Supporting Information

Chemoenzymatic Synthesis of a Chiral Ozanimod Key Intermediate Starting from Naphthalene as Cheap Petrochemical Feedstock

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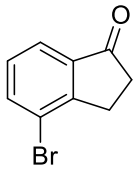
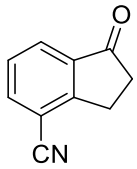
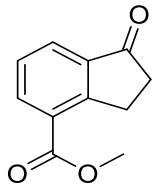
1 Results

1.1 Transamination with transaminase from *Vibrio fluvialis* in phosphate buffer and MeOH

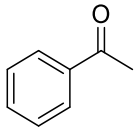
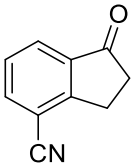
Table S1: Results for transamination with *Vibrio fluvialis* in phosphate buffer and methanol.

	Experiment 1	**Experiment 2**	**Experiment 3**
L-Alanine	24.86 mg 0.28 mmol 3.9 eq	24.53 mg 0.28 mmol 3.9 eq	24.92 mg 0.28 mmol 3.9 eq
Glucose	32.53 mg 0.18 mmol 2.6 eq	32.67 mg 0.18 mmol 2.6 eq	32.71 mg 0.18 mmol 2.6 eq
VF-TA (*Vibrio fluvialis* Transaminase)	77.43 mg 23 U 575 U/mmol$_{substrate}$	77.32 mg 23 U 575 U/mmol$_{substrate}$	77.21 mg 23 U 575 U/mmol$_{substrate}$
GDH (Glucose dehydrogenase)	5.58 mg 30 U 615 U/mmol$_{substrate}$	5.64 mg 30 U 615 U/mmol$_{substrate}$	5.69 mg 30 U 615 U/mmol$_{substrate}$
Phosphate buffer (0.1 M, pH 8.0)	800 µL	800 µL	800 µL
MeOH	200 µL	200 µL	200 µL
PLP (Pyridoxalphosphat) **(10 mM, pH 8.0)**	100 µL	100 µL	100 µL
Ketone	 6.23 mg, 0.04 mmol 1.0 eq	 4.80 mg, 0.04 mmol 1.0 eq	 5.01 mg, 0.03 mmol 1.0 eq
Conversion/%	67	83	69
***ee*-Value**	50	25	99

The experimental part can be found in the manuscript under: Transamination with *Vibrio fluvialis* transaminase (*VF-TA*).

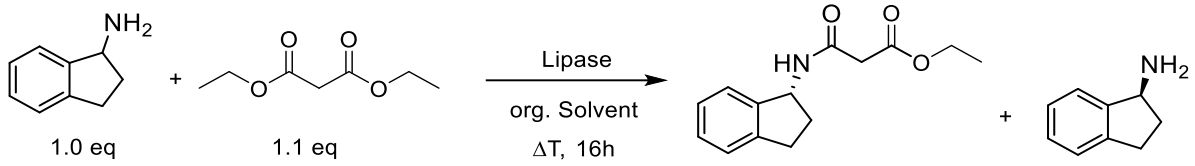
1.2 Transamination with transaminase from *Arthrobacter sp.* in phosphate buffer and DMSO

Table S2: Results for transamination with *Vibrio fluvialis* in phosphate buffer and DMSO**.**

	Experiment 1	**Experiment 3**
Isopropylamine	75 µL 0.90 mmol 2.1 eq	75 µL 0.18 mmol 2.0 eq
DMSO	3.0 mL	600 µL
PLP (Pyridoxalphosphat) **solution (10 mM, pH 8.0)**	4.3 mL	860 µL
ArS-TA (*Arthrobacter sp.* Transaminase)	76 mg	15.2 mg
Phosphate buffer (0.1 M, pH 8.0)	2.7 mL	540 µL
Ketone	 50 µL (51.7 mg) 0.43 mmol 1.00 eq	 13.88 mg, 0.09 mmol 1.0 eq
Conversion/%	34	0

The experimental part can be found in the manuscript under: Transamination with *Arthrobacter sp*. transaminase in DMSO.

1.3 Initial experiments for kinetic resolution with various lipases: screening of suitable lipases



For the initial experiments, 1-aminoindane (20 mg, 15 µmol) was dissolved with diethyl malonate (24 mg, 20 µmol) in organic solvent (256 µL) in Eppendorf vessels. Lipase was added to the reaction solution (6 mg). The reaction solution was stirred for 16 hours at appropriate temperature. Subsequently, the enzyme was filtered off and washed with dichloromethane. The solvent was removed *in vacuo*. Conversion was determined by ^{1}H NMR spectroscopy.

Table S3: Results for initial experiments for kinetic resolution with various lipases

Enzyme[a]	**T/ °C**	**Solvent**	**Conversion/%**
CAL-B	40	*n*-heptane	6
CAL-B	60	*n*-heptane	74
CAL-B	40	MTBE	20
CAL-B	60	MTBE	67
BC	40	toluene	0
BC	60	toluene	4
BC	60	*n*-heptane	24
BC	60	MTBE	3
CR	40	toluene	0
CR	60	toluene	7
CR	60	*n*-heptane	9
CR	60	MTBE	2

[a] Abbreviations: CAL-B: lipase from *Candida antarctica* B; BCL: lipase from *Burkholderia cepacia*; CRL: lipase from *Candida rugosa*. The lipases were used as commercially available samples.

1.4 Screening of solvents, acyl donors and temperature of the CAL-B-catalyzed resolutions

Table S4: Results for solvent-, acyldonor-, temperature-screening of CAL-B-catalyzed reactions

Solvens	Acyldonor	T/°C	t/h	Conv./%[a]	Conv./%[b]	ee_P/%[c]	ee_S/%[d]	E-value[e]
2-MTHF	DEM[f]	60	6	53	50	82	91	32
2-MTHF[i]	DEM[f]	60	26	59	59	70	99	28
Toluene	DEM[f]	60	6	55	53	80	96	36
Toluene	DEM[f]	60	26	55	60	79	97	35
MTBE	DEM[f]	60	6		46	82	69	19
MTBE	DEM[f]	60	26		54	81	95	20
MCH[j]	DEM[f]	60	6	53	49	83	95	40
MCH[j]	DEM[f]	60	26	58	55	70	98	25
Toluene	DEM[f]	80	6	54	49	82	98	46
Toluene	DEM[f]	80	26	65	53	54	99	16
n-heptane	DEM[f]	60	6		50	70	73	12
n-heptane	DEM[f]	60	26		57	59	77	9
2-MTHF[i]	EMA[g]	60	6	55	55	81	99	52
2-MTHF[i]	EMA[g]	60	26	59	58	72	99	31
Toluene	EMA[g]	60	6	57	56	77	97	31
Toluene	EMA[g]	60	26	65	59	70	99	28
MTBE	EMA[g]	60	6	67	68	66	97	20
MTBE	EMA[g]	60	26	70	70	59	99	19
MCH[j]	EMA[g]	60	6	55	54	81	97	39
MCH[j]	EMA[g]	60	26	60	60	67	99	25
2-MTHF[i]	EMA[g]	80	6	55	55	81	99	49
2-MTHF[i]	EMA[g]	80	26	69	56	79	99	44
n-heptane	DEM[f]	60	6		53	87	98	56
n-heptane	DEM[f]	60	26		54	83	99	58

2-MTHF	IMA[h]	60	6	41	97	68	14
2-MTHF	IMA[h]	60	26	43	95	72	84

[a] conv. via ^{1}H-NMR
[b] conv. via HPLC
[c] calc. via HPLC-data
[d] calc. via HPLC-data
[e] calc. via *ee* data[f]
[f] diethyl malonate
[g] ethyl methoxyacetate
[h] isopropyl methoxyacetate
[i] 2-methyl-THF
[j] methylcyclohexane

1.5 CAL-B-catalyzed reaction with 1M substrate loading

Table S5: Results for CAL-B-catalyzed reaction with 1M substrate loading.

t/h	**conv./%**[a]	***ee*$_P$ /%**[b]	***ee*$_S$ /%**[b]	**E-value**
6	47	89	80	42
26	56	73	94	22

[a] conv. via HPLC

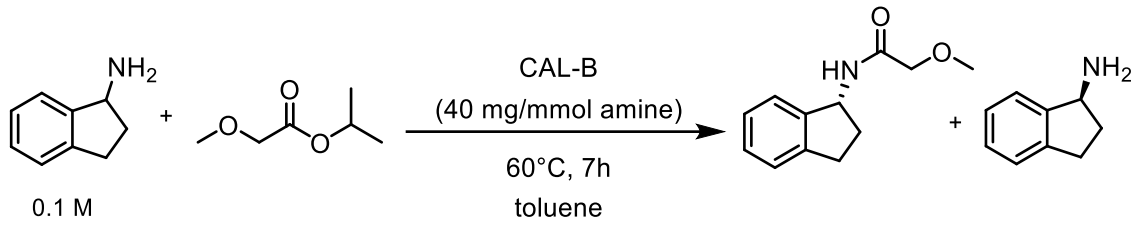
[b] calc. via HPLC

1.6 CAL-B-catalyzed reaction with 1-aminoindane derivatives

Table S6: Results for CAL-B-catalyzed reaction with 1M substrate loading.

R	**Conversion/%**	***ee*$_P$/%**	***ee*$_S$/%**	**E-value**
Br	59	68	99	26
CN	58	71	99	31
$COOCH_3$	65	51	96	11

1.7 Recycling experiments with CAL-B

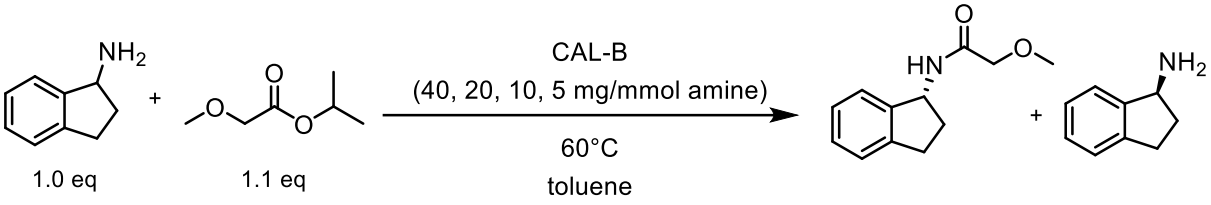


1-Aminoindan (67 mg, 0.50 mmol), isopropyl methoxyacetate (73 mg, 0.55 mmol) and CAL-B (20 mg) were dissolved in 5 mL toluene and stirred at 60°C. After 7 h a 200 µL sample was taken. The sample was acylated with acetyl chloride (9 mg, 0.11 mmol) and triethylamine (15 mg, 0.15 mmol). The reaction was repeated for several days. The sample was acetylated with acetyl chloride (1.1 eq) and triethylamine (1.5 eq) in methylene chloride for one hour. The suspension was washed with hydrogenchlorid (1:1, v/v) and sodium hydogen carbonate. The solvent was removed *in vacuo*. Enantiomeric excess and conversion were determined *via* HPLC.

Table S7: Results for recyclingexperiments with CAL-B

Day	conversion/ %	*ee*(amine)/ %	*ee*(amide)/ %
1	47	91	95
2	45	98	81
3	47	99	87
4	49	96	93
5	52	89	81
6	49	96	93
7	47	91	95

1.8 Reduction of CAL-B amount with 1-aminoindane

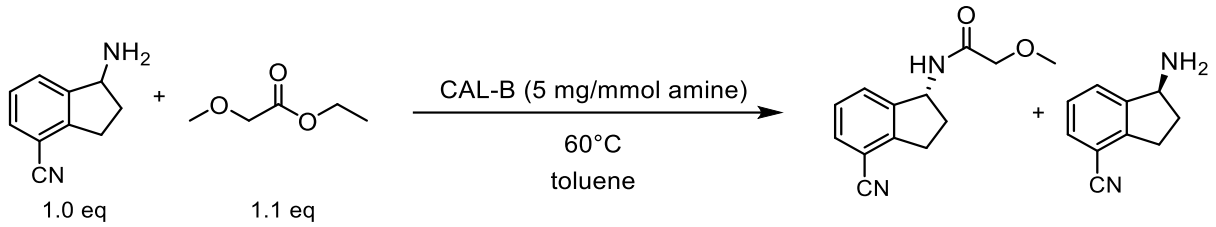


1-Aminoindan (83 mg, 0.63 mmol), isopropyl methoxyacetate (91 mg, 0.69 mmol) and CAL-B (25 mg, 13 mg, 6 mg and 3 mg) were dissolved in 1.25 mL toluene and stirred at 60°C. After 0.5 h, 1 h and 3h 100 µL samples were taken. The samples were acylated with acetyl chloride (4 mg, 0.04 mmol) and triethylamine (8 mg, 0.08 mmol). The suspension was washed with hydrogenchlorid (1:1, v/v) and sodium hydrogen carbonate. The solvent was removed *in vacuo*. Enantiomeric excess and conversion were determined via HPLC.

Table S8: Results for the reduction of the amount of CAL-B with 1- aminoindane

CAL-B mg/ mmol amine	**t/h**	**conversion/ %**	***ee*(Amine)/ %**	***ee*(Amide)/ %**
5.0	0.5	9	9	91
5.0	1	10	11	91
5.0	2	29	38	92
5.0	3	39	59	90
5.0	5	44	74	91
5.0	7	48	85	91
10.0	0.5	19	22	95
10.0	1	31	43	94
10.0	3	46	81	95
20.0	0.5	45	52	93
20.0	1	47	78	94
20.0	3	48	81	91
40.0	0.5	45	78	93
40.0	1	47	86	94
40.0	3	48	87	91

1.9 Reduction of CAL-B amount with 4-cyano-1-aminoindane



4-Cyano-1-aminoindane (37 mg, 0.23 mmol), ethyl methoxyacetate (30 mg, 0.25 mmol) and CAL-B (1.18 mg) were dissolved in 470 µL toluene and stirred at 60°C. After 0.5 h, 1 h, 3h and 5 h 50 µL samples were taken. The samples were acylated with acetyl chloride (1 eq) and triethylamine (1 eq). The suspension was washed with hydrogen chloride (1:1, v/v) and sodium hydrogen carbonate. The solvent was removed *in vacuo*. Enantiomeric excess and conversion were determined via HPLC.

Table S9: Results for the reduction of the amount of CAL-B with 1- aminoindane

t/h	**conversion/ %**	***ee*(Amine)/ %**	***ee*(Amide)/ %**
0.5	33.282	49.204	97.632
1	44.431	78.950	96.742
3	54.019	96.668	82.282
5	56.903	98.878	74.886

2 NMR data

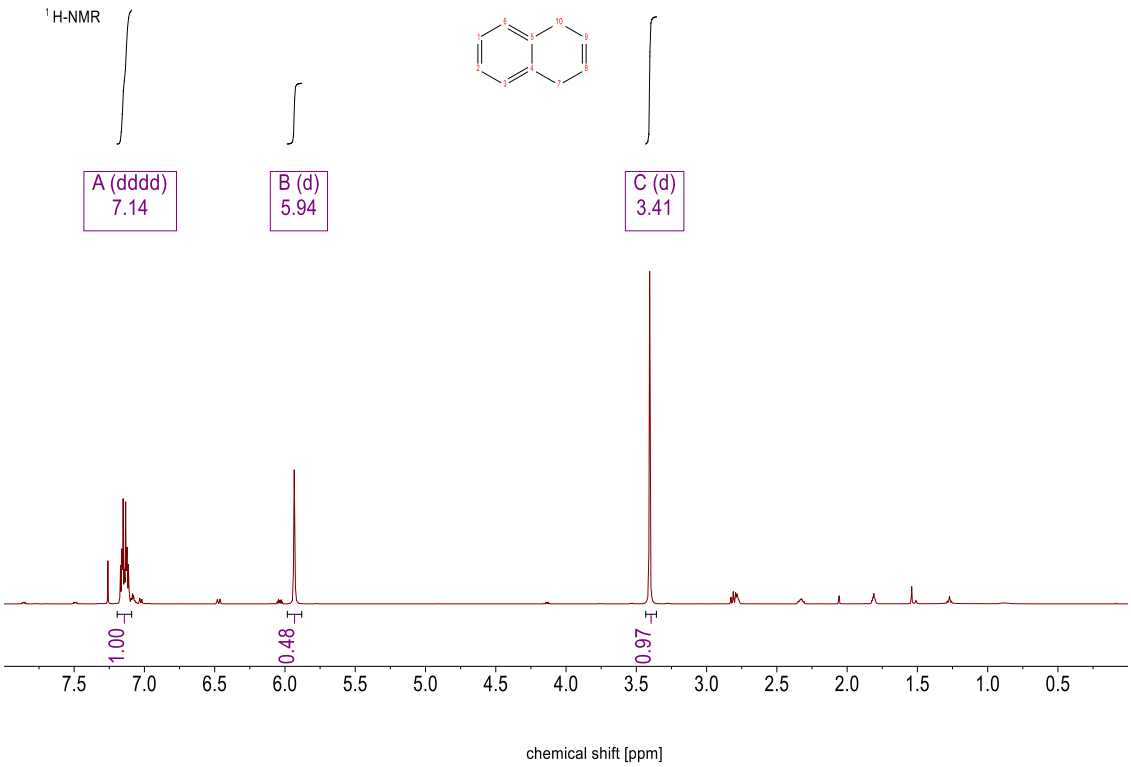


Figure S1: ^{1}H-NMR of 1,4-dihydronaphthalene (**9**)

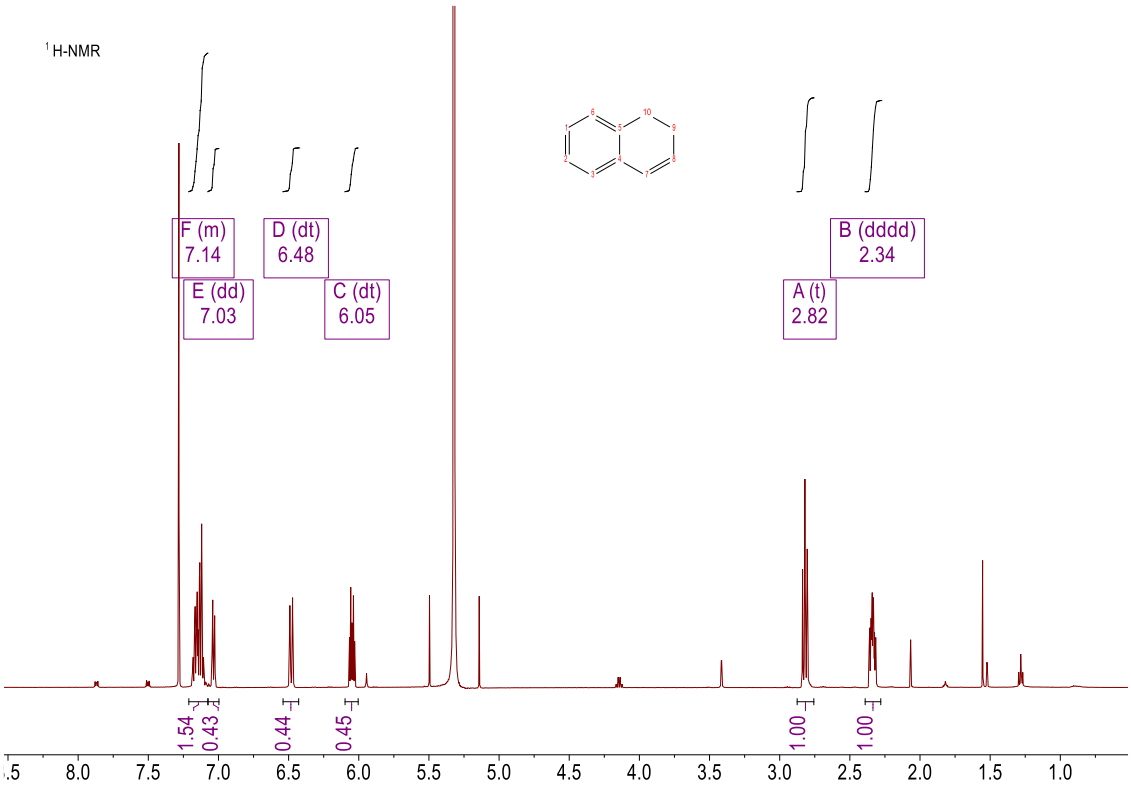


Figure S2: ^{1}H-NMR of 1,2-dihydronaphthalene (**10**)

