A Tandem One-Pot, Microwave-Assisted Synthesis of Regiochemically Differentiated 1,2,4,5-Tetrahydro-1,4-Benzodiazepin-3-ones

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Supporting Information

Materials and Methods: All reagents were purchased from Aldrich unless otherwise mentioned. 2-nitrobenzylamine was obtained from 2-nitrobenzylamine hydrochloride. 6-nitroveratraldehyde and 4′-aminoacetophenone were purchased from Alfa Aesar. Allyl amine was purchased from Acros. Microwave reactions were conducted in a capped vial using a CEM Discover System. All reactions were monitored using thin layer chromatography on 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111, lot # LA2006). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds. Diastereomeric ratios were determined from ^{1}H NMR spectra and LC-MS. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and residual triplet at δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; multipet; dd, double doublet; b, broad. Mass spectra were recorded on a Micromass GCT at 70 eV. IR spectra were recorded on Varian/Digilab Excalibur 3100 High Resolution FT-IR. Automatic LC-MS was performed on a WATERS LCT PREMIER XE ELECTROSPRAY TOF with waters BEH C_{18} column (2.1 mmx 50 mm, 1.7 μm). The eluent was mixture of acetonitrile and water containing 0.05% HCOOH with linear gradient from 10:90 (v:v) acetonitrile-water to 90:10 acetonitrile-water within 10 minutes at 0.7 mL/min. UV absorption detection was conducted at 254 nm.

General Procedure 1 (One-pot, two-steps synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones):

In a 10 mL vial (CEM Discover System) equipped with a magnetic stir bar, 2-nitrobenzylamine (15 mg, 0.099 mmol), 2,2-dimethylpropanal (7 mg, 0.099 mmol), fumaric acid monoethyl ester (14 mg, 0.099 mmol) and *tert*-butyl isocyanide (8 mg, 0.099 mmol) were added to a mixture of 1.8 mL of ethanol and

0.6 mL of distilled water (3:1 ratio). The vial was capped and placed in the microwave. The microwave was then run at 300 W, 60 ^{o}C, for 60 min. After cooling the vial to room temperature, 10 equivalent of Fe(0) powder (40 mess, 55 mg, 0.99 mmol) followed by 0.5-1.0 equivalent of NH_4Cl (5 mg, 0.099 mmol) were added to the same vial (assume the multicomponent acyclic Ugi reaction went to completion). The microwave was then run at 300 W, 150 ^{o}C, 10 bar for 30-45 min. Then the vial was cooled to room temperature, filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

General Procedure 2 (Two-step reaction):

Step 1 (Four component acyclic Ugi reaction):

In a 10 mL round-bottomed flask, 2-nitrobenzylamine (0.5g, 3.3 mmol) was dissolved in 5 mL of MeOH and 2,2-dimethylpropanal (0.237 mg, 3.3 mmol) was added. The mixture was stirred for 10 min. Then fumaric acid monoethyl ester (0.473 g, 3.3 mmol) and *tert*-butyl isocyanide (0.273 mg, 3.3 mmol) were added consecutively. The resulting solution was allowed to stir overnight at room temperature and then quenched with 1 mL of 1N HCl. To the mixture, 5 mL of CH_2Cl_2 was added and the reaction was vigorously stirred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were collected, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

Step 2 (Synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones):

To a 10 mL vial (CEM Discover System) equipped with a magnetic stir bar, 50 mg of the acyclic Ugi product from step 1 was added along with 1.8 mL of ethanol and 0.6 mL of distilled water. Then 10 equivalent of Fe(0) powder (40 mess) followed by 0.5-1.0 equivalent of NH_4Cl were added to the same vial. The vial was capped and placed in the microwave. The microwave was then run for 30-45 min at 150 ^{o}C, 10 bar and 300 W. Then the vial was cooled to room temperature and filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the

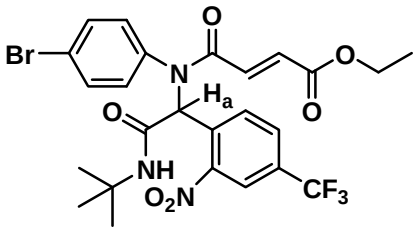
residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

Sealed Tube Reaction Condition (Synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones): :

To a 20 mL sealed tube equipped with a magnetic stir bar, 50 mg of the acyclic Ugi product (**5**) from step 1 was added along with 1.8 mL of ethanol and 0.6 mL of distilled water. Then 10 equivalent of Fe(0) powder (40 mess) followed by 0.5-1.0 equivalent of NH_4Cl were added to the same sealed tube. The sealed tube was placed in the silicone oil bath and heated at 200-205 ^oC for one hour. Then the sealed tube was cooled to room temperature and filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

N.B. : When the reaction was run for an extended period of time in the sealed tube, TLC showed extensive decomposition.

(*E*)-Ethyl 4-((4-bromophenyl)(2-(*tert*-butylamino)-1-(2-nitro-4-(trifluoromethyl)phenyl)-2-oxoethyl)-4-oxobut-2-enoate **(5)**.



(±)-5

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, aryl), 7.64 (d, 2H, *J* = 8.9 Hz, aryl), 7.58 (d, 1H, *J* = 8.1 Hz, aryl), 7.34 (d, 2H, *J* = 8.1 Hz, aryl), 7.10 (br s, 1H, -N<u>H</u>), 6.80 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>=CH-), 6.70 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 6.54 (s, 1H, aryl), 6.00 (s, 1H, H_a), 4.16 (q, 2H, *J* = 8.0 Hz, -OC<u>H_2</u>CH_3), 1.27 (s, 9H, *t*-butyl), 1.25 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>).

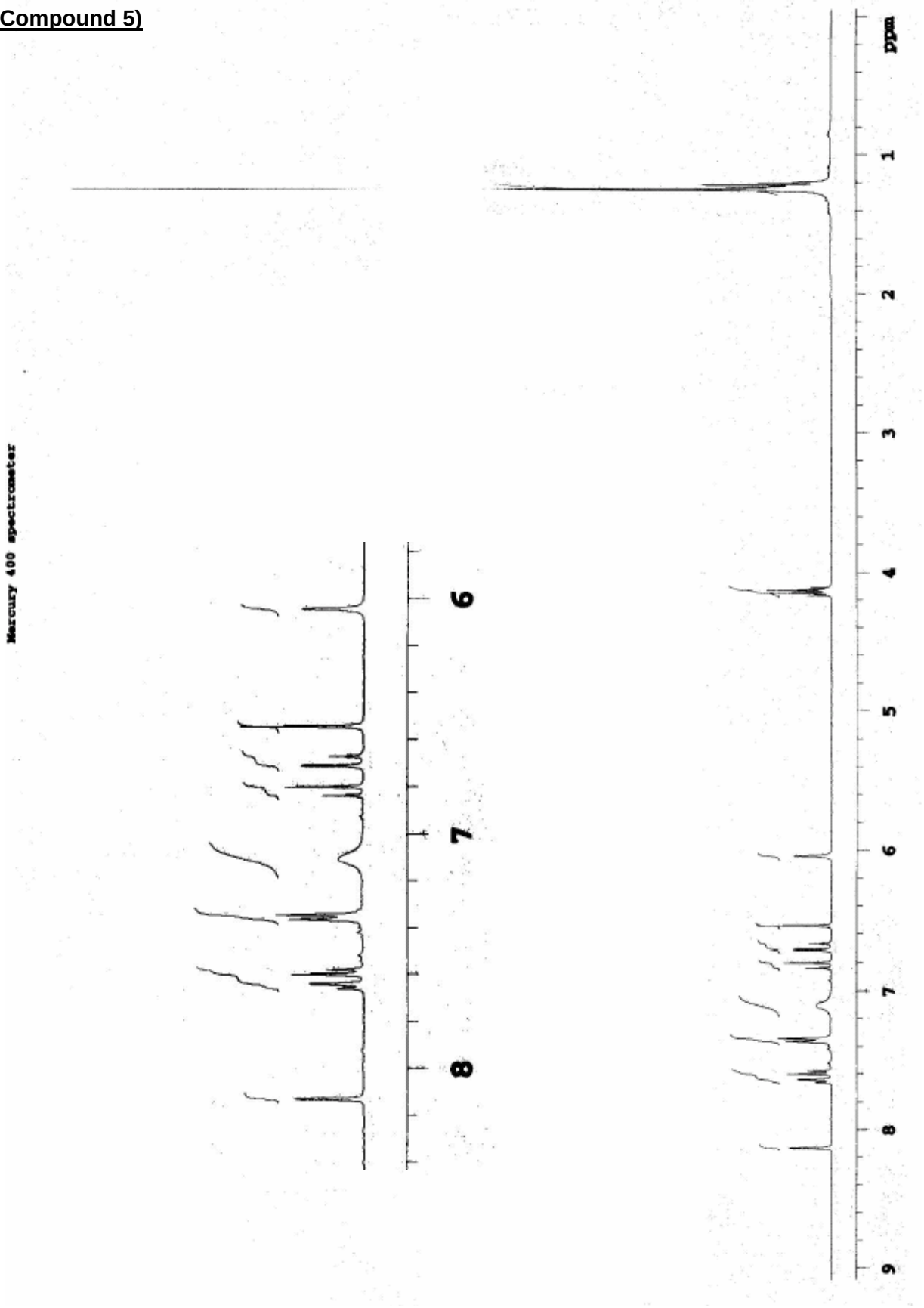
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 165.3, 164.7, 149.9, 137.2, 133.3, 133.2, 133.1, 133.0, 132.9, 132.7, 132.6, 131.6, 129.5, 129.4, 123.6 ($J_{C\text{-}F}$ = 272.2 Hz), 122.4, 122.3, 61.5, 61.1, 52.5, 28.6, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ - 63.51.

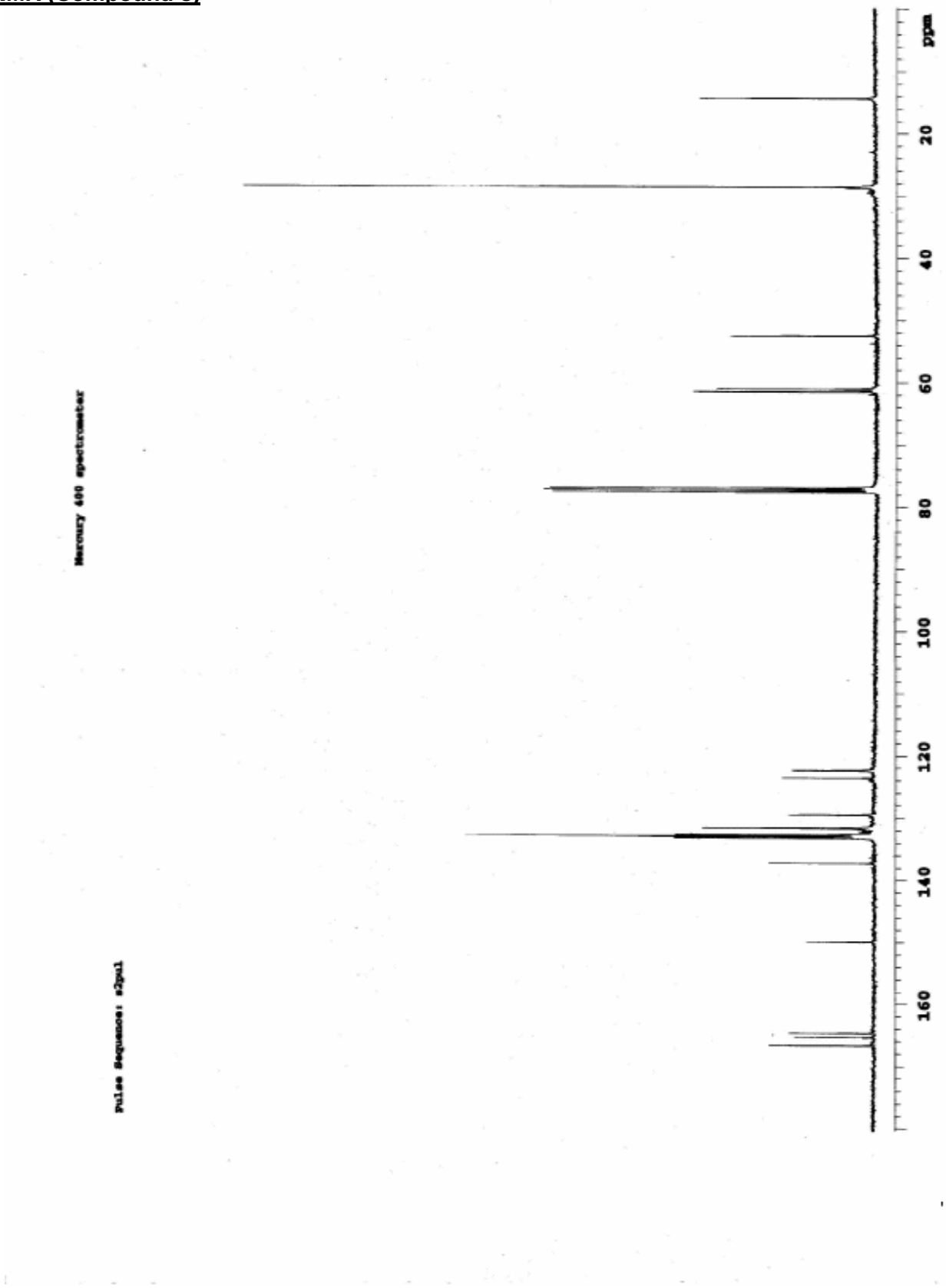
HRMS: EIMS (M^+) calcd for $C_{25}H_{25}BrF_3N_3O_6$ 599.0879 found 599.0889.

IR (neat): 3322, 3070, 2968, 2933, 1714, 1690, 1664, 1542, 1486, 1362, 1324, 1298, 1221, 1154, 1136, 1089, 1033, 975, 654.

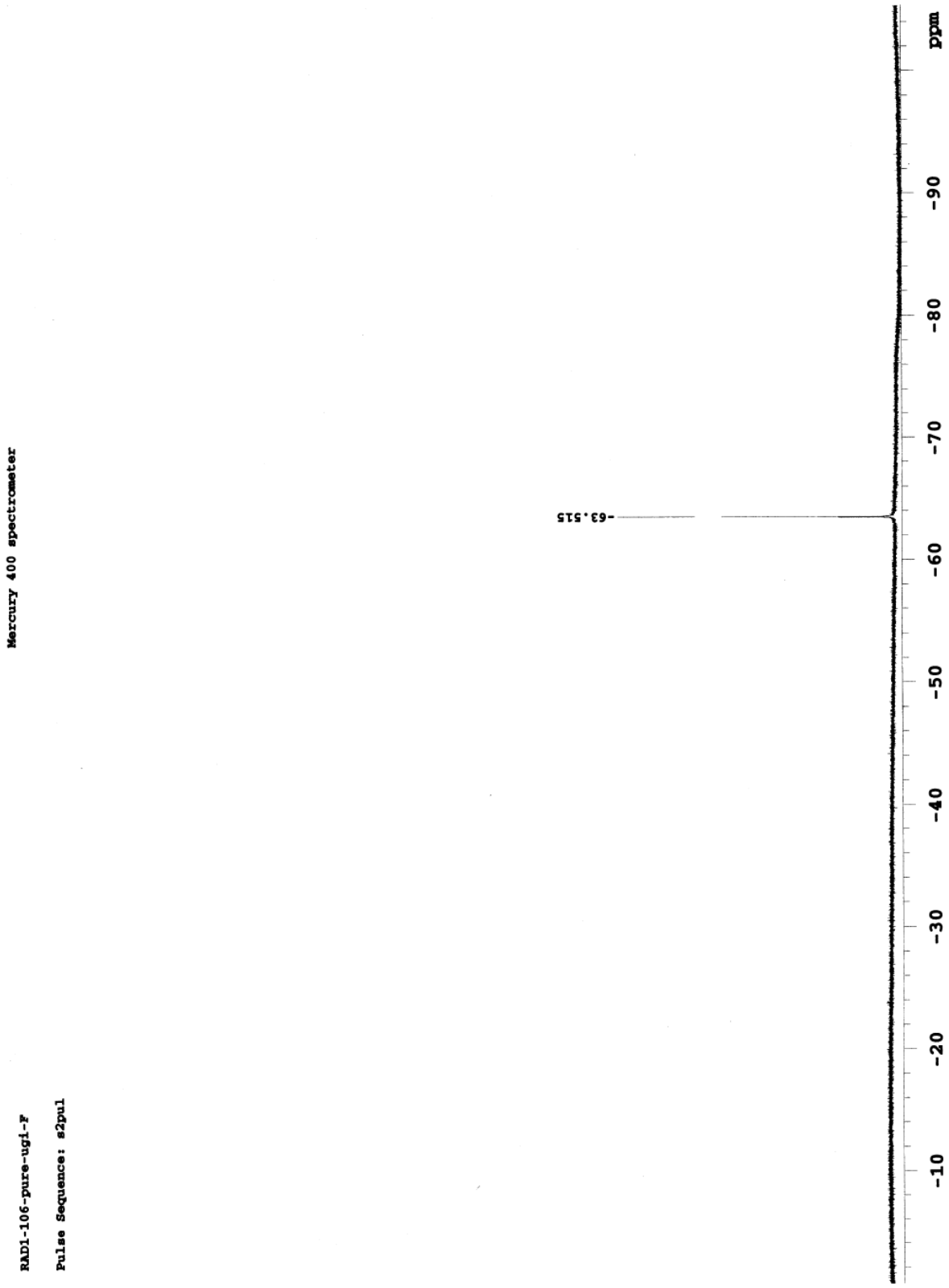
[1]H NMR (Compound 5)



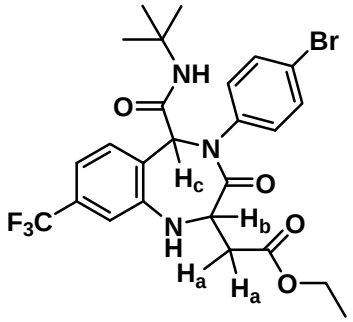
^{13}C NMR (Compound 5)



^{19}F NMR (Compound 5)



Ethyl 2-(4-(4-bromophenyl)-5-(*tert*-butylcaramoyl)-3-oxo-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)acetate **(6)**.[(a)]



(±)-6

^{1}H NMR (400 MHz, $CDCl_3$): **(major)** δ 8.43 (s, 1H, aryl), 7.79 (d, 1H, *J* = 8.1 Hz, aryl), 7.46 – 7.38 (m, 3H, aryl), 7.30 – 7.24 (m, 2H, aryl), 5.92 (s, 1H, H_c), 4.58 (m, 1H, H_b), 4.11 – 3.99 (m, 2H, -OC$\underline{H}_2$CH$_3$), 2.43 (dd, 1H, J_1 = 5.7 Hz, J_2 = 16.2 Hz, H_a), 2.28 (dd, 1H, , J_1 = 8.1 Hz, J_2 = 16.2 Hz, H_a), 1.23 (s, 9H, *t*-butyl), 1,17 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{1}H NMR (400 MHz, $CDCl_3$): **(minor)** δ 8.32 (s, 1H, aryl), 7.43 (d, 1H, *J* = 8.1 Hz, aryl), 7.46 – 7.38 (m, 3H, aryl), 7.30 – 7.24 (m, 2H, aryl), 6.88 (s, 1H, H_c), 4.58 (m, 1H, H_b), 4.28 – 4.20 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.29 (dd, 1H, J_1 = 4.8 Hz, J_2 = 17.2 Hz, H_a), 2.28 (dd, 1H, , J_1 = 7.3 Hz, J_2 = 18.1 Hz, H_a), 1.31 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 1.21 (s, 9H, *t*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): **(major and minor)** δ 172.3, 169.7, 165.8, 165.6, 165.4, 163.3, 150.0, 135.9, 135.7, 132.9, 132.8, 132.7, 130.6, 129.9, 129.8, 129.6, 128.4, 124.0 (q, $^1J_{C\text{-}F}$ = 270.7 Hz), 123.0, 122.9,122.8, 119.1, 119.0, 118.4, 76.9, 71.5, 62.2, 61.6, 61.0, 58.5, 53.4, 53.1, 31.9, 31.2, 29.9, 28.6, 28.5, 14.3, 14.2.

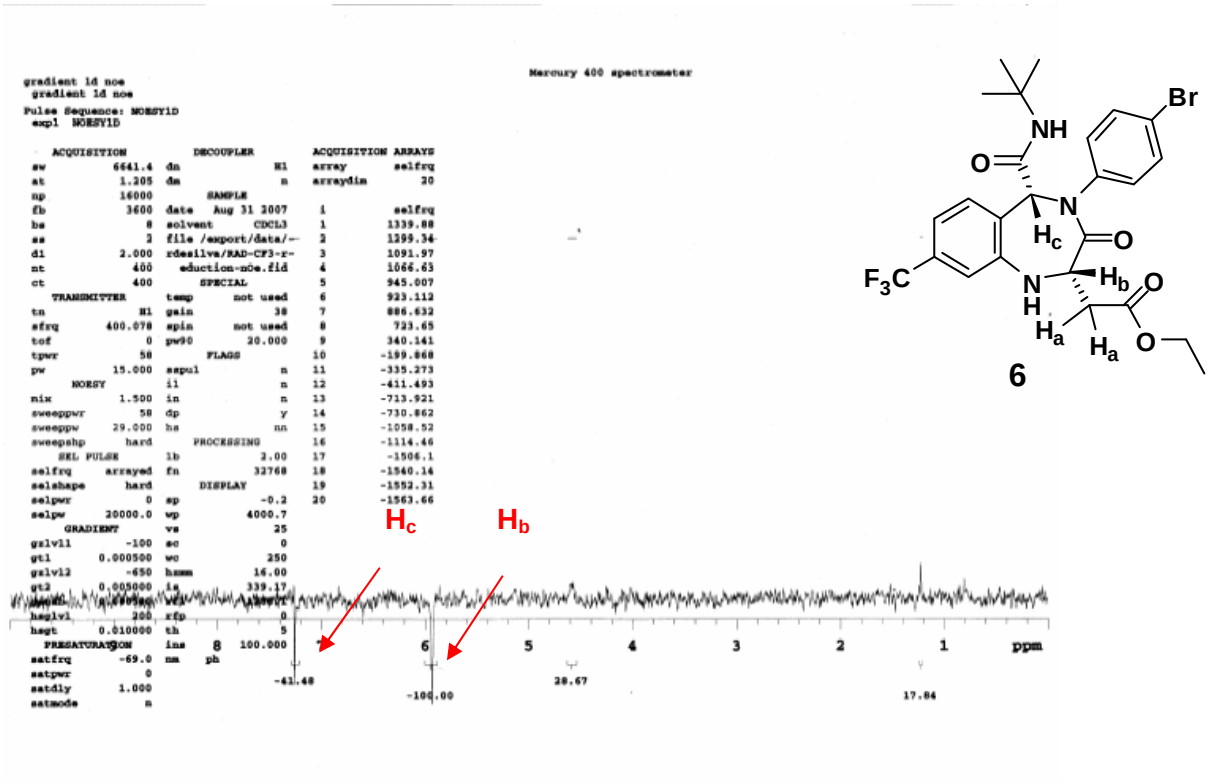
^{19}F NMR (282 MHz, $CDCl_3$): δ – 63.50 (major), - 63.52 (minor).

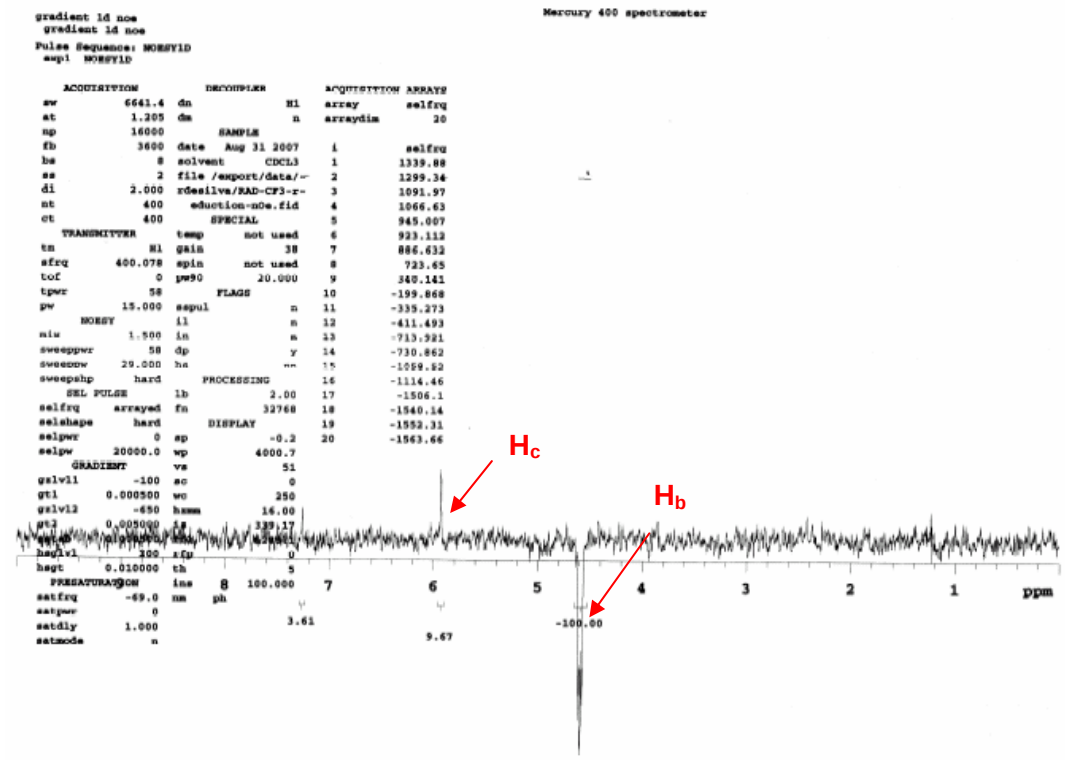
HRMS: EIMS (M^+) calcd for $C_{25}H_{27}BrF_3N_3O_4$ 569.1137 found 569.1130.

IR (neat): 3362, 3019, 2924, 1738, 1738, 1715, 1604, 1456, 1364, 1219, 1046, 968, 747, 676.

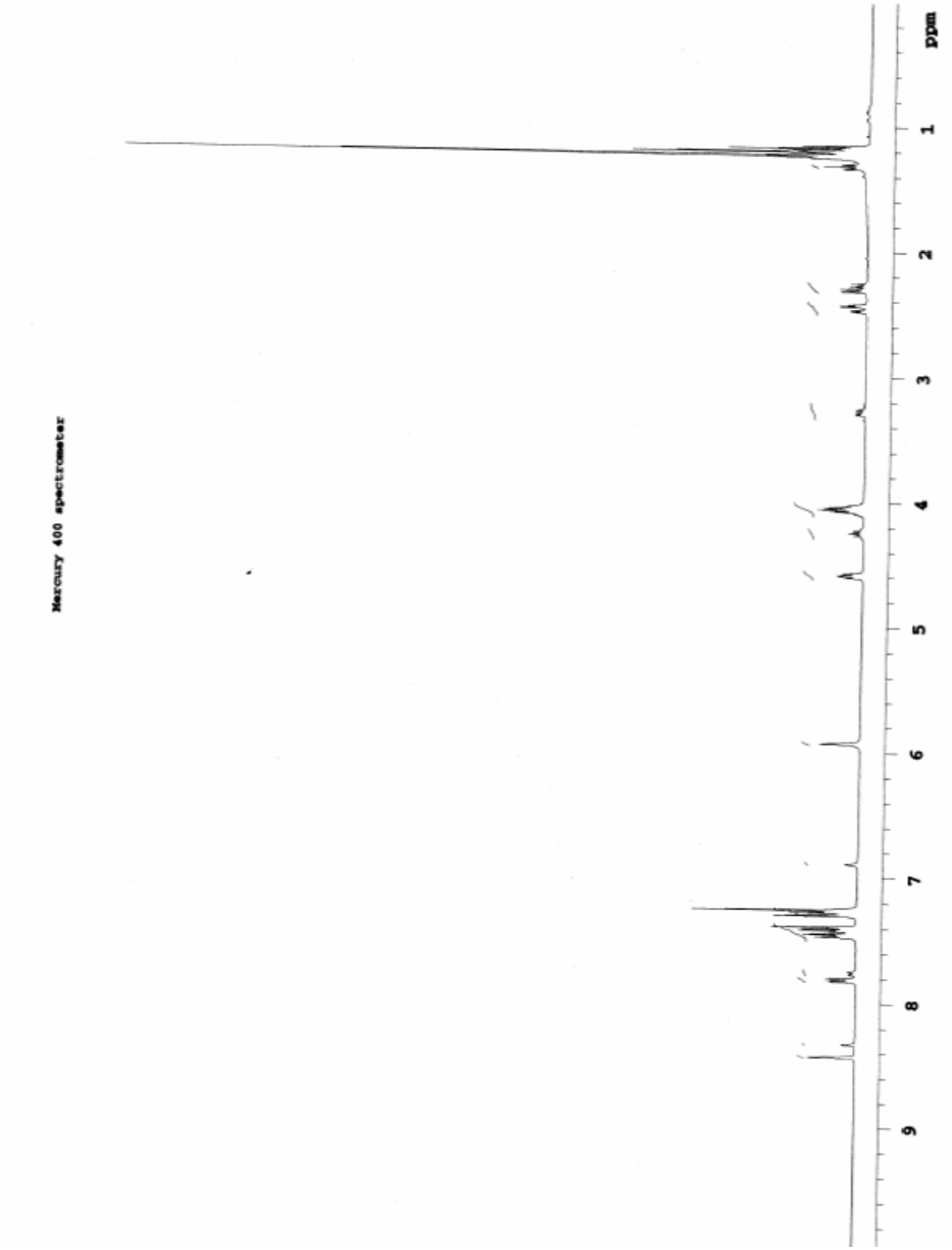
(a) NOe data obtained for the major diastereomer of **6** corresponds well with the published data of a similar structure indicating a *cis* relationship between C_2 and C_5 substituents. See: Ma, D. *et al.*, *Bioorg. Med. Chem. Lett*., **1999**, *9*, 1371-1374.

