A Facile Synthesis of Chiral β-substituted α-Amino Ester Analogue of Indenone via Addition Elimination Reaction

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Under the supervision of Professor Faiz Ahmed Khan.

A thesis submitted to Indian Institute of Technology Hyderabad for the partial requirement of Master of Science Degree in chemistry.

Department of chemistry

April 2016

Declaration

I declare that this written submission represents my ideas in my own words, and wherever others ideas or words have been included; I have adequately cited and given reference of the original sources. I also declare that I have adhered to all principles of academic honestly and integrity and have not misrepresented or fabricated any idea/date/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

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Approval sheet

This thesis entitled –A Facile Synthesis of Chiral β-substituted α-Amino ester Analogue of Indenone via Addition Elimination reaction by -Abdul Shiraj is approved for the degree of Master of Science in chemistry from IIT-Hyderabad.

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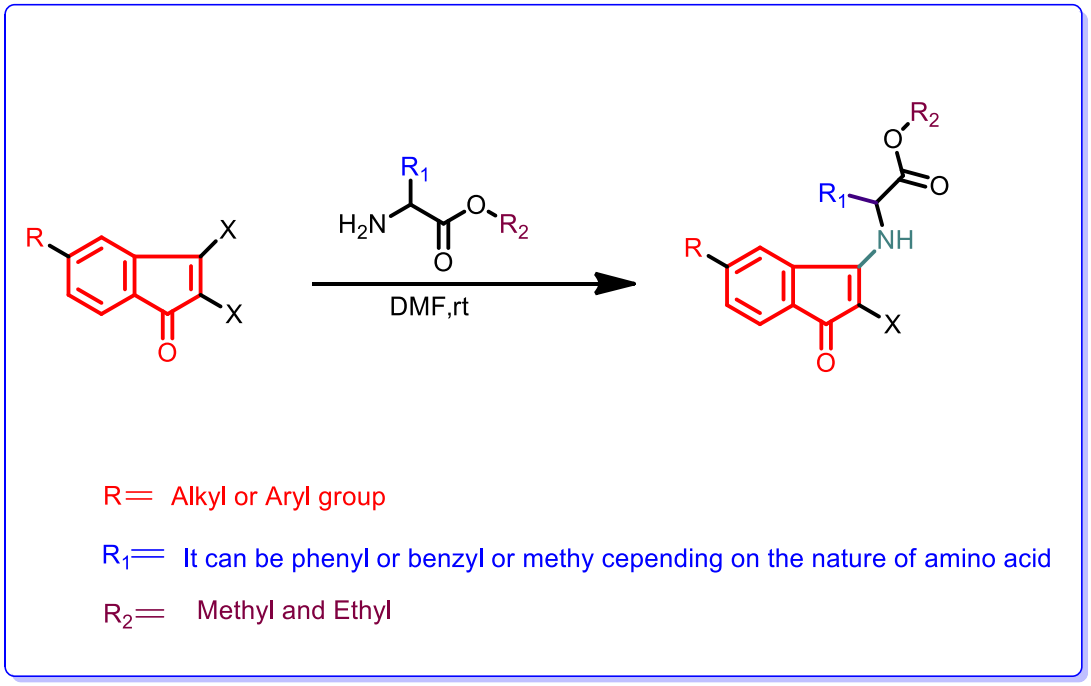
Dedicated to

My Parents

Contents

Abstract:

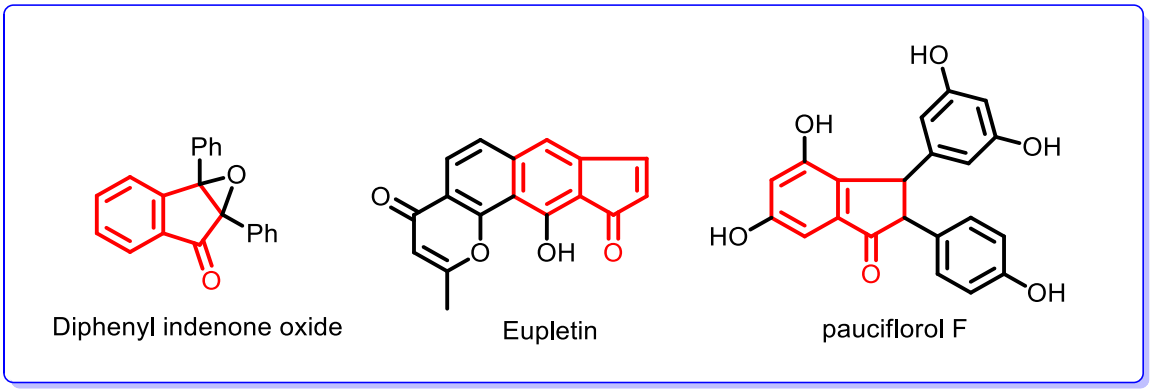
Indenone core is a very important pharmacophore in organic chemistry. α,β substituted chloro or bromo indenones easily undergo addition-elimination reaction with suitable nucleophile like α-amino esters and produce the corresponding chiral β substituted α-amino ester analogue of indenone in an impressive yield. The reaction can be performed in a mild condition without any catalyst, base or acid. Thus formation of C-N bond is possible in this type of reaction in a catalyst free mild condition.



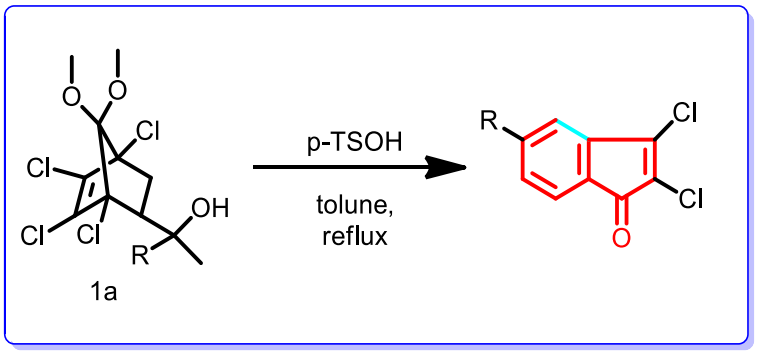
Introduction:

Synthesis of compounds using members of chiral pool is one of the most attractive area of research in chemistry. Among the members of chiral pool, amino acids and their derivatives and sugars were preferentially used for this purpose. Amino acids and their derivatives were generally used to induce chirality in compounds in organic synthesis. One way to use amino acid as a starting material or elaborate it to the target molecule.

Indenone core is an important pharmacophore, which is present in many natural products having substantial biological activity. Indenones can be used as intermediates in the total synthesis of natural products like C-nor-D-homosteroids, indanones and photochromic indenone oxides. In the medicinal chemistry indenone based drugs serve as estrogen binding receptors, precursors for gibberellins and fermentation activators.



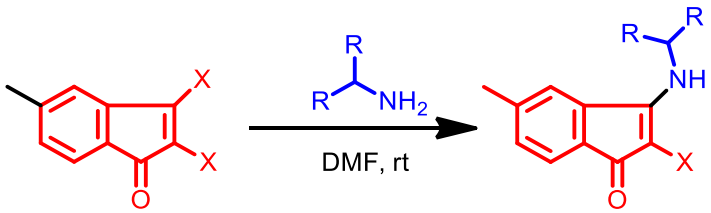
Reported synthesis of indenone from our group involves a domino reaction of tertiary alcohols 1a under acidic medium via cope rearrangement to deliver indenone in an impressive yield. Many other methods were also reported for synthesis indenone.

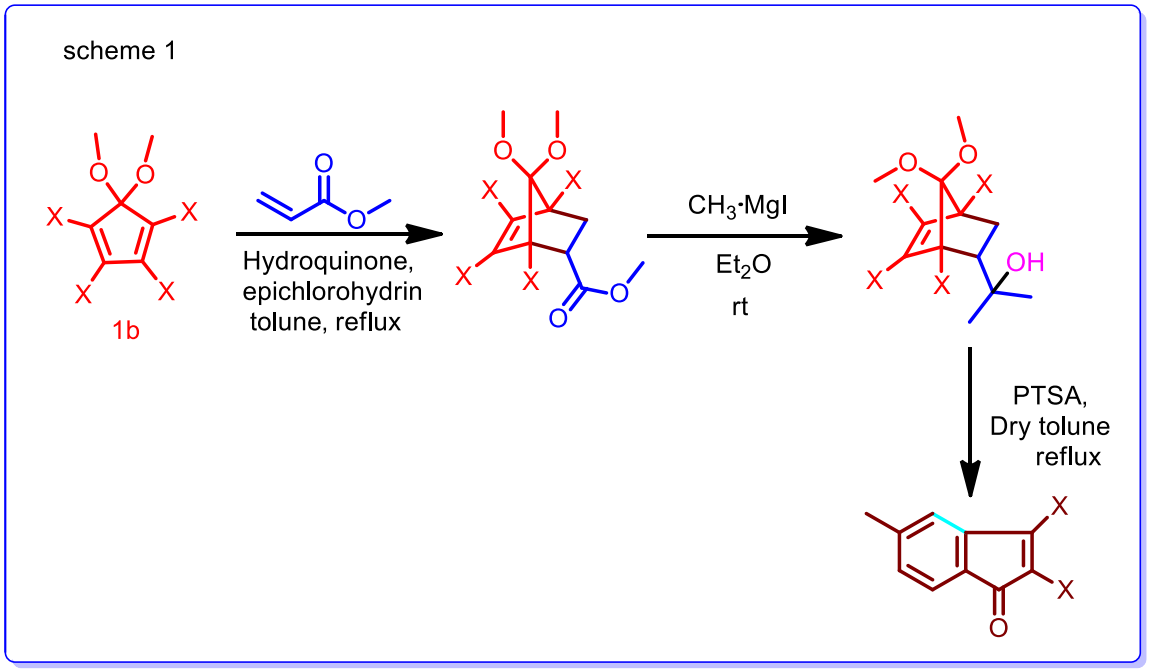


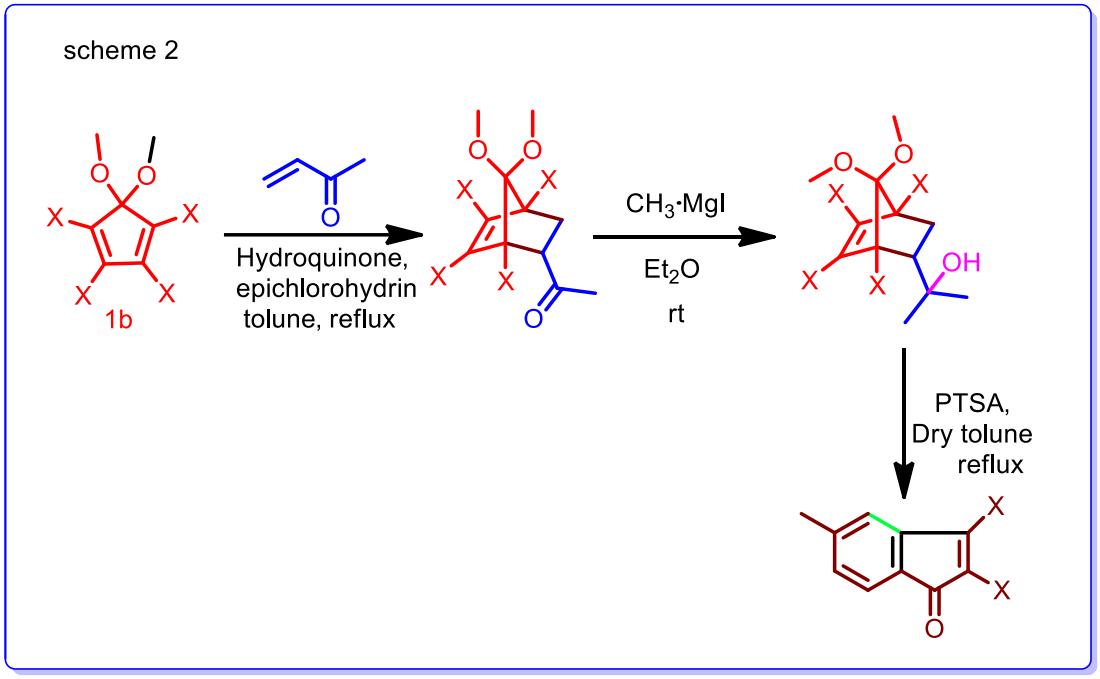
In such a background we thought of synthesizing some β-substituted α-amino ester analogue of various indenones via addition-elimination reaction between various indenones and α-Amino esters. Thus our main aim is to synthesize some β-substituted α-Amino ester analogue of indenone via addition-elimination reaction.

Previous work:

Previously our group reported the synthesis of indenone from bicyclic tertiary alcohol 1a via a domino reaction. The synthesis involves first Diels Alder reaction between tetra-halo dimethoxy compound 1b and methyl acrylate and then treatment of this adduct with excess Grignard reagent to produce tertiary alcohol. Treatment of this tertiary alcohol with TSOH in tolune reflux condition provides indenone in good yield. An alternative synthesis was reported in which the Diels-Alder adduct of methyl vinyl ketone and tetrahalo dimethoxy compound is treated with various Grignard reagent followed by PTSA reaction. Prepared indenone was obtained as a single regioisomer, the regioselectivity leading to a single indenone with excellent yield. The structure of the obtained adduct is supported by NMR, IR and HRMS. At the same time our group reported the addition-elimination reaction between indenone and amines (primary and secondery). Amine adducts were obtained in a good yield under this condition.



