

This version of the ESI published 3 February 2023 replaces the original version published 21 November 2022 as there were some errors in the crystallography data.

# Supporting Information

## An intramolecular hydrogen bond-promoted green Ugi cascade reaction for synthesis of 2,5-diketopiperazines with anticancer activity

Jie Li,<sup>a</sup> Jiu-Hong Huang,<sup>a</sup> Jing-Ya Wang,<sup>a</sup> Zhi-Gang Xu,<sup>a</sup> Zhong-Zhu Chen,<sup>a</sup> Jie Lei<sup>\*a</sup>

<sup>a</sup> College of Pharmacy, National & Local Joint Engineering Research Center of Targeted and Innovative Therapeutics, IATTI, Chongqing University of Arts and Sciences, Chongqing 402160, China.

\*Corresponding author: jlei0916@163.com

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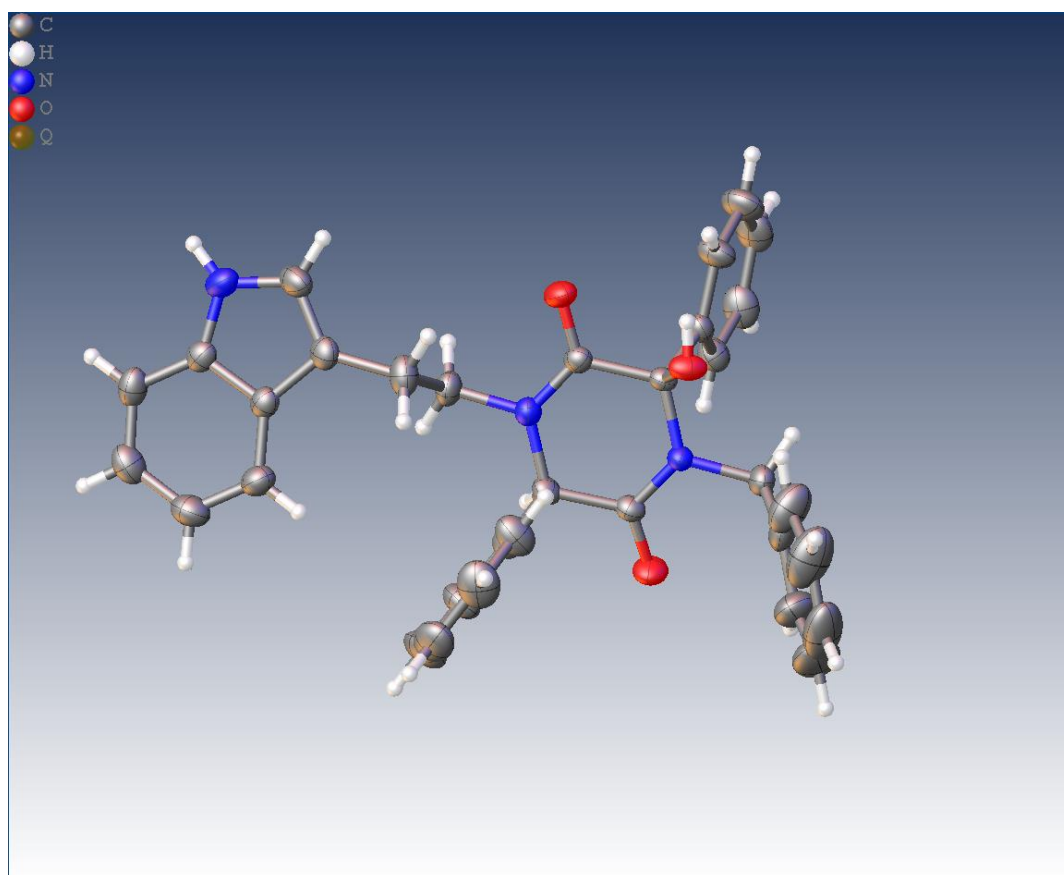
## General Experimental

<sup>1</sup>H and <sup>13</sup>C NMR were recorded on a Bruker 400 spectrometer (Switzerland NMR Nuclear Magnetic Resonance Spectrometer, AVANCE II 400). <sup>1</sup>H NMR data are reported as follows: chemical shift in ppm ( $\delta$ ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), relative intensity. <sup>13</sup>C NMR data are reported as follows: chemical shift in ppm ( $\delta$ ). LC/MS analyses were performed on a Shimadzu-2020 LC-MS instrument (Japanese, Shimadzu, N2G 40-A200.6) using the following conditions: Shim-pack VP-ODS C18 column (reverse phase, 150  $\times$  4.6 mm); a linear gradient from 10% water and 90% acetonitrile to 75% acetonitrile and 25% water over 6.0 min; flow rate of 0.5 mL/min; UV photodiode array detection from 200 to 400 nm. High-resolution mass spectra (HRMS) (Thermo Scientific Q Exactive; Shimadzu 7250, Japanese) were recorded on Thermo Scientific Exactive Plus System. The products were purified by Biotage Isolera<sup>TM</sup> Spektra Systems and hexane/EtOAc solvent systems. All reagents and solvents were obtained from commercial sources and used without further purification.

## General procedures for compounds ( $\pm$ ) 5

A mixture of acid (0.3 mmol), isocyanide (0.3 mmol), amine (0.3 mmol) and aldehyde (0.3 mmol) was stirred overnight in methanol (2.0 mL). The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. The crude compound was directly treated with DIPA (2.0 equiv.) at MW 160  $^{\circ}$ C, 20 min. Then the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na<sub>2</sub>CO<sub>3</sub> and brine. The organic layer was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product.

## X-ray structure and data of ( $\pm$ )5a



**Table 1 Crystal data and structure refinement for ( $\pm$ ) 5a.**

Identification code	( $\pm$ ) <b>5a</b>
Empirical formula	C <sub>33</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>
Formula weight	515.59
Temperature/K	296(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.1229(8)

b/Å	12.8851(13)
c/Å	15.0472(15)
$\alpha$ /°	92.354(2)
$\beta$ /°	103.338(2)
$\gamma$ /°	91.502(2)
Volume/Å <sup>3</sup>	1341.7(2)
Z	2
$\rho_{\text{calc}}$ /g/cm <sup>3</sup>	1.276
$\mu$ /mm <sup>-1</sup>	0.083
F(000)	544.0
Crystal size/mm <sup>3</sup>	0.3 × 0.28 × 0.27
Radiation	MoK $\alpha$ ( $\lambda$ = 0.71073)
2 $\Theta$ range for data collection/°	6.274 to 50
Index ranges	-8 ≤ h ≤ 6, -13 ≤ k ≤ 15, -17 ≤ l ≤ 17
Reflections collected	6862
Independent reflections	4688 [R <sub>int</sub> = 0.0180, R <sub>sigma</sub> = 0.0257]
Data/restraints/parameters	4688/0/354
Goodness-of-fit on F <sup>2</sup>	0.964
Final R indexes [I >= 2 $\sigma$ (I)]	R <sub>1</sub> = 0.0364, wR <sub>2</sub> = 0.1009
Final R indexes [all data]	R <sub>1</sub> = 0.0466, wR <sub>2</sub> = 0.1074
Largest diff. peak/hole / e Å <sup>-3</sup>	0.19/-0.17

**Table 2 Fractional Atomic Coordinates ( $\times 10^4$ ) and Equivalent Isotropic Displacement Parameters ( $\text{\AA}^2 \times 10^3$ ) for ( $\pm$ ) 5a.  $U_{\text{eq}}$  is defined as 1/3 of the trace of the orthogonalised  $U_{\text{IJ}}$  tensor.**

Atom	x	y	z	$U_{\text{eq}}$
O1	10557.7(14)	3169.0(7)	1928.9(7)	42.0(3)
O2	11249.5(12)	2290.6(8)	3661.1(6)	36.0(2)
O3	5012.6(13)	2169.4(8)	3626.4(7)	43.0(3)
N1	8153.5(19)	6911.9(9)	-253.3(8)	43.1(3)
N2	7665.0(16)	3530.7(8)	2211.8(7)	31.2(3)
N3	8041.0(14)	1937.6(8)	3472.9(7)	27.6(2)
C1	5113(2)	7907.1(11)	-378.1(9)	41.3(4)
C2	3618(2)	8065.6(12)	41.0(11)	47.0(4)
C3	3525(2)	7572.5(12)	841.6(11)	48.8(4)
C4	4913(2)	6895.0(11)	1230.8(10)	41.2(3)
C5	6443.6(19)	6704.5(10)	812.6(9)	32.0(3)
C6	6524(2)	7221.0(10)	9.6(9)	33.0(3)
C7	9074(2)	6220.1(11)	352.8(11)	42.9(4)
C8	8100(2)	6067.7(10)	1020.2(9)	36.0(3)
C9	8562(2)	5329.9(11)	1779.5(10)	44.1(4)
C10	7342(2)	4321.8(10)	1512.5(9)	36.9(3)
C11	6147.2(18)	3375.6(10)	2711.5(9)	30.0(3)
C12	6377.7(17)	2436.0(10)	3298.8(8)	28.9(3)

C13	9563.0(17)	2075.3(9)	2977.6(8)	26.2(3)
C14	9262.9(18)	2987.7(10)	2330.0(8)	29.0(3)
C15	5941.9(19)	4342.6(10)	3294.3(9)	33.8(3)
C16	7512(2)	4778.2(13)	3930.6(11)	51.6(4)
C17	7309(3)	5659.3(14)	4458.0(12)	64.3(5)
C18	5551(3)	6105.4(14)	4350.4(13)	65.1(5)
C19	3999(3)	5683.2(14)	3723.8(15)	65.8(5)
C20	4180(2)	4798.8(12)	3191.1(12)	49.7(4)
C21	8224(2)	1054.3(10)	4093.9(9)	35.0(3)
C22	8565(2)	1388.5(11)	5095.6(10)	43.2(4)
C23	10352(3)	1762.0(15)	5579.9(12)	68.4(5)
C24	10677(4)	2050.9(18)	6506.8(14)	92.5(8)
C25	9255(6)	1963.5(18)	6950.8(15)	95.3(9)
C26	7470(5)	1586(2)	6493.6(17)	97.4(9)
C27	7108(3)	1297.5(17)	5558.3(13)	72.9(6)
C28	9630.1(18)	1102.4(9)	2357.6(8)	29.4(3)
C29	11305(2)	869.5(12)	2080.3(11)	43.8(4)
C30	11293(3)	59.1(13)	1438.2(12)	55.1(4)
C31	9640(3)	-531.7(12)	1085.5(11)	52.9(4)
C32	7979(2)	-325.4(12)	1372.6(10)	48.6(4)
C33	7969(2)	494.5(11)	2000.9(9)	38.0(3)

**Table 3 Anisotropic Displacement Parameters ( $\text{\AA}^2 \times 10^3$ ) for ( $\pm$ ) 5a. The Anisotropic displacement factor exponent takes the form:  $-2 \pi^2 [h^2 a^{*2} U_{11} + 2 h k a^* b^* U_{12} + \dots]$ .**

Atom	U11	U22	U33	U23	U13	U12
O1	46.5(6)	38.6(5)	50.4(6)	7.4(4)	29.6(5)	4.1(5)
O2	23.3(5)	53.0(6)	31.8(5)	-4.4(4)	8.0(4)	0.1(4)
O3	26.2(5)	52.0(6)	55.6(6)	11.9(5)	17.6(5)	3.9(4)
N1	56.2(8)	37.9(7)	43.1(7)	4.4(5)	27.0(6)	2.3(6)
N2	34.3(6)	29.4(6)	31.4(6)	4.5(4)	10.1(5)	5.1(5)
N3	25.0(5)	28.7(5)	31.5(6)	5.4(4)	10.2(4)	4.8(4)
C1	55.6(9)	32.8(7)	31.6(7)	3.3(6)	2.4(7)	0.4(7)
C2	43.0(9)	42.9(8)	50.8(9)	-0.6(7)	1.8(7)	8.9(7)
C3	41.8(9)	50.2(9)	57.9(10)	-2.4(7)	19.0(7)	6.2(7)
C4	46.4(9)	41.4(8)	39.9(8)	3.2(6)	18.4(7)	0.3(7)
C5	38.0(7)	26.6(6)	31.5(7)	-0.5(5)	8.9(6)	-1.6(6)
C6	41.3(8)	27.3(6)	30.9(7)	-2.3(5)	10.6(6)	-2.9(6)
C7	43.6(8)	31.2(7)	58.4(9)	0.2(6)	21.3(7)	6.2(6)
C8	40.5(8)	25.6(7)	42.0(8)	1.4(6)	9.6(6)	0.5(6)
C9	48.9(9)	33.1(7)	46.3(8)	5.9(6)	2.1(7)	2.8(7)
C10	44.6(8)	32.7(7)	33.0(7)	7.5(6)	6.8(6)	4.7(6)
C11	23.8(6)	33.3(7)	32.2(7)	1.8(5)	4.5(5)	5.1(5)
C12	23.4(6)	31.6(7)	31.8(6)	-1.6(5)	6.8(5)	1.6(5)
C13	21.7(6)	29.9(6)	27.6(6)	0.1(5)	7.2(5)	2.8(5)

C14	31.7(7)	27.4(6)	29.5(6)	-2.3(5)	11.2(5)	0.3(5)
C15	35.8(7)	32.3(7)	35.2(7)	3.0(5)	11.5(6)	6.7(6)
C16	48.8(9)	52.4(9)	47.6(9)	-8.0(7)	0.0(7)	10.4(8)
C17	83.7(14)	54.7(10)	47.5(10)	-13.7(8)	3.6(9)	1.1(10)
C18	99.3(16)	40.8(9)	63.4(11)	-8.2(8)	36.5(11)	10.0(10)
C19	64.5(12)	48.8(10)	92.9(14)	-3.6(10)	35.5(11)	21.7(9)
C20	39.8(8)	42.6(8)	68.4(11)	-0.7(7)	15.6(8)	10.2(7)
C21	37.8(7)	29.3(7)	40.4(8)	8.1(6)	12.9(6)	4.0(6)
C22	61.7(10)	33.3(7)	39.0(8)	13.0(6)	17.7(7)	11.4(7)
C23	86.7(14)	72.0(12)	41.8(9)	9.4(8)	5.9(9)	-15.0(11)
C24	139(2)	82.6(15)	45.9(11)	5.9(10)	3.4(13)	-18.5(15)
C25	175(3)	69.4(14)	44.1(11)	11.7(10)	26.8(16)	25.1(17)
C26	141(3)	110(2)	63.8(14)	25.3(14)	63.5(17)	42.5(19)
C27	85.7(14)	88.3(14)	58.0(11)	22.3(10)	38.5(11)	21.5(12)
C28	33.3(7)	27.2(6)	28.2(6)	3.3(5)	6.9(5)	7.1(5)
C29	40.8(8)	40.6(8)	53.3(9)	-7.8(7)	18.8(7)	4.8(6)
C30	62.0(11)	49.4(9)	60.8(10)	-11.1(8)	29.8(9)	11.3(8)
C31	76.4(12)	37.8(8)	43.4(9)	-10.8(7)	12.9(8)	10.4(8)
C32	57.4(10)	38.6(8)	42.6(8)	-7.2(6)	-1.4(7)	0.0(7)
C33	36.5(8)	37.3(7)	37.6(7)	-0.7(6)	3.6(6)	4.5(6)



**Table 4 Bond Lengths for ( $\pm$ ) 5a.**

<b>Atom</b>	<b>Atom</b>	<b>Length/Å</b>	<b>Atom</b>	<b>Atom</b>	<b>Length/Å</b>
O1	C14	1.2356 (15)	C11	C15	1.5237 (18)
O2	C13	1.4024 (15)	C13	C14	1.5455 (17)
O3	C12	1.2345 (15)	C13	C28	1.5401 (17)
N1	C6	1.3732 (18)	C15	C16	1.383 (2)
N1	C7	1.370 (2)	C15	C20	1.379 (2)
N2	C10	1.4792 (16)	C16	C17	1.388 (2)
N2	C11	1.4663 (16)	C17	C18	1.370 (3)
N2	C14	1.3323 (17)	C18	C19	1.361 (3)
N3	C12	1.3398 (16)	C19	C20	1.392 (2)
N3	C13	1.4614 (15)	C21	C22	1.513 (2)
N3	C21	1.4915 (16)	C22	C23	1.377 (3)
C1	C2	1.373 (2)	C22	C27	1.381 (2)
C1	C6	1.397 (2)	C23	C24	1.393 (3)
C2	C3	1.399 (2)	C24	C25	1.341 (4)
C3	C4	1.379 (2)	C25	C26	1.365 (4)
C4	C5	1.4011 (19)	C26	C27	1.404 (3)
C5	C6	1.4149 (18)	C28	C29	1.3879 (19)
C5	C8	1.4368 (19)	C28	C33	1.3874 (19)
C7	C8	1.364 (2)	C29	C30	1.392 (2)
C8	C9	1.4998 (19)	C30	C31	1.371 (2)
C9	C10	1.530 (2)	C31	C32	1.378 (2)
C11	C12	1.5182 (17)	C32	C33	1.390 (2)

