Supporting Information

of

Diastereoselective synthesis of isochromans via Cu(II)-catalysed intramolecular Michael-type trapping of oxonium ylides

Alavala Gopi Krishna Reddy,[a] Farrukh Sajjad,[a] Taoda Shi,[a] Zhenghui Kang,[a] Mingliang Ma,[a] Dong Xing,*[a] and Wenhao Hu*[b]

[a]*Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Chemical Engineering, East China Normal University, Shanghai, China, 200062.*

[b]*School of Pharmaceutical Scicences, Sun Yat-sen University, Guangzhou, China, 510006.*

E-mail: dxing@sat.ecnu.edu.cn; huwh9@mail.sysu.edu.cn

Contents

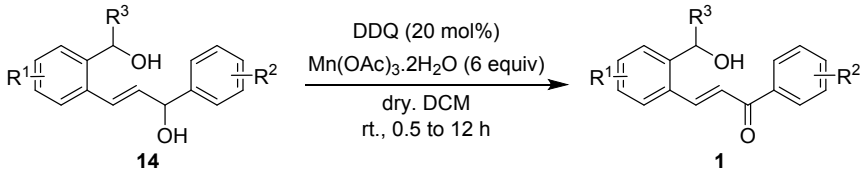
1. General information

All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Brucker Avance III spectrometer by using $CDCl_3$ and DMSO-d_6 solvents. $CDCl_3$ and DMSO-d_6 were set as an internal standards (δ = 7.25 and 2.49) for ^{1}H NMR and (δ = 77.0 and 39.5) for ^{13}C NMR spectra. Chemical shifts are reported in parts per million (ppm) are as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). High-resolution mass spectrometry (HRMS) spectra were recorded on IonSpec FT-ICR or Waters Micromass Q-TOF micro Synapt High Definition Mass Spectrometer. Single crystal X-ray diffraction data were recorded on Bruker-AXS SMART APEX II single crystal X-ray diffractometer. Yields for all compounds are combined yields for all isomers unless otherwise specified.

CH_2Cl_2 was distilled over calcium hydride (CaH_2). 4 Å molecular sieve was dried in a Muffle furnace at 250℃ over 5 hrs. Alcohol-tethered enone substrates were prepared according to literature protocols.[1-5] All small-scale reactions were carried out under argon atmosphere in a well-dried glassware. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. Silica gel (100–200 mesh and 200-300) were used for column chromatography (20–30 g per one gram of crude material).

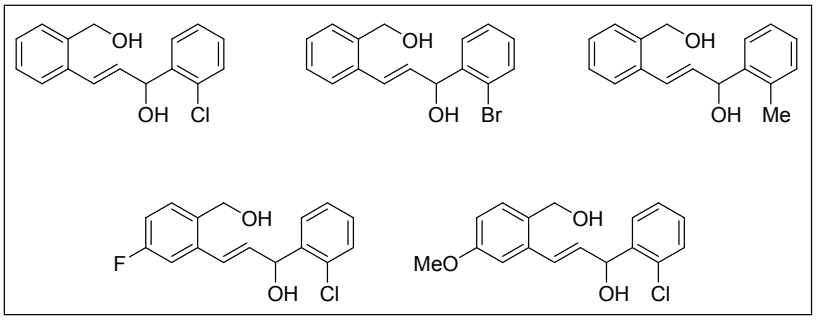
2. Substrate synthesis and experimental procedure:

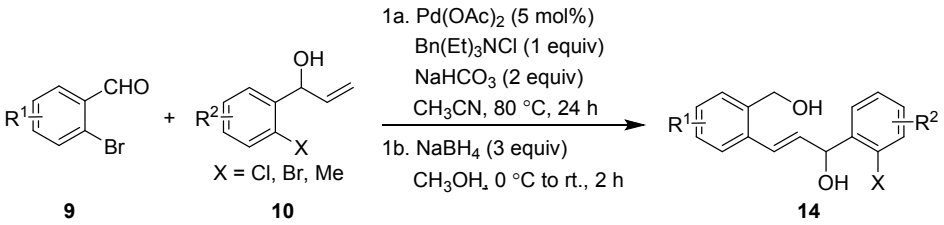
All the alcohol tethered ketones **1** were prepared from the diols **14** by following literature procedures[1]



General procedure (GP-1) for the synthesis of alcohol ketones (1): To an oven-dried vial under nitrogen atmosphere at room temperature were added diol (0.5 mmol), DDQ (20 mol%) and $Mn(OAc)_3 \bullet 2H_2O$ (3 mmol) followed by dry DCM (6 mL). The resultant suspension was stirred for 0.5 to 12 h. After completion of the reaction, the reaction mixture was filtered through a short pad of celite and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography (petroleum ether and ethyl acetate) resulted the alcohol ketones as viscous liquids.

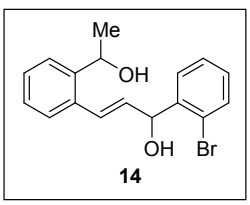
The following diols were prepared from *ortho*-bromoaldehydes **9** and allyl alcohols **10** by following the literature procedures.[2]





To a flame-dried vial under nitrogen atmosphere, were added $Pd(OAc)_2$ (5 mol%), $Bn(Et)_3NCl$ (1.0 mmol), $NaHCO_3$ (2 mmol), 2-bromobenzaldehydes (1.0 mmol) and aryl allylic alcohols (1.2 mmol) followed by dry acetonitrile (6 mL). The resulting reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was then quenched using saturated aq. NH_4Cl solution, and then compound was extracted in ethyl acetate, filtered through a short pad of silica and concentrated under reduced pressure. To the crude residue in methanol (10 mL) at 0 °C was added $NaBH_4$ (3.0 mmol) in portions and allowed the reaction mixture to stir at room temperature for 2 h. The reaction mixture was quenched with saturated aq. NH_4Cl solution, extracted with ethyl acetate (3 × 20 mL) and concentrated under vacuum. Purification of the crude residue by silica gel column chromatography (petroleum ether and ethyl acetate) resulted the diols as viscous liquids.[2]

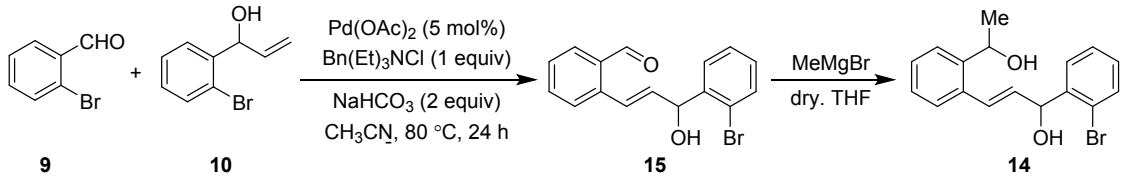
The following diol was prepared from *ortho*-bromoaldehyde **9** and allyl alcohol **10** in stepwise manner by following literature procedures.[2]



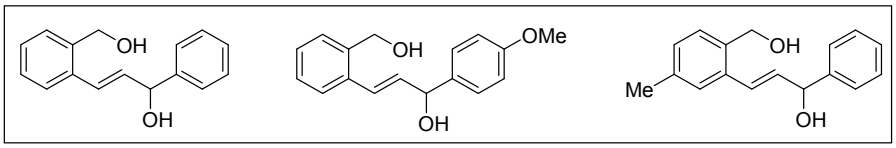
To a flame-dried vial under nitrogen atmosphere, were added $Pd(OAc)_2$ (5 mol%), $Bn(Et)_3NCl$

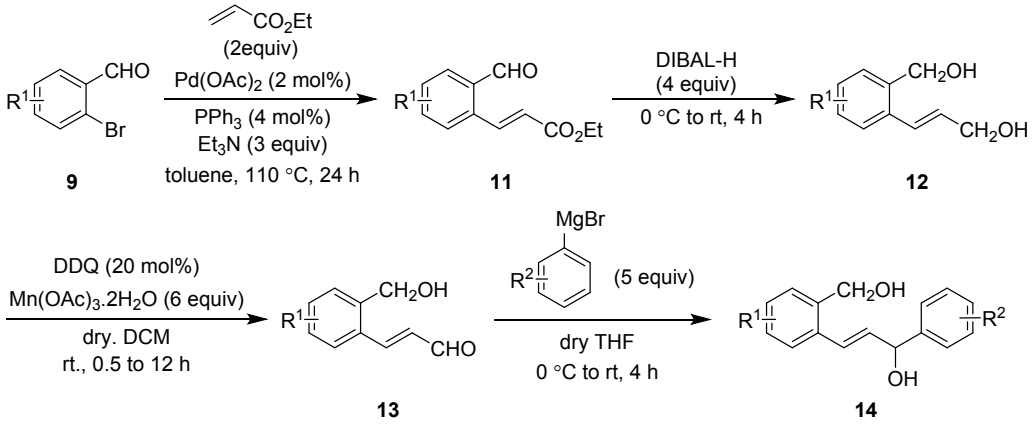
(1.0 mmol), $NaHCO_3$ (2 mmol), 2-bromobenzaldehydes (1.0 mmol) and aryl allylic alcohols (1.2 mmol) followed by dry acetonitrile (6 mL). The resulting reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was then quenched using saturated aq. NH_4Cl solution, and then compound was extracted in ethyl acetate (3 × 15 mL), concentrated under mild vacuum and purified through silica gel chromatography (petroleum ether and ethyl acetate) to afford the aldehyde alcohol **15**.[5]

To the solution of aldehyde alcohol **15** (1 mmol) in dry THF (5 mL) under nitrogen atmosphere at 0 °C was added 1 M solution of methylmagnesium bromide in THF (6 mmol) and the reaction mixture was allowed to room temperature for 6 h and the formation of diol **14** was monitored by TLC. The reaction mixture was quenched using saturated aq. NH_4Cl solution, and then compound was extracted with ethyl acetate (3 × 15 mL), concentrated under reduced pressure and purified through silica gel chromatography (petroleum ether and ethyl acetate) to afford the diol **14**.[5]



The following diols **14** were prepared from *ortho*-bromoaldehydes **9** in stepwise manner by following literature procedures.[1,3-5]





To a flame dried vial under nitrogen atmosphere, were added aldehyde **9** (1 mmol), $Pd(OAc)_2$ (2.5 mol%), PPh_3 (2.5 mol%), Et_3N (3 mmol) and dry toluene (3 mL) followed ethyl acrylate

(2 mmol). The resulting reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was quenched using saturated aq. NH_4Cl solution, extracted with ethyl acetate (3 × 15 mL), concentrated and purified through silica gel chromatography (petroleum ether and ethyl acetate) to yield ester **11**.[3]

To the solution of ester **11** (1 mmol) in dry THF (5 mL) under nitrogen atmosphere at 0 °C was added 1 M DIBAL-H in toluene (4 mmol) and the reaction mixture was allowed to room temperature for 4 h and the formation of diol **12** was monitored by TLC. The reaction mixture was quenched using saturated aq. NH_4Cl solution, and then compound was extracted with ethyl acetate (3 × 20 mL), concentrated under reduced pressure and purified through silica gel chromatography (petroleum ether and ethyl acetate) to afford the diol **12**.[4]

To an oven-dried vial under nitrogen atmosphere at room temperature, were added diol **12** (1 mmol), DDQ (20 mol%) and $Mn(OAc)_3.2H_2O$ (6 mmol) followed by dry DCM (10 mL). The resultant suspension was stirred for 0.5 to 12 h. The reaction mixture was filtered through a short pad of celite and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography (petroleum ether and ethyl acetate) resulted the alcohol aldehyde **13** as viscous liquid.[1]

To the solution of aldehyde **13** (1 mmol) in dry THF (5 mL) under nitrogen atmosphere at 0 °C was added 1 M solution of arylmagnesium bromide in THF (5 mmol) and the reaction mixture was allowed to room temperature for 4 h and the formation of diol **14** was monitored by TLC. The reaction mixture was quenched using saturated aq. NH_4Cl solution, and then compound was extracted with ethyl acetate (3 × 15 mL), concentrated under reduced pressure and purified through silica gel chromatography (petroleum ether and ethyl acetate) to afford the diol **14**.[5]

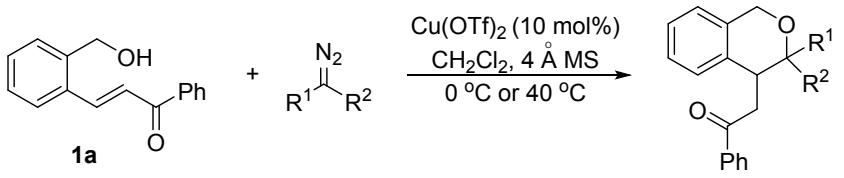
General procedure (GP-2) for the optimizations towards isochroman 3a:

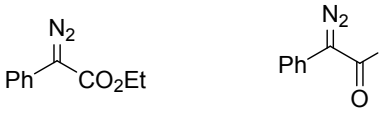
To a flame-dried vial, at room temperature, under an inert atmosphere, were added [Rh]/[Pd]/[Cu]-catalyst (0.002–0.02 mmol) and 4 Å molecular sieves (150 mg) followed by DCM (1.0 mL). To this well-stirred suspension at stated temperature, was added a solution of alcohol enone **1** (48 mg, 0.2 mmol) and diazo-acetate **2** (0.4–0.5 mmol, 2.0 eq) in 1.5 mL of DCM for one hour through a syringe pump. After completion of the addition, stirring was continued at the same temperature. Progress of the reaction was monitored by TLC until complete consumption of alcohol ketone **1**. The reaction mixture was filtered through celite and the filtrate was concentrated to give a residue, which was subjected to ^1H NMR analysis for determination of diastereoselective ratio (dr) values. Purification of the crude mixture by silica gel flash chromatography (eluents: ethyl acetate/petroleum ether).

General procedure (GP-3) for the copper-catalyzed synthesis of isochromans 3:

To a flame-dried vial, at room temperature, under an inert atmosphere, were added $Cu(OTf)_2$ (7 mg, 0.02 mmol) and 4 Å molecular sieves (150 mg) followed by DCM (1.0 mL). To this well-stirred suspension at 40 °C, was added a solution of alcohol enone **1** (48–64 mg, 0.2 mmol) and diazo-acetate **2** (0.5 mmol, 2.5 eq) in 1.5 mL of DCM for one hour through a syringe pump. After completion of the addition, stirring was continued at the same temperature for 12 h. Progress of the isochroman **3** formation was monitored by TLC until the reaction is completed. The reaction mixture was filtered through Celite and the filtrate was concentrated to give a residue, which was subjected to ^1H NMR analysis for determination of diastereoselective ratio (dr) values. Purification of the crude mass by silica gel flash chromatography (eluents: ethyl acetate/petroleum ether; 4:96 to 25:75) afforded pure isochromans **3** as viscous liquid/semi-solid/solid.

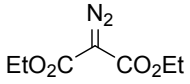
Results on the Screening of other diazo compounds



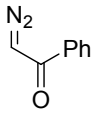


dp: 81%, >20:1 dr

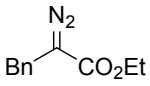
dp not observed
only insertion product



diazo did not decompose
only intramolecular cyclization of **1a**

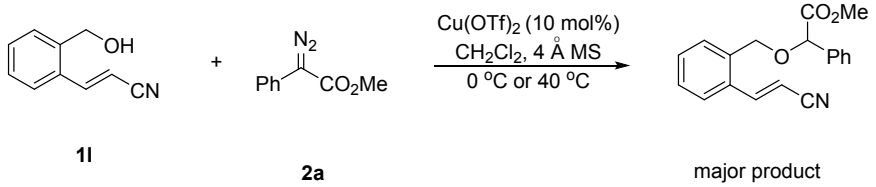


dp not observed
massy

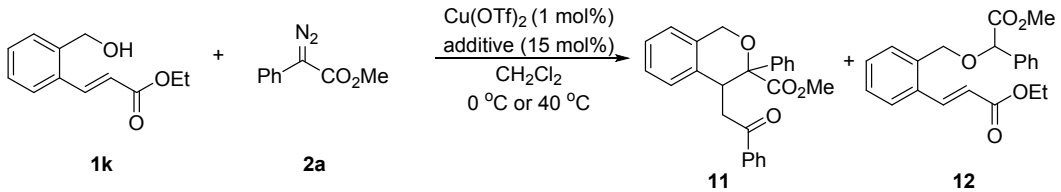


dp not observed
only insertion product

Results on the Screening of other diazo compounds



major product



1k **2a** **11** **12**

Entry	Catalyst	Lewis acid (x mol%)	Solvent	*T* (°C)	conversion	yield of 11	yield of 12
1	$Rh_2(OAc)_4$	-	DCM	RT	100	-	73%
2	$Rh_2(OAc)_4$	$Cu(OTf)_2$ (15)	DCM	RT	100	-	60%
3	$Rh_2(OAc)_4$	$Ag(OCOCF_3)$ (15)	DCM	RT	100	-	65%
4	$Rh_2(OAc)_4$	$InCl_3$ (15)	DCM	RT	90	-	60%
5[a]	$Rh_2(OAc)_4$	-	DCM	RT	100	Not clear	
6[b]	$Rh_2(OAc)_4$	-	DCM	RT	100	Not clear	
7	$Rh_2(OAc)_4$	-	DCM	40	100	Only insertion	
8	$Rh_2(OAc)_4$	-	DCE	40	75	Only insertion	
9	$Rh_2(OAc)_4$	-	toluene	40	100	Only insertion	
10	$Rh_2(OAc)_4$	-	DCM	0	100	Only insertion	
11	$Rh_2(OAc)_4$	-	toluene	0	100	Only insertion	
12	$Rh_2(OAc)_4$	Zr-MS-BINOL (10)	DCM	0	100	Only insertion	
13	$Rh_2(OAc)_4$	$AgSbF_6$ (5)	DCM	0	100	Only insertion	
14	$Rh_2(OAc)_4$	$FeCl_3$ (20)	DCM	0	100	Only insertion	
15	$Rh_2(OAc)_4$	$Sc(OTf)_3$ (10)	DCM	0	100	Only insertion	
16	$Rh_2(OAc)_4$	$Zn(OTf)_2$ (10)	DCM	0	100	Only insertion	

3. Single crystal XRD data of compound 3a (CCDC 1849633):

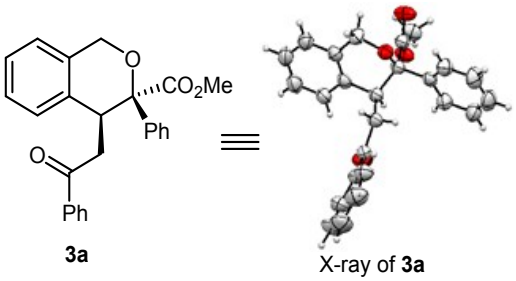
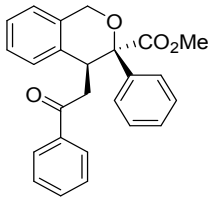


Table of Crystal data and structure refinement for compound 3a

Empirical formula	$C_{25}H_{22}O_4$
Formula weight	386.42
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	15.6081(6)
b/Å	6.1955(2)
c/Å	21.7106(8)
α/°	90
β/°	107.330(4)
γ/°	90
Volume/Å^3	2004.11(13)
Z	4
ρ_{calc}g/cm^3	1.281
μ/mm^{-1}	0.694
F(000)	816.0
Crystal size/mm^3	0.18 × 0.12 × 0.08
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.276 to 134.044
Index ranges	$-18 \le h \le 18$, $-7 \le k \le 5$, $-25 \le l \le 25$
Reflections collected	16400
Independent reflections	3564 [R_{int} = 0.0813, R_{sigma} = 0.0533]
Data/restraints/parameters	3564/0/263

Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0514, wR_2 = 0.1226
Final R indexes [all data]	R_1 = 0.0803, wR_2 = 0.1349
Largest diff. peak/hole / e $Å^{-3}$	0.14/-0.17

4. Characterization data of products:



3a

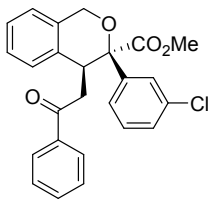
Methyl (3*R*,4*S*)-4-(2-oxo-2-phenylethyl)-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3a):

Pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.22 (m, 6H), 7.16 (dd, *J* = 7.5 and 7.1 Hz, 1H), 7.11 (dd, *J* = 7.1 and 7.0 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 5.34 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.65 (dd, *J* = 9.0 and 3.1 Hz, 1H), 3.50 (s, 3H), 3.05 (dd, *J* = 17.3 and 9.0 Hz, 1H), 2.88 (dd, *J* = 17.3 and 3.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.39, 171.97, 138.55, 137.03, 136.48, 132.83, 131.82, 129.55, 128.59, 128.30, 128.16, 127.92, 126.98, 126.67, 125.55, 124.23, 82.64, 65.73, 52.49, 41.27, 39.82 ppm.

HRMS-ESI: calcd. for $C_{25}H_{22}NaO_4$ $[M + Na]^+$ 409.1410, found 409.1403.



3b

Methyl (3*R*,4*S*)-3-(3-chlorophenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3b):

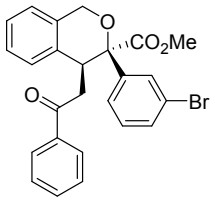
Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 1H),

7.46 (t, *J* = 7.3 Hz, 1H), 7.37 – 7.20 (m, 5H), 7.18 (dd, *J* = 7.3 and 7.3 Hz, 1H), 7.12 (dd, *J* = 7.3 and 7.1 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 5.32 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.62 (dd, *J* = 8.8 and 3.0 Hz, 1H), 3.52 (s, 3H), 3.03 (dd, *J* = 17.2 and 8.8 Hz, 1H), 2.87 (dd, *J* = 17.2 and 3.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.10, 171.48, 140.53, 136.80, 136.07, 134.77, 132.97, 131.60, 129.83, 129.52, 128.42, 128.36, 127.90, 127.11, 126.80, 126.06, 124.23, 123.75, 82.21, 65.76, 52.70, 41.08, 39.96 ppm.

HRMS-ESI: calcd. for $C_{26}H_{24}NaO_4$ $[(M + 2) + Na]^+$ 445.0991, found 445.1133.



3c

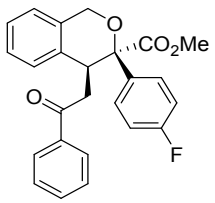
Methyl (3*R*,4*S*)-3-(3-bromophenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3c):

White semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.46 (dd, *J* = 7.5 and 7.1 Hz, 1H), 7.42 – 7.28 (m, 4H), 7.24 – 7.07 (m, 3H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.32 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.60 (dd, *J* = 8.8 and 3.1 Hz, 1H), 3.51 (s, 3H), 3.01 (dd, *J* = 17.2 and 8.8 Hz, 1H), 2.87 (dd, *J* = 17.2 and 3.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.08, 171.45, 140.73, 136.77, 136.03, 132.96, 131.58, 131.35, 130.08, 129.50, 128.89, 128.36, 127.90, 127.11, 126.79, 124.22, 122.97, 82.13, 65.74, 52.69, 41.07, 39.99 ppm.

HRMS-ESI: calcd. for $C_{25}H_{21}BrNaO_4$ $[(M +2) + Na]^+$ 489.0495, found 489.0500.