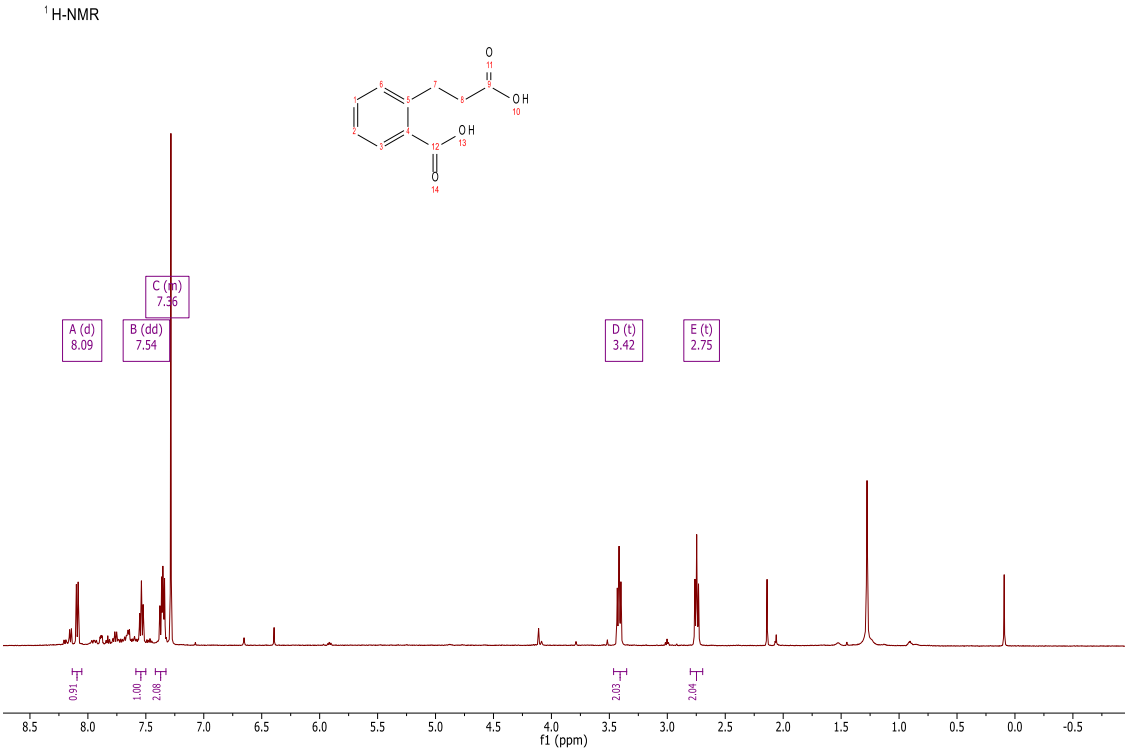


Figure S3: ^{1}H-NMR of 3-(2-carboxyphenyl)propionic acid (**7**)

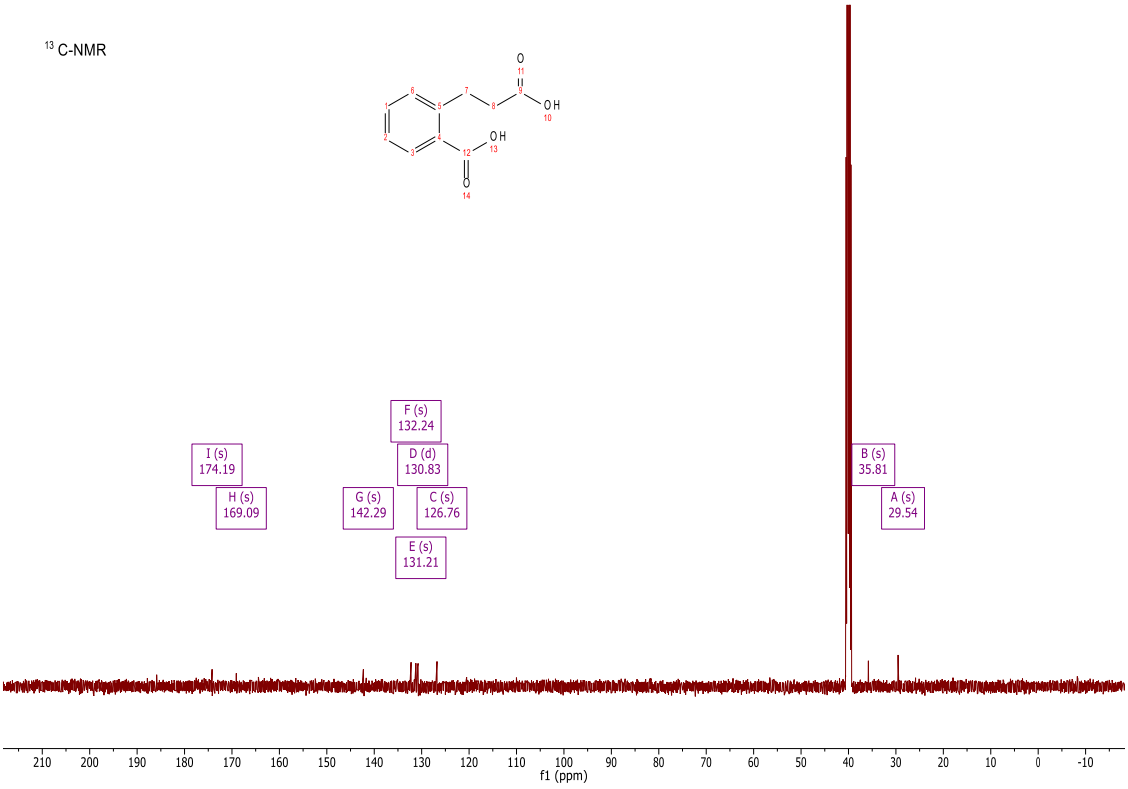


Figure S4: ^{13}C-NMR of 3-(2-carboxyphenyl)propionic acid (**7**)

Figure S5: ^{1}H-NMR of 4-carboxy-1-indanone (**6**)

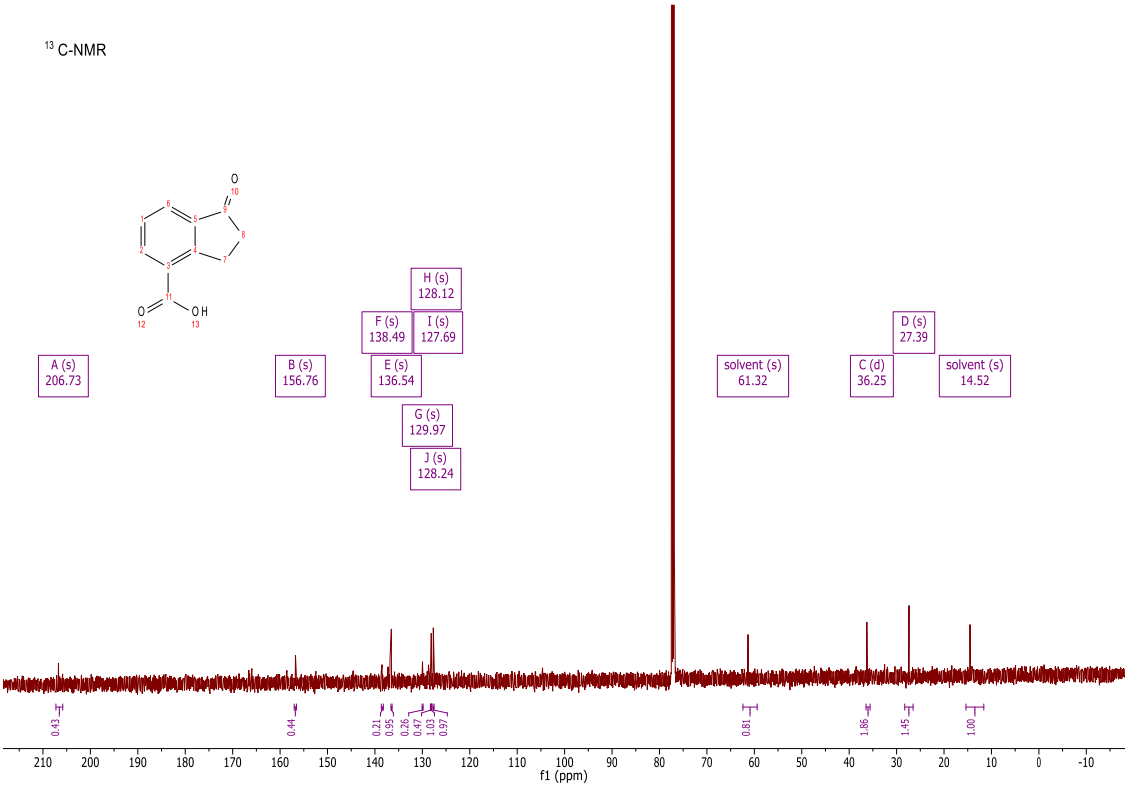


Figure S6: ^{13}C-NMR of 4-carboxy-1-indanone (**6**)

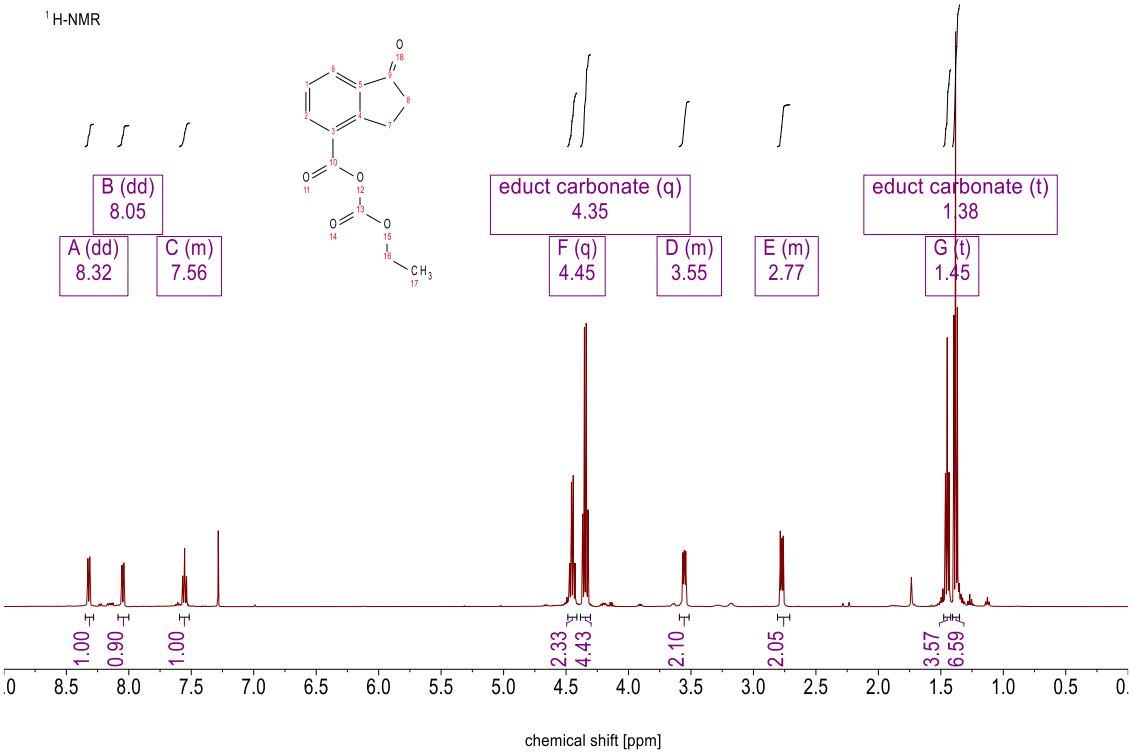


Figure S7: ^{1}H-NMR of 1-oxo-2,3-dihydro-1H-indene-4-carboxylic anhydride

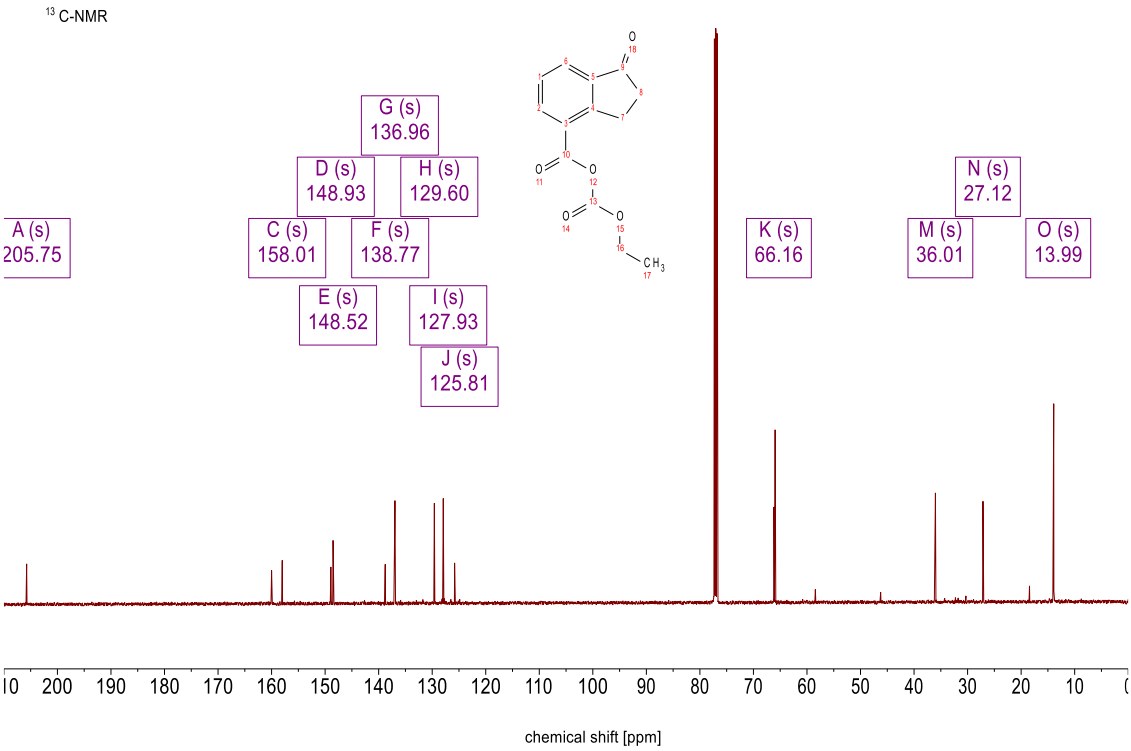


Figure S8: ^{13}C-NMR of 1-oxo-2,3-dihydro-1H-indene-4-carboxylic anhydride

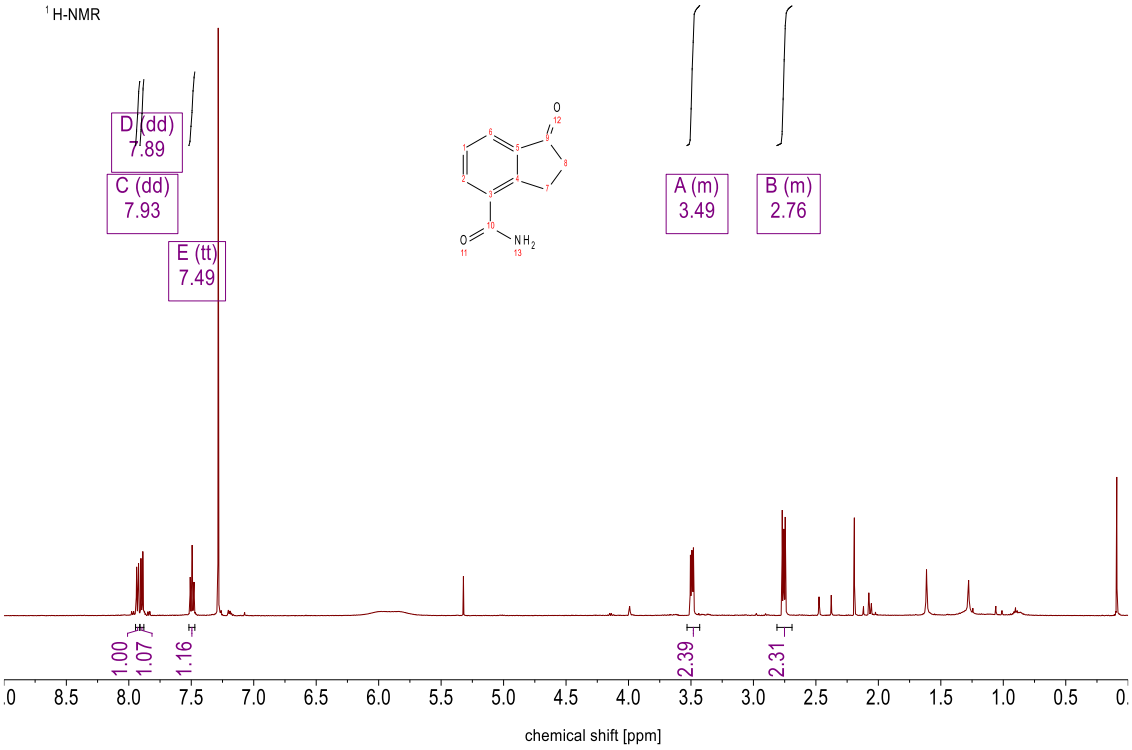


Figure S9: ^{1}H-NMR of 1-oxo-2,3-dihydro-1H-indene-4-carboxamide (**11**)

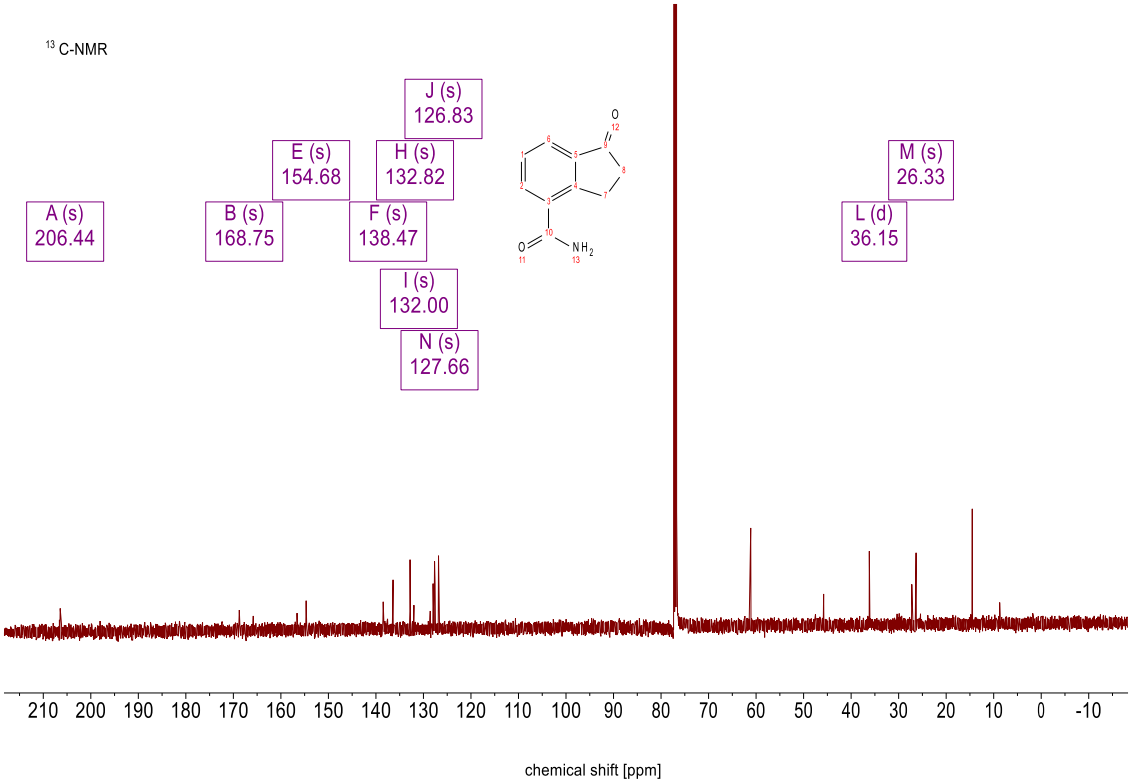


Figure S10: ^{13}C-NMR of 1-oxo-2,3-dihydro-1H-indene-4-carboxamide (**11**)