**Table 5 Bond Angles for ( $\pm$ ) 5a.**

<b>Atom</b>	<b>Atom</b>	<b>Atom</b>	<b>Angle/<math>^{\circ}</math></b>	<b>Atom</b>	<b>Atom</b>	<b>Atom</b>	<b>Angle/<math>^{\circ}</math></b>
C7	N1	C6	108.77 (11)	N3	C13	C14	114.05 (10)
C11	N2	C10	116.89 (10)	N3	C13	C28	110.01 (10)
C14	N2	C10	118.78 (11)	C28	C13	C14	105.19 (9)
C14	N2	C11	124.30 (10)	O1	C14	N2	122.75 (12)
C12	N3	C13	124.34 (10)	O1	C14	C13	116.58 (11)
C12	N3	C21	118.10 (10)	N2	C14	C13	120.66 (10)
C13	N3	C21	116.67 (10)	C16	C15	C11	120.77 (12)
C2	C1	C6	117.93 (13)	C20	C15	C11	120.25 (13)
C1	C2	C3	121.21 (14)	C20	C15	C16	118.97 (14)
C4	C3	C2	121.29 (14)	C15	C16	C17	120.30 (16)
C3	C4	C5	118.92 (13)	C18	C17	C16	120.22 (17)
C4	C5	C6	118.89 (13)	C19	C18	C17	119.85 (16)
C4	C5	C8	133.94 (13)	C18	C19	C20	120.57 (17)
C6	C5	C8	107.17 (12)	C15	C20	C19	120.08 (16)
N1	C6	C1	130.91 (13)	N3	C21	C22	113.85 (11)
N1	C6	C5	107.35 (12)	C23	C22	C21	120.95 (15)
C1	C6	C5	121.73 (13)	C23	C22	C27	118.03 (17)
C8	C7	N1	110.72 (13)	C27	C22	C21	120.99 (16)
C5	C8	C9	126.36 (13)	C22	C23	C24	121.0 (2)
C7	C8	C5	105.99 (12)	C25	C24	C23	120.7 (2)
C7	C8	C9	127.51 (14)	C24	C25	C26	119.9 (2)
C8	C9	C10	109.99 (12)	C25	C26	C27	120.4 (2)
N2	C10	C9	115.03 (11)	C22	C27	C26	120.1 (2)
N2	C11	C12	114.75 (10)	C29	C28	C13	120.68 (12)
N2	C11	C15	111.41 (10)	C29	C28	C33	118.66 (12)
C12	C11	C15	109.51 (10)	C33	C28	C13	120.42 (11)
O3	C12	N3	121.62 (12)	C28	C29	C30	120.28 (15)
O3	C12	C11	117.97 (11)	C31	C30	C29	120.53 (15)
N3	C12	C11	120.38 (11)	C30	C31	C32	119.76 (14)
O2	C13	N3	104.75 (9)	C31	C32	C33	120.08 (15)
O2	C13	C14	108.46 (10)	C28	C33	C32	120.65 (14)
O2	C13	C28	114.62 (10)				

**Table 6 Hydrogen Atom Coordinates ( $\text{\AA}\times 10^4$ ) and Isotropic Displacement Parameters ( $\text{\AA}^2\times 10^3$ ) for ( $\pm$ ) 5a.**

Atom	x	y	z	U(eq)
H2	12189	2281	3433	54
H1	8534	7118	-721	52
H1A	5184	8246	-904	50
H2A	2649	8509	-212	56
H3	2507	7704	1117	59
H4	4834	6570	1762	49
H7	10208	5898	314	51
H9A	8298	5648	2332	53
H9B	9921	5178	1903	53
H10A	5989	4490	1379	44
H10B	7610	4021	955	44
H11	4927	3265	2253	36
H16	8710	4480	4006	62
H17	8370	5948	4886	77
H18	5418	6695	4705	78
H19	2807	5988	3651	79
H20	3111	4515	2765	60
H21A	9286	637	4006	42
H21B	7053	619	3924	42
H23	11358	1822	5284	82
H24	11893	2307	6821	111
H25	9485	2160	7569	114
H26	6488	1520	6804	117
H27	5887	1045	5250	87
H29	12441	1257	2325	53
H30	12415	-83	1247	66
H31	9640	-1070	654	63
H32	6864	-735	1146	58
H33	6838	637	2184	46

### Cell lines and culture

The human prostate tumor cells PC3 and DU145, acute lymphoblastic leukemia cells Jurkat, biphenotypic B-myelomonocytic leukemia cells MV-4-11 were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). The DU145 cells were cultured in high-glucose DMEM (Hyclone, SH30022.01, USA) medium supplemented with 10% fetal bovine serum (FBS, Gibco, 10099, Australia origin). The PC3 cells were cultured with the Ham's F-12K (Kaighn's) Medium (GIBCO, 21127022, USA) supplemented with 10% FBS. The Jurkat and MV-4-11 cells were

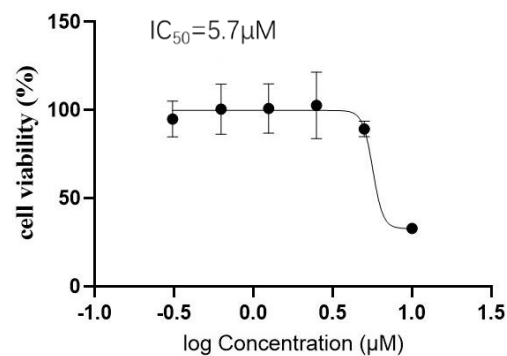
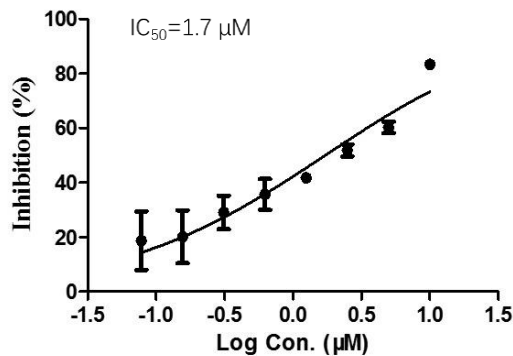
cultured with RPMI 1640 medium (GIBCO, 11875093, USA) supplemented with 10% fetal bovine serum (FBS, Gibco, 10099, Australia). The cells were cultured in the incubator at the 37 °C and 5% CO<sub>2</sub> with humidified atmosphere.

### **Cell viability assay**

The tumor cells were counted and seeded into the 96-well plate containing 100 µL complete medium, the density of cells were  $3 \times 10^3$  cells per well for PC3 and DU145. After incubation for 24 hours, added another 100 µL complete medium containing 10 µM compounds ( $\pm$ ) **5** or equal amount of Dimethyl sulfoxide (DMSO), each treatment was triple replicated. The compound-treated cells were cultured for another 48 hours, 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2-*H*-tetrazolium bromide (MTT, Beyotime, ST316, Shanghai, China) was added, the plate was incubated for another 4 hours. After incubation, removed the medium and added 150 µL DMSO into each well to dissolve the formazan. The optical density (OD) of each well was measured with a microplate reader (Bio-Tek, Winooski, VT, USA) at an absorbance wavelength of 570 nm. Similar to PC3 cells, Jurkat cells and MV-4-11 cells were seeded into the 96-well plate with a density of  $6 \times 10^3$  cells per well, compound-treated cells were cultured for 72 hours and followed by Cell Counting Kit-8 (CCK-8, Beyotime, C0037, Shanghai, China) treatment for another 4 hours. The OD was measured at an absorbance wavelength of 450 nm. The viability of compounds **5** treated cells equal to the ration of OD<sub>compound</sub> to OD<sub>DMSO</sub>. To further evaluate the half maximal inhibitory concentration (IC<sub>50</sub>) of compound ( $\pm$ ) **5c**, MV-4-11 and Jurkat cells were incubated with various concentrations (0, 0.625, 1.25, 2.5, 5, 10 µM) of compound ( $\pm$ ) **5c** for 72 h. The OD of compound-treated cells was measured with CCK-8. The IC<sub>50</sub> values were analyzed by GraphPad Prism 8.

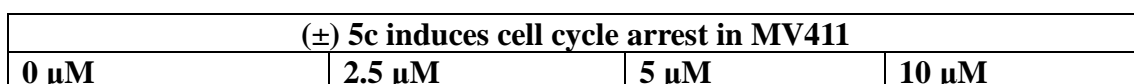
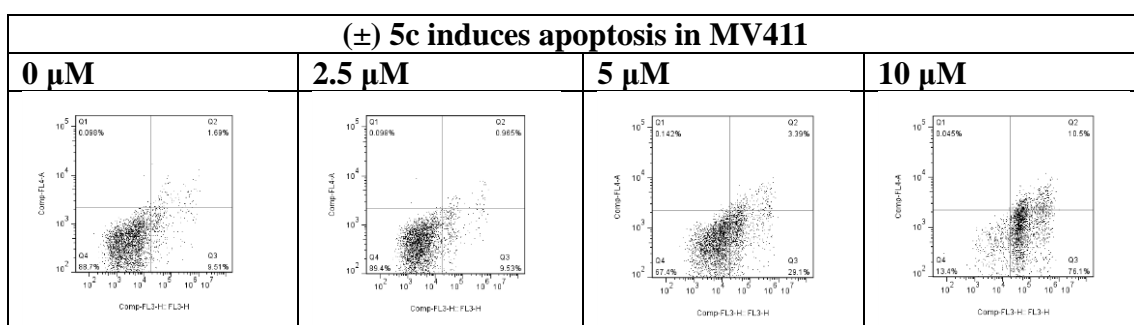
**Transform of ( $\pm$ ) 5c inhibits MV411 IC<sub>50</sub>**

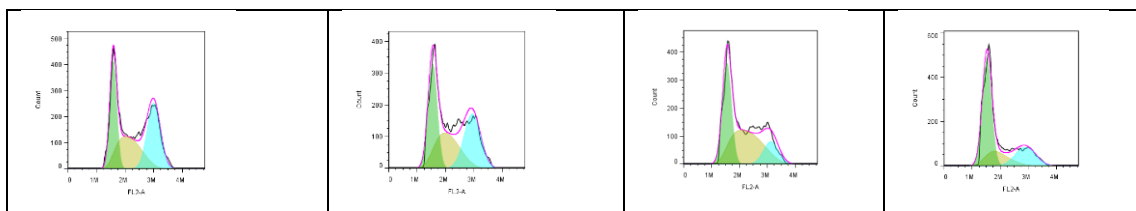
**Transform of ( $\pm$ ) 5e IC<sub>50</sub> in Jurkat**



### Flow cytometry analysis

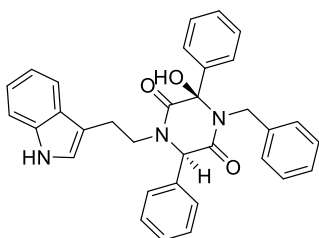
Leukemia cells MV4-11 in the logarithmic growth condition were harvested and seeded into 6-well plates at concentration of 500 thousand per well. The cells were treated with different concentrations of compound ( $\pm$ ) **5 e** or the same amount of DMSO for 48 hours. All cells were collected and analyzed using flow cytometry analysis. For cell cycle analysis, cell were fixed with 70% ethanol at 4 °C for 24 hours, and then washed with PBS for 3 times. Subsequently, cells were stained with PI (50mg/ml, BD Biosciences) and RNase (100mg/ml, Sigma-Aldrich) at 37°C for 30 minutes. The stained cells were analyzed with flow cytometry (Accuri C6, BD biosciences) and the results were recorded. For apoptosis analysis, cells were collected and stained with an Annexin V-FITC/PI apoptosis assay kit following the manufacture’s manual (BD Biosciences). The stained cells were detected with flow cytometry (Accuri C6, BD biosciences). All flow cytometry analysis results were visualized using FlowJo 7.6. The statistical chart of each treatment represents mean $\pm$ SD of 3 (n=3).





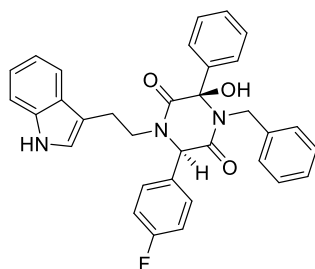
## NMR Characterization Data and Figures of Products

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-3-hydroxy-3,6-diphenylpiperazine-2,5-dione*



(±) **5a**, brown oil, yield 71%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 97%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (s, 1H), 7.53 (d,  $J$  = 7.2 Hz, 2H), 7.47 (d,  $J$  = 7.9 Hz, 1H), 7.39 – 7.28 (m, 4H), 7.24 – 7.20 (m, 1H), 7.18 – 7.09 (m, 6H), 7.06-7.00 (m, 3H), 6.82 (d,  $J$  = 7.7 Hz, 2H), 6.77 (s, 1H), 5.48 (s, 1H), 4.93 (d,  $J$  = 14.1 Hz, 1H), 4.85 (s, 1H), 4.25 (d,  $J$  = 14.1 Hz, 1H), 4.22-4.15 (m, 1H), 3.22 – 3.14 (m, 1H), 3.06 – 3.00 (m, 1H), 2.96 – 2.89 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.95, 165.27, 139.35, 137.93, 136.24, 133.01, 129.36, 129.00, 128.39, 128.17, 127.27, 126.69, 126.28, 122.37, 119.63, 118.32, 111.39, 85.33, 64.85, 47.59, 22.64. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{33}\text{H}_{30}\text{N}_3\text{O}_3^+$  ( $\text{M}+\text{H}$ ) $^+$  516.2287, found 516.2279.

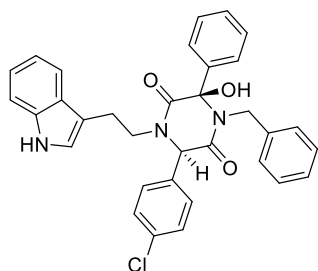
*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(4-fluorophenyl)-3-hydroxy-3-phenylpiperazine-2,5-dione*



(±) **5b**, brown oil, yield 67% (EA/Hex = 30%,  $R_f$  = 0.3), purity 95%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (s, 1H), 7.53 (d,  $J$  = 7.2 Hz, 2H), 7.47 (d,  $J$  = 7.9 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.29 (d,  $J$  = 8.3 Hz, 1H), 7.25 (s, 1H), 7.18-7.13 (m, 3H), 7.08 (d,  $J$  = 7.6 Hz, 2H), 7.02 (t,  $J$  = 7.5 Hz, 1H), 6.82 – 6.66 (m, 5H), 5.50 (s, 1H), 4.93 (d,  $J$  = 14.1 Hz, 1H), 4.77 (s, 1H), 4.28 (d,  $J$  = 14.1 Hz, 1H), 4.21-4.14 (m, 1H), 3.22 – 3.14 (m, 1H), 3.06 – 3.00 (m, 1H), 2.95 – 2.87 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.94, 165.17, 139.38, 137.83, 136.25, 129.39, 128.49, 128.20, 127.34, 126.80,

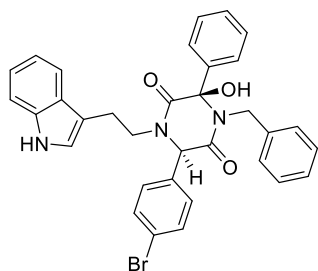
126.18, 122.41, 119.68, 118.25, 115.24, 111.45, 85.22, 64.31, 47.56, 47.35, 22.66.  
HRMS (ESI) m/z calcd for C<sub>33</sub>H<sub>29</sub>FN<sub>3</sub>O<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup> 534.2193, found 534.2199.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(4-chlorophenyl)-3-hydroxy-3-phenylpiperazine-2,5-dione*



(±) **5c**, brown oil, yield 69%, (EA/Hex = 30%, R<sub>f</sub> = 0.3), purity 97%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 (s, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.24 (s, 1H), 7.18-7.13 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.04-6.98 (m, 3H), 6.75-6.69 (m, 3H), 5.50 (s, 1H), 4.92 (d, *J* = 14.1 Hz, 1H), 4.74 (s, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.23 – 3.13 (m, 1H), 3.07 – 2.98 (m, 1H), 2.95 – 2.85 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.94, 164.92, 139.33, 137.79, 136.25, 134.19, 131.55, 129.39, 128.52, 127.98, 127.36, 126.77, 126.15, 122.43, 119.70, 118.23, 111.46, 85.22, 64.40, 47.56, 47.37, 22.66. HRMS (ESI) m/z calcd for C<sub>33</sub>H<sub>29</sub>ClN<sub>3</sub>O<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup> 550.1897, found 550.1889.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(4-bromophenyl)-3-hydroxy-3-phenylpiperazine-2,5-dione*

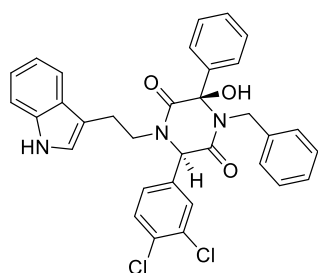


(±) **5d**, brown oil, yield 70%, (EA/Hex = 30%, R<sub>f</sub> = 0.3), purity 97%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 (s, 1H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.41 –



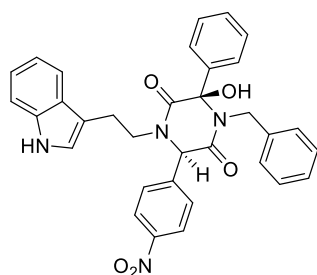
7.32 (m, 3H), 7.29 (d,  $J = 8.3$  Hz, 1H), 7.25 (d,  $J = 3.5$  Hz, 1H), 7.21 – 7.11 (m, 5H), 7.10 – 6.98 (m, 3H), 6.74 (d,  $J = 1.8$  Hz, 1H), 6.64 (d,  $J = 8.4$  Hz, 2H), 5.50 (s, 1H), 4.92 (d,  $J = 14.0$  Hz, 1H), 4.71 (s, 1H), 4.28 (d,  $J = 14.1$  Hz, 1H), 4.23 – 4.12 (m, 1H), 3.24 – 3.12 (m, 1H), 3.08 – 2.97 (m, 1H), 2.95 – 2.85 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.94, 164.82, 139.31, 137.78, 136.25, 132.11, 131.28, 129.40, 128.53, 128.29, 127.36, 126.77, 126.14, 122.43, 119.70, 118.23, 111.46, 85.22, 64.47, 47.56, 47.37, 22.66. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{33}\text{H}_{29}\text{BrN}_3\text{O}_3^+$  ( $\text{M}+\text{H}$ ) $^+$  594.1392, found 594.1395.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(3,4-dichlorophenyl)-3-hydroxy-3-phenylpiperazine-2,5-dione*