3d

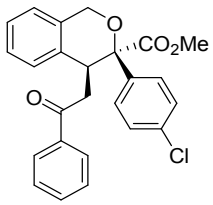
Methyl (3*R*,4*S*)-3-(4-fluorophenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3d):

Pale yellow semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.62 (m, 4H), 7.45 (dd, *J* = 7.5 and 7.1 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.17 (dd, *J* = 7.4 and 7.1 Hz, 1H), 7.12 (t, *J* = 7.1 Hz, 1H), 7.07 – 6.95 (m, 3H), 5.34 (d, *J* = 15.6 Hz, 1H), 5.23 (d, *J* = 15.6 Hz, 1H), 4.65 (dd, *J* = 8.7 and 3.3 Hz, 1H), 3.51 (s, 3H), 3.03 (dd, *J* = 17.4 and 8.7 Hz, 1H), 2.89 (dd, *J* = 17.4 and 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.17, 171.82, 162.48 (d, *J* = 248.0 Hz), 136.84, 136.27, 134.25 (d, *J* = 2.9 Hz), 132.94, 131.64, 129.45, 128.32, 127.86, 127.53 (d, *J* = 8.1 Hz), 127.05, 126.76, 124.23, 115.43 (d, *J* = 21.3 Hz), 82.21, 65.72, 52.57, 41.15, 39.74 ppm.

HRMS-ESI: calcd. for $C_{25}H_{21}FNaO_4$ $[M + Na]^+$ 427.1316, found 427.1308.



3e

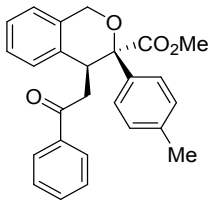
Methyl (3*R*,4*S*)-3-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3e):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 4H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.17 (dd, *J* = 7.3 and 7.3 Hz, 1H), 7.12 (dd, *J* = 7.3 and 7.3 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 5.33 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.64 (dd, *J* = 8.9 and 2.9 Hz, 1H), 3.51 (s, 3H), 3.04 (dd, *J* = 17.4 and 8.9 Hz, 1H), 2.87 (dd, *J* = 17.4 and 2.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.13, 171.64, 137.03, 136.82, 136.17, 134.19, 132.97, 131.61, 129.47, 128.72, 128.33, 127.87, 127.15, 127.09, 126.79, 124.23, 82.25, 65.73, 52.64, 41.15, 39.72 ppm.

HRMS-ESI: calcd. for $C_{25}H_{21}ClNaO_4$ $[M + Na]^+$ 443.1021, found 443.1021.



3f

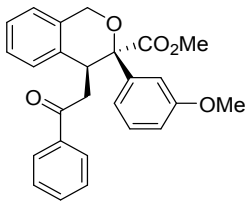
Methyl (3*R*,4*S*)-3-(4-methylphenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3f):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.26 (m, 3H), 7.20 – 7.06 (m, 4H), 7.01 (d, *J* = 7.4 Hz, 1H), 5.34 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.63 (dd, *J* = 9.0 and 2.9 Hz, 1H), 3.49 (s, 3H), 3.04 (dd, *J* = 17.2 and 9.0 Hz, 1H), 2.90 (dd, *J* = 17.2 and 2.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.43, 172.07, 137.87, 136.96, 136.51, 135.54, 132.79, 131.80, 129.51, 129.27, 128.23, 127.91, 126.91, 126.60, 125.39, 124.19, 82.51, 65.66, 52.43, 41.27, 39.74, 21.01 ppm.

HRMS-ESI: calcd. for $C_{26}H_{24}NaO_4$ $[M + Na]^+$ 423.1567, found 423.1573.



3g

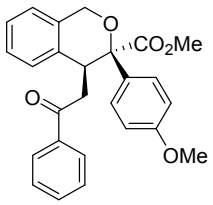
Methyl (3*R*,4*S*)-3-(3-methoxyphenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3g):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.22 (m, 6H), 7.16 (dd, *J* = 7.1 and 7.1 Hz, 1H), 7.11 (dd, *J* = 7.3 and 7.1 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 5.32 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.62 (dd, *J* = 8.9 and 3.3 Hz, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 3.03 (dd, *J* = 17.2 and 8.9 Hz, 1H), 2.92 (dd, *J* = 17.2 and 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.34, 171.83, 159.77, 140.12, 136.97, 136.45, 132.82, 131.73, 129.59, 129.51, 128.29, 127.92, 126.95, 126.67, 124.18, 117.74, 113.97, 111.06, 82.53, 65.70, 55.24, 52.53, 41.29, 39.94 ppm.

HRMS-ESI: calcd. for $C_{26}H_{25}O_5$ $[M + H]^+$ 417.1697, found 417.1683.



12h

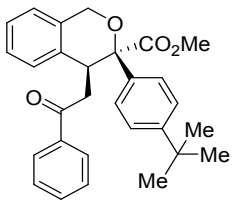
Methyl (3*R*,4*S*)-3-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3h):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.15 (dd, *J* = 7.5 and 7.1 Hz, 1H), 7.10 (dd, *J* = 7.4 and 7.3 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.32 (d, *J* = 15.6 Hz, 1H), 5.20 (d, *J* = 15.6 Hz, 1H), 4.61 (dd, *J* = 8.7 and 3.3 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.02 (dd, *J* = 17.4 and 8.7 Hz, 1H), 2.92 (dd, *J* = 17.4 and 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.50, 171.19, 159.34, 136.97, 136.51, 132.85, 131.81, 130.56, 129.51, 128.29, 127.94, 126.95, 126.84, 126.66, 124.23, 113.91, 82.31, 65.69, 55.20, 52.47, 41.30, 39.73 ppm.

HRMS-ESI: calcd. for $C_{26}H_{25}O_5Na$ $[M + Na]^+$ 439.1516, found 439.1548.



3i

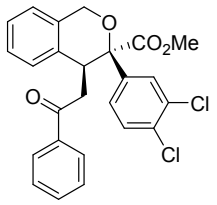
Methyl (3*R*,4*S*)-3-(4-tert-butylphenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3i):

Pale yellow semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.26 (m, 5H), 7.15 (dd, *J* = 7.2 and 7.1 Hz, 1H), 7.10 (dd, *J* = 7.3 and 7.1 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 5.34 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.65 (dd, *J* = 7.5 and 4.3 Hz, 1H), 3.07 – 2.90 (m, 2H), 1.25 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.50, 172.08, 150.95, 137.01, 136.60, 135.32, 132.76, 131.90, 129.48, 128.24, 127.92, 126.89, 126.62, 125.46, 125.19, 124.18, 82.49, 65.66, 52.41, 41.26, 39.80, 34.42, 31.19 ppm.

HRMS-ESI: calcd. for $C_{29}H_{30}NaO_4$ $[M + Na]^+$ 465.2036, found 465.2067.



3j

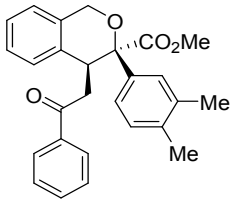
Methyl (3*R*,4*S*)-3-(3,4-dichlorophenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3j):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.42 – 7.27 (m, 4H), 7.18 (dd, *J* = 7.4 and 7.3 Hz, 1H), 7.13 (dd, *J* = 7.3 and 7.3 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 5.32 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.60 (dd, *J* = 8.1 and 3.5 Hz, 1H), 3.52 (s, 3H), 3.00 (dd, *J* = 17.2 and 8.1 Hz, 1H), 2.89 (dd, *J* = 17.2 and 3.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.95, 171.23, 138.68, 136.67, 135.88, 133.08, 132.95, 132.47, 131.48, 130.47, 129.46, 128.38, 128.08, 127.86, 127.20, 126.92, 125.11, 124.24, 81.86, 65.78, 52.80, 41.02, 39.99 ppm.

HRMS-ESI: calcd. for $C_{25}H_{20}Cl_2NaO_4$ $[M + Na]^+$ 477.0631, found 477.0619.



3k

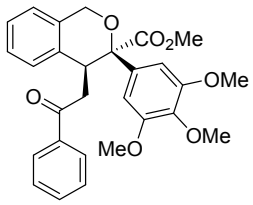
Methyl (3*R*,4*S*)-3-(3,4-dimethylphenyl)-4-(2-oxo-2-phenylethyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3k):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.26 (m, 6H), 7.20 – 7.05 (m, 3H), 7.01 (d, *J* = 7.4 Hz, 1H), 5.32 (d, *J* = 15.6 Hz, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.61 (dd, *J* = 8.2 and 3.9 Hz, 1H), 3.49 (s, 3H), 3.20 – 2.80 (m, 2H), 2.22 (s, 3H), 2.18 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.50, 172.14, 136.96, 136.82, 136.59, 136.52, 135.86, 132.74, 131.80, 129.81, 129.54, 128.20, 127.92, 126.88, 126.62, 126.50, 124.18, 122.86, 82.48, 65.65, 52.46, 41.31, 39.94, 19.91, 19.35 ppm.

HRMS-ESI: calcd. for $C_{27}H_{26}NaO_4$ $[M + Na]^+$ 437.1723, found 437.1725.



3l

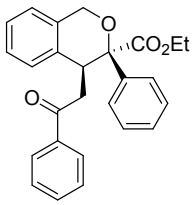
Methyl (3*R*,4*S*)-4-(2-oxo-2-phenylethyl)-3-(3,4,5-trimethoxyphenyl)-3,4-dihydro-1*H*-isochromene-3-carboxylate (3l):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.17 (dd, *J* = 7.3 and 7.0 Hz, 1H), 7.13 (dd, *J* = 7.8 and 7.0 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.91 (s, 2H), 5.29 (d, *J* = 15.6 Hz, 1H), 5.20 (d, *J* = 15.6 Hz, 1H), 4.65 (dd, *J* = 7.8 and 3.9 Hz, 1H), 3.85 (s, 6H), 3.74 (s, 3H), 3.53 (s, 3H), 3.07 (dd, *J* = 17.2 and 3.9 Hz, 1H), 2.89 (dd, *J* = 17.2 and 7.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.37, 171.84, 153.11, 137.48, 136.86, 136.57, 133.96, 132.93, 131.64, 129.27, 128.32, 127.87, 126.98, 126.85, 124.18, 102.75, 82.38, 65.69, 60.70, 56.10, 52.60, 41.46, 40.00 ppm.

HRMS-ESI: calcd. for $C_{28}H_{28}NaO_7$ $[M + Na]^+$ 499.1727, found 499.1756.



3m

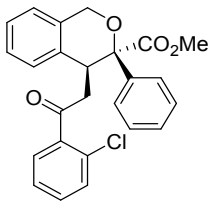
Ethyl (3*R*,4*S*)-4-(2-oxo-2-phenylethyl)-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3m):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.39 – 7.21 (m, 6H), 7.16 (dd, *J* = 7.4 and 7.3 Hz, 1H), 7.10 (dd, *J* = 7.3 and 7.3 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 5.38 (d, *J* = 15.4 Hz, 1H), 5.23 (d, *J* = 15.4 Hz, 1H), 4.64 (dd, *J* = 9.3 and 1.2 Hz, 1H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.08 (dd, *J* = 17.3 and 9.3 Hz, 1H), 2.88 (dd, *J* = 17.3 and 1.2 Hz, 1H), 0.93 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.43, 171.20, 138.54, 137.02, 136.56, 132.82, 132.02, 129.65, 128.50, 128.29, 128.08, 127.90, 126.96, 126.52, 125.58, 124.20, 82.52, 65.71, 61.29, 41.11, 39.97, 13.75 ppm.

HRMS-ESI: calcd. for $C_{26}H_{25}NaO_4$ $[M + Na + H]^+$ 424.1645, found 424.1622.



3n

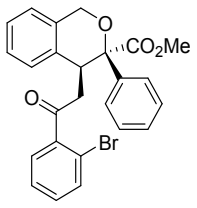
Methyl (3*R*,4*S*)-4-[2-(2-chlorophenyl)-2-oxoethyl]-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3n):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.34 (m, 3H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.26 – 7.09 (m, 5H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 5.31 (d, *J* = 15.4 Hz, 1H), 5.17 (d, *J* = 15.4 Hz, 1H), 4.64 (dd, *J* = 8.8 and 3.3 Hz, 1H), 3.51 (s, 3H), 3.01 (dd, *J* = 17.9 and 8.8 Hz, 1H), 2.87 (dd, *J* = 17.9 and 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.28, 171.86, 139.21, 138.46, 136.23, 131.82, 131.44, 130.62, 130.29, 129.44, 128.59, 128.17, 127.04, 126.76, 126.53, 125.51, 124.18, 82.39, 65.60, 52.51, 45.57, 39.75 ppm.

HRMS-ESI: calcd. for $C_{26}H_{24}NaO_4$ $[(M + 2) + Na]^+$ 445.0991, found 445.0978.



3o

Methyl (3*R*,4*S*)-4-[2-(2-bromophenyl)-2-oxoethyl]-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3o):

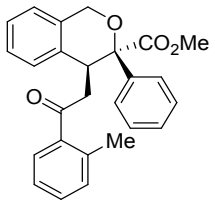
Colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.1 Hz, 2H), 7.50 – 7.34 (m, 4H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.24 – 7.10 (m, 4H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.85 – 6.75 (m, 1H), 5.31 (d, *J* = 15.6 Hz, 1H), 5.17 (d, *J* = 15.6 Hz, 1H), 4.64 (d, *J* = 8.9 and 3.3 Hz, 1H), 3.50 (s, 3H), 2.99 (dd, *J*

= 18.2 and 8.9 Hz, 1H), 2.84 (dd, *J* = 18.2 and 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.98, 171.86, 141.37, 138.50, 136.21, 133.49, 131.84, 131.34, 129.56, 128.63, 128.21, 127.07, 126.79, 126.67, 125.55, 124.18, 118.43, 82.40, 65.63, 52.53, 45.44, 39.53 ppm.

HRMS-ESI: calcd. for $C_{25}H_{22}BrO_4$ $[M + H]^+$ 465.0696, found 465.0721.



3p

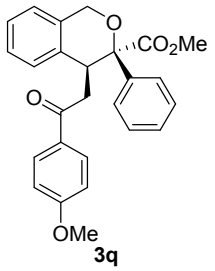
Methyl (3*R*,4*S*)-4-[2-(2-methylphenyl)-2-oxoethyl]-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3p):

White semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.42 – 7.34 (m, 2H), 7.34 – 7.26 (m, 2H), 7.24 – 7.08 (m, 4H), 7.07 – 6.97 (m, 3H), 5.32 (d, *J* = 15.6 Hz, 1H), 5.19 (d, *J* = 15.6 Hz, 1H), 4.63 (dd, *J* = 9.2 and 1.7 Hz, 1H), 3.50 (s, 3H), 2.93 (dd, *J* = 17.4 and 9.2 Hz, 1H), 2.80 (dd, *J* = 17.4 and 1.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.47, 171.99, 138.62, 138.11, 137.67, 136.53, 131.82, 131.66, 131.02, 129.31, 128.62, 128.17, 128.14, 127.02, 126.70, 125.50, 125.39, 124.31, 82.55, 65.65, 52.53, 44.36, 39.77, 20.91 ppm.

HRMS-ESI: calcd. for $C_{26}H_{24}NaO_4$ $[M + Na]^+$ 423.1567, found 423.1573.



3q

Methyl (3*R*,4*S*)-4-[2-(4-methoxyphenyl)-2-oxoethyl]-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3q):

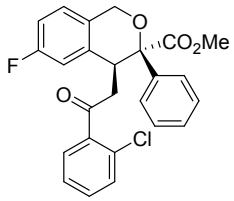
Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.20 (m, 4H), 7.15 (dd, *J* = 7.4 and 7.3 Hz, 1H), 7.09 (dd, *J* = 7.4 and 7.1 Hz, 1H), 7.01 (d, *J* = 7.5

Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.34 (d, *J* = 15.4 Hz, 1H), 5.22 (d, *J* = 15.4 Hz, 1H), 4.63 (dd, *J* = 9.3 and 2.8 Hz, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 2.99 (dd, *J* = 17.1 and 9.3 Hz, 1H), 2.80 (dd, *J* = 17.1 and 2.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.89, 172.02, 163.25, 138.57, 136.54, 131.76, 130.21, 130.13, 129.57, 128.57, 128.12, 126.92, 126.62, 125.54, 124.18, 113.41, 82.66, 65.73, 55.37, 52.49, 40.80, 39.86 ppm.

HRMS-ESI: calcd. for $C_{26}H_{25}O_5$ $[M + H]^+$ 417.1697, found 417.1681.



3r

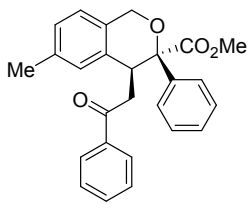
Methyl (3*R*,4*S*)-4-[2-(2-chlorophenyl)-2-oxoethyl]-6-fluoro-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3r):

Colorless viscous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.4 Hz, 2H), 7.39 (dd, *J* = 7.6 and 7.1 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.25 (d, *J* = 2.6 Hz, 2H), 7.20 – 7.07 (m, 2H), 7.05 – 6.95 (m, 2H), 6.91 (ddd, *J* = 8.5, 8.4 and 2.1 Hz, 1H), 5.27 (d, *J* = 15.2 Hz, 1H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.61 (dd, *J* = 9.0 and 3.1 Hz, 1H), 3.54 (s, 3H), 3.01 (dd, *J* = 18.2 and 9.1 Hz, 1H), 2.86 (dd, *J* = 18.2 and 3.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.06, 171.64, 161.27 (d, *J* = 245.8 Hz), 139.04, 138.44 (d, *J* = 7.3 Hz), 138.10, 131.60, 130.66, 130.35, 128.67, 128.63, 128.30, 127.40 (d, *J* = 2.9 Hz), 126.63, 125.89 (d, *J* = 8.1 Hz), 125.44, 116.01(d, *J* = 22.0 Hz), 114.59 (d, *J* = 22.0 Hz), 82.13, 65.23, 52.64, 45.37, 39.63 ppm.

HRMS-ESI: calcd. for $C_{25}H_{20}ClFNaO_4$ $[M + Na]^+$ 461.0926, found 461.0953.



3s

Methyl (3*R*,4*S*)-6-methyl-4-(2-oxo-2-phenylethyl)-3-phenyl-3,4-dihydro-1*H*-

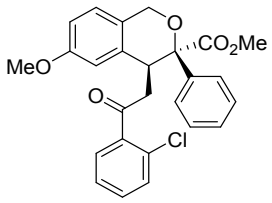
isochromene-3-carboxylate (3s):

White semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.20 (m, 5H), 7.13 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.30 (d, *J* = 15.3 Hz, 1H), 5.20 (d, *J* = 15.3 Hz, 1H), 4.62 (dd, *J* = 8.8 and 3.0 Hz, 1H), 3.51 (s, 3H), 3.02 (dd, *J* = 17.3 and 8.8 Hz, 1H), 2.89 (dd, *J* = 17.3 and 3.0 Hz, 1H), 2.24 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.39, 172.07, 138.60, 137.00, 136.37, 136.23, 132.77, 129.82, 128.59, 128.54, 128.25, 128.10, 127.89, 125.50, 124.05, 82.58, 65.65, 52.52, 41.36, 39.61, 21.08 ppm.

HRMS-ESI: calcd. for $C_{26}H_{24}NaO_4$ $[M + Na]^+$ 423.1567, found 423.1573.



3t

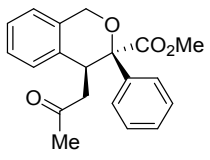
Methyl (3*R*,4*S*)-4-[2-(2-chlorophenyl)-2-oxoethyl]-6-methoxy-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylate (3t):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 2H), 7.38 (dd, *J* = 7.5 and 7.5 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.17 – 7.07 (m, 1H), 6.97 – 6.87 (m, 3H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.24 (d, *J* = 14.8 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H), 4.60 (dd, *J* = 8.6 and 2.9 Hz, 1H), 3.79 (s, 3H), 3.53 (s, 3H), 3.01 (dd, *J* = 18.1 and 8.6 Hz, 1H), 2.87 (dd, *J* = 18.1 and 2.9 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.25, 171.88, 158.16, 139.10, 138.45, 137.60, 131.47, 130.61, 130.32, 128.59, 128.16, 126.54, 125.49, 125.34, 123.61, 114.41, 113.13, 82.24, 65.35, 55.25, 52.54, 45.51, 39.86 ppm.

HRMS-ESI: calcd. for $C_{26}H_{23}ClNaO_5$ $[M + Na]^+$ 473.1126, found 473.1148.



3u

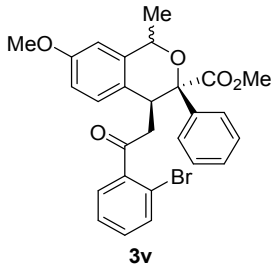
Methyl (3R,4S)-4-(2-oxopropyl)-3-phenylisochromane-3-carboxylate (3u):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 7.5 and 7.3 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.23 – 7.10 (m, 2H), 7.02 (d, *J* = 7.0 Hz, 1H), 5.29 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 15.6 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 1H), 3.49 (s, 3H), 2.42 (d, *J* = 6.0 Hz, 1H), 1.77 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.94, 171.86, 138.54, 136.48, 131.79, 129.27, 128.55, 128.15, 126.96, 126.78, 125.55, 124.22, 82.32, 65.58, 55.50, 46.11, 39.54, 30.67 ppm.

HRMS-ESI: calcd. for $C_{20}H_{20}NaO_4$ $[M + Na]^+$ 347.1254, found 348.1257.



3v

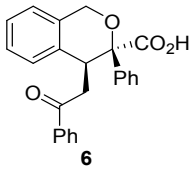
Methyl (3R,4S)-4-(2-(2-bromophenyl)-2-oxoethyl)-7-methoxy-1-methyl-3-phenylisochromane-3-carboxylate (3v):

Colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$; peaks due to the diastereomeric mixture) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.52 – 7.28 (m, 8H), 7.23 – 7.13 (m, 6H), 7.11 – 7.07 (m, 2H), 6.85 – 6.69 (m, 3H), 6.66 (s, 1H), 6.66 (s, 1H), 5.45 – 5.35 (m, 1H), 5.28 – 5.18 (m, 1H), 4.63 (dd, *J* = 9.7 and 2.9 Hz, 1H), 4.55 (dd, *J* = 8.9 and 2.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.51 (s, 3H), 3.40 (s, 3H), 3.05 – 2.90 (m, 2H), 2.88 – 2.75 (m, 2H), 1.83 (d, *J* = 6.4 Hz, 1H), 1.65 (d, *J* = 6.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; peaks due to the diastereomeric mixture) δ 202.36, 172.10, 158.56, 141.57, 138.81, 138.73, 138.10, 134.33, 133.49, 131.29, 130.75, 129.66, 128.59, 128.51, 128.34, 128.26, 128.14, 127.11, 125.87, 125.55, 118.42, 112.72, 112.12, 110.02, 83.00, 71.38, 55.19, 52.73, 52.47, 46.48, 39.21, 24.20 ppm.

HRMS-ESI: calcd. for $C_{27}H_{25}BrNaO_5$ $[M + Na]^+$ 531.0778, found 531.0801.



6

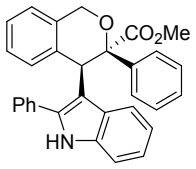
(3*R*,4*S*)-4-(2-oxo-2-phenylethyl)-3-phenyl-3,4-dihydro-1*H*-isochromene-3-carboxylic acid (6):

To a suspension of isochroman **3a** (0.2 mmol) and a mixture of water, THF and methanol (3 mL, 1:1:1) in 20 mL flask at room temperature, was added LiOH (1.0 mmol, 5.0 equiv) and allowed stir at the same temperature for five more minutes. The resultant reaction mixture was kept in a pre-heated oil bath to reflux for 12 h. Monitored the reaction by TLC until complete consumption of isochroman **3a**. The reaction mixture was cooled down to room temperature and quenched with 1 N HCl. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum, affording the crude residue. Purification of the crude mass via silica-gel flash column chromatography using the eluent, petroleum ether and ethyl acetate (80:20 to 10:90) afforded the pure acid **6** as white semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (br.s, 1H), 7.70 – 7.58 (m, 4H), 7.51 (t, J = 7.3 Hz, 1H), 7.45 – 7.32 (m, 4H), 7.27 (t, J = 7.0 Hz, 1H), 7.22 – 7.02 (m, 4H), 5.26 (d, J = 15.3 Hz, 1H), 5.22 (d, J = 15.3 Hz, 1H), 4.50 – 4.40 (m, 1H), 3.03 (d, J = 17.1 and 8.8 Hz, 1H), 2.72 (d, J = 17.1 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 198.18, 172.48, 139.01, 136.52, 136.47, 133.13, 132.50, 128.81, 128.56, 128.34, 127.88, 127.69, 126.76, 126.20, 125.34, 124.40, 81.64, 64.93, 41.11, 39.5 ppm.

