Supporting Information

1,3-Dipolar cycloaddition of nitrile oxides and nitrilimines to (−)-β-caryophyllene: stereoselective synthesis of polycyclic derivatives and their biological testing

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NMR spectra of compounds 9, 14, 16-33.

Figure S1. ¹H NMR spectra of compound **9.**

Figure S2. ¹³C NMR spectra of compound **9.**

Figure S3. ^{1}H NMR spectra of compound **14.**
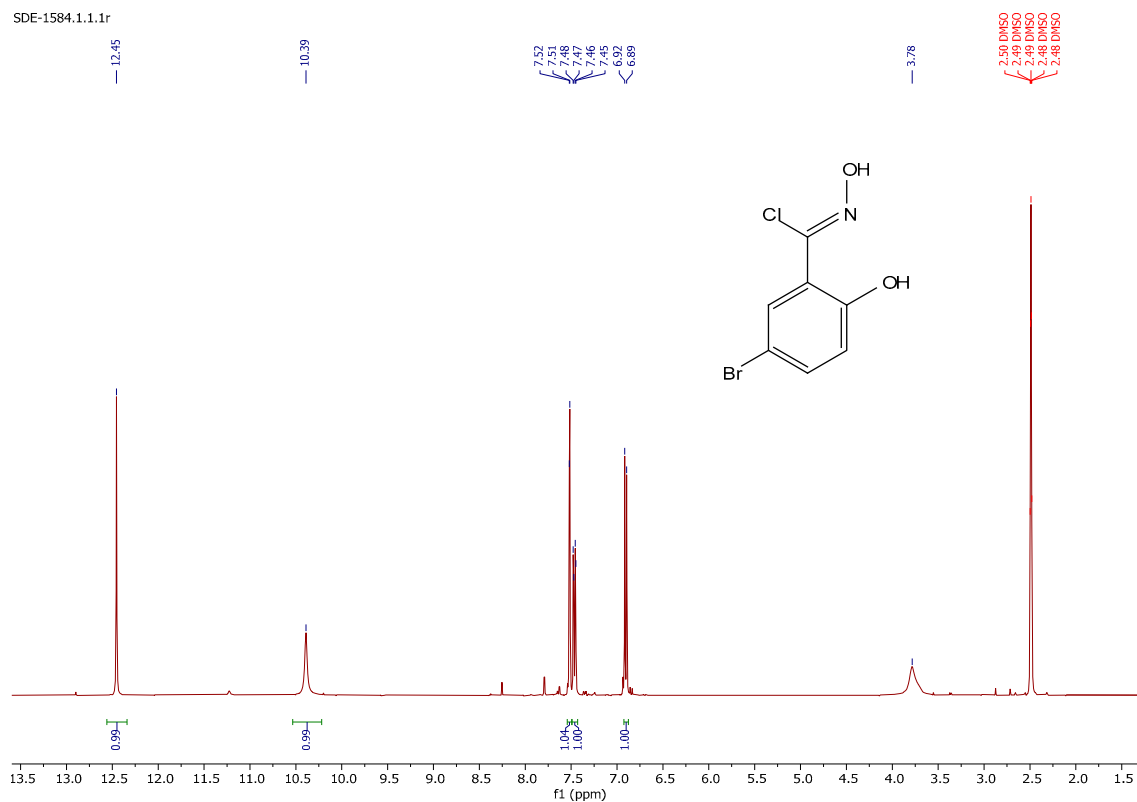

Figure S4. ^{13}C NMR spectra of compound **14.**
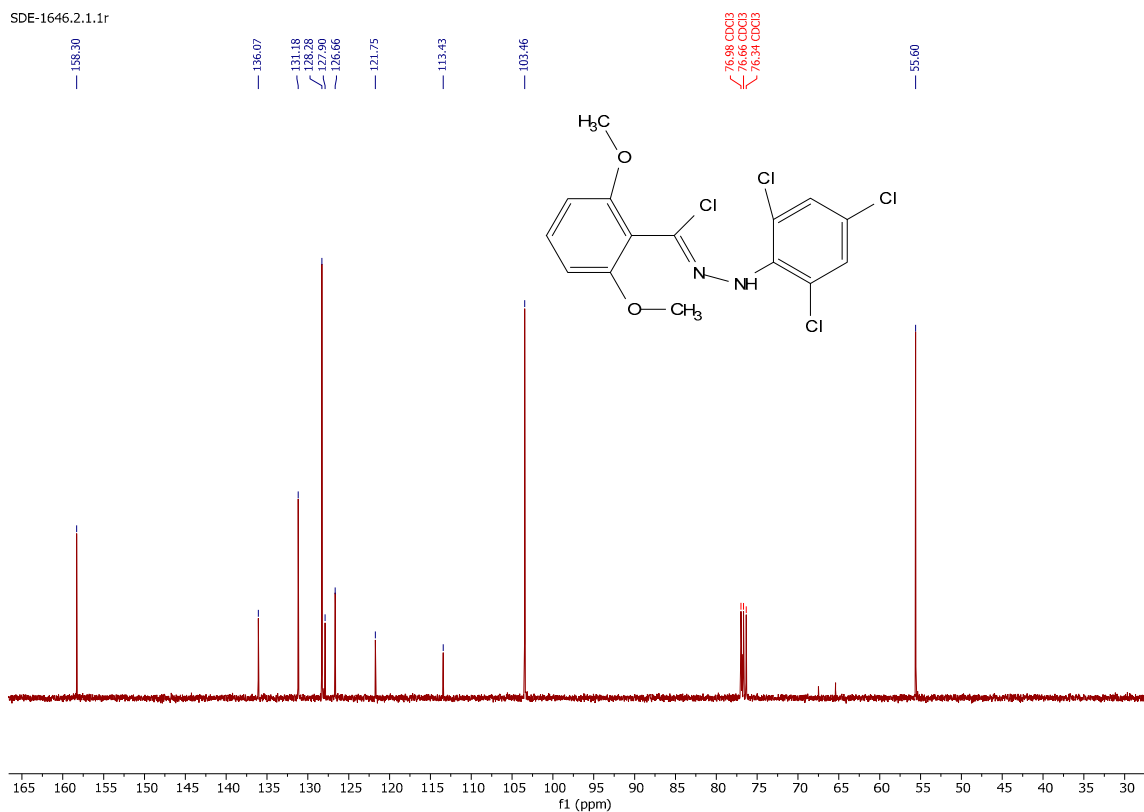
4

Figure S5. ^{1}H NMR spectra of compound **16a.**

Figure S6. ^{13}C NMR spectra of compound **16a.**

Figure S7. HSQC ¹H-¹³C NMR spectra of compound **16a**.
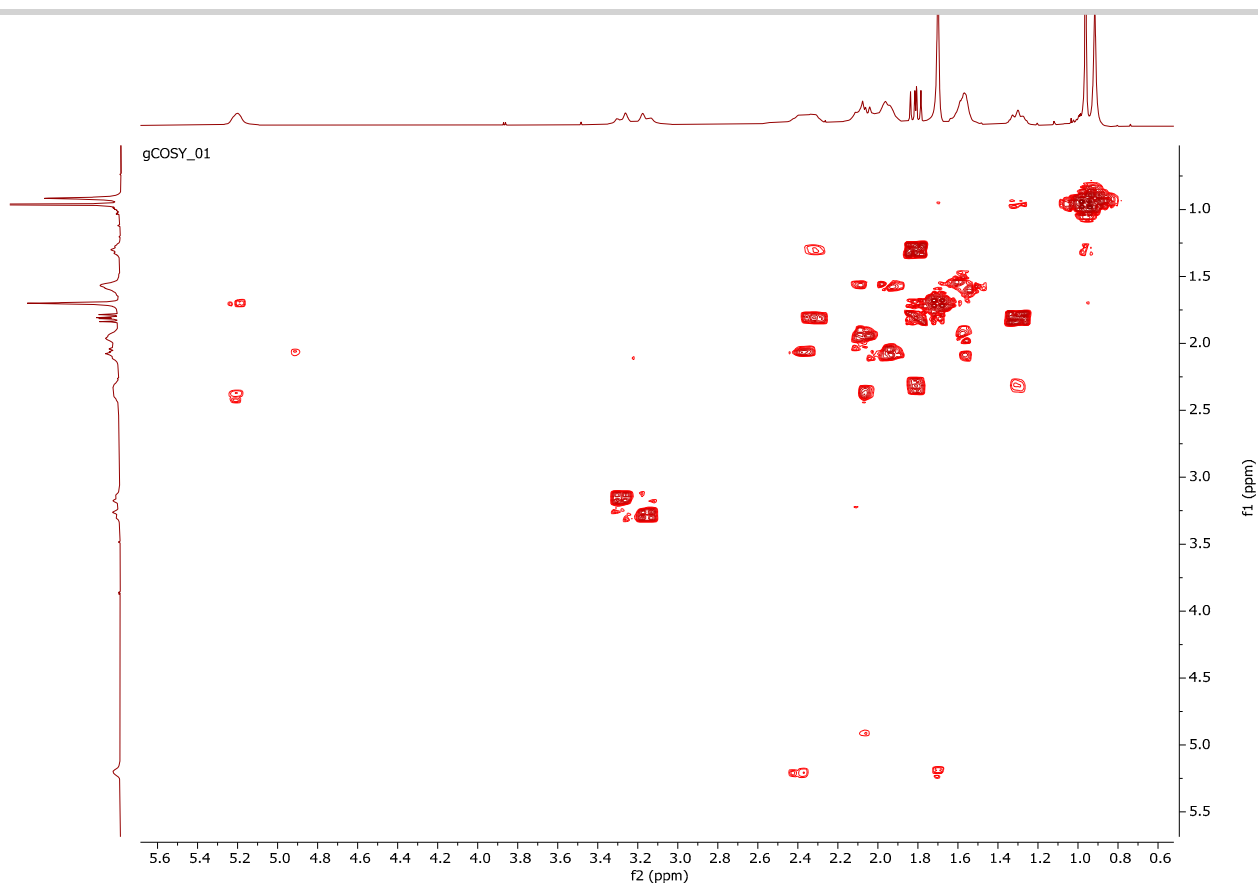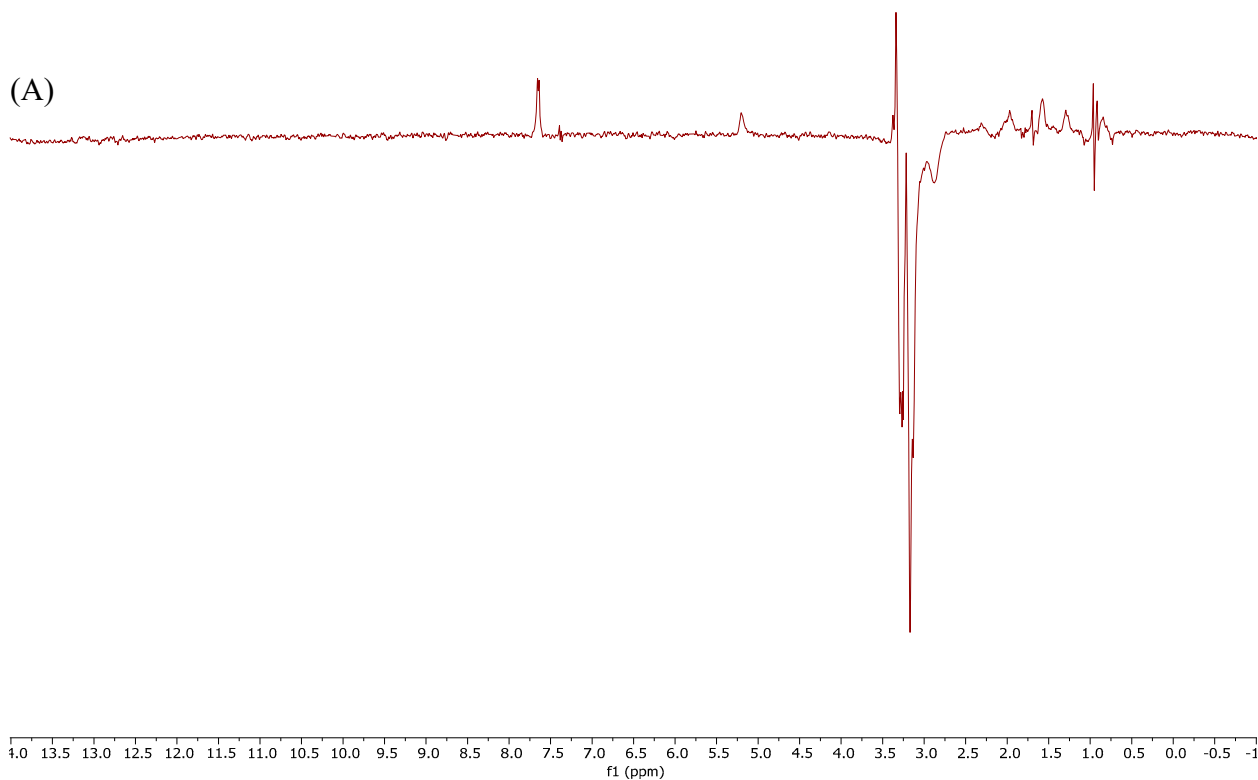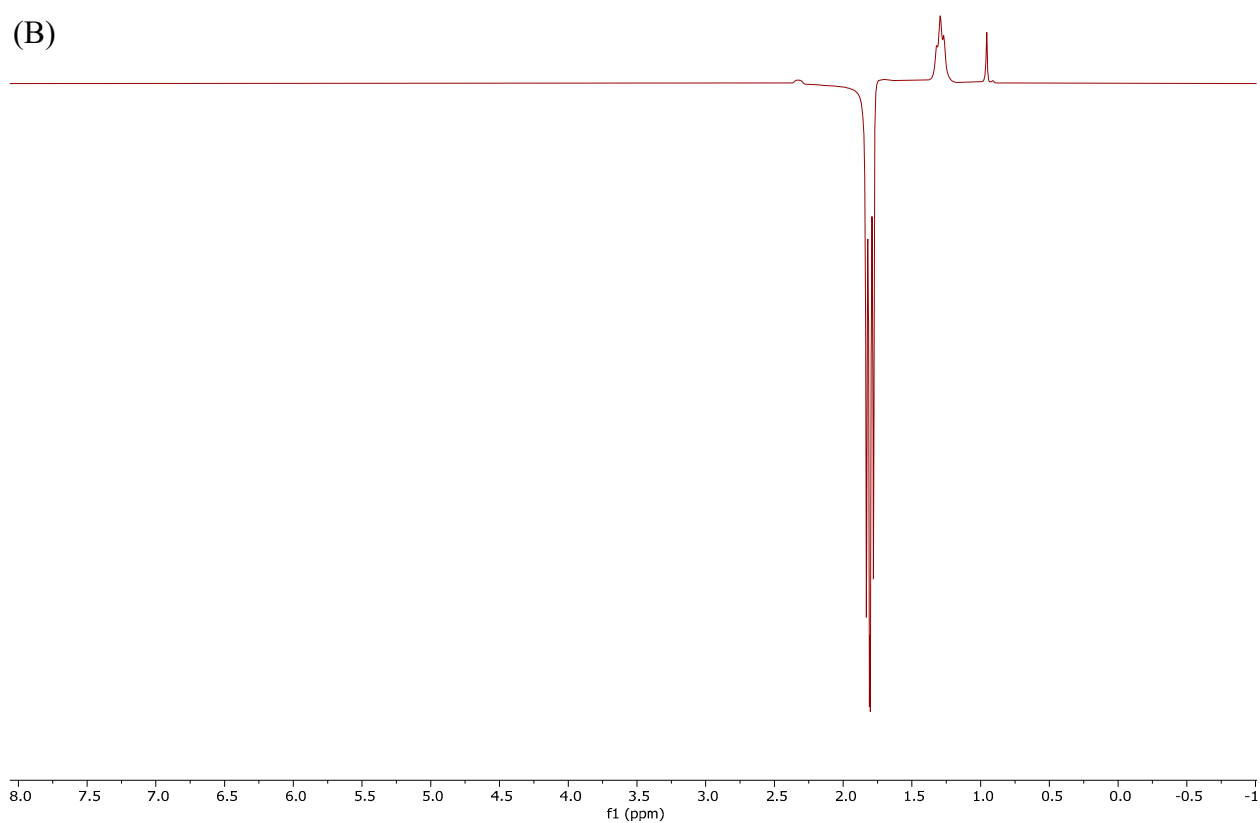

Figure S8. HMBC ¹H-¹³C NMR spectra of compound **16a**.

Figure S9. COSY ^{1}H-^{1}H NMR spectra of compound **16a**.

(A)

(B)

(C)

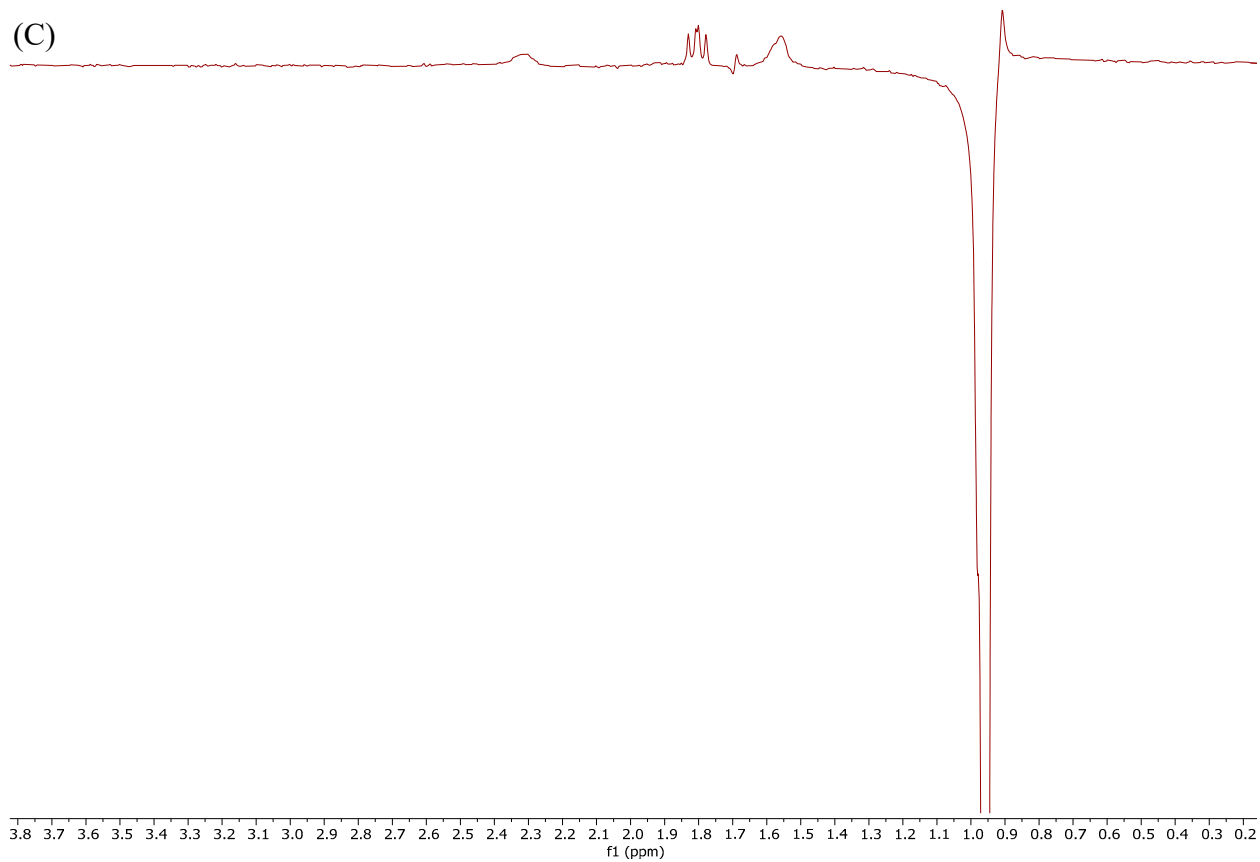Figure S10. ¹H NOESY1D NMR spectra of compound **16a**.

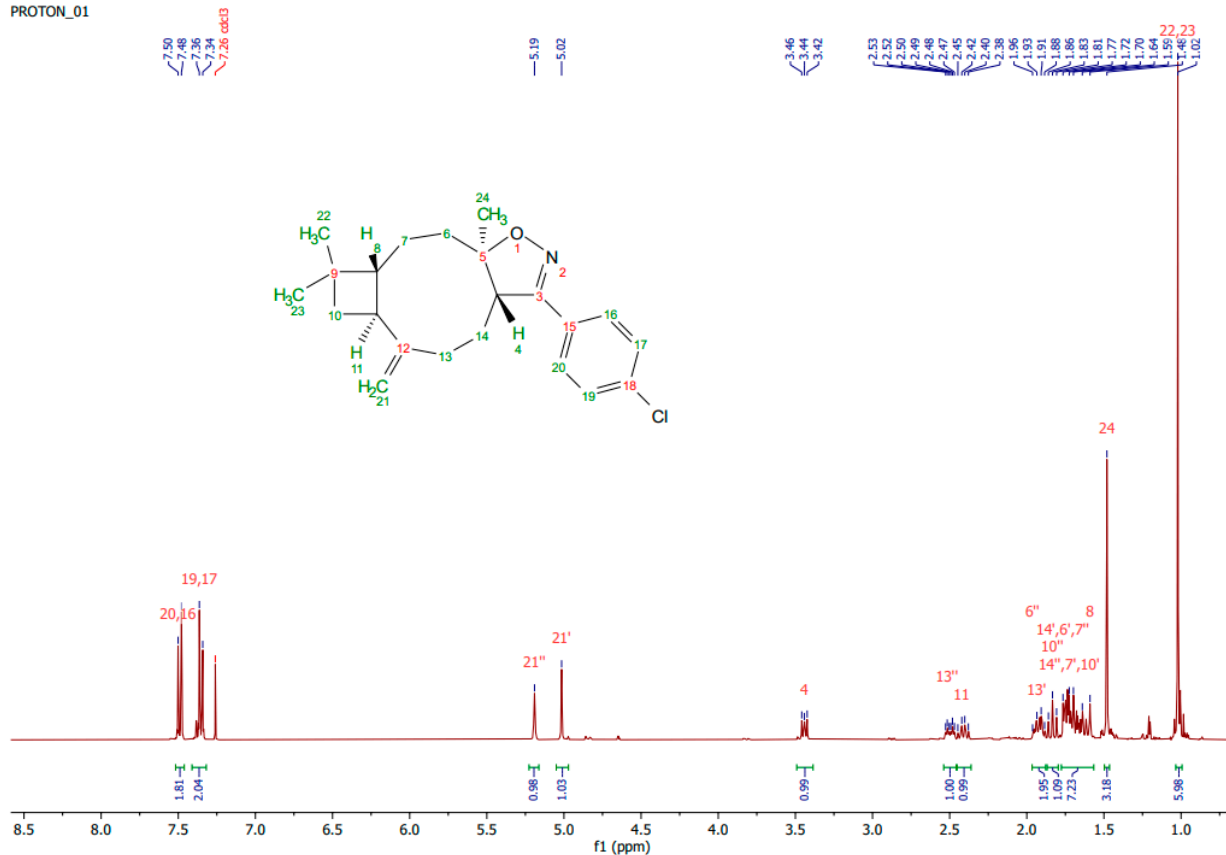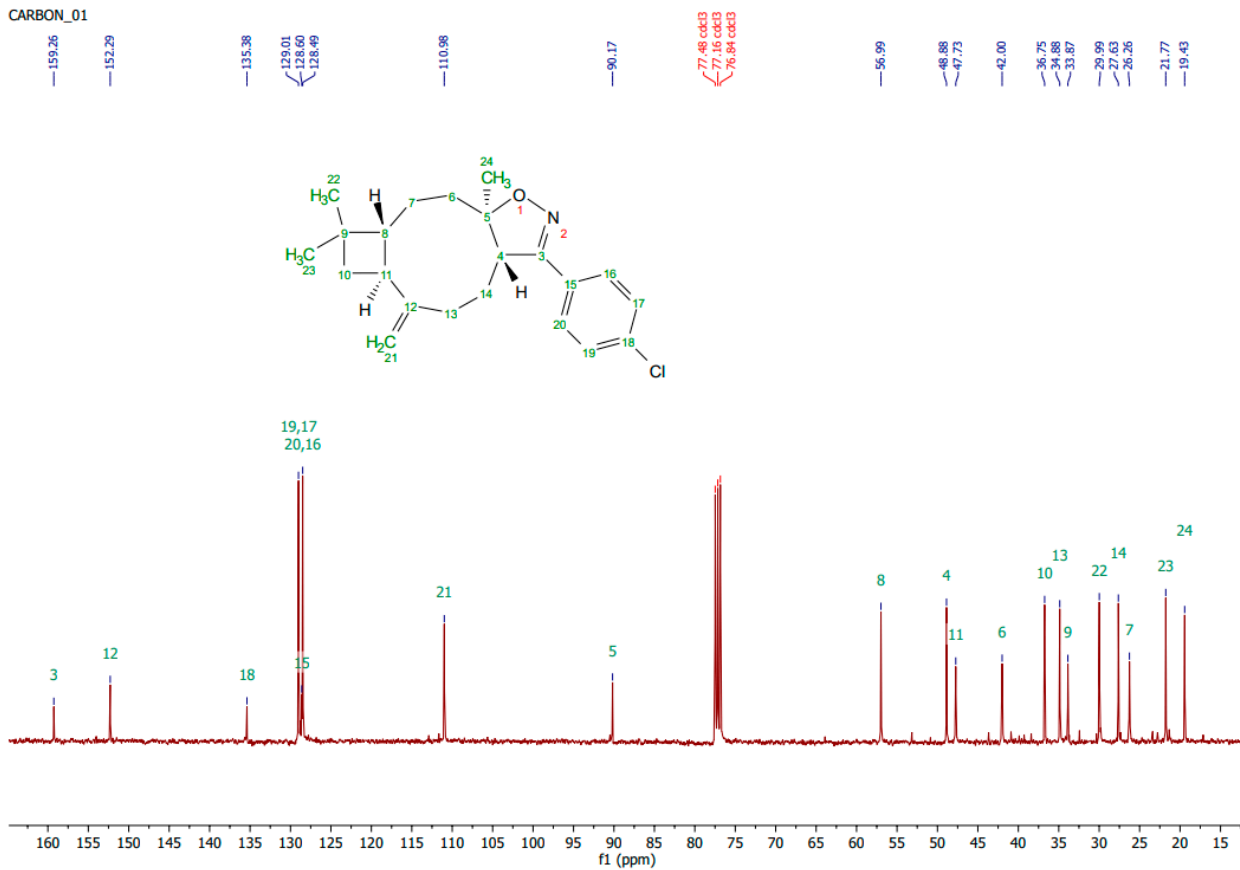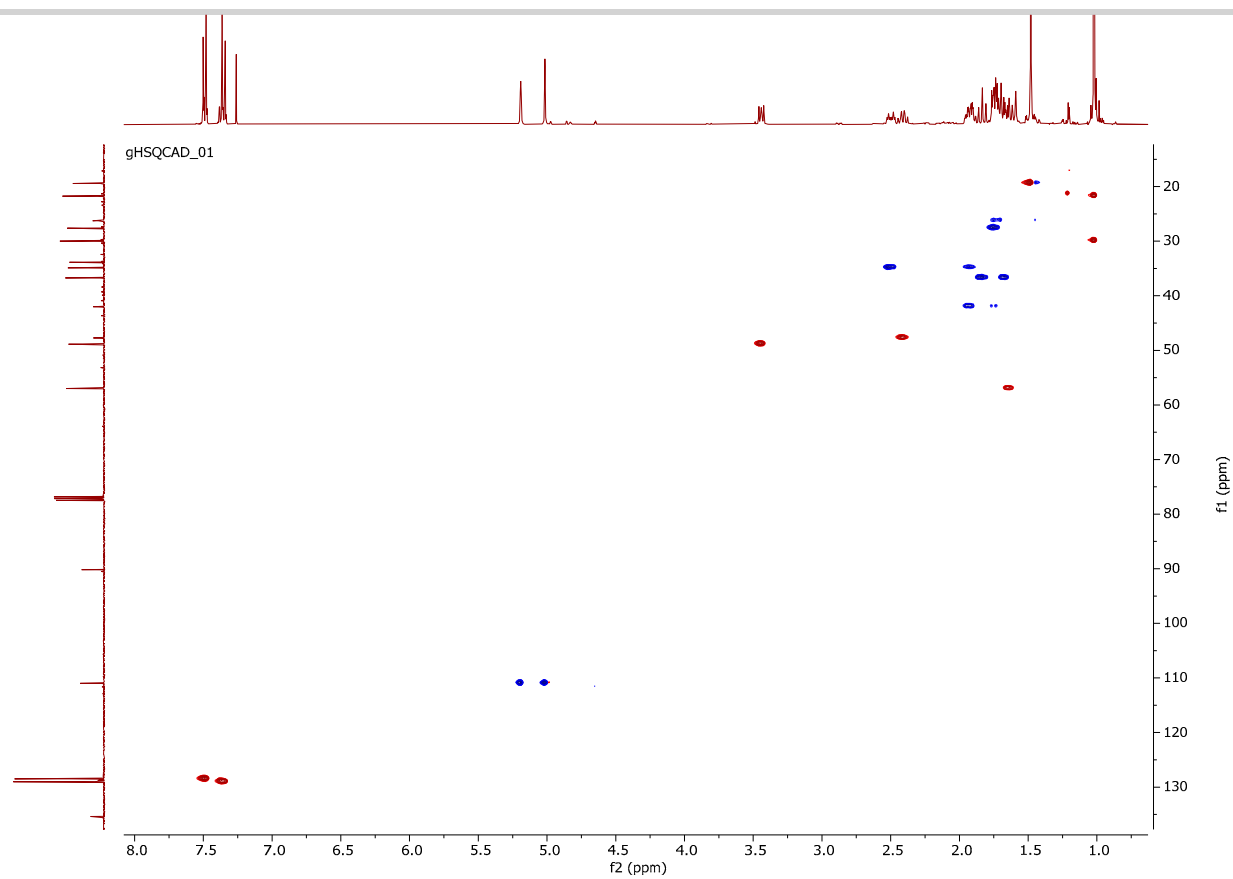Figure S11. ¹H NMR spectra of compound **16b.**

Figure S12. ¹³C NMR spectra of compound **16b.**

Figure S13. HSQC ^{1}H-^{13}C NMR spectra of compound **16b**.
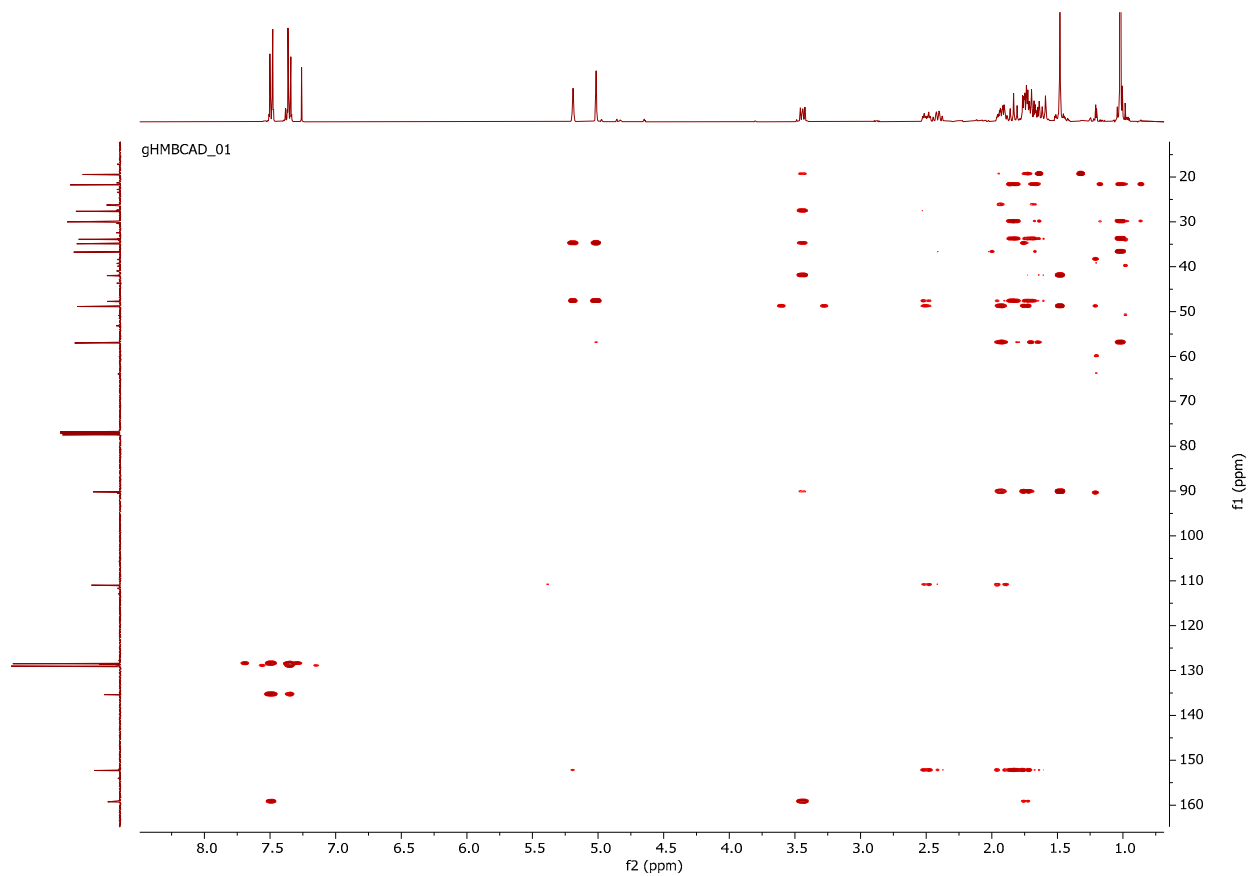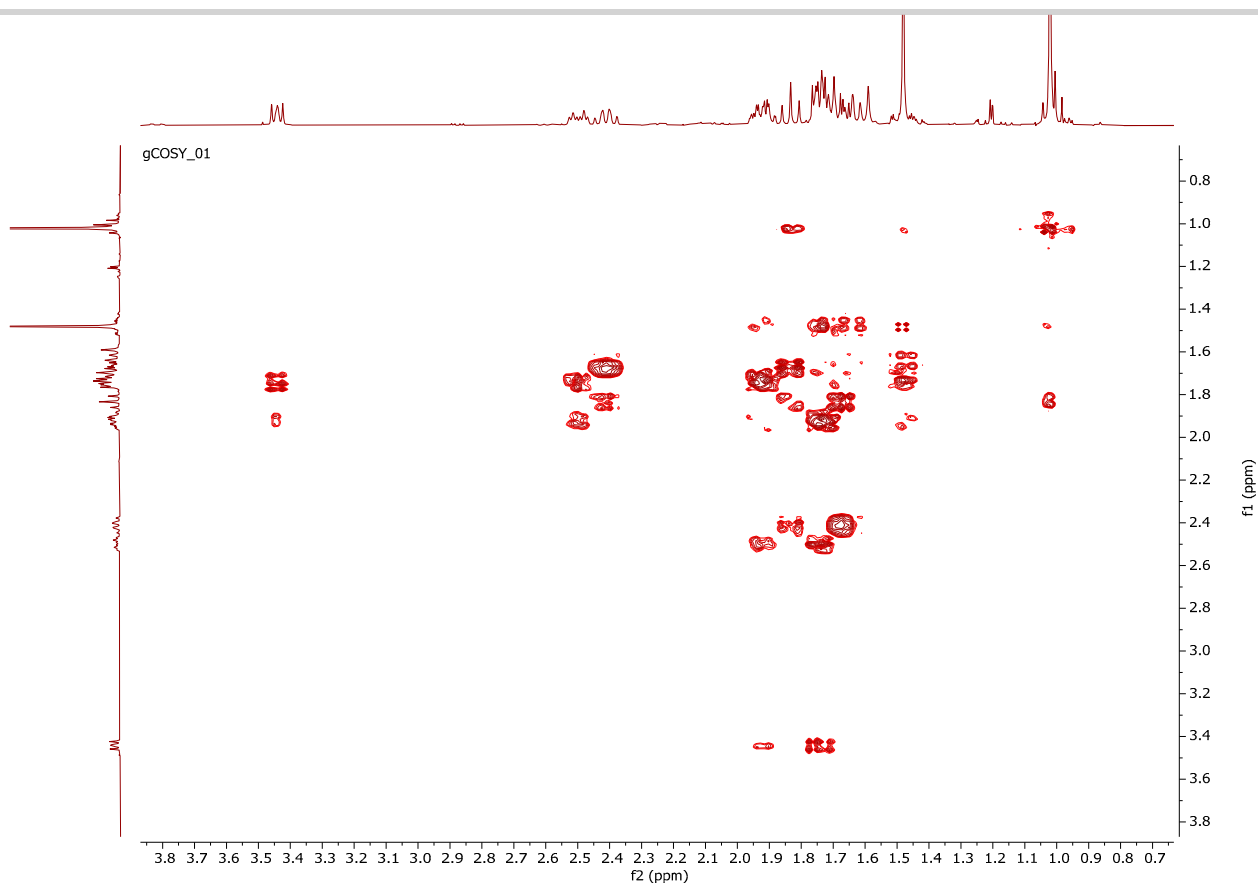

Figure S14. HMBC ^{1}H-^{13}C NMR spectra of compound **16b**.