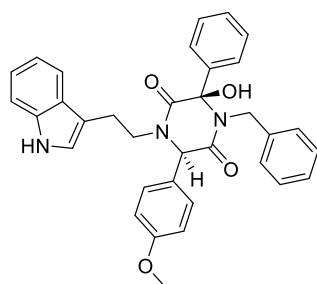
( $\pm$ ) **5e**, red-brown oil, yield 62%, (EA/Hex = 30%,  $R_f = 0.3$ ), purity 94%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (s, 1H), 7.53 (d,  $J = 7.3$  Hz, 2H), 7.46 (d,  $J = 7.9$  Hz, 1H), 7.41 – 7.33 (m, 3H), 7.29 (s, 1H), 7.25 (s, 1H), 7.16 (t,  $J = 7.7$  Hz, 3H), 7.08 (t,  $J = 8.4$  Hz, 3H), 7.02 (t,  $J = 7.5$  Hz, 1H), 6.71 (s, 2H), 6.67–6.65 (m, 1H), 5.56 (s, 1H), 4.93 (d,  $J = 14.0$  Hz, 1H), 4.65 (s, 1H), 4.33 (d,  $J = 14.0$  Hz, 1H), 4.24 – 4.15 (m, 1H), 3.25 – 3.13 (m, 1H), 3.08 – 2.97 (m, 1H), 2.94 – 2.83 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.01, 164.53, 139.18, 137.69, 136.27, 133.24, 132.57, 130.05, 129.46, 128.62, 128.25, 127.44, 126.68, 126.04, 122.49, 119.74, 118.17, 111.52, 111.14, 85.16, 64.07, 47.56, 47.44. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{33}\text{H}_{28}\text{Cl}_2\text{N}_3\text{O}_3^+$  ( $\text{M}+\text{H}$ ) $^+$  584.1508, found 584.1409.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-3-hydroxy-6-(4-nitrophenyl)-3-phenylpiperazine-2,5-dione*



(±) **5f**, red oil, yield 60%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 95%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (d,  $J$  = 8.7 Hz, 2H), 7.64 (s, 1H), 7.54 (d,  $J$  = 7.1 Hz, 2H), 7.46 – 7.35 (m, 4H), 7.30 (d,  $J$  = 8.2 Hz, 1H), 7.23 (t,  $J$  = 7.3 Hz, 1H), 7.17 (t,  $J$  = 7.6 Hz, 1H), 7.09 (t,  $J$  = 7.7 Hz, 2H), 7.05 – 6.98 (m, 3H), 6.90 (d,  $J$  = 8.7 Hz, 2H), 6.71 (d,  $J$  = 2.0 Hz, 1H), 5.61 (s, 1H), 4.93 (d,  $J$  = 14.0 Hz, 1H), 4.76 (s, 1H), 4.35 (d,  $J$  = 14.0 Hz, 1H), 4.30 – 4.20 (m, 1H), 3.26 – 3.16 (m, 1H), 3.10 – 3.01 (m, 1H), 2.94 – 2.88 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.04, 164.19, 147.54, 140.19, 139.27, 137.58, 136.30, 129.46, 128.60, 128.28, 127.51, 126.62, 125.94, 123.11, 122.59, 119.75, 118.09, 111.58, 110.99, 85.11, 64.75, 47.57, 22.72. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{33}\text{H}_{29}\text{N}_4\text{O}_5^+$  ( $\text{M}+\text{H}$ ) $^+$  561.2138, found 561.2095.

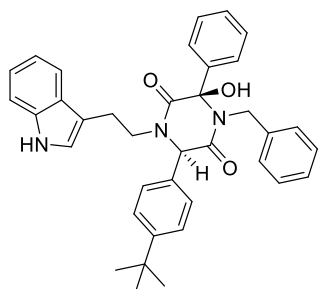
*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-3-hydroxy-6-(4-methoxyphenyl)-3-phenylpiperazine-2,5-dione*



(±) **5g**, brown-yellow oil, yield 82%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 97%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (s, 1H), 7.52 (d,  $J$  = 7.2 Hz, 2H), 7.47 (d,  $J$  = 7.9 Hz, 1H), 7.40 – 7.28 (m, 4H), 7.25 (m, 1H), 7.19-7.13 (m, 5H), 7.02 (t,  $J$  = 7.4 Hz, 1H), 6.78 (d,  $J$  = 1.9 Hz, 1H), 6.73 (d,  $J$  = 8.6 Hz, 2H), 6.58 (d,  $J$  = 8.7 Hz, 2H), 5.45 (s, 1H), 4.92 (d,  $J$  = 14.1 Hz, 1H), 4.80 (s, 1H), 4.23 (d,  $J$  = 14.1 Hz, 1H), 4.18 – 4.09 (m, 1H), 3.71 (s, 3H), 3.22 – 3.11 (m, 1H), 3.08 – 2.91 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.85, 165.53, 159.53, 139.51, 137.95, 136.24, 129.33, 129.01, 128.44, 128.03, 127.25, 126.91, 126.35, 124.99, 122.34, 119.63, 118.35, 113.71, 111.59, 85.35, 64.38,

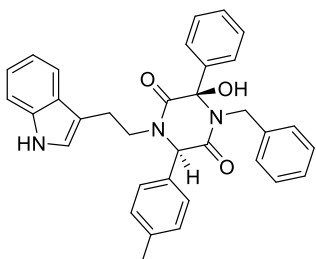
55.31, 47.60, 47.26, 22.64. HRMS (ESI)  $m/z$  calcd for  $C_{34}H_{32}N_3O_4^+$  (M+H)<sup>+</sup> 546.2393, found 546.2356.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-6-(4-(tert-butyl)phenyl)-3-hydroxy-3-phenylpiperazine-2,5-dione*



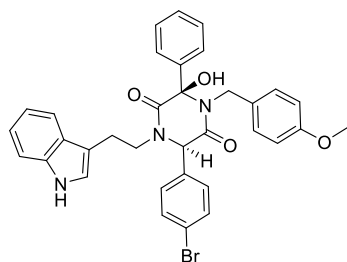
(±) **5h**, brown oil, yield 83%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 96%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.71 (s, 1H), 7.53 (d,  $J$  = 7.2 Hz, 2H), 7.45 (d,  $J$  = 7.9 Hz, 1H), 7.36 (t,  $J$  = 7.2 Hz, 2H), 7.31 (d,  $J$  = 7.1 Hz, 1H), 7.24 (d,  $J$  = 3.0 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.14 (d,  $J$  = 7.5 Hz, 1H), 7.12 – 7.07 (m, 4H), 7.04 (d,  $J$  = 8.4 Hz, 2H), 7.00 (t,  $J$  = 7.5 Hz, 1H), 6.77-6.73 (m, 3H), 5.54 (s, 1H), 4.93 (d,  $J$  = 14.1 Hz, 1H), 4.86 (s, 1H), 4.25 (d,  $J$  = 14.1 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.19-3.12 (m, 1H), 3.07 – 2.91 (m, 2H), 1.22 (s, 9H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.97, 165.57, 151.14, 139.32, 138.00, 136.25, 129.91, 129.33, 128.87, 128.19, 127.26, 126.90, 126.32, 125.23, 122.43, 119.58, 118.35, 111.50, 85.41, 64.60, 47.59, 34.43, 31.24, 22.68, 14.14. HRMS (ESI)  $m/z$  calcd for  $C_{37}H_{38}N_3O_3^+$  (M+H)<sup>+</sup> 572.2913, found 572.2900.

*1-(2-(1H-indol-3-yl)ethyl)-4-benzyl-3-hydroxy-3-phenyl-6-(p-tolyl)piperazine-2,5-dione*



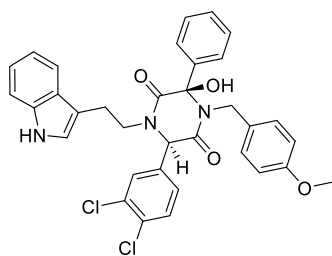
(±) **5i**, brown oil, yield 79%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 95%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (s, 1H), 7.52 (d,  $J$  = 7.1 Hz, 2H), 7.46 (d,  $J$  = 7.9 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.24 (d,  $J$  = 2.6 Hz, 1H), 7.17-7.14 (m, 5H), 7.01 (t,  $J$  = 7.5 Hz, 1H), 6.86 (d,  $J$  = 8.0 Hz, 2H), 6.78 (d,  $J$  = 2.0 Hz, 1H), 6.71 (d,  $J$  = 8.0 Hz, 2H), 5.44 (s, 1H), 4.91 (d,  $J$  = 14.1 Hz, 1H), 4.83 (s, 1H), 4.22 (d,  $J$  = 14.1 Hz, 1H), 4.18-4.11 (m, 1H), 3.20 – 3.13 (m, 1H), 3.05 – 2.90 (m, 2H), 2.24 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.84, 165.36, 139.46, 138.03, 136.22, 130.09, 129.34, 128.93, 127.24, 126.76, 122.33, 119.62, 118.35, 111.58, 85.38, 64.68, 47.63, 22.61, 20.95. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{34}\text{H}_{32}\text{N}_3\text{O}_3^+$  ( $\text{M}+\text{H}$ ) $^+$  530.2444, found 530.2456.

*1-(2-(1H-indol-3-yl)ethyl)-6-(4-bromophenyl)-3-hydroxy-4-(4-methoxybenzyl)-3-phenylpiperazine-2,5-dione*



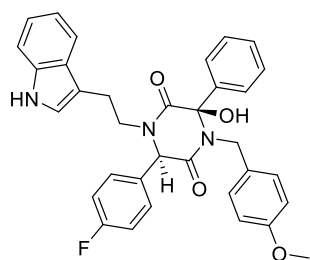
(±) **5j**, brown oil, yield 71%, (EA/Hex = 30%,  $R_f$  = 0.25), purity 97%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (s, 1H), 7.48 – 7.42 (m, 3H), 7.28 (s, 1H), 7.23 (s, 1H), 7.13 (dt,  $J$  = 17.2, 6.3 Hz, 7H), 7.00 (t,  $J$  = 7.4 Hz, 1H), 6.86 (d,  $J$  = 8.1 Hz, 2H), 6.72 (s, 1H), 6.67 (d,  $J$  = 8.0 Hz, 2H), 5.62 (s, 1H), 4.84 (d,  $J$  = 14.0 Hz, 1H), 4.79 (s, 1H), 4.21 (d,  $J$  = 14.0 Hz, 1H), 4.12 (ddd,  $J$  = 12.8, 7.9, 4.8 Hz, 1H), 3.79 (s, 3H), 3.16 – 3.07 (m, 1H), 3.04 – 2.96 (m, 1H), 2.89 (dd,  $J$  = 13.3, 7.5 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.89, 164.81, 158.89, 139.36, 136.25, 132.29, 131.36, 130.86, 129.86, 129.21, 128.51, 126.83, 126.28, 122.58, 122.19, 119.66, 118.29, 113.55, 111.43, 85.41, 64.39, 55.35, 47.42, 47.20, 22.71. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{34}\text{H}_{31}\text{BrN}_3\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  624.1493, found 624.1472.

*1-(2-(1H-indol-3-yl)ethyl)-6-(3,4-dichlorophenyl)-3-hydroxy-4-(4-methoxybenzyl)-3-phenylpiperazine-2,5-dione*



(±) **5k**, brown oil, yield 66%, (EA/Hex = 30%,  $R_f$  = 0.25), purity 95%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (s, 1H), 7.46 (dd,  $J$  = 7.8, 5.7 Hz, 3H), 7.28 (d,  $J$  = 4.1 Hz, 1H), 7.24 (s, 1H), 7.20 – 7.14 (m, 3H), 7.09 (t,  $J$  = 7.5 Hz, 3H), 7.02 (t,  $J$  = 7.4 Hz, 1H), 6.89 (d,  $J$  = 8.6 Hz, 2H), 6.75 – 6.71 (m, 2H), 6.68 (dd,  $J$  = 8.4, 1.8 Hz, 1H), 5.59 (s, 1H), 4.87 (d,  $J$  = 13.9 Hz, 1H), 4.70 (s, 1H), 4.26 (d,  $J$  = 13.9 Hz, 1H), 4.20 – 4.12 (m, 1H), 3.81 (s, 3H), 3.19 – 3.10 (m, 1H), 3.05 – 2.97 (m, 1H), 2.89 (dd,  $J$  = 13.4, 7.7 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.97, 164.46, 158.95, 139.20, 136.24, 133.33, 132.51, 130.92, 130.08, 129.77, 129.48, 128.59, 126.72, 126.08, 122.42, 119.72, 118.23, 113.55, 111.52, 111.23, 85.23, 64.01, 55.36, 47.47, 47.13, 22.70. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{34}\text{H}_{30}\text{Cl}_2\text{N}_3\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  614.1608, found 614.1529.

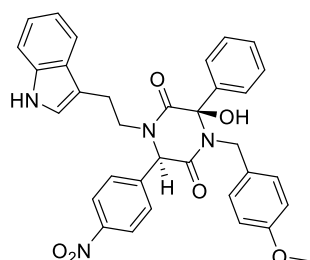
*1-(2-(1H-indol-3-yl)ethyl)-6-(4-fluorophenyl)-3-hydroxy-4-(4-methoxybenzyl)-3-phenylpiperazine-2,5-dione*



(±) **5l**, brown oil, yield 70%, (EA/Hex = 30%,  $R_f$  = 0.25), purity 93%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (s, 1H), 7.46 (dd,  $J$  = 7.8, 4.8 Hz, 3H), 7.27 – 7.23 (m, 2H), 7.18 – 7.10 (m, 5H), 7.01 (t,  $J$  = 7.5 Hz, 1H), 6.87 (d,  $J$  = 8.6 Hz, 2H), 6.80 – 6.70 (m, 5H), 5.60 (s, 1H), 4.85 (d,  $J$  = 16.1 Hz, 2H), 4.21 (d,  $J$  = 14.0 Hz, 1H), 4.13 (ddd,  $J$  = 13.1, 8.3, 4.6 Hz, 1H), 3.80 (s, 3H), 3.18 – 3.08 (m, 1H), 3.05 – 2.97 (m, 1H), 2.91 (dd,  $J$  = 13.2, 7.7 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.89, 165.15, 158.88, 139.41, 136.24, 130.85, 129.91, 129.17, 128.51, 126.85, 126.30, 122.35, 119.64, 118.30,

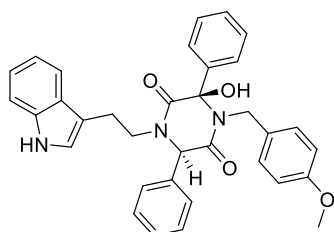
115.30, 115.09, 113.54, 111.45, 85.38, 64.24, 55.34, 47.28, 47.14, 46.93, 22.70.  
HRMS (ESI)  $m/z$  calcd for  $C_{34}H_{31}FN_3O_4^+$  (M+H)<sup>+</sup> 614.1529, found 614.1522.

*1-(2-(1H-indol-3-yl)ethyl)-3-hydroxy-4-(4-methoxybenzyl)-6-(4-nitrophenyl)-3-phenylpiperazine-2,5-dione*



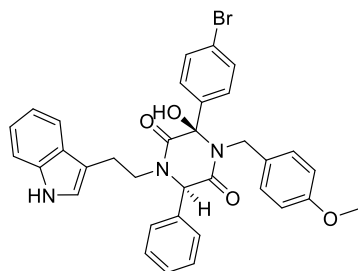
(±) **5m**, brown oil, yield 64%, (EA/Hex = 30%,  $R_f$  = 0.25), purity 91%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.82 (d,  $J$  = 8.8 Hz, 2H), 7.71 (s, 1H), 7.46 (dd,  $J$  = 14.1, 8.2 Hz, 3H), 7.30 (d,  $J$  = 8.2 Hz, 1H), 7.22 (d,  $J$  = 7.3 Hz, 1H), 7.17 (dd,  $J$  = 11.2, 4.0 Hz, 1H), 7.09 (t,  $J$  = 7.8 Hz, 2H), 7.05 – 6.98 (m, 3H), 6.91 (dd,  $J$  = 8.8, 2.2 Hz, 4H), 6.71 (d,  $J$  = 2.2 Hz, 1H), 5.58 (s, 1H), 4.87 (d,  $J$  = 13.9 Hz, 1H), 4.80 (s, 1H), 4.29 (d,  $J$  = 13.9 Hz, 1H), 4.26 – 4.17 (m, 1H), 3.83 (s, 3H), 3.18 (dt,  $J$  = 15.5, 7.9 Hz, 1H), 3.09 – 2.99 (m, 1H), 2.94 – 2.85 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 168.05, 164.10, 159.02, 147.54, 140.25, 139.30, 136.27, 130.96, 129.66, 129.37, 128.59, 127.40, 126.65, 125.99, 123.12, 122.48, 119.75, 118.13, 113.56, 111.56, 111.10, 85.12, 64.72, 55.36, 47.62, 47.07, 29.71, 22.72. HRMS (ESI)  $m/z$  calcd for  $C_{34}H_{31}N_4O_6^+$  (M+H)<sup>+</sup> 591.2293, found 591.2290.

*1-(2-(1H-indol-3-yl)ethyl)-3-hydroxy-4-(4-methoxybenzyl)-3,6-diphenylpiperazine-2,5-dione*



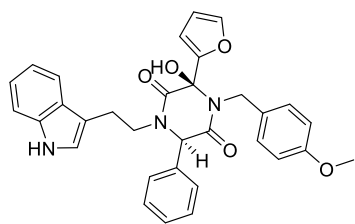
(±) **5n**, brown oil, yield 73%, (EA/Hex = 30%,  $R_f$  = 0.3), purity 92%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (s, 1H), 7.48 (t,  $J$  = 7.0 Hz, 3H), 7.29 (d,  $J$  = 8.1 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.18 – 7.11 (m, 6H), 7.07–7.00 (m, 3H), 6.90–6.84 (m, 4H), 6.78 (d,  $J$  = 1.3 Hz, 1H), 5.49 (s, 1H), 4.92 – 4.83 (m, 2H), 4.22 – 4.12 (m, 2H), 3.82 (s, 3H), 3.20 – 3.10 (m, 1H), 3.07 – 2.99 (m, 1H), 2.97 – 2.88 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.91, 165.20, 158.84, 139.37, 136.20, 133.06, 130.89, 130.01, 129.02, 128.40, 128.26, 126.76, 126.34, 122.30, 119.62, 118.36, 113.48, 111.57, 111.38, 85.35, 64.78, 55.34, 47.44, 47.16, 22.64. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{34}\text{H}_{32}\text{N}_3\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  546.2393, found 546.2388.

