1,3-Dipolar cycloaddition of isatin-derived azomethine ylides with 2*H*-azirines: stereoselective synthesis of 1,3-diazaspiro[bicyclo[3.1.0]hexane]oxindoles

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Supporting Information

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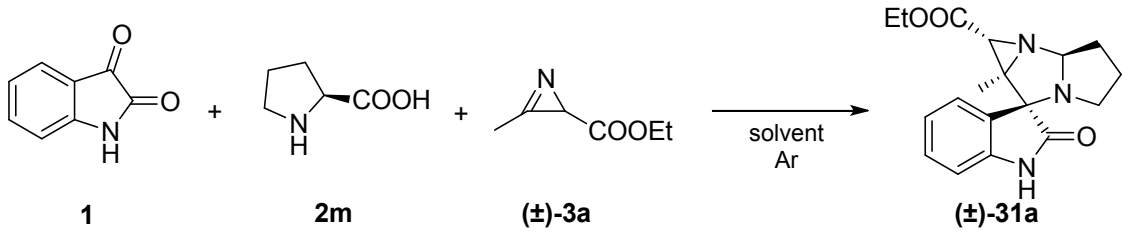
1. Reaction optimization

Table S1. Screening of reaction conditions



1 **2m** **(±)-3a** **(±)-31a**

Entry[a]	Solvent	Solvent (mL)	Temp. (°C)	Time (h)	(±)-3a (equiv.)	Yield (%)[b]
1	MeOH	1	rt	24	1	10
2	EtOH	1	rt	24	1	25
3	**IPA**	**1**	**rt**	**24**	**1**	**44**
4	TFE	1	rt	24	1	6
5	MeCN	1	rt	24	1	10
6	$MeNO_2$	1	rt	24	1	5
7	DMF	1	rt	24	1	28
8	EtOAc	1	rt	24	1	2
9	THF	1	rt	24	1	6
10	Toluene	1	rt	24	1	-
11	$CHCl_3$	1	rt	24	1	16
12	DCM	1	rt	24	1	7
13	IPA	1	rt	24	2	51
14	IPA	1	rt	24	3	60
15	IPA	0.25	rt	24	3	55
16	IPA	0.5	rt	24	3	63
17	IPA	1.5	rt	24	3	62
18	**IPA**	**2**	**rt**	**24**	**3**	**68**
19	IPA	2.5	rt	24	3	63
20	IPA	3	rt	24	3	61
21	IPA	2	0 °C	48	3	58
22	IPA	2	60 °C	4	3	52
23	IPA	2	80 °C	2.5	3	56

[a]Reaction conditions: isatin (0.125 mmol), L-proline (0.15 mmol), 2*H*-azirine, anhydrous solvent, argon atmosphere. [b]Determined by HPLC analysis.

