Supporting Information

Synthesis of 7-Alkylidene-7,12-dihydroindolo[3,2-*d*]benzazepine-6-(5*H*)-ones (Paullones) by Sonogashira-*N*-cyclization-Oxidative Heck Cascade and Characterization as Sirtuin Modulators†

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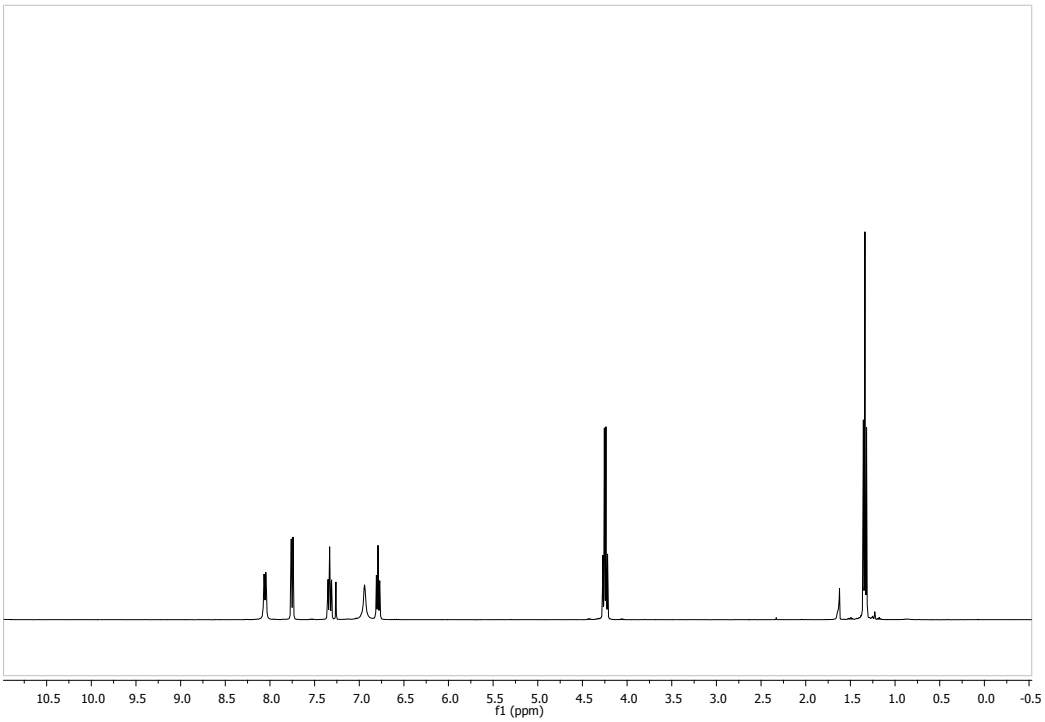
General: Solvents were dried according to published methods and distilled before use except THF, CH_2Cl_2, CH_3CN, MeOH, Et_2O and DMF which were dried using a PuresolvTM solvent purification system. All other reagents were commercial compounds of the highest purity available. Unless otherwise indicated all reactions were carried out under argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical thin layer chromatography (TLC) was performed on aluminium plates with Merck Kieselgel 60F254 and visualised by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolybdic acid. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) or SiliaFlash® P60 (230-400mesh) under pressure. Electron impact (EI) mass spectra were obtained on a Hewlett-Packard HP59970 instrument operating at 70 eV. Alternatively an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA), equipped with a 7T actively shielded magnet was used and ions were generated using an Apollo API electrospray ionization (ESI) source, with a voltage between 1800 and 2200 V (to optimize ionisation efficiency) applied to the needle, and a counter voltage of 450 V applied to the capillary. For ESI spectra samples were prepared by adding a spray solution of 70:29.9:0.1 (v/v/v) CH_3OH/water/formic acid to a solution of the sample at a v/v ratio of 1 to 5% to give the best signal-to-noise ratio. High Resolution mass spectra were taken on a VG Autospec instrument. ^1H NMR spectra were recorded in $CDCl_3$and DMSO-d_6 at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference [$CDCl_3$, δ_H = 7.26 ppm; DMSO-d_6, δ_H = 2.50 ppm]; chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons, assignment). ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at ambient temperature on the same spectrometer at 100 MHz, with the central peak of $CDCl_3$ (δ_C = 77.0 ppm) and DMSO-d_6 (δ_C = 39.52 ppm) as the internal reference. DEPT135 are used to aid in the assignment of signals in the ^{13}C NMR spectra.

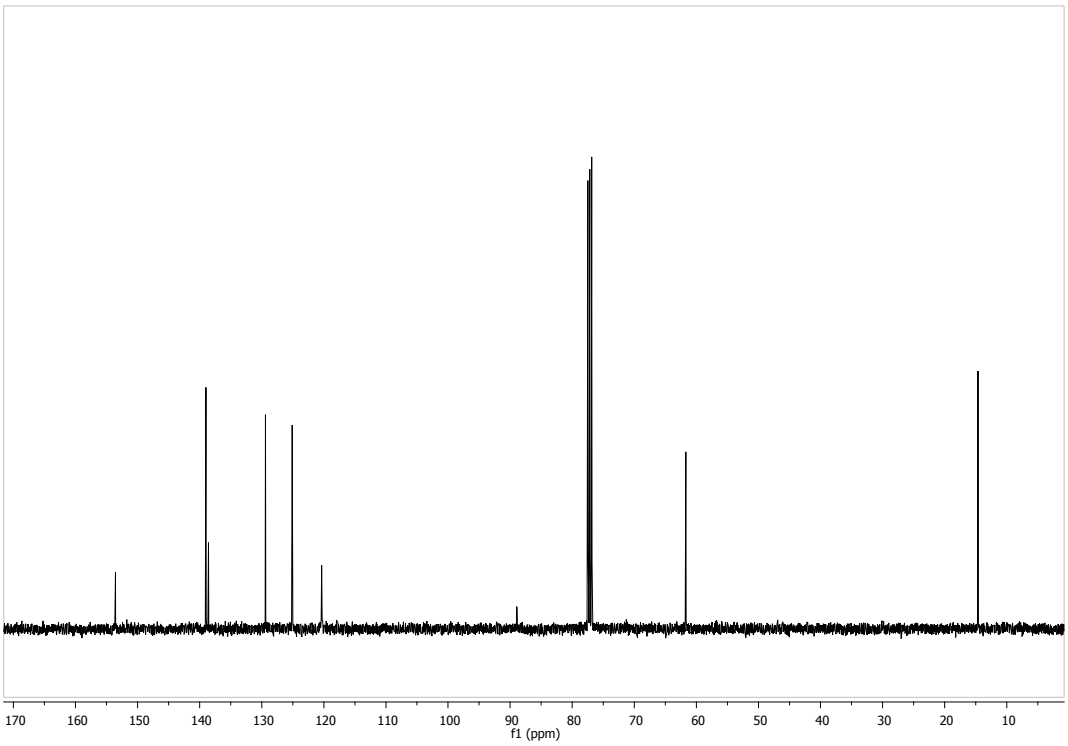
Spectroscopic data

Ethyl (2-Iodophenyl)-carbamate 6b.

^{1}H-NMR (400.16 MHz, $CDCl_3$)

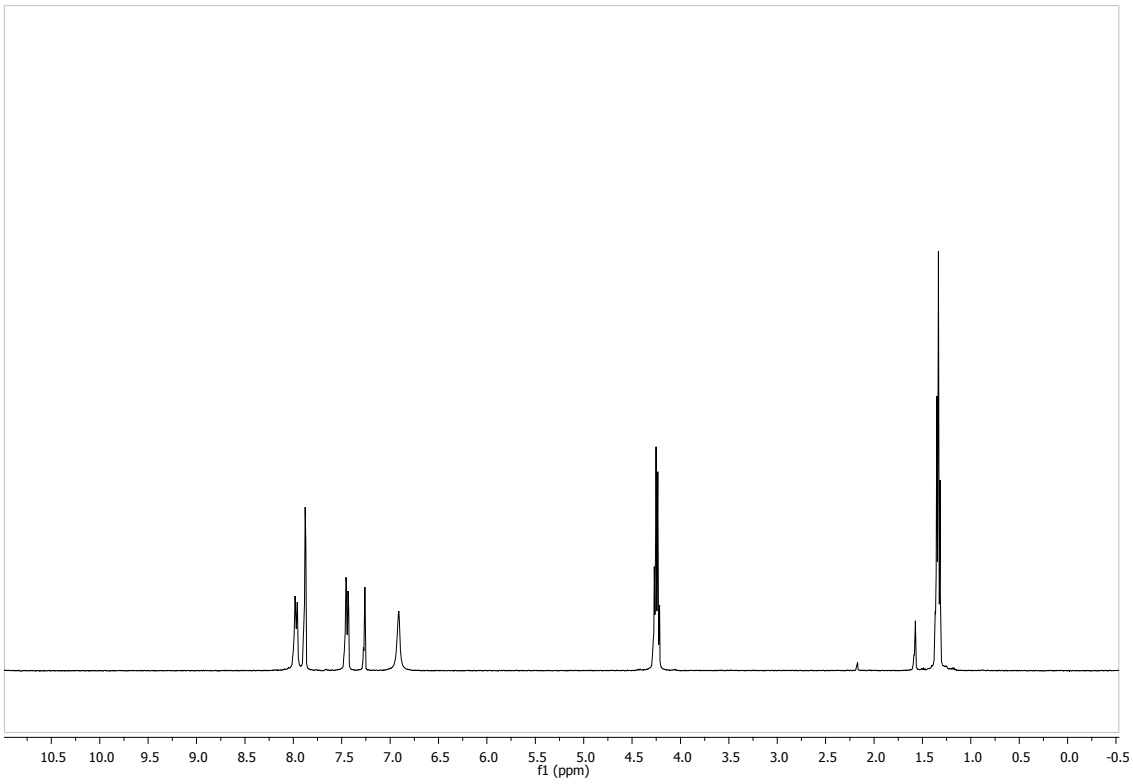


^{13}C-NMR (100.62 MHz, $CDCl_3$)

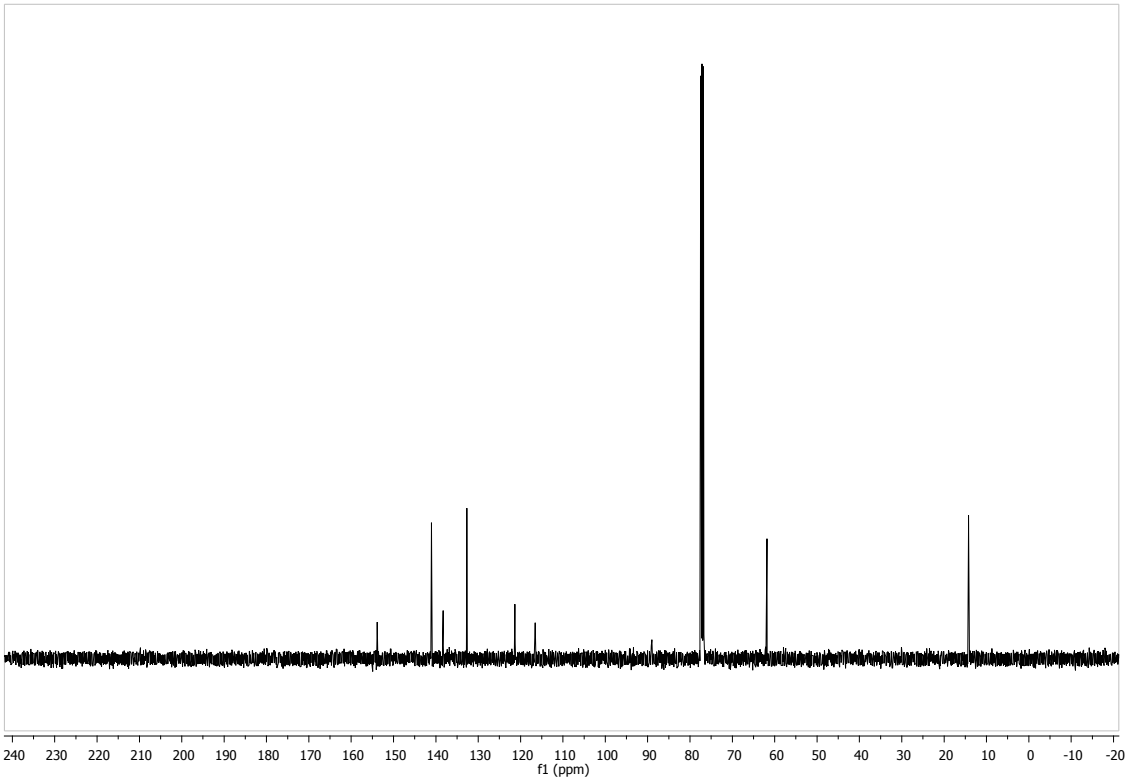


Ethyl (4-Bromo-2-iodophenyl)-formate 6d.

^{1}H-NMR (400.16 MHz, $CDCl_3$)

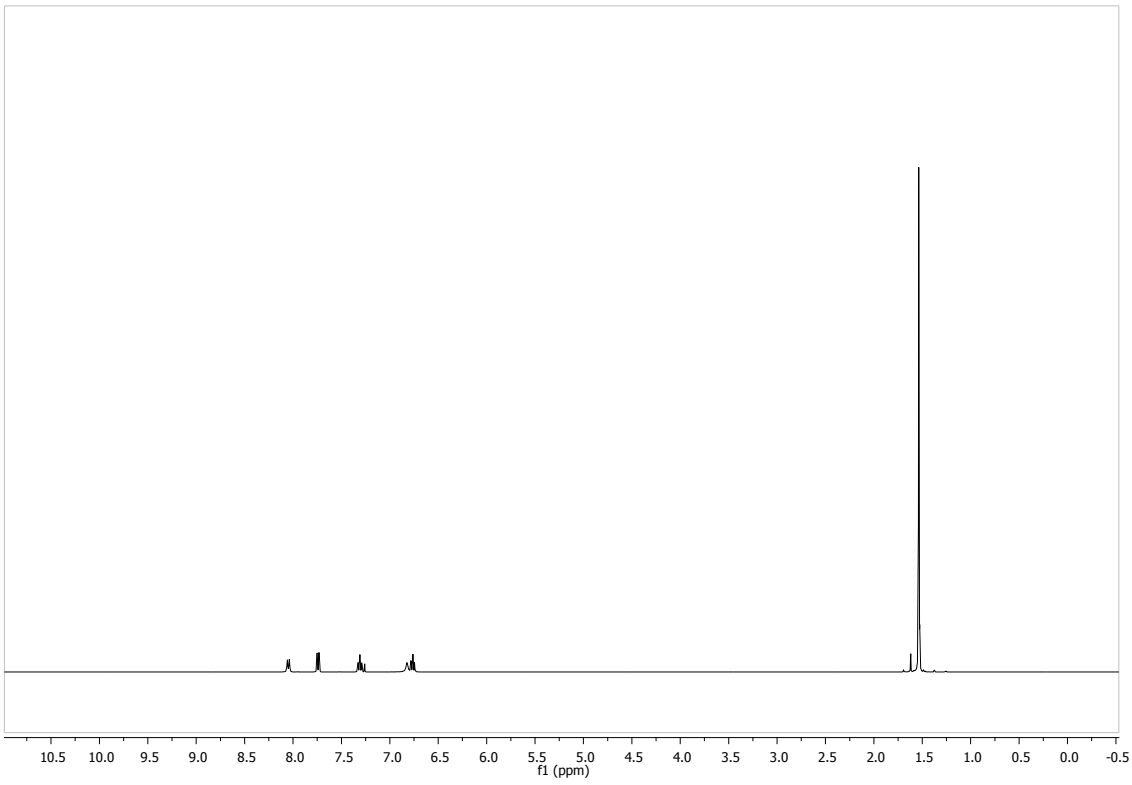


^{13}C-NMR (100.62 MHz, $CDCl_3$)

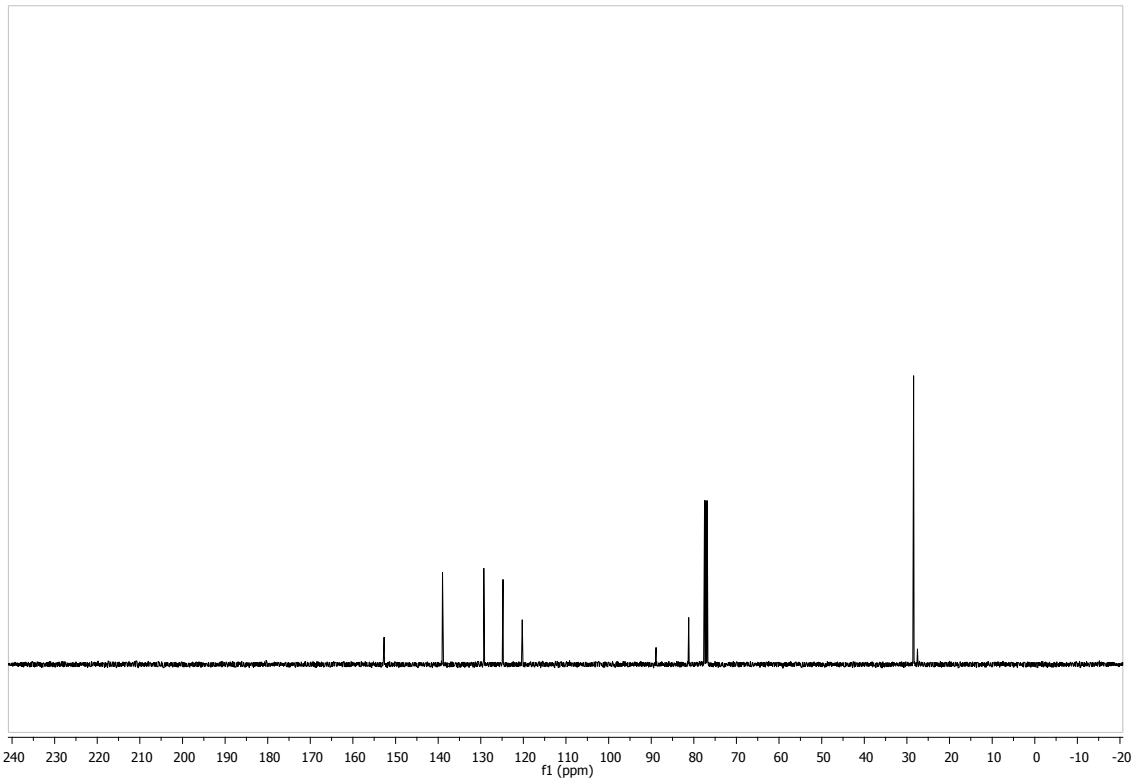


***tert*-Butyl (2-Iodophenyl)-carbamate 6e.**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

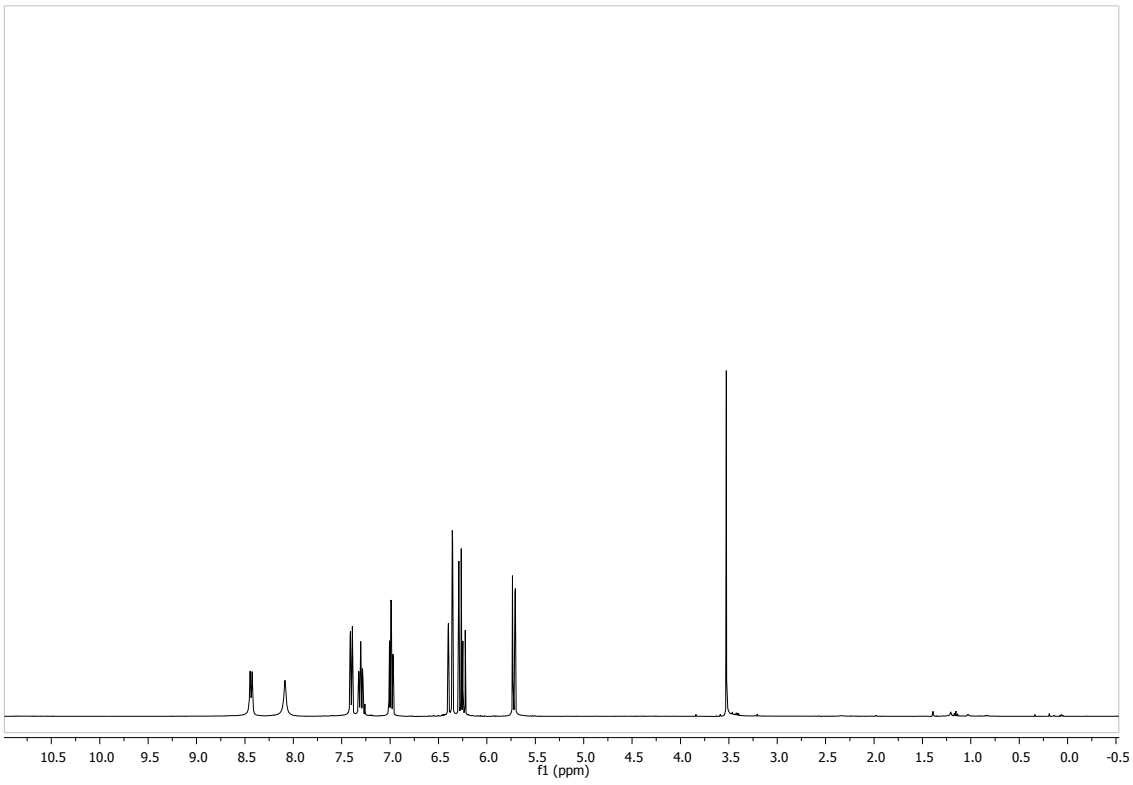


^{13}C-NMR (100.62 MHz $CDCl_3$)