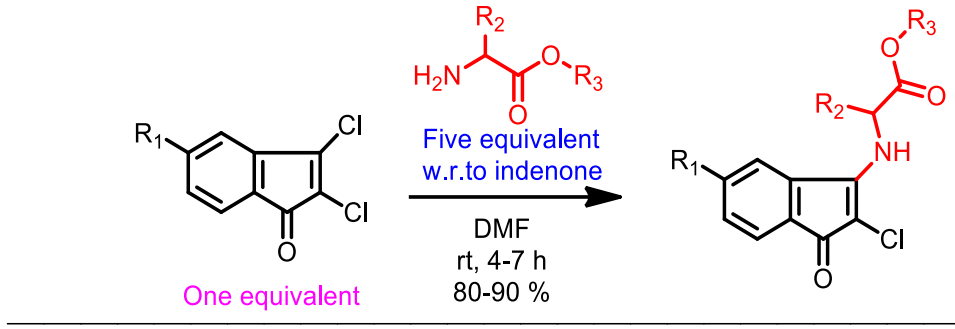


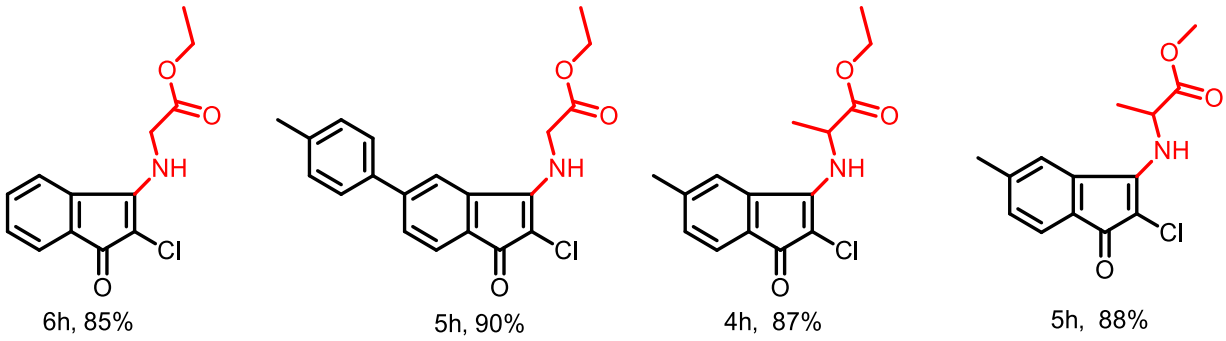


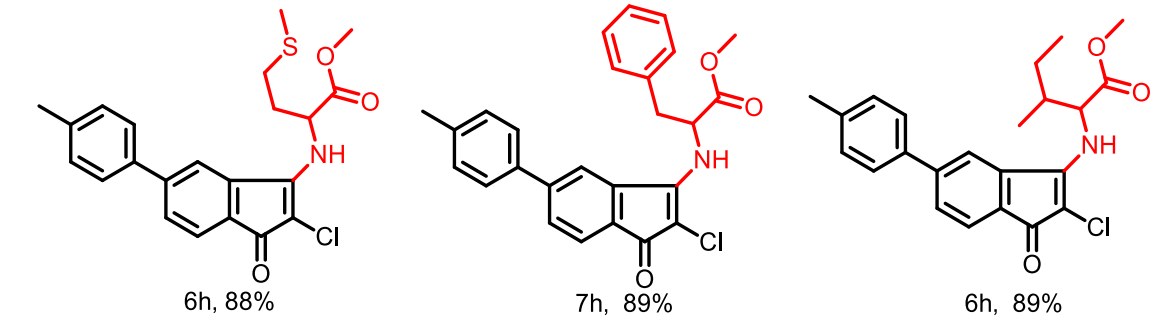
Result and Discussion:

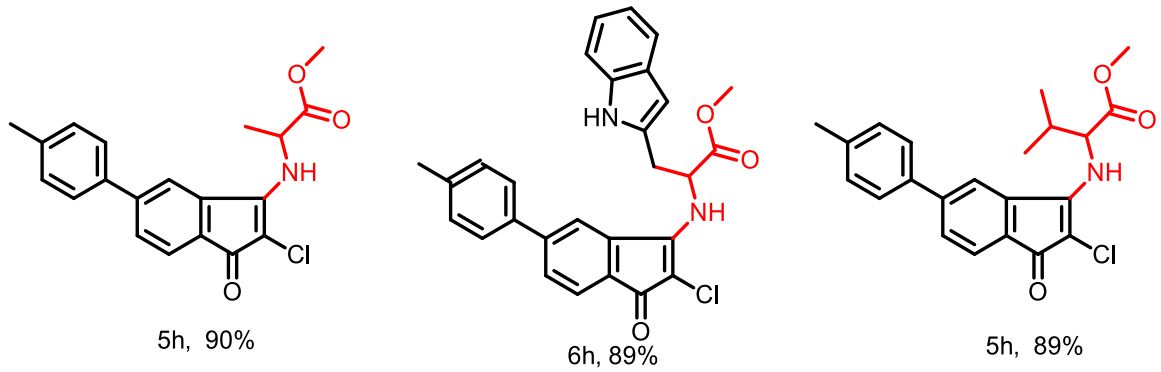
To synthesize the β-substituted α-amino ester derivatives of indenone, first we tried with α-amino acid like glycine and alanine but under room temperature and DMF solvent, the reaction did not work. We have tried other conditions also for amino acid reaction with but it did not work. After that we tried with α-amino esters and found that it works well under the prescribed conditions. But the main difficulty that we faced was the poor yield of the product. Firstly, we have tried with 1:1 equivalent condition, but at this condition the starting material was not fully consumed, then ahead forward and increased the equivalent of free amino acid esters. In the condition of 1:5 equivalent of indenone and free amino acid esters, the starting material was fully consumed and we got 90% yield of the required product. After that we changed the indenone and we used different 'R' group substituted indenone. Among all the indenones that we have used, the indenone having 'Tolyl' group at the fifth position of the indenone moiety works best with most of the α-Amino acid esters and gives impressive yield of the product. The indenones having methyl group at fifth position works best with some of the amino esters like alanine, glycine, tryptophan etc. Similarly, indenones without any substituents at fifth or forth position also react with α-amino esters. The indenone having tolyl group at fifth position always give single product in good yield. The yield of the product does not depend on the size of the 'R' group of the amino acid esters. On an average

it always gives 86% yield. The role of the excess α-amino esters is to some activate the indenone so that it reacts to give a good yield. The reaction scheme, compound synthesized is shown below.



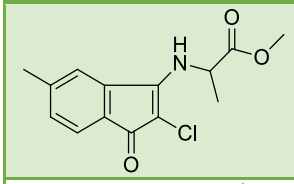
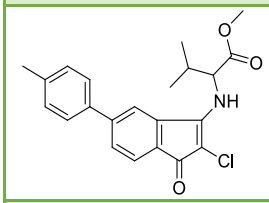
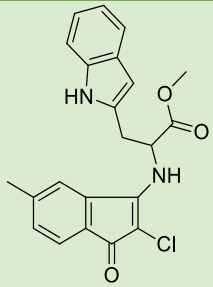
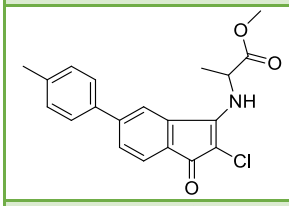
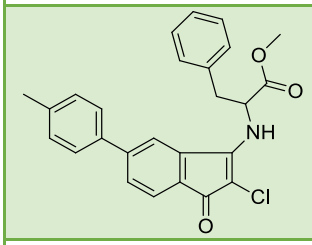
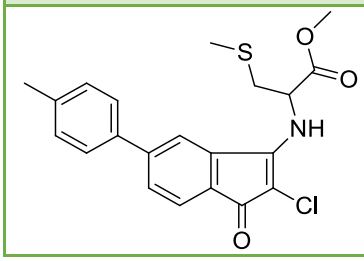


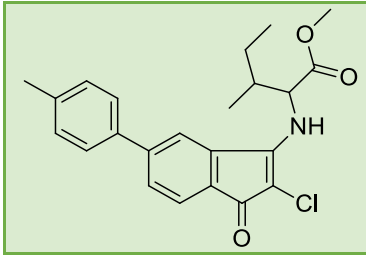




Percentage of yield indicates weight of compound after purified by column chromatography

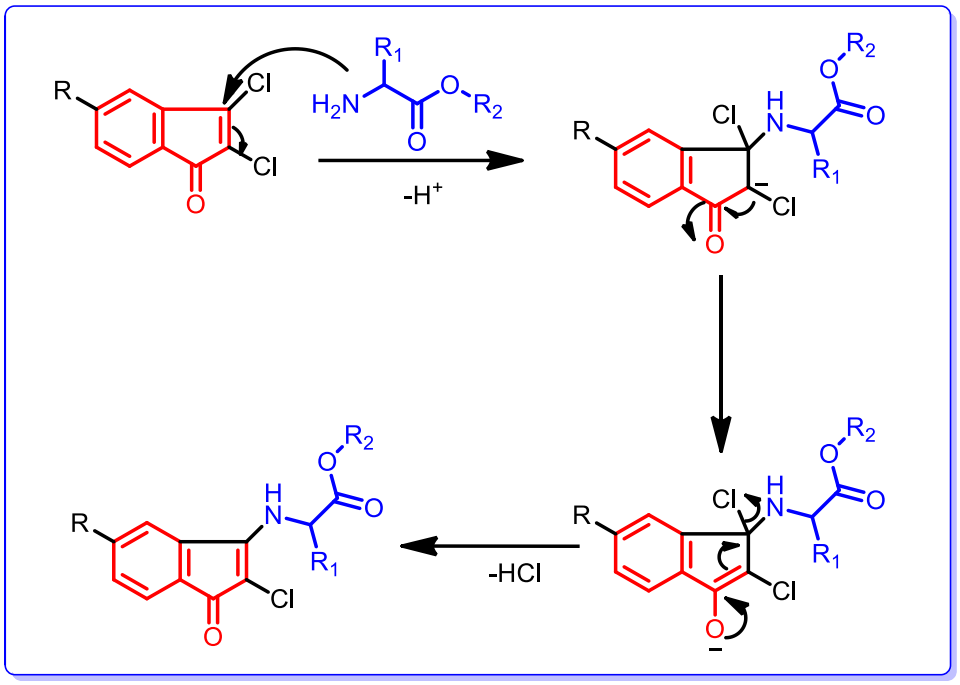
Among the synthesized molecules, seven compounds were optically active so we measured the optical rotation and specific rotation of the synthesized compounds. The optical rotation and specific rotation of the compounds are shown below

Compound Structure	**Temp. of the cell (in ^{0}C)**	**Optical Rotation (in degree)**	**Specific Rotation (in degree)**	**Concentration in g/100 cm^3**
	19.88	-0.0022	-1.557	0.14
	19.95	0.0012	2.900	0.04
	20.00	-0.0609	-50.749	0.12
	19.83	-0.0049	-8.233	0.06
	20.00	-0.537	-895.058	0.06
	20.01	-0.0960	-119.999	0.08

	20.00	-0.0331	-41.350	0.08

Cell-length and wavelength of the light employed is same for all measurement.

Plausible reaction mechanism:



R=Alkyl or Aryl group

Conclusion:

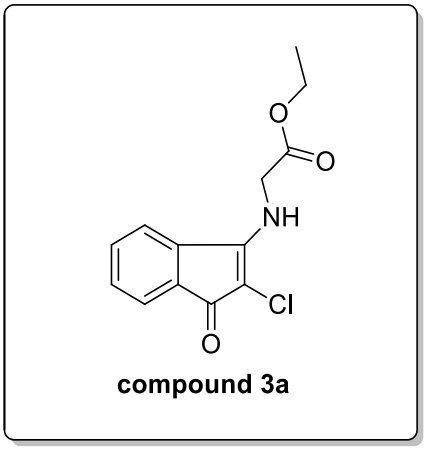
In conclusion, this methodology allows a preferential synthesis of chiral β substituted α-amino acid esters derivatives of indenone derivatives via addition-elimination reaction to give an impressive yield under ambient conditions. Tolyl substituted indenone at the 5-position gives the best yield of the product.

Experimental section:

In this section the procedure for the preparation of all the compounds has been discussed. The required chemicals were purchased from standard commercial sources and some of the starting materials were prepared in the laboratory. All the glass wares were cleaned with soap water followed by washing with acetone and then dried in the hot air oven at 140^0 C for 2 hours. Solvents were distilled and dried using the standard procedures available. For evaporation of solvent Buchi rotary evaporator machine was used. NMR data was collected using bruker 400 MHZ machine, and IR data was collected using broker machine.

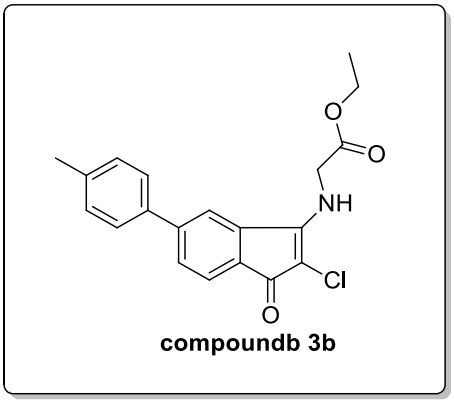
General procedure for preparation of β substituted α-amino ester derivative of indenone: One equivalent of indenone was dissolved in dry DMF and to that α-amino esters added drop wise and the reaction mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), water was added to the reaction mixture and organic phase was extracted using ethyl acetate. The process of extraction was repeated four times. The combined organic layer was dried over sodium sulphate (Na_2SO_4). After removing the solvent under reduced pressure, the crude was purified by column chromatography.

