Supplementary Information (SI) for Organic Chemistry Frontiers.

Total Synthesis and ^{13}C NMR Revision of Nagelamide C

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1. General methods

Unless otherwise noted, all reactions were performed using flame-dried glassware under an atmosphere of argon. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure by rotary evaporation at 35 °C. Reactions were monitored by thin-layer chromatography (TLC) using SiliCycle glass plates pre-coated with silica gel (0.25-mm thickness; 60-Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and staining with a solution of ninhydrin, ethanolic solution of phosphomolybdic acid (PMA), acidic solution of anisoaldehyde, or aqueous solution of potassium permanganate followed by heating. Solid reagents were weighed out in air unless otherwise noted. Reaction work-ups and chromatographic purifications were performed on the bench top in air.

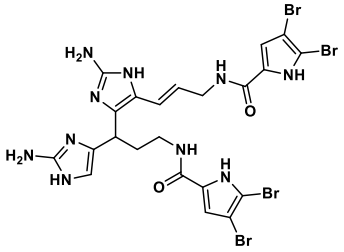
Materials

Dichloromethane (DCM, HPLC grade), methanol (MeOH, reagent grade), hexanes (HPLC grade), ethyl acetate (EtOAc, HPLC grade), chloroform (HPLC grade), acetone (HPLC grade) were purchased from Sigma and used as received. Anhydrous solvents (tetrahydrofuran (THF), dimethylformamide (DMF), triethylamine (Et_3N) were first degassed by sparging with nitrogen and dried by passing through a column of activated alumna on an SG Water solvent purification system. Deionized water was obtained from an in-house system. Silica gel was purchased from SiliCycle (40 μm) and used as received. Unless otherwise noted, all chemicals were purchased from commercial sources at the highest available purity and used as received.

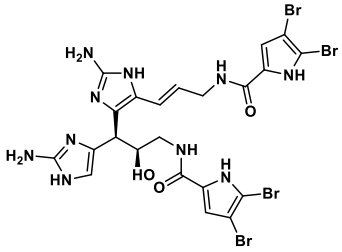
Instrumentation

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded at ambient temperature on 400, 500, 600 MHz Bruker or 500 MHz JEOL NMR spectrometers. Hydrogen chemical shifts are expressed in parts per million (ppm) relative to the residual protio-solvent resonance: $CDCl_3$ δ7.26, CD_3OD δ3.31, DMSO-d_6 δ2.50. For ^{13}C spectra, the centerline of the solvent signal was used as internal reference: $CDCl_3$ δ77.16, CD_3OD δ49.00, DMSO-d_6 δ39.50. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, and m = multiplet, br = broad), coupling constant (J) in hertz (Hz), and integration. High resolution mass spectrometry (HRMS) were acquired in on JEOL AccuTOF (Direct Analysis in Real Time, DART) and Agilent 6545 LC/QTOF MS in the positive mode. HPLC analysis was performed on an Agilent 1260 Infinity II using an Agilent reverse-phase C18 column with a mobile phase of acetonitrile/water/0.1% trifluoroacetic acid.

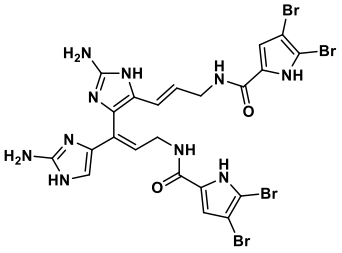
2. Nagelamide alkaloids



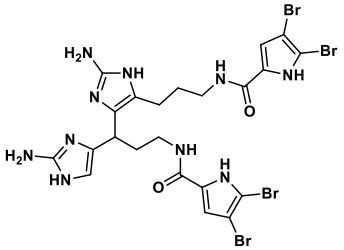
Nagelamide A



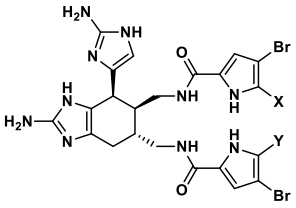
Nagelamide B



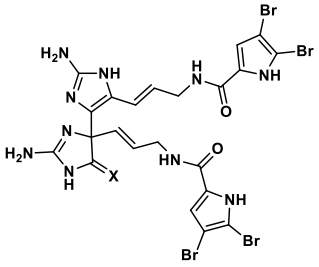
Nagelamide C



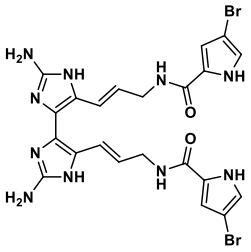
Nagelamide D
(proposed structure)



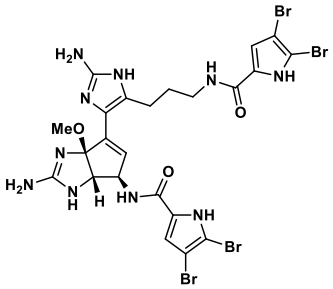
X = Y = H, Nagelamide E
X = Br, Y = H, Nagelamide F
X = Y = Br, Nagelamide G



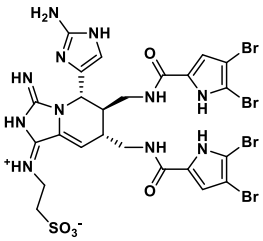
X = $NCH_2Ch_2SO_3$-: Nagelamide H
X = O: Mauritiamine



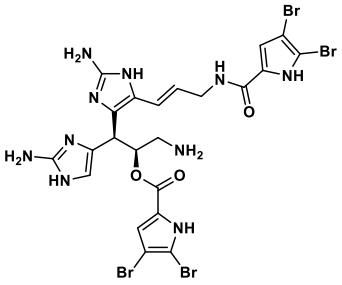
Nagelamide I



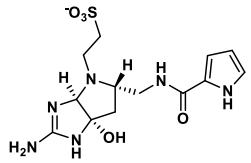
Nagelamide J



Nagelamide K



Nagelamide L



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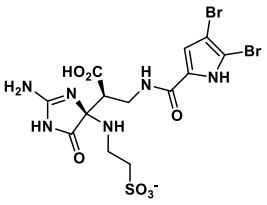
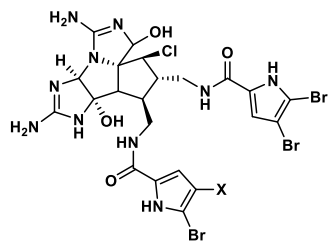
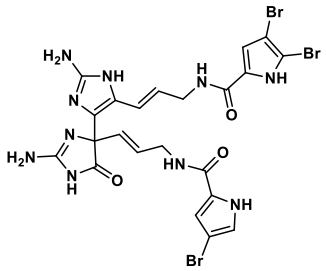


Nagelamide N

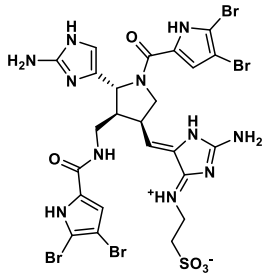
continued



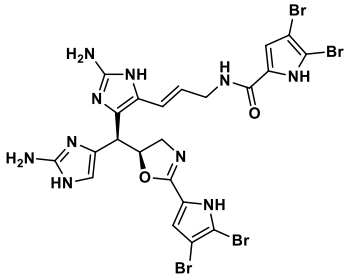
X = H: Nagelamide O
X = Br: Axinellamine A



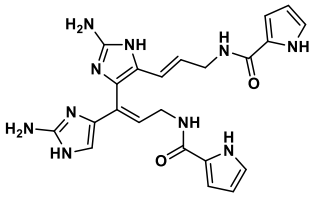
Nagelamide P



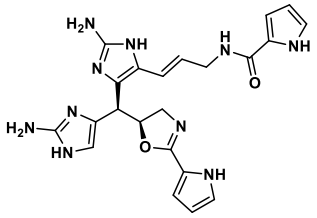
Nagelamide Q



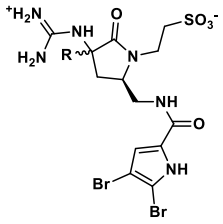
Nagelamide R



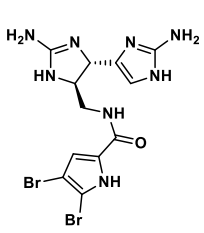
Nagelamide S



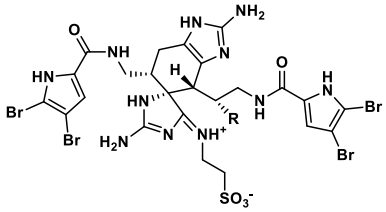
Nagelamide T



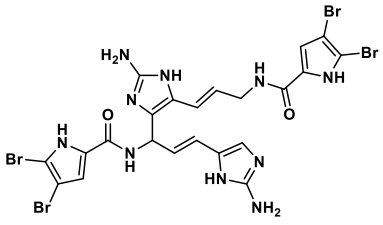
R = β-H: Nagelamide U
R = α-H: Nagelamide V



Nagelamide W



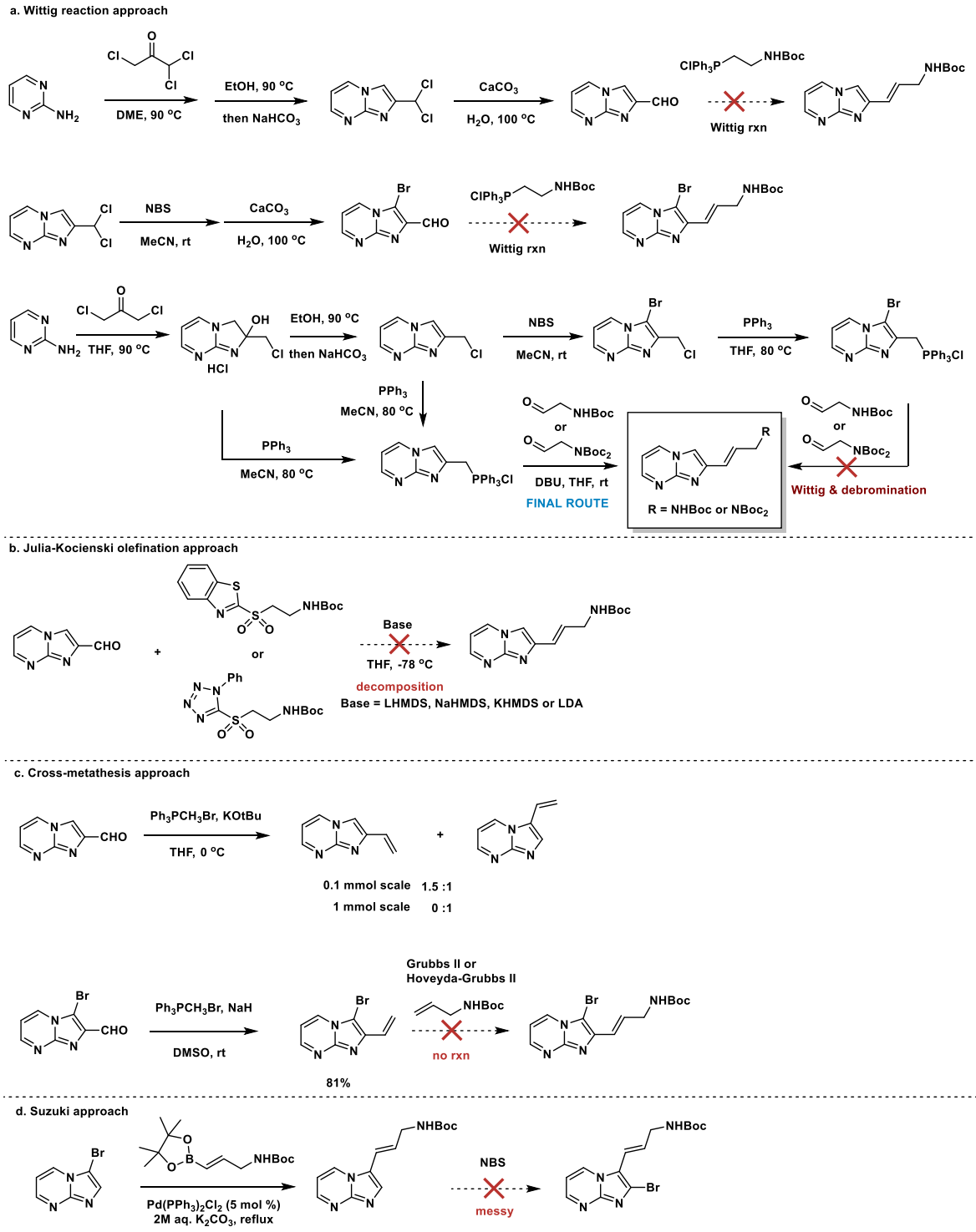
R = OH: Nagelamide X
R = H: Nagelamide Y



Nagelamide Z

Figure S1. Nagelamide alkaloids[1-10]

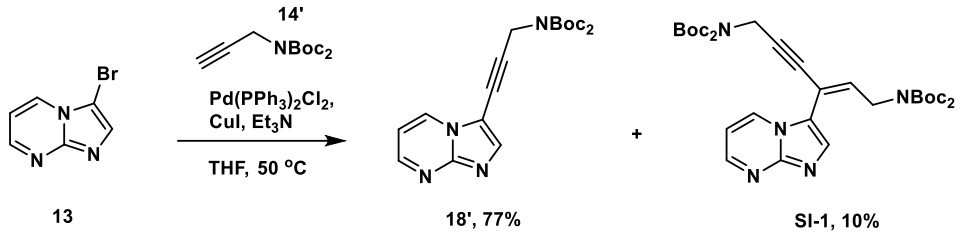
3. Attempted approaches to construct imidazo[1,2-a]pyrimidine derivatives



Scheme S1. a. Wittig olefination approach, b. Julia-Kocienski olefination approach, c. Cross-metathesis approach, d. Suzuki approach

4. Experimental procedures and characterization data

4.1 Sonogashira coupling



Mono-Boc protected **18** was prepared from **13** and **14** according to the previous literature.[11] However, we observed that starting material **13** showed less reactivity with **14'** in the presence of $Pd(PPh_3)_2Cl_2$. A modified procedure was used: to a mixture of imidazo[1,2-a]pyrimidine **13** (2.3 g, 11.7 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (675 mg, 0.58 mmol, 5 mol %), CuI (222 mg, 1.17 mmol, 10 mol %), Et_3N (8.2 mL, 58.4 mmol, 5.0 equiv) in DMF (47 mL) was slowly added a solution of alkyne **14'** (4.47 g, 17.5 mmol, 1.5 equiv) in DMF (10 mL) at room temperature. The resulting solution was warmed to 50 °C and stirred for 2.5 h. The reaction mixture was concentrated in *vacuo*, and purified by column chromatography (silica gel, EtOAc:MeOH 20:1) to afford alkyne **18'** (3.3 g, 9 mmol, 77% yield) as yellow solid. **SI-1** (10% yield) was isolated as a yellow solid.

R_f 0.45 (silica gel, EtOAc:MeOH 20:1), UV active, stains brown in ninhydrin.

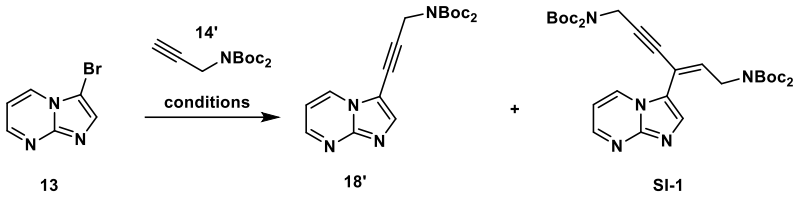
18':

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 – 8.56 (m, 2H), 7.96 (s, 1H), 6.98 (dd, *J* = 6.8, 4.1 Hz, 1H), 4.71 (s, 2H), 1.54 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 151.96, 150.89, 148.50, 139.64, 132.97, 109.46, 107.23, 96.27, 83.56, 69.24, 36.88, 28.23.

The ^{1}H and ^{13}C NMR data of **18'** are consistent with the reported data in literature.[11]

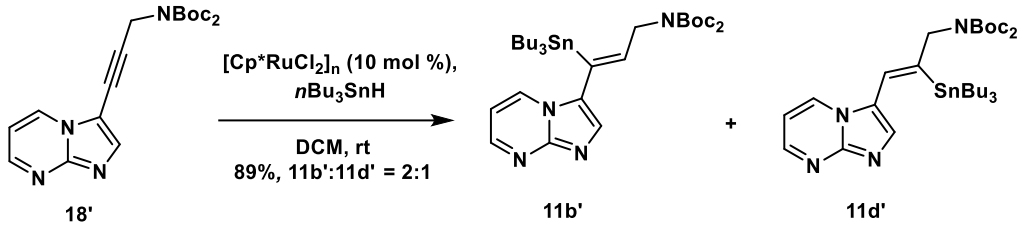
Table S1. Optimization of Sonogashira coupling[a]



	14' (equiv)	Conditions	Result (13: 18': SI-1)
1	1.1	$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), THF, 50 ^{O}C, 16 h	84: 16: 0
2	1.5	$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), THF, 50 ^{O}C, 16 h	73: 22: 5
3	1.1	$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), DMF, 50 ^{O}C, 16 h	69: 31: 0
4	1.1	$Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), DMF, rt, 16 h	87: 13: 0
5	1.1	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), THF, 50 ^{O}C, 16 h	42: 46: 12
6	1.1	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), DMF, 50 ^{O}C, 16 h	57: 43: 0
7[b]	1.5	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), DMF, 50 ^{O}C, 16 h	9: 77: 10
8	2.0	$Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv), DMF, 50 ^{O}C, 16 h	10: 78: 12

[a]0.1 mmol scale, ratio was based on crude ^{1}H NMR, 1,3,5-trimethoxylbenzene as internal standard. [b]2 g scale, isolated yield

4.2 *trans*-Hydrostannylation



To a solution of alkyne **18'** (745 mg, 2.0 mmol, 1.0 equiv) and dichloro(pentamethylcyclopentadienyl)ruthenium(III) polymer (61.4 mg, 0.2 mmol, 10 mol %) in DCM (20 mL) was slowly added *n*Bu_3SnH (0.65 mL, 2.4 mmol, 1.2 equiv) at room temperature. The brown solution quickly turned to black. The resulting solution was stirring for 1 h. At this point, a second portion of *n*Bu_3SnH (0.65 mL, 2.4 mmol, 1.2 equiv) was added and stirred for another 1 h. TLC indicated the starting material consumption. The reaction mixture was concentrated in *vacuo* and purified by column chromatography (silica gel, DCM to DCM:EtOAc = 1:1) to give **11b'/11d'** as yellow oil (1.33 g, 1.8 mmol, 89% yield, 2:1 inseparable mixture).

R_f 0.54 (silica gel, EtOAc:DCM 1:1), UV active, stains brown in ninhydrin.

11b':

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.37 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.46 (s, 1H), 6.79 (dd, *J* = 6.9, 4.0 Hz, 1H), 6.47 (t, *J* = 5.6 Hz, 1H), 4.40 (d, *J* = 5.6 Hz, 2H), 1.51 (s, 18H), 1.43 – 1.38 (m, 6H), 1.27 – 1.21 (m, 6H), 1.01 – 0.95 (m, 6H), 0.83 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.79, 148.60, 148.15, 146.49, 132.27, 131.99, 131.27, 127.89, 108.21, 82.95, 49.24, 29.13, 28.25, 27.38, 13.72, 11.21.

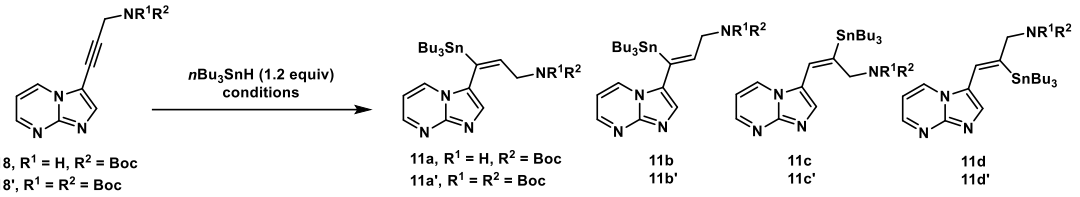
HRMS (ESI): m/z calc'd for $C_{31}H_{53}N_4O_4Sn$ $[M+H]^+$: 665.3089, found: 665.3100.

11d':

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.18 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.66 (d, *J* = 1.0 Hz, 1H), 6.89 (q, *J* = 1.8 Hz, 1H), 6.87 (dd, *J* = 6.8, 4.1 Hz, 1H), 4.55 (d, *J* = 2.1 Hz, 2H), 1.51 (s, 18H), 1.34 – 1.28 (m, 6H), 1.20 – 1.14 (m, 6H), 0.93 – 0.87 (m, 6H), 0.79 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.62, 152.59, 149.43, 148.44, 133.27, 131.01, 123.36, 120.11, 108.68, 82.64, 53.82, 29.08, 28.22, 27.36, 13.67, 10.64.

Table S2. Optimization of *trans*-hydrostannylation[a]



18, R^1 = H, R^2 = Boc
18', R^1 = R^2 = Boc

11a, R^1 = H, R^2 = Boc
11a', R^1 = R^2 = Boc

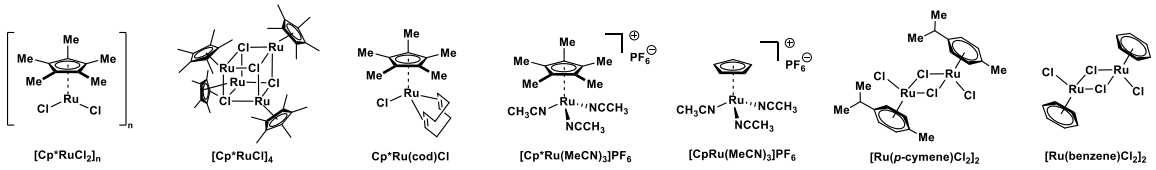
11b
11b'

11c
11c'

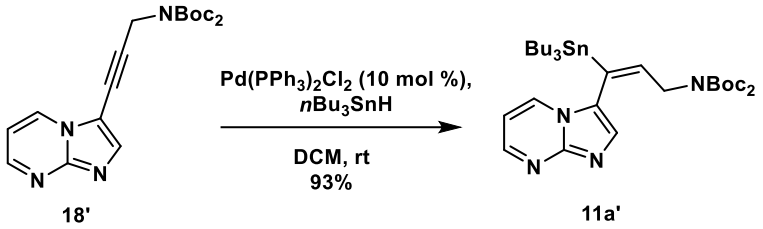
11d
11d'

	R^1, R^2	Conditions	Yield%	11a%	11b%	11c%	11d%
1	H, Boc	$Pd(PPh_3)_2Cl_2$ (10 mol%), DCM, rt	92	100	0	0	0
2	H, Boc	$[Cp^*RuCl]_4$ tetramer (10 mol%), DCM, rt	91	5	23	22	50
3	H, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), DCM, rt	84	6	17	21	56
4	H, Boc	Cp*Ru(cod)Cl (10 mol%), DCM, rt	88	39	12	18	31
5	H, Boc	$[Cp^*Ru(MeCN)_3]PF_6$ (10 mol%), DCM, rt	65	64	0	36	0
6	H, Boc	$[CpRu(MeCN)_3]PF_6$ (10 mol%), DCM, rt	69	51	12	37	0
	R^1, R^2	**Conditions**	**Yield%**	**11a'%**	**11b'%**	**11c'%**	**11d'%**
7	Boc, Boc	$[Cp^*RuCl]_4$ tetramer (10 mol%), DCM, rt	96	20	50	0	30
8	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), DCM, rt	89[c]	5	63	0	32
9	Boc, Boc	$[Cp^*Ru(MeCN)_3]PF_6$ (10 mol%), DCM, rt	72	24	47	0	29
10	Boc, Boc	$[Cp^*Ru(MeCN)_3]OTf$ (10 mol%), DCM, rt	NR	-	-	-	-
11	Boc, Boc	$[CpRu(MeCN)_3]PF_6$ (10 mol%), DCM, rt	87	71	19	0	10
12	Boc, Boc	Cp*Ru(cod)Cl (10 mol%), DCM, rt	82	55	34	0	11
13	Boc, Boc	$[Ru(benzene)Cl_2]_2$ (10 mol%), DCM, rt	69	100	0	0	0
14	Boc, Boc	$[Ru(p\text{-cymene})Cl_2]_2$ (10 mol%), DCM, rt	80	100	0	0	0
15	Boc, Boc	$MgBu_2$ (1.0 equiv), THF, 50 °C	decom.	-	-	-	-
16	Boc, Boc	$ZrCl_4$ (1.0 equiv), THF, rt	52[d]	-	-	-	-
17	Boc, Boc	AIBN (10 mol%), THF, 70 °C	53	100	0	0	0
18	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), DCE, rt	82	6	62	0	32
19	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), $CHCl_3$, rt	34	12	50	0	38
20	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), THF, rt	91	10	60	0	30
21	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), MeCN, rt	21	19	50	0	31
22	Boc, Boc	$[Cp^*RuCl_2]_n$ polymer (10 mol%), acetone, rt	80	8	61	0	31
23	Boc, Boc	$Pd(PPh_3)_2Cl_2$ (10 mol%), DCM, rt	93[e]	100	0	0	0

[a]0.1 mmol scale, ratio in the crude reaction mixture was determined by ^{1}H NMR spectroscopy, 1,3,5-trimethoxylbenzene as internal standard. **18** and **18'** were prepared from *N*-Boc-propargylamine and *N*,*N*-bisBoc propargylamine, respectively. [c]The product was isolated in gram scale, 2.0 equiv *n*-Bu_3SnH was used. [d]**18** was isolated as the product, [e]isolated yield.



4.3 *cis*-Hydrostannylation



To a mixture of alkyne **18'** (37 mg, 0.1 mmol, 1.0 equiv) and $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 10 mol %) in DCM (1 mL) was slowly added $n$$Bu_3SnH$ (32 μL, 0.12 mmol, 1.2 equiv) at room temperature. The resulting solution was stirred for 1 h. The reaction mixture was concentrated in *vacuo*, and purified by column chromatography (silica gel, EtOAc) to afford **11a'** (62 mg, 0.093 mmol, 93% yield) as yellow oil.

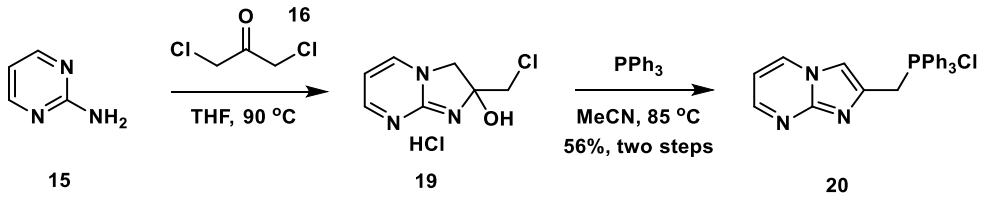
R_f 0.54 (silica gel, EtOAc), UV active, stains brown in ninhydrin.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.56 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.13 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.50 (s, 1H), 6.91 (dd, *J* = 6.8, 4.1 Hz, 1H), 6.13 (t, *J* = 5.4 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 2H), 1.45 (s, 18H), 1.42 – 1.33 (m, 6H), 1.25 – 1.18 (m, 6H), 0.90 – 0.85 (m, 6H), 0.82 (t, *J* = 7.3 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.37, 149.31, 147.72, 146.96, 131.58, 131.11, 124.69, 108.72, 82.86, 46.77, 28.97, 28.17, 27.32, 13.69, 10.57 (one carbon was not found).

HRMS (DART): calc'd for $C_{31}H_{53}N_4O_4Sn$ $[M+H]^+$: 665.3089, found 665.3085.

4.4 Wittig salt formation



A 250 mL round bottom flask was charged with a well-stirred magnetic stir bar. 1,3-dichloroacetone **16** (10.0 g, 7.9 mmol, 1.5 equiv) was added dropwise to a suspension of 2-aminopyrimidine **15** (5.0 g, 5.2 mmol, 1.0 equiv) in THF (50 mL). The resulting mixture was stirred under reflux for 16 h. The resulting slurry was cooled to room temperature and filtered. The yellow solid was washed thoroughly with THF (3 × 20 mL), and then dried in *vacuo* to provide salt **19** as yellow solid which was used for the next step.

To a 250 mL round bottom flask charged with above salt **19** in MeCN (30 mL) was added triphenylphosphine (20.7 g, 7.9 mmol, 1.5 equiv) at room temperature. The yellow suspension was heated at 85 °C for 12 h. A large amount of purple solid formed at which point (~15 h) the solvent was removed under reduced pressure. The resulting suspension was filtered, washed with acetone (3 × 50 mL), and dried under air to afford **20** (13.5 g, 2.9 mmol, 56%, two steps) as pink solid.

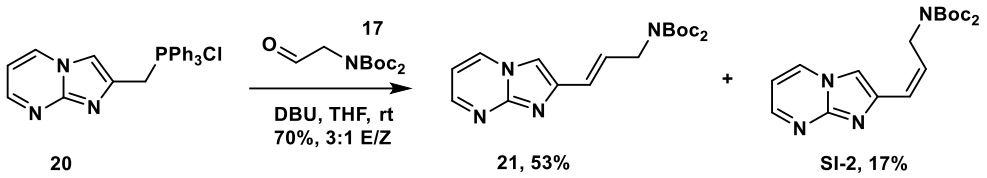
^{1}H NMR (500 MHz, DMSO-d_6): δ 9.02 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.57 (dd, *J* = 4.1, 2.0 Hz, 1H), 7.90 – 7.68 (m, 16H), 7.14 (dd, *J* = 6.7, 4.1 Hz, 1H), 5.52 (d, *J* = 15.4 Hz, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 152.08, 146.64, 135.74, 134.93 (d, *J* = 3.1 Hz), 134.02 (d, *J* = 10.2 Hz), 133.68 (d, *J* = 8.9 Hz), 129.99 (d, *J* = 12.6 Hz), 118.51 (d, *J* = 86.6 Hz), 112.57 (d, *J* = 9.2 Hz), 109.96, 22.99 (d, *J* = 50.7 Hz), 22.79.

^{31}P NMR (162 MHz, DMSO-d_6): δ 22.71.

HRMS (ESI): m/z calc'd for $C_{25}H_{21}N_3P$ $[M]^+$: 394.1468, found: 394.1478.

4.5 Imidazole benzylic Wittig olefination



To a suspension of Wittig salt **20** (5.06 g, 10.9 mmol, 1.0 equiv) and aldehyde **17**[12] (2.82 g, 10.9 mmol, 1.0 equiv) in THF (110 mL) was slowly added DBU (8.3 mL, 54.5 mmol, 5.0 equiv) at room temperature. The resulting pink suspension was vigorously stirred for 16 h, at which point TLC detected reaction completion. The reaction mixture was filtered through Celite (5 cm), washed with THF (3 × 30 mL). The combined organic solution was concentrated and purified by column chromatography (silica gel, DCM:EtOAc 1:1) to afford *E*-isomer **21** (2.17 g, 5.8 mmol, 53% yield) as white solid and *Z*-isomer **SI-2** (693 mg, 1.85 mmol, 17% yield) as white solid.

***E*-isomer 21:**

R_f 0.15 (silica gel, DCM:EtOAc 1:2), UV active, stains brown in ninhydrin.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 4.1, 2.1 Hz, 1H), 8.33 (dd, *J* = 6.7, 2.1 Hz, 1H), 7.42 (s, 1H), 7.04 – 6.67 (m, 2H), 6.57 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.39 (dd, *J* = 6.0, 1.5 Hz, 2H), 1.50 (s, 18H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.40, 150.19, 148.69, 145.41, 132.91, 129.73, 123.16, 108.63, 108.06, 82.60, 48.07, 28.24.

HRMS (DART): calc'd for $C_{19}H_{27}N_4O_4$ $[M+H]^+$: 375.2032, found: 375.2039.

***Z*-isomer SI-2:**

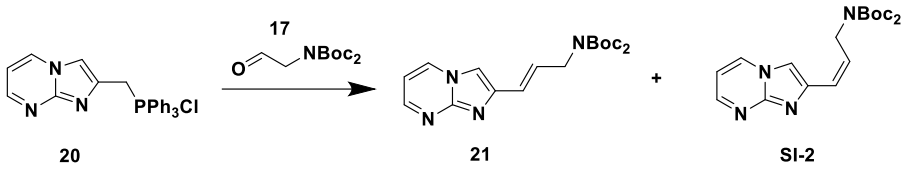
R_f 0.25 (silica gel, DCM:EtOAc 1:2), UV active, stains brown in ninhydrin.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.38 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.51 (s, 1H), 6.83 (dd, *J* = 6.7, 4.1 Hz, 1H), 6.48 (dt, *J* = 11.6, 2.1 Hz, 1H), 5.80 (dt, *J* = 11.6, 5.7 Hz, 1H), 4.99 (dd, *J* = 5.7, 2.1 Hz, 2H), 1.44 (s, 18H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.61, 149.90, 148.22, 145.15, 133.19, 132.89, 120.73, 109.69, 108.75, 82.40, 46.30, 28.16.

HRMS (ESI): m/z calc'd for $C_{19}H_{27}N_4O_4$ $[M+H]^+$: 375.2032, found: 375.2035.

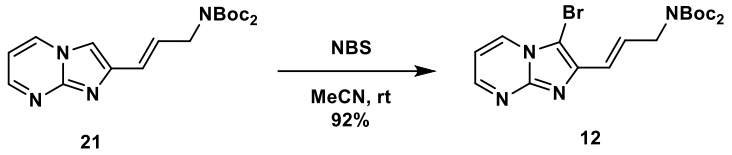
Table S3. Optimization of Wittig olefination[a]



	20 (equiv)	17 (equiv)	Conditions	yield	*E:Z*
1	1	1	KO*t*Bu (2 equiv), THF	40% (not scalable)	*E*
2	2	1	KO*t*Bu (2 equiv), THF	29%	*E*
3	1	2	KO*t*Bu (2 equiv), THF	43%	*E*
4	1	1	KO*t*Bu (2 equiv), premixed substrate, THF	No prd	-
5	1	1	NaOMe (2 equiv), MeOH	No prd	-
6	1	1	NaH (2 equiv), THF	18%	1:1
7	1	1	NaH (2 equiv), THF, 60 °C	11%	1:1
8	1	1	NaH (2 equiv), DMF	No prd	-
9	1	1	KO*t*Bu (2 equiv), dioxane	No prd	-
10	1	1	DBU (5 equiv), THF	70%[b]	3:1
11	1	1	DBU (5 equiv), MeCN	77%	1.5:1
12	1	1	DBU (5 equiv), dioxane	70%	2.7:1
13	1	1	DBU (5 equiv), DCM	71%	1:1
14	1	1	DIPEA (5 equiv), THF	No prd	-
15	1	1	Et_3N (5 equiv), THF	No prd	-
16	1	1	DBN (5 equiv), THF	68%	2.8:1
17	1	1	DBU (5 equiv), MeOH	No prd	-
18	1	1	DBU (5 equiv), THF/DCM (1:1)	61%	1.6:1
19	2	1	DBU (5 equiv), THF	68%	3:1
20	1.5	1	DBU (5 equiv), THF	73%	3:1
21	1	2	DBU (5 equiv), THF	68%	2.5:1
22	1	1	DBU (2 equiv), THF	64%	3.2:1
23	1	1	DBU (3 equiv), THF	56%	2.7:1
24	1	1	DBU (4 equiv), THF	64%	3:1

[a]0.1 mmol scale, 2 mL solvent, rt, 16h, ratio was based on crude ^{1}H NMR, 1,3,5-trimethoxylbenzene as internal standard. [b]isolated yield, gram scale.

4.6 NBS bromination



To a solution of olefin **21** (6.2 g, 16.6 mmol, 1.0 equiv) in MeCN (400 mL) was slowly added a solution of NBS (178 g, 18.0 mmol, 1.1 equiv) in MeCN (20 mL) at room temperature. The orange solution was stirred in dark for 1 h at room temperature. The solvent was removed in *vacuo* to give an off-white solid, which was then triturated by a solution of 10% $Na_2S_2O_3$ in H_2O (500 mL). The solid was filtered, washed with H_2O (3 × 200 mL), and dried under air to afford bromide **12** (6.9 g, 15.2 mmol, 92% yield) as white solid.

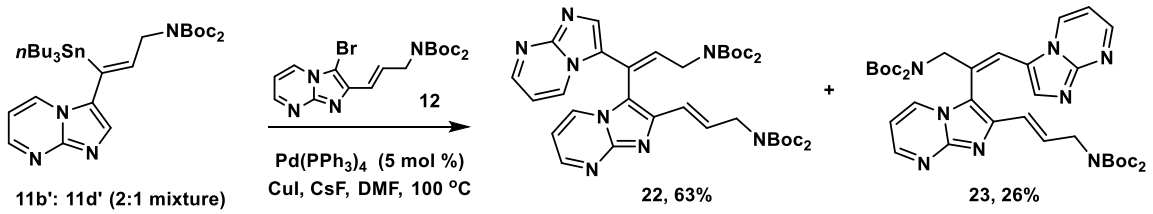
R_f 0.43 (silica gel, DCM:EtOAc 1:1), UV active, stains orange in ninhydrin.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (dd, *J* = 4.2, 2.0 Hz, 1H), 8.34 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.08 – 6.81 (m, 2H), 6.60 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.42 (dd, *J* = 6.0, 1.5 Hz, 2H), 1.51 (s, 18H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.25, 150.52, 148.45, 143.01, 131.79, 131.30, 120.74, 109.21, 92.63, 82.68, 48.08, 28.21.

HRMS (DART): calc'd for $C_{19}H_{26}BrN_4O_4$ $[M+H]^+$: 453.1137, found: 453.1136.

4.7 Stille coupling of diene 11b'/11d' and bromide 12



A solution of stannane **11b'/11d'** (2:1 mixture, 231 mg, 0.35 mmol, 1.1 equiv) and bromide **12** (143 mg, 0.32 mmol, 1.0 equiv) in DMF (3 mL) was treated with $Pd(PPh_3)_4$ (18.2 mg, 0.016 mmol, 5 mol %), CuI (6 mg, 0.032 mmol, 10 mol %), CsF (96 mg, 0.63 mmol, 2.0 equiv) at 100 °C for 16 h. The resulting dark brown solution was concentrated in *vacuo*, and purified by column chromatography (silica gel, $CHCl_3$:MeOH = 20:1 to 15:1) to furnish diene **22** (150 mg, 0.2 mmol, 63% yield) as pale yellow oil and **23** (62 mg, 83 μmol, 26% yield) as pale yellow oil.

22:

R_f 0.40 (silica gel, $CHCl_3$:MeOH 15:1), UV active, stains red in ninhydrin.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.48 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.95 (s, 1H), 7.70 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.67 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.10 (dt, *J* = 15.5, 6.3 Hz, 1H), 6.66 (dd, *J* = 6.9, 4.0 Hz, 1H), 6.63 (dd, *J* = 6.9, 4.1 Hz, 1H), 6.58 (dt, *J* = 15.4, 1.4 Hz, 1H), 6.50 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.49 – 4.34 (m, 3H), 4.19 (dd, *J* = 15.7, 9.3 Hz, 1H), 1.48 (s, 18H), 1.43 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.43, 152.31, 151.37, 150.23, 149.73, 149.27, 144.60, 135.55, 135.06, 132.68, 132.08, 131.70, 121.61, 121.49, 117.31, 114.03, 109.74, 108.84, 83.10, 82.64, 48.16, 44.93, 28.26, 28.17.

HRMS (ESI): m/z calc'd for $C_{38}H_{51}N_8O_8$ $[M+H]^+$: 747.3830, found: 747.3836.