HRMS-ESI: calcd. for $C_{24}H_{20}NaO_4$ $[M + Na]^+$ 395.1259, found 395.1252.



7

Methyl (3R,4R)-3-phenyl-4-(2-phenyl-1H-indol-3-yl)-3,4-dihydro-1H-isochromene-3-carboxylate (7):

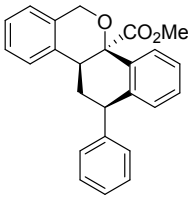
To an oven dried vial (20 mL) at room temperature were added isochroman **3a** (0.2 mmol), $PhNHNH_2$.HCl (0.4 mmol, 2 equiv), DCE (1 mL) and TfOH (1.8 mmol, 9 equiv) followed by

ethanol (1 mL) and this suspension was allowed to stir at the same temperature for 5 more minutes. The resultant reaction mixture was allowed to stir at 80 °C for 48 h. Monitored the reaction by TLC until complete conversion. The reaction mixture was cooled down to room temperature and quenched with aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum, affording the crude residue. Purification of the crude mass via silica-gel flash column chromatography using the eluent, petroleum ether and ethyl acetate (90:10 to 80:20) afforded the pure indole derivative **7** as pale yellow semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (br.s, 1H), 7.90 – 6.50 (m, 18H), 5.45 (d, J = 16.3 Hz, 1H), 5.43 (s, 2H), 5.14 (d, J = 16.3 Hz, 1H), 3.53 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.23, 139.52, 136.64, 135.92, 135.75, 133.09, 132.23, 129.44, 128.46, 127.87, 127.24, 127.13, 126.90, 126.64, 126.14, 124.31, 123.94, 120.90, 120.71, 118.47, 111.42, 110.74, 84.31, 64.85, 52.54, 39.8 ppm.

HRMS-ESI: calcd. for $C_{31}H_{25}NNaO_3$ $[M + Na]^+$ 482.1727, found 482.1724.



8

Methyl (4b*R*,10b*S*,12*R*)-12-phenyl-6,10b,11,12-tetrahydro-4b*H*-dibenzo[c,*h*]chromene-4b-carboxylate (8):

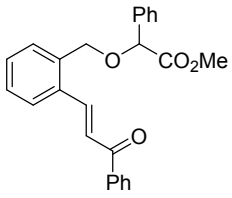
To a solution of isochroman **3a** (0.2 mmol) in methanol (4 mL) at 0 °C, was added $NaBH_4$ (0.6 mmol) in portions for 15 minutes. The resulted reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered through a small pad of silica gel and concentrated under reduced pressure. Traces of solvents were removed under high vacuum. To this crude mass in dry DCM (3 mL) at –20 °C, was added anhydrous $FeCl_3$ (0.24 mmol), stirred the reaction for 1.5 h at the same temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with DCM (3 × 20 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected for ^{1}H-NMR to determine the

diastereoselective ratio (dr). Further, purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 93:7) furnished the product **8** as white semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.31 (dd, *J* = 7.3 and 7.0 Hz, 2H), 7.27 – 7.12 (m, 8H), 7.07 – 6.98 (m, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 5.50 (d, *J* = 15.4 Hz, 1H), 5.02 (d, *J* = 15.4 Hz, 1H), 4.34 – 4.20 (m, 1H), 3.73 (d, *J* = 12.8 Hz, 1H), 3.61 (s, 3H), 2.29 (dq, *J* = 12.8 and 1.8 Hz, 1H), 2.22 – 2.10 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.14, 145.20, 140.25, 135.26, 135.11, 132.58, 129.56, 128.87, 128.71, 128.57, 127.78, 126.99, 126.84, 126.60, 124.09, 77.92, 65.56, 52.39, 47.29, 40.55, 38.84 ppm.

HRMS-ESI: calcd. for $C_{25}H_{22}NaO_3$ $[M + Na]^+$ 393.1467, found 393.1502.



4

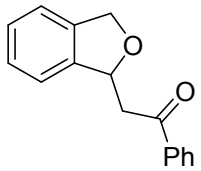
Methyl ({2-[(1E)-3-oxo-3-phenylprop-1-enyl]benzyl}oxy)(phenyl)acetate (4):

To a flame-dried vial, at room temperature, under an inert atmosphere, were added [Rh]-catalyst (0.002 mmol) and 4 Å molecular sieves (150 mg) followed by DCM (1.0 mL). To this well-stirred suspension at stated temperature, was added a solution of alcohol ketone **1** (48 mg, 0.2 mmol) and diazo-acetate **2** (0.4 mmol, 2.0 eq) in 1.5 mL of DCM for one hour through a syringe pump. After completion of the addition, stirring was continued at the same temperature for two hours. Progress of the reaction was monitored by TLC until complete consumption of alcohol ketone **1**. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. Purification of the crude mixture by silica gel flash chromatography (ethyl acetate/petroleum ether, 98:2 to 94:6) afforded the insertion product **4** as Pale yellow viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 15.6 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.27 (m, 11H), 4.99 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 3.71 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.54, 170.99, 141.70, 138.04, 136.51, 135.99, 134.46, 132.77, 130.11, 129.96, 128.80, 128.67, 128.59, 127.65, 127.35, 127.03, 124.57, 80.40, 69.33,

52.35 ppm.



5

2-(1,3-Dihydro-2-benzofuran-1-yl)-1-phenylethanone (5):[6]

To a flame-dried vial, at room temperature, under an inert atmosphere, were added alcohol ketone **1a** (0.2 mmol), $Cu(OTf)_2$ (0.02 mmol) and 4 Å molecular sieves (150 mg) followed by DCM (2.0 mL). The resultant reaction mixture was stirred at 40 °C for 12 h. Progress of the reaction was monitored by TLC until complete consumption of alcohol ketone **1**. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. Purification of the crude mass by silica gel flash chromatography (ethyl acetate/petroleum ether, 98:2 to 94:6) gave the isobenzofuran **5** as a white semi-solid.

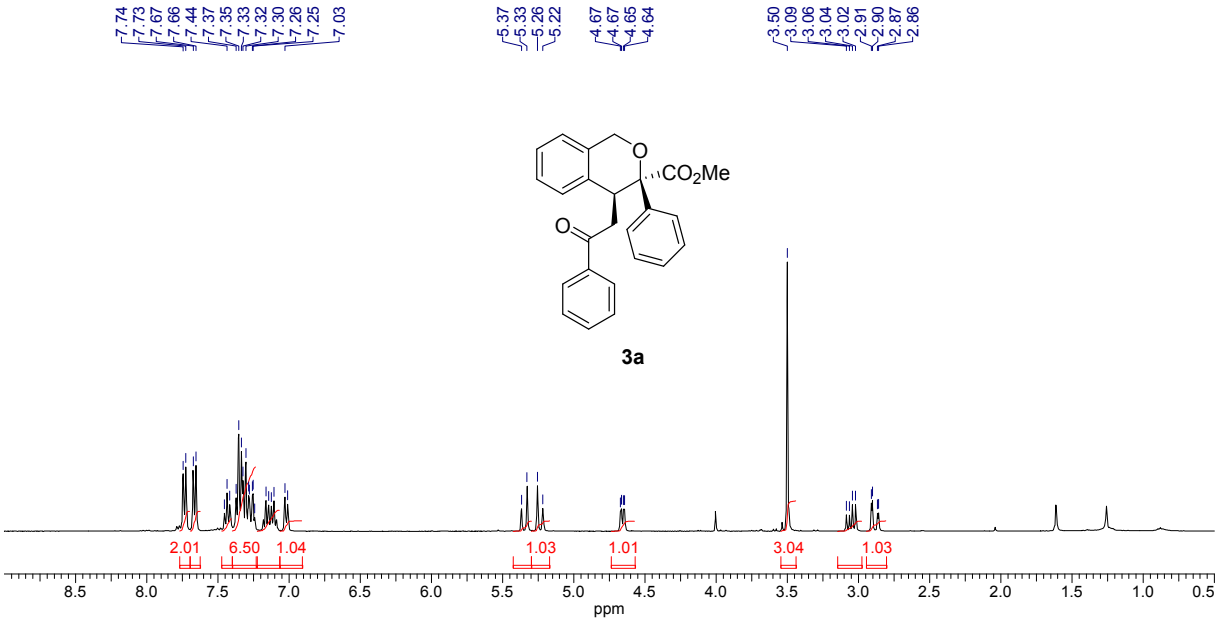
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.43 (dd, *J* = 7.4 and 7.3 Hz, 2H), 7.35 – 7.15 (m, 4H), 5.89 (dd, *J* = 7.3 and 5.0 Hz, 1H), 5.13 (dd, *J* = 12.2 and 1.6 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 3.52 (dd, *J* = 16.7 and 7.3 Hz, 1H), 3.32 (dd, *J* = 16.7 and 5.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.66, 141.29, 139.09, 136.91, 133.09, 128.46, 128.13, 127.62, 127.30, 121.35, 120.89, 79.99, 72.46, 45.45 ppm.

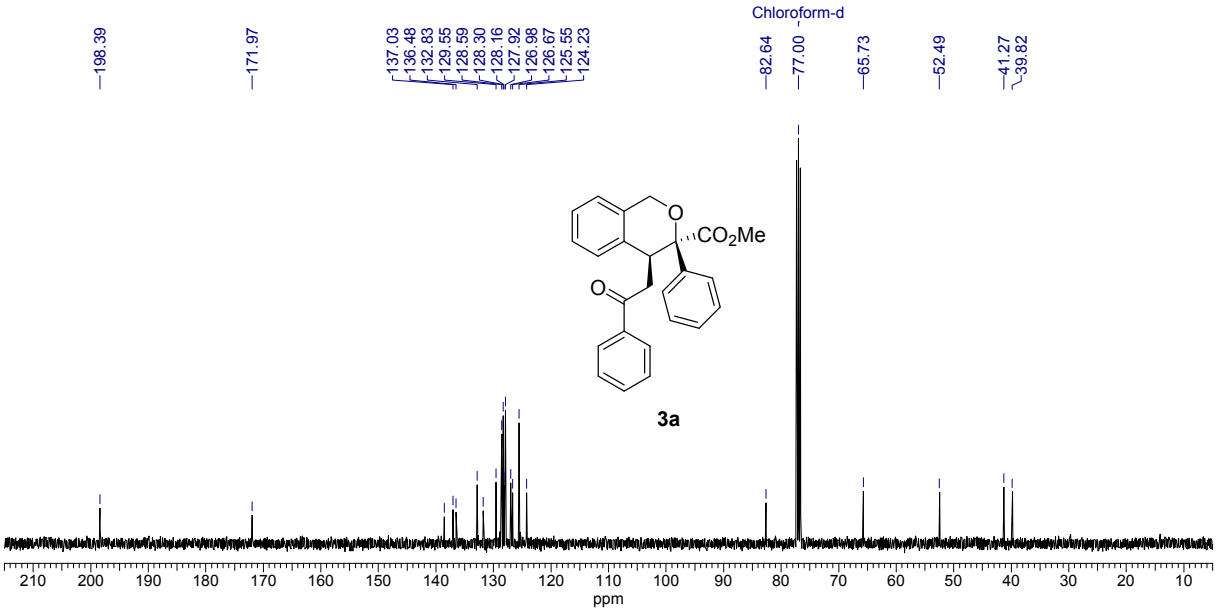
5. References:

(1) C. C. Cosner, P. J. Cabrera, K. M. Byrd, A. M. A. Thomas and P. Helquist, *Org. Lett.*, 2011, **13**, 2071.
(2) J. Krishna, P. Niharika and G. Satyanarayana, *RSC Adv.*, 2015, **5**, 26749.
(3) H. Madhurima, J. Krishna and G. Satyanarayana, *Synthesis*, 2015, **47**, 1245.
(4) Y. Iwama, K. Okano, K. Sugimoto and H. Tokuyama, *Org. Lett.*, 2012, **14**, 2320.
(5) R. Shintani, G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 1057.
(6) X. Liu, B. Sun, Z. Xie, X. Qin, L. Liu and H. Lou, *J. Org. Chem.*, 2013, **78**, 3104.

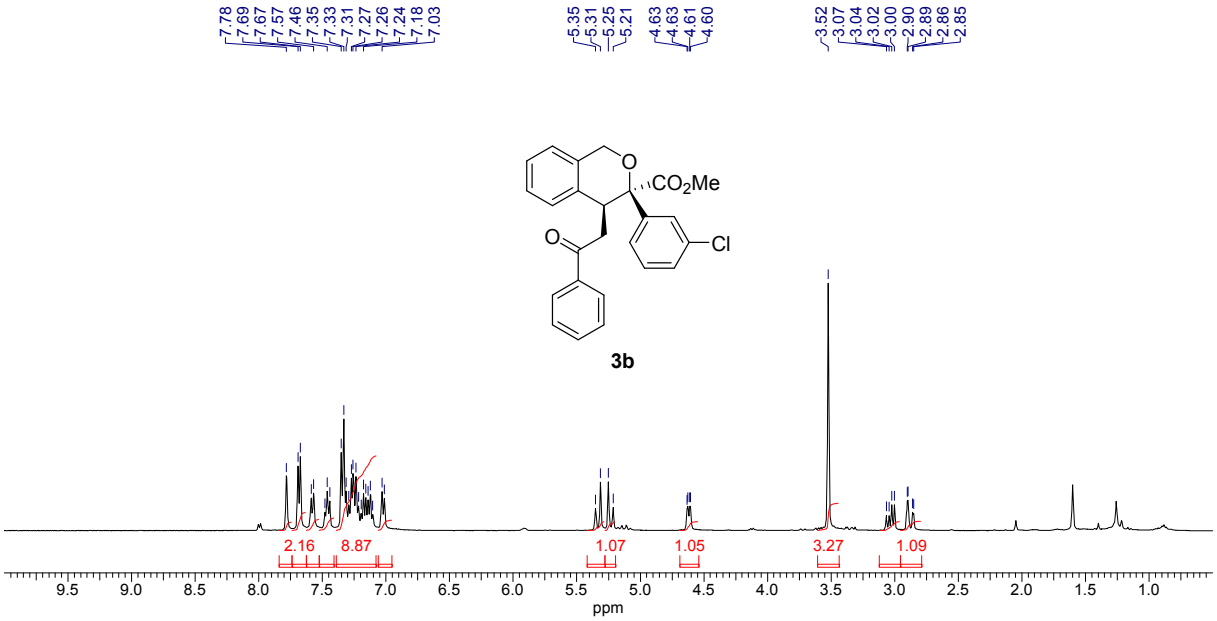
6. NMR Spectra



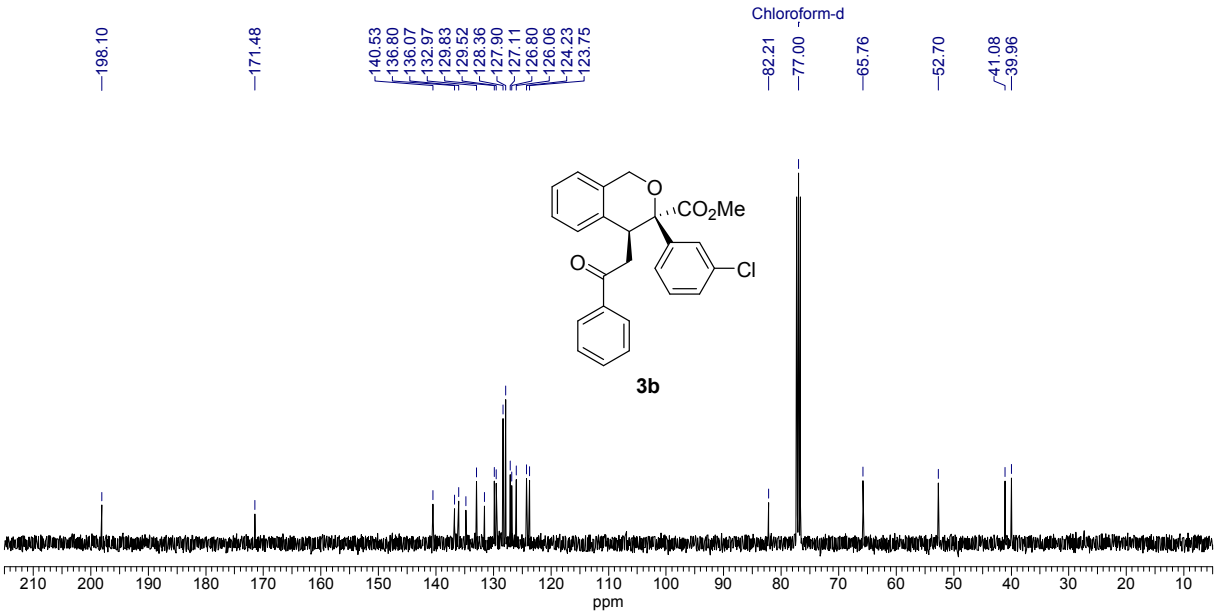
^{1}H NMR (400 MHz) spectrum of compound **3a** in $CDCl_3$



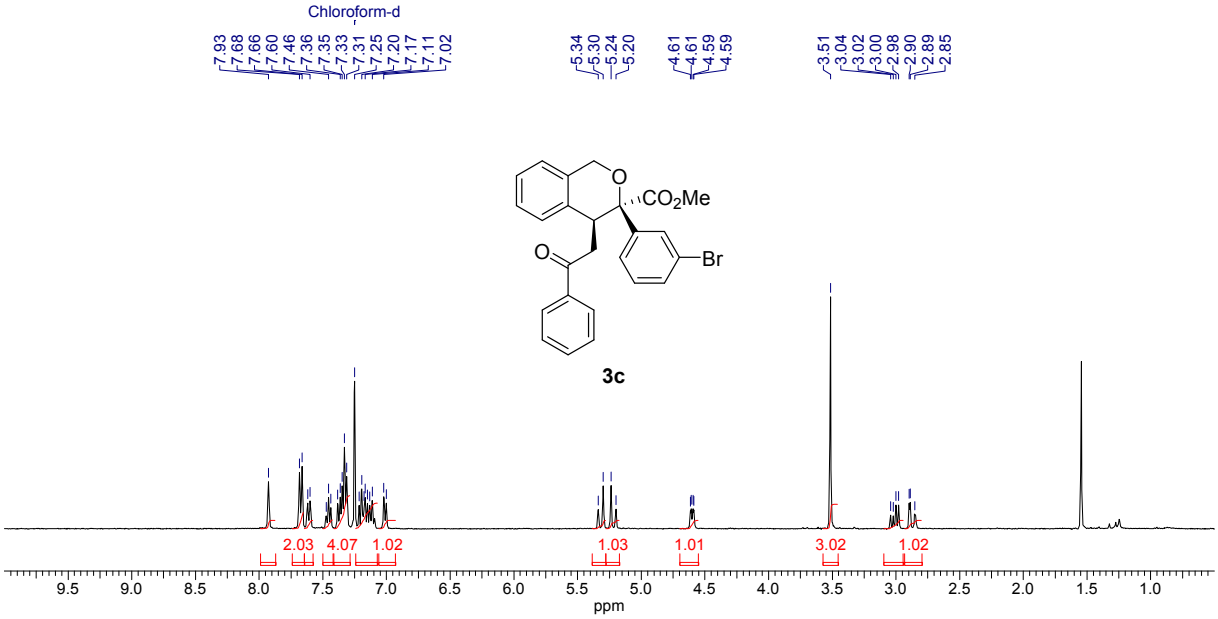
^{13}C NMR (100 MHz) spectrum of compound **3a** in $CDCl_3$



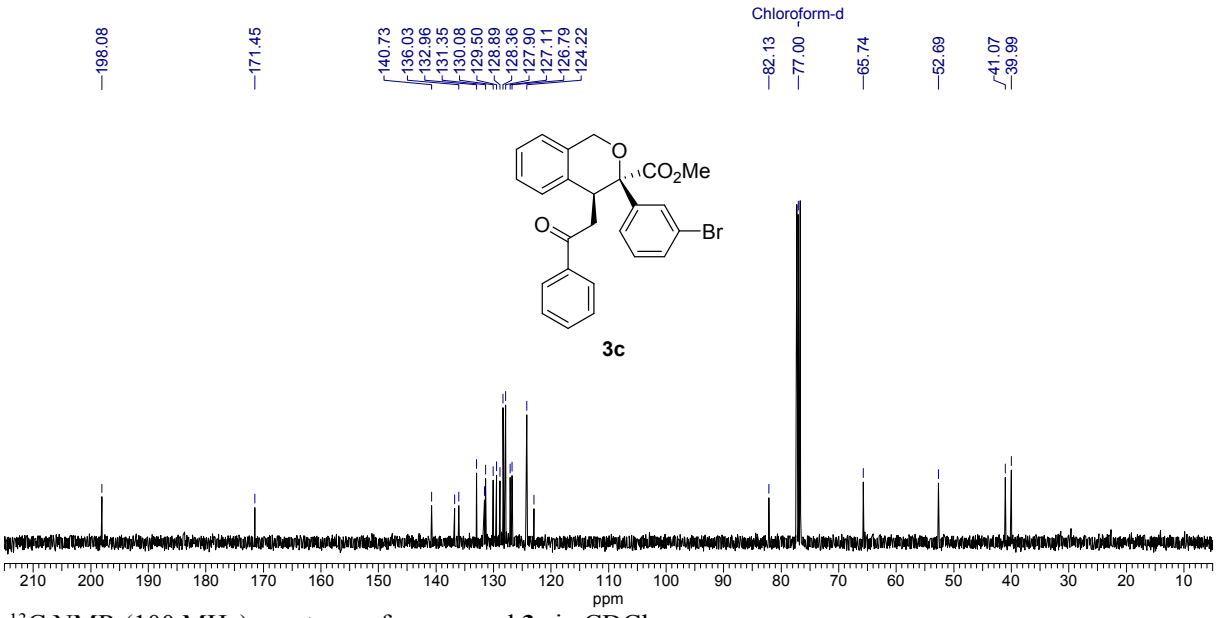
^{1}H NMR (400 MHz) spectrum of compound **3b** in $CDCl_3$



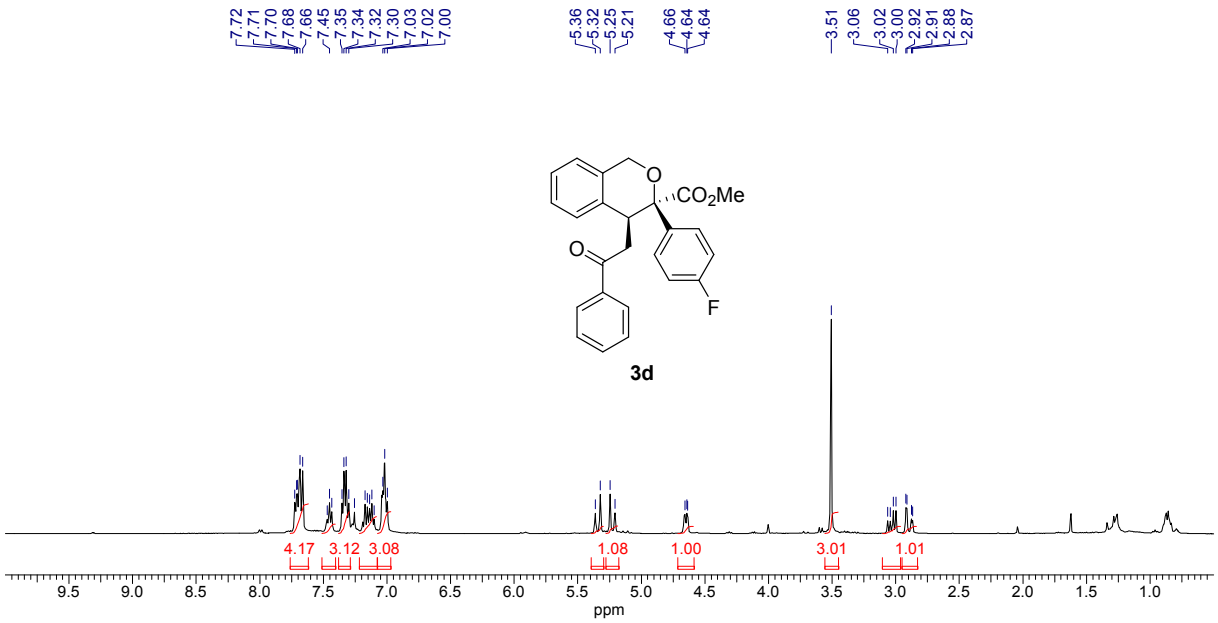
^{13}C NMR (100 MHz) spectrum of compound **3b** in $CDCl_3$