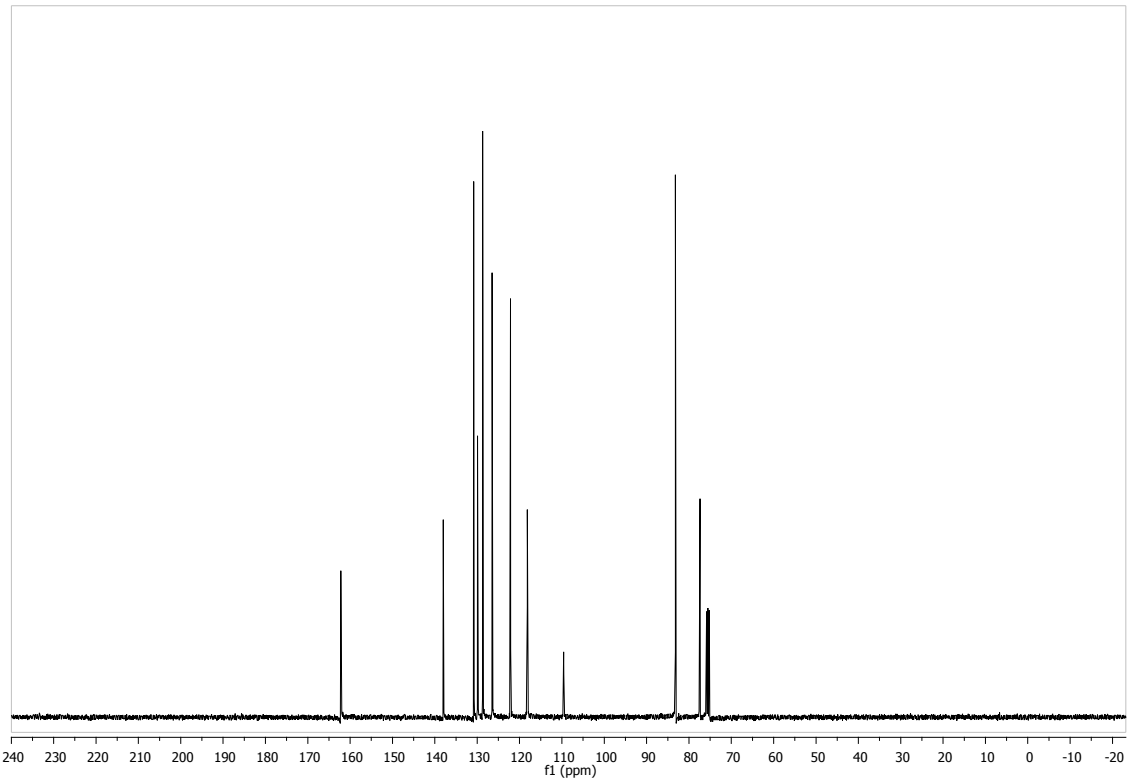


***N*-(2-Ethynylphen-1-yl)-acrylamide 7a.**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

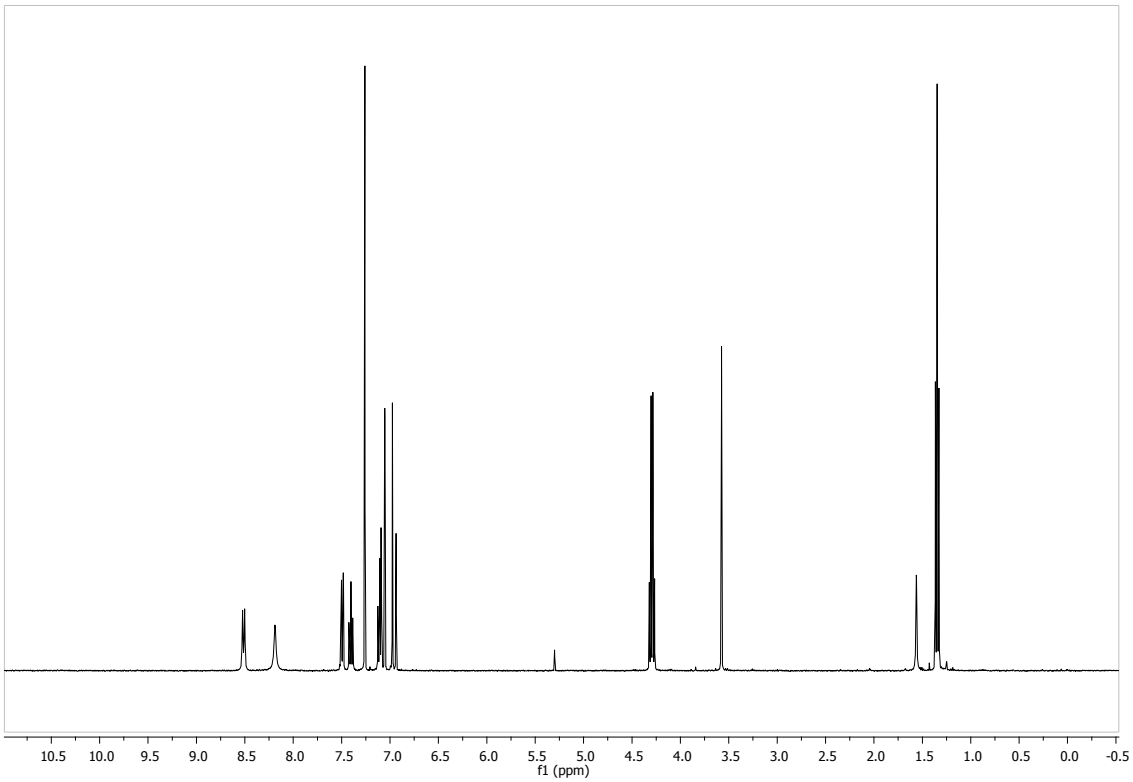


^{13}C-NMR (100.62 MHz $CDCl_3$)

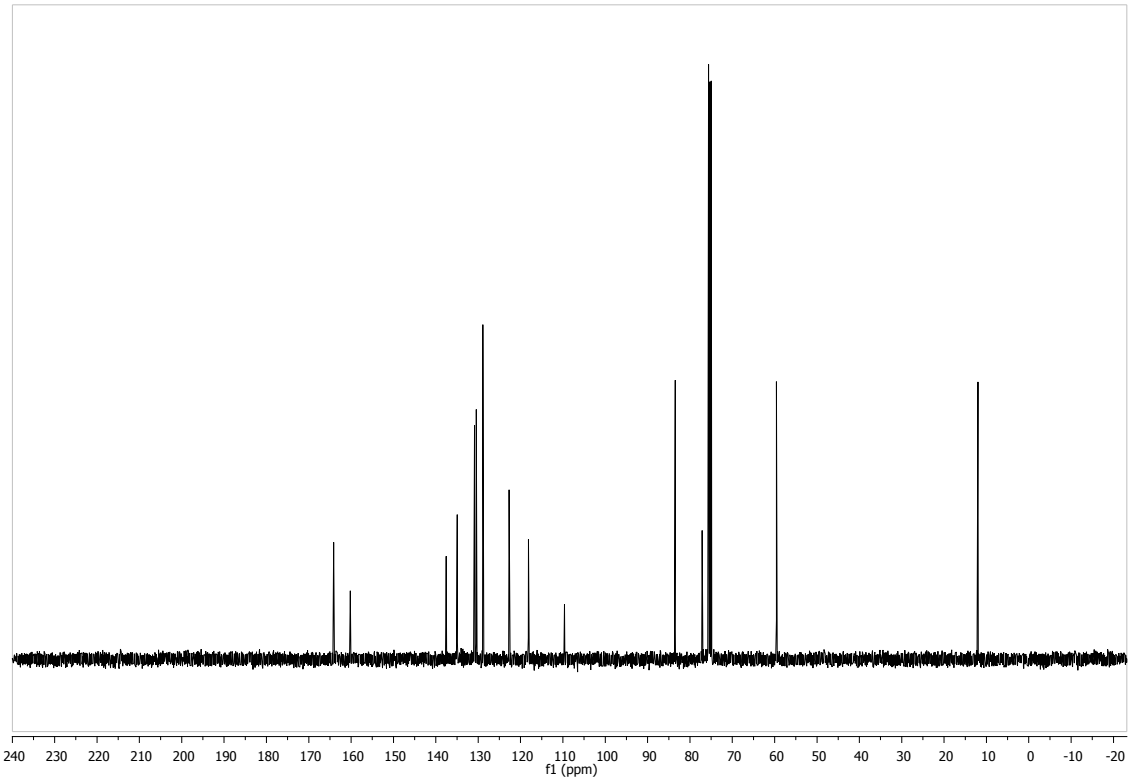


Ethyl (*E*)-4-(2-Ethynylphenylamino)-4-oxobut-2-enoate 7b.

^{1}H-NMR (400.16 MHz, $CDCl_3$)

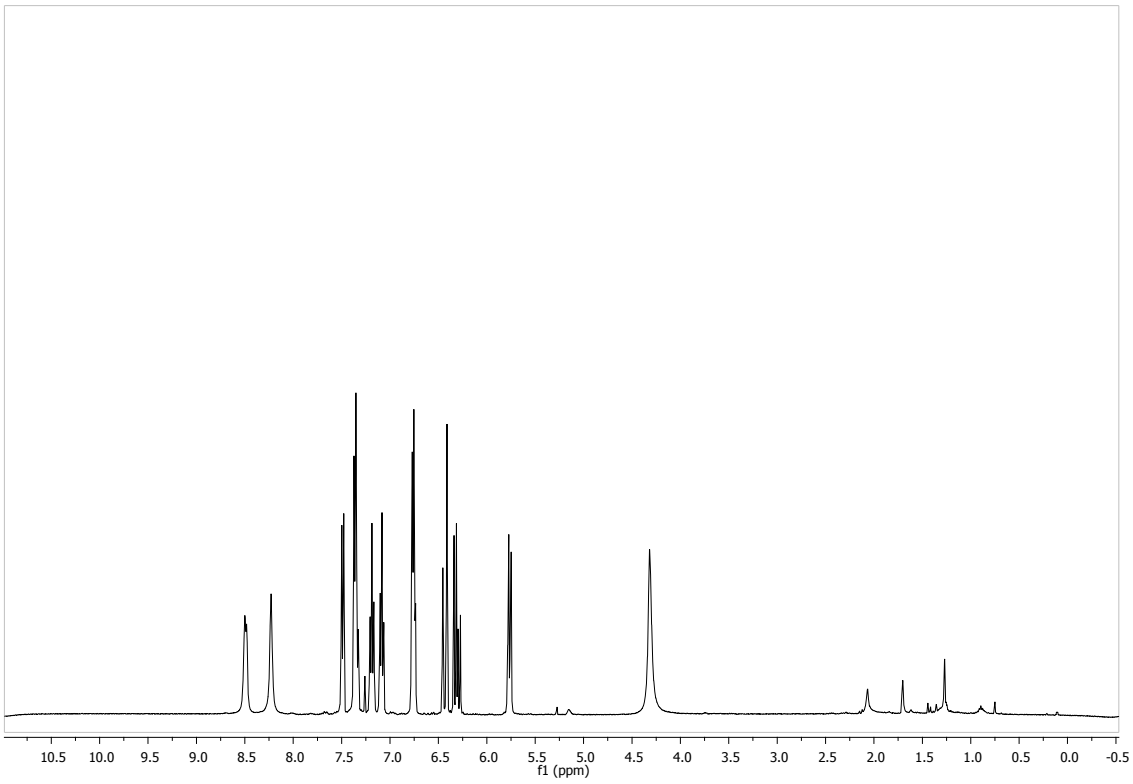


^{13}C-NMR (100.62 MHz, $CDCl_3$)

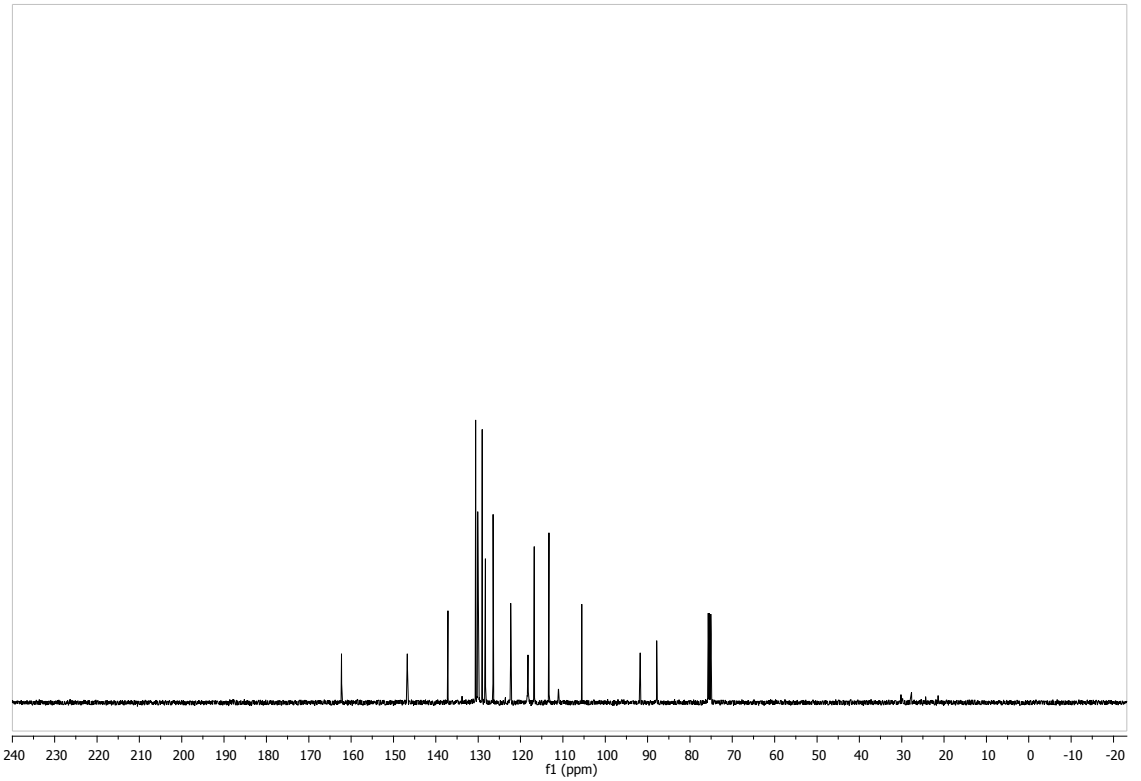


***N*-[2-(2-Aminophen-1-ylethynyl)-phen-1-yl]acrylamide 5aa.**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

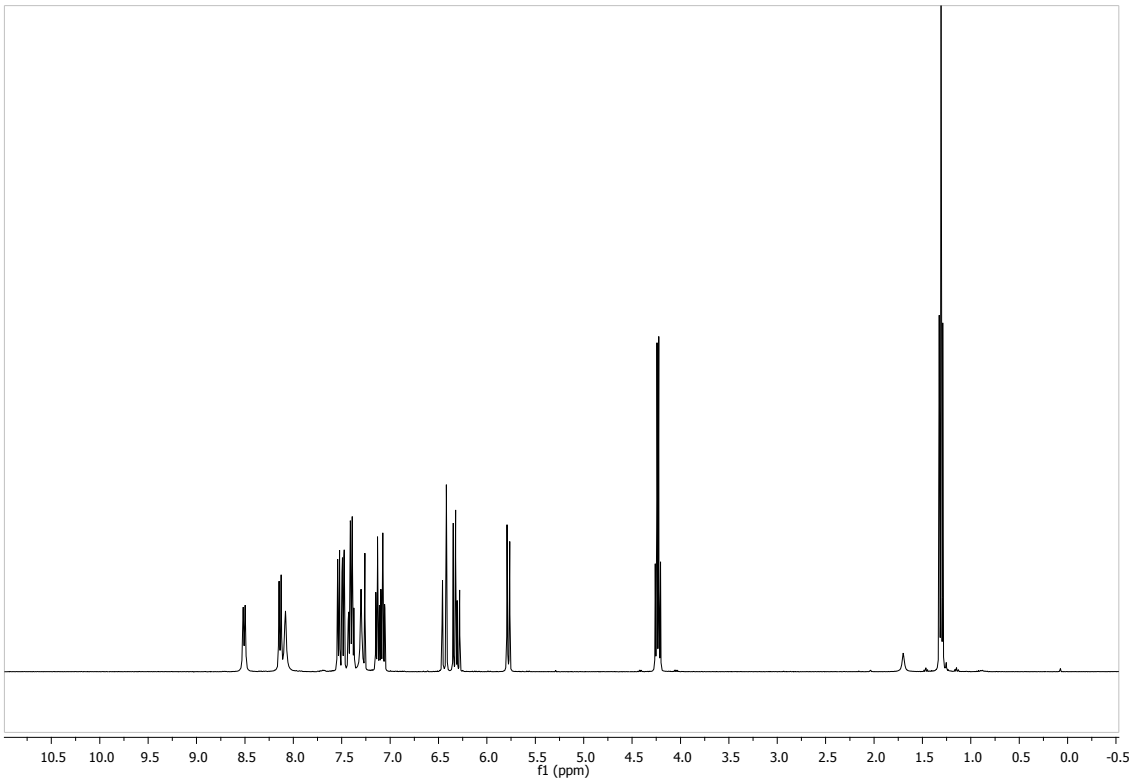


^{13}C-NMR (100.62 MHz, $CDCl_3$)