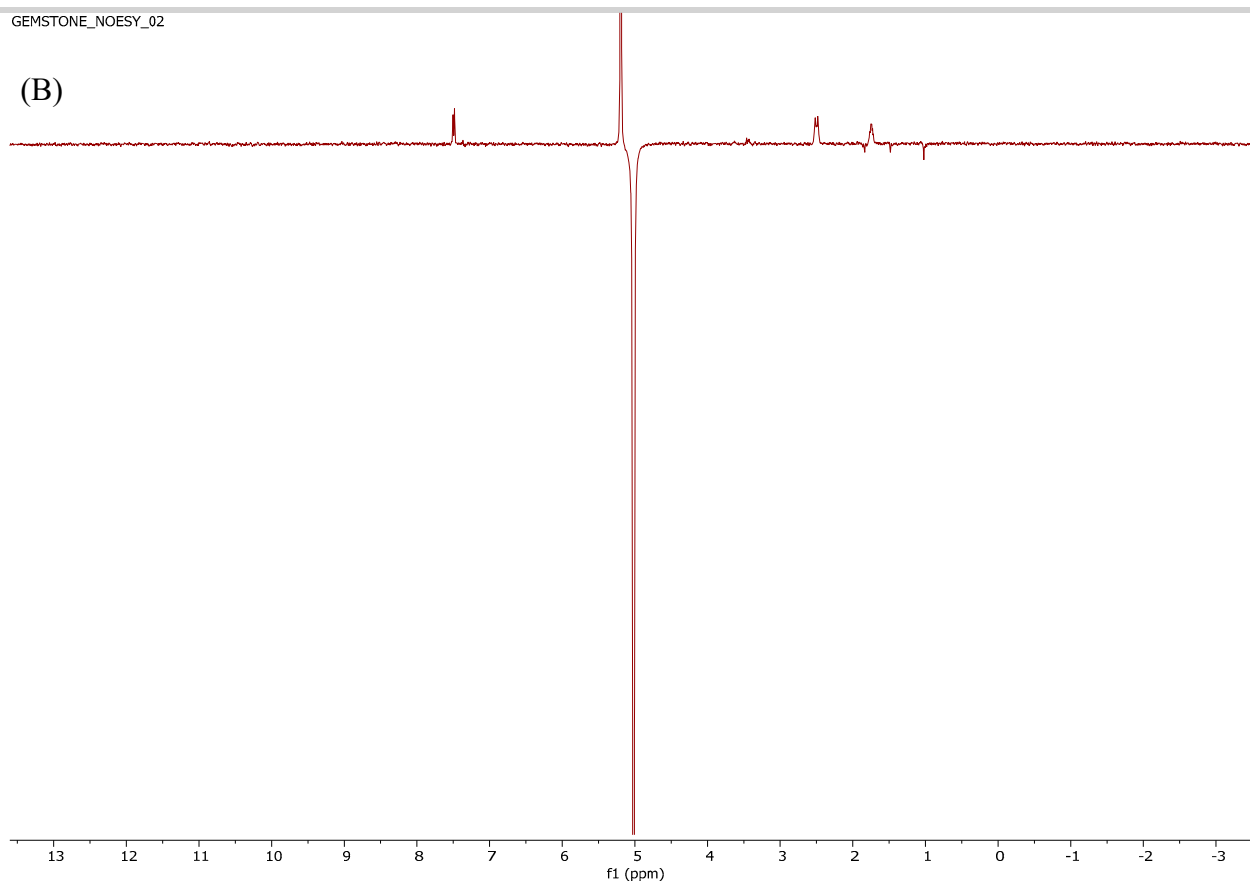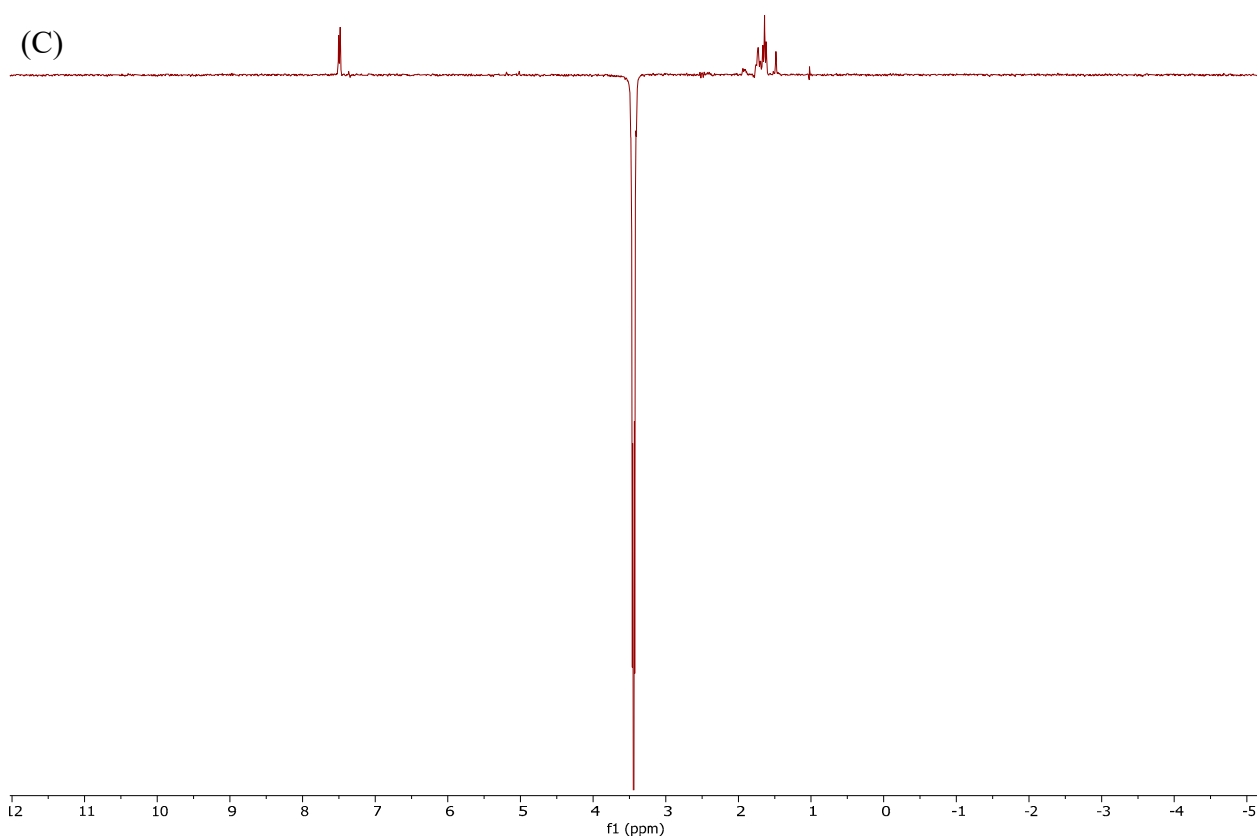Figure S15. COESY ^{1}H-^{1}H NMR spectra of compound **16b**.

GEMSTONE_NOESY_01

(A)

(B)

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

(C)

12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5
f1 (ppm)

12

(D)

f1 (ppm)

(E)

f1 (ppm)

(F)

10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5 -6
f1 (ppm)

(G)

10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5 -6
f1 (ppm)
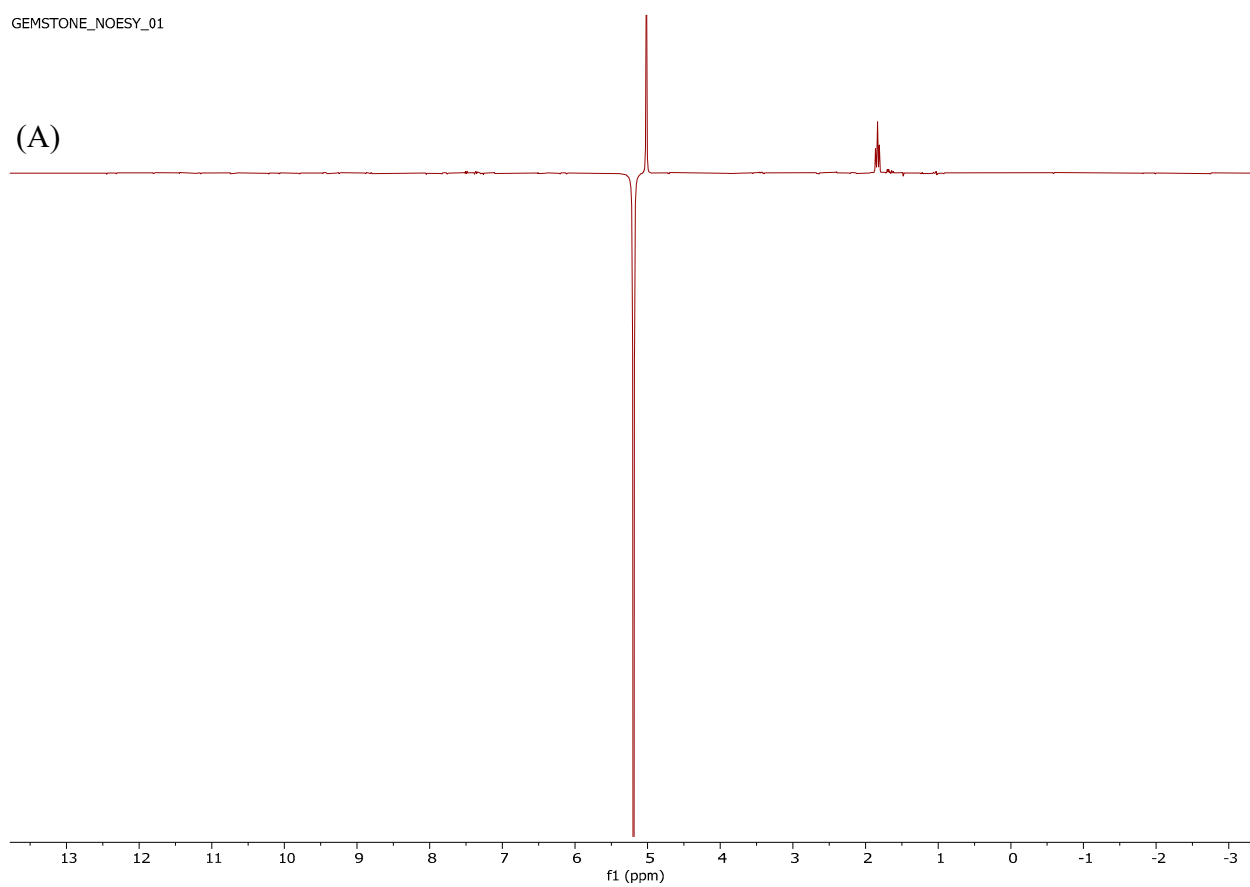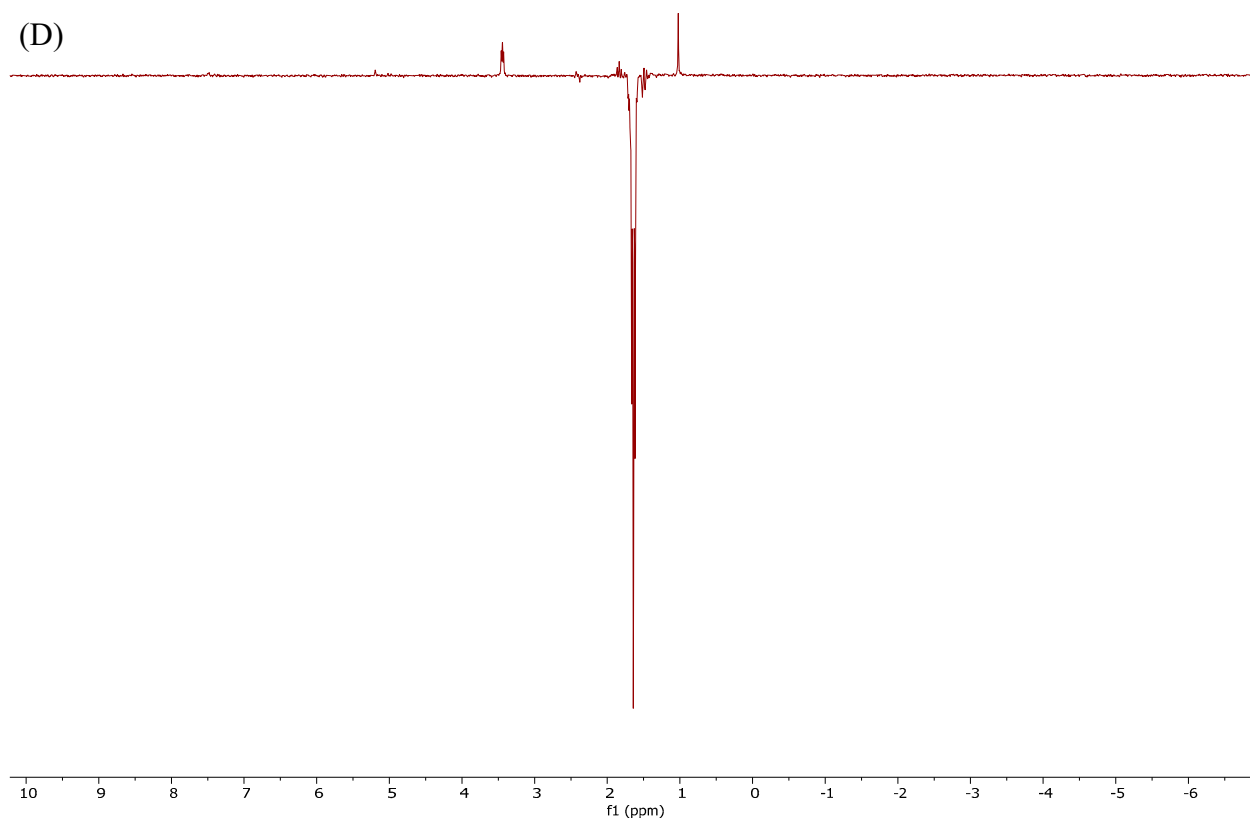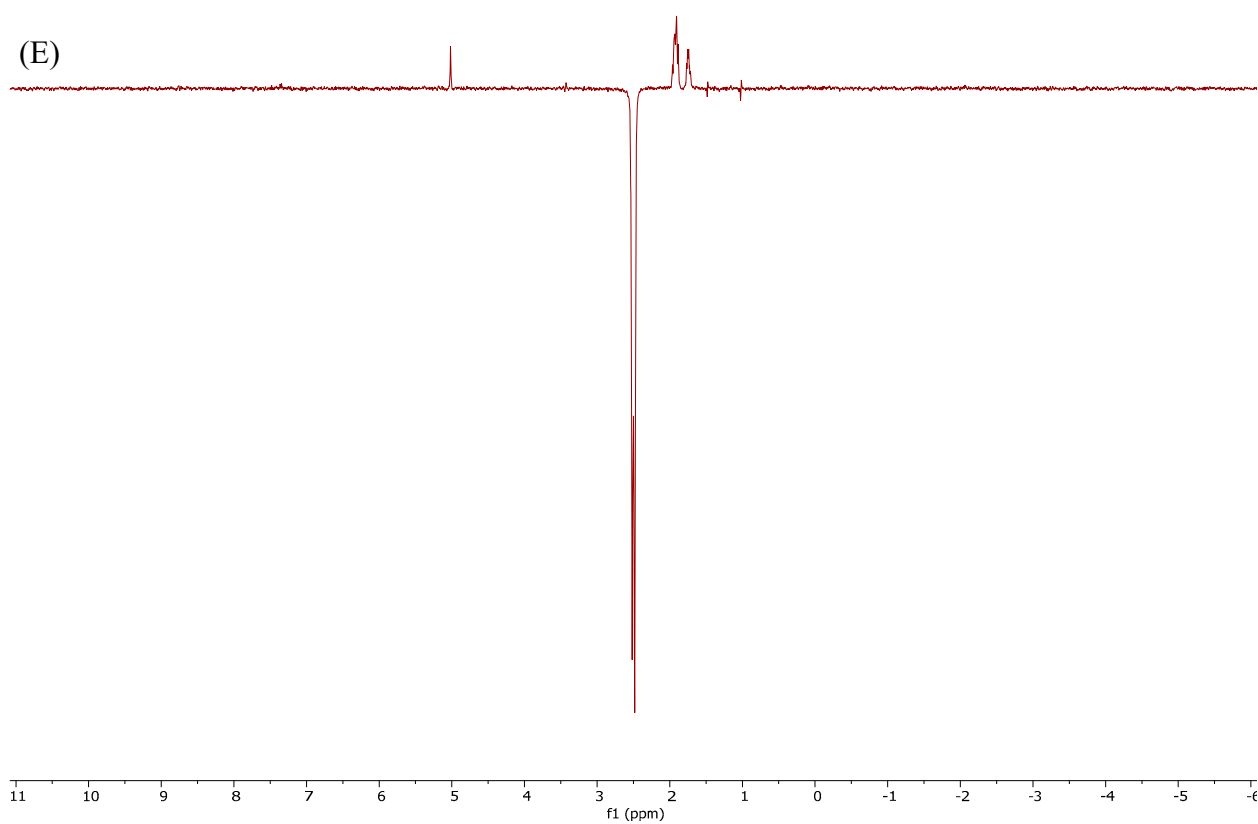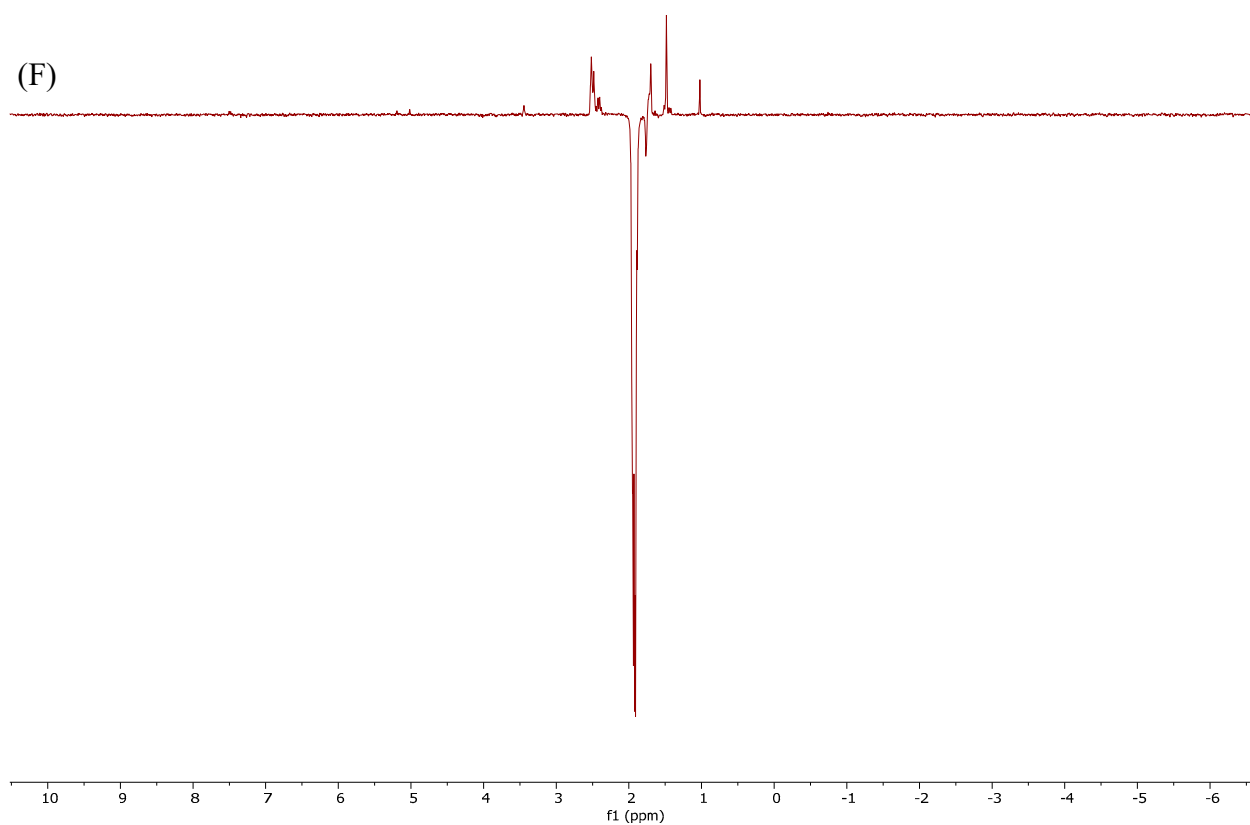
Figure S16. ^{1}H NOESY1D NMR spectra of compound **16b**.

Figure S17. ^{1}H NMR spectra of compound **17a.**

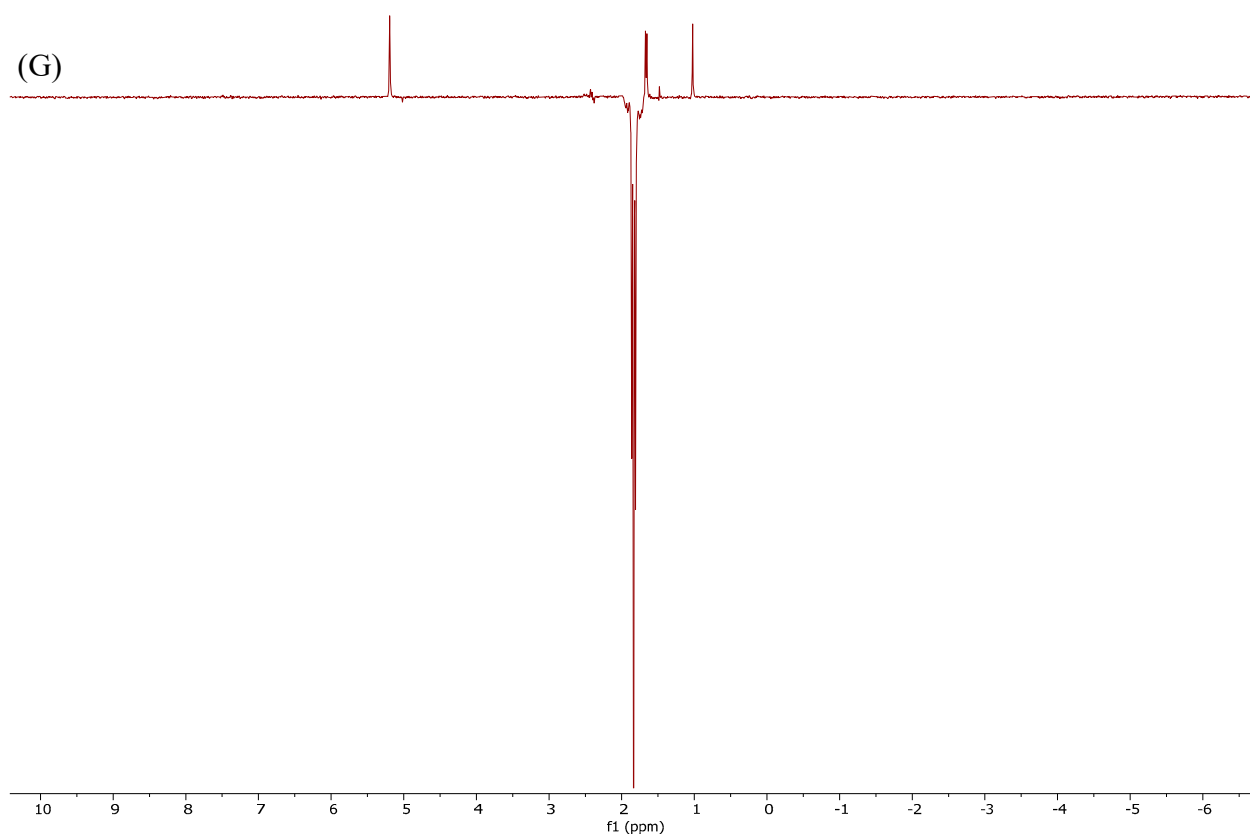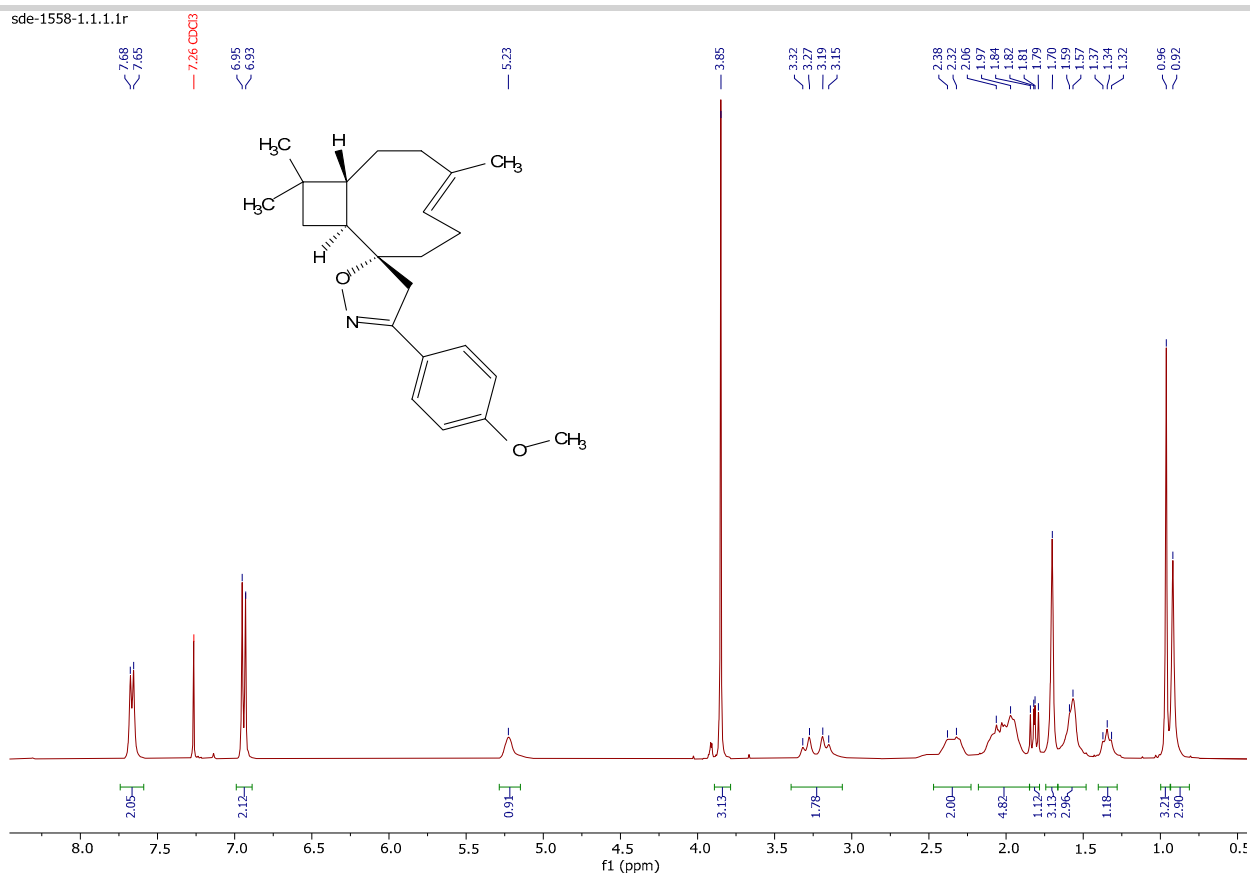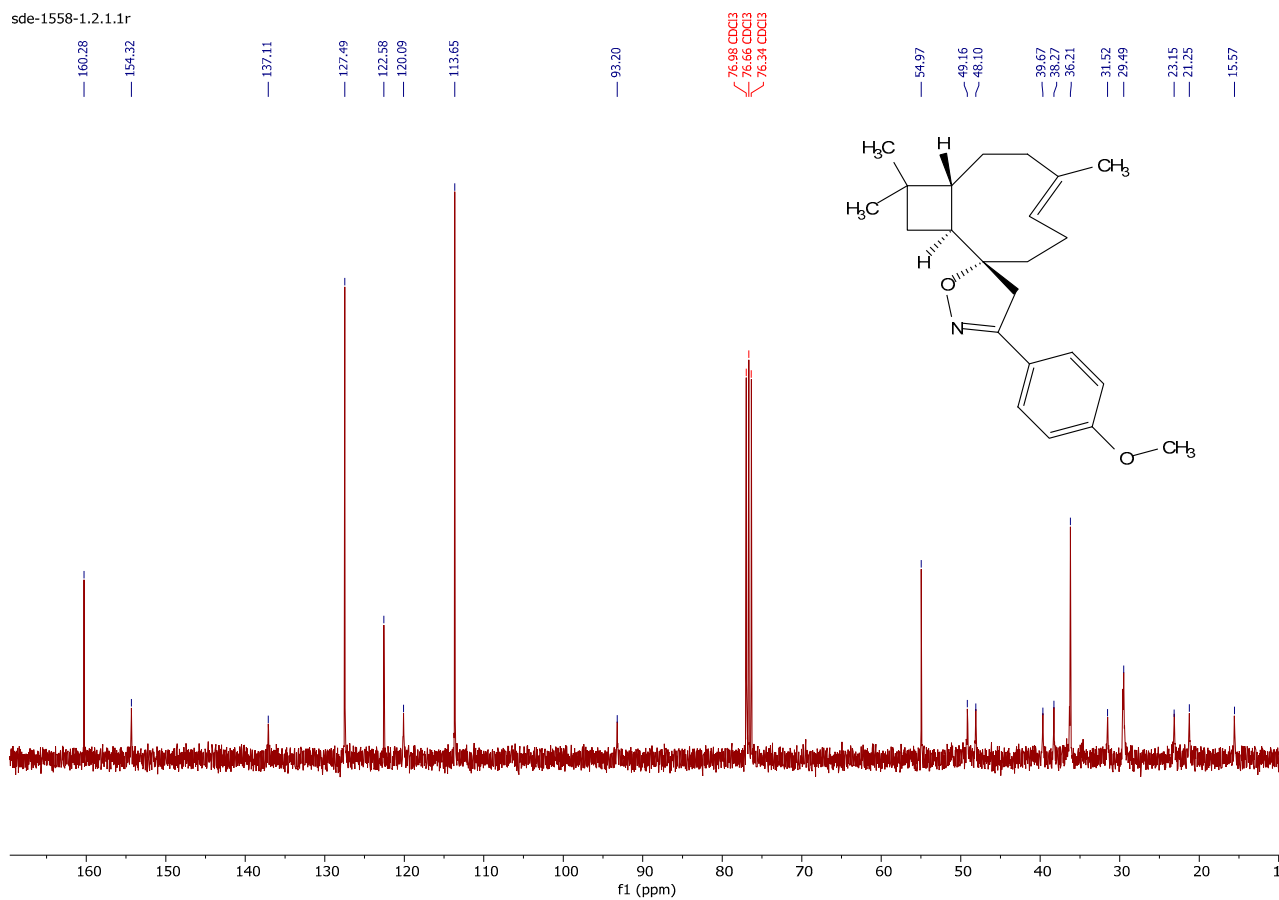Figure S18. ^{13}C NMR spectra of compound **17a.**

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Figure S19. ^{1}H NMR spectra of compound **17b.**
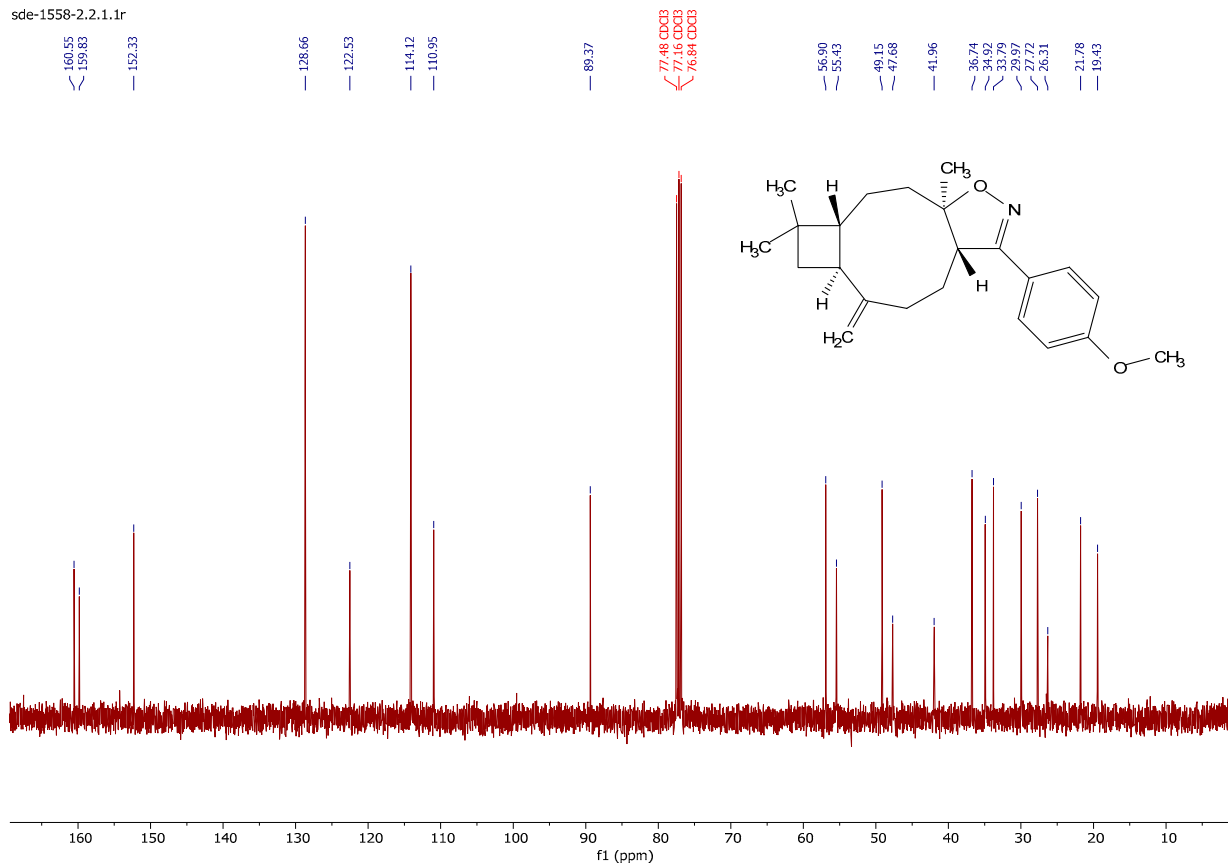
Figure S20. ^{13}C NMR spectra of compound **17b.**
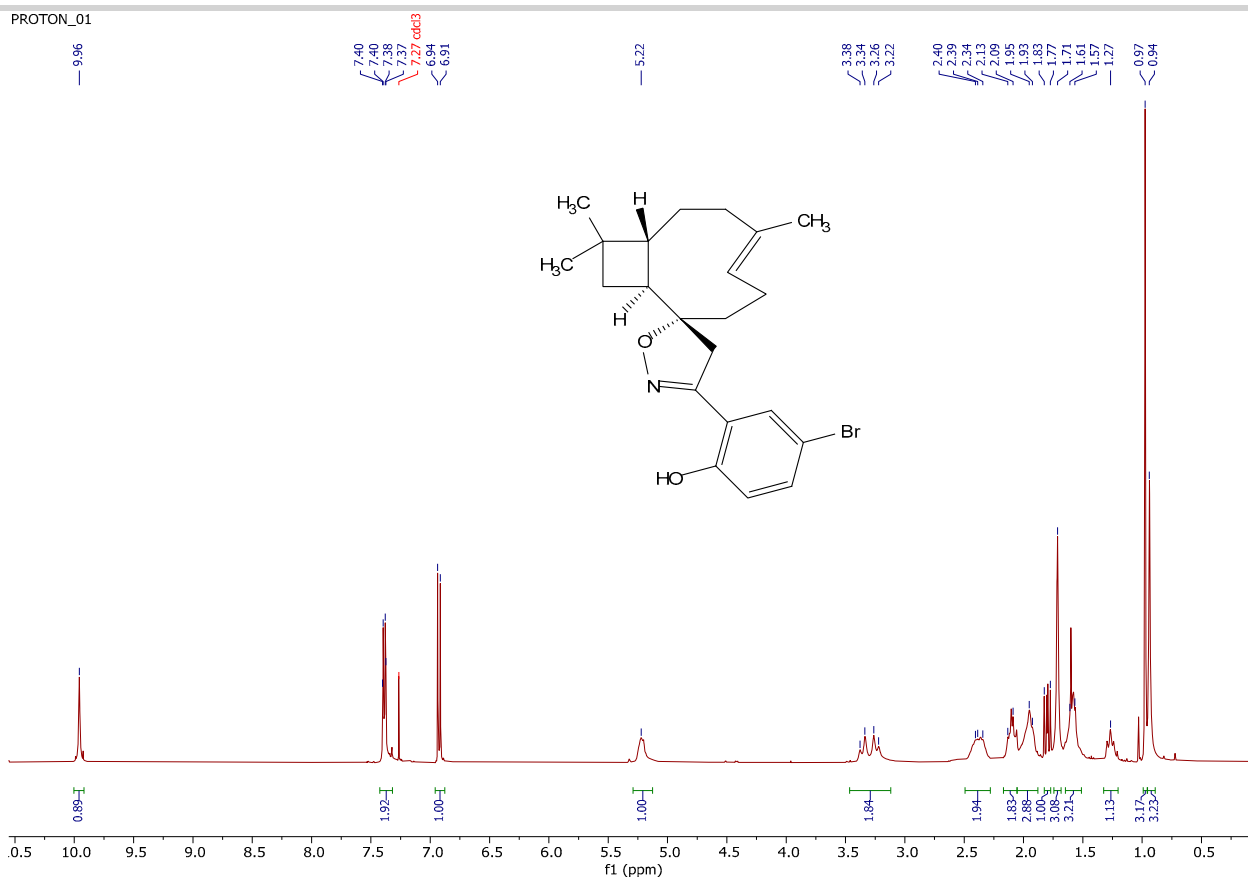
Figure S21. ¹H NMR spectra of compound **18a.**
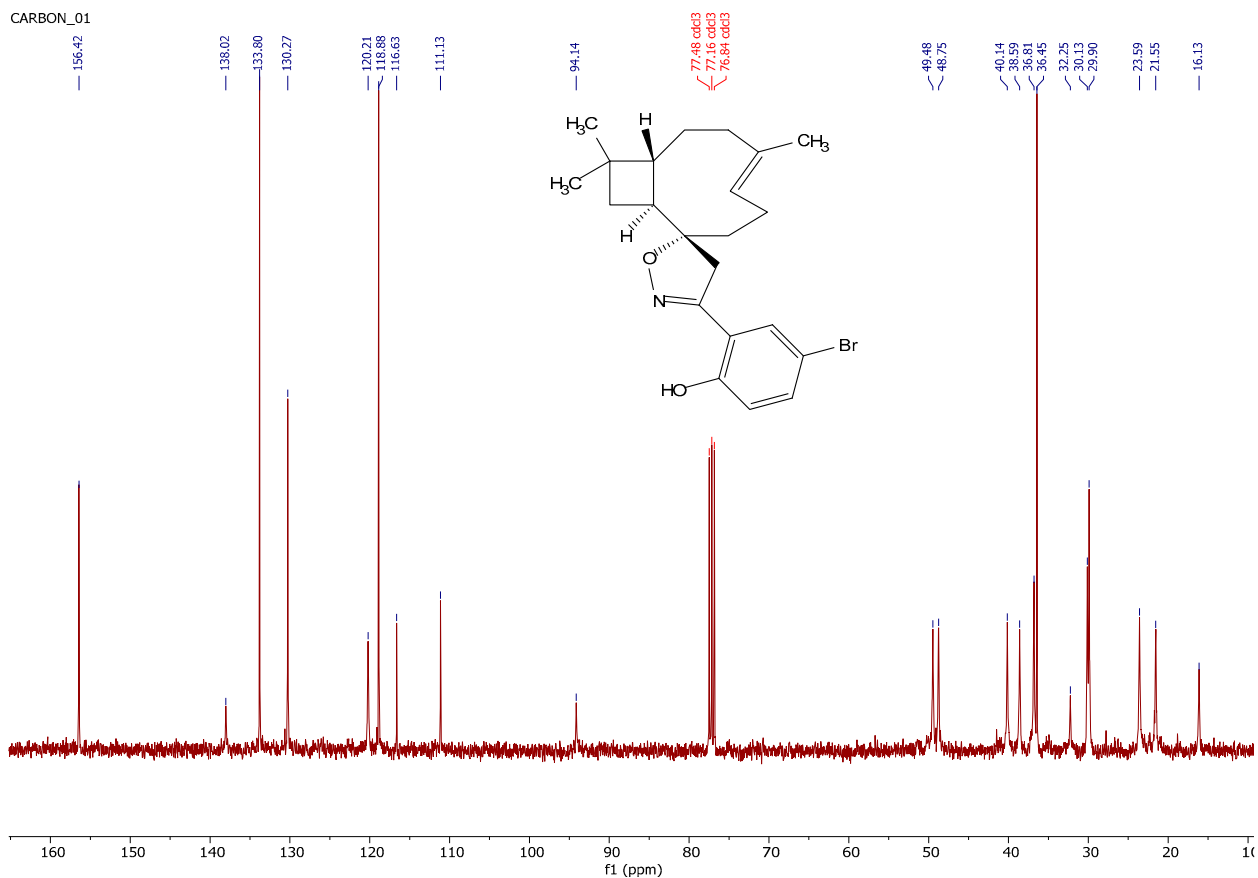
Figure S22. ¹³C NMR spectra of compound **18a.**

