.469044
H	0.447049	2.299778	-3.042392
C	4.624036	-0.440285	-0.855311
H	4.906984	0.518353	-0.393249
H	5.376446	-0.671768	-1.633455
H	4.680299	-1.231103	-0.091443
C	3.229264	2.184793	-2.034326
H	2.456291	2.952616	-2.194908
H	3.962521	2.268408	-2.858656
H	3.754454	2.415095	-1.092832
O	2.389291	-1.017427	1.321205
C	2.753639	0.077973	1.852831
O	2.475382	1.173117	1.216260
C	3.472855	0.141482	3.191743
C	2.548118	0.907640	4.172134
H	2.338919	1.924200	3.800586
H	3.041046	0.986123	5.155933
H	1.590087	0.376094	4.310358
C	3.759532	-1.277549	3.711377
H	4.277557	-1.218441	4.683480
H	4.400746	-1.837056	3.009989

H	2.826477	-1.848790	3.847451
C	4.788211	0.933297	2.992667
H	5.468268	0.405840	2.301686
H	5.302147	1.039665	3.963039
H	4.583579	1.938077	2.588763
C	-1.260766	1.619660	-0.461571
C	-2.163480	2.177876	-1.391491
C	-0.146003	2.380679	-0.035782
C	-1.942257	3.462931	-1.900340
H	-3.028646	1.595798	-1.723482
C	0.071956	3.665792	-0.552615
H	0.490313	2.024429	0.784368
C	-0.823622	4.206563	-1.487117
H	-2.643189	3.887026	-2.625809
H	0.923272	4.253241	-0.195710
H	-0.662650	5.215033	-1.880769
C	-1.454706	0.253397	0.076482
C	-2.808563	-0.203662	0.418336
C	-3.262193	-1.542431	0.197400
C	-0.523430	-1.770840	0.944304
C	-1.134622	-2.797916	-0.003581
H	-1.166996	-1.655935	1.837946
H	0.469653	-2.125010	1.243695
N	-0.381871	-0.481692	0.263123
O	-0.520217	-3.767892	-0.421470
C	-3.082913	-3.558962	-1.248779
H	-3.531506	-4.373172	-0.653498
H	-3.854064	-3.077558	-1.867179
H	-2.294103	-3.991658	-1.878657
C	-4.607554	-1.853411	0.499671
C	-3.709088	0.752940	0.950426
N	-2.453054	-2.541576	-0.387588
C	-5.022344	0.406887	1.259795
C	-5.479436	-0.903233	1.025978
H	-4.974142	-2.868603	0.333341
H	-3.363218	1.773069	1.132095
H	-6.511180	-1.171782	1.267347
Cl	-6.098109	1.596262	1.931496

TS(1-2)[1]
Lowest frequency = -89.9806 cm^{-1}
Charge = 1, Multiplicity = 1

75			
Co	1.455101	-0.229025	-0.436516
C	1.377714	-1.673098	-1.901855
C	2.407725	-1.915218	-0.899720
C	1.633434	-0.405958	-2.507757
C	3.352455	-0.809250	-0.967333
C	2.862646	0.126442	-1.925509
C	0.261759	-2.597749	-2.272921
H	-0.694995	-2.059490	-2.375230
H	0.139878	-3.406331	-1.539779
H	0.491397	-3.051310	-3.255056
C	2.531563	-3.111178	-0.015029
H	1.553294	-3.572824	0.194579
H	3.171953	-3.867743	-0.508285
H	3.006901	-2.839108	0.940422
C	0.866610	0.179655	-3.650480
H	-0.183664	-0.148204	-3.642454
H	1.317632	-0.158876	-4.602619
H	0.886676	1.279005	-3.641090
C	4.605755	-0.676227	-0.164592
H	4.865039	0.380149	-0.001831
H	5.440103	-1.158657	-0.707527
H	4.507615	-1.170550	0.813031
C	3.517557	1.425547	-2.272165
H	2.883132	2.036193	-2.930324
H	4.469393	1.226602	-2.798415
H	3.741875	1.997038	-1.356997
O	1.968458	-0.195425	1.422957
C	2.526708	0.955083	1.694117
O	2.667018	1.825498	0.812362
C	2.933349	1.169799	3.158988
C	1.619861	1.286310	3.973319
H	1.003639	2.127926	3.610796
H	1.854586	1.467348	5.036430
H	1.028403	0.358032	3.899555
C	3.749537	-0.040798	3.660594
H	4.001544	0.093425	4.726588
H	4.696324	-0.140406	3.101248
H	3.176843	-0.976333	3.551086
C	3.751870	2.466471	3.276954
H	4.685117	2.400741	2.692471
H	4.015798	2.646530	4.333296
H	3.179868	3.330220	2.901970
C	-1.079181	1.304552	-1.085629
C	-1.966470	1.727311	-2.097007
C	0.140270	1.995127	-0.897734
C	-1.635897	2.825677	-2.900677
H	-2.907244	1.191308	-2.256141
C	0.459406	3.102097	-1.694305
H	0.800808	1.776069	-0.038370
C	-0.431237	3.520747	-2.694344
H	-2.324002	3.147385	-3.688427
H	1.387017	3.649360	-1.503886
H	-0.194928	4.395739	-3.308094
C	-1.373058	0.172280	-0.185331
C	-2.745214	-0.061237	0.292015
C	-3.287942	-1.365377	0.507533
C	-0.560494	-1.518446	1.294026
C	-1.247624	-2.750815	0.714906
H	-1.183250	-1.073381	2.092913
H	0.409698	-1.807078	1.711046
N	-0.348115	-0.535911	0.229866
O	-0.687402	-3.835619	0.607724
C	-3.255185	-3.740004	-0.242008
H	-3.754601	-4.296697	0.569792
H	-3.996549	-3.422703	-0.989429
H	-2.502669	-4.399607	-0.694989
C	-4.639706	-1.477371	0.901745
C	-3.565798	1.071910	0.514347
N	-2.551394	-2.550797	0.271657
C	-4.890209	0.928525	0.923835
C	-5.436912	-0.353841	1.110126
H	-5.071690	-2.467203	1.064584
H	-3.150887	2.072470	0.374058
H	-6.476635	-0.462957	1.429193
Cl	-5.867584	2.339595	1.202245

I-2[1]
Lowest frequency = 16.6761 cm^{-1}
Charge = 1, Multiplicity = 1

75			
Co	1.412985	0.342710	0.397299

C	1.384061	2.109690	1.461738
C	2.355204	2.099963	0.373964
C	1.697219	1.034742	2.344405
C	3.325307	1.053800	0.665181
C	2.906743	0.378868	1.847776
C	0.262802	3.084079	1.646904
H	-0.676369	2.575050	1.920501
H	0.091004	3.685128	0.743535
H	0.519308	3.770235	2.475143
C	2.426479	3.052482	-0.774312
H	1.437924	3.461080	-1.037645
H	3.087690	3.899313	-0.507037
H	2.856112	2.561358	-1.661723
C	0.986558	0.728894	3.624469
H	-0.073721	1.020626	3.578414
H	1.456776	1.300528	4.446946
H	1.043479	-0.338618	3.882201
C	4.543365	0.740728	-0.140980
H	4.813090	-0.322275	-0.060858
H	5.390192	1.344608	0.236178
H	4.396690	0.989737	-1.201899
C	3.622517	-0.776439	2.473937
H	3.058908	-1.193299	3.321016
H	4.607036	-0.440962	2.848285
H	3.790171	-1.568105	1.724952
O	1.868442	-0.271846	-1.357769
C	2.517861	-1.414799	-1.427690
O	2.815548	-2.085733	-0.429805
C	2.819718	-1.872340	-2.868961
C	1.459564	-2.167146	-3.547827
H	0.904484	-2.947444	-2.997617
H	1.625007	-2.528414	-4.577645
H	0.837413	-1.257357	-3.591972
C	3.547987	-0.745958	-3.633096
H	3.729519	-1.056859	-4.676478
H	4.527492	-0.523697	-3.174313
H	2.946067	0.177738	-3.643198
C	3.682076	-3.144464	-2.825631
H	4.648654	-2.951290	-2.330964
H	3.879962	-3.496950	-3.852730
H	3.173918	-3.946616	-2.266846
C	-0.989836	-0.999578	1.357257
C	-1.830795	-1.271560	2.454380
C	0.285122	-1.616075	1.290939
C	-1.409232	-2.159906	3.453138
H	-2.807947	-0.784310	2.526555
C	0.692122	-2.520273	2.281243
H	0.911225	-1.580614	0.370948
C	-0.158973	-2.796668	3.361197
H	-2.064552	-2.365718	4.305102
H	1.654380	-3.027515	2.174273
H	0.144466	-3.515872	4.128394
C	-1.365953	-0.102608	0.246138
C	-2.748876	-0.027680	-0.243759
C	-3.330740	1.176744	-0.747945
C	-0.610400	1.236553	-1.586301
C	-1.337076	2.545871	-1.291865
H	-1.218414	0.603559	-2.259810
H	0.351625	1.450995	-2.063556
N	-0.372670	0.532160	-0.330131
O	-0.813522	3.644257	-1.435323
C	-3.371138	3.658745	-0.554559
H	-3.891659	4.004451	-1.464398
H	-4.098508	3.493481	0.253179
H	-2.638370	4.425475	-0.268531
C	-4.687310	1.156089	-1.141258
C	-3.536322	-1.203822	-0.187149
N	-2.631073	2.406629	-0.798172
C	-4.867319	-1.195105	-0.600259
C	-5.452249	-0.006407	-1.072702
H	-5.149423	2.068530	-1.524449
H	-3.090136	-2.134107	0.171346
H	-6.496459	-0.002908	-1.395724
Cl	-5.804476	-2.657977	-0.530917

TS(2-3)[1]

Lowest frequency = -971.9727 cm^{-1}

Charge = 1, Multiplicity = 1

75			
Co	-1.590052	-0.349822	0.199862
C	-1.827125	-2.390622	-0.082812
C	-2.653388	-1.638459	-1.002993
C	-2.193920	-2.029794	1.257000
C	-3.568800	-0.850540	-0.206151
C	-3.283319	-1.068122	1.179738
C	-0.794704	-3.418398	-0.429112
H	0.144513	-3.249466	0.124026
H	-0.576133	-3.431184	-1.505544
H	-1.170433	-4.416789	-0.138419
C	-2.663043	-1.724759	-2.497864
H	-1.694893	-2.059307	-2.902164
H	-3.438161	-2.443507	-2.824768
H	-2.911693	-0.748085	-2.944507
C	-1.639246	-2.669683	2.491552
H	-0.543679	-2.773011	2.435495
H	-2.066922	-3.683699	2.601643
H	-1.882474	-2.095828	3.396790
C	-4.623030	0.056906	-0.751762
H	-4.934907	0.810282	-0.012727
H	-5.511992	-0.541686	-1.025585
H	-4.270224	0.576046	-1.655505
C	-4.085860	-0.522220	2.322597
H	-3.607397	-0.726527	3.290991
H	-5.082593	-1.000637	2.332882
H	-4.244463	0.565149	2.231862
O	-1.926324	1.248449	-0.855065
C	-1.441200	2.380185	-0.506757
O	-0.778744	2.540026	0.565258
C	-1.640512	3.586348	-1.430911
C	-0.233674	3.988171	-1.942211
H	0.436406	4.224291	-1.099728
H	-0.318350	4.878309	-2.588370
H	0.218828	3.176478	-2.539448
C	-2.560410	3.233885	-2.611017
H	-2.664629	4.111950	-3.270322
H	-3.566082	2.946306	-2.261674
H	-2.151159	2.400651	-3.206018
C	-2.241741	4.737252	-0.591495
H	-3.239175	4.465386	-0.204129
H	-2.352864	5.634256	-1.223956
H	-1.588942	4.981979	0.261402
C	0.761065	-0.196187	1.742271
C	1.556906	-0.517532	2.856529
C	-0.580925	0.280619	1.893522
C	1.043716	-0.325627	4.146600

H	2.565655	-0.919655	2.718533
C	-1.044687	0.506891	3.206989
H	-0.807943	1.364387	1.138842
C	-0.243081	0.212470	4.319367
H	1.654531	-0.577072	5.019010
H	-2.029313	0.956695	3.364664
H	-0.619940	0.405696	5.329198
C	1.199783	-0.279187	0.346228
C	2.608469	-0.182845	-0.062114
C	3.150873	-0.923983	-1.154356
C	0.509110	-0.205731	-1.946020
C	1.125309	-1.510435	-2.452058
H	1.210488	0.634368	-2.114196
H	-0.419987	-0.020172	-2.495972
N	0.211671	-0.323509	-0.522513
O	0.547783	-2.255105	-3.235366
C	3.001440	-3.057750	-2.430871
H	3.566537	-2.874697	-3.361270
H	3.672709	-3.458025	-1.657583
H	2.196800	-3.771147	-2.655302
C	4.530063	-0.807105	-1.433374
C	3.454591	0.681343	0.673610
N	2.374204	-1.822231	-1.927263
C	4.808885	0.791364	0.360301
C	5.356289	0.034303	-0.690505
H	4.961765	-1.374664	-2.260856
H	3.037126	1.282532	1.484162
H	6.419075	0.121704	-0.930368
Cl	5.821852	1.870738	1.274054

TS(2-3)^3
Lowest frequency = -1393.5213 cm^{-1}
Charge = 1, Multiplicity = 3

75

Co	-1.682228	-0.255137	0.257237
C	-1.765354	-2.455982	-0.480817
C	-2.660064	-1.584978	-1.170442
C	-2.032270	-2.310758	0.924311
C	-3.597972	-1.017187	-0.195445
C	-3.218975	-1.479570	1.096845
C	-0.696873	-3.330251	-1.058917
H	0.299550	-3.072229	-0.657106
H	-0.654306	-3.248893	-2.153452
H	-0.890614	-4.385664	-0.794260
C	-2.737319	-1.349339	-2.646550
H	-1.790105	-1.588129	-3.154937
H	-3.533971	-1.982112	-3.082639
H	-3.002784	-0.301121	-2.862660
C	-1.331921	-3.072727	2.004523
H	-0.279413	-3.264233	1.744949
H	-1.827674	-4.053494	2.137792
H	-1.363450	-2.545571	2.969684
C	-4.772454	-0.154701	-0.540559
H	-5.175380	0.354318	0.348686
H	-5.581229	-0.771220	-0.975254
H	-4.497083	0.611590	-1.282777
C	-3.956612	-1.256300	2.383237
H	-3.309865	-1.430243	3.256318
H	-4.805001	-1.962568	2.454448
H	-4.371001	-0.236785	2.451362
O	-2.087429	1.445112	-0.597139
C	-1.477755	2.505252	-0.206359
O	-0.681022	2.512844	0.784762
C	-1.752028	3.803956	-0.967945
C	-1.462672	3.548917	-2.465853
H	-0.399853	3.297421	-2.628341
H	-1.686904	4.461653	-3.042920
H	-2.084987	2.726066	-2.853803
C	-3.252408	4.138492	-0.772866
H	-3.491393	5.067764	-1.317075
H	-3.488111	4.295485	0.293859
H	-3.891175	3.328753	-1.161741
C	-0.869410	4.941700	-0.427506
H	-1.063256	5.123289	0.641893
H	-1.084514	5.868798	-0.984995
H	0.201393	4.705776	-0.544102
C	0.788664	-0.358953	1.689200
C	1.588776	-0.854414	2.735917
C	-0.534215	0.127659	1.937425
C	1.097191	-0.835743	4.047628
H	2.584433	-1.258948	2.527779
C	-0.985903	0.159834	3.276168
H	-0.702711	1.339132	1.286981
C	-0.176732	-0.304079	4.321827
H	1.713432	-1.224475	4.864282
H	-1.968733	0.584322	3.507757
H	-0.534200	-0.253873	5.355599
C	1.220613	-0.256147	0.285218
C	2.634391	-0.134000	-0.102930
C	3.159486	-0.734835	-1.287390
C	0.532719	0.137428	-1.966922
C	1.128253	-1.084137	-2.664114
H	1.244979	0.984627	-2.023428
H	-0.394153	0.406813	-2.486721
N	0.235062	-0.177938	-0.577676
O	0.547720	-1.684714	-3.559129
C	2.968203	-2.662514	-2.853708
H	3.537114	-2.360042	-3.750110
H	3.630989	-3.182706	-2.147346
H	2.149971	-3.321039	-3.175585
C	4.542146	-0.615118	-1.549327
C	3.501039	0.601385	0.740460
N	2.364458	-1.500917	-2.176363
C	4.857860	0.720602	0.442354
C	5.387649	0.098523	-0.701741
H	4.961814	-1.075963	-2.446351
H	3.098108	1.096935	1.626485
H	6.452471	0.191677	-0.930230
Cl	5.895921	1.643386	1.490503

TS(2-3)^5
Lowest frequency = -1393.5213 cm^{-1}
Charge = 1, Multiplicity = 5

75

Co	-1.512416	-0.280454	0.453106
C	-1.753019	-2.553158	-0.534907
C	-2.733332	-1.725139	-1.175615
C	-1.960081	-2.475007	0.895987
C	-3.580907	-1.172417	-0.153941
C	-3.093310	-1.624443	1.136613
C	-0.705262	-3.399159	-1.184180
H	0.301832	-3.160254	-0.795377
H	-0.690496	-3.271145	-2.274822
H	-0.889173	-4.466288	-0.958440

C	-2.876211	-1.483139	-2.647371
H	-1.931961	-1.665192	-3.184867
H	-3.647978	-2.147917	-3.080135
H	-3.195036	-0.445390	-2.843748
C	-1.167203	-3.211756	1.930918
H	-0.129730	-3.381473	1.601552
H	-1.619940	-4.203662	2.124549
H	-1.141242	-2.666381	2.888189
C	-4.786092	-0.317274	-0.381697
H	-4.990913	0.337225	0.480471
H	-5.679215	-0.953152	-0.536456
H	-4.664283	0.314754	-1.274605
C	-3.750454	-1.368067	2.461254
H	-3.055886	-1.542069	3.297710
H	-4.612887	-2.048817	2.594167
H	-4.136884	-0.337526	2.536751
O	-2.235609	1.370567	-0.461633
C	-1.722113	2.503854	-0.178441
O	-0.859911	2.672914	0.755545
C	-2.117349	3.734707	-0.998548
C	-0.843645	4.201159	-1.749078
H	-0.035384	4.439822	-1.038859
H	-1.075598	5.104664	-2.338014
H	-0.486585	3.422915	-2.447064
C	-3.232282	3.384299	-1.997403
H	-3.492948	4.279452	-2.586696
H	-4.139961	3.037137	-1.476318
H	-2.912288	2.591165	-2.693405
C	-2.582252	4.839758	-0.021108
H	-3.482344	4.523921	0.534557
H	-2.833604	5.750728	-0.590246
H	-1.788630	5.081735	0.703551
C	0.896559	-0.245553	1.705160
C	1.659066	-0.909181	2.685813
C	-0.349057	0.385393	2.037263
C	1.200728	-0.947532	4.009321
H	2.596477	-1.404800	2.412154
C	-0.767289	0.345405	3.387559
H	-0.671542	1.595585	1.310719
C	-0.007784	-0.318191	4.361830
H	1.789095	-1.465576	4.773078
H	-1.687844	0.861582	3.684579
H	-0.344302	-0.333142	5.403810
C	1.287301	-0.179150	0.277875
C	2.678465	-0.036727	-0.154927
C	3.173386	-0.606387	-1.371307
C	0.471260	0.152952	-1.952815
C	1.104470	-1.024775	-2.686892
H	1.122548	1.044755	-2.043016
H	-0.499201	0.360790	-2.419106
N	0.267951	-0.174362	-0.549463
O	0.531616	-1.634903	-3.578217
C	3.008430	-2.507244	-2.968212
H	3.527063	-2.162082	-3.879450
H	3.720737	-3.009481	-2.298148
H	2.208535	-3.196120	-3.271894
C	4.545498	-0.451725	-1.672149
C	3.565850	0.677020	0.688355
N	2.377879	-1.387309	-2.244349
C	4.909469	0.825166	0.352190
C	5.406495	0.251848	-0.832568
H	4.945080	-0.880123	-2.593847
H	3.184580	1.131649	1.605486
H	6.461029	0.370382	-1.094829
Cl	5.972265	1.720849	1.397142

I-3[1]

Lowest frequency = 15.5521 cm^{-1}

Charge = 1, Multiplicity = 1

75

Co	-1.673616	-0.231132	0.204624
C	-2.297512	-2.179469	0.333764
C	-2.822064	-1.636597	-0.906580
C	-2.827235	-1.409321	1.433579
C	-3.624356	-0.508999	-0.559705
C	-3.621759	-0.338407	0.879427
C	-1.454933	-3.408324	0.489301
H	-0.646309	-3.249672	1.222087
H	-1.012125	-3.722641	-0.466256
H	-2.083228	-4.236574	0.867095
C	-2.658778	-2.213718	-2.280846
H	-1.713553	-2.767861	-2.394375
H	-3.486922	-2.917882	-2.486574
H	-2.702605	-1.428525	-3.054024
C	-2.668988	-1.780264	2.876225
H	-1.633984	-2.077143	3.108163
H	-3.326682	-2.641304	3.098534
H	-2.947274	-0.957351	3.549756
C	-4.346646	0.382819	-1.518444
H	-4.410305	1.414995	-1.140939
H	-5.379653	0.011039	-1.654969
H	-3.860273	0.399632	-2.505107
C	-4.464091	0.656376	1.623156
H	-4.265863	0.629909	2.705079
H	-5.535663	0.425924	1.478630
H	-4.298209	1.686278	1.264658
O	-1.577948	1.346159	-0.974037
C	-0.905738	2.395906	-0.883783
O	-0.251642	2.730615	0.207732
C	-0.764929	3.361812	-2.049724
C	0.732924	3.356340	-2.459132
H	1.374635	3.680035	-1.623879
H	0.877684	4.049645	-3.304363
H	1.052613	2.350412	-2.783643
C	-1.644233	2.902259	-3.224462
H	-1.513567	3.596088	-4.070996
H	-2.710703	2.893933	-2.945697
H	-1.368268	1.888694	-3.559501
C	-1.175131	4.777719	-1.575966
H	-2.232687	4.799282	-1.261147
H	-1.051398	5.487589	-2.410704
H	-0.549205	5.112460	-0.733588
C	0.633398	0.084435	1.795541
C	1.438800	0.253626	2.941259
C	-0.756934	0.427109	1.793173
C	0.890999	0.836126	4.088970
H	2.484817	-0.068449	2.933495
C	-1.257579	1.058672	2.948851
H	-0.418288	2.019472	0.901752
C	-0.445253	1.266922	4.077921
H	1.506361	0.969686	4.983595
H	-2.295197	1.403240	2.983100
H	-0.865794	1.759109	4.961439
C	1.109111	-0.385209	0.495669
C	2.532868	-0.451845	0.122650

C	3.077098	-1.523869	-0.642579
C	0.519197	-0.981575	-1.738765
C	1.063698	-2.412666	-1.761726
H	1.288641	-0.280752	-2.117196
H	-0.363308	-0.935895	-2.384945
N	0.146812	-0.630040	-0.371592
O	0.459024	-3.344557	-2.280064
C	2.845482	-3.954242	-1.148067
H	3.452711	-4.114868	-2.055949
H	3.464386	-4.106320	-0.252071
H	2.007259	-4.664102	-1.166892
C	4.465501	-1.543061	-0.896357
C	3.384406	0.597153	0.541920
N	2.277551	-2.594966	-1.111831
C	4.748532	0.566450	0.250936
C	5.299775	-0.517186	-0.454620
H	4.897304	-2.367677	-1.468316
H	2.967074	1.448643	1.083610
H	6.370768	-0.539644	-0.671606
Cl	5.769097	1.878506	0.767782

I-3[3]
Lowest frequency = 14.9946 cm^{-1}
Charge = 1, Multiplicity = 3

75

Co	-1.702781	-0.146123	0.248194
C	-2.365797	-2.282990	-0.179958
C	-2.907419	-1.330325	-1.133515
C	-2.769166	-1.870461	1.115535
C	-3.741067	-0.392527	-0.424918
C	-3.623230	-0.686044	0.970854
C	-1.520611	-3.485317	-0.476817
H	-0.566469	-3.456264	0.080066
H	-1.287597	-3.566348	-1.547319
H	-2.049759	-4.404327	-0.165527
C	-2.782742	-1.403454	-2.625216
H	-1.865114	-1.922114	-2.945115
H	-3.645768	-1.960490	-3.037493
H	-2.803501	-0.397444	-3.076764
C	-2.473545	-2.598372	2.390400
H	-1.470658	-3.054101	2.368691
H	-3.209355	-3.412255	2.534325
H	-2.528812	-1.935381	3.266983
C	-4.586333	0.680953	-1.043220
H	-4.788379	1.496572	-0.330896
H	-5.560644	0.266200	-1.363094
H	-4.098011	1.116285	-1.929021
C	-4.429004	-0.045542	2.062685
H	-4.066849	-0.326562	3.062587
H	-5.479046	-0.385261	1.987726
H	-4.437370	1.054545	1.984013
O	-1.640297	1.691435	-0.869088
C	-0.874986	2.636339	-0.605415
O	-0.182454	2.689558	0.522251
C	-0.644056	3.806608	-1.549684
C	0.855389	3.793518	-1.948251
H	1.503587	3.897497	-1.063231
H	1.054480	4.635646	-2.631830
H	1.118934	2.858976	-2.474308
C	-1.535152	3.649696	-2.793123
H	-1.359268	4.494544	-3.479106
H	-2.603104	3.640643	-2.519459
H	-1.311065	2.713153	-3.330511
C	-0.975278	5.120003	-0.797861
H	-2.033610	5.141917	-0.485861
H	-0.798613	5.975426	-1.471087
H	-0.340984	5.237992	0.095146
C	0.653305	-0.219038	1.817153
C	1.466237	-0.310613	2.966491
C	-0.733267	0.131416	1.916272
C	0.935843	0.022640	4.216980
H	2.505553	-0.642556	2.882882
C	-1.226017	0.486906	3.186028
H	-0.398383	1.875814	1.068139
C	-0.396969	0.454499	4.320180
H	1.562522	-0.044085	5.111397
H	-2.266078	0.802696	3.307657
H	-0.800762	0.748768	5.294751
C	1.113544	-0.415913	0.443669
C	2.532166	-0.498256	0.057414
C	3.003702	-1.422318	-0.920541
C	0.499822	-0.470620	-1.864727
C	0.962776	-1.881726	-2.232517
H	1.308772	0.254760	-2.080596
H	-0.375801	-0.225284	-2.475539
N	0.144624	-0.411746	-0.451574
O	0.334929	-2.607667	-2.992894
C	2.608449	-3.652846	-1.963078
H	3.204267	-3.644067	-2.892468
H	3.213638	-4.044808	-1.133094
H	1.725109	-4.284228	-2.130198
C	4.389974	-1.489796	-1.178086
C	3.453229	0.375081	0.682056
N	2.133363	-2.303301	-1.610263
C	4.814544	0.305918	0.384914
C	5.292321	-0.644365	-0.533993
H	4.767250	-2.203897	-1.913729
H	3.093524	1.125794	1.388880
H	6.360983	-0.699717	-0.756560
Cl	5.922245	1.403392	1.158281

I-3[5]
Lowest frequency = 16.1253 cm^{-1}
Charge = 1, Multiplicity = 5

75

Co	-1.544514	-0.301254	0.502305
C	-1.873366	-2.459507	-0.760978
C	-2.807910	-1.523572	-1.309263
C	-2.074473	-2.516018	0.672305
C	-3.624921	-1.033268	-0.232058
C	-3.168559	-1.645344	1.002191
C	-0.866954	-3.288589	-1.491516
H	0.152021	-3.122047	-1.095265
H	-0.855254	-3.071365	-2.567821
H	-1.090400	-4.362784	-1.351134
C	-2.942805	-1.132020	-2.749803
H	-2.012847	-1.315241	-3.311427
H	-3.753652	-1.705512	-3.238217
H	-3.201678	-0.063433	-2.843167
C	-1.306910	-3.385918	1.620299
H	-0.258417	-3.502885	1.300992
H	-1.754249	-4.398112	1.660434
H	-1.310998	-2.977537	2.643582
C	-4.792135	-0.106744	-0.367607

H	-4.961392	0.475921	0.552389
H	-5.715412	-0.684216	-0.567395
H	-4.649834	0.596620	-1.202452
C	-3.820699	-1.500092	2.346625
H	-3.139548	-1.793305	3.160461
H	-4.714137	-2.150545	2.405852
H	-4.160838	-0.466883	2.531683
O	-2.153698	1.489089	-0.355581
C	-1.618049	2.572189	-0.015288
O	-0.762123	2.656011	0.973833
C	-1.909217	3.875233	-0.747467
C	-0.576652	4.359203	-1.376924
H	0.191108	4.521372	-0.603298
H	-0.751226	5.311072	-1.905826
H	-0.194906	3.627218	-2.110441
C	-2.966824	3.639150	-1.838537
H	-3.162073	4.585148	-2.369982
H	-3.915679	3.283426	-1.404102
H	-2.624432	2.892063	-2.573818
C	-2.408628	4.914994	0.286208
H	-3.347550	4.582110	0.761373
H	-2.604949	5.870658	-0.228058
H	-1.655896	5.085402	1.072308
C	0.898546	-0.447923	1.710312
C	1.719568	-1.113652	2.641328
C	-0.376207	0.088180	2.092622
C	1.301683	-1.227566	3.974344
H	2.672022	-1.552274	2.325074
C	-0.750737	-0.025625	3.450420
H	-0.649054	1.707834	1.395225
C	0.075403	-0.673354	4.382394
H	1.936974	-1.743818	4.700856
H	-1.697620	0.408198	3.794208
H	-0.230114	-0.742631	5.431904
C	1.263326	-0.271071	0.285594
C	2.651291	-0.102558	-0.157529
C	3.126921	-0.595116	-1.413612
C	0.436484	0.249248	-1.902358
C	1.045270	-0.871969	-2.738887
H	1.102765	1.134726	-1.929327
H	-0.532924	0.508678	-2.344356
N	0.236114	-0.185435	-0.527734
O	0.461925	-1.386018	-3.682586
C	2.911685	-2.373152	-3.142438
H	3.426070	-1.970523	-4.032358
H	3.622523	-2.935125	-2.519914
H	2.097228	-3.025132	-3.486355
C	4.496457	-0.434394	-1.722412
C	3.554065	0.556182	0.713243
N	2.308856	-1.300427	-2.329922
C	4.894433	0.716392	0.368523
C	5.374045	0.209759	-0.852712
H	4.880290	-0.808190	-2.674114
H	3.189027	0.957327	1.661258
H	6.426489	0.335231	-1.119987
Cl	5.975414	1.544253	1.451479

8. Experimental details and characterisation data

Compound **5-8** and **11i** were synthesised according to our previously reported ruthenium-catalysed C–H amidation procedure.[1] The synthesis and characterisation of dioxazolones **4a-l** was reported in the same work.[1]

5.1 Catalyst preparation

$Cp^*Co(CO)I_2$

$Cp^*Co(CO)I_2$ was prepared according a literature procedure,[2] by charging a dry 500 mL 3-necked flask, fitted with a reflux condenser and a septum, with $Co_2(CO)_8$ (5.47 g, 16 mmol). The flask was then flushed with N_2 for 10 min. Dry degassed dichloromethane (200 mL) was added, followed by 1,2,3,4,5-pentamethylcyclopentadiene (5.01 g, 36.8 mmol), and the mixture was heated to gentle reflux (45 °C). After 18 h, the volatiles were removed under vacuum, avoiding exposure to air. Keeping the flask under a gentle flow of N_2, dry degassed Et_2O (55 mL) was added to the resulting brown solid followed by careful addition of I_2 (9.75 g, 38.4 mmol) in dry degassed Et_2O (75 mL) [*CAUTION:* exothermic and CO-evolution]. After addition of half of the iodine solution the reaction mixture became difficult to stir; continued addition of the iodine solution gradually made the solution easier to stir. After complete addition, the reaction mixture was stirred at room temperature for 3 hours 30 min before being transferred to a 1 L flask. Silica (80 mL) was added along with heptane (100 mL), and the volatiles were removed in vacuo, to afford a semi-dry solid. This was loaded onto a plug of silica, eluting sequentially with heptane (500 mL), 20% DCM/Heptane (400 mL), 40% DCM/Heptane (400 mL), 60% DCM/Heptane (400 mL). These initial fractions were discarded. Then eluting with 80% DCM in heptane (2.5 L), the dark purple eluate was collected. The volatiles were removed under vacuum to afford $Cp^*Co(CO)I_2$ (13.5 g, 88 %) as a black crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 2.23 (s, 15 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 100.9 (5 C), 11.5 (5 C).

$Cp^*Co(MeCN)_3(SbF_6)_2$

$Cp^*Co(MeCN)_3(SbF_6)_2$ was prepared according to a modified literature procedure,[18] by charging a dry 100 mL flask with $Cp^*Co(CO)I_2$ (1.00 g, 2.10 mmol), in a glovebox under nitrogen atmosphere. A separate 25 mL flask was charged with silver(I) hexafluorostibate(V) (2.53 g, 7.35 mmol). The flasks were removed from the glovebox, and dry degassed CH_3CN (10 mL) was added in each one at room temperature. The solution of $AgSbF_6$ was carefully added to the cobalt solution causing gas evolution and precipitation of a white solid (AgI). The reaction mixture was then stirred at room temperature for additional 3 h. The resulting solid was removed by filtration through a plug of Celite eluting with CH_3CN (20 mL x 3). The filtrate was evaporated in vacuo to approx. 10 mL, then Et_2O (100 mL) was added and a purple solid precipitated. The purple solid was collected by filtration, washed with Et_2O (100 mL) and dried under vacuum to afford $Cp^*Co(MeCN)_3(SbF_6)_2$ as a purple solid (1.629 g, 98 %). **^{1}H NMR** (500 MHz, CD_3NO_2) δ (ppm) 2.55 (s, 9 H), 1.49 (s, 15 C); **^{13}C NMR** (126 MHz, CD_3NO_2) δ (ppm) 132.9 (3 C), 102.4 (5 C), 10.3 (5 C), 4.1 (3 C); **^{19}F NMR** (471 MHz, CD_3NO_2) δ (ppm) -127.18 (m, 6 F).

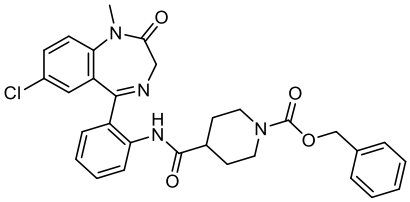
5.2 General procedure A for cobalt-catalysed late-stage C–H amidation

On the benchtop, an oven-dried microwave vial was charged with the appropriate LSF substrate (0.25 mmol), dioxazolone reagent (0.25-0.28 mmol, 1.0-1.1 equiv), and pivalic acid (PivOH, 0.08 mmol, 30 mol%). The vial was moved into a glovebox under N_2 atmosphere, where $Cp^*Co(MeCN)_3(SbF_6)_2$ (0.03 mmol, 10 mol%) was added. The vial was sealed and taken out of the glovebox. Anhydrous EtOAc (0.1 M, 2.5 mL) was then added by syringe under N_2 atmosphere, and the vial was heated to 60 °C overnight (16-18 h). The reaction mixture was then allowed to cool down to room temperature and analysed by LC-MS and SFC-MS. The reaction crude was filtered through a plug of Celite, eluting with EtOAc or EtOAc and MeOH [*In cases of poor solubility of the product, this filtration step was not performed*]. After removal of the volatiles under reduced pressure, the crude material was purified by automated flash column chromatography, on normal or reverse phase. When this was not possible due to challenging separation or poor solubility, purification was performed either by preparative reverse phase HPLC or supercritical fluid chromatography SFC. The relevant fractions were collected, combined and concentrated or lyophilised to afford the desired product.

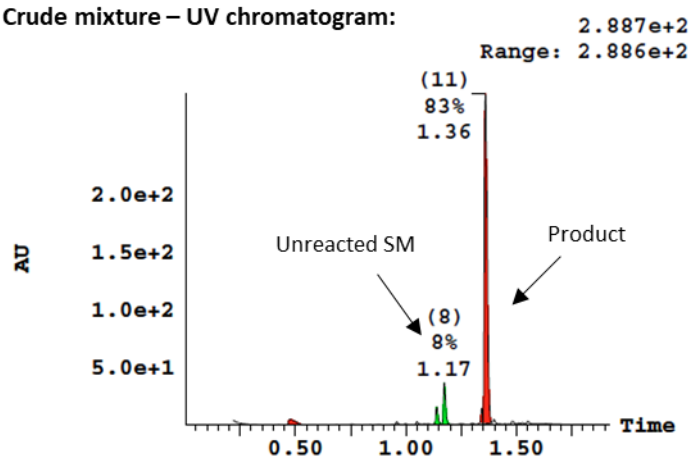
[*Note*: *Although all the reactions were set up in glovebox under N_2 atmosphere, no significant drop in product yield was observed setting up the reaction under air with no exclusion of moisture*.]

5.3 Late-stage functionalisation with bifunctional dioxazolones (10a-10j)

Benzyl 4-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)carbamoyl)piperidine-1-carboxylate (10a)



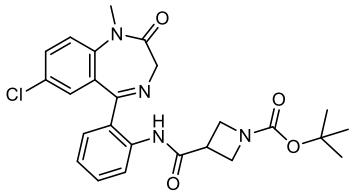
Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:



Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10a** as a white foam (117 mg, 86%). R_f 0.36 (60% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 12.07 (s, 1 H), 8.62 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.44 (ddd, *J* = 8.6, 7.1, 1.8 Hz, 1 H), 7.40–7.28 (m, 6 H), 7.27–7.24 (m, part. overlap with solvent signal, 1 H), 7.07 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.03 (td, *J* = 7.8, 1.3 Hz, 1 H), 5.14 (s, 2 H), 4.78 (d, *J* = 11.0 Hz, 1 H), 4.25 (br s, 2 H), 3.86 (d, *J* = 11.1 Hz, 1 H), 3.39 (s, 3 H), 2.93 (br s, 2 H), 2.45 (tt, *J* = 11.4, 3.7 Hz, 1 H), 1.99 (br s, 2 H), 1.84–1.66 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 173.3, 170.9, 169.7, 155.3, 142.6, 139.6, 136.8, 133.2, 132.0 (2 C), 130.4, 130.3, 129.9, 128.6 (2 C), 128.1, 128.0 (2 C), 123.3, 122.8, 122.6, 121.7, 67.3, 56.3, 44.7 (br), 43.7 and 43.6 (2 C), 34.9, 28.6 (2 C).