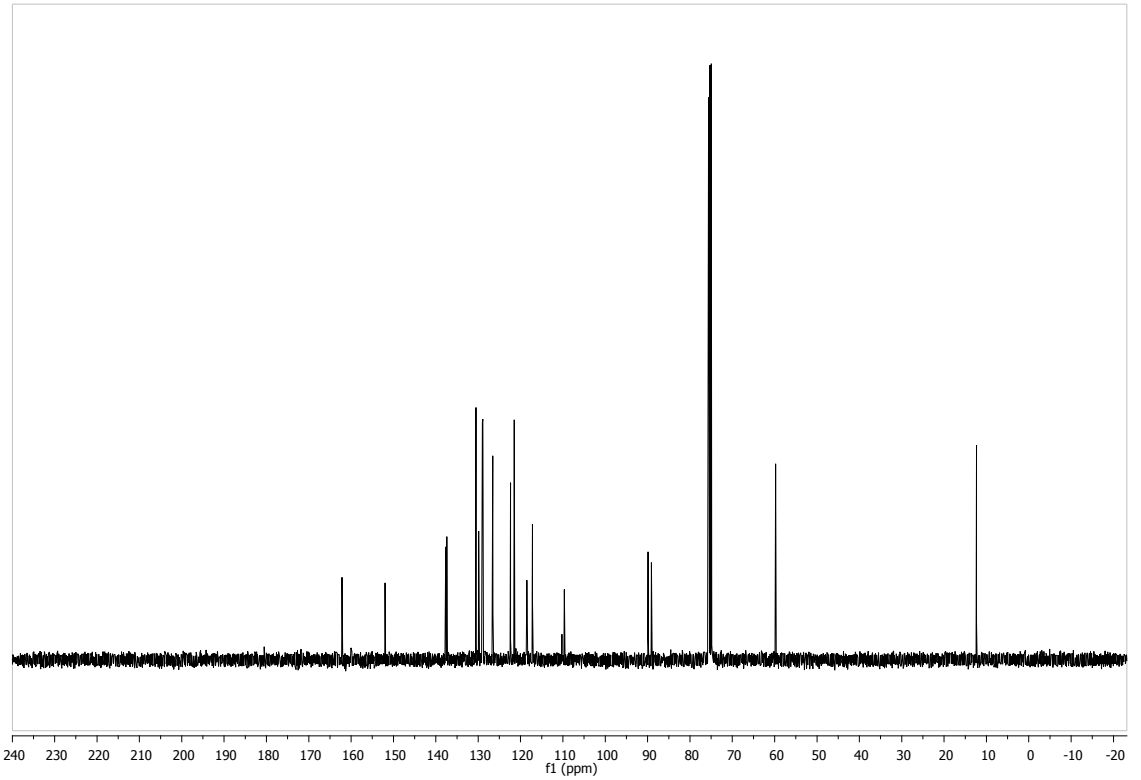


***N*-{2-[(*N*-Ethoxycarbonyl-2-aminophenyl)-ethynyl]-phenyl}-acrylamide 5ab**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

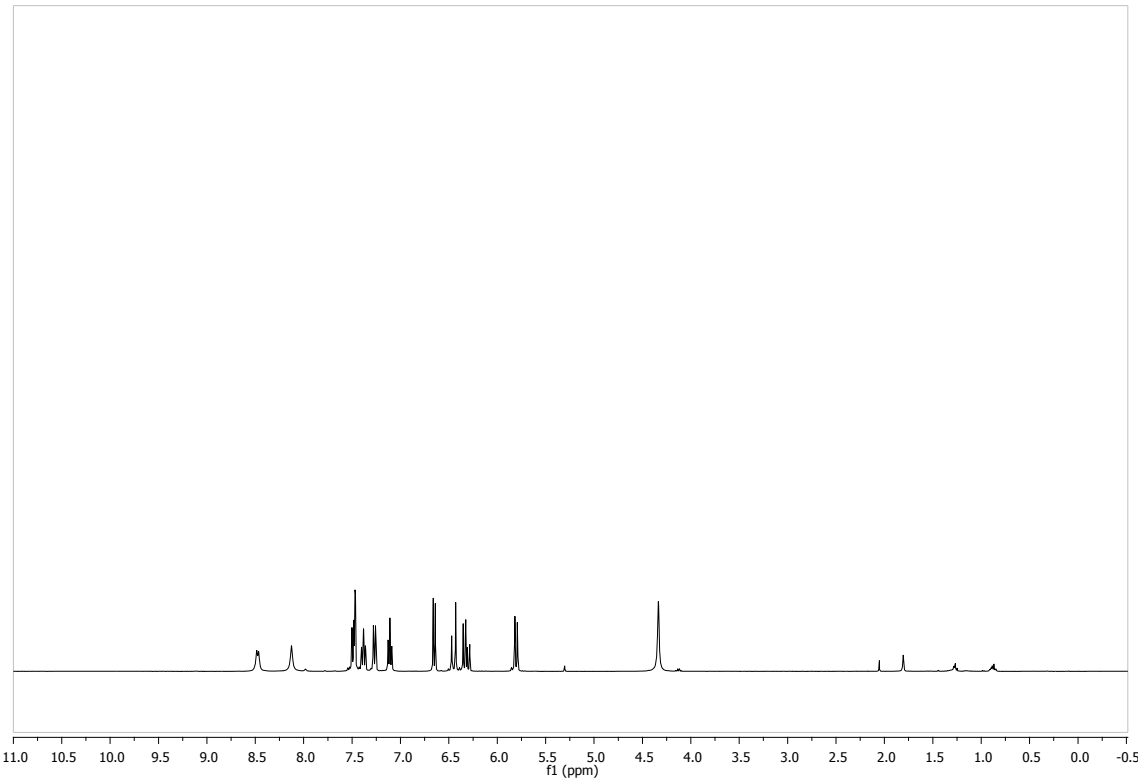


^{13}C-NMR (100.62 MHz, $CDCl_3$)

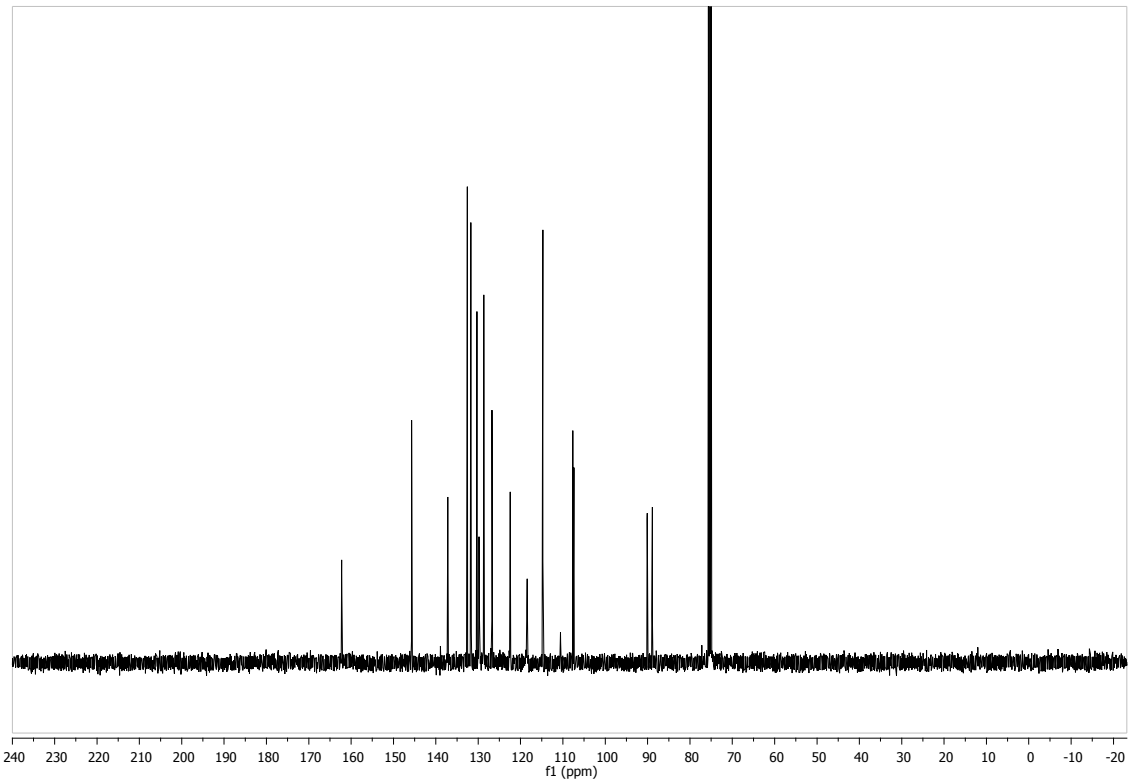


***N*-[2-((2-Amino-5-bromophenyl)-ethynyl)-phenyl]-acrylamide 5ac.**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

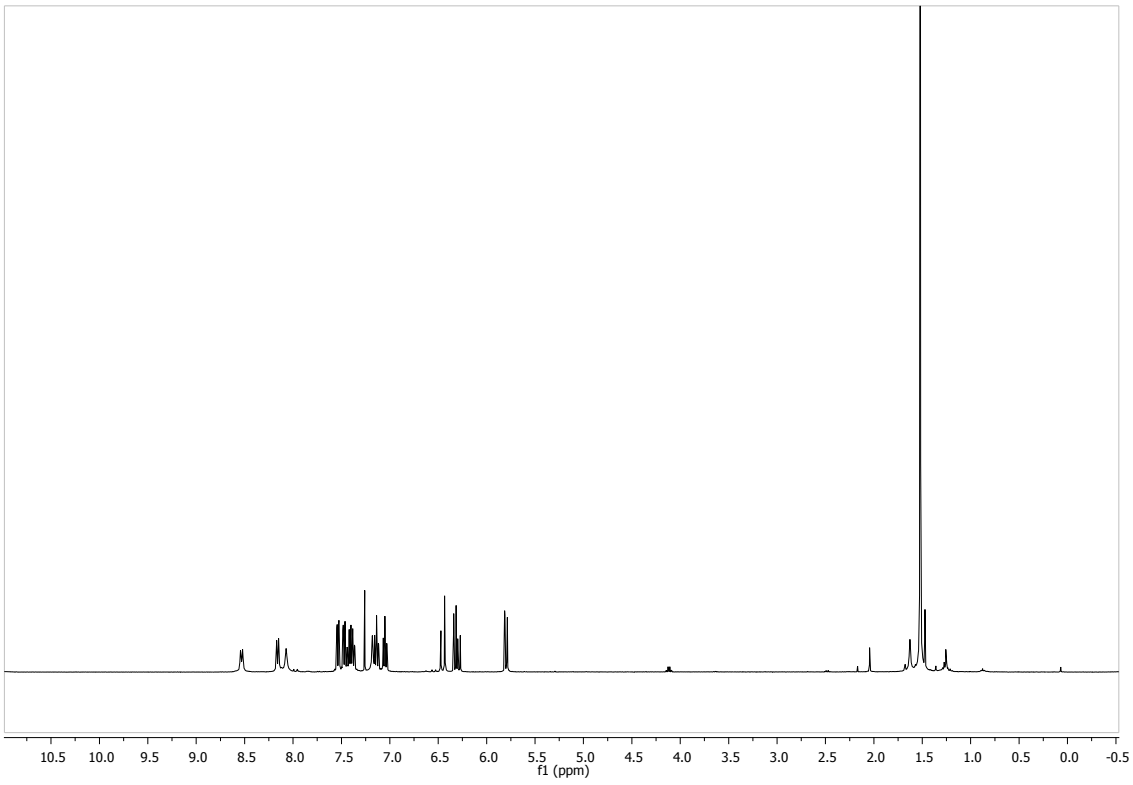


^{13}C-NMR (100.62 MHz, $CDCl_3$)

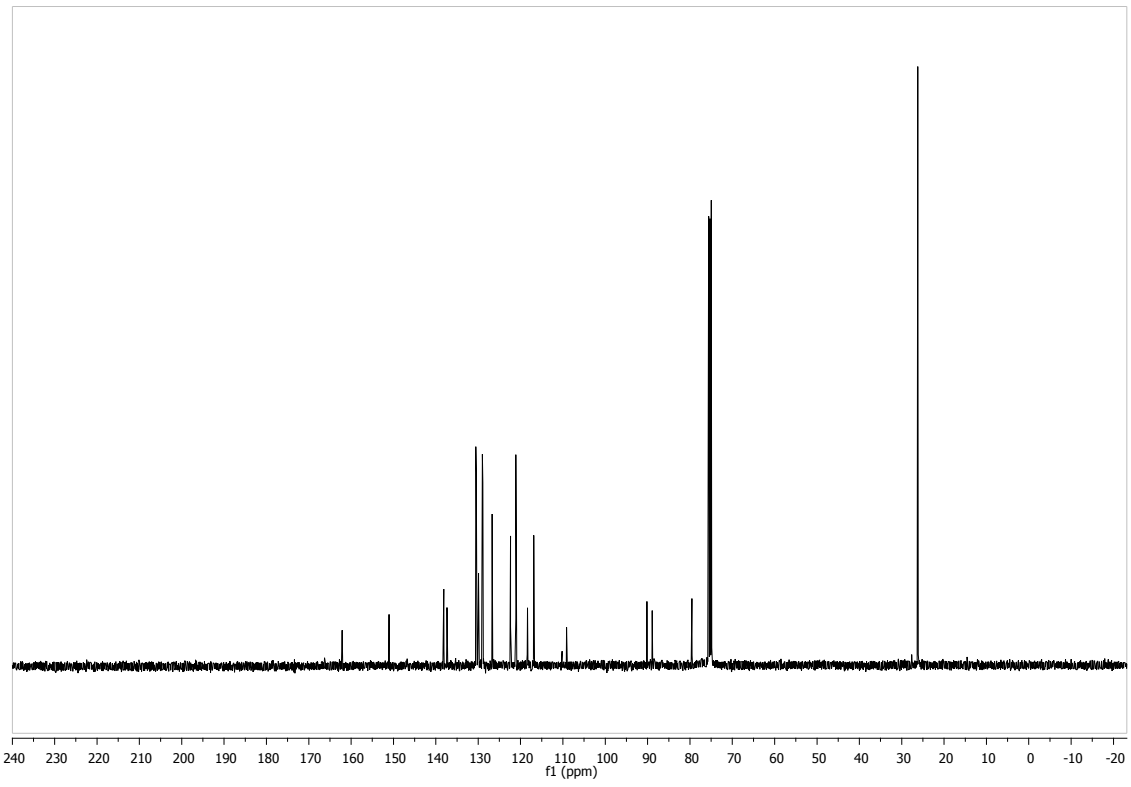


***N*-{2-[(*N*-*tert*-Butoxycarbonyl-2-aminophenyl)-ethynyl]-phenyl}-acrylamide 5ae.**

^{1}H-NMR (400 MHz, $CDCl_3$) ppm.

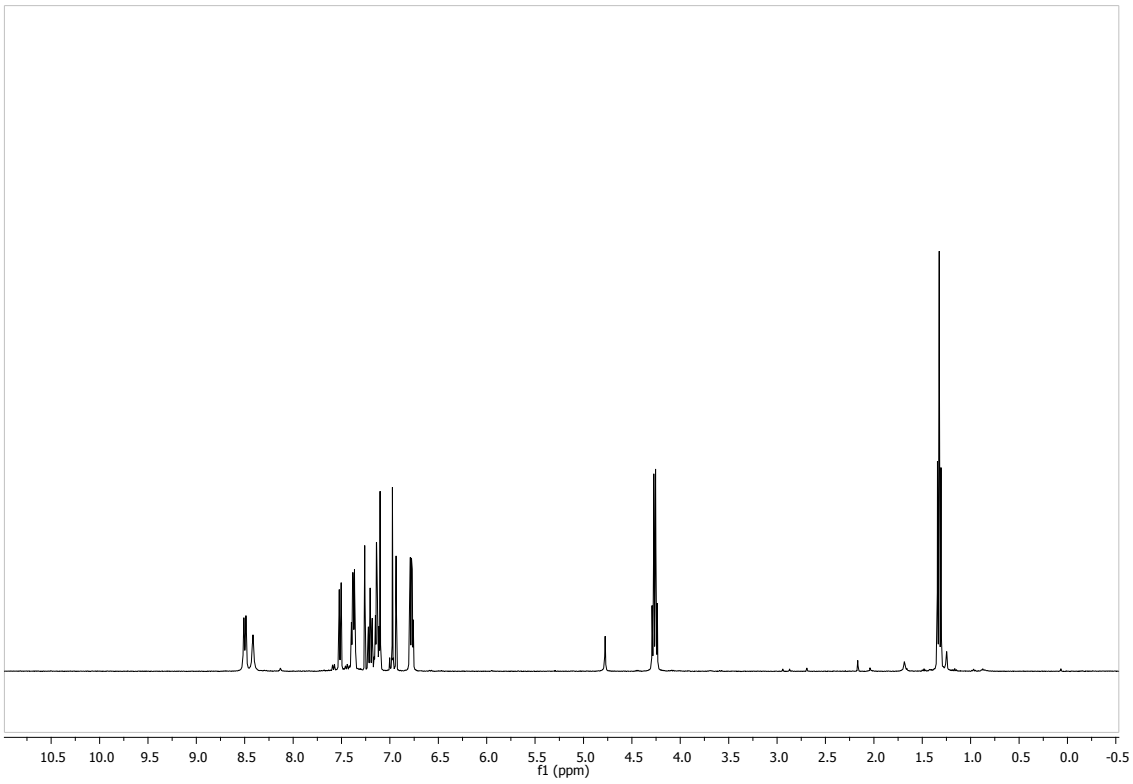


^{13}C-NMR (100.62 MHz, $CDCl_3$) ppm.