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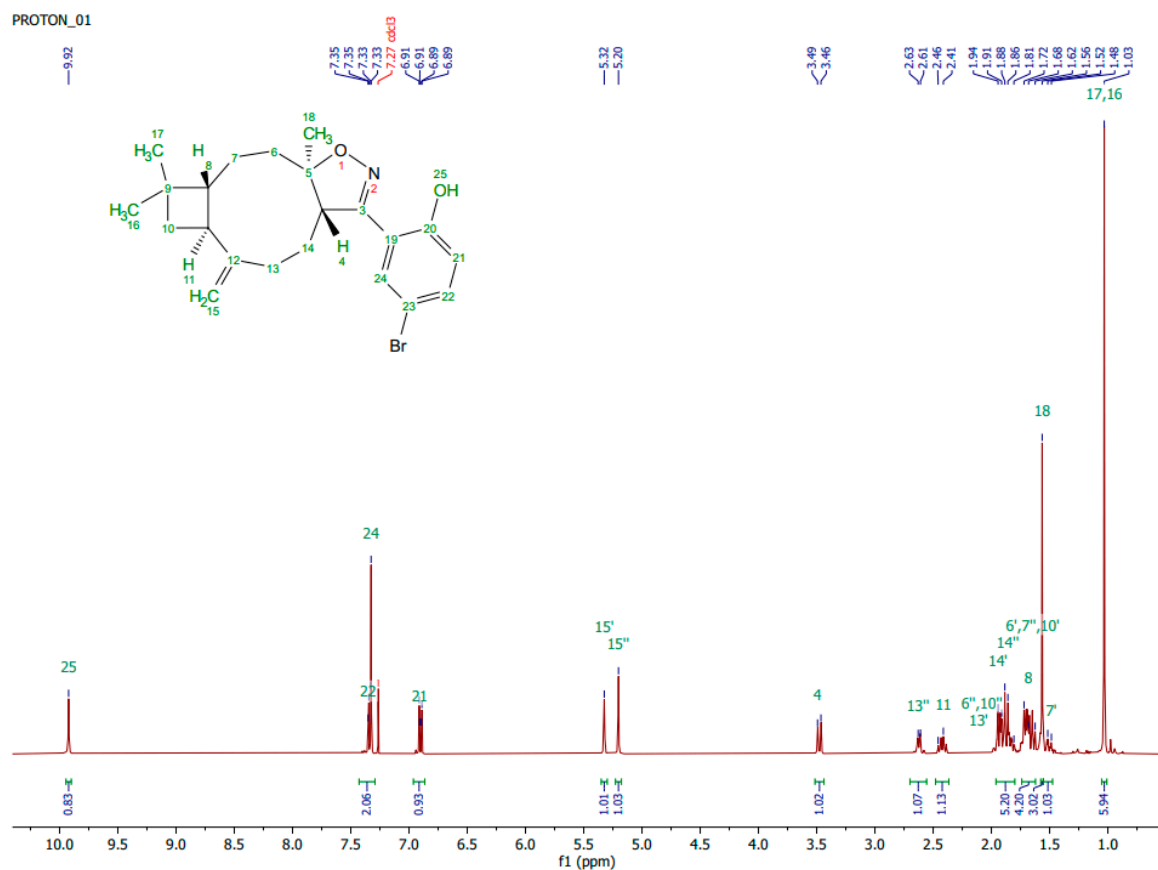
Figure S23. ^{1}H NMR spectra of compound **18b.**

Figure S24. ^{13}C NMR spectra of compound **18b.**

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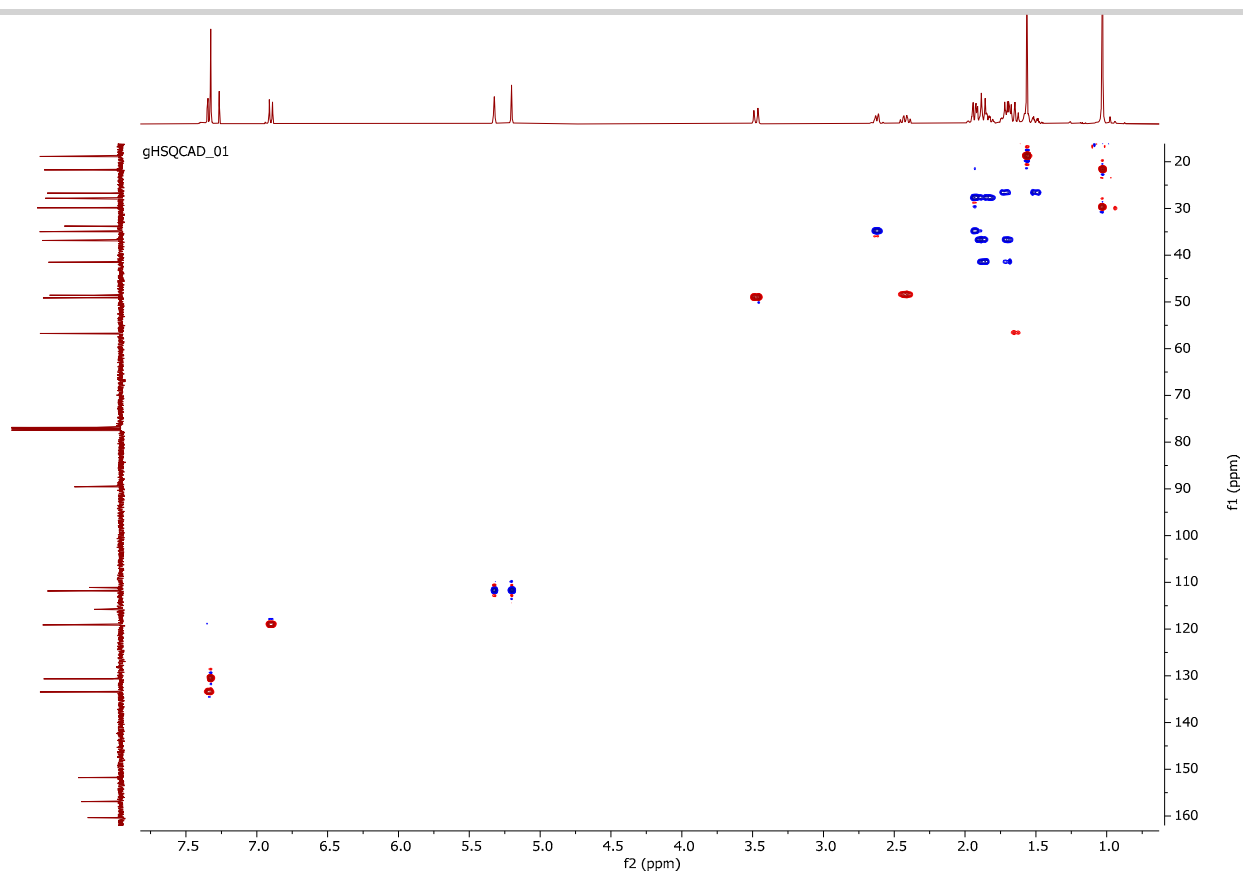
Figure S25. HSQC ^{1}H-^{13}C NMR spectra of compound **18b**.
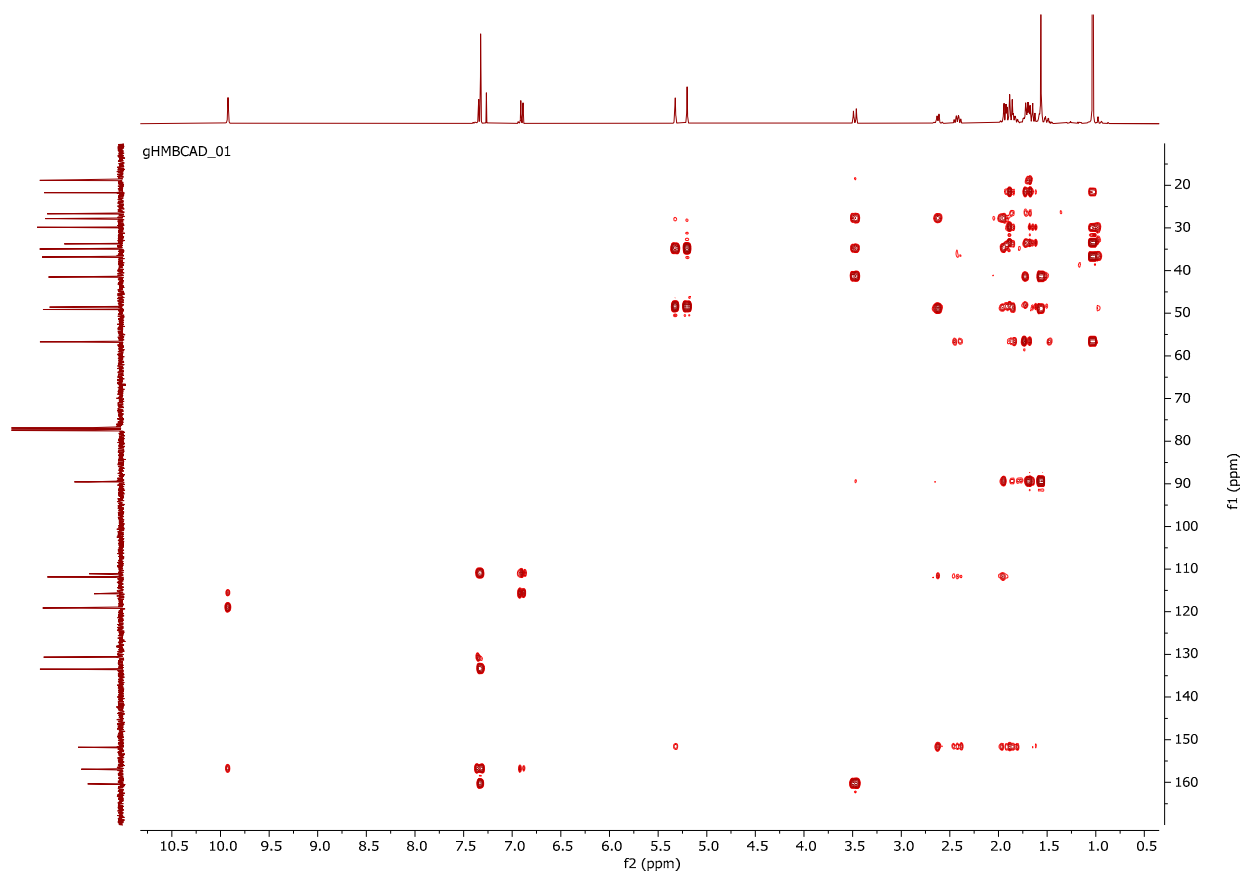
Figure S26. HMBC ^{1}H-^{13}C NMR spectra of compound **18b**.
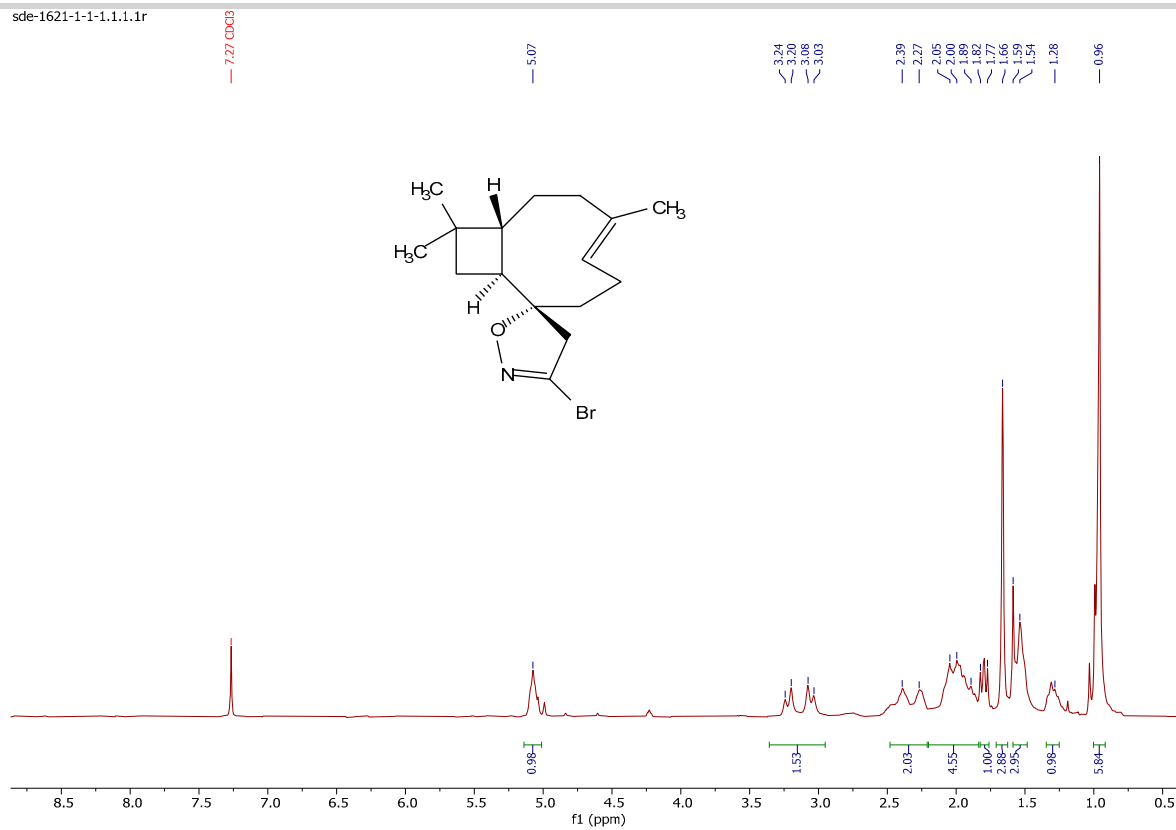
Figure S27. ¹H NMR spectra of compound **19a.**
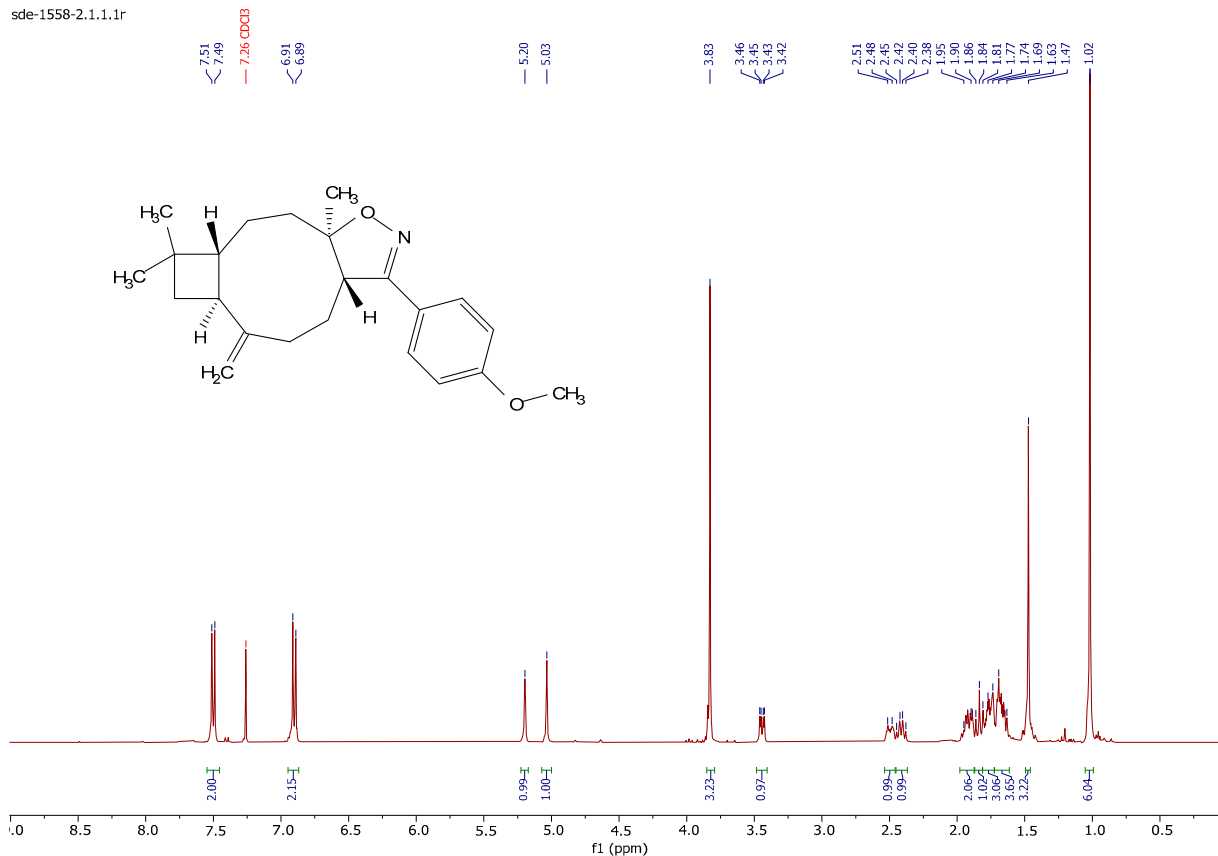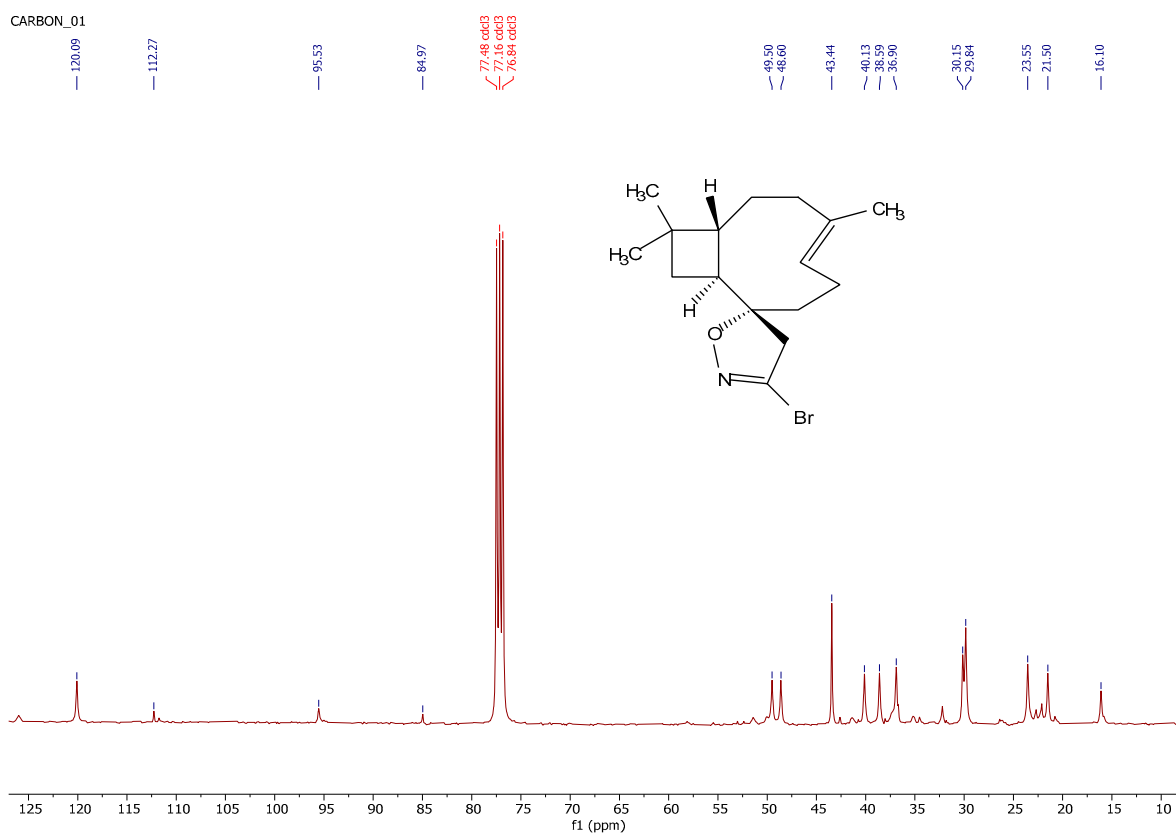
Figure S28. ¹³C NMR spectra of compound **19a.**

Figure S29. ^{1}H NMR spectra of compound **19b.**
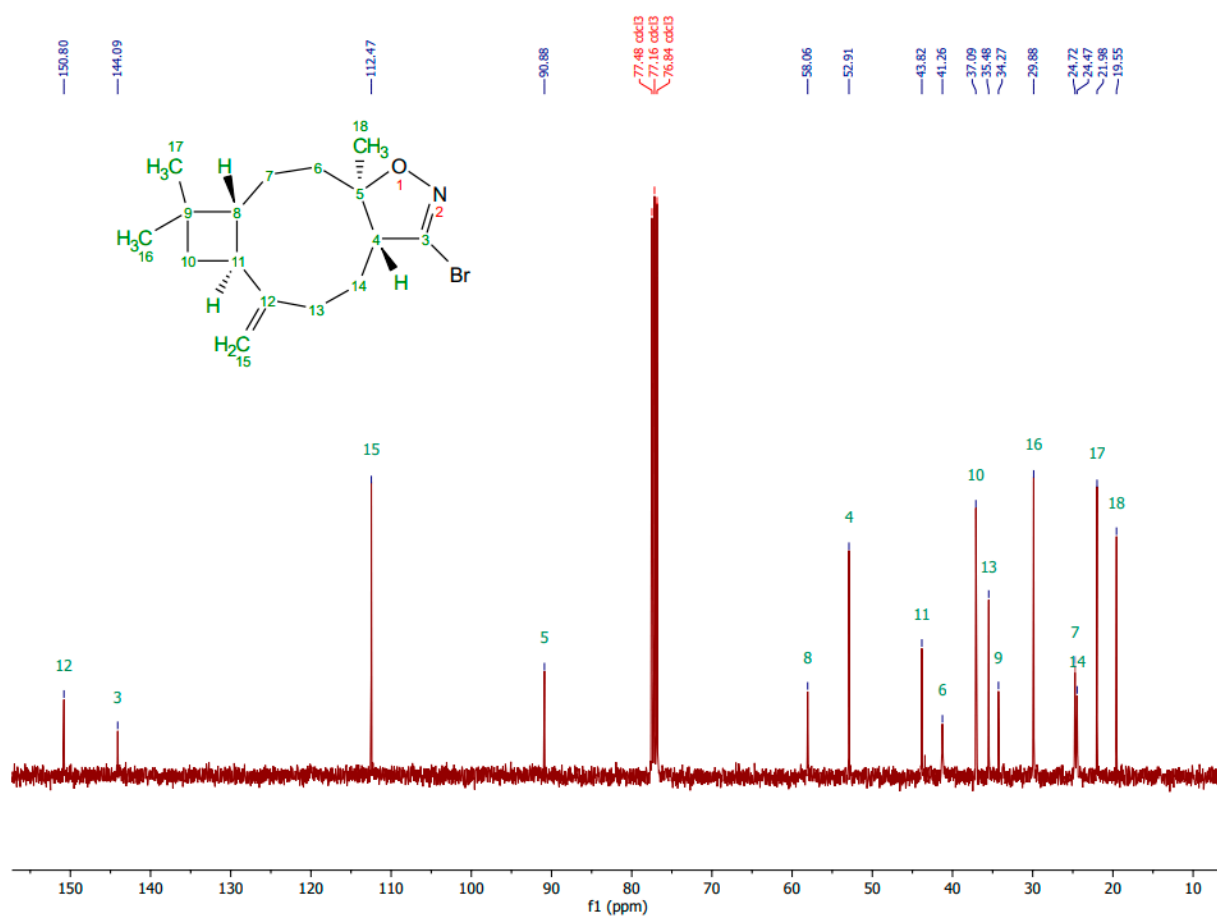
Figure S30. ^{13}C NMR spectra of compound **19b.**

