Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supplemental Information

Chemo-Selective Syntheses of N-*t*-boc-Protected Amino Ester Analogs Through Buchwald Hartwig Amination

Sujit Suwal*, Mahmuda Rahman, Gregory O'Brien, Victoire G. Karambizi, Matthew Wrotny, M. Scott Goodman

Contents:

1. Chemicals and solvents:

Cesium carbonate and Ethyl-2-Chloropyrimidine-5-carboxylate was purchased from Alpha Aesar. PEPPSI-IPr Catalyst, Methyl-6-chloronicotinate, Methyl-6-Bromonicotinate, Methyl-2-chlorobenzoate from Sigma-Aldrich. Methyl-2-bromobenzoate, Ethyl-4-bromobenzoate was bought from Acros Organics. Likewise, Methyl-6-Bromonicotinate, methyl-5-bromonicotinate, methyl-2-bromonicotinate, 6-chloronicotinate, ethyl-2-bromothiazole-4-carboxylate, Methyl-2-chlorothiazole-4-carboxylate, Ethyl-2-chloropyrimidine-5-carboxylate, Methyl-3-bromo pyrimidine-2-carboxylate, Methyl-5-chloropyrazine-2-carboxylate, Methyl-6-chloropyrazine-2-carboxylate, methyl-3-chloropyrazine-2carboxylate, Methyl-3-bromopyrazine-2-carboxylate, and Methyl-2-Chloronicotinate were purchased from Combi-block. Sodium Sulfate and n-Hexanes were purchased from JT-Baker. We used Dichloromethane and Ethyl Acetate obtained from Macron. 1-Boc Piperazine, (S)-2-MethylPiperazine, (3S)-(-)-3-(t-butoxycarbonyl amino) Pyrrolidine were obtained from Oakwood Chemicals. Silica Gel (200-400 mesh) were purchased from Silica-Flash. Di-methoxy-ethane, Ethyl-2-bromobenzoate, Ethyl-3-bromobenzoate were bought from TCI.

2. Instruments:

^{1}H and ^{13}C NMR spectra were recorded in Bruker 400 instrument operating at 400 MHz for 1 H and 100 MHz for ^{13}C NMR using Deuterated-chloroform ($CDCl_3$) or Deuterated-Dimethylsulfoxide (D_6-DMSO) (Cambridge) as a solvent. Chemical shifts δ are reported in ppm, multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextet, sept. = septet, m = multiplet or unresolved and coupling constant J in Hz. For LCMS, we used Ultimate3000-ThermoExactive. IR spectra were recorded in Nicolet iS50 FT-IR. The absorption is reported in cm-1 and the IR bands were assigned as s (strong), m (medium) or w (weak).

3. General Synthesis Protocol:

Method 1:

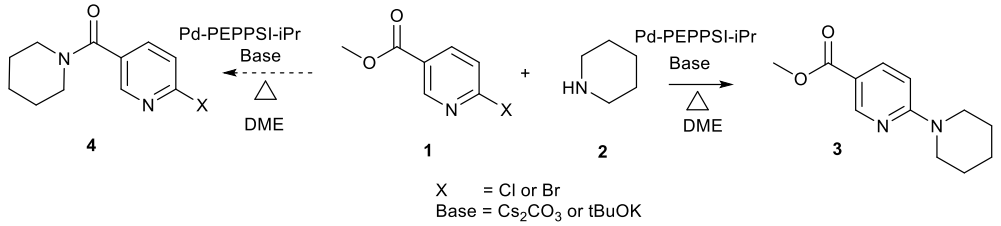
A halo-ester (1x) in a round bottomed flask purged with argon was dissolved with DME under the anhydrous condition. Roughly 3 mol% of Pd-catalyst was added followed by secondary amine (2x) and cesium carbonate (2x). The reaction was heated to 60–80^{o}C in the oil bath. The progress of reaction was monitored by TLC. For heterocyclic ester, the reactions were found to complete within 3-4 hr. Once the reaction was completed, ethyl acetate was added, stirred, and filtered. Residue was washed with excess amount to ethyl acetate. The crude compound was concentrated and purified using flash chromatography through silica using hexane and ethyl acetate solution in a different ratio.

Method 2:

For alkyl halobenzoates, all the experimental precursors and reagents were kept identical except 7 mol% of Pd-catalyst was used and the reaction was incubated overnight up to 120^{o}C.

Scheme 1:

(I) A scheme of chemo-selective BHA cross-coupling between heterocyclic halo-esters and secondary amine.



(II) A general scheme showing for chemo-selective BHA cross-coupling between aryl/heterocyclic halo-esters and N-*t*-boc diamine.

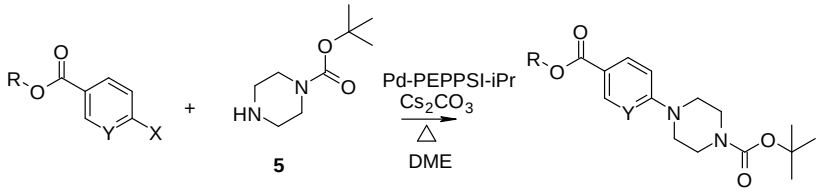


Table 1: A list of BHA products and their yield resulted by reacting different haloesters (left column) and the N-tboc diamines (top row)

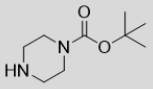
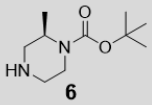
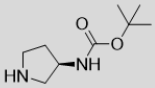
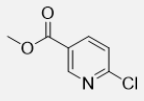
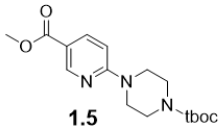
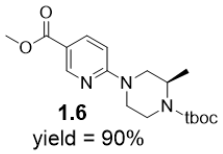
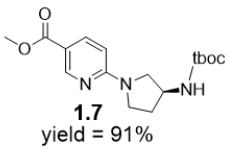
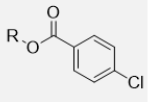
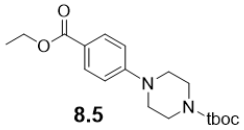
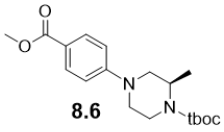
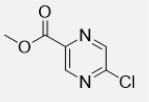
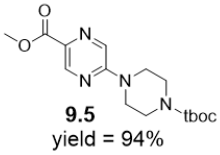
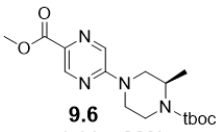
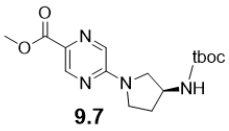
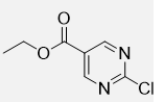
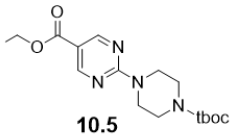
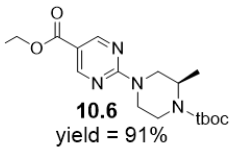
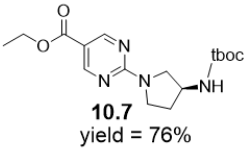
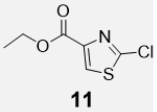
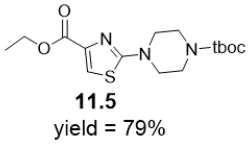
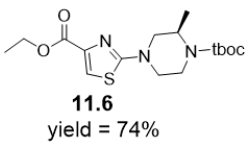
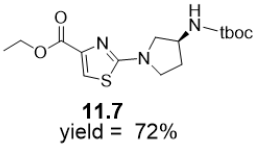
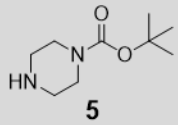
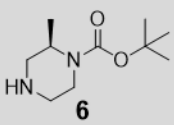
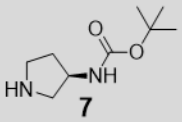
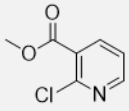
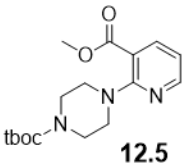
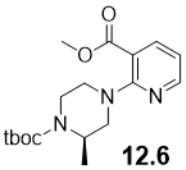
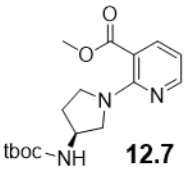
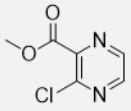
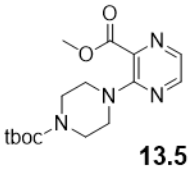
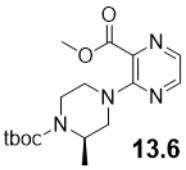
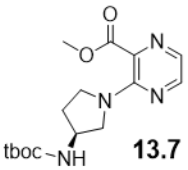
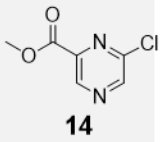
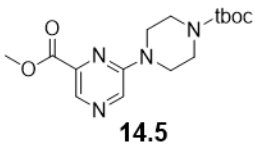
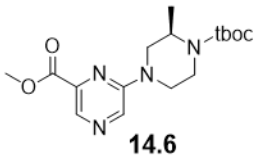
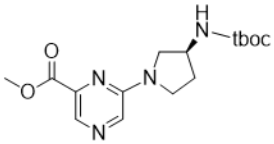
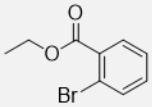
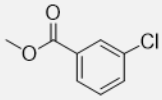
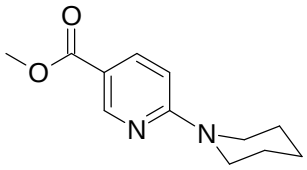
	 5	 6	 7
 1	 **1.5** yield = 95%	 **1.6** yield = 90%	 **1.7** yield = 91%
 8	 **8.5** yield = 82%	 **8.6** yield = 65%	**N.R.**
 9	 **9.5** yield = 94%	 **9.6** yield = 89%	 **9.7** yield = 88%
 10	 **10.5** yield = 95%	 **10.6** yield = 91%	 **10.7** yield = 76%
 11	 **11.5** yield = 79%	 **11.6** yield = 74%	 **11.7** yield = 72%

Table 2: A list of BHA products and their yield resulted by reacting different haloesters (left column) and the N-tboc diamines (top row)

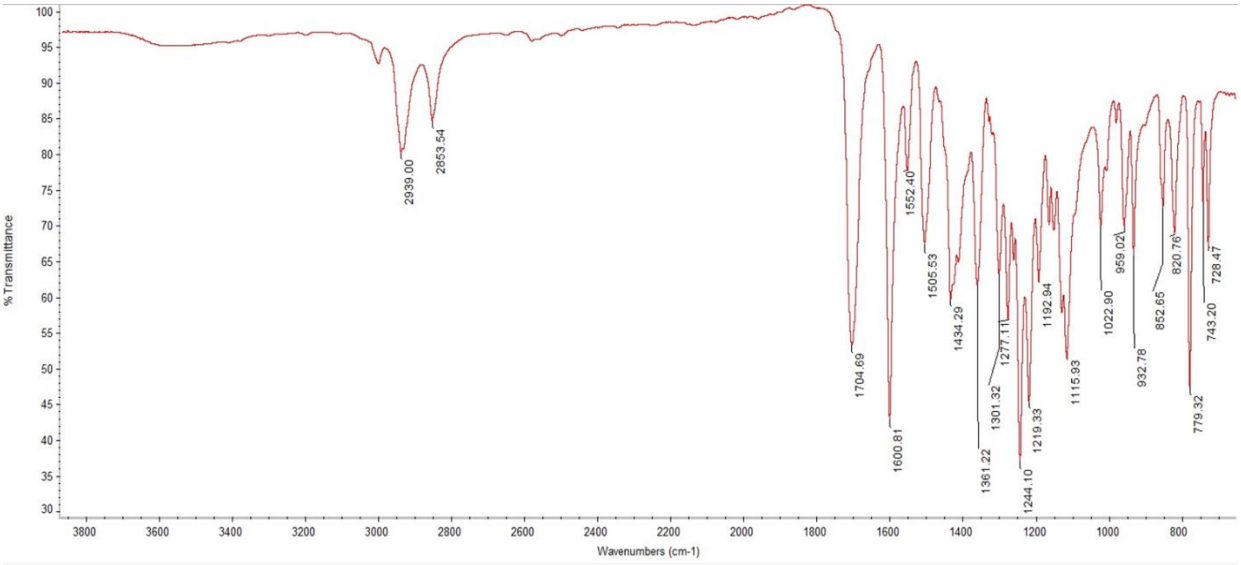
	 5	 6	 7
 12	 **12.5** yield = 84%	 **12.6** yield = 76%	 **12.7** yield = 80%
 13	 **13.5** yield = 82%	 **13.6** yield = 77%	 **13.7** yield = 75%
 14	 **14.5** yield = 77%	 **14.6** yield = 73%	 **14.7** yield = 72%
 15	N.R.	N.R.	N.R.
 16	N.R.	N.R.	N.R.

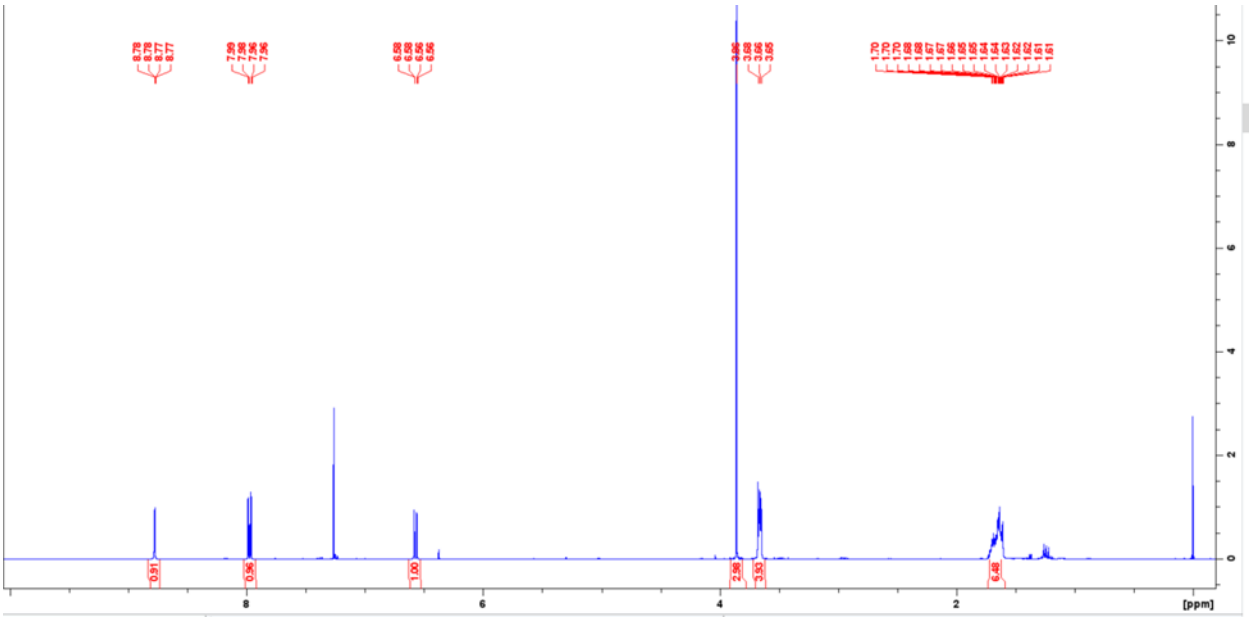
Spectral Analysis:

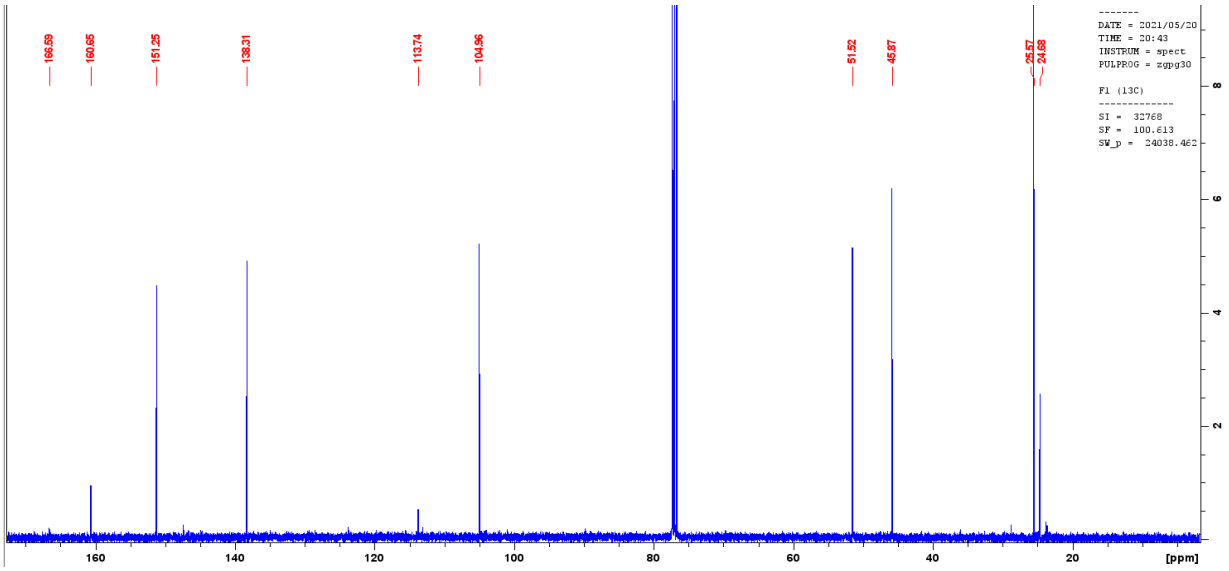
Spectral data of Compound 3



IR (cm^{-1}):2939(w), 2853(w), 1704(s), 1600(s), 1434(m), 1244 (m), 1219 (m), 1115(m); ^{1}HNMR (400 MHz) δ: 8.78 (dd, *J*=2.4, 0.7, 1H), 7.97(dd, *J*=9.0, 2.4, 1H), 6.58-6.56 (dd, J=9.0, 0.7, 1H) 3.86 (s, 3H), 3.6-3.68 (m, 4H), 1.70 – 1.61 (m, 6H); ^{13}CNMR (100 MHz): 166.6, 160.6, 151.3, 138.3, 113.4, 104.9, 51.5, 45.8, 25.6, 24.7; ESI-MS: Observed MH^{+} = 221.1303 (Expected MH^{+} = 221.1212)



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138.31
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25.57
24.68
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TIME = 20:43
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
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SF = 100.613
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140
120
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80
60
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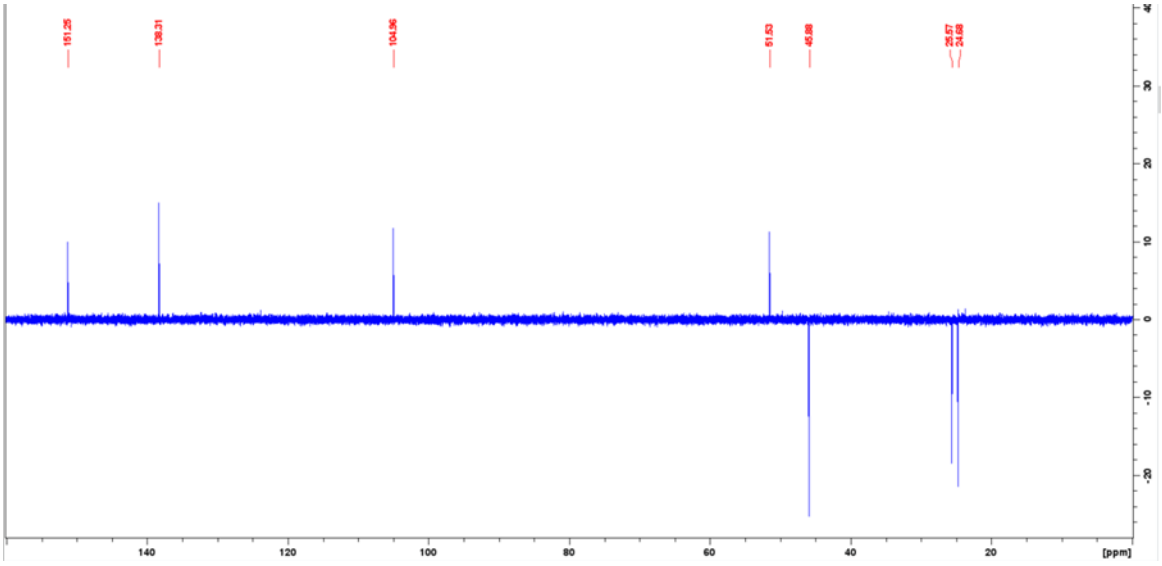
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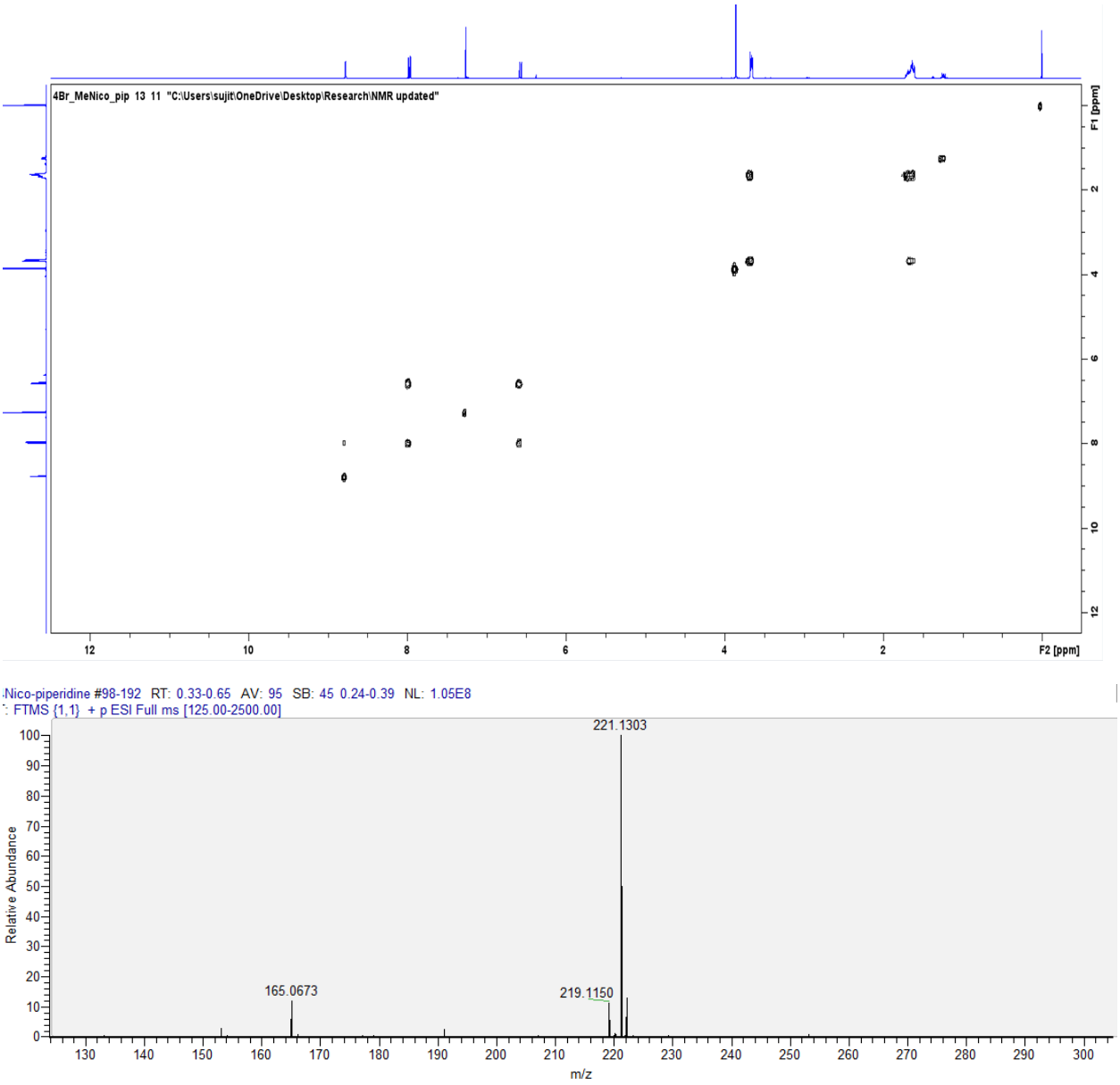
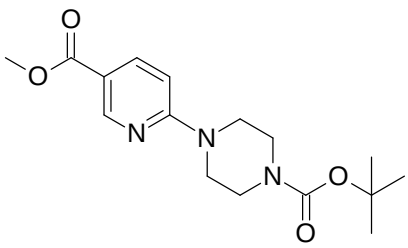


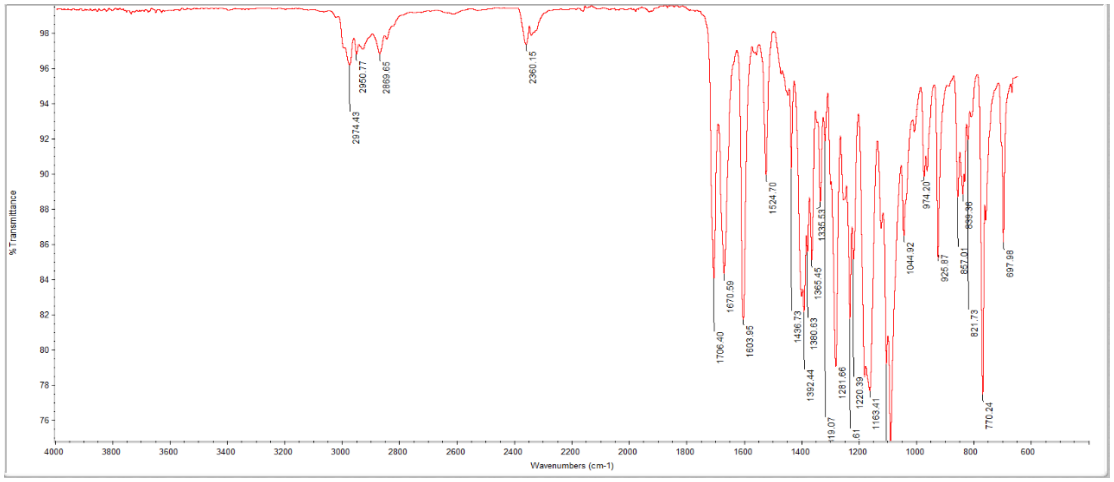
Fig S1: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, ESI-MS of compound 3

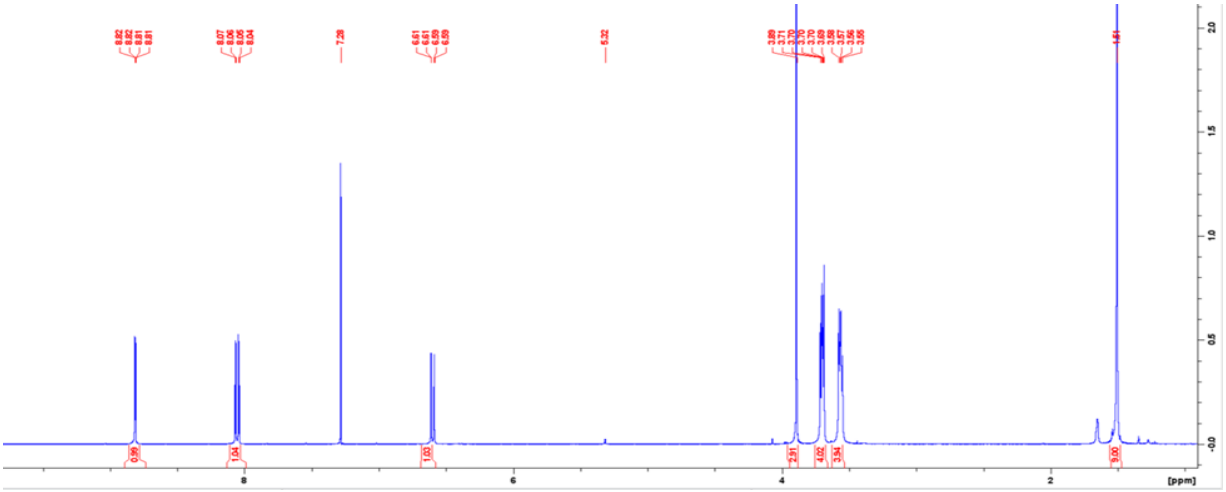
Spectral data of compound 1.5

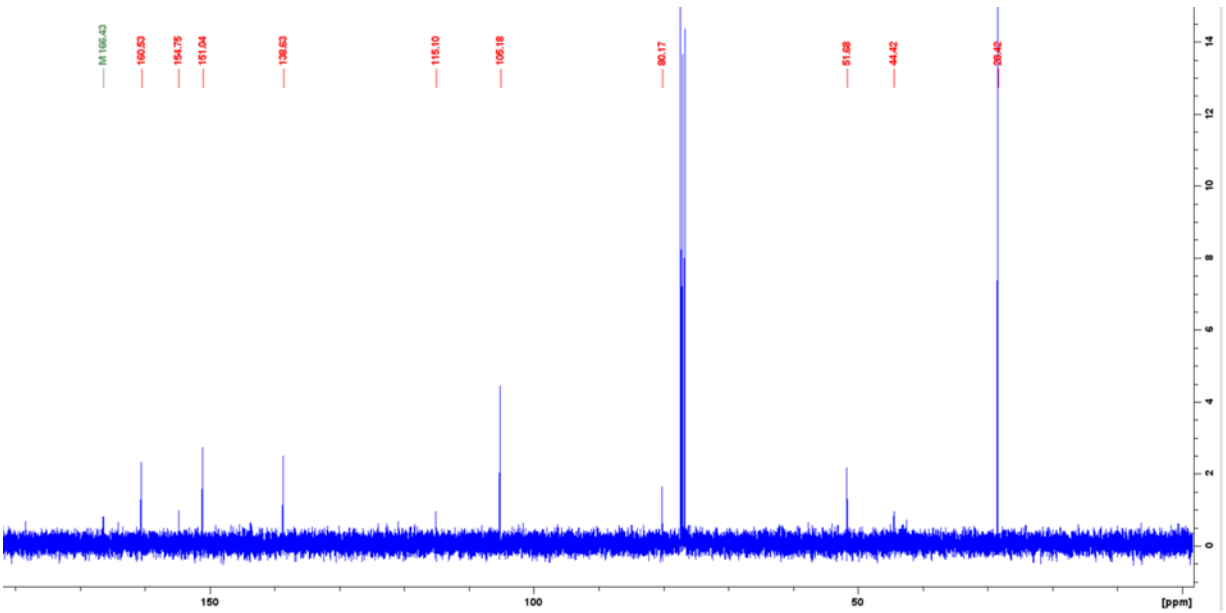


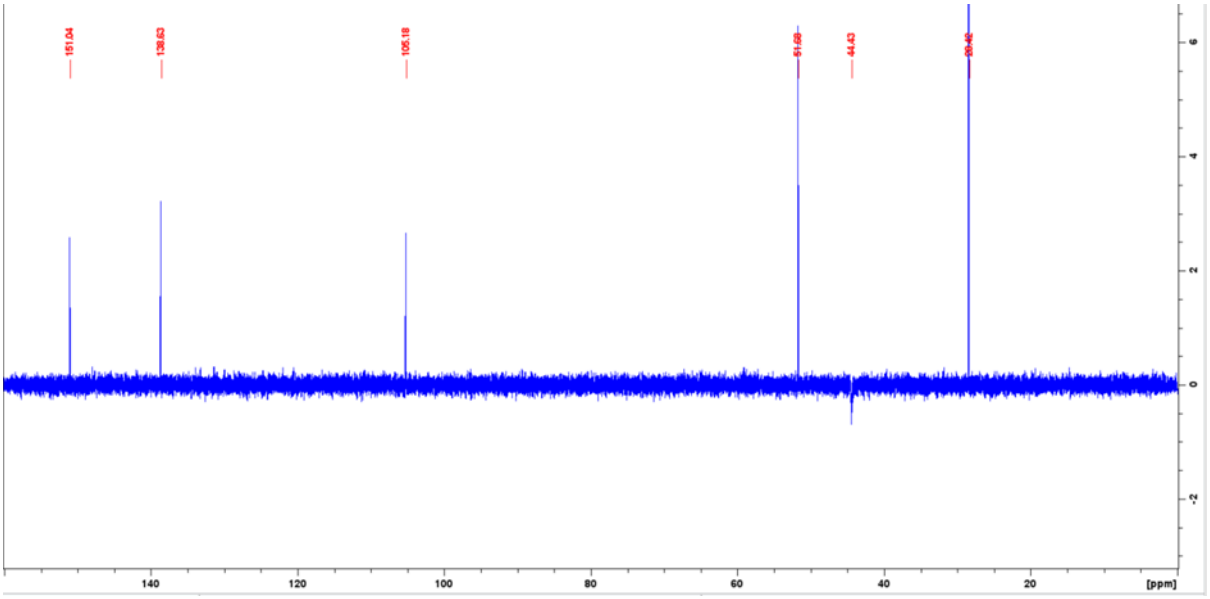
IR (cm^{-1}):2974 (w), 1706 (m), 1670(m), 1603 (m), 1392 (m), 1281(s), 1163 (s), 1080 (s), 770 (s), NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.81 (dd, *J*=2.4, 0.7, 1H), 8.05(dd, *J*=9.0, 2.4, 1H), 6.6 (dd, *J*=9.0, 0.7, 1H), 3.89(s,

3H), 3.70(m, 4H), 3.56(m, 4H), 1.50(t, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.6, 160.6, 154.8, 151.0, 138.3, 115.1, 105.2, 80.2, 51.7, 44.4, 20.42; ESI-MS: MH^+ = 322.1757 (expected MH+ = 322.1689)









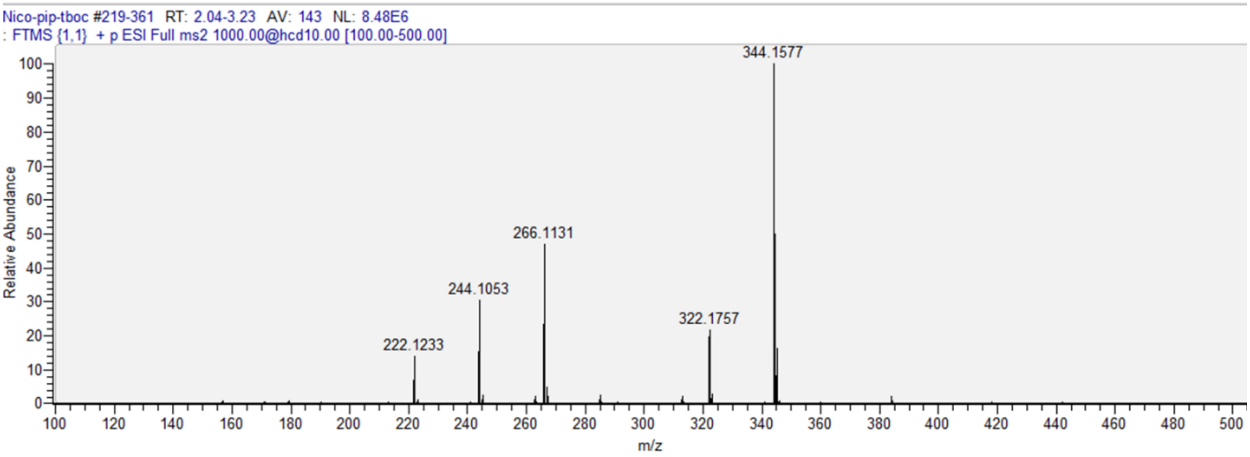
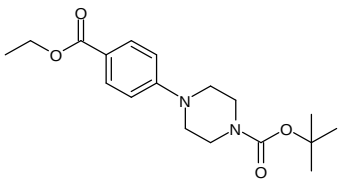


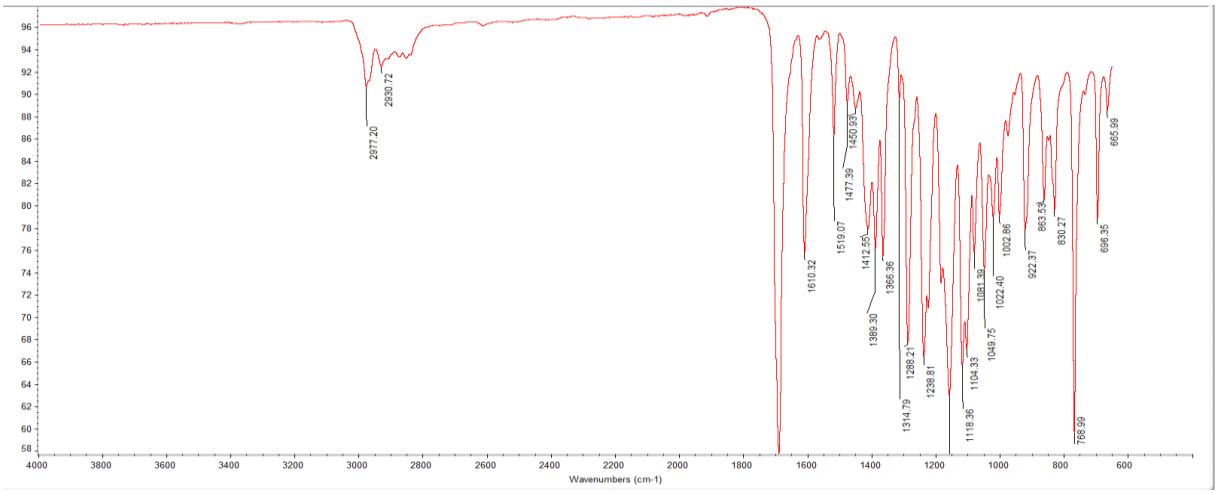
Fig S2: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 1.5

