Supporting Information

3-Substituted 2-Phenyl-Indoles: Privileged Structures for Medicinal Chemistry

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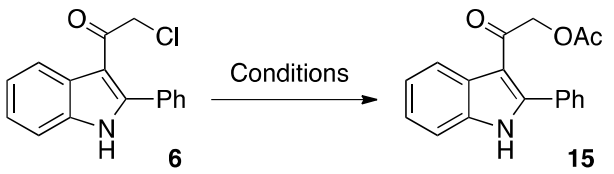
Synthetic optimisation for indoles 1, 3, 5 and 15

Table S1. Nucleophilic substitution on indole **6** using NaOAc, to give indole **15**

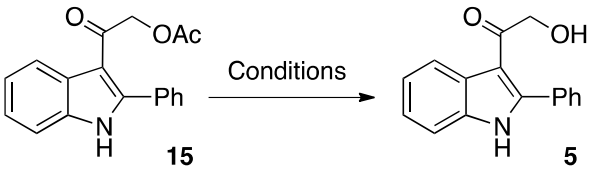


Entry	Solvent	NaOAc (equiv)	*t* (hr)	*t* (°C)	15 [a] (%)	6 [a] (%)
A	DMF	1	5	60	70	22
B	DMSO	1	5	60	91	3
C	MeCN	1	5	60	1	98
D	1-Methoxy-2-propanol	1	5	60	5	94
E	H_2O	1	5	60	-	99
F	^{t}BuOH	1	5	60	-	99
G	DMSO	1.2	2.5	60	93 (90)[b]	-
H	DMSO	2.0	2.5	60	93	-
I	DMSO	5.0	2.5	60	93	-
J	DMSO	1.2	1	80	92	-
K	DMSO	1.2	0.5	100	92	-

[a] Conversion by integration of HPLC peaks detected at 254 nm. [b] Isolated yield.

Conditions: **6** (0.10 g, 0.37 mmol), NaOAc , and solvent (2.5 ml) was stirred at the given temperature in a sealed reaction vessel, and monitored by HPLC-MS.

Table S2. Hydrolysis of indole **15** to give alcohol **5**

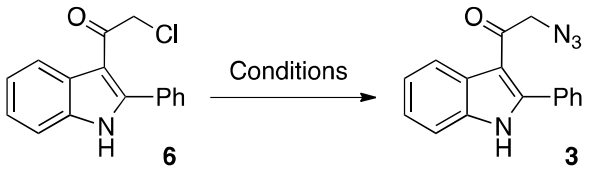


Entry	Solvent	Reagent	Equiv	*t* (hr)	*t* (°C)	**5** [a] (%)	**15** [a] (%)
A	MeOH	HCl (4M aq)	2	3	60	61	4
B	MeOH	NaOH (2M aq)	2	3	60	81	-
C	MeOH	NaOMe	2	3	60	80	2
D	MeOH	HCl (4M aq)	3	5	40	74	10
E	MeOH	NaOMe	2	5	40	61	-
F	THF	HCl (4M aq)	24	8	40	72	8
G	THF	HCl (4M aq)	29	4.5	50	68 (75%)[b]	5
H	Dioxane	HCl (4M aq)	29	1.5	50	66	9

[a] Conversion by integration of HPLC peaks detected at 254 nm. [b] Isolated yield.

Conditions: **15** (0.04-0.08 g, 0.14-0.27 mmol), reagent, and solvent (2 ml) was stirred at the given temperature in a sealed reaction vessel, and monitored by HPLC-MS.

Table S3. Nucleophilic substitution on indole **6** using NaN_3 to give azide **3**

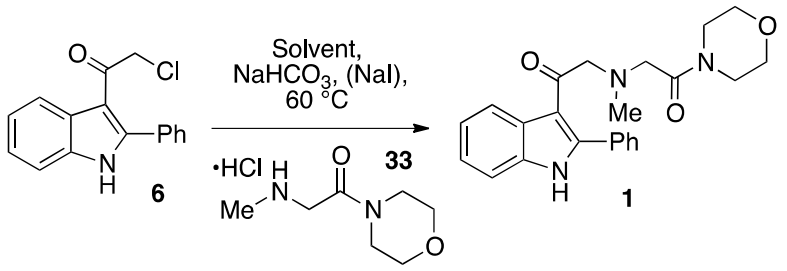


Entry	Solvent	NaN_3 (equiv)	*t* (min)	*t* (°C)	**3** [a] (%)	**6** [a] (%)
A	DMF	1	150	60	85	3
B	DMSO	1	150	60	69	2
C	MeCN	1	150	60	53	46
D	1-Methoxy-2-propanol	1	150	60	57	33
E	Acetone/H_2O[b]	1	150	60	63	30
F	^{t}BuOH	1	150	60	5	94
G	MeCN	1.1	150	80	88	4
H	DMSO	1.1	60	60	39	1
I	DMSO	1.2	15	60	61	1
J	DMSO	1.2	120	r.t	96 (90)[c]	1

[a] Conversion by integration of HPLC peaks detected at 254 nm; SM – Starting material. [b] 4:1 ratio. [c] Isolated yield.

Conditions: **6** (0.075 g, 0.28 mmol), NaN_3 and solvent (2 ml) was stirred at the given temperature in a sealed reaction vessel, and monitored by HPLC-MS.

Table S4. Nucleophilic substitution on indole **6** using amine **33** to produce GPRC6A antagonist **1**

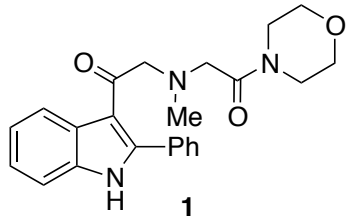


Entry	Solvent	NaI	Ratio 6:1 (%) (t = 1 hr)	Ratio 6:1 (%) (t = 8 hr)
1	Acetone	-	68 : 32	22 : 78
2	Acetone	20 mol%	10 : 90	1 : 99
3	CH_3CN	-	39 : 61	14 : 86
4	CH_3CN	20 mol%	13 : 87	5 : 95
5	DMF	-	30 : 70	7 : 93
6	DMF	20 mol%	13 : 87	5 : 95
7	DMSO	-	27 : 73	7 : 93
8	DMSO	20 mol%	20 : 80	5 : 95

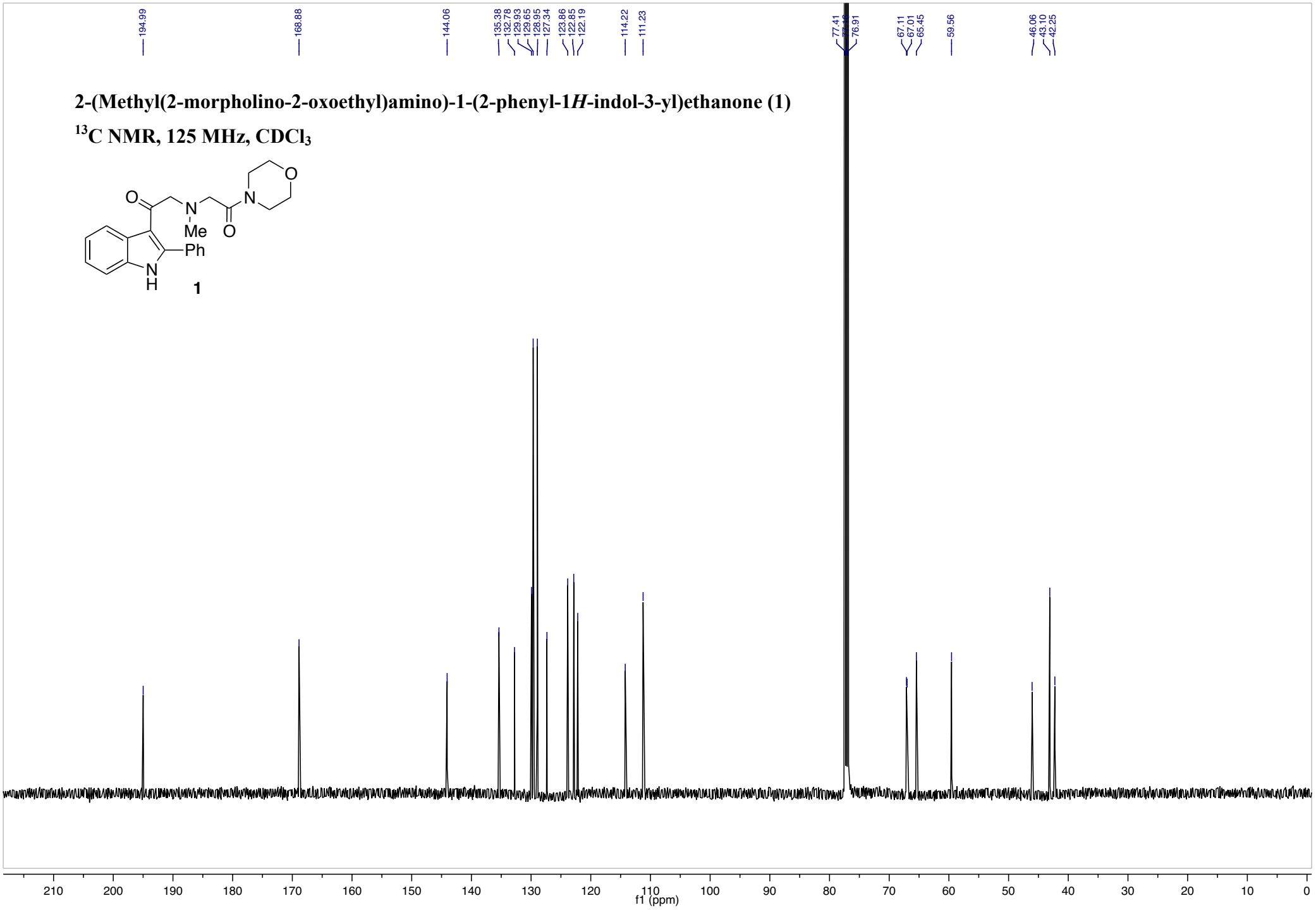
Conditions: Indole **6** (1 equiv), amine **33** (1 equiv), $NaHCO_3$ (2.5 equiv) with or without added NaI (0.2 equiv) was suspended in anhydrous solvent (8 ml/mmol) in a microwave vial, sealed and heated at 60 °C in an oil bath. Aliquots were examined by HPLC-MS after 1 and 8 hr. The ratio between starting material **6** and product **1** detected at 254 nm is shown not accounting for formed side products.

2-(Methyl(2-morpholino-2-oxoethyl)amino)-1-(2-phenyl-1*H*-indol-3-yl)ethanone (1)

^{1}H NMR, 500 MHz, $CDCl_3$

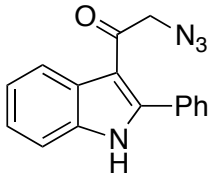


1



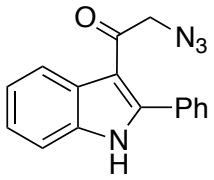
2-Azido-1-(2-phenyl-1*H*-indol-3-yl)ethanone (3)

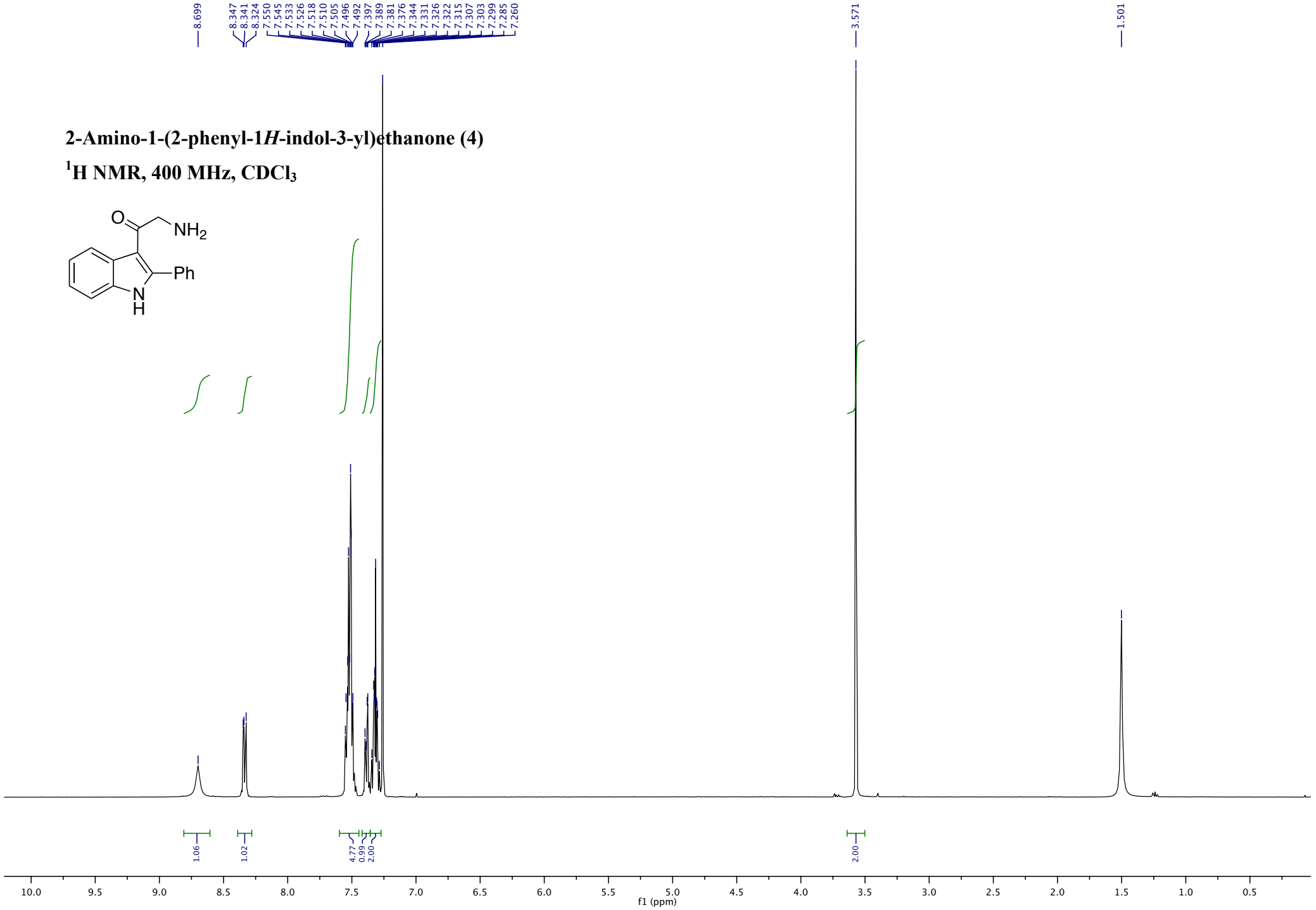
^{1}H NMR, 400 MHz, DMSO-d_6



2-Azido-1-(2-phenyl-1*H*-indol-3-yl)ethanone (3)

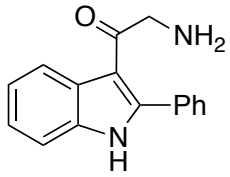
^{13}C NMR, 100 MHz, DMSO-d_6

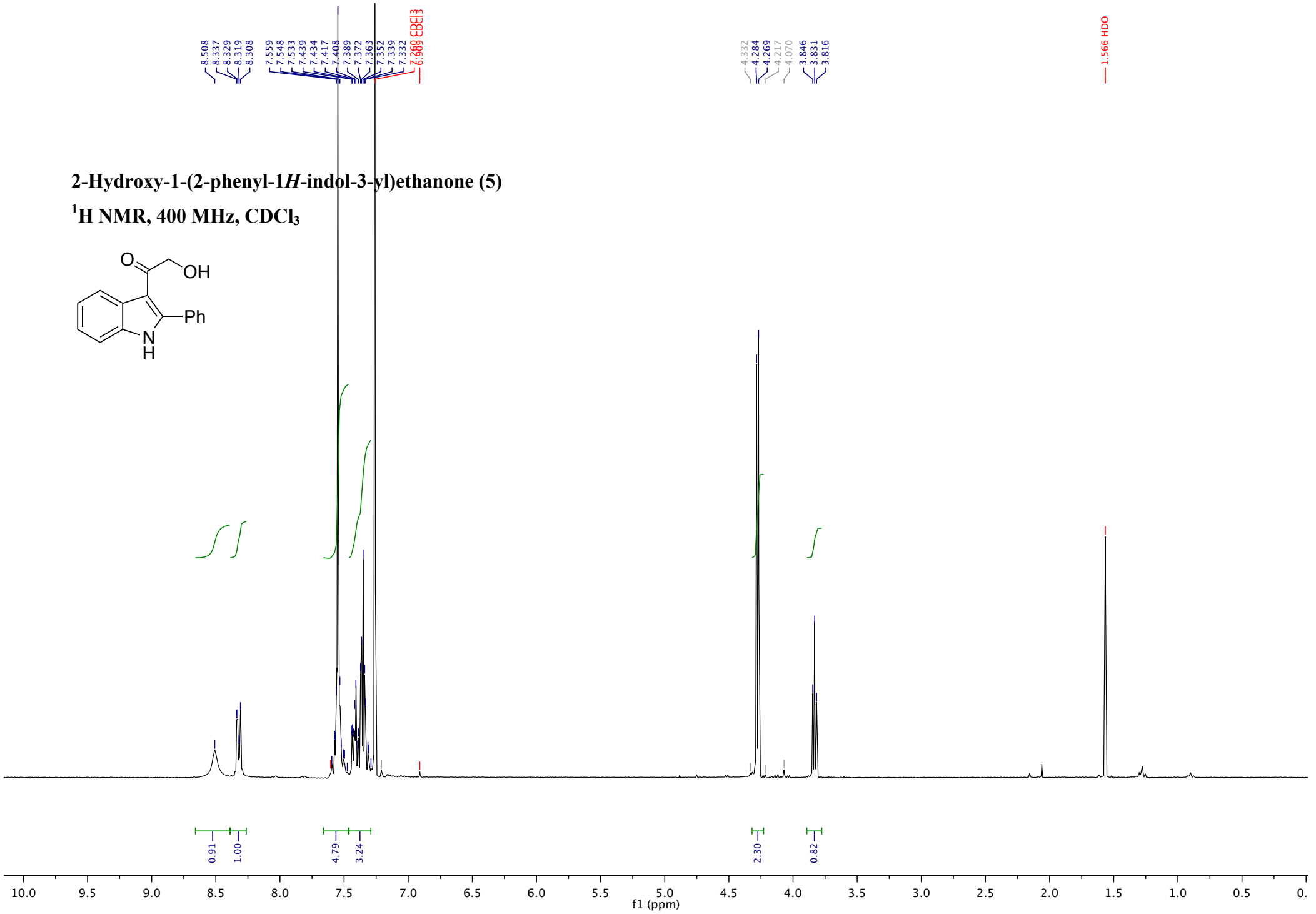




2-Amino-1-(2-phenyl-1*H*-indol-3-yl)ethanone (4)

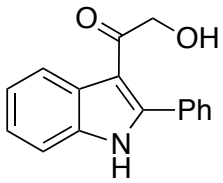
^{13}C NMR, 100 MHz, DMSO-d_6





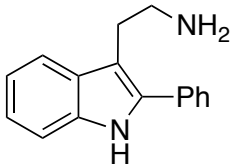
2-Hydroxy-1-(2-phenyl-1*H*-indol-3-yl)ethanone (5)

^{13}C NMR, 100 MHz, $CDCl_3$



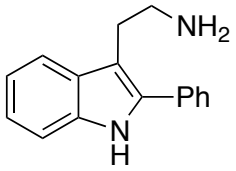
2-(2-Phenyl-1*H*-indol-3-yl)ethanamine (9)

^{1}H NMR, 400 MHz, $CDCl_3$



2-(2-Phenyl-1*H*-indol-3-yl)ethanamine (9)

^{13}C NMR, 100 MHz, $CDCl_3$



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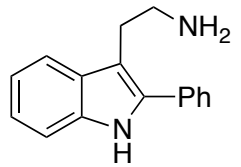
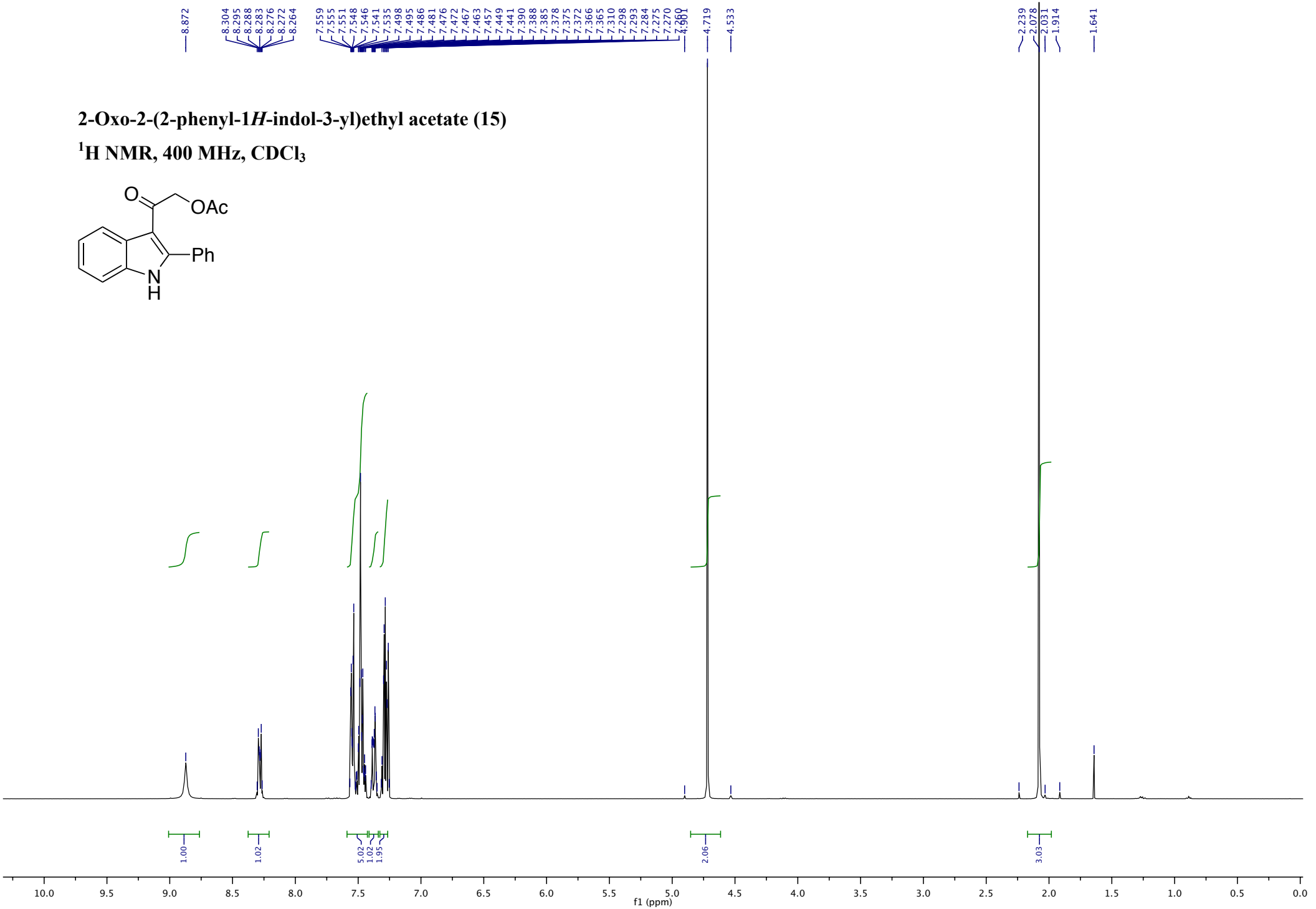


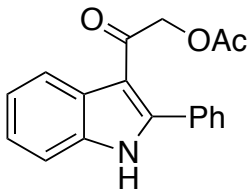
2-(2-Phenyl-1*H*-indol-3-yl)ethanamine (9)

HSQC, 400 MHz, $CDCl_3$



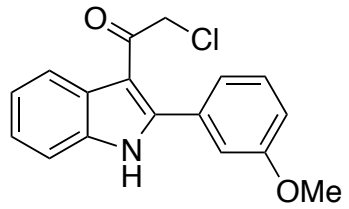
2-Oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl acetate (15)

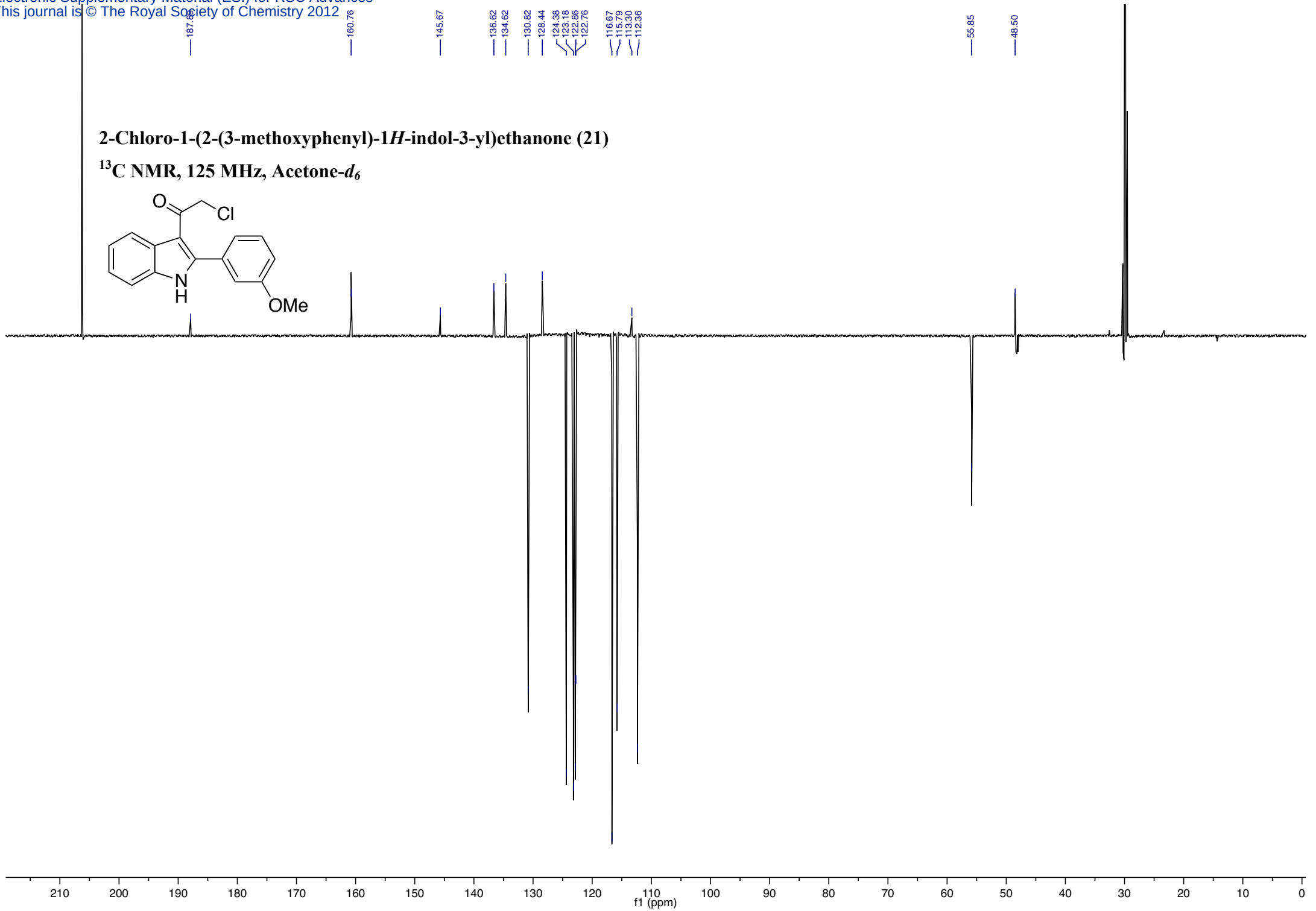
^{13}C NMR, 100 MHz, $CDCl_3$



2-Chloro-1-(2-(3-methoxyphenyl)-1*H*-indol-3-yl)ethanone (21)

