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Highly Diastereoselective Synthesis of Polycyclic Amines *via*-Redox Neutral C-H Functionalization

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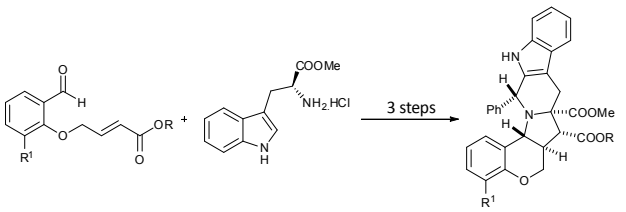
Synthesis of polycyclic amines were achieved by benzoic acid catalysed reaction of 1-aryl THIQs and 1-aryl trypolines with *o*-allyl salicylaldehydes through the *in situ* generated azomethine ylide intermediates that undergo intramolecular [3 + 2]-cycloadditions with four new stereogenic centers in excellent diastereoselectivities under simple and mild conditions.

Introduction

Functionalization of C–H bonds into C–C and/or C–O bonds is an important area of organic synthesis for the construction of biologically active molecules.[1] In this context, selective fuctionalization C–H bonds have been developed during last few years.[2] C–H fuctionalization via intramolecular [3 + 2]-cycloadditions of azomethine ylides is a powerfull tool to construct polycyclic amines from relatively simple precursors.[3-4] Several methods are available to generate azomethine ylides, in the majority of cases, these dipolar species are prepared via decarboxylative condensation of aldehydes with amino acids such as proline and sarcosine. *o*- Allyloxy or *o*-propargyloxy salicylaldehydes and several other systems have been developed for the synthesis of bicyclic,



Raghunathan et al (ref 6)

Scheme 1. Sequential intramolecualr dipolar cycloaddition and Pictet-Spengler cyclization.

tricyclic and even more complex ring systems.[5] Recently Raghunathan *et al*[6] reported the synthesis of polycyclic amines by dipolar cycloaddition and Pictet-Spengler reaction (Scheme 1).

The access of azomethine ylides from a range of simple secondary amines and their application to intramolecular [3 + 2]-cycloadditions was reported.[7] [3 + 2]-Cycloaddition reaction is an attractive strategy to construct multiple C-C or C-hetero bonds. Many works have been reported on the redox-neutral α-C-H functionalization of amines including the α-amination of secondary amines with *o*-amino benzaldehydes and thiosalicylaldehydes.[8-10] In our previous work, we reported the synthesis of polycyclic amines by in situ generation of azomethine ylides followed by intramolecular [3 + 2]-cycloaddition. The reaction was also been successfully carried out with the substrates like pyrrolidine, piperidine, morpholine and thiomorpholine.[11] With an intension of further utility of the underlying methodology to rapidly access new chemical space, this work represents a logical extension of above mentioned work. In continuation of our interest in intramolecular azomethine ylide [3 + 2]-cycloaddition reaction and synthesis novel heterocycles,[12-15] we report herein a method to access azomethine ylides from simple 1-aryl THIQs and 1-aryl trypolines under mild conditions and their intramolecular [3 + 2]- cycloadditions.

Result and discussion

Initially the reaction of *o*-allyl salicylaldehyde **1** with 1-(4-bromophenyl)THIQ **2** was chosen as model reaction to optimize the reaction conditions. Remarkably, the reaction of *o*-allyl salicylaldehyde with 1-aryl-THIQ was found to proceed in the absence of any additive at reflux conditions in toluene giving the desired product **3e** in 55% yield (Table 1, entry 1). As it has been shown that benzoic acid facilitates amine C-H functionalization via azomethine ylides, we tested benzoic acid as an additive used at 20 mol%, that led to marked rate acceleration with the reaction being completed after 5 h (Table 1, entry 2). However, no formation of

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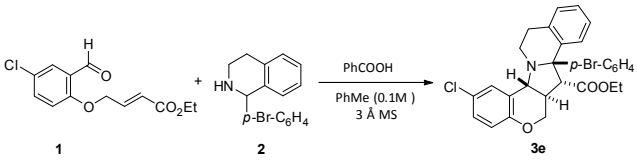
Table 1 Evaluation of reaction conditions

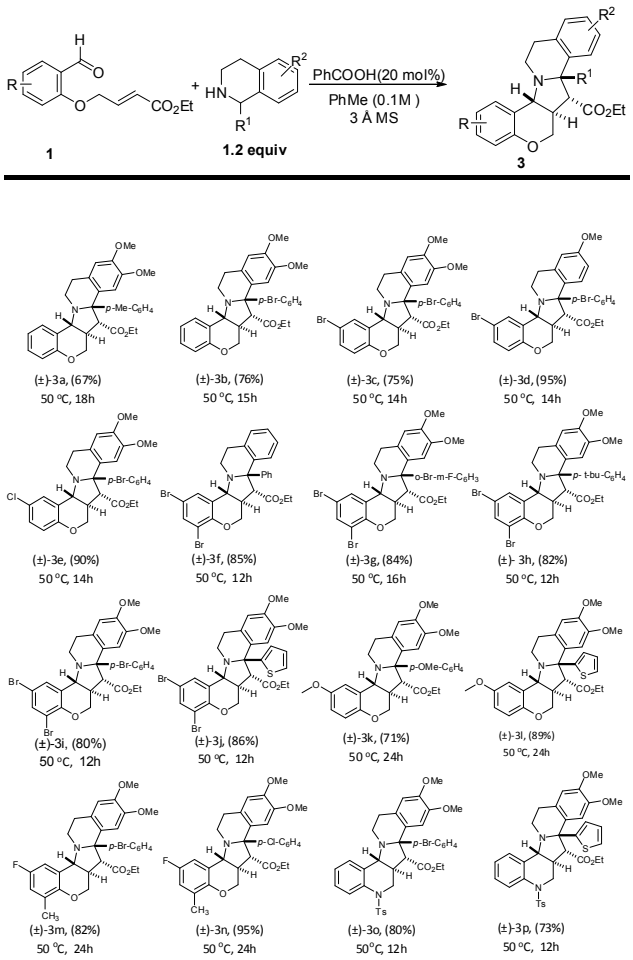


Entry[a]	Additives (mol %)	molecular Sieves	T [^{0} C]	Time [h]	Yield[b] (%)
1	-	-	reflux	18	55
2	$PhCO_2H$ (20)	-	reflux	5	63
3	$PhCO_2H$ (20)	-	100	5	65
4	$PhCO_2H$ (20)	-	80	7	67
5	$PhCO_2H$ (20)	-	60	24	70
6	$PhCO_2H$ (20)	-	50	24	50
7	-	3 Å	reflux	15	61
8	-	3 Å	80	24	60
9	-	3 Å	50	24	NR
10	$PhCO_2H$ (20)	3 Å	RT	24	50
11	$PhCO_2H$ (20)	3 Å	40	18	67
12	$PhCO_2H$ (20)	3 Å	50	14	90
13	$PhCO_2H$ (20)	3 Å	60	14	88
14	$PhCO_2H$ (10)	3 Å	50	24	57
15	$PhCO_2H$ (50)	3 Å	50	12	88
16	CH_3CO_2H(20)	3 Å	50	24	76
17	Ethylhexnoic acid (20)	3 Å	50	24	71
18	CF_3CO_2H(20)	3 Å	50	24	NR
19	PTSA(20)	3 Å	50	24	NR
20	*p*-toluic acid(20)	3 Å	50	24	70

[a] reactions were performed with 1 mmol of **1** and 1.2 mmol of 1-aryl THIQ (**2**).[b]Yields are isolated of chromatographically purified compounds.

product was observed even after 24 hours when the reaction was conducted at 50 ^{o}C in the absence of benzoic acid. (Table 1, entry 9) Addition of 3 Å molecular sieves resulted in marked reduction of the reaction time and slight increase in yield (Table 1, entries 11-13). A good effect was observed when the title reaction was conducted at 50 ^{o}C in the presence of molecular sieves and benzoic acid, leading to the isolation of **3e** in 90% yield after 24 h. A reduction in the loading of benzoic acid to 10 mol% had a negative effect on the yield of **3e** (Table 1, entry 14), where as increasing it to 50 mol%did not offer any significant advantages over the 20 mol% catalyst (Table 1, entry 15). Next when we studied the effects of various acids, it was clear that mild acids like acetic acid and 2-ethyl hexanoic acid were quite less effective (Table 1, entries 16-17) and strong acids such as CF_3COOH, *p*-toluene sulfonoic acid (Table 1, entries 18-19) were ineffective. Finally substituted benzoic acid like *p*-toluic acid was tried that led to the negative effect on yield of **3e**

Scheme 2 Substrate scope for the [3 + 2]-cycloaddition with 1-aryl THIQs



(Table 1, entry 20). Later we screened a number of solvents viz., THF, EtOAc, Xylene, toluene, DMF, CH_3CN and found that toluene was the preferred solvent. We also screened other molecular sieves like 4 Å and 5Å but no significant difference was observed.

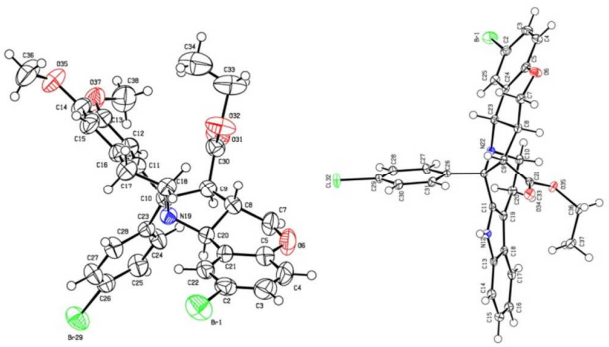
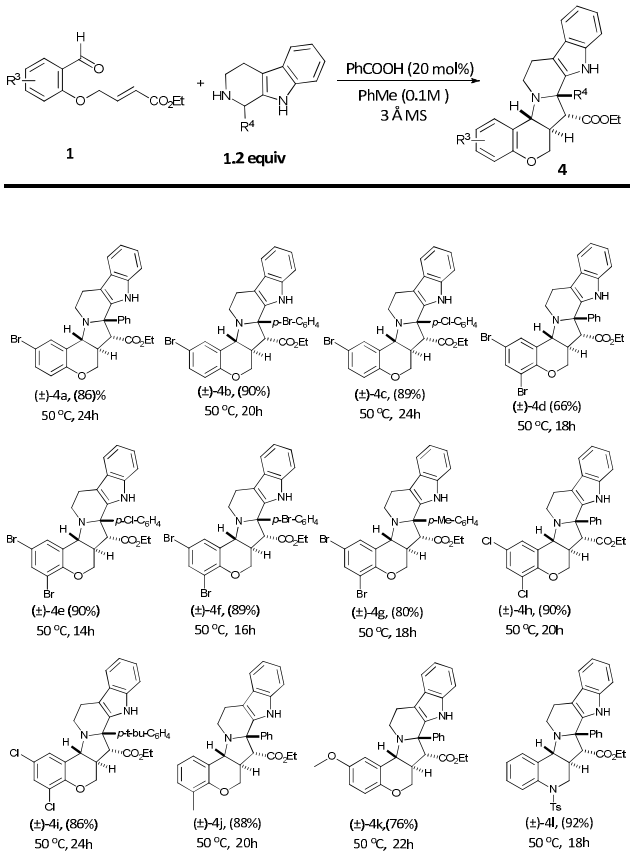


Fig 1. The single crystal XRD structure of compounds **3c** and **4c**

Scheme 3 Substrate scope for the [3 + 2]-cycloaddition with 1-aryl Trypolines.



The generality was established by carrying out the reactions on various substituted 1-aryl THIQs with a range of salicylaldehydes (scheme 2). In all cases, products were obtained in good to excellent yields at 50 °C. Importantly, the scope of the [3 + 2]-cycloaddition could be readily expanded to various 1-aryl THIQ derivatives (scheme 2).

We expanded the scope of this cycloaddition reaction to 1-aryl-trypolines and generated an array of polycyclic amines (scheme 3).

Importantly, in all the cases, the cycloaddition was found to be highly diastereoselective and furnished only a single diastereomer. Heteroaryl species, such as a 2-thiophene carboxyaldehyde also underwent the reaction to give the desired product in good yields without polymerization (**3j**, **3l** and **3p**).

Remarkable tolerance toward electronic demands of substituent's in the salicylaldehyde moiety on the [3 + 2]-cycloaddition reaction was shown. To gain further insight into this intramolecular [3 + 2]-cycloaddition, analogous of 2-aminobenzaldehydes was successfully carried out with an excellent yield (**3o**, **3p** and **4l**) and affording a single diastereomer in all the cases studied. The stereochemistry of the products was unambiguously determined by single X-ray crystal studies for the compounds **3c, 3p** and **4c**.

Conclusion

In summary, the key step is a highly diastereoselective intra molecular [3 + 2] cycloaddition of *in situ* generated azomethine ylides. The overall process is facilitated by the combined action of benzoic acid and molecular sieves. This method provides a convenient access to poly functional *N*-heterocycles with four stereo centres in one step process. Diversified polycyclic amines provided a valuable alternative to the widely used decarboxylative versions of these transformations.

Experimental

Materials and instruments

Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F254 plates. Visualization was accomplished with UV light, potassium permanganate and DragendorffMunier stains followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}HNMR) were recorded on Agilent-400 MHz, Brucker-400/500 MHz and are reported in ppm using $CDCl_3$/DMSO-d_6 as the internal standard (7.24/2.50 ppm). Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Agilent-400 MHz, Brucker-400/500 MHz and are reported in ppm using $CDCl_3$/DMSO-d_6 as the internal standard (77.0/29.8 ppm). Mass spectra were recorded on Agilent mass spectrum.

General procedure for the diastereoseletive intramolecular [3 + 2]-cycloaddition of benzylic amines (scheme 2 and 3)

To a solution of aldehyde (1 mmol, 1 equiv) in toluene (10 mL) was added 3 Å molecular sieves (200 mg), amine (1.2 mmol, 1.2 equiv) and benzoic acid (0.2 mmol, 0.2 equiv). The mixture was stirred at 50 °C and progress was monitored by TLC. When the aldehyde could no longer be detected, the reaction mixture was filtered through a plug of celite and rinsed with EtOAc (20 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (3 x 15 mL) and the combined aqueous layers were extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the was residue purified by silica gel chromatography.

Ethyl 9,10-dimethoxy-7a-(*p*-tolyl)-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3a): White solid; Yield: (67%); MP.160–162 °C; R_f = 0.31 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_Z, $CDCl_3$): δ = 7.77 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 6.50

(s, 1H), 4.58 (dd, *J* = 13.6, 6.4 Hz 1H), 4.04 (t, *J* = 10.8 Hz, 1H), 3.88–3.81 (m, 2H), 3.77 (s, 1H), 3.5–3.70 (m, 2H), 3.67 (s, 3H), 3.35 (d, *J* = 9.6 Hz, 2H), 3.13 (t, *J* = 4.0 Hz, 1H), 2.96 (t, *J* = 11.2 Hz, 1H), 2.67 (d, *J* = 15.2 Hz, 1H), 2.27 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 173.3, 154.4, 147.1, 146.5, 136.3, 129.9, 129.0, 128.0, 127.4, 126.9, 126.8, 122.1, 119.9, 116.5, 111.9, 110.5, 78.6, 69.9, 62.3, 60.8, 58.1, 55.7, 55.6, 42.3, 40.0, 29.5, 20.8, 13.7**;** IR (neat): ν = 2962, 1729 1609, 1577, 1485, 1349, 1225, 1178, 1095, 902, 815, 773, 651 cm^{-1}**;** HRMS (ESI-TOF): *m/z*.calcd. for $C_{31}H_{33}NO_5$ $[M + H]^+$ 500.2359; found 500.2348.

Ethyl 9,10-dimethoxy-7a-(*p*-bromo)-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3b): White solid; Yield (76%); MP 166–168 °C; R_f = 0.31(hexanes/EtOAc 80:20); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.77 (br s, 2H), 7.42–7.40 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 6.52 (app s, 2H), 4.58 (dd, *J* = 14.2, 6.0 Hz, 1H), 4.03 (app d, *J* = 4.4 Hz, 1H), 3.90–3.825 (m, 1H), 3.78 (s, 3H), 3.75–3.69 (m, 2H), 3.67 (s, 3H), 3.35 (br s, 2H), 3.13 (br s, 1H), 2.95 (br s, 1H), 2.65 (d, *J* = 14.4 Hz, 1H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.5, 148.9, 148.6, 147.5, 146.5, 146.7, 131.5, 128.7, 128.5, 127.2, 126.1, 124.8, 124.4, 112.29, 112.2, 112.0, 111.4, 110.5, 110.53**,** 78.4, 69.8, 62.2, 61.1, 57.9, 55.8, 55.6, 41.9, 40.0, 29.4, 13.7; IR (neat): ν 2981, 1709 1610, 1578, 1485, 1349, 1225, 1178, 1095, 910, 815, 793, 621 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd. for $C_{30}H_{30}BrNO_5$ $[M + H]^+$ 564.1307; found 564.1367.

Ethyl 2-bromo-7a-(*p*-bromophenyl)-9,10-dimethoxy-6a,7,7a,12,13,14a-hexahydro-6H,chromeno[3',4'5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3c): White solid; Yield (75%); MP 172–174 °C; R_f = 0.35 (hexanes/EtOAc 80:20); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.75 (d, *J* = 6.8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 3H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 4.59–4.56 (m, 1H), 4.02 (t, *J* = 10.4 Hz, 1H), 3.90–3.84 (m, 1H), 3.39 (s, 1H), 3.76–3.71 (m, 2H), 3.68 (s, 3H), 3.63 (br s, 1H), 3.32 (br s, 1H), 3.17 (br s, 1H), 2.97 (s, 1H), 2.70 (d, *J* = 15.2 Hz, 1H), 1.00 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.7, 153.5, 148.8, 147.4, 146.7, 131.5, 131.1, 129.4, 128.8, 127.3, 123.7, 120.9, 118.5, 112.3, 111.8, 111.7, 110.7, 78.5, 69.7, 62.1, 61.2, 57.9, 55.9, 55.7, 41.9, 40.0, 29.4, 13.8; IR (neat): ν = 2960, 1709, 1654, 1591, 1418, 1328, 1208, 1031, 906, 833, 735, 610 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{30}H_{29}Br_2NO_5$ $[M + H]^+$ 644.0392; found 644.0337.

Ethyl 2-bromo-7a-(*p*-bromophenyl)-9-methoxy-6a,7,7a,12,13,14a-hexahydro-6H,chromeno[3',4'5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3d): White solid; Yield: (95%); MP 180–182 °C; R_f = 0.24 (hexanes/EtOAc 80:20); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.71 (s, 2H), 7.42 (d, *J* = 8.4 Hz, 3H), 7.22 (d, *J* = 9.2 Hz, 1H) 6.87 (br s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 4.58 (dd, *J* = 14.0, 6.4 Hz, 1H), 4.04 (br s, 1H), 3.86–3.81 (m, 1H), 3.79–3.66 (comp, 6H), 3.33 (d, *J* = 9.6 Hz, 3H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.05 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.6, 157.6, 153.6, 148.9, 136.2, 131.5, 131.4, 131.1, 129.7, 129.4, 128.9, 123.8, 120.8, 118.6, 118.5, 112.4, 112.3, 112.2, 76.7, 69.8, 62.1, 61.1, 57.8, 41.8, 39.8, 30.1, 13.8; IR (neat): ν = 2925, 2857, 2254, 1725, 1652, 1610, 1512, 1478, 1379, 990, 856, 790, 609 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{29}H_{27}Br_2NO_4$ $[M + H]^+$ 614.0286; found.614.0250.

Ethyl 2-chloro-9,10-dimethoxy-7a—(*p*-Br-bromophenyl)-9,10-dimethoxy-6a,7,7a,12,13,14a-hexahydro 6H, chromeno [3',4'5] pyrrolo [2,1-*a*]isoquinoline-7-carboxylate (3e): White solid; Yield: (90%); MP 158–160 °C; R_f = 0.32 (hexanes/EtOAc 80:20); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.22 (br s, 1H), 7.00 (dd, *J* = 10.8, 6.8 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 6.0 Hz, 2H), 4.5 (dd, *J* = 13.6, 6.0 Hz, 1H), 3.95 (t, *J* = 10.8 Hz, 1H), 3.85–3.77 (m, 1H), 3.72 (s, 3H), 3.70–3.65 (m, 2H), 3.63–3.56 (m, 4H), 3.29–3.19 (br m, 2H), 3.09 (t, *J* = 12 Hz, 1H), 2.89 (t, *J* = 10.8 Hz, 1H), 2.63 (d, *J* = 15.2 Hz, 1H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.7, 153.0, 147.4, 146.7, 131.4, 128.8, 128.2, 127.4, 126.5, 125.0, 123.2, 120.9, 118.1, 111.9, 111.8, 110.8, 110.7, 78.4, 69.8, 62.2, 61.1 57.9, 55.8, 55.6, 41.9, 40.0, 29.4, 13.7; IR (neat): ν = 2961, 1709, 1652, 1596, 1418, 1328, 1206, 1030, 906, 833, 730, 610 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{30}H_{29}BrClNO_5$ $[M + H]^+$ 598.0917; found 598.0911

Ethyl 2,4-dibromo-7a-phenyl-6a,7,7a,12,13,14a-hexahydro-6H-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3f): White solid; Yield: (85%); MP 152–154 °C; R_f = 0.17 (hexanes/EtOAc 90:10); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.8 (d, *J* = 5.6 Hz, 2H), 7.52 (s, 1H), 7.43 (s, 1H), 7.31 (br s, 2H), 7.19 (br s, 1H), 7.05–6.96 (m, 4H), 4.7 (d, *J* = 10.8 Hz, 1H), 4.13 (t, *J* = 10.8 Hz, 1H), 3.84–3.71 (m, 4H), 3.32 (t, *J* = 12.4 Hz, 3H), 3.0 (br s, 1H), 2.81 (d, *J* = 14.8 Hz, 1H), 1.0 (s, 1H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.5, 155.4, 150.4, 137.2, 134.5, 134.2, 134.0, 128.7, 128.6, 128.4, 127.9, 127.2, 126.3, 125.5, 124.8, 112.2, 111.5, 79.2, 70.6, 62.0, 61.3, 57.4, 41.5, 39.9, 29.7, 13.7; IR (neat): ν = 2960, 1709, 1654, 1591, 1418, 1328, 1208, 1031, 833, 735, 610 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{29}H_{27}Br_2NO_3$ $[M + H]^+$ 584.0180; found 584.0113

Ethyl 2,4-dibromo-7a-(3-bromo-5-flurophenyl)-9,10-dimethoxy-6a,7,7a,12,13,14,-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]iso-quinoline-7-carboxylate (3g): White solid; Yield: (84%); MP 186–188 °C; R_f = 0.22 (hexanes/EtOAc 80:20); ^{1}H NMR (400 $MH_{Z,}$ $CDCl_3$): δ = 7.20 (s, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.02 (s, 1H), 6.85 (s, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 6.48 (s, 1H), 4.17 (m, 1H), 4.04 (t, *J* = 10.4 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.79 (s, 3H), 3.70–3.66 (m, 1H), 3.65 (s, 3H), 3.62–3.56 (m, 1H), 3.2–3.19 (m, 2H), 3.09 (t, *J* = 8.8 Hz, 1H), 2.88 (br s, 1H), 2.63 (d, *J* = 15.6 Hz, 1H), 0.94 (t, *J* = 7.2, 3H); ^{13}C NMR (100 $MH_{Z,}$ $CDCl_3$): δ = 172.5, 148.9, 148.66, 147.5, 146.7, 131.5, 128.7, 128.5, 127.2, 125.1, 124.8, 124.43, 122.4, 121.0, 111.89, 111.84, 110.77, 110.72, 78.5 70.5, 62.1, 61.2, 57.7, 55.8, 55.6, 41.7, 40.0, 29.4, 13.7; IR (neat): ν = 2925, 2853, 2254, 1725, 1652, 1610, 1514, 1478, 1373, 993, 856, 790, 609 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{30}H_{27}Br_3FNO_5$ $[M + H]^+$ 739.9402; found 739.9487.

Ethyl2,4-dibromo-7a-(4-(tert-butyl)phenyl)-9,10-dimethoxy-6a,7,7a,12,13,14,-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoq-uinoline-7-carboxylate (3h): White solid; Yield: (82%); MP 196–

198 °C; R_f = 0.24 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.76 (d, *J* = 8.8 Hz, 2H), 7.49 (s, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 6.52 (s, 1H), 4.59 (dd, *J* = 14.0, 6.4 Hz 1H), 4.13 (t, *J* = 10.4 Hz, 1H), 3.90–3.3.8 (m, 2H), 3.78 (s, 3H), 3.75–3.71 (m, 3H), 3.68 (s, 3H), 3.34–3.14 (m, 3H), 2.99 (t, *J* = 9.6 Hz, 1H), 2.70 (d, *J* = 15.2 Hz, 1H), 1.27 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 172.9, 150.4, 149.7, 147.2, 146.5, 146.2, 133.8, 129.5, 128.7, 127.2, 126.5, 125.8, 125.3, 112.2, 112.2, 112.0, 111.4, 110.5, 78.7, 70.7, 62.0, 61.0, 57.6, 55.8, 55.5, 41.5, 39.9, 34.2, 31.2, 29.5, 13.8; IR (neat): ν = 2945, 2844, 2240, 1739, 1630, 1603, 1532,1479, 1395,910, 856, 797, 621 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{34}H_{37}Br_2NO_5$ $[M + H]^+$ 700.1018; found 700.1067.

Ethyl 2,3-dibromo-7a-(*p*-bromopheny;)-9,10-dimethoxy-6a,7,7a,12 13,14a-chloro-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]iso -quinoline-7-carboxylate (3i): White solid; Yield: (80%); MP 197–199 °C; R_f = 0.20 (hexanes/EtOAc 90:10); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.76 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.22 (s, 1H), 6.52 (d, *J* = 8.7 Hz, 2H), 4.74 (dd, *J* = 14.4 z, 6.4 Hz, 1H), 4.11 (t, *J* = 10.4 Hz, 1H), 3.90–3.84 (m, 1H), 3.79 (s, 3H), 3.77–3.71 (m, 2H), 3.69 (s, 3H), 3.36–3.26 (m, 3H), 3.15 (t, *J* = 11.6 Hz, 1H), 2.97 (d, *J* = 10.8 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$) δ = 172.3, 150.5, 147.7, 146.7, 131.2, 130.1, 129.5, 128.4, 126.8, 126.4, 125.4, 119.3, 118.5, 112.4, 111.6, 111.5, 110.5, 110.4, 76.4, 69.6, 62.6, 61.2, 59.2, 55.8, 55.7, 41.9, 40.3, 29.6,13.7; IR (neat): ν = 2925, 2853, 2254, 1725, 1652, 1610, 1514,1478, 1373, 993, 856, 790, 609 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{30}H_{28}Br_3NO_5$ $[M + H]^+$ 721.9497; found 721.9456.

Ethyl 2,3-dibromo-910-dimethoxy-7a-(thiophenyl-2-yl)-6a,7,7a,12, 13,14a-hexahydro-6*H*-chromeno[3'4':4,5]pyrrolo[2,1-*a*]isoquinoli-ne (3j): White solid; Yield: (86%); MP 150–152 °C; R_f = 0.37 (hexanes/EtOAc 85:15); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.50 (s, 1H), 7.41 (s, 1H), 7.25 (d, *J* =3.6 Hz, 1H), 7.07 (d, *J* = 5.2 H_z, 1H), 6.90 (t, *J* = 5.2 H_z, 1H), 6.64 (s, 1H), 6.52 (s, 1H), 4.72 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.23–4.14 (m, 2H), 3.87–3.83 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H) 3.70–3.68 (m, 1H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.31–3.28 (m, 1H), 3.21 (d, *J* = 10.8 Hz, 2H), 2.97–2.82 (m, 1H), 2.68 (d, *J* = 14.8 Hz, 1H), 0.99 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 172.2, 150.3, 147.6, 146.7, 134.1, 134.1, 134.0, 128.6, 128.3, 126.7, 125.3, 124.8, 124.1, 112.2, 111.5, 110.5, 110.4, 76.4, 70.5, 62.7, 61.2, 59.1, 55.7, 55.5, 41.8, 40.2, 29.0, 13.7; IR (neat): ν = 2980, 2257, 1736, 1614, 1515, 1473, 1337, 1313, 1259, 1108, 943, 792, 641 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{28}H_{27}Br_2NO_5S$ $[M + H]^+$ 649.9956; found 649.9915.

Ethyl 2, 9,10-trimethoxy-7a-(*p*-mthoxyphenyl)-6a,7,7a,12,13,14-hexahydro-6*H*- chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3k): White solid; Yield: (71%); MP 150–152 °C; R_f = 0.27 (hexanes/EtOAc 75:25); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.72 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.78–6.67 (m, 5H), 6.50 (s, 1H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.04–3.92 (m, 4H), 3.89 (s, 3H), 3.81 (s, 3H), 3.74 (s, 6H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.497 (d, *J* = 4.8 Hz, 1H), 3.22 (d, *J* = 9.6 Hz, 1H), 2.99 (d, *J* = 11.2 Hz, 1H), 2.66 (t, *J* = 6.8 Hz, 1H), 1.07 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 171.8, 158.2, 153.3, 149.9, 147.2, 146.4, 136.3, 135.0, 129.3, 127.8, 124.4, 118., 115.8, 113.7, 112.7, 111.1, 111.0, 110.4, 70.4, 68.2, 60.9, 57.3, 55.9, 55.79, 55.73, 55.1, 40.8 , 40.4, 27.9, 13.9; IR (neat): ν = 2979, 2266, 1758, 1625, 1507, 1467, 1342, 1326, 1265, 1108, 949, 783, 649 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{32}H_{35}NO_7$ $[M + H]^+$ 546.2414; found 546.2463

Ethyl2,9,10-trimethoxy-7a-(thiophen-2-yl)-6a,7,7a,12,13,14a-hexa-hydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7 carboxylate (3l): White solid; Yield: (89%); MP 144–146 °C; R_f = 0.29 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.26 (s, 1H) 7.06 (d, *J* = 5.2 Hz, 1H), 6.90 (d, *J* = 5.2 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.69 (s, 1H), 6.53 (s, 1H), 4.55(dd, *J* = 13.6, 5.6 Hz, 1H), 4.22 (d, *J* = 12.4 Hz, 1H), 4.07 (t, *J* = 9.6 Hz, 1H), 3.88–3.83 (m, 1H), 3.80 (s, 6H), 3.78–3.75 (m, 1H), 3.73 (s, 3H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.66–3.30 (m, 1H), 2.92 (t, *J* = 9.6 Hz, 1H), 2.67 (d, *J* = 15.2 Hz, 1H), 1.00 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 172.7, 158.4, 153.2, 148.3, 147.5, 146.6, 128.9, 127.08, 126.5, 125.0, 123.8, 122.5, 117.1, 113.4, 112.3, 111.5, 110.5, 110.4, 76.6, 69.4, 63.3, 61.03, 59.7, 55.8, 55.61, 55.68, 42.6, 40.2, 29.3, 13.7; IR (neat): ν = 2970, 2275, 1755, 1606, 1519, 1469, 1339, 1318, 1261, 1118, 933, 790, 644 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{29}H_{31}NO_6S$ $[M + H]^+$ 523.1872; found 523.1869.

Ethyl 2-fluoro- 9,10-dimethoxy-4-methyl-7a-(*p*-bromo)-6a,7,7a,12, 13,14a-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoli-ne-7-carboxylate (3m): White solid; Yield: (82%); MP 168–170 °C; R_f = 0.54 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.77 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.90 (dd, *J* = 11.2, 5.6 Hz, 1H), 6.75 (dd, *J* = 12.0, 5.6 Hz, 1H), 6.59 (s, 1H), 6.51 (s, 1H), 4.62 (dd, *J* = 13.6, 6 Hz, 1H), 4.02 (t, *J* = 10.0 Hz, 1H), 3.91–3.79 (m, 2H), 3.78 (s, 3H), 3.76–3.70 (m, 2H), 3.68 (s, 3H), 3.34–3.29 (m, 2H), 3.16–3.13 (m, 1H), 2.97 (t, *J* = 10.0 Hz, 1H), 2.68 (d, *J* = 15.6 Hz, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 173.3, 157.2, 154.8, 148.4, 148.4, 147.1, 146.9, 146.5, 136.3, 129.8, 129.0, 127.6, 127.5, 127.4, 126.8, 126.8, 122.3, 122.2, 115.9, 115.6, 112.0, 111.9, 110.6, 110.5, 110.4 110.2, 78.6, 69.7, 62.5, 60.9, 58.1, 55.8, 55.6, 42.1, 40.0, 29.5, 20.79, 20.75, 13.8; IR (neat): ν = 2953, 2842, 2251, 1749, 1648, 1619, 1523,1466, 1402, 992, 871, 798, 630 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{32}H_{34}FNO_5$ $[M + H]^+$ 532.6145; found 532.6185.

Ethyl 2-fluoro-9,10-dimethoxy-4-methyl-7a-(*p*-chloro)-6a,7,7a,12, 13,14a-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoli-ne-7-carboxylate (3n): White solid; Yield: (95%); MP 87–89 °C; R_f = 0.28 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_z, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 4.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.71 (dd, *J* = 4.2 Hz, 1H), 6.56–6.52 (m, 2H) 4.61 (dd, *J* = 4.8 Hz, 1H), 4.00 (t, *J* = 10.8 Hz, 1H), 3.87–3.81 (m, 1H), 3.79–3.68 (m, 6H), 3.32 (d, *J* = 9.6 Hz, 2H), 3.16 (d, *J* = 6.72 Hz, 1H), 2.98 (d, *J* = 10.4 Hz, 1H), 2.74 (d, *J* = 15.6 Hz, 1H), 2.12 (s, 3H), 1.05 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ = 172.8, 157.5, 157.2, 154.8, 148.6, 148.4, 136.4, 132.5, 129.7, 129.4, 128.4, 127.7, 121.8, 116.0, 115.8, 112.4, 112.2, 110.4, 110.0, 78.3, 69.6, 62.7, 61.0, 58.1, 55.0, 42.0, 39.8, 30.2, 29.6, 13.8; IR (neat): ν= 2950, 1691, 1639, 1580, 1410, 1242, 1077, 1045, 901, 831, 754, 615 cm^{-1};

HRMS-(ESI-TOF): *m/z*.calcd for $C_{30}H_{29}ClFNO_4$ $[M + H]^+$ 552.1874; found 552.1815

Ethyl 7a-(*p*-bromophenyl)-9,10-dimethoxy-5-tosyl-5,6,6a,7,7a,12, 13,14a-ocatahydrobezenzo[7,8]indolizino[2,3-*c*]quinoline-7-carbo-xylate (3o): White solid; Yield: (80%); MP 177–179 °C; R_f = 0.24 (hexanes/EtOAc 75:25); ^{1}H NMR (400 MH_Z, $CDCl_3$): δ = 7.86 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.8 Hz. 2H), 7.28 (br d, *J* = 4.8 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.20 (s, 1H), 7.13 (t, *J* = 6.8 Hz), 6.99 (d, *J* = 8 Hz, 2H), 6.46 (s, 1H), 6.40 (s, 1H) 4.55 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.16–3.89 (m, 1H), 3.75 (s, 3H), 3.72–3.66 (m, 1H), 3.63 (s, 3H), 3.59 (d, *J* = 6.0 Hz), 3.39 (t, *J* = 12.0 Hz, 1H), 3.10–2.87 (m, 4H), 2.57–2.51 (m, 2H), 2.27 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ = 172.6, 147.4, 146.6, 143.7, 136.2, 135.0, 131.3, 129.3, 128.7, 127.2, 126.8, 126.5, 124.8, 124.6, 112.0, 111.9, 110.6, 110.6, 78.0, 63.6, 61.0, 59.3, 55.7, 55.5, 50.6, 41.8, 39.4, 29.3, 21.4, 13.8; IR (neat): ν = 2960, 1709, 1654, 1590, 1417, 1256, 1097, 1031, 905, 83, 735, 610 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{37}H_{37}BrN_2O_6S$ $[M + H]^+$ 717.1556; found 717.1560.

Ethyl 2,9,10-dimethoxy-7a-(thiophen-2-yl)-5-tosyl-5,6,6a,7,7a,,12, 13,14a-octaxahydrobenzo[7,8]indolizino [2,3-*c*]quinoline-7-carbox -ylate (3p): White solid; Yield: (73%); MP 167–169 °C; R_f = 0.28 (hexanes/EtOAc 75:25); ^{1}H NMR (400 MH_Z, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 3H), 7.24–7.19 (m, 1H), 7.24–7.19 (m, 2H) 7.13 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 8 Hz, 2H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.87 (t, *J* = 4.4 Hz, 1H), 6.59 (s, 1H), 6.46 (s, 1H), 4.61 (dd, *J* = 16.4, 8.4 Hz, 1H), 3.95–3.91 (m, 1H), 3.76 (s, 3H), 3.73–3.70 (m, 1H), 3.68 (s, 3H), 3.65 (d, *J* = 6.8 Hz, 1H), 3.55 (d, *J* = 8.8 Hz, 1H), 3.44 (t, *J* = 12.0 Hz, 1H), 2.99–2.88 (m, 2H), 2.84 (d, *J* = 12.4 Hz, 1H), 2.51 (d, *J* = 13.6 Hz, 2H), 2.27 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ = 172.4, 147.5, 146.6, 143.6, 136.3, 135.2, 129.4, 128.5, 127.2, 126.9, 126.7, 126.5, 125.1, 124.7, 124.4, 123.9, 111.57, 111.53, 110.4, 110.3, 75.8, 64.4, 61.0, 55.82, 55.8, 55.7, 50.6, 41.5, 39.6, 29.1, 21.5, 13.8; IR (neat): ν = 2960, 1701, 1654, 1591, 1417, 1256, 1097, 1031, 905, 839, 735, 610 cm^{-1}; HRMS-(ESI-TOF): *m/z*.calcd for $C_{35}H_{36}N_2O_6S_2$ $[M + H]^+$ 645.2015; found 645.2087.

(6bR,14bR,15R,15aR)-ethyl 5-bromo-14b-phenyl-1,6b,8,9,14,14b, 15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-b]indole-15-carboxylate (4a). White solid; Yield: (86%); MP 169–171 °C; R_f = 0.31 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 9.96 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.48 (s, 1H), 7.28–7.37 (m, 5H), 7.23 (t, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 3.4 Hz, 1H), 4.09 (t, *J* = 10.8 Hz, 1H), 3.75–3.91 (m, 3H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.31 (d, *J* = 9.2 Hz, 1H), 3.19 (d, *J* = 8.0 Hz, 1H), 2.74–2.84 (m, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MH_Z, DMSO-d_6): δ = 171.9, 153.6, 151.6, 134.6, 134.1, 133.3, 131.0, 129.0, 127.2, 127.1, 125.2, 124.6, 123.3, 123.0, 118.6, 118.4, 117.6, 114.0, 110.1, 68.25, 56.38, 55.92, 50.36, 41.40, 35.27, 33.10, 29.0, 24.7, 23.0, 15.0; IR (neat): ν = 3335, 2933, 1705, 1424, 1410, 1324, 1314, 1221, 1216, 1221, 1219, 1164, 1134, 1089, 1028, 895, 636 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{27}BrN_2O_3$ $[M + H]^+$ 543.1205; found 543.1214.