2. ^{1}H and ^{13}C NMR spectra for all products

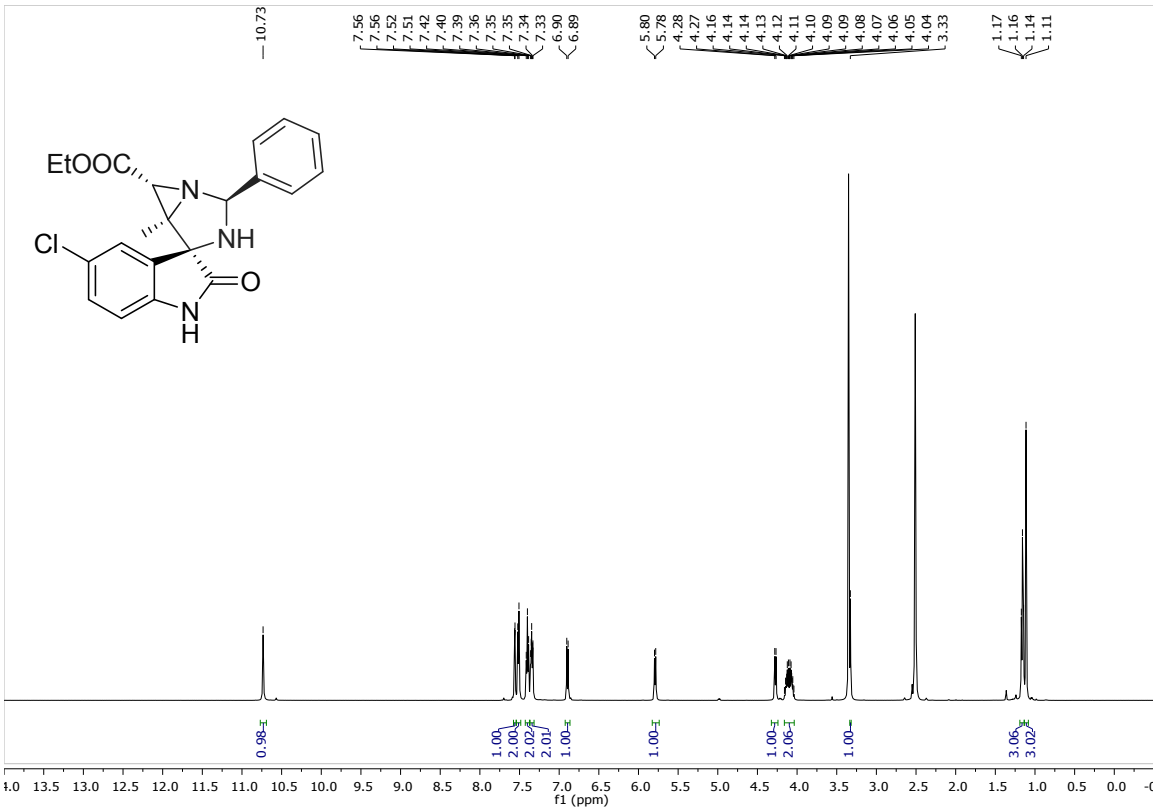


Figure S1. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-5a**

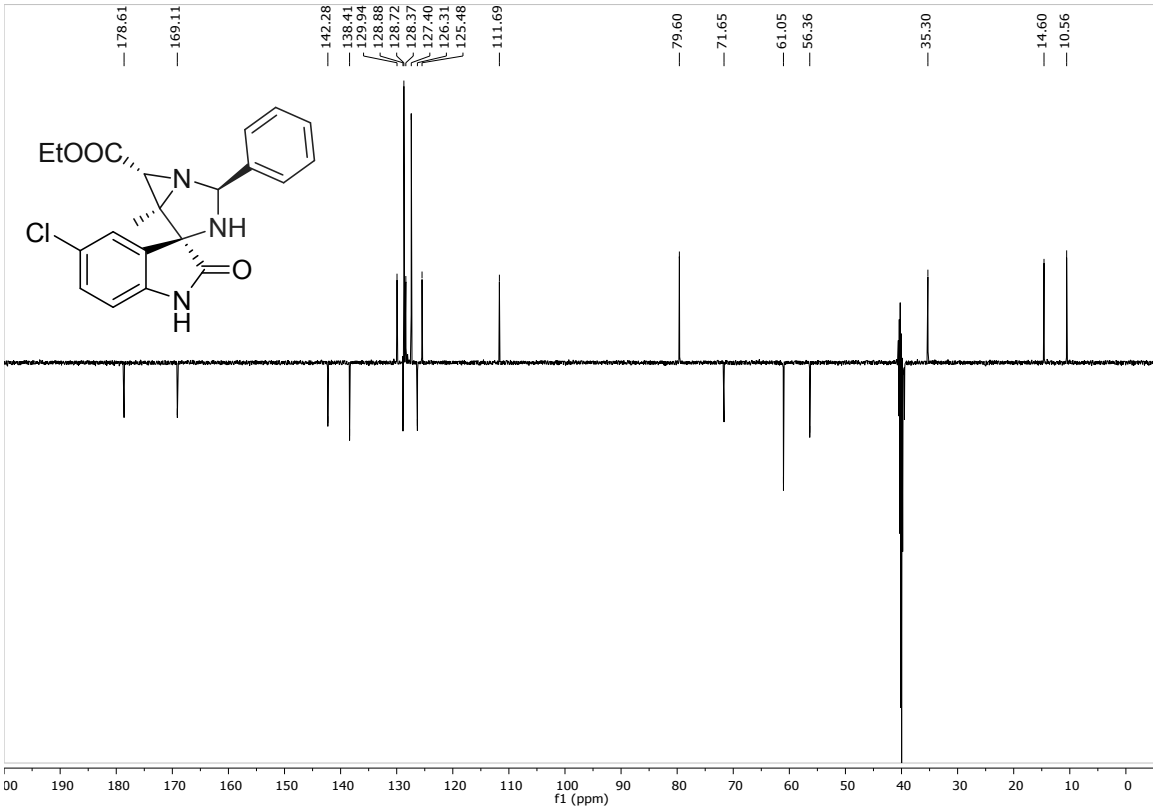


Figure S2. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-5a**

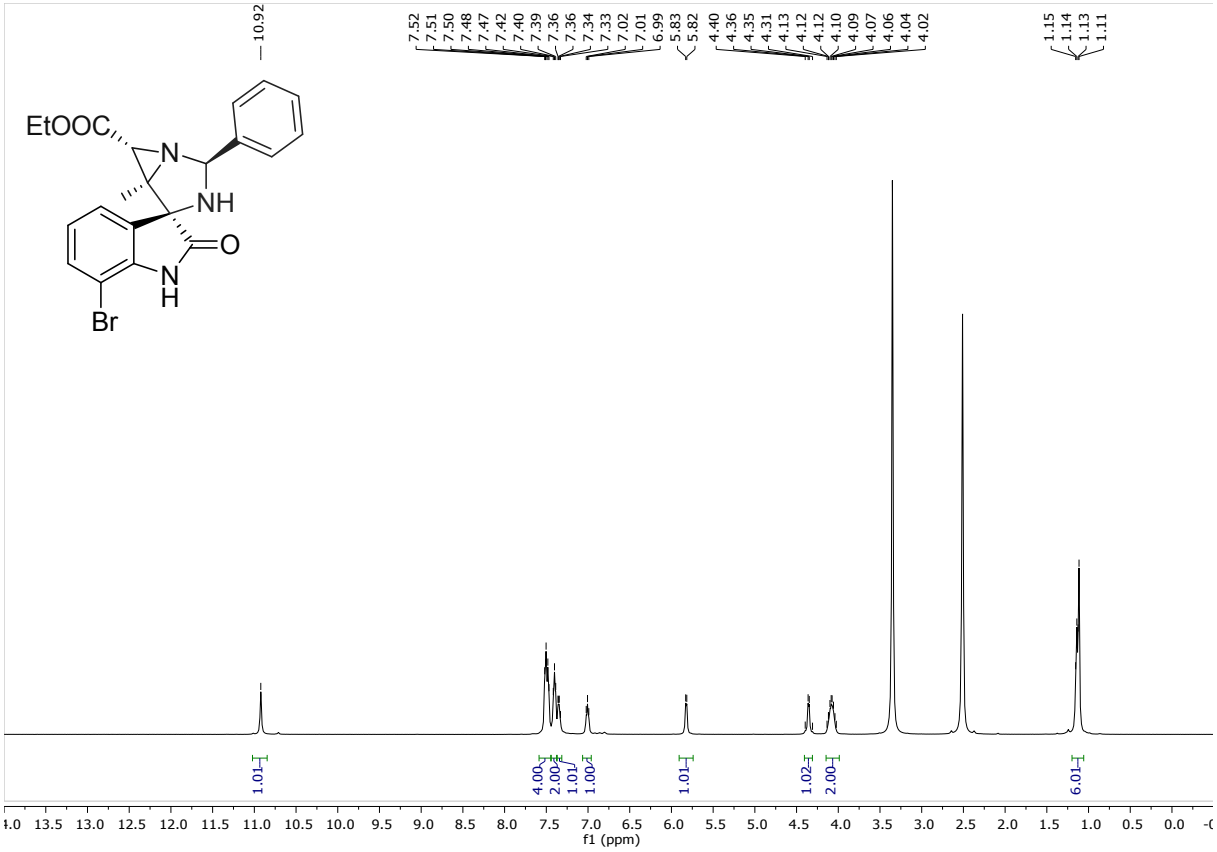


Figure S3. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-6a**

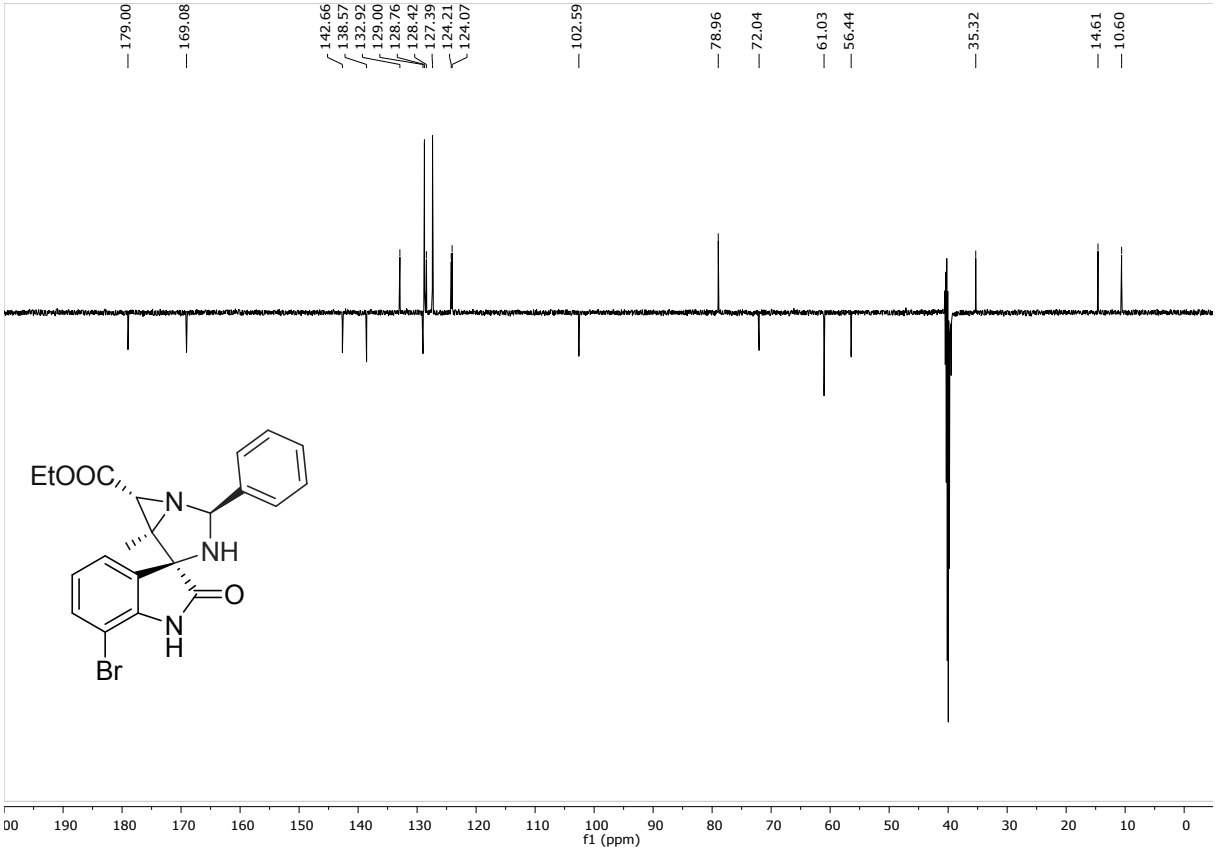


Figure S4. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-6a**

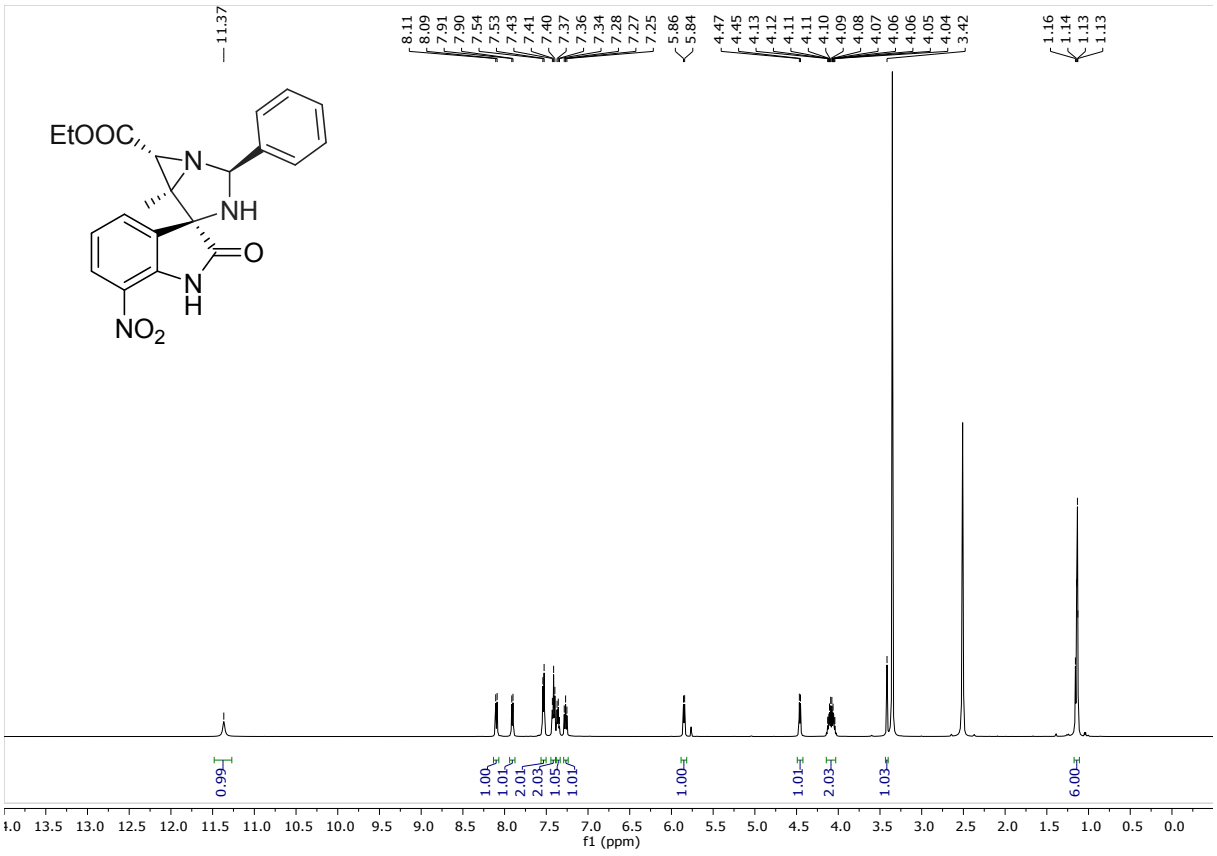


Figure S5. [1]H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-7a**

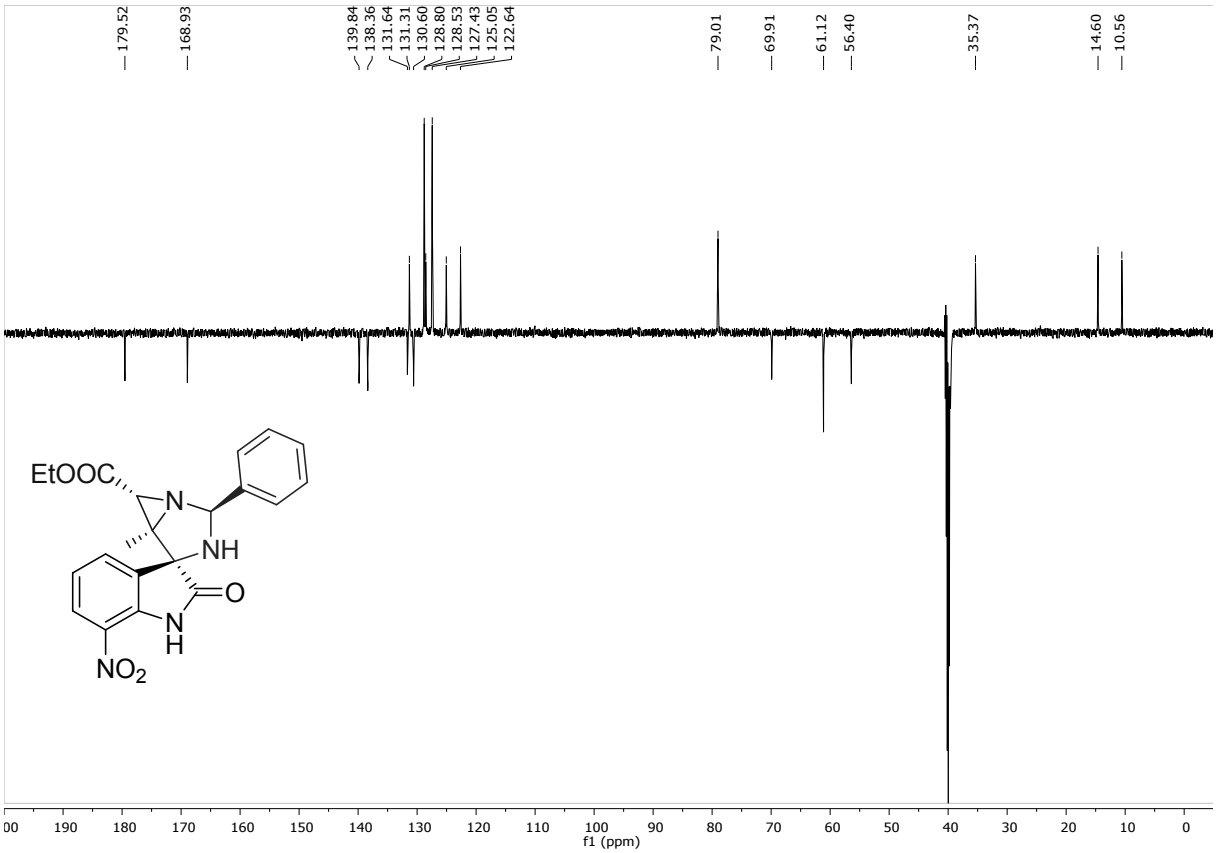


Figure S6. [13]C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-7a**

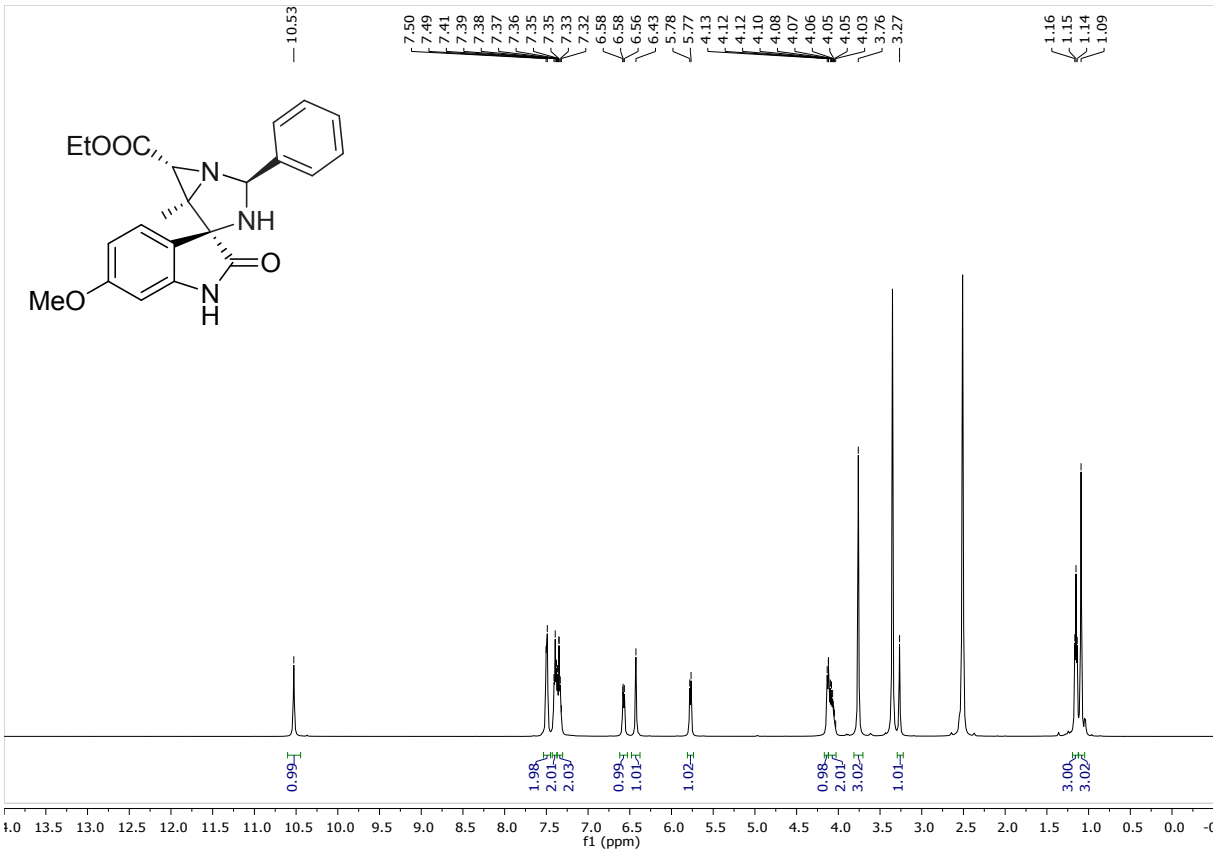


Figure S7. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-8a**

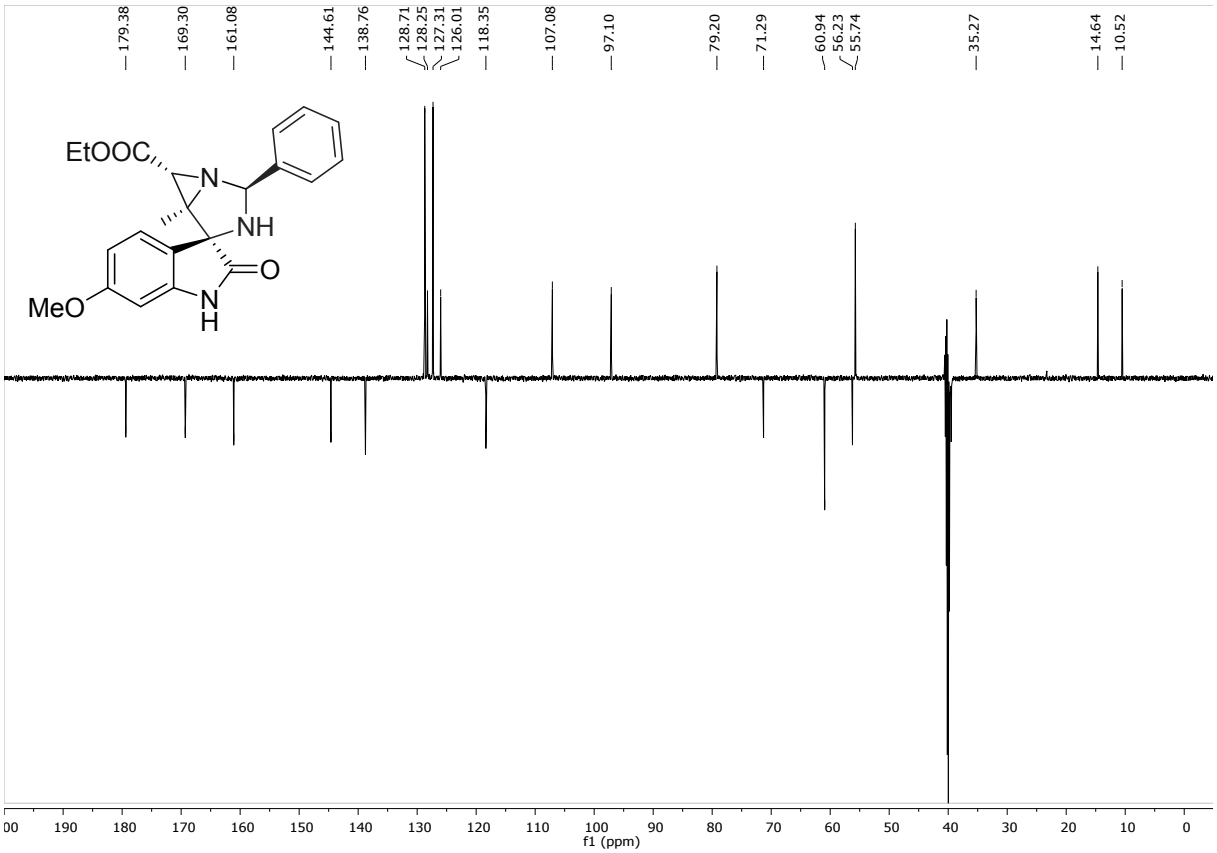


Figure S8. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-8a**

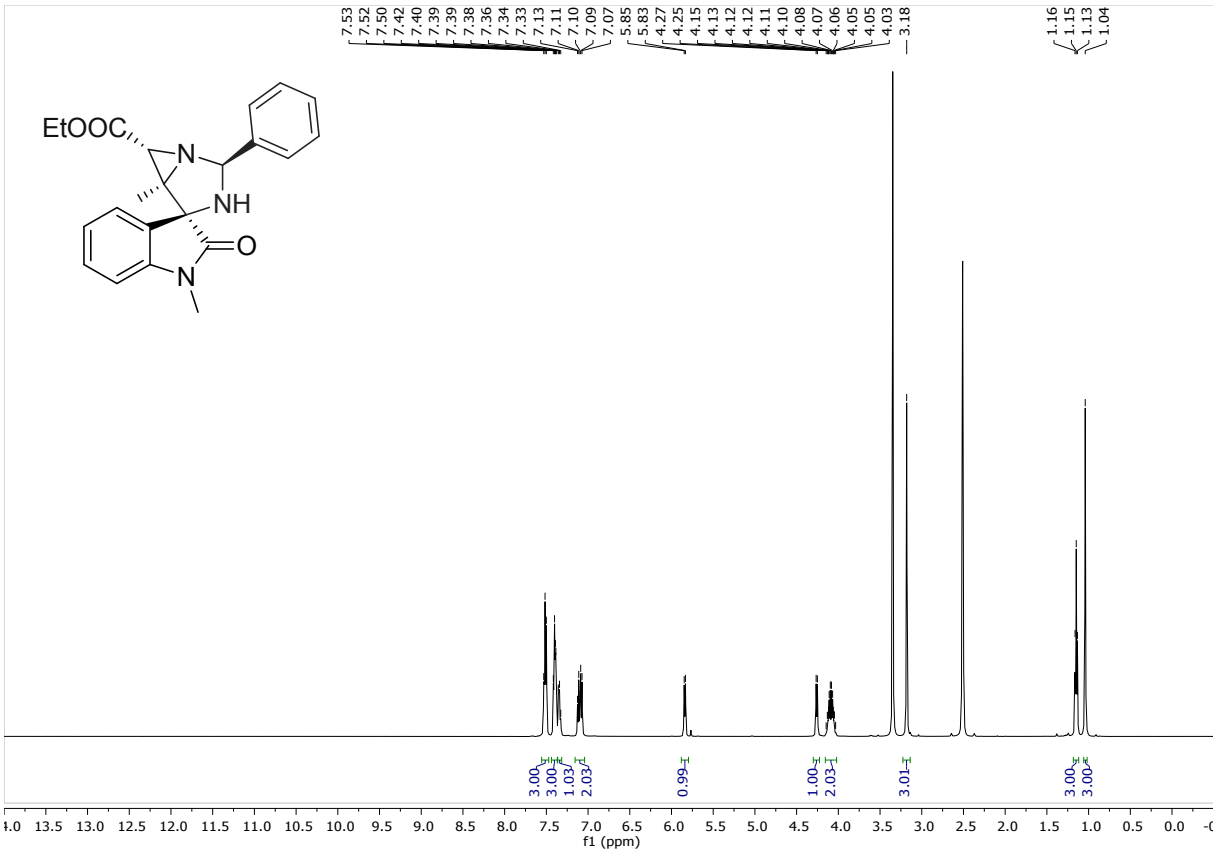


Figure S9. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-9a**

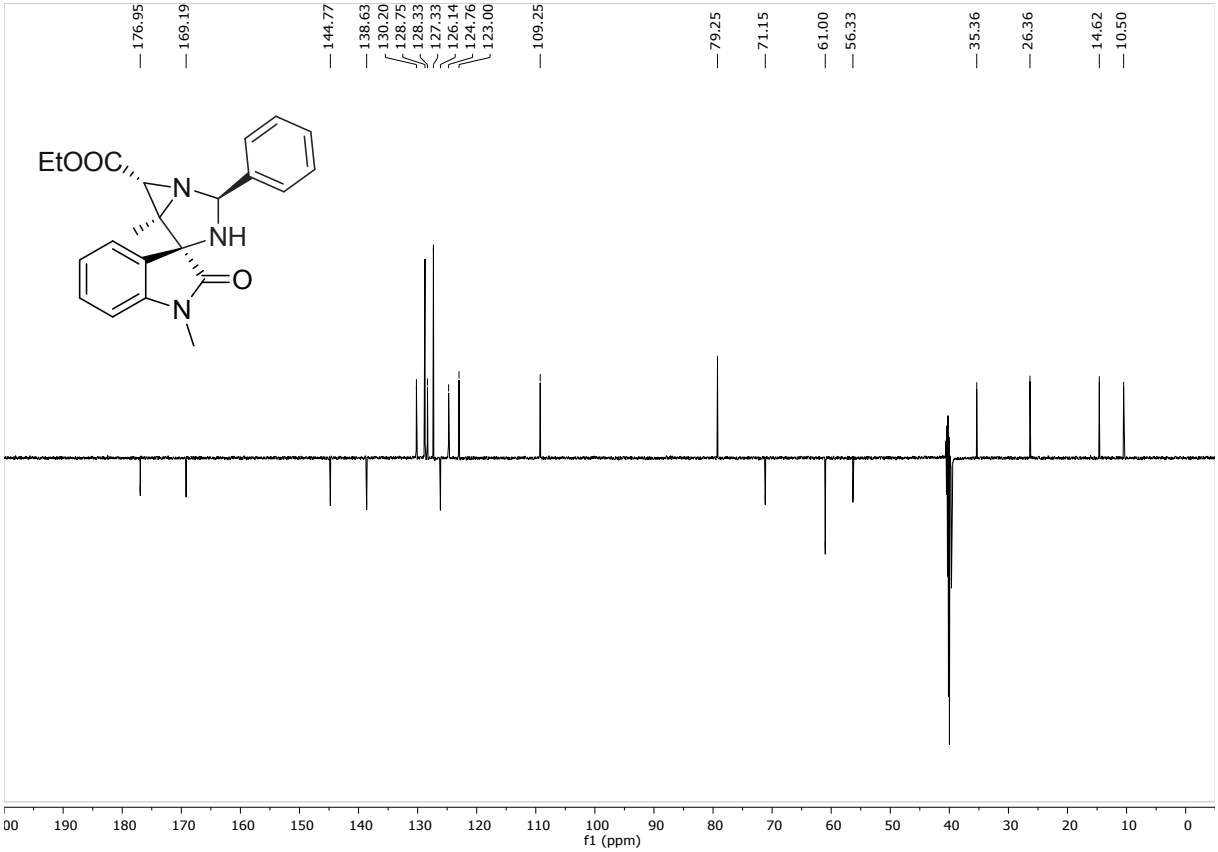


Figure S10. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-9a**

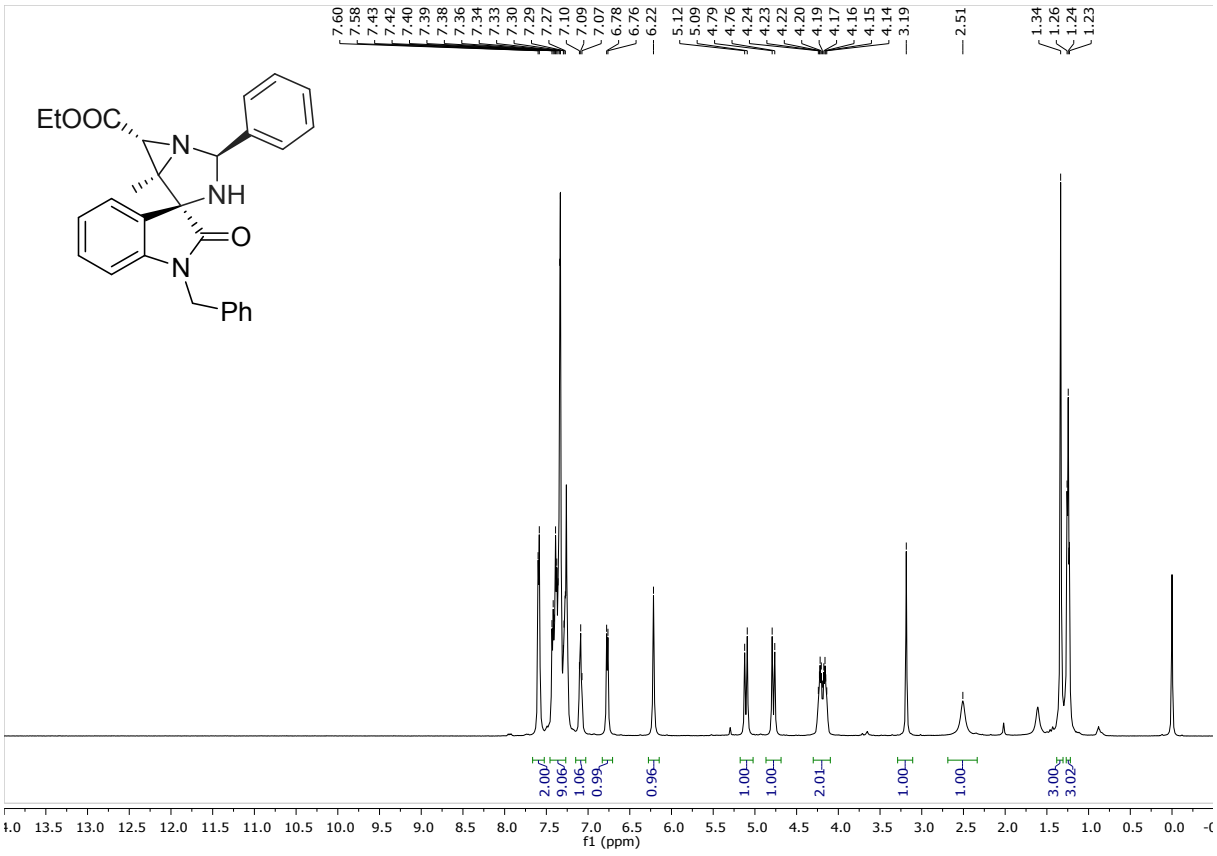


Figure S11. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-10a**

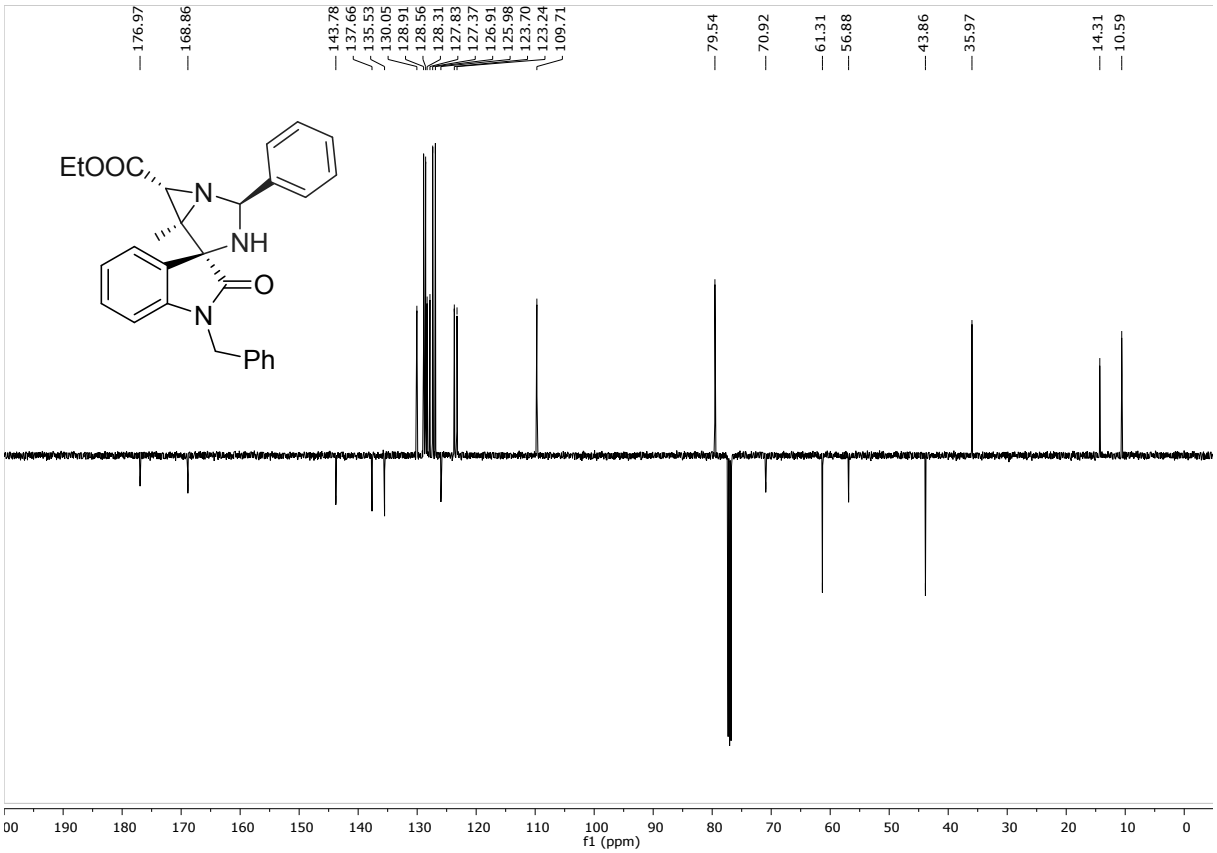


Figure S12. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-10a**