^{1}H NMR, 300 MHz, Acetone-d_6



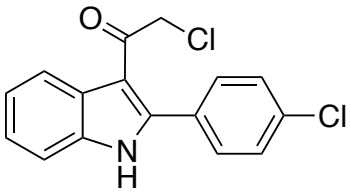


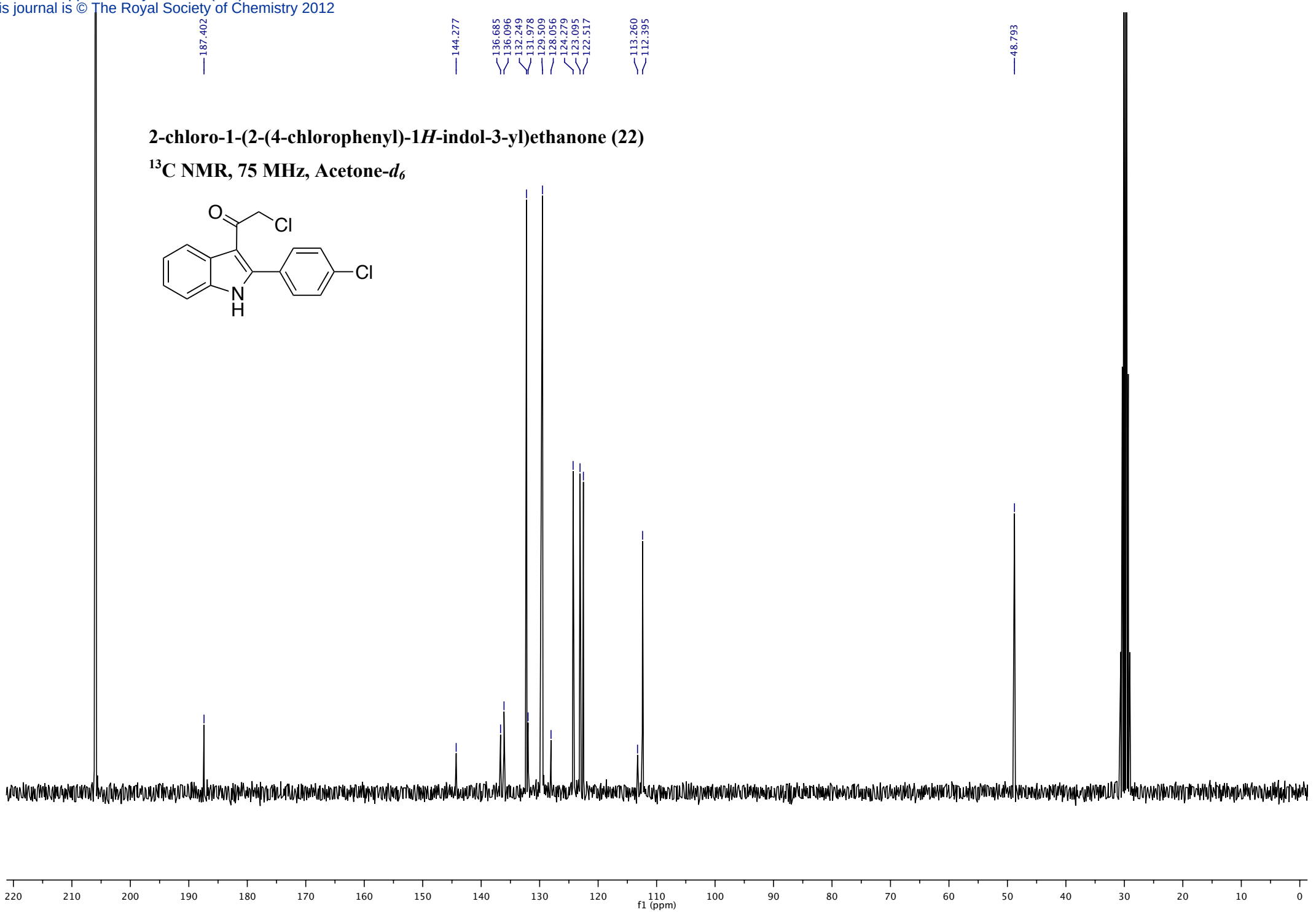
2-Chloro-1-(2-(3-methoxyphenyl)-1*H*-indol-3-yl)ethanone (21)

^{13}C NMR, 125 MHz, Acetone-d_6

2-chloro-1-(2-(4-chlorophenyl)-1*H*-indol-3-yl)ethanone (22)

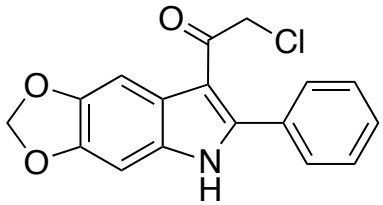
^{1}H NMR, 300 MHz, DMSO-d_6

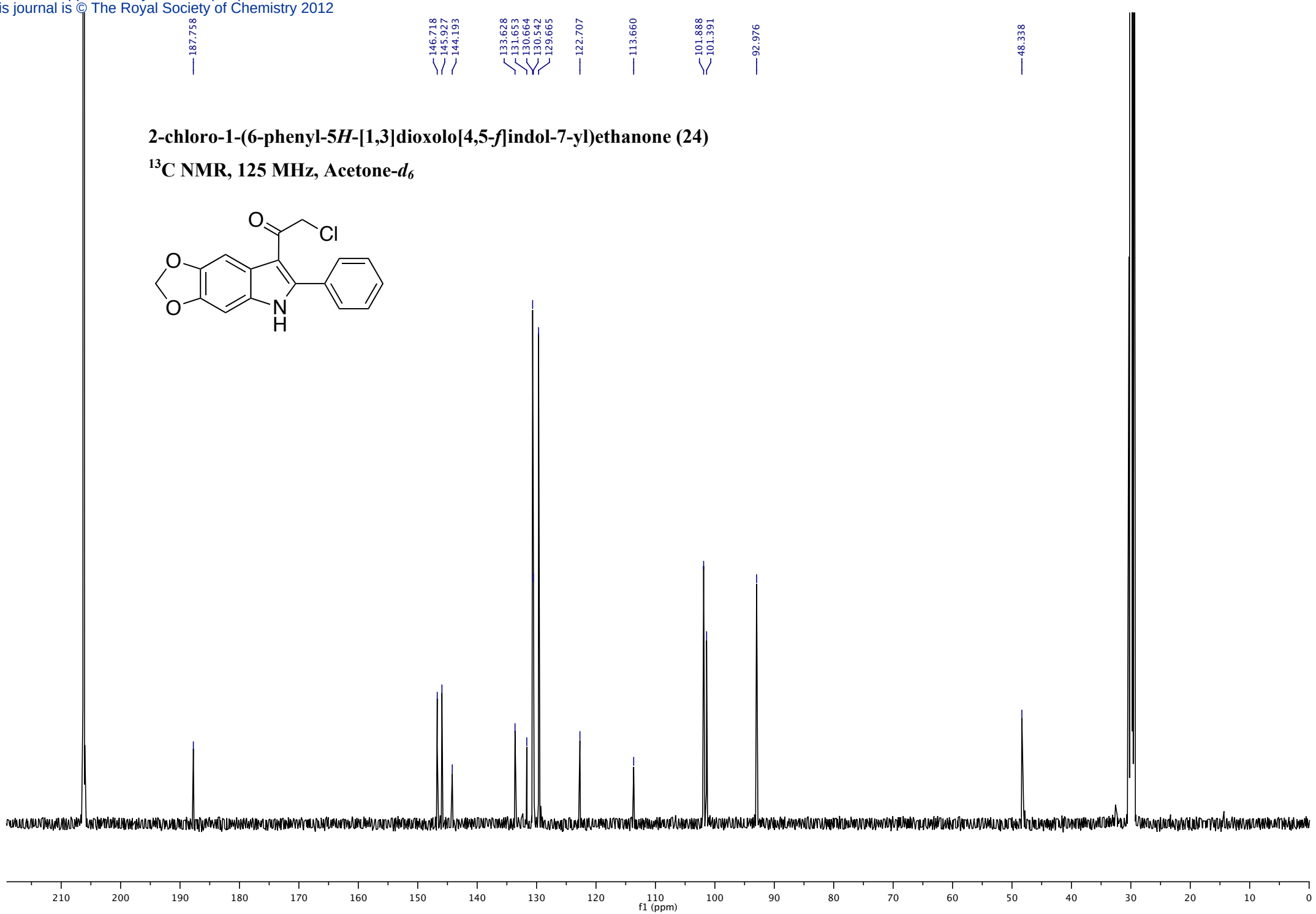




2-chloro-1-(6-phenyl-5*H*-[1,3]dioxolo[4,5-*f*]indol-7-yl)ethanone (24)

^{1}H NMR, 500 MHz, Acetone-d_6



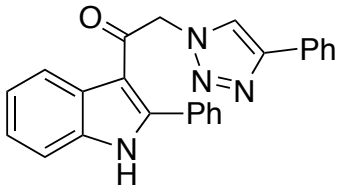


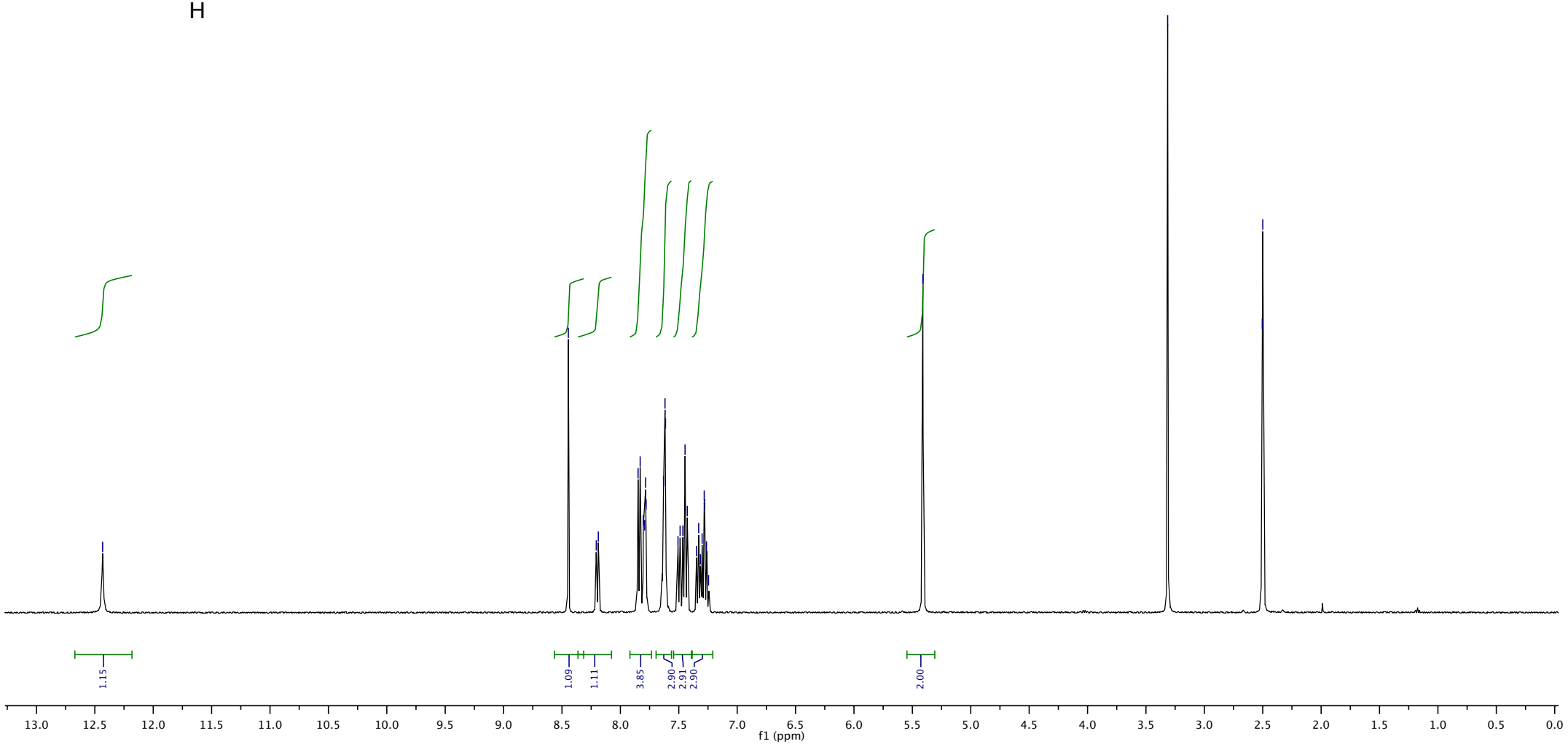
2-chloro-1-(6-phenyl-5*H*-[1,3]dioxolo[4,5-*f*]indol-7-yl)ethanone (24)

^{13}C NMR, 125 MHz, Acetone-d_6

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-1-(2-phenyl-1*H*-indol-3-yl)ethanone (26)

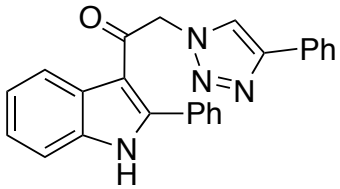
^{1}H NMR, 400 MHz, DMSO-d_6





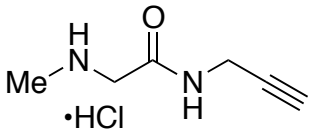
2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-1-(2-phenyl-1*H*-indol-3-yl)ethanone (26)

^{13}C NMR, 100 MHz, DMSO-*d*$_6$



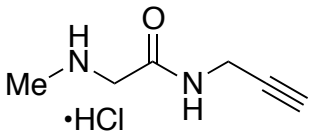
2-(Methylamino)-*N*-(prop-2-yn-1-yl)acetamide hydrochloride (27)

^{1}H NMR, 300 MHz, DMSO-d_6



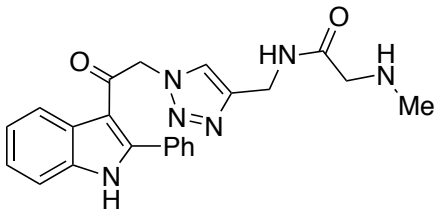
2-(Methylamino)-*N*-(prop-2-yn-1-yl)acetamide hydrochloride (27)

^{13}C NMR, 75 MHz, DMSO-d_6



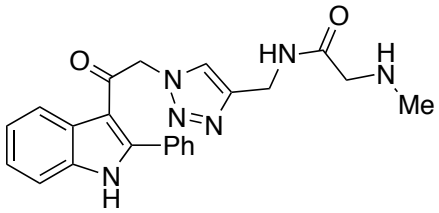
2-(Methylamino)-*N*-((1-(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)acetamide (28)

^{1}H NMR, 400 MHz, $CDCl_3$



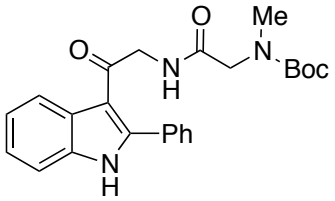
2-(Methylamino)-*N*-((1-(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)acetamide (28)

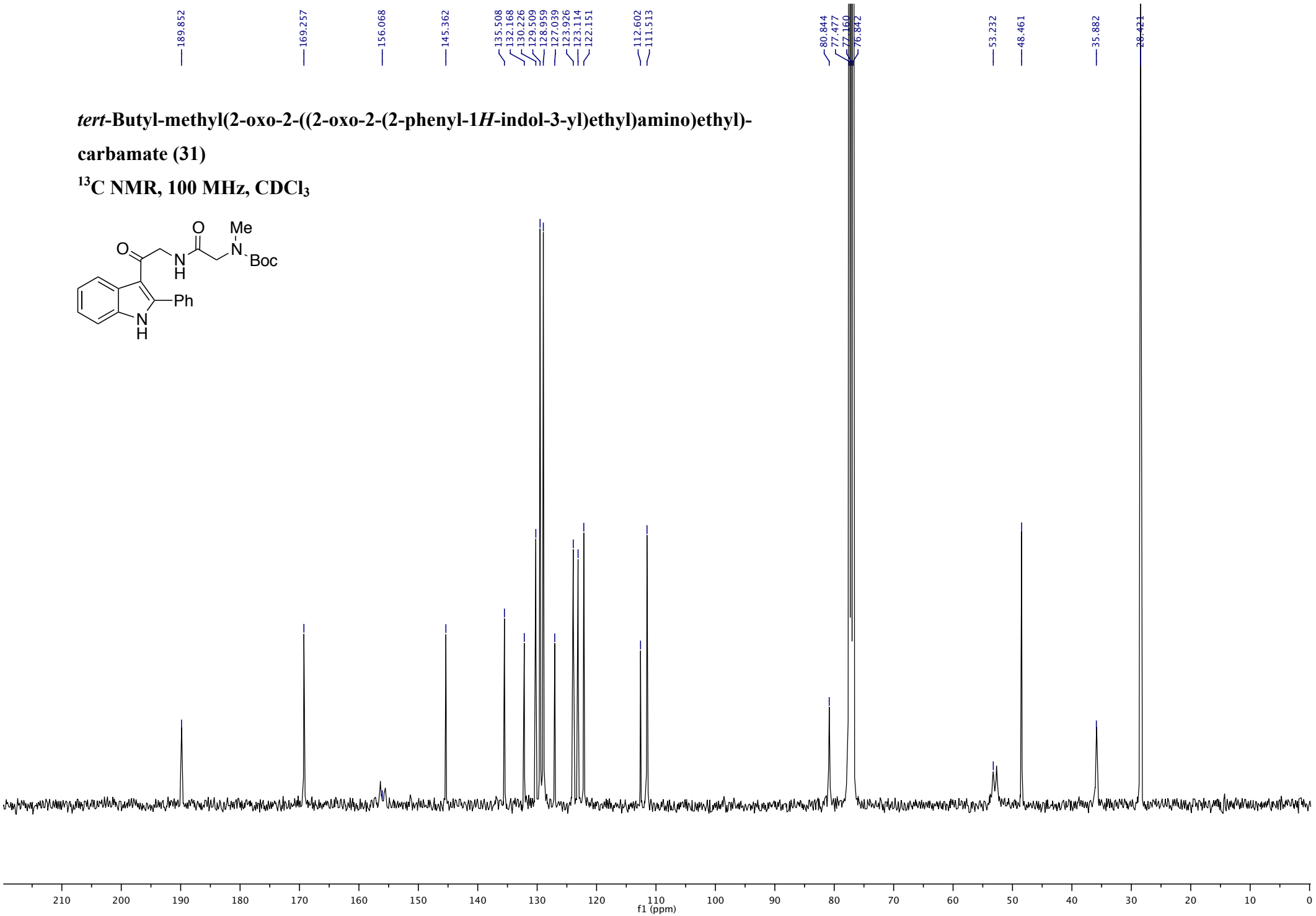
^{13}C NMR, 100 MHz, $CDCl_3$



tert-Butyl-methyl(2-oxo-2-((2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)ethyl)-carbamate (31)

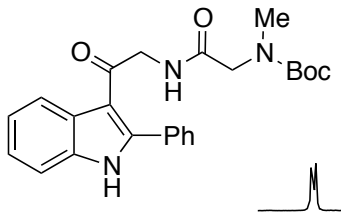
^{1}H NMR, 400 MHz, $CDCl_3$





***tert*-Butyl-methyl(2-oxo-2-((2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)ethyl)-carbamate (31)**

^{13}C NMR, 100 MHz, $CDCl_3$

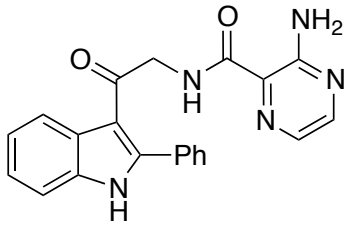


***tert*-Butyl-methyl(2-oxo-2-((2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)ethyl)-carbamate (31)**

HSQC, 400 MHz, $CDCl_3$

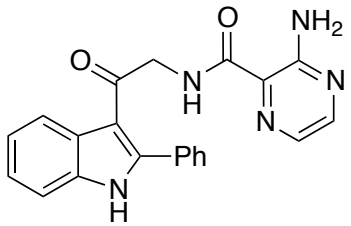
3-Amino-*N*-(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)pyrazine-2-carboxamide (32)

^{1}H NMR, 400 MHz, DMSO-d_6



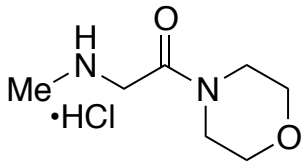
3-Amino-*N*-(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)pyrazine-2-carboxamide (32)

^{13}C NMR, 100 MHz, DMSO-d_6



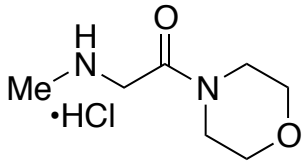
2-(Methylamino)-1-morpholinoethanone hydrochloride (33)

^{1}H NMR, 500 MHz, DMSO-d_6



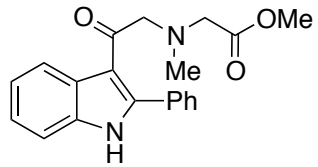
2-(Methylamino)-1-morpholinoethanone hydrochloride (33)

^{13}C NMR, 125 MHz, DMSO-*d*$_6$



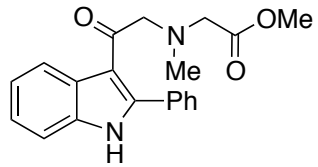
Methyl 2-(methyl(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)acetate (35)

^{1}H NMR, 500 MHz, $CDCl_3$



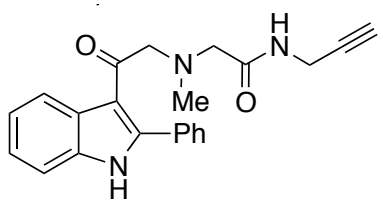
Methyl 2-(methyl(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)acetate (35)

^{13}C NMR, 125 MHz, $CDCl_3$



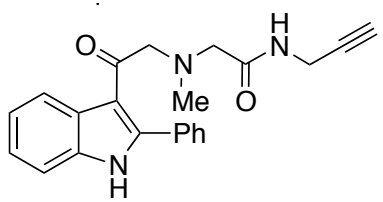
2-(Methyl(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)-*N*-(prop-2-yn-1-yl)acetamide (36)

^{1}H NMR, 500 MHz, $CDCl_3$



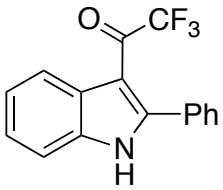
2-(Methyl(2-oxo-2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)-*N*-(prop-2-yn-1-yl)acetamide (36)

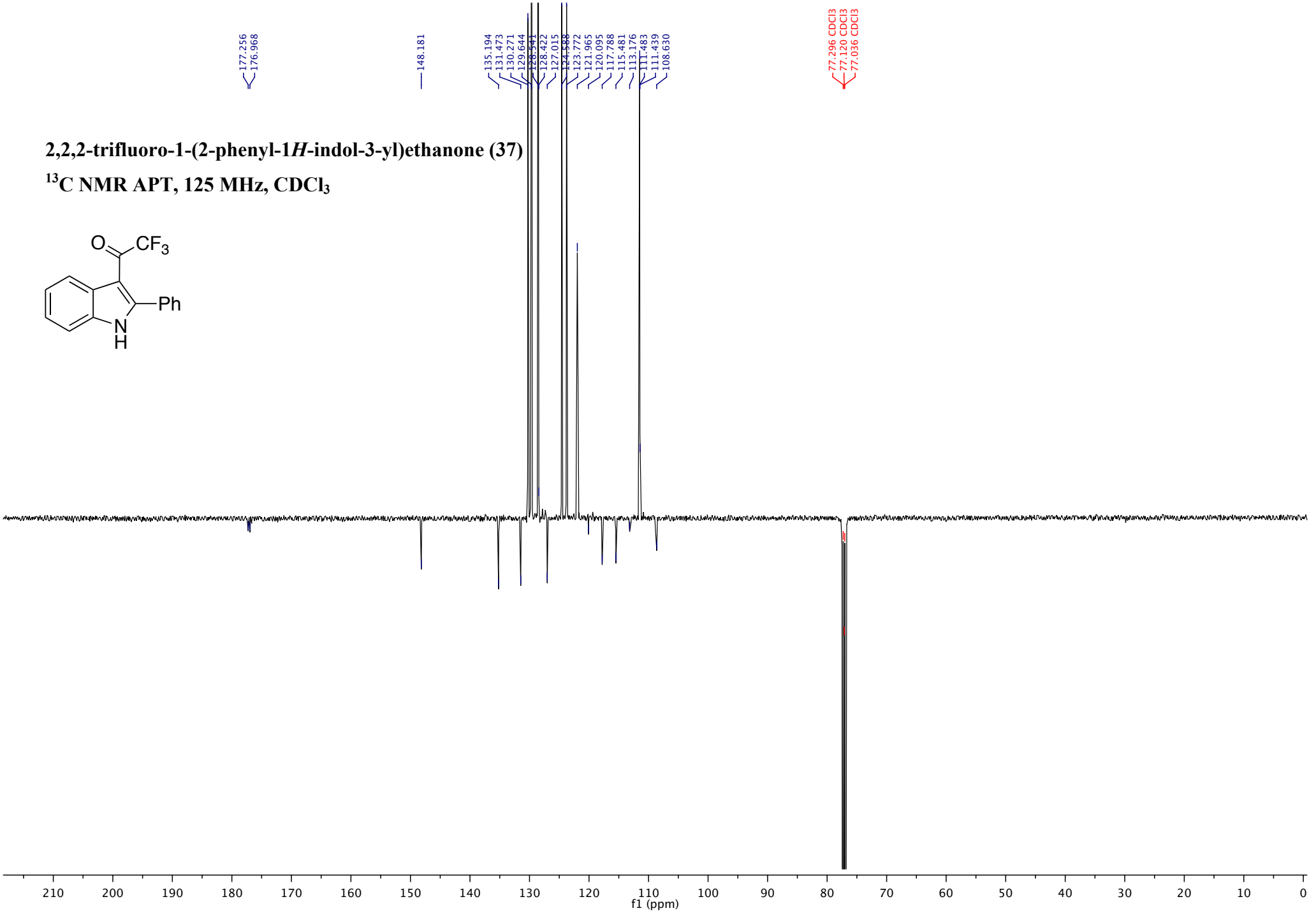
^{13}C NMR, 125 MHz, $CDCl_3$



2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-3-yl)ethanone (37)

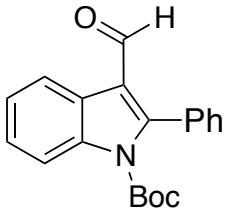
^{1}H NMR, 300 MHz, $CDCl_3$





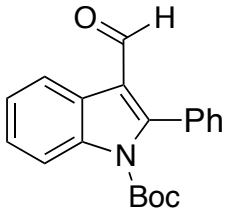
tert-Butyl 3-formyl-2-phenyl-1_H_-indole-1-carboxylate (39)

^{1}H NMR, 500 MHz, $CDCl_3$



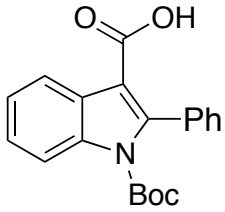
tert-Butyl 3-formyl-2-phenyl-1_H_-indole-1-carboxylate (39)

