

Supporting information

Design, Synthesis, In Silico and In Vitro Pharmacological Profiling of Cannabidiol-like Synthetic Analogues as Multi-Target Anti-Alzheimer's Agents

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¹H NMR, ¹³C NMR, DEPT-135 NMR, 2D COSY NMR, 2D HSQC NMR, 2D HMBC NMR spectra and HRMS (Figures S1-S62)

Single-crystal X-ray diffraction analysis of compound 3i. Tables S1-S4

1. (*R,E*)-3-hydroxy-*N*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzohydrazide, **3a**

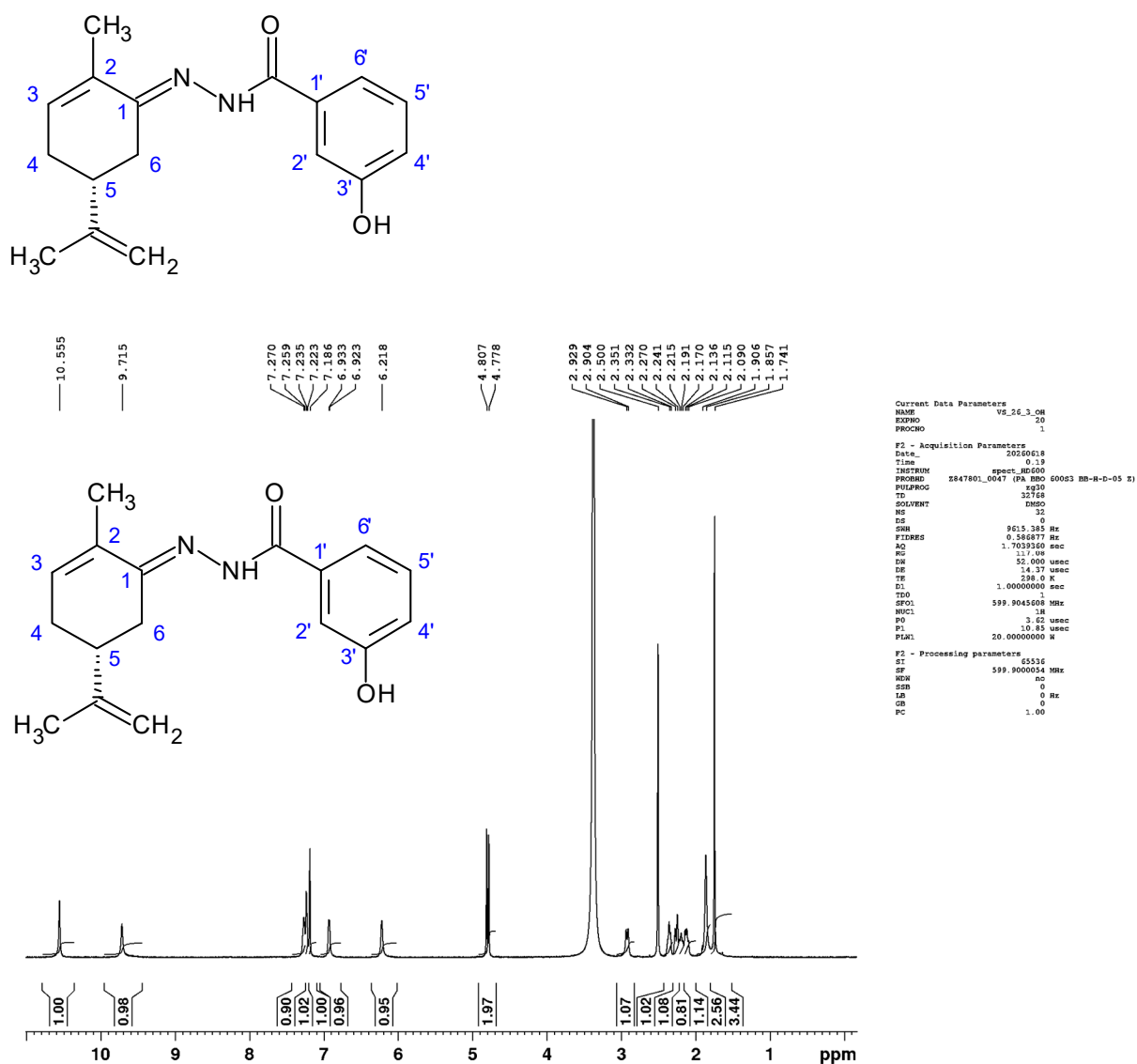


Figure S1. ¹H NMR spectrum of **3a** in DMSO-*d*₆.

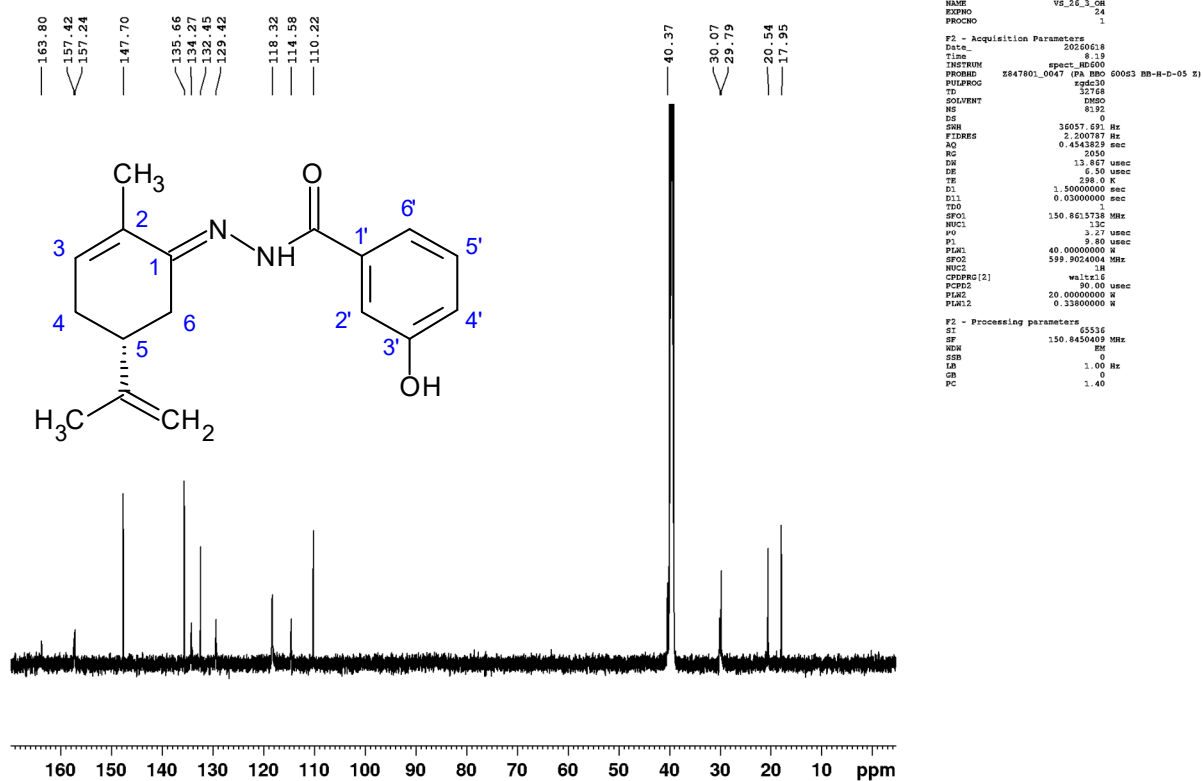


Figure S2. ^{13}C NMR spectrum of **3a** in $\text{DMSO-}d_6$.

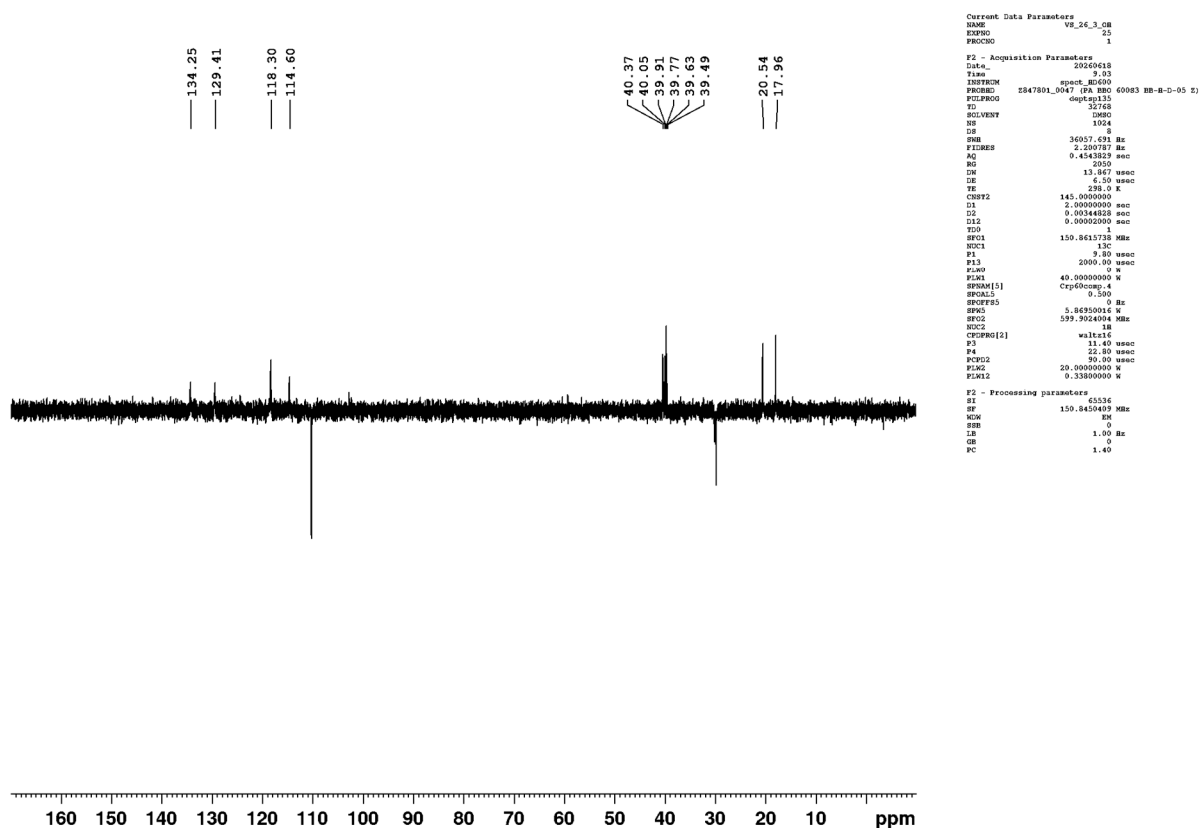


Figure S3. DEPT-135 NMR spectrum of **3a** in $\text{DMSO-}d_6$.

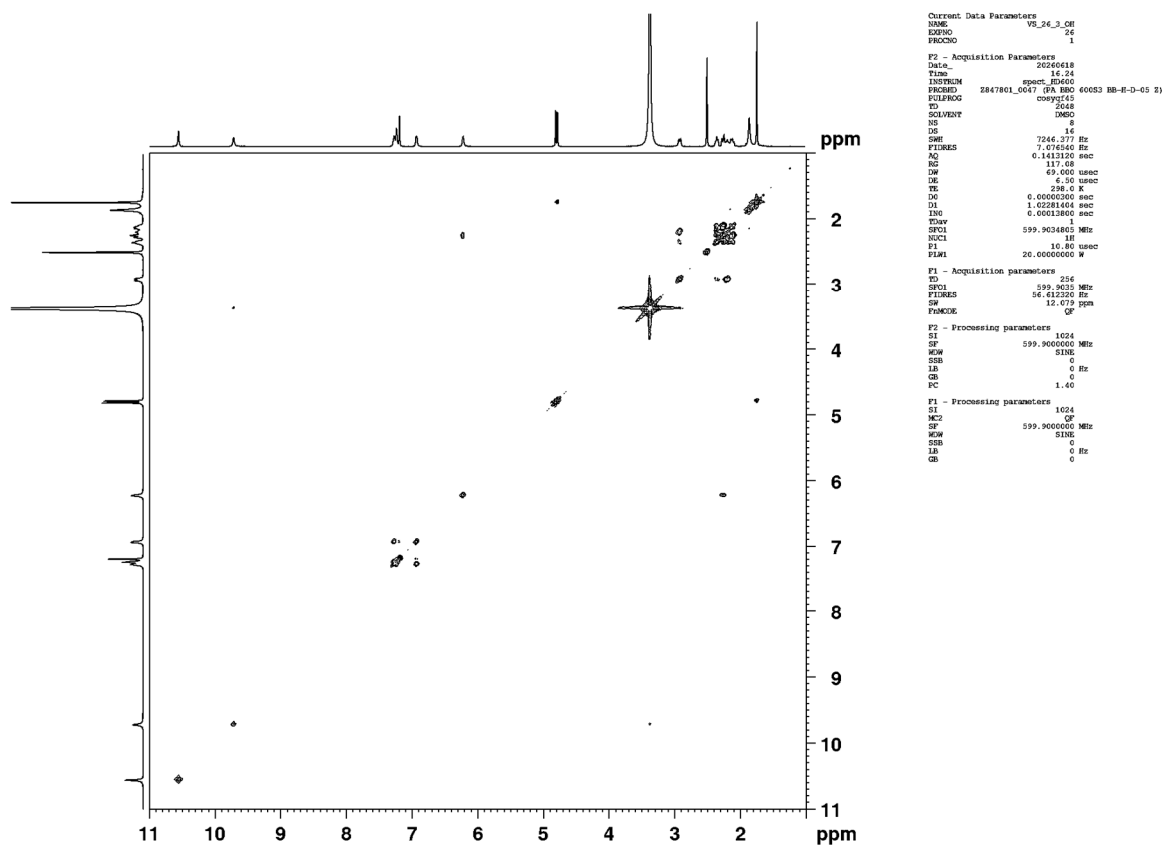


Figure S4. 2D COSY NMR spectrum of **3a** in DMSO- d_6 .

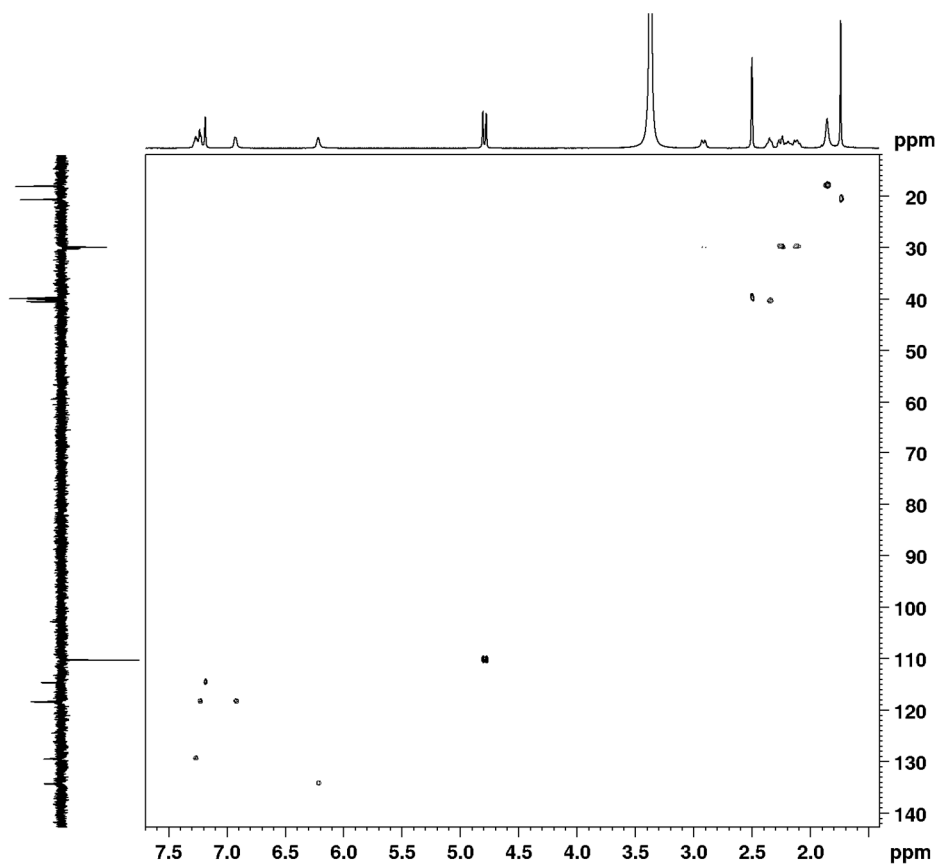


Figure S5. 2D HSQC NMR spectrum of **3a** in DMSO- d_6 .

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T: FTM S + p ESI Full ms [50.0000-750.0000]

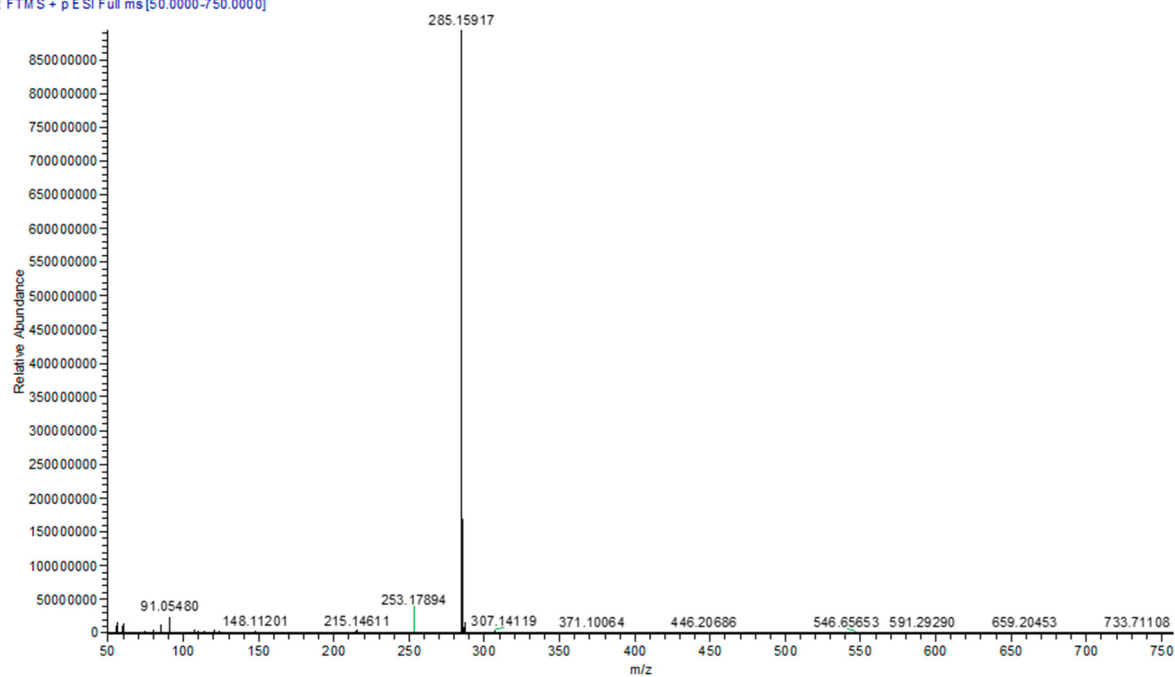


Figure S6. HRMS of **3a**.

2. (*R,E*)-4-hydroxy-*N*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzohydrazide, **3b**

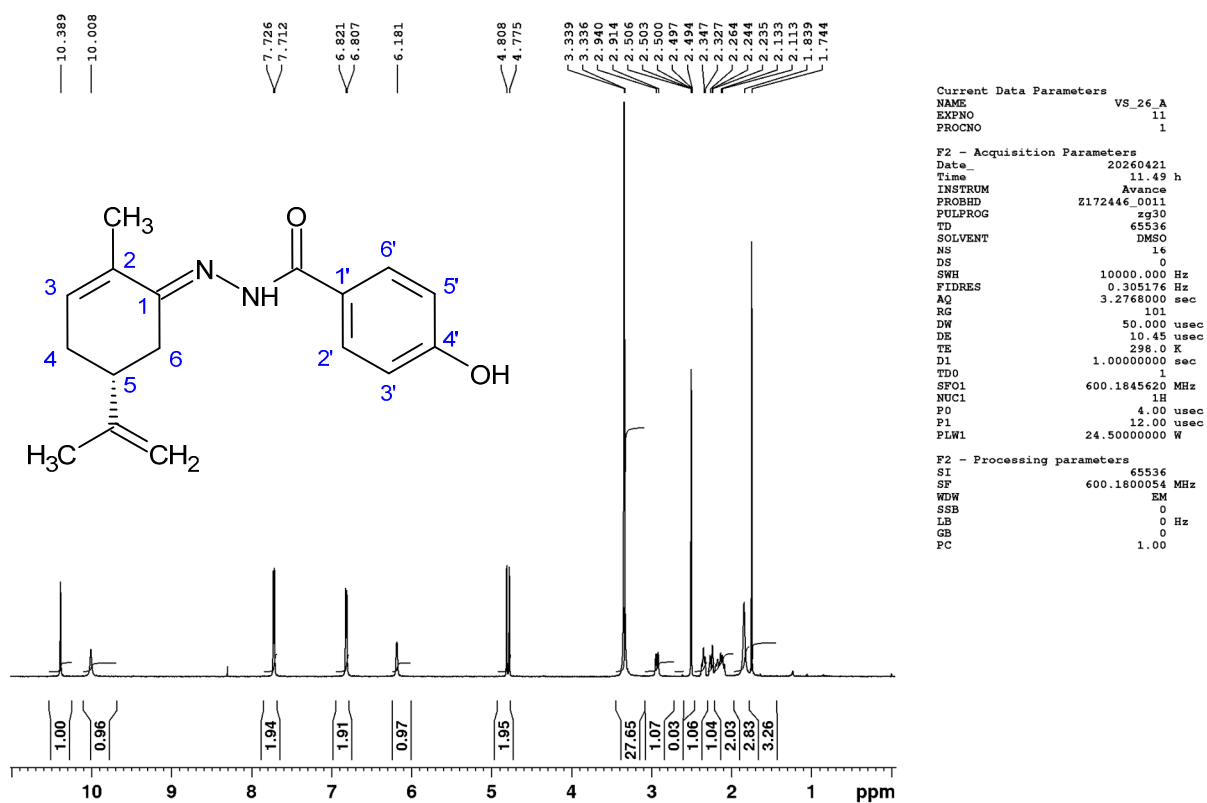


Figure S7. ¹H NMR spectrum of **3b** in DMSO-*d*₆.

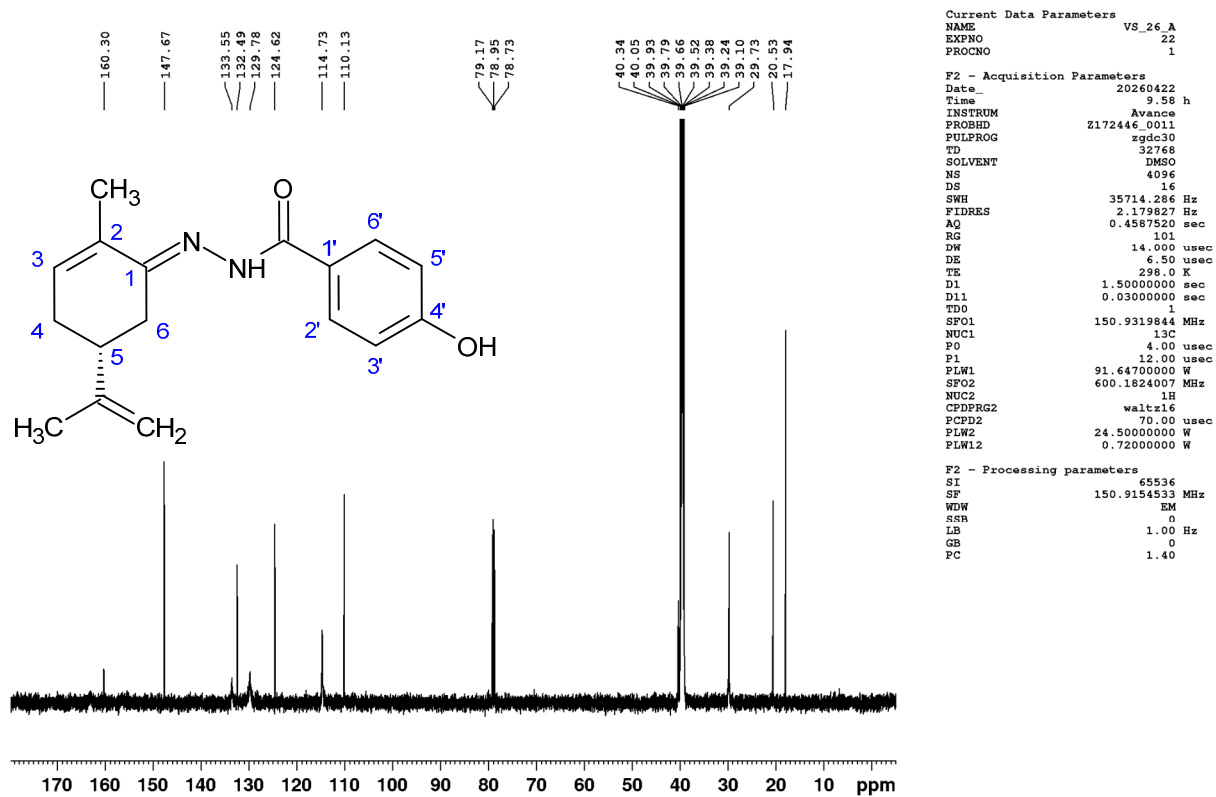


Figure S8. ¹³C NMR spectrum of **3b** in DMSO-*d*₆.

