Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

A New Method to Access Triazole-fused Spiro-guanidines from the Reaction of Isothiocyanates tethered N-Sulfonyl-1,2,3-triazoles and Amines

Hou-Lu Liu,[a] Yu Jiang,[b] Xiang-Ying Tang,[,b] Jian Hao,*[,a] and Min Shi*[,b]*

[a] Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China.

523396330@qq.com.

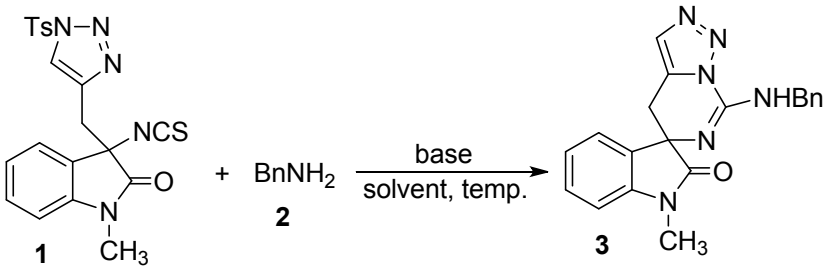
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China. *siocxiangying@mail.sioc.ac.cn*.

mshi@mail.sioc.ac.cn. *Fax 86-21-64166128.*

CONTENTS

General remarks. Unless otherwise stated, all reactions and manipulations were performed using standard Schlenk techniques. All solvents were purified by distillation using standard methods. Commercially available reagents were used without further purification. Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. ^{1}H and ^{13}C NMR spectroscopic were recorded by using a AM-400 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR and ^{13}C-NMR chemical shift were referenced to 0.00 ppm (TMS) and 77.0 ppm ($CDCl_3$), respectively; coupling constants *J* are given in Hz. Infrared spectroscopic were recorded on a Perkin-Elmer PE-983 spectrometer with absorption in cm^{-1}. Mass spectroscopic were recorded by EI, ESI, MALDI and HRMS was measured on a HP-5989 instrument. X-ray diffraction analysis was performed by using a Bruker Smart-1000 or Bruker SMART APEXIIX-ray diffractometer. Flash column chromatography was performed by using 300-400 mesh silica gel. For thin-layer chromatography (TLC), silica gel plates (Huanghai GF254) were used.

Optimization of the reaction conditions



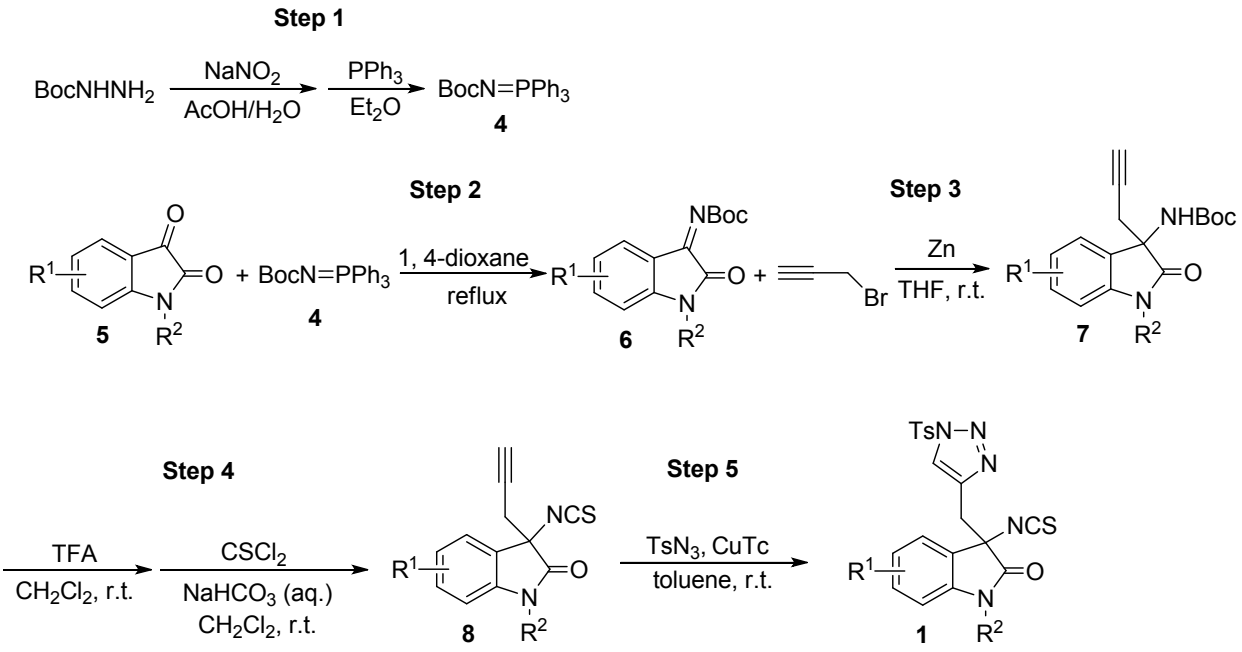
The optimization of reaction condition:[a]

Entry	**1a** (equiv.)	**2a** (equiv.)	Base (equiv.)	Temp. (°C)	Solvent	**3aa** yield[b, c] (%)
1	1.0	1.0	-	120	toluene	trace
2	1.0	1.0	-	120	CH_3CN	trace
3	1.0	1.0	-	120	1,4-dioxane	trace
4	1.0	1.0	-	120	1,3-xylene	trace
5	1.0	1.0	K_2CO_3 (2.0)	120	toluene	42
6	1.0	1.0	K_2CO_3 (2.0)	120	CH_3CN	47
7	1.0	1.0	K_2CO_3 (2.0)	120	1,4-dioxane	45 (32)
8	1.0	1.0	K_2CO_3 (2.0)	120	1,3-xylene	39
9	1.0	1.0	K_2CO_3 (2.0)	120	DMF	trace
10	1.0	1.0	K_2CO_3 (2.0)	120	DCE	trace
11	1.0	1.0	K_2CO_3 (2.0)	120	i-PrOH	40
12	1.0	1.0	K_2CO_3 (2.0)	120	H_2O	20
13	1.0	1.0	K_2CO_3 (1.0)	120	toluene	61 (58)
14	**1.0**	**1.0**	**K_2CO_3 (1.0)**	**120**	**CH_3CN**	**74 (74)**
15	1.0	1.0	K_2CO_3 (1.0)	120	1,4-dioxane	58 (42)
16	1.0	1.0	NaOH (2.0)	120	CH_3CN	37
17	1.0	1.0	KOH (2.0)	120	CH_3CN	32
18	1.0	1.0	Na_2CO_3 (1.0)	120	CH_3CN	14
19	1.0	1.0	Cs_2CO_3 (1.0)	120	CH_3CN	34
20	1.0	1.0	CsOAc (2.0)	120	CH_3CN	trace
21	1.0	1.0	K_3PO_4 (0.67)	120	CH_3CN	65 (63)
22	1.0	1.0	K_2CO_3 (1.0)	100	CH_3CN	67 (65)
23	1.0	1.0	K_2CO_3 (1.0)	80	CH_3CN	64 (63)
24[d]	1.0	1.0	K_2CO_3 (1.0)	120	CH_3CN	67 (65)
25[e]	1.0	1.0	K_2CO_3 (1.0)	120	CH_3CN	60 (56)

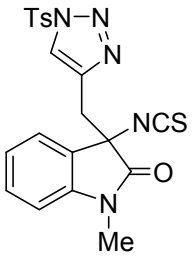
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), in solvent (1.0 mL) at the indicated temperature for 24 h under an Ar atmosphere. [b] Crude product's yields were determined by ^1H NMR spectroscopy (internal standard: 1, 3, 5-trimethoxybenzene). [c] Isolated yields are shown in parentheses. [d] The solvent is 0.5 mL. [e] The solvent is 2.0 mL.

General procedure for synthesis and spectroscopic data of substrates 1

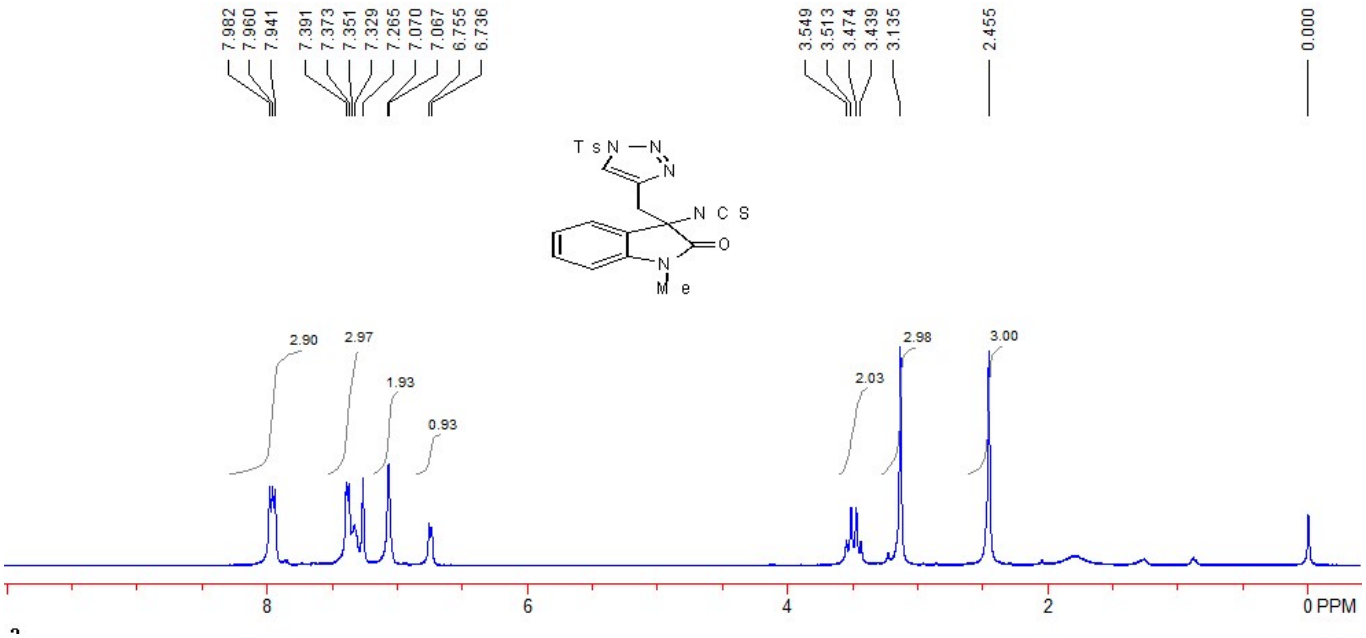
The general procedures for the synthesis of substrates **1** were refer to the references: Step 1,[1] Step 2,[2] Step 3,[3] Step 4,[4] Step 5.[5]

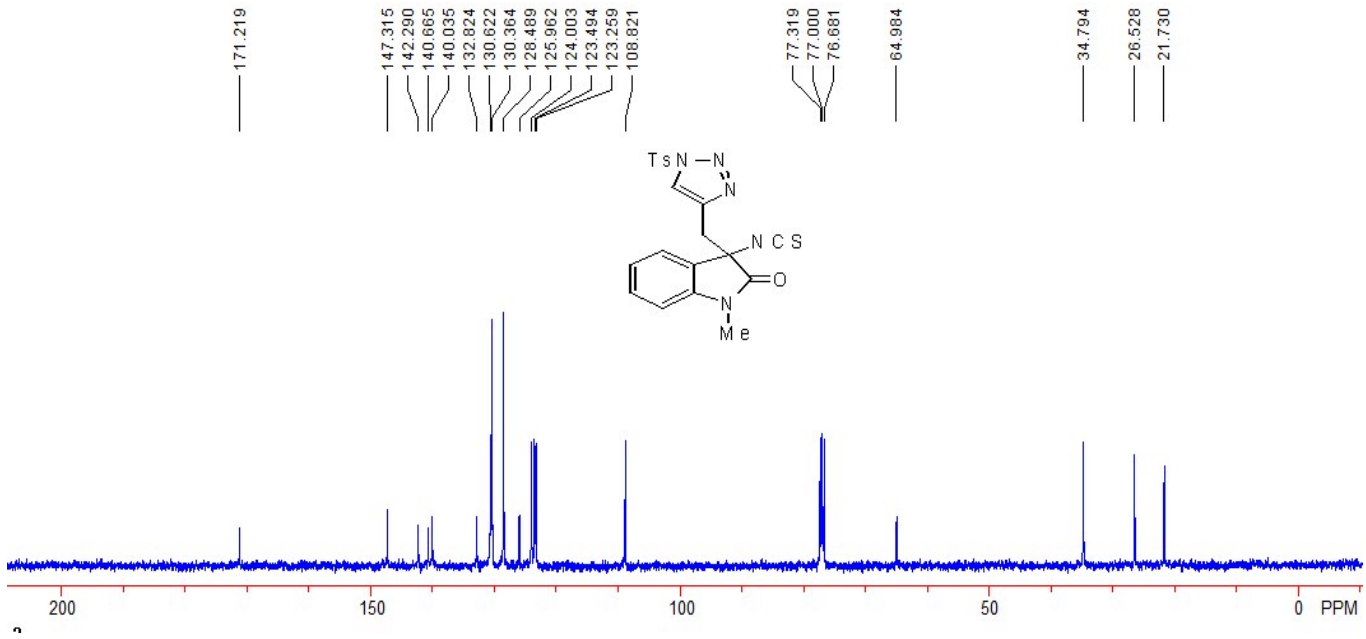


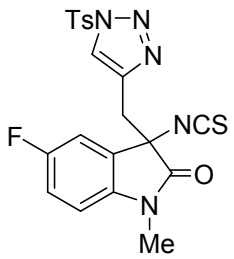
R^1 = Halogen, Methyl, Methoxyl.
R^2 = Methyl, benzyl, allyl, naphthalen-2-ylmethyl, Phenyl.
Ts = Tosyl, CuTc = Copper(I) thiophene-2-carboxylate, Bn = benzyl, Ph = phenyl, PMB = p-Methoxybenzyl.



Compound **1a**: A white solid (2.03 g, 81%); M.p. 72-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.46 (s, 3H), 3.14 (s, 3H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.53 (d, *J* = 14.4 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 7.067-7.070 (m, 2H), 7.33-7.41 (m, 3H), 7.94-7.98 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.7, 26.5, 34.8, 65.0, 108.2, 123.3, 123.5, 124.0, 126.0, 128.5, 130.4, 130.6, 132.8, 140.0, 140.7, 142.3, 147.3, 171.2. IR (neat) ν 3146, 3054, 2244, 1984, 1962, 1720, 16134, 1593, 1496, 1471, 1423, 1393, 1378, 1356, 1335, 1193, 1172, 1129, 1090, 1104, 1013, 984, 964, 898, 761, 729, 698, 667 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}N_5O_3S_2$ (M^++H) requires: 440.0846. Found: 440.0849.

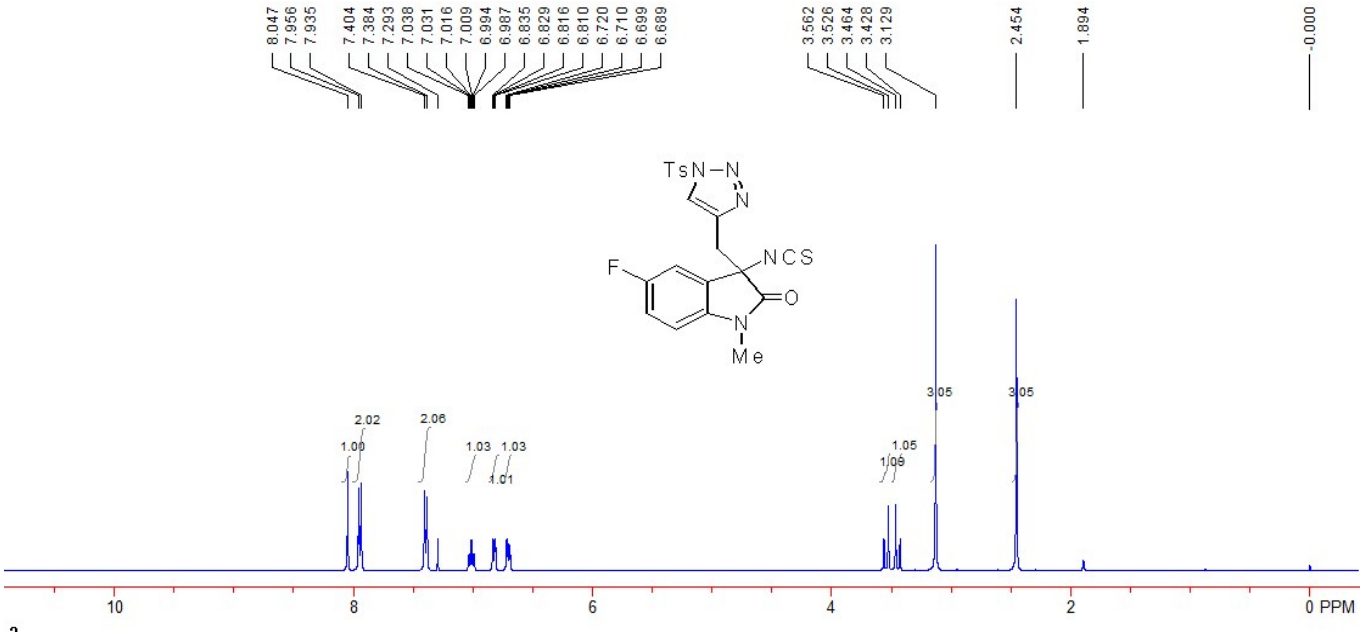


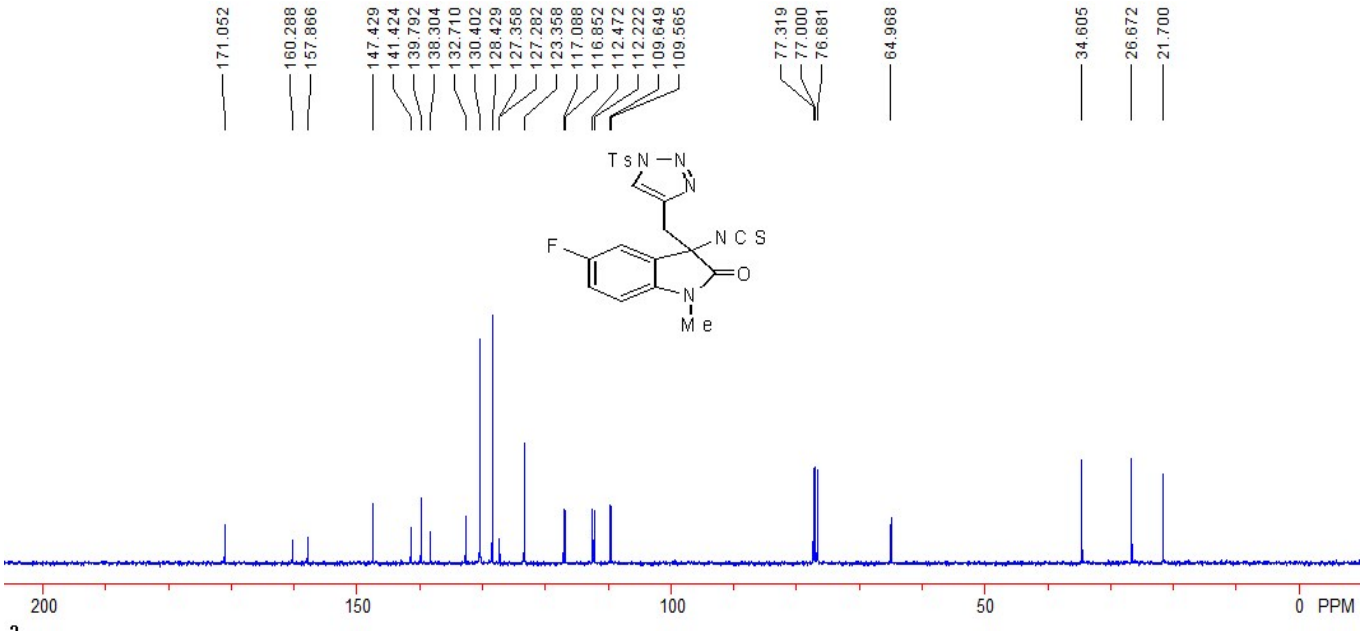


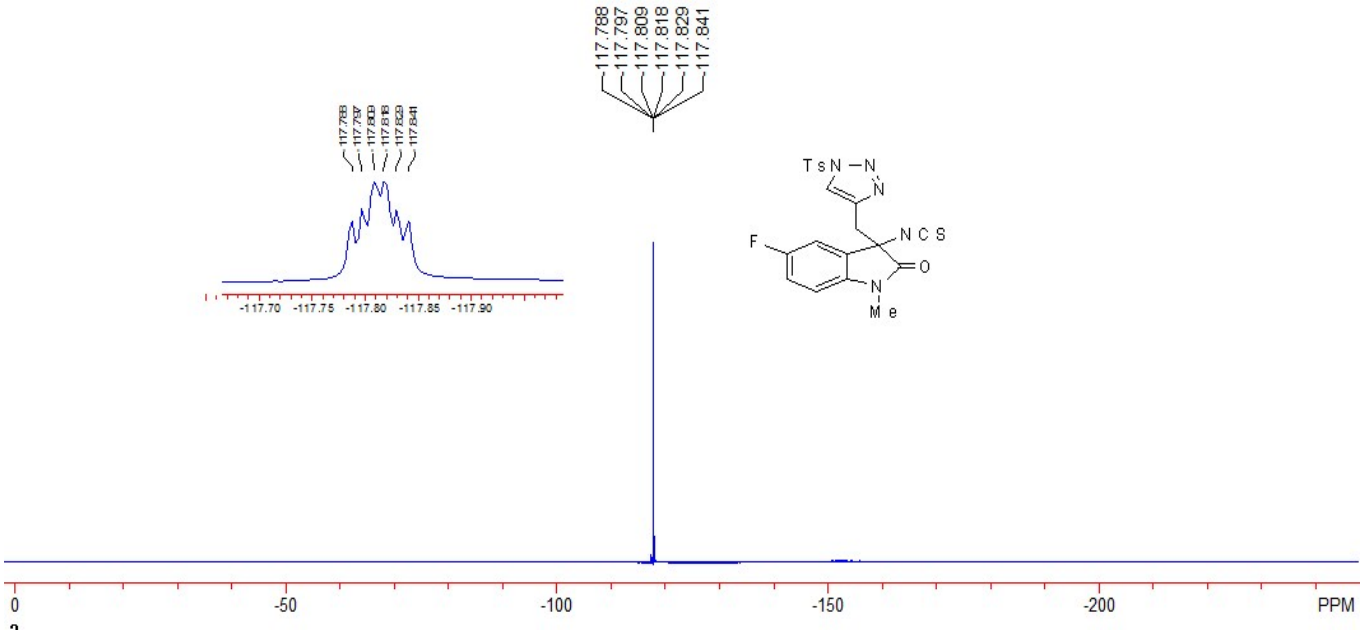


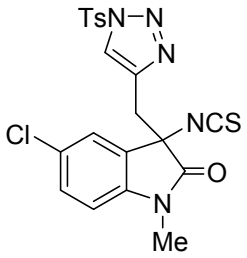
Compound **1b**: A white solid (205 mg, 78%); M.p. 115-117 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H), 3.13 (s, 3H), 3.45 (d, J = 14.4 Hz, 1H), 3.54 (d, J = 14.4 Hz, 1H), 6.70 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 6.82 (dd, J_1 = 7.6 Hz, J_2 = 2.4 Hz, 1H), 7.01 (ddd, J_1 = J_2 = 8.8 Hz, J_3 = 2.8 Hz, 1H), 7.39 (d, J =

8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.7, 26.7, 34.6, 65.0, 109.6 (d, *J* = 8.4 Hz), 112.3 (d, *J* = 25.0 Hz), 117.0 (d, *J* = 23.6 Hz), 123.4, 127.3 (d, *J* = 7.6 Hz), 128.4, 130.4, 132.7, 138.3, 139.8, 141.4, 147.4, 159.1 (d, *J* = 242.2 Hz), 171.1. ^{19}F NMR (376 MHz, $CDCl_3$, TMS) δ -117.841~-117.788 (m). IR (neat) ν 3130, 3082, 2922, 2009, 1723, 1615, 1593, 1496, 1471, 1394, 1211, 1193, 1178, 1021, 971, 905, 812, 731, 679, 666 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{17}FN_5O_3S_2$ (M^++H) requires: 458.0751. Found: 458.0753.

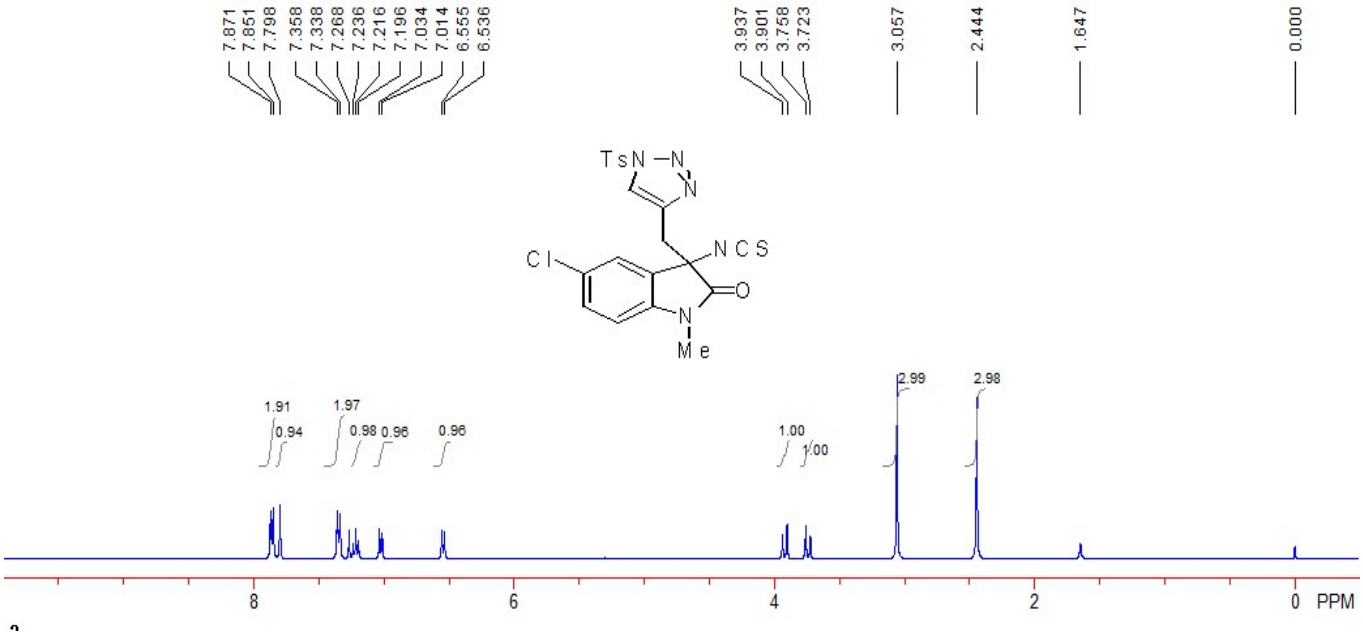


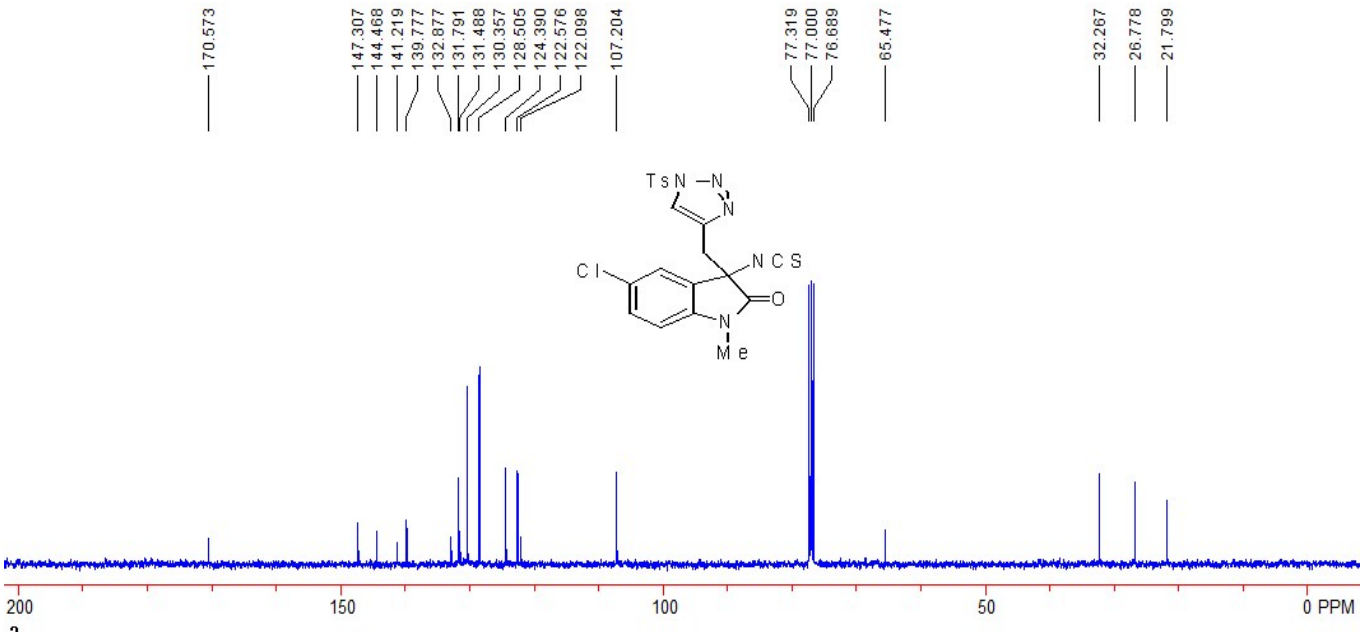


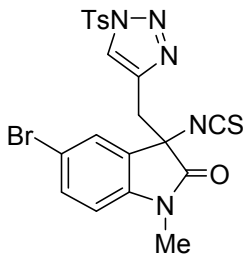




Compound **1c**: A white solid (212 mg, 82%); M.p. 147-149 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.44 (s, 3H), 3.06 (s, 3H), 3.74 (d, J = 14.4 Hz, 1H), 3.92 (d, J = 14.4 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.22 (dd, $J_1 = J_2$ = 8.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.8, 26.8, 32.3, 65.5, 107.2, 122.1, 122.6, 124.4, 128.5, 130.4, 131.5, 131.8, 132.9, 139.8, 141.2, 144.5, 147.3, 170.6. IR (neat) ν 3114, 3074, 2040, 1730, 1609, 1592, 1460, 1389, 1324, 1196, 1182, 1109, 1017, 1005, 965, 860, 774, 701, 668 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{17}ClN_5O_3S_2$ (M^++H) requires: 474.0456. Found: 474.0457.

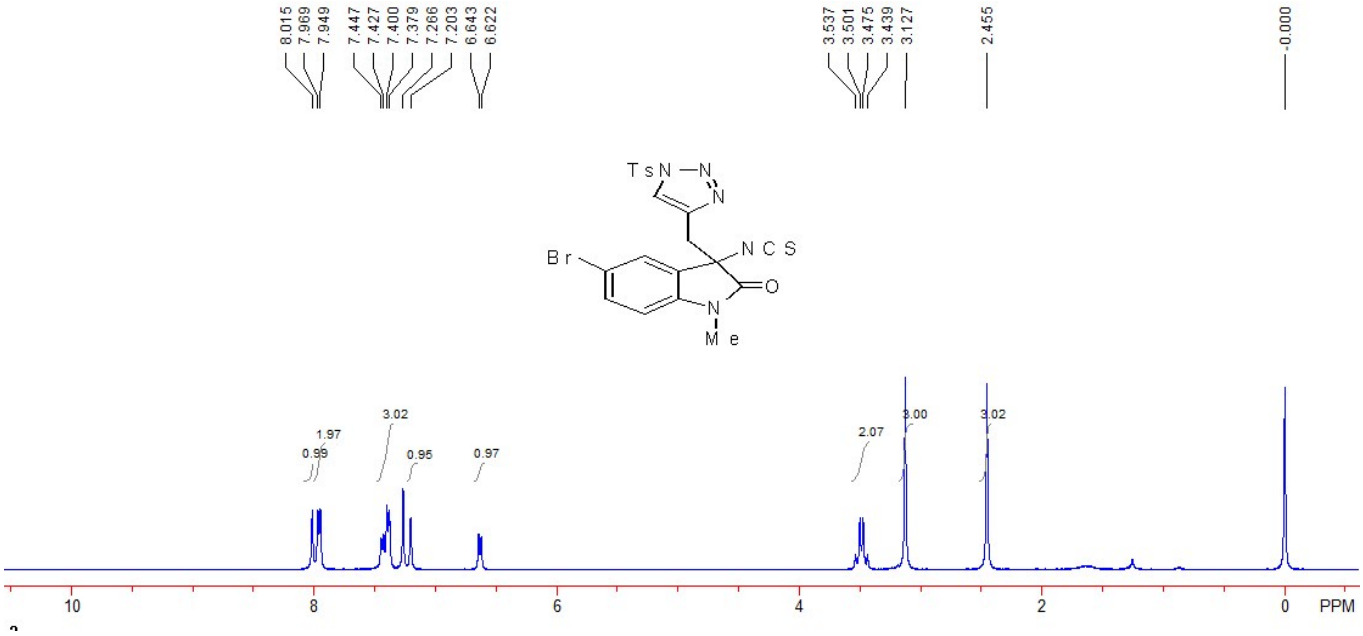


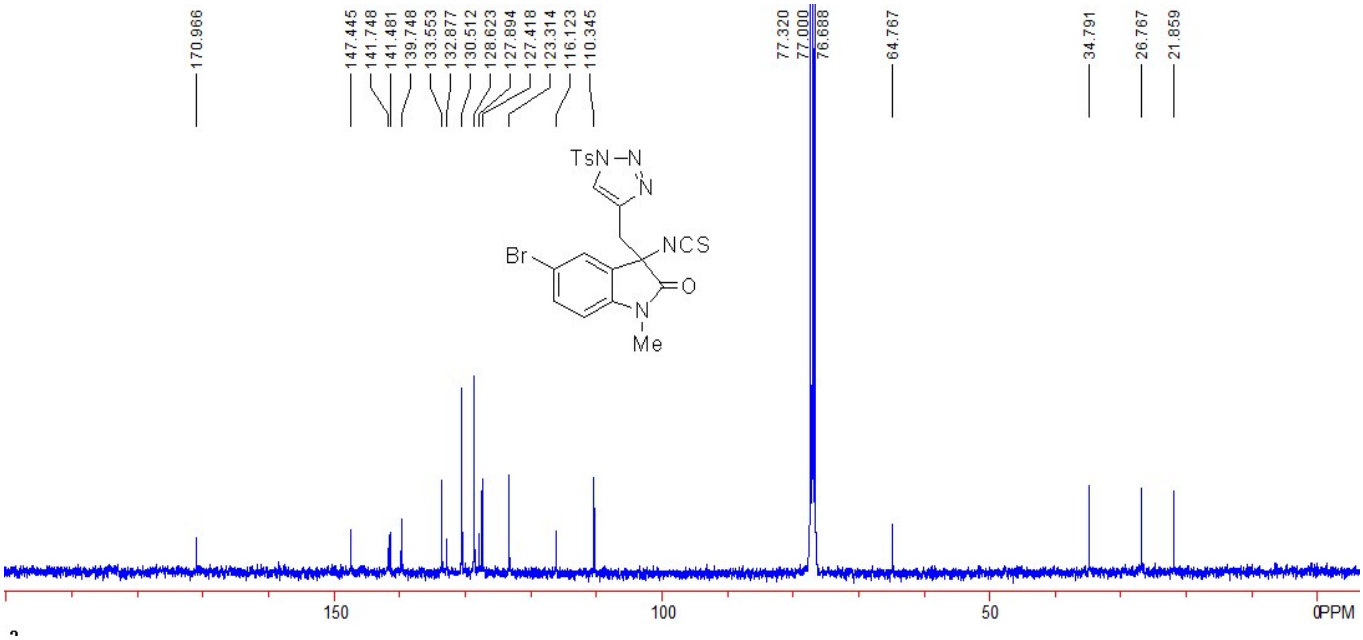


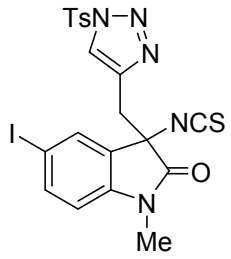


Compound **1d**: A white solid (195 mg, 89%); M.p. 179-181 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.46 (s, 3H), 3.13 (s, 3H), 3.46 (d, J = 14.4 Hz, 1H), 3.52 (d, J = 14.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.38-7.45 (m, 3H), 7.96 (d, J = 8.0 Hz, 2H), 8.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.9,

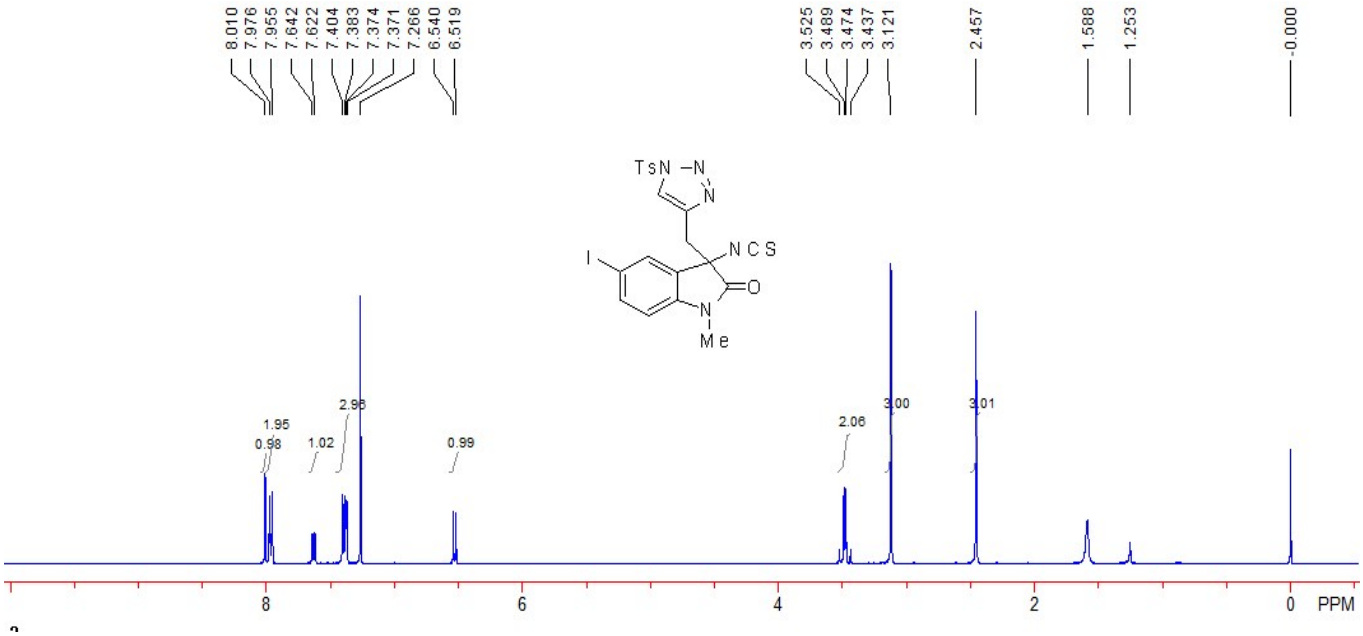
26.8, 34.8, 64.8, 110.3, 116.1, 123.3, 127.4, 127.9, 128.6, 130.5, 132.9, 133.6, 139.7, 141.5, 141.7, 147.4, 171.0. IR (neat) ν 3134, 2022, 1733, 1606, 1486, 1394, 1378, 1269, 1192, 1179, 1099, 1021, 983, 928, 824, 811, 745, 701, 690, 672 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{17}BrN_5O_3S_2$ (M^++H) requires: 517.9951. Found: 517.9949.