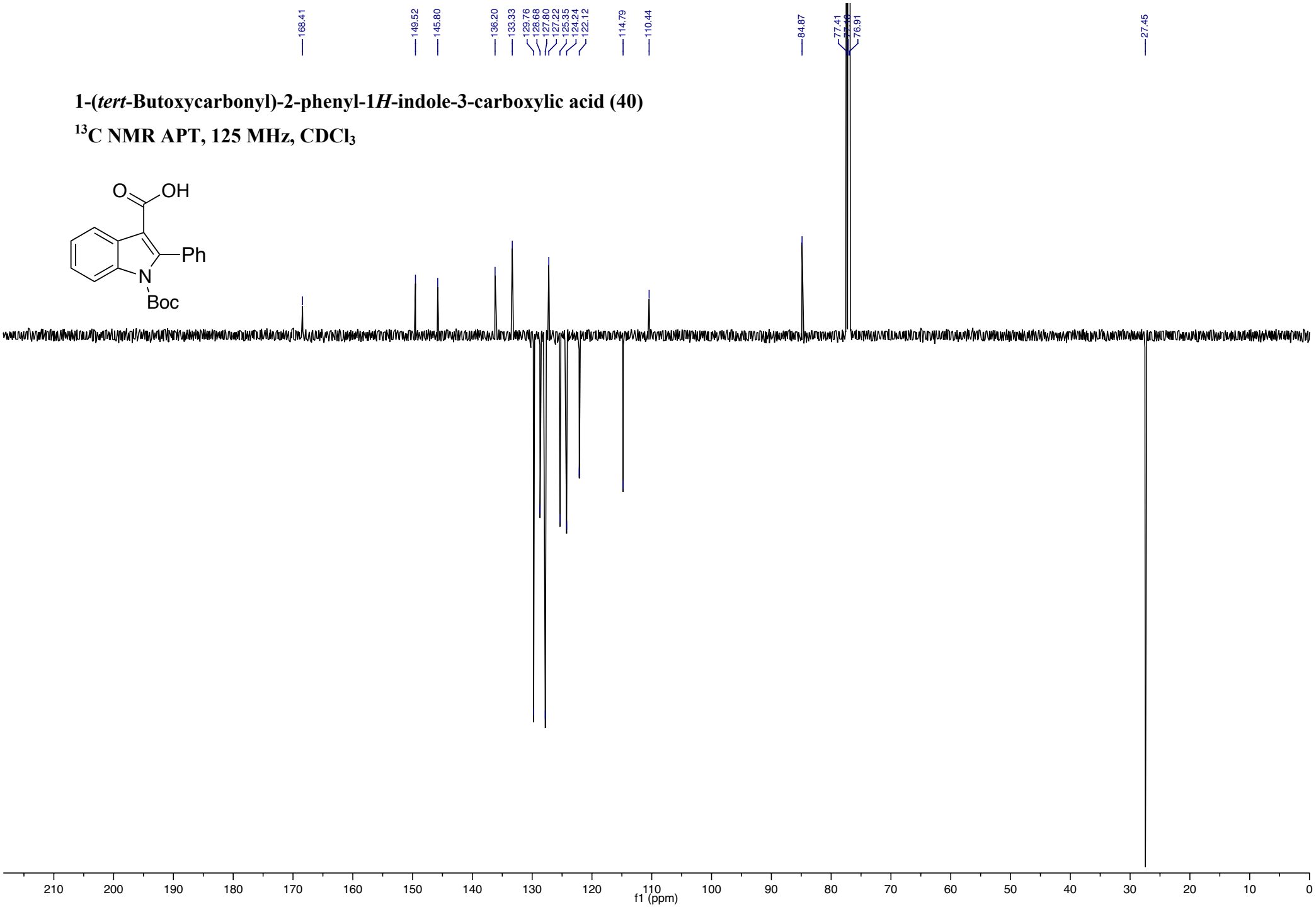
^{13}C NMR, 125 MHz, $CDCl_3$

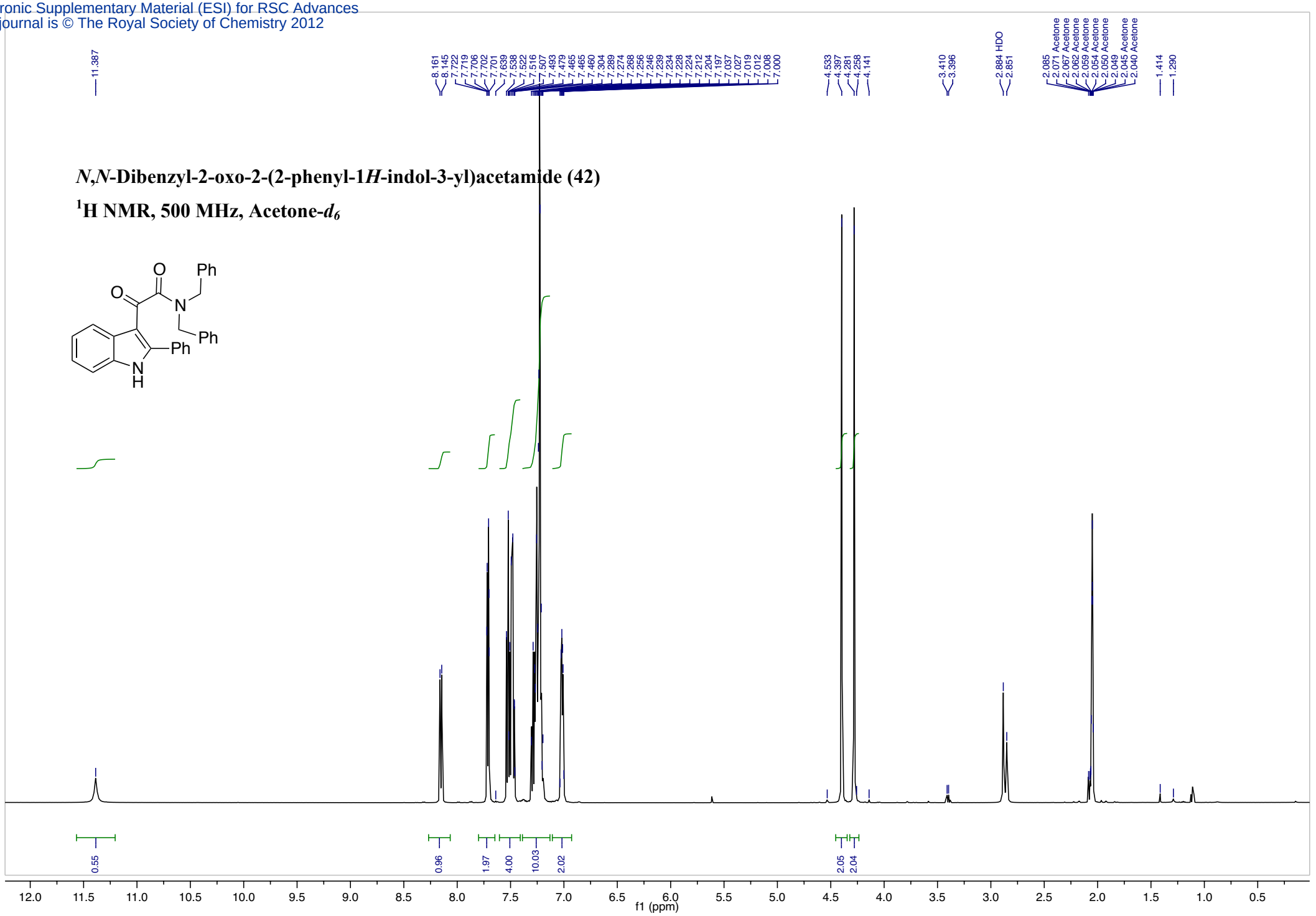


1-(*tert*-Butoxycarbonyl)-2-phenyl-1*H*-indole-3-carboxylic acid (40)

^{1}H NMR, 500 MHz, $CDCl_3$

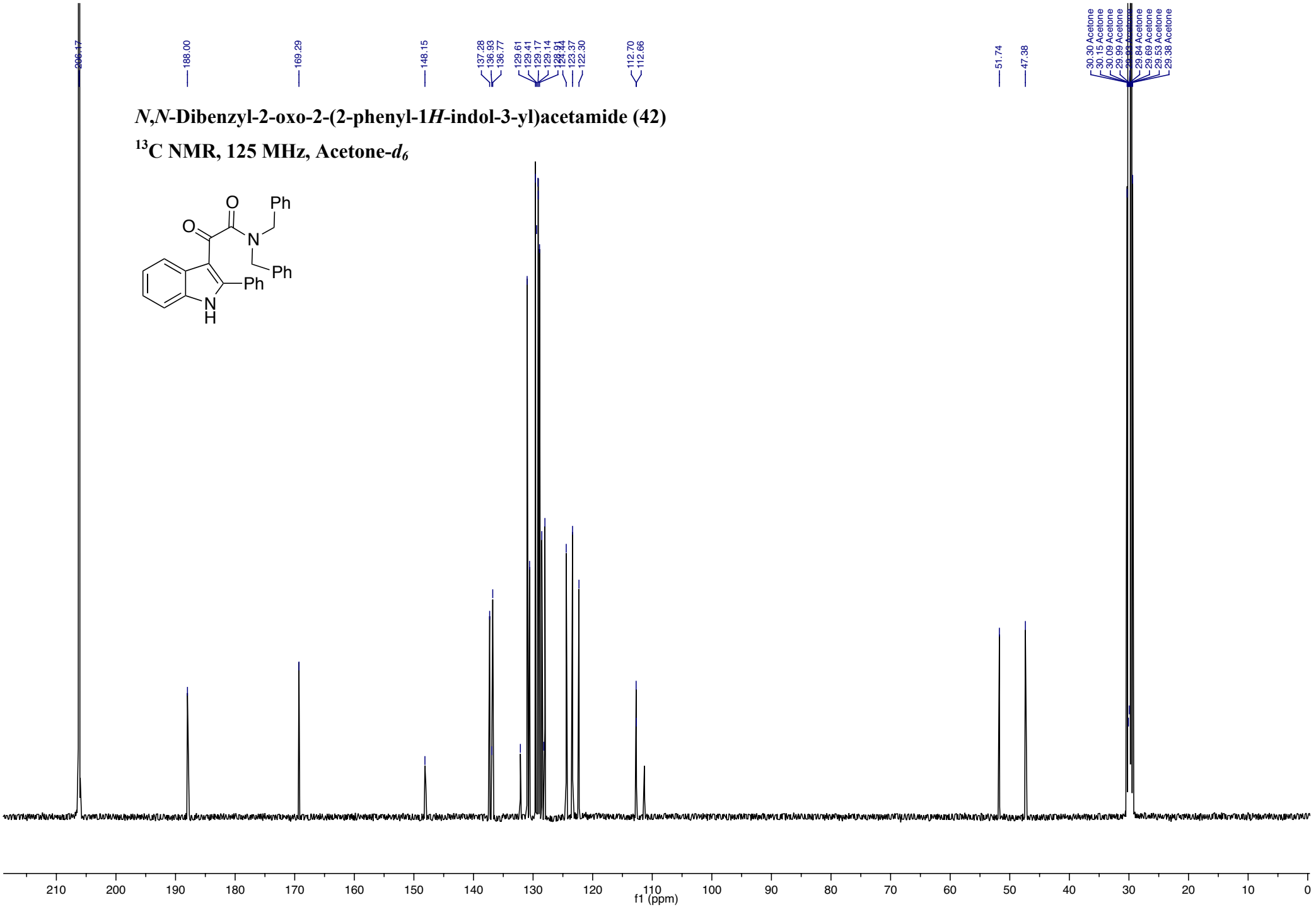






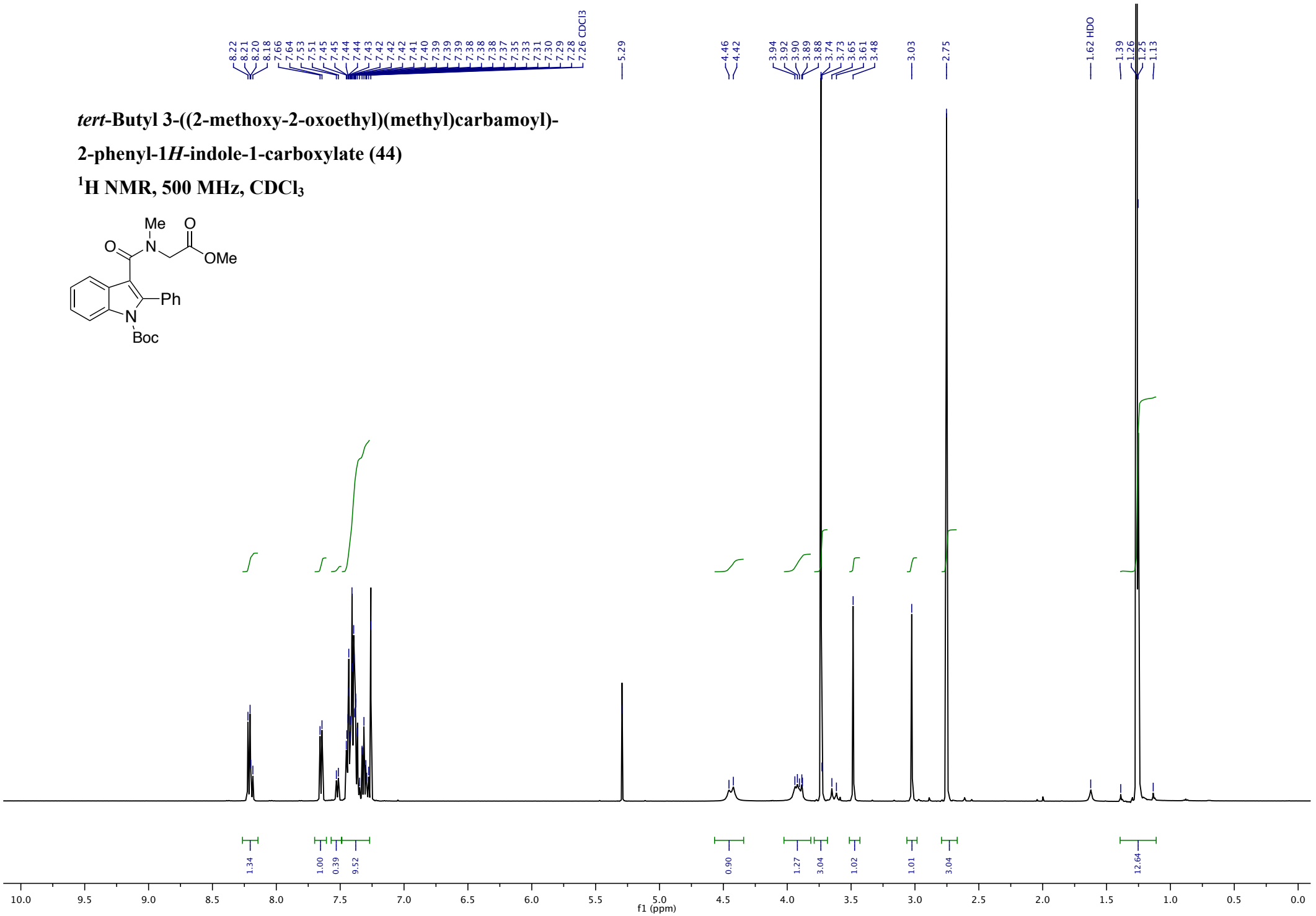
***N*,*N*-Dibenzyl-2-oxo-2-(2-phenyl-1*H*-indol-3-yl)acetamide (42)**

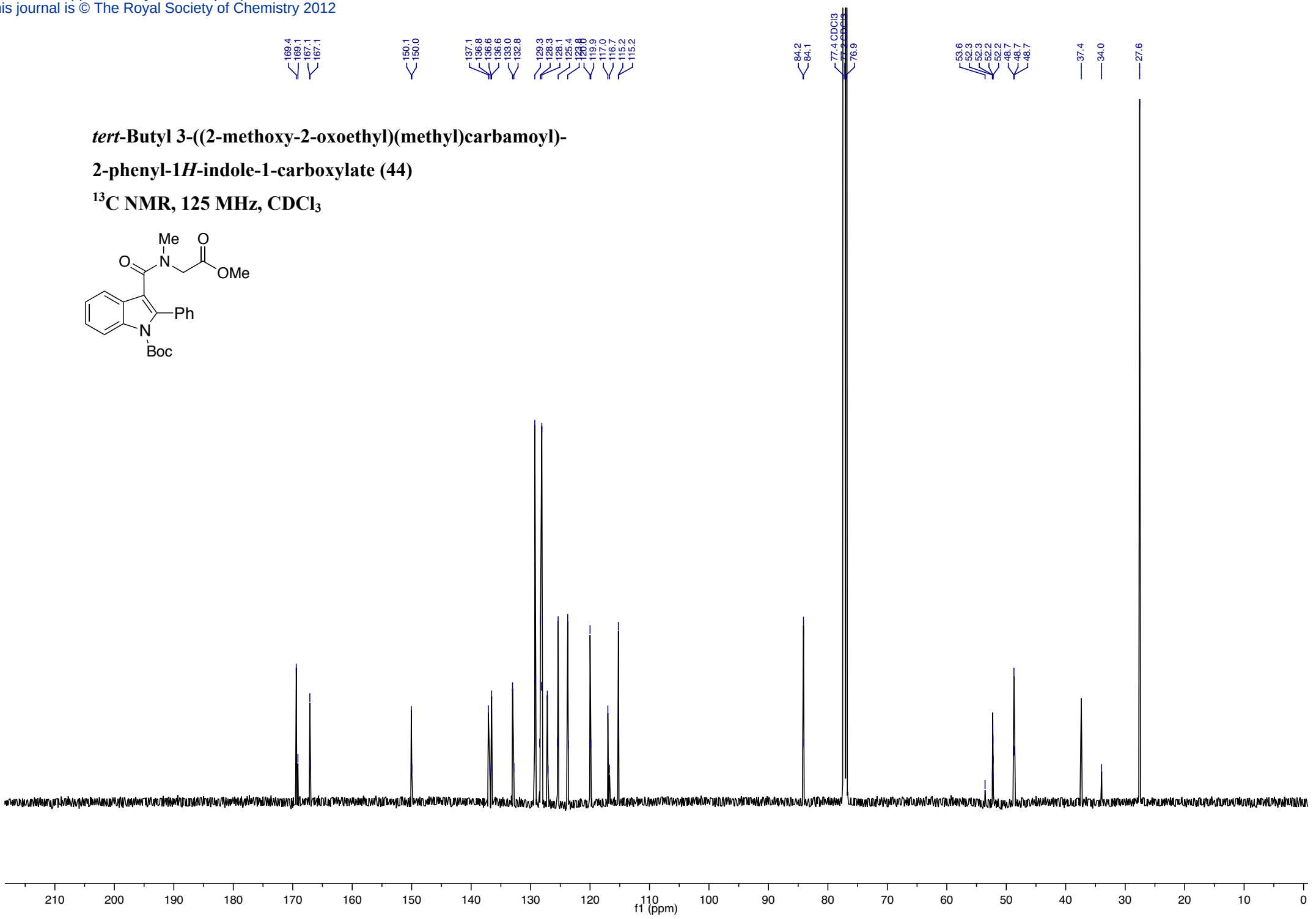
^{1}H NMR, 500 MHz, Acetone-d_6



_N_,_N_-Dibenzyl-2-oxo-2-(2-phenyl-1_H_-indol-3-yl)acetamide (42)

^{13}C NMR, 125 MHz, Acetone-d_6



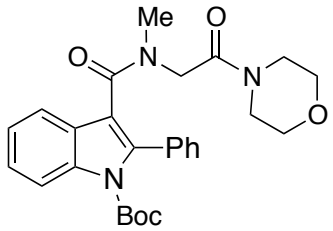


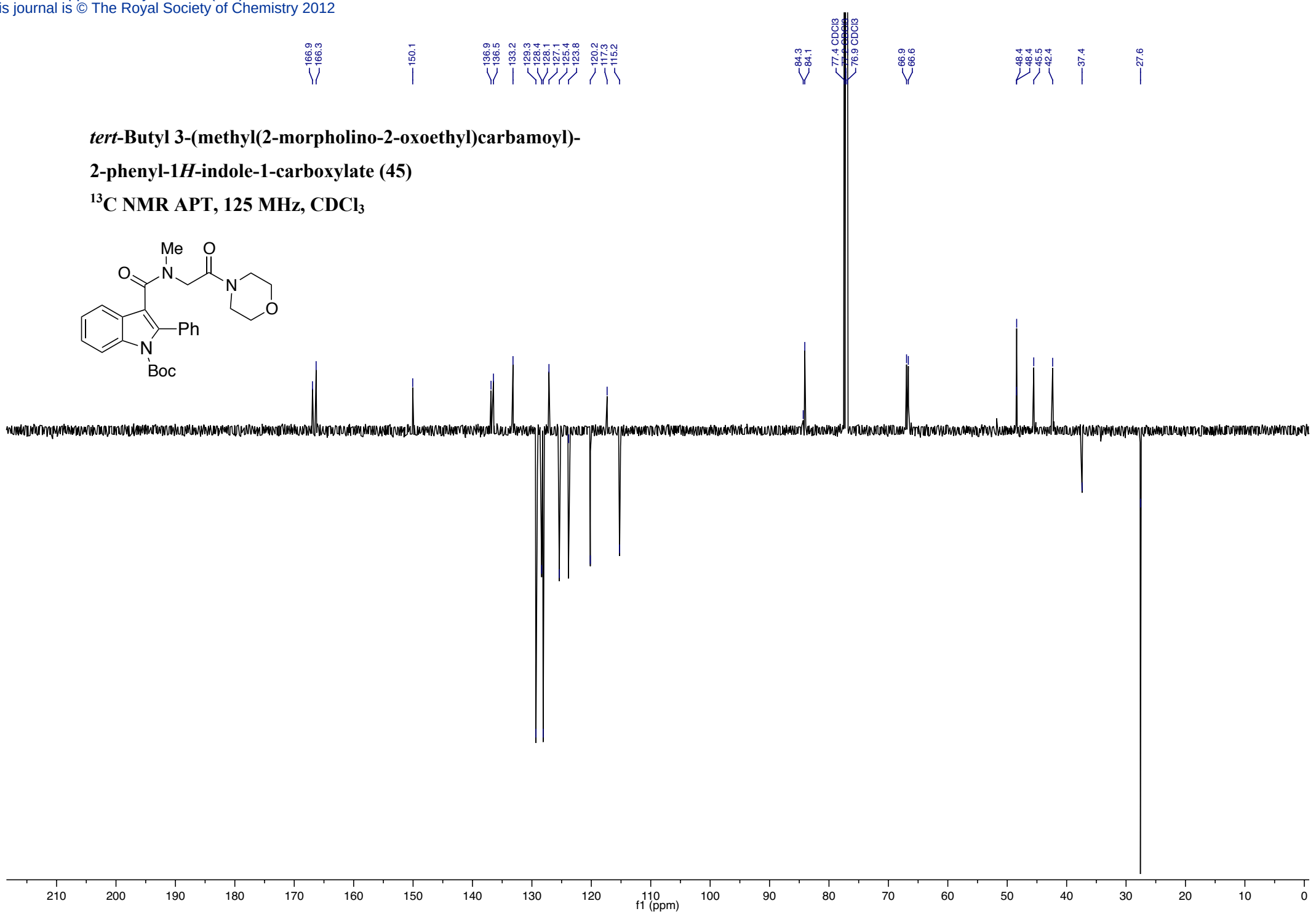
***tert*-Butyl 3-((2-methoxy-2-oxoethyl)(methyl)carbamoyl)-2-phenyl-1*H*-indole-1-carboxylate (44)**

^{13}C NMR, 125 MHz, $CDCl_3$

***tert*-Butyl 3-(methyl(2-morpholino-2-oxoethyl)carbamoyl)-2-phenyl-1*H*-indole-1-carboxylate (45)**

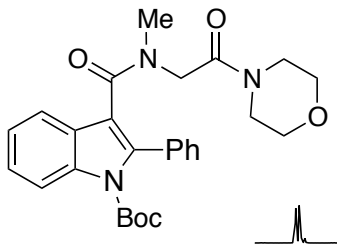
^{1}H NMR, 500 MHz, $CDCl_3$





***tert*-Butyl 3-(methyl(2-morpholino-2-oxoethyl)carbamoyl)-2-phenyl-1*H*-indole-1-carboxylate (45)**

^{13}C NMR APT, 125 MHz, $CDCl_3$

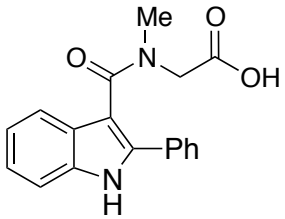


***tert*-Butyl 3-(methyl(2-morpholino-2-oxoethyl)carbamoyl)-2-phenyl-1*H*-indole-1-carboxylate (45)**

HSQC, 500 MHz, $CDCl_3$

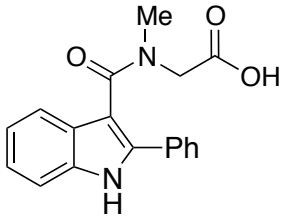
2-(*N*-Methyl-2-phenyl-1*H*-indole-3-carboxamido)acetic acid (46)

^{1}H NMR, 500 MHz, MeOD



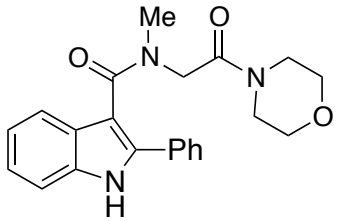
2-(*N*-Methyl-2-phenyl-1*H*-indole-3-carboxamido)acetic acid (46)

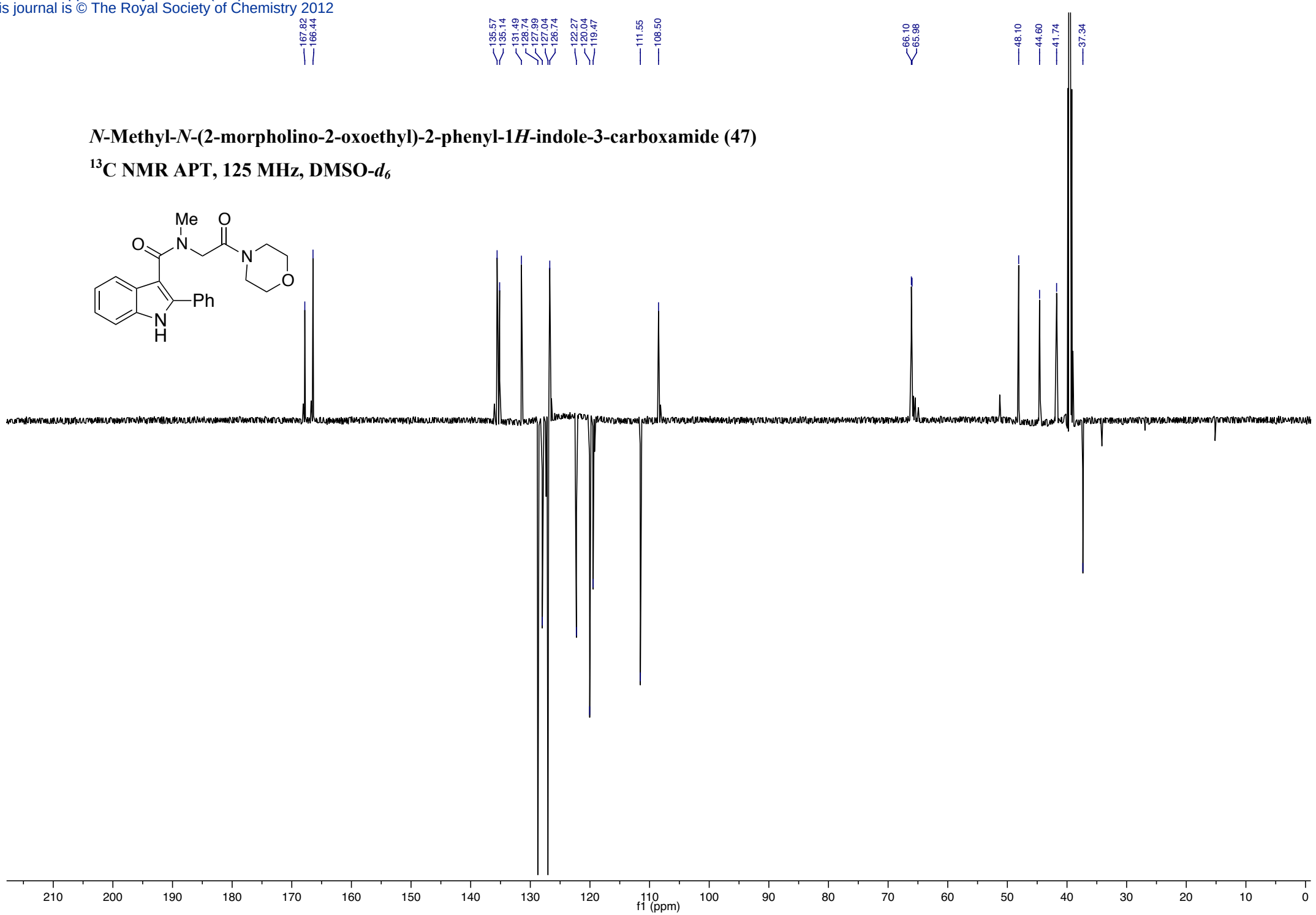
^{13}C NMR, 125 MHz, MeOD



_N_-Methyl-_N_-(2-morpholino-2-oxoethyl)-2-phenyl-1_H_-indole-3-carboxamide (47)