(6bR,14bR,15R,15aR)-ethyl 5-bromo-14b-(4-bromophenyl)-1,6b,8 9,14,14b,15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-b] indole-15-carboxylate (4b). White solid; Yield: (89%); MP 172–174 °C; R_f = 0.34 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 10.05 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H,), 7.47 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 5.2 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 3.8 Hz, 1H), 3.74–3.90 (comp, 3H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.20–3.31 (m, 2H), 2.74–2.86 (m, 3H), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MH_Z DMSO-d_6): δ = 170.2, 150.1, 148.5, 137.7, 133.8, 130.2, 129.8, 128.6, 127.3, 127.2, 126.4, 126.1, 125.1, 123.7, 121.2, 120.5, 119.7, 111.9, 111.7, 74.4, 70.8, 65.0, 62.1, 58.1, 41.3, 39.1, 22.3, 14.2; IR (neat): ν = 3366, 2957, 2924, 1706, 1481, 1461, 1416, 1390, 1370, 1298, 1261, 1248, 1232, 1164, 1097, 996, 953, 898, 872, 842, 814, 785, 677, 663 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{26}Br_2N_3O_3$ $[M + H]^+$ 623.089; found 623.0831.

(6bR,14bR,15R,15aR)-ethyl 5-bromo-14b-(4-chlorophenyl)-1,6b,8, 9,14,14b,15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-b] indole-15-carboxylate (4c). White solid; Yield: (89%); MP 155–157 °C; R_f = 0.32 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 10.10 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 11.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.16 (t, *J* = 10.2 Hz, 1H), 3.93–3.79 (comp, 3H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.22–3.19 (m, 2H), 2.85–2.80 (comp, 3H), 0.98 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MH_Z, DMSO-d_6) δ = 171.1, 151.2, 146.8, 137.1, 133.8, 133.2, 131.7, 129.5, 128.9, 125.8, 125.4, 121.6, 120.6, 118.8, 118.3, 112.8, 111.7, 111.6, 108.9, 73.4, 69.4, 60.3, 60.2, 55.8, 43.8, 41.9, 21.0, 14.1; IR (neat): ν = 3320, 2947, 2915, 1710, 1431, 1416, 1380, 1360, 1298, 1261, 1238, 1220, 1164, 1097, 986, 913, 898, 852, 833, 812, 685, 580 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{26}BrClN_3O_3$ $[M + H]^+$ 577.0815; found 577.0859.

(6bR,14bR,15R,15aR)-ethyl 3,5-dibromo-14b-phenyl-1,6b,8,9,14, 14b,15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-*b*]indole-15-carboxylate (4d). White solid; Yield: (91%); MP 161–163 °C; R_f = 0.32 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MH_Z, DMSO-d_6): δ = 10.05 (s, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.70 (s, 1H), 7.55 (s, 1H), 7.40–7.35 (m, 3H), 7.26 (d, *J* = 7.2 Hz, 2H), 6.97 (t, *J* = 6.6 Hz, 1H), 6.90 (t, *J* = 6.4 Hz, 1H), 4.67 (d, *J* = 10.0 Hz, 1H), 4.25 (t, *J* = 10.4 Hz, 1H), 3.92 (app. t, *J* = 11.0 Hz, 2H), 3.81–3.77 (m, 1H), 3.69 (d, *J* = 9.2 Hz, 1H), 3.39–3.20 (m, 2H), 2.89–2.76 (comp, 3H), 0,99 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (100 MH_Z, DMSO-d_6) δ = 172.1, 150.7, 146.2, 136.8, 134.5, 133.5, 132.3, 129.4, 129.0, 127.9, 126.0, 124.9, 122.6, 119.8, 118.9, 112.6, 112.0, 111.2, 110.9, 75.6, 70.8, 62.1, 61.9, 58.2, 41.8, 40.3, 21.3, 14.0; IR (neat): ν = 3424, 2918, 2850, 1717, 1557, 1486, 1442, 1368, 1339, 1270, 1232, 1207, 1163, 1088, 1012, 986, 892, 862, 832, 761, 742, 727, 713, 670, 638 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{26}Br_2N_2O_3$ $[M + H]^+$ 623.0290; found 623.0240.

(6bR,14bR,15R,15aR)-ethyl 3,5-dibromo-14b-(4-chlorophenyl)-1,6b 8,9,14,14b,15,15a-octahydrochromeno [3',4':2,3]indolizino

8,7-b]indole-15-carboxylate (4e). White solid; Yield: (90%); MP 149–151 °C; R_f = 0.35 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.06 (s, IH), 7.95 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.67 (s, 1H), 7.51 (s, 1H), 7.39 (d, *J* = 8.8Hz, 2 H), 7.34 (d, *J* = 8Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.0 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 4.64 (dd, *J* = 4.0 Hz, 1H), 4.24 (t, *J* = 11.0 Hz, 1H), 3.89 (q, *J* = 4.8 Hz, 2H), 3.74–3.78 (m, 1H), 3.63 (d, *J* = 10 Hz, 1H), 2.25–3.20 (m, 2H), 2.73–2.86 (m, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.2, 150.8, 147.5,137.1, 133.8, 129.0,127.4, 127.1, 126.0, 125.61, 121.5, 118.8, 118.3, 111.9, 111.8, 111.7, 108.8, 75.8, 70.4, 61.4, 65.7, 61.3, 41.6, 40.3, 21.8, 14.0; IR (neat): ν = 3420, 2924, 1718, 1442, 1369, 1339, 1310, 1298, 1270, 1232, 1207, 1164, 1087, 1030, 987, 861, 801, 780, 764, 740, 727, 705, 637 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{25}Br_2ClN_2O_3$ [M + H]$^+$ 657.9900; found 657.0887.

(6bR,14bR,15R,15aR)-ethyl 3,5-dibromo-14b-(4-bromophenyl)-1,6b,8,9,14,14b,15,15a-octahydrochromeno [3',4':2,3]indolizino [8,7-*b*]indole-15-carboxylate (4f). White solid; Yield: (89%); MP 150–152 °C; R_f = 0.32 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (s, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.94–6.91 (m, 3H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.0 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 4.64 (dd, *J* = 3.8 Hz, 1H), 4.2 (t, *J* = 10.8 Hz, 1H), 3.85–3.91 (m, 2H), 3.74–3.78 (m, 3H), 0.93 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 170.9, 149.7, 145.8, 136.1, 132.8, 132.2, 130.7, 128.5, 127.9, 124.8, 124.4, 120.6, 119.6, 117.8, 110.8, 110.7, 110.6, 107.9, 74.4, 69.4, 60.3, 60.2, 55.8, 41.1, 40.6, 20.0, 12.9; IR (neat): ν = 3469, 2924, 1717, 1442, 1369, 1232, 1207, 1163, 1008, 892, 829, 742, 639, 545, 519 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{25}Br_3N_2O_3$ [M + H]$^+$ 700.9394; found 700.9368.

(6bR,14bR,15R,15aR)-ethyl 3,5-dibromo-14b-(p-tolyl)-1,6b,8,9,14, 14b,15,15a-octahydrochromeno [3',4':2,3]indolizino[8,7-b]indole-15-carboxylate (4g). White solid; Yield: (80%); MP 170–172 °C; R_f = 0.34 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.39 (s, 1H), 8.40 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 9.2 Hz, 1H), 3.97–4.02 (m, 4H), 3.69 (d, *J* = 8.0 Hz, 1H), 2.85–2.90 (m, 2H), 2.51 (t, *J* = 5.0 Hz, 2H), 2.40 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.1, 151.8, 144.4, 138.1, 137.0, 135.5, 135.3, 131.5, 129.1, 129.0, 128.0, 127.2, 121.4, 120.8, 120.4, 115.6, 115.5, 114.7, 113.5, 112.3, 72.4, 71.3, 65.6, 59.8, 59.4, 42.9, 41.8, 32.3, 28.9, 23.7, 20.8, 14.0;. IR (neat): ν = 3423, 1710, 1425, 1330, 1252, 1161, 1037, 811, 687, 674 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{31}H_{28}Br_2N_2O_3$ [M + H]$^+$ 637.0446; found 637.0414.

(6b,14b,15,15a)-ethyl 3,5 dichloro-14b-phenyl-1,6b,8,9,14,14b,15, 15a-octahydrochromeno[3',4':2,3] Indolizino[8,7-*b*]Indole -15-carb -oxylate (4h). White solid; Yield: (90%); MP 150–152 °C; R_f = 0.35 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 7.65 (app.d, *J* = 2.0 Hz, 1H), 7.43–7.53 (m, 6H), 7.38–7.41 (dd, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.06–7.10 (m, 1H), 7.0 (t, *J* = 7.0 Hz, 1H), 6.00 (app.q, *J* = 5.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 4.63 (q, *J* = 6.2 Hz, 2H), 4.39 (d, *J* = 9.6 Hz, 1H), 3.86–3.78 (m, 1H), 3.74–3.66 (m, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.65–3.40 (m, 2H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.2, 149.2, 147.5, 136.7, 132.8, 129.2, 128.8, 127.6, 126.3, 126.1, 125.4, 125.1, 124.7, 122.7, 122.2, 119.57, 118.7, 110.8, 110.7, 75.9, 70.8, 62.0, 61.6, 58.1, 41.7, 40.3, 21.3, 13.9; IR (neat): ν = 3435, 2910, 1690, 1420, 1380, 1370, 1309, 1309, 1309, 1242, 1209,1164, 1132, 1120, 1030, 948, 858, 818, 610, 560 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{30}H_{26}Cl_2N_2O_3$ [M + H]$^+$ 533.1320; found 533.1376.

8.(6bR,14bR,15R,15aR)-ethyl 14b-(4-(tert-butyl)phenyl)-3,5-dichloro-1,6b,8,9,14,14b,15,15a-octahydrochromeno[3',4':2,3] indolizino [8,7-b]indole-15-carboxylate (4i): White solid; Yield: (86%); MP 148–150 °C; R_f = 0.32 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.39 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 3H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.38 (s, 1H), 7.23 (t, *J* = 3.2 Hz, 1H), 7.20 (s, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.23 (d, *J* = 15.6 Hz), 3.9–4.04 (m, 4H), 2.85–3.05 (m, 2H), 3.68 (d, *J* = 16.0 Hz, 1H), 2.51 (t, *J* = 6.6 Hz, 3H), 1.31 (s, 9H), 2.51 (t, *J* = 7.0 Hz, 3H), 1.31 (s, 9H), 1.15 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.0, 170.9, 155.2, 153.4, 136.6, 136.2, 134.3, 131.4, 129.1, 128.9, 127.7, 127.2, 126.6, 125.3, 125.0, 120.6, 119.6, 112.7, 71.5, 59.9, 59.3, 52.3, 50.4, 35.2, 34.8, 30.8, 29.0, 23.7, 22.0, 14.0; IR (neat): ν = 3425, 2963, 1737, 1474, 1440, 1370, 1309, 1231, 1209, 1309, 1309, 1231, 1209, 1164, 1144, 1089, 1028, 978, 878, 709, 661, 636 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{34}H_{34}Cl_2N_2O_3$ [M + H]$^+$ 589.1946; found 589.1922.

10.(6bR,14bR,15R,15aR)-ethyl3-methyl-14b-phenyl-1,6b,8,9,14, 14b,15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-*b*]indole-15-carboxylate (4j). White solid; Yield: (88%); MP 149–151 °C; R_f = 0.34 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1H), 7.9 (d, *J* = 7.2 Hz, 2H), 7.35 (q, *J* = 6.9 Hz, 3H), 7.19–7.26 (m, 3H), 6.95 (t, *J* = 6.8 Hz H), 6.86 (m, *J* = 7.5 Hz, 2H), 4.55 (dd, *J* = 4.0 Hz, 1H), 4.06 (t, *J* = 10.8 Hz, 1H), 3.77–3.91 (m, 3H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.38 (t, *J* = 4.6 Hz, 1H), 3.27 (app. d, *J* = 7.2 Hz, 1H), 2.73–2.85 (m, 3H), 2.08 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.8, 152.7, 148.2, 136.6, 133.3, 129.6, 129.1, 127.3, 126.3, 126.2, 126.1, 124.8, 122.0, 121.4, 119.7, 119.4, 118.7, 111.0, 110.7, 75.9, 69.9, 62.6, 61.4, 58.7, 41.7, 40.9, 21.3, 16.5, 13.9; IR (neat): ν = 3410, 2973, 1716, 1459, 1445, 1374, 1340, 1317, 1299, 1273, 1239, 1203,1176, 1159, 1078, 918, 883, 790, 691, 671 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{31}H_{30}N_2O_3$ [M + H]$^+$ 479.2256; found 479.2223.

11.(6bR,14bR,15R,15aR)-ethyl 5-methoxy-14b-phenyl-1,6b,8,9,14, 14b15,15a-octahydrochromeno[3',4':2,3]indolizino[8,7-*b*]indole-15-carboxylate (4k). White solid; Yield: (76%); MP 160–162 °C; R_f = 0.35 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.0 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.28–7.40 (m, 5H), 6.73 (s, 2H), 4.42 (dd, *J* = 3.2 Hz, 1H), 3.99 (q, *J* = 10.8 Hz, 2H), 3.75–3.91 (comp, 2H), 3.73 (s, 3H), 3.39 (App d, *J* = 9.6 Hz, 2H), 3.18 (d, *J* = 11.2 Hz, 2H), 2.73–2.85 (m, 3H), 0.96 (t, *J* = 7 Hz,

3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.7, 153.5, 148.6, 148.0, 146.7, 136.6, 133.2, 129.1, 127.4, 126.3, 126.2, 122.7, 122.0, 119.4, 118.7, 117.4, 113.8, 112.6, 110.9, 110.7, 75.8, 69.7, 62.6, 61.4, 58.5, 56.0, 41.8, 41.0, 21.3, 13.9; IR (neat): ν = 3429, 2962, 1709, 1630, 1492, 1439, 1375, 1271, 1249, 1203, 1165, 1094, 1036, 999, 871, 747, 704 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{31}H_{30}N_2O_4$ $[M + H]^+$ 495.2206; found 495.2208.

(6bR,14bR,15R,15aS)-ethyl 14b-phenyl-2-tosyl-2,6b,8,9,14,14b,15,15a-octahydro-1H-indolo[3',2':7,8]indolizino[2,3-*c*]quinoline-15-carboxylate (4l). White solid; Yield: (92%); MP 156–158 °C; R_f = 0.34 (hexanes/EtOAc 80:20); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.3–7.17 (comp, 10H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 4.9 (dd, *J* = 4.0 Hz, 1H), 3.93 (q, *J* = 3.6 Hz, 1H), 3.74–3.77 (m, 1H), 3.61 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 12.4 Hz, 1H), 3.38 (d, *J* = 12.4 Hz, 1H), 3.01 (d, *J* = 7.6 Hz, 1H), 2.71–2.81 (m, 2H), 2.37 (app d, *J* = 11.2 Hz, 1H), 2.22 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2, 147.8, 143.7, 136.7, 136.6, 135.7, 133.1, 129.5, 129.0,128.5, 127.4, 127.3, 127.2, 126.2, 126.1, 125.1, 124.9, 122.0, 119.3, 118.6, 110.7, 75.0, 64.1, 61.3, 59.4, 50.8, 41.2, 39.0, 21.5, 21.6, 14.0; IR (neat): ν = 3410, 2940, 1716, 1594, 1483, 1448, 1352, 1266, 1163, 1090, 1074, 1046, 1026, 1010, 954, 888 cm^{-1}; HRMS-(ESI-TOF): m/z.calcd for $C_{37}H_{35}N_3O_4S$ $[M + H]^+$ 618.2348; found 618.2327.

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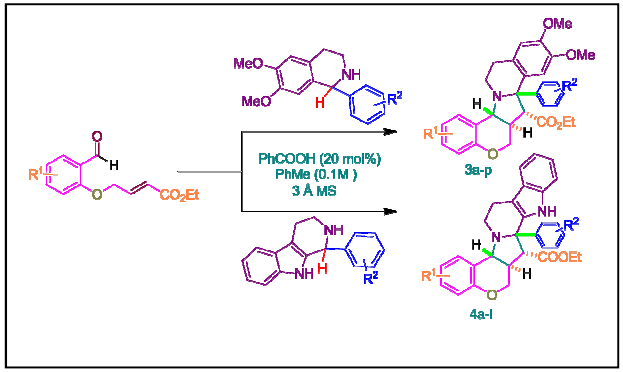
Graphical abstract

Highly Diastereoselective Synthesis of Polycyclic Amines via-Redox Neutral C-H Functionalization

Chottanahalli. S. Pavan Kumar,[1#] Kachigere. B. Harsha,[1#] Nagarakere C. Sandhaya.#[†] Ajjalli. B. Ramesha,[#] Kempegowda Mantelingu, [#*] Kanchugarakopal. S. Rangappa [#*]



Abstarct

Construction of polycyclic amines via C-H functionalization and 3+2 cycloaddition with high diastereoselectivities was achieved under mild conditions.

Supplementary material

Highly Diastereoselective Synthesis of Polycyclic Amines via-Redox Neutral C-H Functionalization

New Journal of Chemistry

Chottanahalli. S. Pavan Kumar,[a#] Kachigere. B. Harsha,[a#] Nagarakere. C. Sandhaya,[a] Ajjalli. B. Ramesha, [a] Kempegowda Mantelingu, [a*] and Kanchugarakoppal. S. Rangappa, [a*]

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Contents.

Date: 01-07-2015

Crystallographic Data

Experimental

Single crystals of suitable dimensions were chosen carefully for X-ray diffraction studies. The X-intensity data were collected at a temperature of 293(2) K on a Bruker Proteum2 CCD diffractometer equipped with an X-ray generator operating at 45 kV and 10 mA, using CuK_α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of φ (0° and 90°), keeping the scan width of 0.5°, exposure time of 2 s, the sample to detector distance of 45.10 mm and 2θ value at 46.6°. The complete data sets were processed using *SAINT PLUS*.[1] The structures were solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs[2]. The geometrical calculations were carried out using the program *PLATON*.[3] The molecular and packing diagrams were generated using the software *MERCURY*.[4] The details of the crystal structure and data refinement are given in Table 1. The list of bond lengths and bond angles of the non-hydrogen atoms are given in Table 4 and Table 5 respectively. Figures **3c, 3p and 4c** represent the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

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Table1:Crystal data and structure refinement details **3c**

Empirical formula	$C_{30}H_{28}Br_2NO_5$	
Formula weight	642.35	
Temperature	296(2) K	
Wavelength	1.54178 Å	
θ range for above	3.50° to 64.52°	
Crystal system	Triclinic	
Space group	P −1	
Cell dimensions		
a = 9.9779(11) Å	b = 11.5105(12) Å	c = 13.4027(14) Å
α = 91.472(6)°	β = 107.929(6)°	γ = 109.296(6)°
Volume	1368.3(3) $Å^3$	
Z	2	
Density(calculated)	1.559 $Mg\,m^{-3}$	
Absorption coefficient	4.094 mm^{-1}	
F_{000}	650	
Crystal size	0.25 × 0.25 × 0.25 mm	
θ range for data collection	3.50° to 64.52°	
Index ranges	$-11 \leq h \leq 11$	
	$-13 \leq k \leq 13$	
	$-15 \leq l \leq 14$	
Reflections collected	13269	
Independent reflections	4454 [$R_{int} = 0.0522$]	
Refinement method	Full matrix least-squares on F^2	
Data / restraints / parameters	4454 / 0 / 346	
Goodness-of-fit on F^2	1.041	
Final [$I > 2\sigma(I)$]	R1 = 0.0609, wR2 = 0.1680	
R indices (all data)	R1 = 0.0758, wR2 = 0.1850	
Largest diff. peak and hole	0.591 and −0.556 e $Å^{-3}$	

Table 2: Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms.

Atom	x	y	z	U_{eq}
Br1	0.81469(9)	0.24281(7)	0.25466(4)	0.0768(3)
C2	0.9232(6)	0.2883(5)	0.4022(4)	0.0523(12)
C3	1.0708(7)	0.2946(5)	0.4393(4)	0.0634(14)
C4	1.1500(6)	0.3276(6)	0.5467(4)	0.0648(15)
C5	1.0816(6)	0.3531(5)	0.6163(4)	0.0530(12)
O6	1.1715(4)	0.3848(4)	0.7209(3)	0.0685(11)
C7	1.1134(5)	0.4155(5)	0.7999(4)	0.0550(12)
C8	0.9463(5)	0.3471(4)	0.7668(3)	0.0411(10)
C9	0.8620(5)	0.3793(4)	0.8337(3)	0.0395(9)
C10	0.7043(5)	0.3737(4)	0.7478(3)	0.0363(9)
C11	0.5649(5)	0.2959(4)	0.7720(3)	0.0384(9)
C12	0.5438(5)	0.3310(4)	0.8646(3)	0.0436(10)
C13	0.4155(6)	0.2724(5)	0.8871(4)	0.0493(11)
C14	0.2980(6)	0.1749(5)	0.8144(4)	0.0523(12)
C15	0.3190(6)	0.1352(5)	0.7238(4)	0.0528(12)
C16	0.4533(5)	0.1946(4)	0.7024(3)	0.0432(10)
C17	0.4746(5)	0.1495(4)	0.6037(4)	0.0485(11)
C18	0.6410(5)	0.1900(4)	0.6187(3)	0.0415(10)
N19	0.7070(4)	0.3276(3)	0.6431(2)	0.0347(7)
C20	0.8702(5)	0.3800(4)	0.6594(3)	0.0373(9)
C21	0.9318(5)	0.3465(4)	0.5785(3)	0.0405(10)
C22	0.8540(5)	0.3154(4)	0.4701(3)	0.0454(10)
C23	0.6951(5)	0.5039(4)	0.7387(3)	0.0342(9)
C24	0.7783(5)	0.6081(4)	0.8140(3)	0.0444(10)
C25	0.7552(6)	0.7196(4)	0.8024(4)	0.0519(12)
C26	0.6462(5)	0.7287(4)	0.7135(3)	0.0433(10)
C27	0.5602(6)	0.6269(4)	0.6373(3)	0.0491(11)
C28	0.5855(6)	0.5161(4)	0.6496(3)	0.0455(10)
Br29	0.60863(7)	0.87909(5)	0.69793(4)	0.0650(3)
C30	0.8472(5)	0.3015(4)	0.9213(3)	0.0441(10)
O31	0.8673(4)	0.3421(3)	1.0093(2)	0.0598(9)
O32	0.8152(5)	0.1812(3)	0.8903(3)	0.0694(11)
C33	0.8062(10)	0.0976(7)	0.9713(5)	0.090(2)
C34	0.6577(12)	0.0543(8)	0.9739(6)	0.112(3)
O35	0.1704(4)	0.1259(4)	0.8383(3)	0.0742(12)
C36	0.0430(7)	0.0430(6)	0.7606(6)	0.086(2)
O37	0.3898(4)	0.3019(4)	0.9775(3)	0.0642(10)
C38	0.5202(7)	0.3633(7)	1.0677(4)	0.0798(19)

Table 3: Anisotropic thermal parameters of the non-hydrogen atoms.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	0.1042(6)	0.0965(5)	0.0485(4)	0.0537(4)	0.0316(4)	0.0129(3)
C2	0.071(4)	0.054(3)	0.052(3)	0.034(3)	0.035(3)	0.020(2)
C3	0.075(4)	0.073(3)	0.068(3)	0.038(3)	0.045(3)	0.022(3)
C4	0.045(3)	0.093(4)	0.074(3)	0.037(3)	0.031(3)	0.022(3)
C5	0.047(3)	0.061(3)	0.059(3)	0.024(2)	0.021(2)	0.020(2)
O6	0.039(2)	0.111(3)	0.060(2)	0.034(2)	0.0135(17)	0.014(2)
C7	0.035(3)	0.072(3)	0.051(3)	0.018(2)	0.008(2)	0.002(2)
C8	0.042(3)	0.041(2)	0.041(2)	0.0184(19)	0.011(2)	0.0079(17)
C9	0.039(2)	0.037(2)	0.039(2)	0.0138(18)	0.0100(19)	0.0051(17)
C10	0.038(2)	0.038(2)	0.0328(19)	0.0143(18)	0.0104(18)	0.0040(16)
C11	0.038(2)	0.033(2)	0.044(2)	0.0133(18)	0.0138(19)	0.0105(17)
C12	0.043(3)	0.043(2)	0.048(2)	0.016(2)	0.017(2)	0.0091(18)
C13	0.049(3)	0.058(3)	0.052(3)	0.023(2)	0.025(2)	0.017(2)
C14	0.045(3)	0.048(3)	0.071(3)	0.013(2)	0.031(3)	0.016(2)
C15	0.038(3)	0.045(2)	0.066(3)	0.004(2)	0.017(2)	0.004(2)
C16	0.040(3)	0.038(2)	0.053(2)	0.0134(19)	0.018(2)	0.0077(18)
C17	0.047(3)	0.041(2)	0.050(2)	0.008(2)	0.015(2)	−0.0030(19)
C18	0.043(3)	0.035(2)	0.046(2)	0.0115(18)	0.016(2)	−0.0005(17)
N19	0.0347(19)	0.0312(16)	0.0377(17)	0.0108(14)	0.0124(15)	0.0030(13)
C20	0.032(2)	0.038(2)	0.042(2)	0.0120(17)	0.0118(19)	0.0073(16)
C21	0.036(2)	0.043(2)	0.049(2)	0.0183(19)	0.018(2)	0.0132(18)
C22	0.046(3)	0.051(2)	0.047(2)	0.024(2)	0.019(2)	0.0135(19)
C23	0.035(2)	0.034(2)	0.0357(19)	0.0113(17)	0.0150(18)	0.0051(15)
C24	0.043(3)	0.040(2)	0.043(2)	0.0184(19)	0.001(2)	0.0016(18)
C25	0.048(3)	0.038(2)	0.056(3)	0.010(2)	0.005(2)	−0.0086(19)
C26	0.046(3)	0.040(2)	0.050(2)	0.019(2)	0.020(2)	0.0073(18)
C27	0.051(3)	0.049(3)	0.044(2)	0.024(2)	0.005(2)	0.0047(19)
C28	0.047(3)	0.044(2)	0.042(2)	0.019(2)	0.007(2)	−0.0032(18)
Br29	0.0777(5)	0.0432(3)	0.0732(4)	0.0313(3)	0.0134(3)	0.0066(2)
C30	0.048(3)	0.049(2)	0.037(2)	0.020(2)	0.013(2)	0.0077(18)
O31	0.071(2)	0.064(2)	0.0369(17)	0.0229(19)	0.0096(16)	0.0032(15)
O32	0.121(3)	0.0490(19)	0.0499(18)	0.035(2)	0.039(2)	0.0185(15)
C33	0.138(7)	0.071(4)	0.075(4)	0.034(4)	0.056(4)	0.030(3)
C34	0.142(8)	0.100(6)	0.092(5)	0.034(5)	0.043(5)	0.039(5)
O35	0.050(2)	0.077(3)	0.094(3)	0.006(2)	0.041(2)	0.012(2)
C36	0.058(4)	0.062(4)	0.142(6)	0.009(3)	0.051(4)	0.006(4)
O37	0.054(2)	0.089(3)	0.058(2)	0.0251(19)	0.0317(18)	0.0117(18)
C38	0.077(4)	0.120(6)	0.052(3)	0.038(4)	0.031(3)	0.012(3)

Table 4: Bond lengths (Å).

Atoms	Length	Atoms	Length
Br1-C2	1.900(5)	C14-C15	1.385(7)
C2-C3	1.377(8)	C15-C16	1.409(7)
C2-C22	1.384(6)	C16-C17	1.508(6)
C3-C4	1.384(8)	C17-C18	1.514(6)
C4-C5	1.389(7)	C18-N19	1.483(5)
C5-O6	1.373(6)	N19-C20	1.480(5)
C5-C21	1.398(7)	C20-C21	1.498(6)
O6-C7	1.441(6)	C21-C22	1.392(6)
C7-C8	1.502(7)	C23-C24	1.382(6)
C8-C9	1.517(6)	C23-C28	1.396(6)
C8-C20	1.530(6)	C24-C25	1.381(7)
C9-C30	1.510(6)	C25-C26	1.377(7)
C9-C10	1.618(6)	C26-C27	1.374(6)
C10-N19	1.499(5)	C26-Br29	1.892(4)
C10-C11	1.520(6)	C27-C28	1.384(7)
C10-C23	1.538(6)	C30-O31	1.189(5)
C11-C16	1.385(6)	C30-O32	1.338(6)
C11-C12	1.393(6)	O32-C33	1.473(6)
C12-C13	1.365(6)	C33-C34	1.411(13)
C13-O37	1.369(6)	O35-C36	1.395(7)
C13-C14	1.398(7)	O37-C38	1.426(7)
C14-O35	1.352(6)		

Table 5: Bond angles (°).

Atoms	Angle	Atoms	Angle
C3-C2-C22	121.2(5)	C11-C16-C15	119.5(4)
C3-C2-Br1	118.9(4)	C11-C16-C17	120.1(4)
C22-C2-Br1	119.9(4)	C15-C16-C17	120.4(4)
C2-C3-C4	119.0(5)	C16-C17-C18	109.9(4)
C3-C4-C5	120.7(5)	N19-C18-C17	108.4(4)
O6-C5-C4	115.3(5)	C20-N19-C18	114.0(3)
O6-C5-C21	124.3(4)	C20-N19-C10	101.0(3)
C4-C5-C21	120.3(5)	C18-N19-C10	112.1(3)
C5-O6-C7	120.2(4)	N19-C20-C21	120.9(4)
O6-C7-C8	110.3(4)	N19-C20-C8	104.9(3)
C7-C8-C9	117.9(4)	C21-C20-C8	110.1(4)
C7-C8-C20	109.0(4)	C22-C21-C5	118.6(4)
C9-C8-C20	101.7(3)	C22-C21-C20	125.2(4)
C30-C9-C8	115.0(4)	C5-C21-C20	116.2(4)
C30-C9-C10	115.1(3)	C2-C22-C21	120.3(5)
C8-C9-C10	104.0(3)	C24-C23-C28	116.9(4)
N19-C10-C11	112.8(3)	C24-C23-C10	126.0(4)
N19-C10-C23	106.2(3)	C28-C23-C10	117.0(4)
C11-C10-C23	106.2(3)	C25-C24-C23	122.1(4)
N19-C10-C9	105.4(3)	C26-C25-C24	119.7(4)
C11-C10-C9	114.4(3)	C27-C26-C25	120.0(4)
C23-C10-C9	111.6(3)	C27-C26-Br29	119.5(4)
C16-C11-C12	118.3(4)	C25-C26-Br29	120.4(3)
C16-C11-C10	122.4(4)	C26-C27-C28	119.6(4)
C12-C11-C10	119.2(4)	C27-C28-C23	121.7(4)
C13-C12-C11	122.6(4)	O31-C30-O32	123.3(4)
C12-C13-O37	125.0(5)	O31-C30-C9	124.4(4)
C12-C13-C14	119.6(4)	O32-C30-C9	112.3(3)
O37-C13-C14	115.4(4)	C30-O32-C33	116.8(4)
O35-C14-C15	124.6(5)	C34-C33-O32	109.0(7)
O35-C14-C13	116.7(4)	C14-O35-C36	118.3(5)
C15-C14-C13	118.7(4)	C13-O37-C38	116.2(4)
C14-C15-C16	121.1(5)		

Table 1: Crystal data and structure refinement details **3P**.

Empirical formula		$C_{35}H_{36}N_2O_6S_2$	
Formula weight		644.78	
Temperature		296(2) K	
Wavelength		1.54178 Å	
cell determination	4501	reflns. for	
θ range for above		2.62° to 64.92°	Crystal
system		Monoclinic	Space group
P 21/c			
Cell dimensions			
a = 17.5740(17) Å		b = 8.9640(9) Å	c = 20.843(2) Å
α = 90.00°		β = 106.682(4)°	γ = 90.00°
Volume		3145.3(5) $Å^3$	
Z		4	
Density(calculated)		1.362 $Mg\,m^{-3}$	
Absorption coefficient		1.943 mm^{-1}	
F_{000}		1360	
Crystal size		0.27 × 0.27 × 0.27 mm	
θ range for data collection		2.62° to 64.92°	
Index ranges		$-20 \leq h \leq 20$	
		$-10 \leq k \leq 10$	
		$-24 \leq l \leq 20$	
Reflections collected		14873	
Independent reflections		5126 [$R_{int} = 0.0399$]	
Absorption correction		multi-scan	
Refinement method		Full matrix least-squares on F^2	
Data / restraints / parameters		5126 / 0 / 410	
Goodness-of-fit on F^2		1.078	
Final [$I > 2\sigma(I)$]		R1 = 0.0545, wR2 = 0.1671	
R indices (all data)		R1 = 0.0596, wR2 = 0.1727	
Largest diff. peak and hole		0.752 and −0.630 e $Å^{-3}$	

Table 2: Bond lengths (Å).

Atoms	Length	Atoms	Length
S36-O38	1.427(2)	C9-C10	1.532(3)
S36-O37	1.428(3)	C4-C5	1.404(3)
S36-N14	1.670(2)	C4-C3	1.501(3)
S36-C39	1.757(3)	C7-C8	1.378(3)
S26-C25	1.690(3)	C7-C6	1.407(4)
S26-C22	1.704(2)	C21-C20	1.503(3)
O33-C31	1.337(3)	C21-C182	1.504(3)
O33-C34	1.453(3)	C20-C19	1.388(4)
O27-C7	1.374(3)	C20-C15	1.406(4)
O27-C28	1.413(4)	C15-C16	1.404(4)
O29-C6	1.374(3)	C12-C13	1.516(3)
O29-C30	1.421(4)	C3-C2	1.513(3)
O32-C31	1.199(3)	C5-C6	1.373(4)
N1-C2	1.470(3)	C19-C18	1.384(4)
N1-C21	1.481(3)	C16-C17	1.375(5)
N1-C10	1.495(3)	C39-C44	1.389(5)
N14-C15	1.441(4)	C39-C40	1.391(4)
N14-C13	1.488(3)	C18-C17	1.372(5)
C23-C24	1.468(4)	C24-C25	1.343(5)
C23-C22	1.489(4)	C40-C41	1.373(4)
C22-C10	1.520(3)	C41-C42	1.383(5)
C11-C31	1.516(3)	C42-C43	1.390(4)
C11-C12	1.525(3)	C42-C45	1.504(5)
C11-C10	1.631(3)	C44-C43	1.364(5)
C9-C4	1.378(4)	C34-C35	1.476(5)
C9-C8	1.405(3)		

Table 1: Crystal data and structure refinement details **4C.**

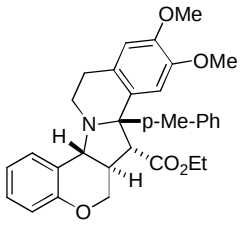
Empirical formula	$C_{30}H_{26}BrClN_2O_3$	
Formula weight	577.89	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Reflns. for cell determination	4104	
θ range for above	6.72° to 64.51°	
Crystal system	Triclinic	
Space group	P −1	
Cell dimensions		
a = 9.5848(7) Å	b = 11.0031(8) Å	c = 14.0353(11) Å
α = 87.764(2)°	β = 70.878(2)°	γ = 65.624(2)°
Volume	1265.88(16) $Å^3$	
Z	2	
Density(calculated)	1.516 $Mg\,m^{-3}$	
Absorption coefficient	3.478 mm^{-1}	
F_{000}	592	
Crystal size	0.25 × 0.25 × 0.25 mm	
θ range for data collection	6.72° to 64.51°	
Index ranges	$-11 \le h \le 11$	
	$-12 \le k \le 12$	
	$-16 \le l \le 16$	
Reflections collected	14548	
Independent reflections	4174 [$R_{int} = 0.0313$]	
Absorption correction	multi-scan	
Refinement method	Full matrix least-squares on F^2	
Data / restraints / parameters	4174 / 0 / 335	
Goodness-of-fit on F^2	1.103	
Final [$I > 2\sigma(I)$]	R1 = 0.0331, wR2 = 0.0959	
R indices (all data)	R1 = 0.0335, wR2 = 0.0965	
Largest diff. peak and hole	0.376 and −0.584 e $Å^{-3}$	

Table 2: Bond lengths (Å).