*1-(2-(1H-indol-3-yl)ethyl)-3-(4-bromophenyl)-3-hydroxy-4-(4-methoxybenzyl)-6-phenylpiperazine-2,5-dione*



(±) **5o**, brown oil, yield 78% (EA/Hex = 30%,  $R_f$  = 0.25), purity 94%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (s, 1H), 7.45 – 7.40 (m, 3H), 7.21 (d,  $J$  = 5.9 Hz, 4H), 7.11 (d,  $J$  = 7.9 Hz, 3H), 6.98 (t,  $J$  = 8.2 Hz, 3H), 6.85 (dd,  $J$  = 15.6, 8.1 Hz, 4H), 6.72 (s, 1H), 5.63 (s, 1H), 4.93 (s, 1H), 4.80 (d,  $J$  = 14.0 Hz, 1H), 4.16 (dd,  $J$  = 15.5, 8.5 Hz, 2H), 3.77 (s, 3H), 3.09 (dd,  $J$  = 14.1, 7.0 Hz, 1H), 3.01 – 2.90 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.52, 165.16, 158.90, 138.47, 136.26, 133.09, 131.44, 130.81, 129.78, 128.72, 128.18, 126.92, 126.68, 123.44, 122.33, 119.62, 118.34, 113.58, 111.46, 85.25, 64.67, 55.35, 47.61, 47.02, 22.73. HRMS (ESI)  $m/z$  calcd for  $\text{C}_{34}\text{H}_{31}\text{BrN}_3\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  624.1487, found 624.1493.

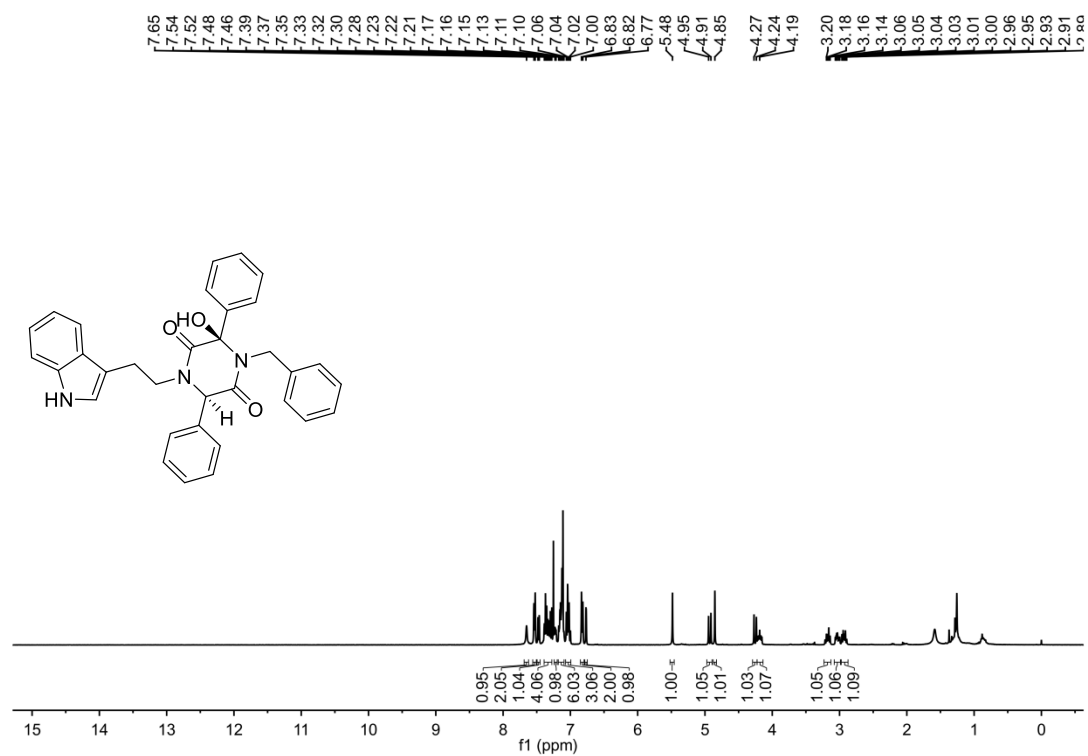
*1-(2-(1H-indol-3-yl)ethyl)-3-(furan-2-yl)-3-hydroxy-4-(4-methoxybenzyl)-6-phenylpiperazine-2,5-dione*



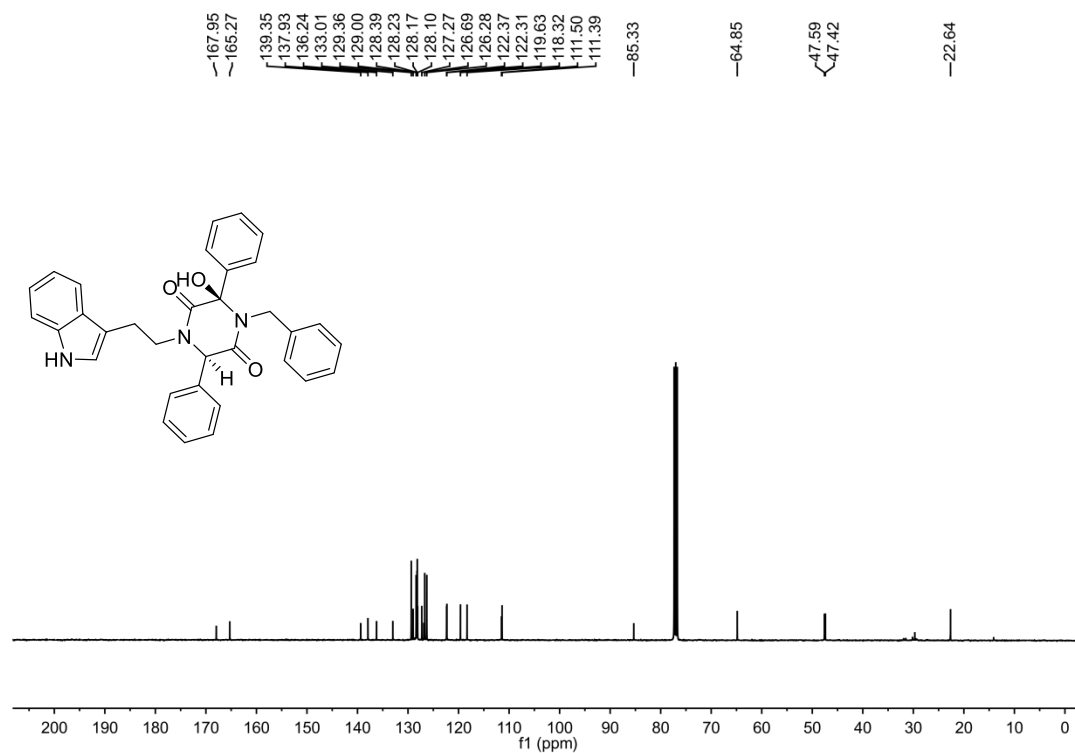
(±) **5p**, brown oil, yield 70%, (EA/Hex = 30%,  $R_f$  = 0.25), purity 95%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.89 (s, 1H), 7.45 (d,  $J$  = 7.9 Hz, 1H), 7.39 (d,  $J$  = 8.5 Hz, 2H), 7.25 – 7.17 (m, 5H), 7.13 (t,  $J$  = 7.6 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.83 (d,  $J$  = 8.5 Hz, 2H), 6.77 (d,  $J$  = 1.5 Hz, 1H), 6.20 – 6.10 (m, 2H), 5.49 (s, 1H), 4.87 (s, 1H), 4.70 (d,  $J$  = 14.2 Hz, 1H), 4.34 (d,  $J$  = 14.1 Hz, 1H), 4.15 (t,  $J$  = 8.9 Hz, 1H), 3.78 (s, 3H), 3.11 (dd,  $J$  = 19.4, 9.8 Hz, 1H), 3.04 – 2.95 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.76, 164.96, 158.79, 151.35, 143.08, 136.26, 134.04, 130.69, 129.83, 128.42, 126.98, 122.28, 119.57, 118.41, 113.50, 111.50, 110.92, 109.93, 81.34, 65.00, 55.31, 47.42, 46.64, 22.68. HRMS (ESI)  $m/z$  calcd for C<sub>32</sub>H<sub>30</sub>N<sub>3</sub>O<sub>5</sub><sup>+</sup>(M+H)<sup>+</sup> 536.2177, found 536.2180



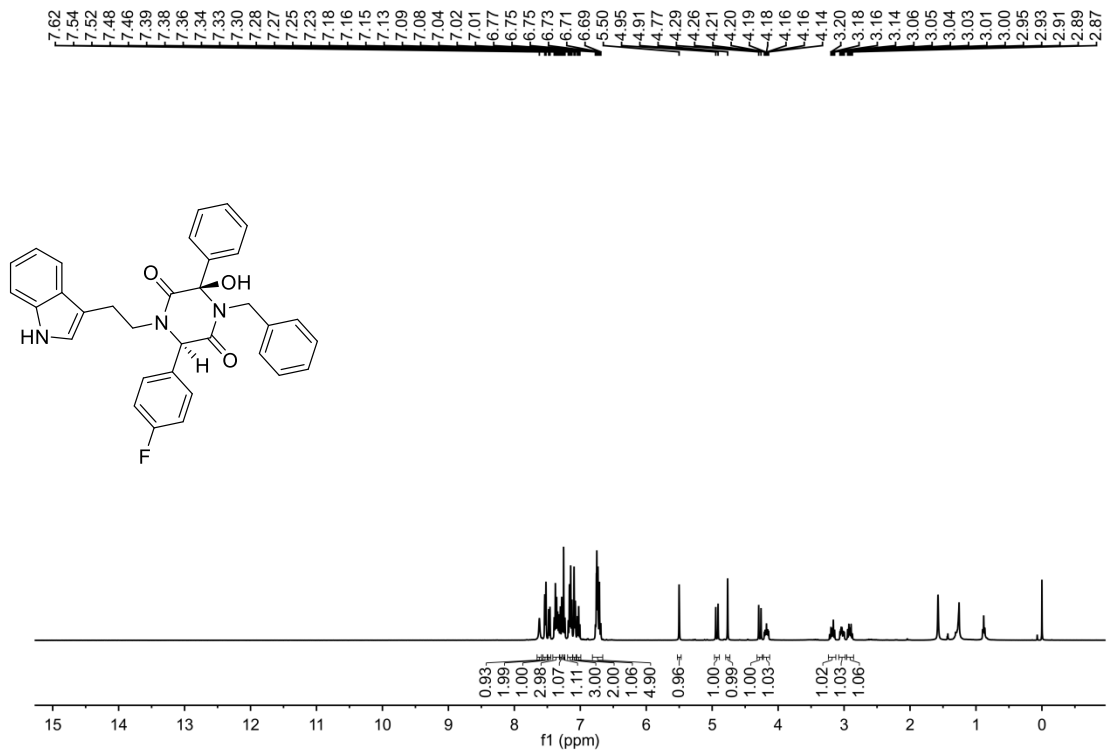
## NMR Characterization Figures of Products



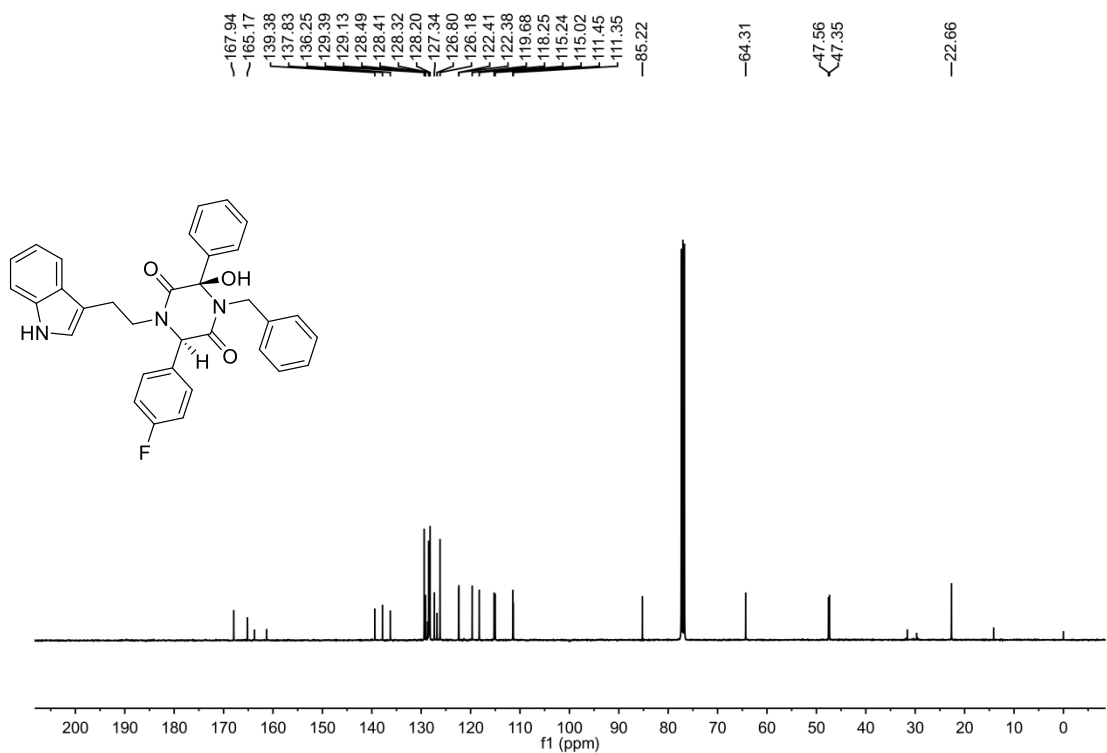
<sup>1</sup>H NMR spectrum of (±) 5a



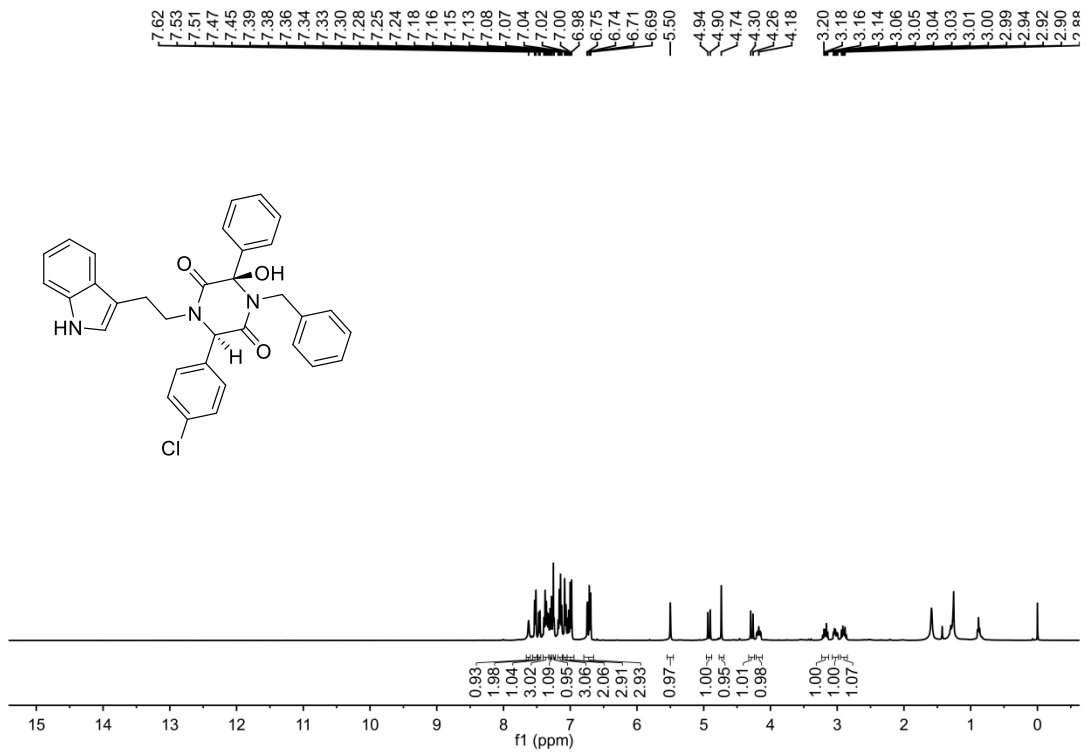
<sup>13</sup>C NMR spectrum of (±) 5a



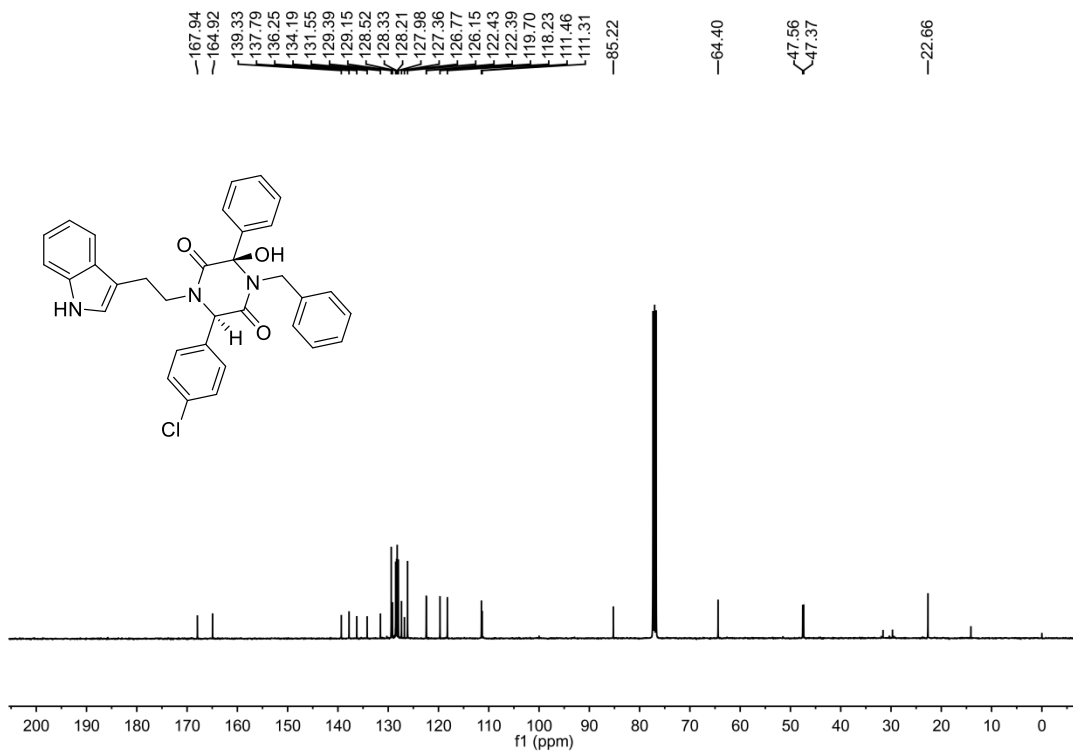
<sup>1</sup>H NMR spectrum of (±) **5b**