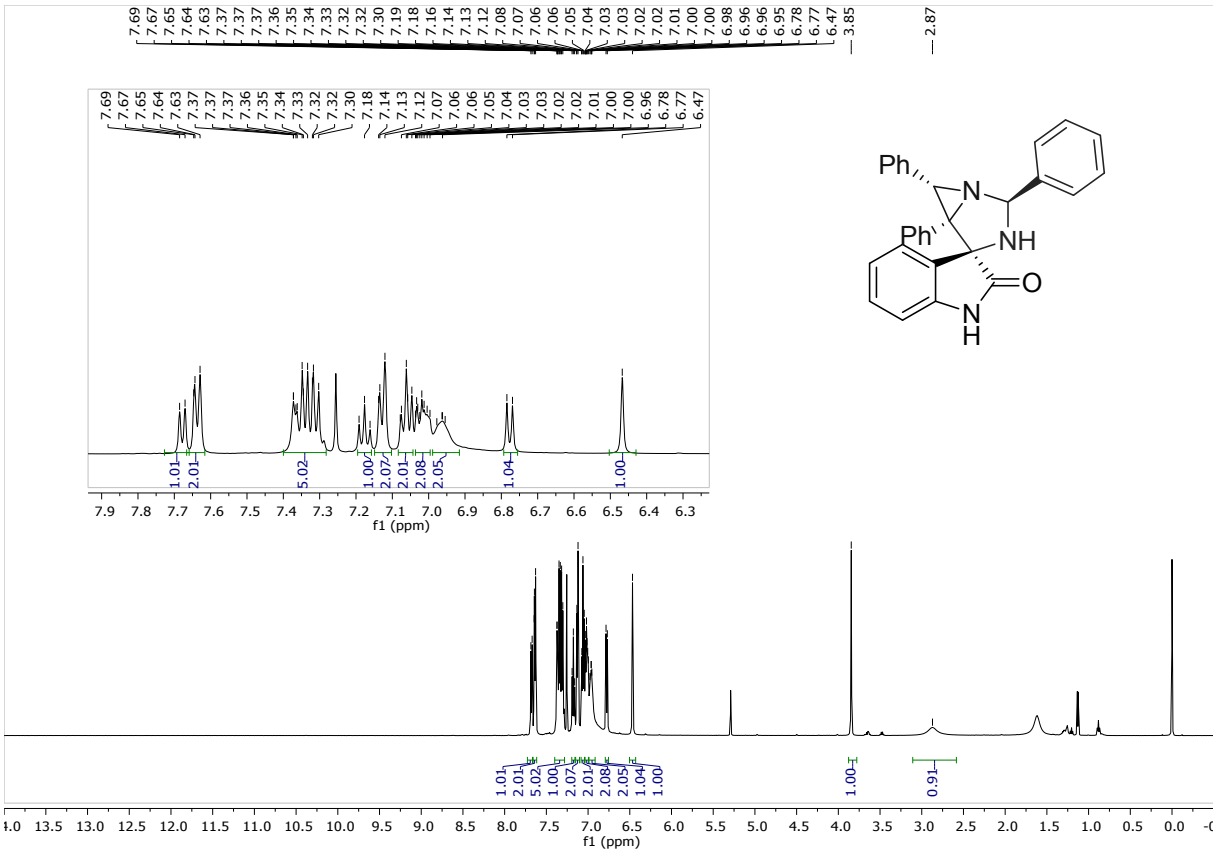


Figure S13. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-11a**

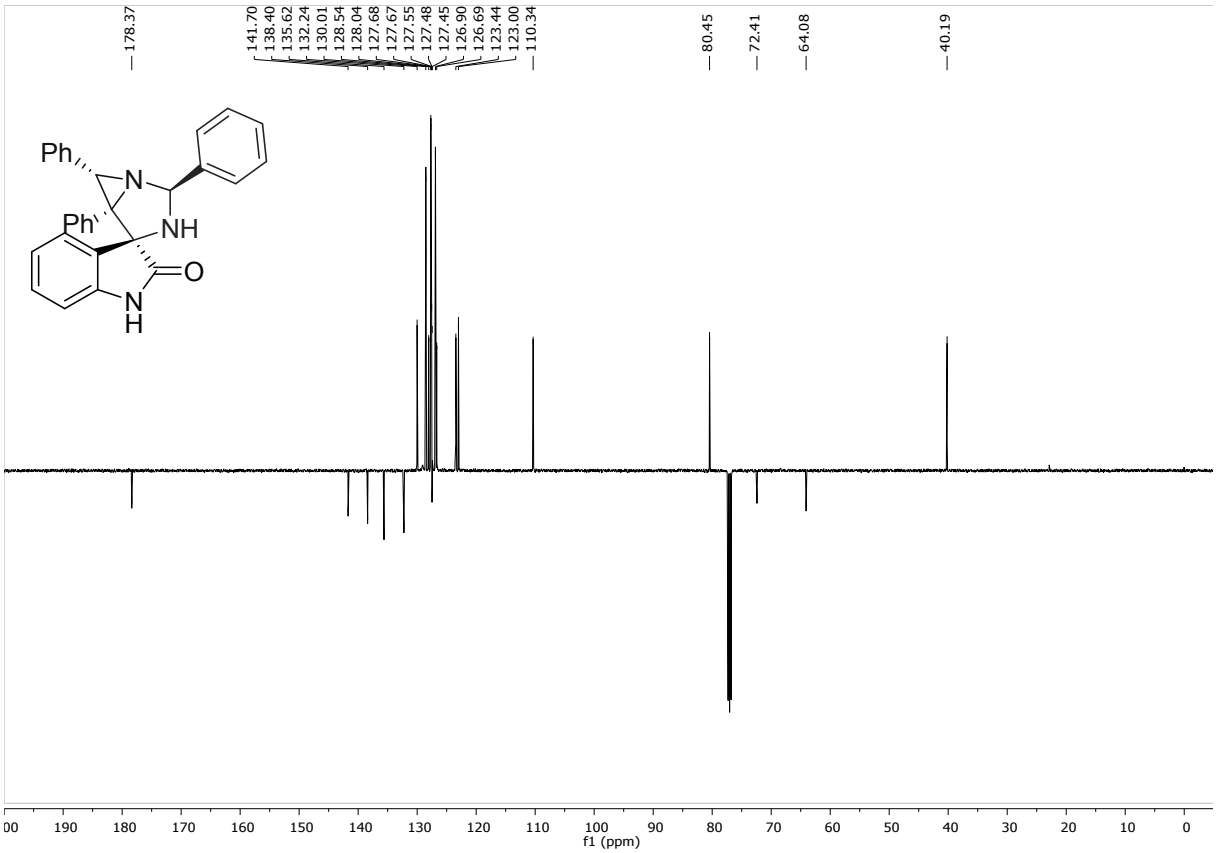


Figure S14. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-11a**

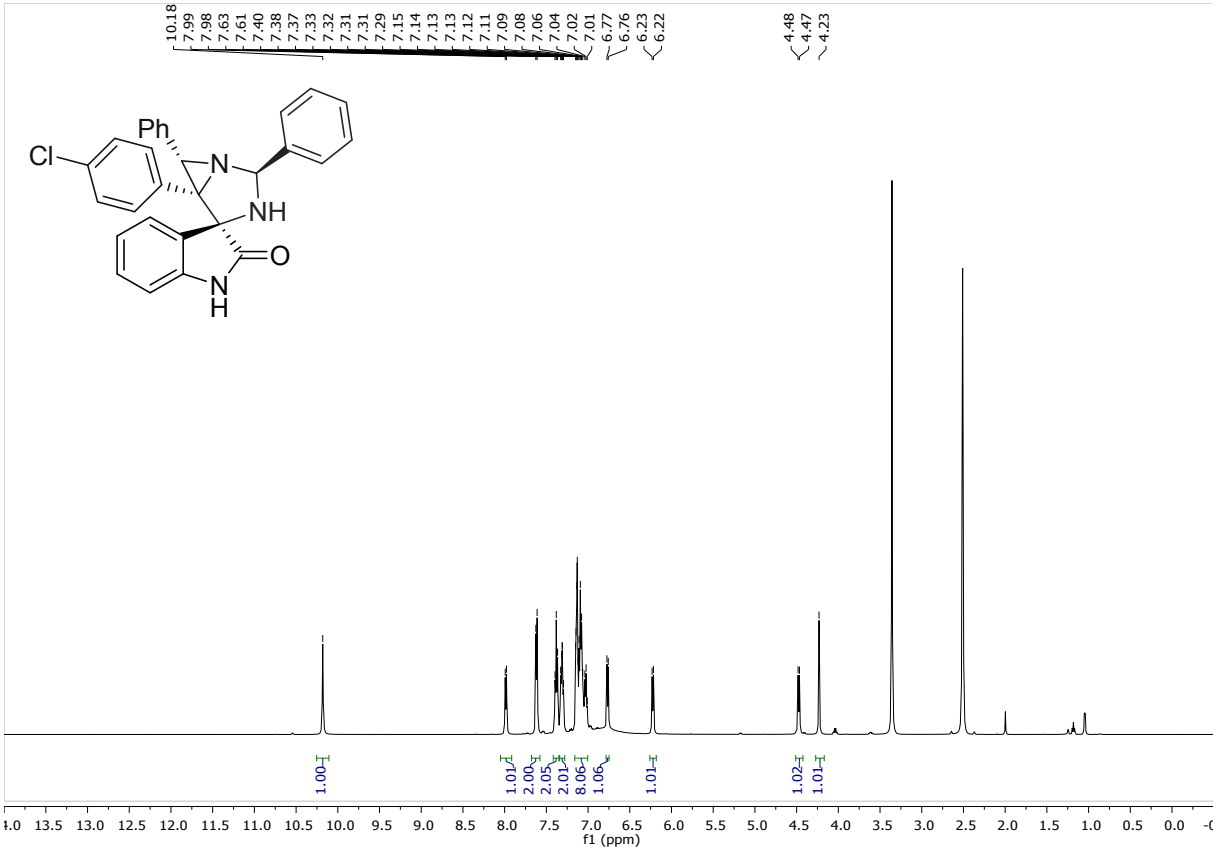


Figure S15. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-13a**

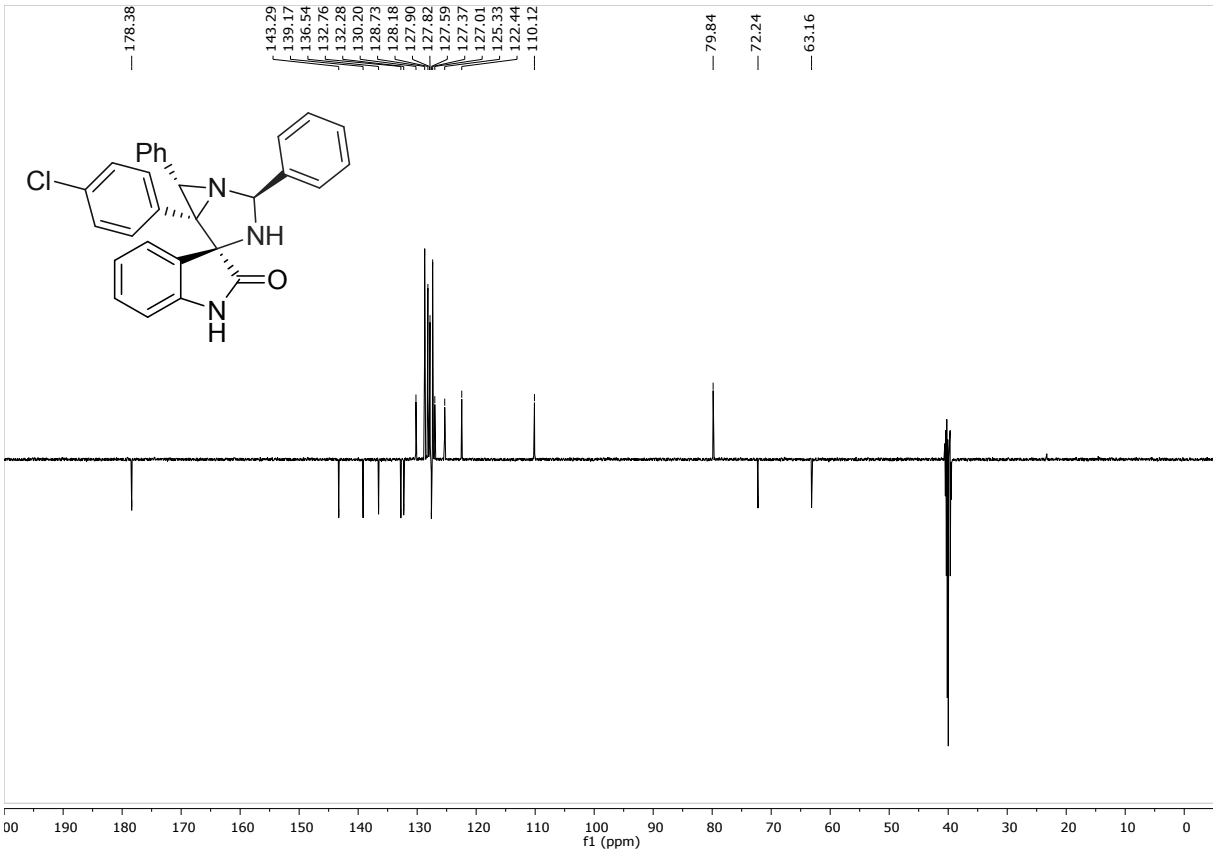


Figure S16. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-13a**

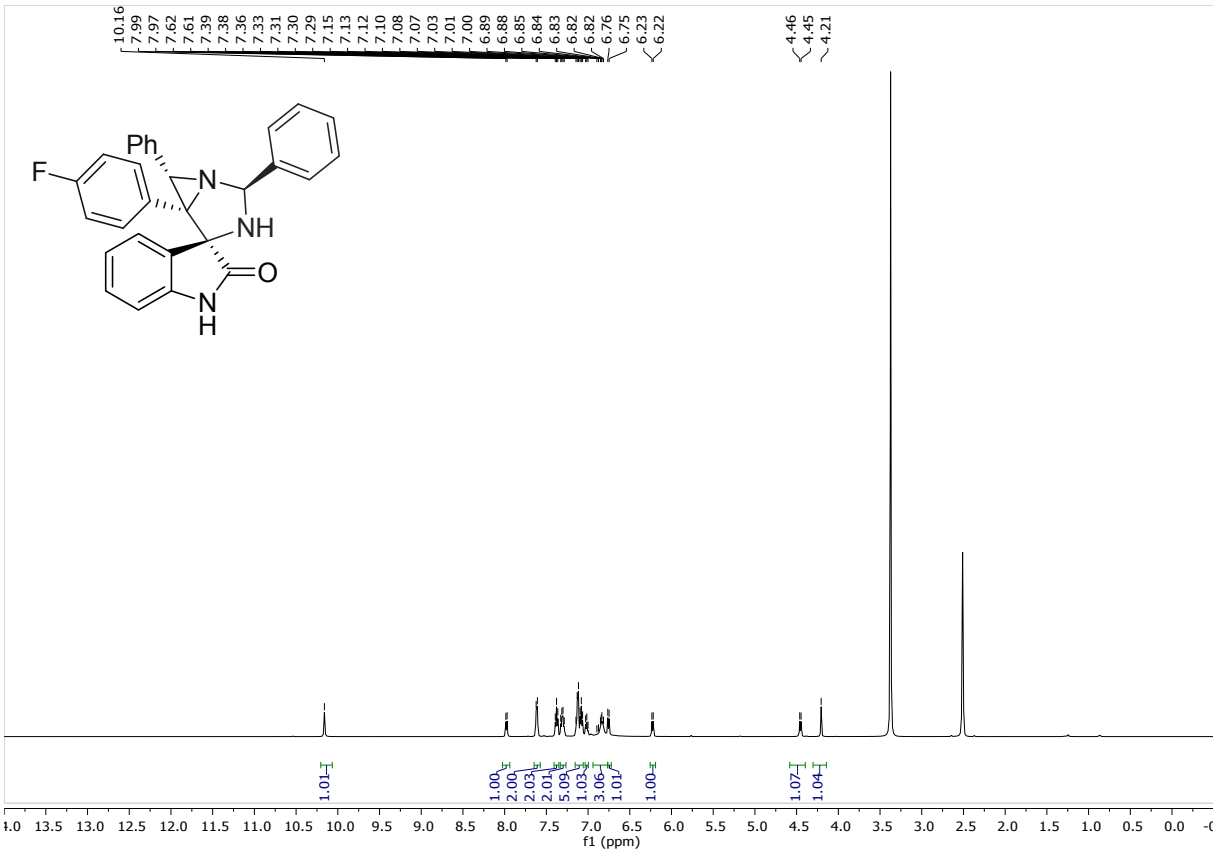


Figure S17. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-14a**

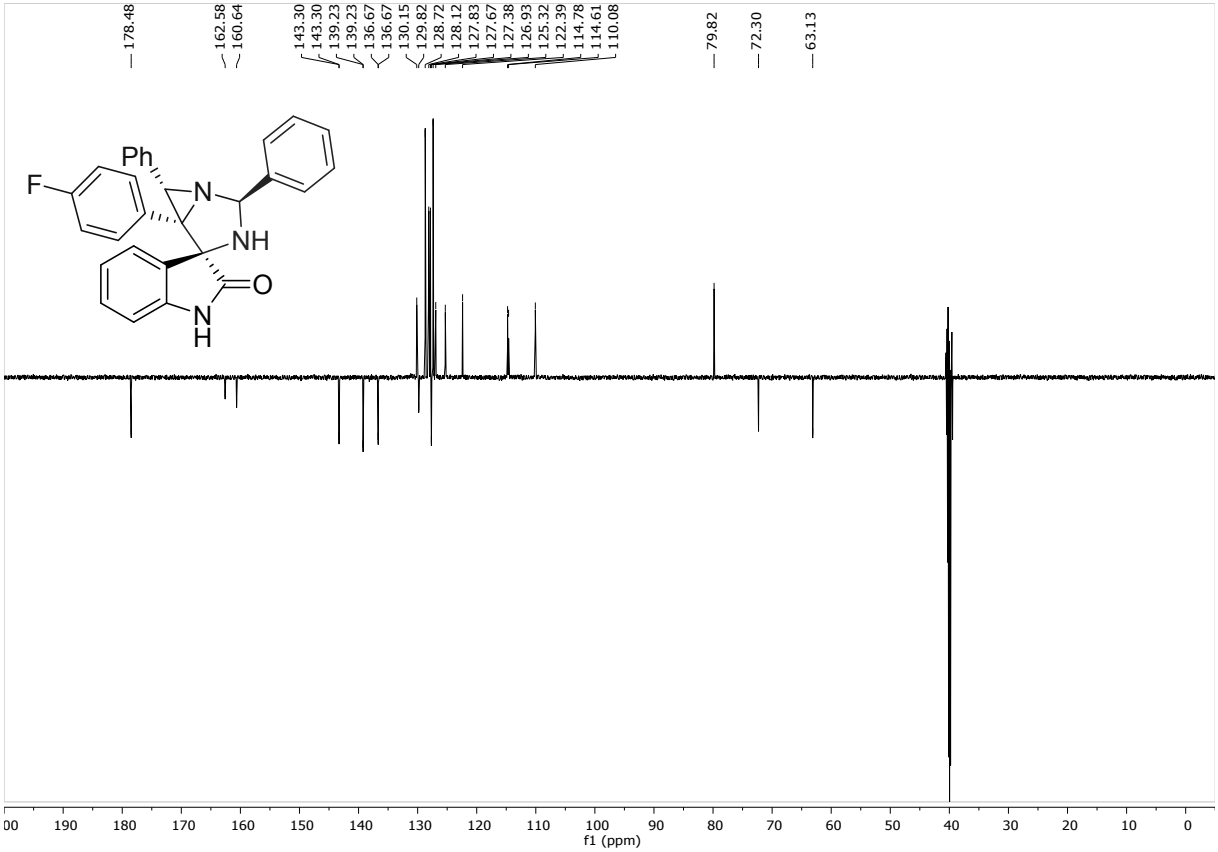


Figure S18. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-14a**

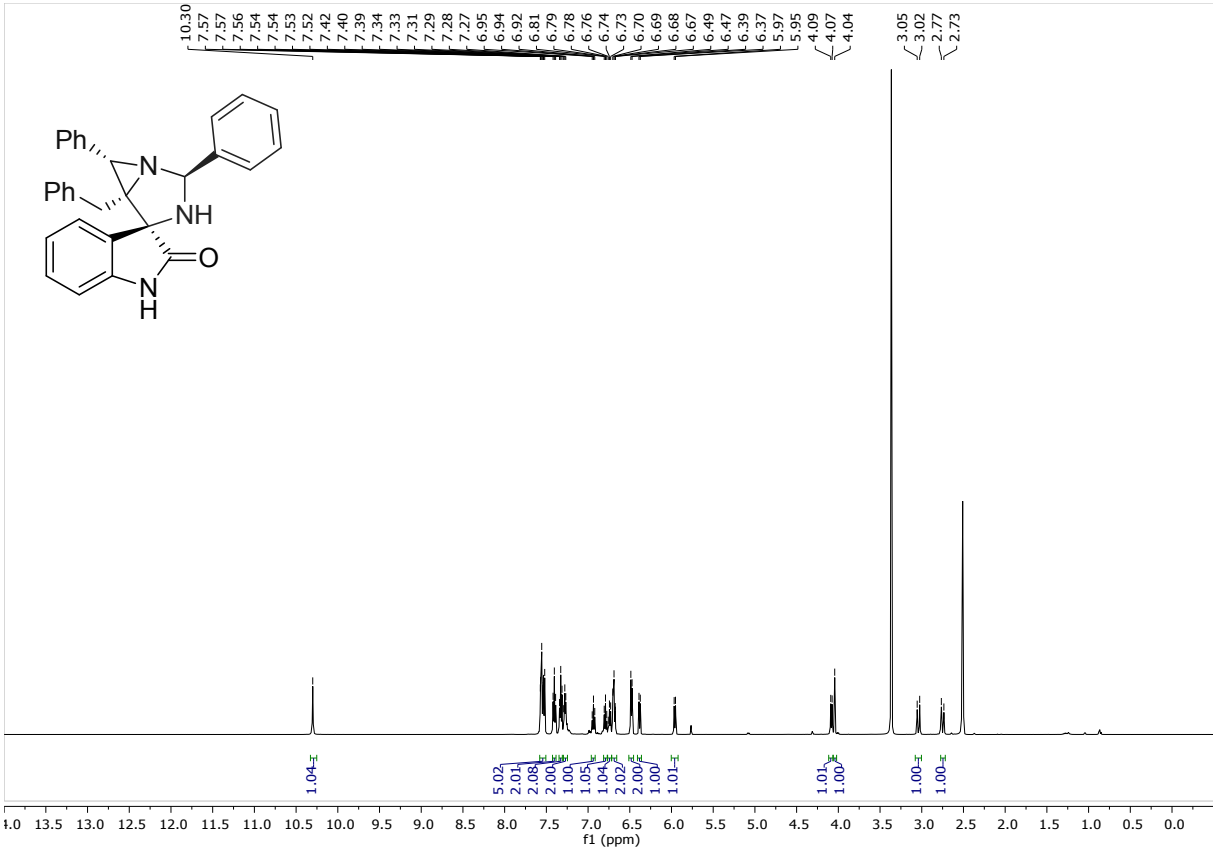


Figure S19. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-15a**

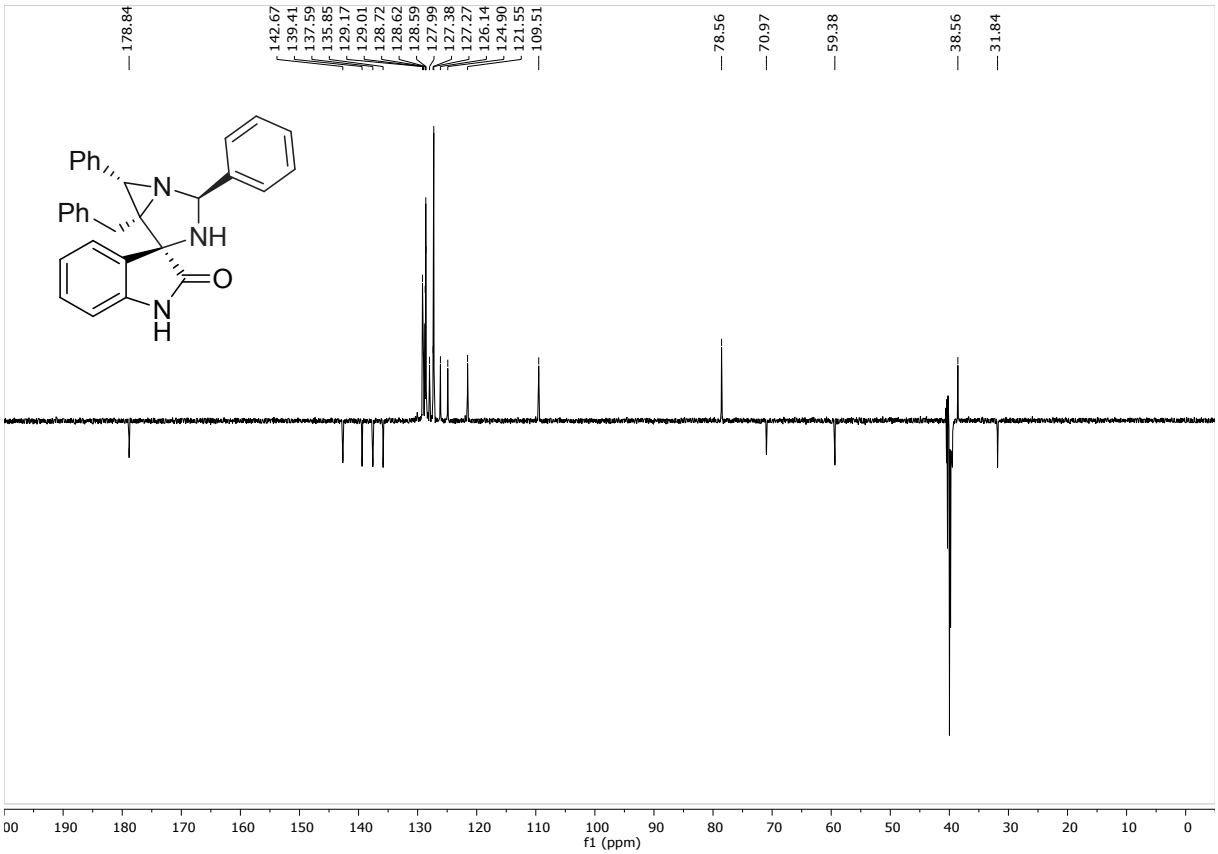


Figure S20. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-15a**

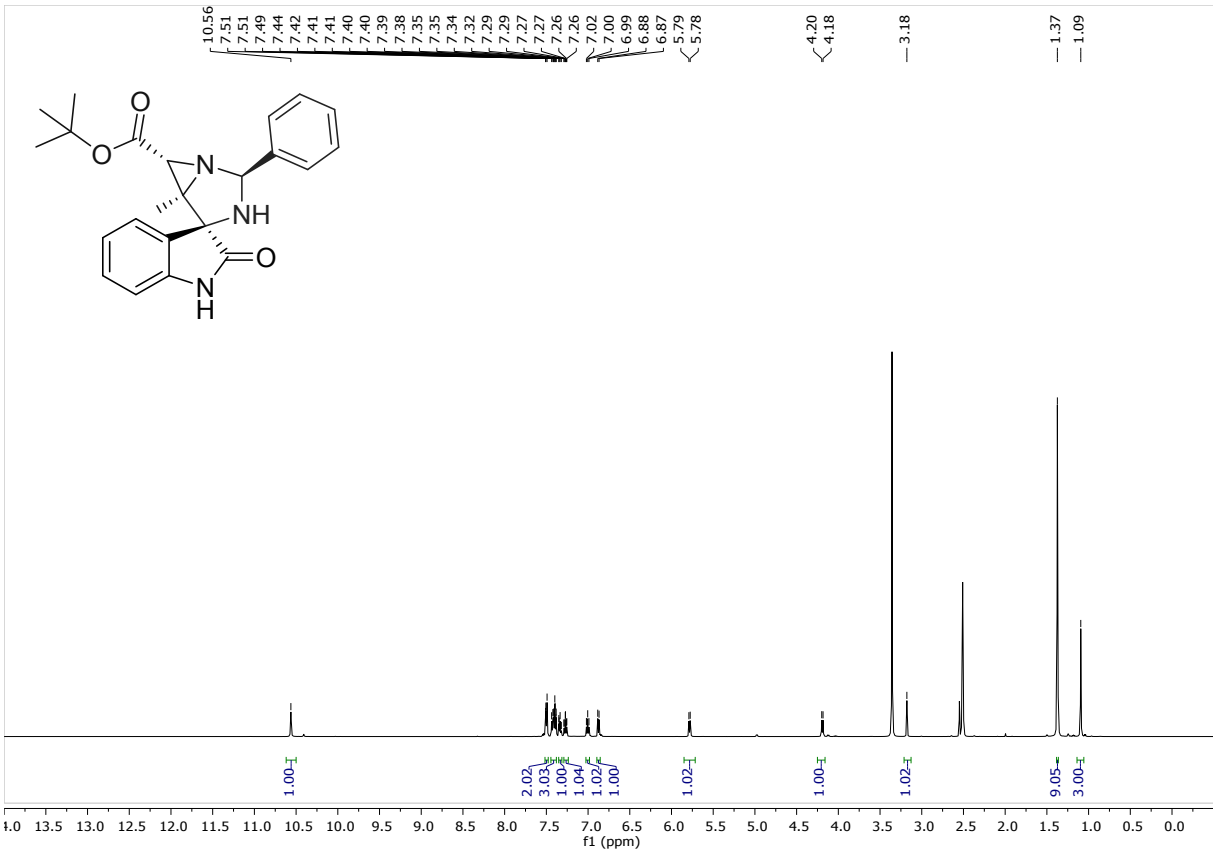


Figure S21. [1]H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-16a**

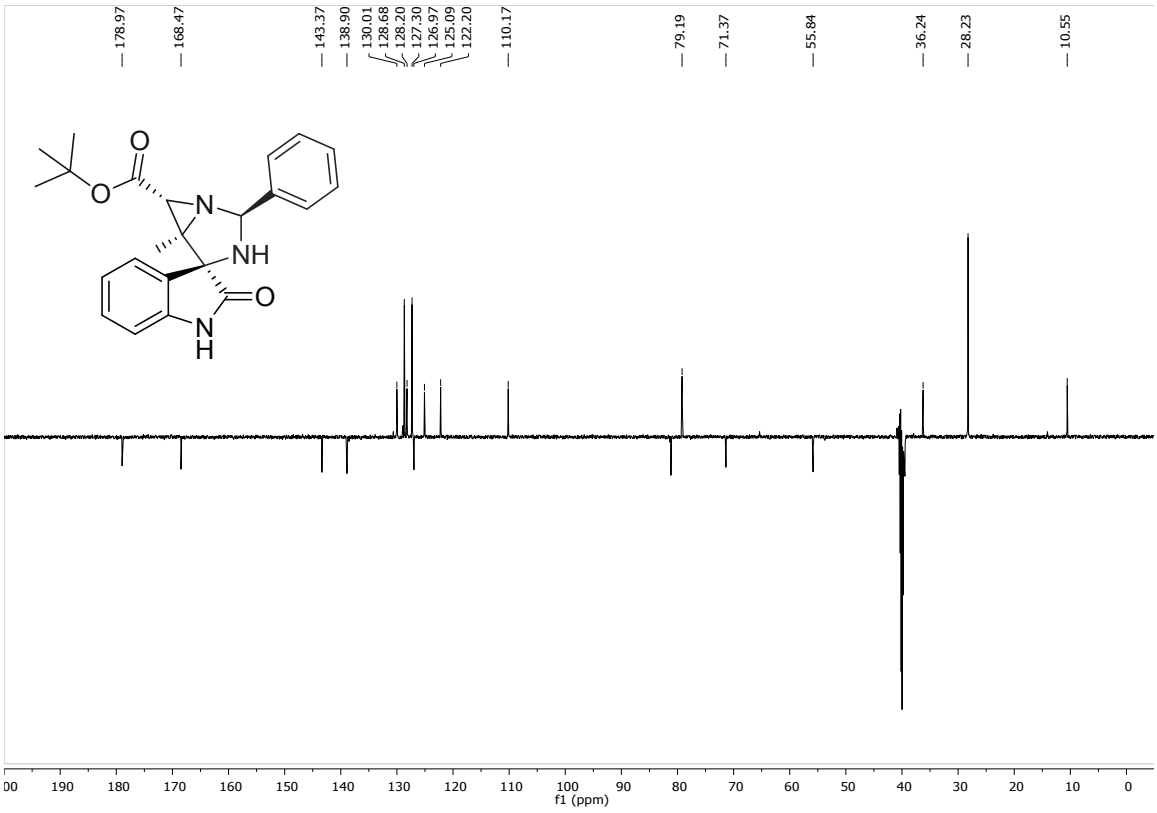


Figure S22. [13]C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-16a**

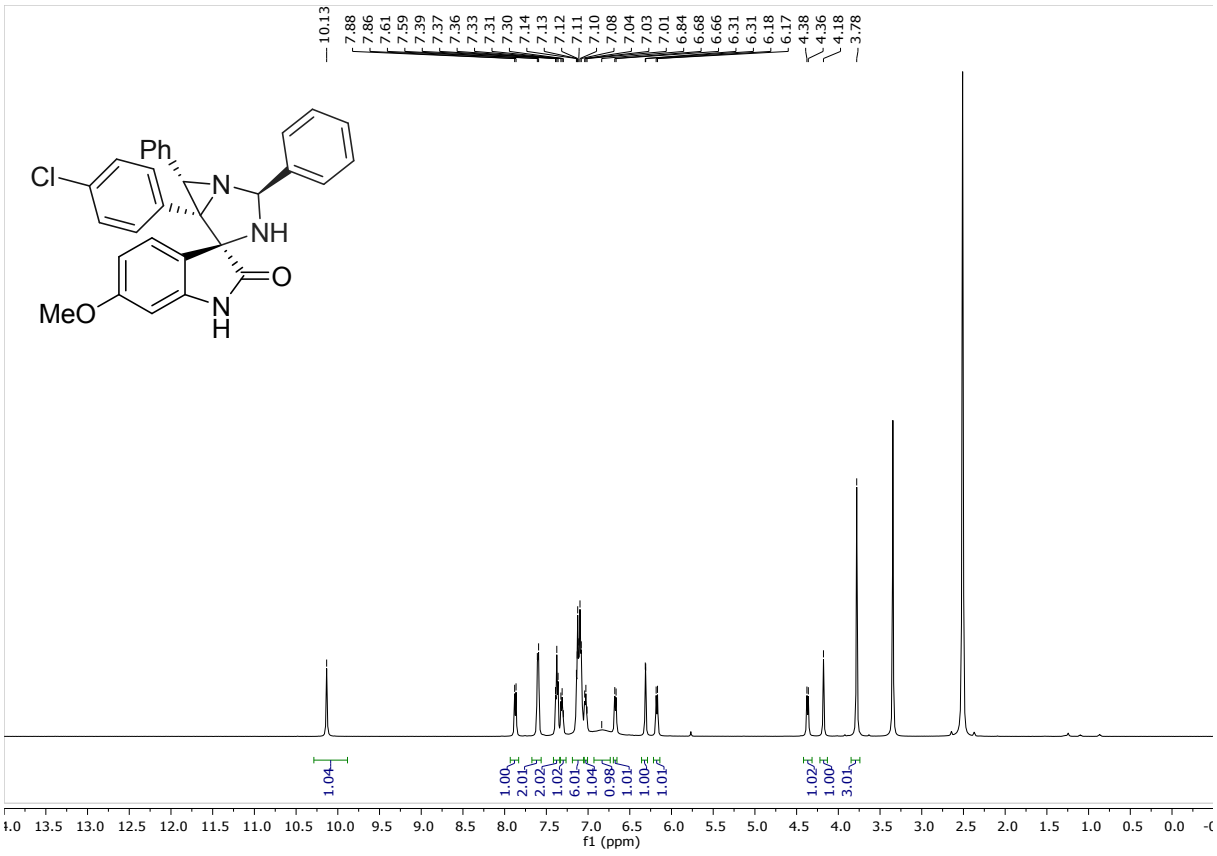


Figure S23. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-18a**

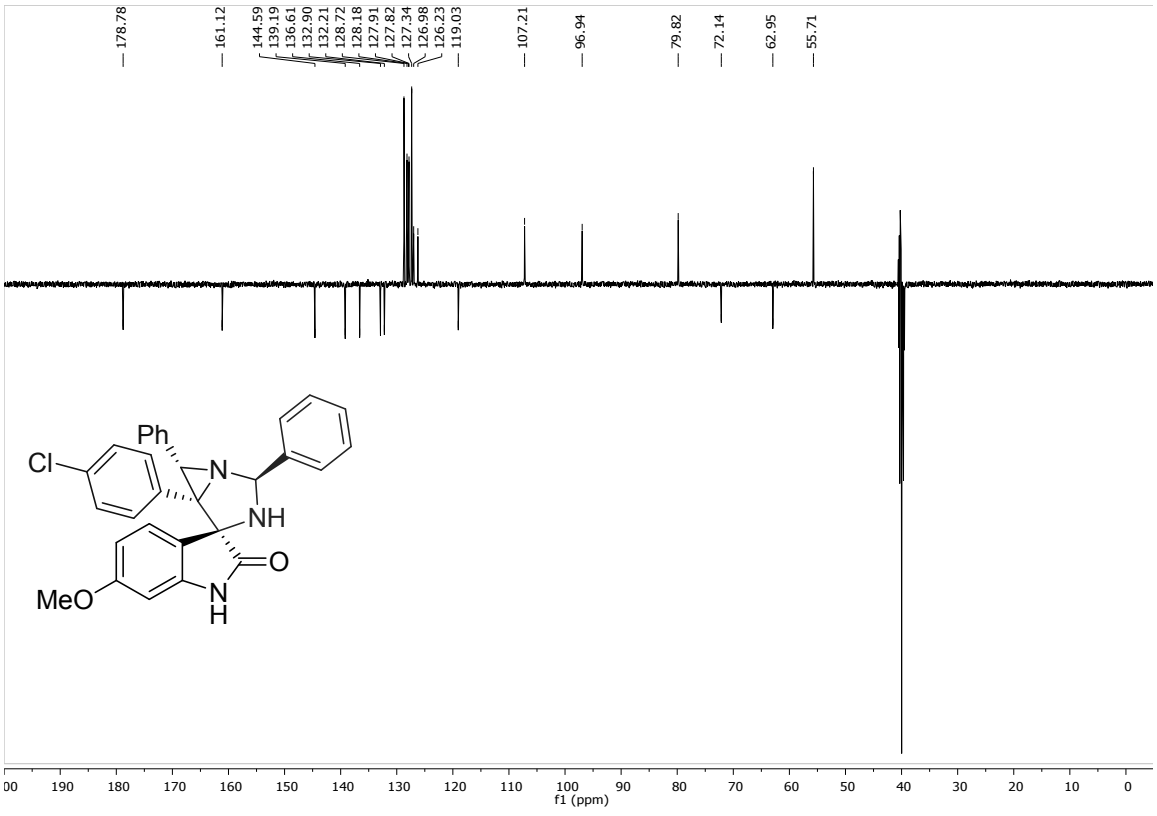


Figure S24. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-18a**