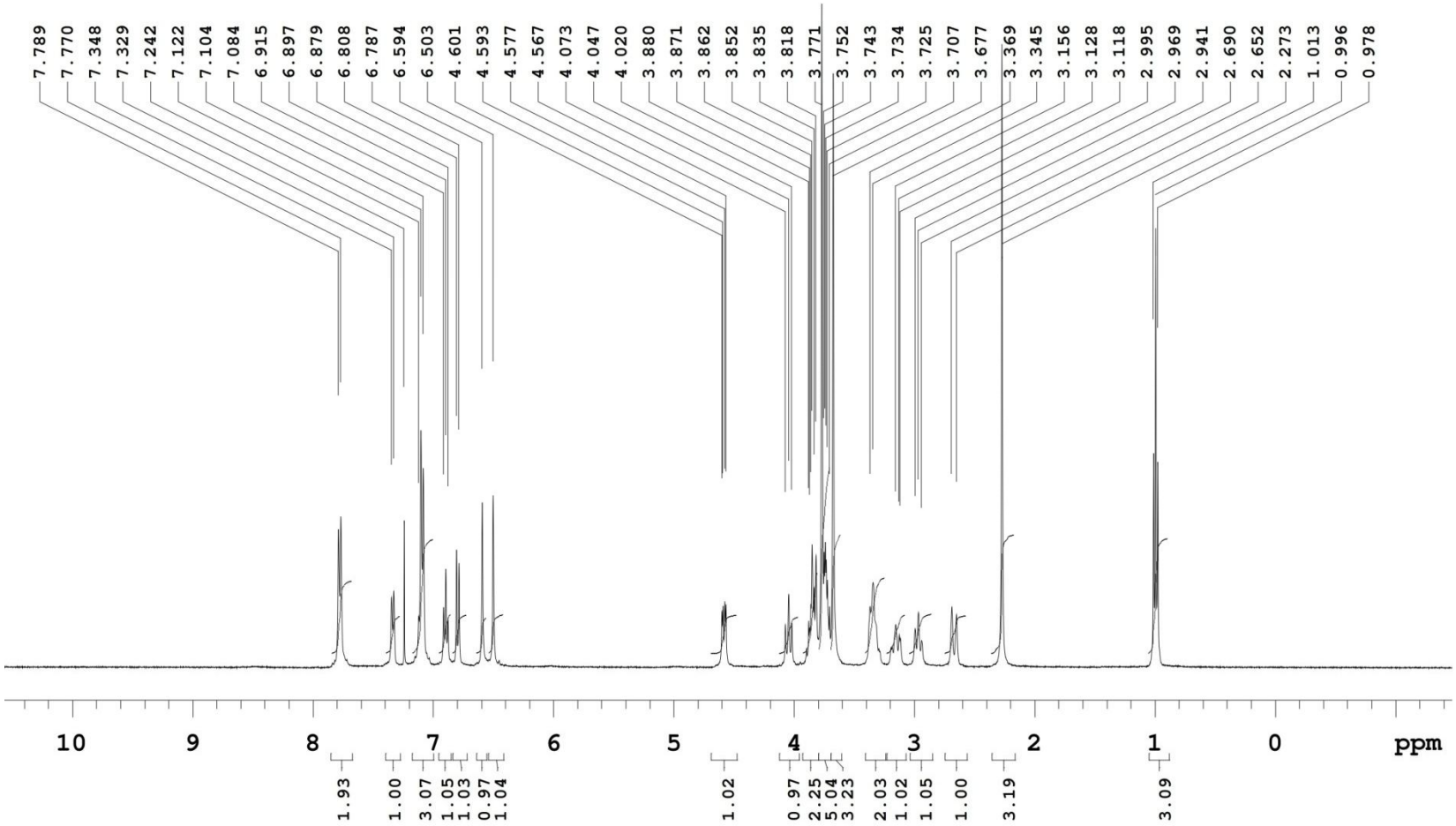
Atoms	Length	Atoms	Length
Br1-C2	1.904(2)	C15-C16	1.406(3)
C2-C25	1.381(3)	C16-C17	1.384(3)
C2-C3	1.387(3)	C17-C18	1.402(3)
C3-C4	1.376(3)	C18-C19	1.435(3)
C4-C5	1.390(3)	C19-C20	1.495(3)
C5-O6	1.369(3)	C20-C21	1.532(3)
C5-C24	1.403(3)	C21-N22	1.484(2)
O6-C7	1.443(3)	N22-C23	1.478(3)
C7-C8	1.516(3)	C23-C24	1.499(3)
C8-C23	1.523(3)	C24-C25	1.395(3)
C8-C9	1.532(3)	C26-C31	1.387(3)
C9-C33	1.514(3)	C26-C27	1.397(3)
C9-C10	1.614(3)	C27-C28	1.386(3)
C10-N22	1.493(3)	C28-C29	1.387(3)
C10-C11	1.504(3)	C29-C30	1.381(3)
C10-C26	1.546(3)	C29-Cl32	1.741(2)
C11-C19	1.360(3)	C30-C31	1.395(3)
C11-N12	1.378(3)	C33-O34	1.209(3)
N12-C13	1.378(3)	C33-O35	1.334(2)
C13-C14	1.392(3)	O35-C36	1.456(2)
C13-C18	1.420(3)	C36-C37	1.506(3)
C14-C15	1.385(3)		

Table 3: Bond angles (°).

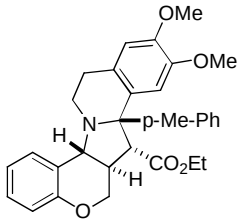
Atoms	Angle	Atoms	Angle
C25-C2-C3	121.0(2)	C17-C18-C13	118.72(19)
C25-C2-Br1	120.01(17)	C17-C18-C19	134.58(19)
C3-C2-Br1	118.95(17)	C13-C18-C19	106.68(17)
C4-C3-C2	119.3(2)	C11-C19-C18	106.57(18)
C3-C4-C5	120.7(2)	C11-C19-C20	121.23(18)
O6-C5-C4	115.67(19)	C18-C19-C20	132.19(18)
O6-C5-C24	124.4(2)	C19-C20-C21	108.48(16)
C4-C5-C24	119.9(2)	N22-C21-C20	109.64(16)
C5-O6-C7	118.03(16)	C23-N22-C21	115.14(15)
O6-C7-C8	108.07(17)	C23-N22-C10	100.67(14)
C7-C8-C23	109.03(16)	C21-N22-C10	114.62(15)
C7-C8-C9	120.24(17)	N22-C23-C24	120.64(17)
C23-C8-C9	101.80(16)	N22-C23-C8	104.31(15)
C33-C9-C8	111.98(16)	C24-C23-C8	110.13(16)
C33-C9-C10	114.35(15)	C25-C24-C5	118.84(19)
C8-C9-C10	102.51(15)	C25-C24-C23	123.36(19)
N22-C10-C11	109.88(16)	C5-C24-C23	117.67(18)
N22-C10-C26	107.57(15)	C2-C25-C24	120.1(2)
C11-C10-C26	105.35(15)	C31-C26-C27	118.56(18)
N22-C10-C9	106.39(15)	C31-C26-C10	123.30(17)
C11-C10-C9	115.43(15)	C27-C26-C10	117.75(17)
C26-C10-C9	112.01(15)	C28-C27-C26	121.25(19)
C19-C11-N12	110.83(17)	C27-C28-C29	119.01(19)
C19-C11-C10	125.37(18)	C30-C29-C28	120.90(18)
N12-C11-C10	123.40(17)	C30-C29-Cl32	120.10(16)
C11-N12-C13	108.13(16)	C28-C29-Cl32	118.99(16)
N12-C13-C14	129.87(19)	C29-C30-C31	119.46(19)
N12-C13-C18	107.78(17)	C26-C31-C30	120.78(19)
C14-C13-C18	122.35(19)	O34-C33-O35	123.99(18)
C15-C14-C13	117.6(2)	O34-C33-C9	124.55(18)
C14-C15-C16	121.1(2)	O35-C33-C9	111.45(16)
C17-C16-C15	121.2(2)	C33-O35-C36	118.01(15)
C16-C17-C18	119.00(19)	O35-C36-C37	110.88(16)