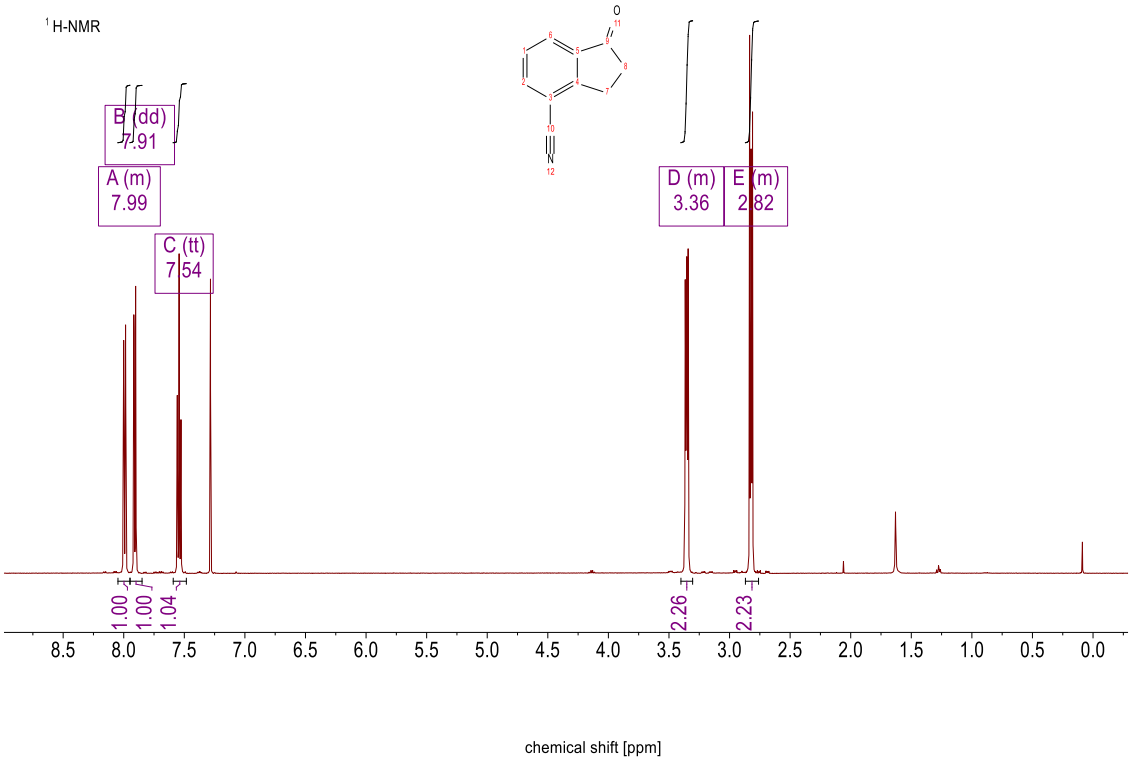


Figure S11: ^{1}H-NMR of 4-cyano-1-indanone (**4**)

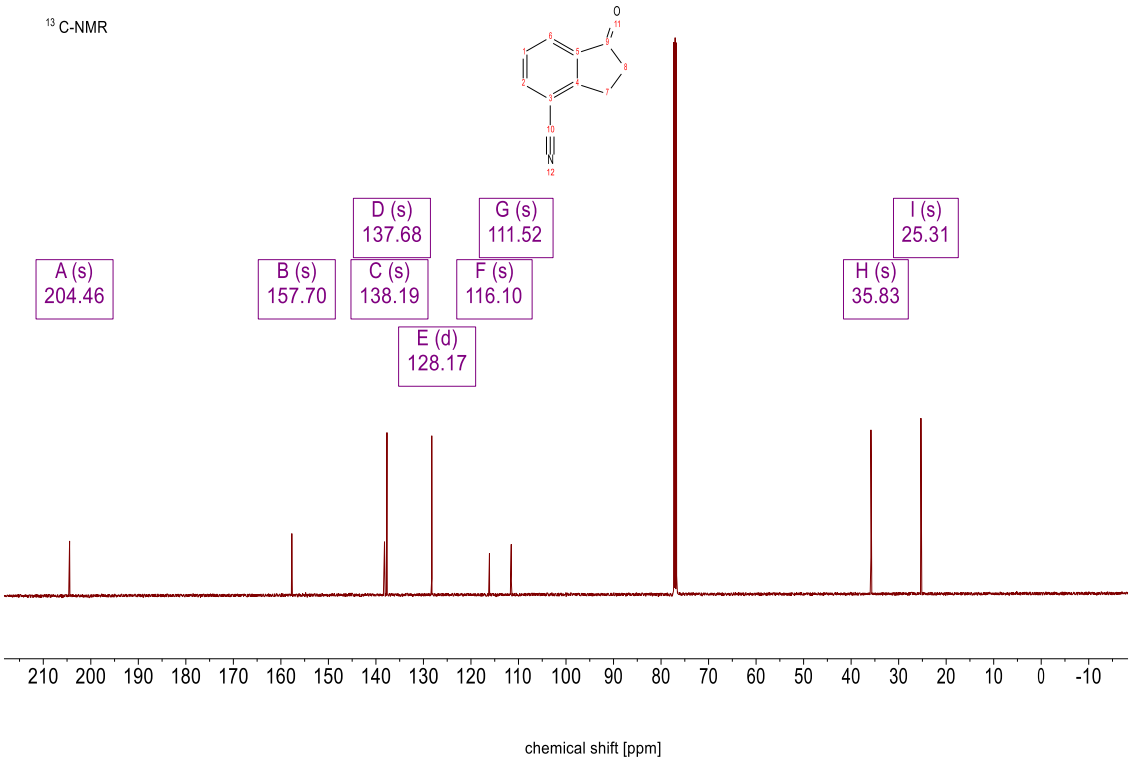


Figure S12: ^{13}C-NMR of 4-cyano-1-indanone (**4**)