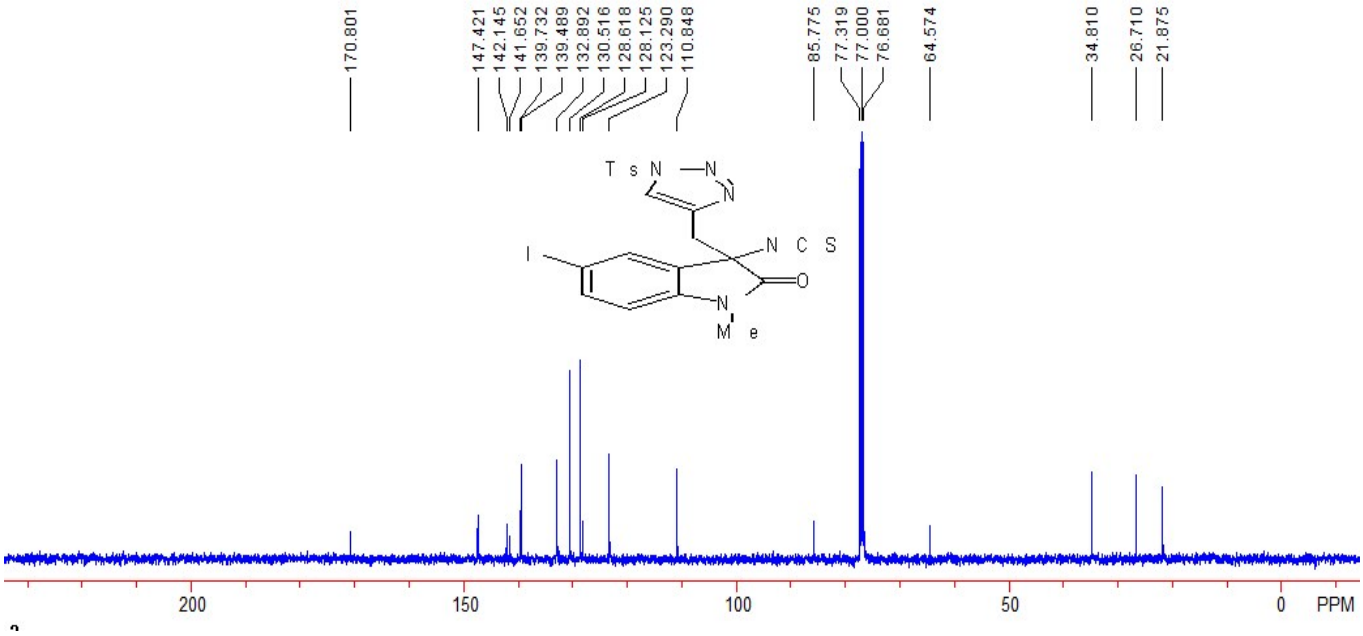


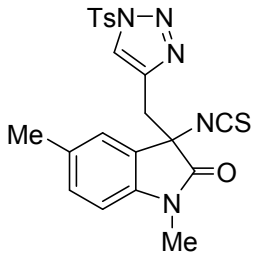




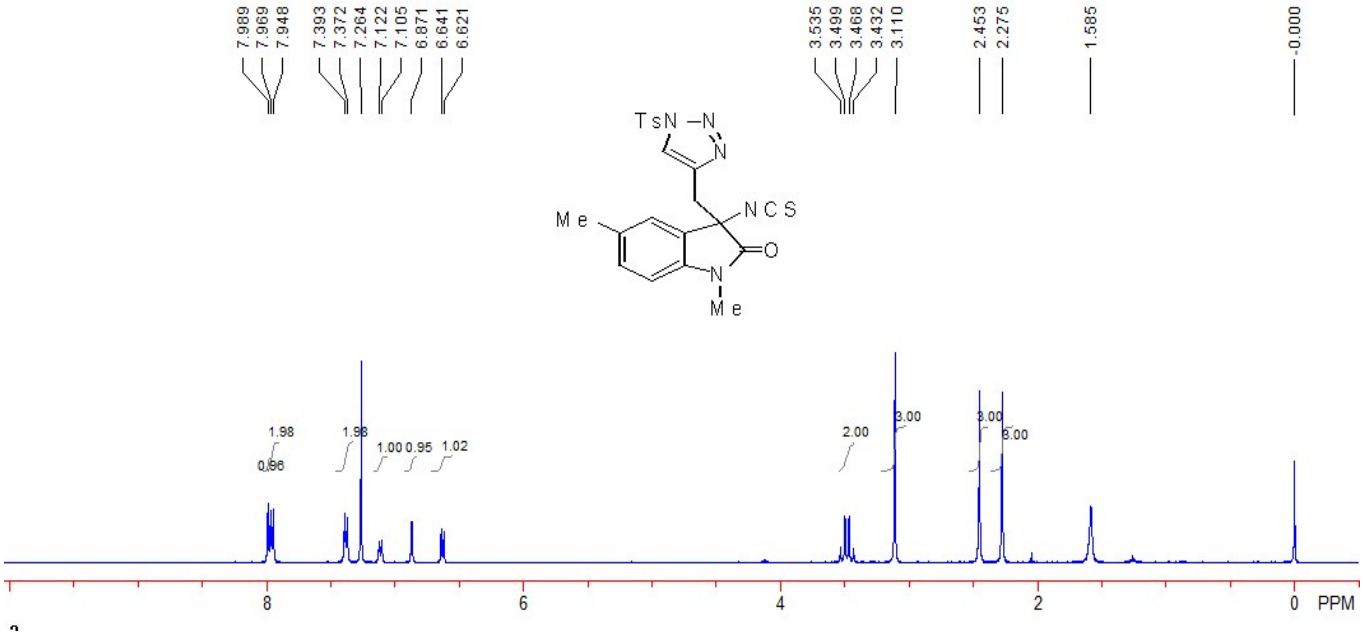
Compound **1e**: A white solid (203 mg, 88%); M.p. 173-175 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.46 (s, 3H), 3.12 (s, 3H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.51 (d, *J* = 14.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 7.37-7.40 (m, 3H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 8.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.9, 26.7, 34.8, 64.6, 85.8, 110.8, 123.3, 128.1, 128.6, 130.5, 132.9, 139.5, 139.7, 141.7, 142.1, 147.4, 170.8. IR (neat) ν 3134, 3078, 2022, 1732, 1602, 1484, 1459, 1397, 1377, 1361, 1348, 1300, 1266, 1252, 1191, 1178, 1097, 1021, 980, 925, 821, 810, 745, 670 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{17}IN_5O_3S_2$ (M^++H) requires: 565.9812. Found: 565.9809.

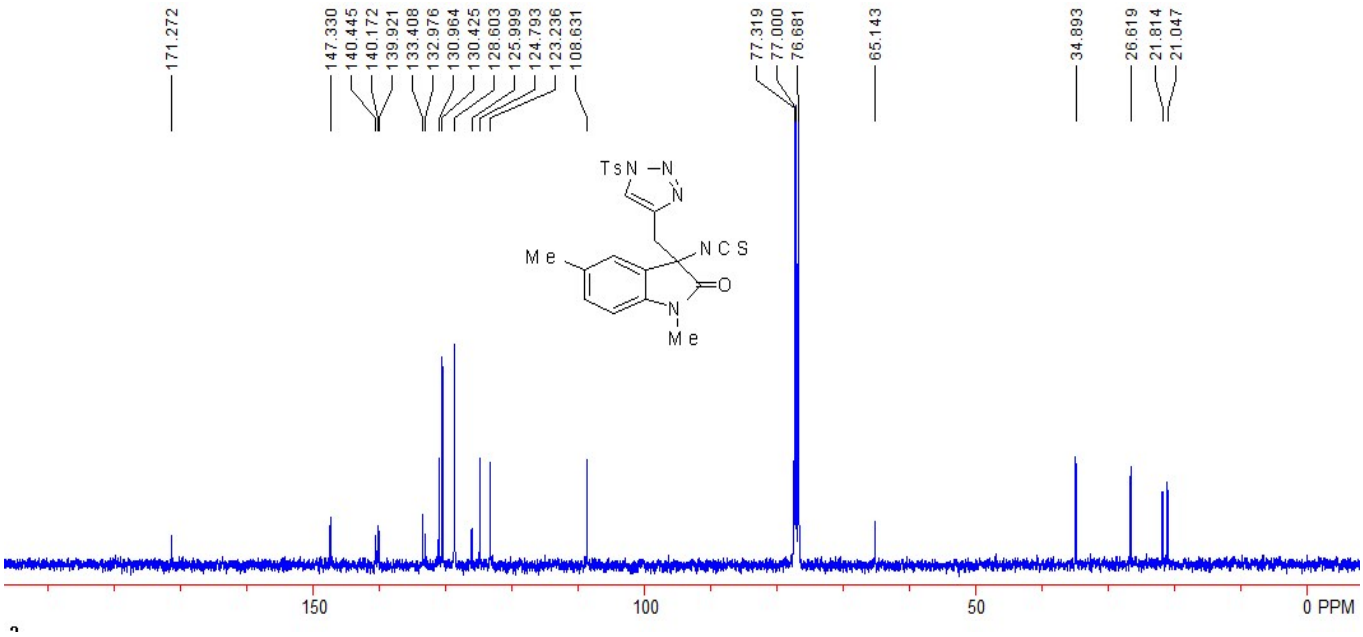


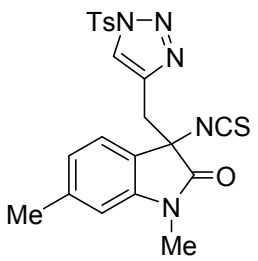




Compound **1f**: A white solid (222 mg, 84%); M.p. 169-171 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.28 (s, 3H), 2.45 (s, 3H), 3.11 (s, 3H), 3.45 (d, J = 14.4 Hz, 1H), 3.52 (d, J = 14.4 Hz, 1H), 6.63 (d, J = 8.0 Hz 1H), 6.87 (s, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 21.8, 26.6, 34.9, 65.1, 108.6, 123.2, 124.8, 126.0, 128.6, 130.4, 131.0, 133.0, 133.4, 140.0, 140.2, 140.4, 147.3, 171.3. IR (neat) ν 3131, 3082, 2918, 2029, 1723, 1618, 1504, 1396, 1364, 1332, 1303, 1259, 1191, 1179, 1092, 1023, 980, 928, 814, 746, 695, 680, 665 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{20}N_5O_3S_2$ (M^++H) requires: 454.1002. Found: 454.1005.

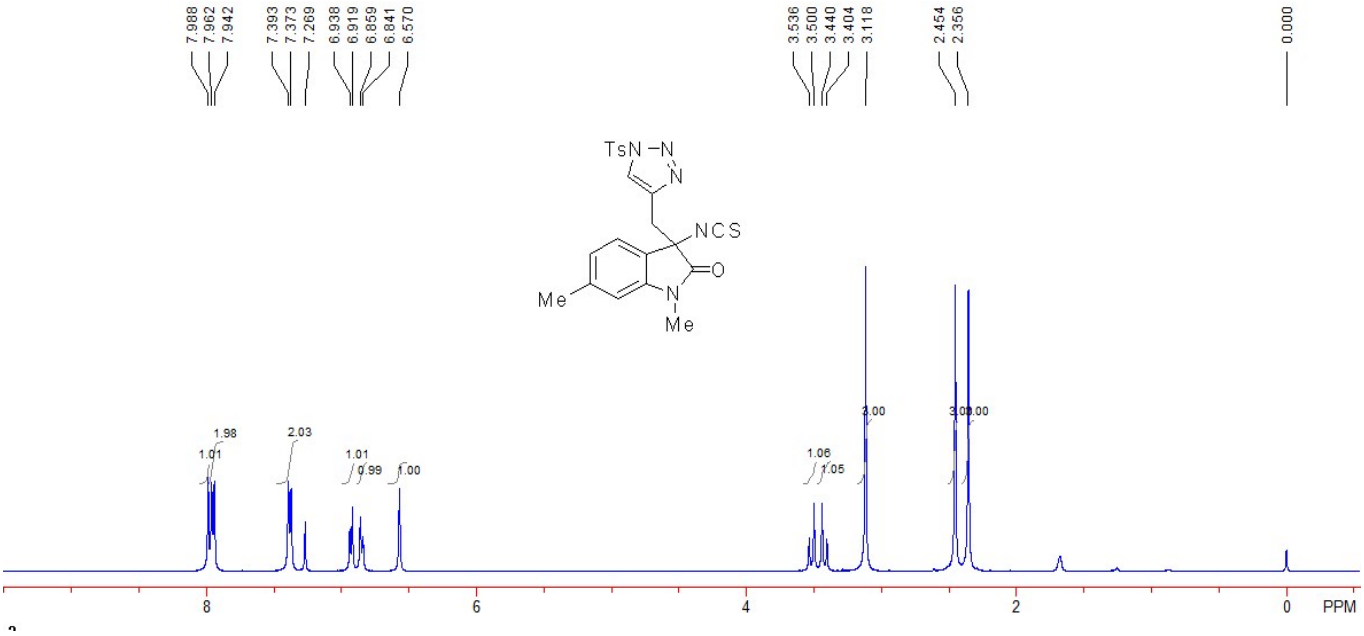


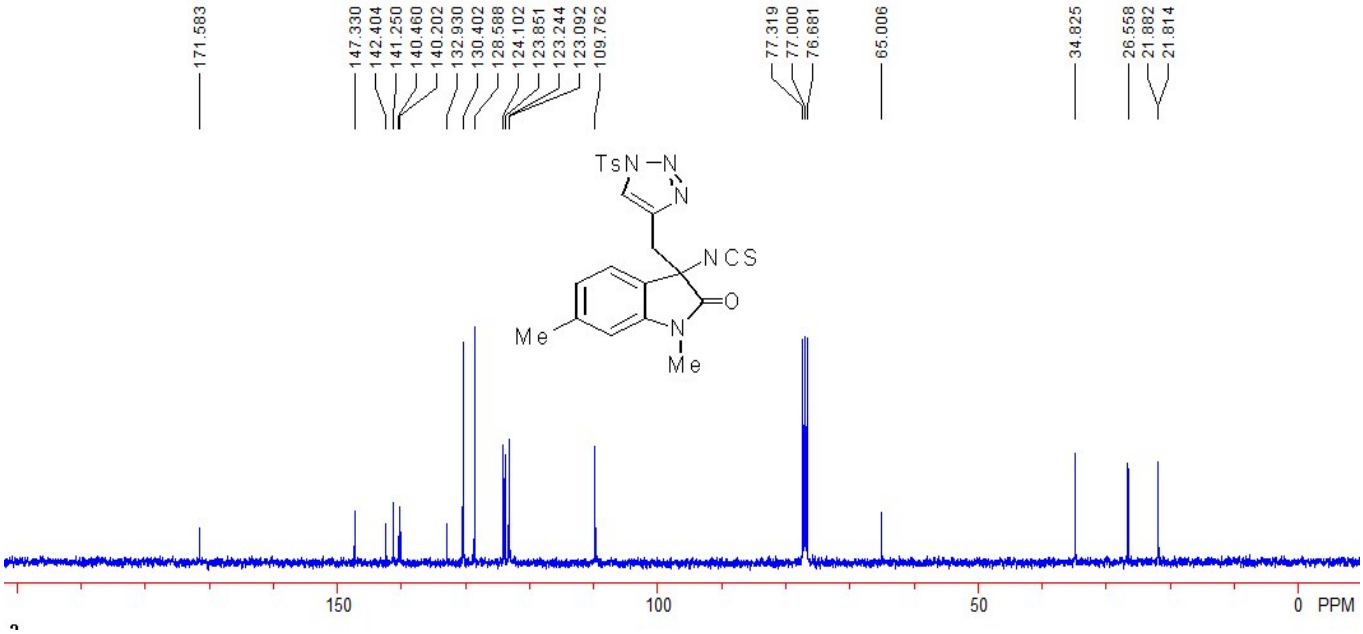


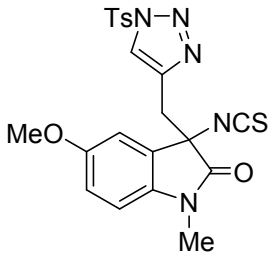


Compound **1g**: A white solid (220 mg, 83%); M.p. 183-185 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.36 (s, 3H), 2.45 (s, 3H), 3.12 (s, 3H), 3.42 (d, J = 14.4 Hz, 1H), 3.52 (d, J = 14.4 Hz, 1H), 6.57 (s, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 7.99 (s,

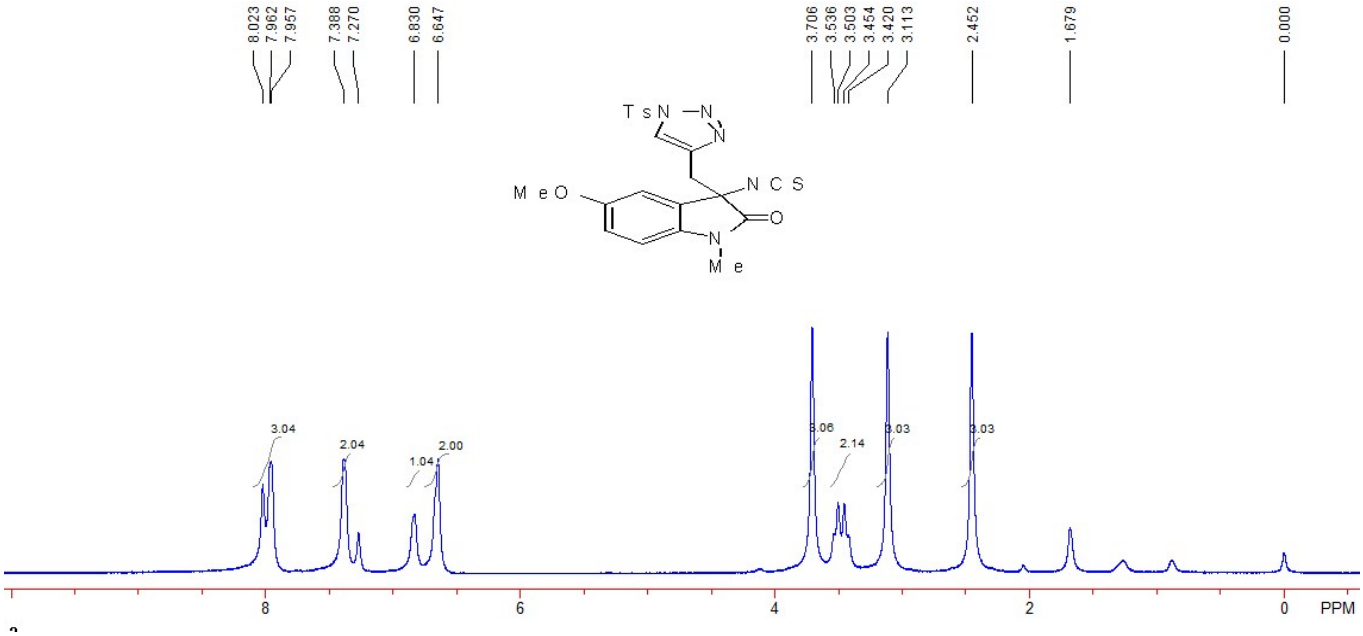
1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.8, 21.9, 26.6, 34.8, 65.0, 109.8, 123.1, 123.2, 123.9, 124.1, 128.6, 130.4, 132.9, 140.2, 140.5, 141.3, 142.4, 147.3, 171.6. IR (neat) ν 3140, 3090, 2929, 2019, 1726, 1617, 1455, 1390, 1371, 1199, 1192, 1178, 1163, 1085, 1006, 970, 941, 808, 747, 717, 701, 694, 667 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{20}N_5O_3S_2$ (M^++H) requires: 454.1002. Found: 454.1004.

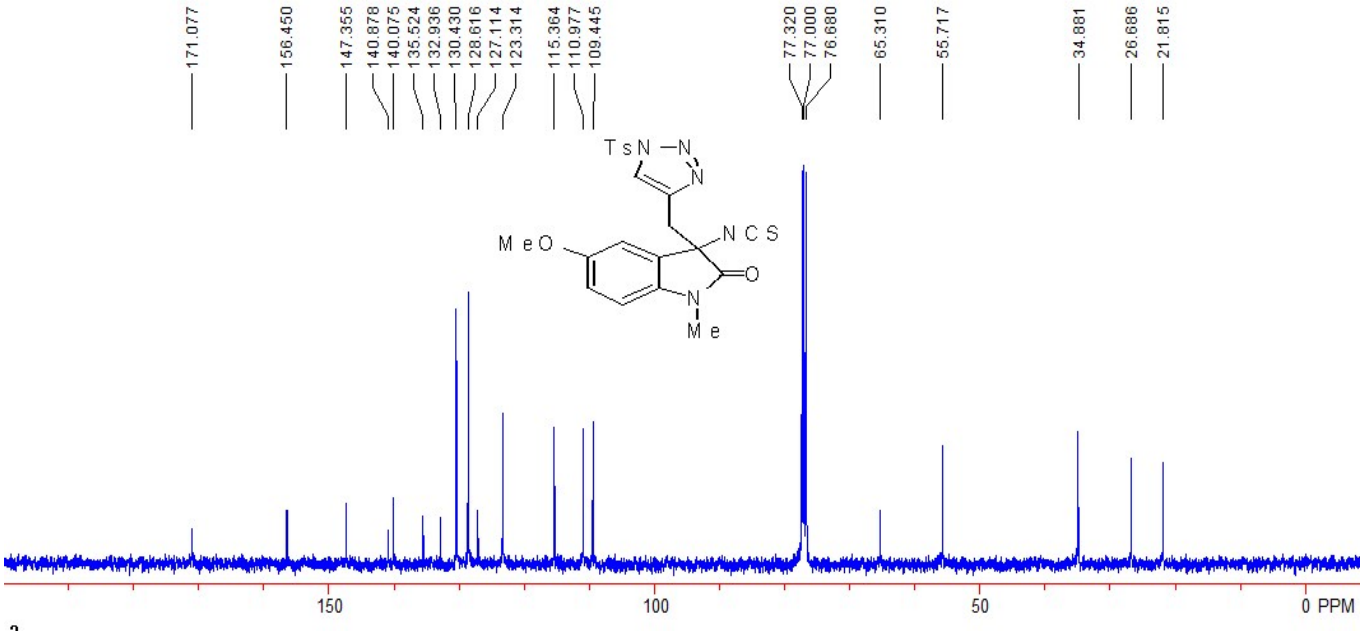


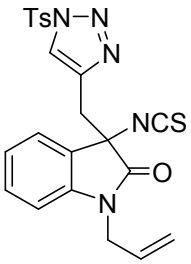




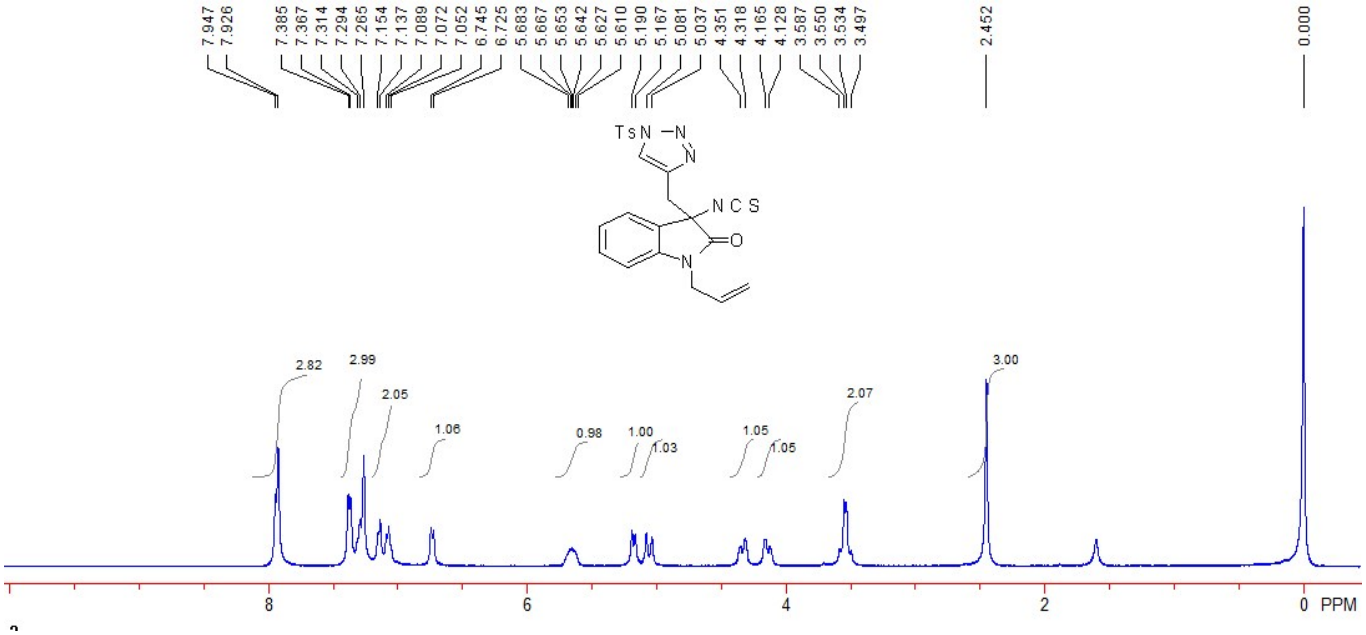
Compound **1h**: A white solid (189 mg, 70%); M.p. 171-173 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H), 3.11 (s, 3H), 3.44 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 3.71 (s, 3H), 6.65 (s, 2H), 6.83 (s, 1H), 7.39 (s, 2H), 7.69-8.02 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.8, 26.7, 34.9, 55.7, 65.3, 109.4, 111.0, 115.4, 123.3, 127.1, 128.6, 130.4, 132.9, 135.5, 140.1, 140.9, 147.4, 156.5, 171.1. IR (neat) ν 3118, 3082, 2830, 2009, 1715, 1605, 1595, 1499, 1475, 1395, 1378, 1364, 1287, 1219, 1193, 1179, 1155, 1120, 1092, 1037, 1021, 1016, 976, 930, 867, 812, 805, 784, 679, 664 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{20}N_5O_4S_2$ (M^++H) requires: 470.0951. Found: 470.0955.

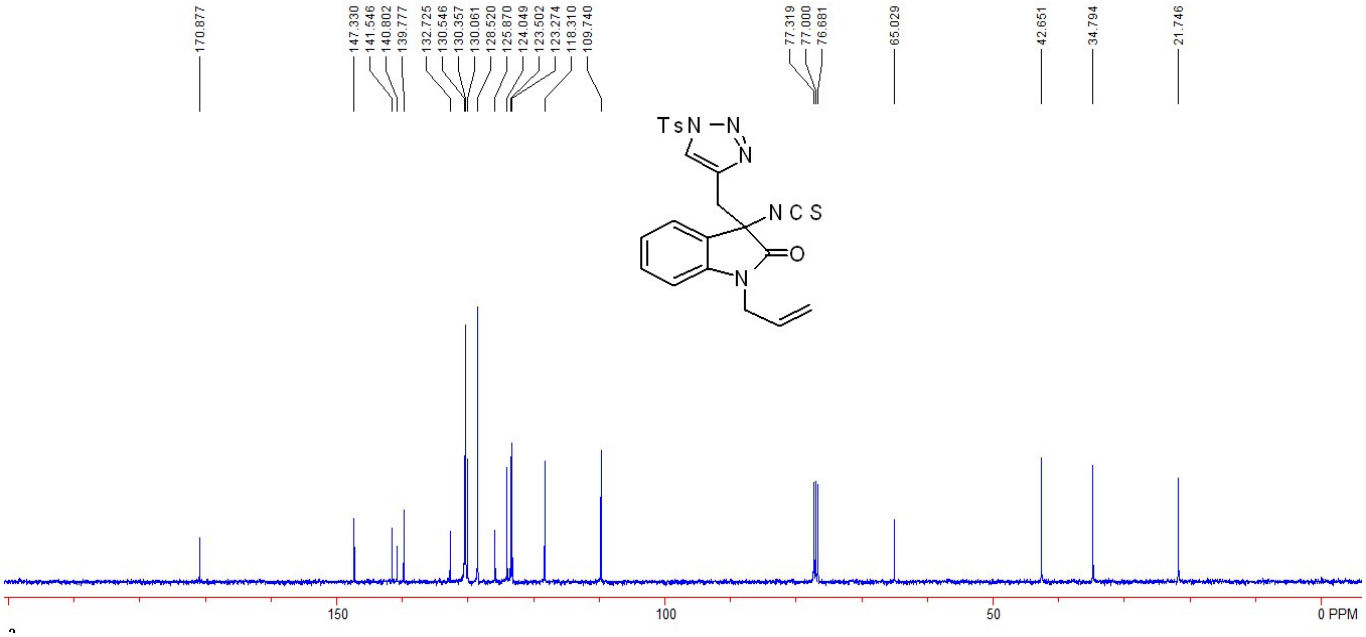


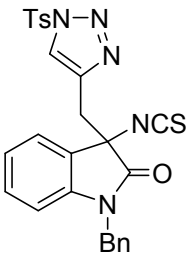




Compound **1i**: A white solid (374 mg, 65%); M.p. 139-141 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.45 (s, 3H), 3.52 (d, *J* = 14.8 Hz, 1H), 3.57 (d, *J* = 14.8 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 5.06 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 9.2 Hz, 1H), 5.61-5.68 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 7.05-7.15 (m, 2H), 7.29-7.39 (m, 3H), 7.93-7.95 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.7, 34.8, 42.7, 65.0, 109.7, 118.3, 123.3, 123.5, 124.0, 125.9, 128.5, 130.1, 130.4, 130.5, 132.7, 139.8, 140.8, 141.5, 147.3, 170.9. IR (neat) ν 3142, 2922, 2850, 1991, 1732, 1615, 1489, 1386, 1333, 1195, 1184, 1090, 1014, 978, 968, 926, 845, 751, 731, 702, 671 cm^{-1}. HRMS (ESI) Calcd. for $C_{22}H_{20}N_5O_3S_2$ (M^++H) requires: 466.1002. Found: 466.1001.