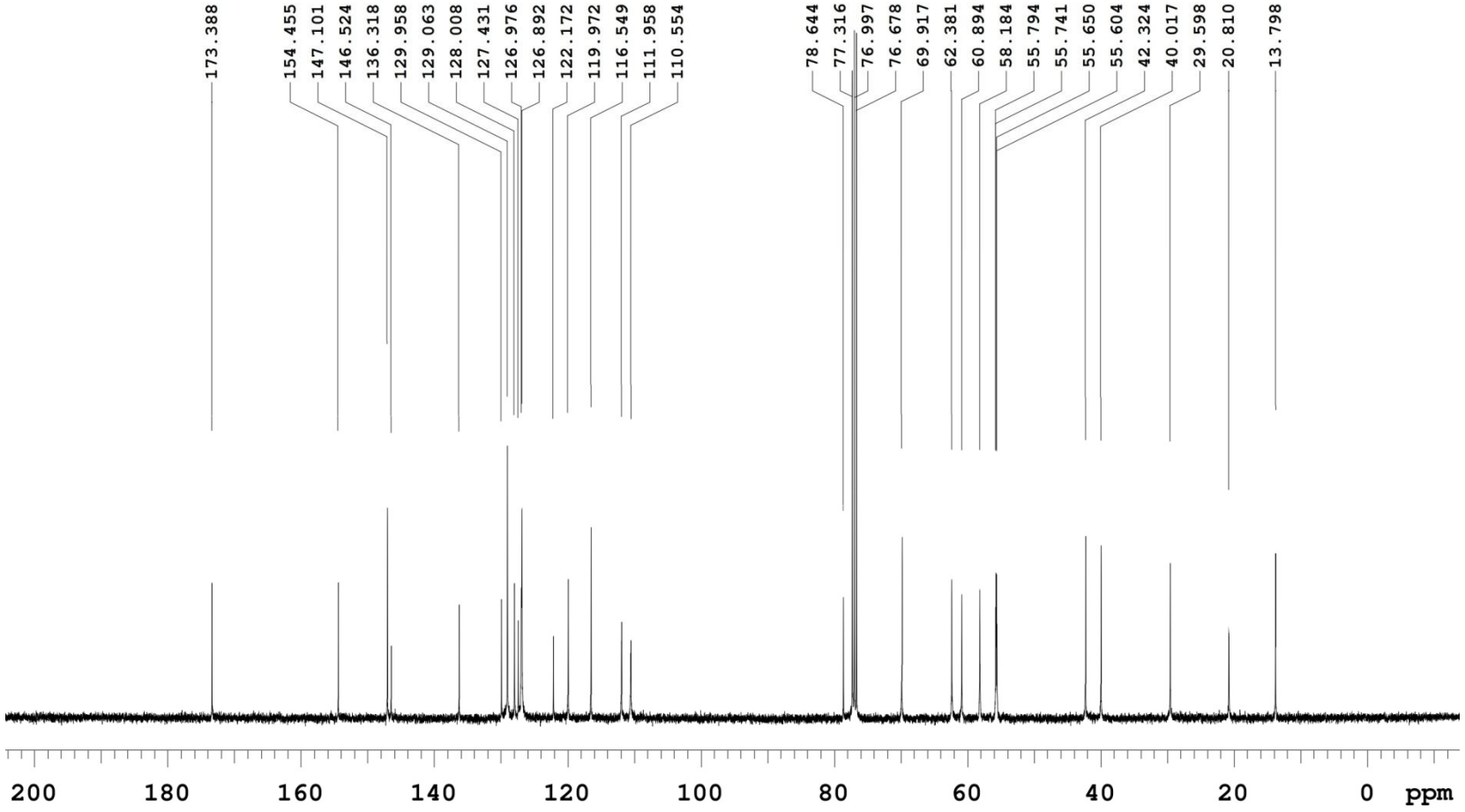
3a



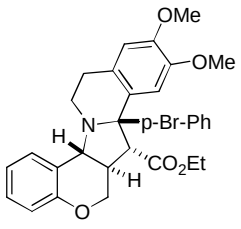
^{13}C NMR of **3a** in $CDCl_3$



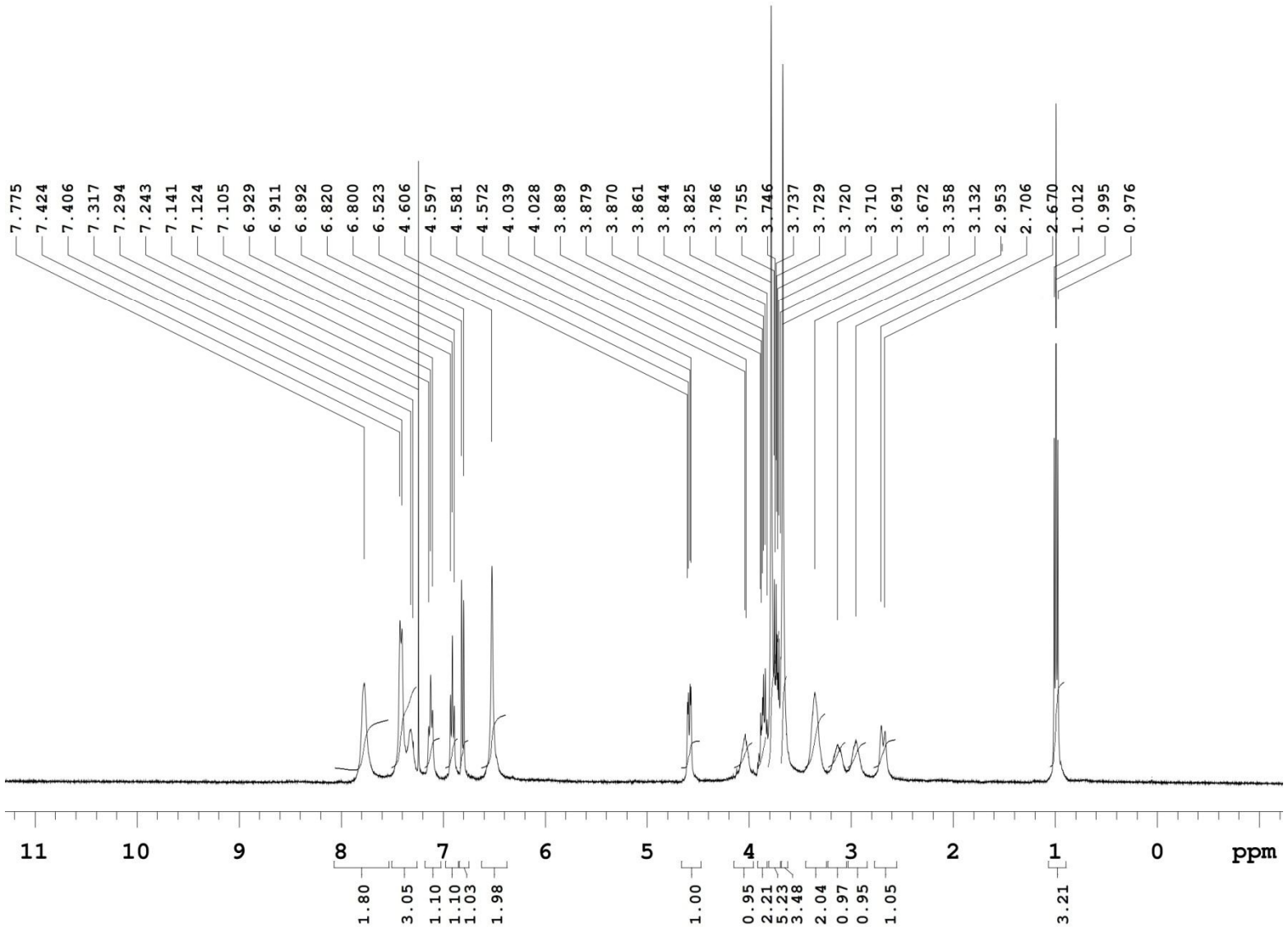
3a



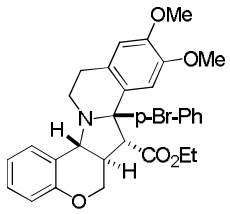
^{1}H NMR of **3b** in $CDCl_3$



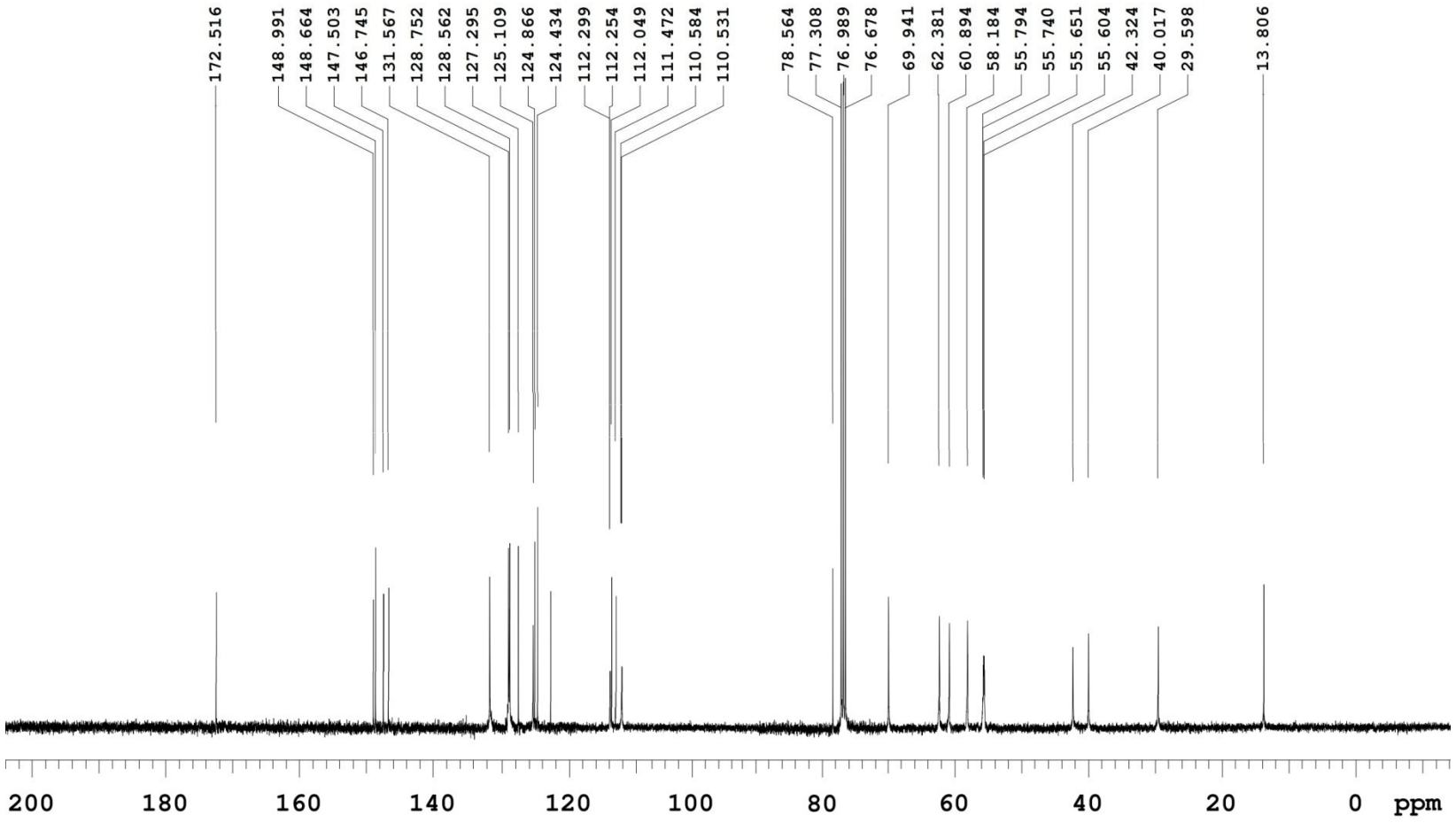
3b



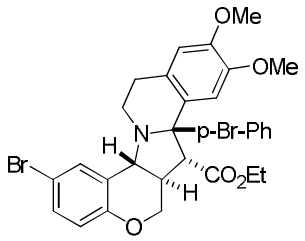
^{13}C NMR of 3b in $CDCl_3$

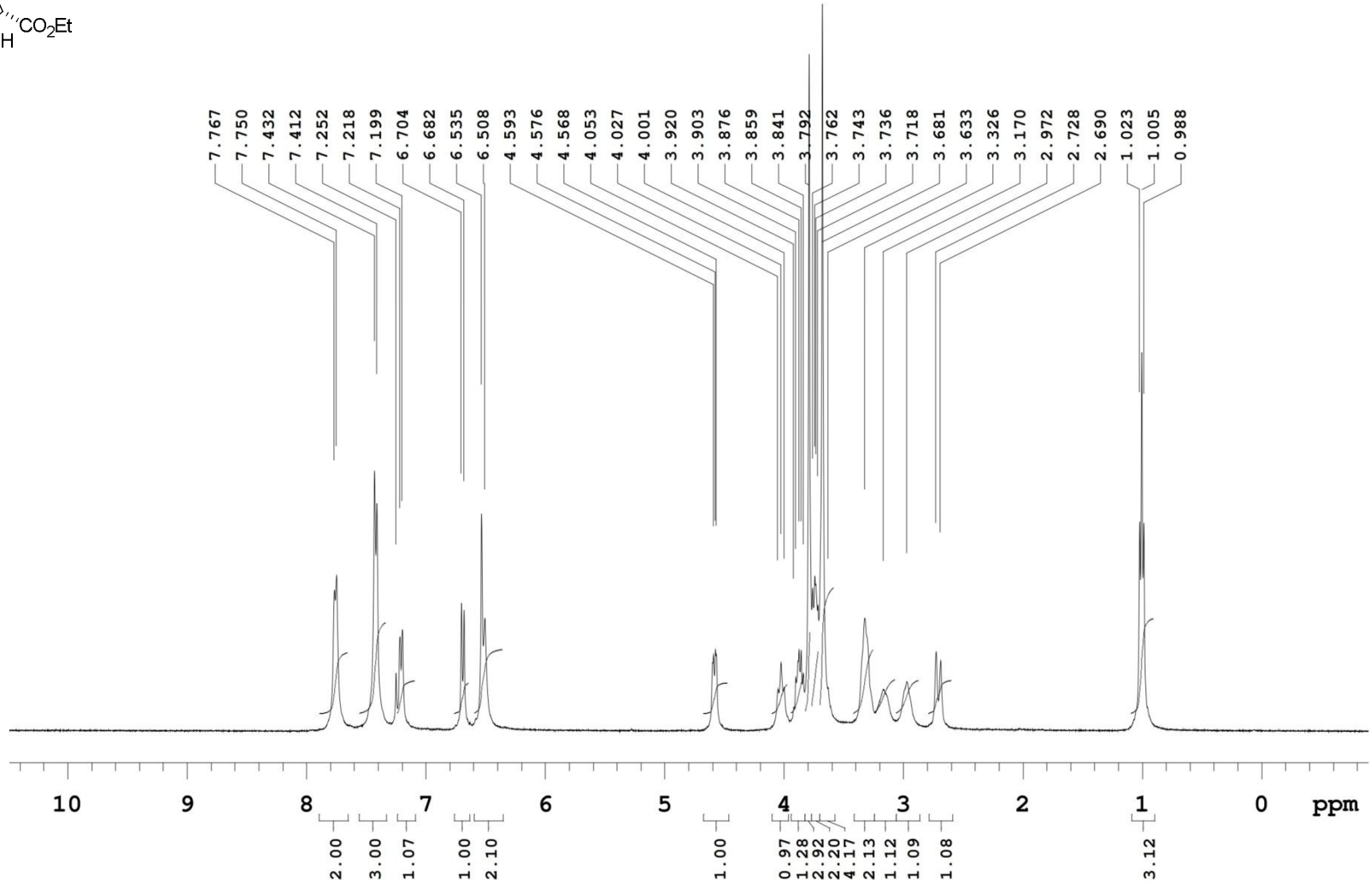


3b

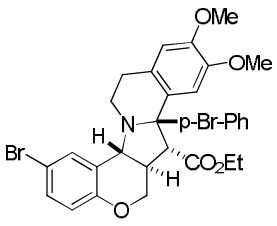


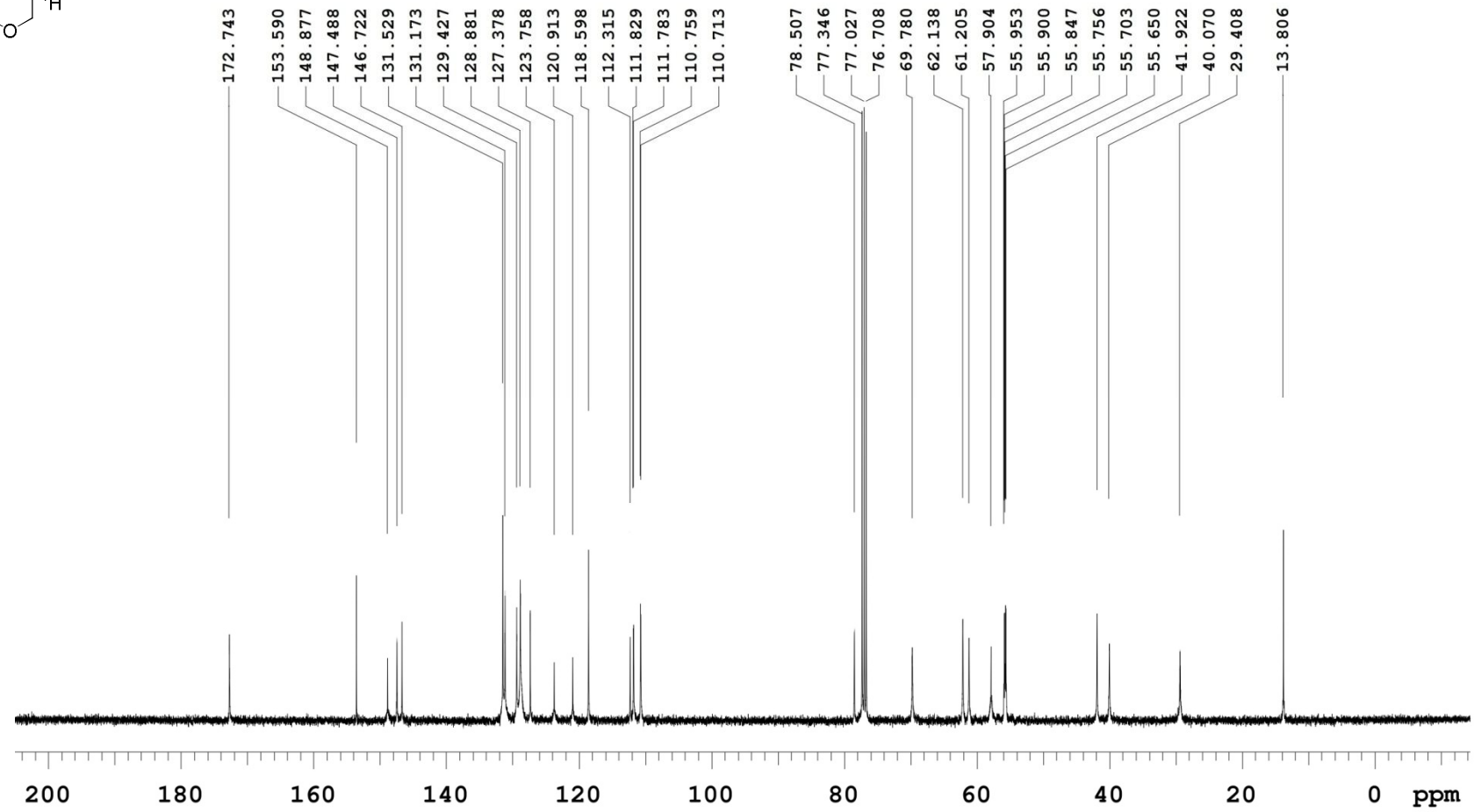
^{1}H NMR of **3c** in $CDCl_3$



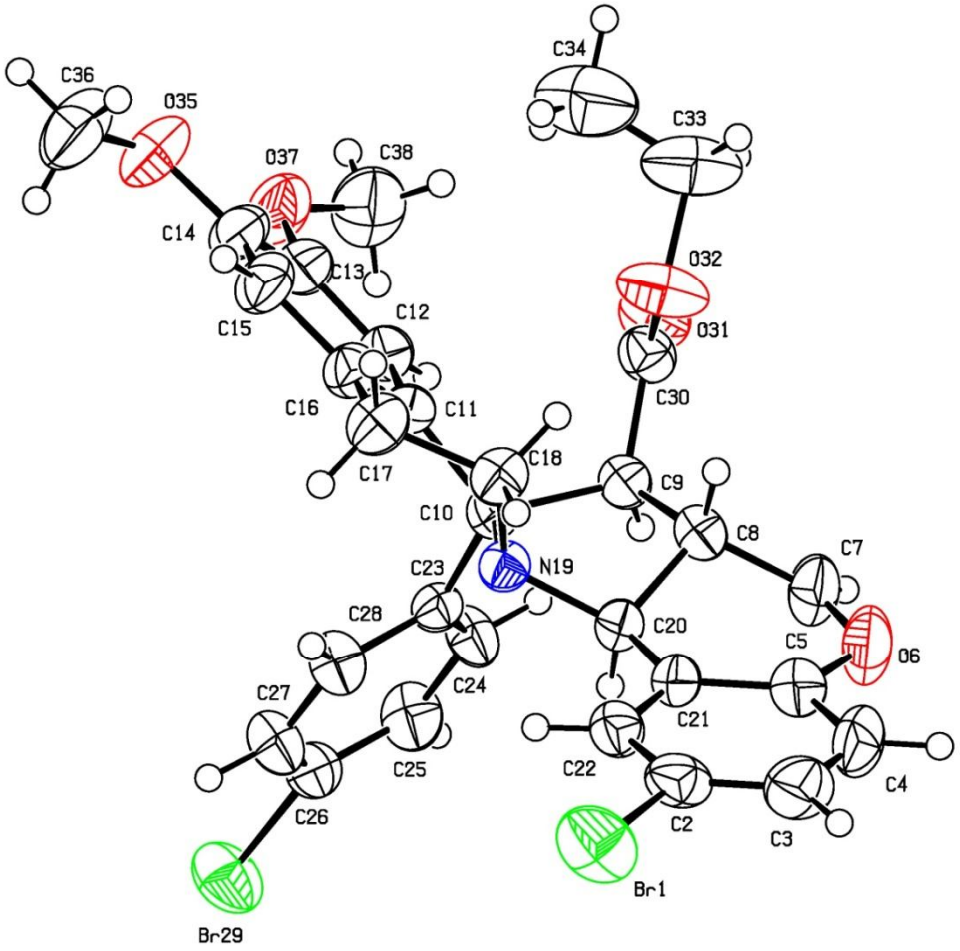


^{13}C NMR of **3c** in $CDCl_3$

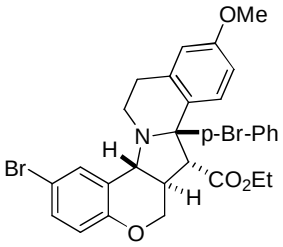




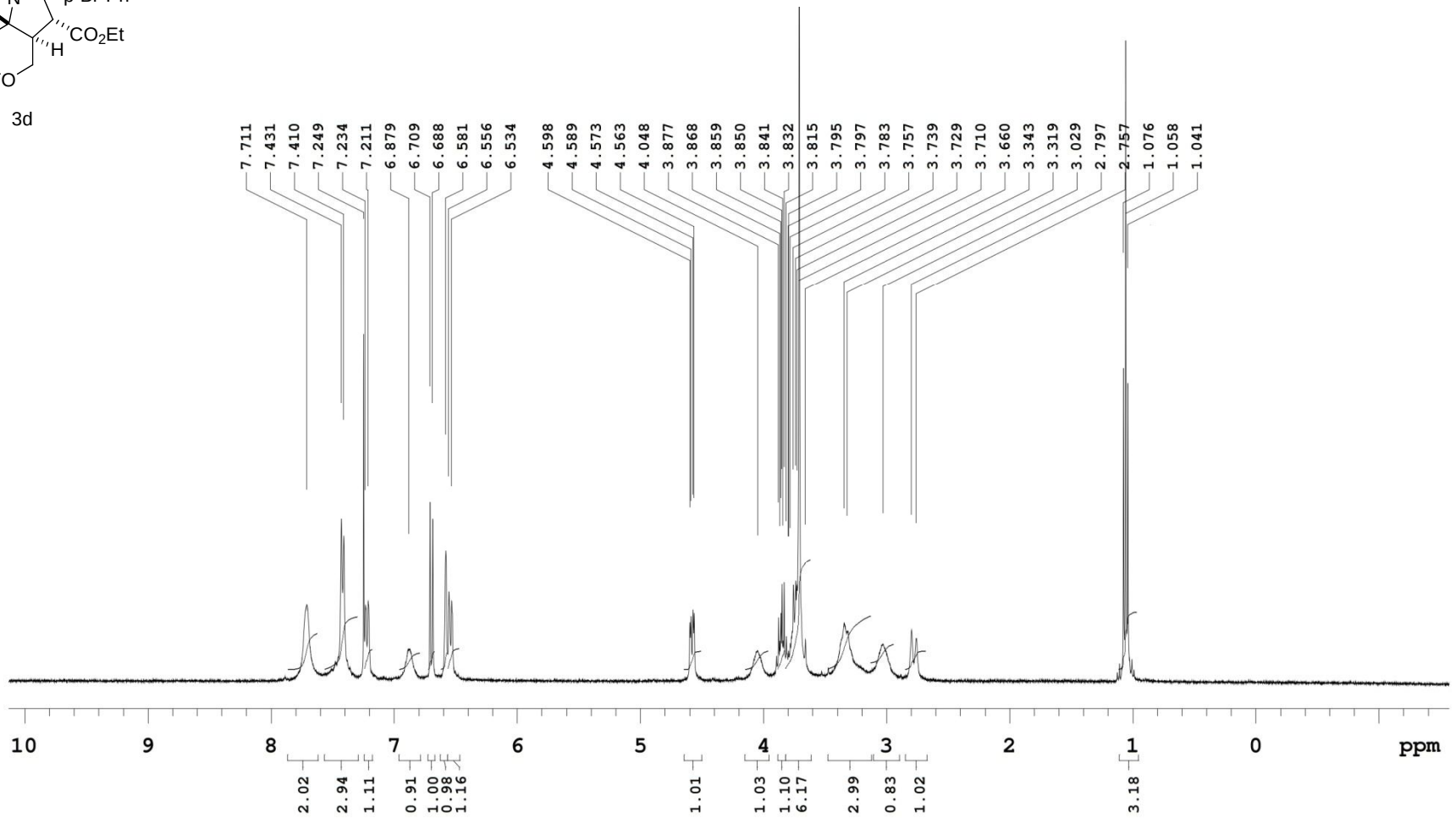
ORTEP diagram of **3c**



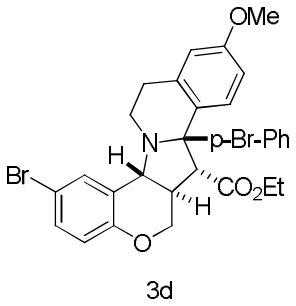
^{1}H NMR of **3d** in $CDCl_3$



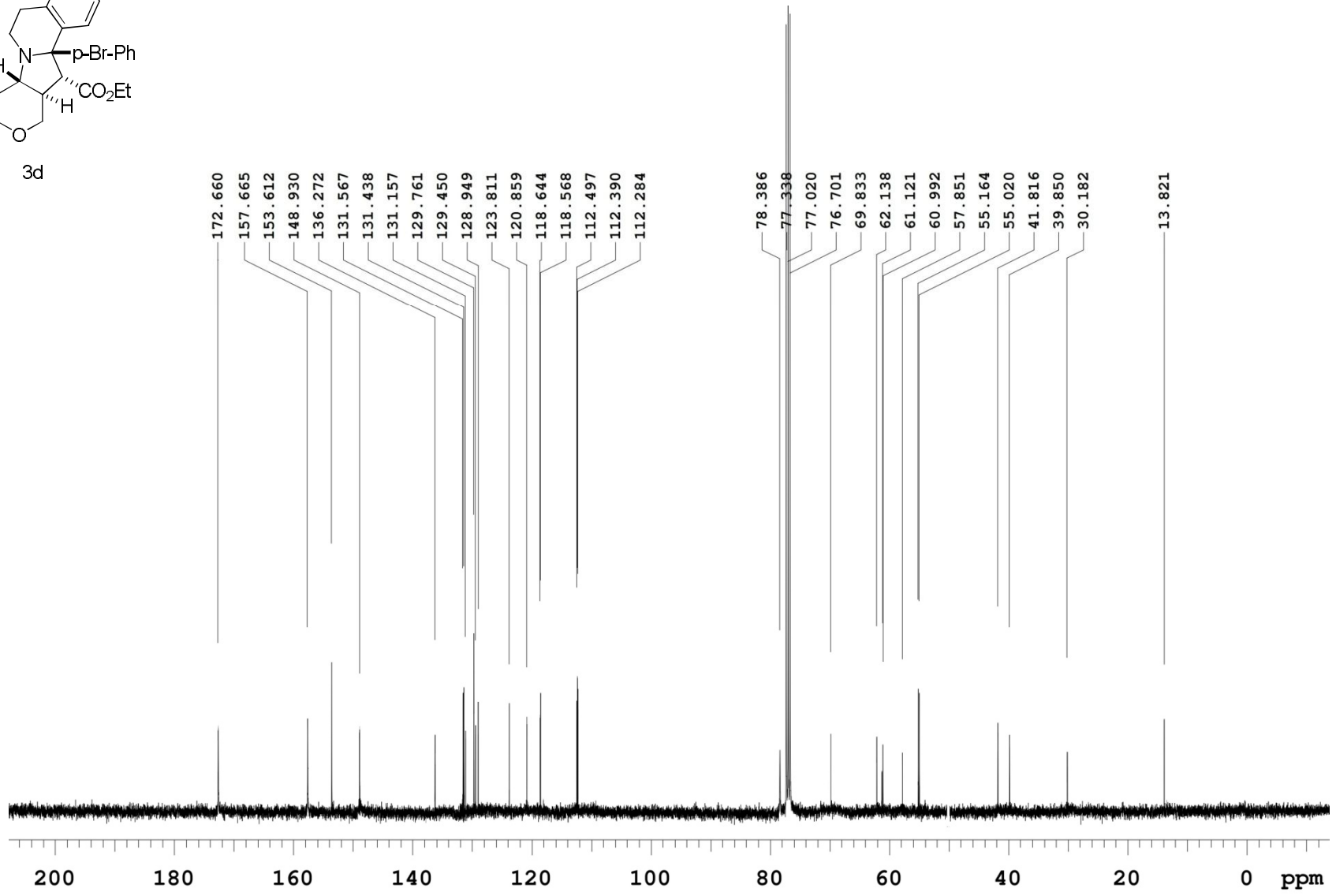
3d



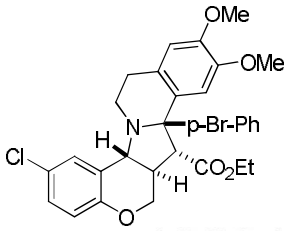
^{13}C NMR of **3d** in $CDCl_3$

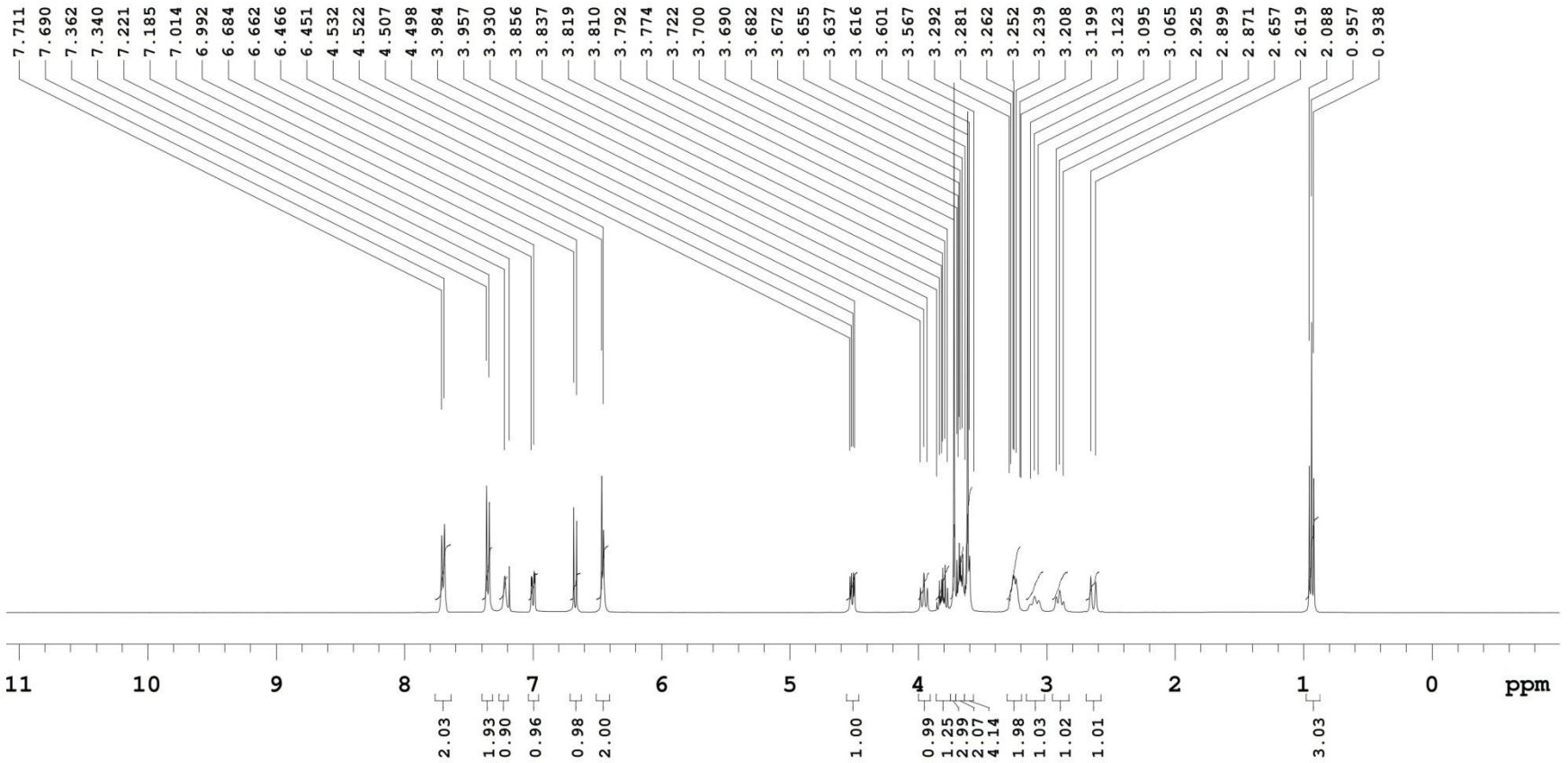


3d

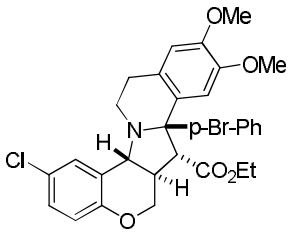


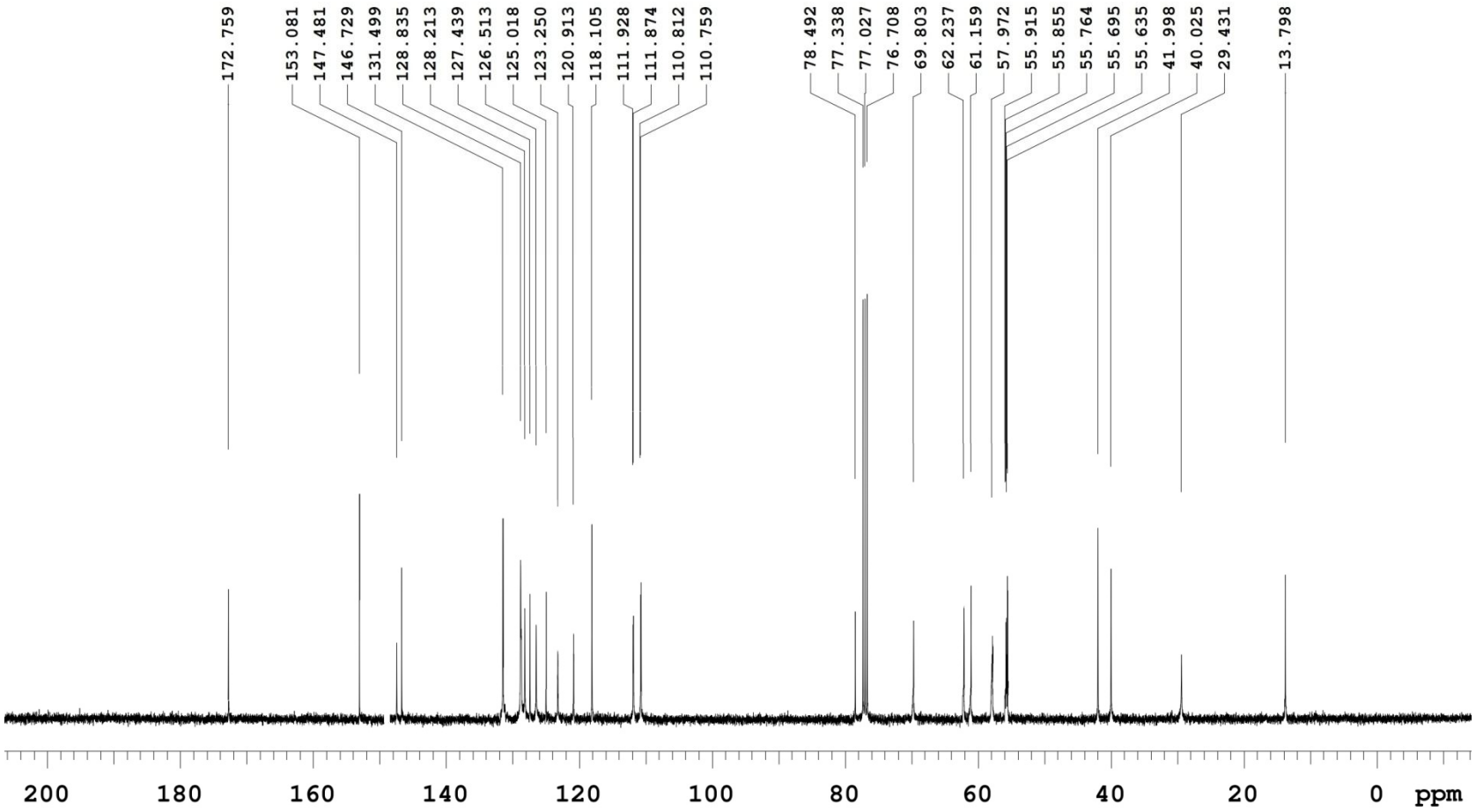
^{1}H NMR of **3e** in $CDCl_3$



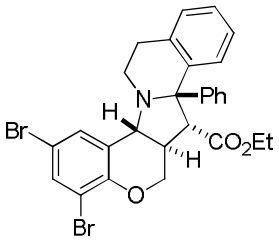


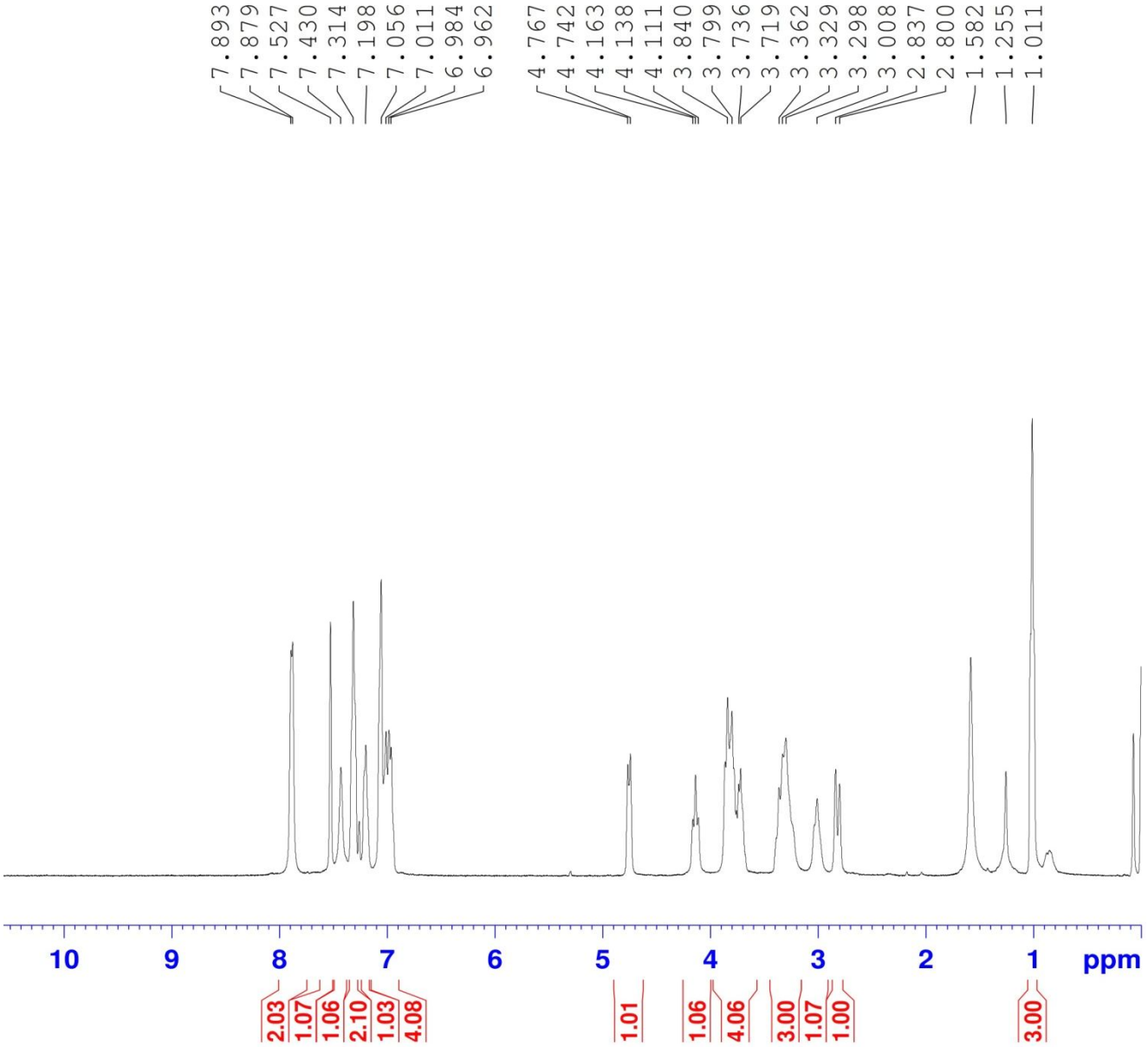
^{13}C NMR of **3e** in $CDCl_3$



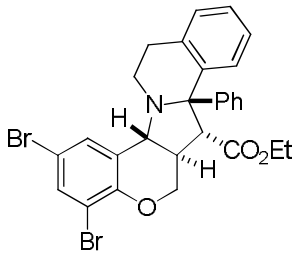


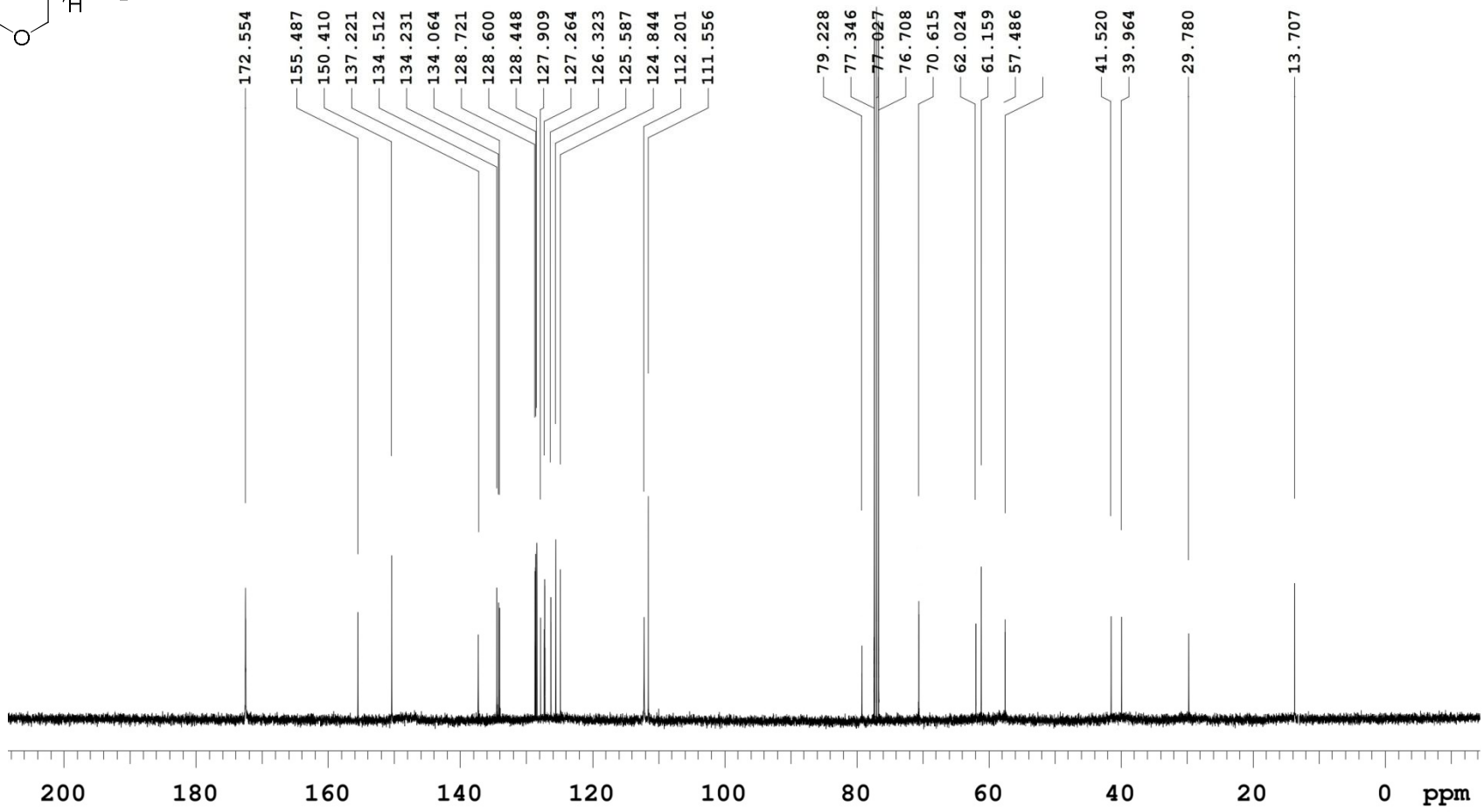
^{1}H NMR of **3f** in $CDCl_3$



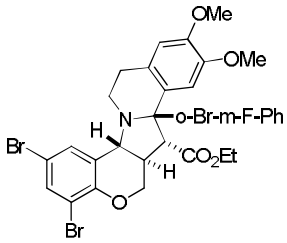


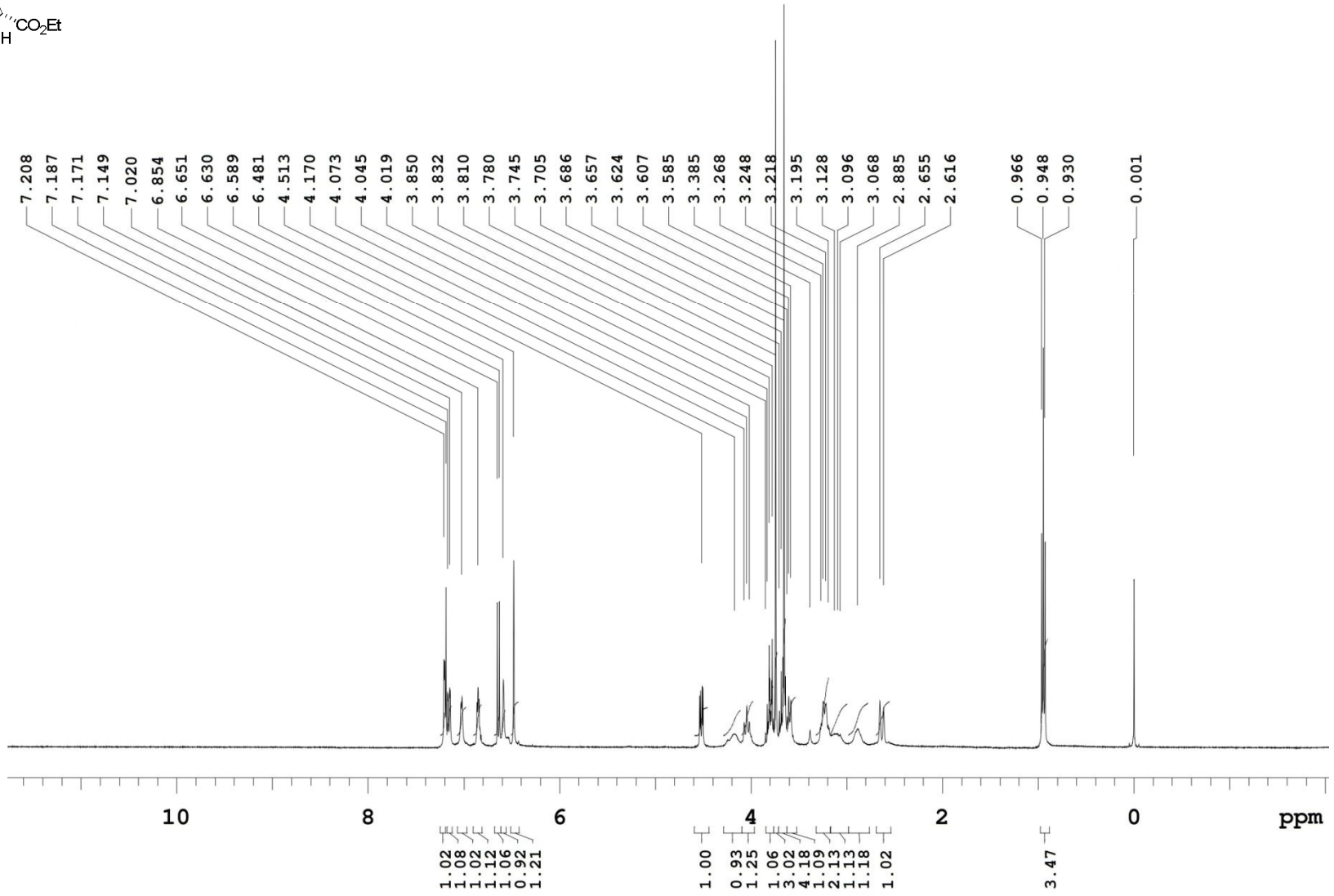
^{13}C NMR of **3f** in $CDCl_3$



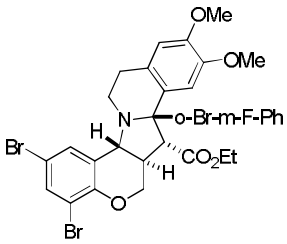


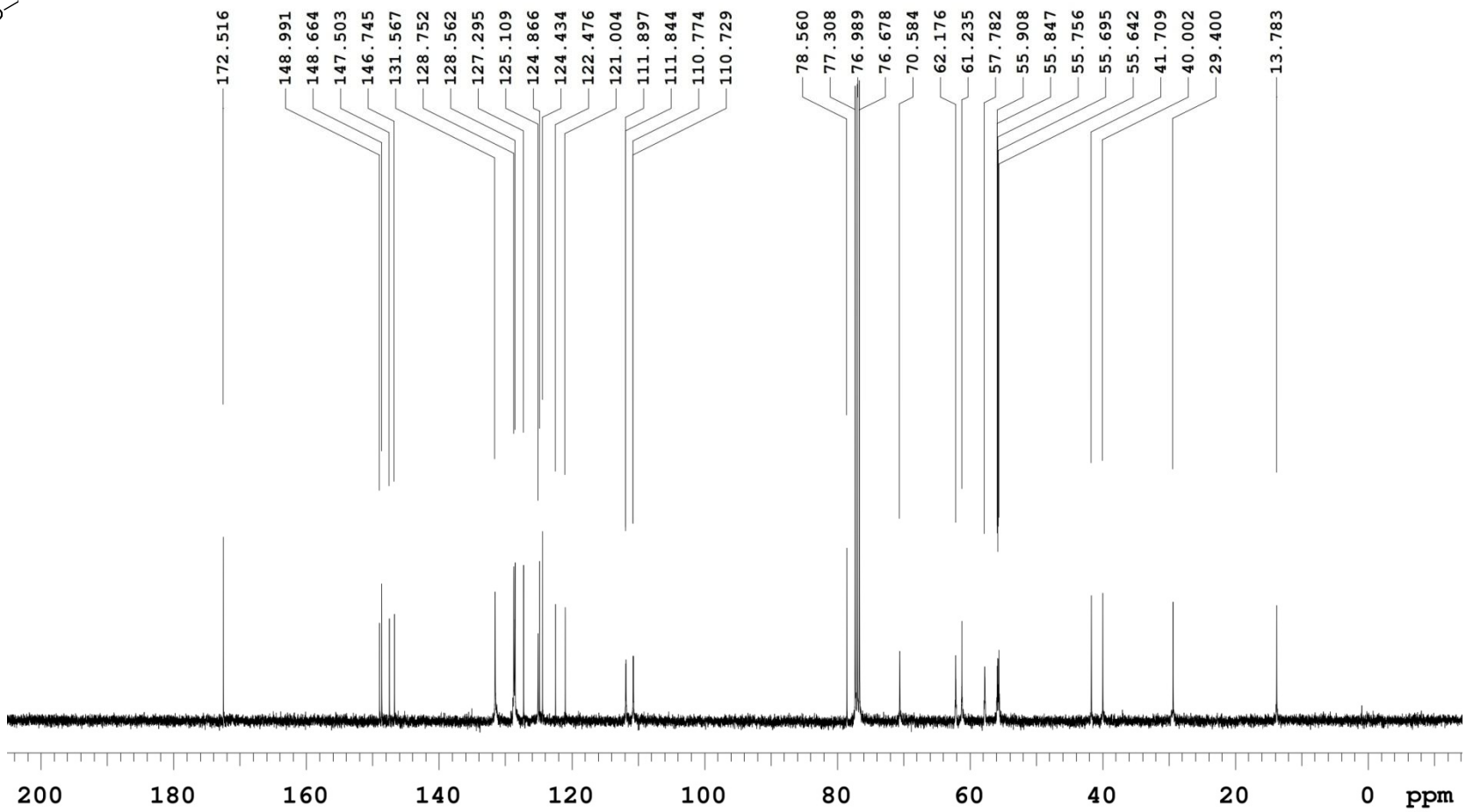
^{1}H NMR of 3qin in $CDCl_3$



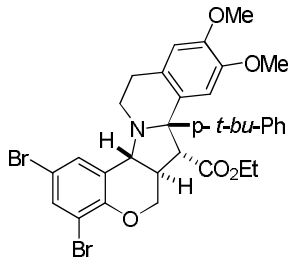


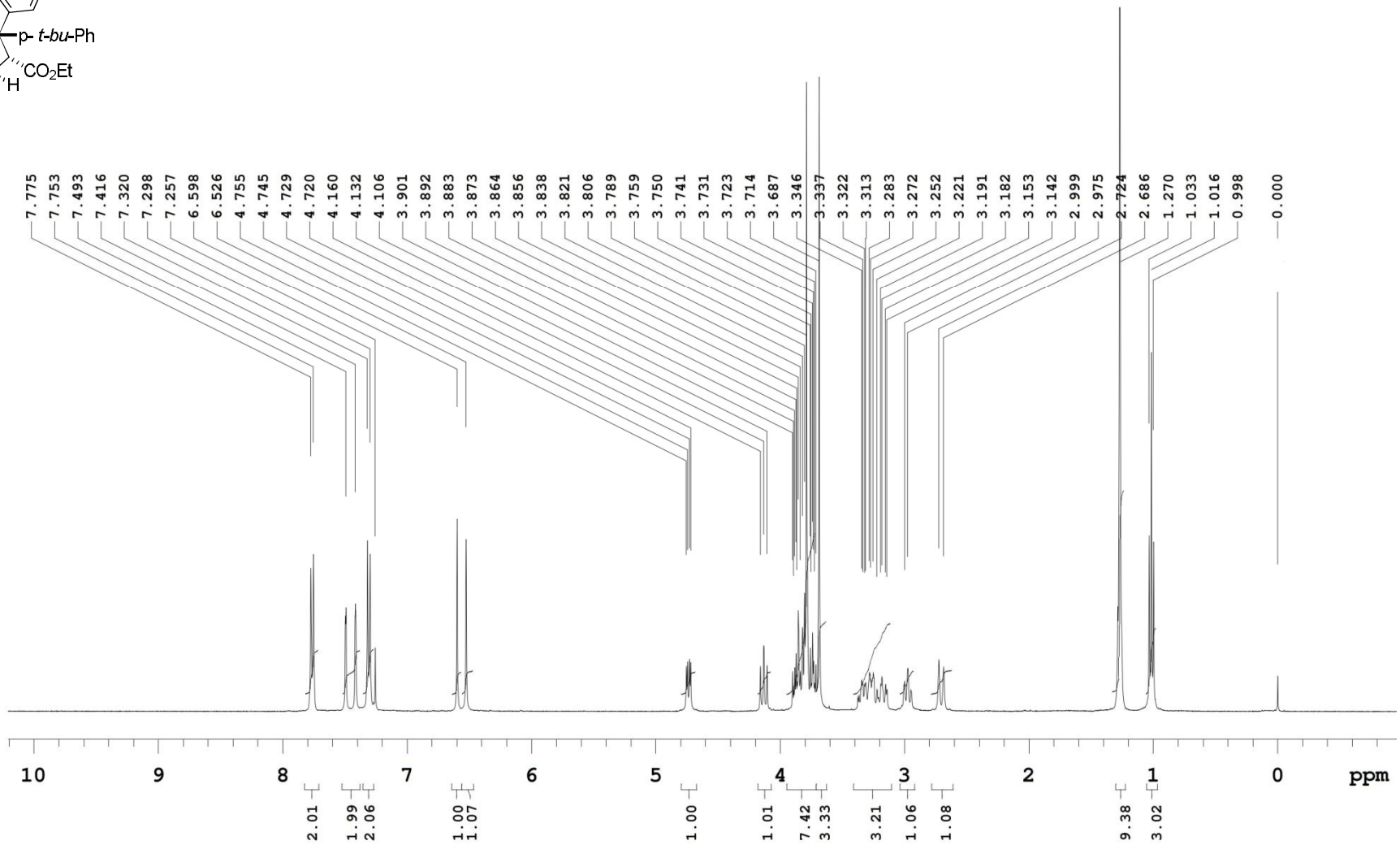
^{13}C NMR of 3g in $CDCl_3$



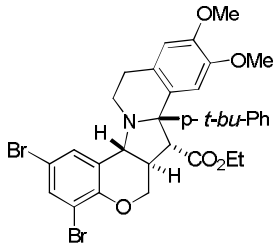


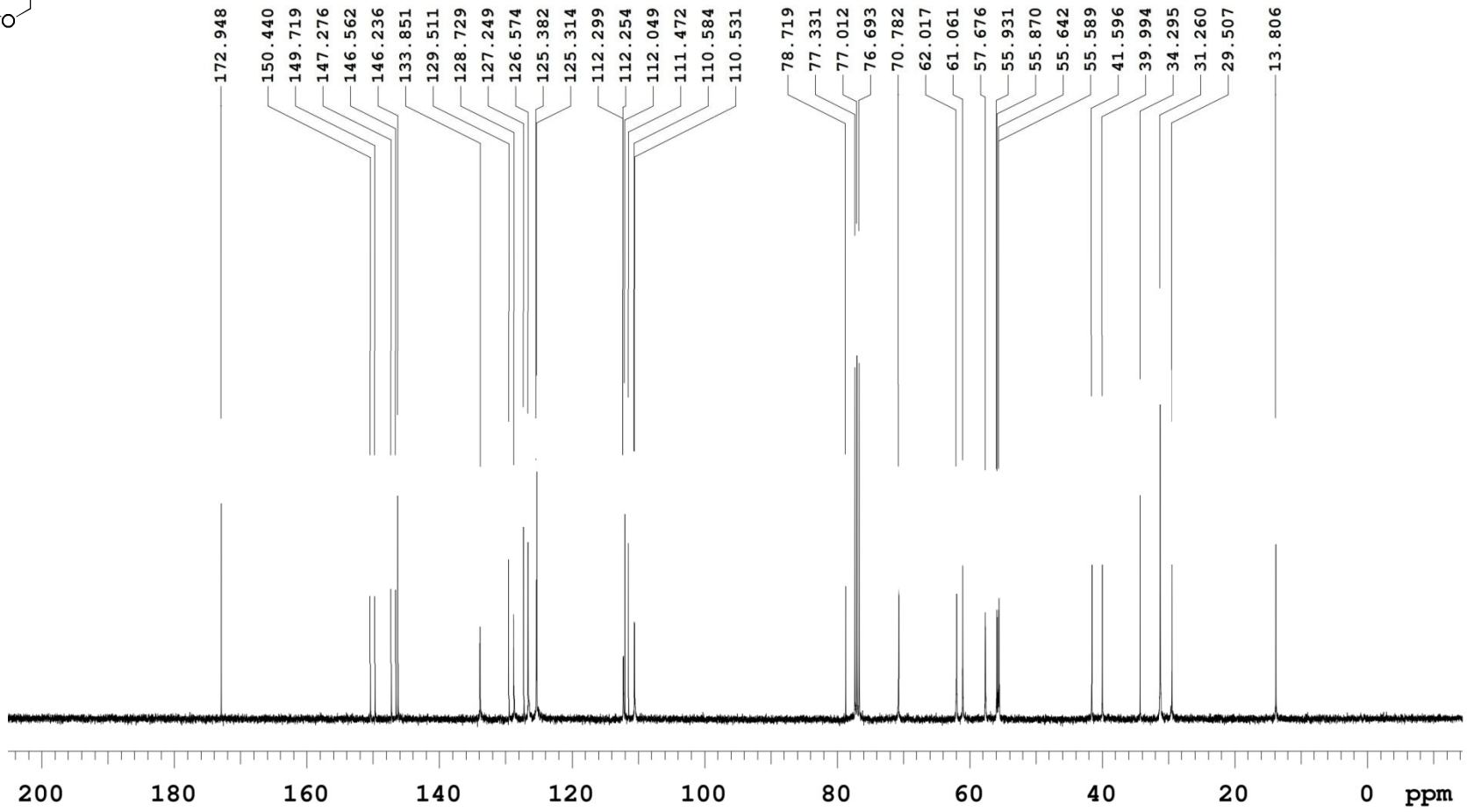
^{1}H NMR of **3h** in $CDCl_3$



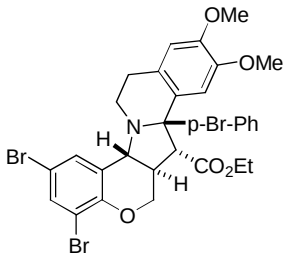


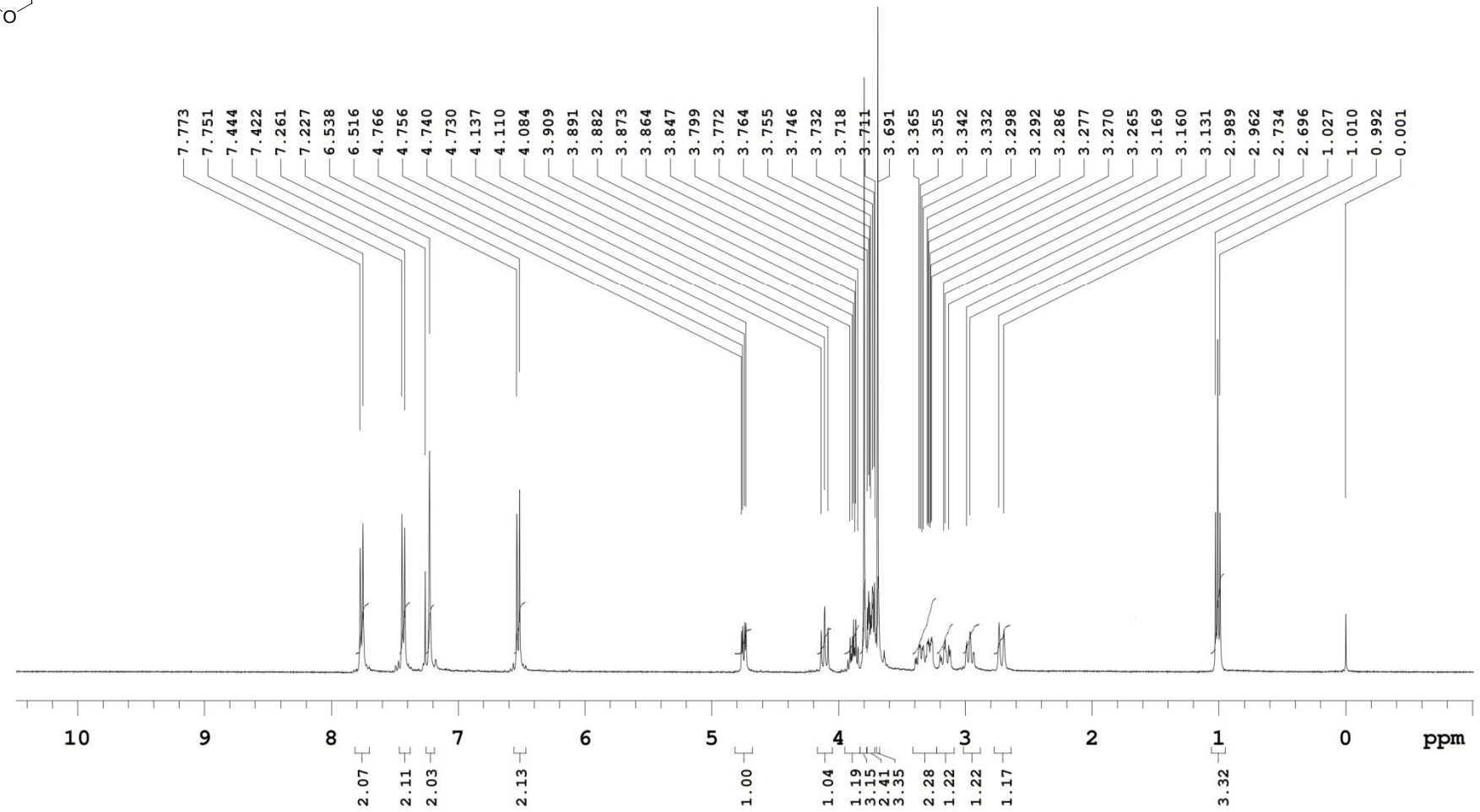
^{13}C NMR of **3hin** $CDCl_3$



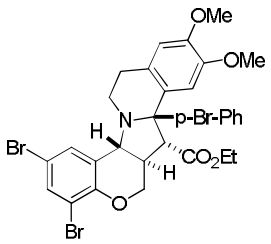


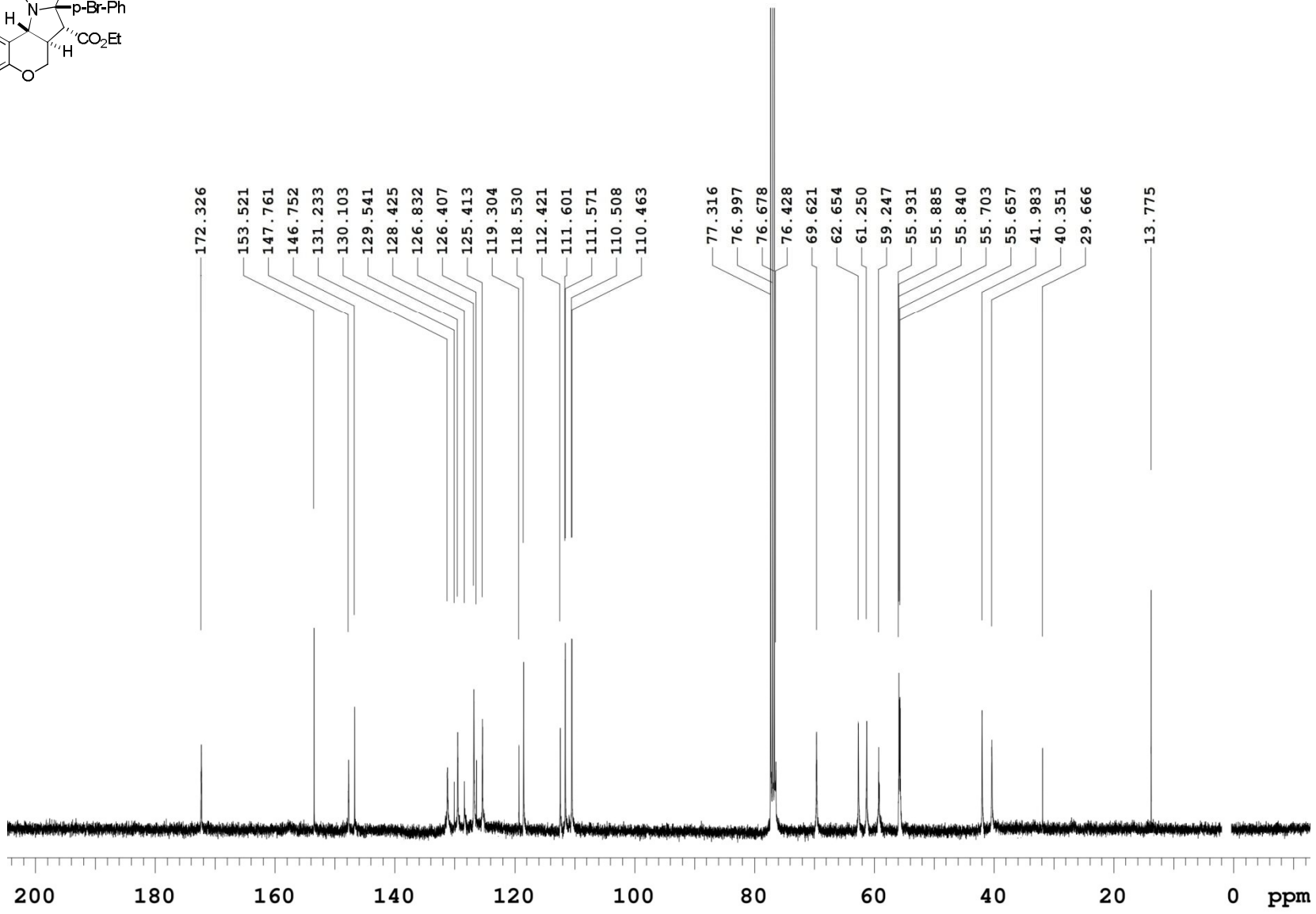
^{1}H NMR of **3i** in $CDCl_3$





^{13}C NMR of **3i** in $CDCl_3$





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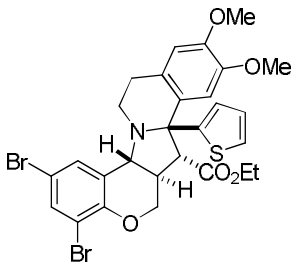