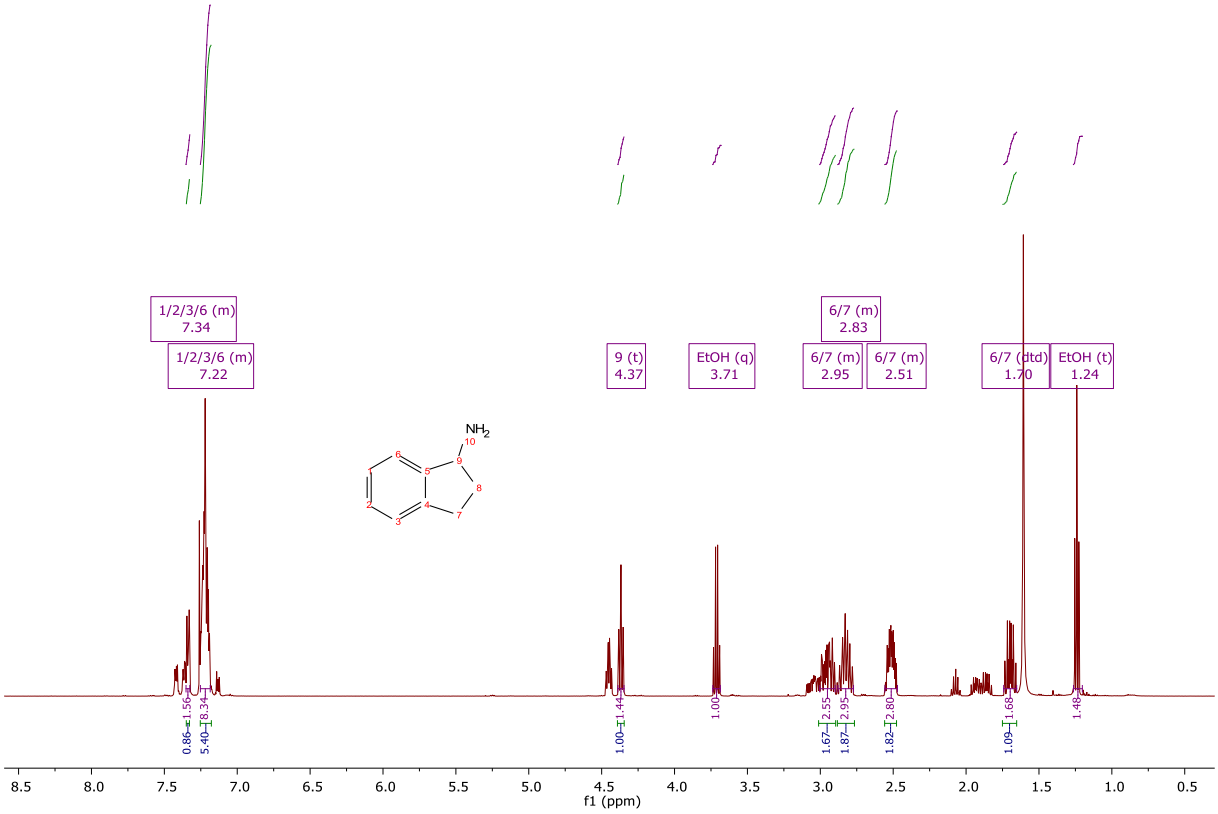


Figure S13: ^{1}H-NMR of 1-aminoindane *(rac-**24**)*

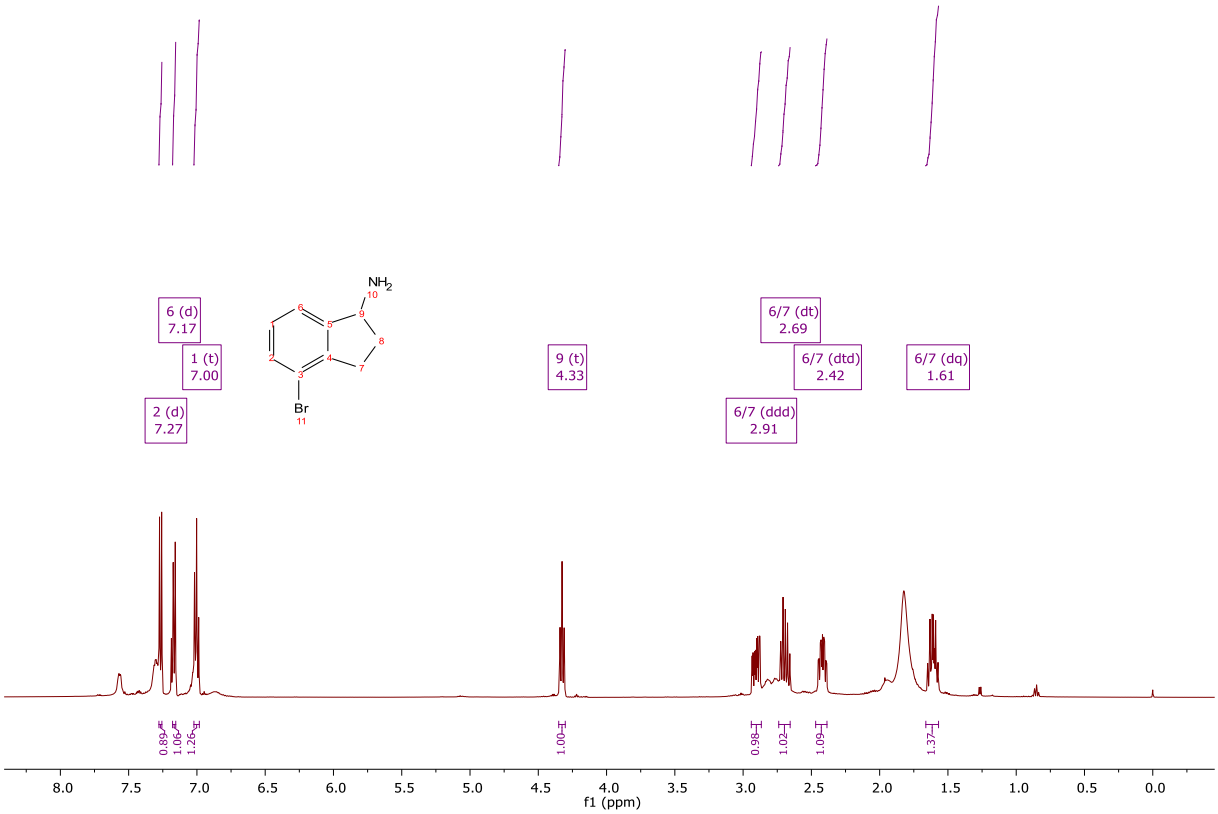


Figure S14: ^{1}H-NMR of 4-bromo-1-aminoindane *(rac-**25**)*

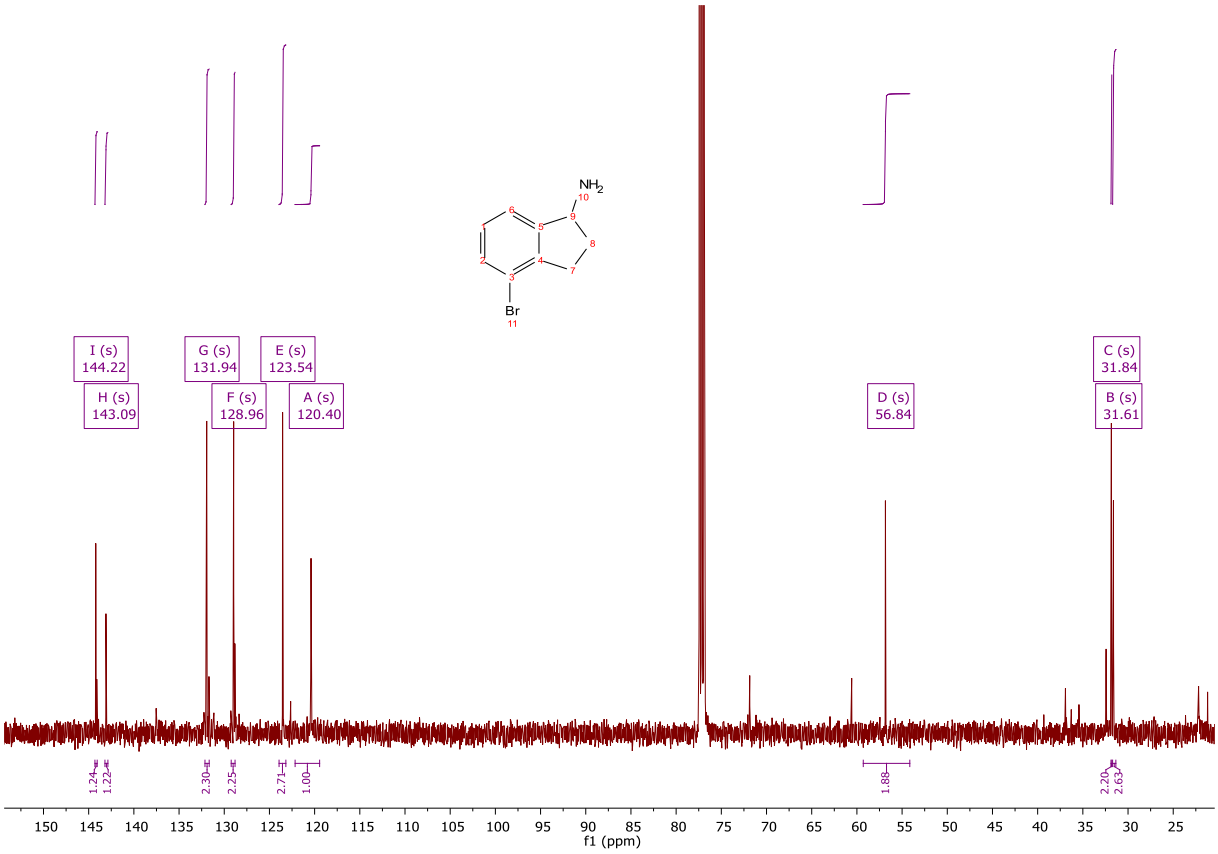


Figure S15: ^{13}C-NMR of 4-bromo-1-aminoindan *(rac-**25**)*

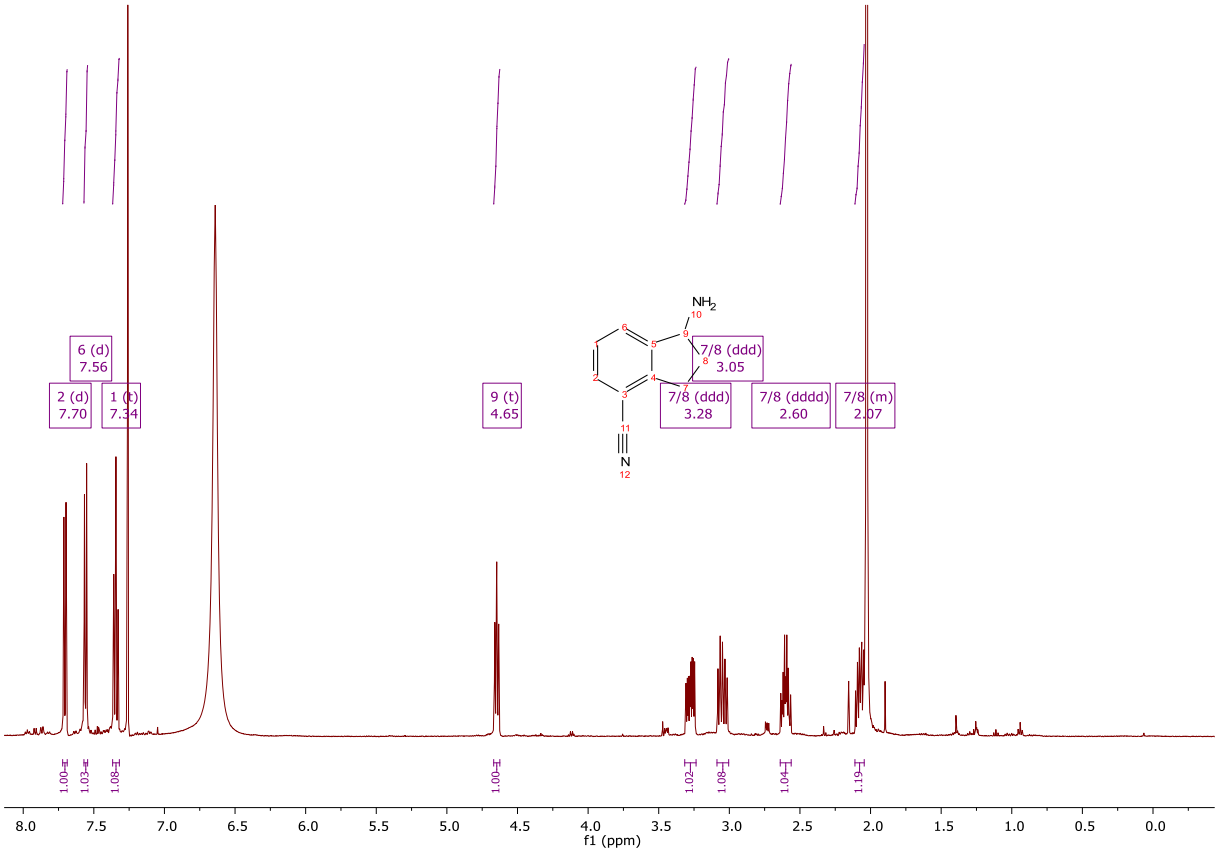


Figure S16: ^{1}H-NMR of 4-cyano-1-aminoindan *(rac-**8**)*

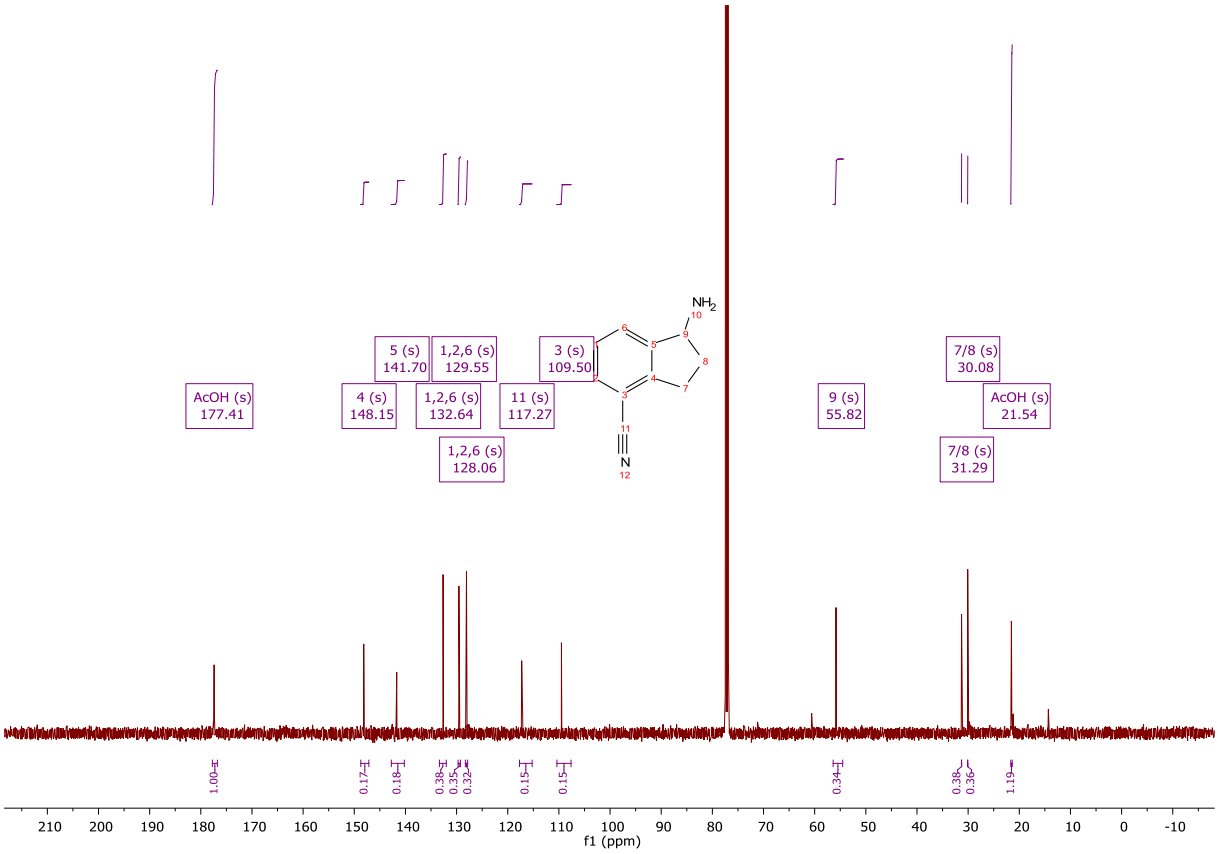


Figure S17: ^{13}C-NMR of 4-cyano-1-aminoindane *(rac-**8**)*

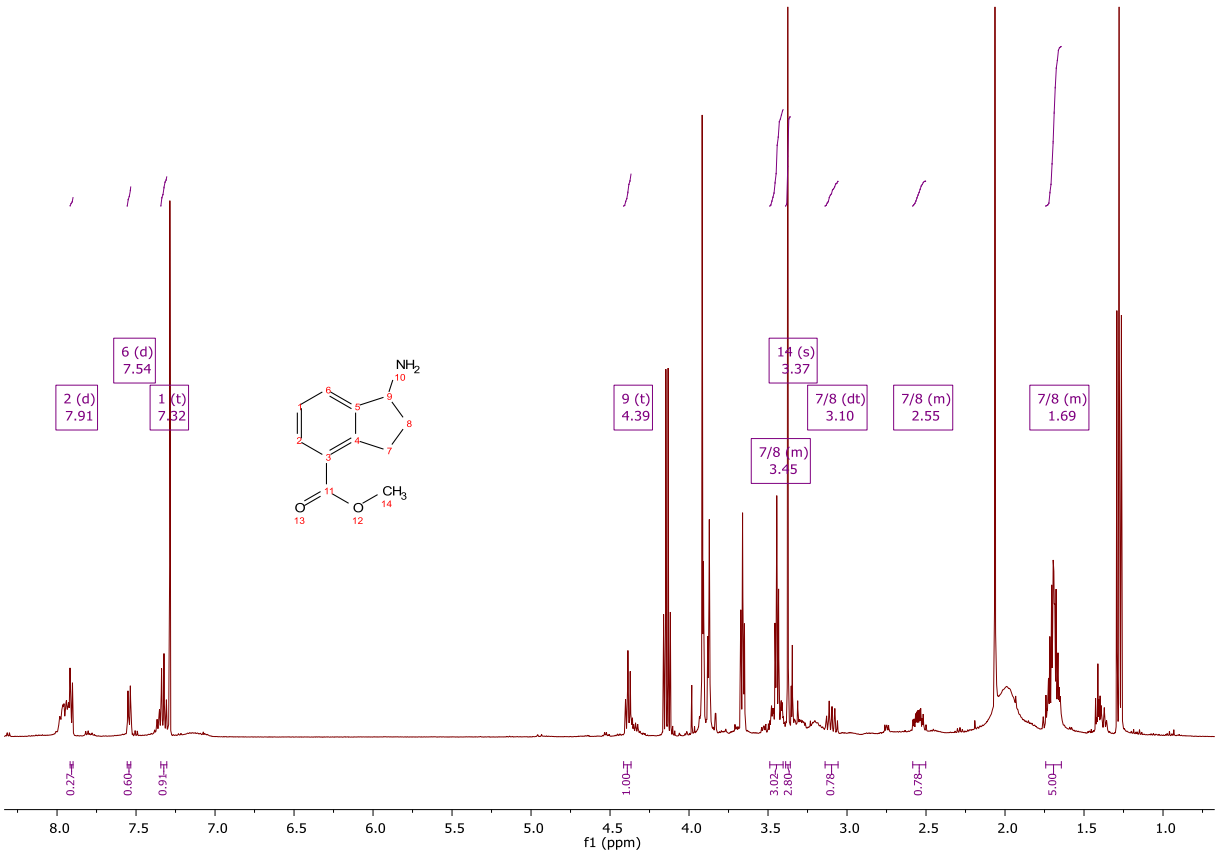


Figure S18: ^{1}H-NMR of methyl 1-amino-2,3-dihydro-1H-indene-4-carboxylate *(rac-**26**)*

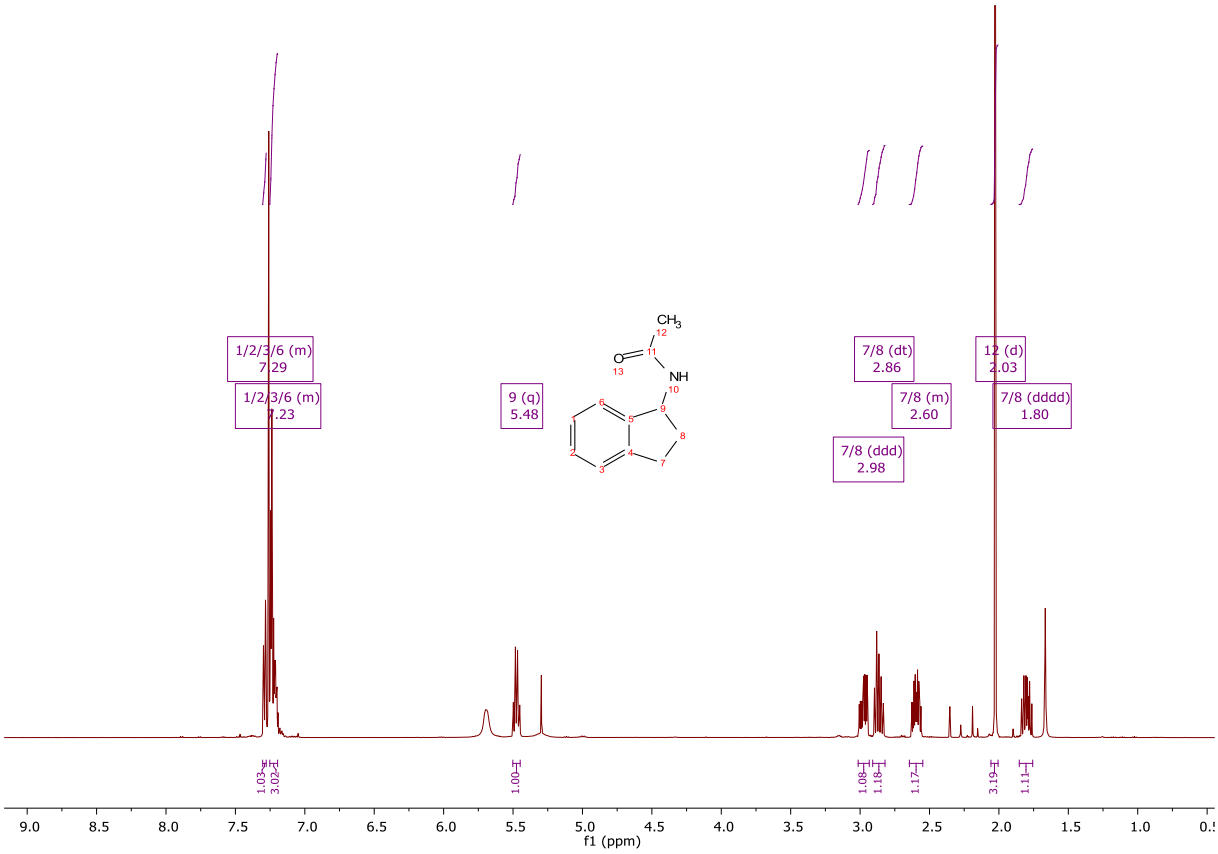


Figure S19: ^{1}H-NMR of N-(2,3-dihydro-1H-inden-1-yl)acetamide (**36**)

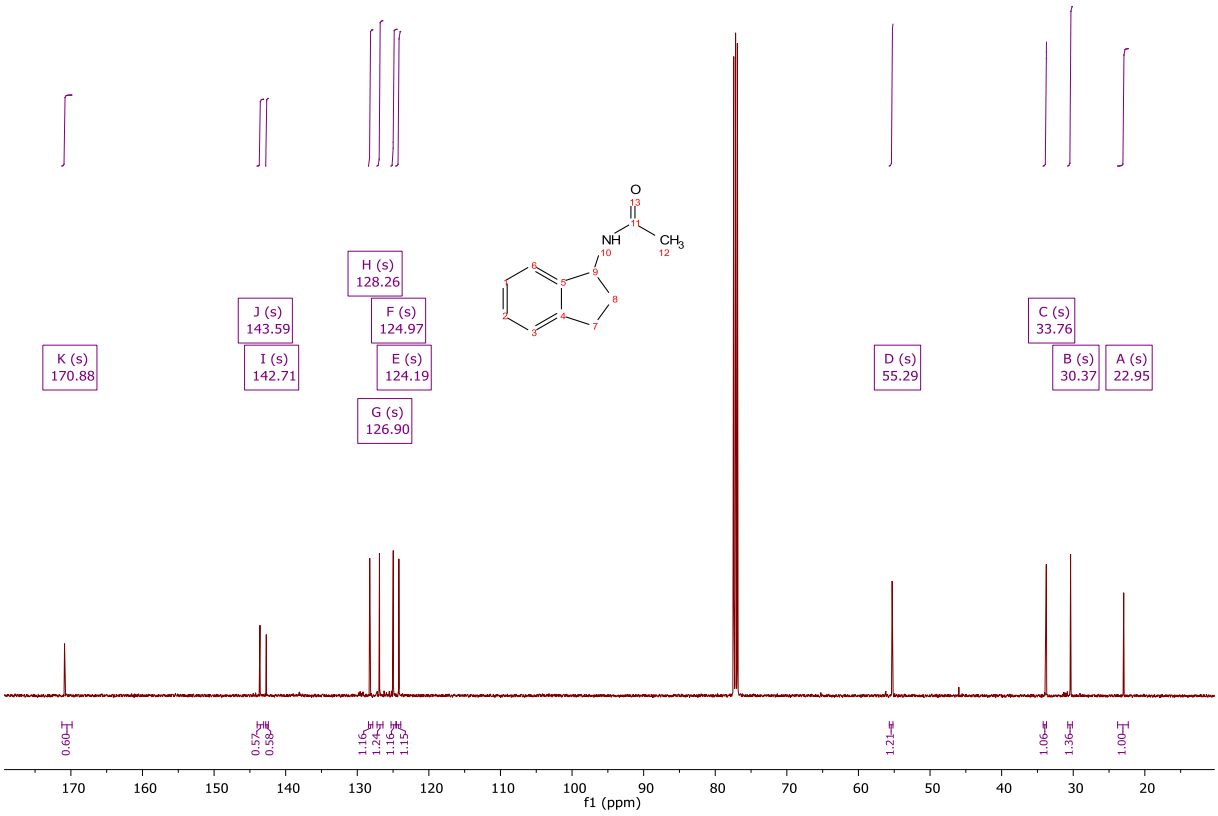


Figure S20: ^{13}C-NMR of N-(2,3-dihydro-1H-inden-1-yl)acetamide (**36**)

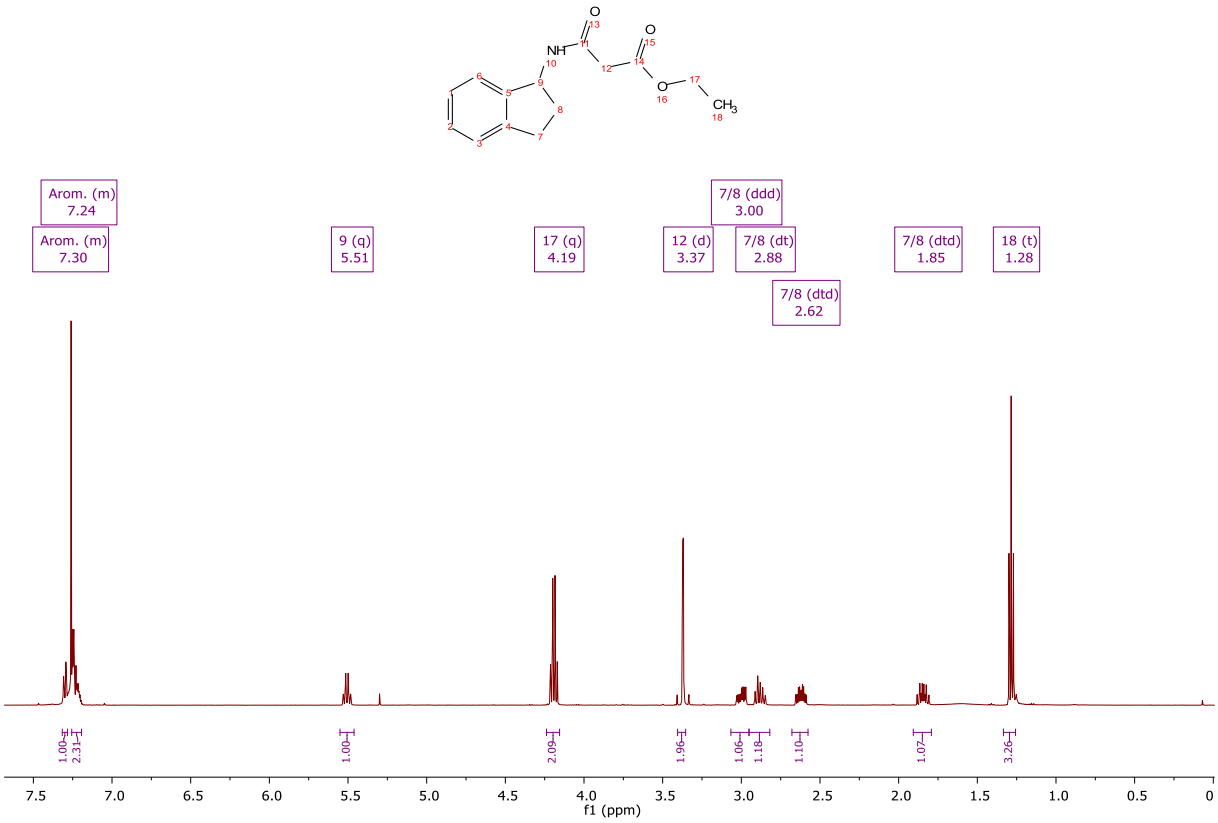


Figure S21: ^{1}H-NMR of ethyl-3-((2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**31**)

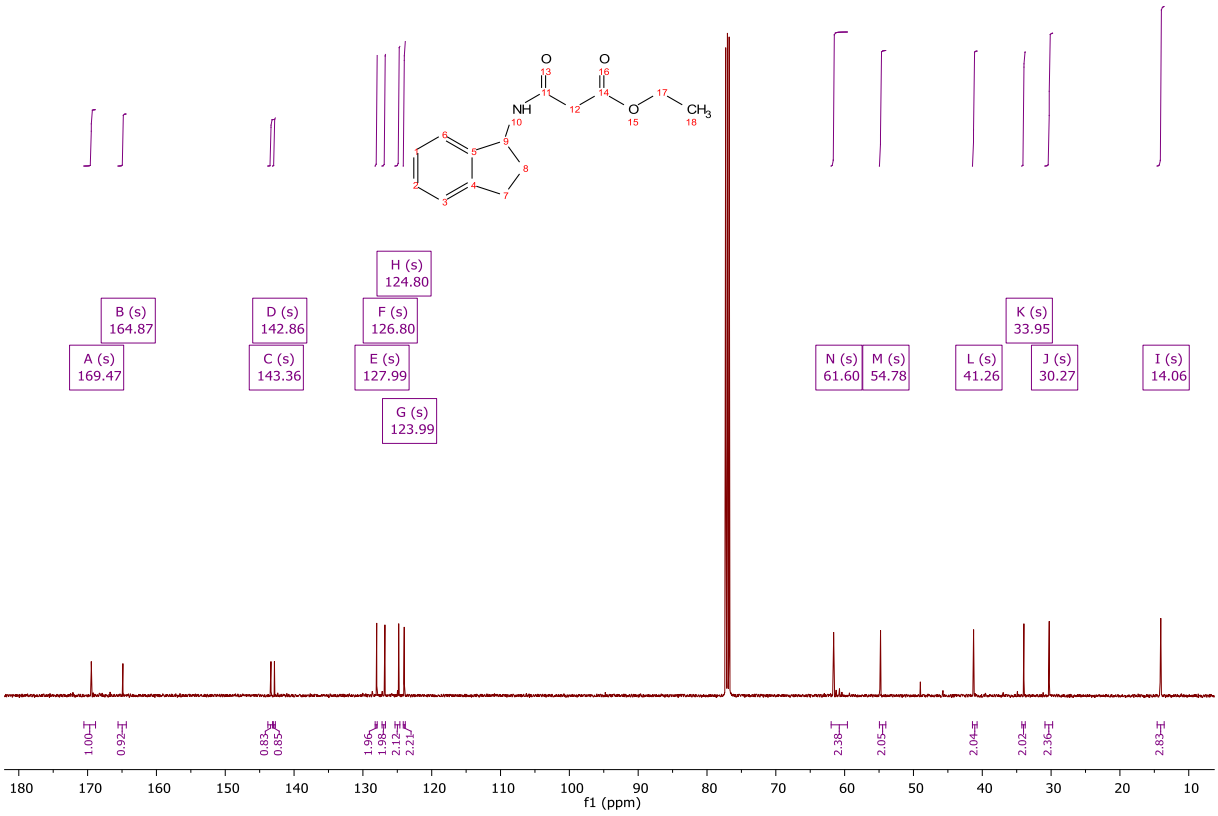


Figure S22: ^{13}C-NMR of ethyl-3-((2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**31**)

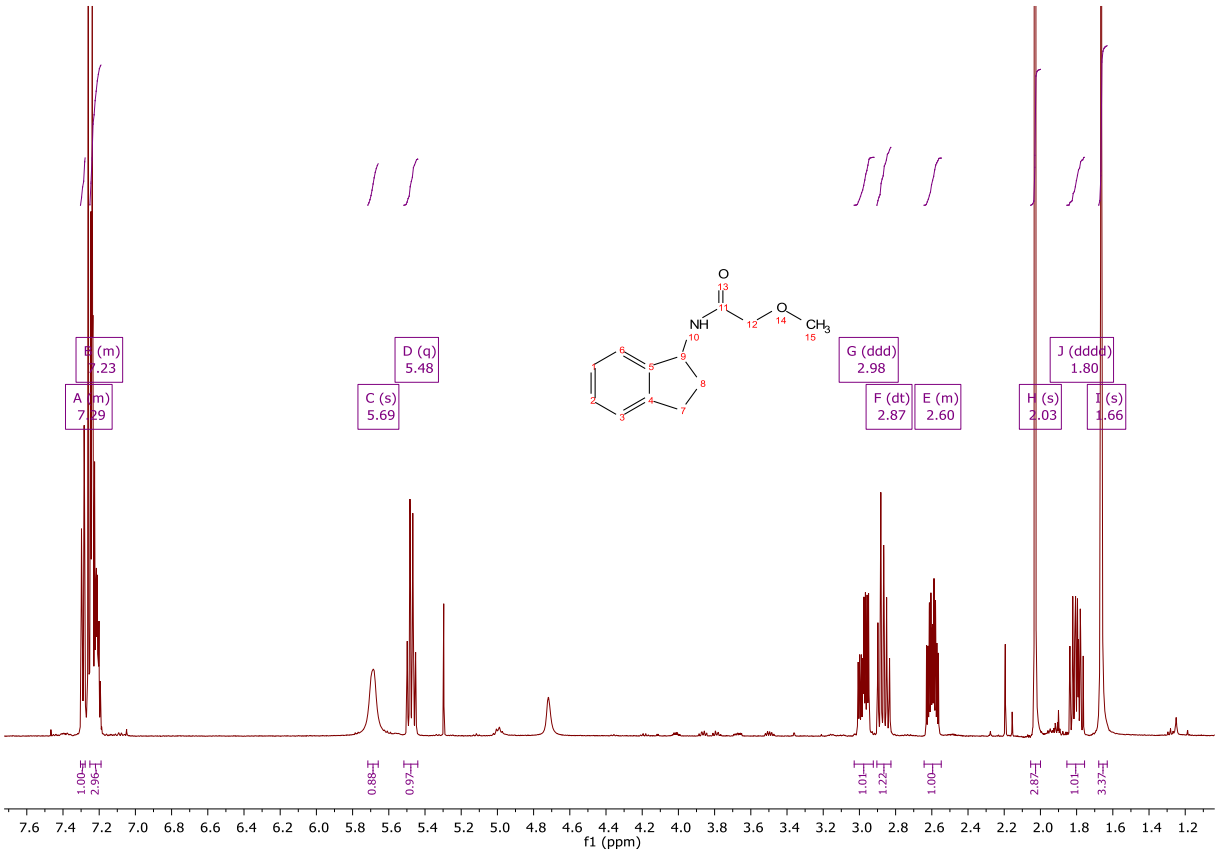


Figure S23: ^{1}H-NMR of *N*-(2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**30**)