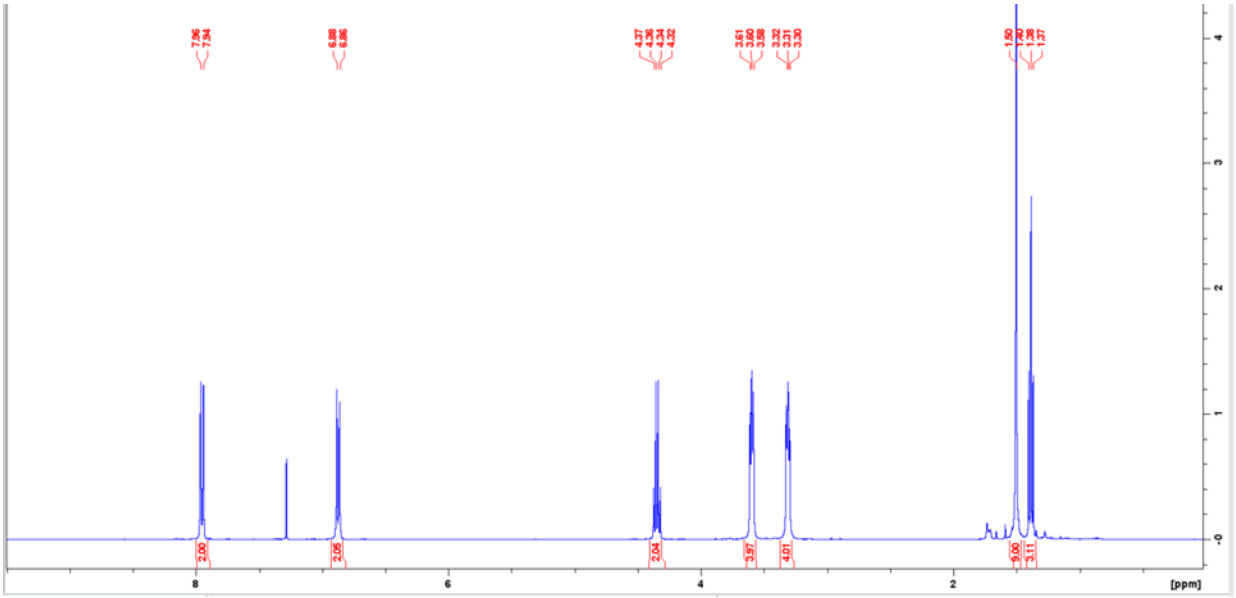
Spectral data of Compound 8.5

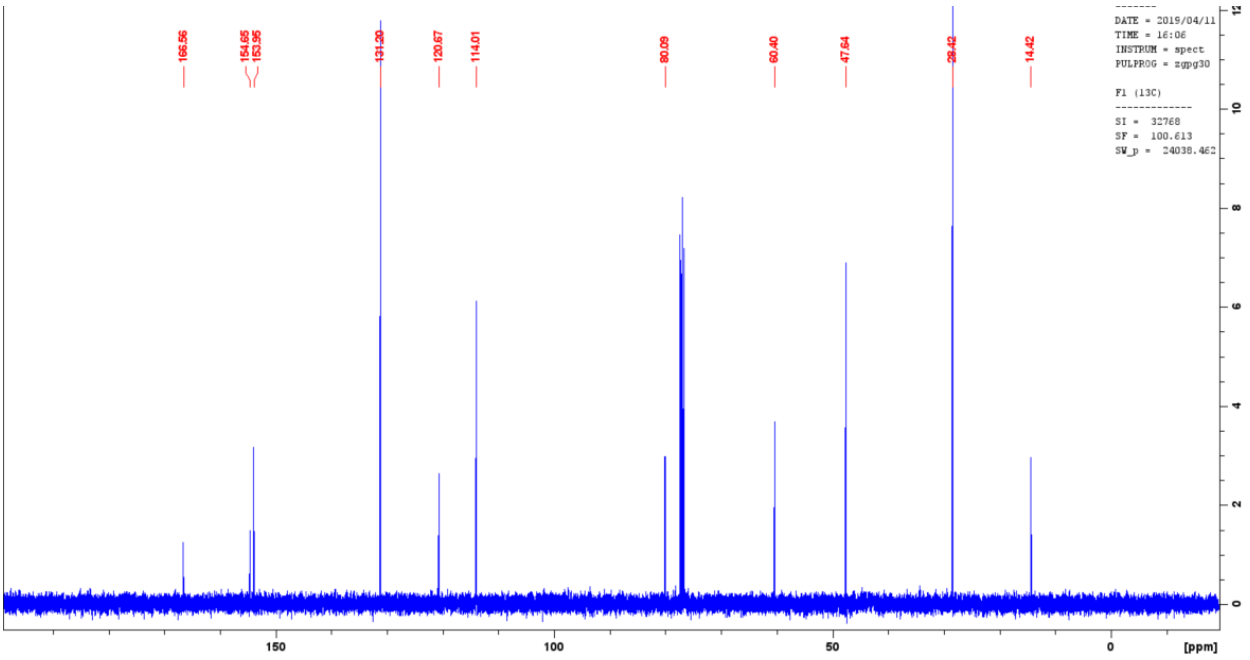


IR (cm^{-1}): 2977(s), 1690 (s), 1610 (m), 1519 (s), 1288 (m), 1238 (m), 1160 (m), 1118 (m), 769 (s); NMR (400MHz, $CDCl_3$, [ppm]) δ: 7.96 (d, *J*=8.9 Hz, 2H), 6.88(d, *J*=8.9 Hz, 2H), 4.35 (q, *J*=7.1 Hz, 2H), 3.59(m, *J*=4.9H, 4H), 3.30(m, *J*=4.9Hz, 4H), 1.50(s, 9H), 1.38(t, *J*=7.1Hz, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.5,

154.6, 153.9, 131.2, 120.6, 114.0, 80.1, 60.4, 47.6, 28.4, 14.4; ESI-MS: MH+ = 335.1962 (expected MH+ = 335.1893)






166.56
154.65
153.95
131.20
120.67
114.01
80.09
60.40
47.64
28.42
14.42
DATE = 2019/04/11
TIME = 16:06
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PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
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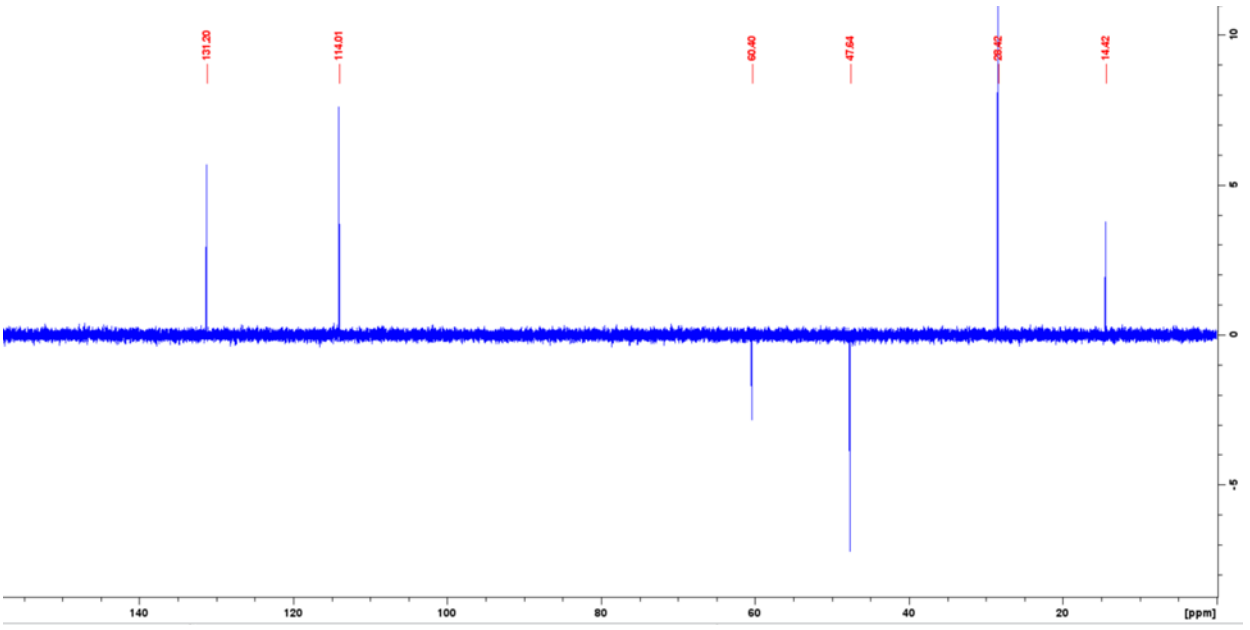
100
50
0
[ppm]


131.20
114.01
60.40
47.64
28.42
14.42
140
120
100
80
60
40
20
[ppm]

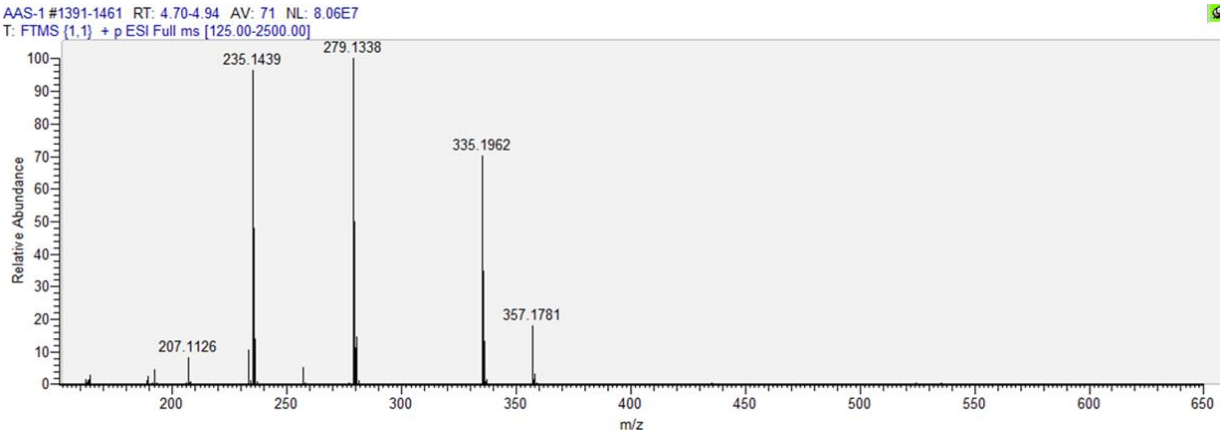
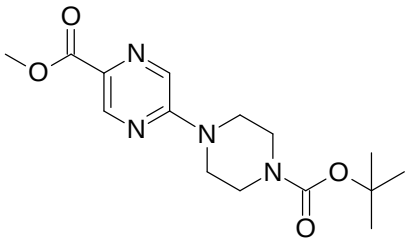
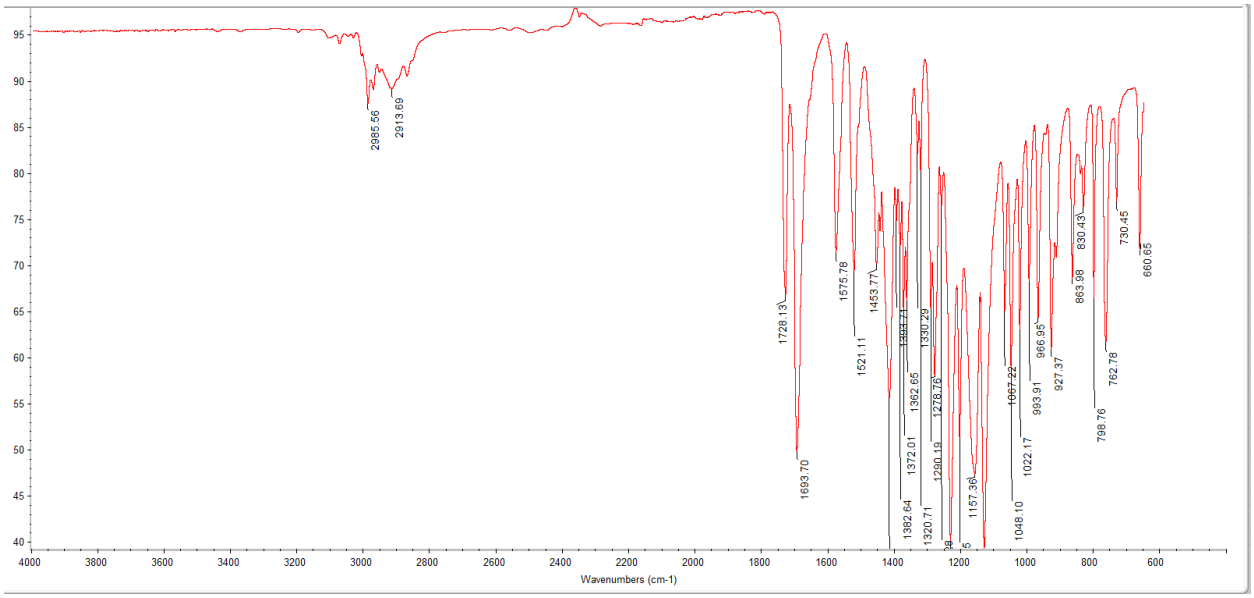


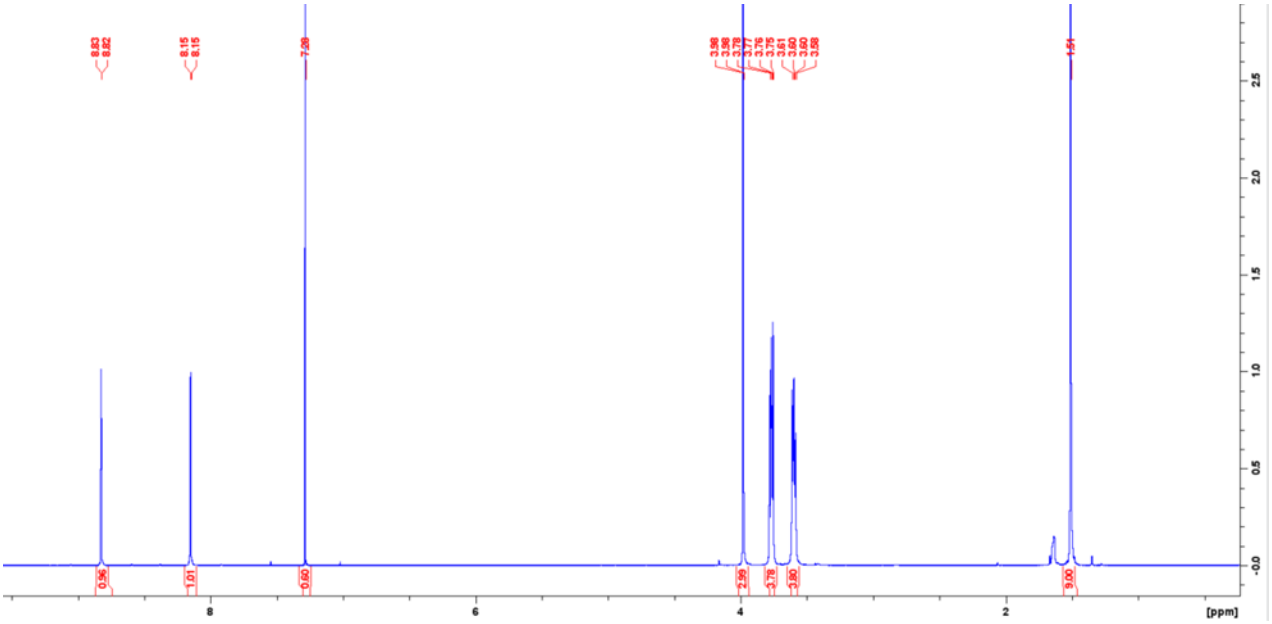
Fig S3: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 8.5

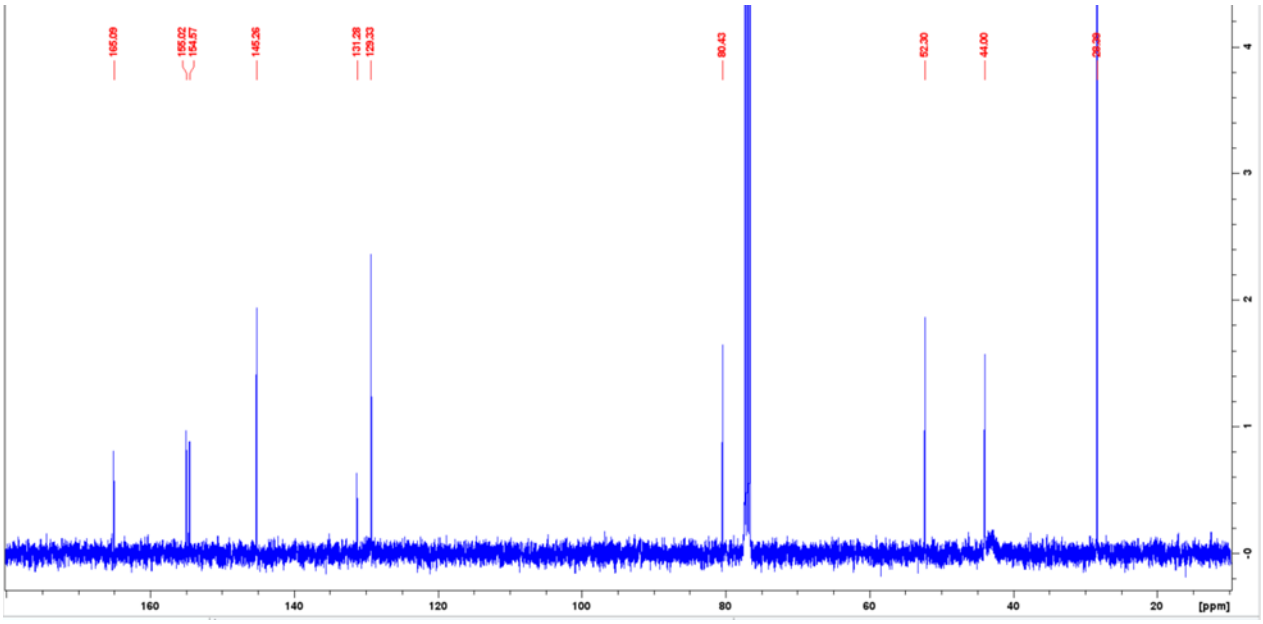
Spectral data of 9.5

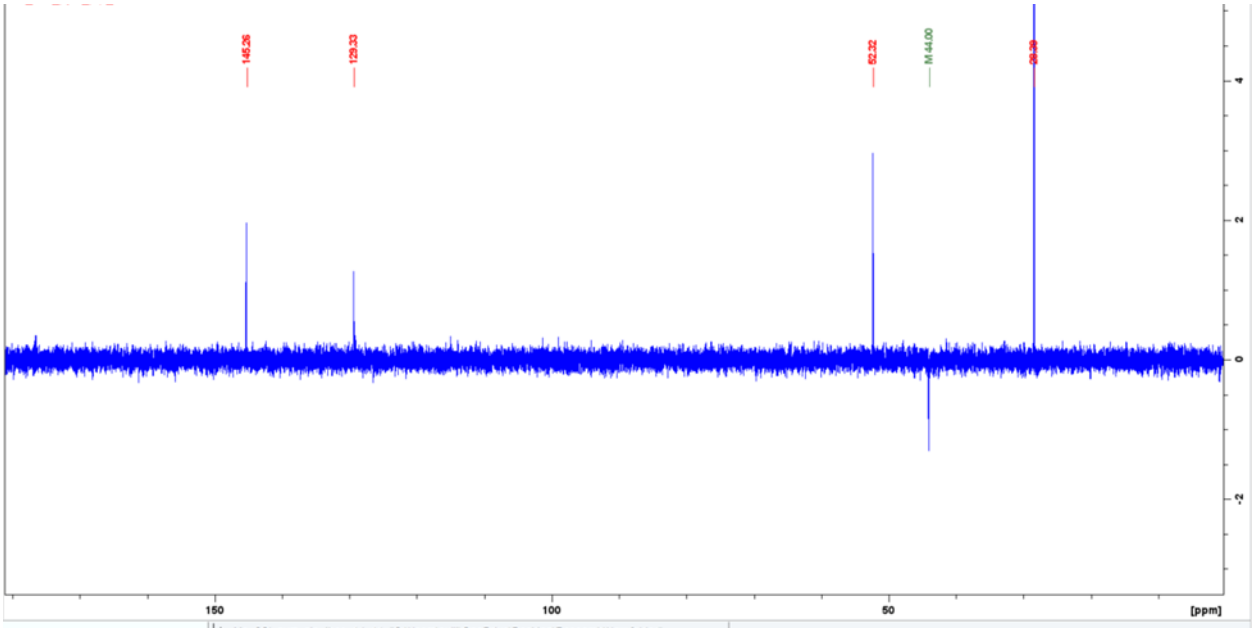


IR (cm^{-1}): 2985(w), 1728(m), 1693 (s), 1420 (m), 1382 (s), 1238 (s), 1157 (m), 1140 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.82 (d, *J*=1.3 Hz, 1H), 8.15(d, *J*=1.3 Hz, 1H), 3.97 (s, 3H), 3.77 – 3.75(m, 4H), 3.60(m, 4H), 1.50(s, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]): 165.1.5, 155.0, 154.6, 145.3, 131.3, 129.3, 80.4, 52.3,43.9, 28.4; ESI-MS: MH^+ = 323.1707 (expected MH^+ = 323.1641)




8.83
8.82
8.15
8.15
7.26
3.96
3.96
3.79
3.77
3.76
3.75
3.61
3.60
3.60
3.59
1.64
0.96
1.01
0.60
2.99
3.78
3.90
9.00
8
6
4
2
[ppm]


165.09
155.02
154.57
145.26
131.28
129.33
80.43
62.30
44.00
28.38
160
140
120
100
80
60
40
20
[ppm]



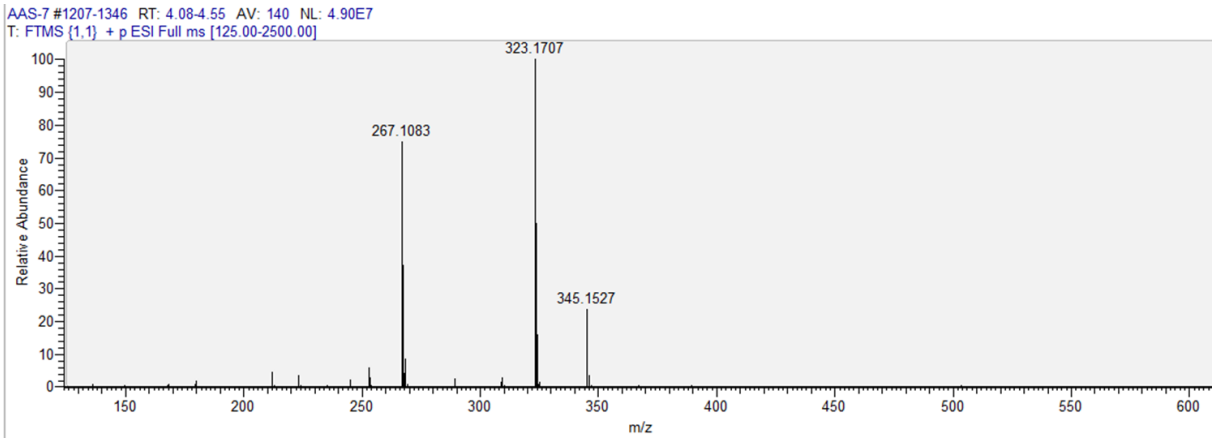
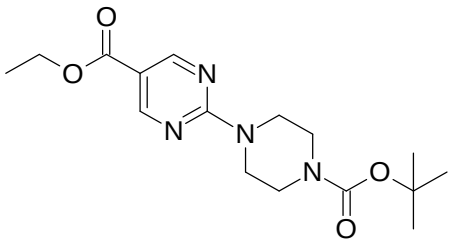


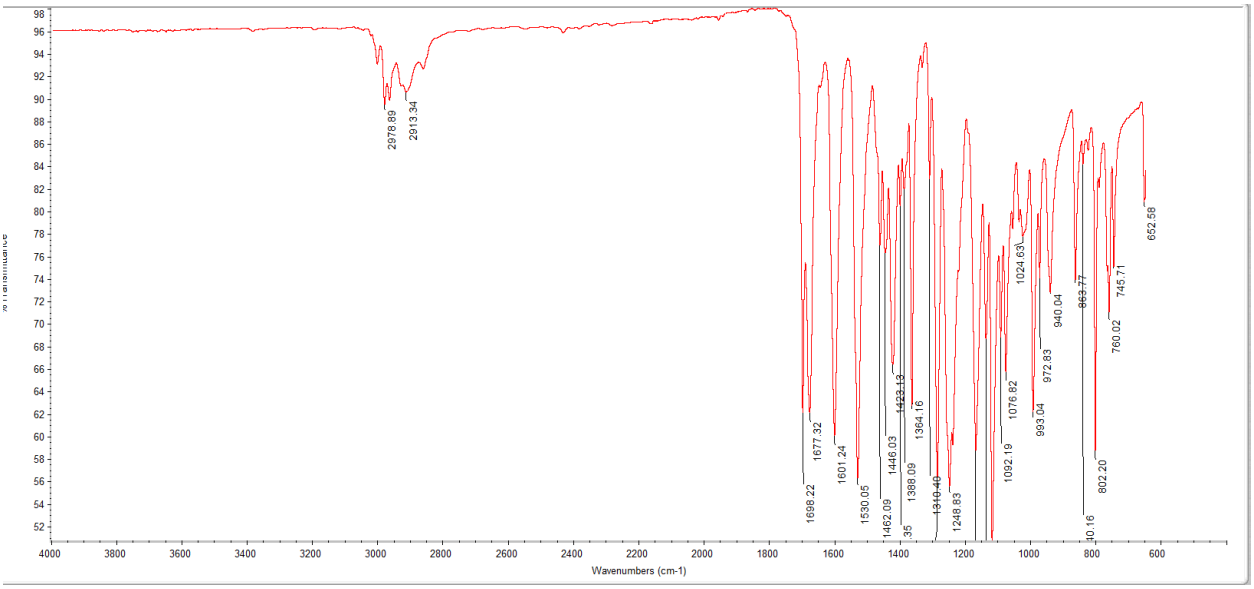
Fig S4: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 9.5

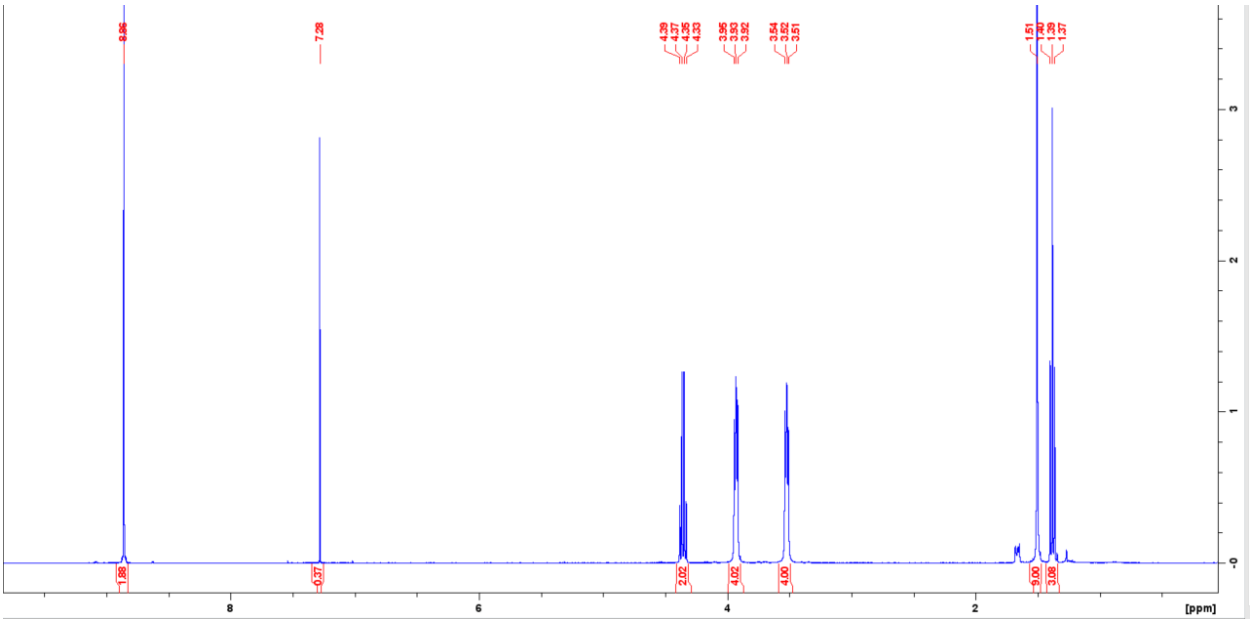
Spectral data of 10.5

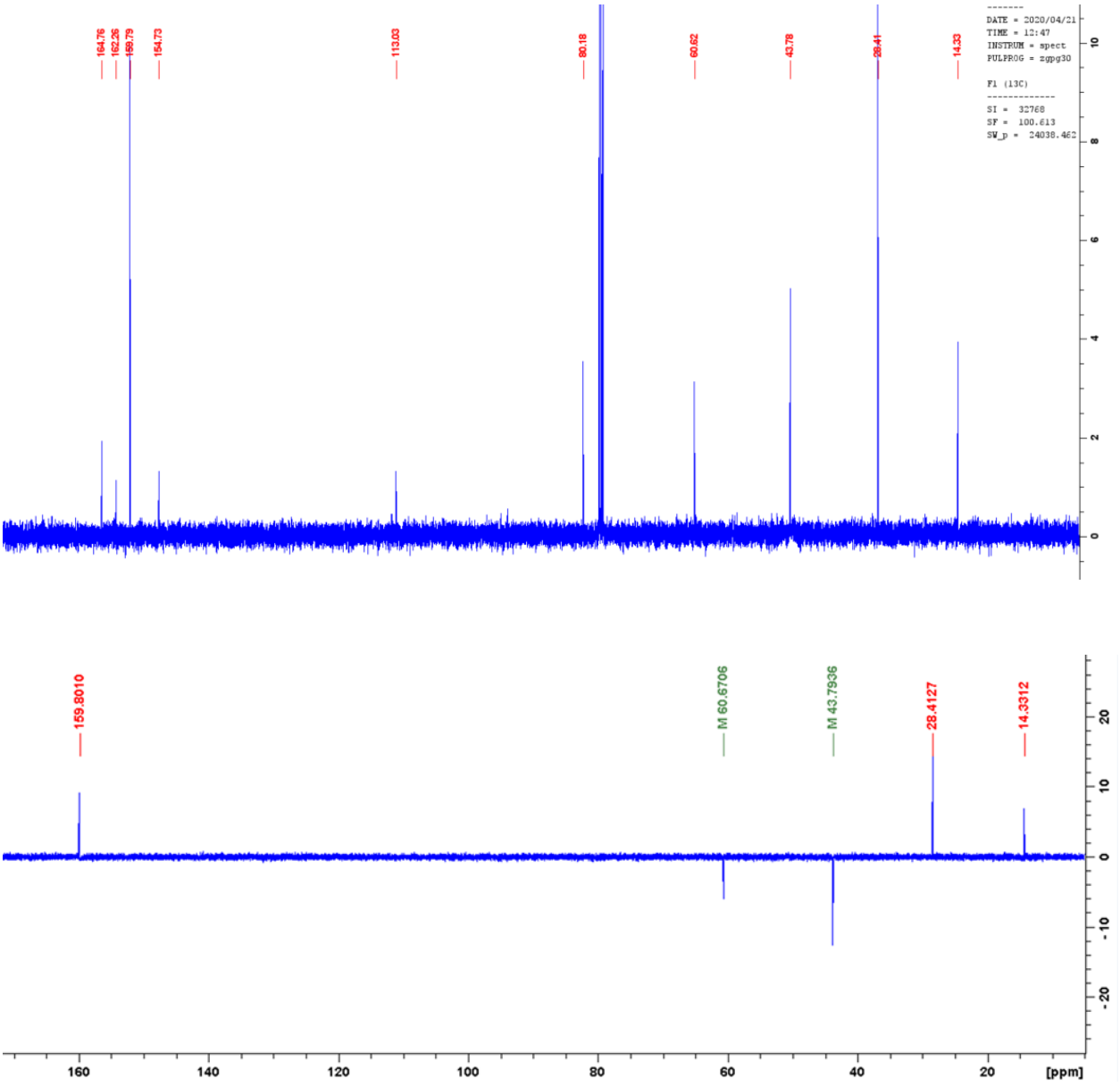


IR (cm^{-1}): 2978 (w), 1698 (s), 1677 (s), 1601 (s), 1530 (s), 1310 (s), 1248 (s), 1100(s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.86 (s, 2H), 4.38-4.33 (q, *J*=7.1, 2H), 3.94-3.91 (m, 4H), 3.53-3.5 (m, 4H), 1.50 (s, 9H), 1.38 (t,

J=7.1, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 164.7, 162.3, 159.8, 154.7, 113.0, 80.2, 60.6, 43.7, 28.4; 14.3; ESI-MS: MH^+ = 337.1798 (expected MH^+ = 337.1798)






164.76
162.26
159.79
154.73
113.03
80.18
60.62
43.78
28.41
14.33
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TIME = 12:47
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SI = 32768
SF = 100.613
SW_p = 24038.462
159.8010
M 60.6706
M 43.7936
28.4127
14.3312
160
140
120
100
80
60
40
20
[ppm]

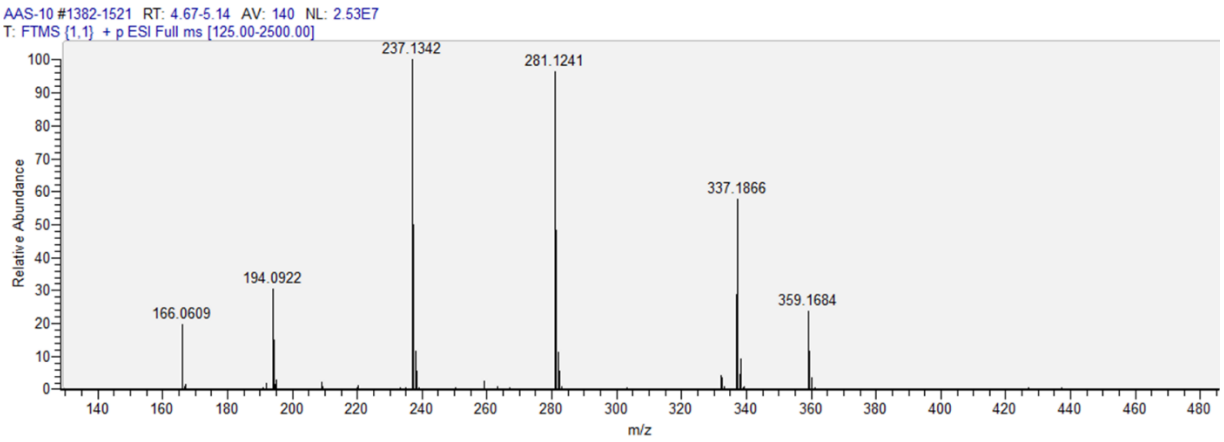
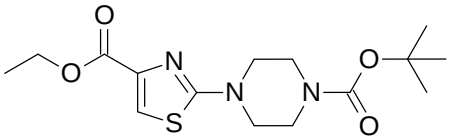
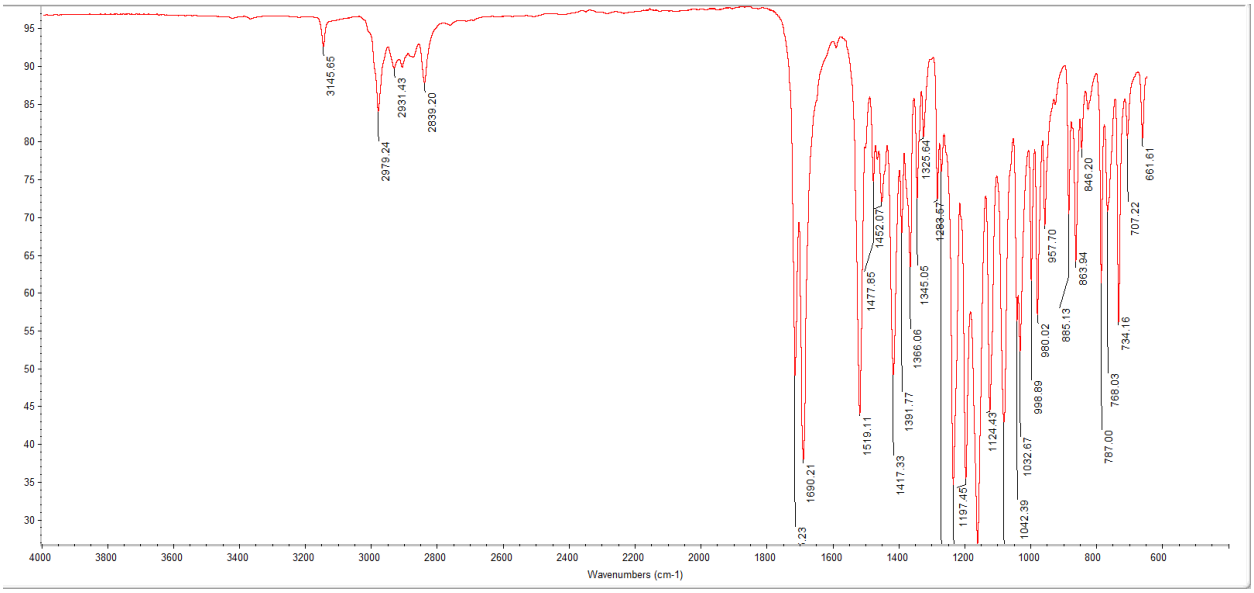


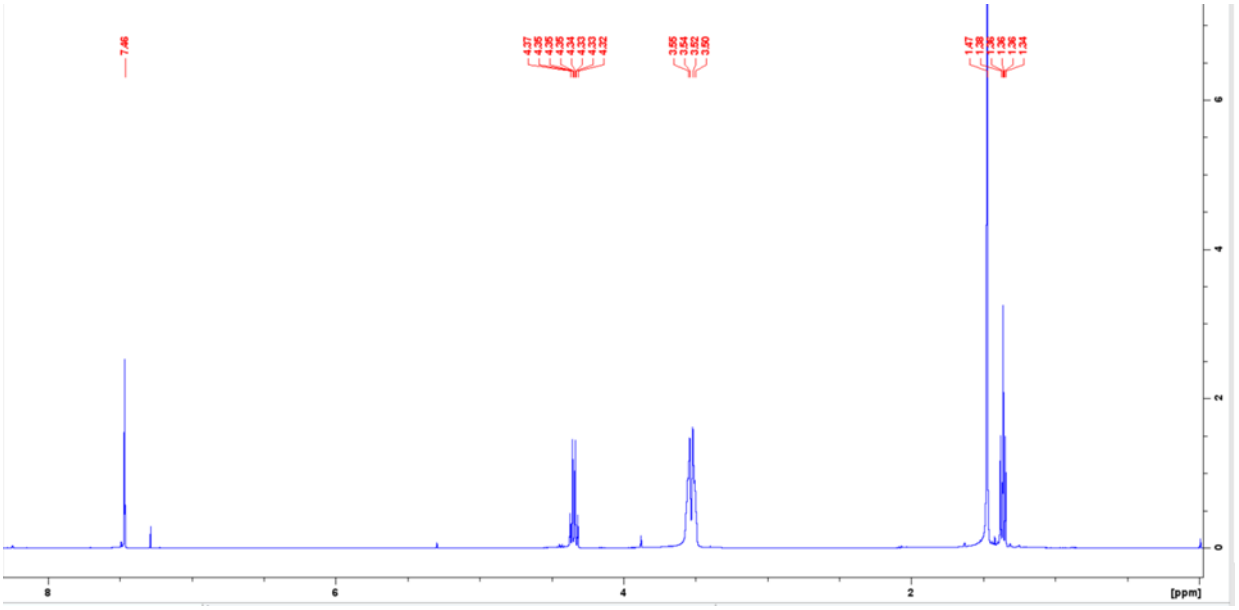
Fig S5: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 10.5