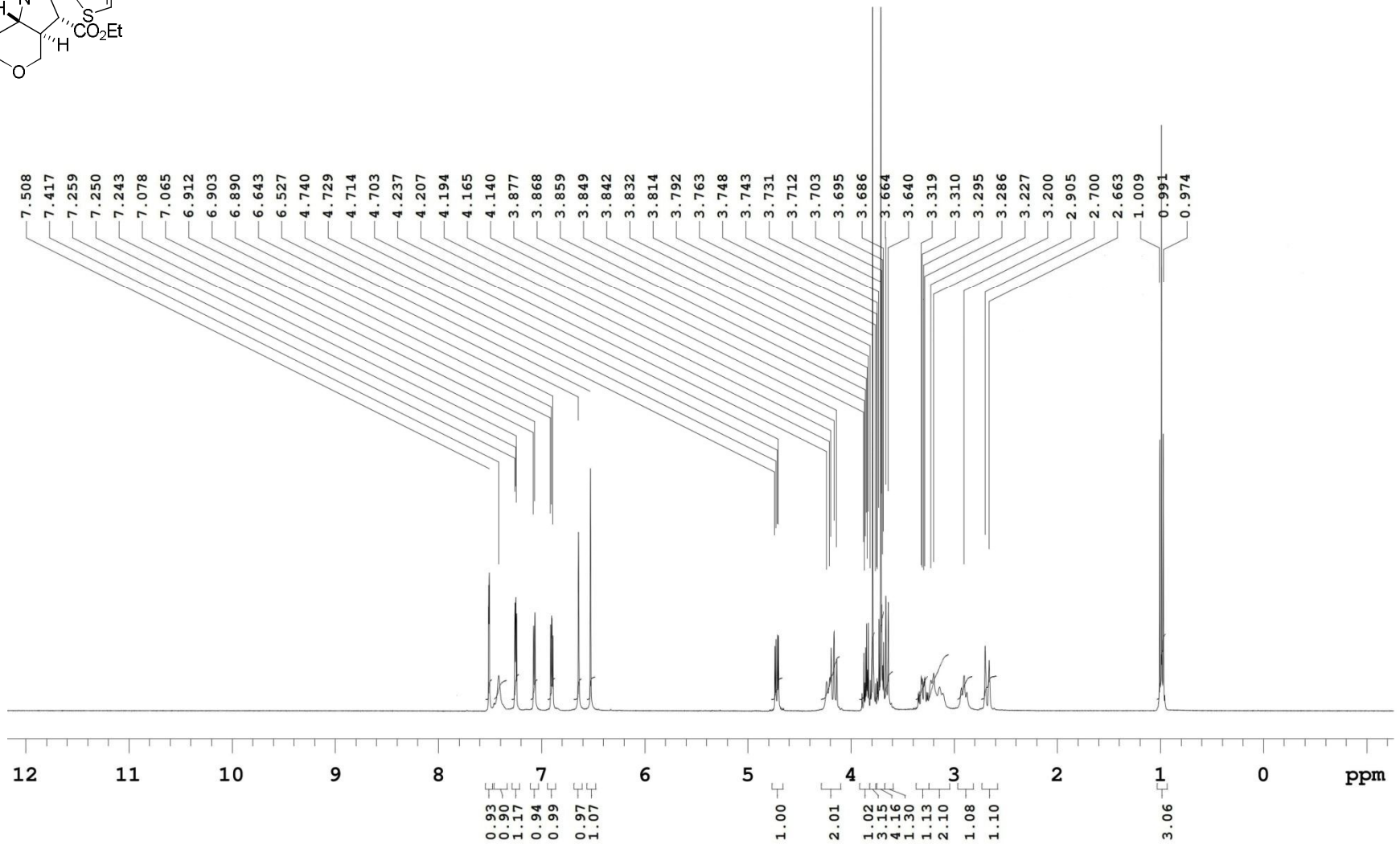

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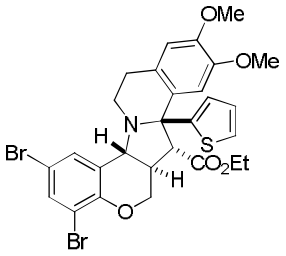
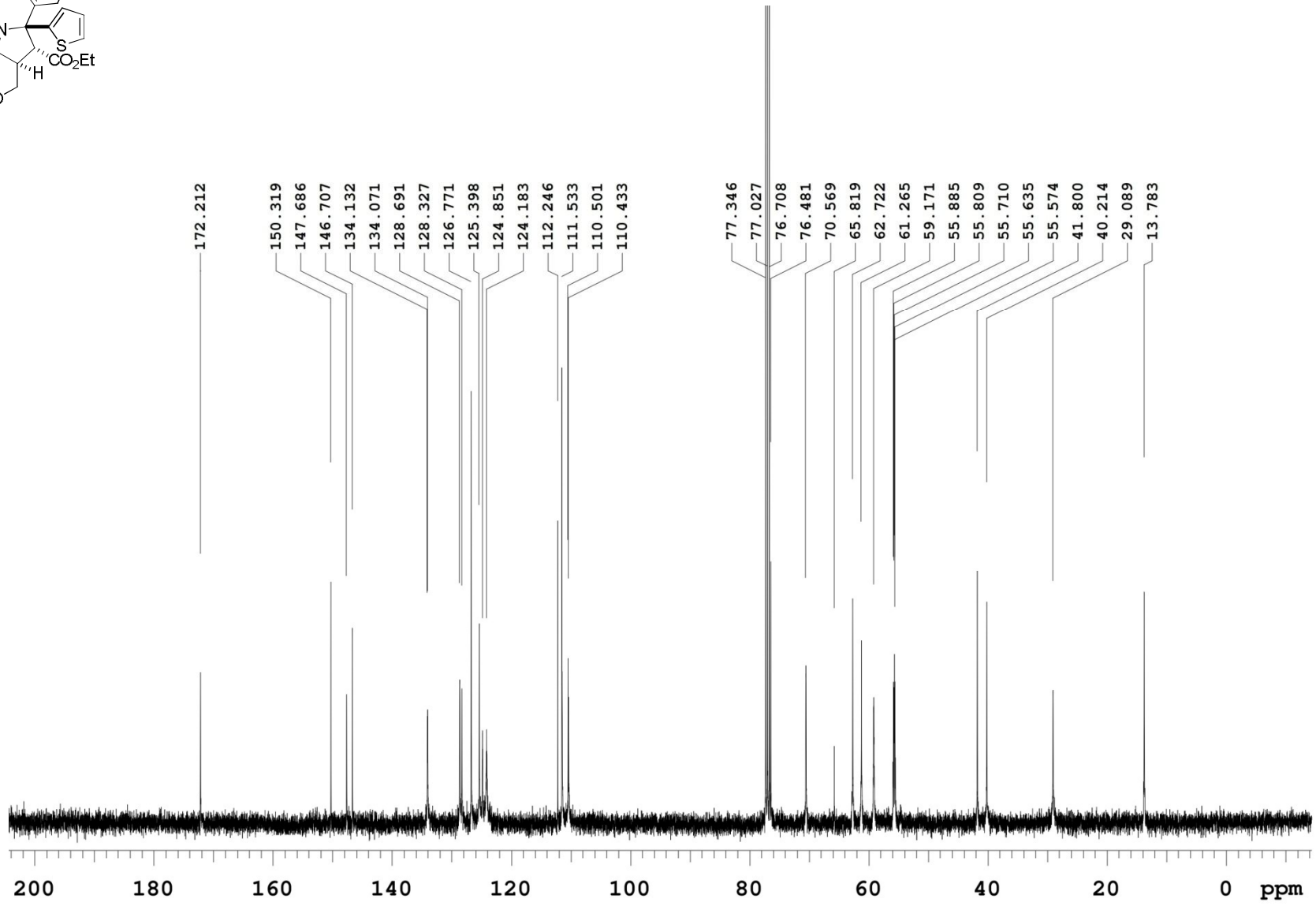
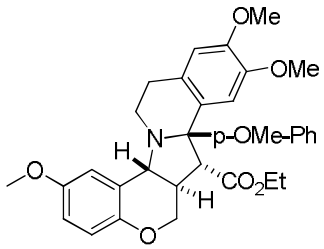
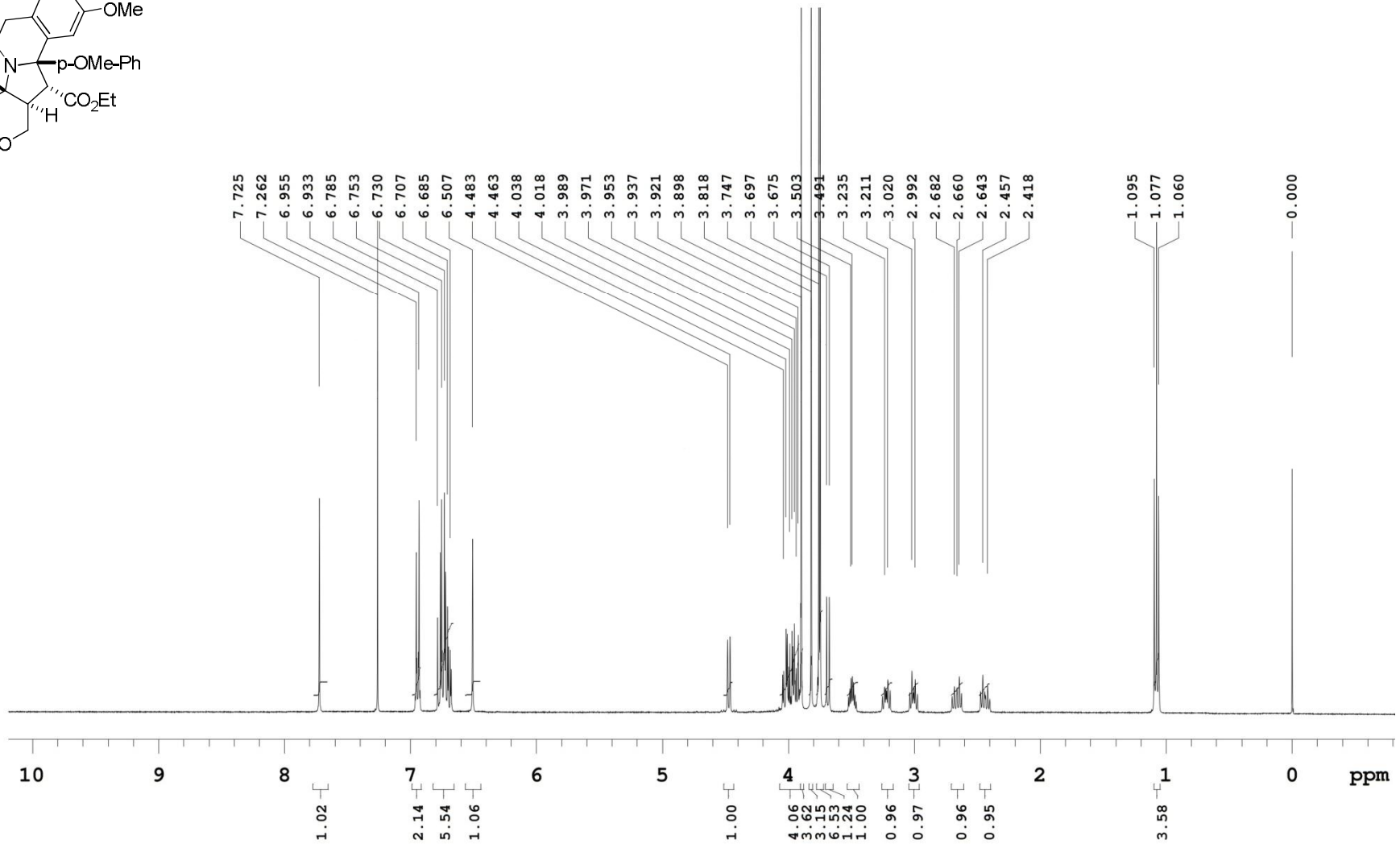


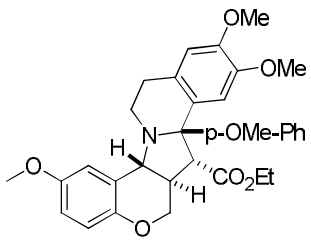


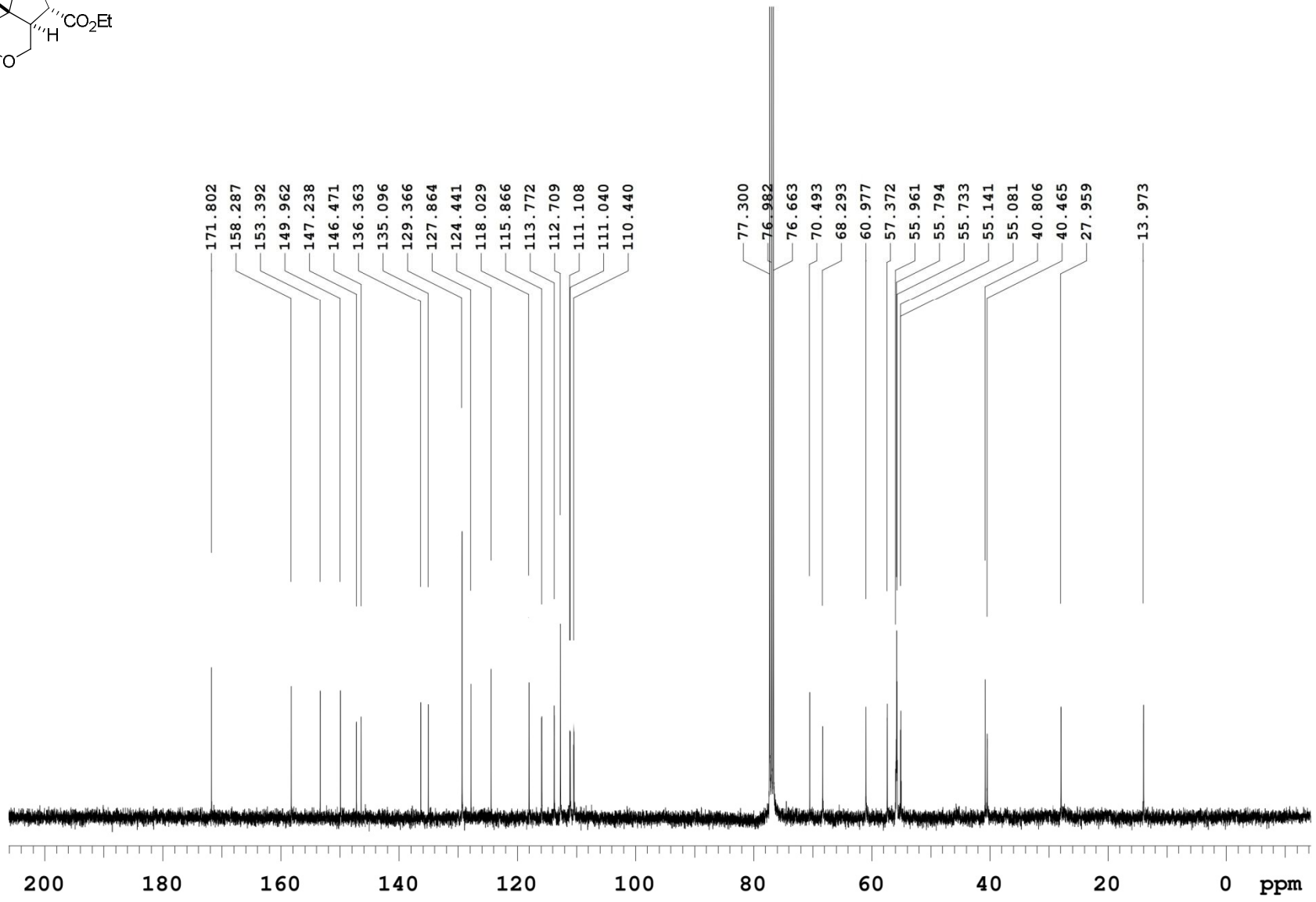
^{1}H NMR of **3k** in $CDCl_3$



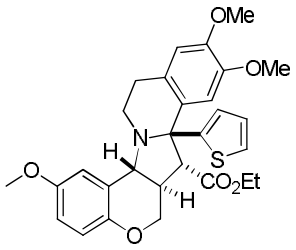


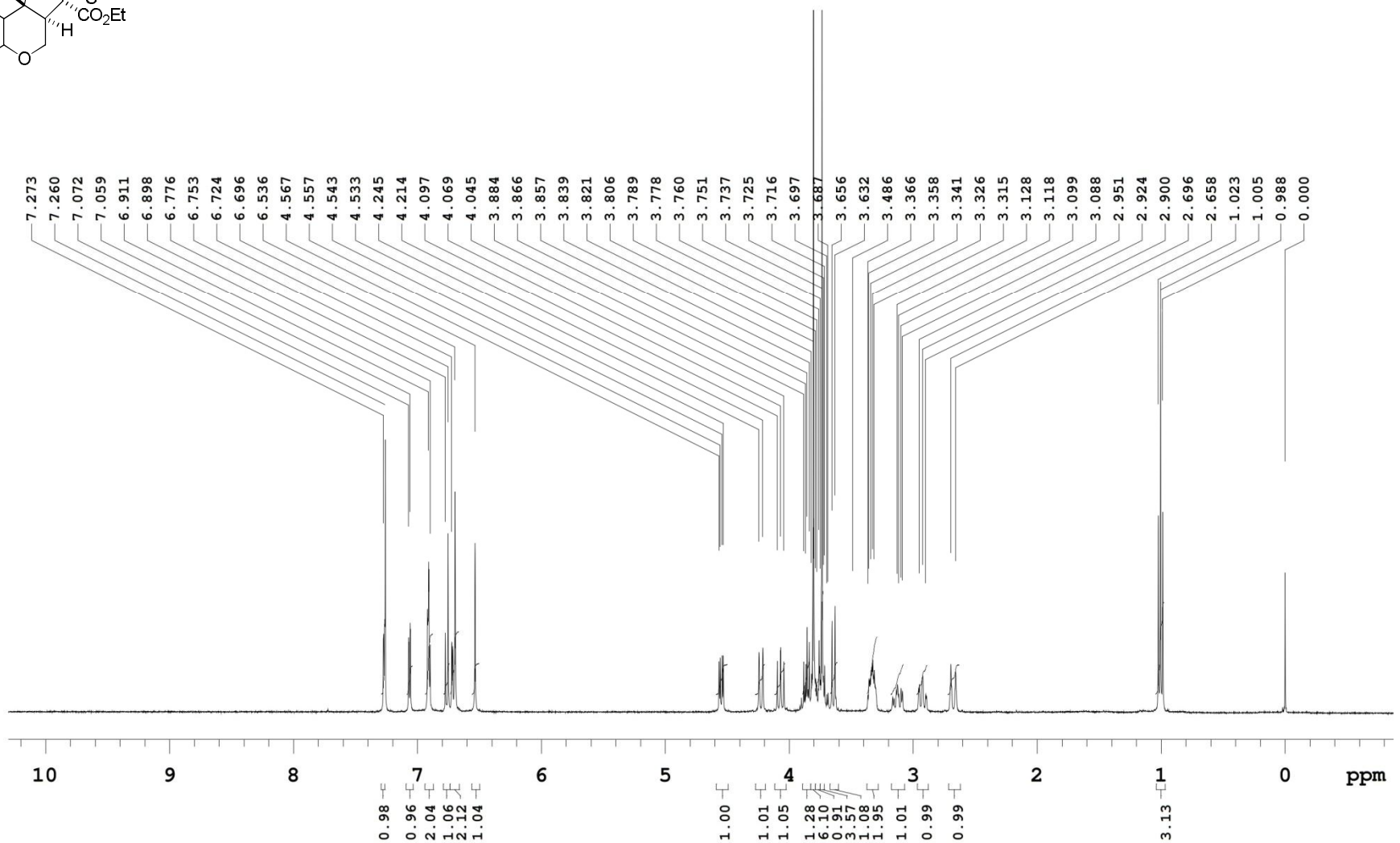
^{13}C NMR of **3k** in $CDCl_3$





^{1}H NMR of **3l** in $CDCl_3$





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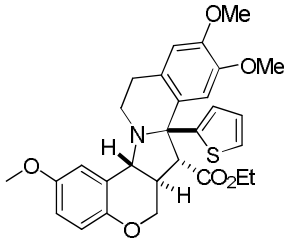
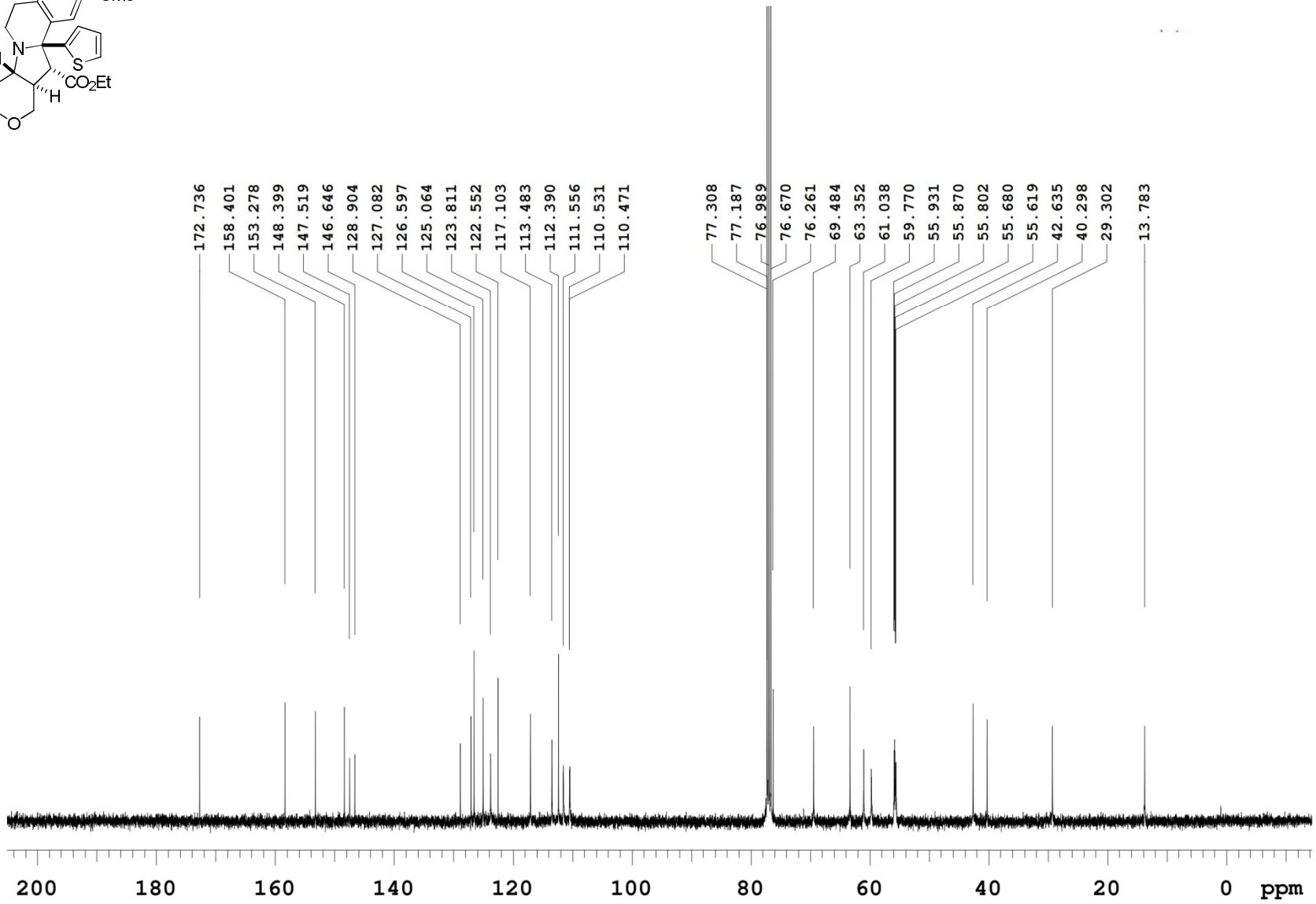
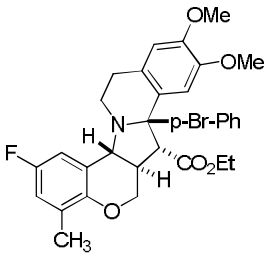
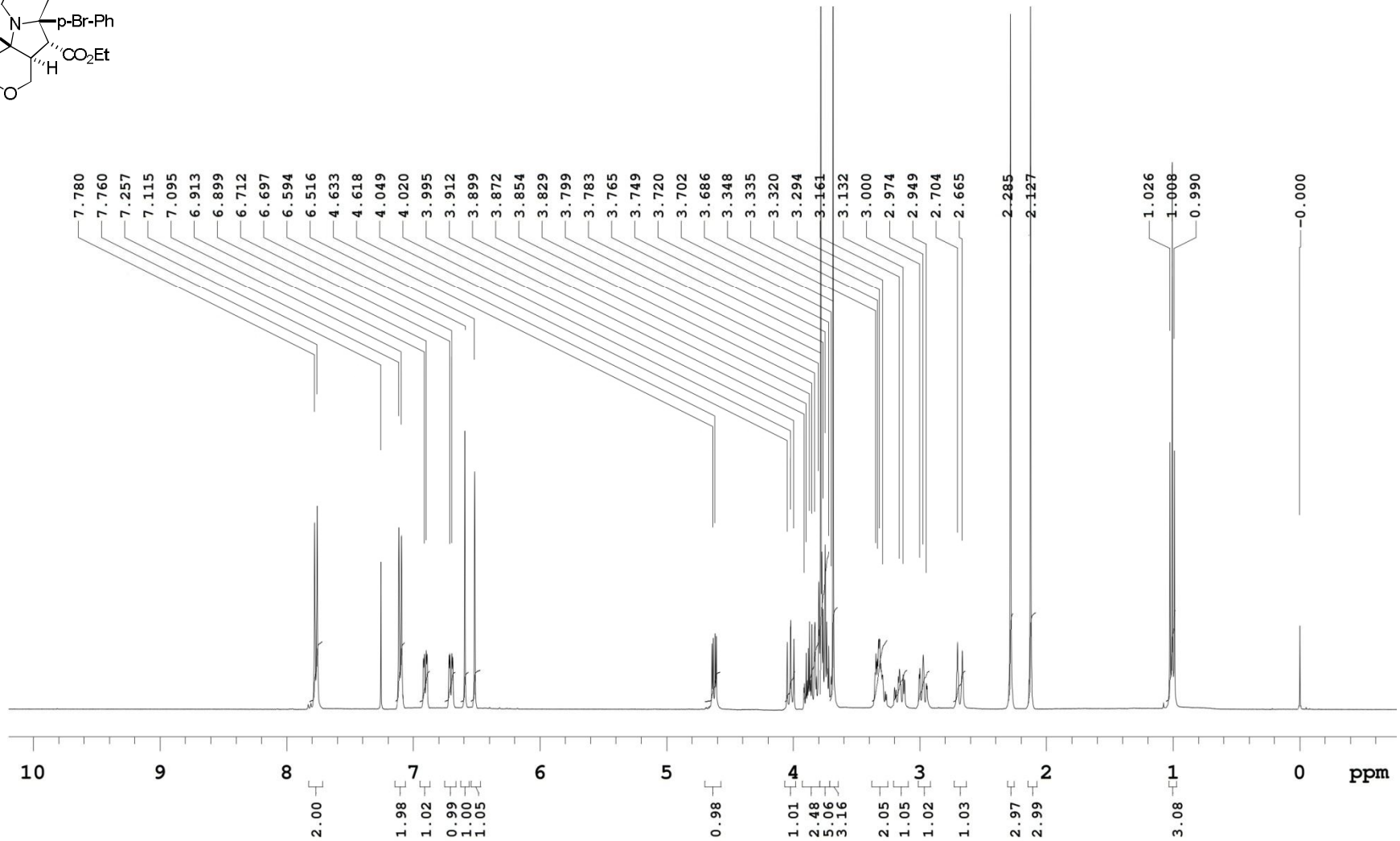