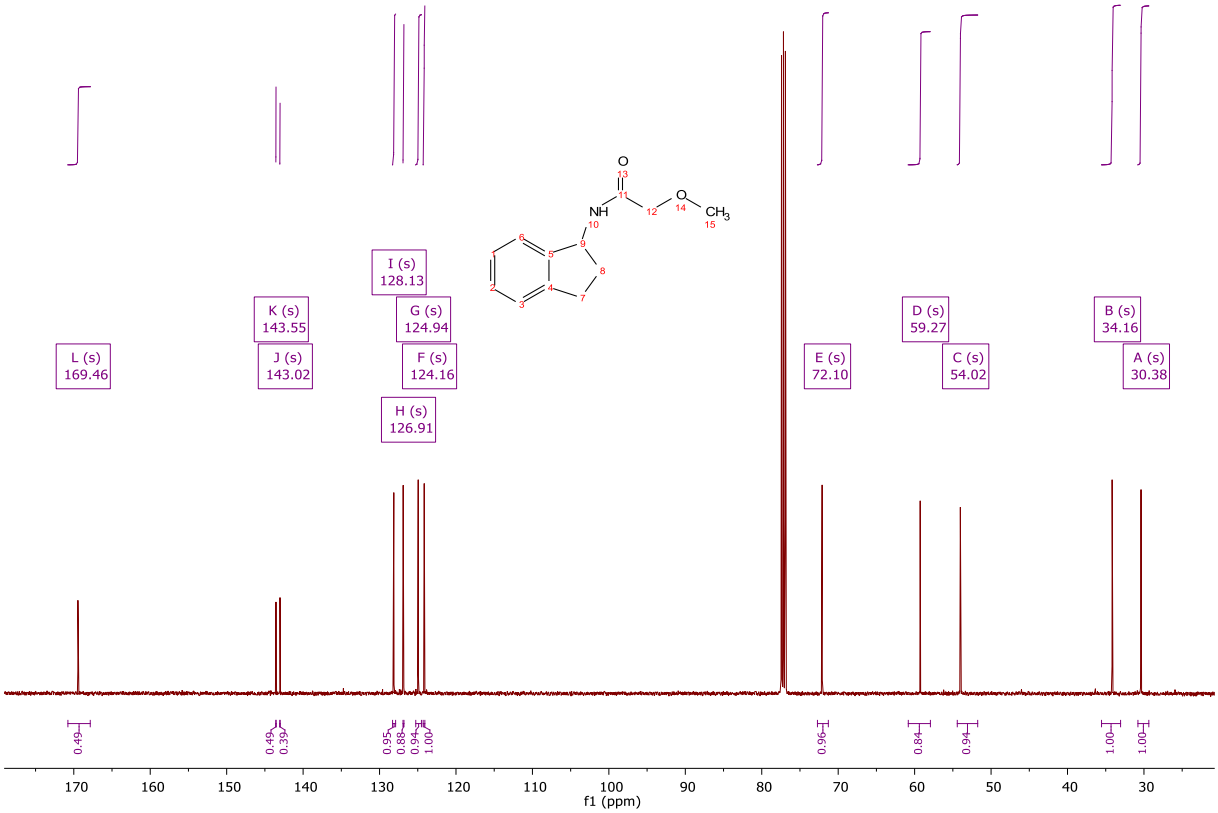


Figure S24:^{13}C-NMR of *N*-(2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**30**)

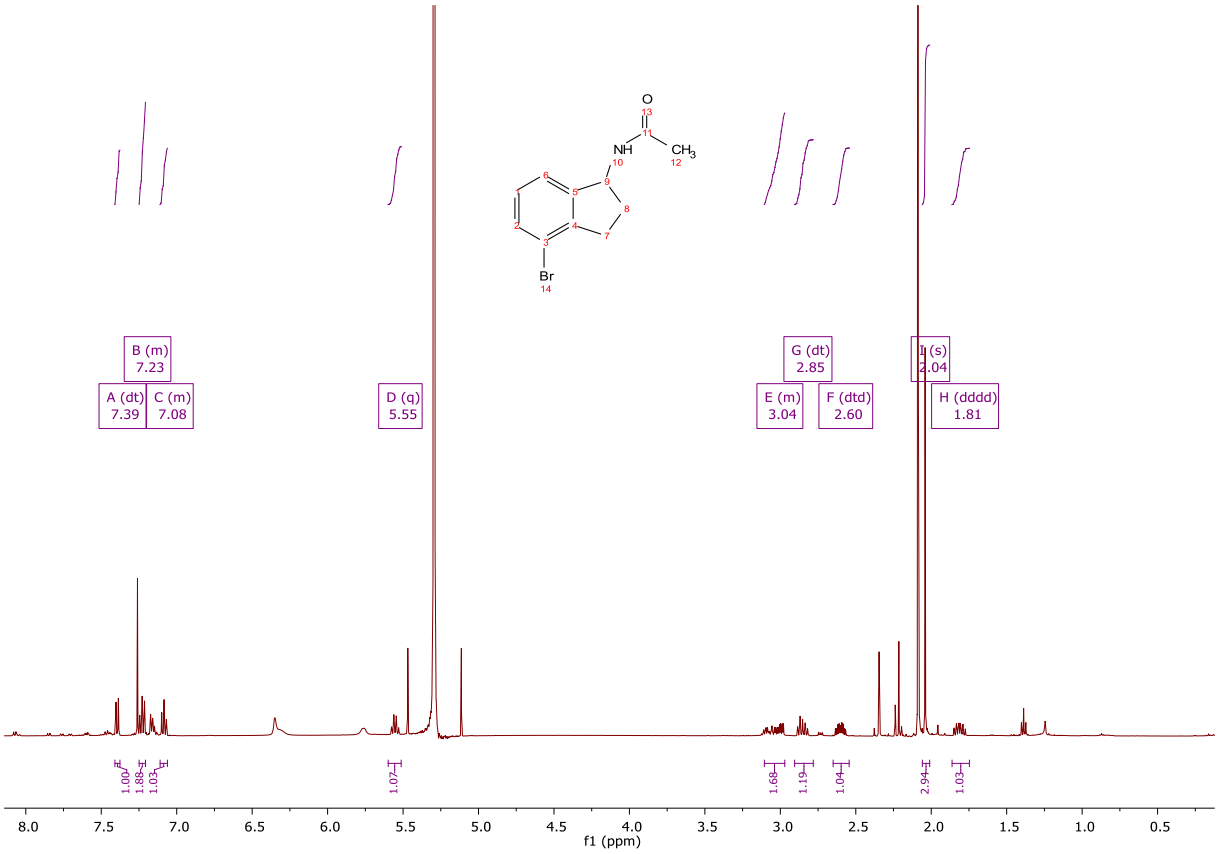


Figure S25: ^{1}H-NMR of *N*-(4-bromo-2,3-dihydro-1H-inden-1-yl)acetamide (**37**)

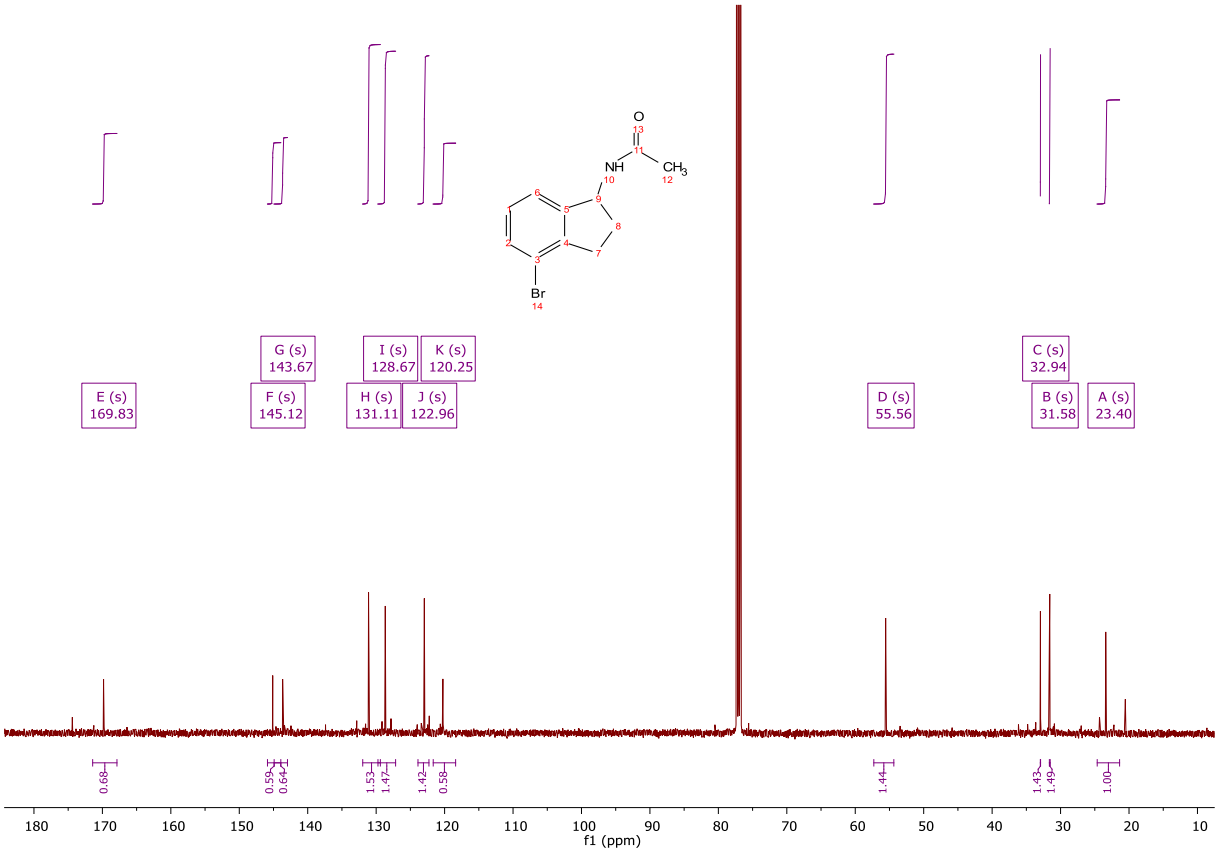


Figure S26: ^{13}C-NMR of *N*-(4-bromo-2,3-dihydro-1H-inden-1-yl)acetamide (**37**)

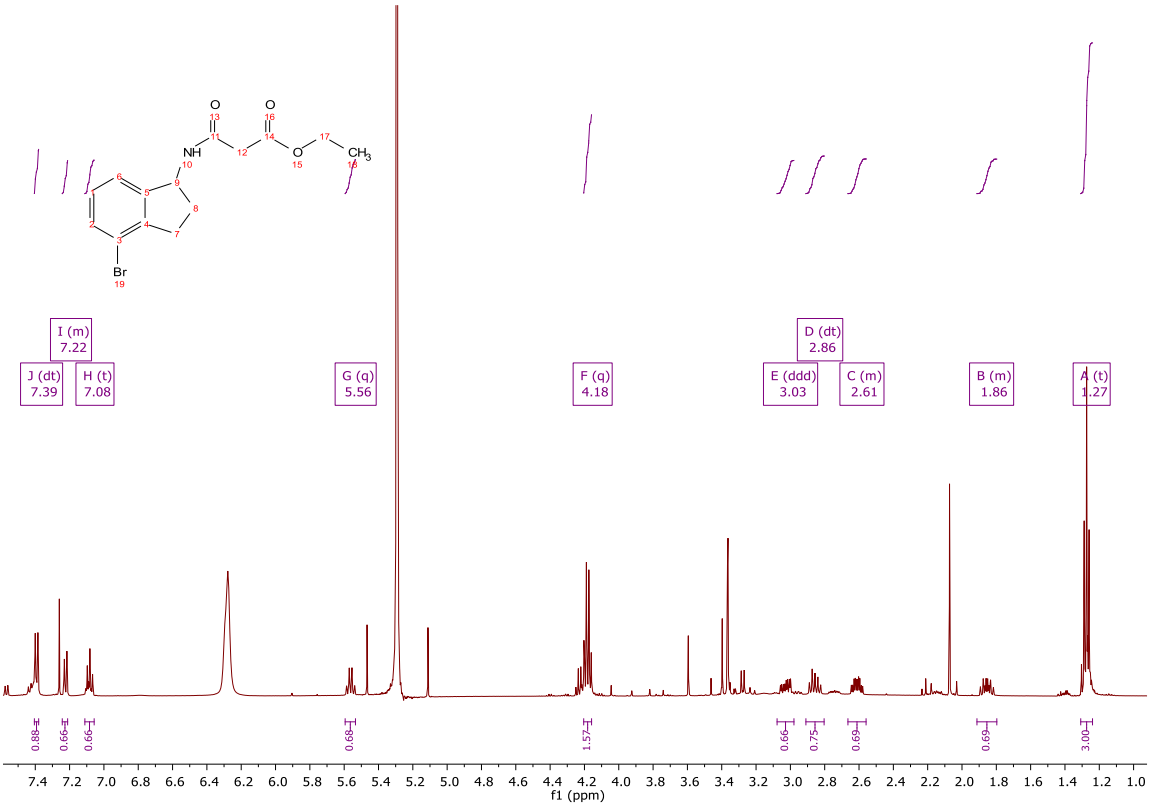


Figure S27: ^{1}H-NMR of ethyl 3-((4-bromo-2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**33**)

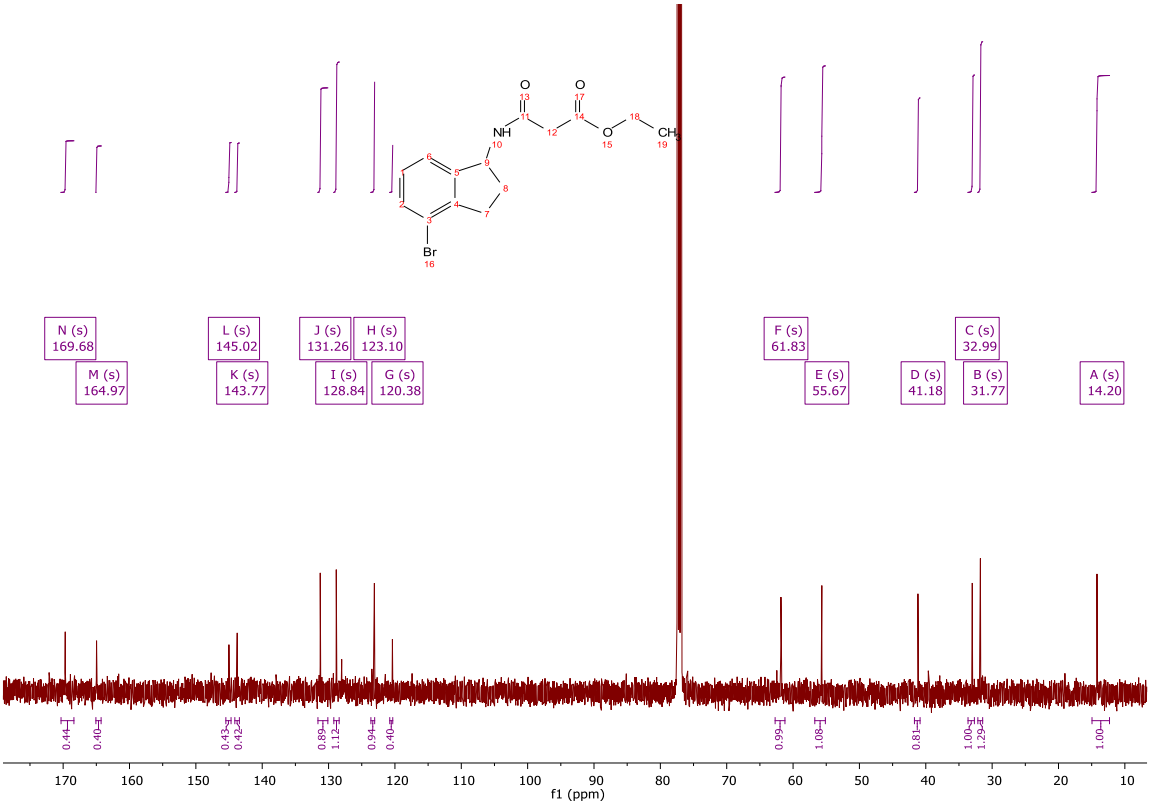


Figure S28: ^{13}C-NMR of ethyl 3-((4-bromo-2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**33**)

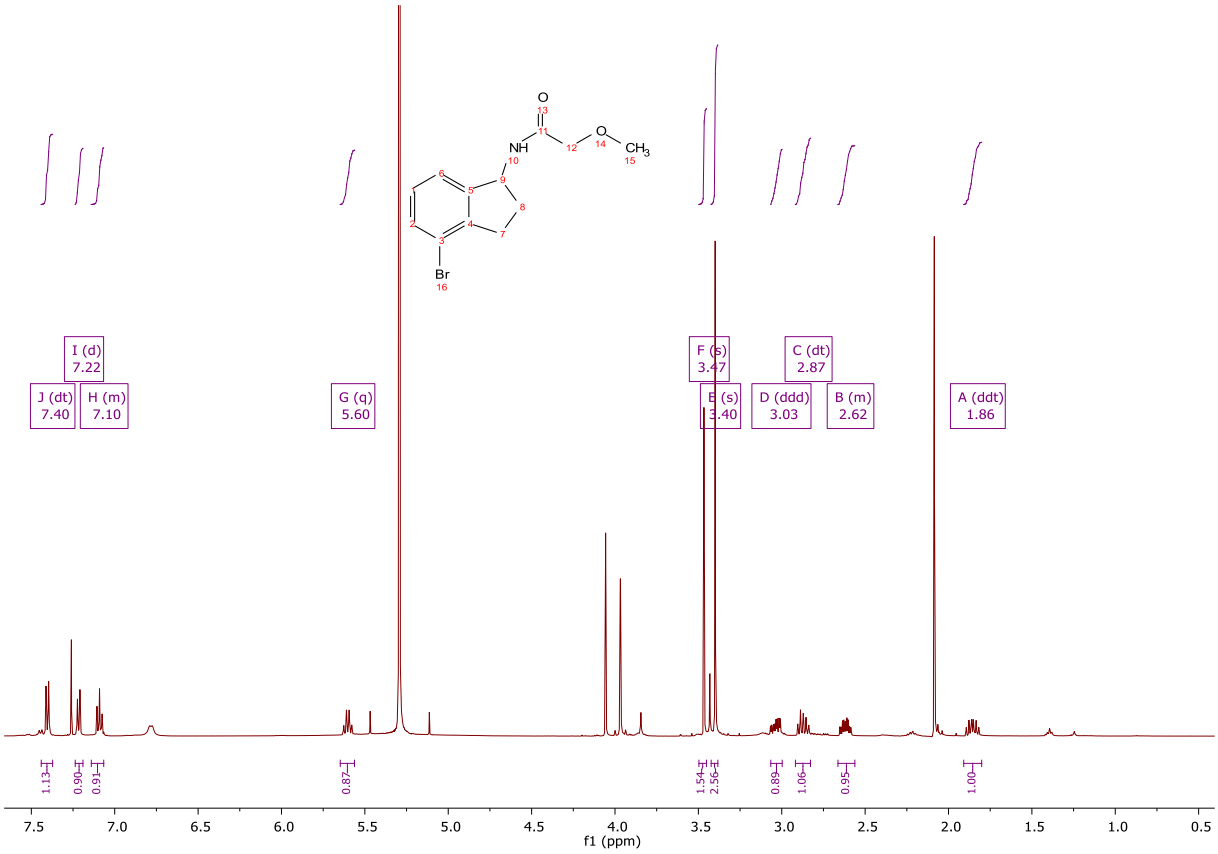


Figure S29: ^{1}H-NMR of *N*-(4-bromo-2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**32**)