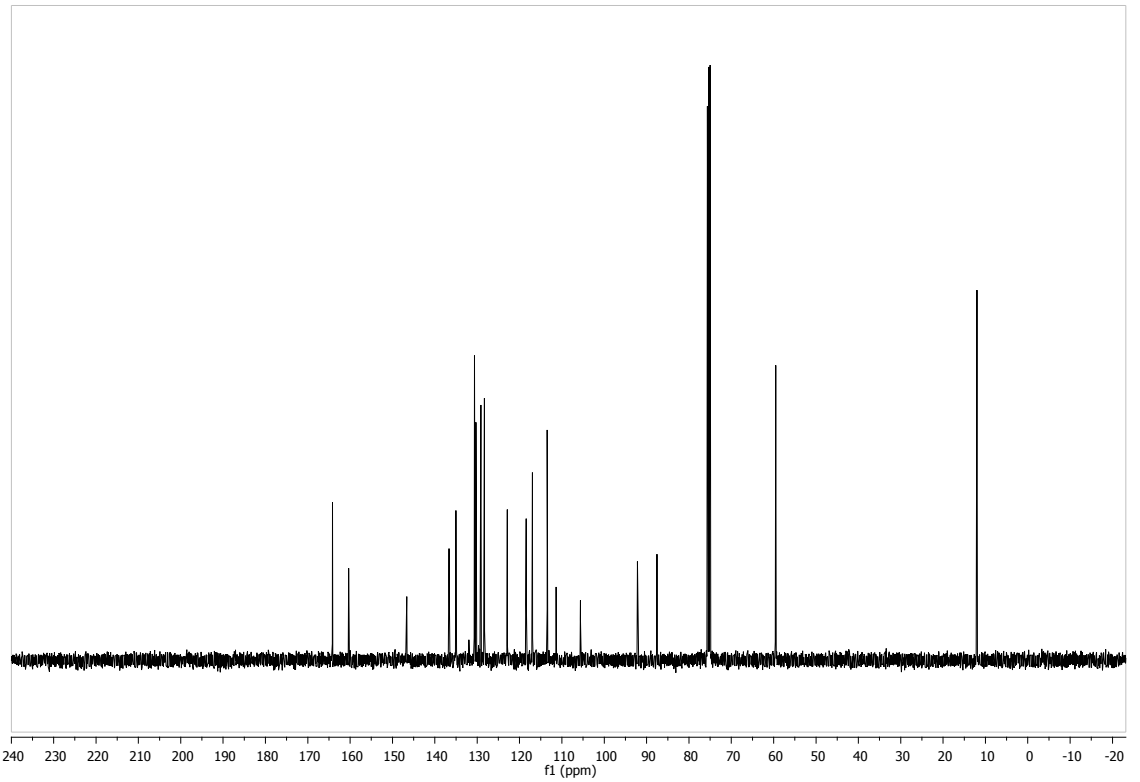


Ethyl (*E*)-4-[(2-(2-Aminophenylethynyl)-phenyl)amino]-4-oxobut-2-enoate 5ba

^{1}H-NMR (400.16 MHz, $CDCl_3$)

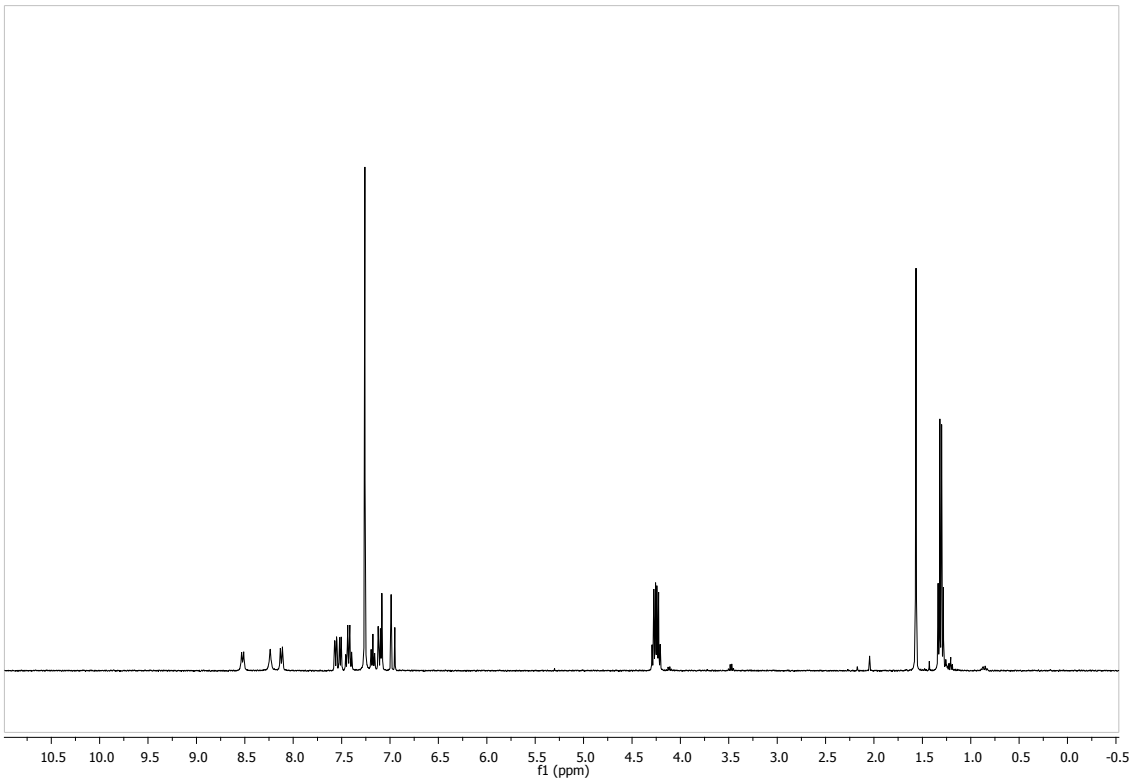


^{13}C-NMR (100.62 MHz, $CDCl_3$)

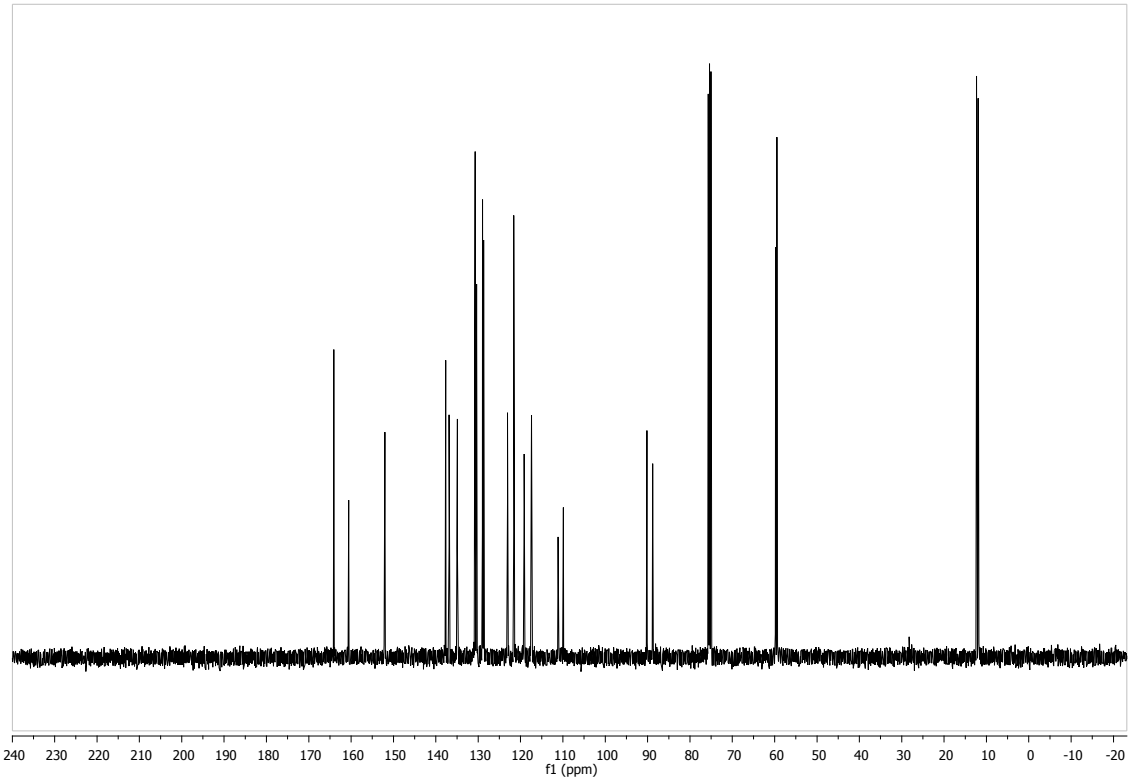


Ethyl (*E*)-4-((2-(2-Ethoxycarbonylamino-phenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5bb

^{1}H-NMR (400.16 MHz, $CDCl_3$)

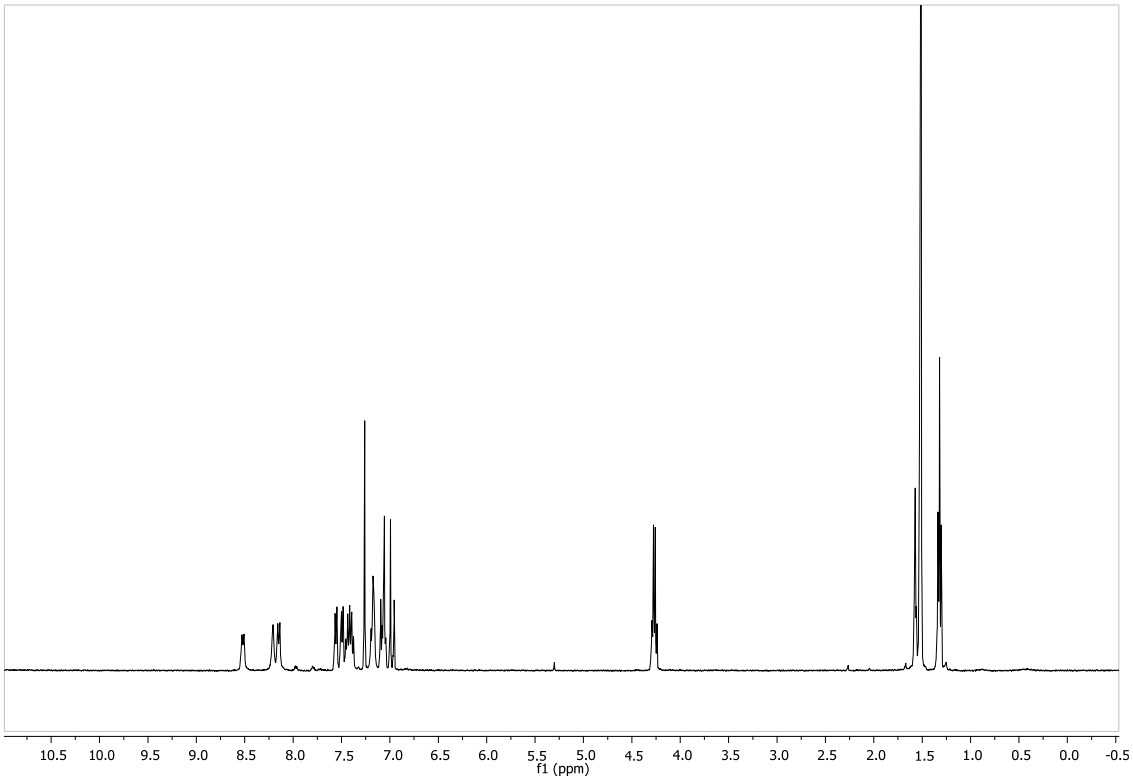


^{13}C-NMR (100.62 MHz, $CDCl_3$)

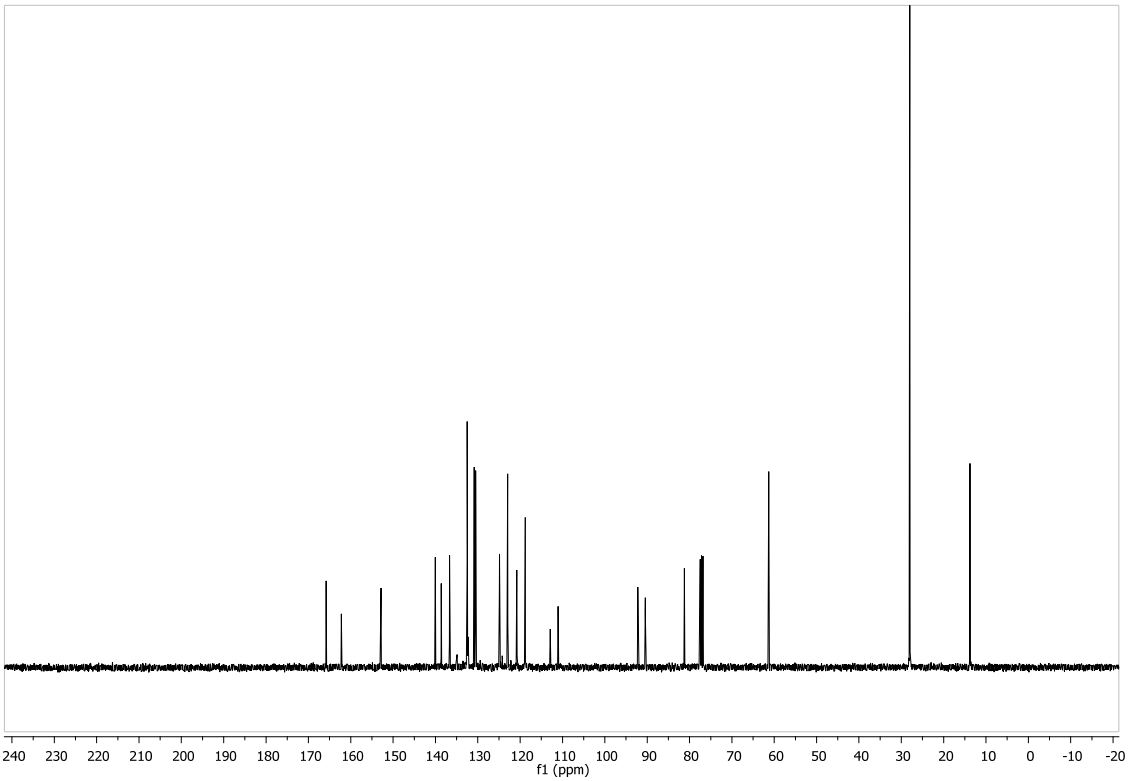


Ethyl (*E*)-4-((2-((2-*tert*-Butoxycarbonylamino-phenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5be

^{1}H-NMR (400.16 MHz, $CDCl_3$)

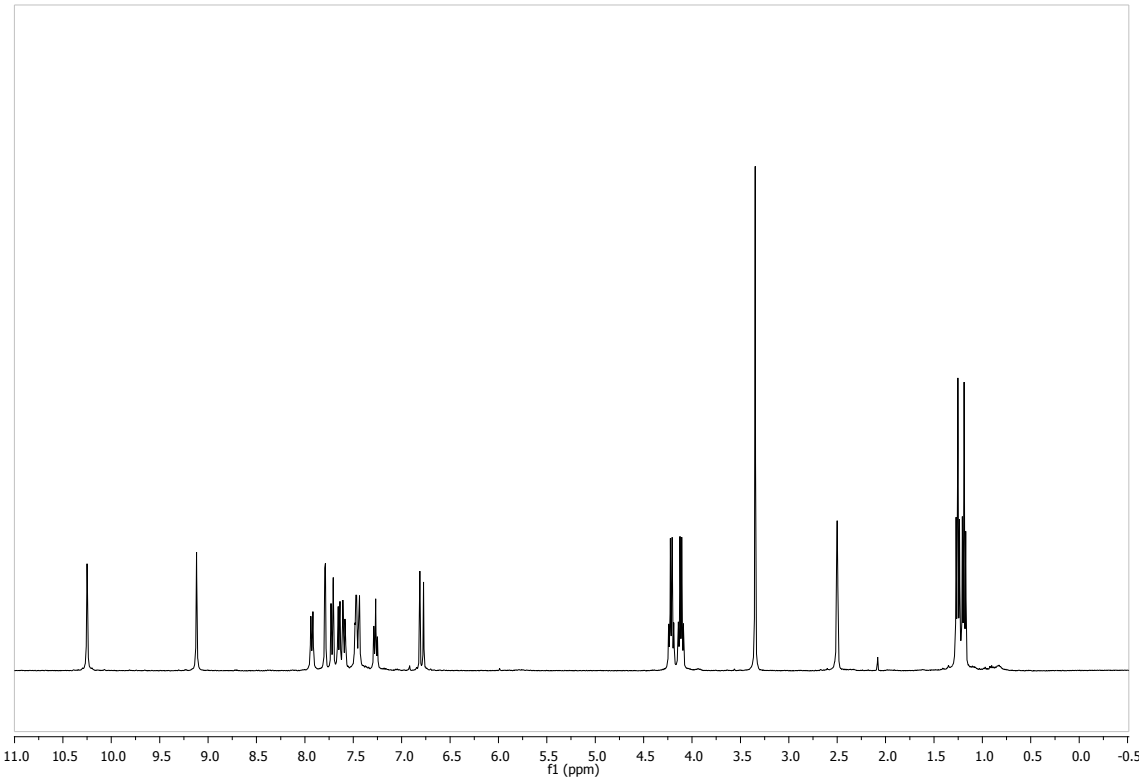


^{13}C-NMR (100.62 MHz, $CDCl_3$)

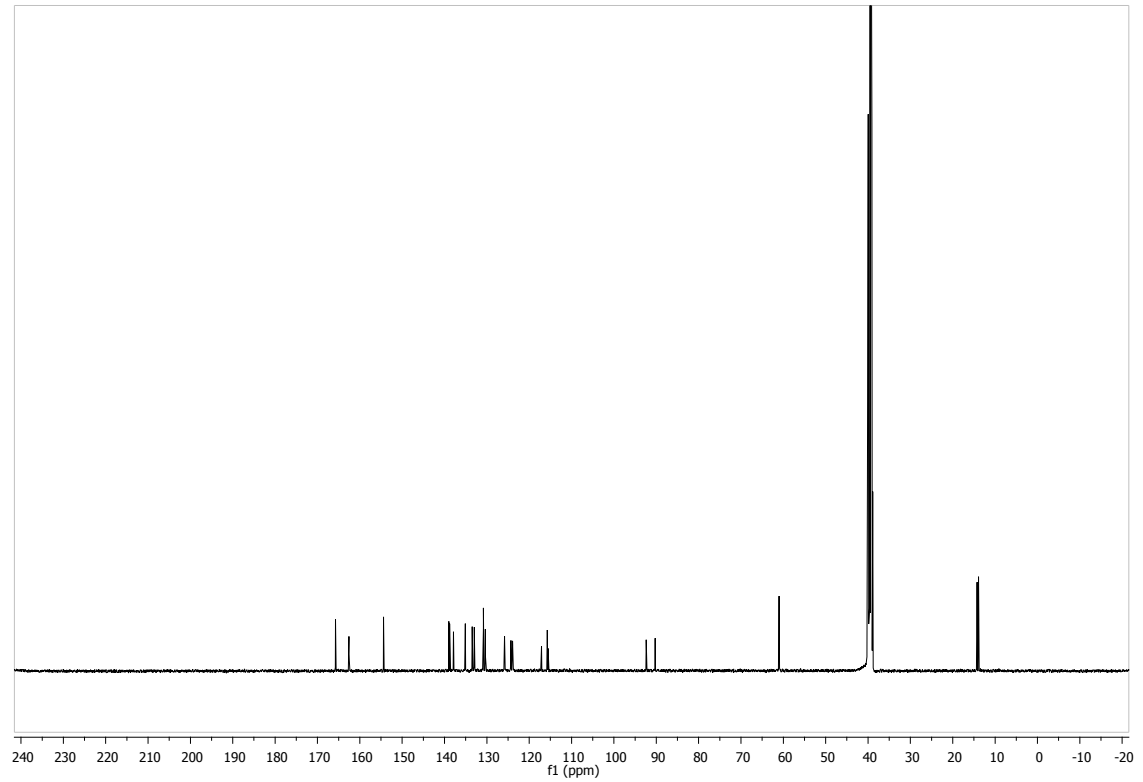


Ethyl (*E*)-4-((2-((5-Bromo-2-ethoxycarbonylaminophenyl)-ethynyl)-phenyl)-amino)-4-oxobut-2-enoate 5bd

^{1}H-NMR (400.16 MHz, DMSO-d_6)

