Synthesis and Discovery of Andrographolide Derivatives as Nonsteroidal Farnesoid X Receptor (FXR) Antagonists

Zhuyun Liu,[a,§] Wai-Kit Law,[b] Decai Wang,[a] Xin Nie,[a] Dekuan Sheng,[a] Genrui Song,[a] Kai Guo,[c] Ping Wei,[c] Pingkai Ouyang,[c] Chi-Wai Wong,[*,b] Guo-Chun Zhou[*,a]

[a] School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing 211816, PR China

[b] NeuMed Pharmaceuticals Limited, Shatin, N.T., Hong Kong, PR China

[c] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, PR China

[§] Current address: Department of Pharmaceutical and Chemical Engineering, Taizhou Polytechnic College, Taizhou 225300, Jiangsu, PR China

Corresponding Authors:

*(G.-C.Z.) Tel: 86-25-58139415, E-mail: gczhou@njtech.edu.cn; *(C.-W.W.) Tel: 852-67487218, E-mail: wongcw@neumedpharma.com.hk

Contents:

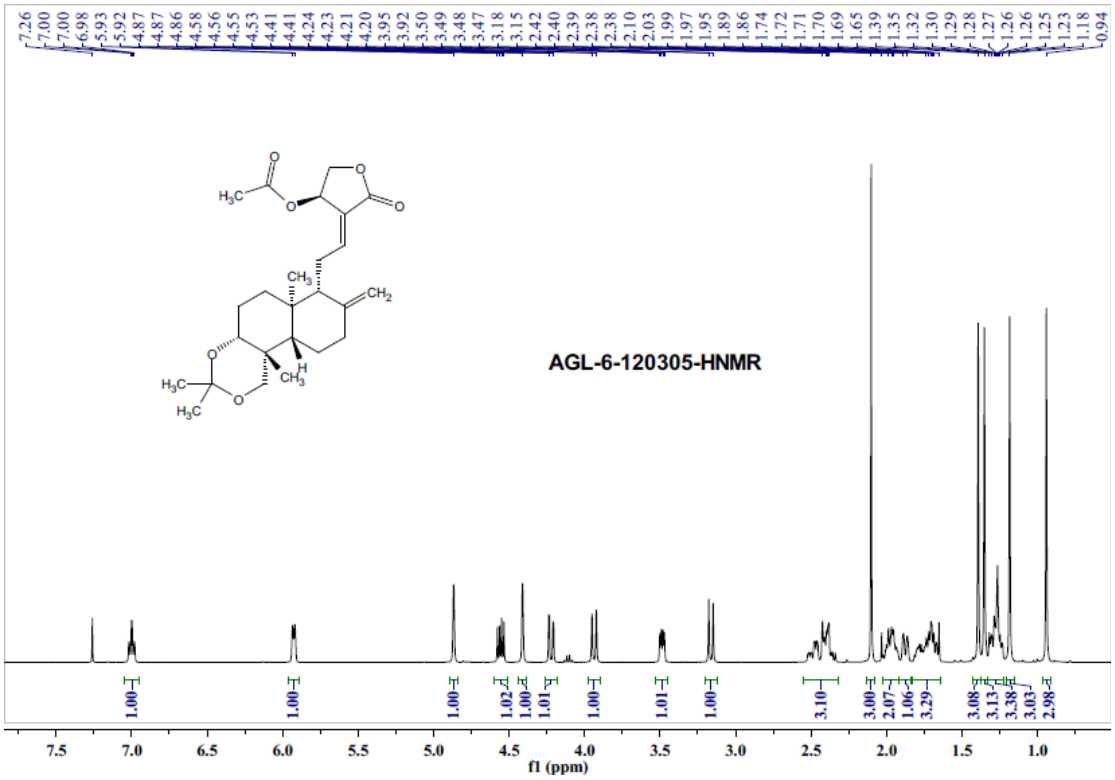
Table s1. Calculated Data of Lipinski's Rule of Five

entry	cmpd[a)]	R	14-isomer	MW	H-bond donors	H-bond acceptors	ClogP[b)]
1	**10a**	H	β	466.6	0	5	6.5108
2	**12a**	H	β	426.5	2	5	4.4698
3	**10b**	4'-NO_2	β	511.6	0	8	6.5538
4	**12b**	4'-NO_2	β	471.5	2	8	4.5128
5	**10c**	3'-NO_2	β	511.6	0	8	6.5538
6	**12c**	3'-NO_2	β	471.5	2	8	4.5128
7	**10d**	2'-NO_2	β	511.6	0	8	6.5538
8	**12d**	2'-NO_2	β	471.5	2	8	4.5128
9	**10e**	2'-CO_2Et	β	538.7	0	7	7.0238
10	**12e**	2'-CO_2Et	β	498.6	2	7	4.9828
11	**10f**	2'-OCH_3	β	496.6	0	6	6.2498
12	**12f**	2'-OCH_3	β	456.6	2	6	4.2088
13	**10g**	2'-OCH_3-4'-NO_2	β	541.6	0	9	6.2723
14	**12g**	2'-OCH_3-4'-NO_2	β	501.6	2	9	4.2313
15	**10h**	2'-CH_3-4'-NO_2	β	525.6	0	8	7.0528
16	**12h**	2'-CH_3-4'-NO_2	β	485.6	2	8	5.0118
17	**10i**	2'-F-4'-NO_2	β	529.6	0	9	6.5458
18	**12i**	2'-F-4'-NO_2	β	489.5	2	9	4.5048
19	**11b**	4'-NO_2	α	511.6	0	8	6.5538
20	**13b**	4'-NO_2	α	471.5	2	8	4.5128
21	**11g**	2'-OCH_3-4'-NO_2	α	541.6	0	9	6.2723
22	**13g**	2'-OCH_3-4'-NO_2	α	501.6	2	9	4.2313
23	**1, andrographolide**		α	350.4	3	5	2.1186
24	**5**		α	390.5	1	5	4.1598
25	**6**		β	432.5	0	6	5.0182
26	**7**		β	392.5	2	6	2.9772
27	**8**		β	350.4	3	5	2.1186
28	**9**		β	390.5	1	5	4.1598

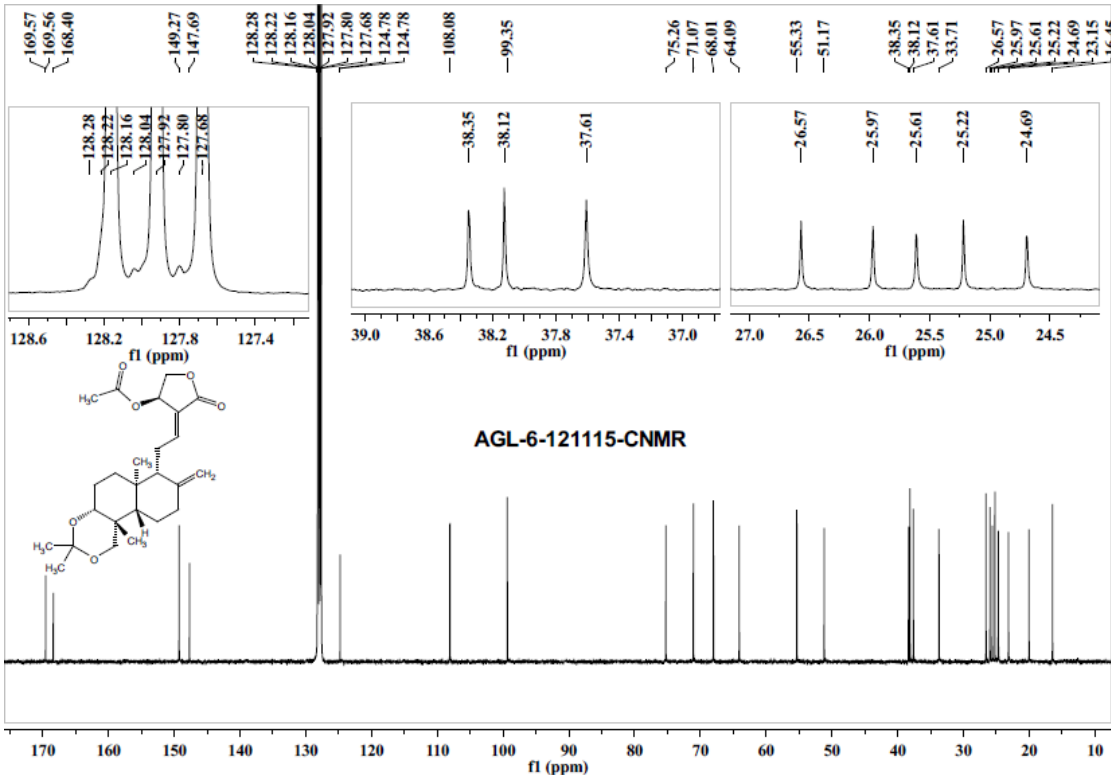
[a)] See Scheme 2. [b)] calculated by Chem3D Ultra 8.0.