NOe data for the major diastereomer (compound 6)

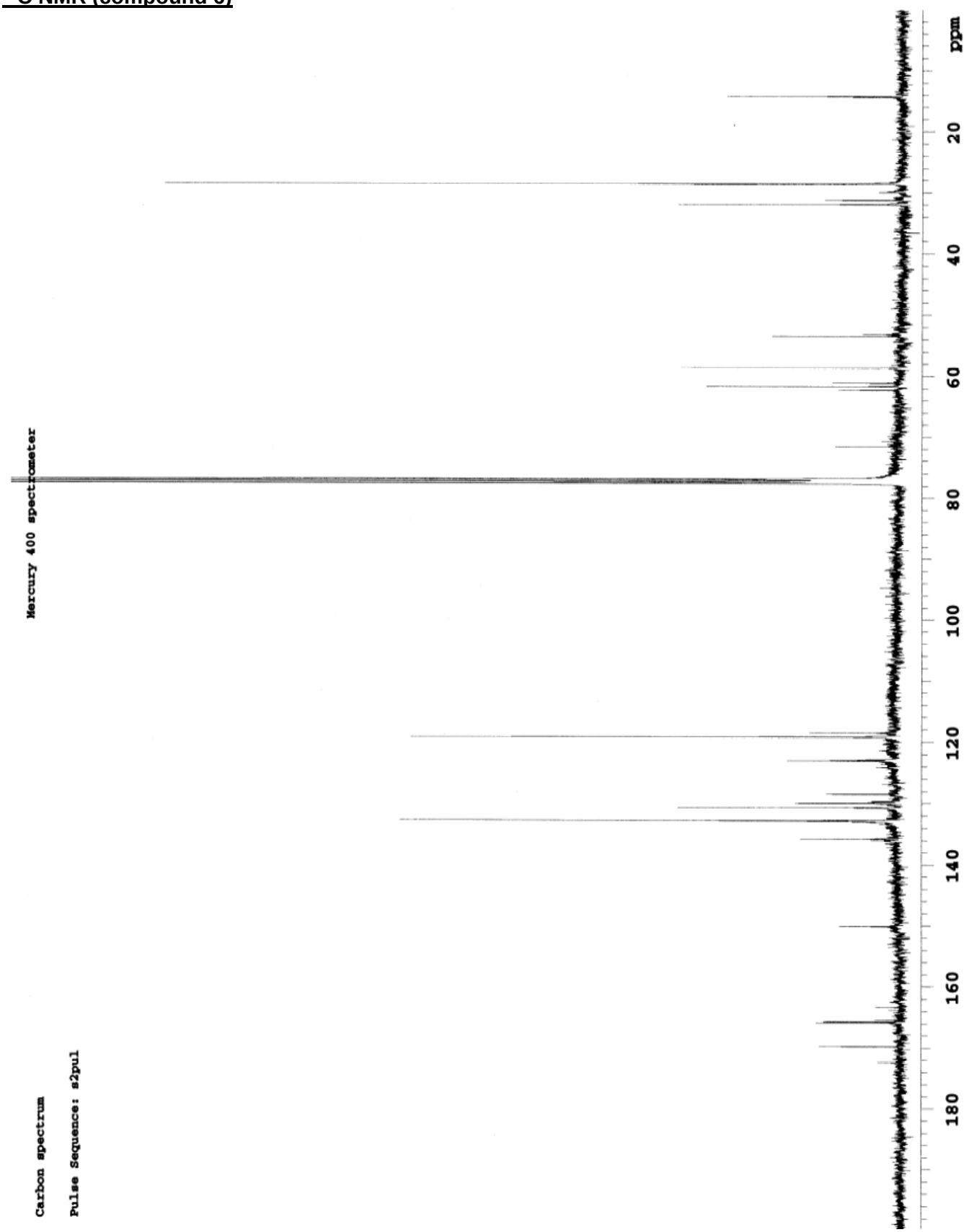




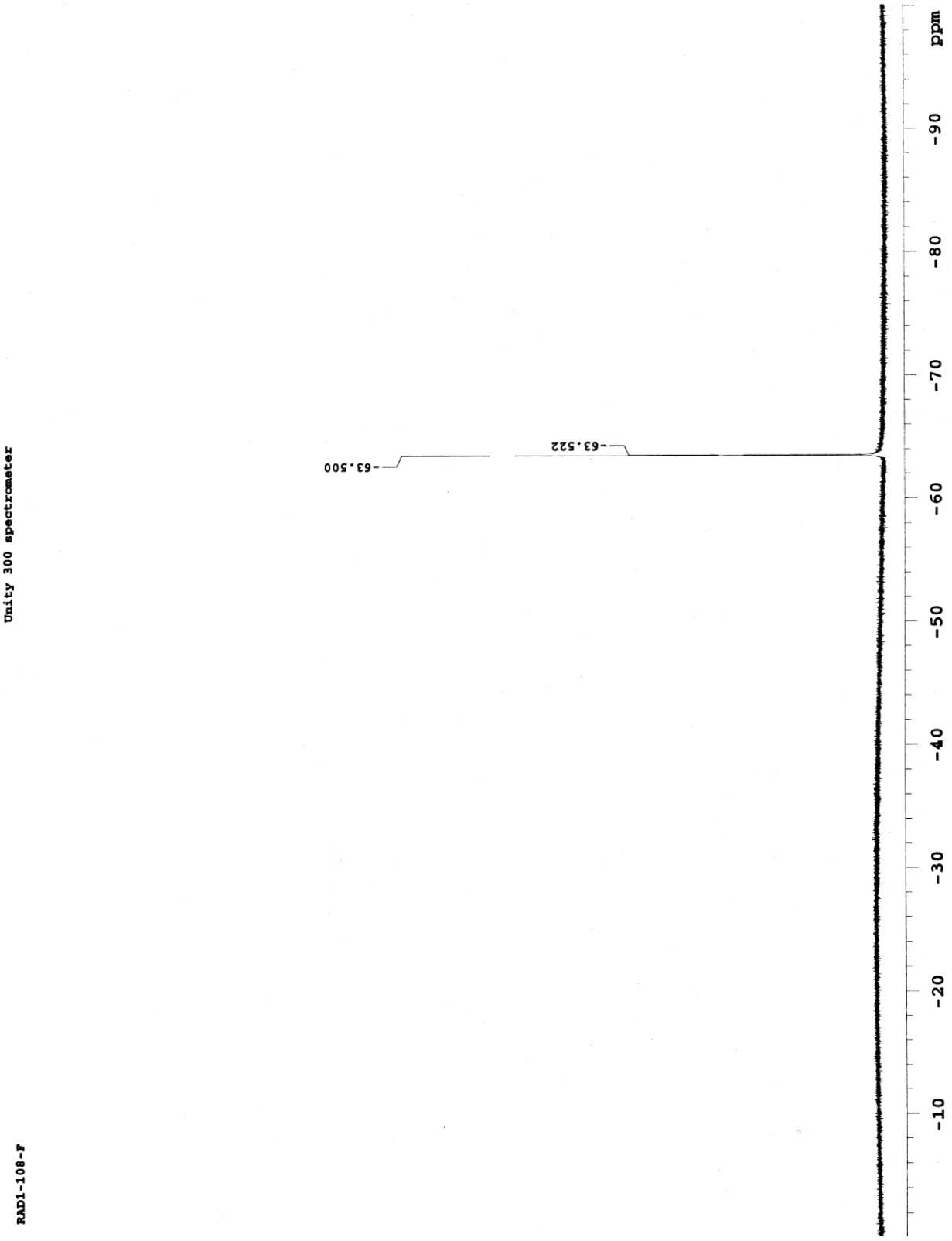
[1]H NMR (compound 6)



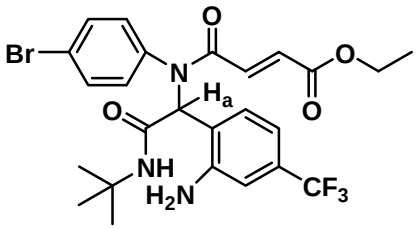
^{13}C NMR (compound 6)



^{19}F NMR (Compound 6)



(*E*)-ethyl 4-((1-(2-amino-4-(trifluoromethyl)phenyl)-2-(*tert*-butylamino)-2-oxoethyl)(4-bromophenyl) amino)-4-oxobut-2-enoate **(7)**.



(±)-7

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>=CH-), 6.84 (m, 2H, aryl), 6.74 (m, 3H, aryl), 6.65 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 6.56 (s, 1H, aryl), 6.24 (s, 1H, aryl), 5.40 (s, 1H, H_a), 4.24 (s, 2H, -N<u>H</u>$_2$), 4.16 (q, 2H, *J* = 8.0 Hz, -OC<u>H</u>$_2$CH$_3$), 1.27 (s, 9H, *t*-butyl), 1.21 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

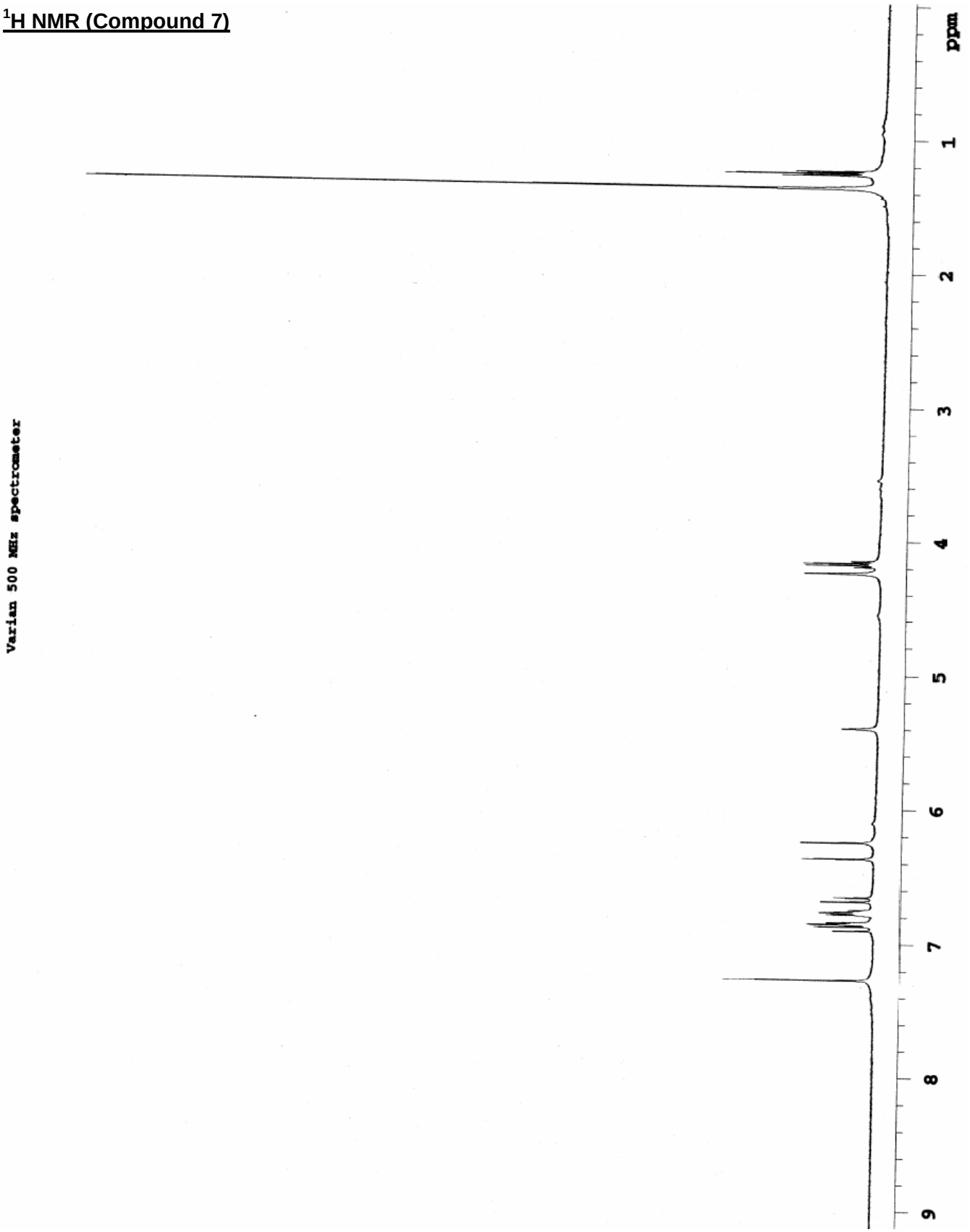
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 167.0, 166.0, 137.6, 133.4, 133.3, 133.2, 133.1, 133.0, 132.9, 132.8, 132.7, 132.2, 131.7, 131.6, 123.6, 119.4 ($^1J_{C\text{-}F}$ = 270.6 Hz), 118.7, 61.5, 59.7, 47.9, 28.6, 19.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ – 63.51.

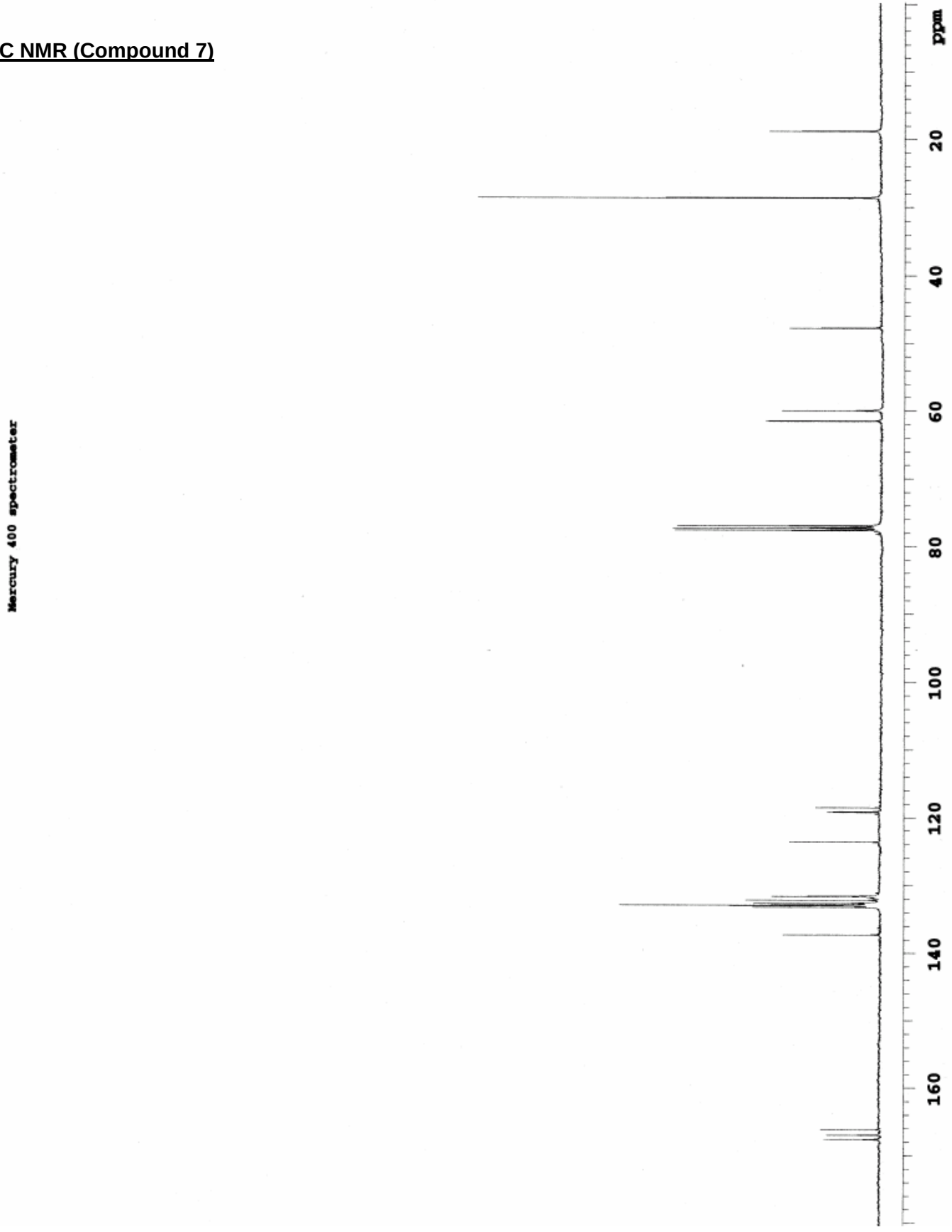
HRMS: EIMS (M^+) calcd for $C_{25}H_{27}BrF_3N_3O_4$ 569.1137 found 569.1139.

IR (neat): 3402, 3270, 3068, 2963, 1716, 1681, 1367, 1244, 1159, 1064, 784, 751.

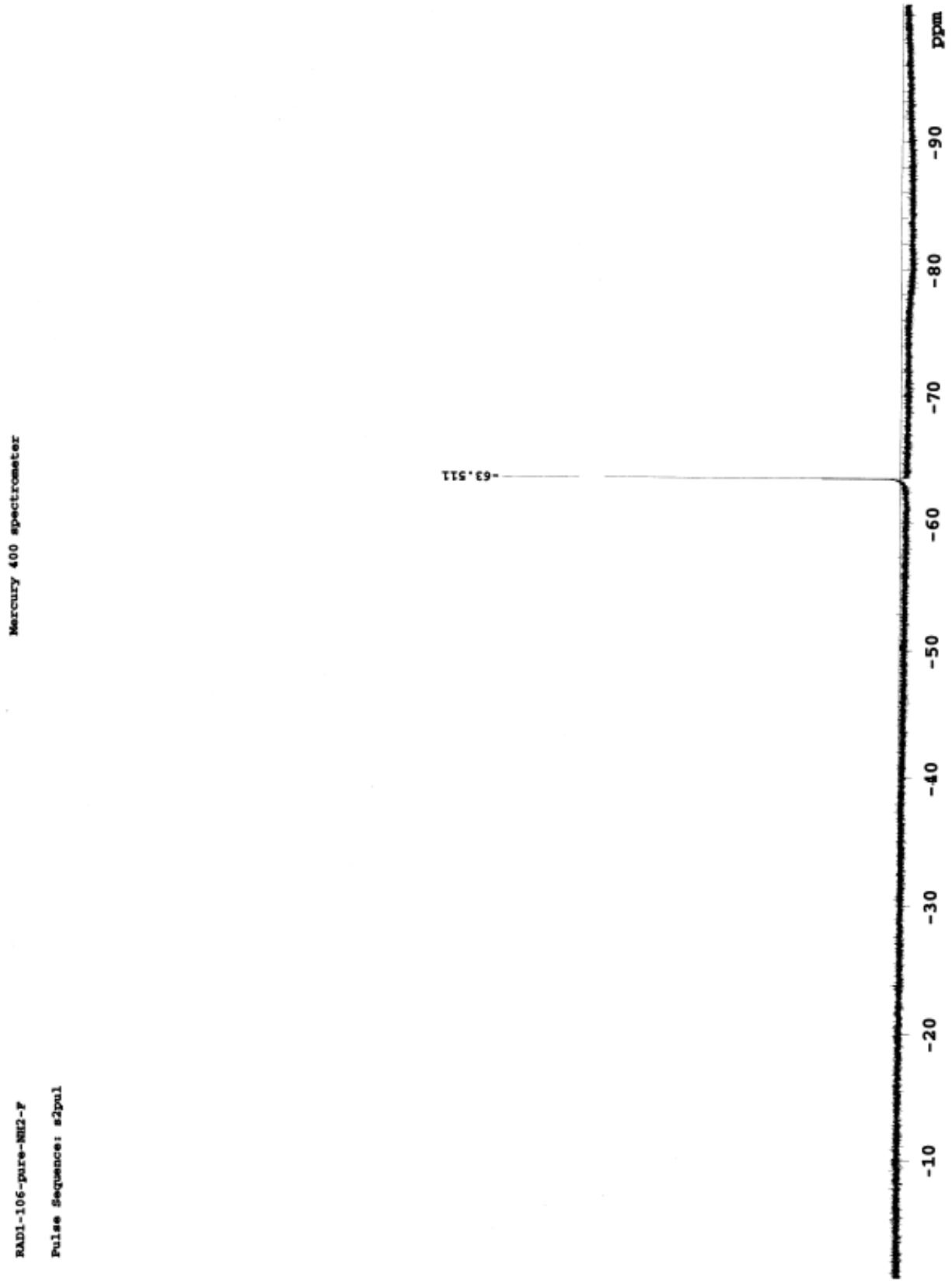
^{1}H NMR (Compound 7)



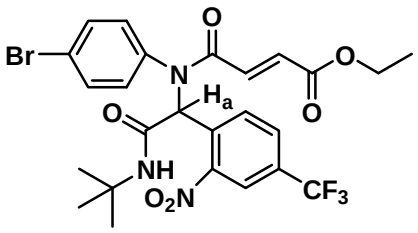
^{13}C NMR (Compound 7)



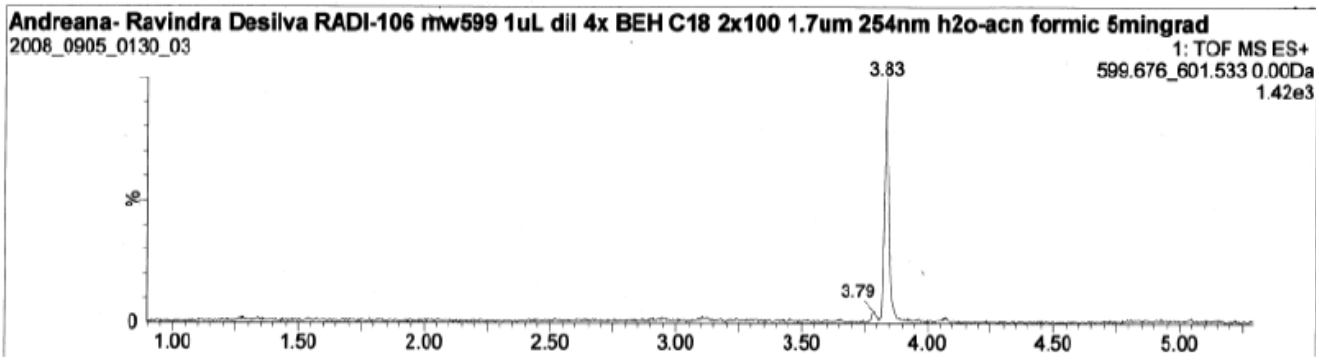
^{19}F NMR (Compound 7)



LC-MS Data for Thermal (Sealed Tube) Cyclization of Compound 5 to 6



(±)-5

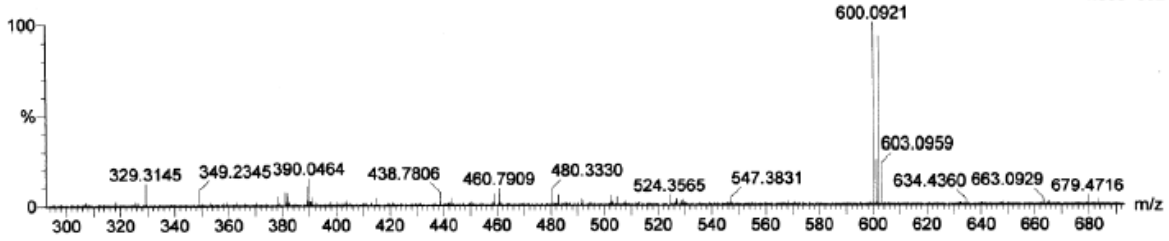


Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
613 formula(e) evaluated with 2 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-25 H: 0-1000 N: 0-4 O: 0-6 F: 0-3 23Na: 0-1 Br: 0-1

Andreana- Ravindra Desilva RADI-106 mw599 1uL dil 4x BEH C18 2x100 1.7um 254nm h2o-acn formic 5mingrad
DOPH
2008_0905_0130_03 1287 (3.869) Cm (1283:1289-1318:1339x2.000)
LCT Premier 05-Sep-2008 15:20:08
1: TOF MS ES+
4.65e+002



Minimum:				-1.5			
Maximum:		5.0	20.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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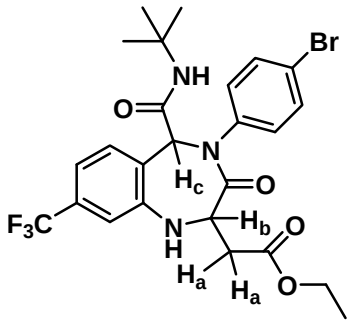
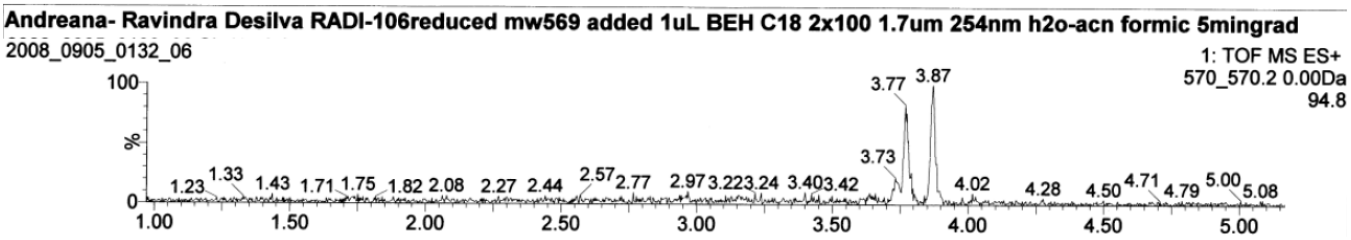
	600.0957	-3.6	-6.0	12.5	27.4	1.0	C25 H26 N3 O6 F3 Br


Br
NH
O
N
H_c
O
F_3C
N
H
H_b
O
H_a
H_a
O

(±)-6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2008_0905_0132_06
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570_570.2 0.00Da
94.8
100
%
0
3.77
3.87
3.73
1.23
1.33
1.43
1.71
1.75
1.82
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2.44
2.57
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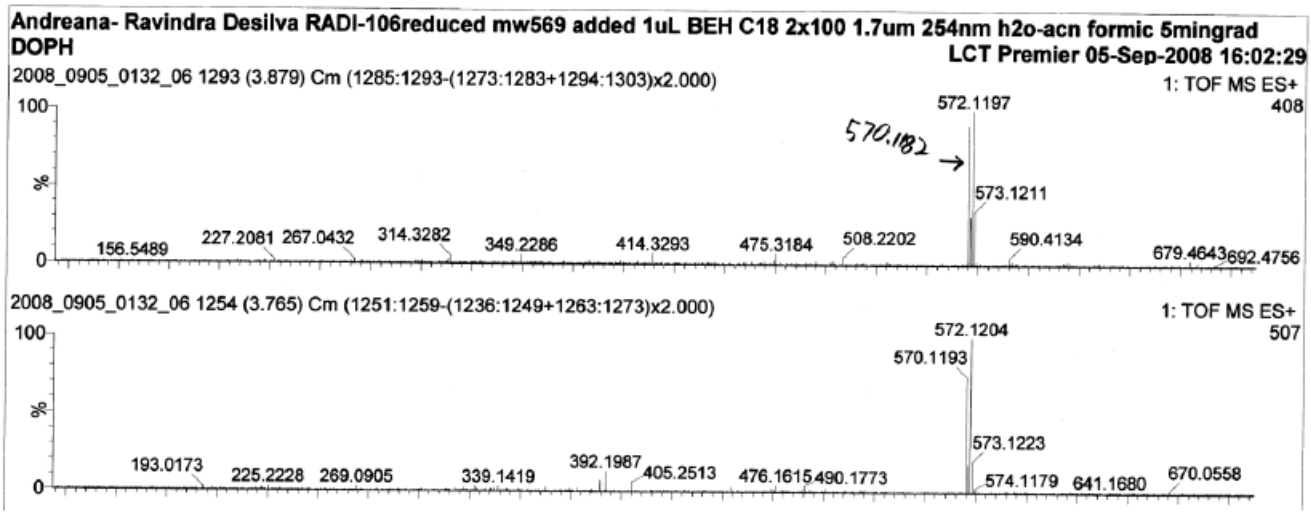
5.00


Andreana- Ravindra Desilva RADI-106reduced mw569 added 1uL BEH C18 2x100 1.7um 254nm h2o-acn formic 5mingrad
DOPH
LCT Premier 05-Sep-2008 16:02:29
2008_0905_0132_06 1293 (3.879) Cm (1285:1293-(1273:1283+1294:1303)x2.000)
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100
%
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314.3282
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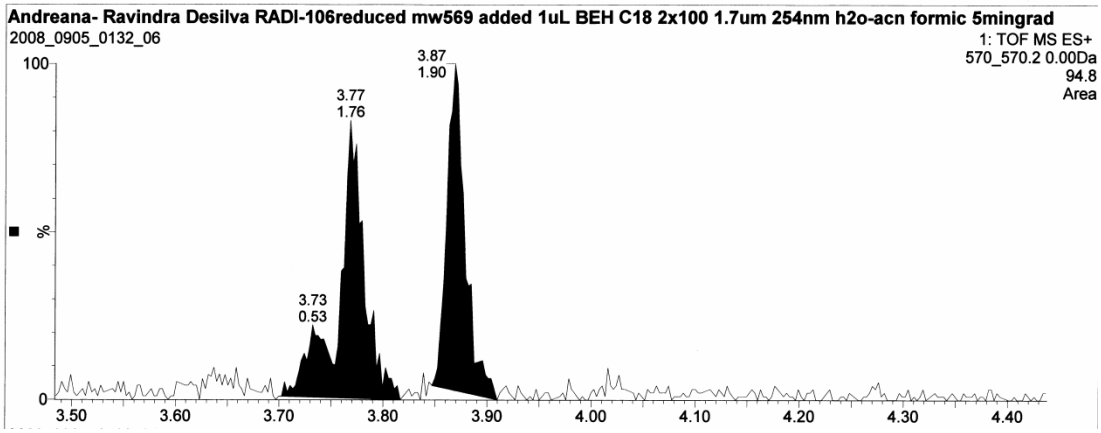
Andreana- Ravindra Desilva RADI-106reduced mw569 added 1uL BEH C18 2x100 1.7um 254nm h2o-acn formic 5mingrad
2008_0905_0132_06
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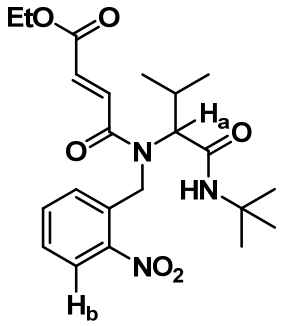
Area
100
%
0
3.87
1.90
3.77
1.76
3.73
0.53
3.50
3.60
3.70
3.80
3.90
4.00
4.10
4.20
4.30
4.40

(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(2-nitrobenzyl)amino)-4-oxobut-2-enoate **(8)**.