General procedure for synthesis of α-amino esters: To an ice cold solution of amino acid (one equivalent) in methanol or ethanol three equivalent of thionyl chloride was added slowly over a period of 30 minutes. Then the solution was allowed to stir at ice cold solution for 30 minutes. After that, the reaction mixture was refluxed for 4 hours and then the solvent was removed under reduced pressure and the residue was treated with aqueous sodium carbonate and the compound was extracted by washing with ethyl acetate. The combined organic layer was dried over sodium sulphate and after removing ethyl acetate under reduced pressure pure α-amino esters was obtained.



compound 3a

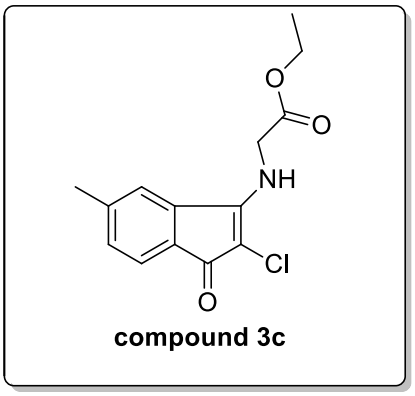
Compound 3a-Red Crystalline solid, Melting point 157^0C, Yield 85%, ^{1}HNMR (400 MHZ, DMSO-D_6) δ 8.79(s, 1H), 7.65(d, 1H), 7.47(t, 1H), 7.41-7.32(m, 2H) 4.56(d, 2H), 4.19(q, 2H), 1.22(t, 3H); ^{13}CNMR(100MHZ , DMSO-D_6) δ 14.06, 44.63, 61.14, 118.25, 119.89, 130.23,131.48,169.26; IR (Neat) 3314, 3020, 2950,1757, 1684, 1618, 1532, 1314, 1210, 899, 815, 746, 667,633 cm^{-1}, HRMS(ESI) m/z Calculated For $C_{13}H_{12}ClNO_3$ 266.0578, $(M+H)^+$ 266.0597



compoundb 3b

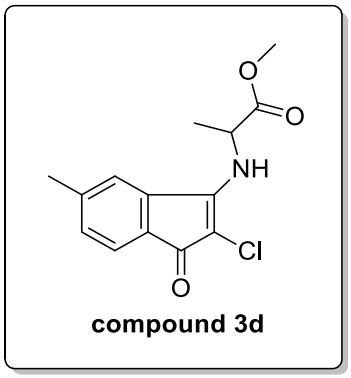
Compound 3b-Red crystalline solid, Melting point 180^0 C, Yield 90%, ^{1}HNMR (400 MHZ, DMSO-D_6) δ 8.87(s, 1H), 8.06(s, 1H), 7.64(m, 3H), 7.38(d, 1H),

7.32(d, 2H), 4.54(d, 2H), 4.2(q, 2H), 2.36(s, 3H), 1.23(t, 3H); ^{13}CNMR (100MHZ , DMSO-D_6) δ 14.02, 20.68, 44.68, 61.08, 94.36, 117.00, 120.35, 126.43, 127.56, 129.63, 130.63, 136.12, 137.83, 138.17, 143.31, 156.20, 169.36, 185.10; IR(Neat) 3300, 3010, 2950, 1750, 1680, 1600, 1312, 1211, 1023, 840, 753,667 cm^{-1},HRMS(ESI) m/z Calculated for $C_{20}H_{18}ClNO_3$ 356.1048, $(M+H)^+$ 356.1061.



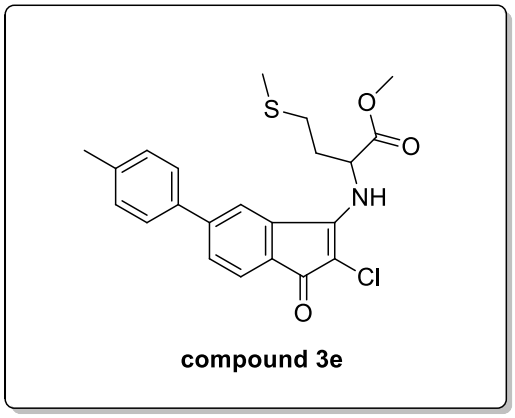
compound 3c

Compound 3c-Red crystalline solid, Melting point 175^0 C, Yield 87%, ^{1}HNMR (400 MHZ,DMSO-D_6) δ 8.73(s, 1H), 7.52(s, 1H), 7.27(m, 2H), 4.57(d, 2H), 4.24(q, 2H), 2.41(s, 3H), 1.26(t,3H); ^{13}CNMR(100MHZ , DMSO-D_6) δ 14.02, 21.47, 44.65, 61.06, 93.79, 119.56, 119.88, 129.48, 129.96, 137.59, 141.78, 156.33, 169.37, 185.40; IR(Neat) 3300, 3010, 2955, 1730, 1670, 1559, 1532, 1414, 1353, 1210, 1153, 1098, 1023, 899, 815, 746, 665 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{14}H_{14}ClNO_3$ 280.0735, $(M+H)^+$ 280.0742.



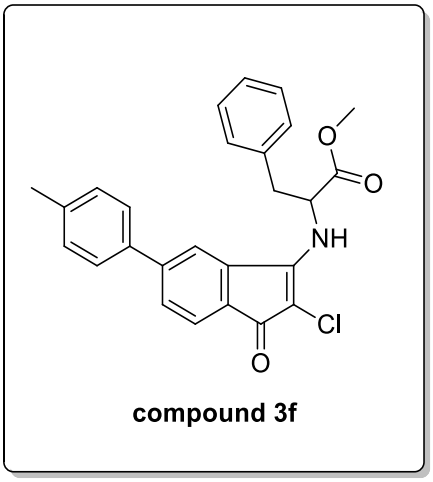
compound 3d

Compound 3d-Red crystalline solid, Melting point 151^{0}C,Yield 88%,^{1}HNMR (400 MHZ,DMSO-D_6) δ 8.29(s, 1H), 7.69(m, 1H), 7.20(m, 2H), 5.16(q, 1H) 3.71(s, 3H), 2.36(s, 3H), 1.55(d, 3H); ^{13}CNMR(100MHZ , DMSO-D_6) δ 10.75, 17.76, 21.43, 28.98, 51.52, 51.62, 52.54, 119.83, 120.13, 129.41, 129.87, 137.63, 141.63, 141.78, 172.19, 172.35; IR(Neat) 3300, 3020, 2945, 1715, 1685, 1618, 1573, 1532, 1441, 1353, 1210, 1098, 1023, 899, 815, 746, 667, 633 cm^{-1} , HRMS(ESI) m/z Calculated for $C_{14}H_{14}ClNO_3$ 280.0735, $(M+H)^+$ 280.0736.



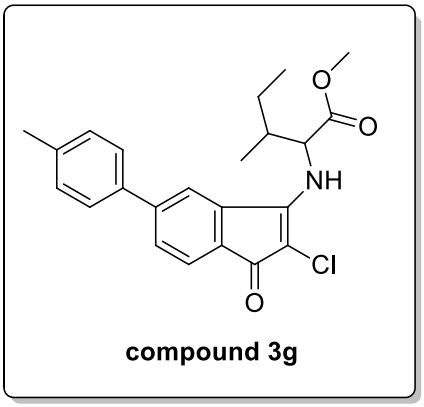
compound 3e

Compound 3e-Red crystalline solid, Yield 88%,^{1}HNMR(400 MHZ,DMSO-D_6) δ 8.39(d, 1H), 8.21(s, 1H), 7.66(t, 3H), 7.39(d, 1H), 7.33(d, 2H), 5.35(t, 1H) 3.75(s, 3H), 2.70(m, 2H), 2.37(s, 3H), 2.23(q, 2H), 2.09(s, 3H); ^{13}CNMR (100 MHZ,DMSO-D_6) δ 14.44, 20.70, 29.65, 30.74, 52.71, 54.73, 94.47, 119.51, 120.40, 126.53, 127.55, 129.58, 130.33, 136.13, 137.85, 138.23, 143.46, 155.77, 171.77, 185.28; IR(Neat) 3314, 3010, 2990, 2950, 2900, 1755, 1685, 1532, 1414, 1353, 1314, 1210, 1098, 899, 746, 633 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{22}H_{22}ClNO_3$ 416.1082, $(M+H)^+$ 416.1084.



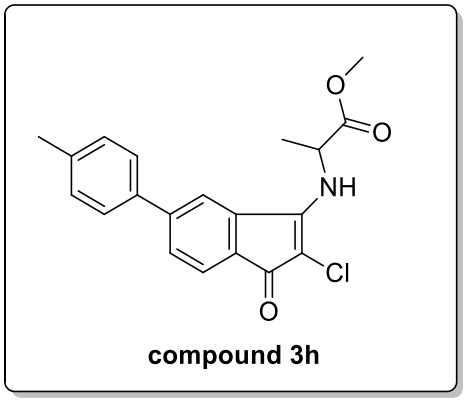
compound 3f

Compound 3f-Red crystalline solid, Melting point 100^0C, Yield 89%, ^{1}HNMR (400 MHZ,DMSO-D_6) δ 8.57(d, 1H), 8.18(s, 1H), 7.63(d, 3H), 7.33(m, 5H), 7.28(t, 2H), 7.19(t, 2H), 5.45(d, 1H), 3.75(s, 3H), 3.34(d, 1H), 3.23(t, 3H), 2.37(s, 3H);); ^{13}CNMR(100MHZ , DMSO-D_6) δ 20.70, 37.30, 51.30, 52.65, 55.68, 57.36, 94.16, 117.26,120.38, 126.24, 126.49, 126.77, 127.52, 128.08, 128.39, 129.05, 129.16, 129.61, 130.24, 136.10, 136.80, 137.88, 138.16, 143.41, 155.28, 171.20, 175.28, 185.14; IR(Neat) 3300, 3030, 2900, 1735, 1685, 1618, 1569, 1532, 1414, 1353, 1263, 1210, 1098, 1023, 858, 746 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{26}H_{22}ClNO_3$ 432.1361, $(M+H)^+$ 432.1356.



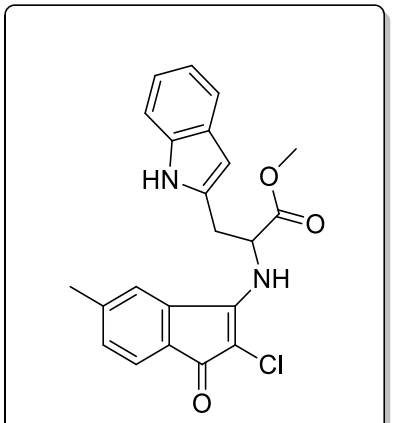
compound 3g

Compound 3g-Red crystalline solid, Melting point 170^0C,Yield 89%,^{1}HNMR (400 MHZ,DMSO-D_6) δ 8.36(s, 1H), 8.32(s, 1H), 7.75(q, 3H), 7.35(dd, 3H), 5.09(t, 1H), 3.79(s,3H), 2.39(s, 3H), 2.15(m, 1H), 1.6(m, 1H), 1.4(m, 1H), 1.0(d, 3H),0.83(t, 3H);^{13}CNMR (100 MHZ, DMSO-D_6) δ 10.58, 15.03, 20.70, 25.06, 25.26, 52.30,60.16, 62.54, 62.39, 94.08, 117.74, 120.35, 126.56, 127.49, 129.55, 130.31, 136.10, 137.84,138.19, 143.44, 155.39, 171.30, 174.59, 185.27; IR(Neat) 3300, 2900, 2195, 1720, 1685, 1565, 1532, 1414, 1353, 1210, 1153, 1098, 1028, 899, 852, 815, 746 cm^{-1} ,HRMS(ESI) m/z Calculated for $C_{23}H_{24}ClNO_3$ 398.1517, $(M+H)^+$ 398.1526.



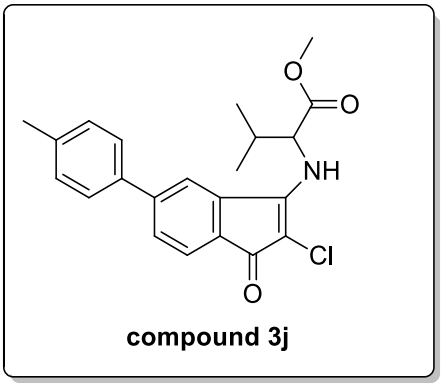
compound 3h

Compound 3h-Red crystalline solid, Melting point 181^0C,Yield 90%,^{1}HNMR (400 MHZ,DMSO-D_6) δ 8.45(d, 1H), 8.21(s, 1H), 7.65(t, 3H), 7.34(dd, 3H), 5.21(t, 1H), 3.73(s, 3H), 2.36(s, 3H), 1.59(d, 3H); ^{13}CNMR (100 MHZ, DMSO-D_6) δ 17.96, 20.70, 51.70, 52.61, 94.43, 117.44, 120.34, 126.48, 127.47, 129.58, 130.47, 136.09, 137.84, 138.20, 143.31, 155.33, 172.36, 185.19;IR(Neat) 3300, 1735, 1685, 1600, 1569,1562,1532, 1510, 1414, 1314, 1263, 1023, 899, 852, 815, 746 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{20}H_{18}ClNO_3$ 356.1048, $(M+H)^+$ 356.1063 $(M+Na)^+$ 378.0885.



compound 3i

Compound 3i- Red crystalline solid, Yield 89%, ^{1}HNMR(400 MHZ, DMSO-D_6) δ 10.89(s, 1H), 8.34(s, 1H), 7.60(t, 3H), 7.33(d, 1H), 7.24(s, 1H), 7.13(m, 2H), 7.05(t, 1H), 7.02(s, 1H), 5.75(s, 2H), 3.74(d, 3H), 2.88(s, 2H), 2.73(s, 3H), 2.5(t, 1H); ^{13}CNMR (100 MHZ, DMSO-D_6) δ 21.45, 27.49, 27.58, 30.73, 35.74, 52.62, 52.66, 54.88, 56.80, 109.23, 111.56, 117.85, 118.56, 119.86, 121.11, 123.88, 126.79, 129.87,136.09,141.60, 141.76, 162.26, 171.52, 171.64; IR(Neat) 3300, 2998,1715, 1684, 1600,1590,1588,1572, 1560, 1550, 1540, 1414,1153,1263, 1023, 1098, 899, 852, 745 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{22}H_{19}ClN_2O_3$ 395.1157, $(M+H)^+$ 395.1162.