NMR spectra

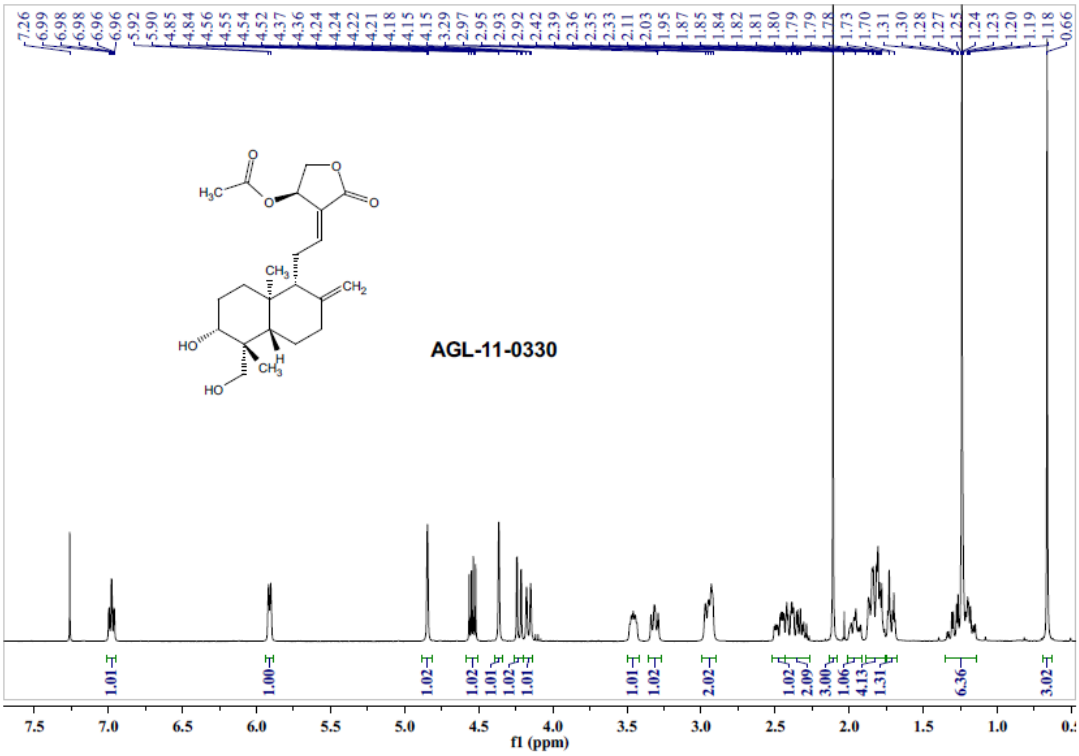
^{1}H NMR of **Compound 6:**



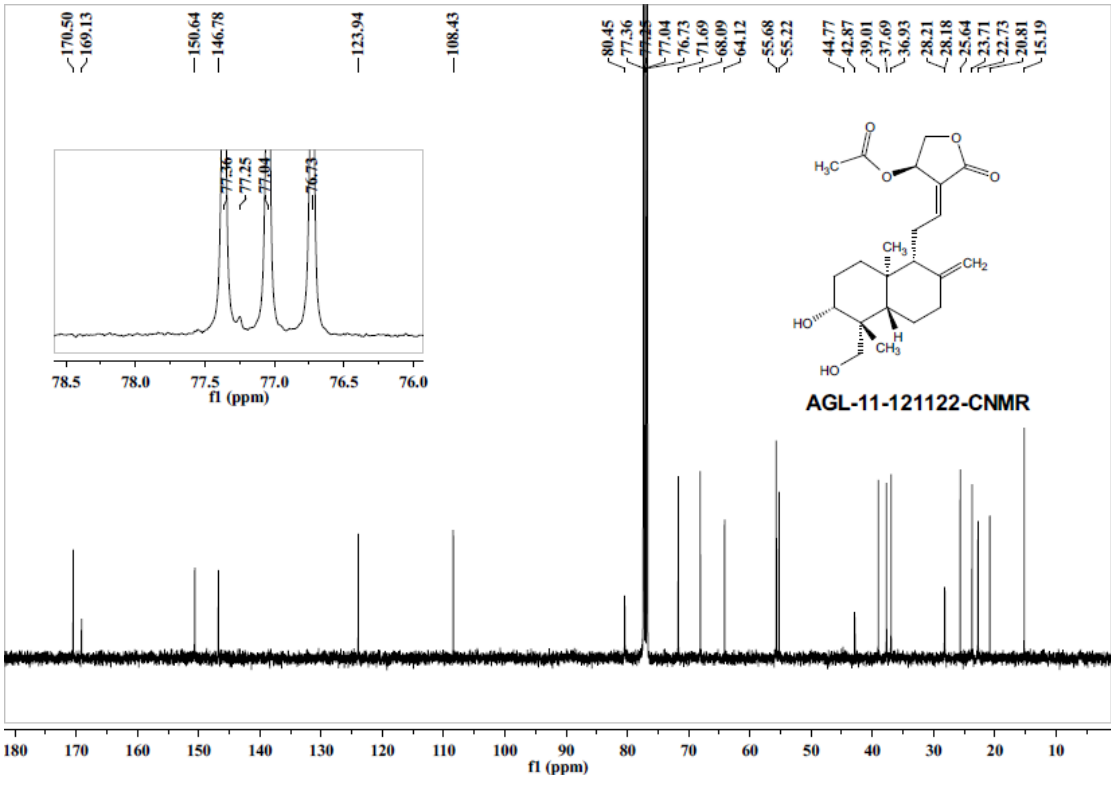
^{13}C NMR of **Compound 6:**



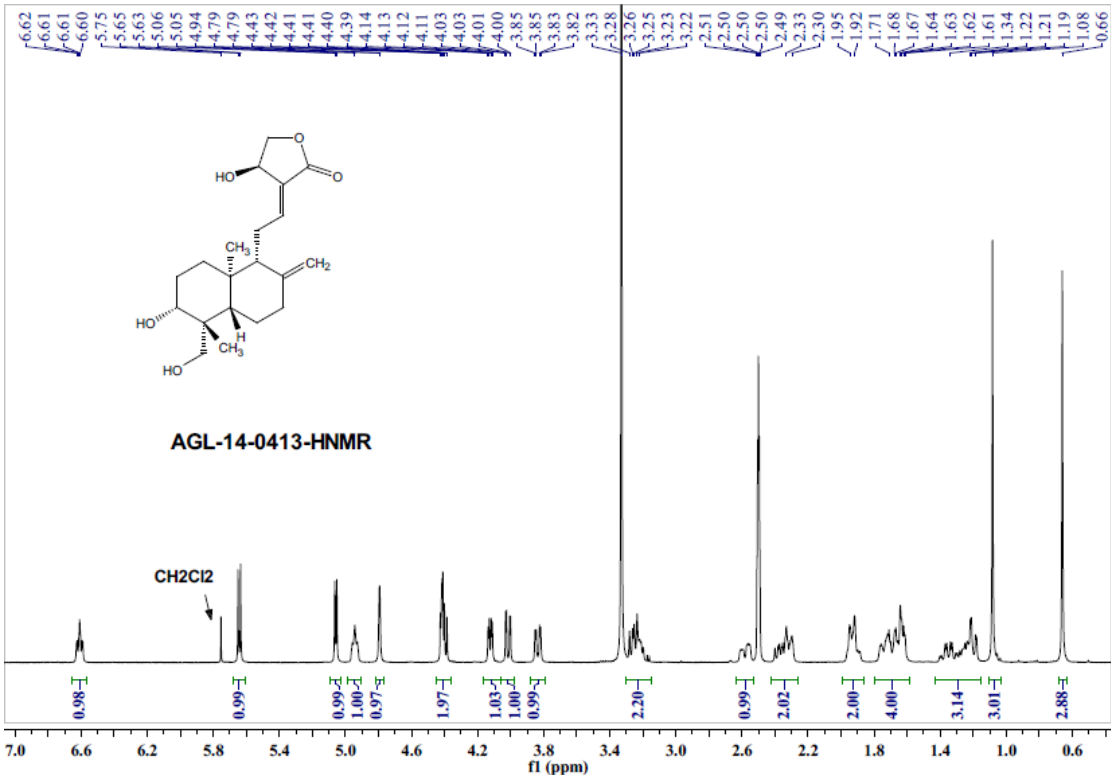
^{1}H NMR of **Compound 7:**



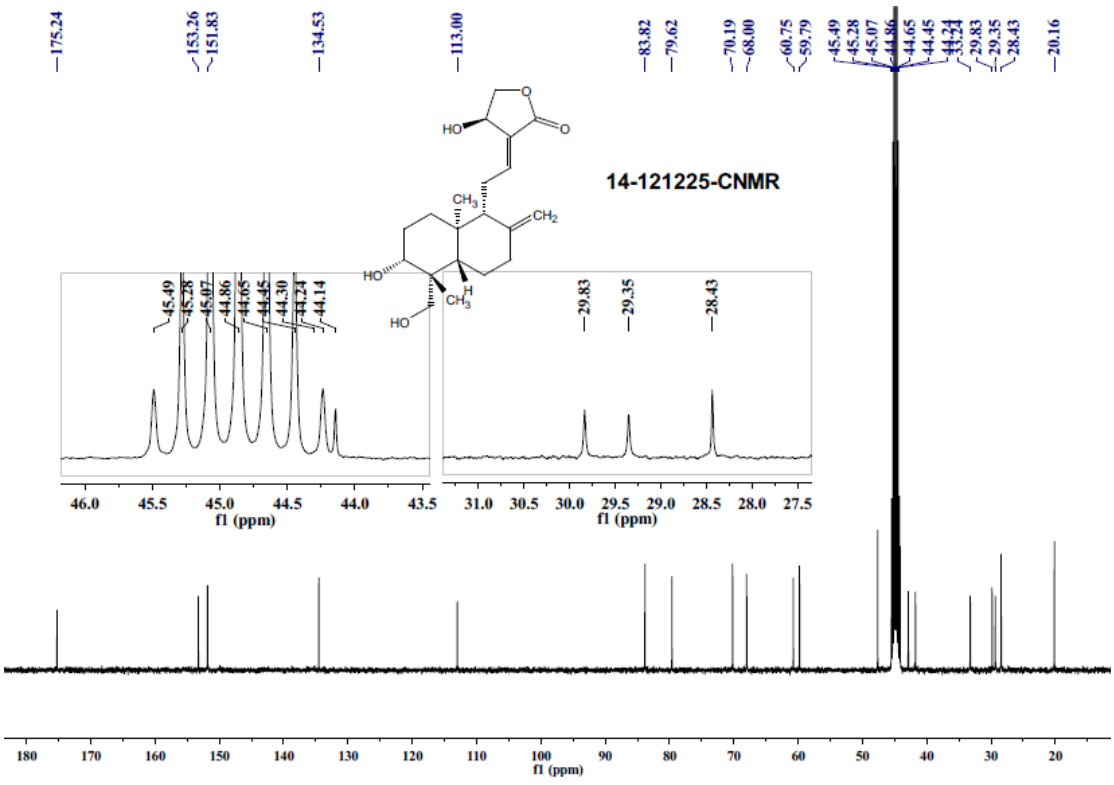