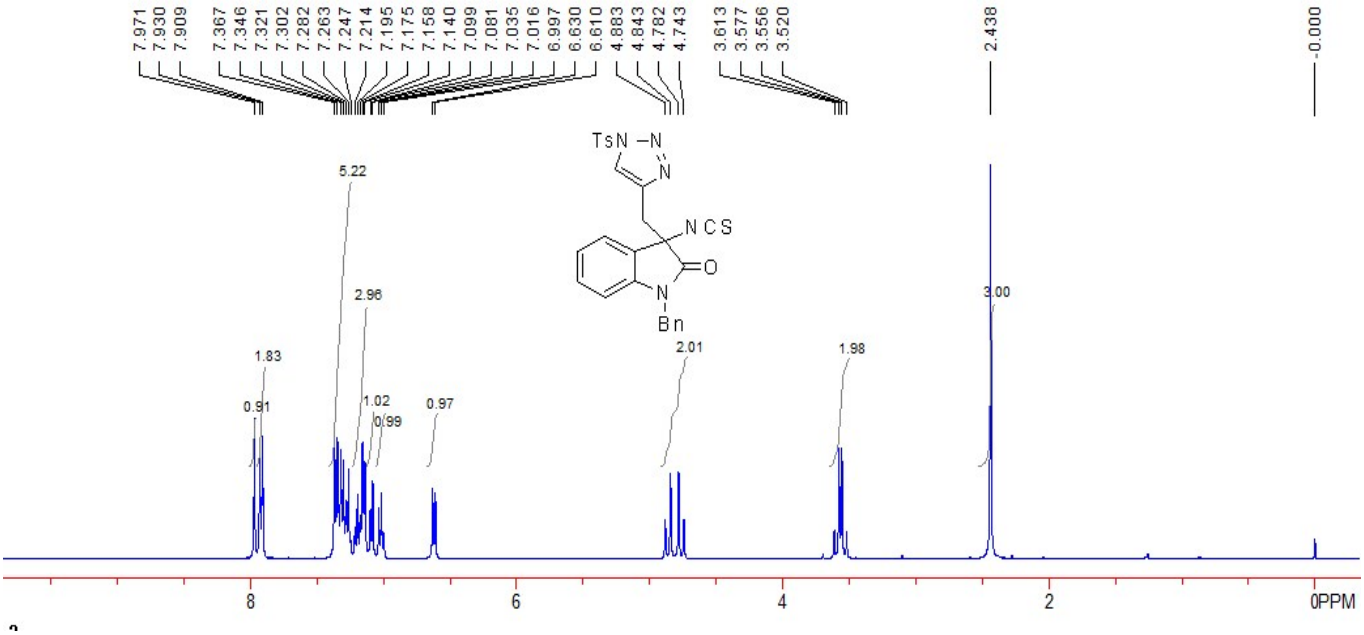


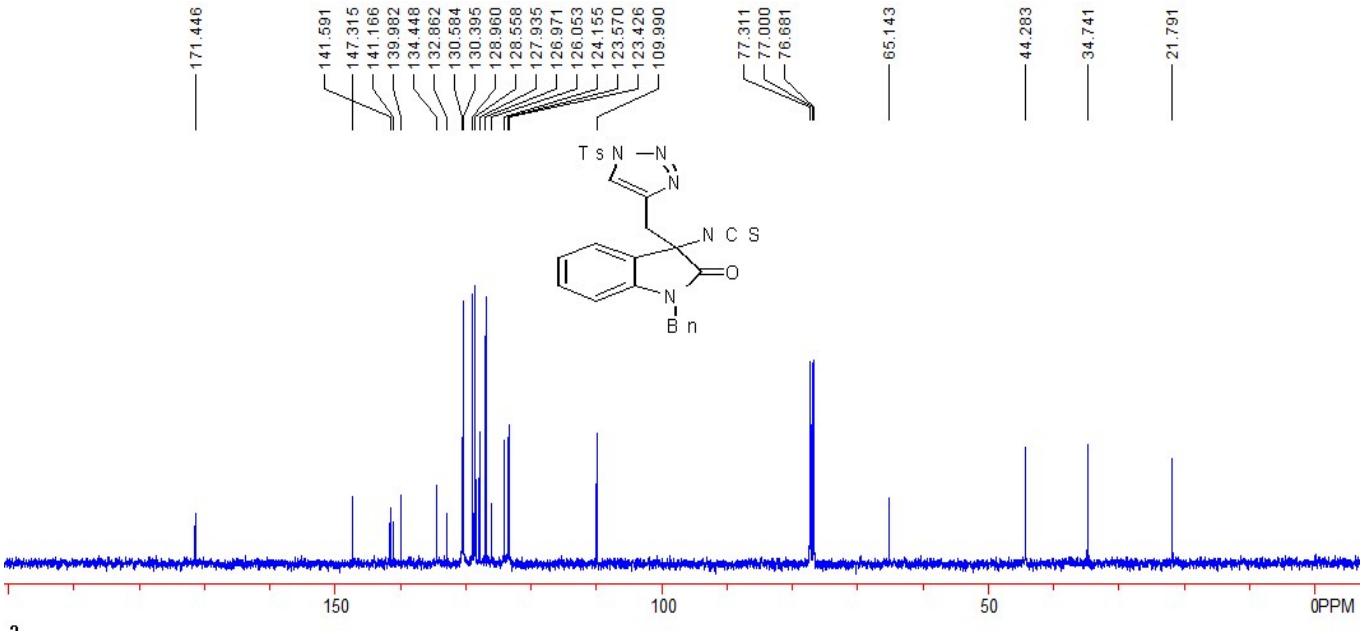


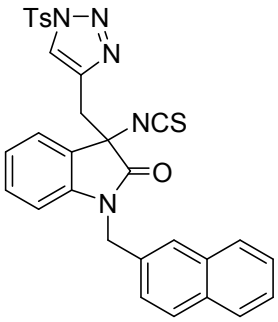


Compound **1j**: A white solid (127 mg, 79%); M.p. 154-156 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.44 (s, 3H), 3.54 (d, J = 14.4 Hz, 1H), 3.60 (d, J = 14.4 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 4.86 (d, J = 15.6 Hz, 1H), 6.62 (d, J = 4.0 Hz, 1H), 7.02 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.14-7.37 (m,

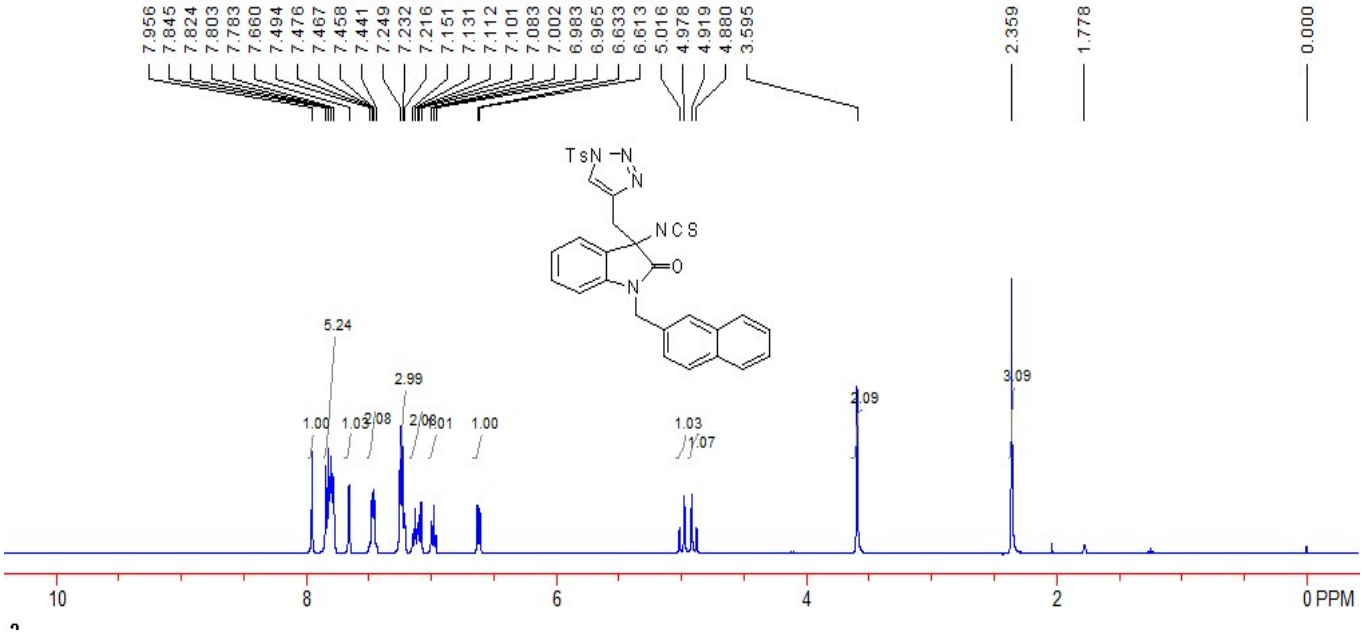
8H), 7.92 (d, J = 8.4 Hz, 2H), 7.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.8, 34.7, 44.3, 65.1 110.0, 123.4, 123.6, 124.2, 126.1, 127.0, 127.9, 128.6, 129.0, 130.4, 130.6, 132.9, 134.4, 140.0, 141.2, 141.6, 147.3, 171.4. IR (neat) ν 3166, 1977, 1722, 1617, 1491, 1469, 1388, 1380, 1366, 1354, 1193, 1176, 1090, 1011, 971, 956, 899, 809, 803, 761, 745, 726, 695, 677 cm^{-1}. HRMS (ESI) Calcd. for $C_{26}H_{22}N_5O_3S_2$ (M^++H) requires: 516.1159. Found: 516.1159.

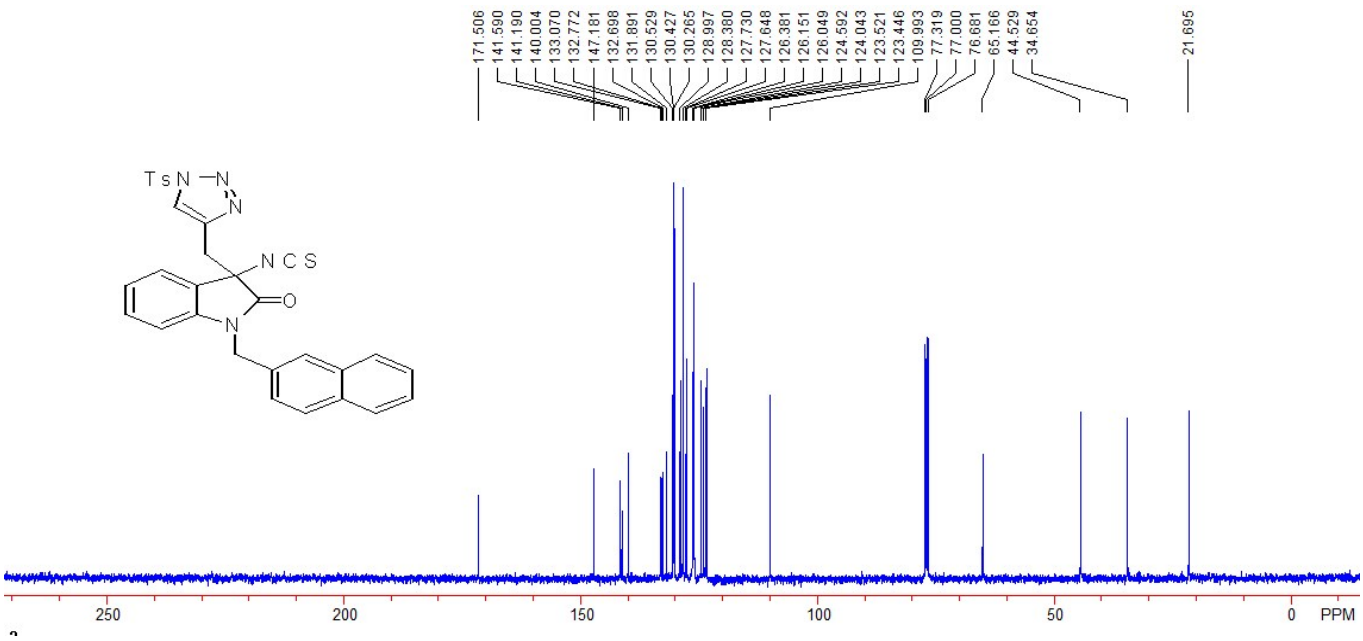


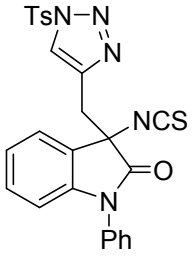




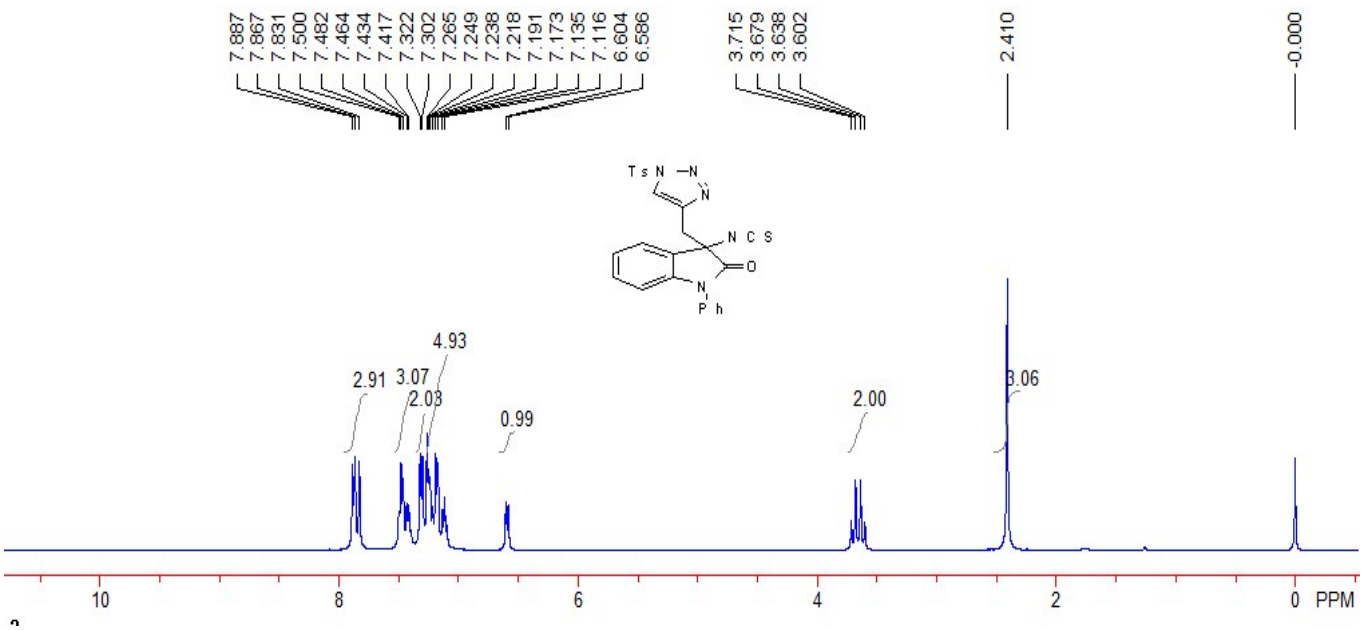
Compound **1k**: A white solid (198 mg, 88%); M.p. 126-128 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.36 (s, 3H), 3.60 (s, 2H), 4.90 (d, J = 15.6 Hz, 1H), 5.00 (d, J = 15.6 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.98 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.08-7.15 (m, 2H), 7.22-7.25 (m, 3H), 7.44-7.49 (m, 2H), 7.66 (s, 1H), 7.78-7.85 (m, 5H), 7.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.7, 34.7, 44.5, 65.2, 110.0, 123.4, 123.5, 124.0, 124.6, 126.0, 126.2, 126.4, 127.6, 127.7, 128.4, 129.0, 130.3, 130.4, 130.5, 131.9, 132.7, 132.8, 133.1, 140.0, 141.2, 141.6, 147.2, 171.5. IR (neat) ν 3675, 2987, 2901, 2361, 2010, 1731, 1613, 1488, 1468, 1394, 1375, 1337, 1195, 1180, 1076, 1066, 1012, 982, 899, 813, 752, 701, 669 cm^{-1}. HRMS (ESI) Calcd. for $C_{30}H_{24}N_5O_3S_2$ (M^++H) requires: 566.1315. Found: 566.1315.

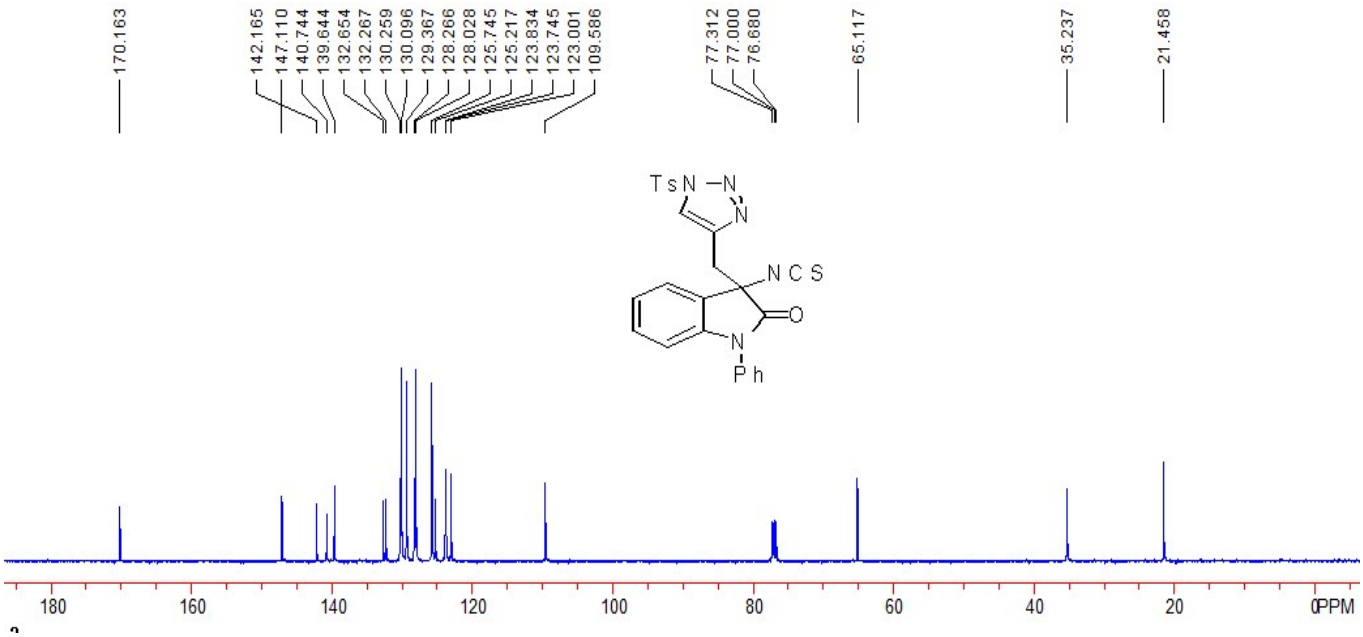






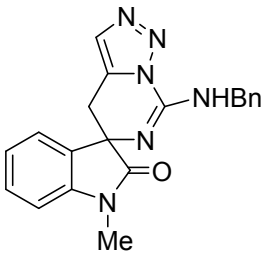
Compound **1l**: A white solid (404 mg, 69%); M.p. 139-141 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.41 (s, 3H), 3.62 (d, J = 14.4 Hz, 1H), 3.70 (d, J = 14.4 Hz, 1H), 6.60 (d, J = 7.2 Hz, 1H), 7.12-7.50 (m, 10H), 7.83-7.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.5, 35.2, 65.1, 109.6, 123.0, 123.7, 123.8, 125.2, 125.7, 128.0, 128.3, 129.4, 130.1, 130.3, 132.3, 132.7, 139.6, 140.7, 142.2, 147.1, 170.2. IR (neat) ν 3162, 3092, 2923, 2016, 1727, 1069, 1595, 1499, 1469, 1392, 1372, 1327, 1196, 1179, 1010, 972, 957, 813, 761, 723, 698, 667 cm^{-1}. HRMS (ESI) Calcd. for $C_{25}H_{20}N_5O_3S_2$ (M^++H) requires: 502.1002. Found: 502.1001.


7.887
7.867
7.831
7.500
7.482
7.464
7.434
7.417
7.322
7.302
7.265
7.249
7.238
7.218
7.191
7.173
7.135
7.116
6.604
6.586
3.715
3.679
3.638
3.602
2.410
-0.000
Ts N —N
N
N C S
O
N
Ph
4.93
2.91
3.07
2.03
0.99
2.00
3.06
10
8
6
4
2
0 PPM

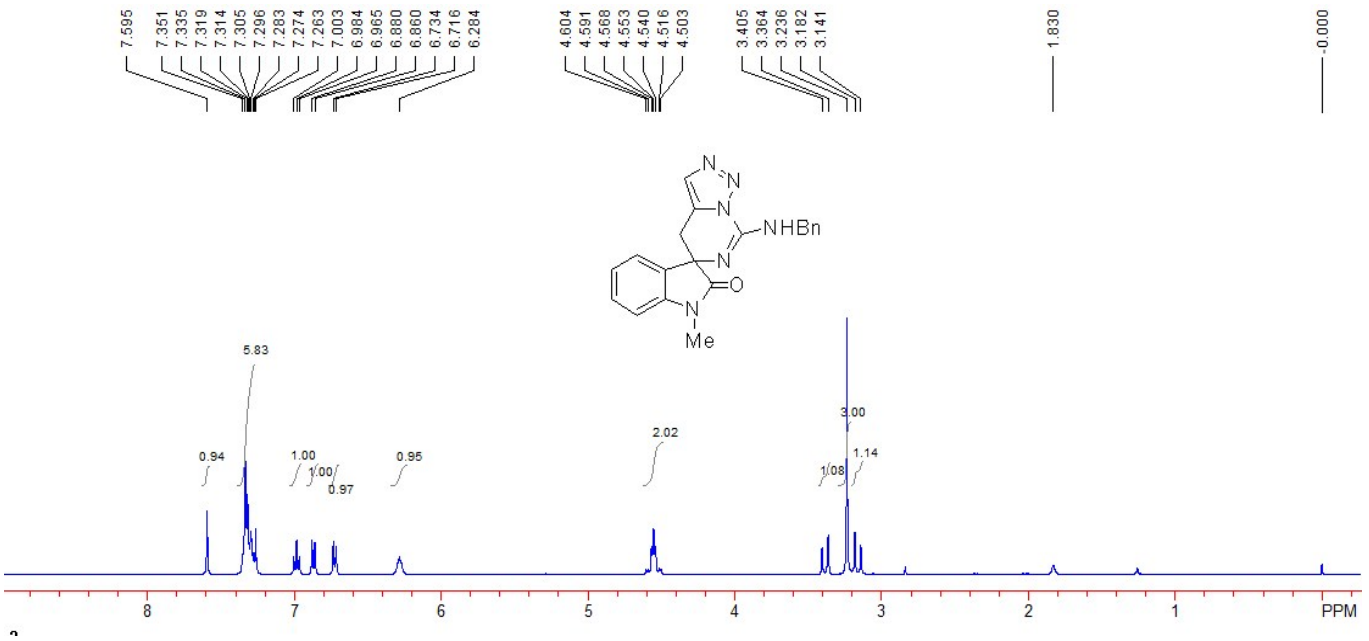

170.163
142.165
147.110
140.744
139.644
132.654
132.267
130.259
130.096
129.367
128.266
128.028
125.745
125.217
123.834
123.745
123.001
109.586
77.312
77.000
76.680
65.117
35.237
21.458
Ts N —N
N
N C S
O
N
Ph
180
160
140
120
100
80
60
40
20
0PPM

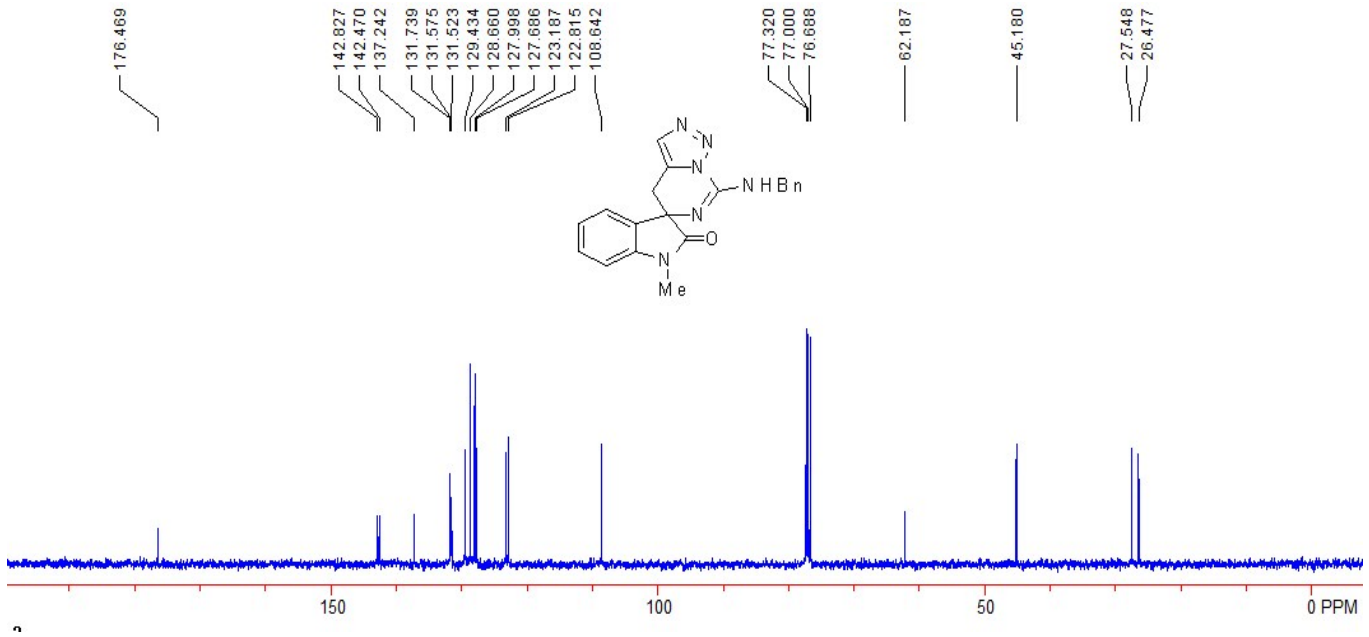
General procedure for synthesis and spectroscopic data of products 3

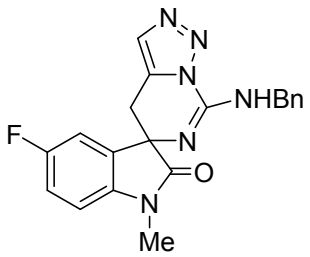
A flame-vacuum dried sealed tube with a magnetic stir bar was charged with **1** (0.1 mmol, 1.0 equiv.), K_2CO_3 (0.1 mmol, 1.0 equiv.), **2** (0.1 mmol, 1.0 equiv.), and acetonitrile (1.0 mL) under Ar atmosphere. The mixture was stirred for 1 h at 80 °C in a pre-heated oil bath, and then warmed up to 120 °C. The reaction mixture was stirred at 120 °C for the indicated time. The reaction mixture was then cooled to ambient temperature, filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel to provide the desired product.



Compound **3aa**: A white solid (27 mg, 74%); M.p. 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (d, J = 16.4 Hz, 1H), 3.24 (s, 3H), 3.38 (d, J = 16.4 Hz, 1H), 4.50-4.60 (m, 2H), 6.28 (s, 1H), 6.73 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.98 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.27-7.35 (m, 6H), 7.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.5, 45.2, 62.2, 108.6, 122.8, 123.2, 127.7, 128.0, 128.7, 129.4, 131.5, 131.6, 131.7, 137.2, 142.5, 142.8, 176.5. IR (neat) ν 3311, 2922, 1703, 1654, 1616, 1518, 1494, 1470, 1445, 1374, 1322, 1266, 1236, 1132, 1091, 978, 894, 874, 746, 696 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{19}N_6O$ (M^++H) requires: 359.1615. Found: 359.1617.

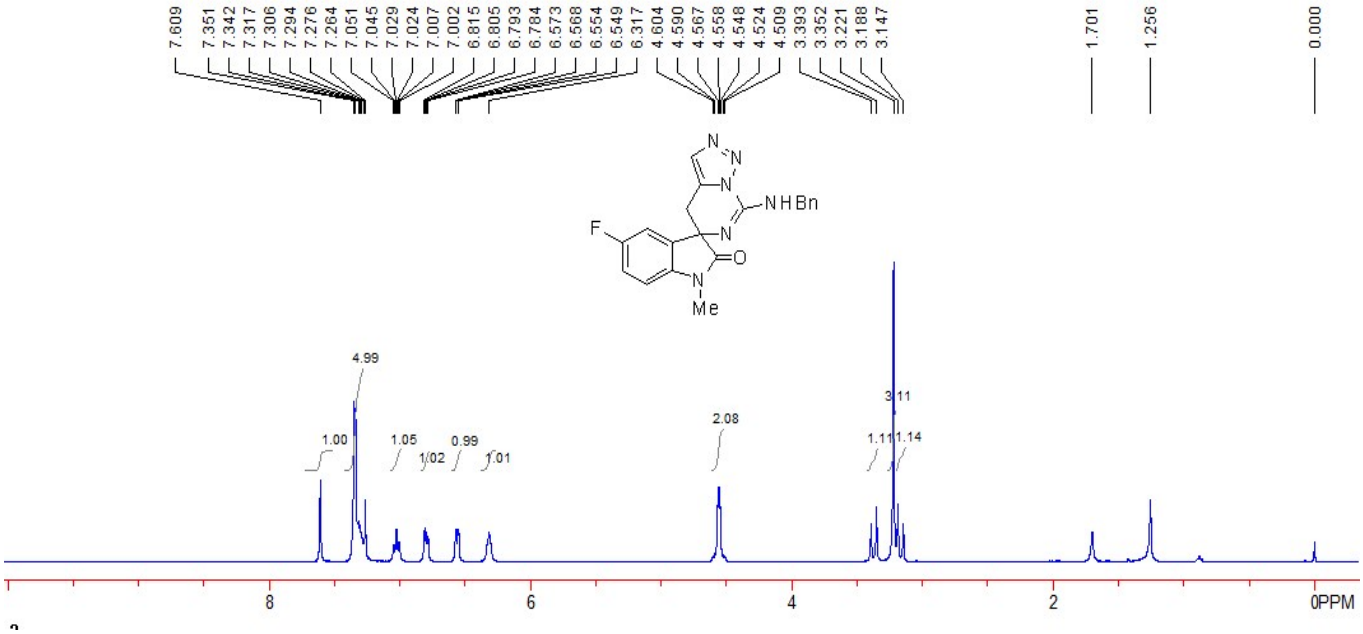


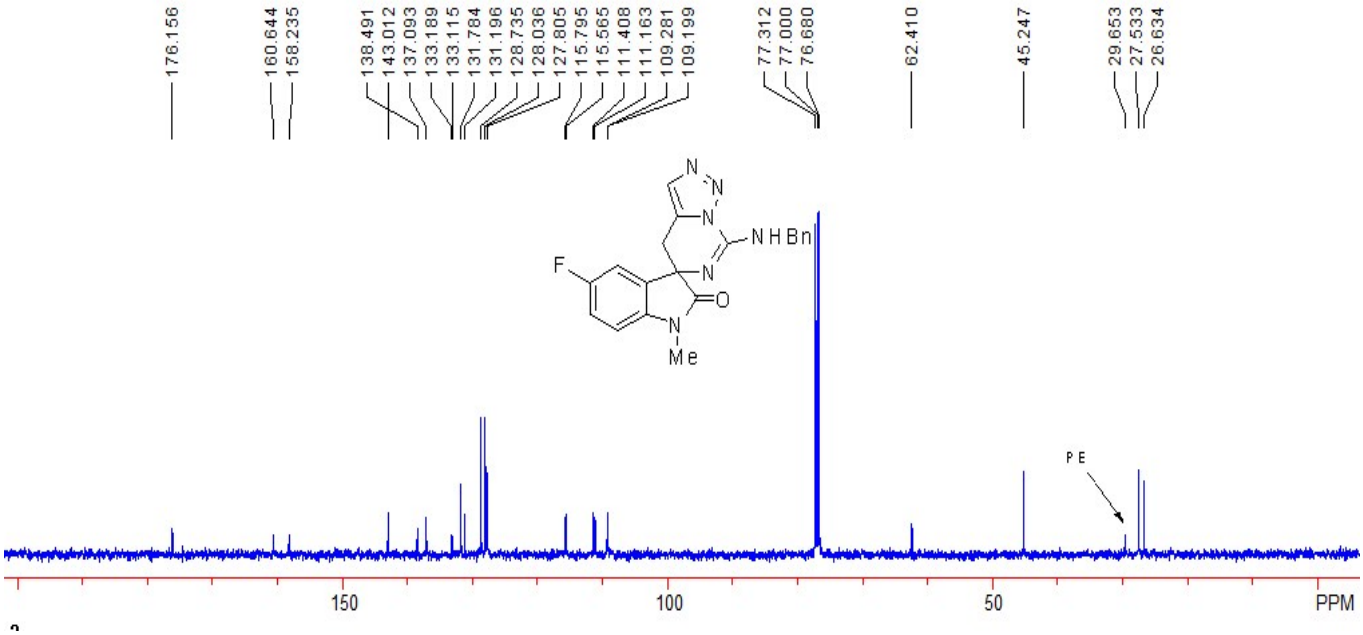


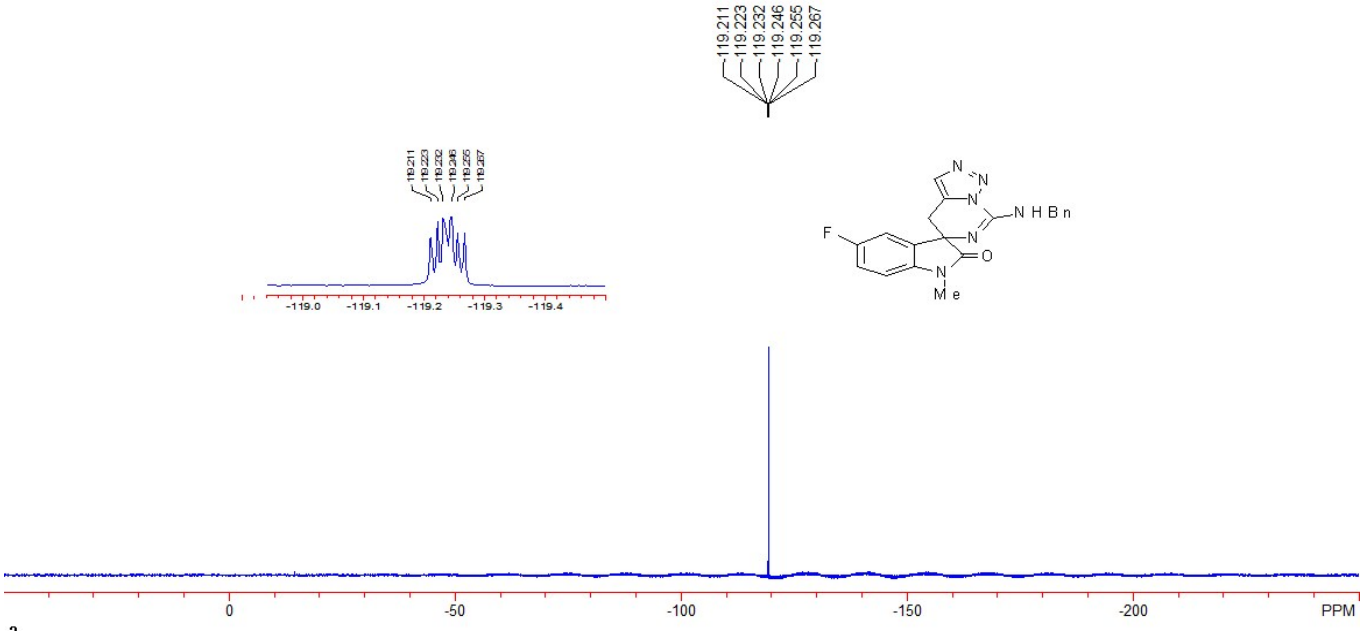


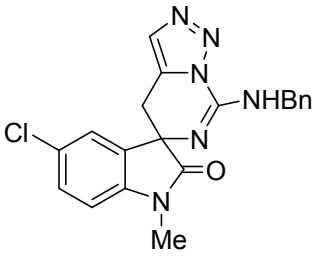
Compound **3ba**: A white solid (26 mg, 68%); M.p. 197-199 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.17 (d, J = 16.4 Hz, 1H), 3.22 (s, 3H), 3.37 (d, J = 16.4 Hz, 1H), 4.51-4.60 (m, 2H), 6.32 (s, 1H), 6.56 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 6.80 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H), 7.03 (ddd, J_1 = J_2 = 8.8 Hz, J_3

= 2.0 Hz, 1H), 7.28-7.35 (m, 5H), 7.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.6, 27.5, 45.2, 62.4, 109.2 (d, *J* = 8.2 Hz), 111.3 (d, *J* = 24.5 Hz), 115.7 (d, *J* = 23.0 Hz), 127.8, 128.0, 128.7, 131.2, 131.8, 133.2 (d, *J* = 7.4 Hz), 137.1, 138.5, 143.0, 159.4 (d, *J* = 240.9 Hz), 176.2. ^{19}F NMR (376 MHz, $CDCl_3$, TMS) δ -119.267~-119.211 (m). IR (neat) ν 3355, 2926, 2850, 1712, 1658, 1625, 1515, 1495, 1473, 1443, 1420, 1361, 1314, 1262, 1235, 1128, 1098, 977, 838, 818, 757, 765, 750, 695 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}FN_6O$ (M^++H) requires: 377.1521. Found: 377.1524.