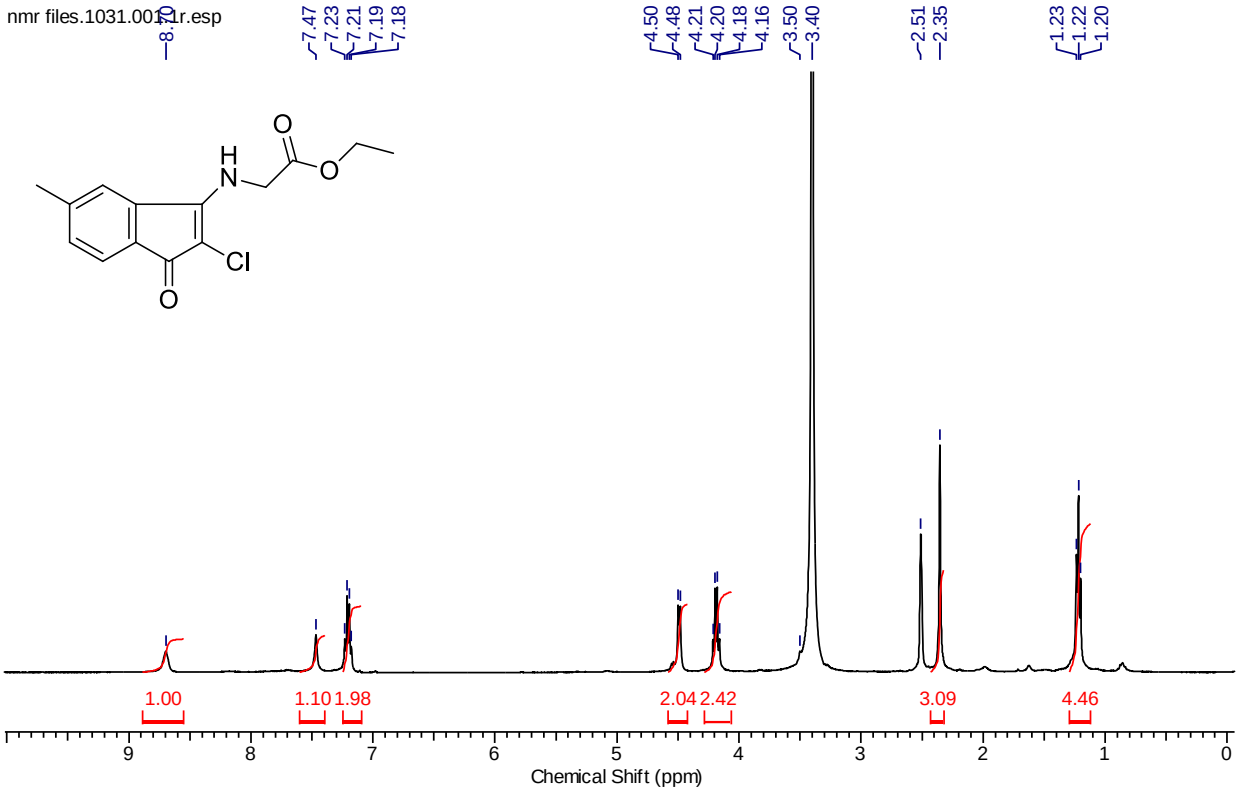
compound 3j

Compound 3j- Red crystalline solid, Yield 89%, ^{1}HNMR(400 MHZ, DMSO-D_6) δ 8.38(s, 1H), 8.34(s, 1H), 7.67(d, 3H), 7.35(dd, 3H), 5.03(t, 1H), 3.75(s, 3H), 2.34(s, 3H), 1.22(m, 1H), 1.00(dd, 6H); ^{13}CNMR (100 MHZ, DMSO-D_6) δ 16.10, 17.82, 18.18, 18.30, 18.68, 18.97, 20.70, 26.62, 30.04, 30.72, 30.90, 35.74, 51.94, 52.31, 54.87, 61.45, 64, 94.09, 117.17, 120.33, 126.56, 127.47,129.54, 130.33, 136.10, 137.83, 138.20, 143.42,155.53, 162.26, 171.21, 171.14, 185.29; IR(Neat) 3300, 2990, 3010, 1725, 1685, 1600,1580, 1560, 1540,1520, 1414, 1353, 1263, 1210, 1098, 1023, 899, 852, 815, 746, 667, 667 cm^{-1}, HRMS(ESI) m/z Calculated for $C_{22}H_{22}ClNO_3$ 366.1361, $(M+H)^+$ 384.1358.