^{13}C NMR of **Compound 7:**



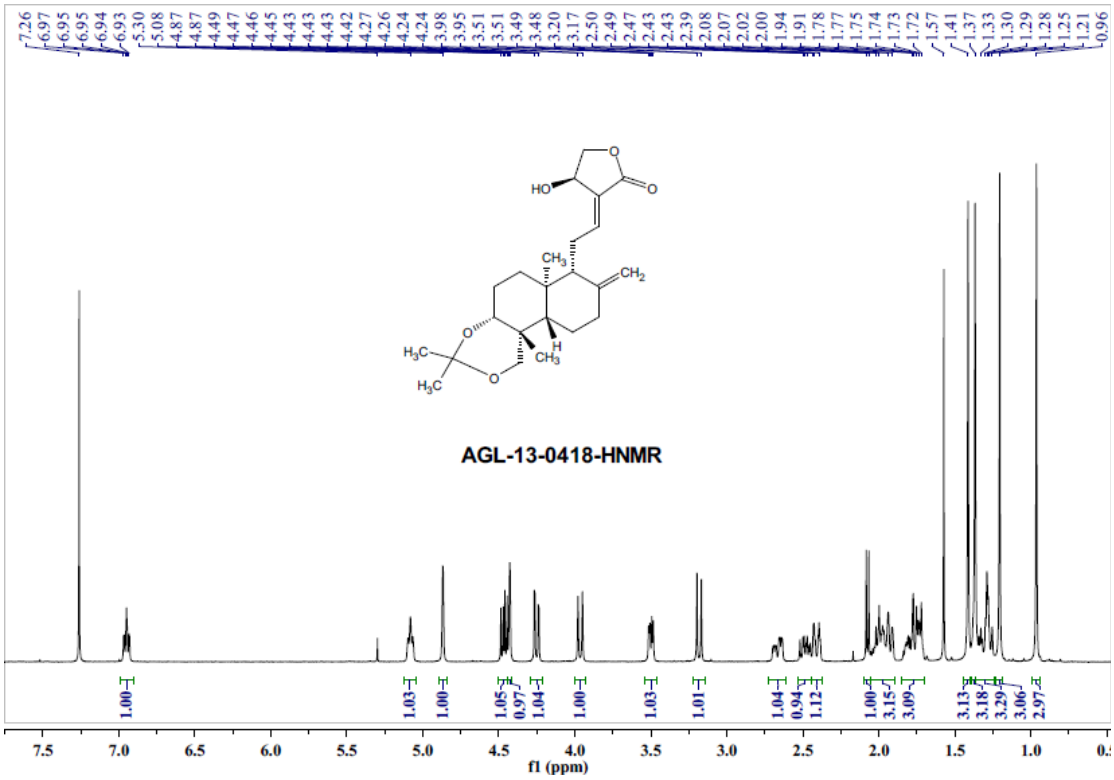
^{1}H NMR of **Compound 8:**



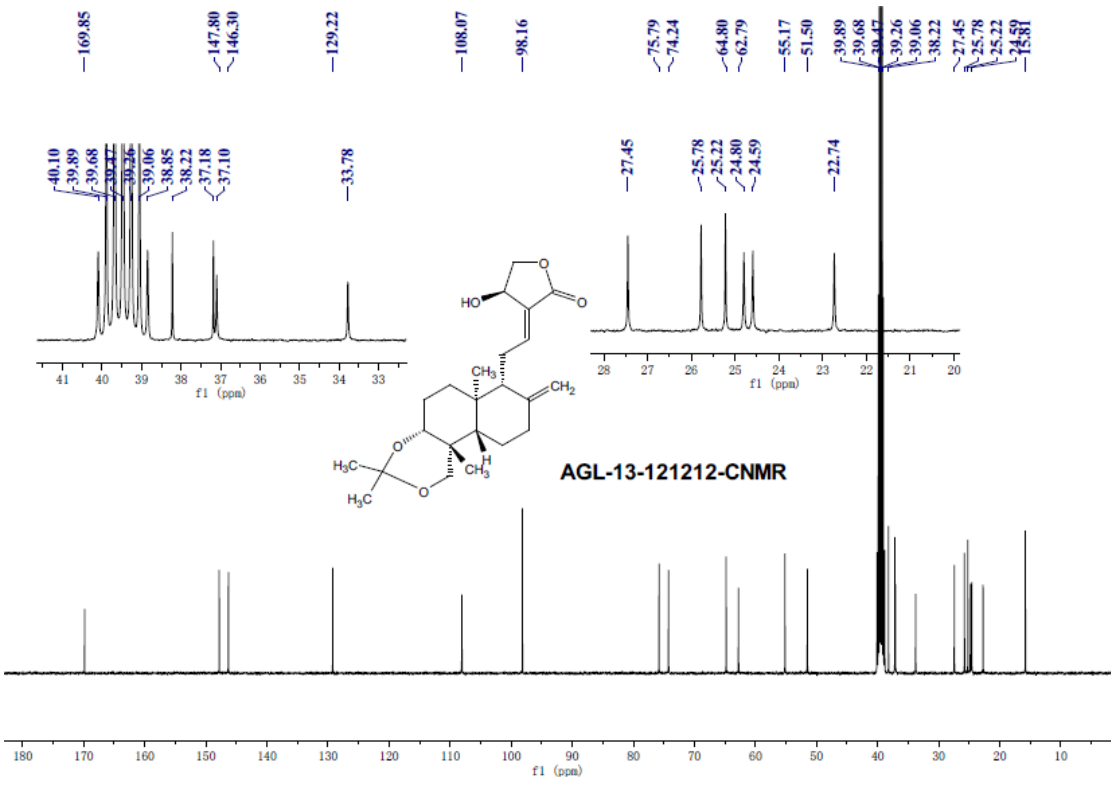
^{13}C NMR of **Compound 8:**



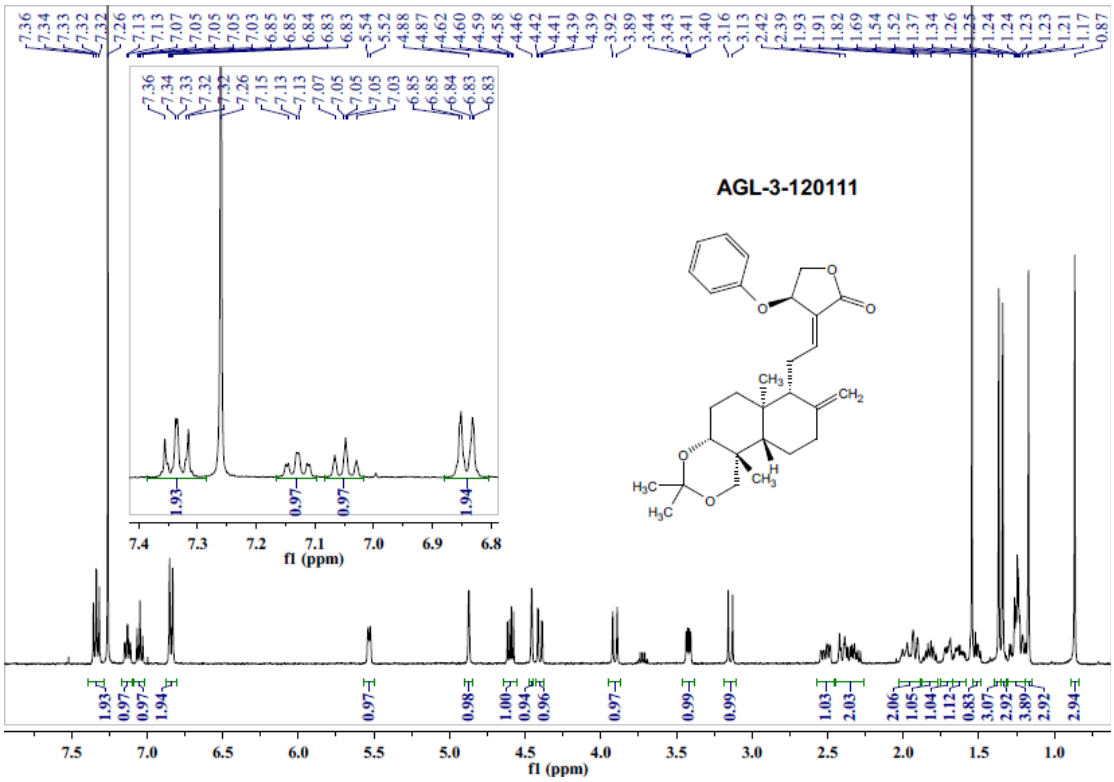
[1]H NMR of **Compound 9:**



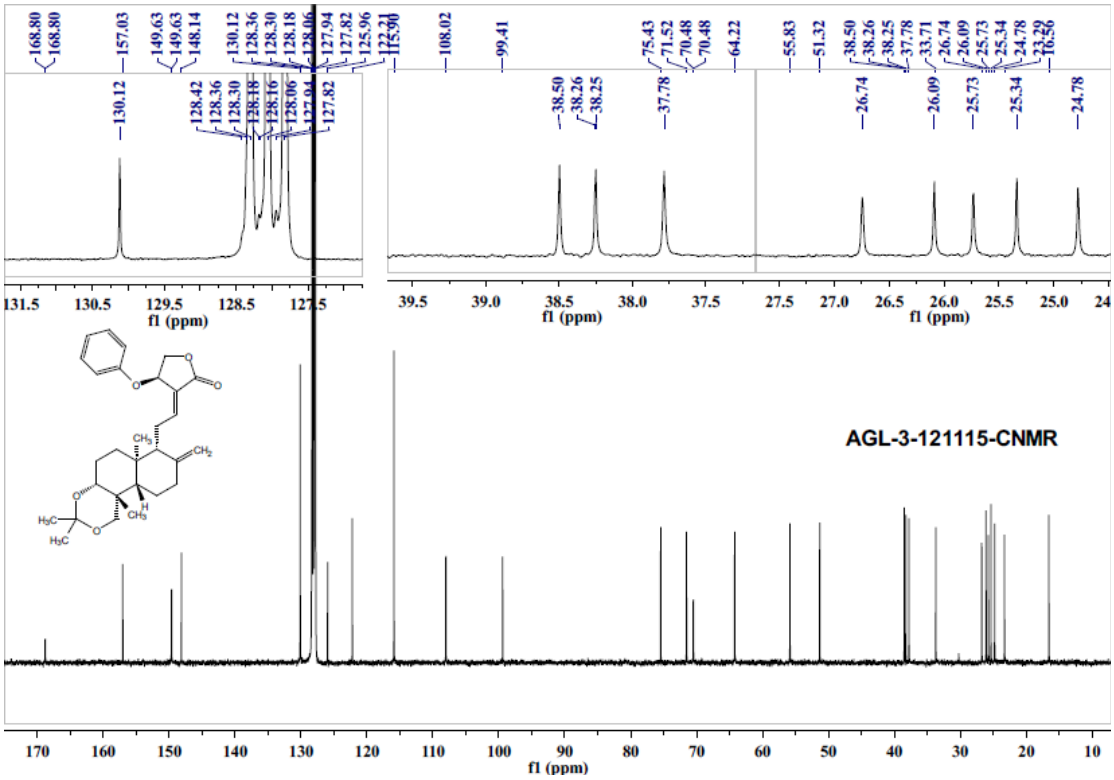