23:

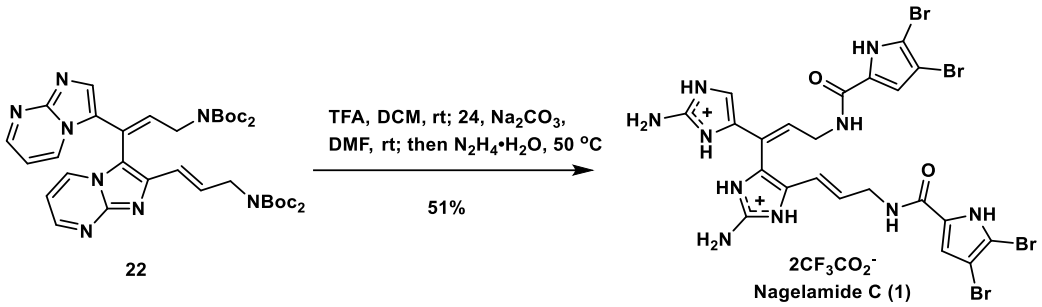
R_f 0.37 (silica gel, $CHCl_3$:MeOH 15:1), UV active, stains orange in ninhydrin.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.50 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.41 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.96 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.11 (s, 1H), 6.97 (dd, *J* = 6.9, 4.1 Hz, 1H), 6.90 (dt, *J* = 15.5, 5.9 Hz, 1H), 6.70 (s, 1H), 6.68 (dd, *J* = 6.8, 4.1 Hz, 1H), 6.51 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.70 (dd, *J* = 16.1, 1.5 Hz, 1H), 4.65 (dd, *J* = 16.1, 1.3 Hz, 1H), 4.37 (ddd, *J* = 15.9, 5.7, 1.6 Hz, 1H), 4.30 (ddd, *J* = 15.9, 6.9, 1.4 Hz, 1H), 1.40 (s, 18H), 1.38 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.79, 152.21, 150.57, 150.14, 149.00, 148.97, 142.76, 135.33, 131.41, 130.69, 124.07, 121.77, 118.98, 118.53, 115.93, 109.44, 108.66, 83.33, 82.48, 51.84, 48.22, 28.12, 28.06.

HRMS (ESI): m/z calc'd for $C_{38}H_{51}N_8O_8$ $[M+H]^+$: 747.3830, found: 747.3836.

4.8 Synthesis of nagelamide C



To a solution of diene **22** (6.0 mg, 8.0 μmol, 1.0 equiv) in DCM (1 mL) was slowly added TFA (0.1 mL) at room temperature. The reaction was stirred for 1 h at the same temperature. The solvent was removed under reduced pressure to afford a dark red residue. The residue was dissolved in DMF (0.5 mL). Na_2CO_3 (8.5 mg, 0.08 mmol, 10.0 equiv) was added at room temperature. After vigorous stirring for 30 min, 4,5-dibromo-2-trichloroacetylpyrrole **24** (17.8 mg, 0.048 mmol, 6.0 equiv) was added as solid then stirred for 12 h. The solvent was removed under vacuum, hydrazine hydrate (0.2 mL) was added at room temperature. The vial was gently warmed to 50 °C and stirred for 15 min, at which point a dark red solution was formed. Excess amount of hydrazine was quickly removed under high vacuum. The residue was dissolved in MeOH (2 mL), then filtered through a short pad of Celite (1 cm) and washed with MeOH (2 mL). The combined MeOH solution was added TFA (50 μL), then concentrated and purified on C18 silica gel column to furnish nagelamide C (4.1 mg, 4.1 μmol, 51% yield) as off white solid.

HPLC: Agilent ZORBAX Eclipse Plus C18 column (4.6 × 250 mm, 5 μm). Samples were eluted with a linear gradient of 0% acetonitrile – water containing 0.1% TFA → 100% acetonitrile containing 0.1% TFA over 11 min (flow rate 1.0 mL/min, UV detection at 254 nm), t_R = 9.29 min.

Purification: C18 silica gel (25 g, 40 μm), 100% H_2O/0.1% TFA to 30% MeCN/70% H_2O/0.1% TFA.

^{1}H NMR (600 MHz, DMSO-d_6) δ 13.10 (s, 1H), 12.93 (s, 1H), 12.77 (s, 1H), 12.72 (d, *J* = 2.9 Hz, 1H), 12.69 (d, *J* = 2.8 Hz, 1H), 12.49 (s, 1H), 8.49 (t, *J* = 5.7 Hz, 1H), 8.46 (t, *J* = 5.8 Hz, 1H), 7.86 (s, 2H), 7.72 (s, 2H), 6.93 (d, *J* = 2.7 Hz, 1H), 6.92 (d, *J* = 2.7 Hz, 1H), 6.79 (s, 1H), 6.25 (t, *J* = 6.7 Hz, 1H), 6.17 (dt, *J* = 16.1, 5.9 Hz, 1H), 6.05 (d, *J* = 16.0 Hz, 1H), 3.95 (t, *J* = 5.7 Hz, 2H), 3.86 (t, *J* = 6.2 Hz, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 158.81, 158.73, 148.23, 148.07, 129.47, 127.94, 127.82 (two carbons), 125.45, 123.37, 116.81, 116.60, 115.91, 112.86, 112.72, 112.52, 104.84, 104.73, 97.90 (two carbons), 40.24, 37.47.

^{19}F NMR (565 MHz, DMSO-d_6) δ -74.17.

Nagelamide C free base:

^{1}H NMR (600 MHz, CD_3OD) δ 6.81 (s, 1H), 6.79 (s, 1H), 6.23 (s, 1H), 6.15 (d, *J* = 16.0 Hz, 1H), 6.02 (t, *J* = 6.9 Hz, 1H), 5.90 (dt, *J* = 15.9, 6.1 Hz, 1H), 3.96 (t, *J* = 6.9 Hz, 4H).

HRMS (ESI): m/z calc'd for $C_{22}H_{21}Br_4N_{10}O_2$ $[M+H]^+$: 772.8582, found: 772.8575.

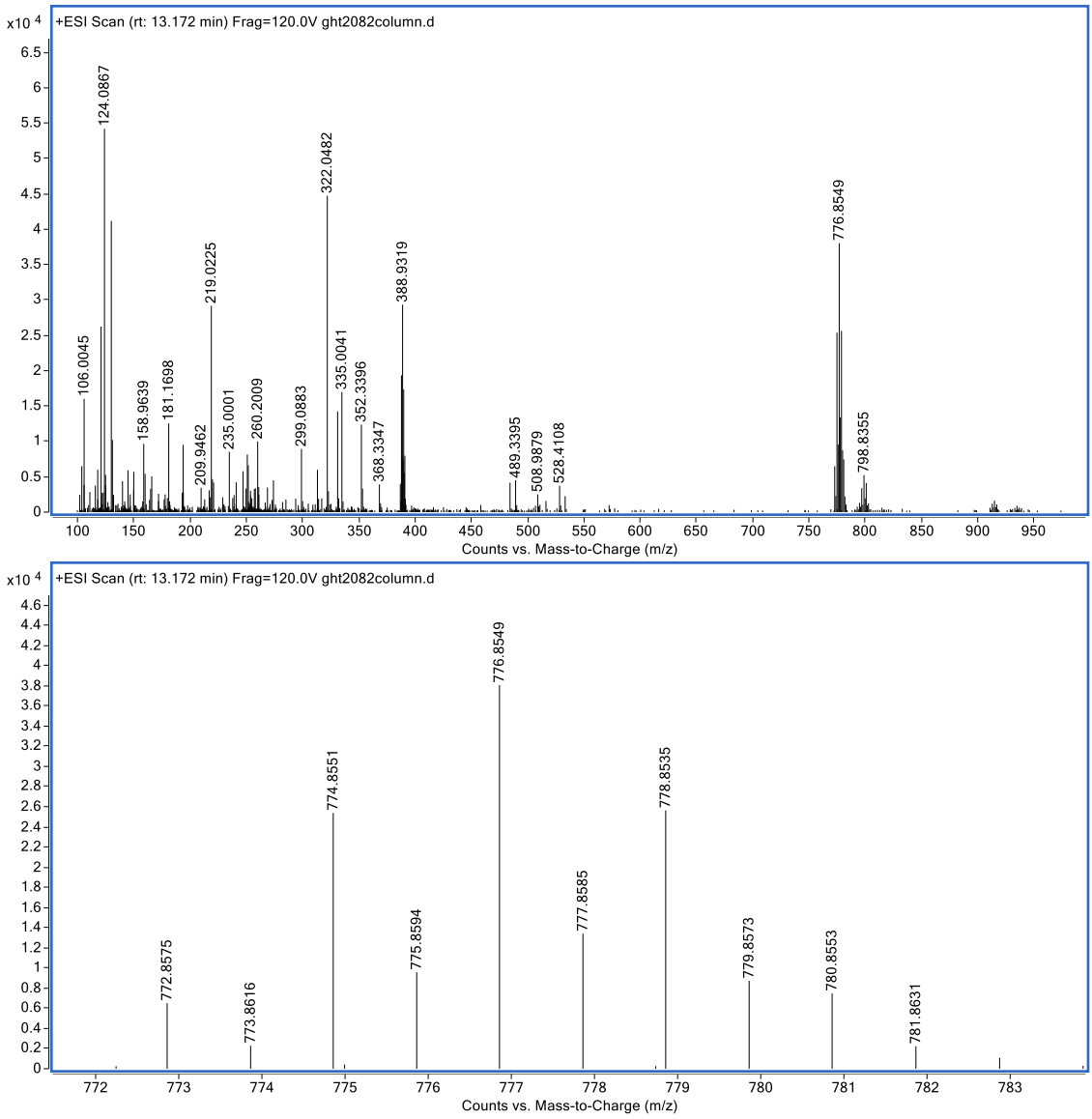


Figure S2. HRMS of nagelamide C

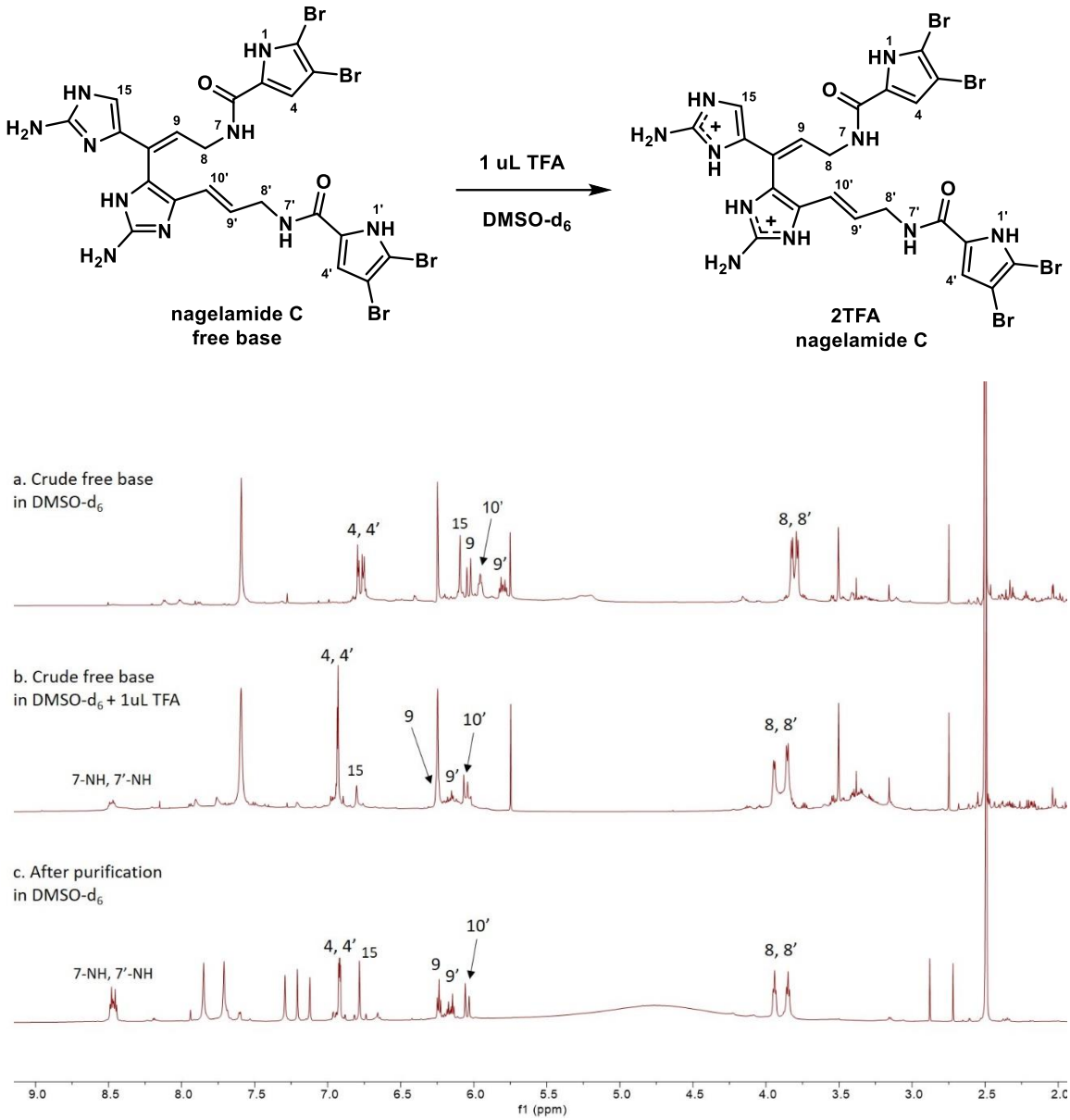
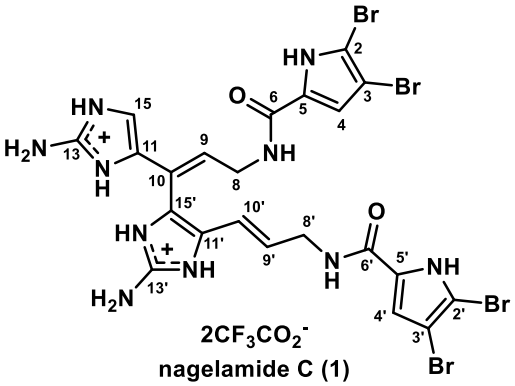


Figure S3. In situ TFA salt formation of nagelamide C free base

a. ^{1}H NMR of crude nagelamide C free base in DMSO-d_6 (600 MHz)
b. ^{1}H NMR of crude nagelamide C TFA salt after addition of 1 µL TFA
c. ^{1}H NMR of purified nagelamide C TFA salt in DMSO-d_6 (600 MHz)



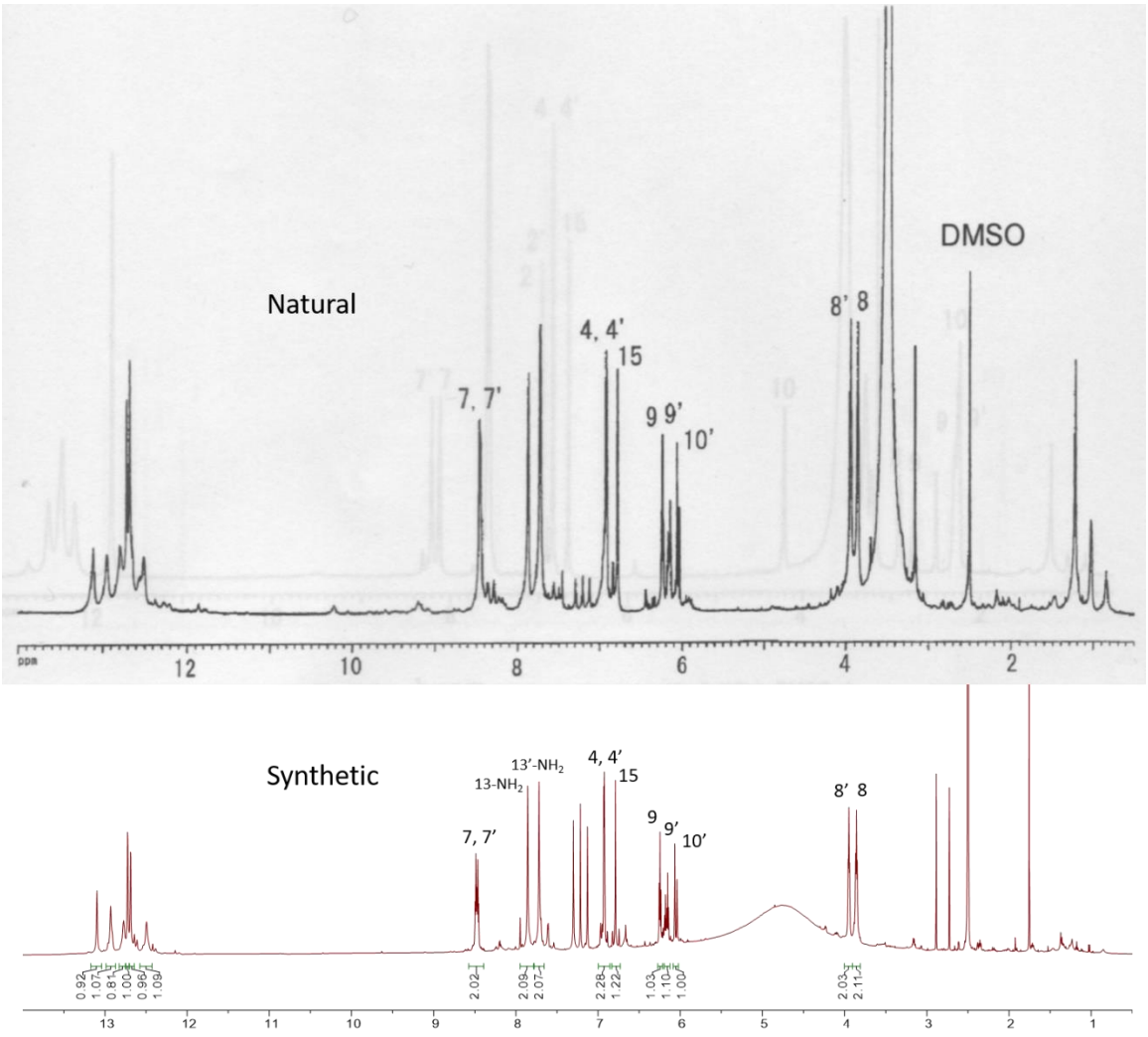


Figure S4. ^{1}H NMR spectra comparison of the natural and synthetic nagelamide C

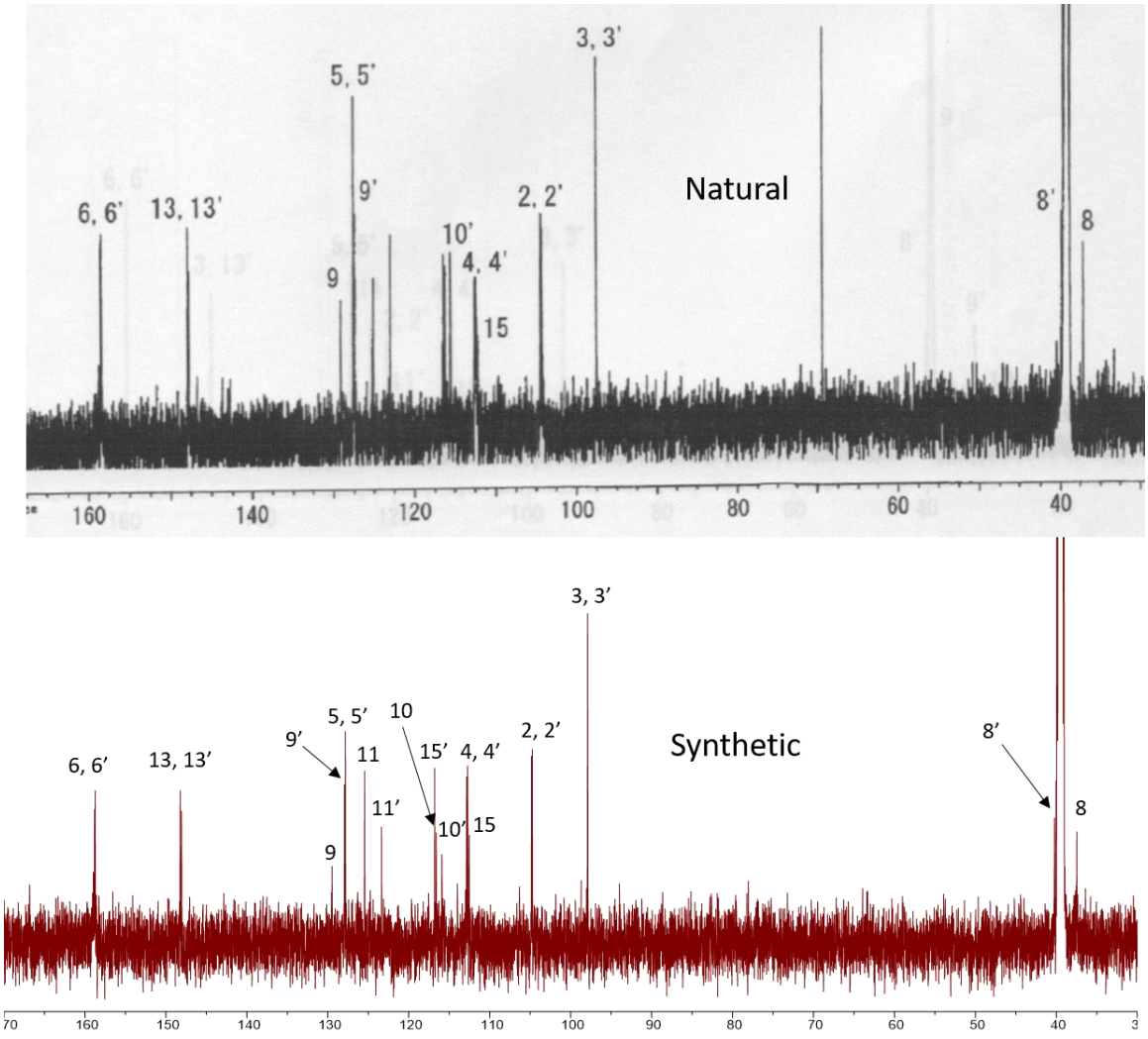
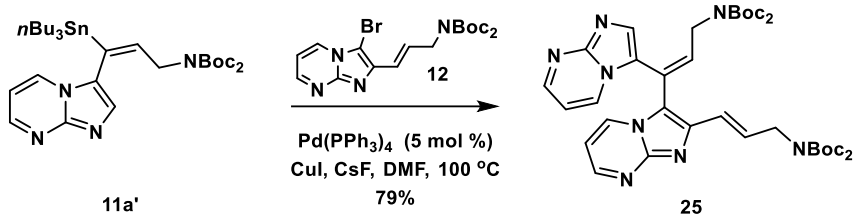


Figure S5. ^{13}C NMR spectra comparison of the natural and synthetic nagelamide C

4.9 Stille coupling of diene 11a' and bromide 12



A mixture of *cis*-adduct **11a'** (130 mg, 0.2 mmol, 1.1 equiv), bromide **12** (81 mg, 0.18 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (10 mg, 9 μmol, 5 mol %), CuI (3.4 mg, 18 μmol, 10 mol %), CsF (55 mg, 0.36 mmol, 2.0 equiv) in DMF (5 mL) was stirred at 100 °C for 16 h. The reaction mixture was concentrated in *vacuo*, and purified by column chromatography (silica gel, $CHCl_3$:MeOH = 20:1 to 15:1) to give diene **25** (106 mg, 0.14 mmol, 79% yield) as pale yellow oil.

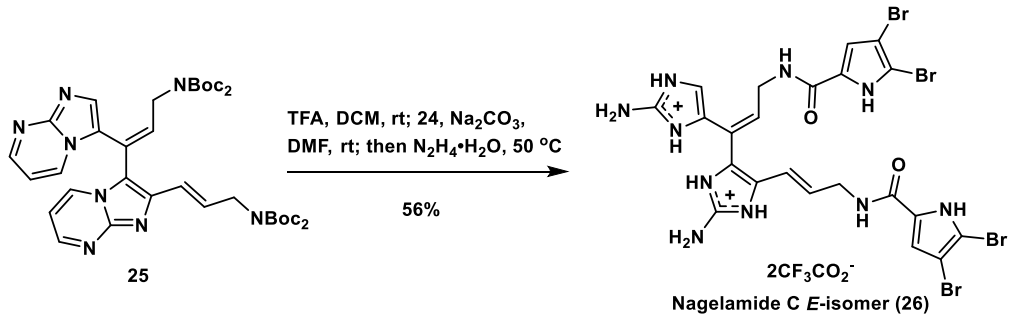
R_f 0.40 (silica gel, $CHCl_3$:MeOH 15:1), UV active, stains red in ninhydrin.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.46 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.14 (s, 1H), 7.80 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.56 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.03 (dt, *J* = 15.4, 6.7 Hz, 1H), 6.69 (dd, *J* = 15.4, 1.4 Hz, 1H), 6.65 (dd, *J* = 6.9, 4.0 Hz, 1H), 6.61 (dd, *J* = 6.9, 4.1 Hz, 1H), 6.23 (t, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 6.0 Hz, 2H), 4.36 (dd, *J* = 6.7, 1.4 Hz, 2H), 1.50 (s, 18H), 1.49 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.61, 152.38, 151.14, 150.75, 149.51, 148.55, 143.61, 138.97, 137.50, 133.09, 132.20, 131.38, 121.18, 117.67, 117.03, 115.84, 109.68, 109.09, 83.39, 82.55, 48.41, 45.48, 28.29, 28.25.

HRMS (ESI): m/z calc'd for $C_{38}H_{51}N_8O_8$ $[M+H]^+$: 747.3830, found: 747.3838.

4.10 Synthesis of nagelamide C *E*-isomer



To a solution of diene **25** (5.7 mg, 7.7 μmol, 1.0 equiv) in DCM (1 mL) was slowly added TFA (0.1 mL) at room temperature. The reaction was stirred for 1 h at the same temperature. The solvent was removed under vacuum to afford a dark residue. The residue was dissolved in DMF (0.5 mL). Na_2CO_3 (8.2 mg, 0.077 mmol, 10.0 equiv) was added at room temperature. After vigorous stirring for 30 min, 4,5-dibromo-2-trichloroacetylpyrrole **24** (17.0 mg, 0.046 mmol, 6.0 equiv) was stirred for 12 h, the solvent was removed under vacuum. Hydrazine hydrate (0.2 mL) was added at room temperature. The vial was gently warmed to 50 °C and stirred for 15 min. A dark red solution was formed. Excess amount of hydrazine was quickly removed under high vacuum. The residue was

dissolved in MeOH (2 mL), then filtered through a short pad of Celite (1 cm) and washed with MeOH (2 mL). The combined MeOH solution was added TFA (50 μL), then concentrated and purified on C18 silica gel column to furnish nagelamide C *E*-isomer **26** (4.3 mg, 4.3 μmol, 56% yield) as off white solid.

HPLC: Agilent ZORBAX Eclipse Plus C18 column (4.6 × 250 mm, 5 μm). Samples were eluted with a linear gradient of 0% acetonitrile – water containing 0.1% TFA → 100% acetonitrile containing 0.1% TFA over 11 min (flow rate 1.0 mL/min, UV detection at 254 nm), t_R = 9.38 min.

Purification: C18 silica gel (25 g, 40 μm), 100% H_2O/0.1% TFA to 30% MeCN/70% H_2O/0.1% TFA.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.79 (s, 1H), 12.74 (d, *J* = 2.8 Hz, 1H), 12.64 (d, *J* = 2.8 Hz, 1H), 12.57 (s, 1H), 12.47 (s, 1H), 12.43 (s, 1H), 8.54 (t, *J* = 5.6 Hz, 1H), 8.41 (t, *J* = 5.8 Hz, 1H), 7.66 (s, 2H), 7.60 (s, 2H), 7.20 (s, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 6.17 – 6.05 (m, 2H), 5.90 (t, *J* = 6.8 Hz, 1H), 4.11 (t, *J* = 6.2 Hz, 2H), 3.89 (t, *J* = 5.2 Hz, 2H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 159.10, 158.69, 147.59, 147.56, 133.05, 128.01, 127.89, 127.73, 122.47, 121.74, 120.70, 116.70, 116.28, 114.65, 112.91, 112.64, 105.04, 104.78, 97.96, 97.91, 40.58, 37.85.

^{19}F NMR (565 MHz, DMSO-d_6) δ -74.10.

Nagelamide C *E*-isomer free base:

^{1}H NMR (600 MHz, CD_3OD) δ 6.82 (s, 1H), 6.80 (s, 1H), 6.33 (s, 1H), 6.13 (d, *J* = 15.8 Hz, 1H), 5.83 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.66 (t, *J* = 7.1 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 6.4 Hz, 2H).

HRMS (ESI): m/z calc'd for $C_{22}H_{21}Br_4N_{10}O_2$ $[M+H]^+$: 772.8582, found: 772.8570.

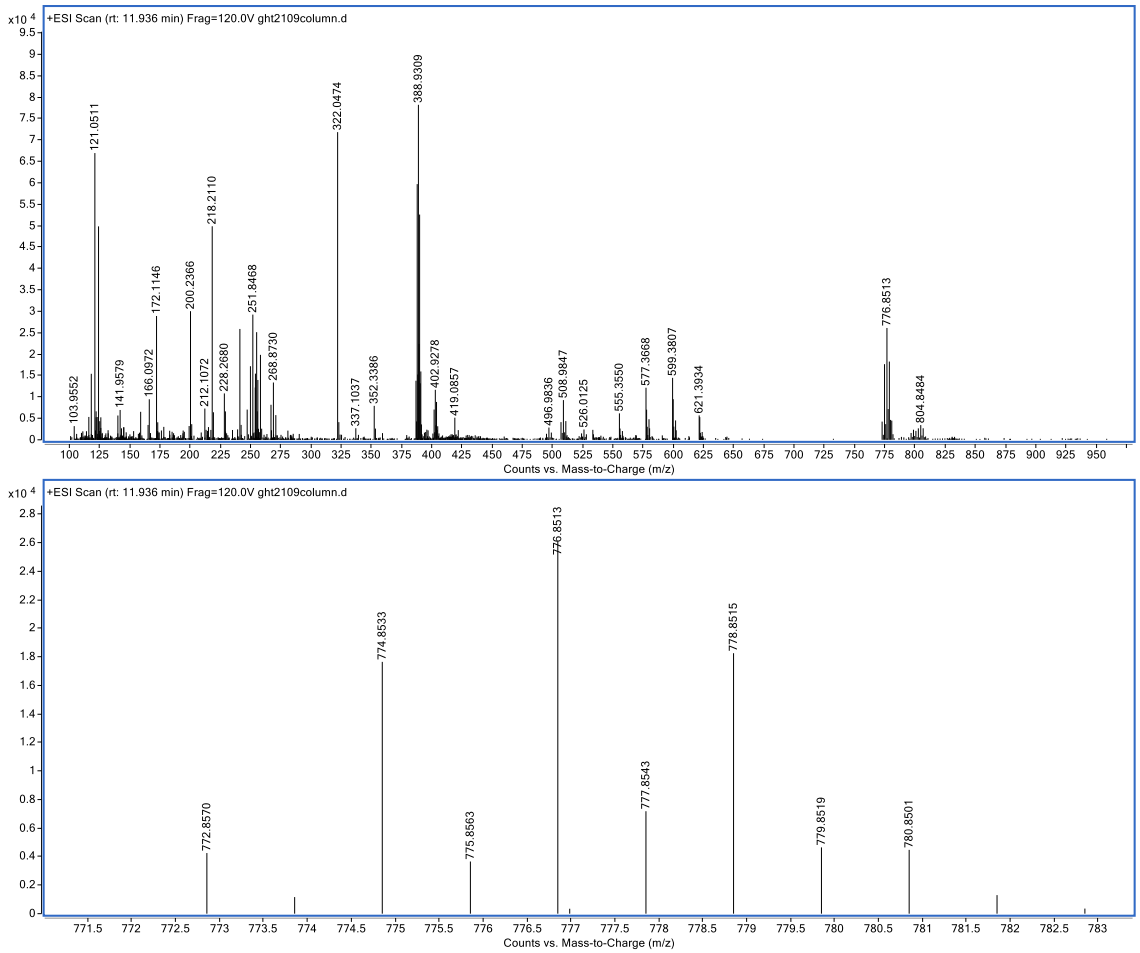


Figure S6. HRMS of nagelamide C *E*-isomer

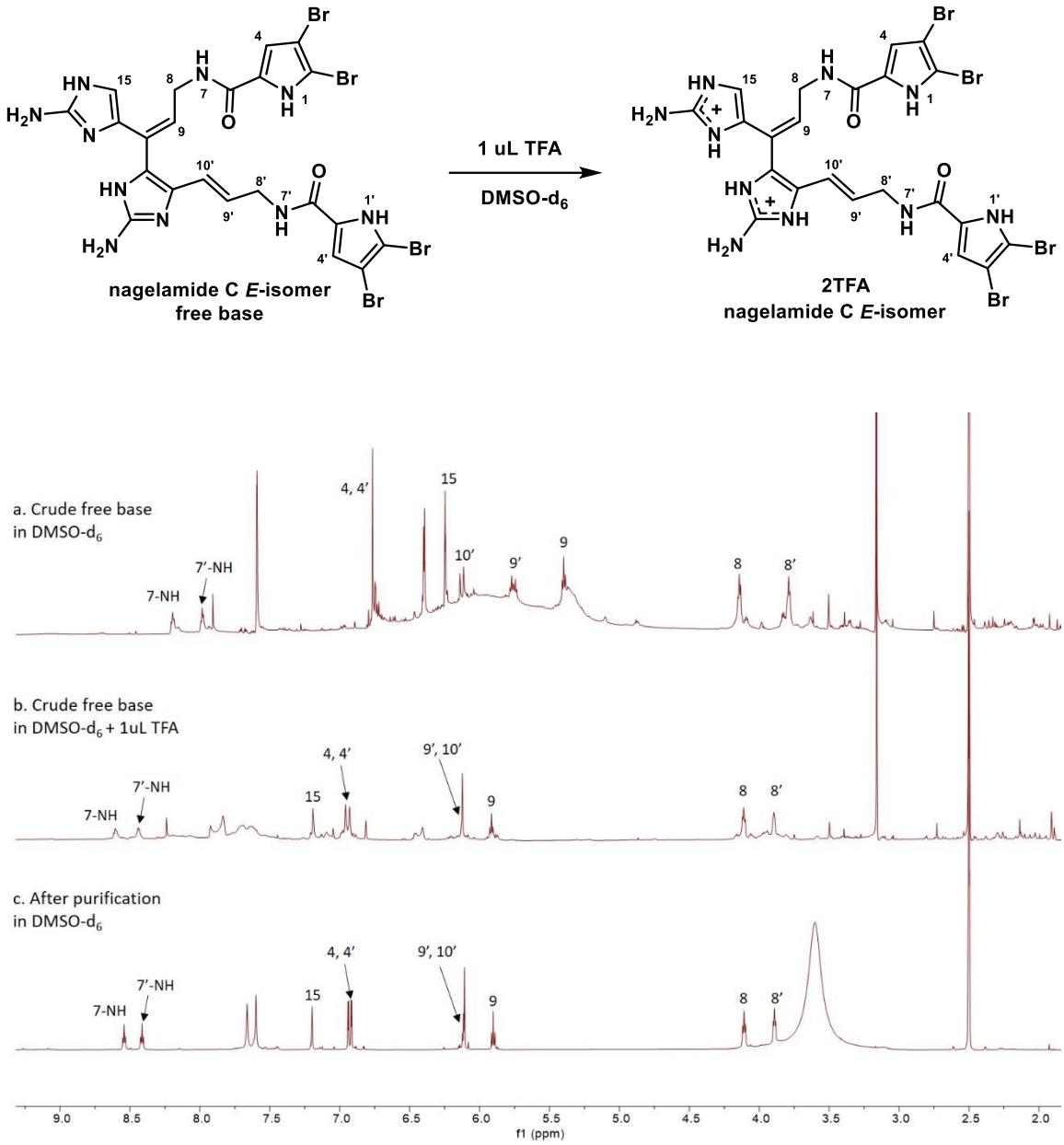
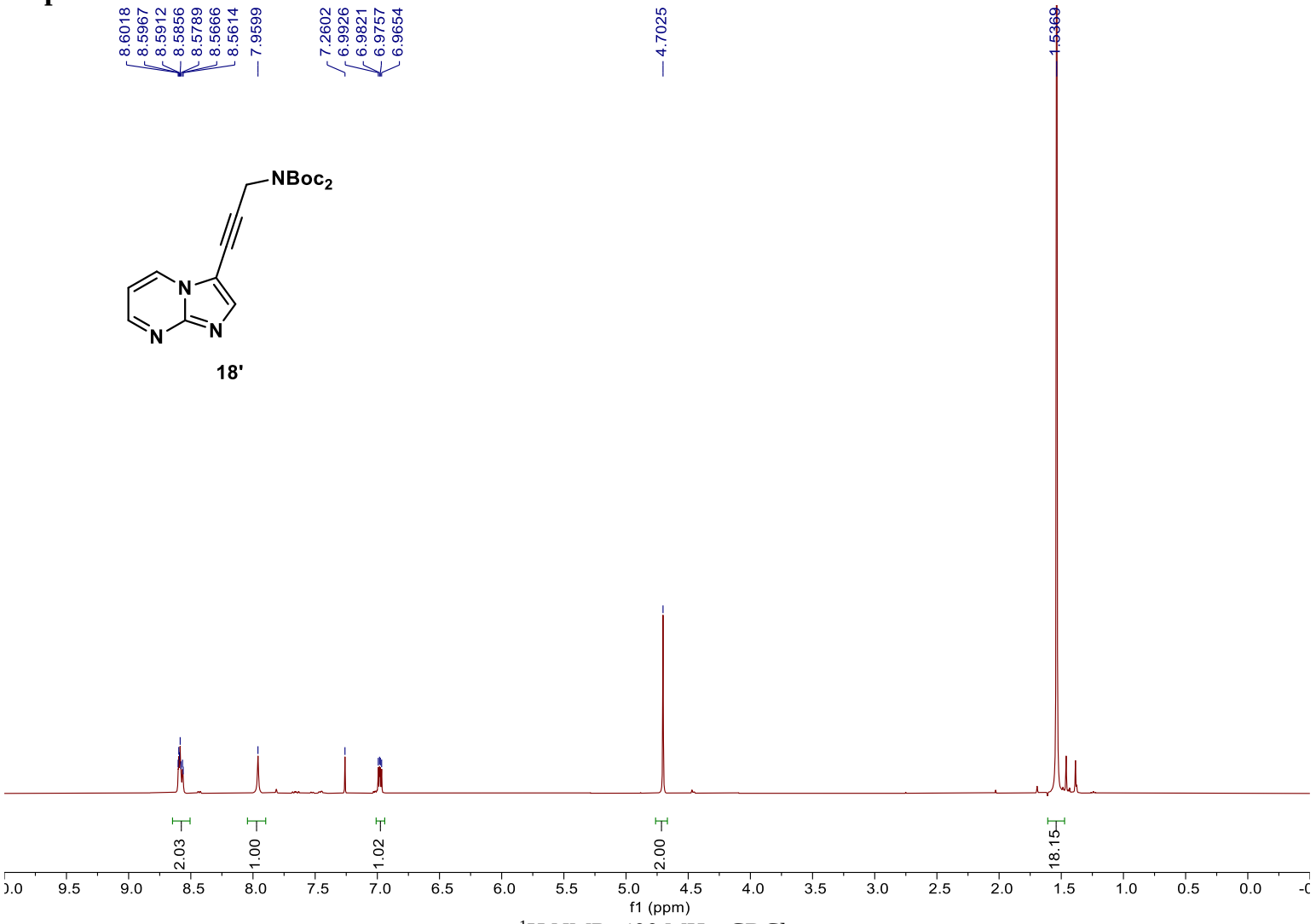