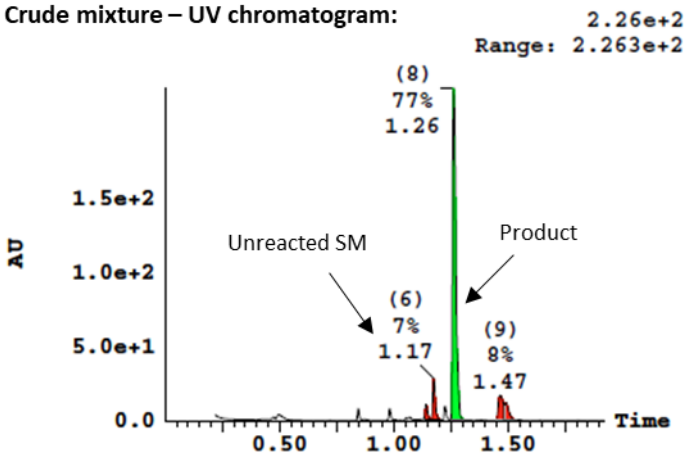
The spectroscopic data was consistent with what reported in the literature.[1]

***tert*-Butyl 3-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)carbamoyl)azetidine-1-carboxylate (10b)**



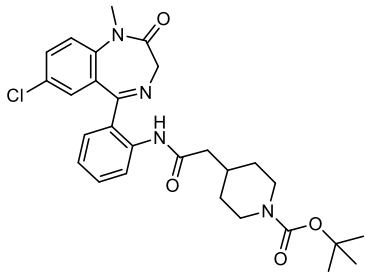
Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl 3-(5-oxo-1,4,2-dioxazol-

3-yl)azetidine-1-carboxylate **4b** (66.6 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

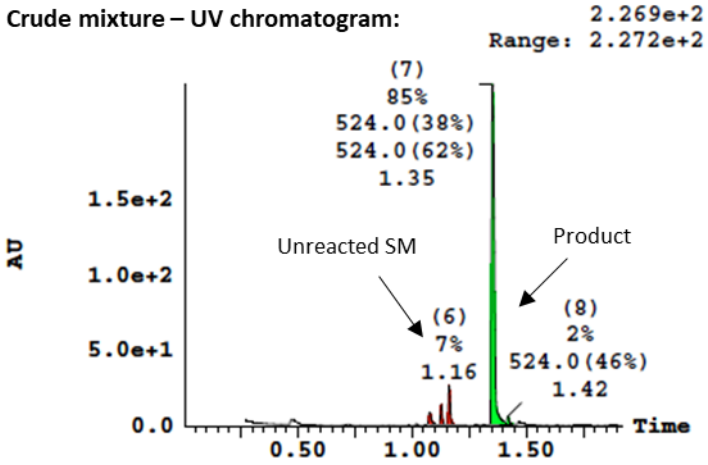


Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10b** as a colourless oil (102 mg, 84%). R_f 0.27 (60% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 12.13 (s, 1 H), 8.57 (d, *J* = 8.4 Hz, 1 H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.45 (ddd, *J* = 8.7, 7.0, 2.0 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.28–7.23 (m, part. overlap with solvent signal, 1 H), 7.11–7.02 (m, 2 H), 4.78 (d, *J* = 11.2 Hz, 1 H), 4.24–4.08 (m, 4 H), 3.84 (d, *J* = 11.1 Hz, 1 H), 3.44–3.31 (m, 4 H), 1.43 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.0, 170.8, 169.4, 156.2, 142.6, 139.2, 133.1, 132.12, 132.08, 130.3, 130.0, 129.8, 123.2, 122.9, 122.8, 121.7, 79.9, 55.9, 51.6 (br, 2 C), 35.2, 34.9, 28.4 (3 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{25}H_{27}ClN_4O_4$, 483.1799; found, 483.1805.

***tert*-Butyl 4-(2-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)amino)-2-oxoethyl)piperidine-1-carboxylate (10c)**

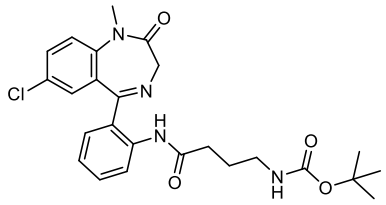


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl 4-((5-oxo-1,4,2-dioxazol-3-yl)methyl)piperidine-1-carboxylate **4c** (78.0 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

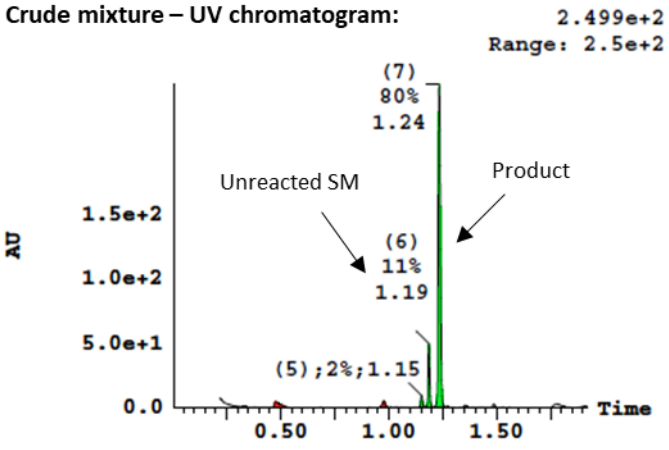


Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10c** as a colourless oil (112 mg, 85%). R_f 0.32 (60% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.90 (s, 1 H), 8.57 (d, *J* = 8.4 Hz, 1 H), 7.53 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.43 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.28–7.24 (m, part. overlap with solvent signal, 1 H), 7.08–6.98 (m, 2 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.08 (br s, 2 H), 3.85 (d, *J* = 11.1 Hz, 1 H), 3.38 (s, 3 H), 2.72 (br s, 2 H), 2.29 (qd, *J* = 14.4, 7.0 Hz, 2 H), 2.06 (dtt, *J* = 15.4, 8.0, 3.8 Hz, 1 H), 1.80–1.69 (br m, 2 H), 1.43 (s, 9 H), 1.27–1.10 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 170.9, 170.7, 169.5, 154.8, 142.6, 139.4, 133.1, 132.0, 131.9, 130.3, 130.2, 129.8, 123.0, 122.7, 122.5, 121.6, 79.4, 56.1, 45.4, 43.7 (br, 2 C), 34.8, 33.6, 32.0 (br, 2 C), 28.5 (3 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{28}H_{33}ClN_4O_4$, 525.2269; found, 525.2275.

***tert*-Butyl (4-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)amino)-4-oxobutyl)carbamate (10d)**

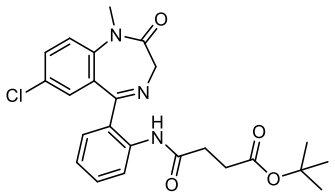


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl (3-(5-oxo-1,4,2-dioxazol-3-yl)propyl)carbamate **4d** (67.2 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

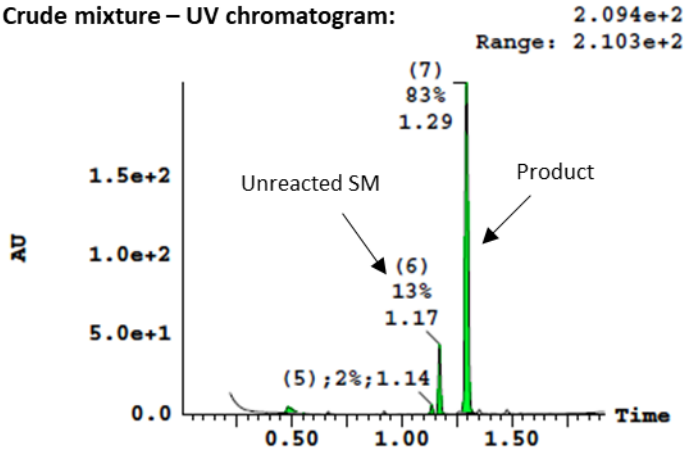


Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10d** as a colourless oil (104 mg, 86%). R_f 0.30 (60% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.91 (s, 1 H), 8.58 (d, *J* = 8.4 Hz, 1 H), 7.52 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.45–7.39 (m, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 7.27–7.23 (m, part. overlap with solvent signal, 1 H), 7.08–6.98 (m, 2 H), 4.89–4.75 (m, 2 H), 3.85 (d, *J* = 11.0 Hz, 1 H), 3.38 (s, 3 H), 3.27–3.14 (m, 2 H), 2.42 (hept, *J* = 7.6 Hz, 2 H), 1.92 (p, *J* = 7.1 Hz, 2 H), 1.41 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.4, 170.7, 169.6, 156.0, 142.5, 139.5, 133.0, 131.81, 131.76, 130.4, 130.2, 129.7, 123.2, 122.7, 122.4, 121.6, 79.2, 56.2, 40.1, 35.6, 34.8, 28.4 (3 C), 25.8; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{25}H_{29}ClN_4O_4$, 485.1956; found, 485.1957.

***tert*-Butyl 4-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)amino)-4-oxobutanoate (10e)**

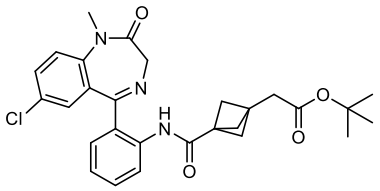


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl 3-(5-oxo-1,4,2-dioxazol-3-yl)propanoate **4e** (59.2 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

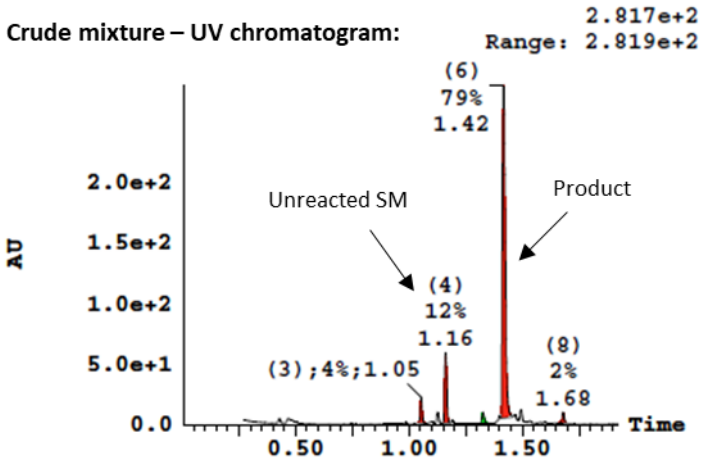


Purification by automated flash column chromatography (5-60% EtOAc/heptane) afforded derivative **10e** as a colourless oil (92.8 mg, 81%). R_f 0.12 (30% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.91 (s, 1 H), 8.57 (d, *J* = 8.4 Hz, 1 H), 7.53 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.42 (ddd, *J* = 8.6, 7.0, 1.9 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 7.24 (d, *J* = 2.4 Hz, 1 H), 7.08–6.97 (m, 2 H), 4.84 (d, *J* = 11.1 Hz, 1 H), 3.85 (d, *J* = 11.0 Hz, 1 H), 3.39 (s, 3 H), 2.73–2.59 (m, 4 H), 1.42 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.9, 170.53, 170.51, 169.7, 142.5, 139.5, 132.9, 131.8, 131.7, 130.5, 130.2, 129.7, 123.3, 122.6, 122.3, 121.6, 80.7, 56.3, 34.8, 32.9, 30.6, 28.1 (3 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{24}H_{26}ClN_3O_4$, 456.1690; found, 456.1698.

***tert*-Butyl 2-(3-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)carbamoyl)bicyclo[1.1.1]pentan-1-yl)acetate (10f)**

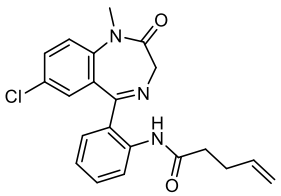


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl 2-(3-(5-oxo-1,4,2-dioxazol-3-yl)bicyclo[1.1.1]pentan-1-yl)acetate **4f** (73.5 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:



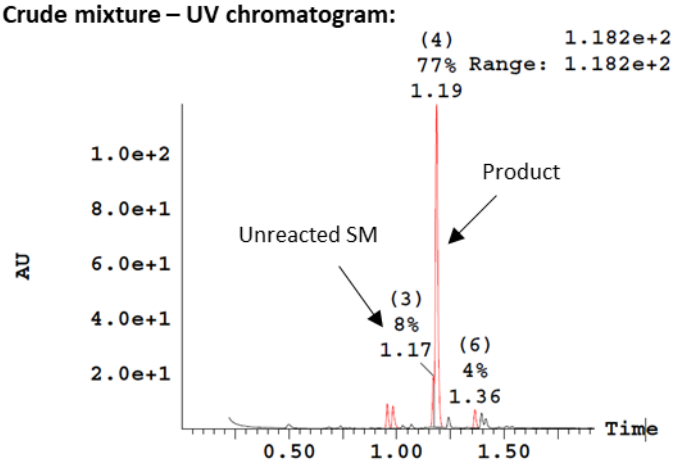
Purification by automated flash column chromatography (5-80% EtOAc/heptane) afforded derivative **10f** as an off-white solid (103 mg, 81%). R_f 0.20 (40% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 12.11 (s, 1 H), 8.63 (d, *J* = 8.4 Hz, 1 H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.44 (ddd, *J* = 8.6, 7.1, 1.8 Hz, 1 H), 7.31 (d, *J* = 8.9 Hz, 1 H), 7.28–7.24 (m, part. overlap with solvent signal, 1 H), 7.07 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.02 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1 H), 4.79 (d, *J* = 11.1 Hz, 1 H), 3.87 (d, *J* = 11.1 Hz, 1 H), 3.39 (s, 3 H), 2.48 (s, 2 H), 2.18–2.05 (m, 6 H), 1.46 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 170.7, 170.2, 169.6, 168.9, 142.6, 139.5, 133.0, 131.93, 131.88, 130.34, 130.30, 129.7, 123.0, 122.7, 122.4, 121.3, 80.7, 56.0, 52.1 (3 C), 41.3, 38.6, 35.5, 34.9, 28.2 (3 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{28}H_{30}ClN_3O_4$, 508.2003; found, 508.2010.

***N*-(2-(7-Chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[e][1,4]diazepin-5-yl)phenyl)pent-4-enamide (10g)**



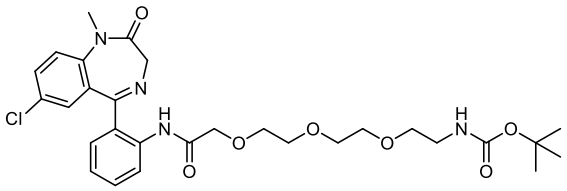
Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 10.1 mg, 0.04 mmol) and 3-(but-3-en-1-yl)-1,4,2-dioxazol-5-one **4g** (5.45 mg, 0.04 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:



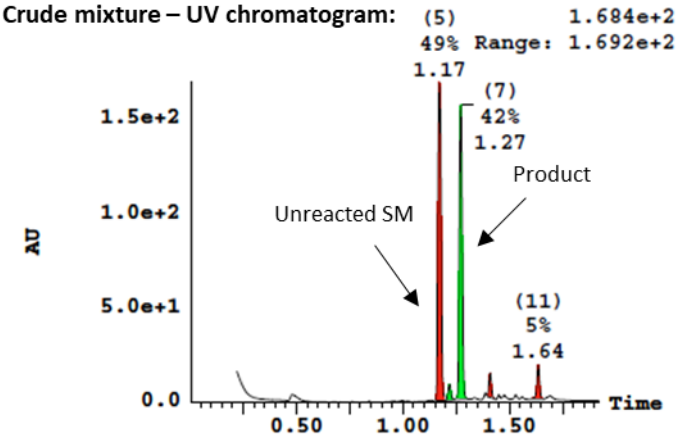
Purification by automated flash column chromatography (10-100% EtOAc/heptane) afforded derivative **10g** as a colourless oil (9.3 mg, containing approx. 8% unreacted SM, corrected yield 66%). R_f 0.29 (40% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.90 (s, 1 H), 8.61 (d, *J* = 8.4 Hz, 1 H), 7.53 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.43 (ddd, *J* = 8.7, 7.1, 1.9 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.28–7.24 (m, part. overlap with solvent signal, 1 H), 7.05 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.01 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1 H), 5.88 (dddd, *J* = 16.7, 9.8, 4.9, 2.5 Hz, 1 H), 5.11 (dd, *J* = 17.1, 1.6 Hz, 1 H), 5.02 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.82 (d, *J* = 11.0 Hz, 1 H), 3.86 (d, *J* = 11.0 Hz, 1 H), 3.39 (s, 3 H), 2.56–2.43 (m, 4 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.2, 170.7, 169.7, 142.5, 139.6, 136.8, 133.0, 131.8 (2 C), 130.5, 130.2, 129.7, 123.1, 122.6, 122.3, 121.6, 115.7, 56.3, 37.7, 34.8, 29.4; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{21}H_{20}ClN_3O_2$, 382.1322; found, 382.1332.

***tert*-Butyl (2-(2-(2-((2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)amino)-2-oxoethoxy)ethoxy)ethoxy)ethyl)carbamate (10h)**



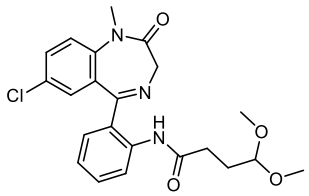
Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and *tert*-butyl (2-(2-(2-((5-oxo-1,4,2-dioxazol-3-yl)methoxy)ethoxy)ethoxy)ethyl)carbamate **4h** (78.0 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:

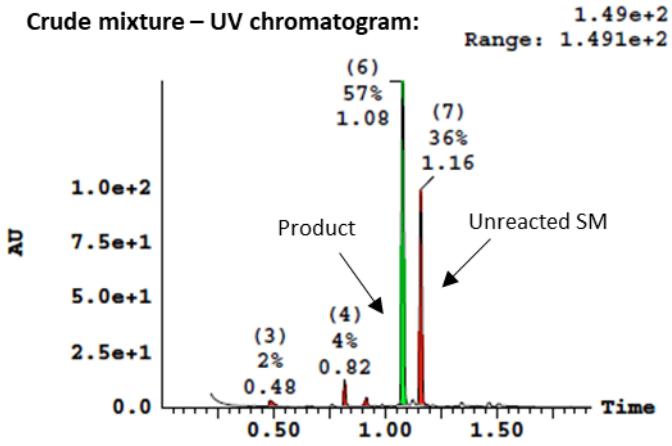


Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10h** as a colourless oil (48.1 mg, 33%). R_f 0.14 (70% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 12.23 (s, 1 H), 8.60 (d, *J* = 8.3 Hz, 1 H), 7.52 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.44 (ddd, *J* = 8.6, 5.7, 3.3 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 7.23 (d, *J* = 2.5 Hz, 1 H), 7.09–7.03 (m, 2 H), 5.14 (br m, 1 H), 4.86 (d, *J* = 11.0 Hz, 1 H), 4.22–4.10 (m, 2 H), 3.87–3.77 (m, 4 H), 3.77–3.65 (m, 3 H), 3.65–3.59 (m, 2 H), 3.50 (t, *J* = 5.2 Hz, 2 H), 3.39 (s, 3 H), 3.31–3.22 (m, 2 H), 1.41 (s, 9 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 169.8, 169.7, 169.1, 156.1, 142.6, 138.3, 132.7, 131.8, 131.5, 130.5, 130.1, 129.7, 124.7, 123.0, 122.6, 121.9, 79.2, 71.5, 71.1, 70.6 (2 C), 70.4, 70.1, 56.2, 40.3, 34.9, 28.4 (3 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{29}H_{37}ClN_4O_7$, 589.2429; found, 589.2437.

_N_-(2-(7-Chloro-1-methyl-2-oxo-2,3-dihydro-1_H_-benzo[e][1,4]diazepin-5-yl)phenyl)-4,4-dimethoxybutanamide (10i)

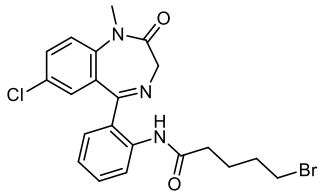


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and 3-(3,3-dimethoxypropyl)-1,4,2-dioxazol-5-one **4i** (52.0 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:

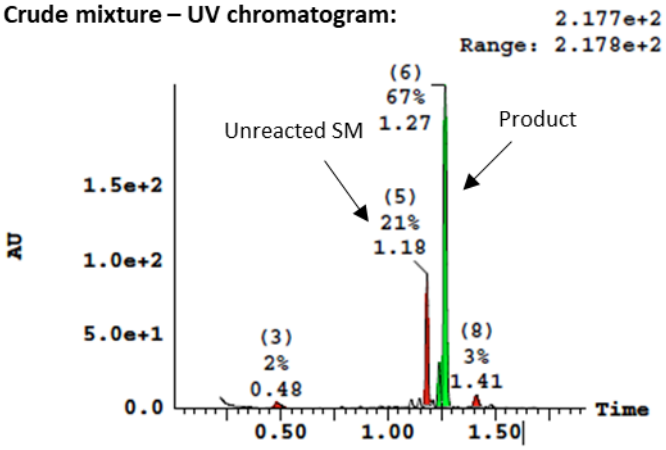


Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **10i** as a colourless oil (64.6 mg, 60%). R_f 0.22 (60% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.77 (s, 1 H), 8.54 (d, *J* = 8.4 Hz, 1 H), 7.55 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.44 (ddd, *J* = 8.6, 6.9, 2.0 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 7.27 (d, *J* = 2.5 Hz, 1 H), 7.09–7.00 (m, 2 H), 4.82 (d, *J* = 11.2 Hz, 1 H), 4.46 (t, *J* = 5.6 Hz, 1 H), 3.86 (d, *J* = 11.2 Hz, 1 H), 3.40 (s, 3 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.46 (td, *J* = 7.5, 5.0 Hz, 2 H), 2.03 (td, *J* = 7.7, 5.3 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.5, 170.9, 169.5, 142.6, 139.4, 133.0, 132.1, 132.0, 130.4, 130.2, 129.8, 123.2, 122.7, 122.5, 121.8, 103.8, 56.0, 53.4, 53.1, 34.9, 33.0, 28.2; **HRMS** (m/z): $[M–MeOH+H]^+$ calcd. for $C_{22}H_{24}ClN_3O_4$, 398.1275; found, 398.1271.

5-Bromo-*N*-(2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)phenyl)pentanamide (10j)



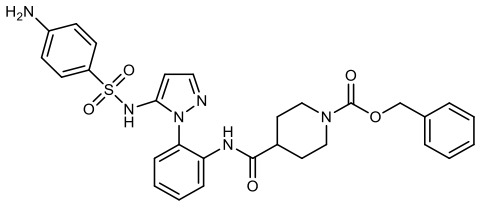
Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and 3-(4-bromobutyl)-1,4,2-dioxazol-5-one **4j** (61.1 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:



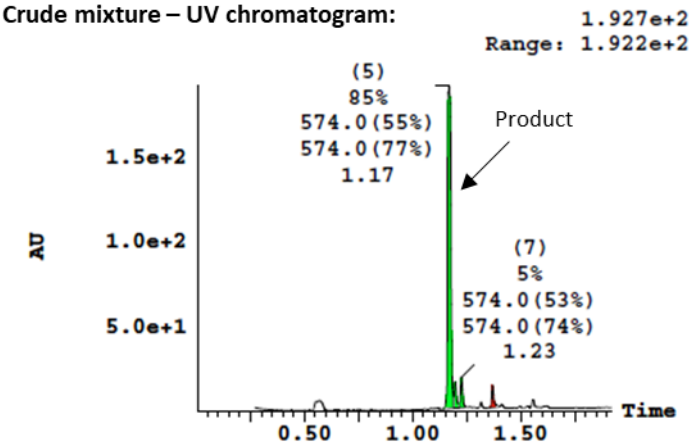
Purification by automated flash column chromatography (10-80% EtOAc/heptane) afforded derivative **10j** as a yellow oil (82.3 mg, 71%). R_f 0.26 (40% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.98 (s, 1 H), 8.61 (d, *J* = 8.4 Hz, 1 H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.44 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.27 (d, *J* = 2.5 Hz, 1 H), 7.07 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.02 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1 H), 4.84 (d, *J* = 11.0 Hz, 1 H), 3.87 (d, *J* = 11.1 Hz, 1 H), 3.46 (t, *J* = 6.5 Hz, 2 H), 3.40 (s, 3 H), 2.44 (td, *J* = 7.2, 1.2 Hz, 2 H), 2.01–1.94 (m, 2 H), 1.94–1.87 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 171.3, 170.7, 169.7, 142.5, 139.6, 133.1, 131.84, 131.82, 130.4, 130.2, 129.7, 123.0, 122.7, 122.4, 121.6, 56.3, 37.4, 34.8, 33.3, 32.1, 24.1; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{21}H_{21}{}^{79}BrClN_3O_2$, 462.0584; found, 462.0583.

5.4 Late-stage functionalisation of pharmaceuticals (11a-11n)

Benzyl 4-((2-(5-((4-aminophenyl)sulfonamido)-1*H*-pyrazol-1-yl)phenyl)carbamoyl)piperidine-1-carboxylate (11a)



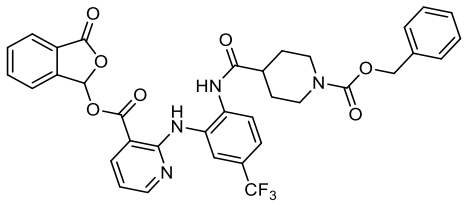
Prepared according to **General procedure A**, using 4-amino-*N*-(1-phenyl-1*H*-pyrazol-5-yl)benzenesulfonamide (s*ulfaphenazole*, 88.1 mg, 0.28 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (94.5 mg, 0.31 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:



Purification by automated flash column chromatography (15-100% EtOAc/heptane) afforded derivative **11a** as a pale yellow oil (157 mg, 98%). R_f 0.20 (70% EtOAc/heptane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.86 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.59 (d, *J* = 2.1 Hz, 1 H), 7.48 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.41–7.37 (m, 2 H), 7.37–7.33 (m, 4 H), 7.33–7.28 (m, 1 H), 7.24 (td, *J* = 7.7, 1.4 Hz, 1 H), 6.99 (dd, *J* = 7.9, 1.5 Hz, 1 H), 6.65–6.59 (m, 2 H), 6.09 (d, *J* = 2.1 Hz, 1 H), 5.12 (s, 2 H), 4.09 (br dt, *J* = 13.5, 3.4 Hz, 2 H), 2.88 (br s, 2 H), 2.43 (tt, *J* = 11.4, 3.8 Hz, 1 H), 1.74–1.66 (m, 2 H), 1.47 (dtd, *J* = 13.3, 11.8, 4.3 Hz, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 175.5, 156.8, 154.9, 141.6, 141.5, 139.0, 138.2, 135.5, 131.8, 131.0, 130.4 (2 C), 129.6 (2 C), 129.4, 129.1, 128.9 (2 C), 126.8, 126.4, 126.2, 114.2 (2 C), 102.6, 68.3, 44.4, 44.2, 29.4 (2 C).

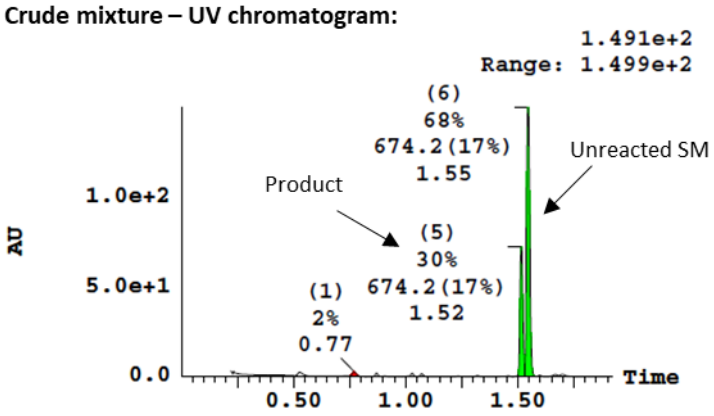
The spectroscopic data was consistent with what reported in the literature.[1]

3-Oxo-1,3-dihydroisobenzofuran-1-yl 2-((2-(1-((benzyloxy)carbonyl)piperidine-4-carboxamido)-5-(trifluoromethyl)phenyl)amino)nicotinate (11b)



Prepared according to **General procedure A**, using 3-oxo-1,3-dihydroisobenzofuran-1-yl 2-((3-(trifluoromethyl)phenyl)amino)nicotinate (*talniflumate,* 104 mg, 0.25 mmol) and benzyl 4-(5-oxo-

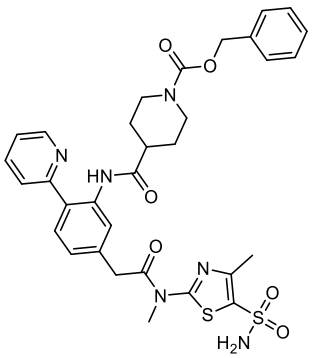
1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using basic mobile phase and the UV chromatogram is shown below:



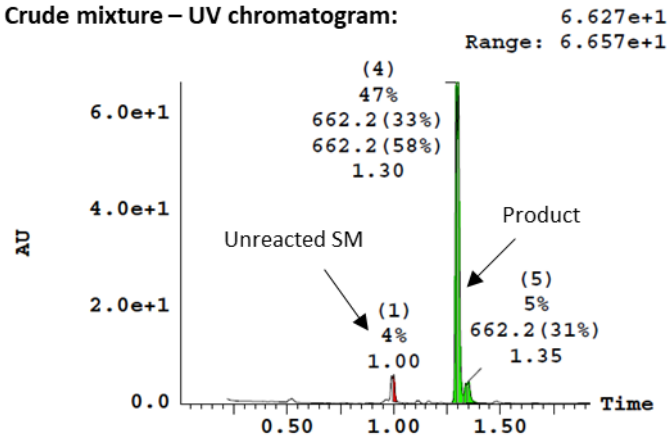
Purification by automated flash column chromatography (0-70% EtOAc/heptane) afforded derivative **11b** as a pale-yellow solid (48.2 mg, 29%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 9.74 (s, 1 H), 8.34 (dd, *J* = 4.8, 2.0 Hz, 1 H), 8.22 (dd, *J* = 7.9, 1.9 Hz, 1 H), 8.17 (s, 1 H), 8.10 (d, *J* = 8.6 Hz, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.92–7.79 (m, 2 H), 7.76–7.69 (m, 2 H), 7.65 (s, 1 H), 7.50 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.40–7.28 (m, 5 H), 6.79 (dd, *J* = 7.9, 4.8 Hz, 1 H), 5.11 (s, 2 H), 4.19 (br s, 2 H), 2.87 (br s, 2 H), 2.43 (tt, *J* = 11.3, 3.7 Hz, 1 H), 1.82–1.97 (m, 2 H), 1.59–1.75 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 172.9, 167.5, 165.9, 156.6, 155.2, 153.5, 143.7, 141.9, 136.7, 135.4 (br), 135.1, 131.7, 130.7 (br), 128.5 (2 C), 128.0, 127.9 (2 C), 127.5 (q, $^2J_{C\text{-}F}$ = 32.7), 126.5, 126.1, 124.7, 123.8, 123.7 (q, $^1J_{C\text{-}F}$ = 272.6), 123.3 (br), 122.8 (br), 114.6, 106.7, 93.3, 67.2, 43.7 (br, 2 C), 43.3, 28.4, 28.3; **^{19}F NMR** (471 MHz, $CDCl_3$) δ (ppm) -62.2 (s, 3 F).

The spectroscopic data was consistent with what reported in the literature.[1]

Benzyl 4-((5-(2-(methyl(4-methyl-5-sulfamoylthiazol-2-yl)amino)-2-oxoethyl)-2-(pyridin-2-yl)phenyl)carbamoyl)piperidine-1-carboxylate (11c)



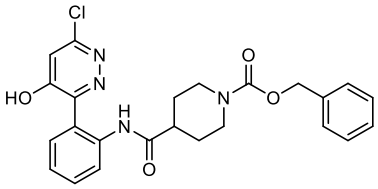
Prepared according to **General procedure A**, using *N*-methyl-*N*-(4-methyl-5-sulfamoylthiazol-2-yl)-2-(4-(pyridin-2-yl)phenyl)acetamide (*pritelivir*, 20.1 mg, 0.05 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (16.7 mg, 0.06 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:



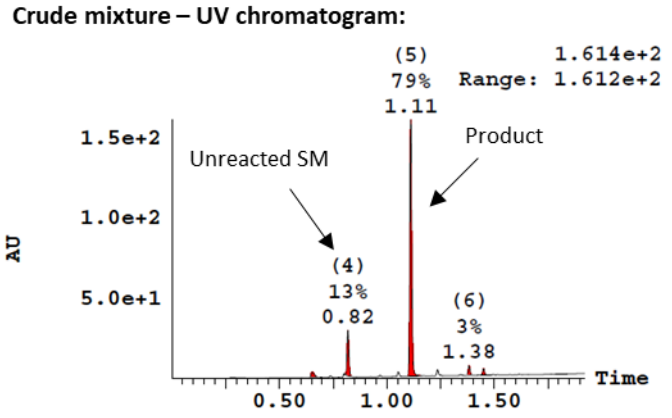
Purification by automated reverse phase flash column chromatography (5-95% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11c** as a white solid (24.3 mg, 73%). **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm) 12.12 (s, 1 H), 8.69 (dd, *J* = 5.1, 1.7 Hz, 1 H), 8.27 (s, 1 H), 7.98 (td, *J* = 7.8, 1.9 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 1 H), 7.81 (d, *J* = 8.1 Hz, 1 H), 7.64 (s, 2 H), 7.43 (dd, *J* = 7.5, 4.9 Hz, 1 H), 7.39–7.29 (m, 5 H), 7.12 (dd, *J* = 8.2, 1.9 Hz, 1 H), 5.09 (s, 2 H), 4.21 (s, 2 H), 4.04 (dt, *J* = 13.4, 3.7 Hz, 2 H), 3.71 (s, 3 H), 2.93 (br s, 2 H), 2.59–2.53 (m, 1 H), 2.48 (s, 3 H), 1.93–1.84 (br m, 2 H), 1.49 (qd, *J* = 12.3, 4.2 Hz, 2 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm) 172.4, 171.6, 158.4, 156.8, 154.4, 148.1, 147.8, 138.1, 137.1, 137.0, 135.8, 129.2, 128.4 (2 C), 128.3, 127.8, 127.5 (2 C), 125.2, 125.1, 123.1, 123.0, 122.4, 66.1, 43.1 (2 C), 43.0, 40.5, 34.2, 28.1 (br, 2C), 16.1.

The spectroscopic data was consistent with what reported in the literature.[1]

Benzyl 4-((2-(6-chloro-4-hydroxypyridazin-3-yl)phenyl)carbamoyl)piperidine-1-carboxylate (11d)

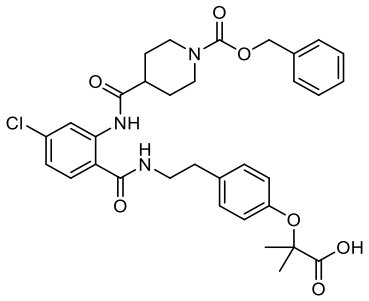


Prepared according to **General procedure A**, using 6-chloro-3-phenylpyridazin-4-ol (*pyridafol*, 51.7 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:

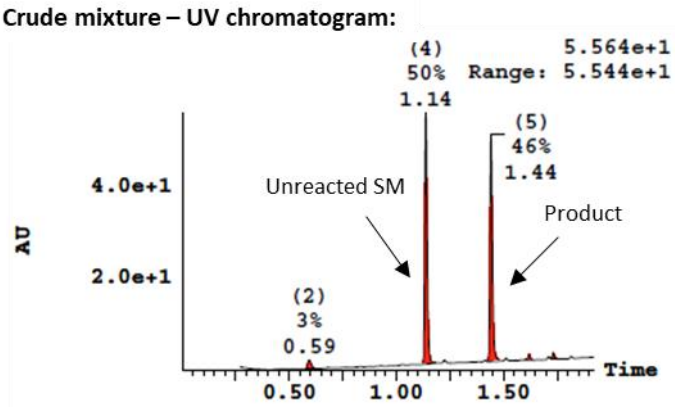


Purification by automated reverse phase flash column chromatography (5-95% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11d** as a white solid (56.2 mg, 48%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 10.08 (s, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.44 (td, *J* = 7.7, 1.6 Hz, 1 H), 7.39–7.27 (m, 5 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.52 (s, 1 H), 5.14 (s, 2 H), 4.15 (br s, 2 H), 2.97 (br s, 2 H), 2.52 (tt, *J* = 10.8, 3.8 Hz, 1 H), 1.99 (s, 1 H), 1.89 (br d, *J* = 11.3 Hz, 2 H), 1.81–1.70 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 175.8, 170.9, 155.4, 154.9, 143.7, 136.8, 136.3, 131.5, 130.4, 128.9, 128.6 (2 C), 128.2, 128.0 (2 C), 126.2, 125.9, 116.5, 67.4, 43.4 (2 C), 43.2, 28.4 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{24}H_{23}ClN_4O_4$, 467.1481; found, 467.1479.

2-(4-(2-(2-(1-((Benzyloxy)carbonyl)piperidine-4-carboxamido)-4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoic acid (11e)



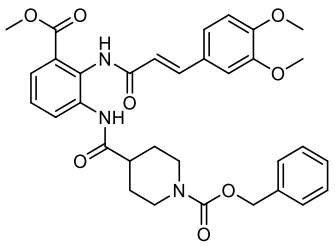
Prepared according to **General procedure A**, using 2-(4-(2-(4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoic acid (*bezafibrate,* 90.5 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:



Purification by preparative reverse phase HPLC (50-90% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11e** as a white solid (48.6 mg, 31%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.32 (s, 1 H), 8.66 (d, *J* = 2.1 Hz, 1 H), 7.39–7.34 (m, 4 H), 7.34–7.29 (m, 1 H), 7.18 (d, *J* = 8.5 Hz, 1 H), 7.15–7.08 (m, 2 H), 6.97 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.91–6.86 (m, 2 H), 6.31 (br s, 1 H), 5.14 (s, 2 H), 4.24 (br s, 2 H), 3.67 (br s, 2 H), 2.97–2.85 (m, 4 H), 2.47 (tt, *J* = 11.4, 3.7 Hz, 1 H), 1.95 (br d, *J* = 13.0 Hz, 2 H), 1.78–1.66 (m, 2 H), 1.58 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 176.0, 173.3, 168.3, 155.4, 153.4, 140.6, 138.8, 136.7, 133.0, 129.6 (2 C), 128.5 (2 C), 128.1, 127.9 (2 C), 127.3, 122.9, 121.4, 120.8 (2 C), 118.2, 79.8, 67.3, 44.3, 43.5 (2 C), 40.9, 34.6, 28.3 (2 C), 25.1 (2 C).