[13]C NMR of **Compound 9:**



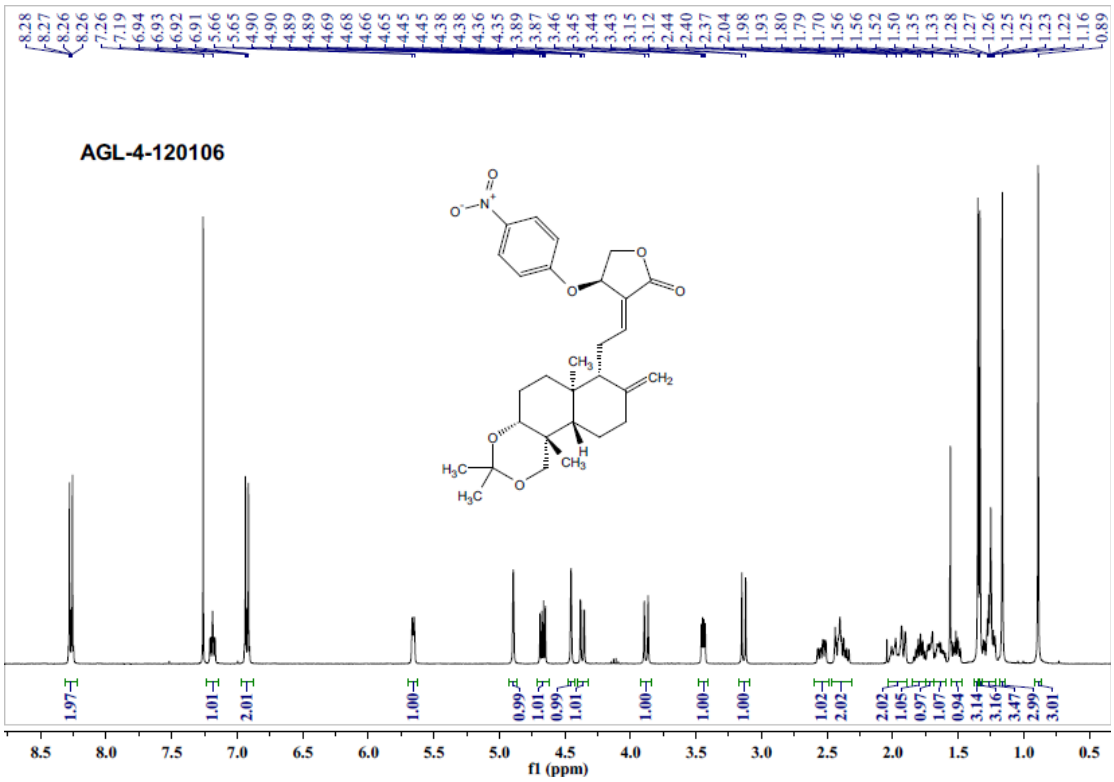
^{1}H NMR of **Compound 10a:**



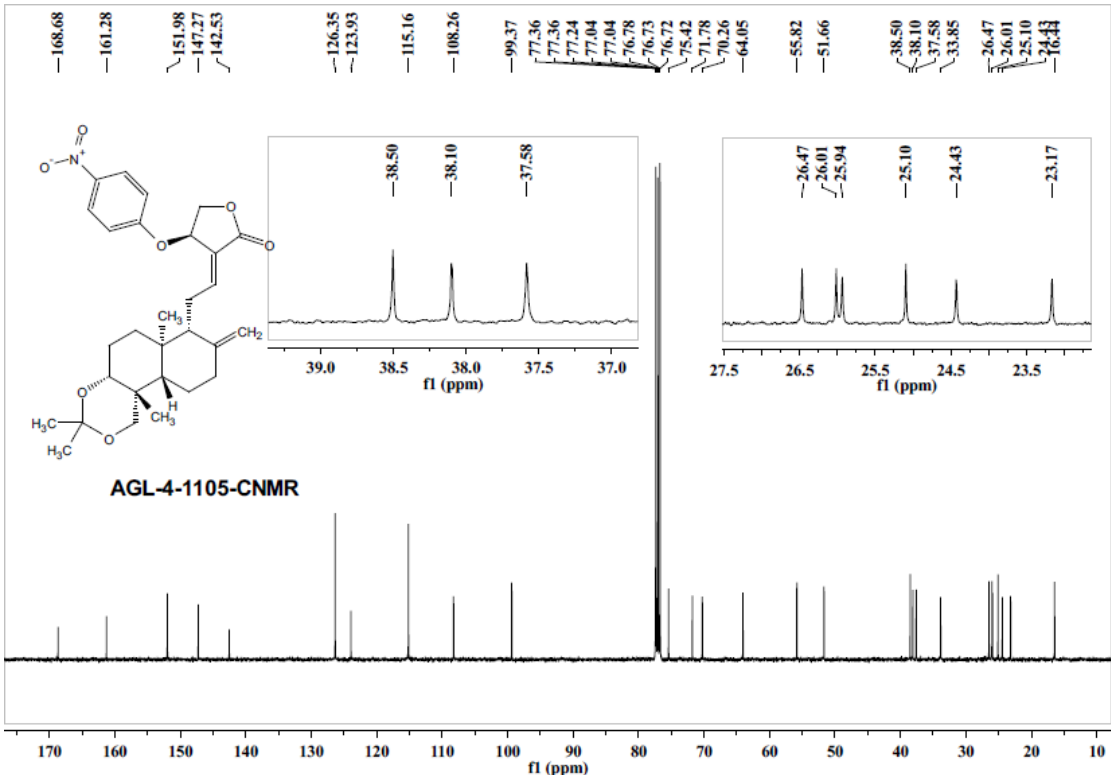
^{13}C NMR of **Compound 10a:**



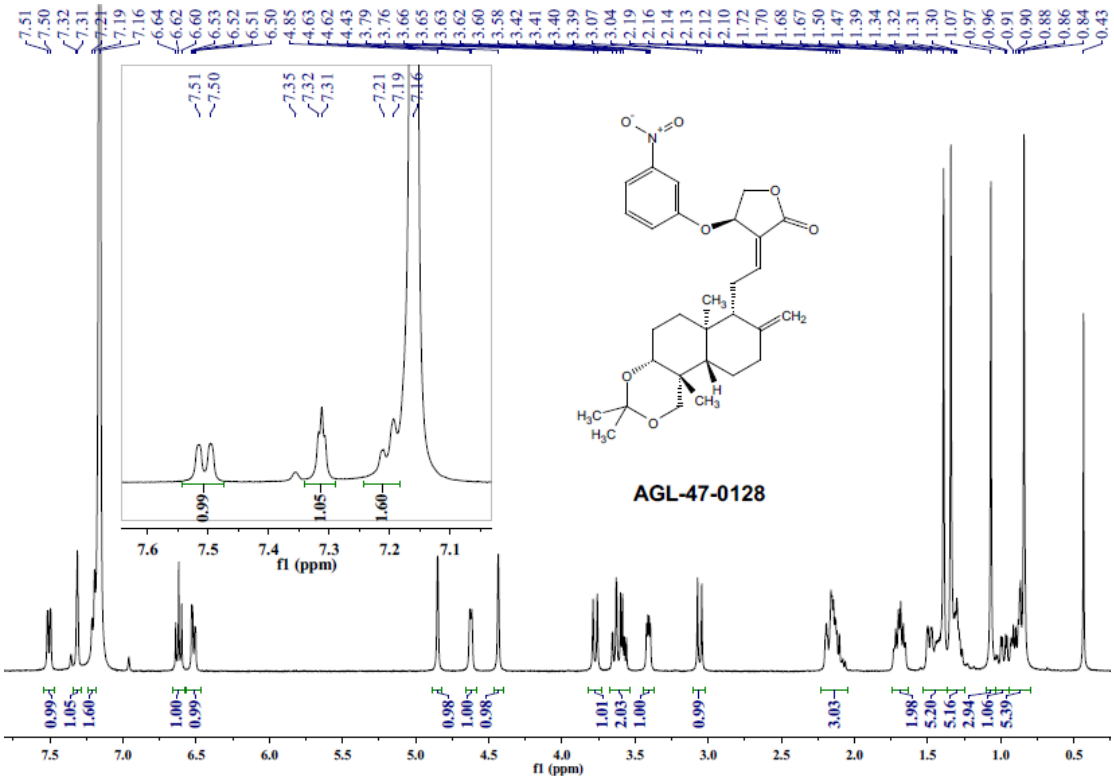
^{1}H NMR of **Compound 10b:**