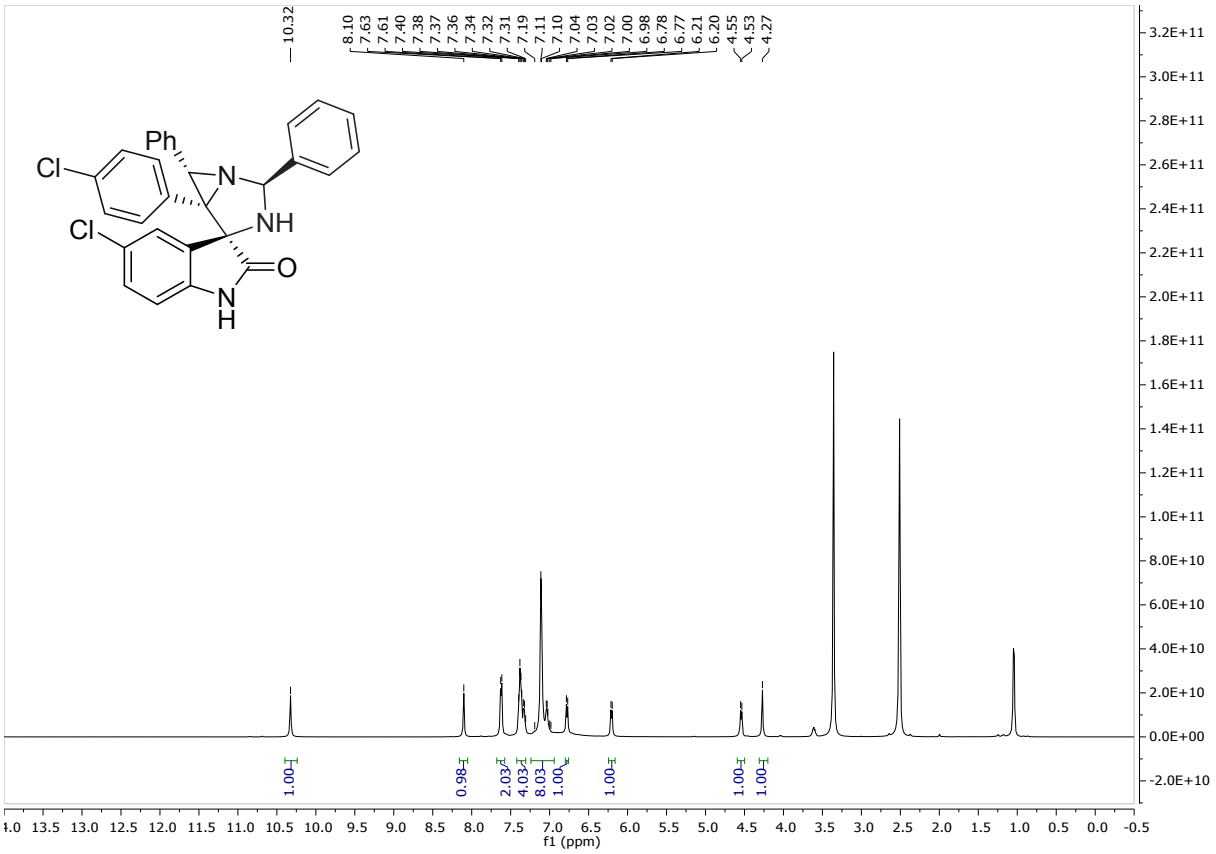


Figure S25. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-19a**

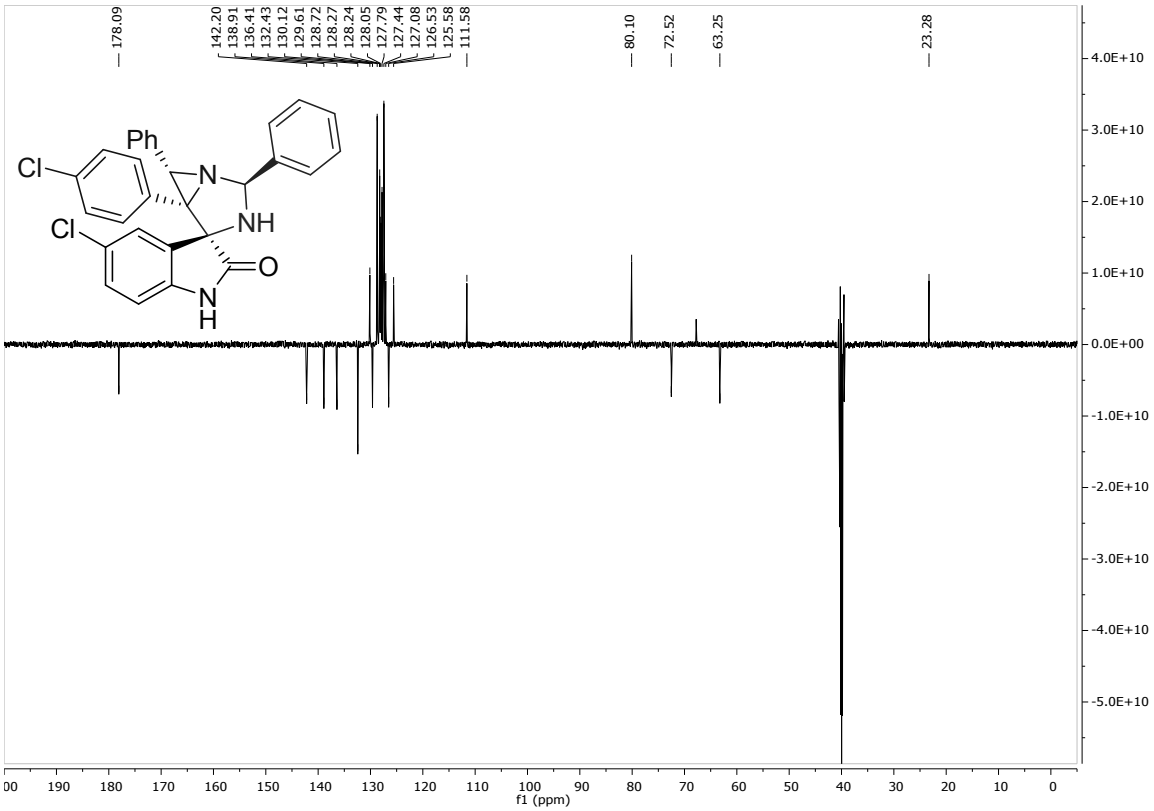


Figure S26. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-19a**

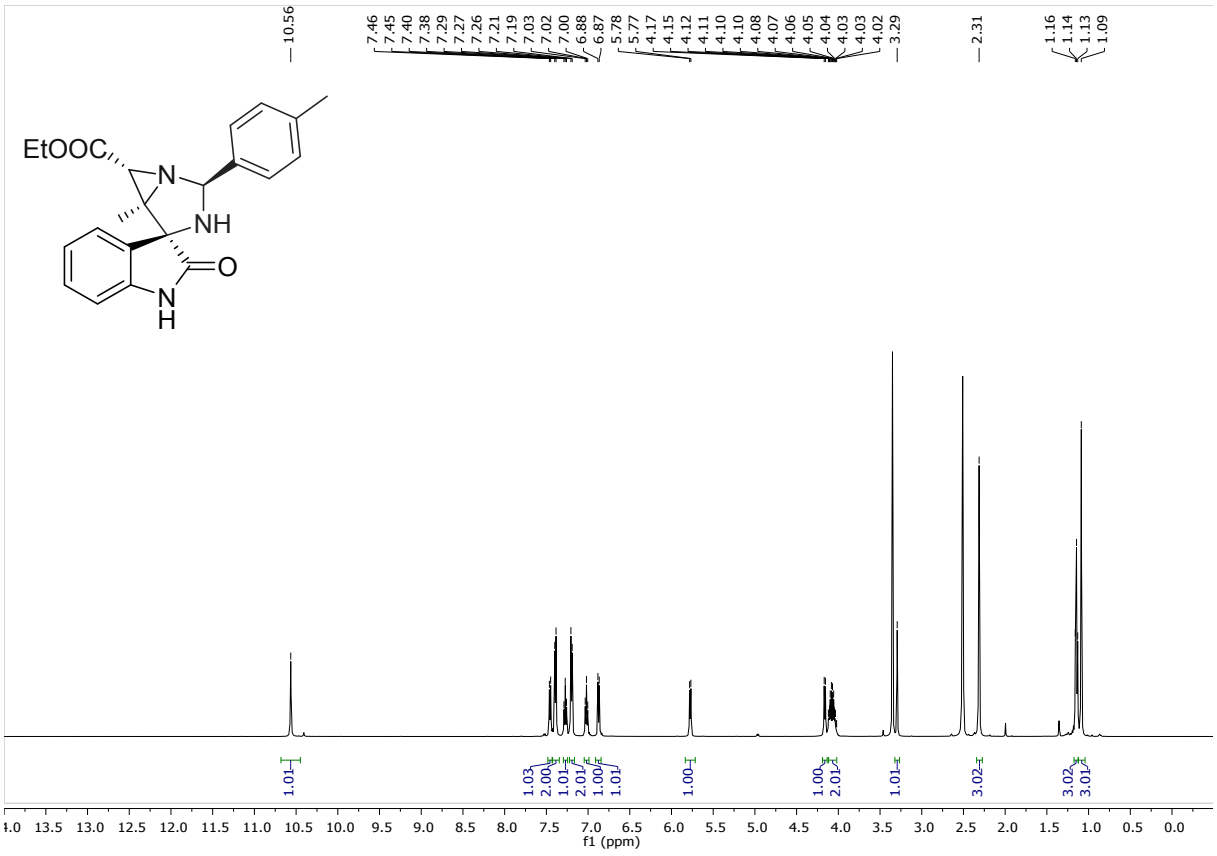


Figure S27. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-20a**

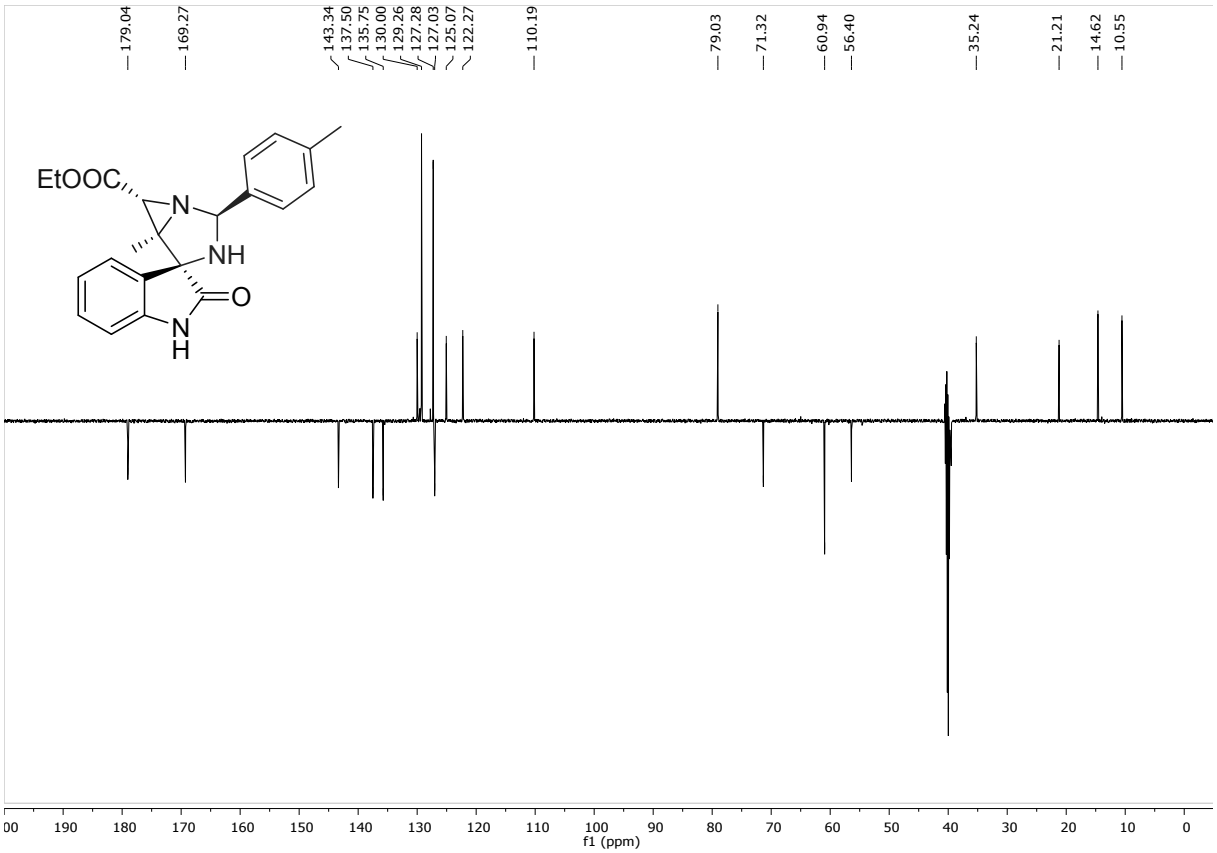


Figure S28. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-20a**

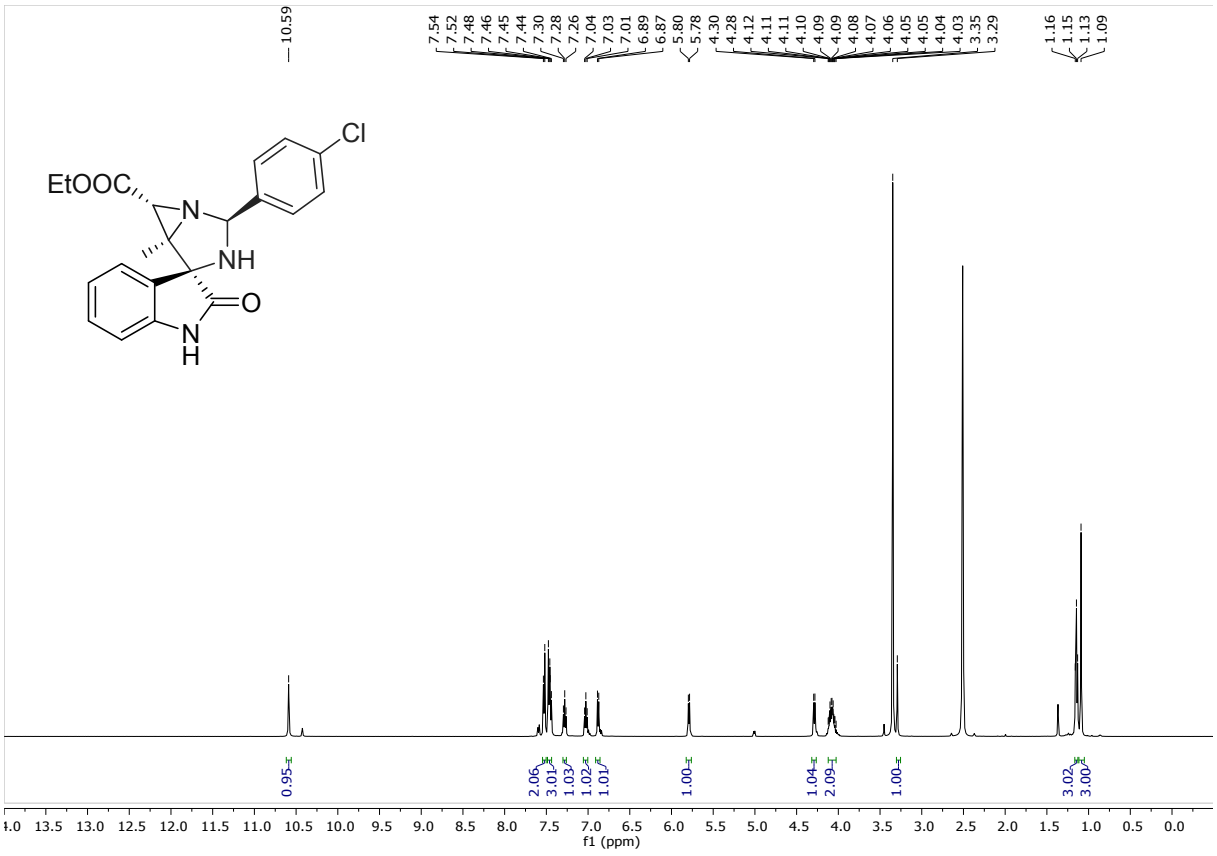


Figure S29. [1]H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-21a**

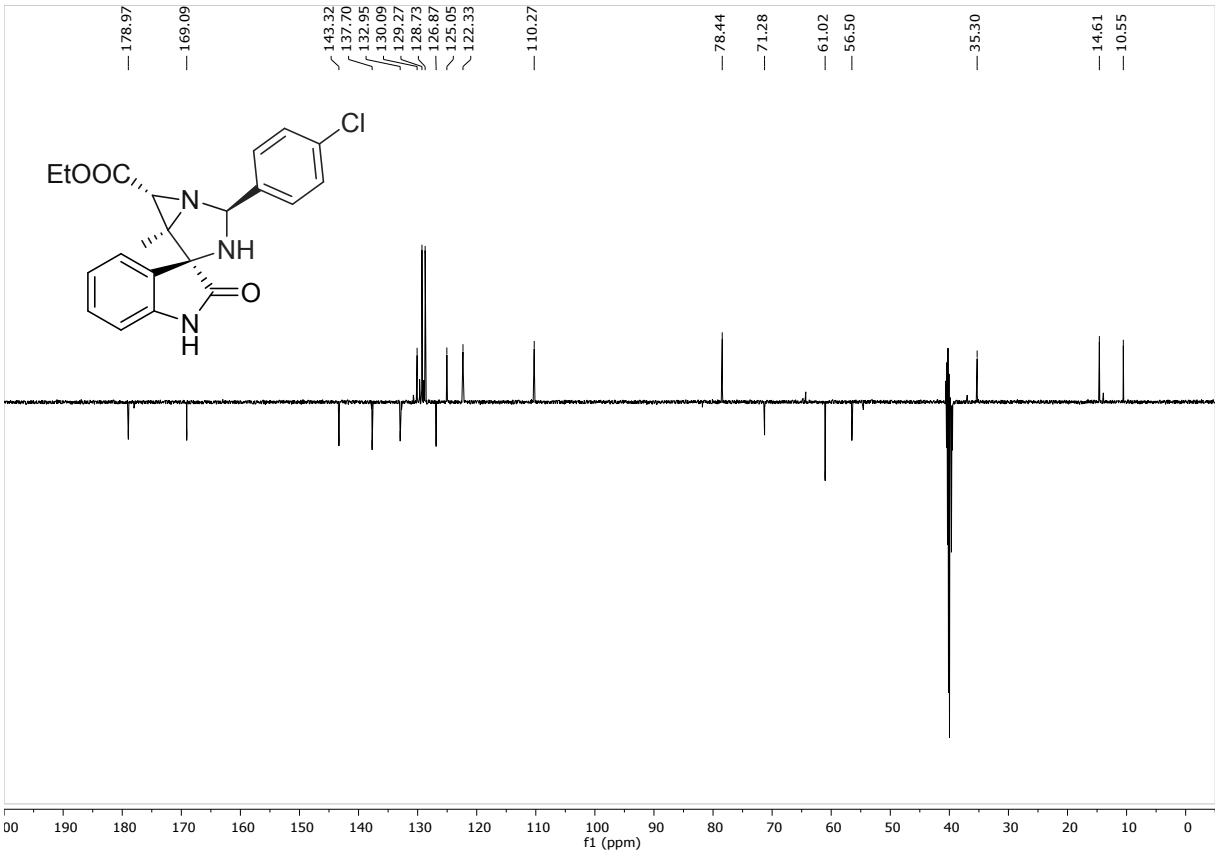


Figure S30. [13]C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-21a**

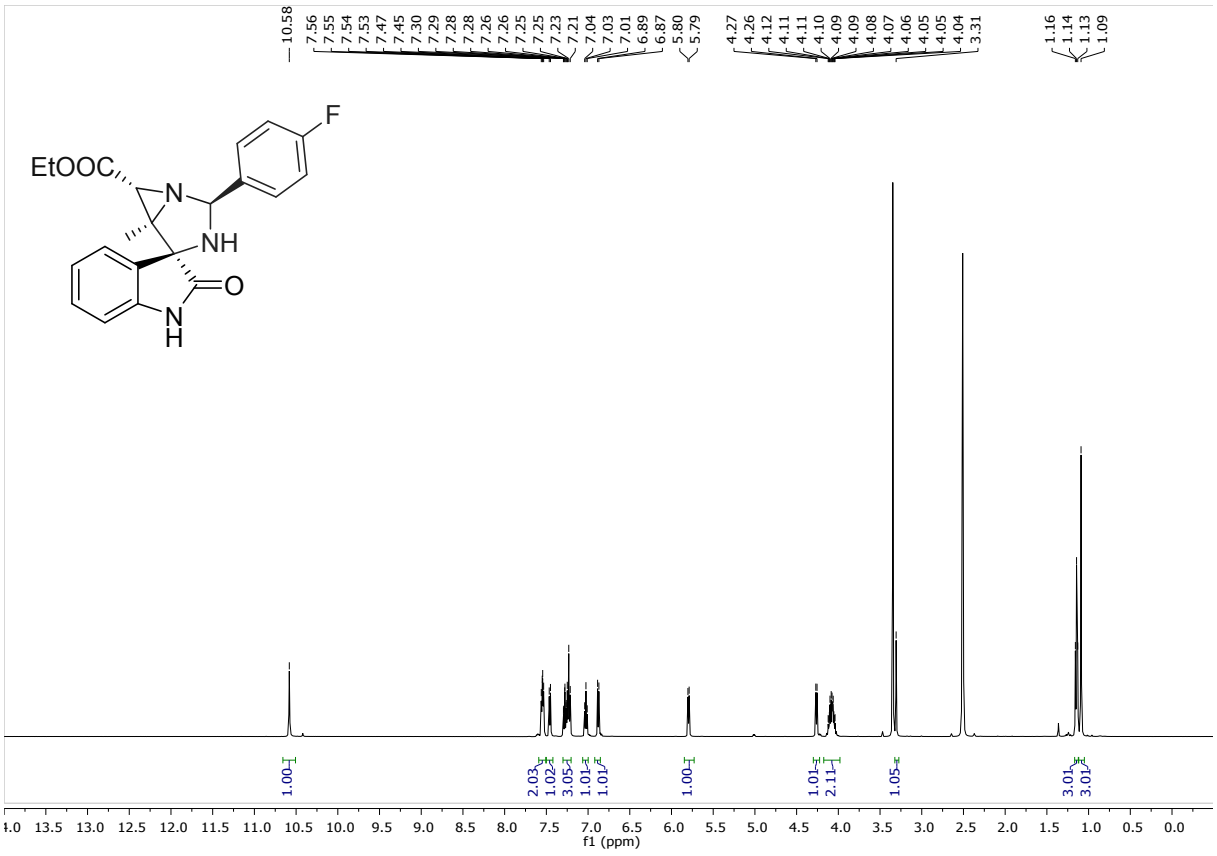


Figure S31. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-22a**

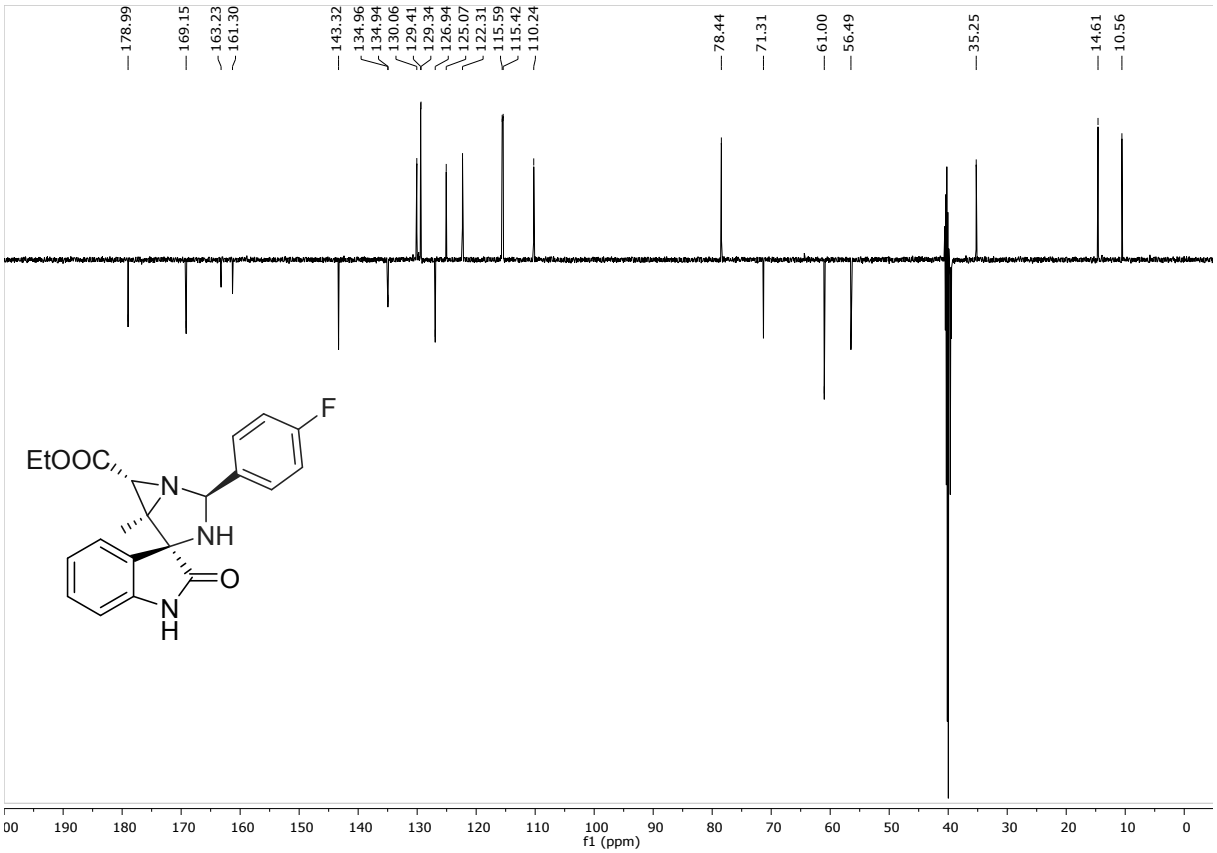


Figure S32. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-22a**

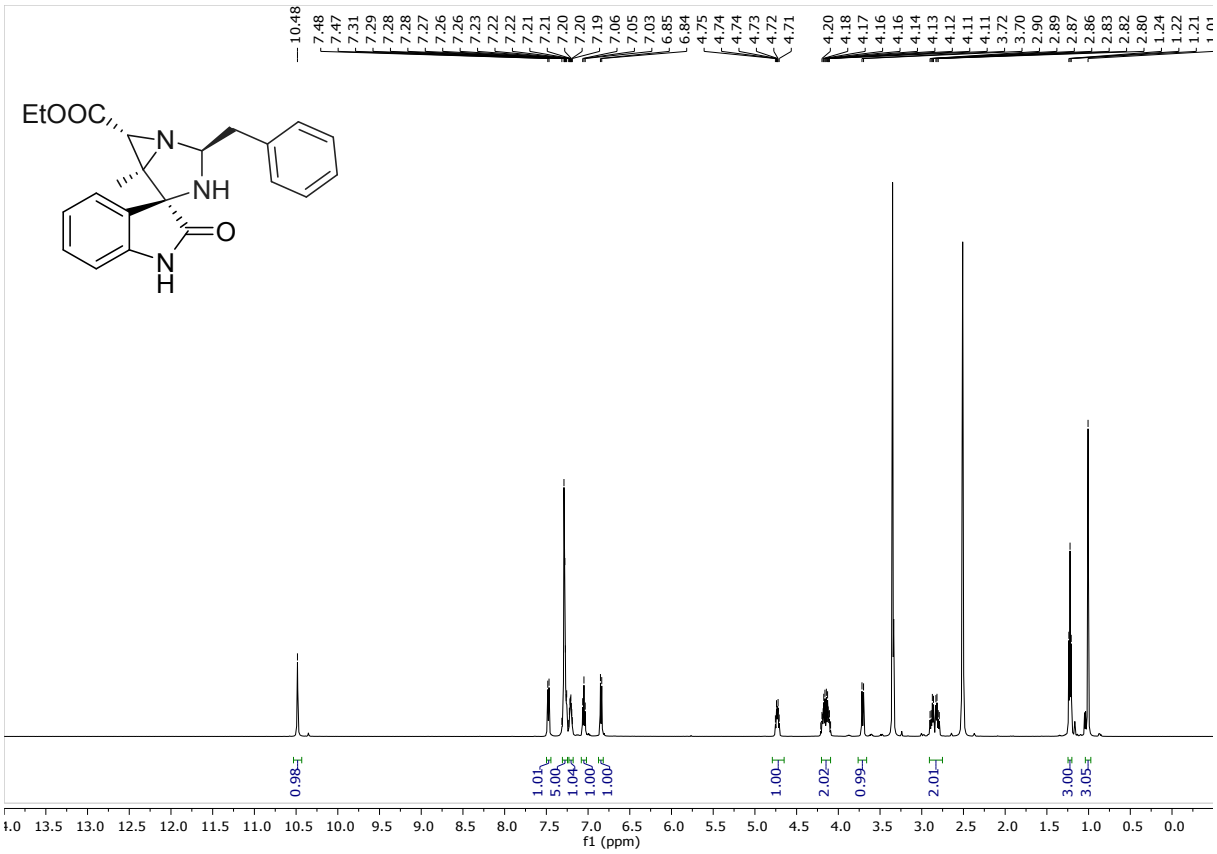


Figure S33. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-23a**

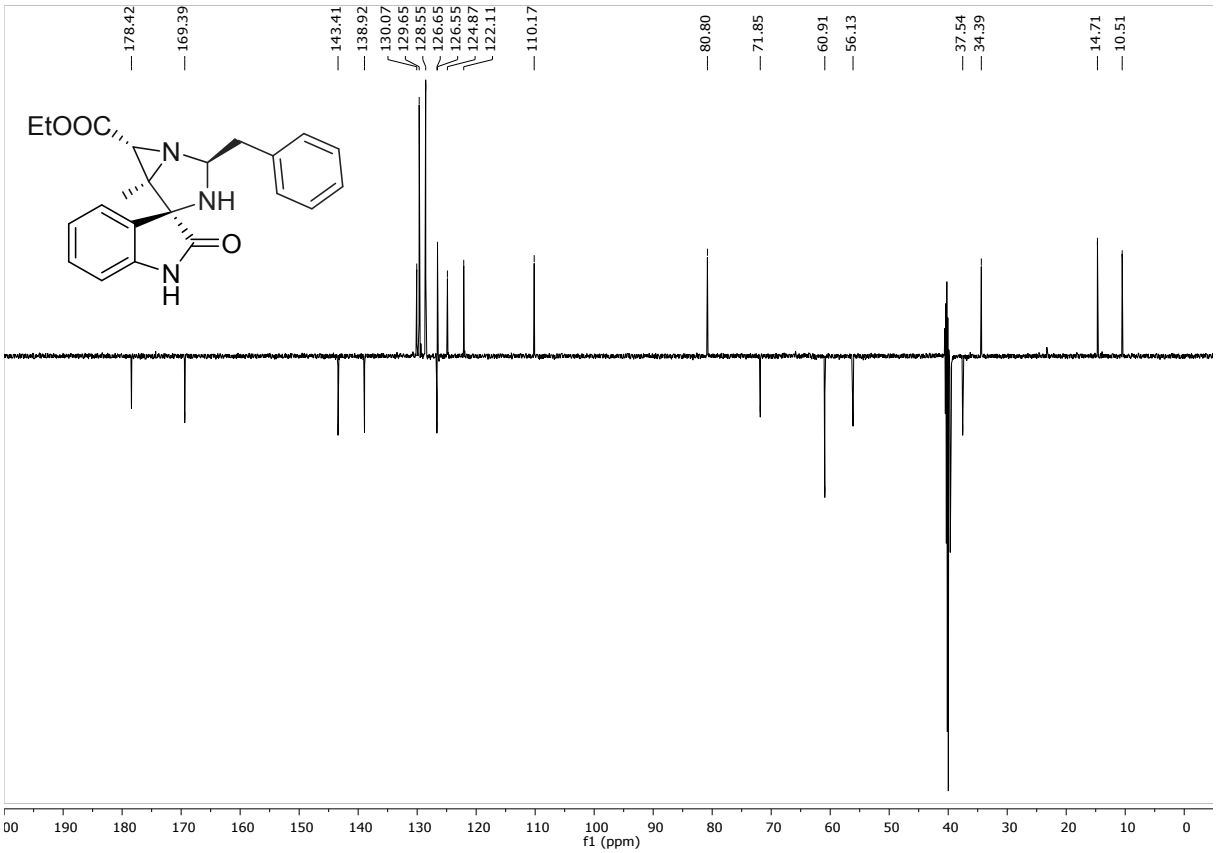


Figure S34. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-23a**

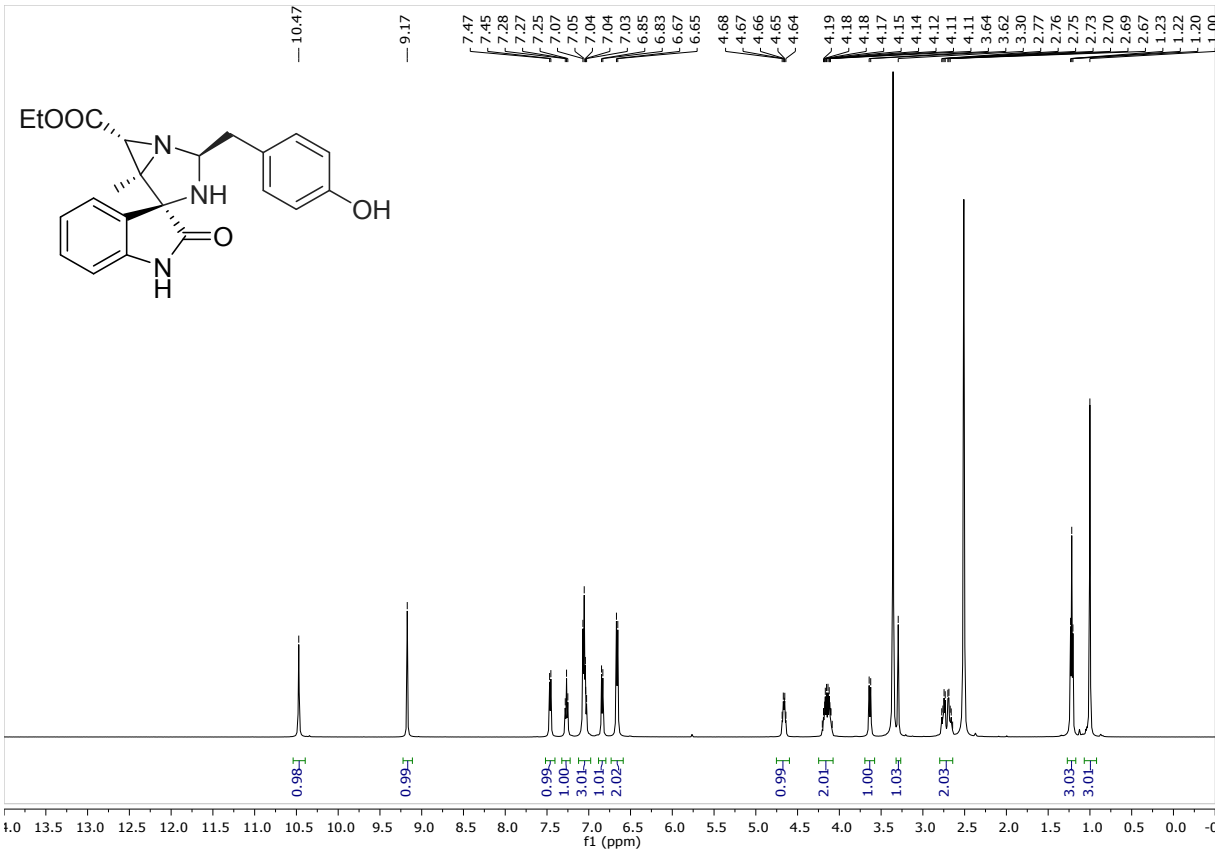


Figure S35. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-24a**

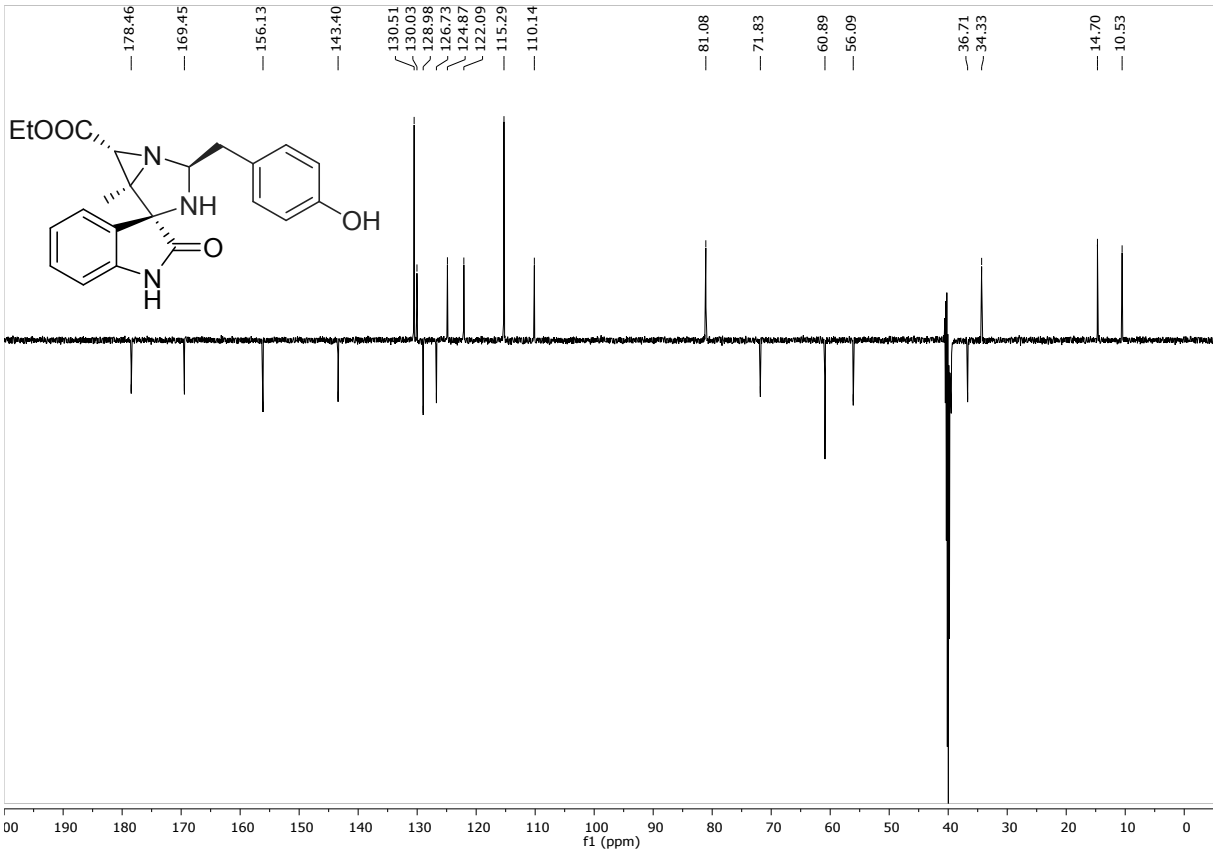


Figure S36. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-24a**

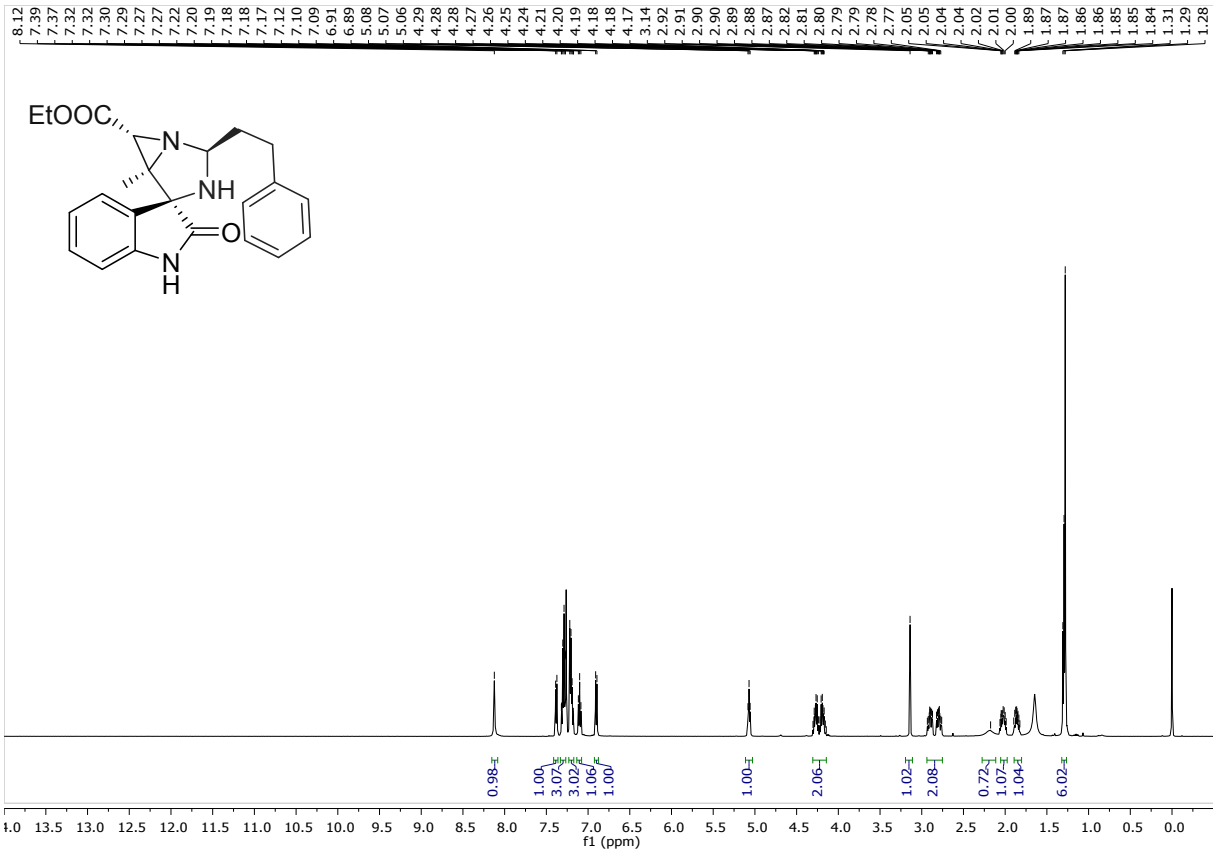