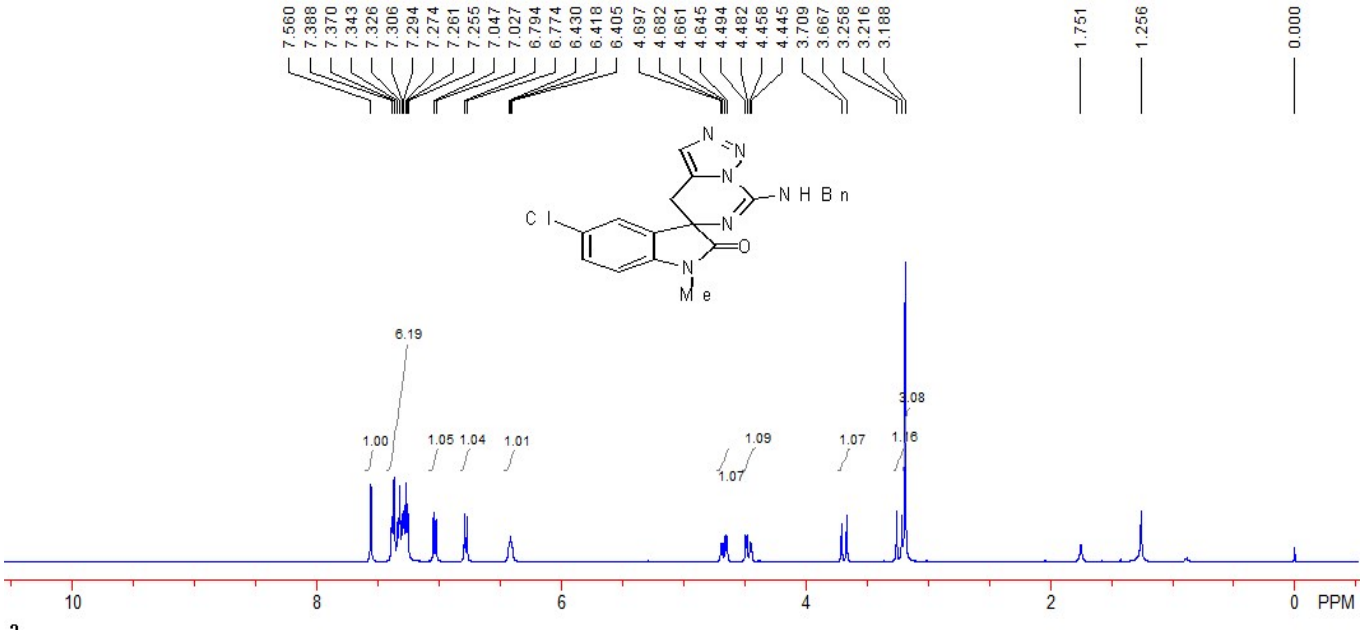


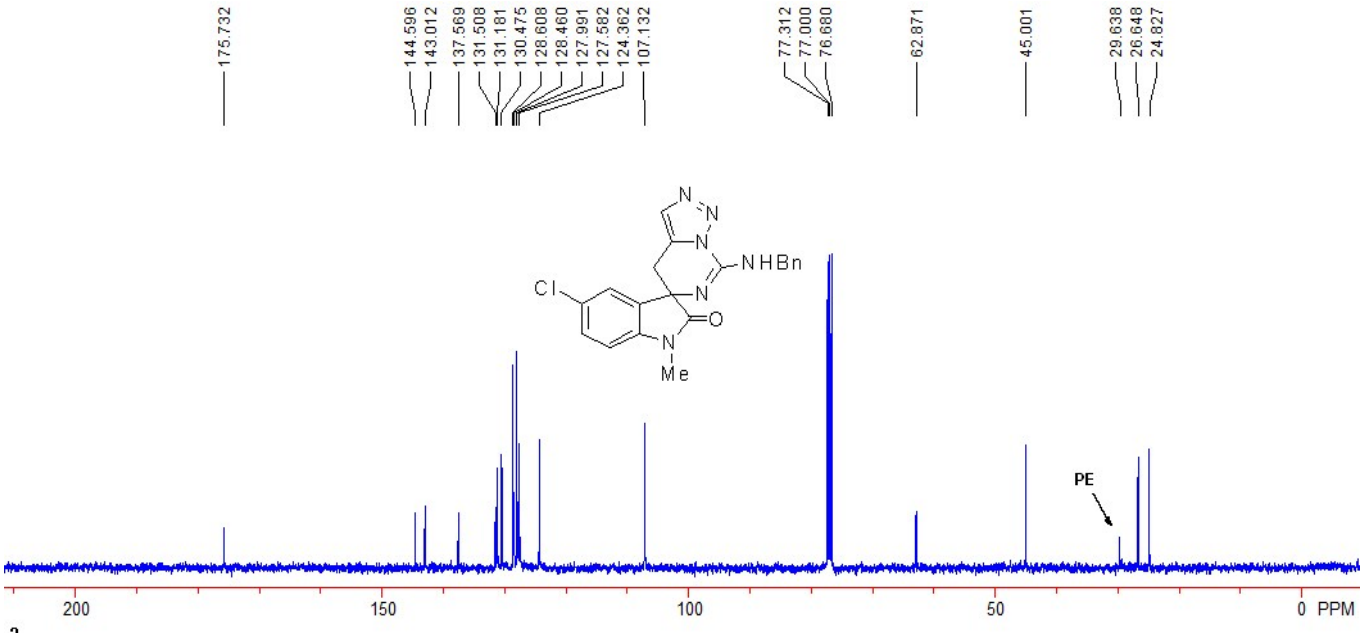


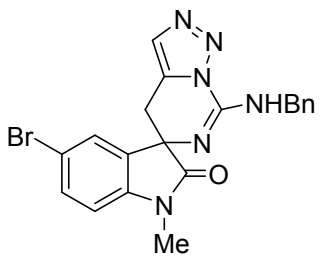




Compound **3ca**: A white solid (32 mg, 81%); M.p. 185-187 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.19 (s, 3H), 3.24 (d, J = 16.8 Hz, 1H), 3.69 (d, J = 16.8 Hz, 1H), 4.47 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H), 4.67 (dd, J_1 = 14.4 Hz, J_2 = 6.0 Hz, 1H), 6.42 (dd, J_1 = J_2 = 4.8 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.26-7.39 (m, 6H), 7.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 24.8, 26.6, 45.0, 62.9, 107.1, 124.4, 127.6, 128.0, 128.5, 128.6, 130.5, 131.2, 131.5, 137.6, 143.0, 144.6, 175.7. IR (neat) ν 3362, 2998, 2920, 2845, 1726, 1670, 1608, 1582, 1518, 1452, 1419, 1365, 1276, 1136, 1115, 983, 905, 841, 809, 779, 750, 732, 694 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}ClN_6O$ (M^++H) requires: 393.1225. Found: 393.1227.

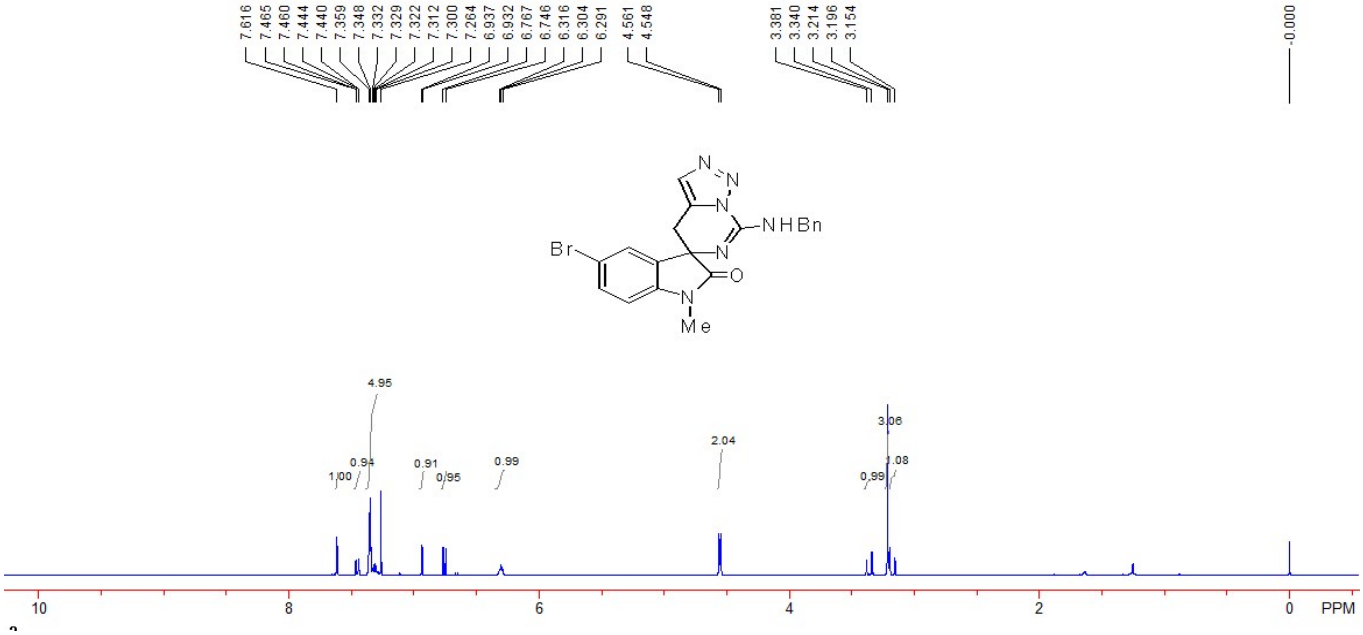


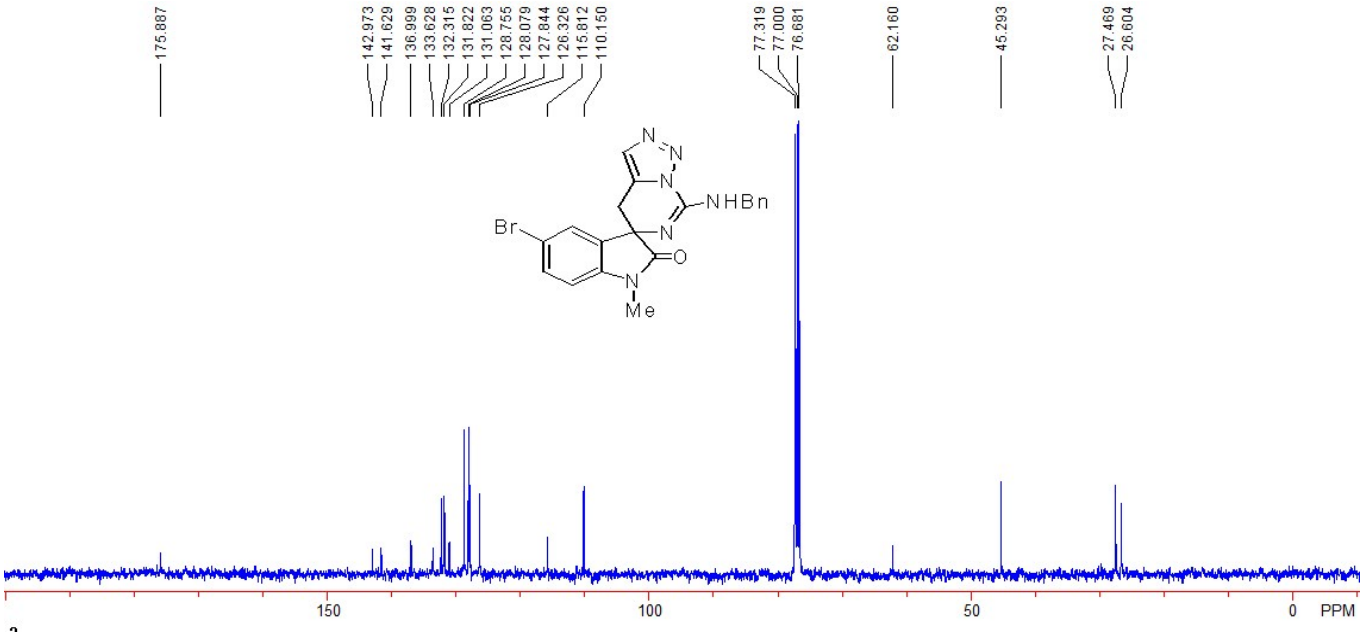


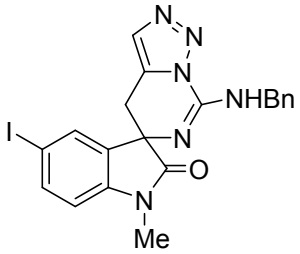


Compound **3da**: A white solid (33 mg, 76%); M.p. 178-180 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.18 (d, J = 16.8 Hz, 1H), 3.21 (s, 3H), 3.36 (d, J = 16.4 Hz, 1H), 4.55 (d, J = 5.2 Hz, 2H), 6.30 (dd, $J_1 = J_2$ = 4.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 7.30-7.36 (m, 5H), 7.45 (dd, J_1 = 8.0 Hz,

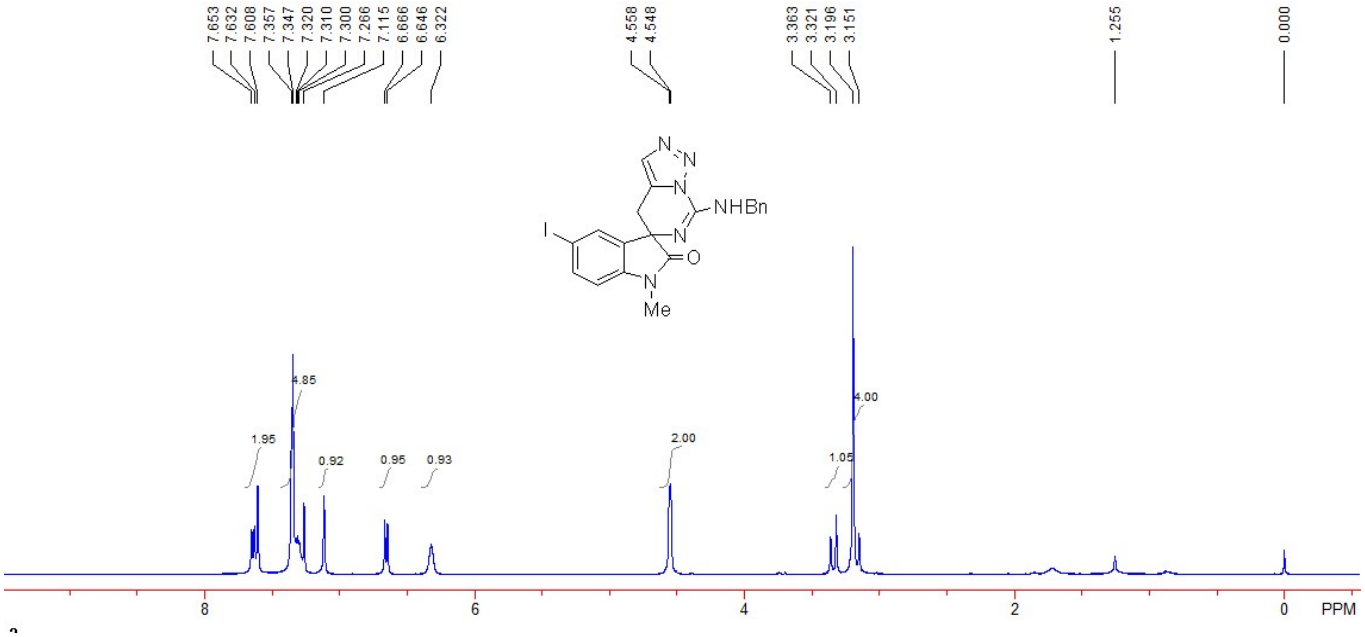
J_2 = 1.6 Hz, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.6, 27.5, 45.3, 62.2, 110.2, 115.8, 126.3, 127.8, 128.1, 128.8, 131.1, 131.8, 132.3, 133.6, 137.0, 141.6, 143.0, 175.9. IR (neat) ν 3356, 3140, 3059, 3015, 2929, 1714, 1664, 1606, 1515, 1483, 1425, 1360, 1345, 1325, 1271, 1253, 1232, 1131, 1106, 1089, 978, 905, 819, 806, 724, 690, 677 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}BrN_6O$ (M^++H) requires: 437.0720. Found: 437.0722.

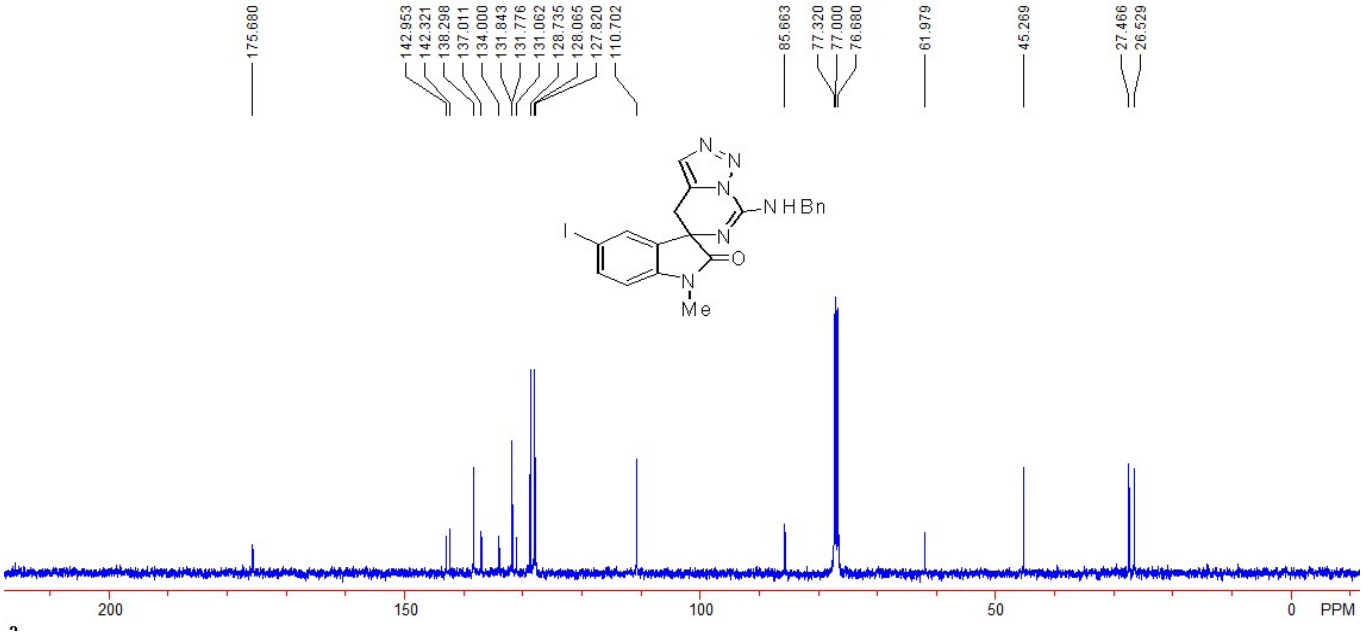


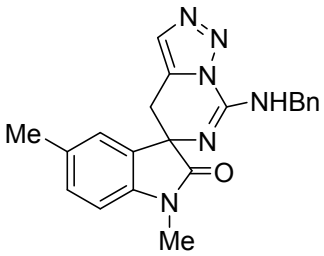




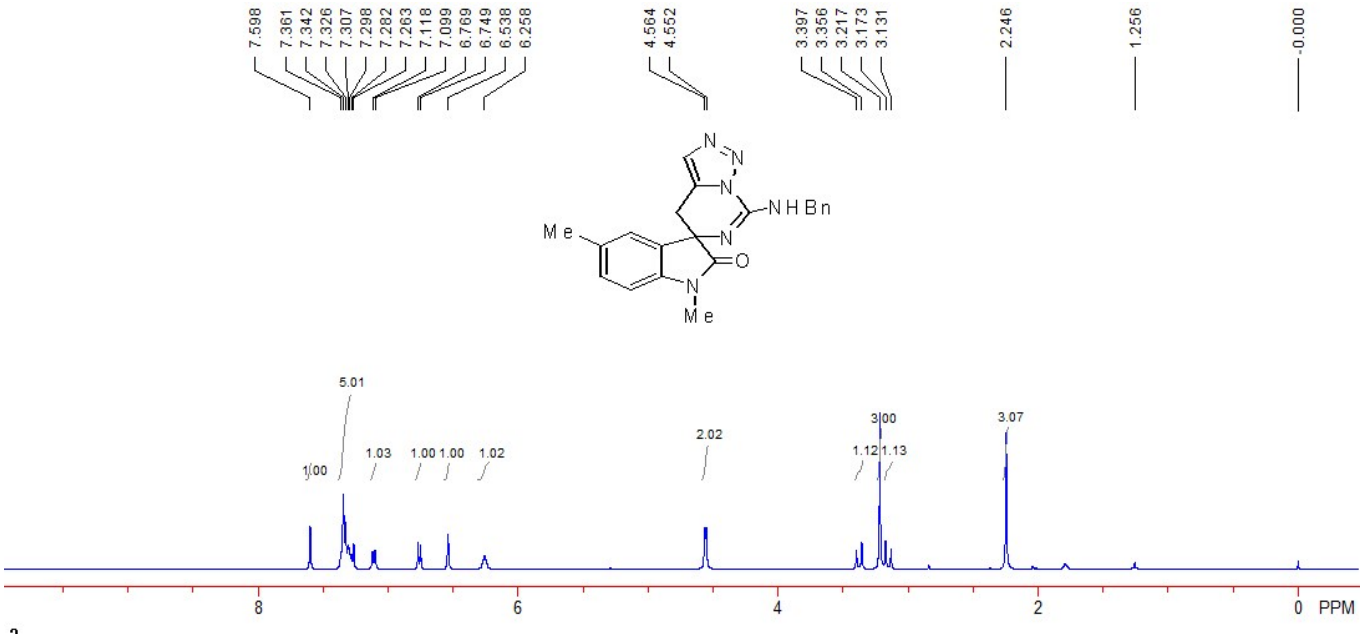
Compound **3ea**: A white solid (35 mg, 72%); M.p. 222-224 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.15-3.20 (m, 4H), 3.34 (d, *J* = 16.8 Hz, 1H), 4.55 (d, *J* = 4.0 Hz, 2H), 6.32 (s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.30-7.36 (m, 5H), 7.61 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.5, 45.3, 62.0, 85.7, 110.7, 127.8, 128.1, 128.7, 131.1, 131.77, 131.84, 134.0, 137.0, 138.3, 142.3, 143.0, 175.7. IR (neat) ν 3337, 3056, 2926, 1698, 1656, 1607, 1529, 1485, 1467, 1450, 1415, 1358, 1319, 1258, 1237, 1103, 978, 836, 817, 735, 697, 674 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}IN_6O$ (M^++H) requires: 485.0581. Found: 485.0582.

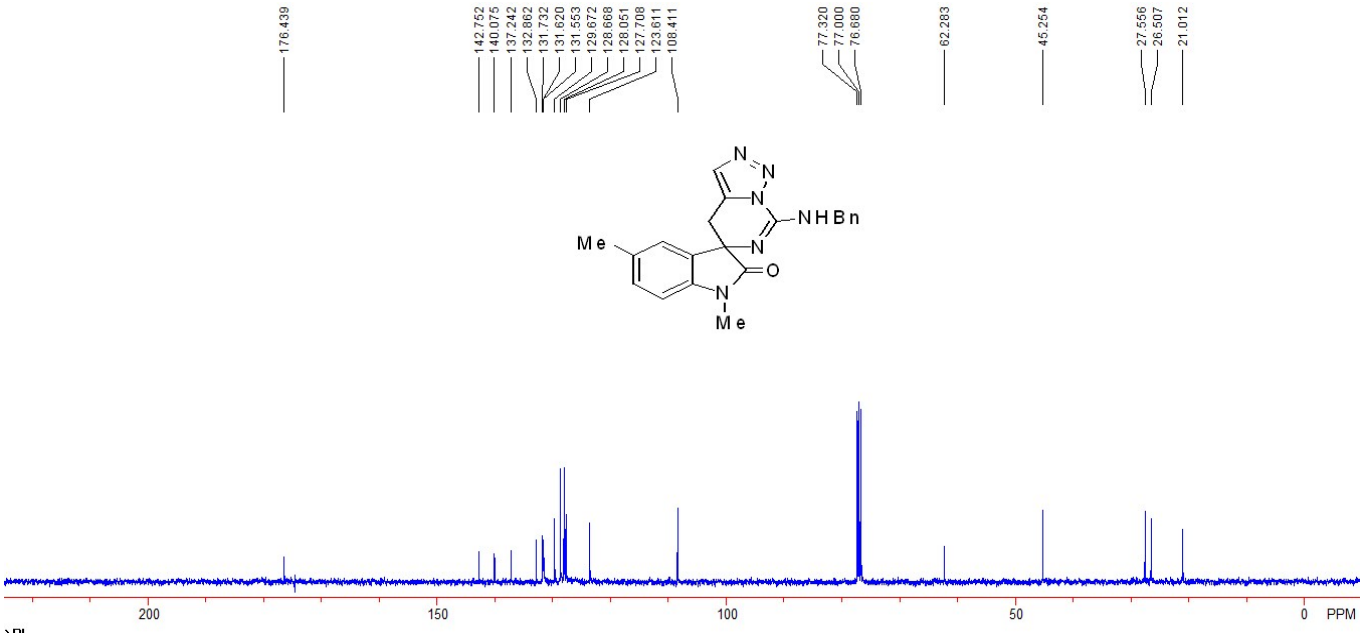


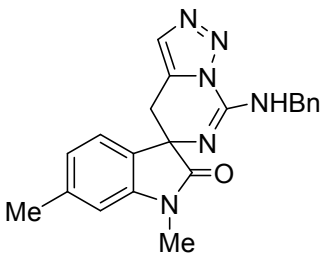




Compound **3fa**: A white solid (32 mg, 86%); M.p. 196-198 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.25 (s, 3H), 3.15 (d, *J* = 16.8 Hz, 1H), 3.22 (s, 3H), 3.37 (d, *J* = 16.8 Hz, 1H), 4.56 (d, *J* = 4.8 Hz, 2H), 6.26 (s, 1H), 6.54 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.28-7.36 (m, 5H), 7.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 26.5, 27.6, 45.2, 62.3, 108.4, 123.6, 127.7, 128.1, 128.7, 129.7, 131.55, 131.62, 131.7, 132.9, 137.2, 140.1, 142.8, 176.4. IR (neat) ν 3339, 3138, 2934, 1711, 1665, 1618, 1508, 1494, 1446, 1422, 1363, 1311, 1256, 1129, 978, 913, 816, 758, 729, 690 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{21}N_6O$ (M^++H) requires: 373.1771. Found: 373.1773.

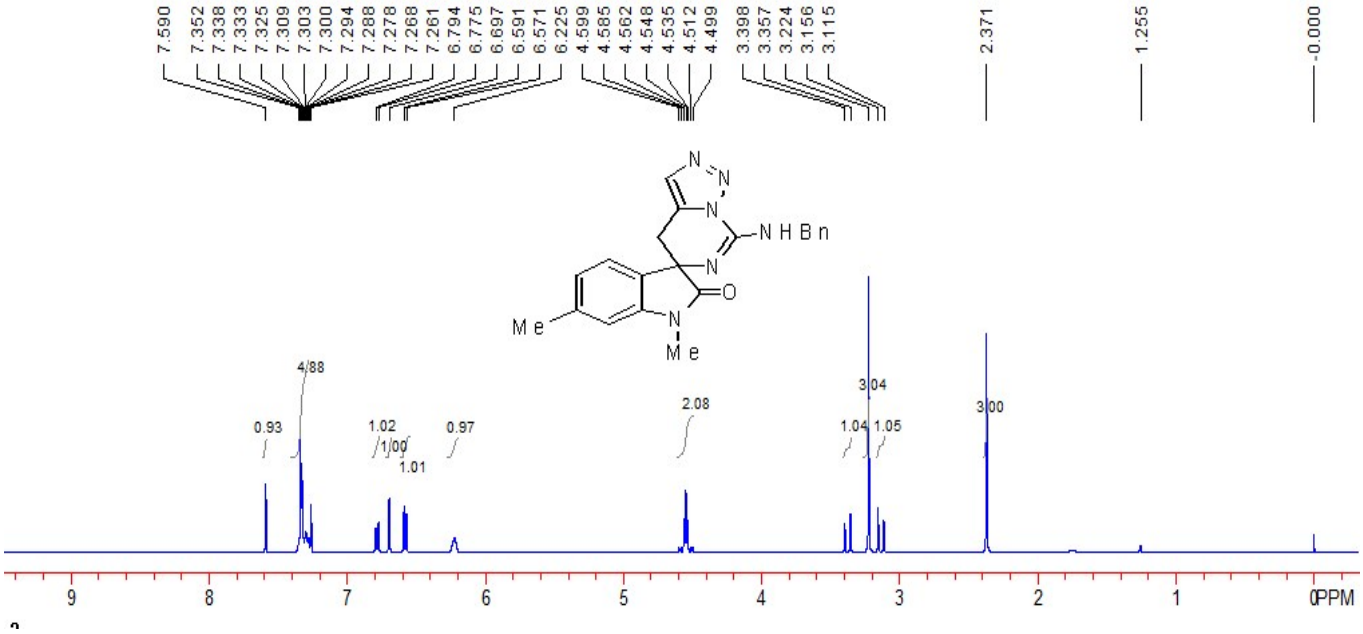


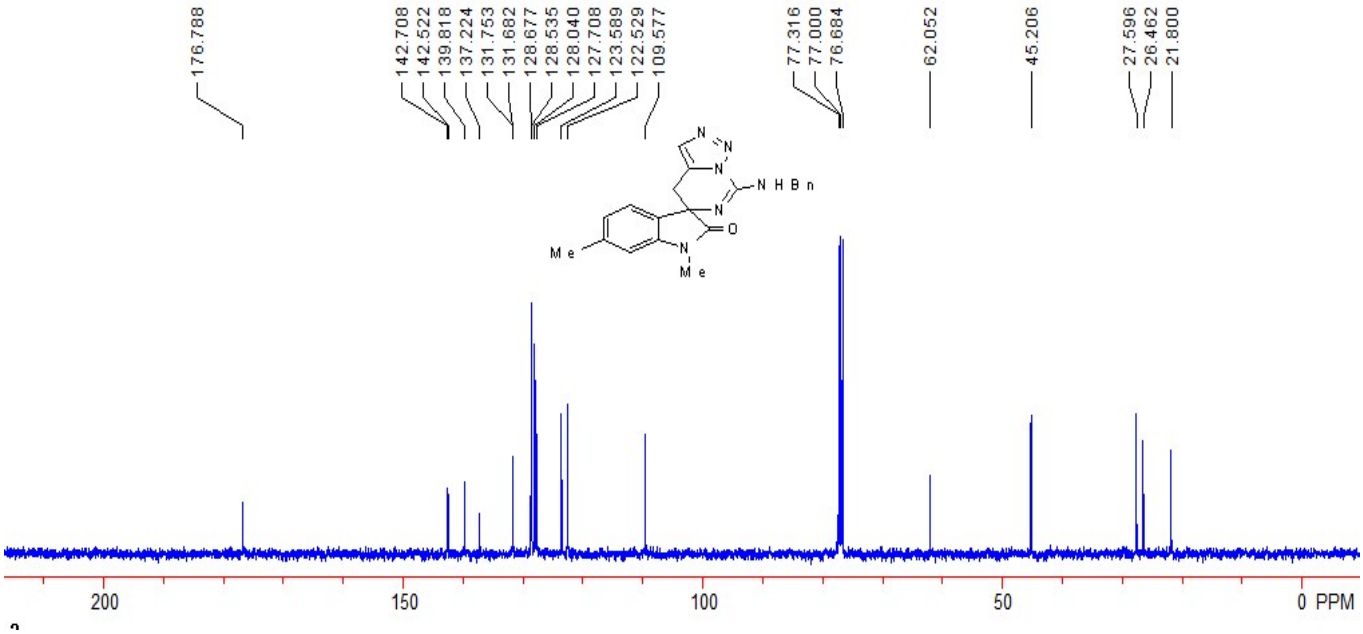


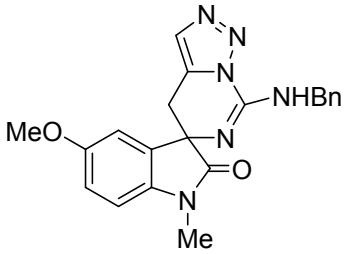


Compound **3ga**: A white solid (35 mg, 94%); M.p. 229-231 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.37 (s, 3H), 3.13 (d, *J* = 16.4 Hz, 1H), 3.22 (s, 3H), 3.38 (d, *J* = 16.4 Hz, 1H), 4.50-4.60 (m, 2H), 6.23 (s, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 7.28-7.35 (m, 5H), 7.59 (s, 1H). ^{13}C NMR

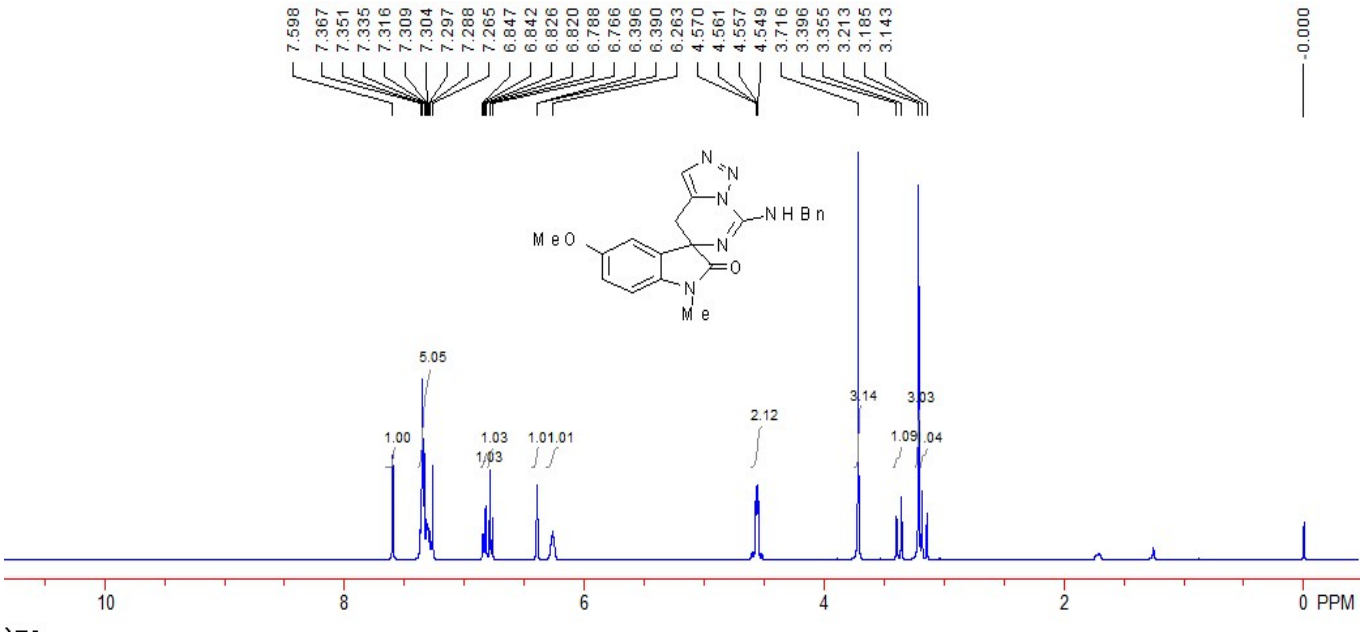
(100 MHz, $CDCl_3$, TMS) δ 21.8, 26.5, 27.6, 45.2, 62.1, 109.6, 122.5, 123.6, 127.7, 128.0, 128.5, 128.7, 131.7, 131.8, 137.2, 139.8, 142.5, 142.7, 176.8. IR (neat) ν 3360, 3134, 2926, 1707, 1657, 1624, 1530, 1443, 1416, 1372, 1315, 1260, 1235, 1134, 1092, 989, 976, 969, 882, 866, 802, 756, 700 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{21}N_6O$ (M^++H) requires: 373.1771. Found: 373.1772.