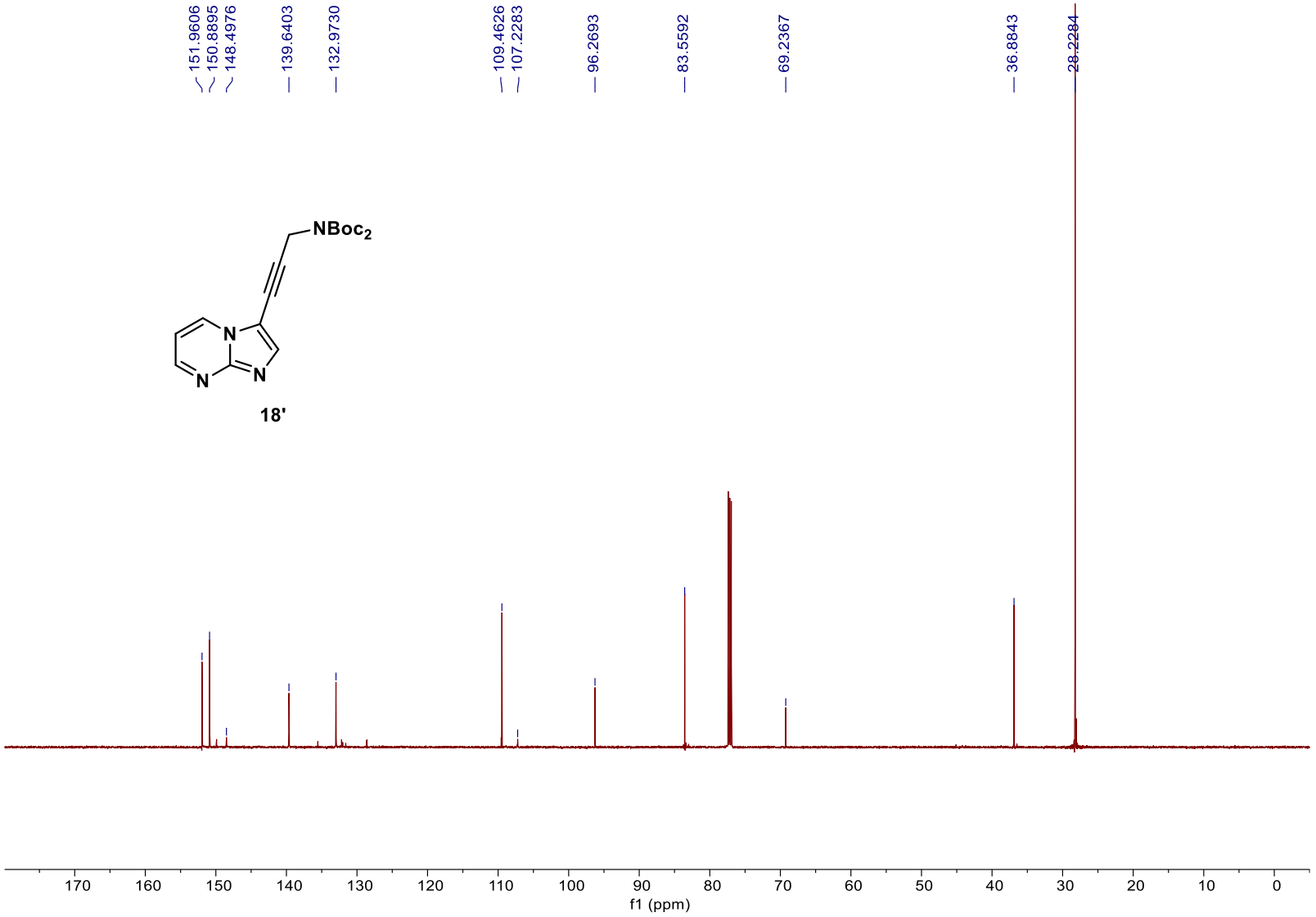
Figure S7. In situ TFA salt formation of nagelamide C *E*-isomer free base

a. ^{1}H NMR of crude nagelamide C *E*-isomer free base in DMSO-d_6 (600 MHz)
b. ^{1}H NMR of crude nagelamide C *E*-isomer TFA salt after addition of 1 μL TFA
c. ^{1}H NMR of purified nagelamide C *E*-isomer TFA salt in DMSO-d_6 (600 MHz)