Spectral data of 11.5



IR (cm^{-1}): 3145 (w), 2979 (w), 2829 (w), 1700 (m), 1690 (s), 1519 (m), 1417 (m), 1219 (s), 1197 (s), 1130 (s), 1080 (m); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 7.46 (s, 1H), 4.35 (q, *J*=7.0 Hz, 2H), 3.52(m, 8H), 1.47(s, 9H), 1.36 (t, *J*=7.0 Hz, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 170.8, 161.6, 154.5, 144.0, 116.7, 80.3, 61.1, 48.3, 28.4; 14.3; ESI-MS: MH^+ = 342.1474 (expected MH^+ = 342.1409)




7.46
4.37
4.36
4.35
4.34
4.33
4.32
3.55
3.54
3.52
3.50
1.47
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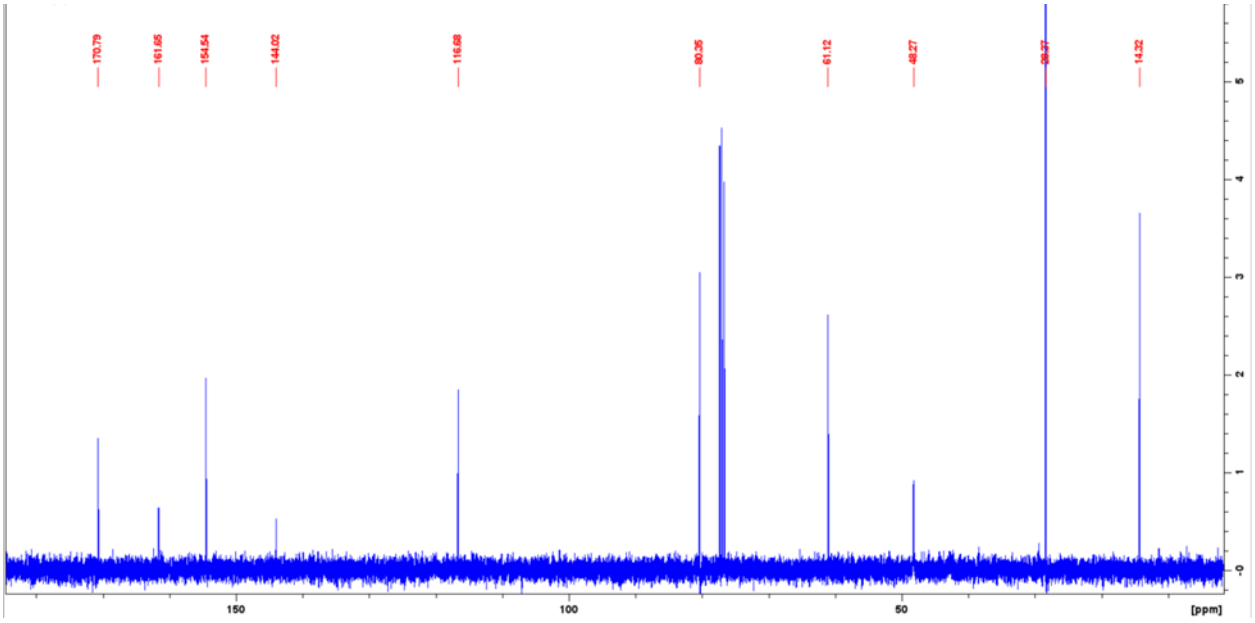
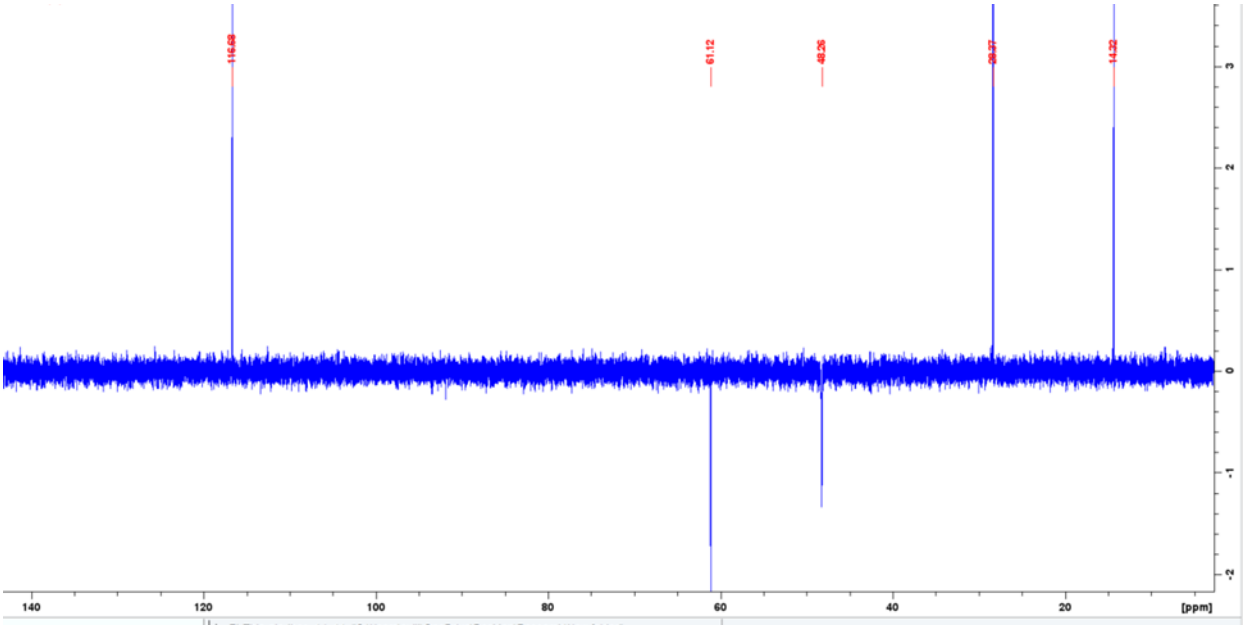
1.36
1.36
1.36
1.34
8
6
4
2
[ppm]


170.79
161.65
154.54
144.02
116.68
80.36
61.12
48.27
28.27
14.32
150
100
50
[ppm]



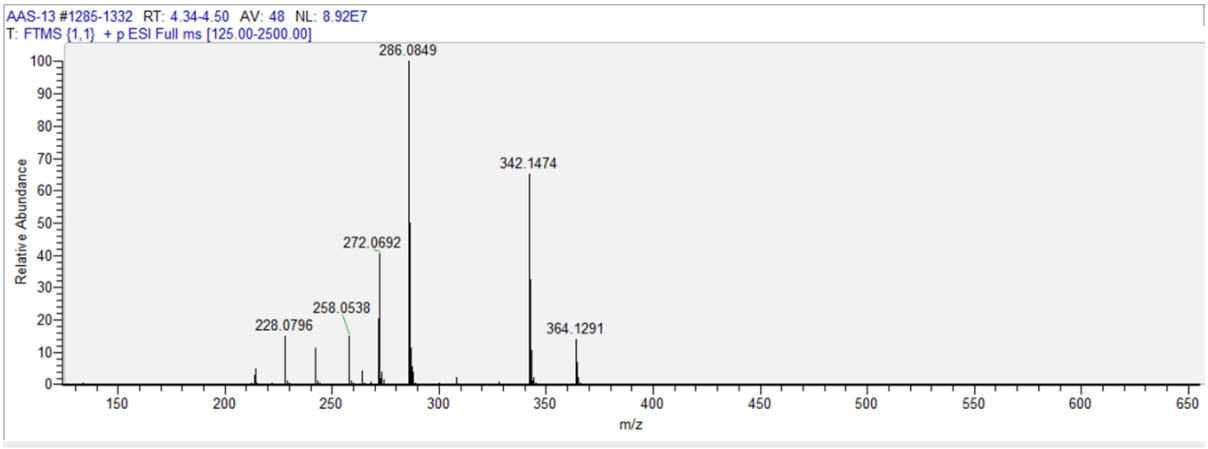
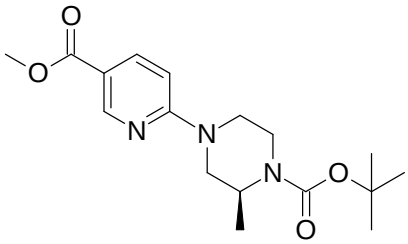


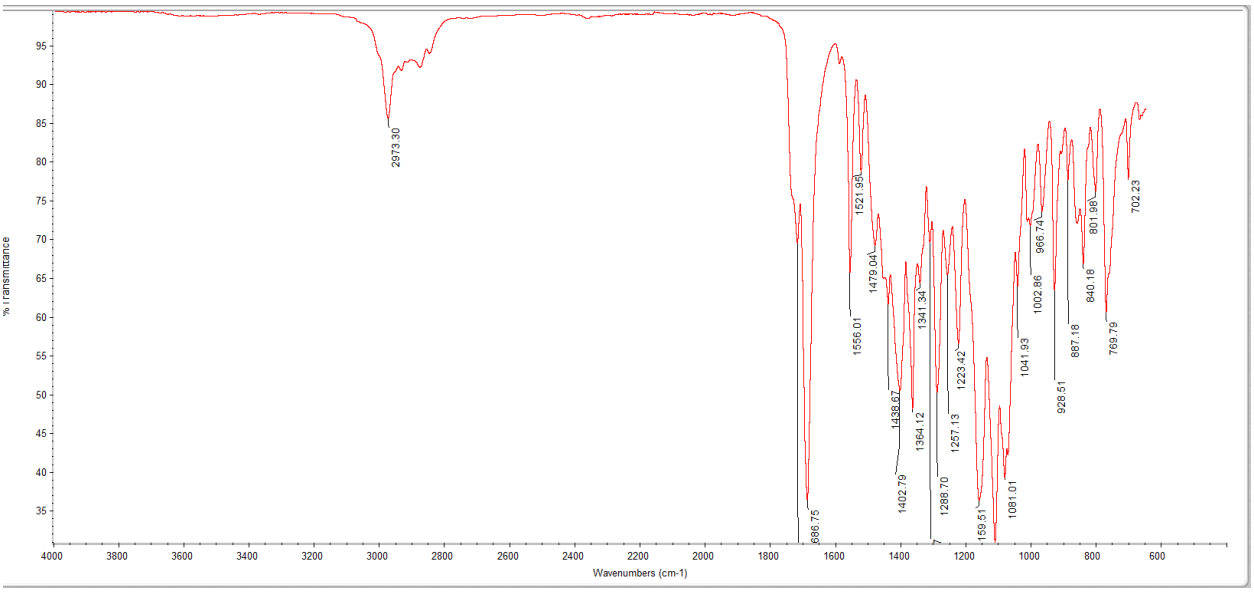
Fig S6: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 11.

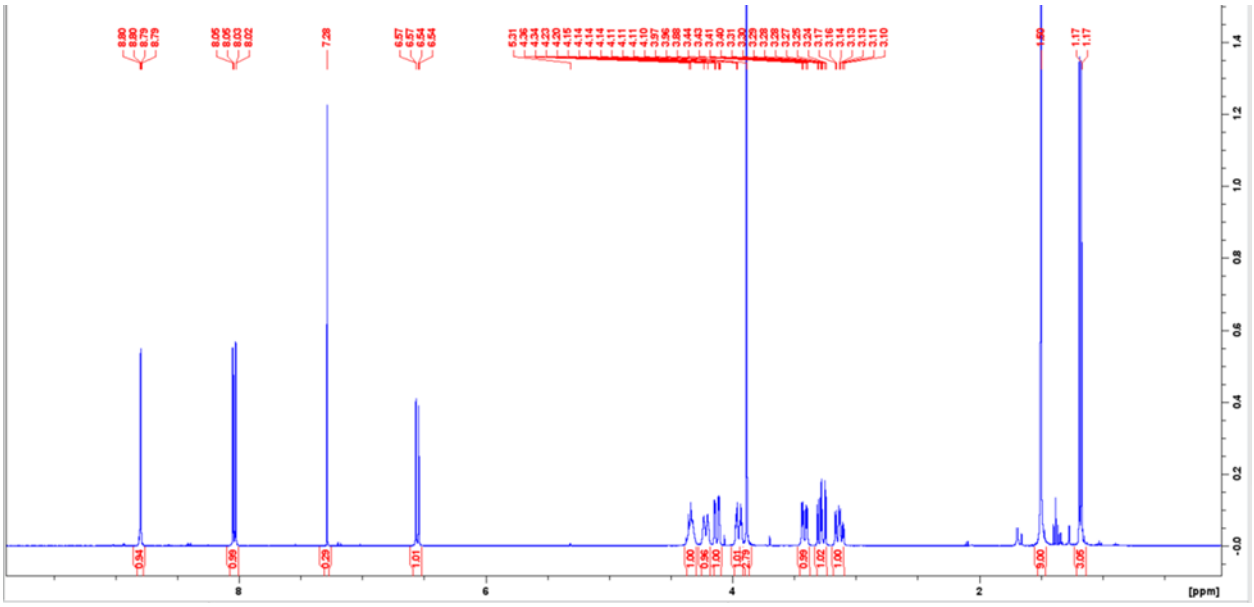
Spectral Data 1.6

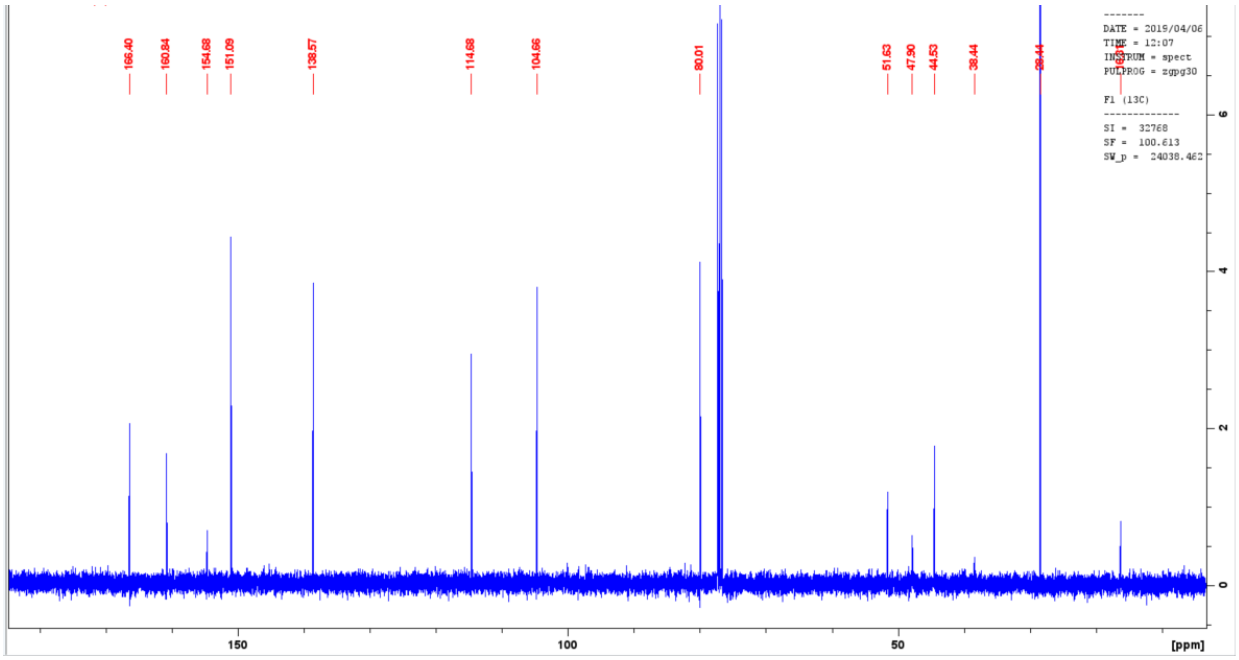


IR (cm^{-1}): 2973 (w), 1720 (w), 1686 (s), 1556 (w), 1438 (w), 1402 (w), 1159 (s), 1100 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.79 (dd, 1H), 8.03 (dd, 1H), 6.55 (dd, 1H), 4.35 (bs, 1H), 4.23-4.20(dm, 1H), 4.15-4.10 (dq, 1H), 3.97-3.92 (dt, 1H), 3.88 (s, 3H), 3.44-3.39(dd, 1H), 3.31-3.24 (m, 1H), 3.17-3.09 (td, 1H), 1.50 (s, 9H),

1.71 (d, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.4, 160.8, 154.7, 151.1, 138.6, 114.7, 104.7, 80.0, 51.6, 47.9, 44.5, 28.4; 16.3; ESI-MS: MH^+ = 336.1916 (expected MH^+ = 336.1845)






166.40
160.84
154.68
151.09
138.57
114.68
104.66
80.01
51.63
47.90
44.53
38.44
29.44
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PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
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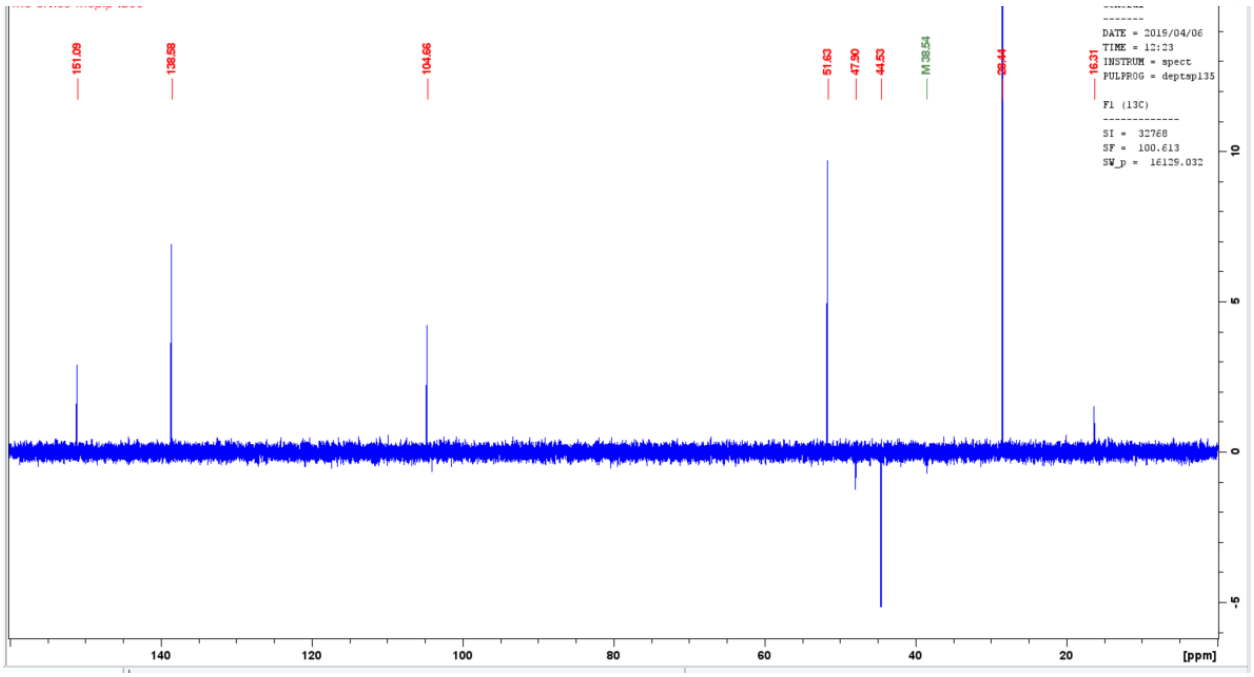
100
50
[ppm]


151.09
138.58
104.66
51.63
47.90
44.53
M 38.54
29.44
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TIME = 12:23
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PULPROG = deptsp135
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SF = 100.613
SW_p = 16129.032
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120
100
80
60
40
20
[ppm]

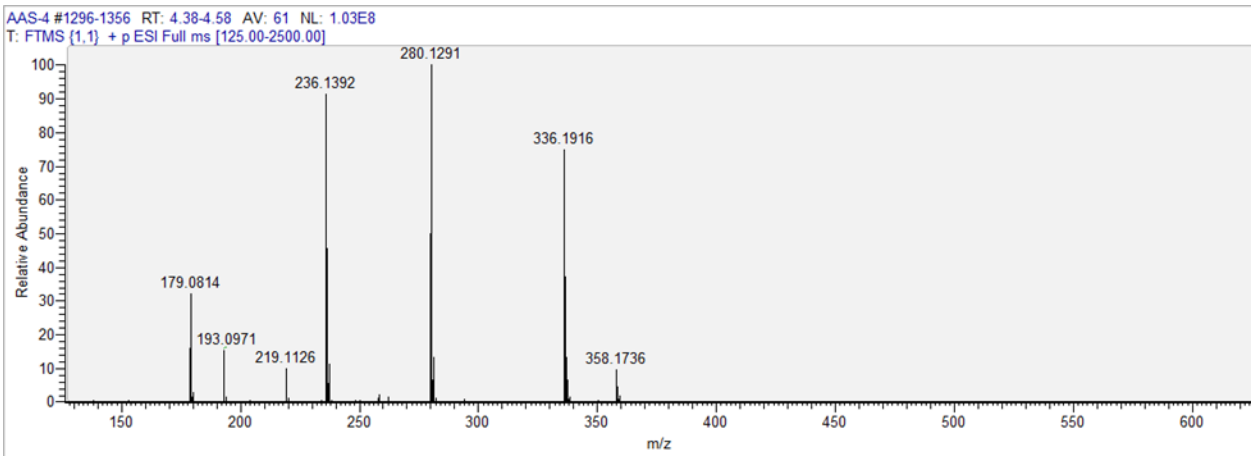
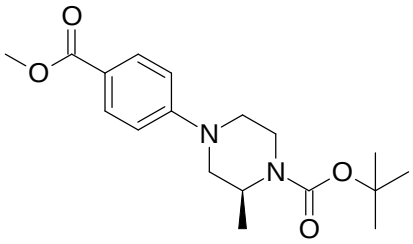
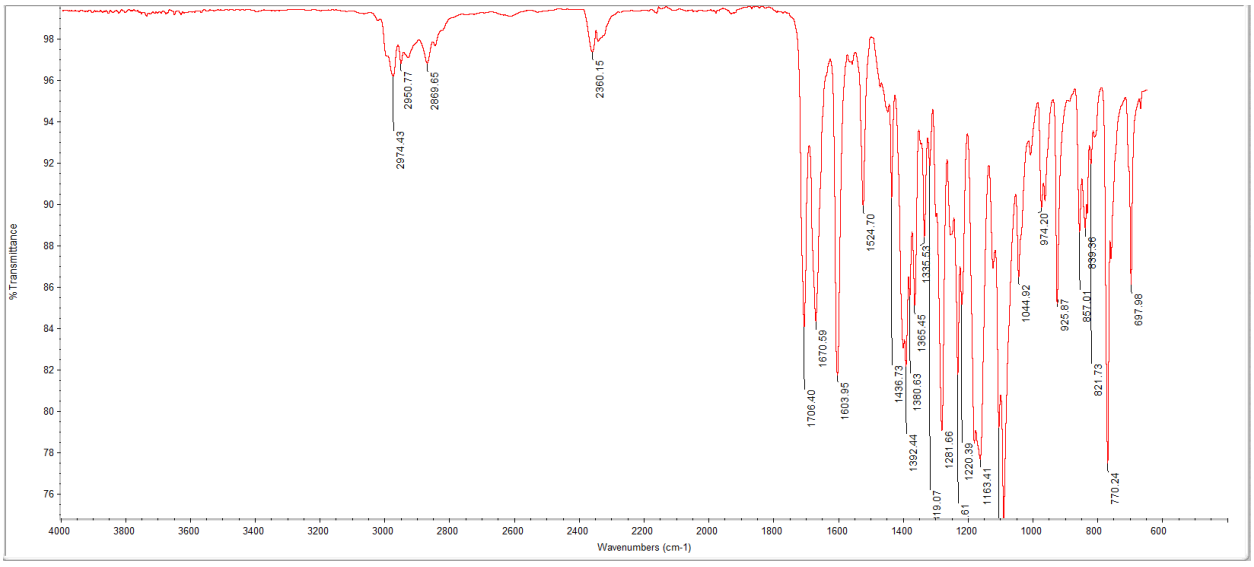


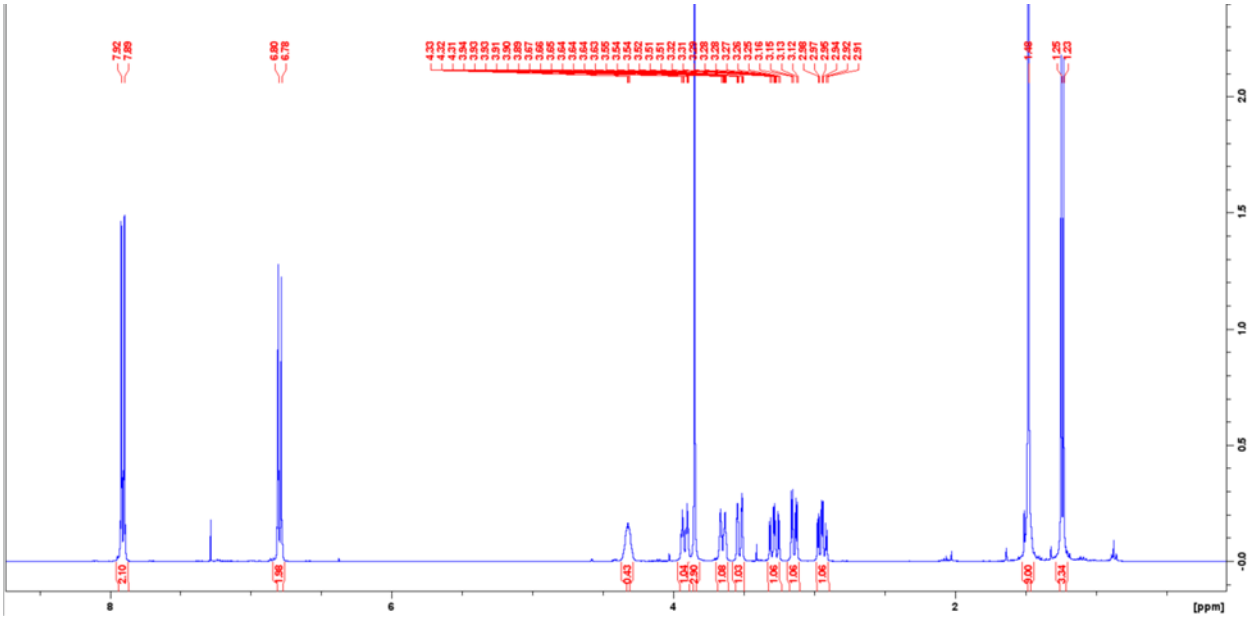
Fig S7: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 1.6

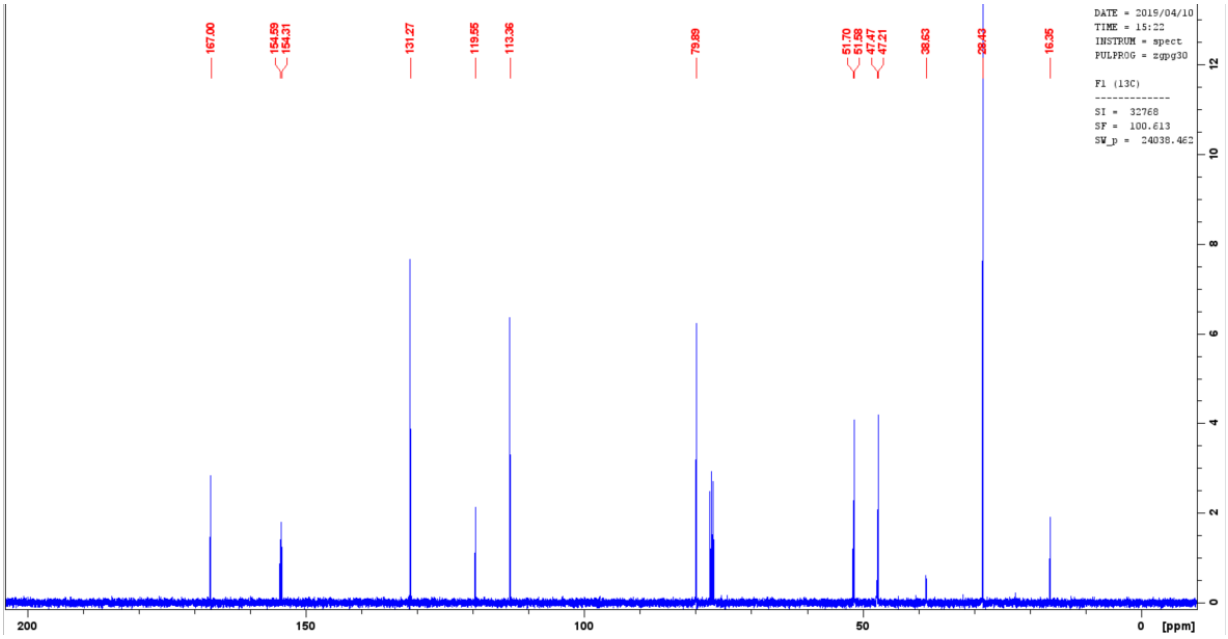
Spectral data of 8.6



IR (cm^{-1}): 2974 (w), 1706 (m), 1670 (m), 1603(m), 1392 (m), 1281 (m), 1220 (m), 1100 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 7.90 (d, 2H), 6.79 (d, 2H), 4.32(m, 1H), 3.94 -3.89 (td, 1H), 3.84 (s, 3H), 3.66-3.63 (dm, 1H), 3.55-3.51 (dm, 1H), 3.31-3.25 (m, 1H), 3.16-3.12 (dd, 1H), 2.97-2.91 (td, 1H), 1.47(s, 9H), 1.23 (d, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.4, 160.8, 154.7, 151.1, 138.6, 114.7.3, 104.6, 80.0, 51.6, 47.9, 44.5, 28.4; 16.3; ESI-MS: MH^+ = 335.1963 (expected MH^+ = 335.1893)




7.92
7.89
6.80
6.78
1.49
1.25
1.23
2.10
1.98
0.43
1.04
2.90
1.06
1.03
1.06
1.06
1.06
6.00
3.34
8
6
4
2
[ppm]


167.00
154.59
154.31
131.27
119.55
113.36
79.89
51.70
51.58
47.47
47.21
38.63
28.43
16.35
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TIME = 15:22
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PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
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100
50
0
[ppm]

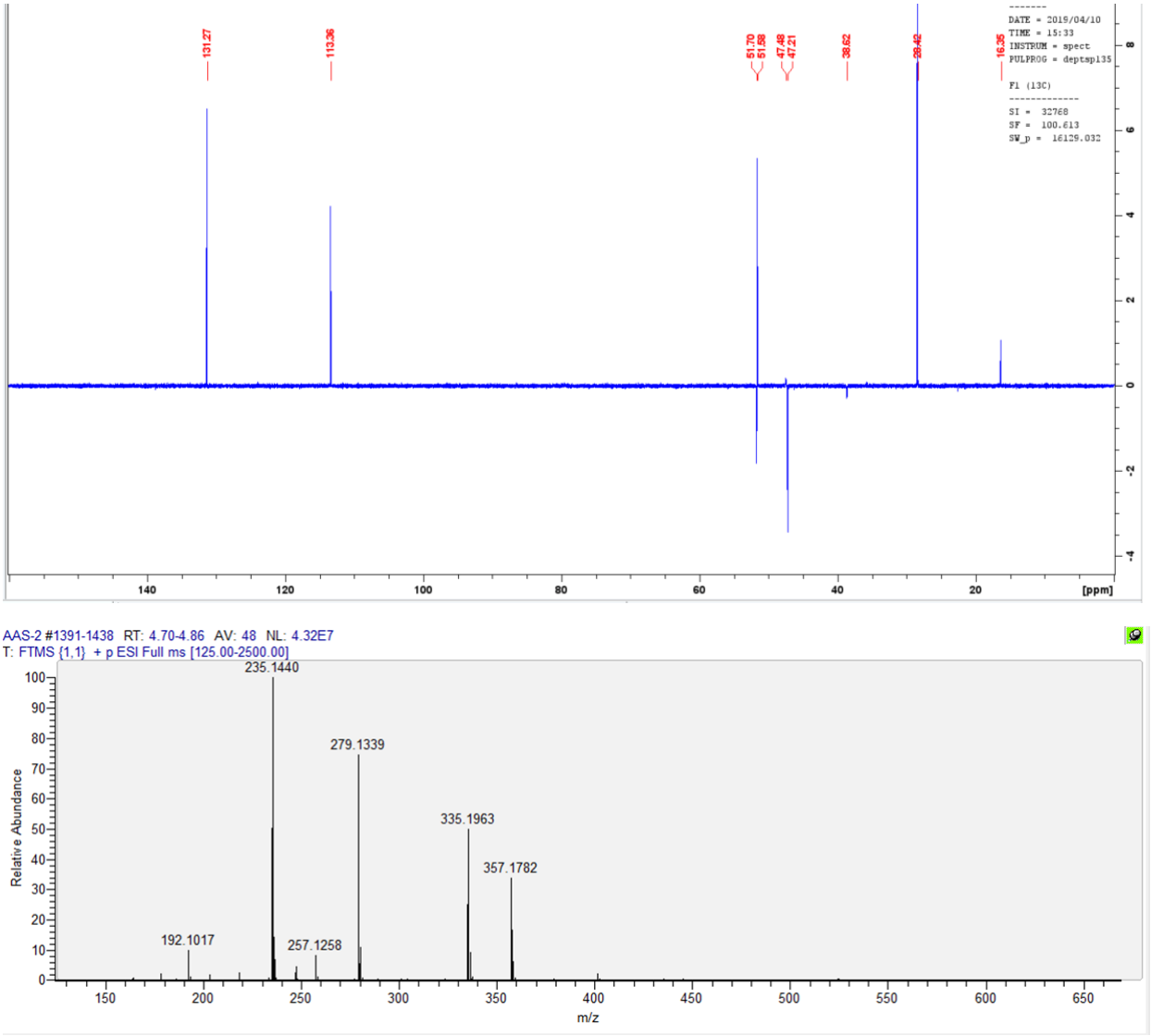
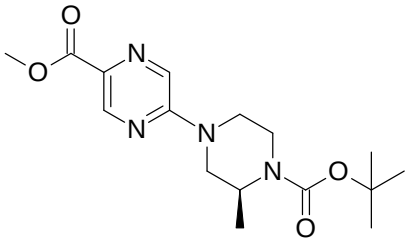


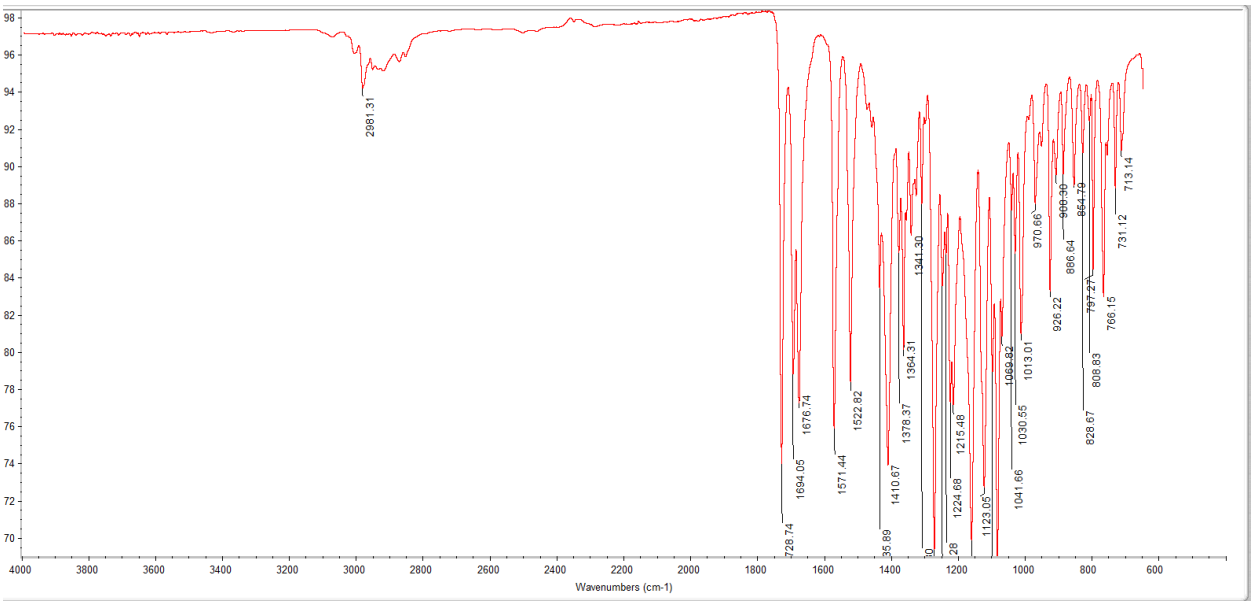
Fig S8: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 8.6