Spectral data

^{1}HNMR (400 MHZ), ^{13}CNMR (100 MHZ) in DMSO-D_6

Compound 3a-3j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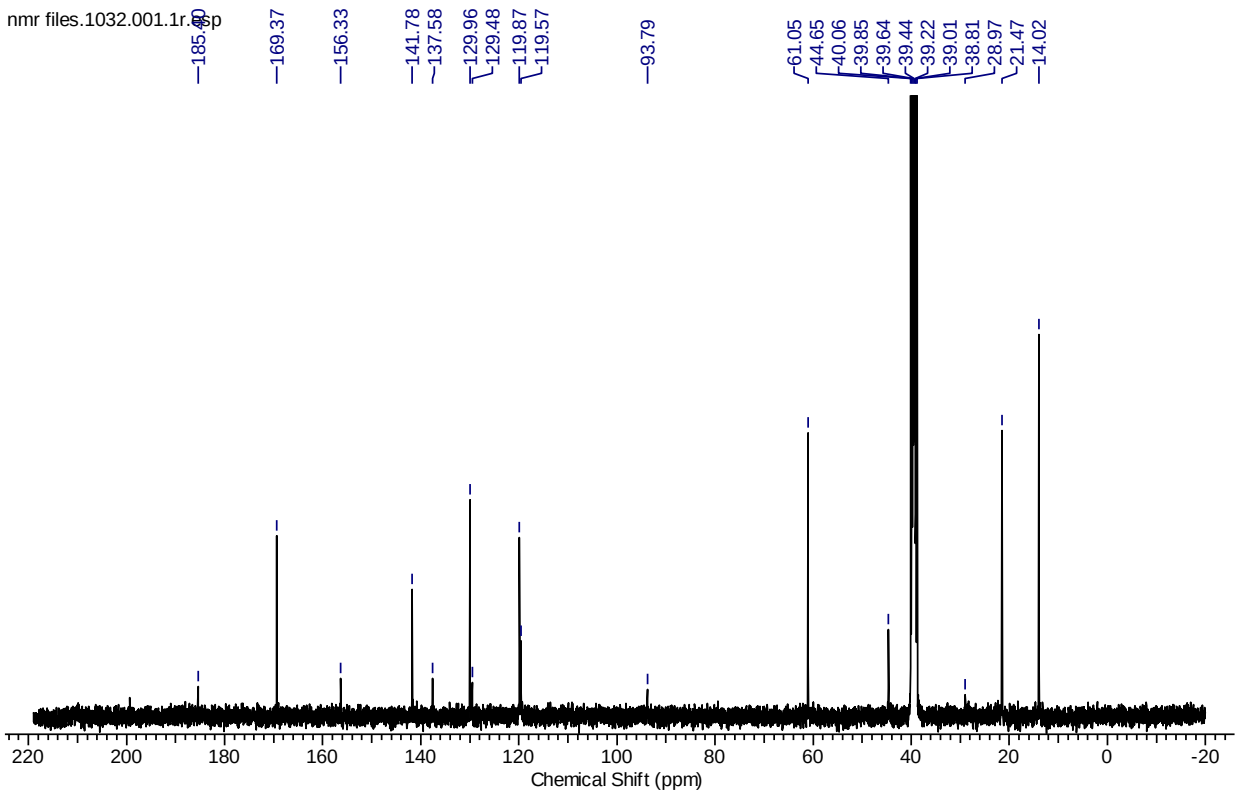
4.16
3.50
3.40
2.51
2.35
1.23
1.22
1.20
H
N
O
O
O
Cl
1.00
1.10
1.98
2.04
2.42
3.09
4.46
Chemical Shift (ppm)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40.06
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39.64
39.44
39.22
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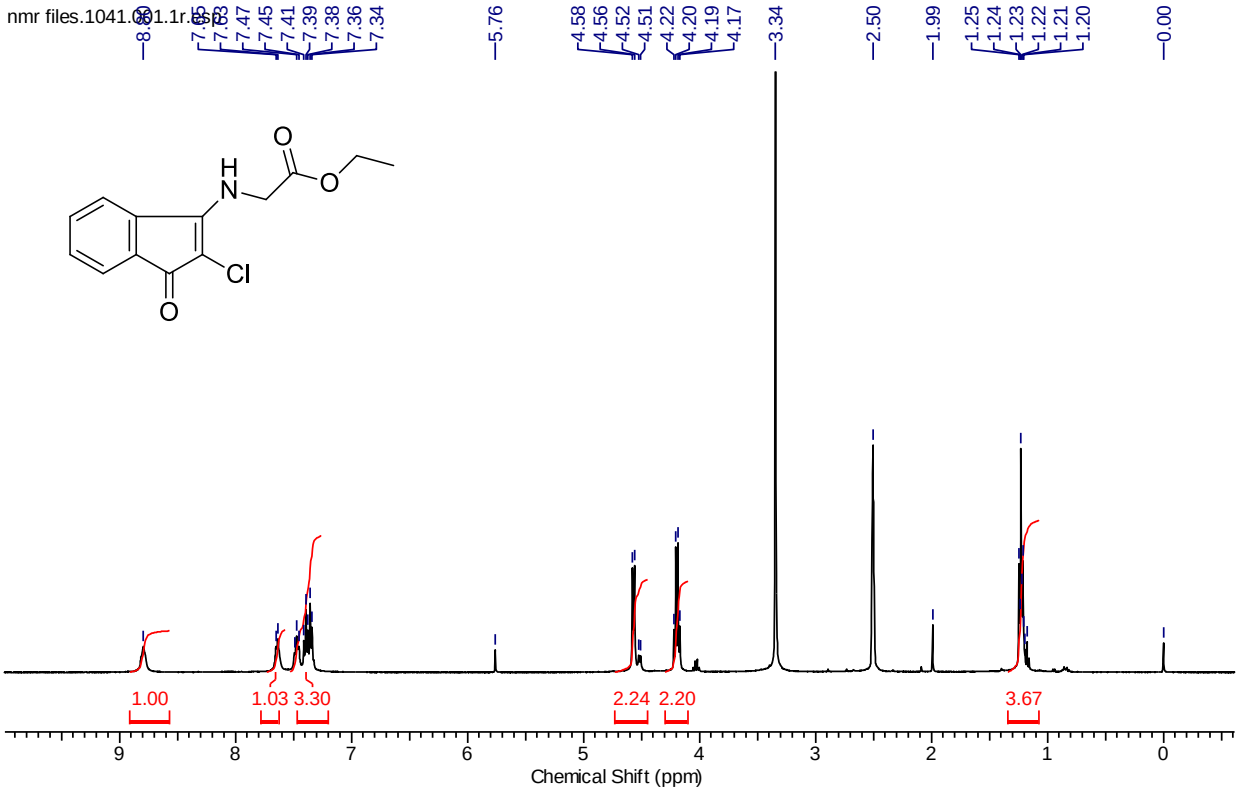
38.81
28.97
21.47
14.02
Chemical Shift (ppm)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4.52
4.51
4.22
4.20
4.19
4.17
3.34
2.50
1.99
1.25
1.24
1.23
1.22
1.21
1.20
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O
H
N
O
O
Cl
O
1.00
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7
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5
4
3
2
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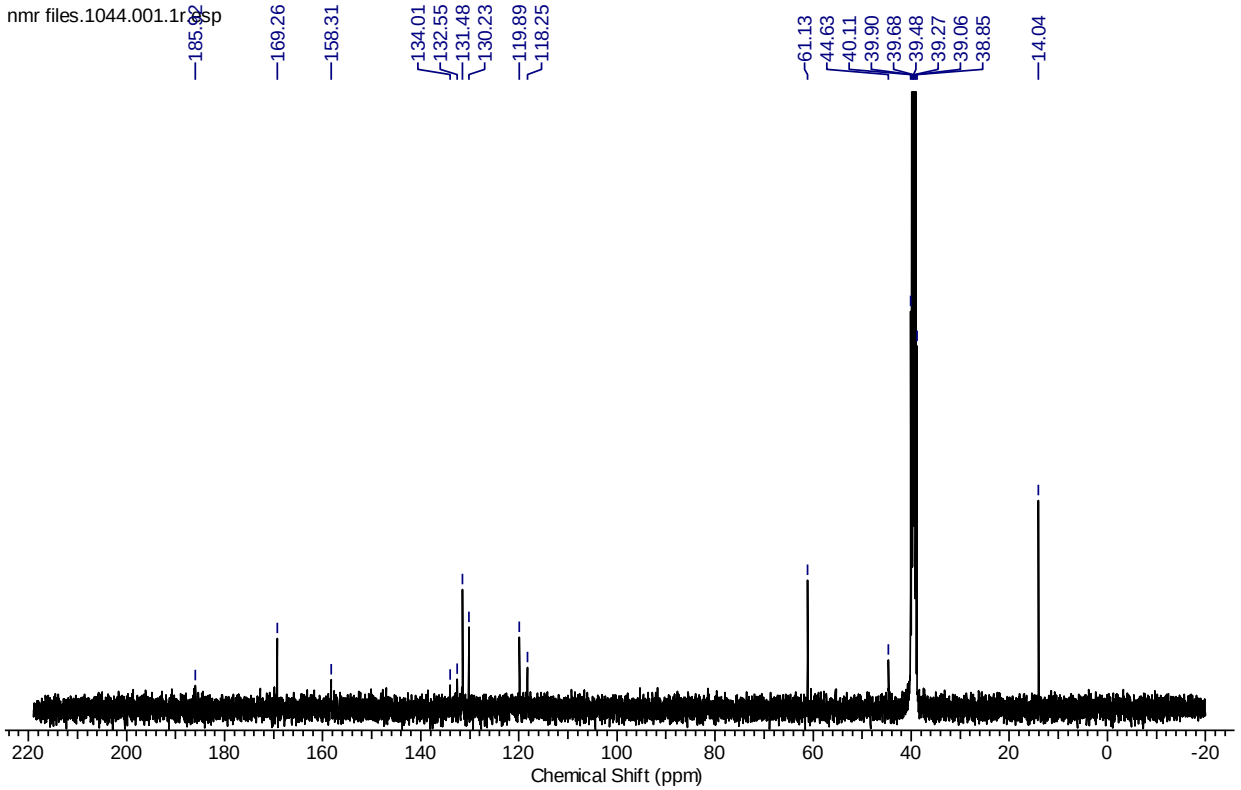
Chemical Shift (ppm)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40.11
39.90
39.68
39.48
39.27
39.06
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140
120
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60
40
20
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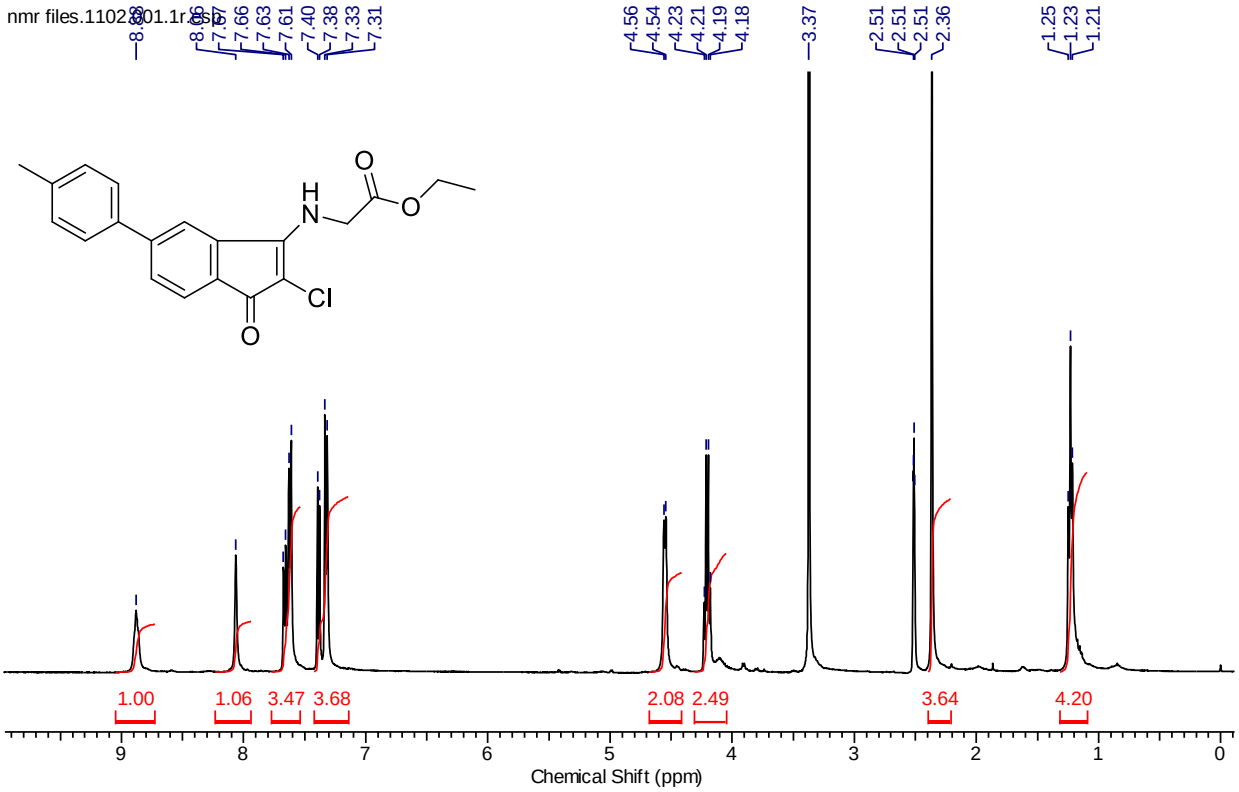
-20
Chemical Shift (ppm)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4.19
4.18
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2.51
2.51
2.36
1.25
1.23
1.21
O
H
N
O
Cl
O
1.00
1.06
3.47
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8