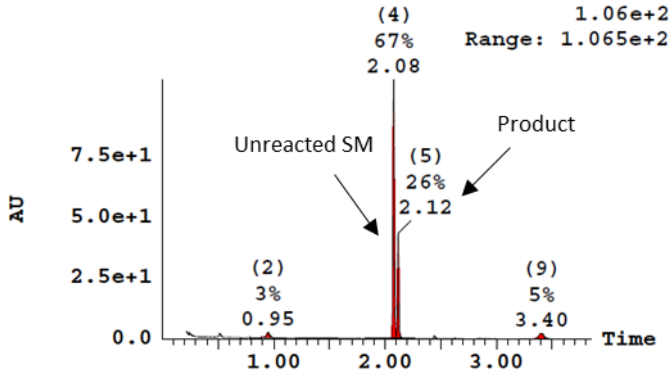
The spectroscopic data was consistent with what reported in the literature.[1]

Benzyl (*E*)-4-((2-(3-(3,4-dimethoxyphenyl)acrylamido)-3-(methoxycarbonyl)phenyl)carbamoyl)piperidine-1-carboxylate (11f)



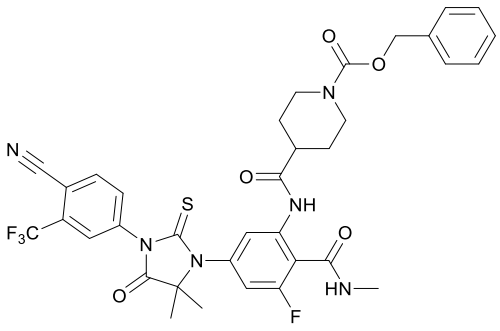
Prepared according to **General procedure A**, using (*E*)-2-(3-(3,4-dimethoxyphenyl)acrylamido)benzoic acid (*tranilast,* 85.0 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using basic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:



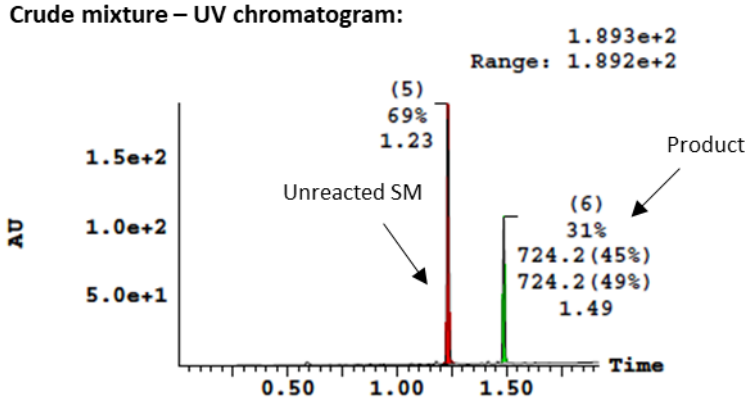
Purification by supercritical fluid chromatography SFC (15-20% MeOH/H_2O/NH_3 97/3/0.5 in supercritical CO_2, 254 nm) afforded derivative **11f** as a white solid (33.9 mg, 23%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 10.69 (s, 1 H), 9.41 (s, 1 H), 8.02 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.87 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.75 (d, *J* = 15.5 Hz, 1 H), 7.37–7.27 (m, 6 H), 7.19 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.12 (d, *J* = 2.0 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 6.58 (d, *J* = 15.4 Hz, 1 H), 5.11 (br s, 2 H), 4.20 (br s, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 2.90 (br s, 2 H), 2.45 (tt, *J* = 11.3, 3.7 Hz, 1 H), 1.93 (br s, 2 H), 1.81–1.66 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 173.1, 168.6, 166.3, 155.3, 151.5, 149.4, 144.0, 136.9, 132.4, 132.1, 132.0, 128.6 (2 C), 128.1, 128.0, 127.9 (2 C), 127.2, 125.4, 123.2, 121.2, 117.7, 111.2, 109.8, 67.2, 56.1 (2 C), 52.8, 43.8, 43.5 (2 C), 28.5 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{33}H_{35}N_3O_8$, 602.6635; found, 602.6629.

Benzyl 4-((5-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-3-fluoro-2-(methylcarbamoyl)phenyl)carbamoyl)piperidine-1-carboxylate (11g)



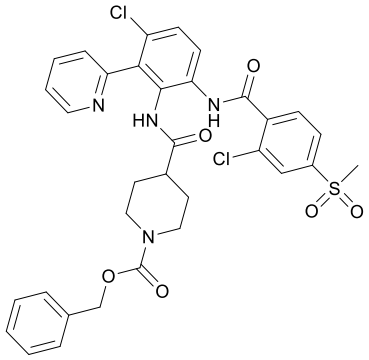
On the benchtop, an oven-dried microwave vial was charged with 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide (*enzalutamide,* 116 mg, 0.25 mmol), benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (114 mg, 0.38 mmol) and pivalic acid (PivOH, 77.1 mg, 0.75 mmol, 300 mol%). The vial was moved into a glovebox under N_2 atmosphere, where $Cp^*Co(MeCN)_3(SbF_6)_2$ (197 mg, 0.25 mmol, 100 mol%) was added. The vial was sealed and taken out of the glovebox. Anhydrous EtOAc (0.1 M, 2.5 mL) was then added by syringe under N_2 atmosphere, and the vial was stirred at 60 °C for 16 h. The reaction mixture was then allowed to cool down to room temperature and analysed by LC-MS, using acidic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:

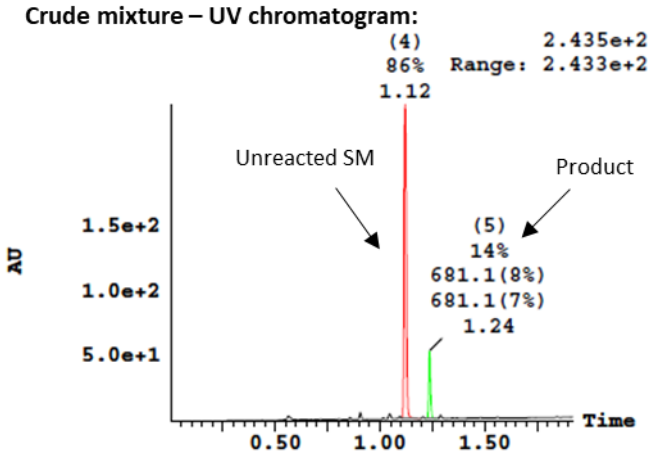


The reaction crude was filtered through a plug of silica, eluting with EtOAc. After removal of the volatiles under reduced pressure, the crude material was purified by automated reverse phase flash column chromatography (30-80% MeCN in HCO_2H buffer, 254 nm) to afford derivative **11g** as a white solid (30.5 mg, 17%).**^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 12.03 (s, 1 H), 8.66 (d, *J* = 2.1 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.93 (d, *J* = 2.0 Hz, 1 H), 7.81 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.40–7.28 (m, 5 H), 7.00–6.84 (m, 2 H), 5.14 (s, 2 H), 4.26 (br s, 2 H), 3.05 (d, *J* = 4.7 Hz, 3 H), 2.91 (br s, 2 H), 2.51 (tt, *J* = 11.5, 3.3 Hz, 1 H), 1.98 (br s, 2 H), 1.82–1.68 (m, 2 H), 1.65 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 179.6, 174.7, 173.8, 165.3, 161.1 (d, $^1J_{C\text{-}F}$ = 246.9), 155.3, 143.2 (d, $^3J_{C\text{-}F}$ = 6.2), 139.1 (d, $^2J_{C\text{-}F}$ = 14.6), 137.0, 136.9, 135.5, 133.9 (q, $^2J_{C\text{-}F}$ = 33.3), 132.3, 128.7 (2 C), 128.2, 128.0 (2 C), 127.3 (q, $^3J_{C\text{-}F}$ = 4.9), 122.0 (q, $^1J_{C\text{-}F}$ = 274.4), 118.4 (d, $^4J_{C\text{-}F}$ = = 2.9), 114.9, 111.9 (d, $^2J_{C\text{-}F}$ = 28.0), 110.6, 108.7 (d, $^3J_{C\text{-}F}$ = 13.8), 67.3, 67.0, 44.8, 43.5 (2 C), 28.4 (2 C), 27.1, 24.0 (2 C); **^{19}F NMR** (471 MHz, $CDCl_3$) δ (ppm) -62.0 (s, 3 F), -108.4; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{35}H_{32}F_4N_6O_5S$, 725.2164; found, 725.2165.

Benzyl 4-((3-chloro-6-(2-chloro-4-(methylsulfonyl)benzamido)-2-(pyridin-2-yl)phenyl)carbamoyl)piperidine-1-carboxylate (11h)

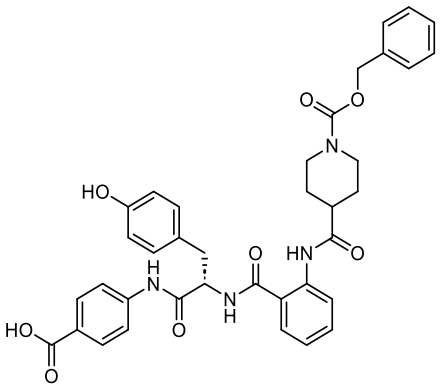


Prepared according to **General procedure A**, using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (*vismodegib*, 105 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:



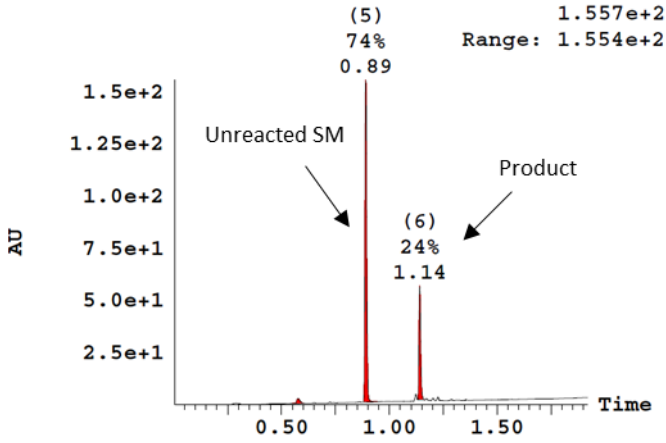
Purification by preparative reverse phase HPLC (30-70% MeCN in NH_4HCO_3 buffer, 254 nm) afforded derivative **11h** as a white solid (17.0 mg, 10%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 9.70 (s, 1 H), 9.21 (s, 1 H), 8.64 (d, *J* = 5.0 Hz, 1 H), 8.12 (d, *J* = 8.9 Hz, 1 H), 8.02 (d, *J* = 1.6 Hz, 1 H), 7.96 (t, *J* = 7.8 Hz, 1 H), 7.90 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.53 (d, *J* = 8.9 Hz, 1 H), 7.47–7.40 (m, 1 H), 7.39–7.28 (m, 5 H), 5.11 (s, 2 H), 4.04 (br d, *J* = 13.6 Hz, 2 H), 3.09 (s, 3 H), 2.75 (br s, 2 H), 2.34 (t, *J* = 11.5 Hz, 1 H), 1.54 (br d, *J* = 12.8 Hz, 2 H), 1.36–1.21 (m, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 174.3, 163.7, 155.2, 154.6, 148.9, 143.4, 140.8, 137.3, 136.7, 132.3, 131.1, 130.6, 130.0, 129.5, 129.3, 128.70 (2 C), 128.65, 128.3, 128.1 (2 C), 128.0, 127.6, 127.0, 126.2, 123.6, 67.4, 44.6, 43.5, 43.3 (2 C), 28.3 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{33}H_{30}Cl_2N_4O_6S$, 681.1336; found, 681.1337.

(*S*)-4-(2-(2-(1-((Benzyloxy)carbonyl)piperidine-4-carboxamido)benzamido)-3-(4-hydroxyphenyl)propanamido)benzoic acid (11j)



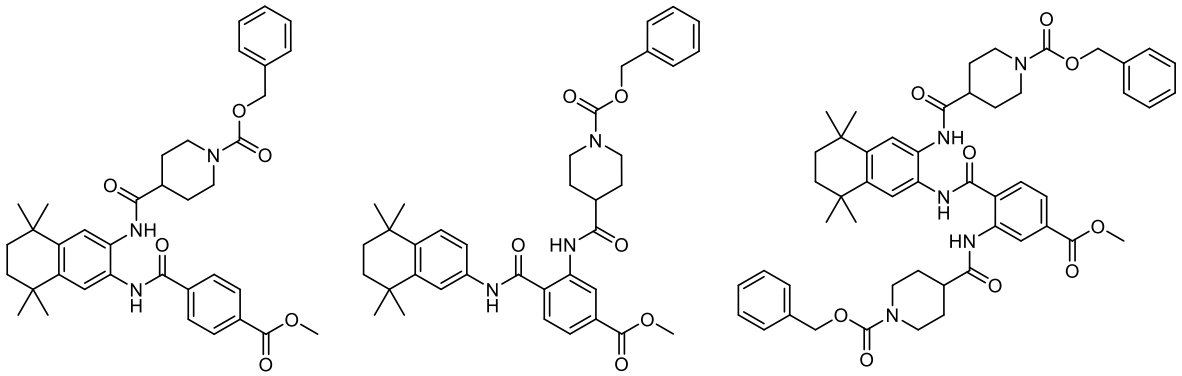
Prepared according to **General procedure A**, using (*S*)-4-(2-benzamido-3-(4-hydroxyphenyl)propanamido)benzoic acid (*bentiromide*, 101 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:



Purification by preparative reverse phase HPLC (15-60% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11j** as a white solid (41.9 mg, 25%). **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm) 12.76 (s, 1 H), 10.84 (s, 1 H), 10.49 (s, 1 H), 9.21 (br s, 1 H), 9.00 (d, *J* = 8.0 Hz, 1 H), 8.26 (d, *J* = 8.3 Hz, 1 H), 7.92 (d, *J* = 8.6 Hz, 2 H), 7.76 (d, *J* = 8.7 Hz, 2 H), 7.67 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.51–7.44 (m, 1 H), 7.41–7.27 (m, 5 H), 7.22–7.12 (m, 3 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 5.05 (br s, 2 H), 4.82 (ddd, *J* = 10.5, 7.9, 4.4 Hz, 1 H), 4.04–3.90 (br m, 2 H), 3.10 (dd, *J* = 13.9, 4.4 Hz, 1 H), 2.96 (dd, *J* = 13.9, 10.6 Hz, 1 H), 2.82 (br s, 2 H), 2.45 (tt, *J* = 11.5, 3.7 Hz, 1 H), 1.83–1.72 (br m, 2 H), 1.42 (pd, *J* = 11.9, 4.3 Hz, 2 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm) 172.6, 170.8, 168.5, 166.9, 155.9, 154.3, 142.9, 138.2, 137.0, 131.8, 130.4 (2 C), 130.2 (2 C), 128.45 (2 C), 128.36, 127.8 (2 C), 127.5 (2 C), 125.4, 122.8, 121.9, 120.8, 118.7 (2 C), 114.9 (2 C), 66.2, 56.1, 43.1, 42.9 (2 C), 36.2, 28.0 (br, 2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{37}H_{36}N_4O_8$, 665.2611; found, 665.2618.

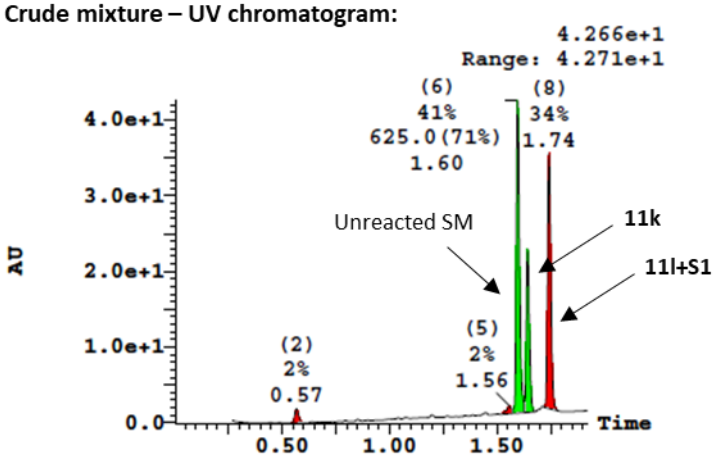
Benzyl 4-((3-(4-(methoxycarbonyl)benzamido)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)piperidine-1-carboxylate (11k), benzyl 4-((5-(methoxycarbonyl)-2-((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)phenyl)carbamoyl)piperidine-1-carboxylate (11l) and benzyl 4-((3-(2-(1-((benzyloxy)carbonyl)piperidine-4-carboxamido)-4-(methoxycarbonyl)benzamido)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)piperidine-1-carboxylate (S1)



11k **11l** **S1**

Prepared according to **General procedure A**, using 4-((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl)benzoic acid (*tamibarotene,* 91.3 mg, 0.25 mmol) and benzyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate **4a** (83.7 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LCMS using acidic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:



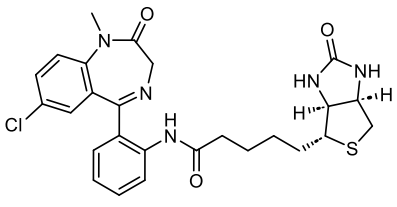
Purification by preparative reverse phase HPLC (50-95% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11k** as a white solid (37.7 mg, 24%), followed by a 7:3 mixture of **11l** and bis-functionalised derivative **S1**. Subsequent purification by supercritical fluid chromatography SFC (35% IPA/DEA 100/20mM in supercritical CO_2, 230 nm) afforded derivatives **11l** (27.5 mg, 18%) and **S1** (19.3 mg, 9%) as white solids.

11k: **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 10.86 (s, 1 H), 9.09 (s, 1 H), 8.52–8.42 (m, 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 7.51 (dd, *J* = 8.4, 2.3 Hz, 1 H), 7.45 (d, *J* = 2.4 Hz, 1 H), 7.40–7.28 (m, 6 H), 5.13 (s, 2 H), 4.25 (br s, 2 H), 3.80 (s, 3 H), 2.89 (br s, 2 H), 2.46 (tt, *J* = 11.5, 3.8 Hz, 1 H), 1.95 (br s, 2 H), 1.85–1.72 (br m, 2 H), 1.70 (s, 4 H), 1.31 (s, 6 H), 1.29 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 173.5, 166.6, 166.2, 155.3, 146.1, 142.6, 139.3, 136.8, 134.7, 133.6, 128.6 (2 C), 128.1, 128.0 (2 C), 127.5, 127.2, 125.0, 124.0, 122.6, 119.0, 118.9, 67.3, 52.6, 44.4, 43.5 (2 C), 35. (2 C), 34.6, 34.2, 32.0 (4 C), 28.4 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{37}H_{43}N_3O_6$, 626.3230; found, 626.3239.

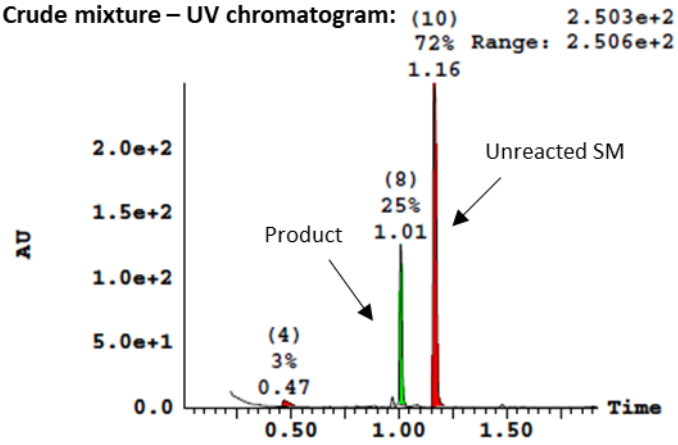
11l: **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 9.18 (s, 1 H), 8.18–8.11 (m, 3 H), 8.02–7.96 (m, 2 H), 7.57 (s, 1 H), 7.38–7.28 (m, 5 H), 7.19 (s, 1 H), 5.11 (s, 2 H), 4.19 (br s, 2 H), 3.96 (s, 3 H), 2.82 (br s, 2 H), 2.43 (tt, *J* = 11.5, 3.8 Hz, 1 H), 1.90–1.81 (m, 2 H), 1.76–1.61 (m, 6 H), 1.25 (s, 6 H), 1.21 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 174.1, 166.4, 165.0, 155.3, 144.2, 143.8, 138.0, 136.7, 133.2, 130.1 (2 C), 128.7 (2 C), 128.4, 128.2, 128.0 (2 C), 127.6, 127.5 (2 C), 124.0, 123.0, 67.4, 52.6, 43.5, 43.4 (2 C), 34.9 (2 C), 34.3, 34.2, 31.88 (2 C), 31.86 (2 C), 28.6 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{37}H_{43}N_3O_6$, 626.3230; found, 626.3232.

S1: **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 11.36 (s, 1 H), 9.45 (s, 1 H), 9.27 (s, 1 H), 7.85–7.70 (m, 3 H), 7.61 (s, 1 H), 7.42–7.28 (m, 10 H), 7.09 (s, 1 H), 5.11 (s, 4 H), 4.21 (br s, 4 H), 3.93 (s, 3 H), 2.84 (s, 4 H), 2.45 (t, *J* = 12.0 Hz, 2 H), 2.01–1.81 (m, 4 H), 1.69 (s, 8 H), 1.30 (s, 6 H), 1.25 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 174.5, 173.5, 166.8, 166.2, 155.33, 155.26, 144.6, 144.3, 140.3, 136.8, 136.7, 134.2, 128.7–128.6 (4 C), 128.23, 128.17, 128.14, 128.08 (2 C), 128.0 (2 C), 127.4, 127.2, 124.4, 124.1, 123.4, 122.8, 122.7, 67.4, 67.3, 52.7, 44.5, 43.6, 43.5 (2 C), 43.3 (2 C), 34.9 (2 C), 34.4, 34.3, 31.9 (4 C), 28.7 (br, 2 C), 28.5 (2 C); **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{51}H_{59}N_5O_9$, 886.4386; found, 886.4392.

***N*-(2-(7-Chloro-1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[e][1,4]diazepin-5-yl)phenyl)-5-((3a*S*,4*R*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (11m)**

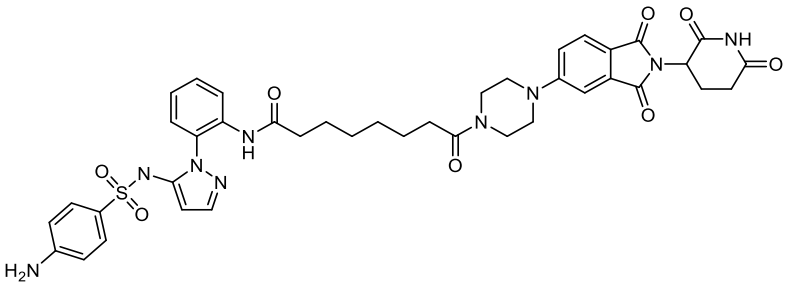


Prepared according to **General procedure A**, using 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (*diazepam,* 71.2 mg, 0.25 mmol) and 3-(4-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)butyl)-1,4,2-dioxazol-5-one **4k** (78.0 mg, 0.28 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using basic mobile phase and the UV chromatogram is shown below:



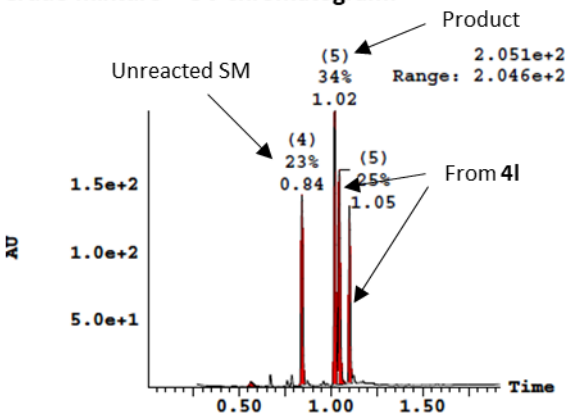
Purification by preparative reverse phase HPLC (15-55% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11m** as a white solid (19.6 mg, 15%). **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm) 10.47–10.31 (m, 1 H), 7.80 (t, *J* = 7.4 Hz, 1 H), 7.66 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.57 (d, *J* = 8.9 Hz, 1 H), 7.47 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.26 (br d, *J* = 7.5 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.07 (s, 1 H), 6.44 (br d, *J* = 5.0 Hz, 1 H), 6.36 (br s, 1 H), 4.61 (d, *J* = 11.0 Hz, 1 H), 4.29 (dd, *J* = 7.7, 5.0 Hz, 1 H), 4.15–4.08 (m, 1 H), 3.81 (dd, *J* = 10.9, 6.1 Hz, 1 H), 3.32 (s, 3 H), 3.12–3.03 (m, 1 H), 2.80 (ddd, *J* = 12.7, 7.9, 5.1 Hz, 1 H), 2.60–2.53 (m, 1 H), 2.14–1.98 (m, 2 H), 1.65–1.54 (m, 1 H), 1.52–1.35 (m, 3 H), 1.35–1.19 (m, 2 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm) 170.8, 168.69, 168.66, 162.7, 142.4, 137.2, 131.8, 131.3, 130.7, 130.3, 129.5 (br), 128.7, 127.7, 124.0 (br), 123.8, 61.1, 59.2, 56.4, 55.4, 39.6, 36.1 (br), 34.6, 28.2, 28.14, 28.06, 24.9; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{26}H_{28}ClN_5O_3S$, 526.1680; found, 526.1686.

(±)-*N*-(2-(5-((4-Aminophenyl)sulfonamido)-1*H*-pyrazol-1-yl)phenyl)-8-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)-8-oxooctanamide (11n)



Prepared according to **General procedure A**, using 4-amino-*N*-(1-phenyl-1*H*-pyrazol-5-yl)benzenesulfonamide (*sulfaphenazole*, 47.2 mg, 0.15 mmol) and (±)-2-(2,6-dioxopiperidin-3-yl)-5-(4-(7-(5-oxo-1,4,2-dioxazol-3-yl)heptanoyl)piperazin-1-yl)isoindoline-1,3-dione **4l** (88.9 mg, 0.17 mmol) as substrates. The crude reaction mixture was analysed by LC-MS using acidic mobile phase and the UV chromatogram is shown below:

Crude mixture – UV chromatogram:

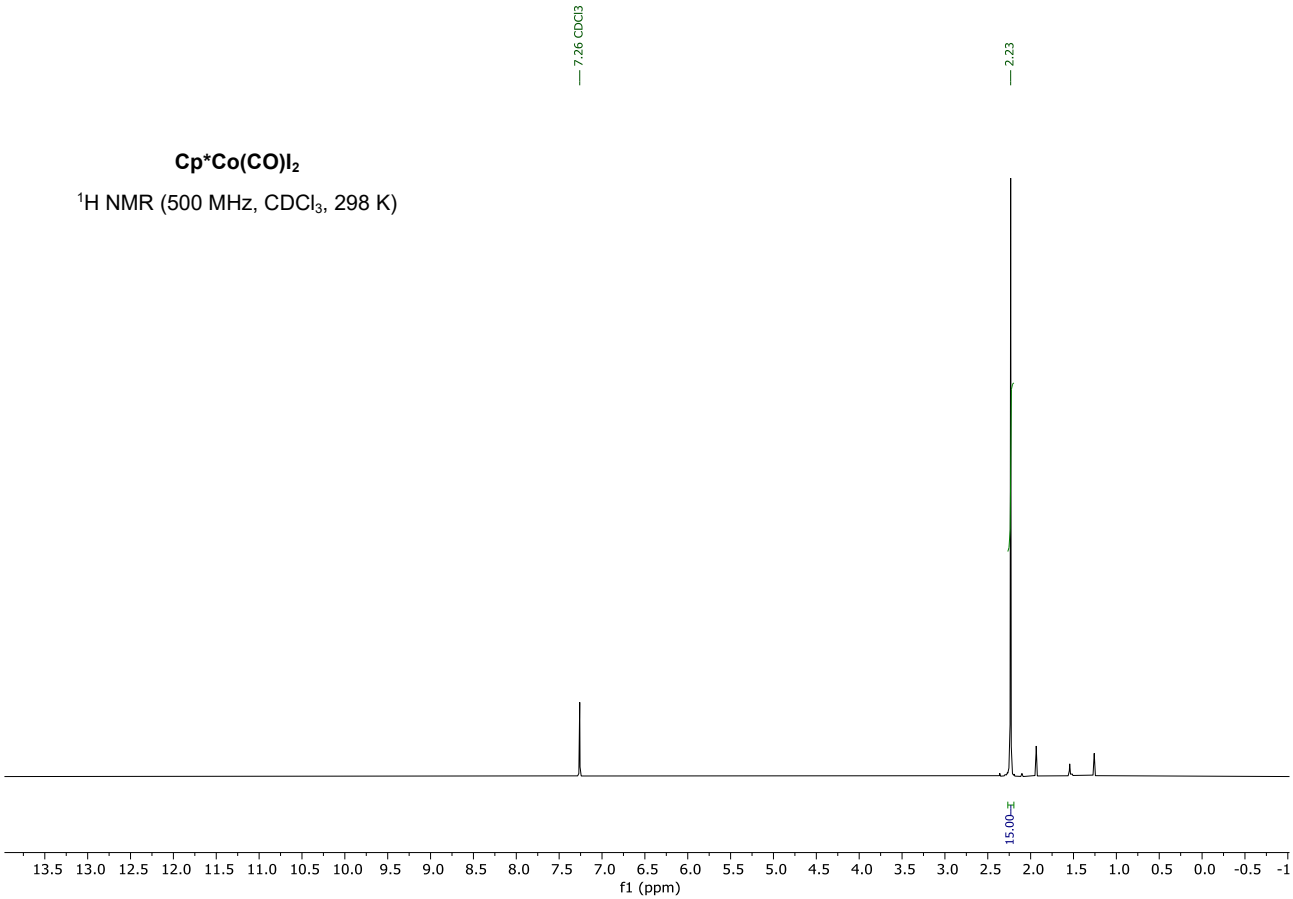


Purification by preparative reverse phase HPLC (15-55% MeCN in HCO_2H buffer, 254 nm) afforded derivative **11n** as a yellow solid (49.3 mg, 41%). **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm) 11.10 (s, 1 H), 9.80 (s, 1 H), 8.60 (s, 1 H), 7.99 (d, *J* = 8.2 Hz, 1 H), 7.70 (d, *J* = 8.5 Hz, 1 H), 7.62 (d, *J* = 2.0 Hz, 1 H), 7.45 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.38–7.31 (m, 3 H), 7.26–7.15 (m, 2 H), 7.08 (dd, *J* = 7.9, 1.6 Hz, 1 H), 6.59 (d, *J* = 8.7 Hz, 2 H), 6.11 (br s, 2 H), 5.86 (d, *J* = 2.0 Hz, 1 H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1 H), 3.60 (br s, 4 H), 3.52–3.42 (m, 4 H), 2.89 (ddd, *J* = 16.6, 13.6, 5.3 Hz, 1 H), 2.65–2.51 (m, 2 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 2.17 (t, *J* = 7.3 Hz, 2 H), 2.06–1.97 (m, 1 H), 1.53–1.38 (m, 4H), 1.29–1.14 (m, 4 H); **^{13}C NMR** (126 MHz, DMSO-d_6) δ (ppm) 172.9, 171.0, 170.9, 170.1, 167.6, 167.0, 154.9, 153.3, 140.3, 137.0 (br), 134.2, 133.9, 129.1, 129.0 (2 C), 127.8, 125.0, 124.2, 124.0, 123.7, 118.5, 117.8, 112.6 (3 C), 108.0, 101.1 (br), 48.8, 46.8, 46.6, 44.1, 40.4, 36.4, 32.2, 31.0, 28.5, 28.2, 24.8, 24.5, 22.2; **HRMS** (m/z): $[M+H]^+$ calcd. for $C_{40}H_{43}N_9O_8S$, 810.3034; found, 810.3036.

6. ^{1}H and ^{13}C NMR spectra

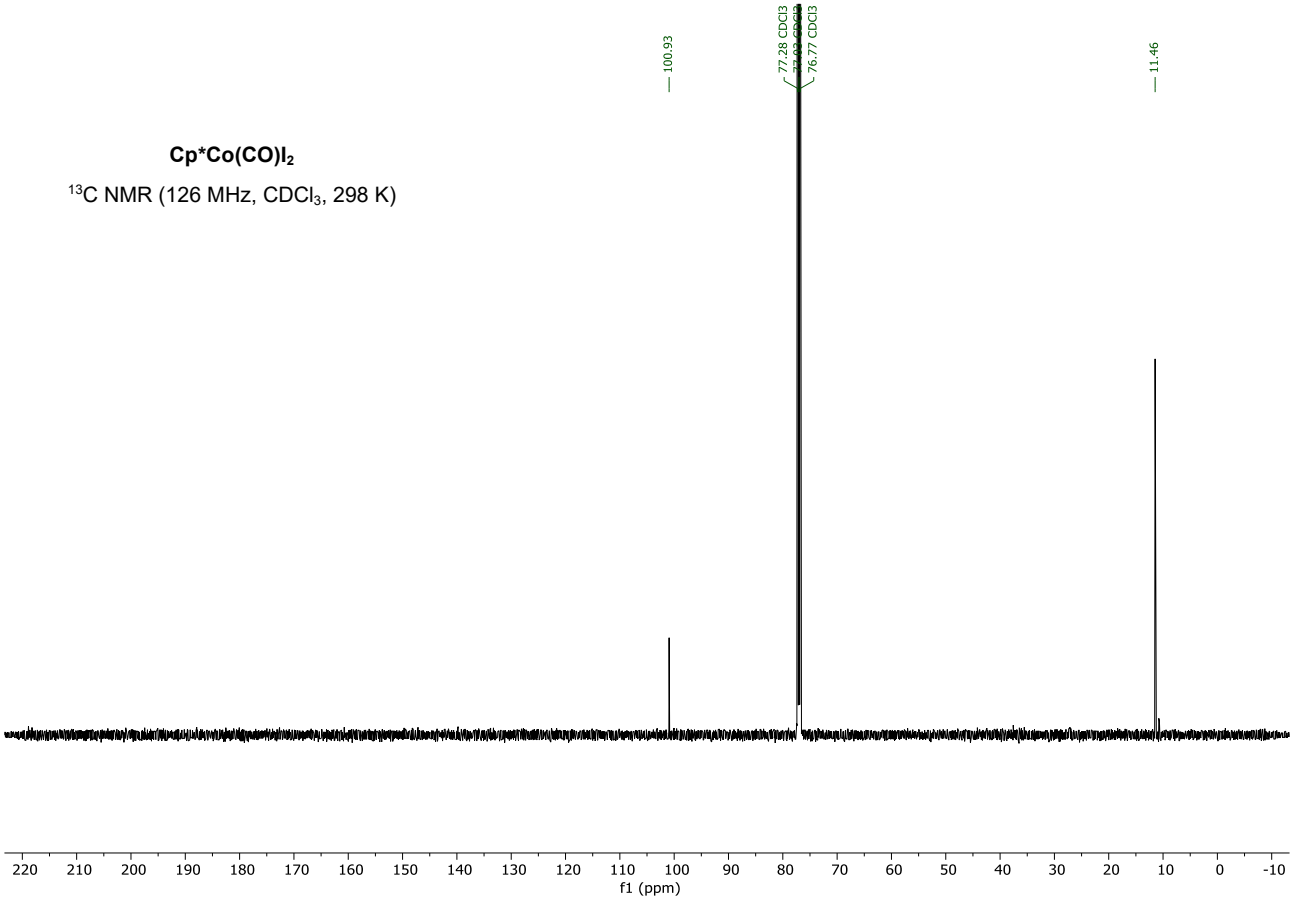
$Cp^*Co(CO)I_2$

^1H NMR (500 MHz, $CDCl_3$, 298 K)



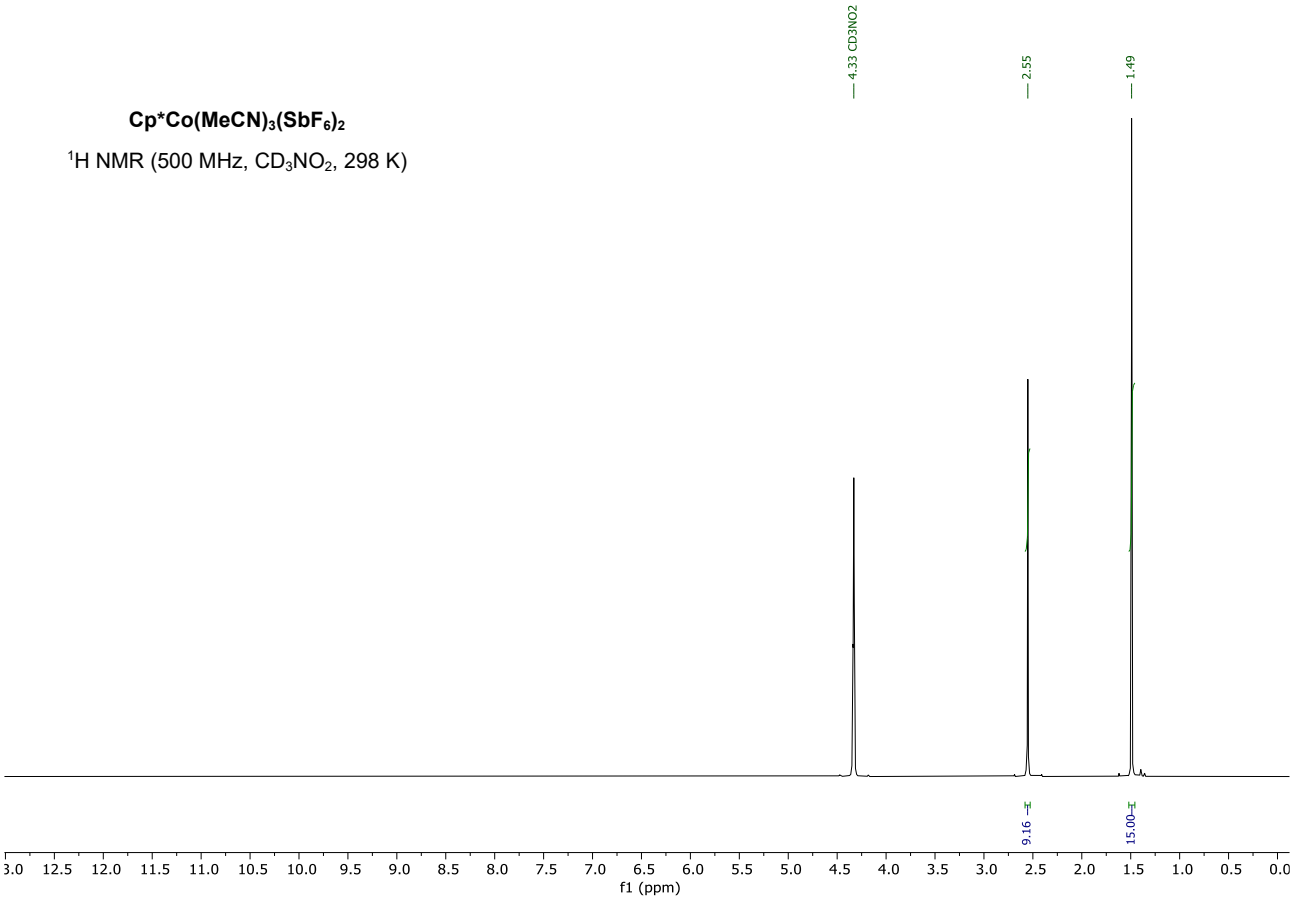
$Cp^*Co(CO)I_2$

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



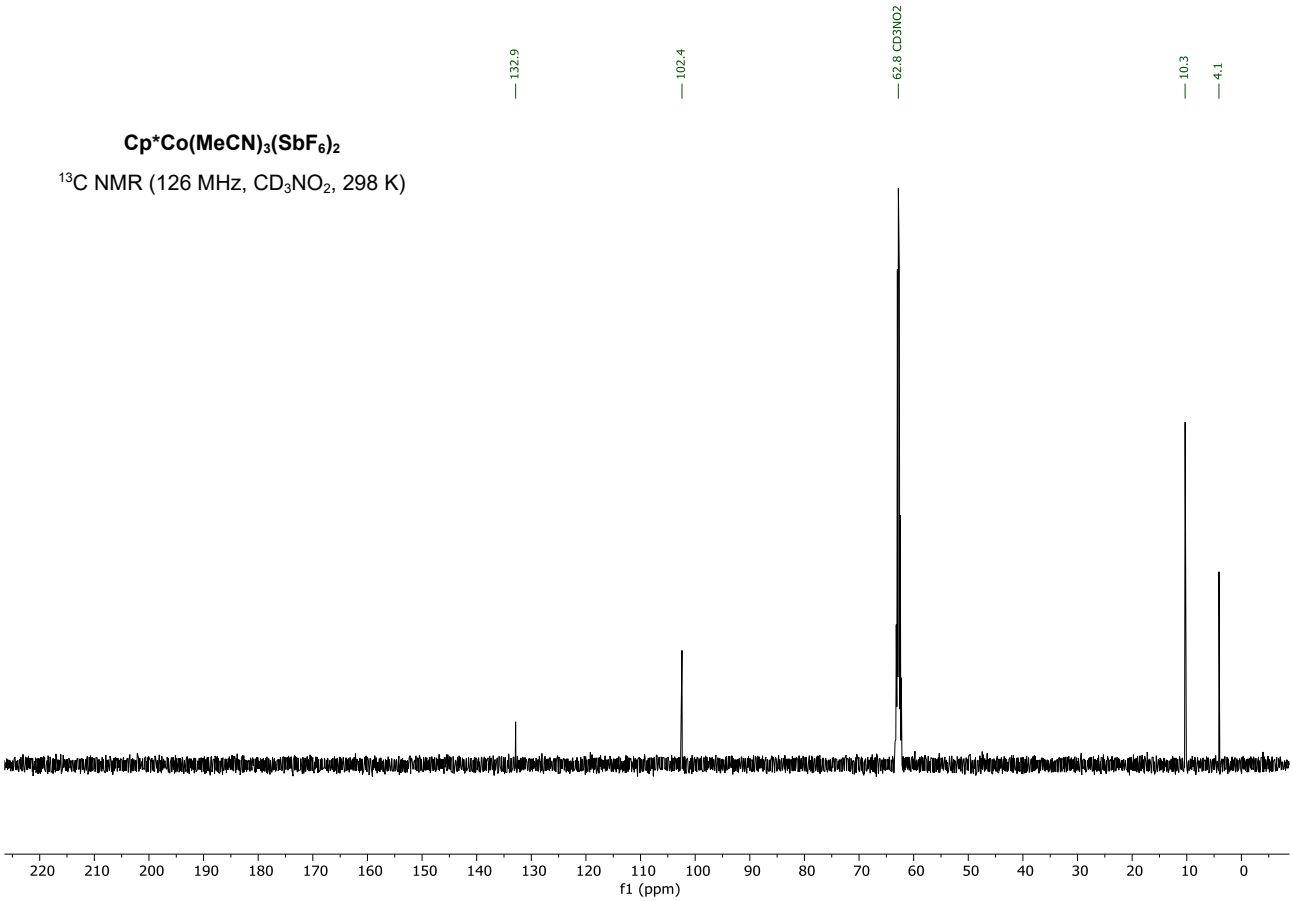
$Cp^*Co(MeCN)_3(SbF_6)_2$

^1H NMR (500 MHz, CD_3NO_2, 298 K)