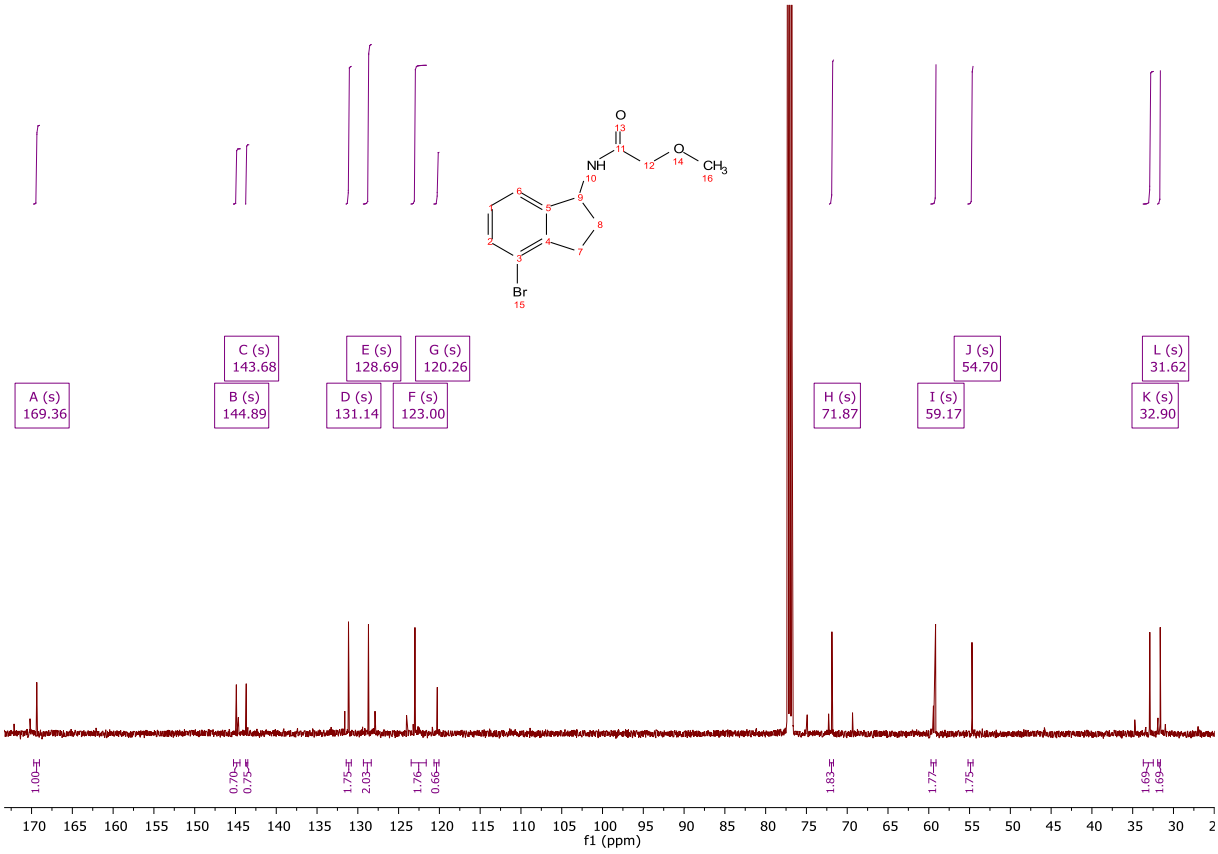


Figure S30: ^{13}C-NMR of *N*-(4-bromo-2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**32**)

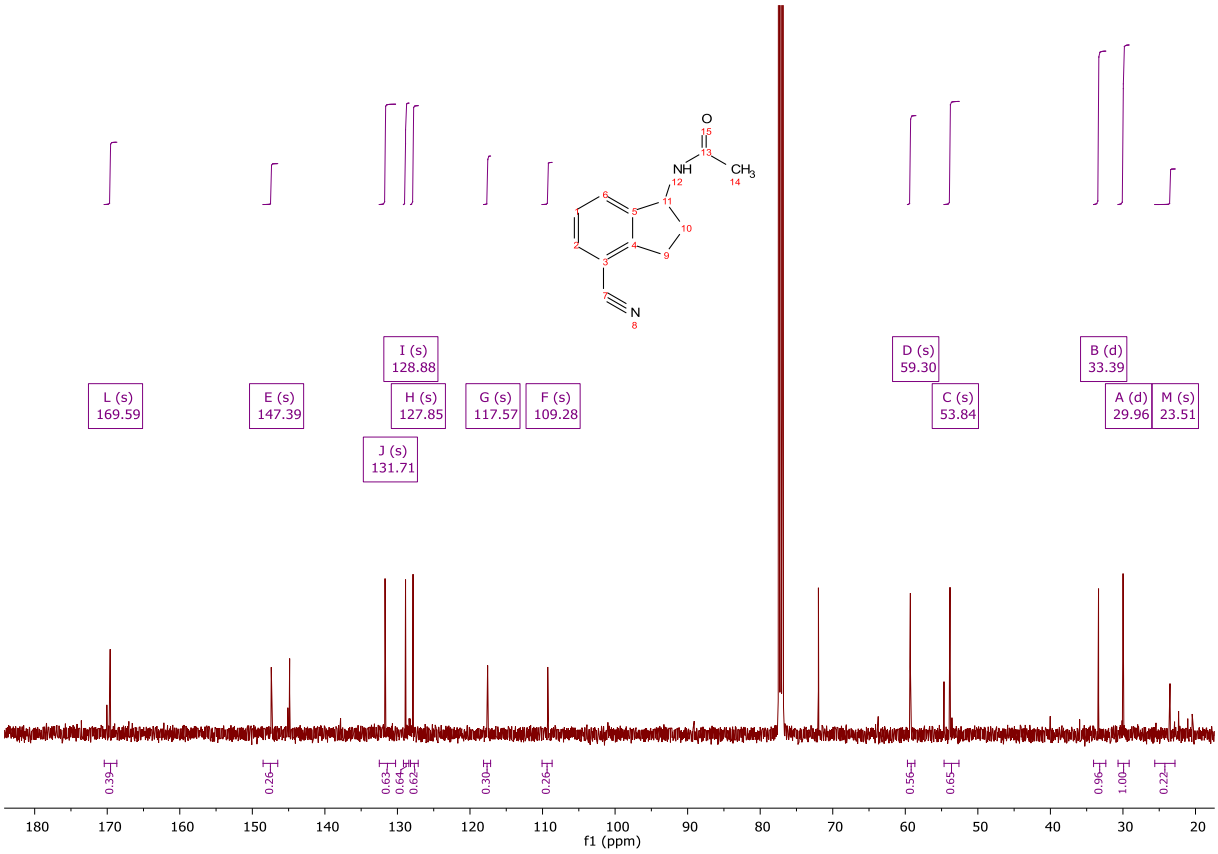


Figure S31: ^{13}C-NMR of *N*-(4-cyano-2,3-dihydro-1H-inden-1-yl)acetamide (**37**)

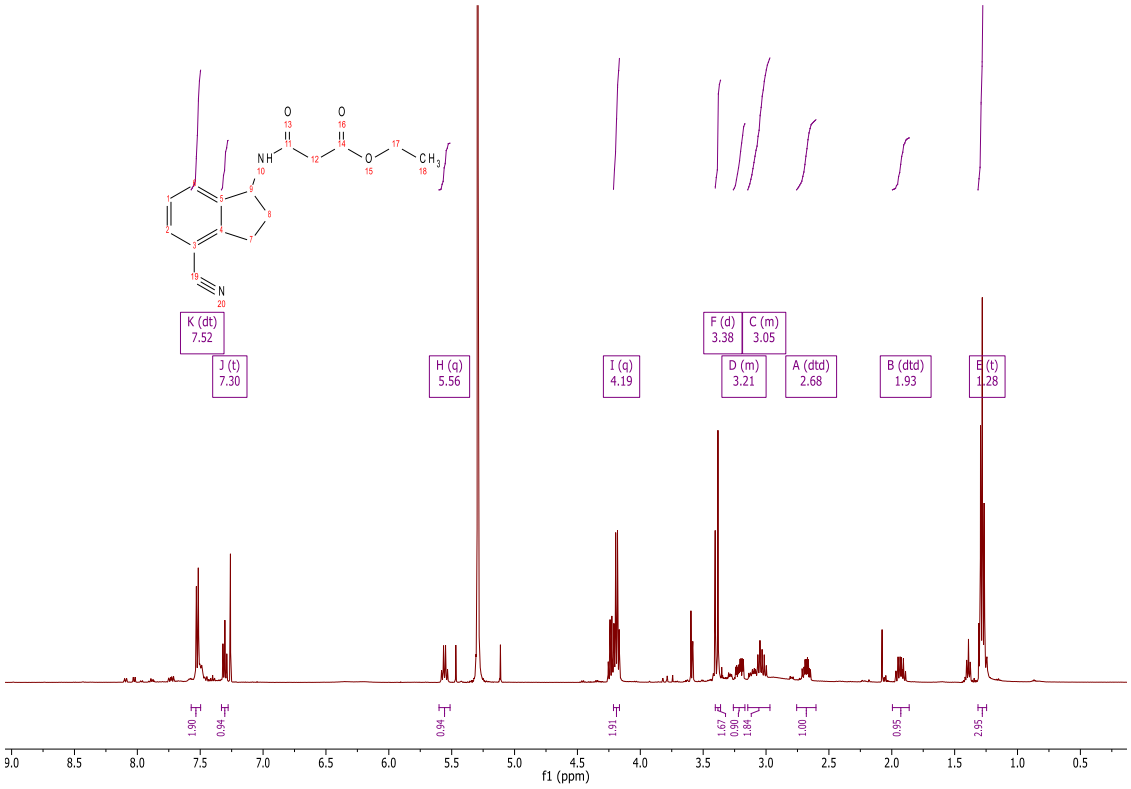


Figure S32: ^{1}H-NMR of ethyl 3-((4-cyano-2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**34**)

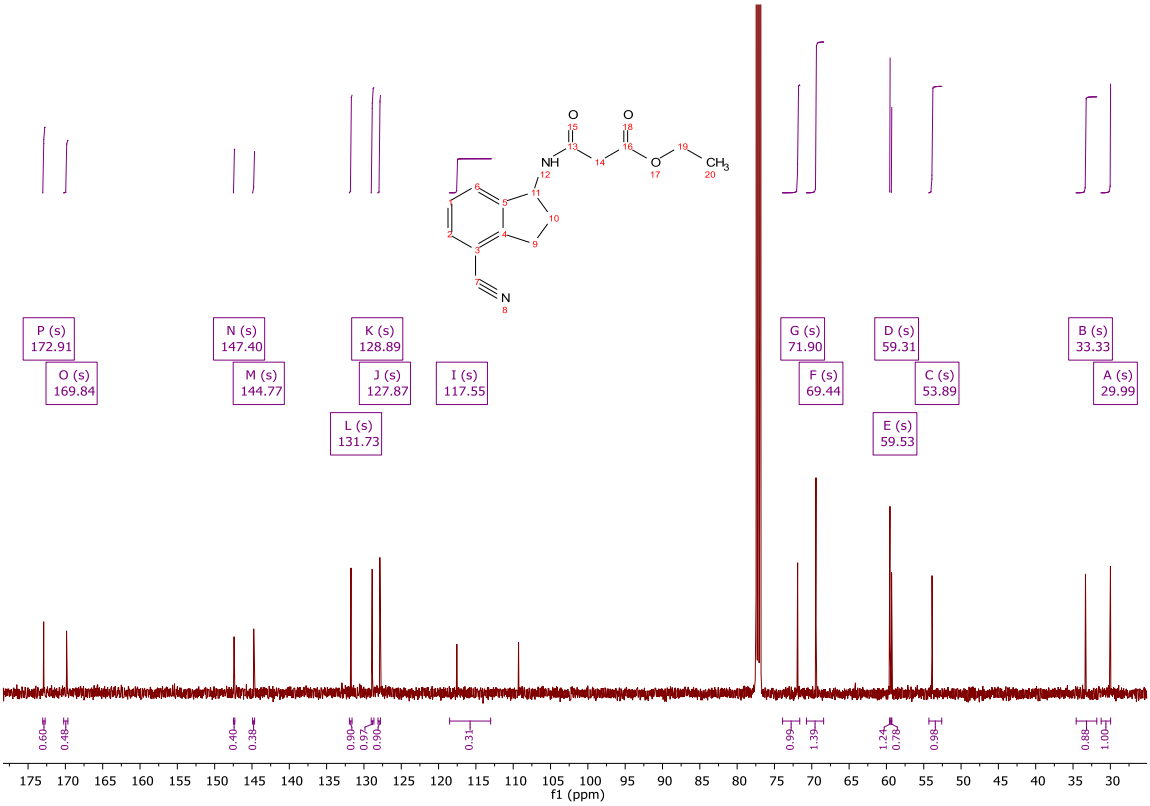


Figure S33: ^{13}C-NMR of ethyl 3-((4-cyano-2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**34**)

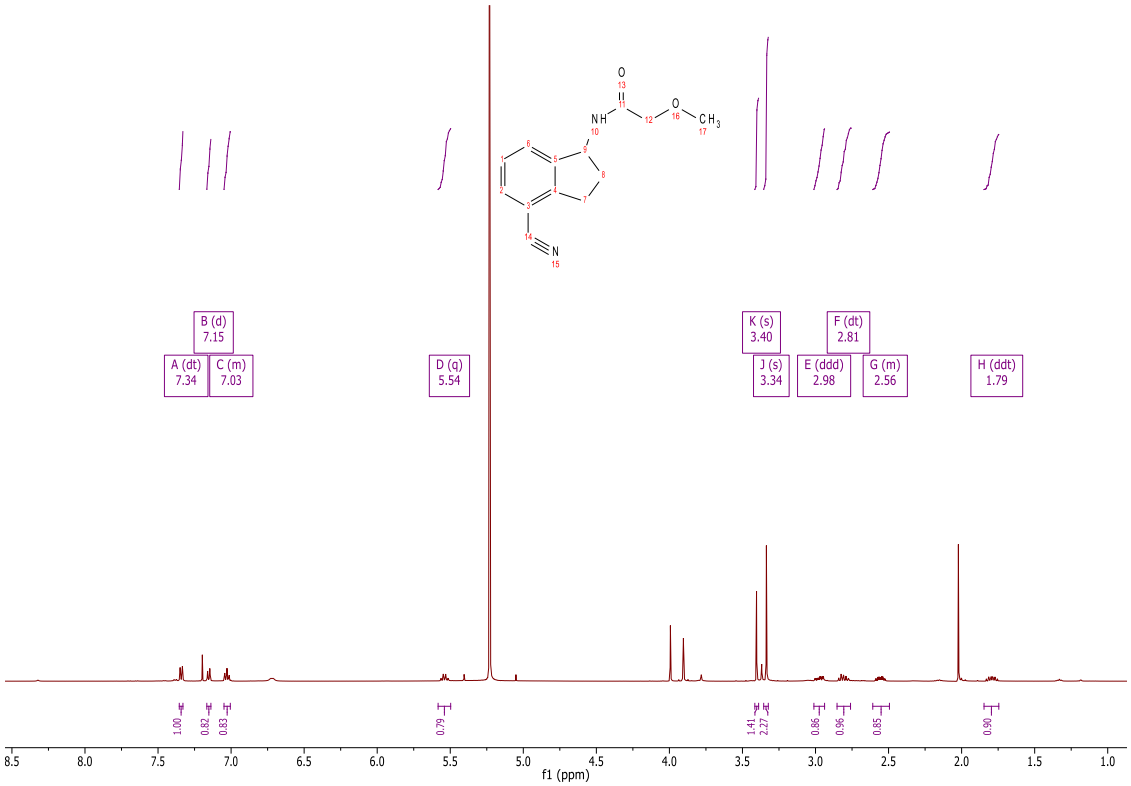


Figure S34: ^{1}H-NMR of N-(4-cyano-2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**9**)

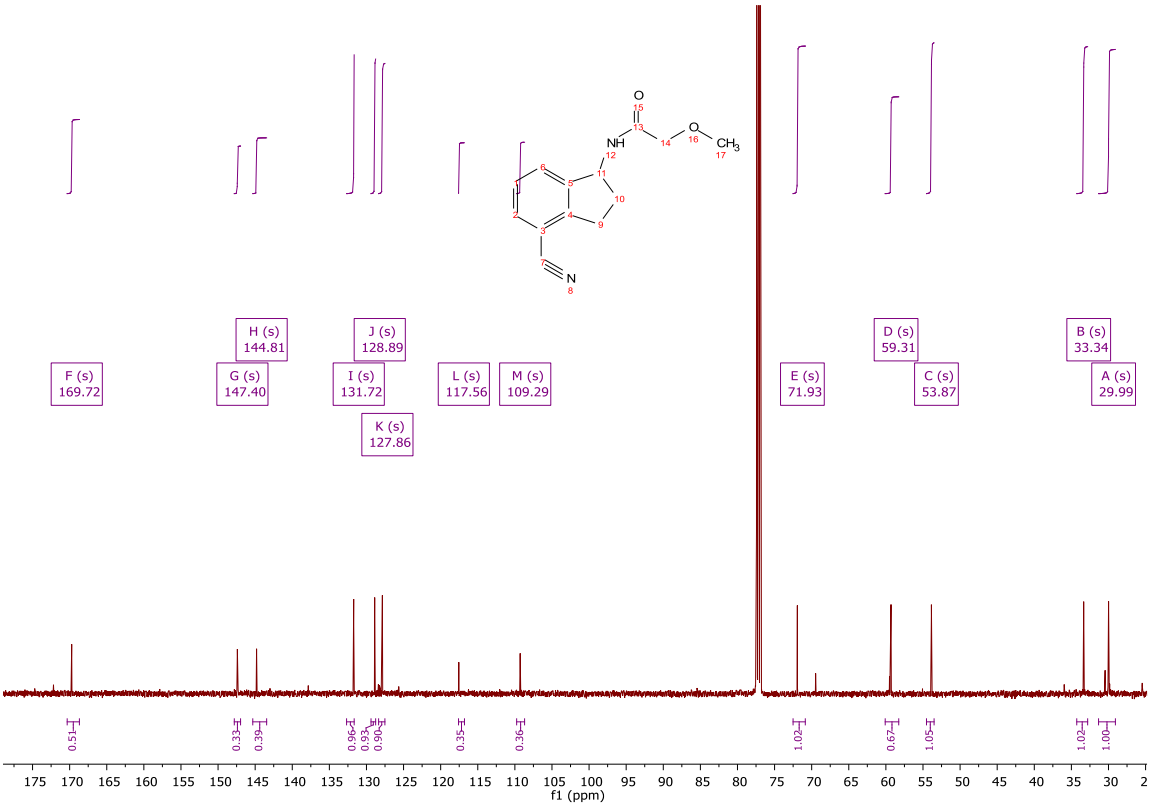


Figure S35: ^{13}C-NMR of N-(4-cyano-2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**9**)

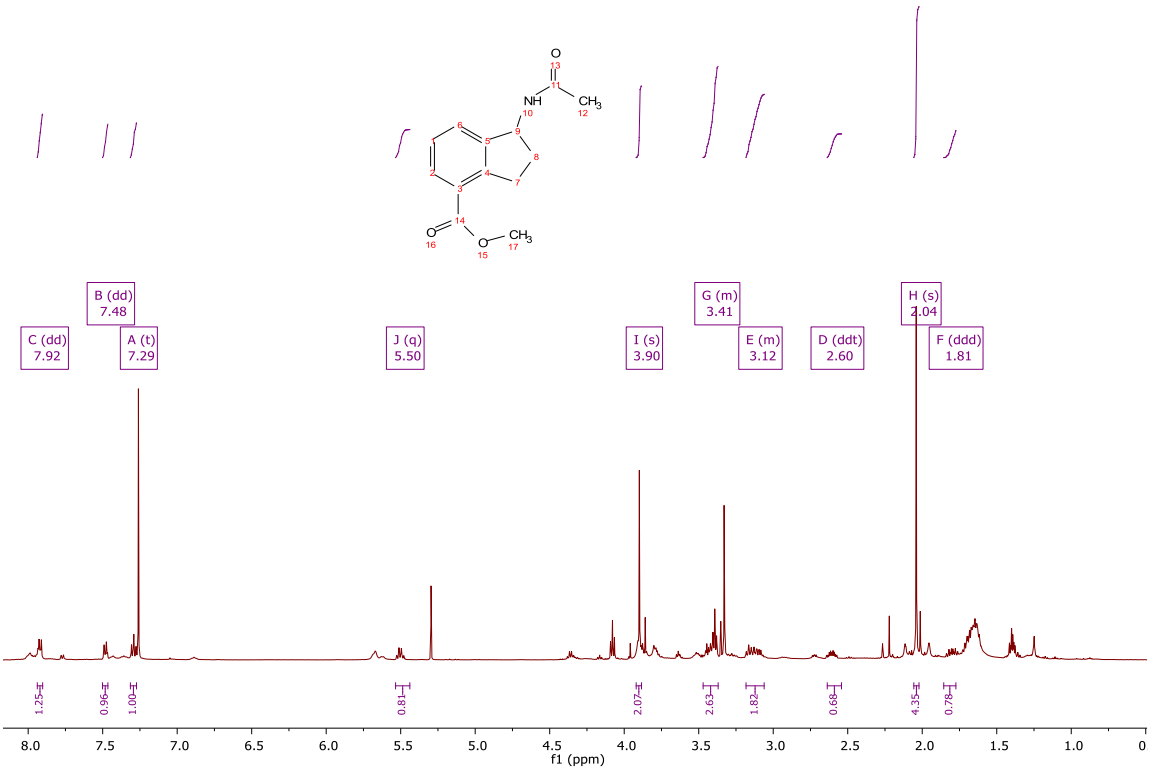


Figure S36: ^{1}H-NMR of methyl-1-acetamido-2,3-dihydro-1H-indene-4-carboxylate (**39**)