^{1}H NMR, 500 MHz, DMSO-d_6





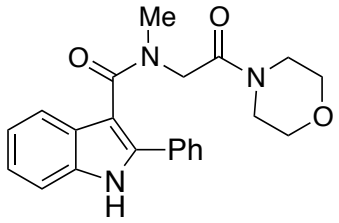
_N_-Methyl-_N_-(2-morpholino-2-oxoethyl)-2-phenyl-1_H_-indole-3-carboxamide (47)

^{13}C NMR APT, 125 MHz, DMSO-d_6

T = 25 °C

***N*-Methyl-*N*-(2-morpholino-2-oxoethyl)-2-phenyl-1*H*-indole-3-carboxamide (47)**

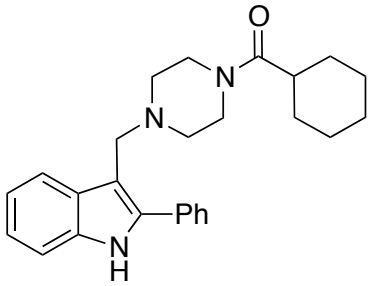
^{1}H NMR, 300 MHz, DMSO-d_6



T = 80 °C

Cyclohexyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (53)

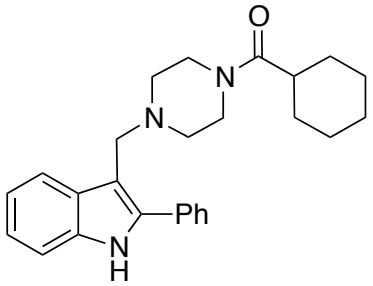
^{1}H NMR, 400 MHz, DMSO-d_6

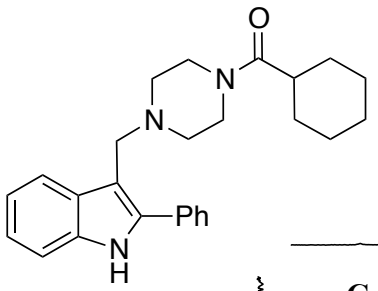


Electronic Supplementary Material (ESI) for RSC Advances

Cyclohexyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (53)

^{13}C NMR, 100 MHz, DMSO-d_6



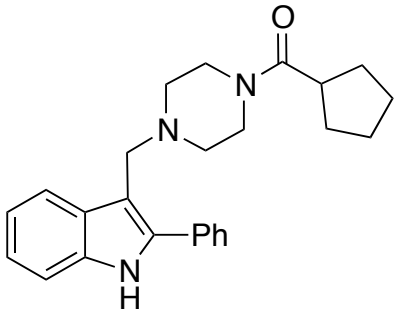


Cyclohexyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (53)

HSQC, 400 MHz, DMSO-d_6

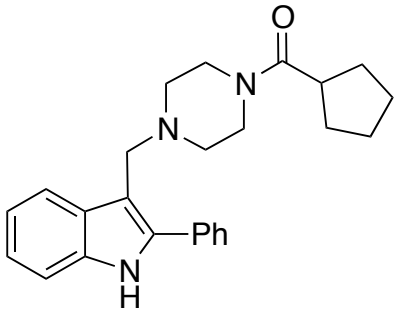
Cyclopentyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (54)

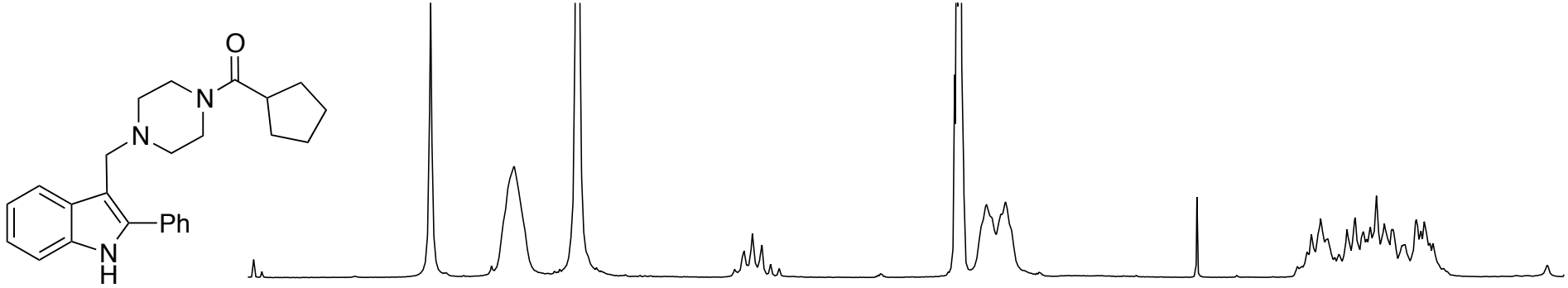
^{1}H NMR, 400 MHz, DMSO-d_6



Cyclopentyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (54)

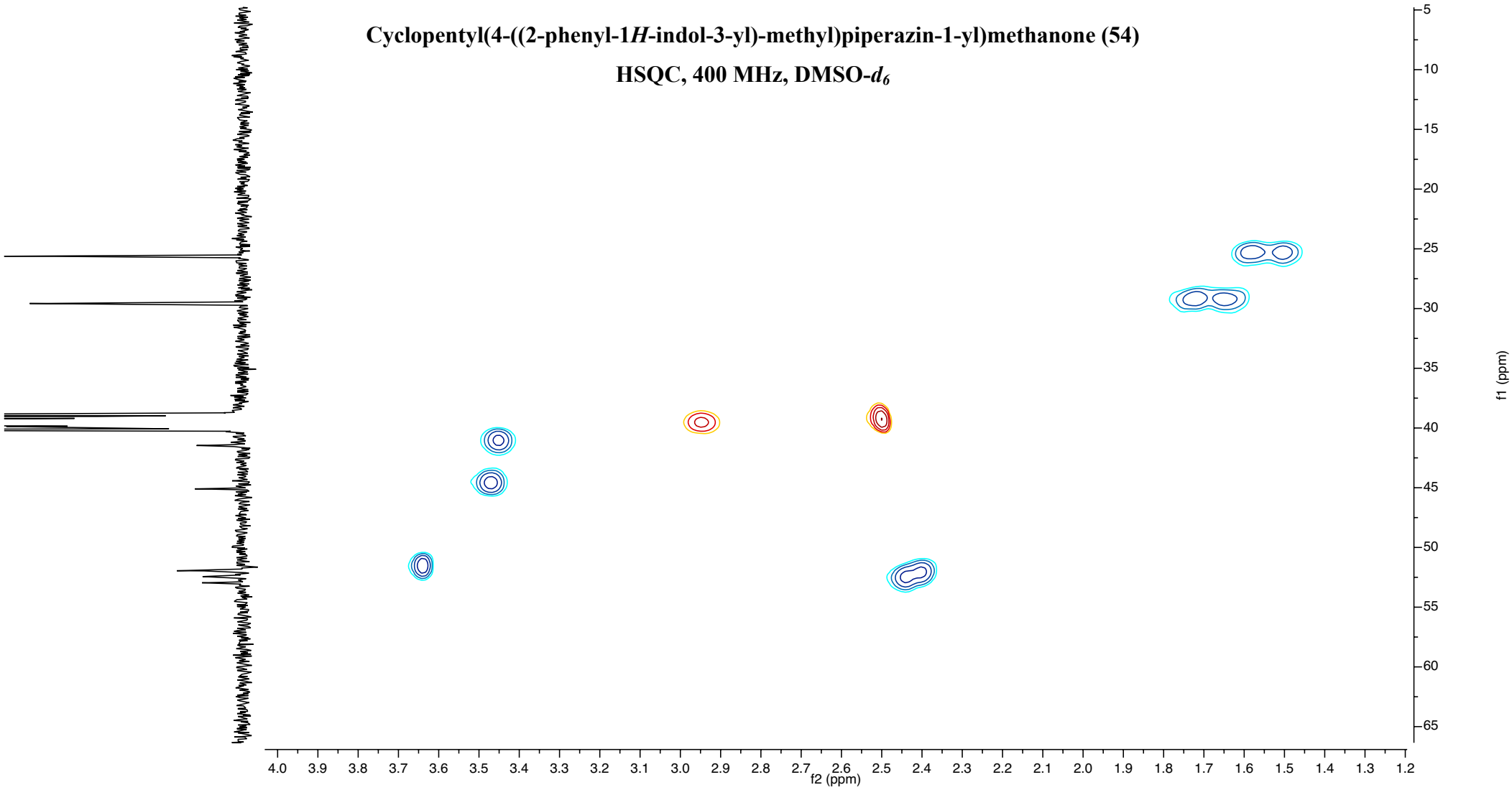
^{13}C NMR, 100 MHz, DMSO-d_6





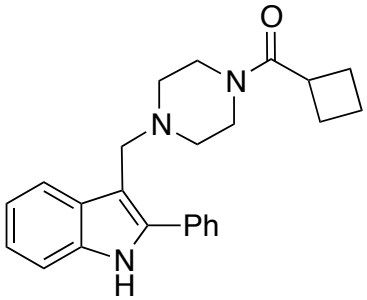
Cyclopentyl(4-((2-phenyl-1*H*-indol-3-yl)-methyl)piperazin-1-yl)methanone (54)

HSQC, 400 MHz, DMSO-d_6



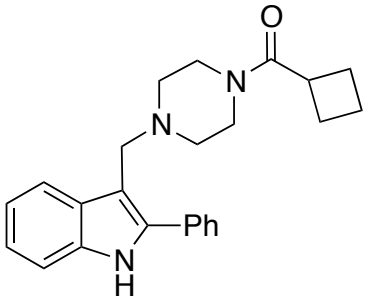
Cyclobutyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (55)

^{1}H NMR, 400 MHz, DMSO-d_6



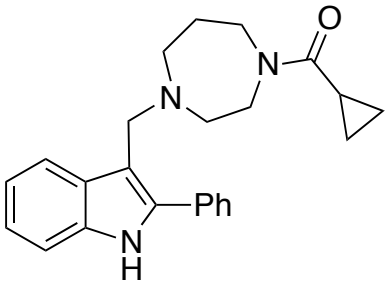
Cyclobutyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)piperazin-1-yl)methanone (55)

^{13}C NMR, 100 MHz, DMSO-d_6



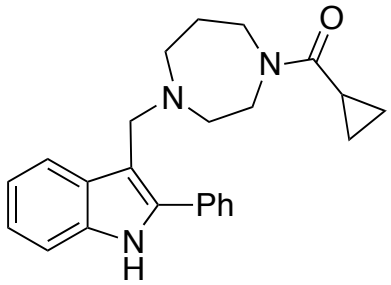
Cyclopropyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)-1,4-diazepan-1-yl)methanone (56)

^{1}H NMR, 300 MHz, DMSO-d_6



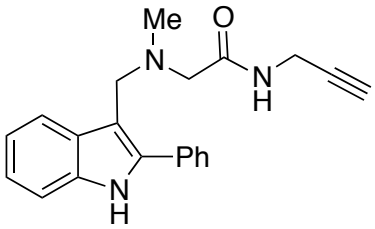
Cyclopropyl(4-((2-phenyl-1*H*-indol-3-yl)methyl)-1,4-diazepan-1-yl)methanone (56)

^{13}C NMR APT, 125 MHz, DMSO-d_6



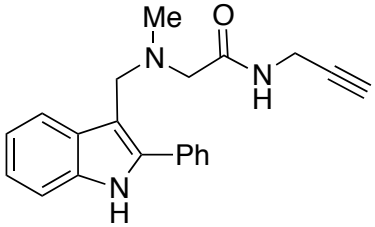
2-(Methyl((2-phenyl-1*H*-indol-3-yl)methyl)amino)-*N*-(prop-2-yn-1-yl)acetamide (57)

^{1}H NMR, 300 MHz, $CDCl_3$



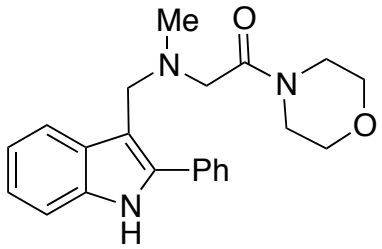
2-(Methyl((2-phenyl-1*H*-indol-3-yl)methyl)amino)-*N*-(prop-2-yn-1-yl)acetamide (57)

^{13}C NMR, 75 MHz, $CDCl_3$



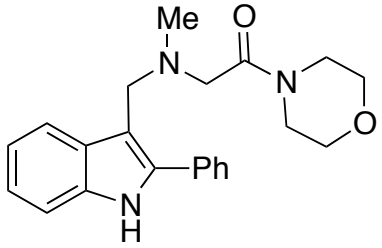
2-(Methyl((2-phenyl-1*H*-indol-3-yl)methyl)amino)-1-morpholinoethanone (58)

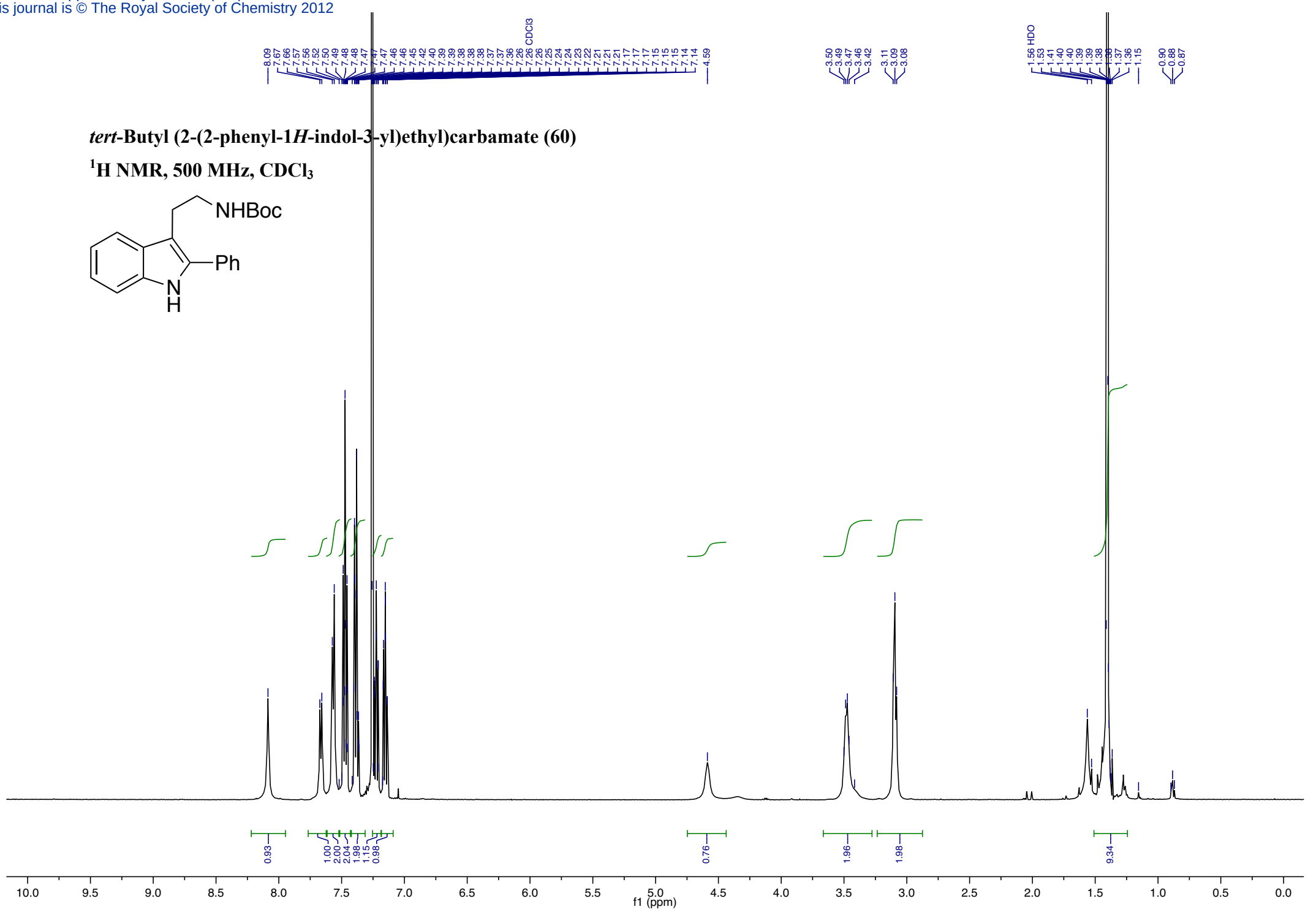
^{1}H NMR, 500 MHz, MeOD



2-(Methyl((2-phenyl-1*H*-indol-3-yl)methyl)amino)-1-morpholinoethanone (58)

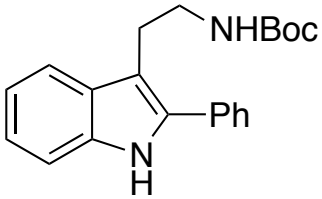
^{13}C NMR APT, 125 MHz, MeOD

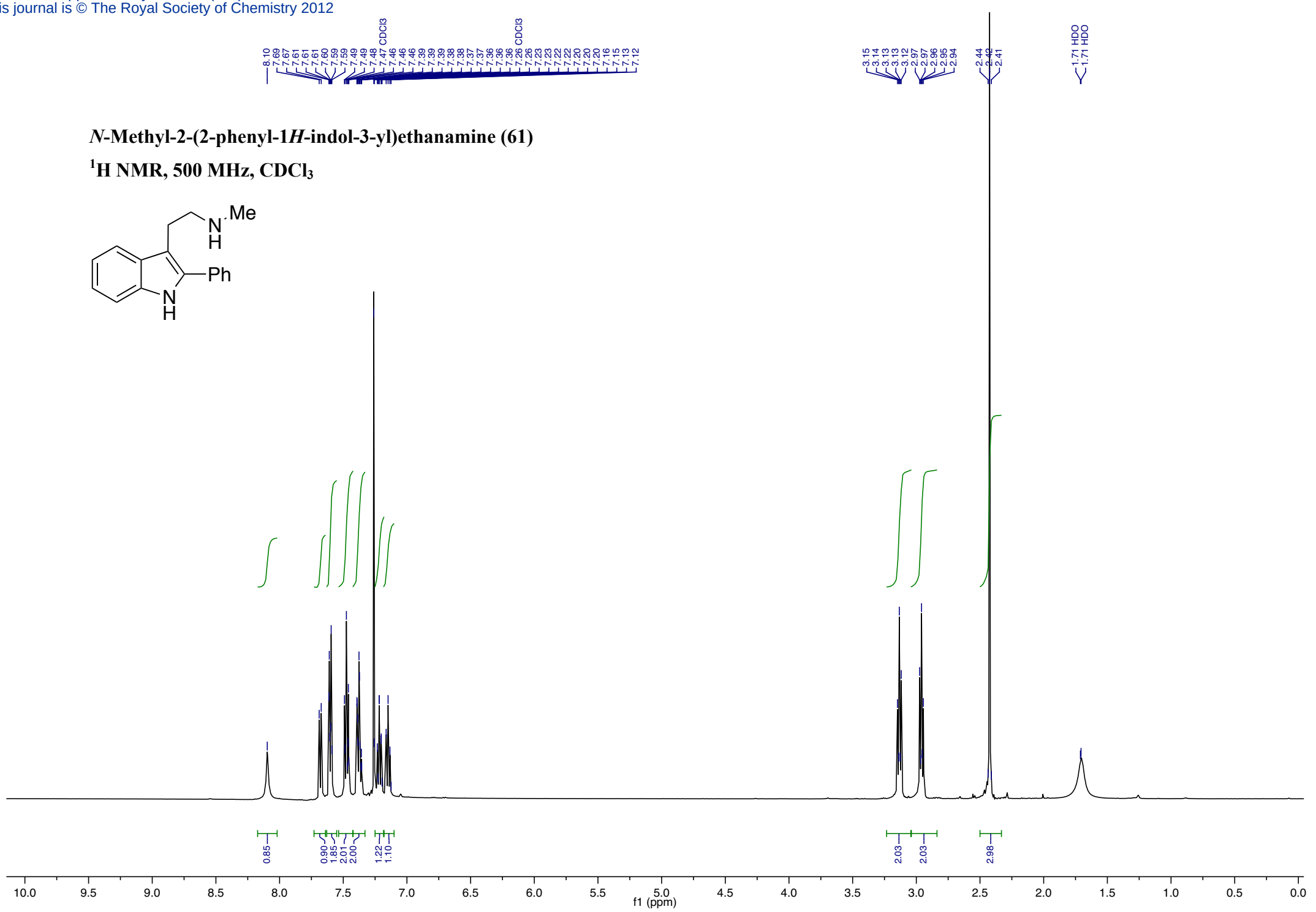




tert-Butyl (2-(2-phenyl-1*H*-indol-3-yl)ethyl)carbamate (60)

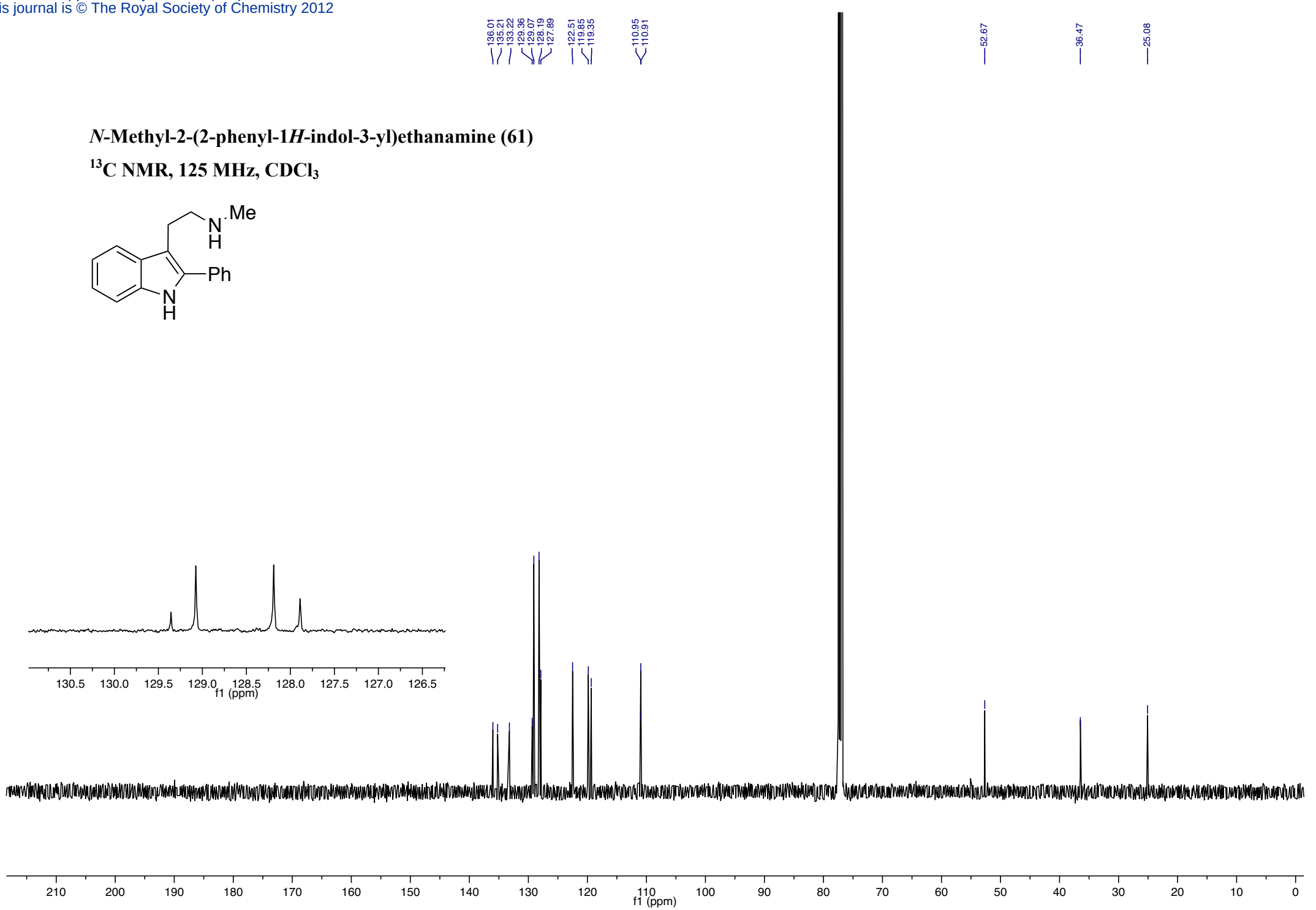
^{13}C NMR, 125 MHz, $CDCl_3$





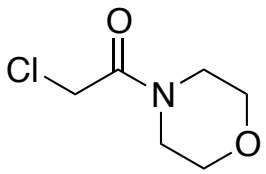
_N_-Methyl-2-(2-phenyl-1_H_-indol-3-yl)ethanamine (61)

^{1}H NMR, 500 MHz, $CDCl_3$



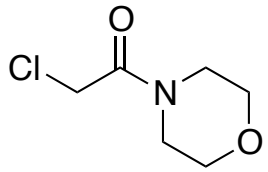
2-Chloro-1-morpholinoethanone (62)

^{1}H NMR, 400 MHz, $CDCl_3$



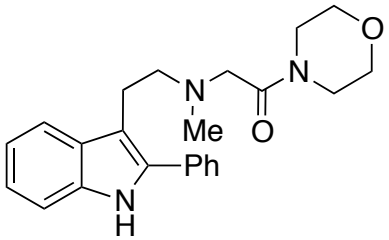
2-Chloro-1-morpholinoethanone (62)

^{13}C NMR, 100 MHz, $CDCl_3$



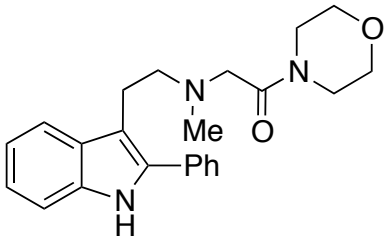
2-(Methyl(2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)-1-morpholinoethanone (63)

^{1}H NMR, 500 MHz, $CDCl_3$



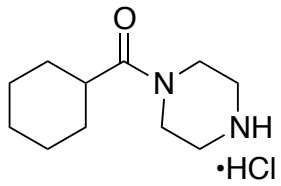
2-(Methyl(2-(2-phenyl-1*H*-indol-3-yl)ethyl)amino)-1-morpholinoethanone (63)

^{13}C NMR, 125 MHz, $CDCl_3$



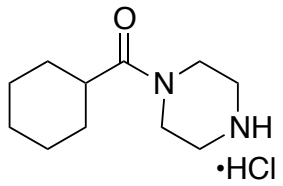
Cyclohexyl(piperazin-1-yl)methanone (64)