Figure S31. HSQC ^{1}H-^{13}C NMR spectra of compound **19b**.
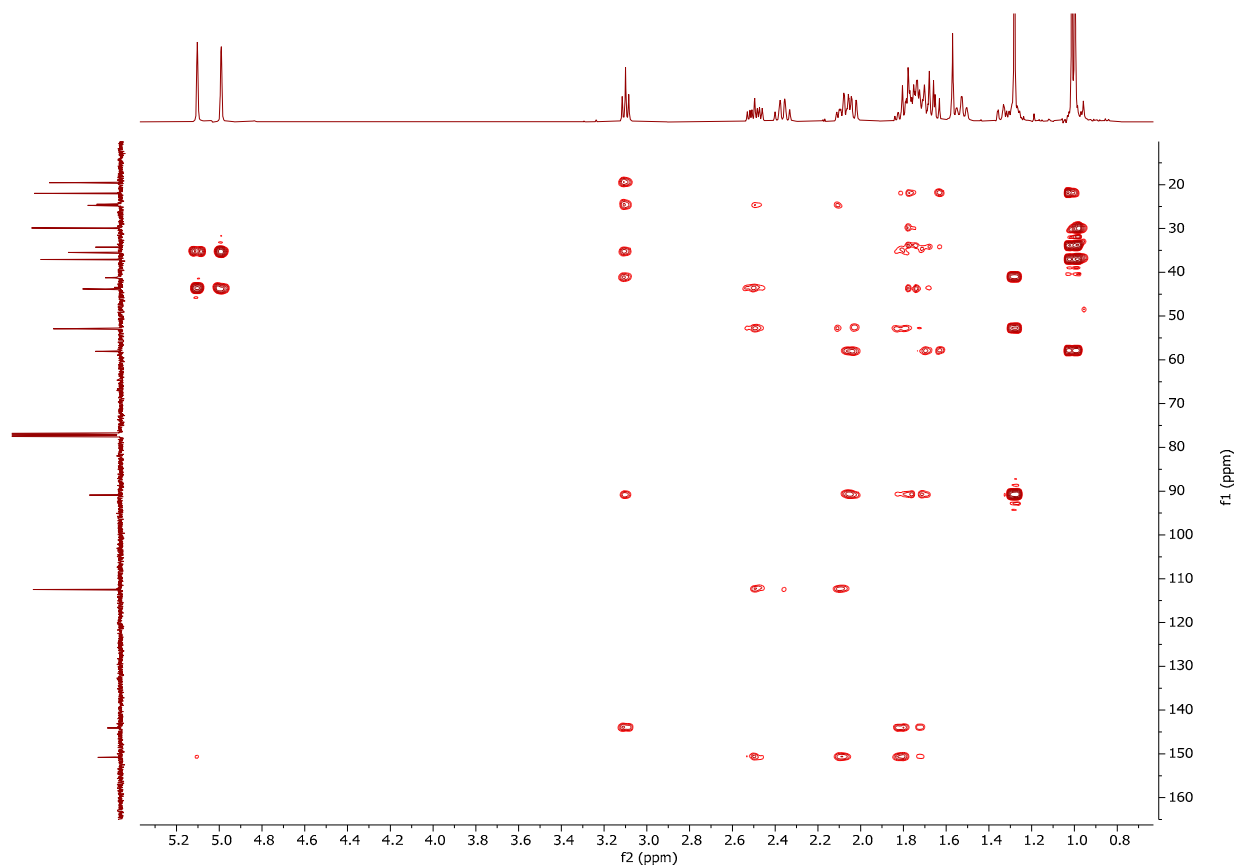
Figure S32. HMBC ^{1}H-^{13}C NMR spectra of compound **19b**.
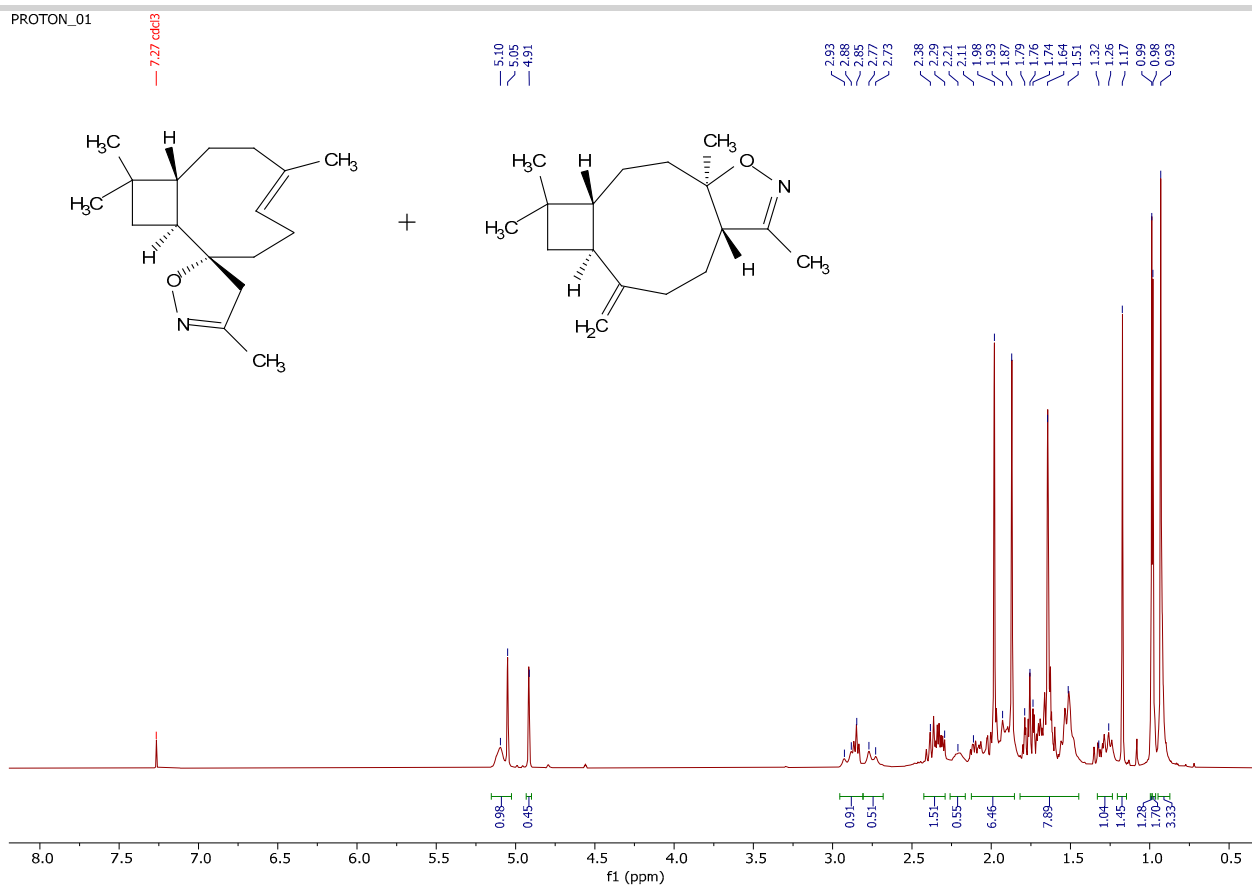
Figure S33. ^{1}H NMR spectra of mixture of compounds **20a** and **20b**.
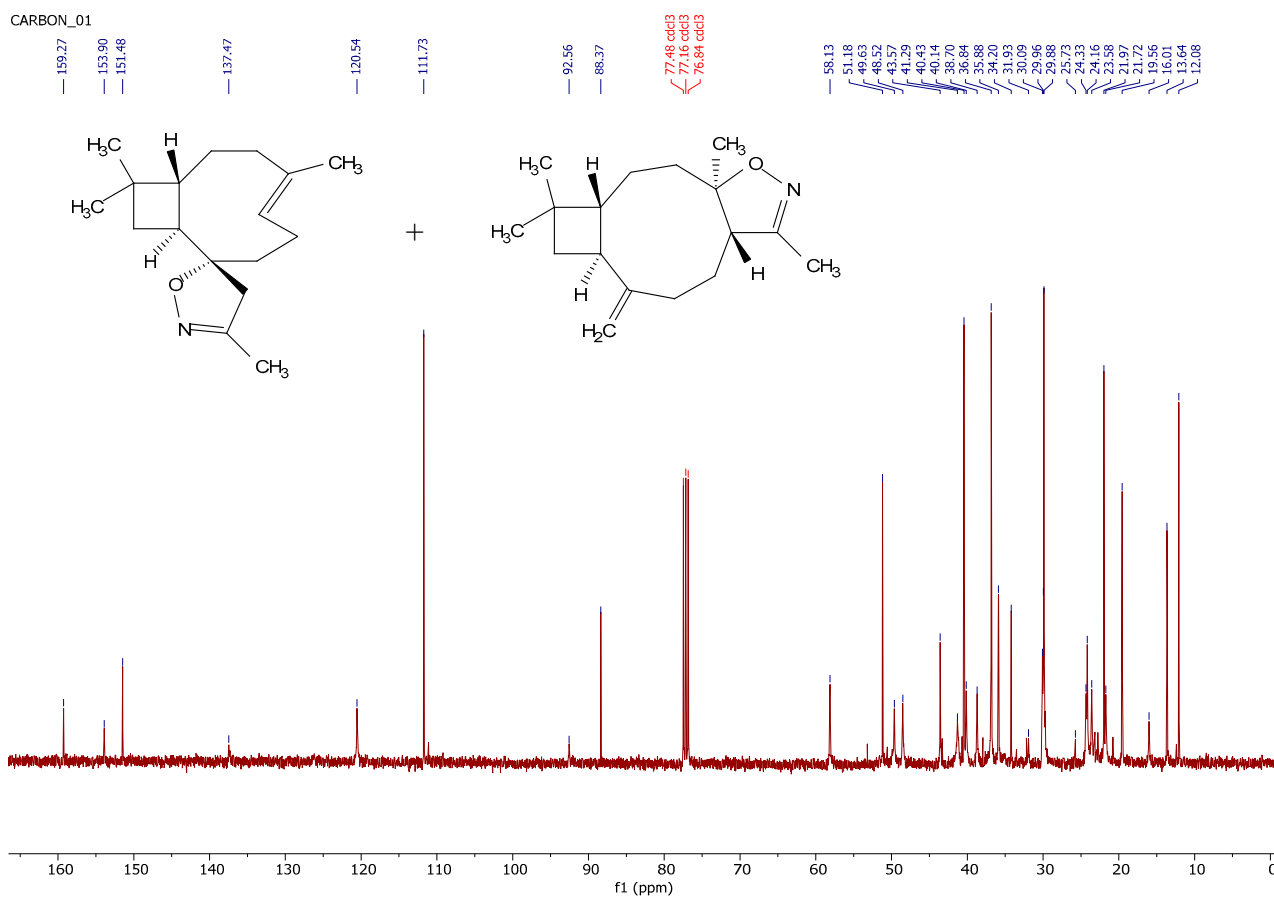
Figure S34. ^{13}C NMR spectra of mixture of compounds **20a** and **20b**.
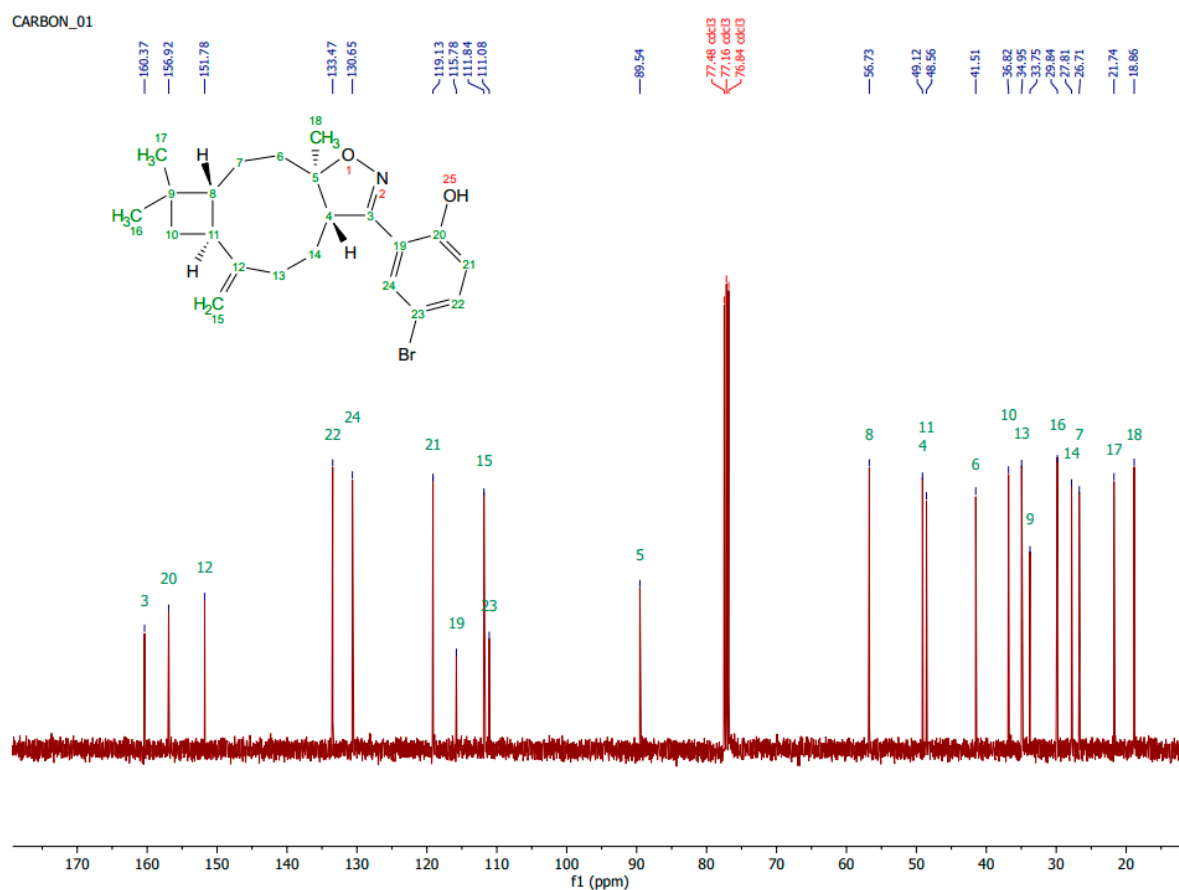
PROTON_01
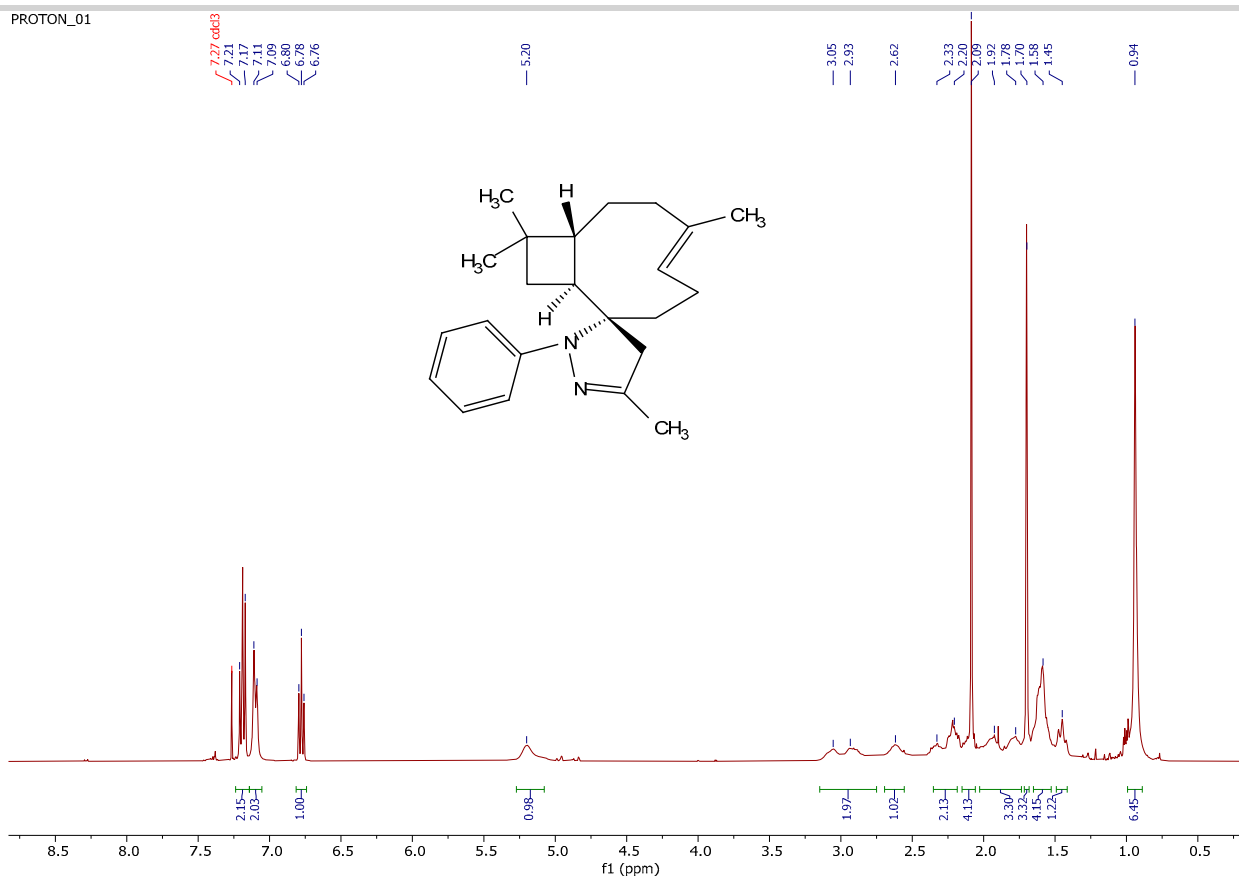
Figure S35. ^{1}H NMR spectra of compound **21a.**

CARBON_01
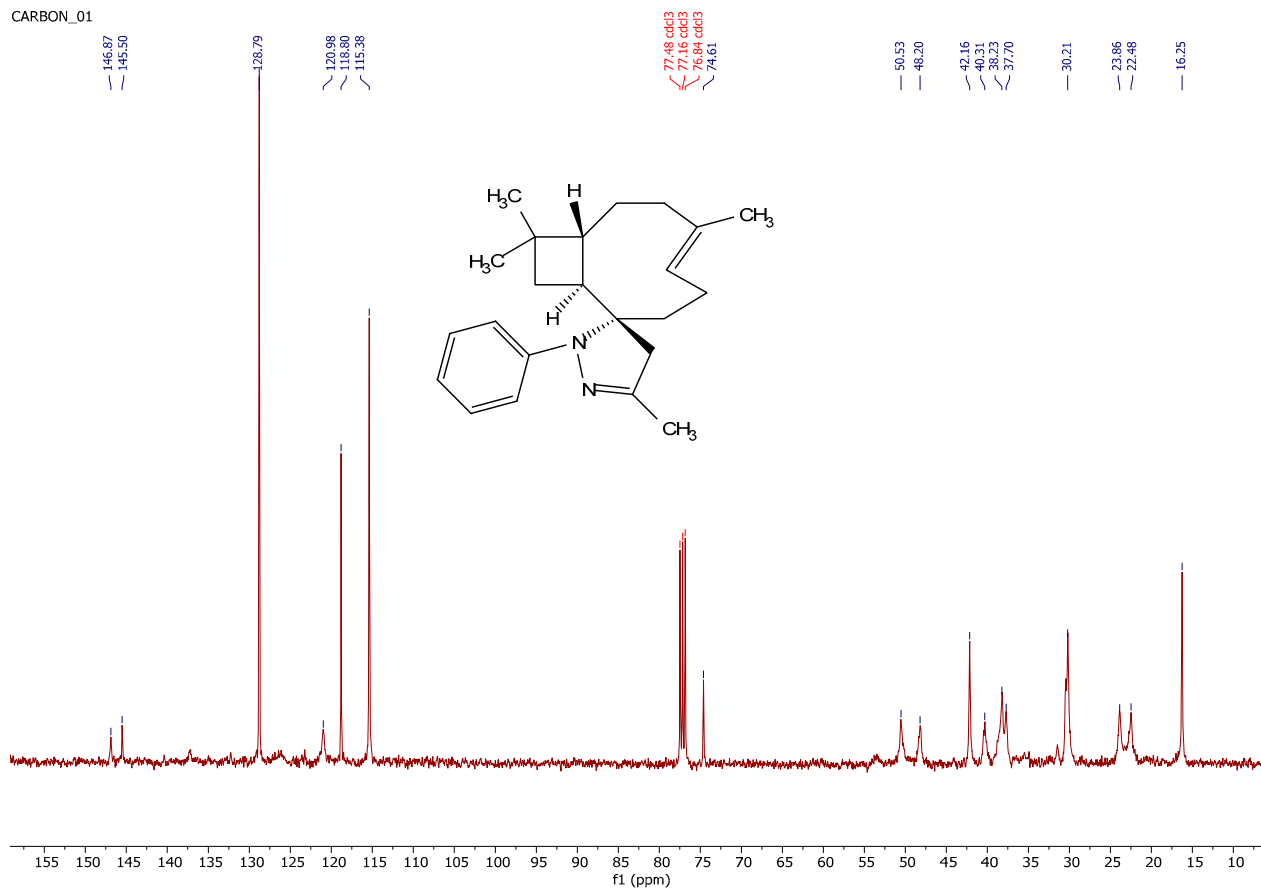
Figure S36. ^{13}C NMR spectra of compound **21a.**

Figure S37. ¹H NMR spectra of compound **21b.**

Figure S38. ¹³C NMR spectra of compound **21b.**

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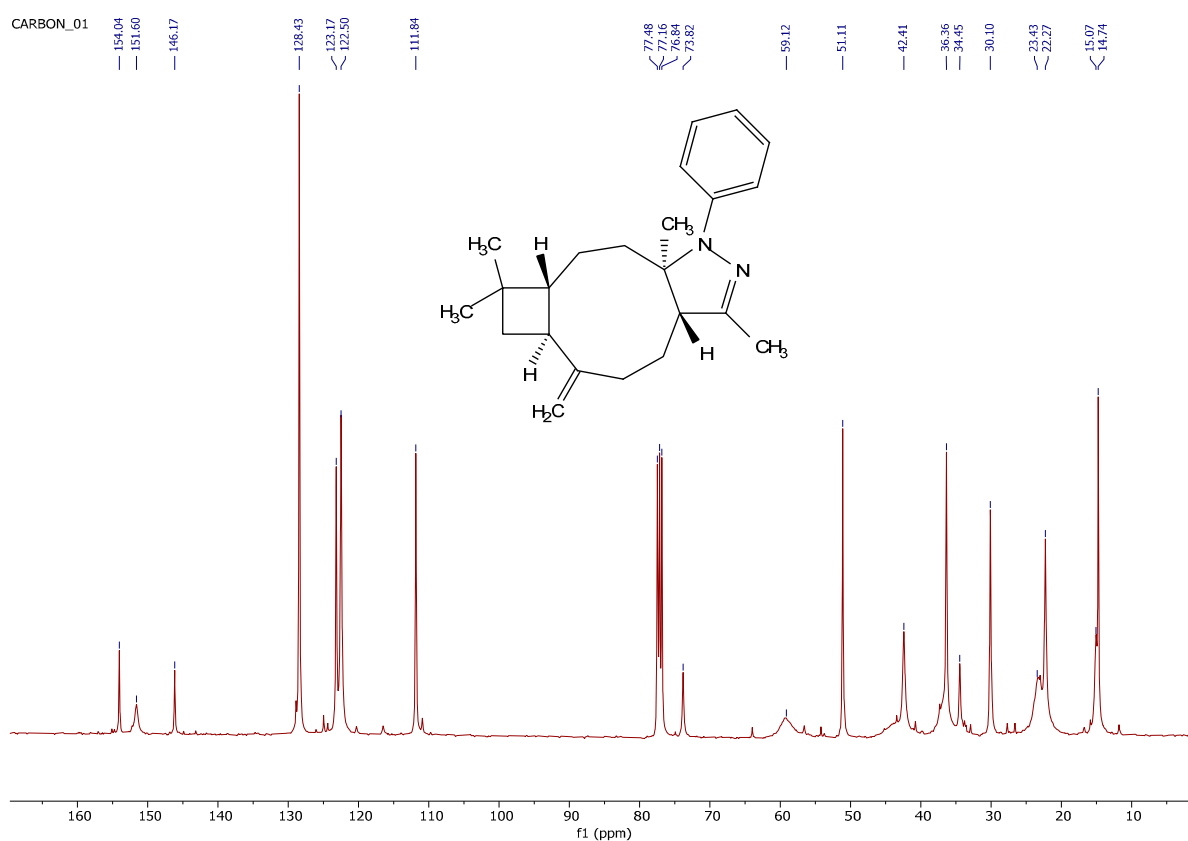
Figure S39. HSQC ^{1}H-^{13}C NMR spectra of compound **21b**.
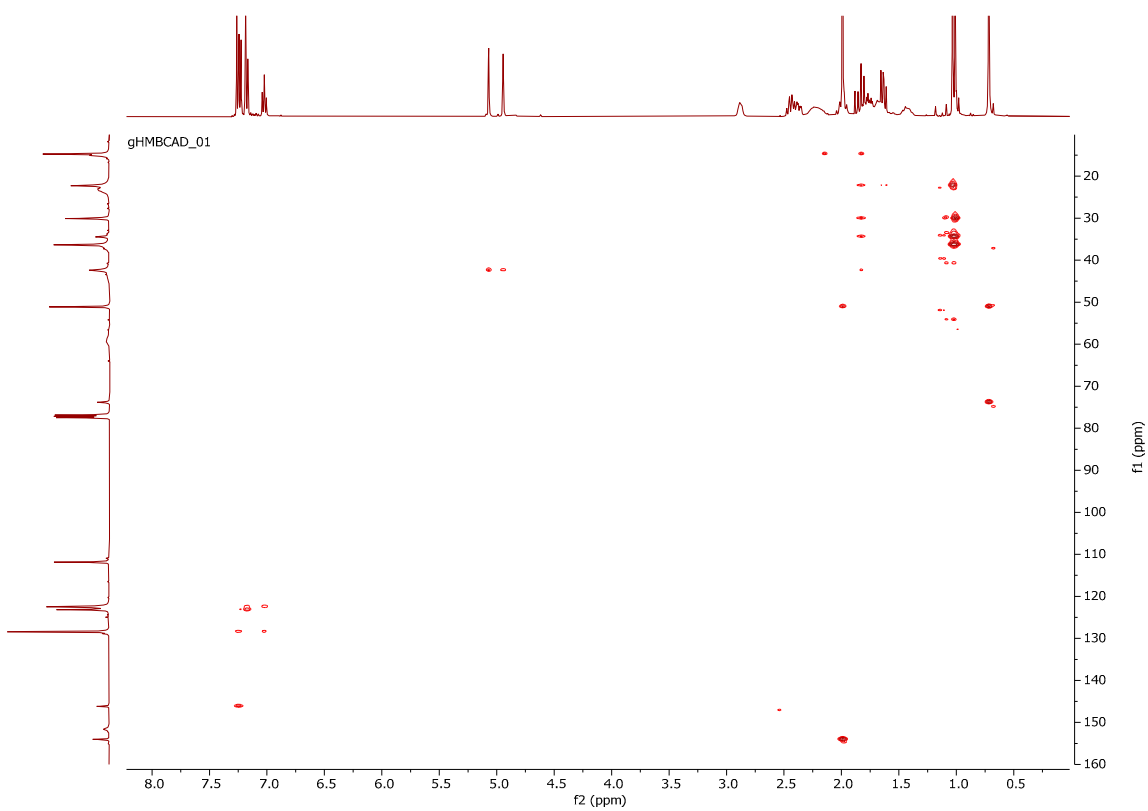
Figure S40. HMBC ^{1}H-^{13}C NMR spectra of compound **21b**.
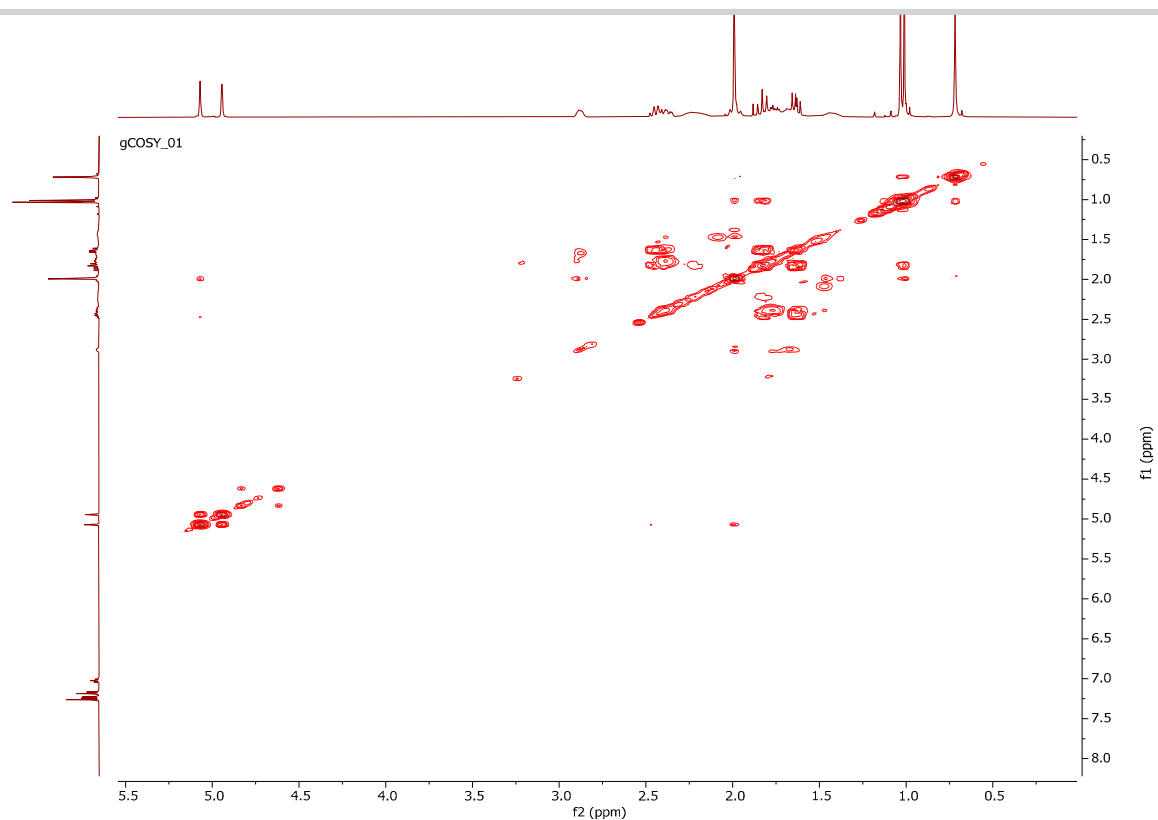
Figure S41. COESY ^{1}H-^{1}H NMR spectra of compound **21b**.
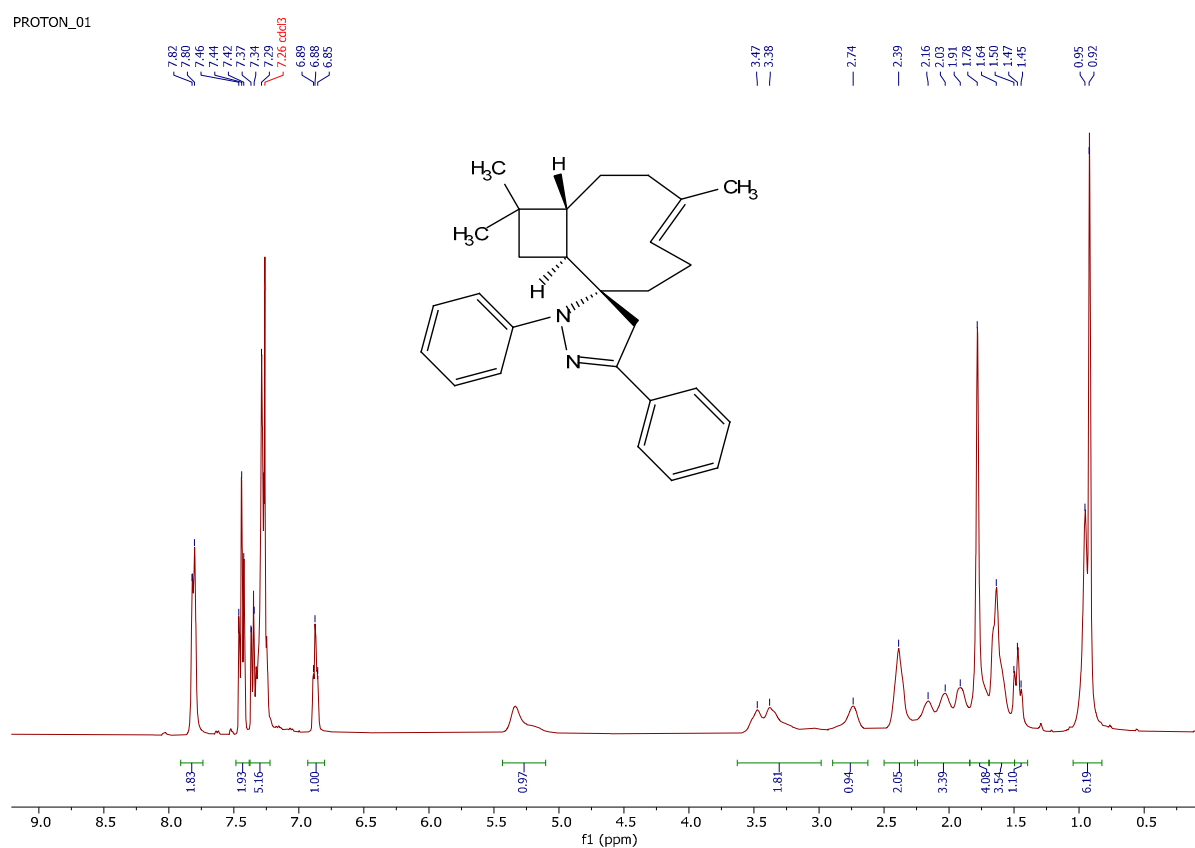
Figure S42. ^{1}H NMR spectra of compound **22a.**
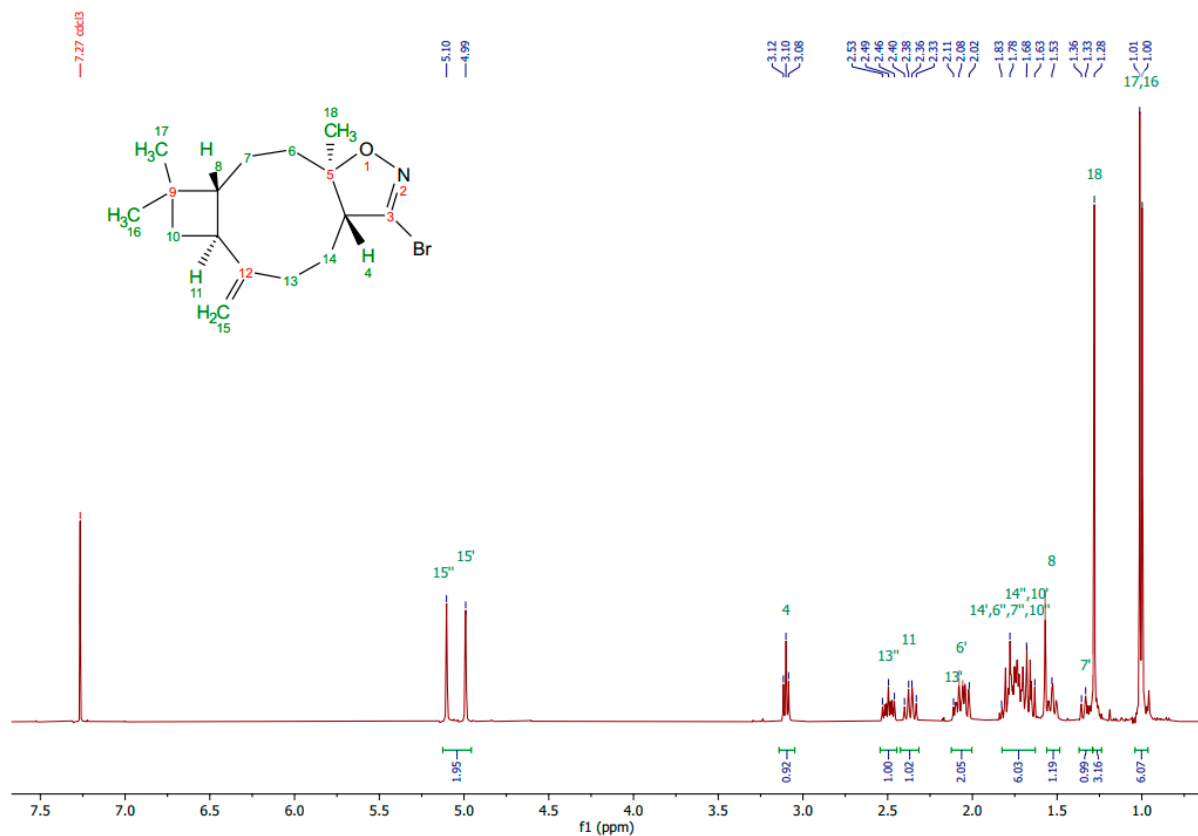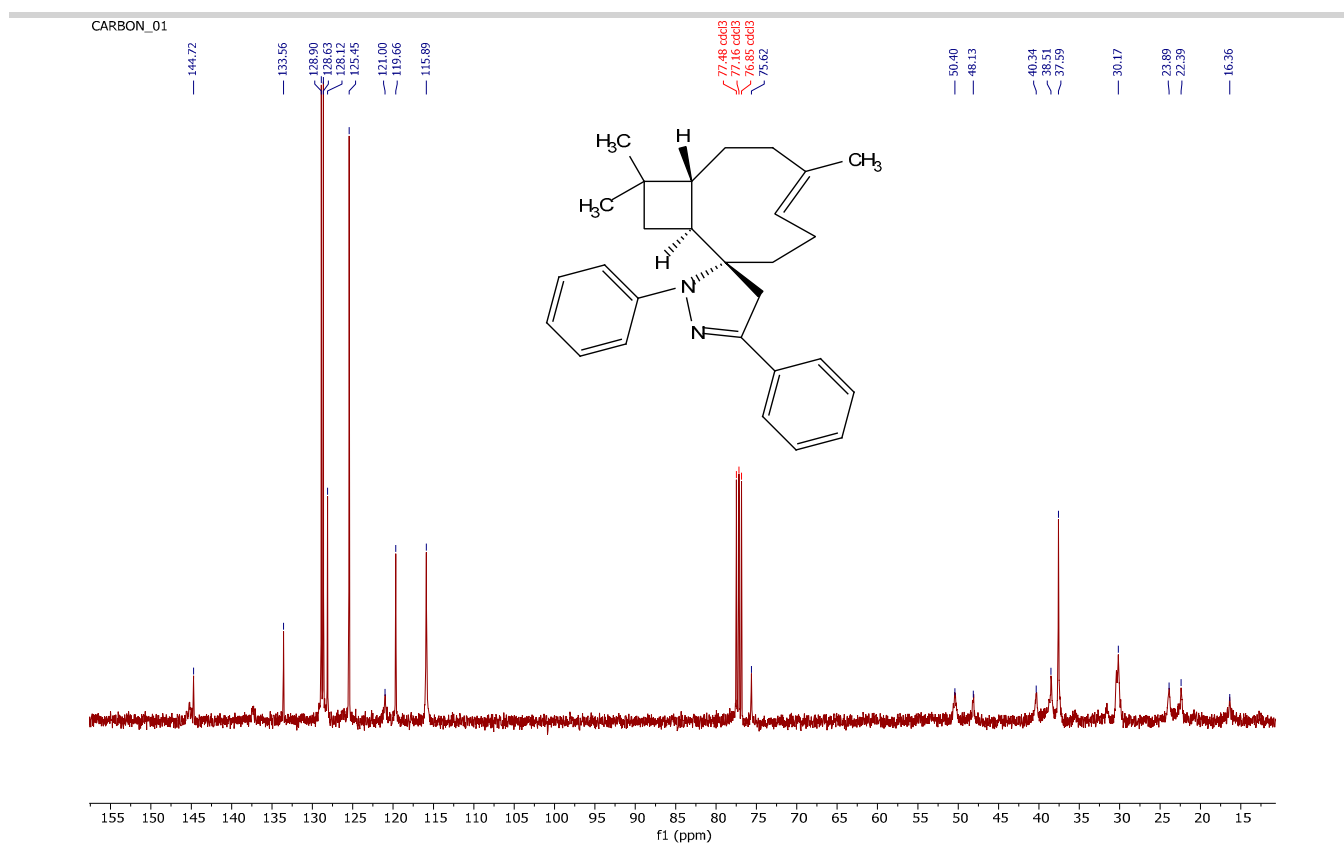
Figure S43. ^{13}C NMR spectra of compound **22a.**

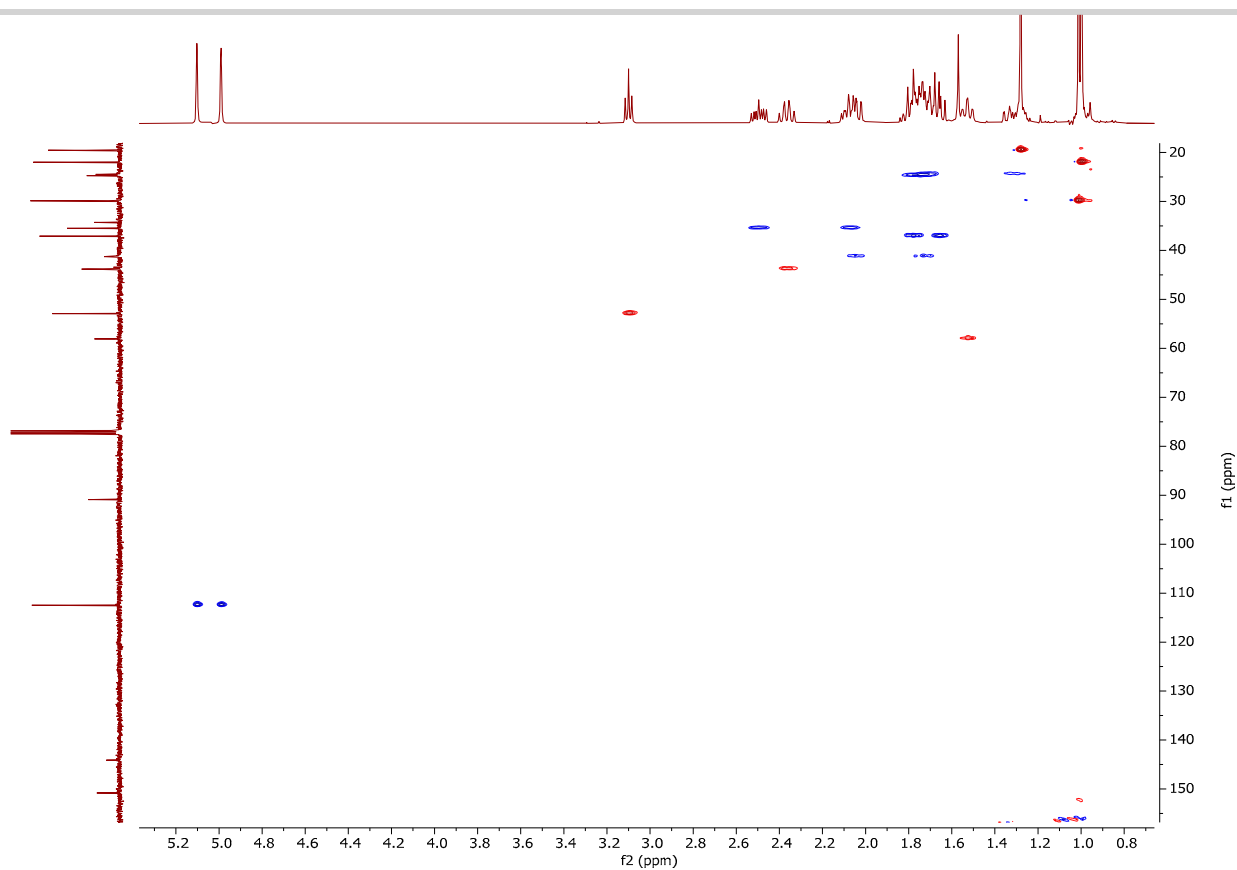Figure S44. ^{1}H NMR spectra of compound **22b.**

152.89
152.51
144.90
133.43
128.58
128.38
128.09
126.82
122.66
121.40
111.64
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
72.84
56.96
49.79
45.80
38.53
36.62
35.73
33.82
30.14
26.85
24.77
22.14
18.50

f1 (ppm)

Figure S45. ^{13}C NMR spectra of compound **22b.**

7.35
7.34
7.29
7.27
7.26 cdcl3
7.24
7.23
7.22
6.60
6.58
5.15
3.81
3.48
3.17
2.61
2.29
2.26
2.24
2.15
2.02
1.77
1.61
1.52
0.95
0.92

0.75
1.45
0.73
2.00
0.95
6.17
0.88
0.97
1.05
1.96
1.12
4.09
7.05
6.01

f1 (ppm)

Figure S46. ^{1}H NMR spectra of compound **23a.**

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Figure S47. ¹³C NMR spectra of compound **23a.**