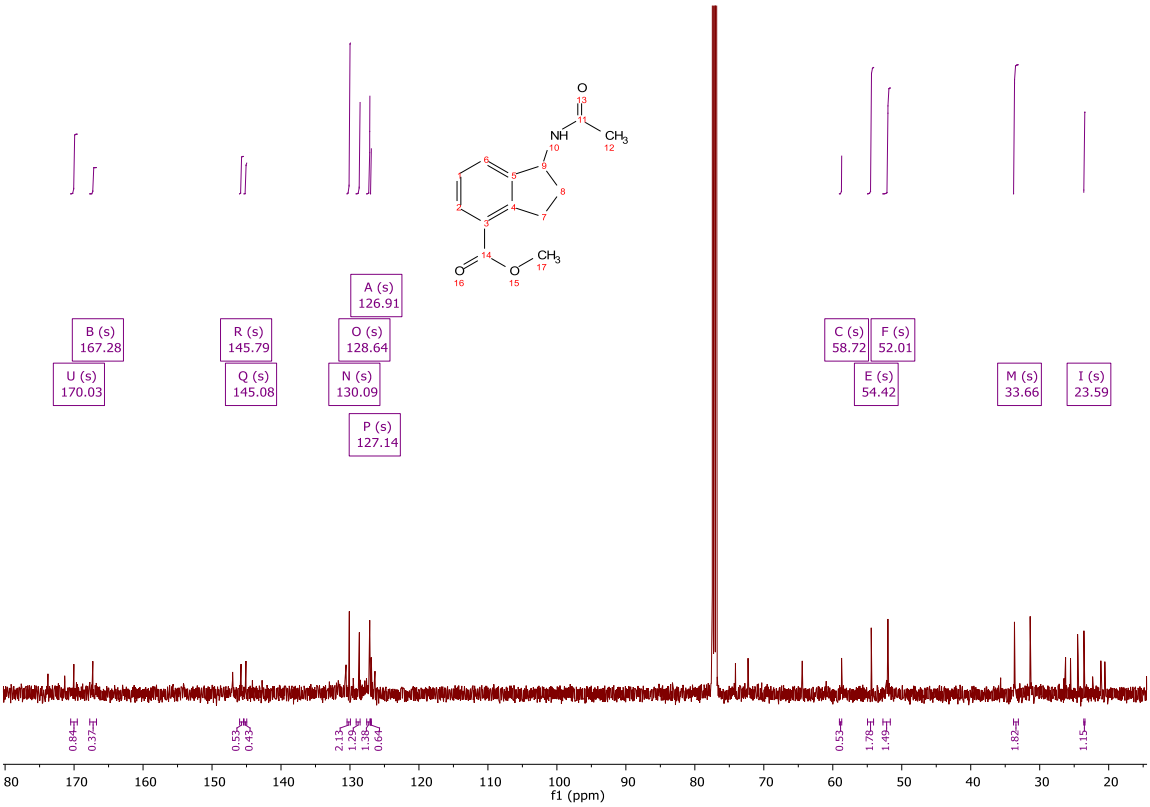


Figure S37: ^{13}C-NMR of methyl-1-acetamido-2,3-dihydro-1H-indene-4-carboxylate (**39**)

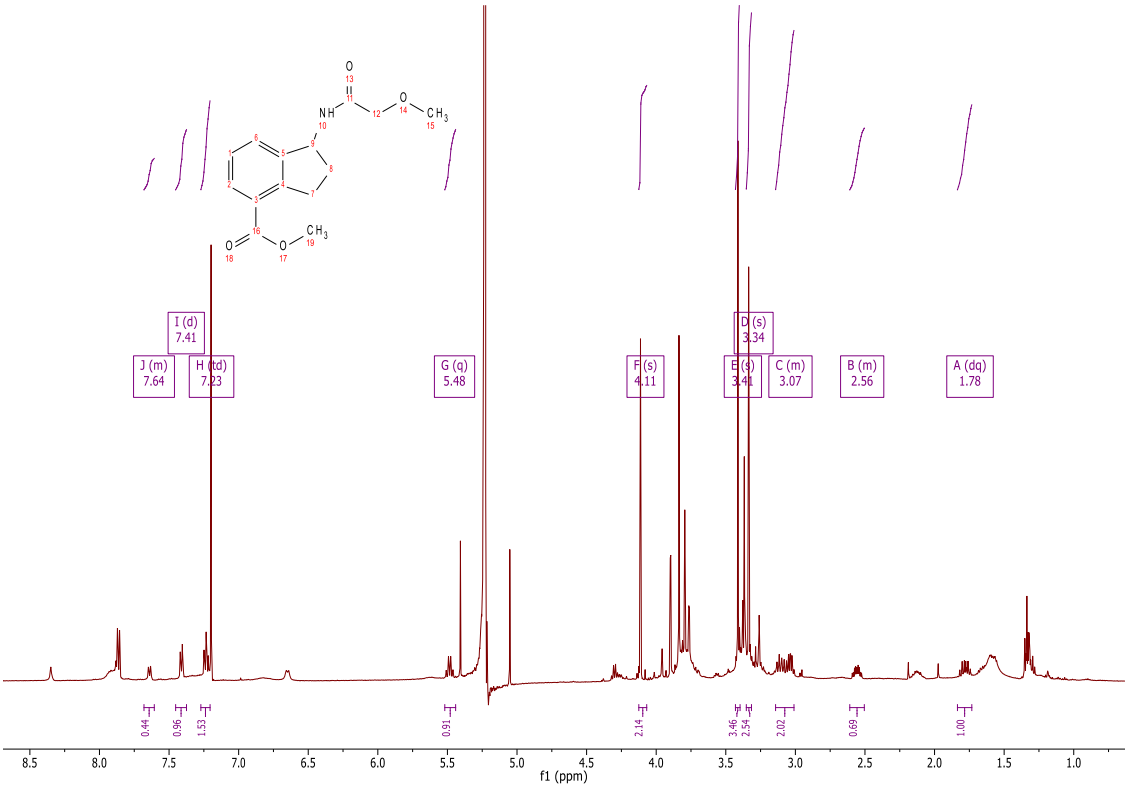


Figure S38: ^{1}H-NMR of methyl 1-(2-methoxyacetamido)-2,3-dihydro-1H-indene-4-carboxylate (**35**)

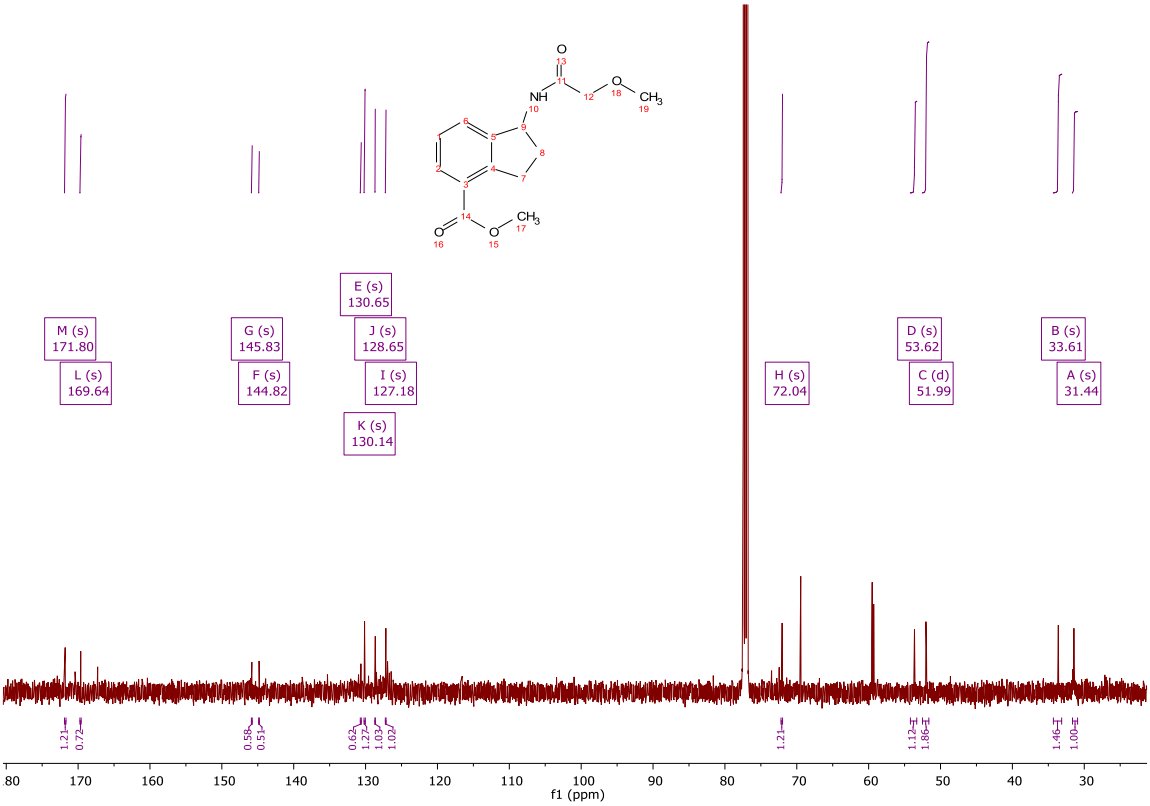


Figure S39: ^{13}C-NMR of methyl 1-(2-methoxyacetamido)-2,3-dihydro-1H-indene-4-carboxylate (**35**)

3 GC data

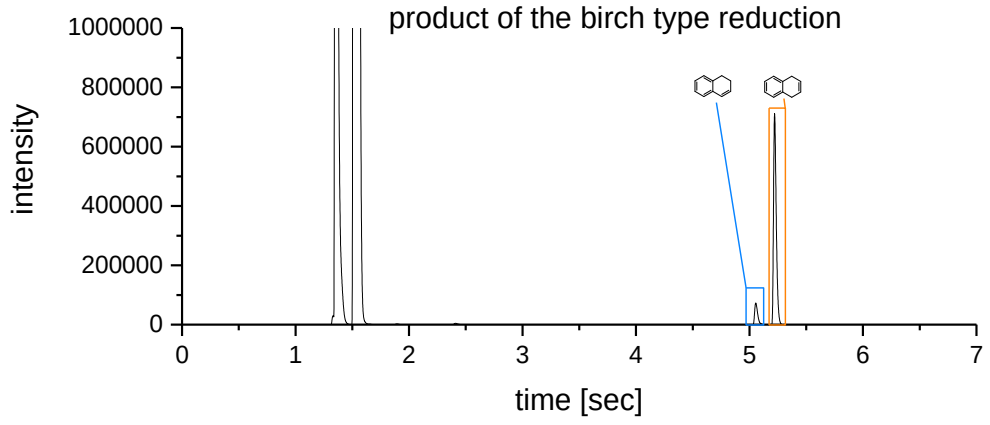


Figure S40: Rearrangement of 1,4-dihydronaphthalene (**9**) to 1,2-dihydronaphthalene (**10**), GC parameters: pressure 131.9 kPa, total flow 198.2 mL/min, linear velocity 44.2 cm/sec, purge flow 3 m/min, split ration 90, temperature profile 40 °C-150 °C (20 °C/min)-154 °C (2 °C/min)-180 °C (20 °C/min), SPL1 200 °C, FID1 250 °C, sampling rate 40 msec.

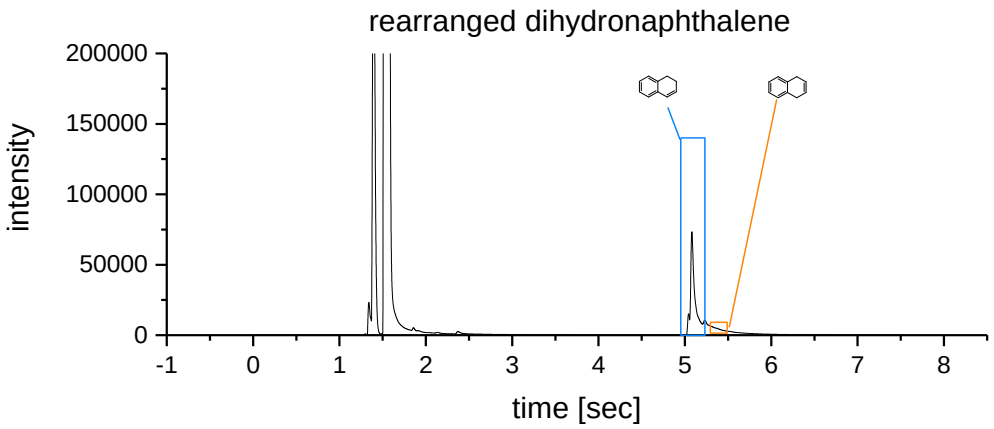


Figure S41: Rearrangement of 1,4-dihydronaphthalene (**9**) to 1,2-dihydronaphthalene (**10**), GC parameters: pressure 131.9 kPa, total flow 198.2 mL/min, linear velocity 44.2 cm/sec, purge flow 3 m/min, split ration 90, temperature profile 40 °C-150 °C (20 °C/min)-154 °C (2 °C/min)-180 °C (20 °C/min), SPL1 200 °C, FID1 250 °C, sampling rate 40 msec.

4 HPLC data

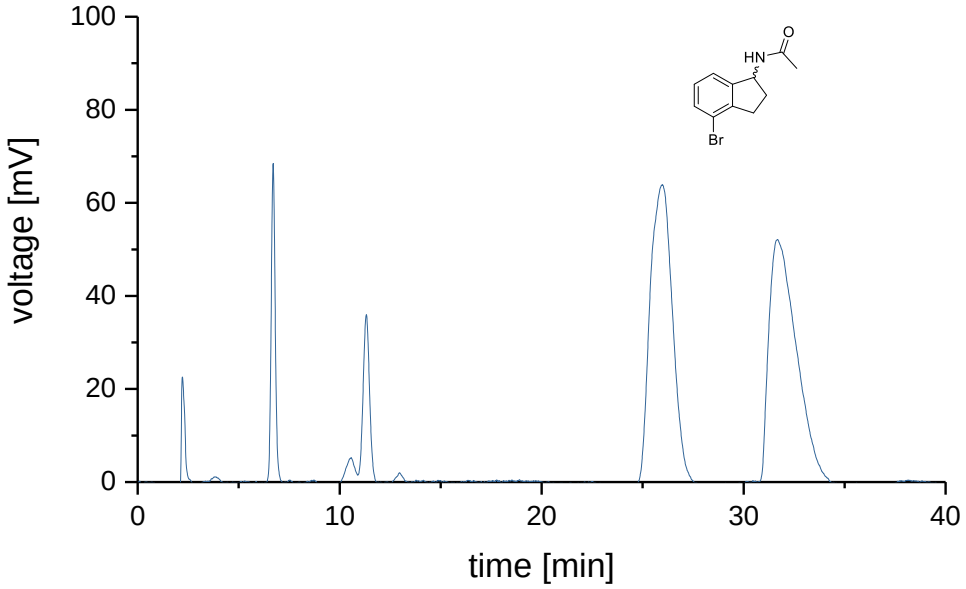


Figure S42: HPLC-Chromatogram of N-(4-bromo-2,3-dihydro-1H-inden-1-yl)acetamide (**32**), AD-H, 95:5 IPA/CO_2, 2.0 mL/min, 10 mPa back pressure, 220 nm

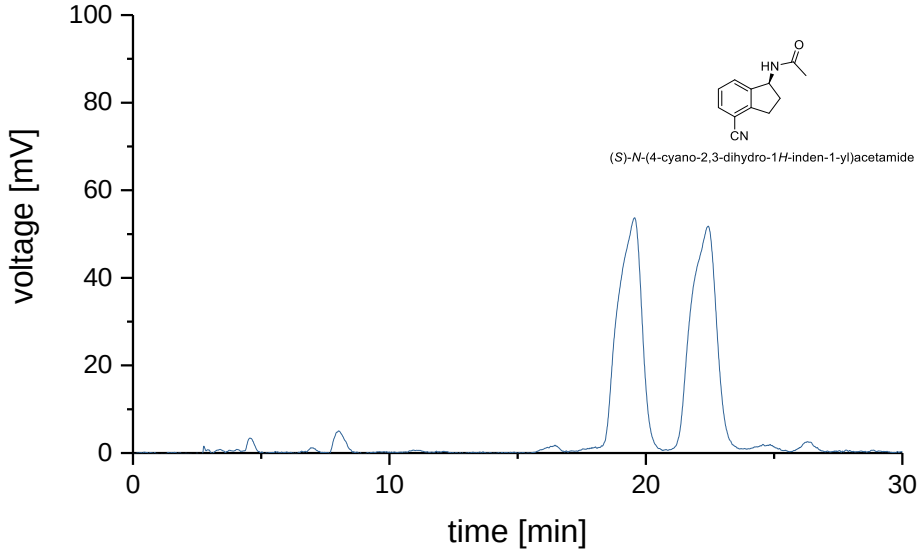


Figure S43: HPLC-Chromatogram of N-(4-cyano-2,3-dihydro-1H-inden-1-yl)acetamide (**37**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

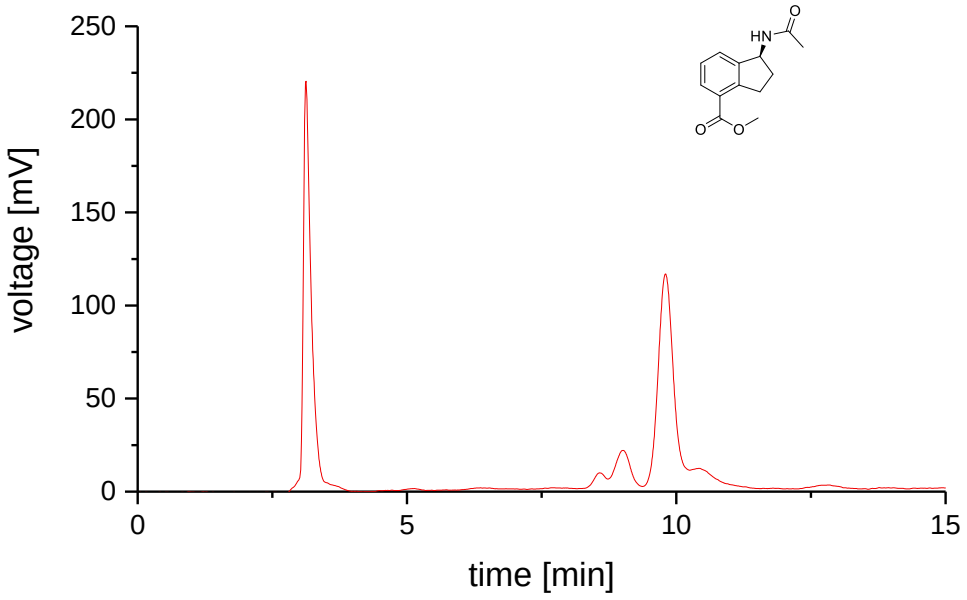


Figure S44: HPLC-Chromatogram of methyl-1-acetamido-2,3-dihydro-1H-indene-4-carboxylate (**39**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