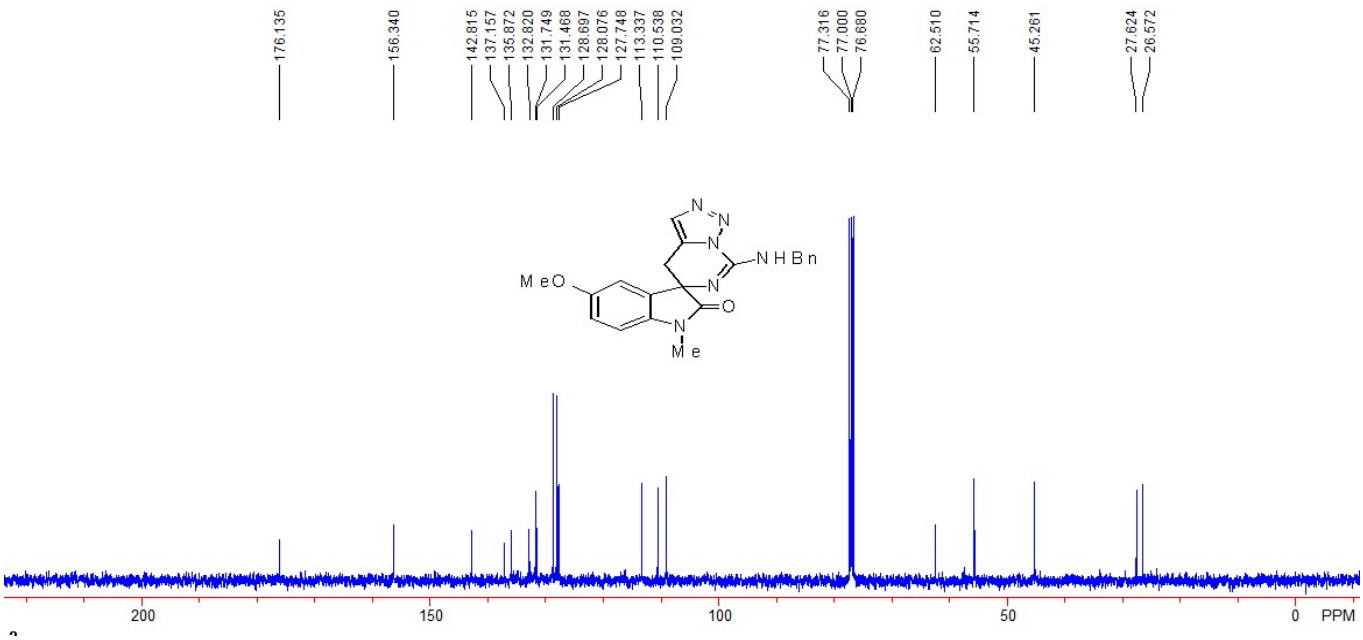


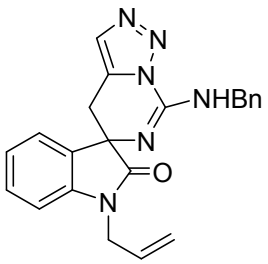




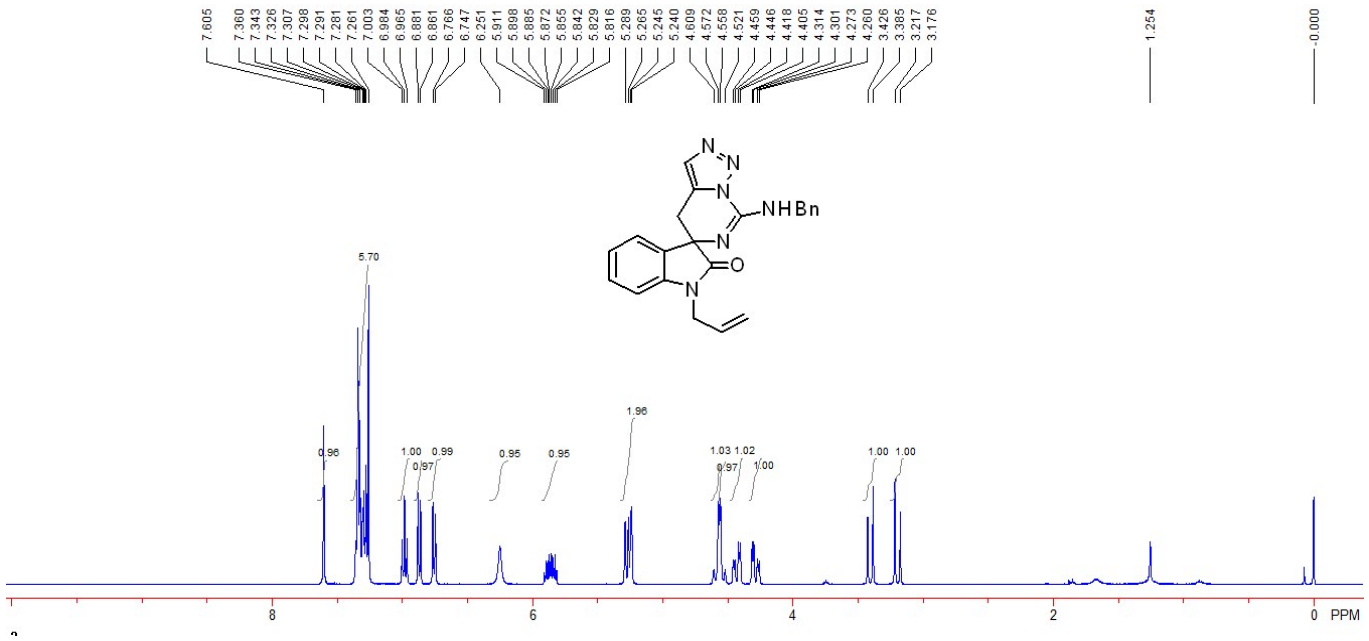
Compound **3ha**: A white solid (36 mg, 92%); M.p. 176-178 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (d, J = 16.8 Hz, 1H), 3.21 (s, 3H), 3.38 (d, J = 16.8 Hz, 1H), 3.72 (s, 3H), 4.51-4.61 (m, 2H), 6.26 (s, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.83 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.29-7.37 (m, 5H), 7.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.6, 27.6, 45.3, 55.7, 62.5, 109.0, 110.5, 113.3, 127.7, 128.1, 128.7, 131.5, 131.7, 132.8, 135.9, 137.2, 142.8, 156.3, 176.1. IR (neat) ν 3283, 1702, 1649, 1609, 1525, 1494, 1469, 1427, 1368, 1319, 1252, 1236, 1224, 1163, 1128, 1101, 977, 846, 815, 744, 709, 695 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{21}N_6O_2$ (M^++H) requires: 389.1721. Found: 389.1720.

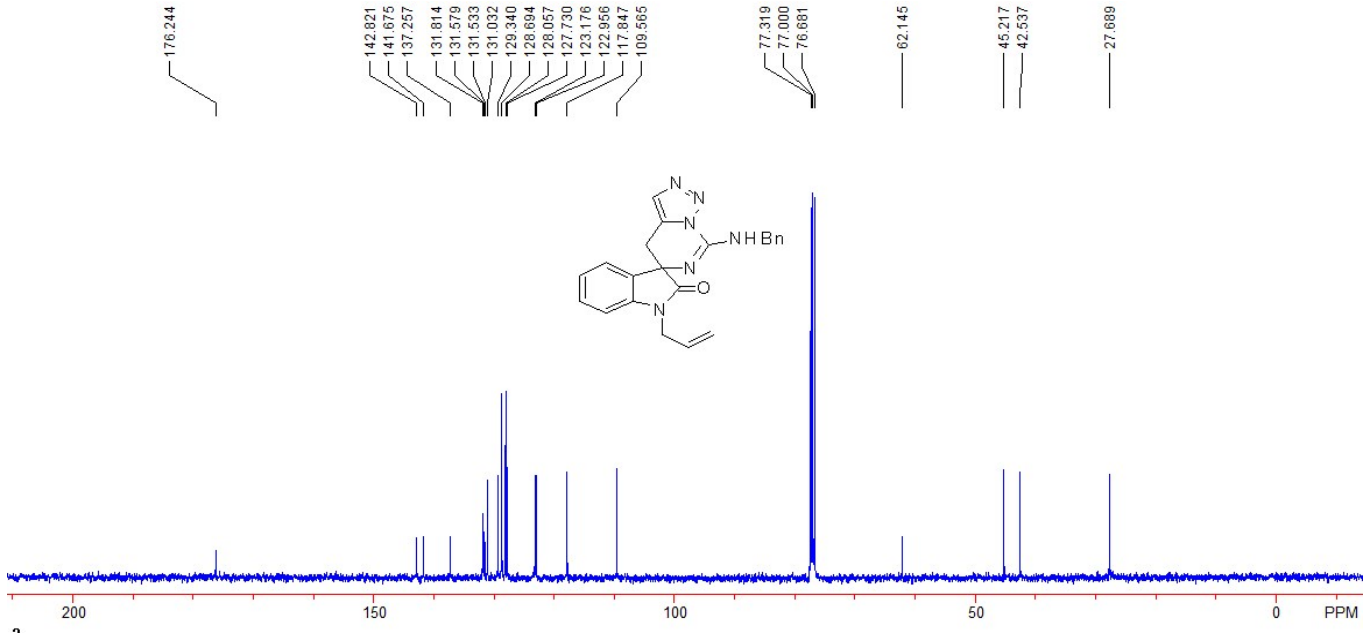


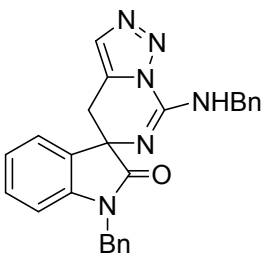




Compound **3ia**: A white solid (27 mg, 69%); M.p. 148-150 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.20 (d, J = 16.4 Hz, 1H), 3.41 (d, J = 16.4 Hz, 1H), 4.29 (dd, J_1 = 16.4 Hz, J_2 = 5.2 Hz, 1H), 4.43 (dd, J_1 = 16.4 Hz, J_2 = 5.2 Hz, 1H), 4.45 (d, J = 10.8 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 5.24-5.29 (m, 2H), 5.83-5.91 (m, 1H), 6.25 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.98 (dd, J_1 = J_2 = 7.6 Hz, 1H), 7.28-7.36 (m, 6H), 7.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 27.7, 42.5, 45.2, 62.1, 109.6, 117.8, 123.0, 123.2, 127.7, 128.1, 128.7, 129.3, 131.0, 131.5, 131.6, 131.8, 137.3, 141.7, 142.8, 176.2. IR (neat) ν 3356, 3051, 2979, 2931, 1725, 1661, 1609, 1537, 1487, 1468, 1443, 1362, 1329, 1258, 1237, 1196, 985, 912, 755, 729, 690 cm^{-1}. HRMS (ESI) Calcd. for $C_{22}H_{21}N_6O$ (M^++H) requires: 385.1771. Found: 385.1772.

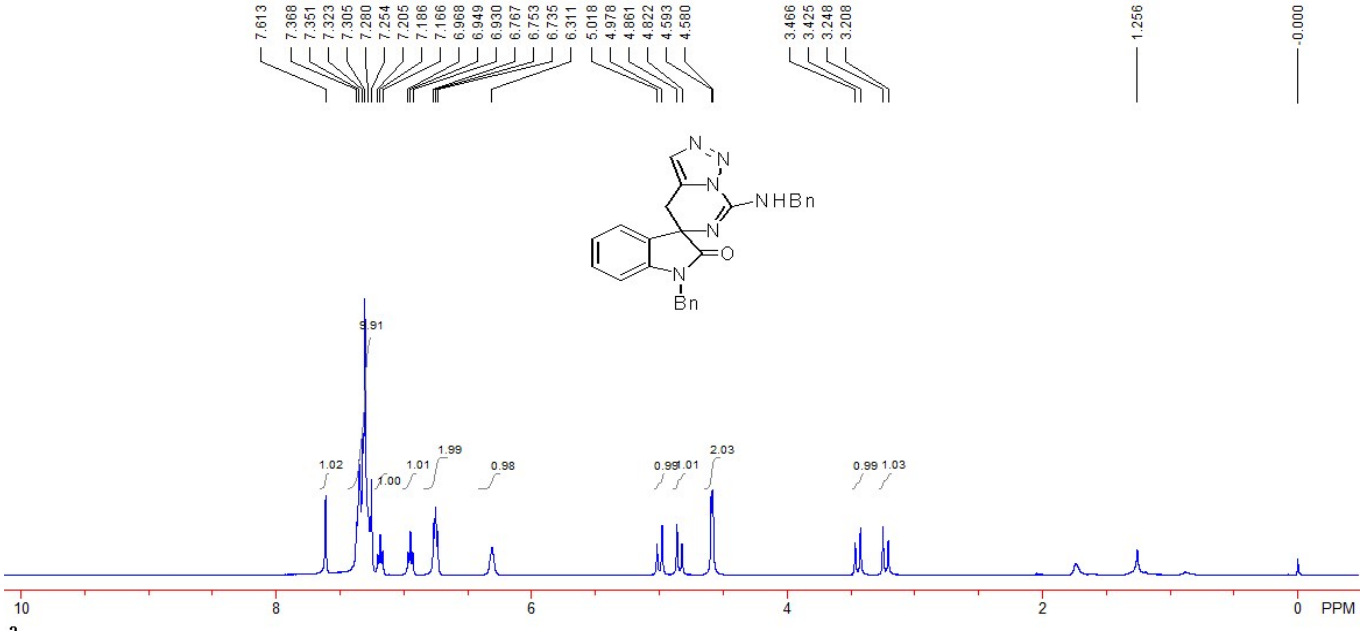


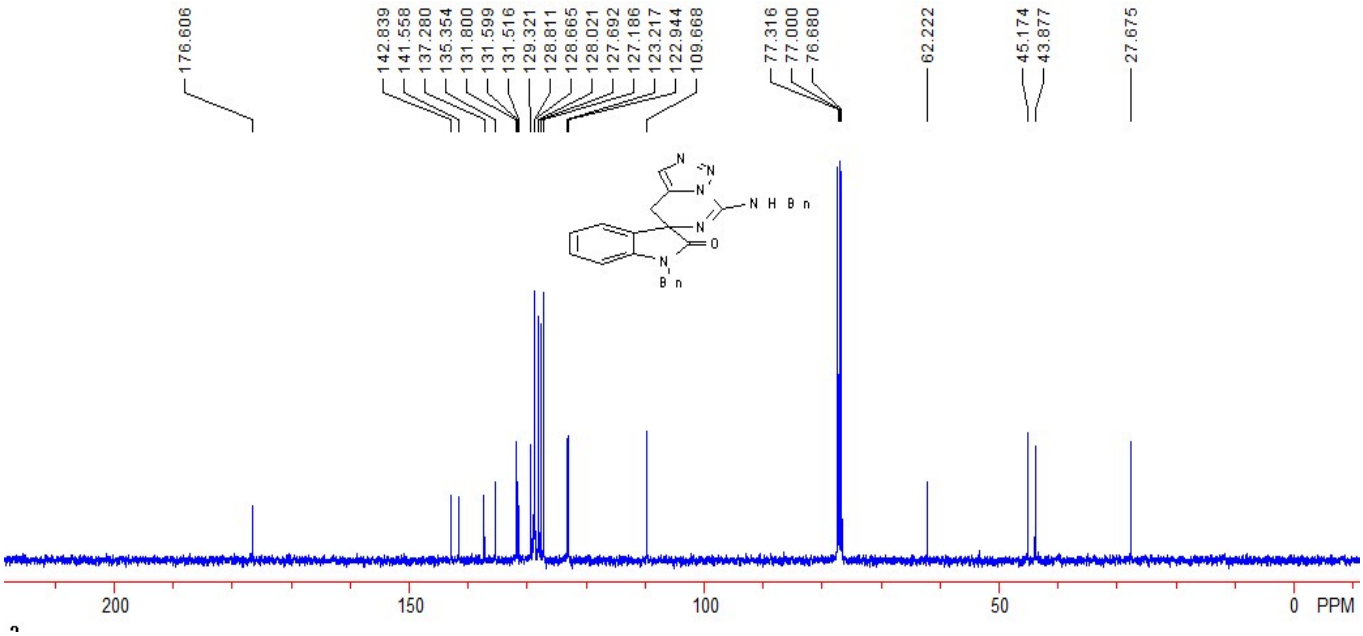


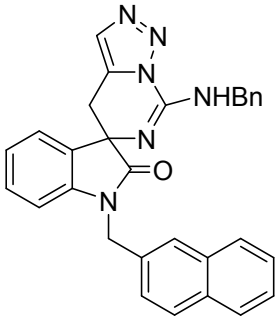


Compound **3ja**: A white solid (39 mg, 89%); M.p. 166-168 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.22 (d, J = 16.4 Hz, 1H), 3.45 (d, J = 16.4 Hz, 1H), 4.59 (d, J = 5.2 Hz, 2H), 4.84 (d, J = 16.0 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 6.31 (s, 1H), 6.74-6.77 (m, 2H), 6.95 (dd, J_1 = J_2 = 7.6 Hz, 1H), 7.19 (dd, J_1 = J_2 =

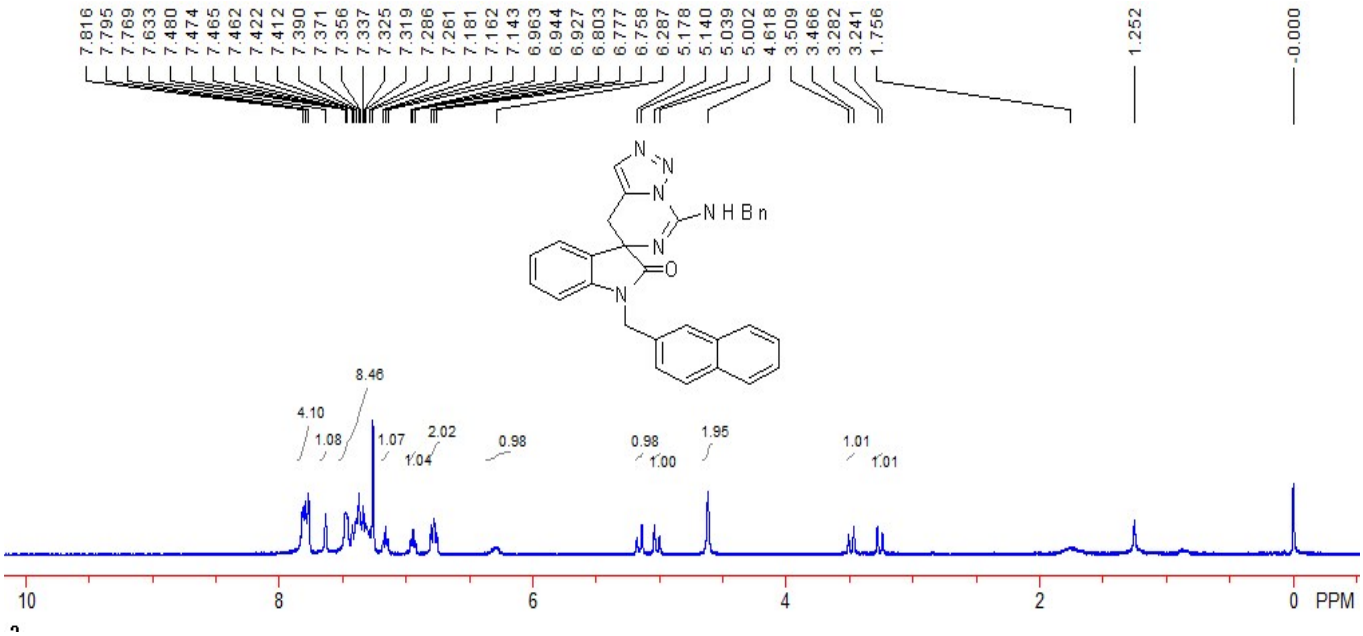
7.6 Hz, 1H), 7.25-7.37 (m, 10H), 7.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 27.7, 43.9, 45.2, 62.2, 109.7, 122.9, 123.2, 127.2, 127.7, 128.0, 128.7, 128.8, 129.3, 131.5, 131.6, 131.8, 135.4, 137.3, 141.6, 142.8, 176.6. IR (neat) ν 3311, 2922, 1711, 1655, 1612, 1530, 1486, 1463, 1354, 1326, 1169, 1127, 1078, 973, 875, 837, 767, 728, 694, 661 cm^{-1}. HRMS (ESI) Calcd. for $C_{26}H_{23}N_6O$ (M^++H) requires: 435.1928. Found: 439.1929.

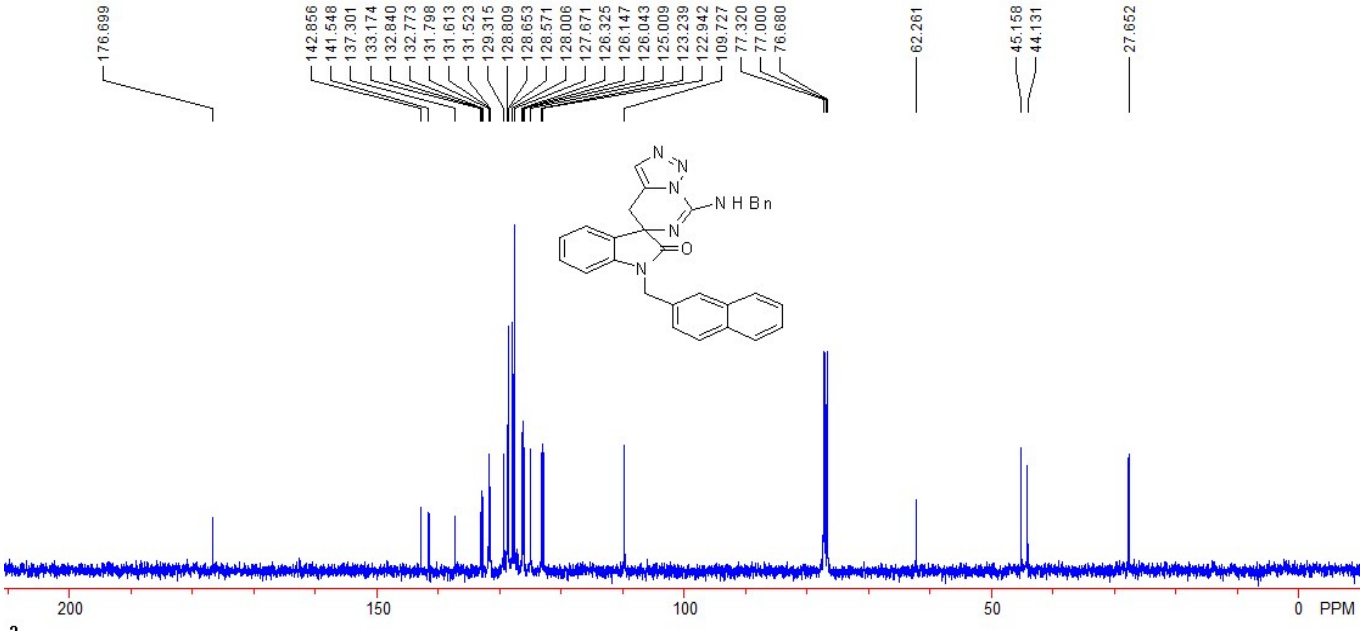


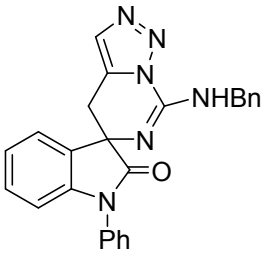




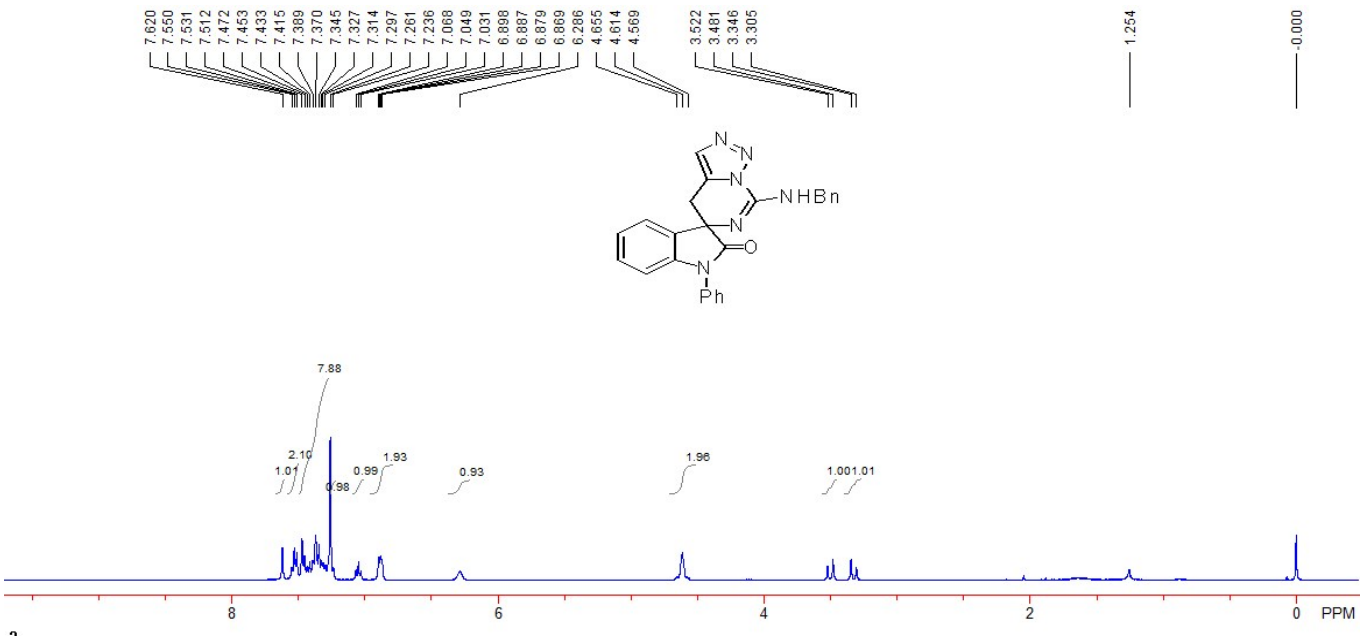
Compound **3ka**: A white solid (38 mg, 79%); M.p. 83-85 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.26 (d, *J* = 16.4 Hz, 1H), 3.49 (d, *J* = 16.4 Hz, 1H), 4.62 (s, 2H), 5.02 (d, *J* = 15.2 Hz, 1H), 5.16 (d, *J* = 15.2 Hz, 1H), 6.29 (s, 1H), 6.76-6.80 (m, 2H), 6.93-6.96 (m, 1H), 7.14-7.18 (m, 1H), 7.29-7.48 (m, 8H), 7.63 (s, 1H), 7.77-7.82 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 27.7, 44.1, 45.2, 62.3, 109.7, 122.9, 123.2, 125.0, 126.0, 126.1, 126.3, 127.7, 128.0, 128.6, 128.7, 128.8, 129.3, 131.5, 131.6, 131.8, 132.77, 132.84, 133.2, 137.3, 141.5, 142.9, 176.7. IR (neat) ν 3417, 3339, 3056, 2923, 2848, 1716, 1657, 1611, 1522, 1487, 1466, 1356, 1327, 1260, 1236, 1192, 1172, 1129, 1101, 974, 815, 746, 697, 665 cm^{-1}. HRMS (ESI) Calcd. for $C_{30}H_{25}N_6O$ (M^++H) requires: 485.2084. Found: 485.2085.

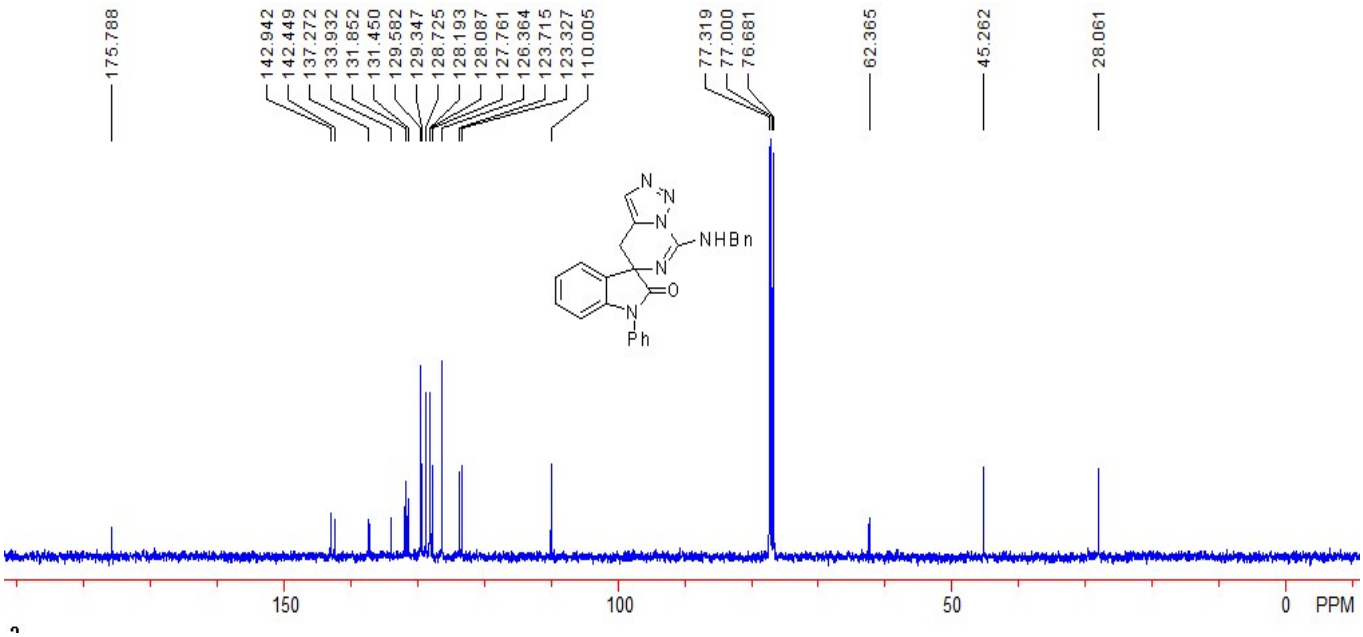


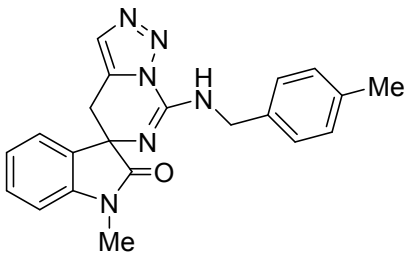




Compound **3la**: A white solid (28 mg, 67%); M.p. 189-191 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.32 (d, J = 16.4 Hz, 1H), 3.50 (d, J = 16.4 Hz, 1H), 4.57-4.66 (m, 2H), 6.29 (s, 1H), 6.87-6.90 (m, 2H), 7.05 (dd, J_1 = J_2 = 7.2 Hz, 1H), 7.24-7.47 (m, 9H), 7.51-7.55 (m, 2H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 28.1, 45.3, 62.4, 110.0, 123.3, 123.7, 126.4, 127.8, 128.1, 128.2, 128.7, 129.3, 129.6, 131.5, 131.9, 133.9, 137.3, 142.4, 142.9, 175.8. IR (neat) ν 3659, 3378, 2988, 2970, 2901, 1719, 1661, 1607, 1521, 1498, 1465, 1375, 1319, 1262, 1245, 1217, 1128, 1102, 1066, 1057, 1028, 886, 748, 697, 661 cm^{-1}. HRMS (ESI) Calcd. for $C_{25}H_{21}N_6O$ (M^++H) requires: 421.1771. Found: 421.1774.