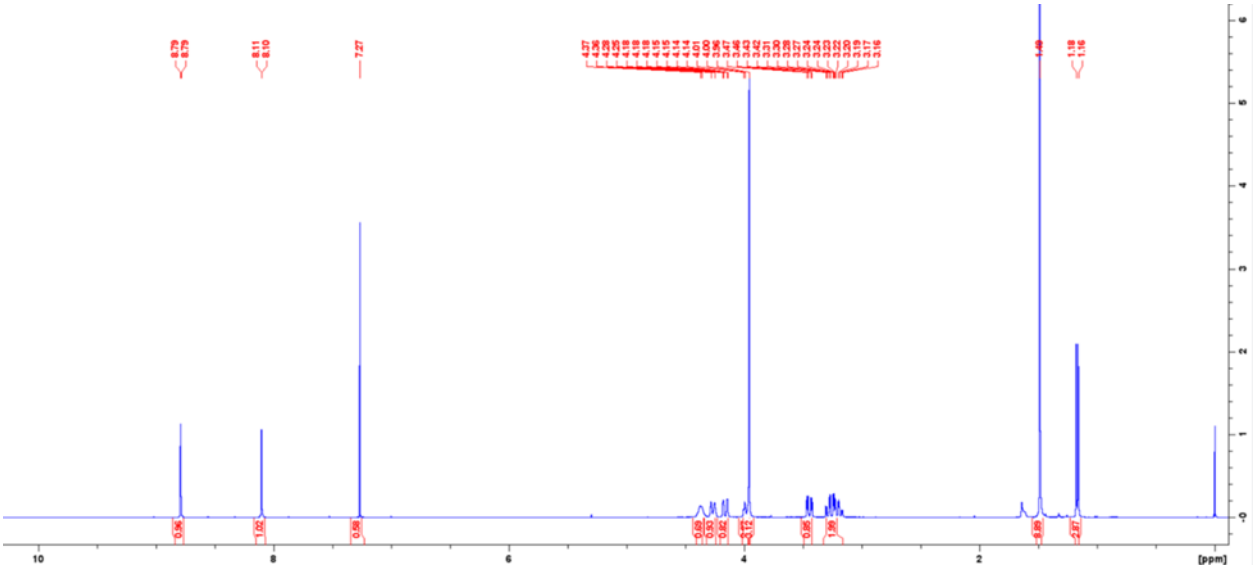
Spectral Data of 9.6

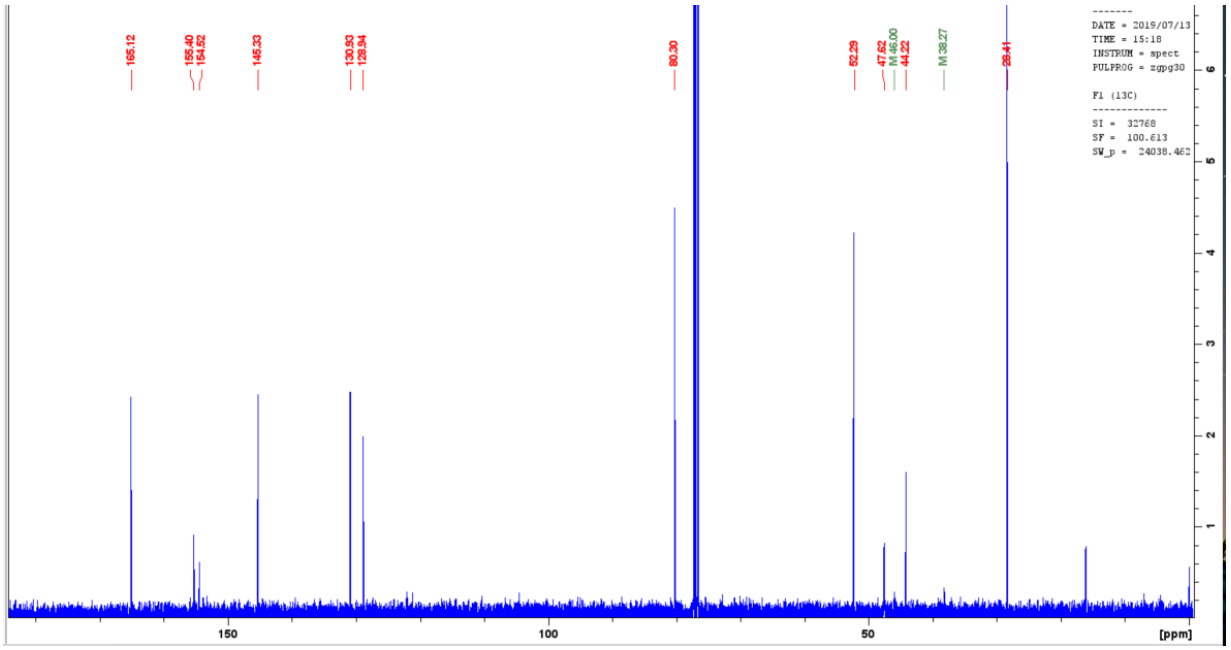


IR (cm^{-1}): 2981 (w), 1728 (s), 1694 (m), 1676(m), 1522 (m), 1470 (s), 1410 (s), 1270 (s), 1160 (s), 1080 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.79 (d, *J*=1.3, 1H), 8.10 (d, *J*=1.3, 1H), 4.37 (bs, 1H), 4.29-4.26 (d, *J*=11.7, 1H), 4.18 – 4.14 (m, 1H), 4.0 (m, 1H), 3.96 (s, 3H), 3.47 – 3.42 (dd, *J*=4.1, 13.4, 1H), 3.31 – 3.16 (m, 2H),

1.50 (s, 9H), 1.18 (d, *J*=6.7, 3H), CNMR (100 MHz, $CDCl_3$, [ppm]): 165.1, 155.4, 154.5, 145.3, 130.9, 128.9, 80.3, 52.3, 47.6, 44.2, 28.4, 16.1; ESI-MS: MH^+ = 337.1863 (expected MH^+ = 337.1798)






165.12
155.40
154.82
145.33
130.93
128.94
80.30
52.29
47.62
M 46.00
44.22
M 38.27
28.41
DATE = 2019/07/13
TIME = 15:18
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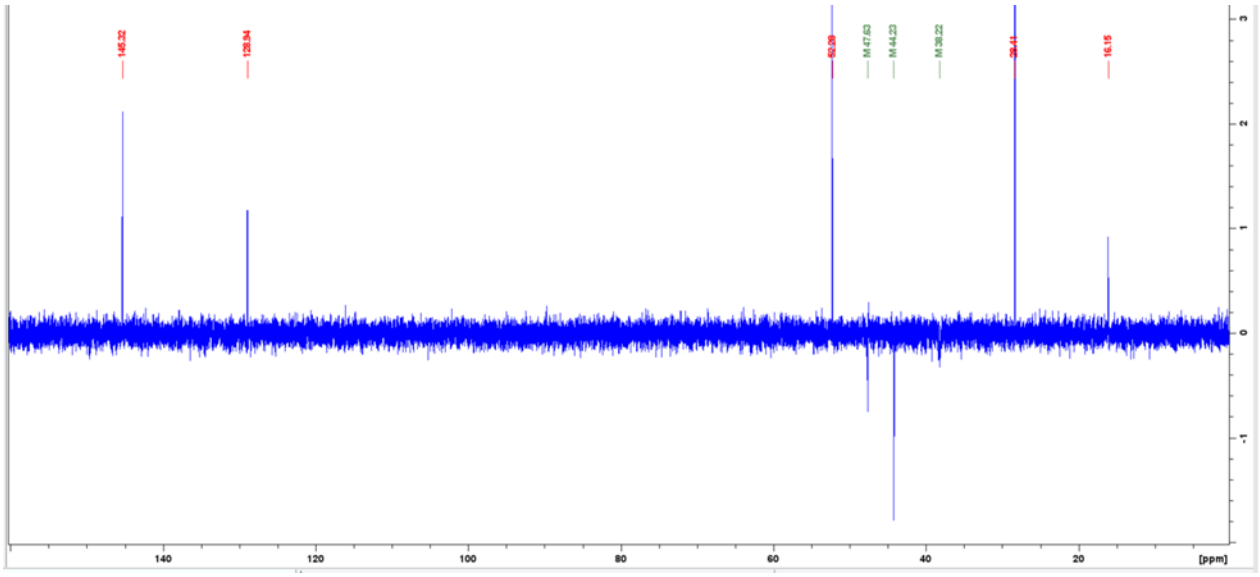
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
150
100
50
[ppm]


145.32
129.94
52.29
M 47.63
M 44.23
M 38.22
28.41
15.15
140
120
100
80
60
40
20
[ppm]

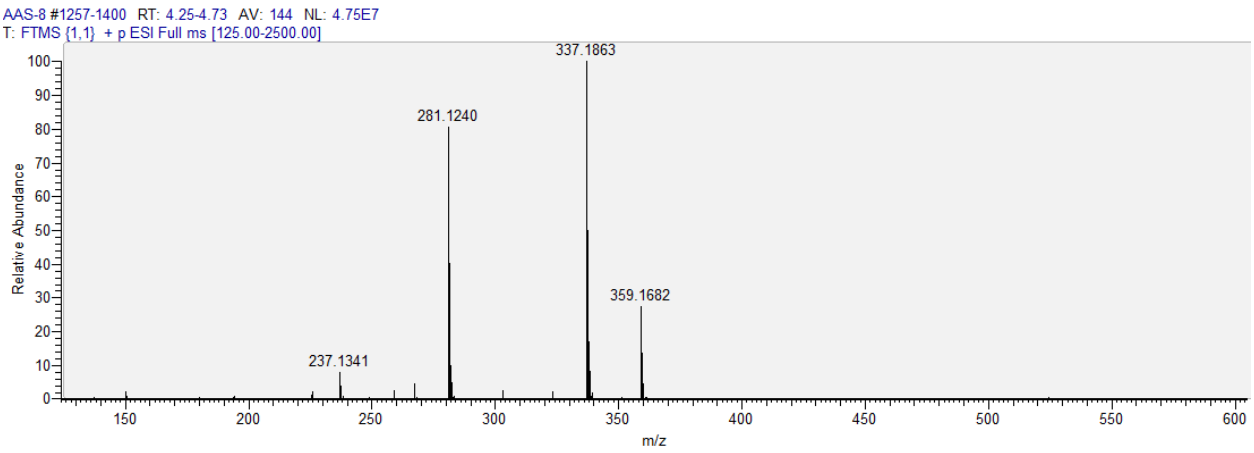
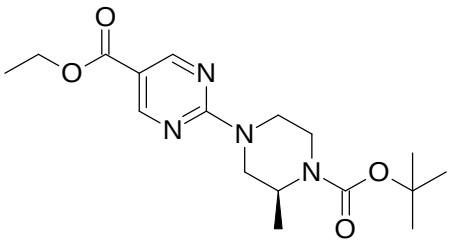
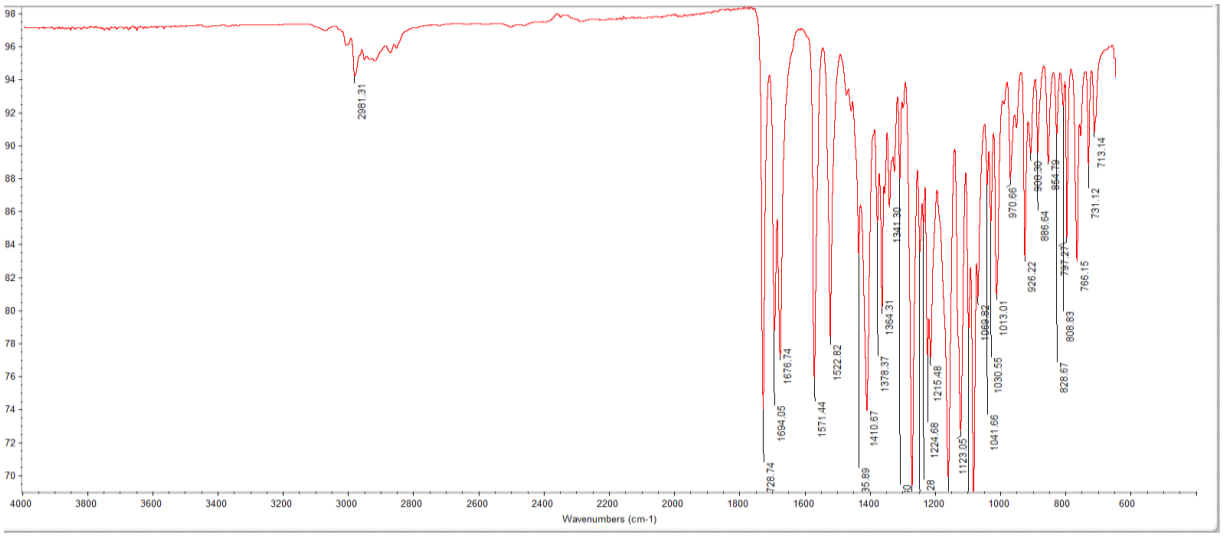


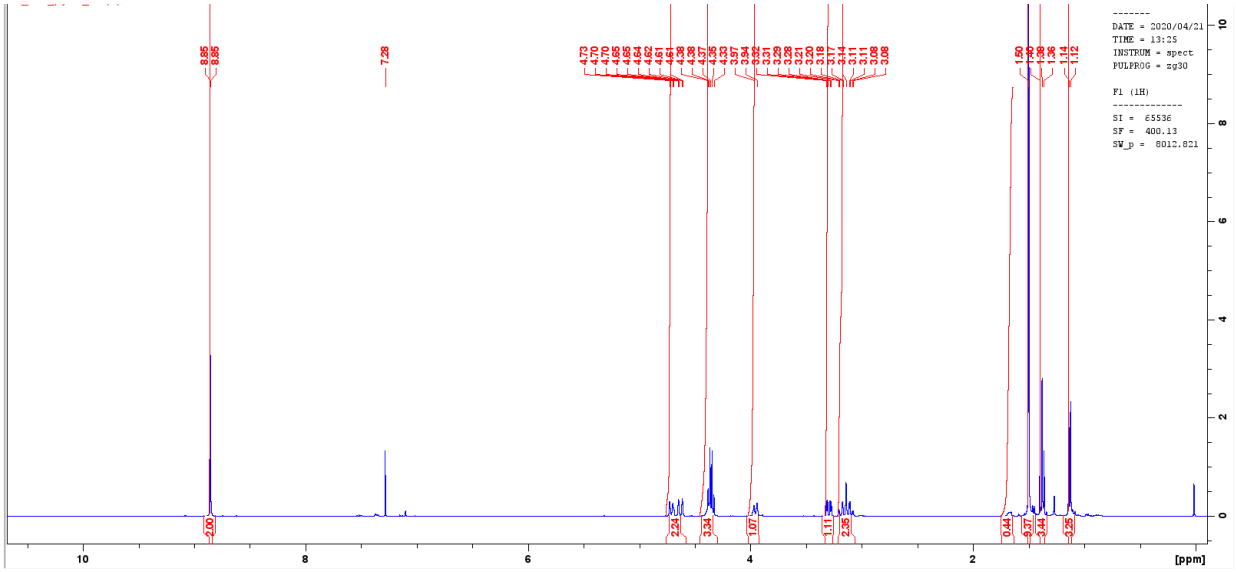
Fig S9: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 9.6

Spectral data of 10.6



IR (cm^{-1}): 2981 (w), 1728 (s), 1694 (s), 1676 (s), 1552 (m), 1410 (s), 1225 (s), 1123 (m), 1075 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.85 (d, 2H), 4.73 – 4.69 (bd, 1H), 4.65 – 4.61 (dt, 1H), 4.33-4.38 (m, 3H), 3.95 (bd, 1H), 3.31-3.27 (dd, *J*=3.9, 13.4, 1H), 3.21 – 3.08 (m, 2H), 1.50 (s, 9H), 1.38 (t, *J*=7.15, 3H), 1.13 (d, *J*= 6.7, 3H), CNMR (100 MHz, $CDCl_3$, [ppm]): 164.8, 162.9, 159.8, 154.6, 112.8, 80.0, 60.8, 47.6, 47.5, 43.8, 38.4; 28.4, 15.5, 14.3; ESI-MS: MH^+ = 350.2024 (expected MH^+ = 350.1954)

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SI = 65536
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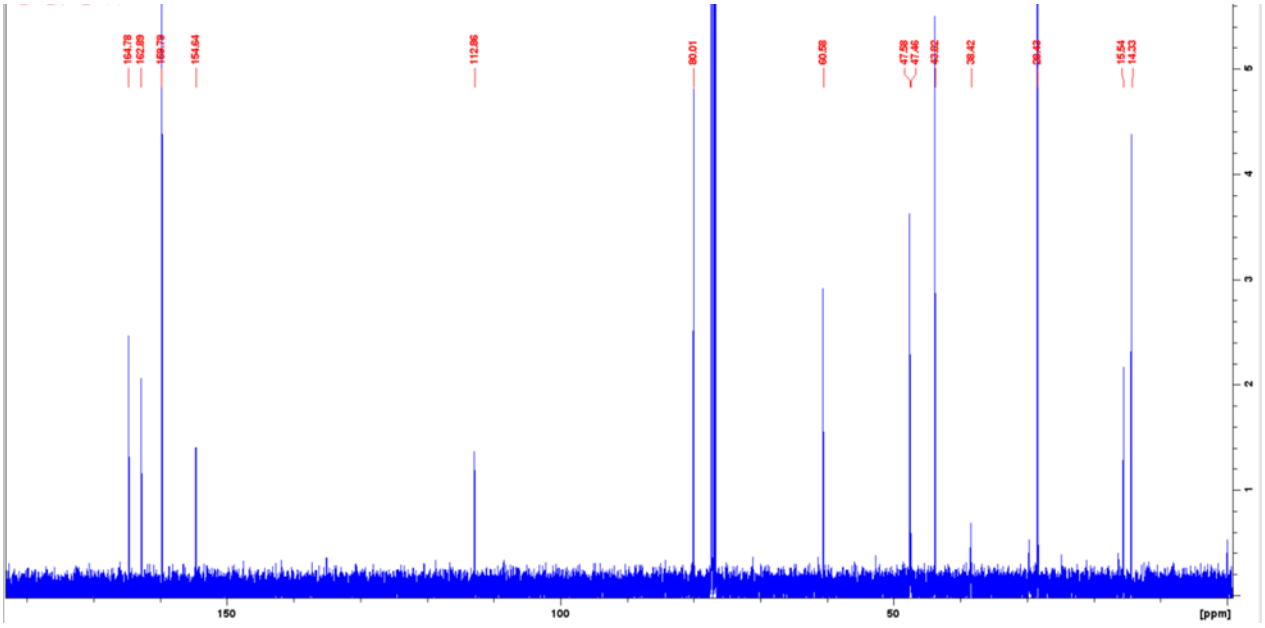
SW_p = 8012.821
[ppm]


[ppm]

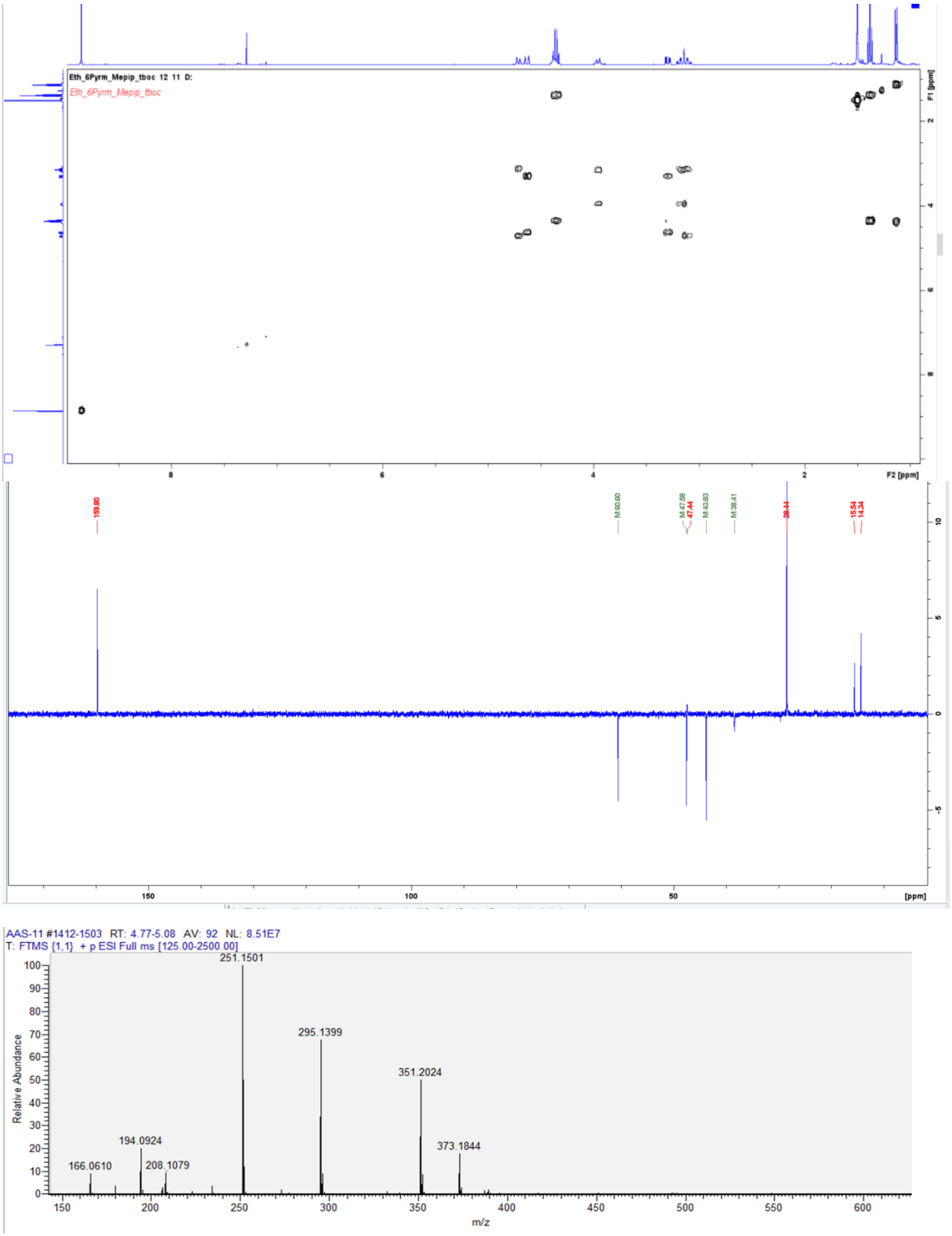
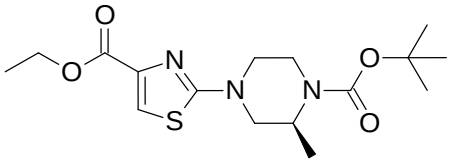
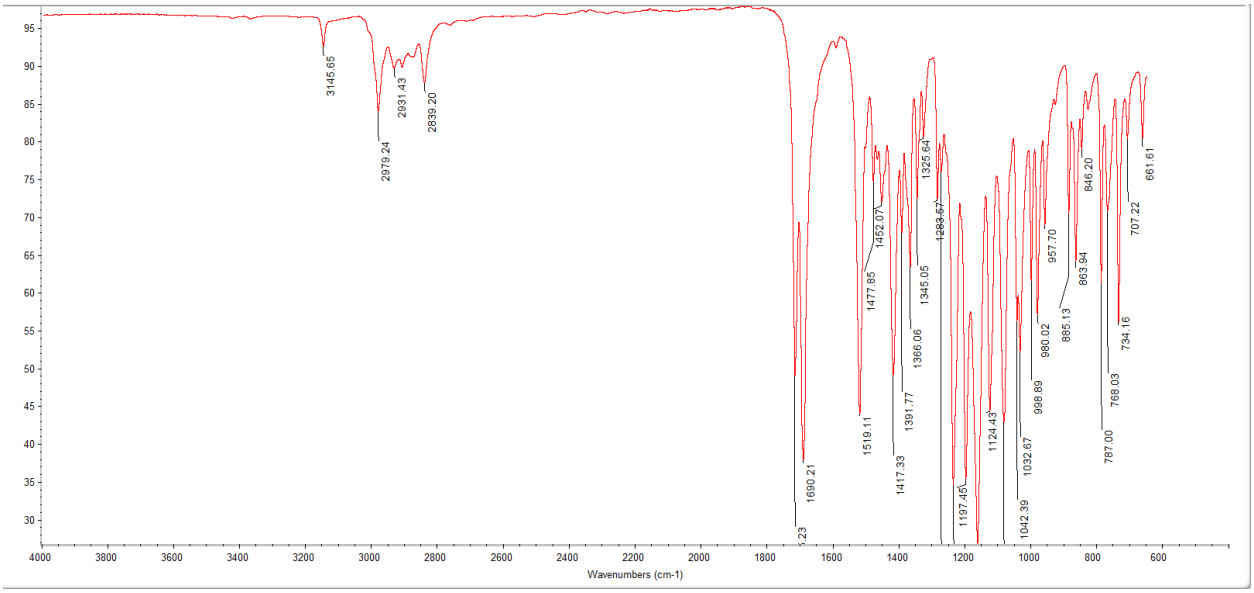


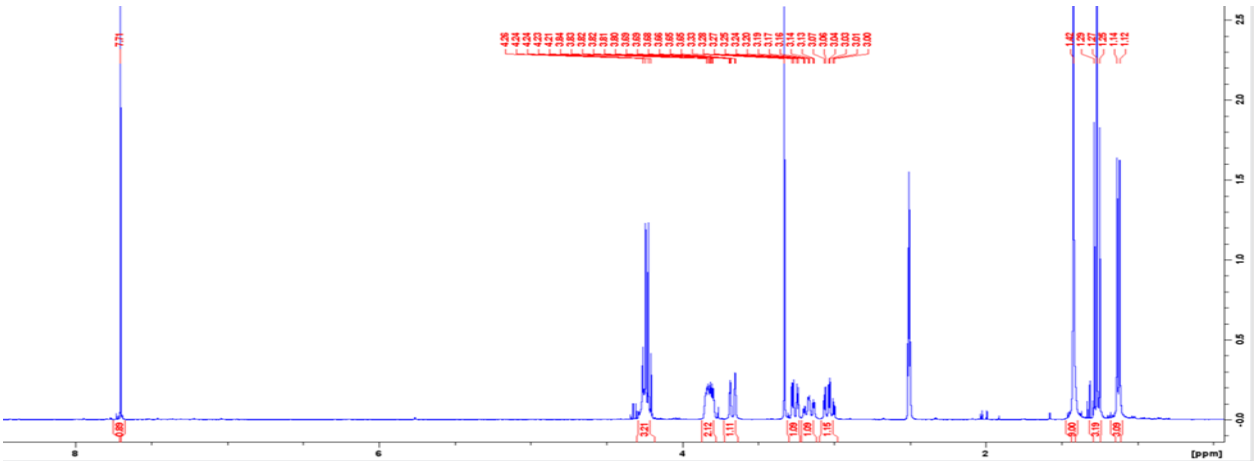
Fig S10: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, ESI-MS of compound 10.6

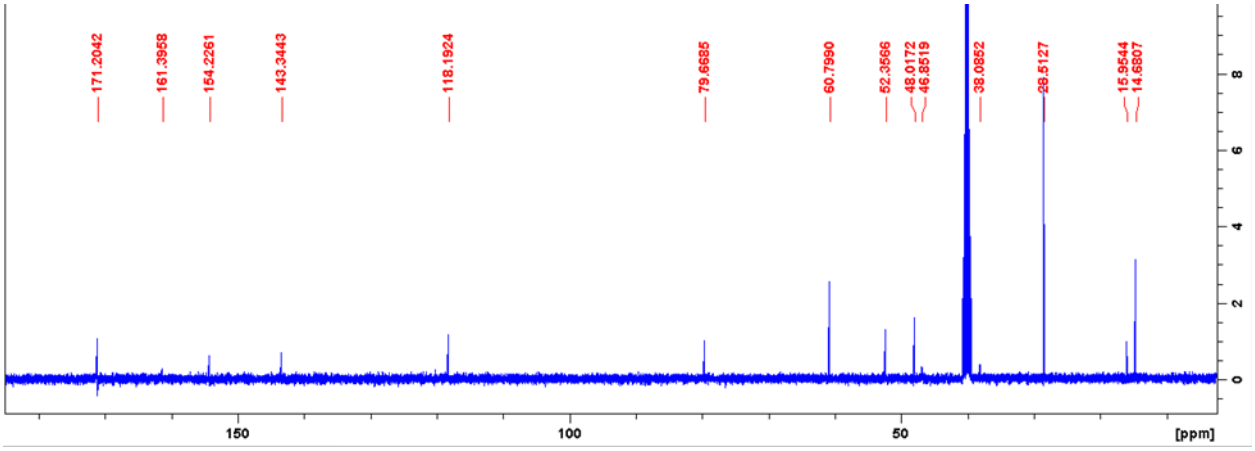
Spectral Data 11.6

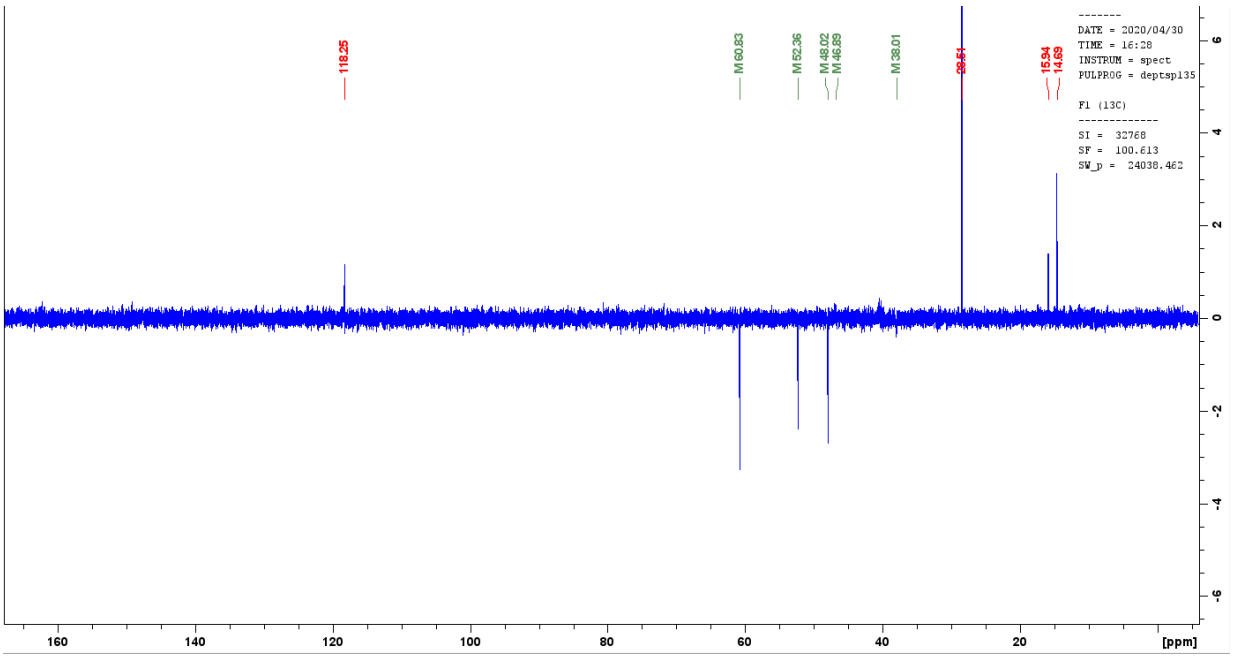


IR (cm^{-1}): 3145 (w), 2979 (w), 2829 (w), 1700 (m), 1690 (s), 1519 (m), 1417 (m), 1219 (s), 1197 (s), 1130 (s), 1080 (m); NMR (400 MHz, DMSO-D6, [ppm]) δ: 7.71 (s, 1H), 4.21-4.26 (m, 3H), 3.84-3.80 (m, *J*=7.1, 2H), 3.69-3.65 (m, 1H), 3.28-3.2 (dd, *J*=4.0, 13.0, 1H), 3.20-3.13 (m, 1H), 3.07 - 3.00 (td, *J*=3.5, 11.7, 1H), 1.42 (s, 9H); 1.27 (t, *J*= 7.1, 3H), 1.12 (d, *J*= 6.7, 3H); CNMR (100 MHz, DMSO-D6, [ppm]): 171.2, 161.4, 154.2, 143.3, 118.2, 79.7, 60.8, 52.4, 48.0, 46.8, 38.1, 28.5, 15.9, 14.7; ESI-MS: MH^+ = 356.1631 (expected MH^+ = 356.1566)









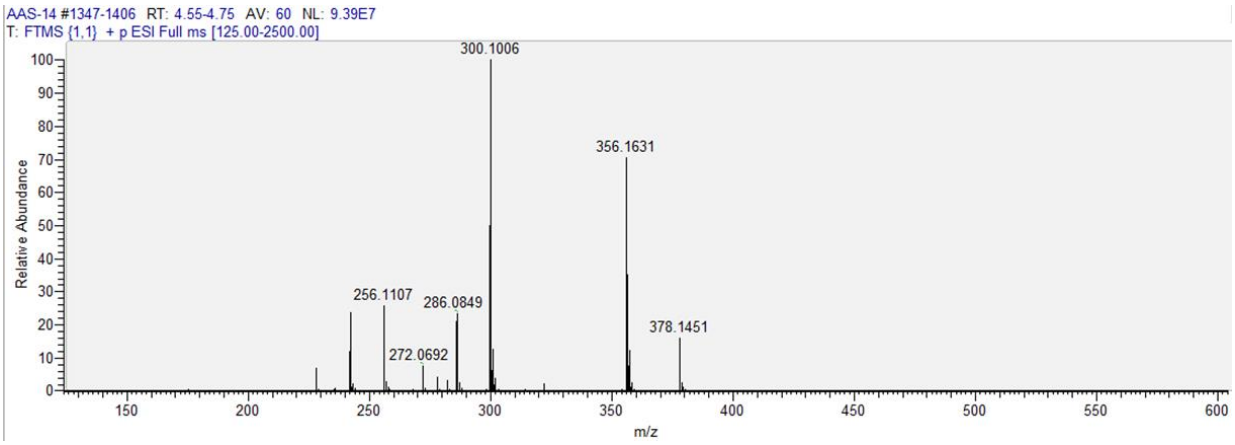
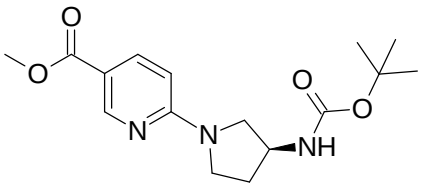
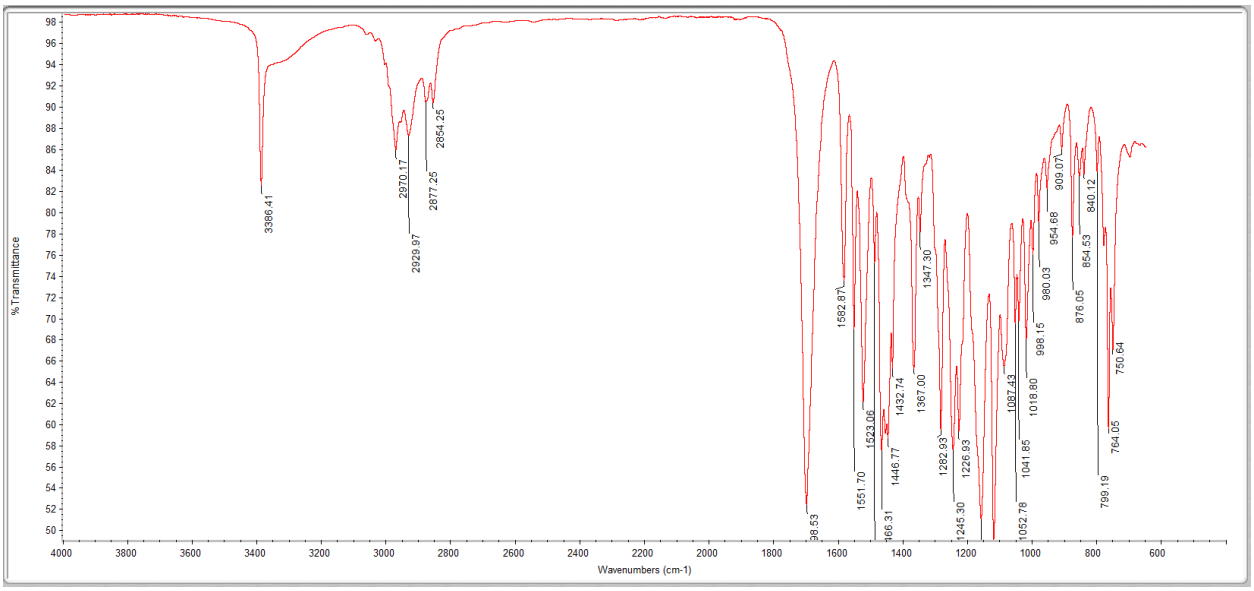


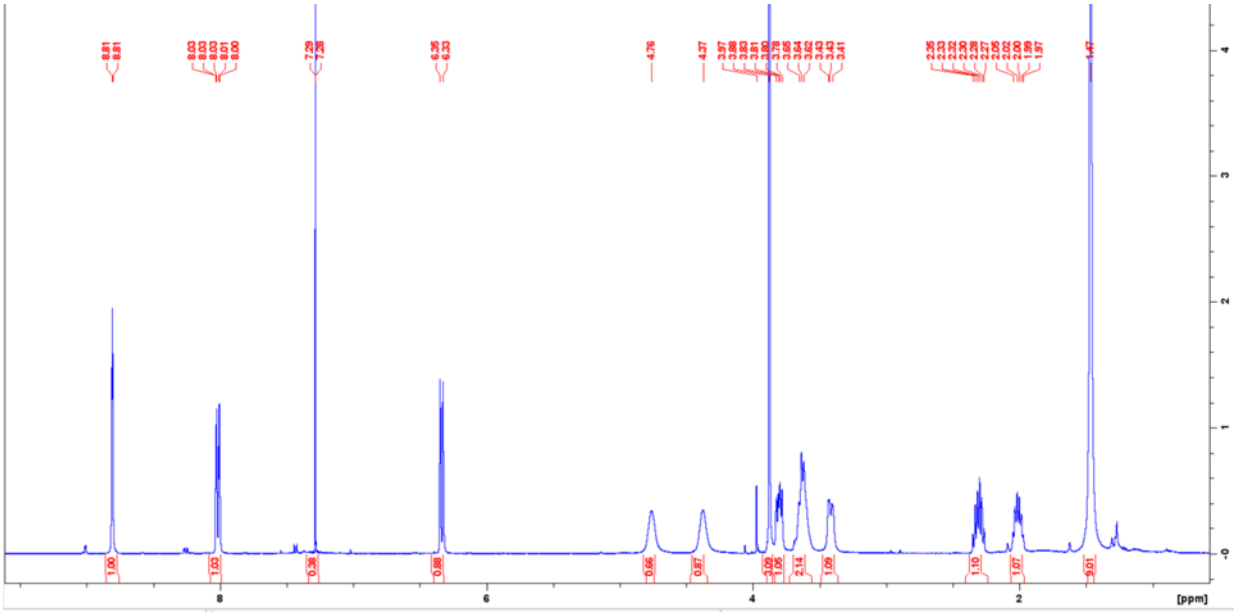
Fig S11: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 11.6