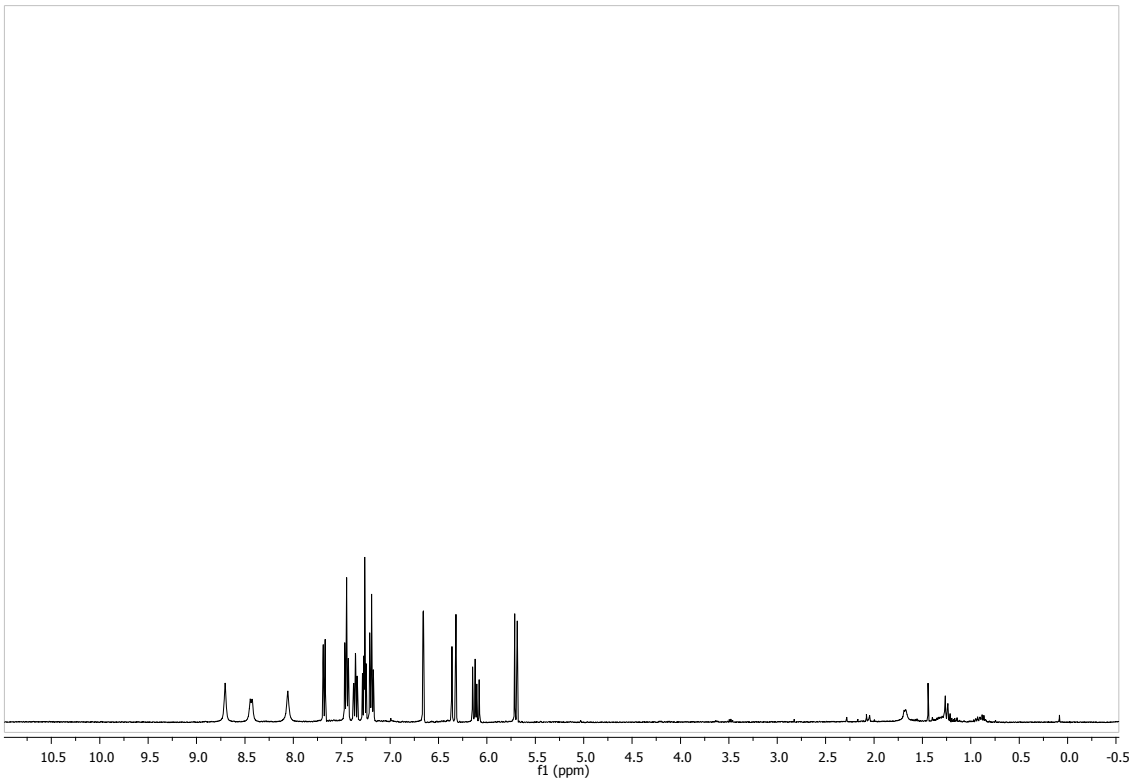


^{13}C-NMR (100.62 MHz, DMSO-d_6)

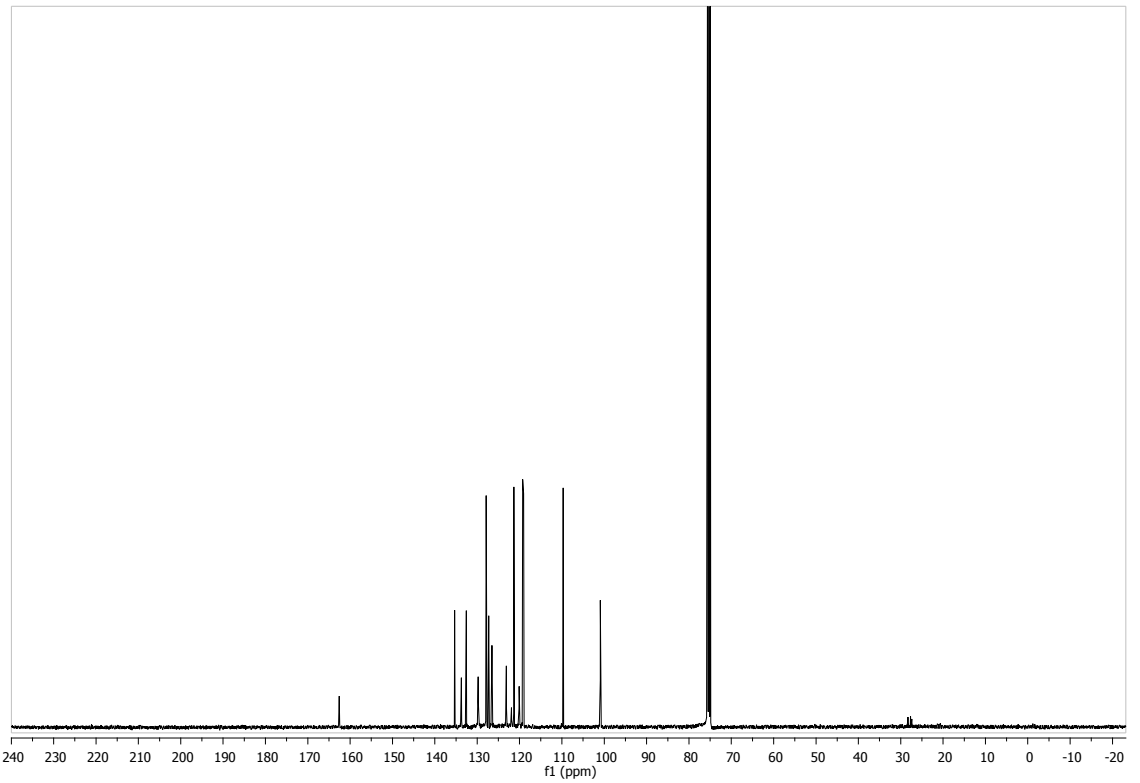


7-Methylene-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]indole 9aa

^{1}H-NMR (400.16 MHz, $CDCl_3$)

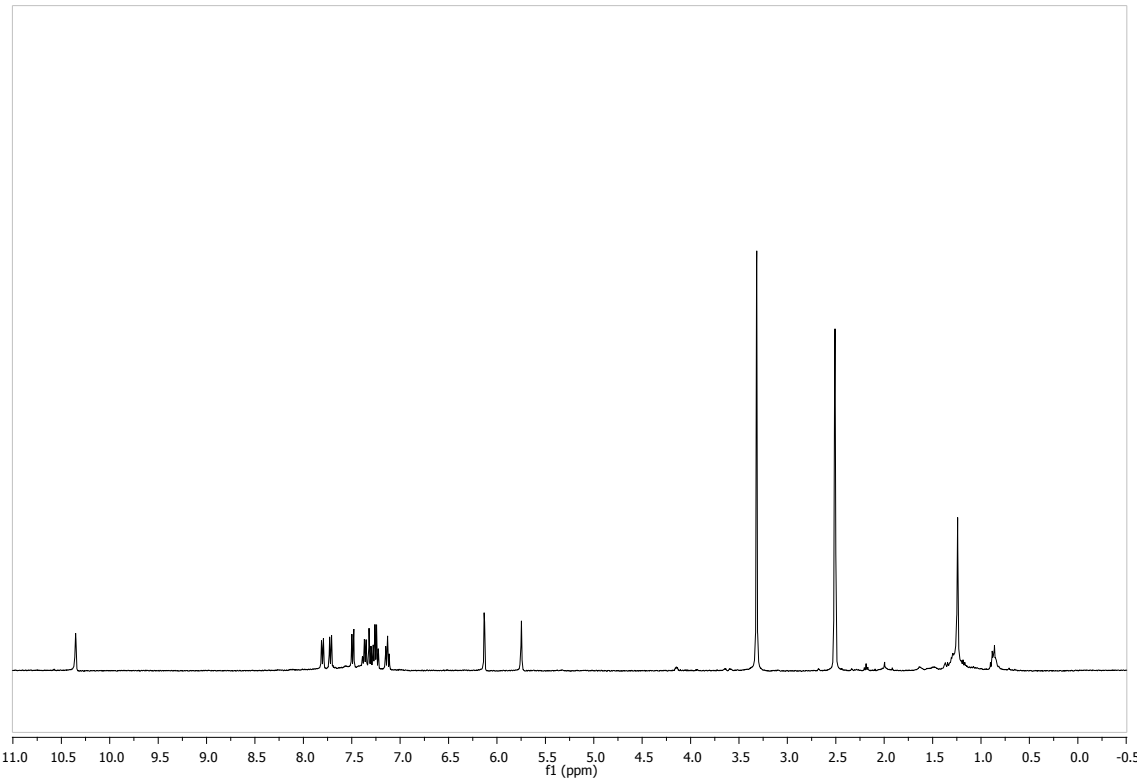


^{13}C-NMR (100.62 MHz, $CDCl_3$)

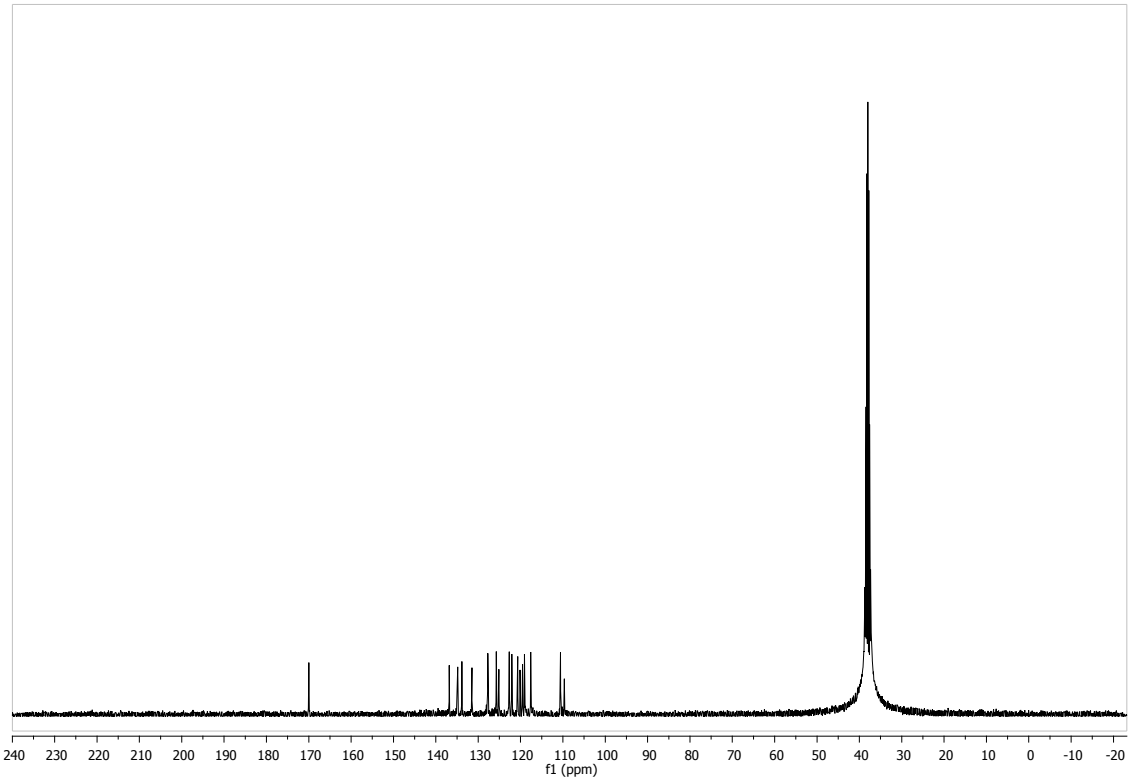


***N*-(2-Indol-2-yl-phenyl)-acrylamide 4aa**

^{1}H-NMR (400.16 MHz, DMSO-d_6)

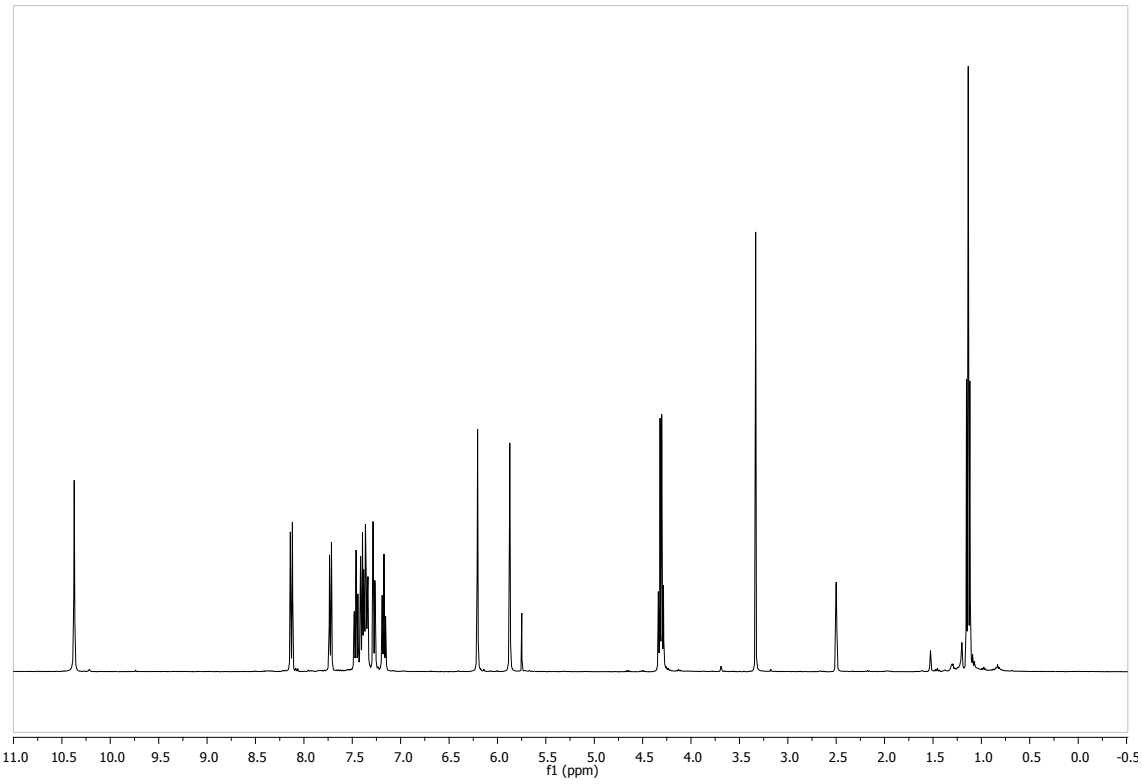


^{13}C-NMR (100.62 MHz, DMSO-d_6)



Ethyl 7-Methylene-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4ab

^{1}H-NMR (400.16 MHz, DMSO-d_6)



^{13}C-NMR (100.62 MHz, DMSO-d_6)

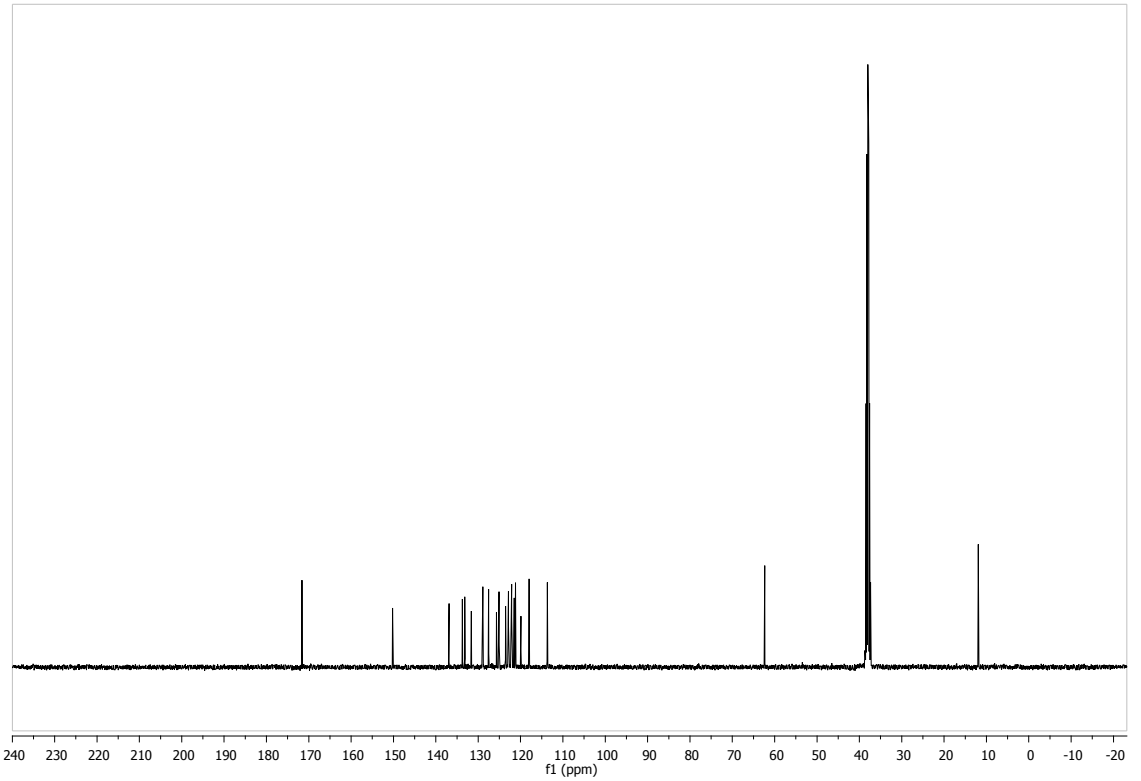


TABLE 1. CRYSTAL DATA AND STRUCTURE REFINEMENT FOR 4ab

Empirical formula $C_{20}H_{16}N_2O_3$

Formula weight 332.35

Temperature 293 K

Wavelength 0.71073 Å

Crystal system Monoclinic

Space group P2(1)/c

Unit cell dimensions a = 9.2474(15) Å α = 90°.

b = 21.492(3) Å β = 93.323(3)°.

c = 8.1455(13) Å γ = 90°.

Volume 1616.2(4) Å3

Z 4

Density (calculated) 1.366 Mg/m3

Absorption coefficient 0.093 mm-1

F(000) 696

Crystal size 0.49 x 0.48 x 0.23 mm3

Theta range for data collection 1.90 to 25.07°.