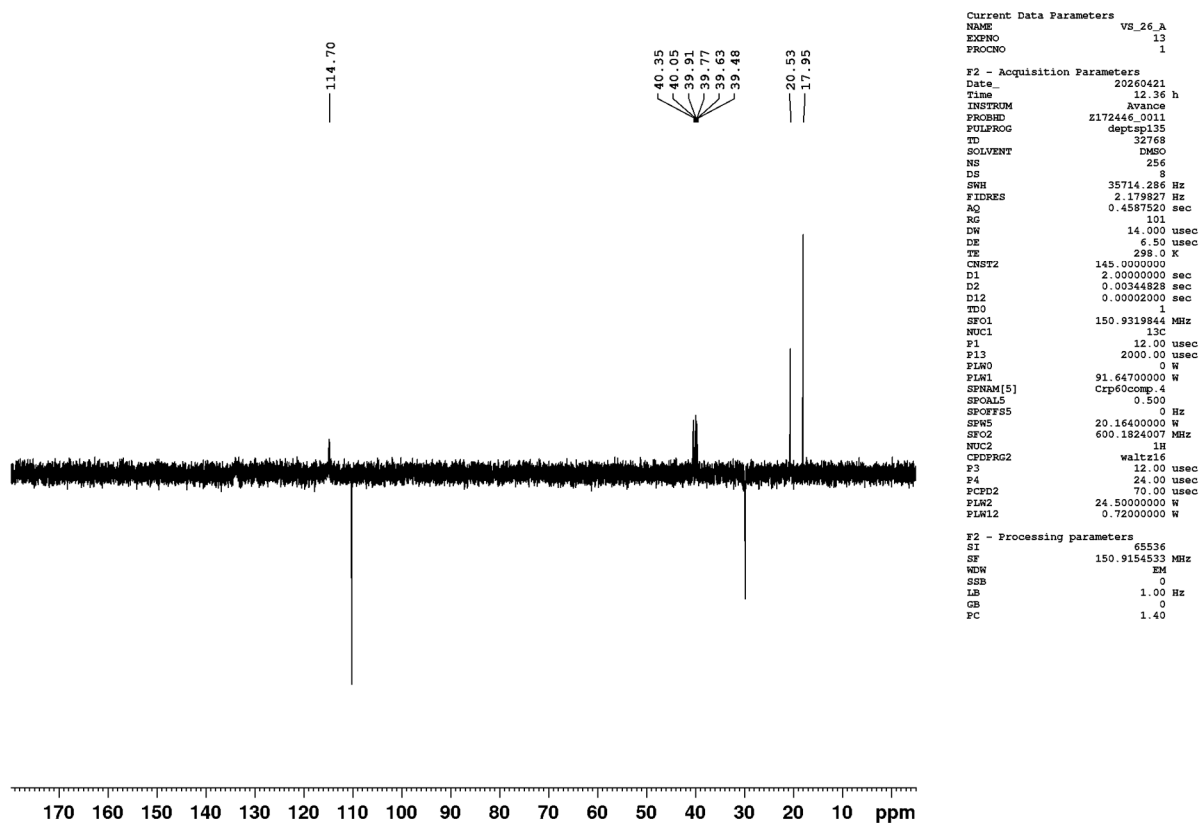


Figure S9. DEPT-135 NMR spectrum of **3b** in DMSO-*d*₆.

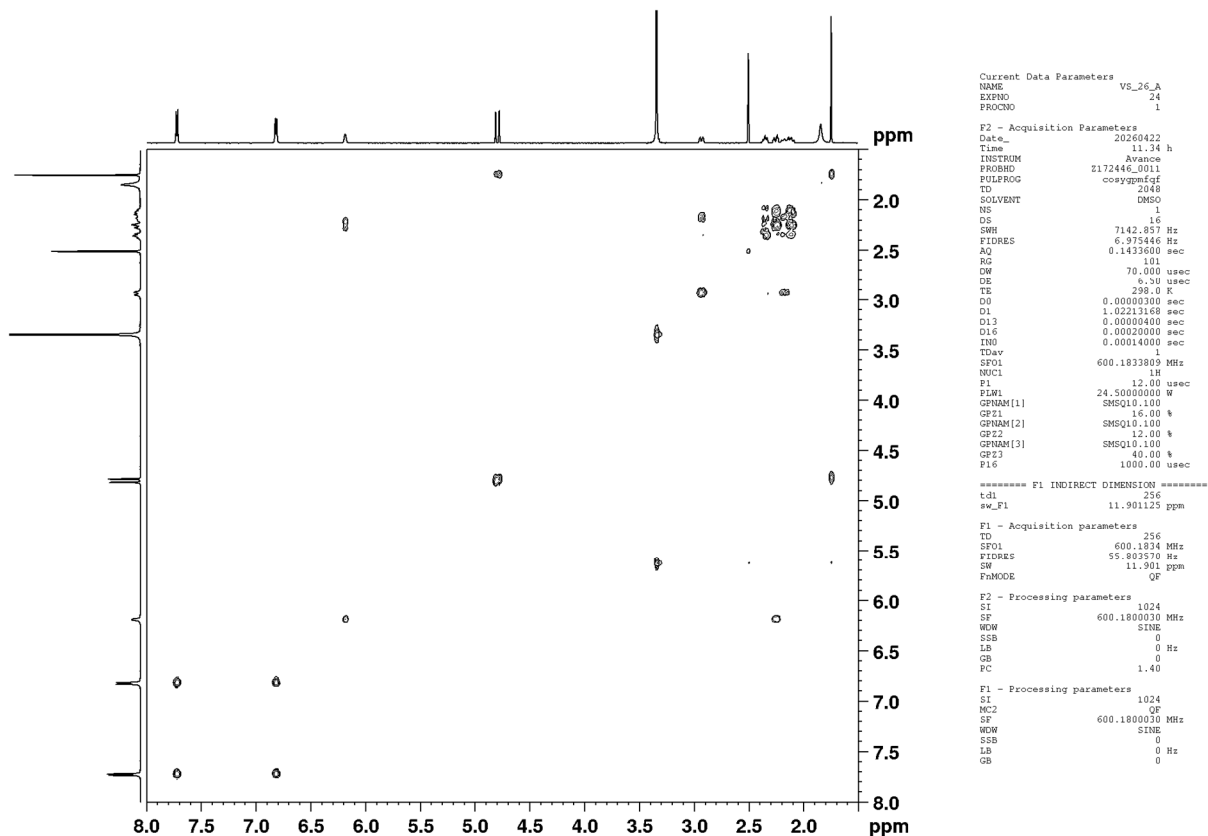


Figure S10. 2D COSY NMR spectrum of **3b** in DMSO-*d*₆.

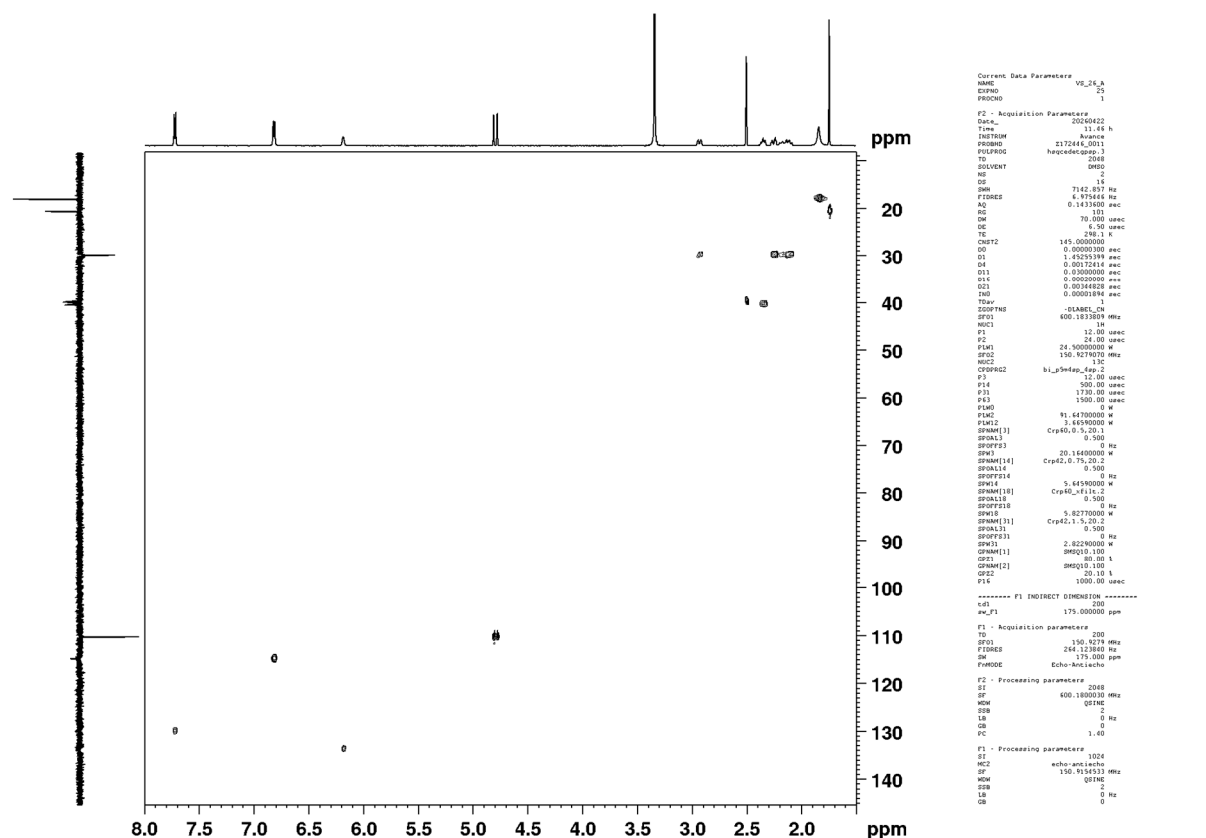


Figure S11. 2D HSQC NMR spectrum of **3b** in DMSO-*d*₆.

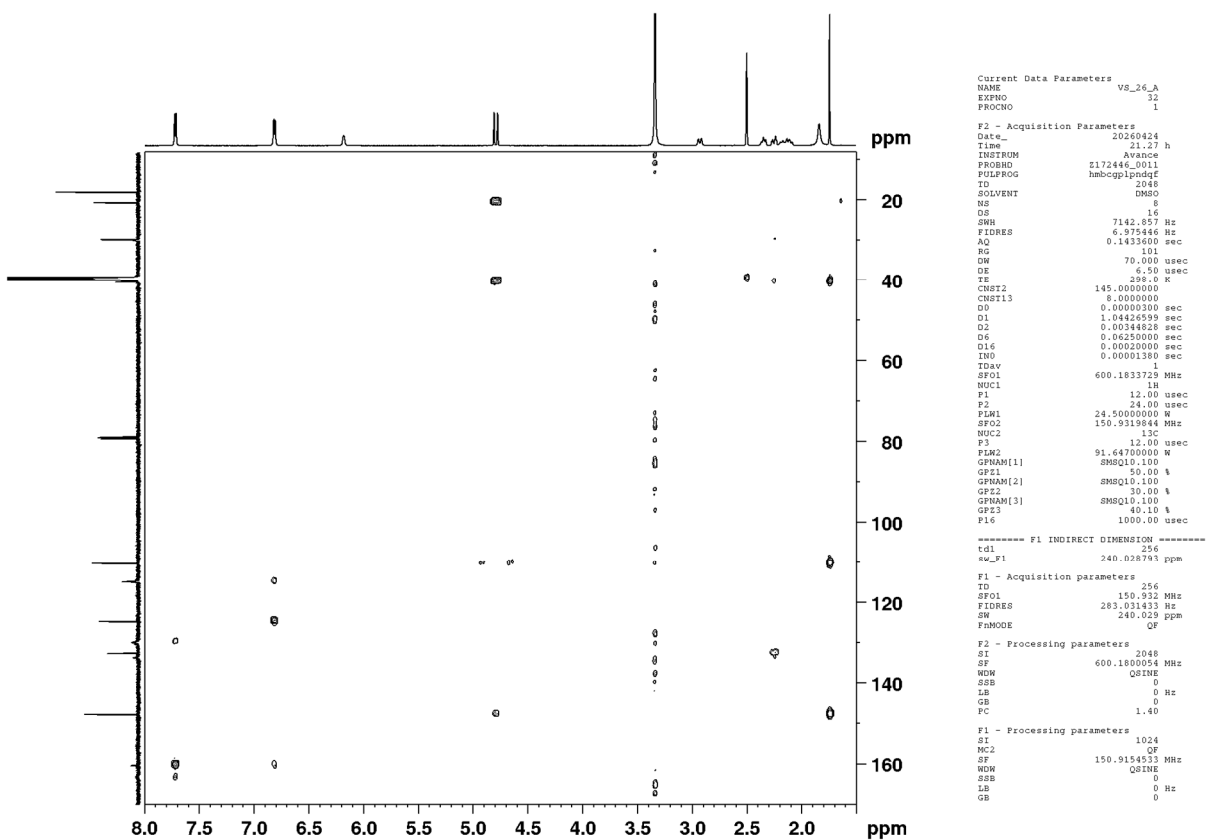


Figure S12. 2D HMBC NMR spectrum of **3b** in DMSO-*d*₆.

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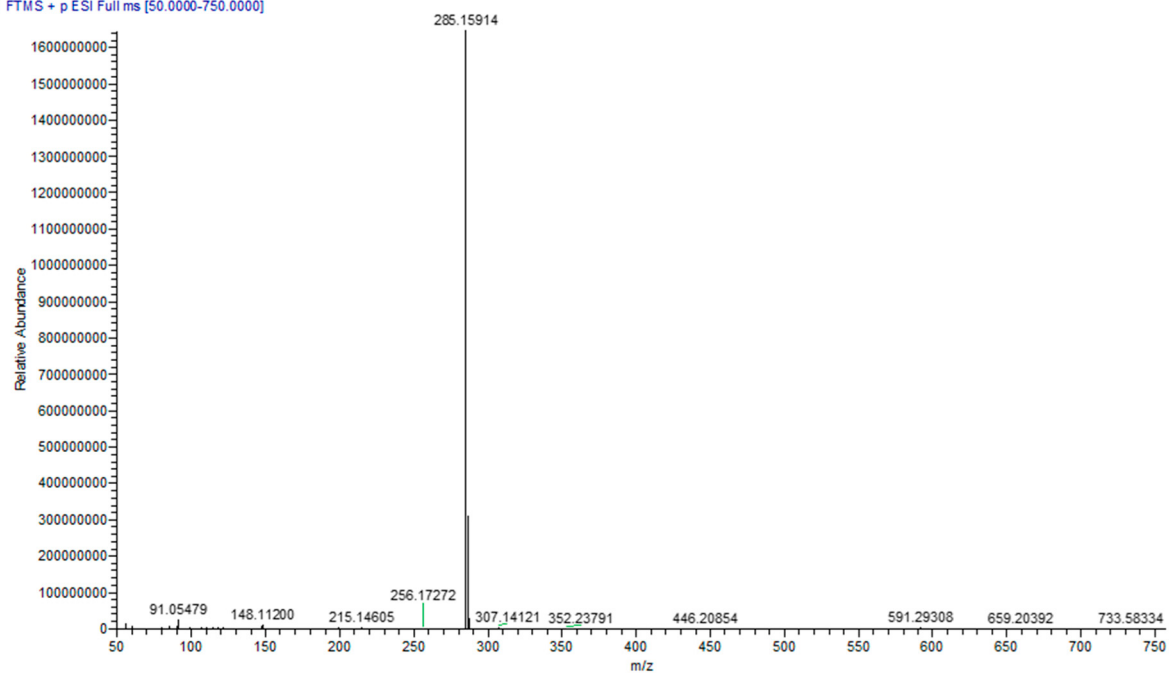


Figure S13. HRMS of **3b**.

3. (*R,E*)-2,4-dihydroxy-*N'*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene) benzohydrazide, **3c**

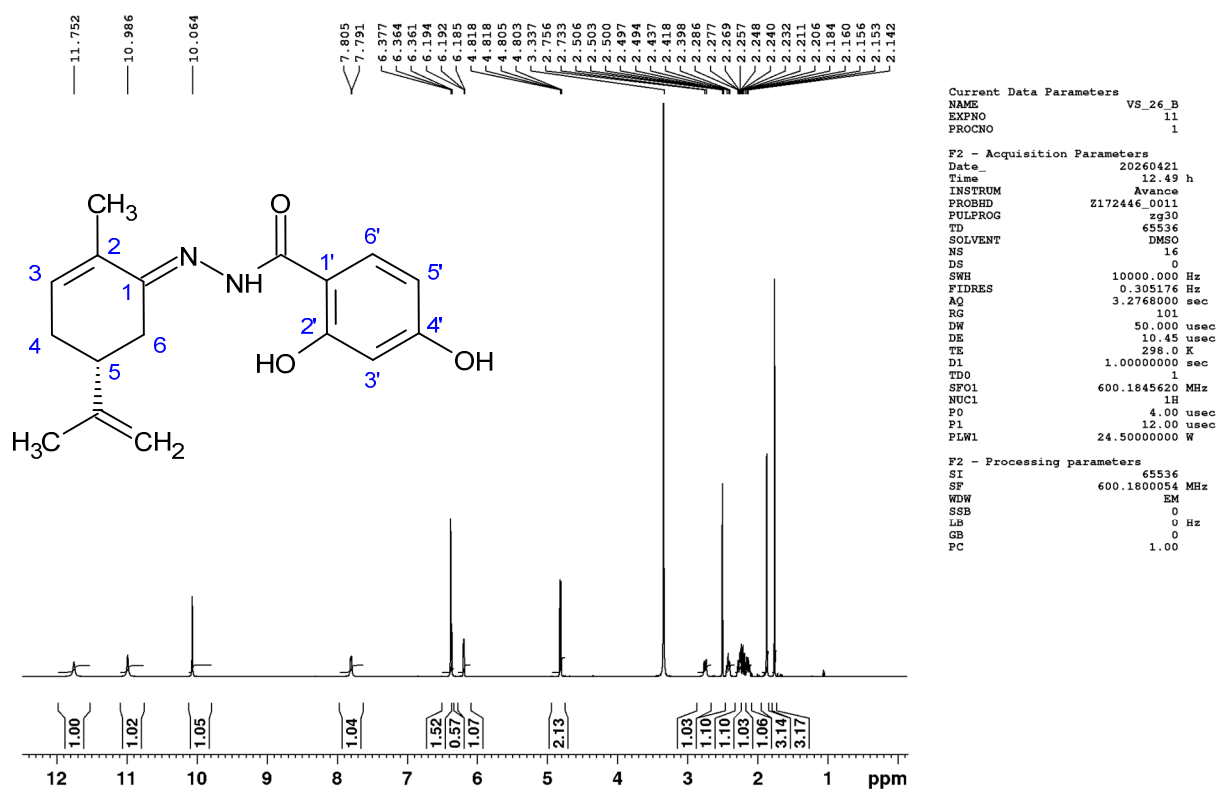


Figure S14. ¹H NMR spectrum of **3c** in DMSO-*d*₆.

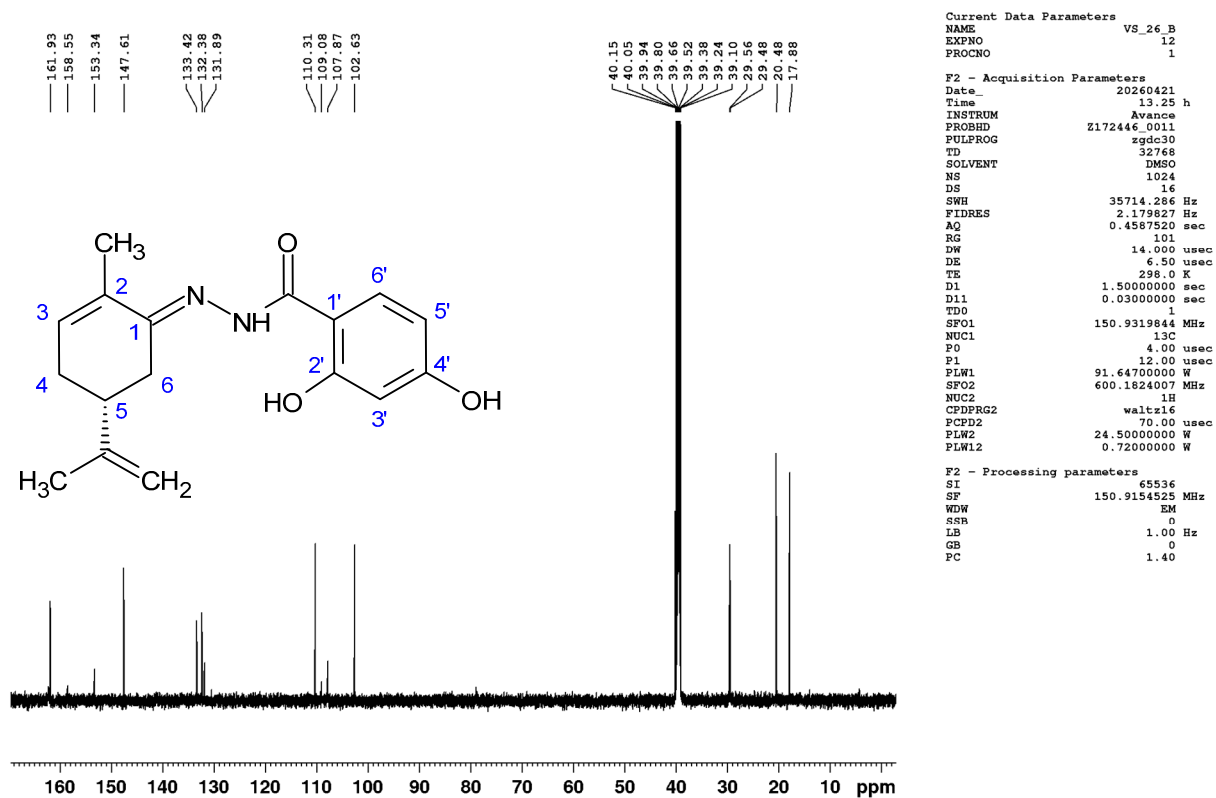


Figure S15. ¹³C NMR spectrum of **3c** in DMSO-*d*₆.

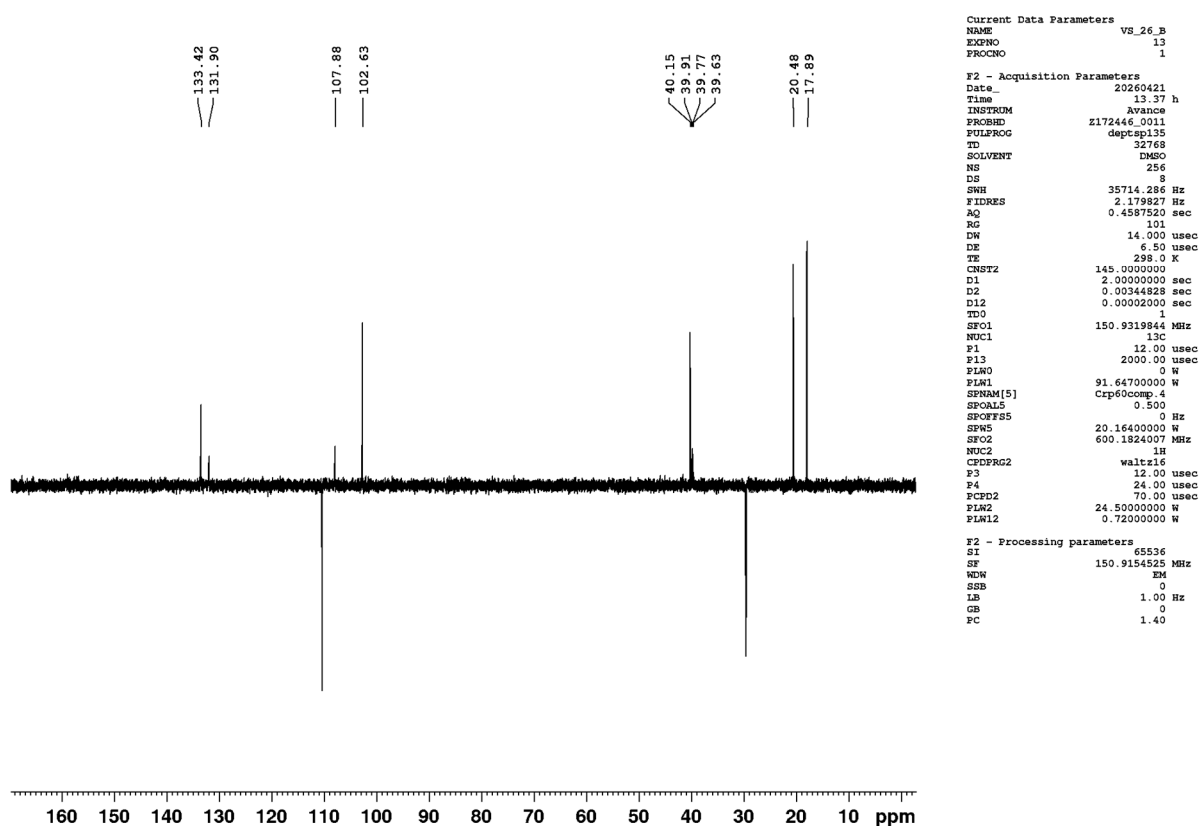


Figure S16. DEPT-135 NMR spectrum of **3c** in DMSO-*d*₆.