Figure S37. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-25a**

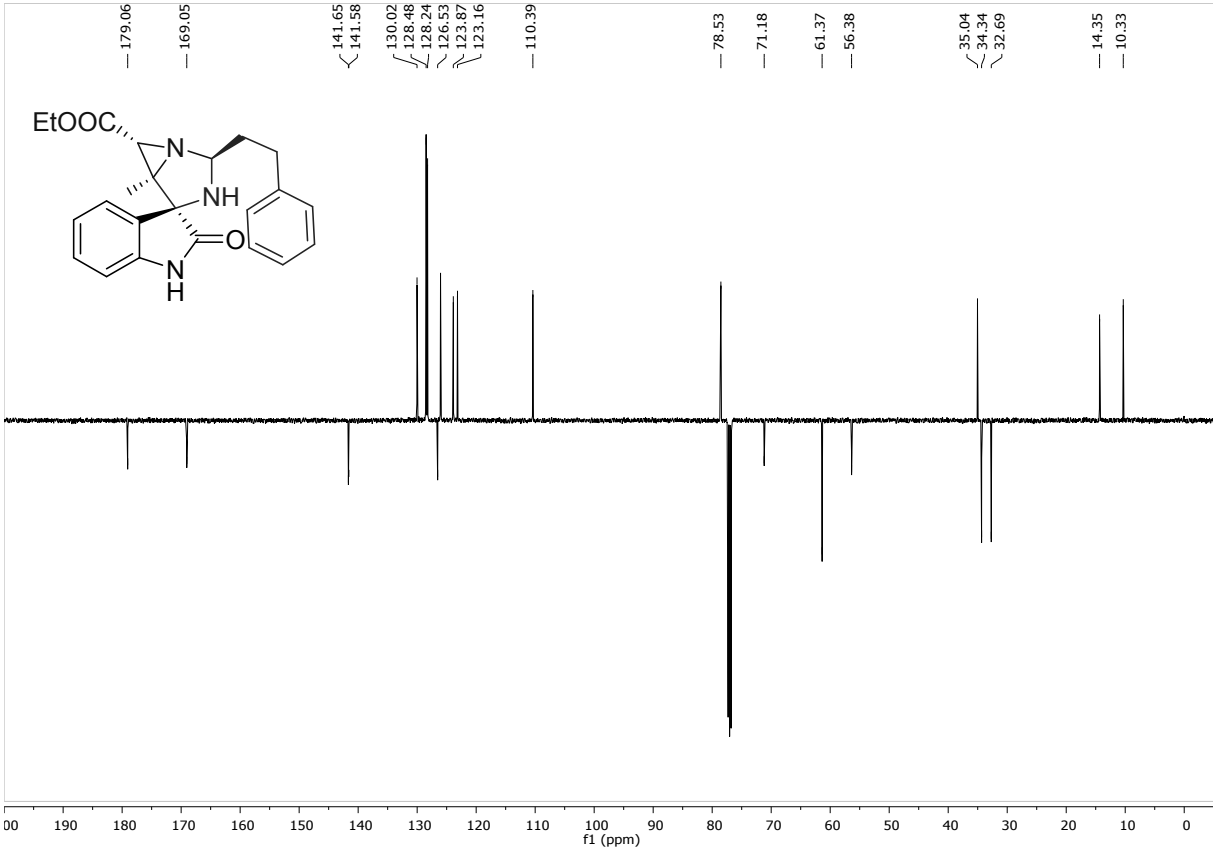


Figure S38. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-25a**

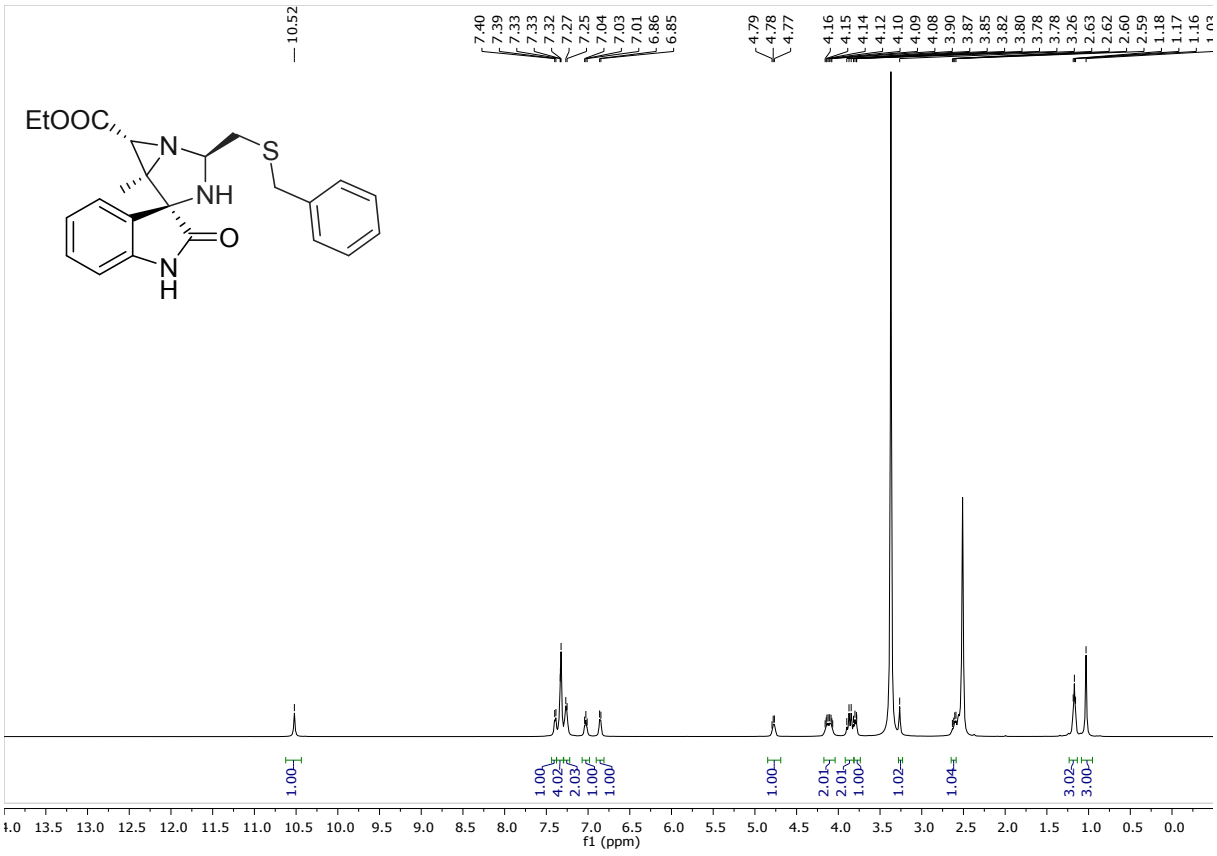


Figure S39. [1]H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-26a**

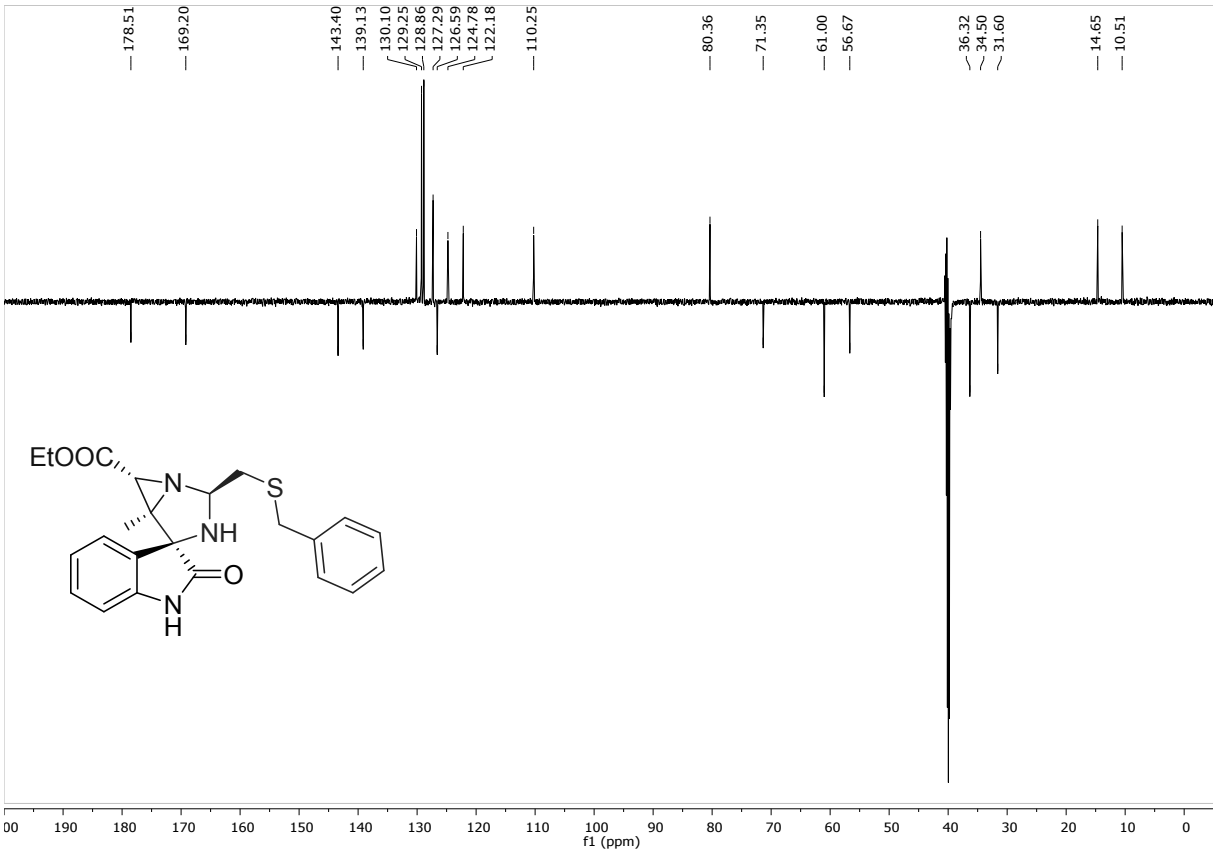


Figure S40. [13]C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-26a**

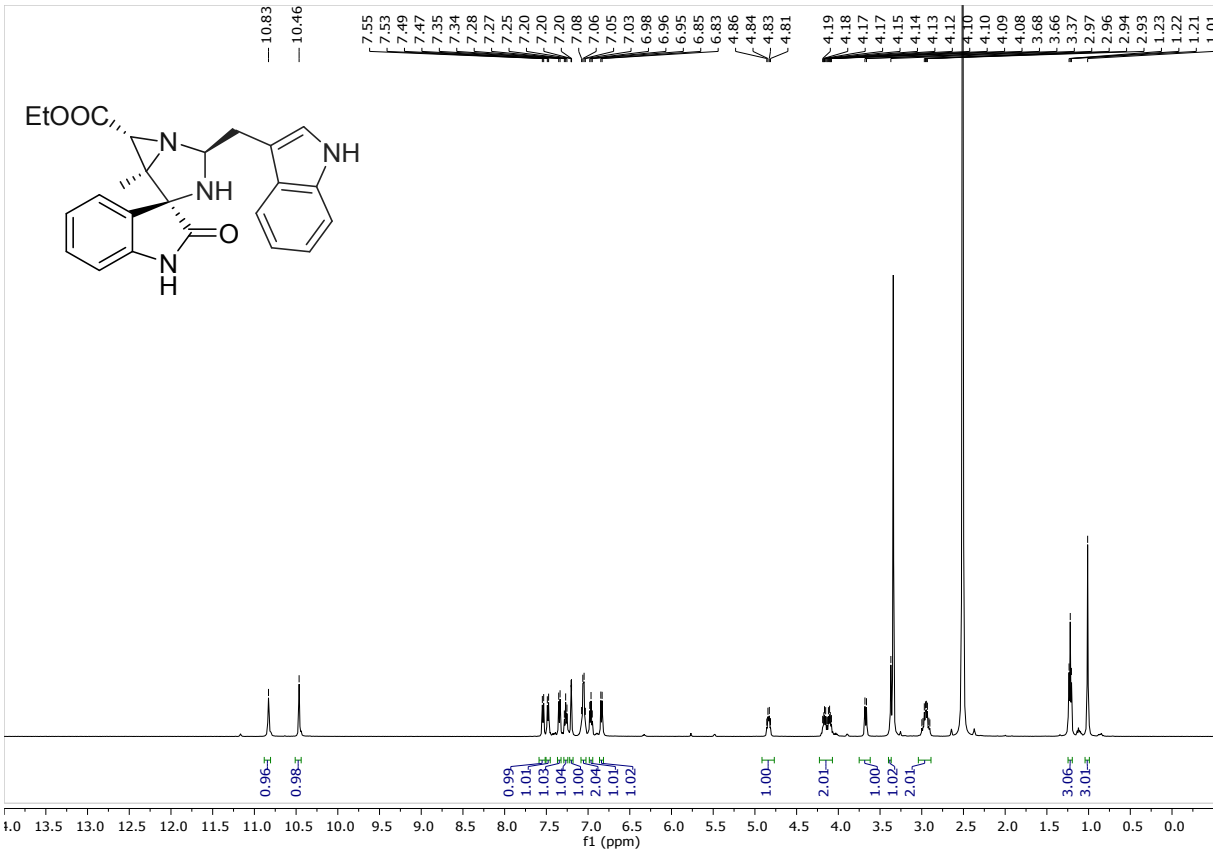


Figure S41. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-27a**

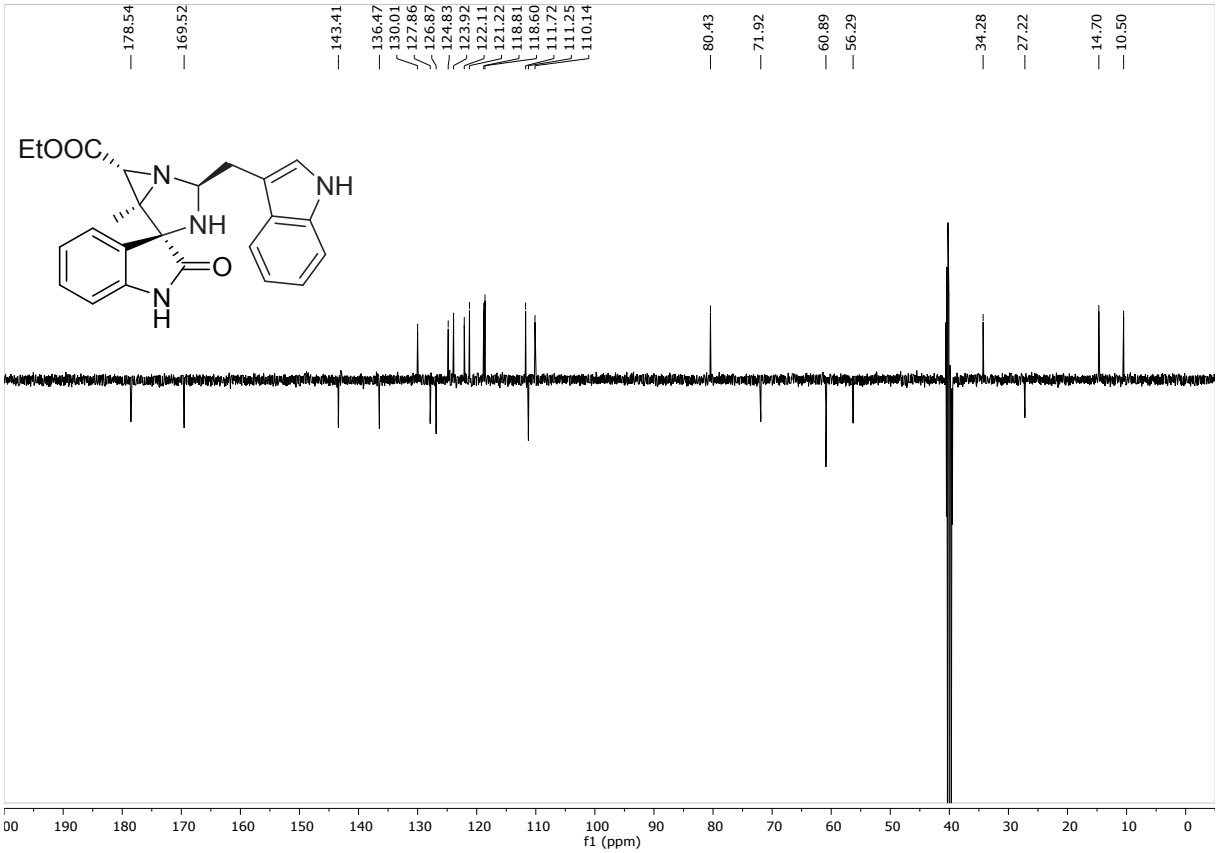


Figure S42. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-27a**

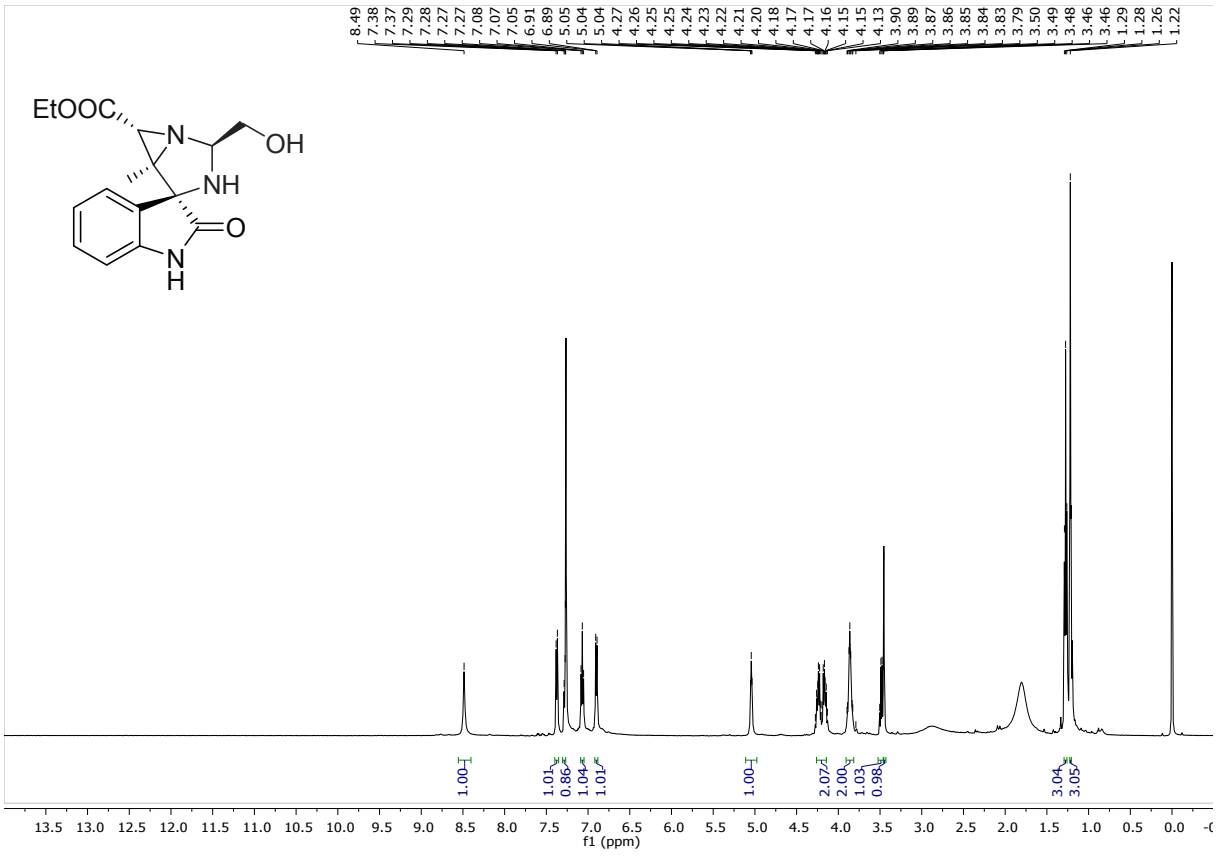


Figure S43. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-28a**

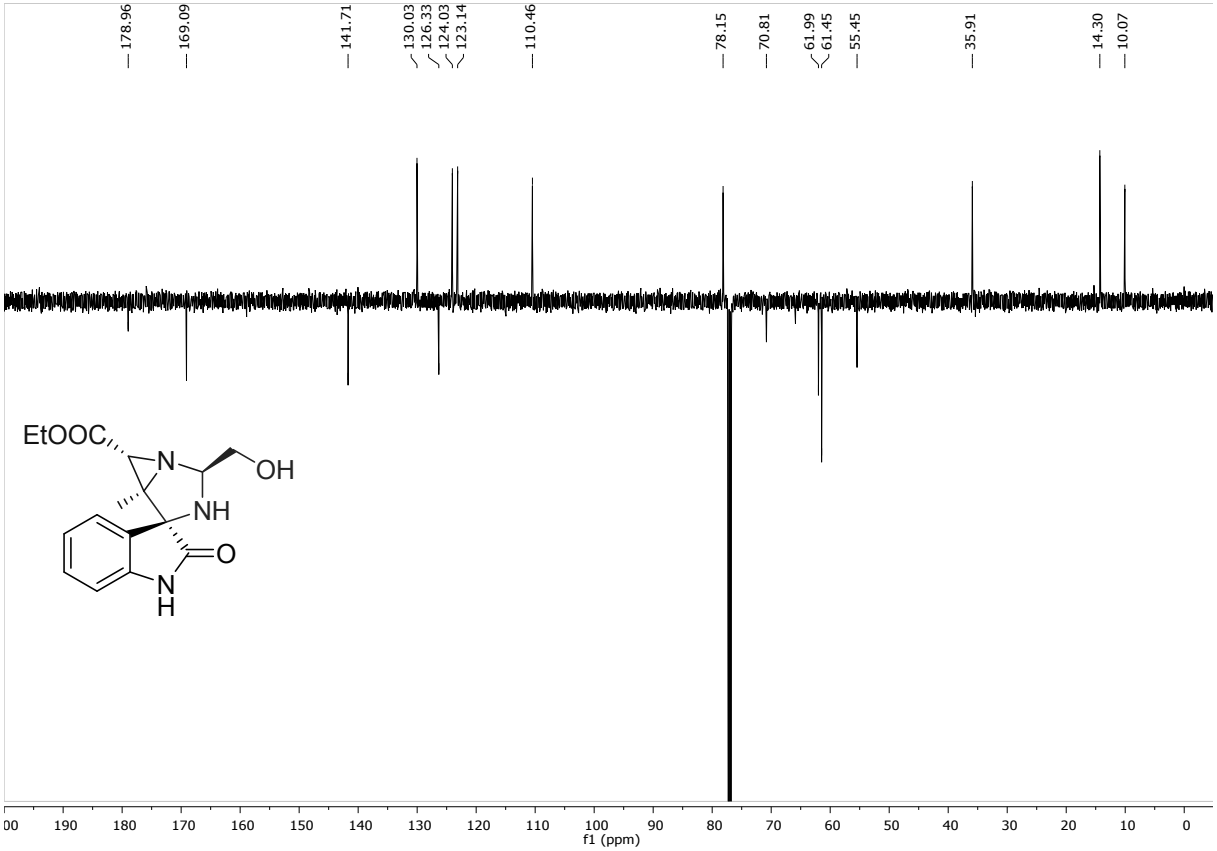


Figure S44. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-28a**

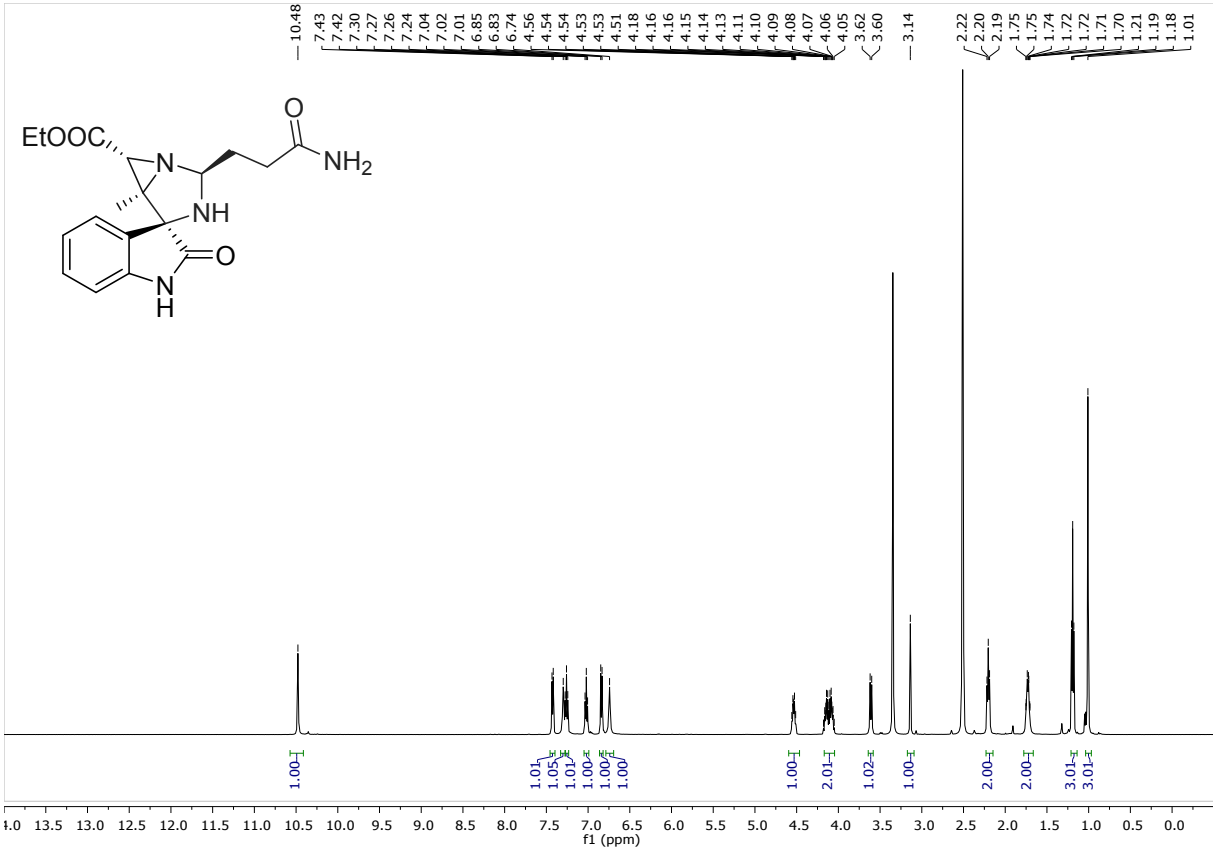


Figure S45. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-29a**

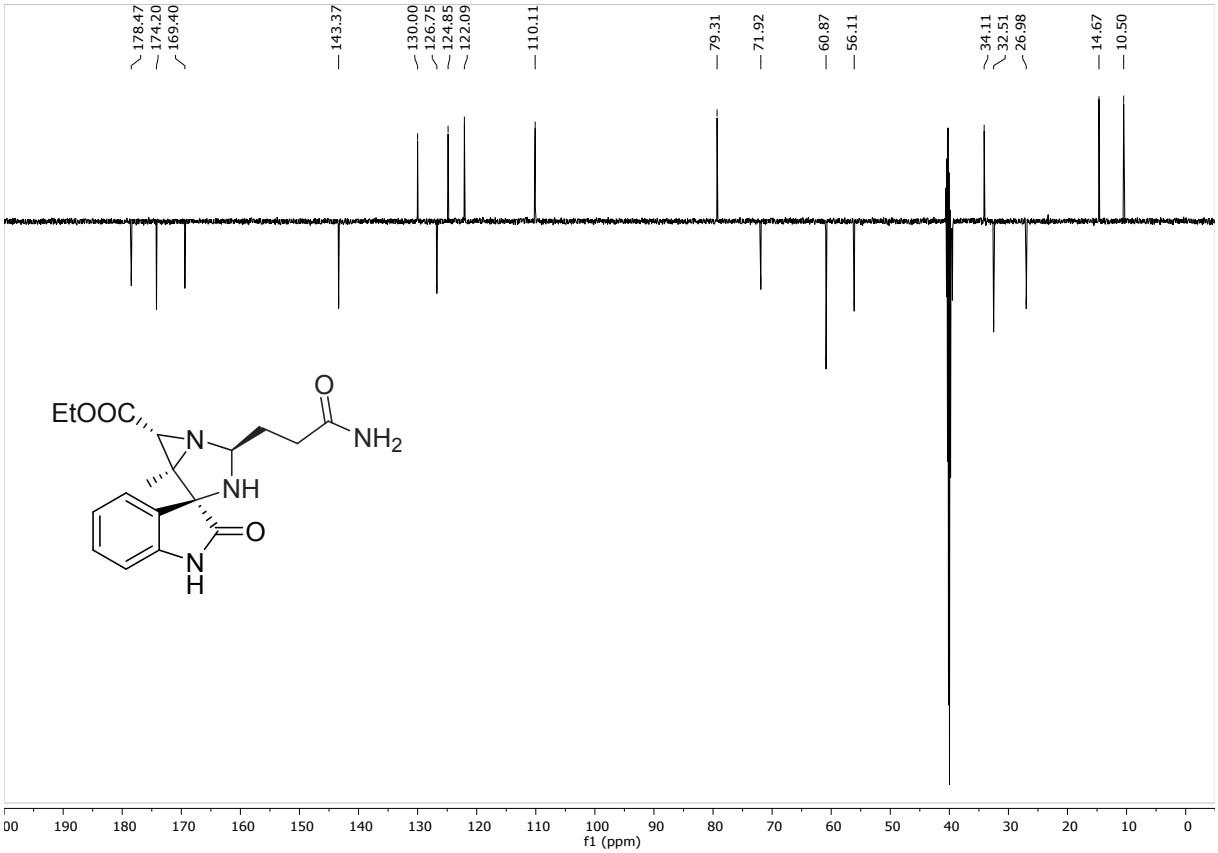


Figure S46. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-29a**

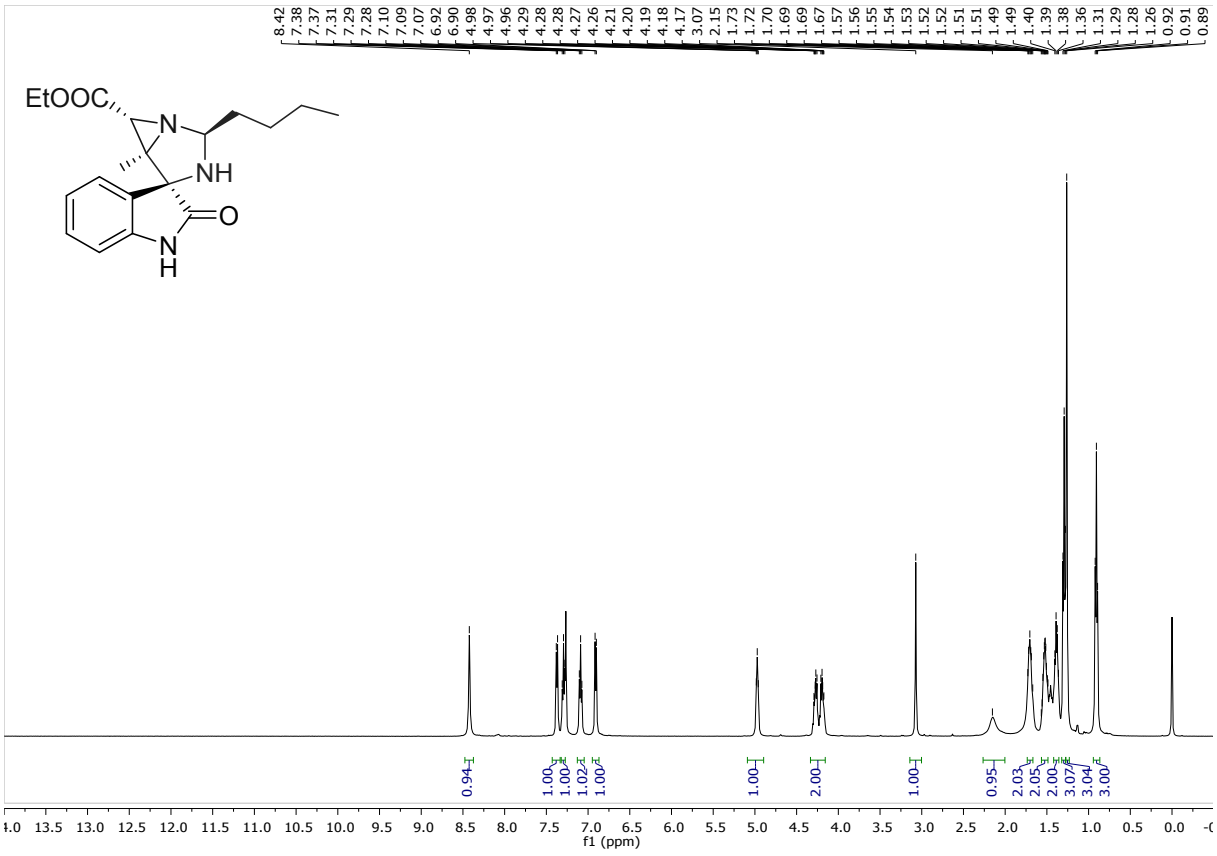


Figure S47. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-30a**

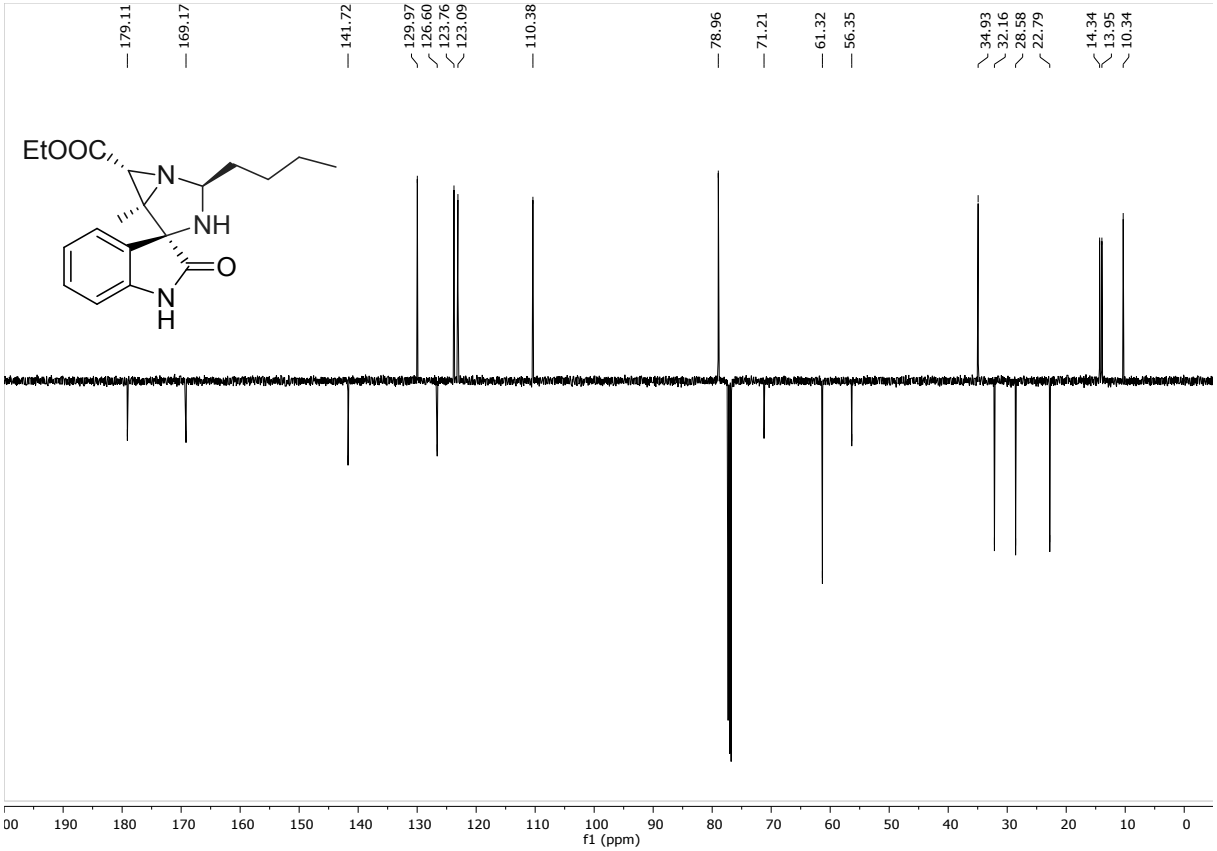


Figure S48. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-30a**

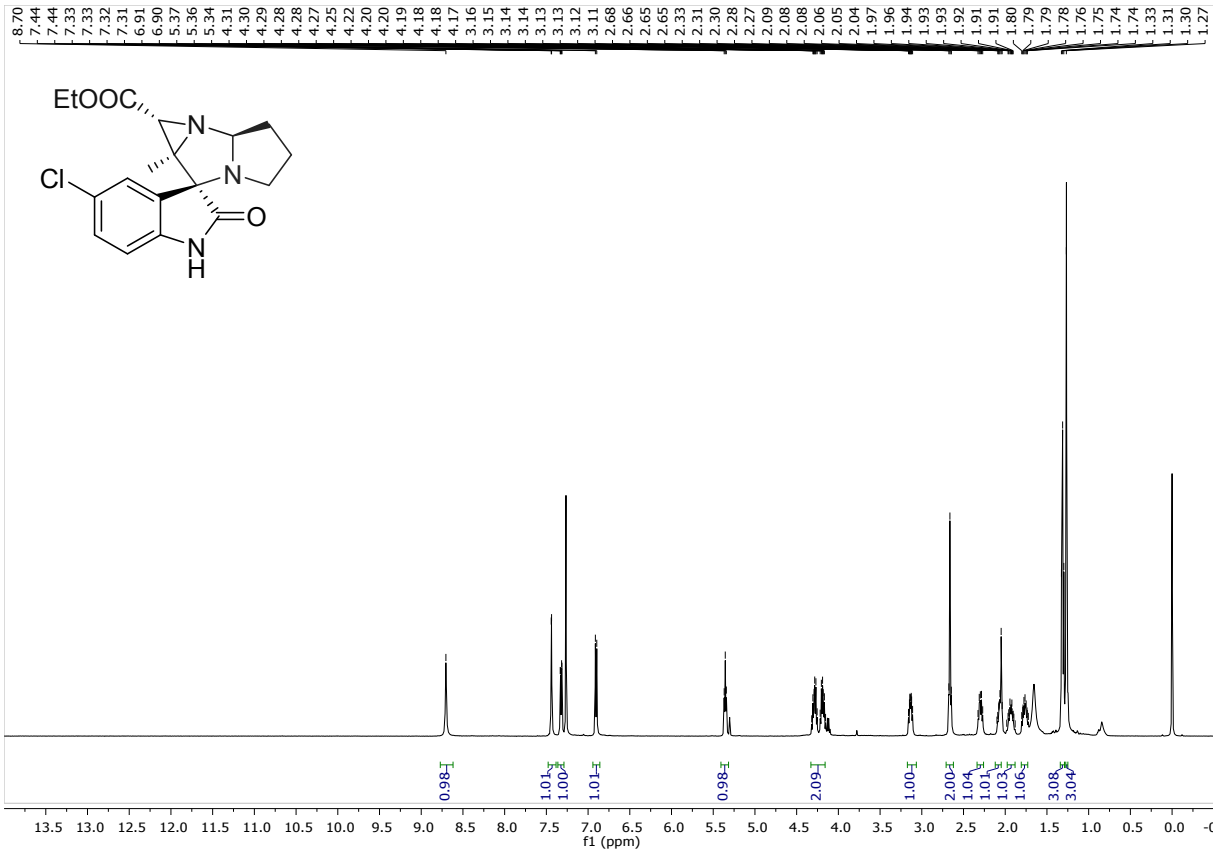