Spectral data of 1.7



IR (cm^{-1}): 3386 (w), 2970 (w), 1698(s), 1523 (m) 1466(s), 1446(s), 1367(m), 1160(s), 1120(s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.80 (d, *J*=2.2, 1H), 8.03-8.00 (dd, *J*= 2.2, 8.8, 1H), 6.33-6.35 (d, *J*= 8.8, 1H), 4.76(bs, 1H), 4.37 (bs, 1H), 3.88 (s, 3H), 3.83-3.78 (dd, 1H), 3.66-3.62 (m, 2H), 3.43-3.40 (m, 1H), 2.35-2.26 (sext, *J*=6.6, 1H), 2.05-1.97 (sext, *J*=6.6, 1H), 1.47 (s, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.7, 158.8, 155.3, 151.4, 138.1, 114.1,105.4, 52.8, 51.6, 44.9, 31.6, 28.4; ESI-MS: MH^+ = 322.1762 (expected MH^+ = 322.1689)





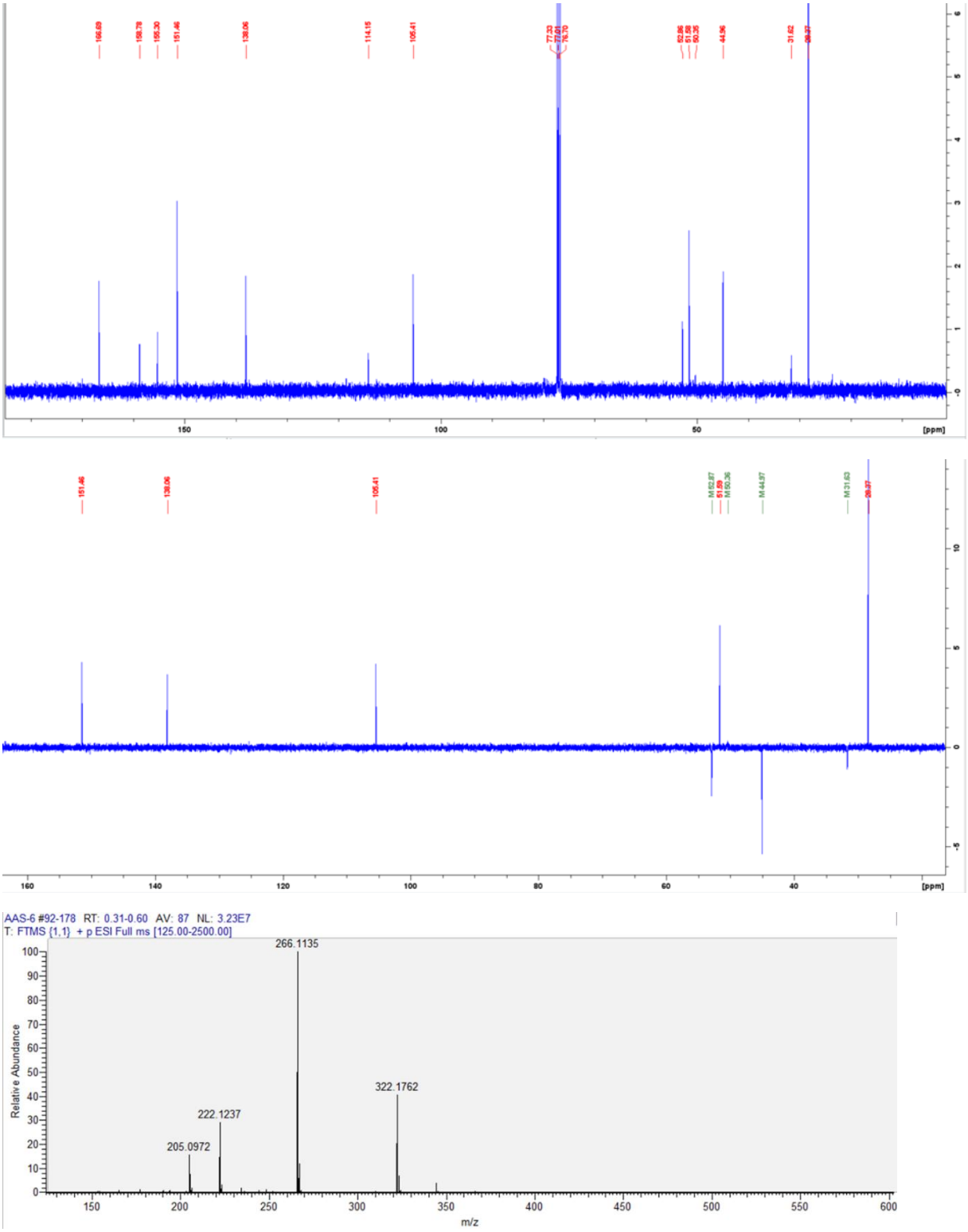
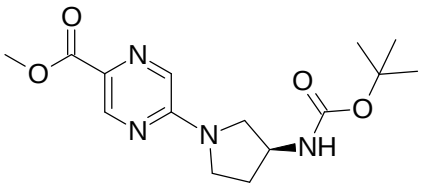
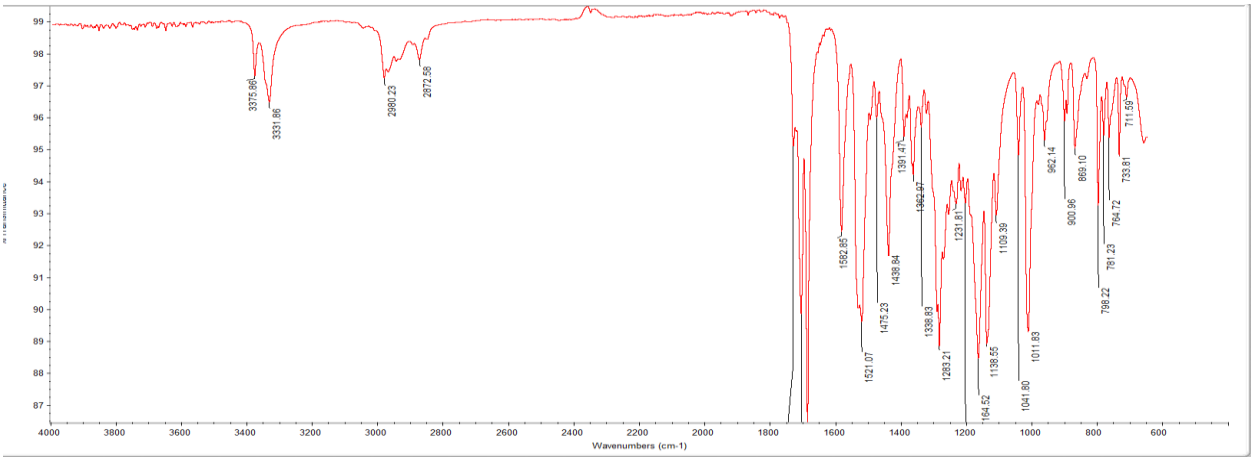


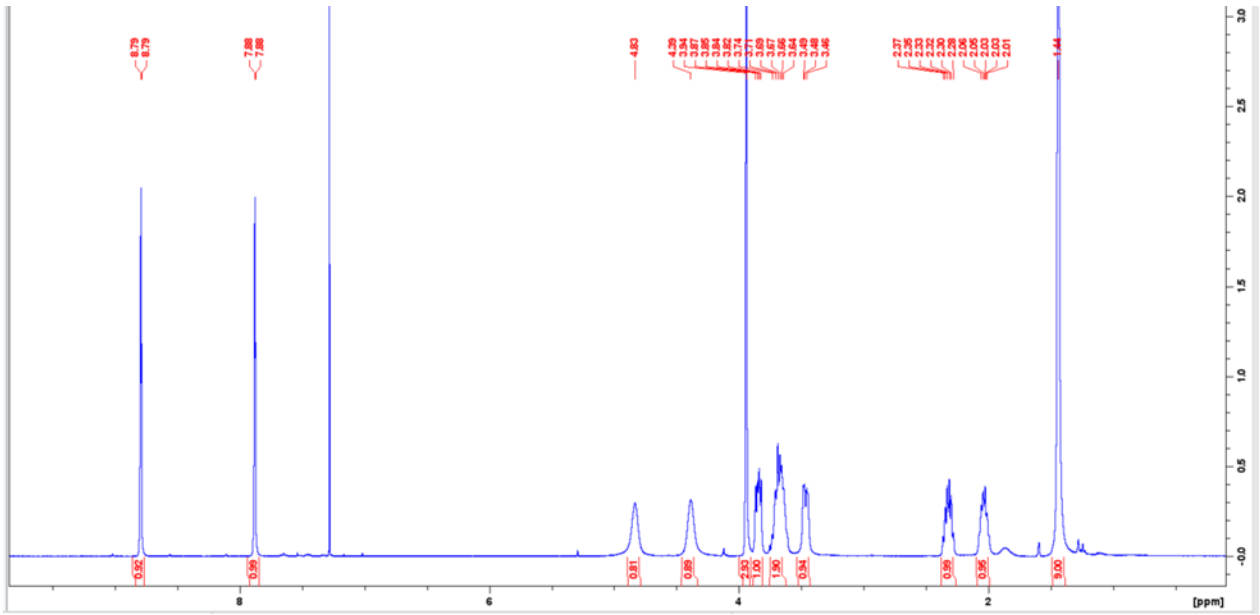
Fig S12: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 1.7

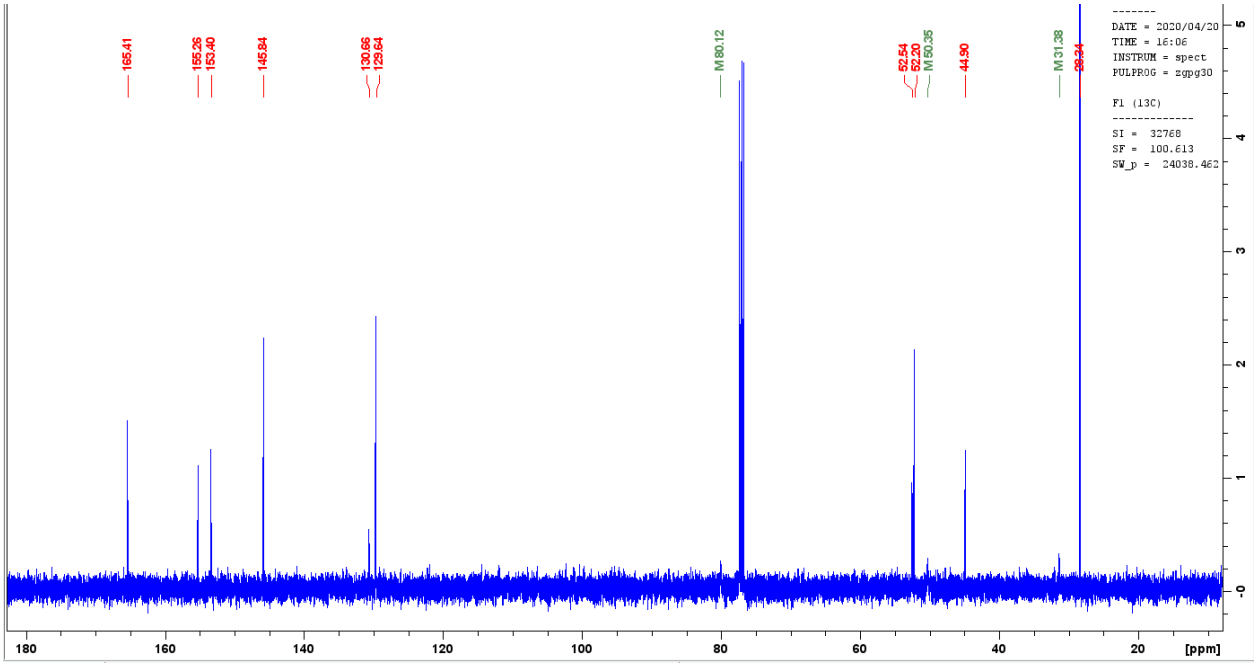
Spectral data of 9.7

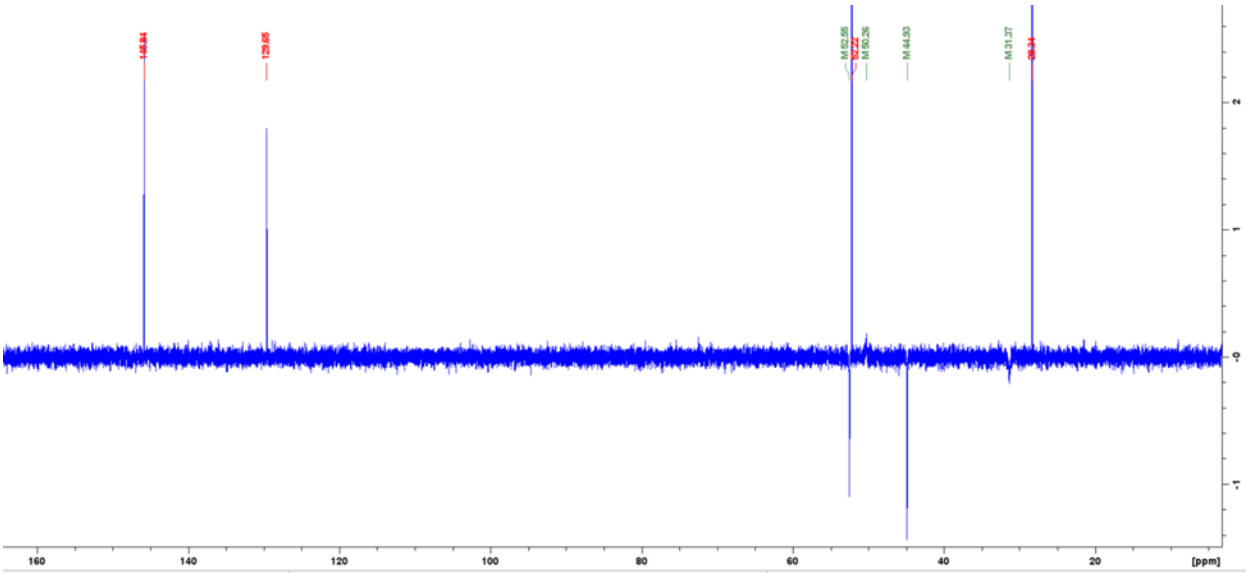


IR (cm^{-1}): 3375(w), 3331(w), 2980(s), 2872(w), 1710(s), 1698(s),1582(w), 1521 (m), 1283(m),1164 (m), 1138(m), 1011(m) ; NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.79 (d, *J*=2.5, 1H), 7.88 (d, *J*=2.5, 1H), 4.83 (bs, 1H), 4.38 (bs, 1H), 3.94 (s, 3H), 3.87-3.82 (dd, *J*=6.2, 1H), 3.74-3.64 (m, 2H), 3.49-3.46 (dd, *J*=6.2, 1H), 2.37-2.28 (sext, *J*=6.6, 1H), 2.06-2.01 (sext, *J*=6.6, 1H), 1.44 (s, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]): 165.4, 155.3, 153.4, 145.8, 130.6, 129.6, 80.1, 52.5, 52.2, 44.9, 31.4, 28.3; ESI-MS: Observed MH^+ = 323.1709 (Expected MH^+ = 323.1641)






165.41
155.26
153.40
145.84
130.66
129.64
M 80.12
52.54
52.30
M 50.35
44.90
M 31.38
29.34
DATE = 2020/04/20
TIME = 16:06
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
180
160
140
120
100
80
60
40
20
[ppm]


145.84
129.65
M 52.55
52.22
M 50.26
M 44.93
M 31.37
29.34
160
140
120
100
80
60
40
20
[ppm]

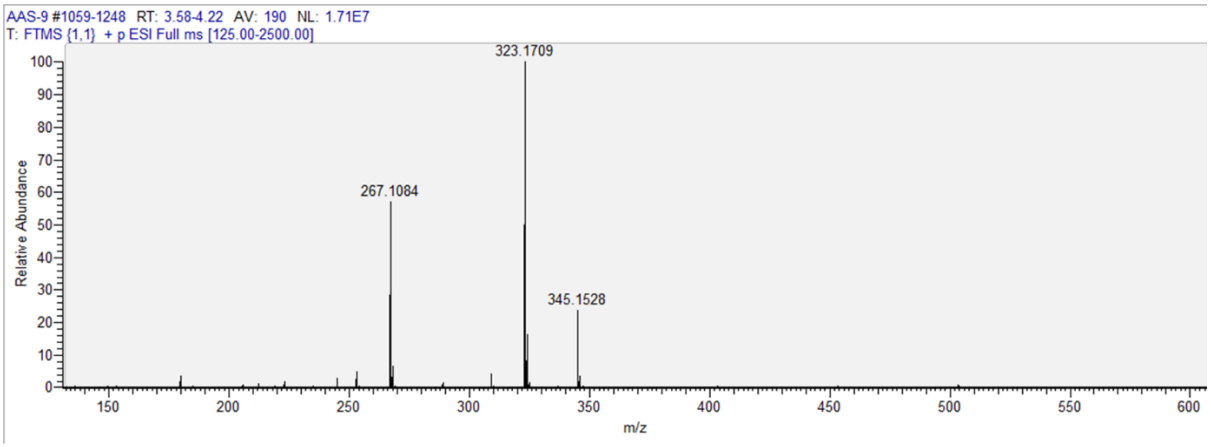
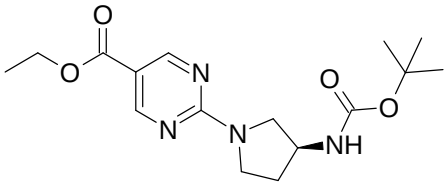
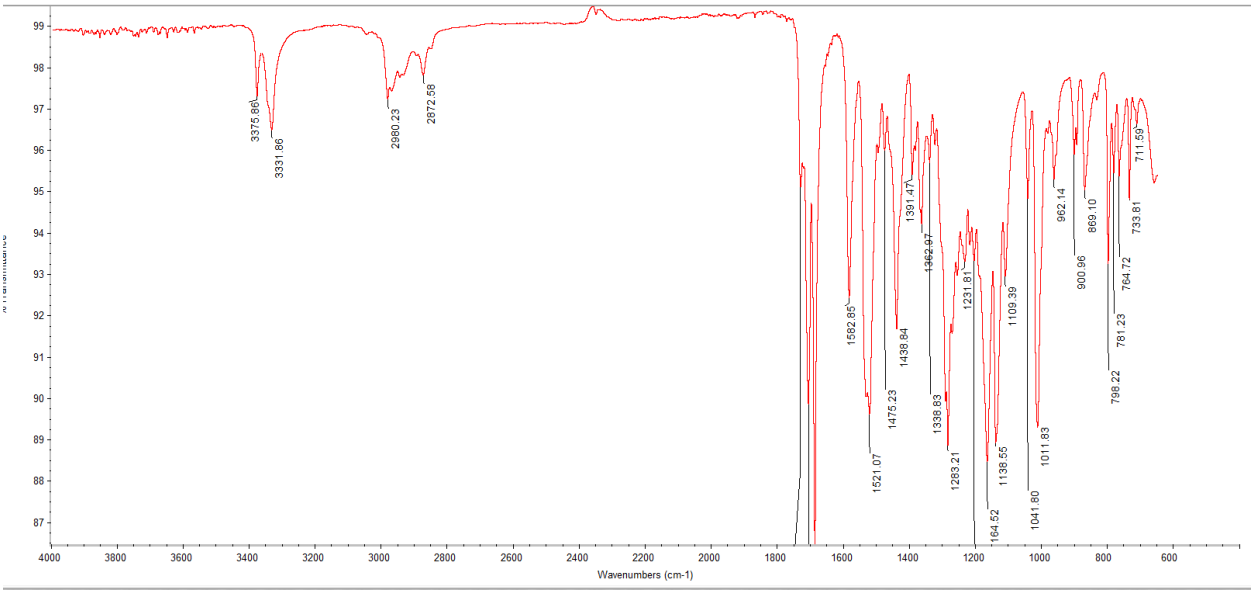


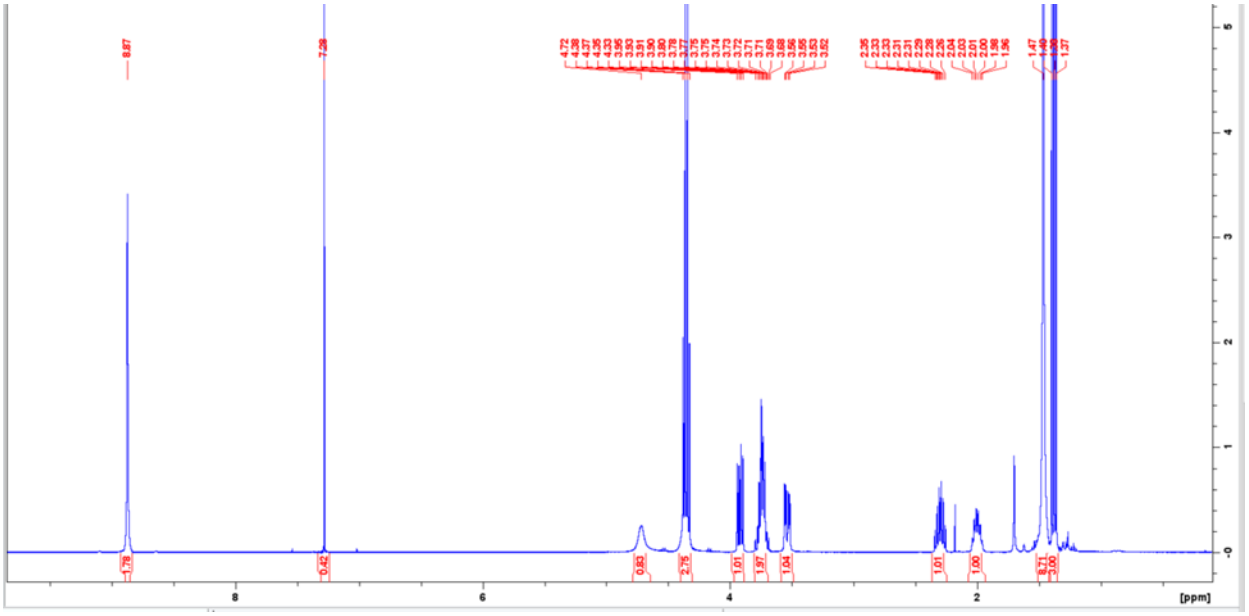
Fig S13: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 9.7

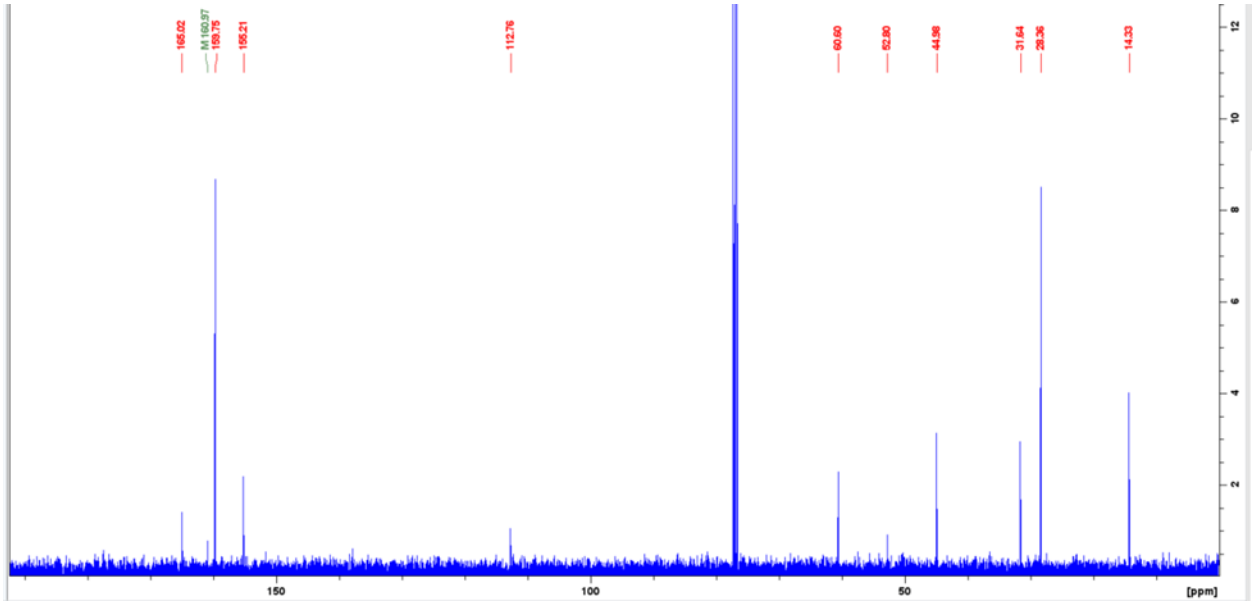
Spectral Data of 10.7

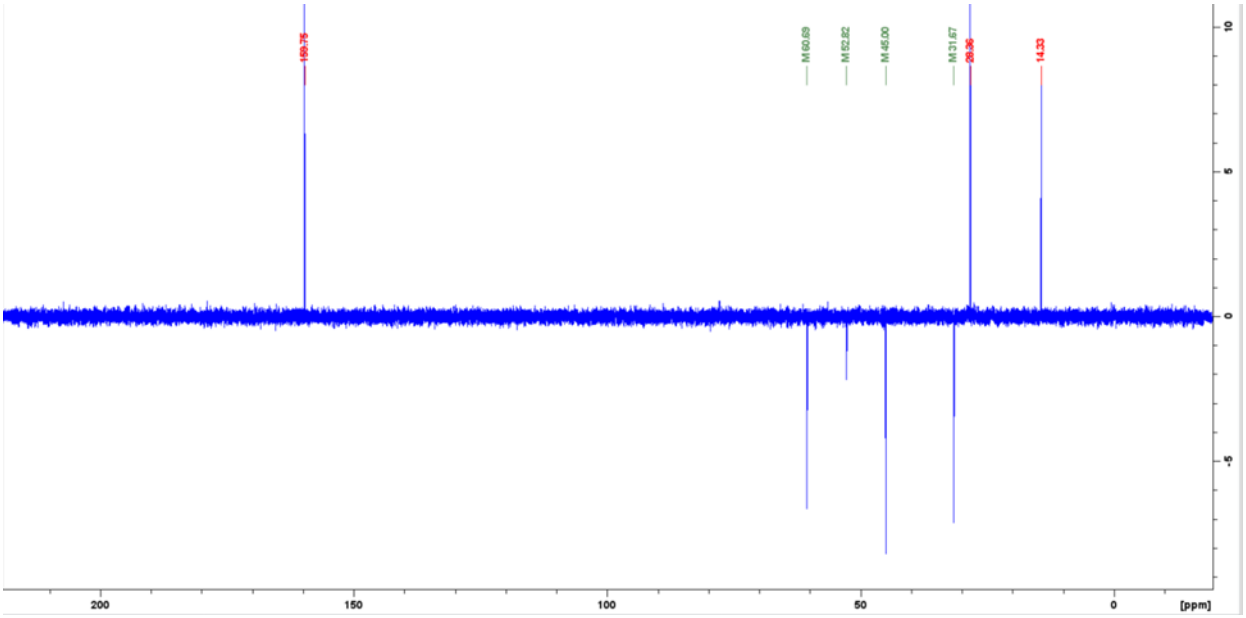


IR (cm^{-1}): 3375(w), 3331(w), 2980(s), 2872(w), 1710(s), 1698(s),1582(w), 1521 (m), 1283(m),1164 (m), 1138(m), 1011(m); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.87 (s, 2H), 4.72 (s, 1H), 4.38-4.33 (m, 3H), 3.95-3.91 (dd, *J*=4.3, 12.2, 1H), 3.80-3.68 (m, 2H), 3.56-3.52 (dd, *J*= 4.5, 12.2, 1H), 2.35-2.26 (m, 1H), 2.04 – 1.96(sext, *J*=6.1, 1H), 1.47 (s, 9H), 1.40-1.37 (t, *J*=7.1, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]): 165.0, 160.9, 159.7, 155.2, 112.7, 60.6, 52.8, 44.9, 31.6, 28.3, 14.3; ESI-MS: MH^+ = 337.1870 (expected MH^+ = 337.1798)




8.87
7.26
1.78
0.42
0.83
2.75
1.01
1.97
1.04
1.01
1.00
3.71
3.00
8
6
4
2
[ppm]


165.02
M1 160.97
159.75
155.21
112.76
60.60
52.80
44.98
31.64
29.36
14.33
150
100
50
[ppm]



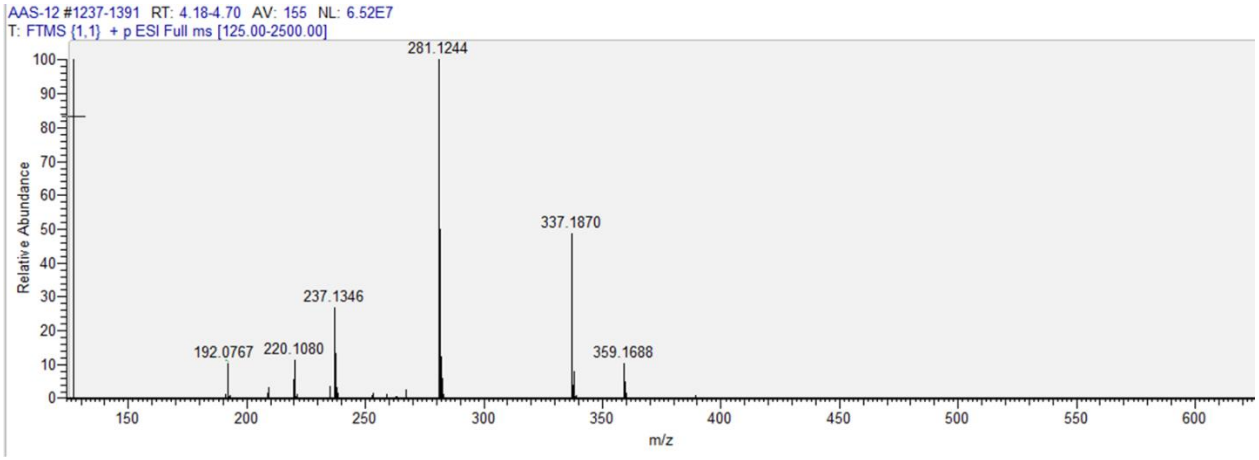
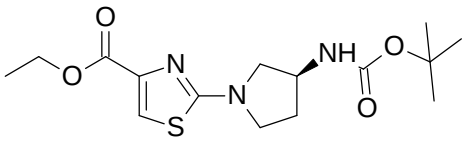
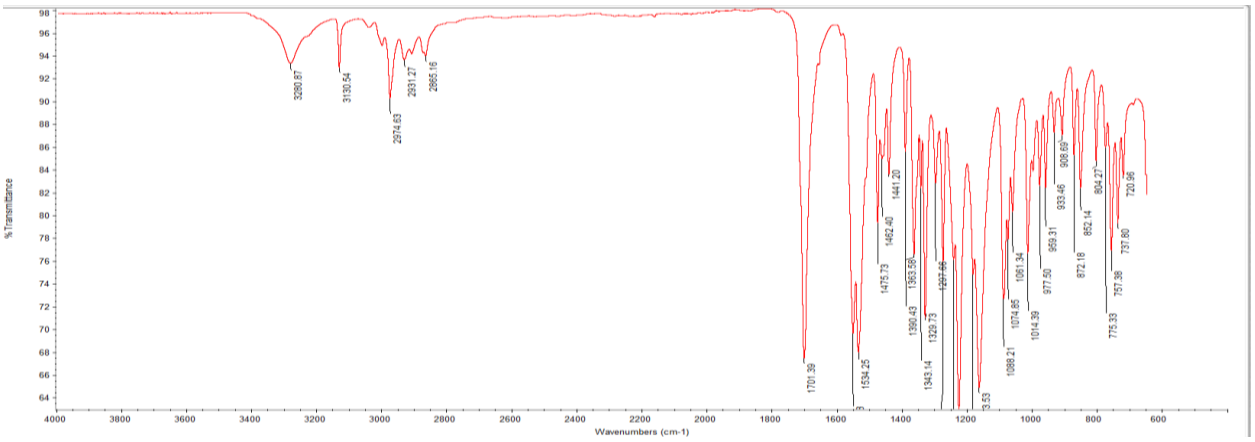


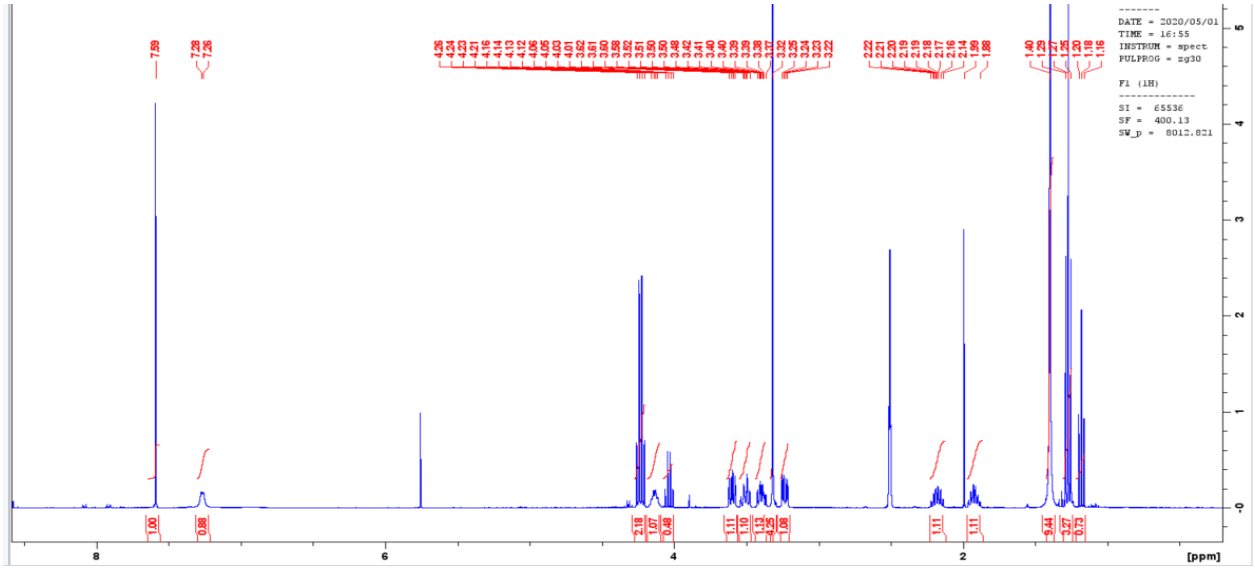
Fig S14: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 10.7

Spectral data of 11.7



IR (cm^{-1}): 3280(w), 3130(w), 2974(w), 2930(w), 1701(s), 1550(s),1534(s), 1329(m), 1240(s), 1153(s), 1088(m); NMR (400 MHz, DMSO-D6, [ppm]) δ: 7.59 (s, 1H), 7.27 (bd, 1H), 4.26-4.21 (q, *J*=7.1, 2H), 4.17-4.11 (m, 1H),3.62-3.58 (dd, *J*=6.2, 1H), 3.54-3.48 (m, 1H), 3.42-3.36 (m, 1H), 3.25-3.22 (dd, *J*=4.5,10.3, 1H), 2.22-2.14 (m, 1H), 1.96-1.88 (m, 1H), 1.40 (s, 9H), 1.27-1.25 (t, *J*= 7.1, 3H); CNMR (100 MHz, DMSO-D6, [ppm]): 166.9, 161.6, 155.7, 143.8, 117.1, 78.4, 60.7, 55.4, 50.6, 48.2, 31.3, 28.6, 14.7; ESI-MS: MH^{+} = 342.1477 (expected MH^{+} = 342.1409)


% Transmittance
Wavenumbers (cm-1)
3280.87
3130.54
2974.63
2931.27
2865.16
1701.39
1534.25
1475.73
1462.49
1441.20
1390.43
1363.58
1343.14
1329.73
1307.66
1088.21
1074.85
1061.34
1014.39
977.50
959.31
933.46
908.69
872.18
852.14
804.27
775.33
757.38
737.80
720.96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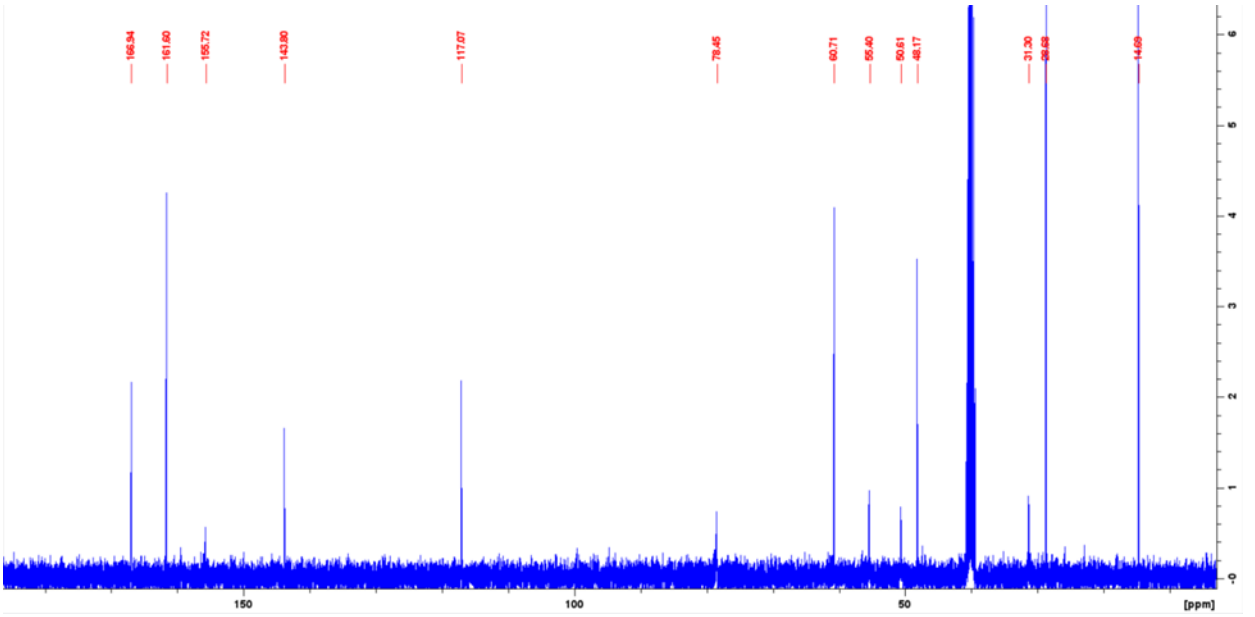
SI = 65536
SF = 400.13
SW_p = 8012.821
[ppm]