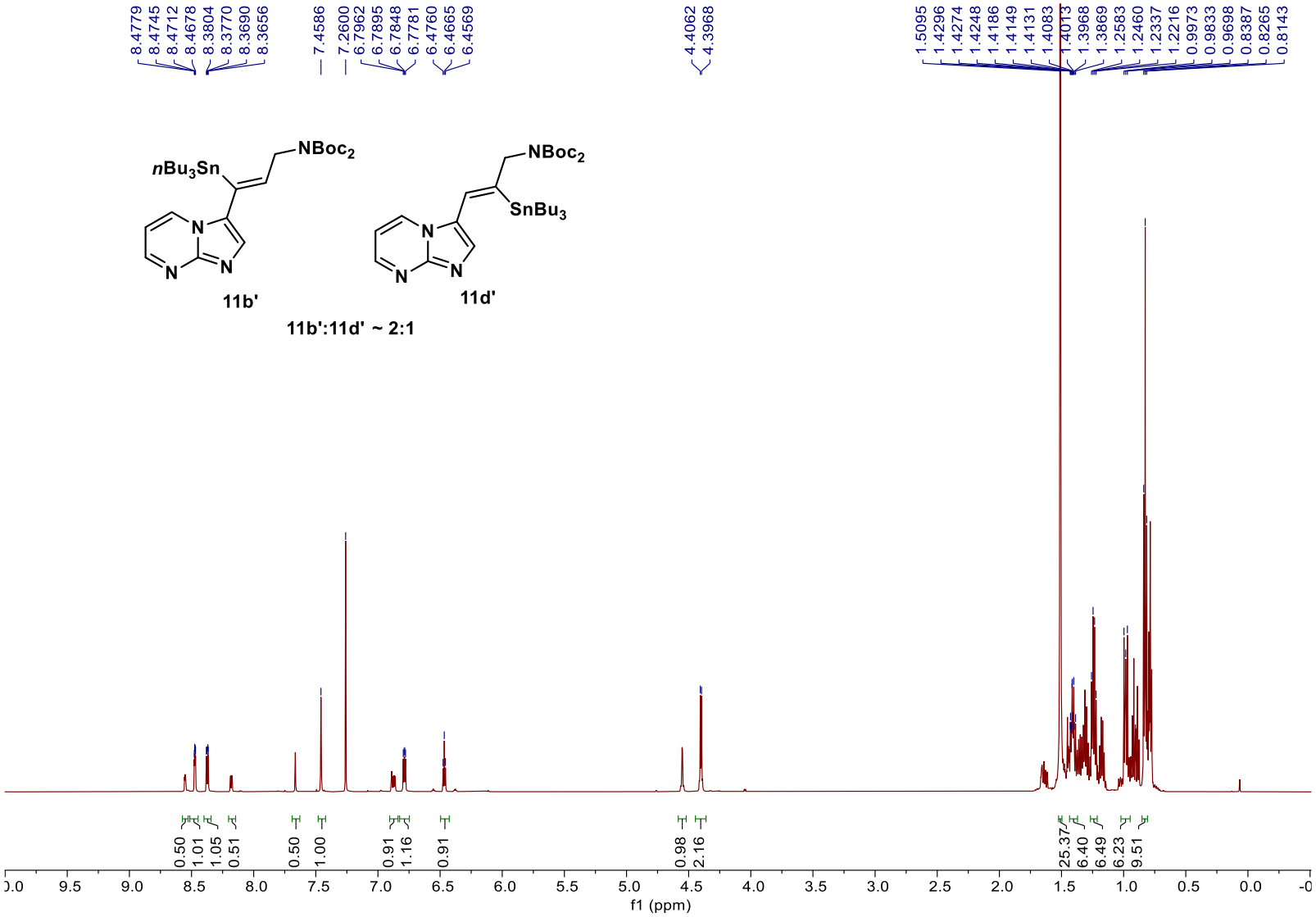
5. NMR Spectra



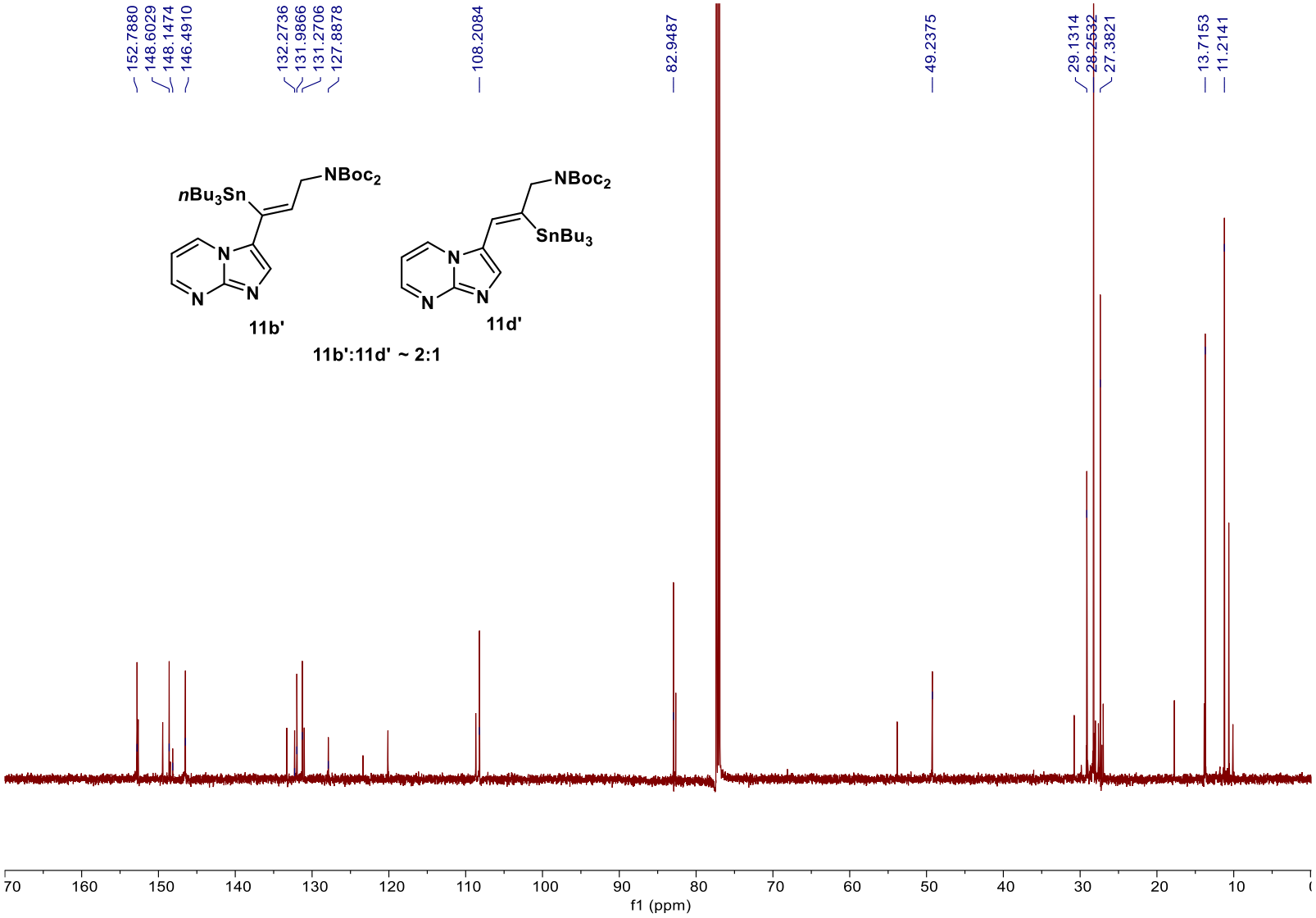
^{1}H NMR, 400 MHz, $CDCl_3$



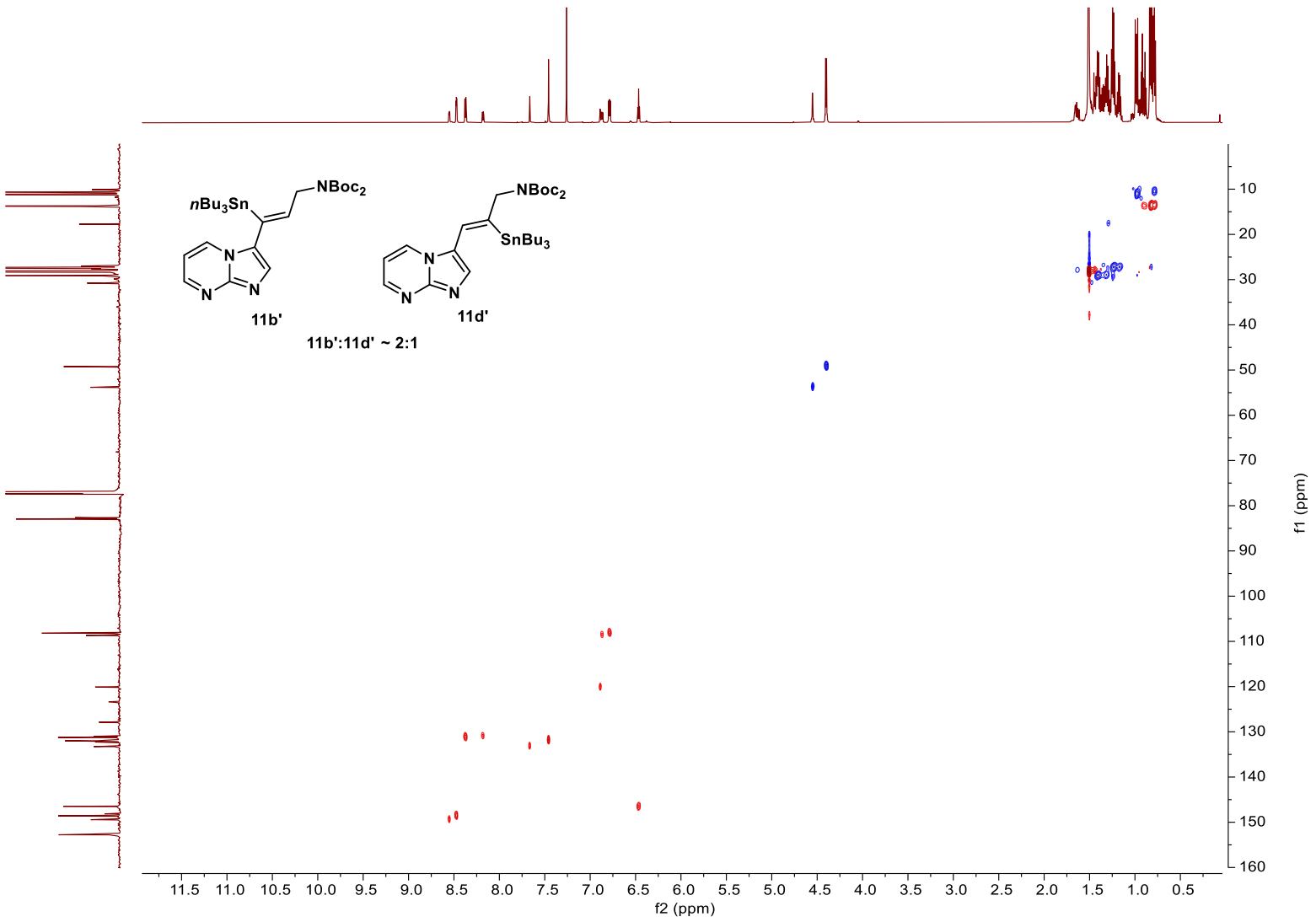
^{13}C NMR, 151 MHz, $CDCl_3$



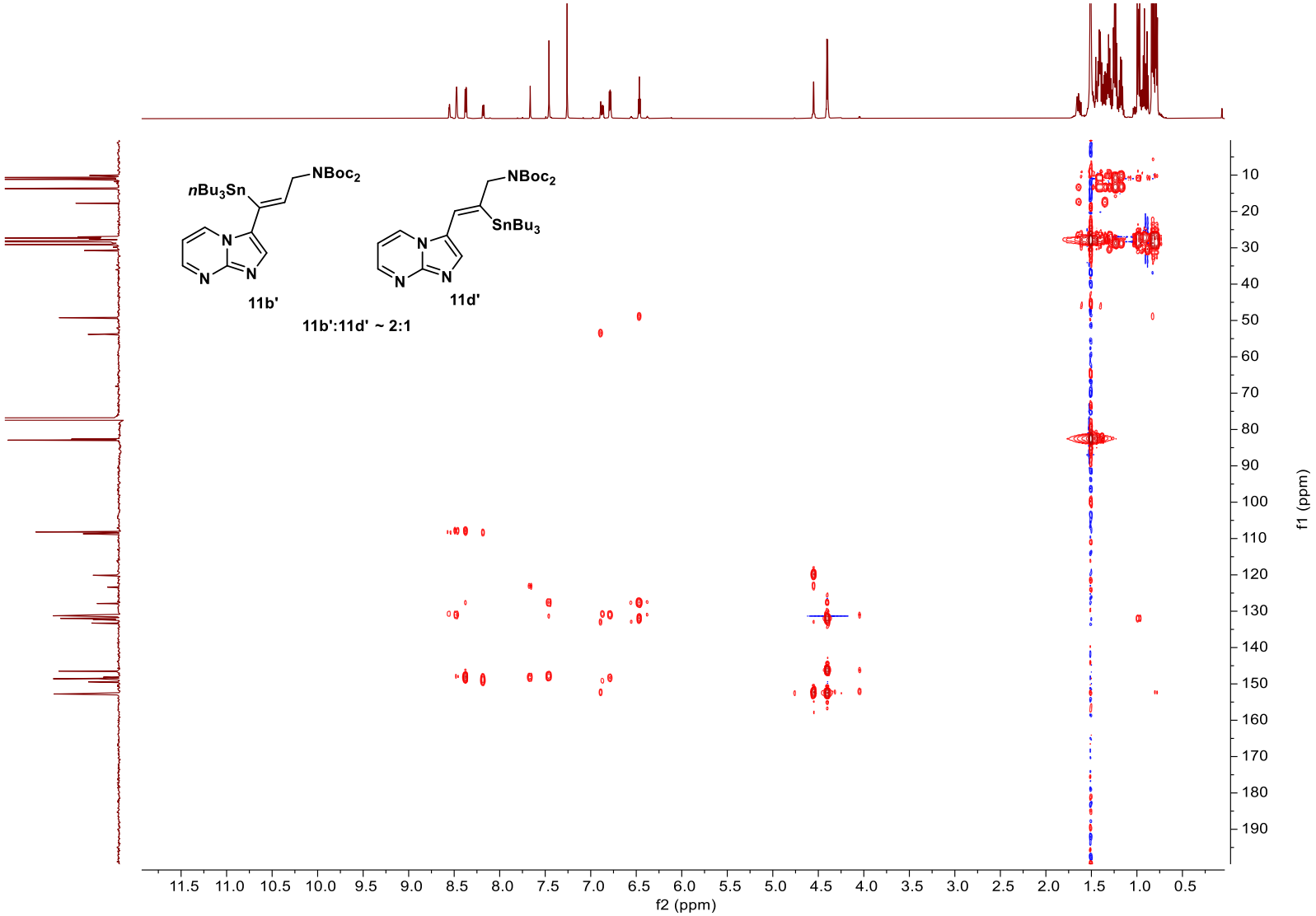
^{1}H NMR, 600 MHz, $CDCl_3$



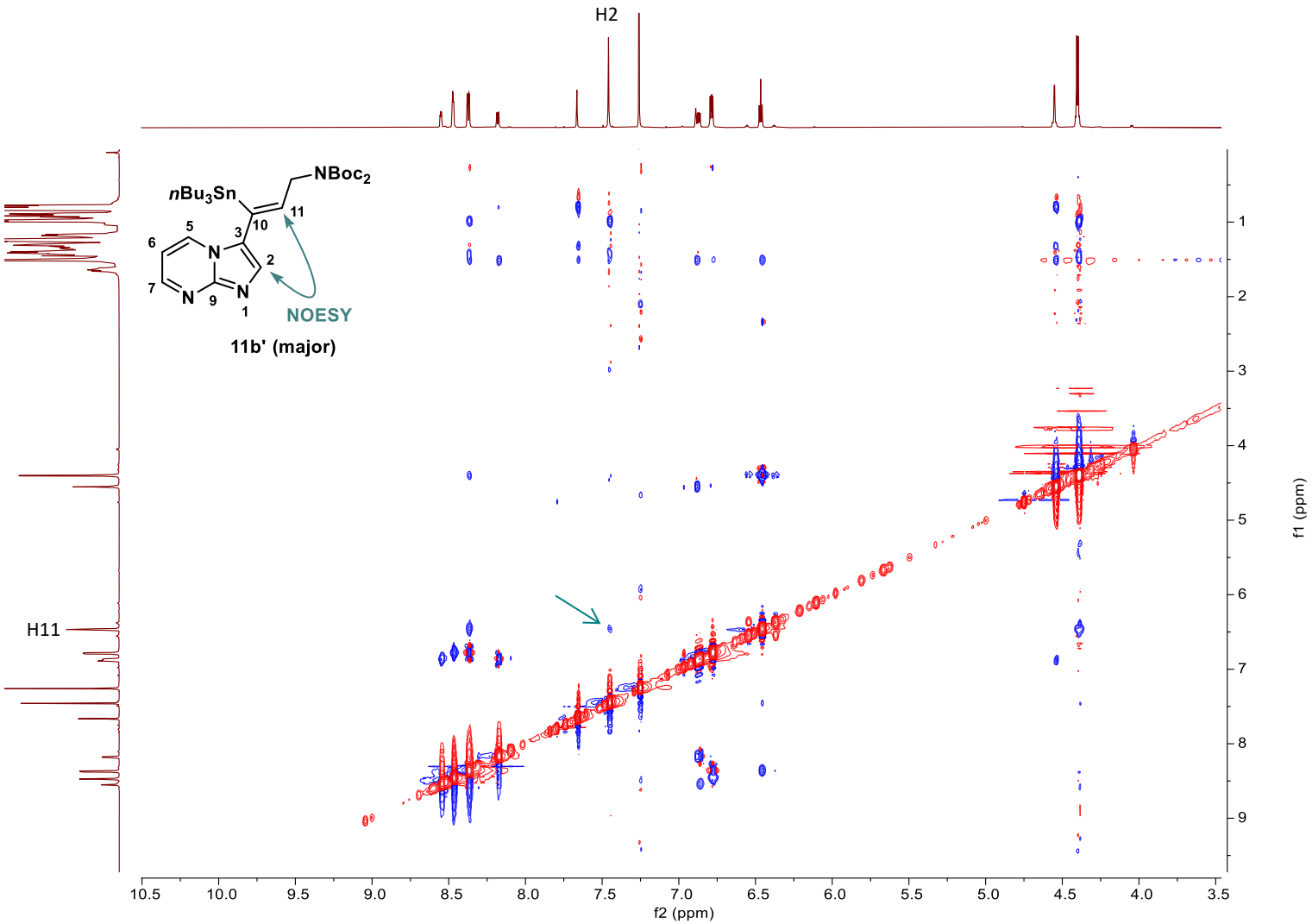
^{13}C NMR, 151 MHz, $CDCl_3$



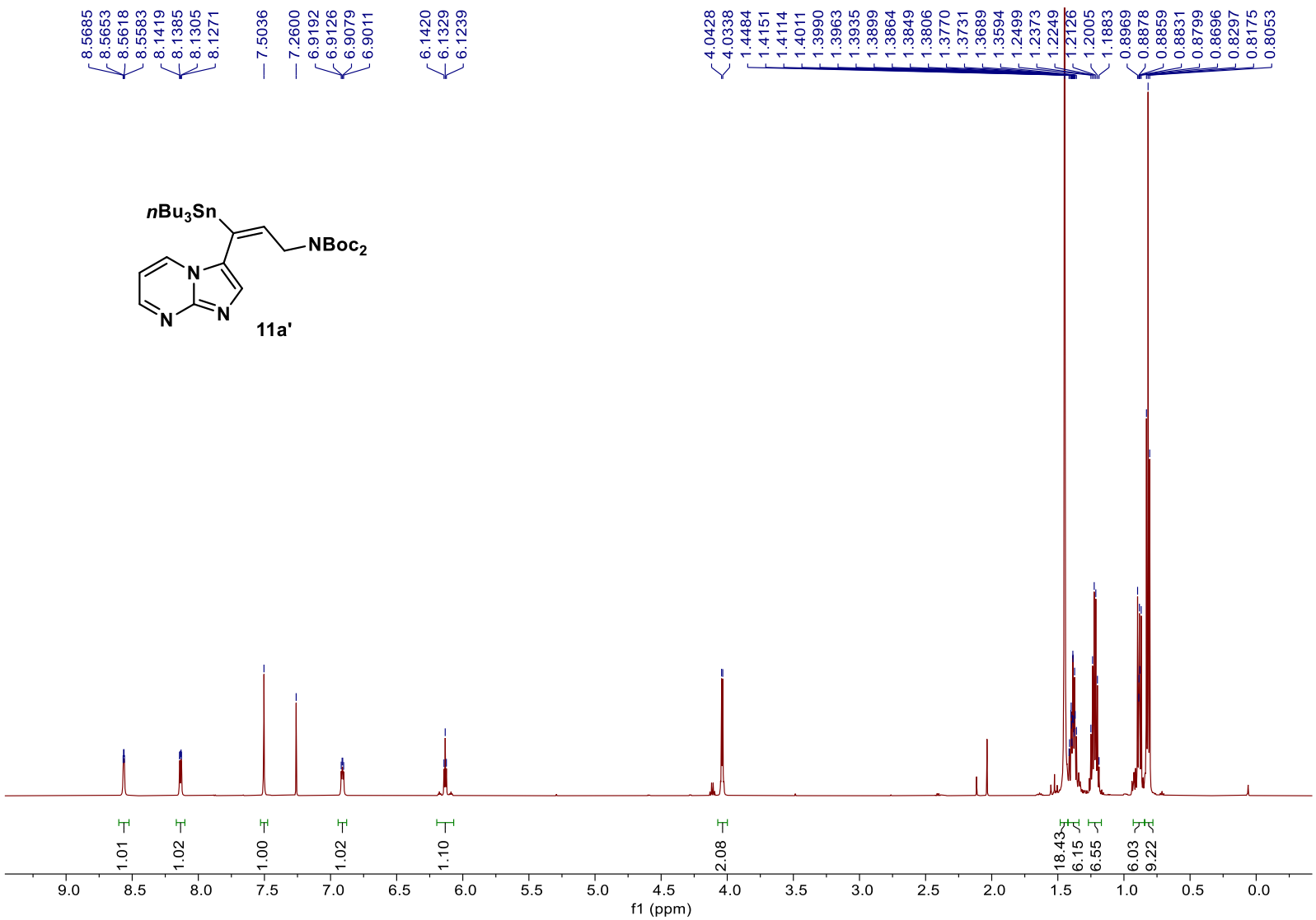
HSQC, 600 MHz, $CDCl_3$



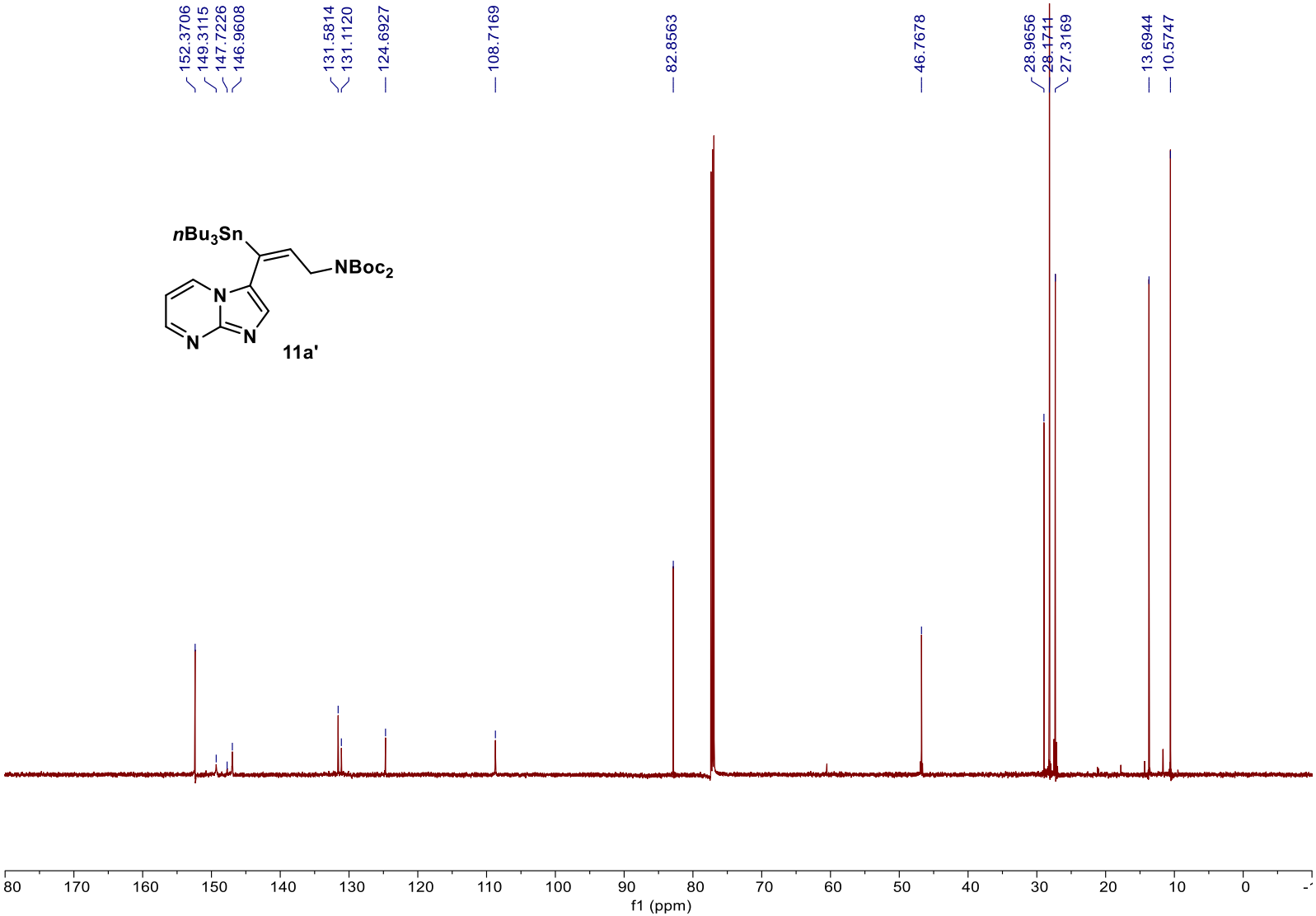
HMBC, 600 MHz, $CDCl_3$



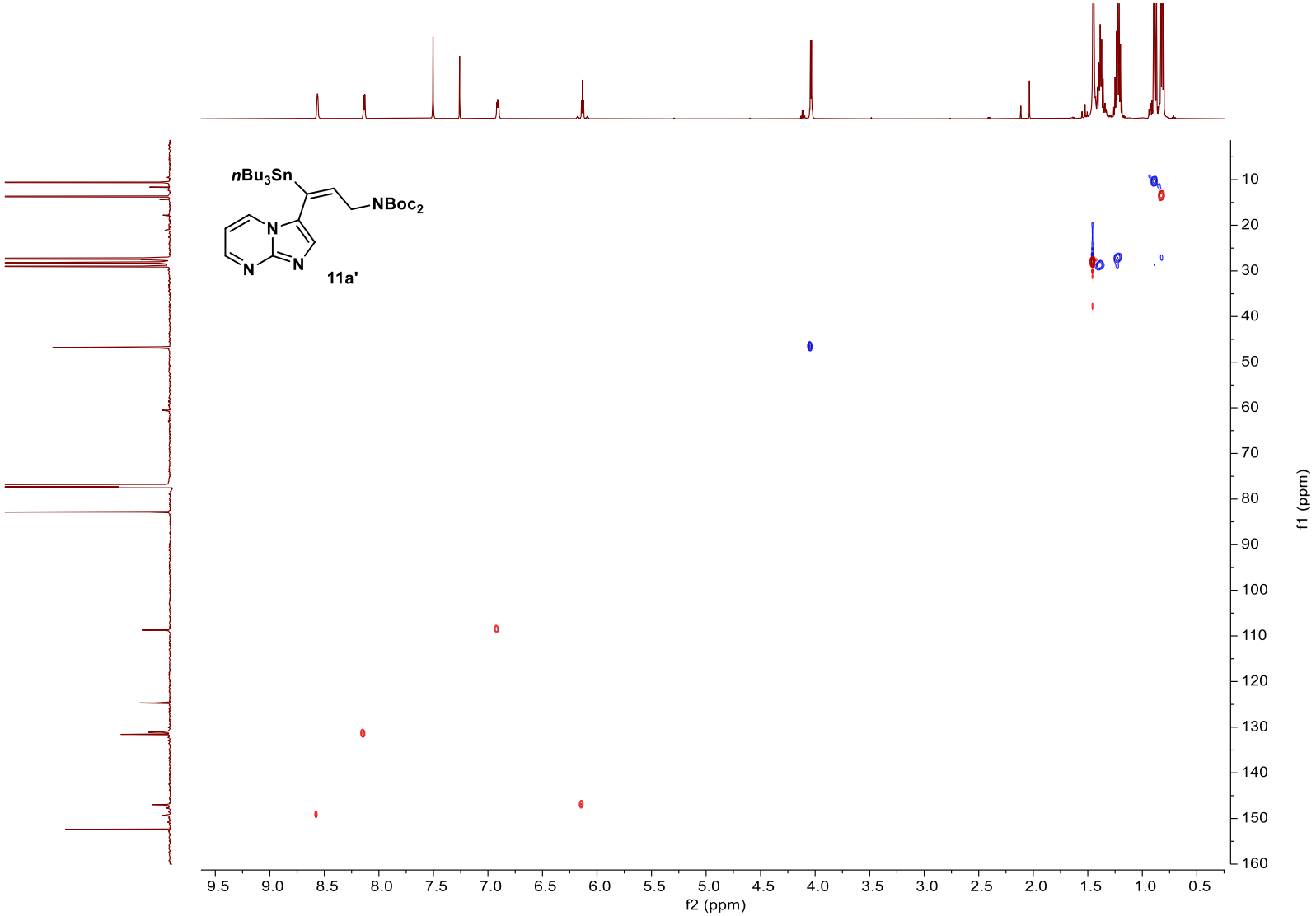
NOESY, 600 MHz, $CDCl_3$



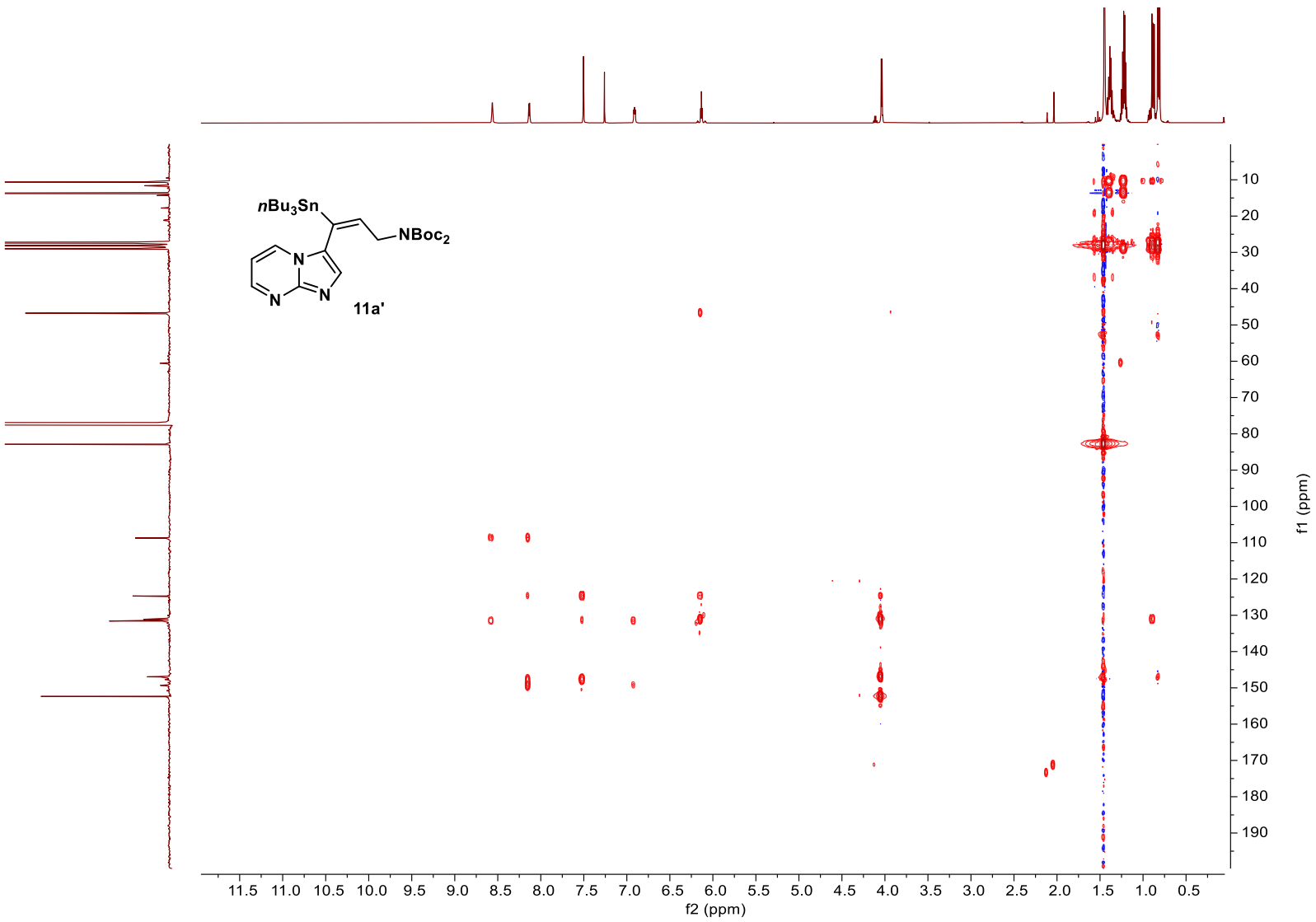
^{1}H NMR, 600 MHz, $CDCl_3$



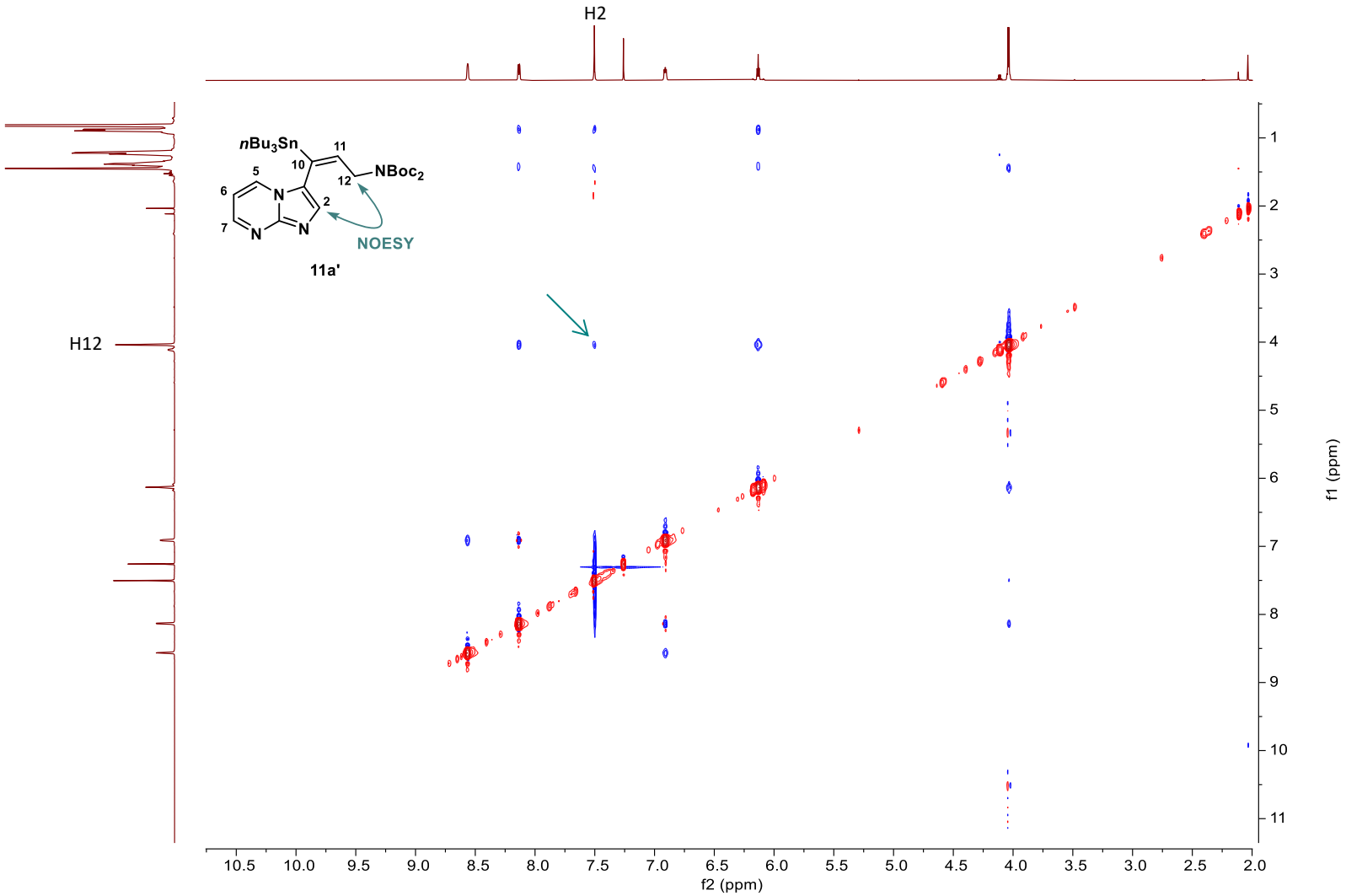
^{13}C NMR, 151 MHz, $CDCl_3$



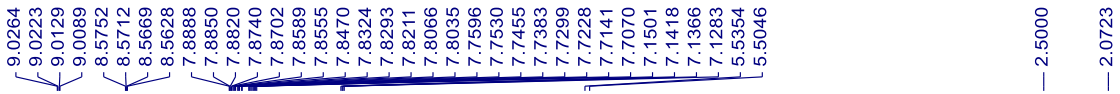
HSQC, 600 MHz, $CDCl_3$

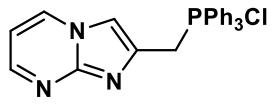


HMBC, 600 MHz, $CDCl_3$



NOESY, 600 MHz, $CDCl_3$





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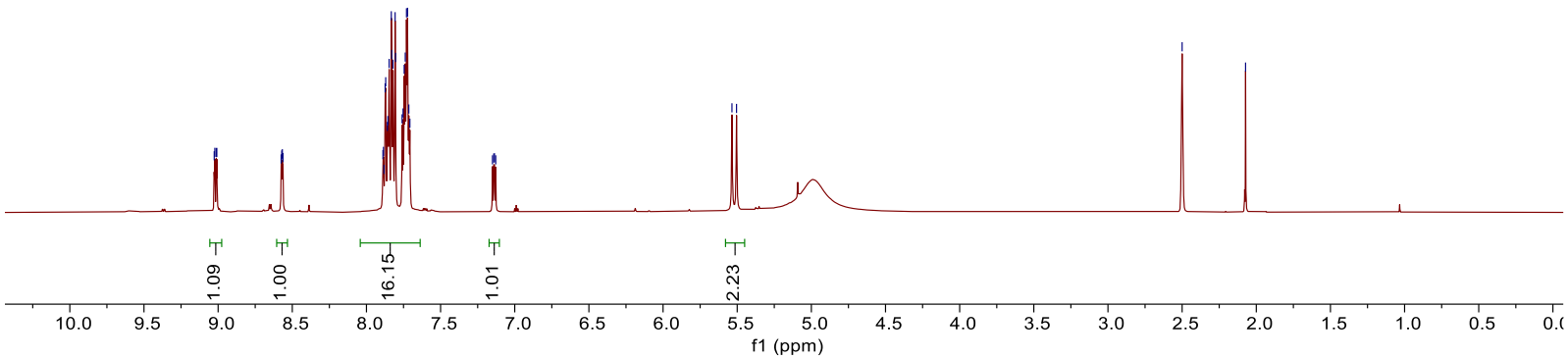
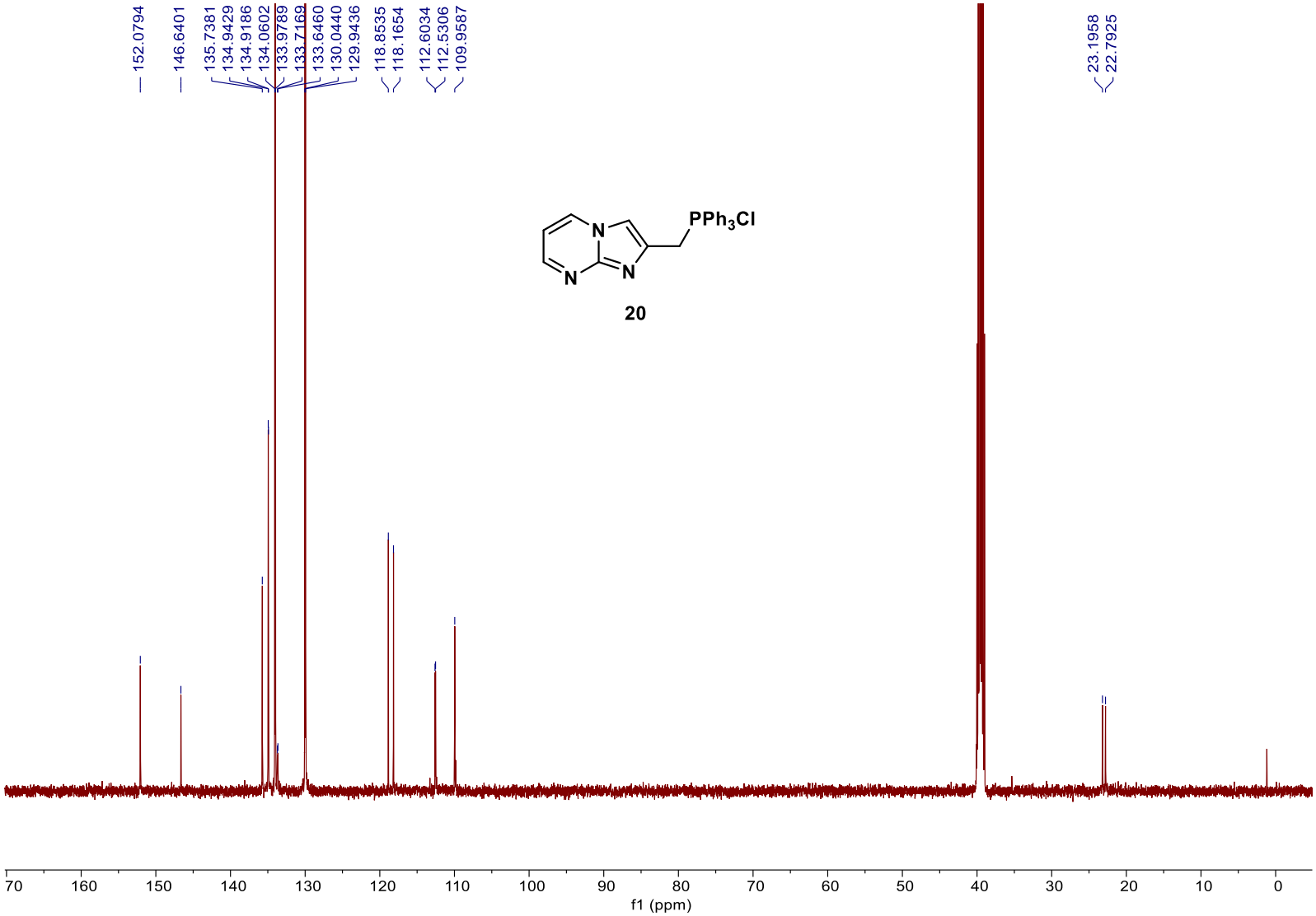
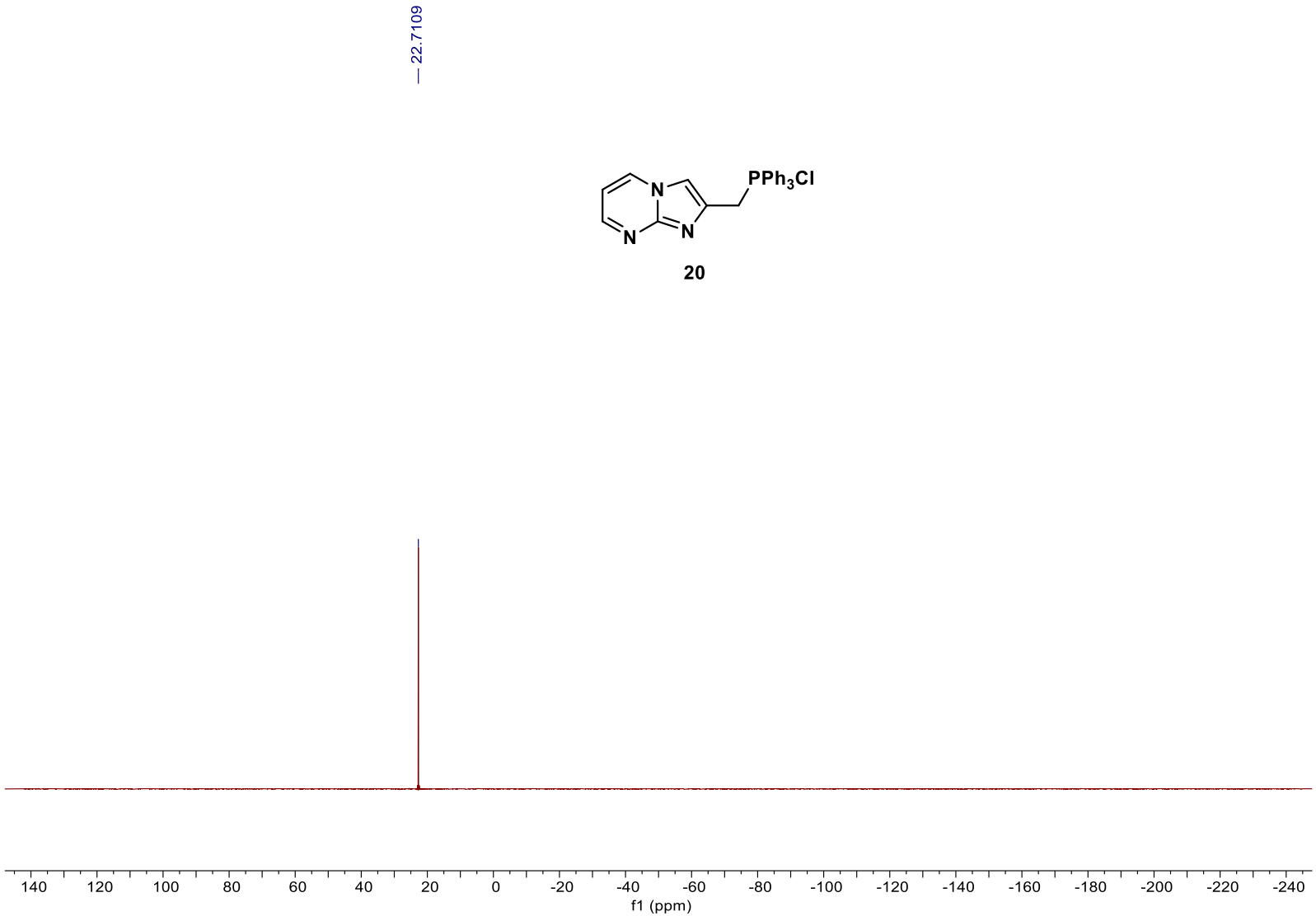