Figure S49. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-32a**

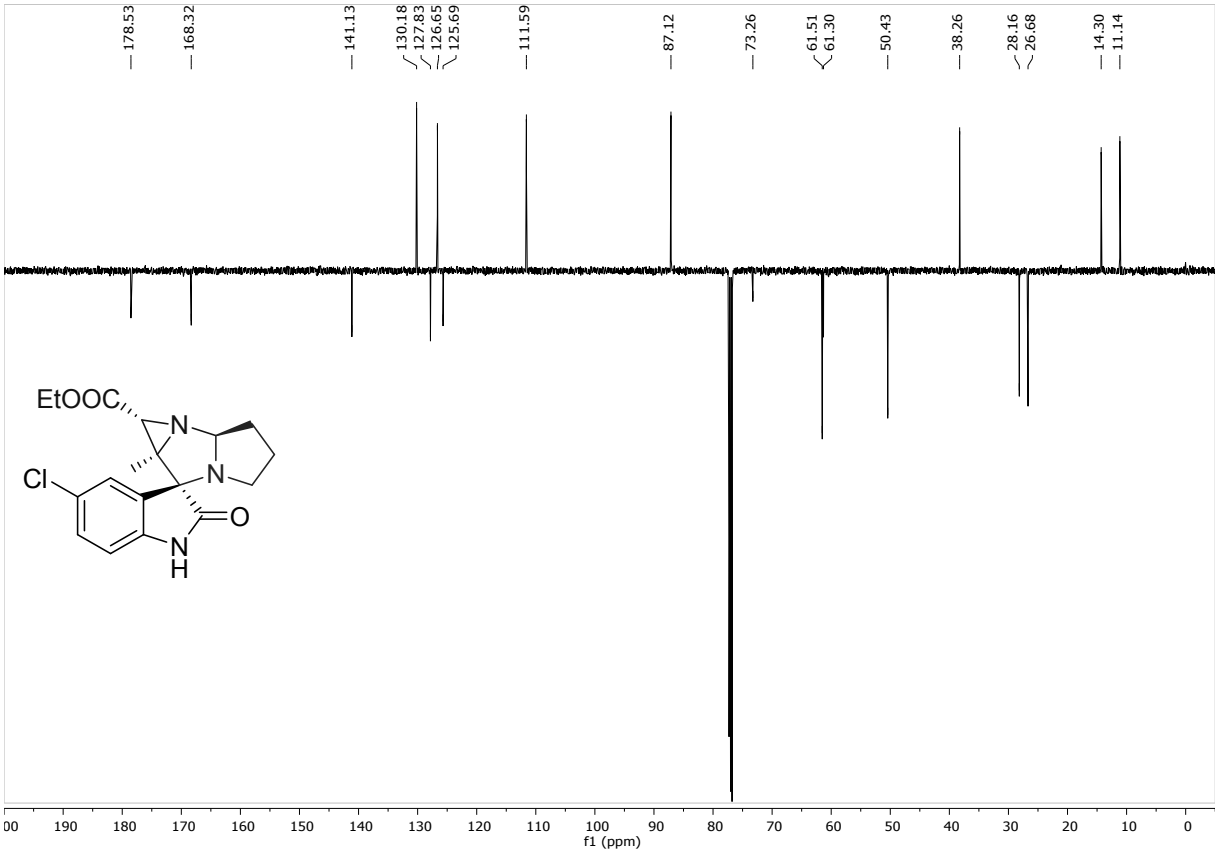


Figure S50. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-32a**

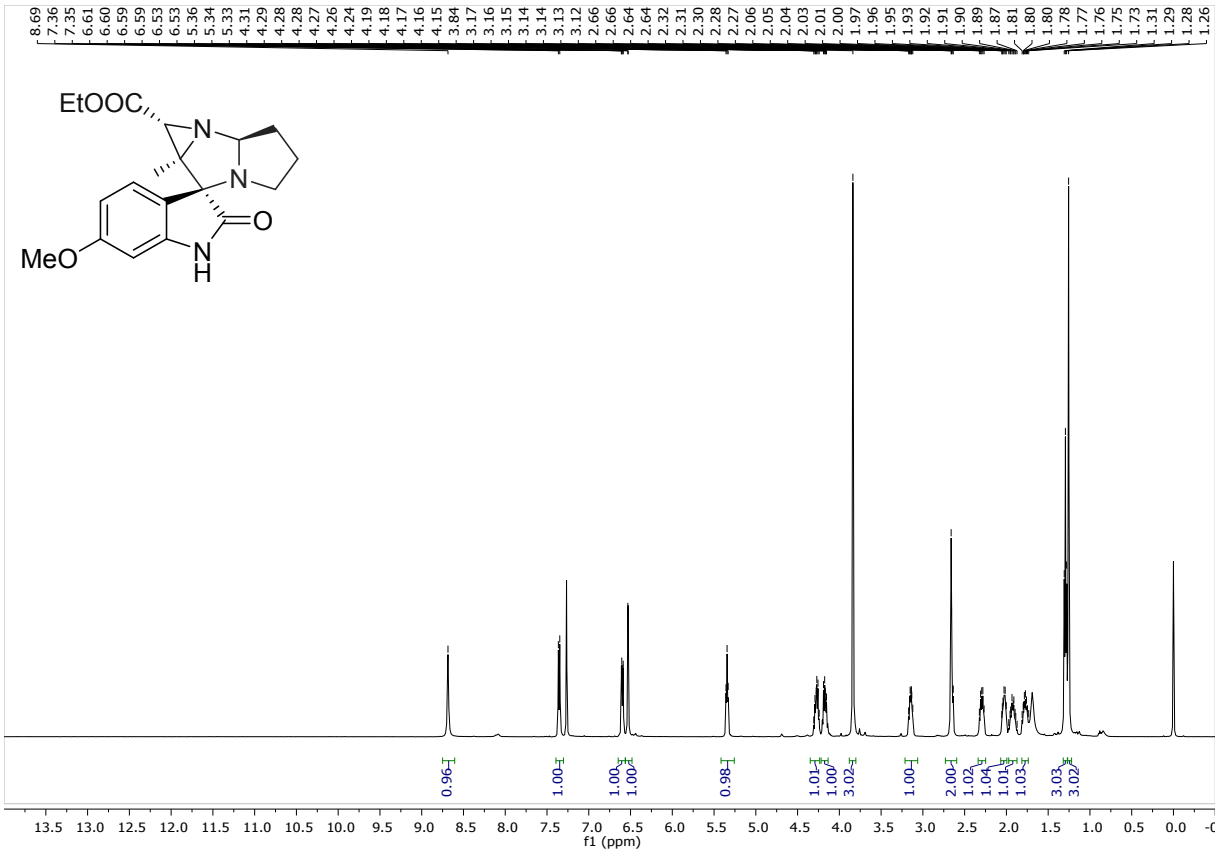


Figure S51. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-33a**

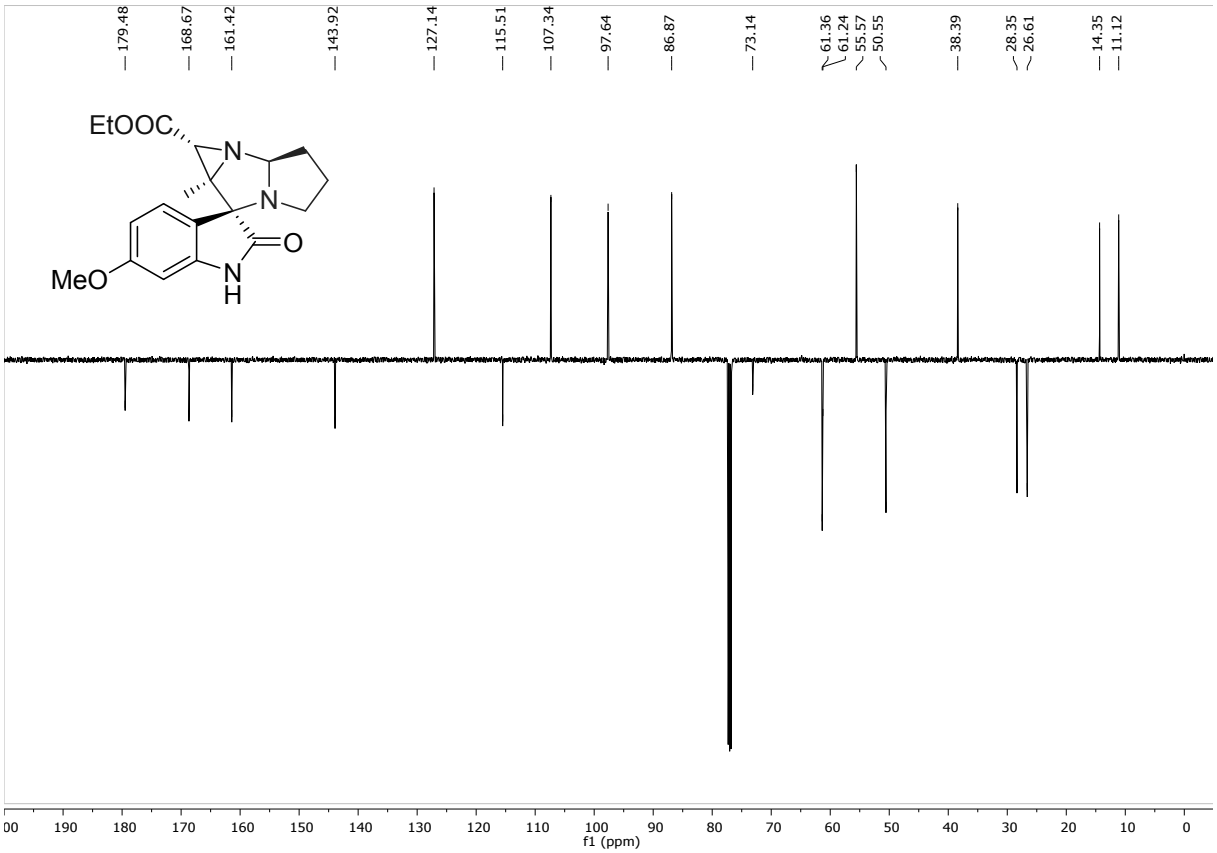


Figure S52. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-33a**

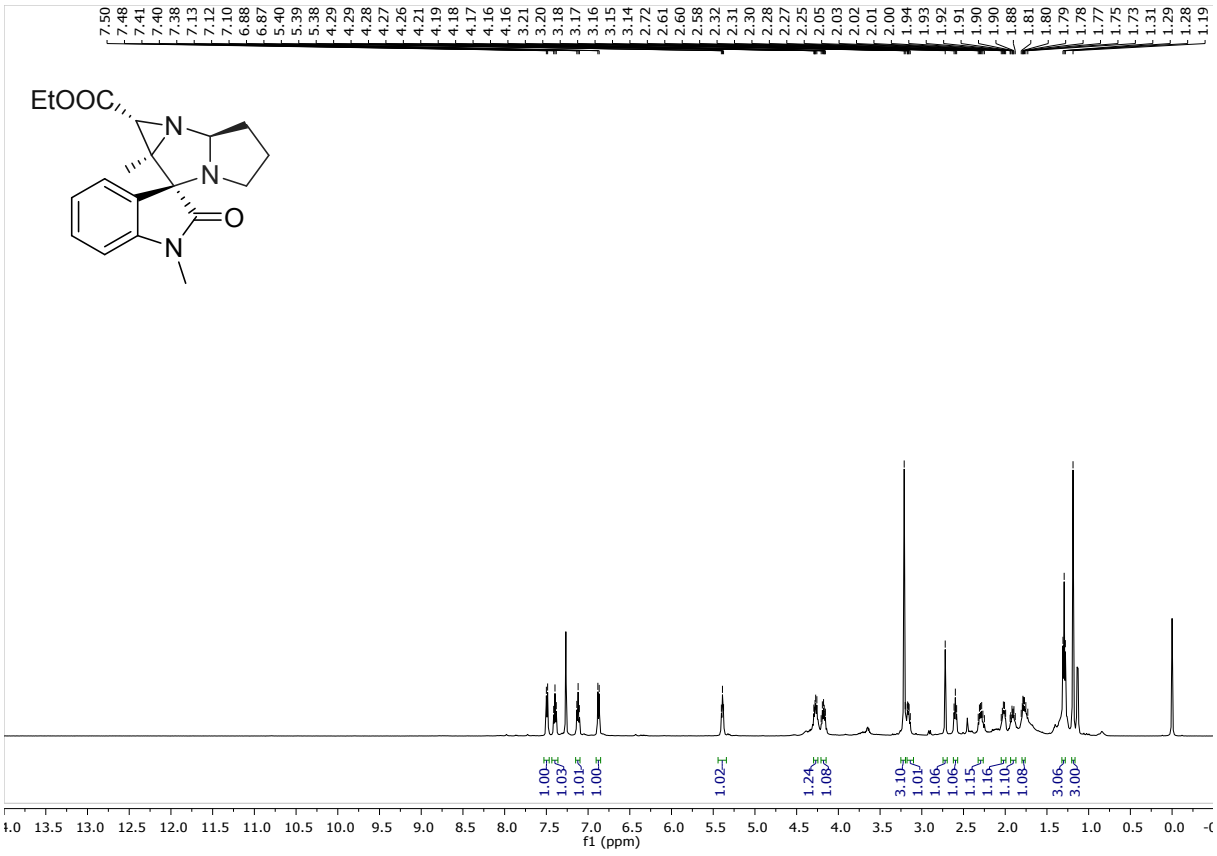


Figure S53. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-34a**

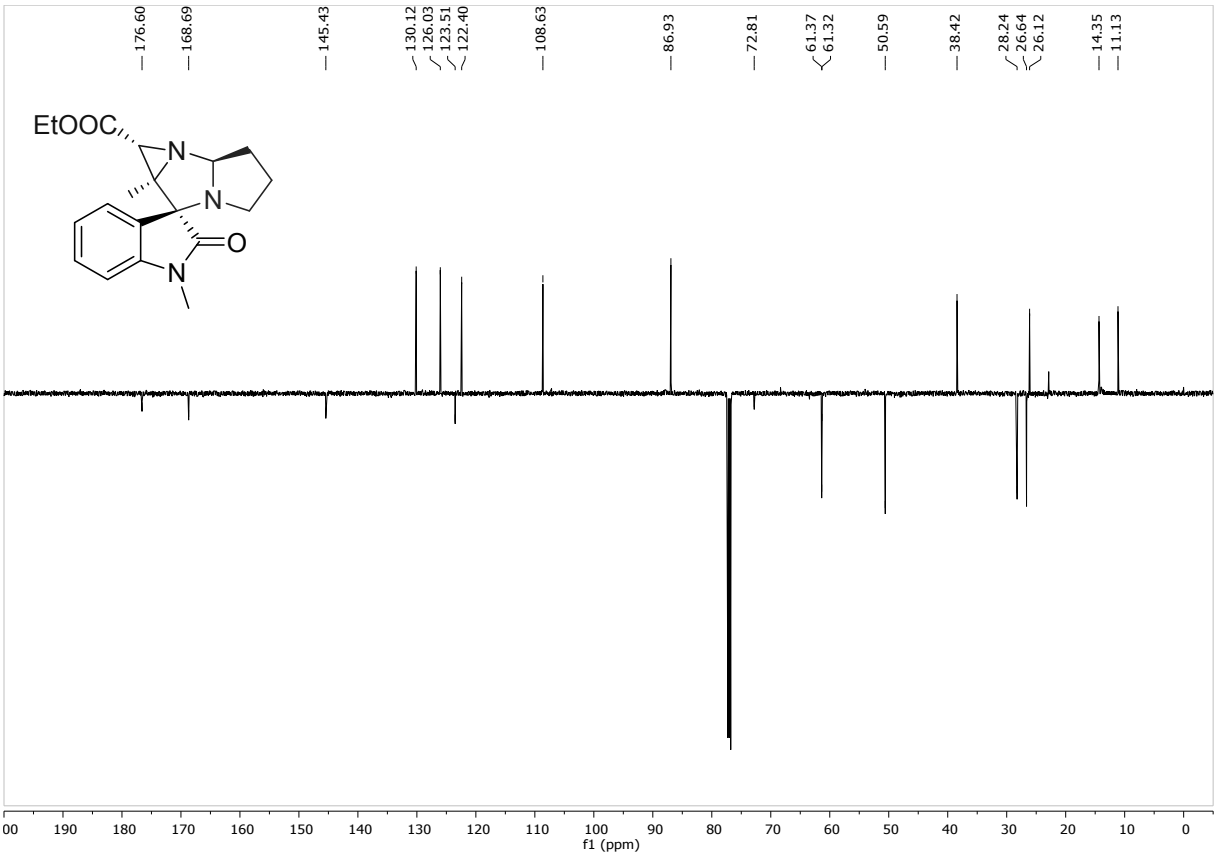


Figure S54. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-34a**

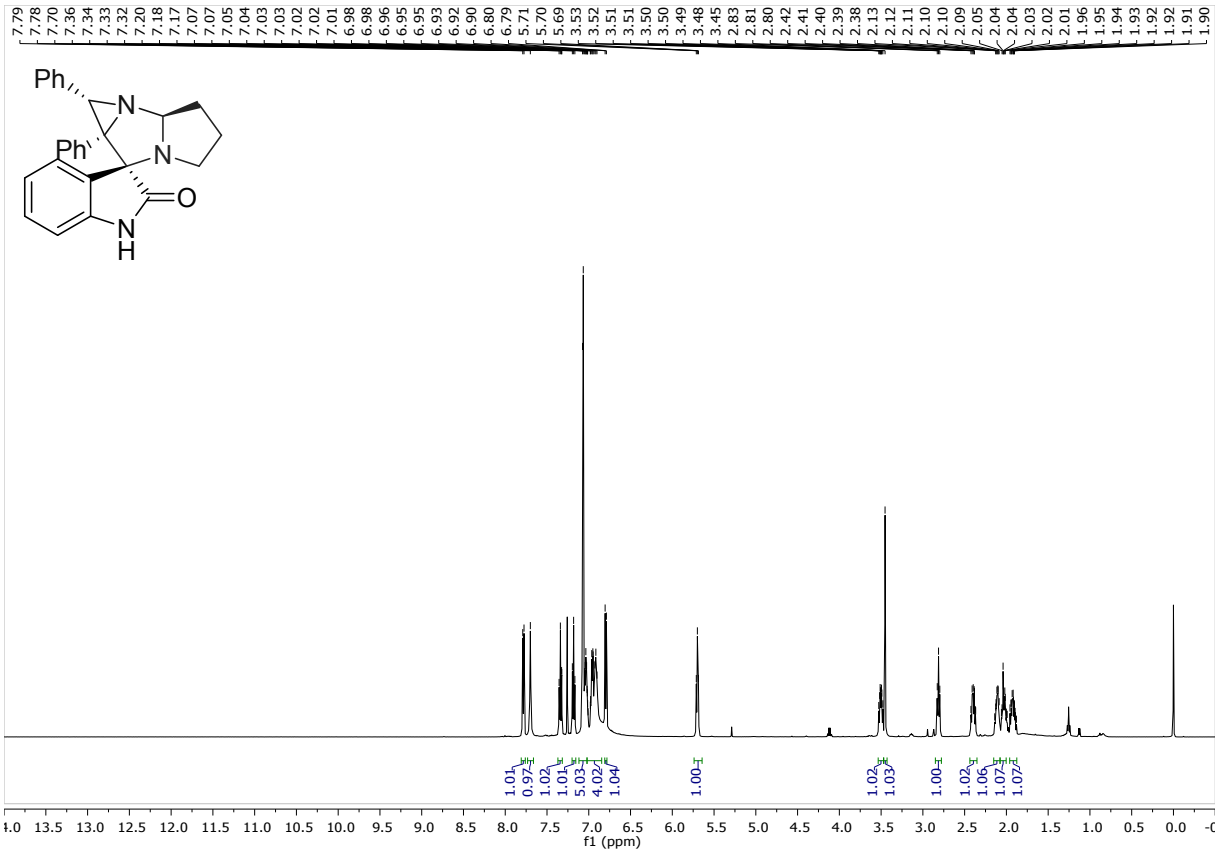


Figure S55. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-35a**

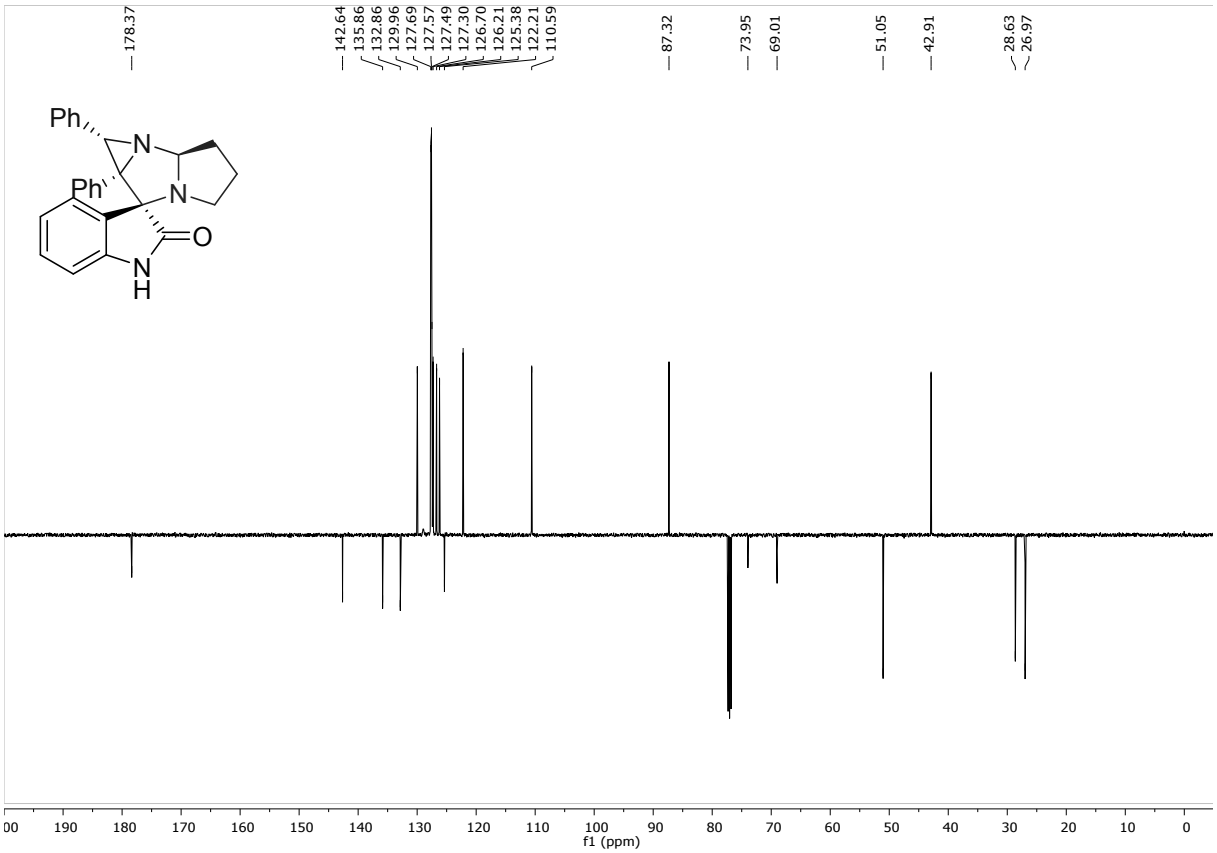


Figure S56. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-35a**

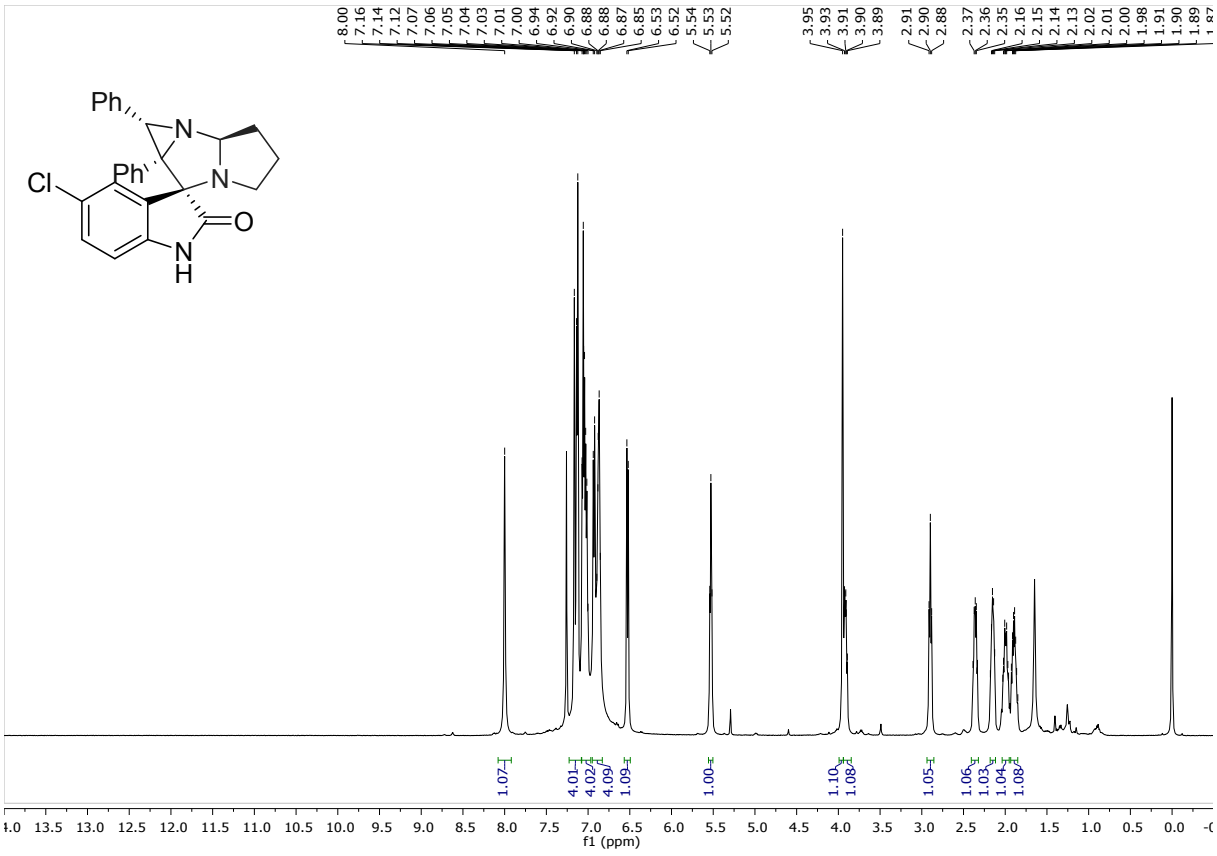


Figure S57. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-36a**

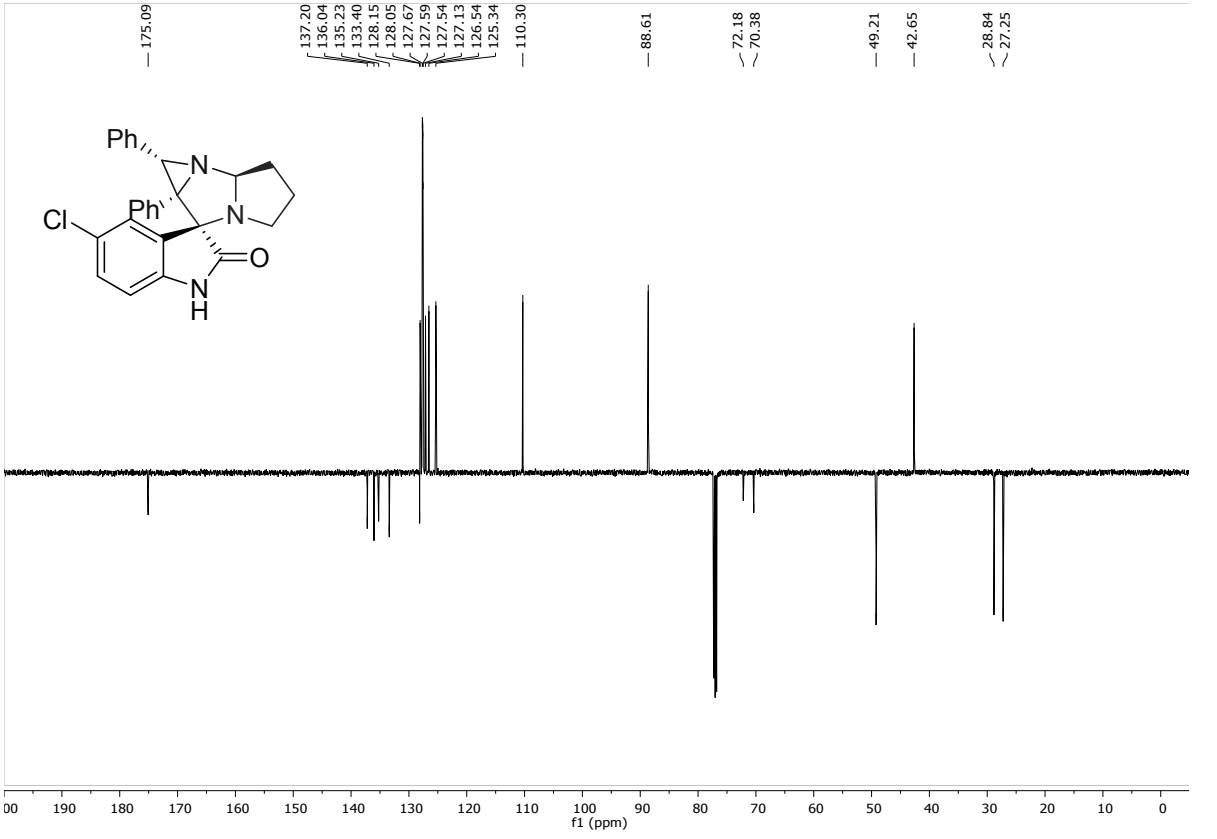


Figure S58. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-36a**

3. 1D and 2D NMR specra of compounds (±)-4a and (±)-4b

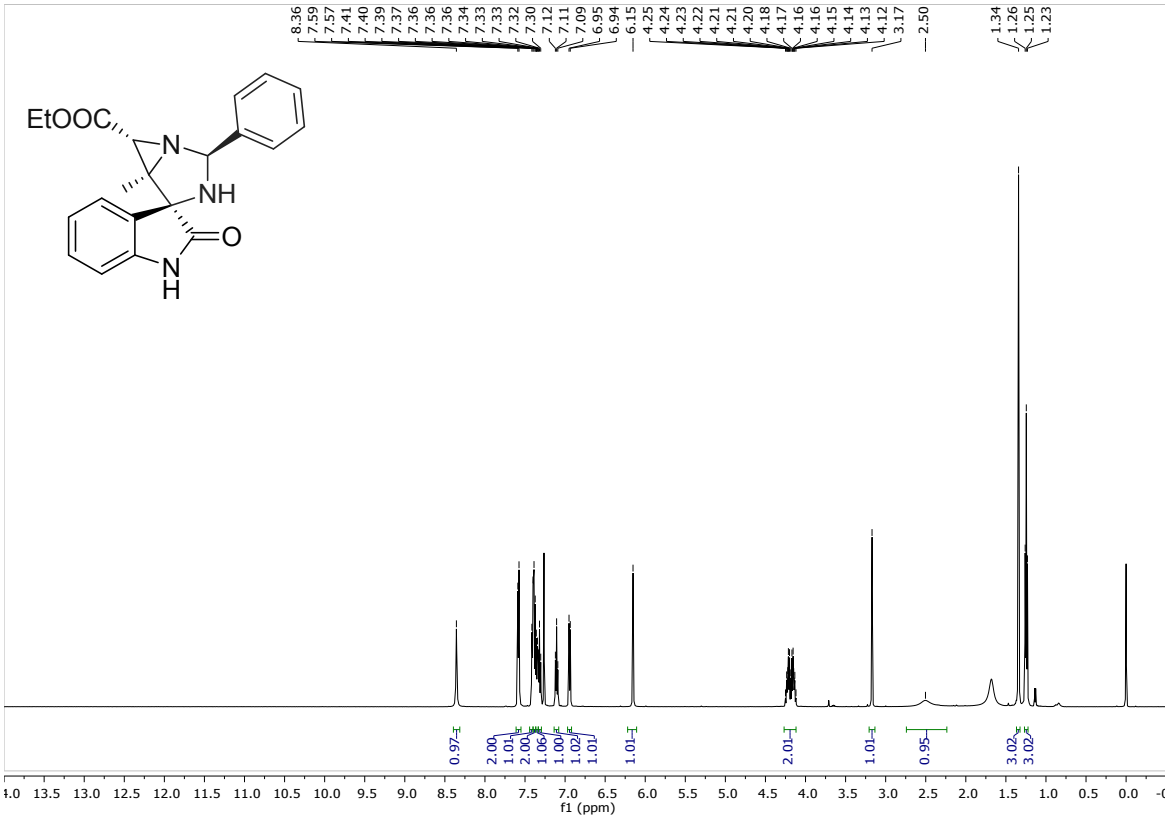


Figure S59. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the compound **(±)-4a**

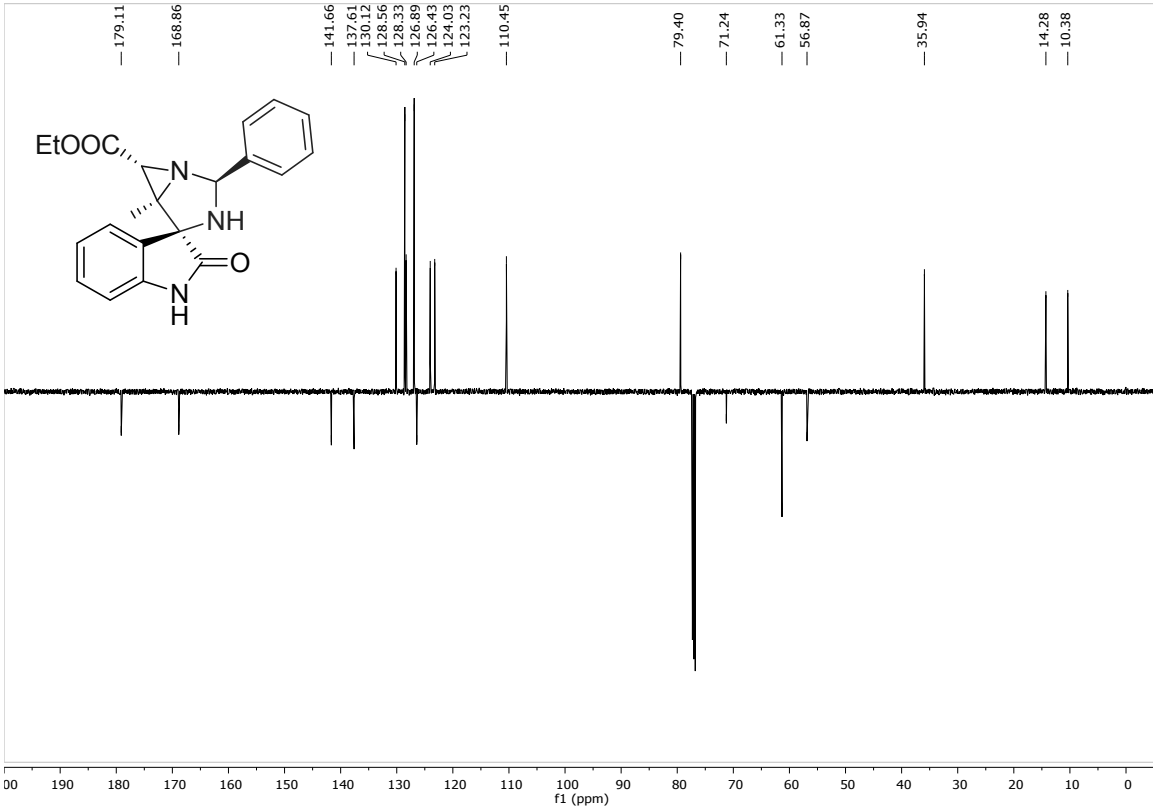


Figure S60. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of the compound **(±)-4a**