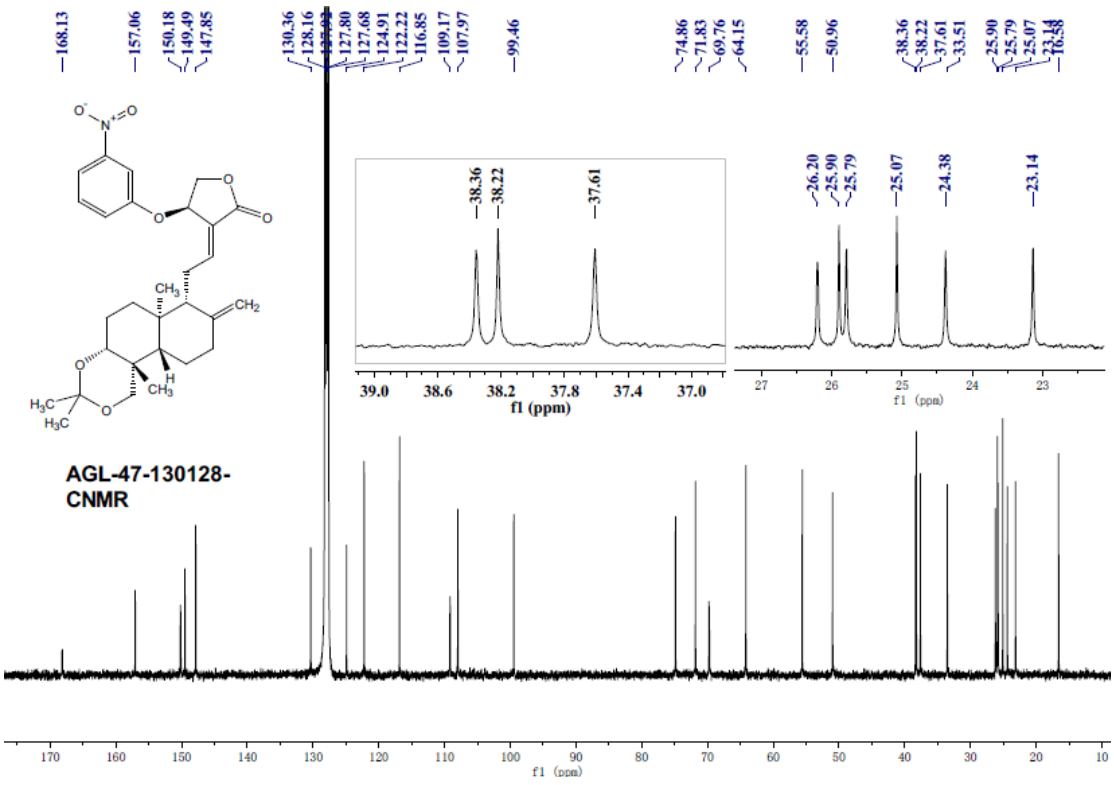
^{13}C NMR of **Compound 10b:**



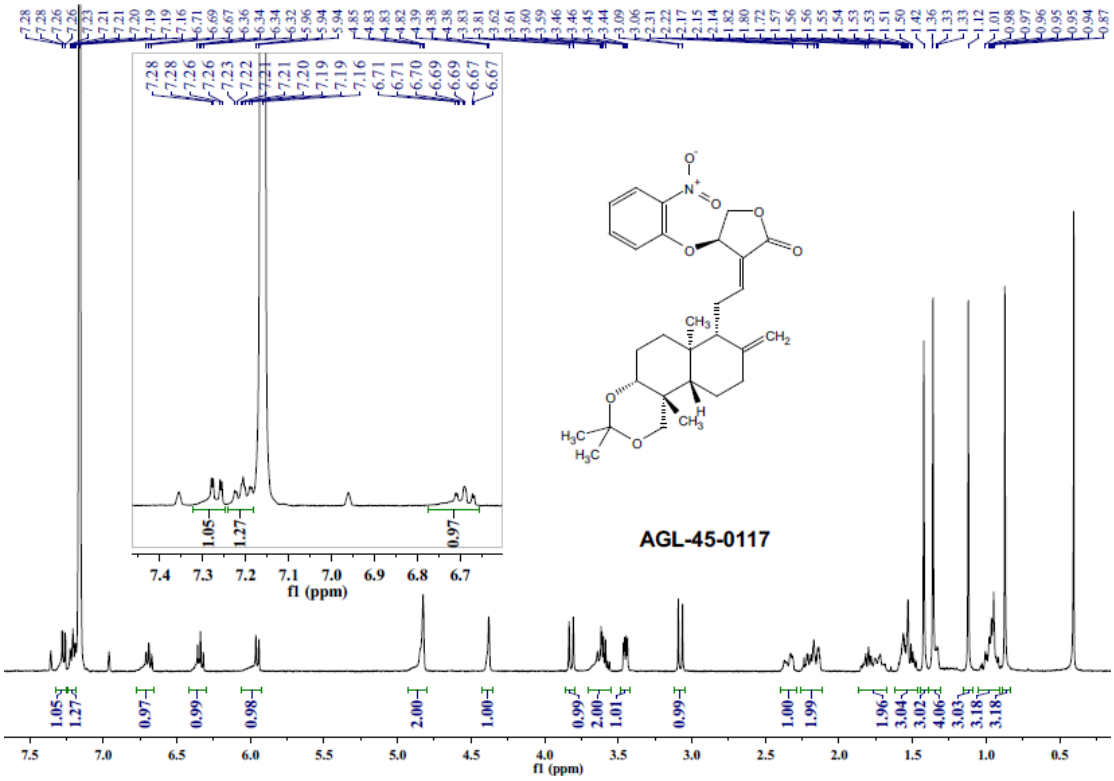
^{1}H NMR of **Compound 10c:**



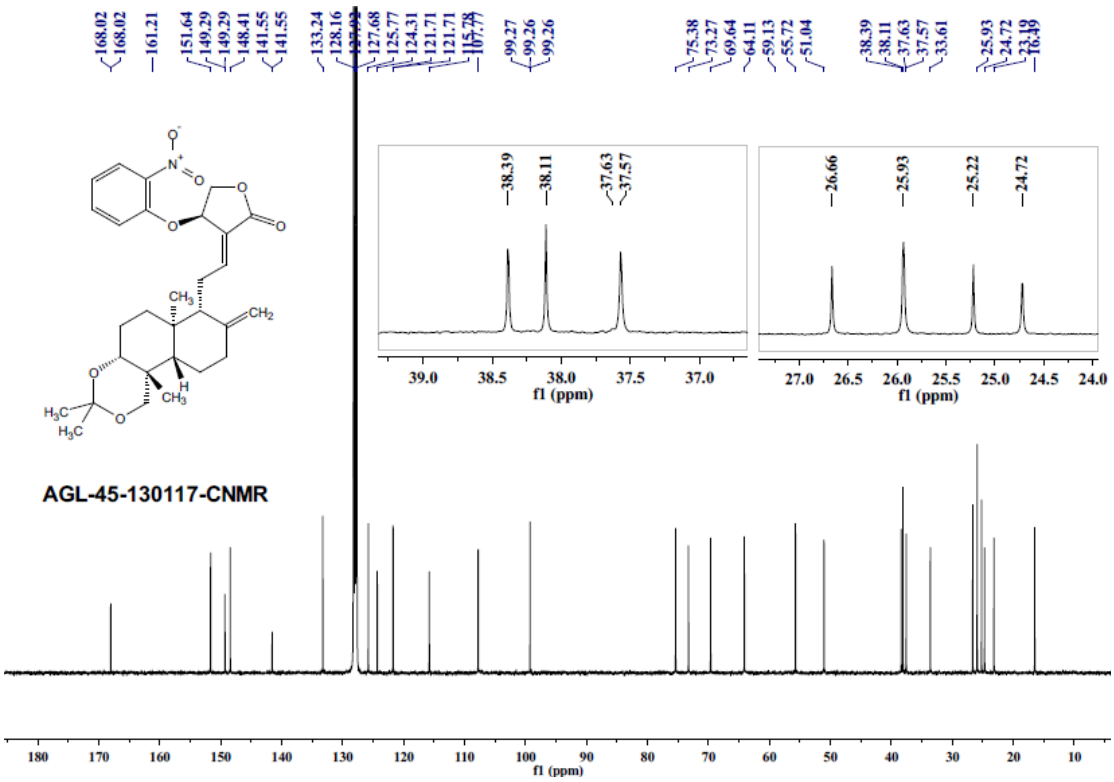
^{13}C NMR of **Compound 10c:**



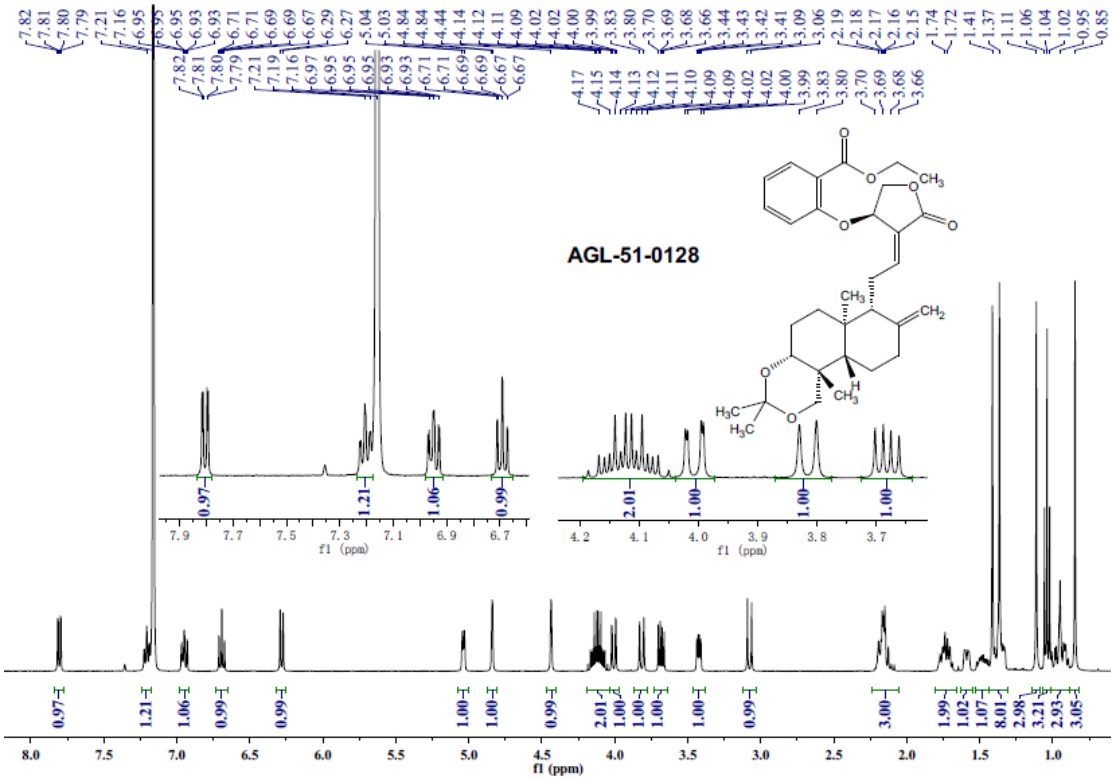
^{1}H NMR of **Compound 10d:**