Index ranges $-11 \leq h \leq 10$, $-25 \leq k \leq 25$, $-9 \leq l \leq 9$

Reflections collected 12062

Independent reflections 2852 [R(int) = 0.0223]

Completeness to theta = 25.00° 99.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.7452 and 0.6754

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 2852 / 0 / 231

Goodness-of-fit on F2 1.033

Final R indices [I>2sigma(I)] R1 = 0.0339, wR2 = 0.0859

R indices (all data) R1 = 0.0444, wR2 = 0.0959

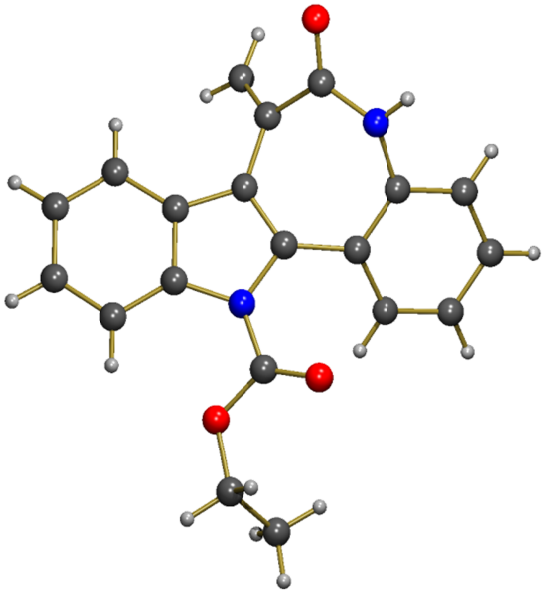
Largest diff. peak and hole 0.171 and -0.173 e.Å-3

TABLE 2. ATOMIC COORDINATES (x 10^4) AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS (Å^{2}x 10^3) FOR. 4ab.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

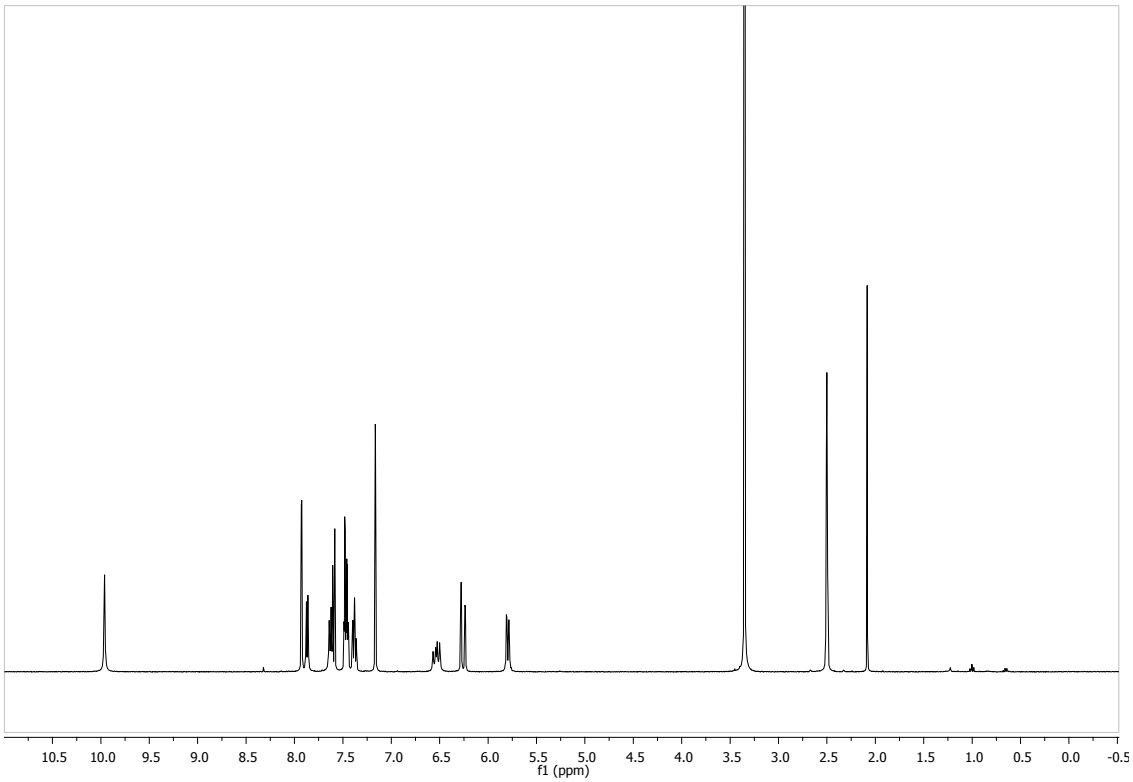
	x	y	z	U(eq)
N(1)	9059(1)	4467(1)	1358(2)	40(1)
C(2)	10371(2)	4487(1)	2174(2)	40(1)
C(3)	10594(2)	4124(1)	3733(2)	40(1)
C(4)	11338(2)	4378(1)	4997(2)	61(1)
N(5)	8778(1)	2609(1)	3116(2)	36(1)
C(6)	8796(2)	3265(1)	3010(2)	34(1)
C(7)	10099(2)	3474(1)	3669(2)	36(1)
C(7B)	10948(2)	2943(1)	4216(2)	38(1)
C(8)	12352(2)	2882(1)	4935(2)	48(1)
C(9)	12896(2)	2299(1)	5262(2)	57(1)
C(10)	12062(2)	1775(1)	4883(2)	58(1)
C(11)	10675(2)	1816(1)	4182(2)	50(1)
C(11B)	10120(2)	2411(1)	3860(2)	38(1)
C(12)	7716(2)	4247(1)	1897(2)	36(1)
C(13)	7531(2)	3657(1)	2580(2)	34(1)
C(14)	6126(2)	3491(1)	2987(2)	39(1)
C(15)	4969(2)	3890(1)	2707(2)	46(1)
C(16)	5170(2)	4469(1)	2028(2)	49(1)
C(17)	6537(2)	4646(1)	1624(2)	45(1)

C(18)	7739(2)	2226(1)	2318(2)	39(1)
O(19)	7811(1)	1658(1)	2963(1)	51(1)
C(20)	6830(2)	1196(1)	2226(2)	57(1)
C(21)	5346(2)	1276(1)	2808(3)	79(1)
O(22)	6920(1)	2394(1)	1217(1)	49(1)
O(23)	11368(1)	4790(1)	1618(2)	54(1)

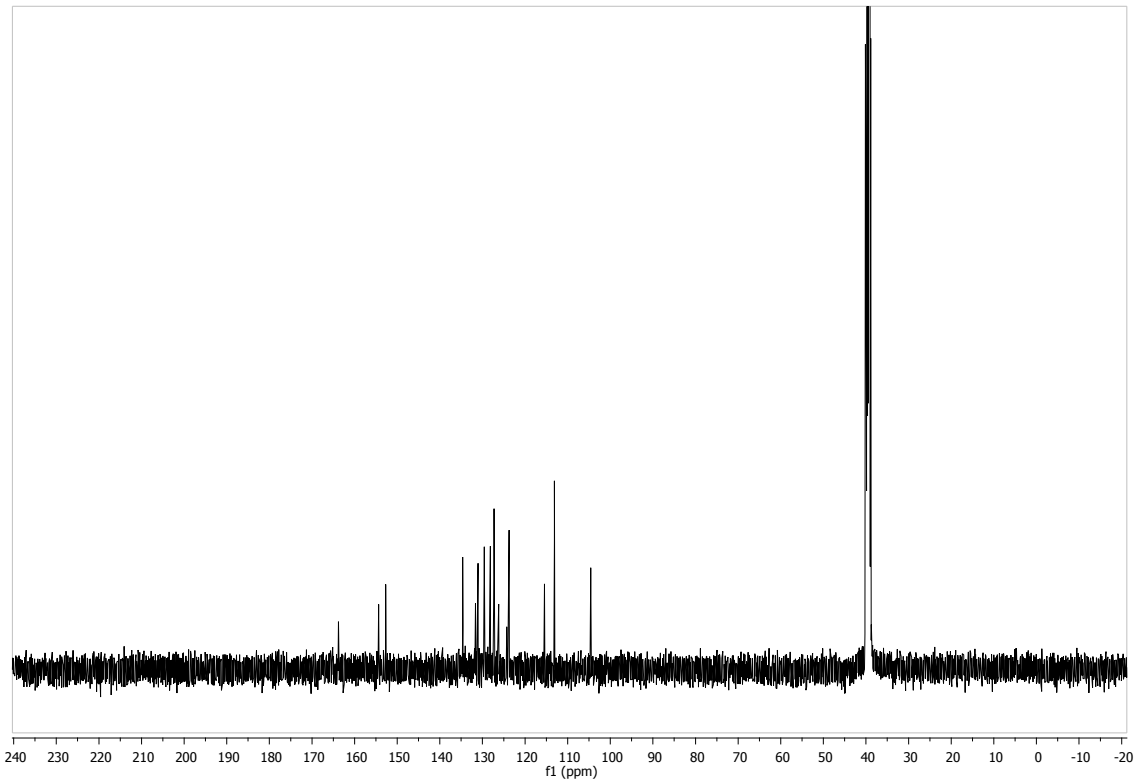


9-Bromo-7-Methylene-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]indole 9ac

^{1}H-NMR (400.16 MHz, DMSO-d_6)

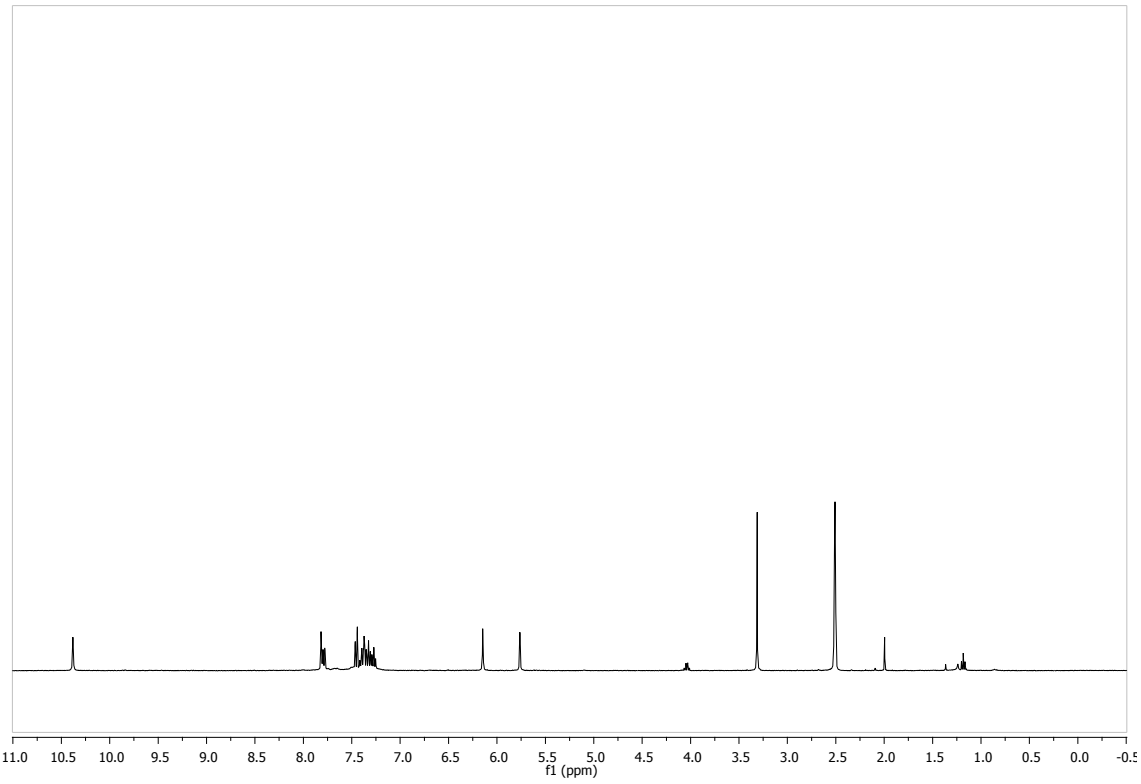


^{13}C-NMR (100.62 MHz, DMSO-d_6)

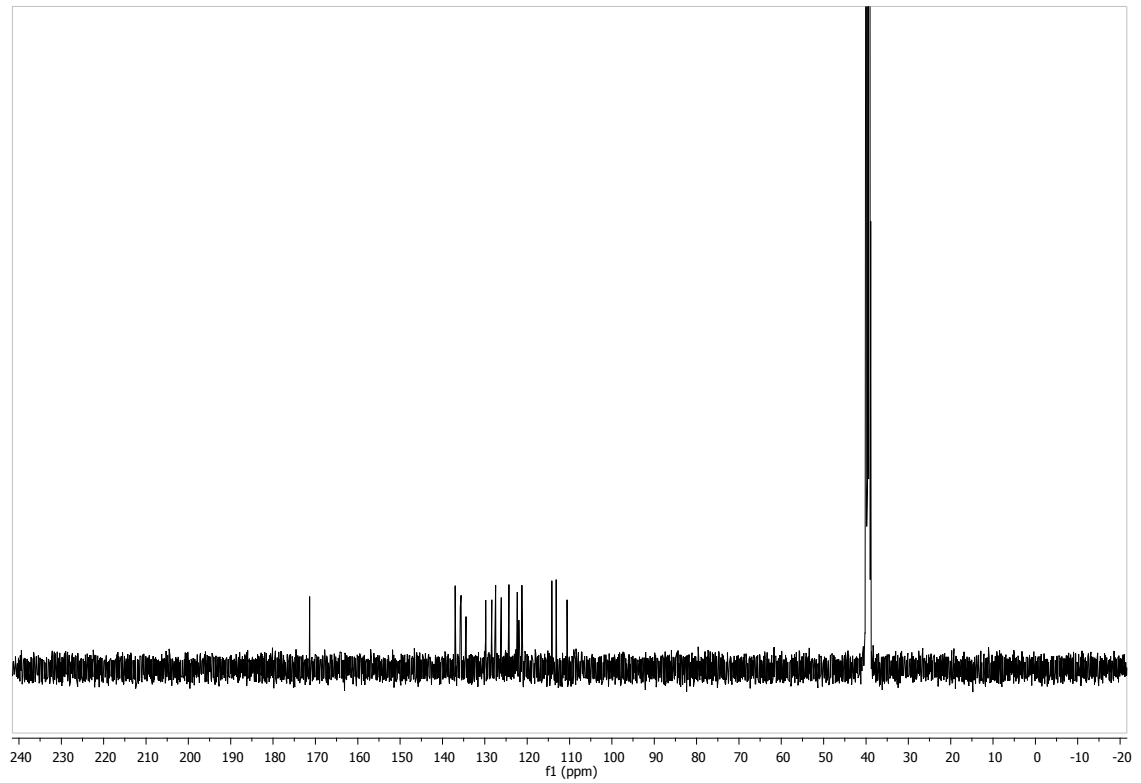


***N*-(2-(5-Bromo-indol-2-yl)-phenyl)-acrylamide 4ac.**

^{1}H-NMR (400.16 MHz, $CDCl_3$)

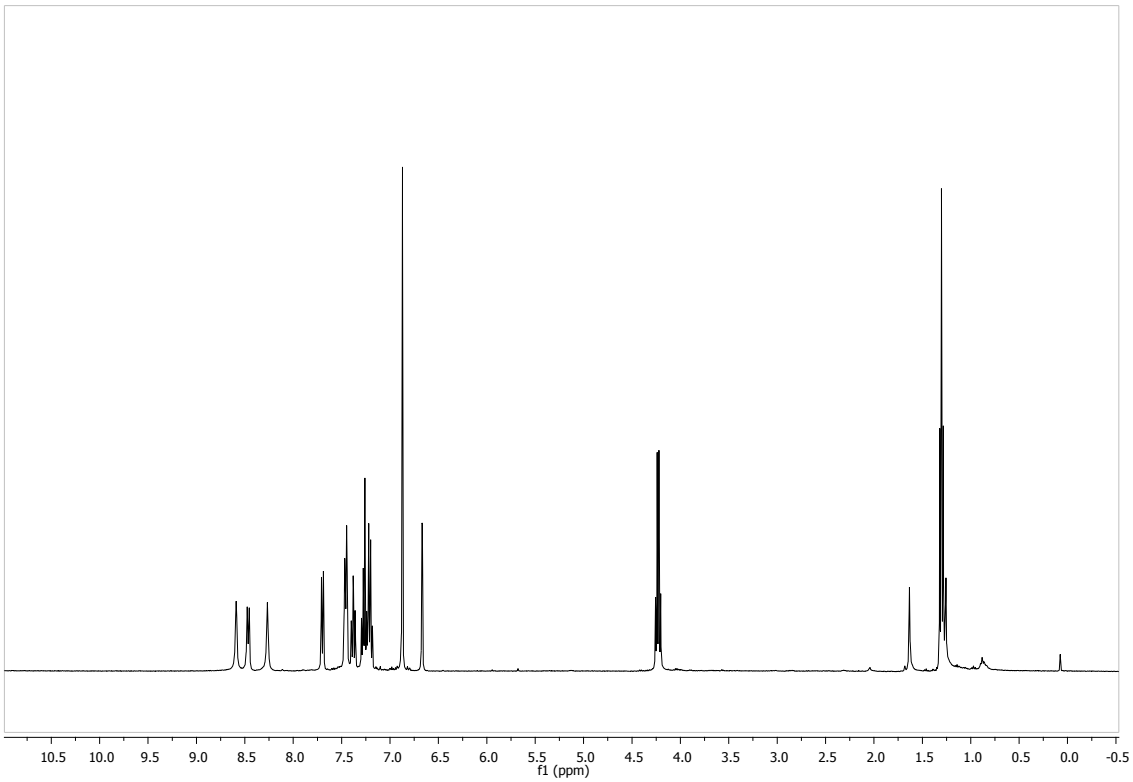


^{13}C-NMR (100.62 MHz, $CDCl_3$)

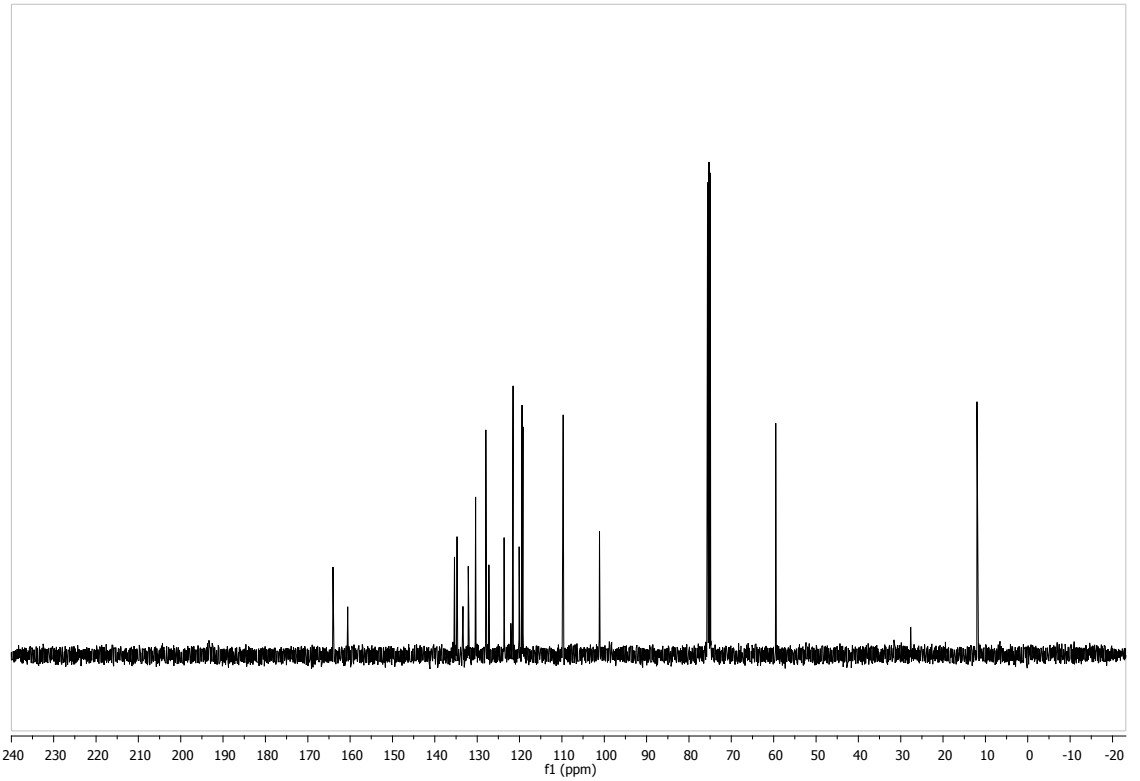


Ethyl (*E*)-4-(2-(1*H*-Indol-2-yl)-phenylamino)-4-oxobut-2-enoate 9ba.