7
6
5
4
3
2
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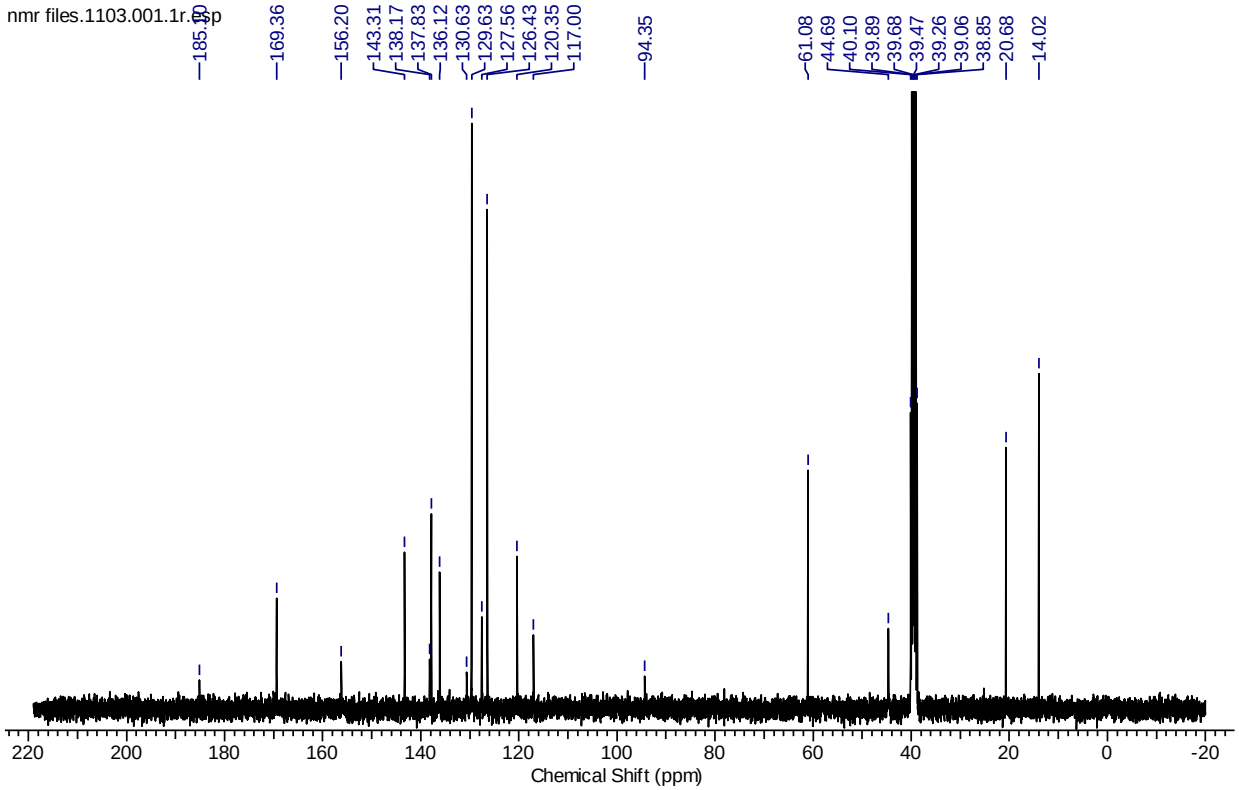
Chemical Shift (ppm)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117.00
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44.69
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39.89
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39.47
39.26
39.06
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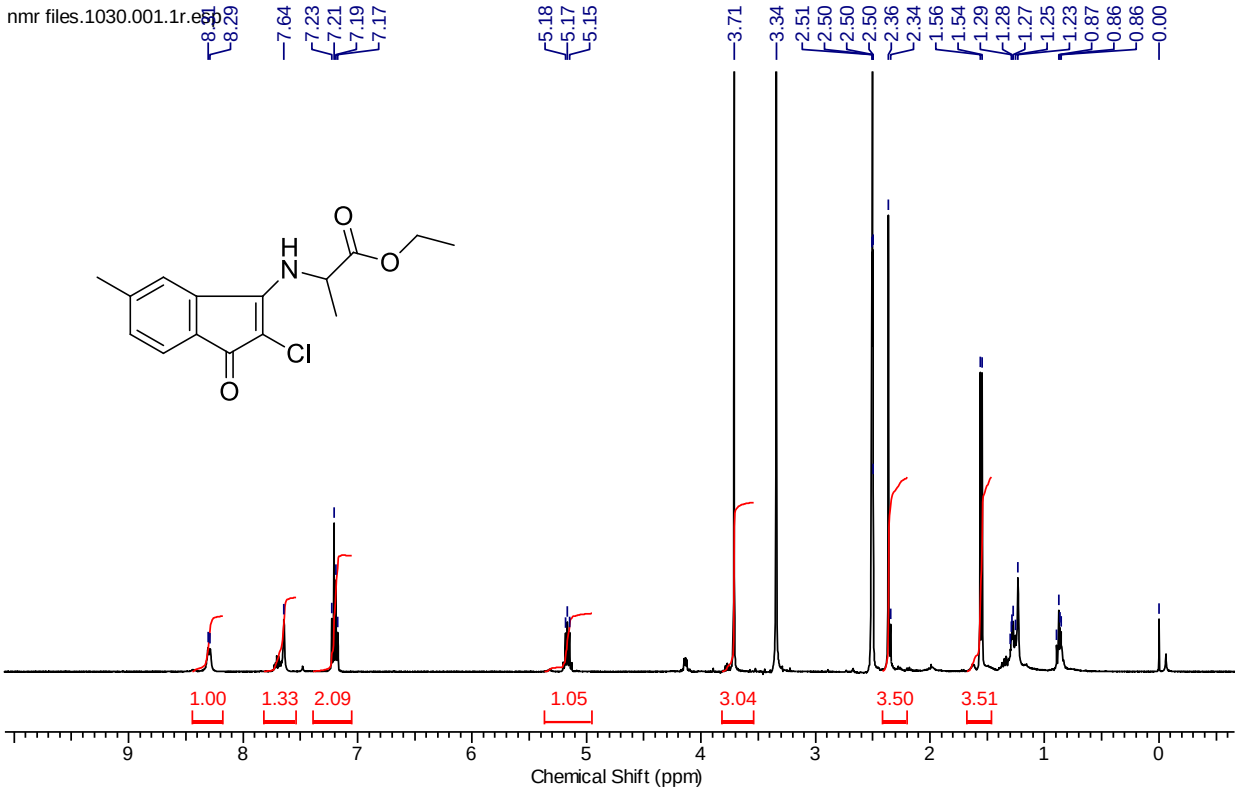
Chemical Shift (ppm)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2.50
2.50
2.50
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1.28
1.27
1.25
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0.86
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O
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Cl
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3.51
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7
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5
4
3
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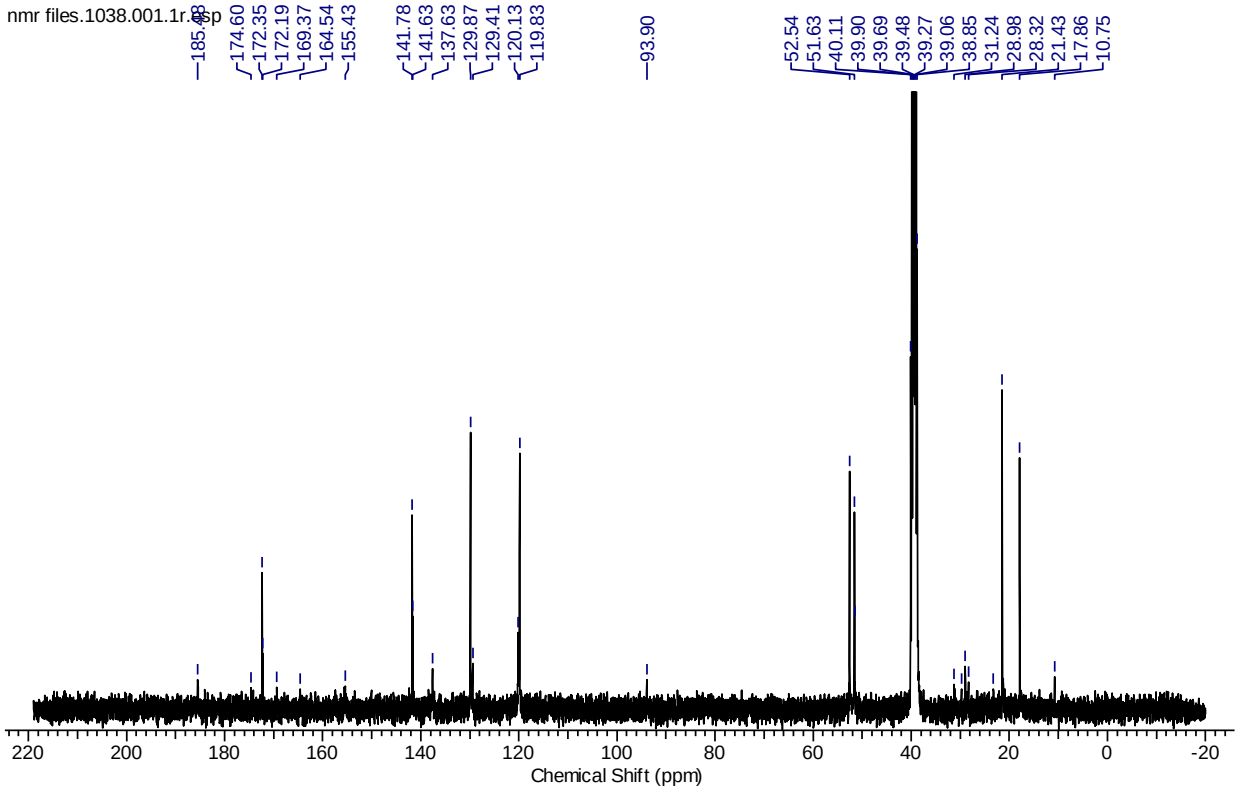
Chemical Shift (ppm)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93.90
52.54
51.63
40.11
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39.48
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28.98
28.32
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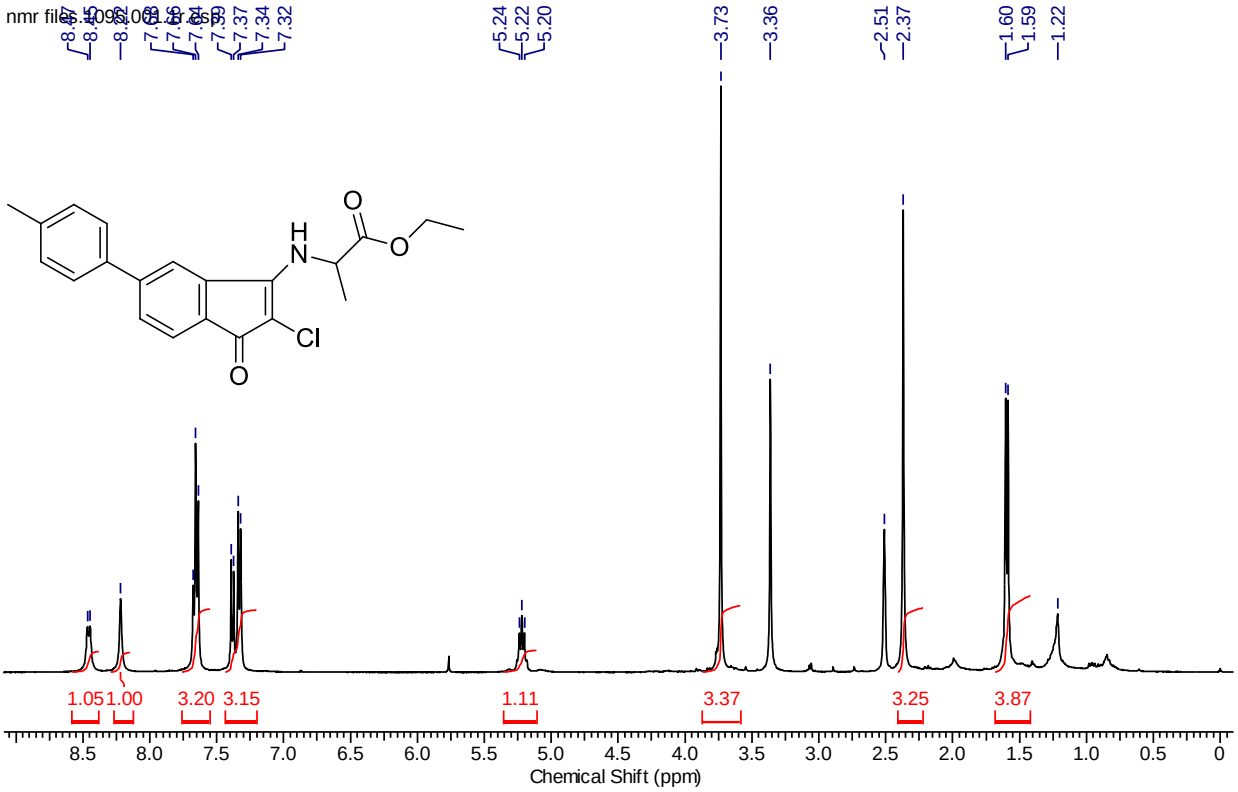
Chemical Shift (ppm)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2.37
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1.59