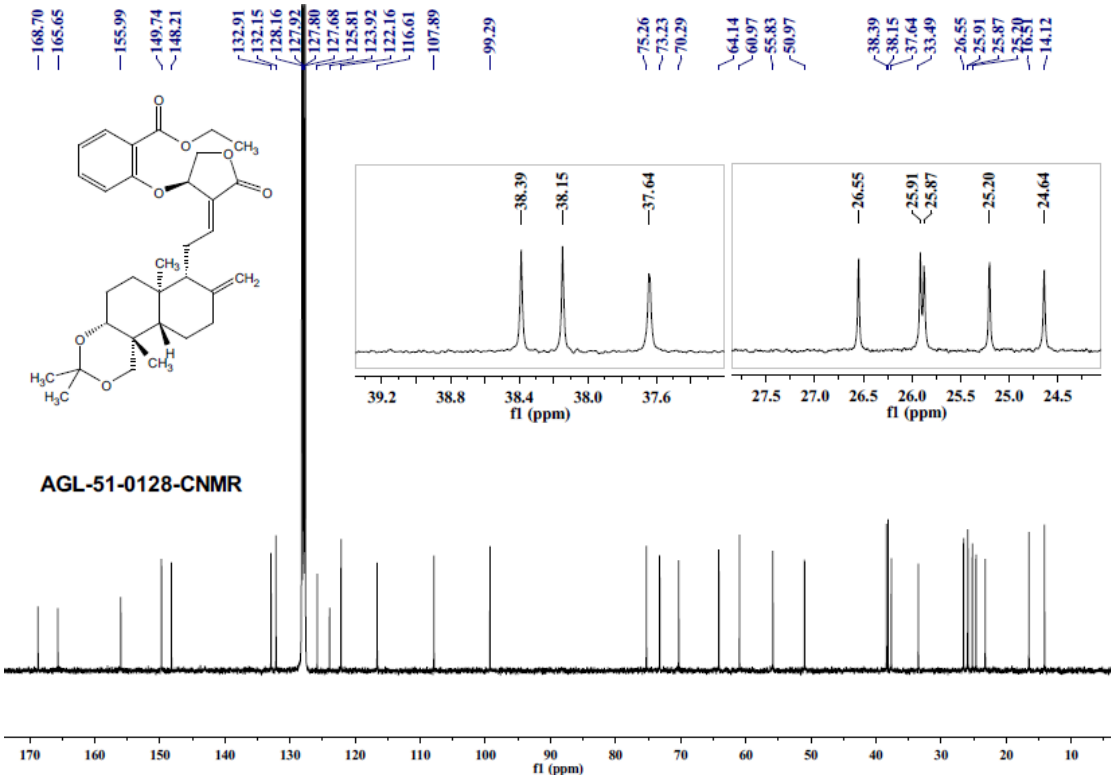
^{13}C NMR of **Compound 10d:**



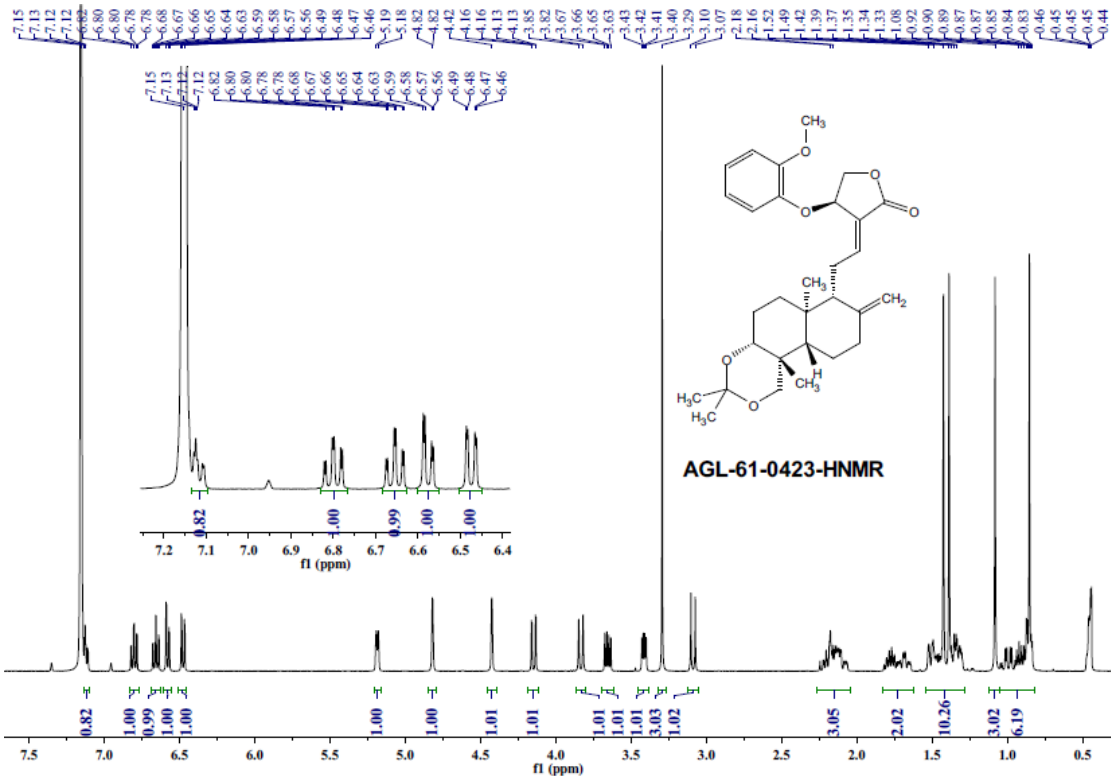
^{1}H NMR of **Compound 10e:**



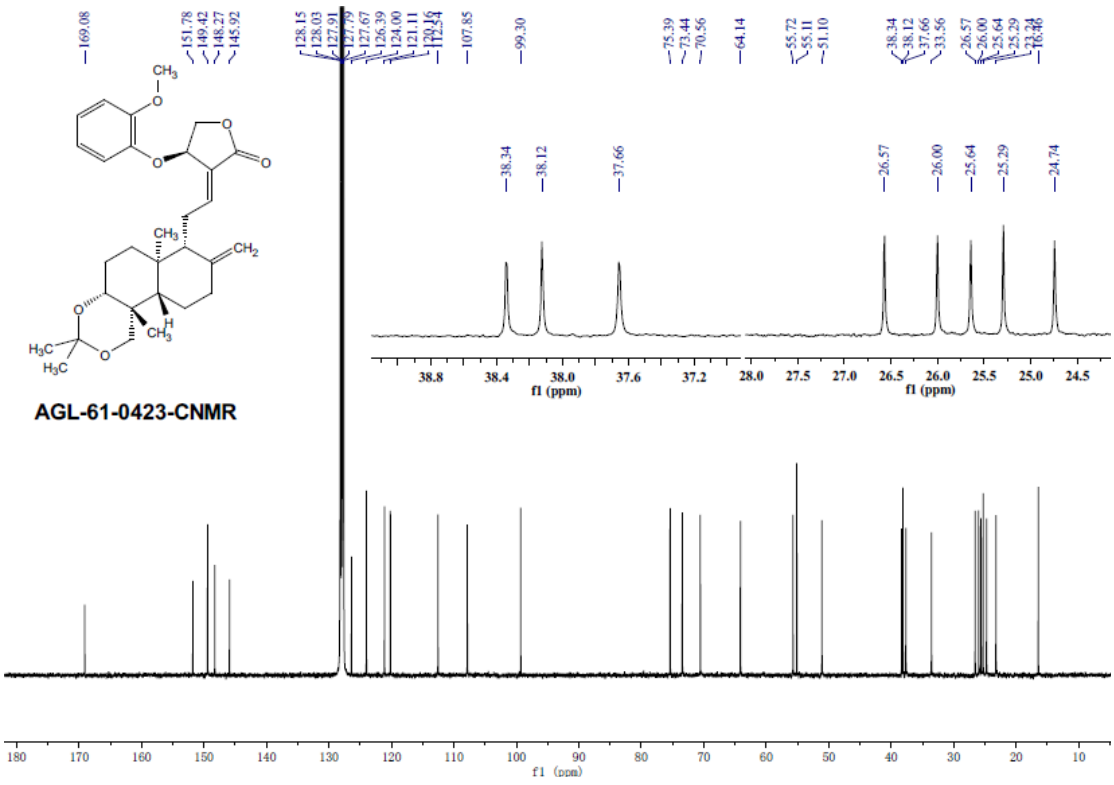
^{13}C NMR of **Compound 10e:**



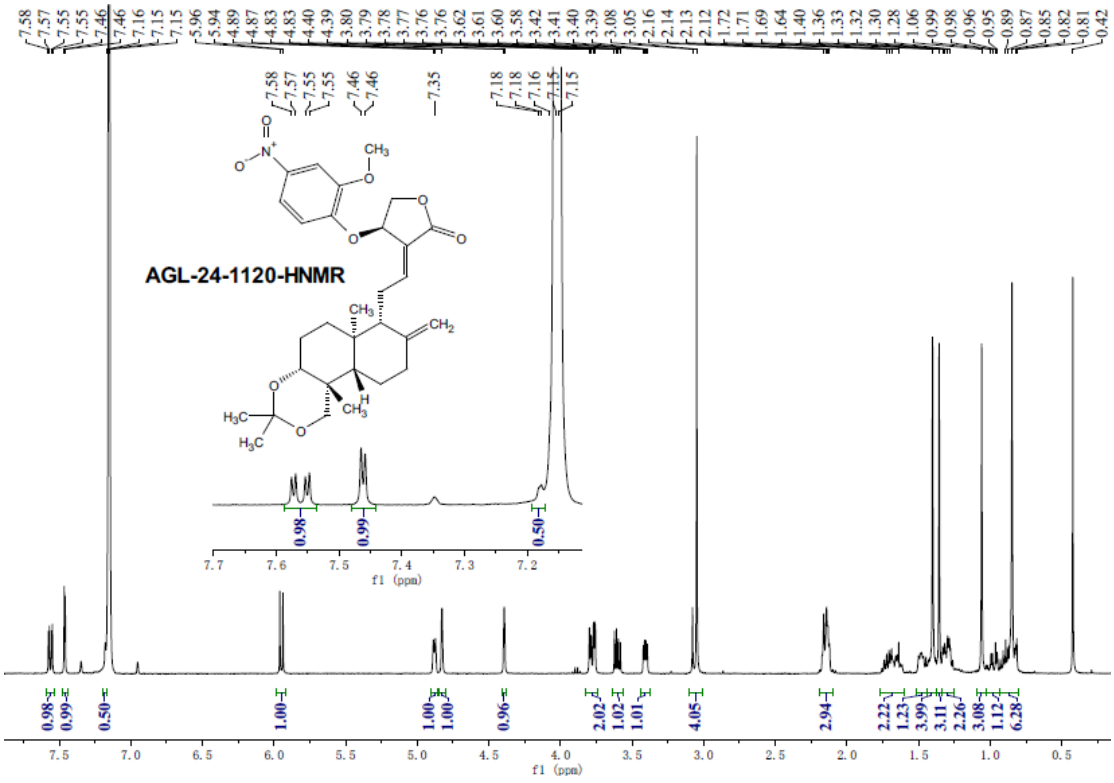