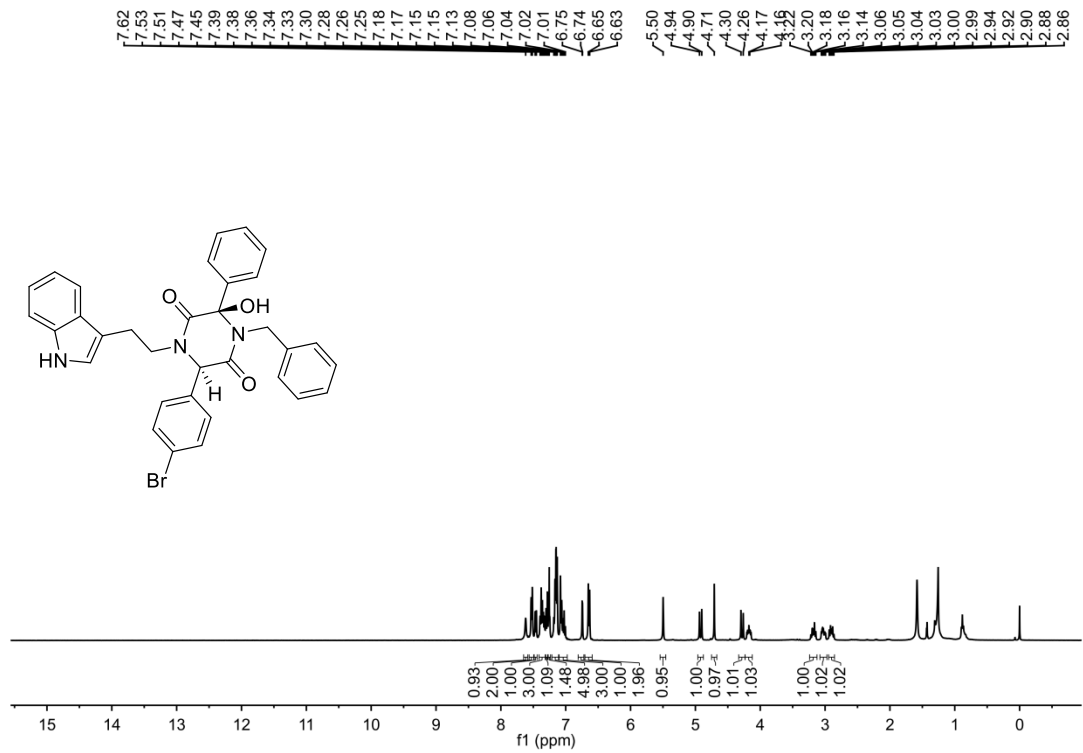
<sup>13</sup>C NMR spectrum of (±) **5b**



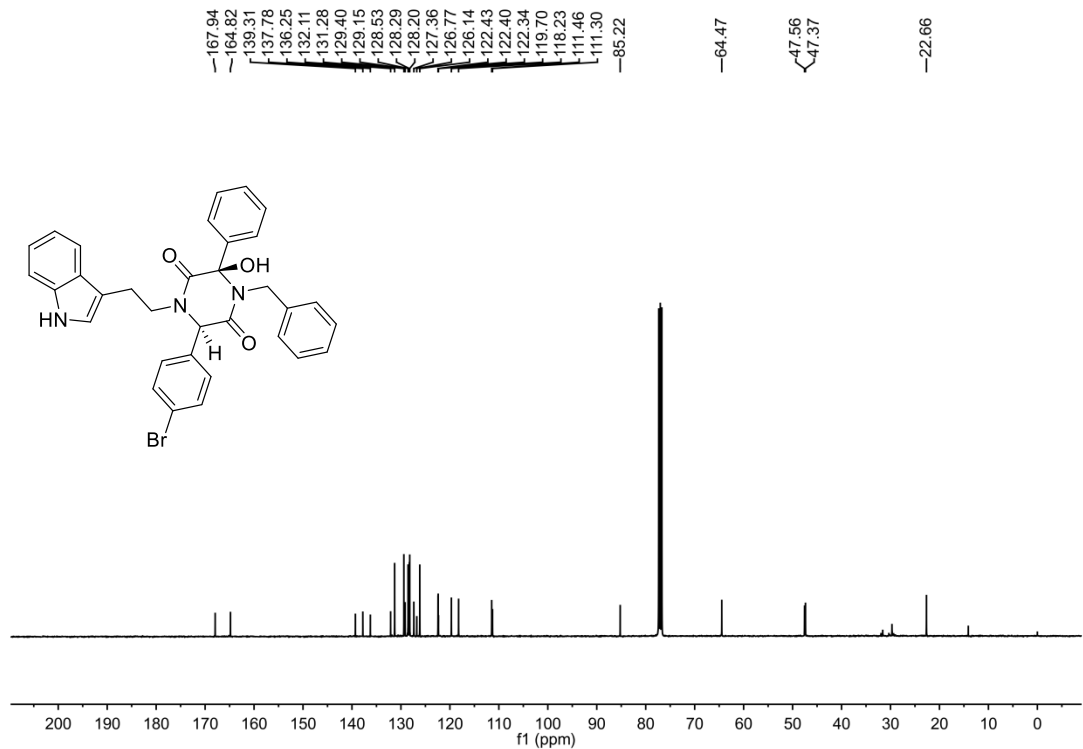
<sup>1</sup>H NMR spectrum of ( $\pm$ ) **5c**



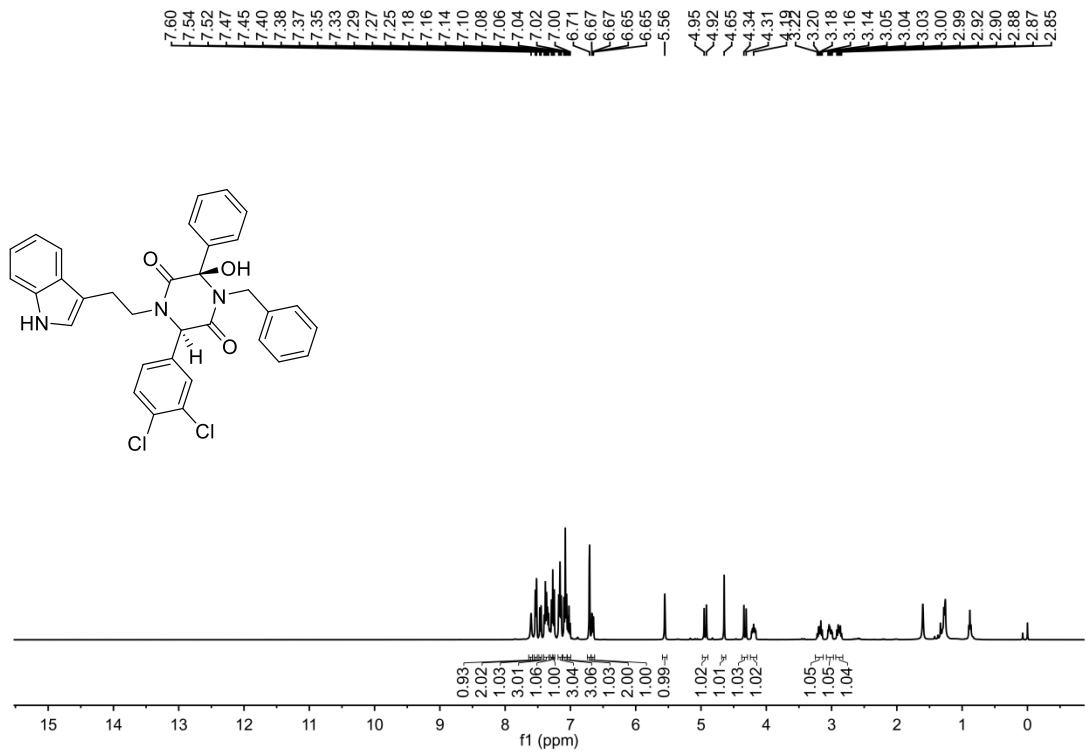
<sup>13</sup>C NMR spectrum of ( $\pm$ ) **5c**



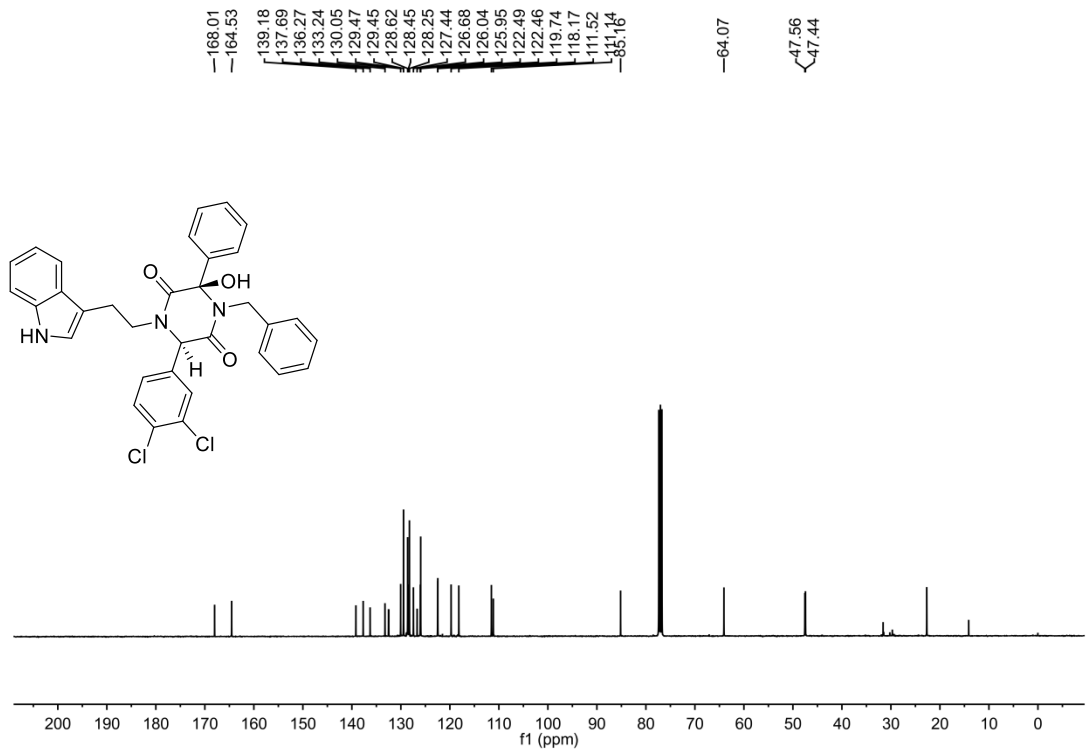
$^1\text{H}$  NMR spectrum of ( $\pm$ ) **5d**



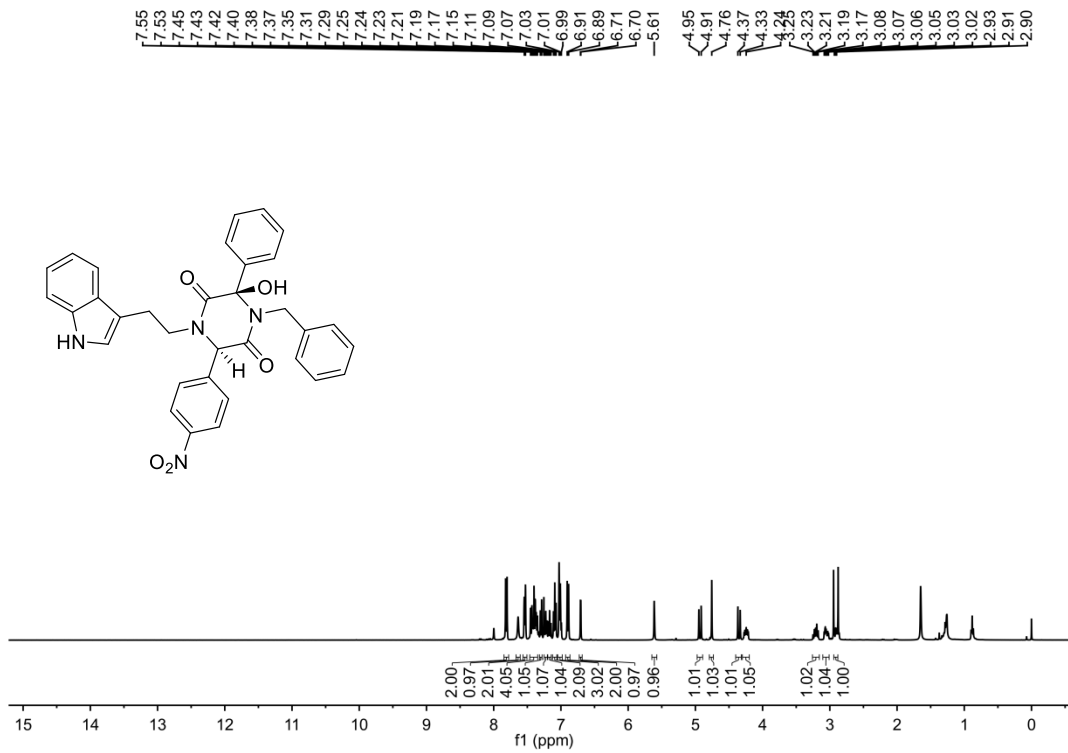
$^{13}\text{C}$  NMR spectrum of ( $\pm$ ) **5d**



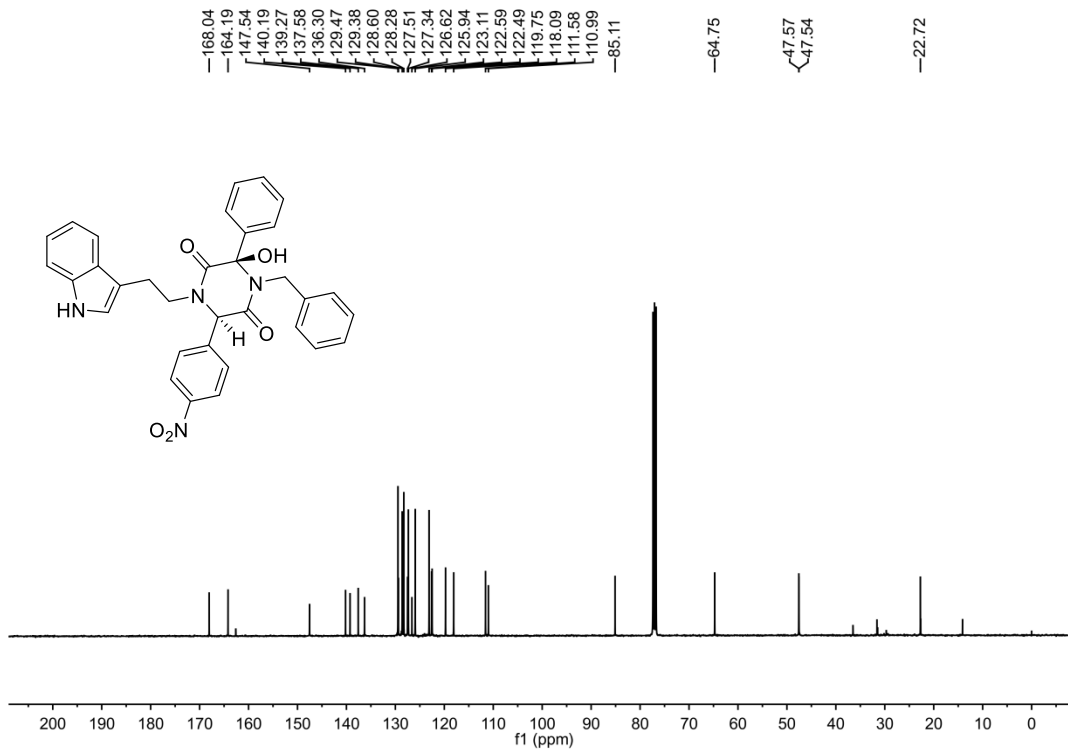
<sup>1</sup>H NMR spectrum of ( $\pm$ ) **5e**



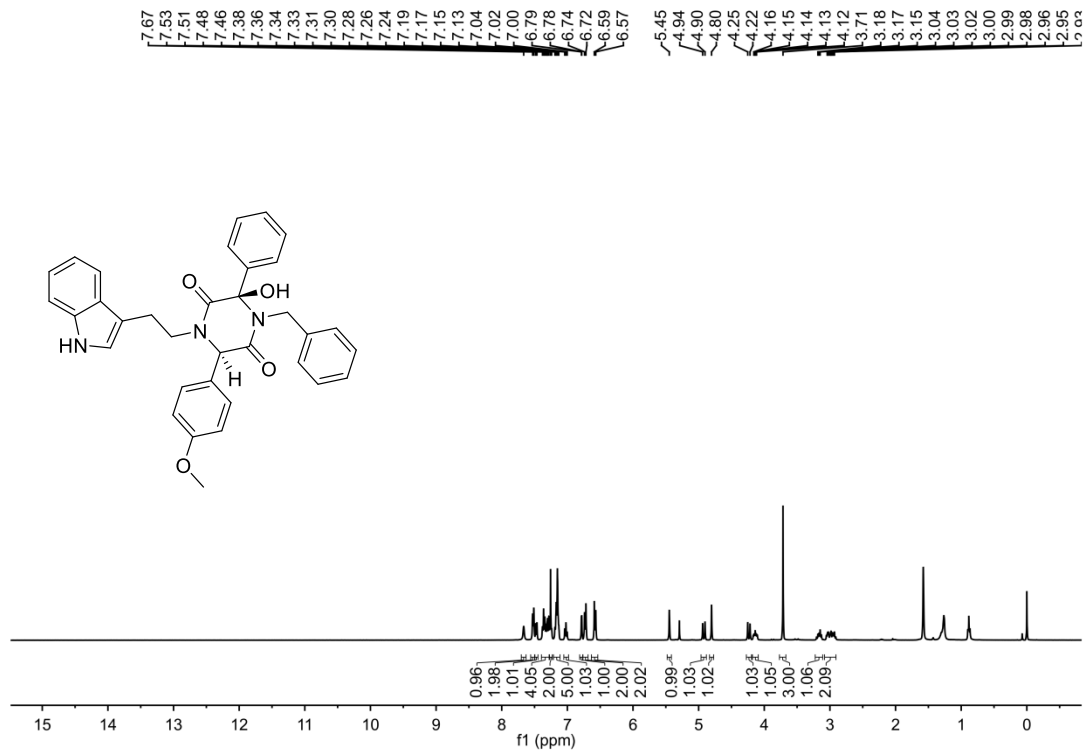
<sup>13</sup>C NMR spectrum of ( $\pm$ ) **5e**