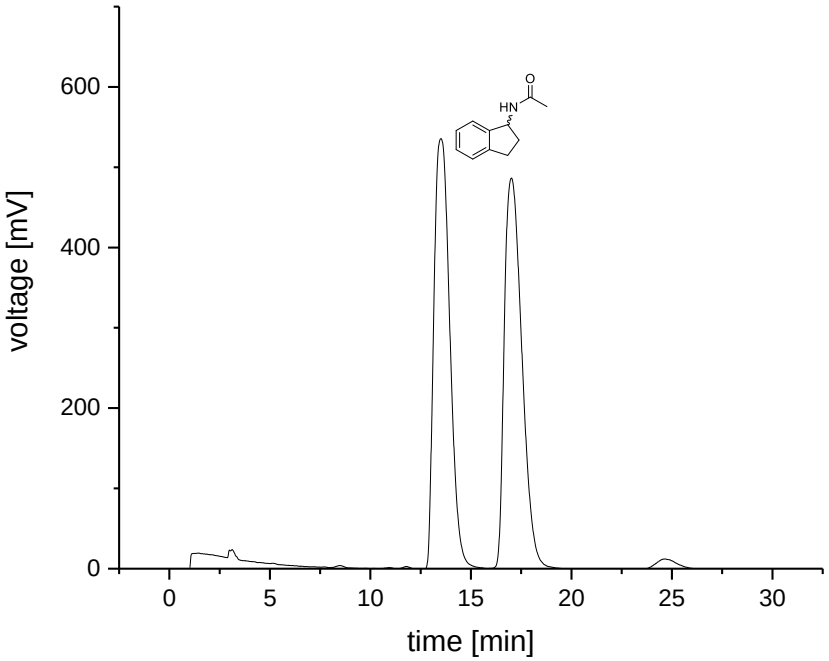


Figure S45: HPLC-Chromatogram of N-(2,3-dihydro-1H-inden-1-yl)acetamide (**36**), AD-H, 95:5 IPA/CO_2, 2.0 mL/min, 10 mPa back pressure, 220 nm

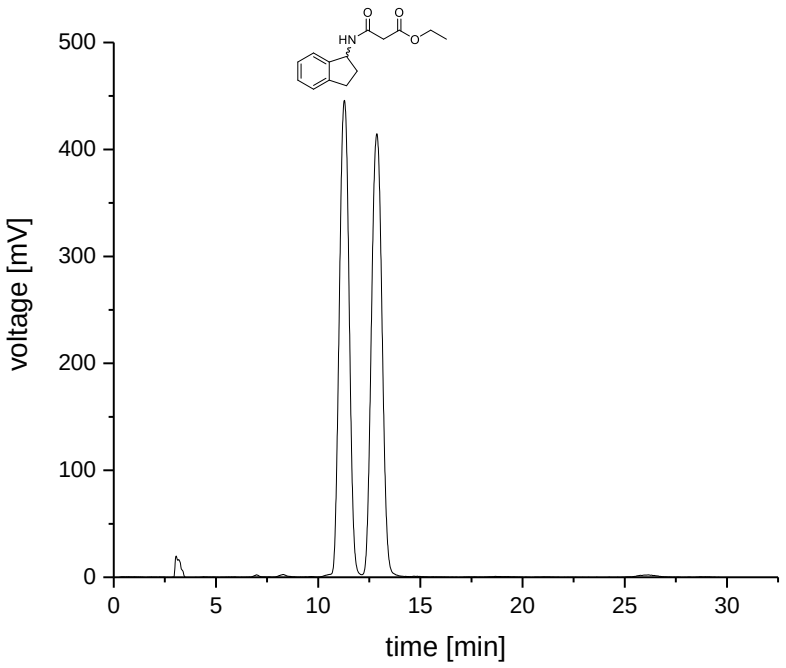


Figure S46: HPLC-Chromatogram of ethyl-3-((2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**31**) AD-H, 95:5 IPA/CO_2, 2.0 mL/min, 10 mPa back pressure, 220 nm

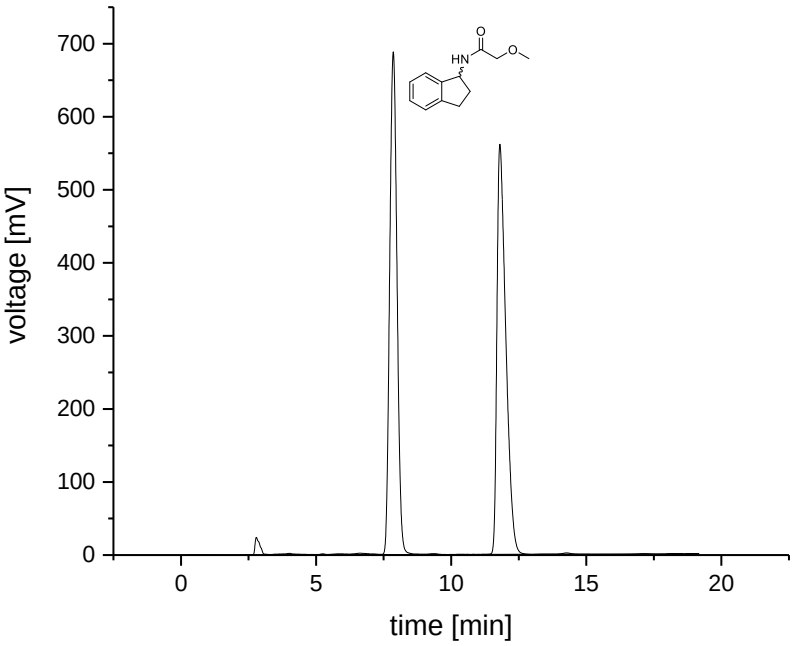


Figure S47: HPLC-Chromatogram of N-(2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**30**) (**31**) AD-H, 95:5 IPA/CO_2, 2.0 mL/min, 10 mPa back pressure, 220 nm

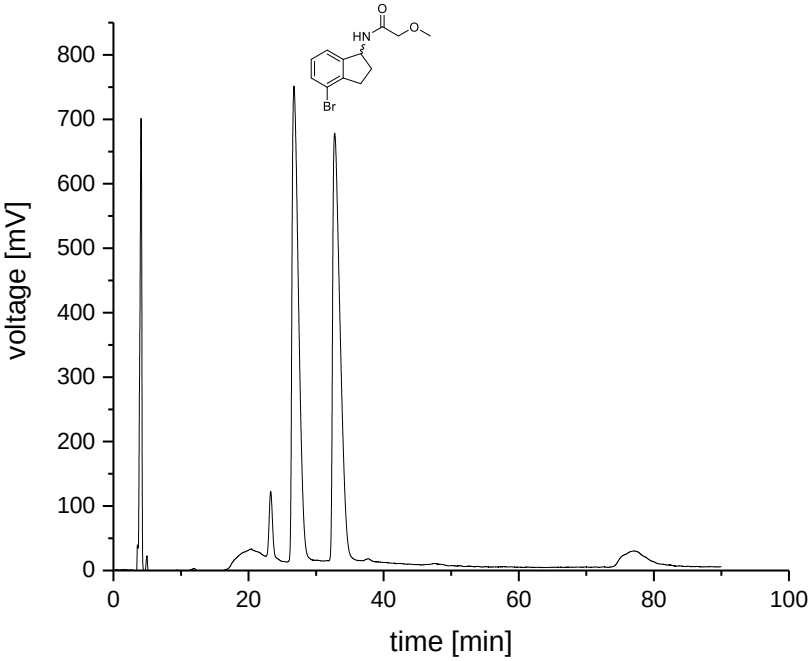


Figure S48: HPLC-Chromatogram of N-(4-bromo-2,3-dihydro-1H-inden-1-yl)acetamide (**37**)
AD-H, 95:5 IPA/CO_2, 2.0 mL/min, 10 mPa back pressure, 220 nm

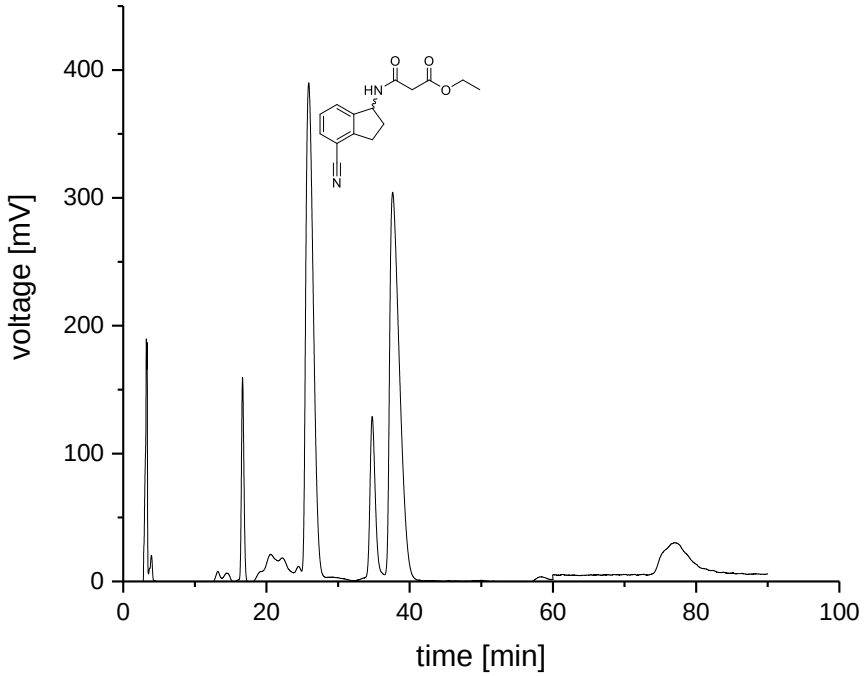


Figure S49: HPLC-Chromatogram of ethyl 3-((4-cyano-2,3-dihydro-1H-inden-1-yl)amino)-3-oxopropanoate (**34**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

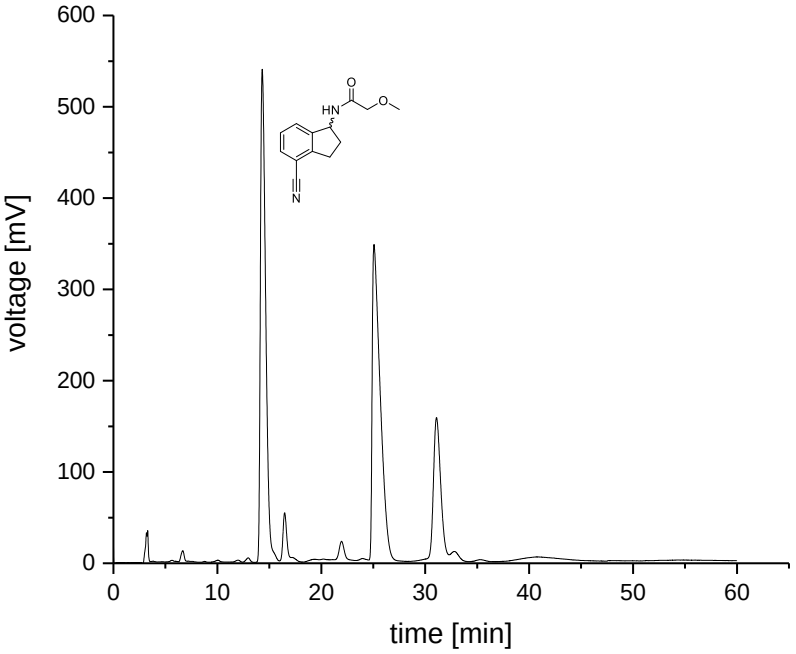


Figure S50: HPLC-Chromatogram of N-(4-cyano-2,3-dihydro-1H-inden-1-yl)-2-methoxyacetamide (**9**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

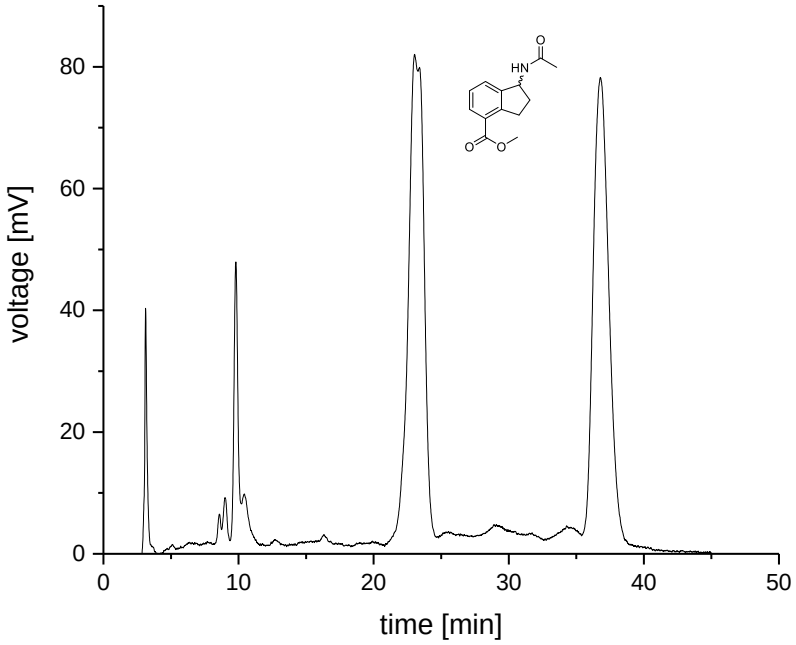


Figure S51: HPLC-Chromatogram of methyl-1-acetamido-2,3-dihydro-1H-indene-4-carboxylate (**39**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

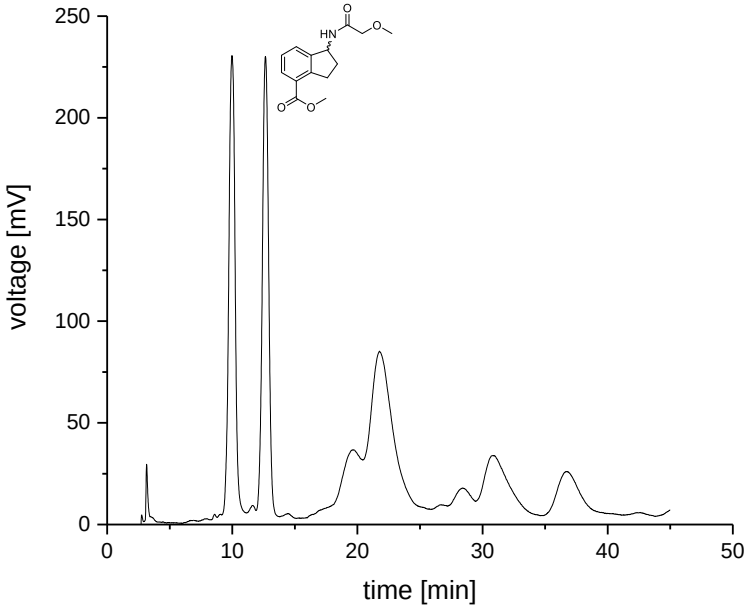


Figure S52: HPLC-Chromatogram of methyl 1-(2-methoxyacetamido)-2,3-dihydro-1H-indene-4-carboxylate (**35**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

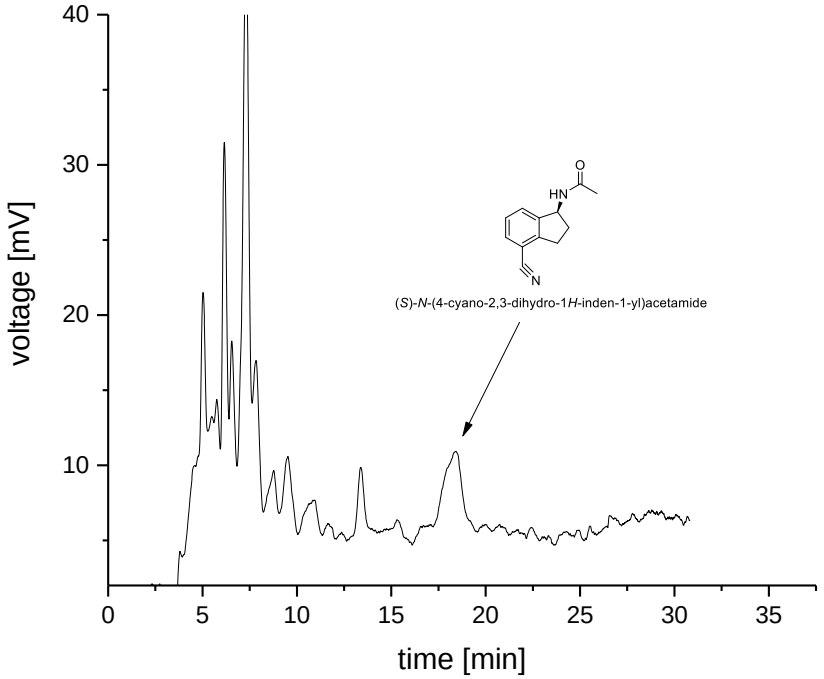


Figure S53: HPLC-Chromatogram of (*S*)-N-(4-cyano-2,3-dihydro-1H-inden-1-yl)acetamide (**37**), OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm. Commercially available at *Fluorochem*®.

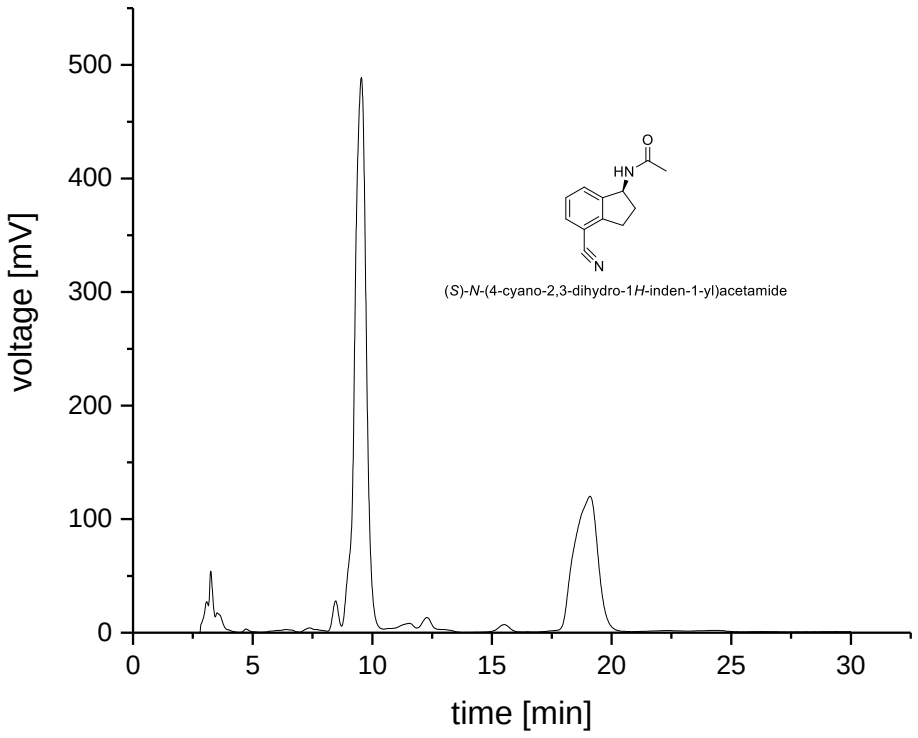


Figure S54: HPLC-Chromatogram of (*S*)-N-(4-cyano-2,3-dihydro-1H-inden-1-yl)acetamide (**37**), Derivatisation of (*S*)-**2**, OJ-H, 95:5 IPA/CO_2, 1.5 mL/min, 10 mPa back pressure, 220 nm

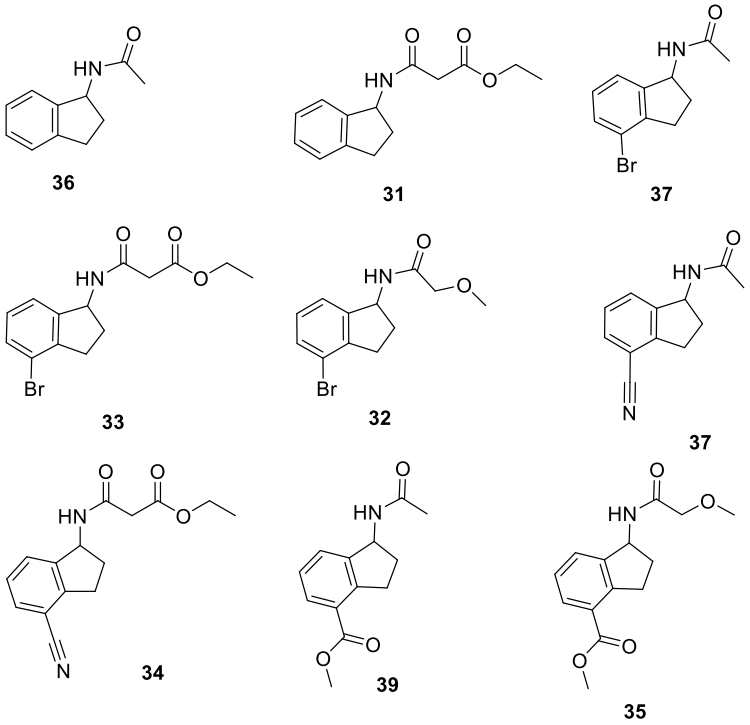


Figure S55: Overview of not shown but numbered molecules in the manuscript.