(±)-8

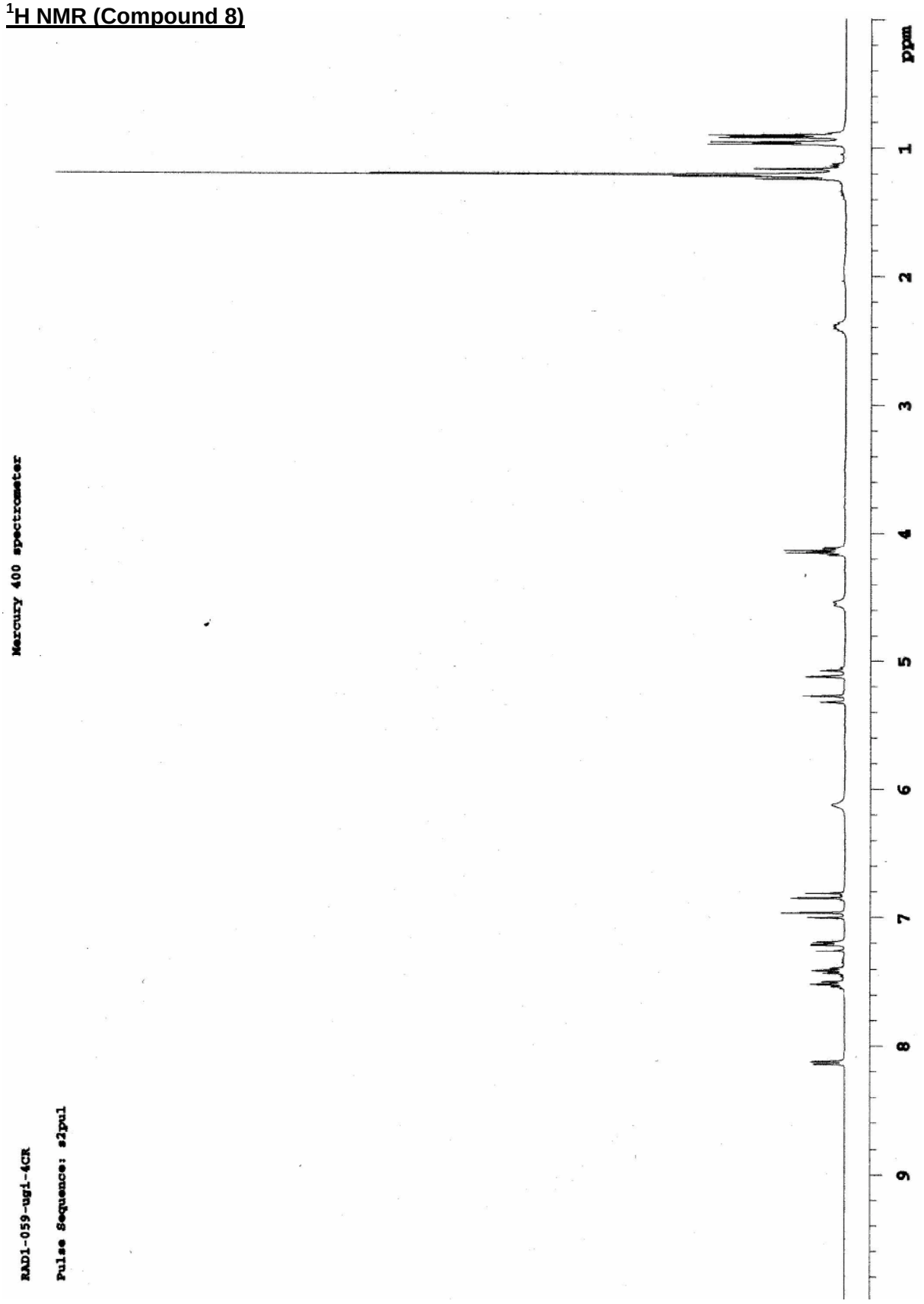
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d,1H, H_b), 7.51 (dd, 1H, J_1 = 7.1 Hz, J_2 = 6.48 Hz, aryl), 7.41 (dd, 1H, J_1 = 10.5, J_2 = 7.3, aryl), 7.20 (d, 1H, J = 8.1 Hz, aryl), 6.98 (d, 1H, J = 14.6 Hz, -C<u>H</u>=CH-), 6.82 (d, 1H, J = 14.6 Hz, -CH=C<u>H</u>-), 6.12 (br s, 1H, -N<u>H</u>), 5.30 (d, 1H, J = 18.7 Hz, Bn), 5.10 (d, 1H, J = 19.7 Hz, Bn), 4.55 (d, 1H, J = 10.5 Hz, H_a), 4.13 (m, 2H, -OC<u>H_2</u>CH_3), 2.38 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.20 (m, 12H, -OCH_2C<u>H_3</u> and *t*-butyl overlap), 0.95 (d, 3H, J = 6.5 Hz, -CH(C<u>H_3</u>$)_2$), 0.90 (d, 3H, J = 7.3 Hz. -CH(C<u>H_3</u>$)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 166.7, 165.0, 133.8, 133.6, 133.2, 132.6, 128.2, 128.0, 127.9, 125.6, 61.2, 51.5, 46.0, 28.5, 28.4, 27.9, 19.2, 18.6, 14.0.

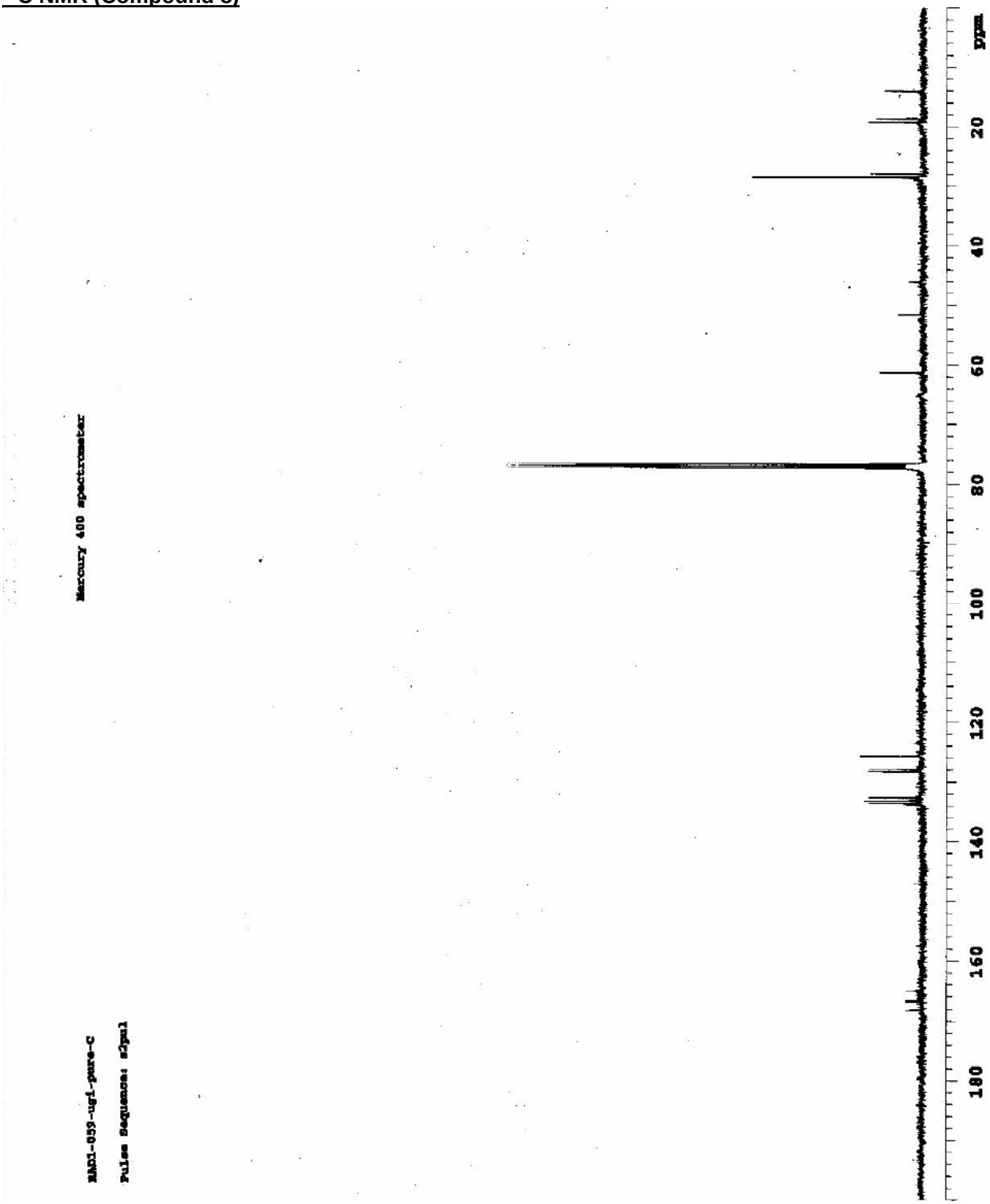
HRMS: EIMS (M^+) calcd for $C_{22}H_{31}N_3O_6$ 433.2213, found 433.2210.

IR (neat): 3322, 3071, 2968, 2934, 1720, 1678, 1655, 11528, 1449, 1365, 1296, 1218, 1178, 971, 731.

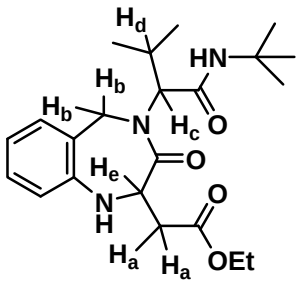
^{1}H NMR (Compound 8)



^{13}C NMR (Compound 8)



Ethyl 2-(4-(1-(tert-butylamino)-3-methyl-1-oxobutan-2-yl)-3-oxo-2,3,4,5-tetrahydro-1H-benzo[*e*][1,4]diazepin-2-yl)acetate **(9)**.[(b)]



(±)-9

^{1}H NMR (400 MHz, $CDCl_3$): (**major**) δ 6.70 (t, 1H, *J* = 7.3 Hz, aryl), 6.65 (t, 1H, *J* = 7.3 Hz, aryl), 6.53 (d, 1H, *J* = 7.2 Hz, aryl), 6.50 (d, 1H, *J* = 8.1 Hz, aryl), 5.64 (s, 1H, -NH), 5.08 (d, 1H, *J* = 17.0 Hz, H_b), 5.00 (d, 1H, *J* = 7.3 Hz, H_c), 4.54 (d, 1H, *J* = 17.0 Hz, H_b), 4.42 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.1 Hz, H_e), 4.16 (m, 2H, -OC$\underline{H}_2$CH$_3$), 2.70 (dd, 1H, J_1 = 10.1 Hz, J_2 = 5.7 Hz, H_a), 2.60 (dd, 1H, J_1 = 11.0 Hz, J_2 = 4.9 Hz, H_a), 2.20 (m, 1H, H_d), 1.27 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.94 (s, 9H, *t*-butyl), 0.80 (d, 3H, *J* = 6.8 Hz, -CH(C$\underline{H}_3$)$_2$), 0.50 (d, 3H, *J* = 6.8 Hz, -CH(C$\underline{H}_3$)$_2$).

^{1}H NMR (400 MHz, $CDCl_3$): (**minor**) δ 7.10 (t, 1H, *J* = 7.3 Hz, aryl), 7.00 (t, 2H, *J* = 7.3 Hz, aryl), 6.90 (d, 1H, *J* = 8.1 Hz, aryl), 5.70 (s, 1H, -NH), 5.20 (d, 1H, *J* = 17.0 Hz, H_b), 5.10 (d, 1H, *J* = 17.0 Hz, H_b), 5.00 (d, 1H, *J* = 7.0 Hz, H_c), 4.42 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.1 Hz, H_e), 4.16 (m, 2H, -OC$\underline{H}_2$CH$_3$), 2.90 (dd, 2H, J_1 = 15.8 Hz, J_2 = 6.5 Hz, H_a), 2.40 (m, 1H, H_d), 1.32 (s, 9H, *t*-butyl), 1.28 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.97 (d, 3H, *J* = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$), 0.90 (d, 3H, *J* = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$).

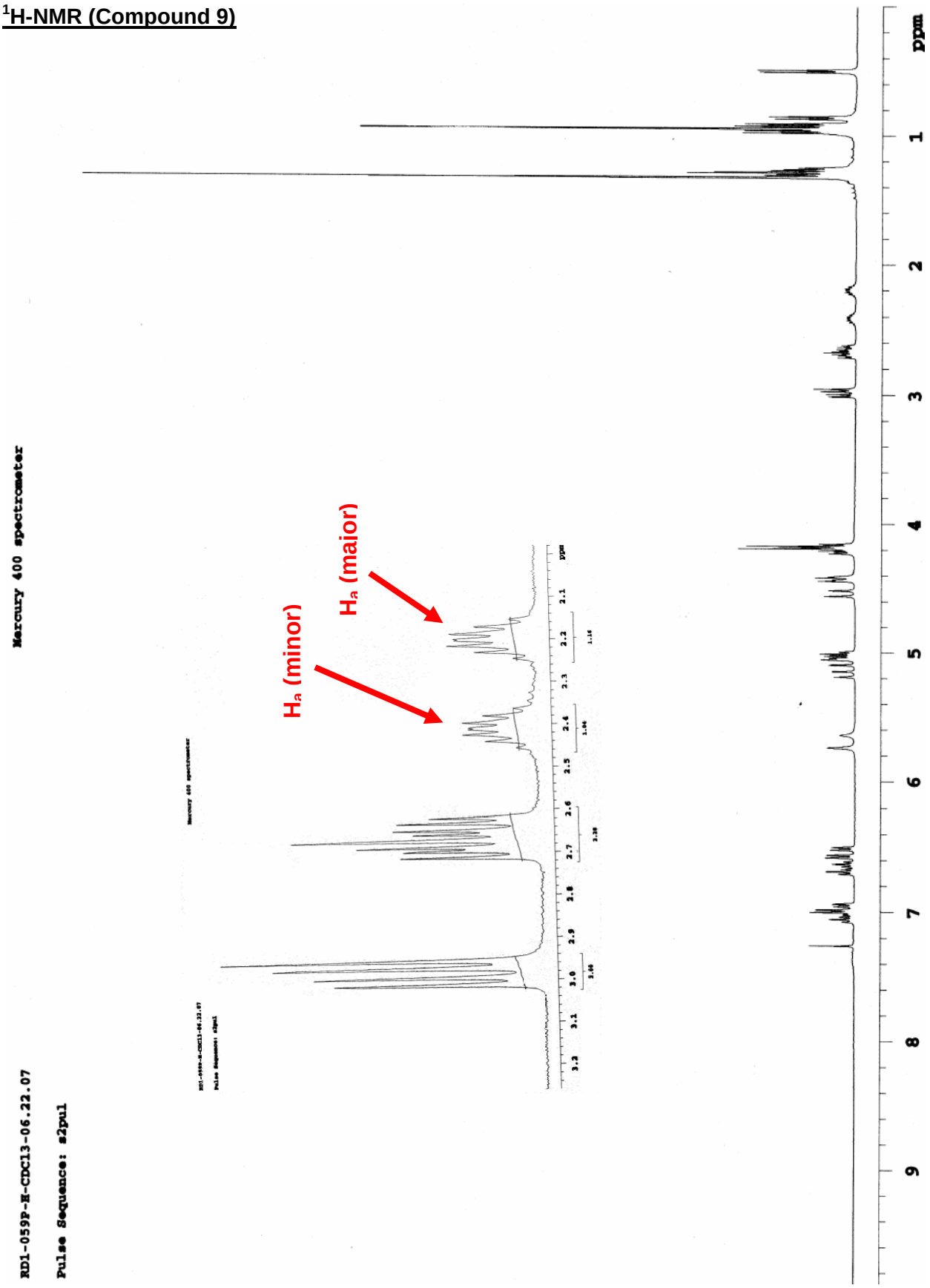
^{13}C NMR (100 MHz, $CDCl_3$): (**major and minor**) δ 171.6, 171.3, 171.1, 170.5, 169.4, 168.2, 144.9, 144.6, 131.2, 129.6, 128.8, 120.9, 119.8, 119.3, 119.1, 118.7, 117.3, 116.8, 63.7, 62.8, 60.9, 60.8, 59.7, 52.3, 51.5, 51.4, 50.9, 46.6, 46.2, 36.17, 36.1, 29.6, 28.5, 28.3, 28.0, 27.3, 25.9, 19.5, 18.6, 18.4, 14.2, 14.1.

HRMS: EIMS (M^+) calcd for $C_{22}H_{33}N_3O_4$ 403.2471 found 403.2472.

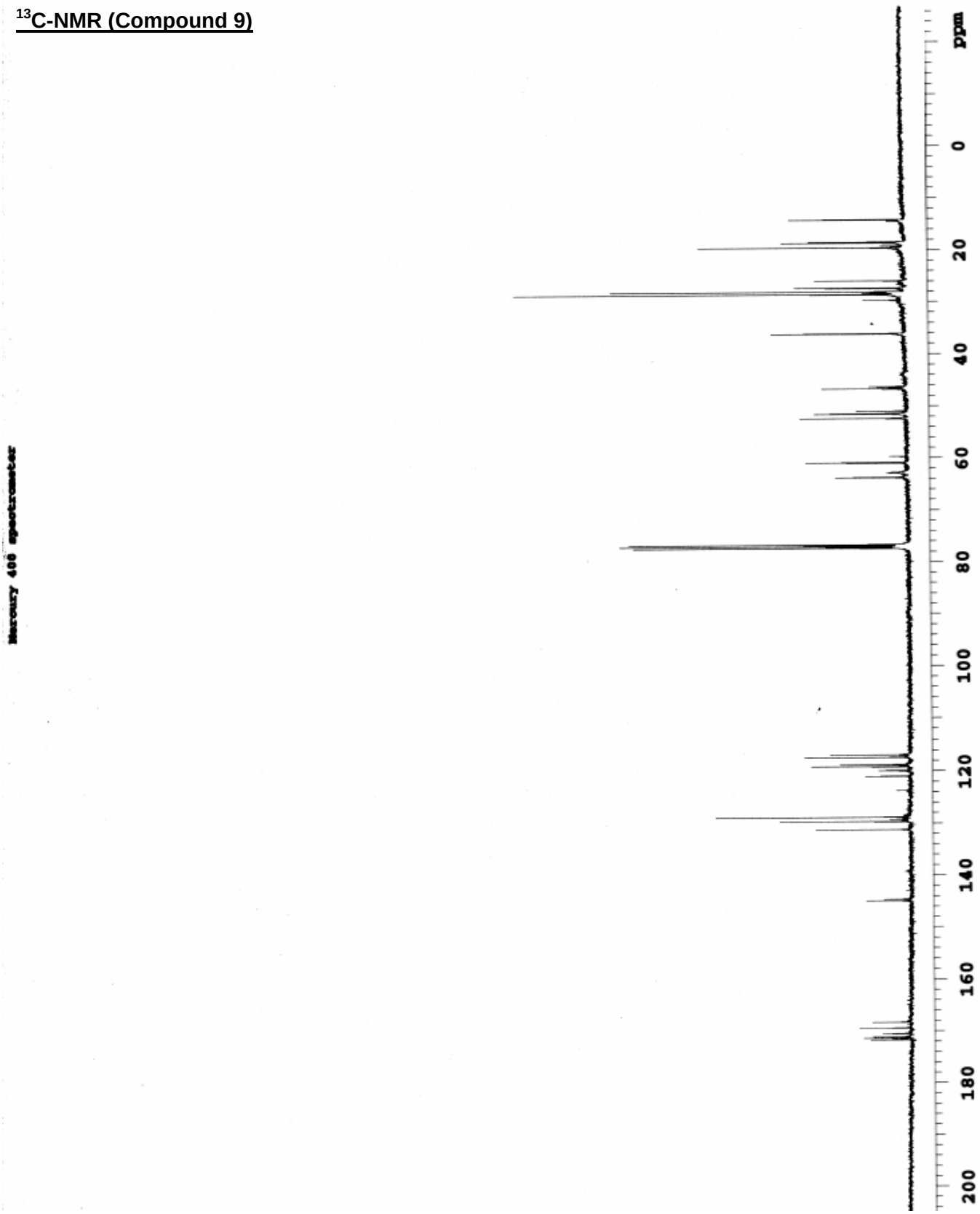
IR (neat): 3339, 3066, 2967, 2873, 1714, 1635, 1612, 1537, 1426, 1362, 1204, 1043, 752.

(b) Diastereomeric ratios for this compound and all the other 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones are based on the peak areas of H_a (major) and H_a (minor) of ^{1}H-NMR of crude products.

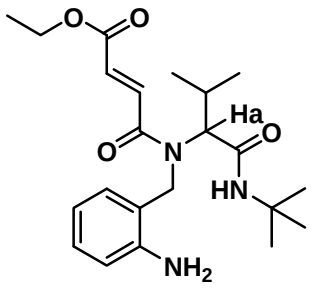
^{1}H-NMR (Compound 9)



^{13}C-NMR (Compound 9)



(*E*)-ethyl-4((2-aminobenzyl)(1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate **(10)**.



(±)-10

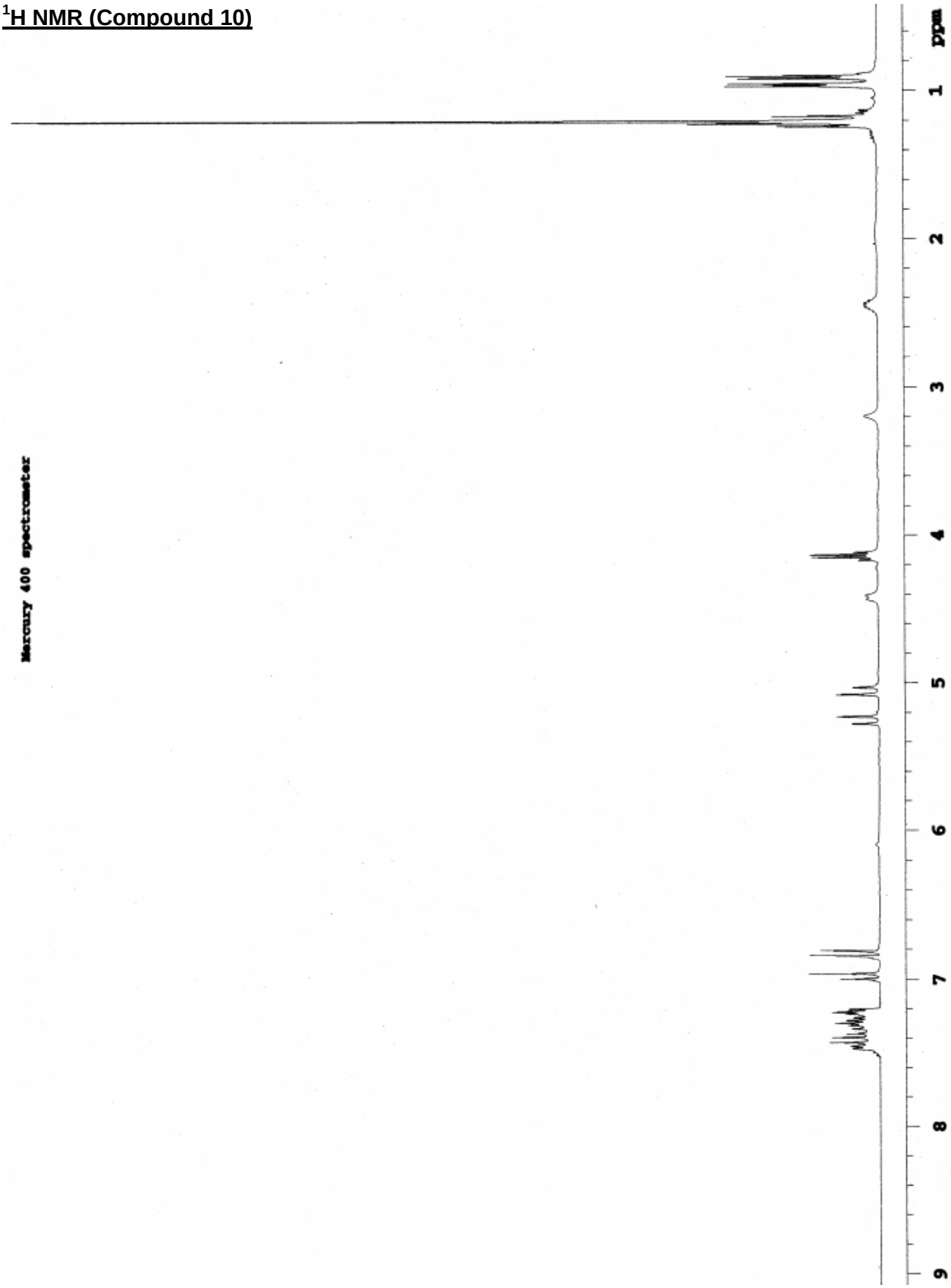
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.20 (M, 4H, aryl), 7.41 (dd, 1H, J_1 = 10.5, J_2 = 7.3, aryl), 6.98 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>=CH-), 6.83 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 5.25 (d, 1H, *J* = 18.7 Hz, Bn), 5.00 (d, 1H, *J* = 19.5 Hz, Bn), 4.40 (d, 1H, *J* = 10.6 Hz, H_a), 4.13 (m, 2H, -OC<u>H_2</u>CH_3), 3.20 (br s, 2H, -N<u>H_2</u>), 2.42 (m, 1H, -C<u>H</u>$(CH_3)_2$), 1.20 (m, 12H, -OCH_2C<u>H_3</u> and *t*-butyl overlap), 0.95 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H_3</u>$)_2$), 0.90 (d, 3H, *J* = 7.3 Hz, -CH(C<u>H_3</u>$)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 166.8, 165.0, 131.8, 131.0, 130.9, 130.6, 130.3, 129.5, 129.0, 128.6, 61.2, 61.1, 51.8, 46.0, 28.9, 28.2, 27.8, 19.2, 18.6, 14.2.

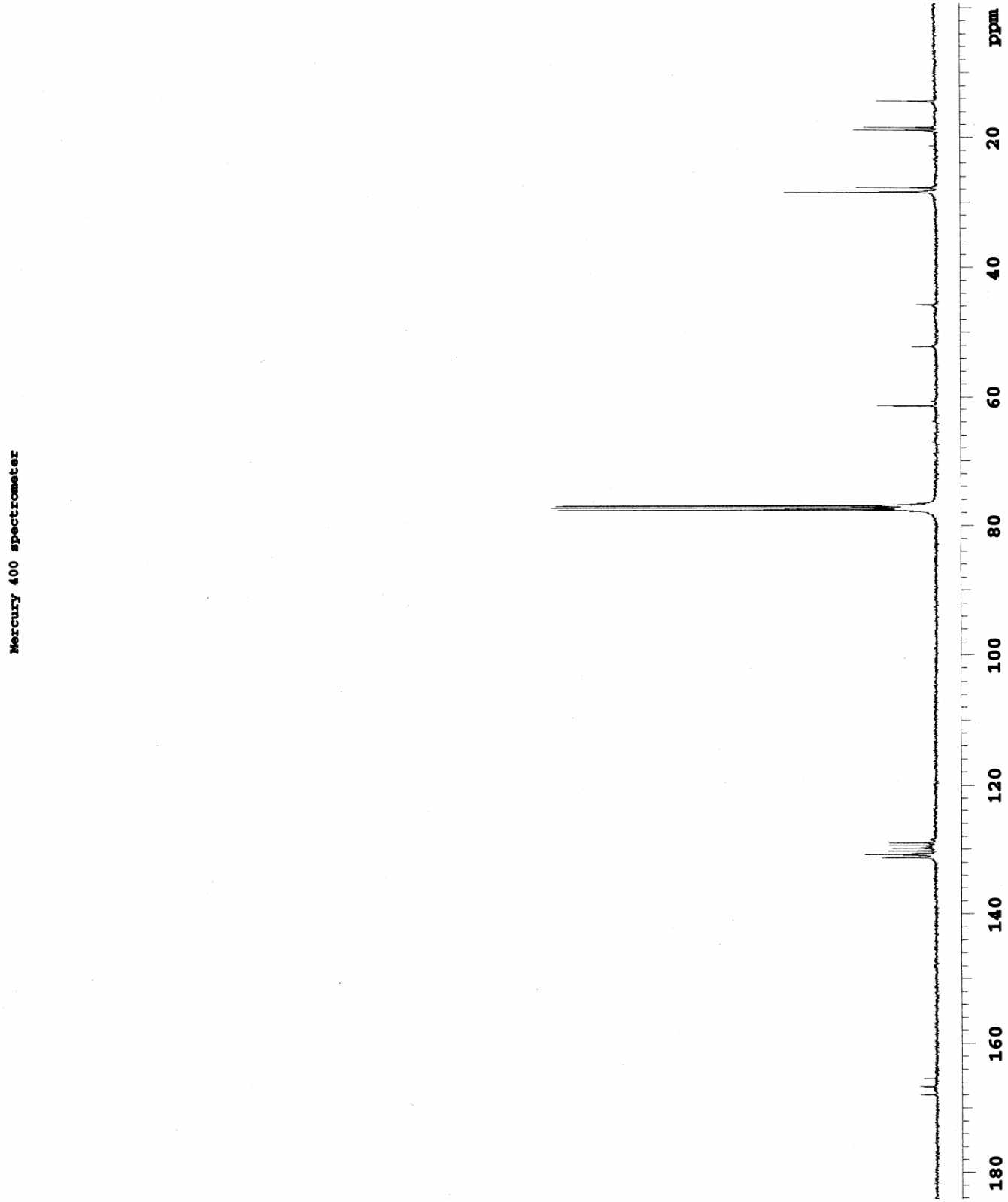
HRMS: EIMS (M^+) calcd for $C_{22}H_{33}N_3O_4$ 403.2471 found 403.2480.