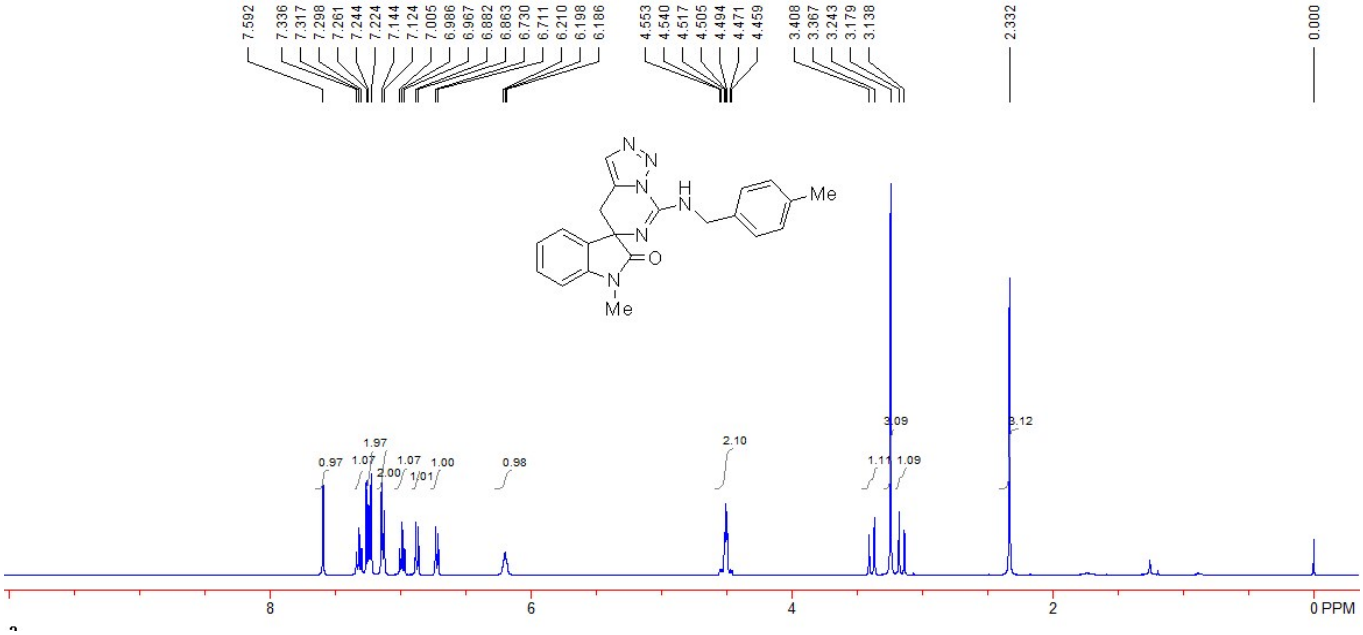


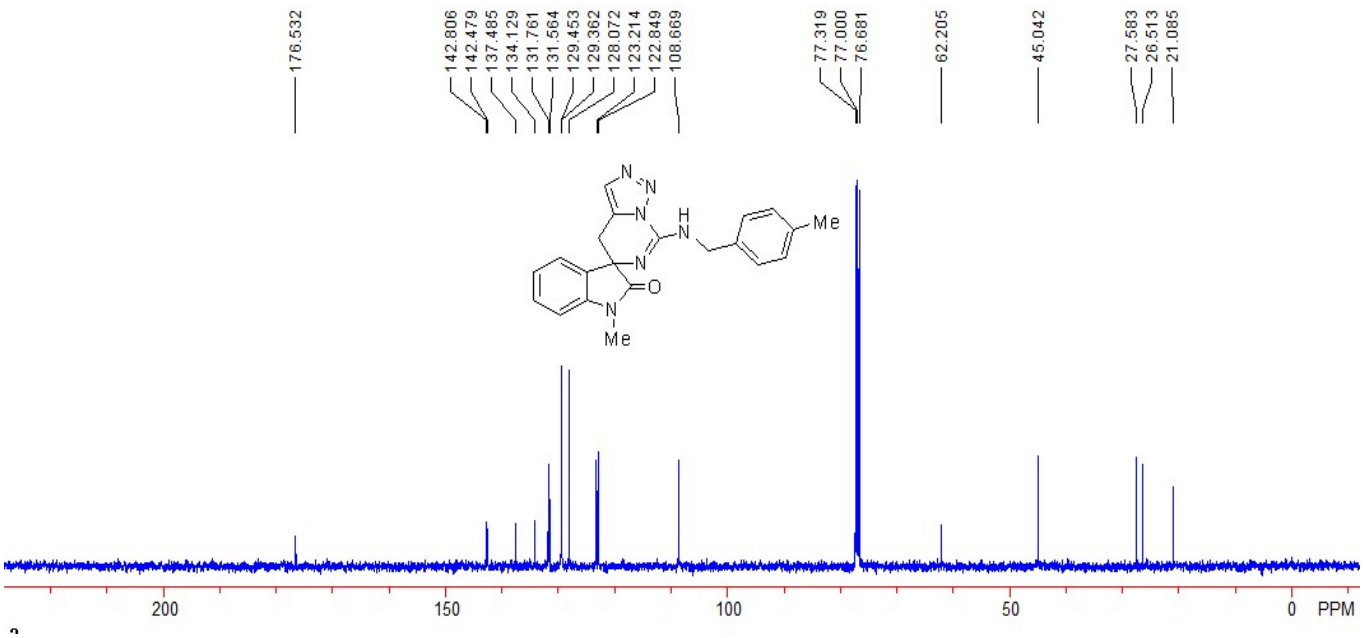


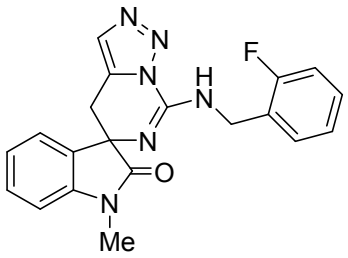


Compound **3ab**: A white solid (26 mg, 71%); M.p. 182-184 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.33 (s, 3H), 3.16 (d, J = 15.8 Hz, 1H), 3.24 (s, 3H), 3.39 (d, J = 15.8 Hz, 1H), 4.46-4.55 (m, 2H), 6.20 (t, J = 4.8 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.99 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.13 (d, J

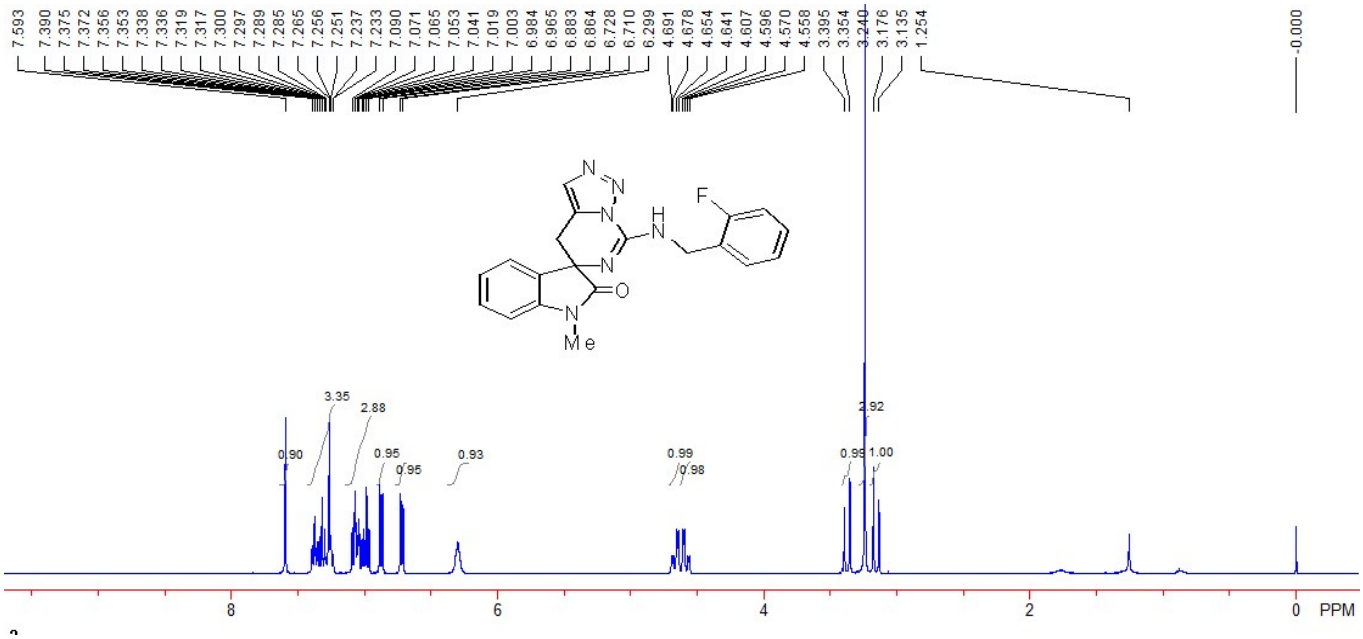
= 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.32 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.1, 26.5, 27.6, 45.0, 62.2, 108.7, 122.8, 123.2, 128.1, 129.4, 129.5, 131.6, 131.8, 134.1, 137.5, 142.5, 142.8, 176.5. IR (neat) ν 3307, 2942, 1704, 1654, 1615, 1522, 1495, 1470, 1447, 1423, 1374, 1351, 1321, 1269, 1241, 1133, 1091, 1018, 977, 889, 869, 837, 817, 747, 690 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{21}N_6O$ (M^++H) requires: 373.1771. Found: 373.1772.

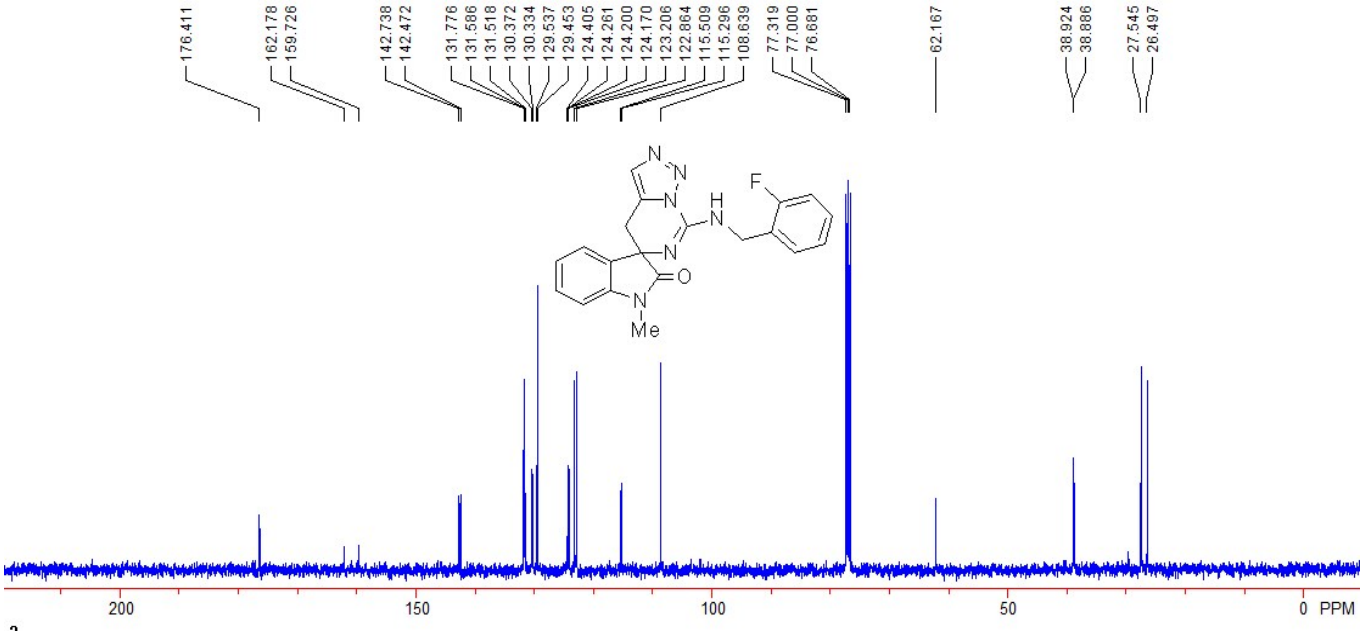


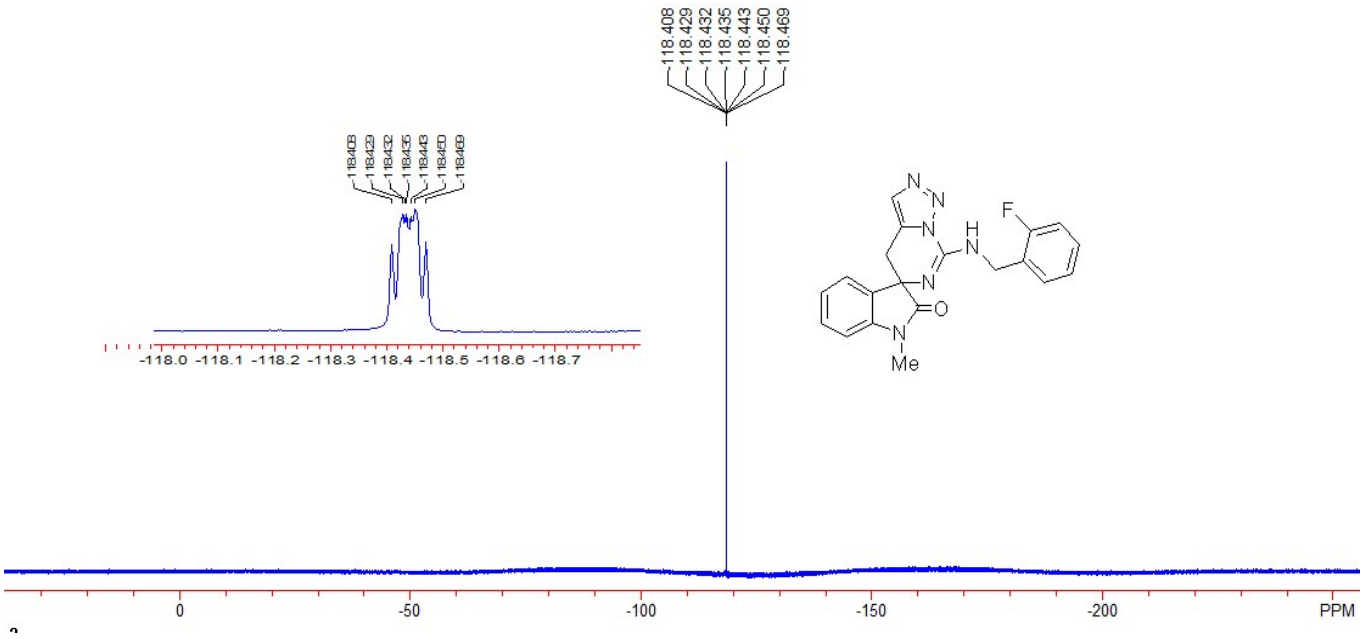


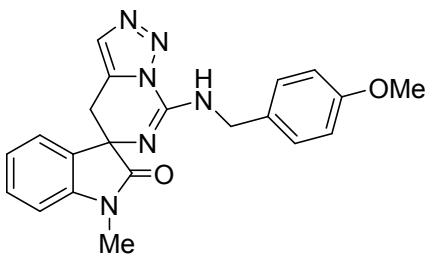


Compound **3ac**: A white solid (25 mg, 65%); M.p. 158-160 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (d, J = 16.4 Hz, 1H), 3.24 (s, 3H), 3.37 (d, J = 16.4 Hz, 1H), 4.58 (dd, J_1 = 15.2 Hz, J_2 = 5.2 Hz, 1H), 4.66 (dd, J_1 = 15.2 Hz, J_2 = 5.2 Hz, 1H), 6.30 (t, J = 4.4 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.97-7.09 (m, 3H), 7.23-7.39 (m, 3H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.5, 38.9 (d, J = 3.8 Hz), 62.2, 108.6, 115.4 (d, J = 21.3 Hz), 122.9, 123.2, 124.2 (d, J = 3.0 Hz), 124.3 (d, J = 14.4 Hz), 129.45, 129.54, 130.3, 130.4, 131.6 (d, J = 6.8 Hz), 131.8, 142.6 (d, J = 26.6 Hz), 161.0 (d, J = 245.2 Hz), 176.4. ^{19}F NMR (376 MHz, $CDCl_3$, TMS) δ -118.469~-118.408 (m). IR (neat) ν 3351, 2962, 2923, 2895, 1707, 1659, 1610, 1522, 1490, 1470 ,1448, 1370, 1317, 1258, 1236, 1135, 1091, 976, 891, 839, 755, 690, 659 cm^{-1}. HRMS (ESI) Calcd. for $C_{20}H_{18}FN_6O$ (M^++H) requires: 377.1521. Found: 377.1524.



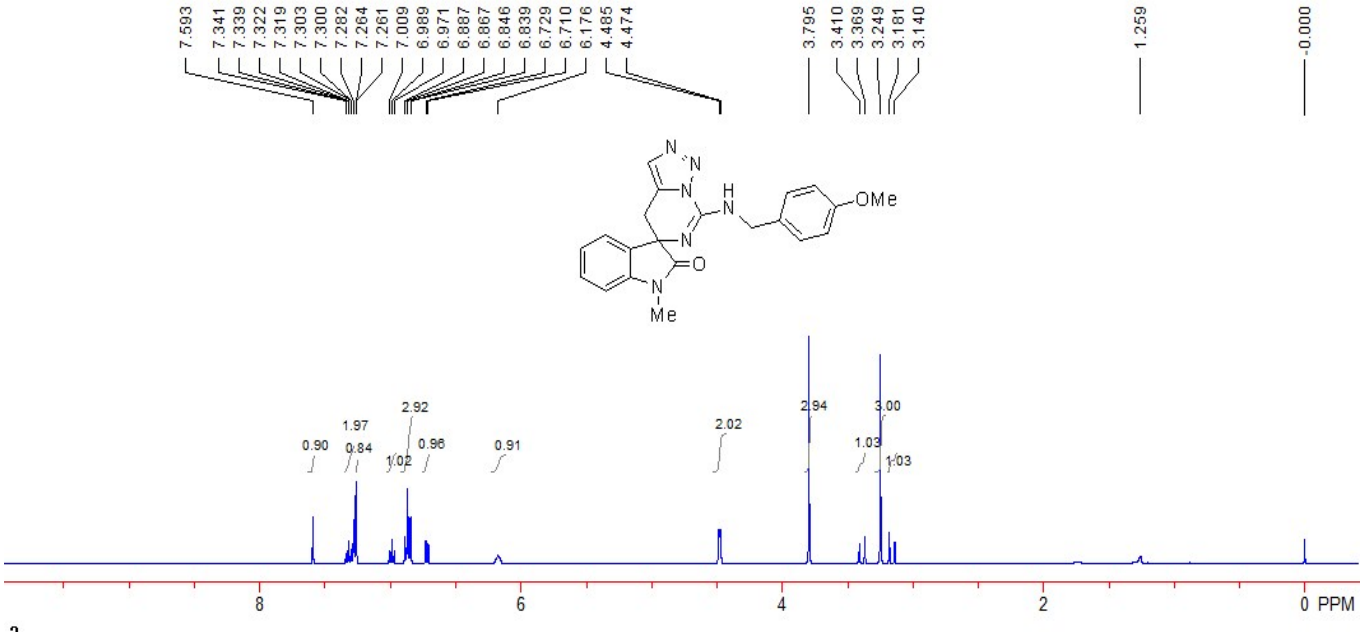


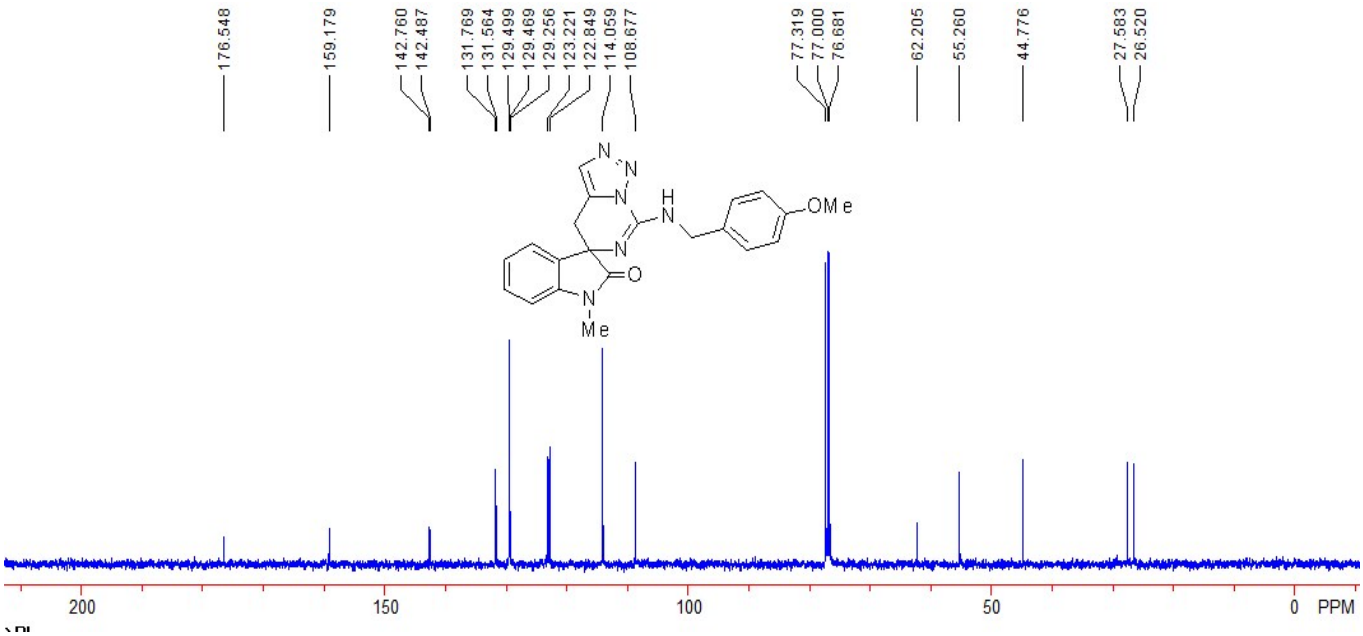


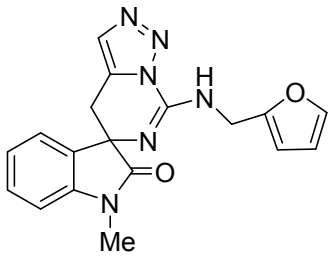


Compound **3ad**: A white solid (27 mg, 69%); M.p. 88-90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (d, J = 16.4 Hz, 1H), 3.25 (s, 3H), 3.39 (d, J = 16.4 Hz, 1H), 3.80 (s, 3H), 4.48 (d, J = 4.4 Hz, 2H), 6.18 (s, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.84-6.89 (m, 3H), 6.99 (dd, $J_1 = J_2$ = 7.2 Hz, 1H), 7.26-7.34 (m, 3H), 7.59

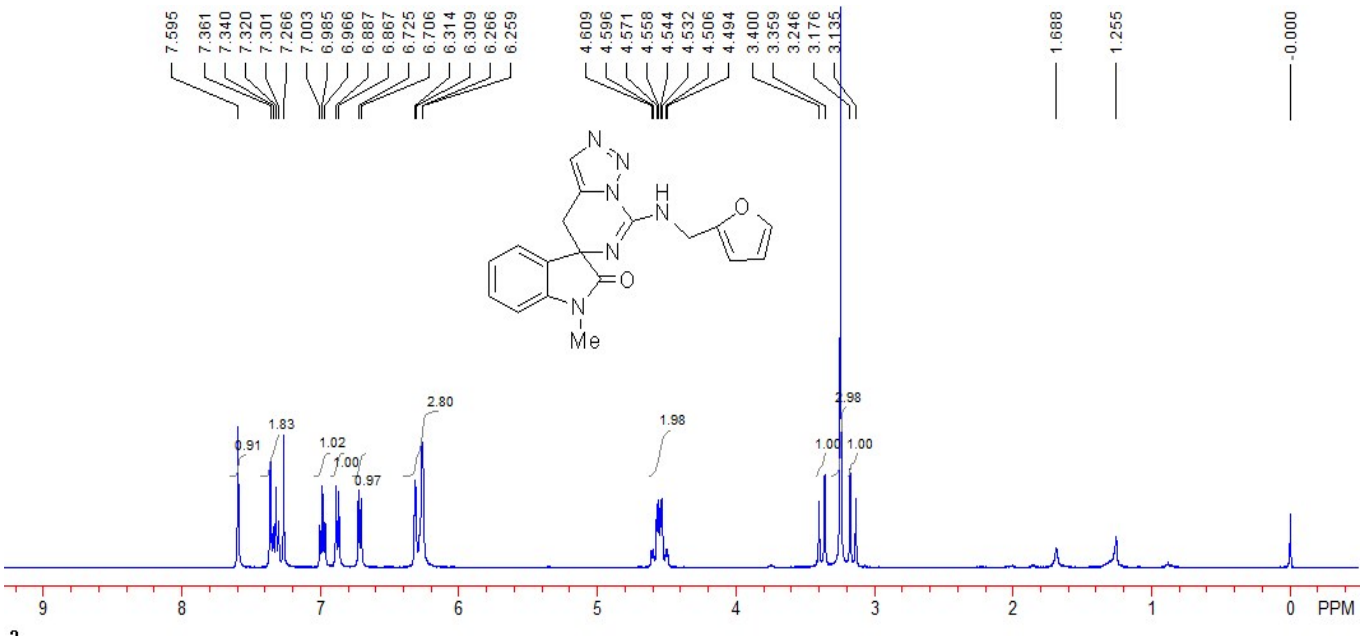
(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.6, 44.8, 55.2, 62.2, 108.7, 114.1, 122.8, 123.2, 129.3, 129.47, 129.50, 131.6, 131.8, 142.5, 142.8, 159.2, 176.5. IR (neat) ν 3347, 2930, 1716, 1658, 1611, 1511, 1493, 1469, 1444, 1421, 1371, 1351, 1325, 1238, 1176, 1128, 1090, 1029, 976, 891, 819, 751, 690, 653 cm^{-1}. HRMS (ESI) Calcd. for $C_{21}H_{21}N_6O_2$ (M^++H) requires: 389.1721. Found: 389.1717.

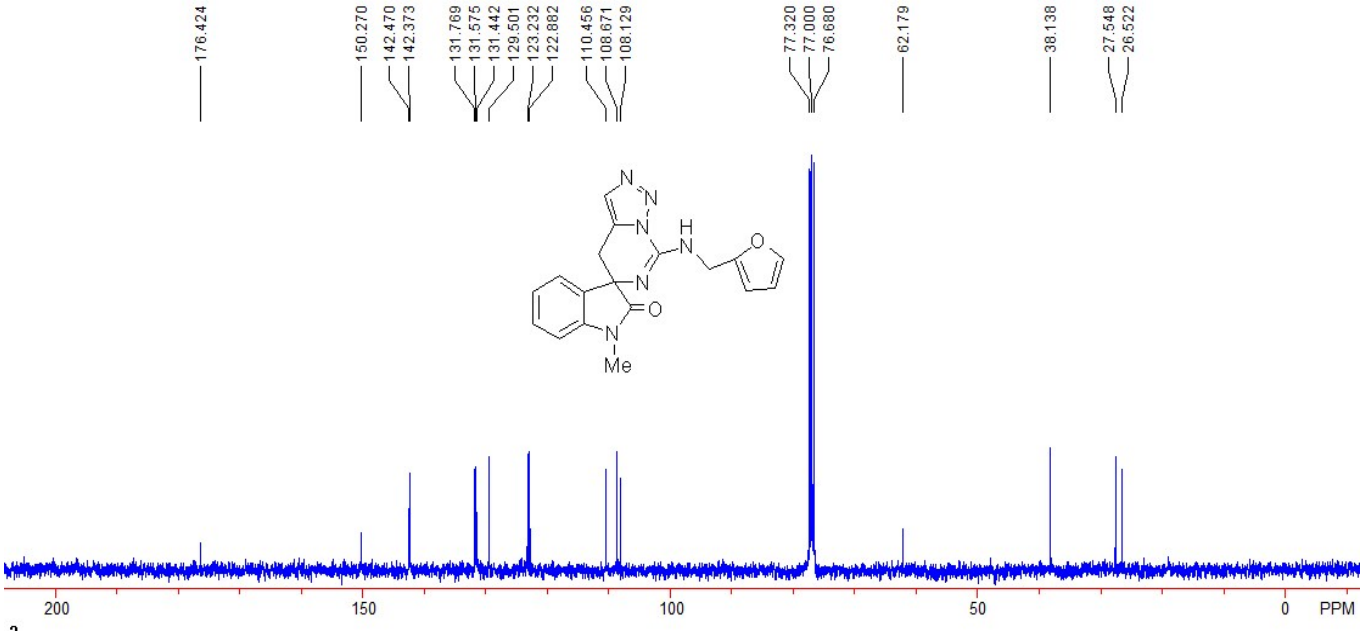


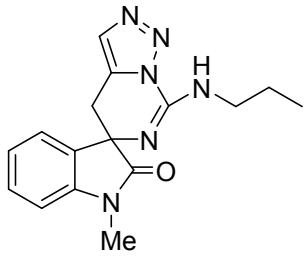




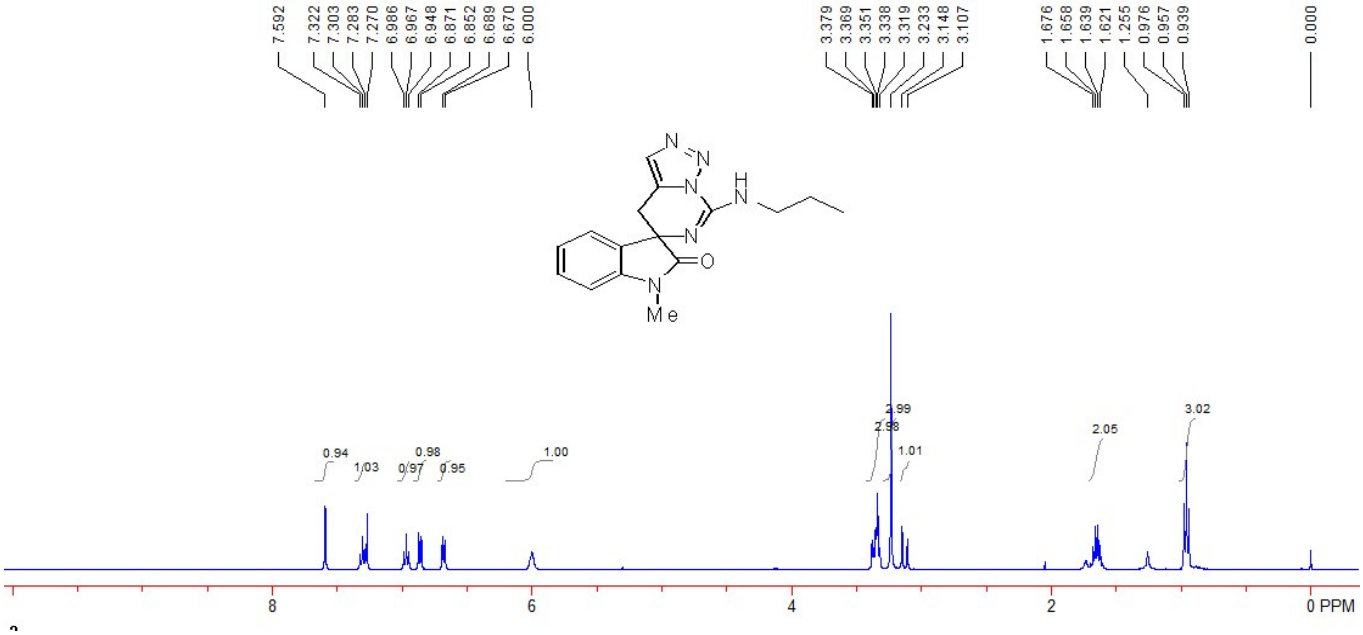
Compound **3ae**: A white solid (29 mg, 83%); M.p. 169-171 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.16 (d, J = 16.4 Hz, 1H), 3.25 (s, 3H), 3.38 (d, J = 16.4 Hz, 1H), 4.49-4.61 (m, 2H), 6.26-6.31 (m, 3H), 6.72 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.99 (dd, $J_1 = J_2$ = 7.2 Hz, 1H), 7.30-7.36 (m, 2H), 7.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.5, 38.1, 62.2, 108.1, 108.7, 110.5, 122.9, 123.2, 129.5, 131.4, 131.6, 131.8, 142.4, 142.5, 150.3, 176.4. IR (neat) ν 3339, 3154, 2922, 1702, 1655, 1611, 1529, 1494, 1471, 1450, 1421, 1373, 1353, 1327, 1265, 1238, 1141, 1125, 1024, 972, 921, 865, 748, 694, 658 cm^{-1}. HRMS (ESI) Calcd. for $C_{18}H_{17}N_6O_2$ (M^++H) requires: 349.1408. Found: 349.1409.

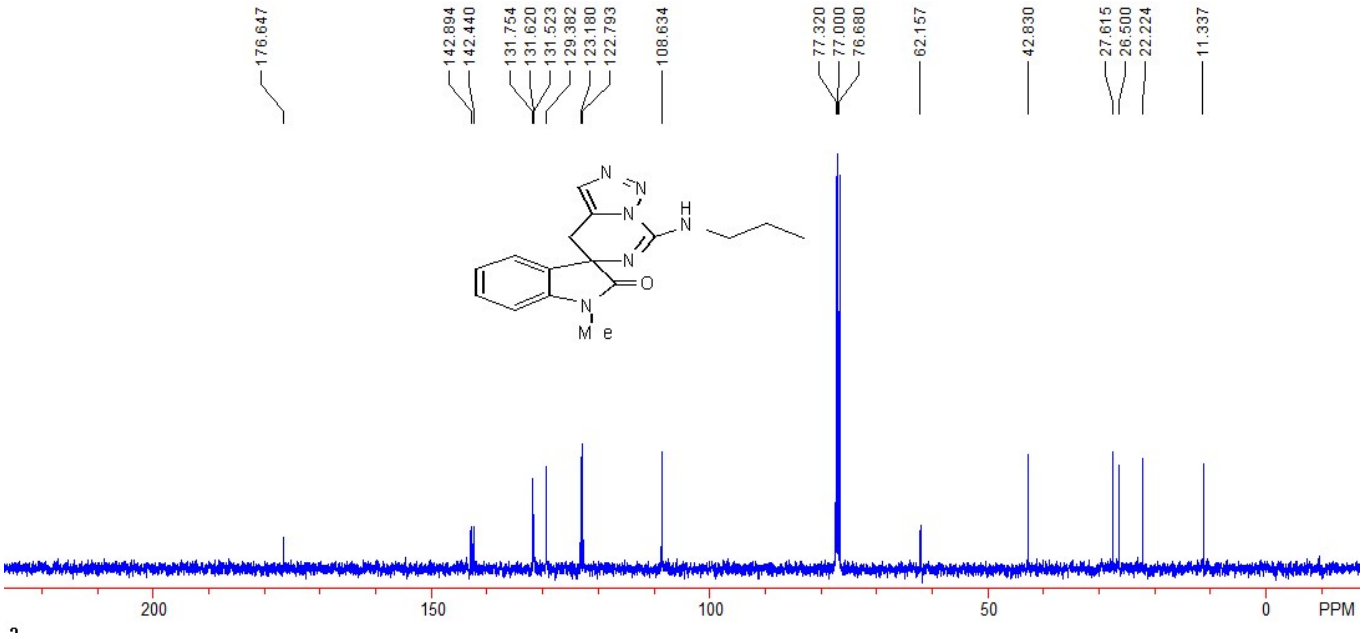


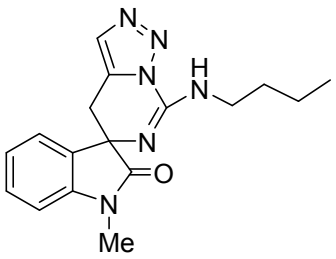




Compound **3af**: A white solid (25 mg, 82%); M.p. 158-160 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.96 (t, J = 7.6 Hz, 3H), 1.60-1.68 (m, 2H), 3.13 (d, J = 16.4 Hz, 1H), 3.23 (s, 3H), 3.32-3.38 (m, 3H), 6.00 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.97 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.30 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 11.3, 22.2, 26.5, 27.6, 42.8, 62.2, 108.6, 122.8, 123.2, 129.4, 131.5, 131.6, 131.8, 142.4, 142.9, 176.6. IR (neat) ν 3309, 2970, 2926, 2874, 1717, 1707, 1655, 1612, 1526, 1493, 1469, 1443, 1420, 1371, 1351, 1325, 1255, 1235, 1157, 1135, 1092, 986, 925, 747, 691, 659 cm^{-1}. HRMS (ESI) Calcd. for $C_{16}H_{19}N_6O$ (M^++H) requires: 311.1615. Found: 311.1615.