166.94
161.60
155.72
143.80
117.07
78.45
60.71
55.40
50.61
48.17
31.30
28.68
14.69
[ppm]

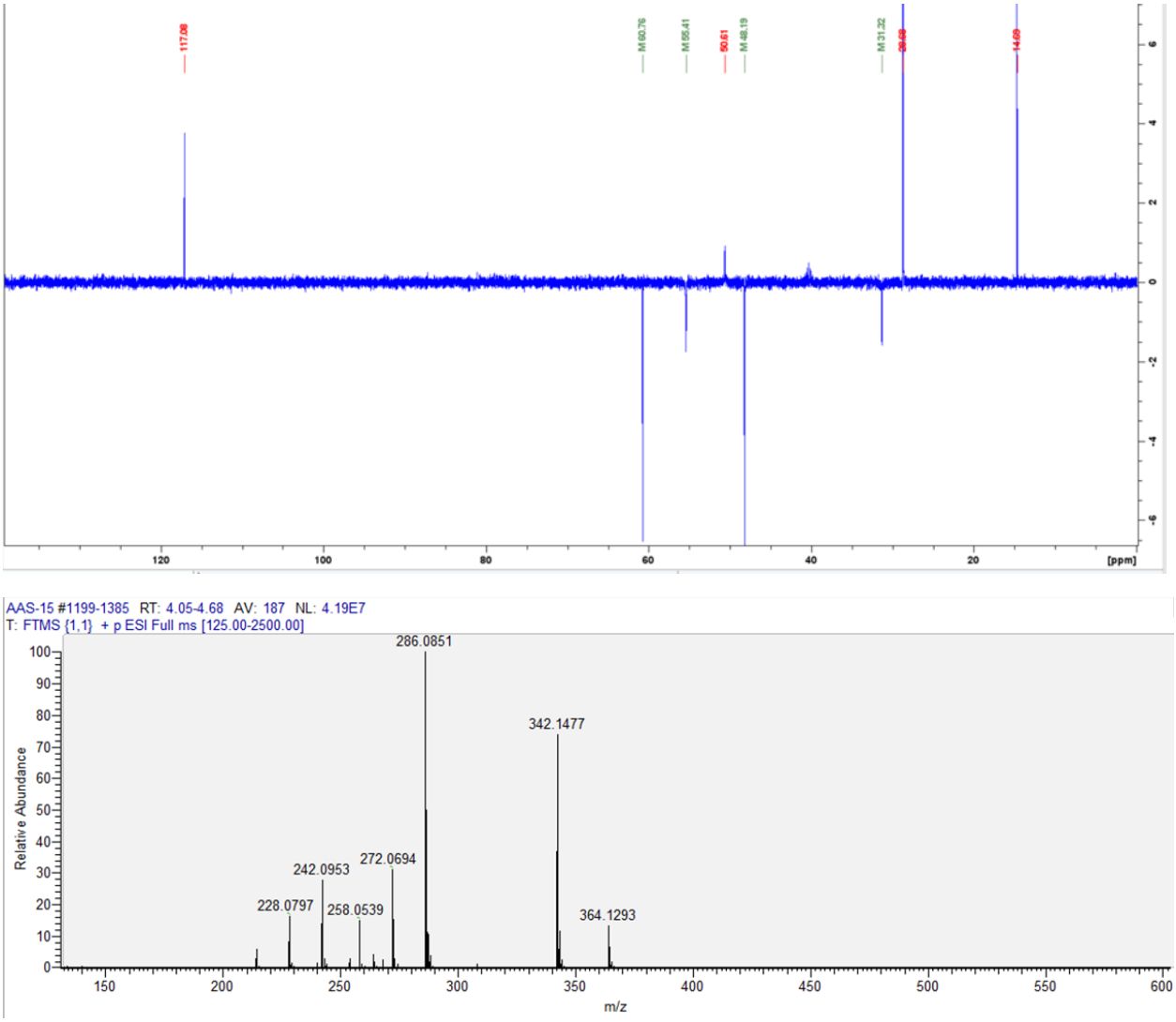
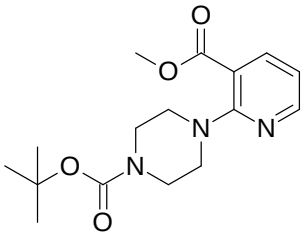
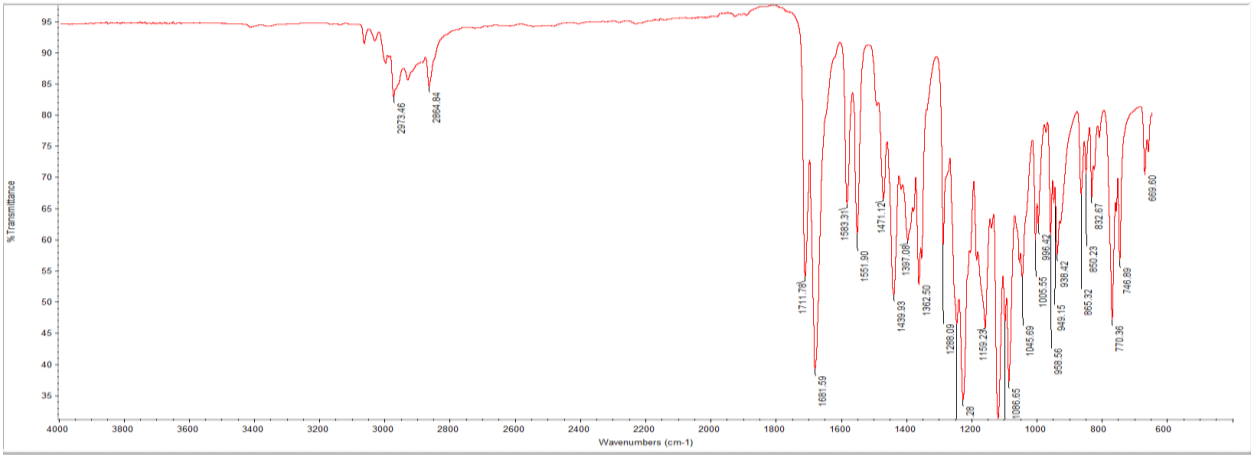


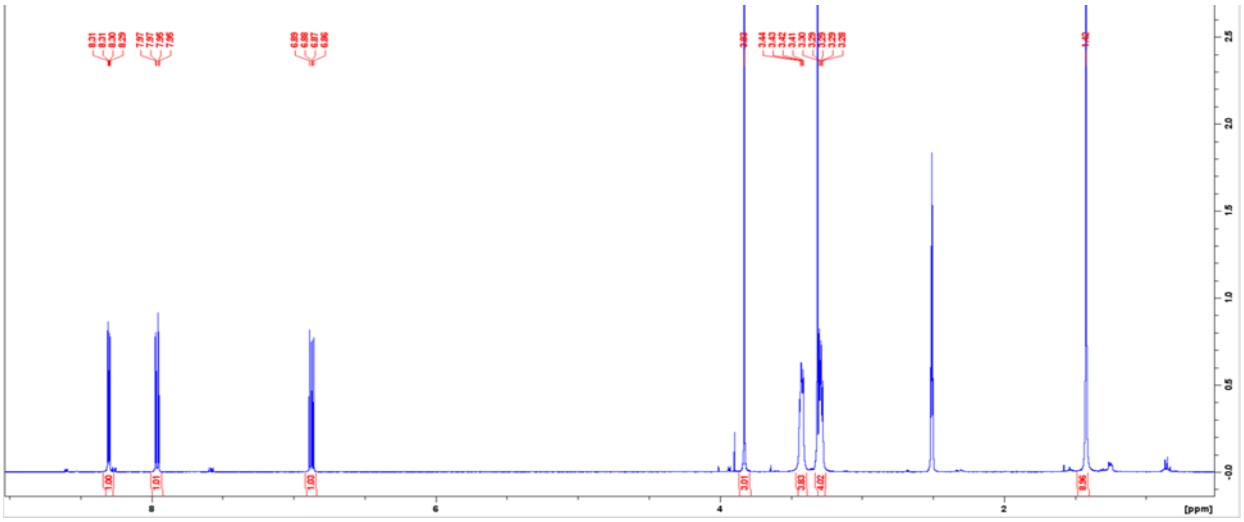
Fig S15: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 11.7

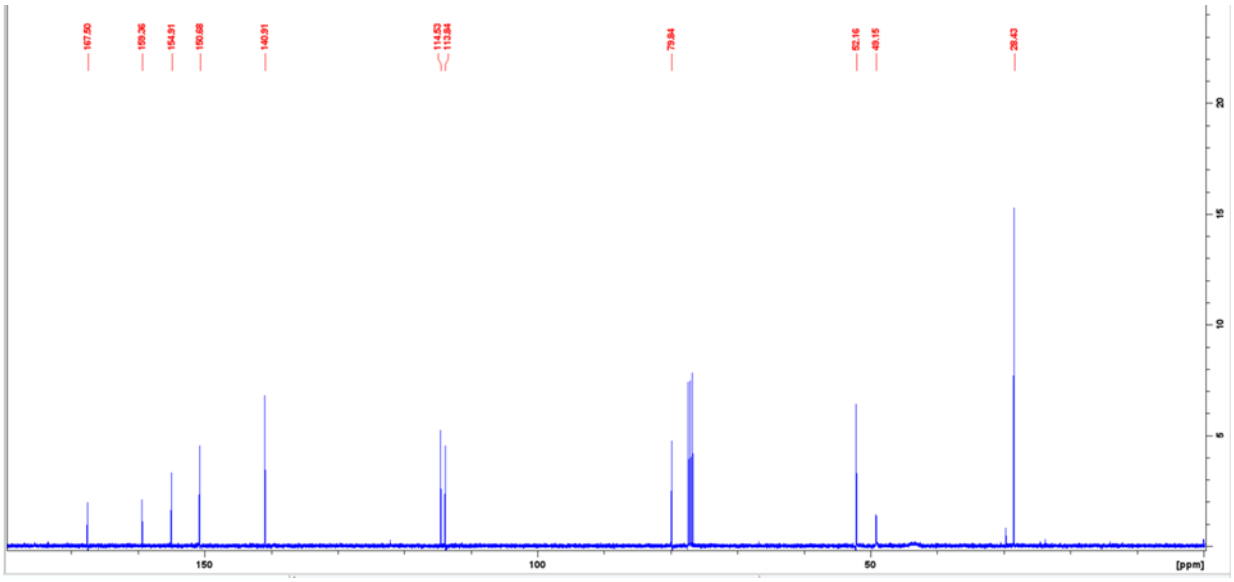
Spectral data of 12.5

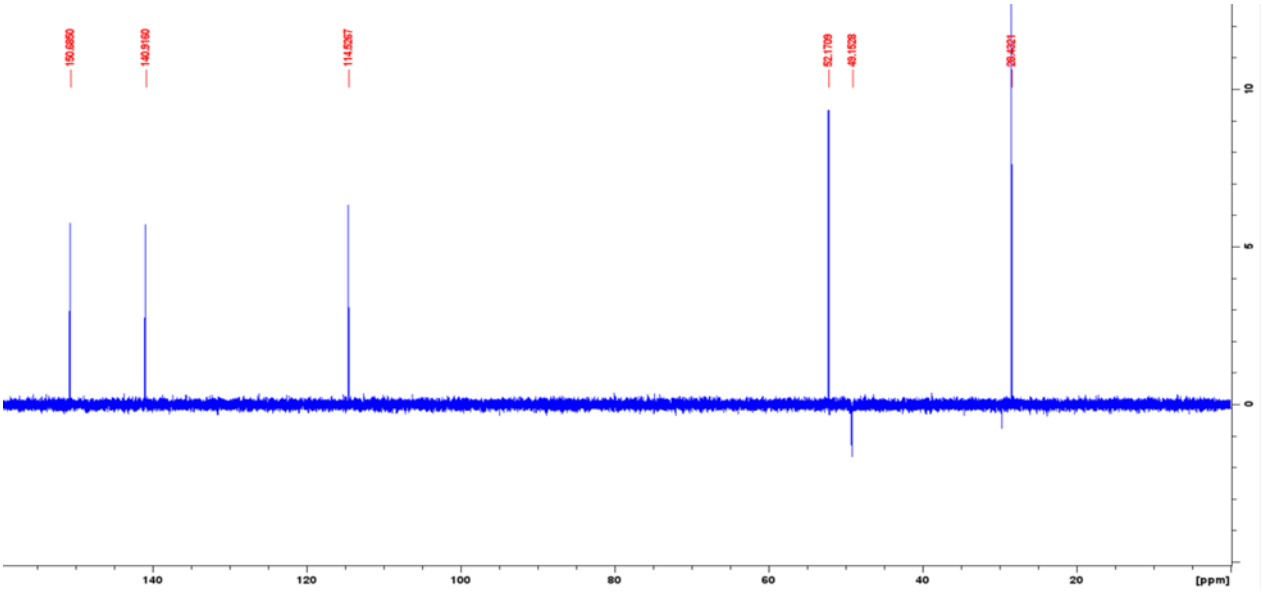


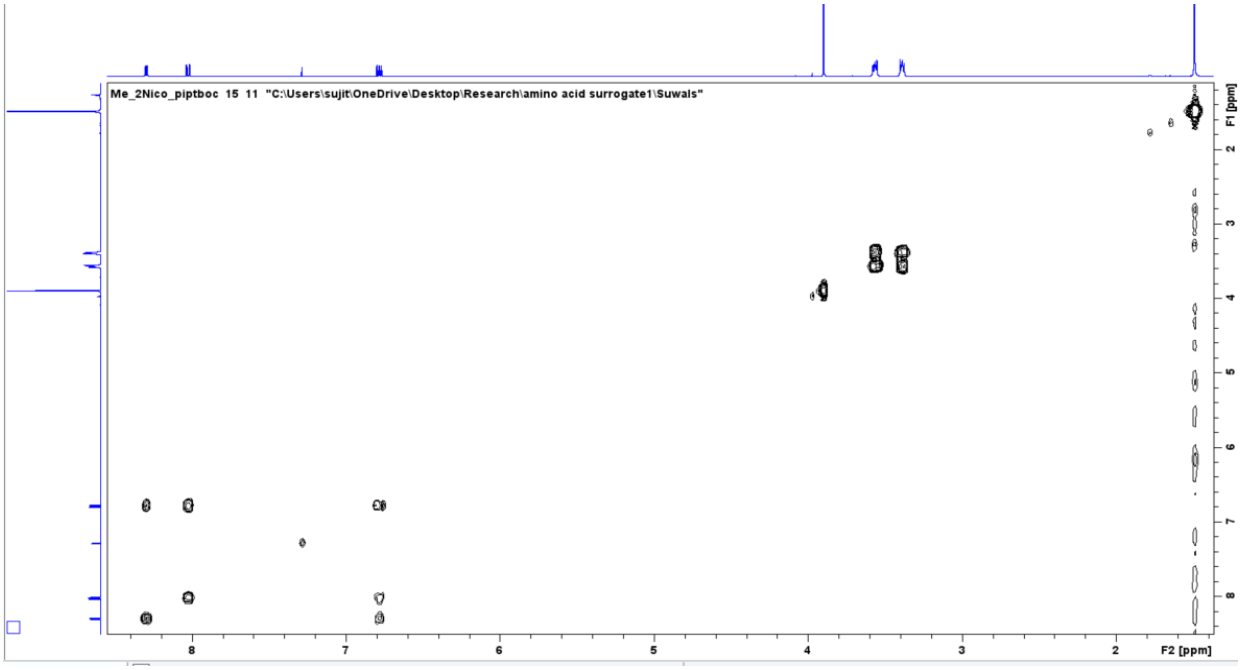
IR (cm^{-1}): 2974(w), 2864(w), 1711(m), 1681 (s), 1583(m), 1551(m), 1439(m), 1200(s), 1120(s), 1086(s); NMR (400 MHz, DMSO-D6, [ppm]) δ: 8.31-8.29 (dd, *J*=4.6, 1.9, 1H), 7.97-7.95 (dd, *J*=1.9, 7.6, 1H), 6.89-6.86 (dd, *J*=4.6, 7.6, 1H), 3.83 (s, 3H), 3.44-3.41 (m, 4H), 3.30-3.28 (m, 4H), 1.42 (s, 9H); CNMR (100 MHz, DMSO-D6, [ppm]): 167.5, 159.3, 154.9, 150.6, 140.9, 114.5, 113.8, 79.8, 52.1, 49.1, 28.4; ESI-MS: MH^+ = 322.1753 (Expected MH^+ = 322.1689)


% Transmittance
Wavenumbers (cm-1)
2973.46
2894.84
1711.78
1681.59
1583.31
1551.90
1471.12
1439.93
1397.08
1362.59
1298.09
1159.29
1086.85
1045.69
1005.65
966.42
958.56
949.15
938.42
895.32
850.23
832.87
770.36
746.89
699.60


[ppm]


167.50
159.36
154.91
150.68
140.91
114.53
113.84
79.84
52.16
49.15
28.43
[ppm]


150.8850
140.9160
114.5257
52.1709
49.1528
28.4421
140
120
100
80
60
40
20
[ppm]


Me_2Nico_piptboc 15 11 "C:\Users\sujit\OneDrive\Desktop\Research\amino acid surrogate1\Suwals"
F1 [ppm]
F2 [ppm]

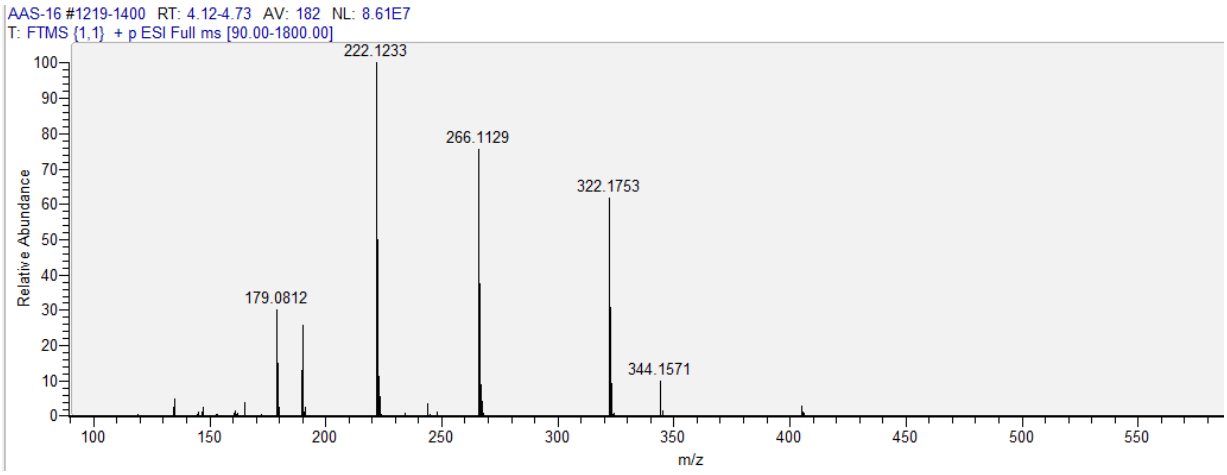
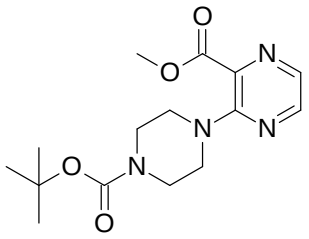
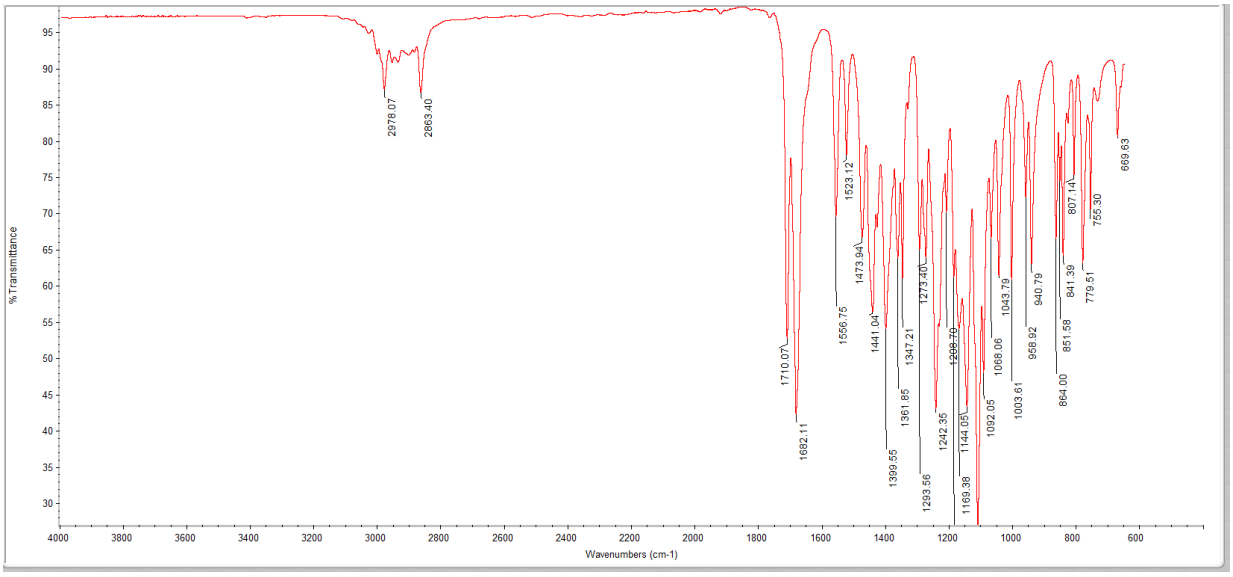


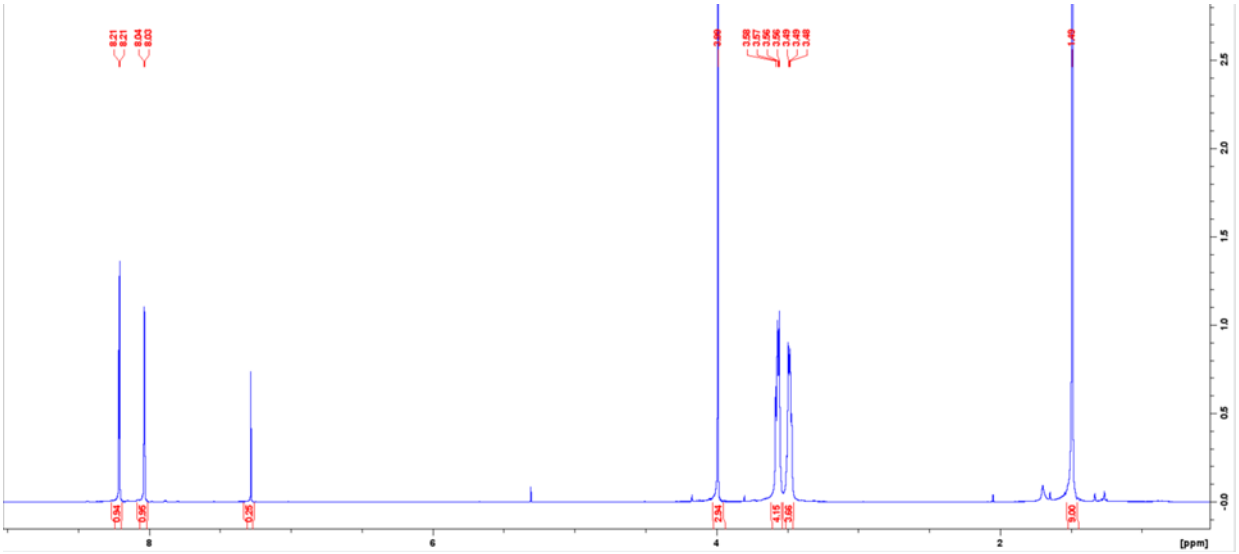
Fig S16: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY ESI-MS of compound 12.5

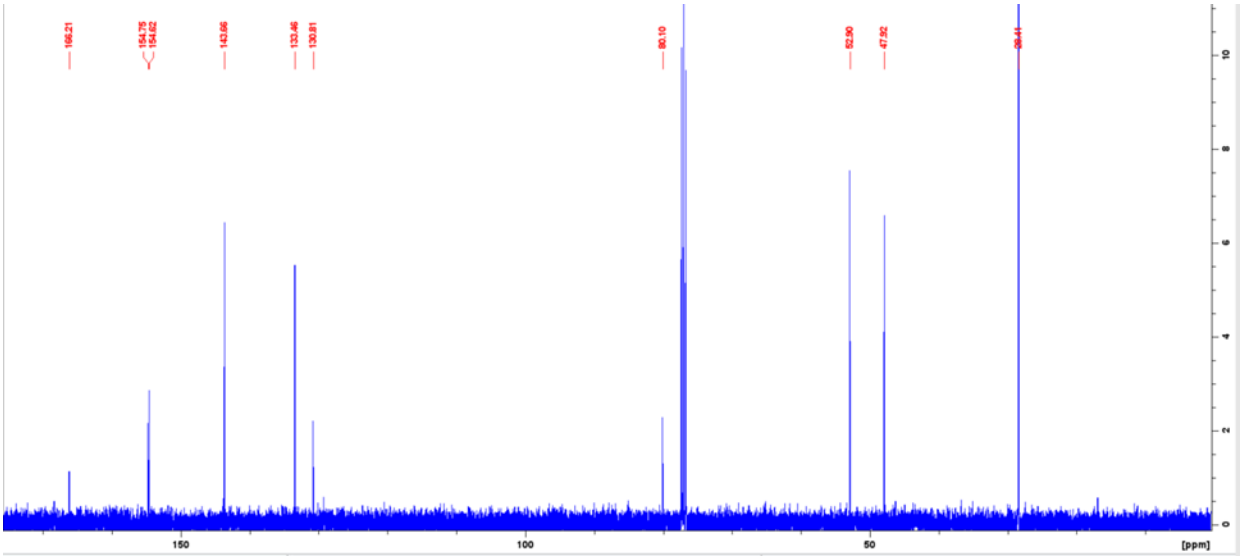
Spectral data of 13.5

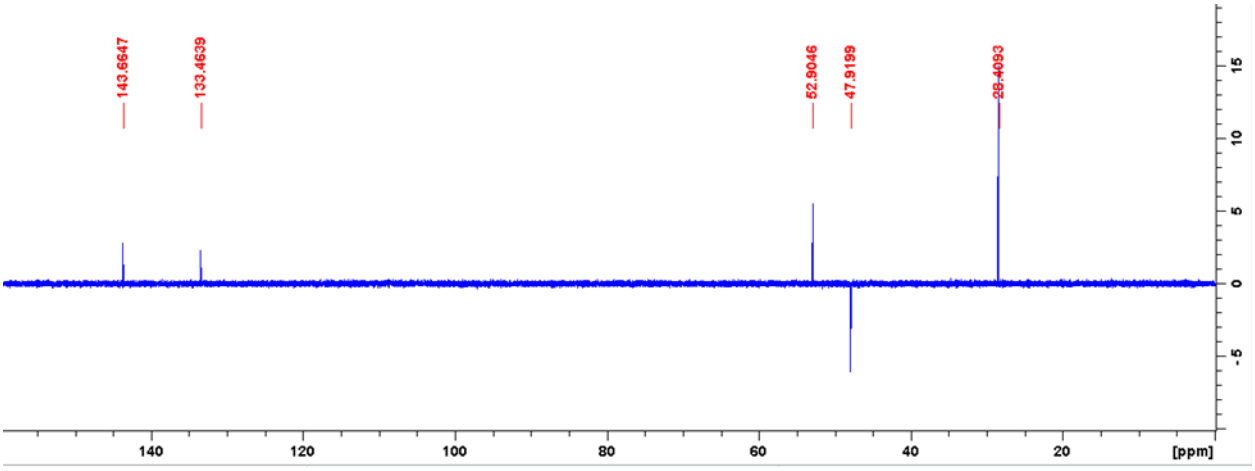


IR (cm^{-1}): 2978(w), 2863(w), 1710(m), 1682(s), 1556(w), 1399(m), 1242(m), 1144(m),1110(s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.21 (d, *J*=2.3Hz, 1H), 8.03 (d, *J*=2.3Hz, 1H), 3.99 (s, 3H), 3.58-3.56(m, 4H), 3.49 - 3.47(m, 4H), 1.49 (s, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]): 166.2, 154.7, 154.6, 143.6, 133.5, 130.8, 80.1, 52.9, 47.9, 28.4; ESI-MS: MH^+ = 323.1708 (Expected MH^+ = 323.1641)




8.21
8.21
8.04
8.03
3.58
3.57
3.56
3.56
3.49
3.49
3.48
1.49
0.34
0.35
0.25
2.34
4.15
3.66
3.00
8
6
4
2
[ppm]


166.21
154.75
154.62
143.66
133.46
130.81
80.10
52.90
47.92
28.41
150
100
50
[ppm]


143.6647
133.4639
52.9046
47.9199
28.4093
140
120
100
80
60
40
20
[ppm]

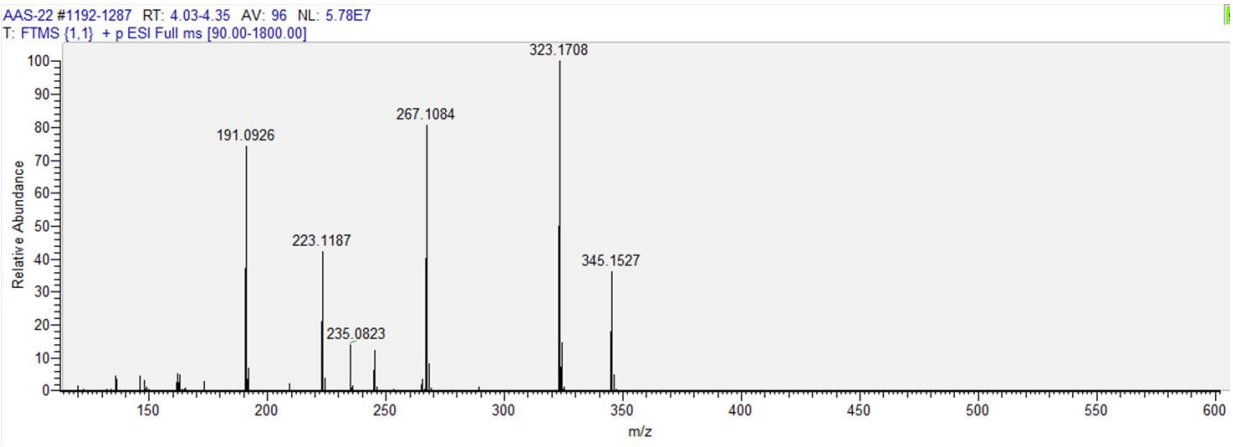
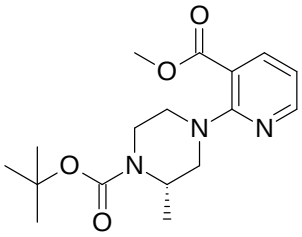
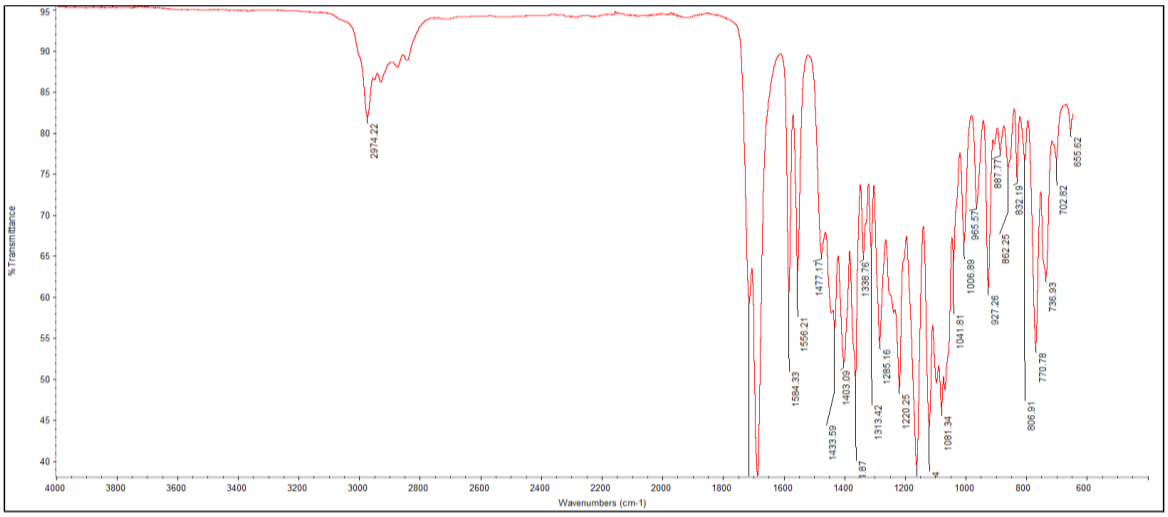


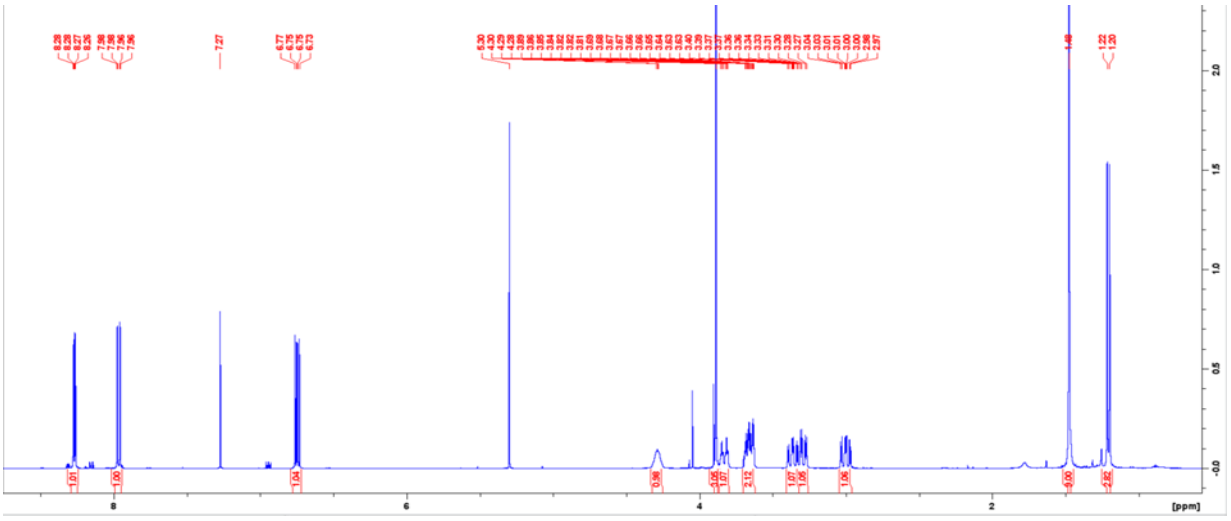
Fig S17: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 13.5