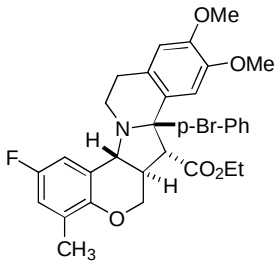


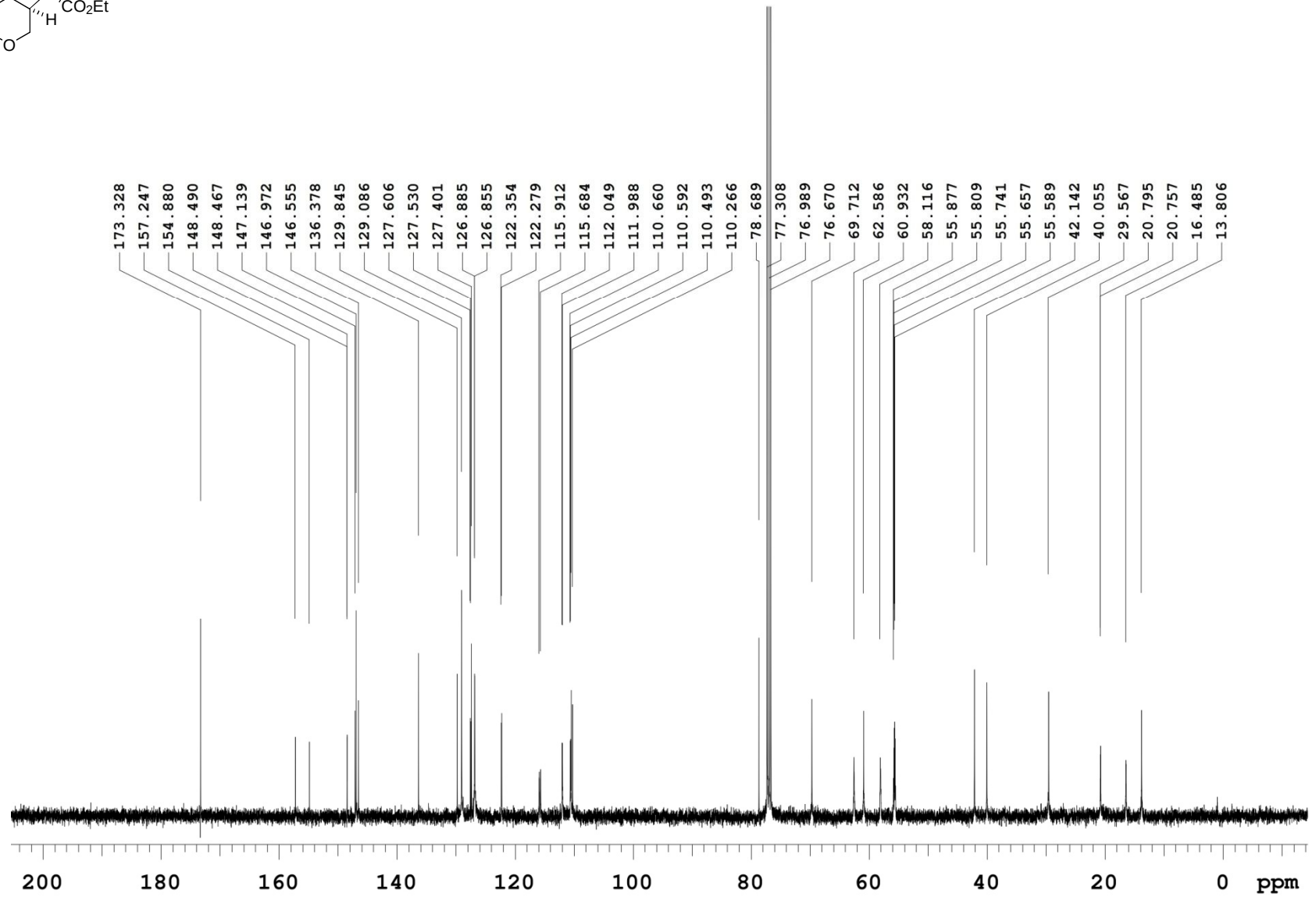
^{13}C NMR of **3m** in $CDCl_3$



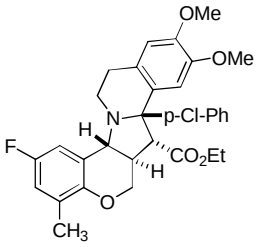


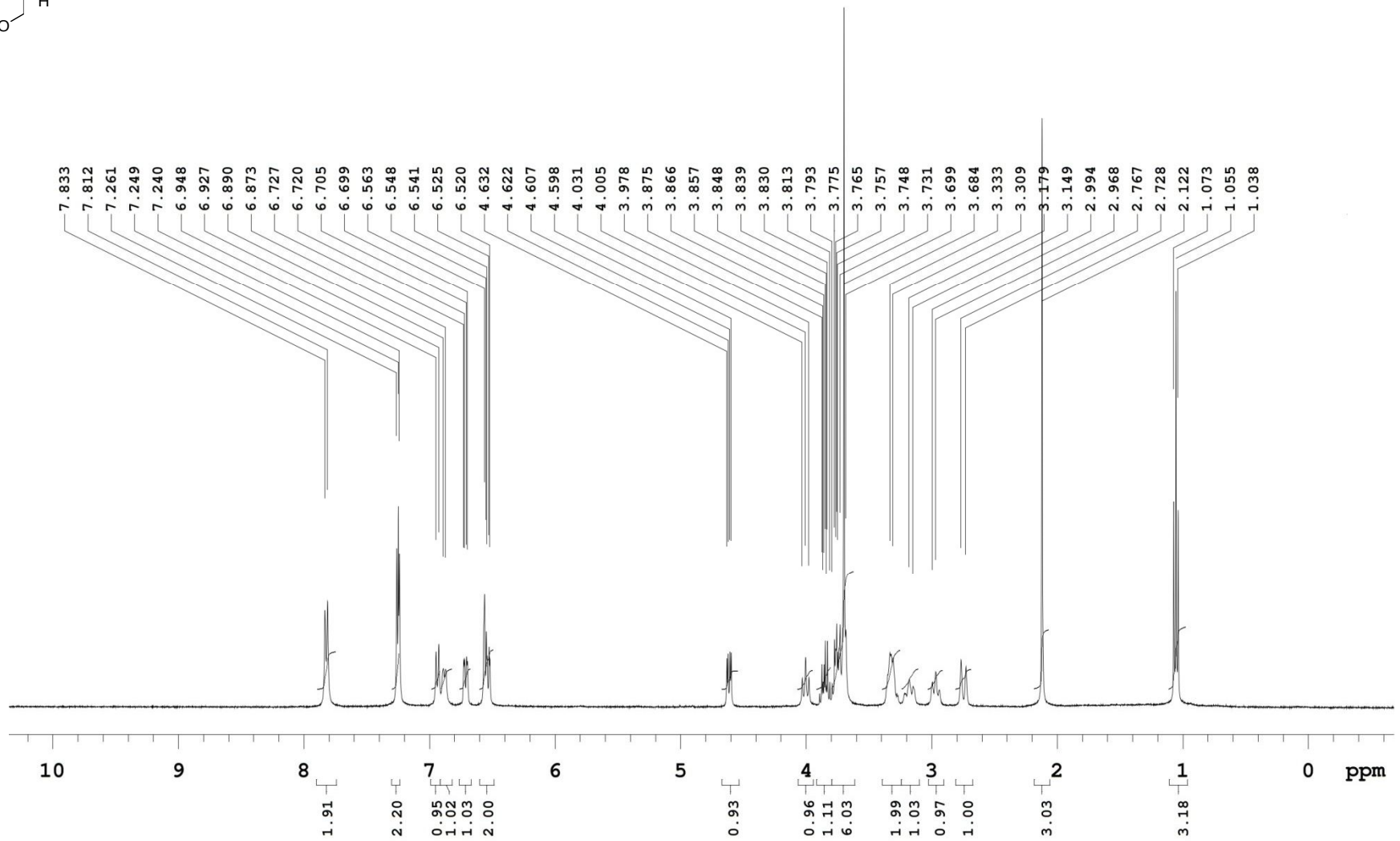
^{13}C NMR of 3m in $CDCl_3$



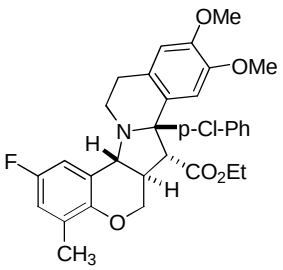


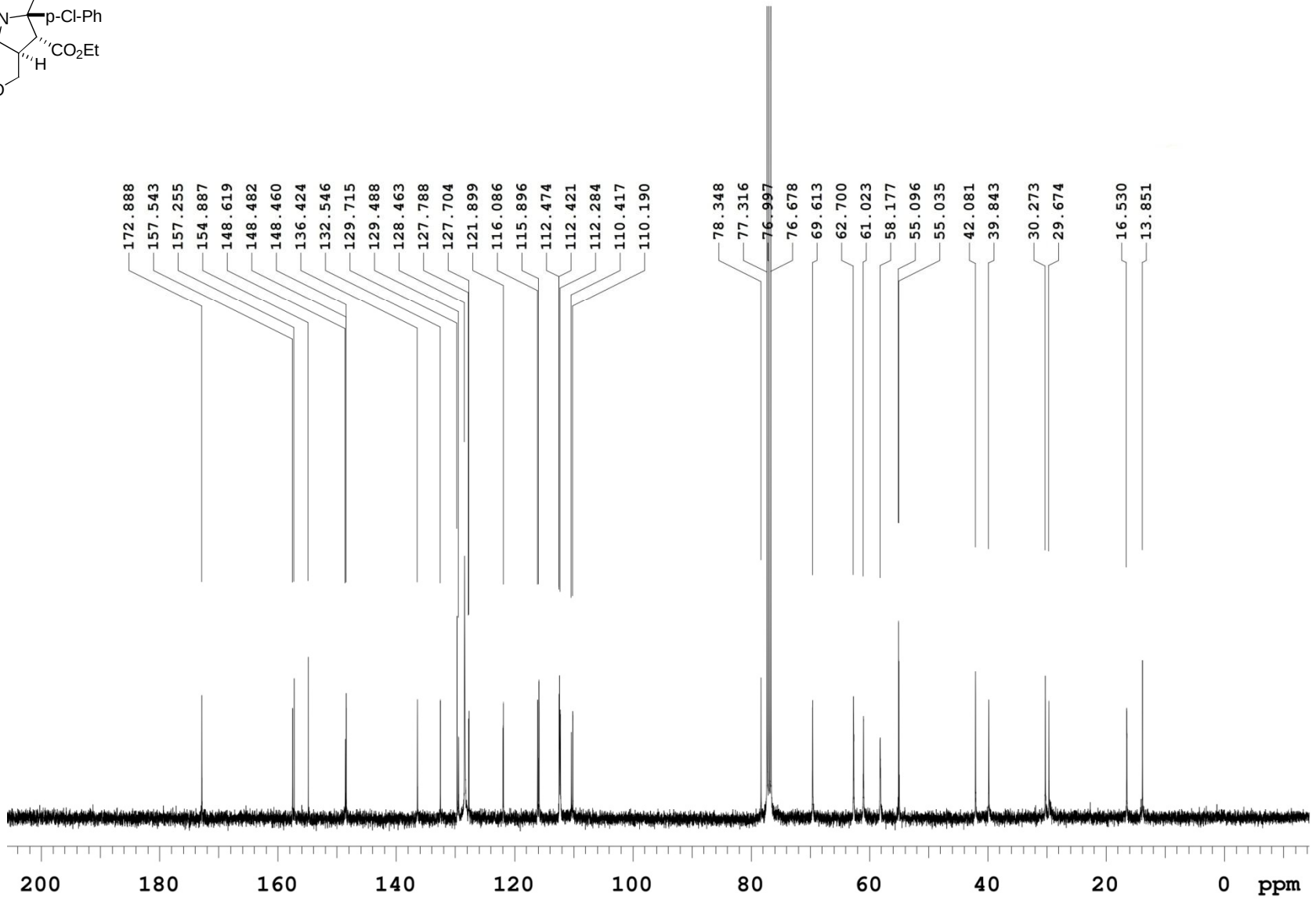
^{1}H NMR of **3n** in $CDCl_3$



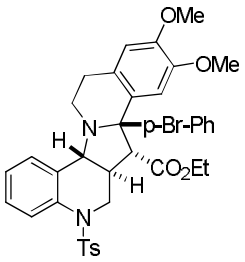


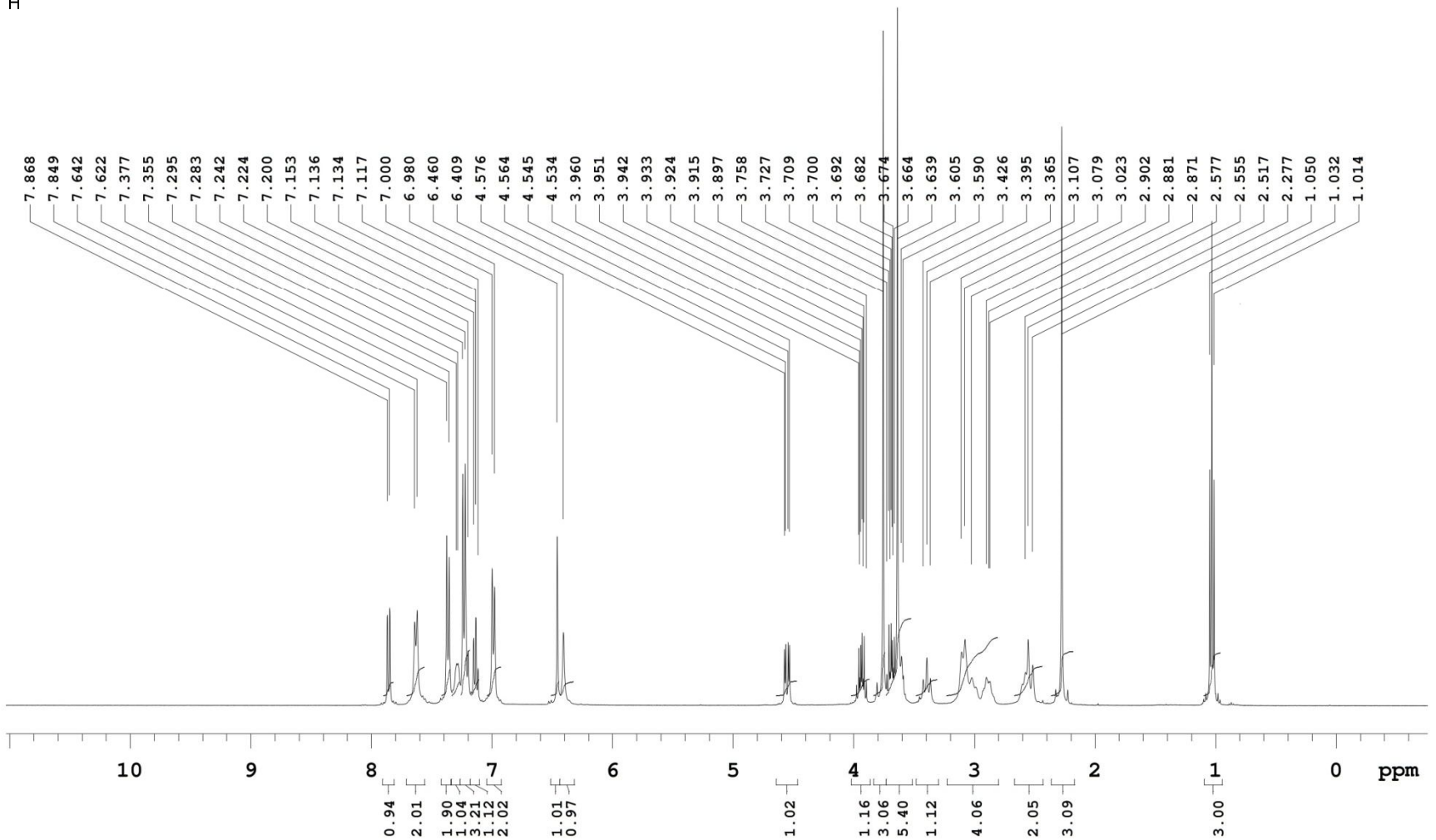
^{13}C NMR of **3n** in $CDCl_3$



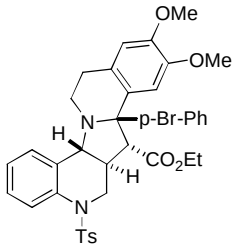


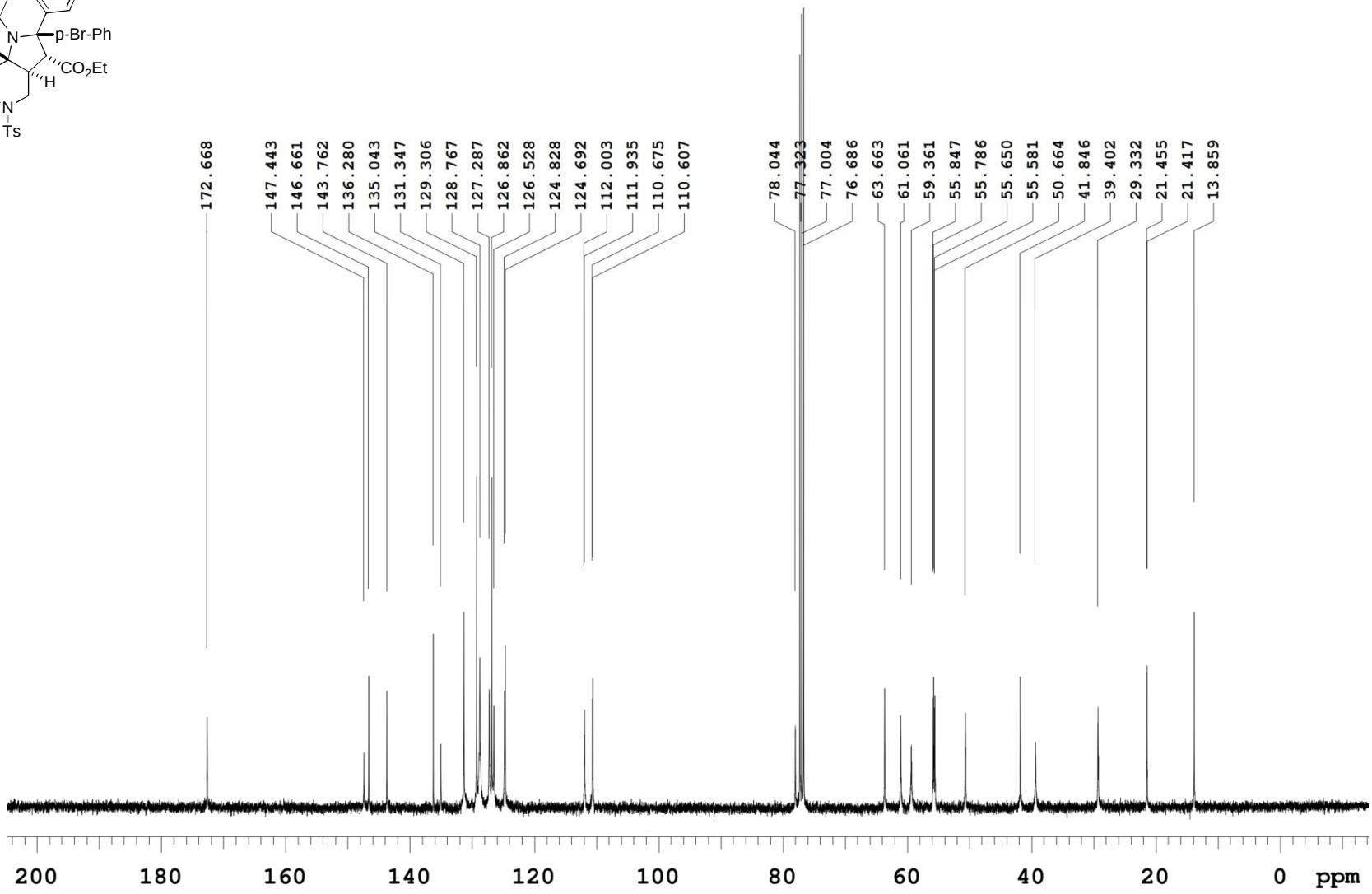
^{1}H NMR of **3o** in $CDCl_3$





^{13}C NMR of **3o** in $CDCl_3$





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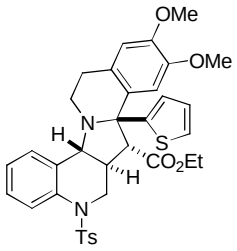
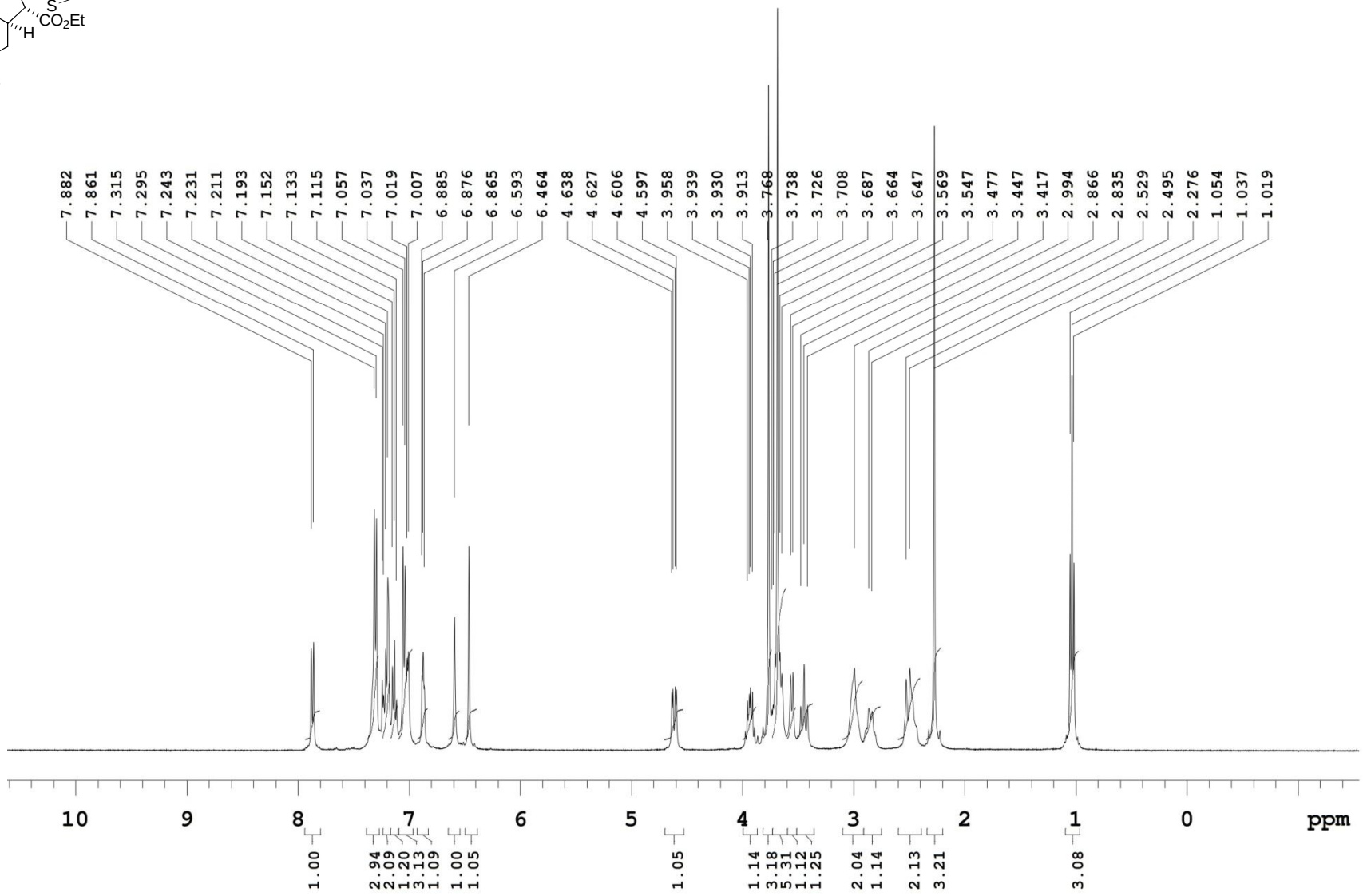
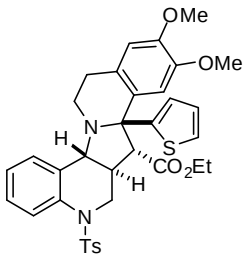
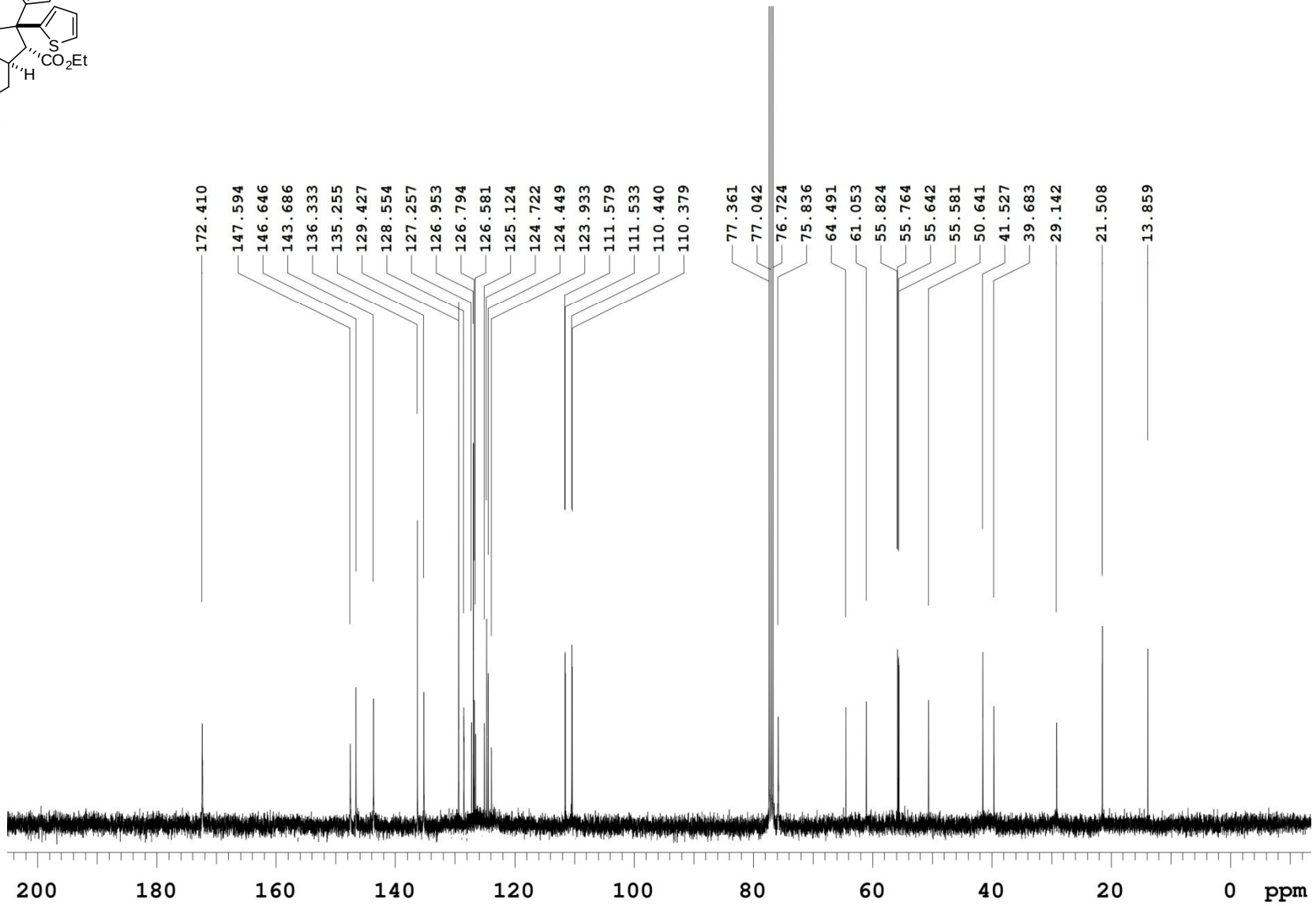