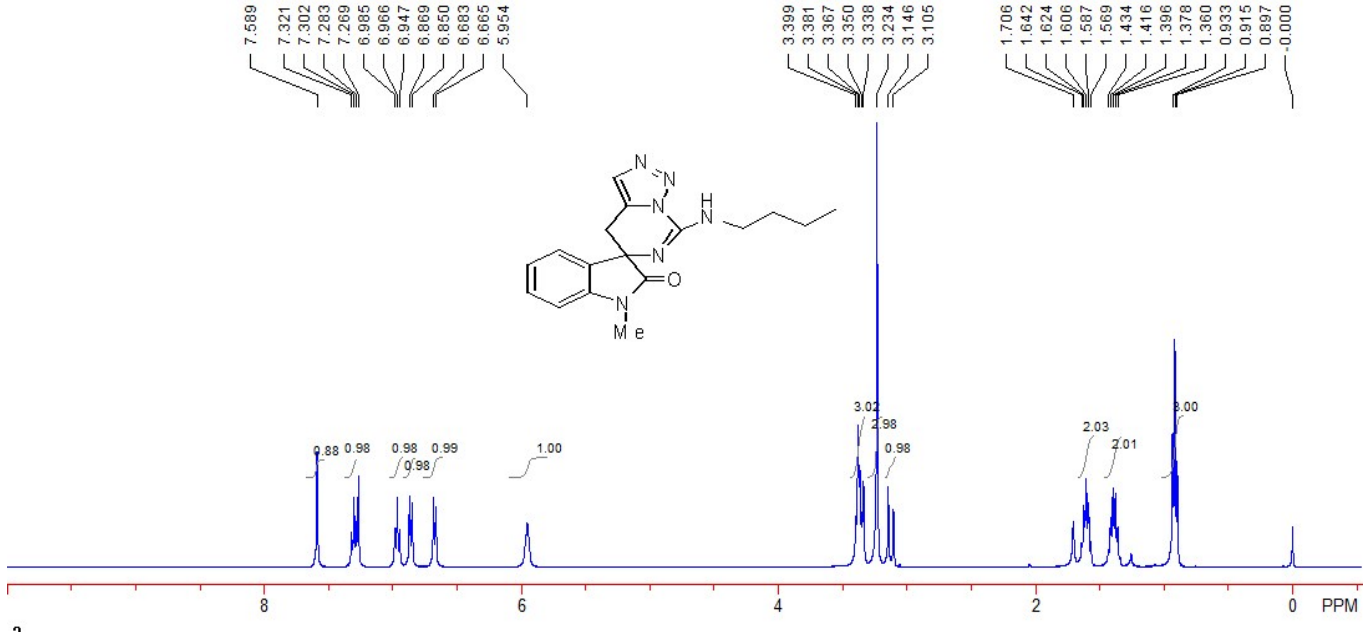


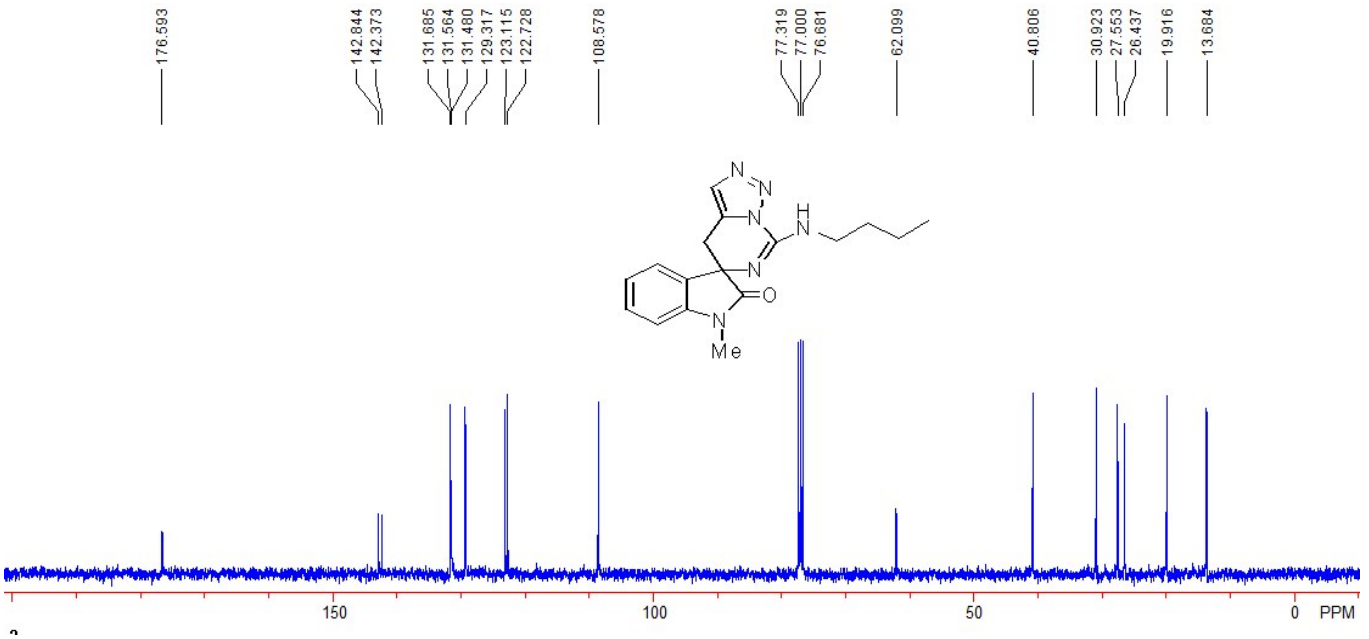


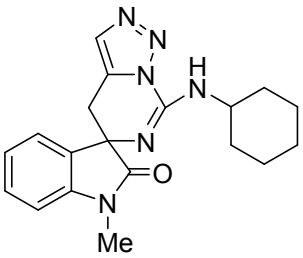


Compound **3ag**: A white solid (24 mg, 72%); M.p. 133-135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.92 (t, J = 7.2 Hz, 3H), 1.36-1.43 (m, 2H), 1.57-1.64 (m, 2H), 3.13 (d, J = 16.4 Hz, 1H), 3.23 (s, 3H), 3.34-3.40 (m, 3H), 5.95 (s, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.97 (dd, J_1 = J_2 = 7.6 Hz,

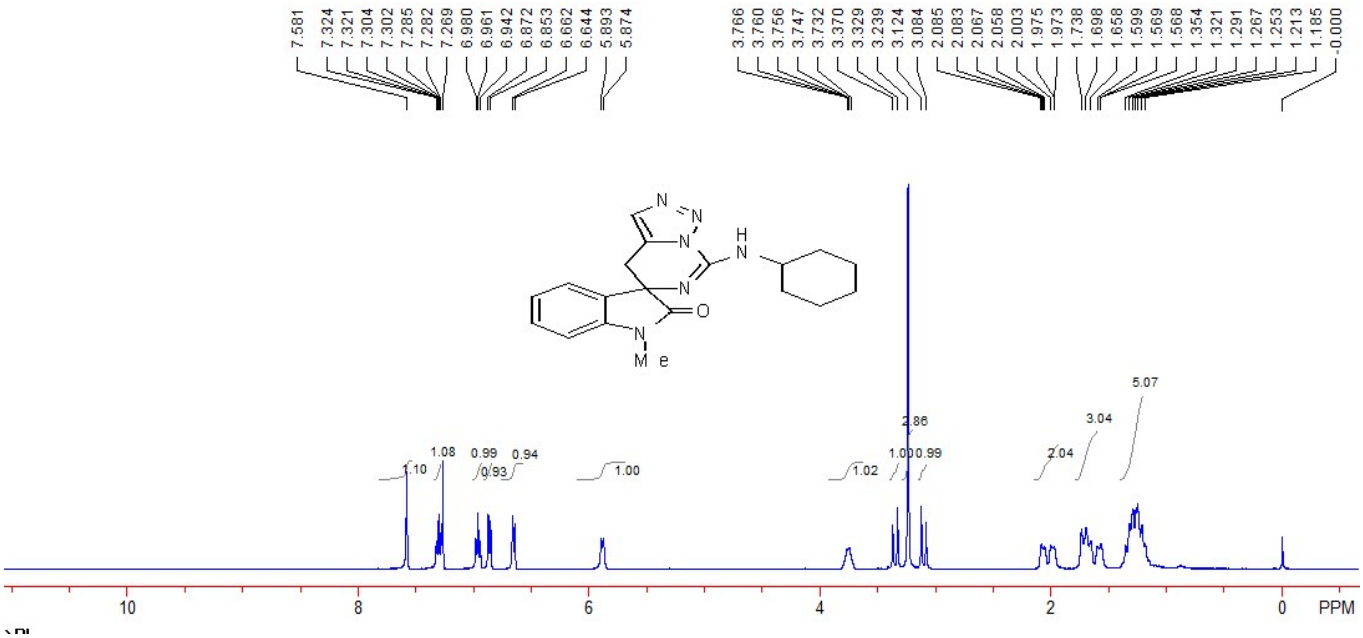
1H), 7.30 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.7, 19.9, 26.4, 27.6, 30.9, 40.8, 62.1, 108.6, 122.7, 123.1, 129.3, 131.5, 131.6, 131.7, 142.4, 142.8, 176.6. IR (neat) ν 3299, 2930, 1716, 1710, 1652, 1612, 1539, 1493, 1471, 1447, 1421, 1371, 1346, 1325, 1259, 1237, 1139, 1126, 1093, 987, 972, 895, 817, 748, 692, 659 cm^{-1}. HRMS (ESI) Calcd. for $C_{17}H_{21}N_6O$ (M^++H) requires: 325.1771. Found: 325.1773.

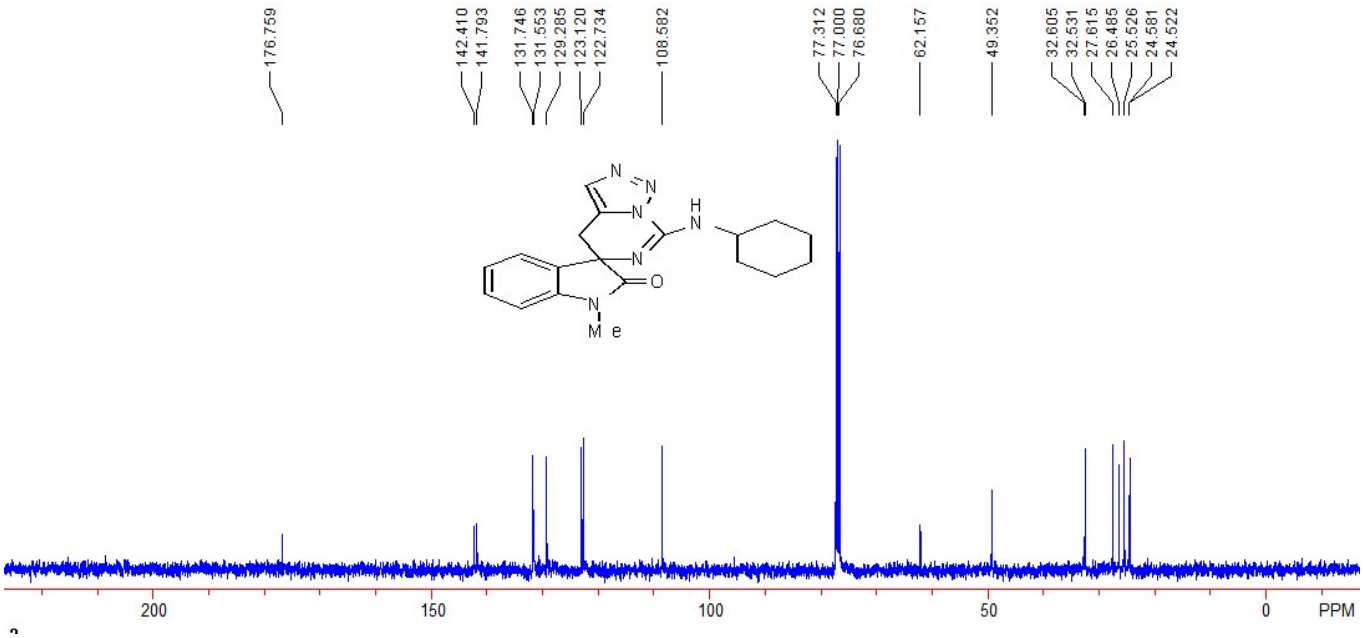


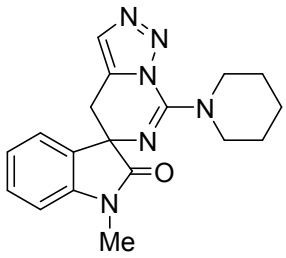




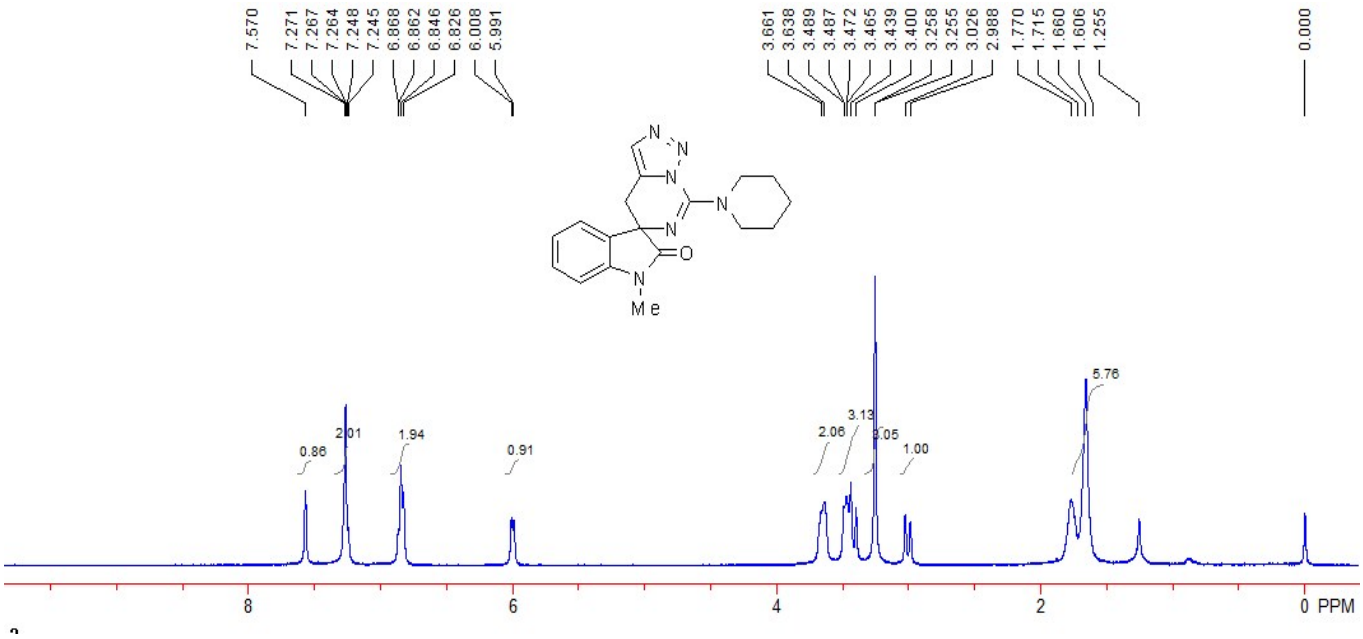
Compound **3ah**: A light yellow solid (30 mg, 86%); M.p. 235-237 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.19-1.35 (m, 5H), 1.57-1.74 (m, 3H), 1.97-2.09 (m, 2H), 3.10 (d, J = 16.4 Hz, 1H), 3.24 (s, 3H), 3.35 (d, J = 16.4 Hz, 1H), 3.73-3.77 (m, 1H), 5.88 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.96 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.28-7.32 (m, 1H), 7.58 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 24.5, 24.6, 25.5, 26.5, 27.6, 32.5, 32.6, 49.4, 62.2, 108.6, 122.7, 123.1, 129.3, 131.6, 131.7, 141.8, 142.4, 176.8. IR (neat) ν 3230, 2933, 2850, 1721, 1655, 1608, 1523, 1491, 1469, 1442, 1375, 1338, 1246, 1232, 1125, 1087, 1000, 983, 937, 889, 819, 751, 733, 706, 691 cm^{-1}. HRMS (ESI) Calcd. for $C_{19}H_{23}N_6O$ (M^++H) requires: 351.1928. Found: 351.1928.

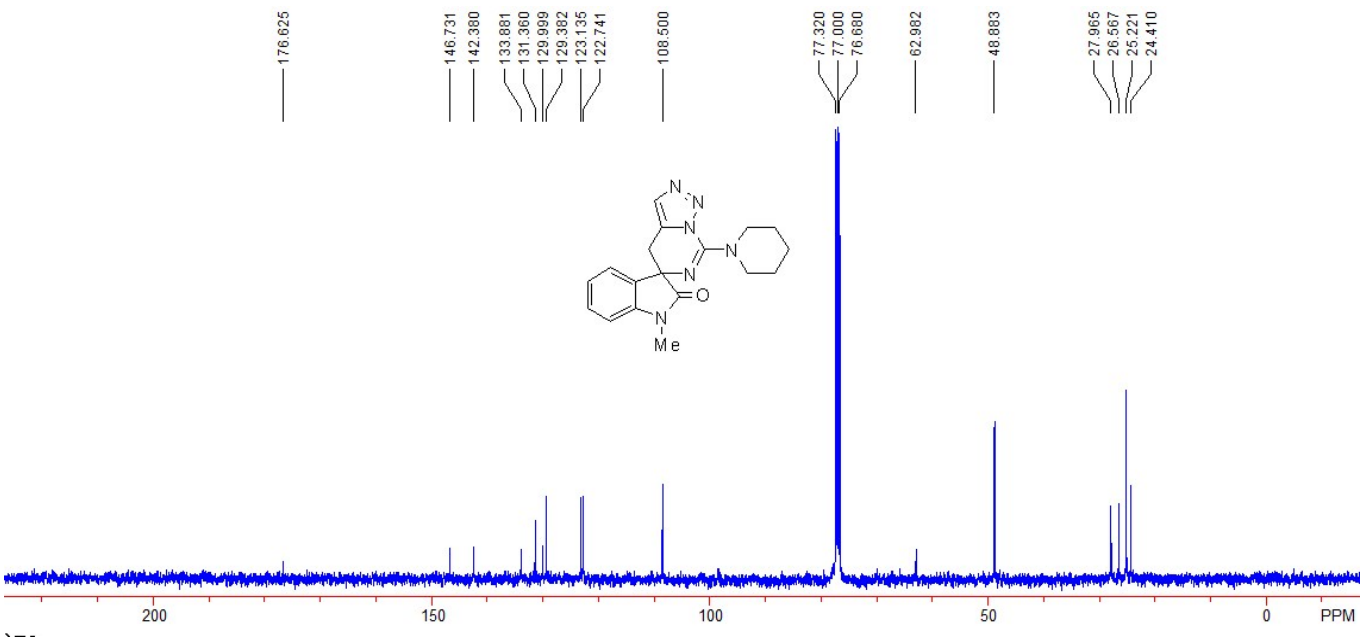


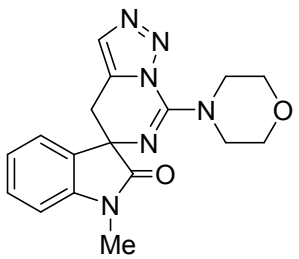




Compound **3ai**: A white solid (18 mg, 54%); M.p. 107-109 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.66 (s, 6H), 3.01 (d, J = 15.2 Hz, 1H), 3.26 (s, 3H), 3.40-3.49 (m, 3H), 3.64-3.66 (m, 2H), 6.00 (d, J = 6.8 Hz, 1H), 6.83-6.87 (m, 2H), 7.25-7.27 (m, 1H), 7.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 24.4, 25.2, 26.6, 28.0, 48.9, 63.0, 108.5, 122.7, 123.1, 129.4, 130.0, 131.4, 133.9, 142.4, 146.7, 176.6. IR (neat) ν 2937, 2920, 2845, 1716, 1613, 1494, 1421, 1371, 1348, 1256, 1242, 1229, 1126, 1105, 1091, 978, 928, 904, 843, 748, 704, 684 cm^{-1}. HRMS (ESI) Calcd. for $C_{18}H_{21}N_6O$ (M^++H) requires: 337.1771. Found: 337.1772.

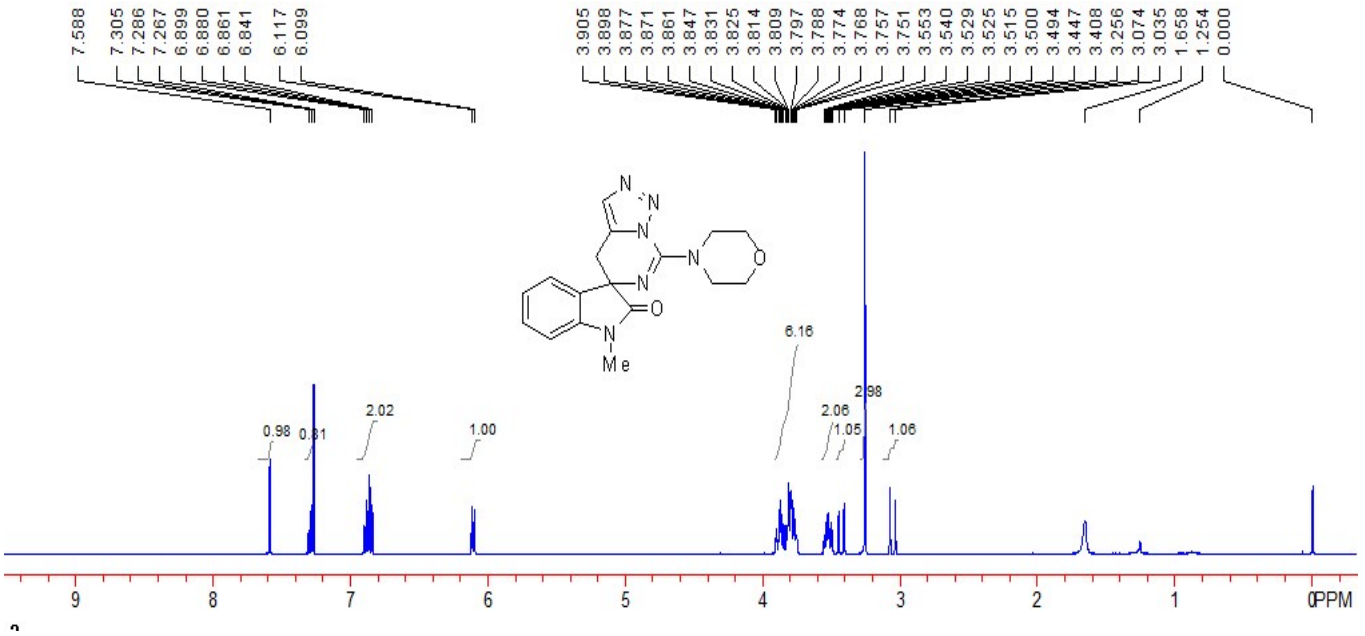


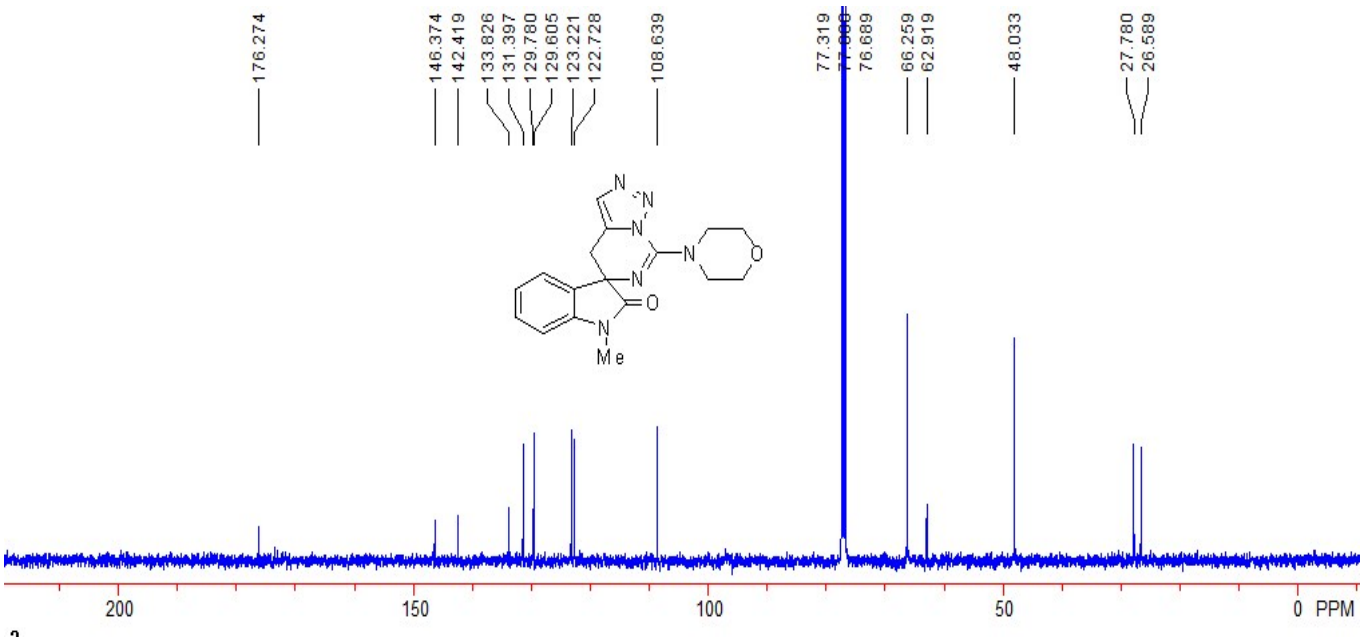




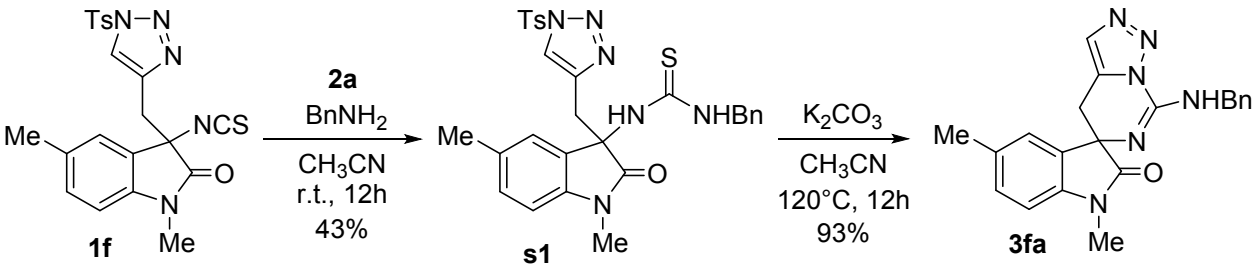
Compound **3aj**: A white solid (18 mg, 52%); M.p. 78-80 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.05 (d, *J* = 15.6 Hz, 1H), 3.26 (s, 3H), 3.43 (d, *J* = 15.6 Hz, 1H), 3.49-3.55 (m, 2H), 3.75-3.91 (m, 6H), 6.11 (d, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.59 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.6, 27.8, 48.0, 62.9, 66.3, 108.6, 122.7, 123.2, 129.6, 129.8, 131.4, 133.8, 142.4, 146.4, 176.3. IR (neat) ν 3056, 2956, 2915, 2856, 1716, 1627, 1611, 1492, 1470, 1421, 1369, 1349, 1269, 1259, 1236, 1113, 1091, 1068, 1026, 976, 942, 911, 751, 726, 705, 689 cm^{-1}. HRMS (ESI) Calcd. for $C_{17}H_{19}N_6O_2$ (M^++H) requires: 339.1564. Found: 339.1564.

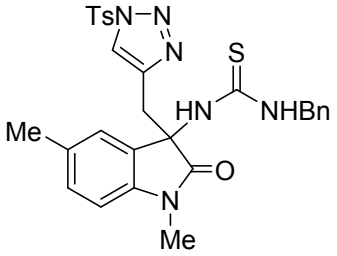




Verification experiments and related spectroscopic data

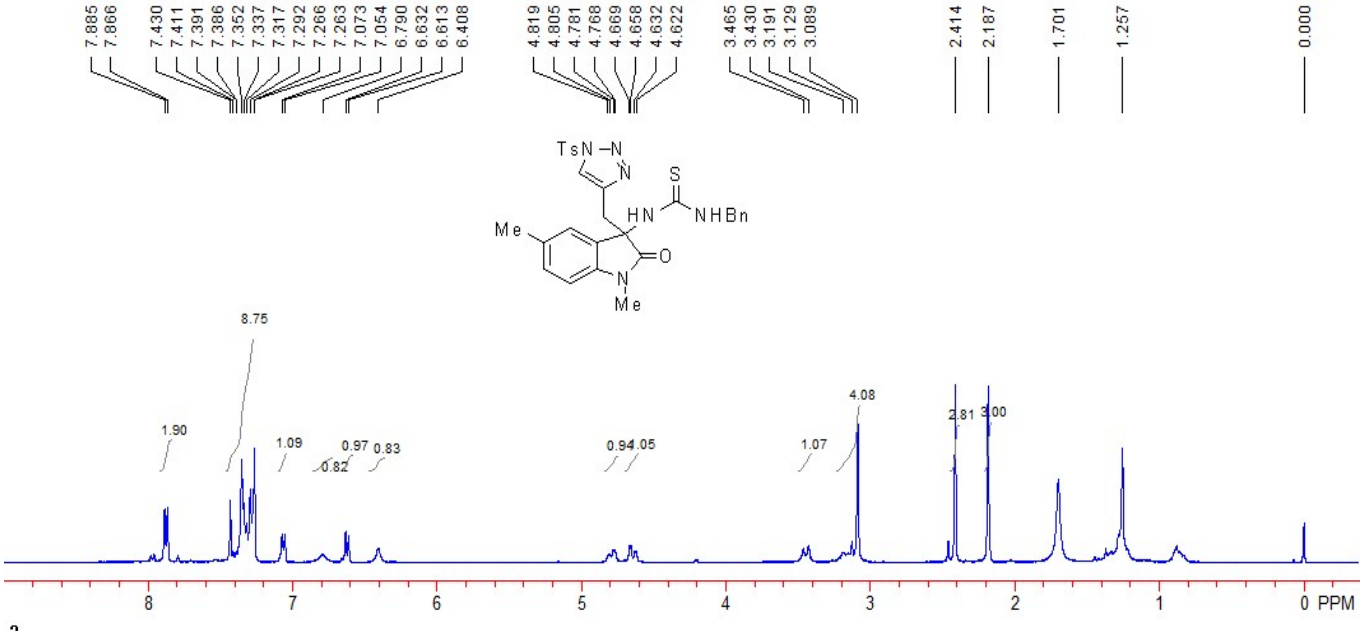


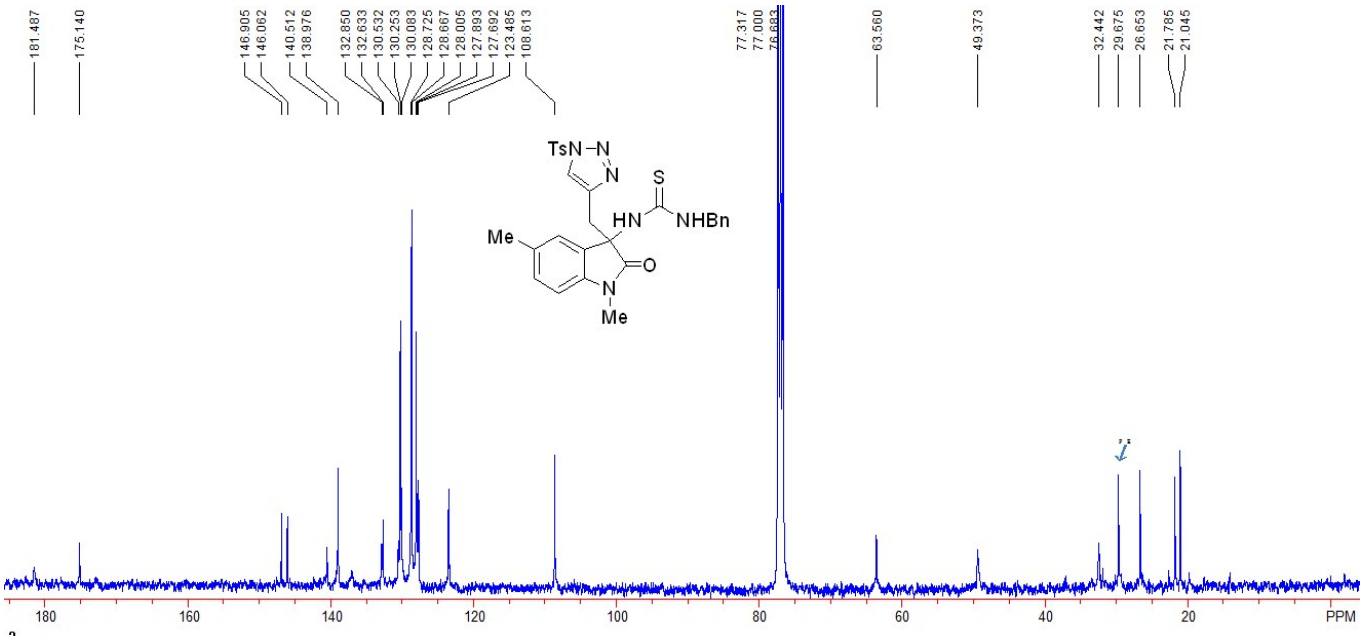
A flame-vacuum dried sealed tube with a magnetic stir bar was charged with **1f** (0.1 mmol, 1.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), and acetonitrile (1.0 mL) under Ar atmosphere. The mixture was stirred at room temperature for 12h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel to provide **s1**. Then, the **s1** (0.43 mmol, 1.0 equiv.) together with K_2CO_3 (0.43 mmol, 1.0 equiv.) and acetonitrile (0.5 mL) were added into a flame-vacuum dried sealed tube equipped with a magnetic stir bar under Ar atmosphere. The mixture then was stirred in a pre-heated 120 ^oC oil bath for 12h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to provide15 mg **3fa** (total yield: 40%).

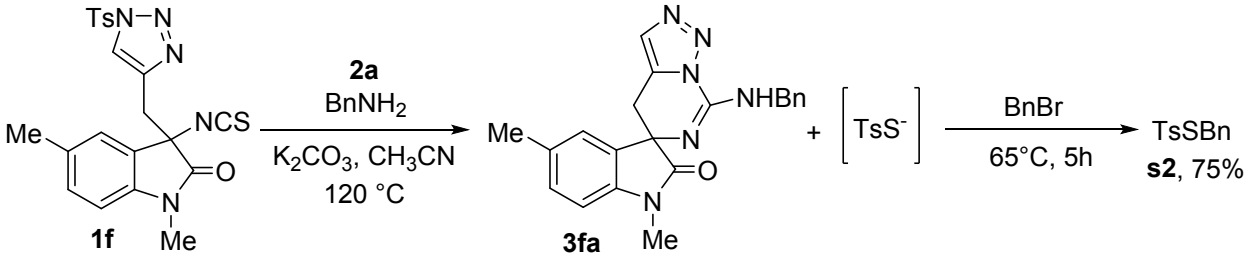


Compound **s1**: A light yellow solid (24 mg, 43%); M.p. 103-105 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.19 (s, 3H), 2.41 (s, 3H), 3.09-3.19 (m, 4H), 3.45 (d, J = 14.0 Hz, 1H), 4.65 (dd, J_1 = 14.6 Hz, J_2 = 4.0 Hz, 1H), 4.79 (dd, J_1 = 14.6 Hz, J_2 = 5.2 Hz, 1H), 6.41 (s, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.27-7.43 (m, 9H), 7.87-7.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 21.8, 26.7, 32.4, 49.4, 63.6, 108.6, 123.5, 127.7,127.9, 128.0, 128.67, 128.73, 130.1, 130.3, 130.5, 132.6, 132.9, 139.0, 140.5, 146.1, 146.9, 175.1, 181.5. IR (neat) ν 3650, 3004, 2926, 2848, 2831, 2362, 2101, 1691, 1635, 1598, 1485, 1480, 1450, 1380, 1319, 1290, 1261, 1224, 1196, 1168, 1150, 1124, 1039, 987, 866, 799, 770, 751, 699, 668 cm^{-1}. HRMS (ESI) Calcd. for $C_{28}H_{29}N_6O_3S_2$ (M^++H) requires: 561.1737.

Found: 561.1740.