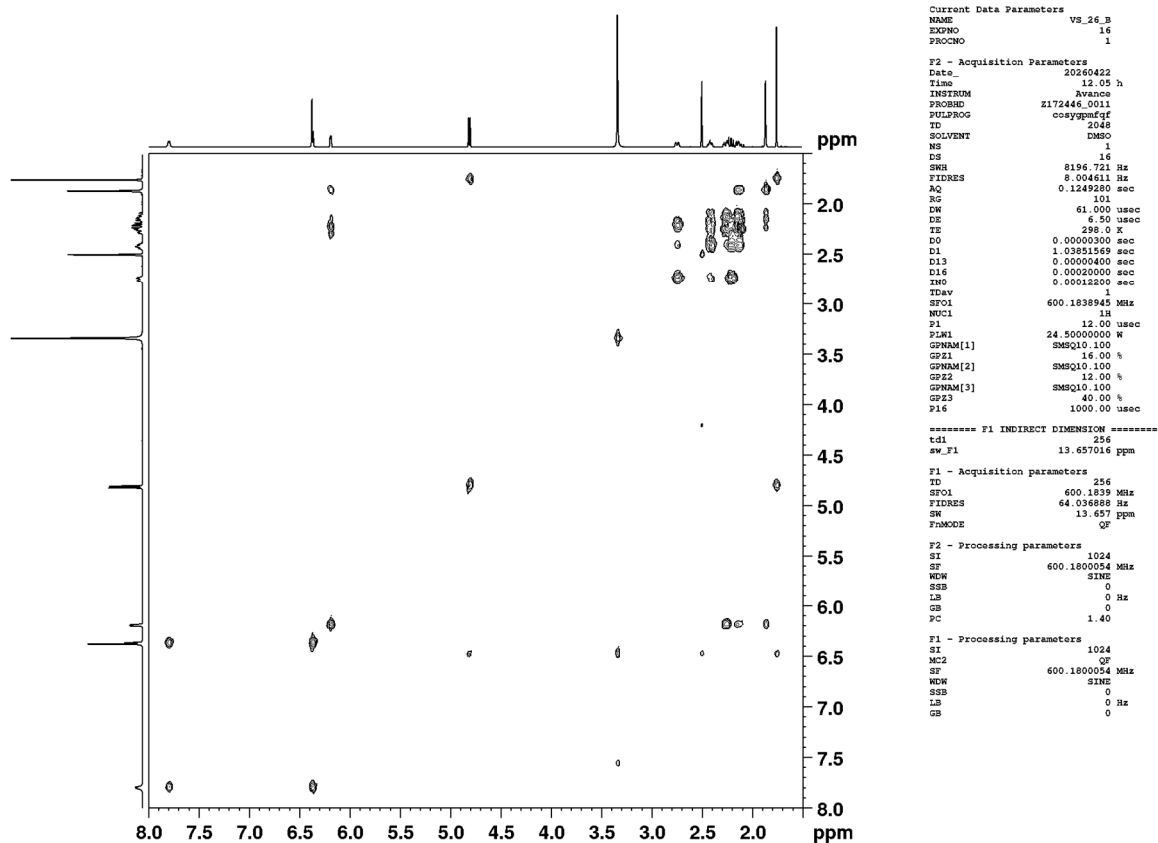


Figure S17. 2D COSY NMR spectrum of **3c** in DMSO- d_6 .

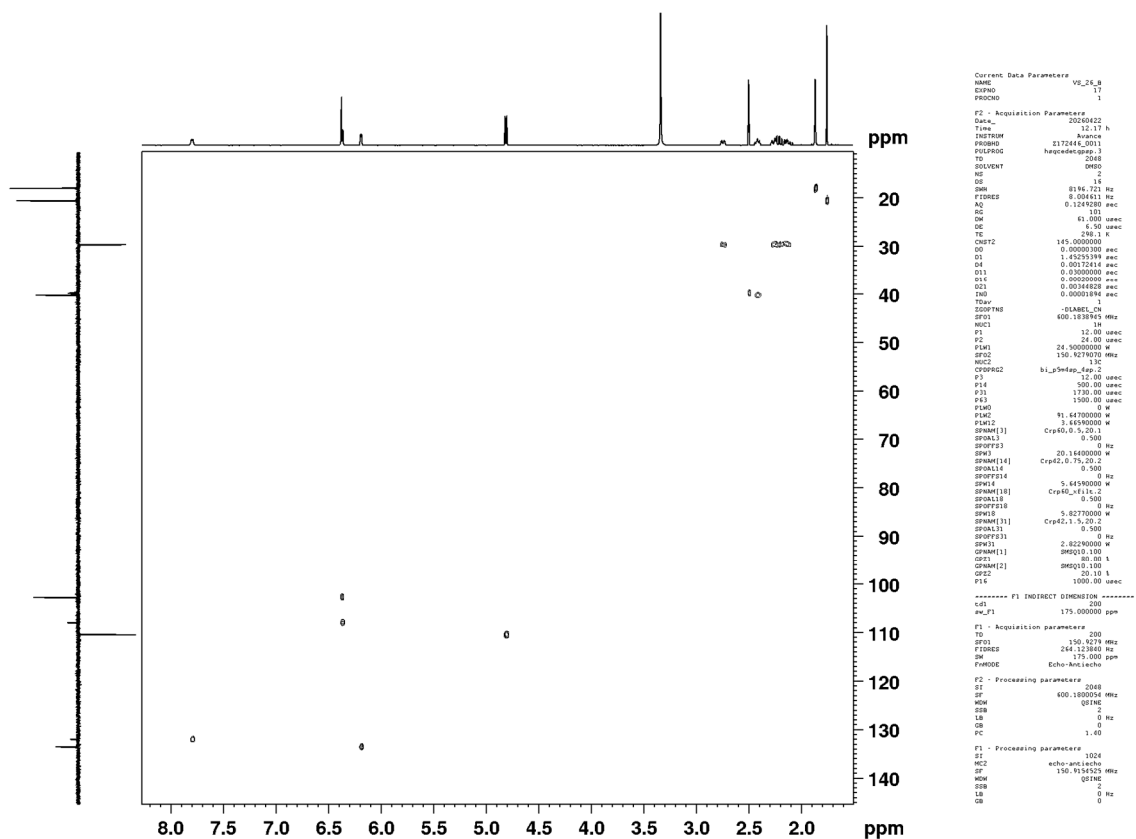


Figure S18. 2D HSQC NMR spectrum of **3c** in DMSO- d_6 .

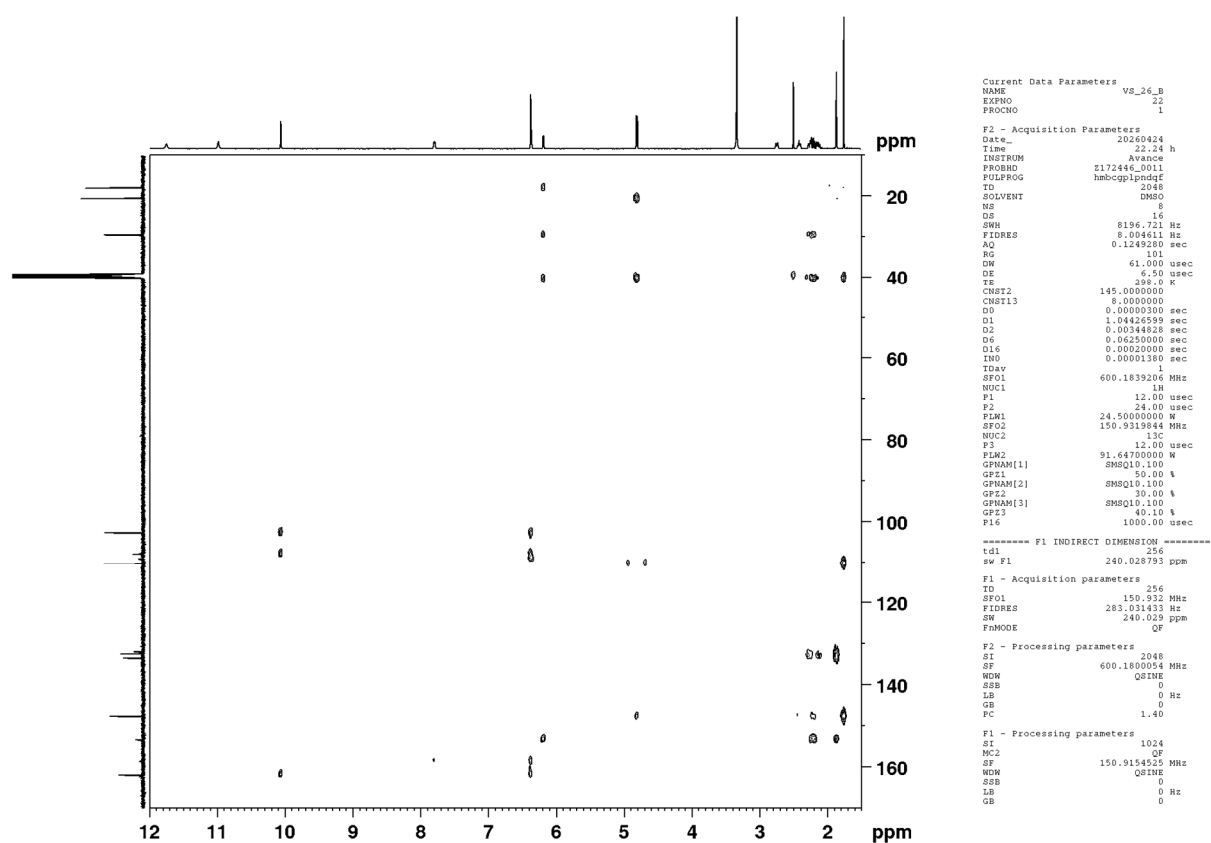


Figure S19. 2D HMBC NMR spectrum of **3c** in DMSO-*d*₆.

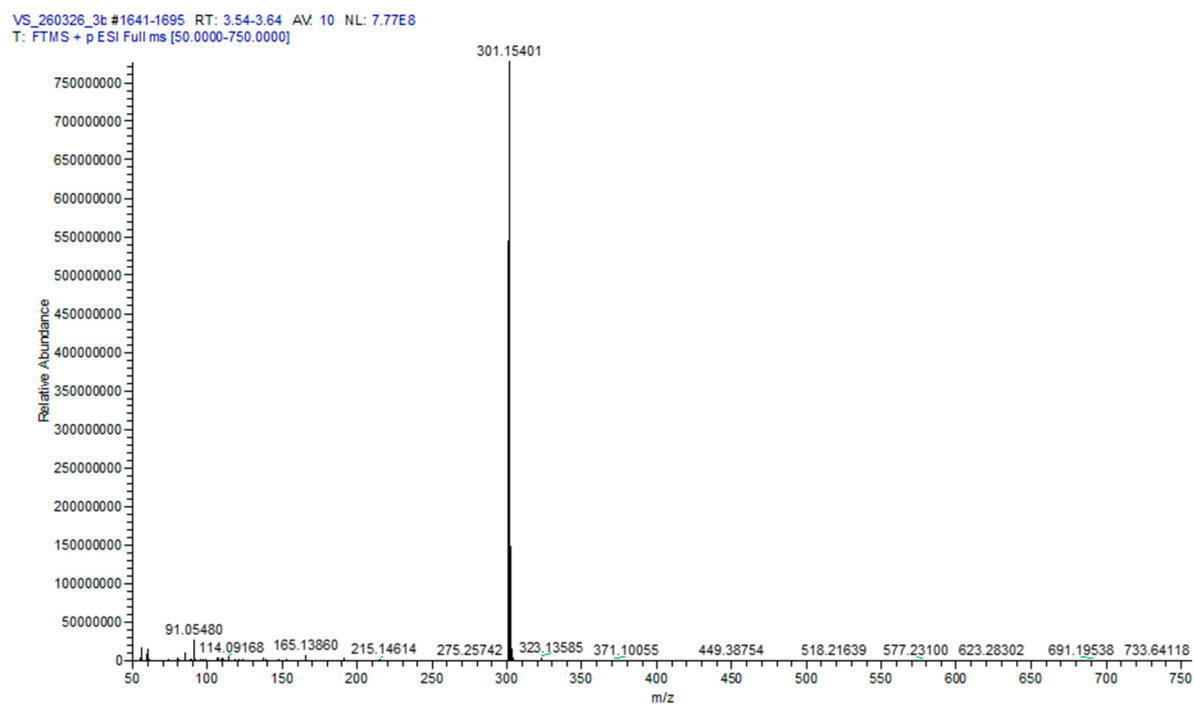


Figure 20S. HRMS of **3c**.

(*R,E*)-4-methoxy-*N'*-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene]benzohydrazide, **3d**

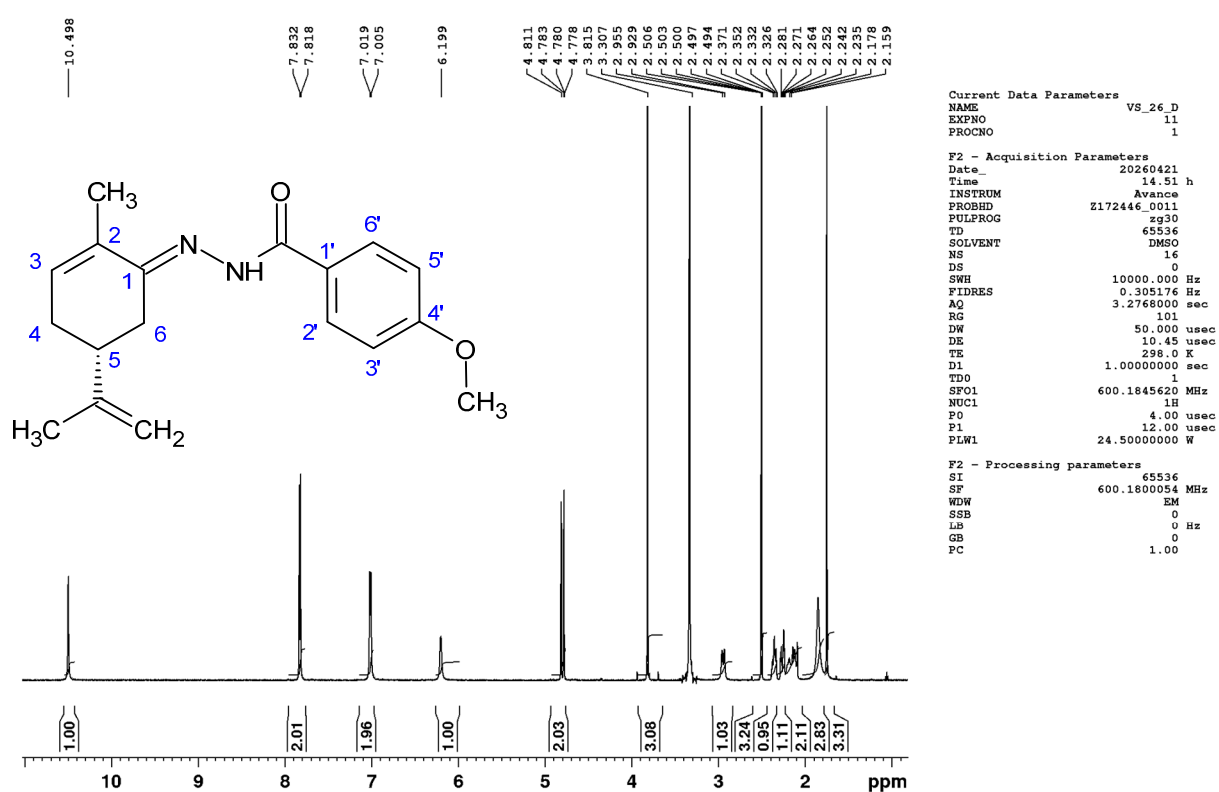


Figure S21. ¹H NMR spectrum of **3d** in DMSO-*d*₆.

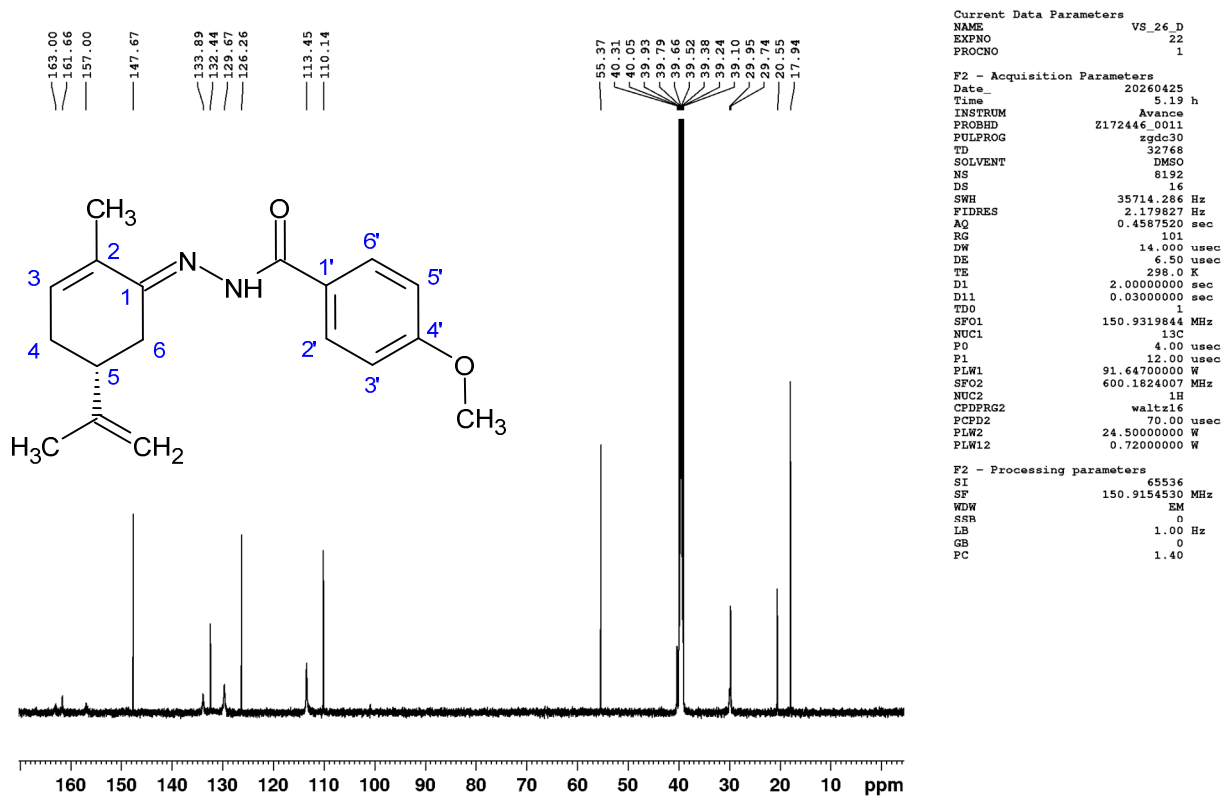


Figure S22. ^{13}C NMR spectrum of **3d** in $\text{DMSO}-d_6$.

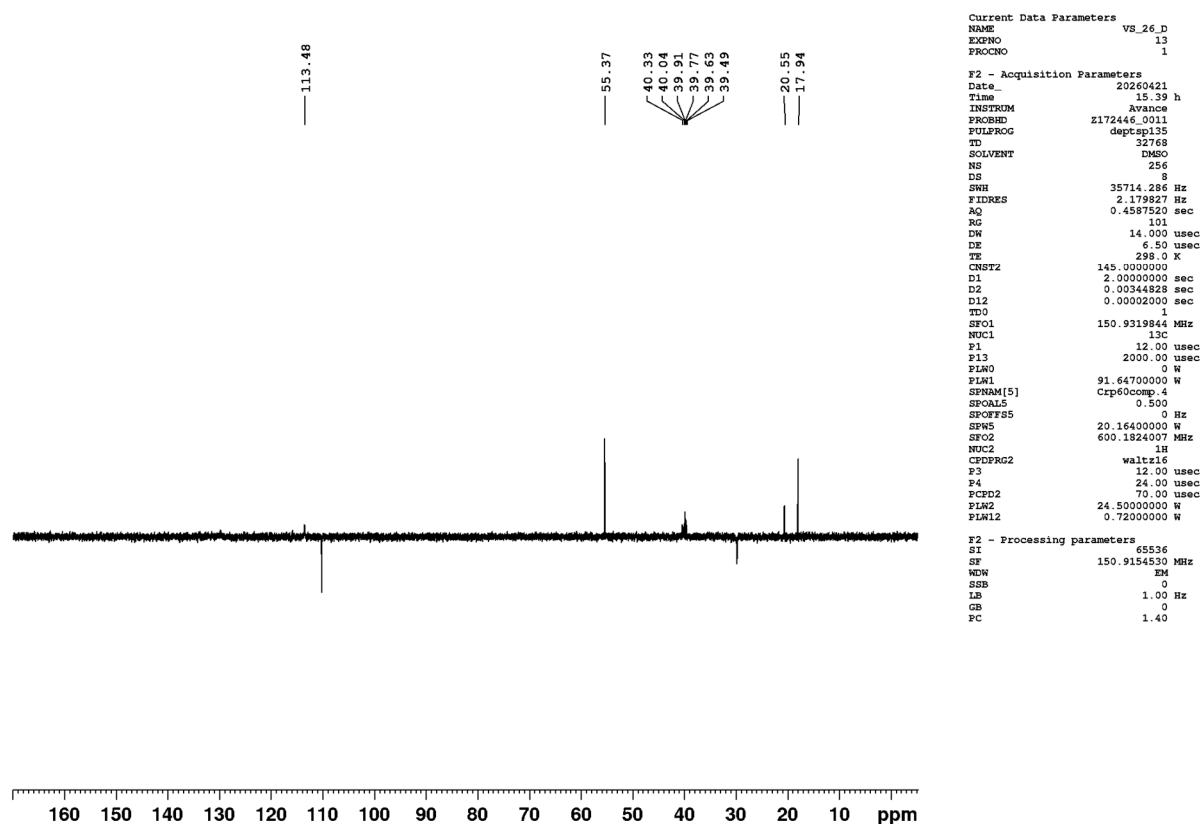


Figure S23. DEPT-135 NMR spectrum of **3d** in $\text{DMSO}-d_6$.

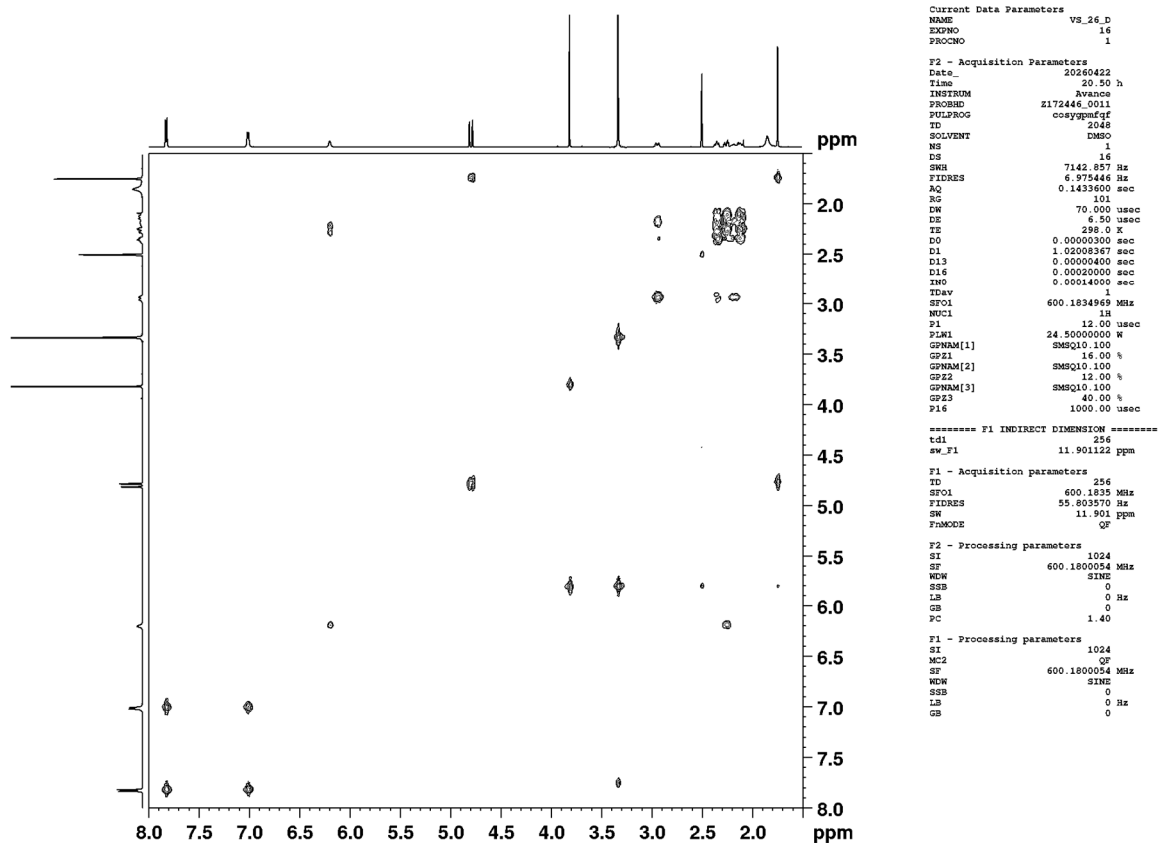


Figure S24. 2D COSY NMR spectrum of **3d** in DMSO-*d*₆.