^{1}H NMR, 300 MHz, DMSO-d_6



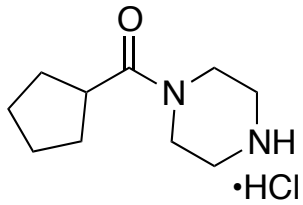
Cyclohexyl(piperazin-1-yl)methanone (64)

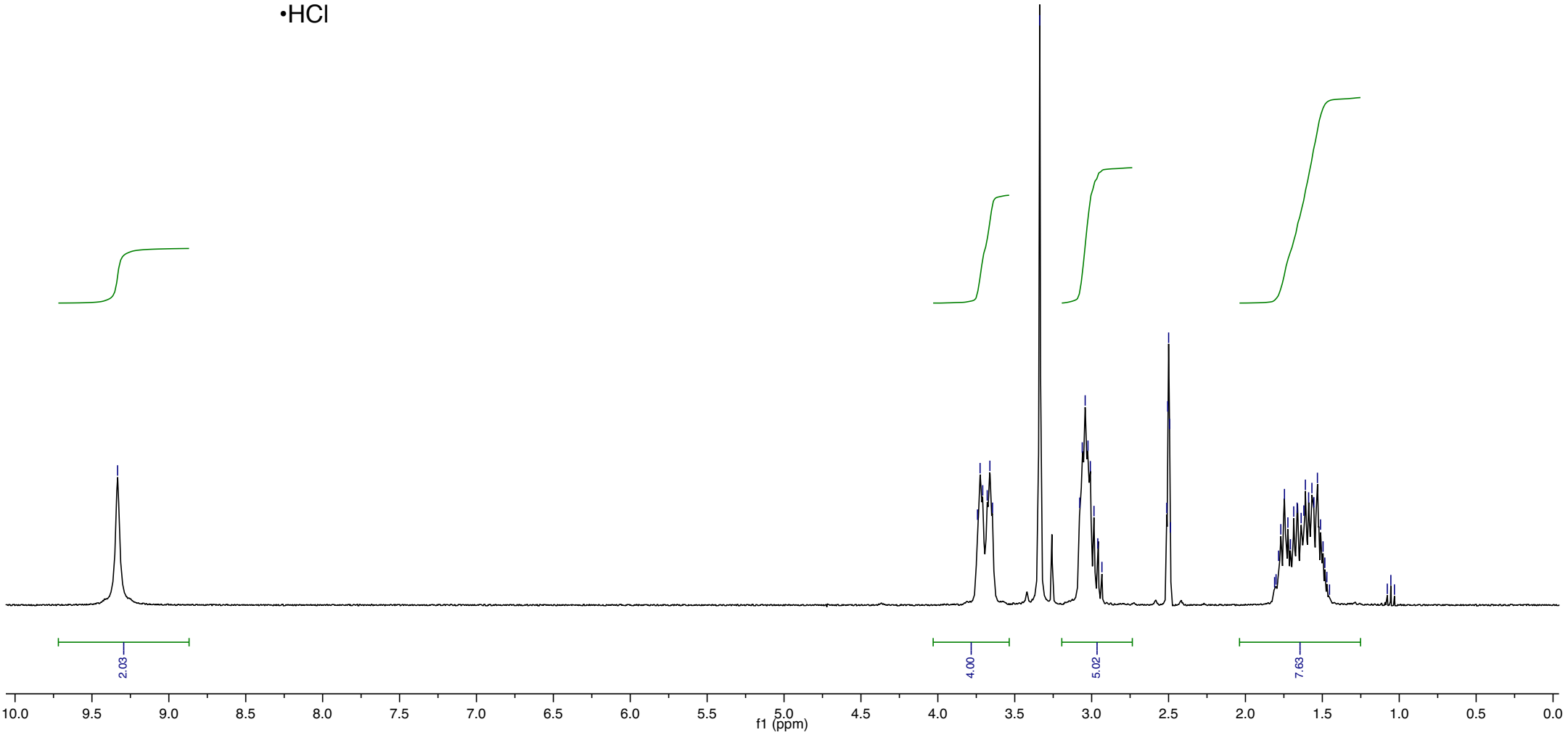
^{13}C NMR, 75 MHz, MeOD



Cyclopentyl(piperazin-1-yl)methanone (65)

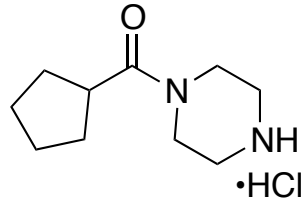
^{1}H NMR, 300 MHz, DMSO-d_6





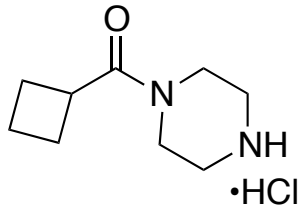
Cyclopentyl(piperazin-1-yl)methanone (65)

^{13}C NMR, 75 MHz, MeOD



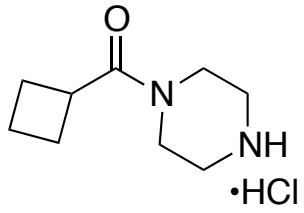
Cyclobutyl(piperazin-1-yl)methanone hydrochloride (66)

^{1}H NMR, 400 MHz, D_2O



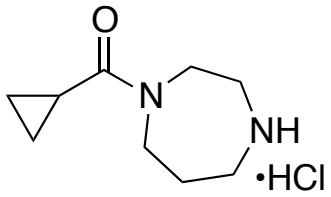
Cyclobutyl(piperazin-1-yl)methanone hydrochloride (66)

^{13}C NMR, 100 MHz, D_2O-DMSO-d_6



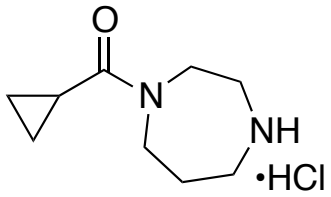
Cyclopropyl(1,4-diazepan-1-yl)methanone hydrochloride (67)

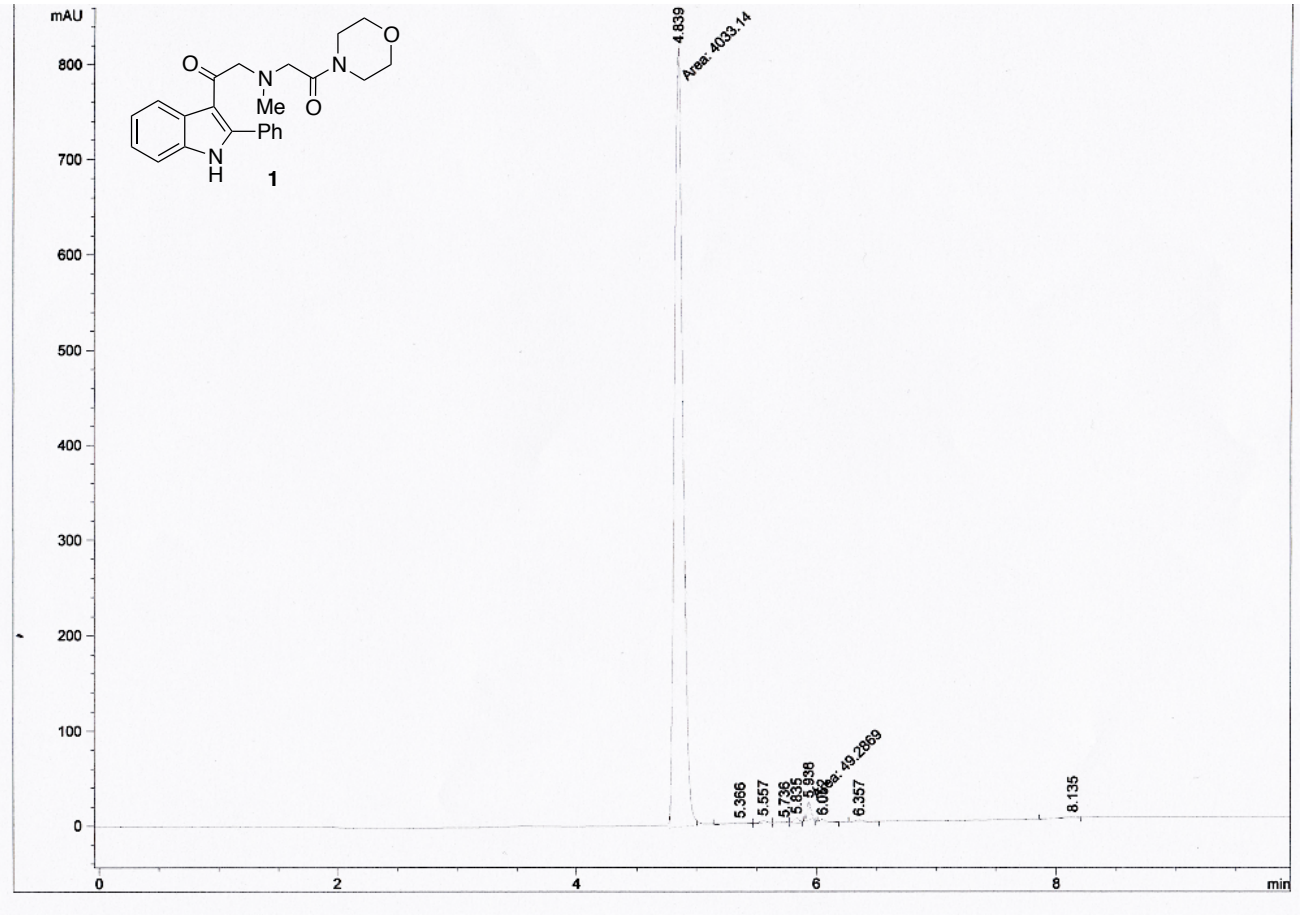
^{1}H NMR, 300 MHz, DMSO-d_6

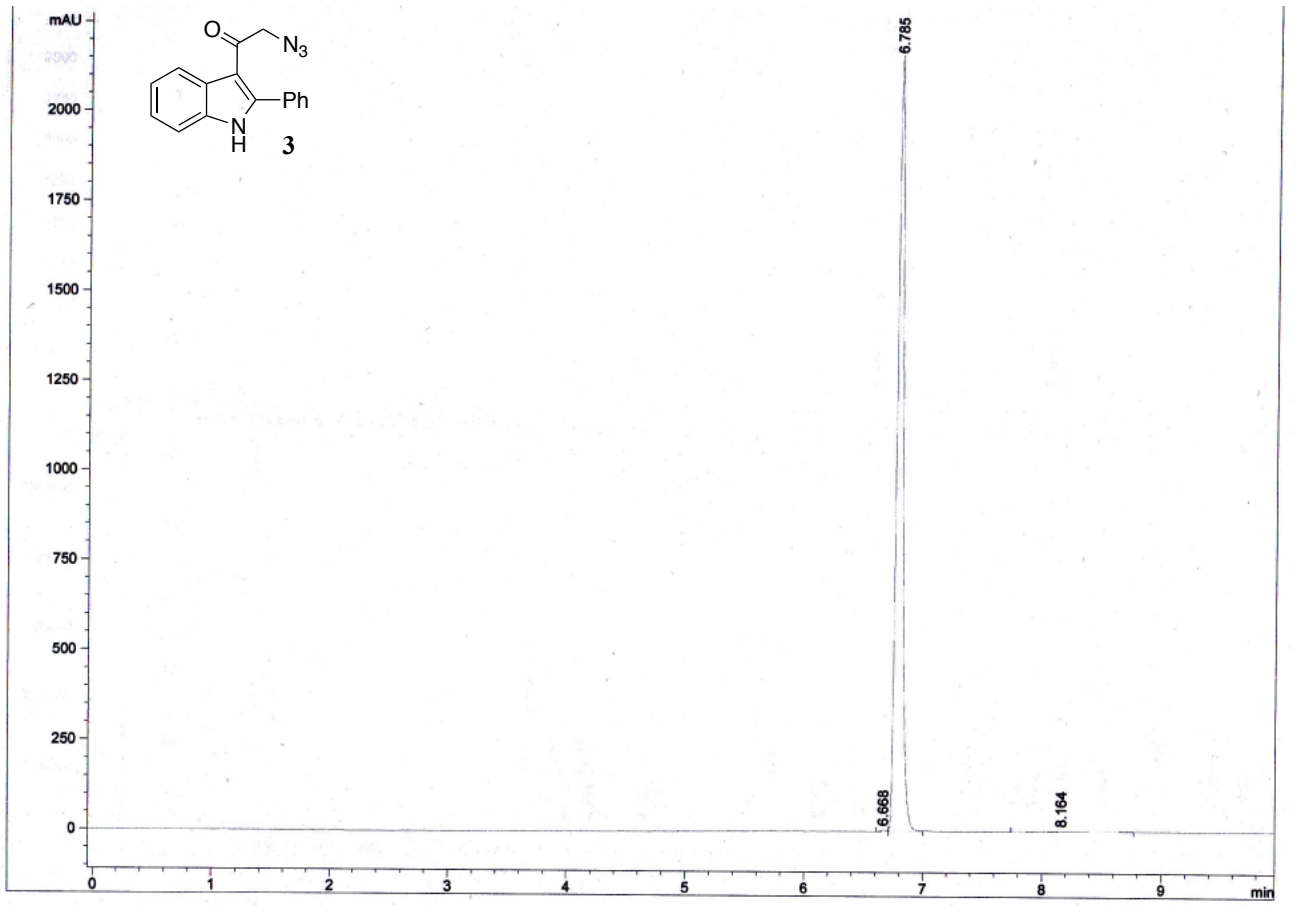


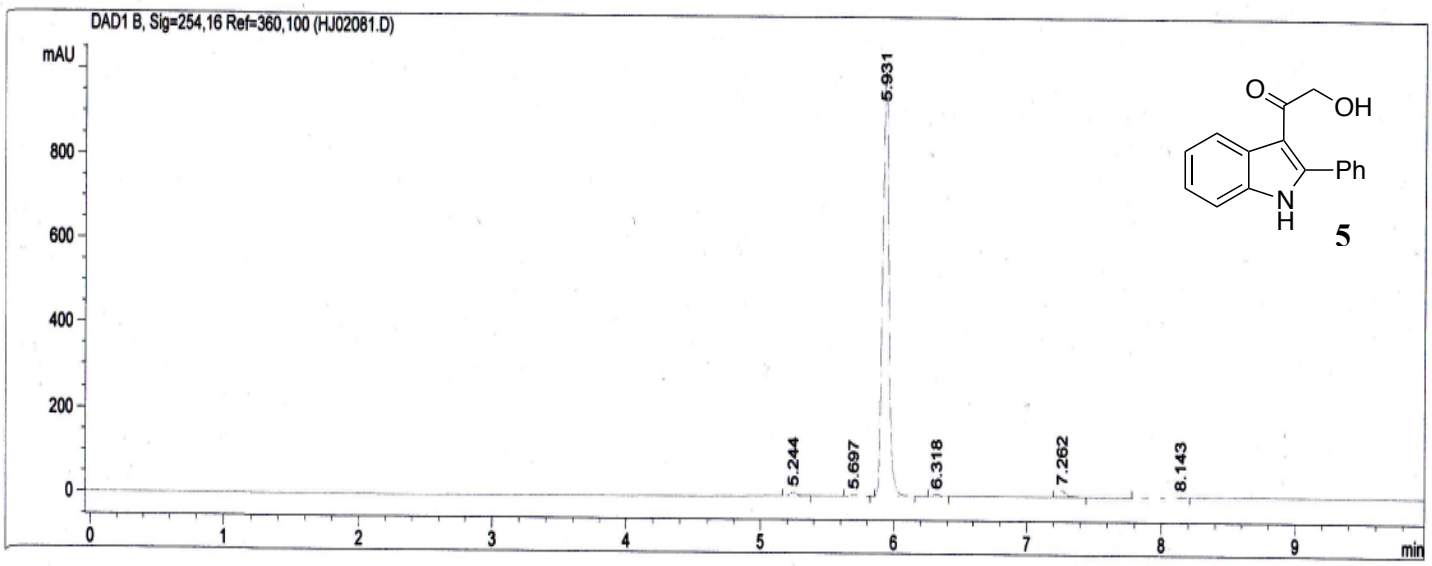
Cyclopropyl(1,4-diazepan-1-yl)methanone hydrochloride (67)