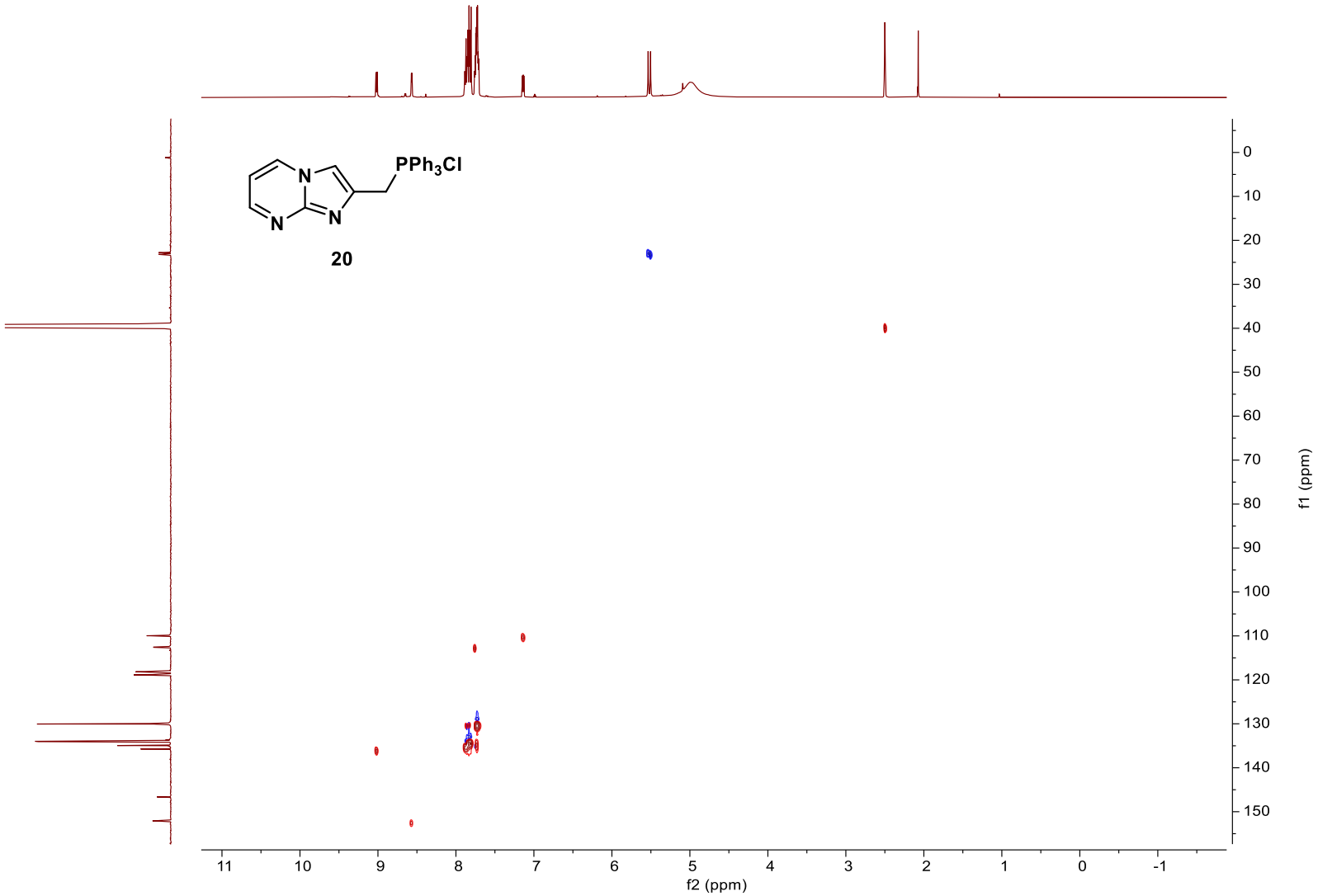
^{1}H NMR, 500 MHz, DMSO-d_6



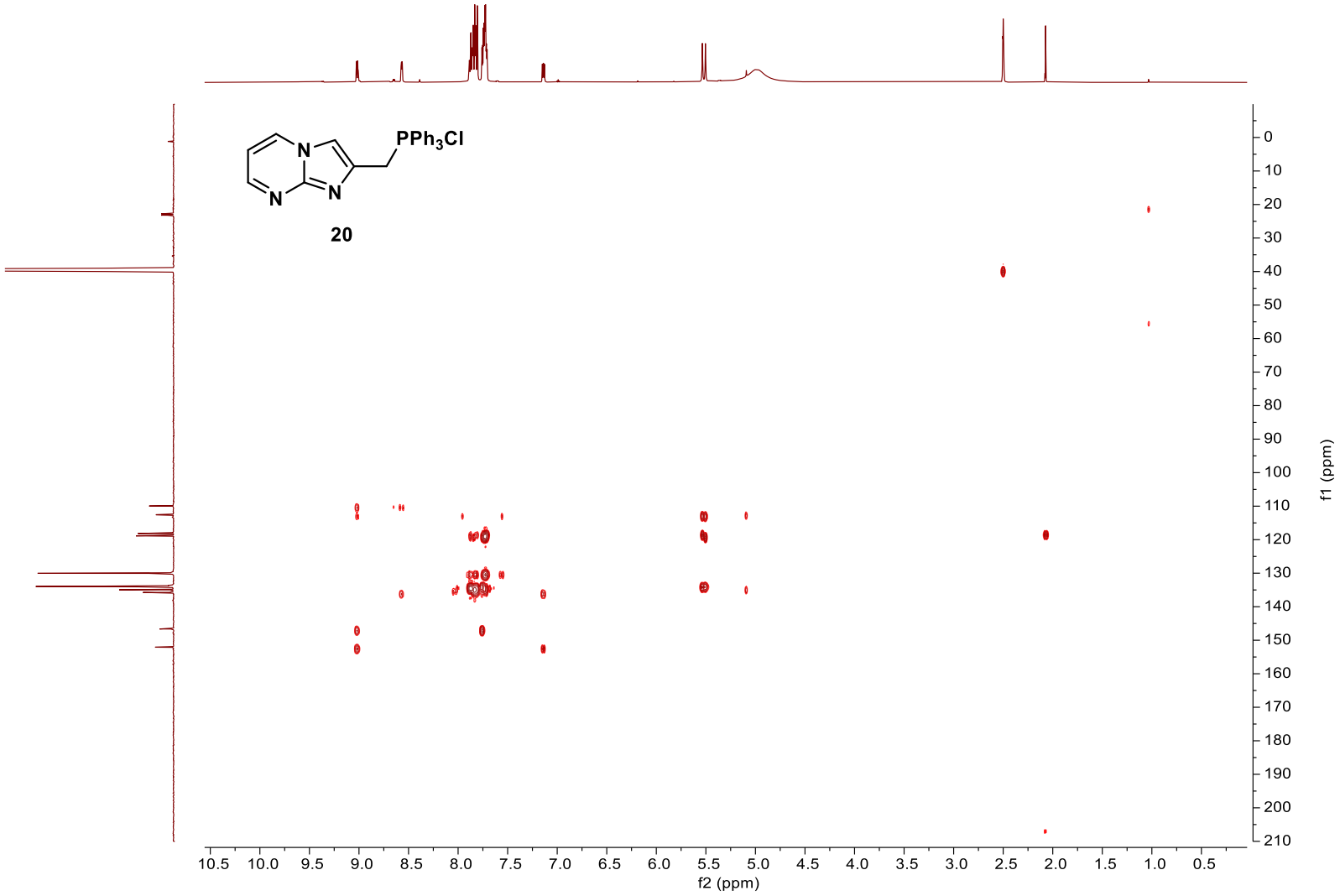
^{13}C NMR, 126 MHz, DMSO-d_6



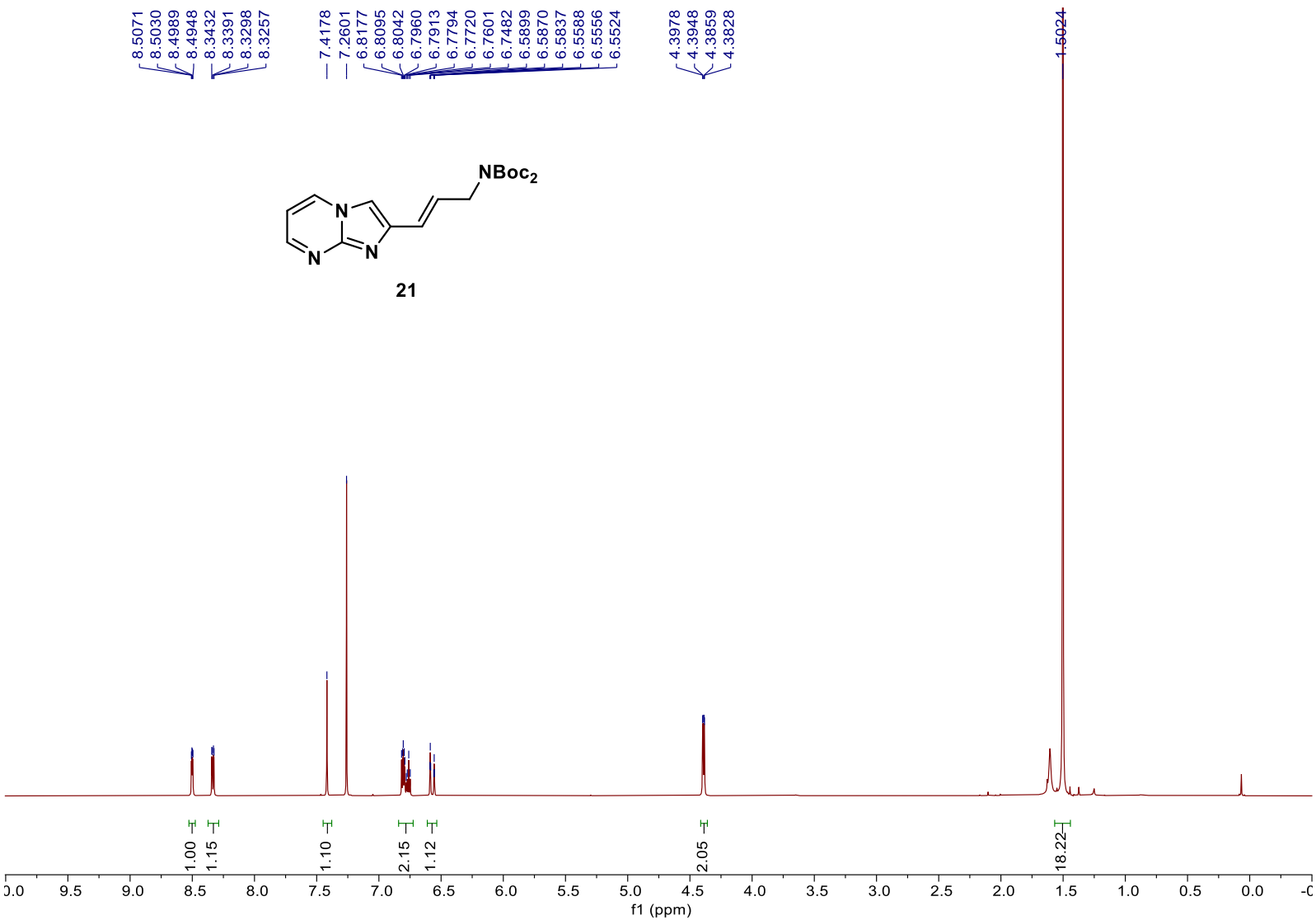
^{13}P NMR, 162 MHz, DMSO-d_6



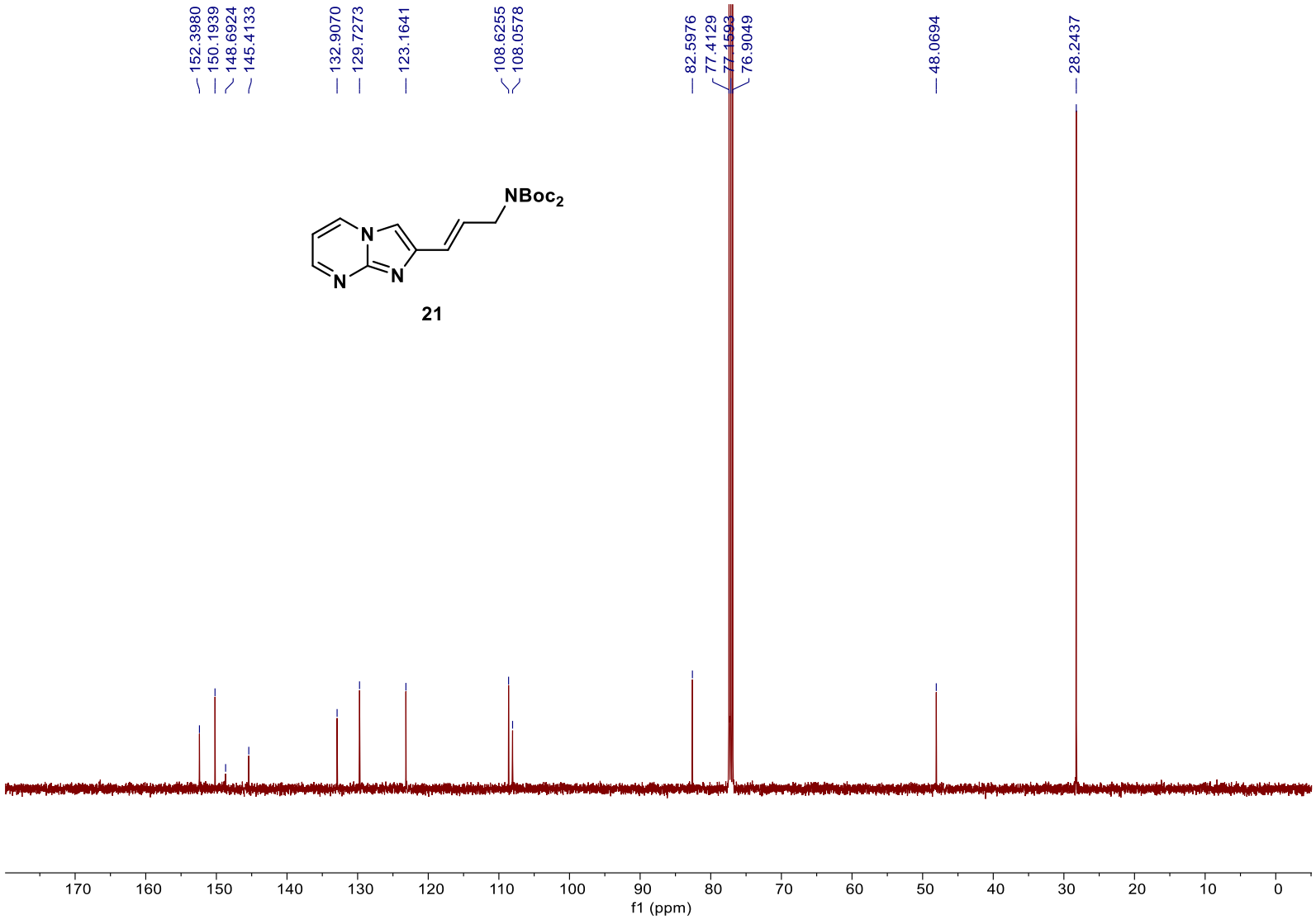
HSQC, 500 MHz, DMSO-d_6



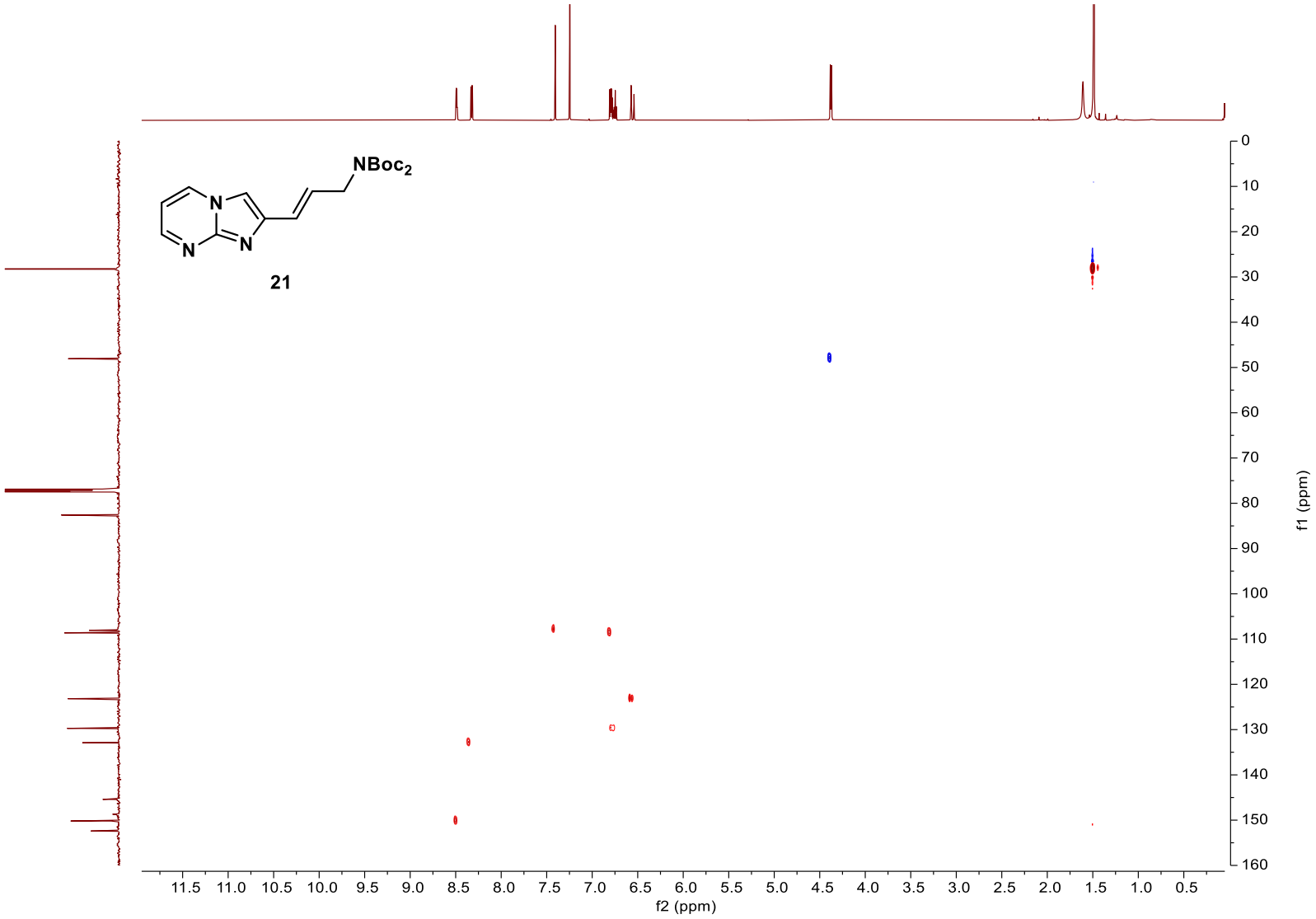
HMBC, 500 MHz, DMSO-d_6



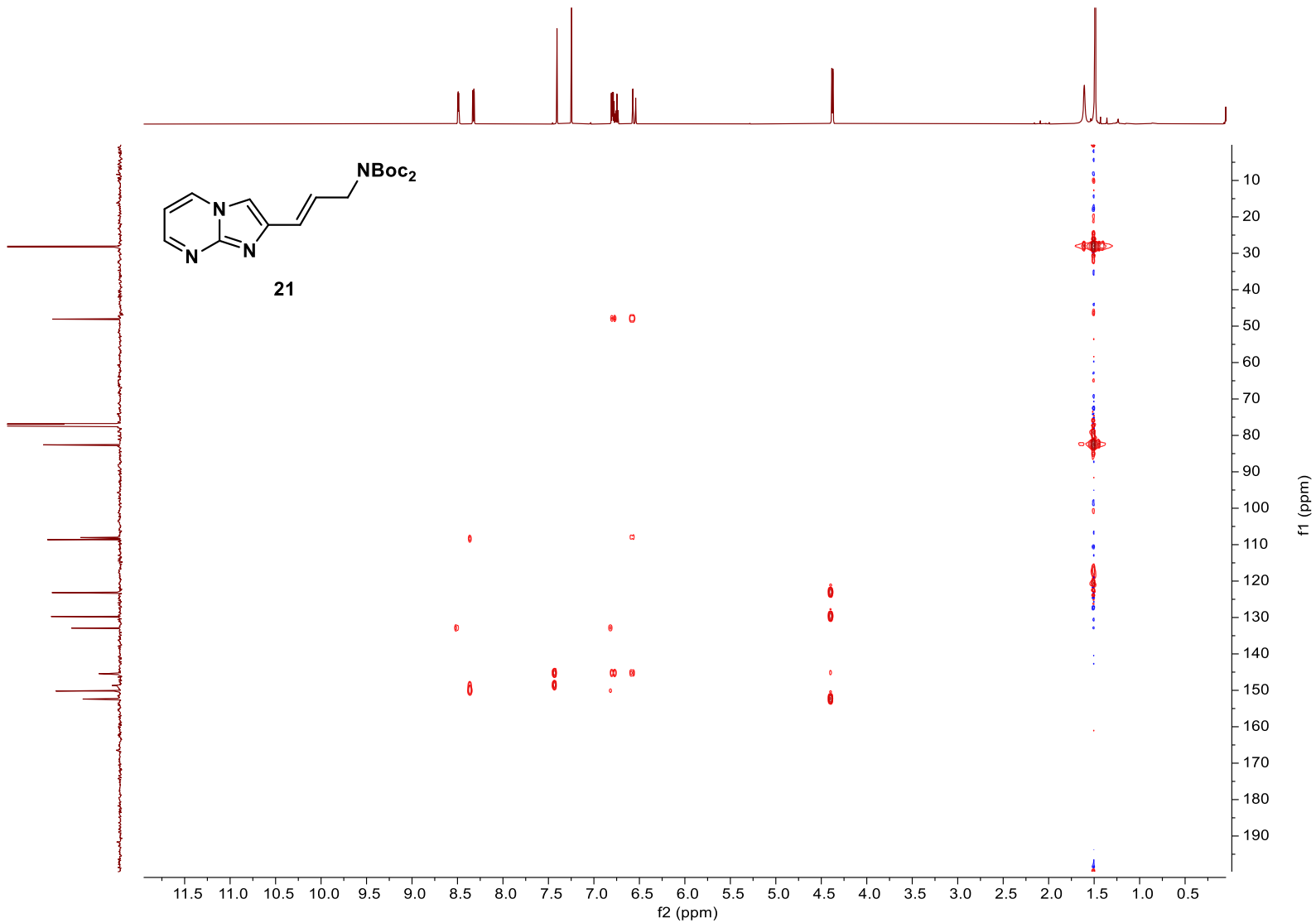
^{1}H NMR, 500 MHz, $CDCl_3$



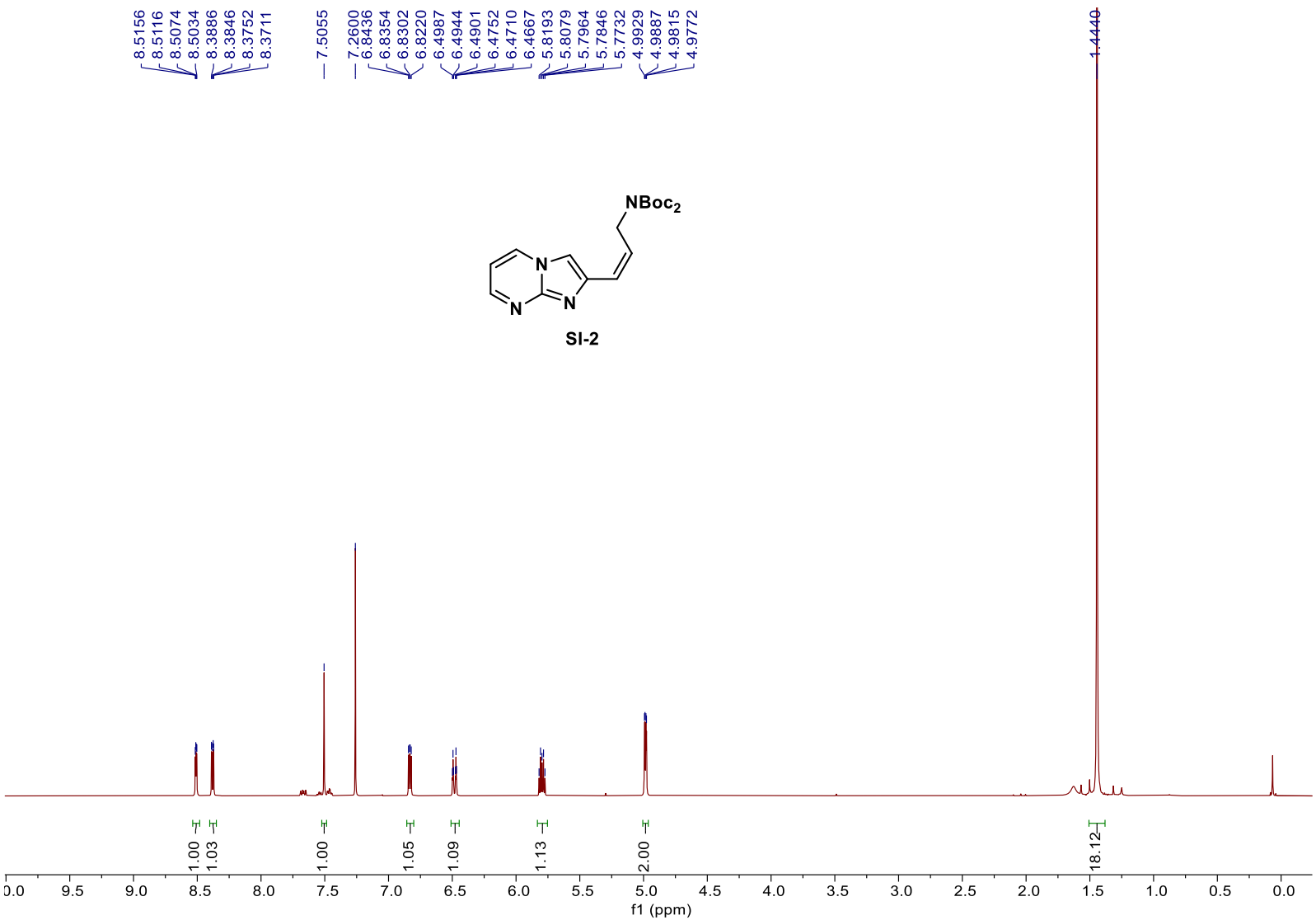
^{13}C NMR, 126 MHz, $CDCl_3$



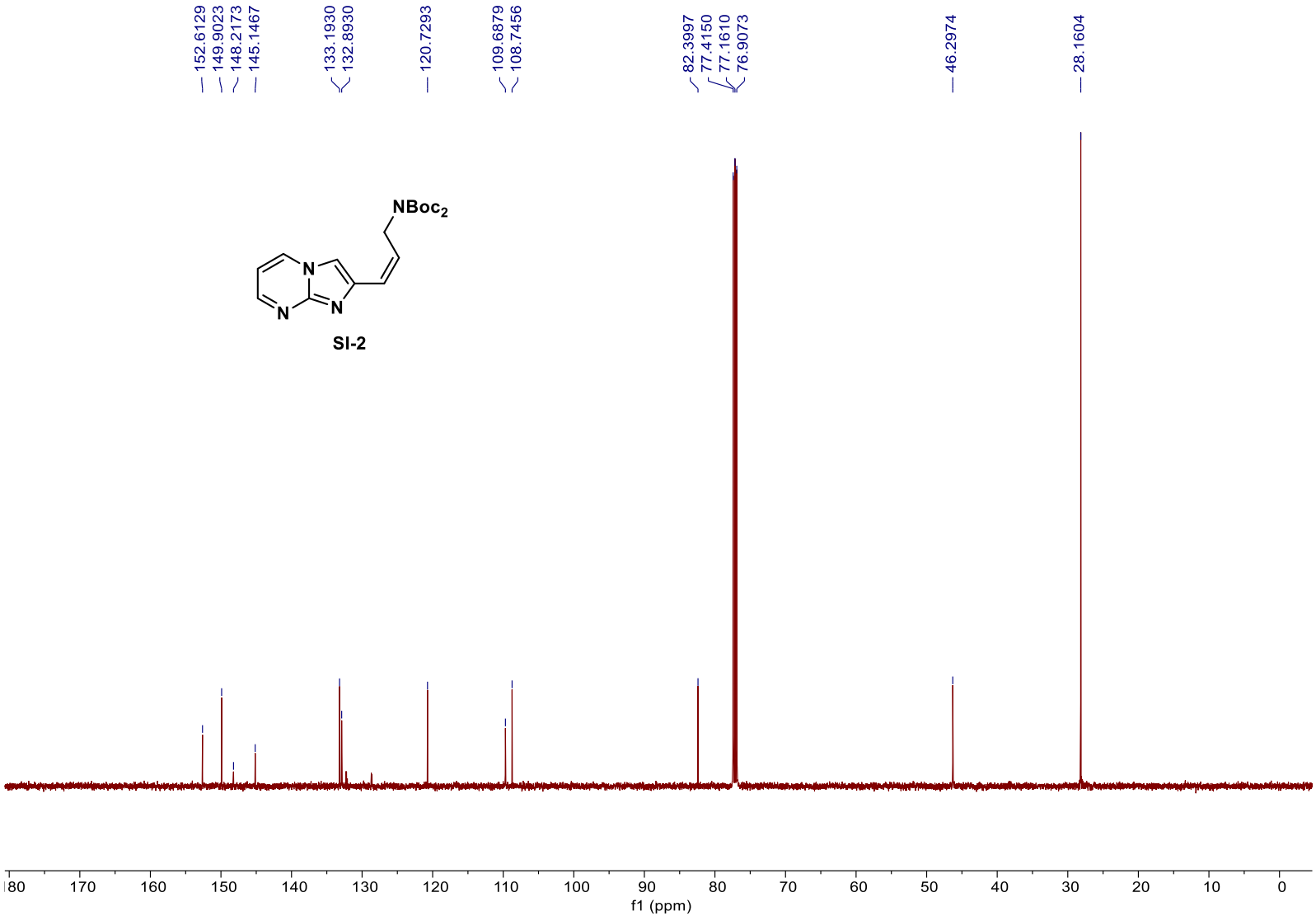
HSQC, 500 MHz, $CDCl_3$



HMBC, 500 MHz, $CDCl_3$



^{1}H NMR, 500 MHz, $CDCl_3$



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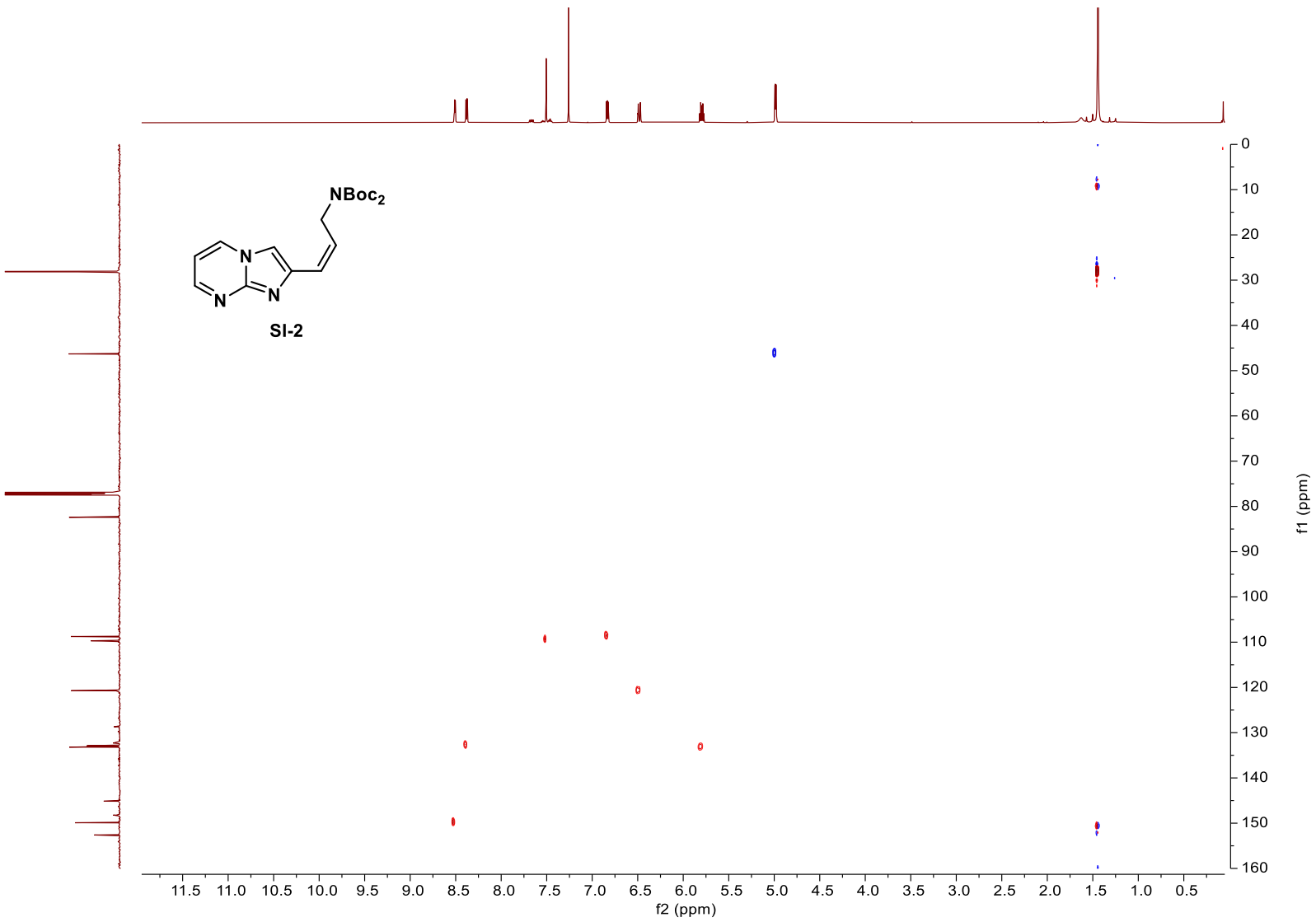
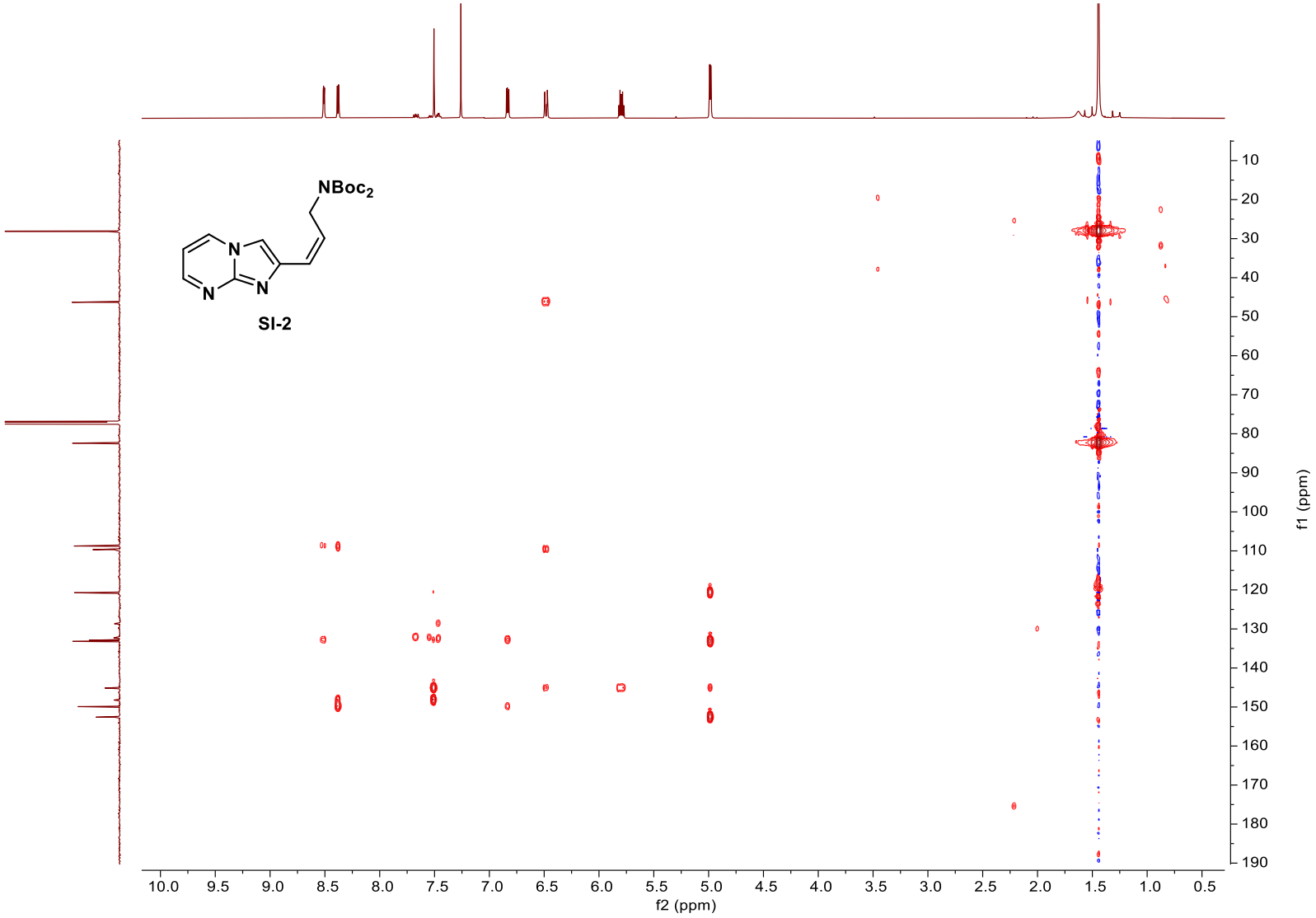
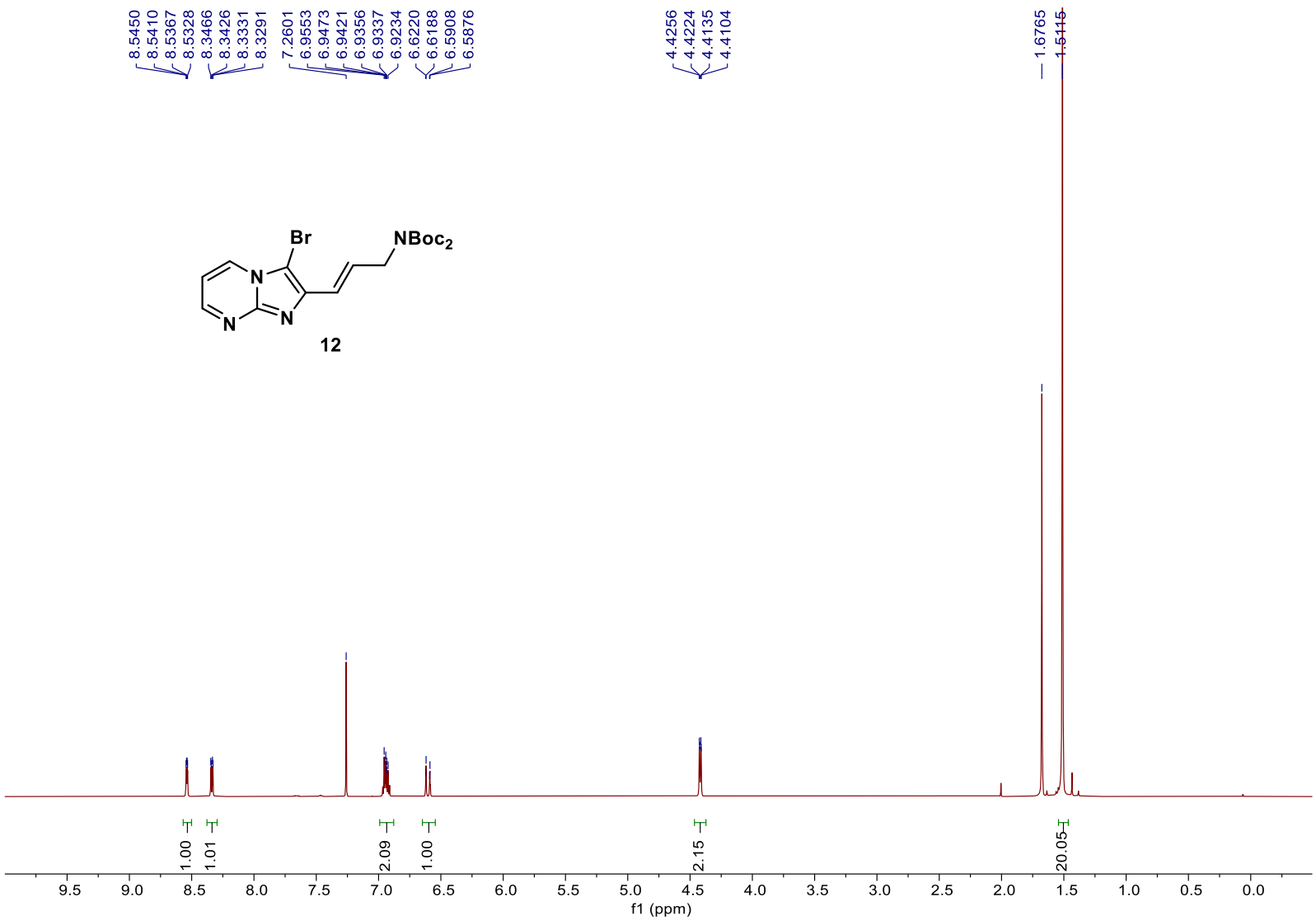


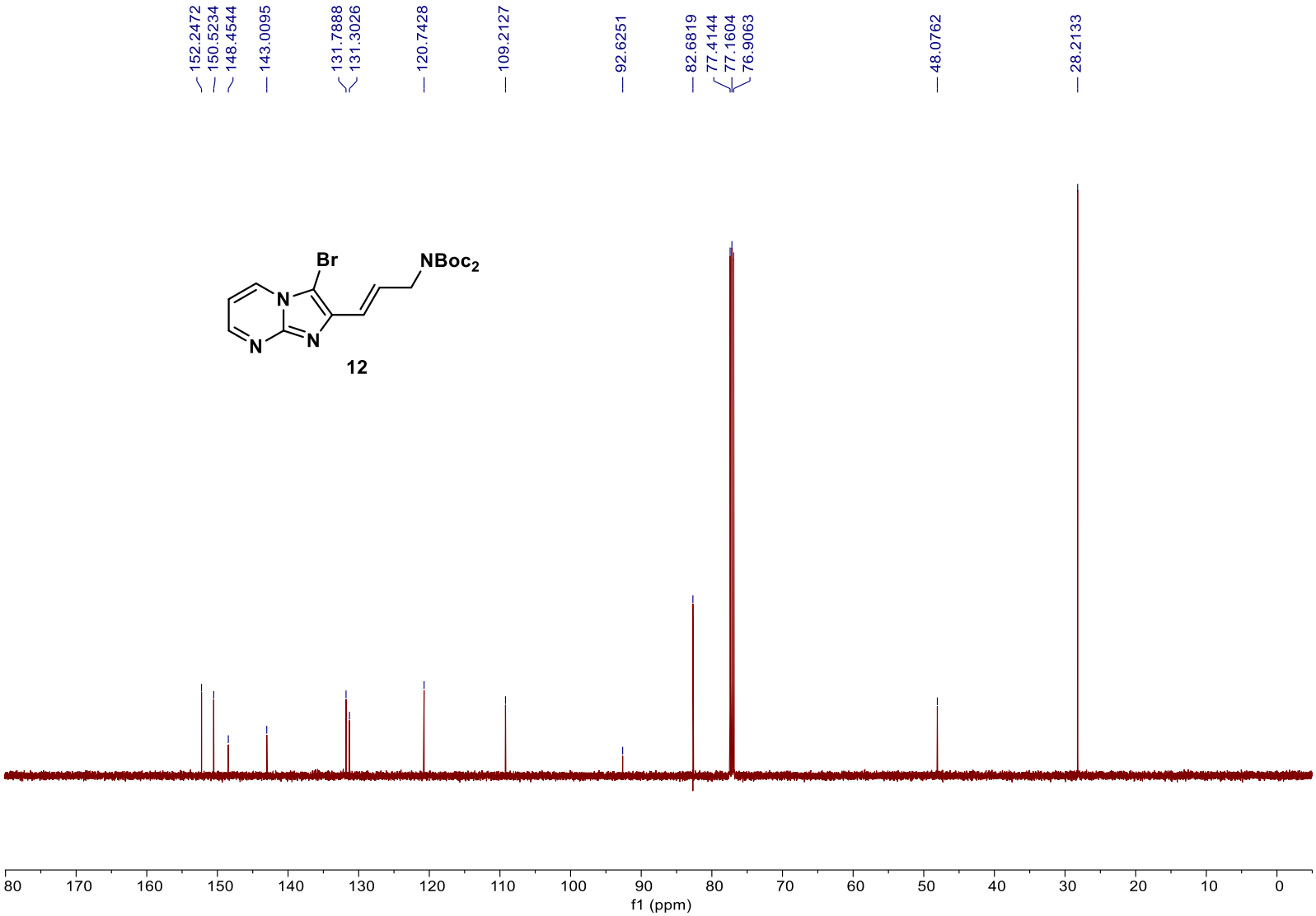
HSQC, 500 MHz, $CDCl_3$



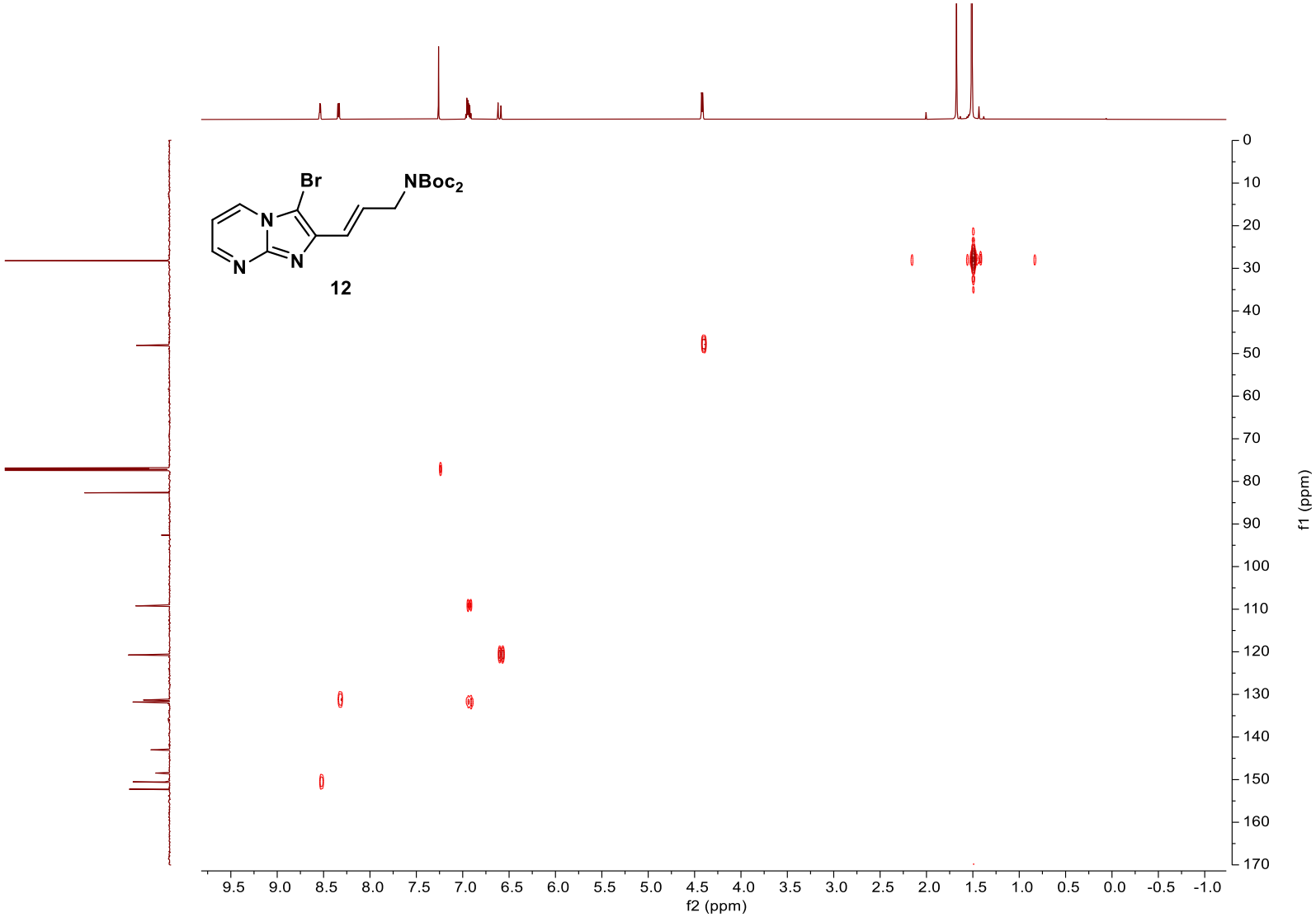
HMBC, 500 MHz, $CDCl_3$



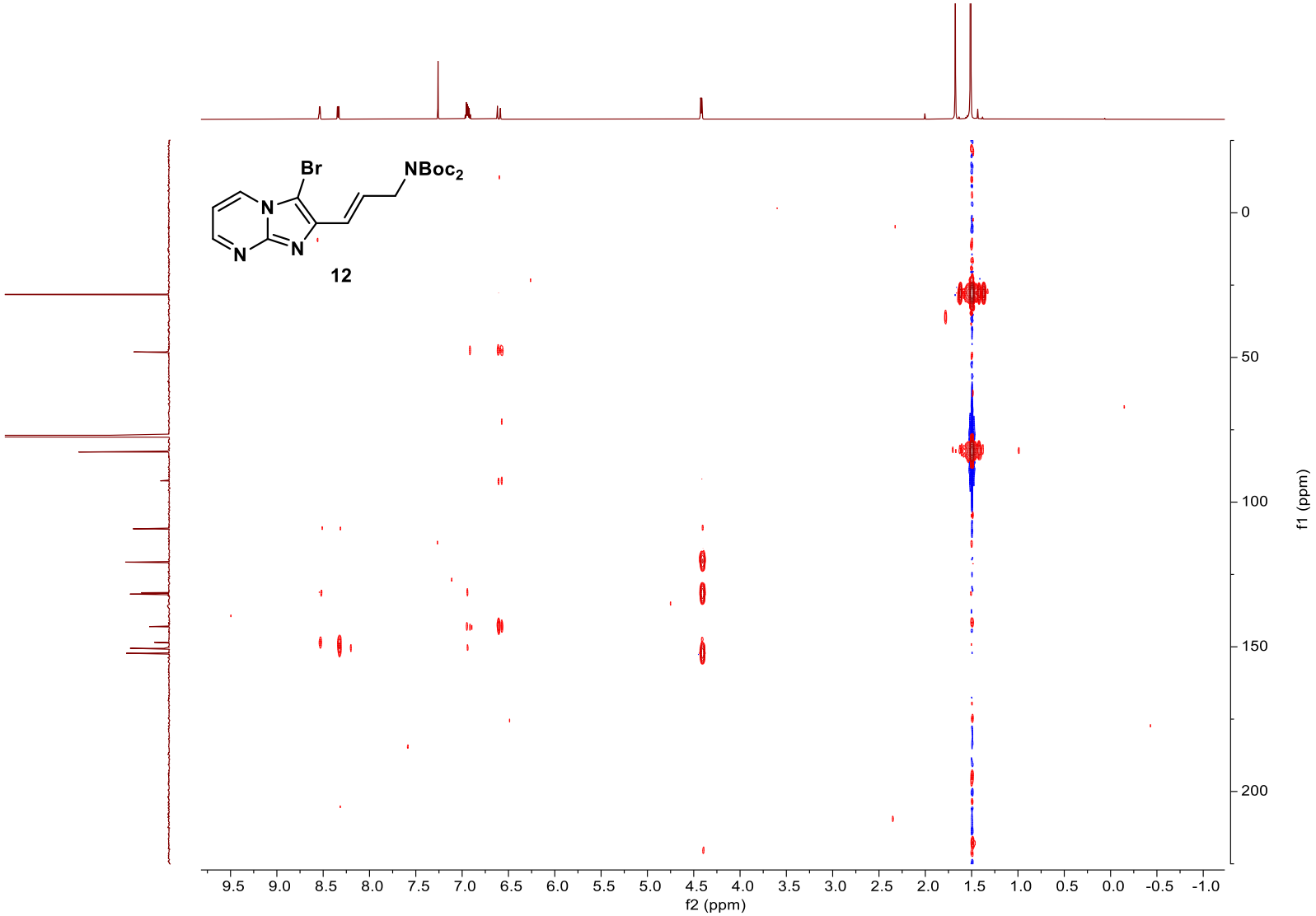
^{1}H NMR, 500 MHz, $CDCl_3$



^{13}C NMR, 126 MHz, $CDCl_3$



HMQC, 500 MHz, $CDCl_3$



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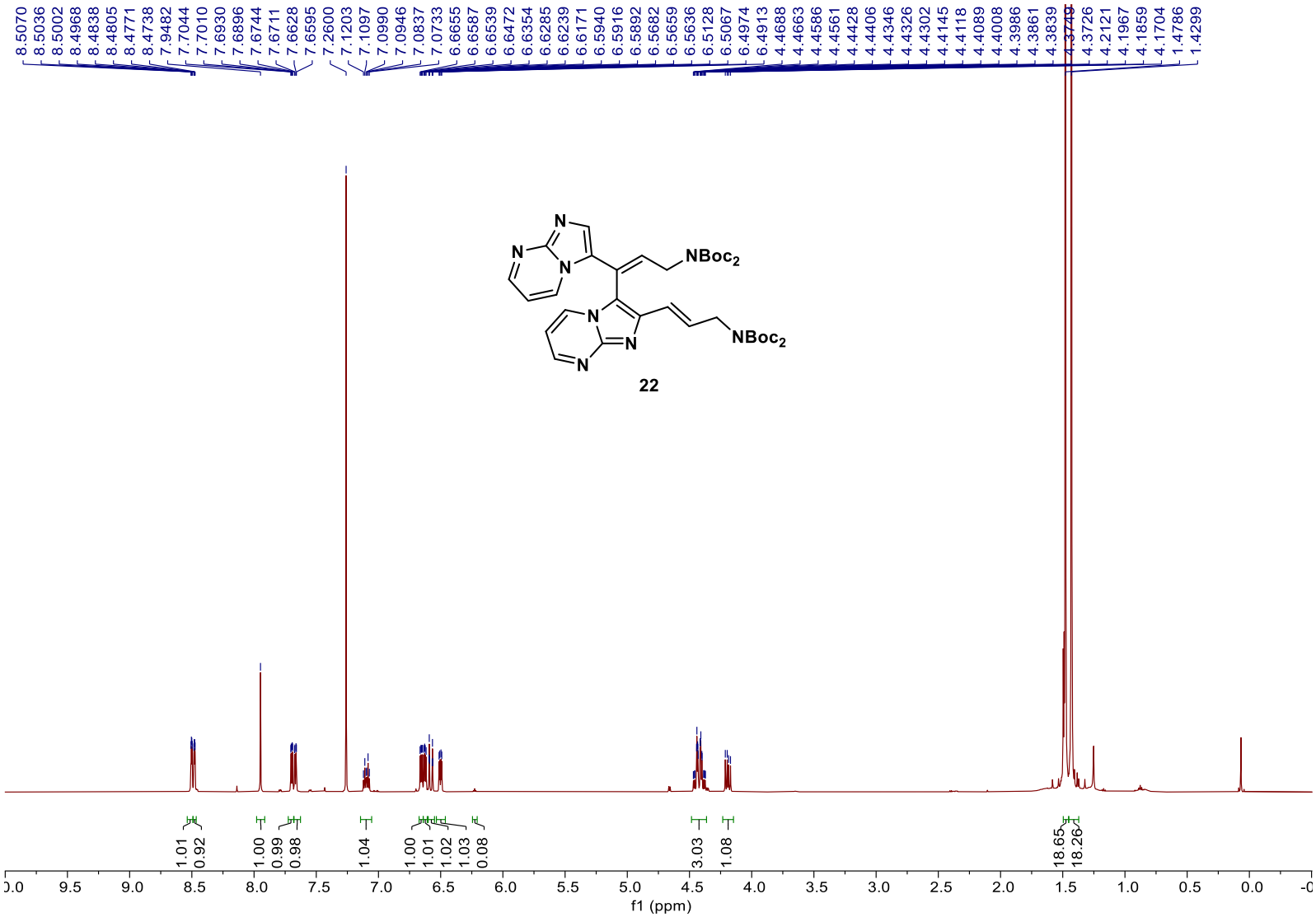
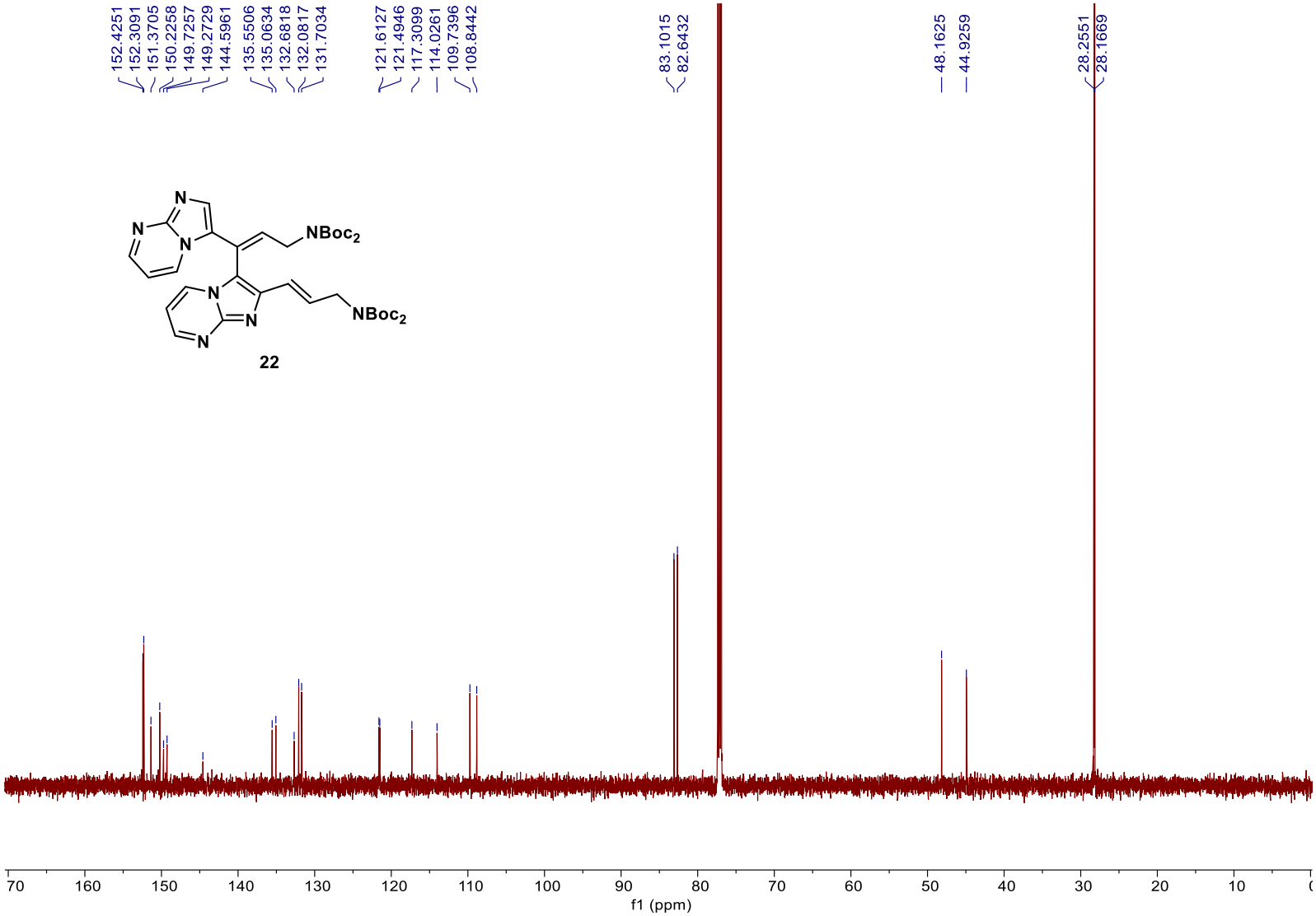
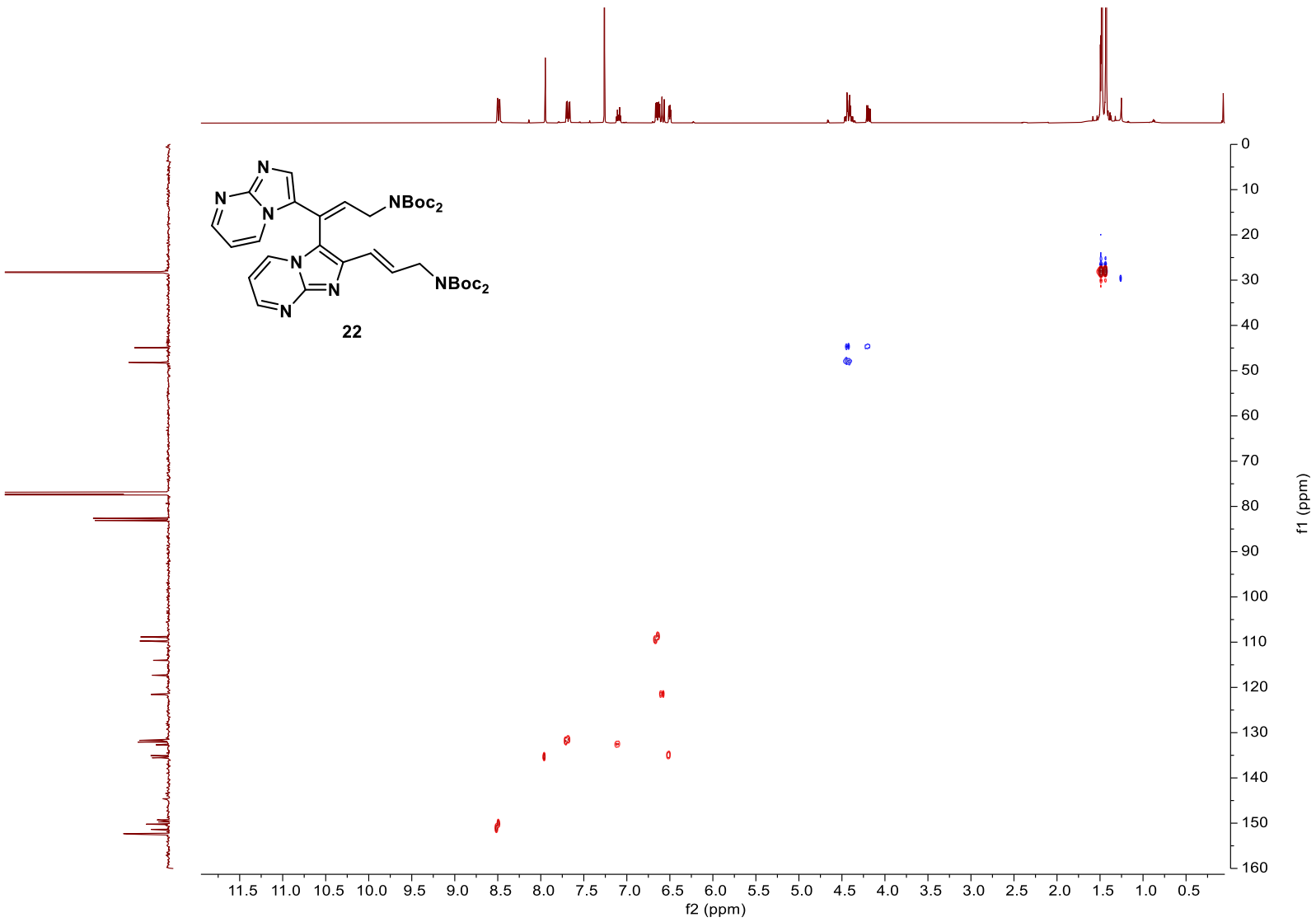