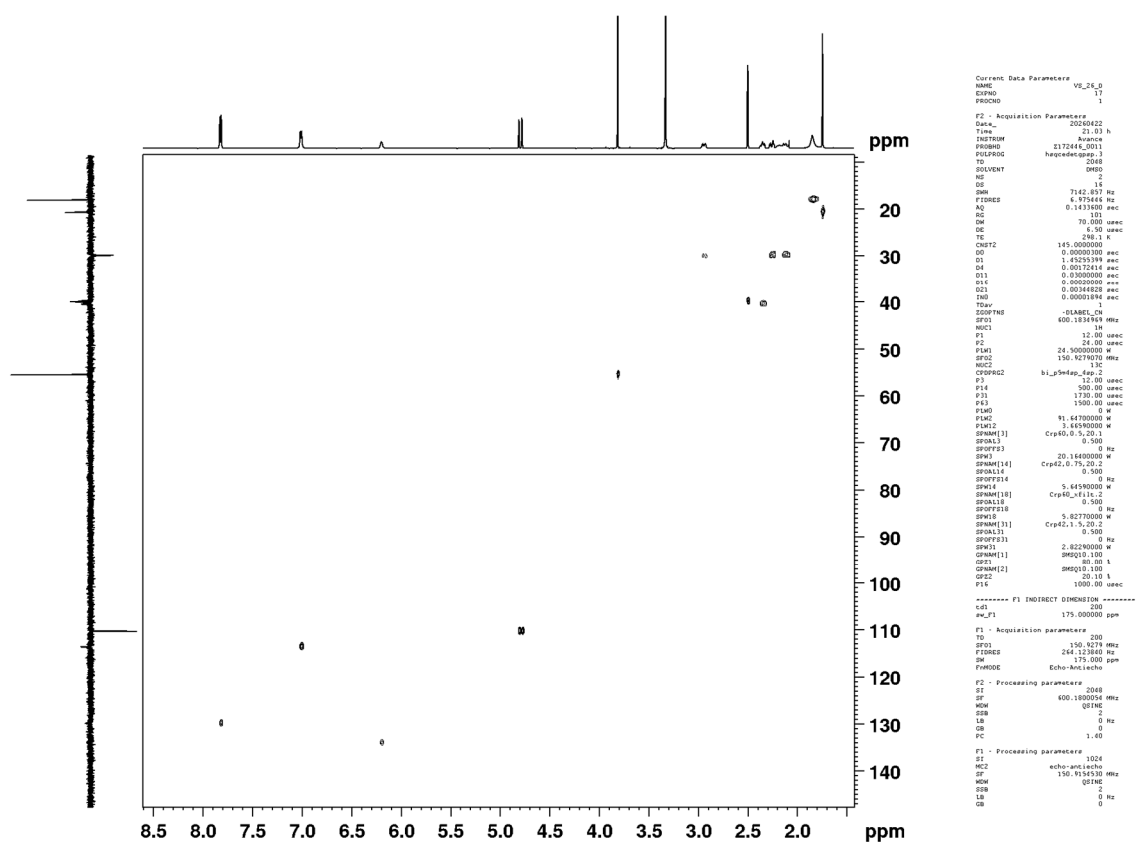


Figure S25. 2D HSQC NMR spectrum of **3d** in DMSO-*d*₆.

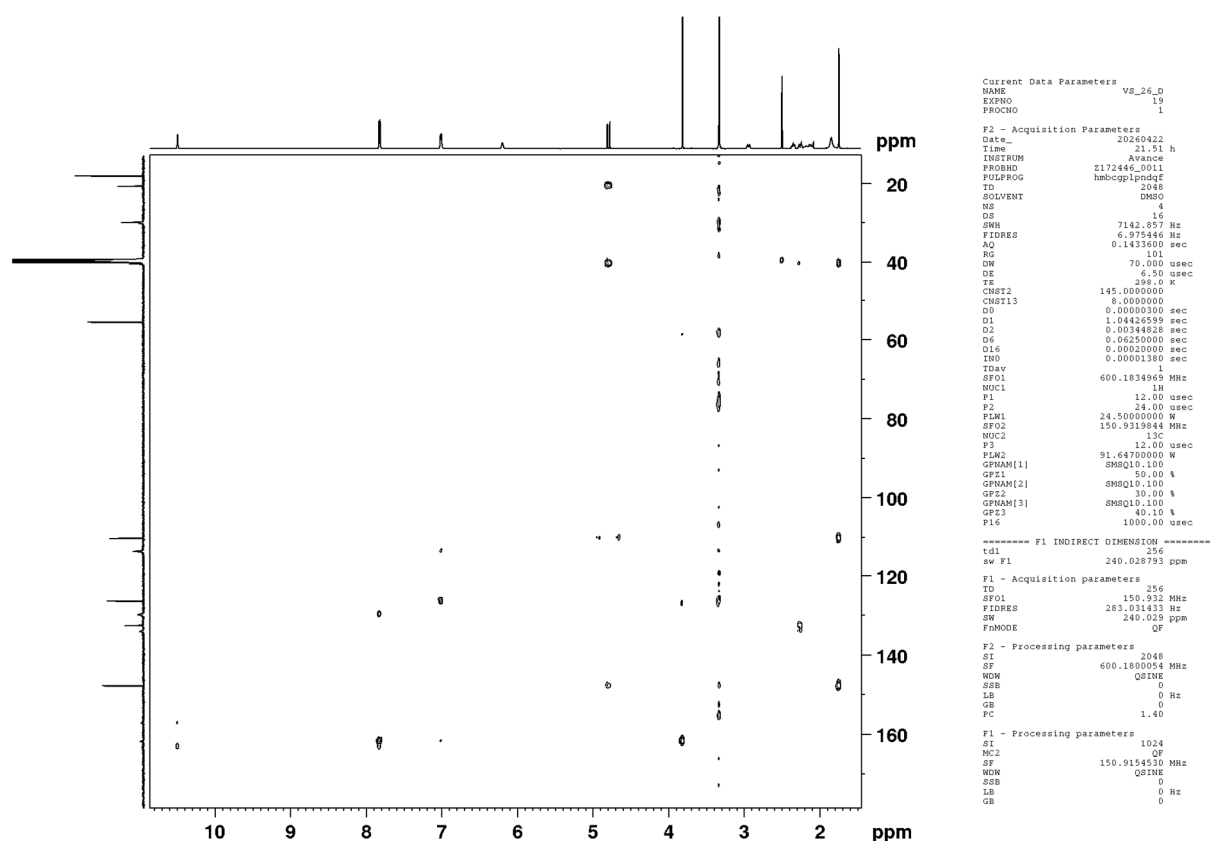


Figure S26. 2D HMBC NMR spectrum of **3d** in DMSO- d_6 .

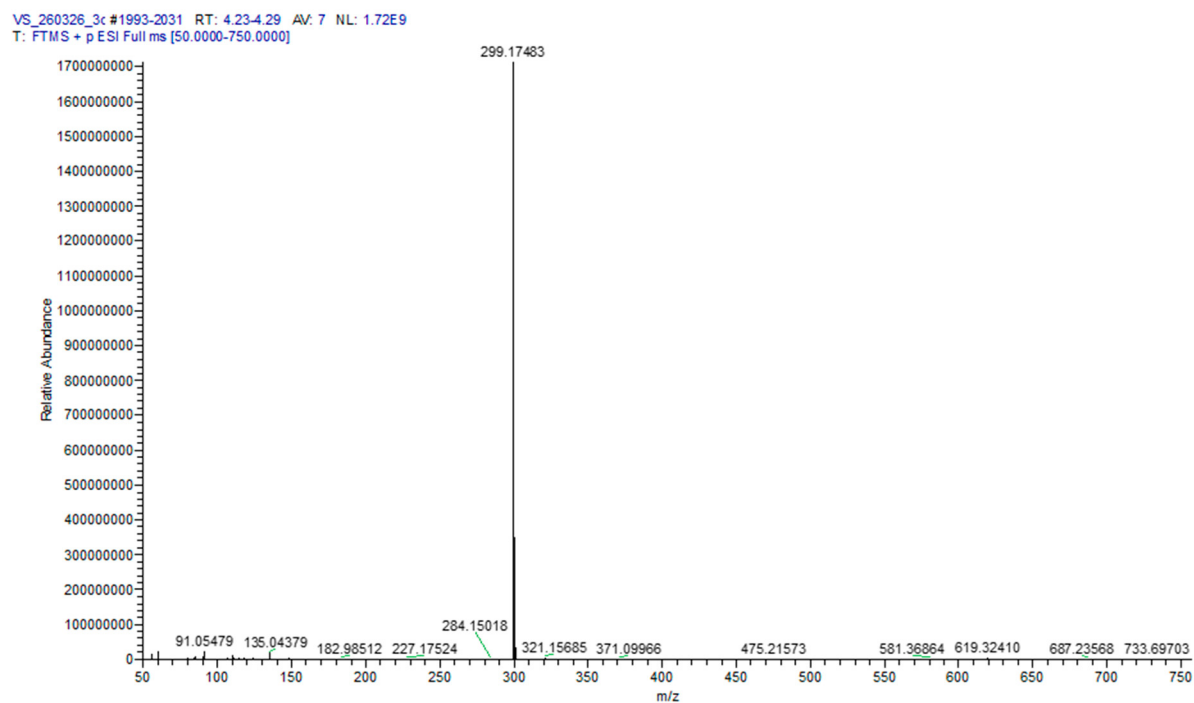


Figure S27. HRMS of **3d**.

4. (*R,E*)-2-methoxy-*N'*-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene]benzohydrazide, **3e**

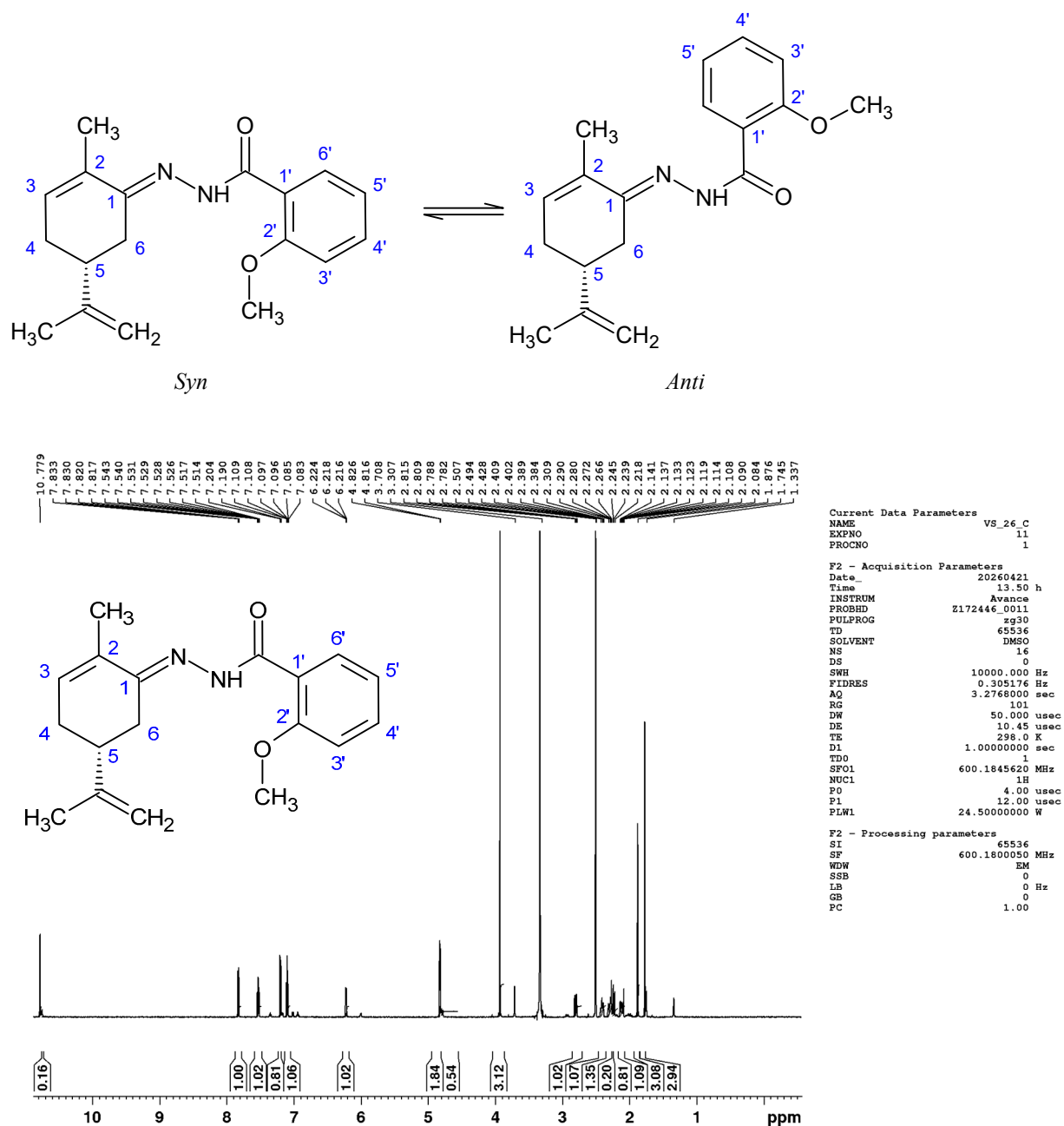


Figure S28. ¹H NMR spectrum of **3e** in DMSO-*d*₆.

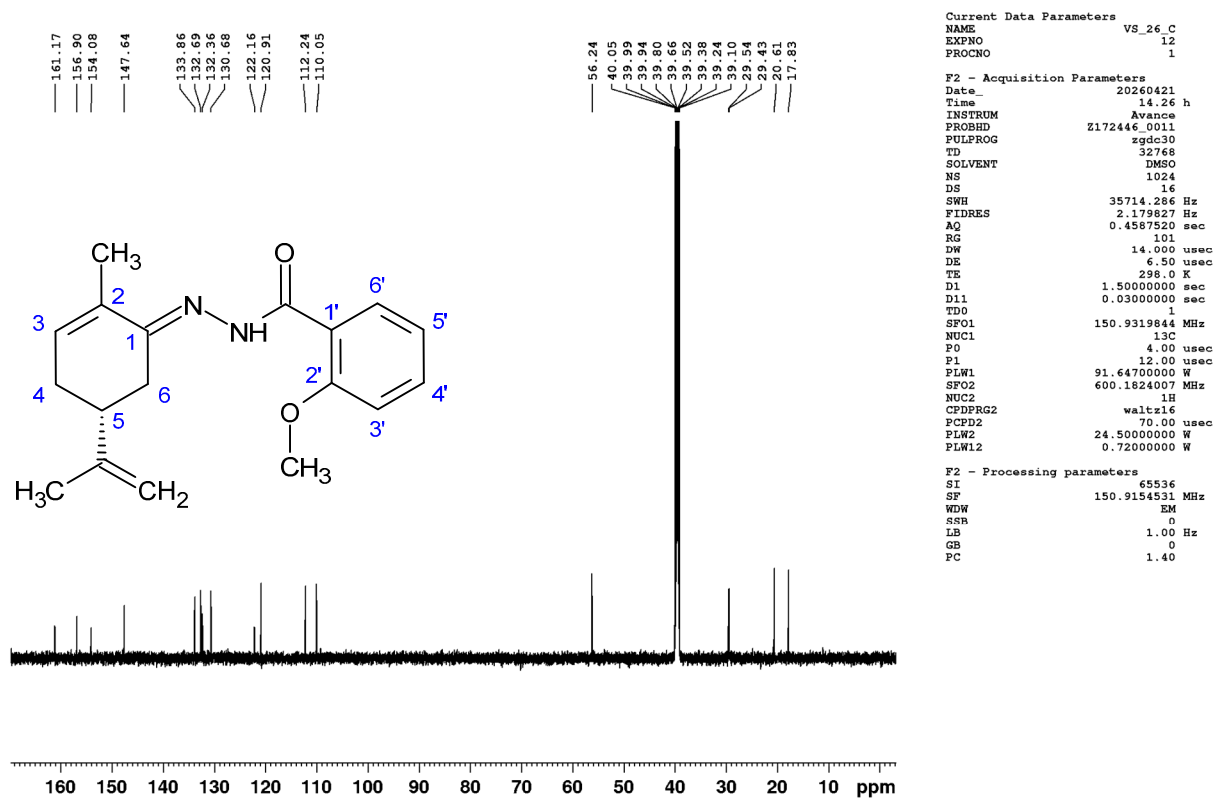


Figure S29. ¹³C NMR spectrum of **3e** in DMSO-*d*₆.

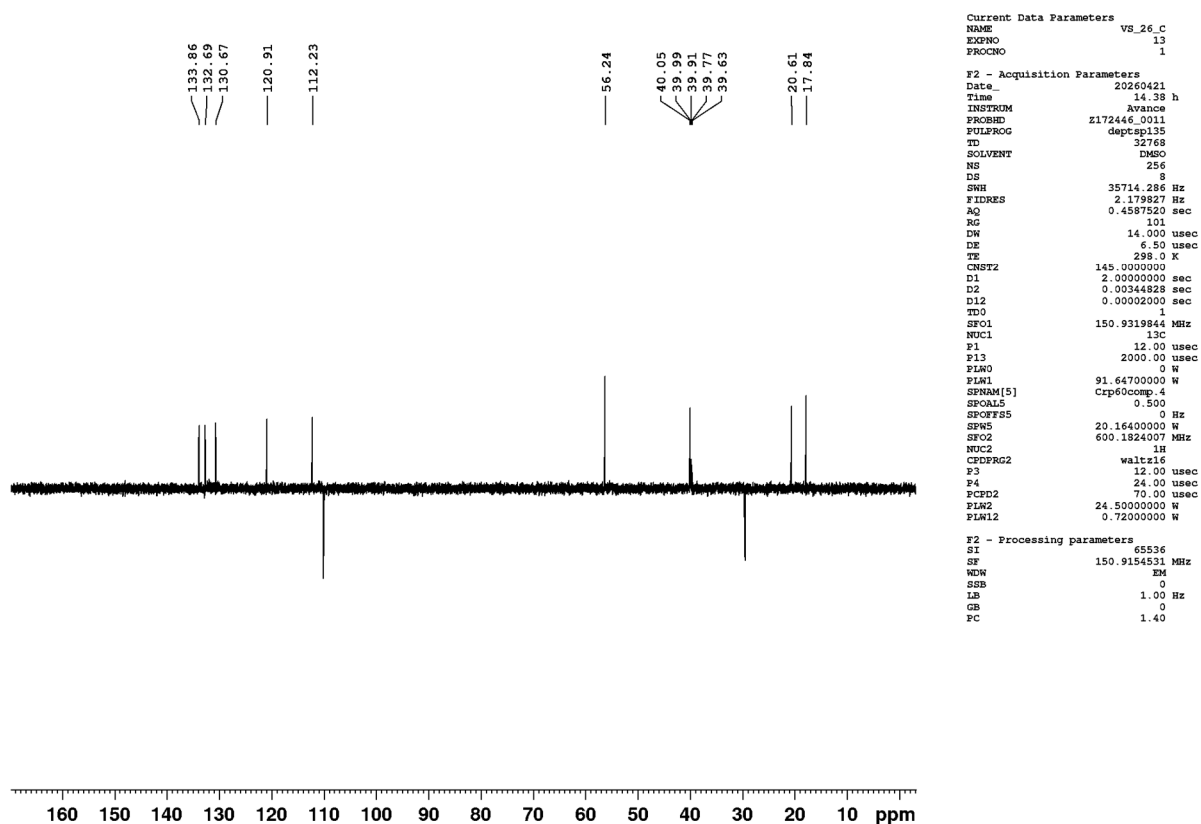


Figure 30S. DEPT-135 NMR spectrum of **3e** in DMSO-*d*₆.

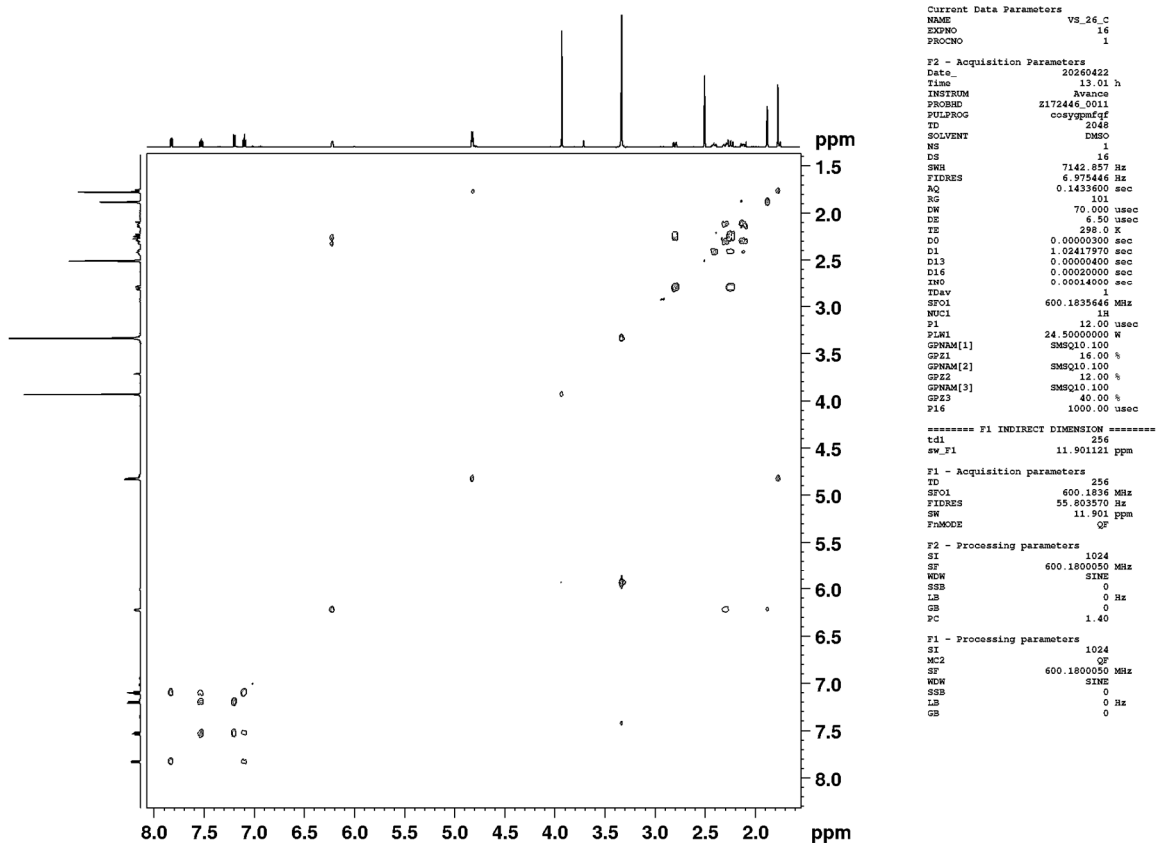


Figure S31. 2D COSY NMR spectrum of **3e** in DMSO- d_6 .

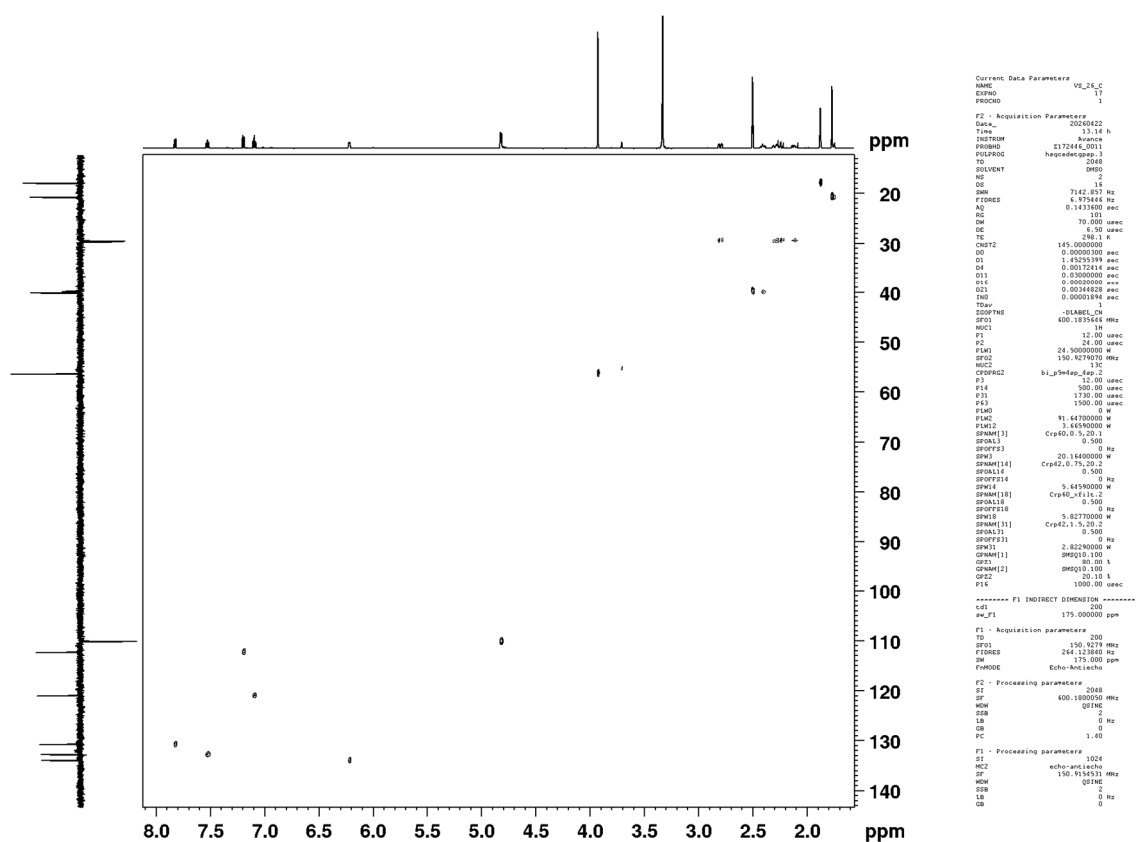


Figure S32. 2D HSQC NMR spectrum of **3e** in DMSO- d_6 .