IR (neat): 3452, 3400, 3021, 2814, 1690, 1600, 1537, 1290 1060.

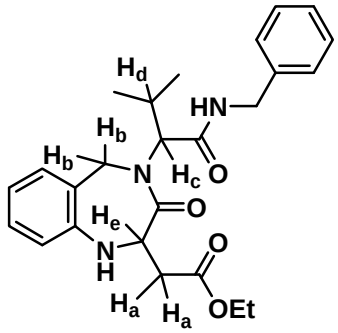
^{1}H NMR (Compound 10)



^{13}C NMR (Compound 10)



Ethyl 2-(4-(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo [*e*][1,4] diazepin-2yl)acetate **(11)**.



(±)-11

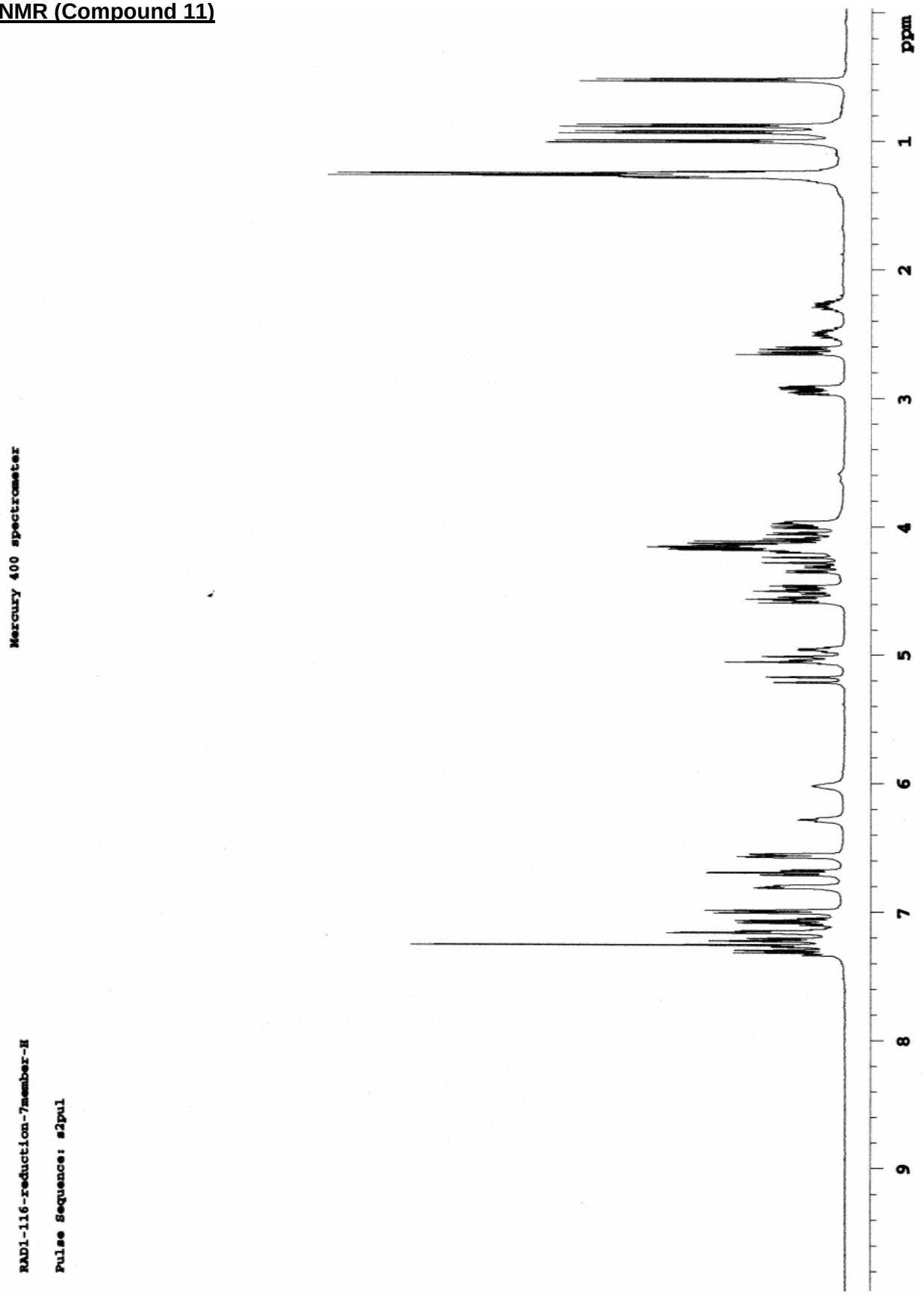
^{1}HNMR (400 MHz, $CDCl_3$): **(major and minor)** δ 7.35 - 6.98 (m, 12H, aryl), 6.80 (bd, 2H, *J* = 5.0 Hz, aryl), 6.70 (t, 2H, *J* = 7.3 Hz, aryl), 6.54 (dd, 2H, J_1 = 8.1 Hz, J_2 = 3.2 Hz, aryl), 6.28 (bt, 1H, *J* = 5.7 Hz, NH), 6.00 (br s, 1H, -N<u>H</u>), 5.20 (d, 1H, *J* = 16.2 Hz, H_b), 5.10 – 4.95 (m, 3H, 2 x H_b , *J* = 16.2 Hz , *J* = 16.0 Hz and -N<u>H</u> overlap), 4.60 – 4.45 (m, 3H, 2 x H_e and H_b overlap), 4.31 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.23 (d, 1H, *J* = 16.2 Hz, Bn), 4.20 – 4.10 (m, 5H, H_c, -N<u>H</u>, -OC<u>H_2</u>CH_3, and Bn overlap), 4.01 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 3.98 (br d, 1H, *J* = 5.7 Hz, H_c), 2.96 – 2.90 (m, 2H, -OC<u>H_2</u>CH_3), 2.63 (dd, 2H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H_a), 2.49 (m, 2H, H_a), 2.27 (m, 2H, 2x H_d), 1.28 – 1.23 (m, 6H, -OCH_2C<u>H_3</u>), 0.99 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H_3</u>)$_2$), 0.92 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H_3</u>)$_2$) , 0.87 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H_3</u>)$_2$, 0.51 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H_3</u>)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): **(major and minor)** δ 172.2, 171.6, 171.4, 170.7, 170.1, 169.4, 145.3, 145.0, 138.2, 137.9, 131.0, 130.0, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 127.8, 127.7, 127.4, 121.0, 120.1, 119.3, 119.1, 117.7, 117.3, 63.6, 61.2, 61.2, 60.6, 52.6, 52.0, 47.2, 46.8, 43.4, 36.5, 36.4, 29.93, 27.4, 26.5, 21.3, 19.9, 19.8, 18.9, 14.4, 14.3.

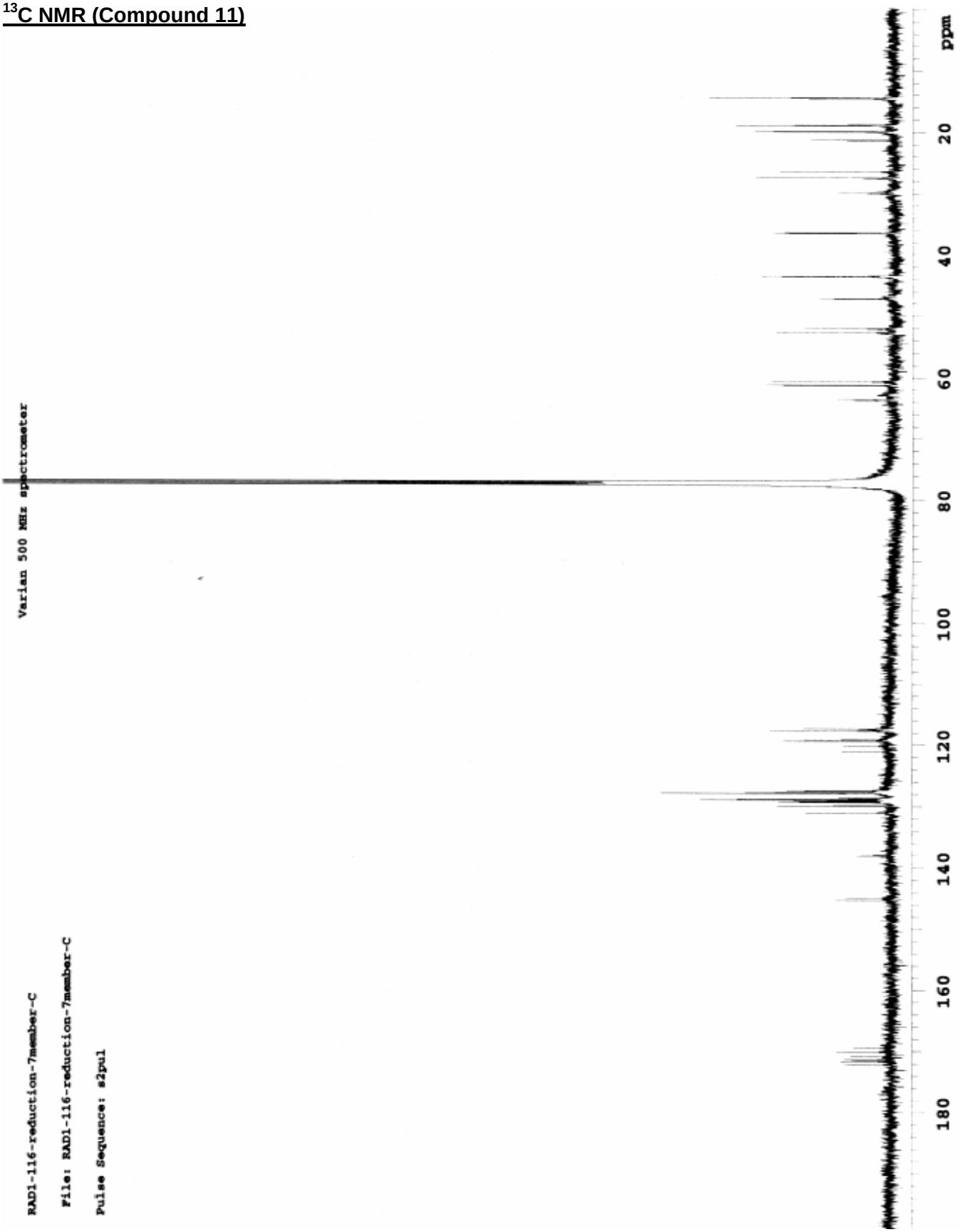
HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2328.

IR (neat): 3331, 3030, 2965, 2933, 2873, 1715, 1644, 1494, 1452, 1365, 1221, 1174, 1029, 969, 748, 700.

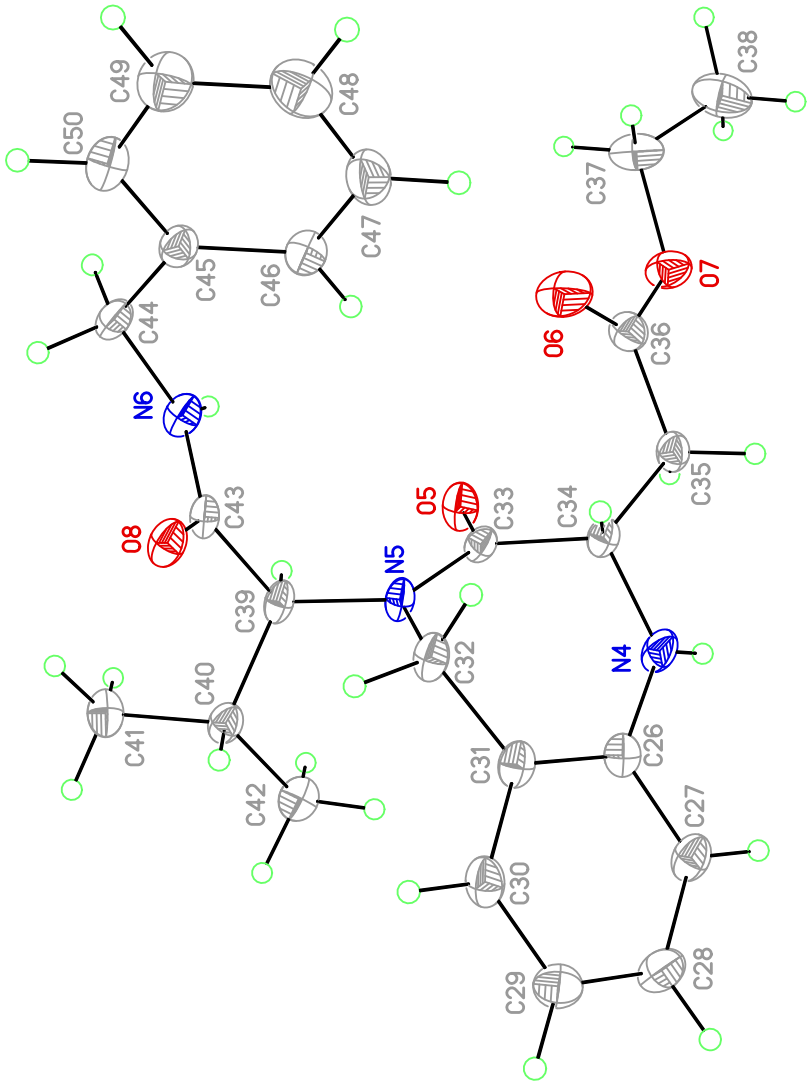
^{1}H NMR (Compound 11)



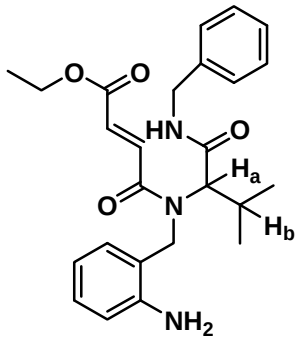
^{13}C NMR (Compound 11)



Crystal Structure of Compound (11)



(*E*)-ethyl 4-((2-aminobenzyl)(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate **(12)**



(±)-12

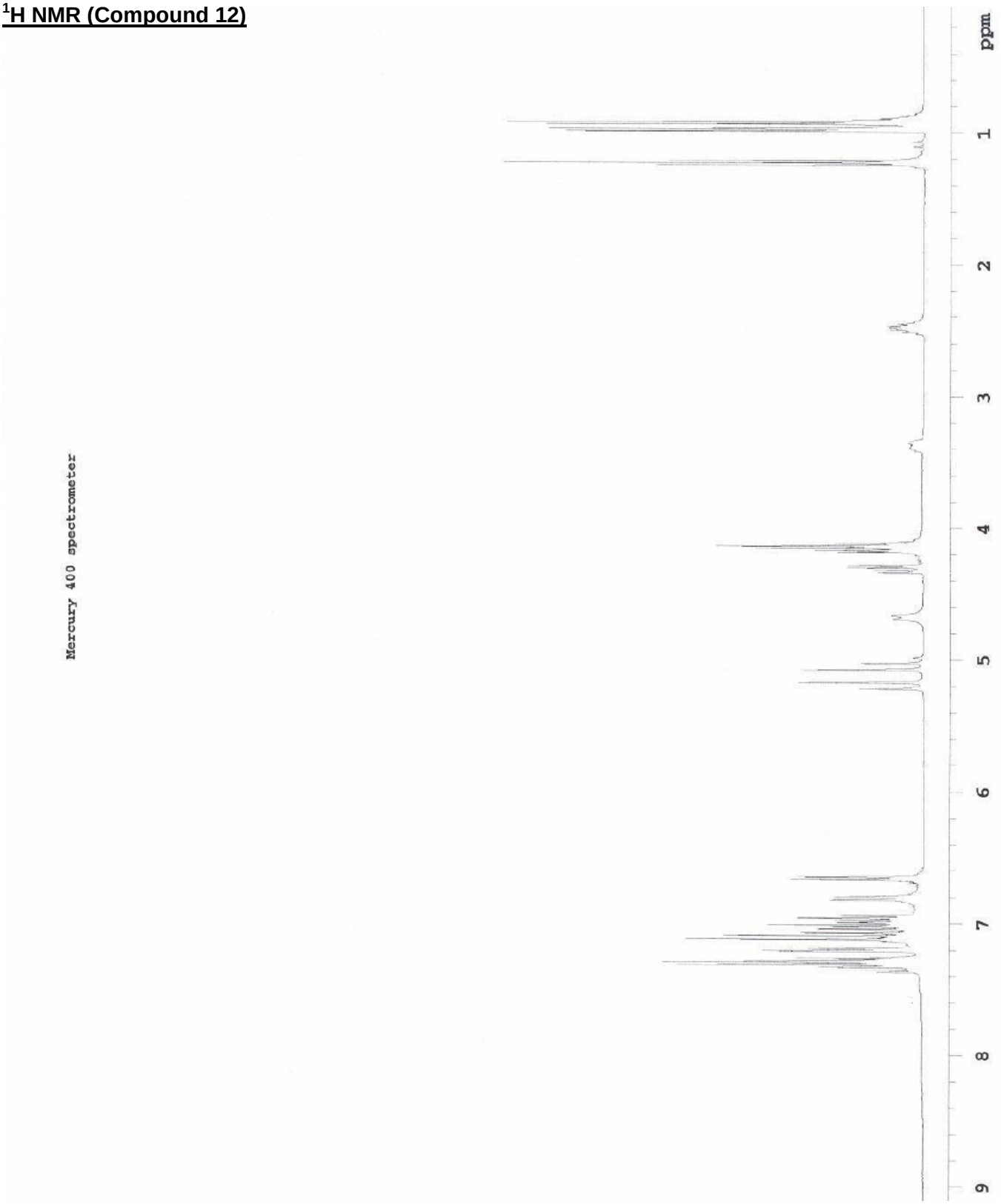
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 - 6.95 (m, 9H, aryl, and -C<u>H</u>=CH-, *J* = 15.4 Hz,), 6.80 (1H, *J* = 8.0 Hz, aryl), 6.70 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 5.18 (d, 1H, *J* = 19.4 Hz, Bn), 5.00 (d, 1H, *J* = 19.4 Hz, Bn), 4.72 (br d, 1H, *J* = 10.5 Hz, H_a), 4.33 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.12 (m, 3H, Bn and -OC<u>H</u>$_2$CH$_3$ overlap), 3.40 (br s, 2H, NH_2), 2.44 (m, 1H, H_b), 1.23 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.95 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$), 0.90 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169, 167.2, 165.3, 137.4, 133.3, 132.6, 131.6, 128.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.6, 127.3, 126.0, 64.8, 61.6, 46.2, 43.8, 27.8, 19.1, 18.1, 14.1.

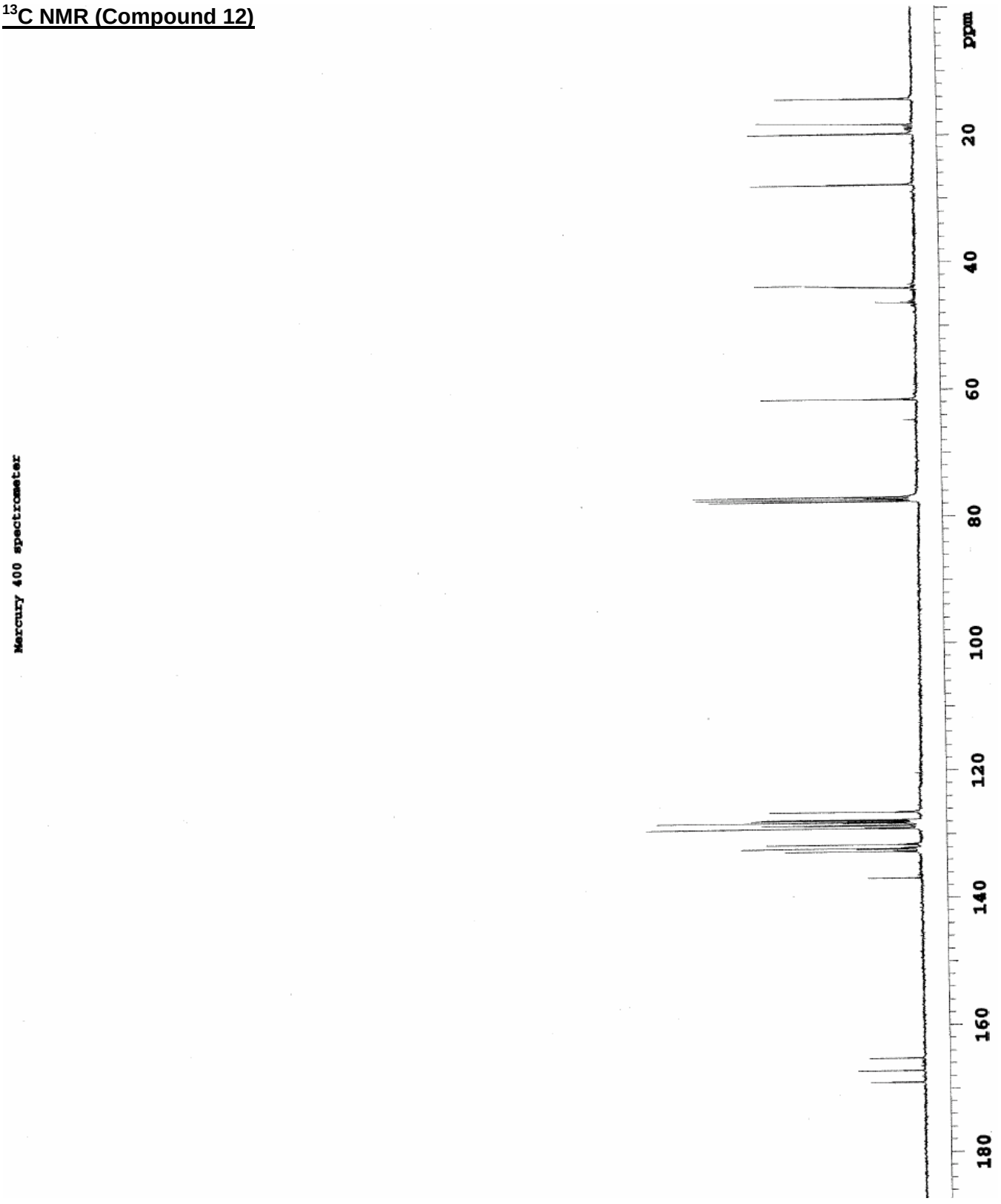
HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2321.

IR (neat): 3552, 3395, 3000, 2965, 2933, 2873, 1781, 1644, 1367, 1360, 1215, 1166, 1023, 900.

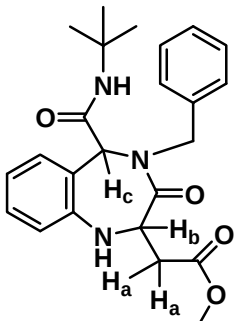
^{1}H NMR (Compound 12)



^{13}C NMR (Compound 12)



Ethyl 2-(4-benzyl-5-(*tert*-butylcarbamoyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl) acetate **(13)**.



(±)-13

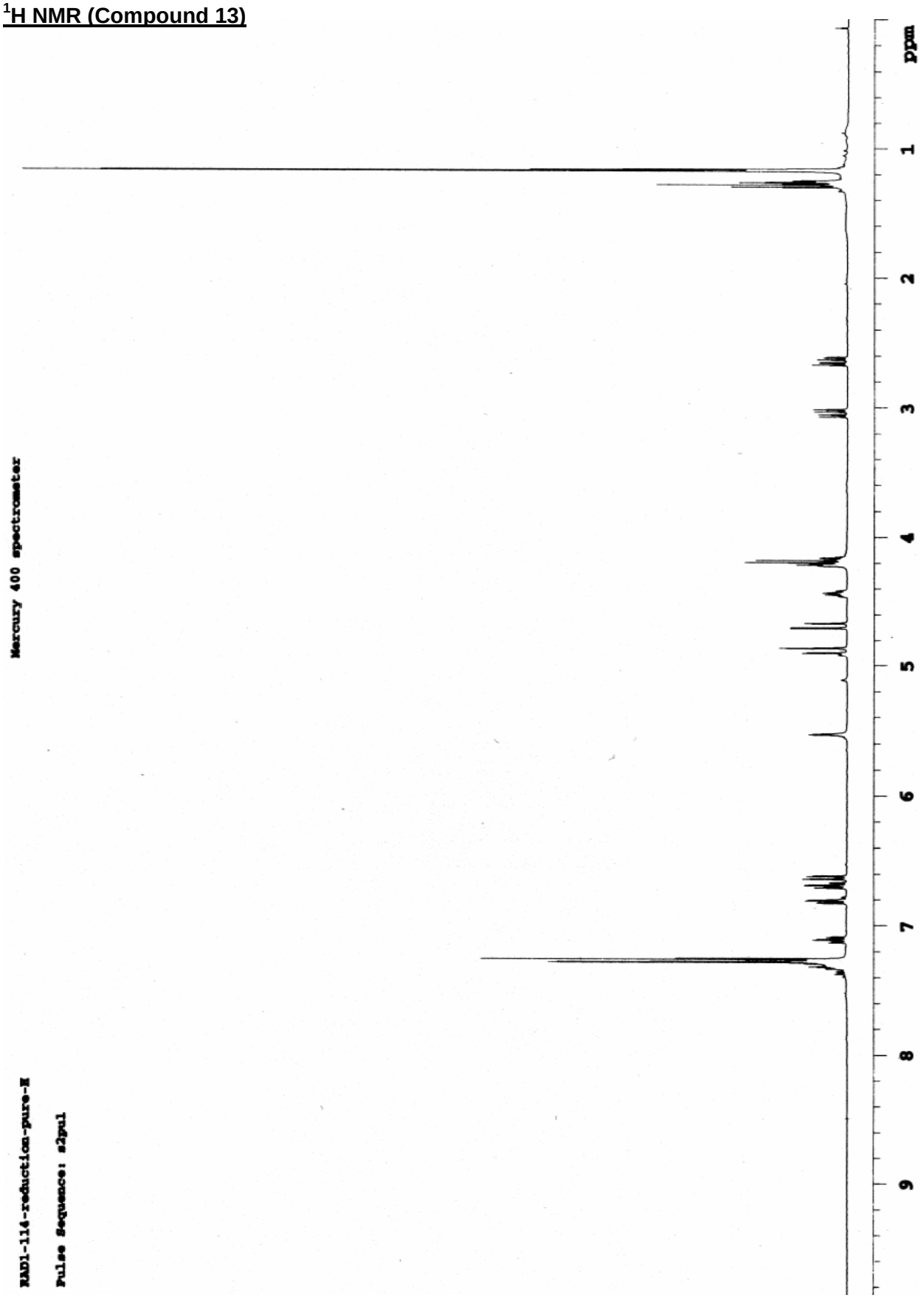
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 5H, aryl), 7.11 (t, 1H, *J* = 7.3 Hz, aryl), 6.82 (d, 1H, *J* = 7.3 Hz, aryl), 6.68 (t, 1H, *J* = 7.3 Hz, aryl), 6.64 (d, 1H, *J* = 8.1 Hz, aryl), 5.52 (s, 1H, H_c), 4.85 (d, 1H, *J* = 15.4 Hz, Bn), 4.66 (d, 1H, *J* = 15.4 Hz, Bn), 4.45 – 4.41 (m, 1H, H_b), 4.16 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.04 (dd, 1H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H_a), 2.64 (dd, 1H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H_a), 1.27 (t, 3H, *J* = 7.2 Hz, -OCH$_2$C$\underline{H}_3$), 1.17 (s, 9H, *t*-butyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 170.37, 169.1, 144.2, 137.0, 132.7, 129.8, 129.3, 129.2, 129.0, 128.9, 128.8, 128.2, 119.2, 118.7, 66.9, 61.1, 52.8, 52.6, 51.9, 36.1, 28.5, 28.4, 28.2, 14.4.

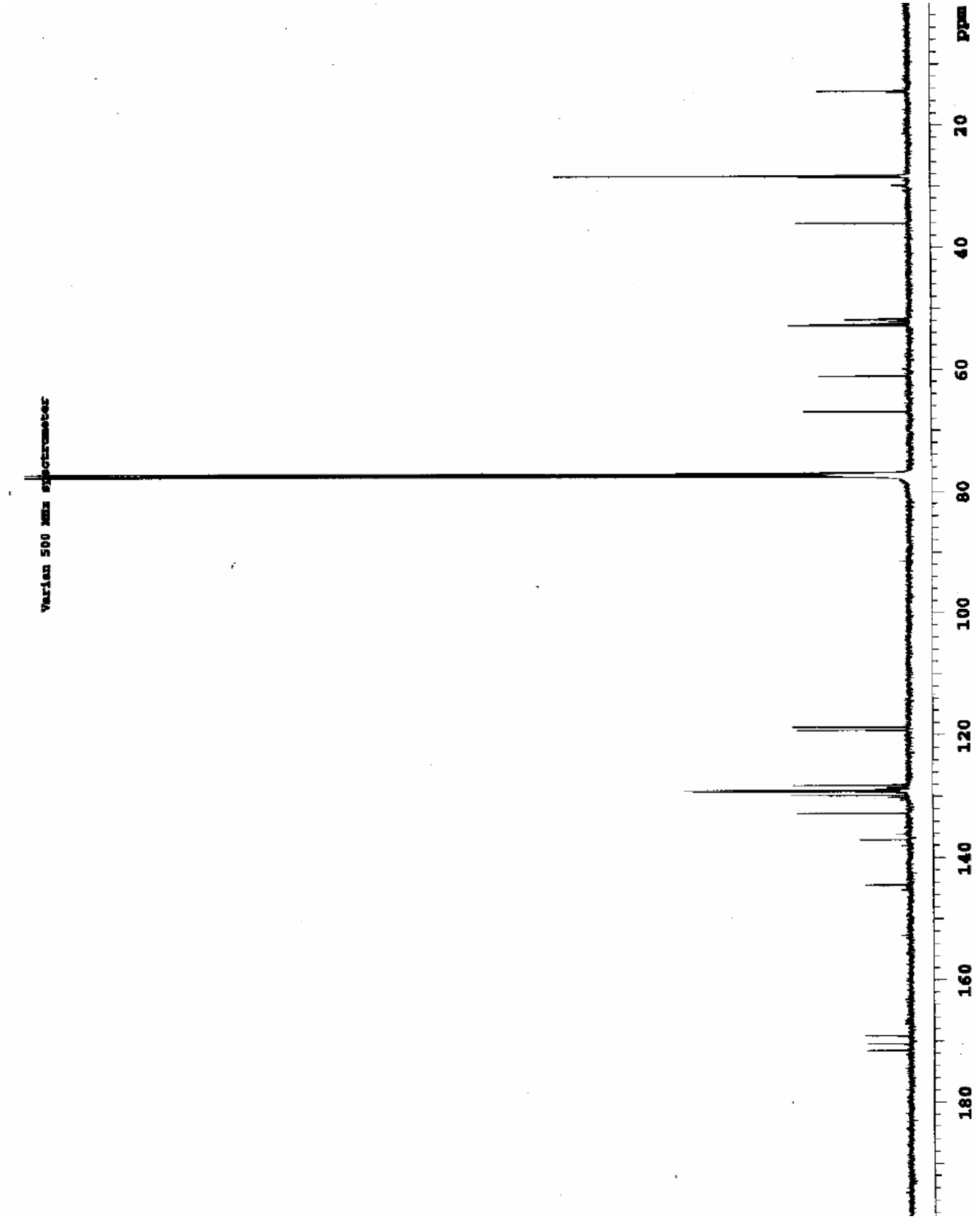
HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2323.