^{1}H NMR of **Compound 10f:**



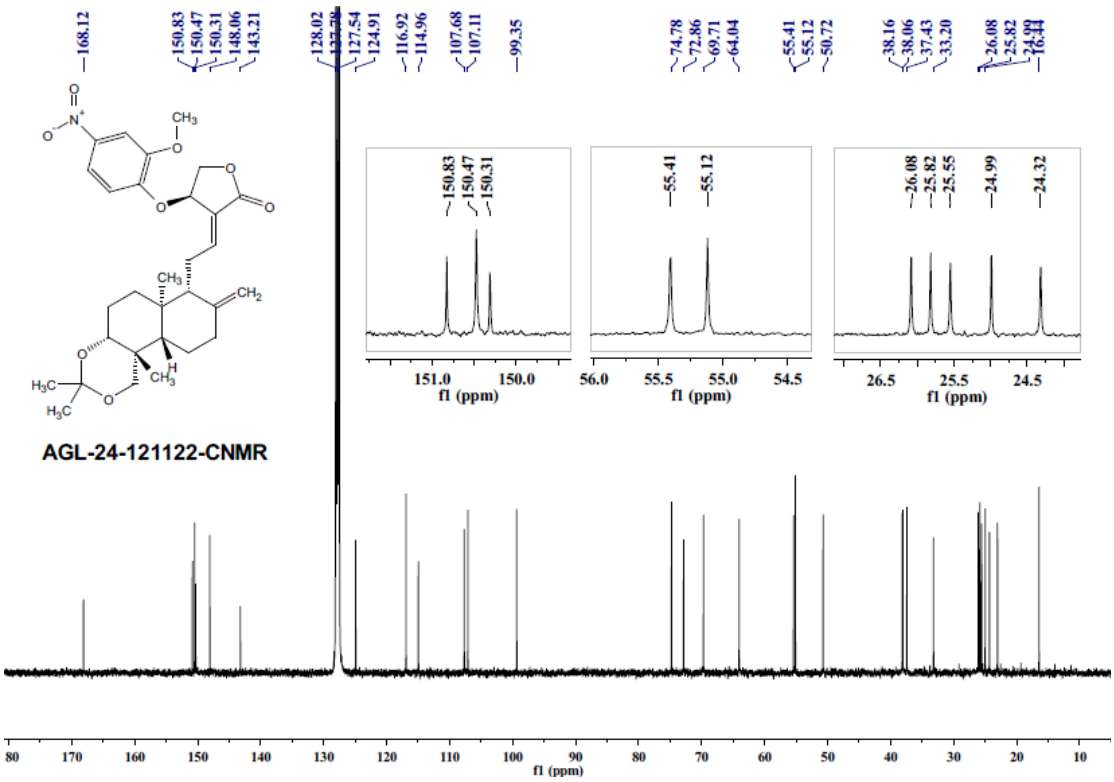
^{13}C NMR of **Compound 10f:**



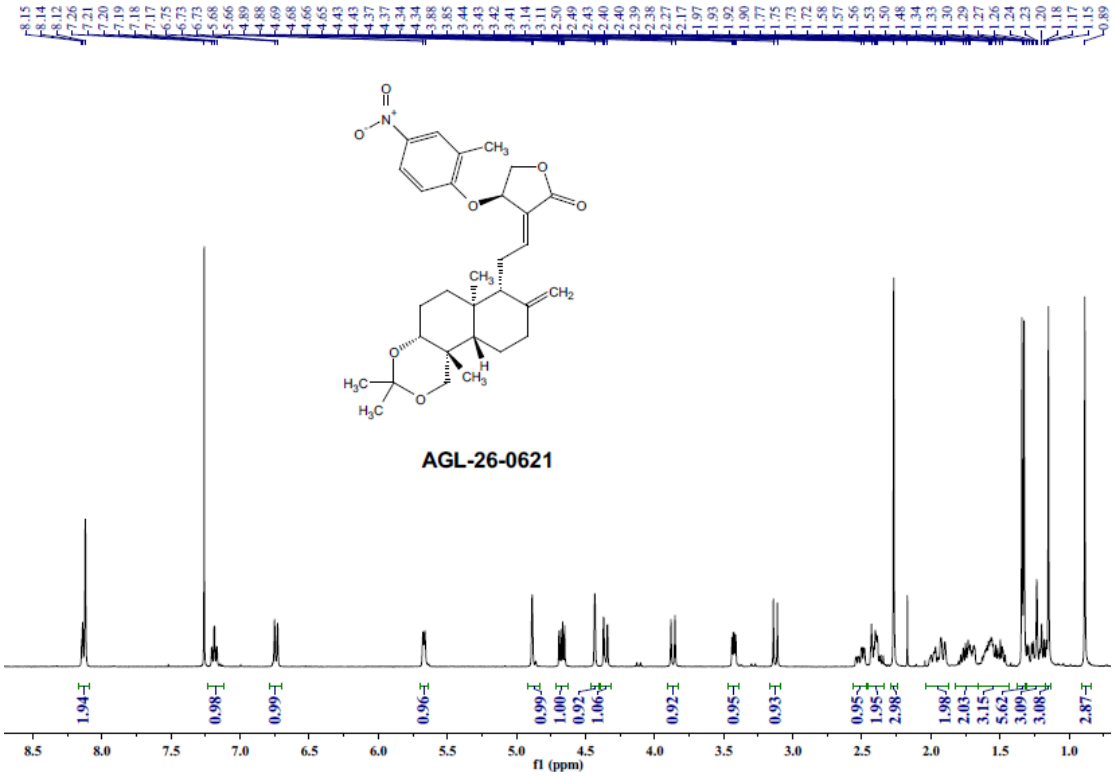
^{1}H NMR of **Compound 10g:**



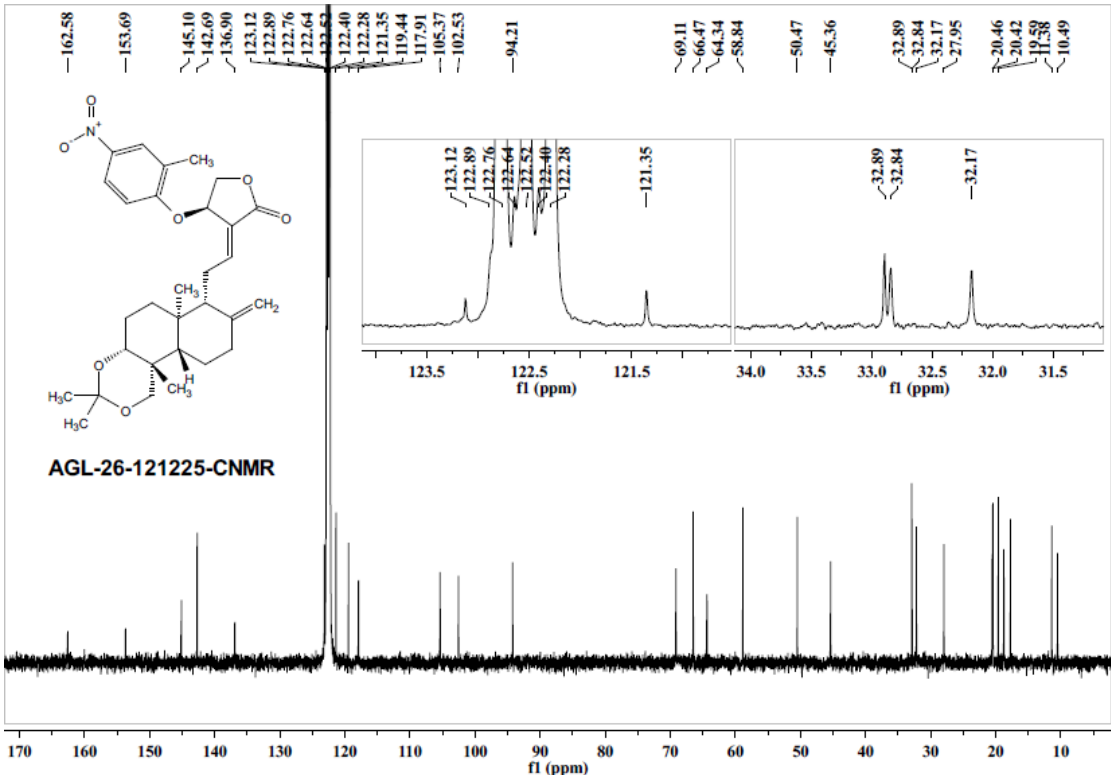
^{13}C NMR of **Compound 10g:**



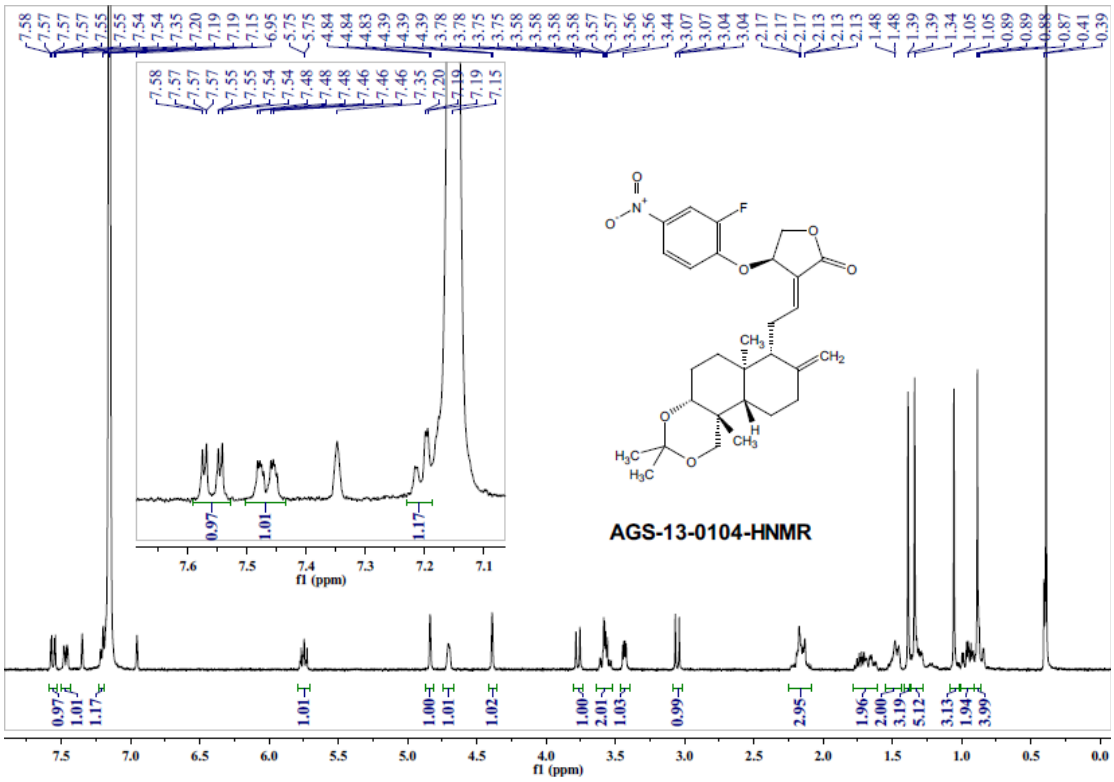