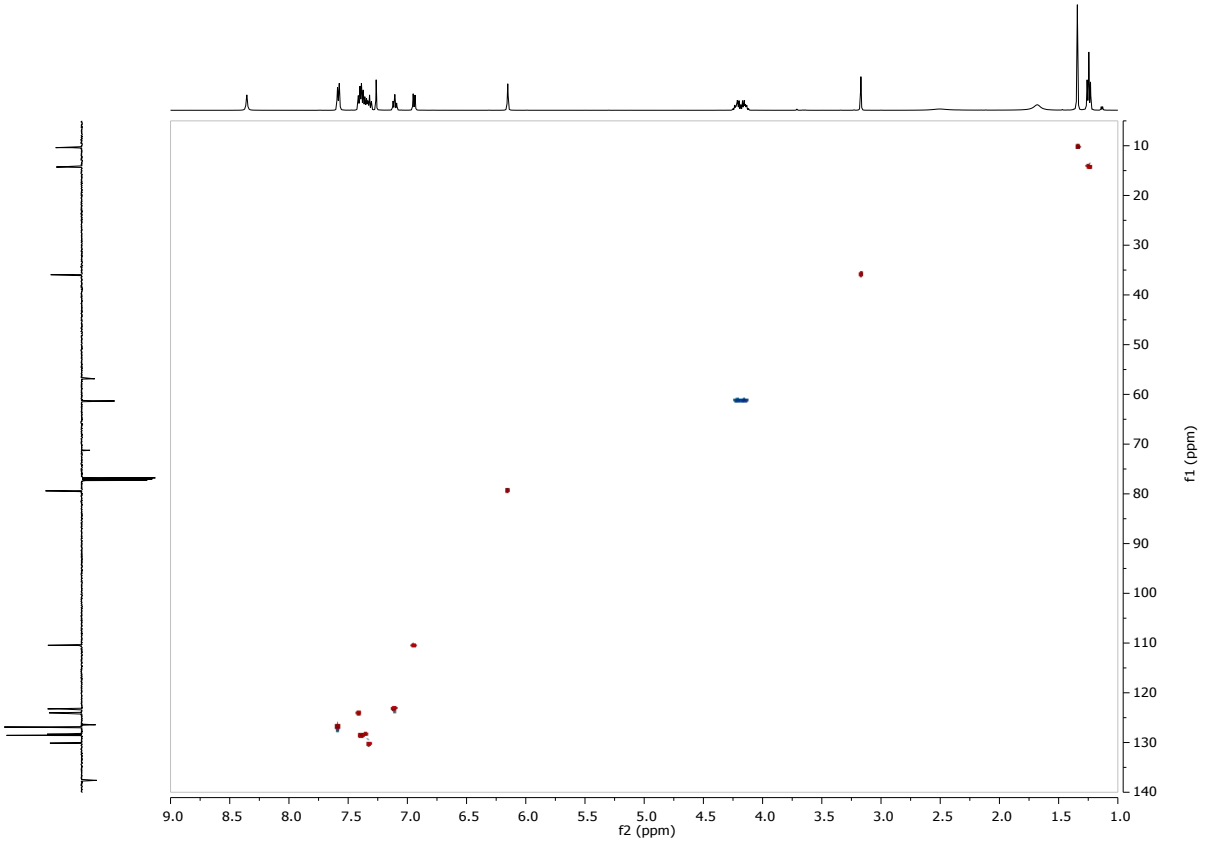


Figure S61. HSQC spectrum of the compound **(±)-4a** in $CDCl_3$

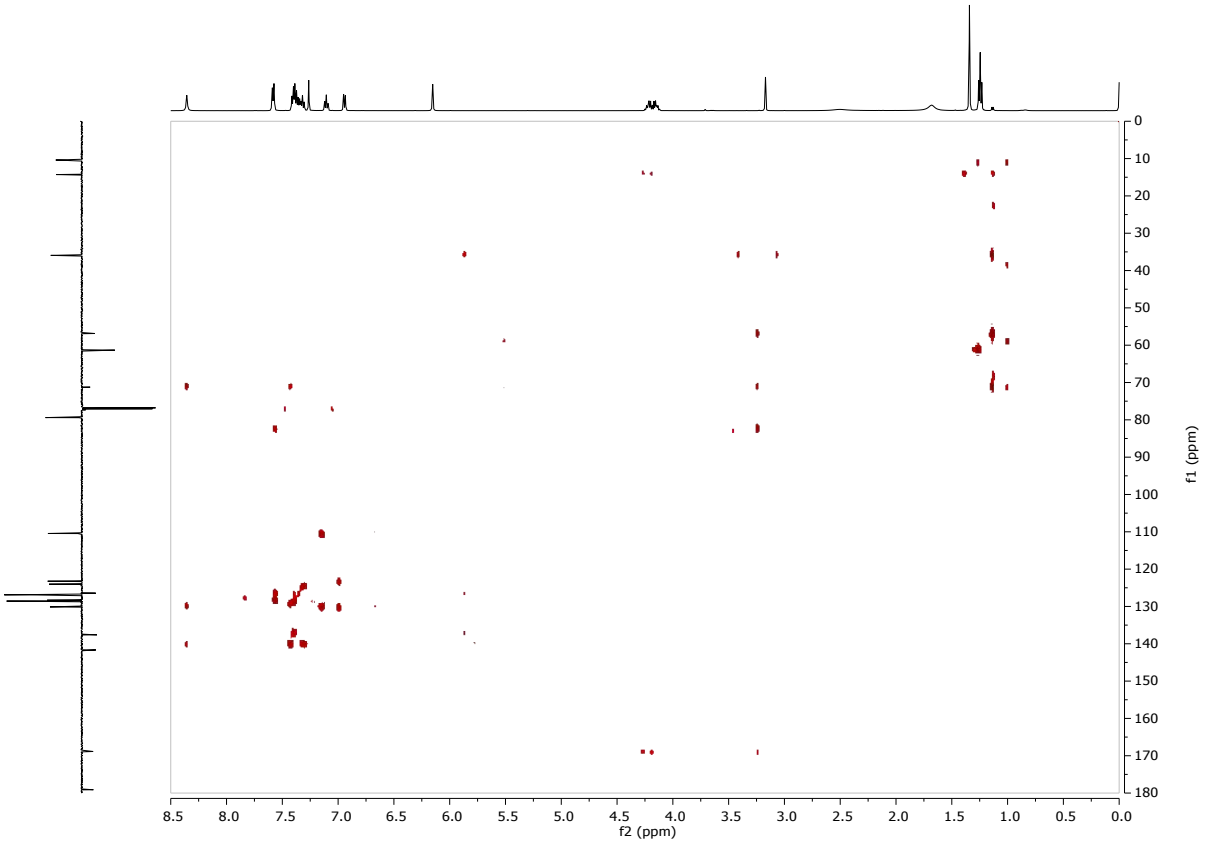


Figure S62. HMBC spectrum of the compound **(±)-4a** in $CDCl_3$

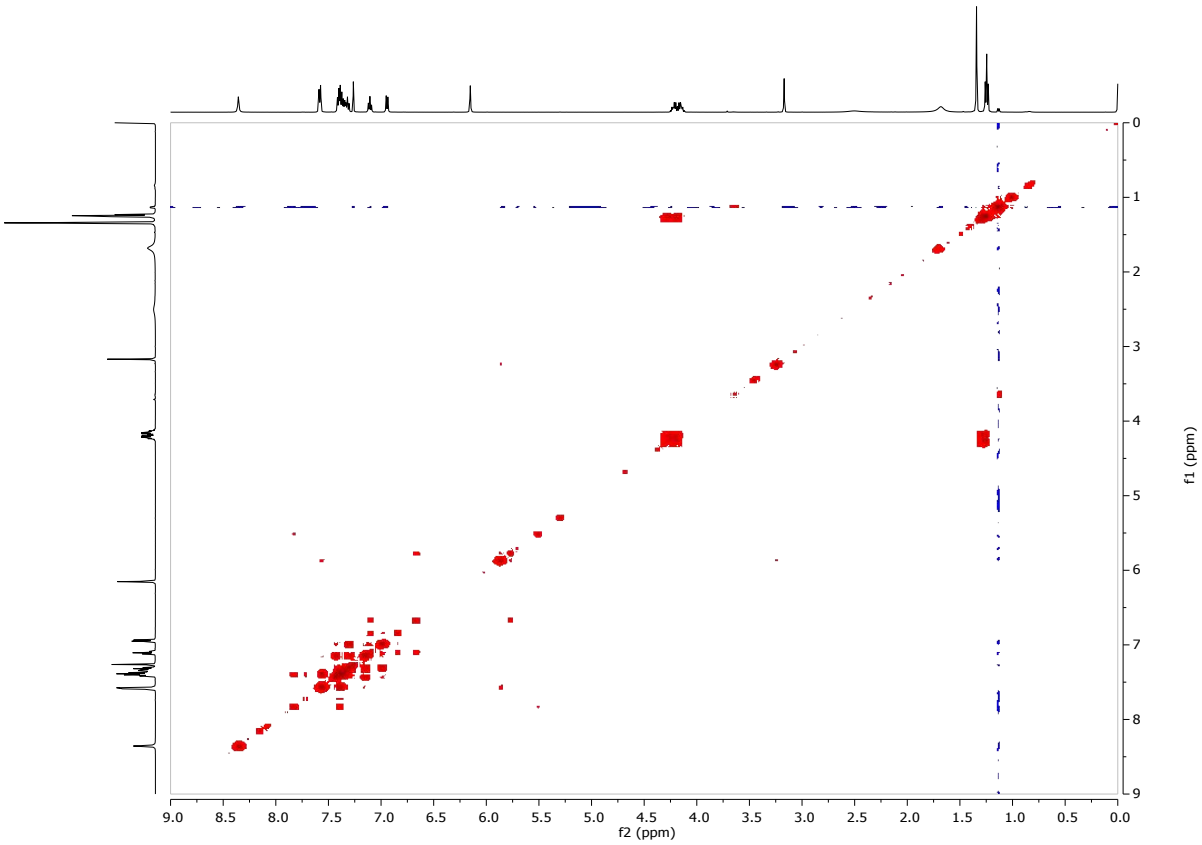


Figure S63. COSY spectrum of the compound **(±)-4a** in $CDCl_3$

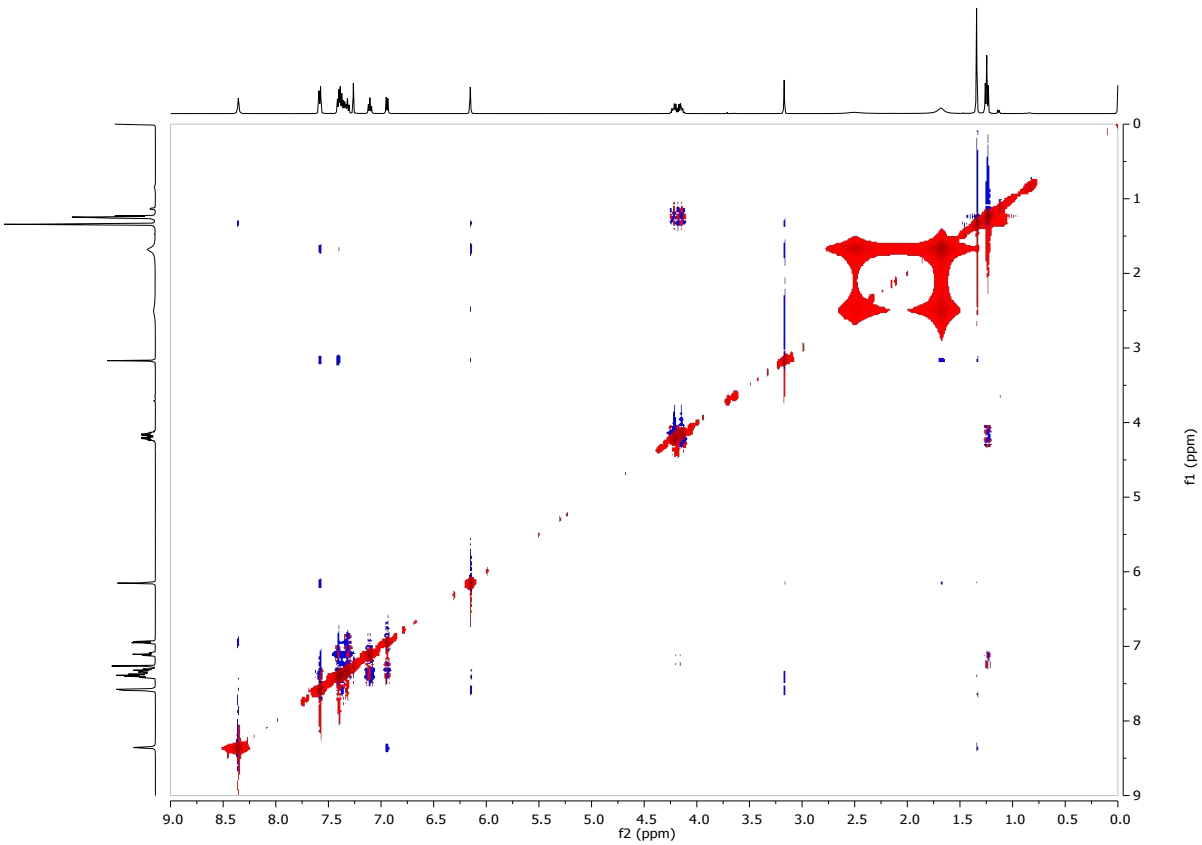


Figure S64. COSY spectrum of the compound **(±)-4a** in $CDCl_3$

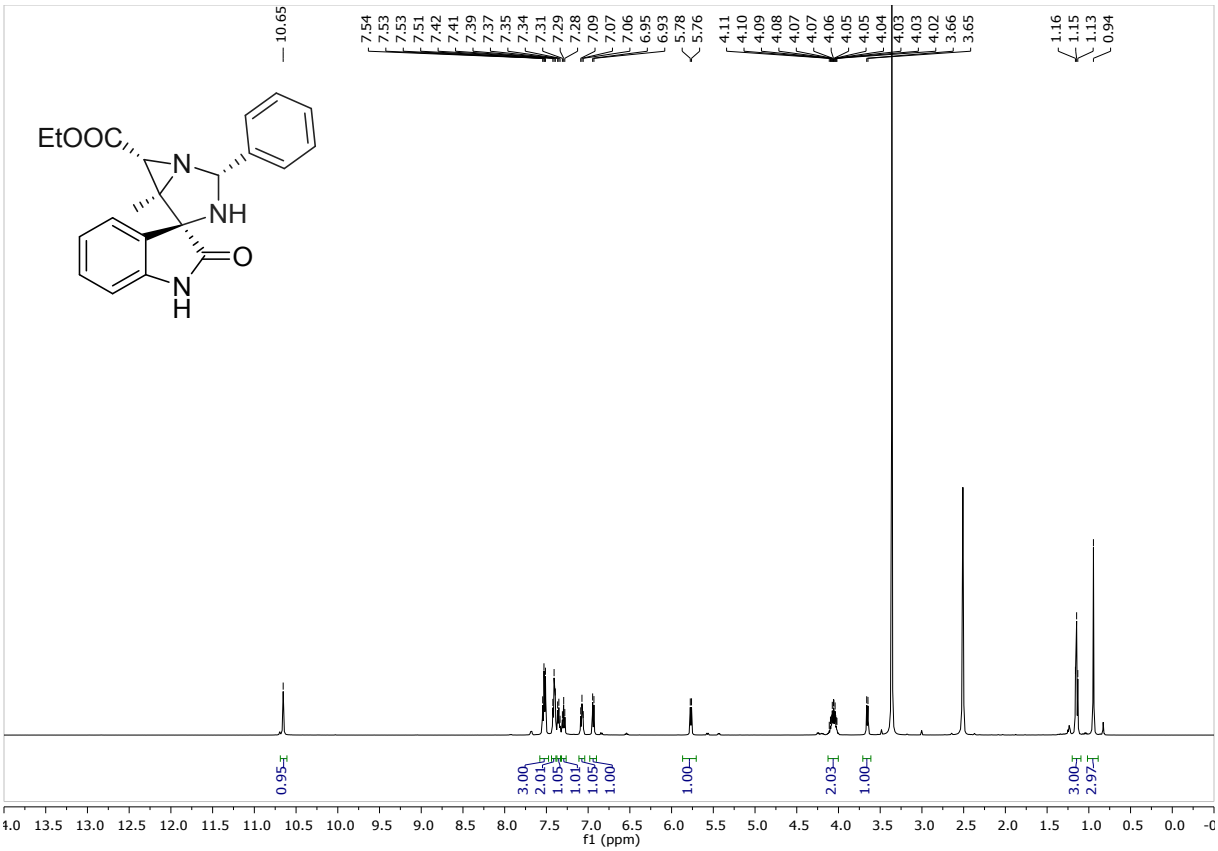


Figure S65. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-4b**

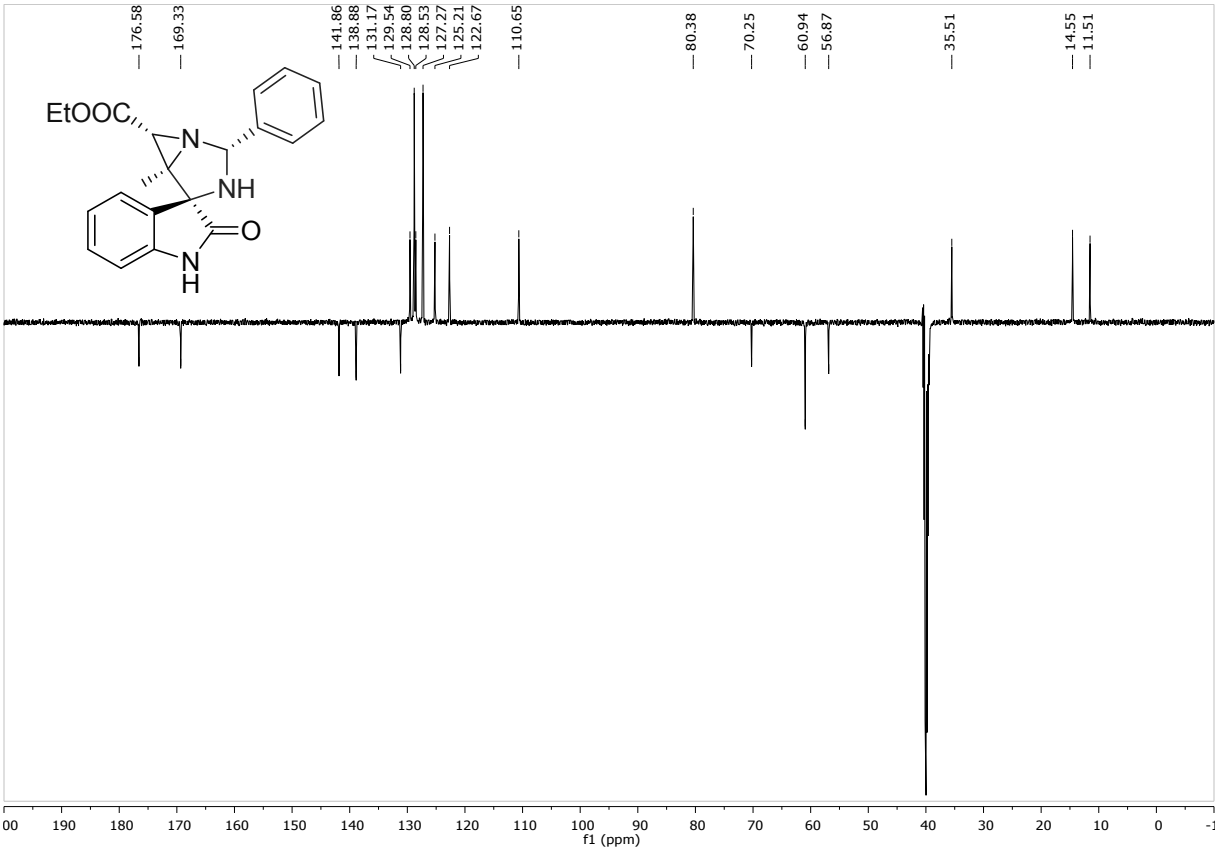


Figure S66. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-4b**

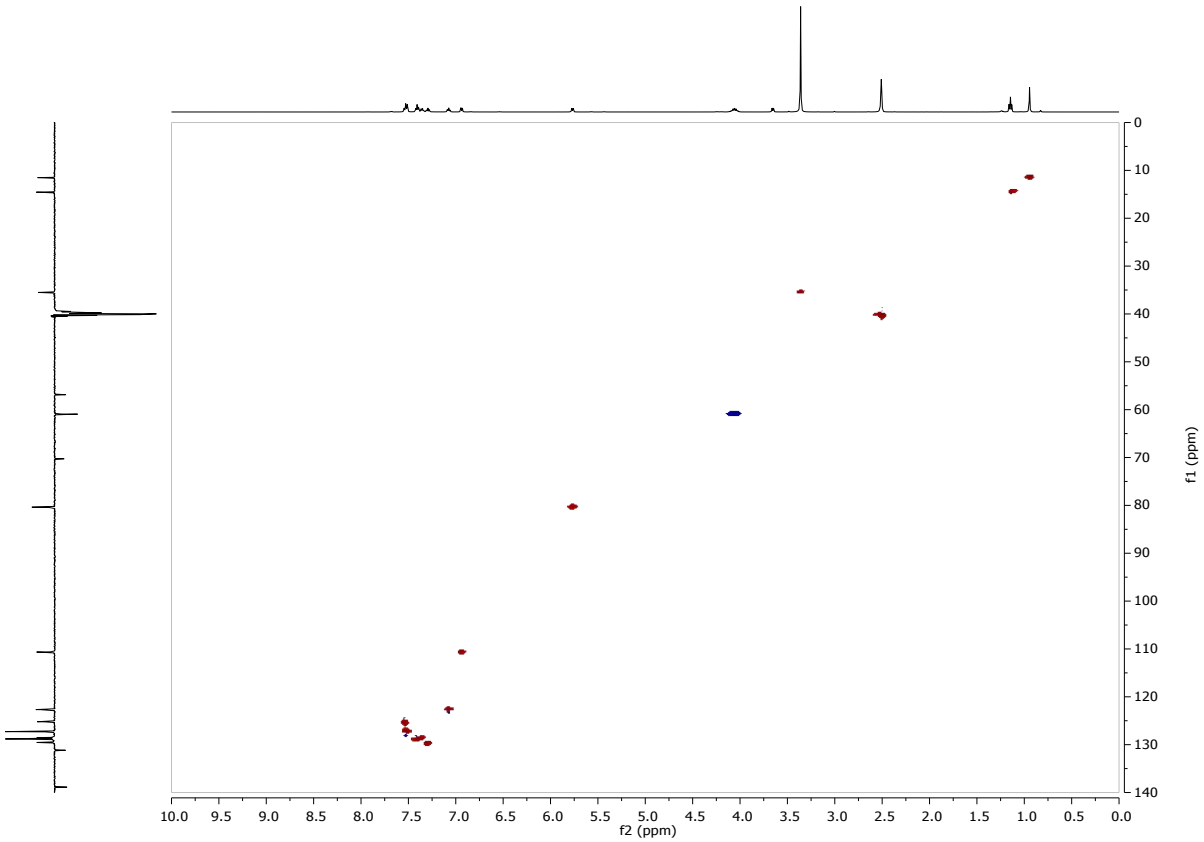


Figure S67. HSQC spectrum of the compound **(±)-4b** in DMSO-d_6

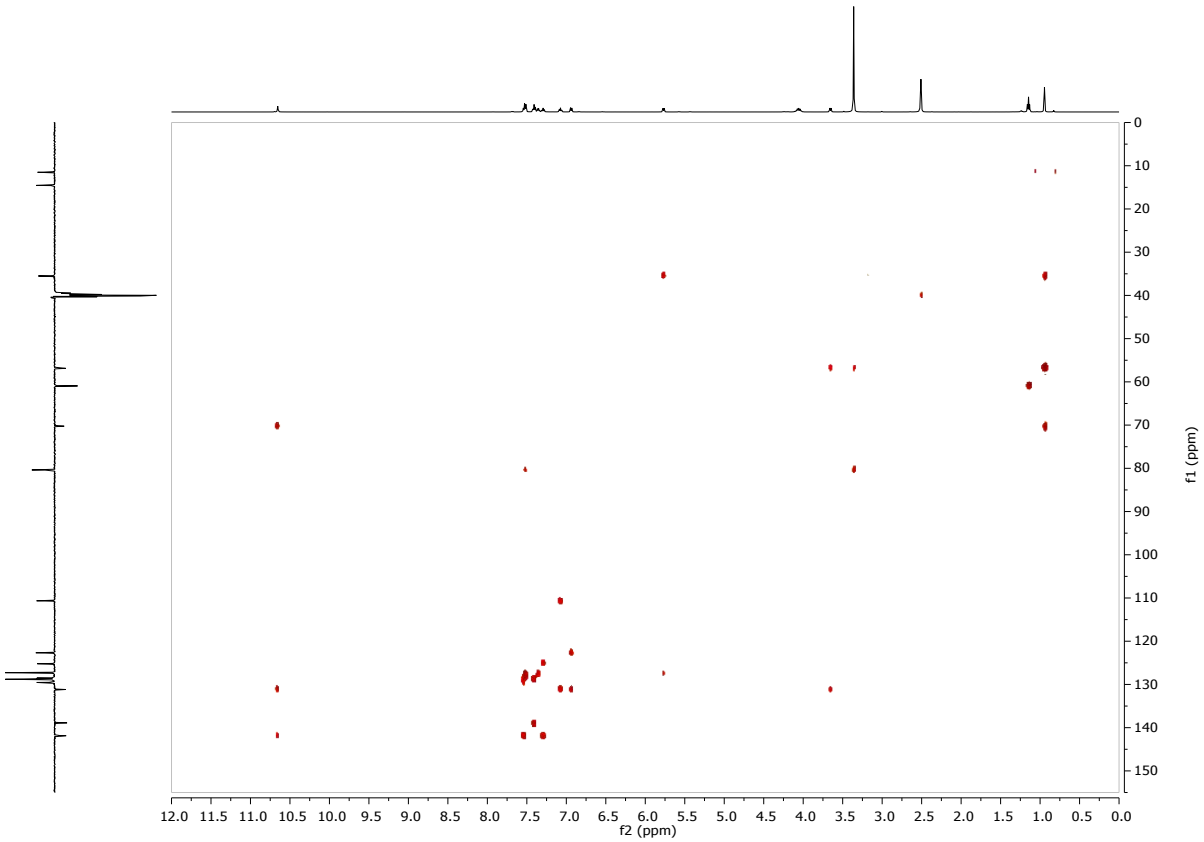


Figure S68. HMBC spectrum of the compound **(±)-4b** in DMSO-d_6

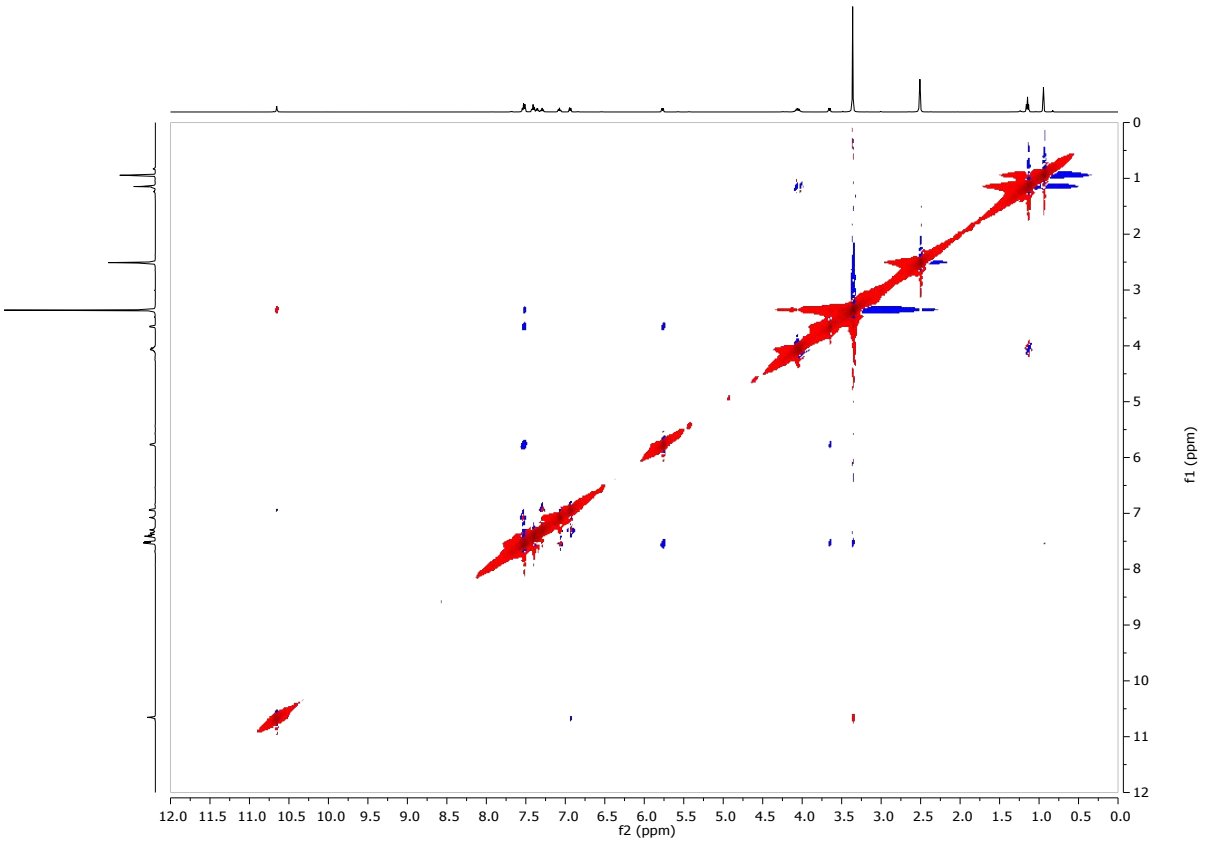


Figure S69. NOESY spectrum of the compound **(±)-4b** in DMSO-d_6

4. 1D and 2D NMR specra of compound (±)-12a

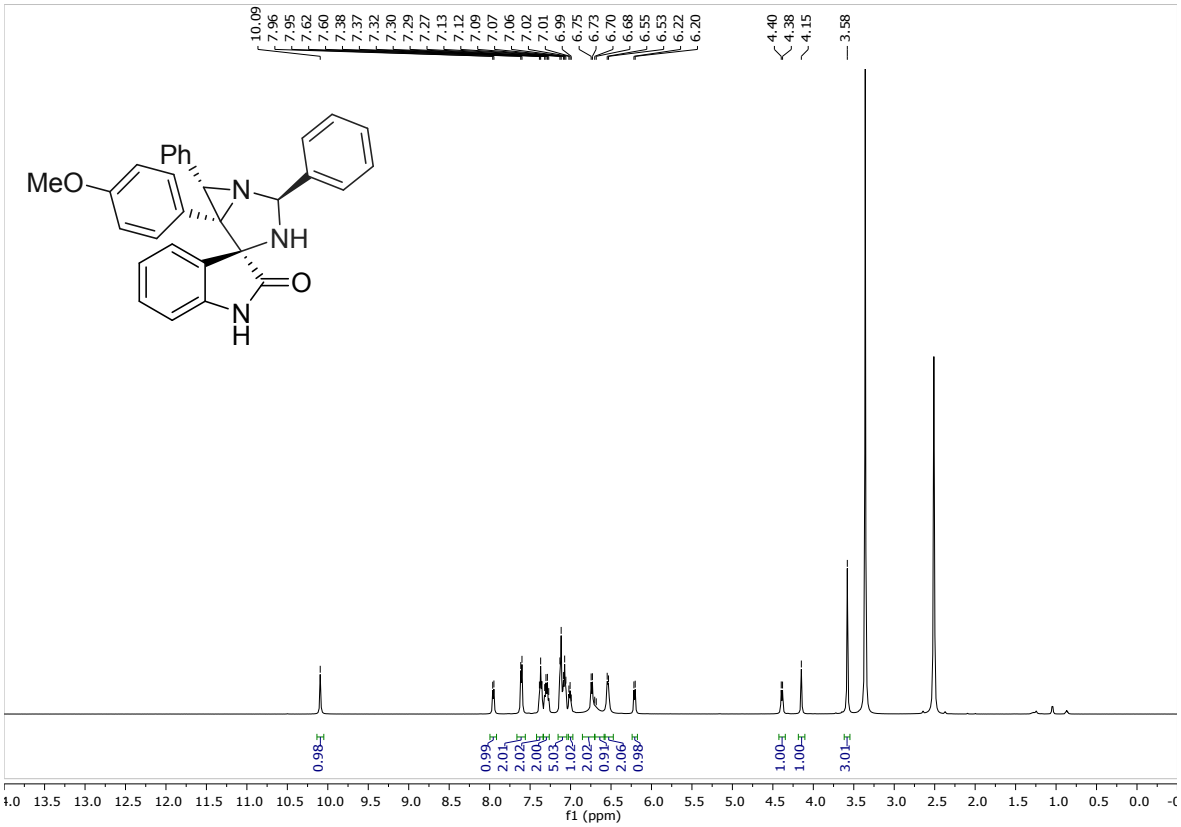


Figure S70. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-12a**

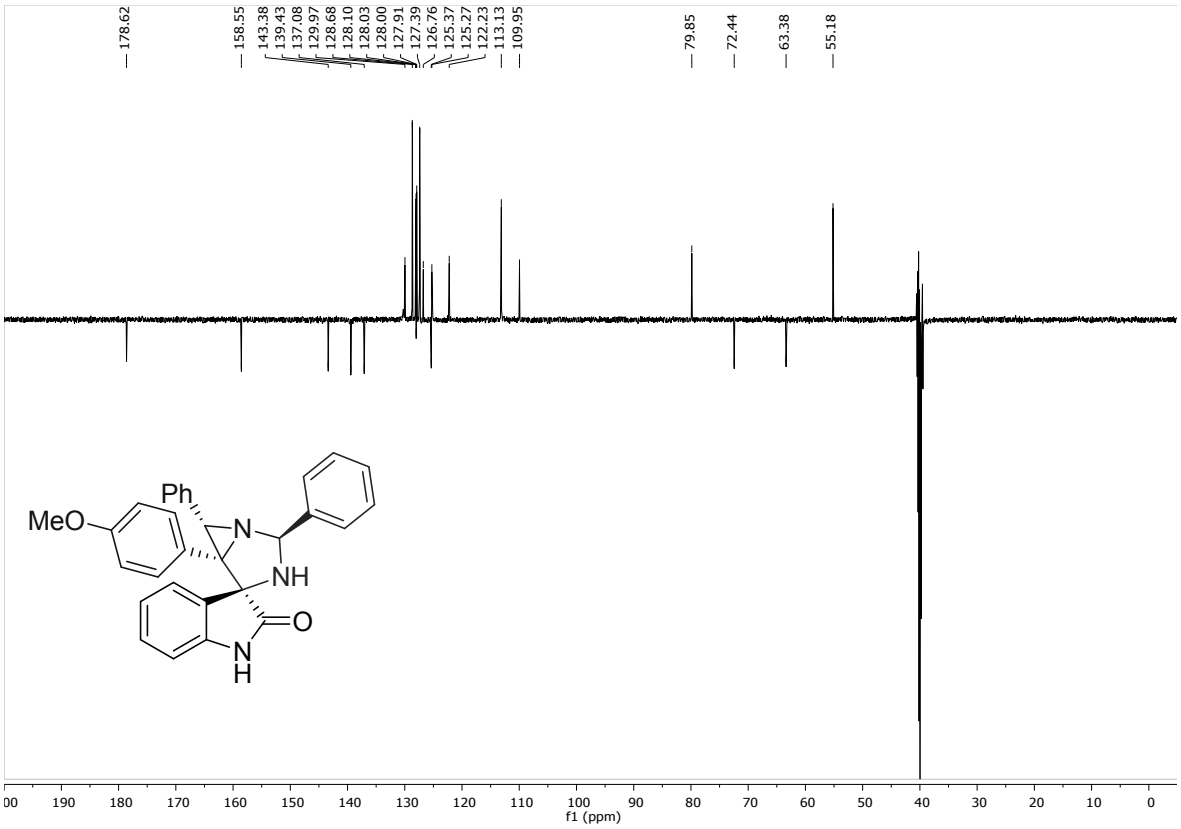


Figure S71. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-12a**

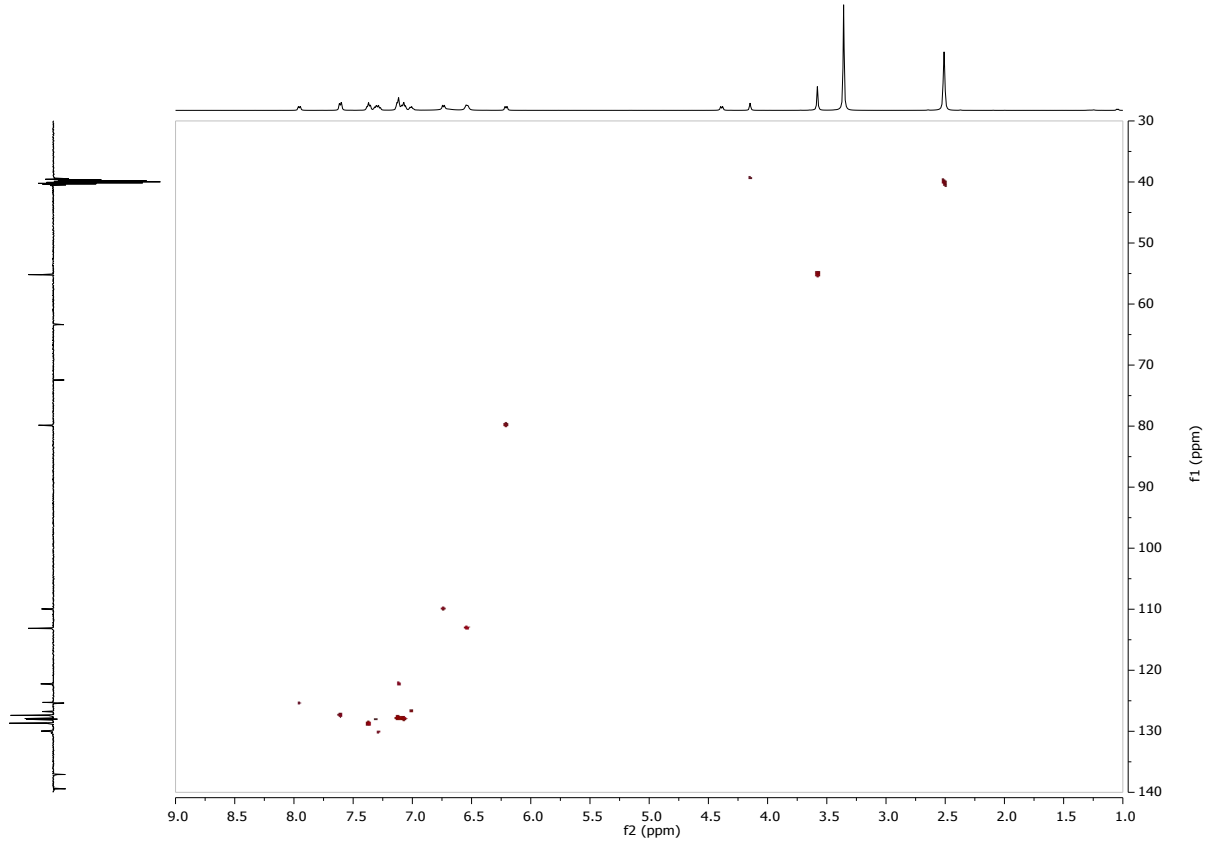


Figure S72. HSQC spectrum of the compound **(±)-12a** in DMSO-d_6

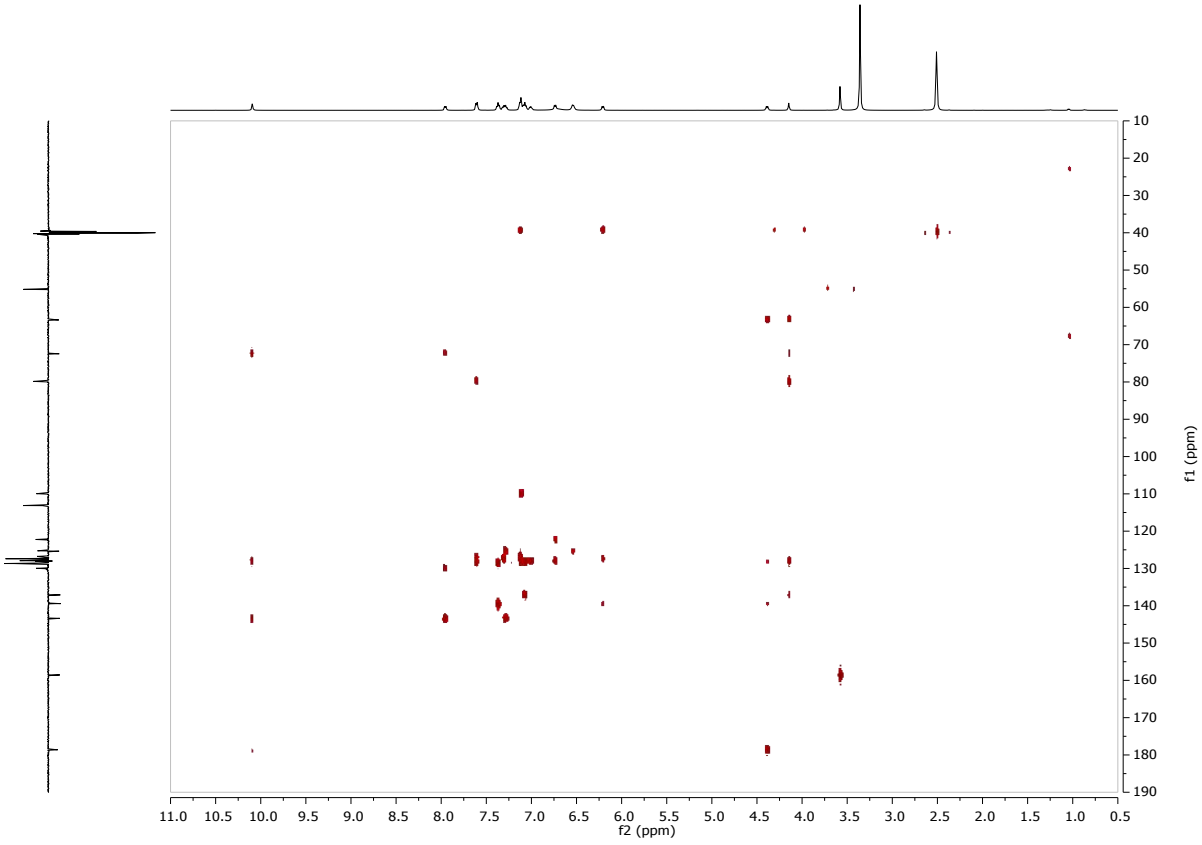


Figure S73. HMBC spectrum of the compound **(±)-12a** in DMSO-d_6

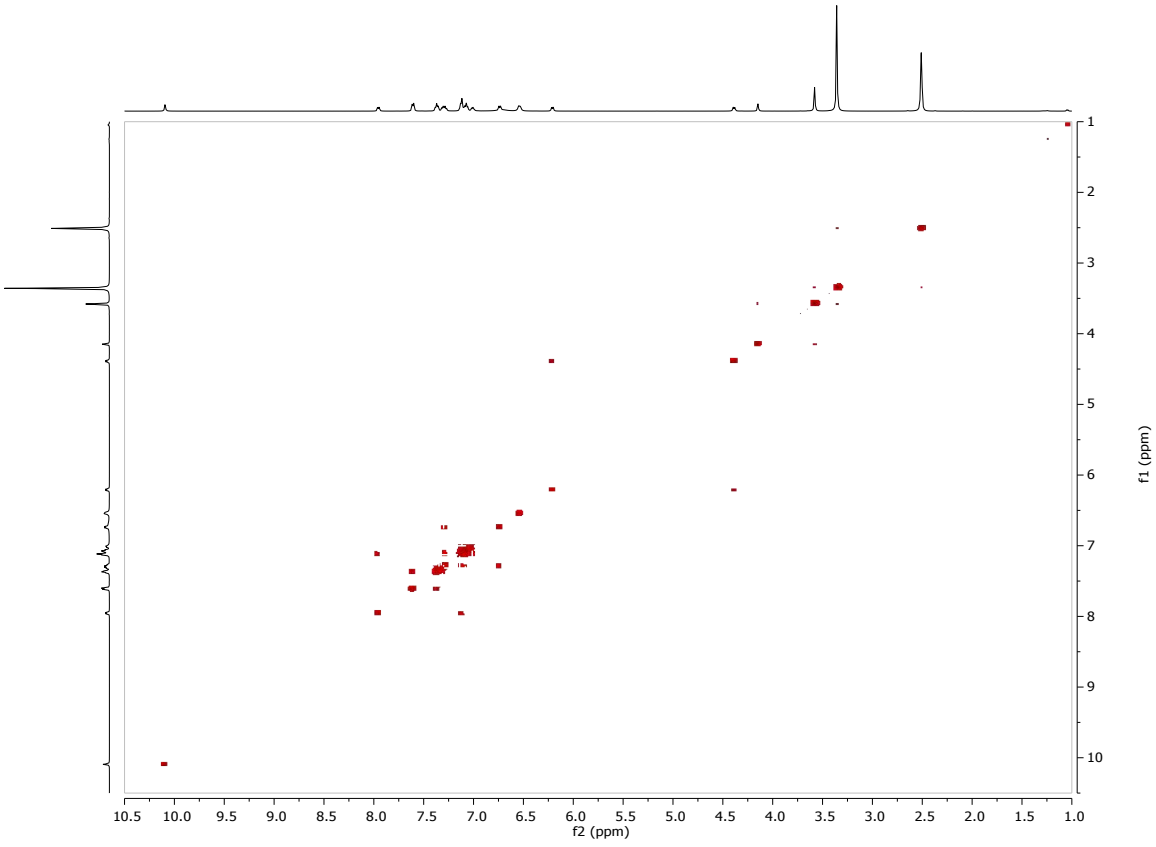


Figure S74. COSY spectrum of the compound **(±)-12a** in DMSO-d_6

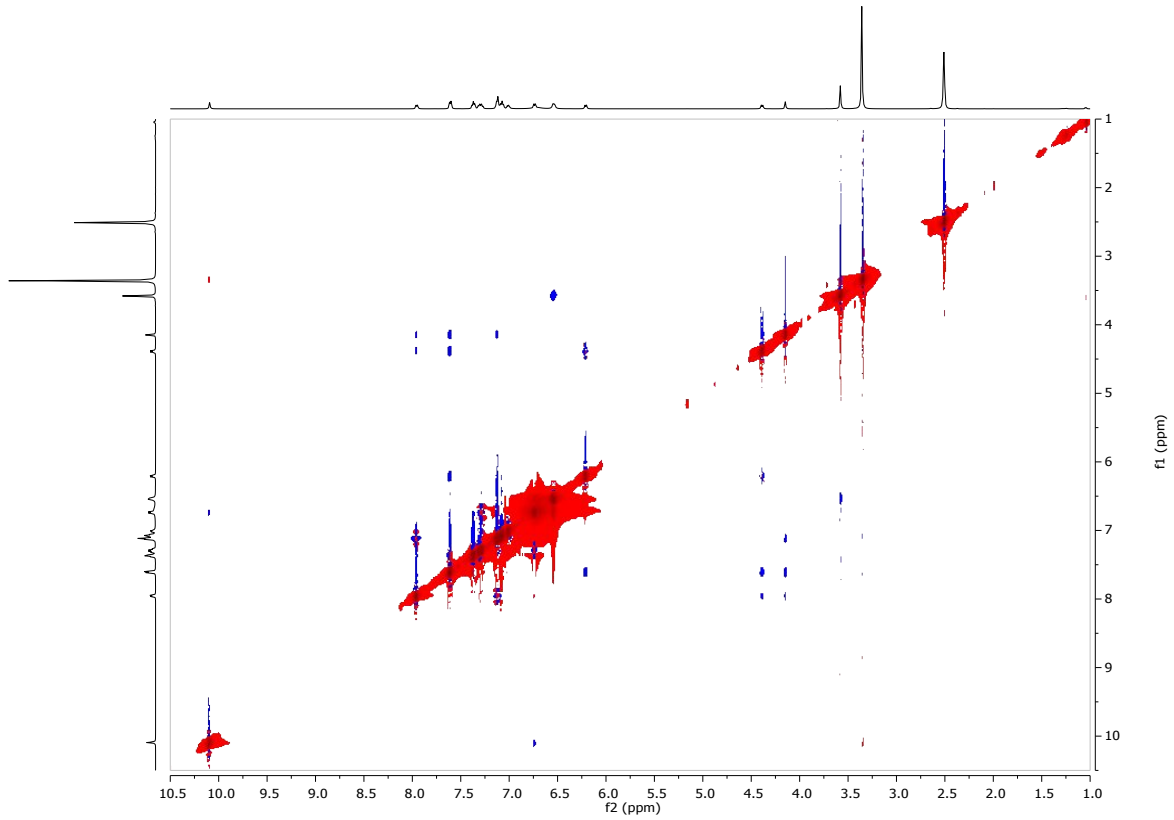


Figure S75. NOESY spectrum of the compound **(±)-12a** in DMSO-d_6

5. 1D and 2D NMR specra of compound (±)-17a

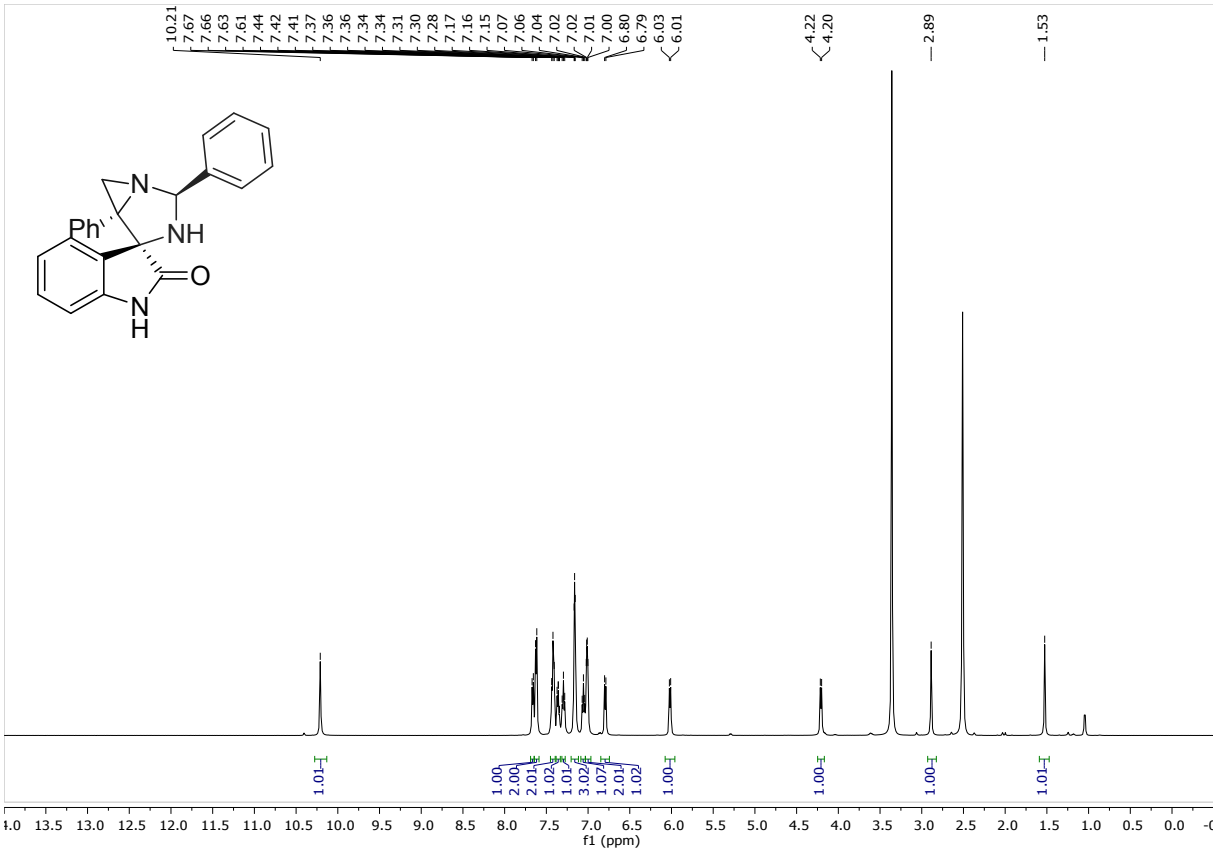


Figure S76. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-17a**

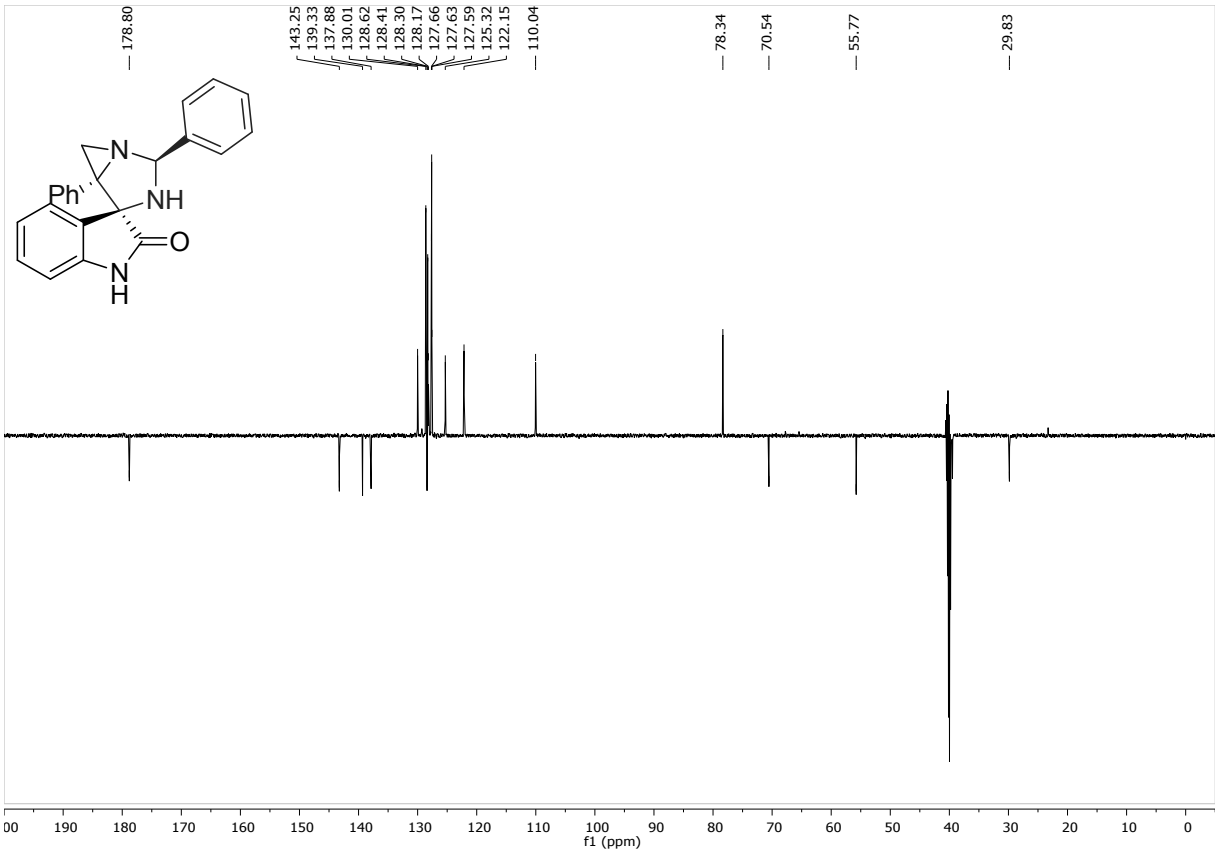


Figure S77. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-17a**

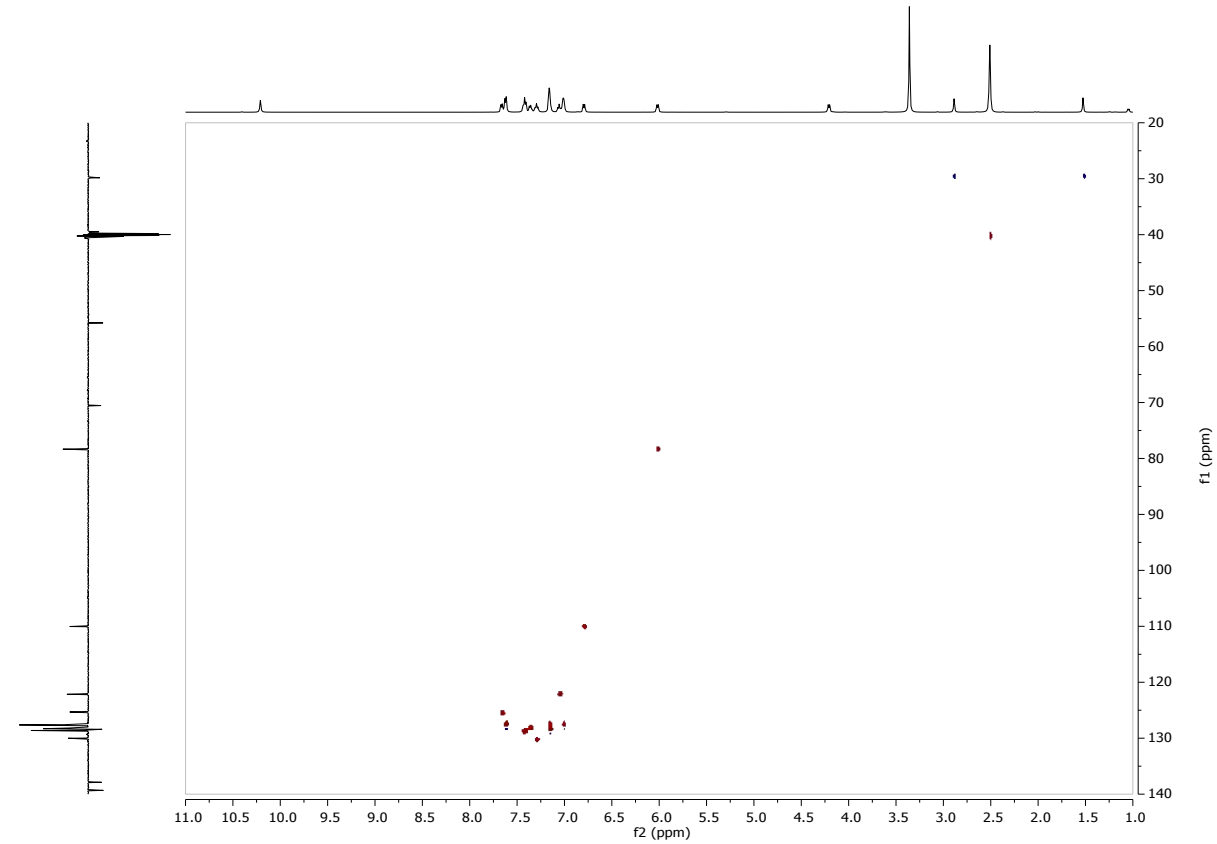


Figure S78. HSQC spectrum of the compound **(±)-17a** in DMSO-d_6

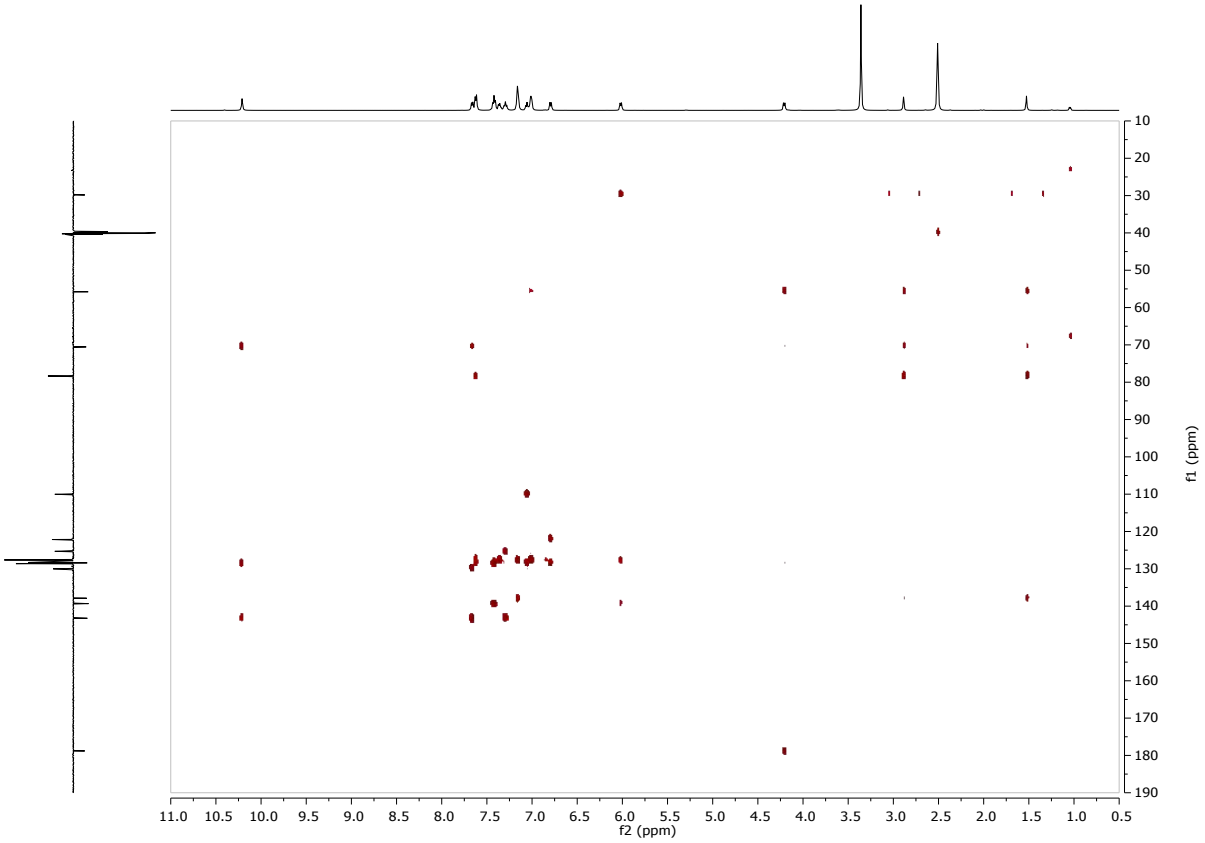


Figure S79. HMBC spectrum of the compound **(±)-17a** in DMSO-d_6

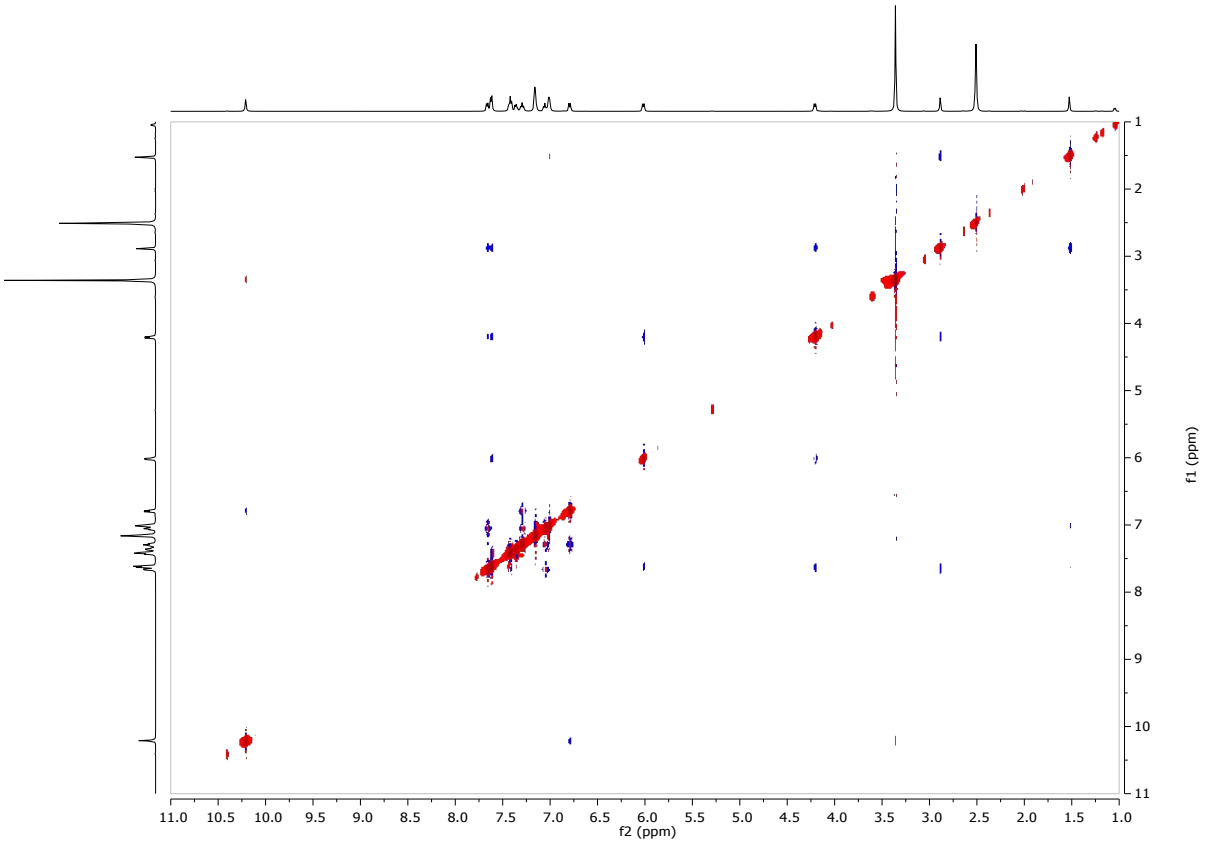


Figure S80. NOESY spectrum of the compound **(±)-17a** in DMSO-d_6

6. 1D and 2D NMR specra of compound (±)-31a

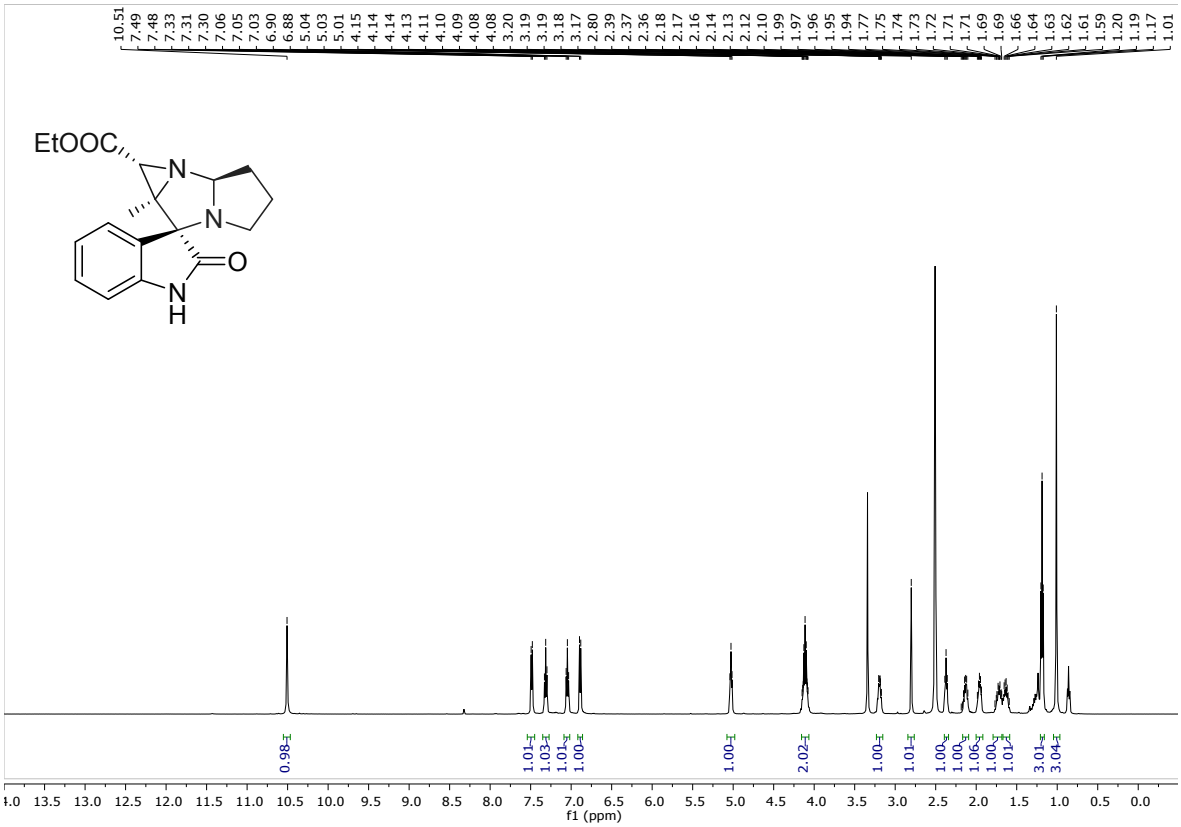


Figure S81. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of the compound **(±)-31a**