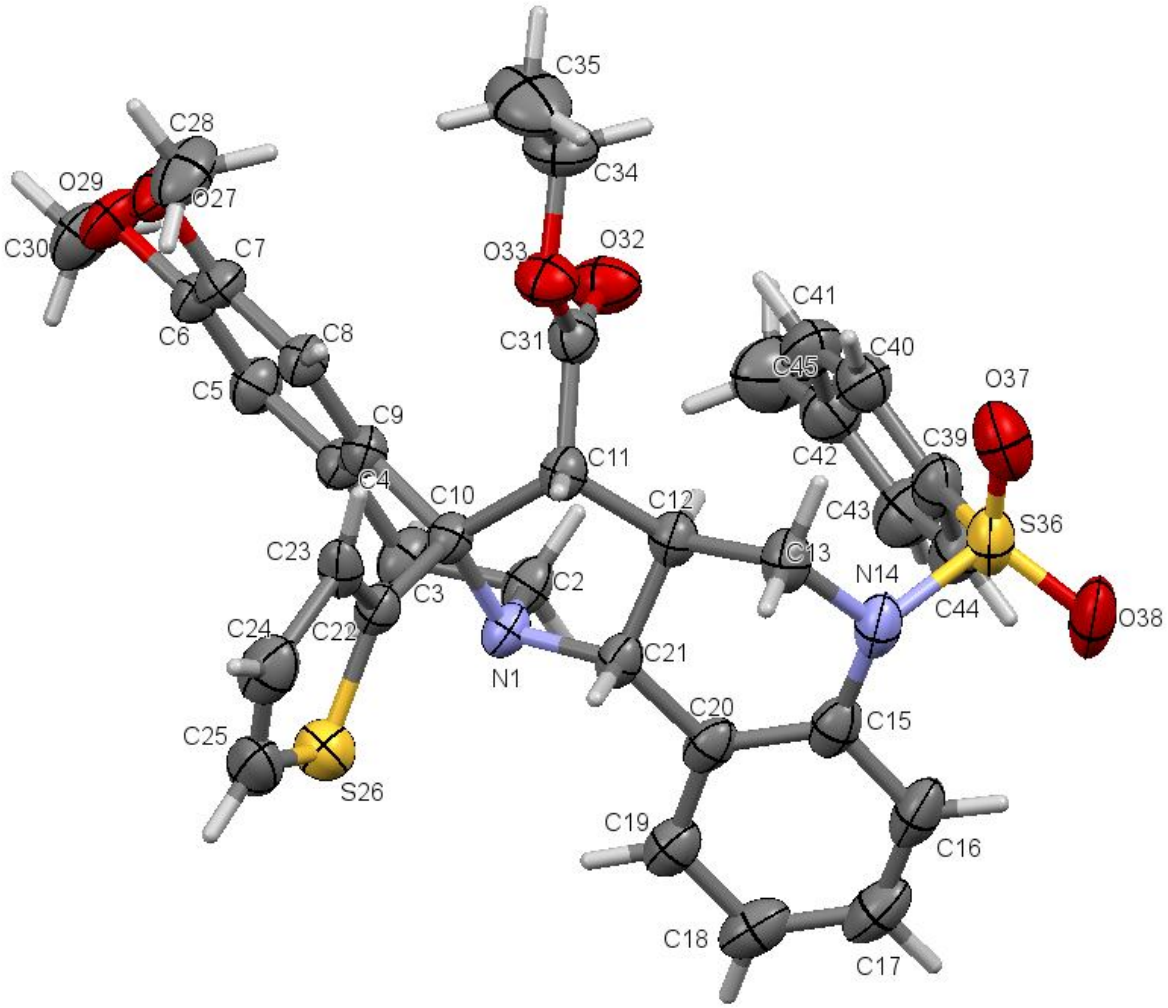


^{13}C NMR of **3p** in $CDCl_3$

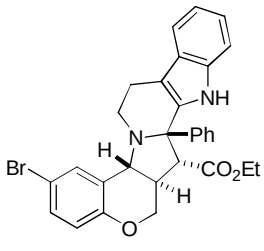


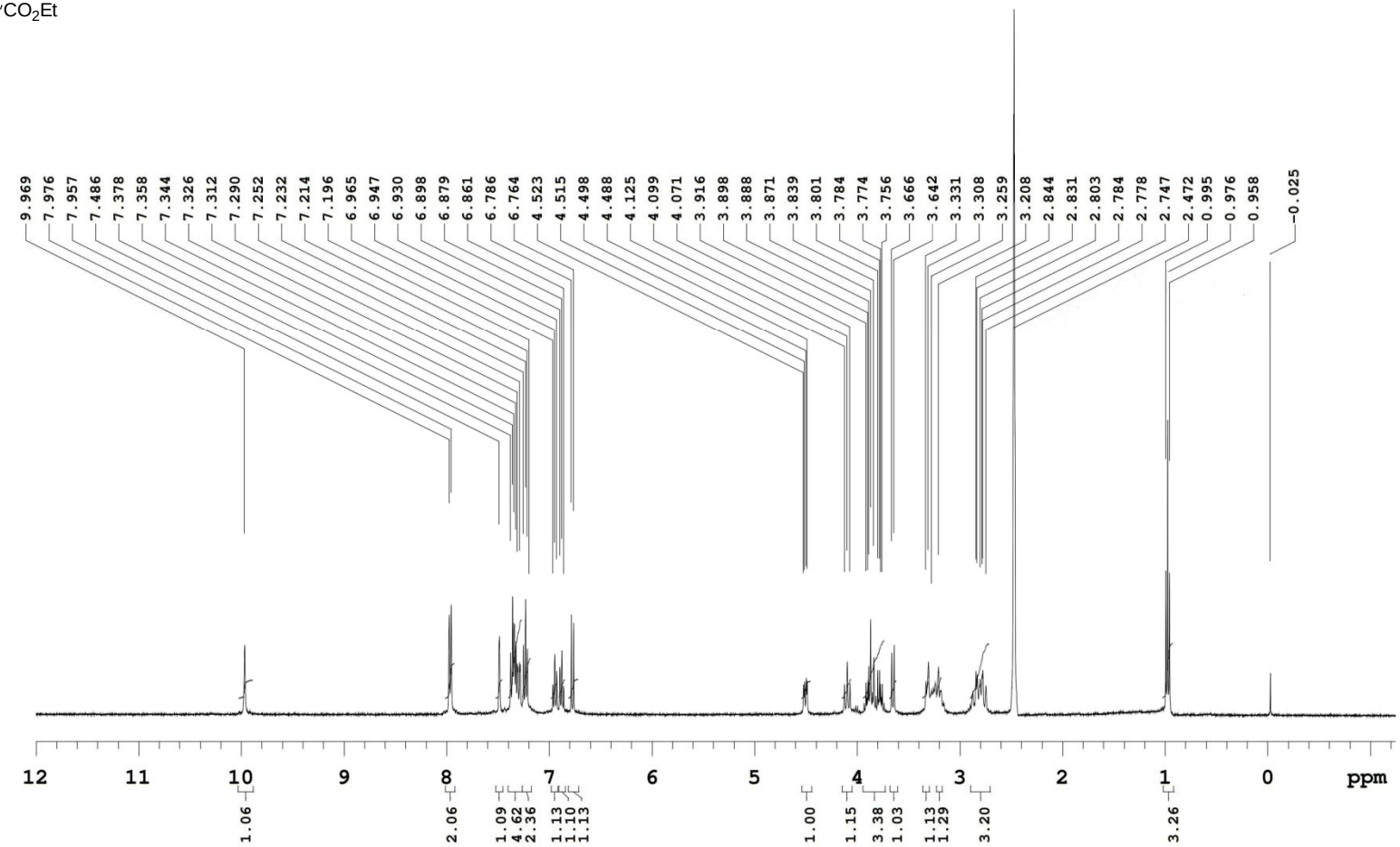


ORTEP Diagram Of 3p

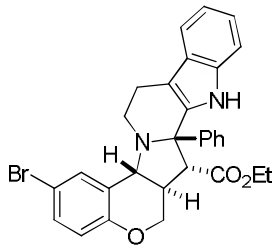


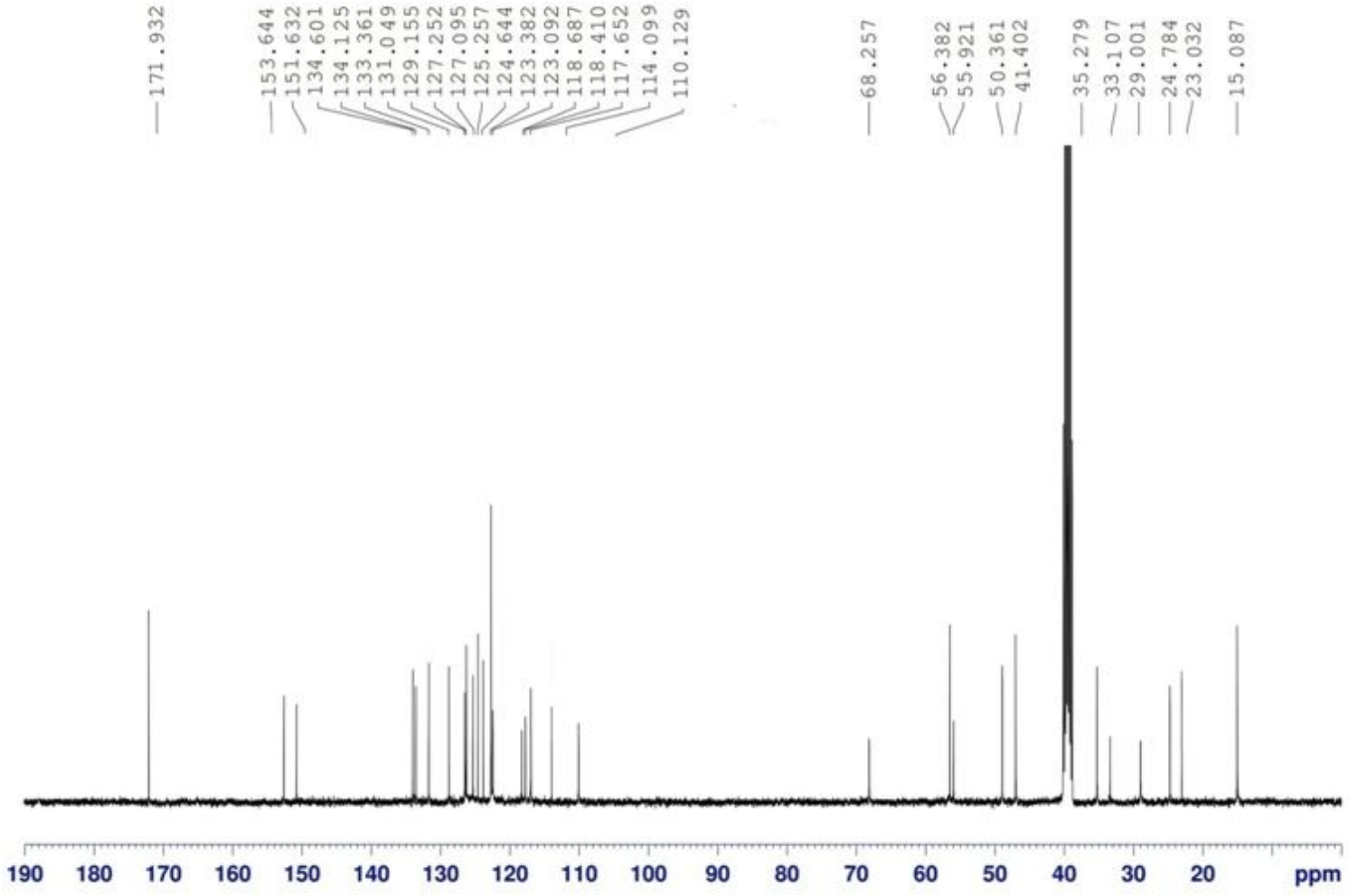
^{1}H NMR of **4a** in DMSO-d6



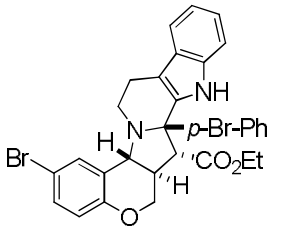


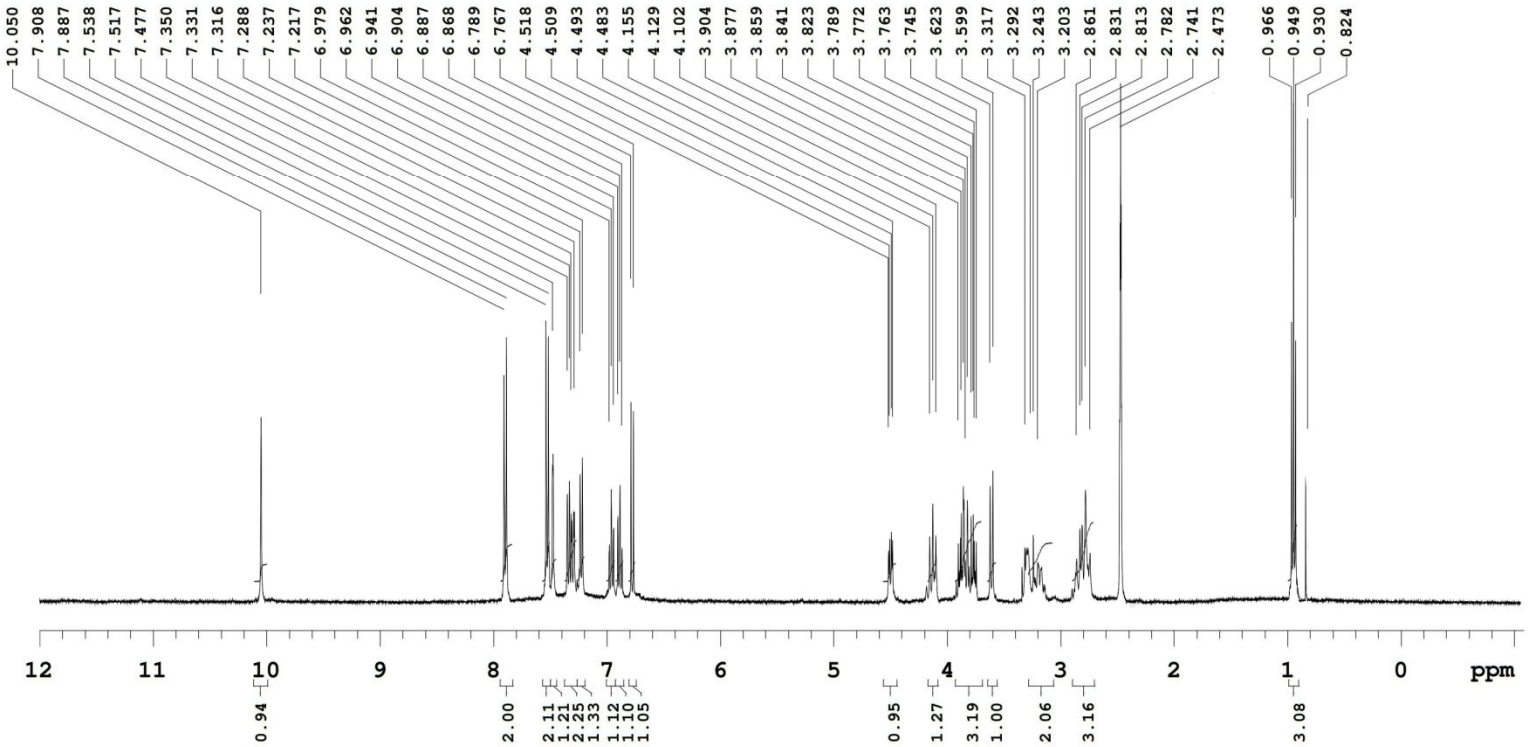
^{13}C NMR of **4a** in DMSO-d6



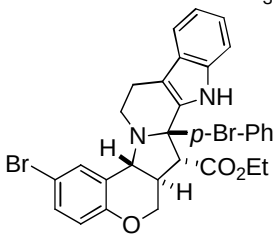


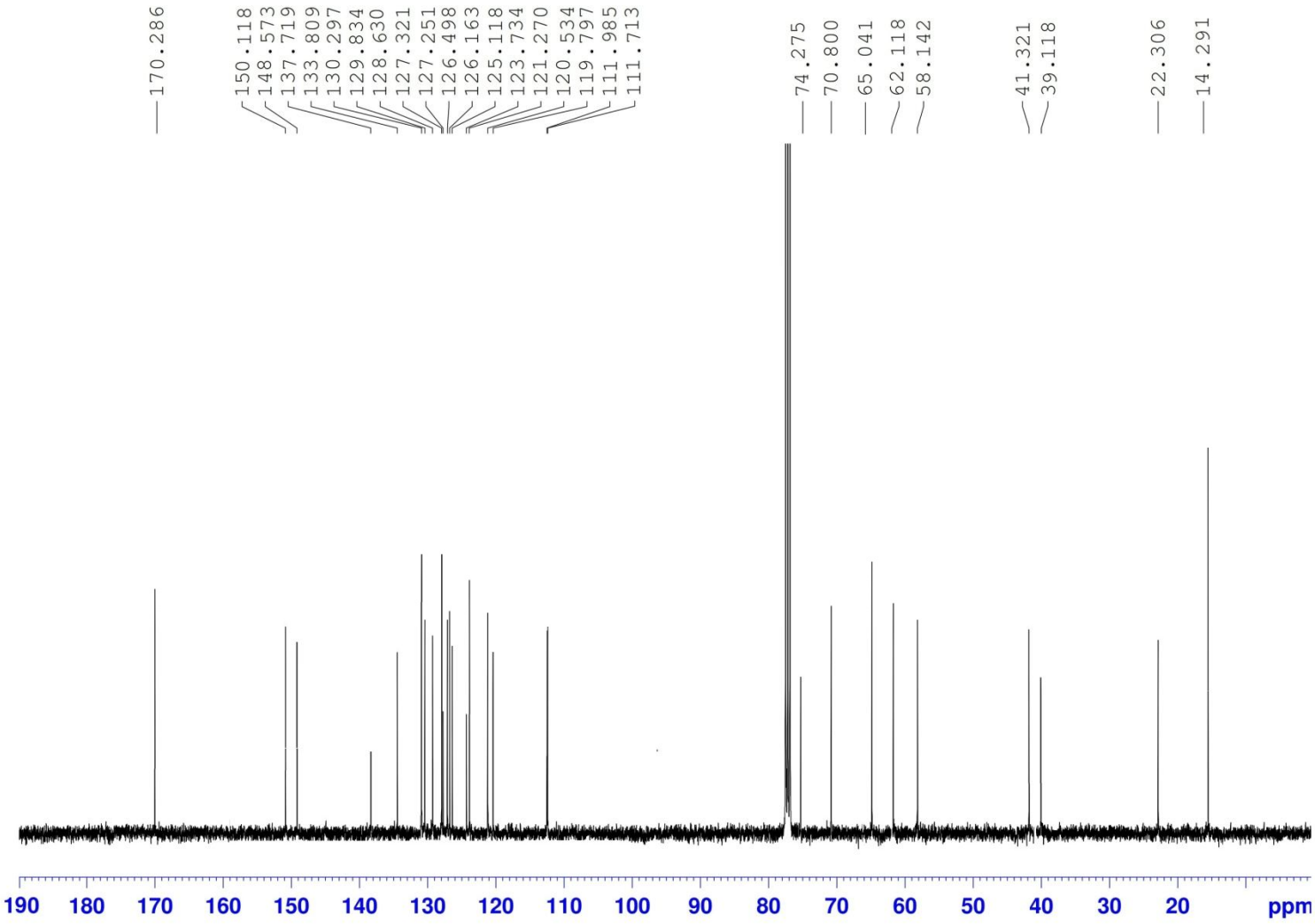
^{1}H NMR of **4b** in DMSO-d6



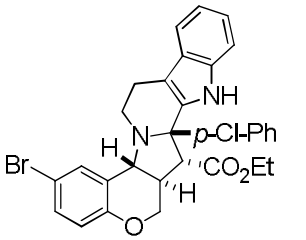


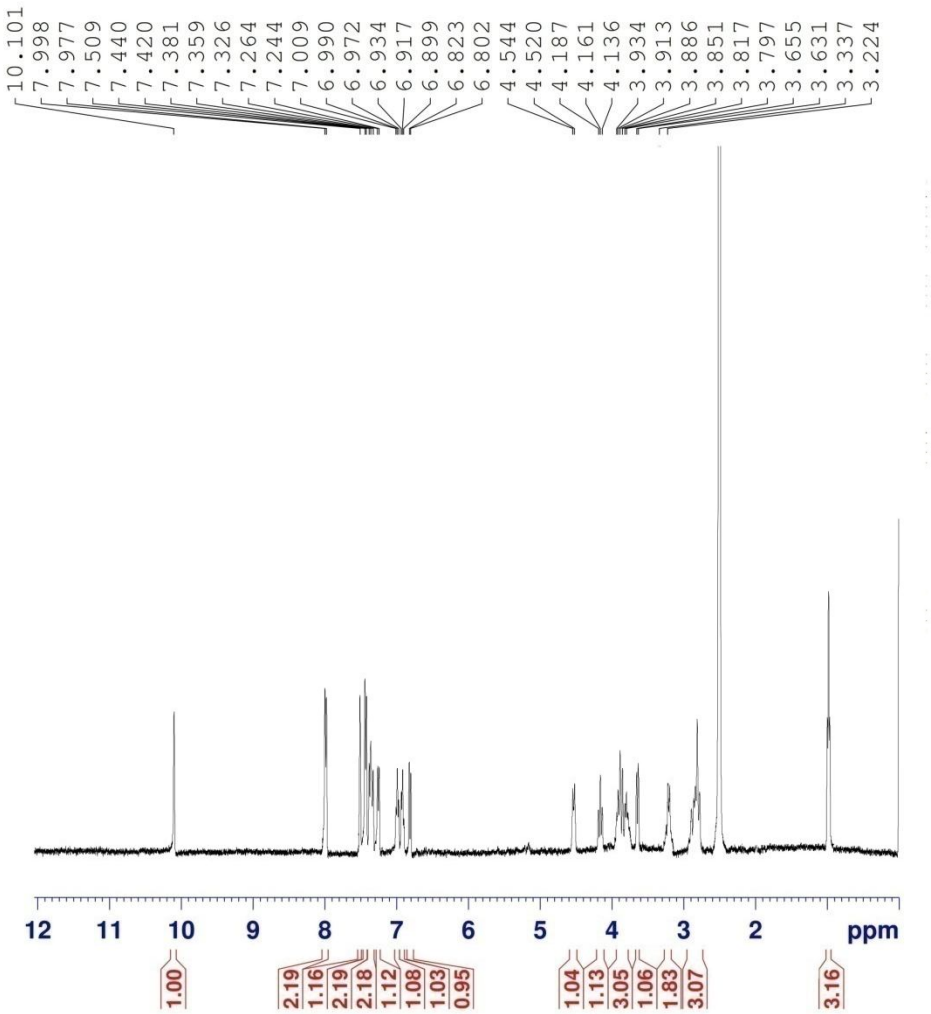
^{13}C NMR of **4b** in $CDCl_3$



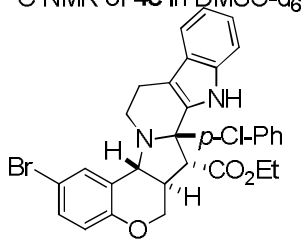


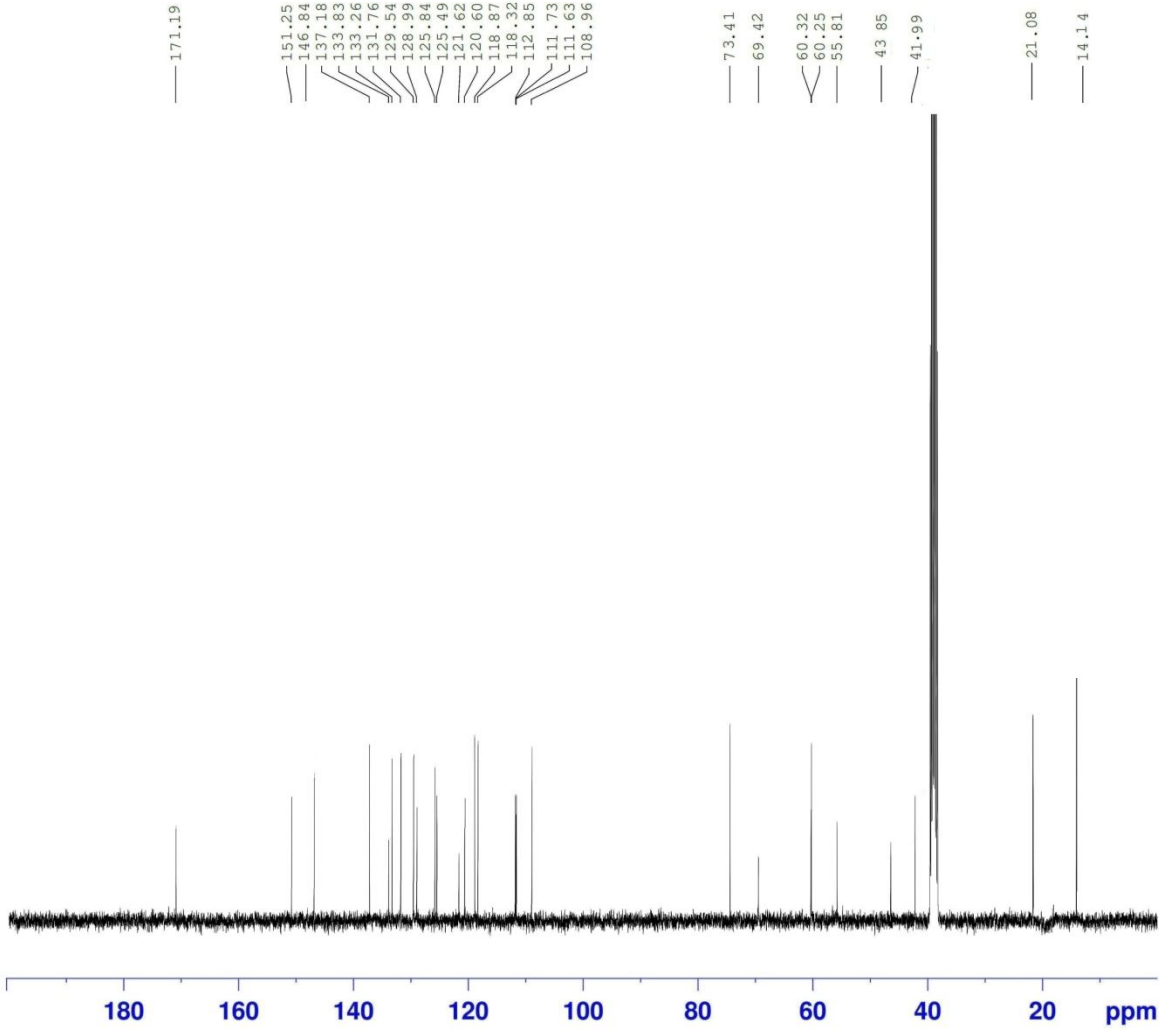
^{1}H NMR of **4c** in DMSO-d_6



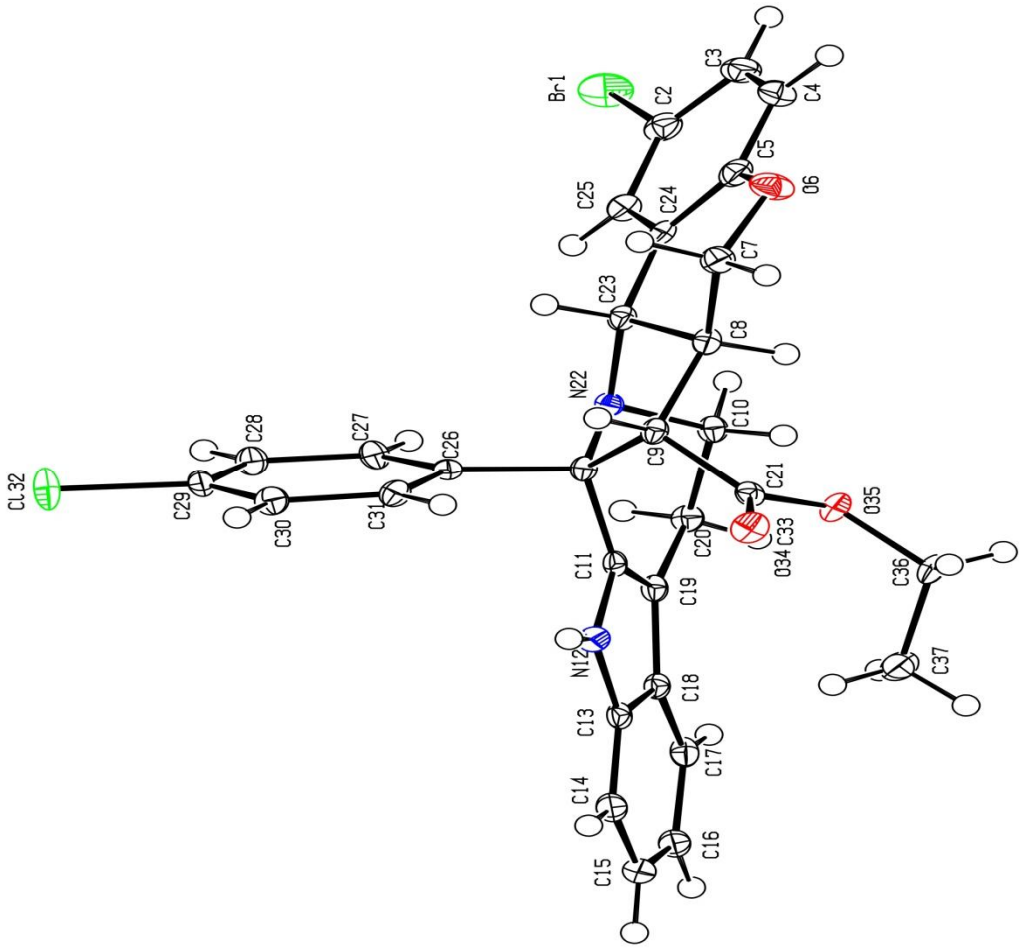


^{13}C NMR of **4c** in DMSO-d_6

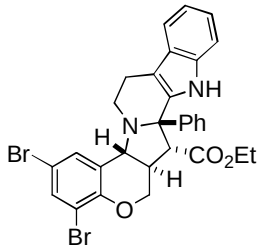


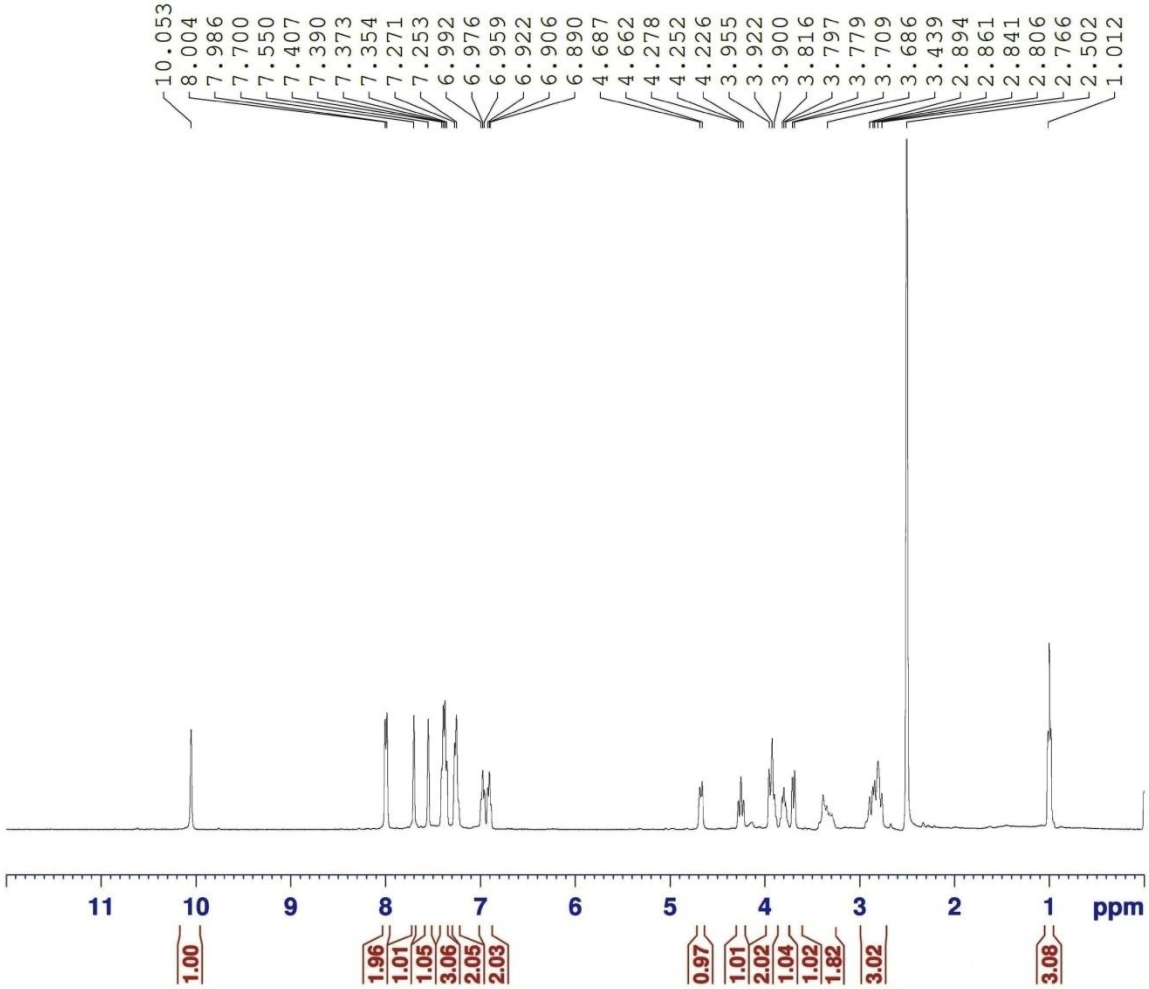


ORTEP diagram of **4c**

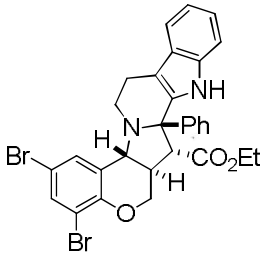


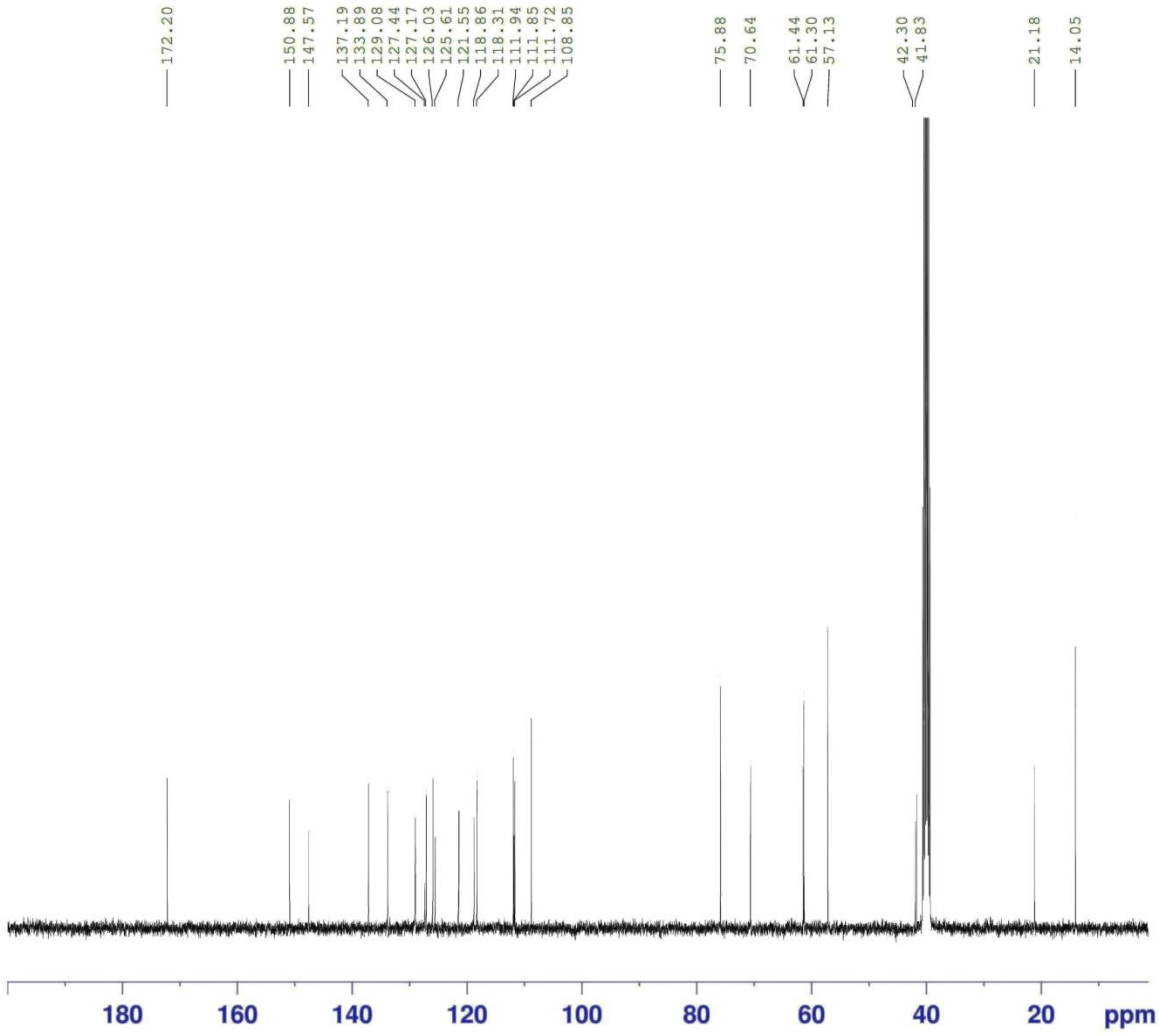
^{1}H NMR of **4d** in DMSO-d_6



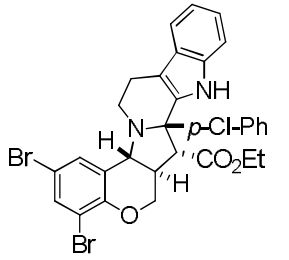


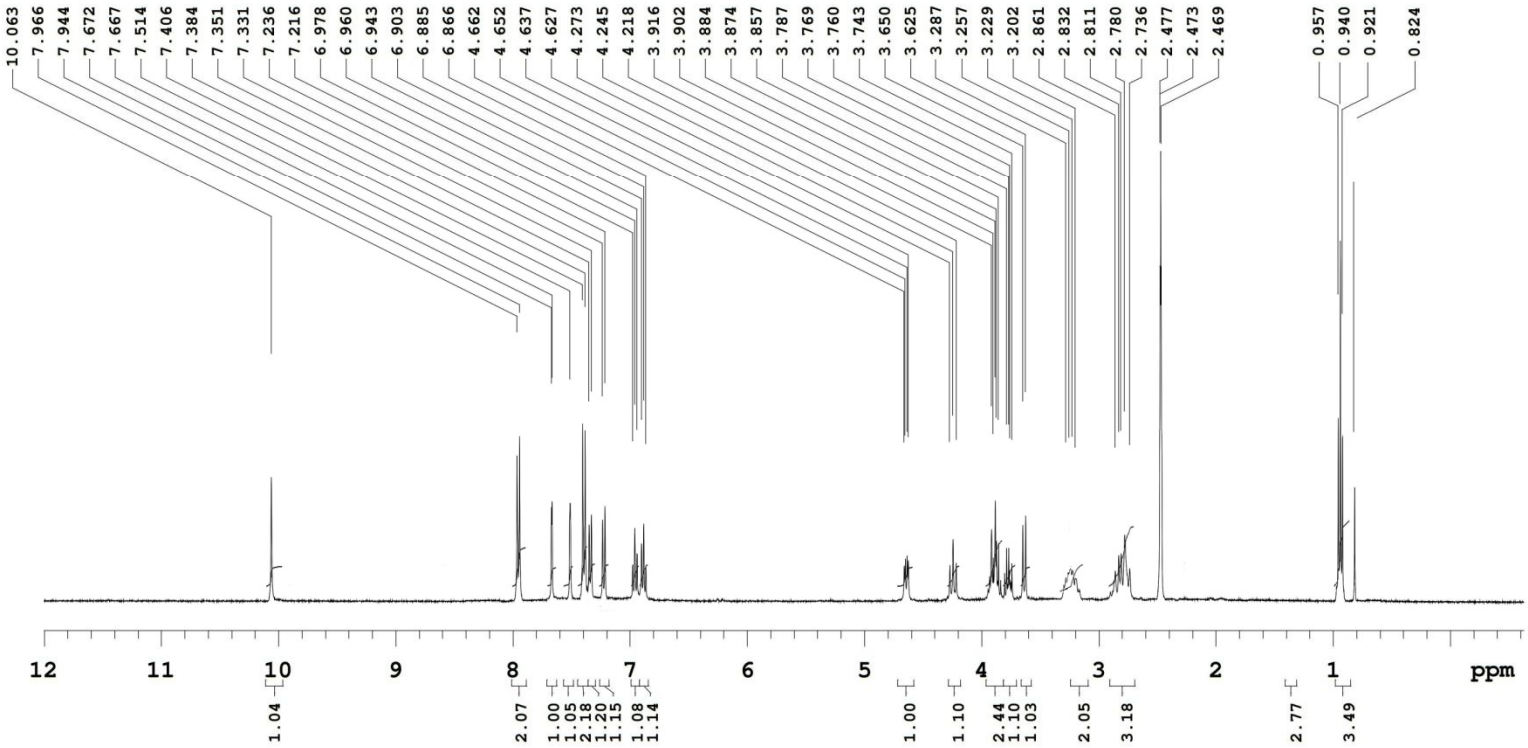
^{13}C NMR of **4d** in DMSO-d_6



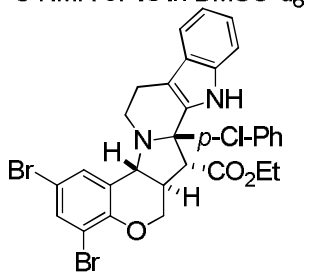


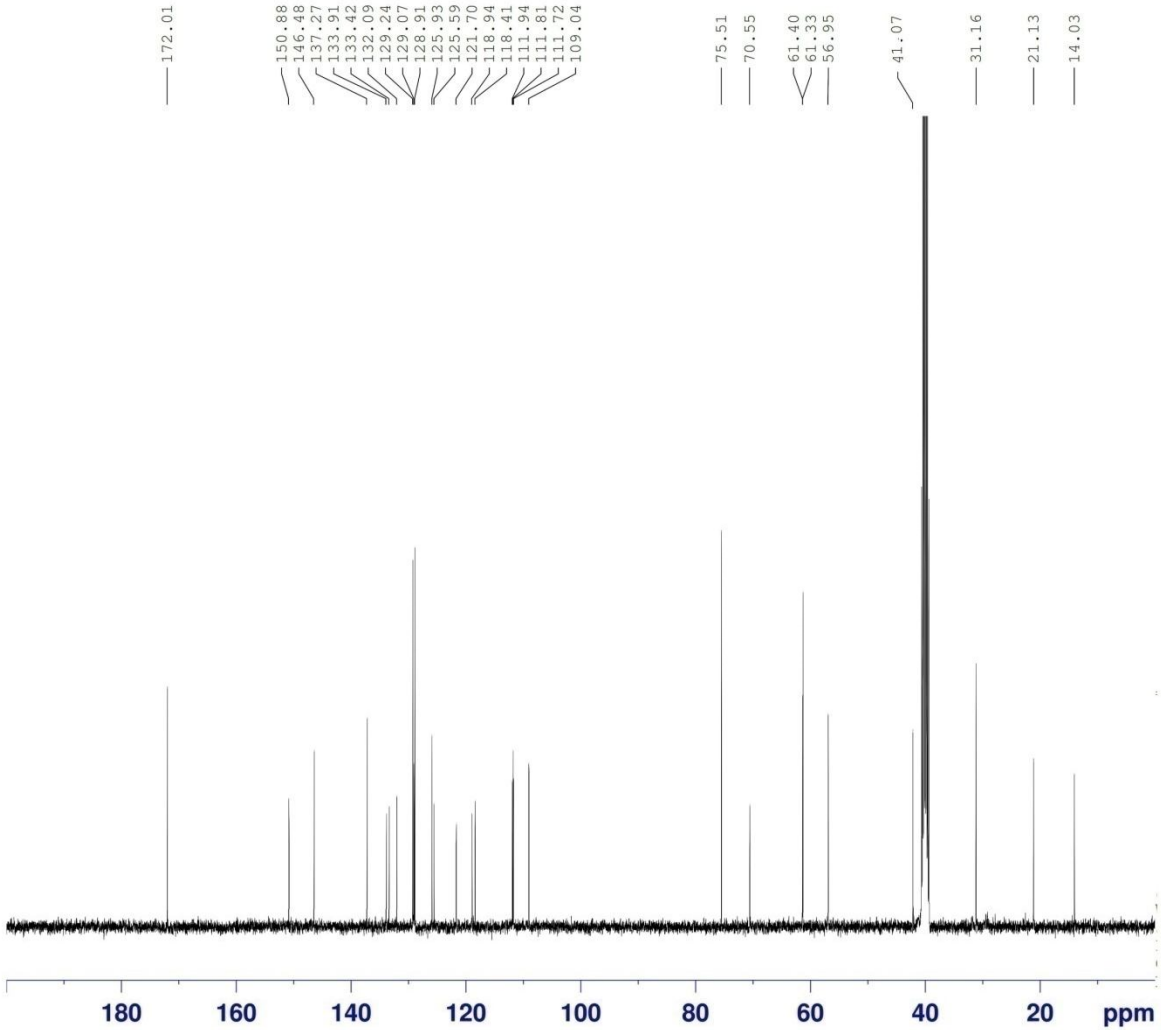
^{1}H NMR of **4e** in DMSO-d_6



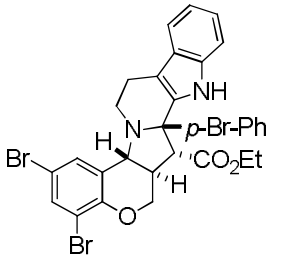


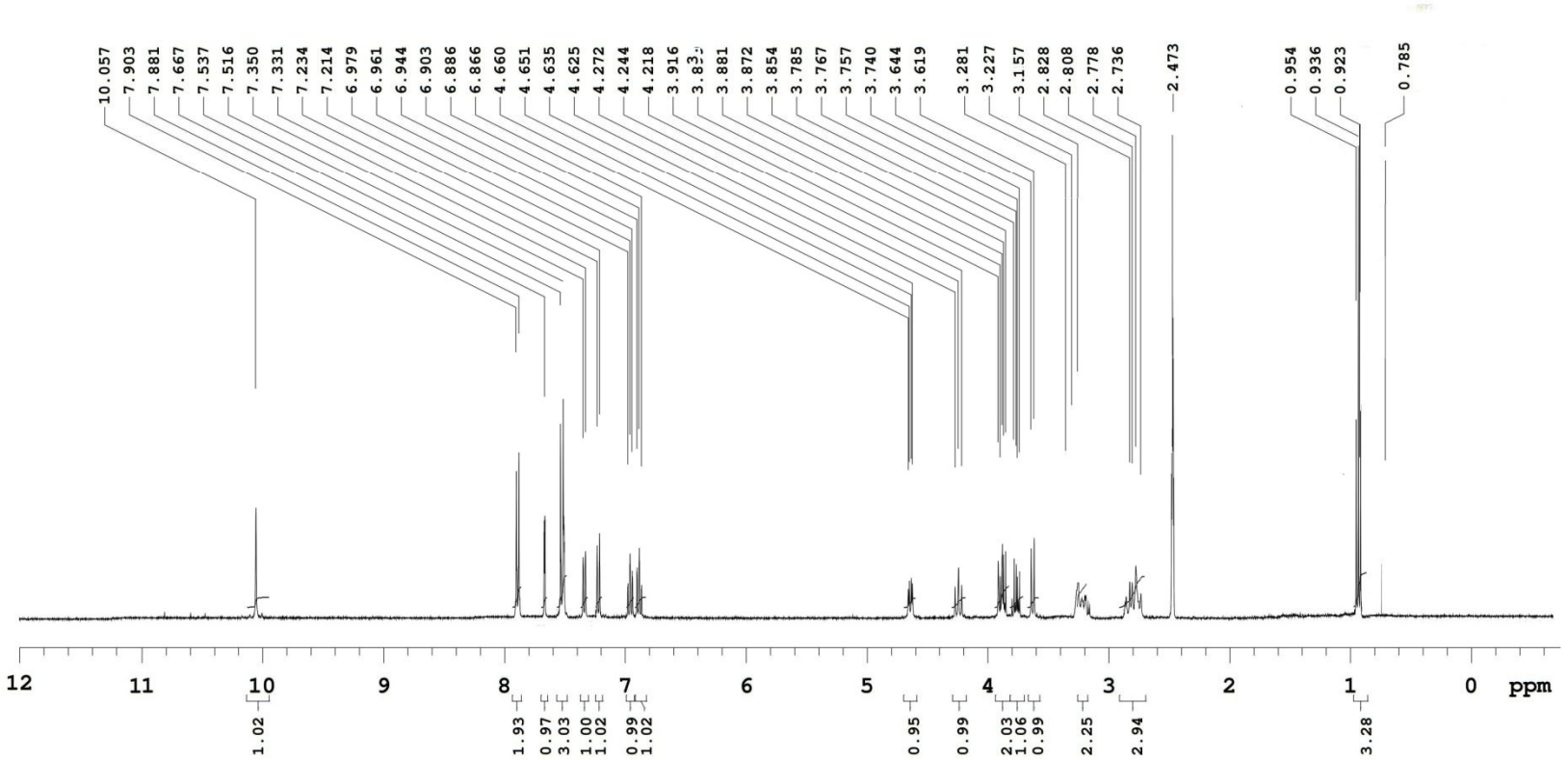
^{13}C NMR of **4e** in DMSO-d_6



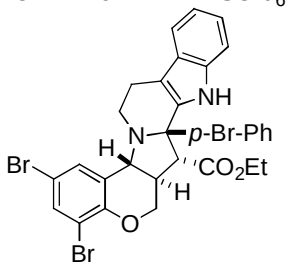