IR (neat): 3318, 2928, 2856, 1714, 1682, 1515, 1451, 1240, 1096, 1047, 847, 750.

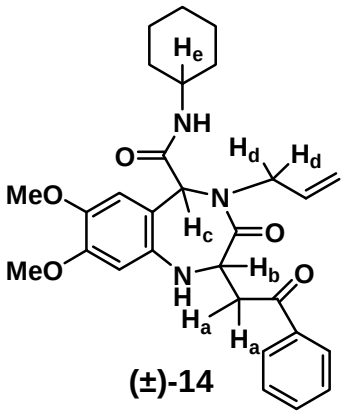
^{1}H NMR (Compound 13)



^{13}C NMR (Compound 13)



4-allyl-*N*-cyclohexyl-7,8-dimethoxy-3-oxo-2-(2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[*e*] [1,4] diazepine-5-carboxamide **(14)**.



(±)-14

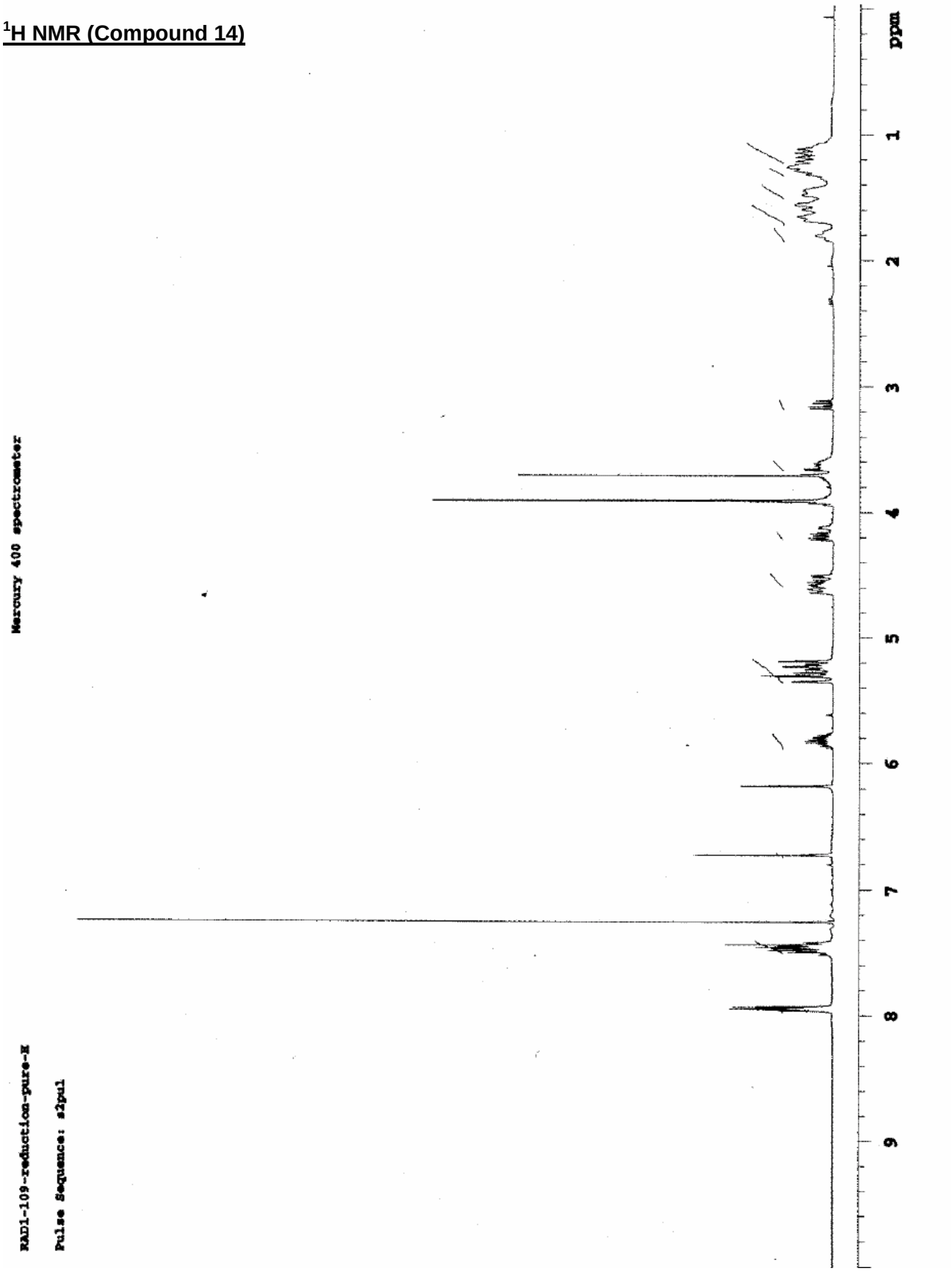
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H, aryl), 7.51-7.41 (m, 4H, aryl), 6.61 (s, 1H, aryl), 6.18 (s, 1H, H_c,), 5.87 – 5.77 (m, 1H, -C<u>H</u>=CH_2), 5.31 – 5.18 (m, 2H, -CH=C<u>H_2</u>), 4.64 – 4.50 (m, 2H, H_d), 4.20 (dd, 1H, J_1 = 6.5 Hz, J_2 = 7.3 Hz, H_b), 4.10 (br d, 1H, J = 4.8 Hz, -N<u>H</u>), 3.90 (s, 3H, -OC<u>H_3</u>), 3.70 (s, 3H, -OC<u>H_3</u>), 3.66 – 3.58 (m, 2H, H_e and H_a overlap), 3.18 (dd, 1H, J_1 = 5.0 Hz, J_2 = 16.4 Hz, H_a), 1.80 – 1.00 (m, 10H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 166.8, 155.6, 146.6, 143.4, 133.2, 133.8, 132.0, 129.2, 128.9, 128.8, 128.7, 127.6, 112.6, 112.7, 105.9, 104.0, 96.0, 65.9, 63.2, 56.7, 56.5, 52.4, 49.2, 32.7, 32.6, 24.98, 24.9, 24.7.

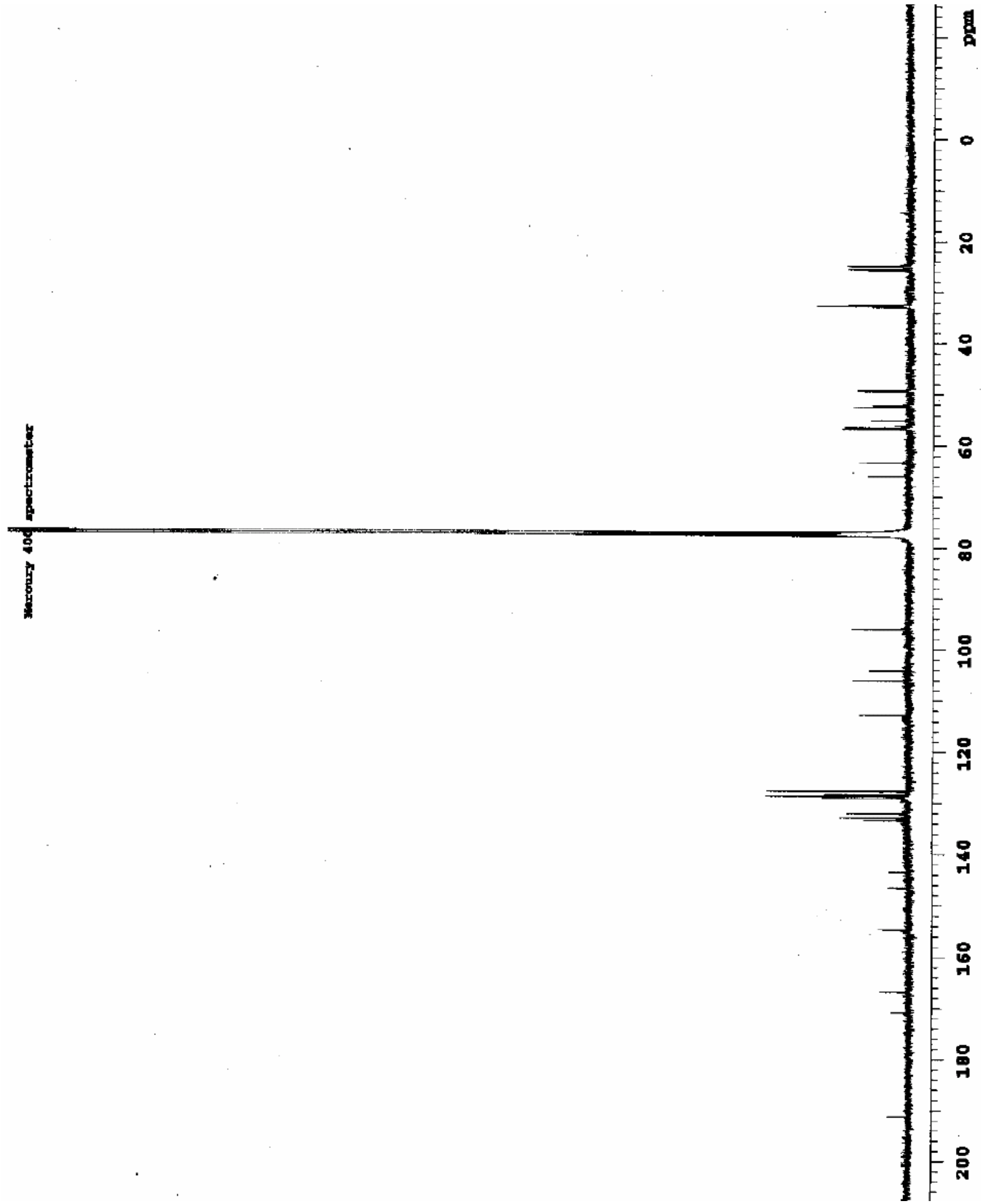
HRMS: EIMS (M^+) calcd for $C_{29}H_{35}N_3O_5$ 505.2577 found 505.2589.

IR (neat): 3320, 2927, 2854, 1740, 1608, 1454, 1373, 1240, 1047, 969, 751.

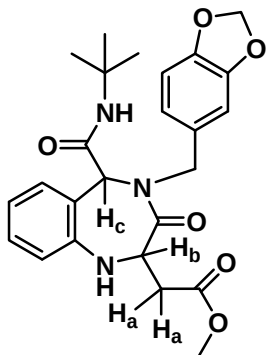
^{1}H NMR (Compound 14)



^{13}NMR (Compound 14)



Ethyl 2-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(*tert*-butylcarbamoyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo [*e*][1,4]diazepin-2-yl)acetate **(15)**.



(±)-15

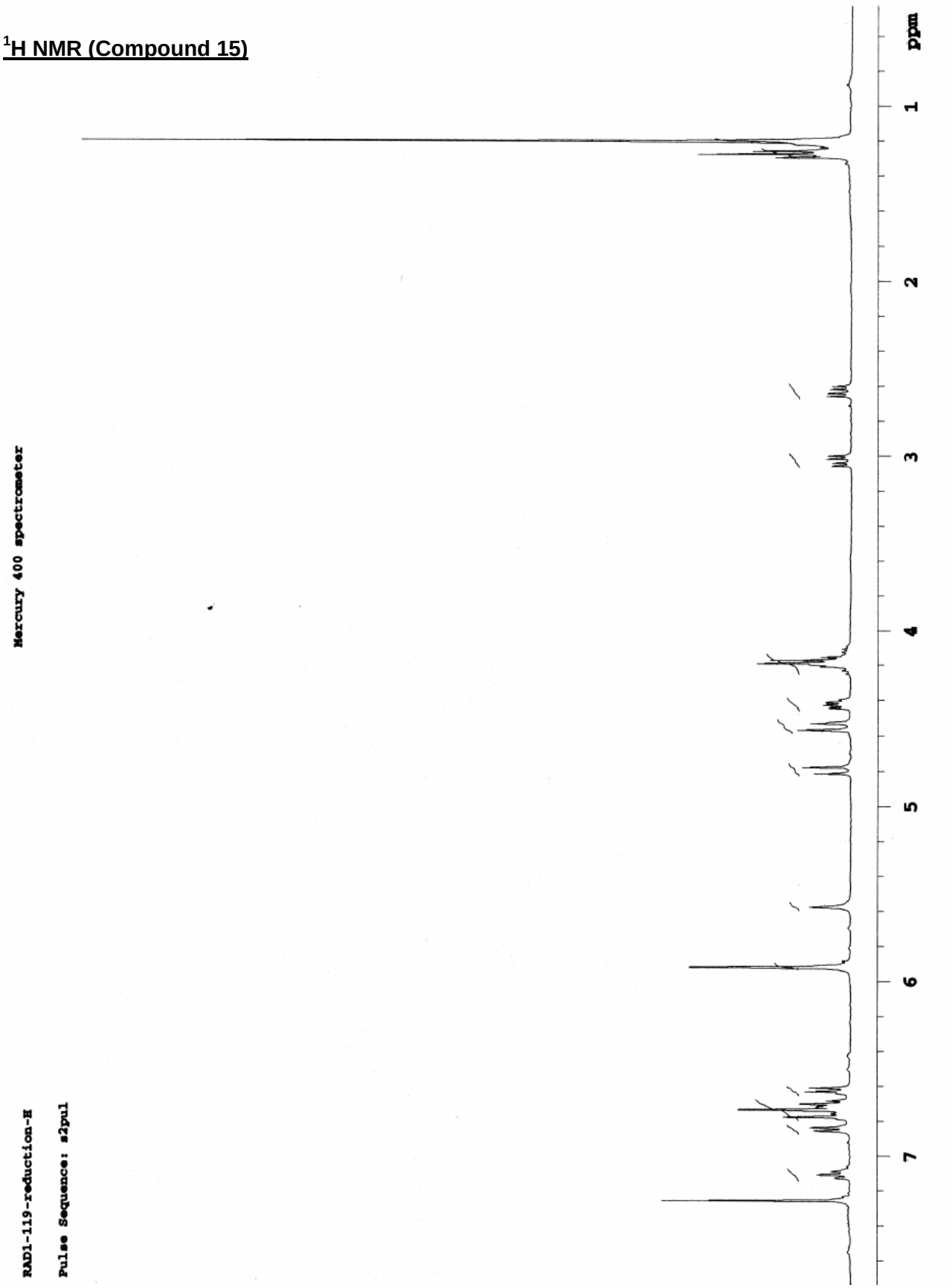
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (m, 1H, aryl), 6.85 – 6.61 (m, 6H, aryl), 5.91 (s, 2H, -OC$\underline{H}_2$O-), 5.57 (s, 1H, H_c), 4.77 (d, 1H, *J* = 14.6 Hz, Bn), 4.52 (d, 1H, *J* = 14.6 Hz, Bn), 4.42 (dd, 1H, J_1 = 5.6 Hz, J_2 = 6.5 Hz, H_b), 4.19 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.02 (dd, 1H, J_1 = 7.3 Hz, J_2 = 16.2 Hz, H_a), 2.62 (dd, 1H, J_1 = 7.3 Hz, J_2 = 16.2 Hz, H_a), 1.27 (t, 3H, *J* = 6.5 Hz, -OCH$_2$C$\underline{H}_3$), 1.20 (s, 9H, *t*-butyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 170.3, 169.1, 148.4, 147.6, 144.4, 132.7, 129.9, 129.8, 126.6, 122.4, 119.1, 118.7, 109.2, 108.6, 101.3, 66.7, 61.1, 52.8, 52.2, 51.8, 36.1, 28.5, 14.4.

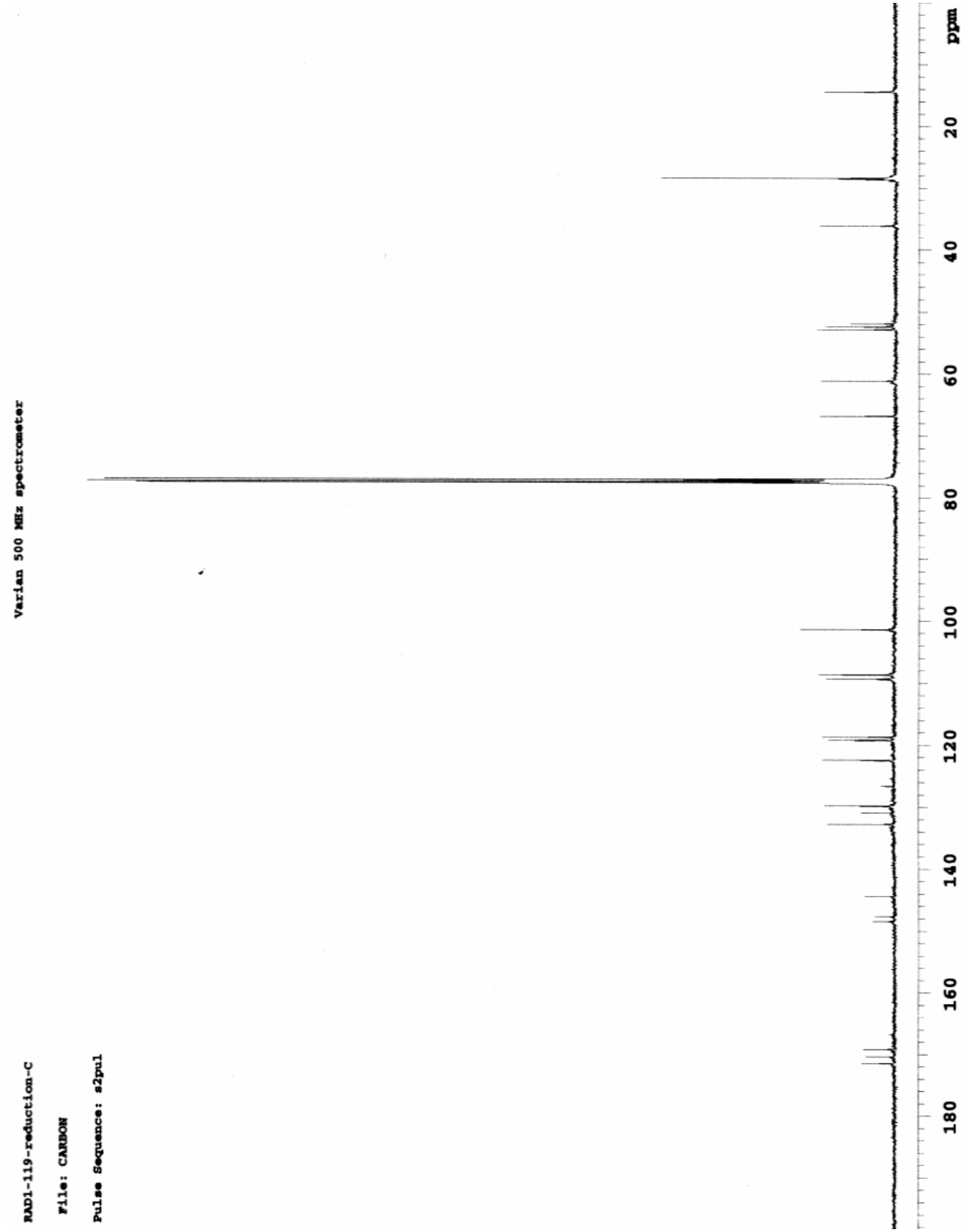
HRMS: EIMS (M^+) calcd for $C_{26}H_{31}N_3O_6$ 481.2213 found 481.2218.

IR (neat): 3348, 2976, 2934, 1734, 1662, 1608, 1503, 1444, 1368, 1245, 1183, 1100, 1039, 930, 808, 674.

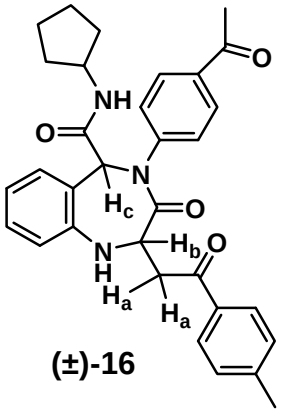
^{1}H NMR (Compound 15)



^{13}C NMR (Compound 15)



4-(4-acetylphenyl)-*N*-cyclopentyl-3-oxo-2-(2-oxo-2-*p*-tolylethyl)-2,3,4,5-tetrahydro-1-*H*-benzo [*e*][1,4] diazepine-5-carboxamide **(16)**.



(±)-16

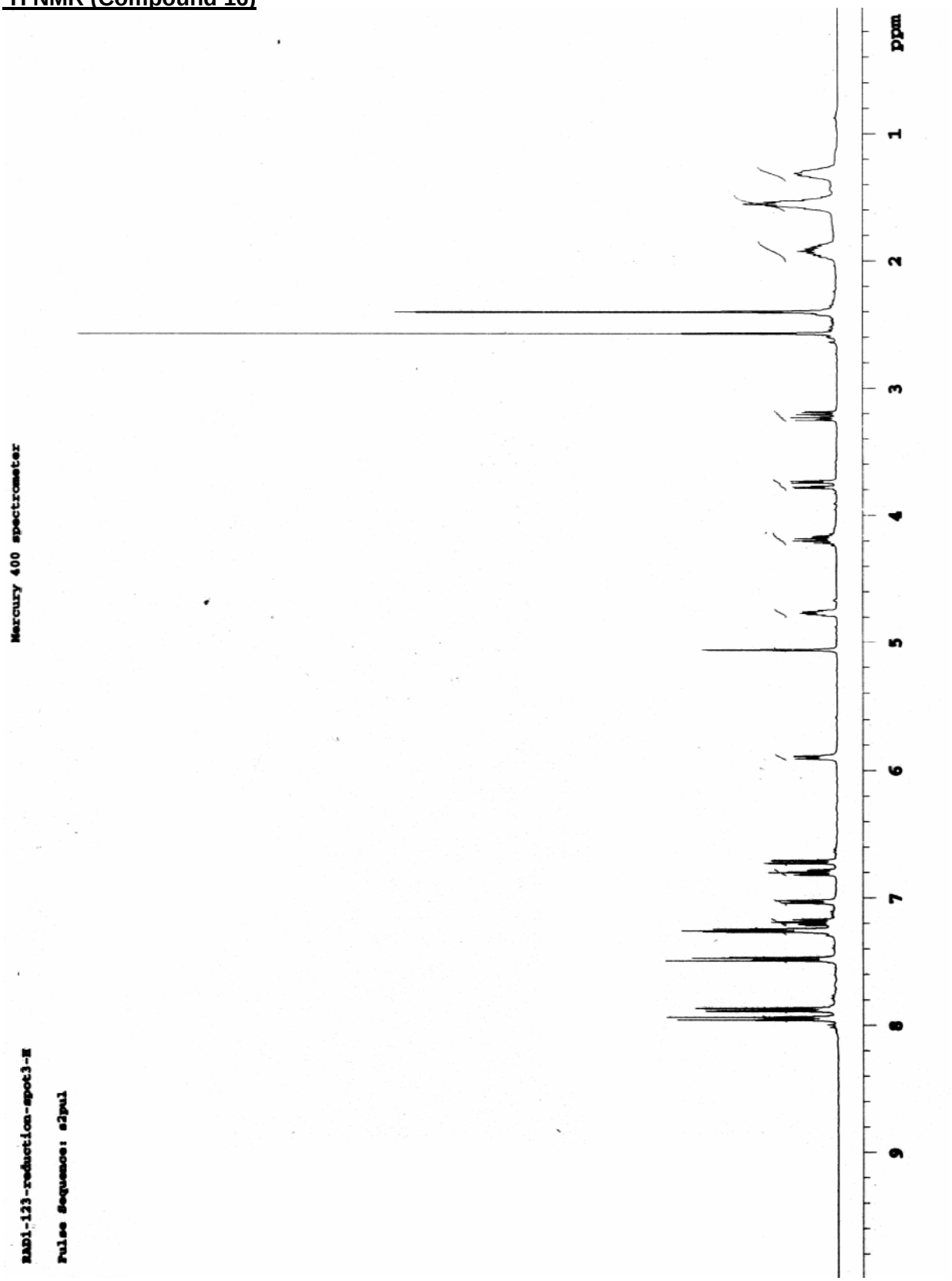
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 2H, *J* = 8.1 Hz, aryl), 7.86 (d, 2H, *J* = 8.9 Hz, aryl), 7.46 (d, 2H, *J* = 8.1 Hz, aryl), 7.25 (m, 2H, aryl), 7.19 (m, 1H, aryl), 7.02 (d, 1H, *J* = 7.3 Hz, aryl), 6.80 (t, 1H, *J* = 7.3 Hz, aryl), 6.70 (d, 1H, *J* = 8.0 Hz, aryl), 5.90 (d, 1H, *J* = 8.1 Hz, -N<u>H</u>), 5.06 (s, 1H, H_c), 4.76 (m, 1H, H_b), 4.19 (m, 1H, Cp), 3.76 (dd, 1H, J_1 = 17.0 Hz, J_2 = 5.0 Hz, H_a), 3.20 (dd, 1H, J_1 = 17.0 Hz, J_2 = 7.0 Hz, H_a), 2.57 (s, 3H, -C<u>H</u>$_3$), 2.40 (s, 3H, -C<u>H</u>$_3$), 1.96 – 1.87 (m, 2H, Cp), 1.60 – 1.49 (m, 4H, Cp), 1.36 – 1.24 (m, 2H, Cp).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 197.4, 170.1, 169.6, 148.5, 145.1, 144.7, 135.8, 134.0, 132.0, 130.5, 129.8, 129.6, 128.6, 127.1, 119.6, 119.2, 119.0, 118.9, 118.8, 70.3, 53.3, 52.4, 39.7, 33.1, 32.8, 26.8, 23.8, 21.9.

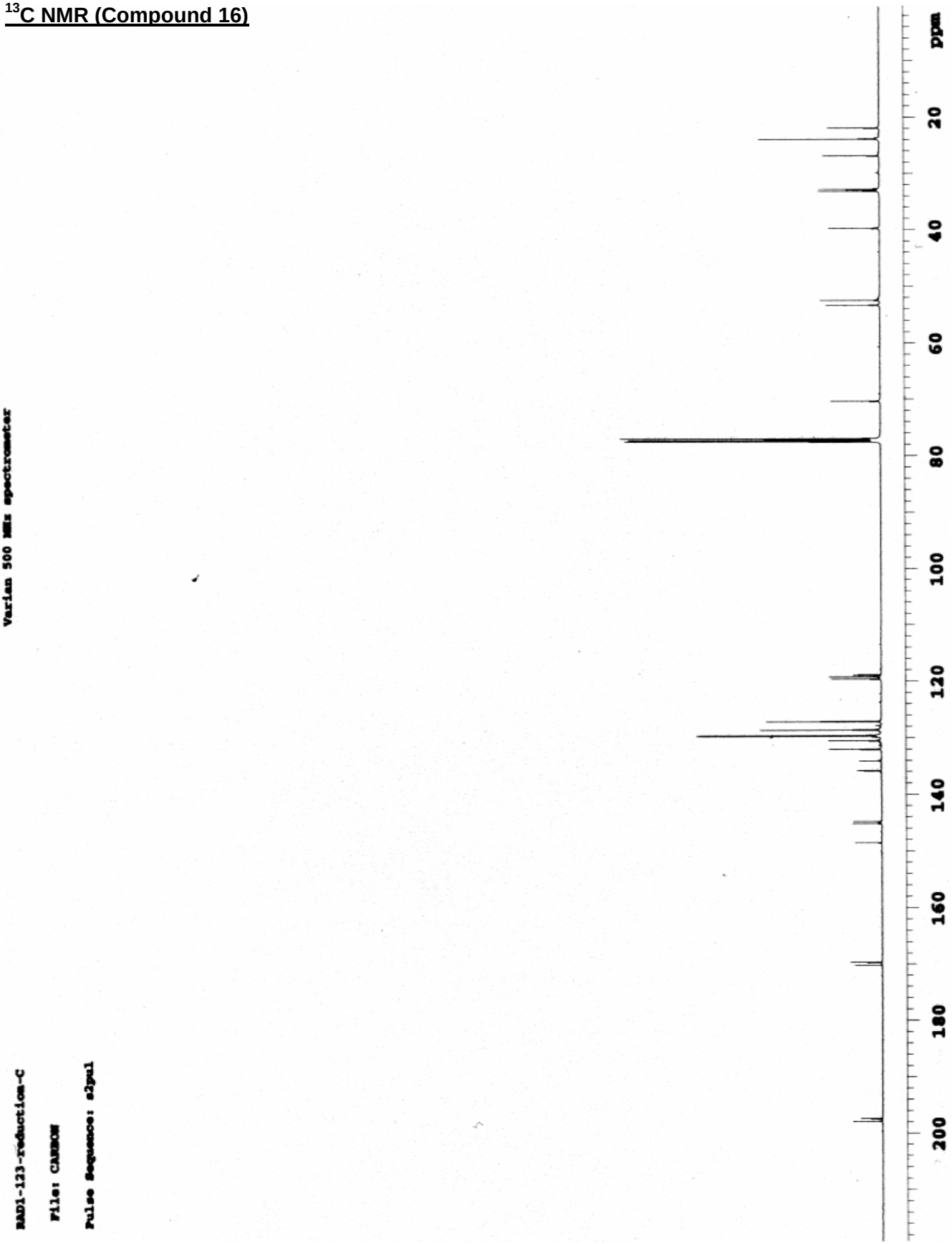
HRMS: EIMS (M^+) calcd for $C_{32}H_{33}N_3O_4$ 523.2471 found 523.2466.