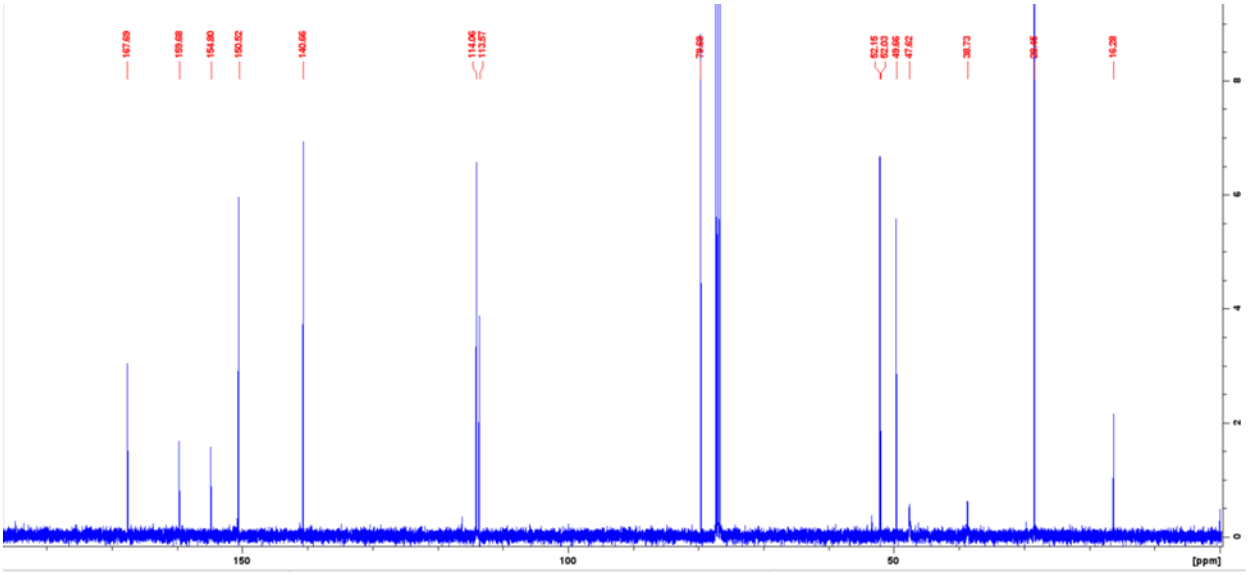
Spectral data of 12.6

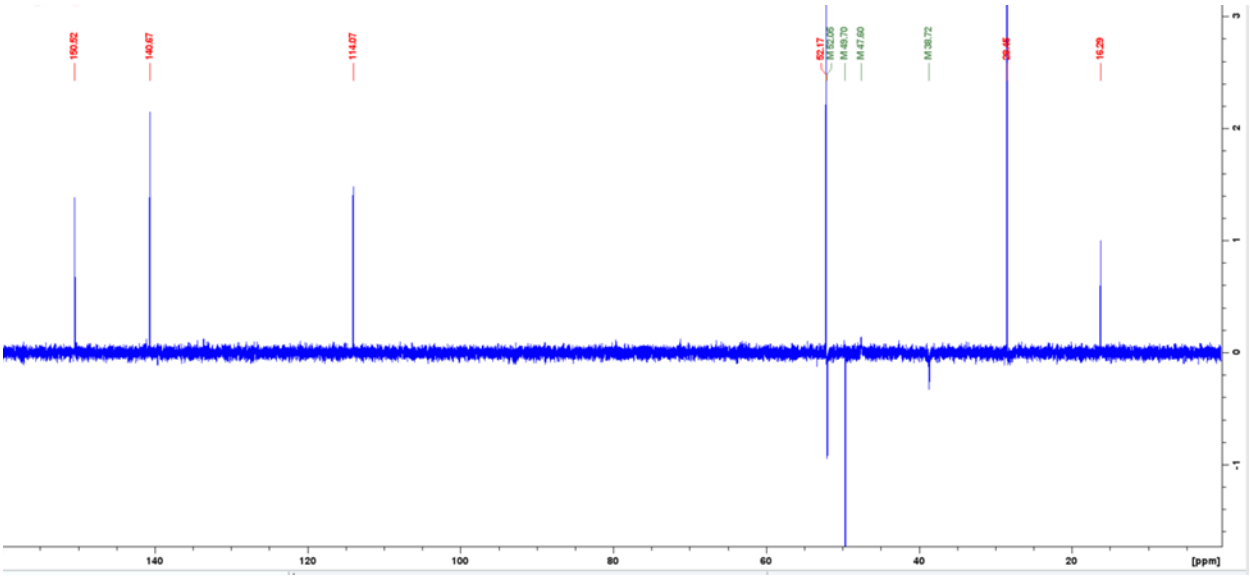


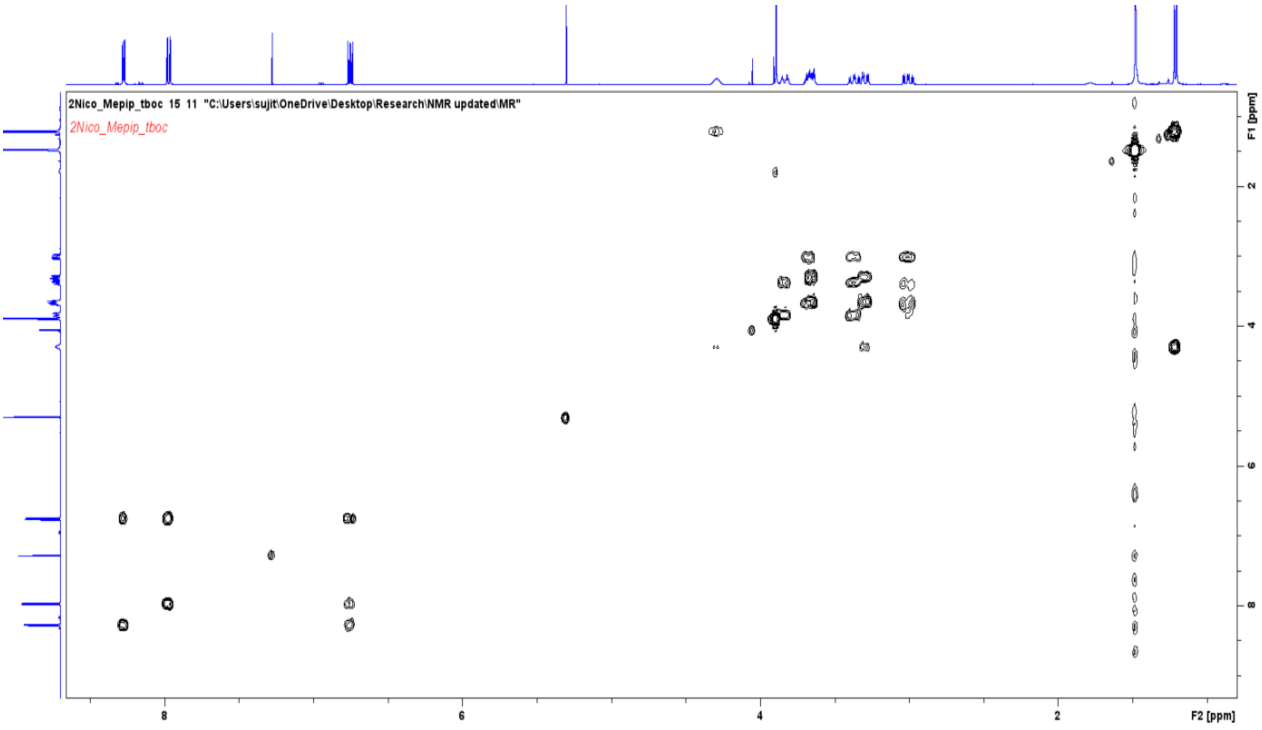
IR (cm^{-1}): 2974(w), 1690(w), 1574(m), 1565(m), 1556(w), 1351(m), 1242(m), 1160(s),1081(s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.28-8.26 (dd, *J*=4.6, 1.9, 1H), 7.98-7.96 (dd, *J*=1.9, 7.6, 1H), 6.77-6.73 (dd, *J*=4.6, 7.6, 1H), 4.28 (bs, 1H), 3.89 (s, 3H), 3.86-3.81 (dt, *J*=3.1, 13.14, 1H), 3.70-3.68 (m, 2H), 3.40-3.27 (m, 2H) 3.04-2.97 (m, 1H), 1.48 (s, 9H), 1.20 (d, *J*=6.5 Hz, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]) δ: 167.7, 159.7, 154.8, 150.5, 140.7, 114.0, 113.6, 79.7, 52.2, 52.0, 49.7, 28.5, 16.28; ESI-MS: Observed Mass MH^+: 336.1914 (Exact Mass MH^+: 336.1845)











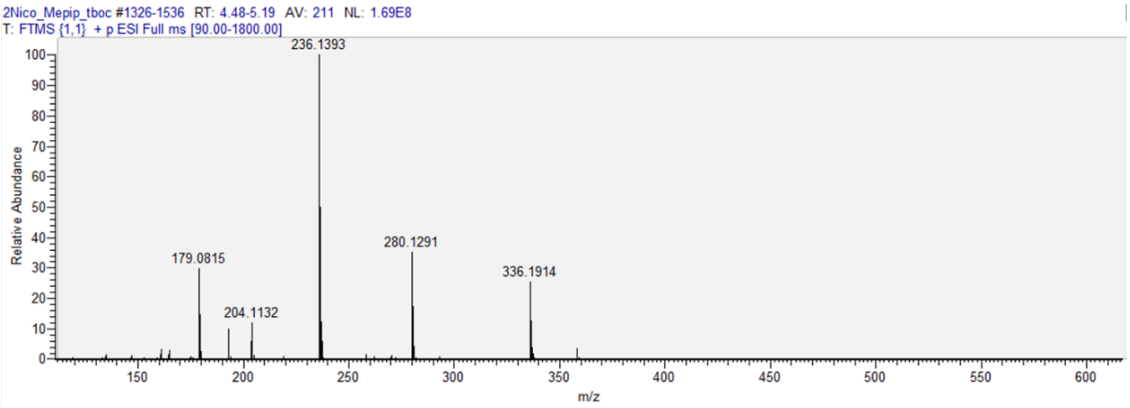
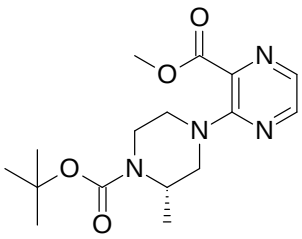
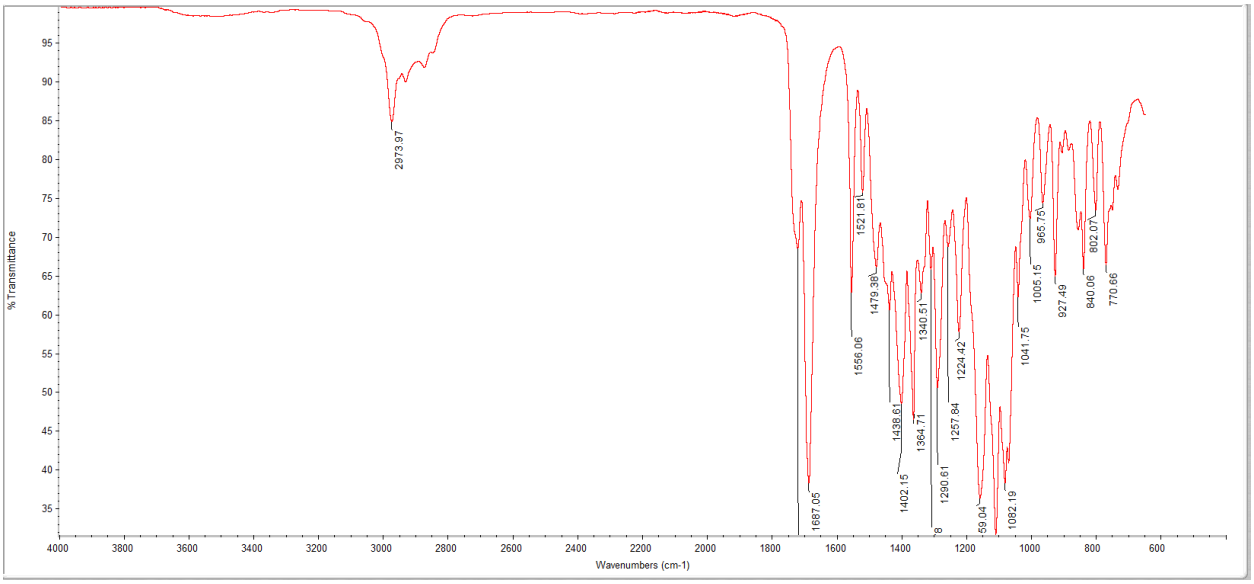


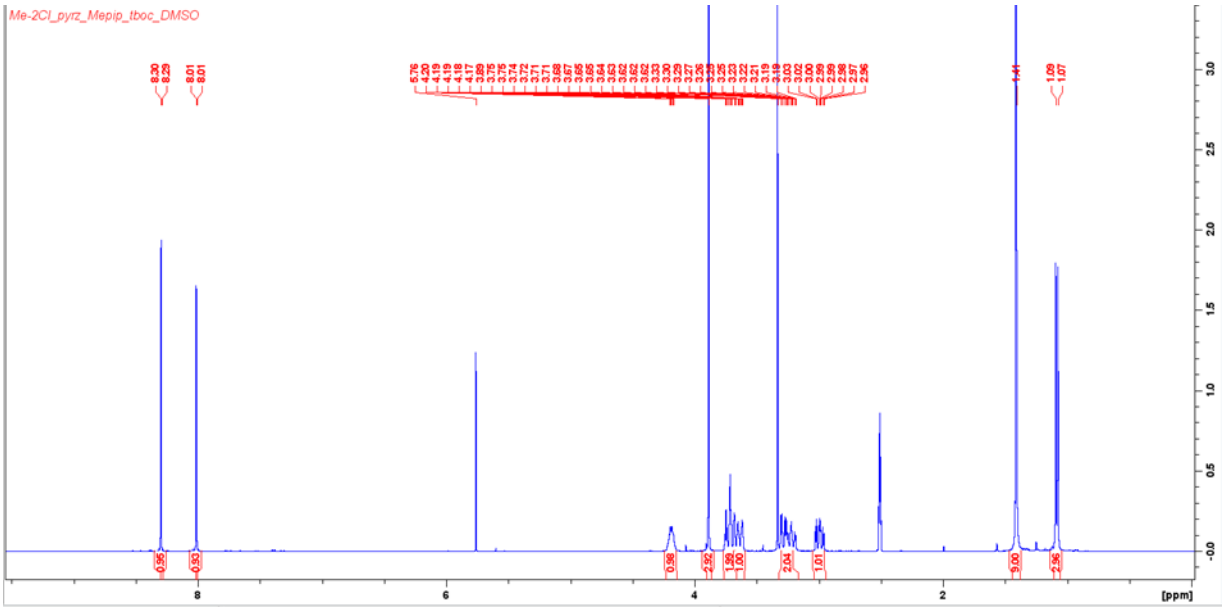
Fig S18: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, ESI-MS of compound 12.5

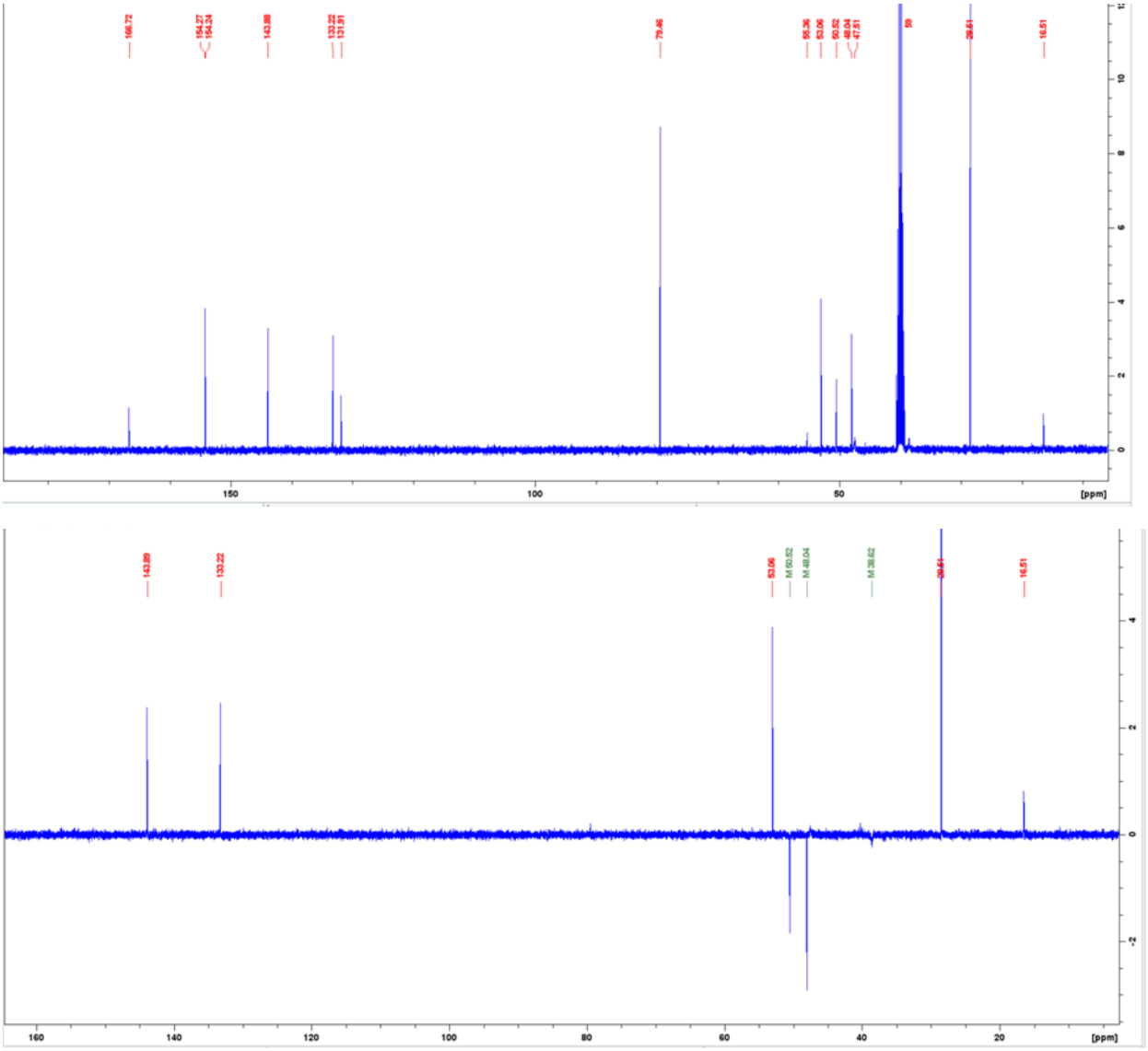
Spectral data of 13.6



IR (cm^{-1}): 2979 (w), 1720 (w), 1687 (s),1556 (w), 1402 (m), 1364 (m), 1159(s),1110 (s), 1082 (s); NMR (400mHz, DMSO-D6, [ppm]) δ: 8.30-8.29 (d, *J*=2.3, 1H), 8.01 (d, *J*=2.3, 1H), 4.19 (bs, 1H), 3.89 (s, 3H), 3.75 -3.67 (m, 2H), 3.65 -3.62 (m, 1H), 3.30-3.19 (m, 2H), 3.03-2.96 (m, 1H), 1.41 (s, 9H), 1.07-1.09 (d, *J*=6.62, 3H); CNMR (100 MHz, DMSO-D6, [ppm]) δ: 166.7, 154.3, 154.2, 143.9, 133.2, 131.9, 79.5, 55.3, 53.1, 50.5, 48.0, 28.5, 16.5; ESI-MS: MH^+ = 337.1866 (Expected MH^+ = 337.1798)







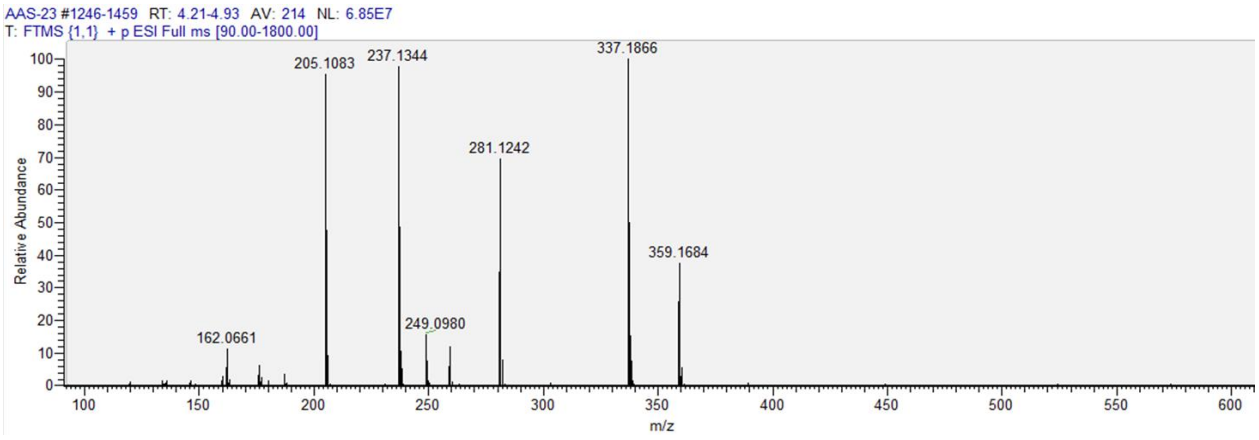
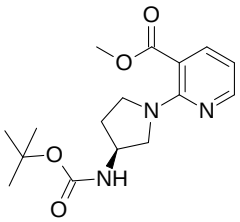
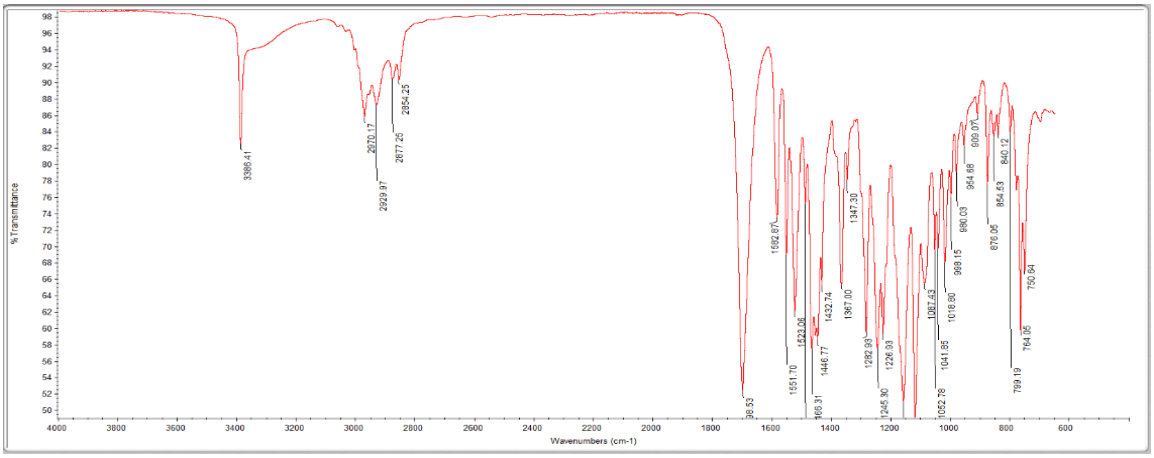


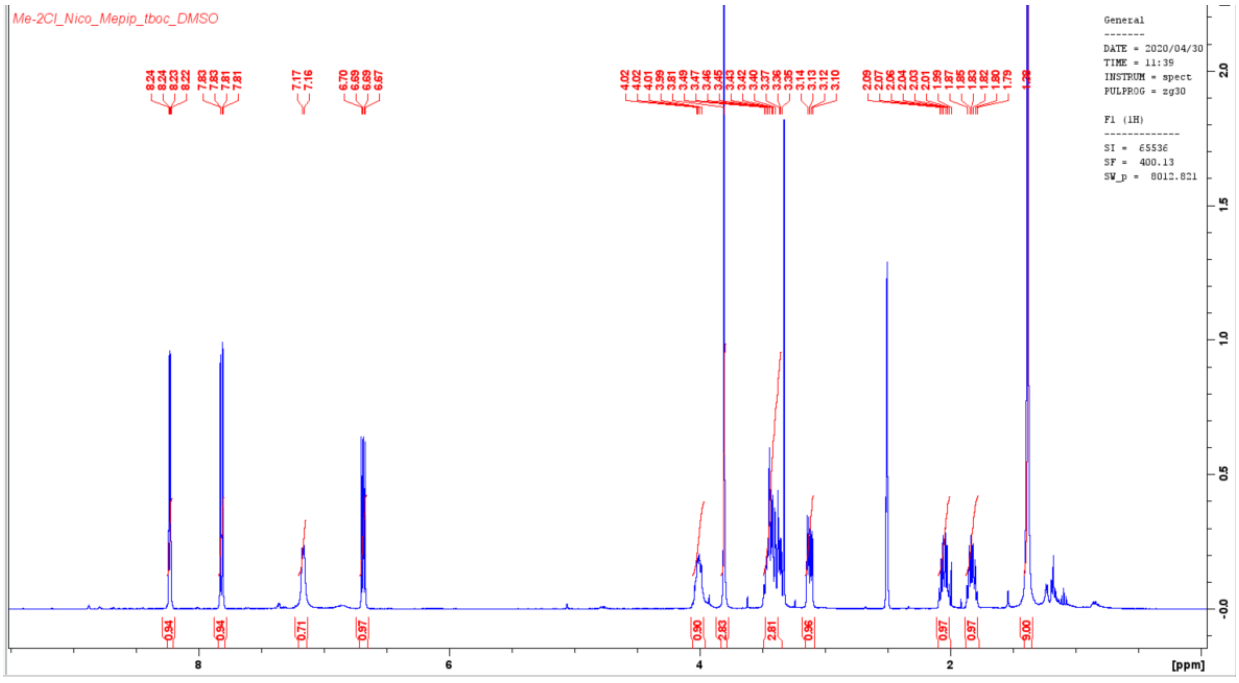
Fig S19: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 13.5

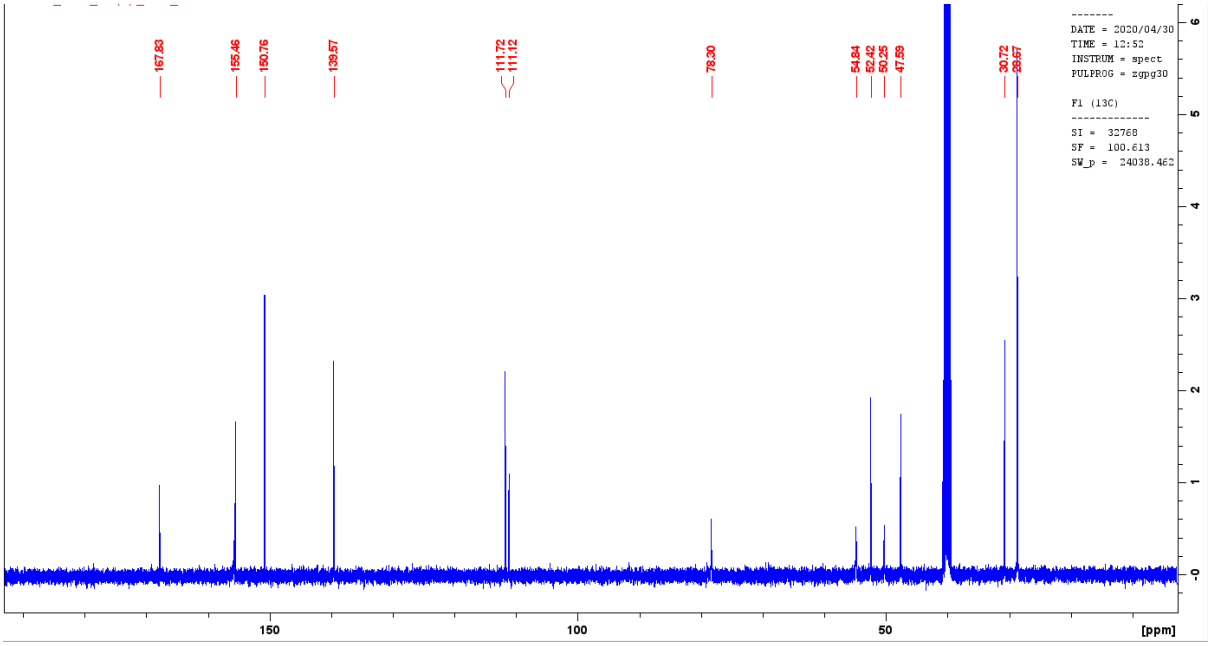
Spectral data of 12.7



IR (cm^{-1}): 3386(w), 2970(w), 2929(w), 2877(w), 1696(s), 1582(w), 1551(w),1523(m),1465(m), 1446(m), 1245(m), 1120(s); NMR (400mHz, DMSO-D6, [ppm]) δ: 8.24-8.22 (dd, *J* =1.9, 4.7, 1H), 7.83-7.81 (dd, *J*=1.9, 7.5, 1H), 7.17 (d, 1H), 6.70-6.67 (dd, *J*=4.7, 7.6, 1H), 4.01 (bs, 1H), 3.81(s, 3H), 3.49 -3.35(m, 3H), 2.09-2.01 (sext, *J*=6.0, 1H), 1.87 -1.79 (sext, *J*=5.6, 1H), 1.38 (s, 9H); CNMR (100 MHz, DMSO-D6, [ppm]) δ: 167.8, 155.5, 150.8, 139.6, 131.9, 111.7, 111.1, 78.3, 54.8, 52.42, 52.41, 50.2, 47.6, 30.7, 28.7; ESI-MS: MH^+ = 322.1756 (Expected MH^+ = 322.1689)






167.83
155.46
150.76
139.57
111.72
111.12
78.30
54.84
52.42
50.25
47.59
30.72
28.67
DATE = 2020/04/30
TIME = 12:52
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PULPROG = zgpg30
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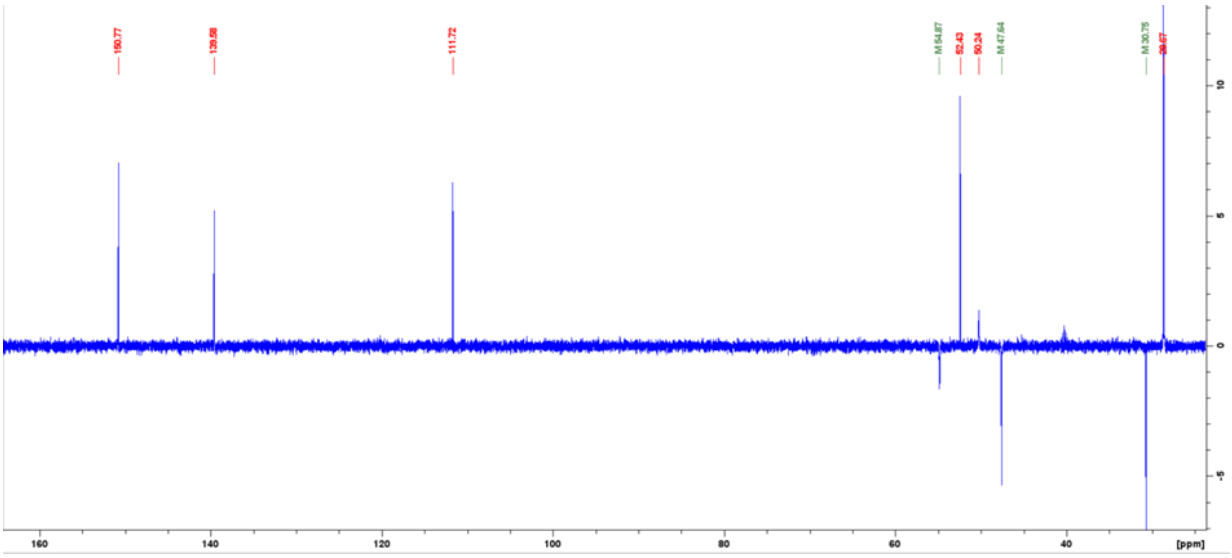
SI = 32768
SF = 100.613
SW_p = 24038.462
150
100
50
[ppm]


160
140
120
100
80
60
40
[ppm]

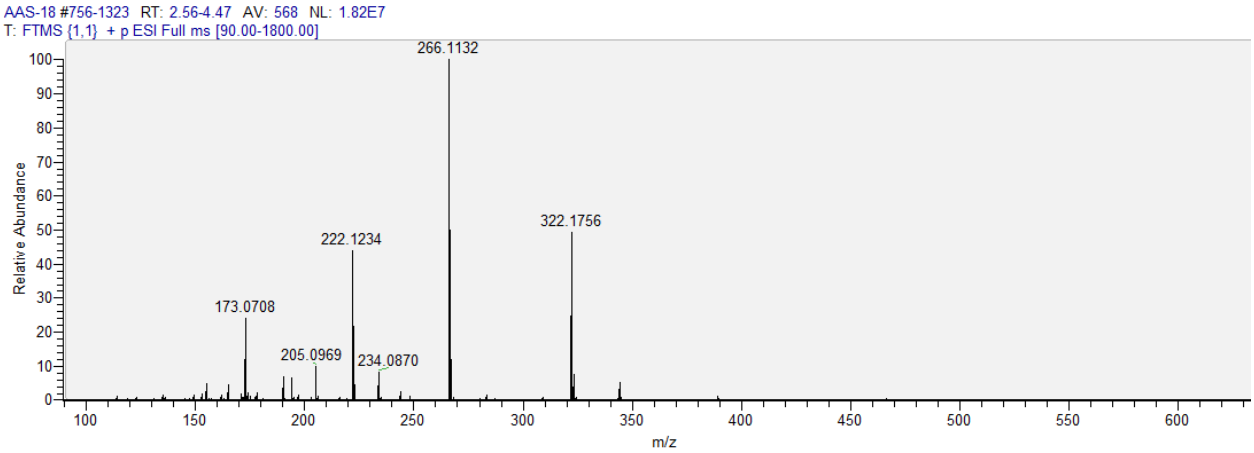
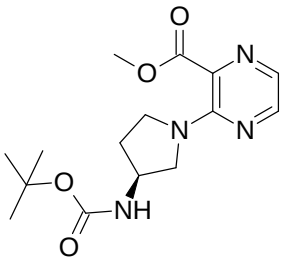
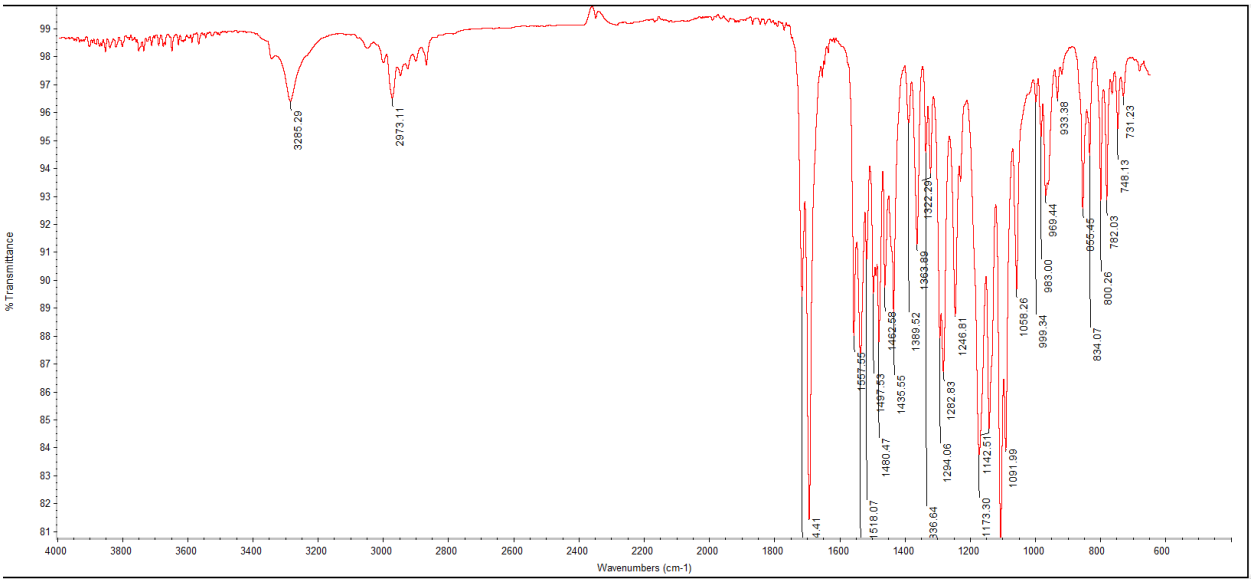


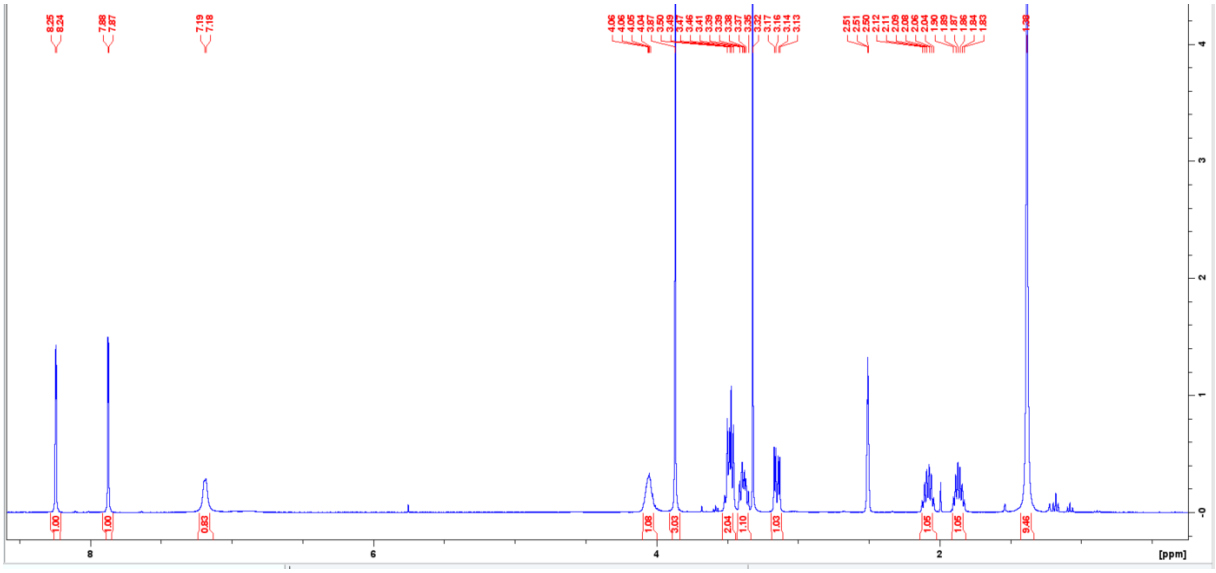
Fig S20: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 12.7

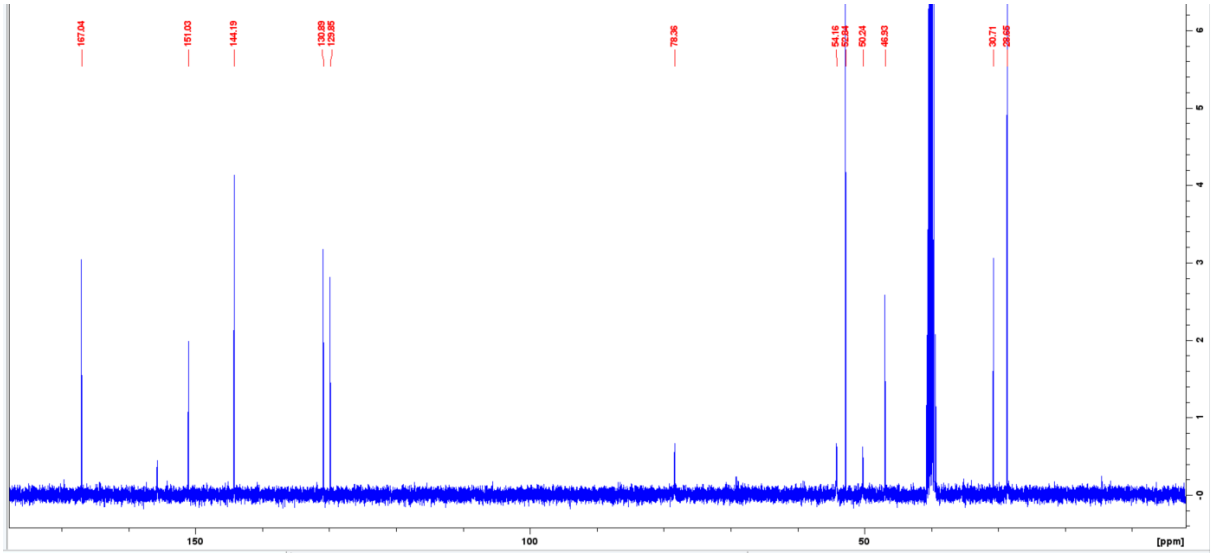
Spectral data of 13.7



IR (cm^{-1}): 3386(w), 2973(w), 1694(s), 1557(w), 1497(m), 1462(m), 1294(m), 1282(m), 1173(m), 1110(s); NMR (400mHz, DMSO-D6, [ppm]) δ: 8.25-8.24 (d, *J*=1.9Hz, 4.7Hz, 1H), 7.88-7.87 (d, *J*=1.9Hz, 7.6Hz, 1H), 7.18 (d, 1H), 4.05 (bm, 1H), 3.87 (s, 3H), 3.50 – 3.46 (dd, *J*=5.3 Hz, 10.7 Hz, 1H), 3.50-1.99 (m, 2H), (dd, *J*=4.6, 11.2, 1H), 2.12-2.04 (m,1H), 1.90-1.83 (m, 1H), 1.38 (s, 9H); CNMR (100 MHz, DMSO-D6, [ppm]): 167.0151.0, 144.2, 130.9, 129.8, 78.3, 54.1, 52.9, 50.2, 46.9, 30.7, 28.7; ESI-MS: MH^+ = 323.1714 (Expected MH^+ = 323.1641)