Figure S48. ¹H NMR spectra of compound **23b.**
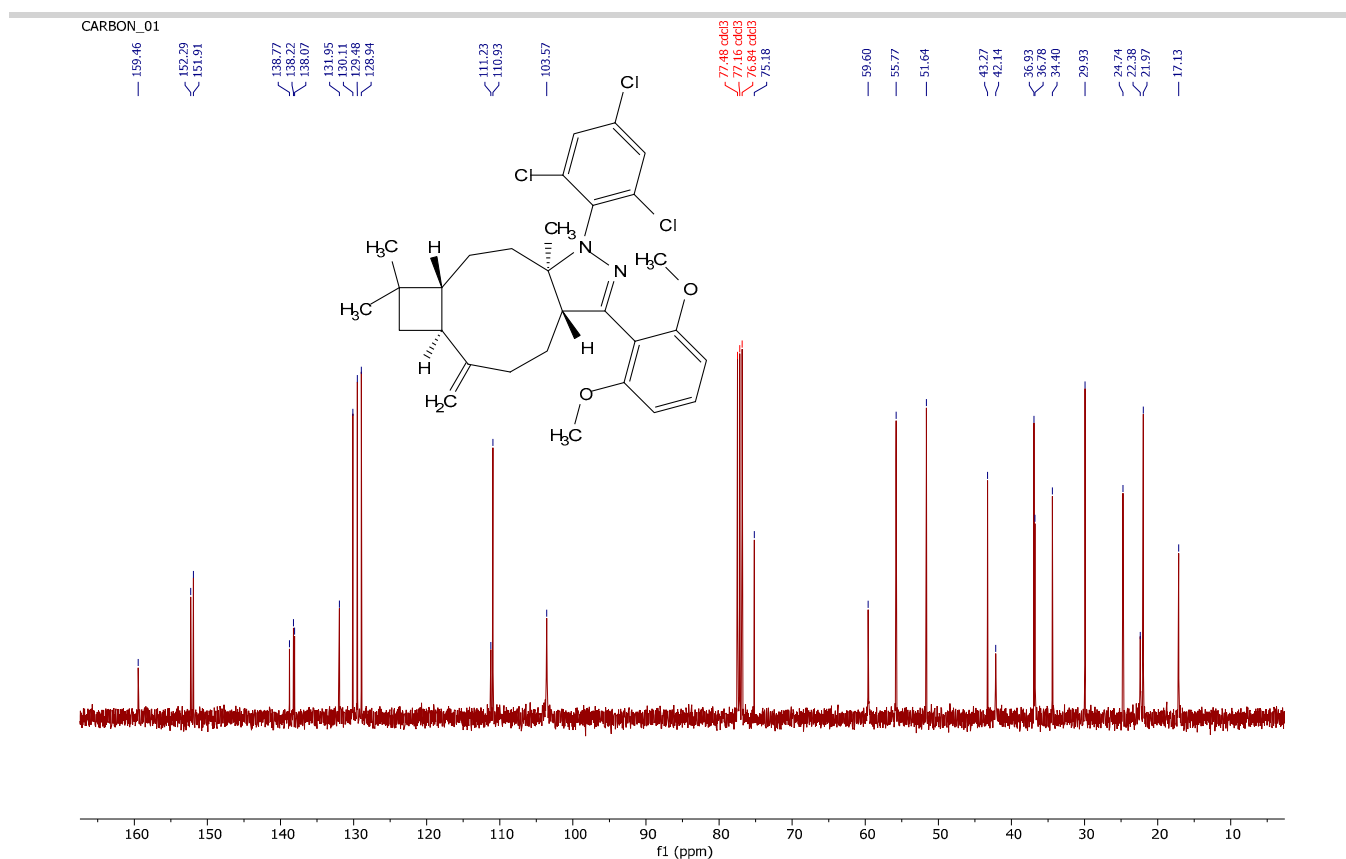
Figure S49. ¹³C NMR spectra of compound **23b.**
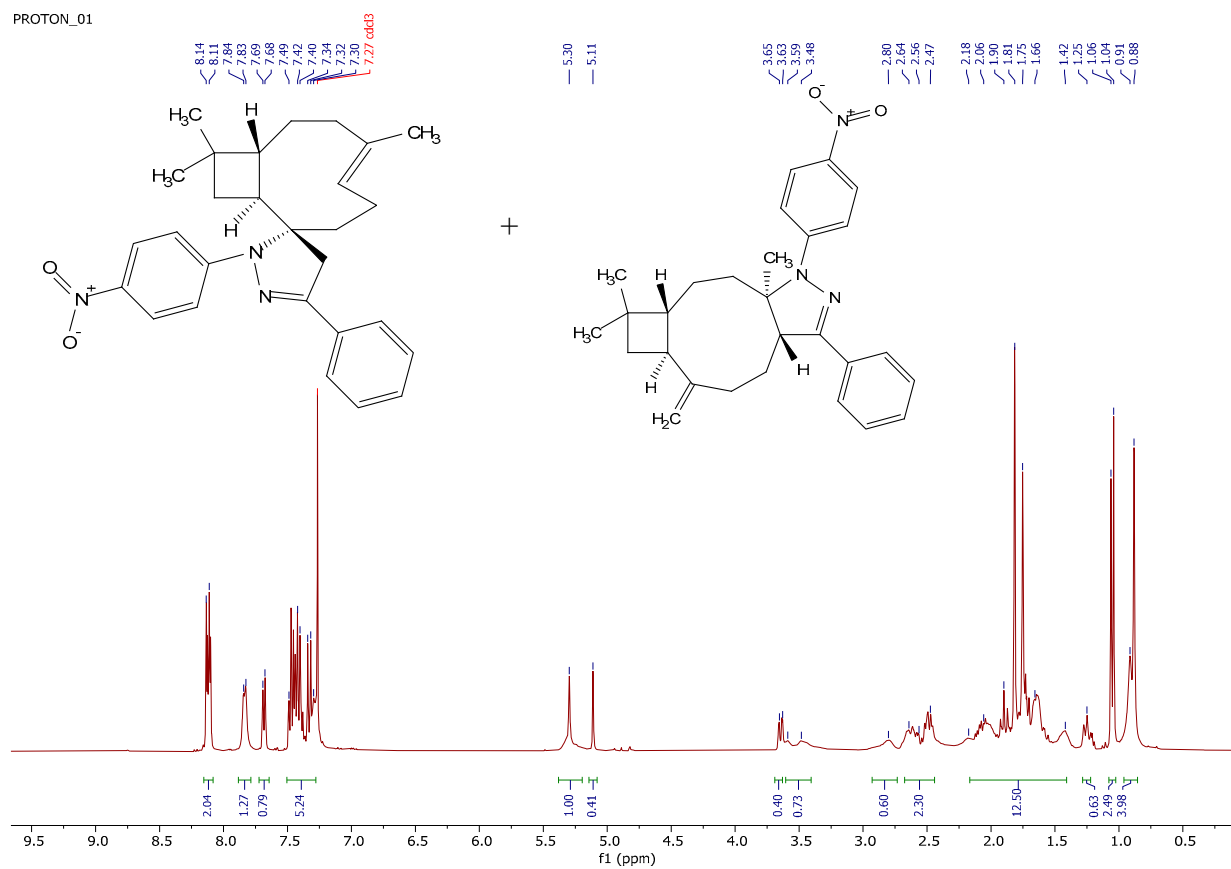
Figure S50. ¹H NMR spectra of mixture of compounds **24a** and **24b**.
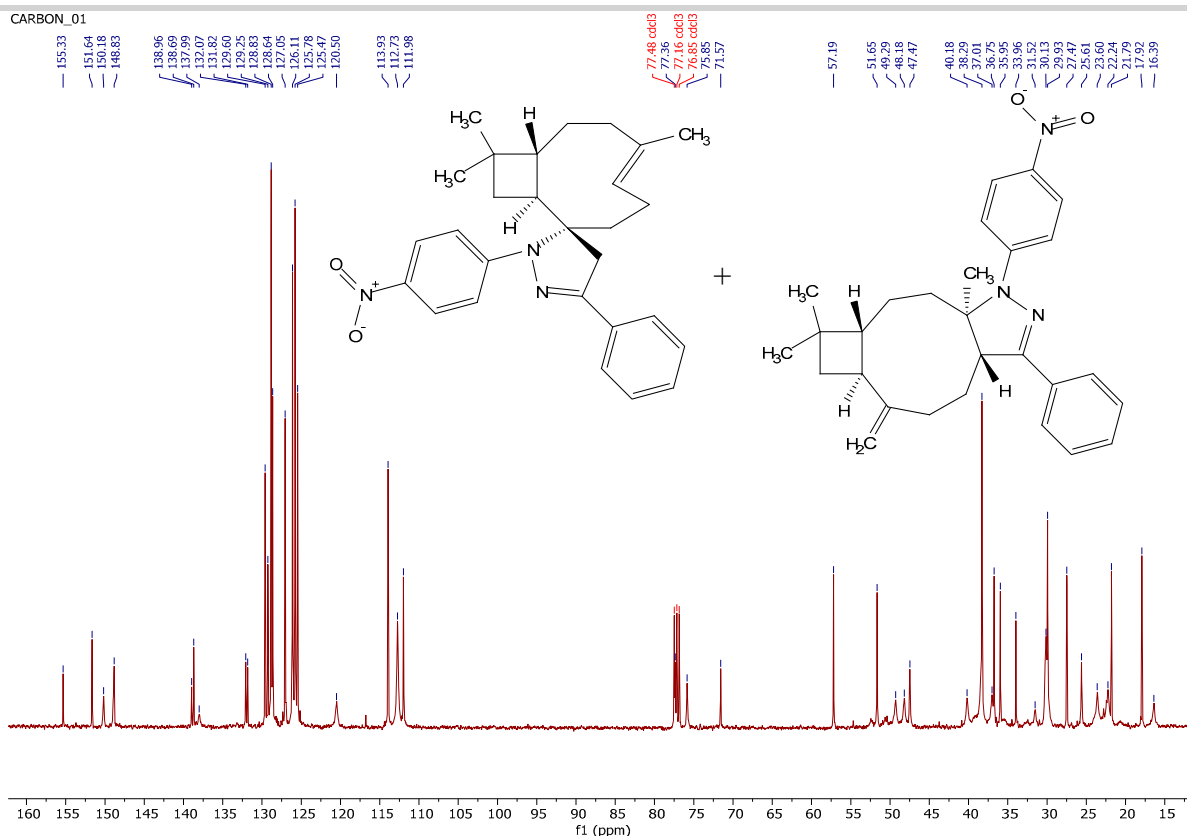
Figure S51. ¹³C NMR spectra of mixture of compounds **24a** and **24b**.
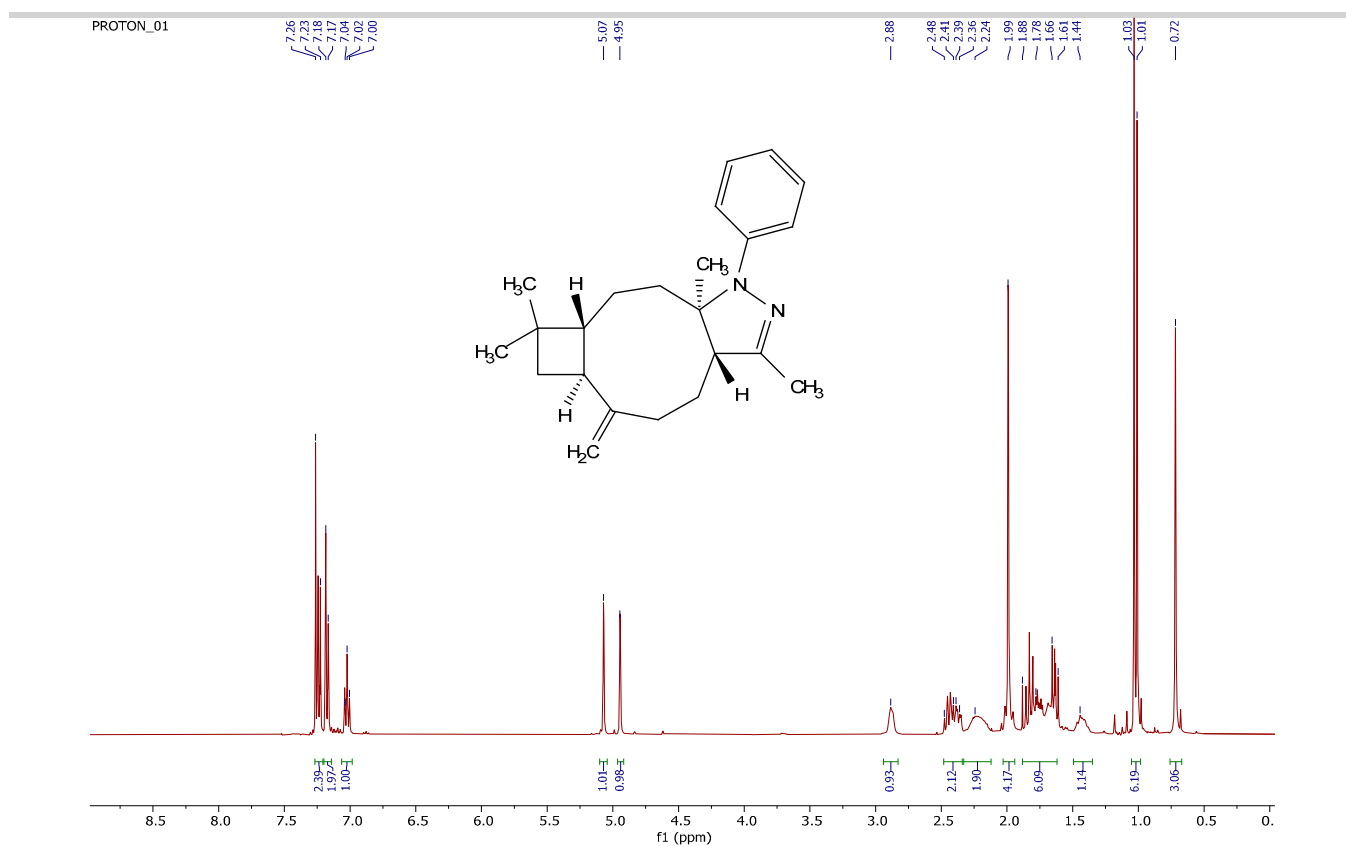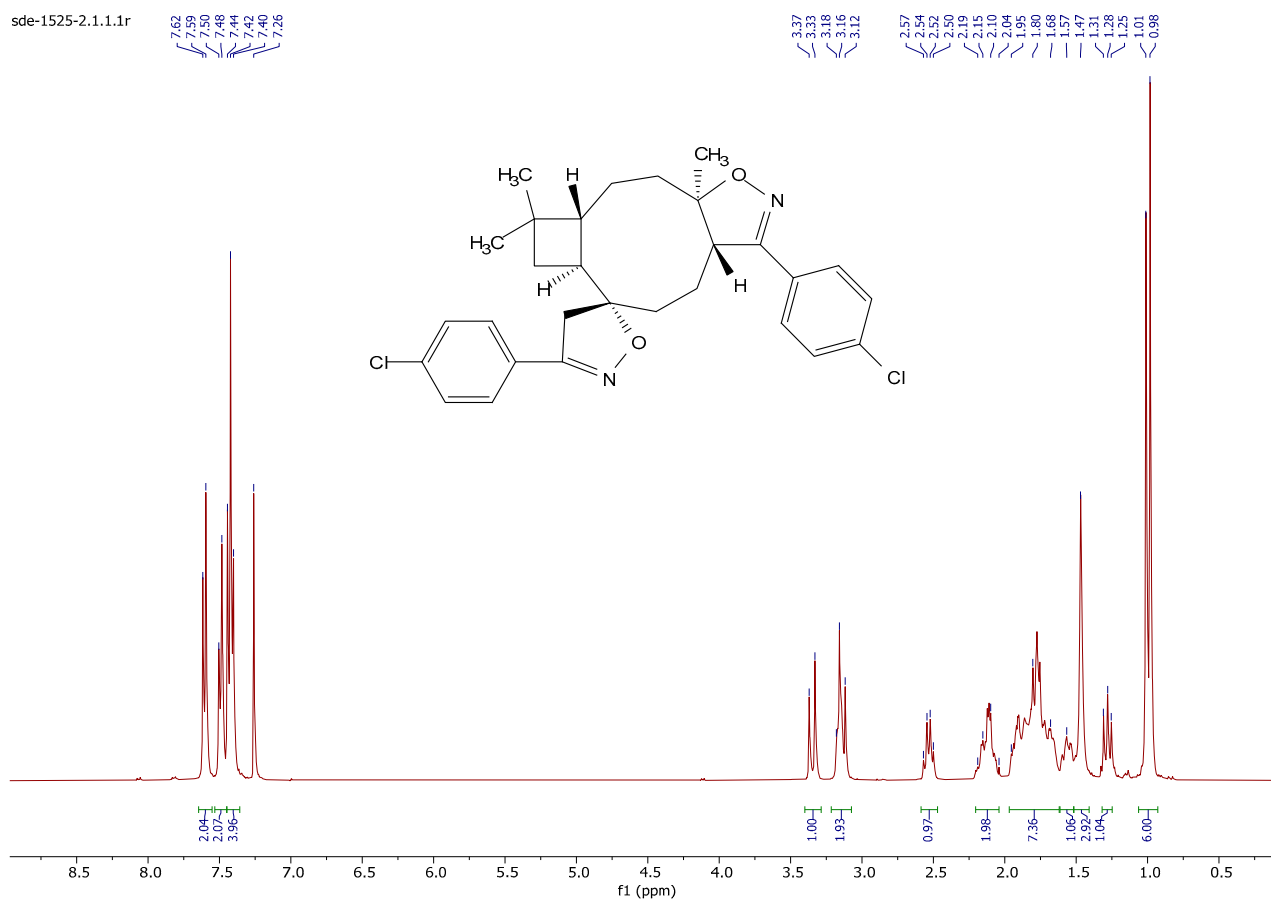

Figure S52. ¹H NMR spectra of compound **25.**
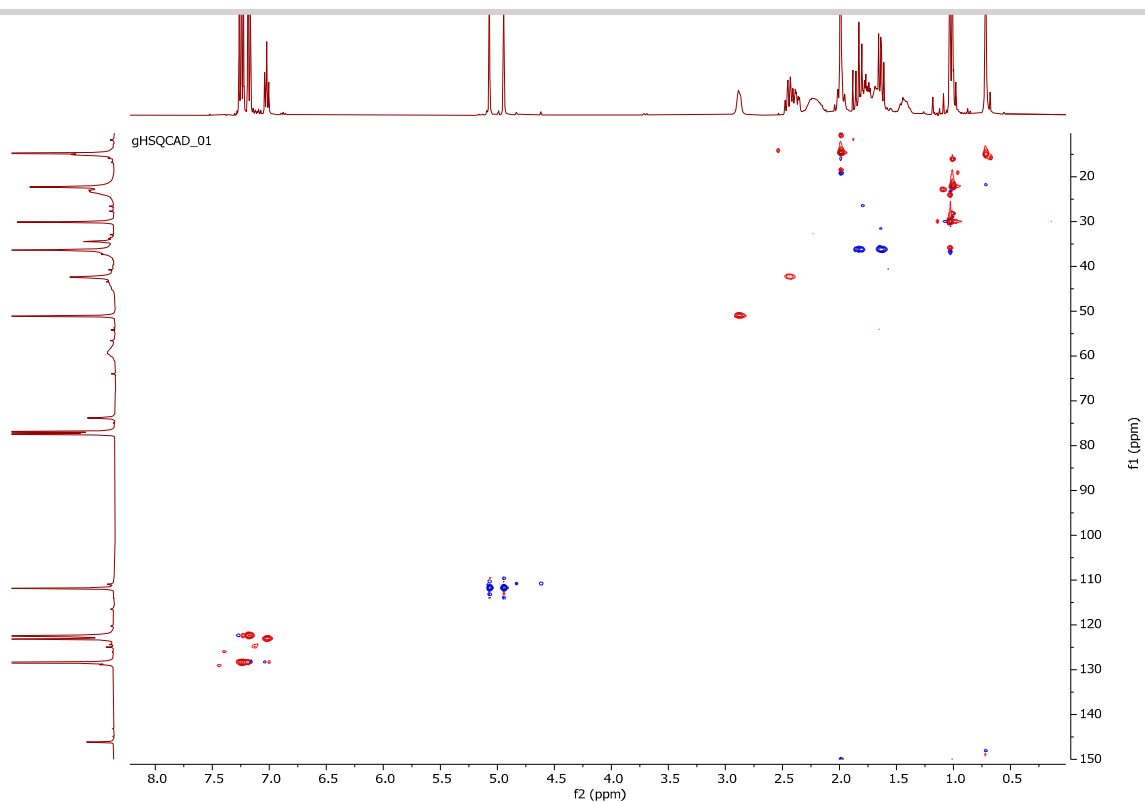
Figure S53. ^{13}C NMR spectra of compound **25.**

Figure S54. ^{1}H NMR spectra of compound **26.**

Figure S55. ^{13}C NMR spectra of compound **26.**
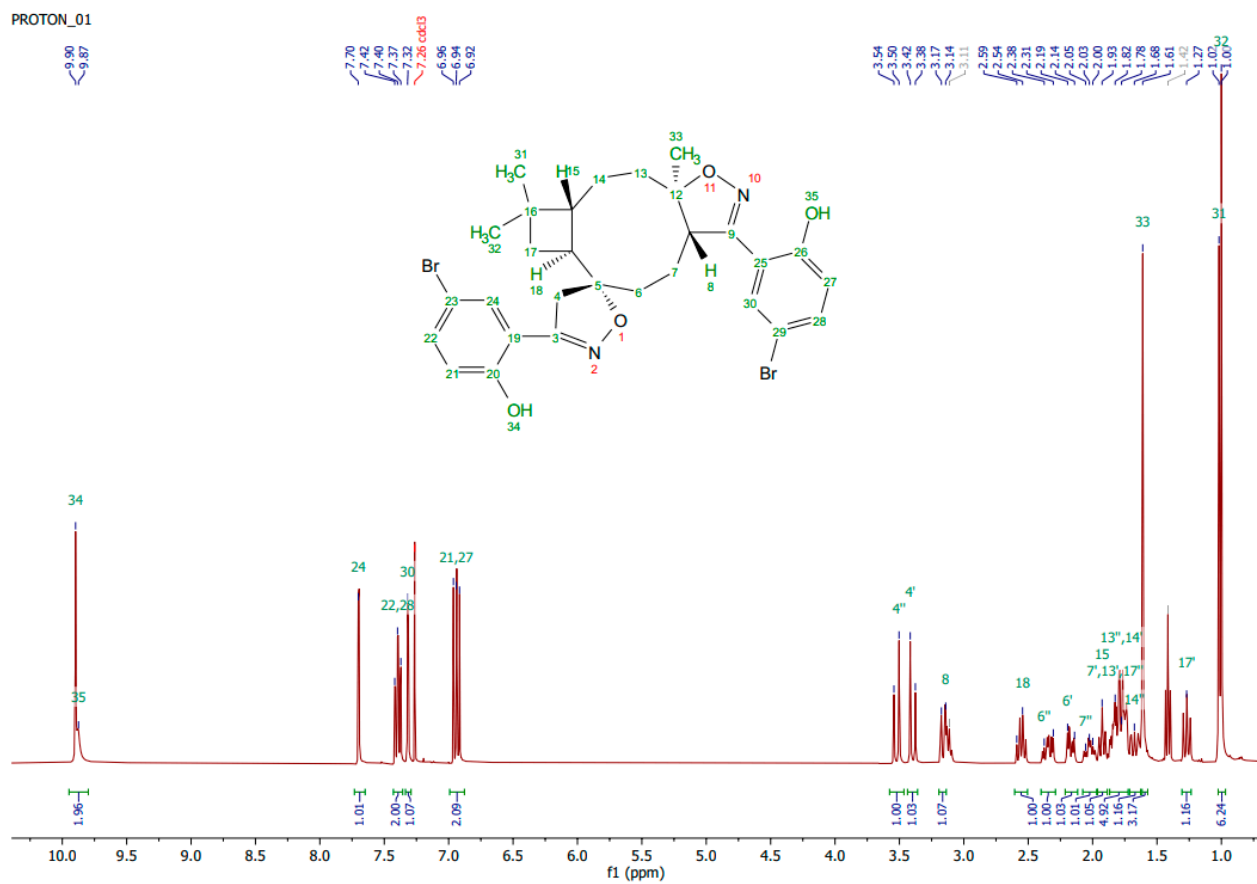
Figure S56. ^{1}H NMR spectra of compound **27.**

Figure S67. ^{13}C NMR spectra of compound **27.**
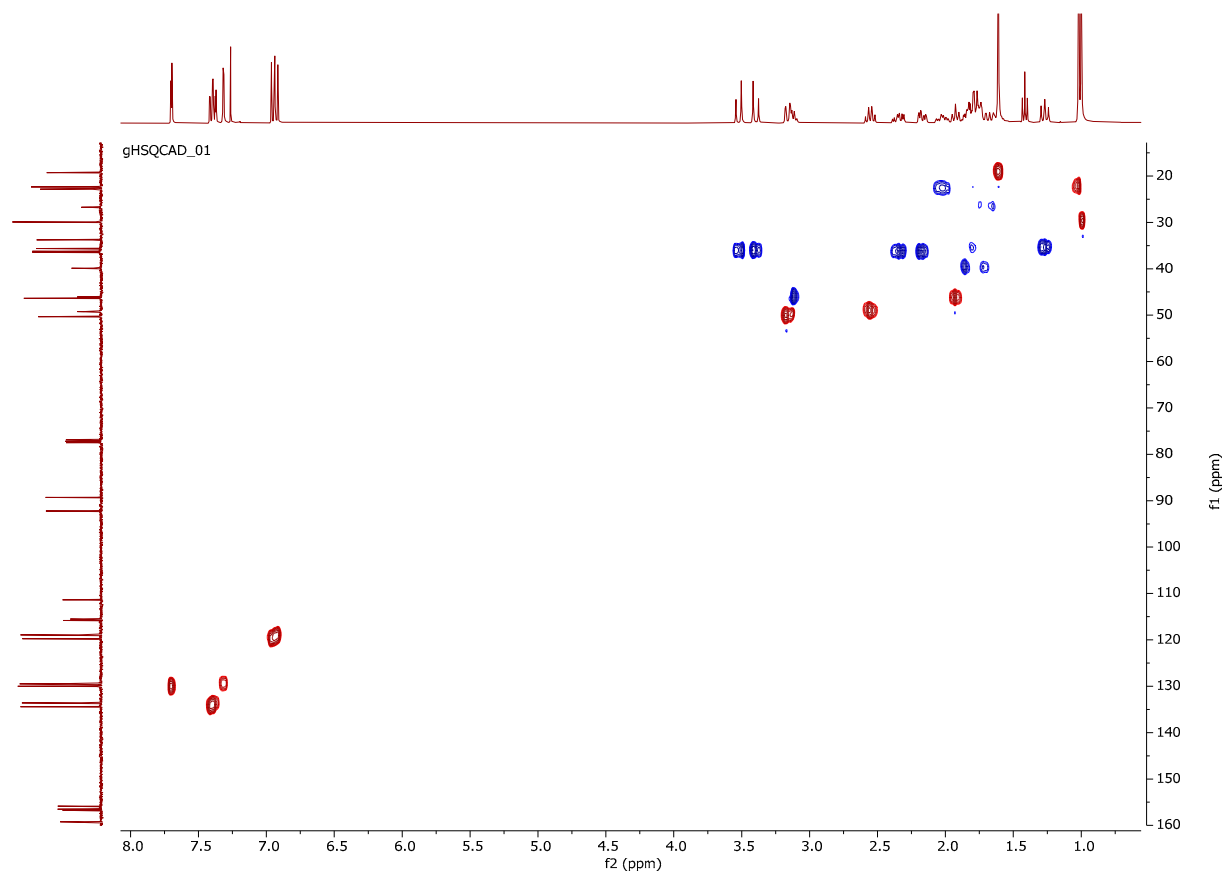
Figure S58. HSQC ^{1}H-^{13}C NMR spectra of compound **27**.