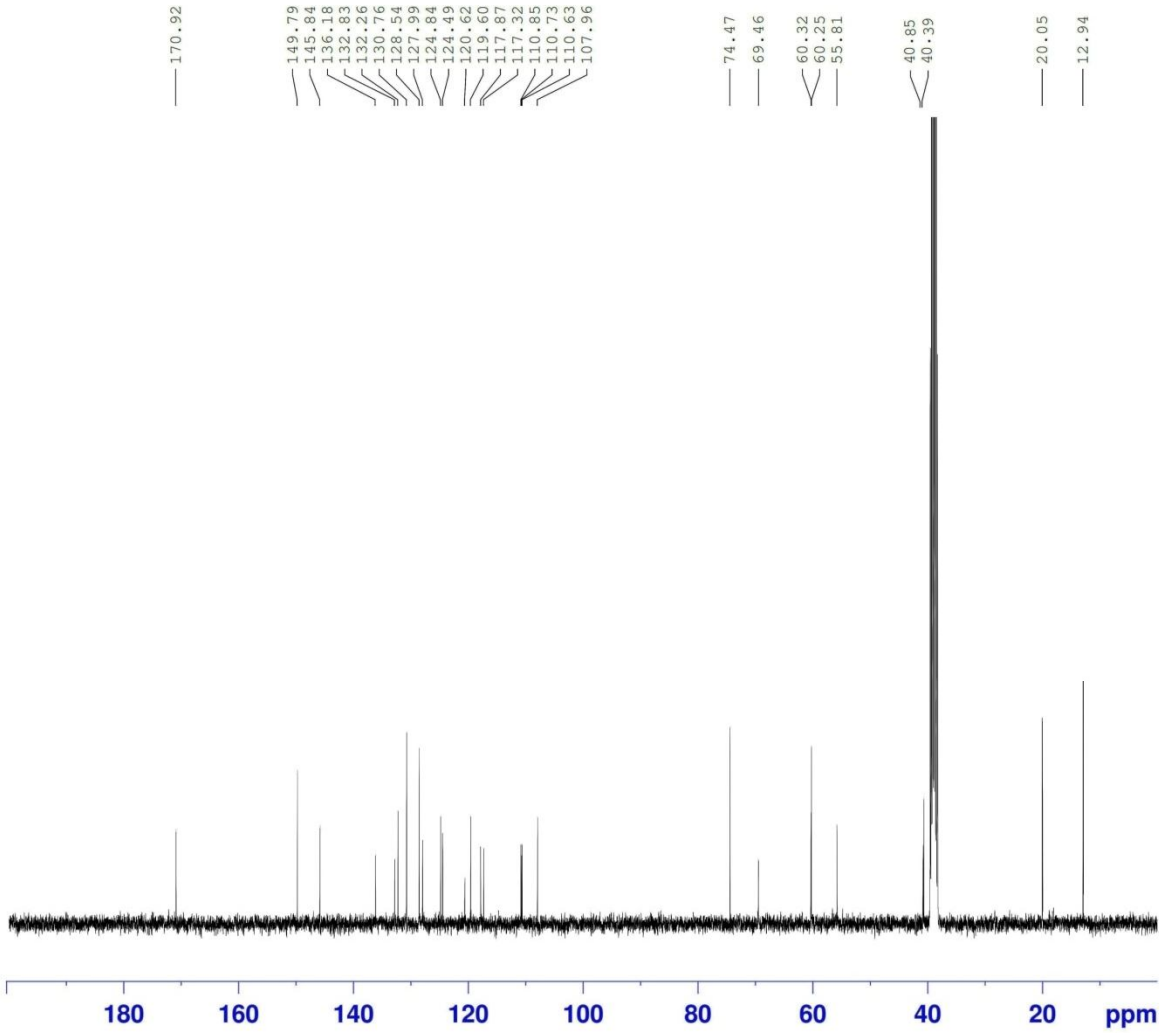
^{1}H NMR of **4f** in DMSO-d_6



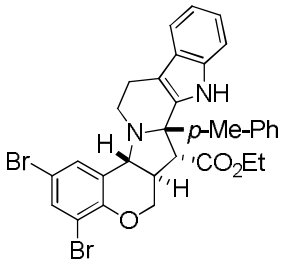


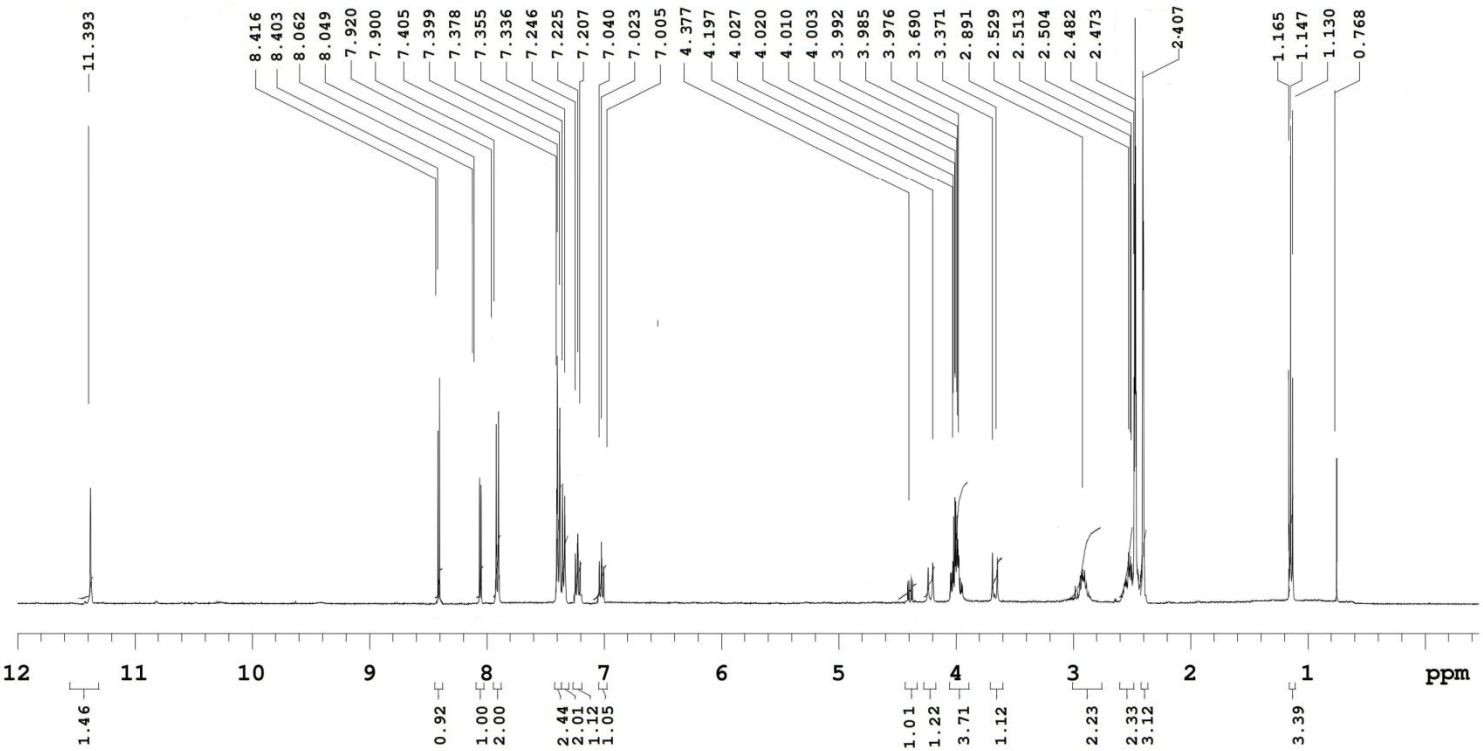
^{13}C NMR of **4f** in DMSO-d_6



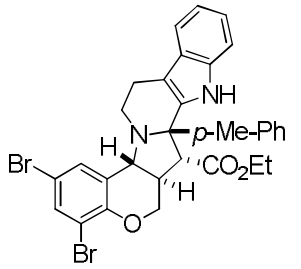


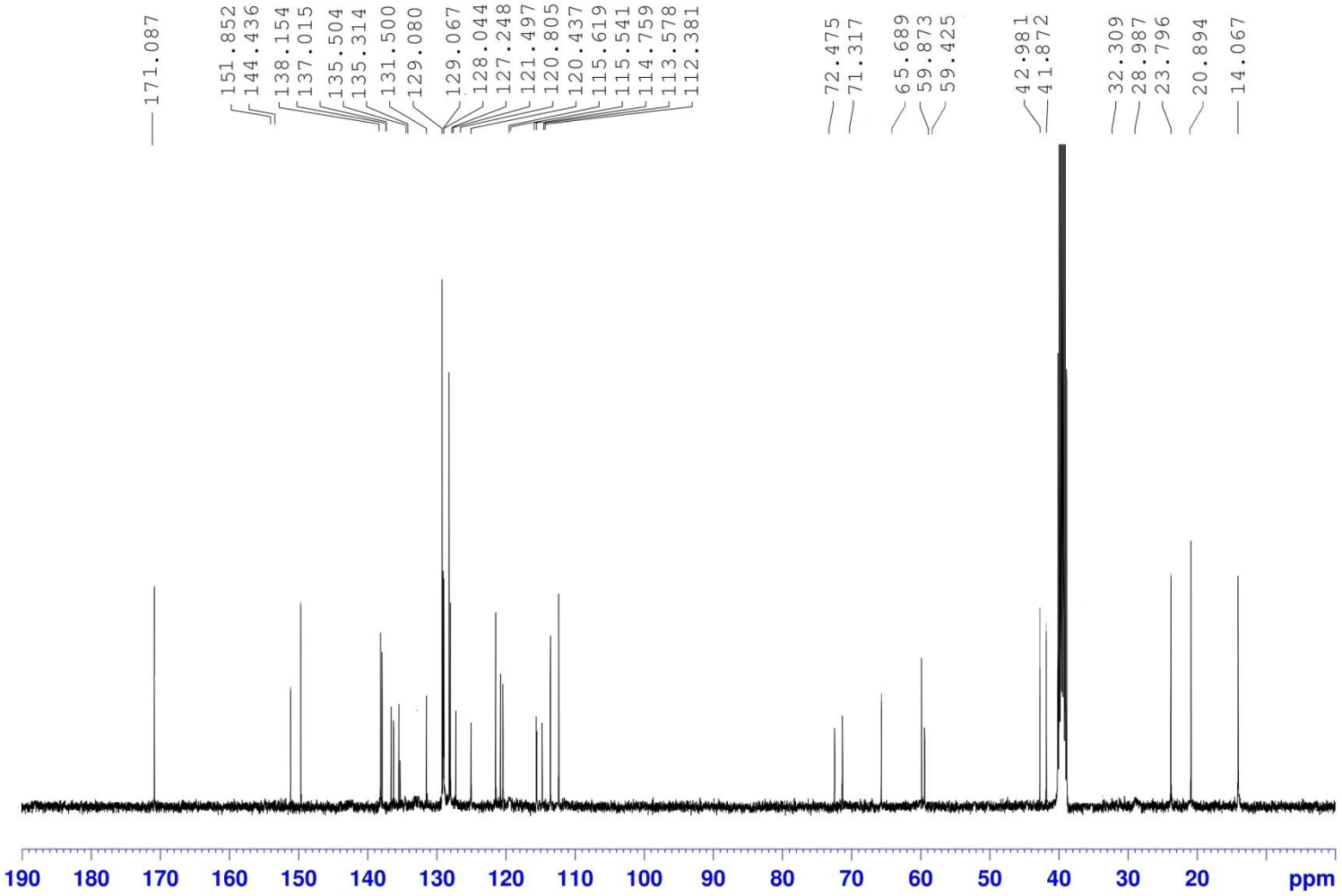
^{1}H NMR of **4g** in DMSO-d_6



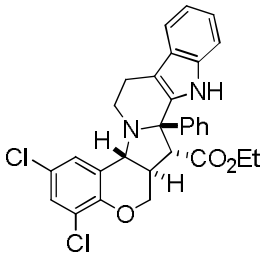


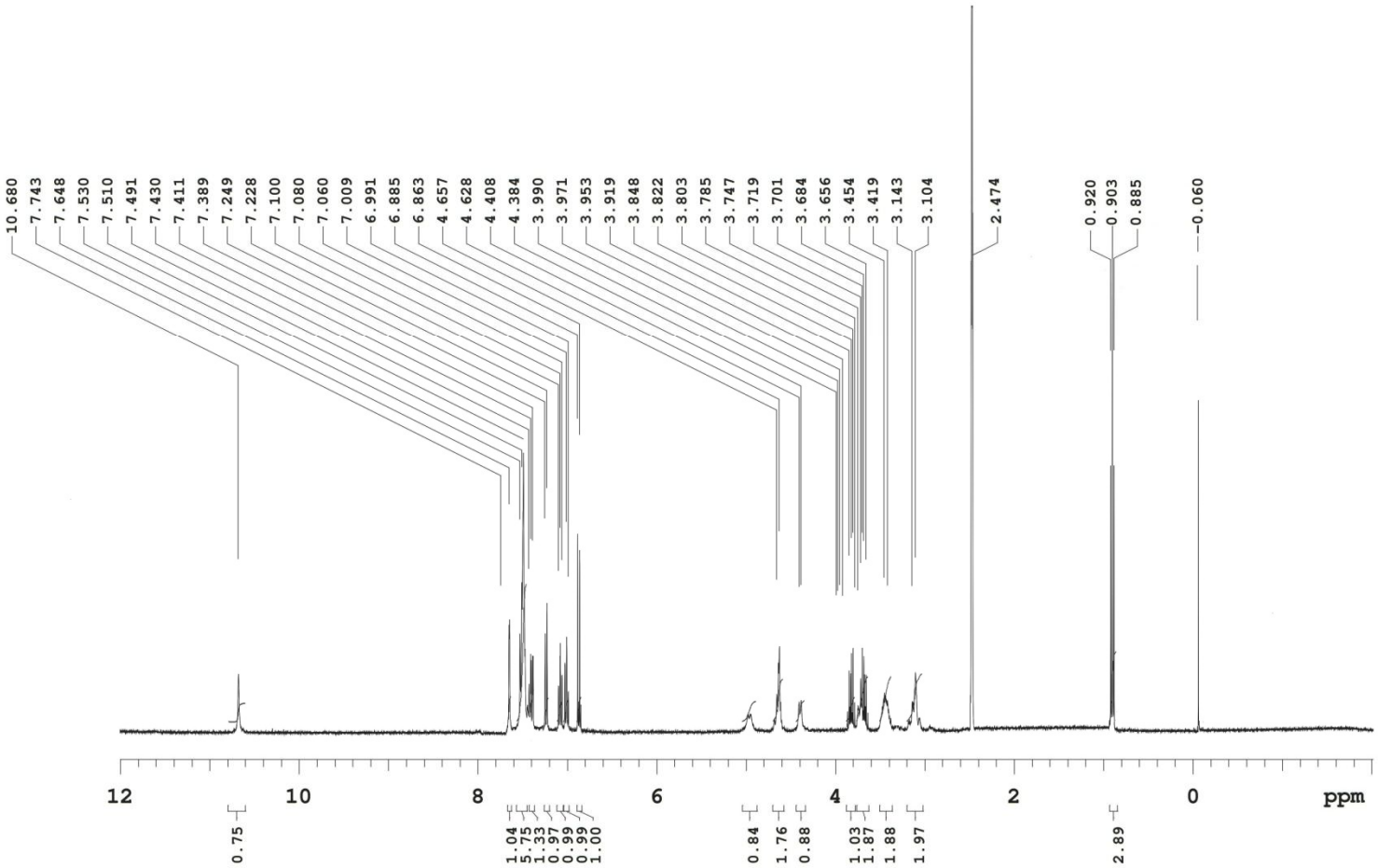
^{13}C NMR of **4g** in DMSO-d_6



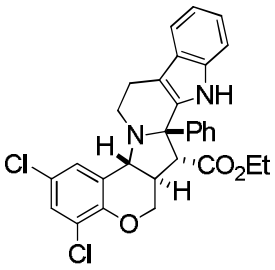


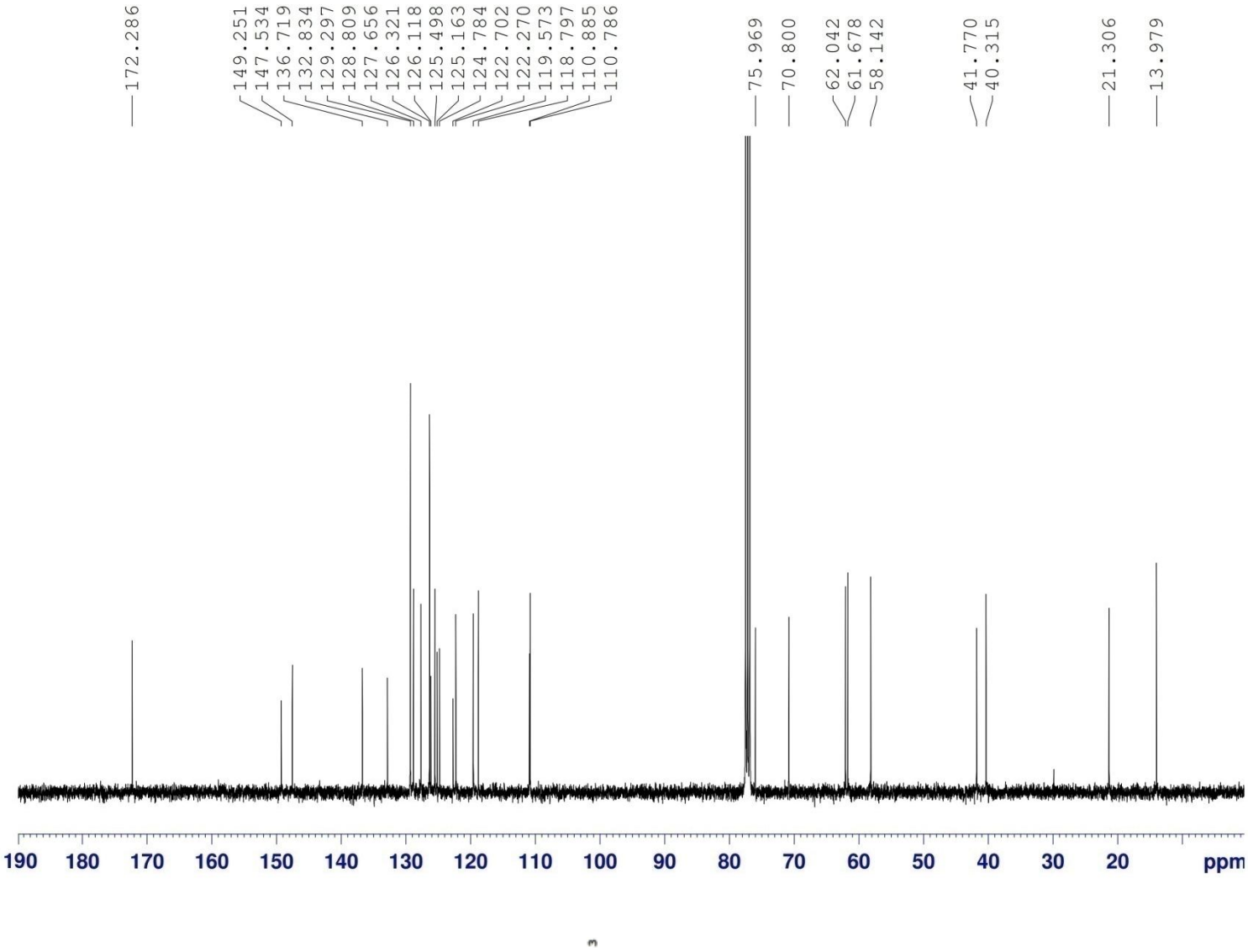
^{1}H NMR of **4h** in DMSO-d_6



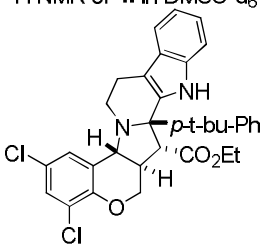


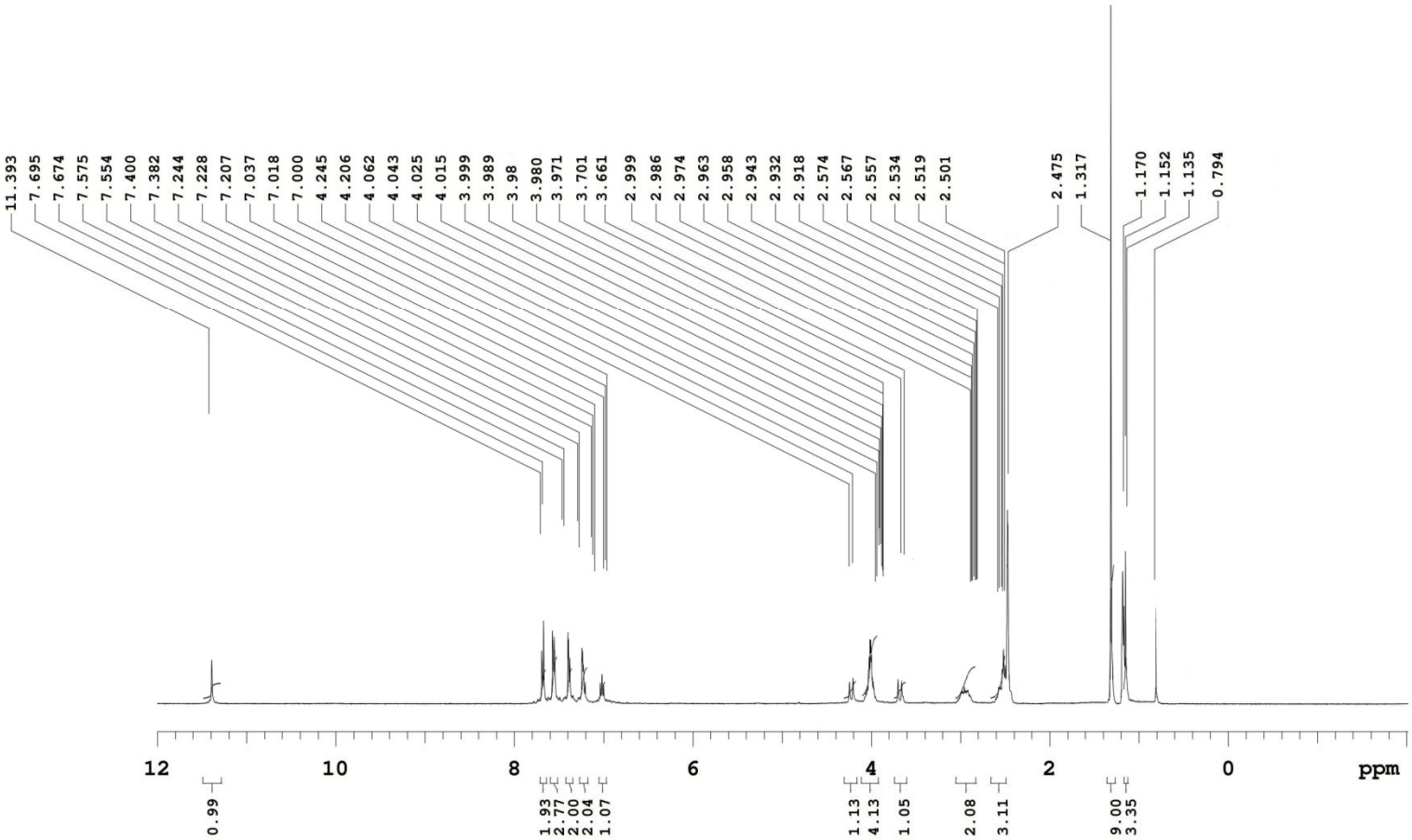
^{13}C NMR of **4h** in $CDCl_3$



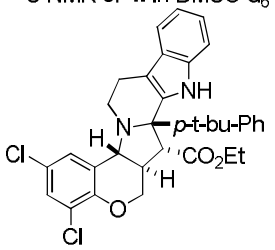


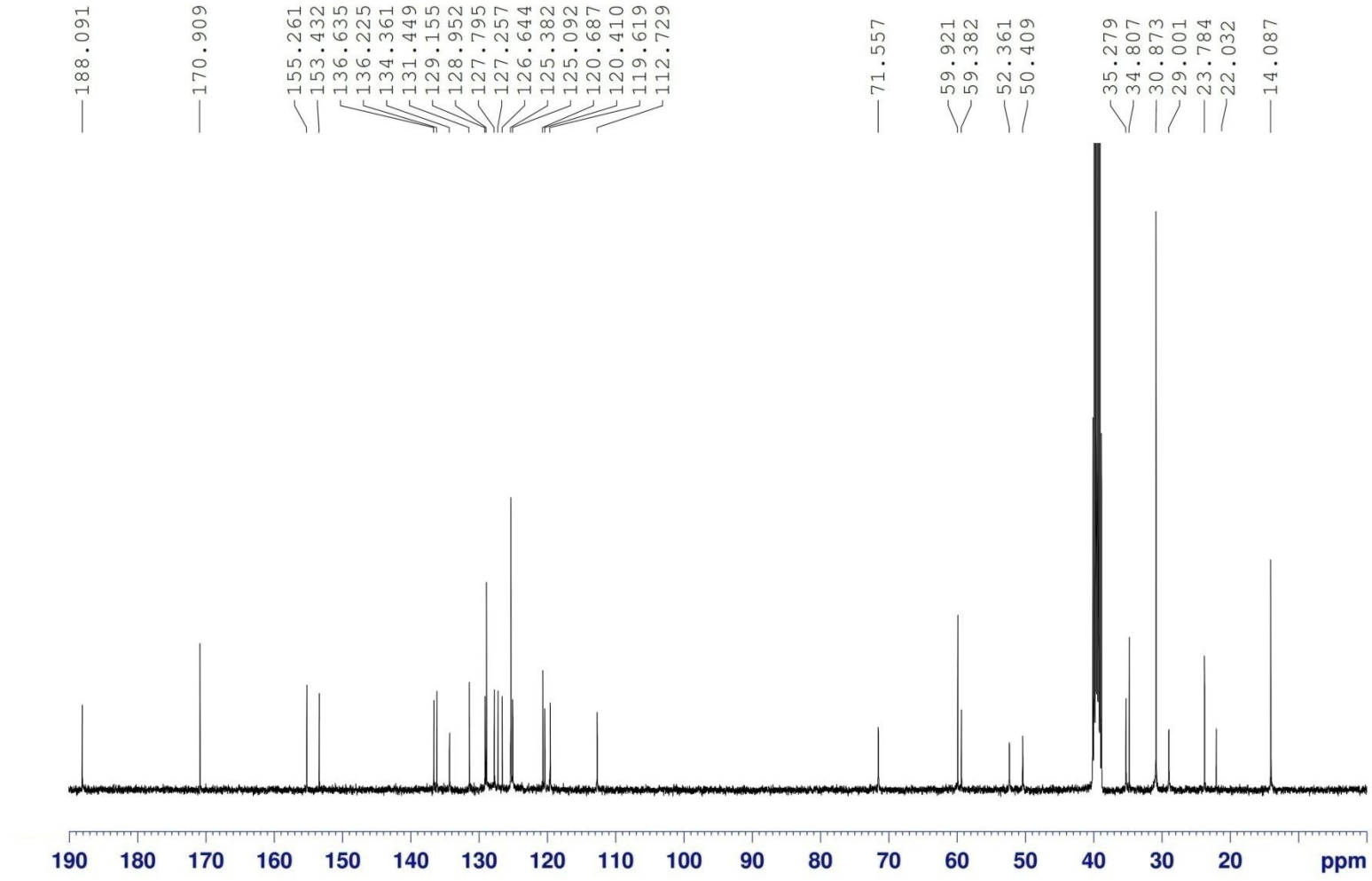
^{1}H NMR of **4i** in DMSO-d_6



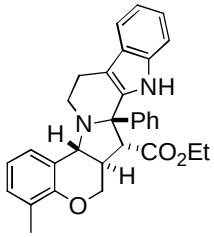


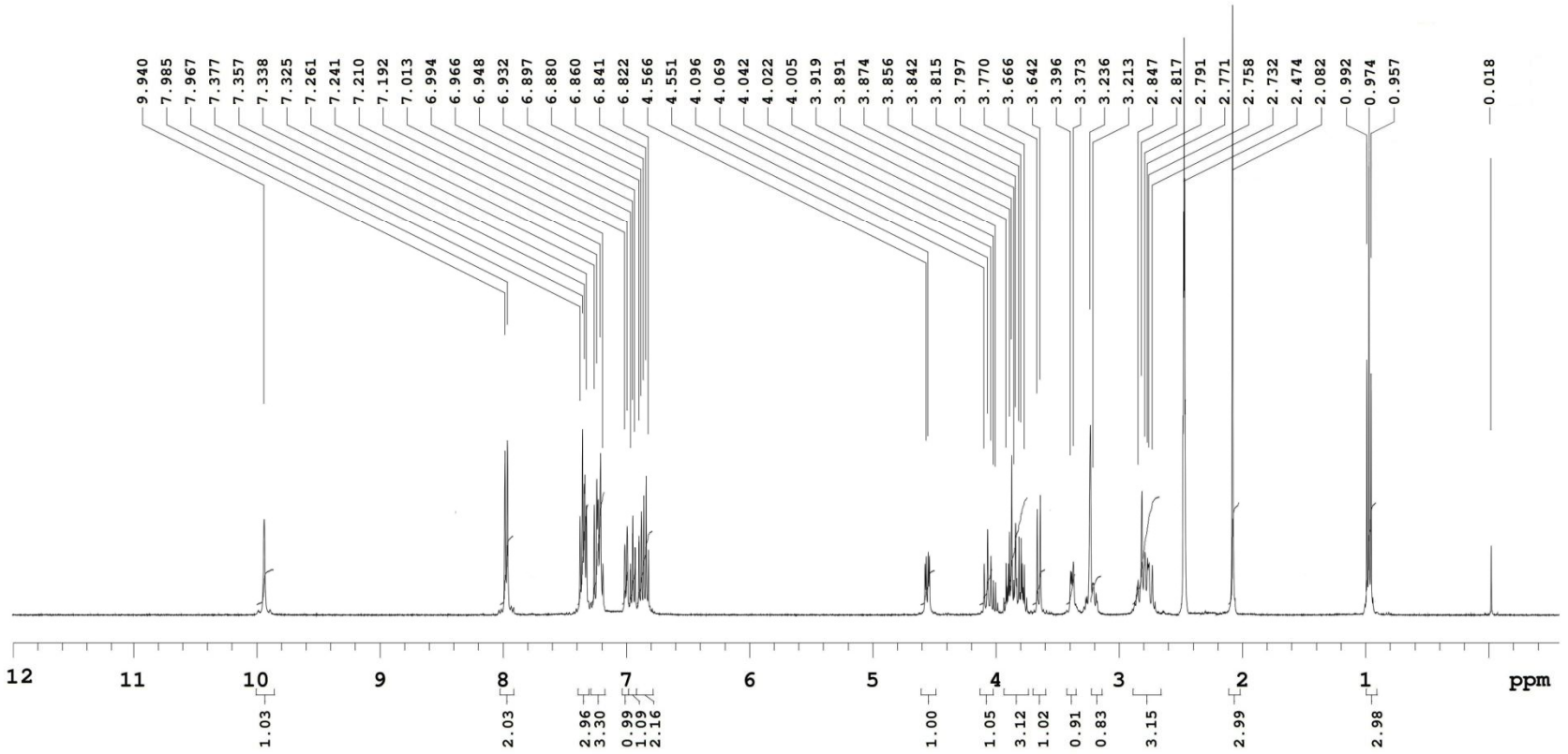
^{13}C NMR of **4i** in DMSO-d_6



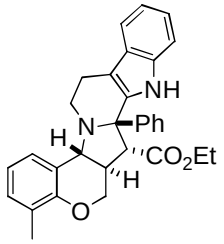


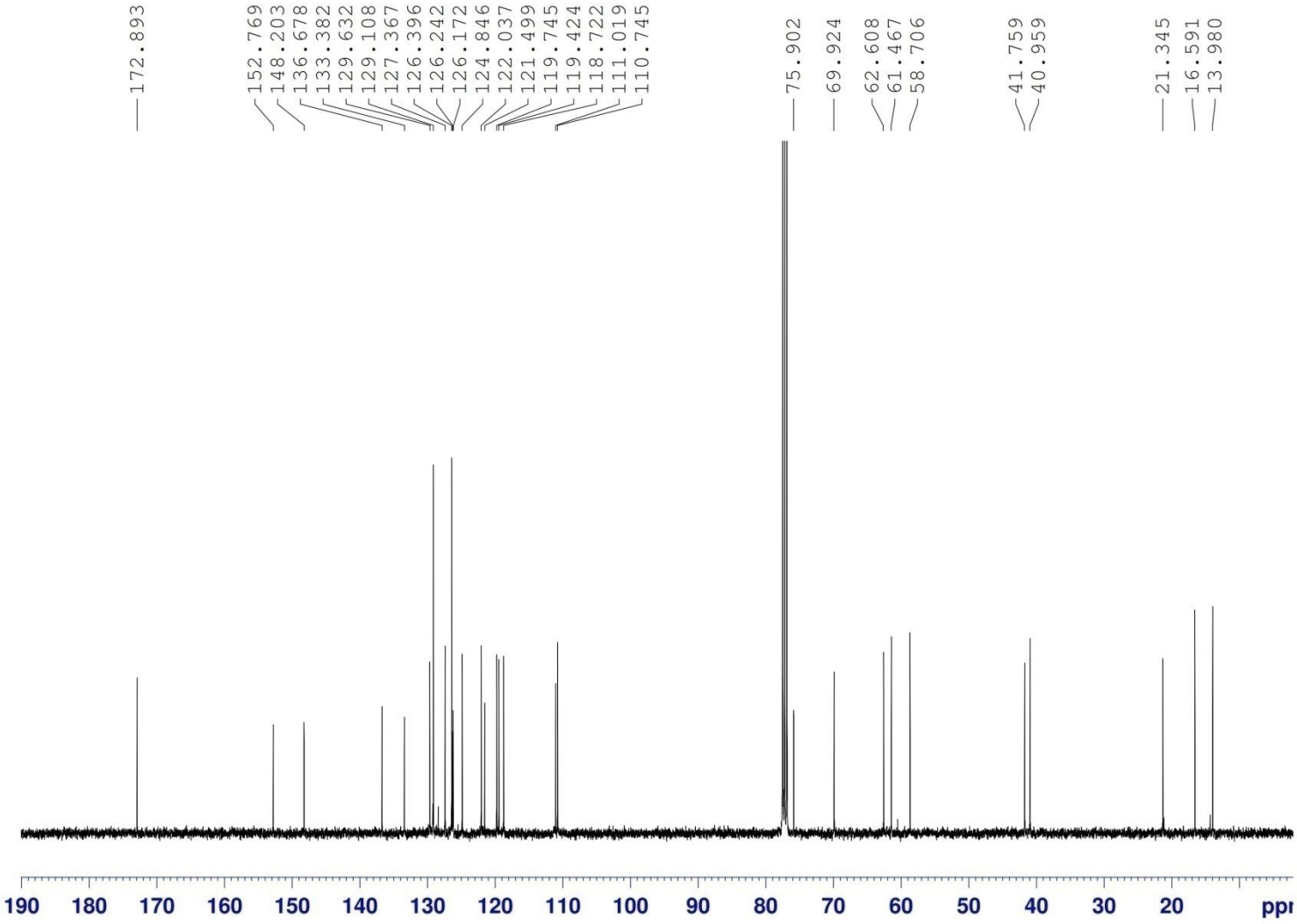
^{1}H NMR of **4j** in DMSO-d_6



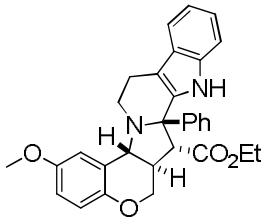


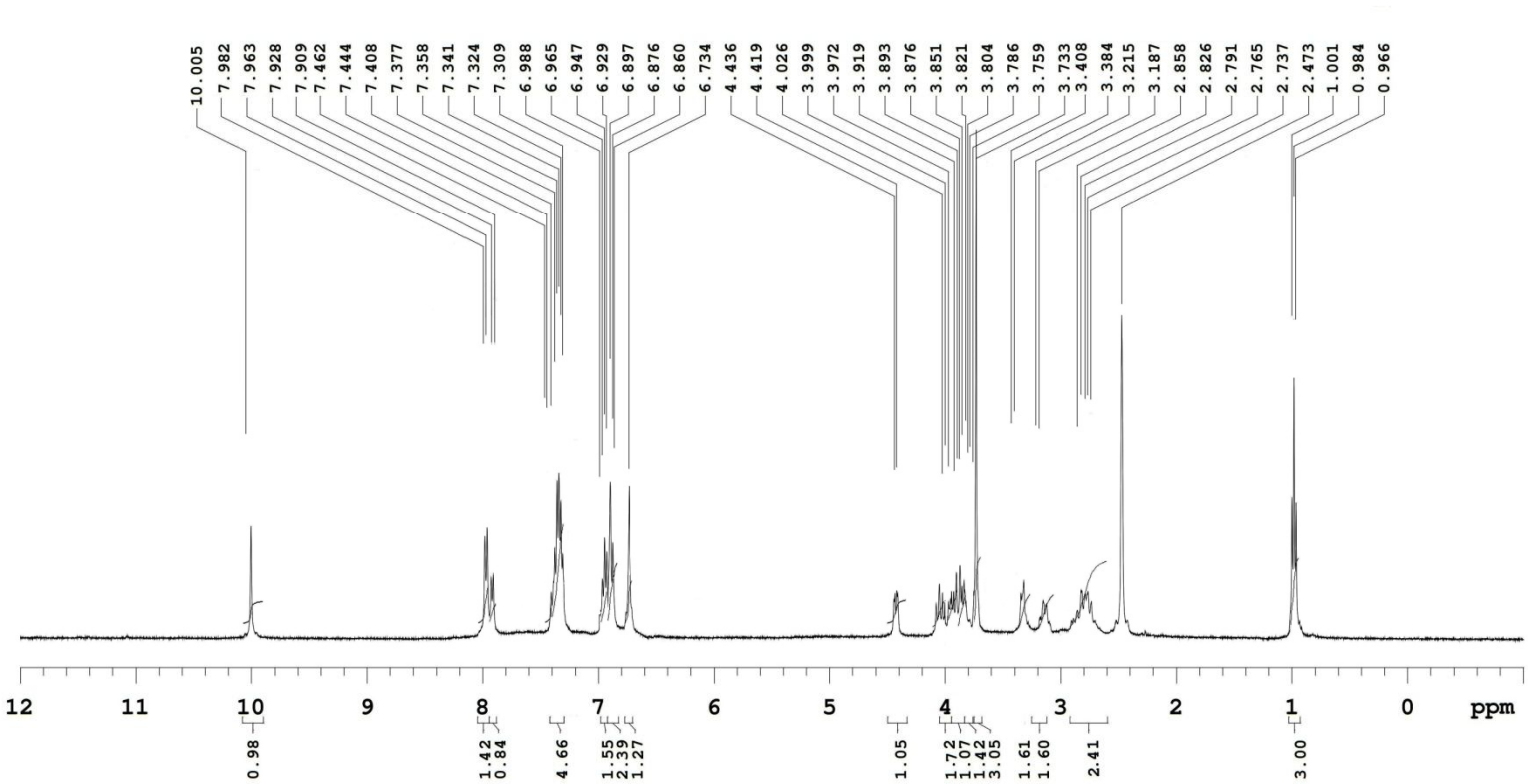
^{13}C NMR of **4j** in $CDCl_3$



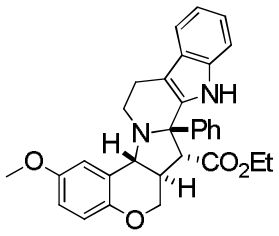


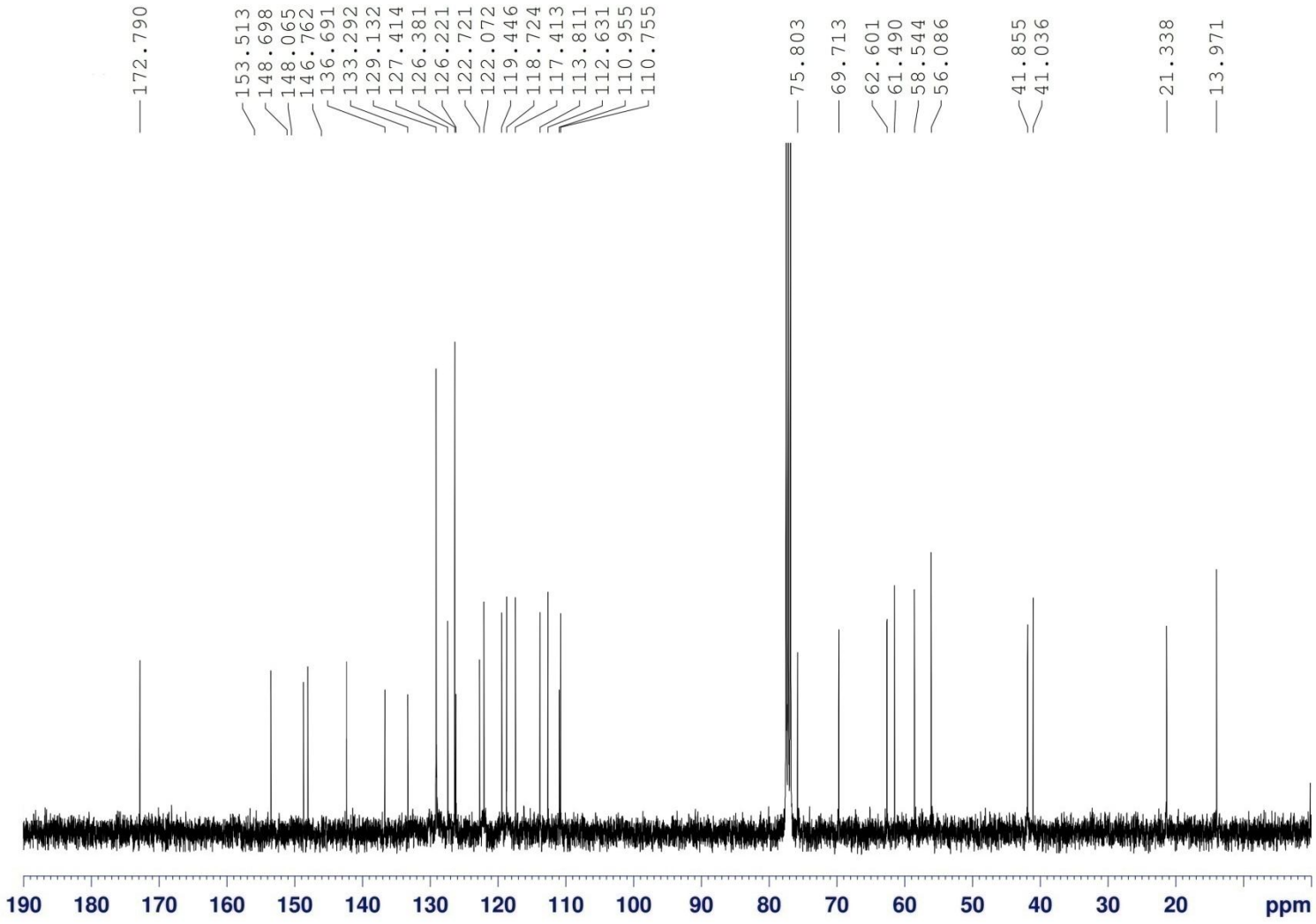
^{1}H NMR of **4k** in DMSO-d_6



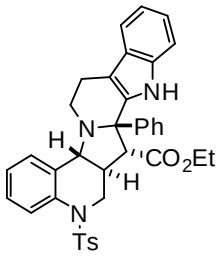


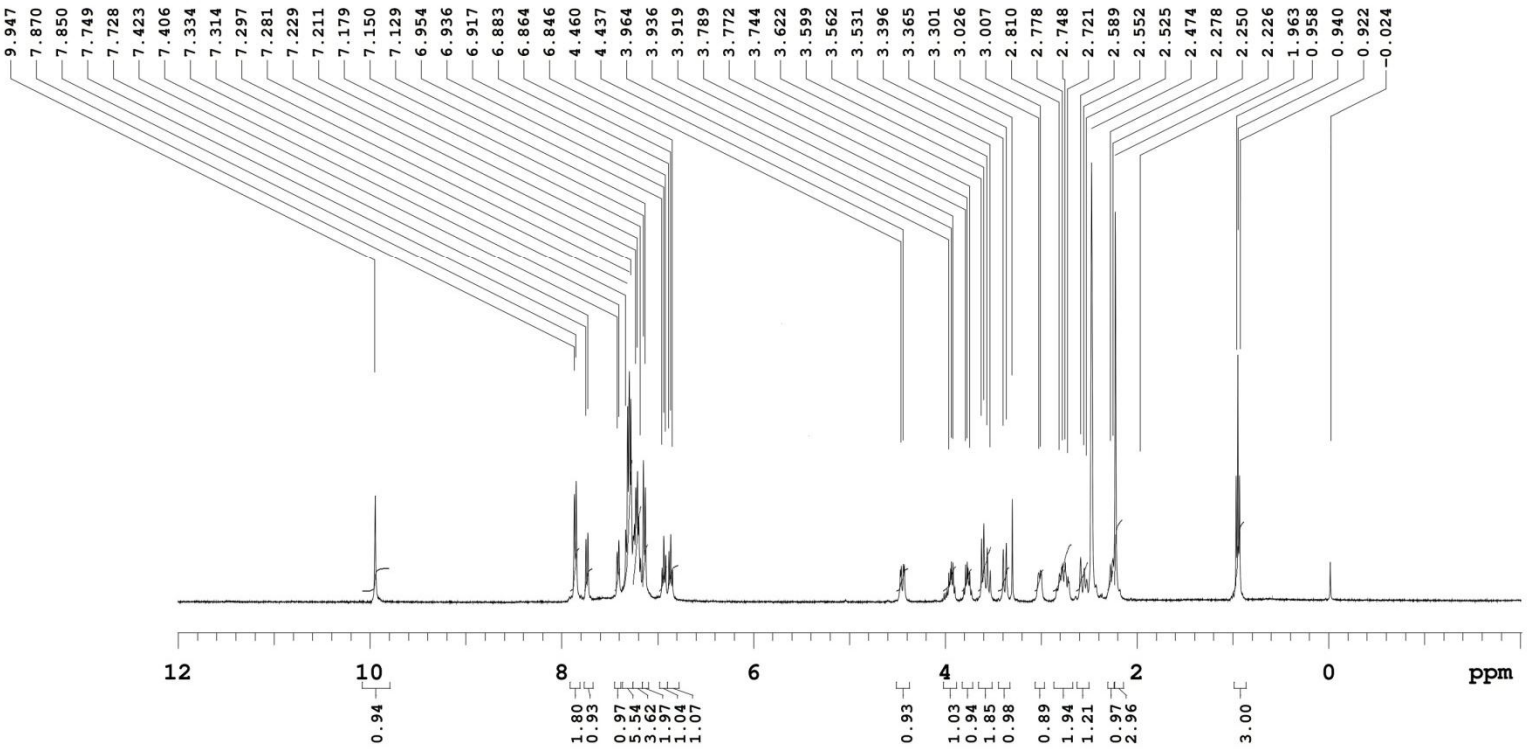
^{13}C NMR of **4k** in $CDCl_3$





^{1}H NMR of **4l** in DMSO-d_6





^{13}C NMR of **4l** in $CDCl_3$