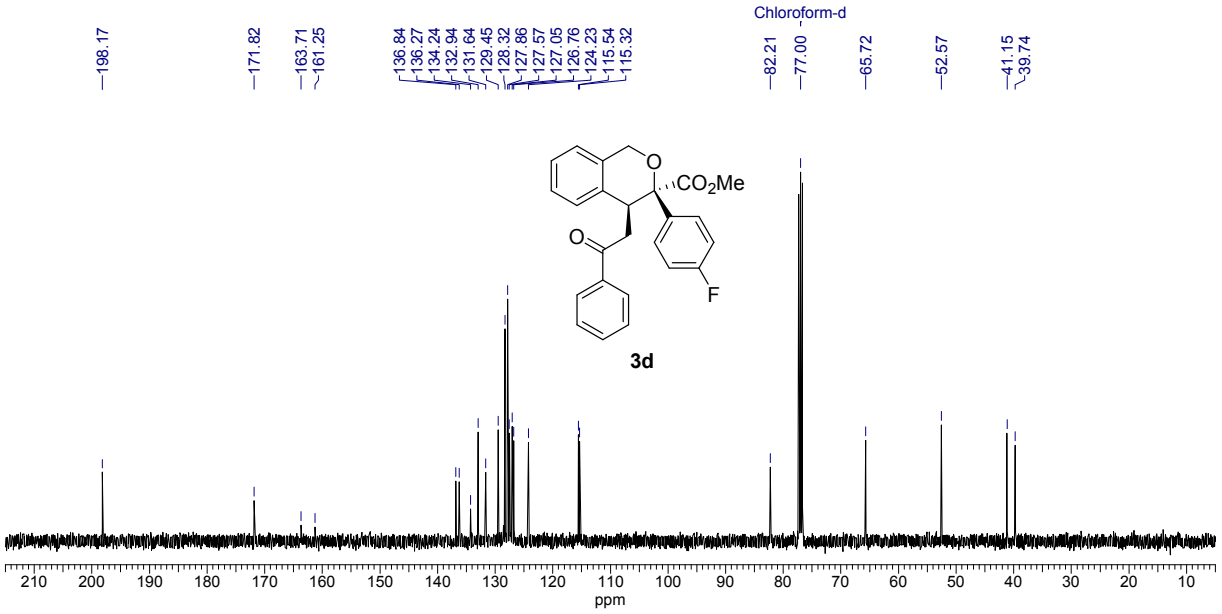
^{1}H NMR (400 MHz) spectrum of compound **3c** in $CDCl_3$



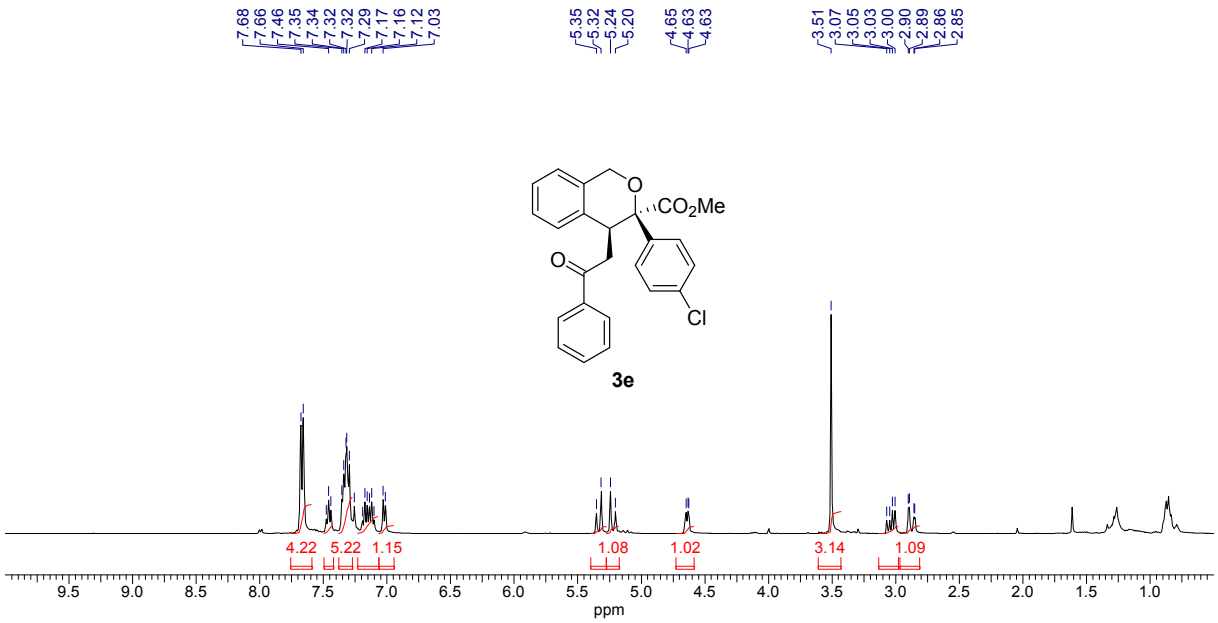
^{13}C NMR (100 MHz) spectrum of compound **3c** in $CDCl_3$



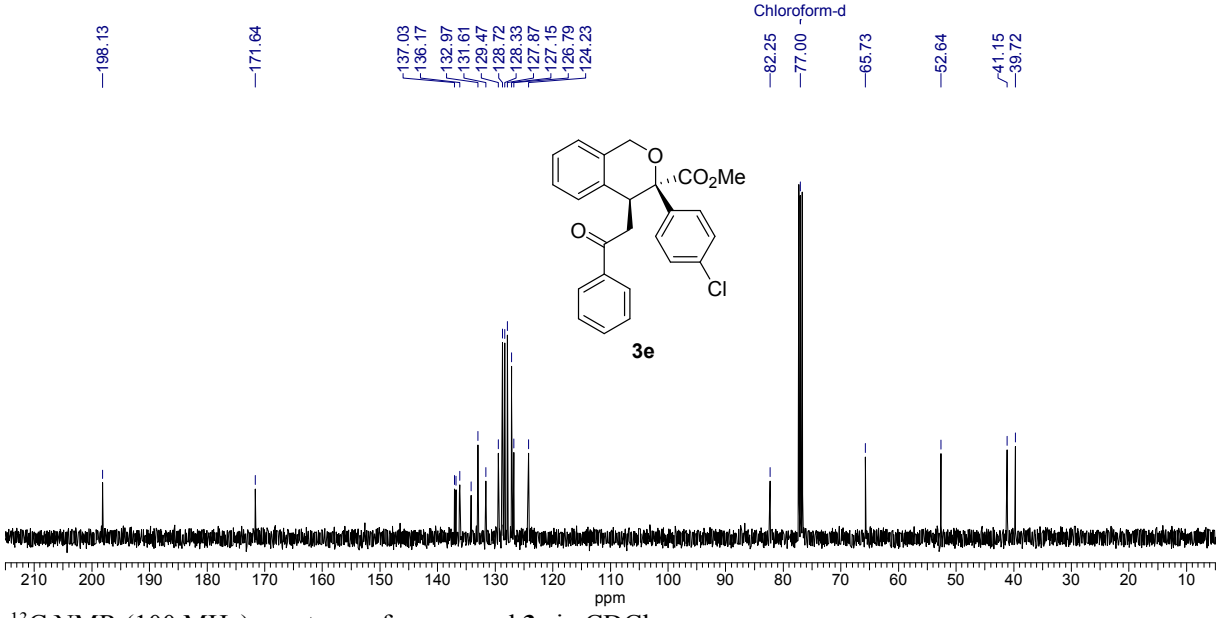
^{1}H NMR (400 MHz) spectrum of compound **3d** in $CDCl_3$



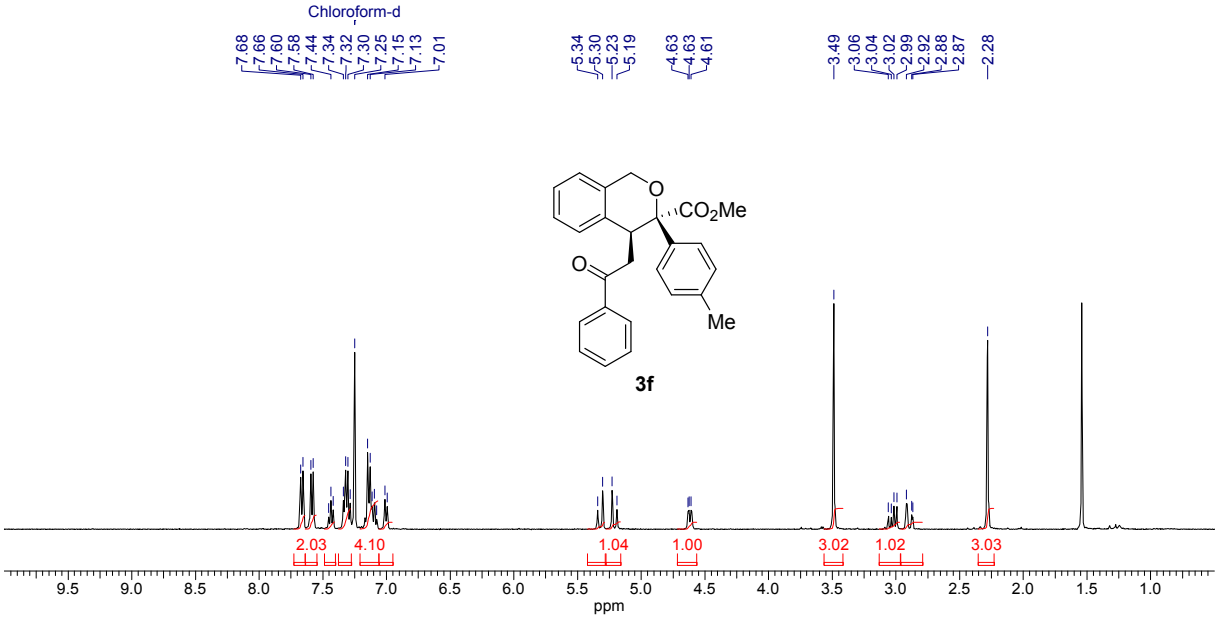
^{13}C NMR (100 MHz) spectrum of compound **3d** in $CDCl_3$



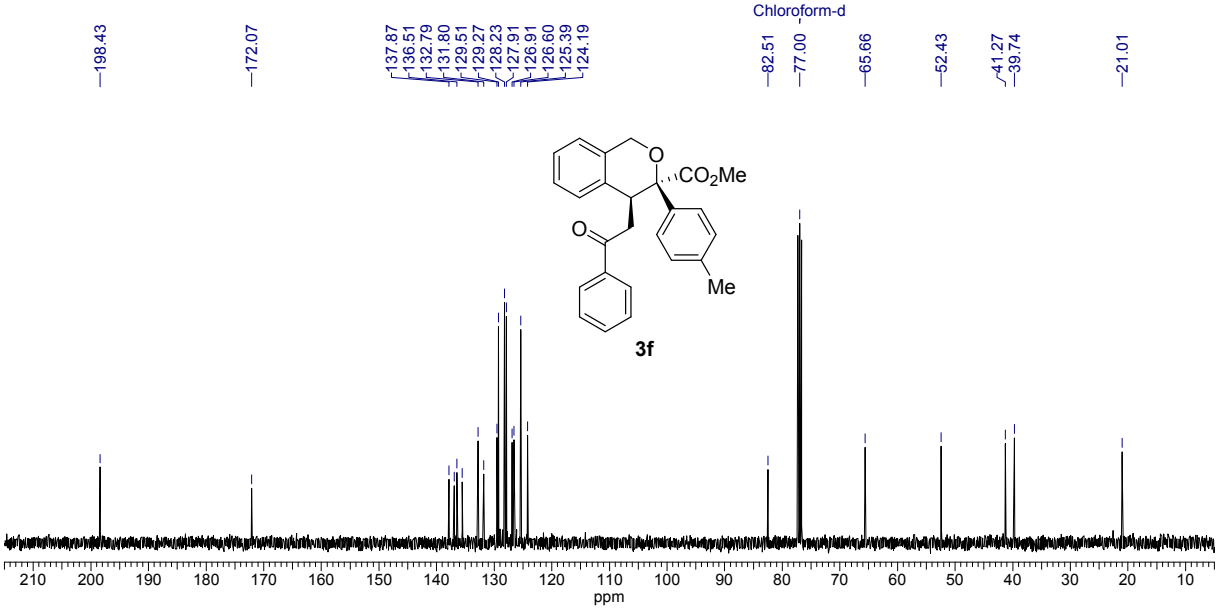
^{1}H NMR (400 MHz) spectrum of compound **3e** in $CDCl_3$



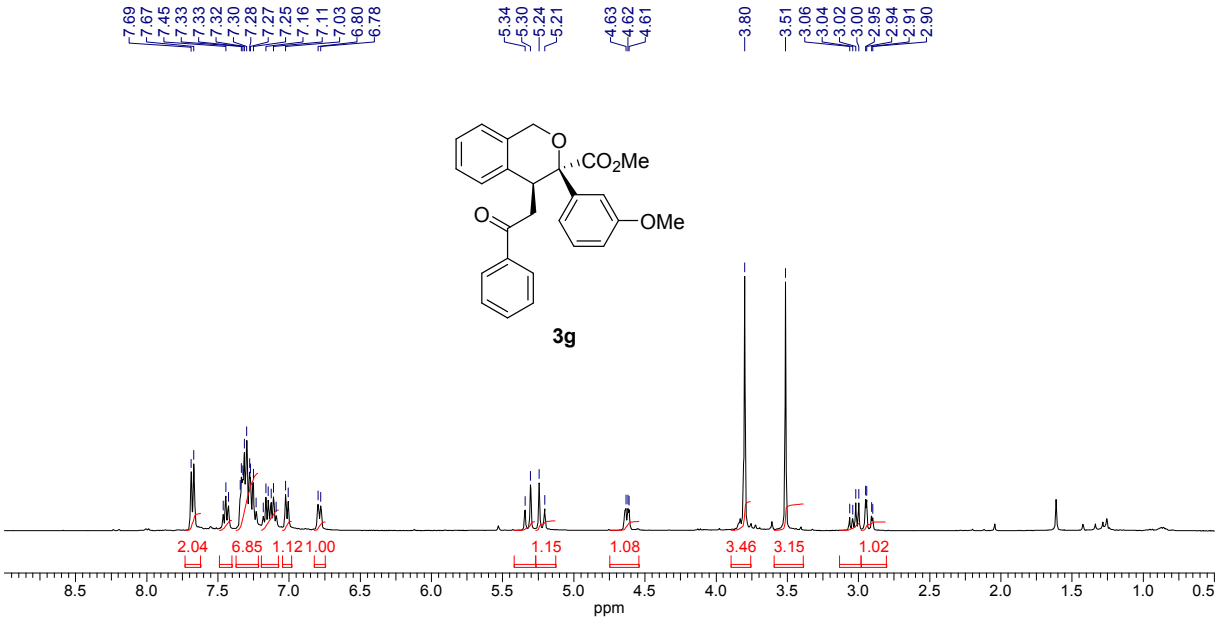
^{13}C NMR (100 MHz) spectrum of compound **3e** in $CDCl_3$



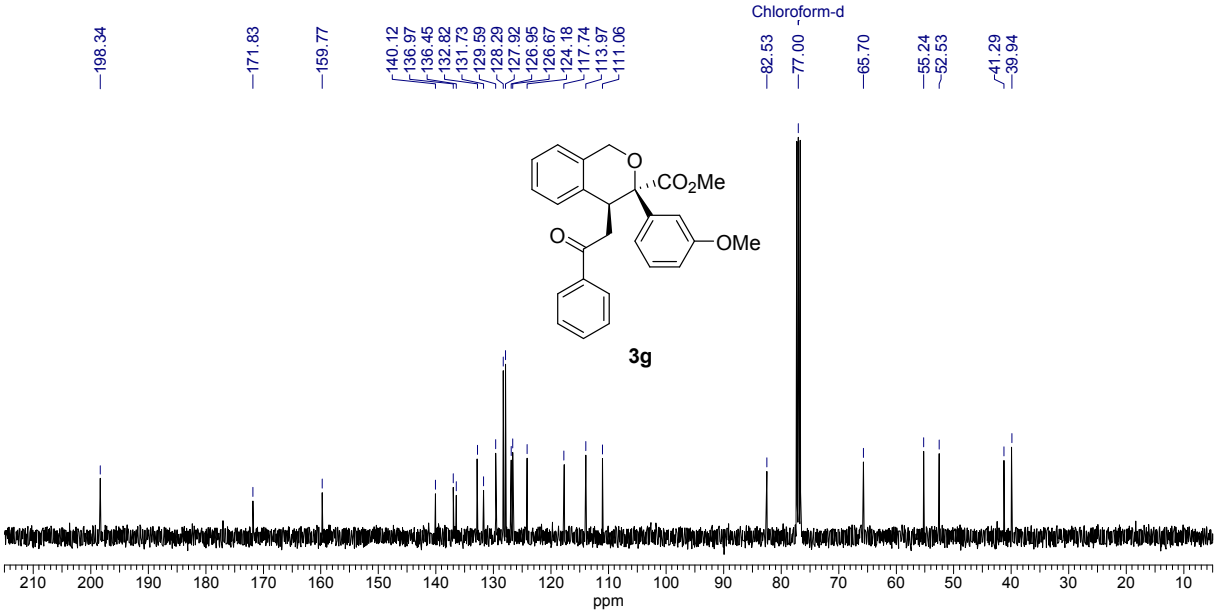
^{1}H NMR (400 MHz) spectrum of compound **3f** in $CDCl_3$



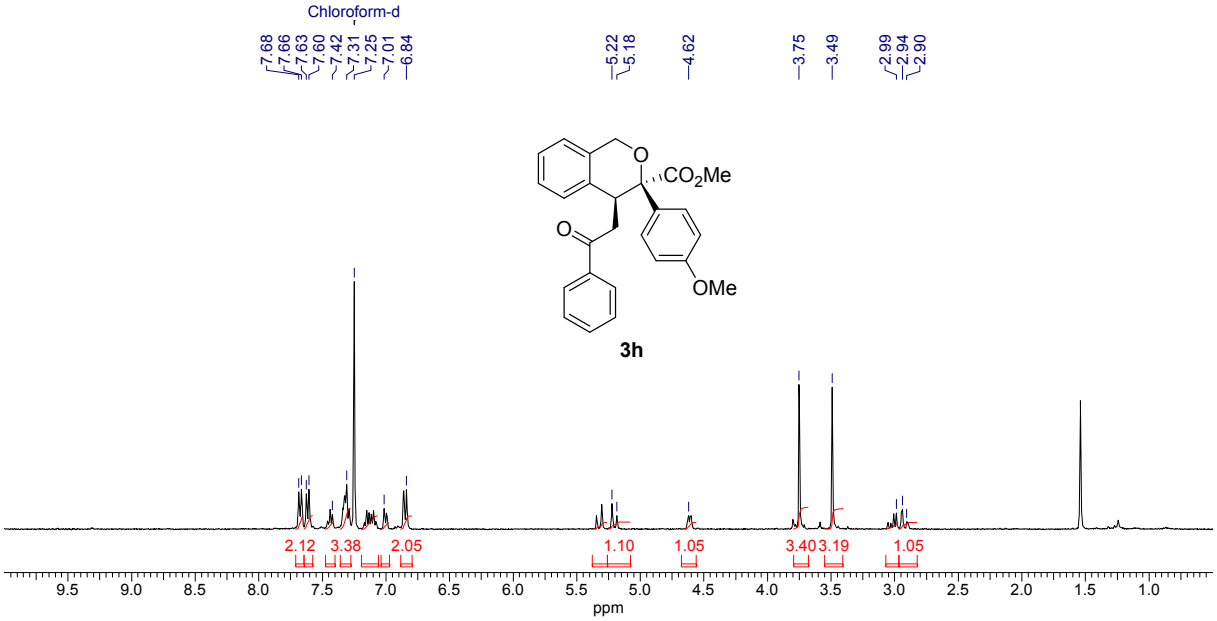
^{13}C NMR (100 MHz) spectrum of compound **3f** in $CDCl_3$



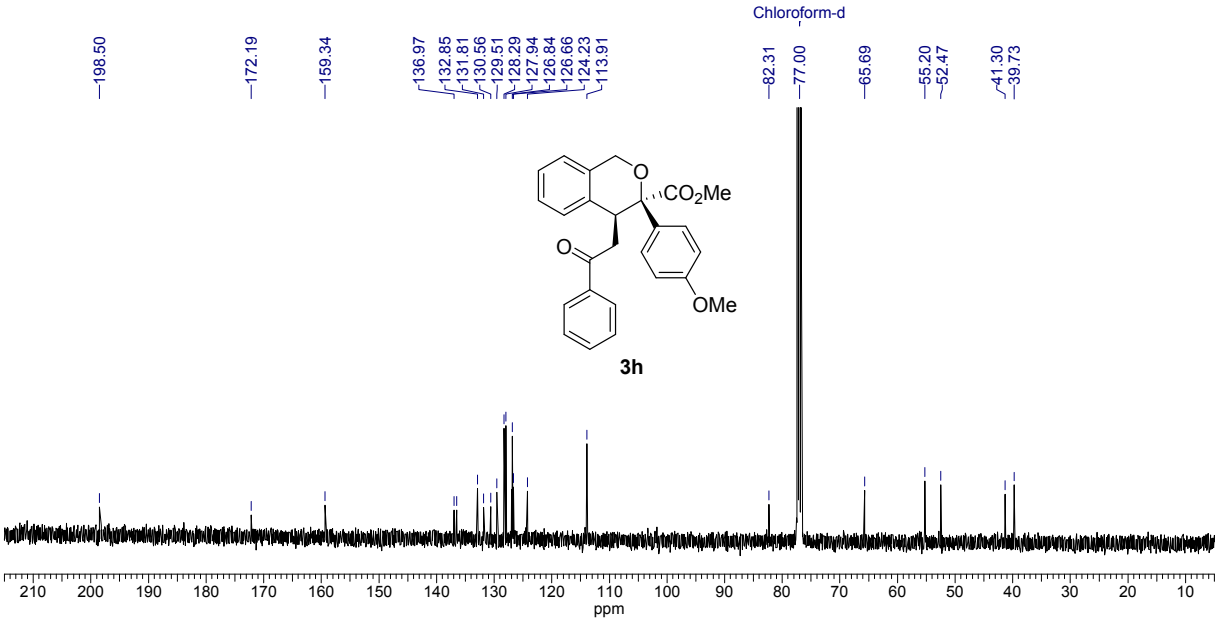
^{1}H NMR (400 MHz) spectrum of compound **3g** in $CDCl_3$