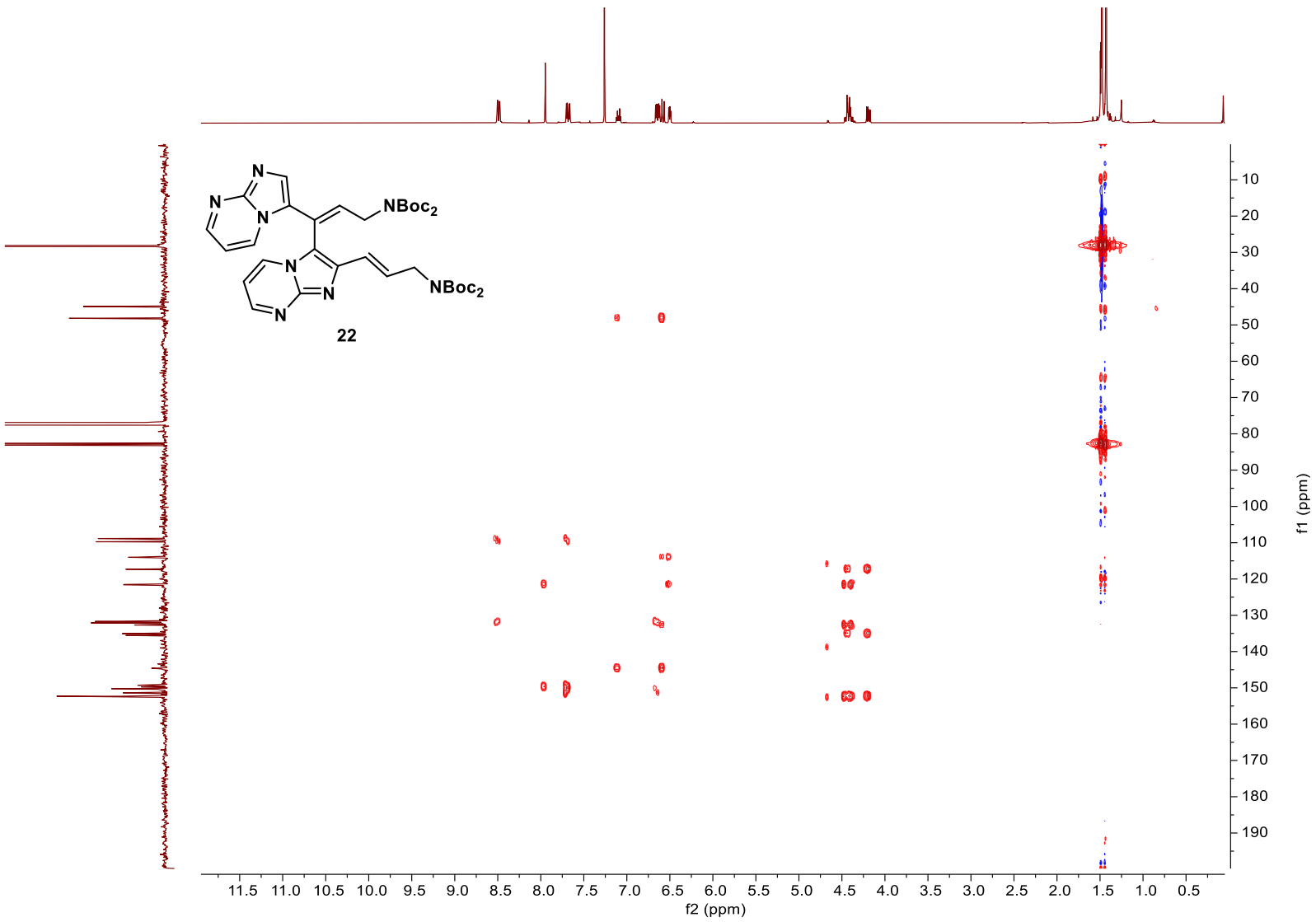
^{1}H NMR, 600 MHz, $CDCl_3$



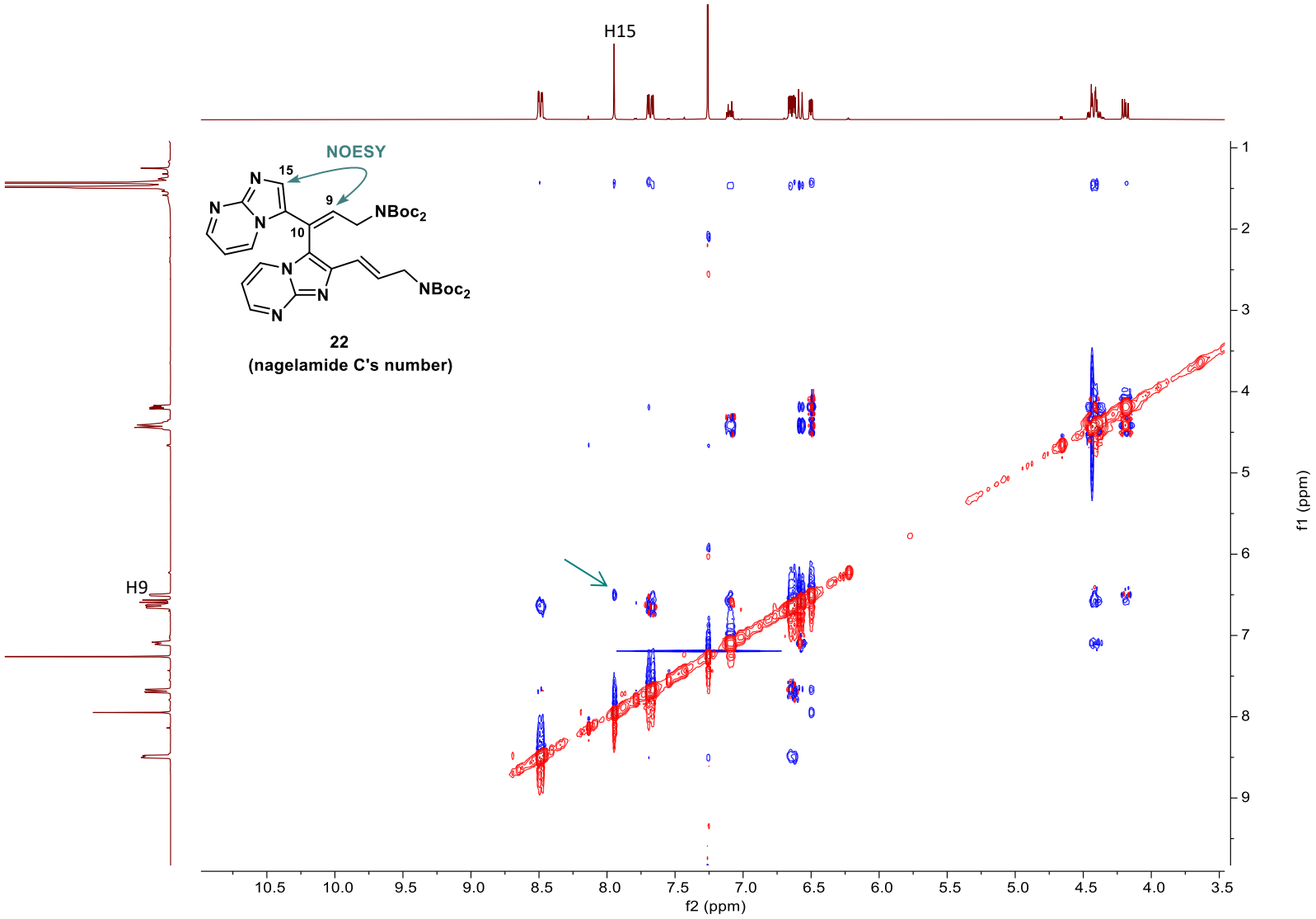
^{13}C NMR, 151 MHz, $CDCl_3$



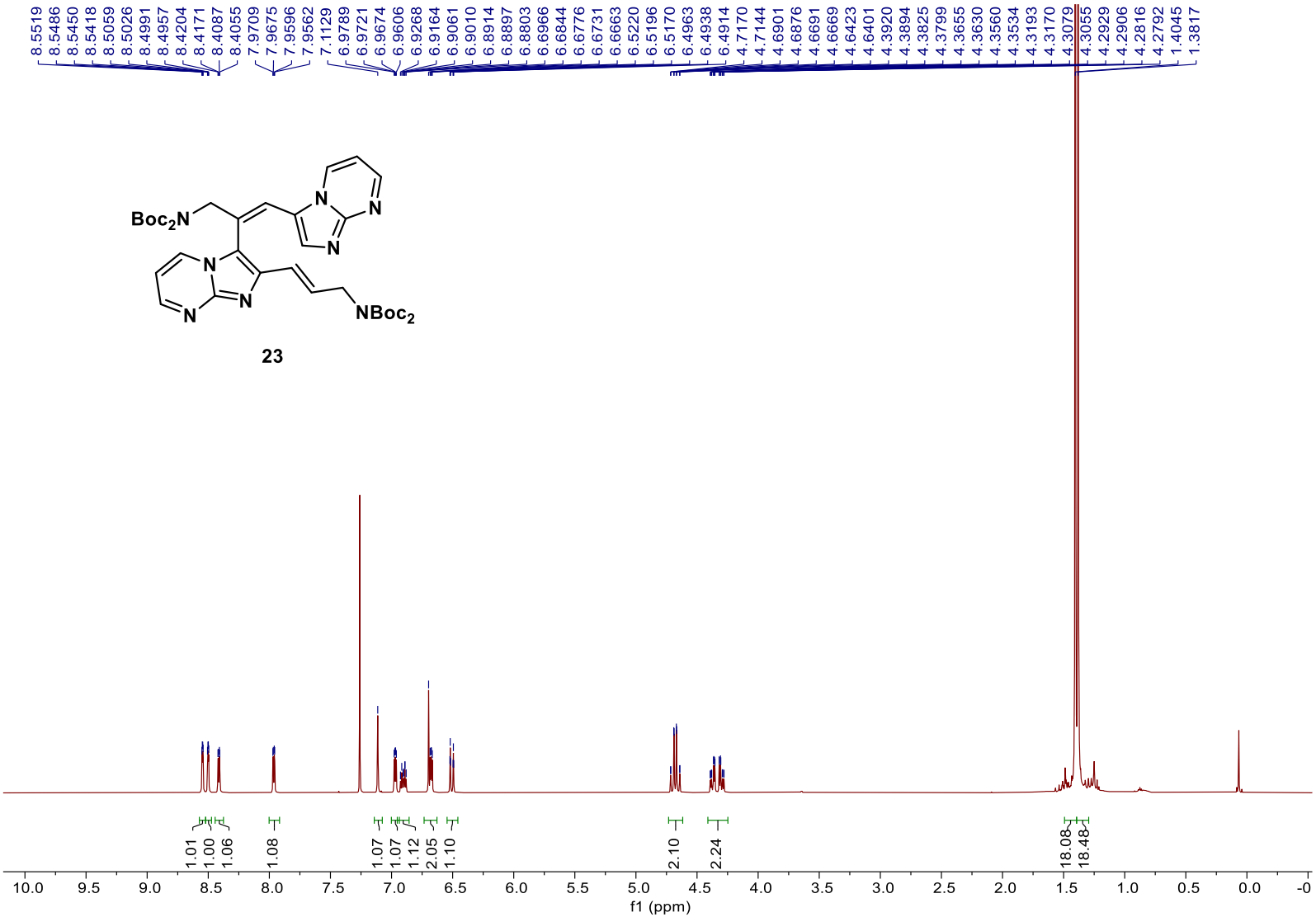
HSQC, 600 MHz, $CDCl_3$



HMBC, 600 MHz, $CDCl_3$



NOESY, 600 MHz, $CDCl_3$



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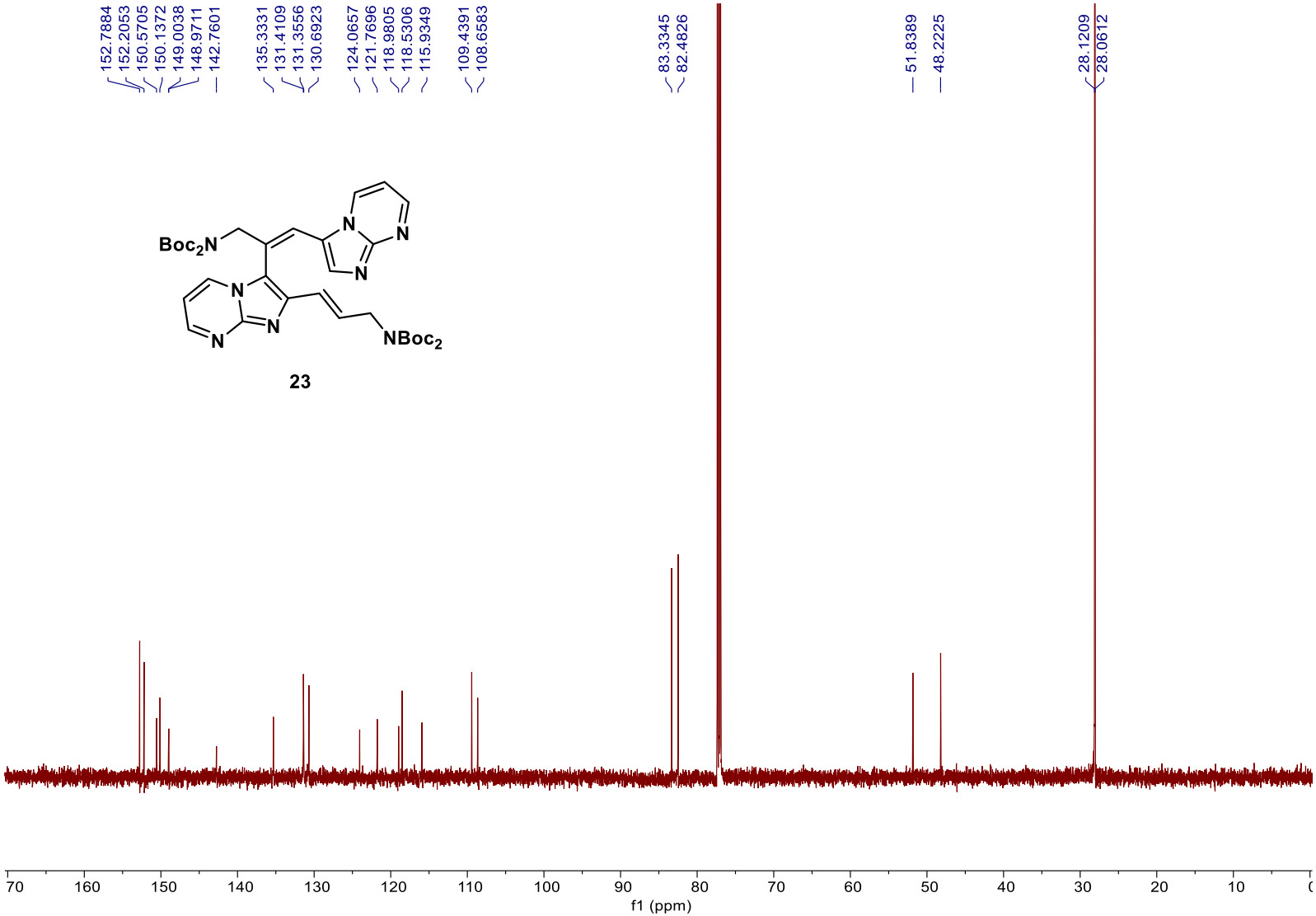
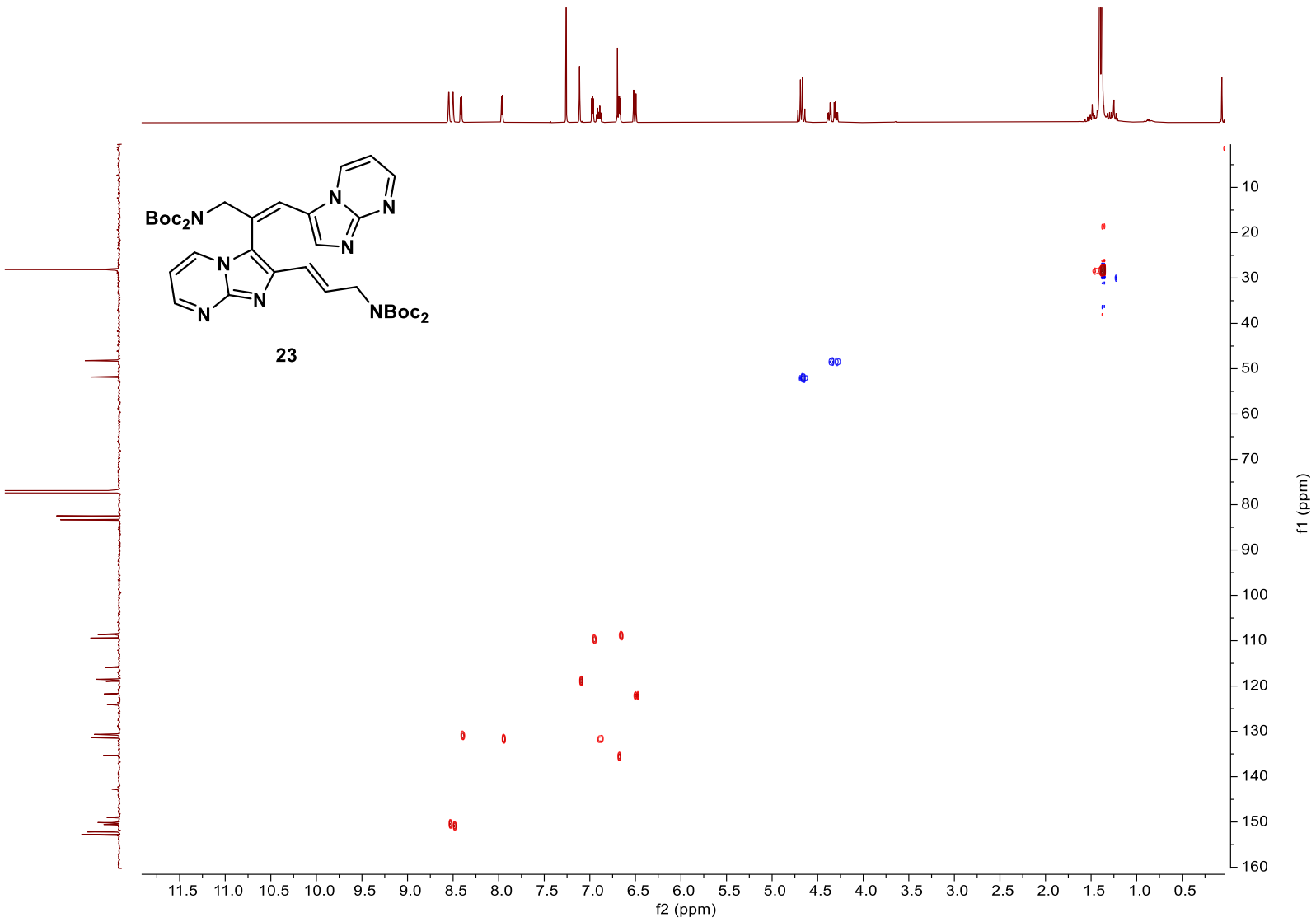
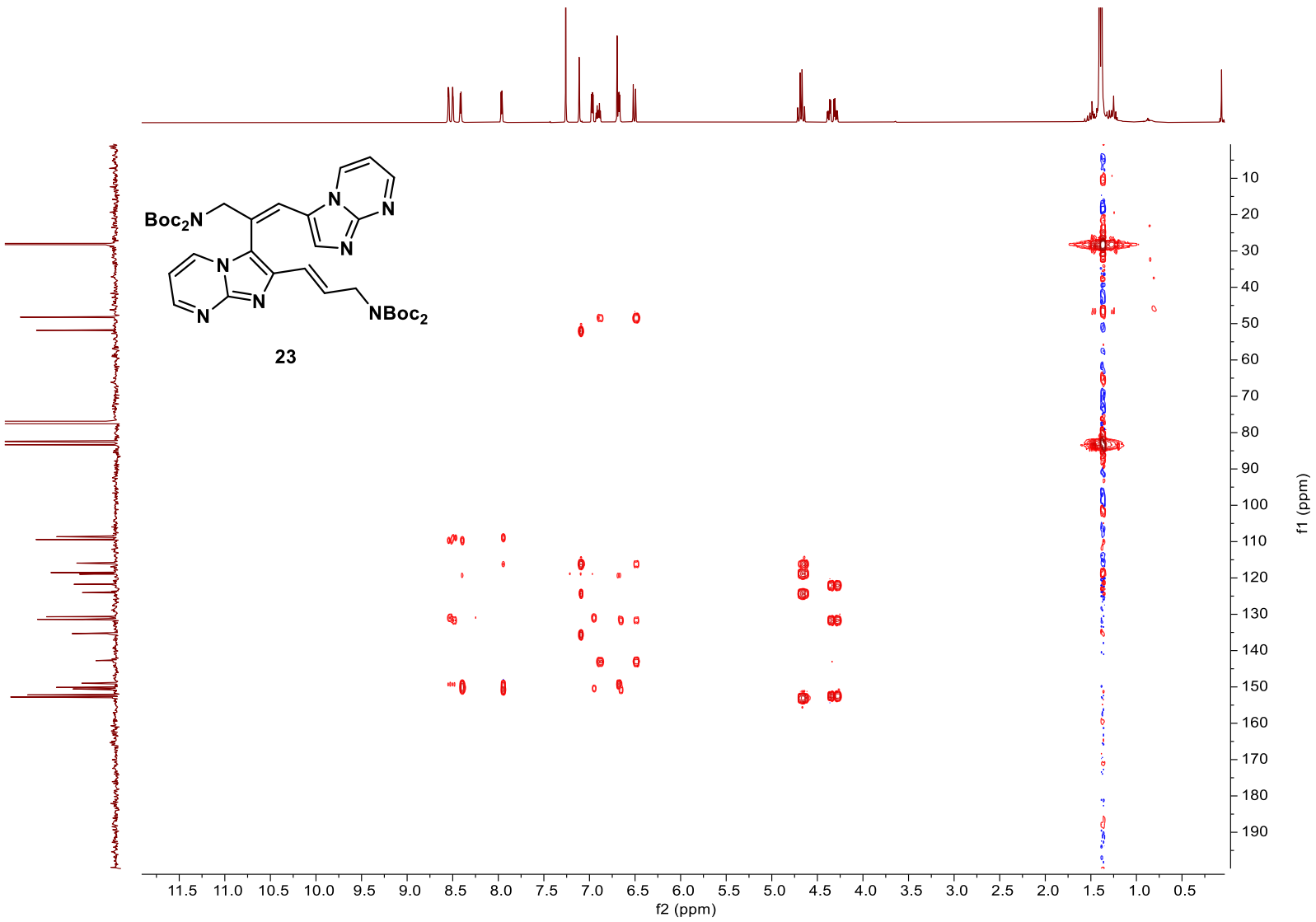
^{1}H NMR, 600 MHz, $CDCl_3$