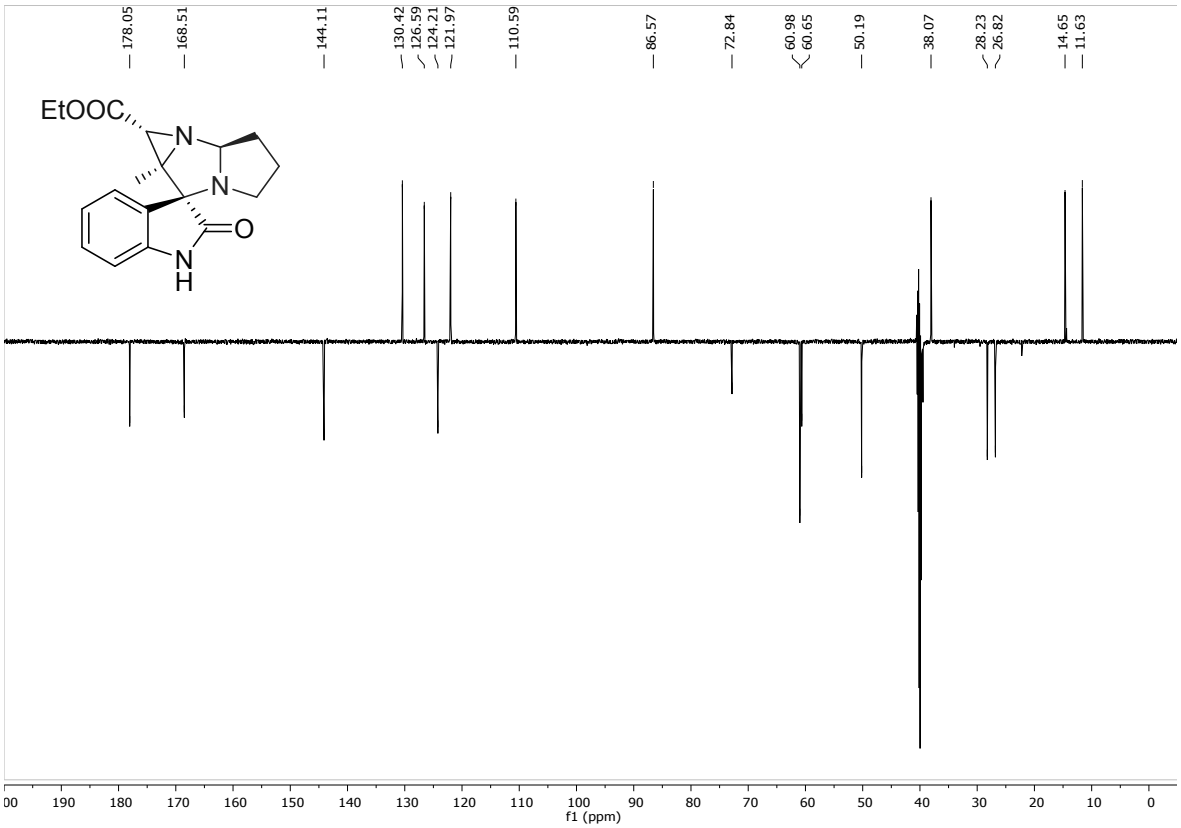


Figure S82. ^{13}C NMR spectrum (126 MHz, DMSO-d_6) of the compound **(±)-31a**

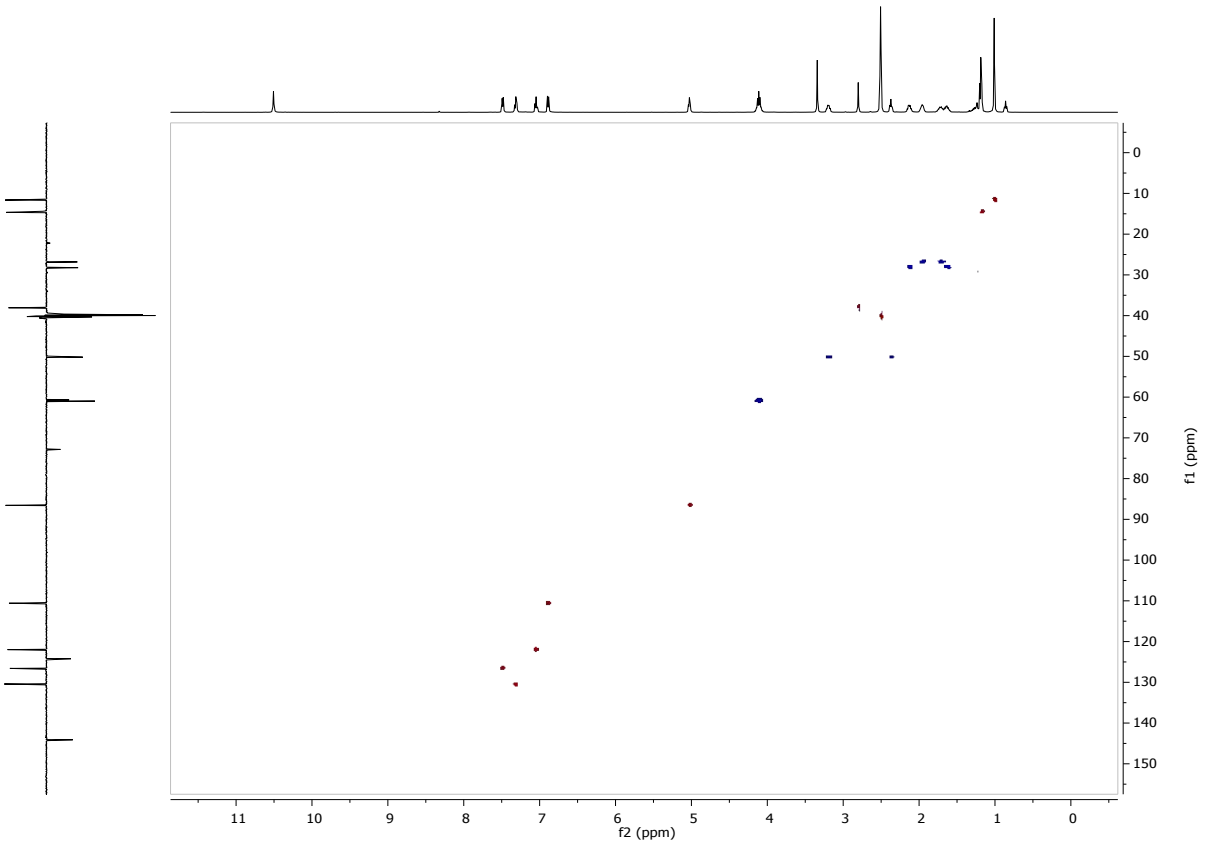


Figure S83. HSQC spectrum of the compound **(±)-31a** in DMSO-d_6

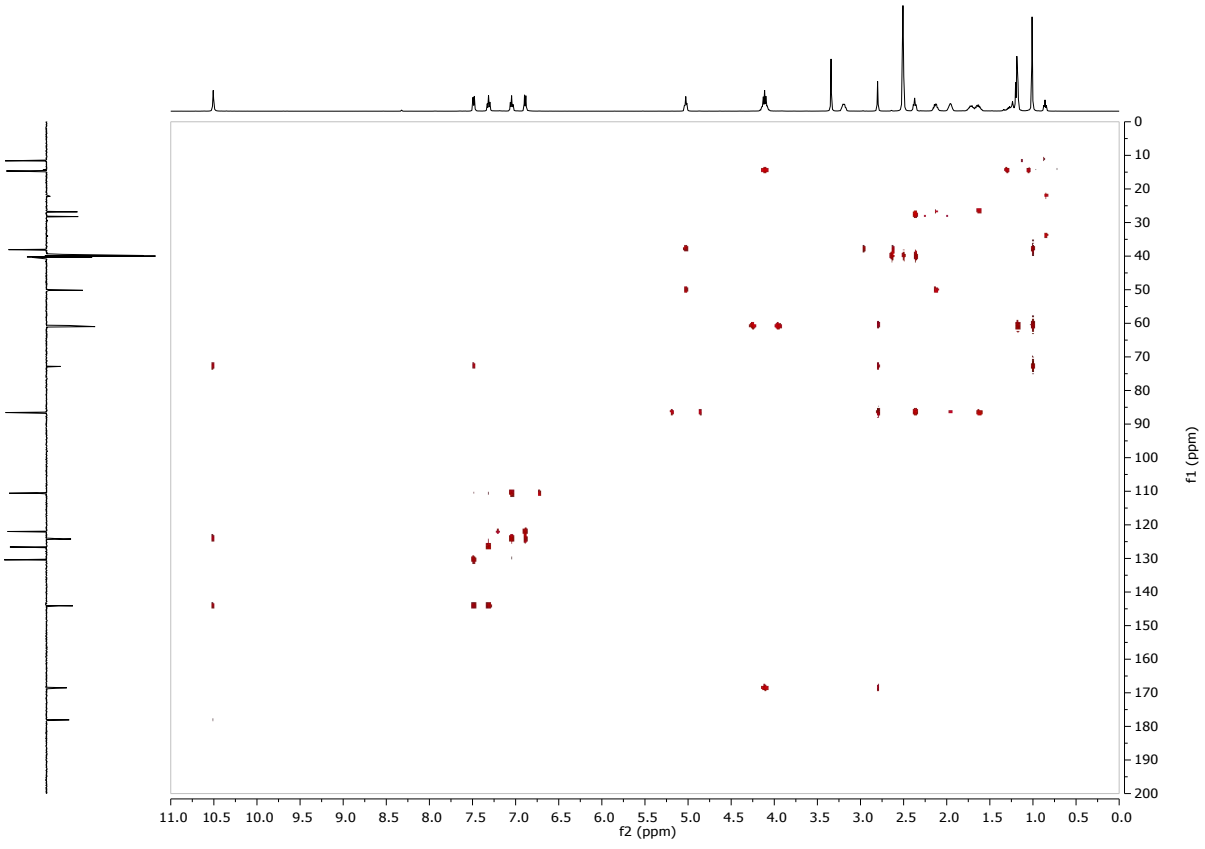


Figure S84. HMBC spectrum of the compound **(±)-31a** in DMSO-d_6

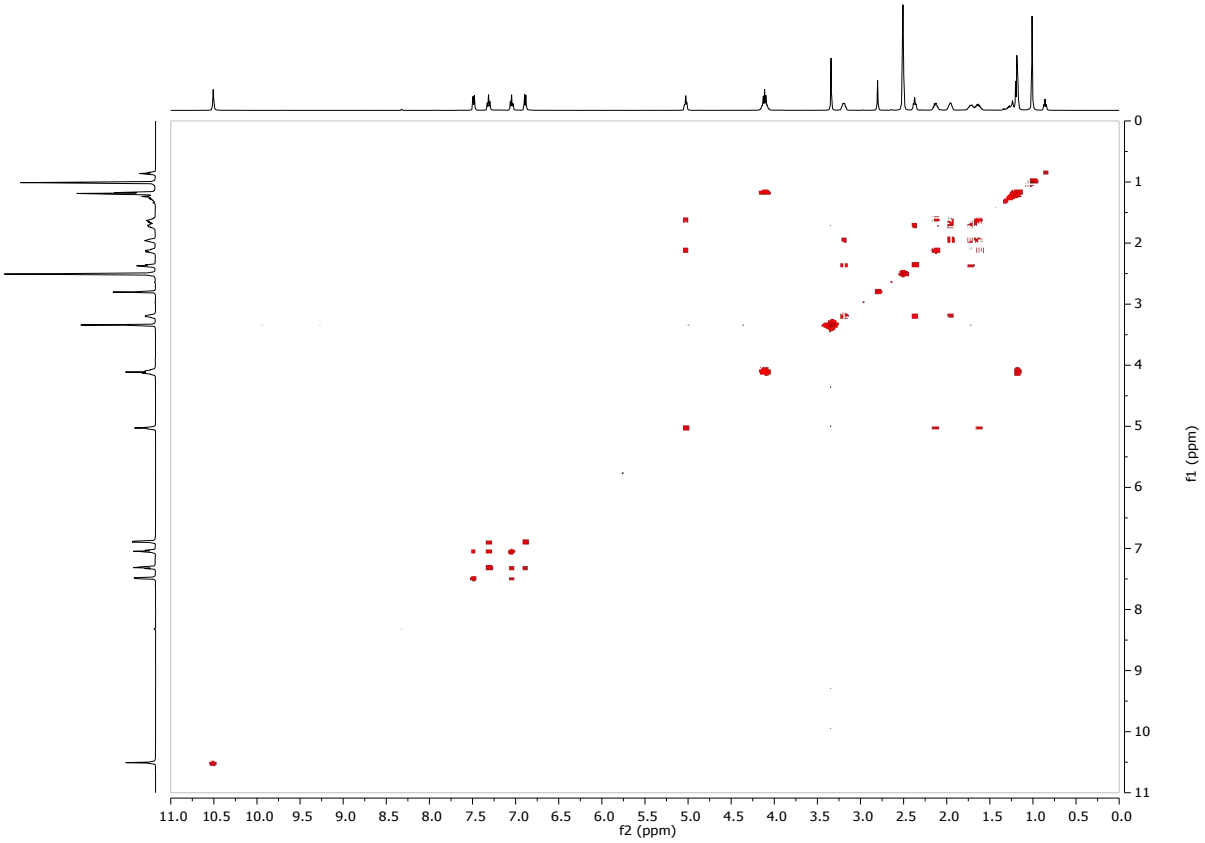


Figure S85. COSY spectrum of the compound **(±)-31a** in DMSO-d_6

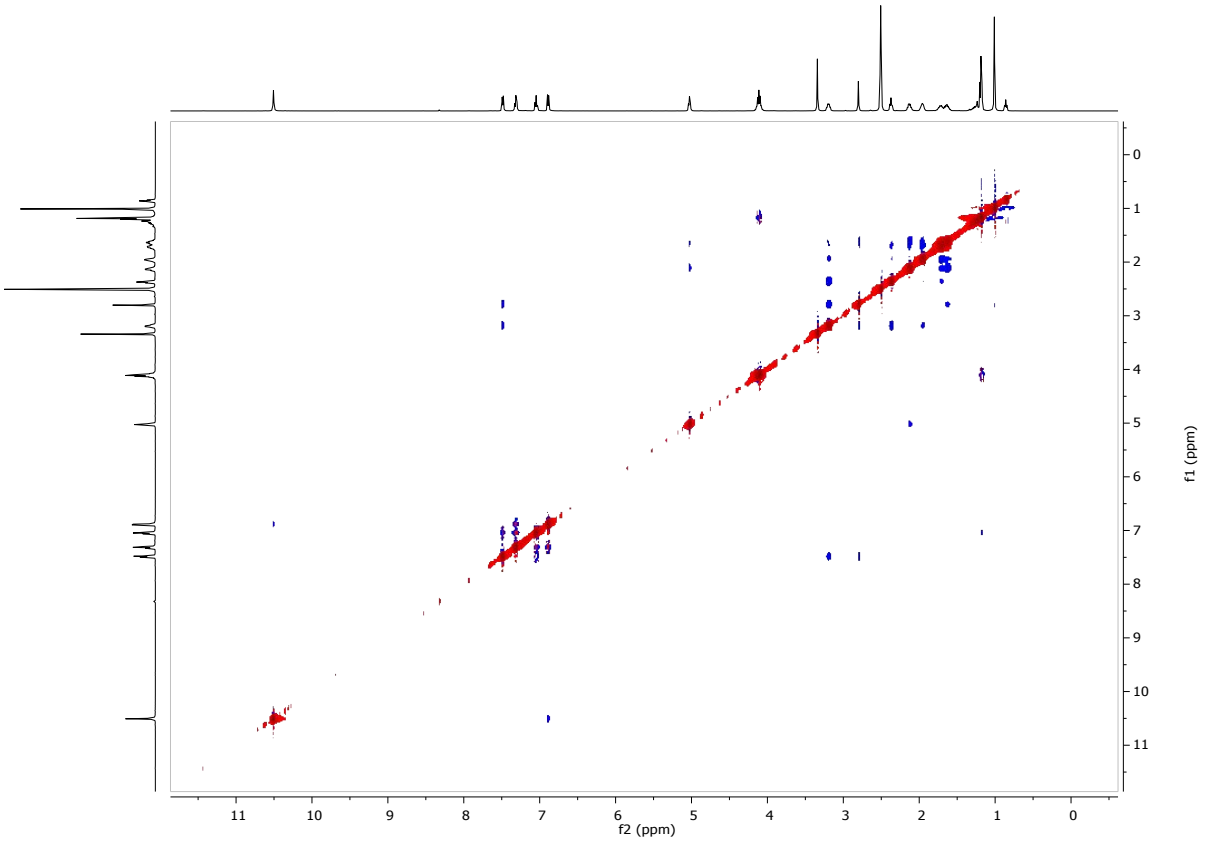


Figure S86. NOESY spectrum of the compound **(±)-31a** in DMSO-d_6

7. Crystallographic studies of compounds (±)-4a and (±)-31a

7.1. Experimental

Racemic compounds **(±)-4a** and **(±)-31a** were crystallized from dichloromethane and tetrahydrofuran, respectively. X-ray diffraction data were collected on a Rigaku XtaLab Synergy-R diffractometer using Cu -Kα radiation (λ= 1.54184 Å). Data reduction was carried out using the software provided with the diffractometer (CrysAlisPro 1.171.40.14e (Rigaku OD, 2018)). The structure was solved by direct methods using Olex2 v1.2 and refined by full-matrix least-squares techniques (SHELXL-2014/7) on F^2.[1,2] Hydrogen atoms were refined in the riding positions for both structures. The crystallographic parameters, data collection, and structure refinement details are summarized in Table S2. Compound **(±)-4a** crystallized in space group $P2_12_12_1$, with one molecule per asymmetric unit. The crystal showed partial merohedral twinning, with fraction of 0.2068 for the inverted structure. Flack-x parameter refined to a value of 0.2(2). Compound **(±)-31a** crystallized in space group P21/n. The asymmetric unit contains one molecule of **(±)-31a** and a tetrahydrofuran molecule with occupancy of 0.5, with a crystallographic inversion center within the tetrahydrofuran ring. Geometric and rigid-bond restraints were applied to the disordered tetrahydrofuran molecule. The structures were analyzed using Mercury program.[3] Validation was carried out using CheckCIF/PLATON.[4] The figures were created using Mercury and PyMOL.[5] Structures of **(±)-4a** and **(±)-31a** were deposited with the Cambridge Crystallographic Data Centre and can be obtained free of charge with CCDC deposition numbers CCDC 1890661 and CCDC 1890659, respectively.

Table S2. X-ray crystallograqphic data and structural refinements details for **(±)-4a** and **(±)-31a**

Compound	**(±)-4a**	**(±)-31a**
CCDC reference number	CCDC 1890661	CCDC 1890659
Asymmetric unit contents Empirical formula Formula weight	 $C_{21}H_{23}N_3O_3$ 363.41	 $C_{20}H_{25}N_3O_{3.5}$ 363.43
Temperature (K)	299.0 (2)	298.0 (2)
Wavelength (Å)	1.54184	1.54184
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$

Unit cell dimensions *a, b, c* (Å) α, β, γ (°)	9.7567(1), 13.6713(1), 14.3251(1) 90.0, 90.0, 90.0	10.65608(8),16.5098(1),10.94821(9) 90.0, 99.8206(8), 90.0
V (Å)	1910.77(3)	1897.89(3)
Z	4	4
D_{calc} (g /cm^3)	1.263	1.272
θ_{min}, θ_{max} (°)	6.476, 75.450	4.897, 75.480
Reflections collected/unique	21399 / 3820	41156, 3824
R_{int}	0.0192	0.0241
Completeness to θ_{max} (%)	98.2	97.1
Data/restraints/parameters	3820 / 0 / 253	3824 / 5 / 264
Goodness-of-fit (GOF) on F^2	1.062	1.039
R1 / *wR2* [$I > 2\sigma(I)$]	0.0311 / 0.0820	0.0440 / 0.1185
R1 / *wR2* (all data)	0.0317 / 0.0833	0.0462 / 0.1205
Largest difference peak/hole (e/ Å^3)	0.154 / -0.163	0.245 -0.202

7.2. Results

Configuration of chirality centers were confirmed by the crystal structures of **(±)-4a** and **(±)-31a**. The structures are shown in **Figure** S**87**, and selected geometric parameters are compiled in **Table S3**. Interestingly, **(±)-4a** crystallized in space group $P2_12_12_1$ containing only one of the enantiomers in the unit cell. However it showed partial racemic twinning, resulting a ratio of 0.8 : 0.2 for the two enantiomers in the crystal investigated. **(±)-31a** crystallized in a centrosymmetric space group, thus contains the 1 : 1 raceme mixture. The five membered ring (N2-C10-N3-C8-C9) is in an envelope conformation with the N3 being the puckering atom because of the steric constraints caused by the fused cyclopropane moiety. In **(±)-31a** the C10-N3-C14-C15-C16 ring shows an envelope conformation similarly, with the atom opposite to the sterically constrained part being the puckering atom (C15). Minor differences between respective bond lengths and bond angles of the two structures can be explained by the attachment of the second five-membered ring in **(±)-31a.**

Crystal packing of **(±)-4a** (**Figure S88**) shows a 3D hydrogen bonded network of molecules. In order to understand the formation of partial racemic twinnig, we compared the direction dependence of molecular contacts in the structure. A column-like association of molecules is connected by N1-H1…N2 hydrogen bonds parallel to unit cell axis *b*. Perpendicular to this direction, longer N3-H3…O2 hydrogen bonds connect the 'column' to neighboring molecules and the phenyl groups fit between the phenyl and oxindole moieties of neighboring molecules in a cog-like way, forming edge-to-face aromatic contacts with the oxindole moieties of those. In the third dimension a smooth edge of the column is formed by its oxindole and acetyl groups. By comparing the shapes of columns formed by the inverted molecules, we speculate that these inverted columns rotated around unit cell axis c by 180° could fit this interaction pattern (**Figure S89**).

Crystal packing of **(±)-31a** (**Figure S90**) shows hydrogen bonded layers of molecules parallel to **b** and **a+c** vectors, with disordered tetrahydrofuran molecules sitting between the layers. The aromatic ring is involved mainly in C-H..π type interactions established with aliphatic groups.

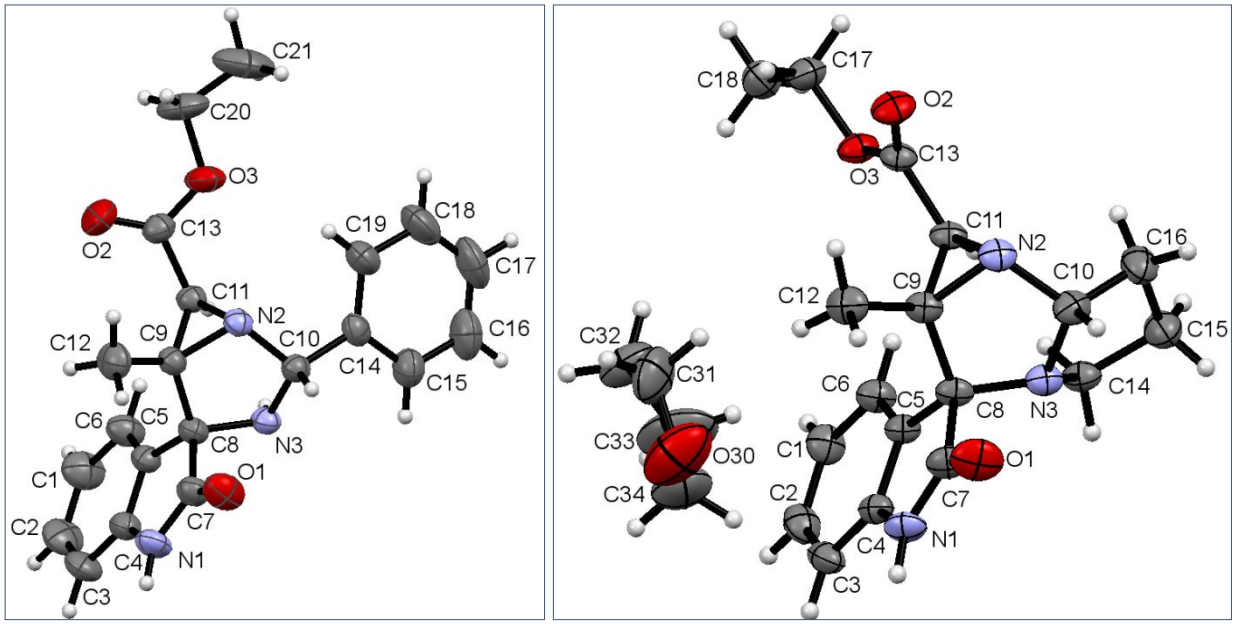


Figure S87. Crystal structures of compounds **(±)-4a** and **(±)-31a**, respectively. Atomic displacement ellipsoids are contoured at the 0.3 probability level.

Table S3. Selected geometric parameters of **(±)-4a** and **(±)-31a**. (Variances in the last digits are shown in parentheses.) Atom names are listed for **(±)-4a** and **(±)-31a**

Compound	**(±)-4a**	**(±)-31a**
Geometric parameter		
Bond lengths (Å), bond angles and torsion angles(°)		
N2-C10	1.492(2)	1.487(2)
C10-N3	1.467(2)	1.475(2)
N3-C8	1.471(2)	1.458 (2)
C8-C9	1.541(2)	1.536 (2)
C9-N2	1.487(2)	1.471(2)
C9-C11	1.482(2)	1.499(2)
C11-N2	1.483(2)	1.471(2)
N2-C10-N3	108.4(1)	108.3(1)
C10-N3-C8	105.6(1)	107.8(1)
N3-C8-C9	105.3(1)	104.9(1)
C8-C9-N2	106.9(1)	108.8(1)
C9-N2-C10	105.7 (1)	105.8(1)
C9-C11-N2	60.20(9)	59.39(8)
C11-N2-C9	59.9(1)	61.25(8)
N3-C8-C7	107.7(1)	106.4(1)
N3-C8-C5	113.2(1)	117.5(1)
C9-C8-C7	111.0(1)	111.1(1)
C9-C8-C5	117.3(1)	115.4(1)
N2-C11-C13-O3	75.1	179.7
C13-O3-C20-C21 (C13-O3-C17-C18)	177.3	175.68
RMS deviation of the ring atoms from the plane (Å)		
N2-C10-N3-C8-C9	0.1199	0.0897
C10-N3-C14-C15-C16	-	0.1608
C1-C2-C3-N1-C4-C5-C6-C7-C8-O1	0.0107	0.0520

Angle between ring planes		
N2-C10-N3-C8-C9 / N2-C9-C11	80.05(8)	79.57(7)
N2-C10-N3-C8-C9 / C1-C2-C3-N1-C4-C5-C6-C7-C8-O1	85.52(4)	81.83(3)
Hydrogen bonds (for D-H…A hydrogen bond: D…A distance/ H…A distance / D-H-A angle)		
N3-H3…O2[a] C11-H11…O2[a] N1-H1…N2[b]	3.245 / 2.384 / 161.26 3.472 / 2.502 / 170.41 2.981 / 2.151 / 161.99	
N1-H1…O2[c] C14-H14A…O1[d]		2.974 / 2.151 / 159.91 3.301 / 2.456 / 145.35

[a] O2 atom of the symmetry equivalent molecule trans formed by [x+1/2, -y+1/2, -z]

[b] N2 atom of the symmetry equivalent molecule trans formed by [-x, y-1/2, -z+1/2]

[c] O2 atom of the symmetry equivalent molecule trans formed by [-x+3/2, y-1/2, -z+3/2]

[d] O1 atom of the symmetry equivalent molecule trans formed by [x-1/2, -y+1/2, z-1/2]

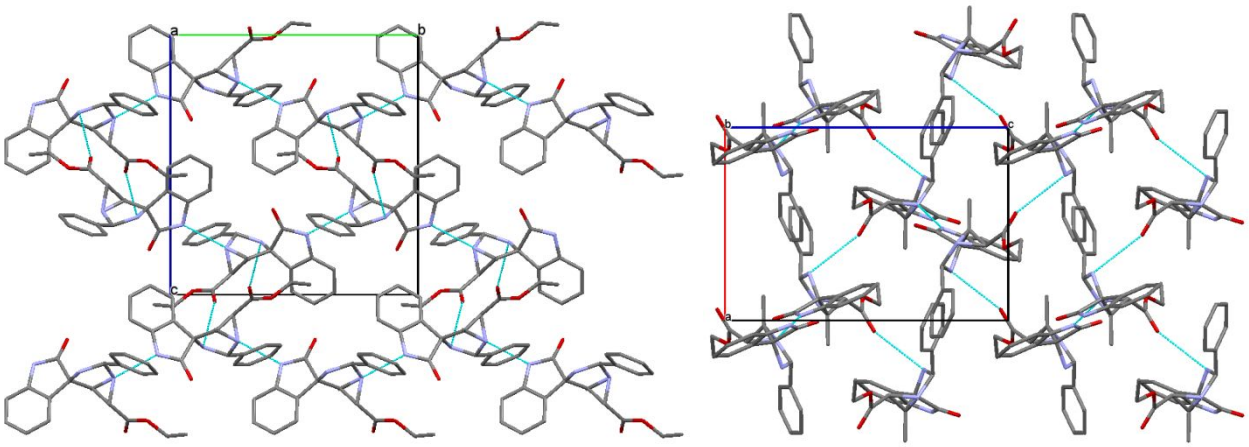


Figure S88. Crystal packing of **(±)-4a** (left: view along unit cell axis *a;* right: view along unit cell axis *b*). Intermolecular hydrogen bonds N3-H3…O2 and N1-H1…N2 are shown in cyan. While N3-H3…O2 hydrogen bonds form a 2D network parallel to the *ac* plane (right); N1-H1…N2 hydrogen bonds connect molecules along unit cell axis *b* (left). (Hydrogen atoms are not shown.)

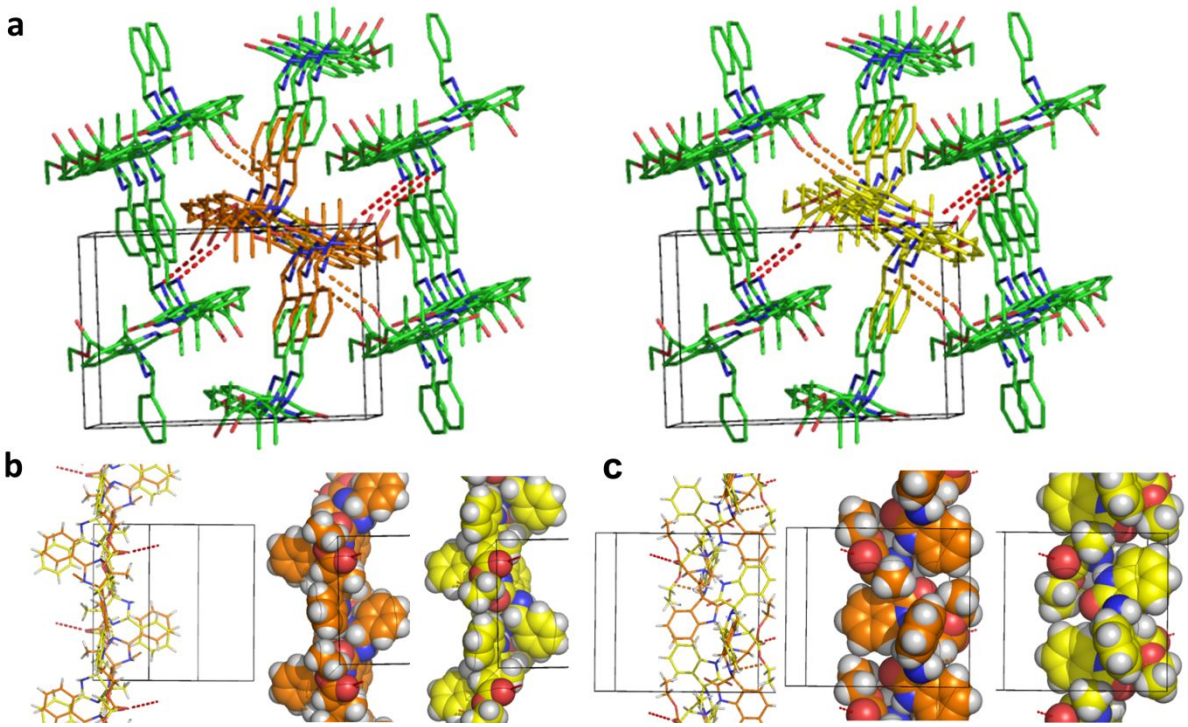


Figure S89. Accommodation of a series of **(±)-4a** molecules (referred to as "column") (orange carbon atoms) in the crystal structure (**a**, left), with neighboring molecules shown (green carbon atoms). The phenyl groups fit in a cog-like way, the oxindole and acetyl groups form a smooth edge. Three types of hydrogen bonds are shown in yellow, orange and red. **a,** (view along unit cell axis *b*) right: a column cut out from the inverted structure fits in the cog-like and smooth edges and can form hydrogen bonds shown in yellow and red (yellow carbon atoms). The inverted column was rotated around axis *c* by 180°. **b**, and **c,** Comparison of the shapes of rod-like molecule structures: cog-like and smooth edges, respectively. (Hydrogen atoms are not shown.)

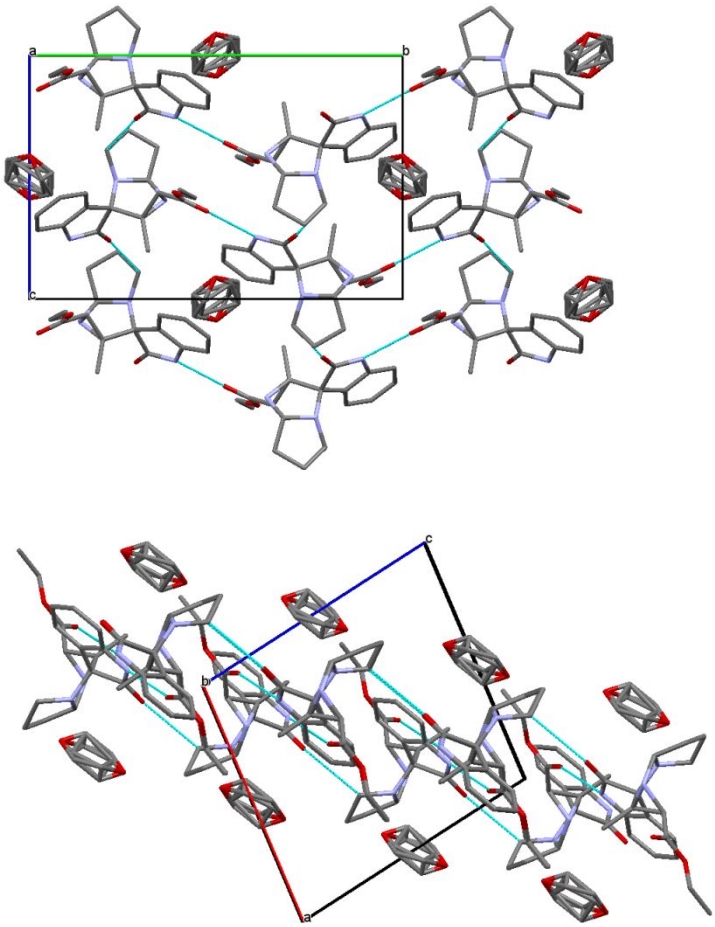


Figure S90. Crystal packing of **(±)-31a** (left: view along unit cell axis *a;* right: view along unit cell axis *b*). Intermolecular hydrogen bonds N1-H1…O2 and C14-H14A…O1 are shown in cyan. Hydrogen bonds form a 2D network parallel to unit cell axis *b* and **a+c**. The disordered solvent molecules are accommodated between layers od hydrogen bonded molecules. (Hydrogen atoms are not shown.)

8. References

1. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst*. **2009**, 42, 339–341.
2. Sheldrick, G. M. *Acta Cryst*. **2015**, C71, 3–8.
3. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Cryst*. **2006**, 39, 453–457.
4. Spek, A. L. *Acta Cryst*. **2009**, D65, 148–155.
5. DeLano, W. L. (2002) *The PyMOL Molecular Graphics System*, DeLano Scientific, San Carlos, CA