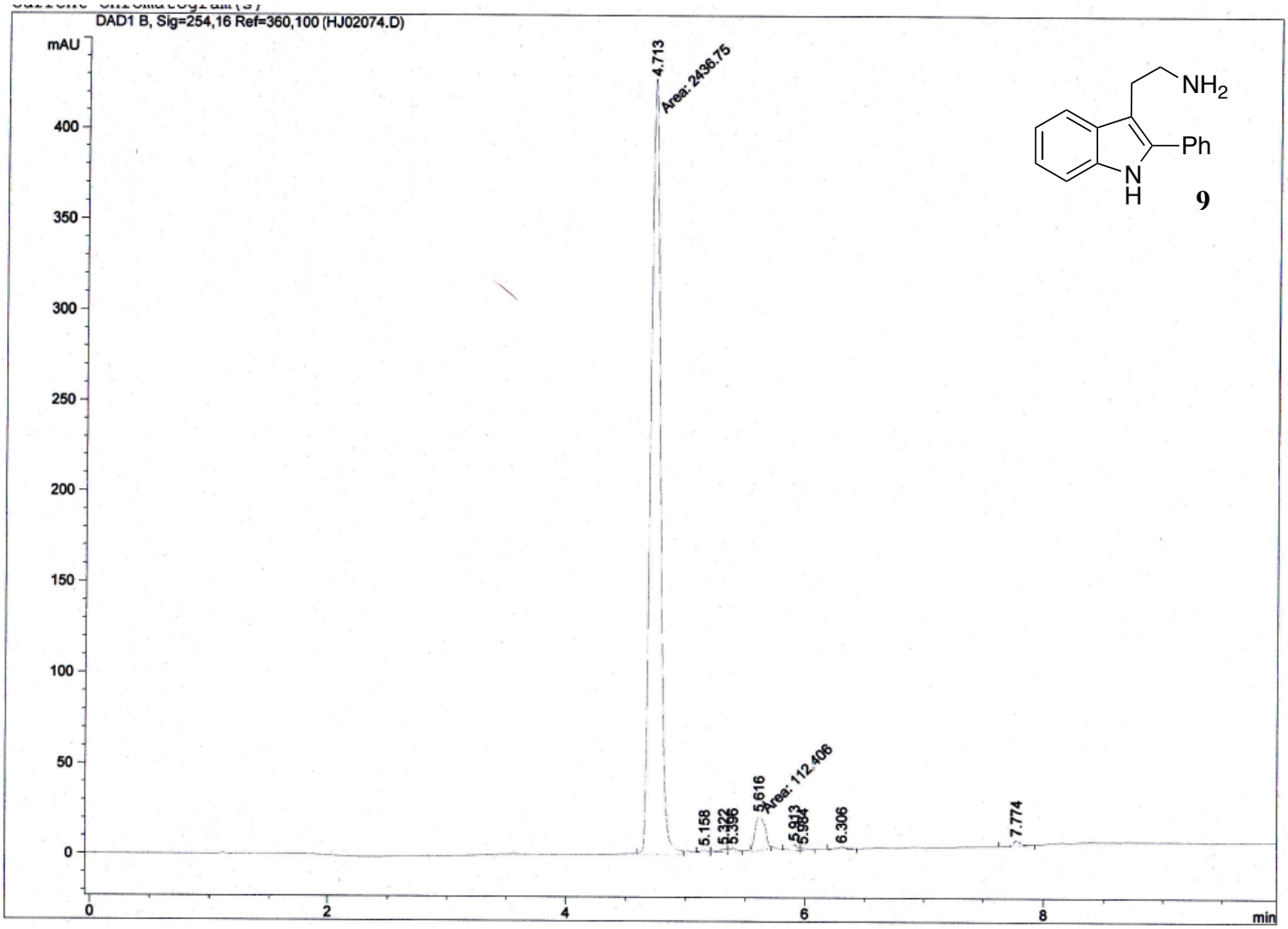
^{13}C NMR, 75 MHz, DMSO-d_6

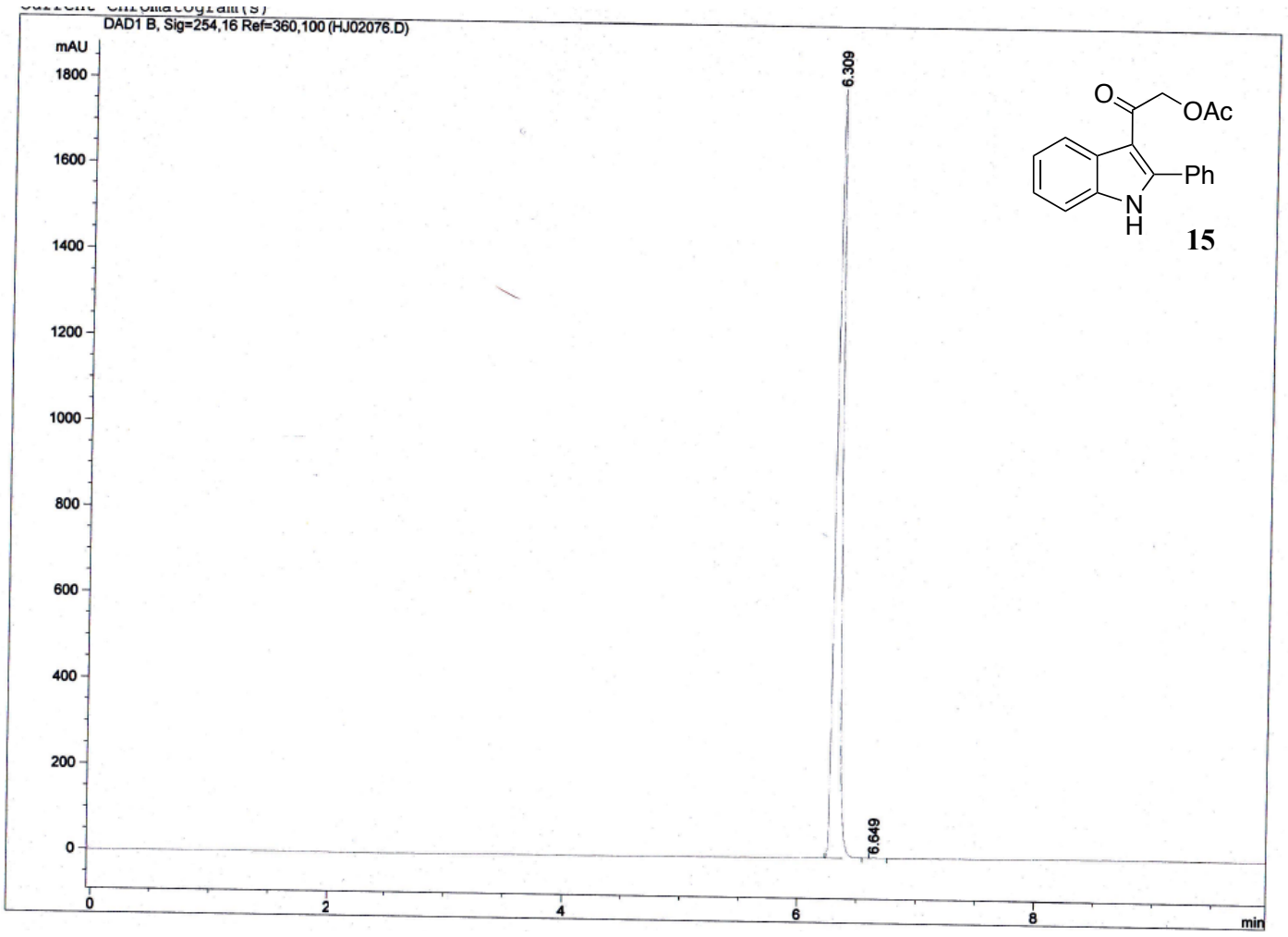


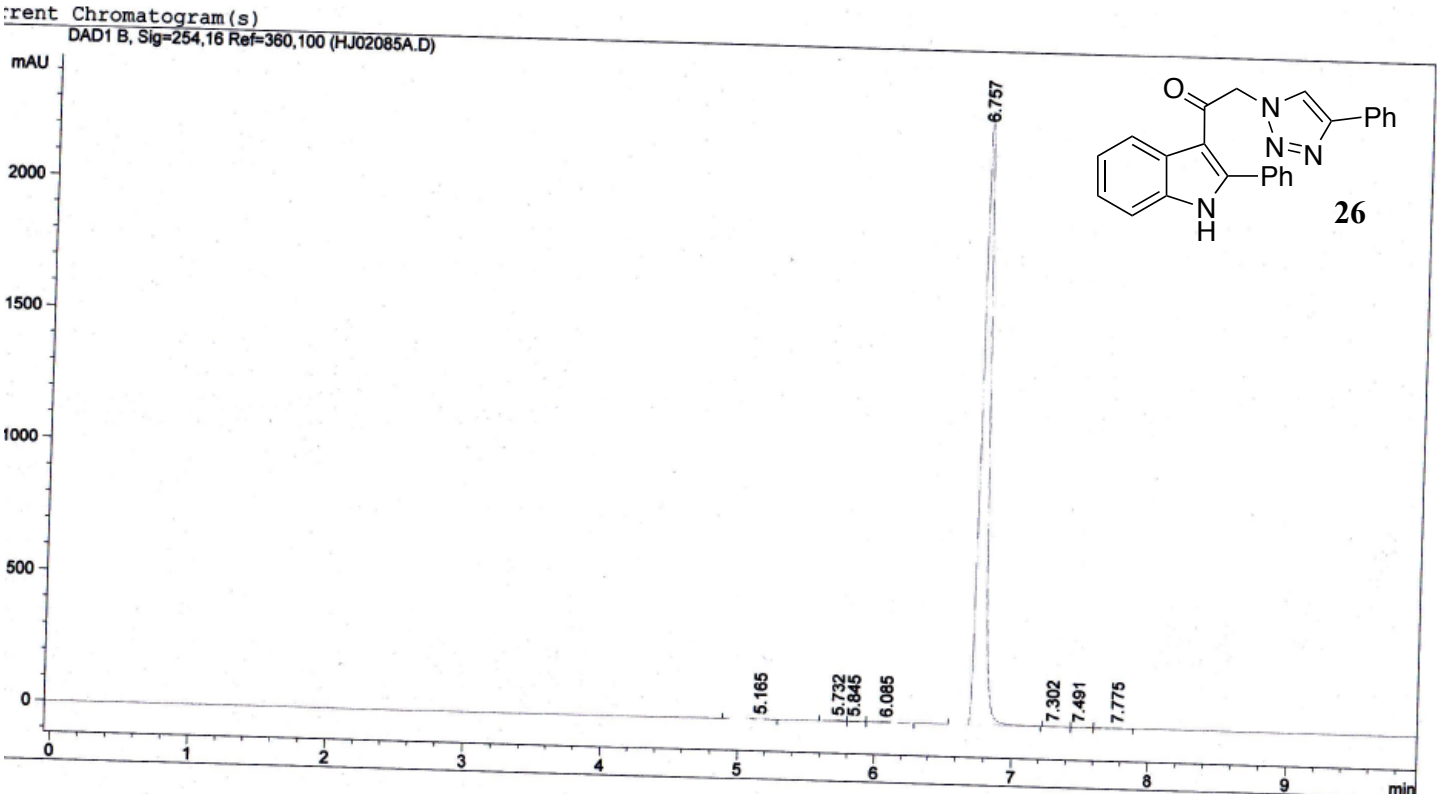


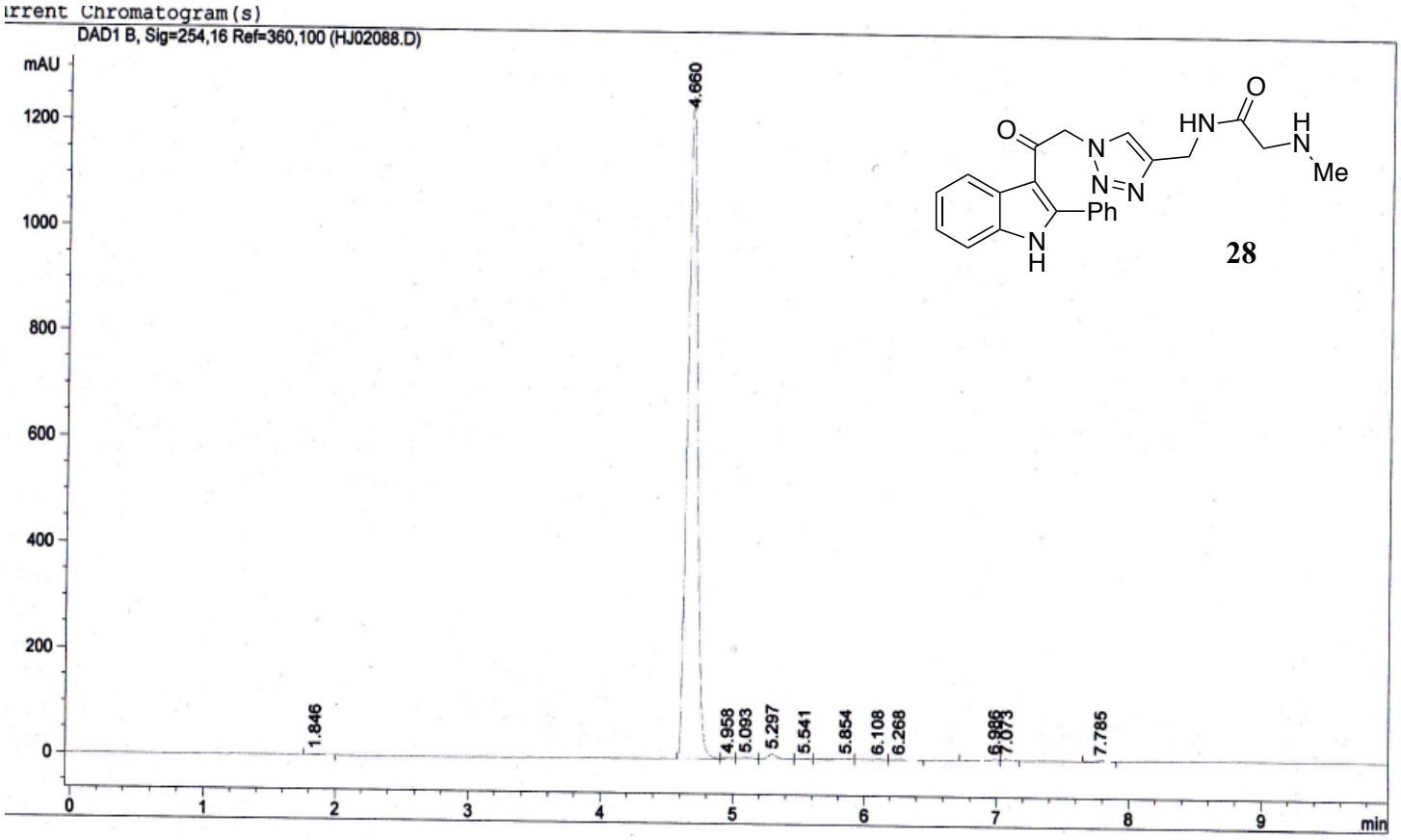


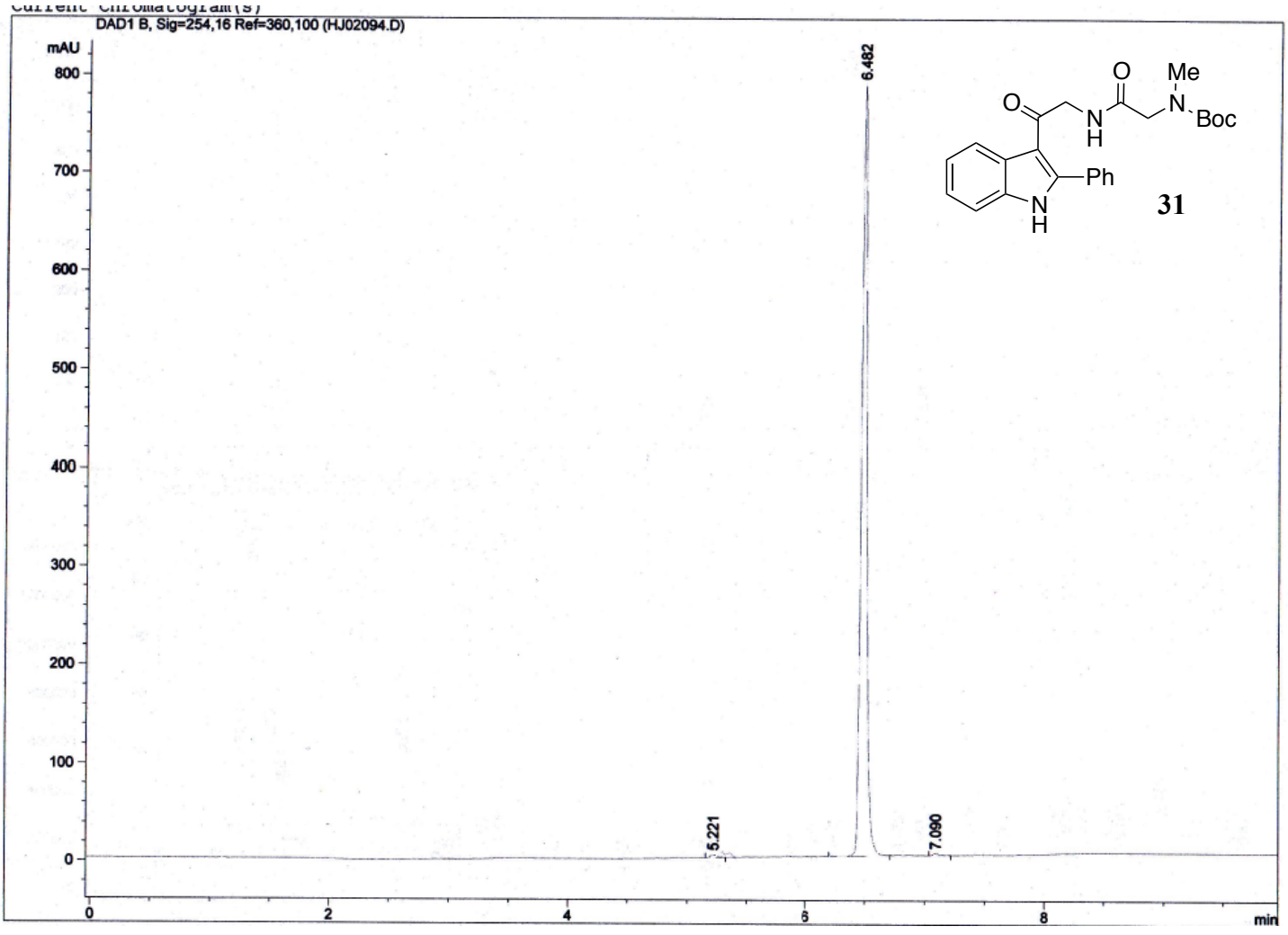


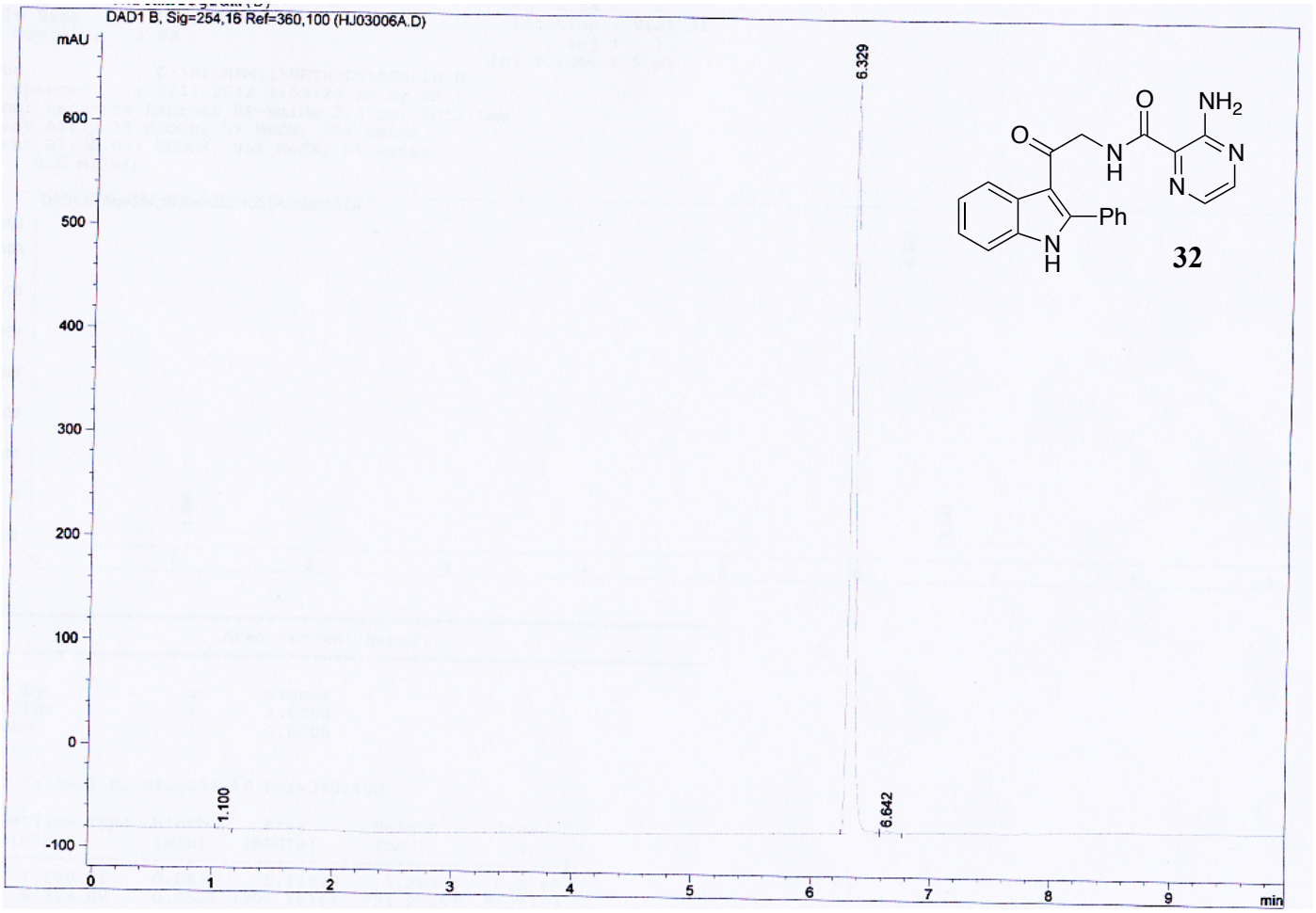


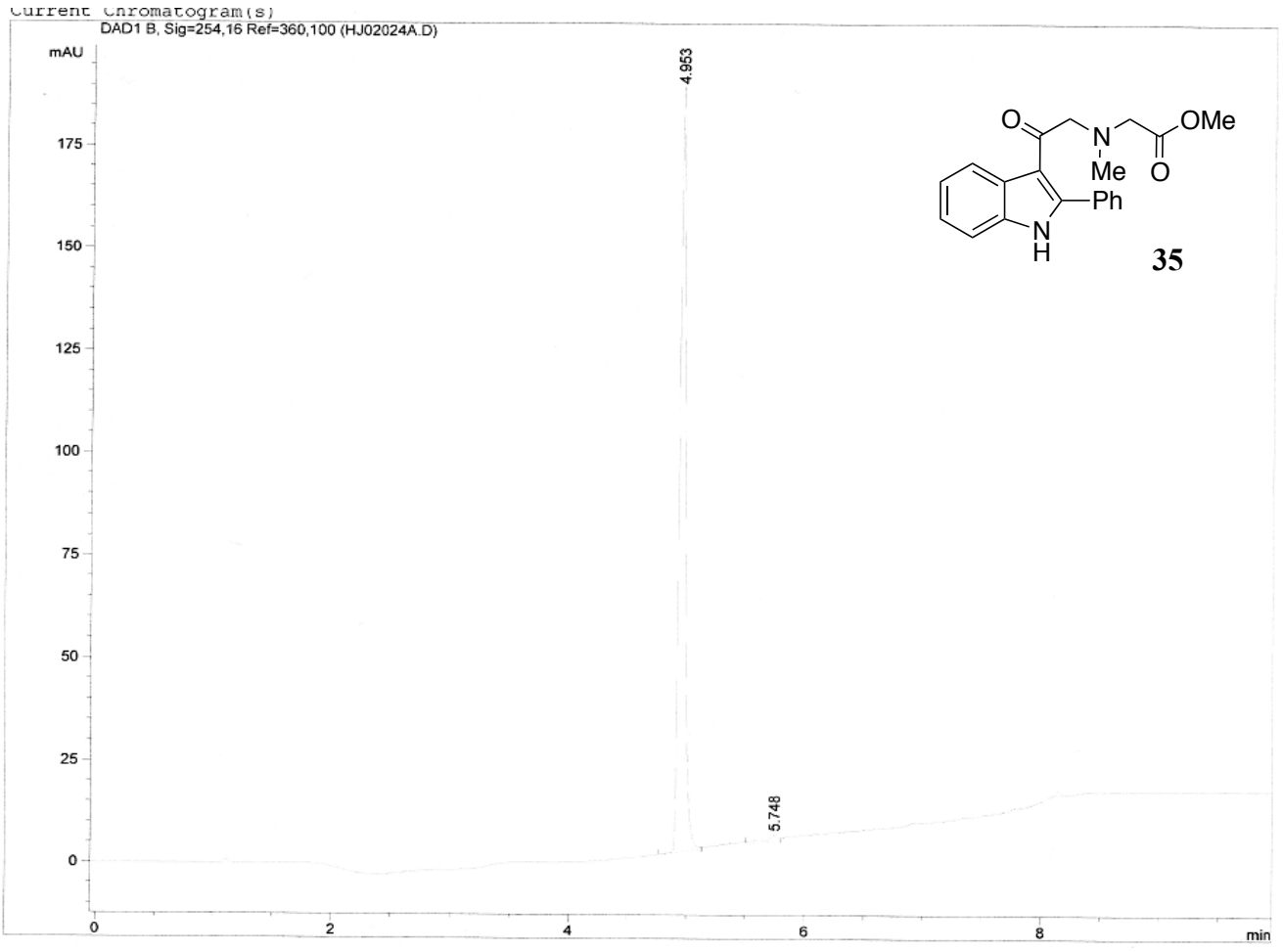


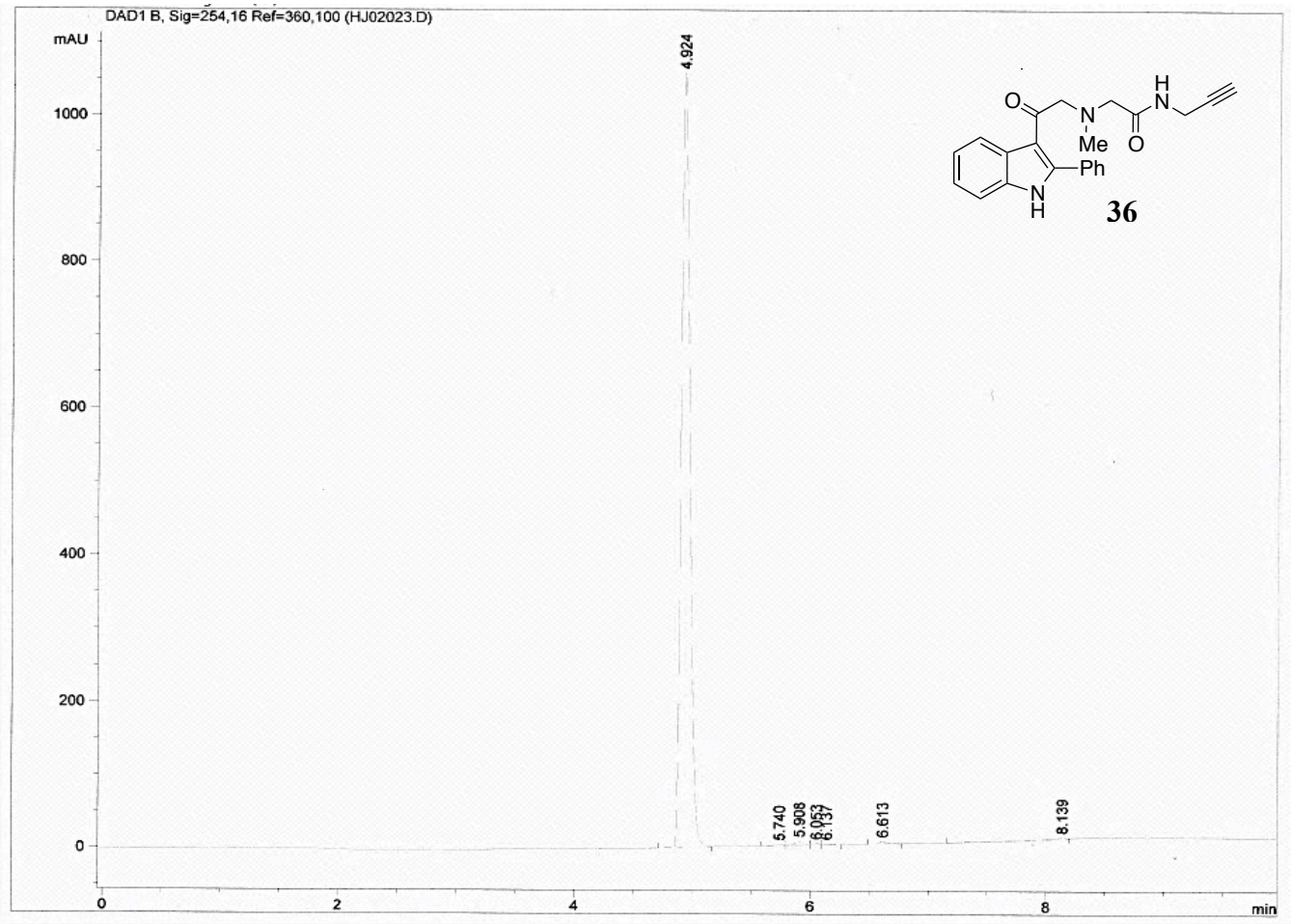


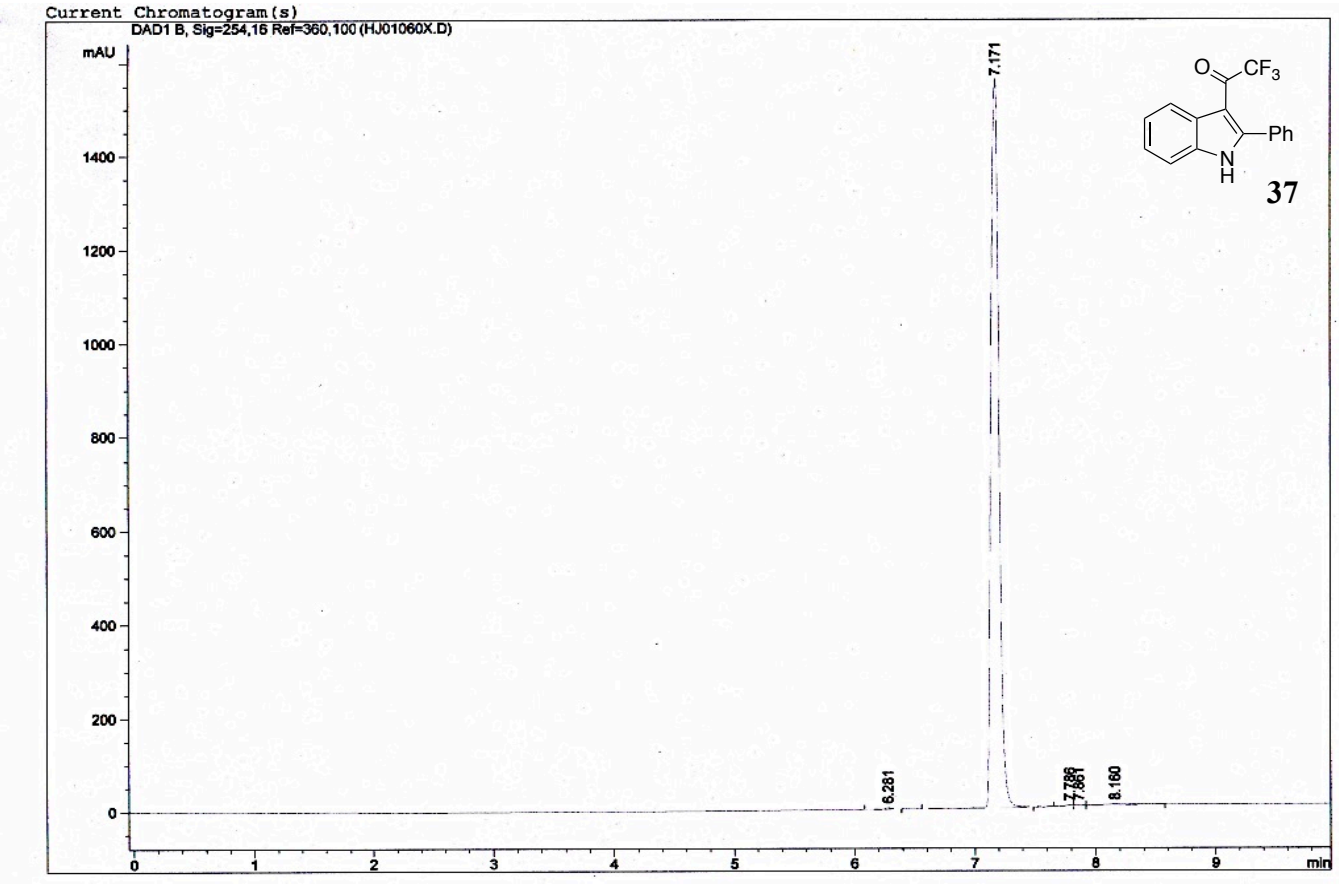


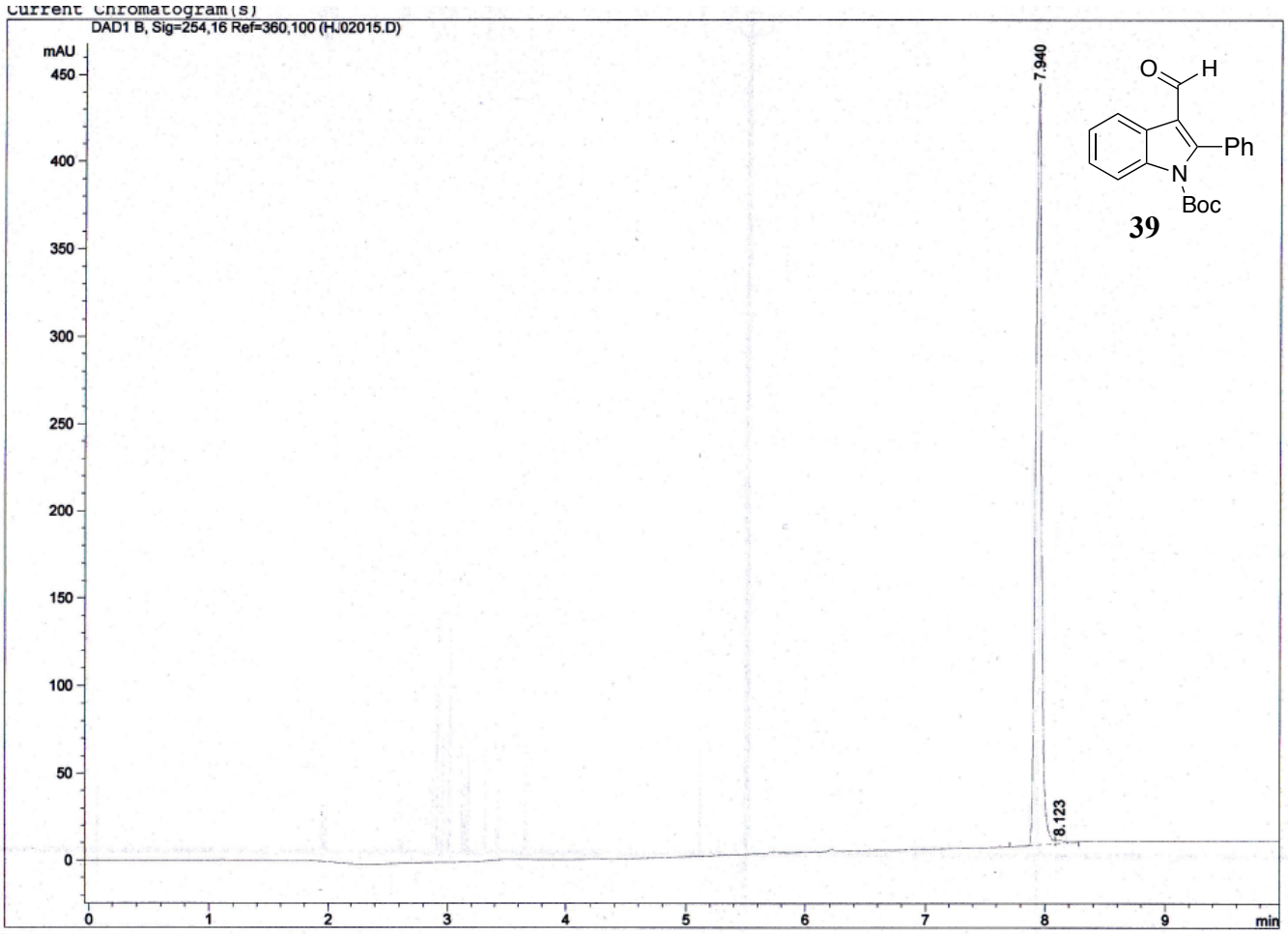


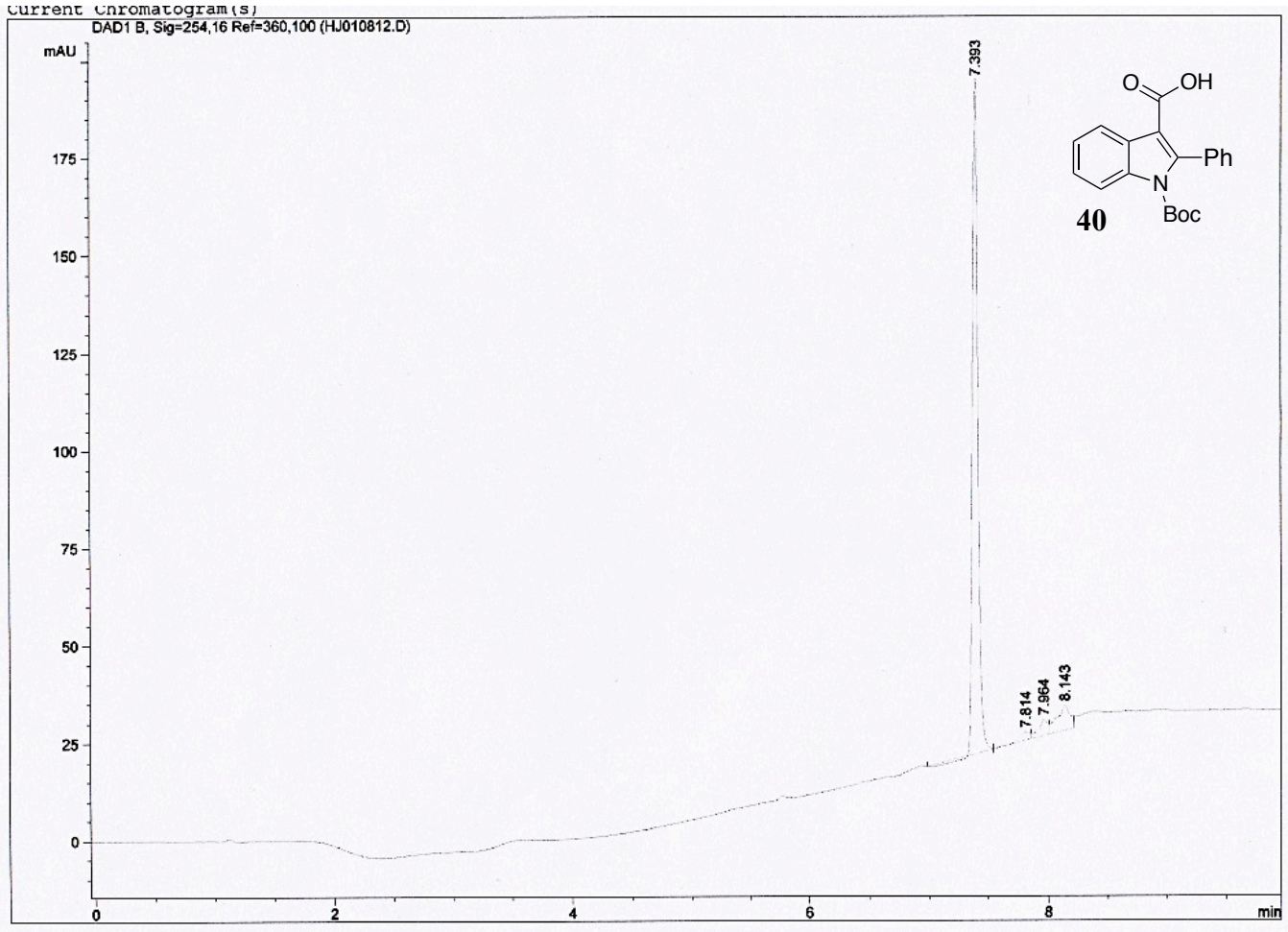

DAD1 B, Sig=254,16 Ref=360,100 (HJ03006A.D)
mAU
600
500
400
300
200
100
0
-100
1.100
6.329
6.642
0
1
2
3
4
5
6
7
8
9
min
O
NH2
O
N
H
N
N
Ph
N
H
32