^{1}H-NMR (400.16 MHz, $CDCl_3$)

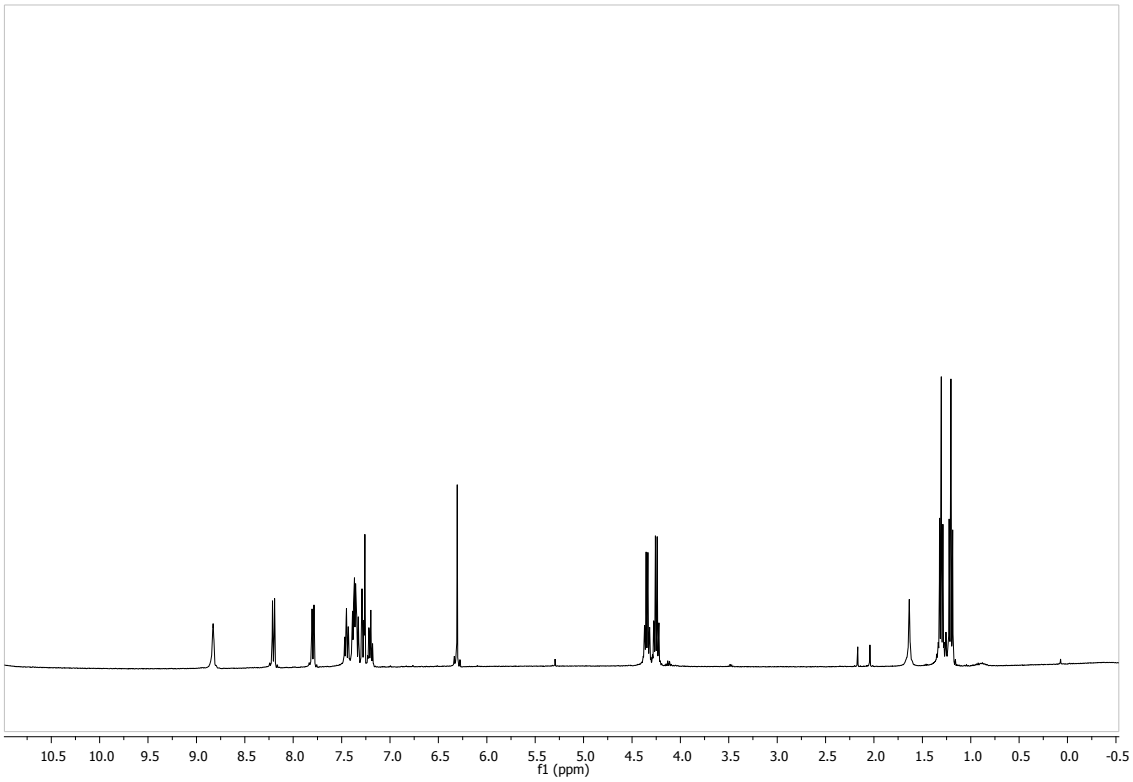


^{13}C-NMR (100.62 MHz, $CDCl_3$)



Ethyl 7-(2-Ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4bb

^{1}H-NMR (400.16 MHz, $CDCl_3$)



^{13}C-NMR (100.62 MHz, $CDCl_3$)

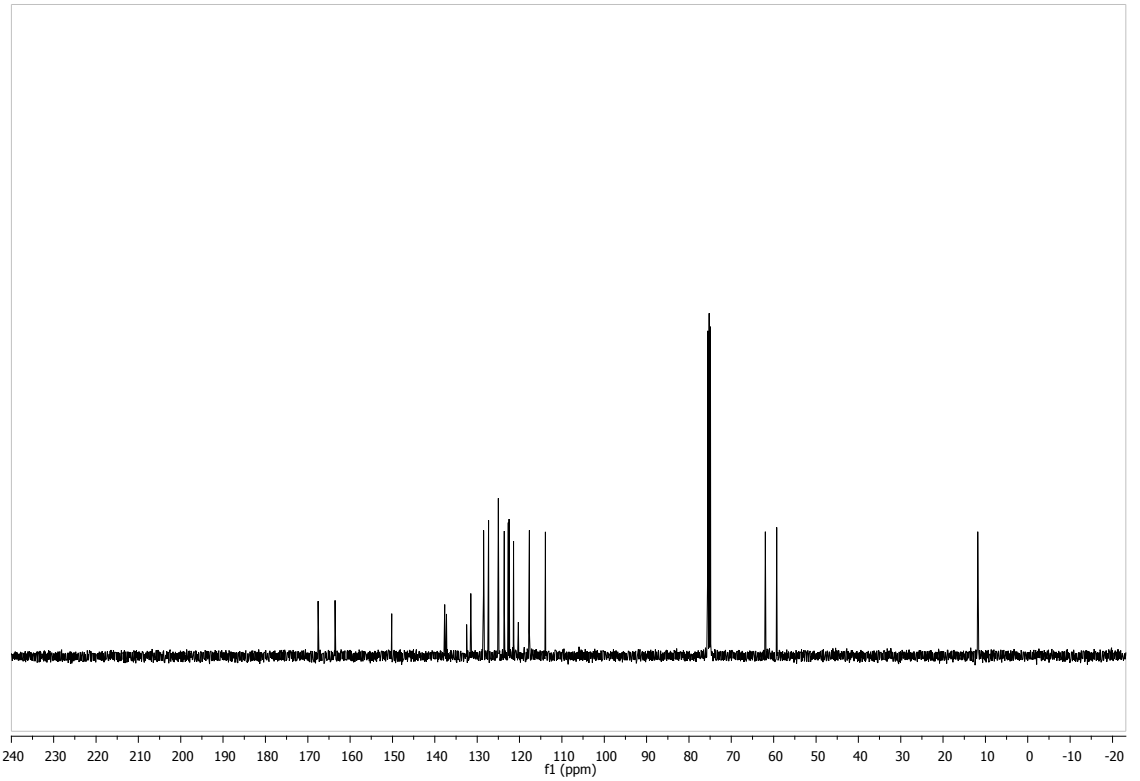


TABLE 1. CRYSTAL DATA AND STRUCTURE REFINEMENT FOR 4bb

Empirical formula $C_{23}H_{20}N_2O_5$

Formula weight 404.41

Temperature 293(2) K

Wavelength 0.71073 Å

Crystal system Monoclinic

Space group P2(1)/c

Unit cell dimensions a = 10.7866(18) Å α = 90°.

b = 14.366(2) Å β = 111.734(3)°.

c = 13.573(2) Å γ = 90°.

Volume 1953.7(6) Å3

Z 4

Density (calculated) 1.375 Mg/m3

Absorption coefficient 0.098 mm-1

F(000) 848

Crystal size 0.52 x 0.38 x 0.20 mm3

Theta range for data collection 2.03 to 25.02°.

Index ranges -12≤h≤12, -17≤k≤17, -16≤l≤16

Reflections collected 14633

Independent reflections 3447 [R(int) = 0.0305]

Completeness to theta = 25.00° 99.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.7452 and 0.7142

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 3447 / 0 / 277

Goodness-of-fit on F2 1.021

Final R indices [I>2sigma(I)] R1 = 0.0376, wR2 = 0.0853

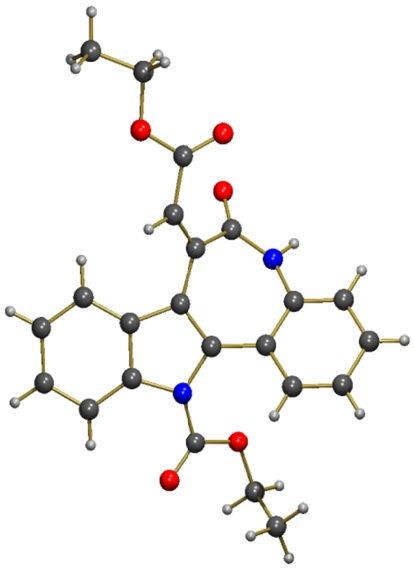
R indices (all data) R1 = 0.0676, wR2 = 0.1058

Largest diff. peak and hole 0.272 and -0.181 e.Å-3.

TABLE 2. ATOMIC COORDINATES (x 10^4) AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS (Å^{2}x 10^3) FOR. 4bb.

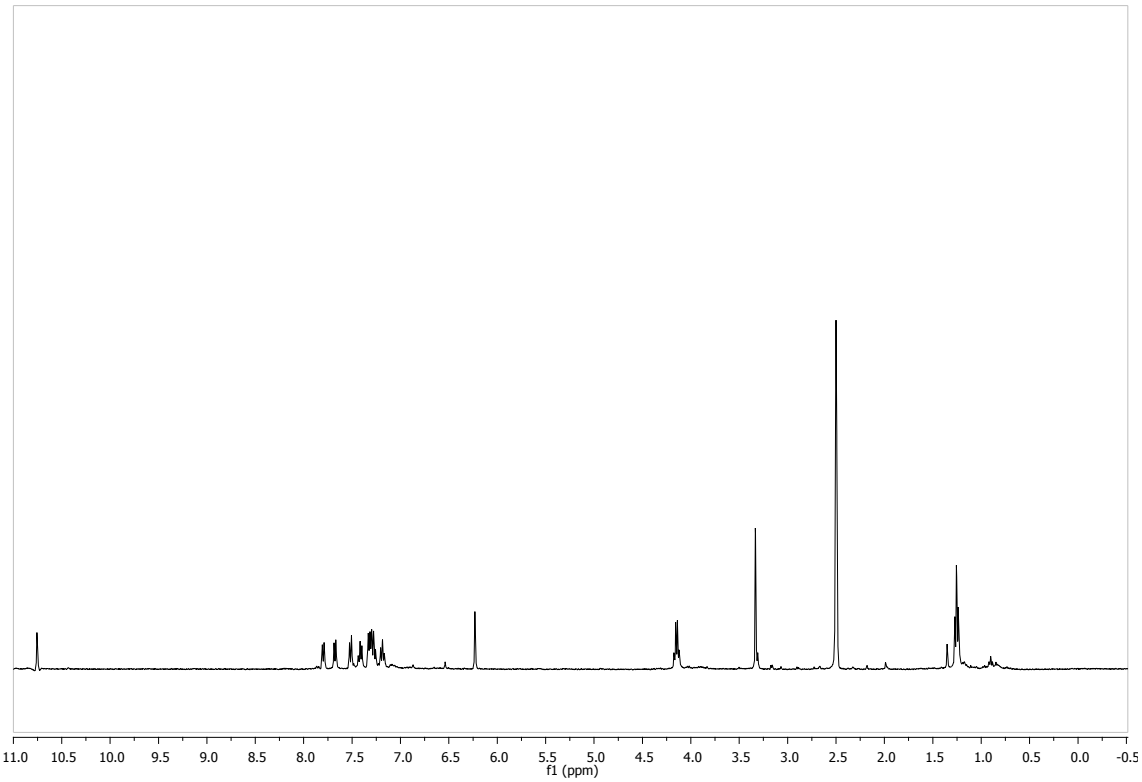
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	4581(2)	171(1)	8346(1)	46(1)
C(2)	3459(2)	151(2)	8584(2)	43(1)
O(3)	3282(2)	-470(1)	9128(1)	60(1)
C(4)	2430(2)	889(1)	8106(2)	41(1)
C(5)	1796(2)	1324(2)	8655(2)	46(1)
C(6)	2058(2)	1223(1)	9796(2)	45(1)
O(7)	3125(2)	1104(1)	10496(1)	61(1)
O(8)	925(1)	1317(1)	9960(1)	58(1)
C(9)	1000(2)	1269(2)	11048(2)	64(1)
C(10)	-368(3)	1320(2)	11030(2)	80(1)
N(11)	2061(2)	1283(1)	5335(1)	42(1)
C(12)	2852(2)	1148(1)	6424(2)	40(1)
C(13)	2015(2)	1019(1)	6958(2)	41(1)
C(13B)	650(2)	1071(1)	6215(2)	43(1)
C(14)	-581(2)	972(2)	6323(2)	51(1)
C(15)	-1724(2)	1055(2)	5434(2)	57(1)
C(16)	-1659(2)	1212(2)	4446(2)	57(1)
C(17)	-454(2)	1306(2)	4316(2)	52(1)
C(17B)	695(2)	1238(1)	5216(2)	44(1)
C(18)	5070(2)	871(1)	7851(2)	41(1)
C(19)	4287(2)	1317(1)	6904(2)	39(1)
C(20)	4912(2)	1980(2)	6485(2)	47(1)
C(21)	6257(2)	2164(2)	6950(2)	56(1)
C(22)	7018(2)	1695(2)	7865(2)	59(1)
C(23)	6425(2)	1068(2)	8318(2)	51(1)
C(24)	2421(2)	1197(2)	4447(2)	44(1)
O(25)	1697(2)	1429(1)	3577(1)	61(1)
O(26)	3616(1)	819(1)	4691(1)	48(1)
C(27)	4089(3)	751(2)	3814(2)	64(1)
C(28)	4572(3)	1661(2)	3579(2)	90(1)

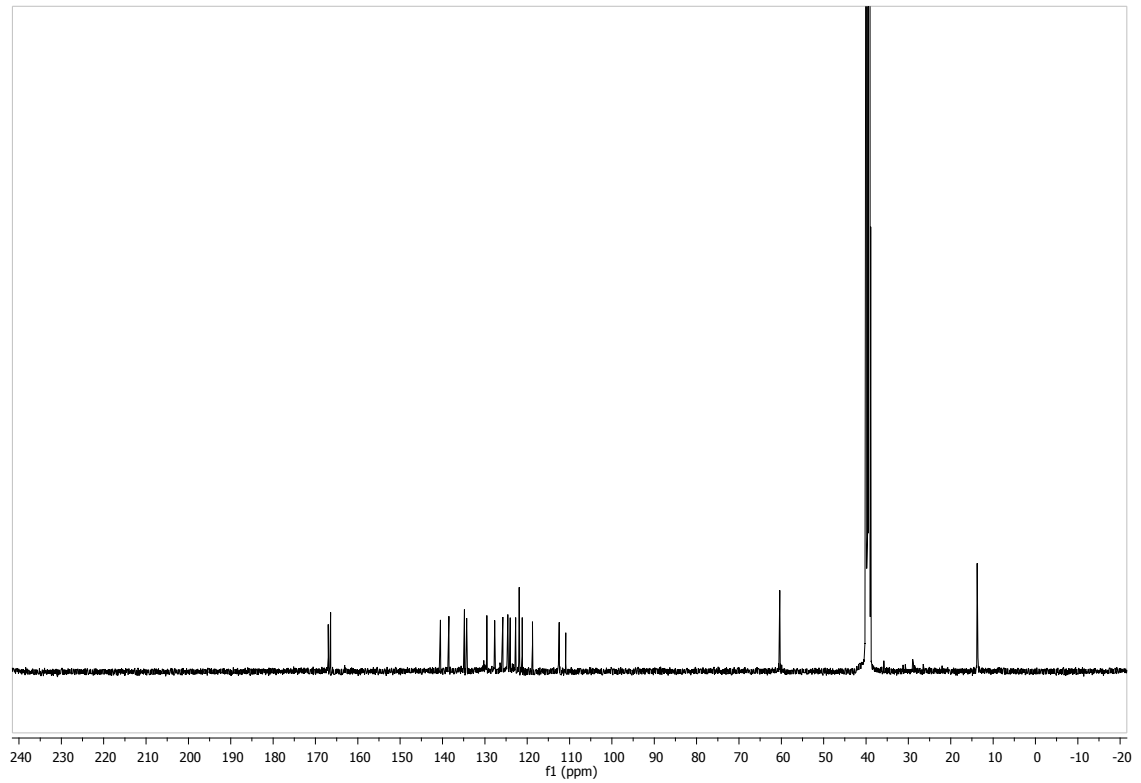


7-(2-Ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[*b*]azepino[4,5-*b*]indole 10bb.

^{1}H-NMR (400.16 MHz, DMSO-d_6)

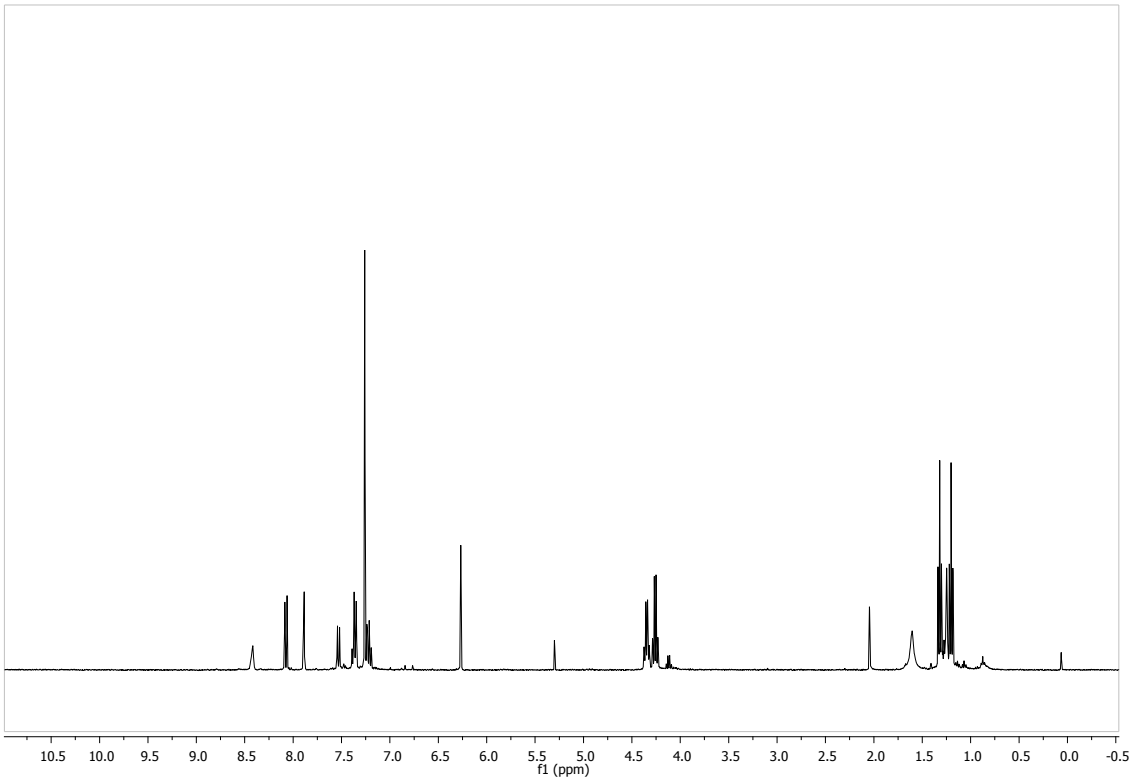


^{13}C-NMR (100.62 MHz, DMSO-d_6)

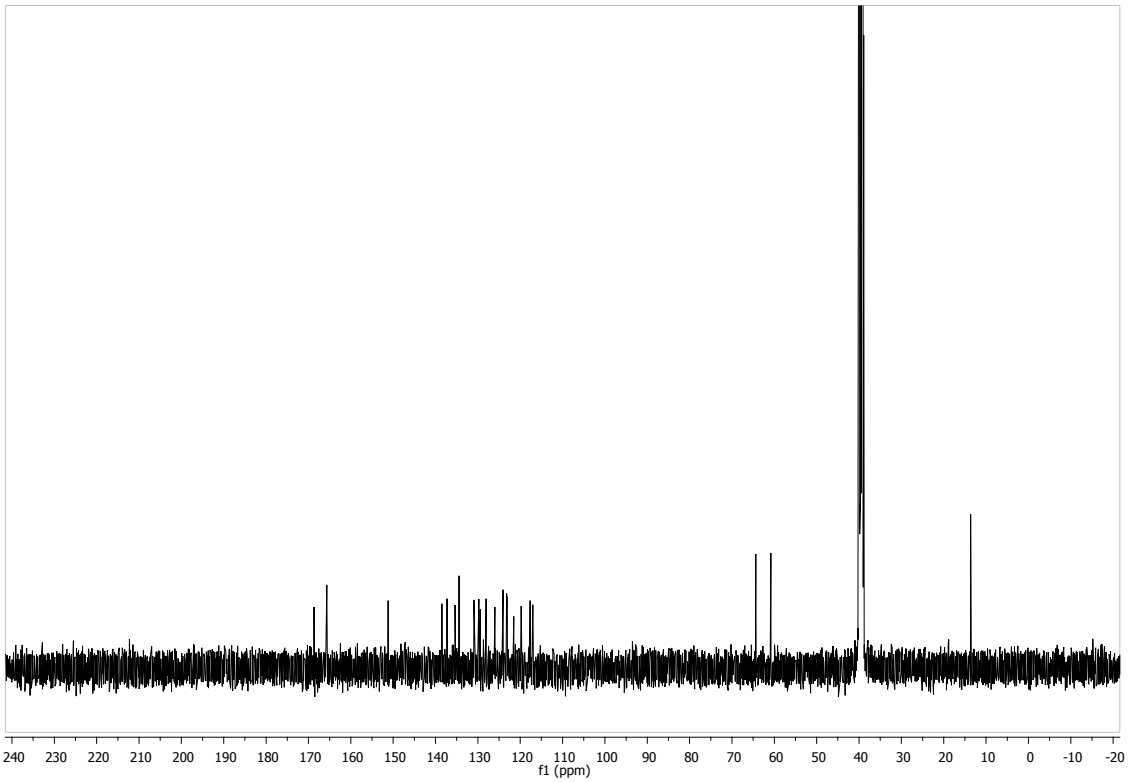


Ethyl 9-Bromo-7-(2-ethoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4bd.