IR (neat): 3348, 2957, 2870, 1735, 1679, 1601, 1508, 1494, 1426, 1406, 1224, 1203, 1181, 824, 754.

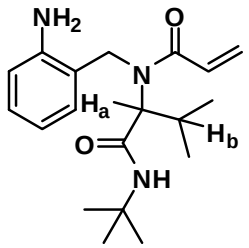
^{1}H NMR (Compound 16)



^{13}C NMR (Compound 16)



2-(*N*-(2-aminobenzyl)acrylamido)-*N*-*tert*-butyl-3-methylbutanamide **(17)**.



(±)-17

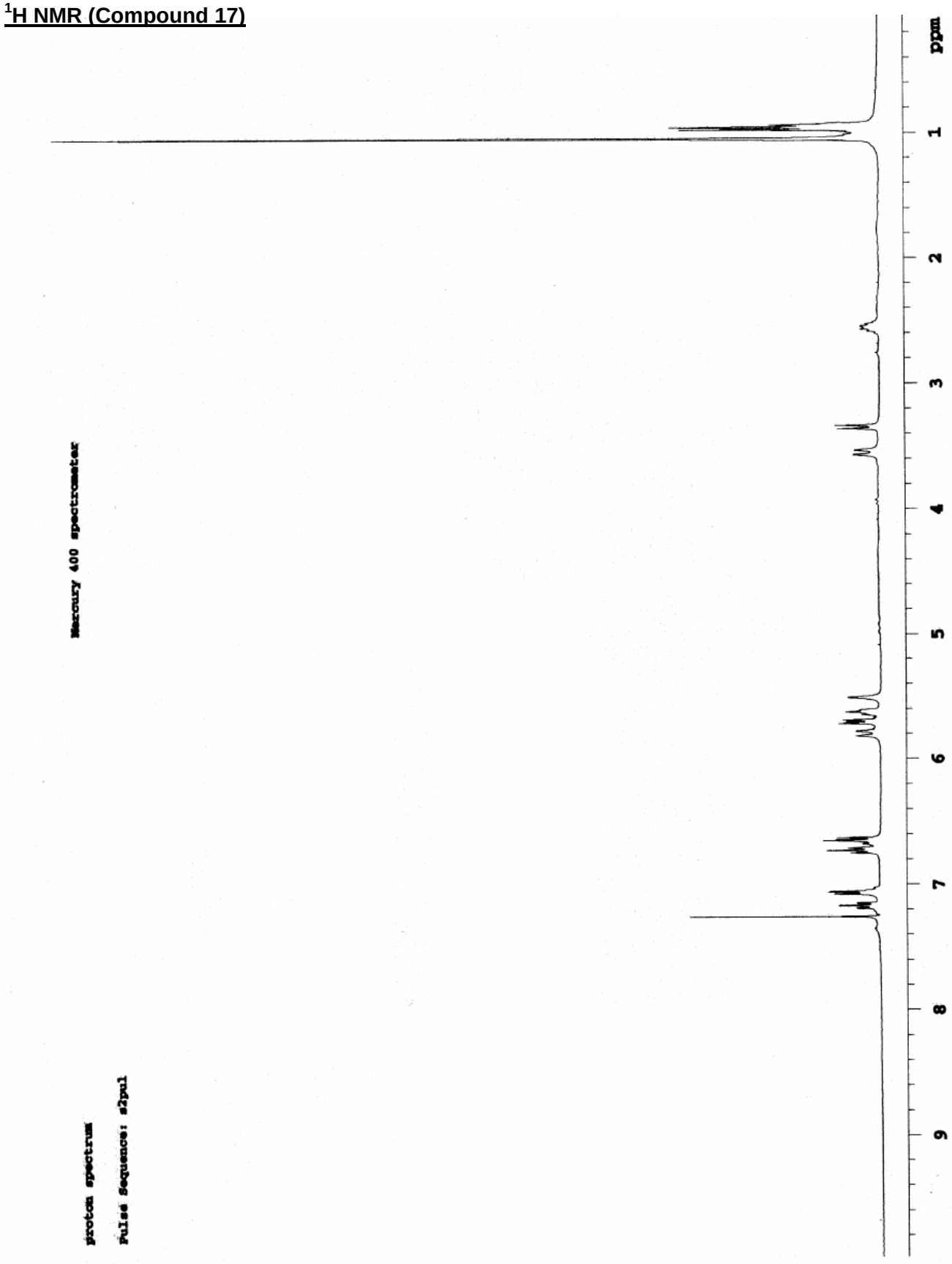
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 1H, aryl), 7.10 (d, 1H, *J* = 7.5 Hz, aryl), 6.70 (m, 1H, aryl), 6.65 (m, 3H, aryl and NH_2 overlap), 5.80 (d, 1H, *J* = 19.0 Hz, Bn), 5.70 (m, 1H, -CH=C$\underline{H}_2$), 5.60 (m, 1H, -C$\underline{H}$=CH_2), 5.50 (br s, 1H, -CH=C$\underline{H}_2$), 3.60 (d, 1H, *J* = 19.0 Hz, Bn), 3.36 (d, 1H, *J* = 10.5 Hz, H_a), 2.55 – 2.60 (m, 1H, H_b), 1.10 (s, 9H, *t*-butyl), 0.96 (m, 6H, 2x –CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 168.0, 131.2, 133.4, 130.6, 129.6, 128.2, 128.1, 127.4, 119.4, 118.2, 60.6, 51.4, 44.8, 28.5, 23.8, 19.2.

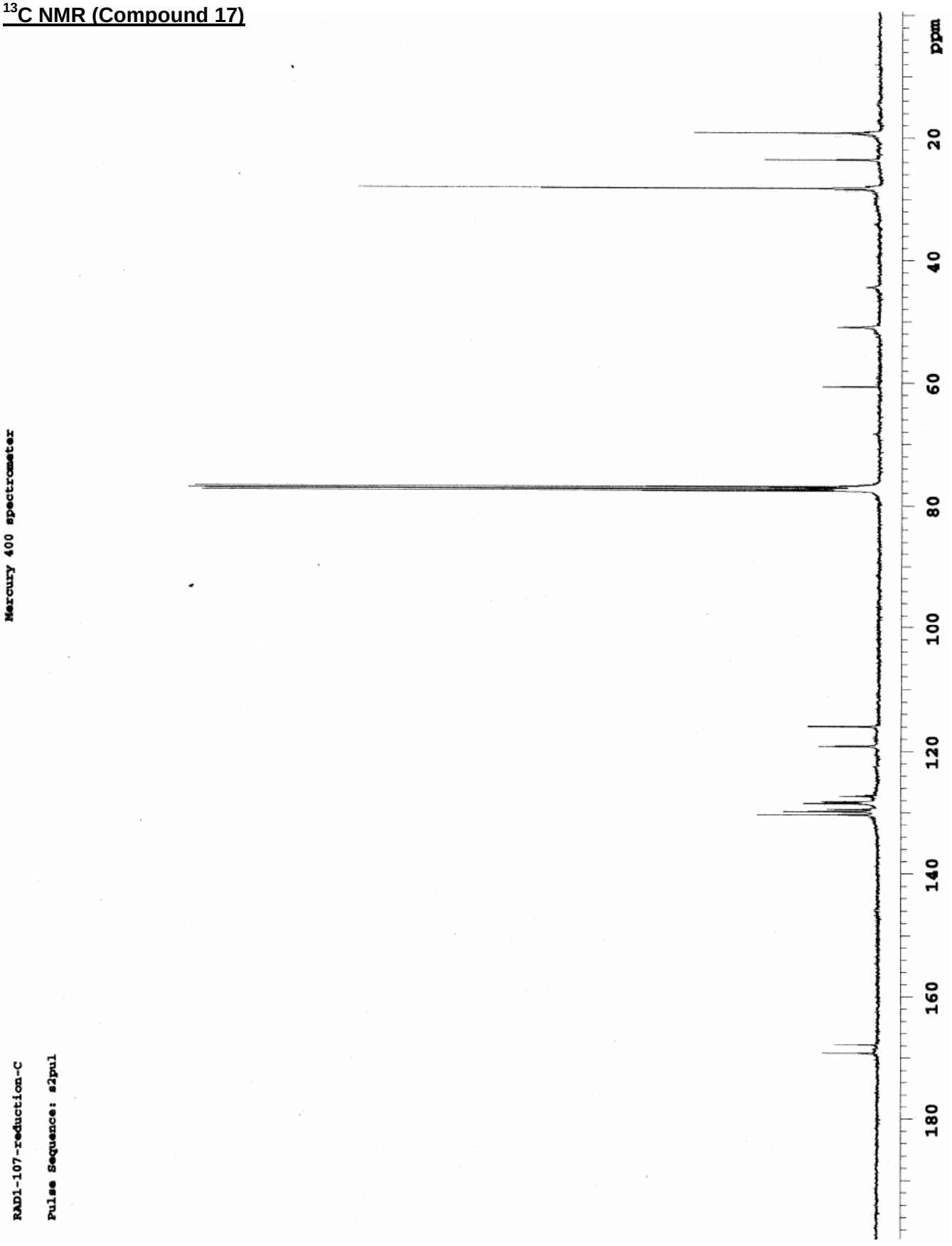
HRMS: EIMS (M^+) calcd for $C_{19}H_{29}N_3O_2$ 331.2260 found 331.2267.

IR (neat): 3423.03, 3326.61, 2966.95, 2873.42, 1735.62, 1671.02, 1641.13, 1456.96, 1221.68.

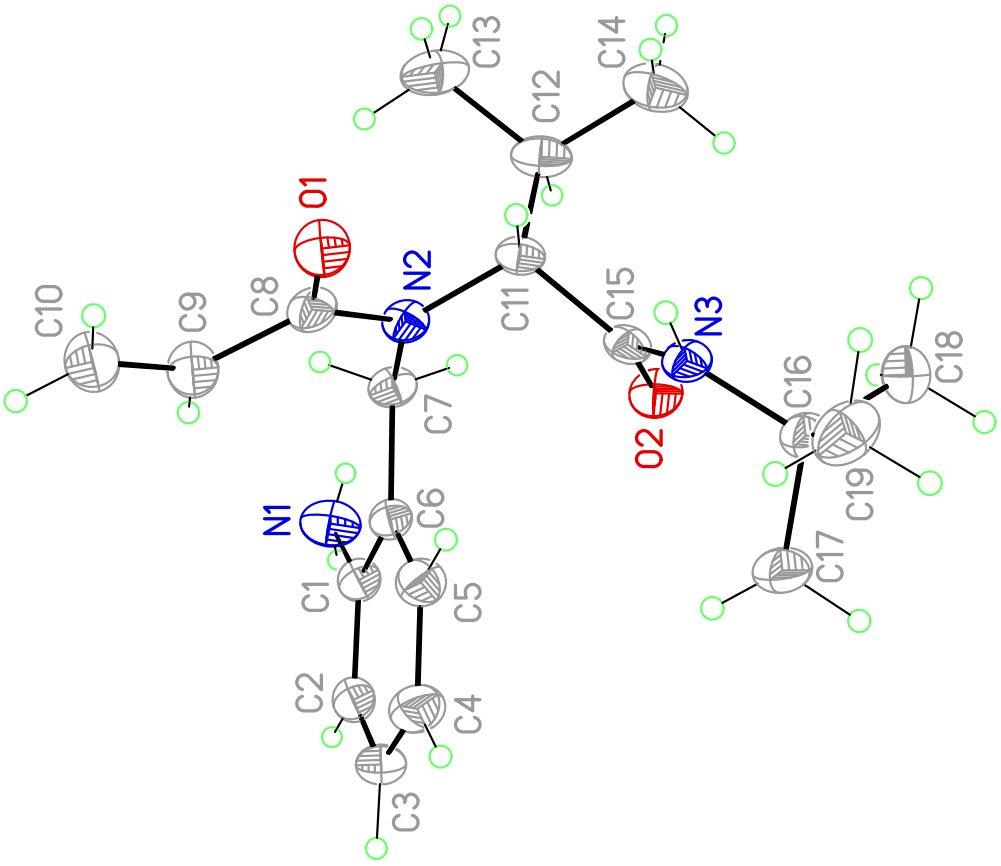
^{1}H NMR (Compound 17)



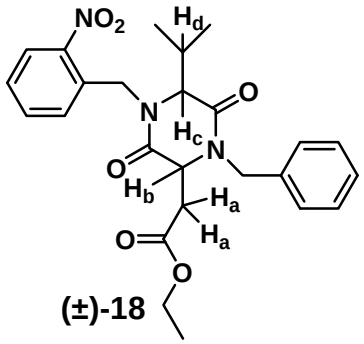
^{13}C NMR (Compound 17)



Crystal Structure of Compound (17)



Ethyl 2-(1-benzyl-5-isopropyl-4-(2-nitrobenzyl)-3,6-dioxopiperazin-2-yl)acetate **(18)**.



(±)-18

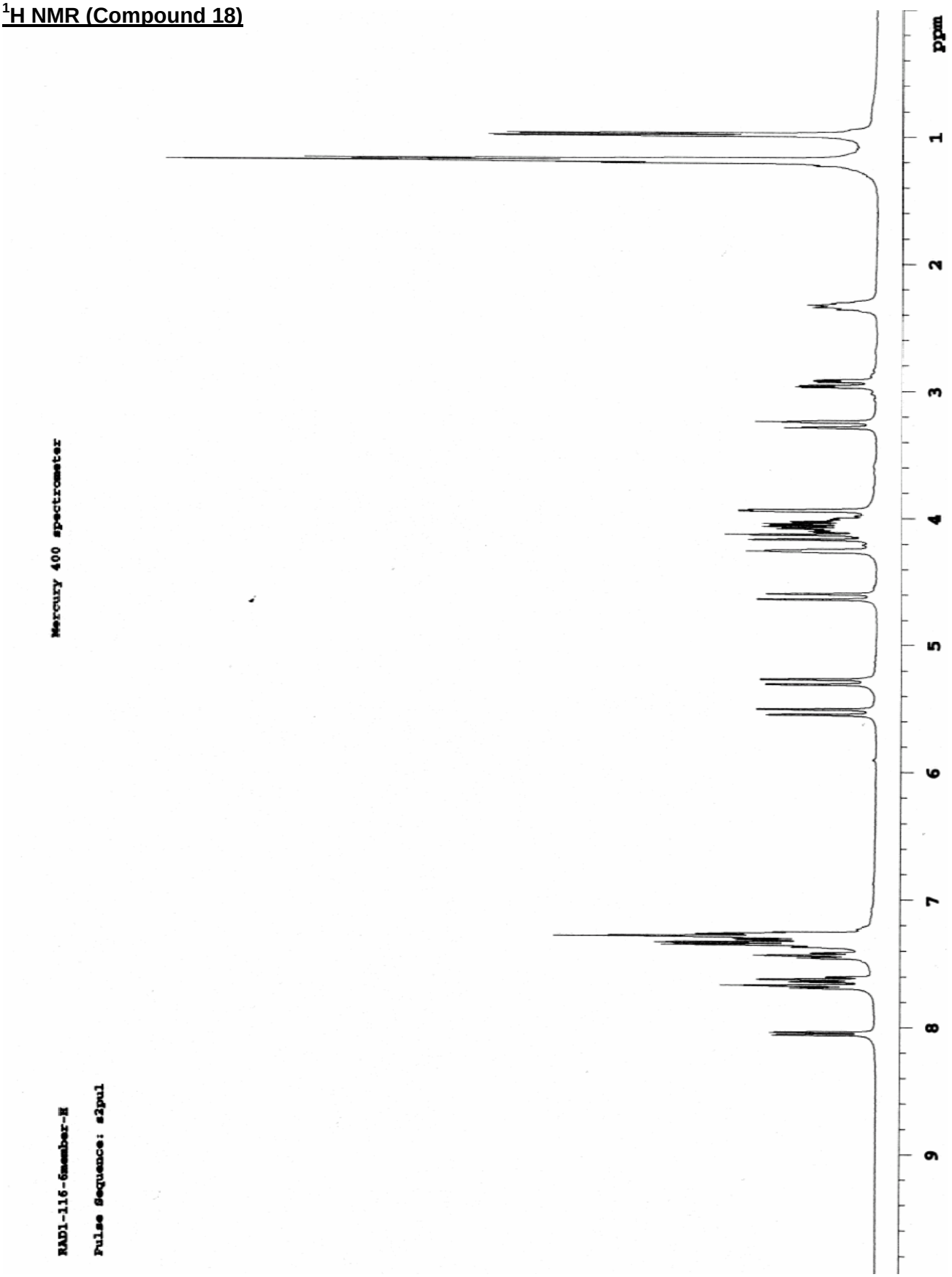
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H, *J* = 7.9 Hz, aryl), 7. 69 – 7.59 (m, 2H, aryl), 7.45 – 7.25 (m, 6H, aryl), 5.54 (d, 1H, *J* = 17.0 Hz, Bn), 5.28 (d, 1H, *J* = 15.2 Hz, Bn), 4.62 (d, 1H, *J* = 17.0 Hz, Bn), 4.26 – 3.93 (m, 5H, Bn, H_b, H_c and $-OC\underline{H}_2CH_3$ overlap), 3.60 (dd, 1H, J_1 = 3.0 Hz, J_2 = 17.7 Hz, H_a), 2.94 (dd, 1H, , J_1 = 5.0 Hz, J_2 = 17.7 Hz, H_a), 2.34 (m, 1H, H_d), 1.19 (m, 6H, $-OCH_2C\underline{H}_3$ and $-CH(C\underline{H}_3)_2$ overlap), 0.98 (d, 3H, *J* = 6.7 Hz, $-CH(C\underline{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.8, 165.9, 148.5, 136.0, 134.2, 134.1, 131.6, 129.3, 129.1, 128.5, 128.2, 125.3, 125.2, 65.9, 61.2, 55.1, 47.1, 45.8, 34.6, 32.5, 20.2, 17.6, 14.2.

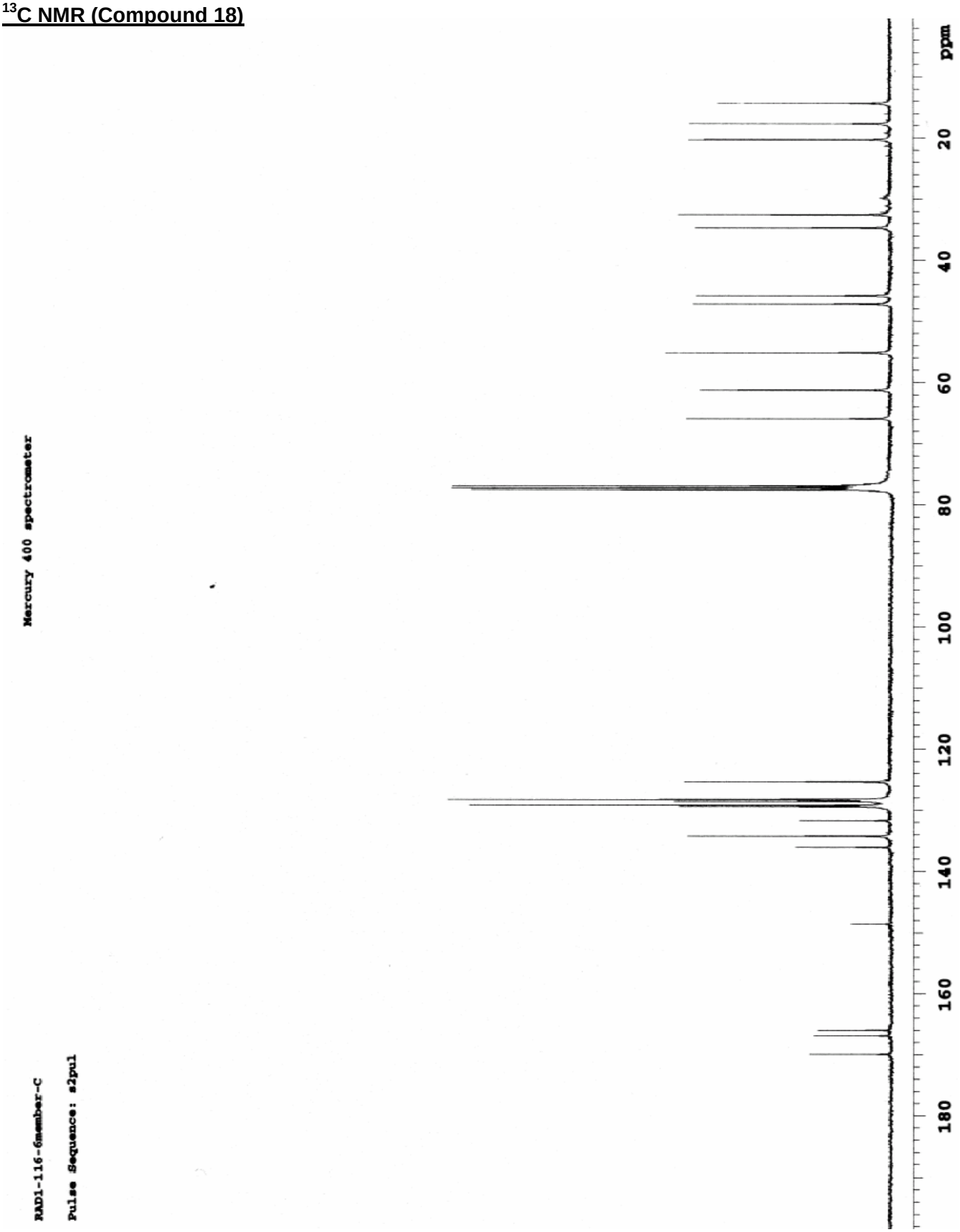
HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2053.

IR (neat): 3309, 3065, 2965, 2934, 2876, 1733, 1660, 1526, 1446, 1294, 1222, 1192, 1030, 727, 701.

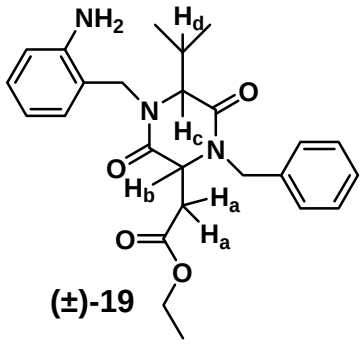
^{1}H NMR (Compound 18)



^{13}C NMR (Compound 18)



Ethyl 2-(4-(2-aminobenzyl)-1-benzyl-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate **(19)**.



(±)-19

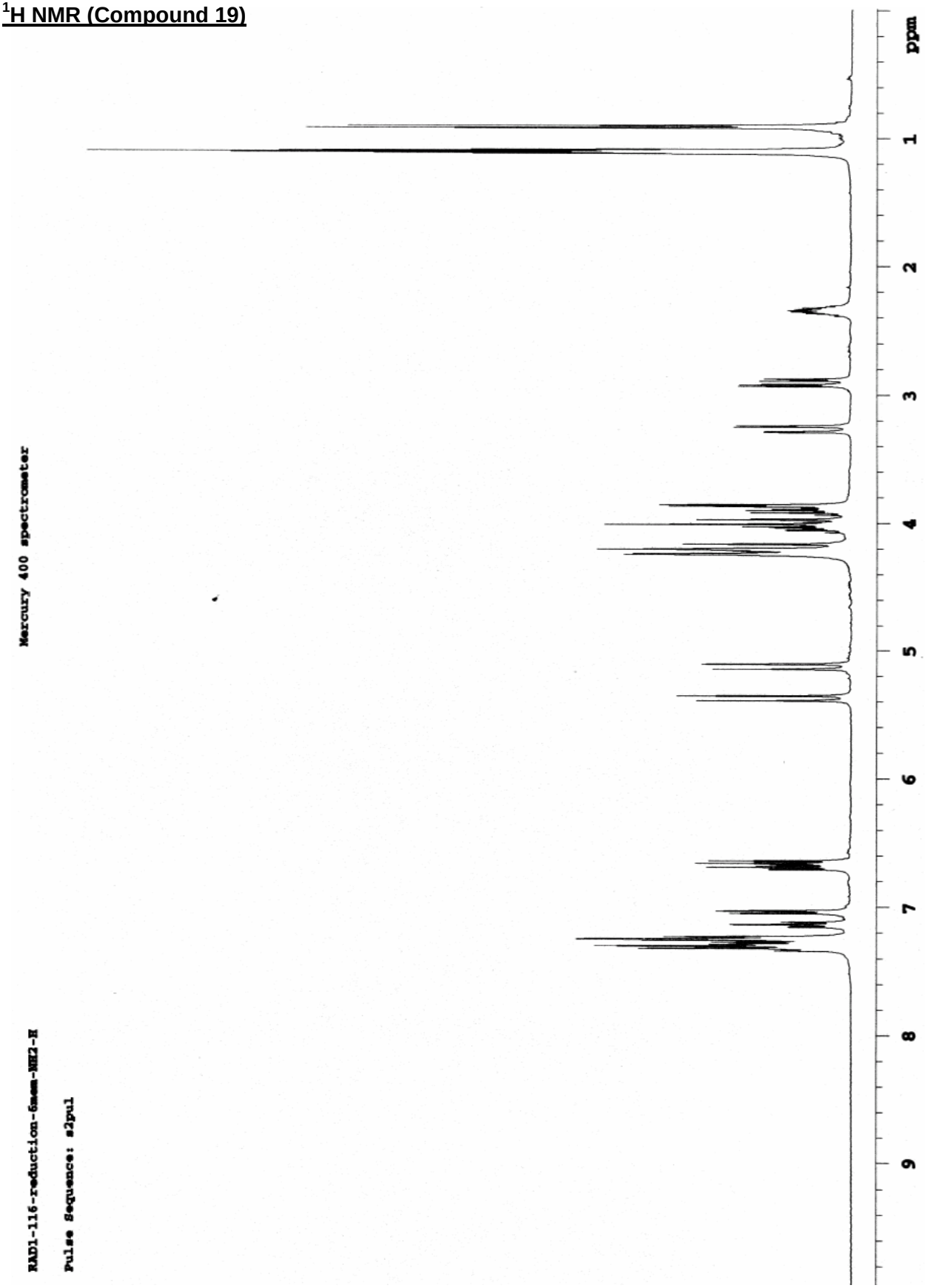
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 -7.20 (m, 5H, aryl), 7.10 (t, 1H, *J* = 6.5 Hz, aryl), 7.00 (d, 1H, *J* = 7.3 Hz, aryl), 6.70 (m, 2H, aryl), 5.38 (d, 1H, *J* = 14.6 Hz, Bn), 5.10 (d, 1H, *J* = 15.4 Hz, Bn), 4.24 – 3.85 (m, 6H, Bn, H_b, H_c, and –OC$\underline{H}_2$CH$_3$), 3.26 (dd, 1H, J_1= 17.0 Hz, J_2 = 2.6 Hz, H_a), 2.90 (dd, 1H, J_1= 17.0 Hz, J_2 = 4.8 Hz, H_a), 2.37 – 2.30 (m, 1H, H_d overlap), 1.10 (m, 6H, –OCH$_2$C$\underline{H}_3$ and -CH(C$\underline{H}_3$)$_2$ overlap), 0.80 (d, 3H, *J* = 6.4 Hz, -CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.4, 165.9, 146.5, 136.0, 132.0, 130.0, 129.0, 128.3, 128.0, 117.8, 117.5, 116.1, 62.4, 61.2, 55.5, 47.1, 45.8, 35.4, 31.6, 20.1, 17.0, 14.1.

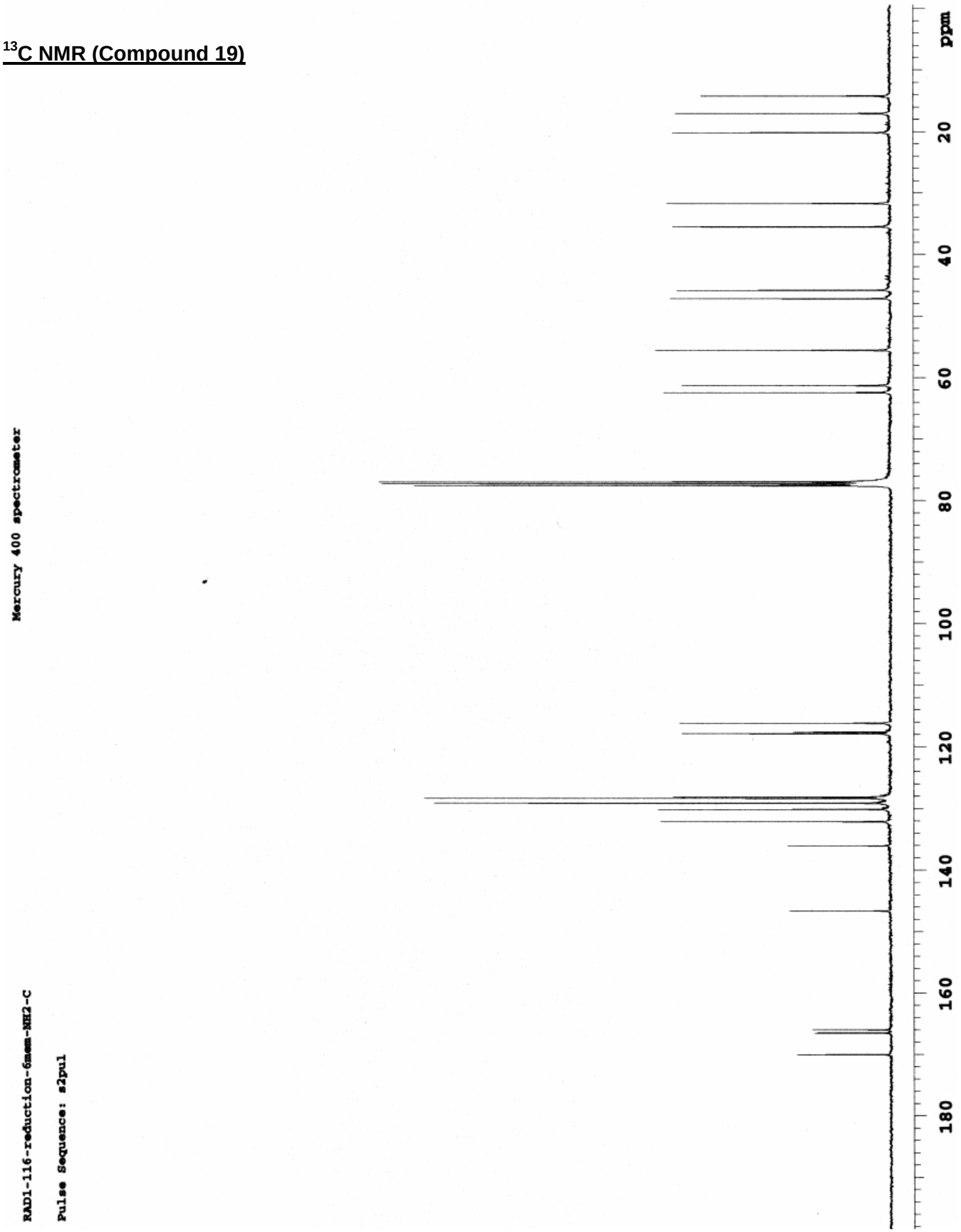
HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2312.