8.25
8.24
7.88
7.87
7.19
7.18
4.06
4.06
4.05
4.04
3.97
3.49
3.47
3.46
3.41
3.39
3.38
3.37
3.35
3.32
3.17
3.16
3.14
3.13
2.51
2.51
2.50
2.12
2.11
2.09
2.06
2.04
1.90
1.87
1.86
1.84
1.83
1.29
1.00
1.00
0.93
1.08
3.03
2.04
1.10
1.03
1.05
1.05
9.46
8
6
4
2
[ppm]


167.04
151.03
144.19
130.89
129.85
78.36
54.16
52.64
50.24
46.93
30.71
28.66
150
100
50
[ppm]

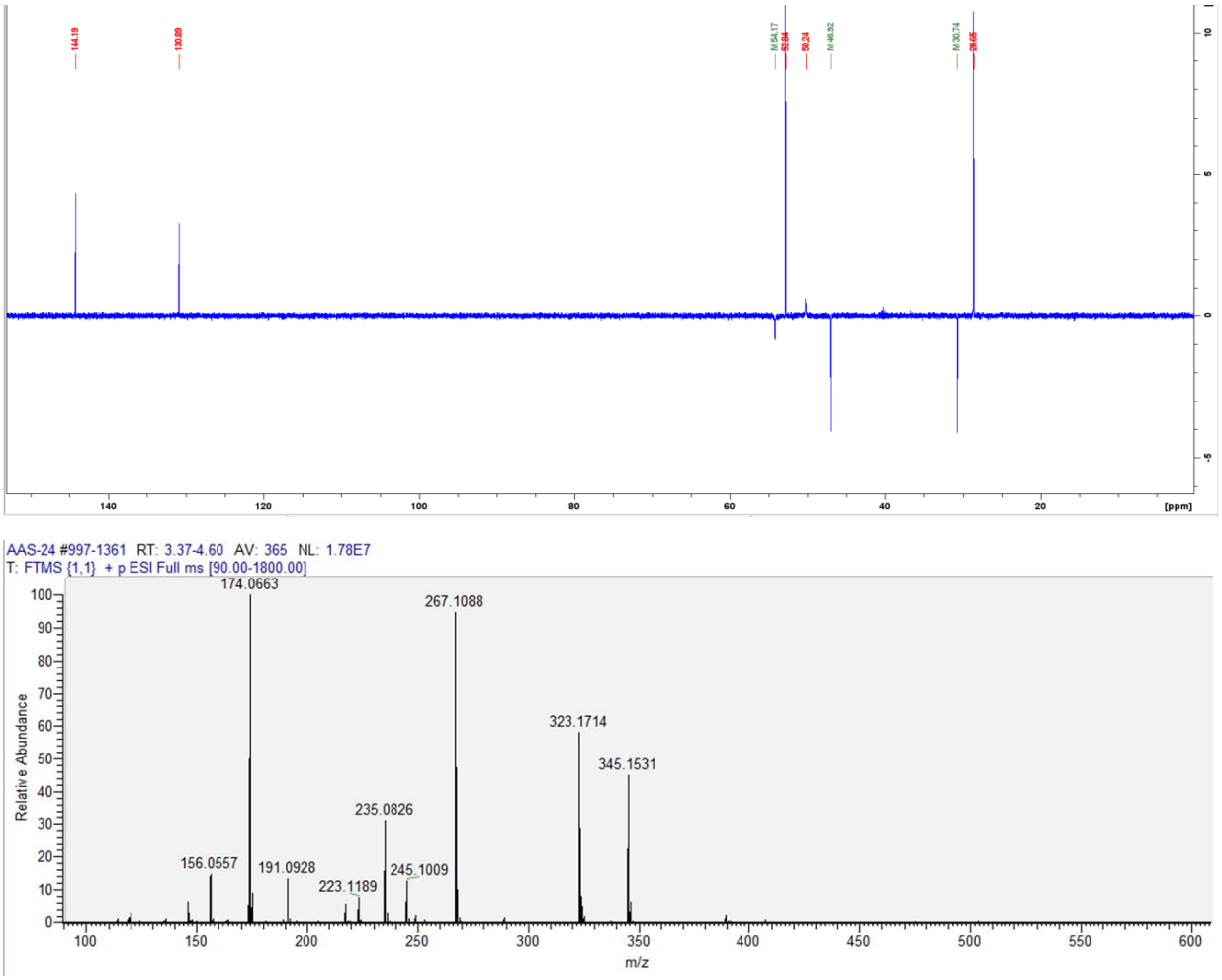
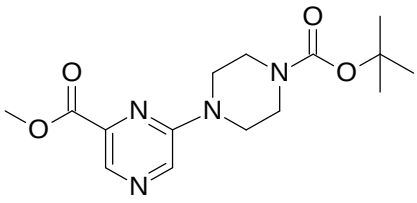
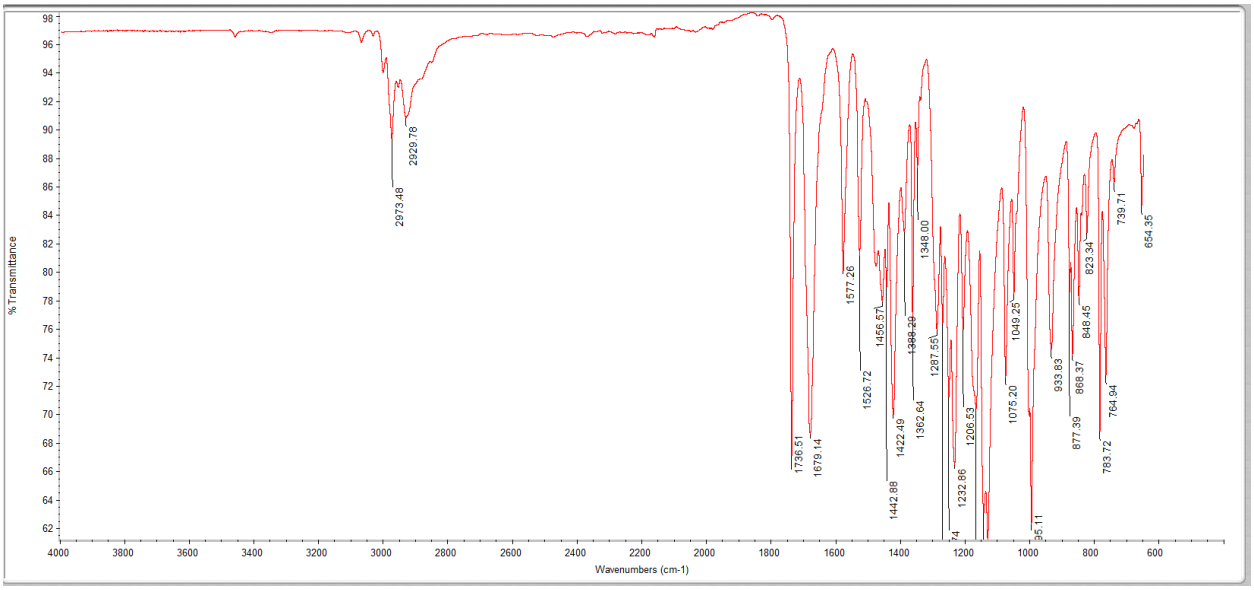


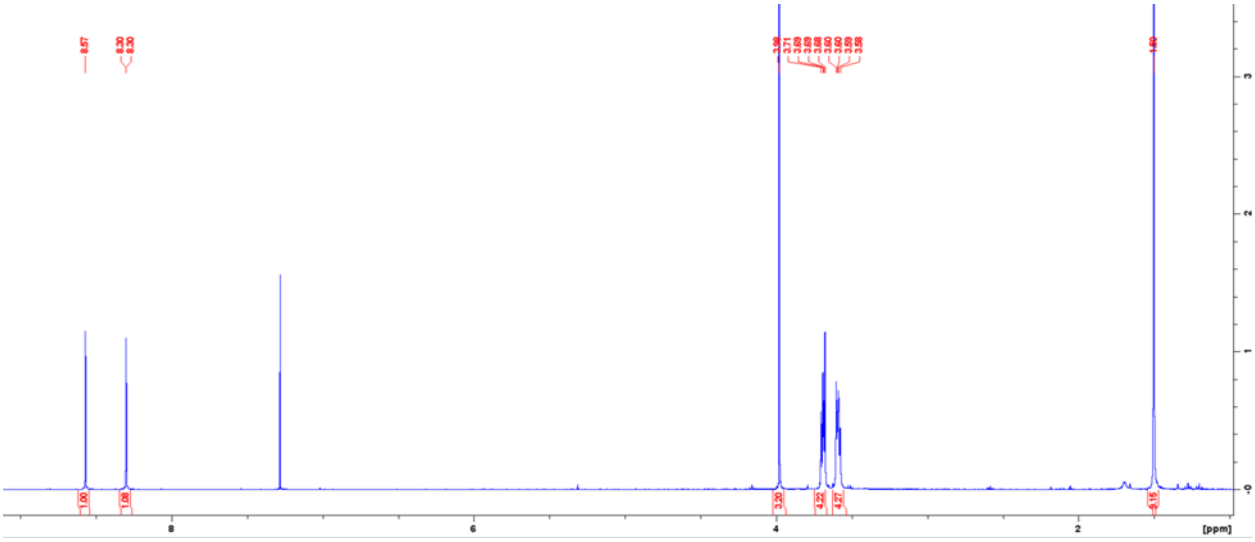
Fig S21: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 13.7

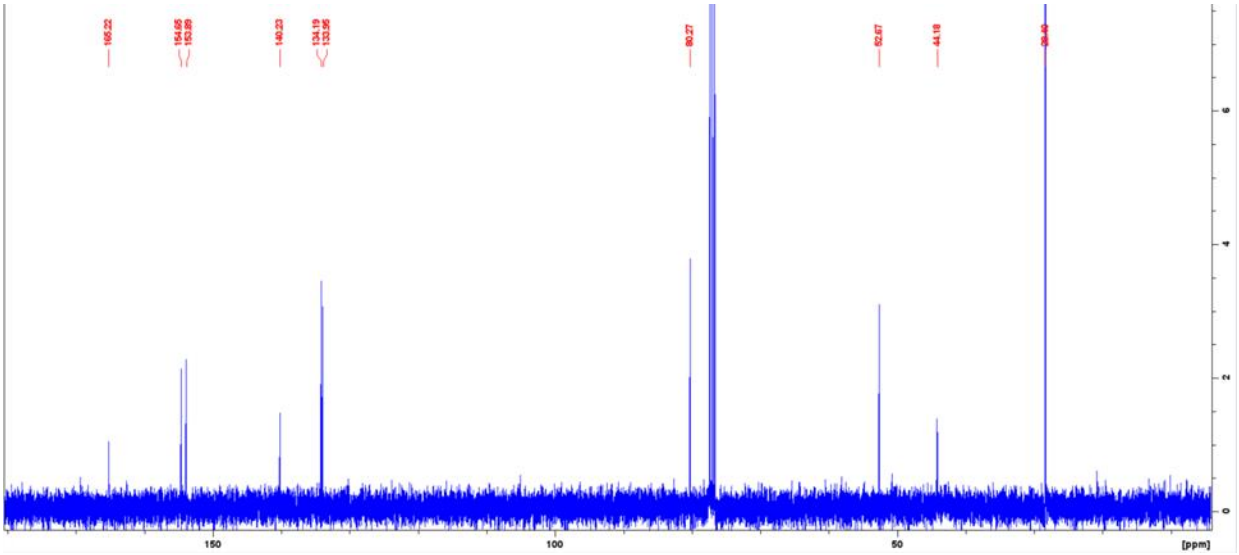
Spectral data of 14.5



IR (cm^{-1}): 2973(w), 2929(w), 1736(m), 1679 (s), 1577 (w), 1526(w), 1422(m), 1232w (s), 1135 (s), 1140 (s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.57 (bs, 1H), 8.15(bd, 1H), 3.98 (s, 3H), 3.71-3.68 (m, 4H), 3.60-358 (m, 4H), 1.50 (s, 9H); CNMR (100 MHz, $CDCl_3$, [ppm]) δ: 165.2, 154.6, 153.9, 140.2, 134.2, 133.9, 80.3, 52.6, 44.2, 28.4; ESI-MS: MH^+ = 323.1717 (expected MH^+ = 323.1641)


% Transmittance
Wavenumbers (cm-1)
2973.48
2929.78
1736.51
1676.14
1577.26
1526.72
1456.67
1442.88
1422.49
1388.29
1362.64
1348.00
1287.55
1232.86
1206.53
1075.20
1049.25
933.83
877.39
868.37
848.45
823.34
783.72
764.94
739.71
654.35


[ppm]


[ppm]

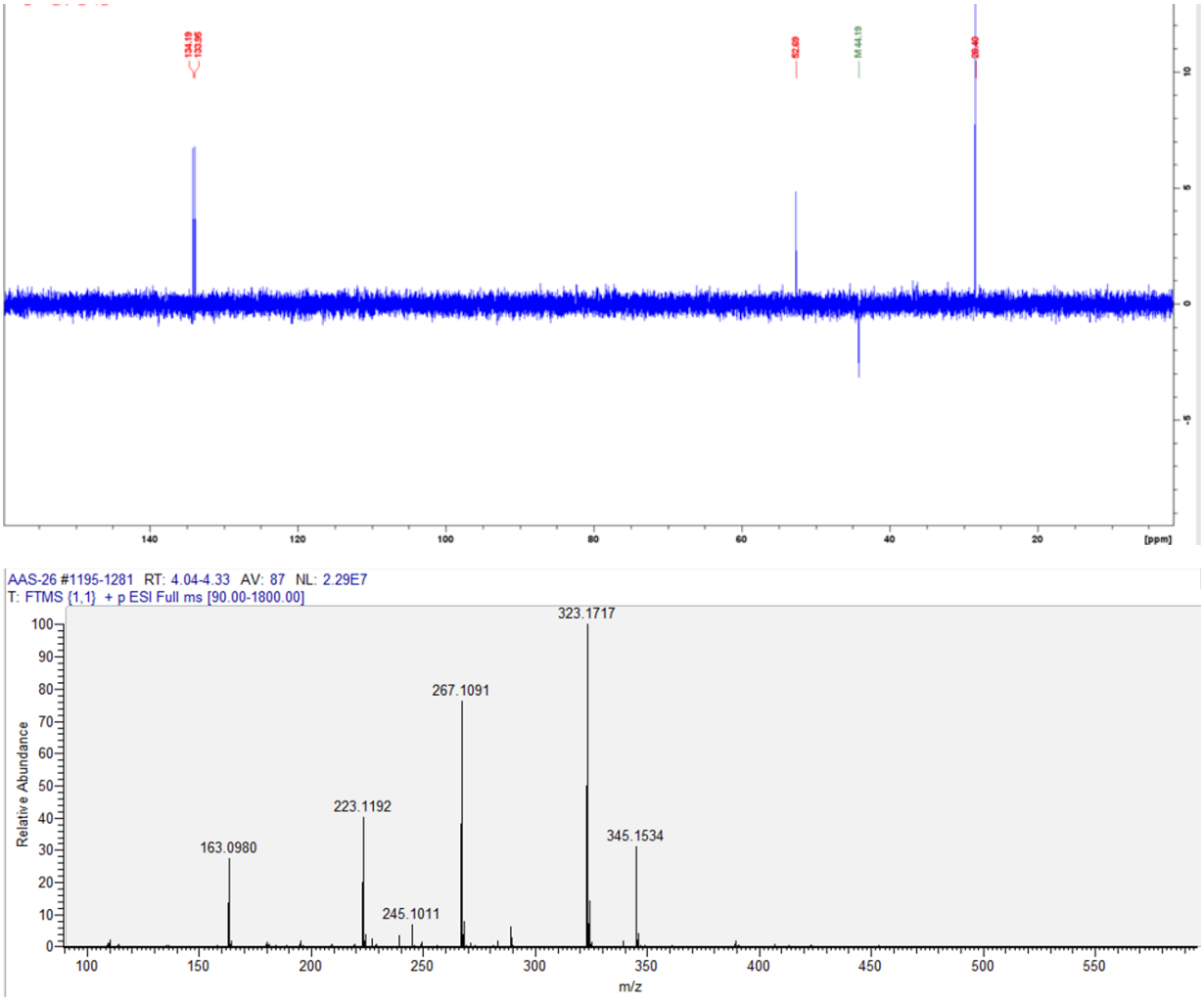
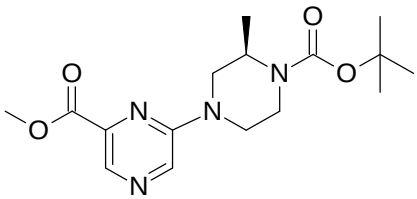
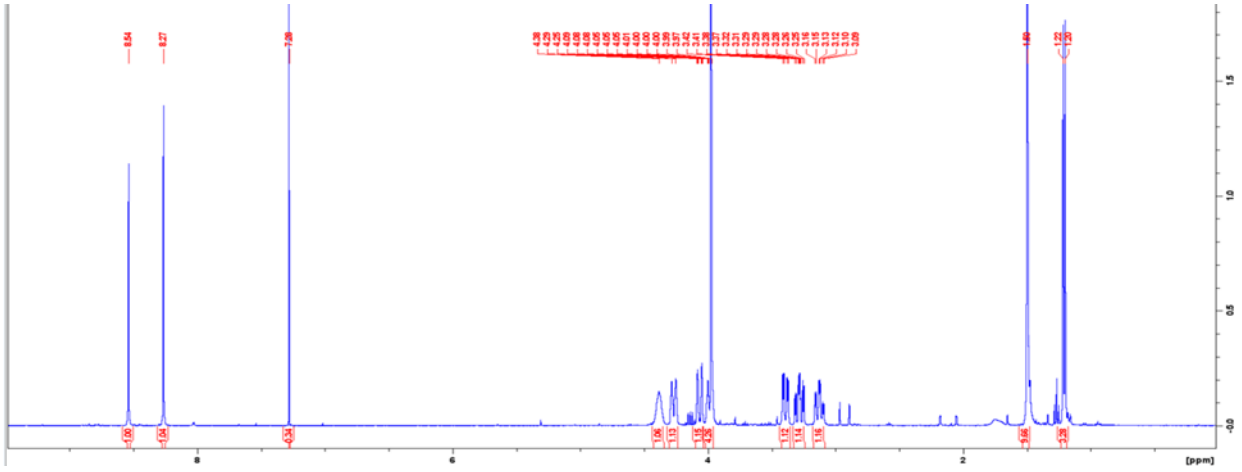


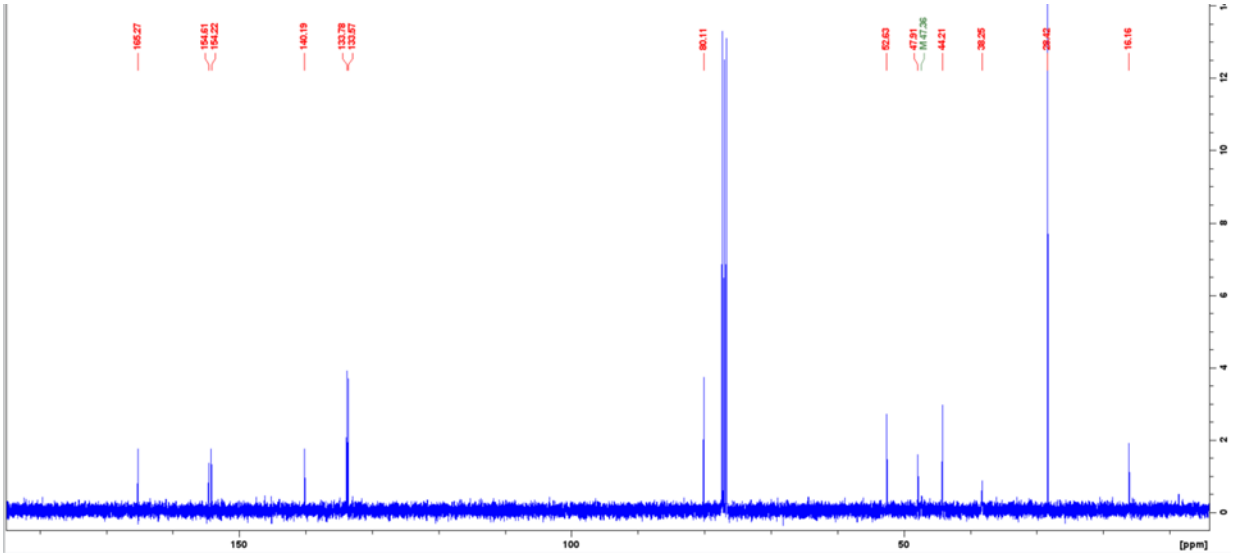
Fig S22: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 14.5

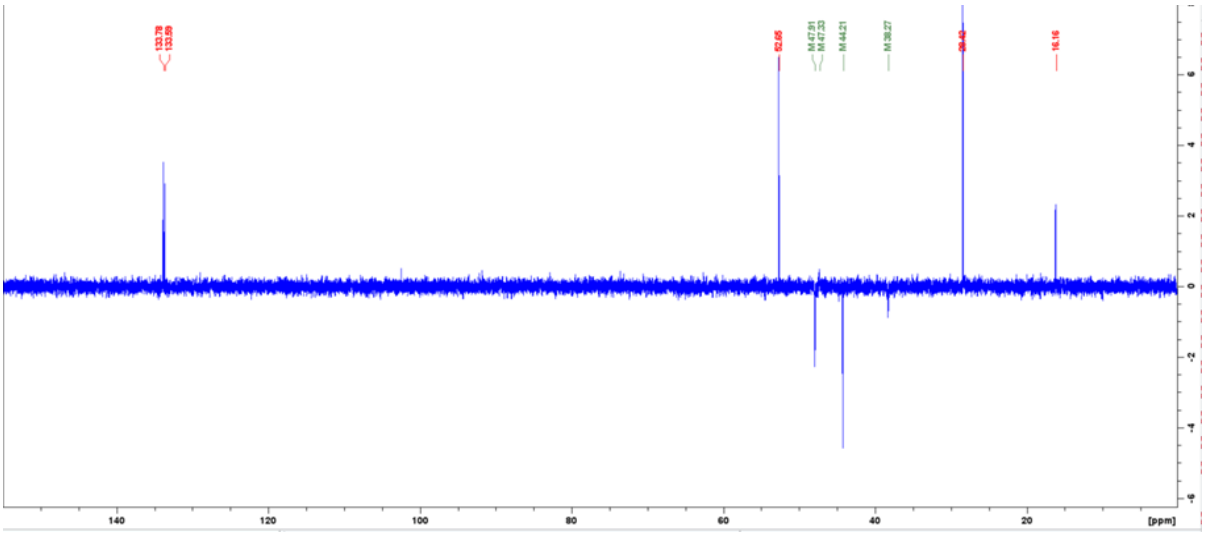
Spectral data of 14.6



IR (cm^{-1}): 2977(w), 2877(w), 1748(m), 1686(s), 1573(m), 1393(m), 1364(m), 1289(m), 1150(s), 1025(s); NMR (400 MHz, $CDCl_3$, [ppm]) δ: 8.54 (s,1H), 8.27 (s, 1H), 4.38 (bm, 1H), 4.29 – 4.25 (bd, 1H), 4.09 – 4.05 (m, 1H), 4.01-3.99 (m, 1H), 3.97 (s, 3H), 3.42 – 3.37(dd, *J*=4.0, 13.1, 1H), 3.32 – 3.25(m, 1H), 3.16 – 3.09 (dt, *J*=3.85, 12.1, 1H), 1.50 (s, 9H), 1.22-1.20 (d, J=6.6, 3H); CNMR (100 MHz, $CDCl_3$, [ppm]) δ: 165.2, 154.6, 154.2, 140.2, 133.8, 133.6, 80.1, 52.6, 47.9, 44.2, 28.4, 16.2; ESI-MS: MH^+ = 337.1857 (Expected MH^+ = 337.1798)


8.54
8.27
7.28
1.60
1.22
[ppm]


165.27
154.61
154.22
140.19
133.78
133.57
80.11
62.63
47.91
M 47.36
44.21
38.25
38.42
16.16
[ppm]


133.78
133.69
62.95
M 47.91
M 47.20
M 44.21
M 38.27
38.42
16.16
[ppm]

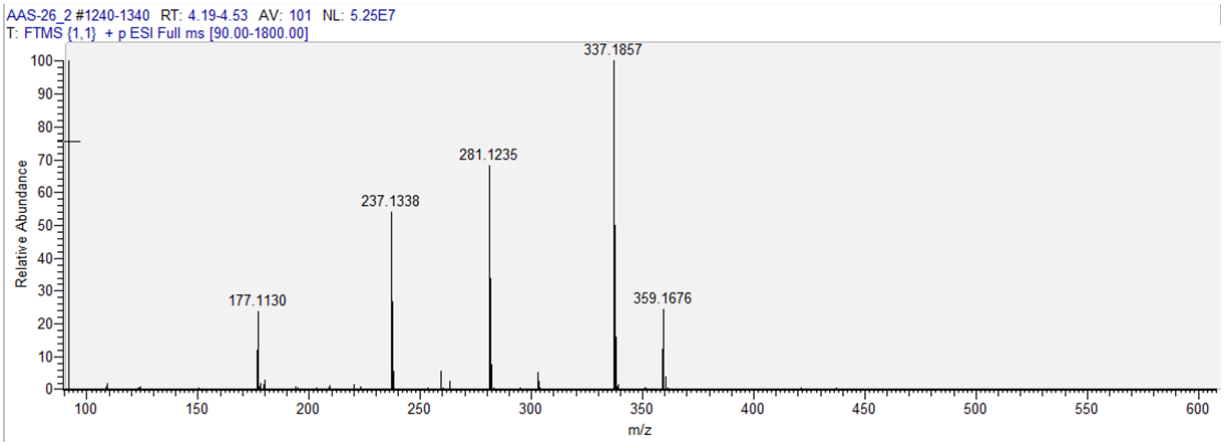
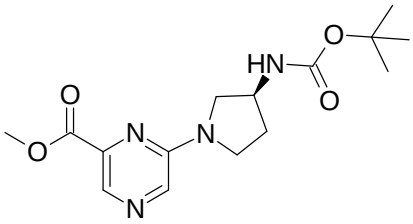
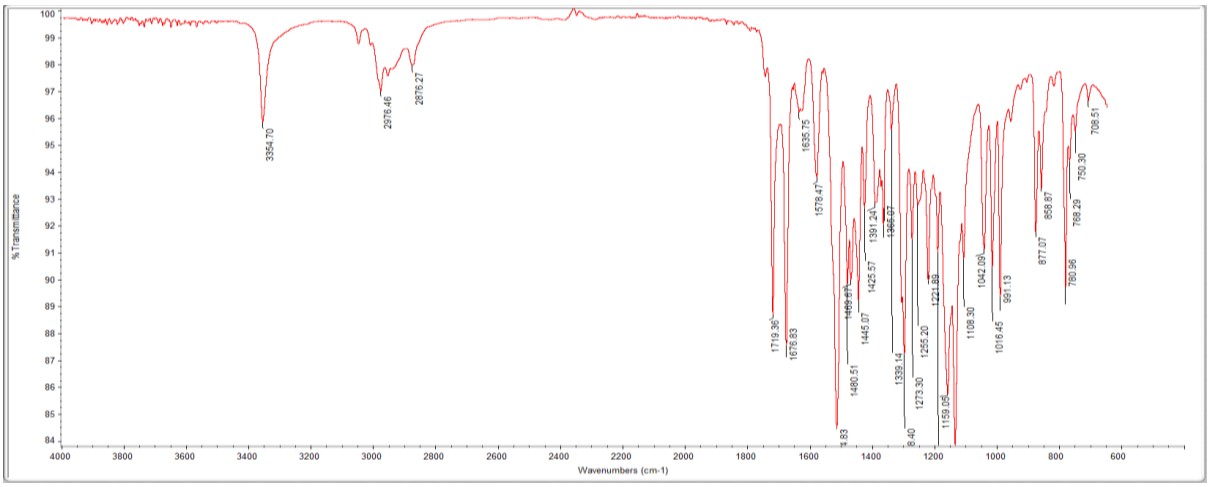


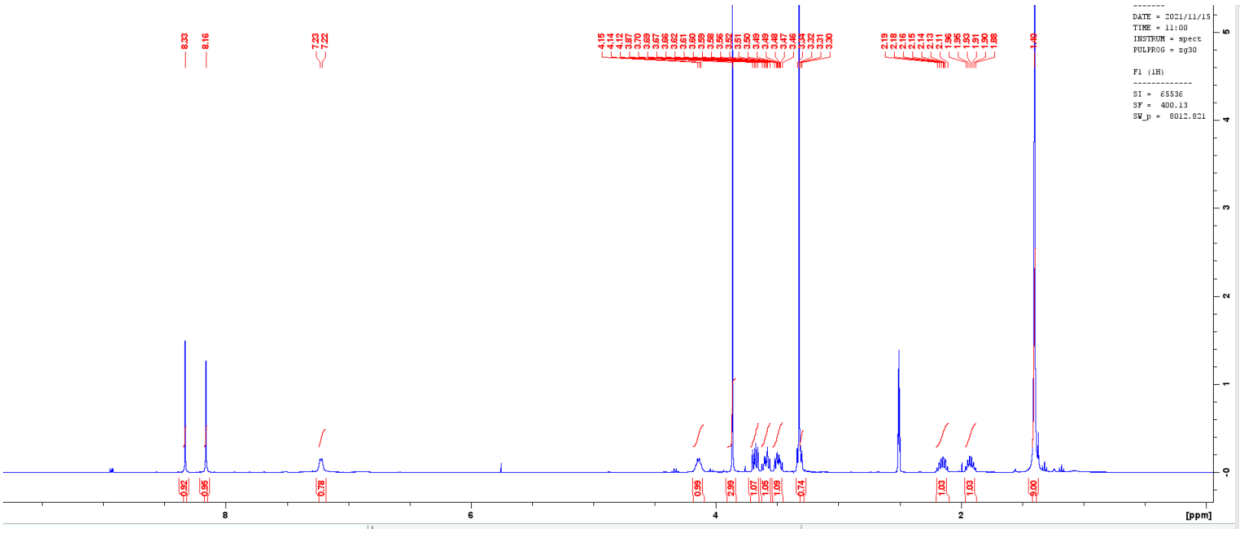
Fig S23: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 14.6

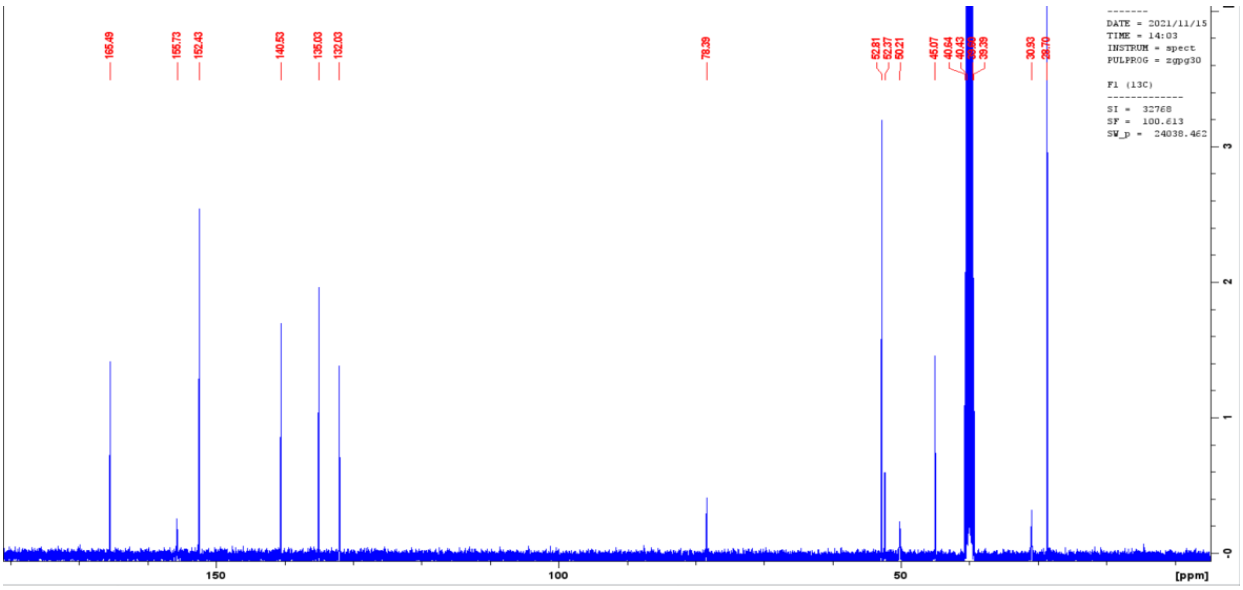
Spectral data of 14.7

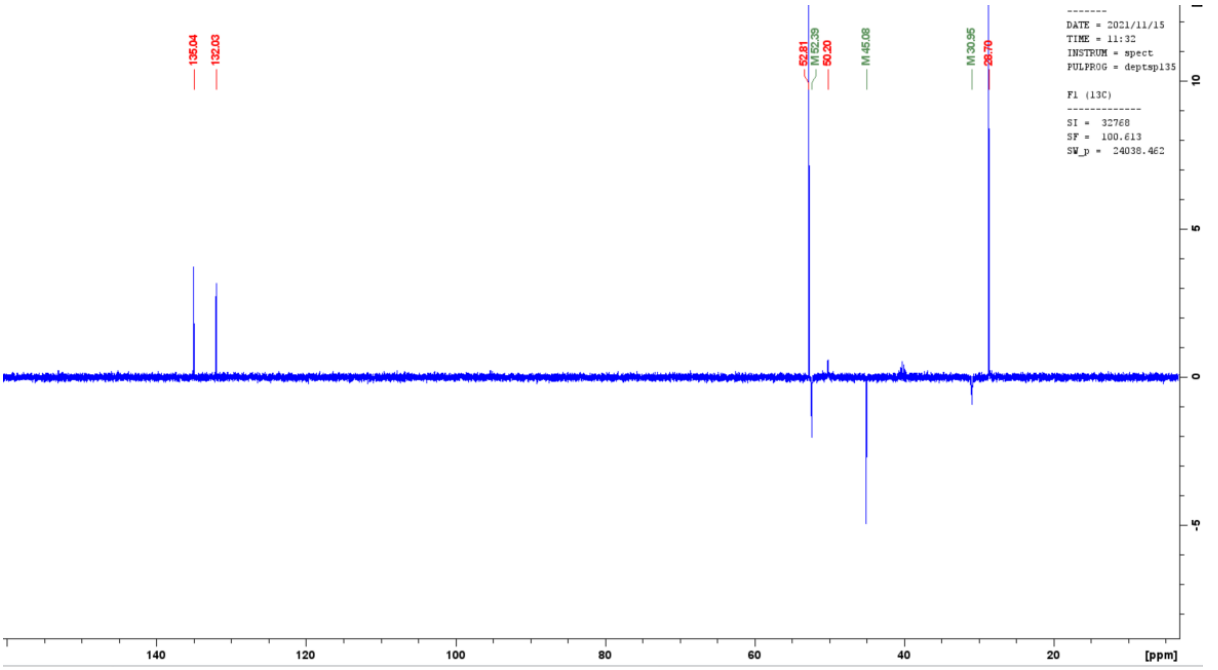


IR (cm^{-1}): 3354(m), 2976(w), 2876(w), 1719(s), 1676(s), 1504(s), 1480(w), 1445(w), 1339(m), 1288(w), 1159(s), 1016(s); NMR (400 MHz, DMSO-D6, [ppm]) δ: 8.33 (s, 1H), 8.16 (s, 1H), 7.23 (d, 1H), 4.14 (bm, 1H), 3.87 (s, 3H), 3.70 – 3.66 (dd, *J*= 6.1, 11, 1H), 3.62 – 3.56 (m, 1H), 3.52 – 3.46 (m, 1H), 3.34-3.30 (dd, *J* =6.1, 11, 1H), 2.19-2.11 (sext, *J*=6.2, 1H), 1.96-1.88 (m, *J* =7.1, 1H), 1.40 (s, 9H); CNMR (100 MHz, DMSO-D6, [ppm]) δ: 165.5, 155.7, 152.4, 140.5, 135.0, 132.0, 78.4, 52.8, 52.4, 50.2, 45.0, 30.9, 28.9; ESI-MS: MH^+ = 323.1718 (Expected MH^+ = 323.1641)




DATE = 2021/11/15
TIME = 11:00
INSTRUM = spect
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 400.13
SW_p = 8012.821
[ppm]


DATE = 2021/11/15
TIME = 14:03
INSTRUM = spect
PULPROG = zgpg30
F1 (13C)
SI = 32768
SF = 100.613
SW_p = 24038.462
[ppm]



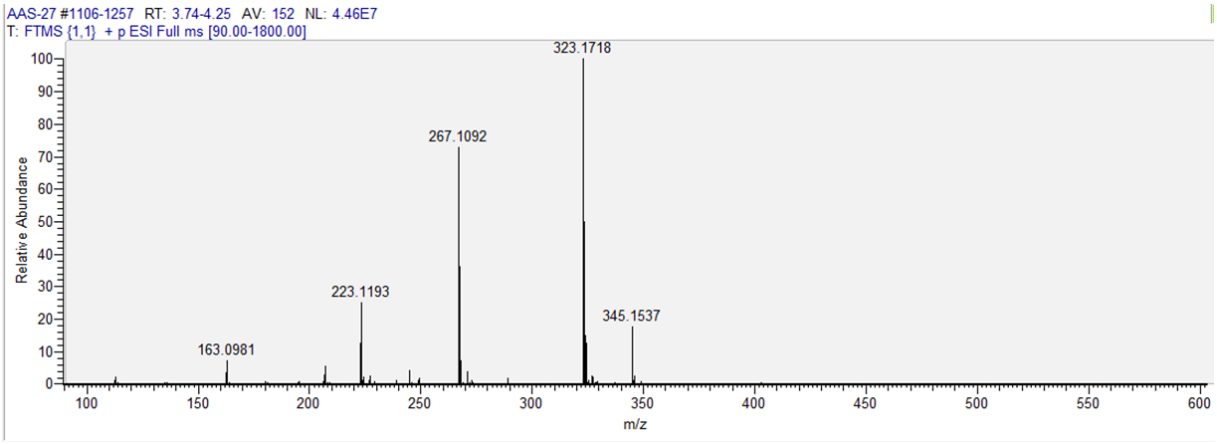


Fig S24: Figure representing IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, ESI-MS of compound 14.7