$Cp^*Co(MeCN)_3(SbF_6)_2$

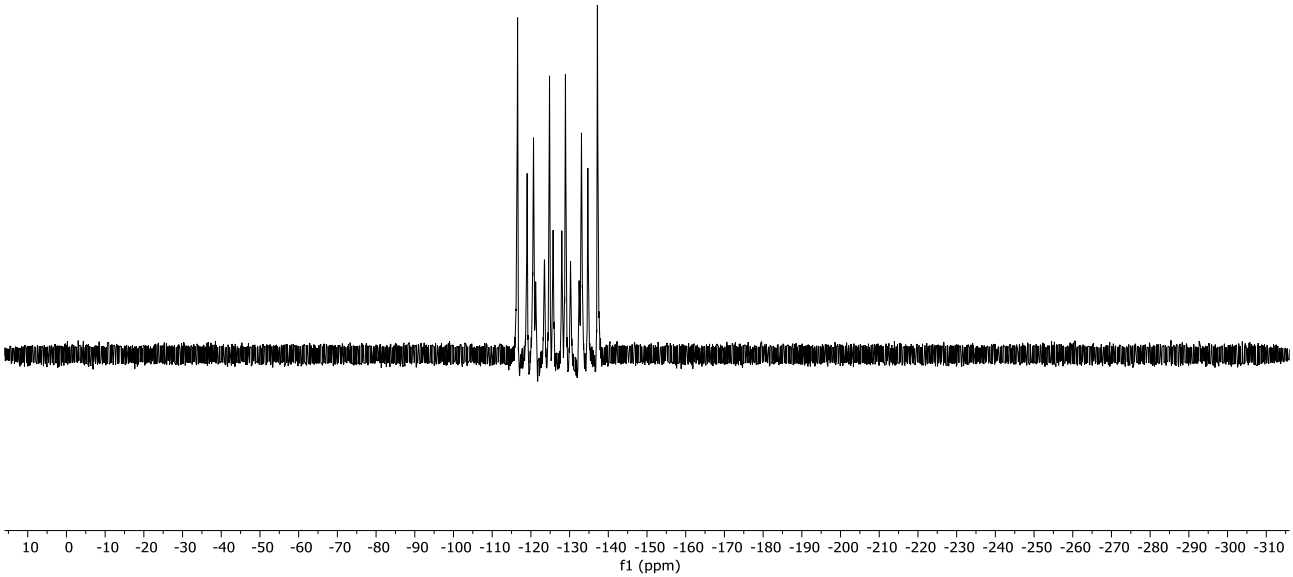
^{13}C NMR (126 MHz, CD_3NO_2, 298 K)

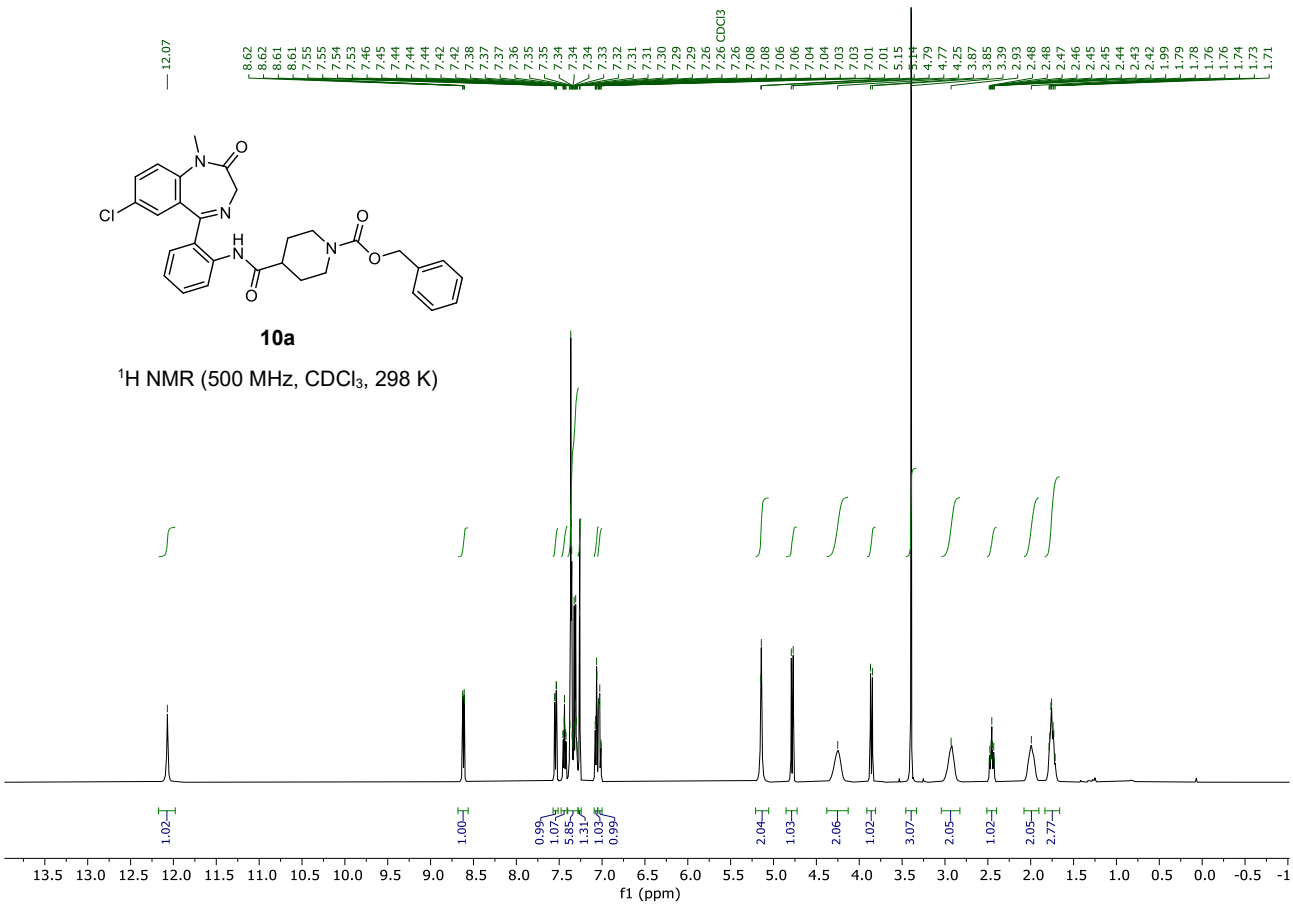


-116.54
-119.03
-120.66
-121.27
-123.49
-124.80
-125.75
-127.99
-128.94
-130.25
-132.48
-133.08
-134.71
-137.19

$Cp^*Co(MeCN)_3(SbF_6)_2$

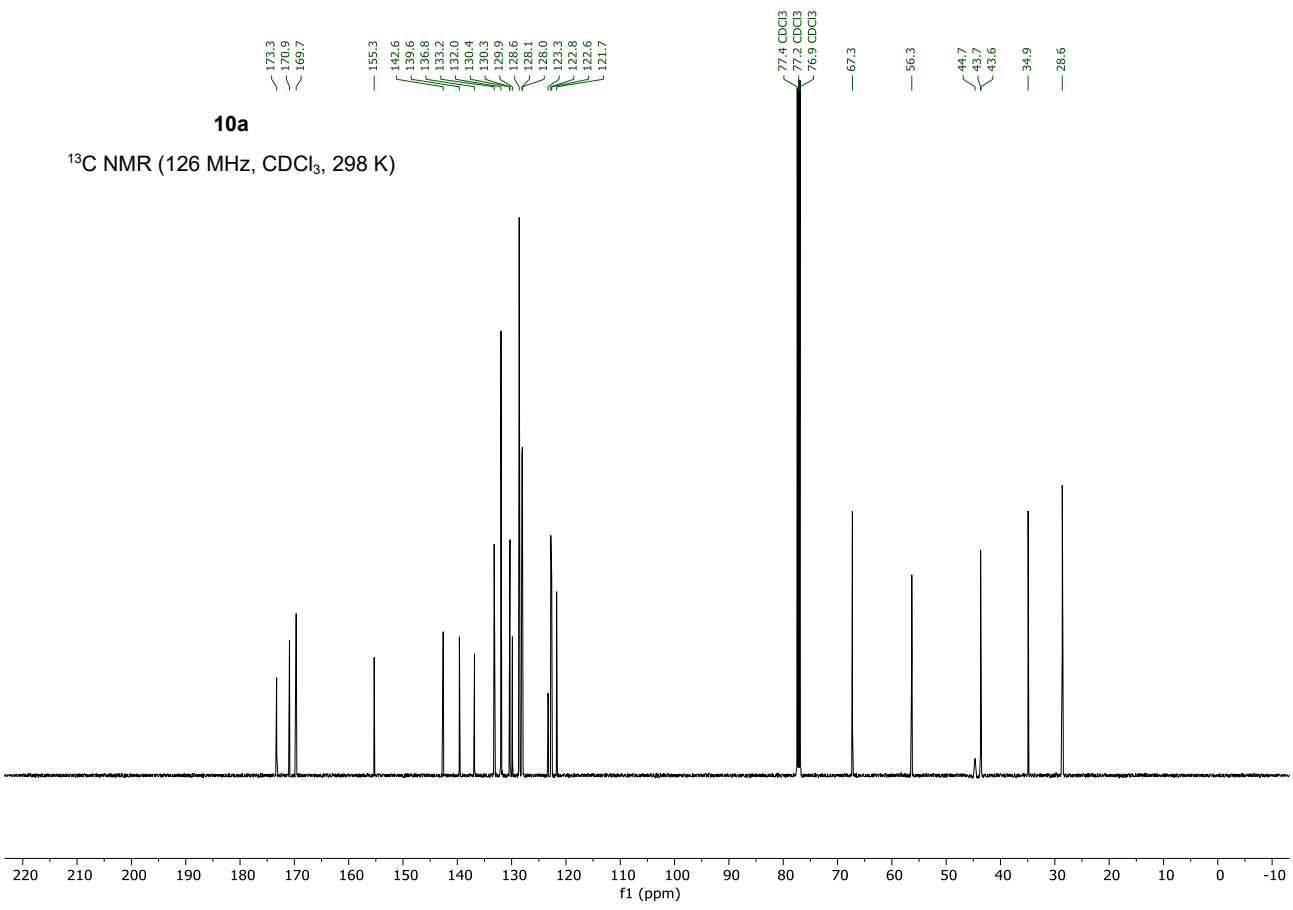
^{19}F NMR (471 MHz, CD_3NO_2, 298 K)





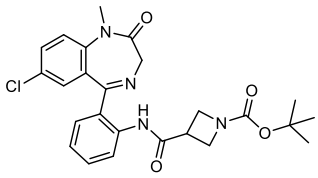
10a

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



10a

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

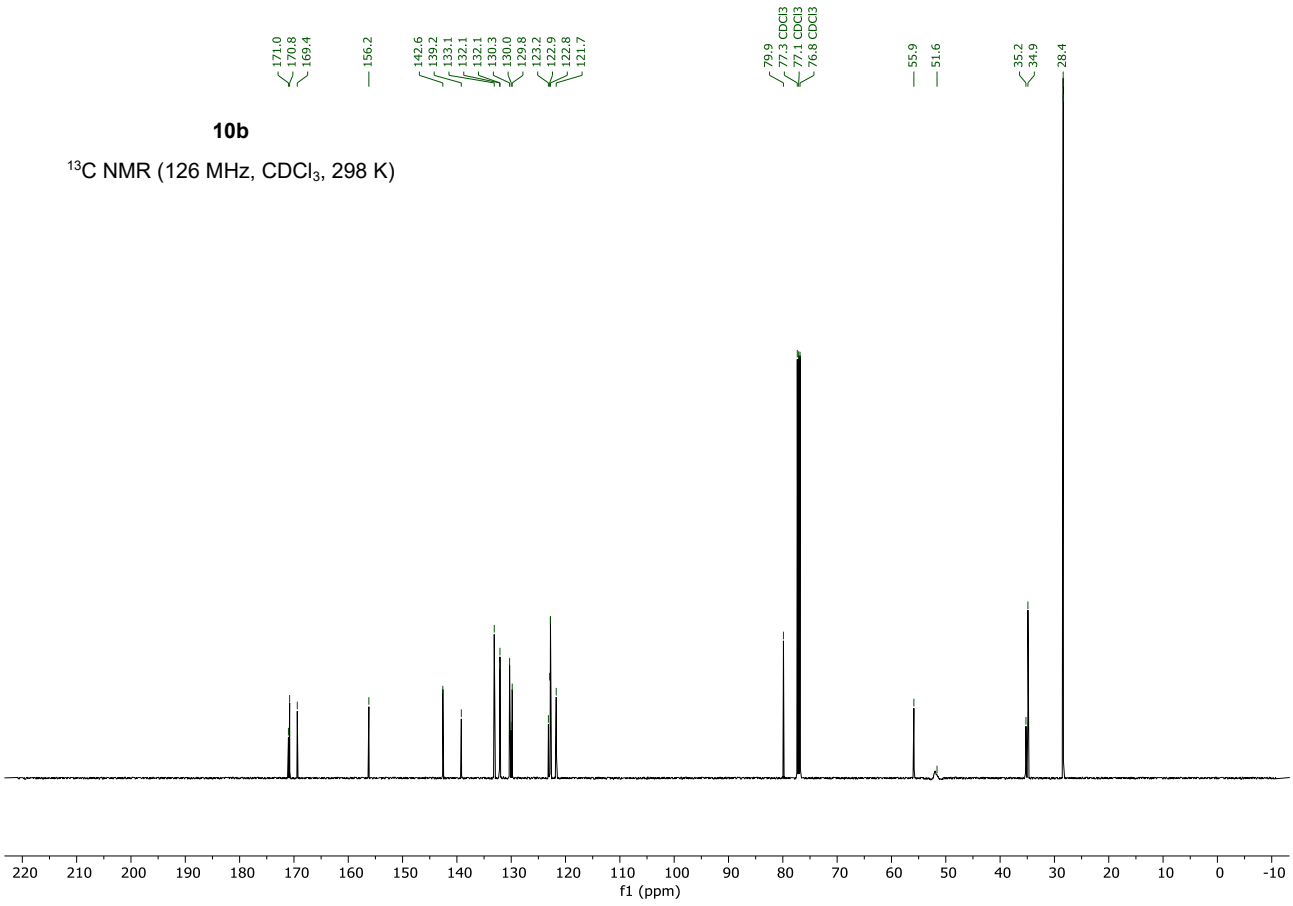


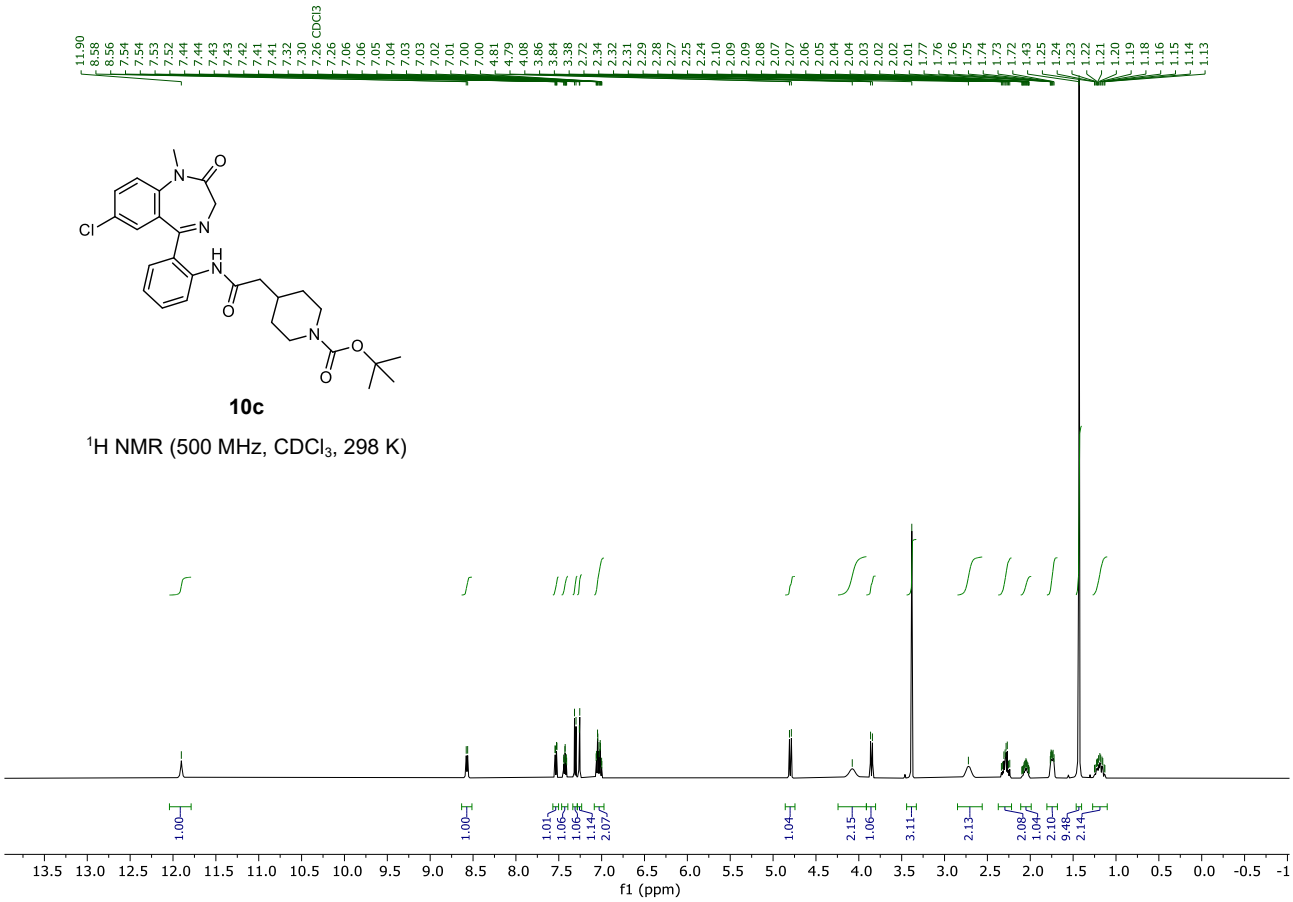
10b

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

10b

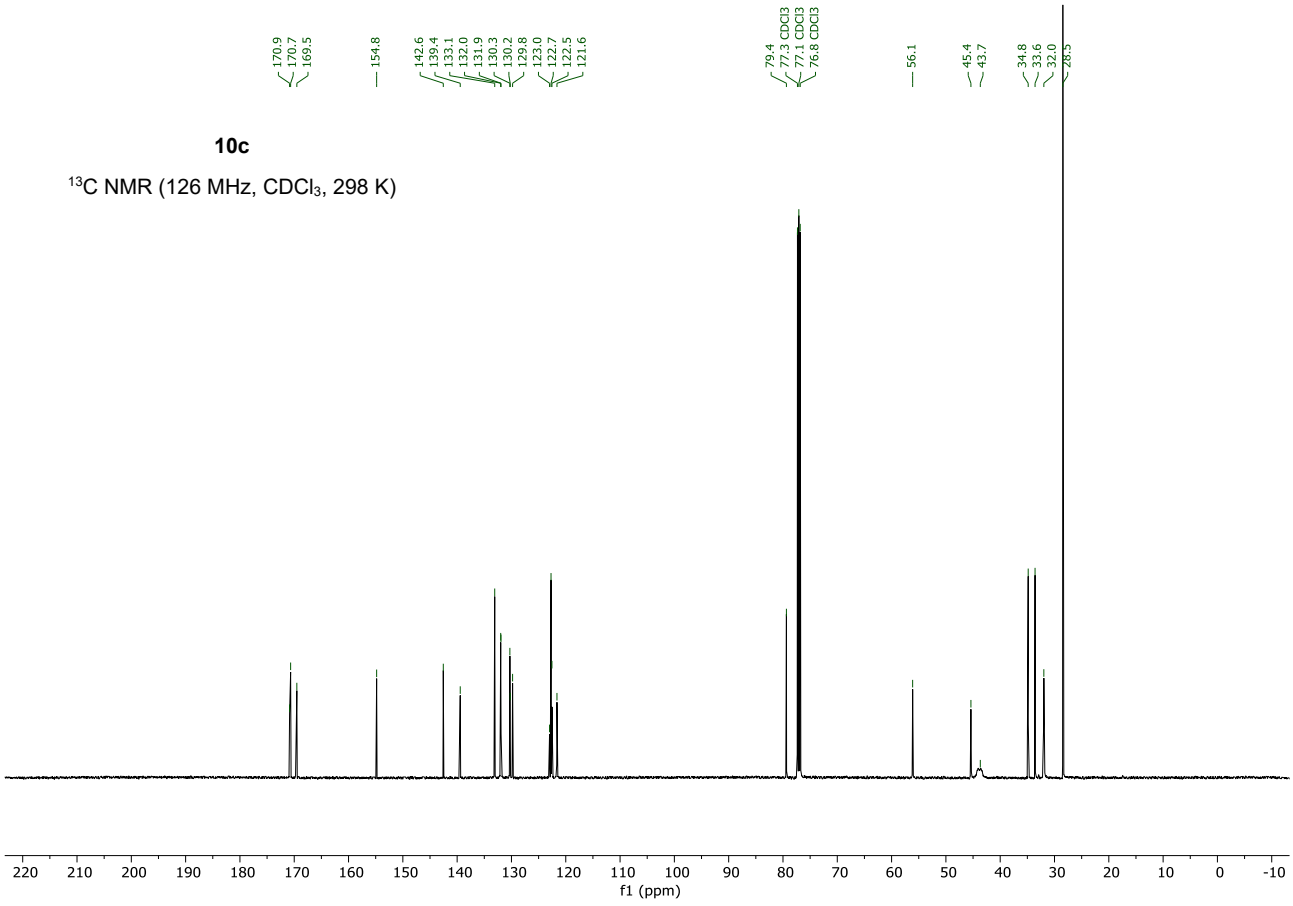
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)





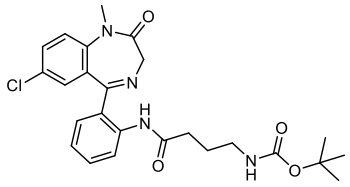
10c

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



10c

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

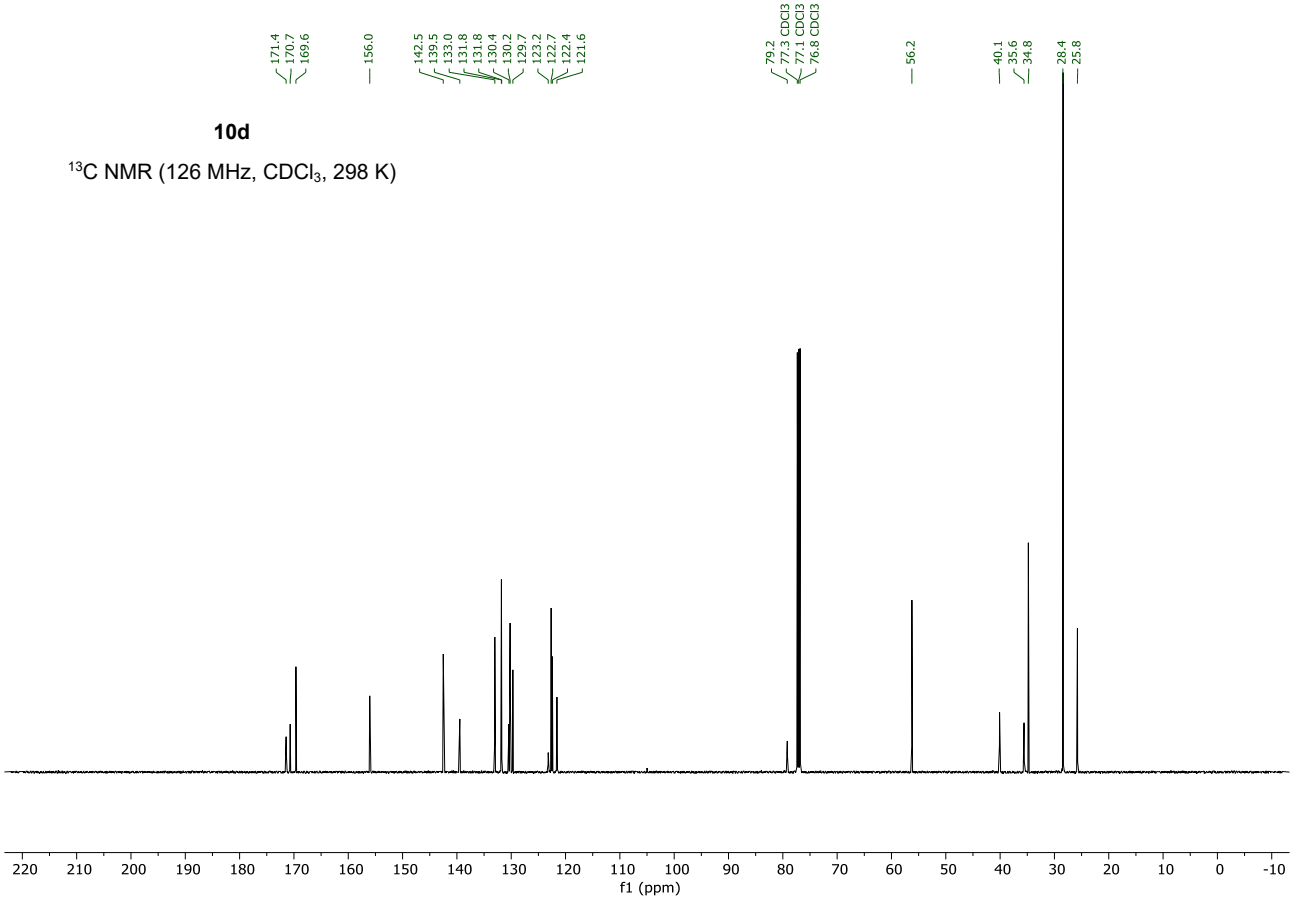


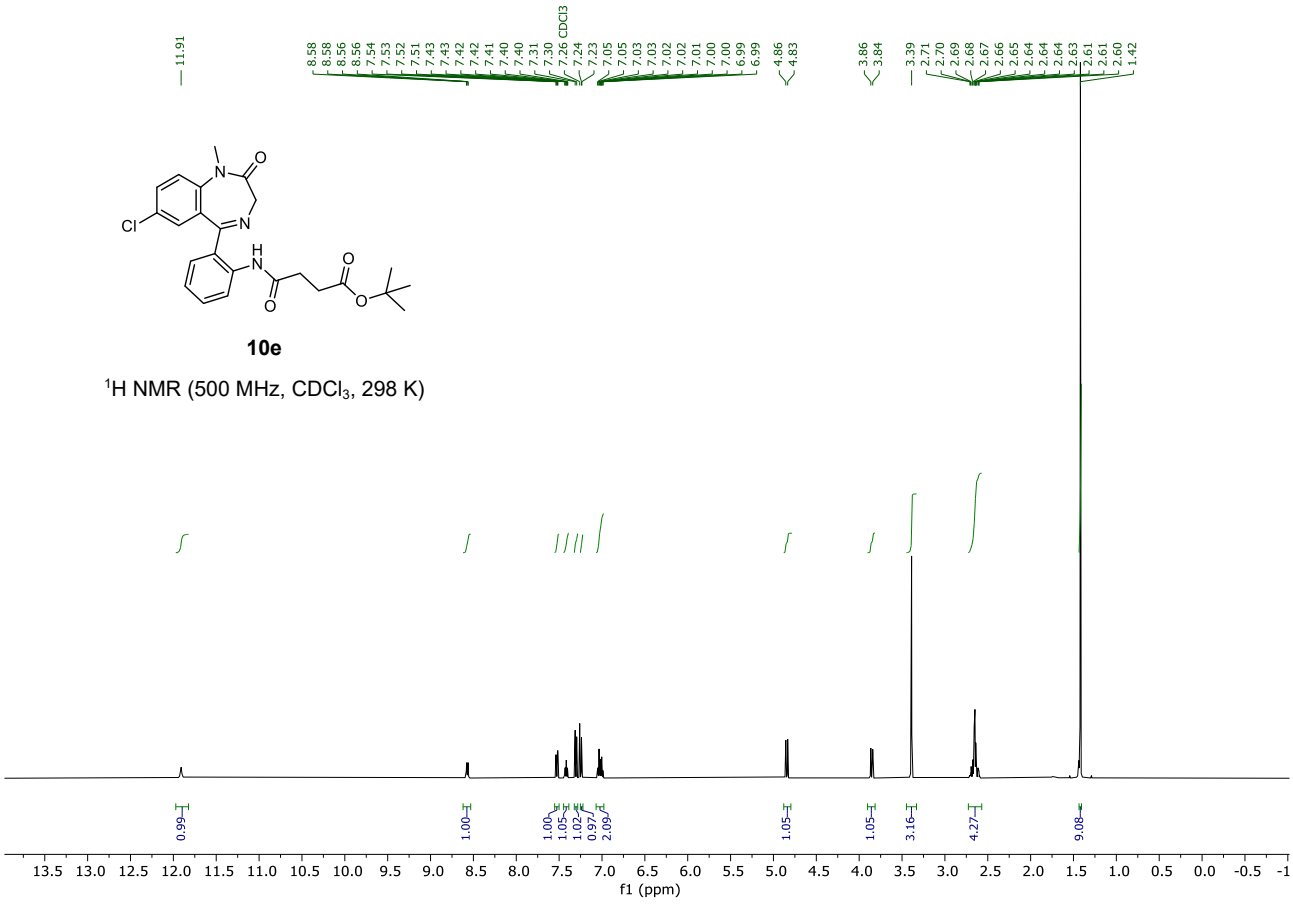
10d

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

10d

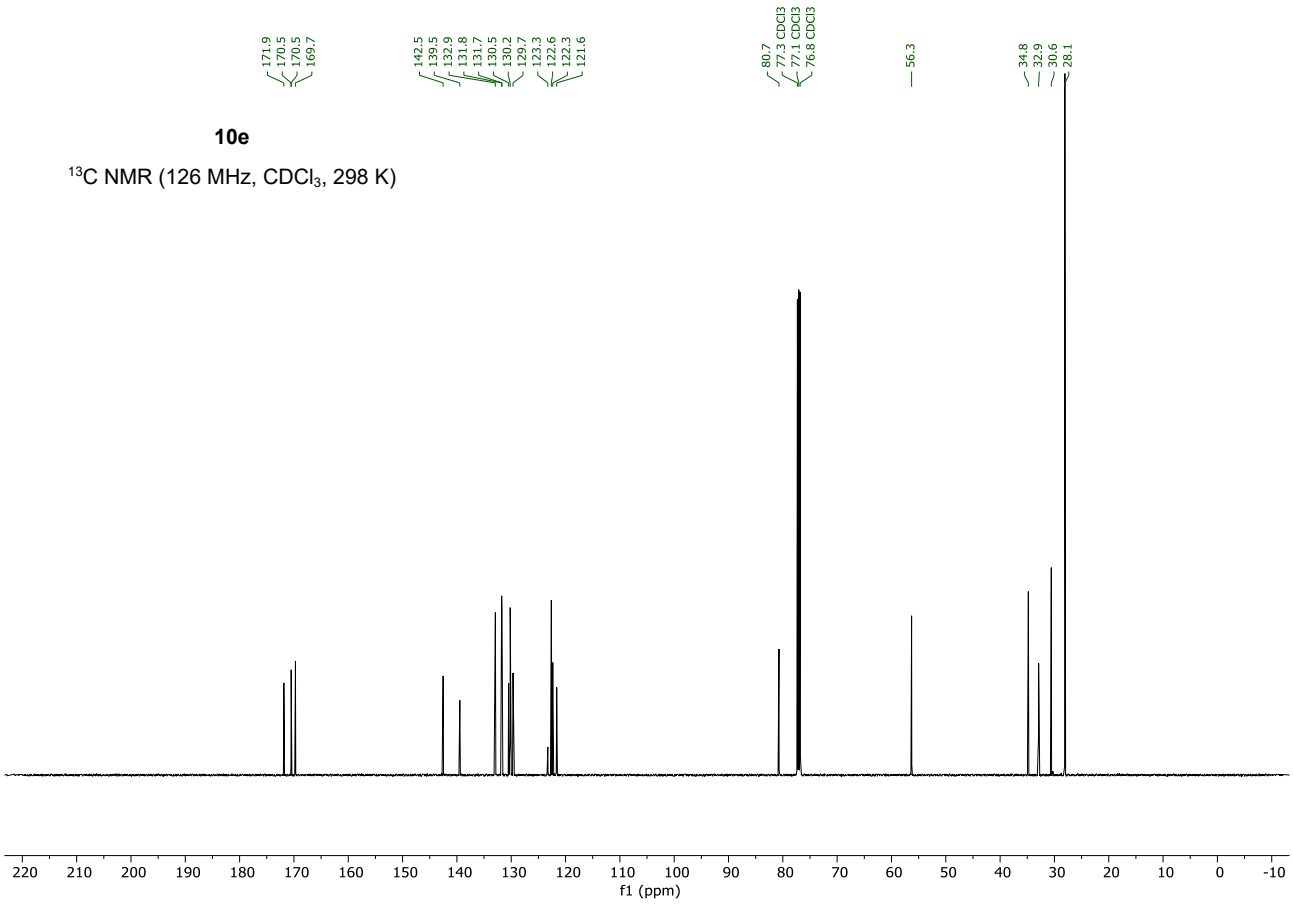
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)