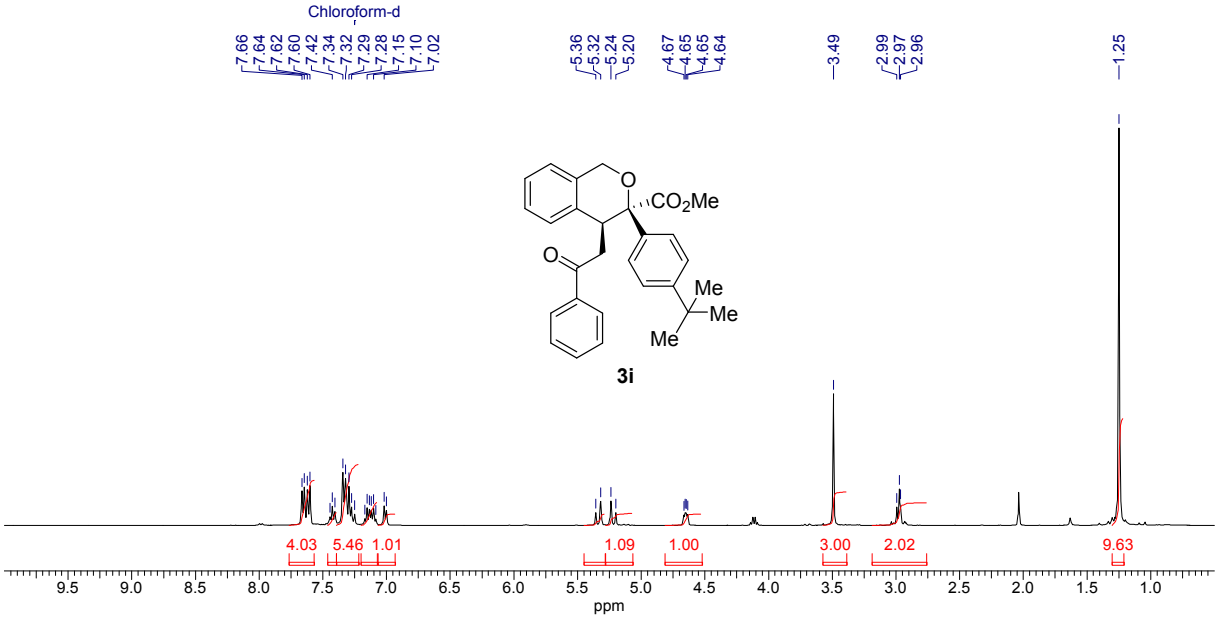
^{13}C NMR (100 MHz) spectrum of compound **3g** in $CDCl_3$



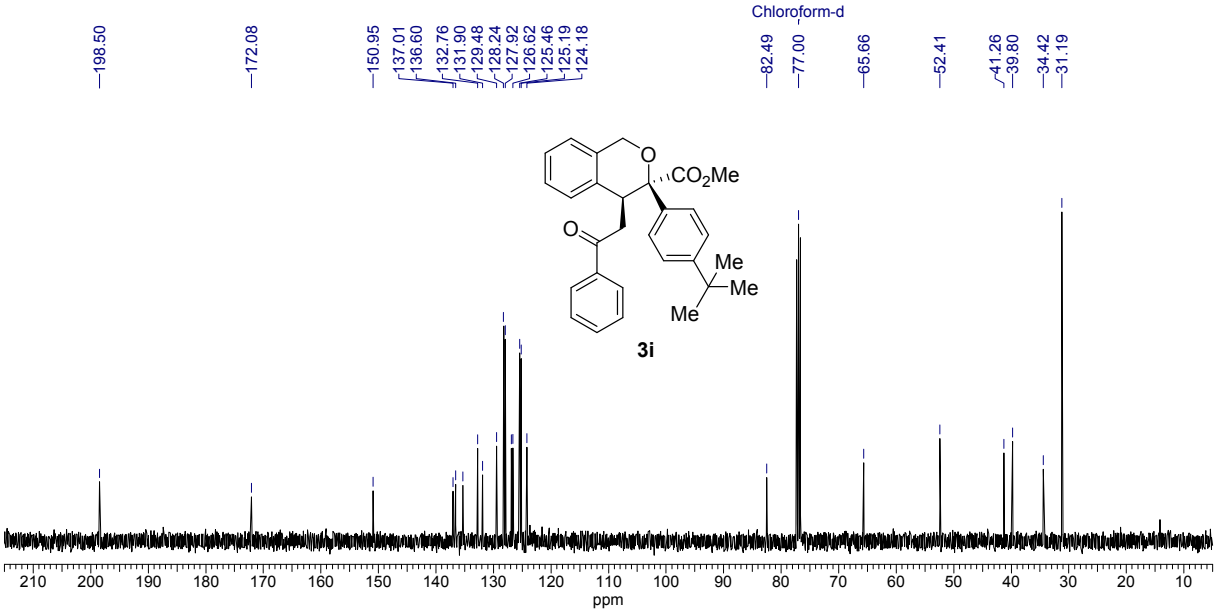
^{1}H NMR (400 MHz) spectrum of compound **3h** in $CDCl_3$



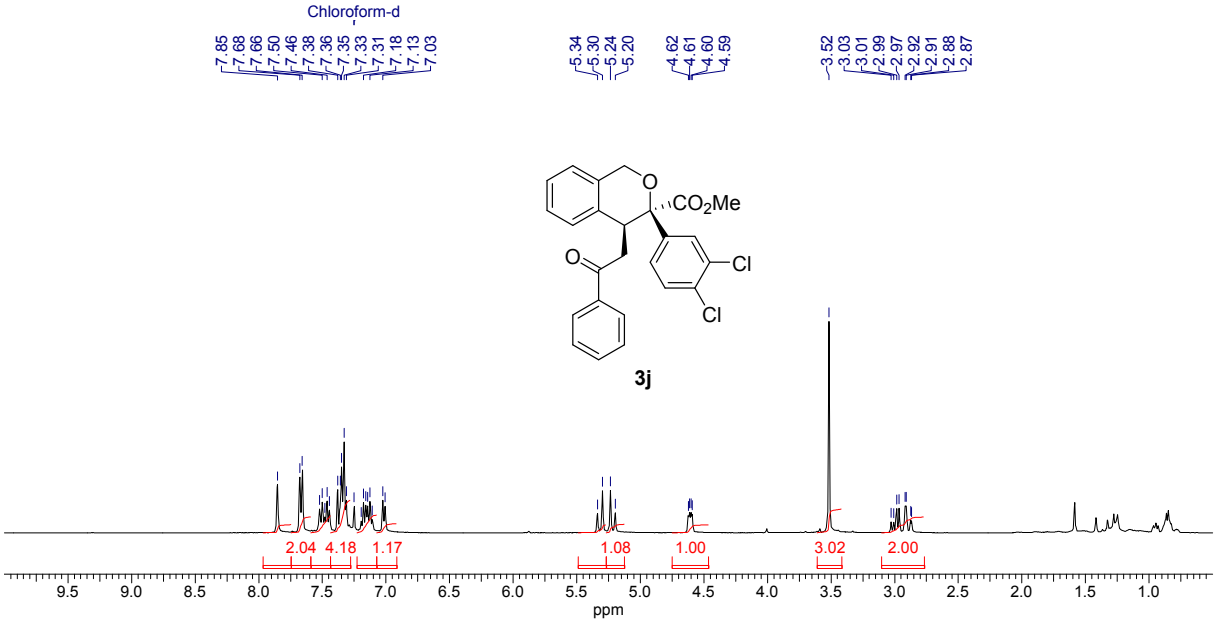
^{13}C NMR (100 MHz) spectrum of compound **3h** in $CDCl_3$



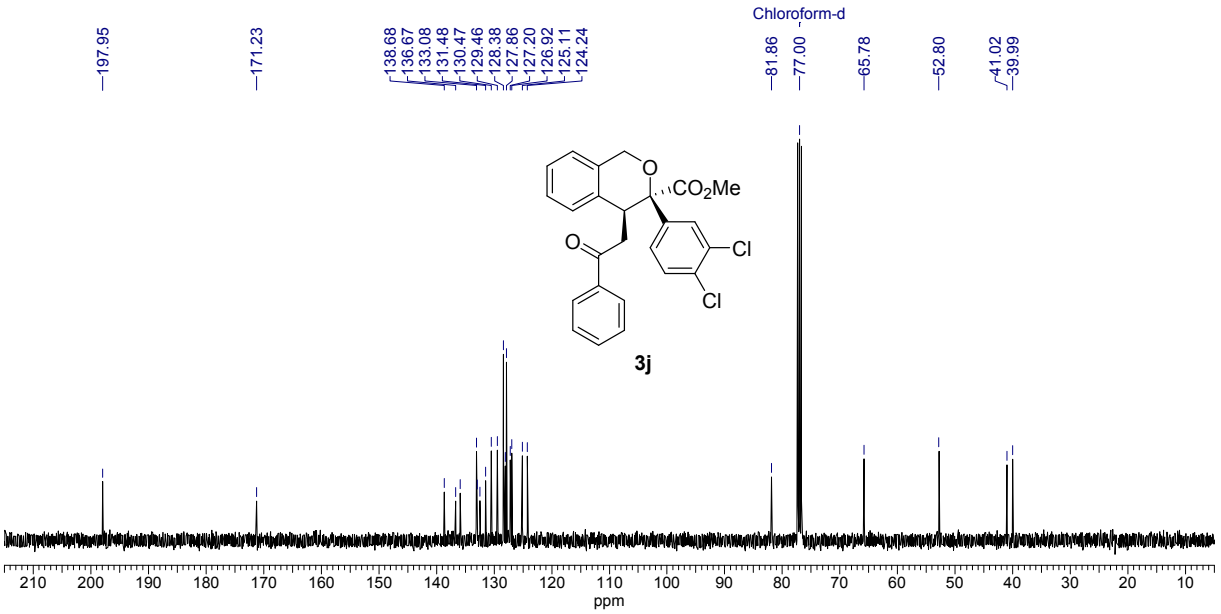
^{1}H NMR (400 MHz) spectrum of compound **3i** in $CDCl_3$



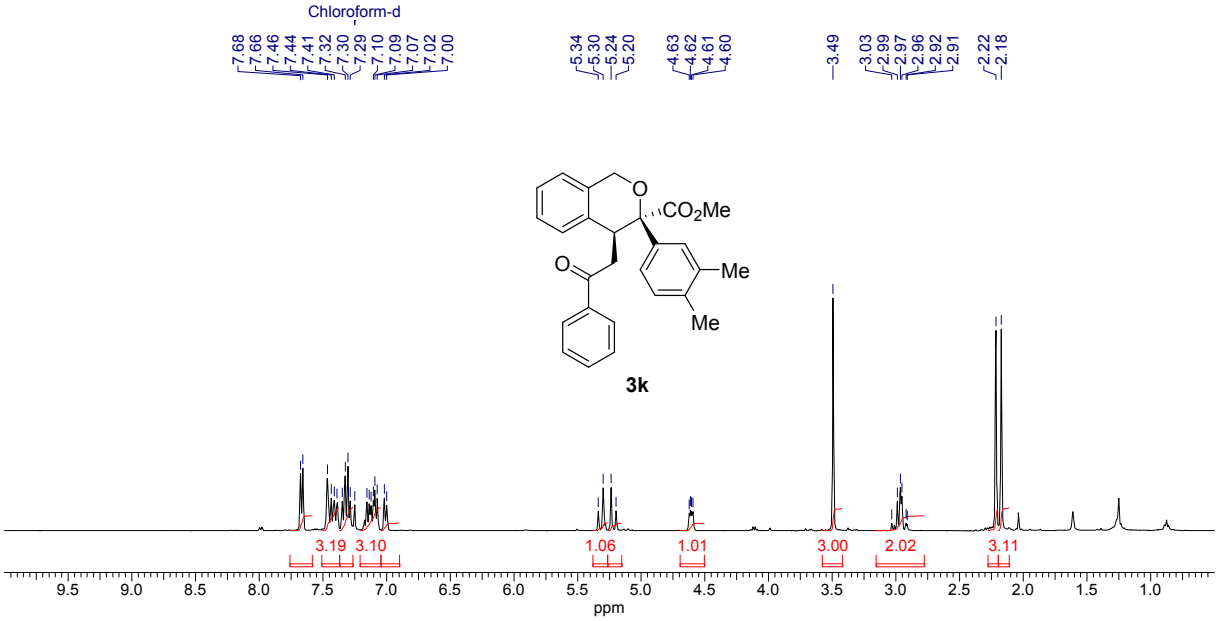
^{13}C NMR (100 MHz) spectrum of compound **3i** in $CDCl_3$



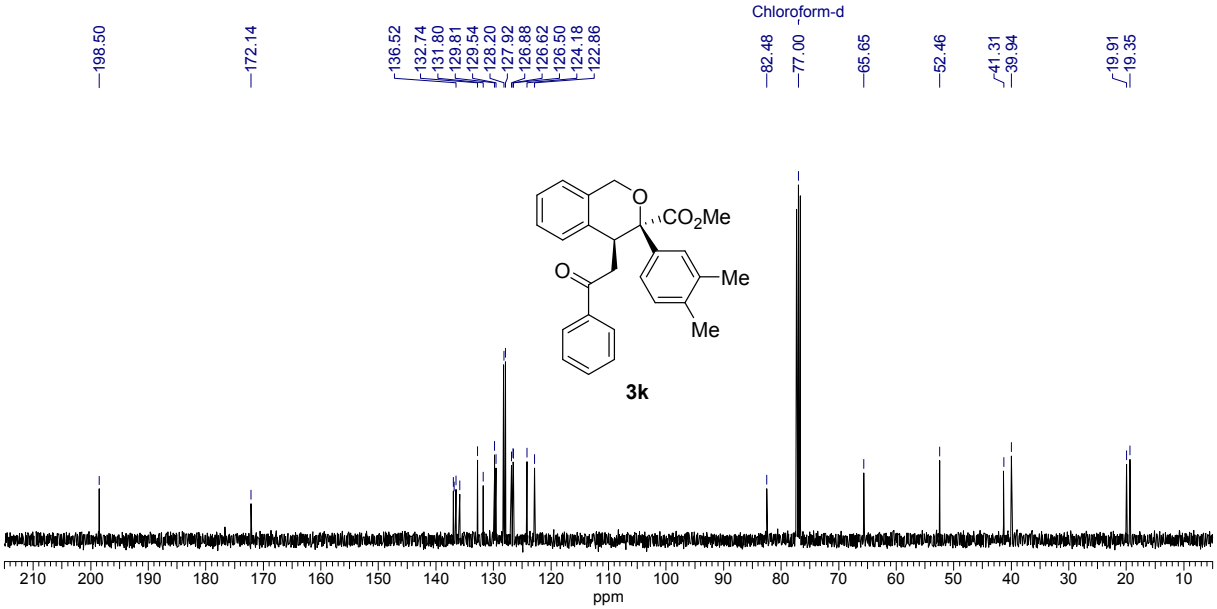
^{1}H NMR (400 MHz) spectrum of compound **3j** in $CDCl_3$



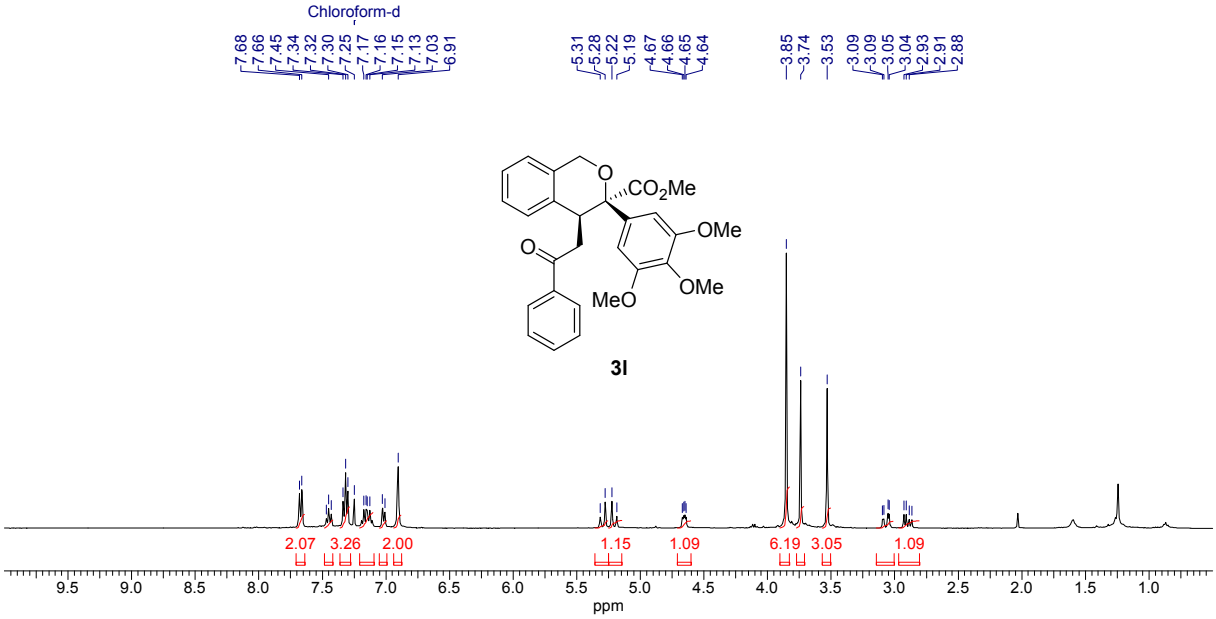
^{13}C NMR (100 MHz) spectrum of compound **3j** in $CDCl_3$



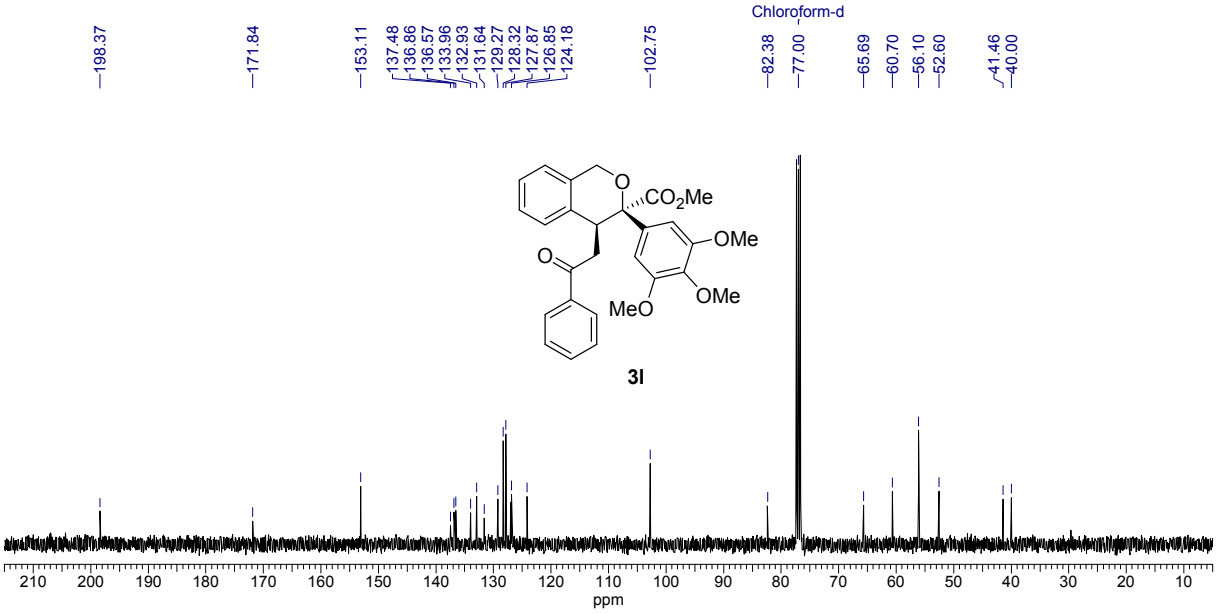
^{1}H NMR (400 MHz) spectrum of compound **3k** in $CDCl_3$



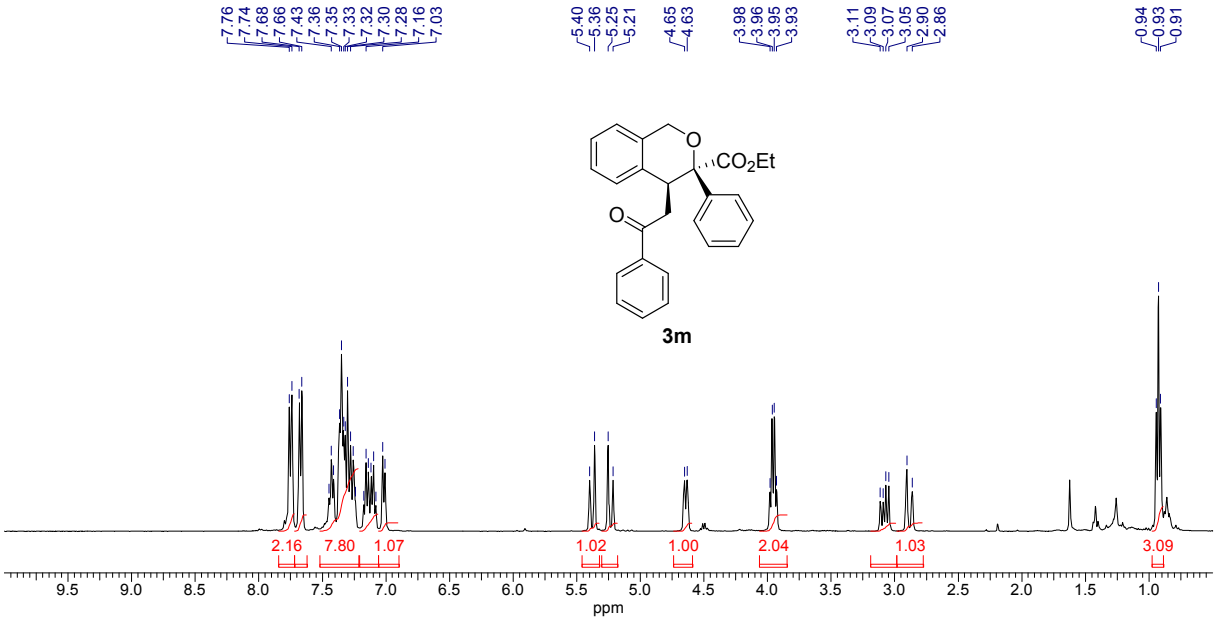
^{13}C NMR (100 MHz) spectrum of compound **3k** in $CDCl_3$



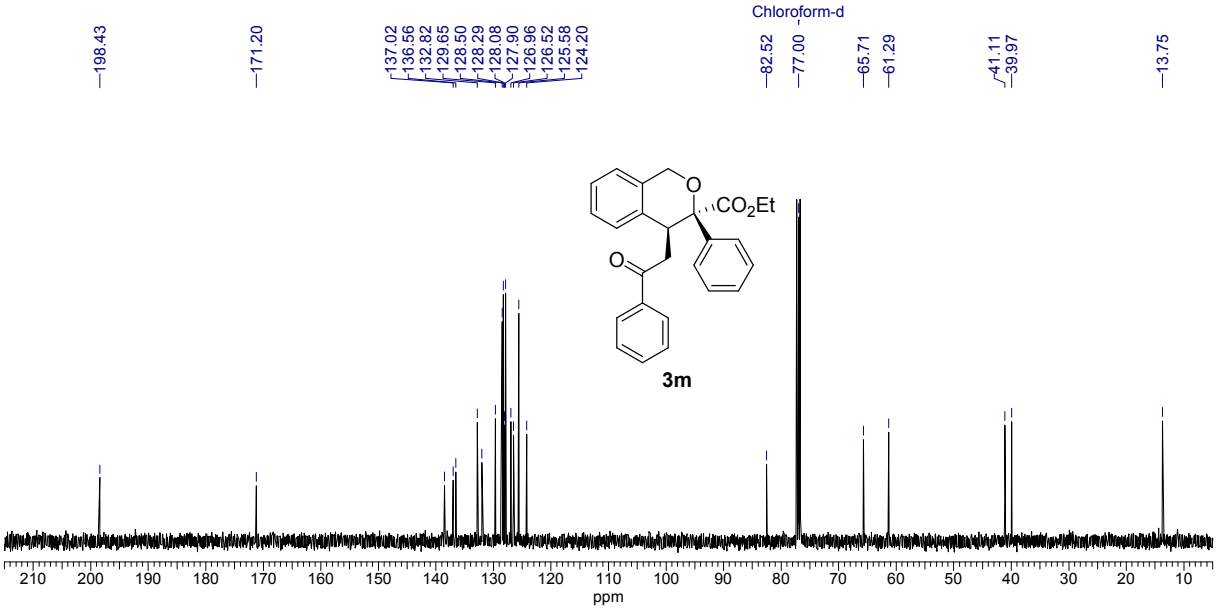
^{1}H NMR (400 MHz) spectrum of compound **3l** in $CDCl_3$