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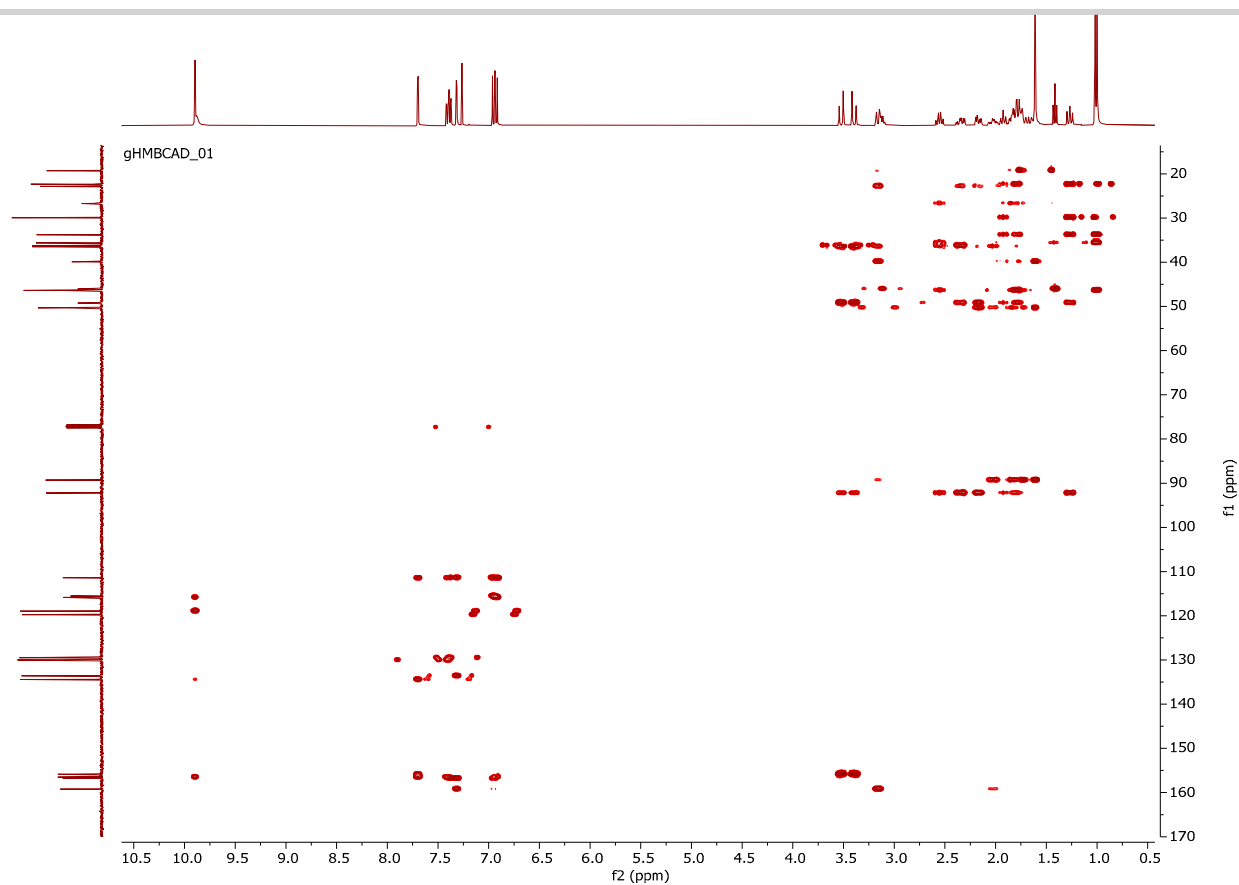
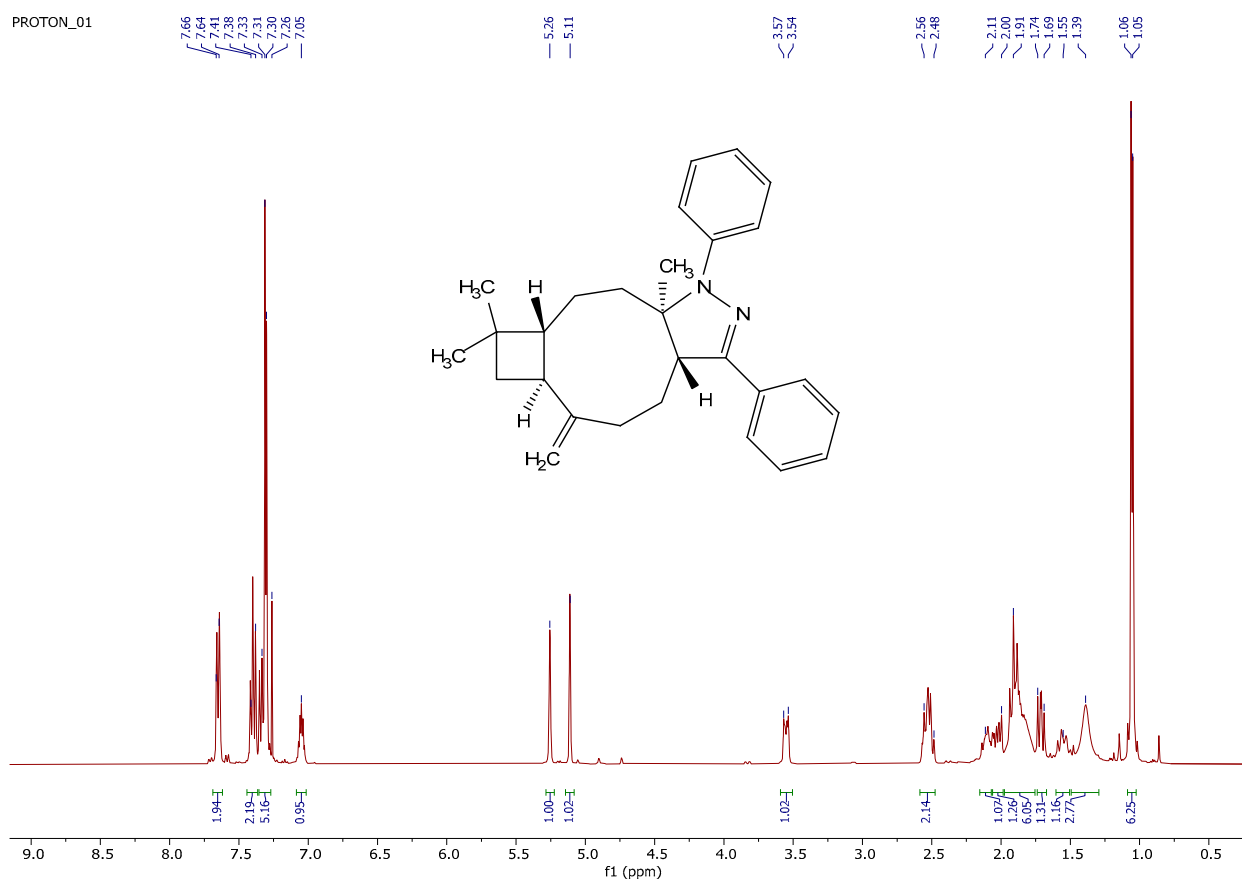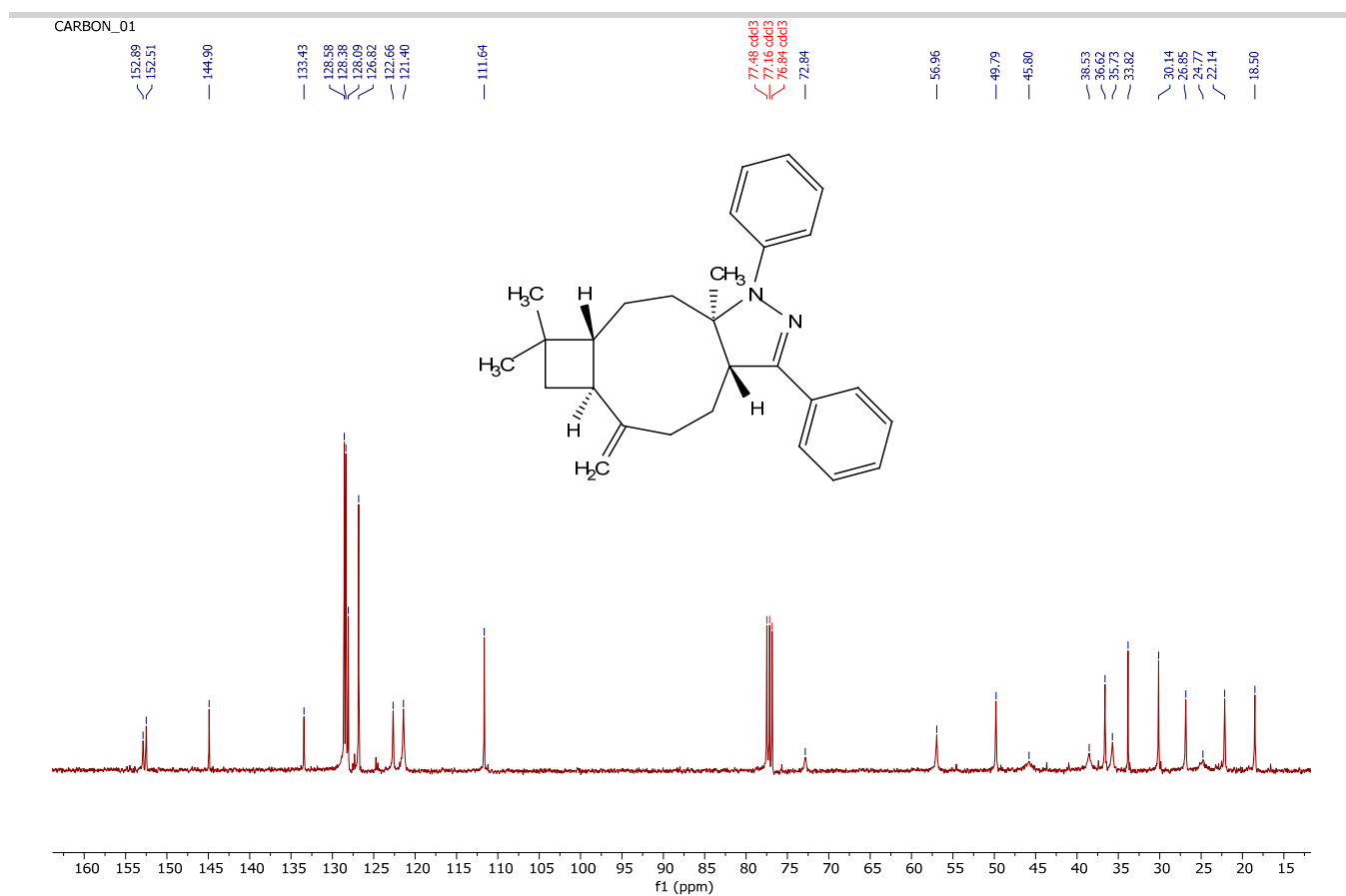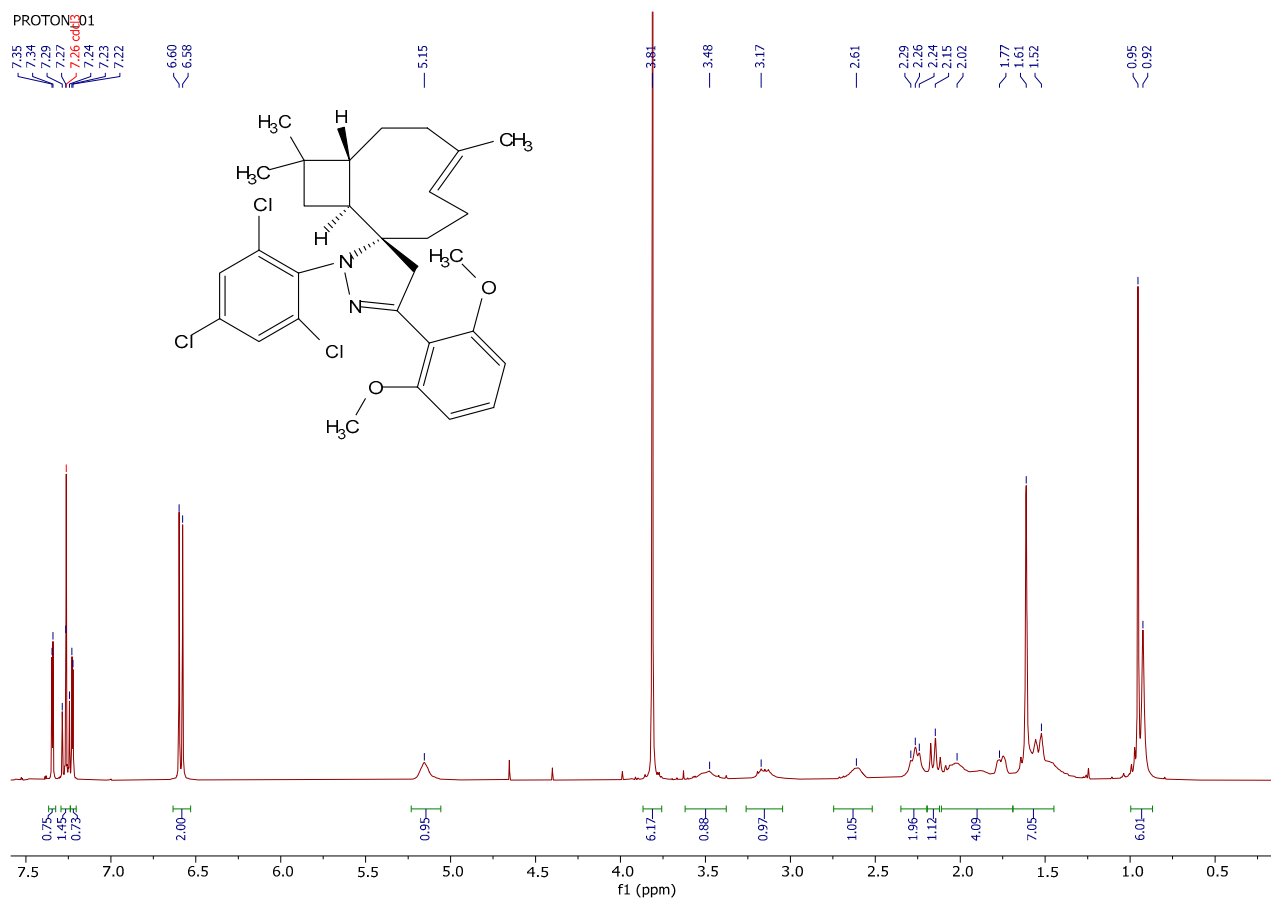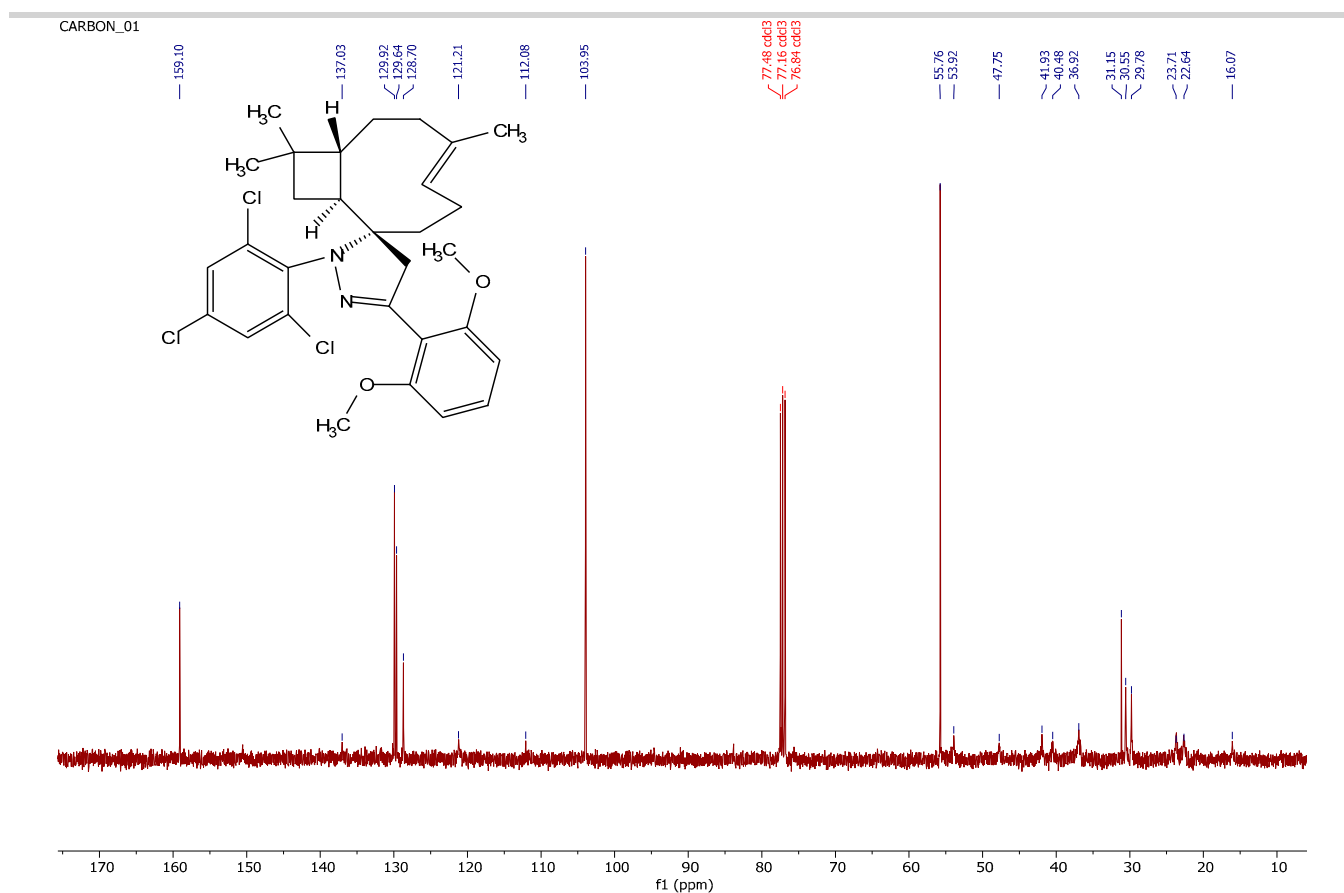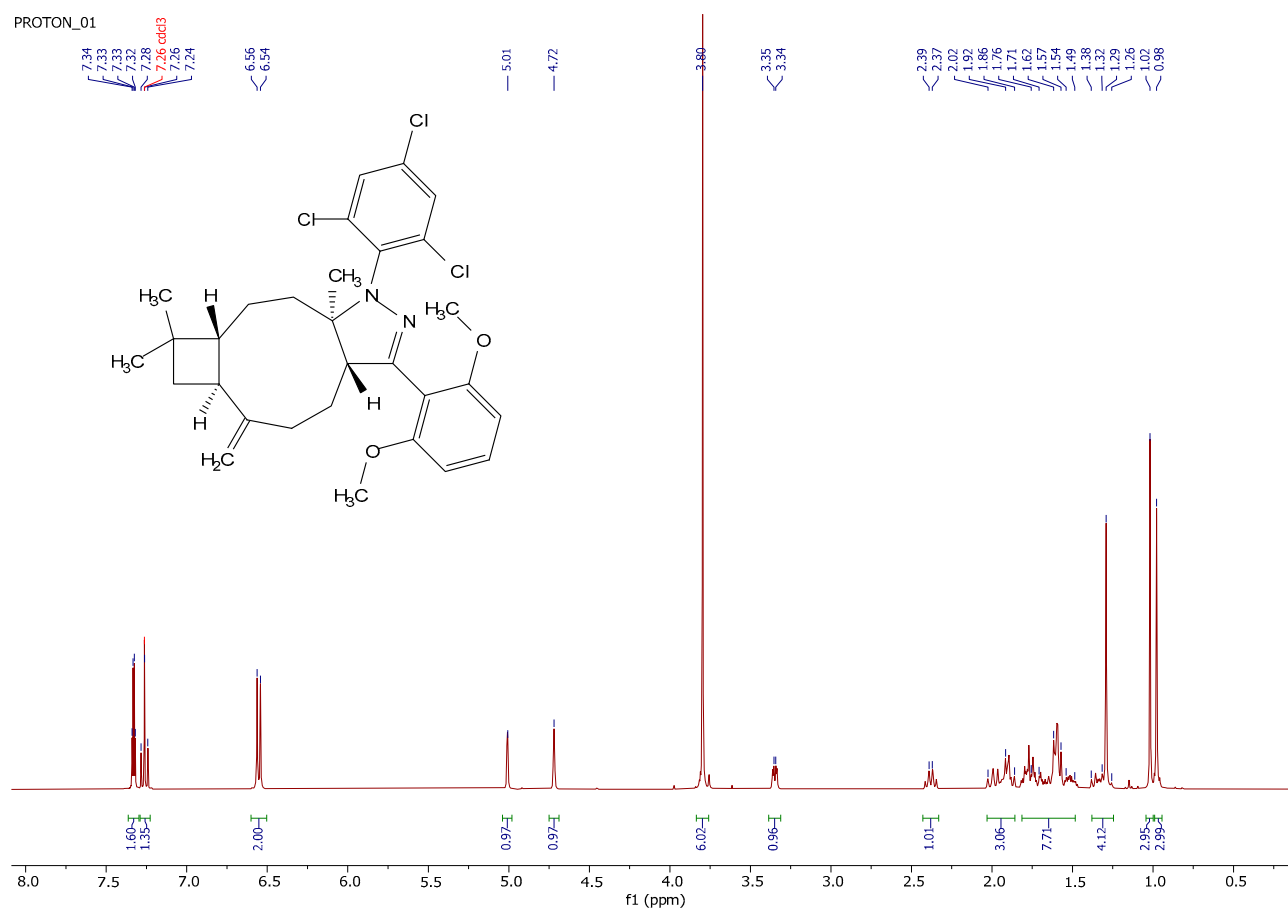Figure S59. HMBC ^{1}H-^{13}C NMR spectra of compound **27**.
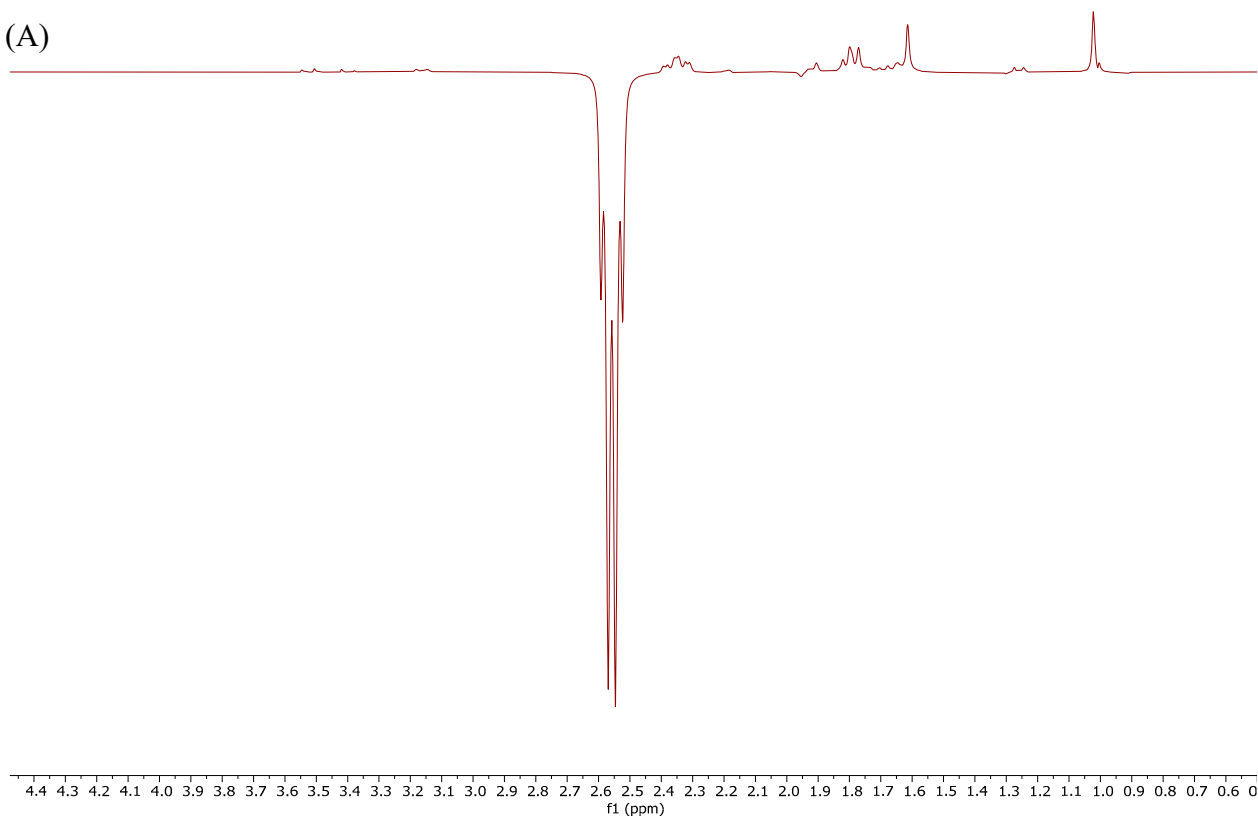
Selective band center: 3.52 (ppm); width: 27.6 (Hz)

(B)

10.0   9.5   9.0   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0
f1 (ppm)
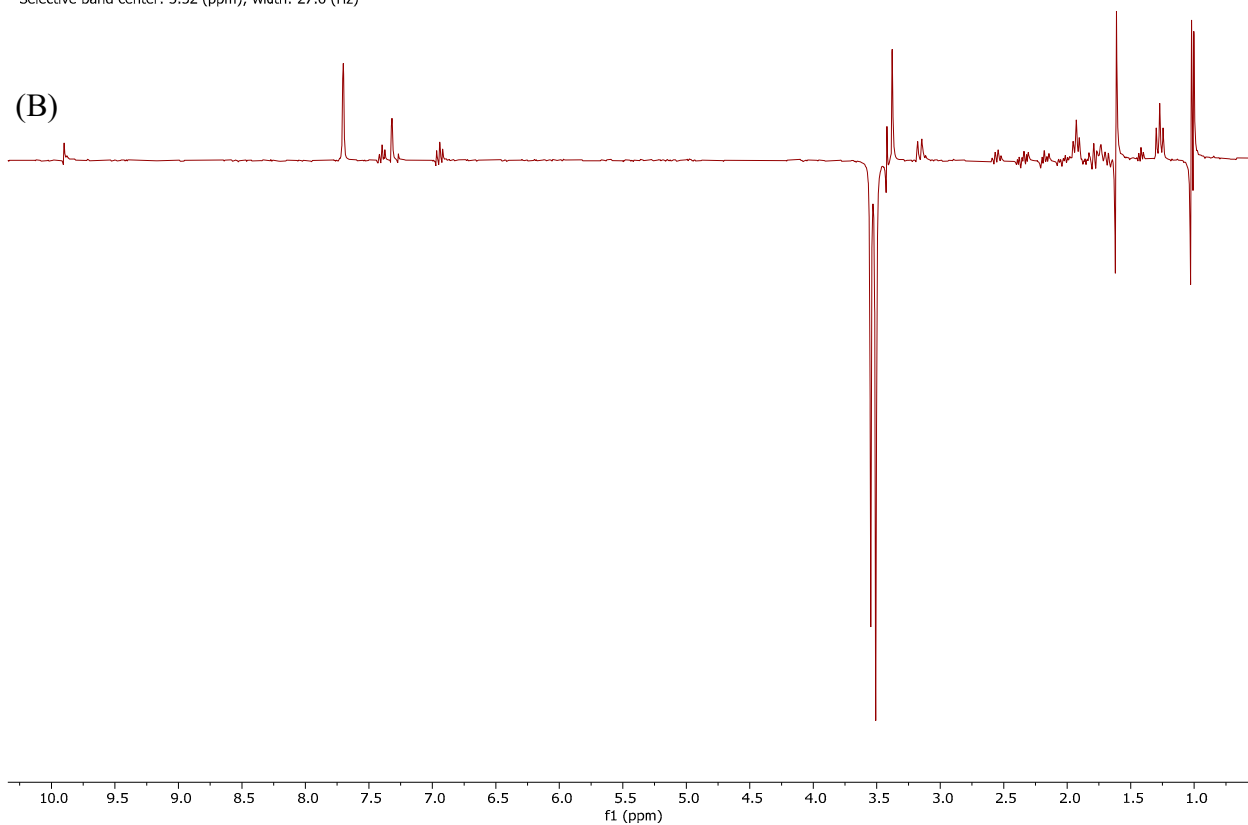
NOESY1D_04

Selective band center: 3.40 (ppm); width: 23.6 (Hz)

(C)

10.0   9.5   9.0   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0
f1 (ppm)
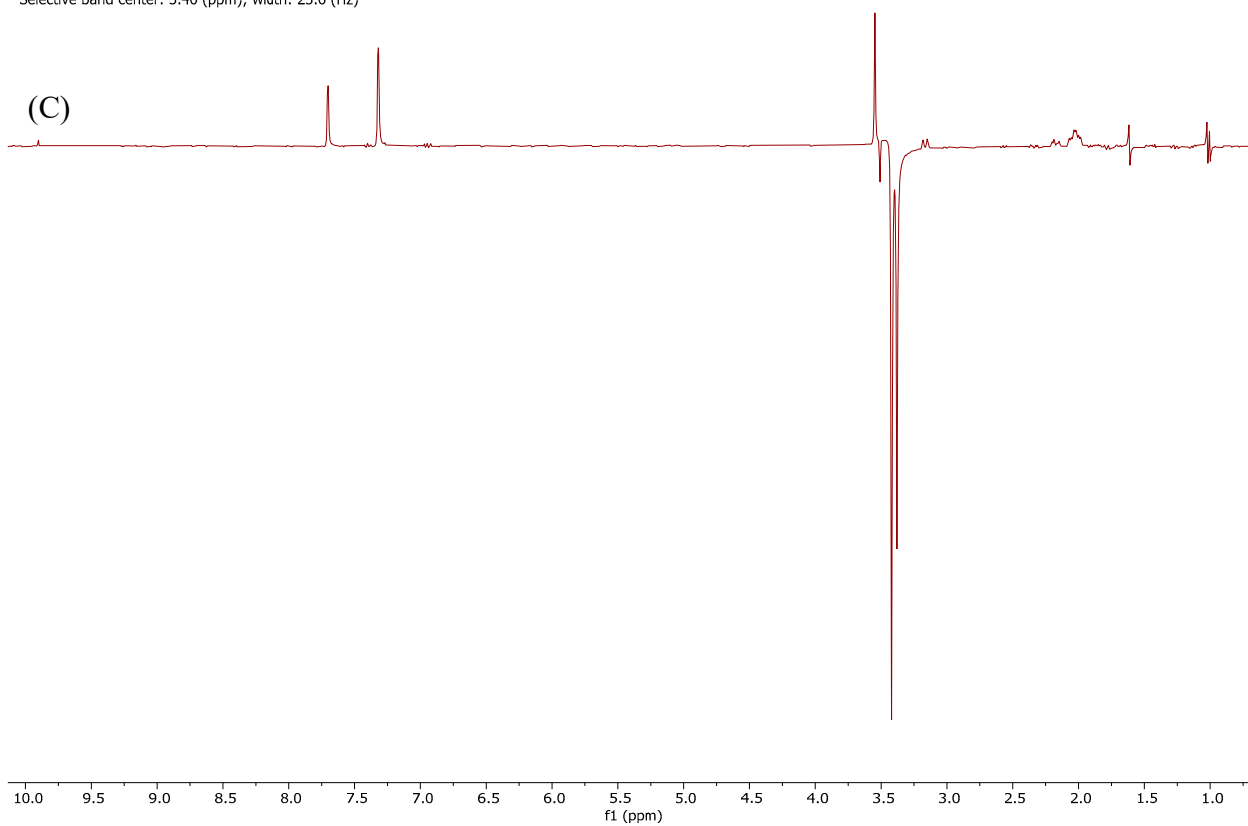
Selective band center: 1.27 (ppm); width: 29.0 (Hz)

(D)

5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f1 (ppm)
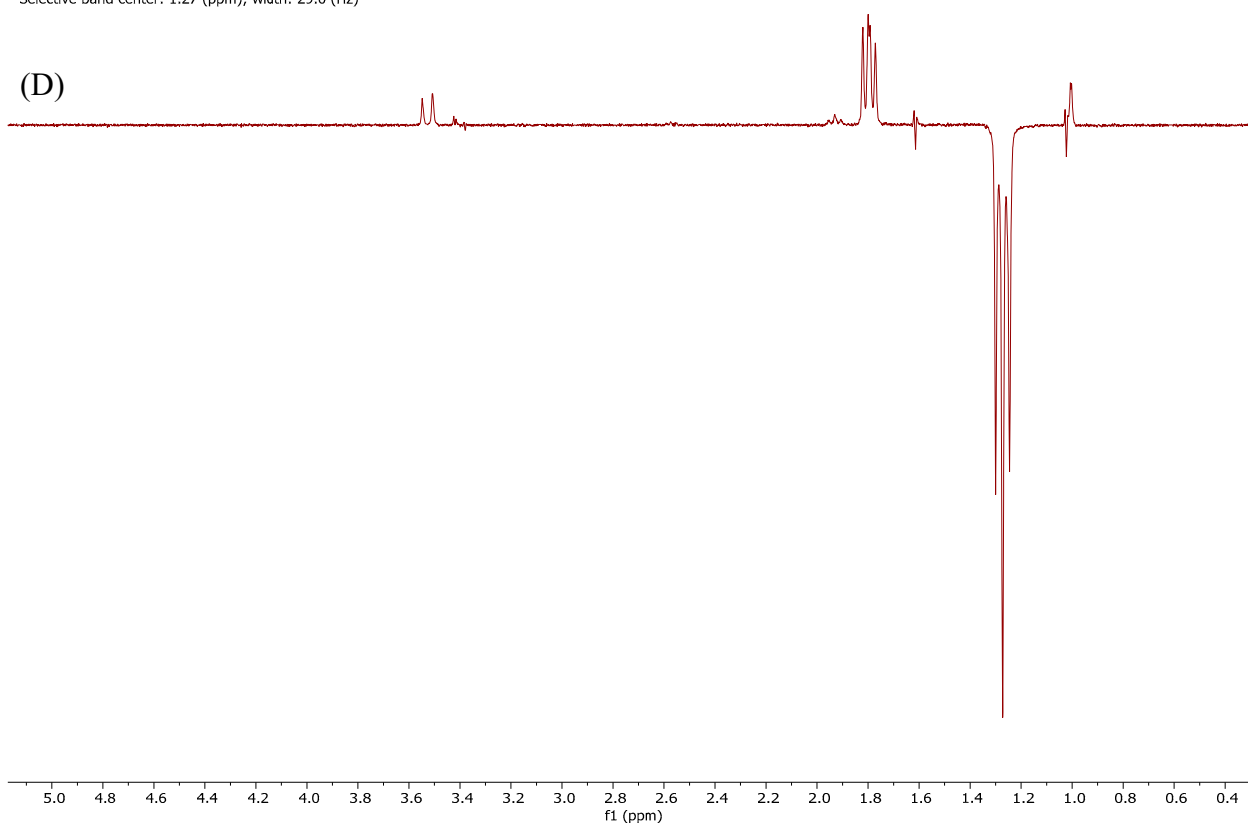
NOESY1D_06

Selective band center: 1.93 (ppm); width: 28.2 (Hz)

(E)

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f1 (ppm)
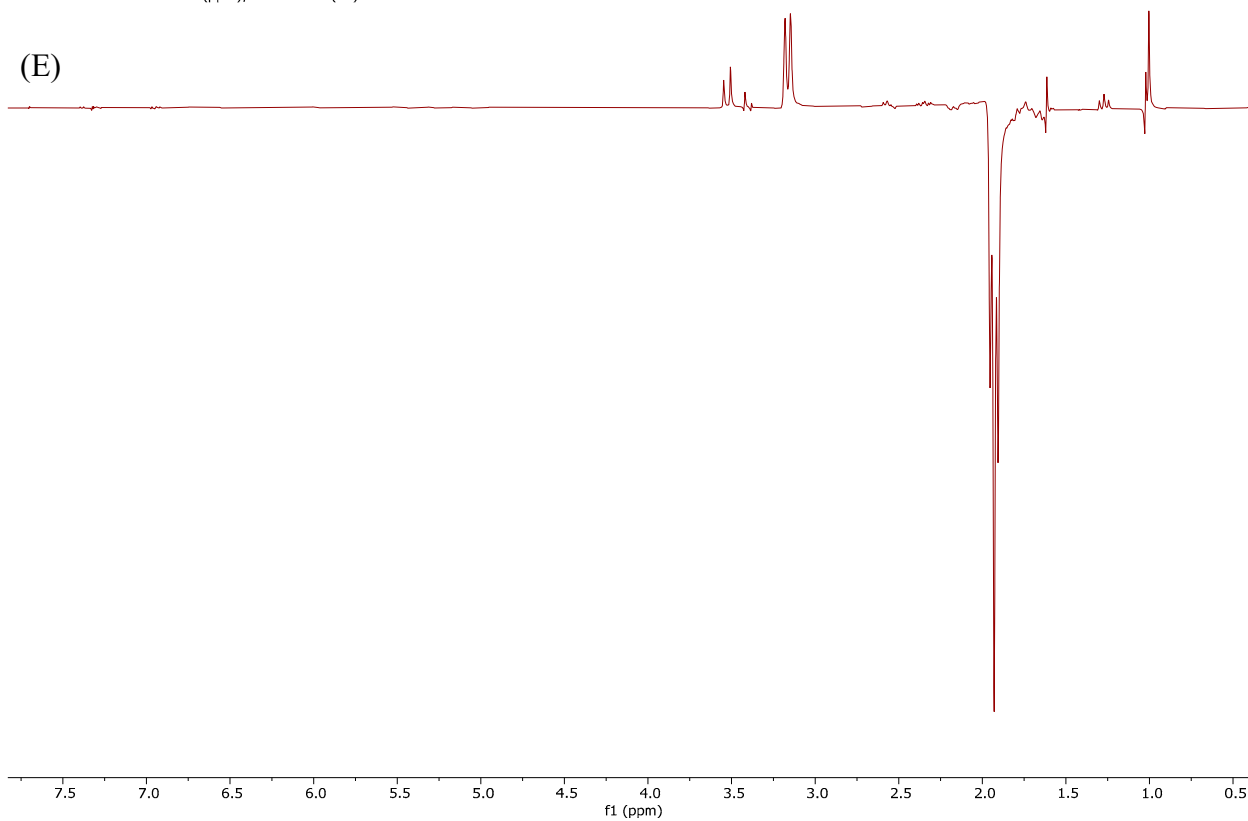
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(F)

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f1 (ppm)
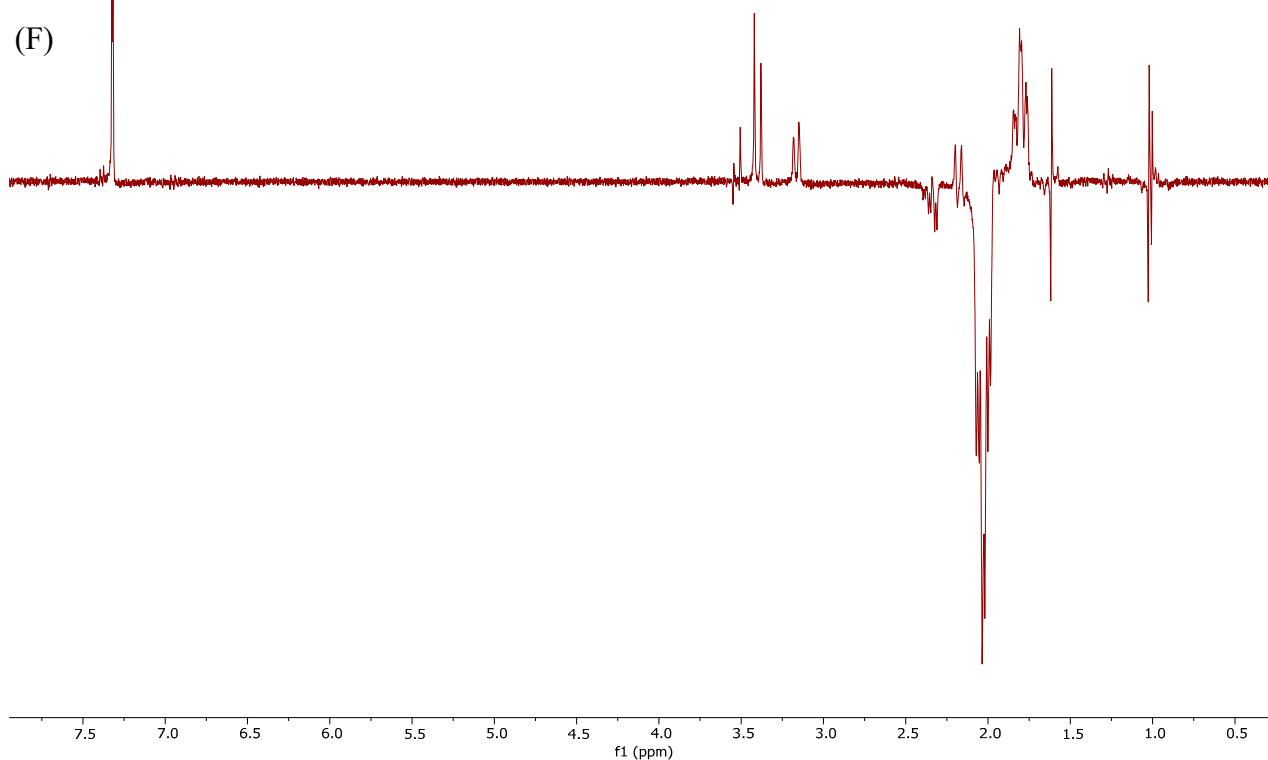
NOESY1D_09

Selective band center: 2.35 (ppm); width: 43.6 (Hz)

(G)