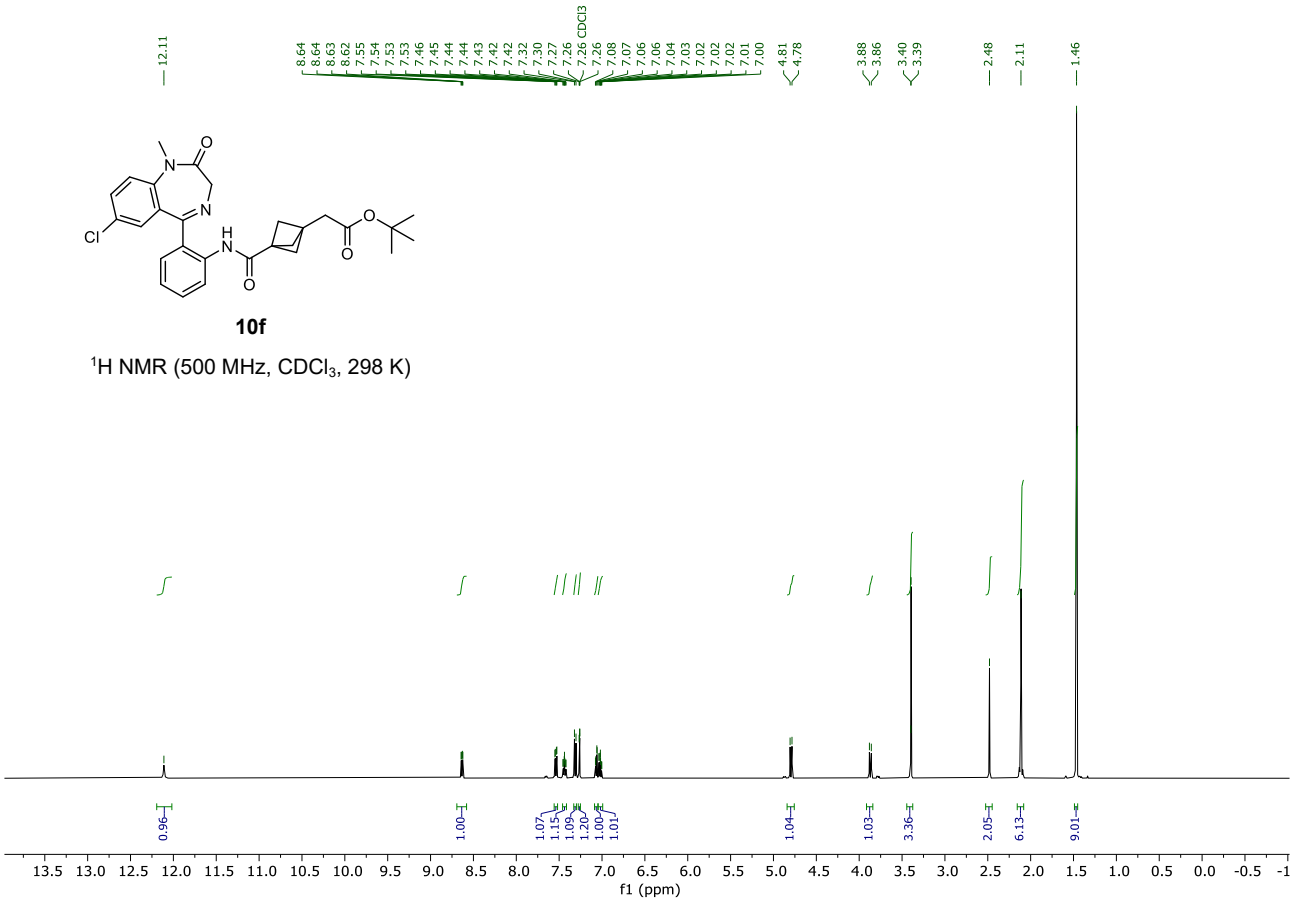
10e

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



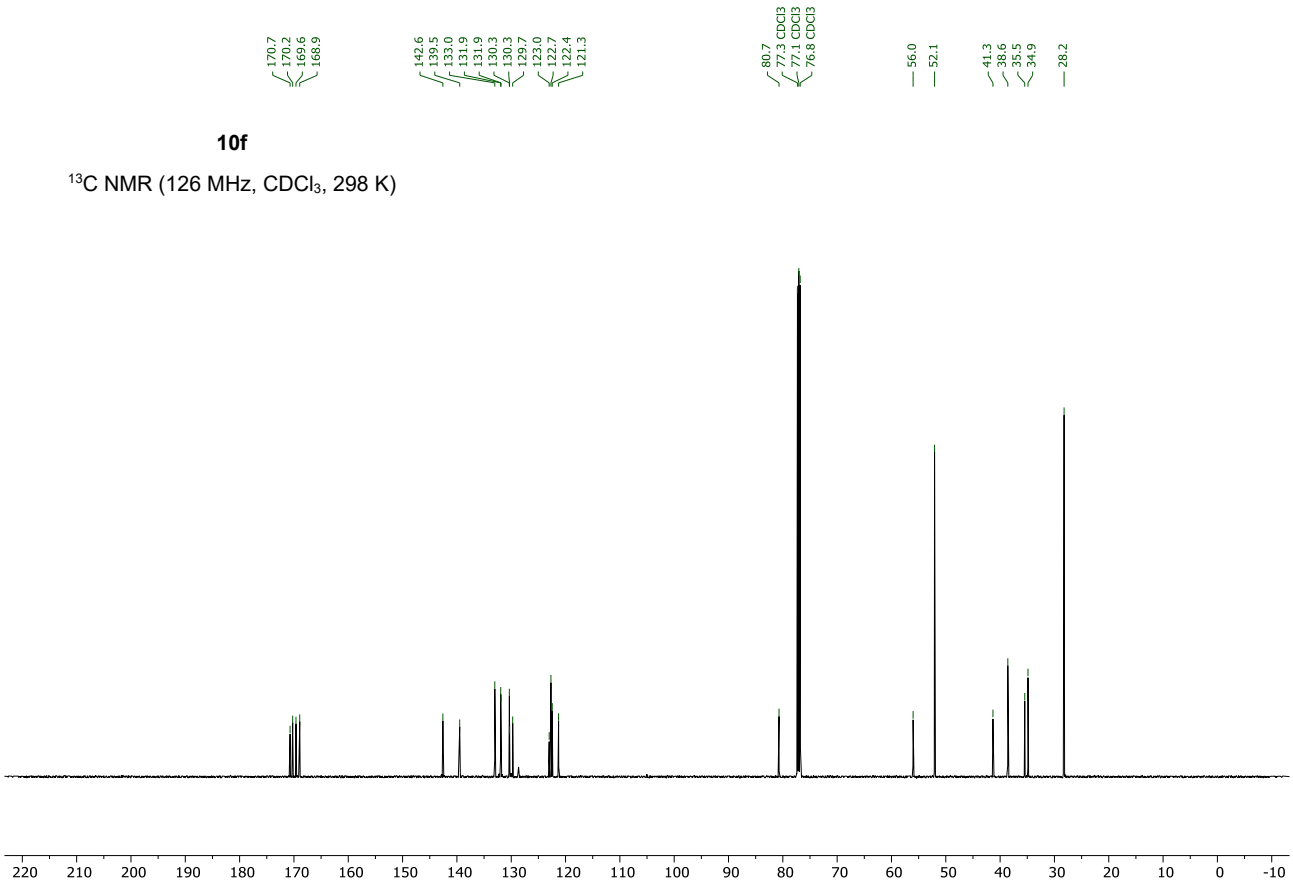
10e

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



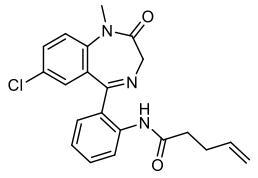
10f

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



10f

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

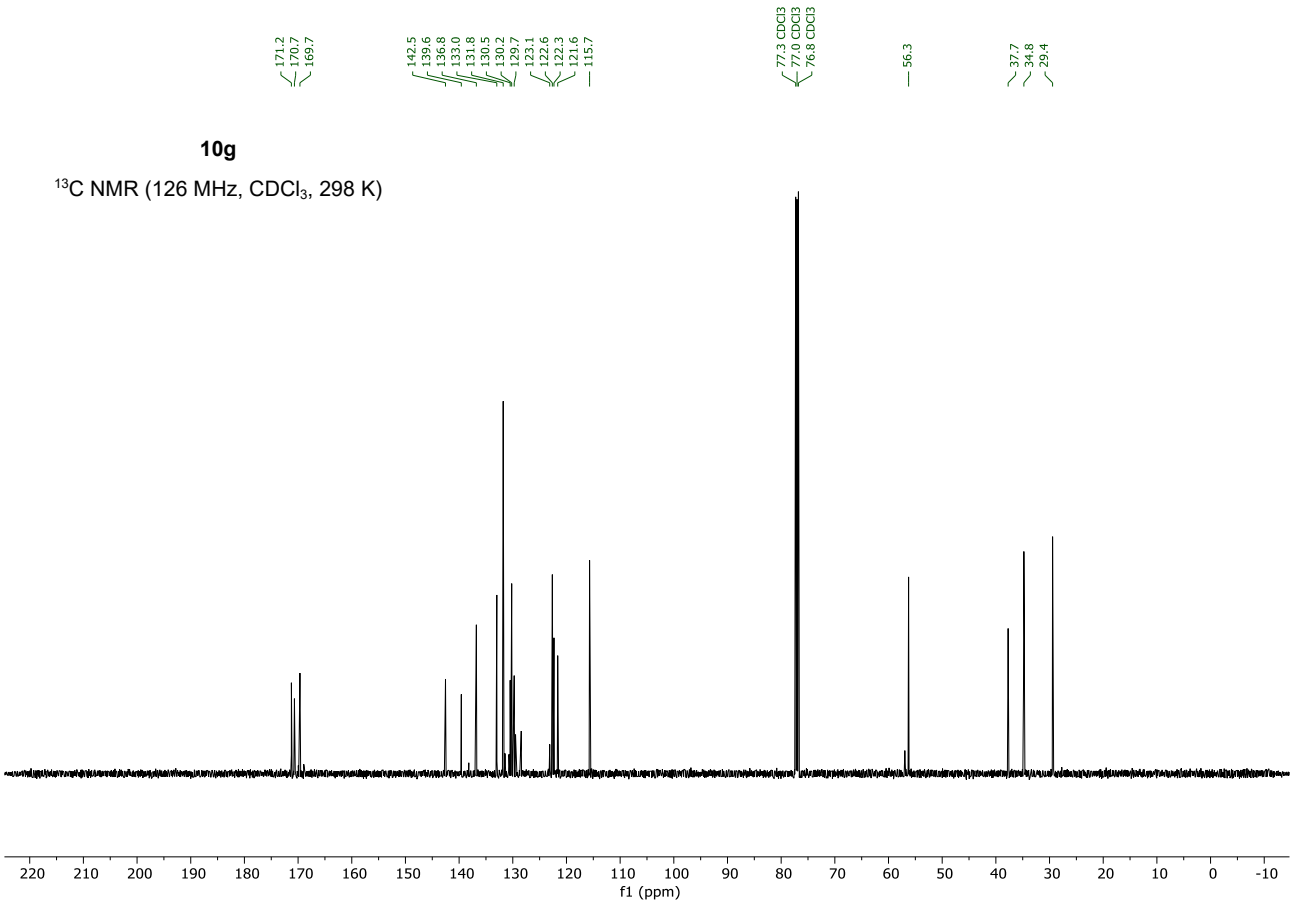


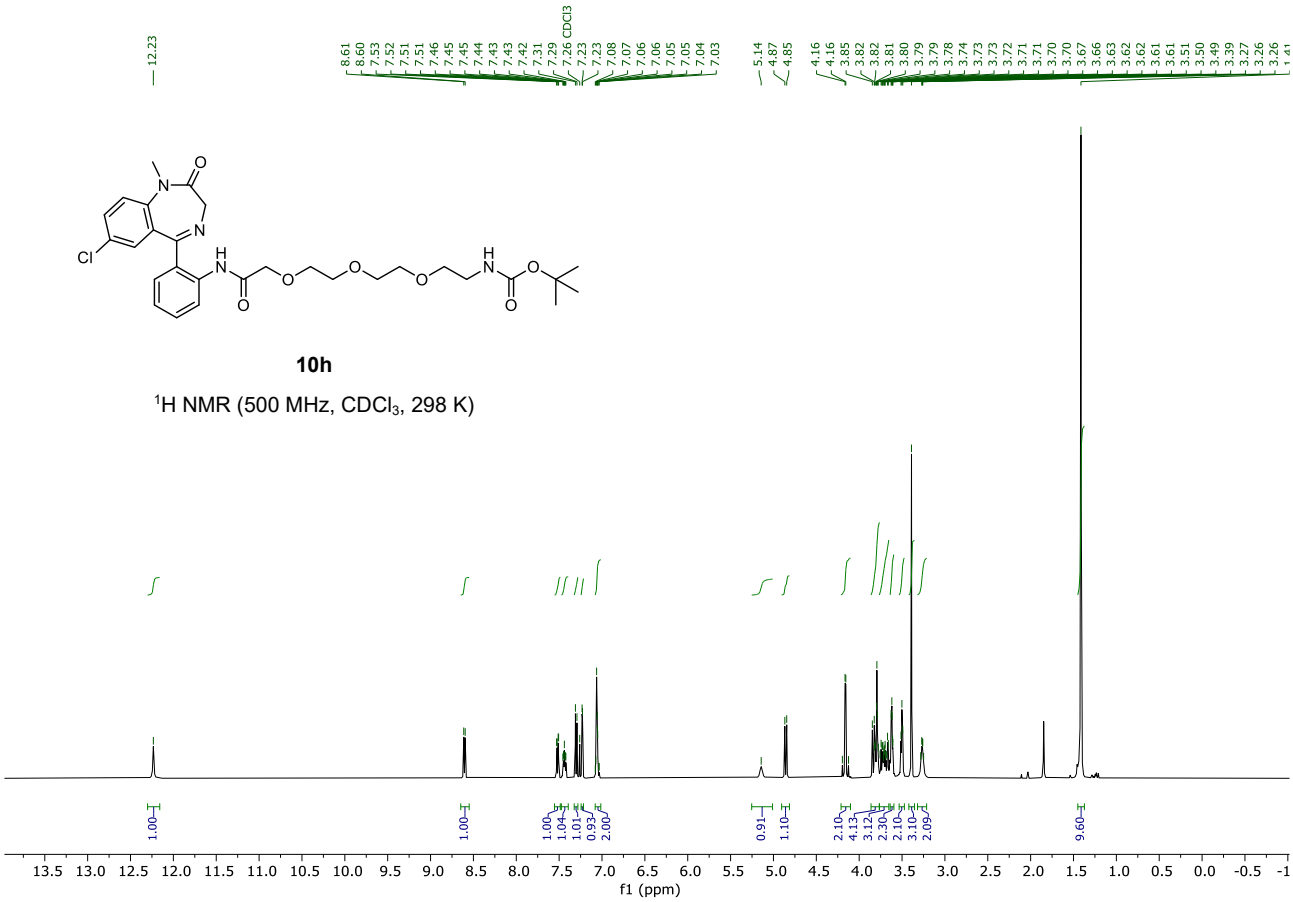
10g

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

10g

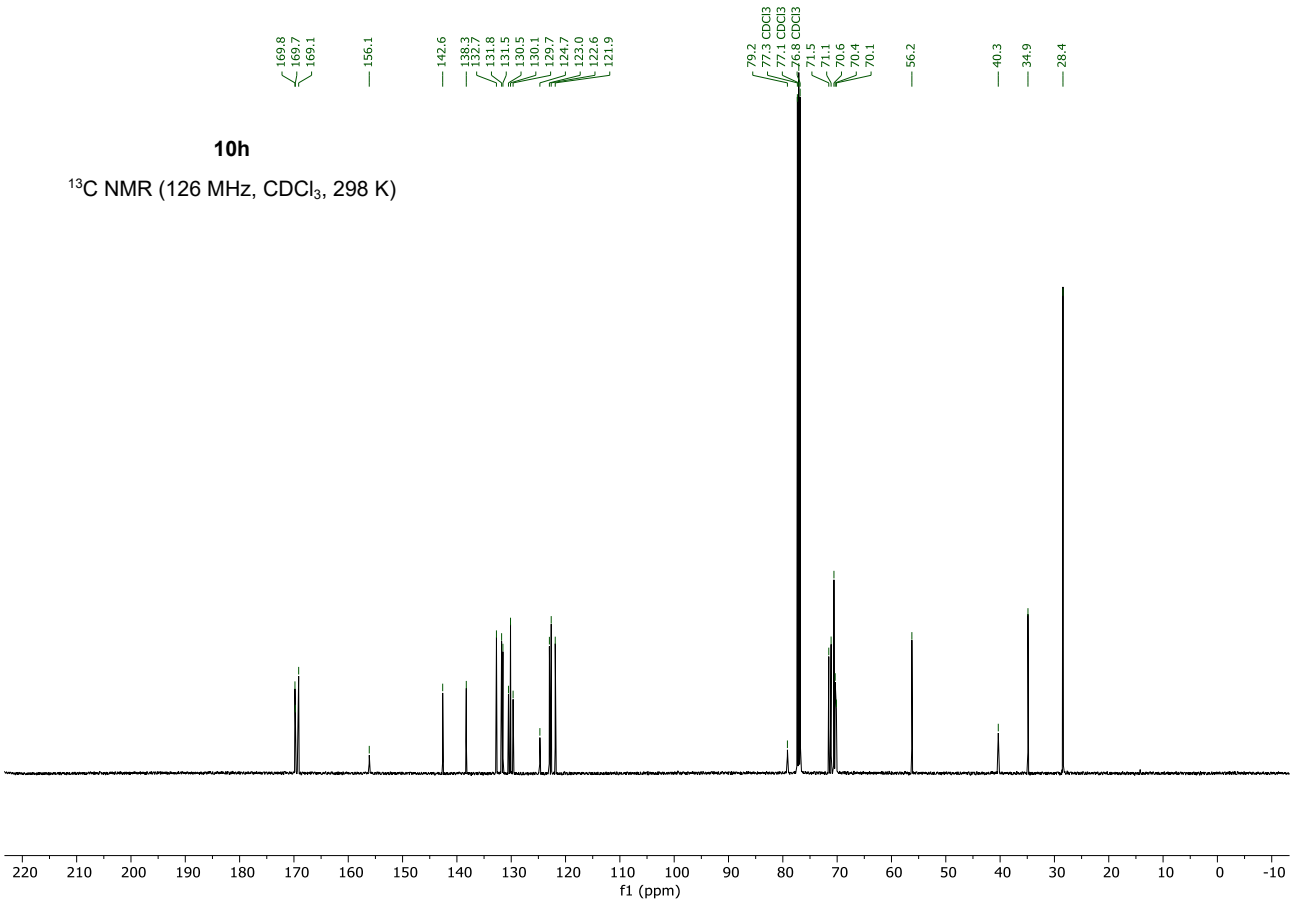
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)





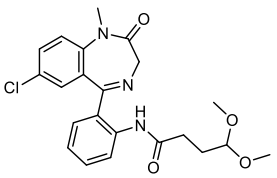
10h

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



10h

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

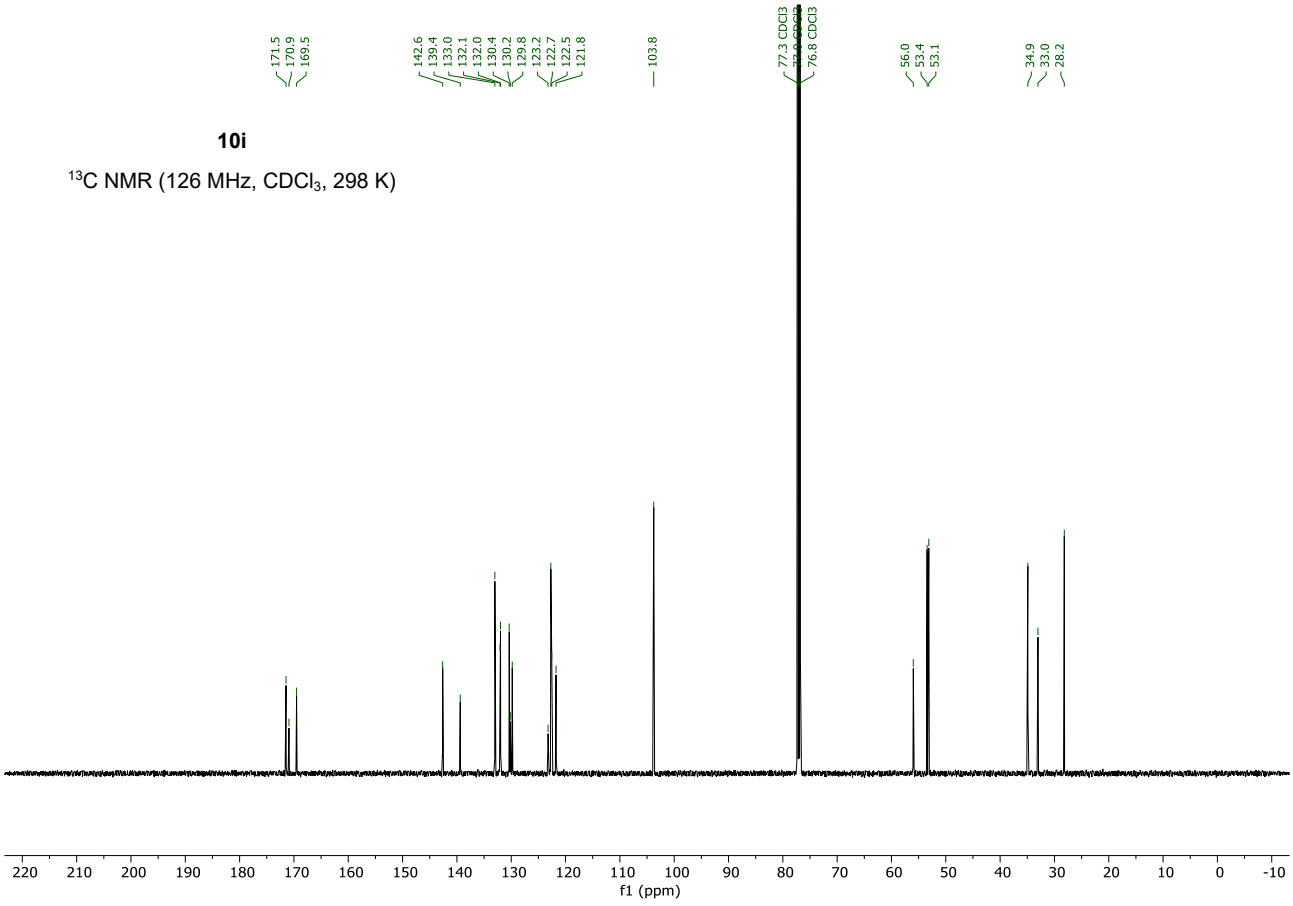


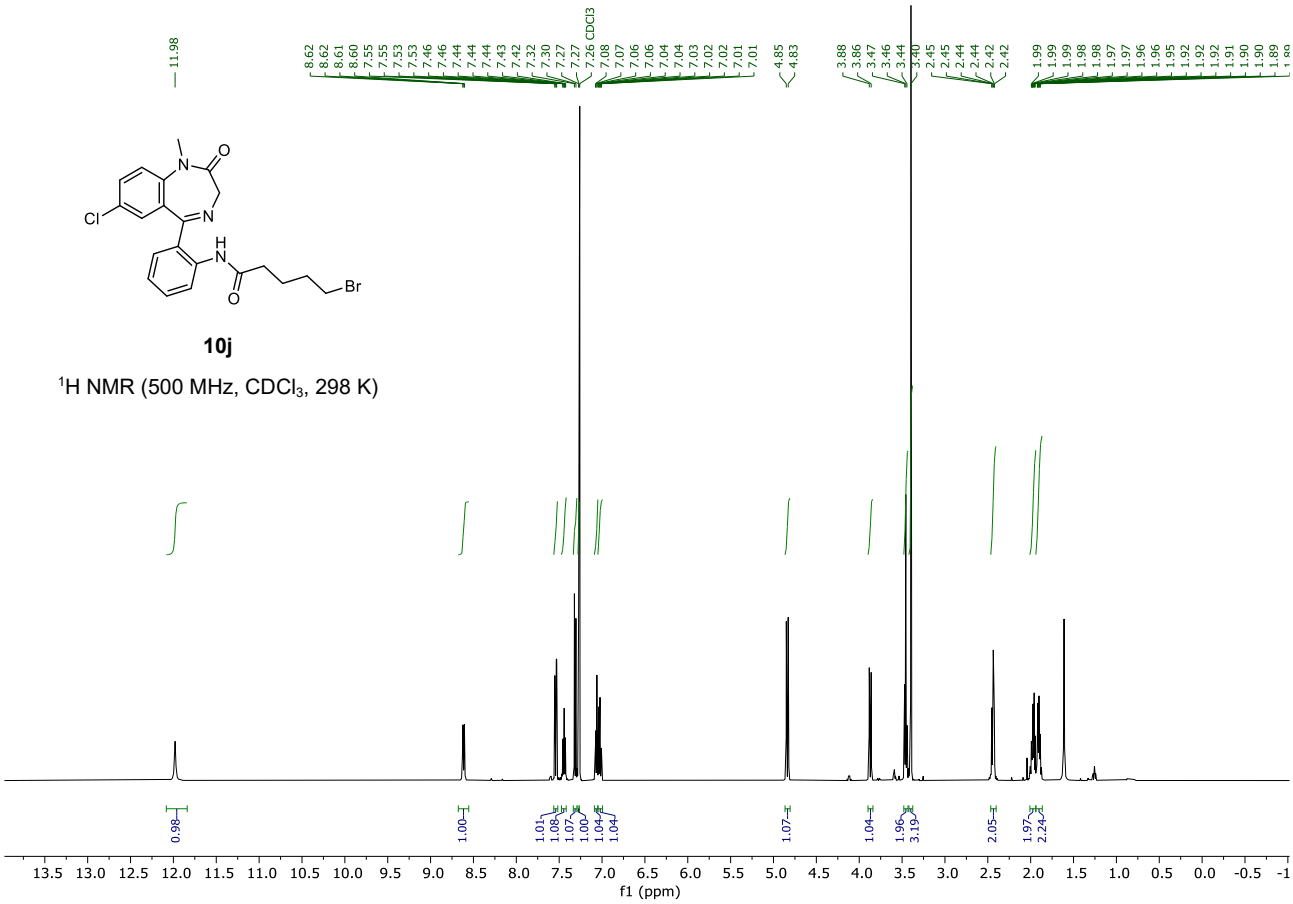
10i

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

10i

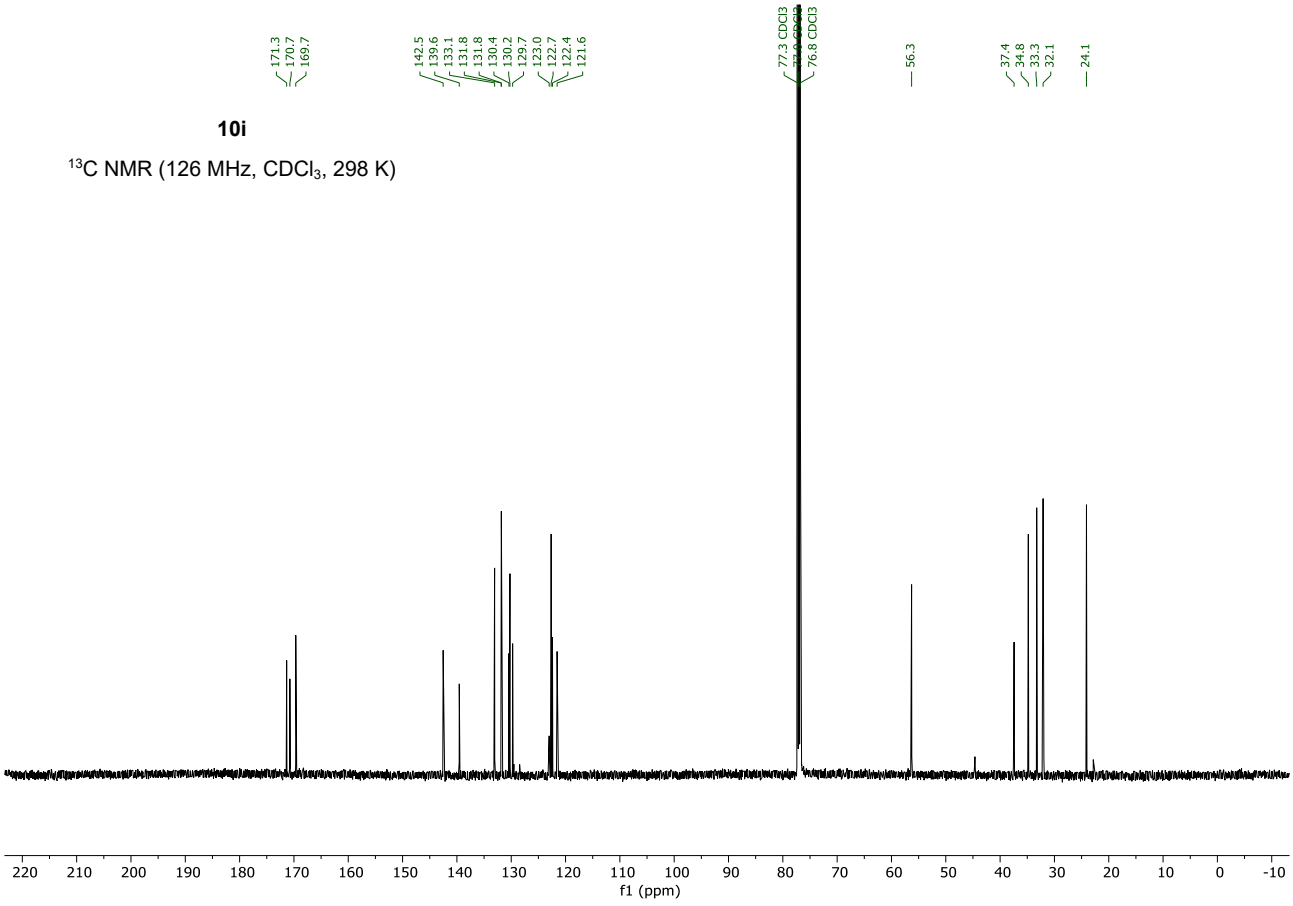
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)





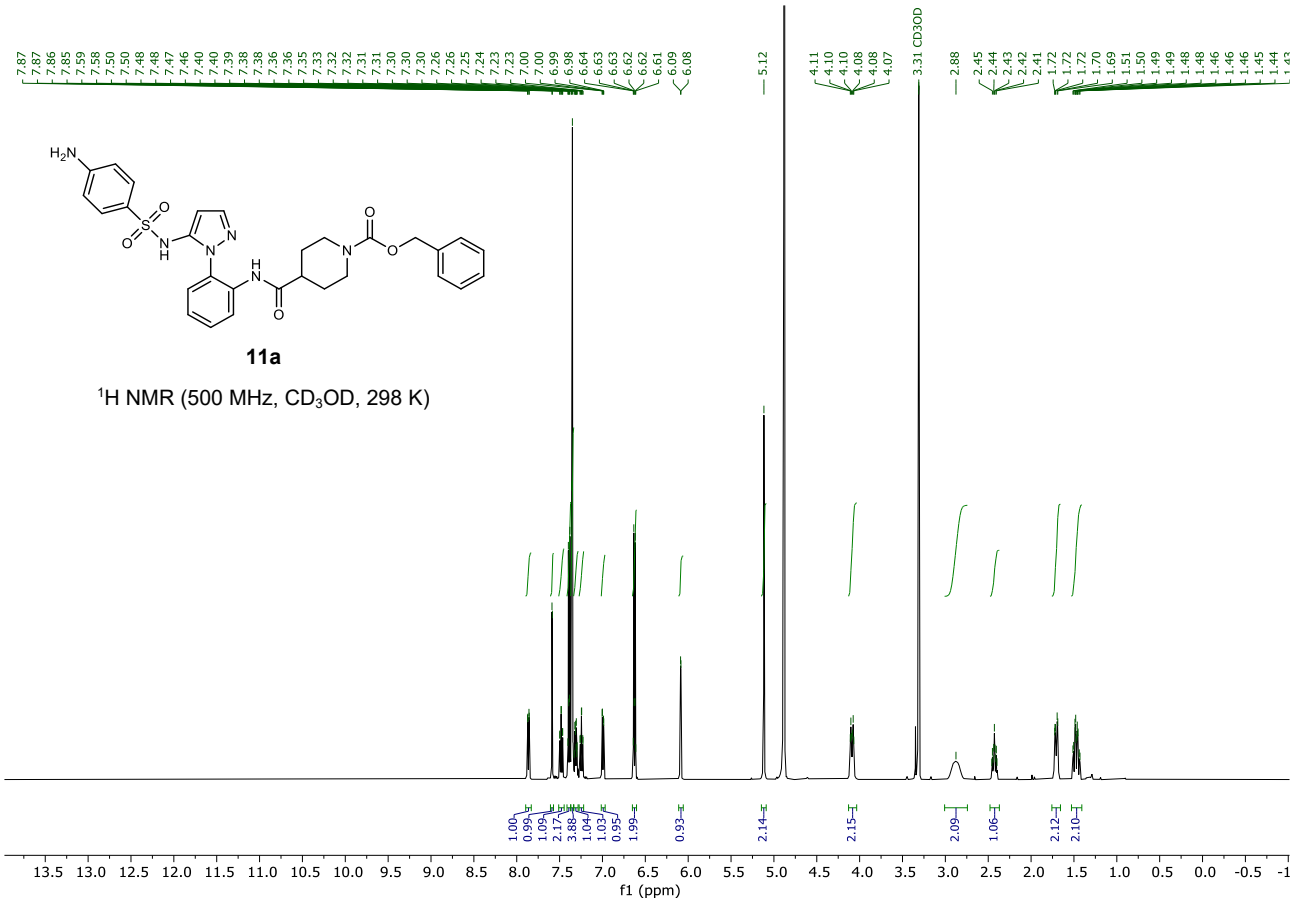
10j

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



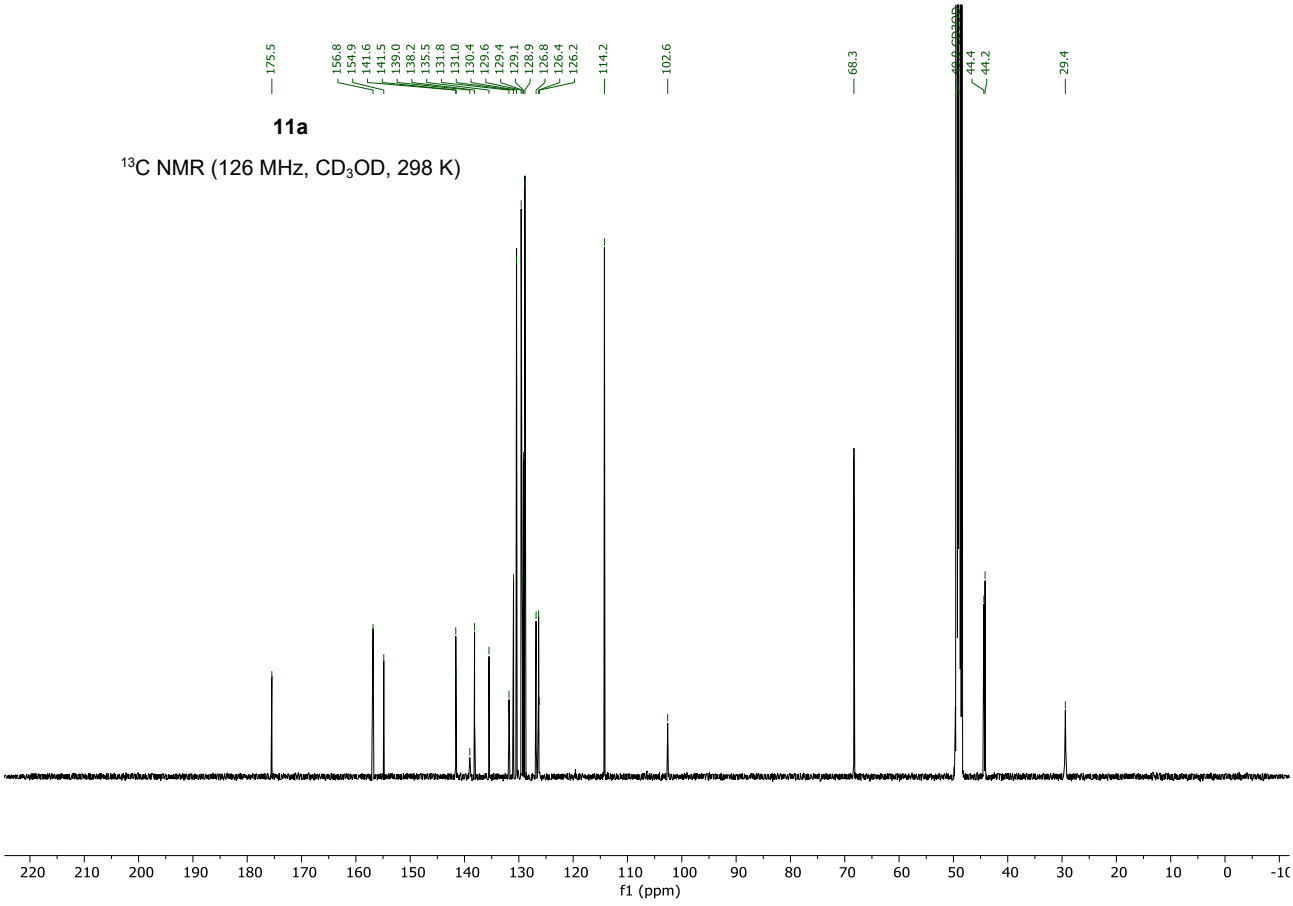
10i

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



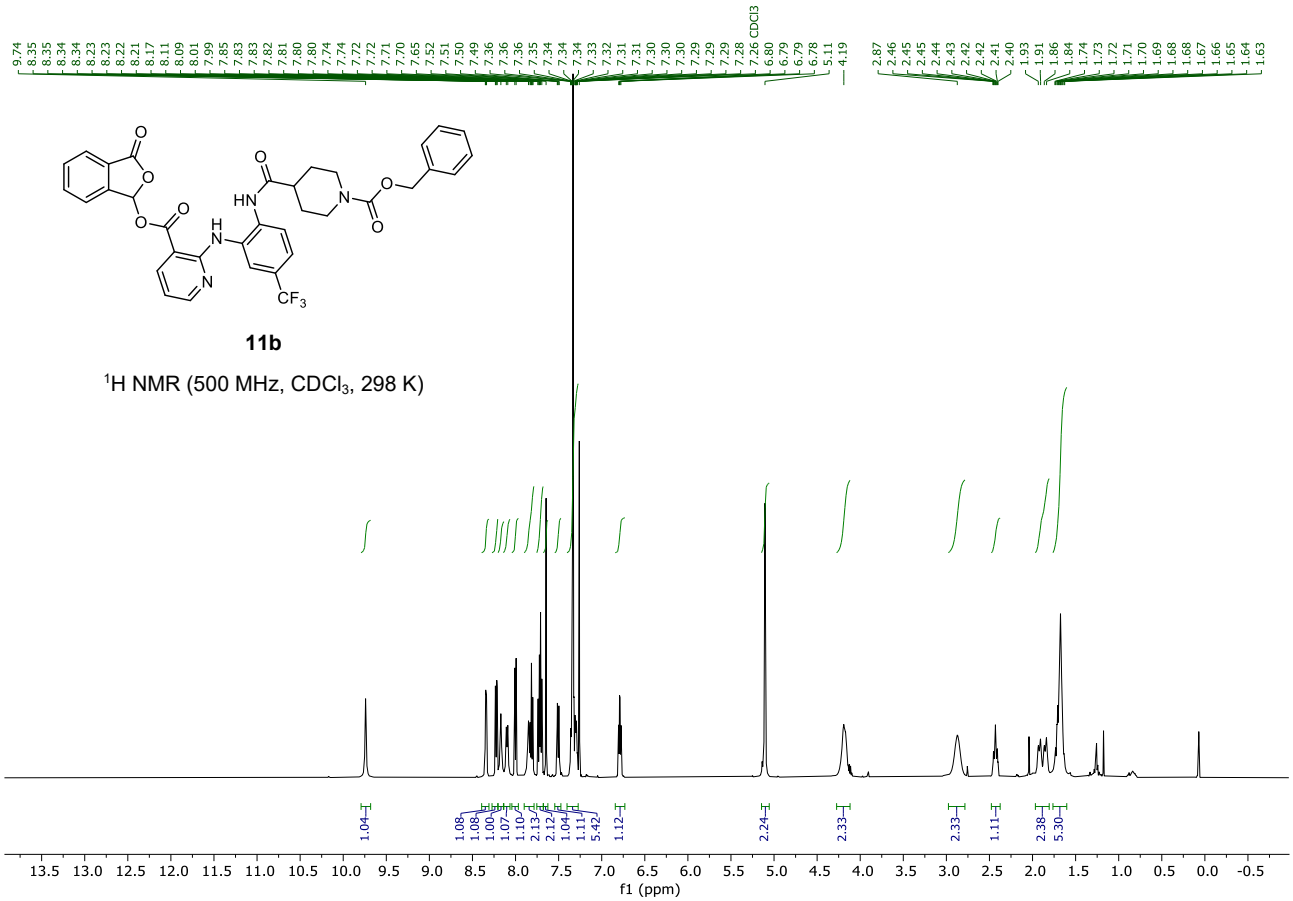
11a

^{1}H NMR (500 MHz, CD_3OD, 298 K)



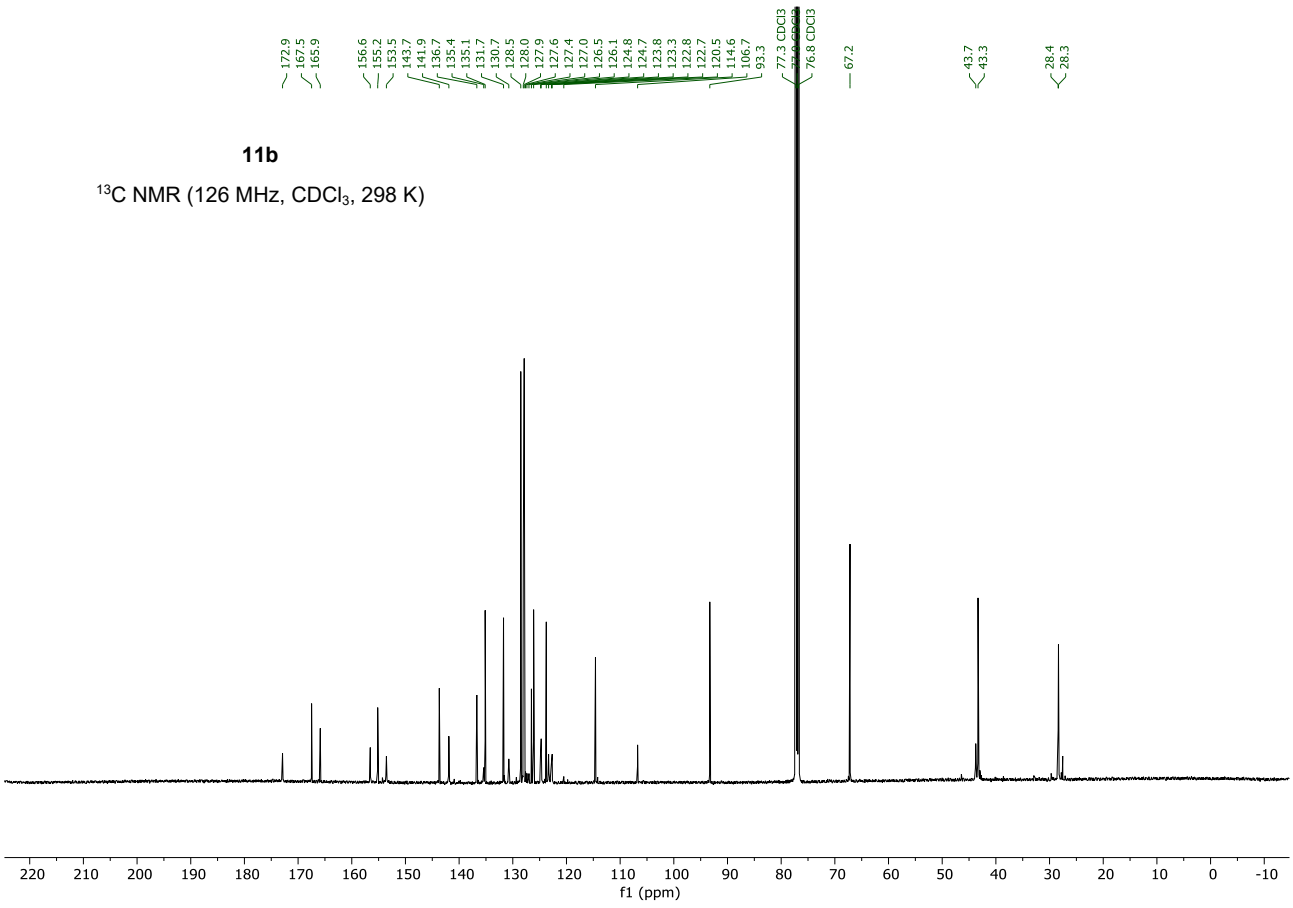
11a

^{13}C NMR (126 MHz, CD_3OD, 298 K)