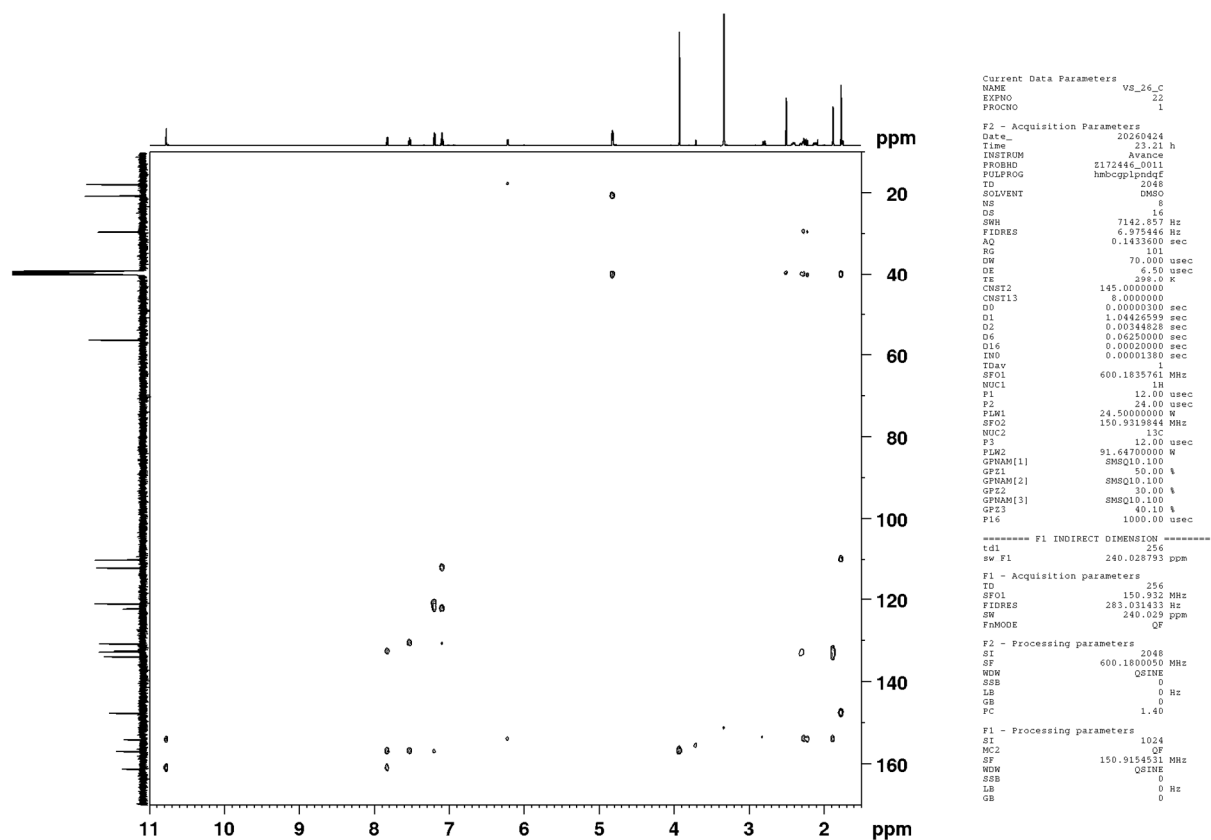


Figure S33. 2D HMBC NMR spectrum of **3e** in DMSO- d_6 .

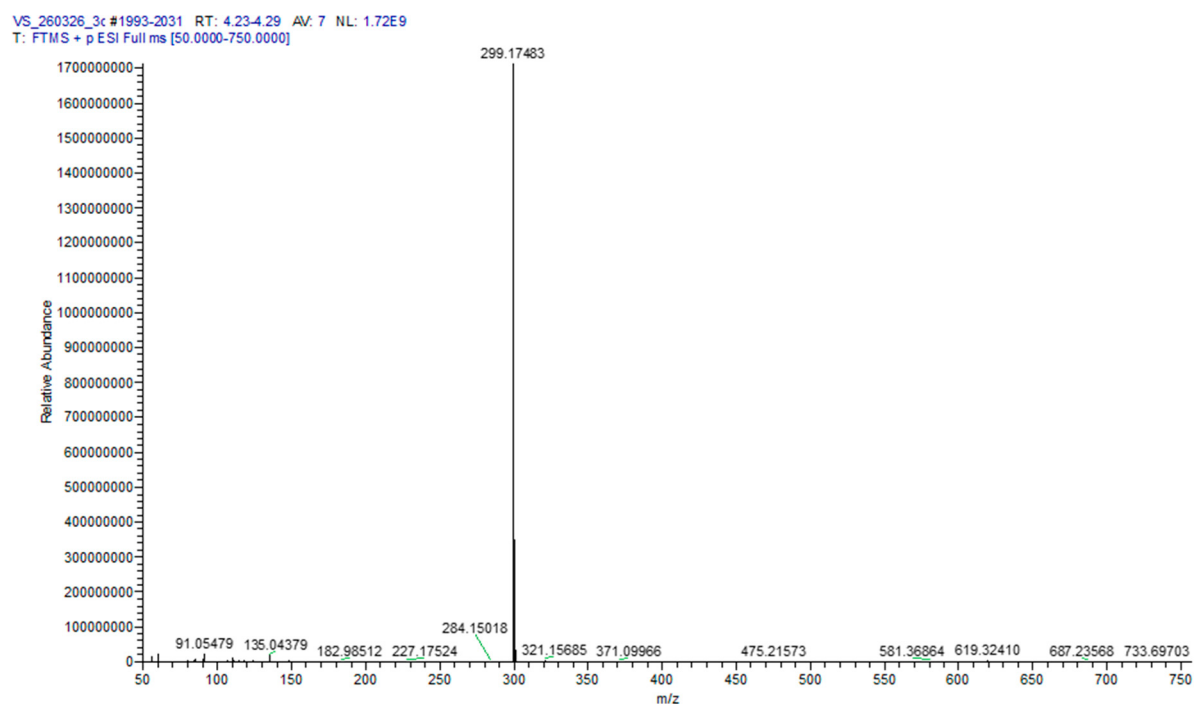


Figure S34. HRMS of **3e**.



6. (R,E)-4-(dimethylamino)-N'-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene] benzohydrazide, **3f**

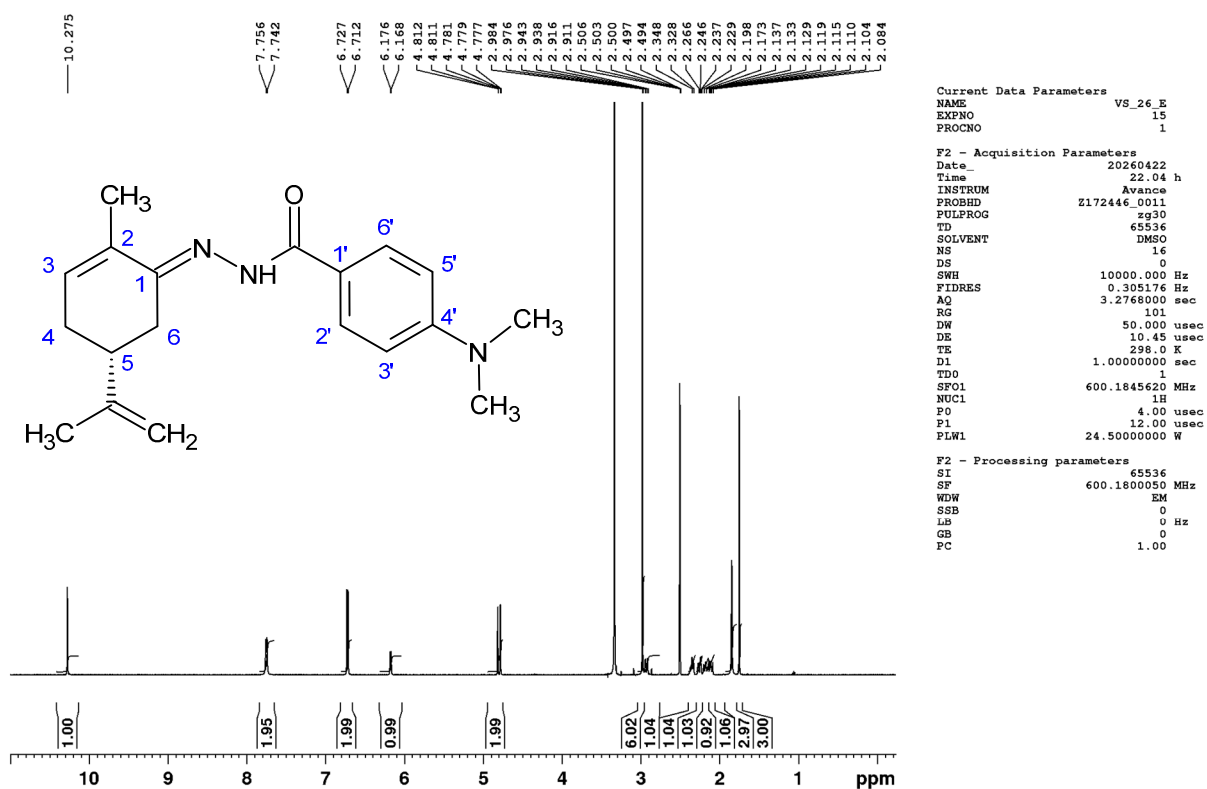


Figure S35. ^1H NMR spectrum of **3f** in $\text{DMSO}-d_6$.

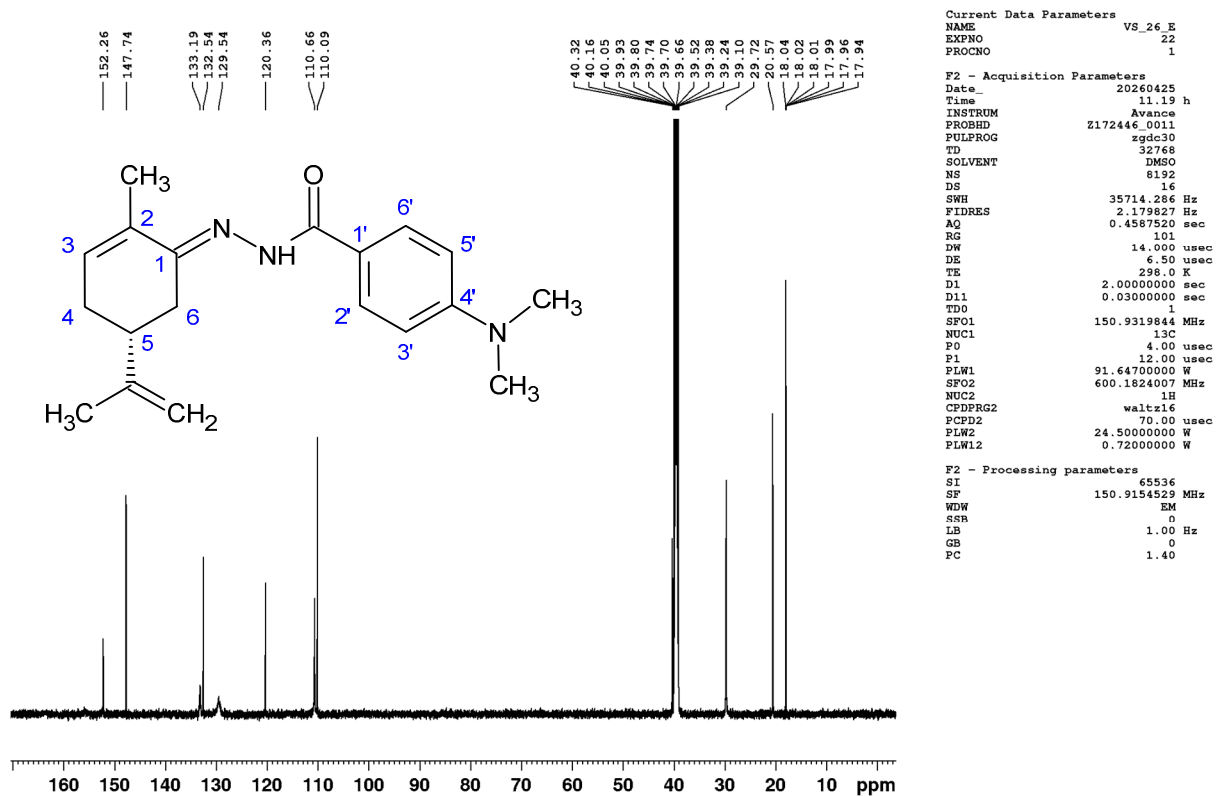


Figure S36. ^{13}C NMR spectrum of **3f** in $\text{DMSO}-d_6$.

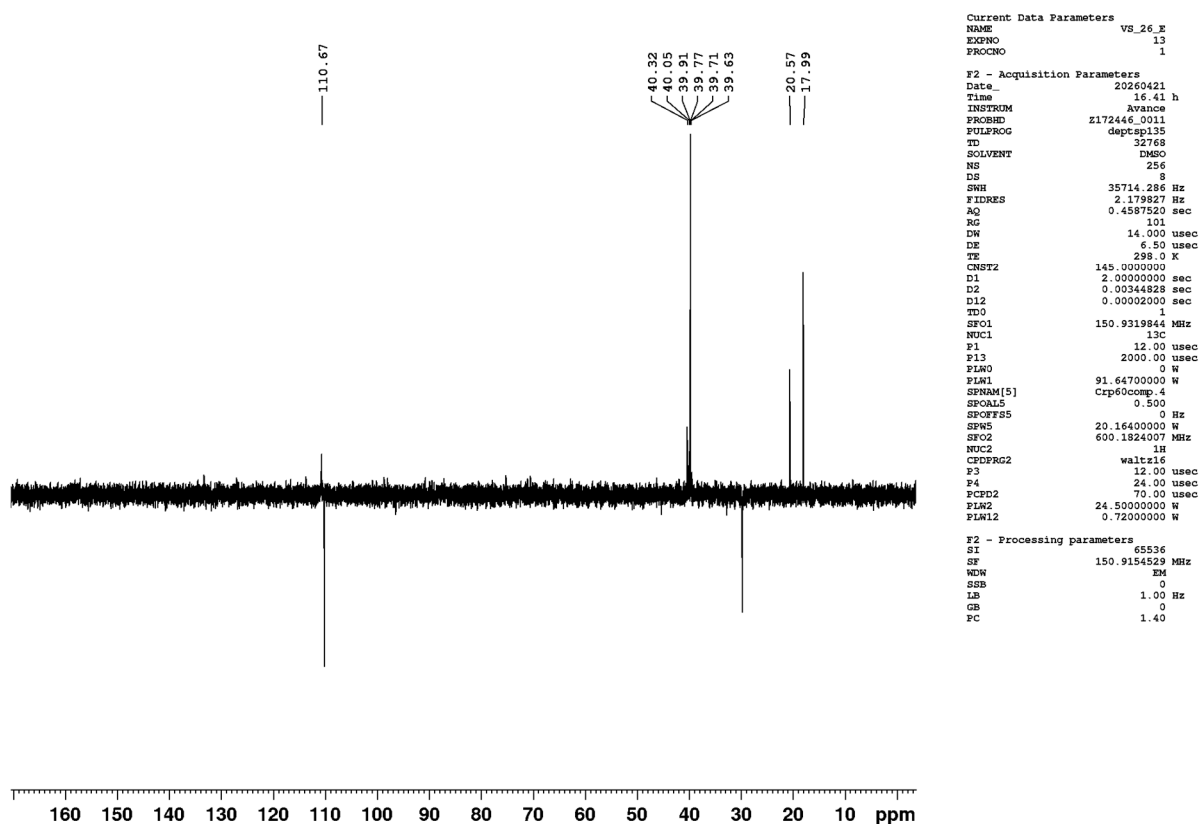


Figure S37. DEPT-135 NMR spectrum of **3f** in $\text{DMSO}-d_6$.

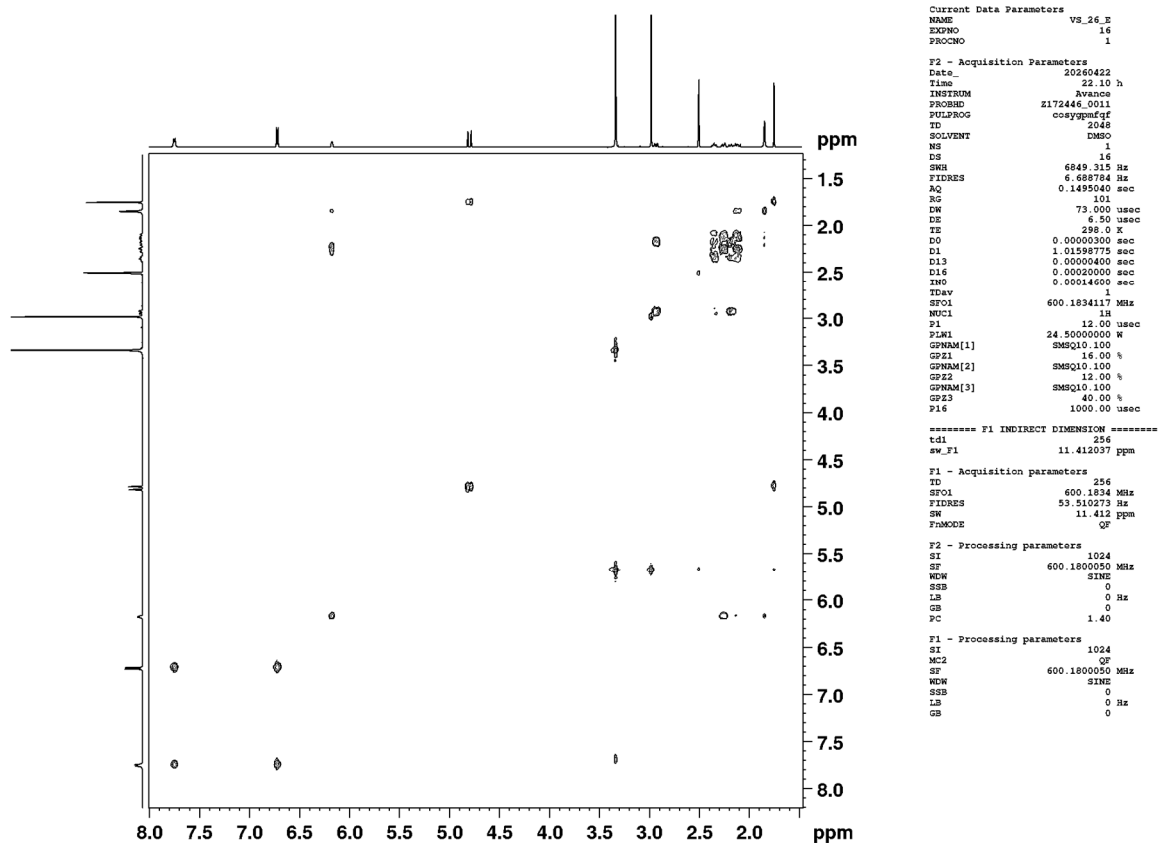


Figure S38. 2D COSY NMR spectrum of **3f** in DMSO- d_6 .

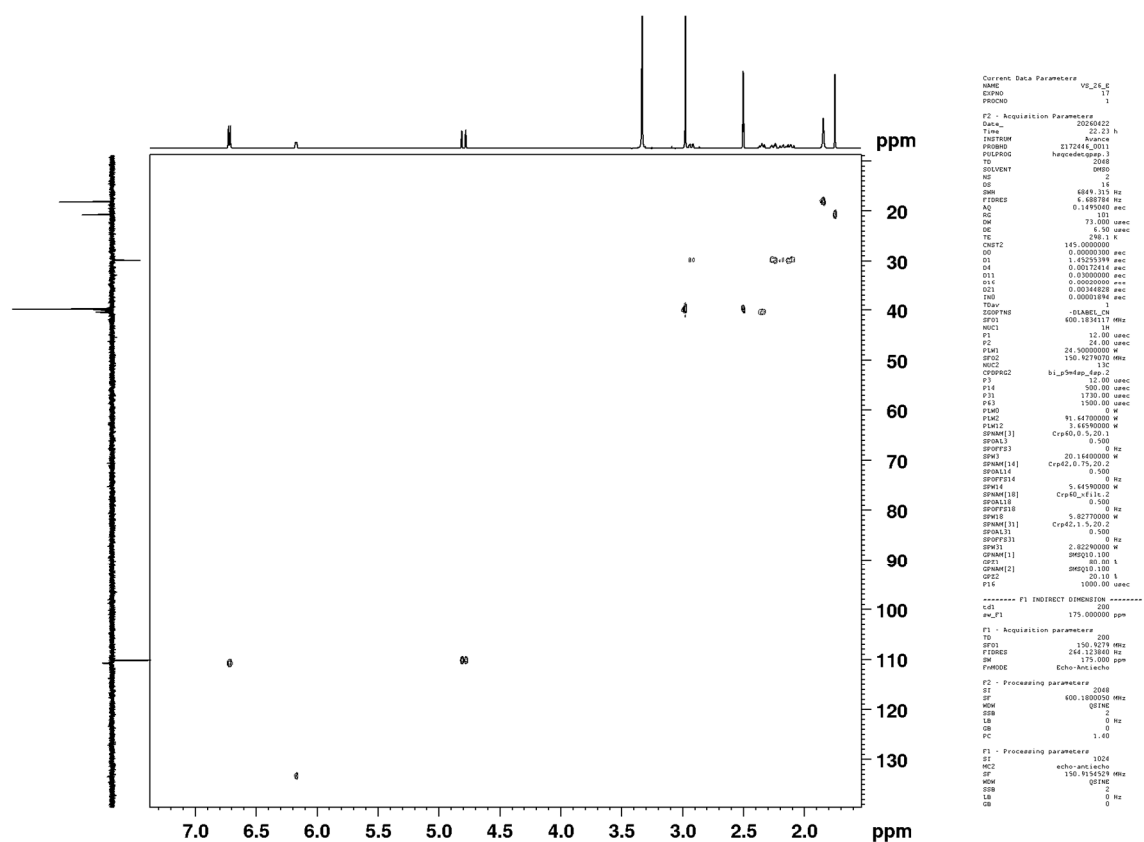


Figure S39. 2D HSQC NMR spectrum of **3f** in DMSO- d_6 .

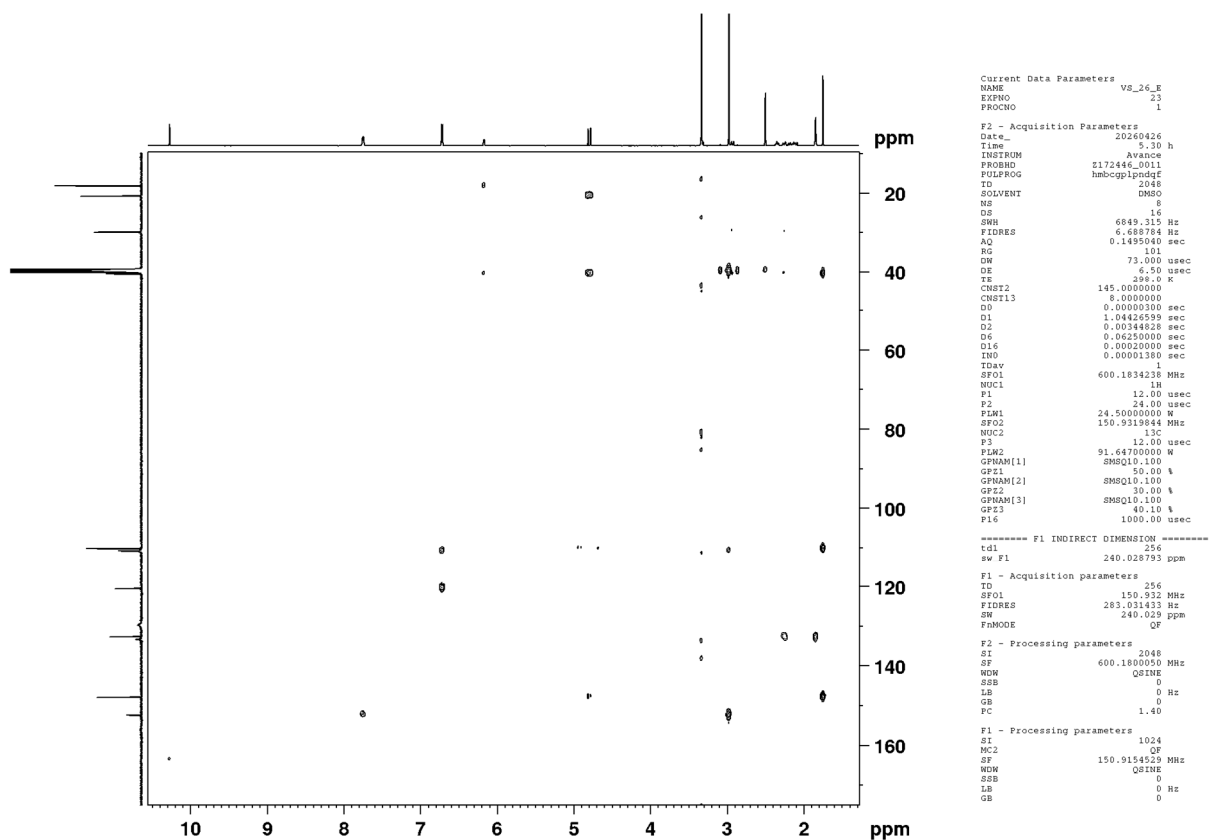


Figure 40S. 2D HMBC NMR spectrum of **3f** in DMSO-*d*₆.