IR (neat): 3447, 3367, 3251, 2965, 2935, 2876, 1732, 1652, 1584, 1496, 1445, 1374, 1294, 1250, 1194, 1164, 1031, 919, 750, 736, 709.

^{1}H NMR (Compound 19)

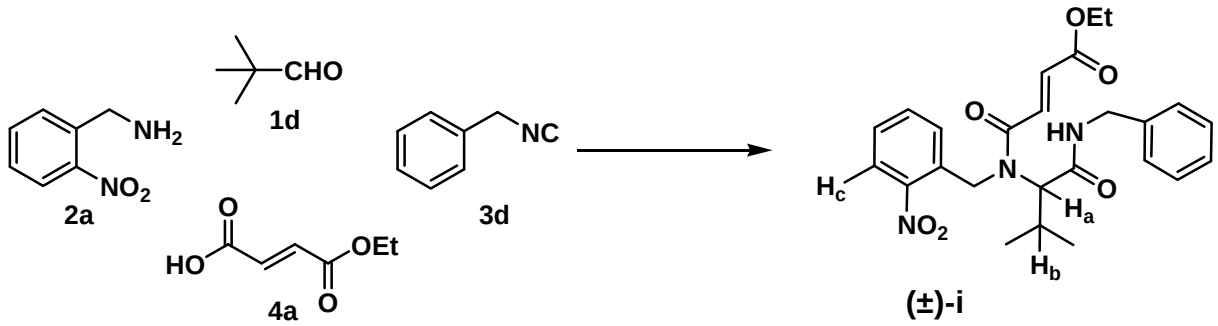


^{13}C NMR (Compound 19)



Additional Data

(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)(2-nitrobenzyl)amino)-4-oxobut-2-enoate **(i)**.



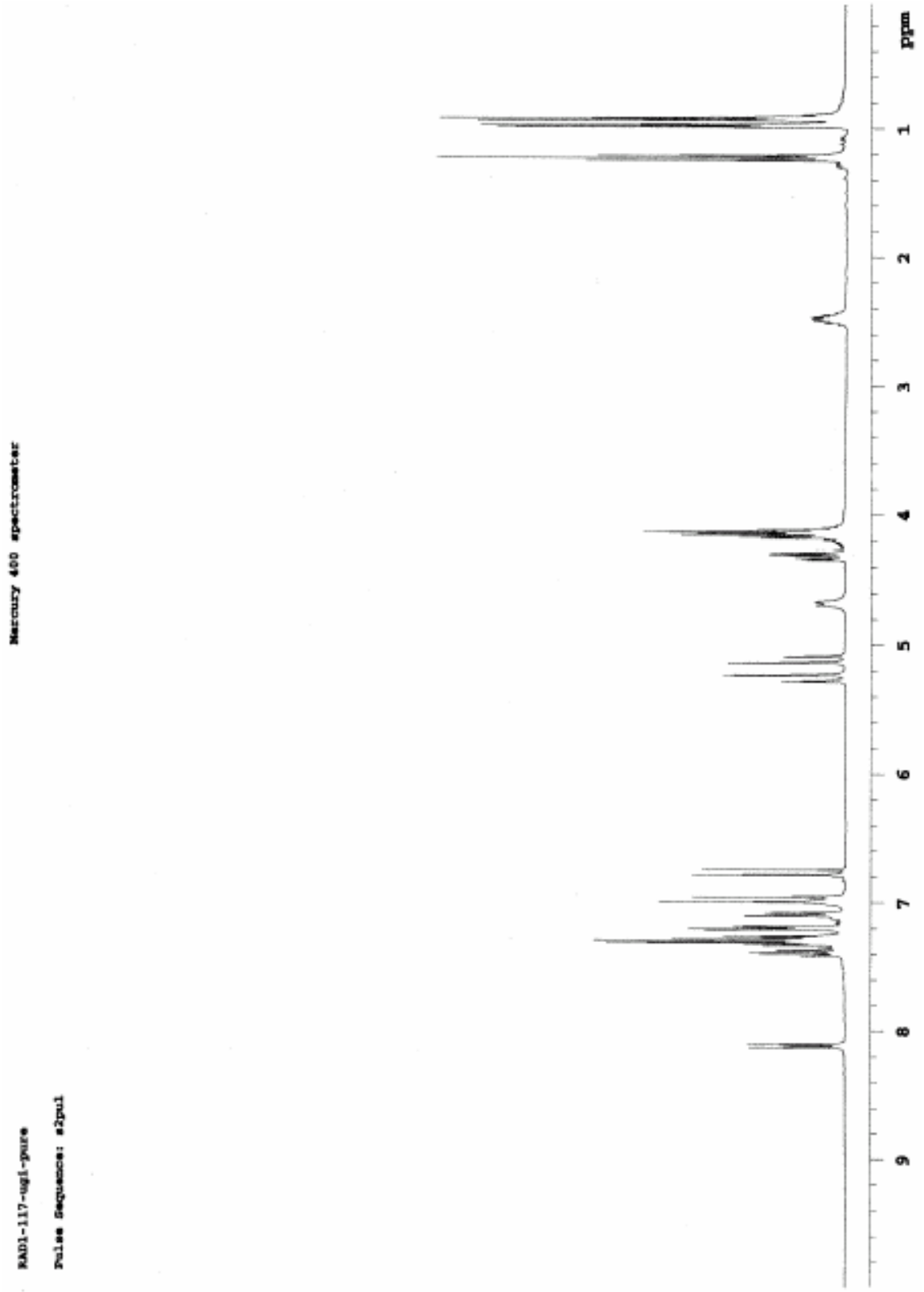
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 8.1 Hz, H_c), 7.37 (t, 1H, *J* = 8.1 Hz, aryl), 7.28 (m, 4H, aryl), 7.1 (br s, 1H, aryl), 7.00 (br s, 1H, aryl), 6.99 (br s, 1H, aryl), 6.95 (d, 1H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 6.70 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 5.20 (d, 1H, *J* = 19.4 Hz, Bn), 5.00 (d, 1H, *J* = 19.4 Hz, Bn), 4.60 (br d, 1H, *J* = 10.5 Hz, H_a), 4.30 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.14 (m, 3H, Bn and -OC<u>H_2</u>CH_3 overlap), 2.45 (m, 1H, H_b), 1.22 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>), 0.97 (d, 3H, *J* = 6.5 Hz, -CH_2(C<u>H_3</u>)$_2$), 0.91 (d, 3H, *J* = 6.5 Hz, -CH_2(C<u>H_3</u>)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 167.1, 165.1, 147.5, 137.9, 133.9, 133.6, 133.4, 133.3, 132.8, 128.9, 128.5, 128.1, 128.0, 127.9, 127.6, 125.9, 65.0, 61.6, 46.5, 43.5, 27.7, 19.1, 18.9, 14.2.

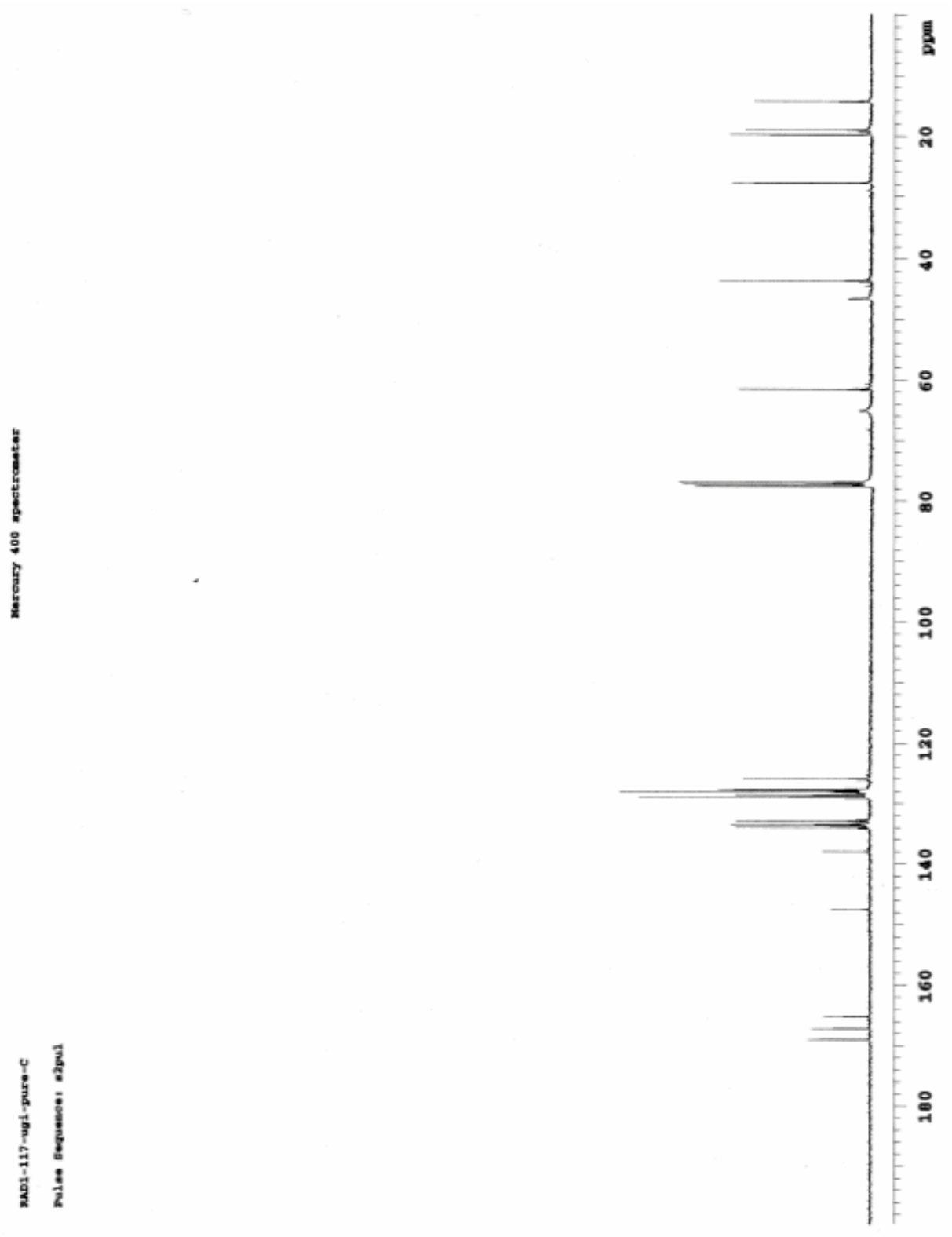
HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2050.

IR (neat): 3323, 3066, 3032, 2966, 2873, 1717, 1655, 1525, 1498, 1442, 1342, 1298, 1174, 1164, 1031, 970, 727, 700.

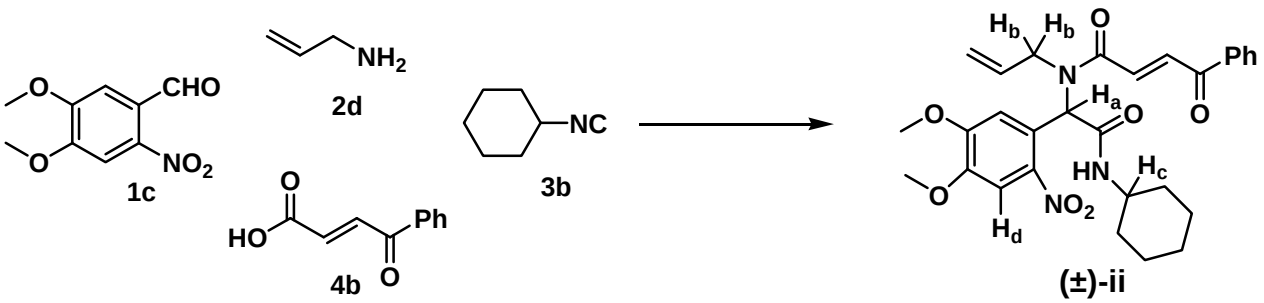
<u>^{1}H NMR (Compound i)</u>



^{13}C NMR (Compound i)



(*E*)-*N*-allyl-*N*-(2-(cyclohexylamino)-1-(4,5-dimethoxy-2-nitrophenyl)-2-oxoethyl)-4-oxo-4-phenylbut-2-enamide **(ii)**.



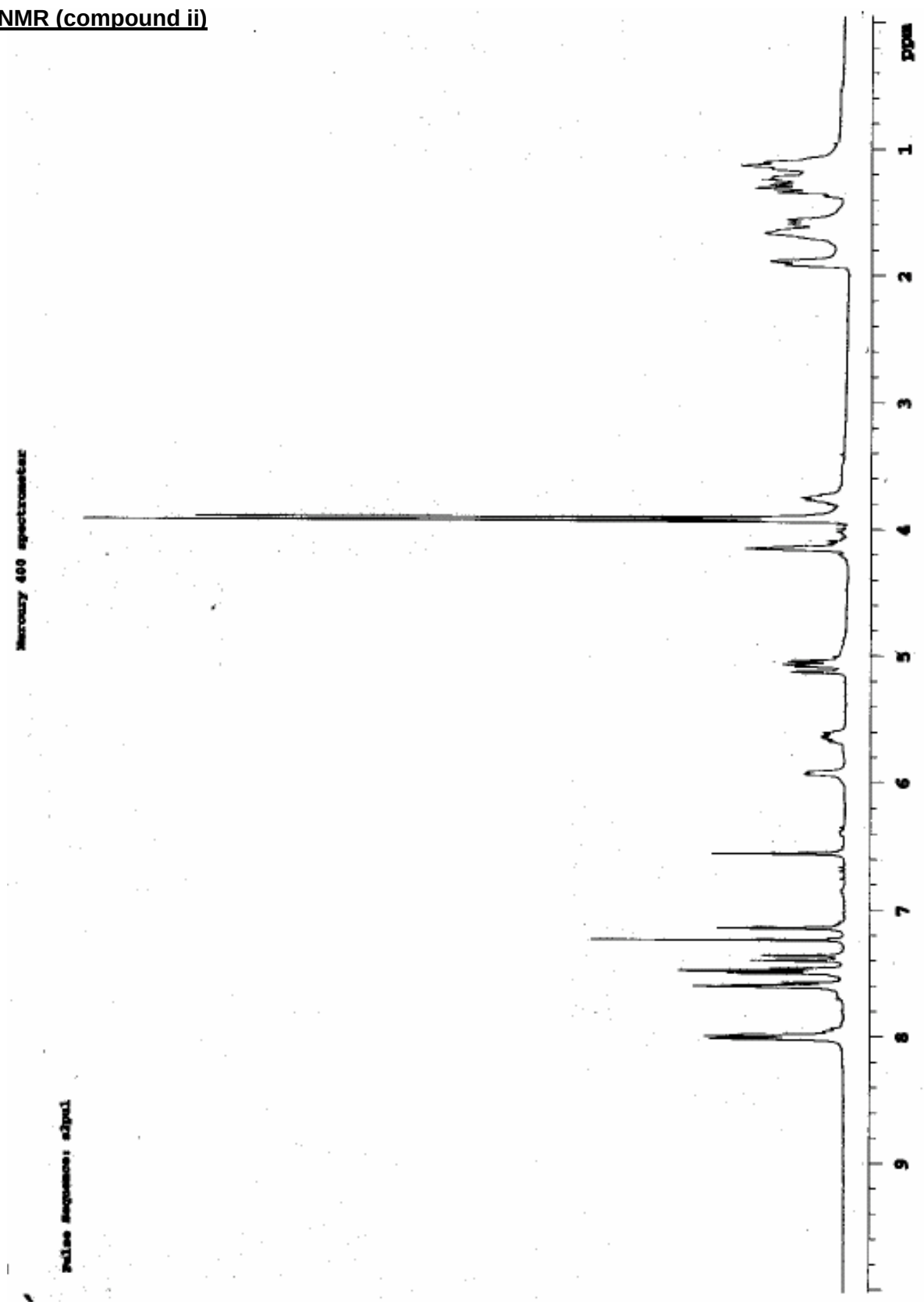
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.90 (m, 3H, aryl), 7.60 – 7.57 (m, 2H, aryl), 7.51 – 7.46 (m, 2H, aryl and C<u>H</u>=CH-), 7.36 (d, 1H, *J* = 15.0 Hz, -CH=C<u>H</u>-), 7.14 (s, 1H, H_d), 6.55 (s, 1H, H_a), 5.91 (br d, 1H, *J* = 6.4 Hz, -N<u>H</u>), 5.66 – 5.59 (m, 1H, -C<u>H</u>=CH_2), 5.12 (d, 1H, *J* = 17.0 Hz, -CH=C<u>H_2</u>), 5.08 (d, 1H, *J* = 17.0 Hz, -CH=C<u>H_2</u>), 4.15 (br s, 2H, H_b), 3.94 (s, 3H, -OC<u>H_3</u>), 3.91 (s, 3H, -OC<u>H_3</u>), 3.70 (m, 1H, H_c), 1.91 – 1.10 (m, 10H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 167.4, 166.4, 152.9, 148.8, 142.3, 136.7, 135.2, 133.7, 133.4, 132.4, 128.8, 128.7, 124.3, 117.6, 112.1, 108.5, 58.9, 56.5, 56.4, 49.0, 48.9, 32.5, 25.4, 24.7, 24.6.

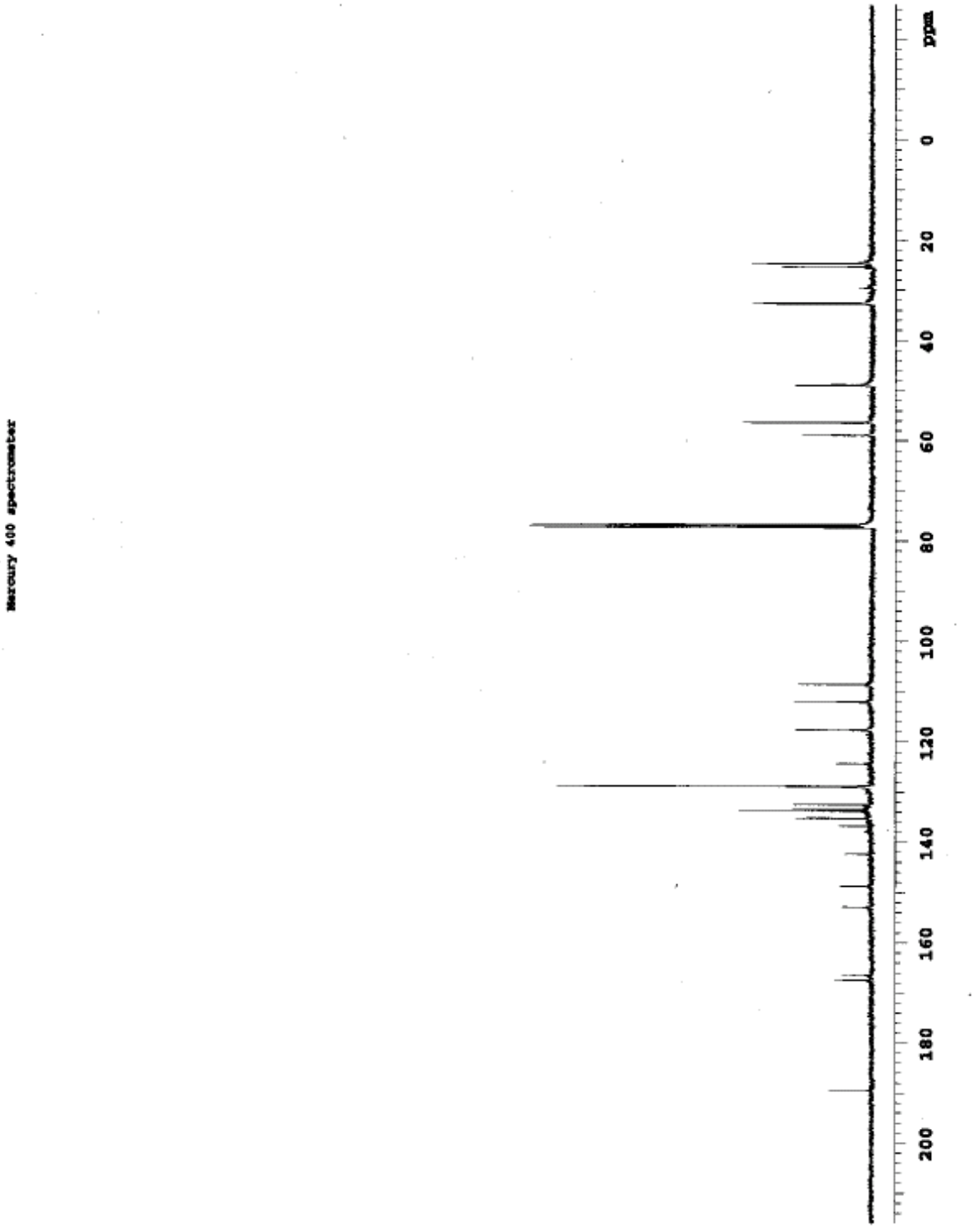
HRMS: EIMS (M^+) calcd for $C_{29}H_{33}N_3O_7$ 535.2319 found 535.2311.

IR (neat): 3321, 3068, 2932, 2854, 1711, 1675, 1643, 1521, 1449, 1410, 1358, 1332, 1275, 1217, 1063, 924.

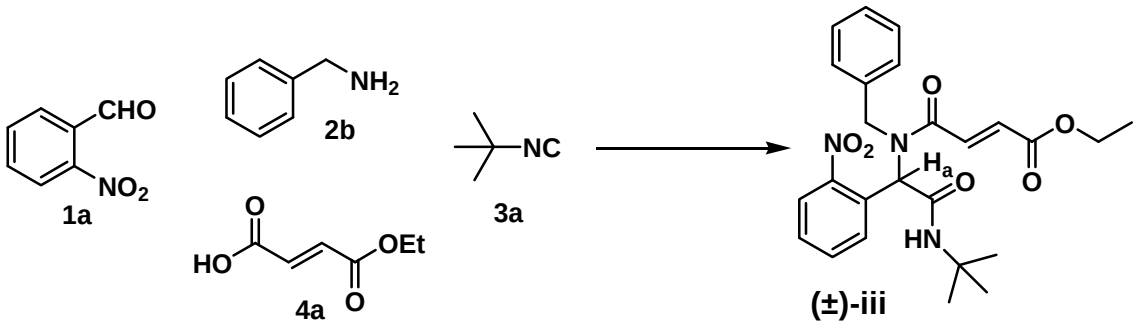
^{1}H NMR (compound ii)



^{13}C NMR (Compound ii)



(*E*)-Ethyl 4-(benzyl(2-*tert*-butylamino)-1-(2-nitrophenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate **(iii)**.



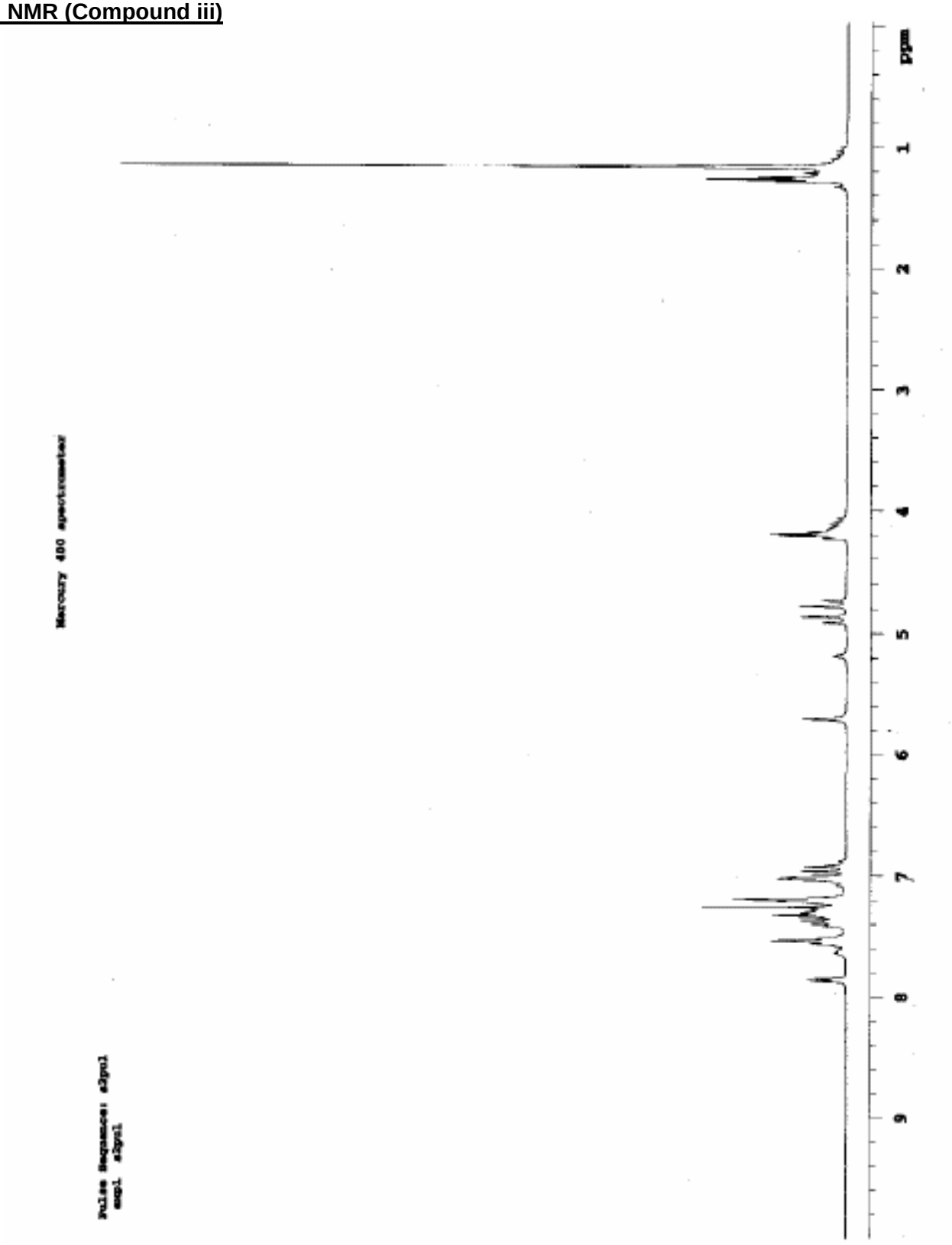
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 1H, *J* = 7.3 Hz, aryl), 7.57 – 7.49 (m, 2H, aryl), 7.41 – 7.19 (m, 5H, aryl and -CH=CH- overlap), 7.02 (br d, 2H, *J* = 7.3 Hz, aryl), 6.92 (d, 1H, *J* = 15.0 Hz -CH=CH-), 5.70 (s, 1H, H_a), 5.19 (s, 1H, -NH), 4.88 (d, 1H, *J* = 17.8 Hz, Bn), 4.74 (d, 1H, *J* = 17.8 Hz, Bn), 4.19 (m, 2H, $-OCH_2CH_3$), 1.30 (m, 3H, $-OCH_2CH_3$), 1.20 (s, 9H, *t*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 166.4, 165.5, 149.6, 136.5, 133.8, 133.4, 133.2, 130.5, 129.9, 129.7, 129.4, 128.9, 128.7, 128.5, 127.8, 126.5, 125.4, 62.9, 61.4, 60.2, 52.2, 50.6, 28.4, 14.3.