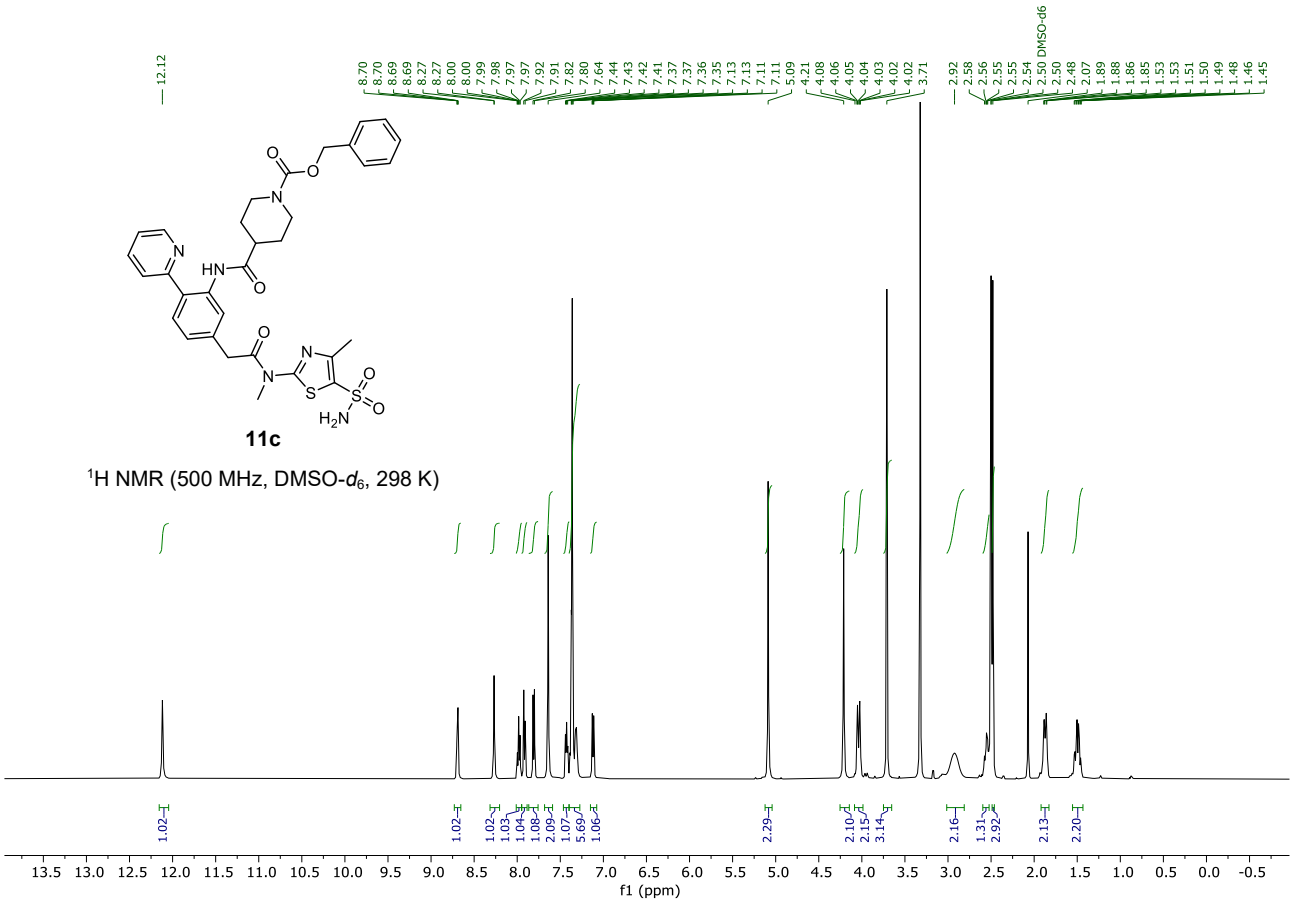
11b

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



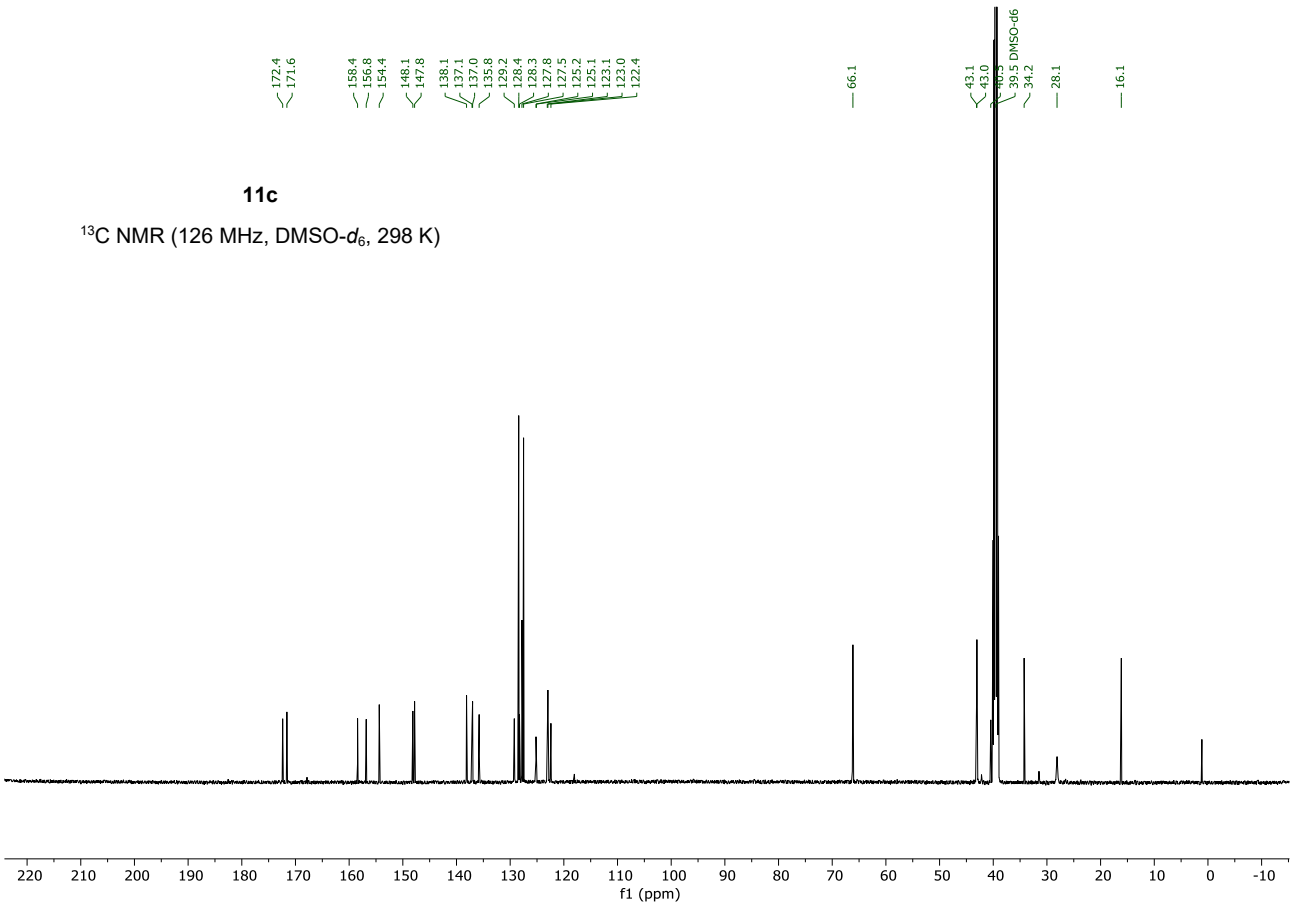
11b

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



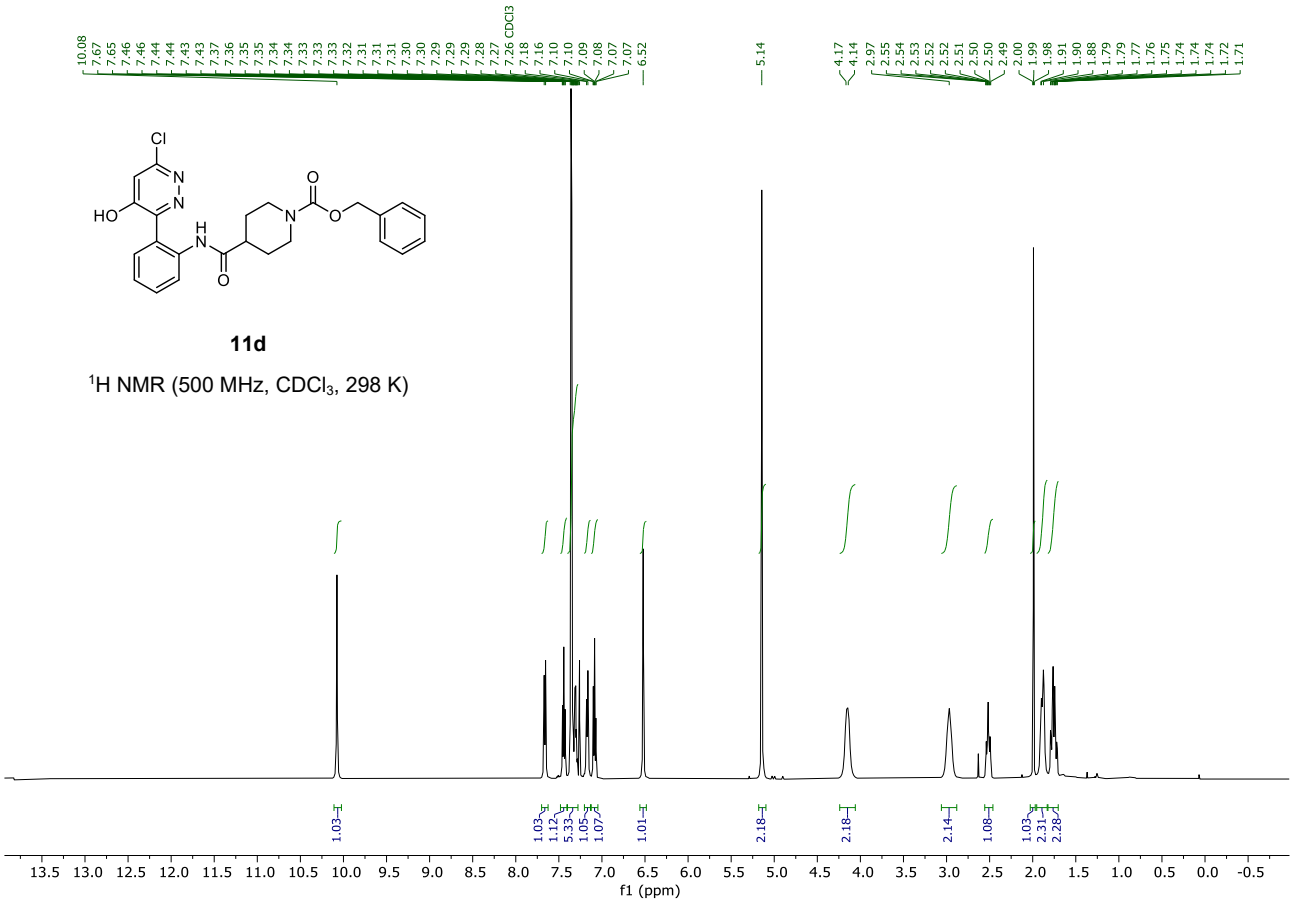
11c

^{1}H NMR (500 MHz, DMSO-d_6, 298 K)



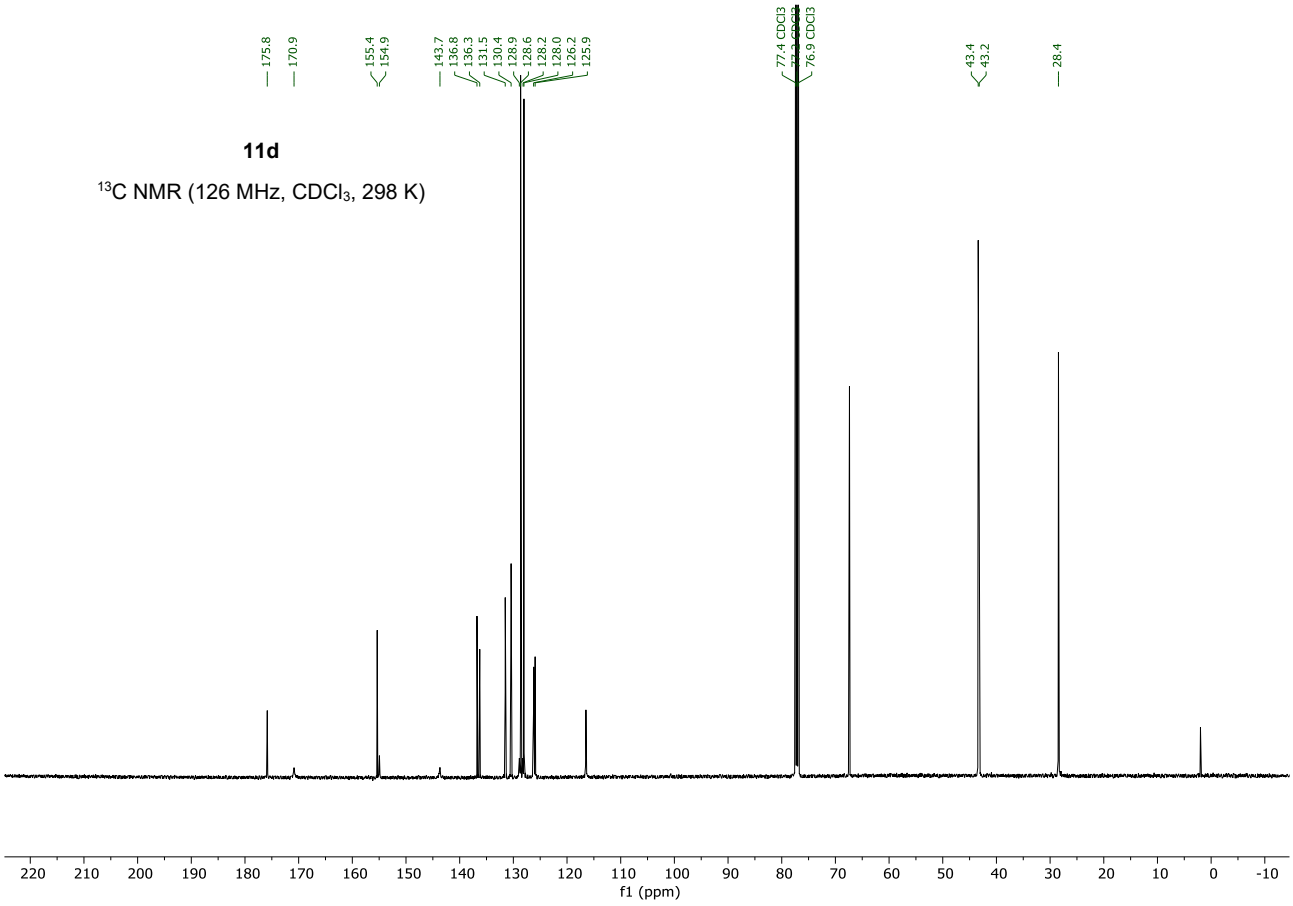
11c

^{13}C NMR (126 MHz, DMSO-d_6, 298 K)



11d

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

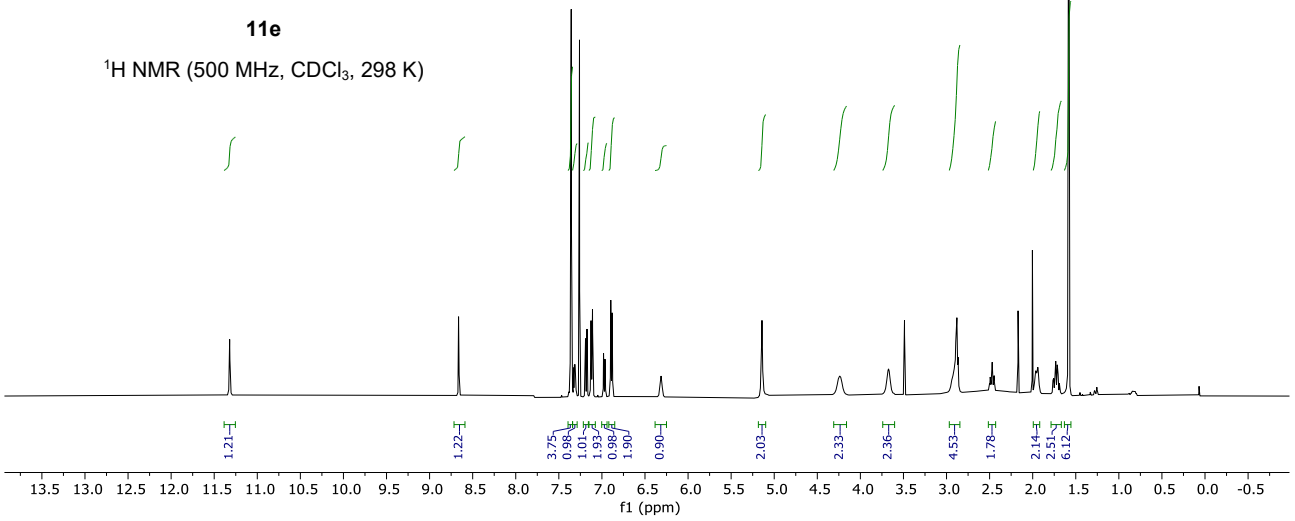


11d

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

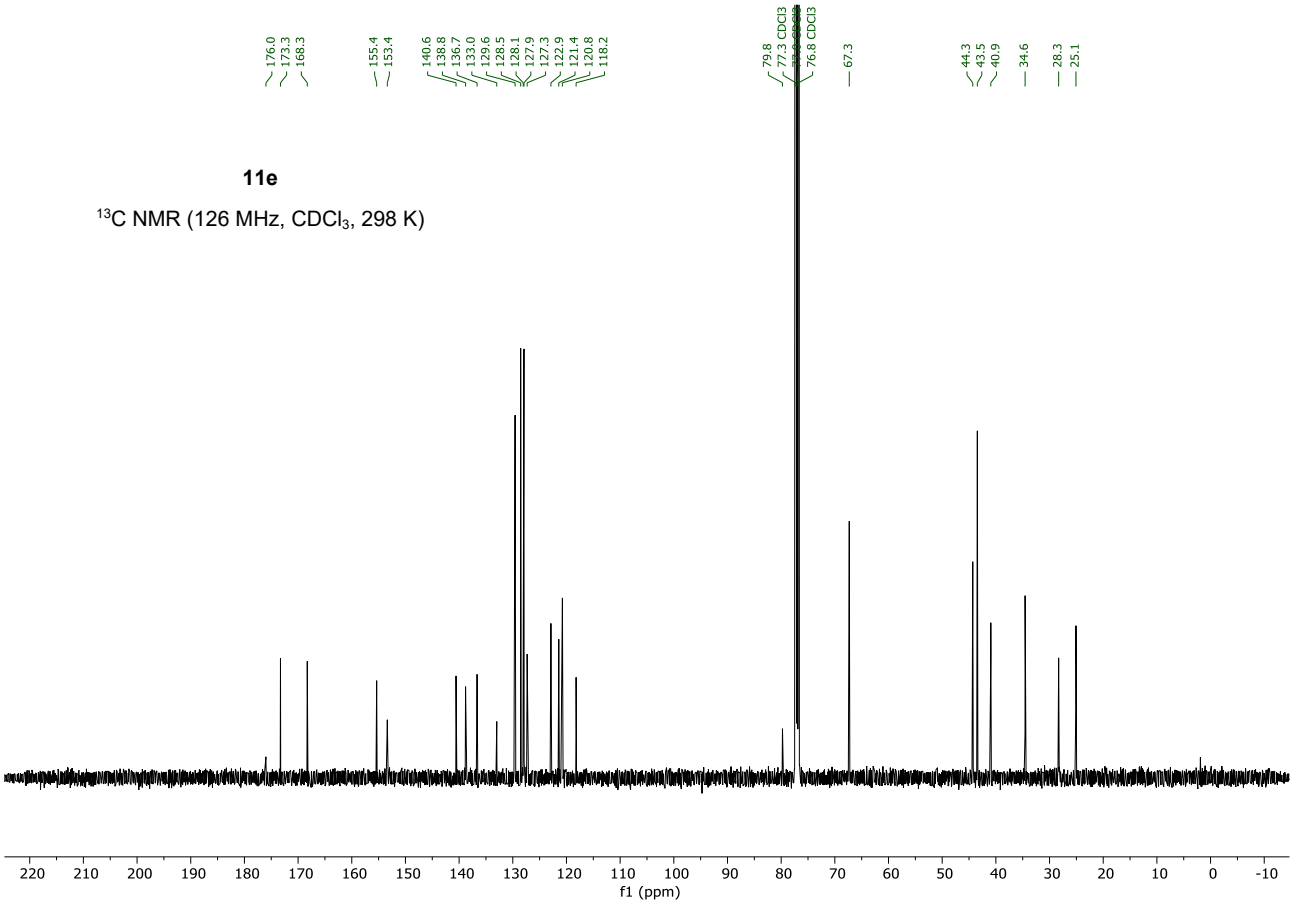
11e

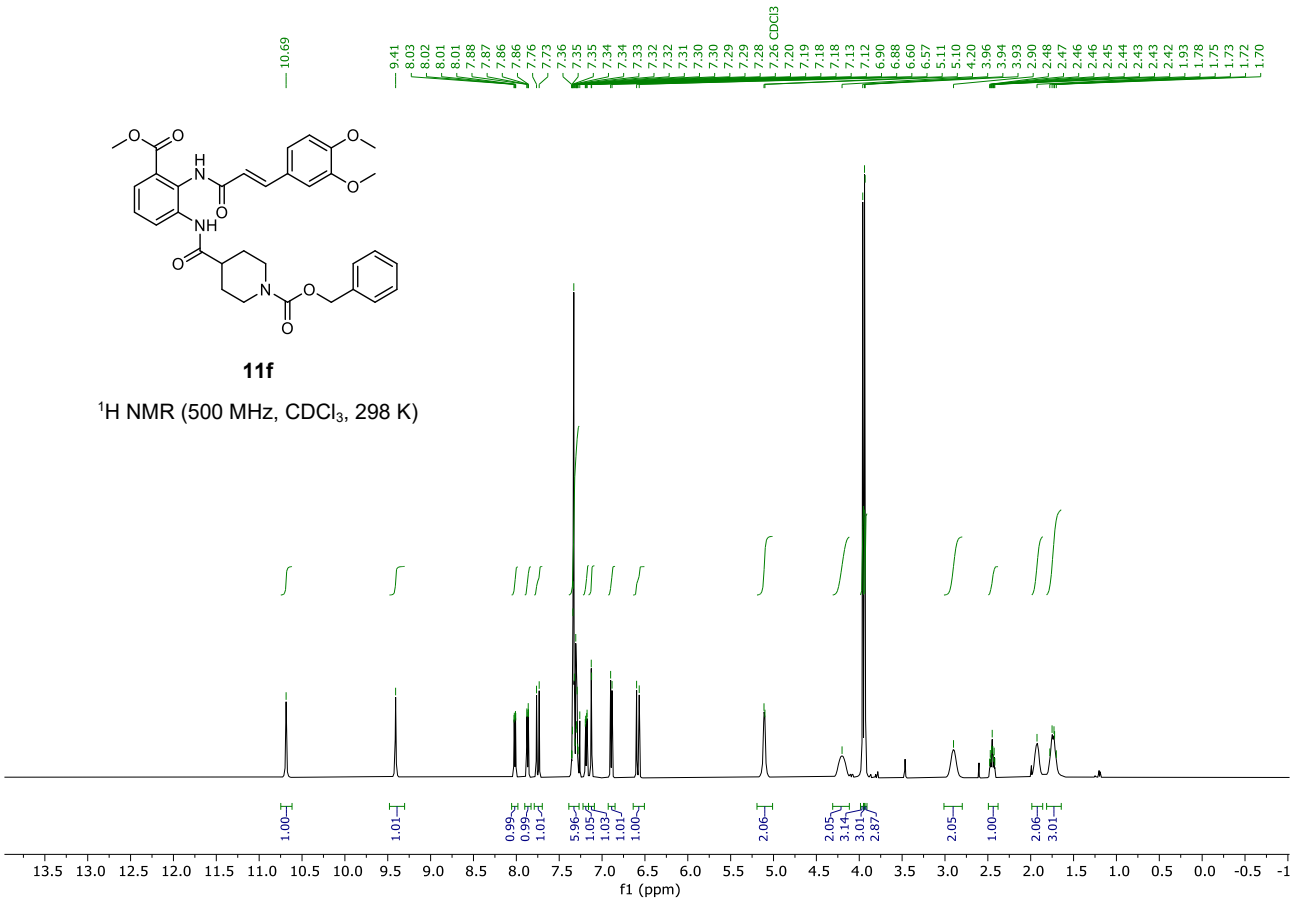
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



11e

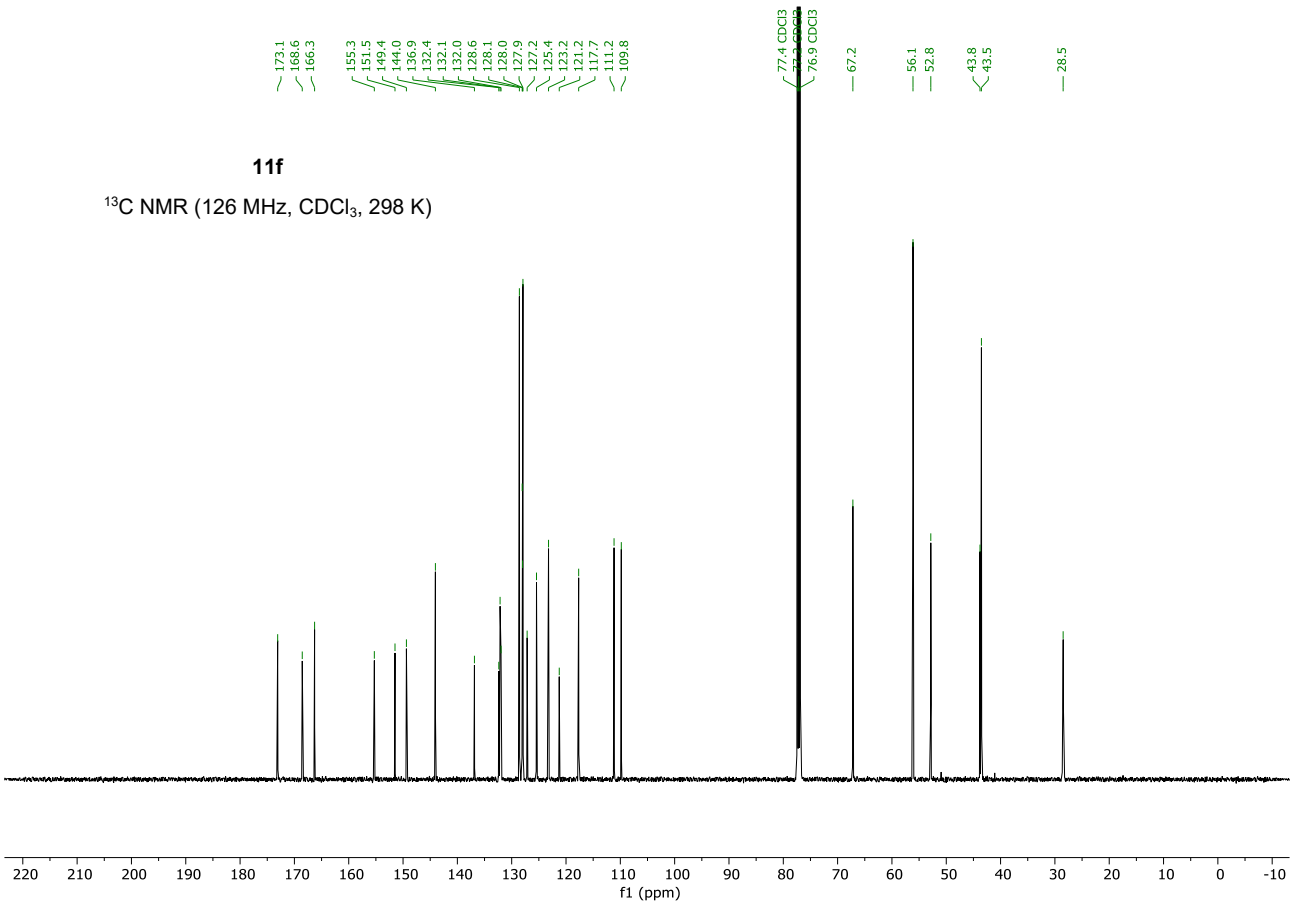
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)





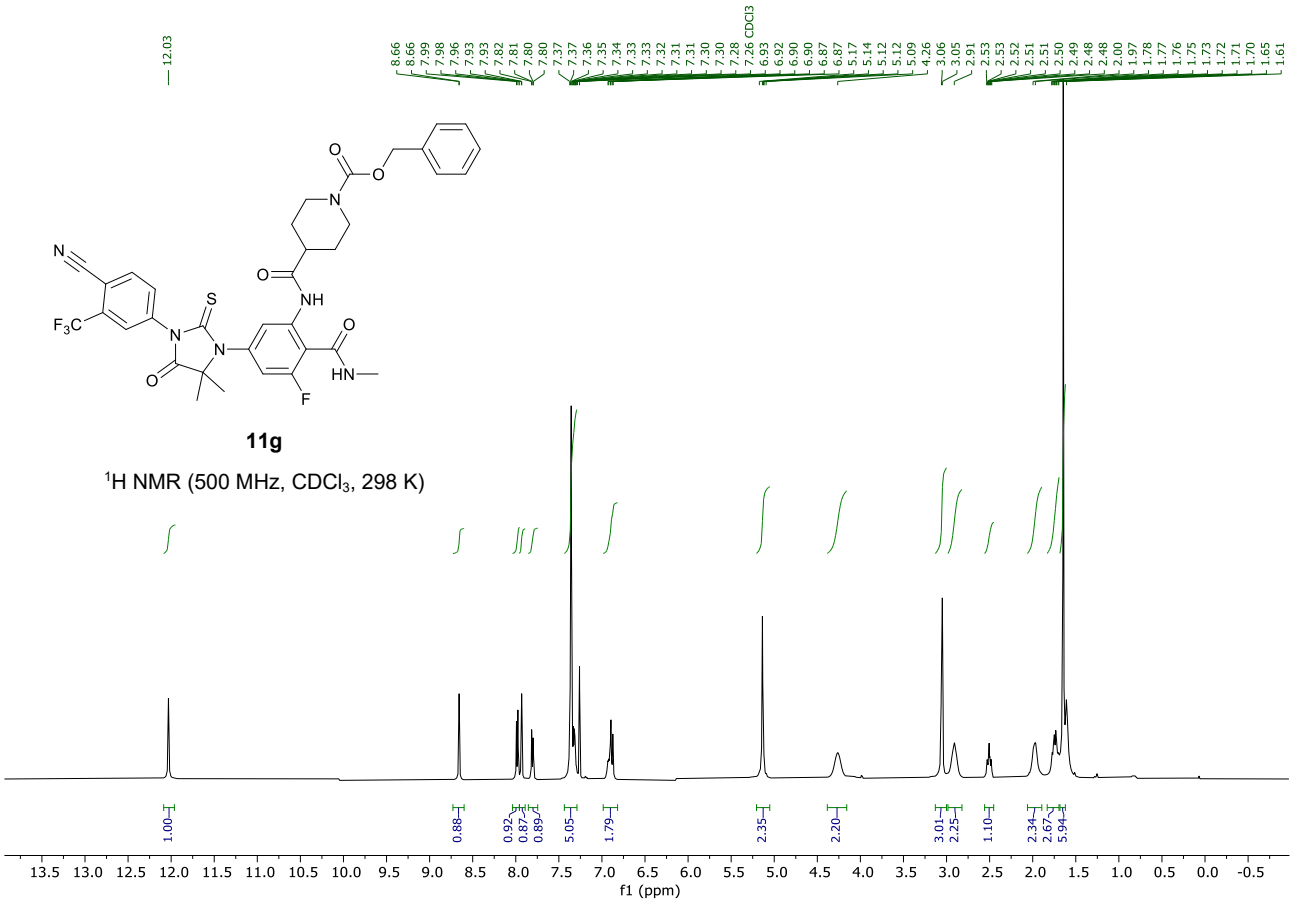
11f

^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



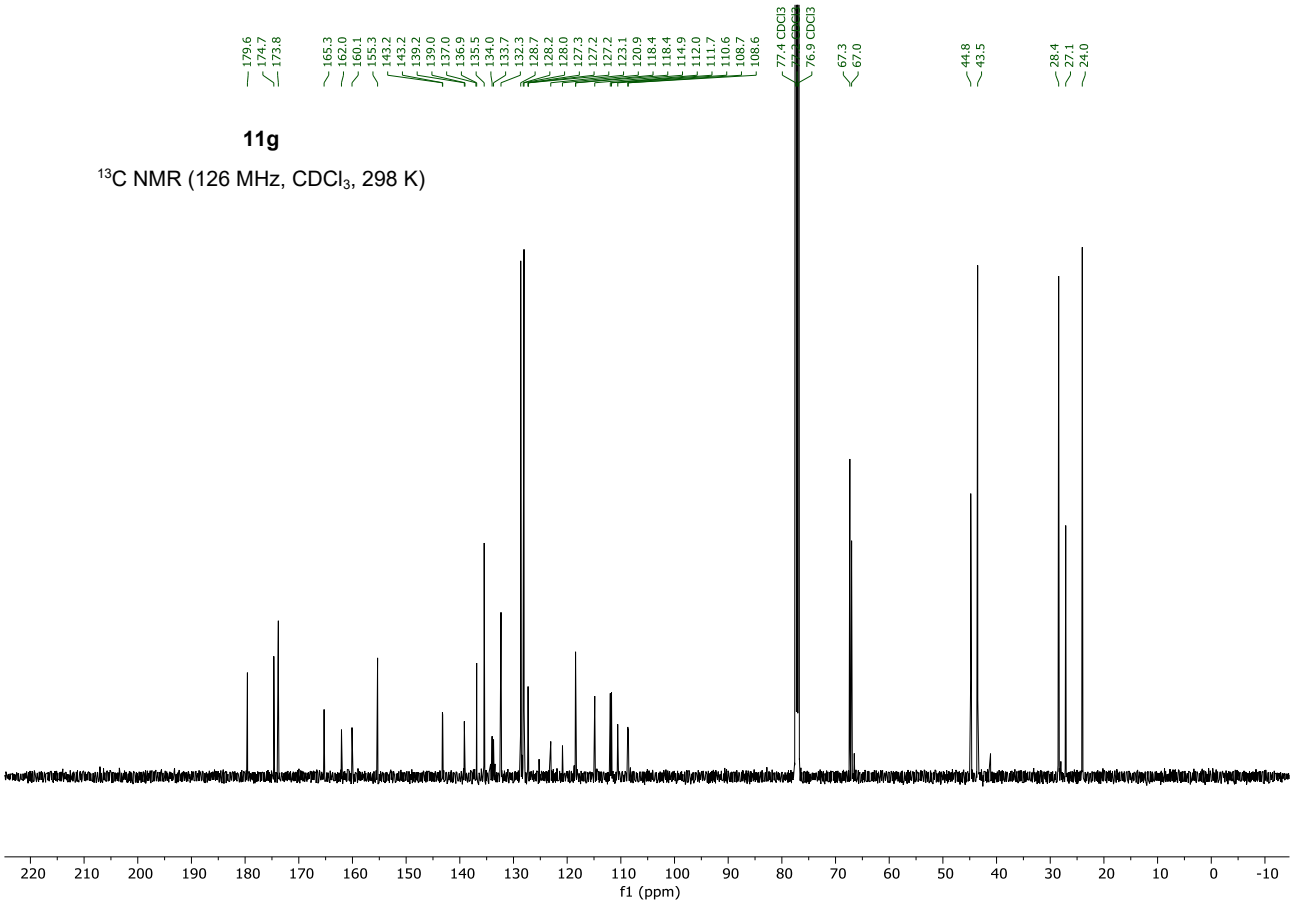
11f

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



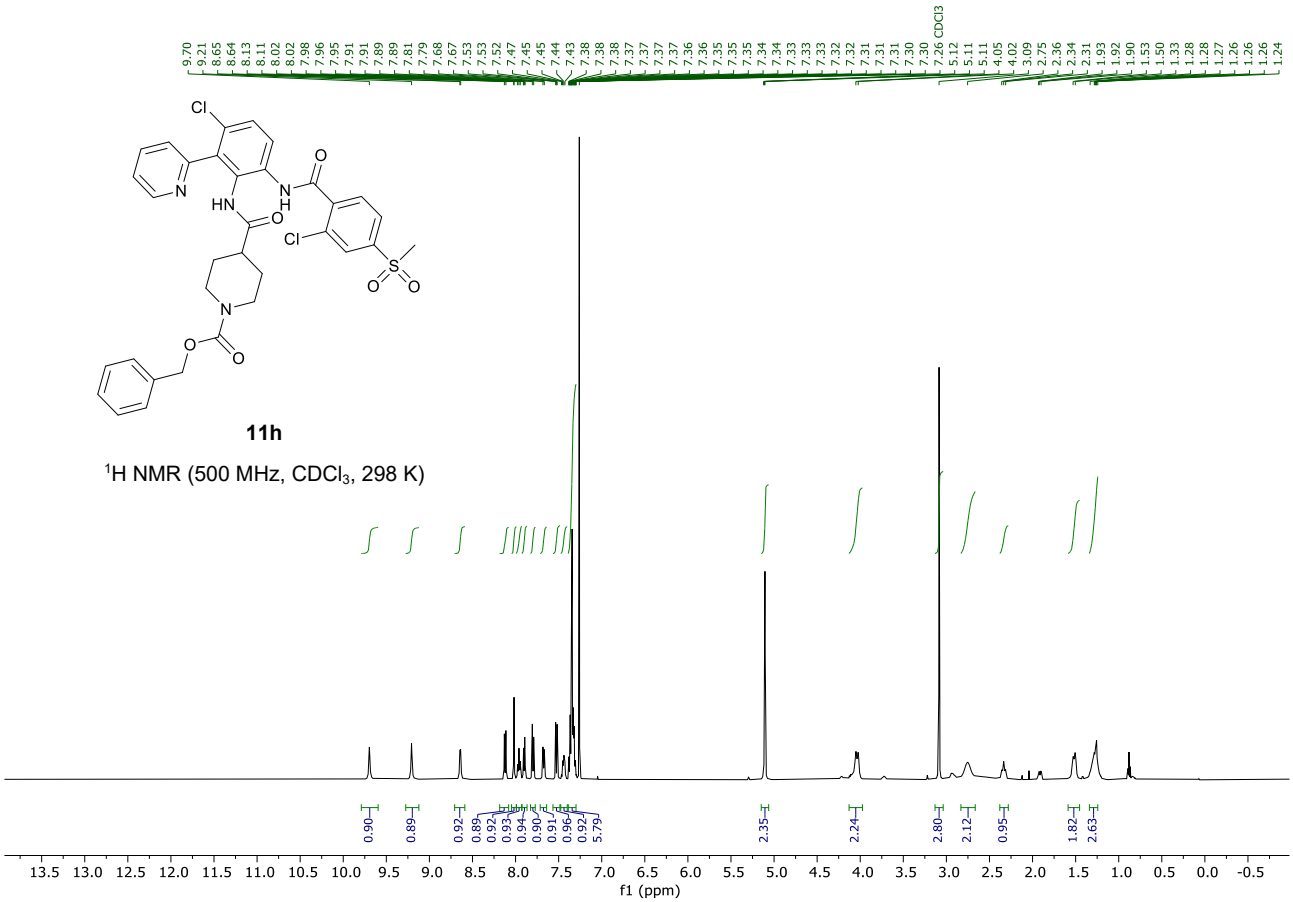
11g

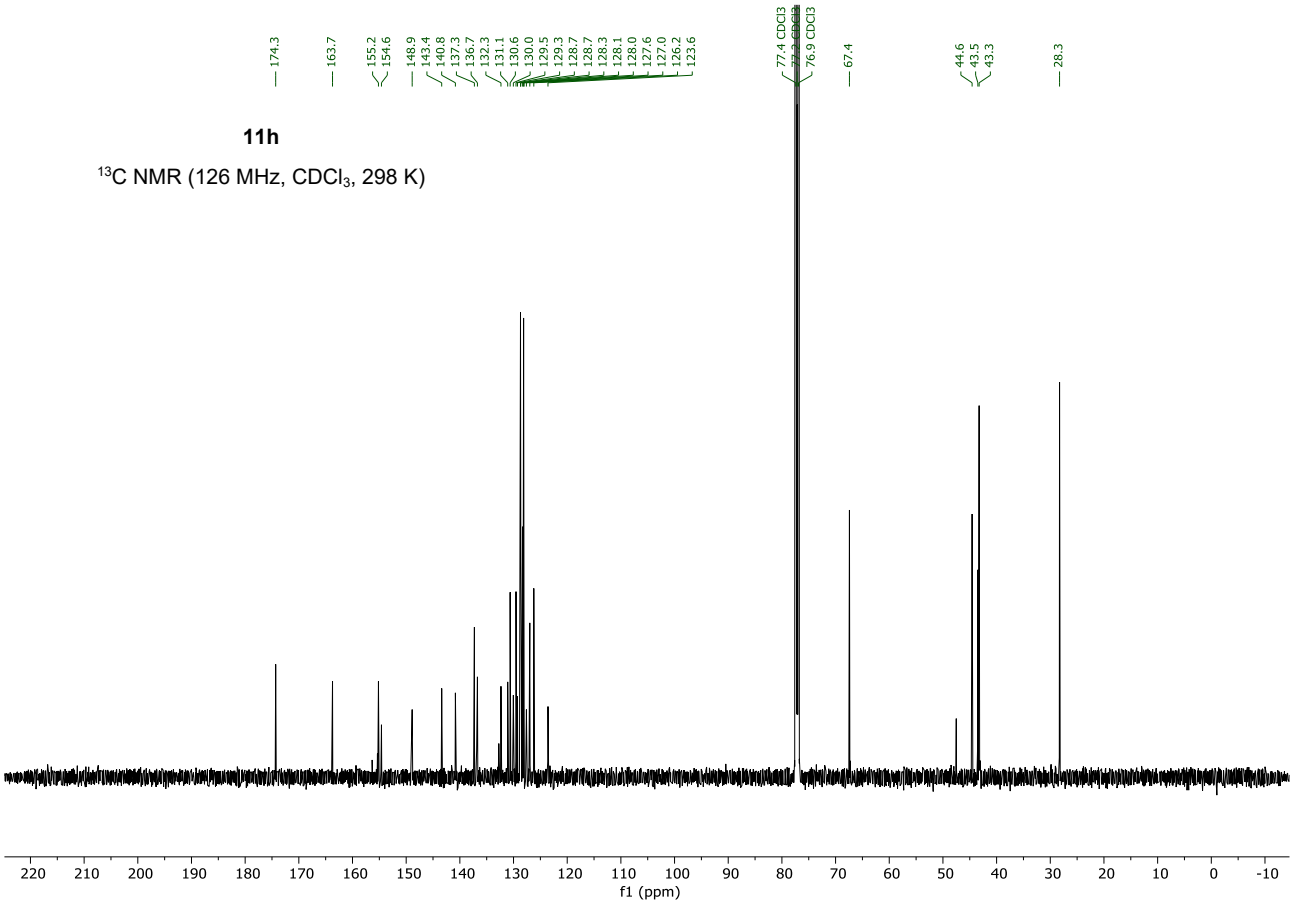
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