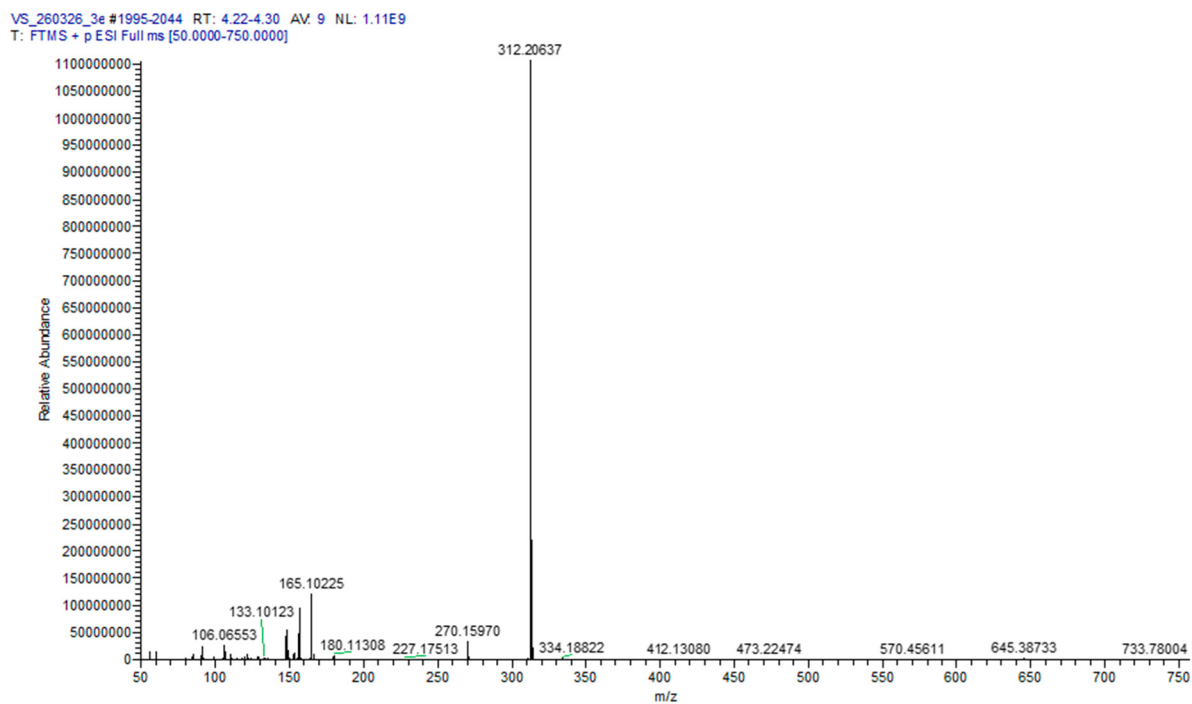


Figure S41. HRMS of **3f**.

7. (R,E)-2-(1*H*-indol-3-yl)-*N'*-[2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene] acetohydrazide, **3g**

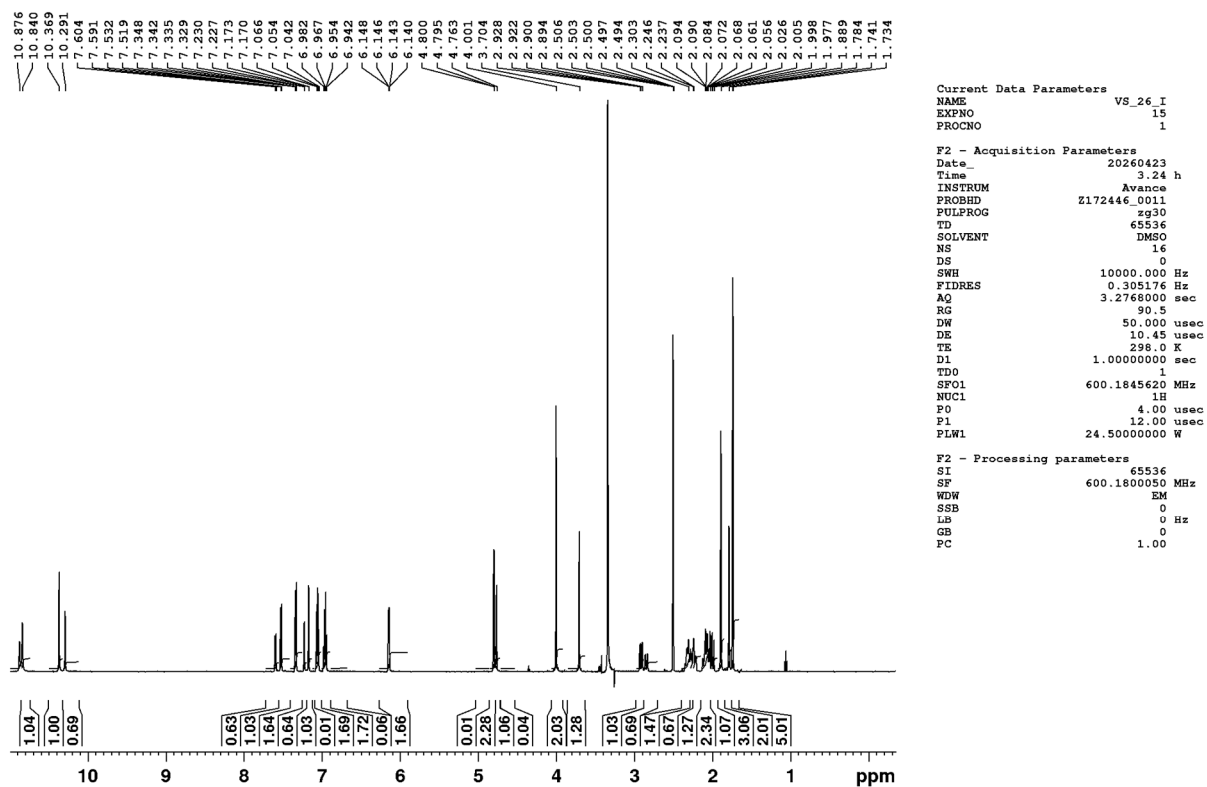
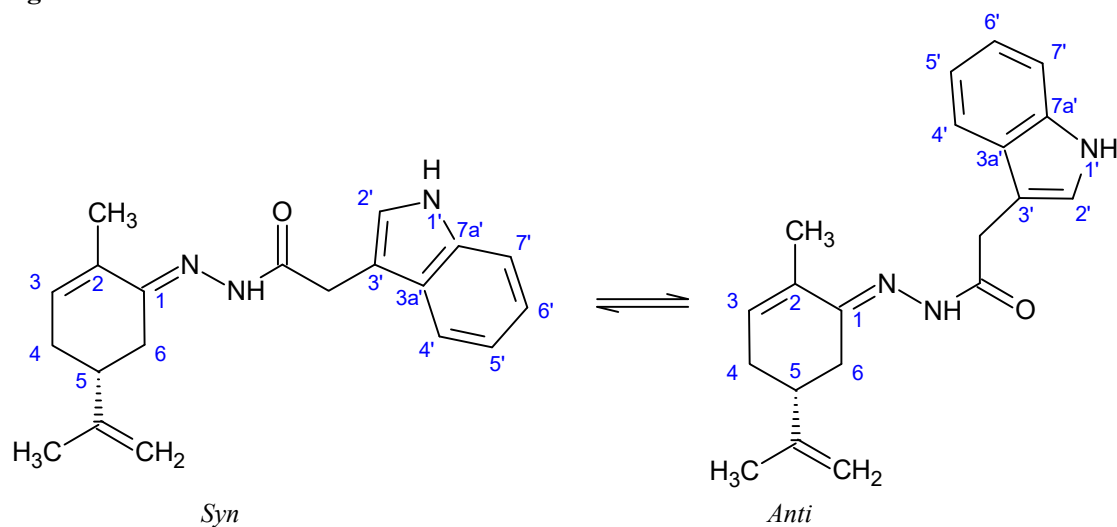


Figure S42. ¹H NMR spectrum of **3g** in DMSO-*d*₆.

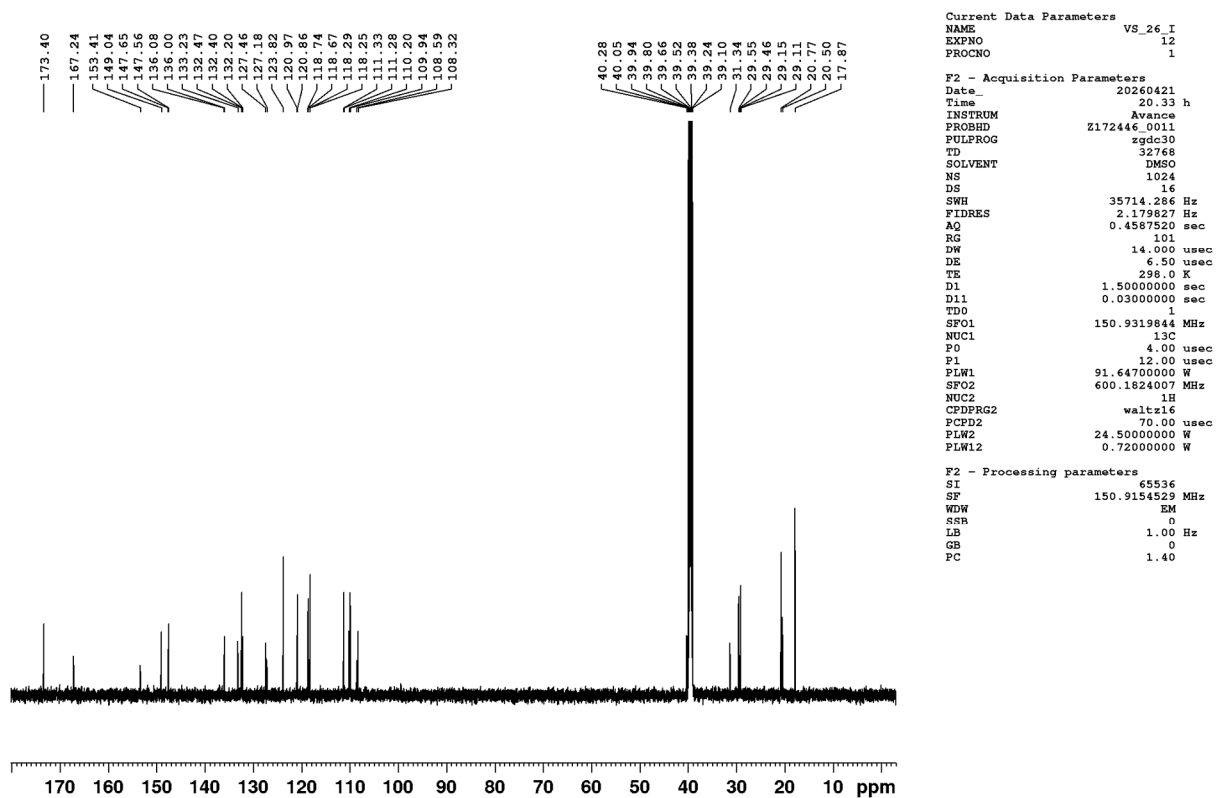


Figure S43. ^{13}C NMR spectrum of **3g** in $\text{DMSO}-d_6$.

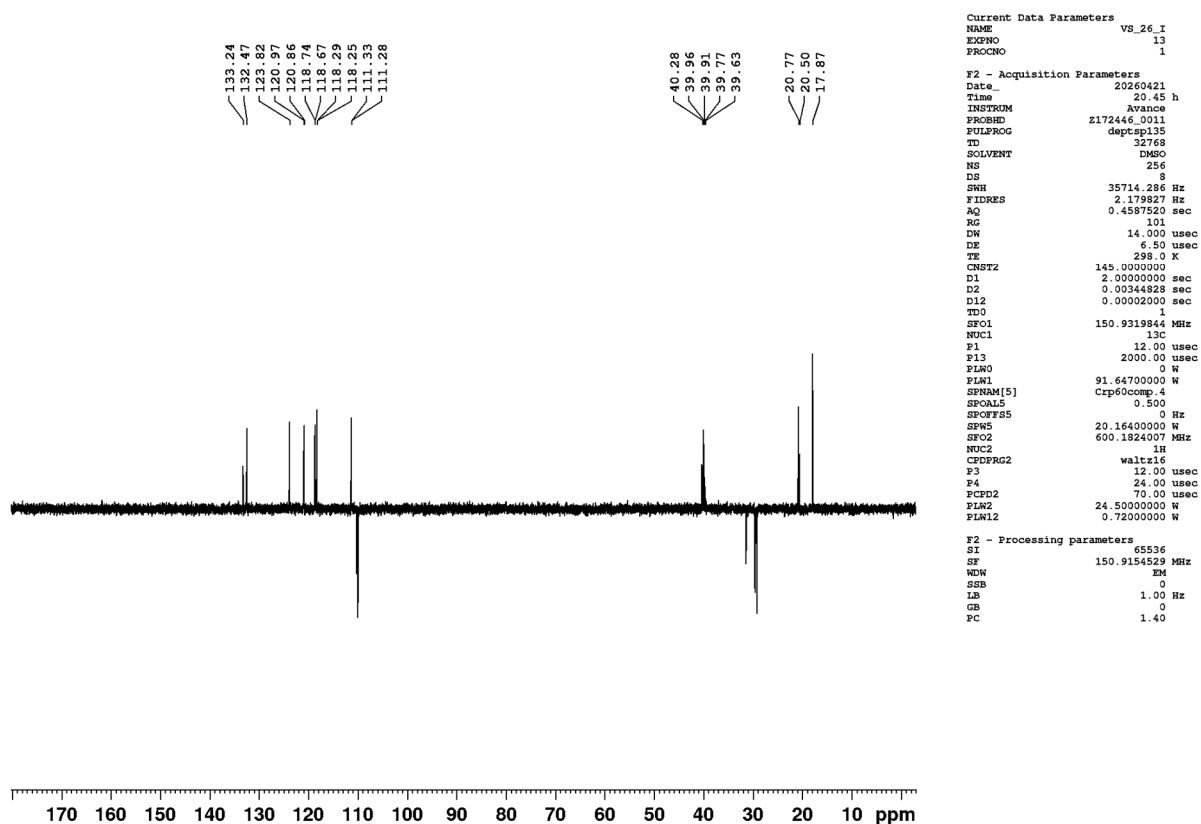


Figure S44. DEPT-135 NMR spectrum of **3g** in $\text{DMSO}-d_6$.

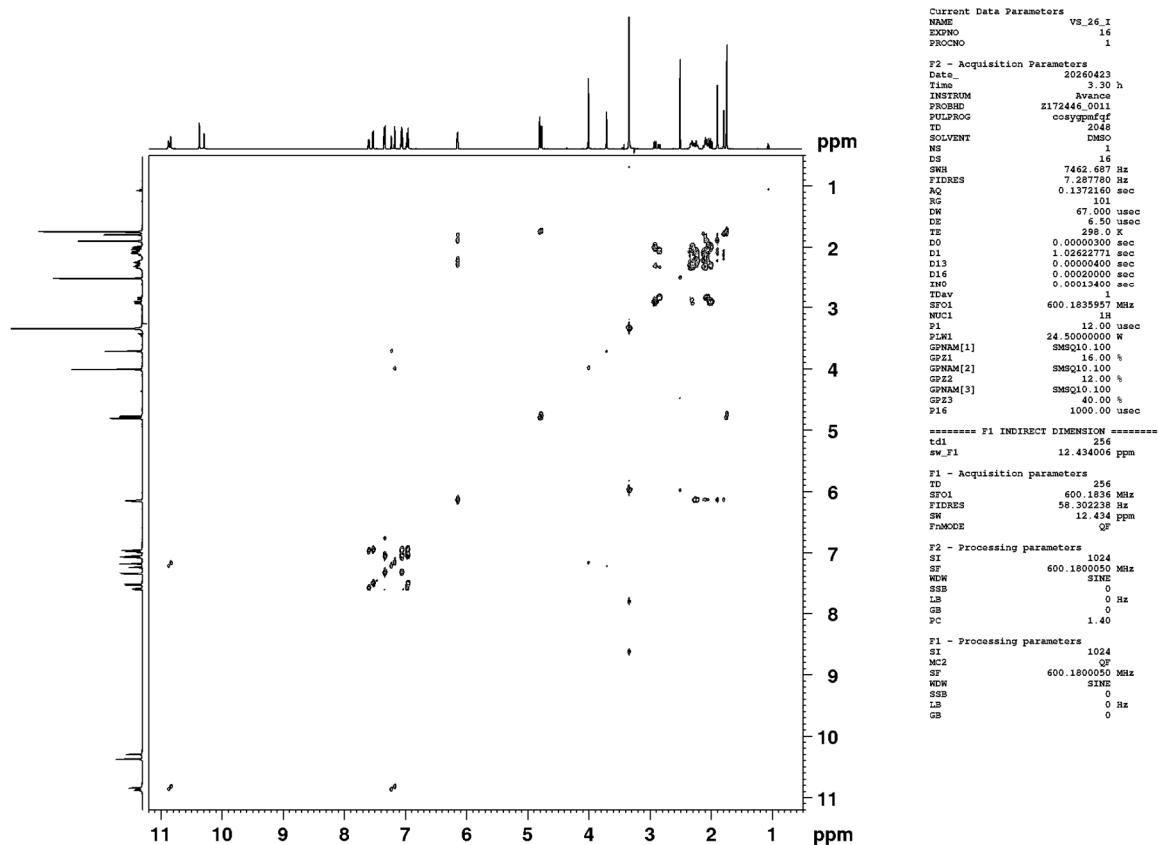


Figure S45. 2D COSY NMR spectrum of **3g** in DMSO-*d*₆.

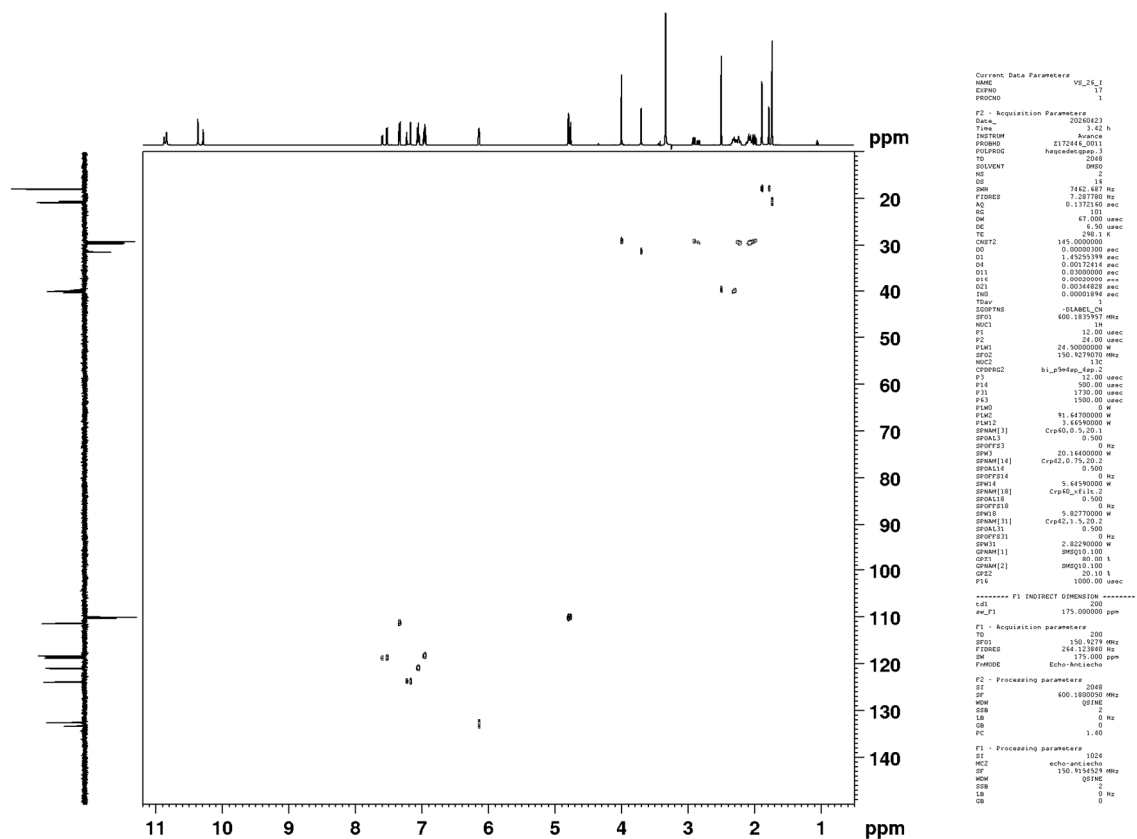


Figure S46. 2D HSQC NMR spectrum of **3g** in DMSO-*d*₆.

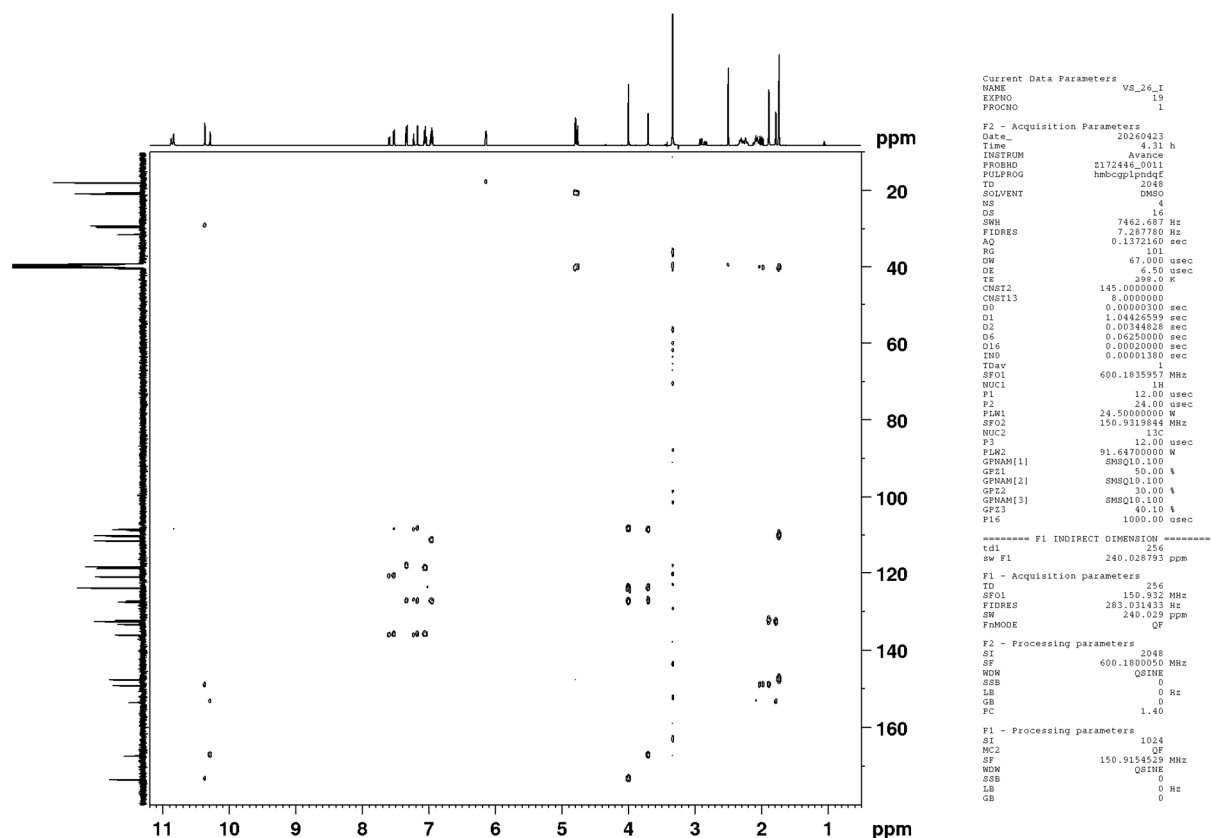


Figure S47. 2D HMBC NMR spectrum of **3g** in DMSO-*d*₆.

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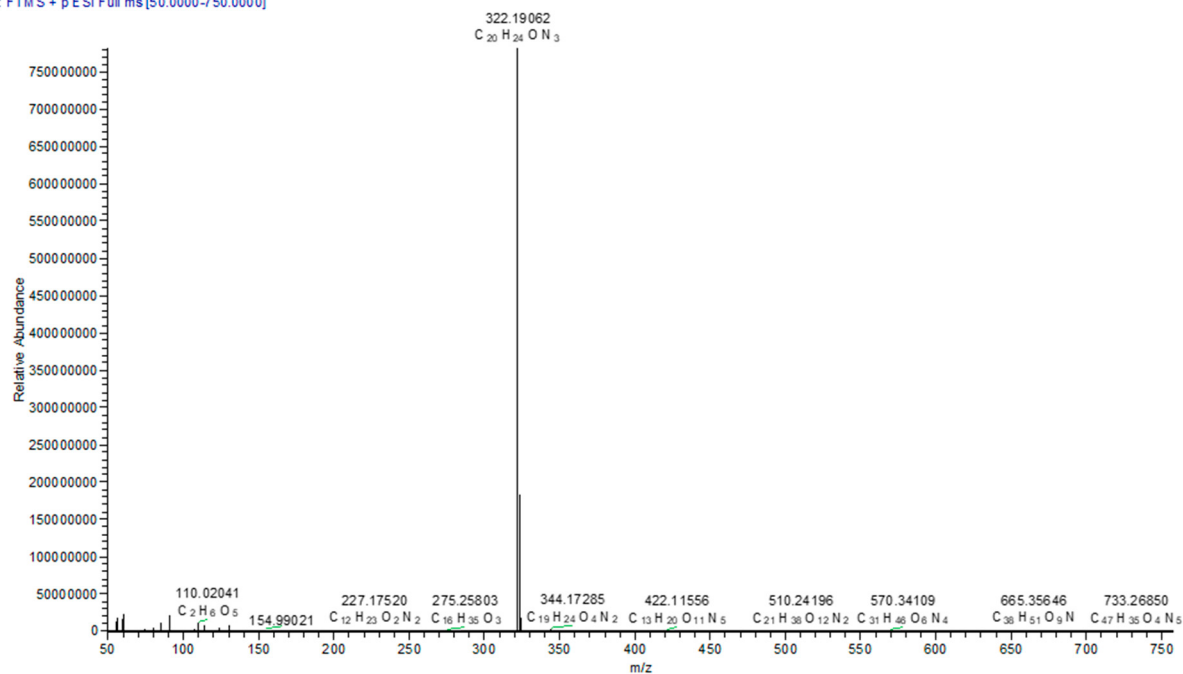


Figure S48. HRMS of **3g**.