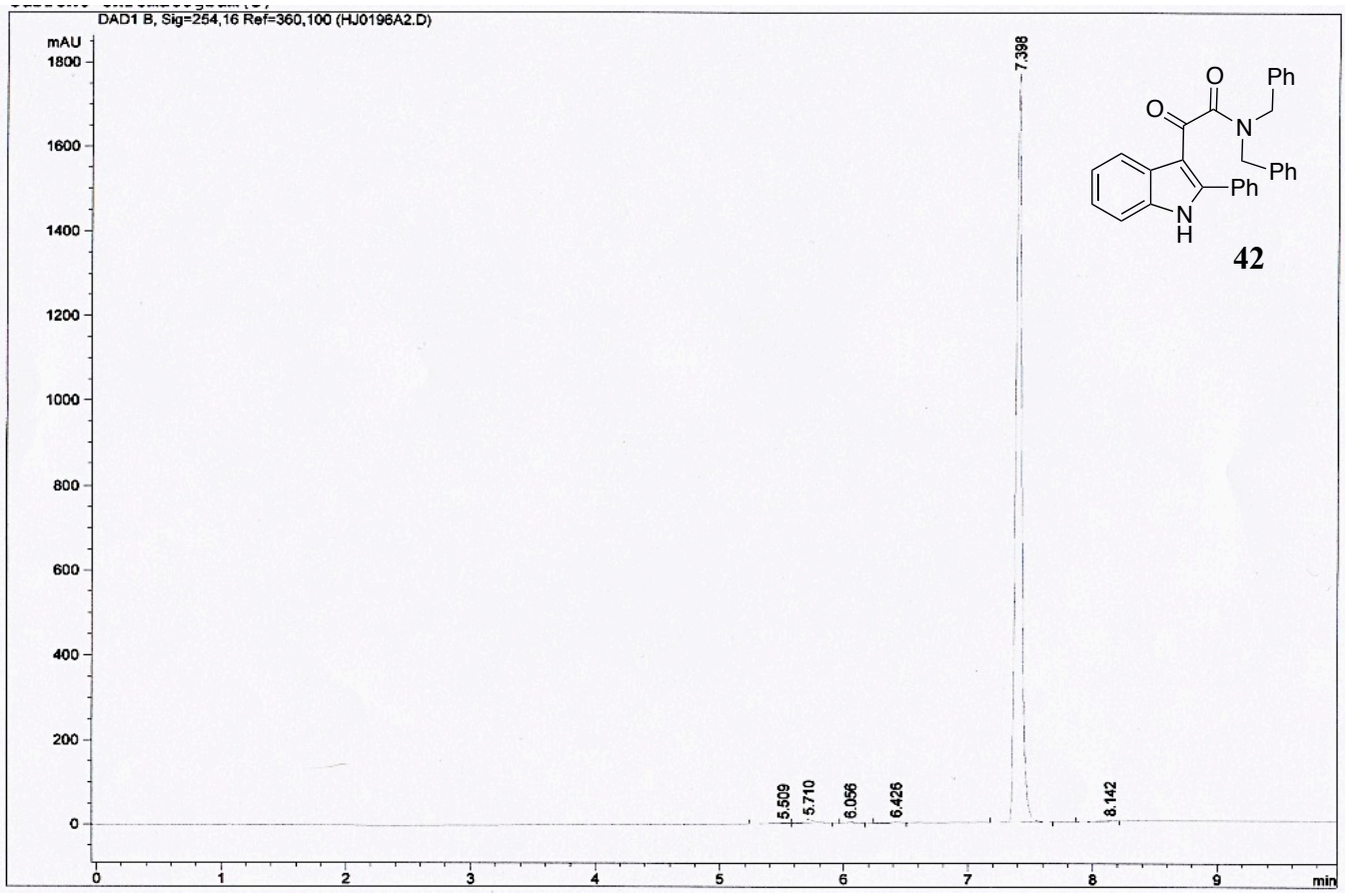

Current Chromatogram(s)
DAD1 B, Sig=254,16 Ref=360,100 (HJ02024A.D)
mAU
175
150
125
100
75
50
25
0
4.953
5.748
0
2
4
6
8
min
O
N
OMe
Me
O
Ph
N
H
35