1.22
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H
N
O
Cl
O
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3.37
3.25
3.87
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7.0
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6.0
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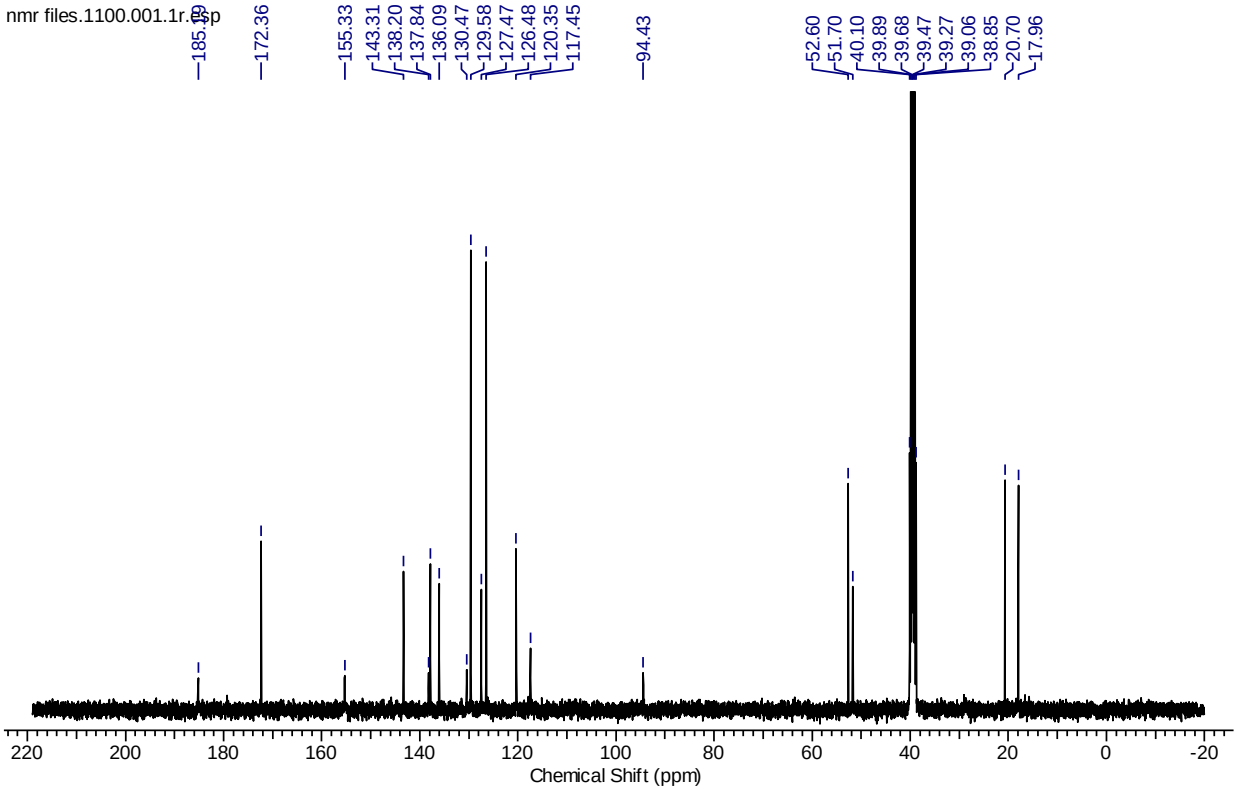
Chemical Shift (ppm)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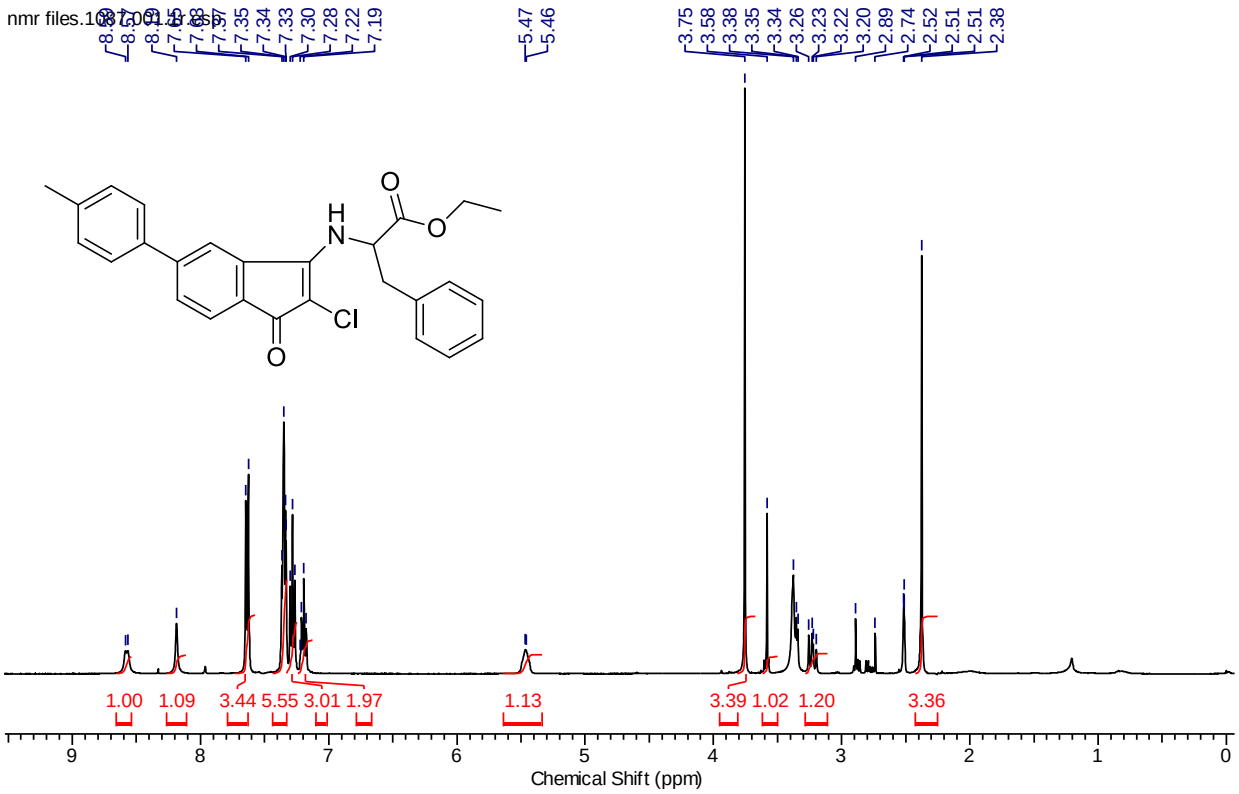
Chemical Shift (ppm)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5.46
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3.34
3.26
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3.22
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2.74
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2.51
2.51
2.38
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N
O
O
O
Cl
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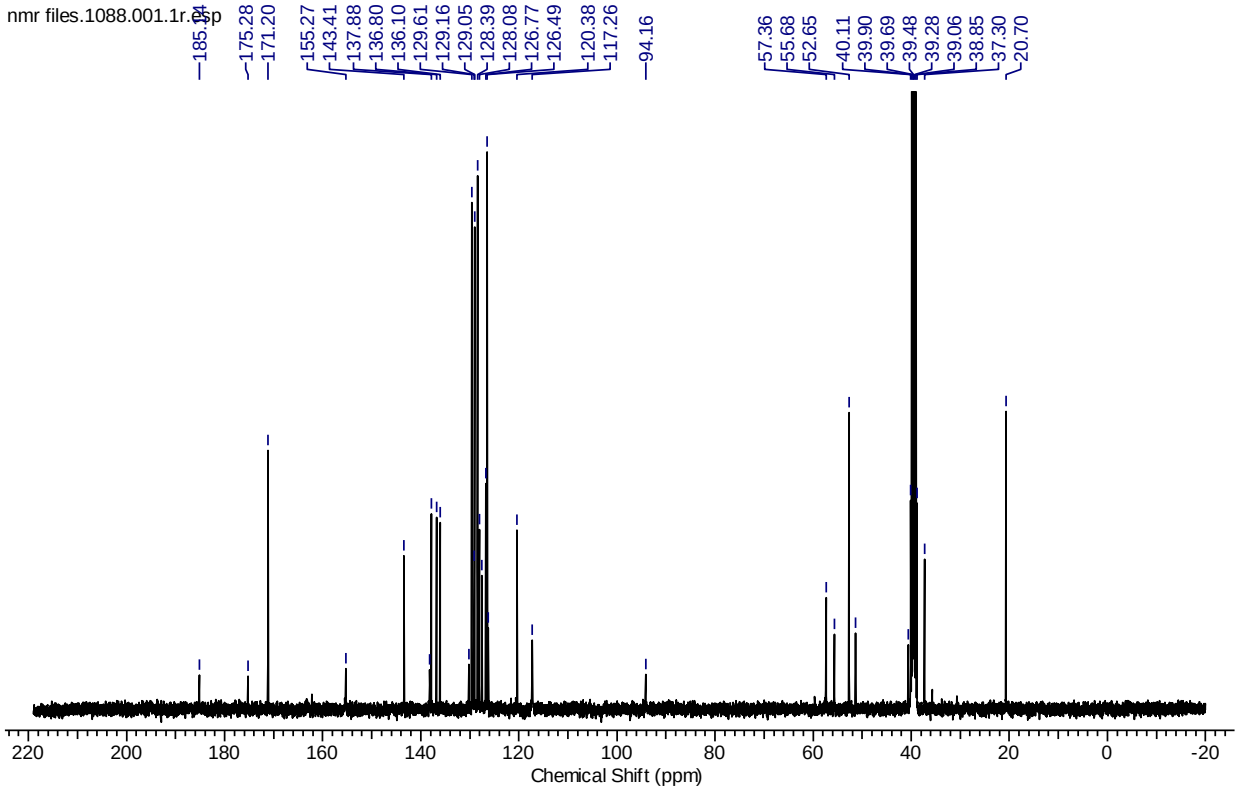
Chemical Shift (ppm)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60
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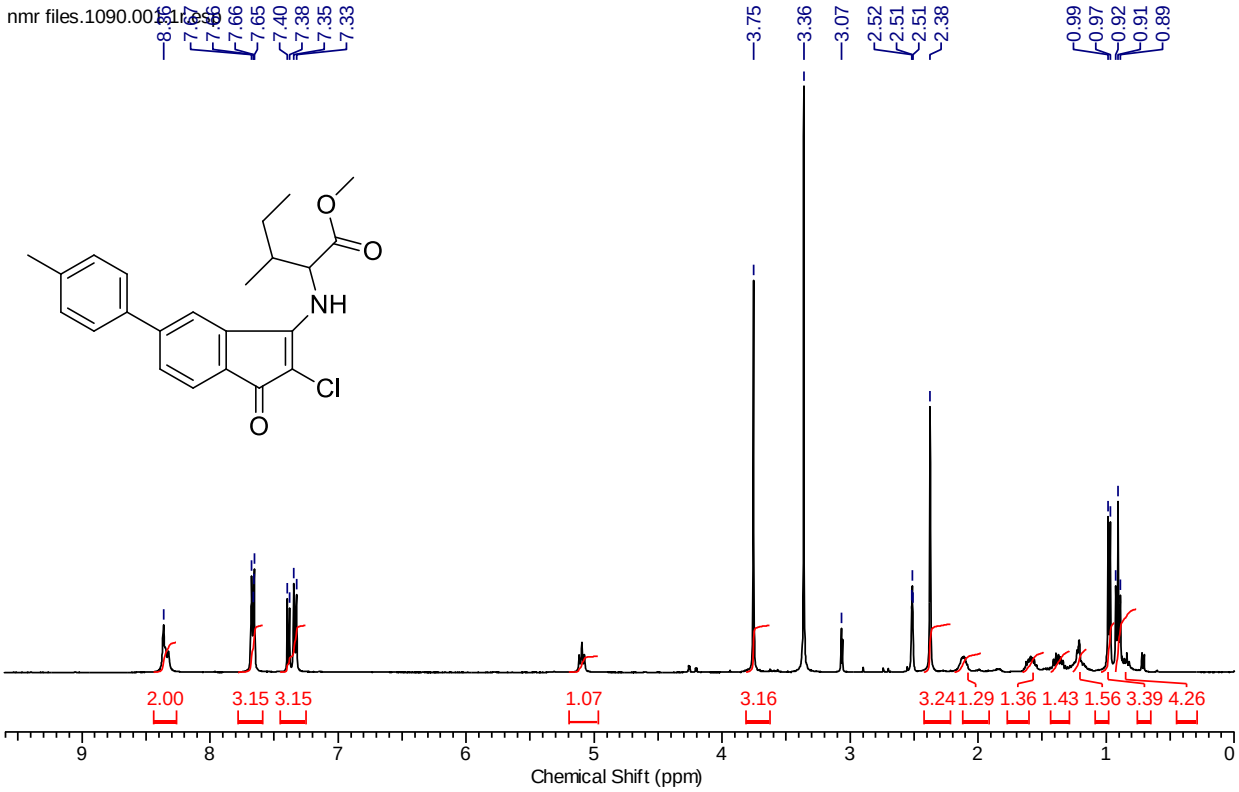
Chemical Shift (ppm)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2.51
2.38
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0.92
0.91
0.89
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O
NH
Cl
O
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3.24
1.29
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4
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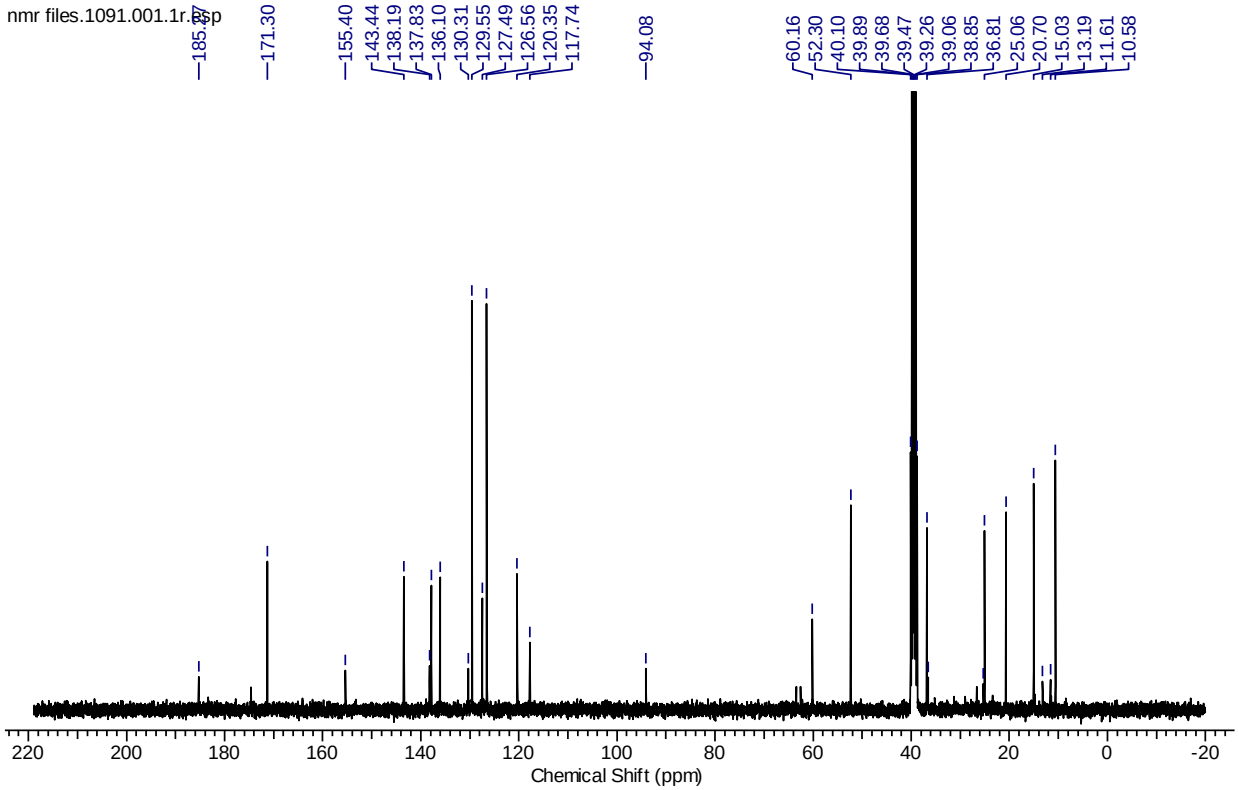