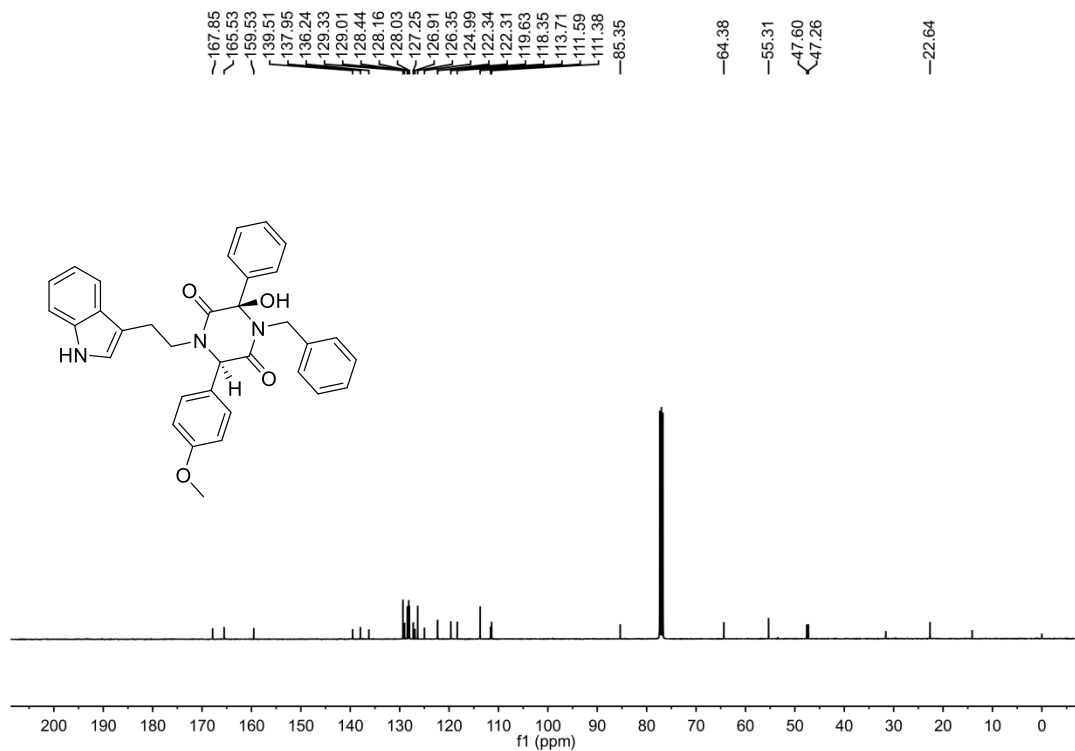
<sup>1</sup>H NMR spectrum of ( $\pm$ ) **5f**



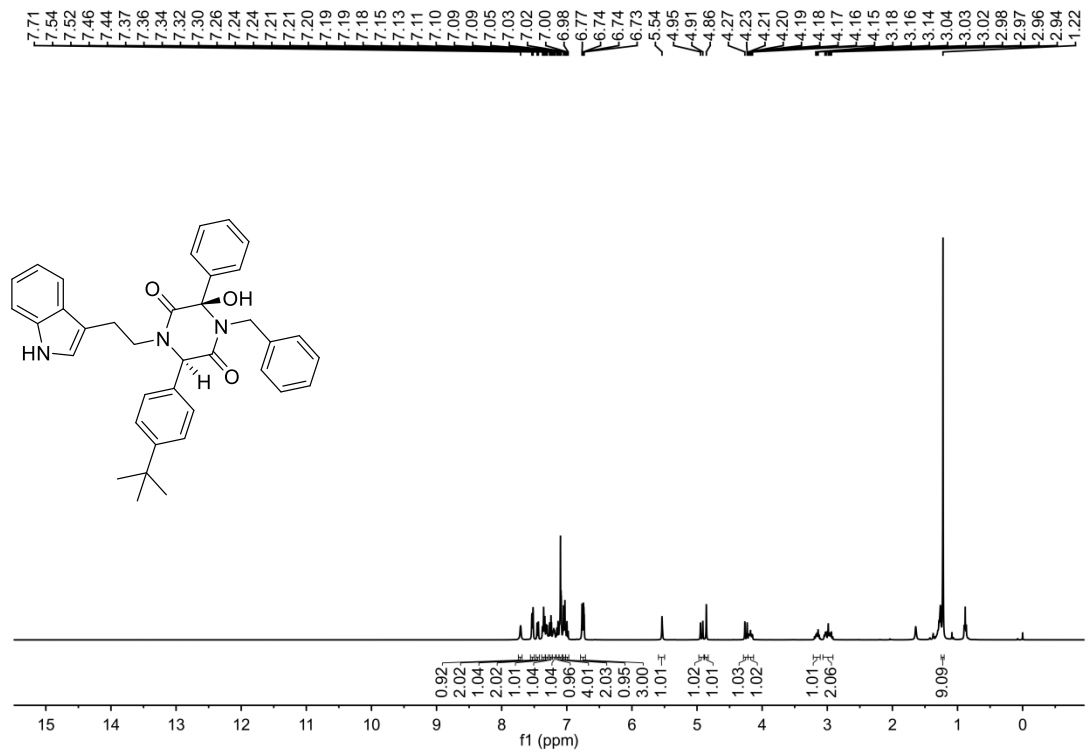
<sup>13</sup>C NMR spectrum of ( $\pm$ ) **5f**



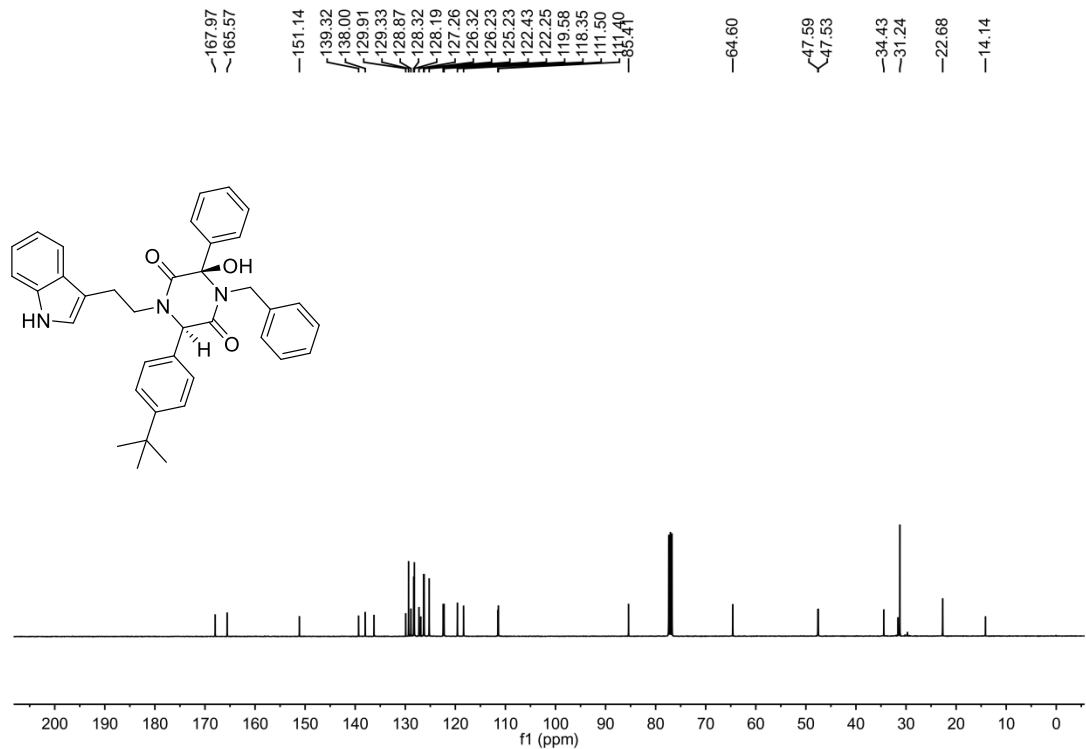
**<sup>1</sup>H NMR spectrum of (±) 5g**



**<sup>13</sup>C NMR spectrum of (±) 5g**

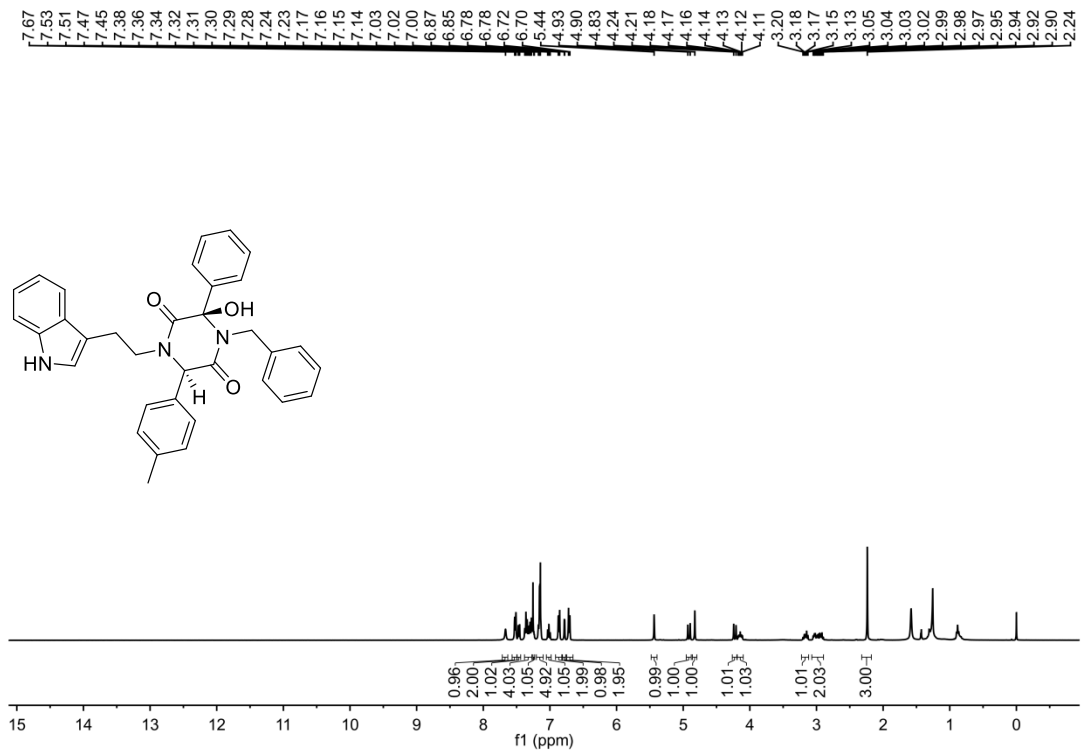


$^1\text{H}$  NMR spectrum of ( $\pm$ ) **5h**

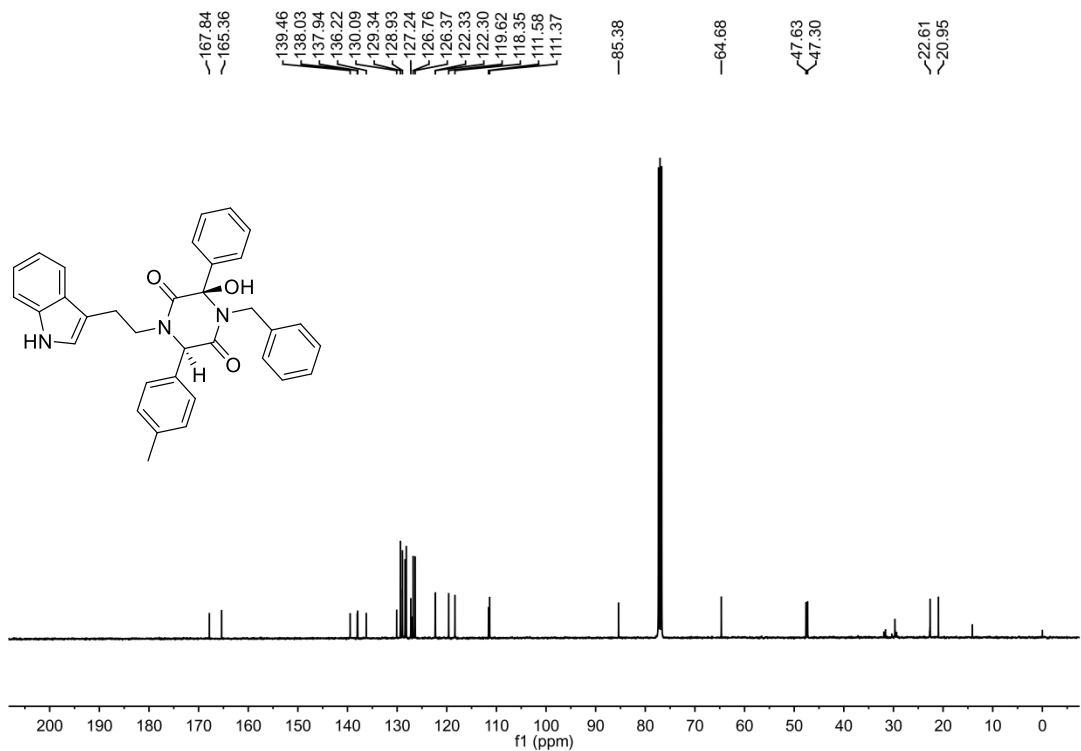


$^{13}\text{C}$  NMR spectrum of ( $\pm$ ) **5h**

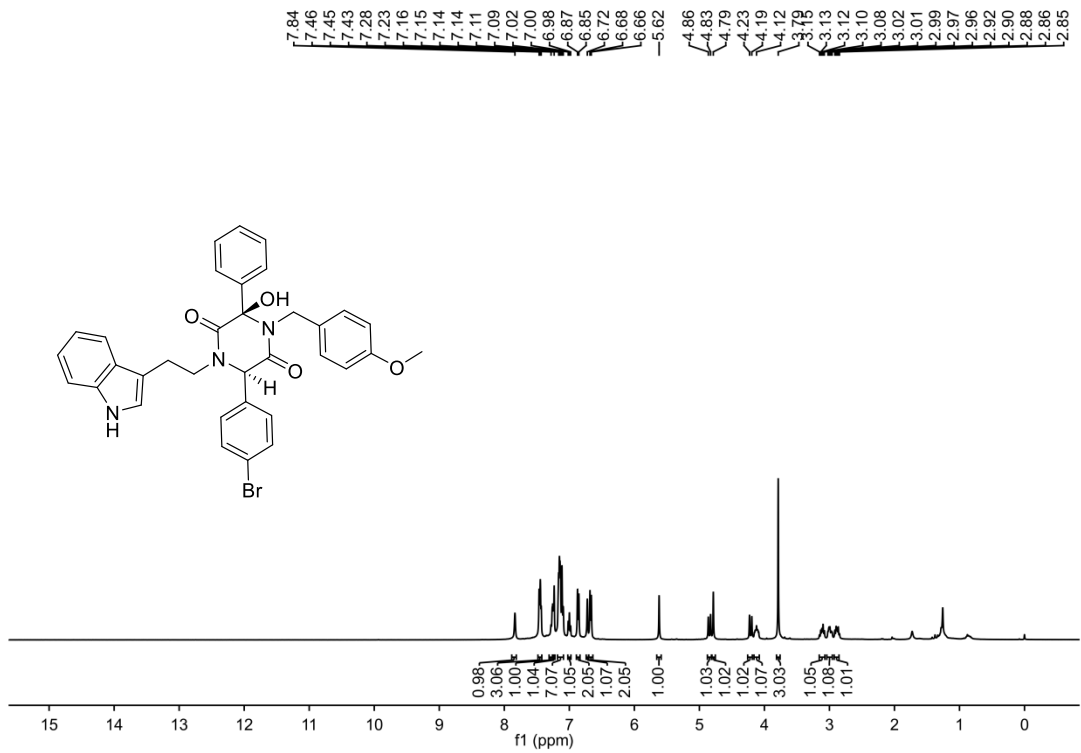




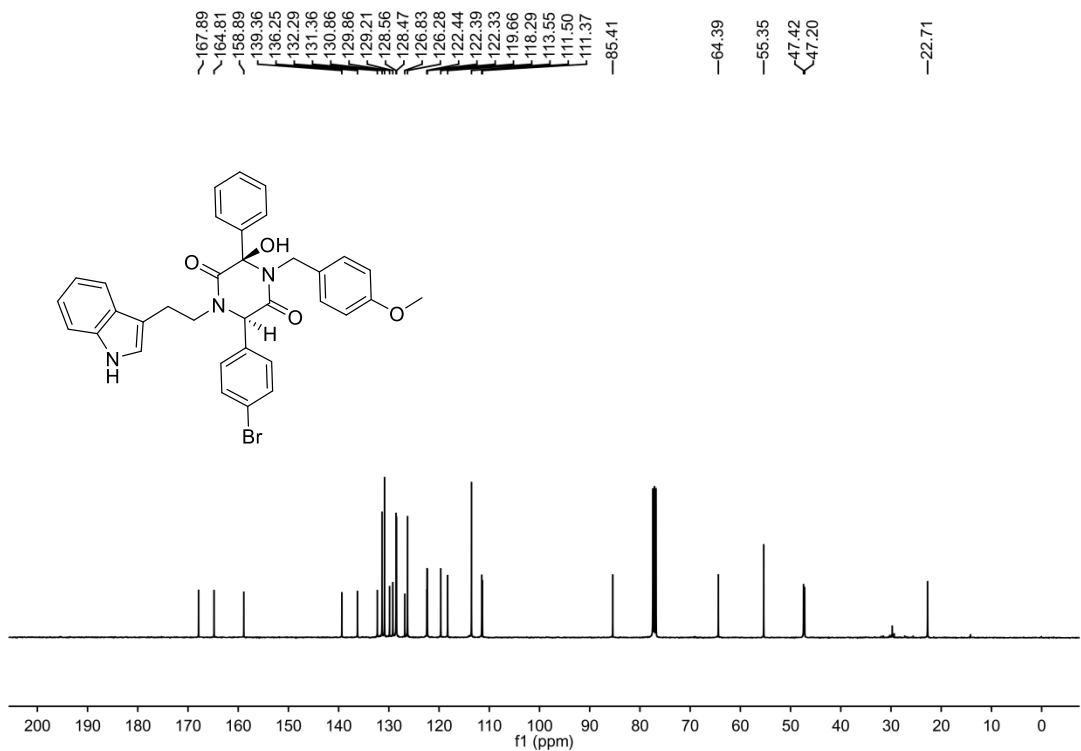
**<sup>1</sup>H NMR spectrum of (±) 5i**