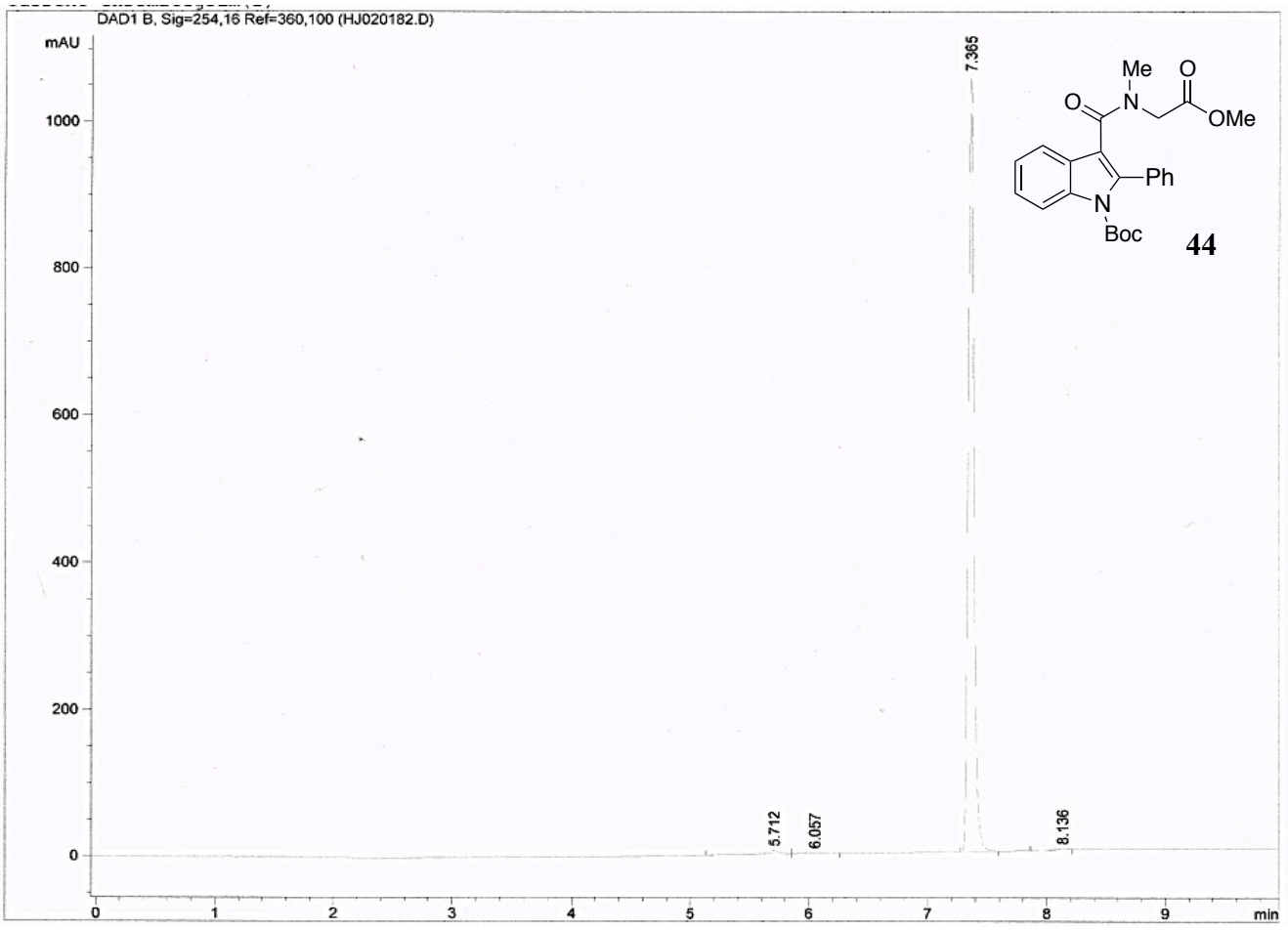




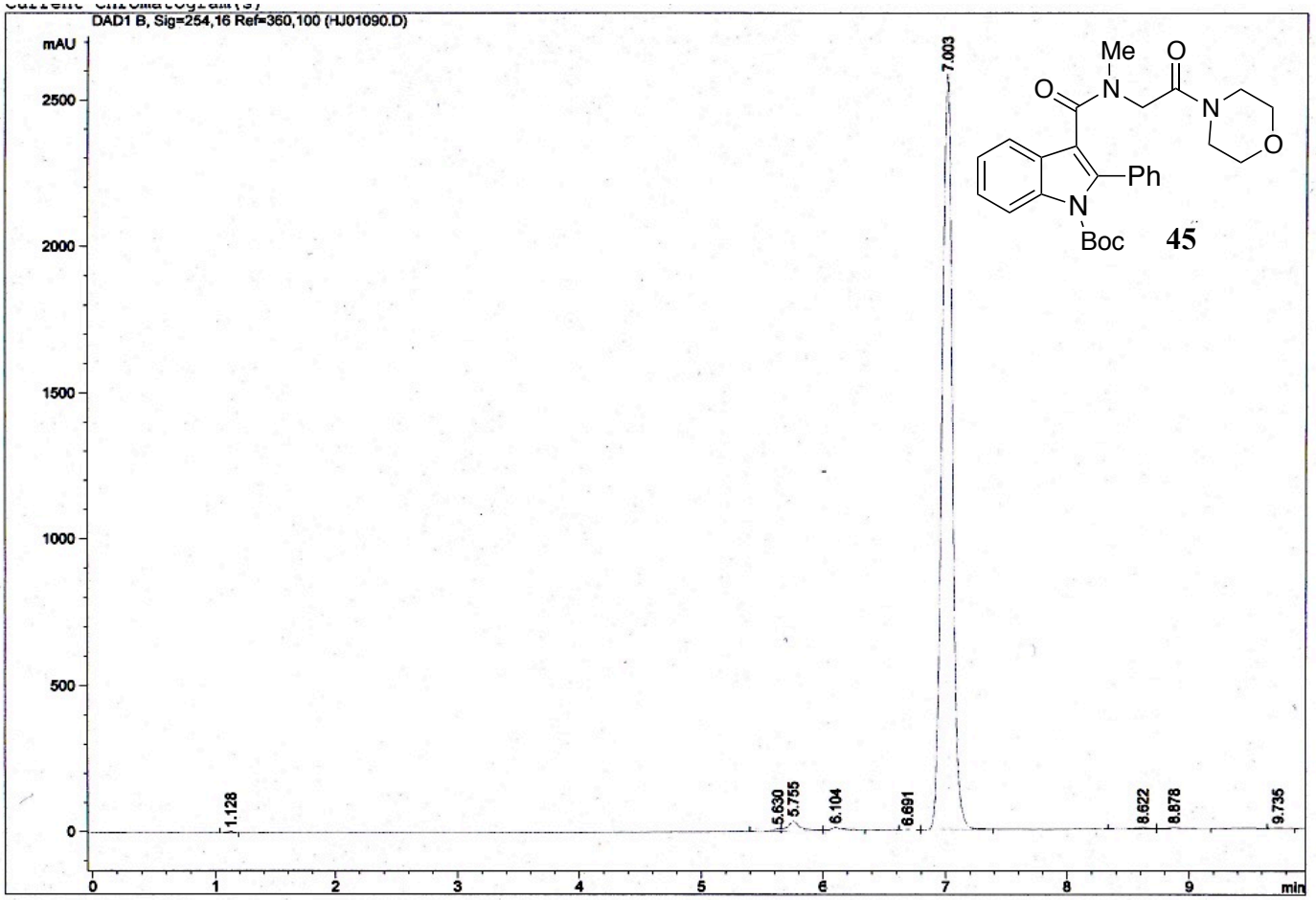


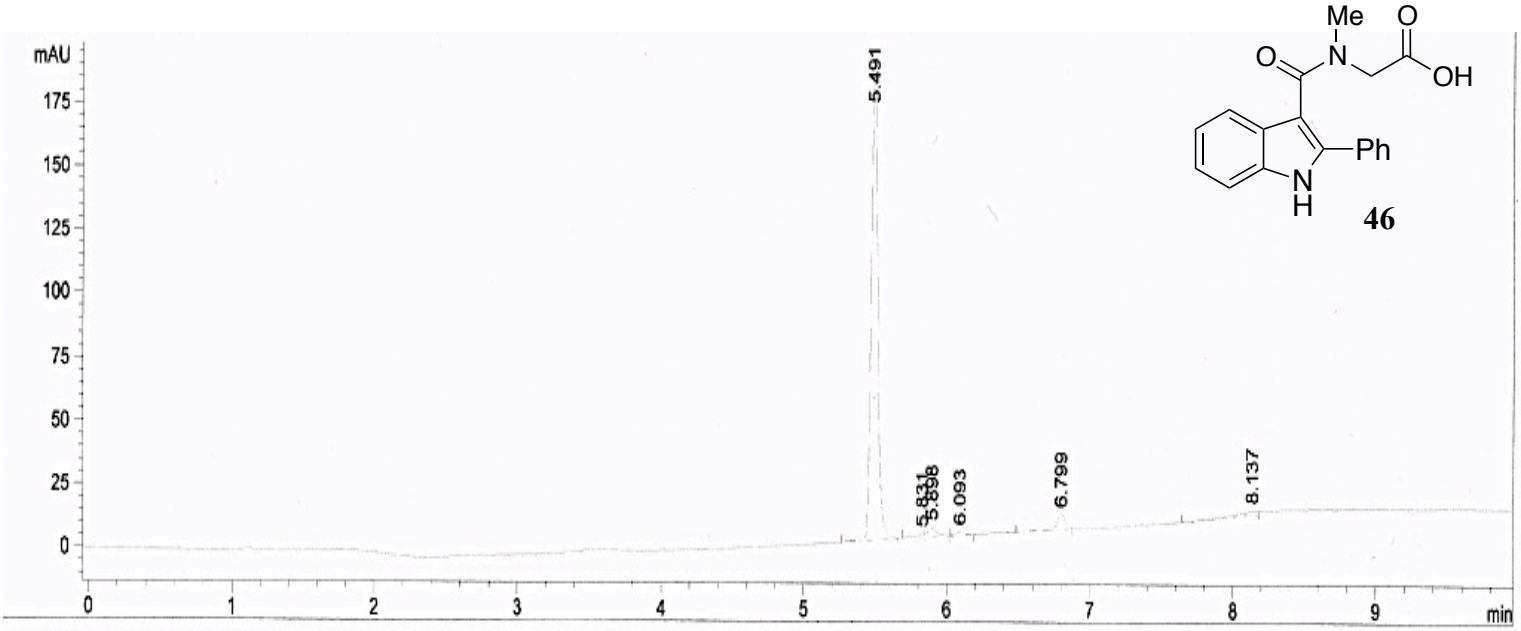


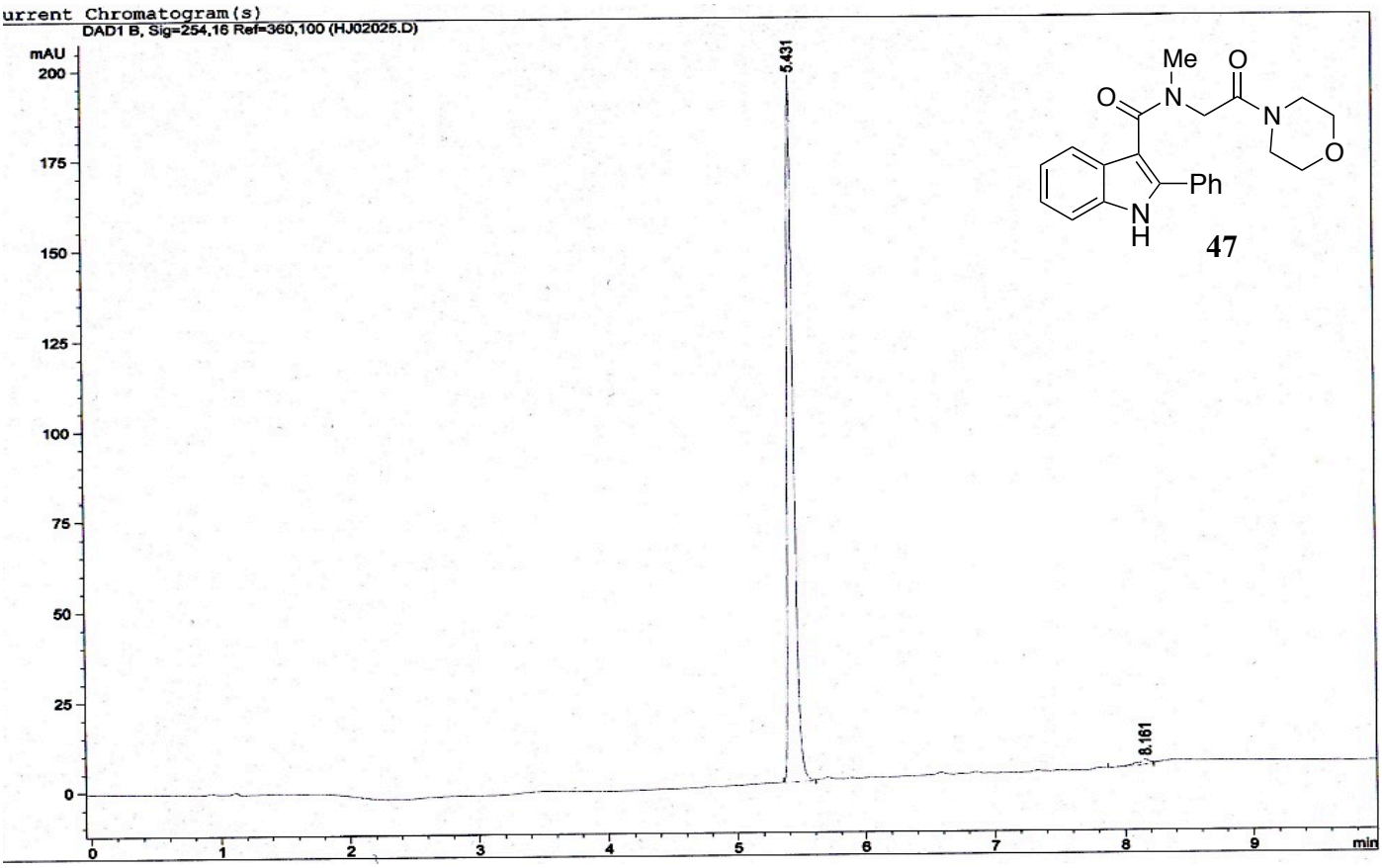
42

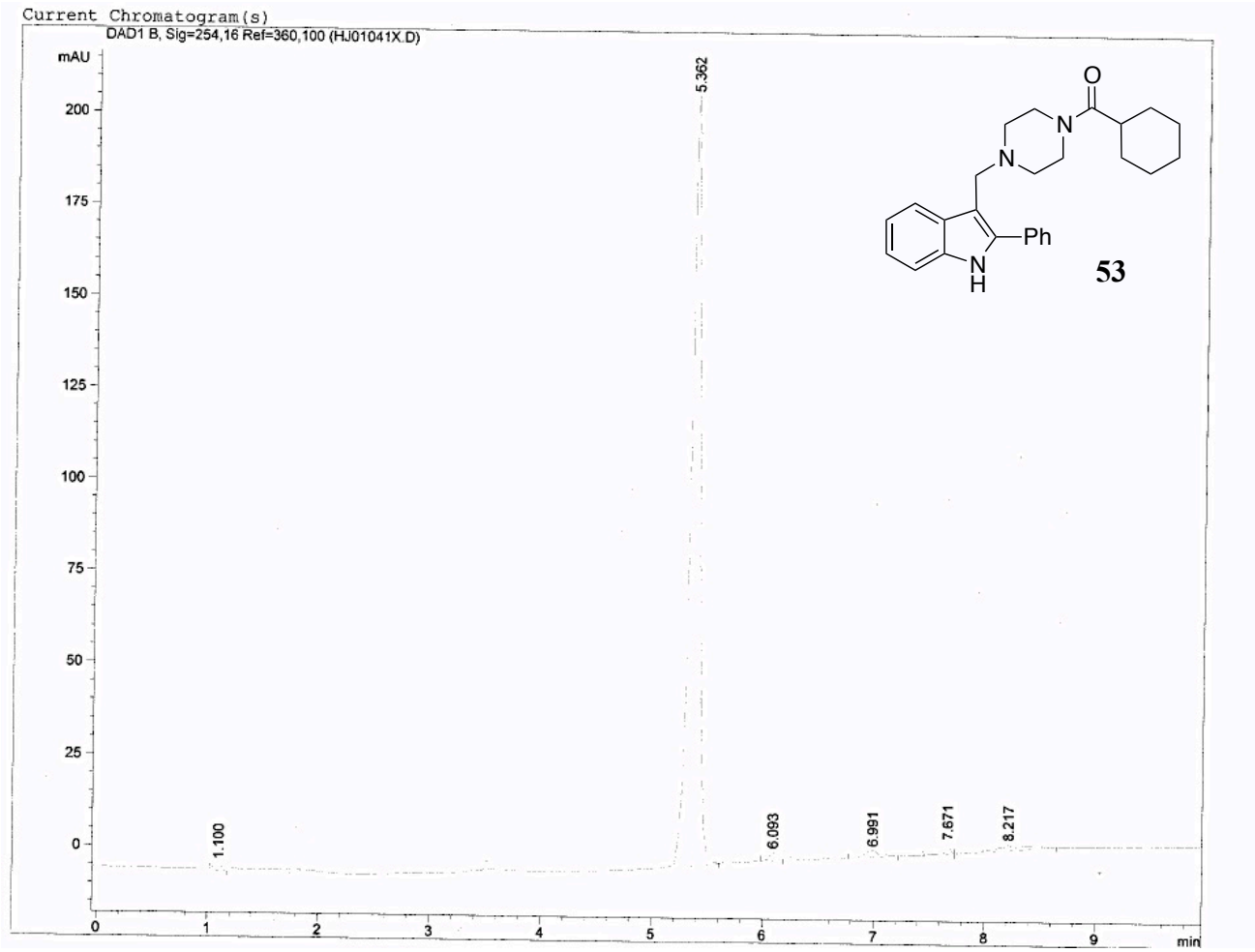


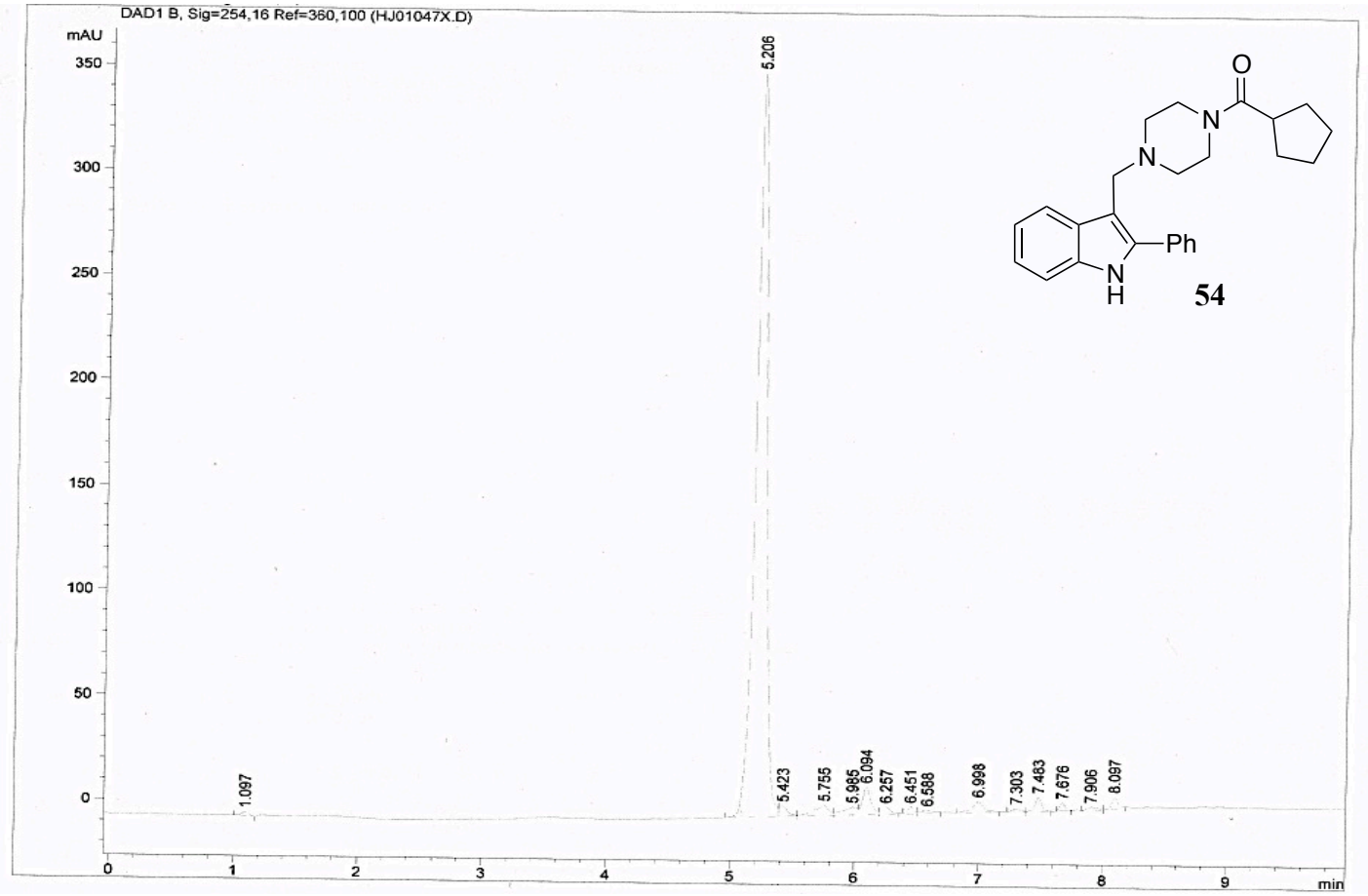
44



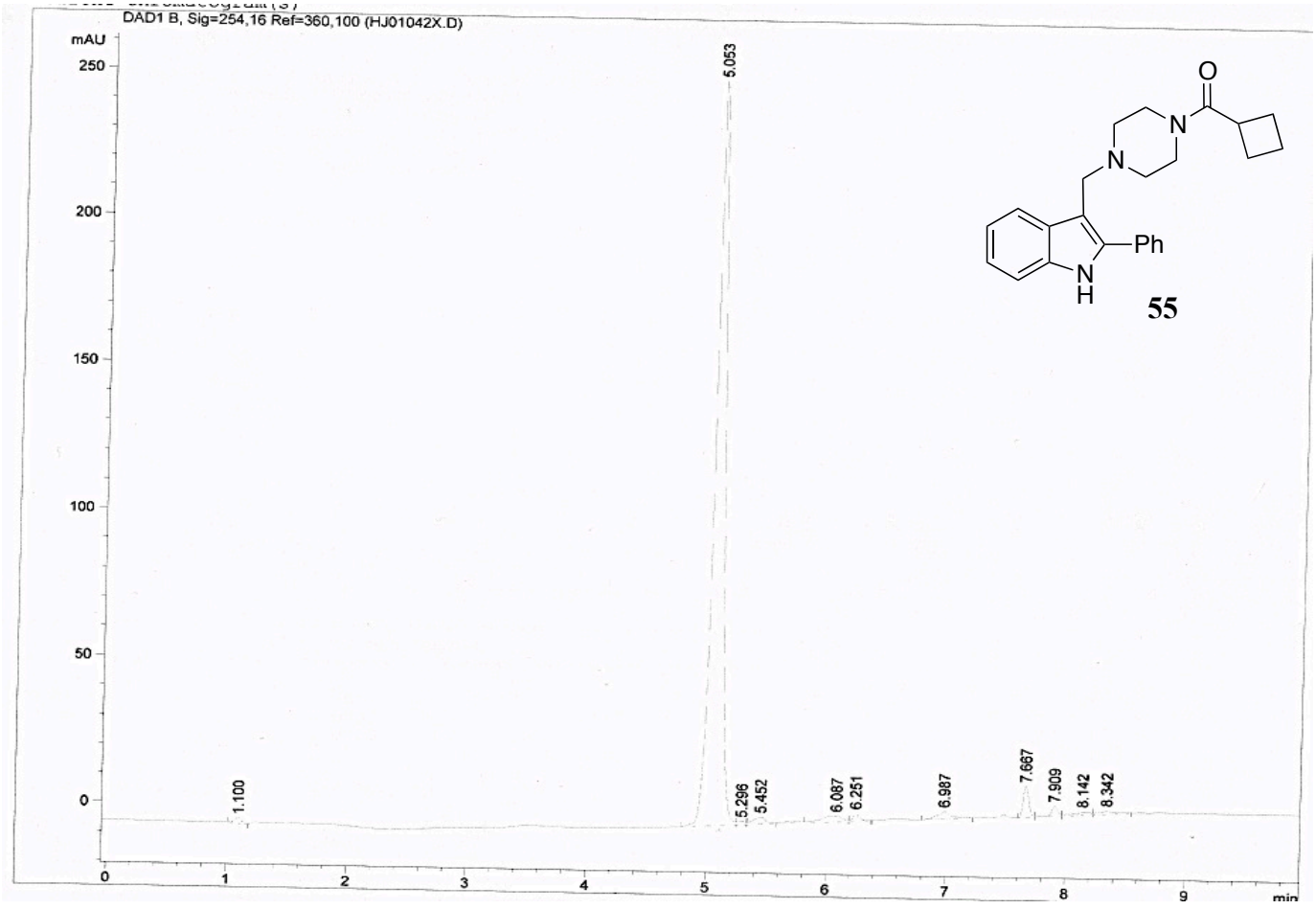




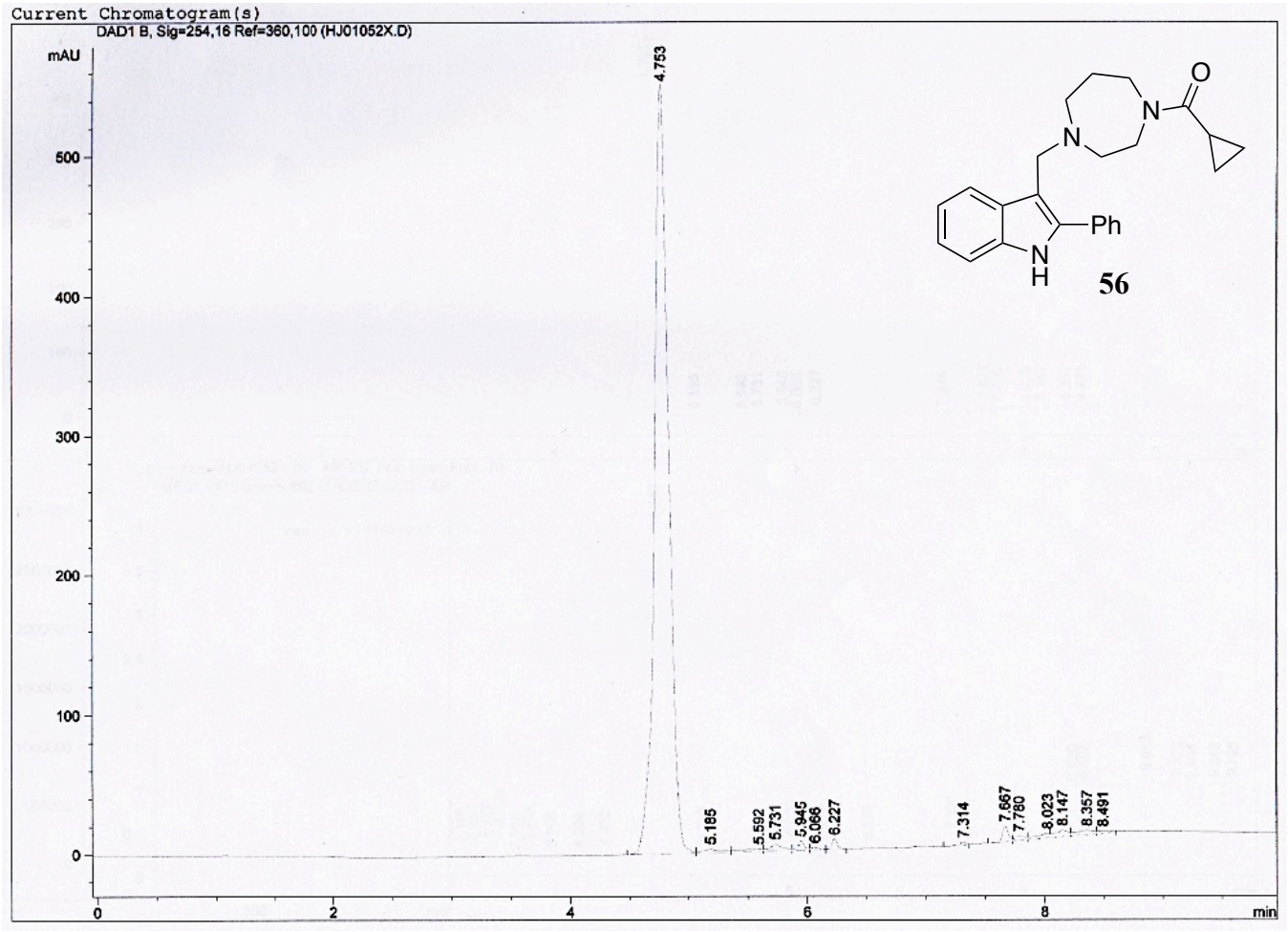


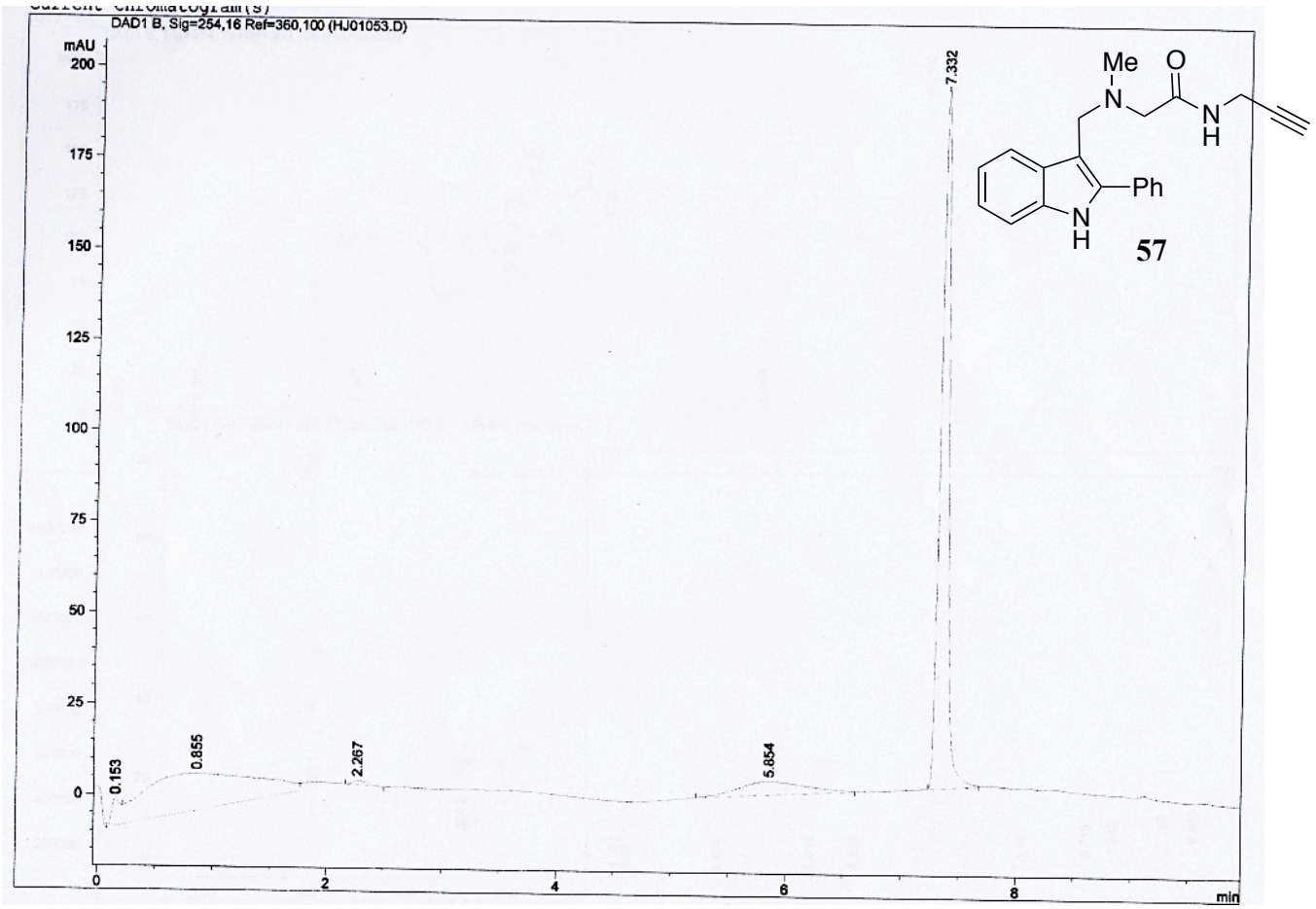


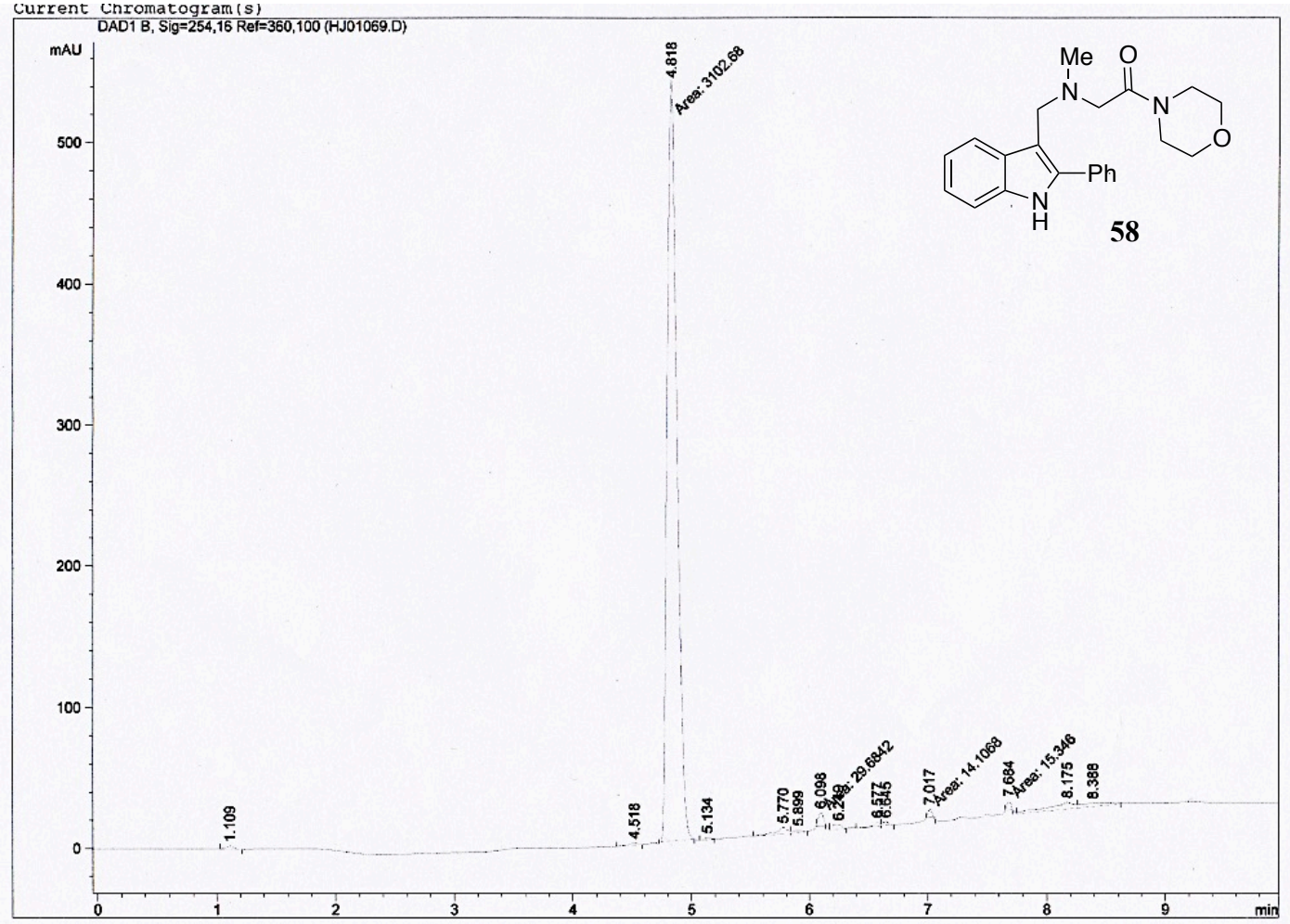
54

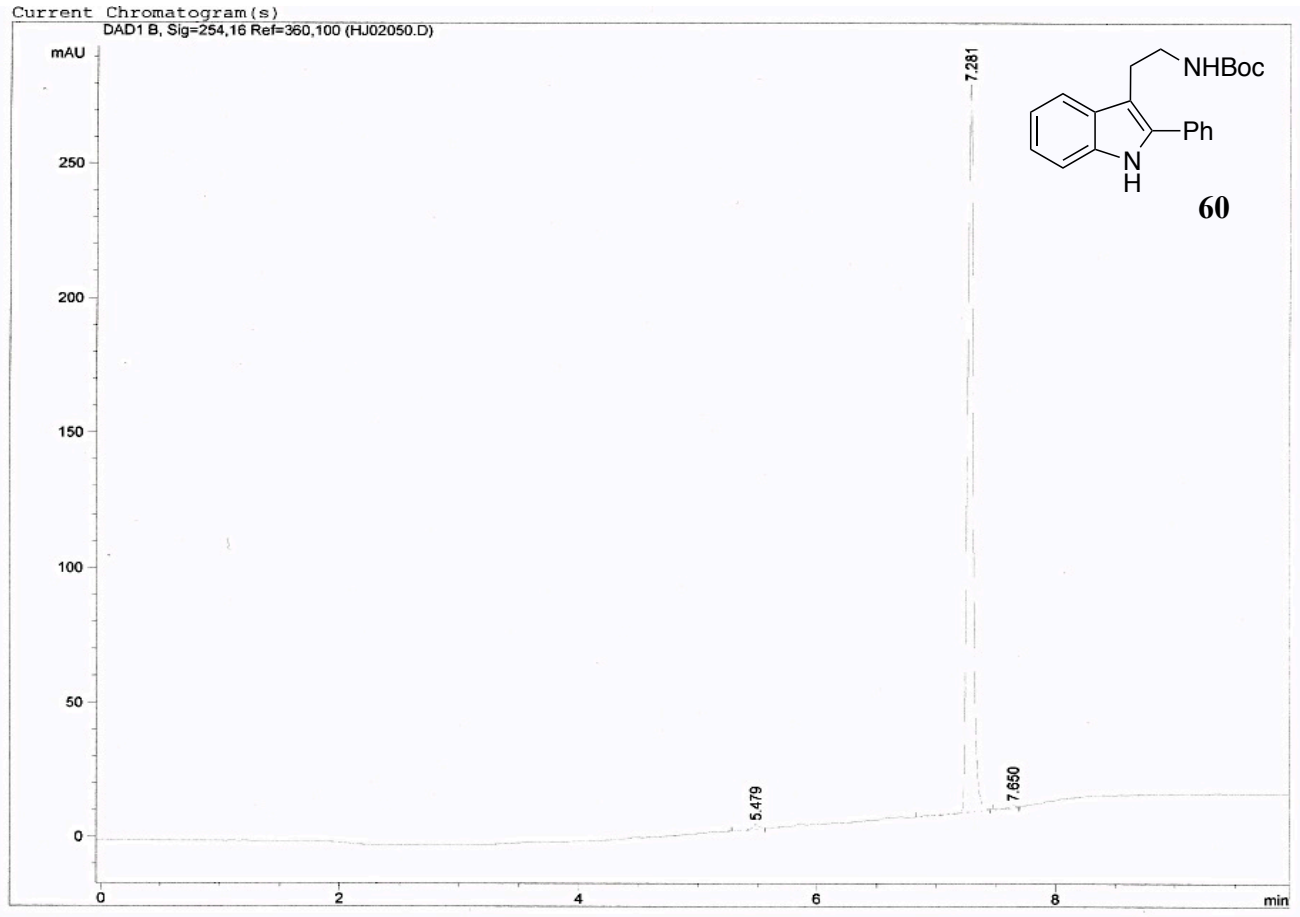


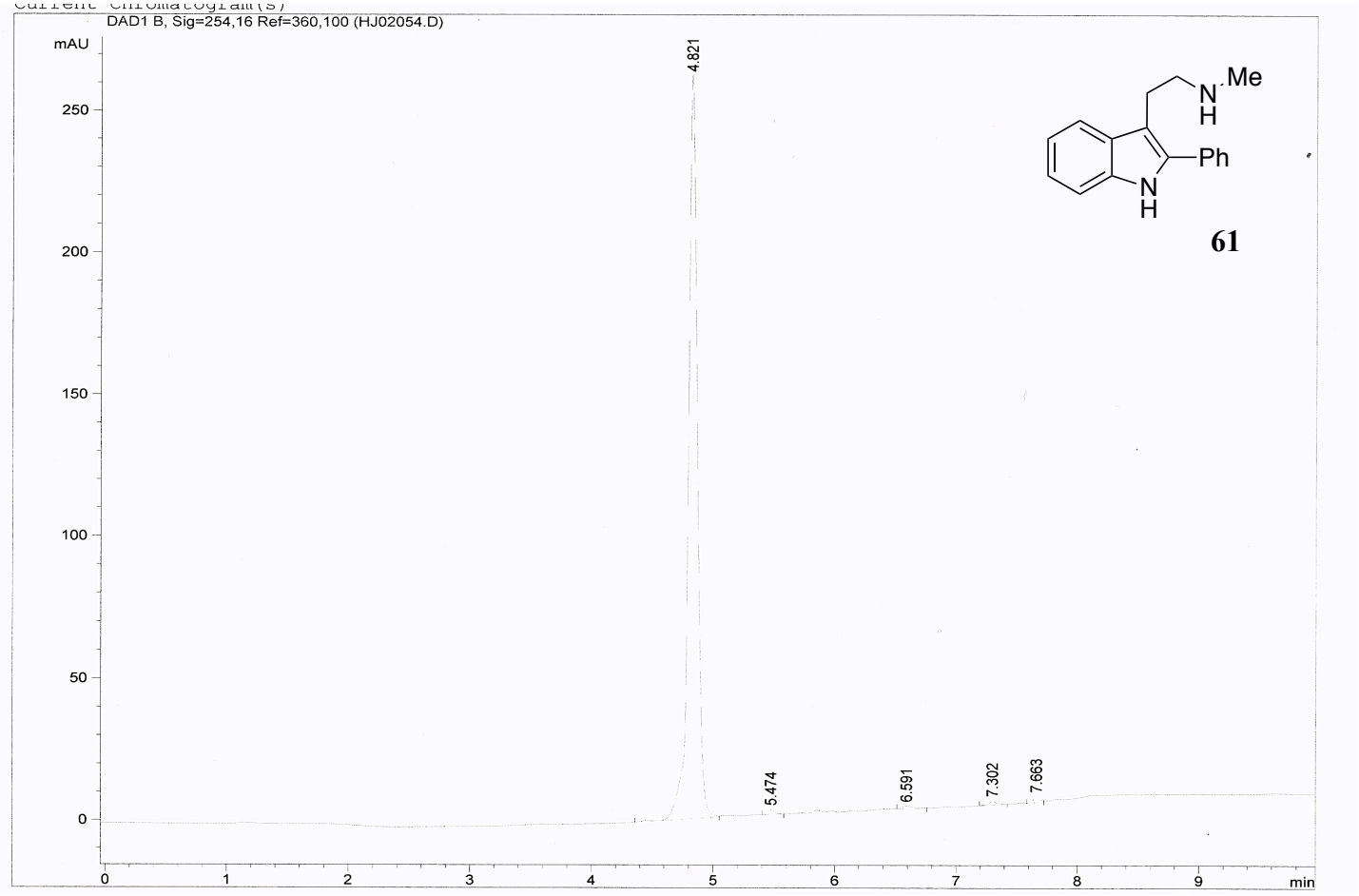
55


Current Chromatogram(s)
DAD1 B, Sig=254,16 Ref=360,100 (HJ01052X.D)
mAU
500
400
300
200
100
0
4.753
5.185
5.592
5.731
5.945
6.066
6.227
7.314
7.667
7.780
8.023
8.147
8.357
8.491
0
2
4
6
8
min
O
N
N
Ph
N
H
56

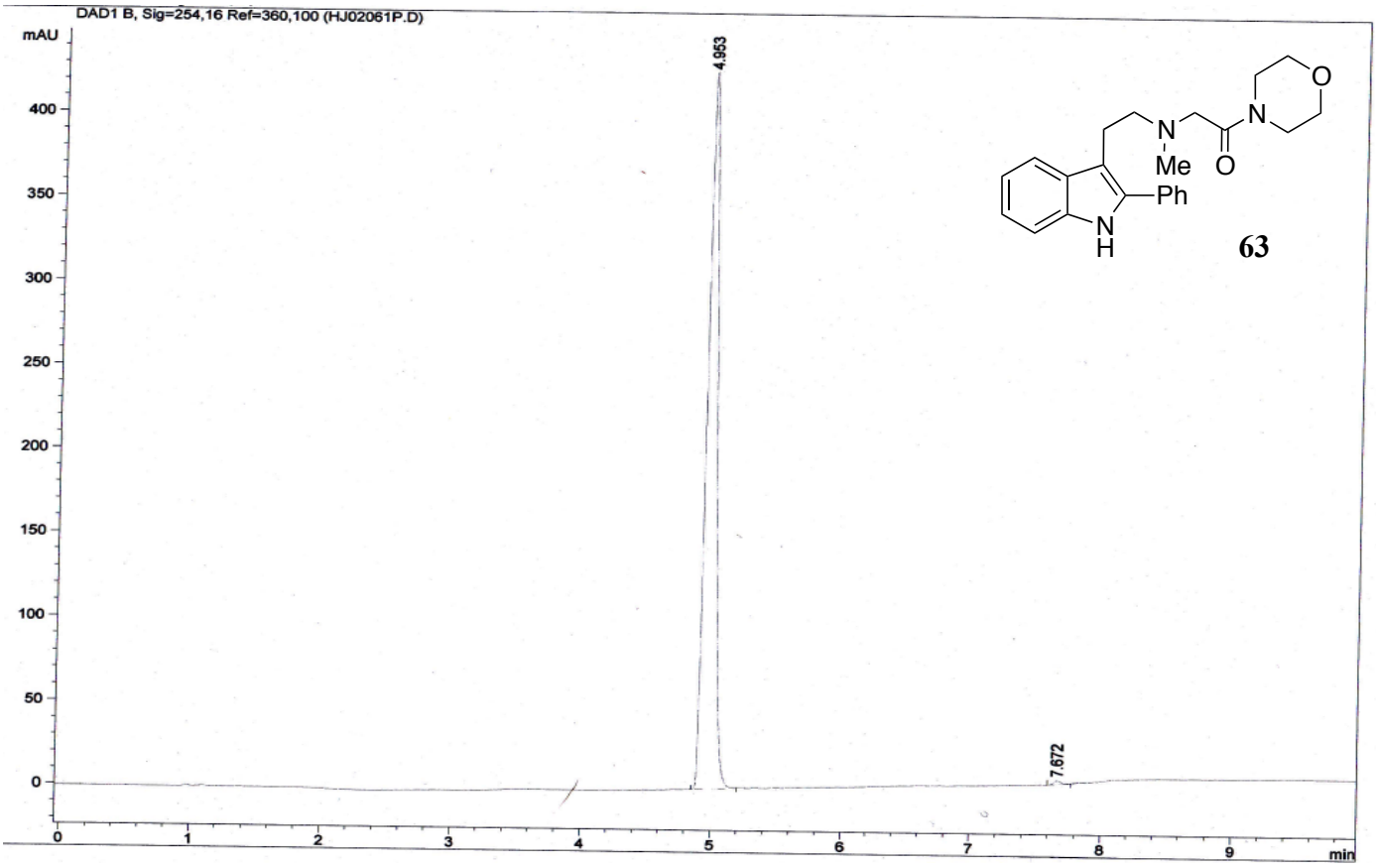

DAD1 B, Sig=254,16 Ref=360,100 (HJ01053.D)
mAU
200
175
150
125
100
75
50
25
0
0.153
0.855
2.267
5.854
7.332
0
2
4
6
8
min
Me
O
N
N
H
Ph
N
H
57


Current Chromatogram(s)
DAD1 B, Sig=254,16 Ref=360,100 (HJ01069.D)
mAU
4.818
Area: 3102.68
1.109
4.518
5.134
5.770
5.899
6.098
6.577
7.017
Area: 14.1068
7.684
Area: 15.346
8.175
8.388
min
Me
O
N
N
O
Ph
N
H
58


Current Chromatogram(s)
DAD1 B, Sig=254,16 Ref=360,100 (HJ02050.D)
mAU
7.281
5.479
7.650
min
NHBoc
Ph
N
H
60



61



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