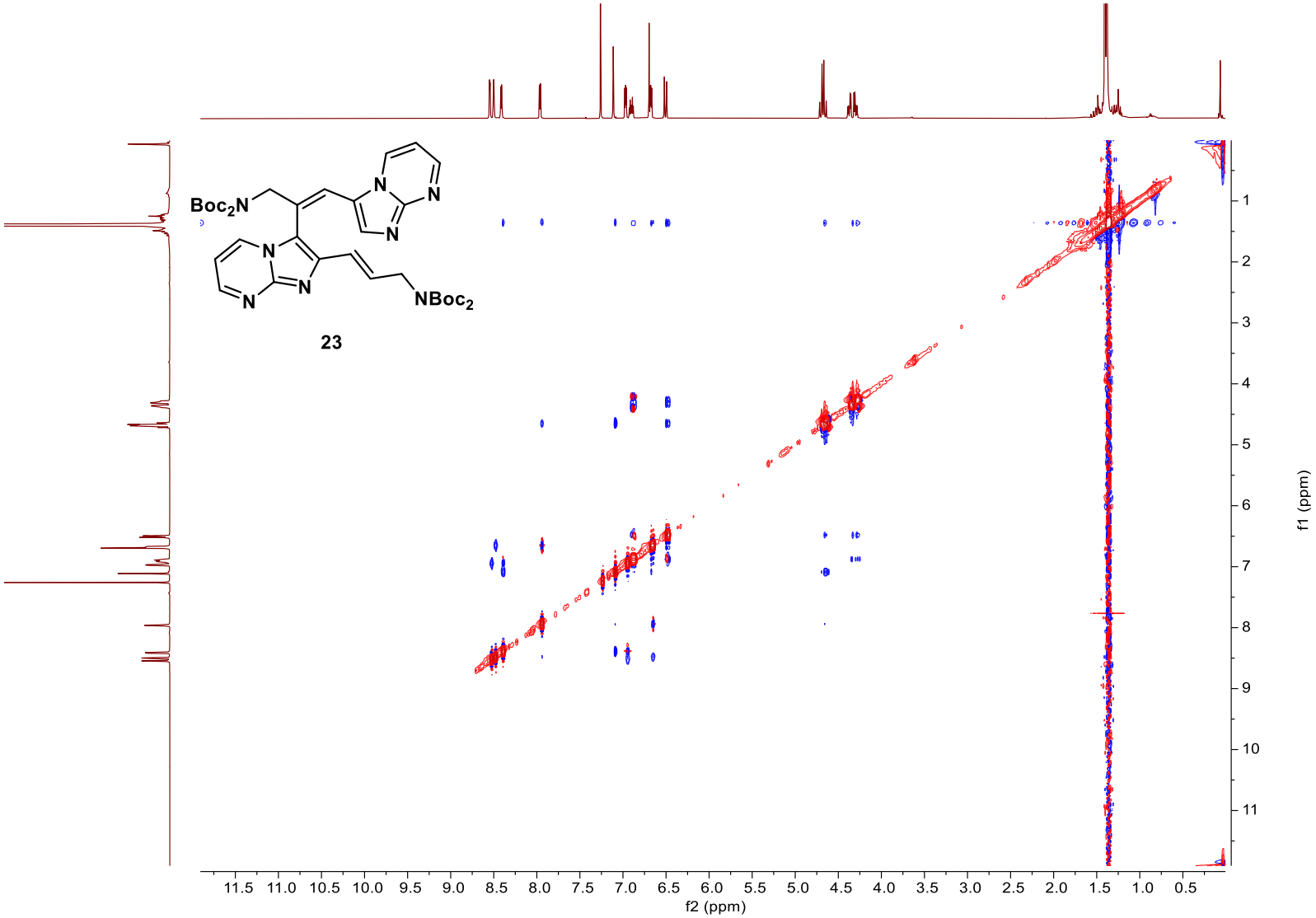
^{13}C NMR, 151 MHz, $CDCl_3$



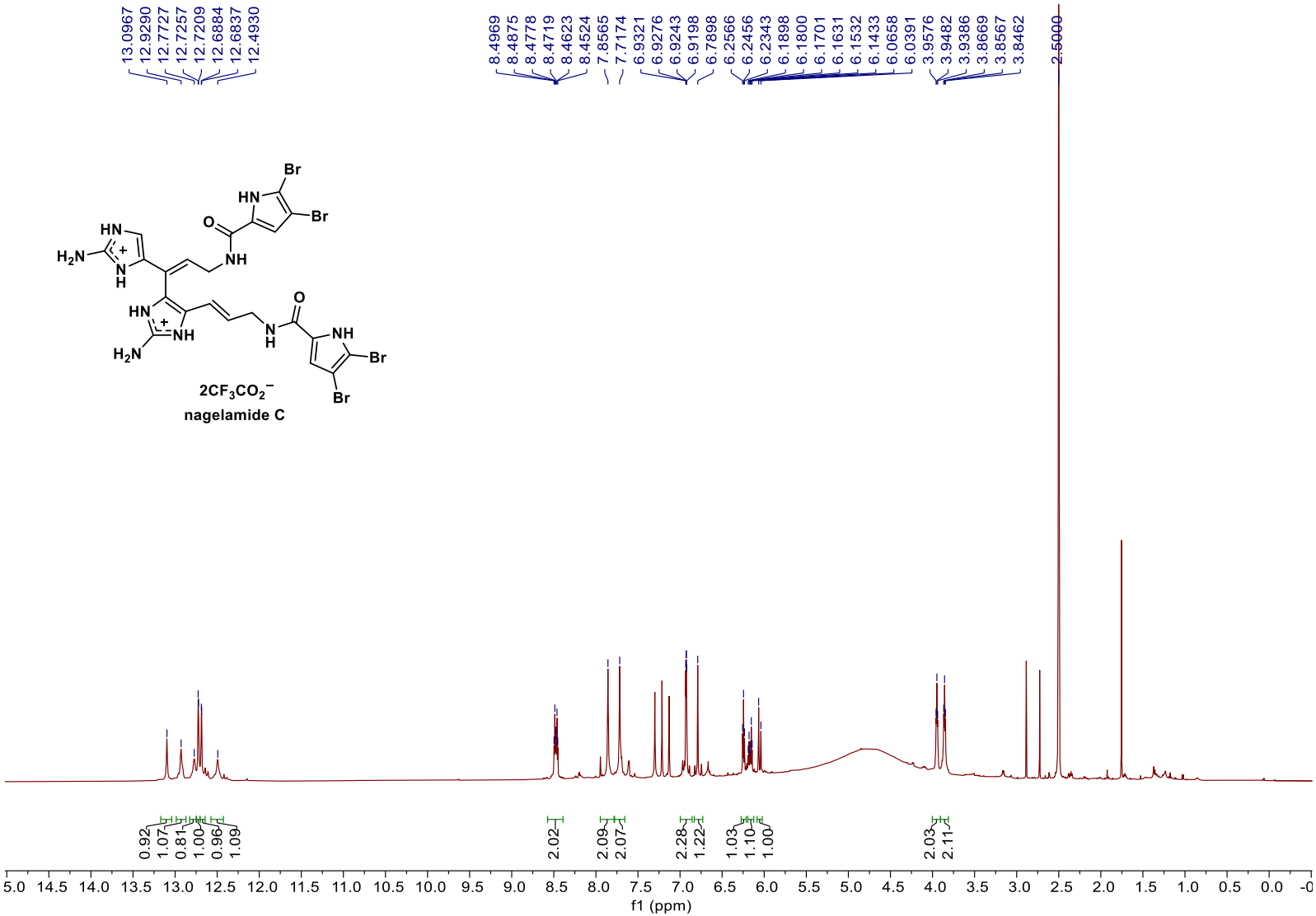
HSQC, 600 MHz, $CDCl_3$



HMBC, 600 MHz, $CDCl_3$



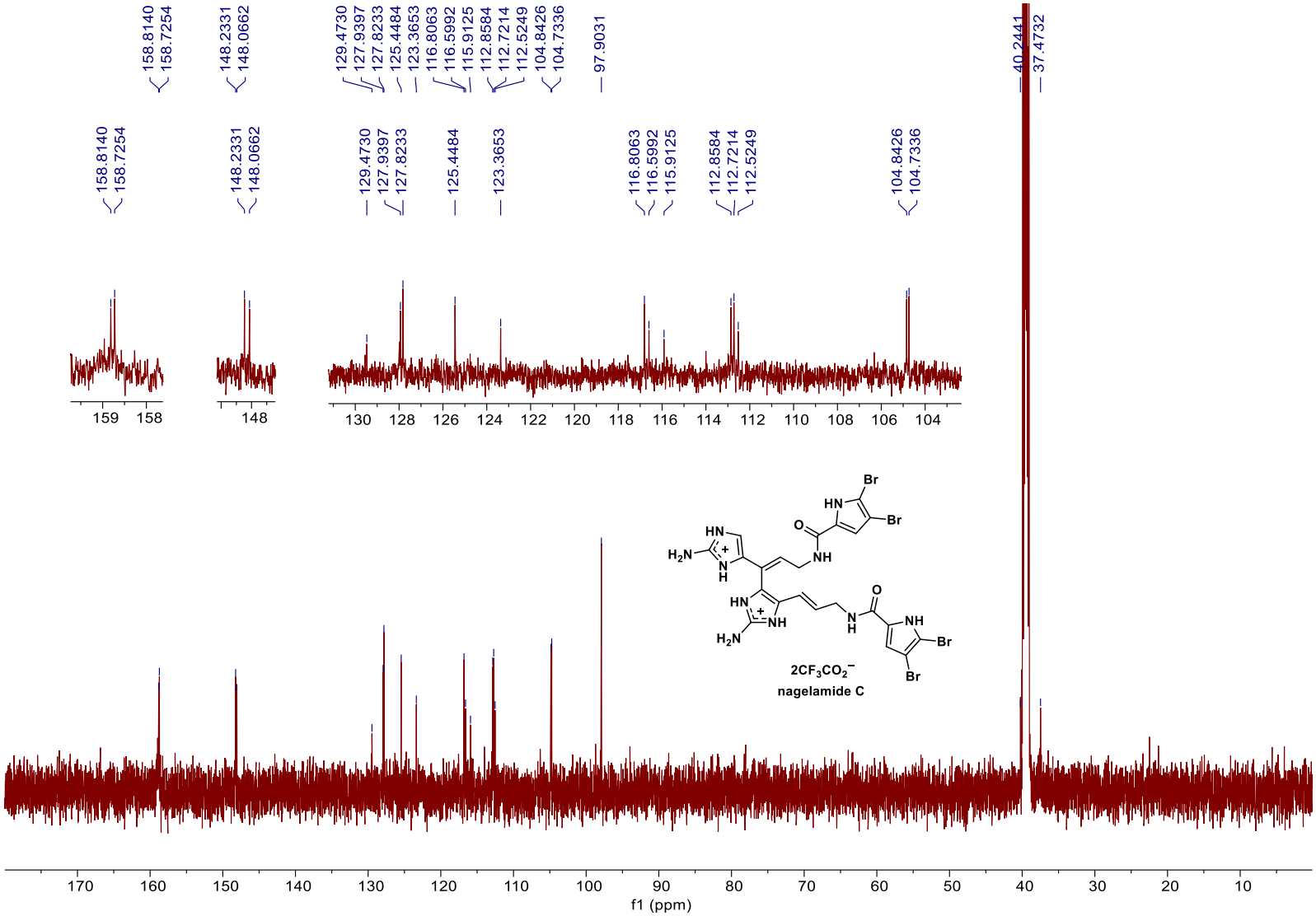
NOESY, 600 MHz, $CDCl_3$



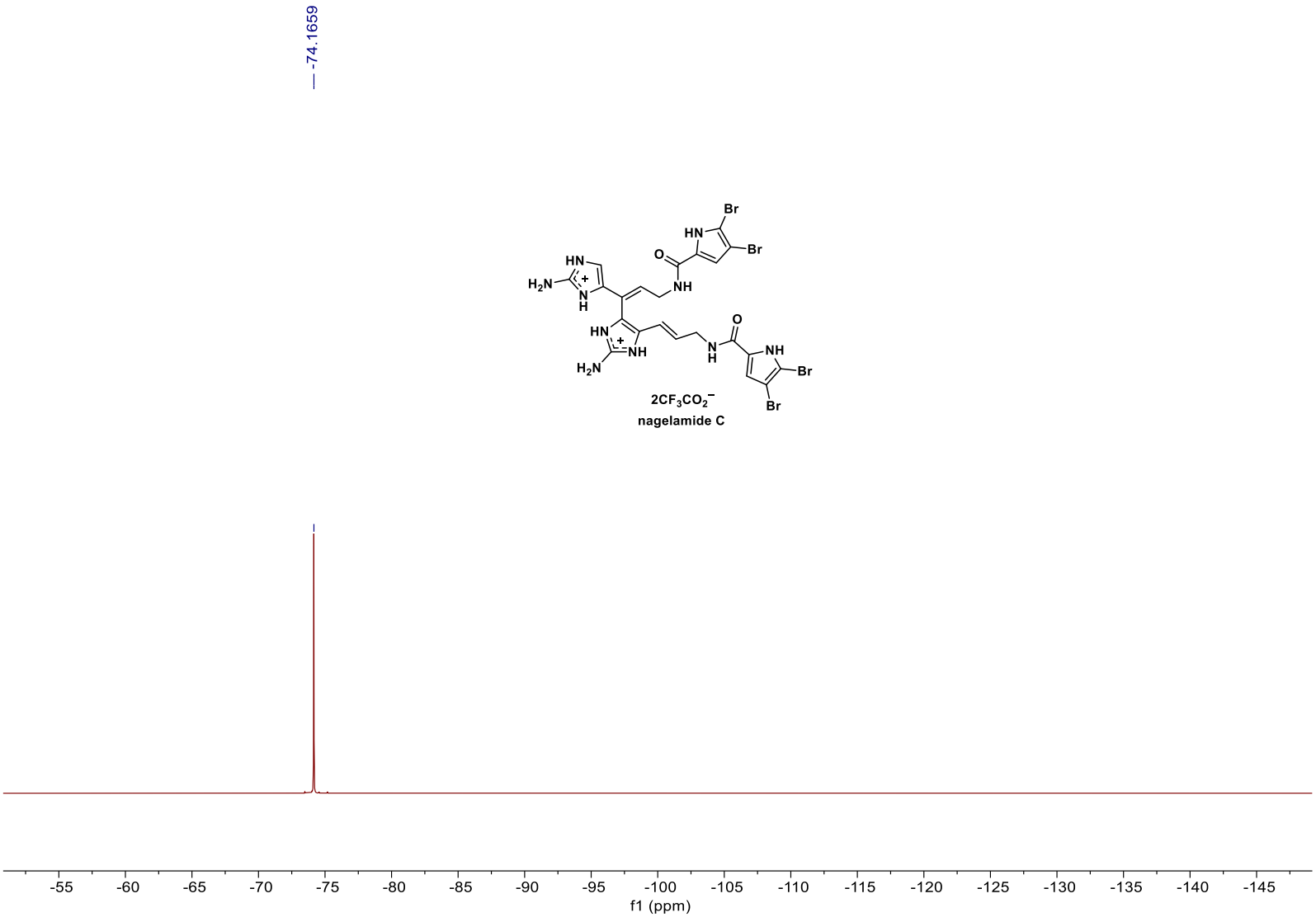
$2CF_3CO_2^-$

nagelamide C

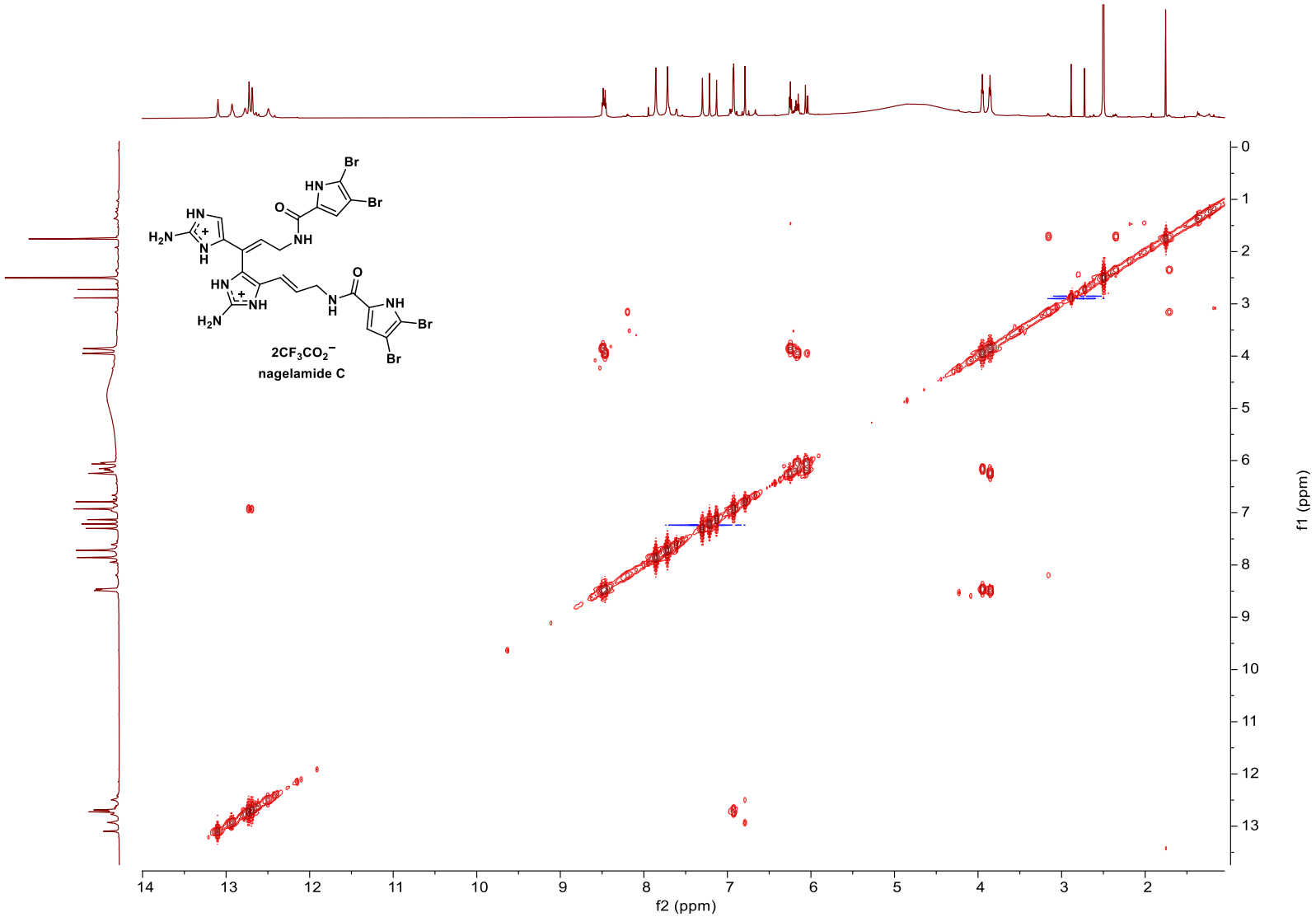
^{1}H NMR, 600 MHz, DMSO-d_6



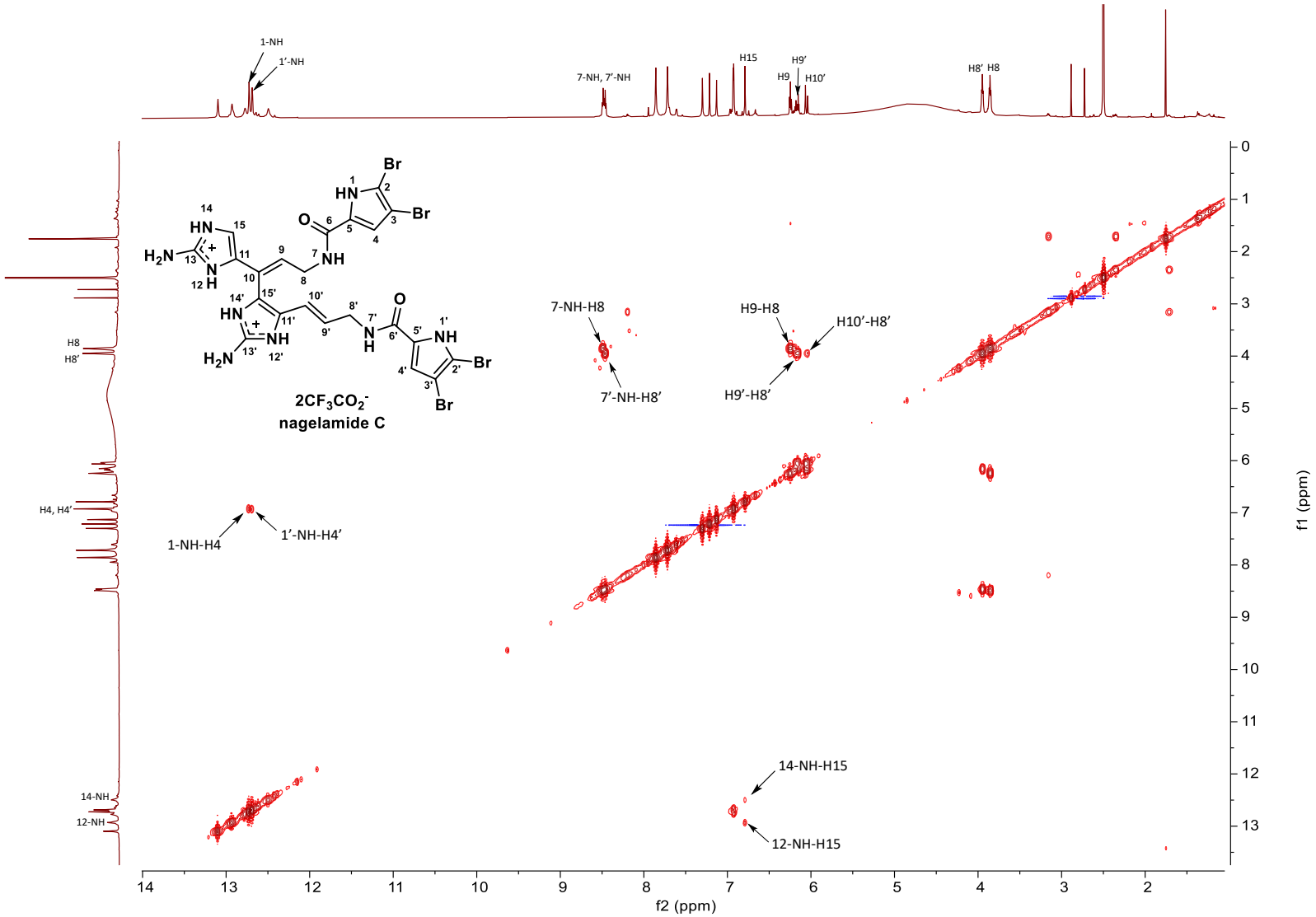
^{13}C NMR, 151 MHz, DMSO-d_6



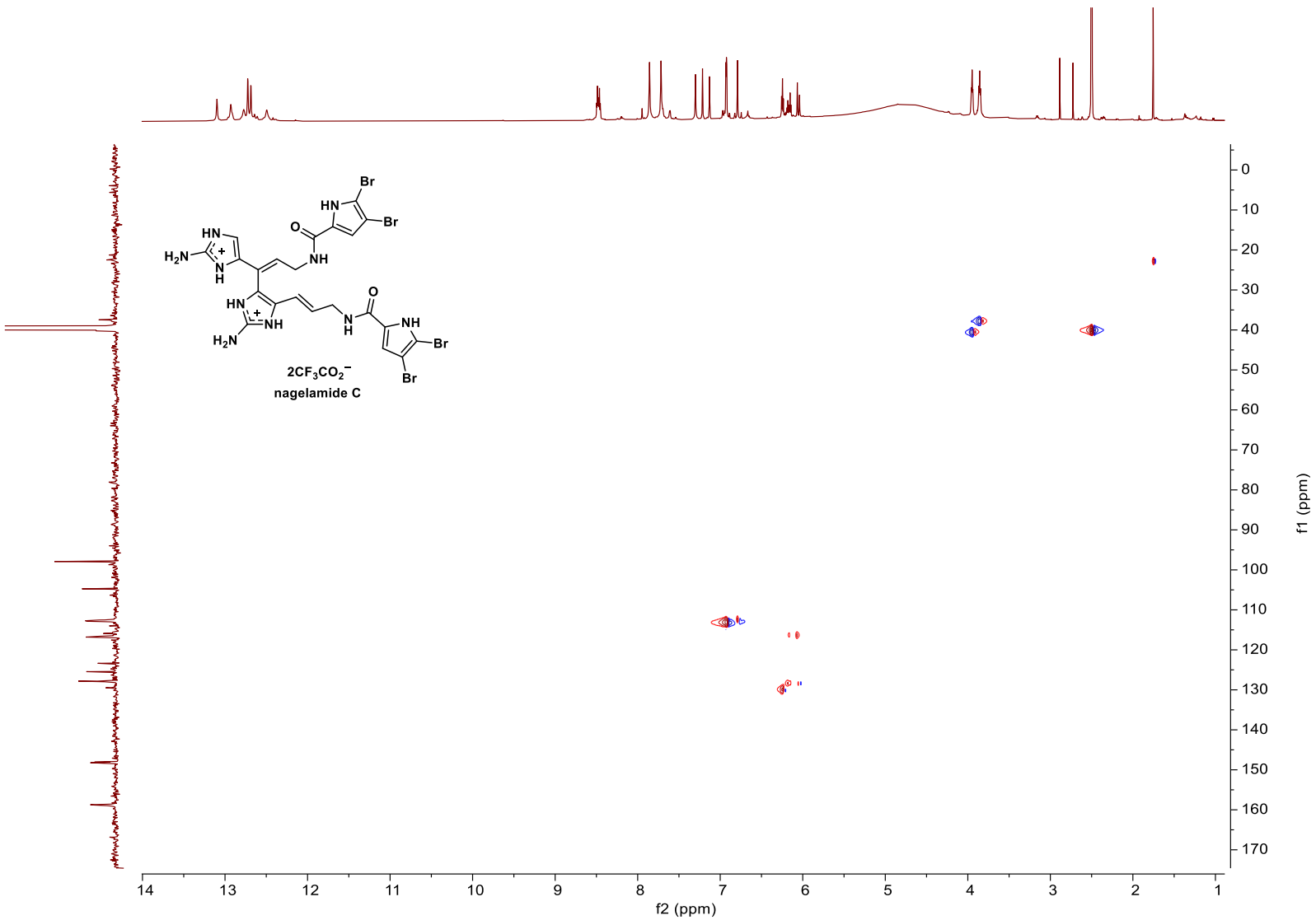
^{19}F NMR, 565 MHz, DMSO-d_6



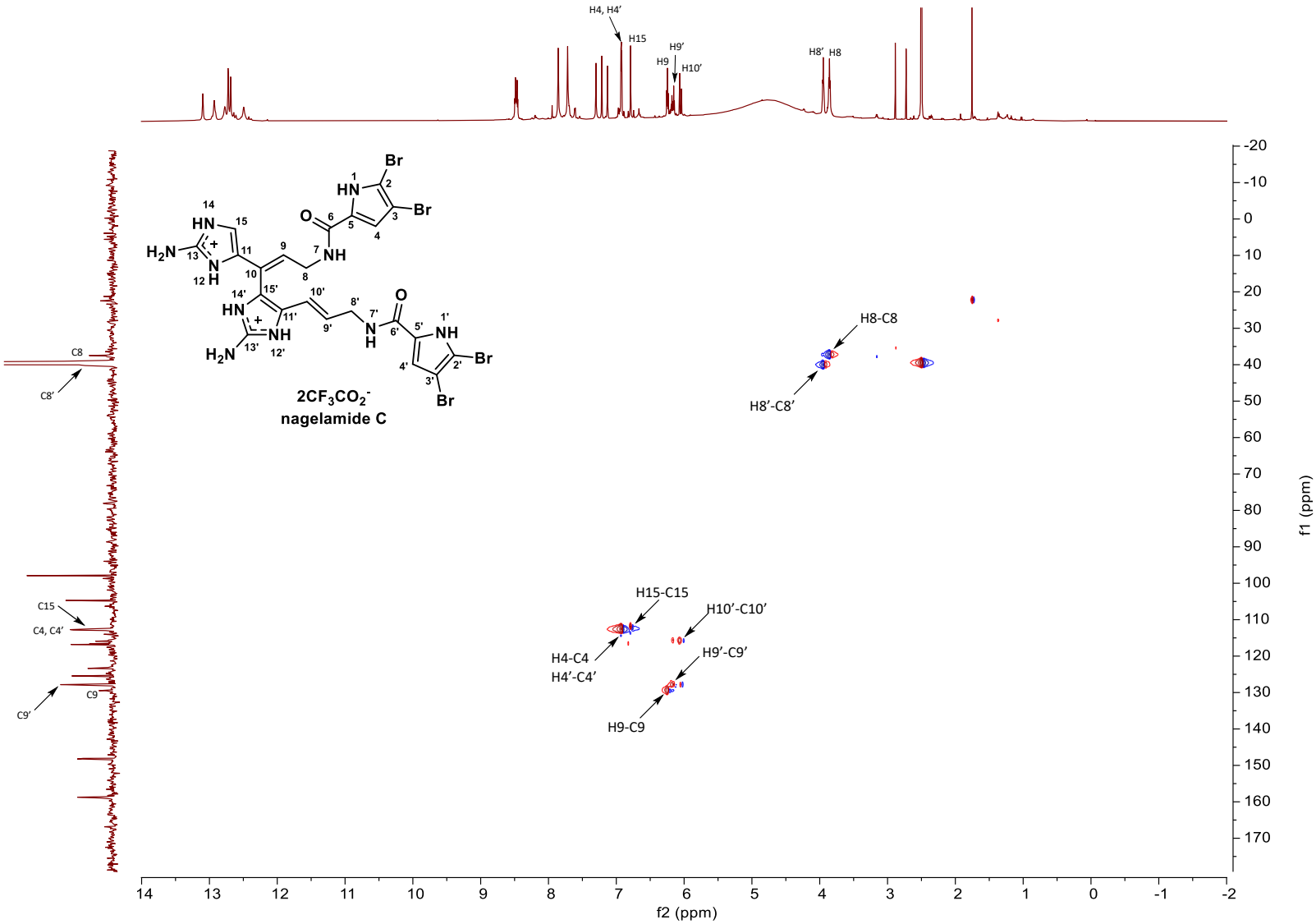
^{1}H-^{1}H COSY, 600 MHz, DMSO-d_6



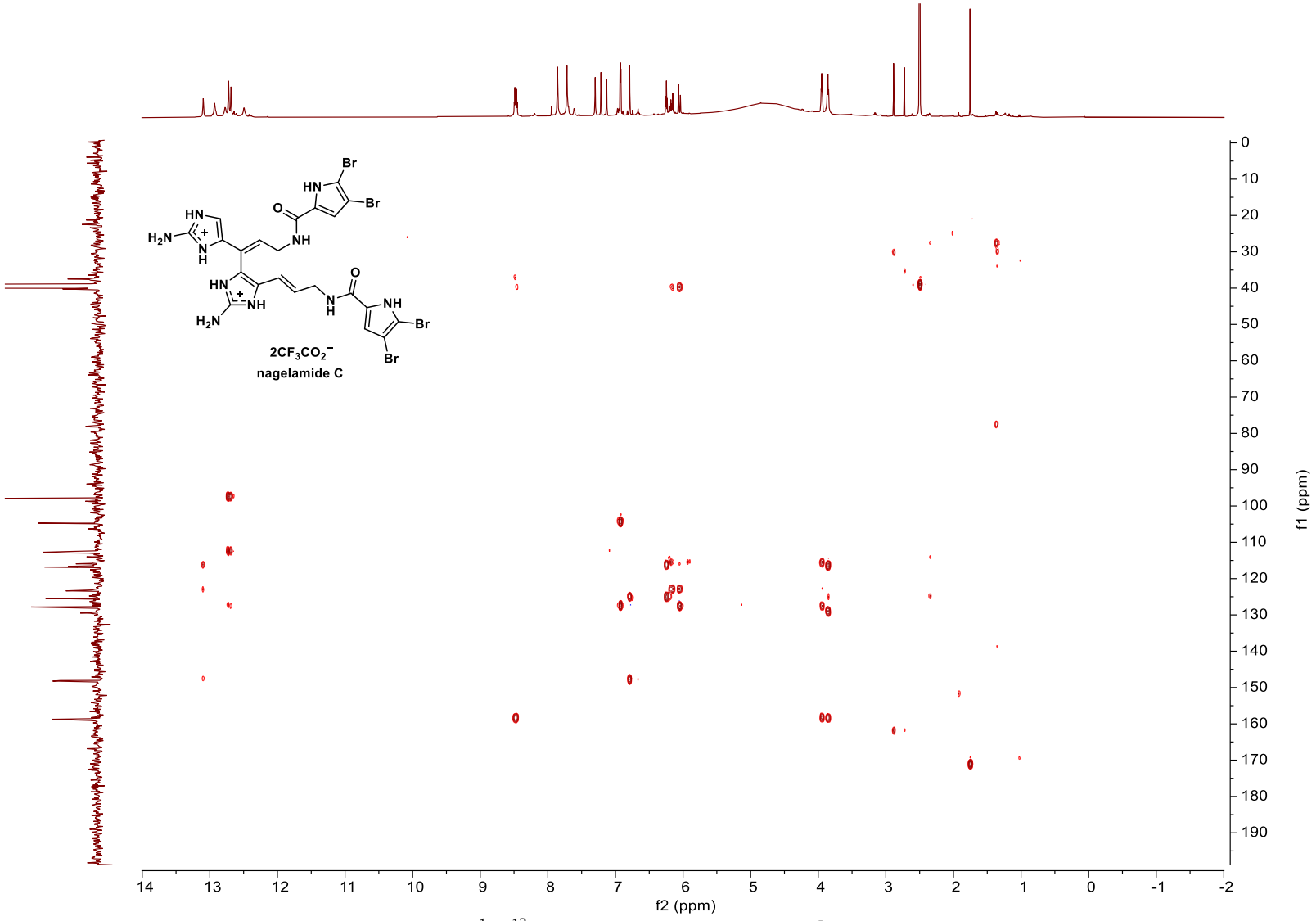
^{1}H-^{1}H COSY with annotation, 600 MHz, DMSO-d$_6$



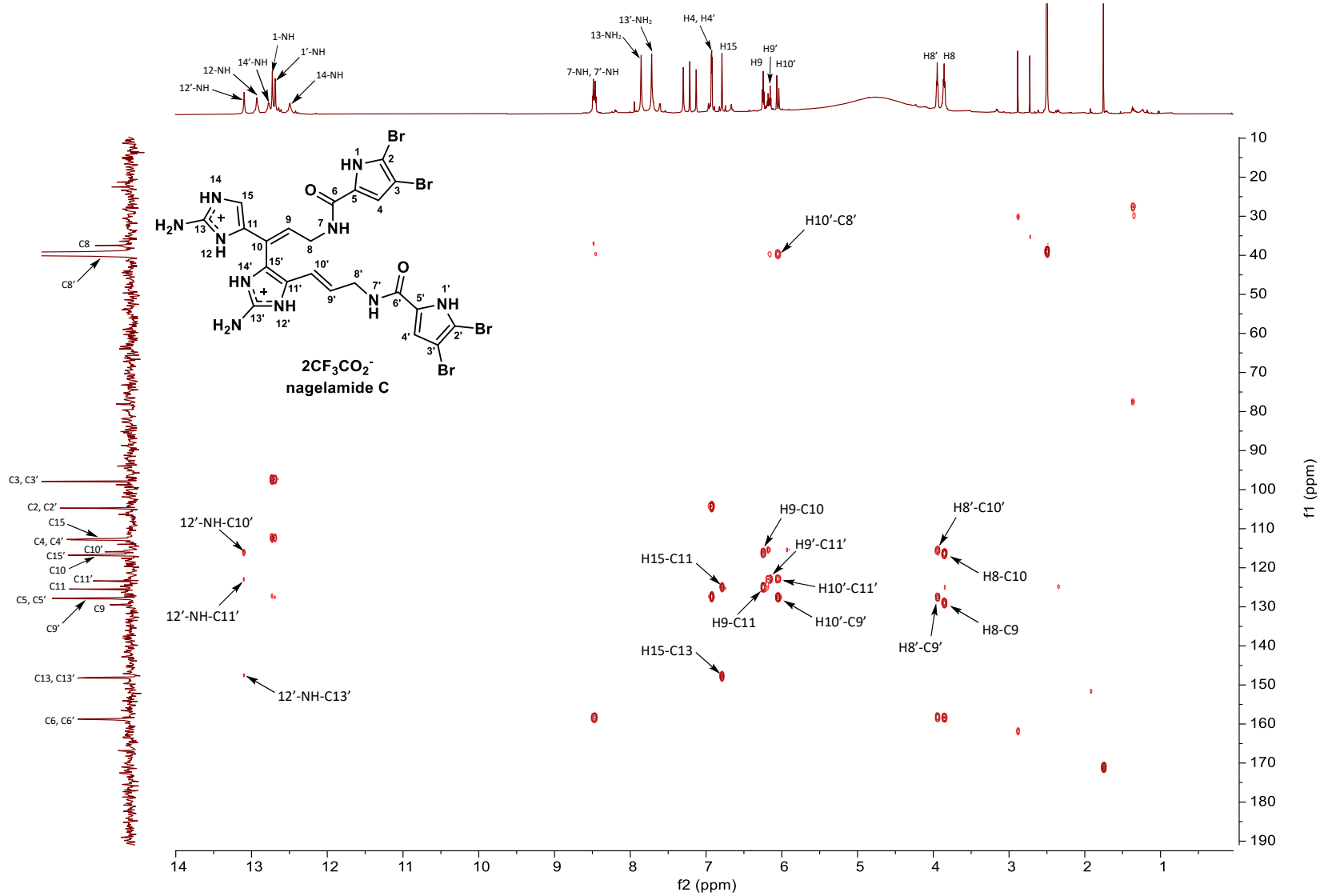
^{1}H-^{13}C HSQC, 600 MHz, DMSO-d_6



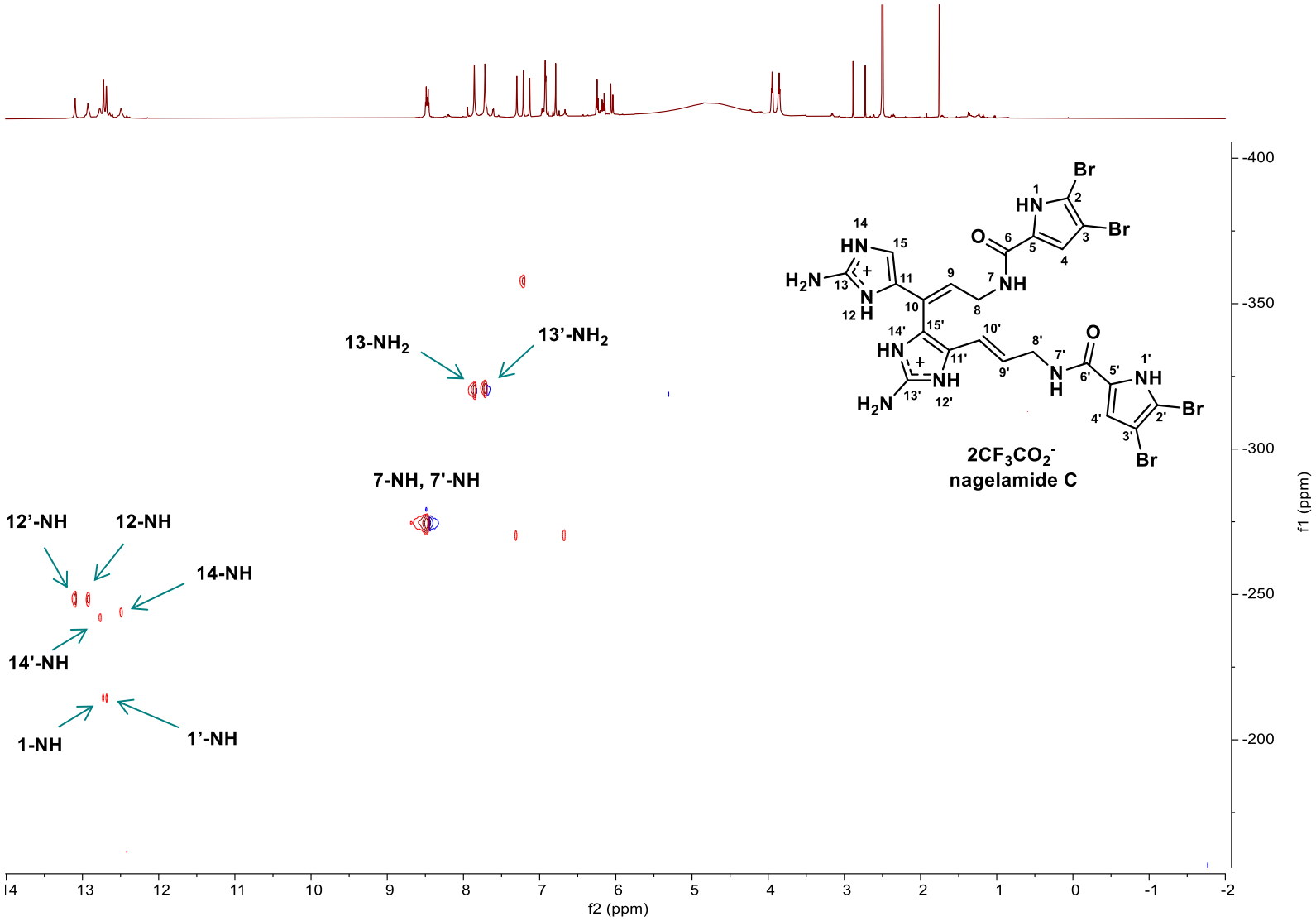
^{1}H-^{13}C HSQC with annotation, 600 MHz, DMSO-d_6



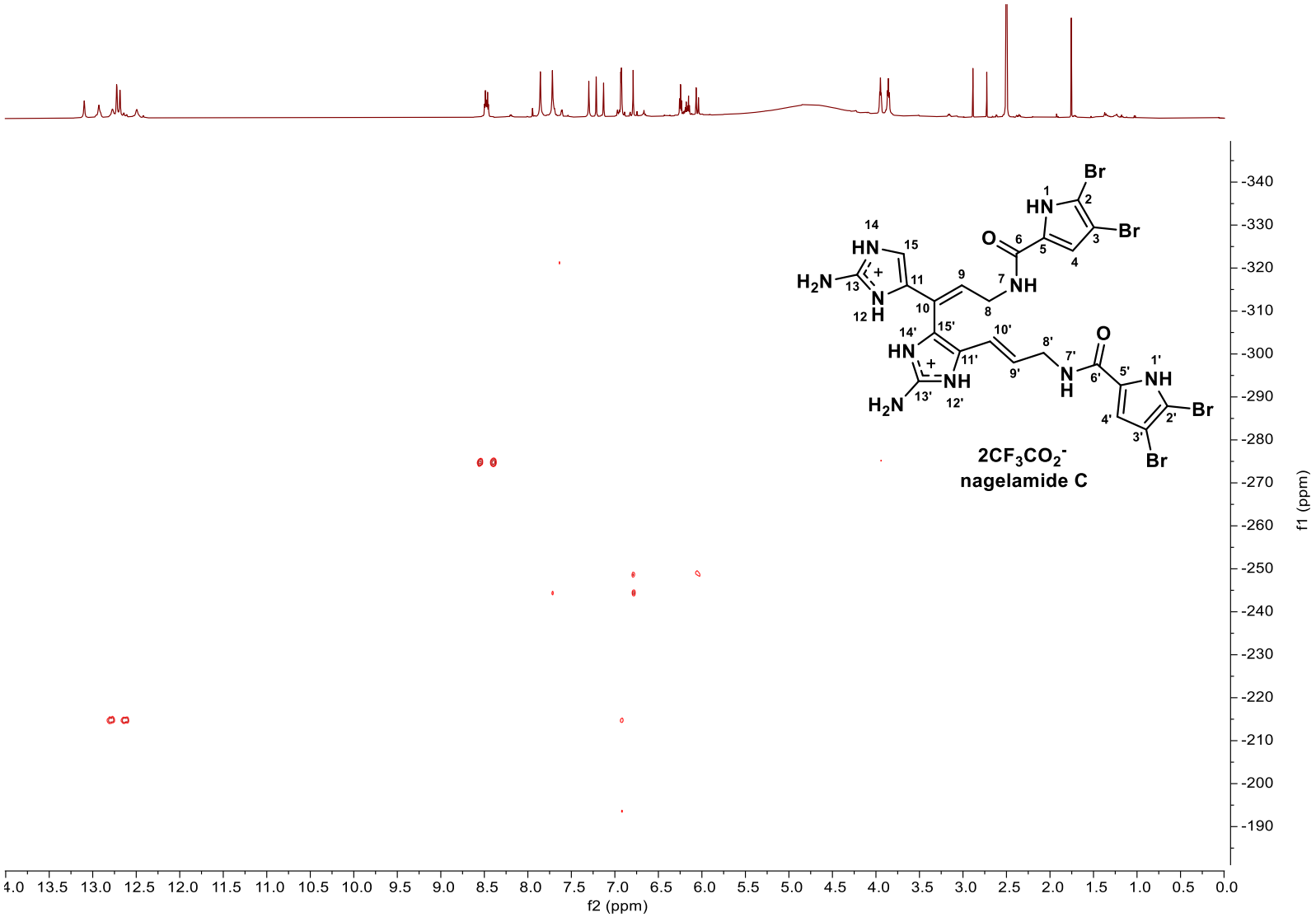
^{1}H-^{13}C HMBC, 600 MHz, DMSO-d_6



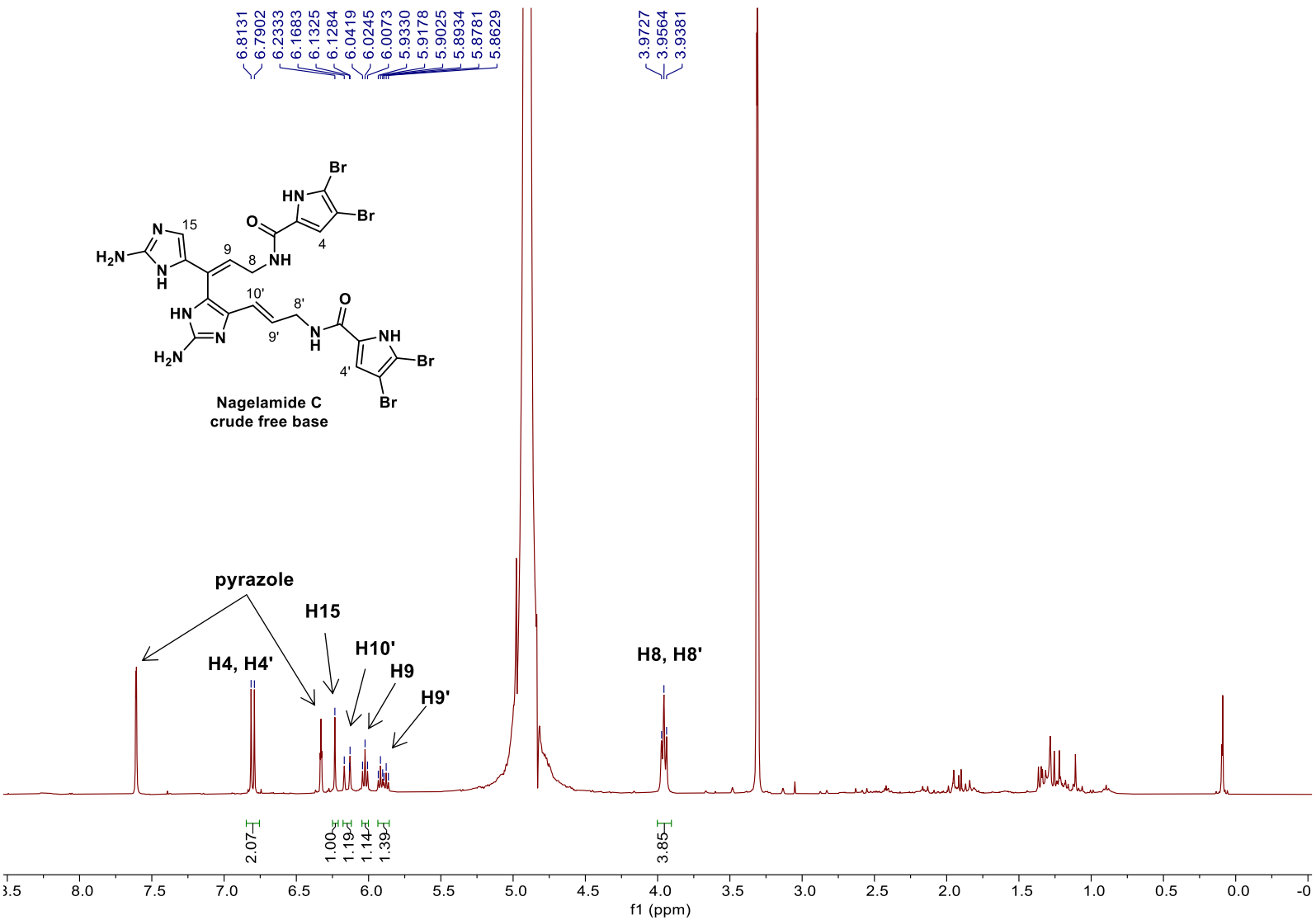
^{1}H-^{13}C HMBC with annotation, 600 MHz, DMSO-d$_6$