4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f1 (ppm)
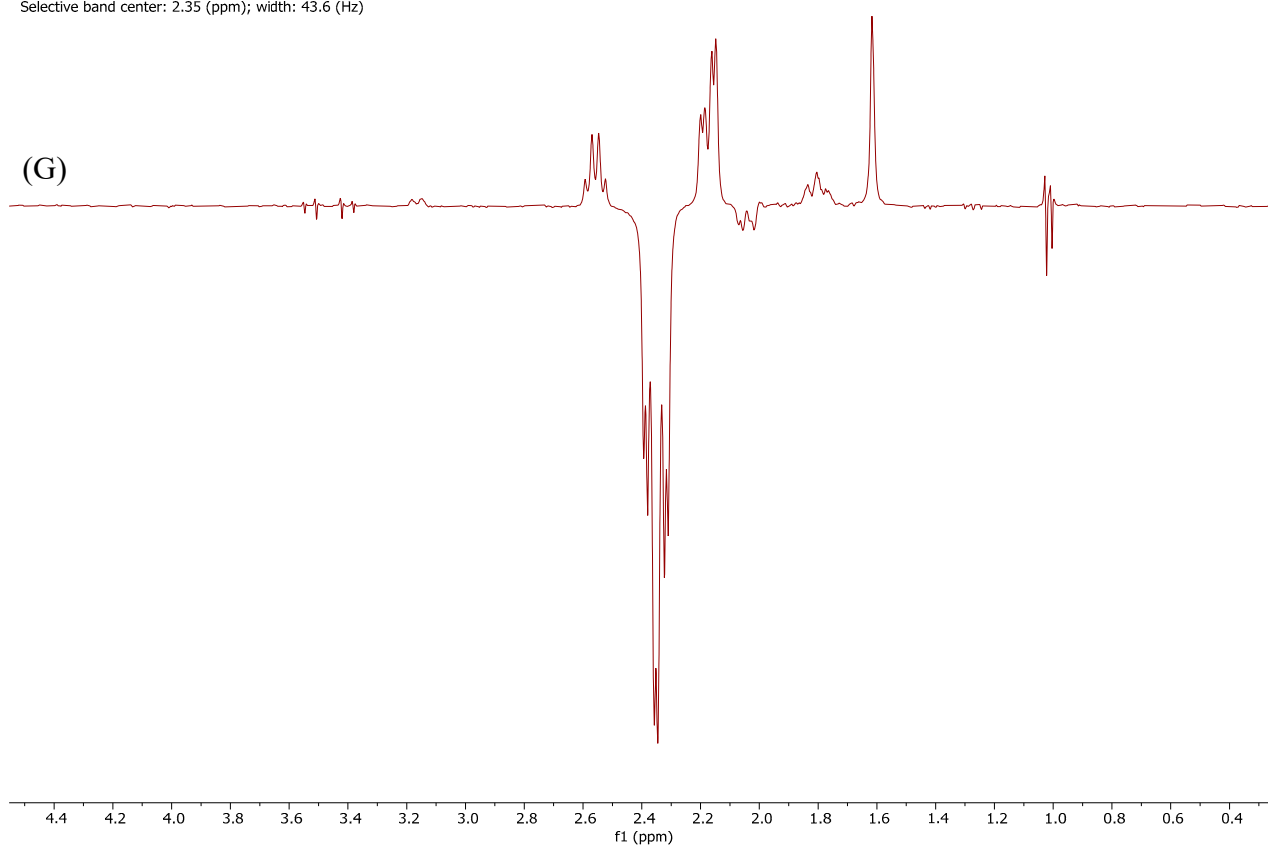
Figure S60. ^{1}H NOESY1D NMR spectra compound **27**.
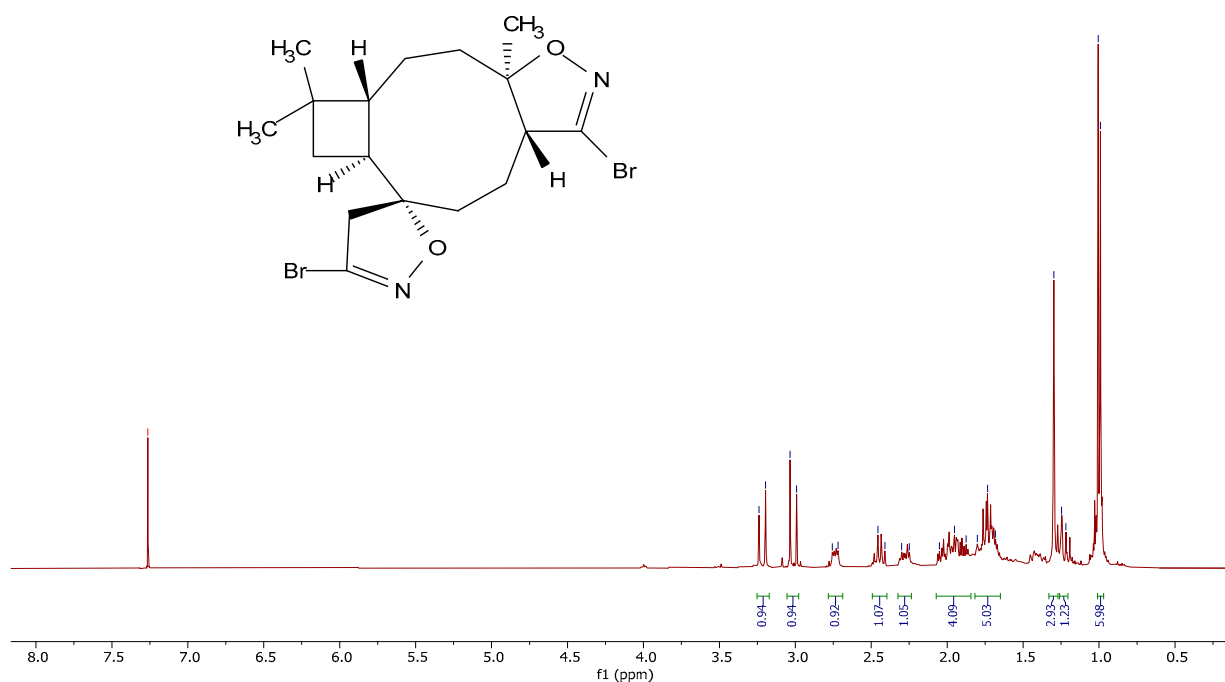
Figure S61. ^{1}H NMR spectra of compound **28.**
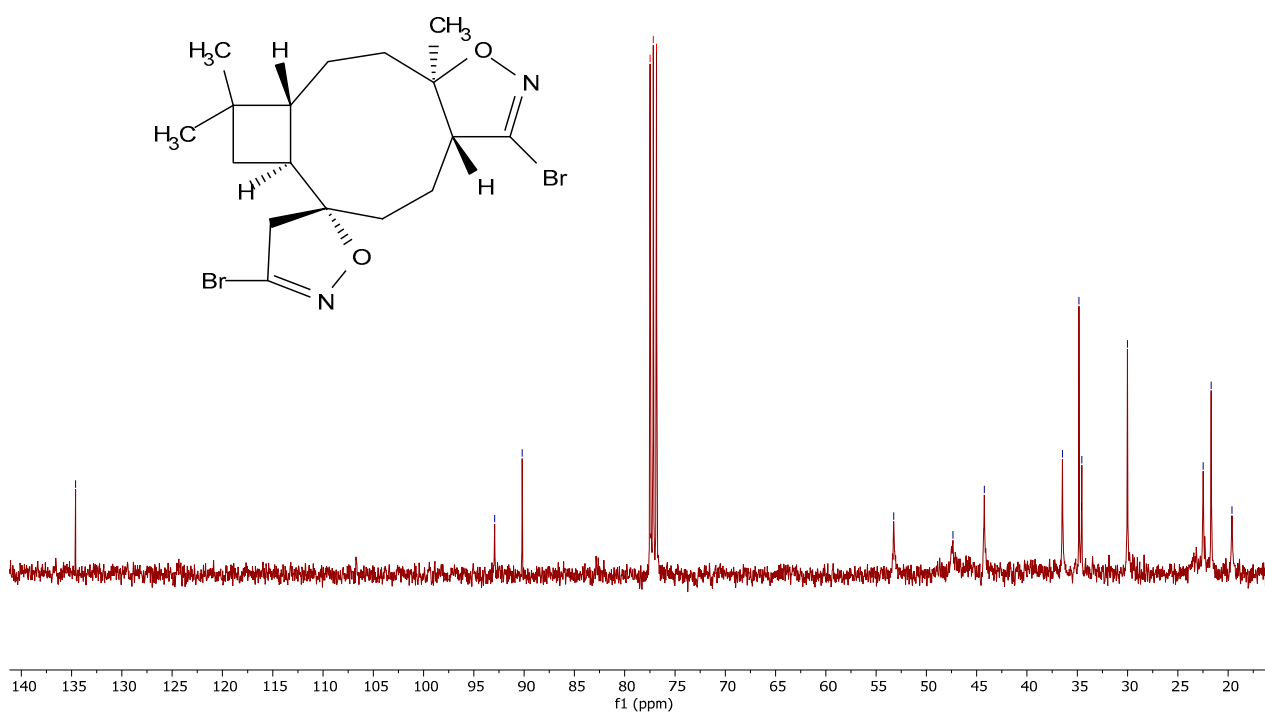
Figure S62. ^{13}C NMR spectra of compound **28.**
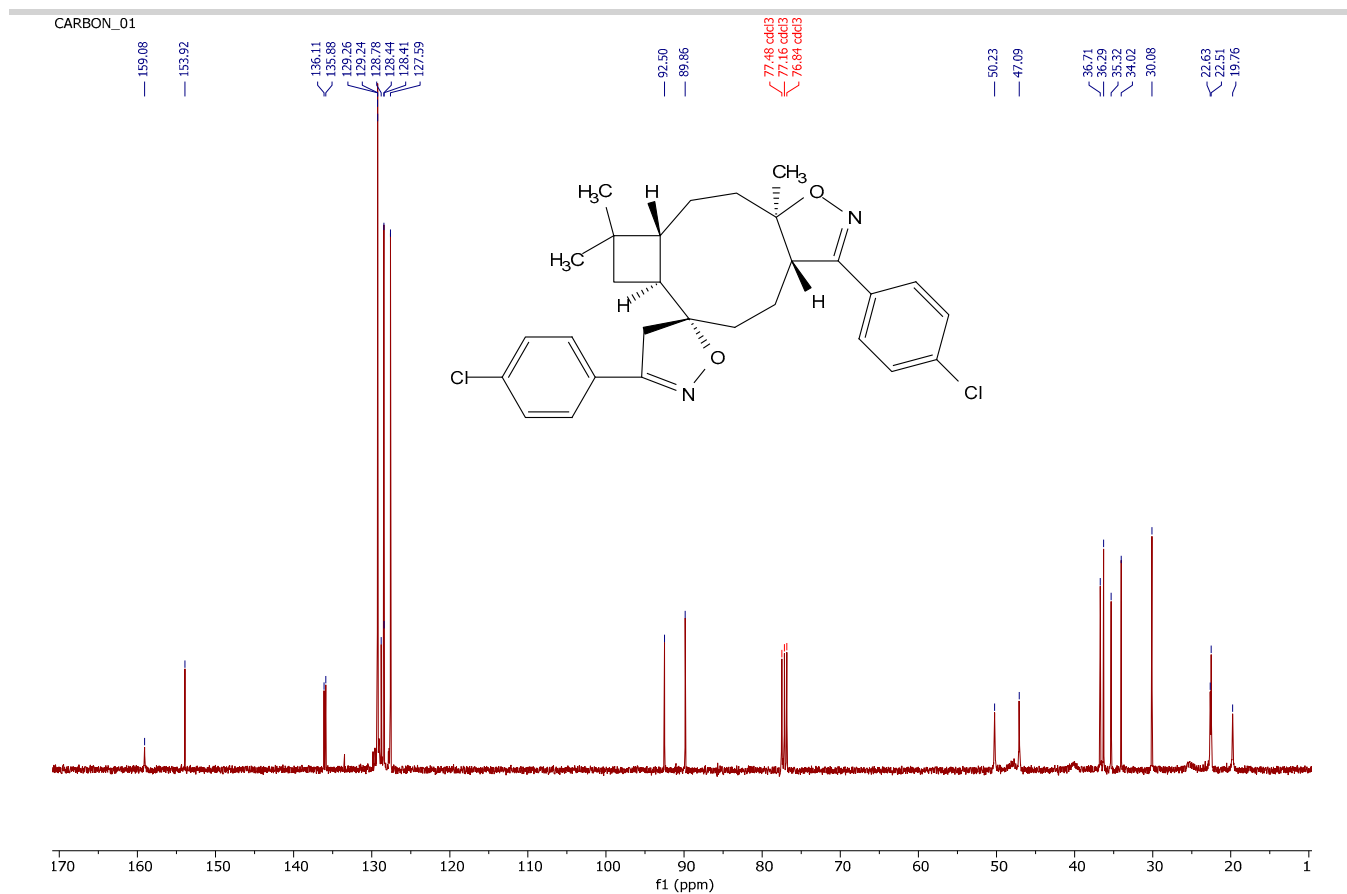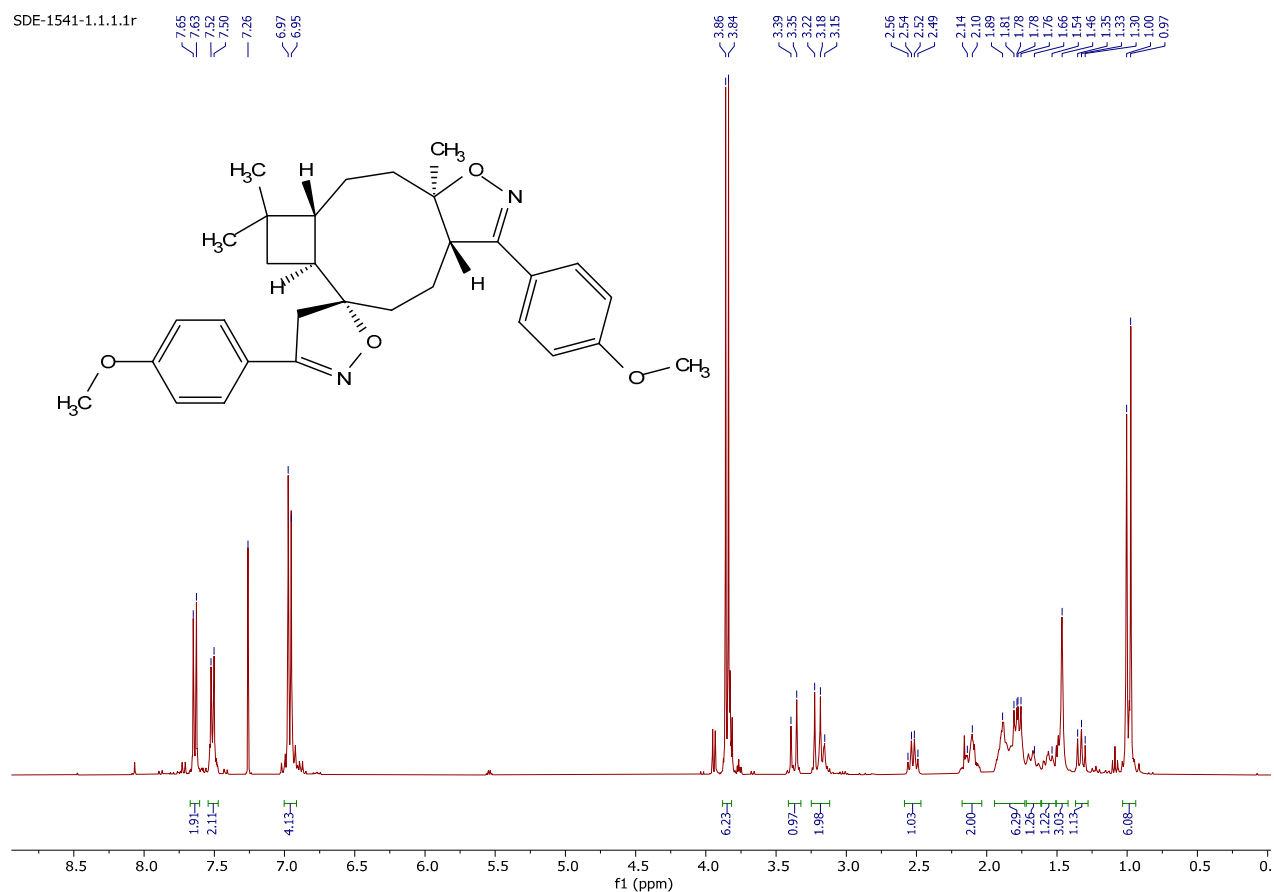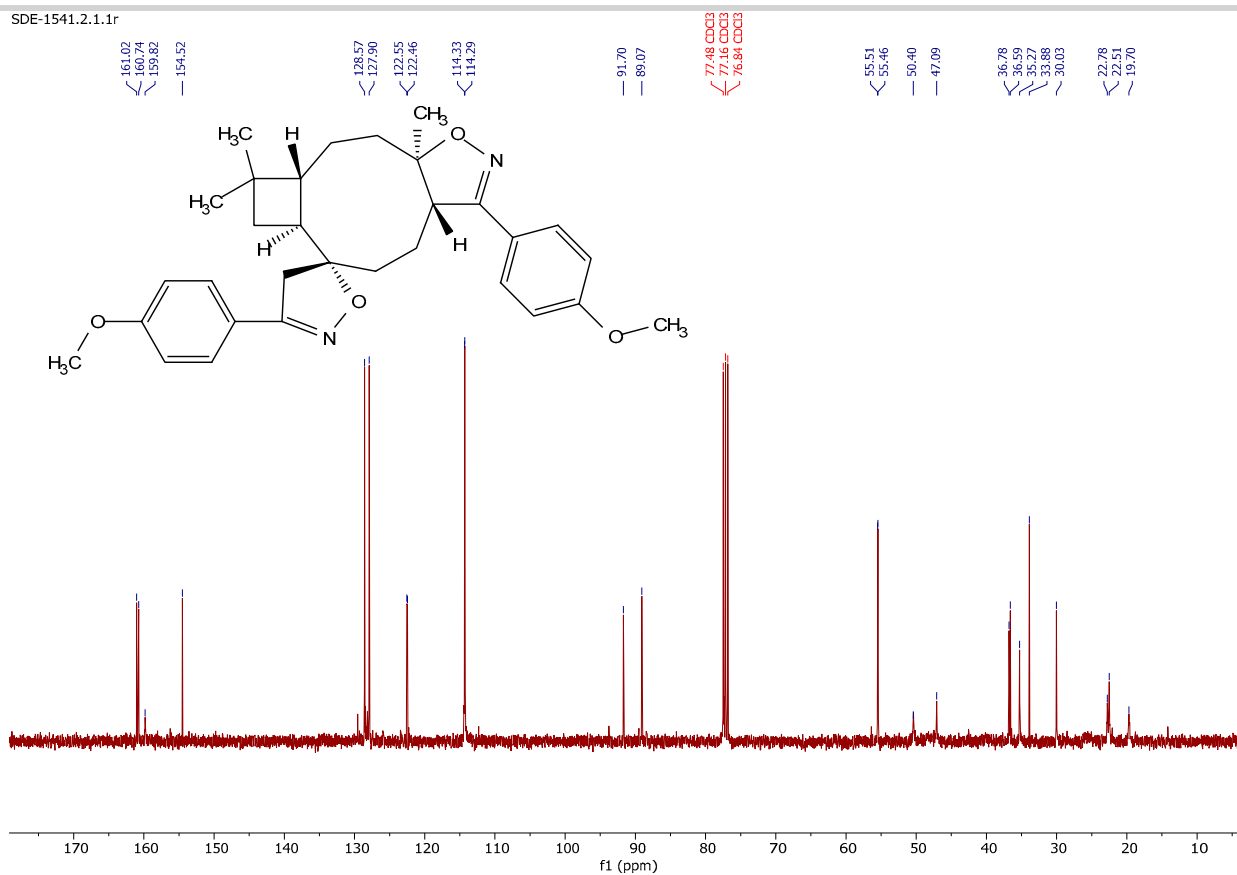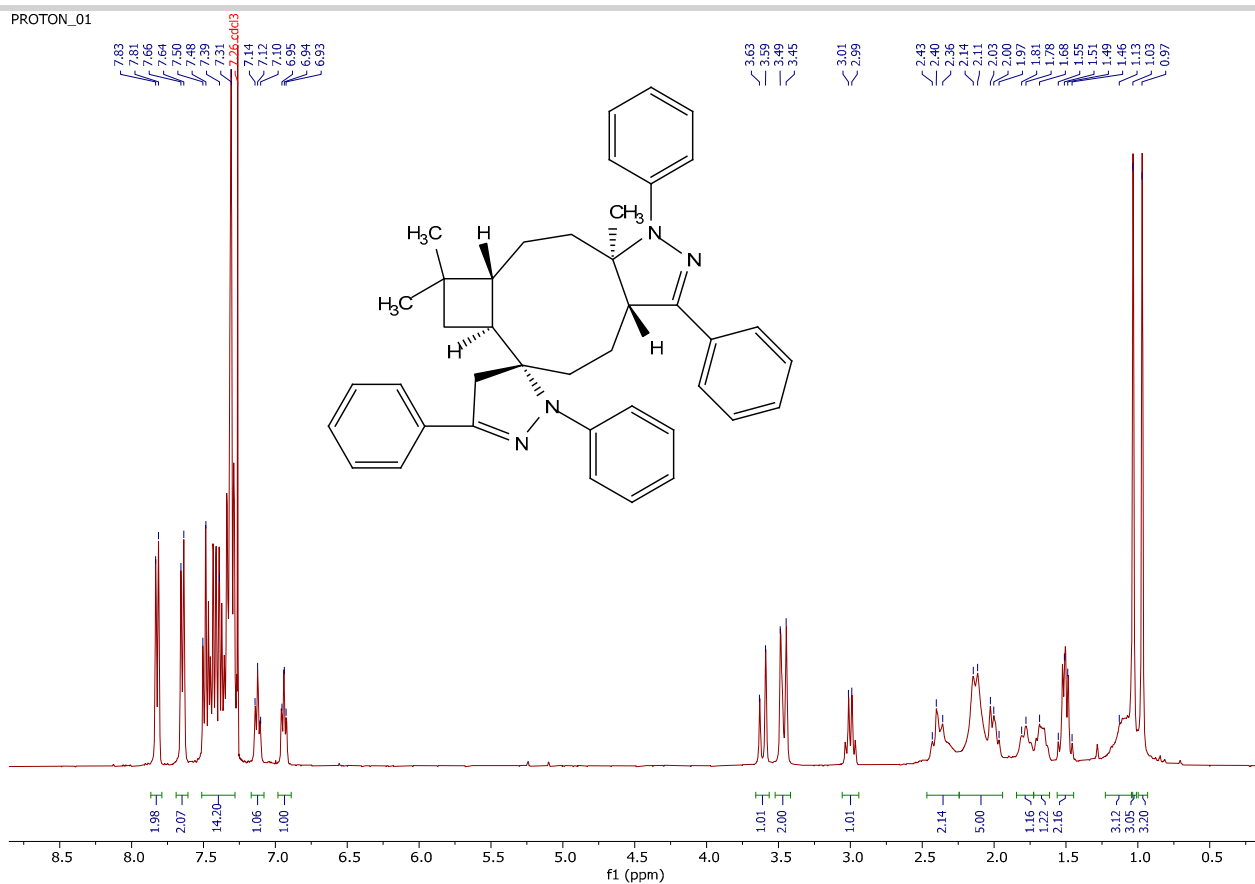
Figure S63. ^{1}H NMR spectra of compound **29.**
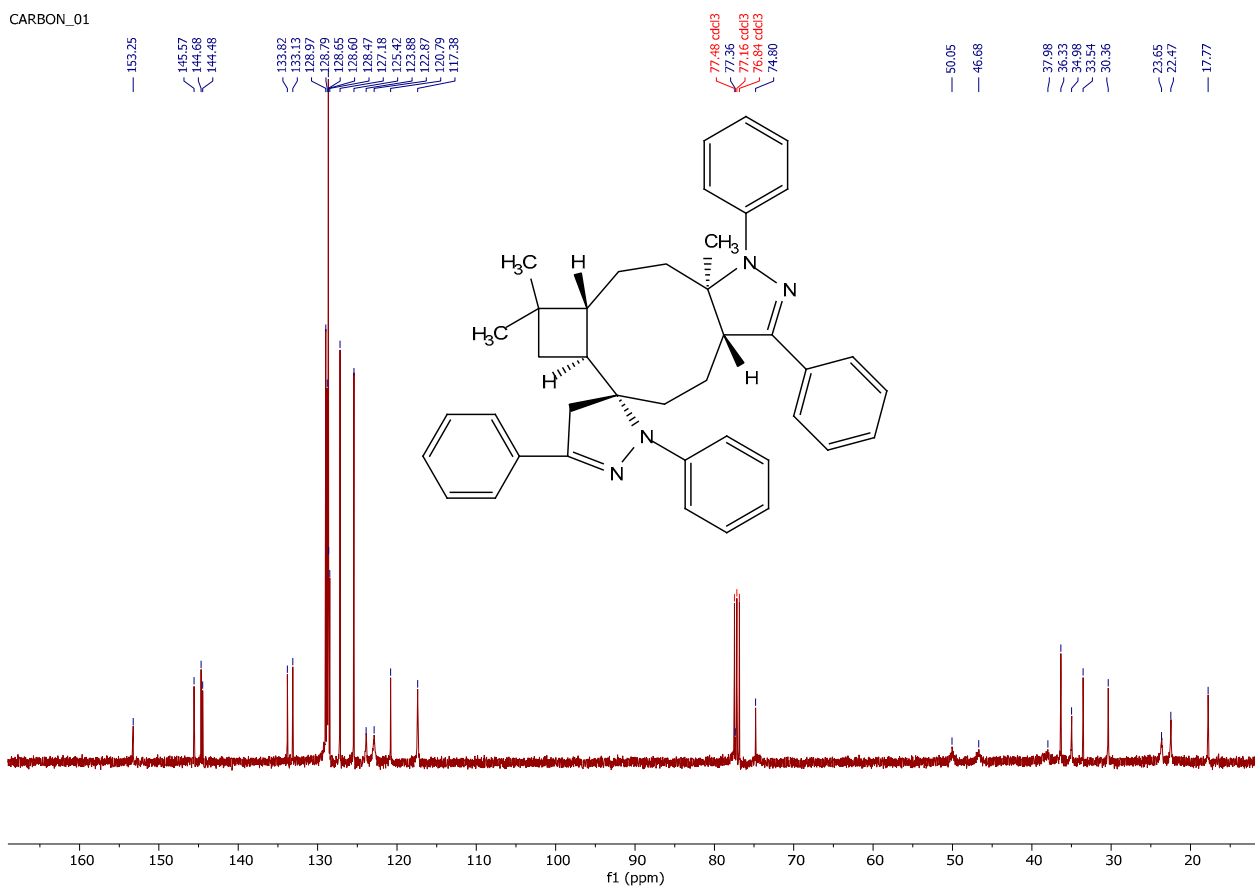
Figure S64. ^{13}C NMR spectra of compound **29.**
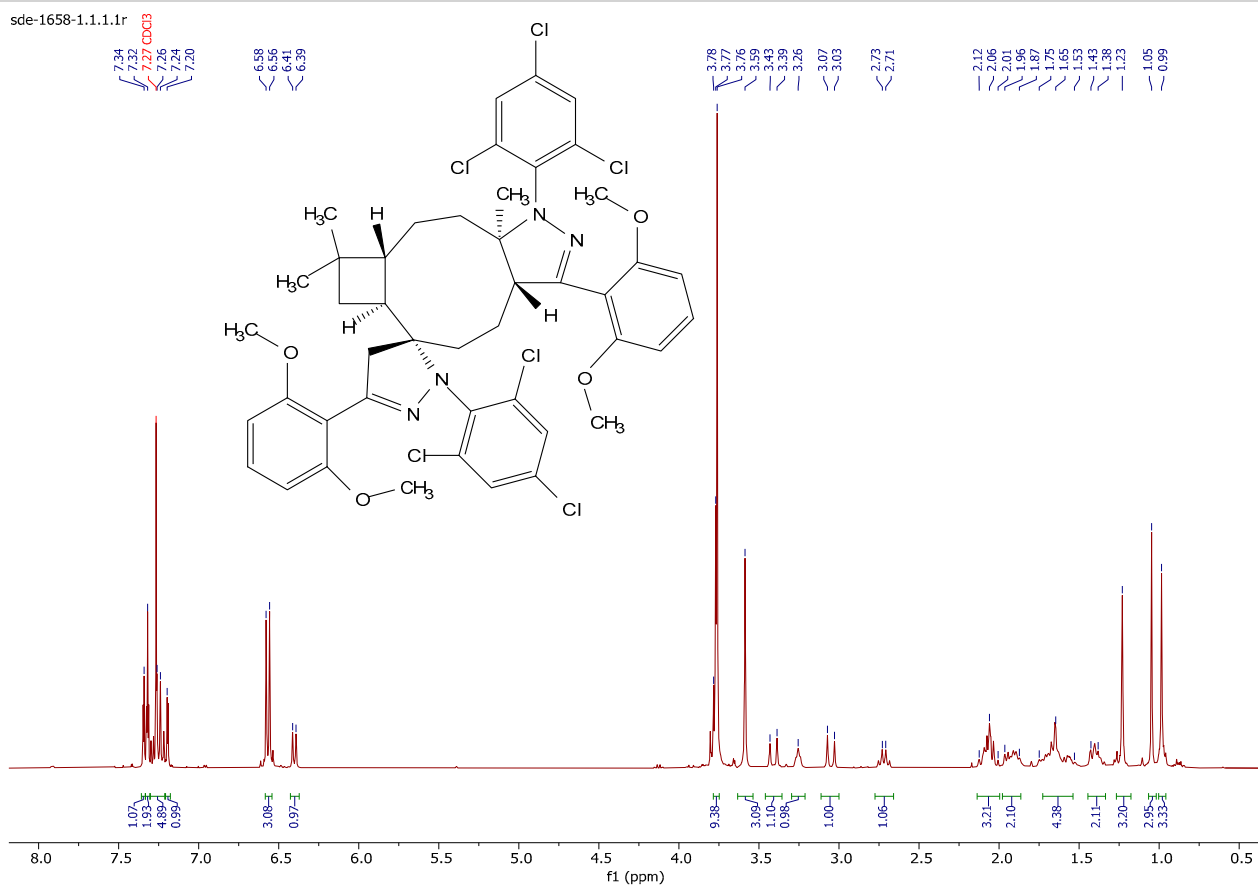
Figure S65. ^{1}H NMR spectra of compound **30.**
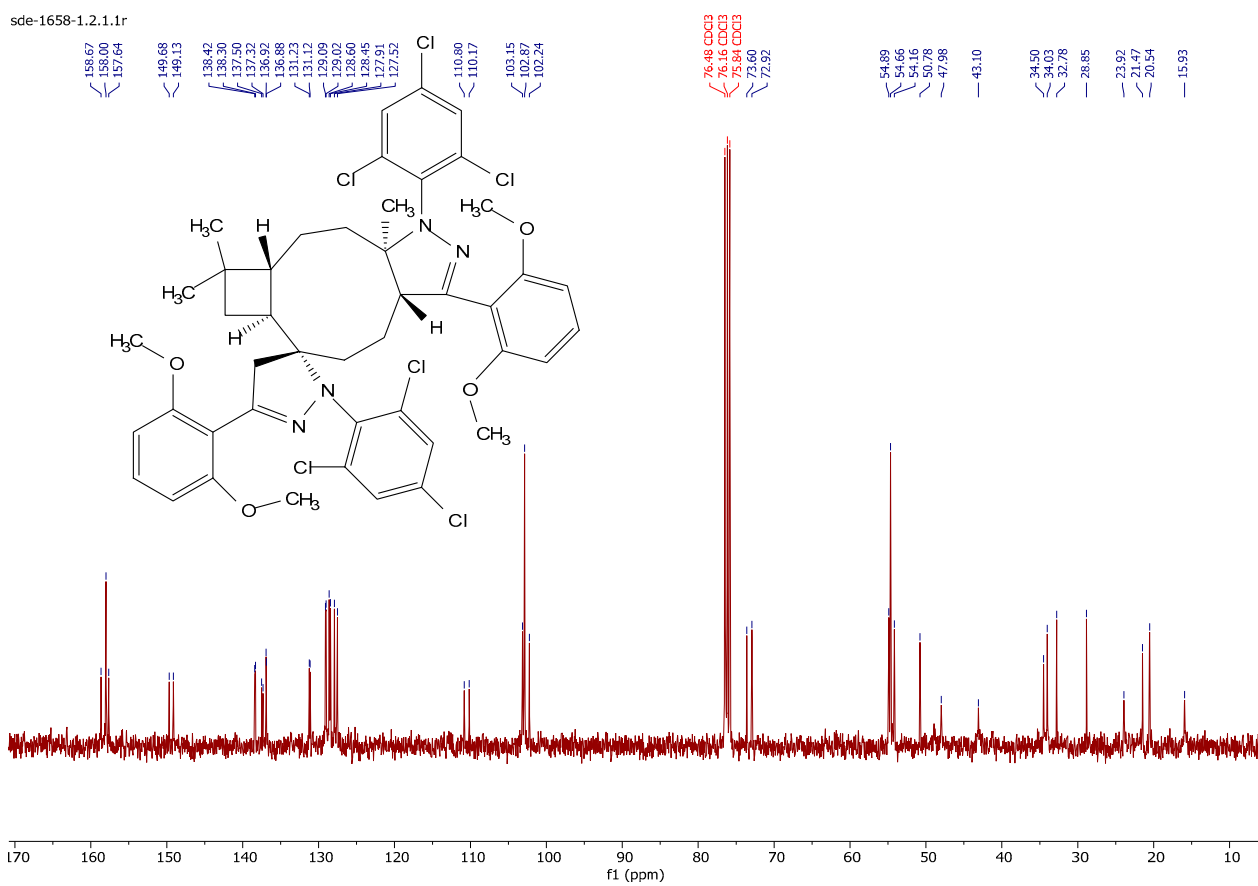
Figure S66. ^{13}C NMR spectra of compound **30.**
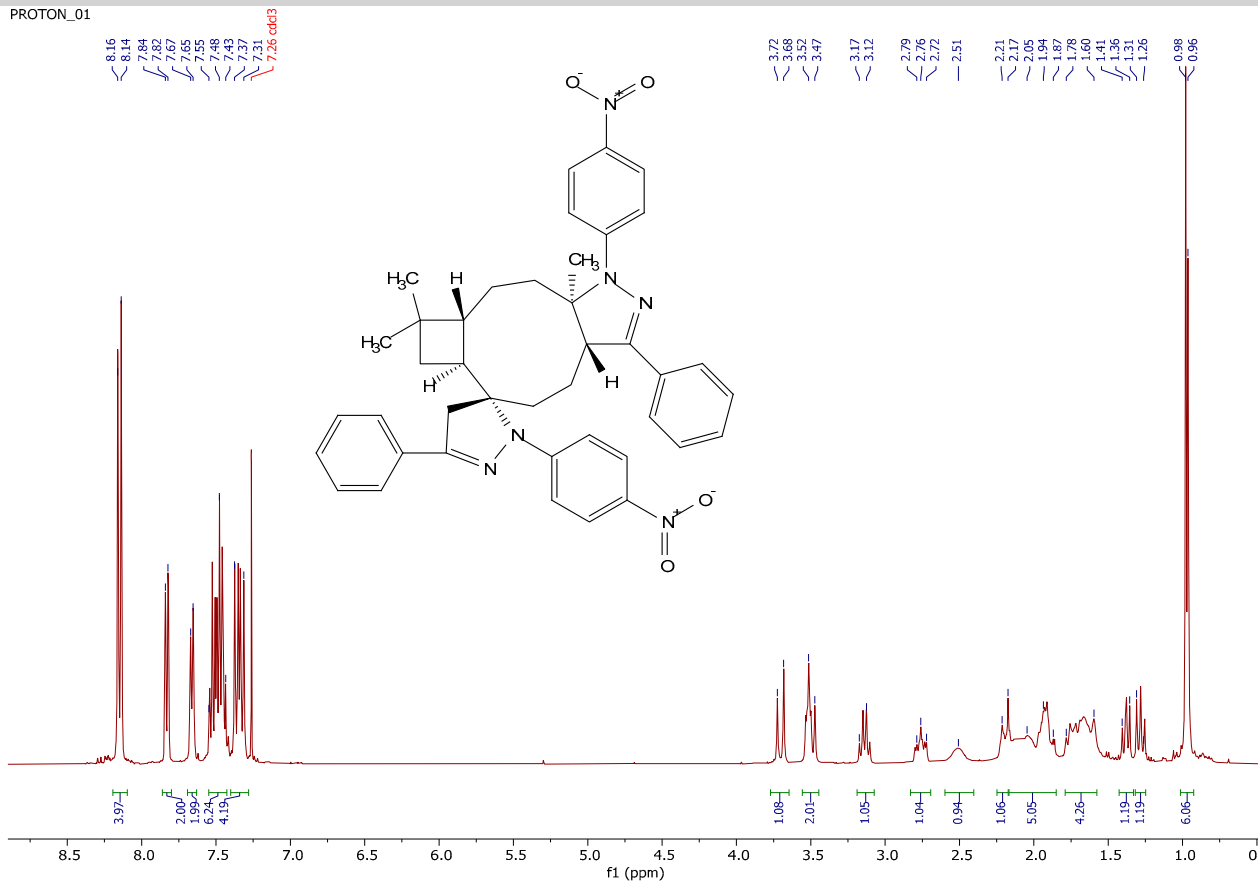
Figure S67. ^{1}H NMR spectra of compound **31.**
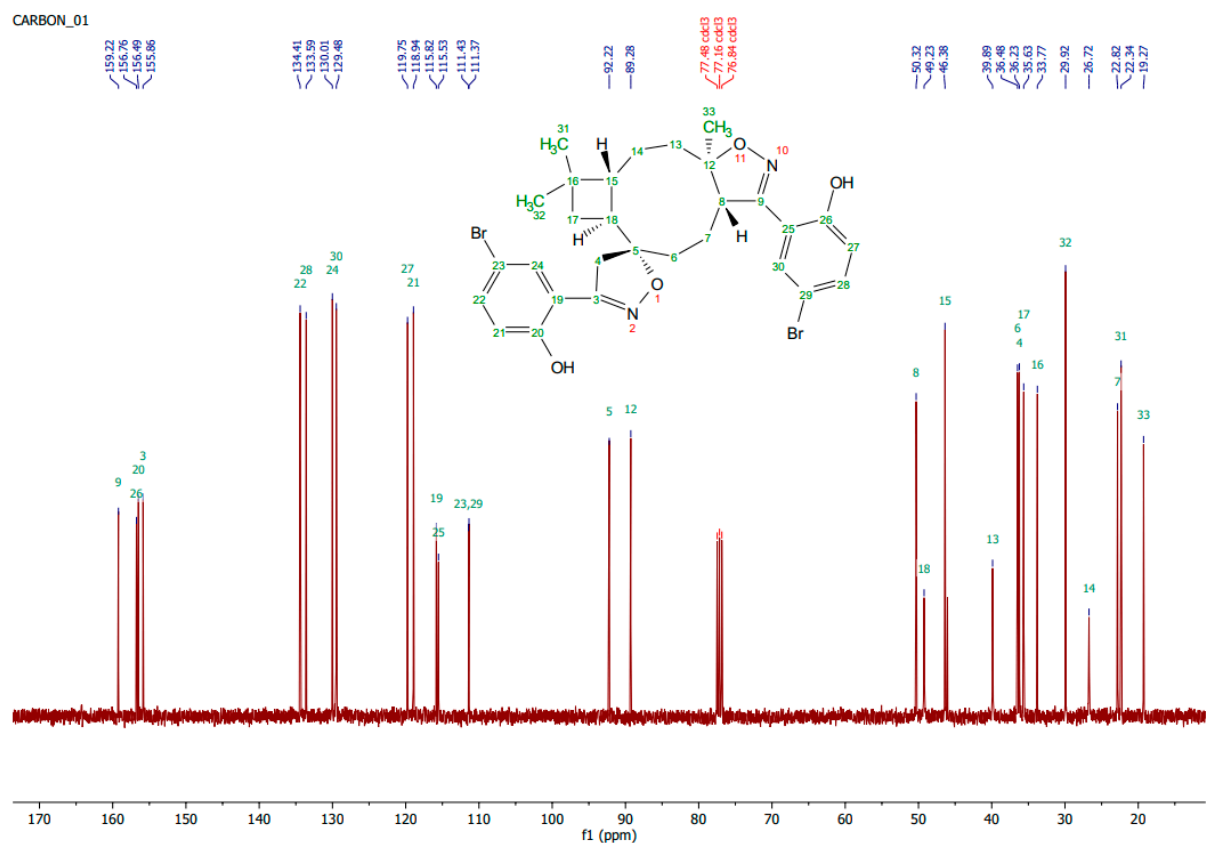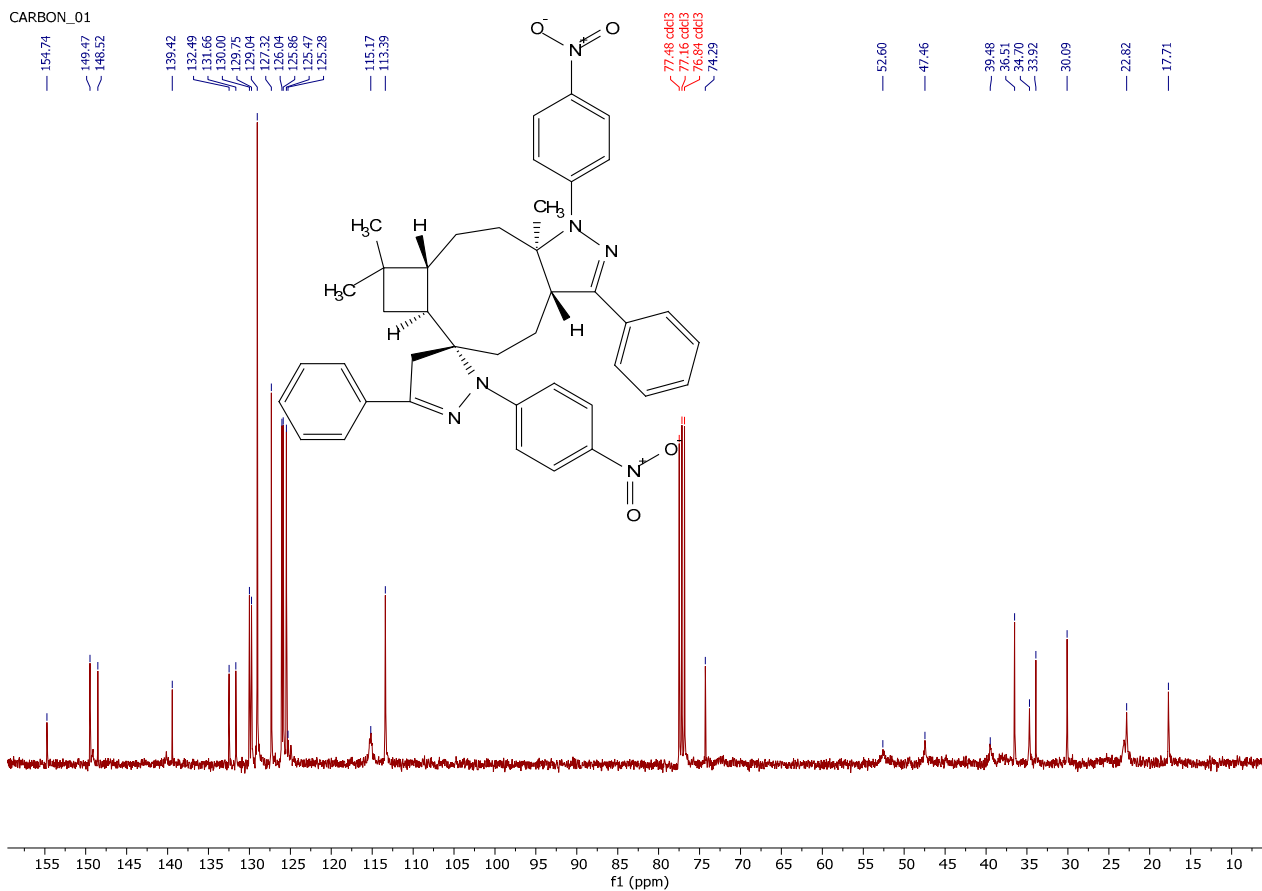