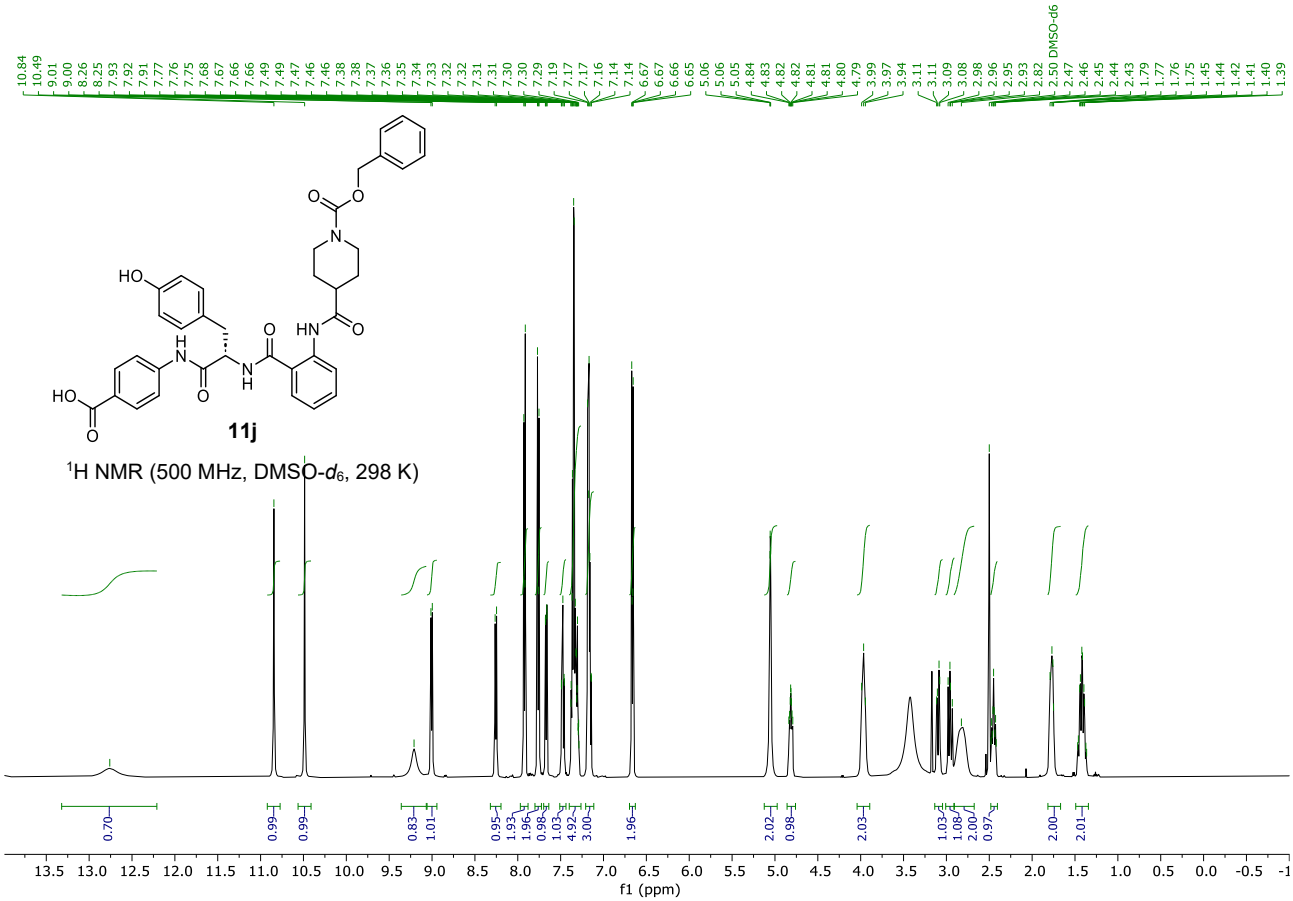


11g

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

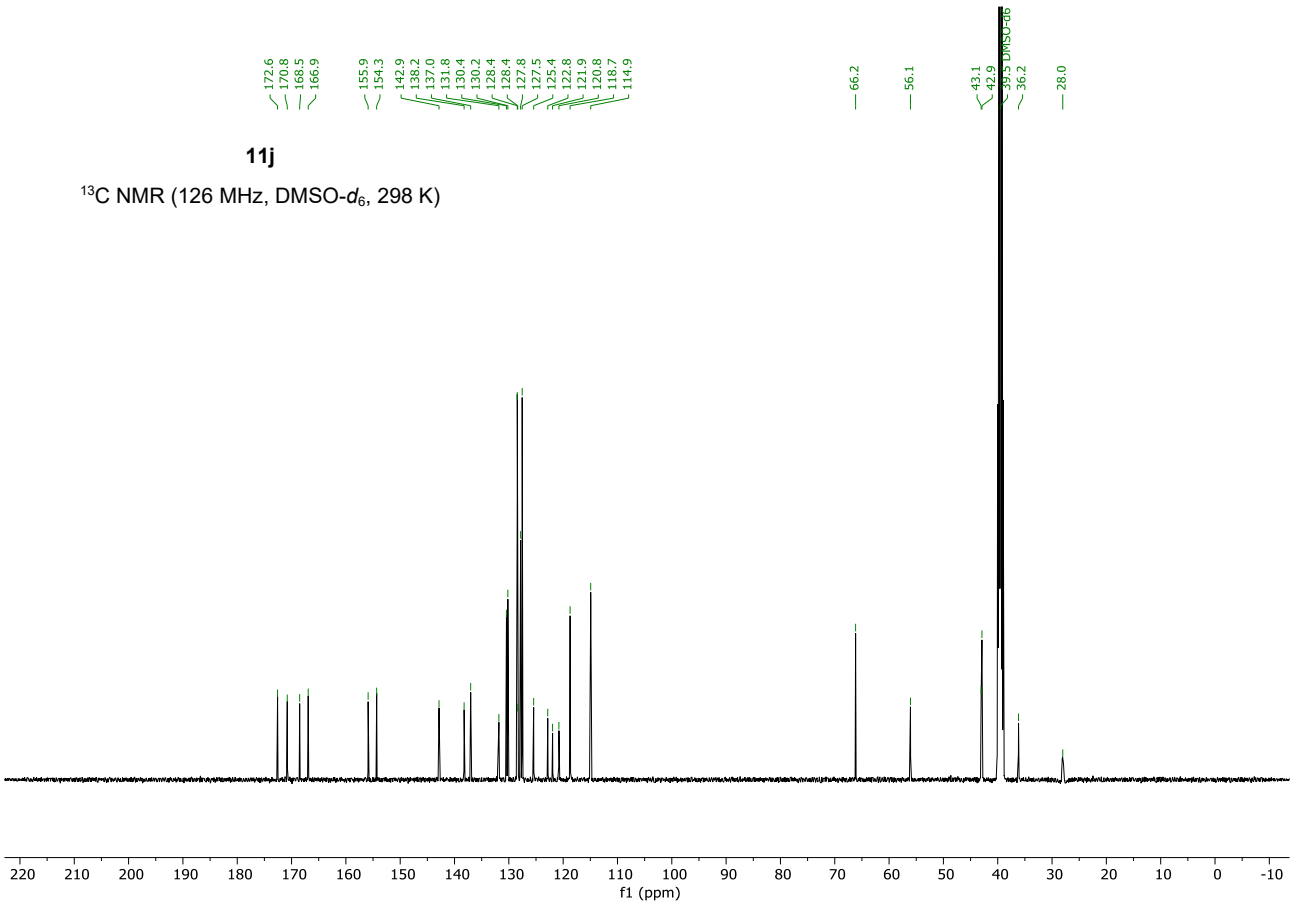

Cl
N
HN
O
N
H
O
Cl
S
O
O
N
O
O
O
11h
1H NMR (500 MHz, CDCl3, 298 K)
f1 (ppm)


11h
13C NMR (126 MHz, CDCl3, 298 K)
f1 (ppm)



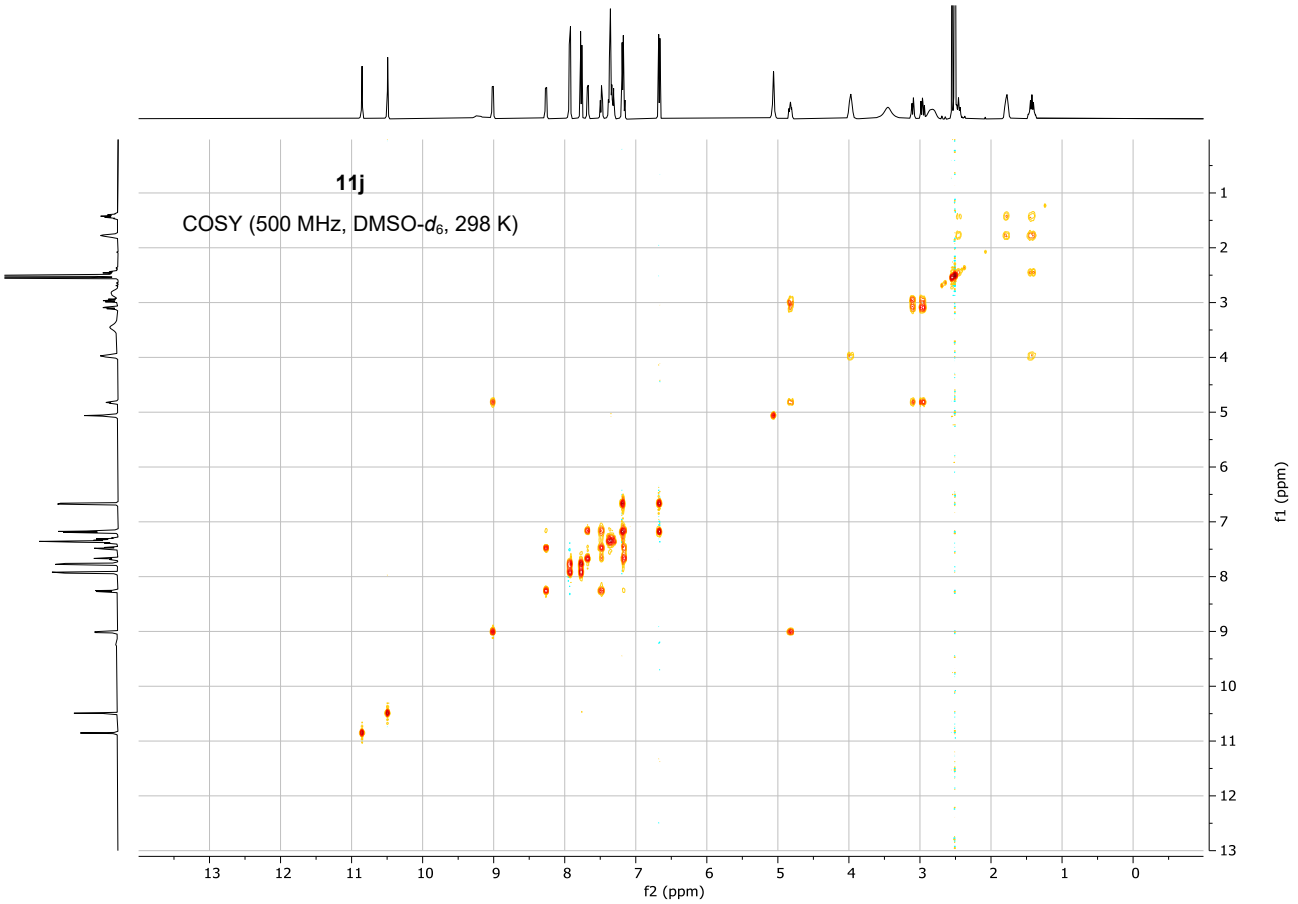
11j

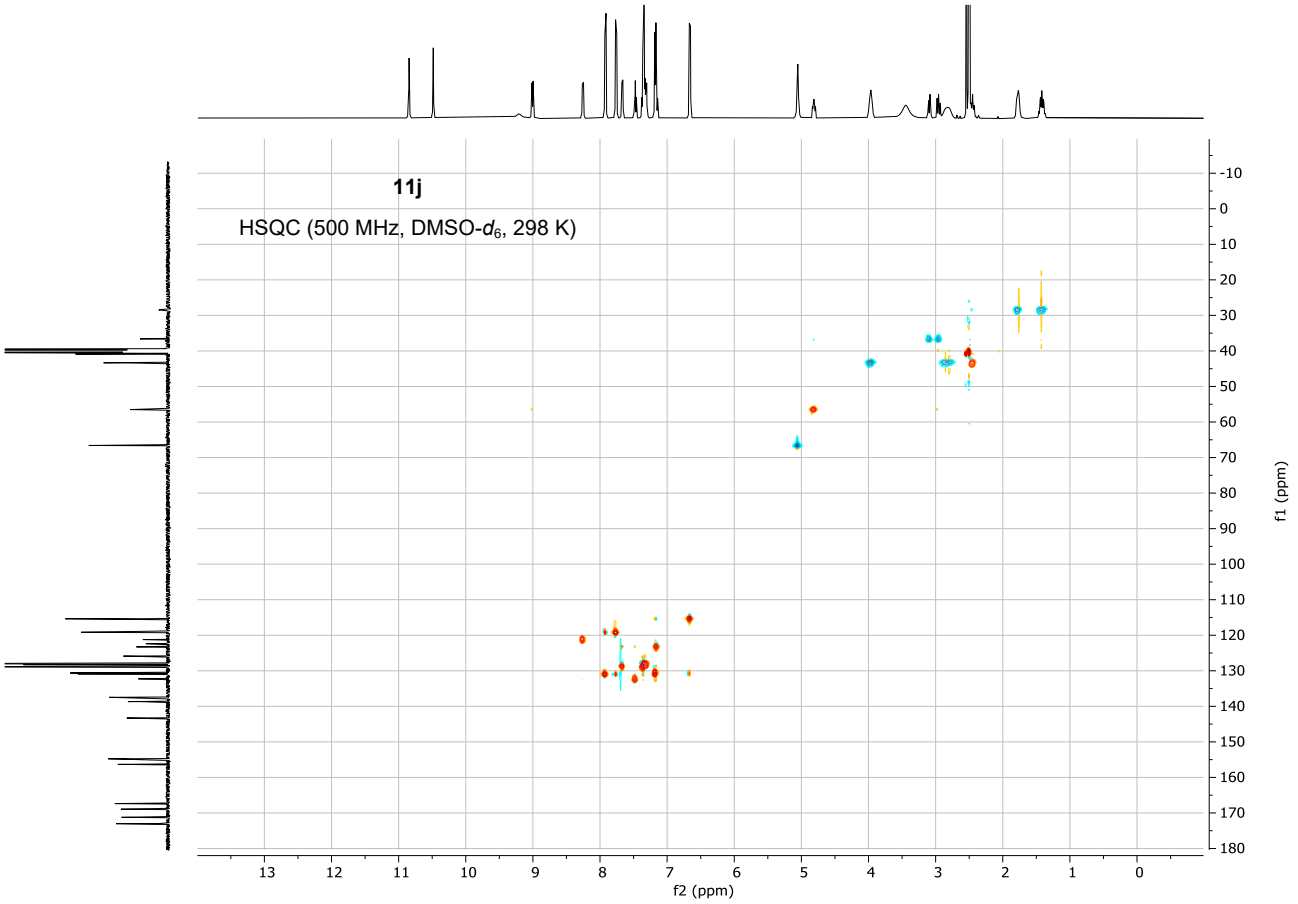
^{1}H NMR (500 MHz, DMSO-d_6, 298 K)

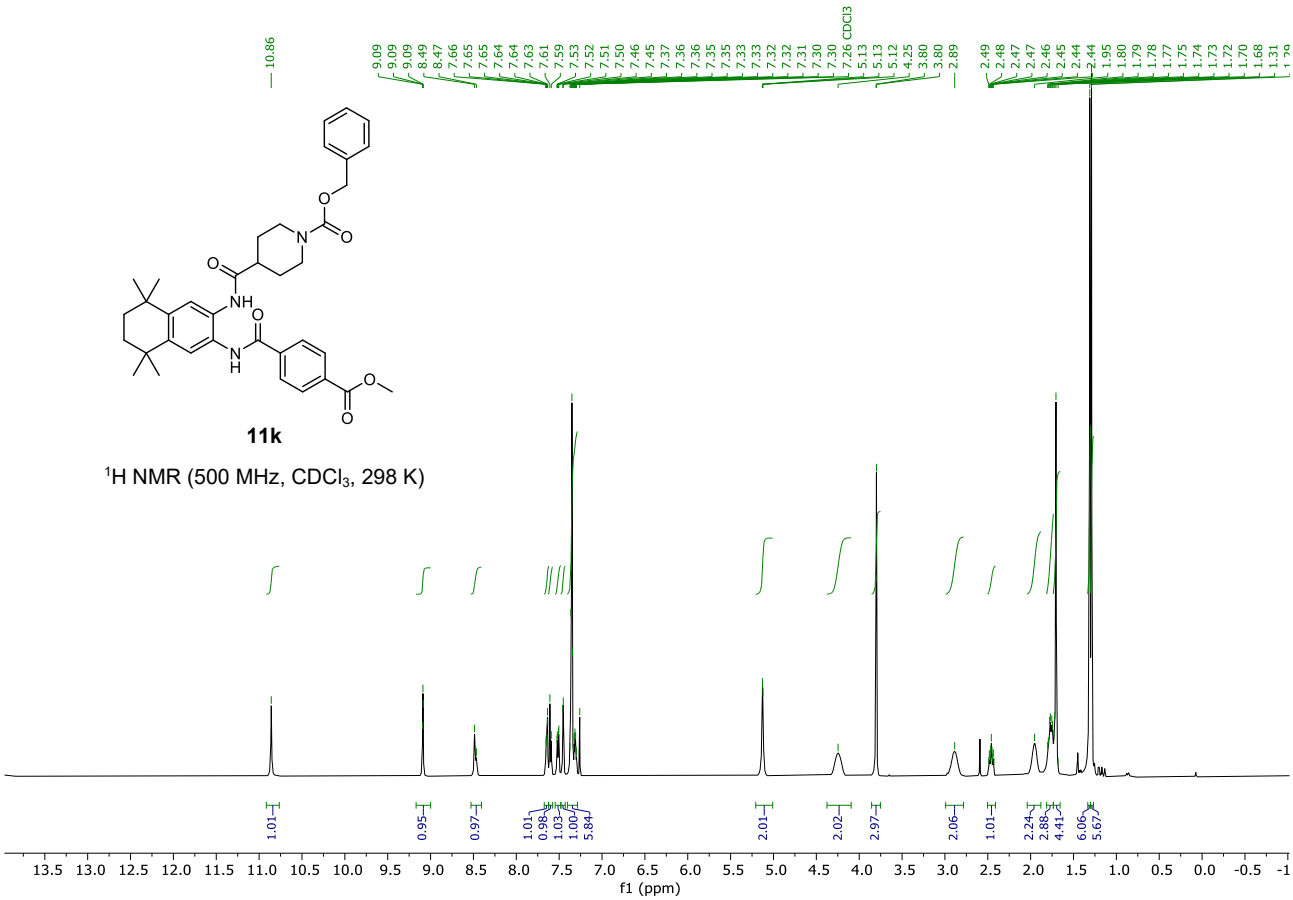


11j

^{13}C NMR (126 MHz, DMSO-d_6, 298 K)

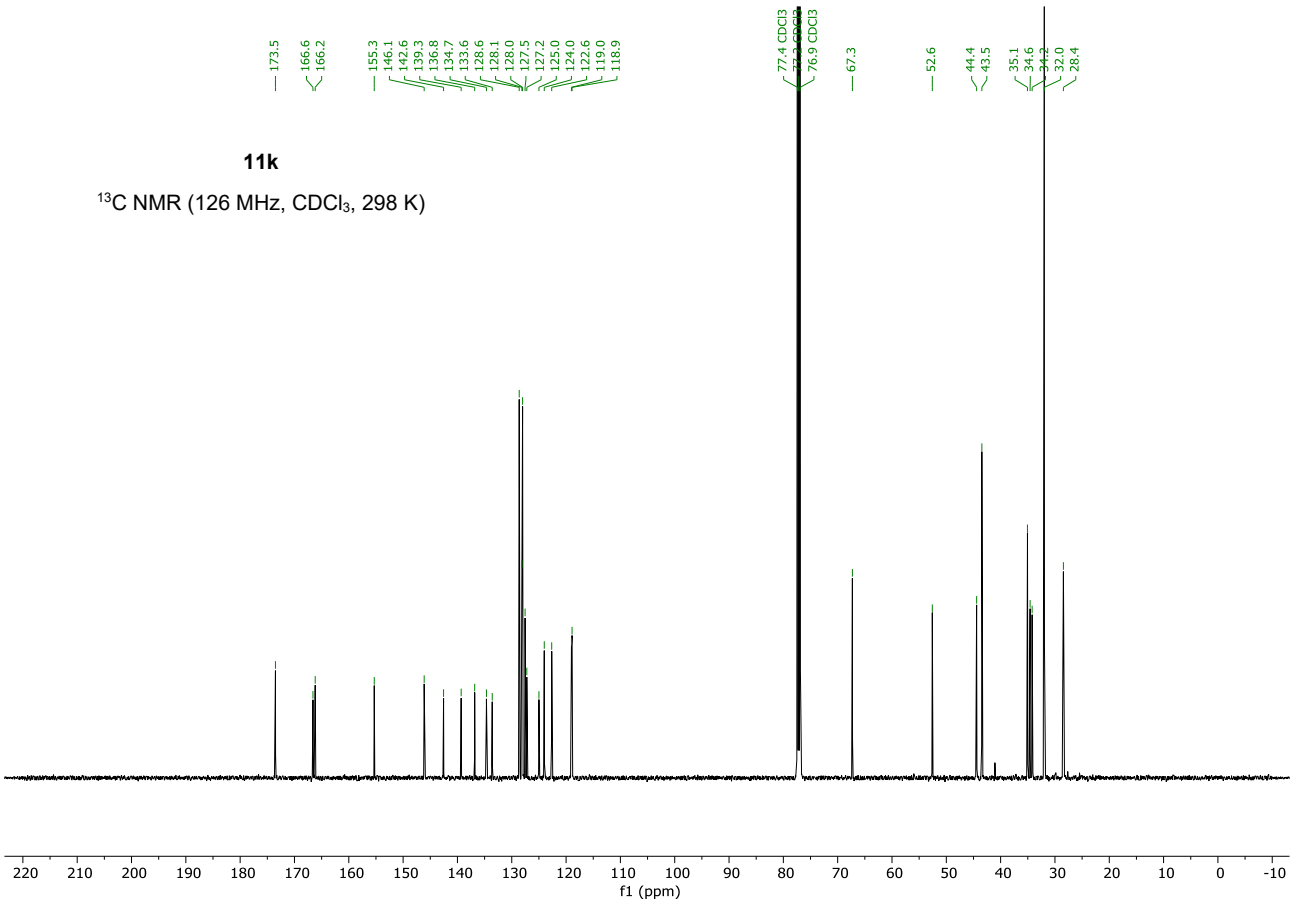

11j
COSY (500 MHz, DMSO-d_6, 298 K)
f2 (ppm)
f1 (ppm)


11j
HSQC (500 MHz, DMSO-d_6, 298 K)
f2 (ppm)
f1 (ppm)



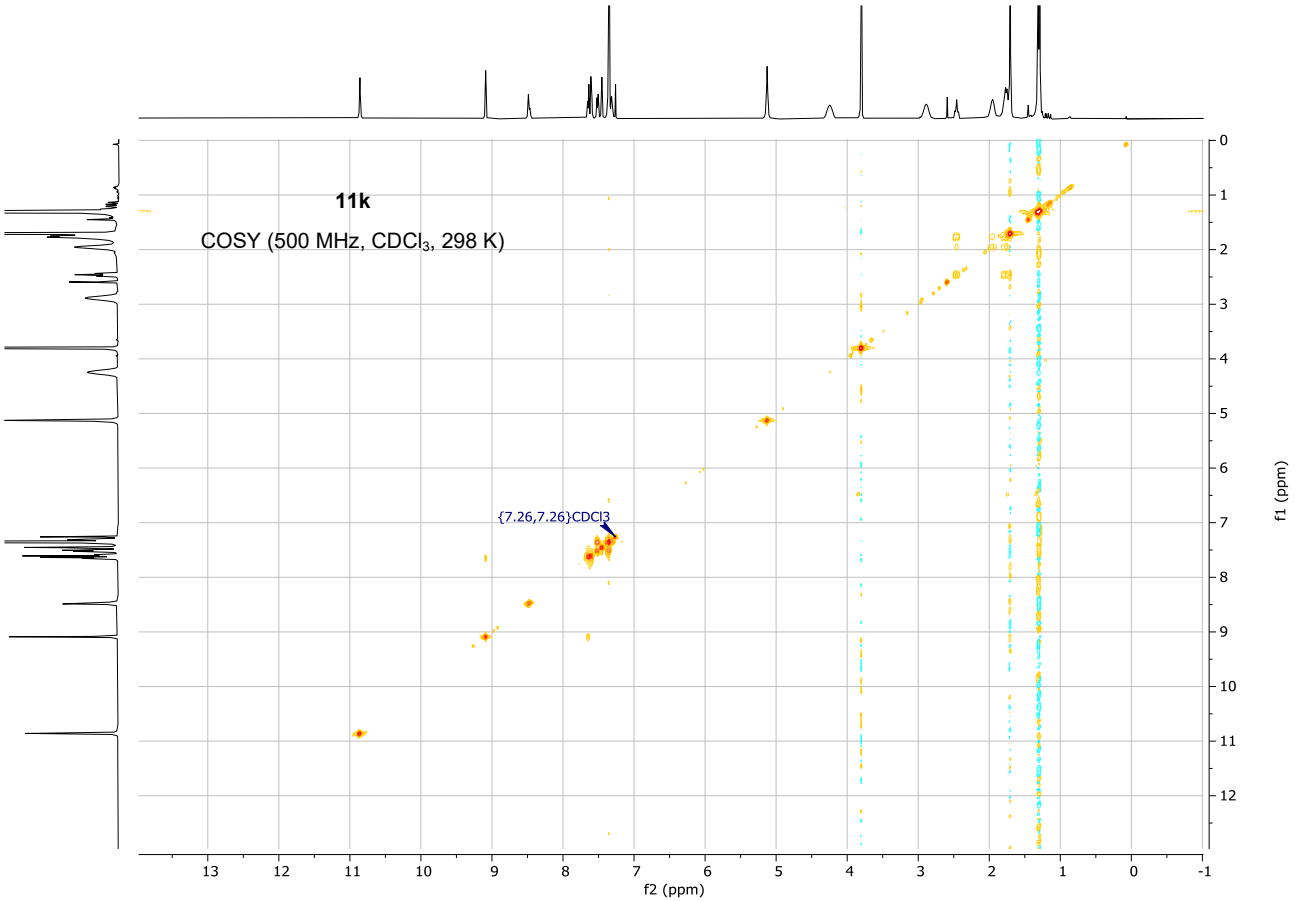
11k

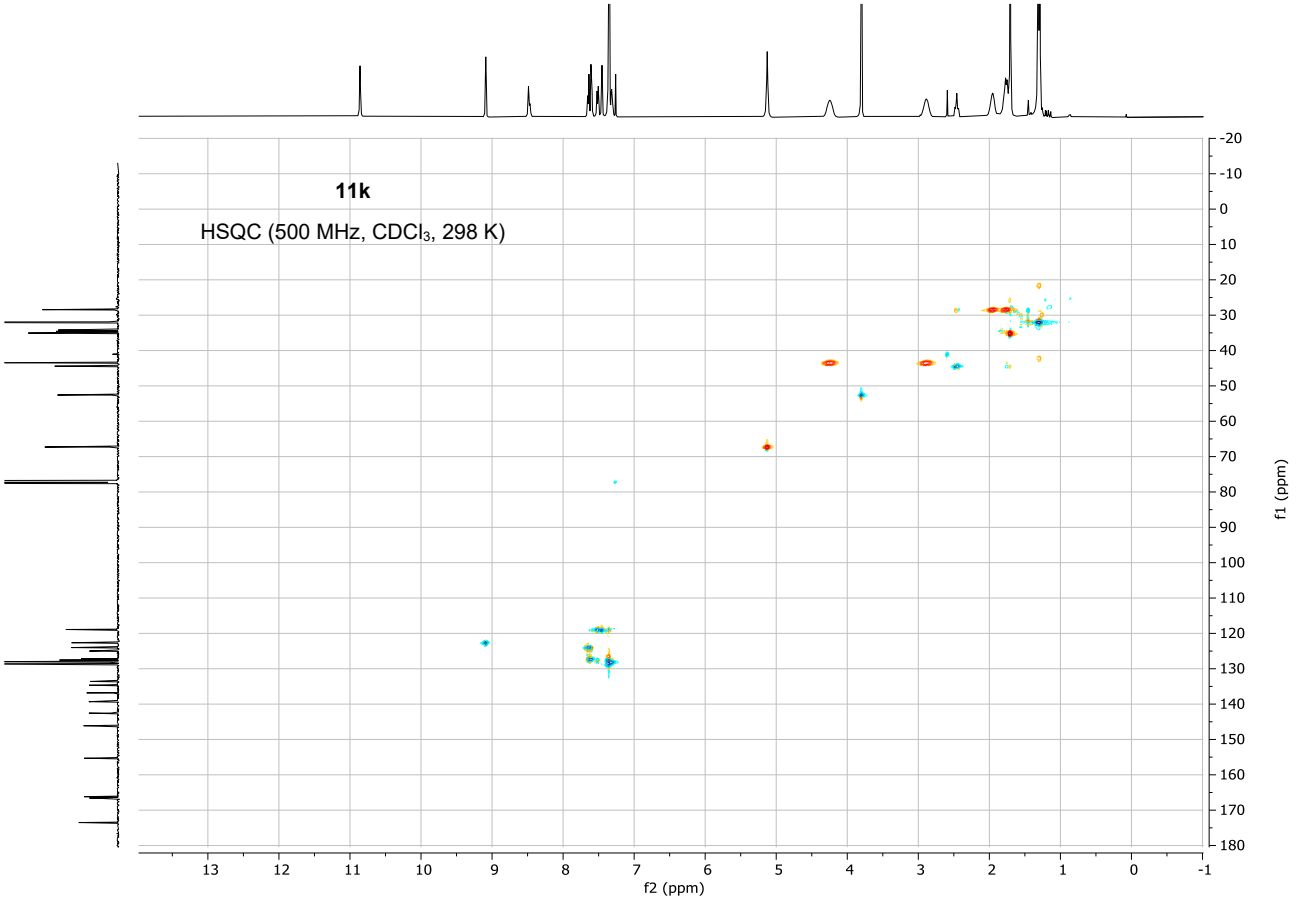
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

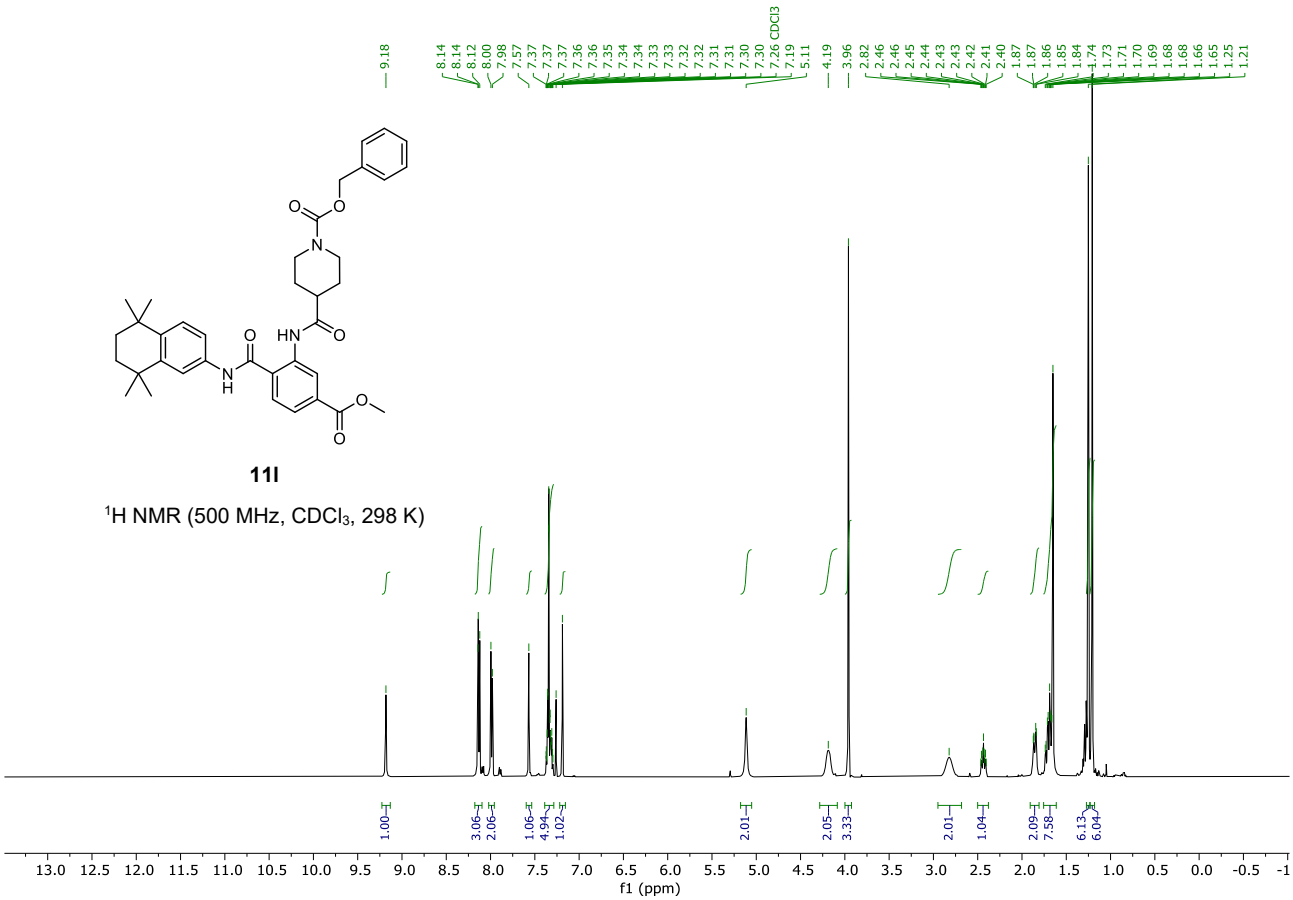


11k

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)