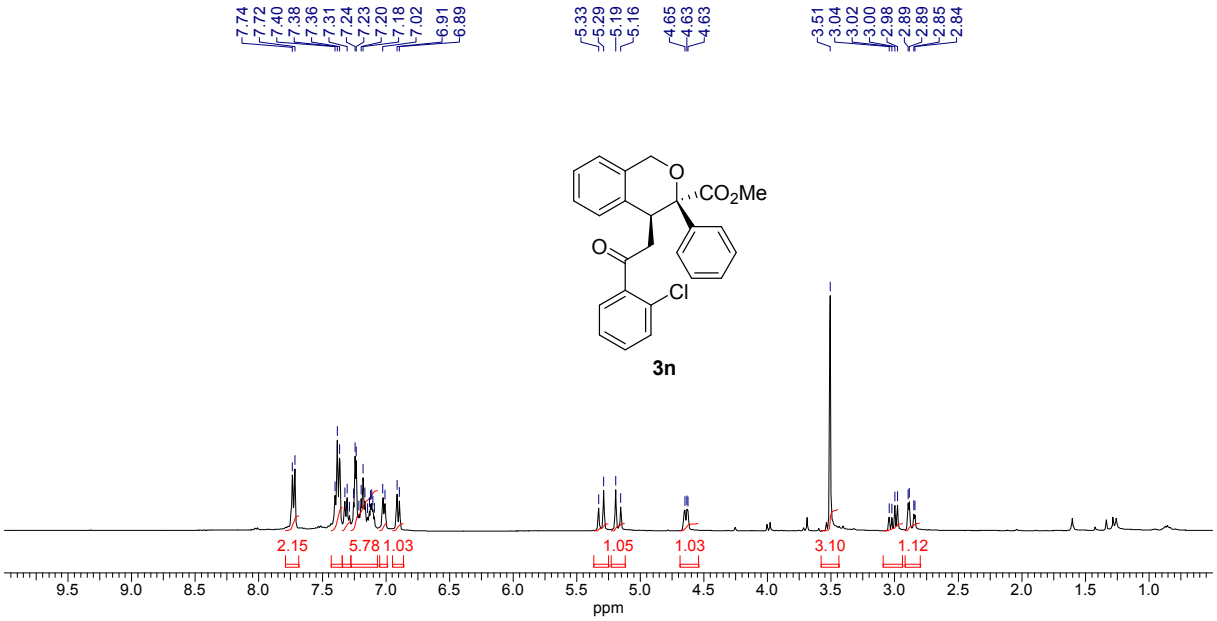
^{13}C NMR (100 MHz) spectrum of compound **3l** in $CDCl_3$



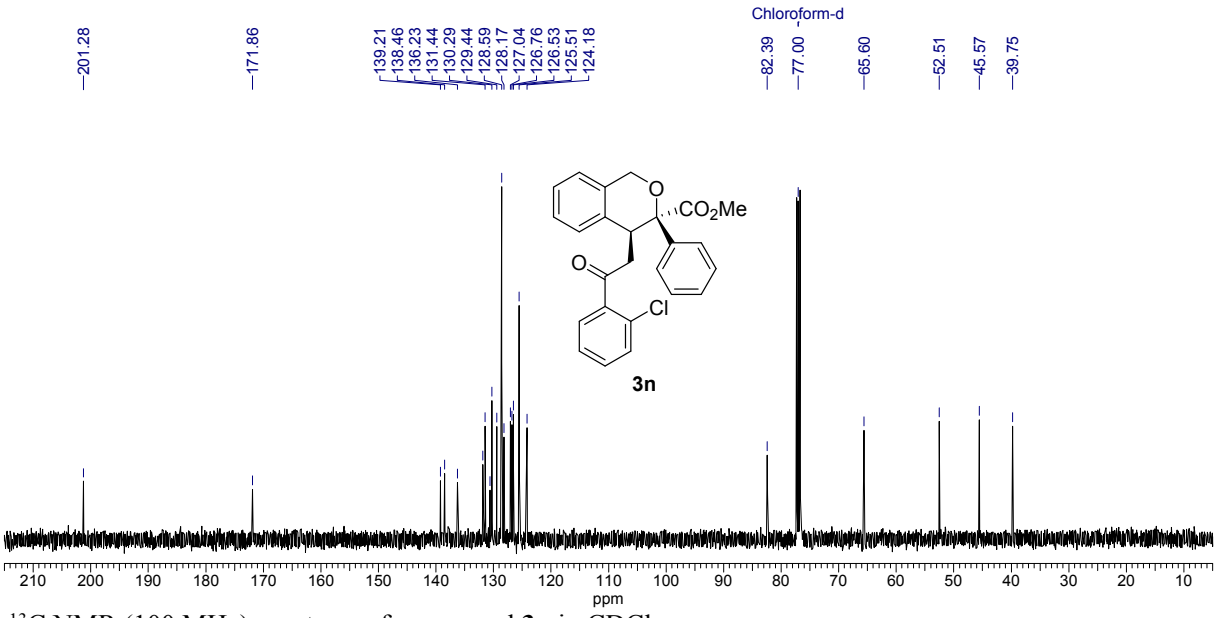
^{1}H NMR (400 MHz) spectrum of compound **12m** in $CDCl_3$



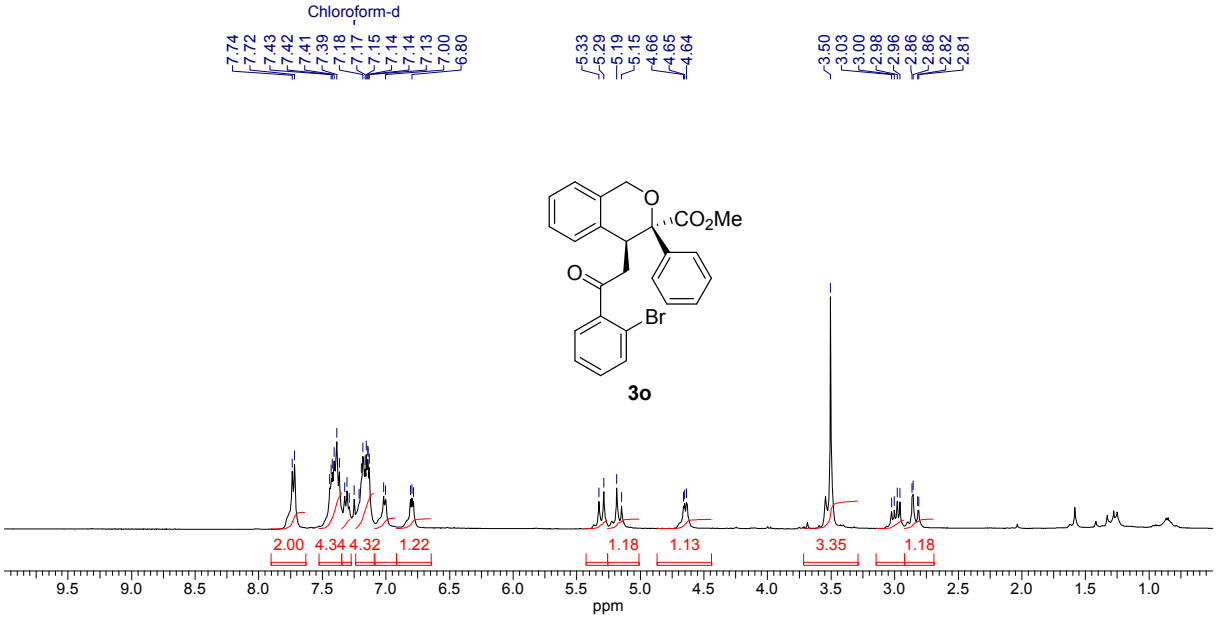
^{13}C NMR (100 MHz) spectrum of compound **3m** in $CDCl_3$



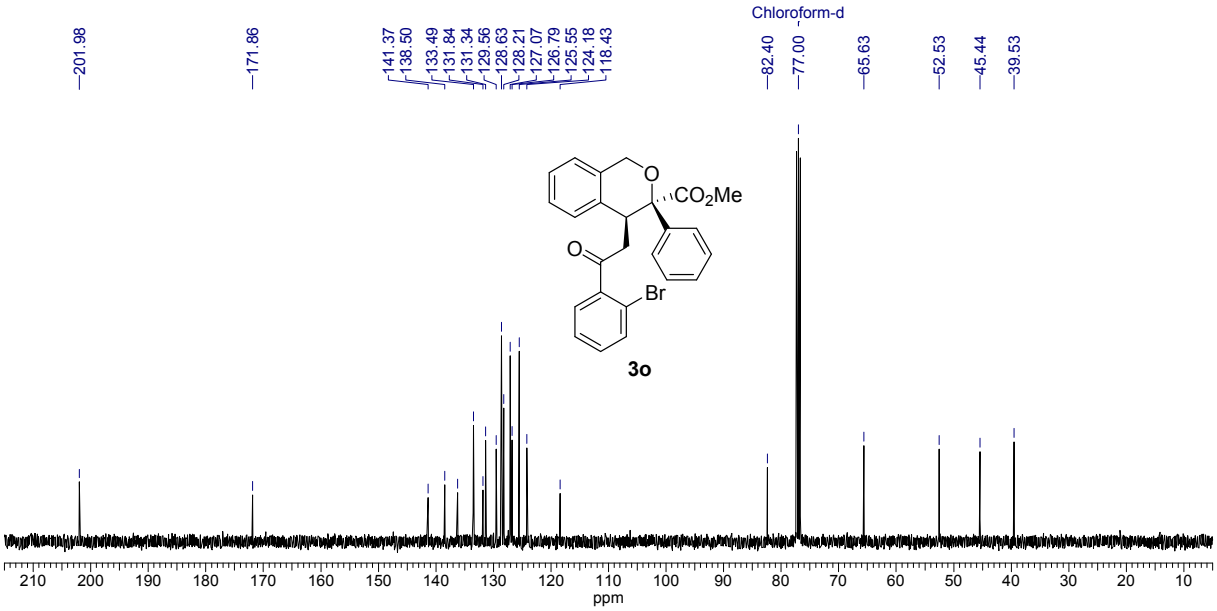
^{1}H NMR (400 MHz) spectrum of compound **3n** in $CDCl_3$



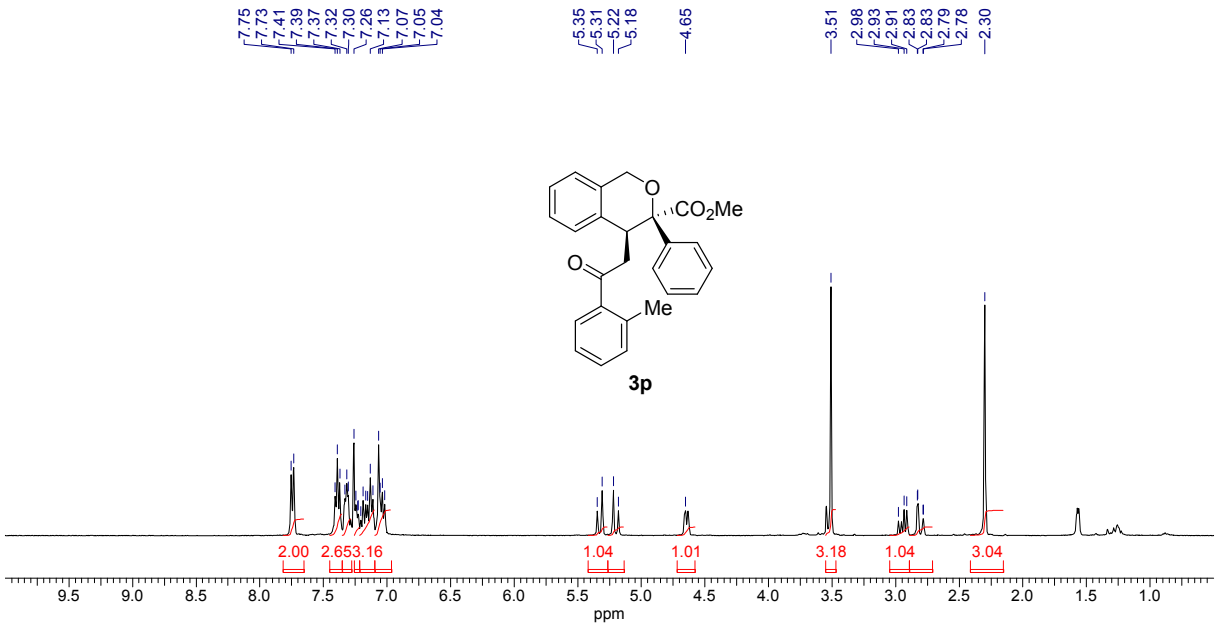
^{13}C NMR (100 MHz) spectrum of compound **3n** in $CDCl_3$



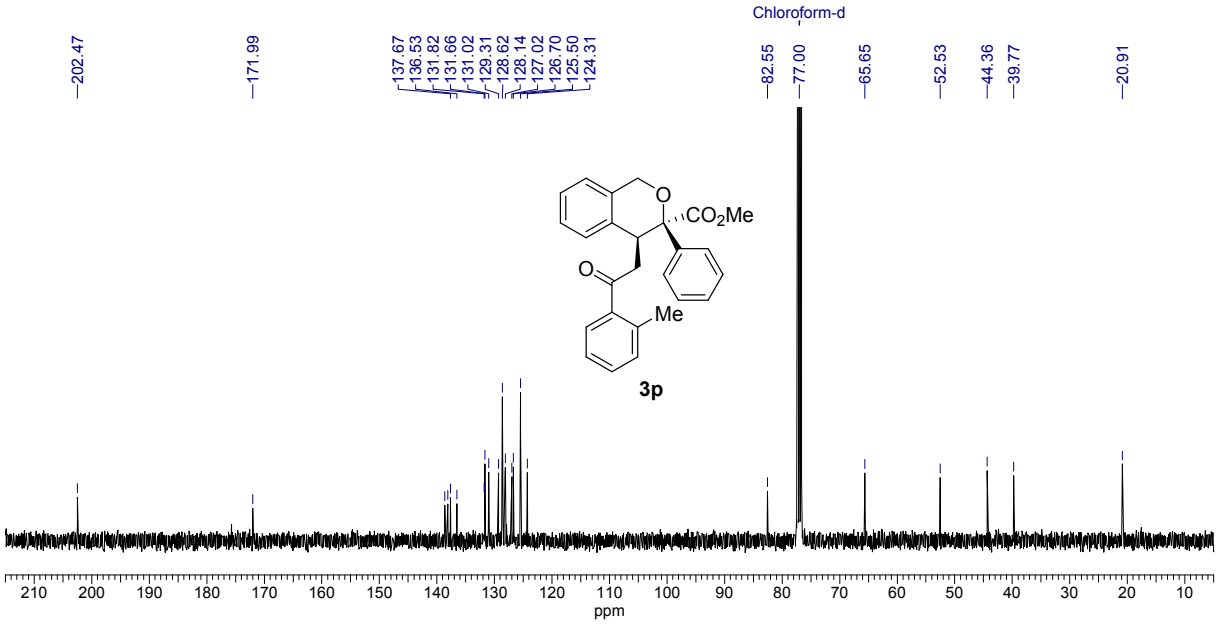
^{1}H NMR (400 MHz) spectrum of compound **3o** in $CDCl_3$



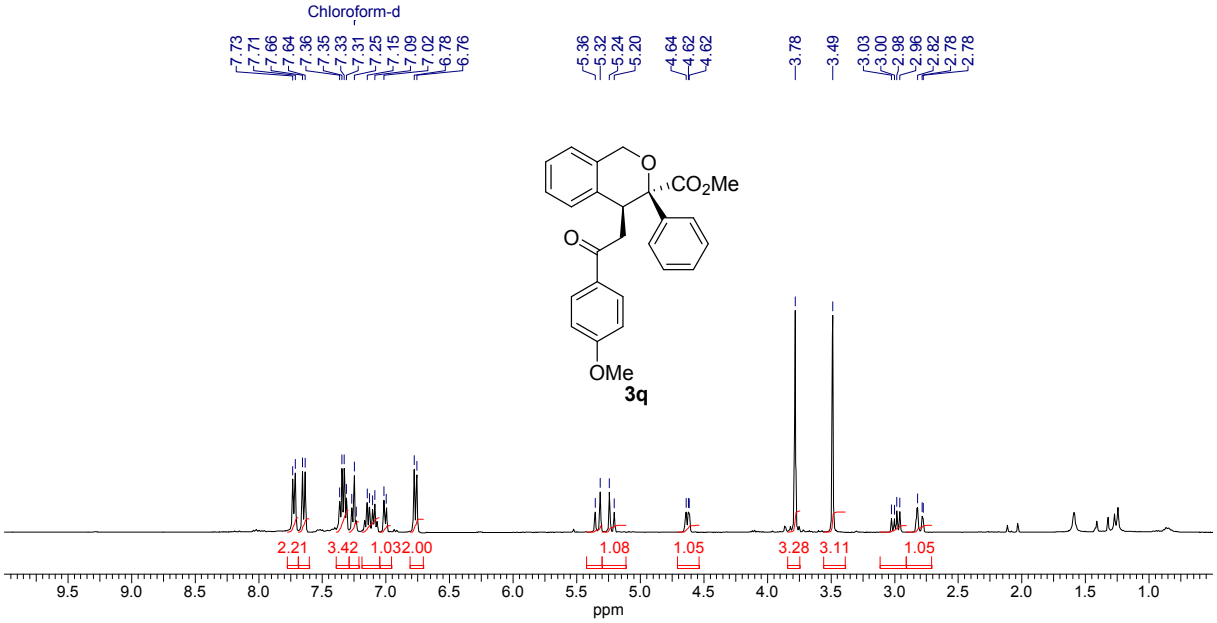
^{13}C NMR (100 MHz) spectrum of compound **3o** in $CDCl_3$



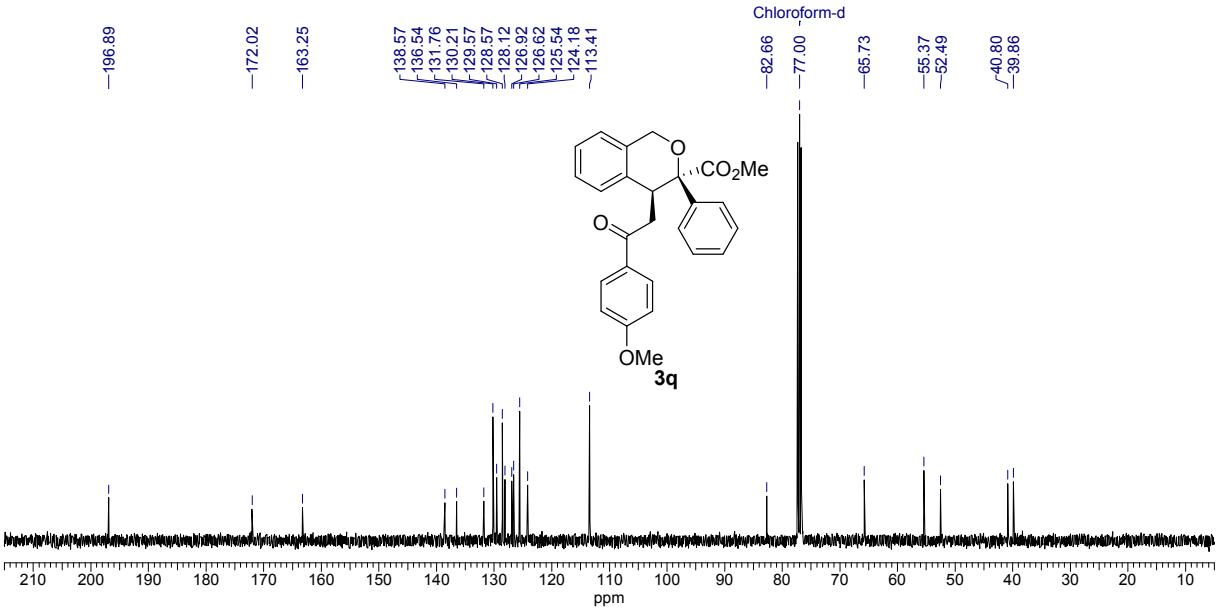
^{1}H NMR (400 MHz) spectrum of compound **3p** in $CDCl_3$



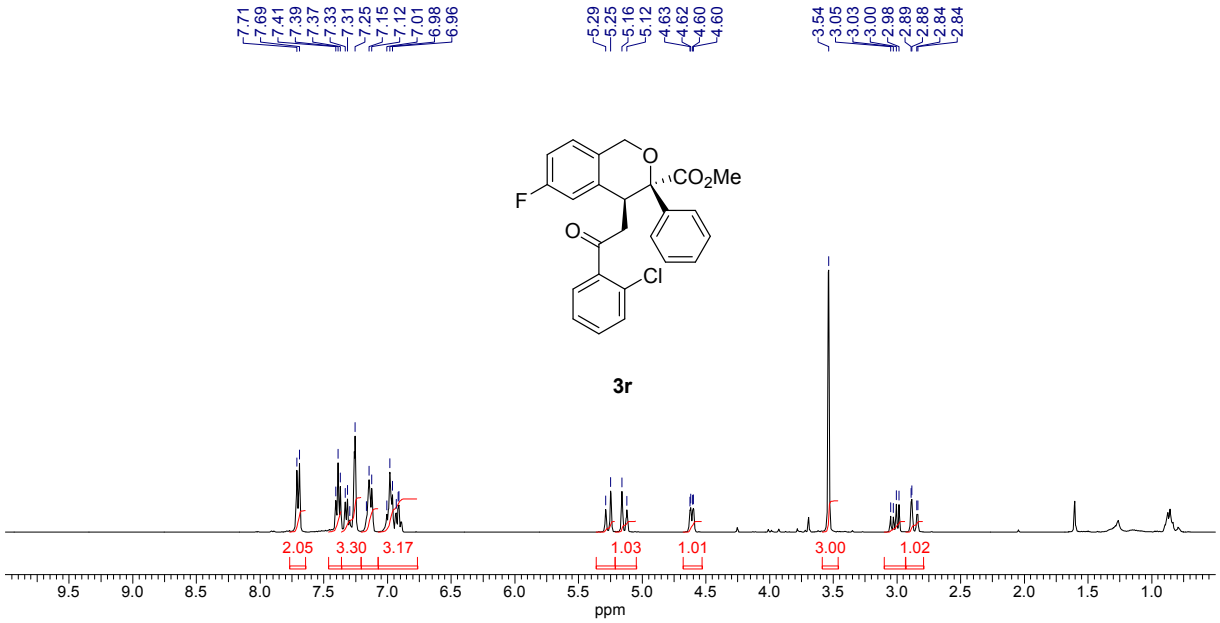
^{13}C NMR (100 MHz) spectrum of compound **3p** in $CDCl_3$