Figure S68. ^{13}C NMR spectra of compound **31.**

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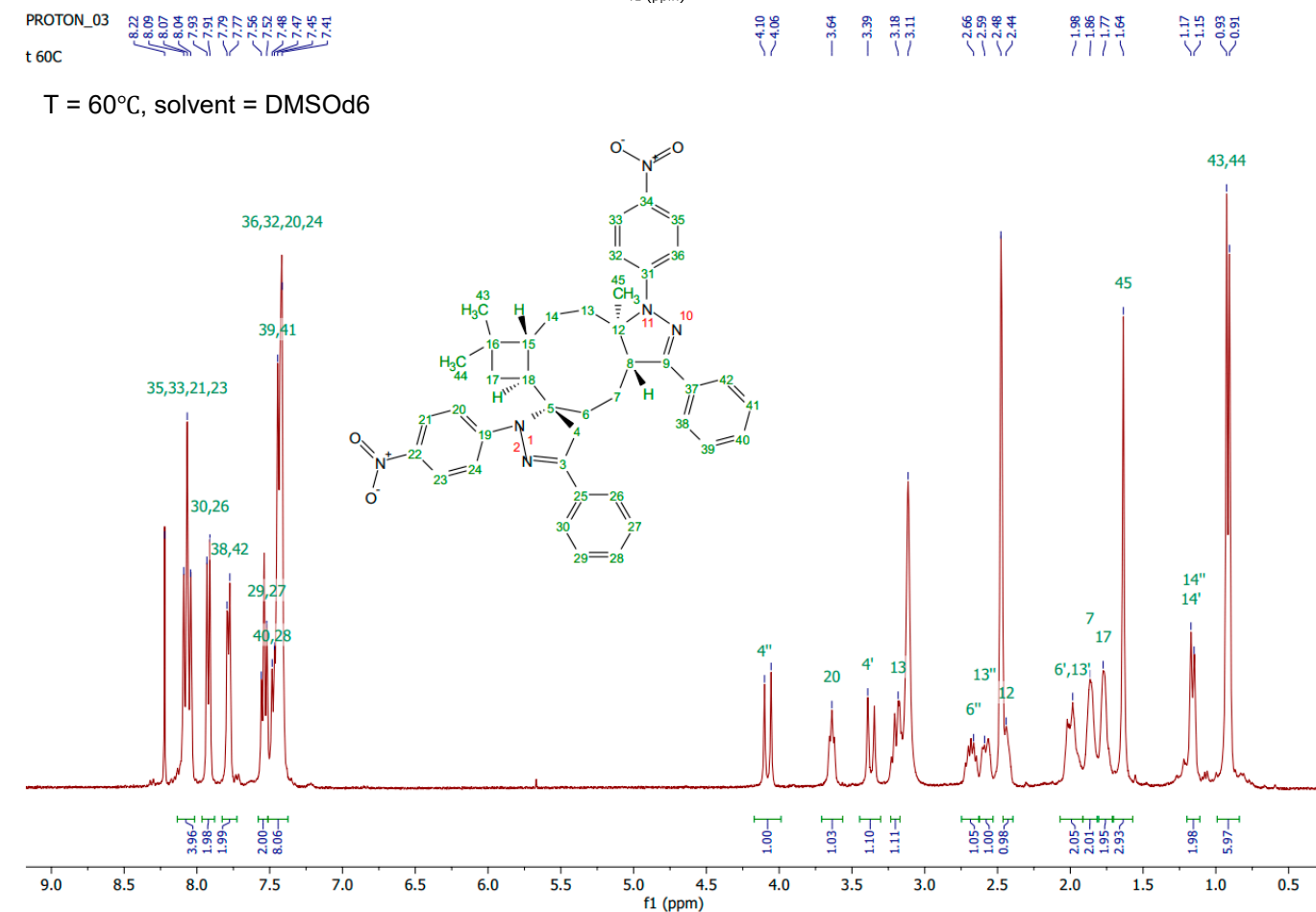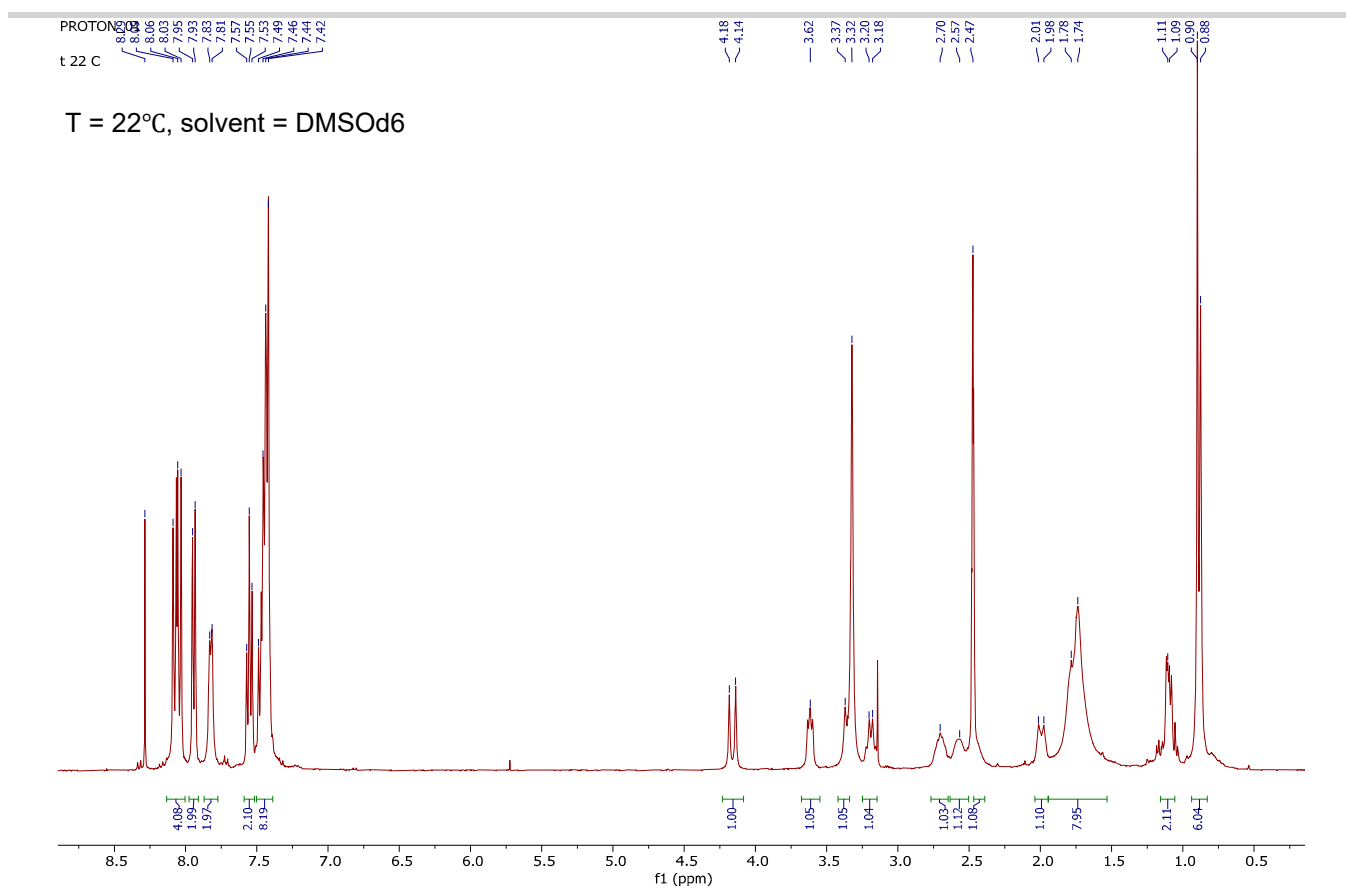
Figure S69. ^{1}H NMR spectra of compound **31** at different temperatures.
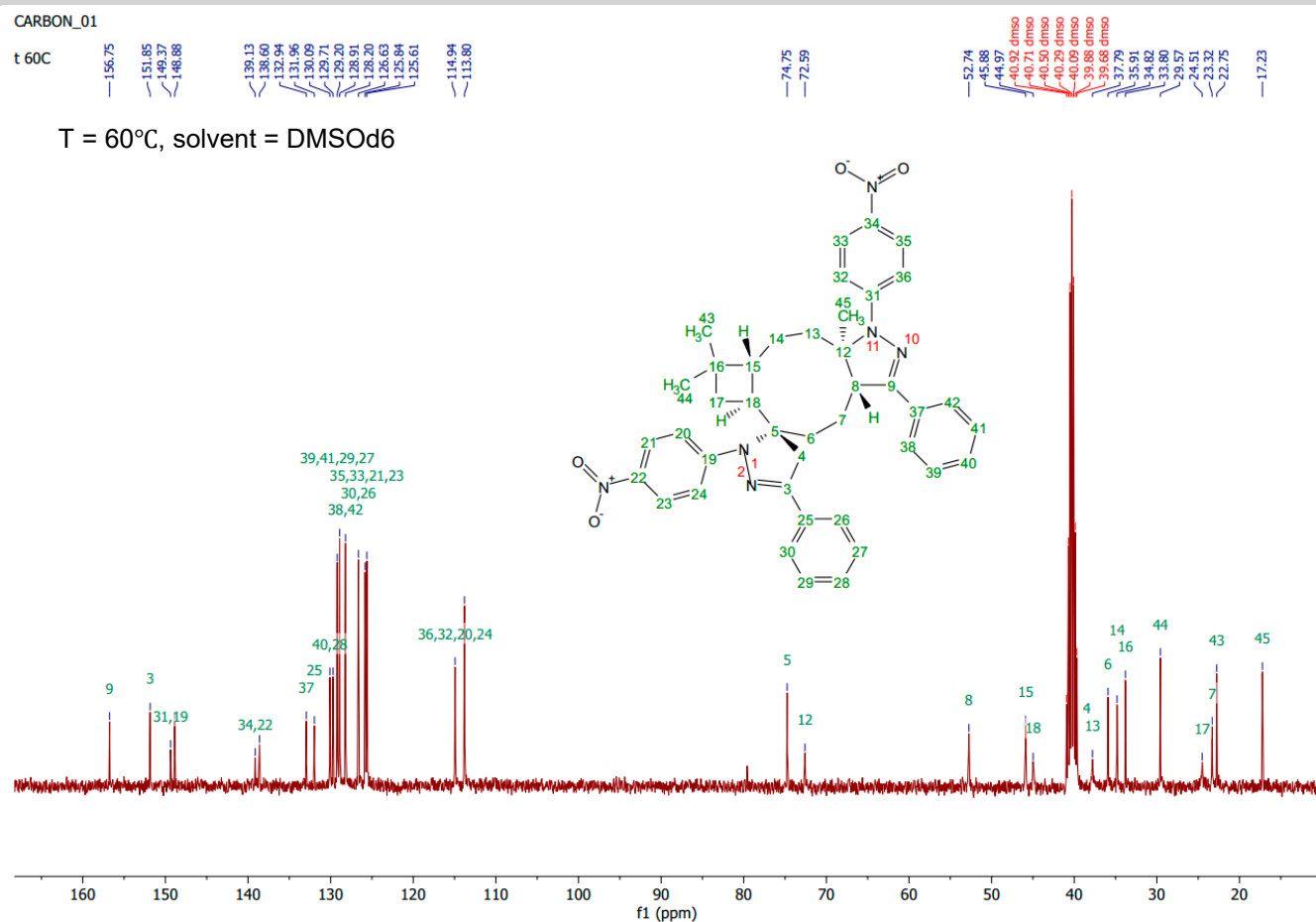
Figure S70. ^{13}C NMR spectra of compound **31** (T = 60℃).
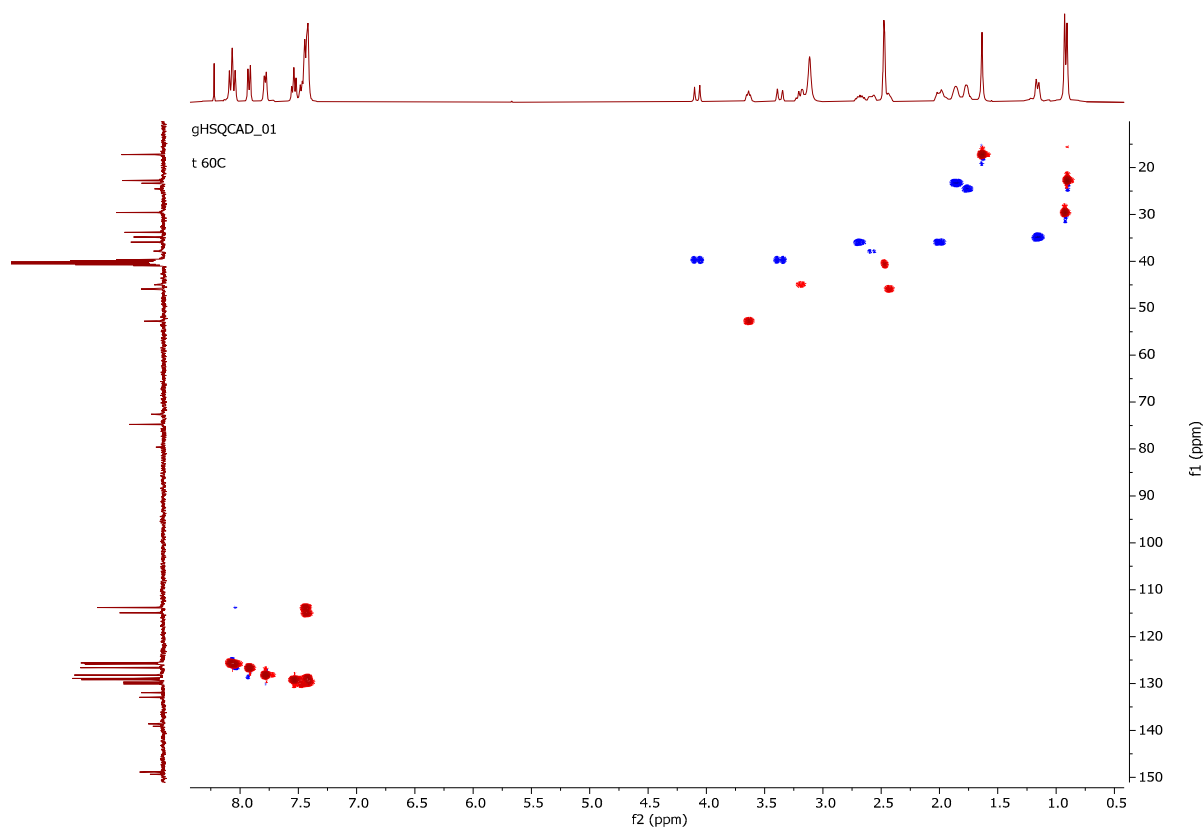
Figure S71. HSQC ^{1}H-^{13}C NMR spectra of compound **31** (T = 60℃).
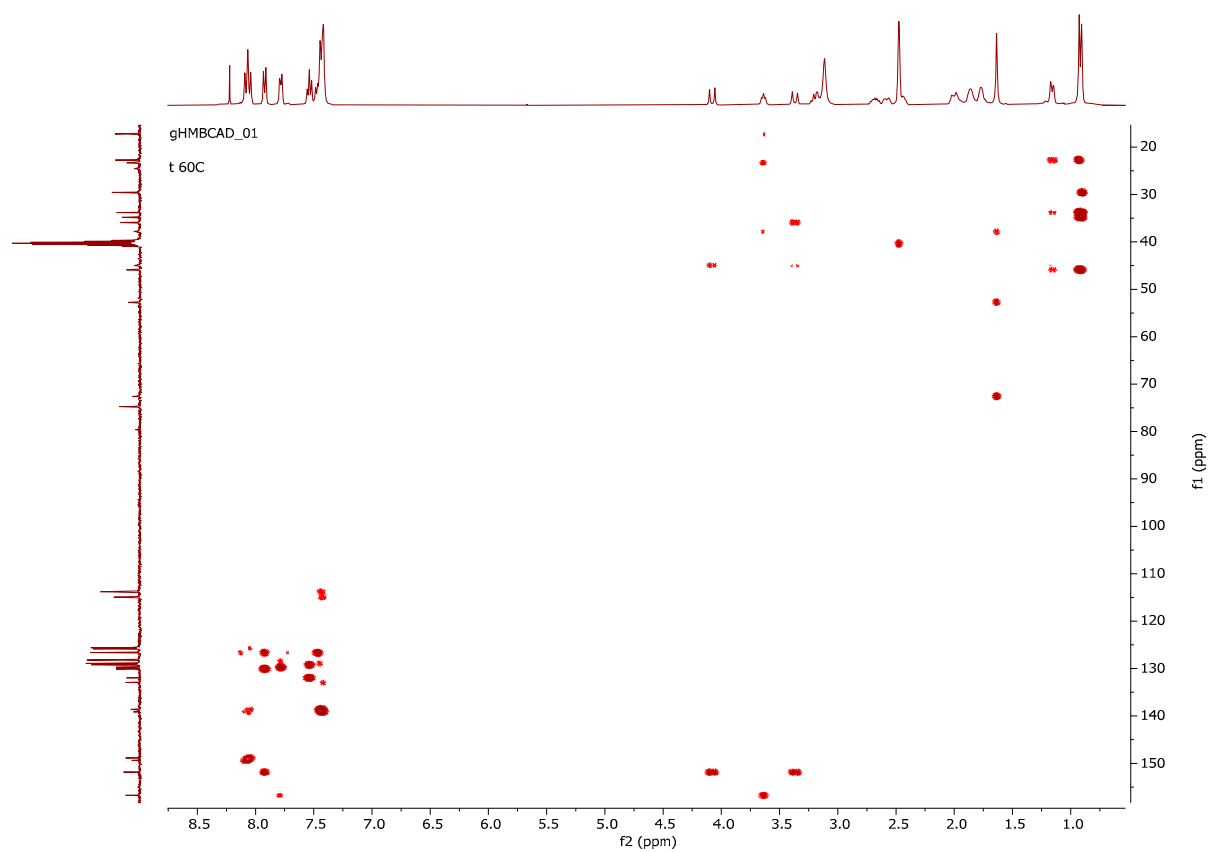
Figure S72. HMBC ^{1}H-^{13}C NMR spectra of compound **31** (T = 60℃).
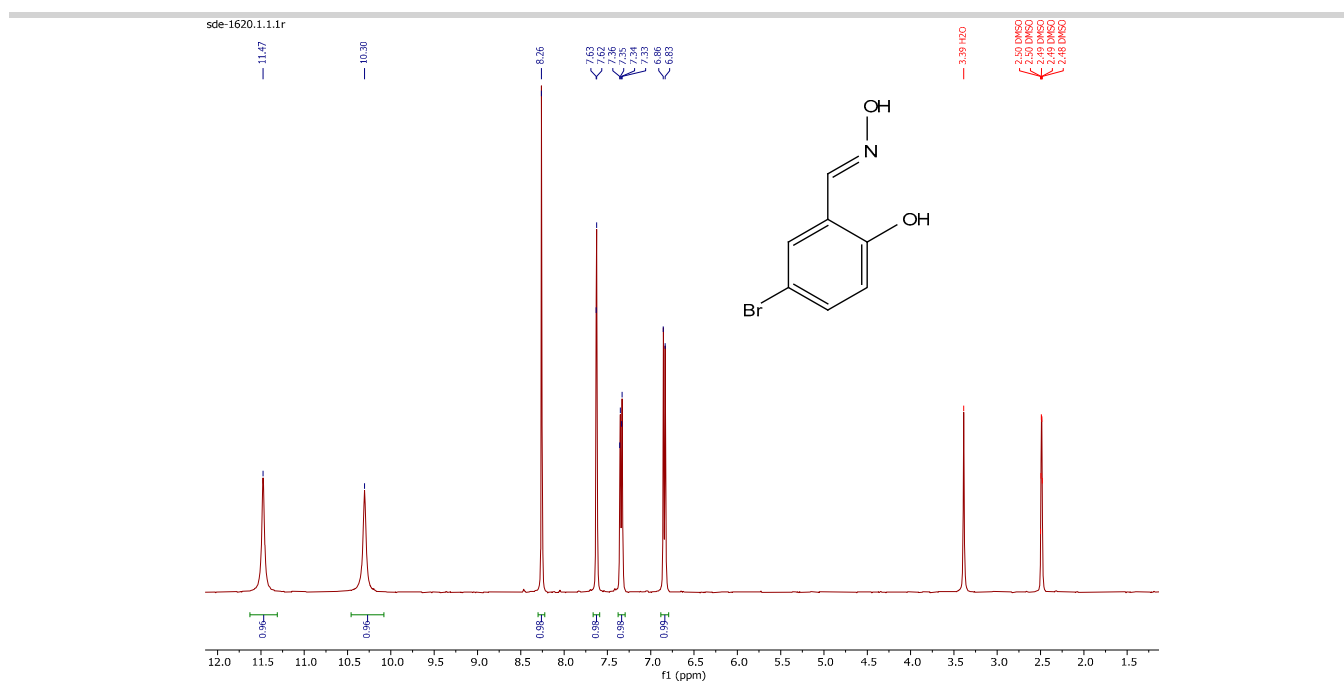
Figure S73. ^{1}H NMR spectra of compound **32.**
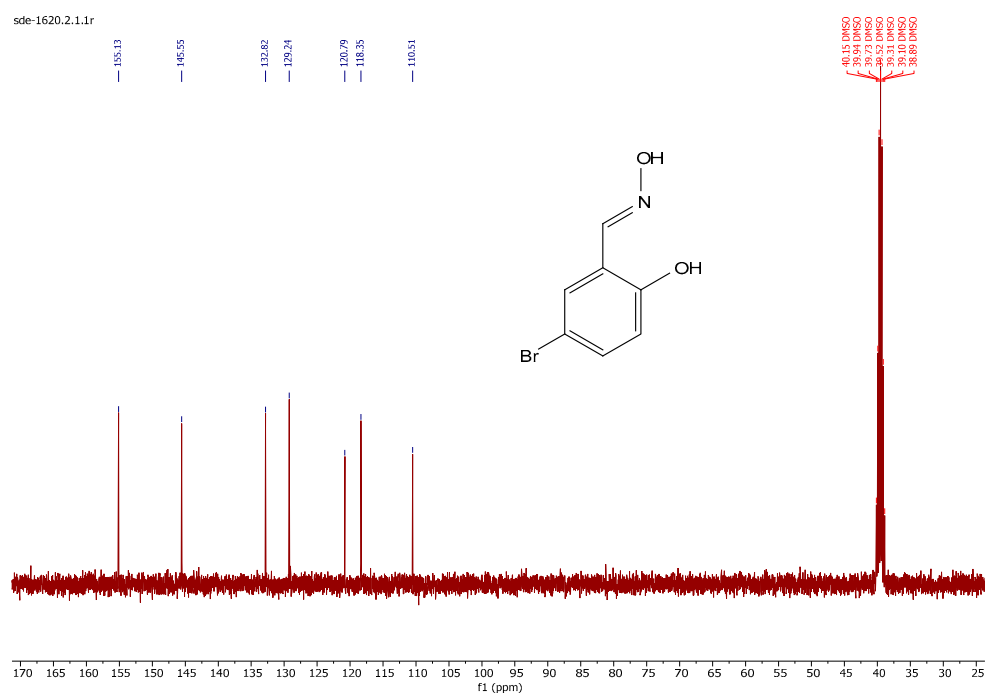
Figure S74. ^{13}C NMR spectra of compound **32.**
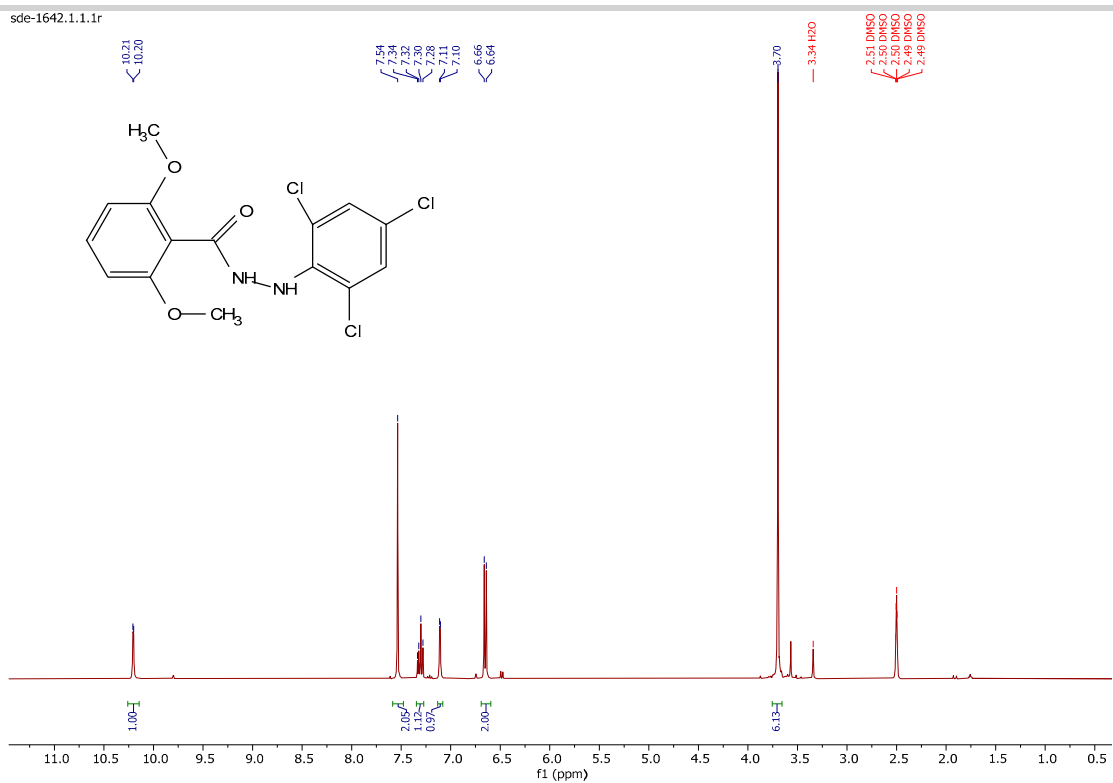
Figure S75. ¹H NMR spectra of compound **33.**
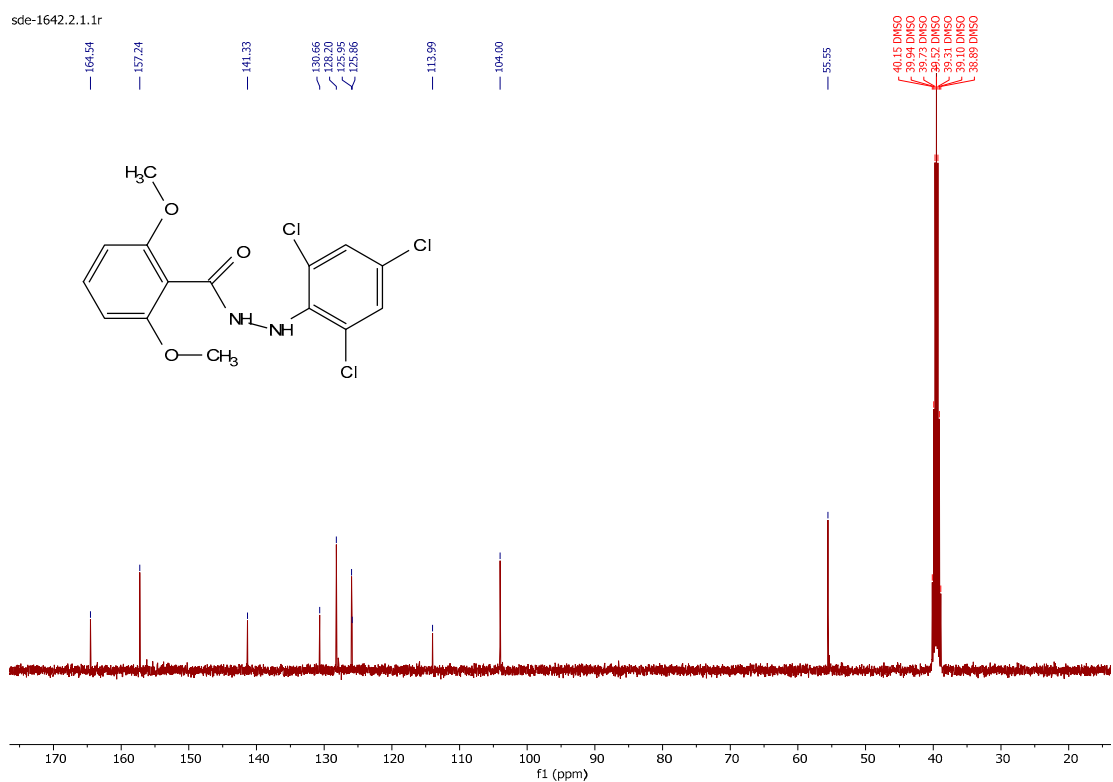
Figure S76. ¹³C NMR spectra of compound **33.**

Table S1. Crystal data and structure refinement for compound 18a.

|	
Identification code	(18a) sde1619_1)
Empirical formula	C22 H28 Br N O2
Formula weight	418.36
Temperature	295(2) K
Wavelength	1.54186 Å
Crystal system	Orthorhombic
Space group	C 2 2 21
Unit cell dimensions	a = 11.2541(3) Å = 90°.
	b = 15.6197(6) Å = 90°.
	c = 23.7474(9) Å = 90°.
Volume	4174.5(3) $Å^3$
Z	8
Density (calculated)	1.331 Mg/m^3
Absorption coefficient	2.794 mm^{-1}
F(000)	1744
Theta range for data collection	3.723 to 66.596°.
Index ranges	-13<=h<=9, -18<=k<=18, -22<=l<=28
Reflections collected	14857
Independent reflections	3653 [R(int) = 0.0692]
Completeness to theta = 66.596°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3653 / 0 / 243
Goodness-of-fit on F^2	0.960
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.0977
R indices (all data)	R1 = 0.0570, wR2 = 0.1025
Absolute structure parameter	-0.038(18)
Extinction coefficient	0.00069(9)
Largest diff. peak and hole	0.329 and -0.369 e. $Å^{-3}$

Table S2. Hydrogen bonds for 18a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...N(1)	0.79(8)	1.88(8)	2.615(7)	155(7)

Symmetry transformations used to generate equivalent atoms:

Table S3. Crystal data and structure refinement for compound 21a.

Identification code	21a
Empirical formula	C23 H32 N2
Formula weight	336.50
Temperature	295(2) K
Wavelength	1.54186 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 8.3636(5) Å $\qquad$ = 90°.
	b = 21.3520(10) Å $\qquad$ = 91.916(5)°.
	c = 11.436 Å $\qquad$ = 90°.
Volume	2041.15(16) Å^3
Z	4
Density (calculated)	1.095 Mg/m^3
Absorption coefficient	0.477 mm^{-1}
F(000)	736
Theta range for data collection	4.141 to 66.521°.
Index ranges	-9<=h<=9, -25<=k<=25, -3<=l<=13
Reflections collected	13382
Independent reflections	6437 [R(int) = 0.1363]
Completeness to theta = 66.521°	95.4 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6437 / 1 / 464
Goodness-of-fit on F^2	0.756
Final R indices [I>2sigma(I)]	R1 = 0.0590, wR2 = 0.1278
R indices (all data)	R1 = 0.1580, wR2 = 0.1482
Absolute structure parameter	-1.3(10)
Extinction coefficient	0.0047(5)
Largest diff. peak and hole	0.191 and -0.223 e.Å^{-3}

Table S4. Crystal data and structure refinement for compound 21b

Identification code	21b (sde1516_1)
Empirical formula	C23 H32 N2
Formula weight	336.50
Temperature	295(2) K
Wavelength	1.54186 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.0538(6) Å $\quad$ a= 90°.
	b = 11.7944(9) Å $\quad$ b= 90°.
	c = 23.4880(10) Å $\quad$ g = 90°.
Volume	1954.1(2) Å^3
Z	4
Density (calculated)	1.144 Mg/m^3
Absorption coefficient	0.498 mm^{-1}
F(000)	736
Theta range for data collection	5.315 to 67.007°.
Index ranges	-8<=h<=5, -14<=k<=13, -27<=l<=27
Reflections collected	18687
Independent reflections	3394 [R(int) = 0.0466]
Completeness to theta = 67.008°	98.3 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3394 / 0 / 251
Goodness-of-fit on F^2	0.890
Final R indices [I>2sigma(I)]	R1 = 0.0300, wR2 = 0.0611
R indices (all data)	R1 = 0.0442, wR2 = 0.0647
Absolute structure parameter	-0.4(3)
Extinction coefficient	0.0076(4)
Largest diff. peak and hole	0.108 and -0.091 e. Å^{-3}

Table S5. Cytotoxic effect of compounds 17a (SDE-1525), 21a (SDE-1558-1), 23a (SDE-1615-1), and 25 (SDE-1650-2) on a variety of cell lines, including colon cancer (HCT116, HT-29), breast cancer (MCF7, SKBR3), melanoma (SK-MEL-28), lung cancer (A549), prostate cancer (DU145), and normal cell (HEK-293), with IC_{50} values.

Organ	Cell lines	Curves *in vitro* study with IC_{50} values
Colon cancer	HCT116	
	HT-29	

Breast cancer	MCF7	
	SKBR3	
Melanoma	SK-MEL-28	

Lung cancer	A549	
Prostate cancer	DU145	
Normal cell	HEK-293	