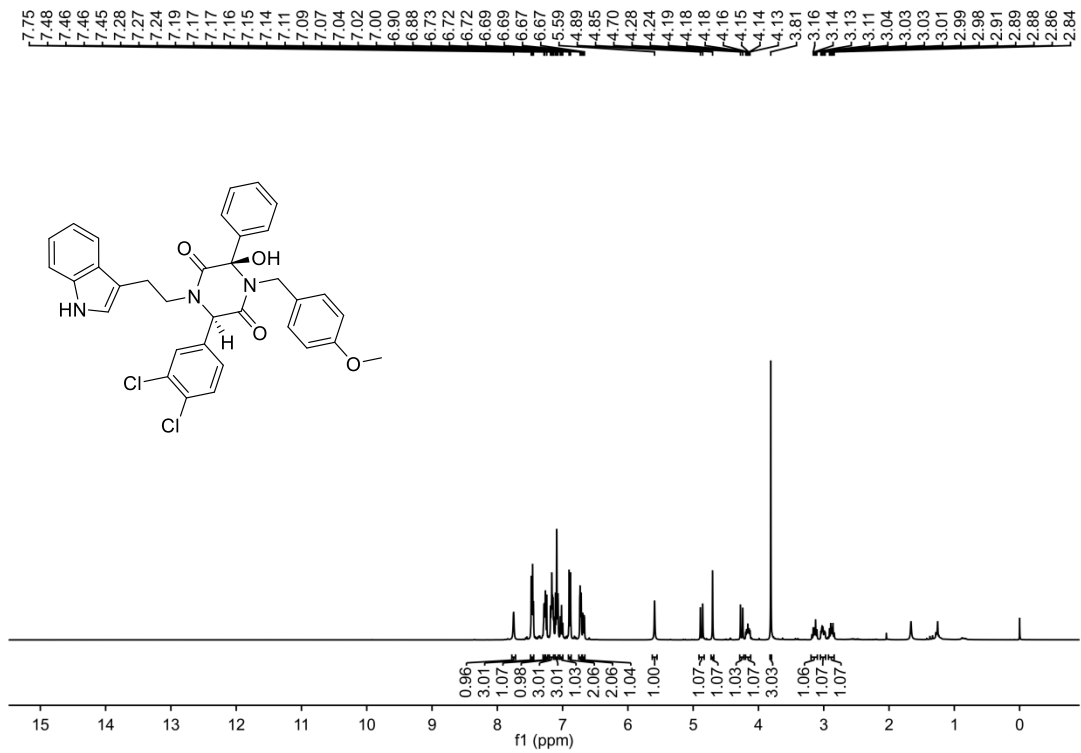
**<sup>13</sup>C NMR spectrum of (±) 5i**



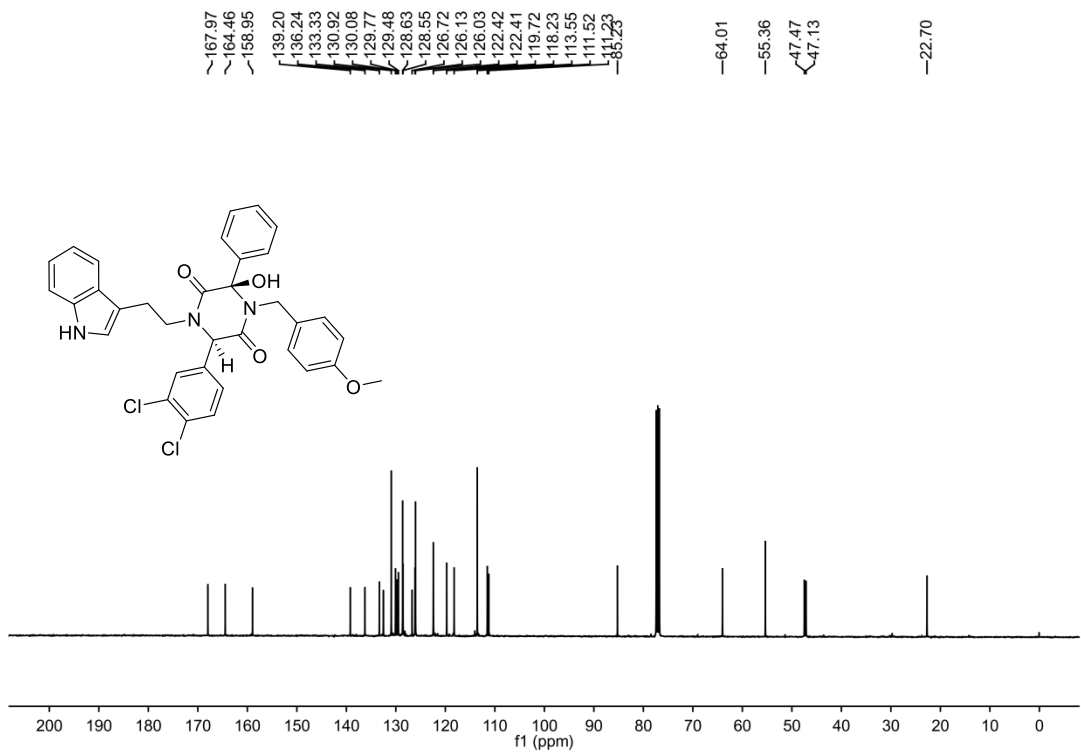
**<sup>1</sup>H NMR spectrum of (±) 5j**



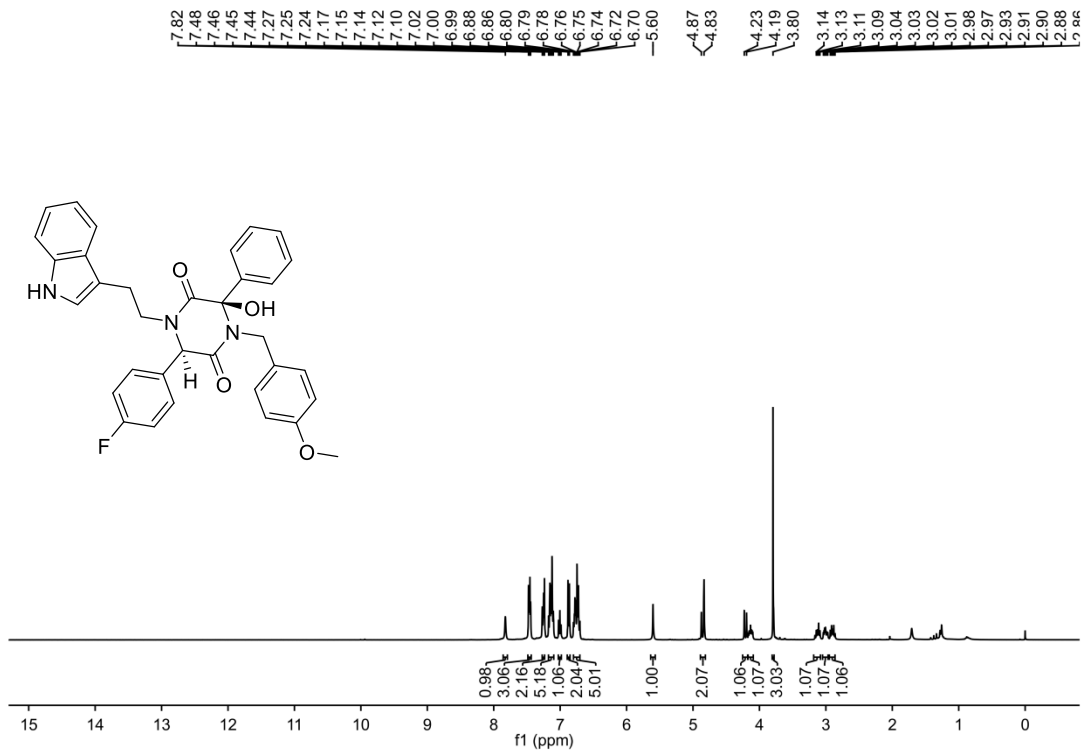
**<sup>13</sup>C NMR spectrum of (±) 5j**



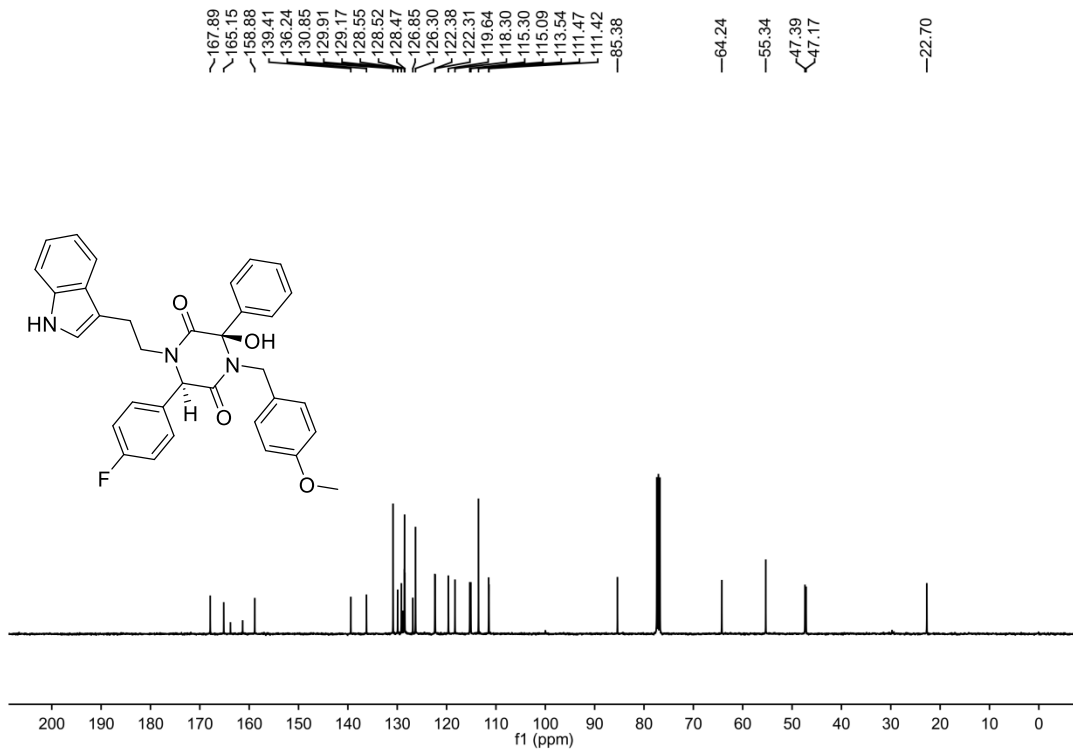
<sup>1</sup>H NMR spectrum of (±) 5k



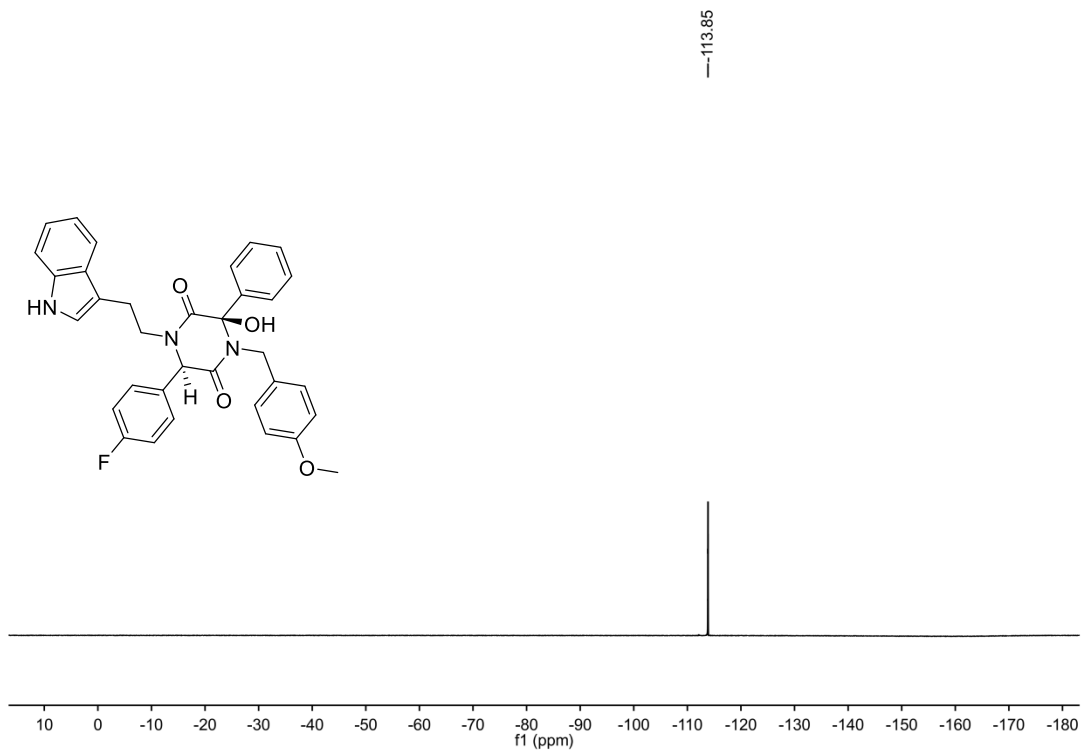
<sup>13</sup>C NMR spectrum of (±) 5k



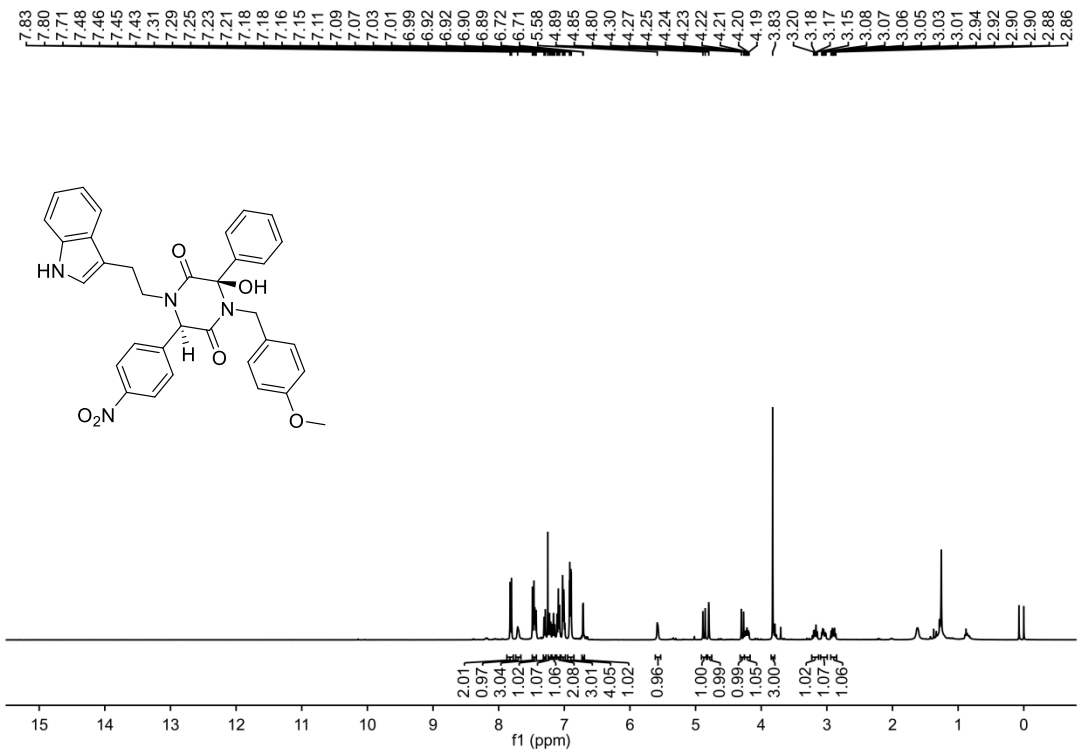
$^1\text{H}$  NMR spectrum of ( $\pm$ ) **51**