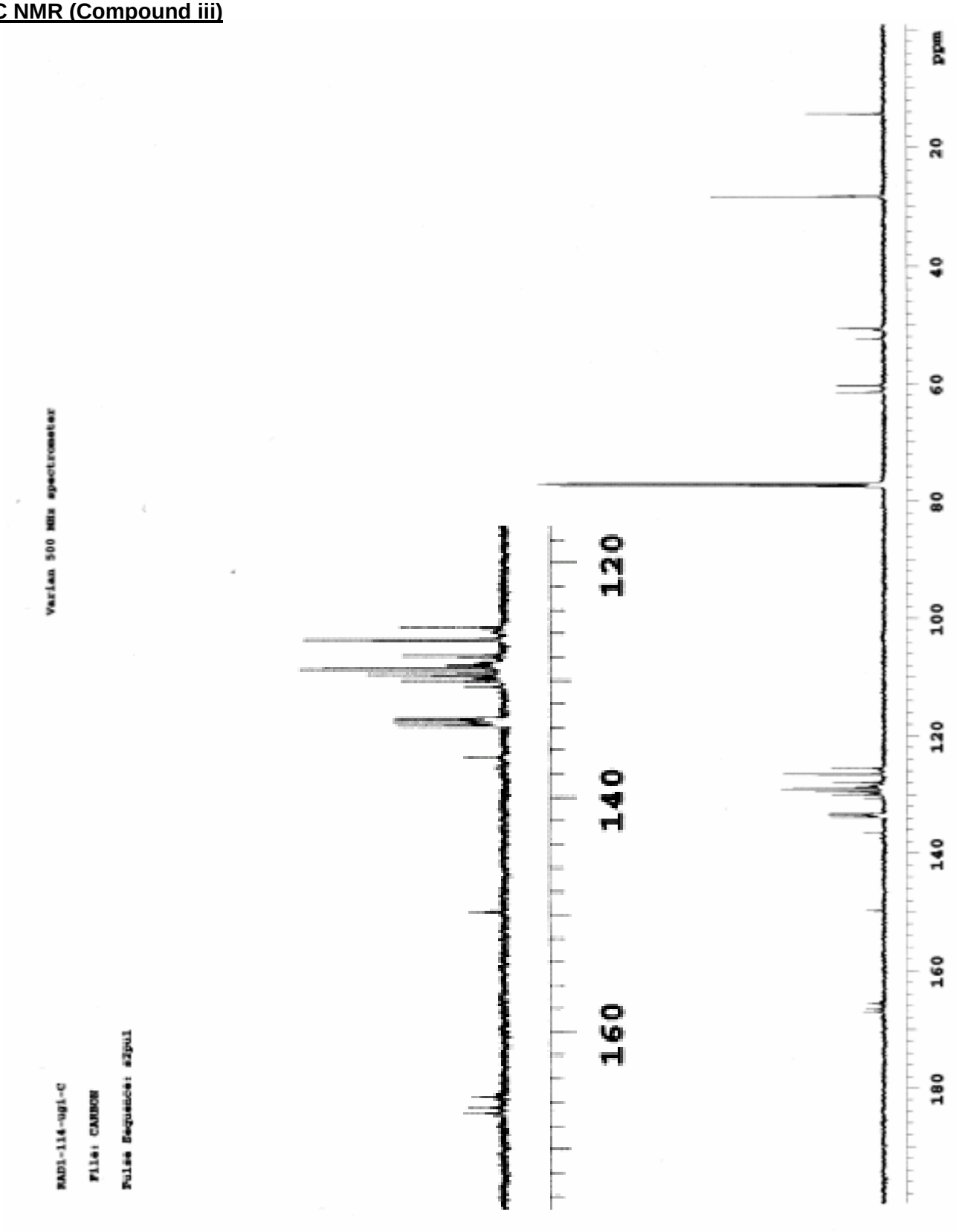
HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2048.

IR (neat): 3325, 2969, 2930, 1720, 1678, 1644, 1620, 1525, 1453, 1418, 1363, 1348, 1222, 1031, 976, 853, 790, 718.

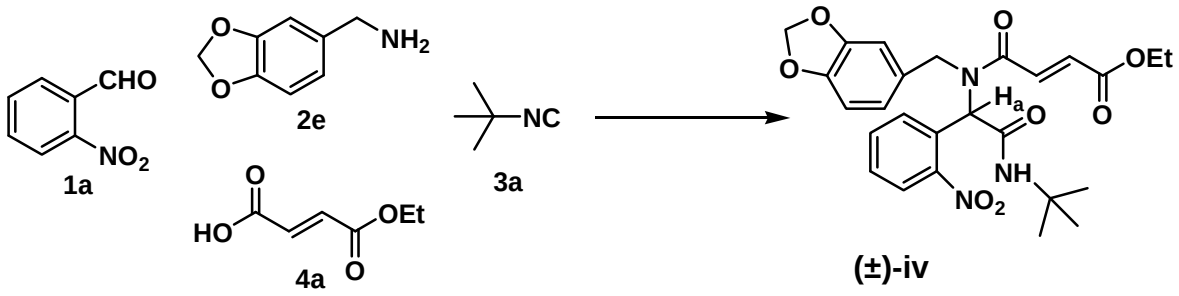
^{1}H NMR (Compound iii)



^{13}C NMR (Compound iii)



(*E*)-Ethyl 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)(2-(*tert*-butylamino)-1-(2-oxoethyl)amino-4-oxobut-2-enoate **(iv)**.



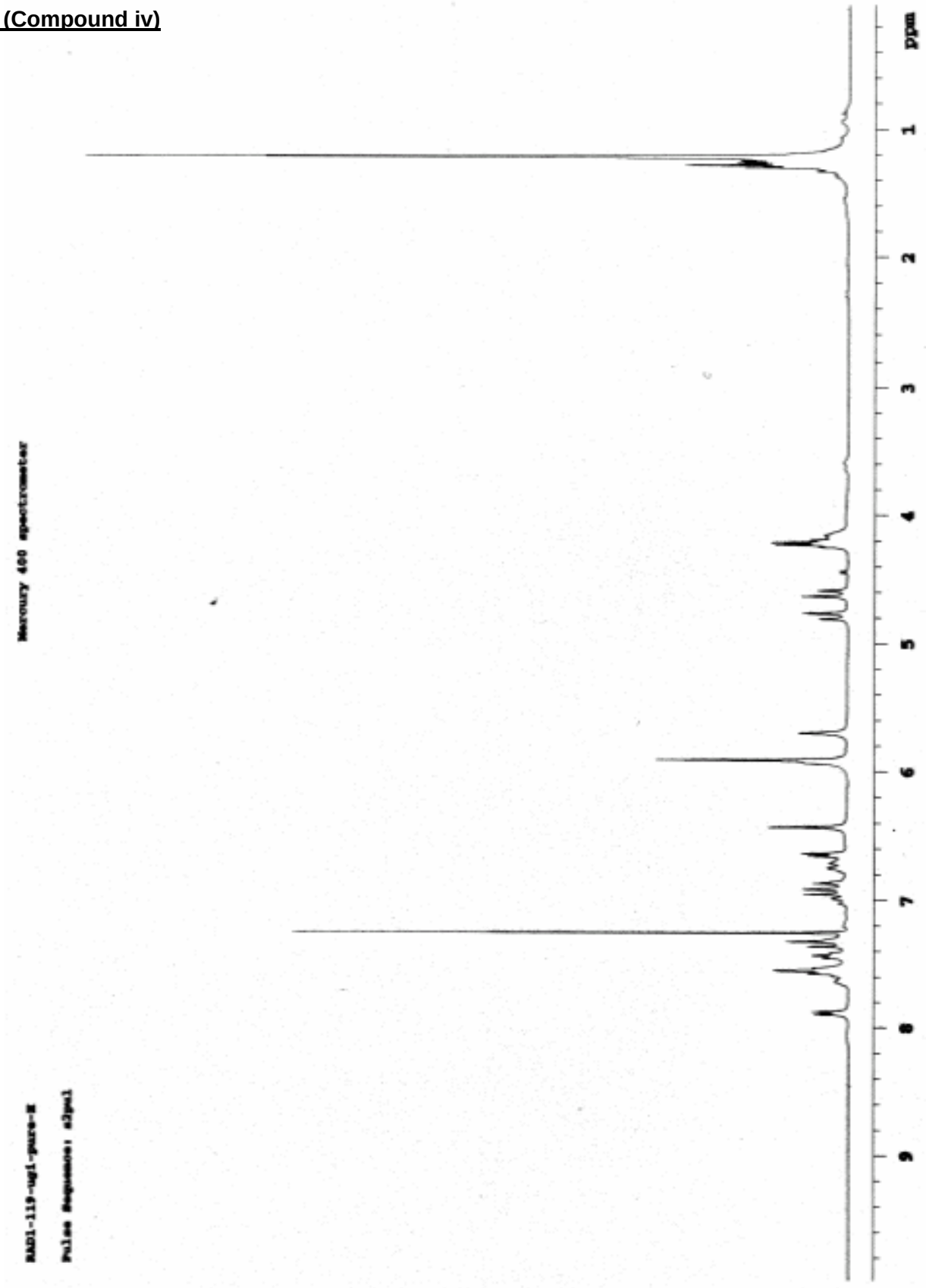
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H, *J* = 8.1 Hz, aryl), 7.63 – 7.24 (m, 3H, aryl and -C<u>H</u>=CH-), 7.02 – 6.85 (m, 2H, aryl and -CH=C<u>H</u>- overlap), 6.75 – 6.63 (m, 2H, aryl), 6.43 (s, 1H, aryl), 5.91 (s, 2H, -OC<u>H</u>$_2$O-), 5.70 (s, 1H, H_a), 4.76 (d, 1H, *J* = 17.0 Hz, Bn), 4.58 (d, 1H, *J* = 17.0 Hz, Bn), 4.21 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 1.28 (t, 3H, *J* = 6.5 Hz, -OCH$_2$C<u>H</u>$_3$), 1.22 (s, 9H, *t*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 166.3, 165.5, 149.7, 148.3, 147.8, 147.3, 133.7, 133.4, 133.3, 133.2, 130.3, 130.1, 129.5, 125.4, 122.4, 120.0, 108.6, 107.1, 101.4, 61.5, 60.3, 52.3, 50.7, 28.5, 14.3.

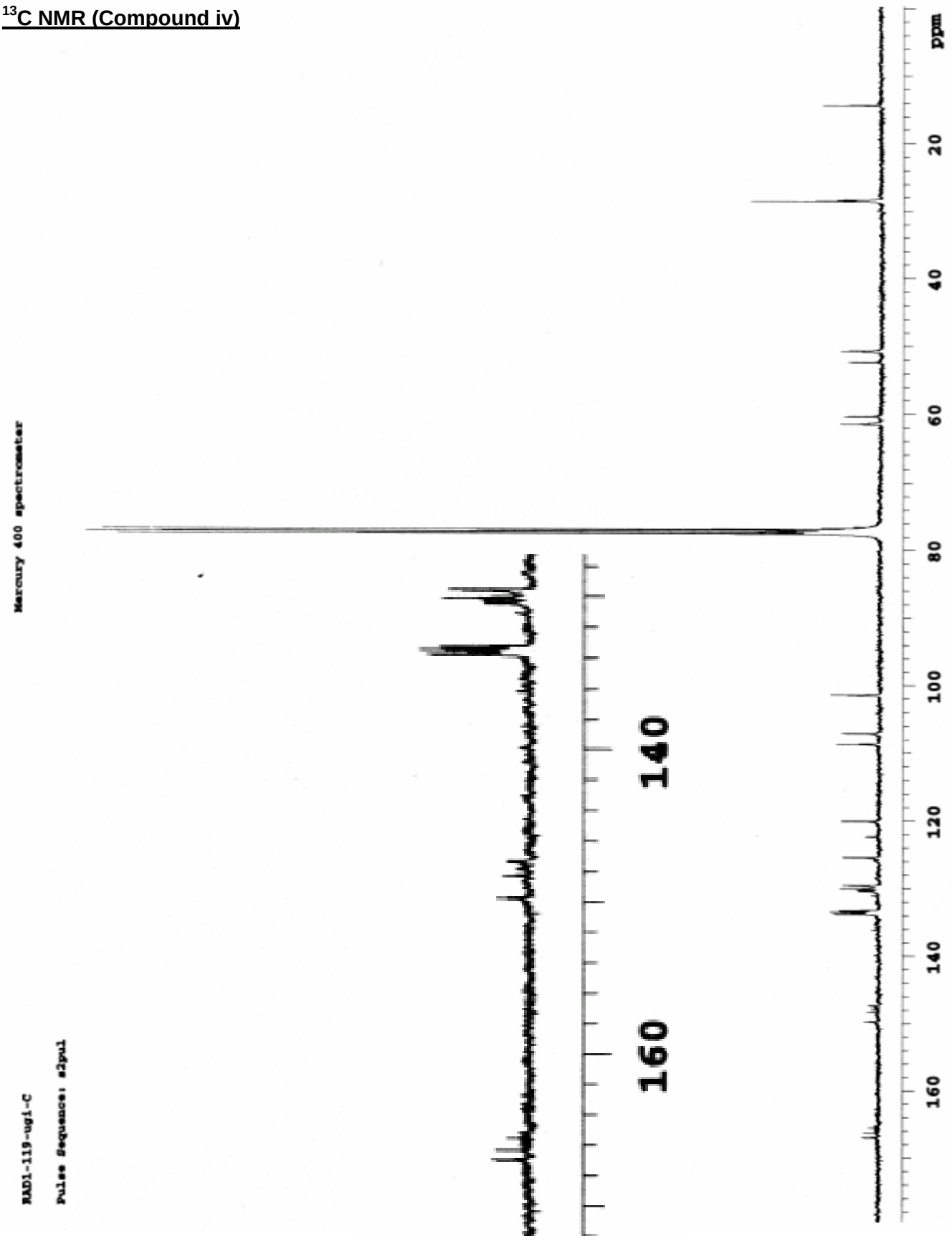
HRMS: EIMS (M^+) calcd for $C_{26}H_{29}N_3O_8$ 511.1955 found 511.1947.

IR (neat): 3339, 3074, 2970, 1829, 1715, 1685, 1657, 1629, 1490, 1420, 1393, 1364, 1296, 1243, 1223, 1173, 1095, 1037, 973, 926, 808, 657.

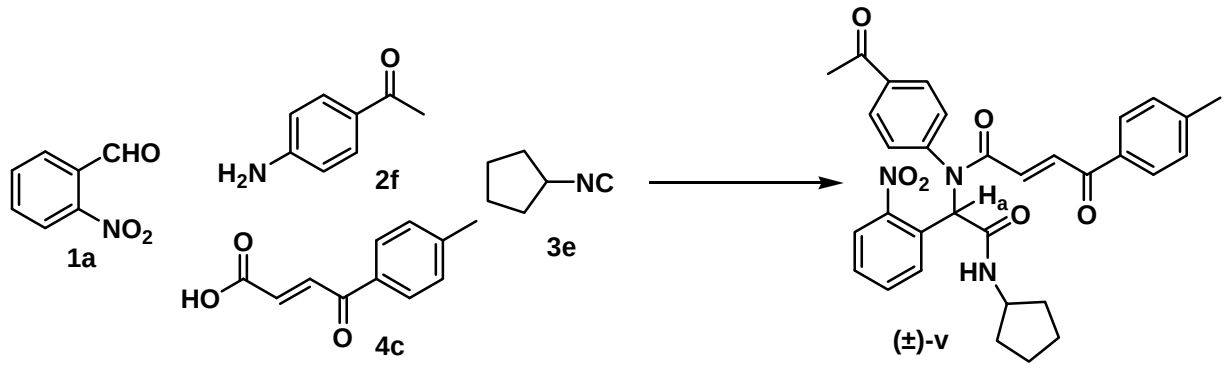
^{1}H NMR (Compound iv)



^{13}C NMR (Compound iv)



(*E*)-*N*-(4-acetylphenyl)-*N*-(2-(cyclopentylamino)-1-(2-nitrophenyl)-2-oxoethyl)-4-oxo-4-*p*-tolylbut-2-enamide **(v)**.



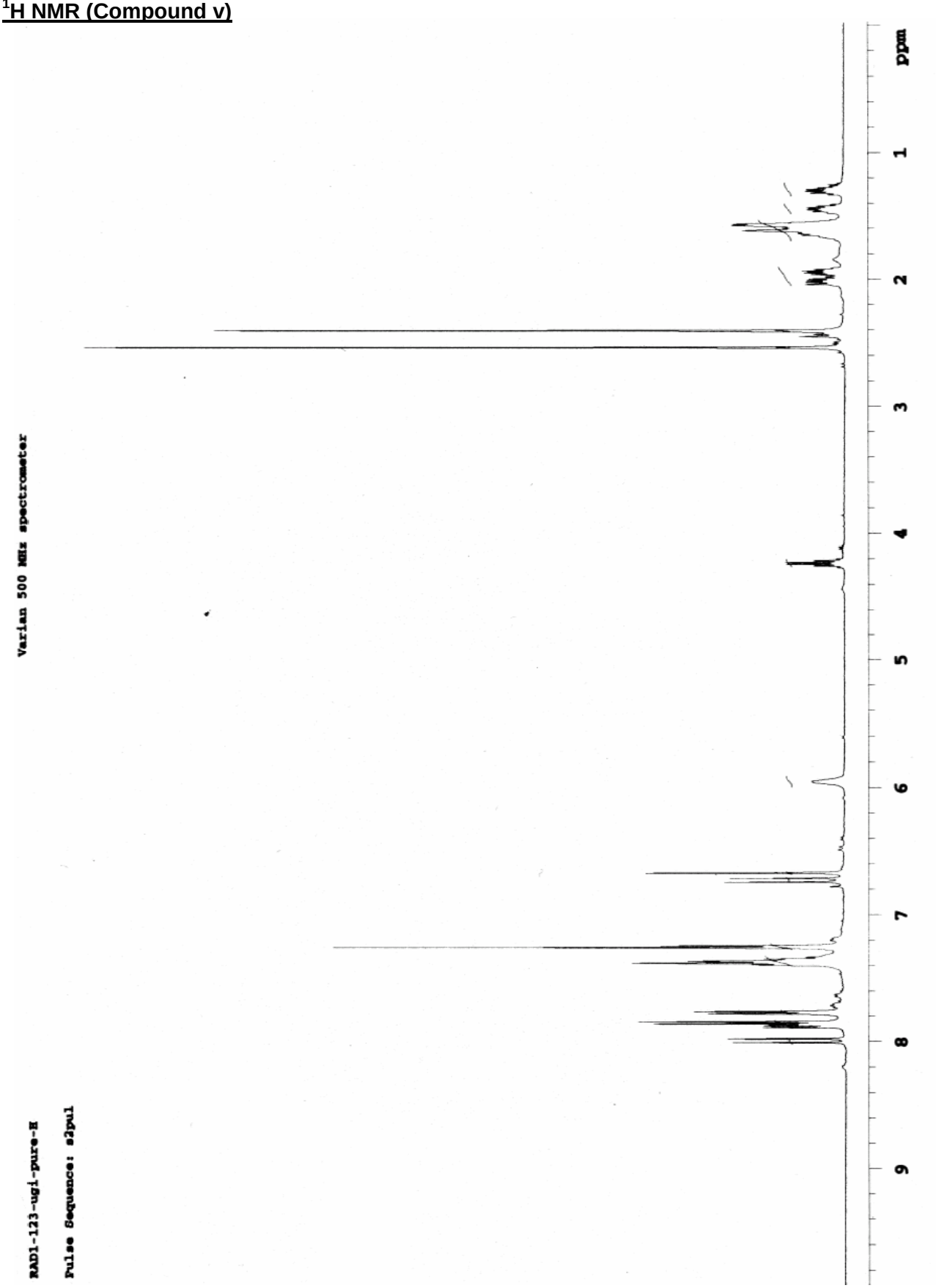
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 14.9 Hz, C<u>H</u>=CH-), 7.88 – 7.84 (m, 3H, aryl), 7.76 (d, 2H, *J* = 7.3 Hz, aryl), 7.39 – 7.33 (m, 5H, aryl), 7.24 (d, 2H, *J* = 7.0 Hz, aryl), 6.71 (d, 1H, *J* = 15.0 Hz, -CH=C<u>H</u>-), 6.67 (s, 1H, H_a), 5.94 (s, 1H, -N<u>H</u>), 4.24 (m, 1H, Cp), 2.53 (s, 3H, -C<u>H</u>$_3$), 2.40 (s, 3H, -C<u>H</u>$_3$), 2.03 – 1.91 (m, 2H, Cp), 1.68 – 1.53 (m, 4H, Cp), 1.47 – 1.41 (m, 1H, Cp), 1.32 – 1.25 (m, 1H, Cp).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.2, 188.9, 168.1, 164.9, 145.1, 142.7, 137.1, 135.4, 135.3, 134.6, 134.5, 133.3, 133.2, 132.2, 132.1, 130.6, 130.2, 129.7, 129.4, 129.2, 129.1, 129.0, 128.9, 128.5, 125.1, 60.7, 52.2, 33.0, 26.9, 24.0, 23.9, 22.0.

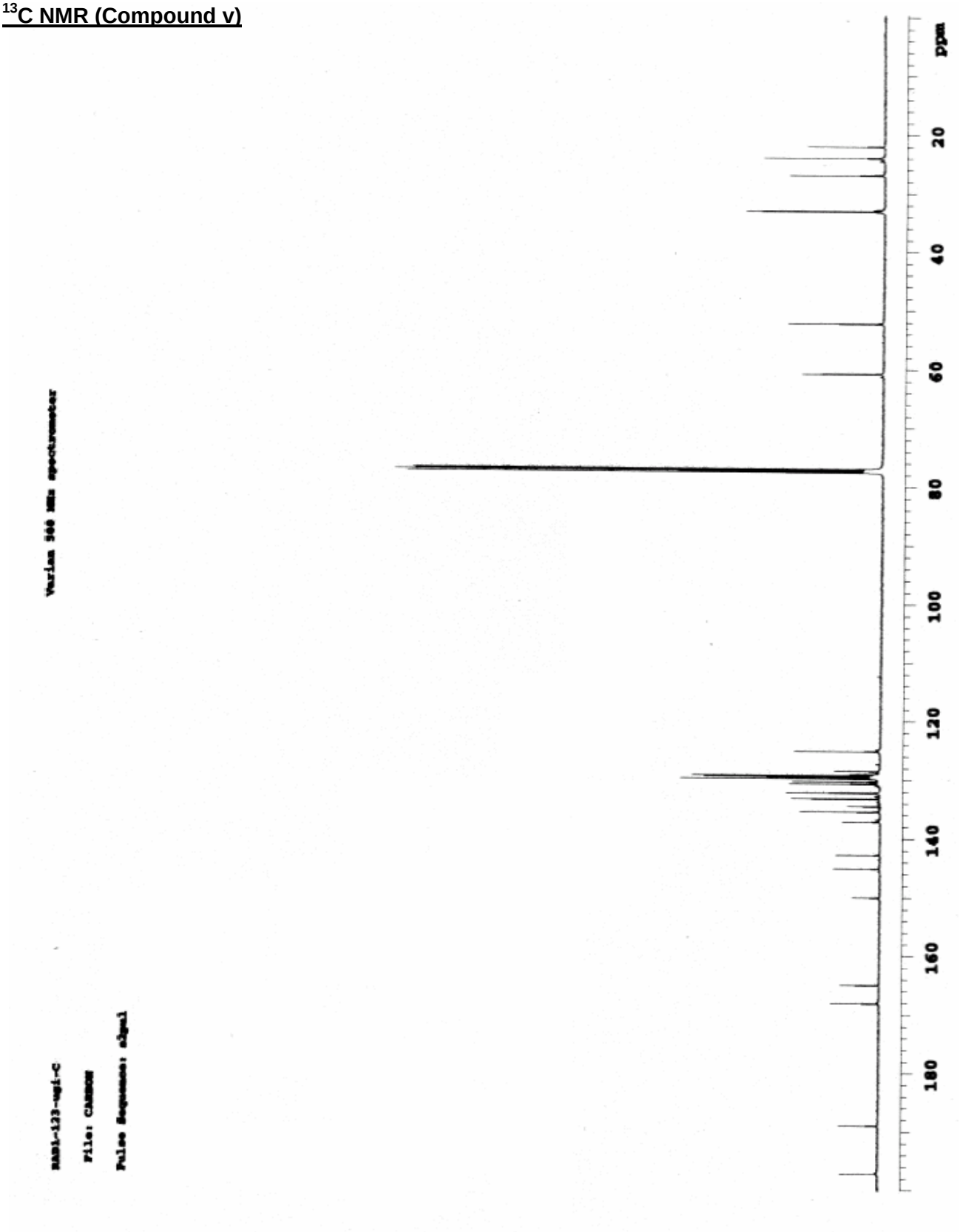
HRMS: EIMS (M^+) calcd for $C_{32}H_{31}N_3O_6$ 553.2213 found 553.2218.

IR (neat): 3309, 3067, 2916, 2869, 1712, 1684, 1647, 1599, 1526, 1443, 1407, 1350, 1292, 1262, 1194, 1181, 1027, 1013, 969, 858, 789, 741, 704.

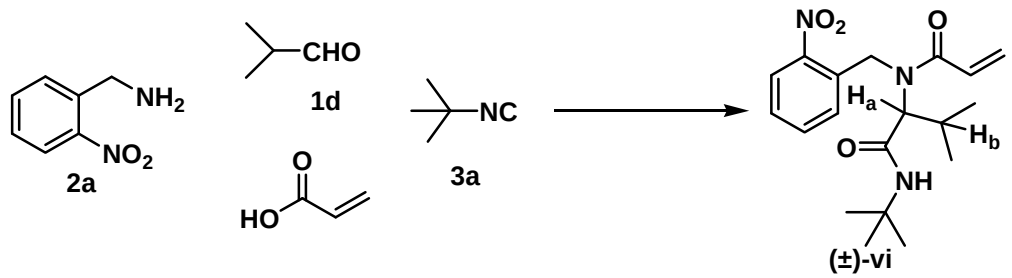
^{1}H NMR (Compound v)



^{13}C NMR (Compound v)



N-*tert*-butyl-3-methyl-2-(*N*-(2-nitrobenzyl)acrylamido)butanamide **(vi)**.



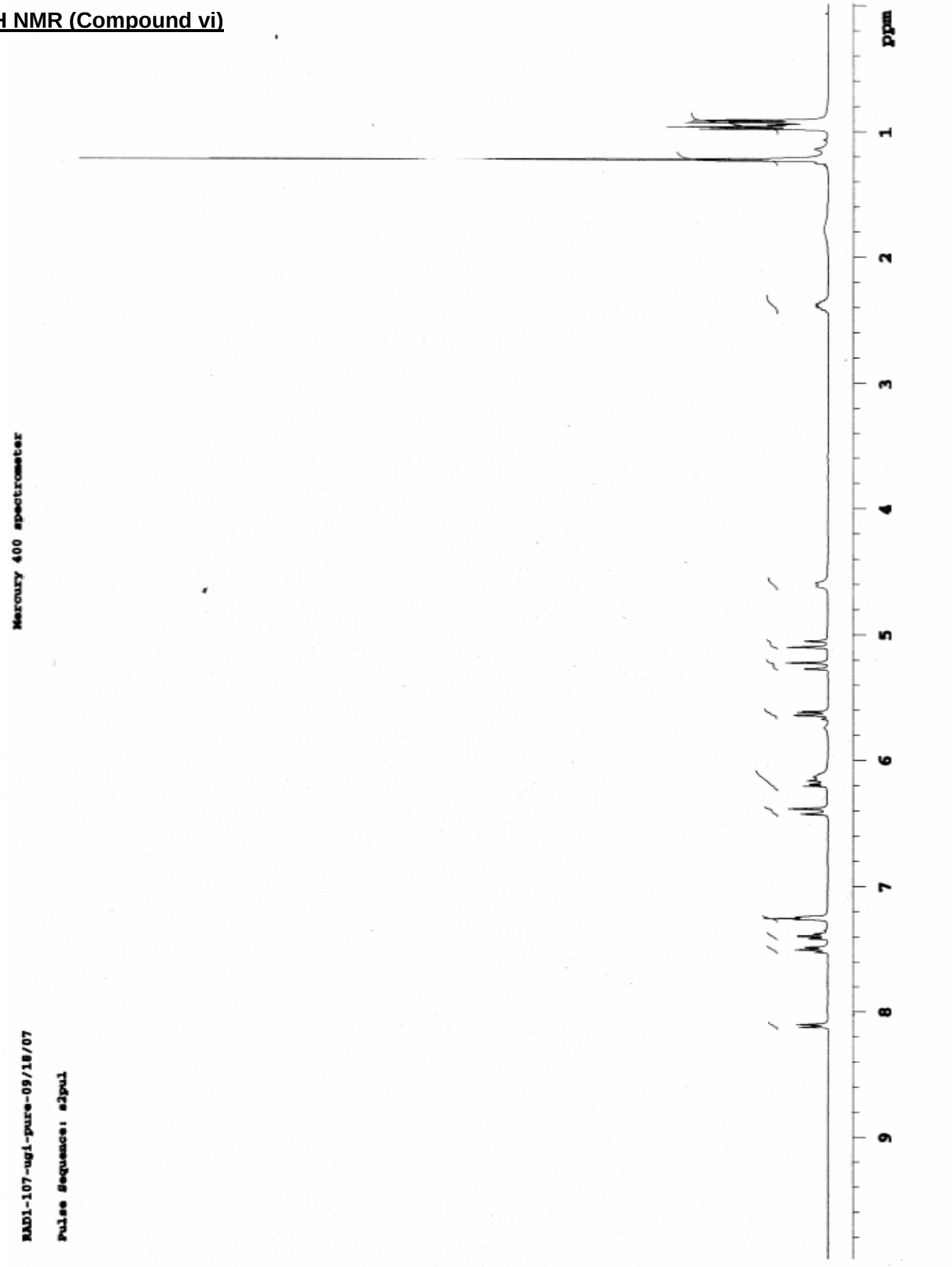
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 7.4 Hz, aryl), 7.50 (t, 1H, *J* = 7.3 Hz, aryl), 7.40 (t, 1H, *J* = 7.3 Hz, aryl), 7.25 (m, 1H, aryl), 6.40 (d, 1H, *J* = 16.2 Hz, -CH=C$\underline{H}_2$), 6.16 (m, 1H, -C$\underline{H}$=CH_2), 5.62 (d, 1H, *J* = 16.0 Hz, -CH=C$\underline{H}_2$), 5.24 (d, 1H, *J* = 19.5 Hz, Bn), 5.60 (d, 1H, *J* = 19.5 Hz, Bn), 4.60 (d, 1H, *J* = 10.5 Hz, H_a), 2.43 – 2.34 (m, 1H, H_b), 1.22 (s, 9H, *t*-butyl), 0.96 (d, 3H, *J* = 6.5 Hz, -CH($C\underline{H}_3$)$_2$) , 0.91 (d, 3H, *J* = 6.5 Hz, -CH($C\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.0, 148.6, 133.4, 130.1, 128.2, 128.1, 127.9, 127.1, 125.4, 59.6, 51.4, 45.8, 28.6, 28.4, 27.8, 19.3, 18.6.

HRMS: EIMS (M^+) calcd for $C_{19}H_{27}N_3O_4$ 361.2002 found 361.2005.

IR (neat): 3328, 3077, 2965, 2874, 1714, 1675, 1644, 1525, 1448, 1344, 1301, 1222, 1194, 1060, 971, 861, 728,676.

^{1}H NMR (Compound vi)



^{13}C NMR (Compound vi)