8. (*R,E*)-*N'*-[2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene]-1*H*-indole-3-carbohydrazide, **3h**

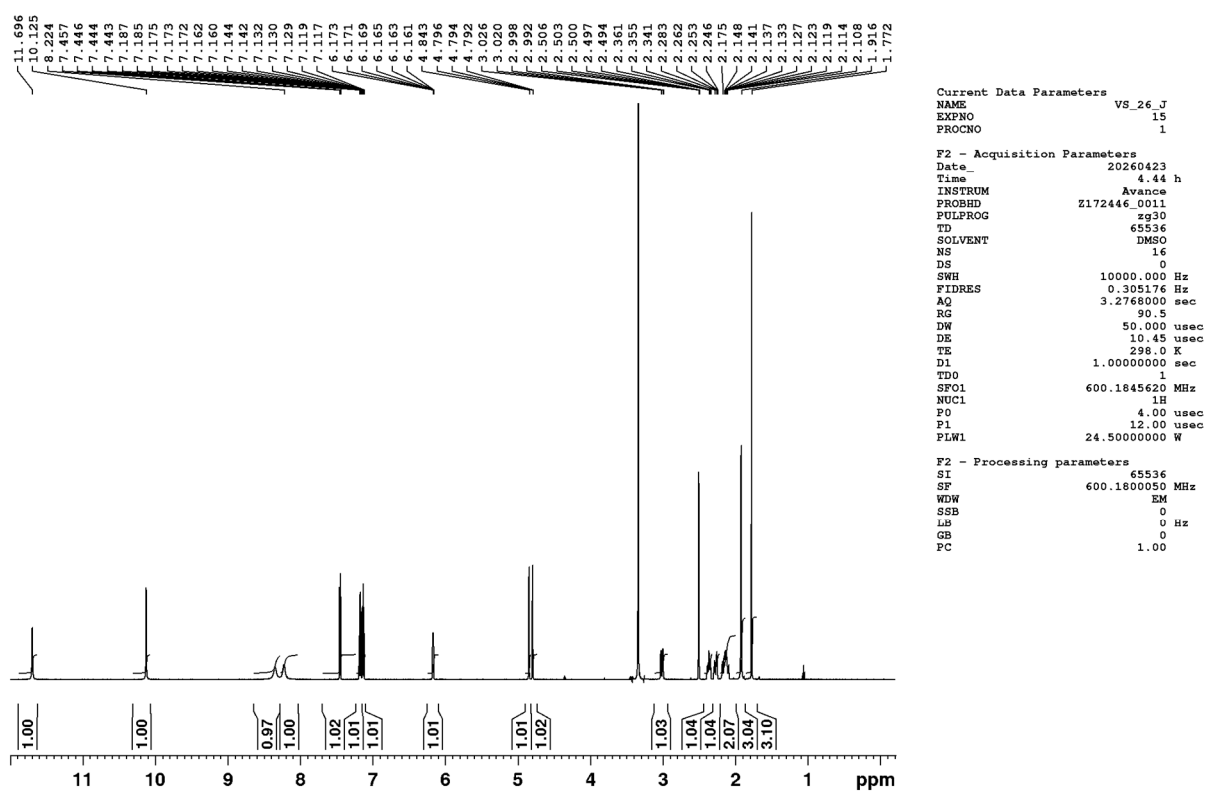
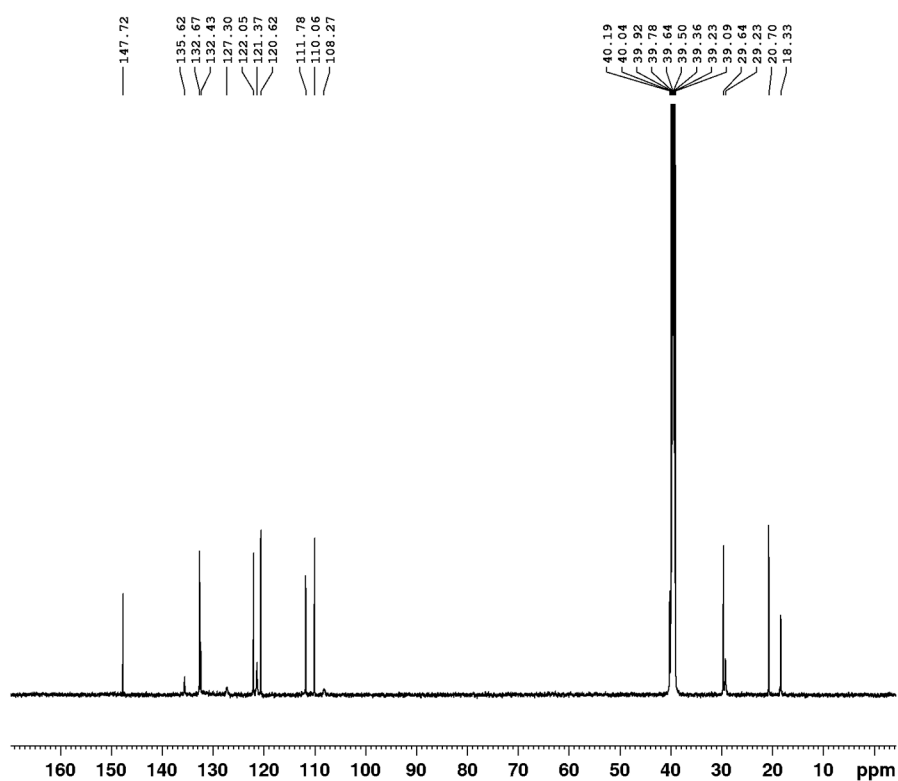


Figure S49. ¹H NMR spectrum of **3h** in DMSO-*d*₆.



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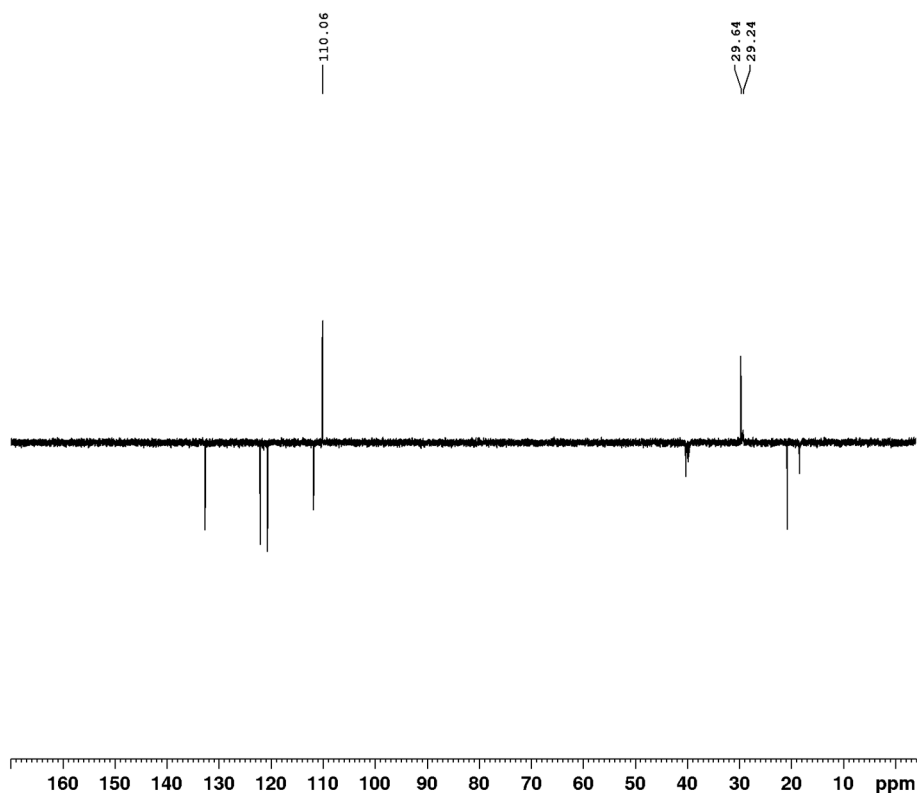
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PROCNO        1

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DS            16
SWH           35714.286 Hz
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AQ            0.4587520 sec
RG            101
DE            14.000 usec
TE            298.0 K
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NUC1          13C
P0            4.00 usec
P1            12.00 usec
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Figure 50S. ^{13}C NMR spectrum of **3h** in $\text{DMSO}-d_6$.



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NUC1          13C
P1            12.00 usec
P13           2000.00 usec
PLW1          91.64700000 W
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SFO2          600.1824007 MHz
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CPDPRG2       waltz16
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Figure S51. DEPT-135 NMR spectrum of **3h** in $\text{DMSO}-d_6$.

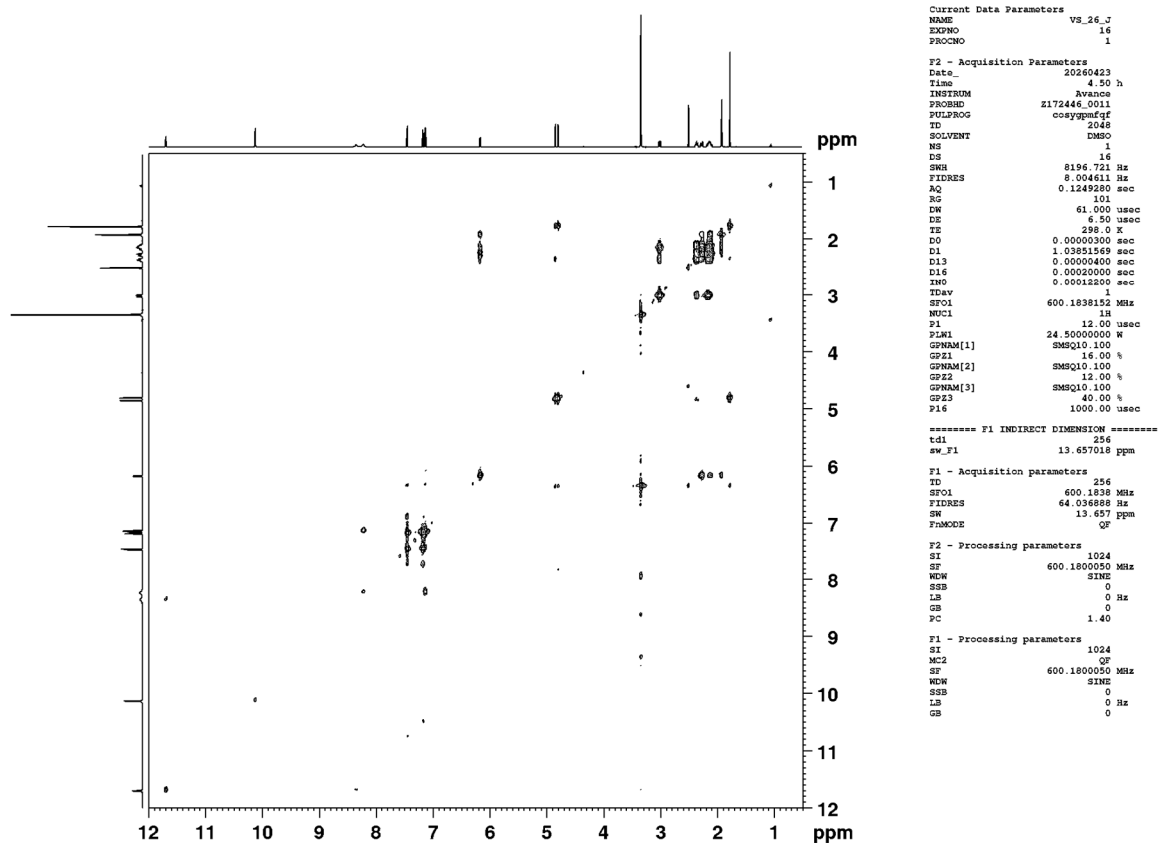


Figure S52. 2D COSY NMR spectrum of **3h** in DMSO- d_6 .

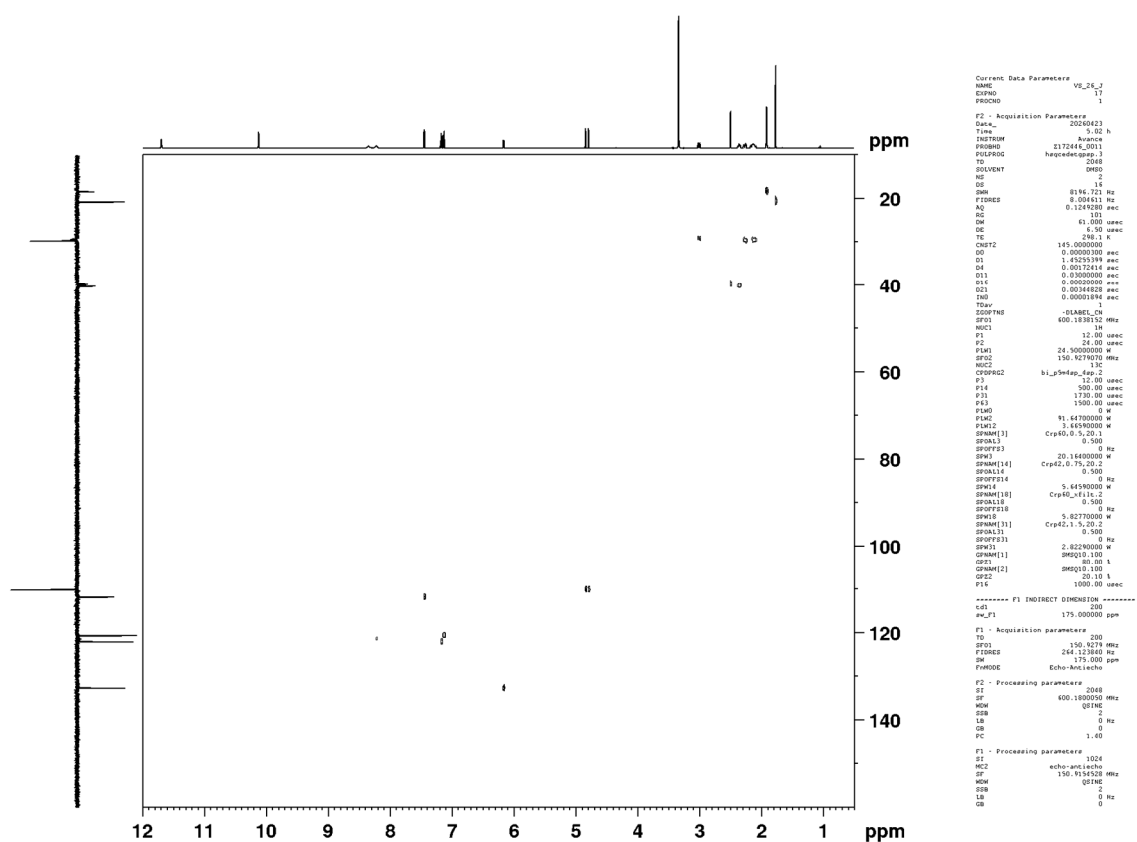


Figure S53. 2D HSQC NMR spectrum of **3h** in DMSO- d_6 .

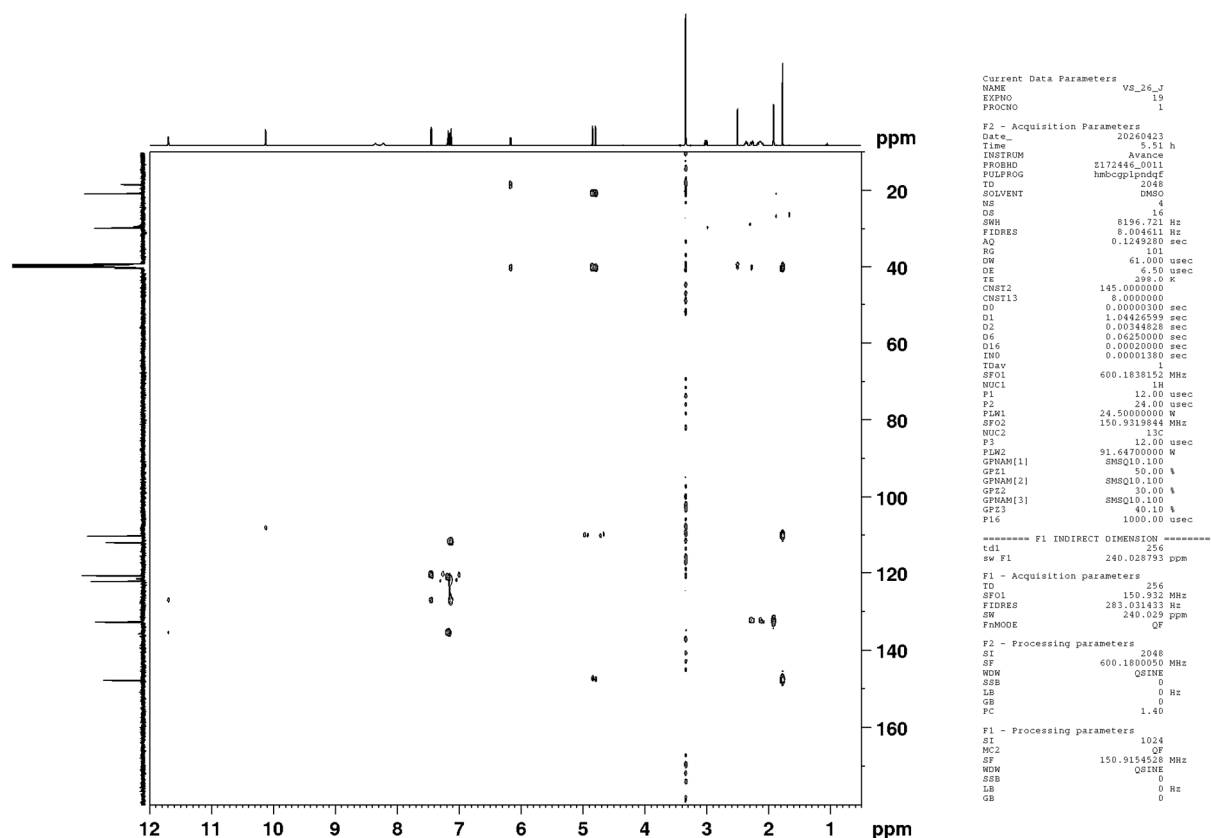


Figure S54. 2D HMBC NMR spectrum of **3h** in DMSO-*d*₆.

VS_260227_01 #1880-1928 RT: 4.01-4.09 AV: 8 NL: 9.03E8
T: FTM S + p ESI Full ms [50.0000-750.0000]

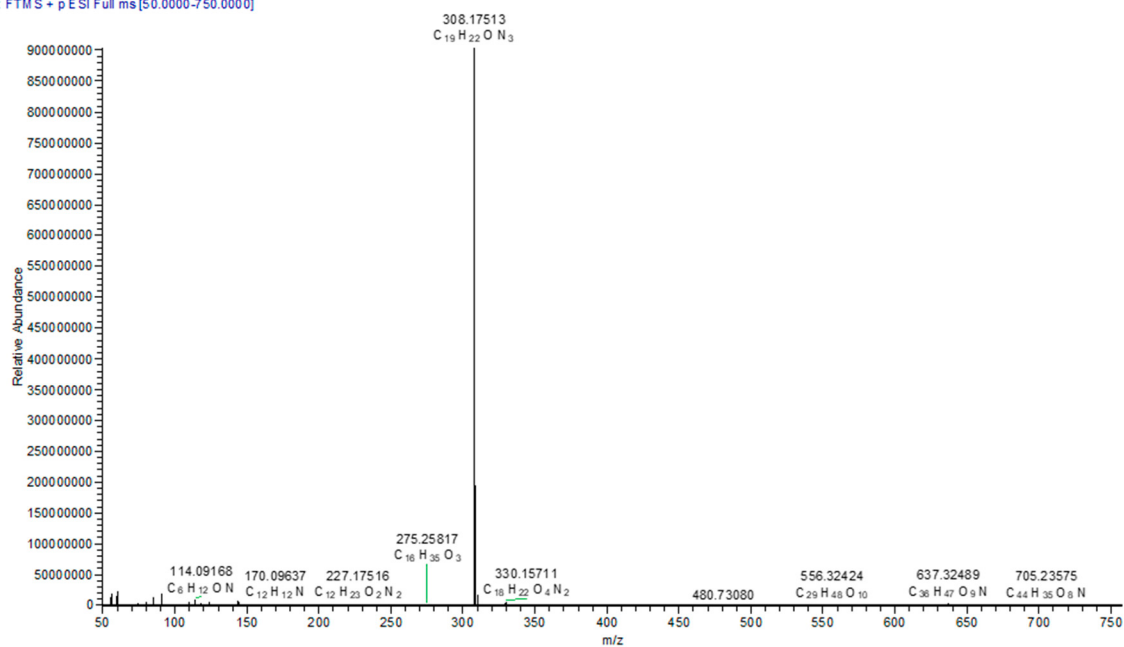


Figure S55. HRMS of **3h**.

9. (*R,E*)-*N'*-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)isonicotinohydrazide, **3i**

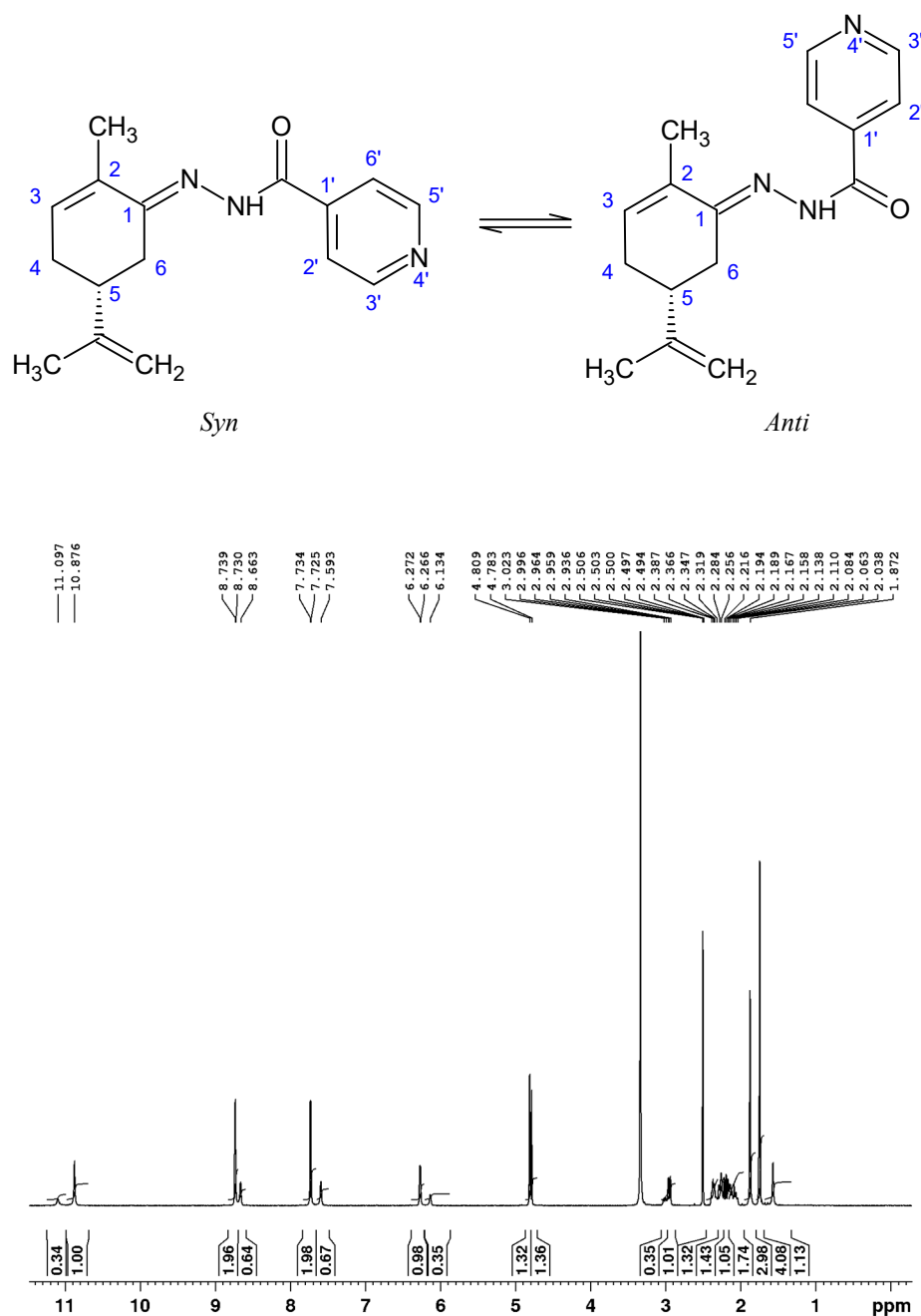


Figure S56. ^1H NMR spectrum of **3i** in $\text{DMSO}-d_6$.