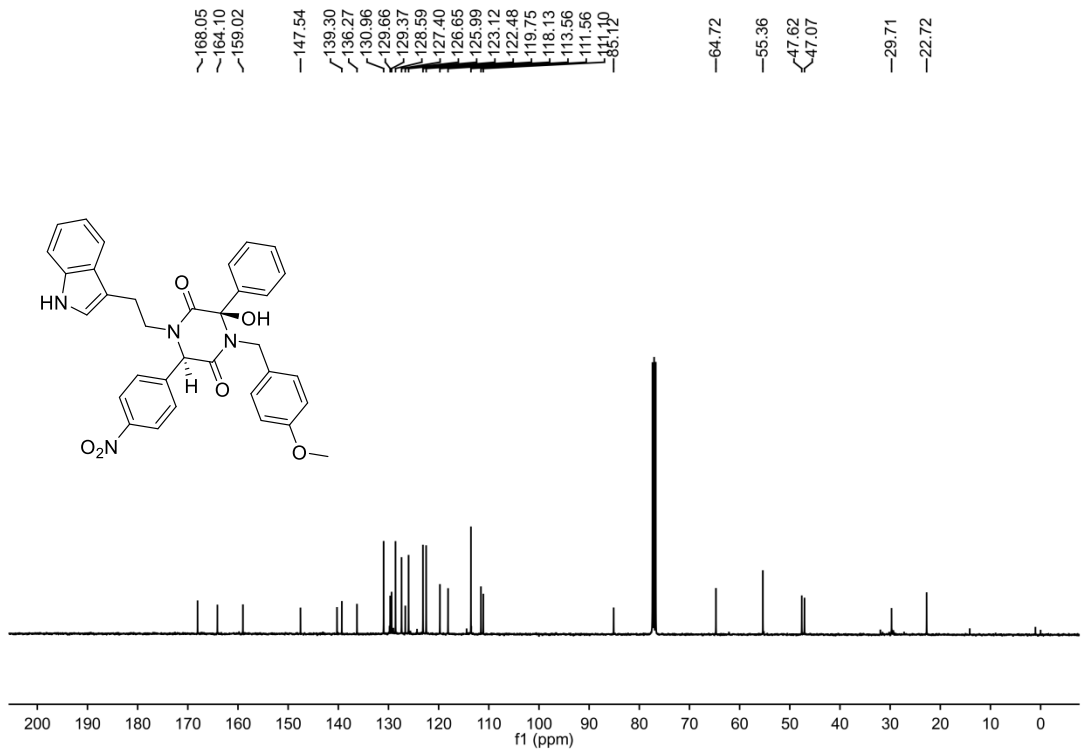
$^{13}\text{C}$  NMR spectrum of ( $\pm$ ) **51**



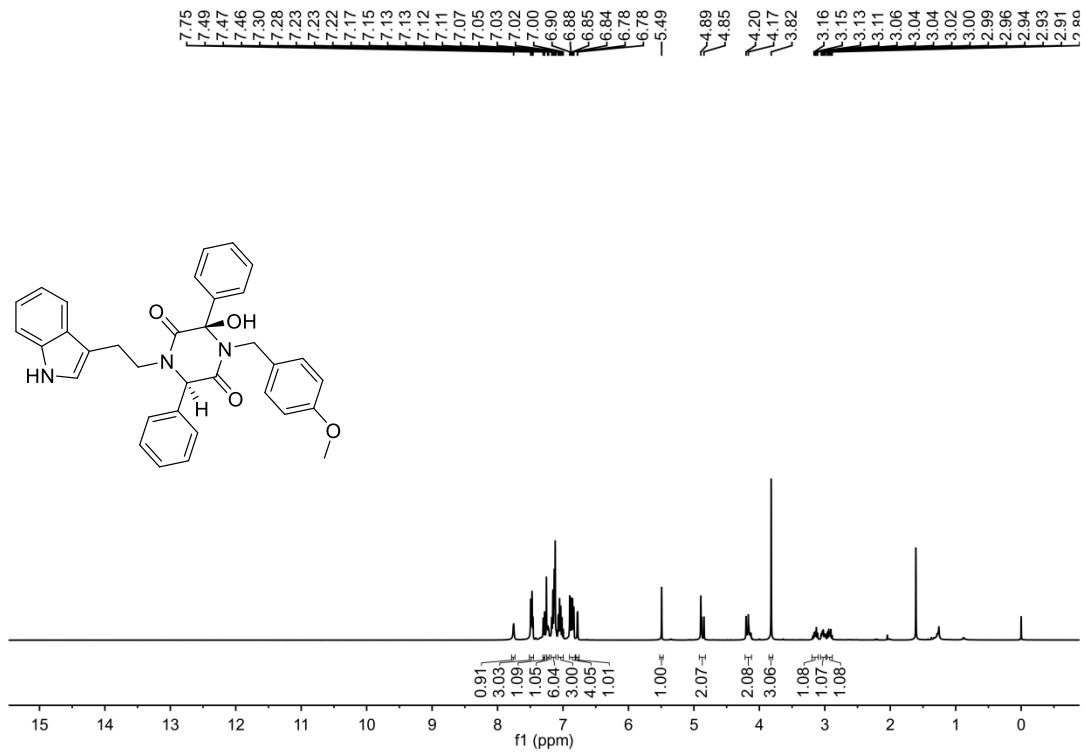
$^{19}\text{F}$  NMR spectrum of ( $\pm$ ) **51**



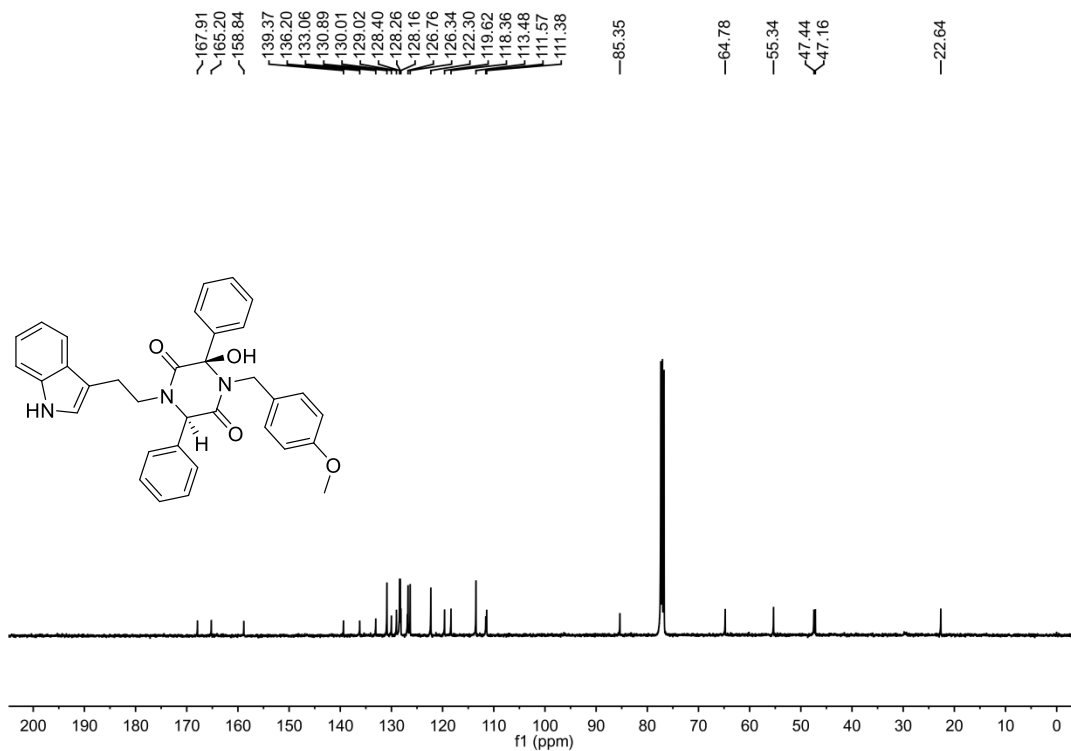
<sup>1</sup>H NMR spectrum of (±) 5m



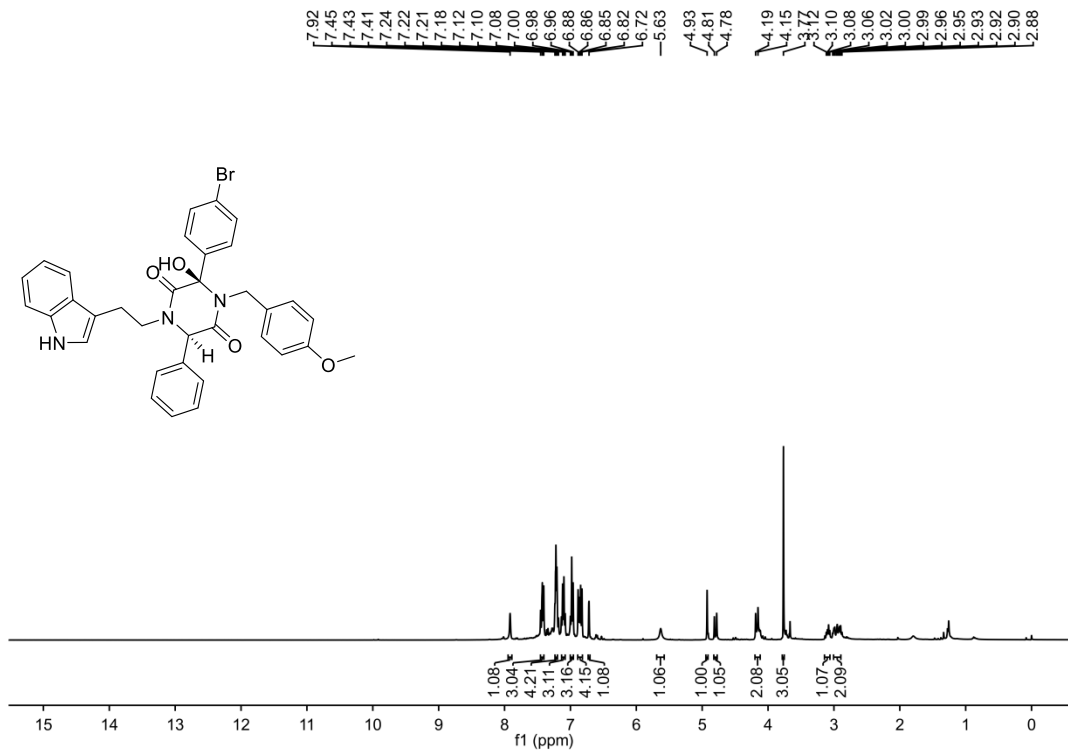
<sup>13</sup>C NMR spectrum of (±) 5m



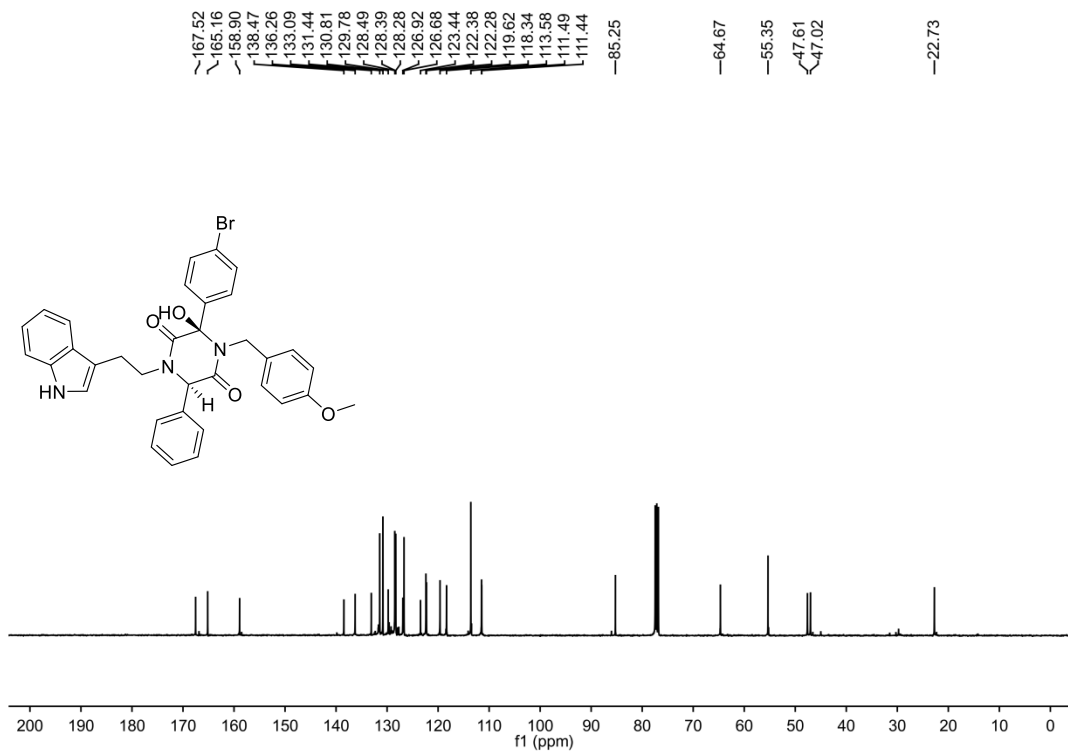
$^1\text{H}$  NMR spectrum of ( $\pm$ ) **5n**



$^{13}\text{C}$  NMR spectrum of ( $\pm$ ) **5n**

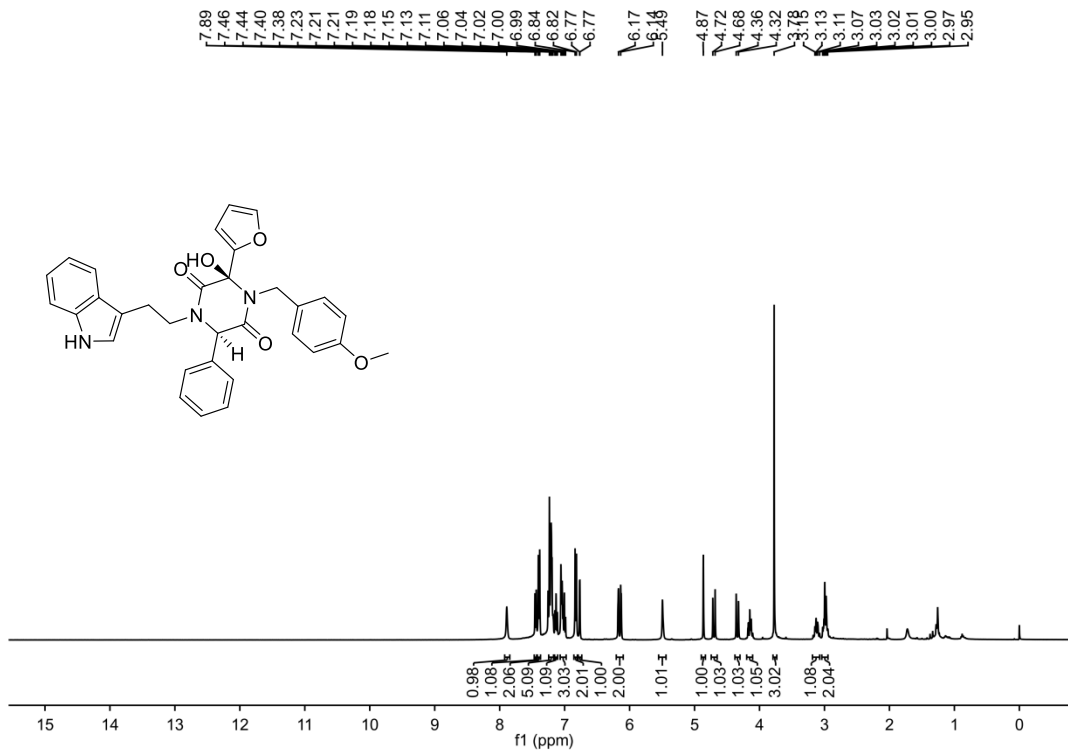


<sup>1</sup>H NMR spectrum of (±) 50

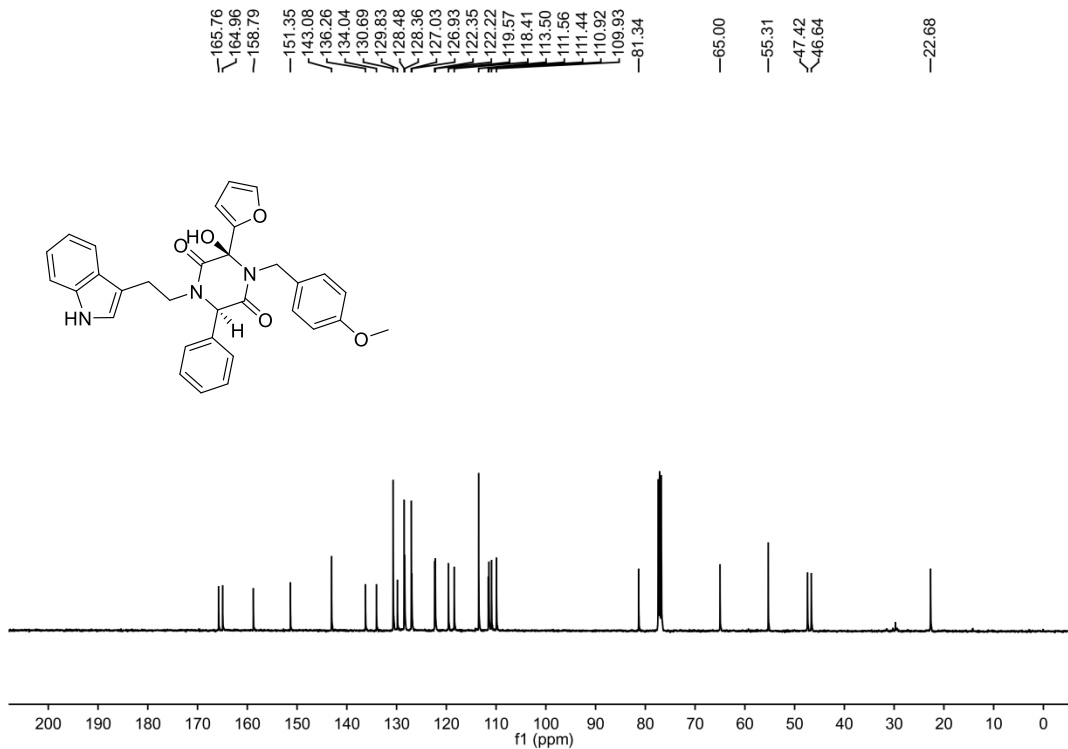


<sup>13</sup>C NMR spectrum of (±) 50





<sup>1</sup>H NMR spectrum of ( $\pm$ ) **5p**



<sup>13</sup>C NMR spectrum of ( $\pm$ ) **5p**