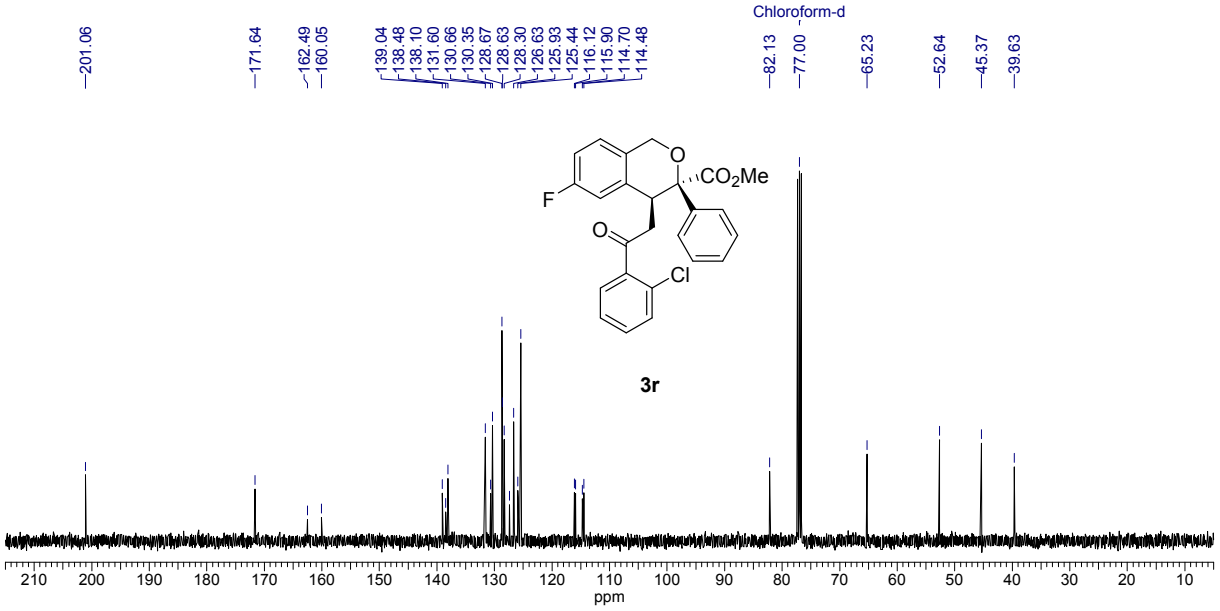
^{1}H NMR (400 MHz) spectrum of compound **3q** in $CDCl_3$



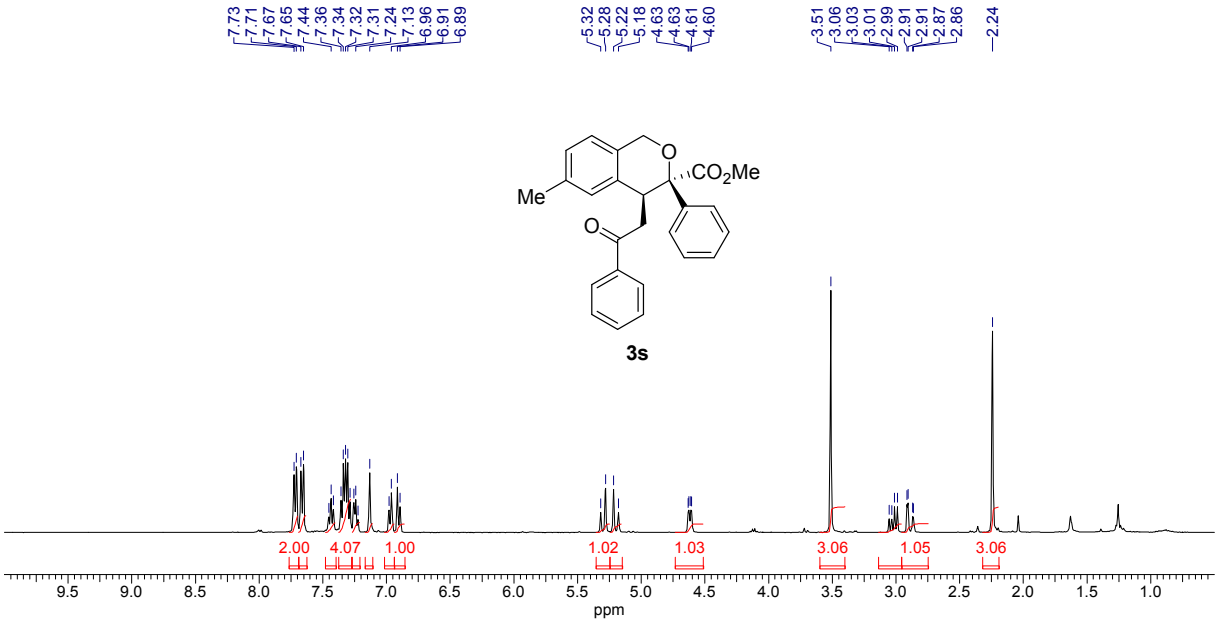
^{13}C NMR (100 MHz) spectrum of compound **3q** in $CDCl_3$



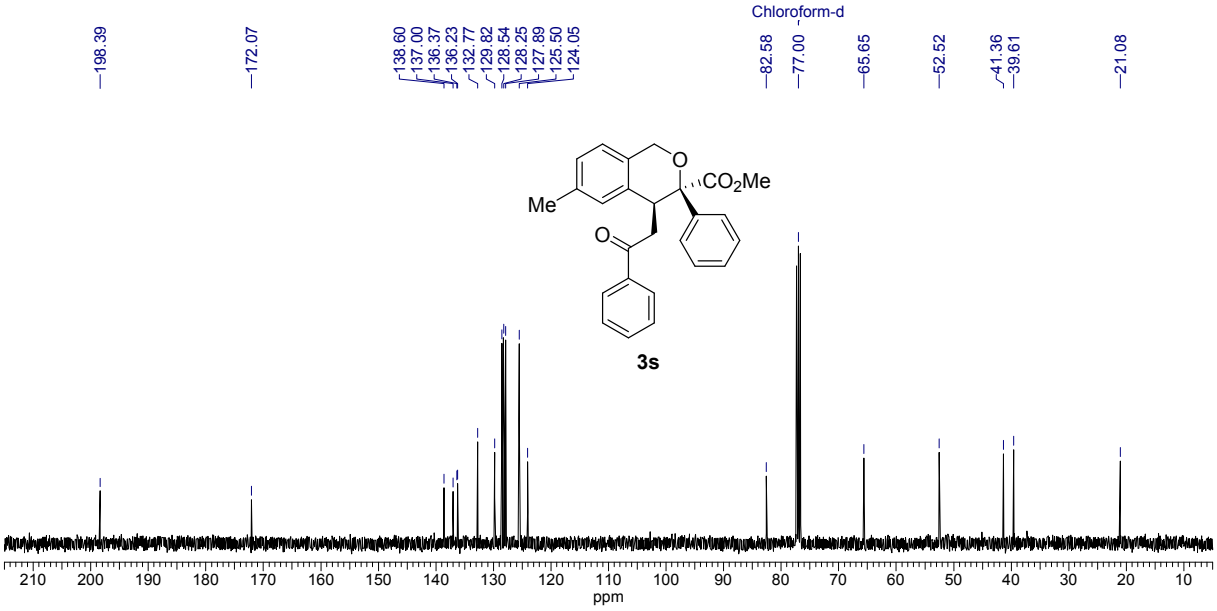
^{1}H NMR (400 MHz) spectrum of compound **3r** in $CDCl_3$



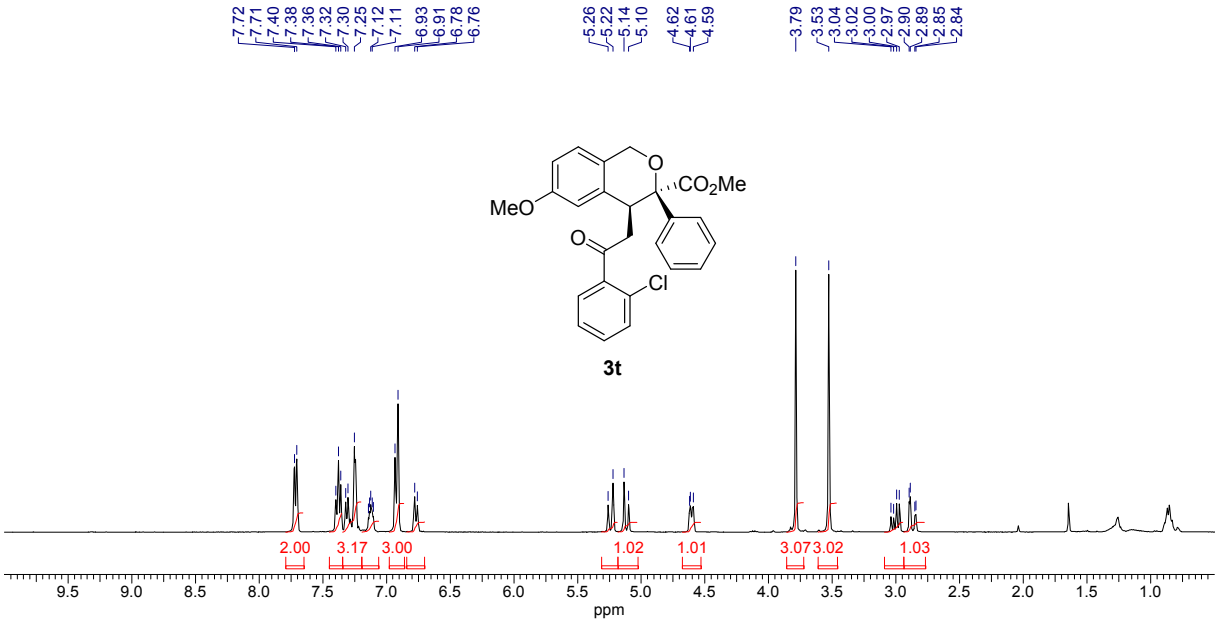
^{13}C NMR (100 MHz) spectrum of compound **3r** in $CDCl_3$



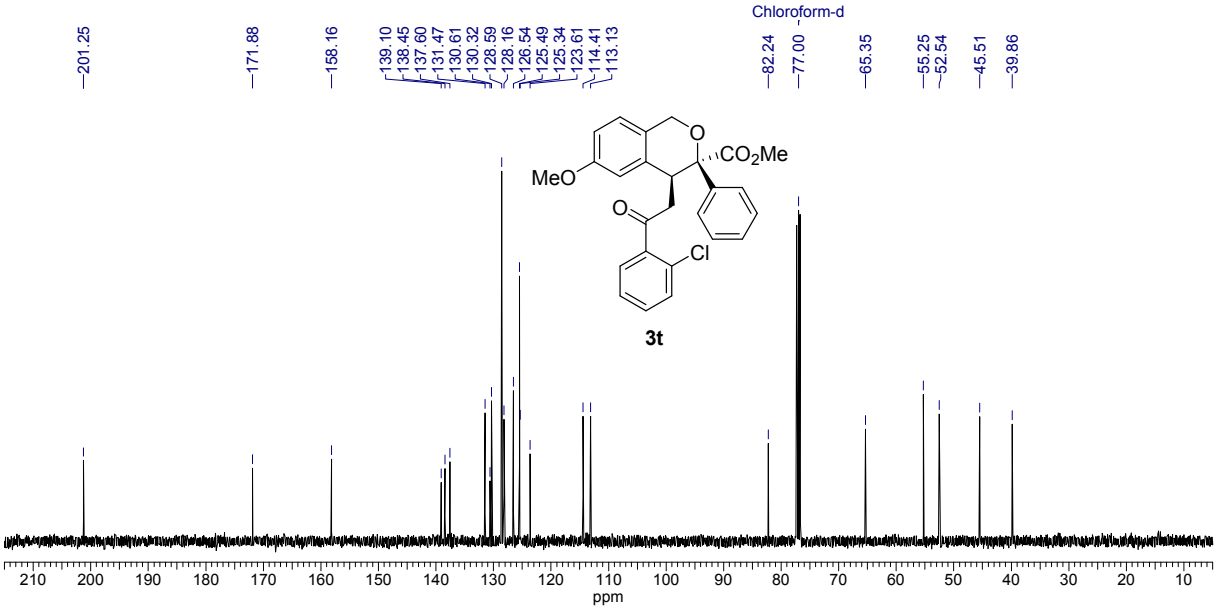
^{1}H NMR (400 MHz) spectrum of compound **3s** in $CDCl_3$



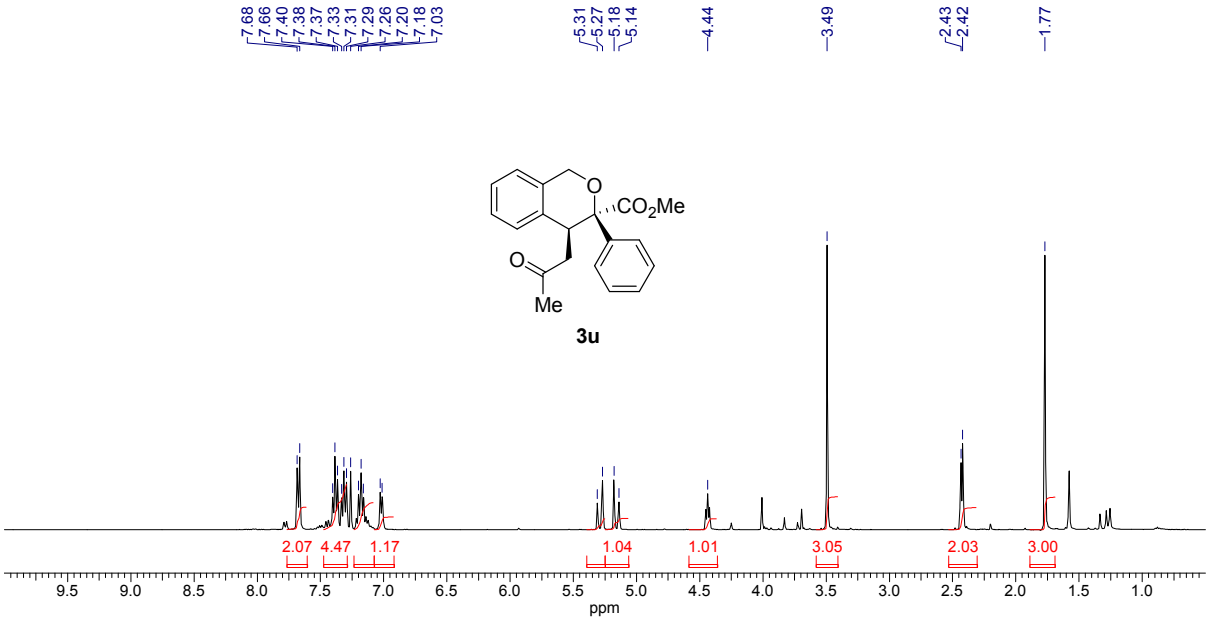
^{13}C NMR (100 MHz) spectrum of compound **3s** in $CDCl_3$



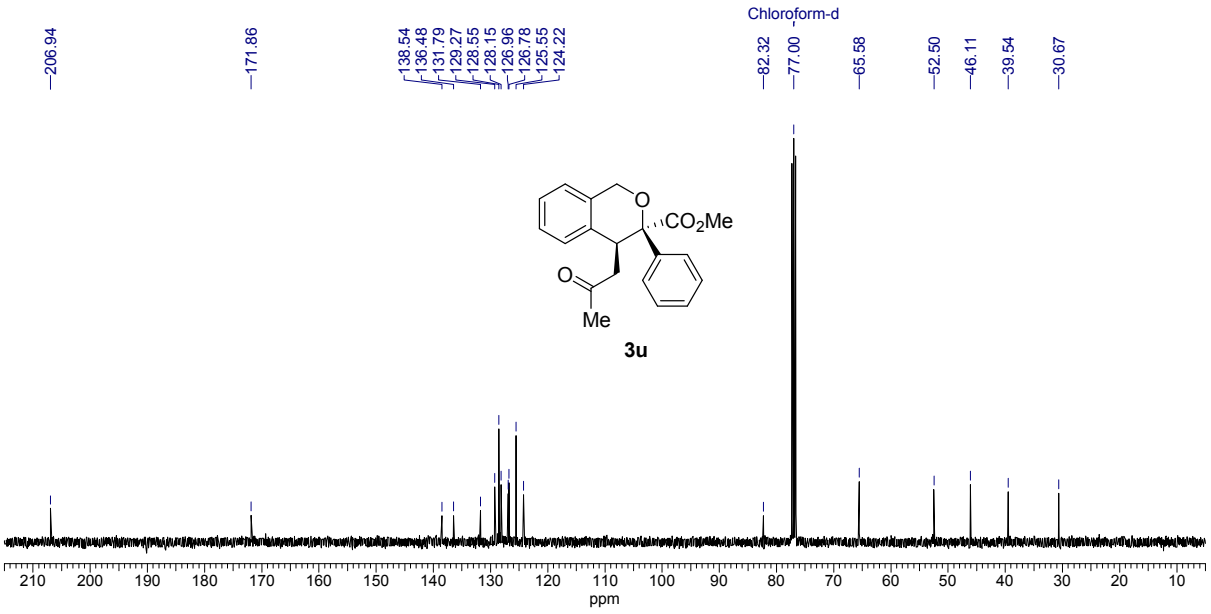
^{1}H NMR (400 MHz) spectrum of compound **3t** in $CDCl_3$



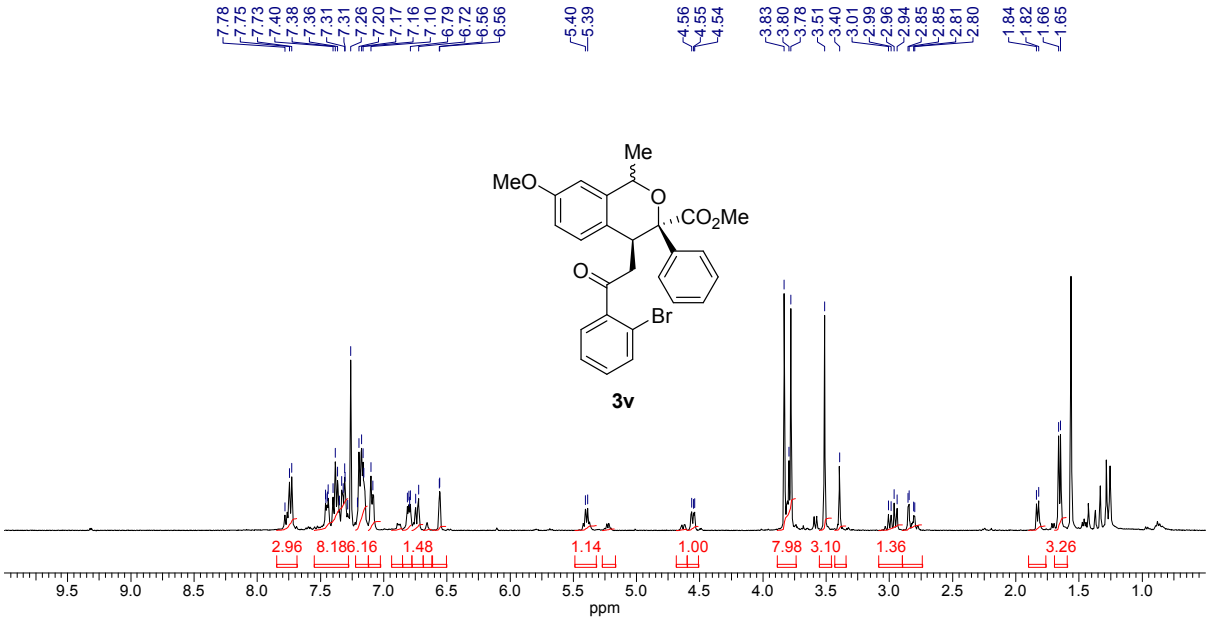
^{13}C NMR (100 MHz) spectrum of compound **3t** in $CDCl_3$



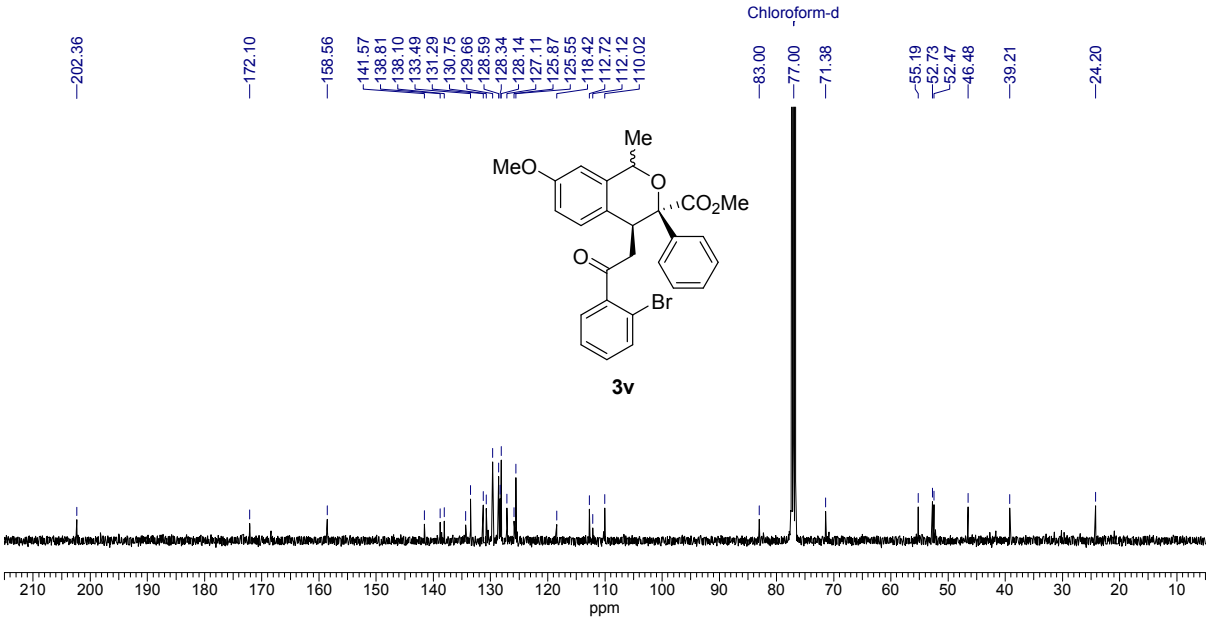
^{1}H NMR (400 MHz) spectrum of compound **3u** in $CDCl_3$