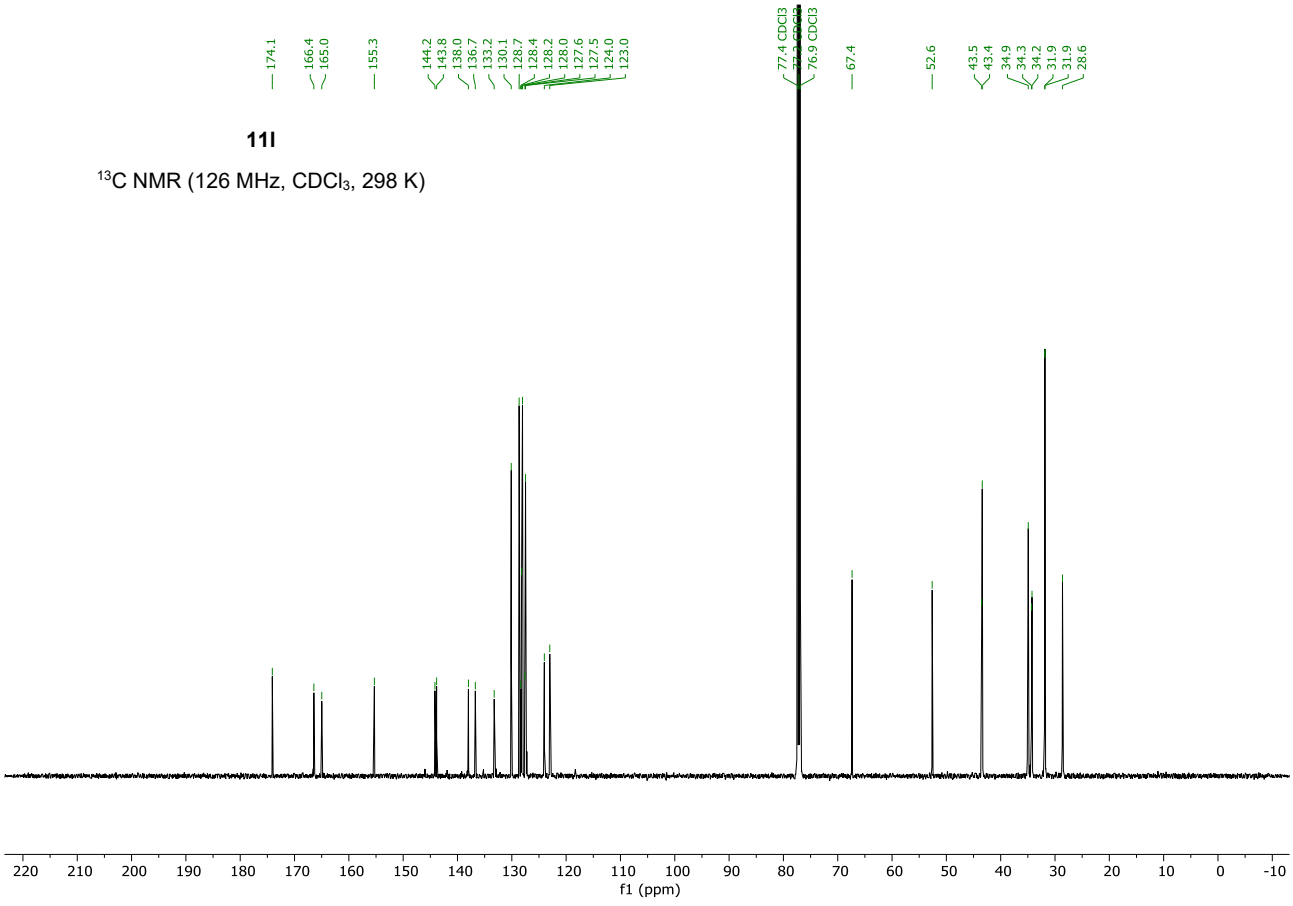

11k
COSY (500 MHz, CDCl3, 298 K)
{7.26,7.26}CDCl3
f2 (ppm)
f1 (ppm)


11k
HSQC (500 MHz, CDCl3, 298 K)
f2 (ppm)
f1 (ppm)



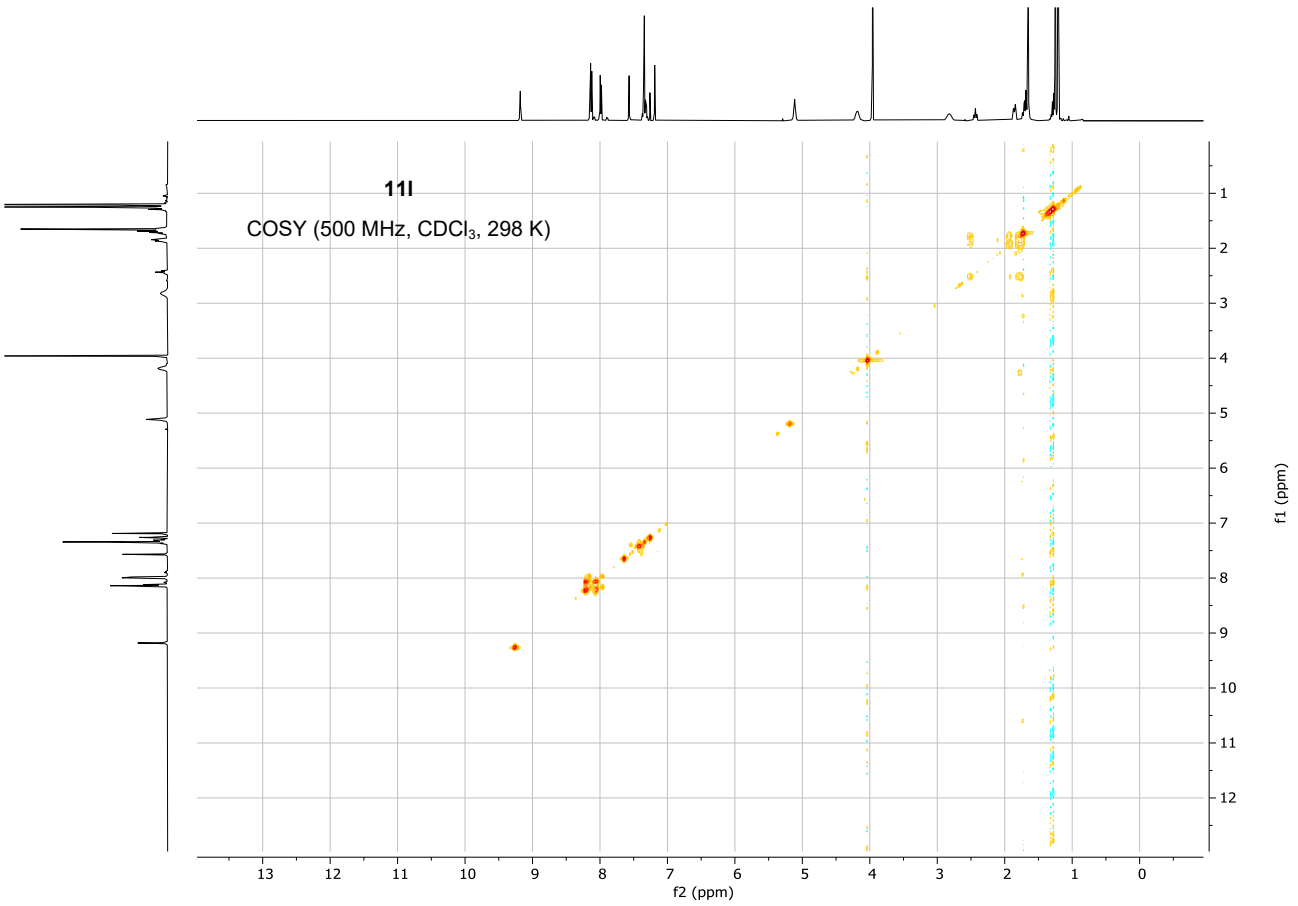
11l

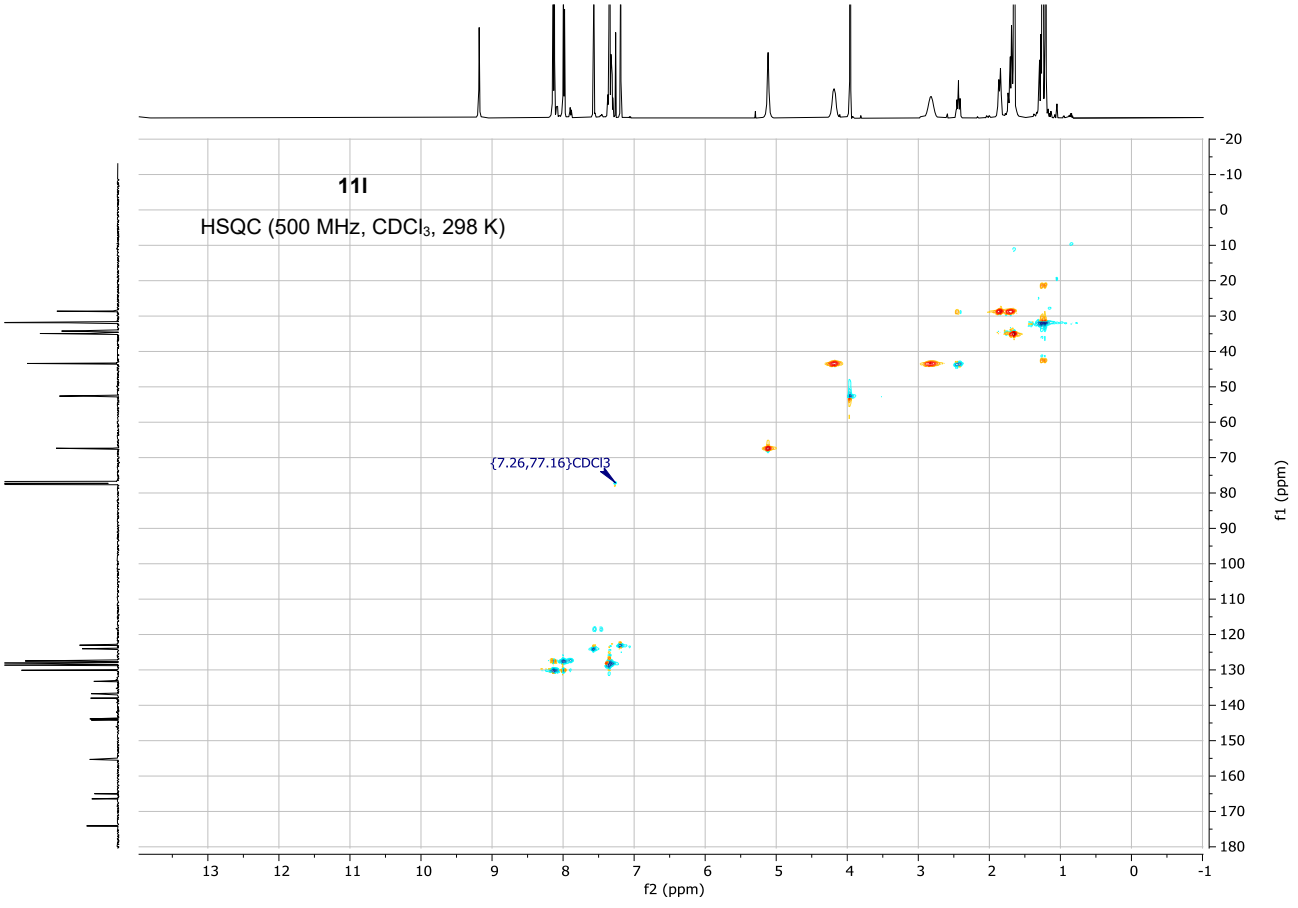
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

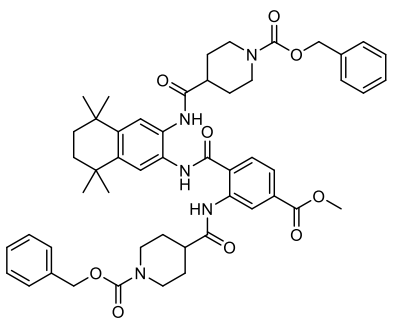


11l

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)


11l
COSY (500 MHz, CDCl3, 298 K)
f2 (ppm)
f1 (ppm)


11l
HSQC (500 MHz, CDCl3, 298 K)
{7.26,77.16}CDCl3
f2 (ppm)
f1 (ppm)

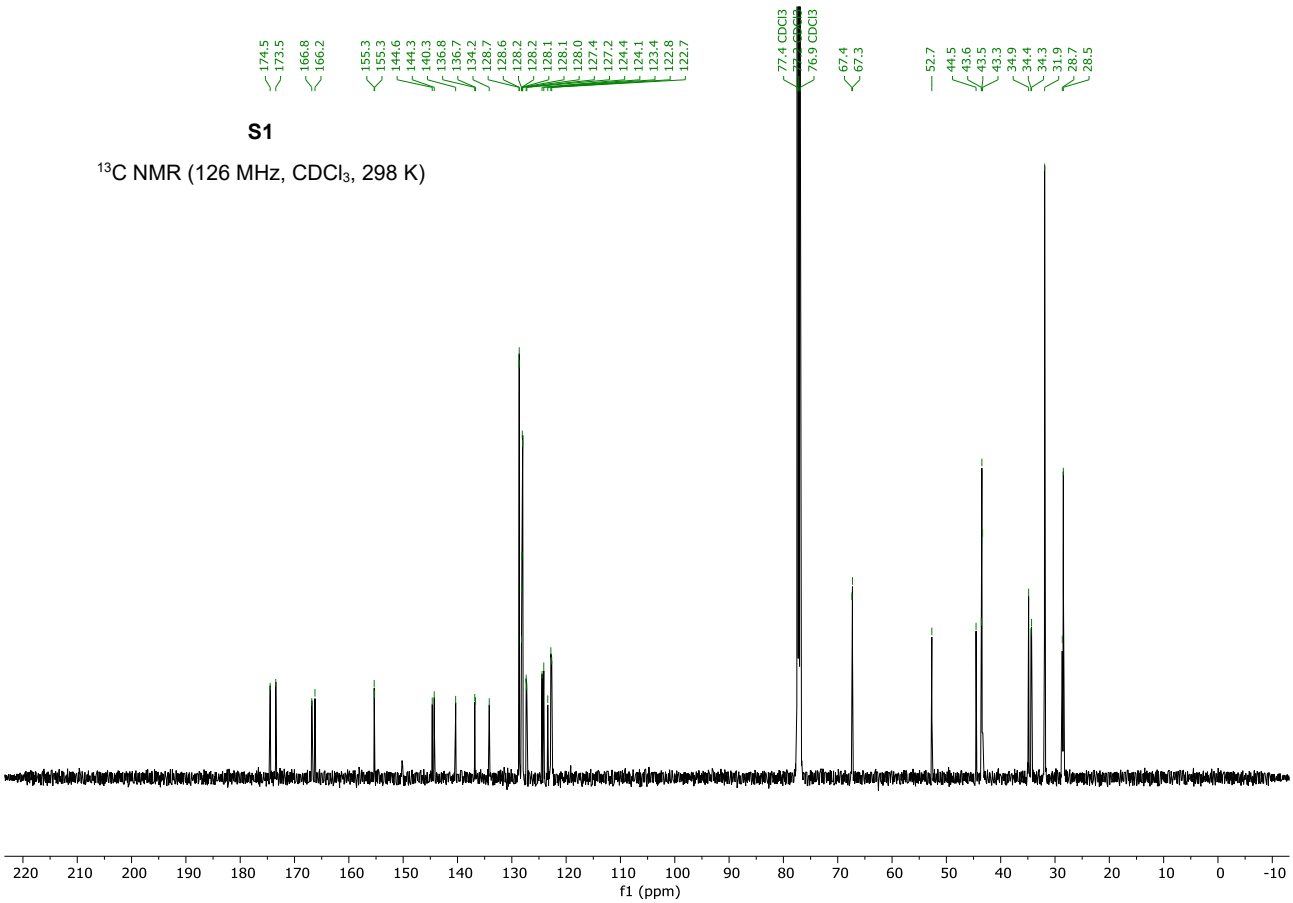


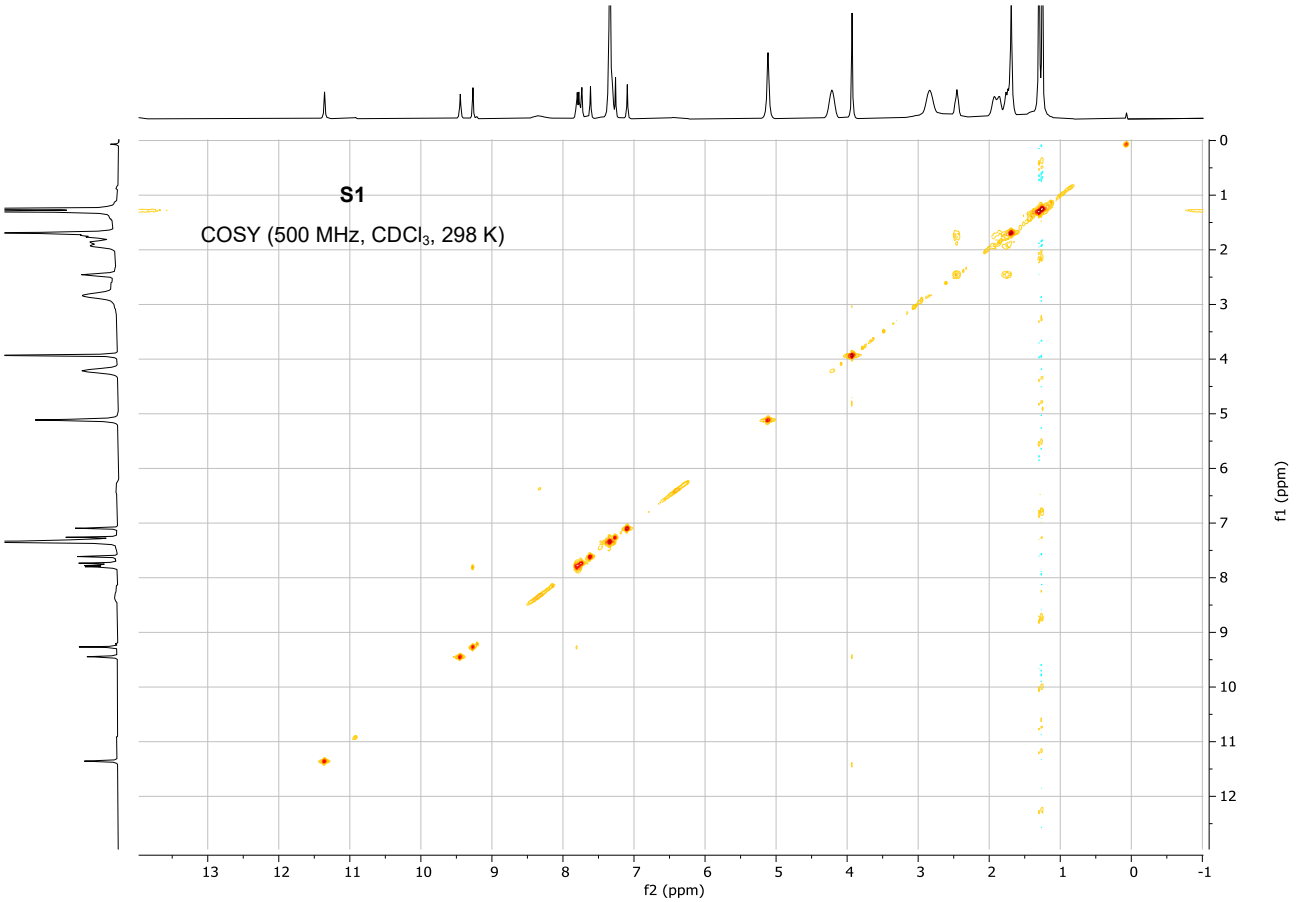
S1

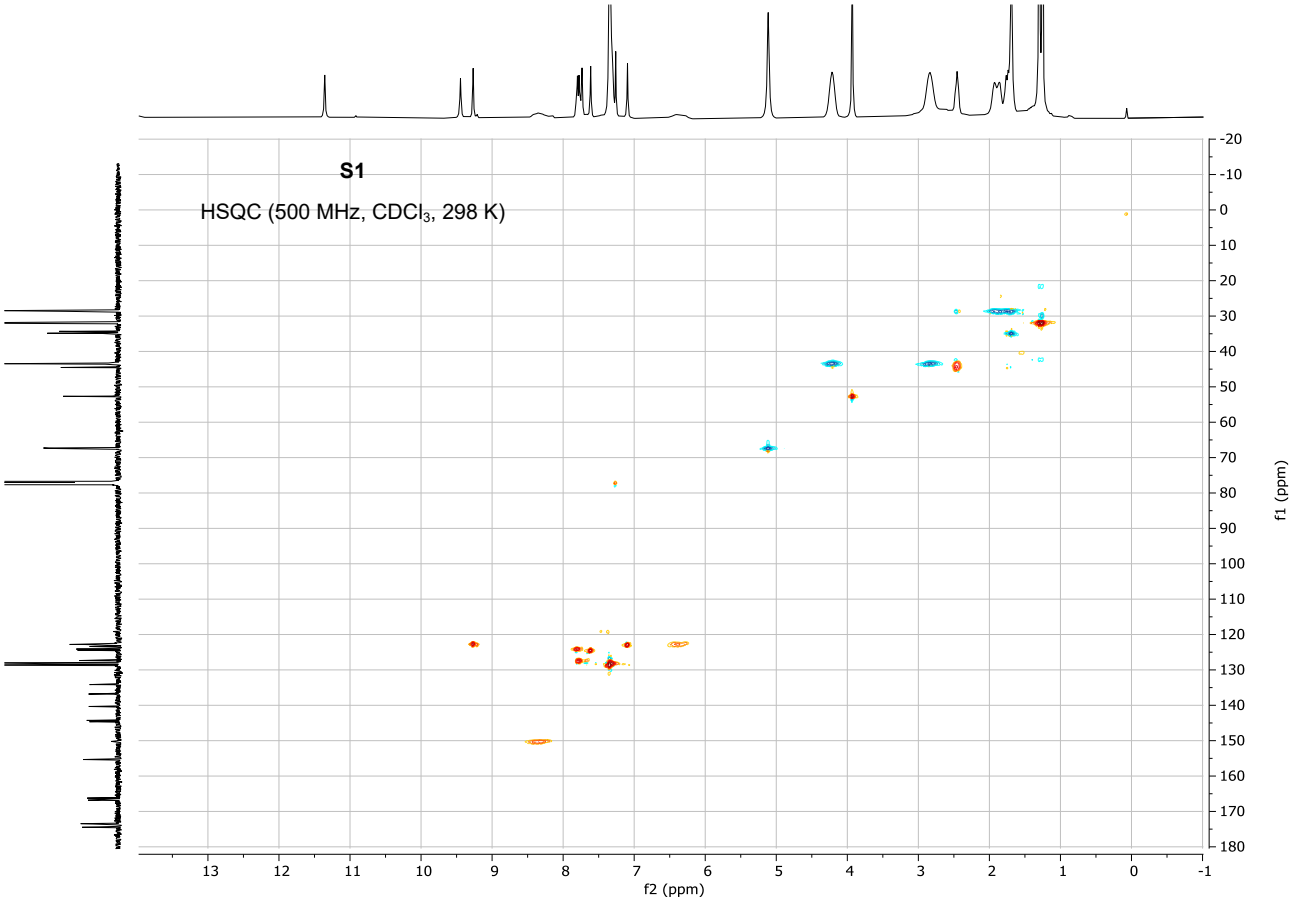
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)

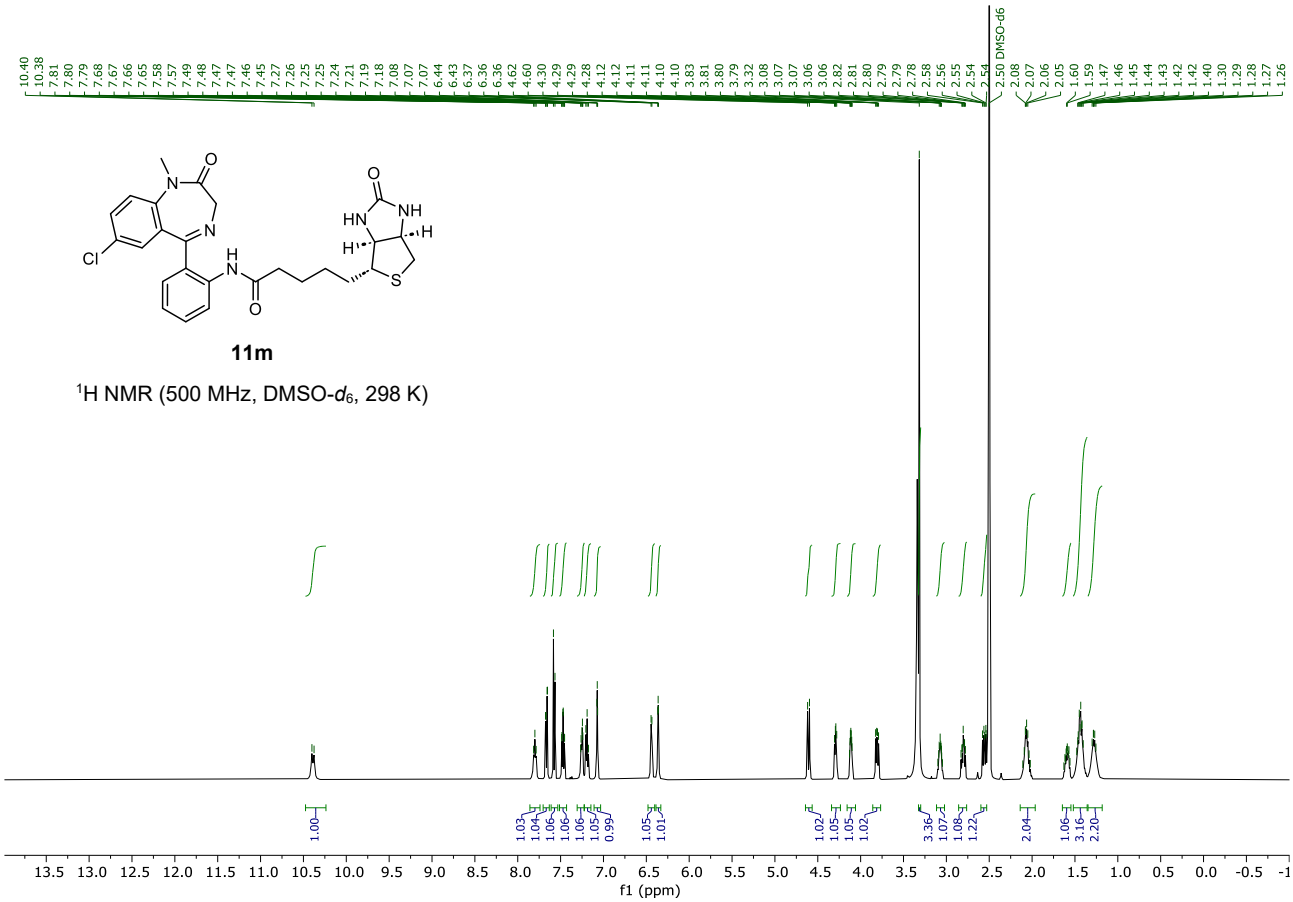
S1

^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



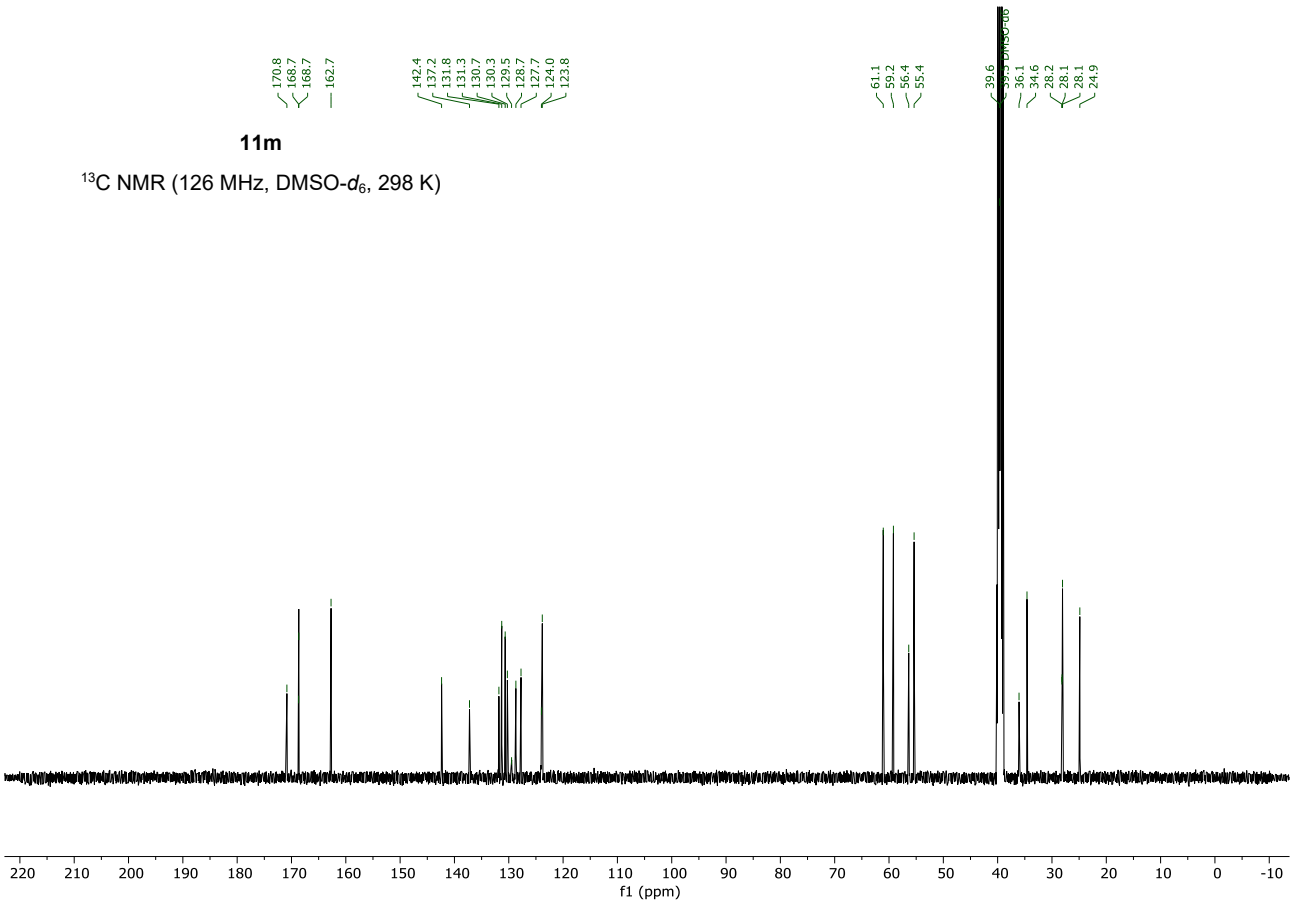

S1
COSY (500 MHz, CDCl3, 298 K)
f2 (ppm)
f1 (ppm)


S1
HSQC (500 MHz, CDCl3, 298 K)
f2 (ppm)
f1 (ppm)



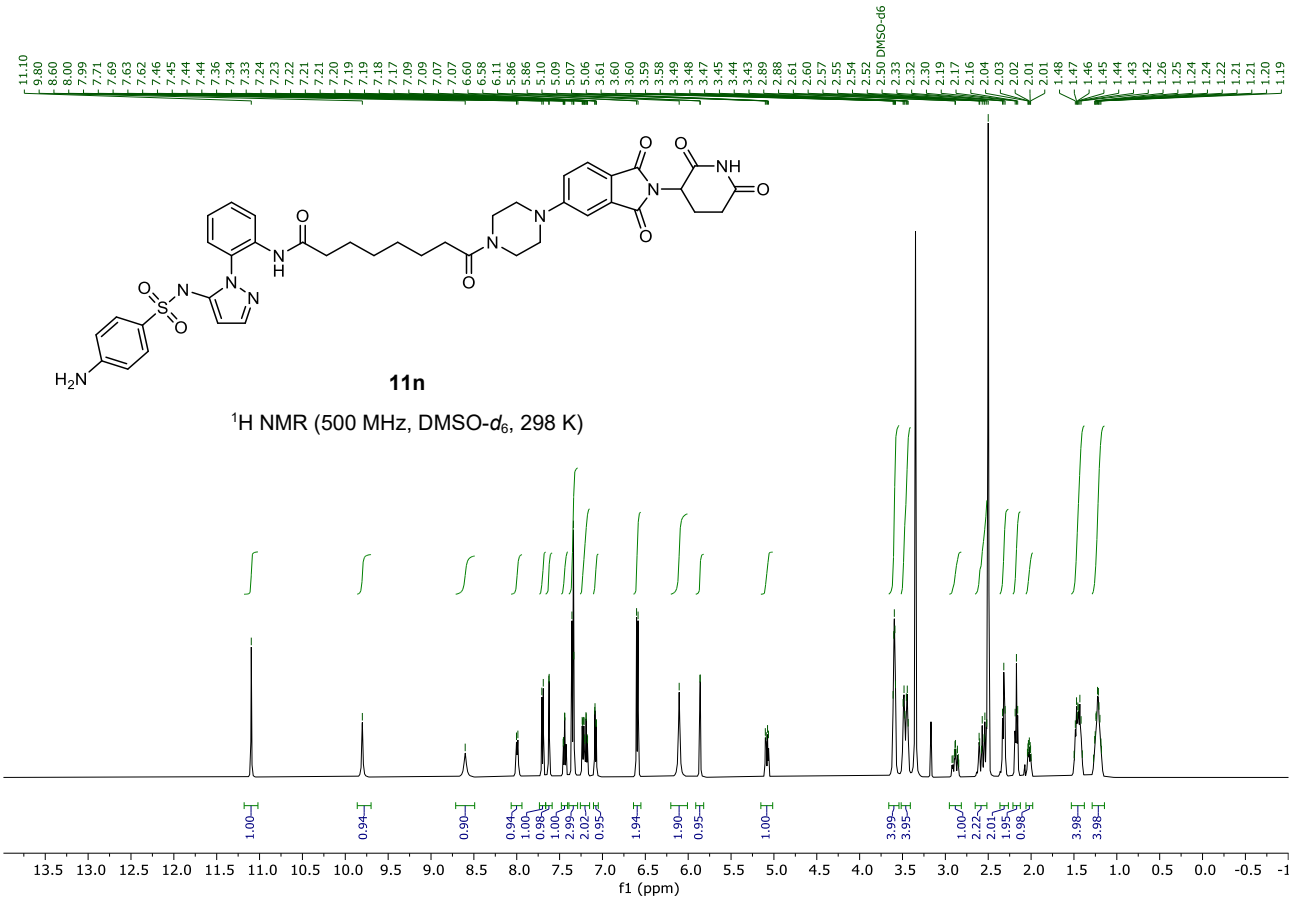
11m

^{1}H NMR (500 MHz, DMSO-d_6, 298 K)



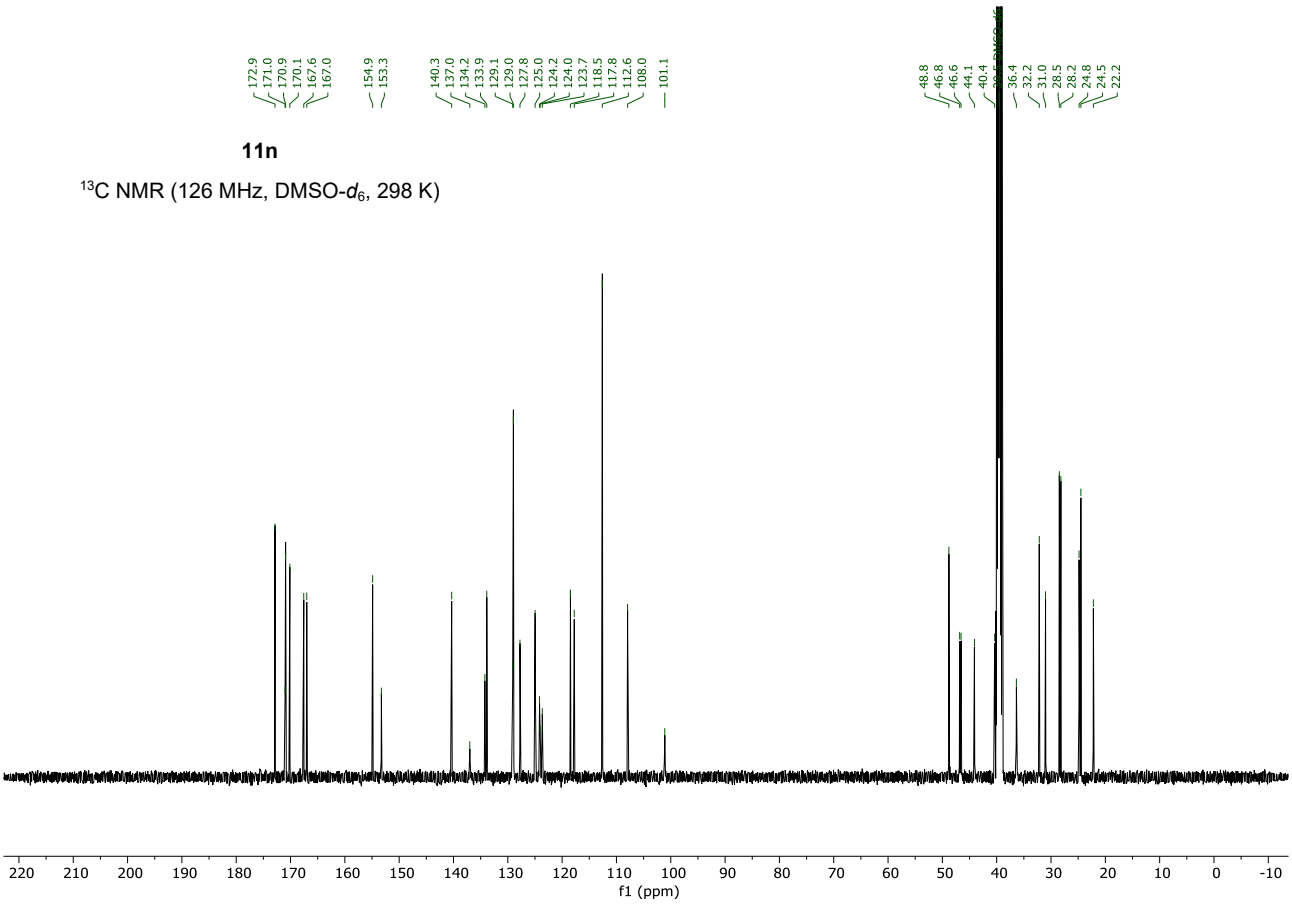
11m

^{13}C NMR (126 MHz, DMSO-d_6, 298 K)



11n

^{1}H NMR (500 MHz, DMSO-d_6, 298 K)



11n

^{13}C NMR (126 MHz, DMSO-d_6, 298 K)

7. References

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