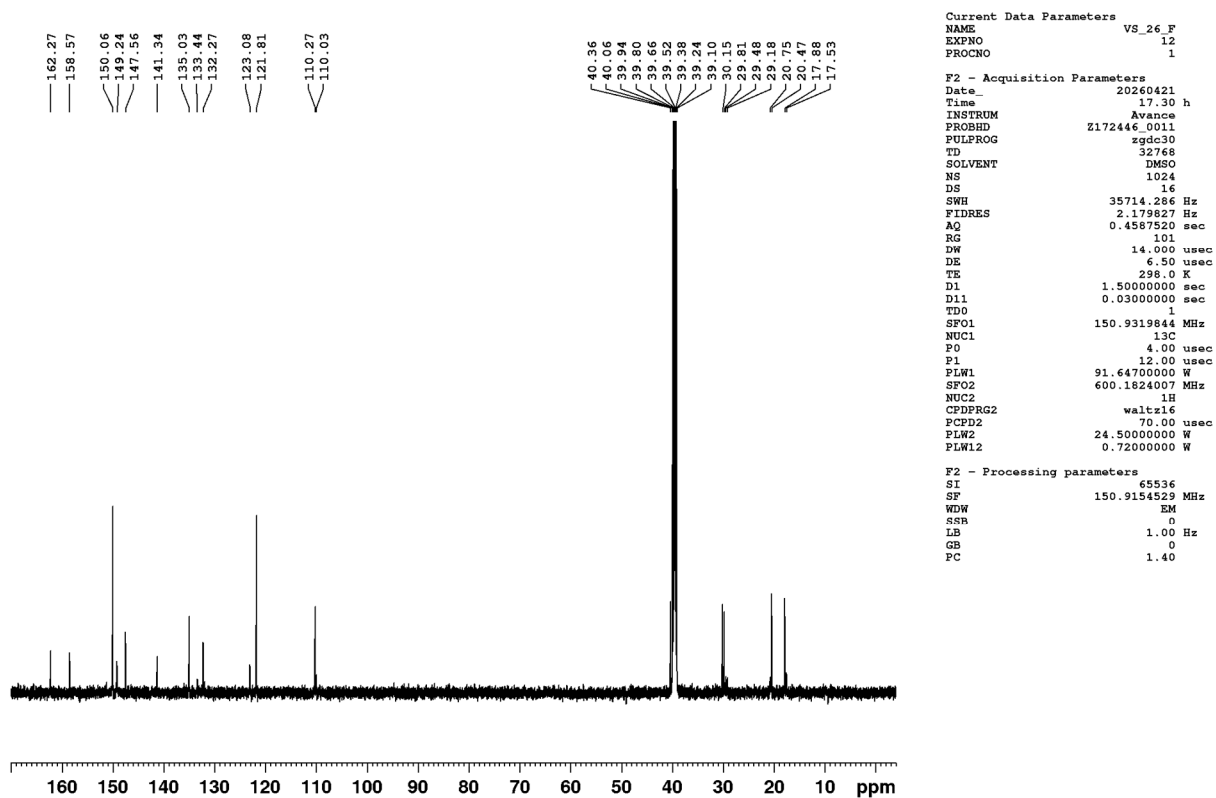


Figure S57. ^{13}C NMR spectrum of **3i** in $\text{DMSO}-d_6$.

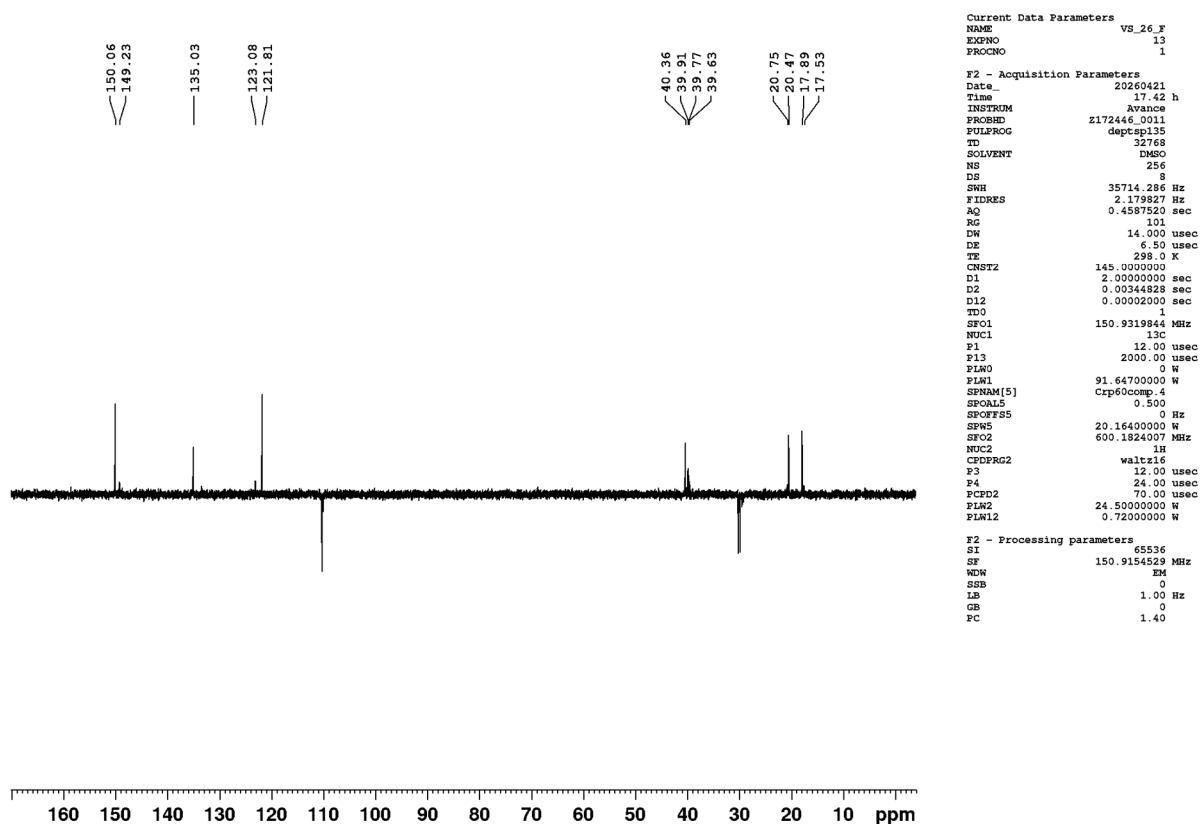


Figure S58. DEPT-135 NMR spectrum of **3i** in $\text{DMSO}-d_6$.

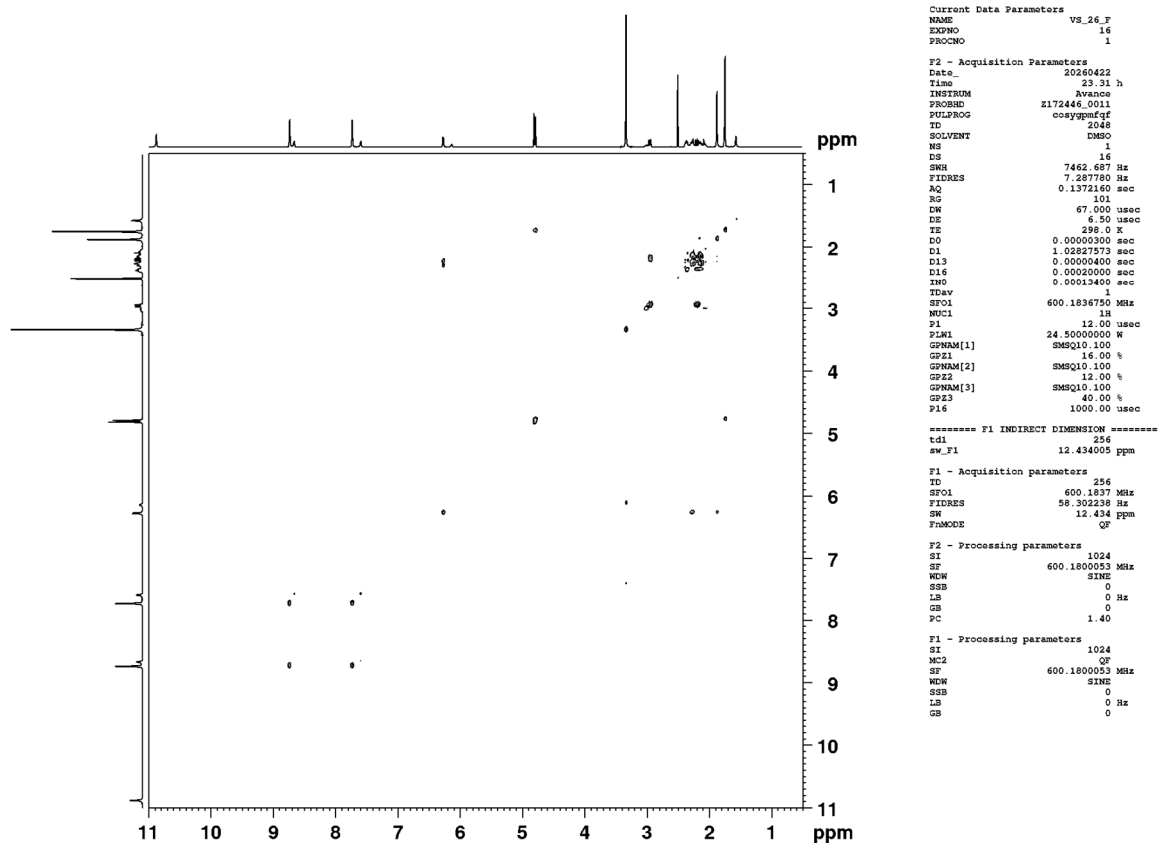


Figure S59. 2D COSY NMR spectrum of **3i** in DMSO- d_6 .

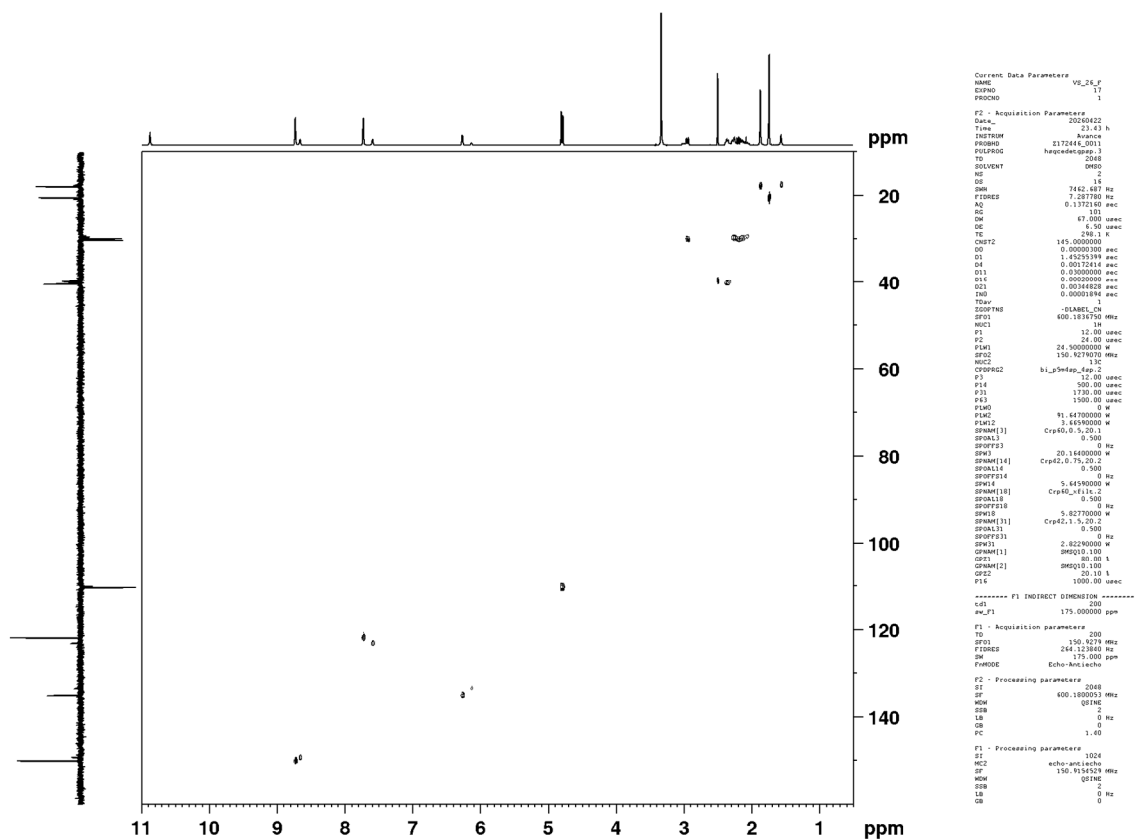


Figure 60S. 2D HSQC NMR spectrum of **3i** in DMSO- d_6 .

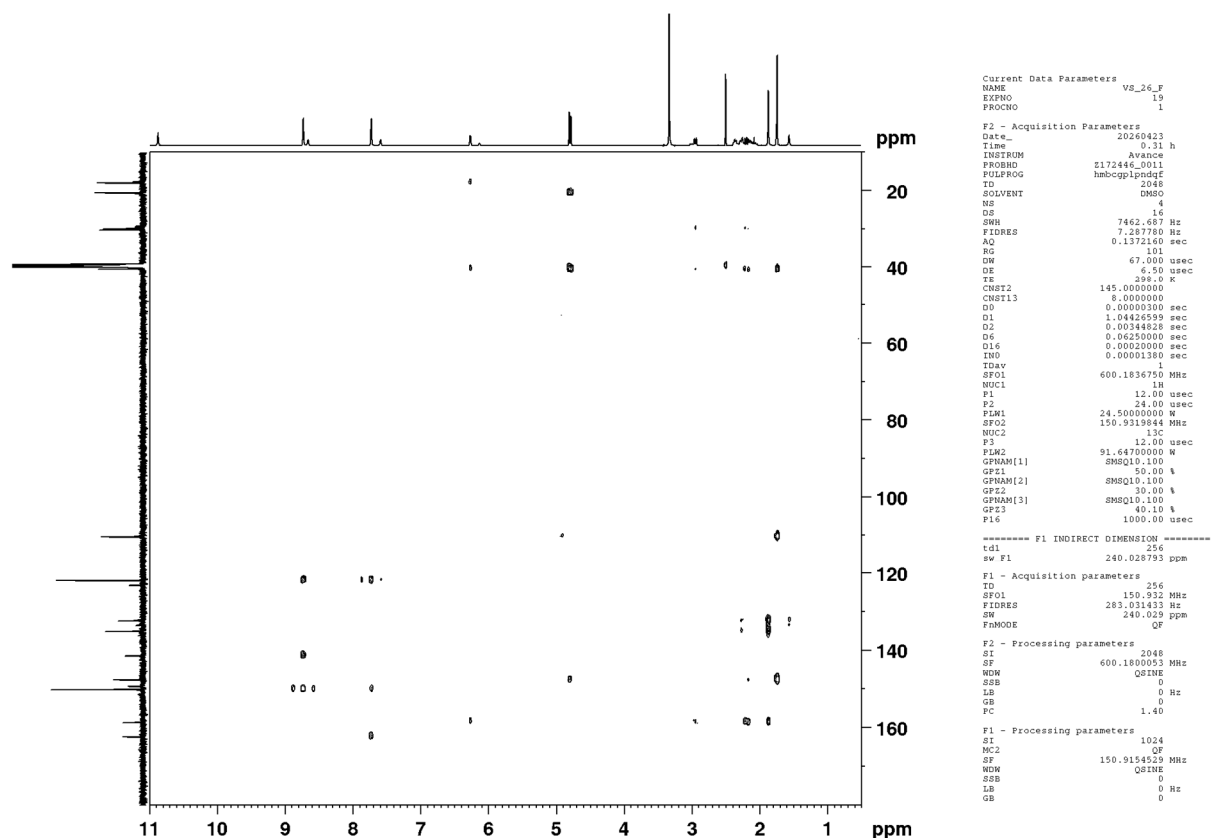


Figure S61. 2D HMBC NMR spectrum of **3i** in DMSO- d_6 .

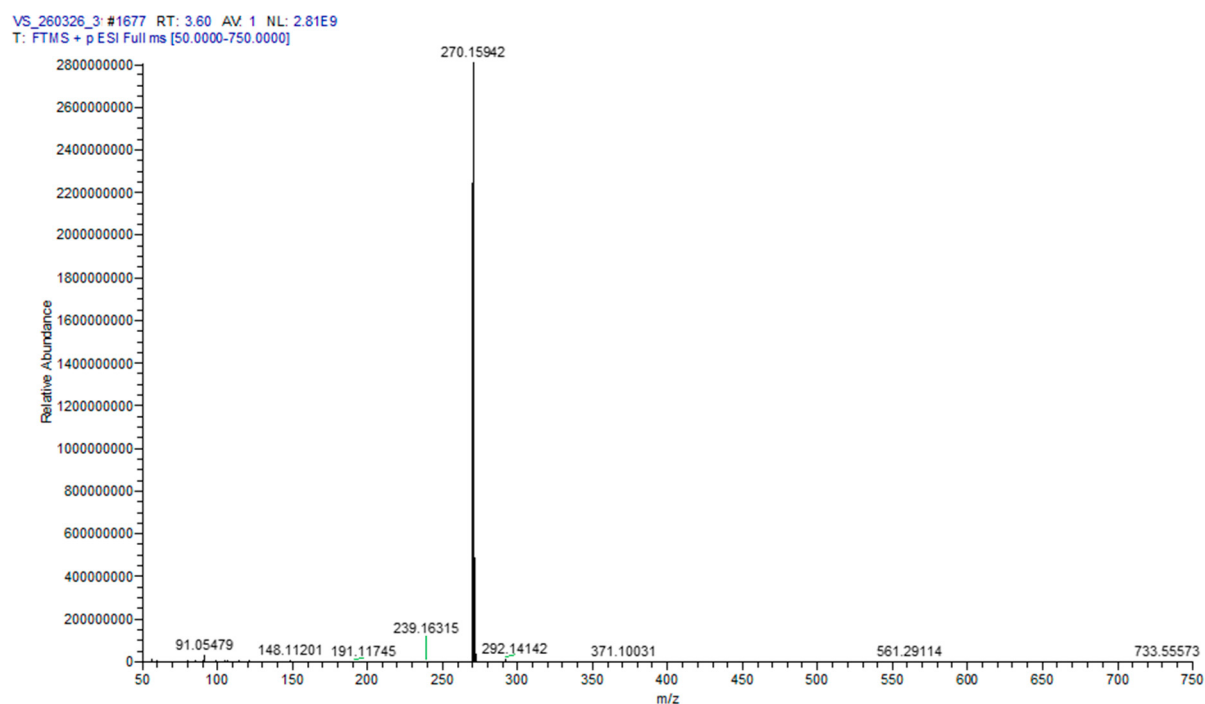


Figure S62. HRMS of **3i**.

Table S1. Hydrogen Bonds and weak interactions for **3i**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
C61	H61	O82 ¹	0.93	2.60	3.172(4)	120.4
C61	H61	N102 ¹	0.93	2.57	3.493(4)	174.4
C162	H16A	O81	0.97	2.61	3.082(4)	110.5
C162	H16A	N101	0.97	2.52	3.481(4)	168.4
C161	H16C	N102 ¹	0.97	2.55	3.476(4)	159.1
N91	H91	O82 ¹	0.95(3)	2.01(3)	2.941(3)	166(3)
N92	H92	O81	0.88(3)	2.04(3)	2.904(3)	167(3)

Symmetry operation: ¹ $I-x, I/2+y, I-z$ **Table S2.** Bond lengths for **3i**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O82	C72	1.228(3)	C162	C152	1.524(4)
O81	C71	1.228(3)	C122	C132	1.326(5)
N101	N91	1.395(3)	C122	C172	1.512(5)
N101	C111	1.287(4)	N41	C51	1.322(5)
N91	C71	1.346(4)	N41	C31	1.319(6)
N92	N102	1.388(3)	C62	C52	1.379(5)
N92	C72	1.344(4)	C152	C182	1.514(5)
N102	C112	1.291(4)	C152	C142	1.505(5)
C11	C71	1.492(4)	C131	C121	1.330(5)
C11	C61	1.375(4)	C131	C141	1.486(5)
C11	C21	1.376(5)	N42	C52	1.328(5)
C12	C22	1.381(4)	C121	C171	1.499(5)
C12	C72	1.490(4)	C182	C192	1.399(6)
C12	C62	1.377(4)	C182	C202	1.378(6)
C61	C51	1.385(5)	C181	C151	1.503(5)
C112	C162	1.494(4)	C181	C201	1.337(6)
C112	C122	1.470(4)	C181	C191	1.488(6)
C22	C32	1.379(5)	C151	C141	1.519(5)
C111	C121	1.470(4)	C151	C161	1.523(5)
C111	C161	1.504(4)	C132	C142	1.488(5)
C32	N42	1.319(5)	C21	C31	1.363(5)

Table S3. Bond angles for **3i**.

Atom Atom Atom	Angle/°	Atom Atom Atom	Angle/°
C111 N101 N91	117.9(2)	C132 C122 C172	122.4(3)
C71 N91 N101	117.1(2)	C31 N41 C51	115.9(4)
C72 N92 N102	118.3(2)	C12 C62 C52	119.2(3)
C112 N102 N92	117.2(2)	C182 C152 C162	110.4(3)
C61 C11 C71	125.4(3)	C142 C152 C162	109.6(3)
C61 C11 C21	117.1(3)	C142 C152 C182	114.8(3)
C21 C11 C71	117.6(3)	C121 C131 C141	125.6(3)
C22 C12 C72	123.9(3)	C32 N42 C52	115.1(3)
C62 C12 C22	117.3(3)	C111 C121 C171	118.6(3)
C62 C12 C72	118.7(3)	C131 C121 C111	119.4(3)
O81 C71 N91	123.6(3)	C131 C121 C171	121.9(3)
O81 C71 C11	118.9(3)	C192 C182 C152	120.4(4)
N91 C71 C11	117.4(2)	C202 C182 C152	118.8(4)
C11 C61 C51	118.8(3)	C202 C182 C192	120.8(4)
N102 C112 C162	125.1(3)	C201 C181 C151	120.1(4)
N102 C112 C122	116.9(3)	C201 C181 C191	121.6(4)
C122 C112 C162	117.8(3)	C191 C181 C151	118.3(4)
C32 C22 C12	118.4(3)	N41 C51 C61	124.2(3)
O82 C72 N92	124.3(3)	C181 C151 C141	114.0(3)
O82 C72 C12	119.9(3)	C181 C151 C161	112.4(3)
N92 C72 C12	115.8(2)	C141 C151 C161	109.9(3)
N101 C111 C121	116.0(3)	C122 C132 C142	125.3(3)
N101 C111 C161	127.0(3)	C131 C141 C151	111.7(3)
C121 C111 C161	117.0(3)	C31 C21 C11	119.7(4)
N42 C32 C22	125.4(3)	C111 C161 C151	110.9(3)
C112 C162 C152	114.4(3)	N42 C52 C62	124.5(4)
C112 C122 C172	118.3(3)	C132 C142 C152	110.7(3)
C132 C122 C112	119.1(3)	N41 C31 C21	124.4(4)

Table S4. Torsion angles for **3i**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N101	N91	C71	O81	7.2(4)	C32	N42	C52	C62	-1.2(7)
N101	N91	C71	C11	-172.1(2)	C162	C112	C122	C132	-6.1(5)
N101	C111	C121	C131	-172.9(3)	C162	C112	C122	C172	178.0(3)
N101	C111	C121	C171	9.4(5)	C162	C152	C182	C192	-73.9(5)
N101	C111	C161	C151	142.0(3)	C162	C152	C182	C202	104.4(4)
N91	N101	C111	C121	-175.6(3)	C162	C152	C142	C132	-51.1(4)
N91	N101	C111	C161	3.6(5)	C122	C112	C162	C152	-22.5(4)
N92	N102	C112	C162	2.2(5)	C122	C132	C142	C152	25.5(6)
N92	N102	C112	C122	-172.6(3)	C62	C12	C22	C32	-0.5(5)
N102	N92	C72	O82	3.9(5)	C62	C12	C72	O82	-37.4(4)
N102	N92	C72	C12	-174.4(2)	C62	C12	C72	N92	141.0(3)
N102	C112	C162	C152	162.8(3)	C121	C111	C161	C151	-38.8(4)
N102	C112	C122	C132	169.0(3)	C121	C131	C141	C151	16.6(6)
N102	C112	C122	C172	-6.9(5)	C182	C152	C142	C132	-176.0(3)
C11	C61	C51	N41	-0.3(6)	C181	C151	C141	C131	-173.8(4)
C11	C21	C31	N41	-3.4(8)	C181	C151	C161	C111	-173.9(3)
C12	C22	C32	N42	-0.6(6)	C51	N41	C31	C21	3.1(8)
C12	C62	C52	N42	0.2(7)	C141	C131	C121	C111	3.8(6)
C71	C11	C61	C51	-178.9(3)	C141	C131	C121	C171	-178.6(4)
C71	C11	C21	C31	-179.3(4)	C141	C151	C161	C111	58.0(3)
C61	C11	C71	O81	155.8(3)	C21	C11	C71	O81	-23.3(4)
C61	C11	C71	N91	-24.9(4)	C21	C11	C71	N91	156.0(3)
C61	C11	C21	C31	1.6(6)	C21	C11	C61	C51	0.1(5)
C112	C162	C152	C182	178.5(3)	C161	C111	C121	C131	7.8(5)
C112	C162	C152	C142	51.1(4)	C161	C111	C121	C171	-169.9(3)
C112	C122	C132	C142	4.6(6)	C161	C151	C141	C131	-46.6(4)
C22	C12	C72	O82	141.1(3)	C142	C152	C182	C192	50.5(5)
C22	C12	C72	N92	-40.5(4)	C142	C152	C182	C202	-131.1(4)
C22	C12	C62	C52	0.6(5)	C172	C122	C132	C142	-179.7(4)
C22	C32	N42	C52	1.4(6)	C31	N41	C51	C61	-1.2(7)
C72	N92	N102	C112	172.1(3)	C201	C181	C151	C141	-118.6(4)
C72	C12	C22	C32	-179.0(3)	C201	C181	C151	C161	115.5(4)
C72	C12	C62	C52	179.2(3)	C191	C181	C151	C141	62.7(5)
C111	N101	N91	C71	-171.9(3)	C191	C181	C151	C161	-63.2(5)