^{1}H-NMR (400.16 MHz, $CDCl_3$)

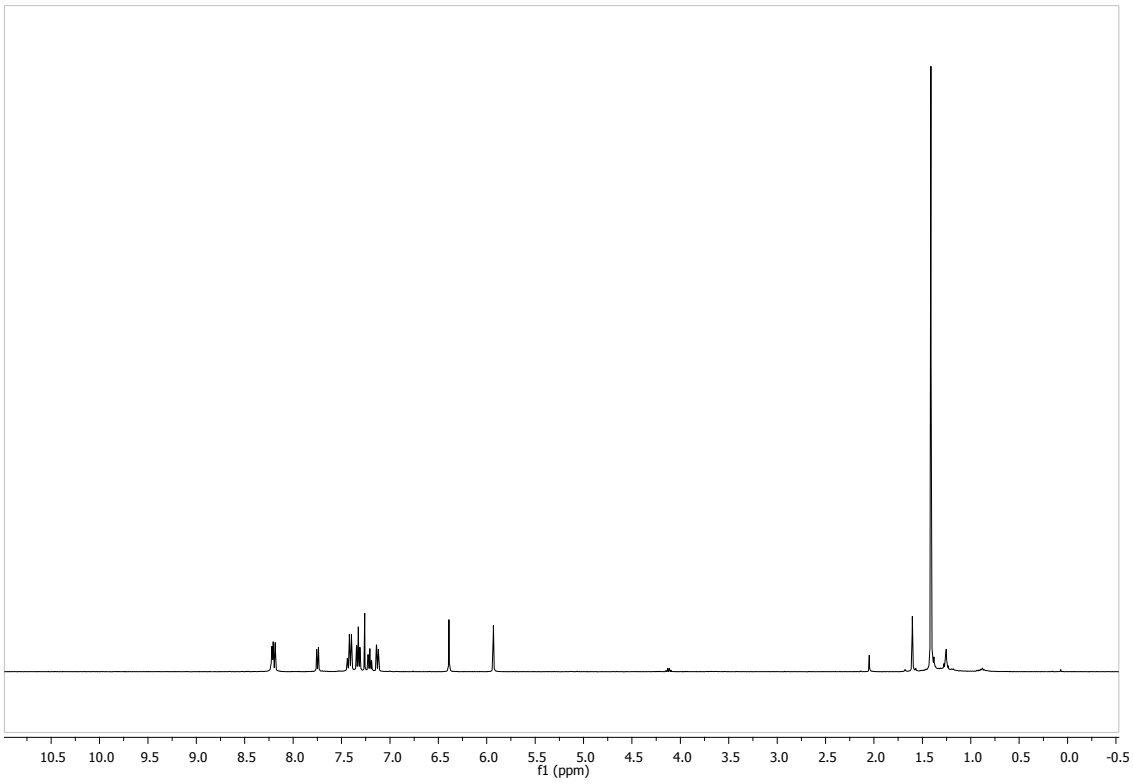


^{13}C-NMR (100.62 MHz, DMSO-d_6)

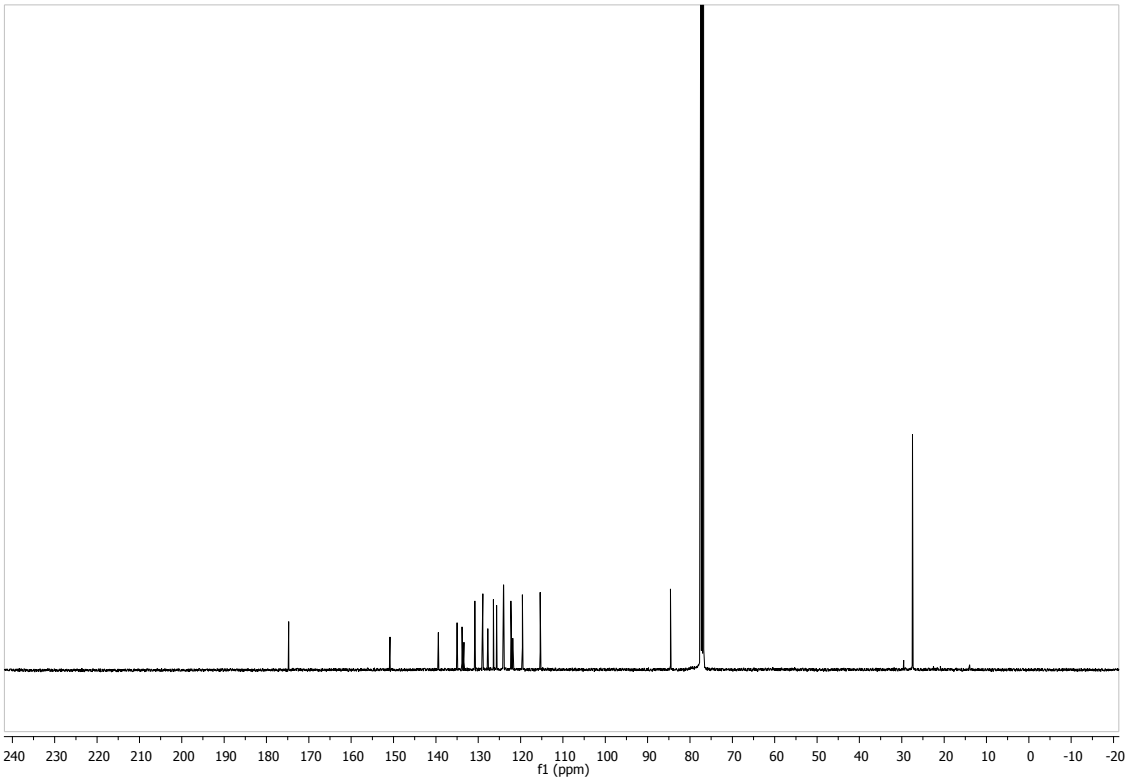


***tert*-Butyl 7-methylene-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-b]indole-12(5H)-carboxylate 4ae**

^{1}H-NMR (400 MHz, $CDCl_3$)

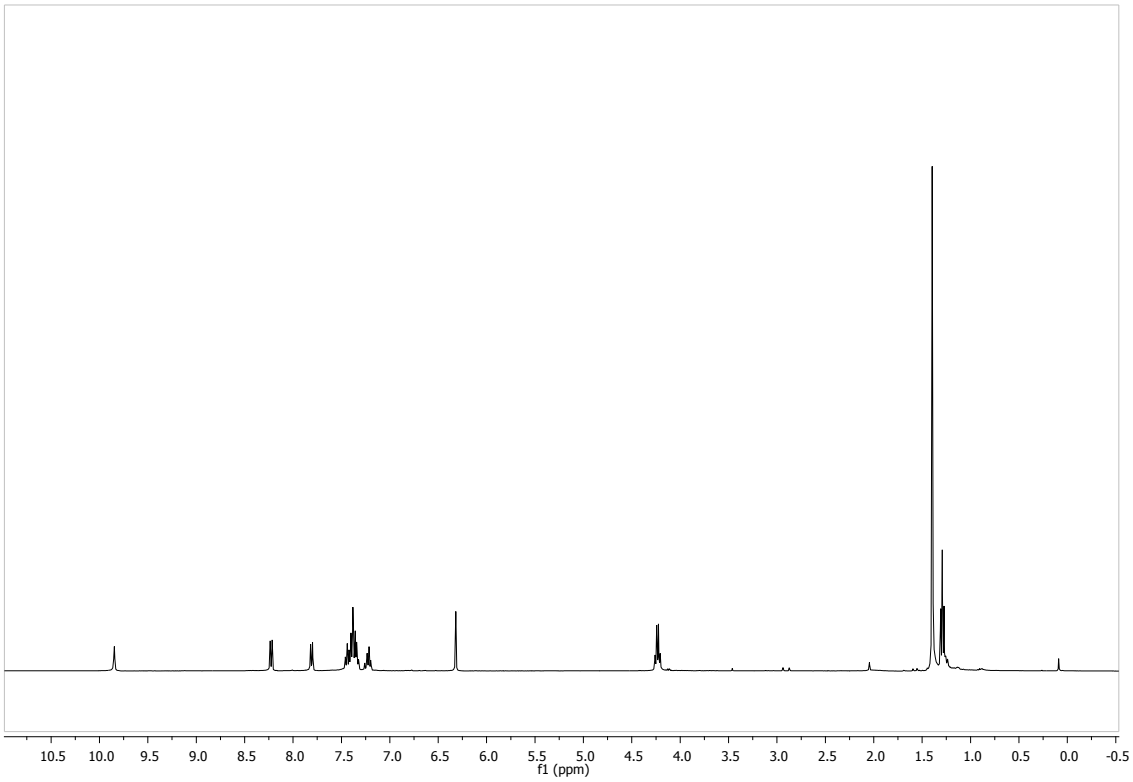


^{13}C-NMR (100 MHz, $CDCl_3$)

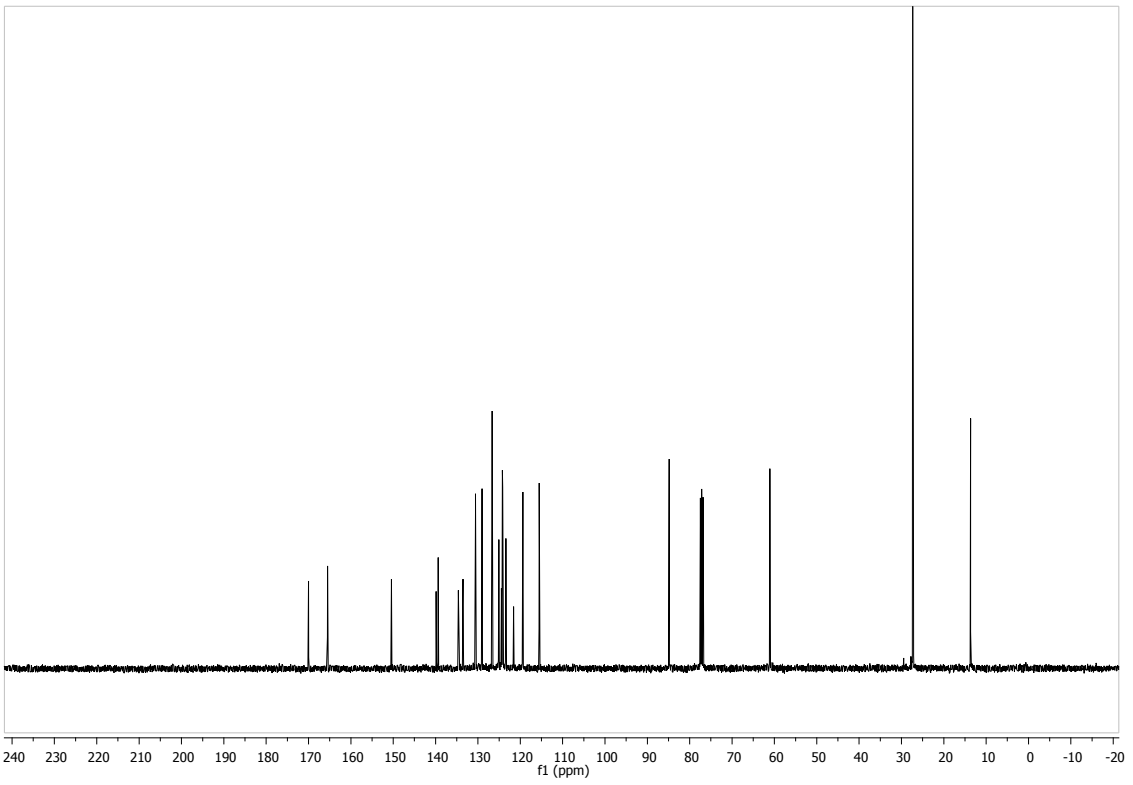


Ethyl 7-(2-*tert*-Butoxy-2-oxoethylene)-6-oxo-6,7-dihydrobenzo[2,3]azepino[4,5-*b*]indole-12(5*H*)-carboxylate 4be

^{1}H-NMR (400 MHz, $CDCl_3$)

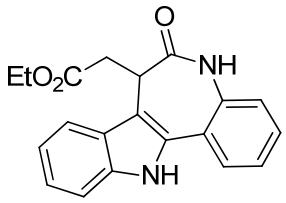


^{13}C-NMR (100 MHz, $CDCl_3$)



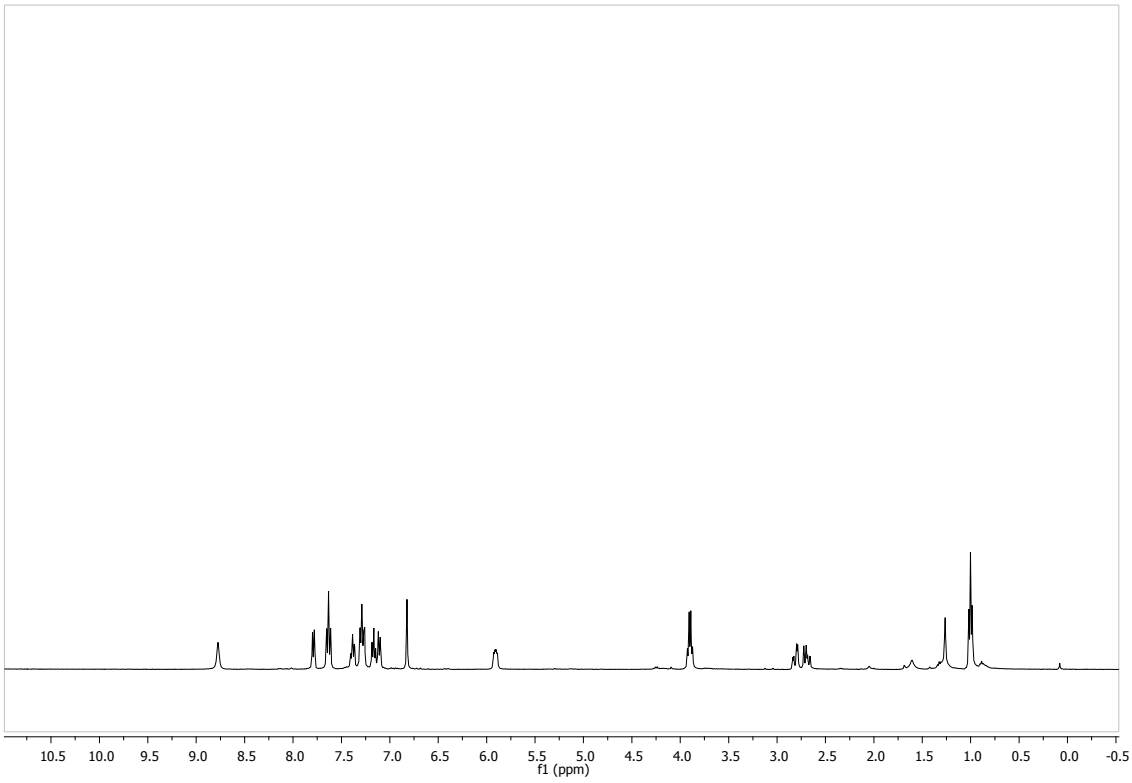
In Table 1, entry 10, the product corresponding to the conjugate addition was also obtained in 42% yield.

Data for ethyl 2-(6-oxo-5,6,7,12-tetrahydrobenzo[2,3]azepino[4,5-*b*]indol-7-yl)acetate.

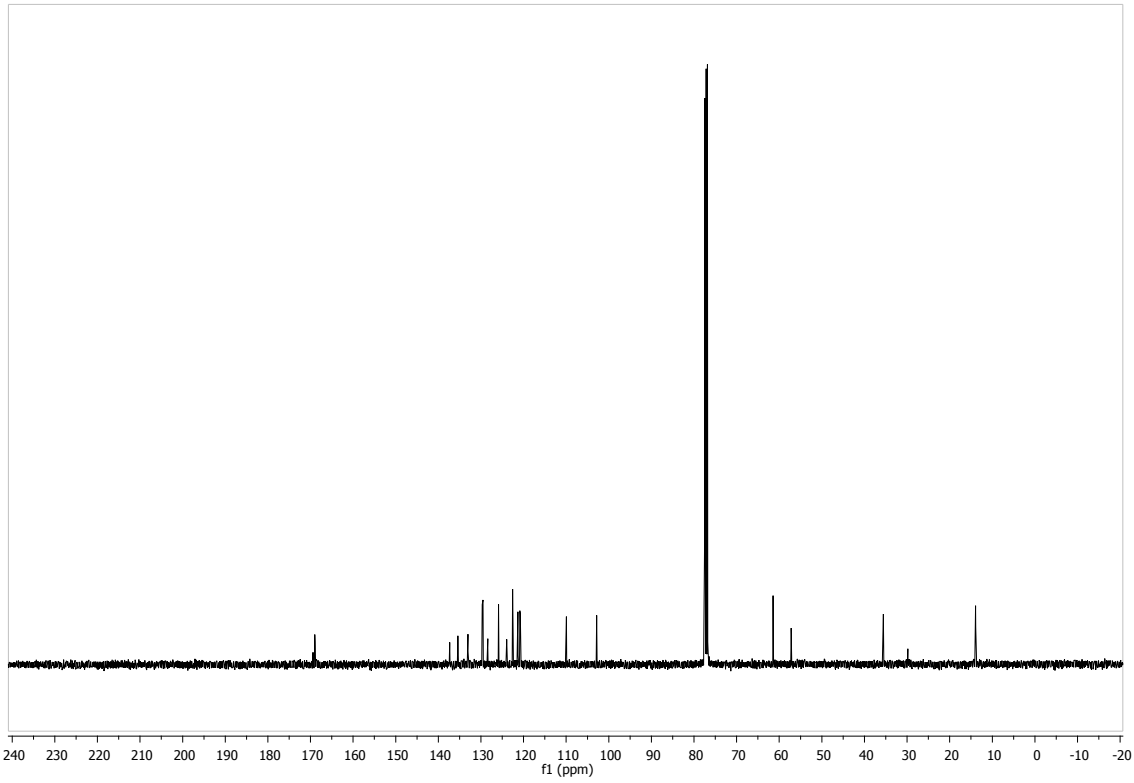


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H, NH), 7.79 (d, *J* = 7.7 Hz, 1H, ArH), 7.63 (t, *J* = 8.2 Hz, 2H, ArH), 7.39 (t, *J* = 7.5 Hz, 1H, ArH), 7.29 (t, *J* = 7.6 Hz, 2H, ArH), 7.17 (t, *J* = 7.5 Hz, 1H, ArH), 7.11 (d, *J* = 7.9 Hz, 1H, ArH), 6.82 (s, 1H, NH), 5.91 (dd, *J* = 9.9, 4.9 Hz, 1H, Csp^3-H), 3.90 (q, *J* = 7.1 Hz, 2H, O-$\underline{CH_2}CH_3$), 2.81 (dd, *J* = 15.9, 4.9 Hz, 1H, CH_{2A}), 2.69 (dd, *J* = 15.9, 9.9 Hz, 1H, CH_{2B}), 1.00 (t, *J* = 7.1 Hz, 3H, O-$CH_2\underline{CH_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 168.9, 137.3, 135.4, 133.0, 129.7, 129.5, 128.3, 125.8, 123.9, 122.5, 121.3, 120.8, 120.7, 109.9, 102.8, 61.4, 57.1, 35.5, 13.9.

^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)



OPTIMIZATION OF THE SYNTHESIS OF COMPOUND 5aa