Chemical Shift (ppm)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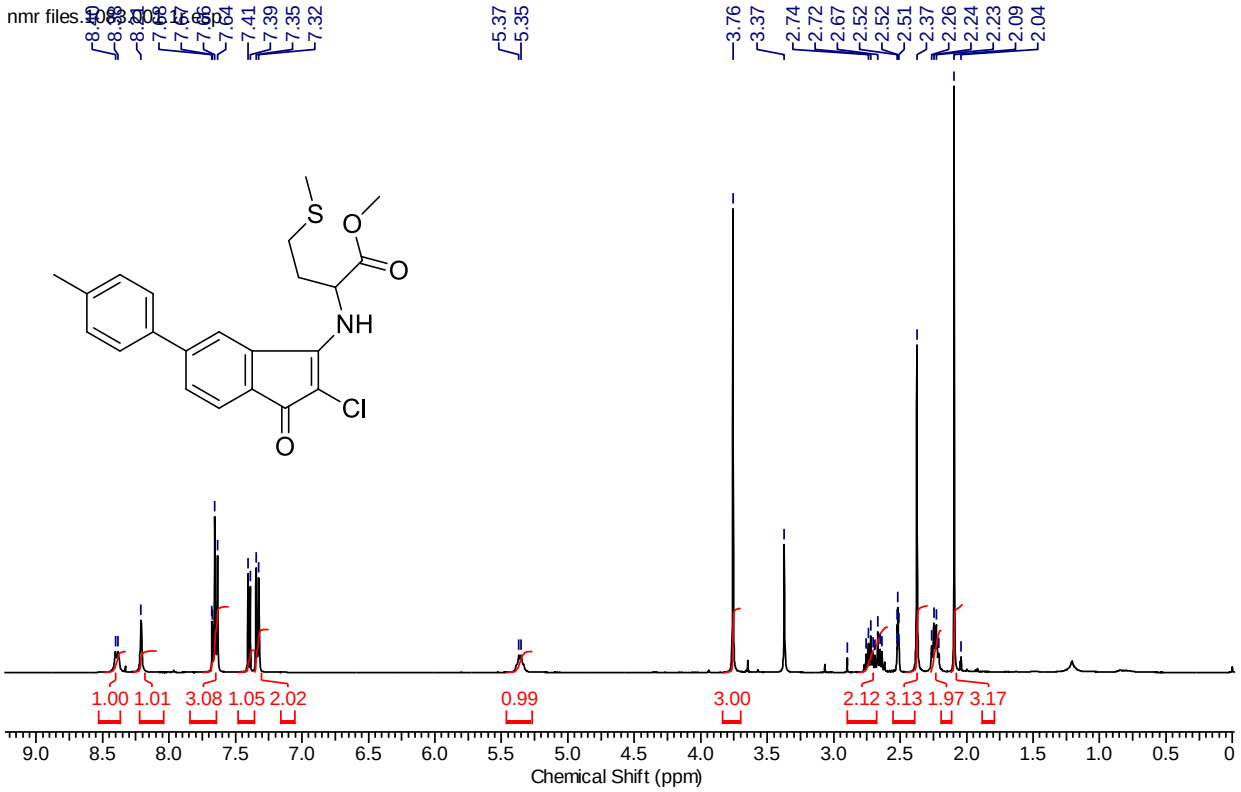
Chemical Shift (ppm)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2.24
2.23
2.09
2.04
S
O
O
NH
Cl
O
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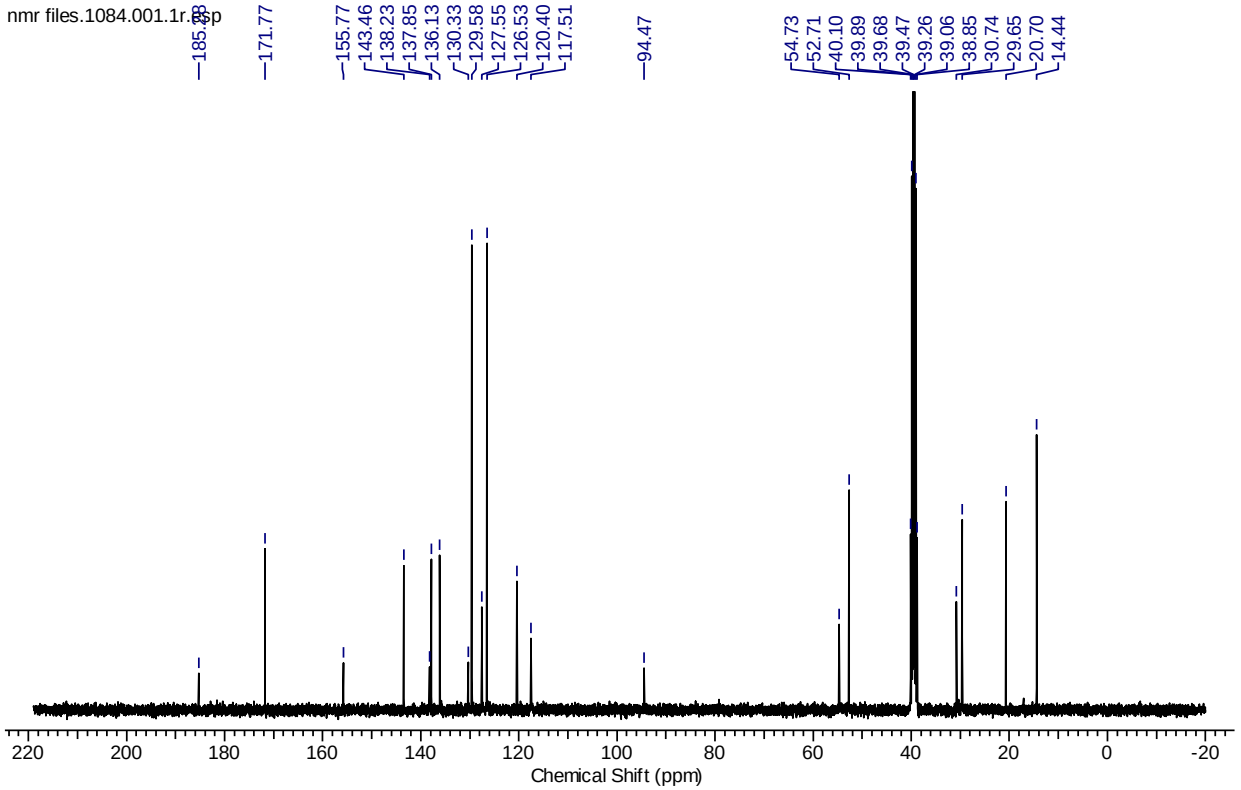
3.00
2.12 3.13 1.97 3.17
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)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39.89
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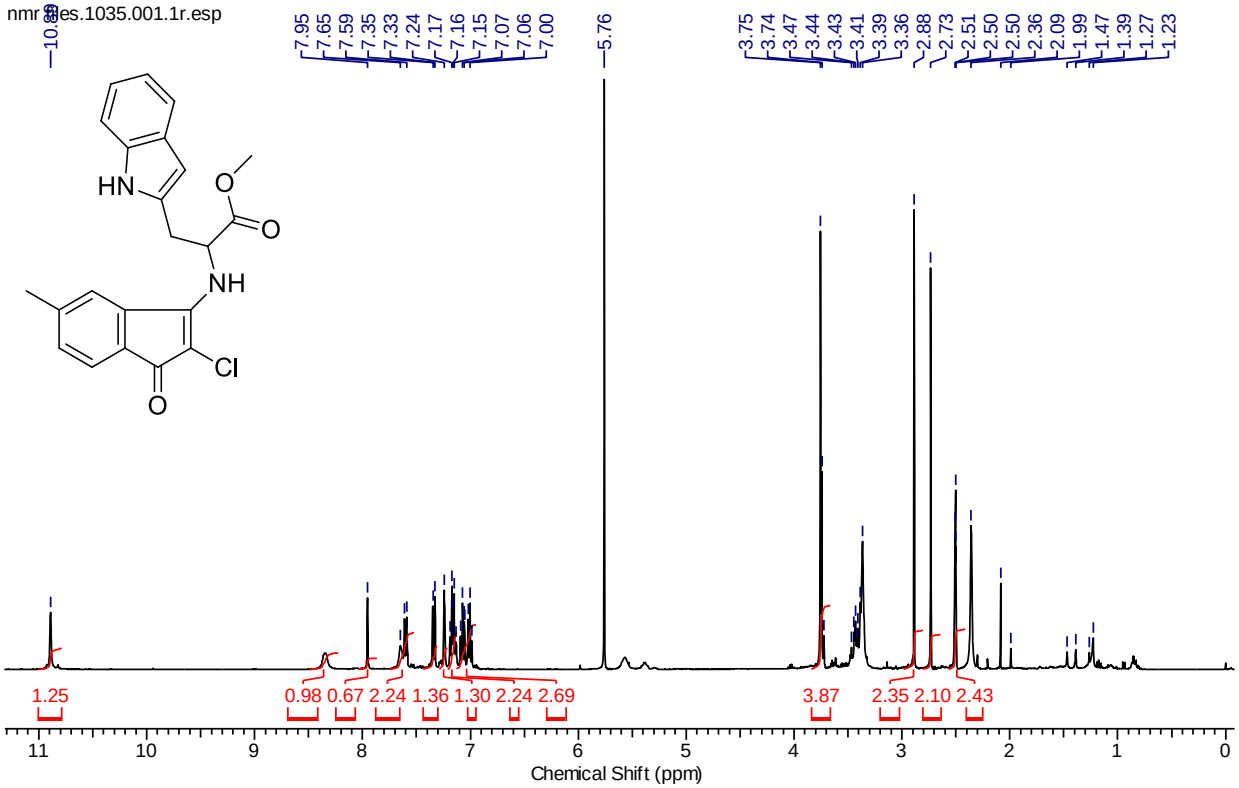
Chemical Shift (ppm)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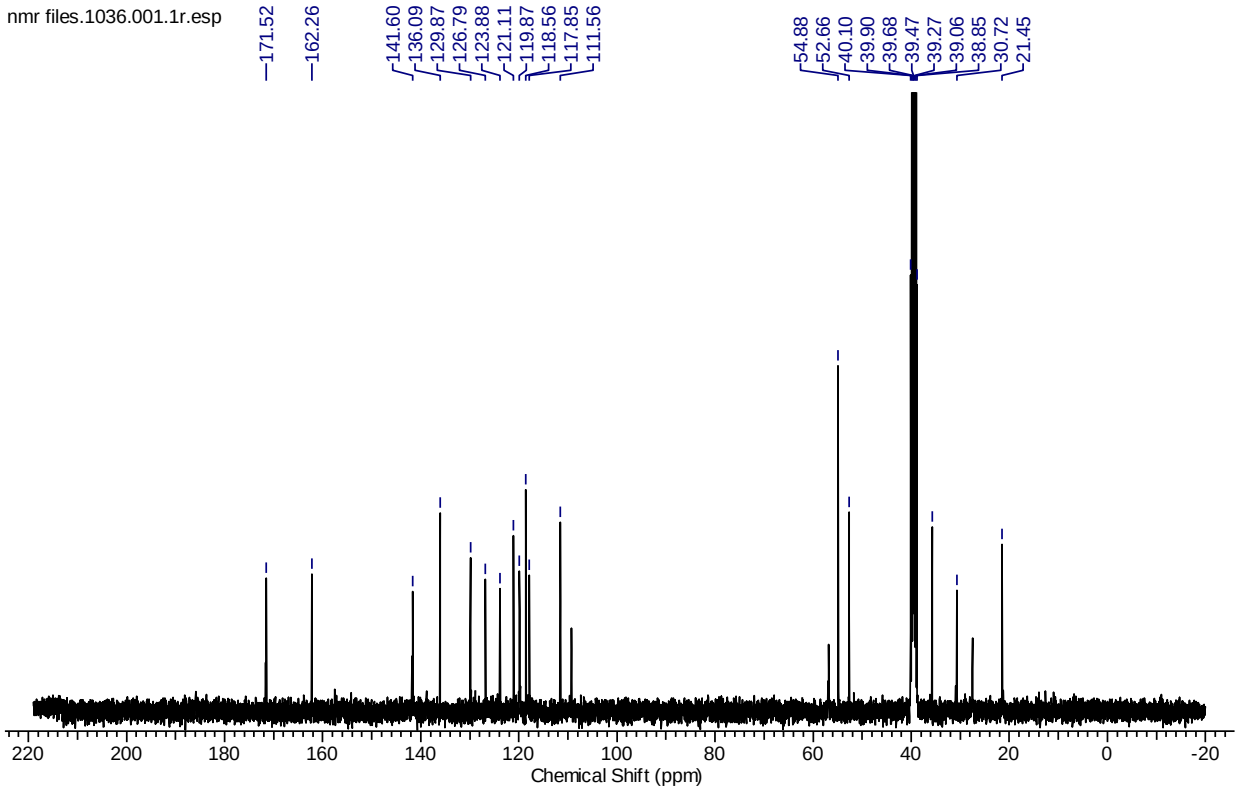
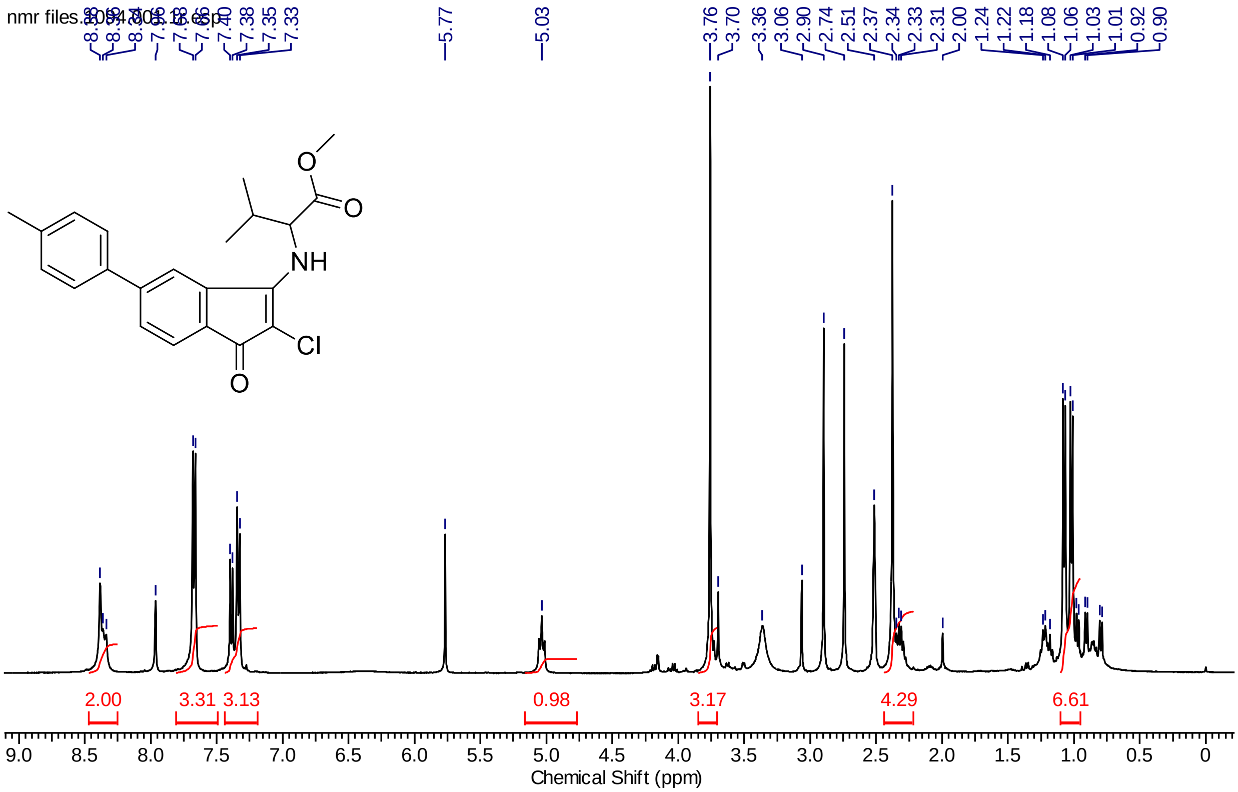
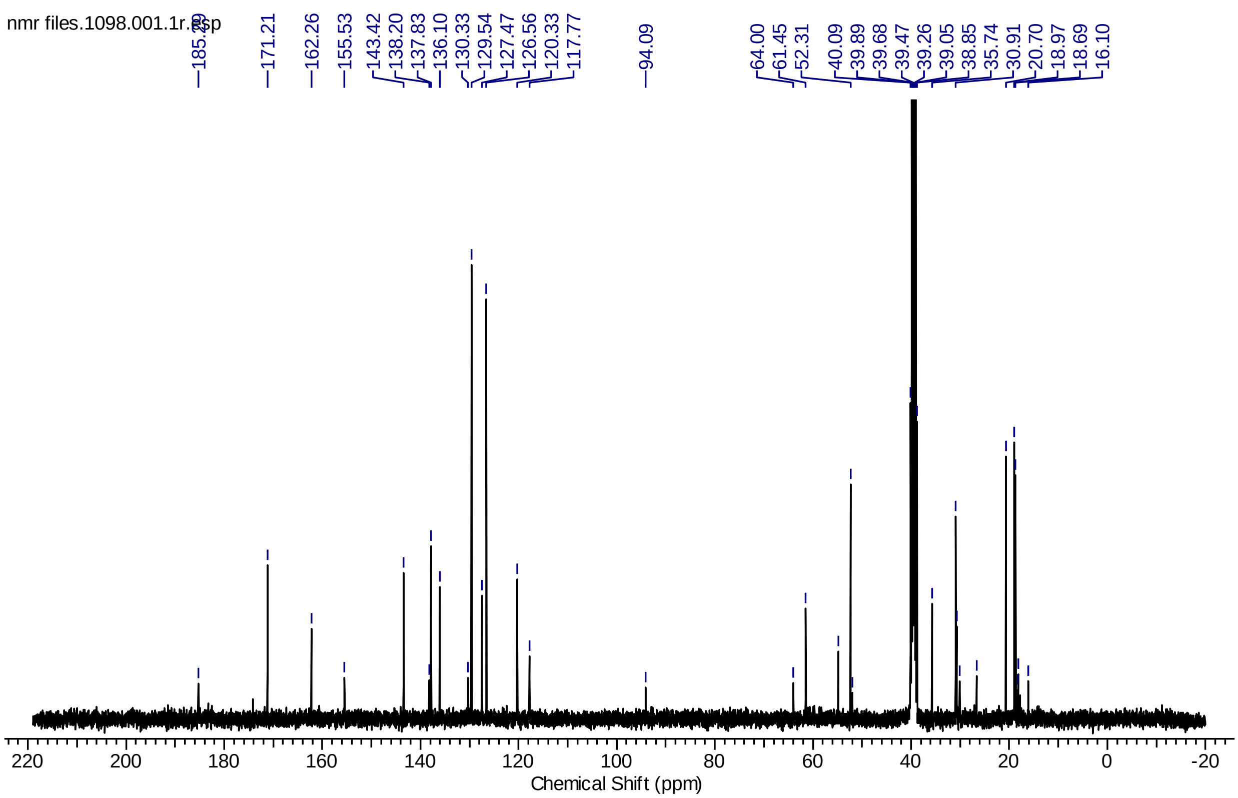
2.10
2.43
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


nmr files.1036.001.1r.esp
171.52
162.26
141.60
136.09
129.87
126.79
123.88
121.11
119.87
118.56
117.85
111.56
54.88
52.66
40.10
39.90
39.68
39.47
39.27
39.06
38.85
30.72
21.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


5.77
5.03
3.76
3.70
3.36
3.06
2.90
2.74
2.51
2.37
2.34
2.33
2.31
2.00
1.24
1.22
1.18
1.08
1.06
1.03
1.01
0.92
0.90
O
O
NH
Cl
O
2.00
3.31
3.13
0.98
3.17
4.29
6.61
Chemical Shift (ppm)


nmr files.1098.001.1r.esp
171.21
162.26
155.53
143.42
138.20
137.83
136.10
130.33
129.54
127.47
126.56
120.33
117.77
94.09
64.00
61.45
52.31
40.09
39.89
39.68
39.47
39.26
39.05
38.85
35.74
30.91
20.70
18.97
18.69
16.10
Chemical Shift (ppm)

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