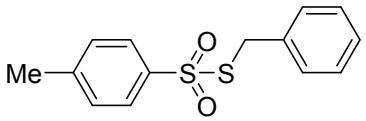




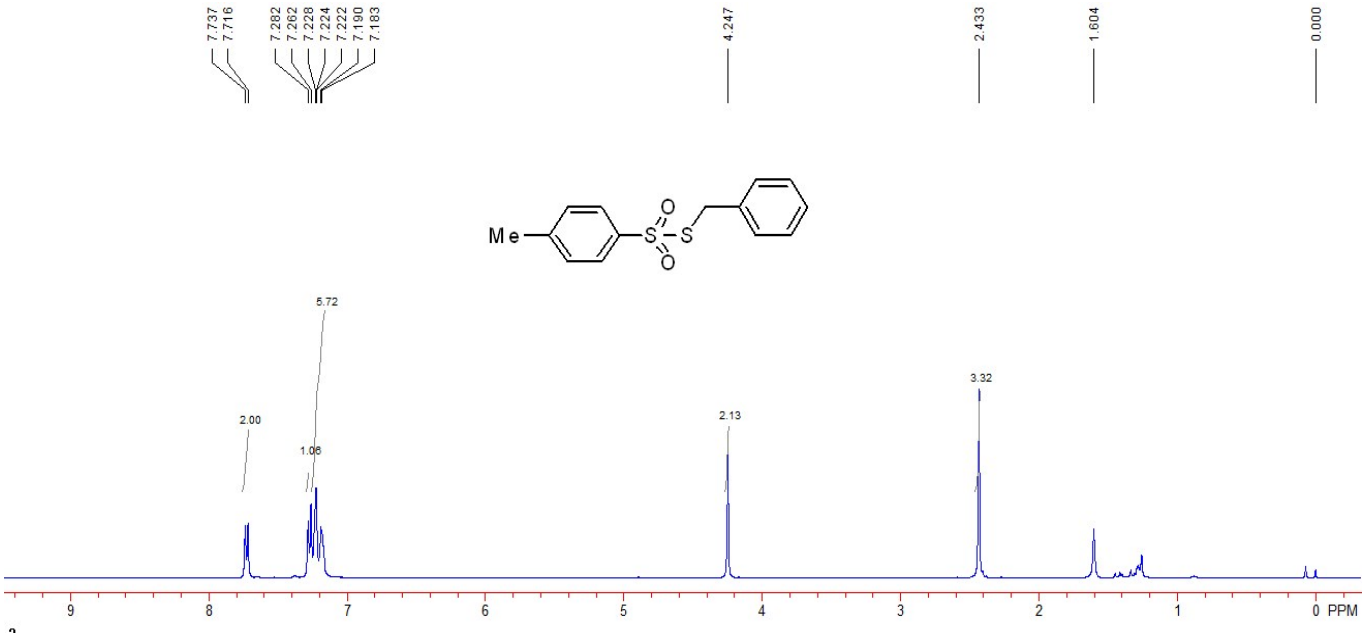


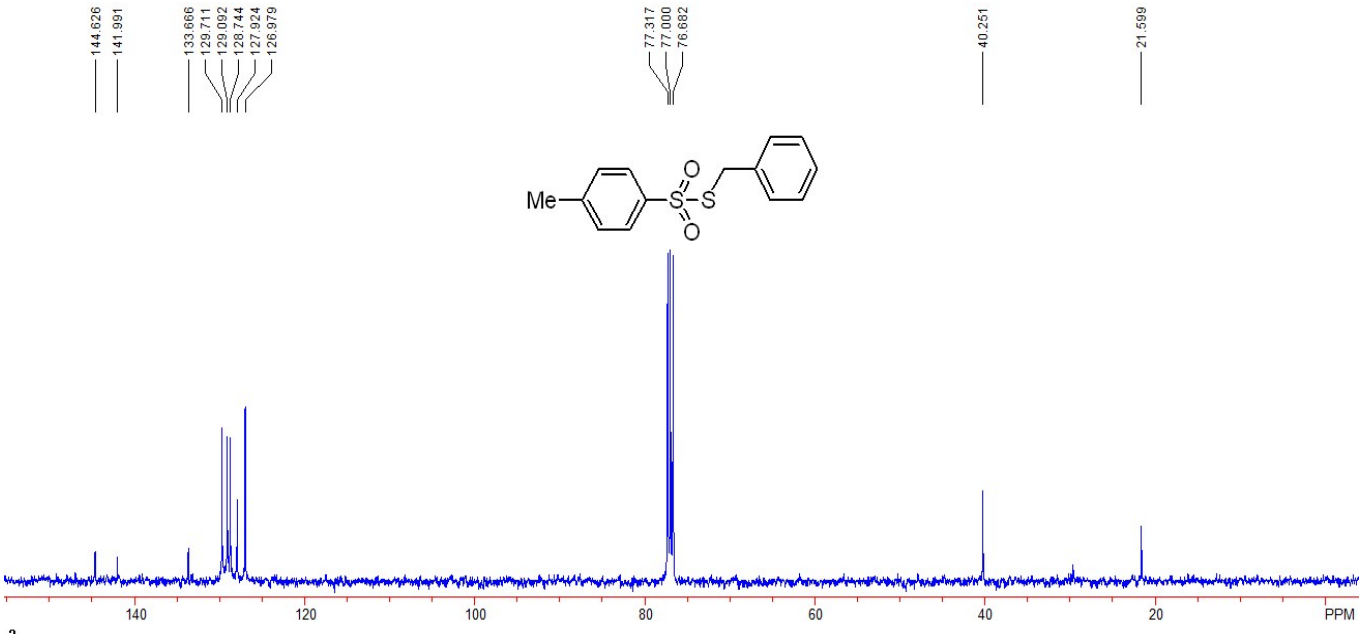
A flame-vacuum dried sealed tube with a magnetic stir bar was charged with **1f** (0.1 mmol, 1.0 equiv.),

K_2CO_3 (0.1 mmol, 1.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), and acetonitrile (1.0 mL) under Ar atmosphere. The mixture was stirred for 1 h at 80 °C in a pre-heated oil bath, and then warmed up to 120 °C. After stirring for 12h at 120 °C, the reaction mixture was cooled to 65 °C and added BnBr (0.6 mmol, 6.0 equiv.). The result mixture was stirred at 65 °C for 5h, and then cooled to ambient temperature. In the end, it was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel to provide **s2**.

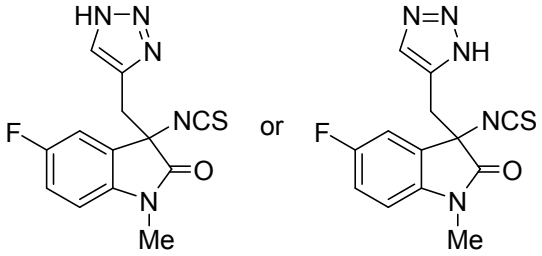


Compound **s2**: A yellow oil (21 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.43 (s, 3H), 4.25 (s, 2H), 7.18-7.23 (m, 6H), 7.28 (s, 1H), 7.72-7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.6, 40.3, 127.0, 127.9, 128.7, 129.1, 129.7, 133.7, 142.0, 144.6. HRMS (ESI) Calcd. for $C_{14}H_{18}NO_2S_2$ (M^++NH_4) requires: 296.0773. Found: 296.0775.

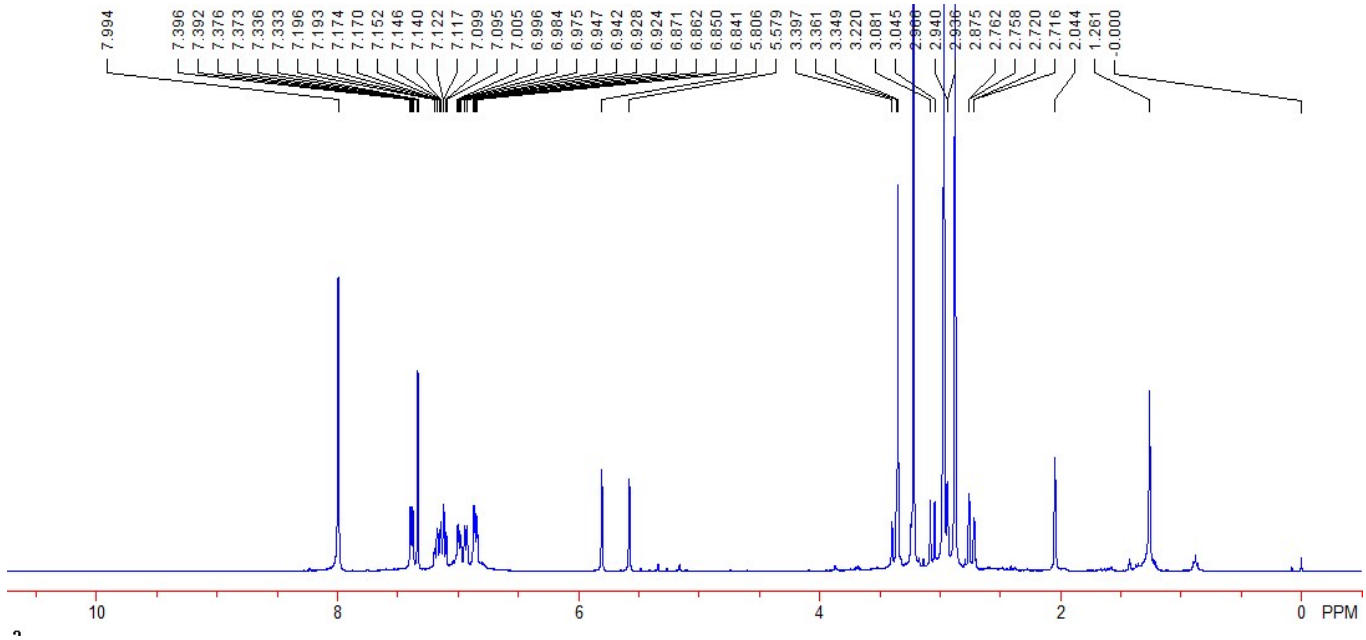


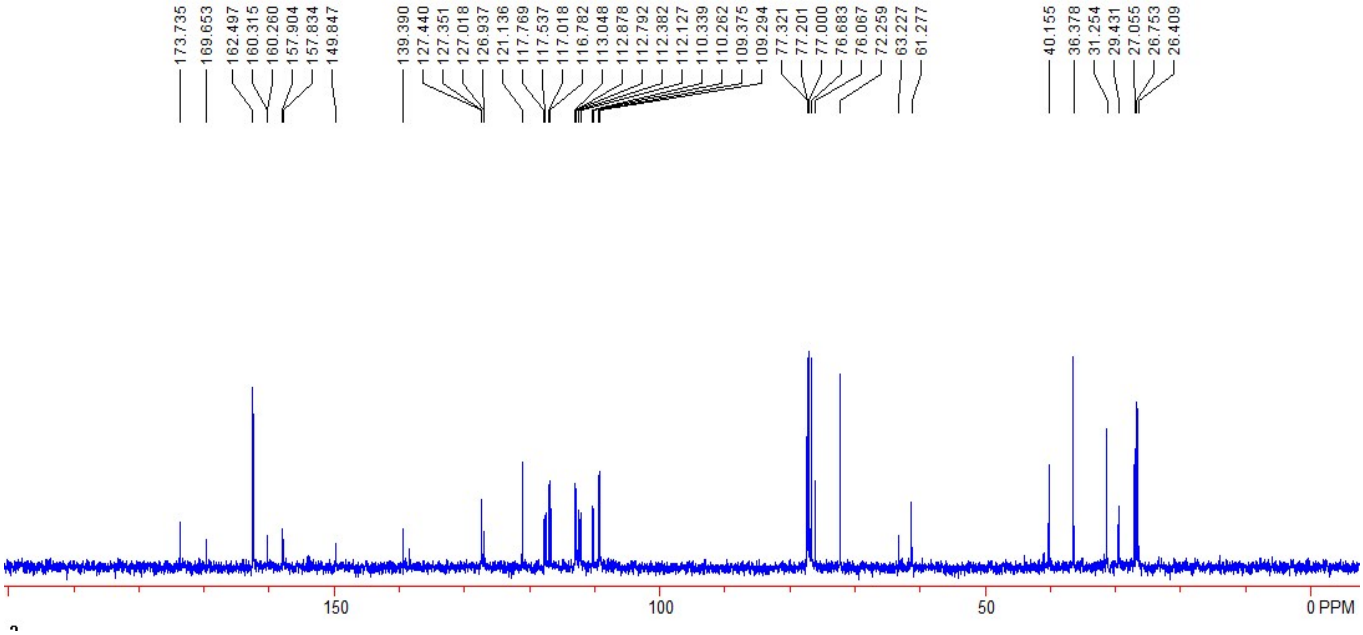


The preparation method of **1m**, see reference 6.

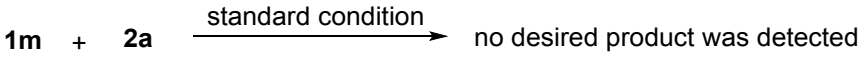


Compound **1m**: unstable, light-red oil, HRMS (ESI) Calcd. for $C_{13}H_{11}FN_5OS$ (M^++H) requires: 304.0663. Found: 304.0665.



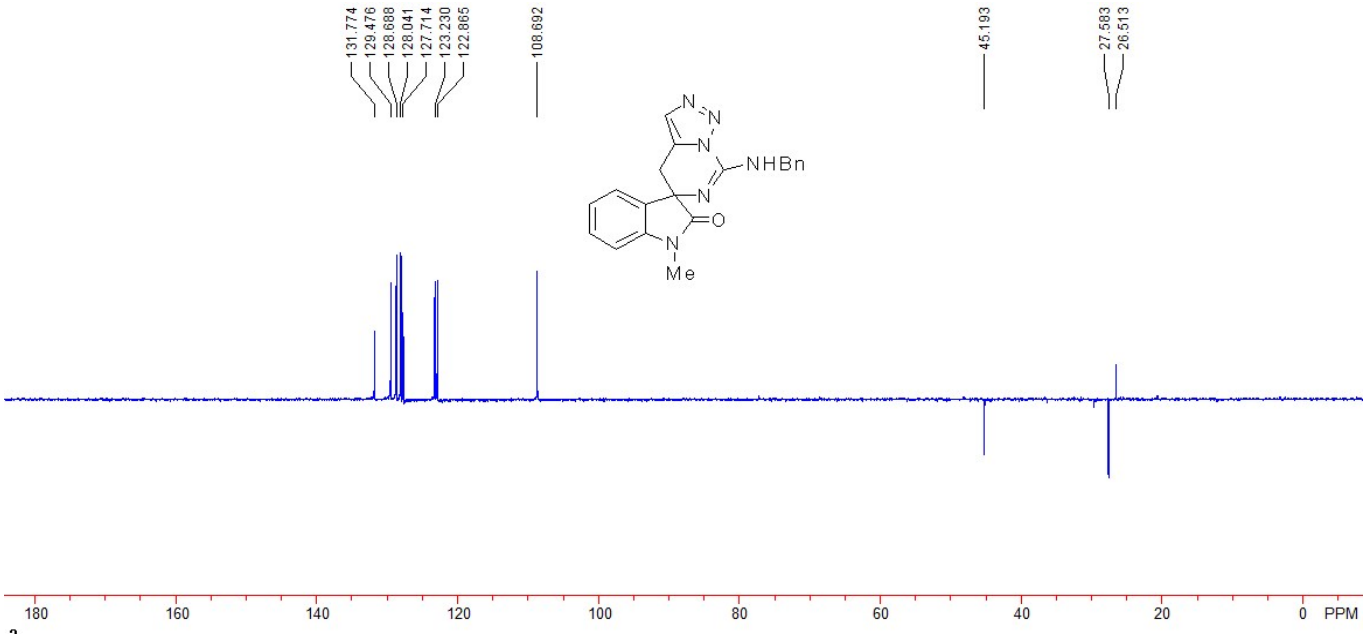


When **1m** was used to react with **2a** under the standard condition, no desired product was detected.

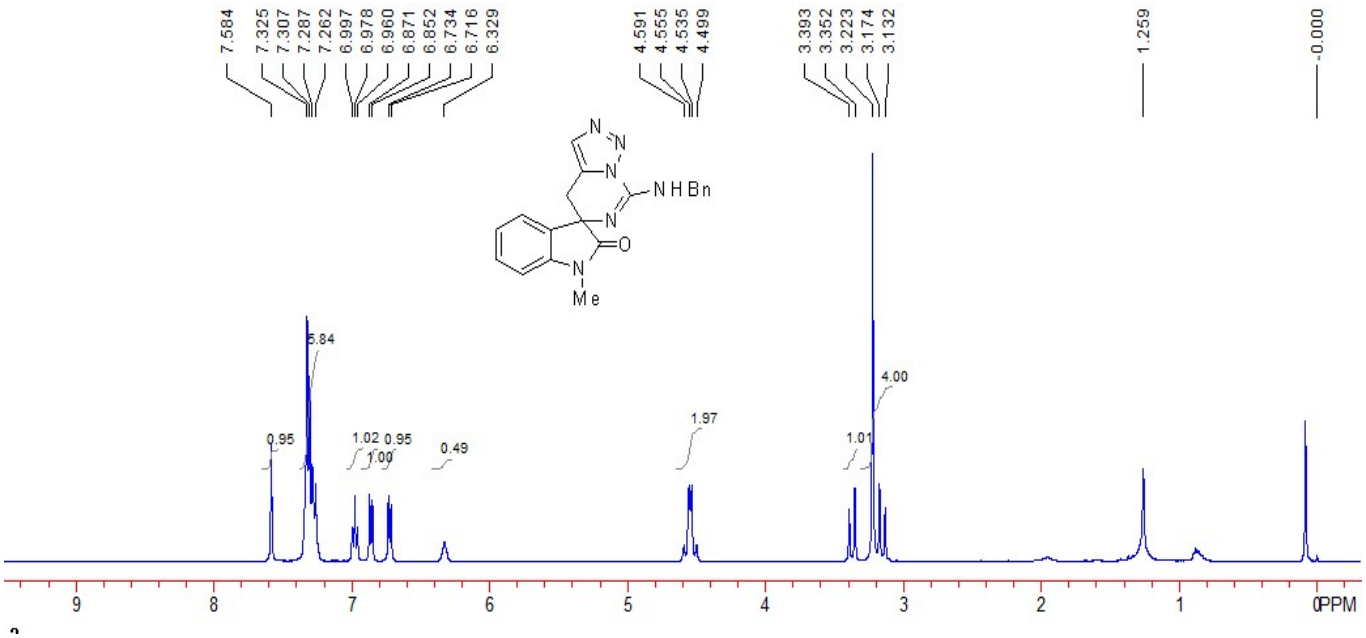


The DEPT-135 and H-D exchange spectrum of 3aa, 3ae and 3ah

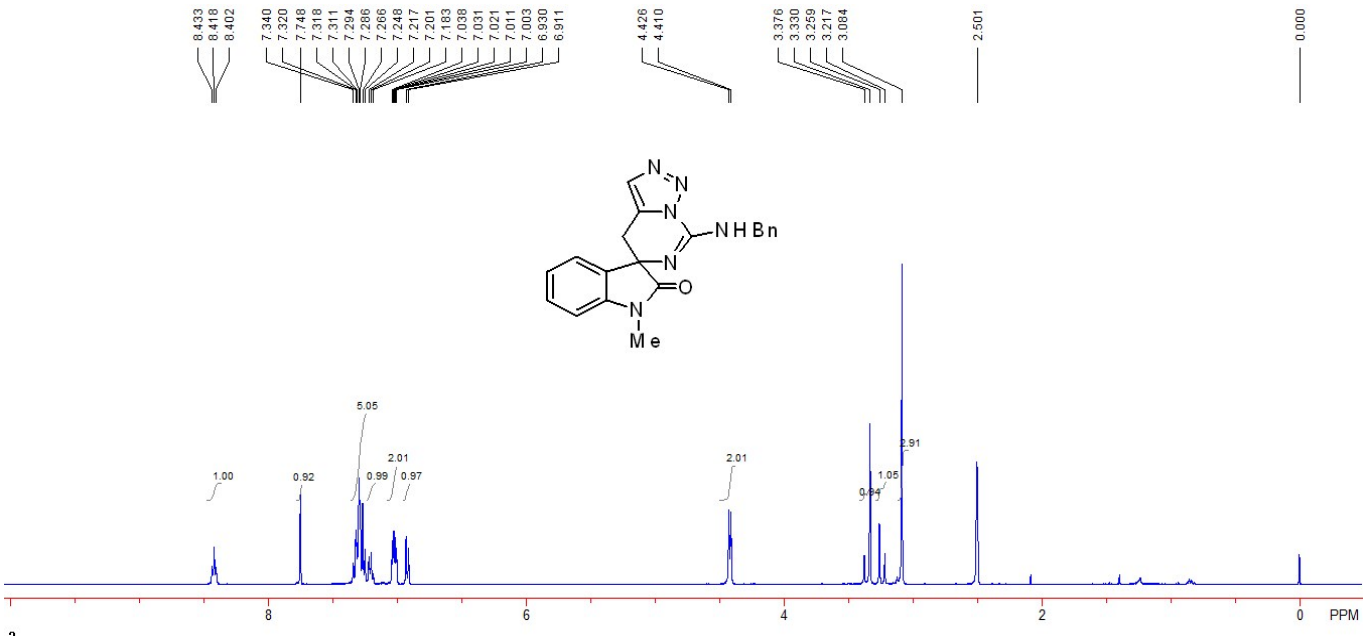
The DEPT-135 spectrum of **3aa**



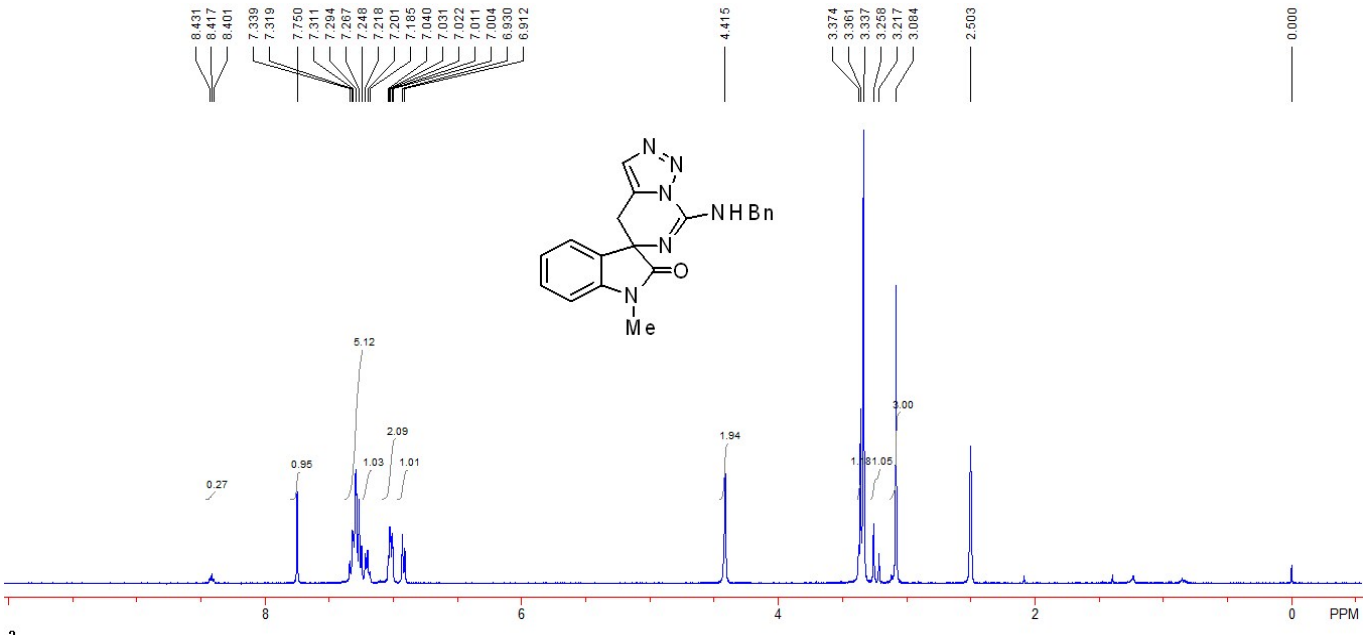
The H-D exchange spectrum of **3aa**



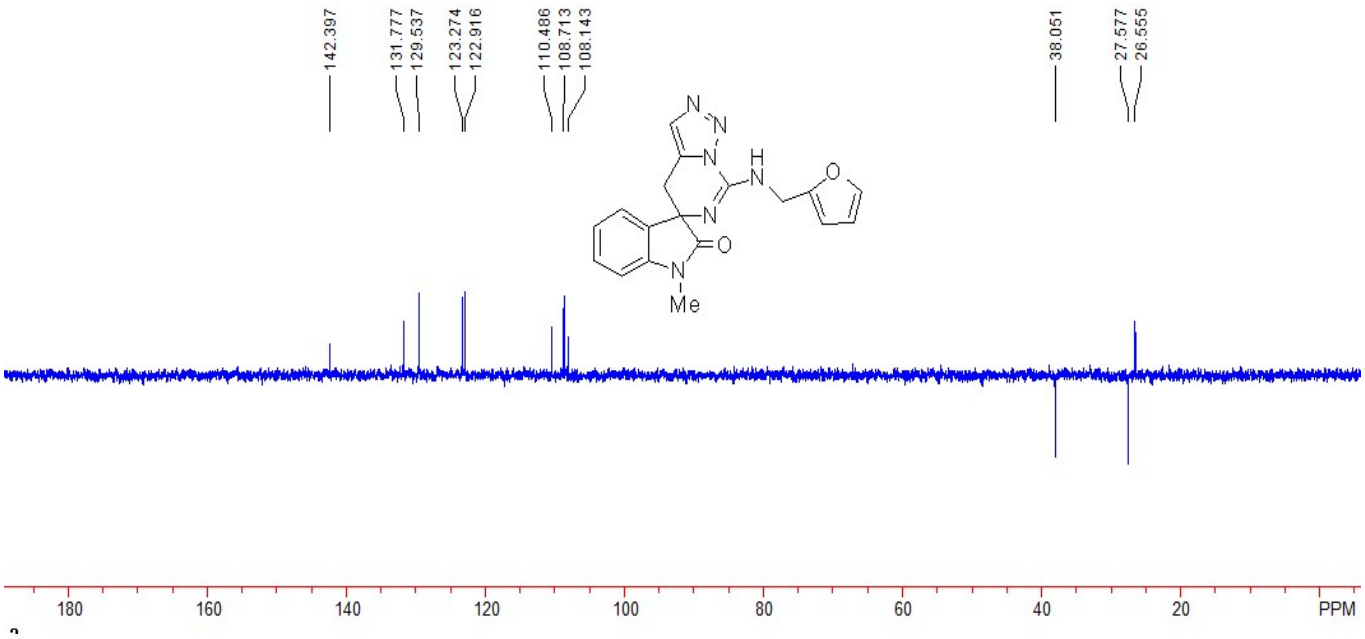
The ^{1}H-NMR spectrum (DMSO-d_6) of **3aa**



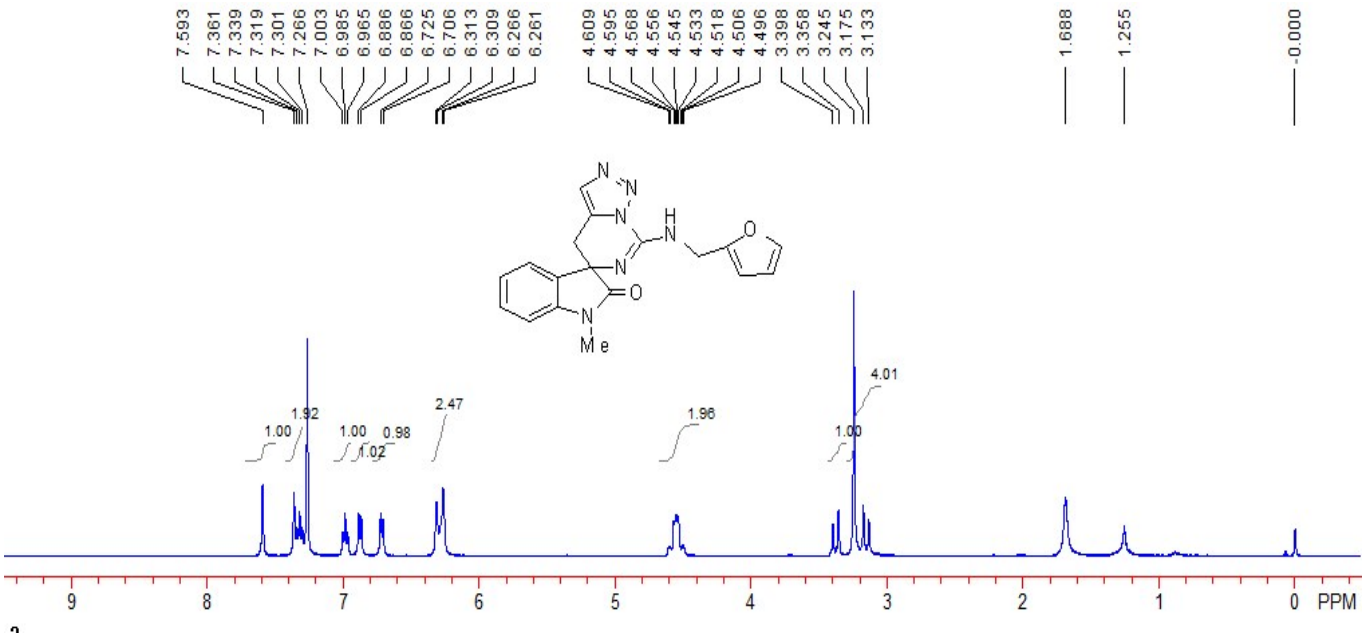
The H-D exchange spectrum (DMSO-d_6) of **3aa**



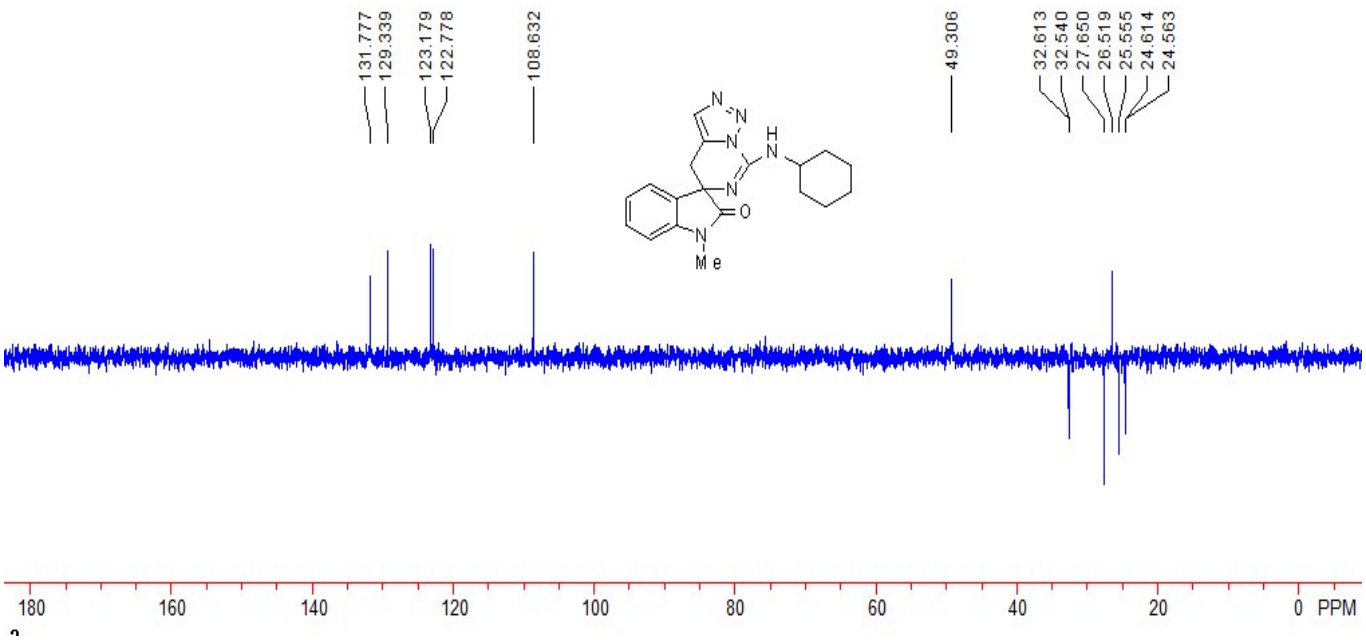
The DEPT-135 spectrum of **3ae**



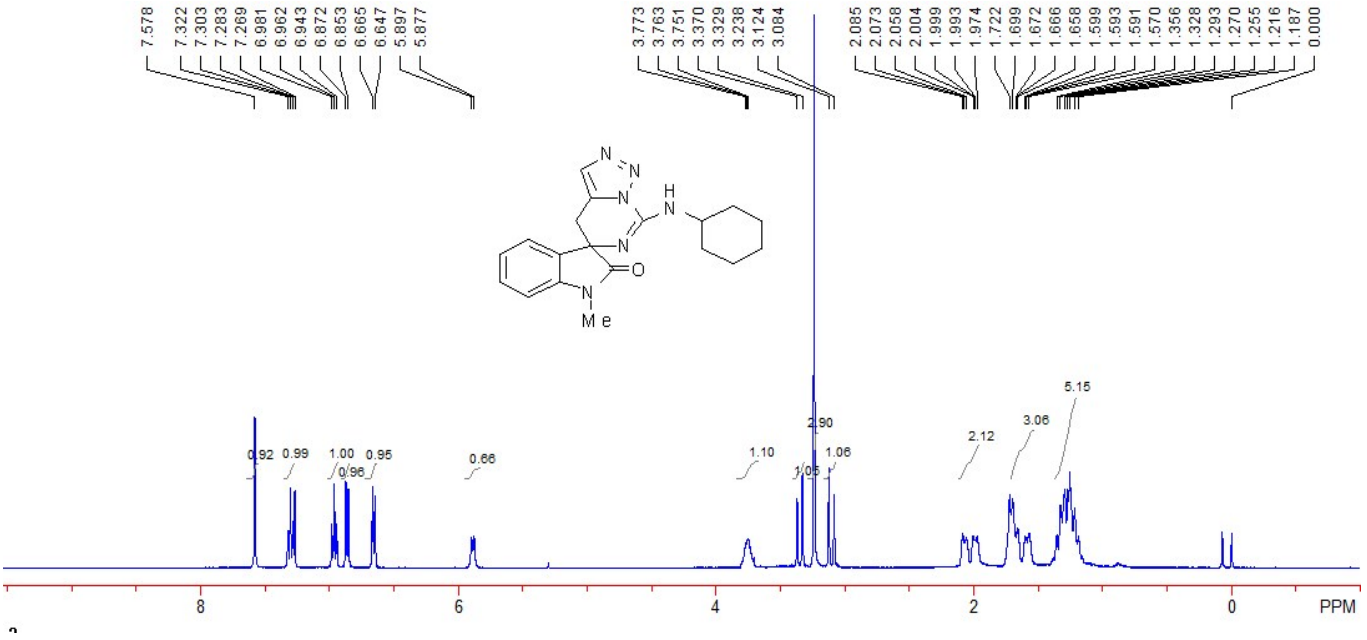
The H-D exchange spectrum of **3ae**



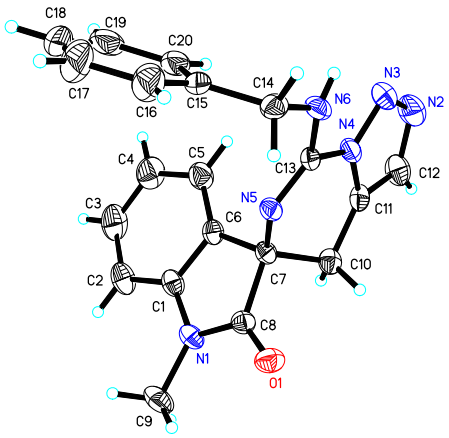
The DEPT-135 spectrum of **3ah**



The H-D exchange spectrum of **3ah**



X-ray data of 3aa



The crystal data of **3aa** have been deposited in CCDC with number 949993. Empirical Formula: $C_{20}H_{18}N_6O$; Formula Weight: 358.40; Crystal Color, Habit: colorless, Crystal Dimensions: 0.234 x 0.175 x 0.123 mm^3; Crystal System: Monoclinic; Lattice Parameters: a = 20.5231(17)Å, b = 9.5667(8)Å, c = 20.3255(18)Å, α = 90°, β = 115.091 (2)°, γ = 90°, V = 3461.1 (5)$Å^3$; Space group: P2(1)/c; Z = 8; D_{calc}= 1.317 g/cm^3; F_{000} = 1504; Final R indices [I>2sigma(I)] R1 = 0.0799, wR2 = 0.1656.

Reference

(1) **Step 1**, see (a) J. Vidal, S. Damestoy, L. Guy, J. C. Hannachi, A. Aubry, A. Collet, *Chem. Eur. J.* **1997**, *3*, 1691. (b) J. Vidal, L. Guy, S. Stérin, A. Collet, *J. Org. Chem.* **1993**, *58*, 4791. (c) P. Calí, M. Begtrup, *Synthesis* **2002**, 63.

(2) **Step 2**, see (a) M. Holmquist, G. Blay, J. R. Pedro, *Chem. Commun.* **2014**, *50*, 9309. (b) W. J. Yan, D. W., J. C. Feng, P. Li, D. P. Zhao, R. Wang, *Org. Lett.* **2012**, *14*, 2512.

(3) **Step 3**, see J. Leģros, F. Meyer, M. Coliboeuf, B. Crousse, D. Bonnet-Delpon, J. P. Béģué, *J. Org. Chem.* **2003**, *68*, 6444.

(4) **Step 4**, see T. Saito, Y. Sonoki, T. Otani, N. Kutsumura, *Org. Biomol. Chem.* **2014**, *12*, 8398.

(5) **Step 5**, see R. Q. Ran, S. D. Xiu, C. Y. Li, *Org. Lett.* **2014**, *16*, 6394.

(6) B. Allen, D. Robert, B. Clay, B. Daniel, G. Daniel, N. Stewart A., H. Mark R., K. Peter G., Z. H. Qui, P. Joseph E., Y. John, WO 2011/112731 A2.