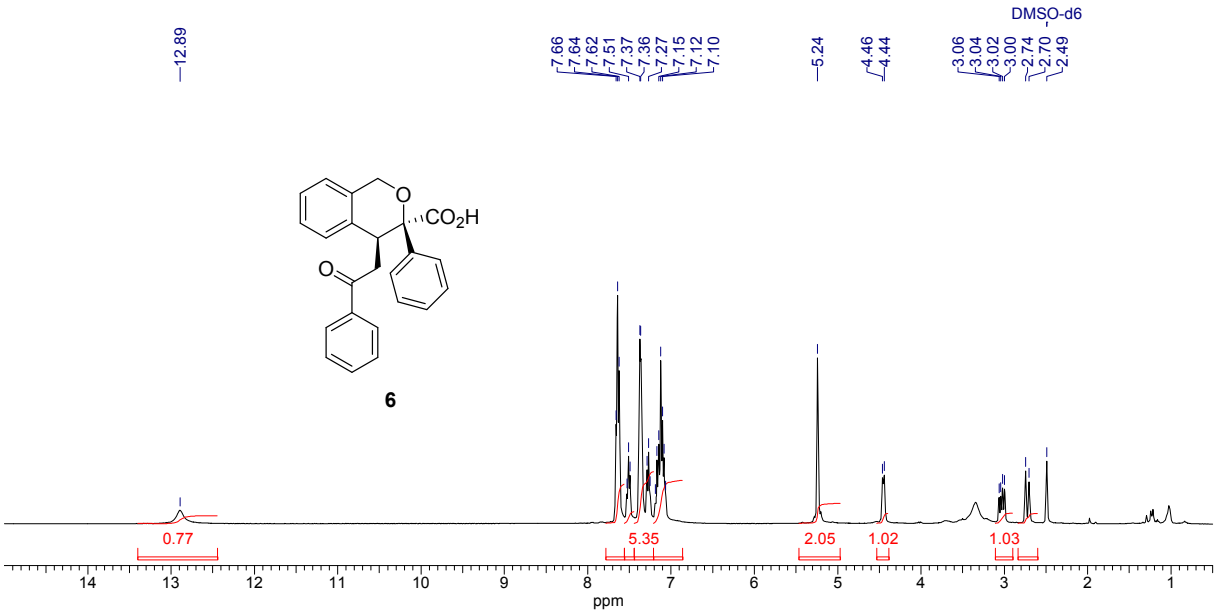
^{13}C NMR (100 MHz) spectrum of compound **3u** in $CDCl_3$



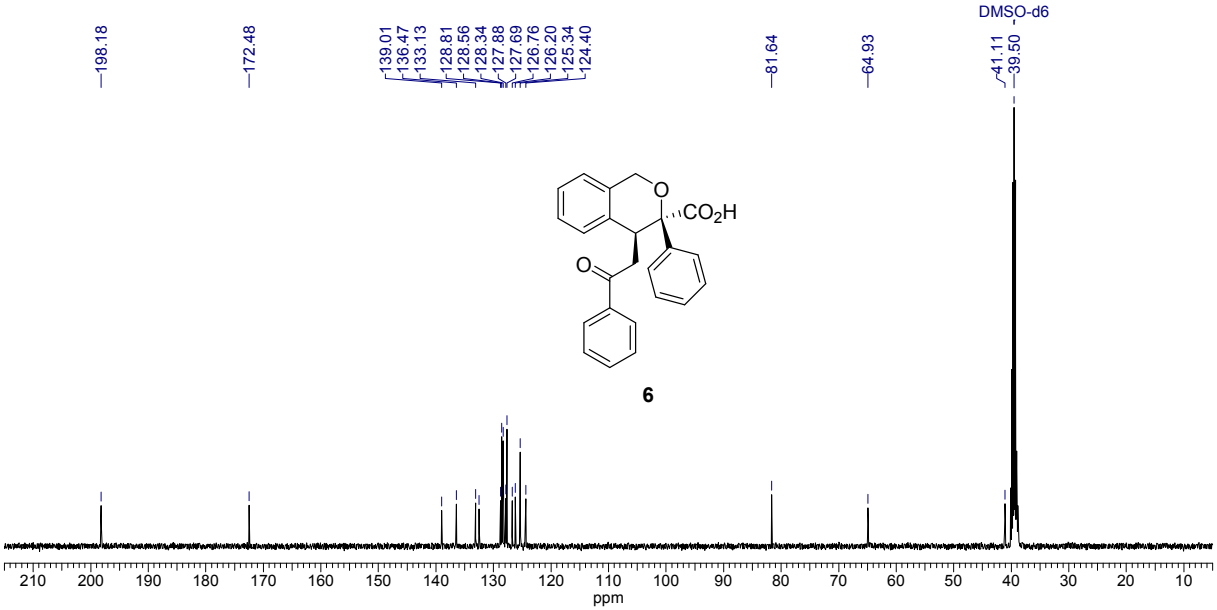
^{1}H NMR (400 MHz) spectrum of compound **3t** in $CDCl_3$



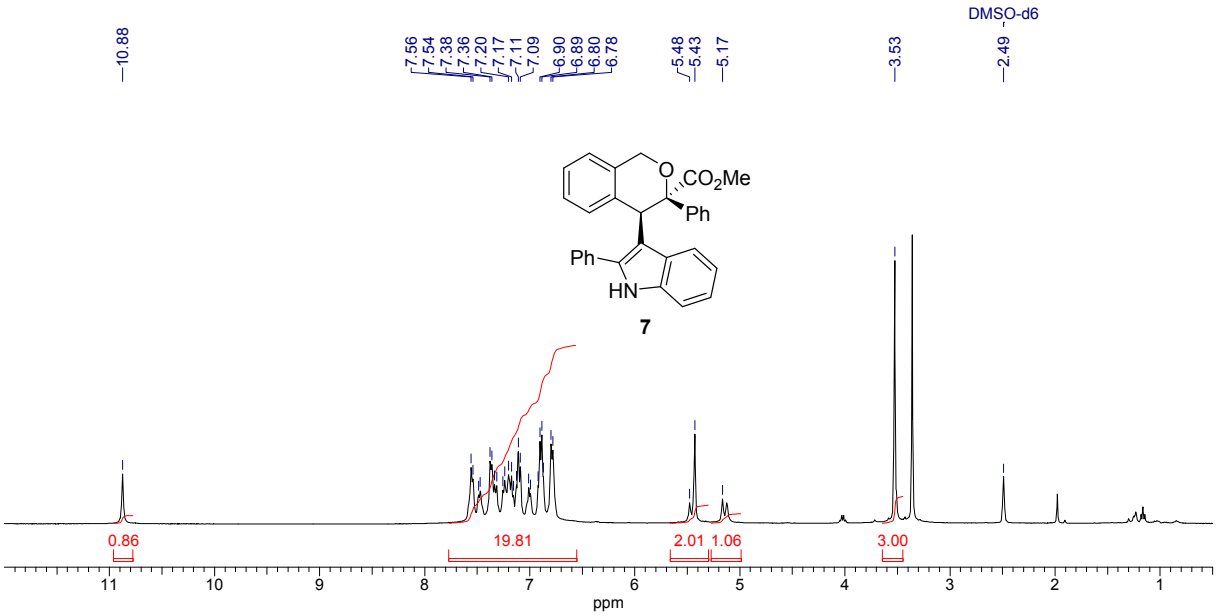
^{13}C NMR (100 MHz) spectrum of compound **3v** in $CDCl_3$



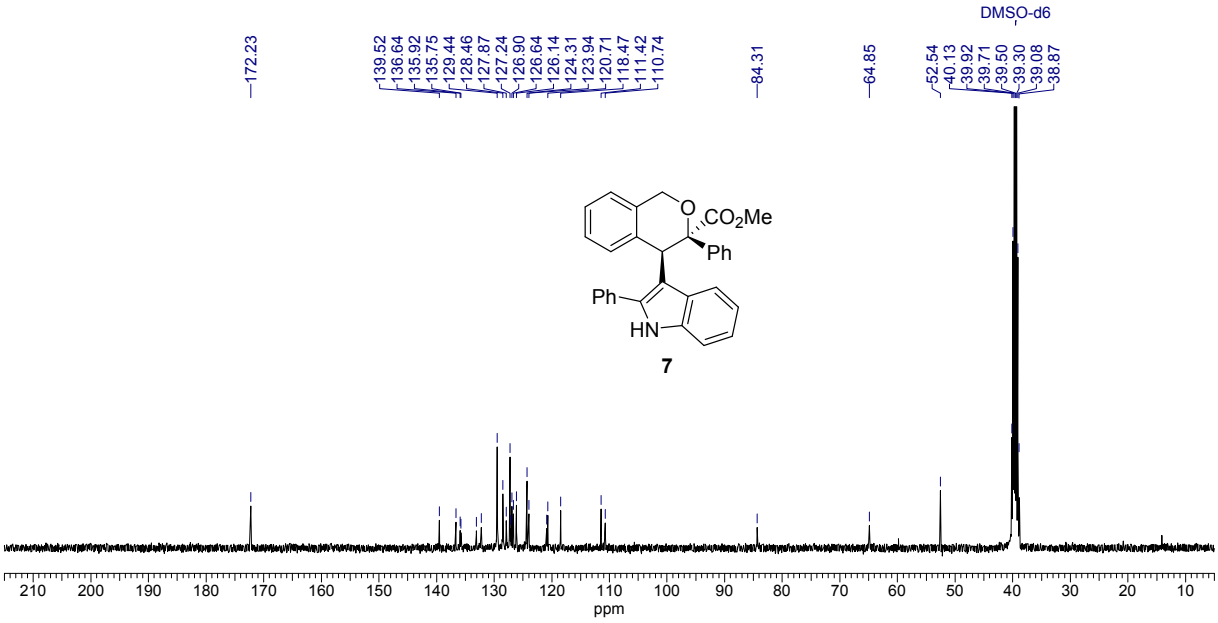
^{1}H NMR (400 MHz) spectrum of compound **6** in DMSO-d_6



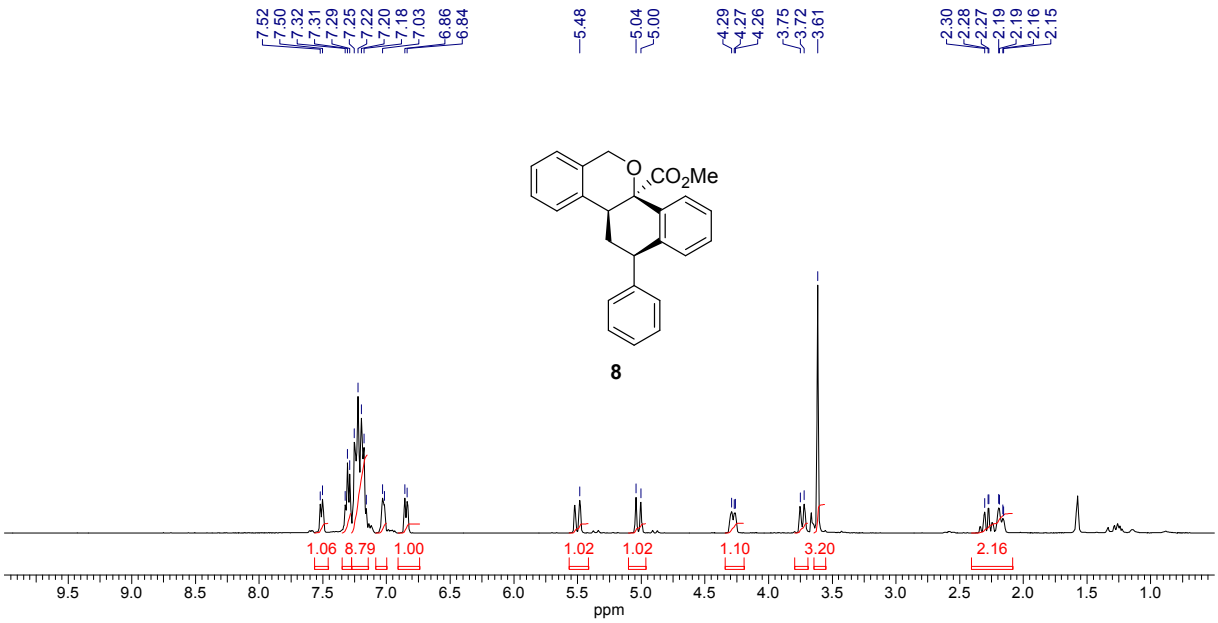
^{13}C NMR (100 MHz) spectrum of compound **6** in DMSO-d_6



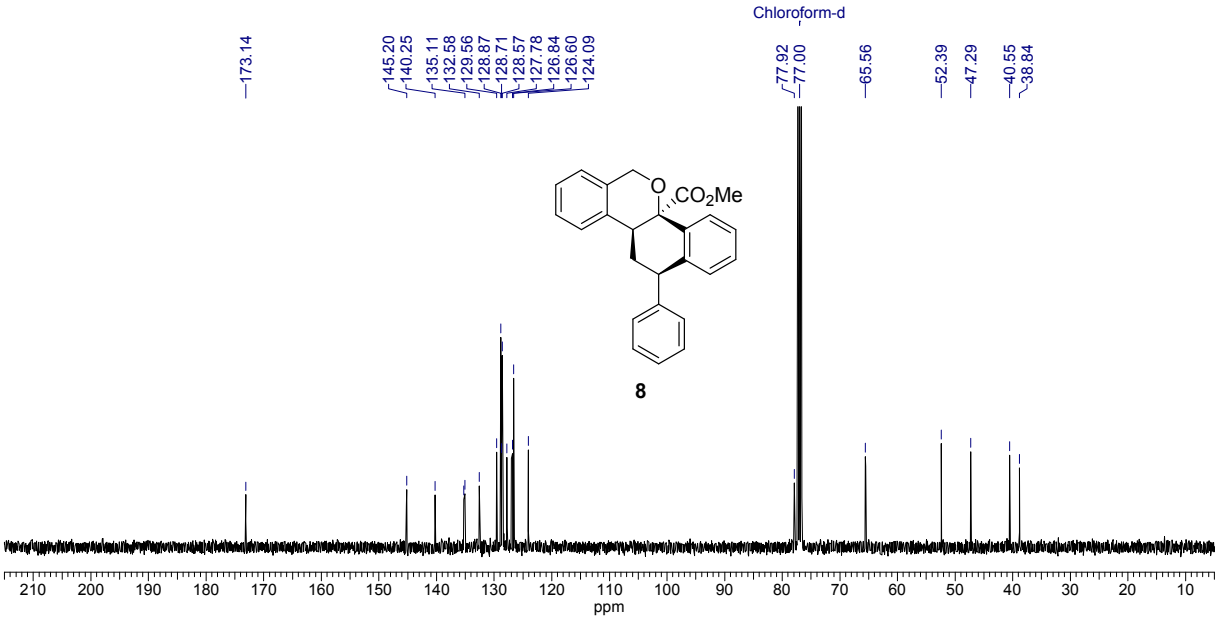
^{1}H NMR (400 MHz) spectrum of compound **7** in DMSO-d_6



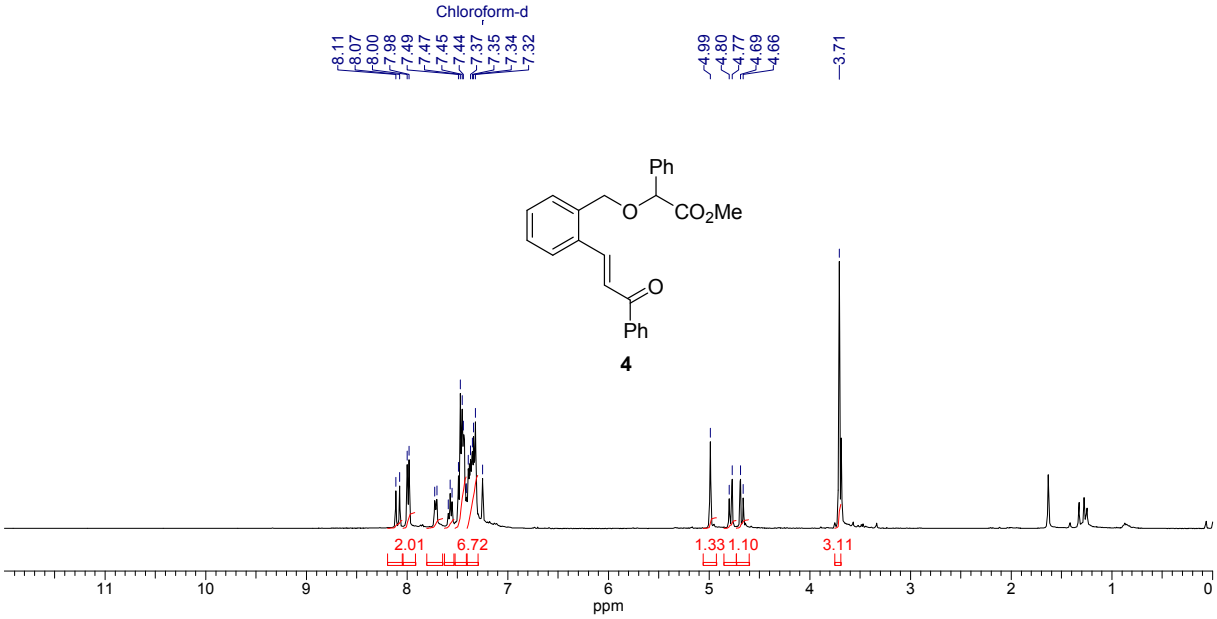
^{13}C NMR (100 MHz) spectrum of compound **7** in DMSO-d_6



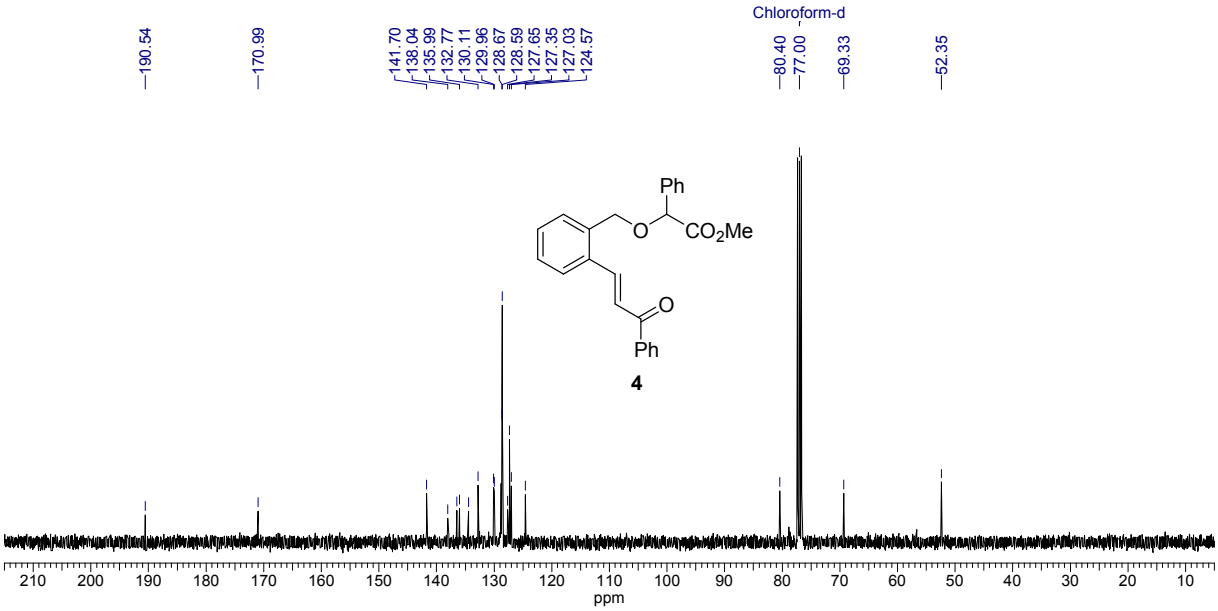
^{1}H NMR (400 MHz) spectrum of compound **8** in $CDCl_3$



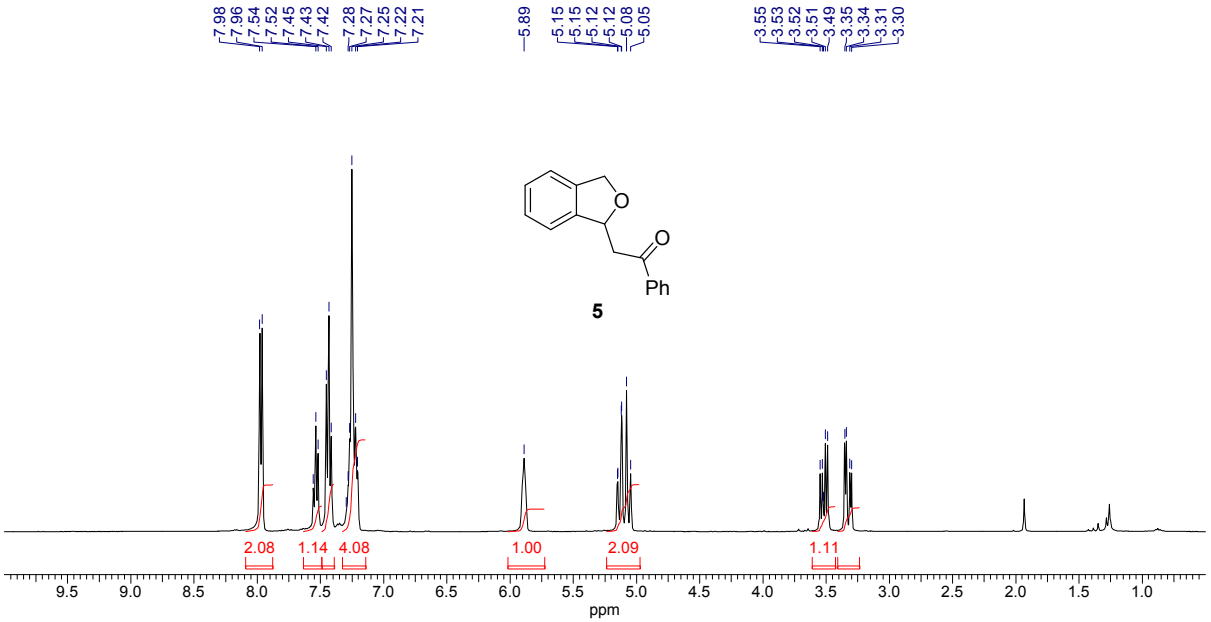
^{13}C NMR (100 MHz) spectrum of compound **8** in $CDCl_3$



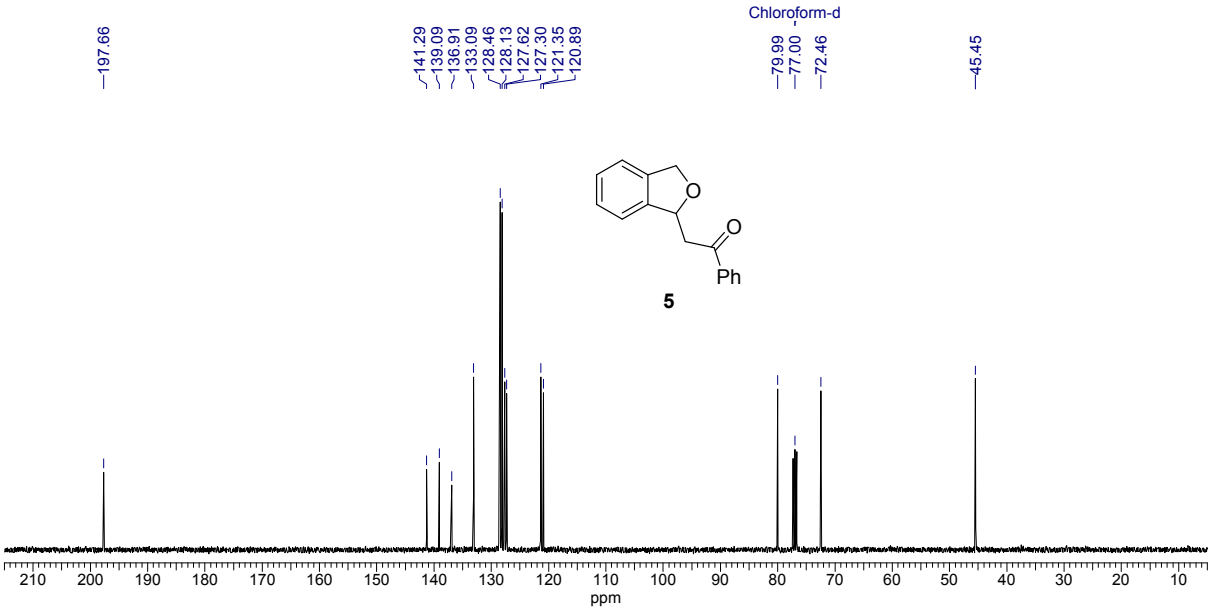
^{1}H NMR (400 MHz) spectrum of compound **4** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **4** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **5** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **5** in $CDCl_3$