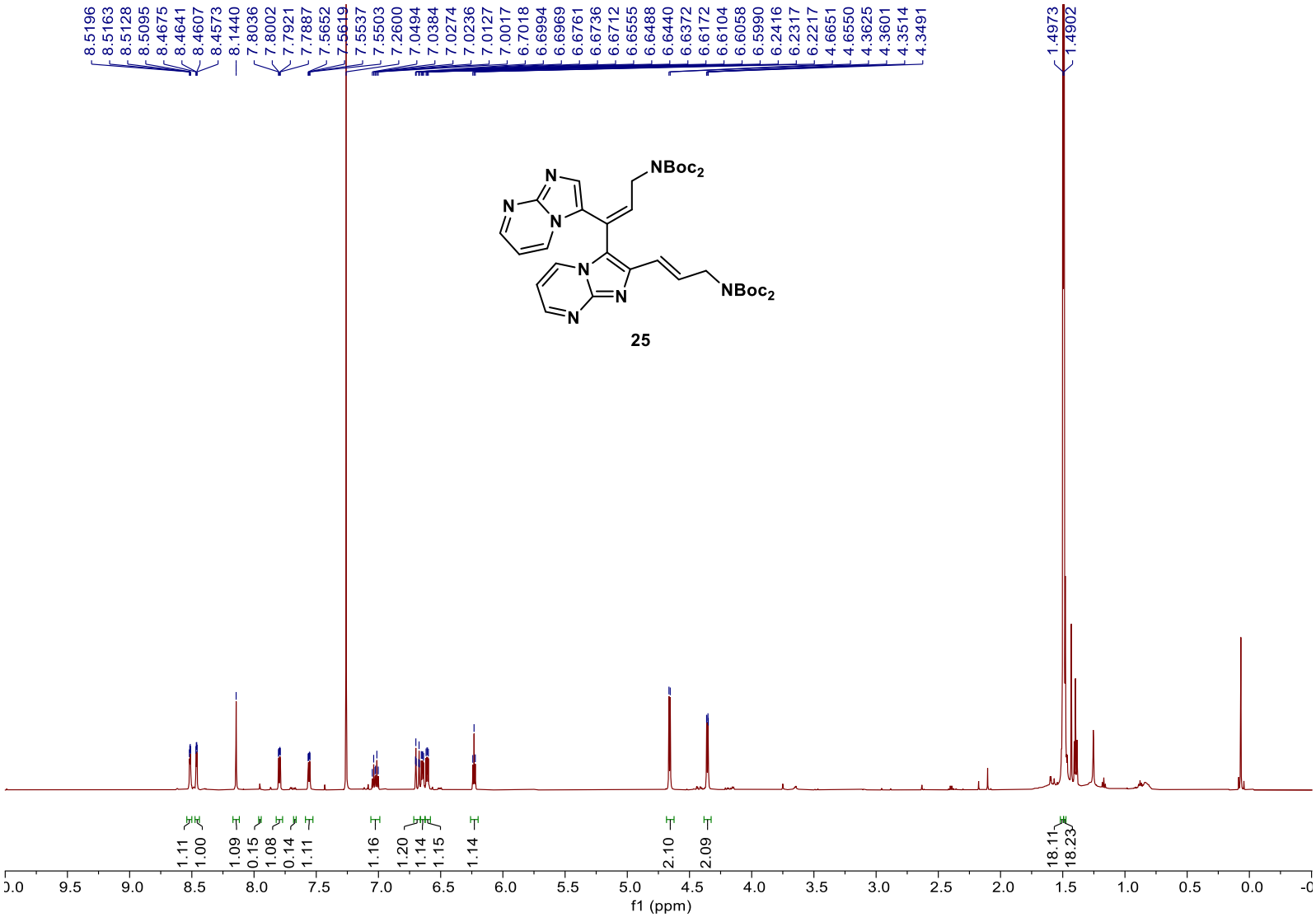
^{1}H-^{15}N-HSQC, 600 MHz, DMSO-d_6



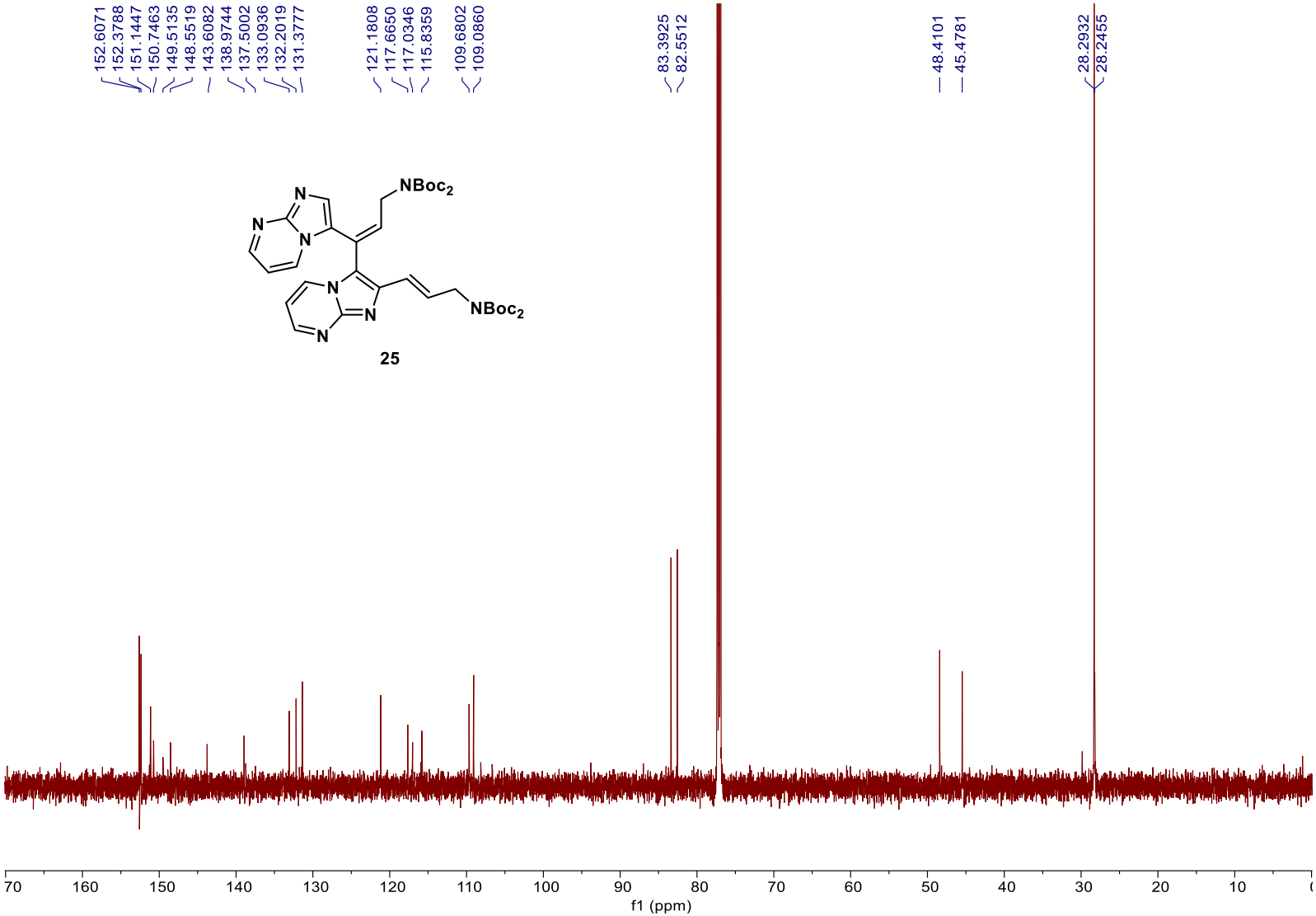
^{1}H-^{15}N-HMBC, 600 MHz, DMSO-d_6



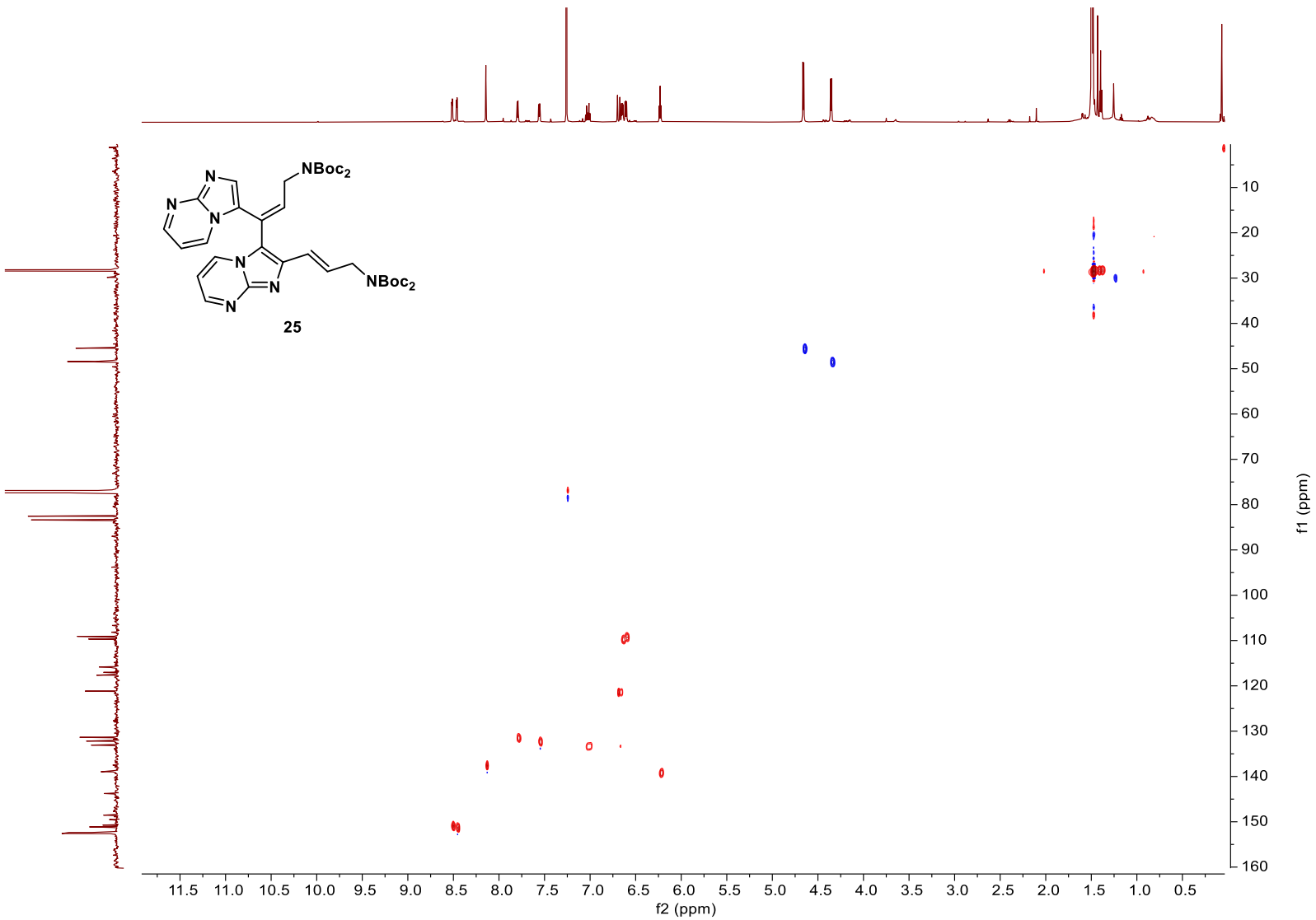
^{1}H NMR, 600 MHz, CD_3OD



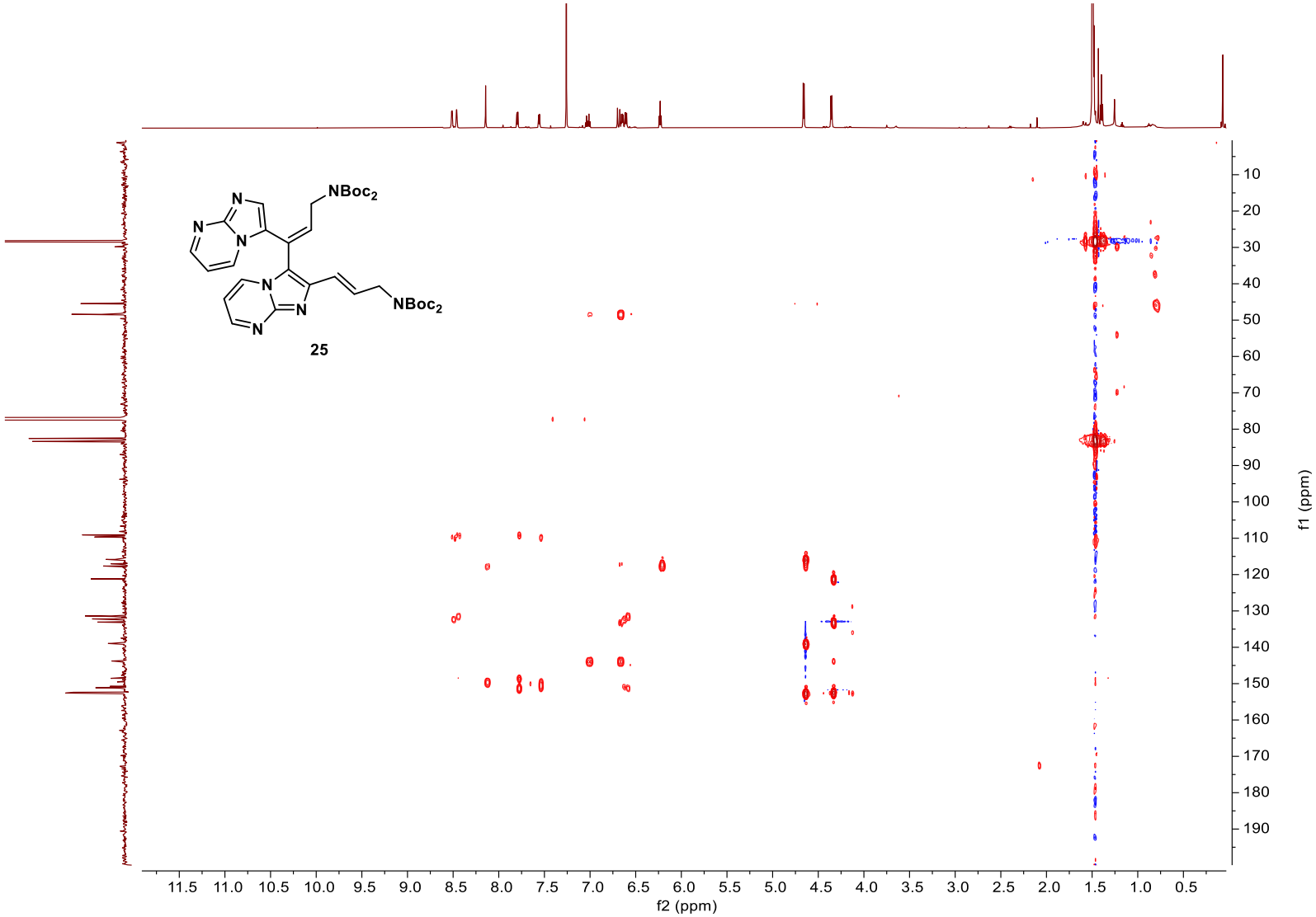
^{1}H NMR, 600 MHz, $CDCl_3$



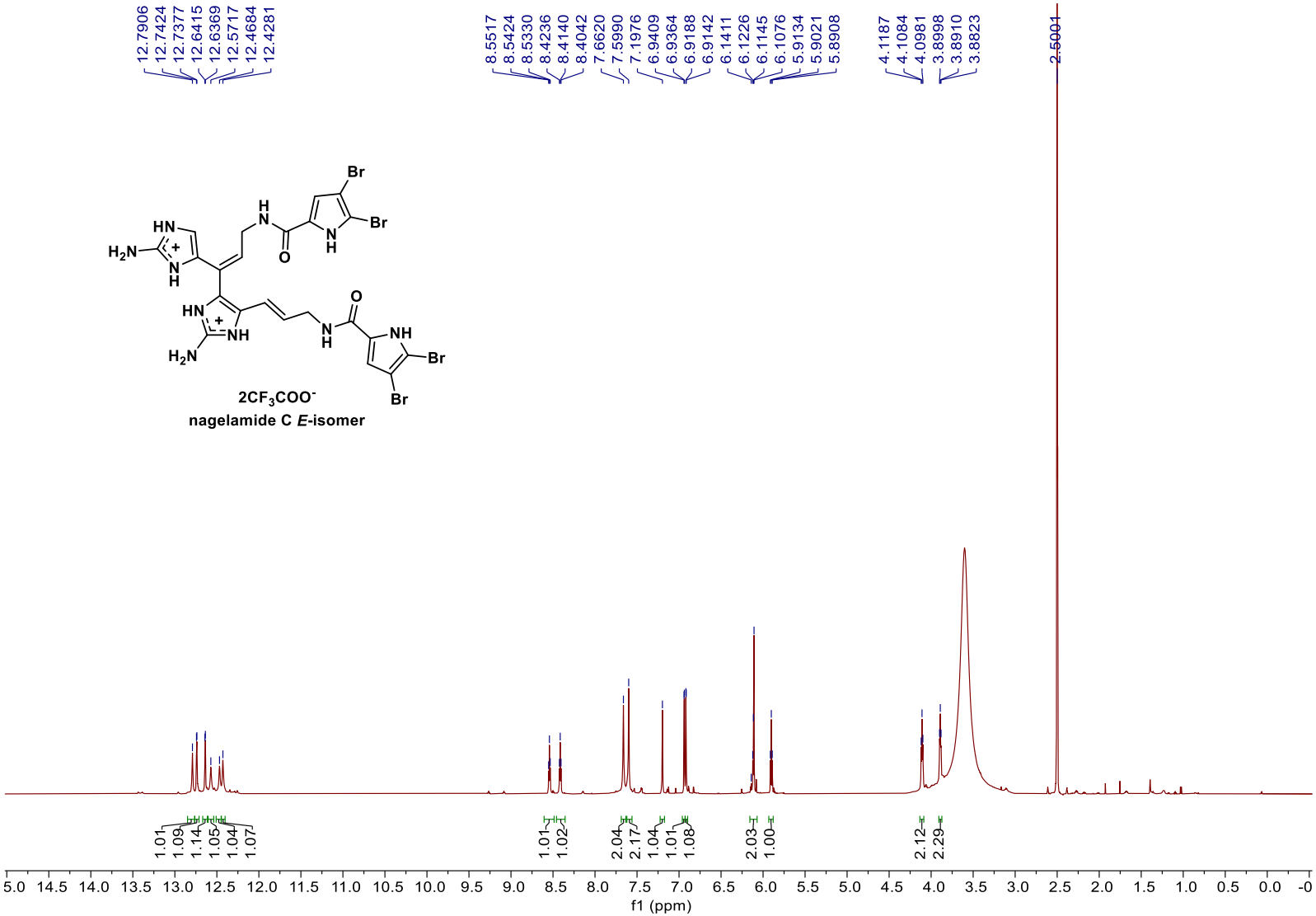
^{13}C NMR, 151 MHz, $CDCl_3$



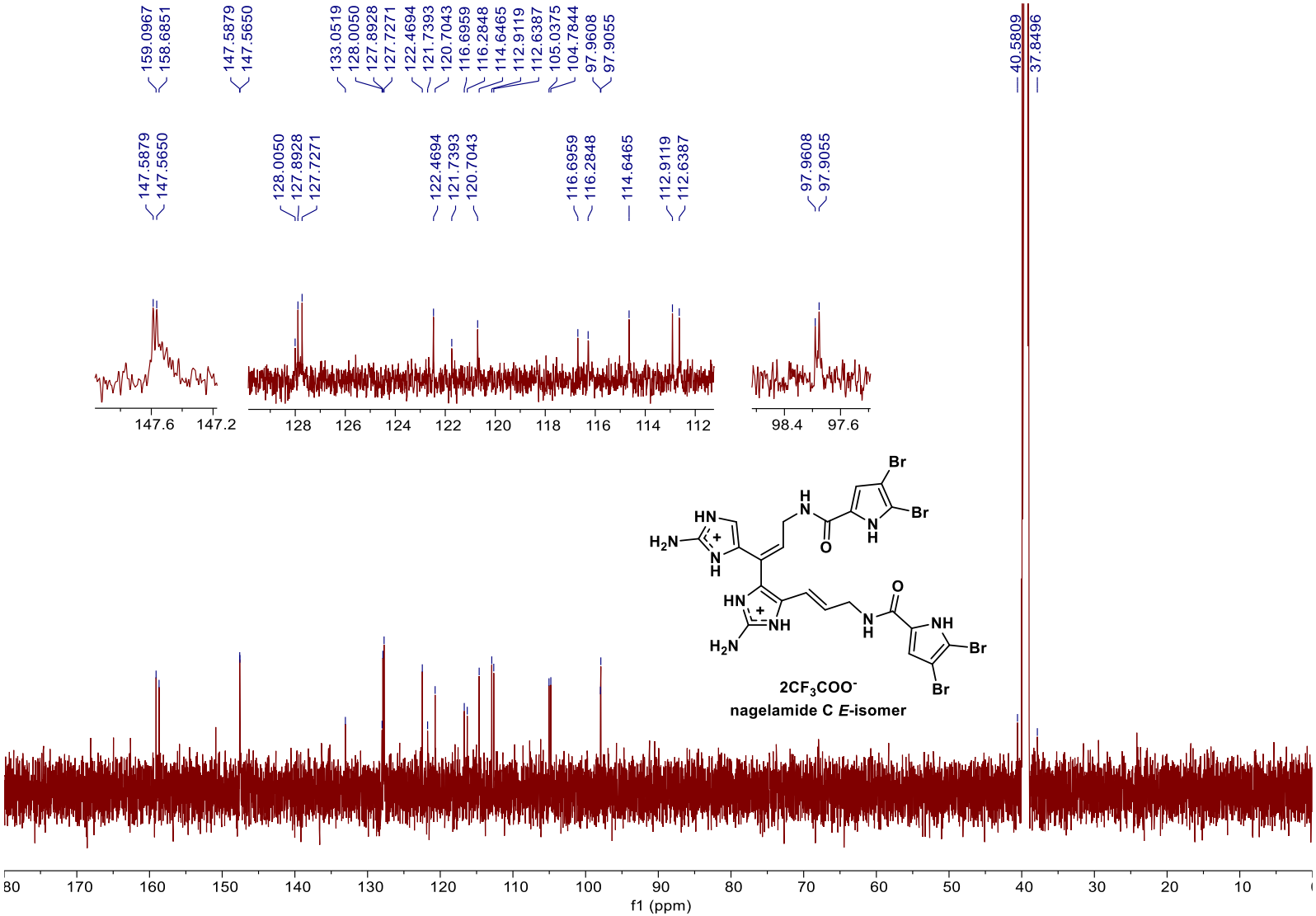
HSQC, 600 MHz, $CDCl_3$



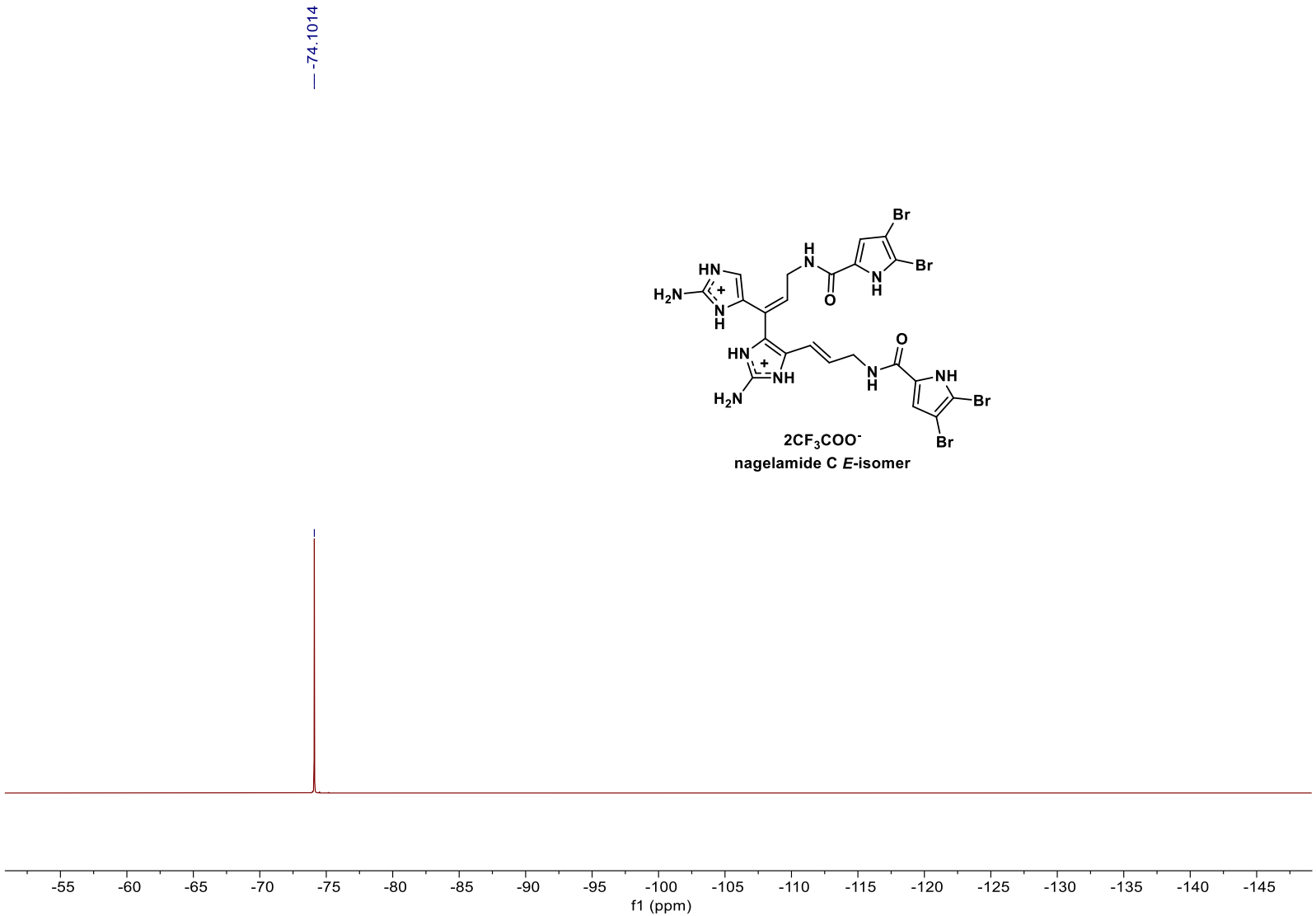
HMBC, 600 MHz, $CDCl_3$



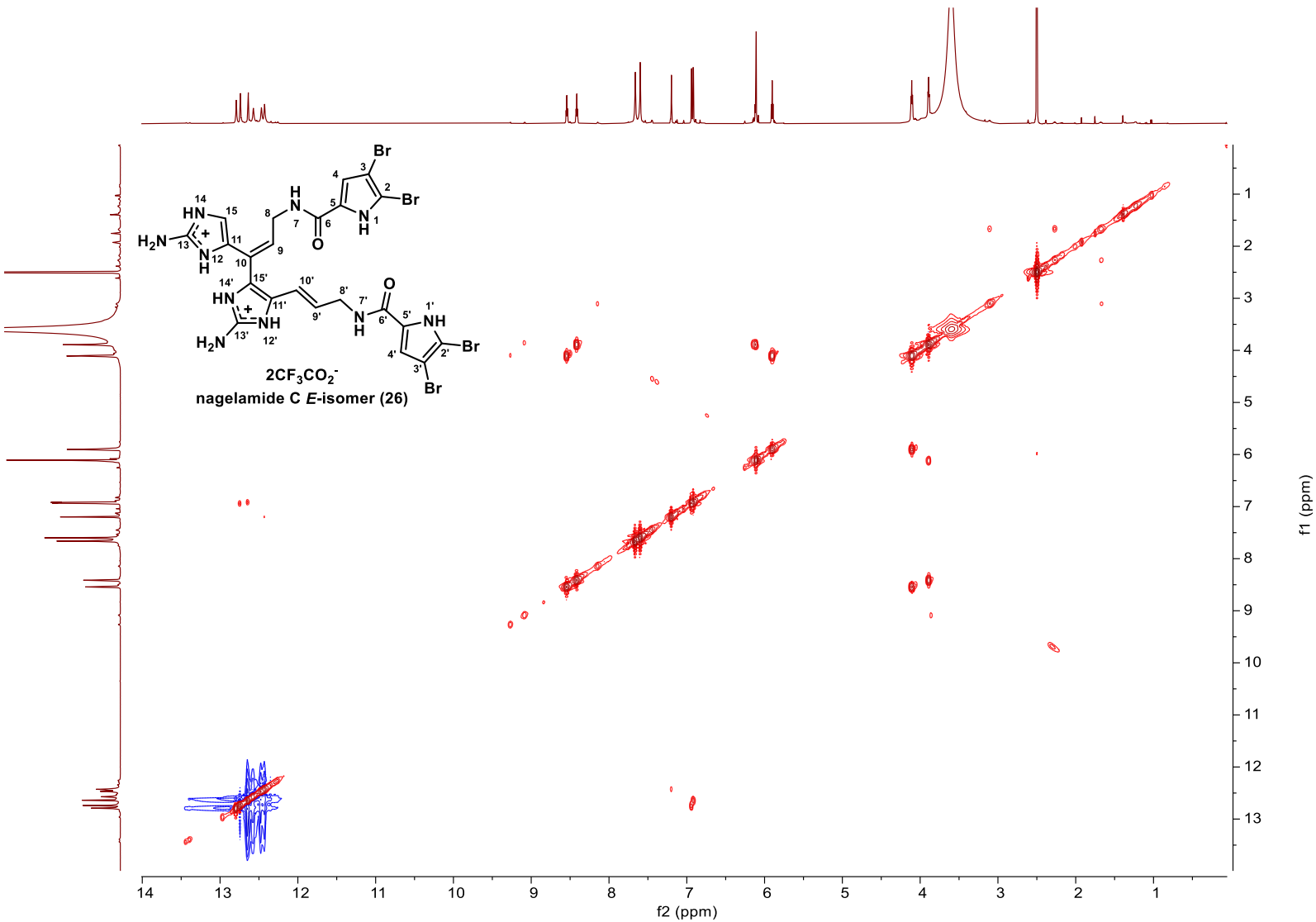
^{1}H NMR, 600 MHz, DMSO-d_6



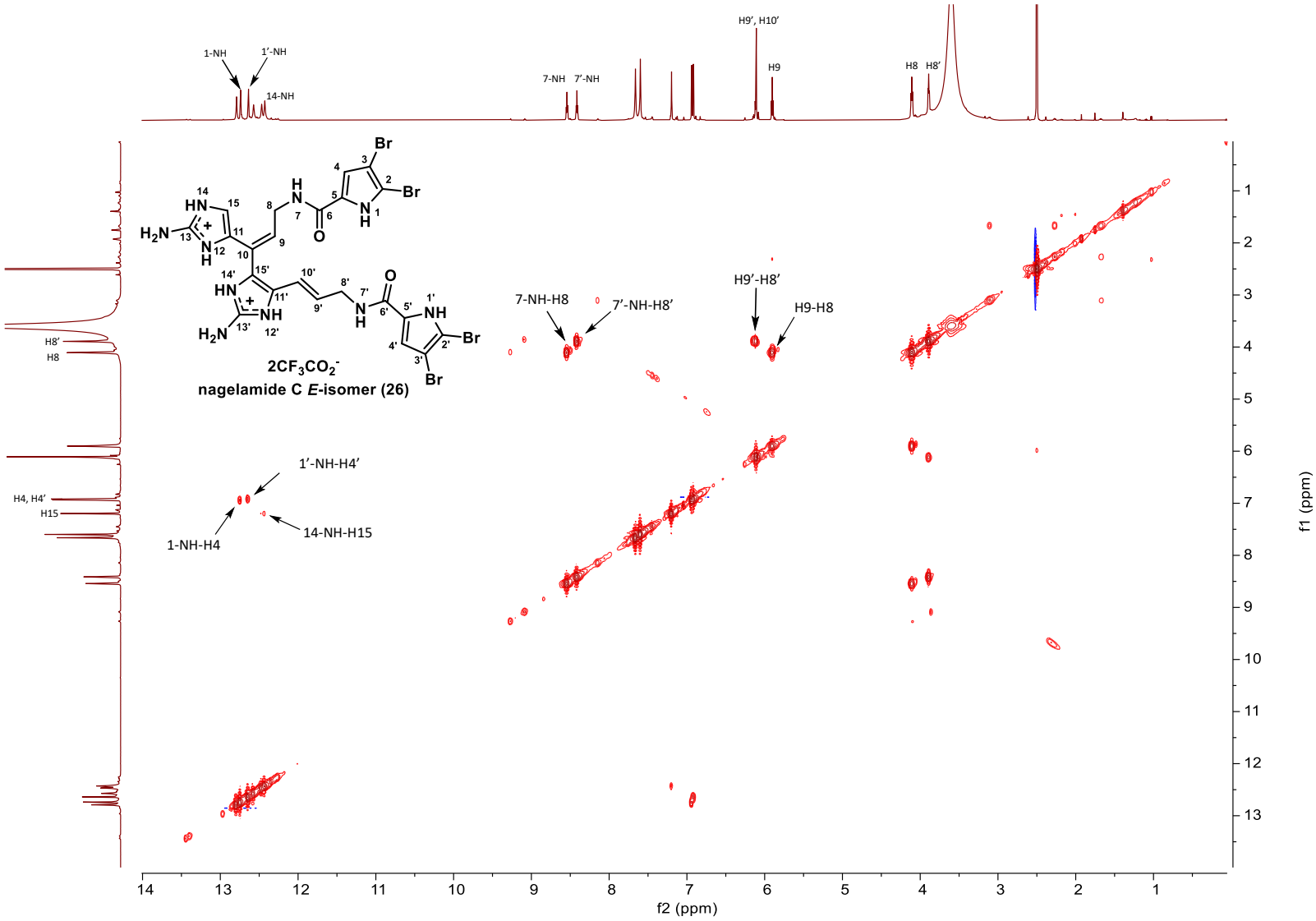
^{13}C NMR, 151 MHz, DMSO-d_6



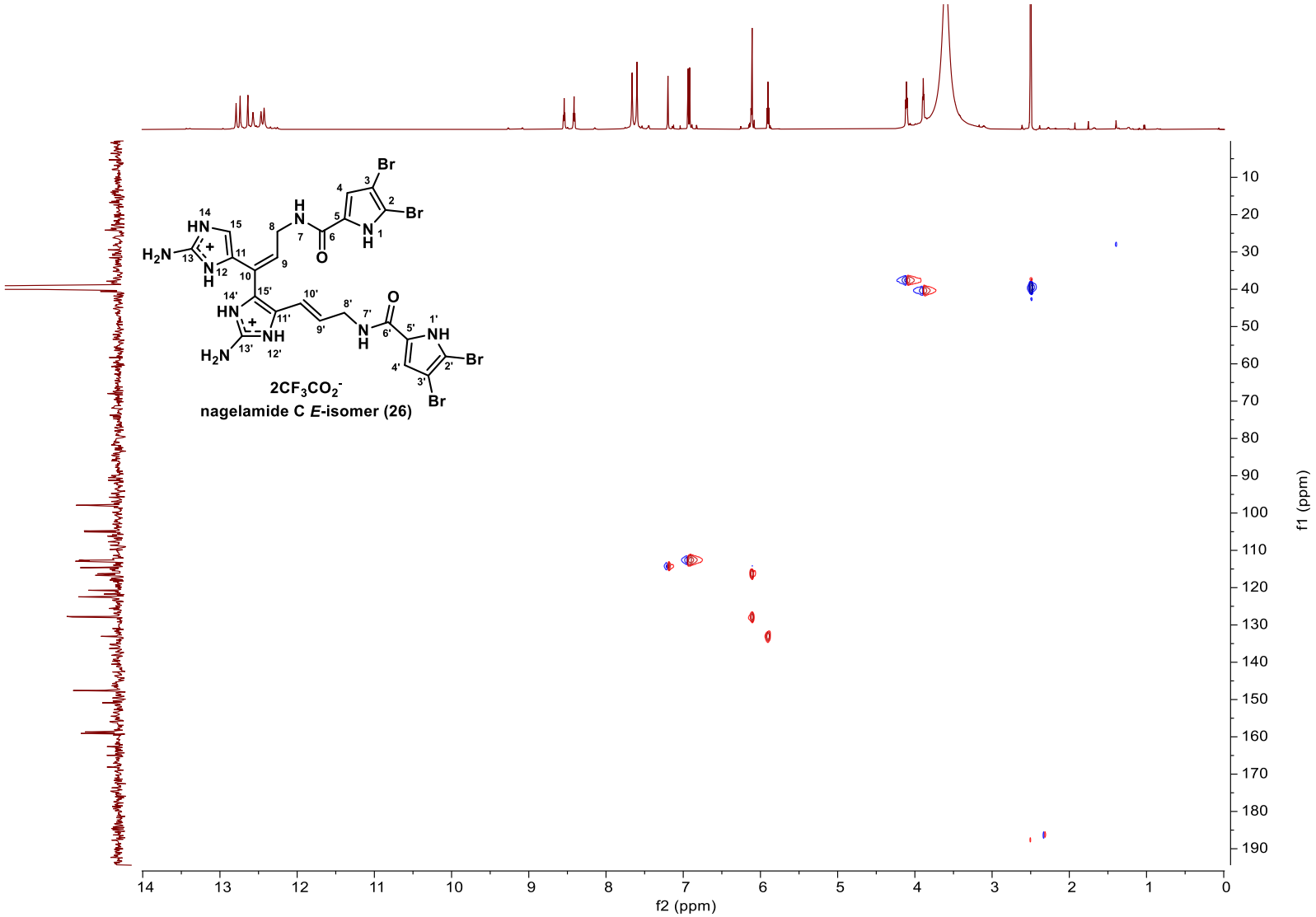
^{19}F NMR, 565 MHz, DMSO-d_6



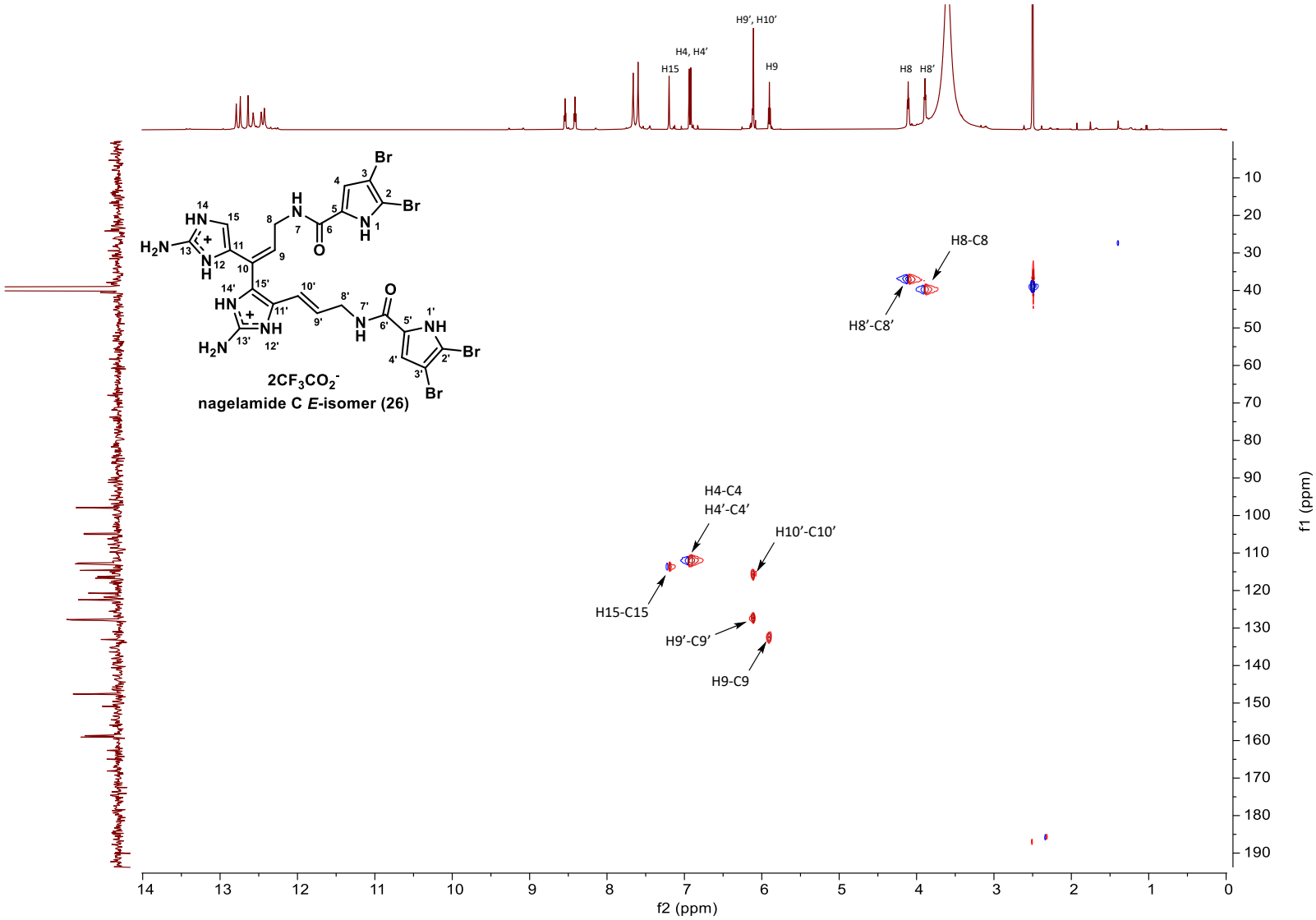
^{1}H-^{1}H COSY, 600 MHz, DMSO-d$_6$



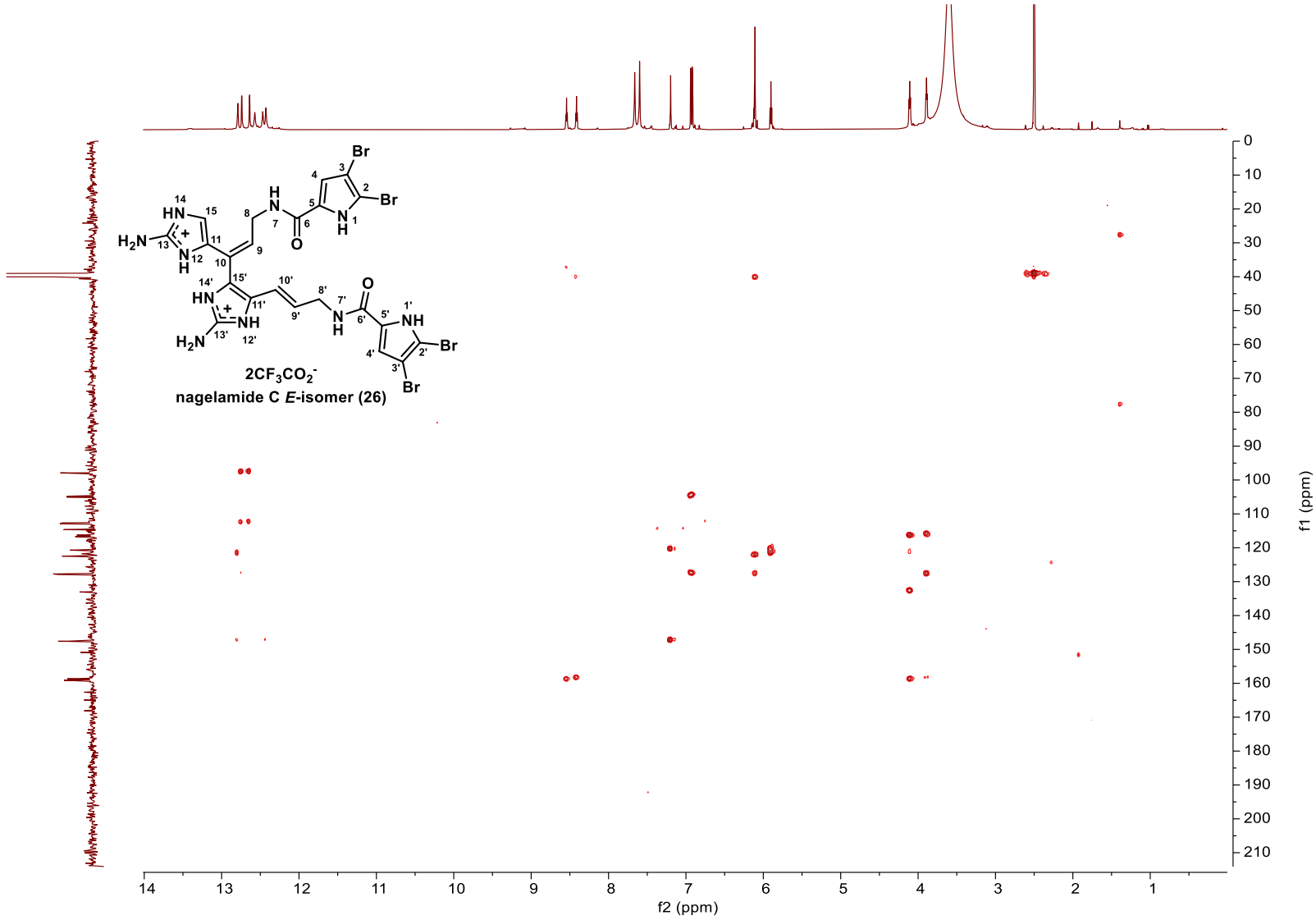
^{1}H-^{1}H COSY with annotation, 600 MHz, DMSO-d$_6$



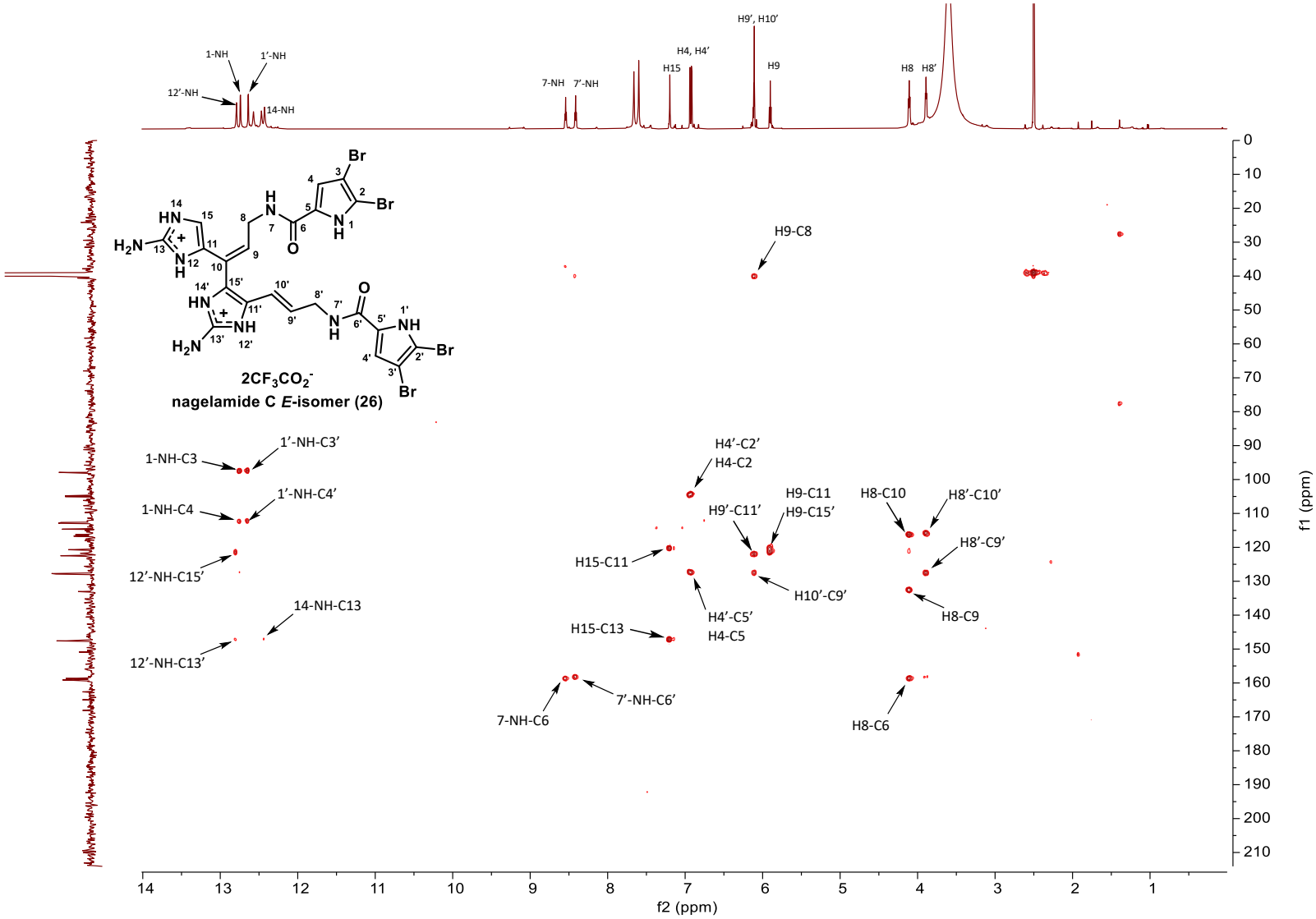
^{1}H-^{13}C HSQC, 600 MHz, DMSO-d_6



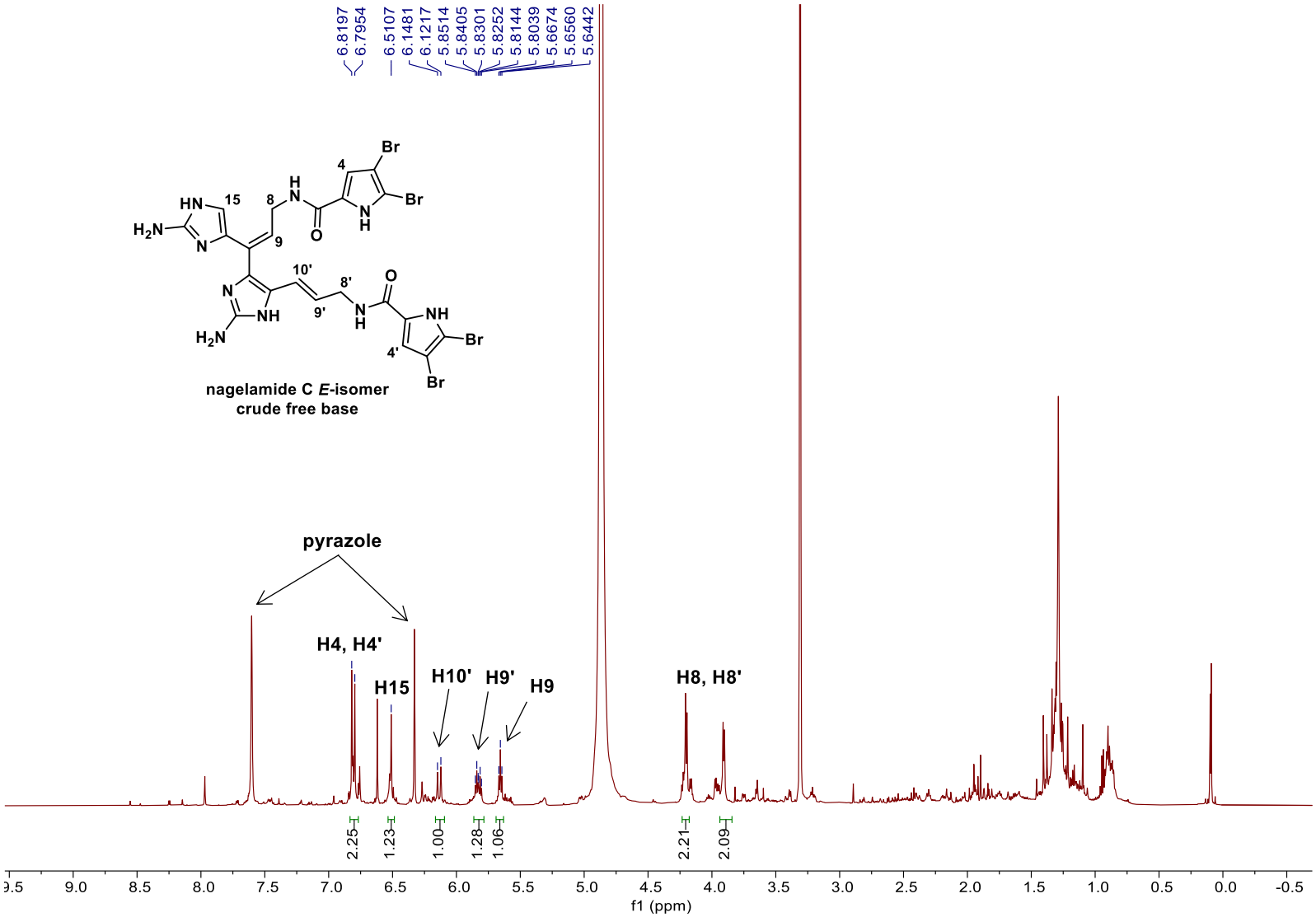
^{1}H-^{13}C HSQC with annotation, 600 MHz, DMSO-d_6



^{1}H-^{13}C HMBC, 600 MHz, DMSO-d_6



^{1}H-^{13}C HMBC with annotation, 600 MHz, DMSO-d$_6$



^{1}H NMR, 600 MHz, CD_3OD

6. References

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