^{1}H NMR of **Compound 10h:**



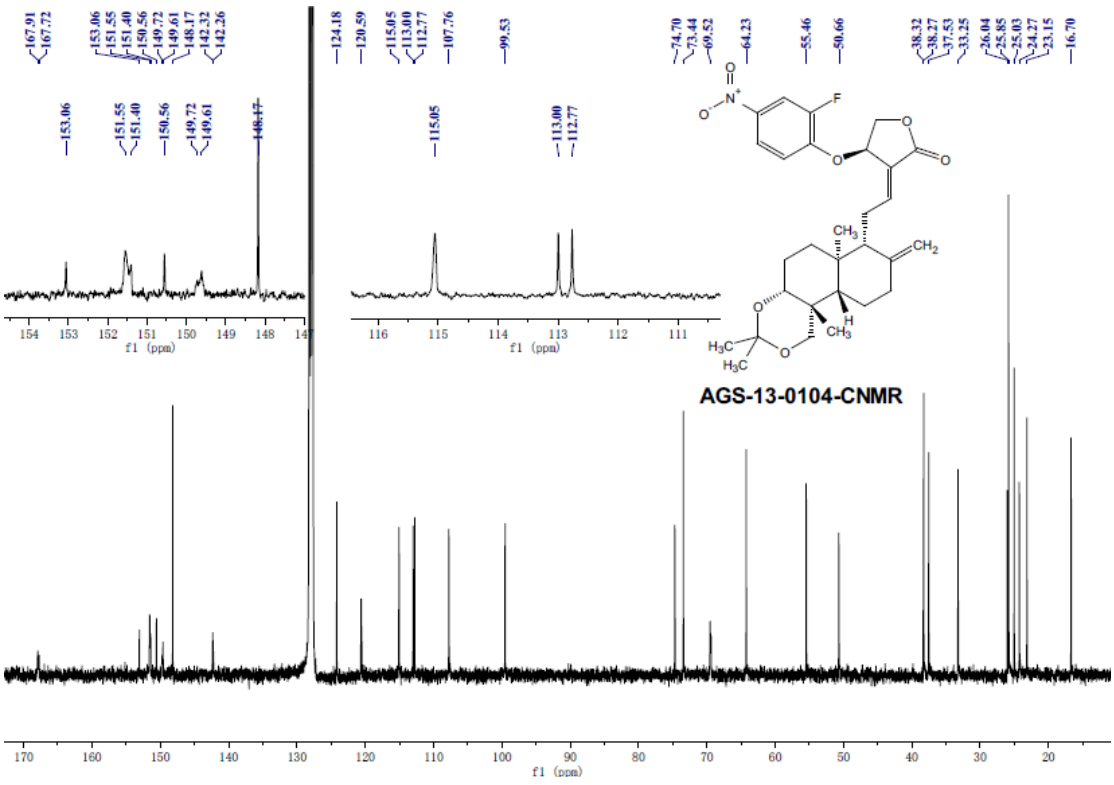
^{13}C NMR of **Compound 10h:**



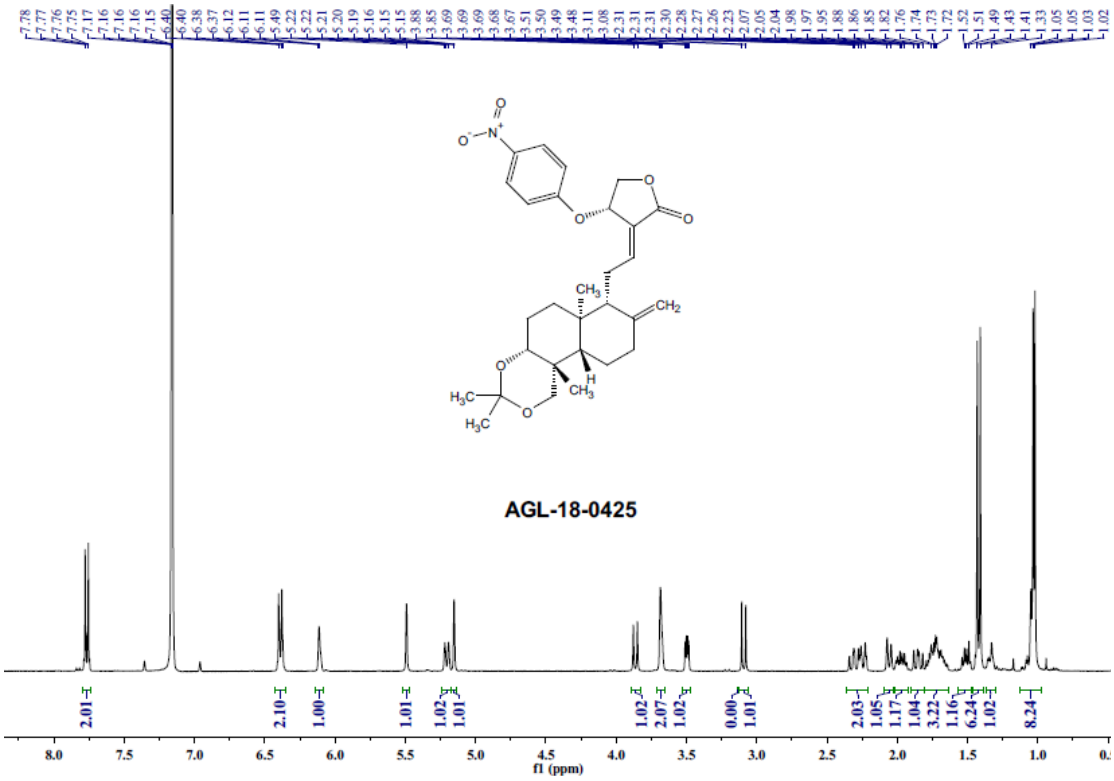
^{1}H NMR of **Compound 10i:**



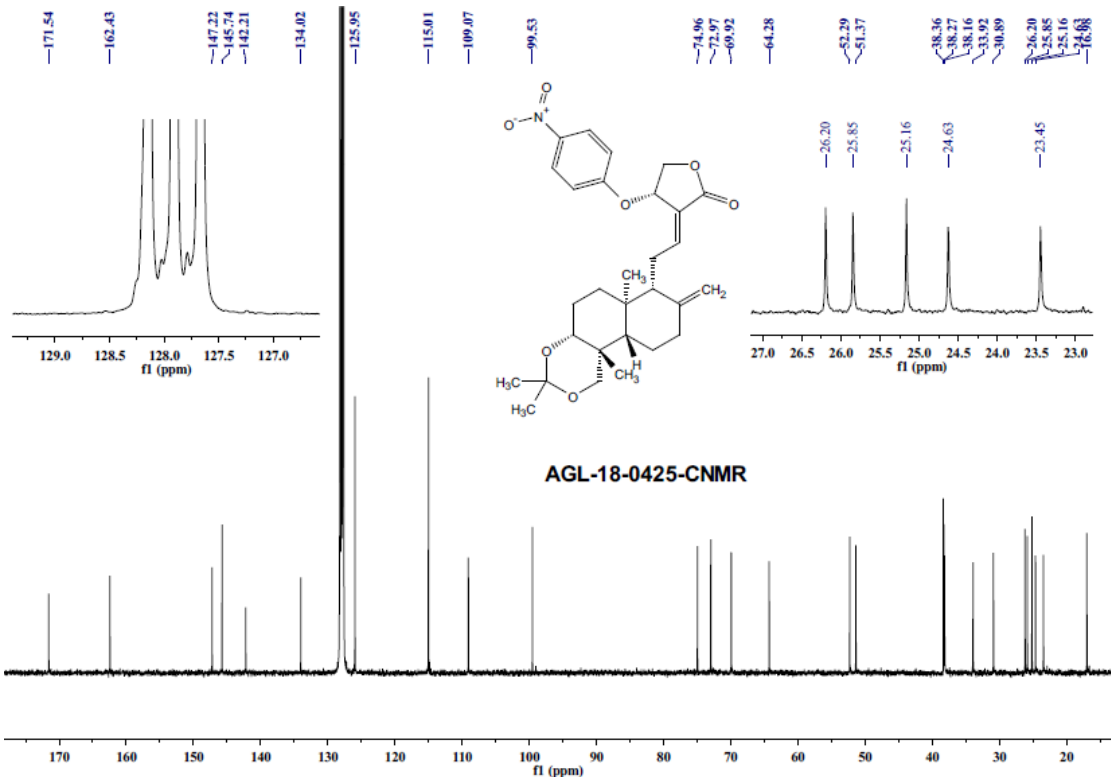
^{13}C NMR of **Compound 10i:**



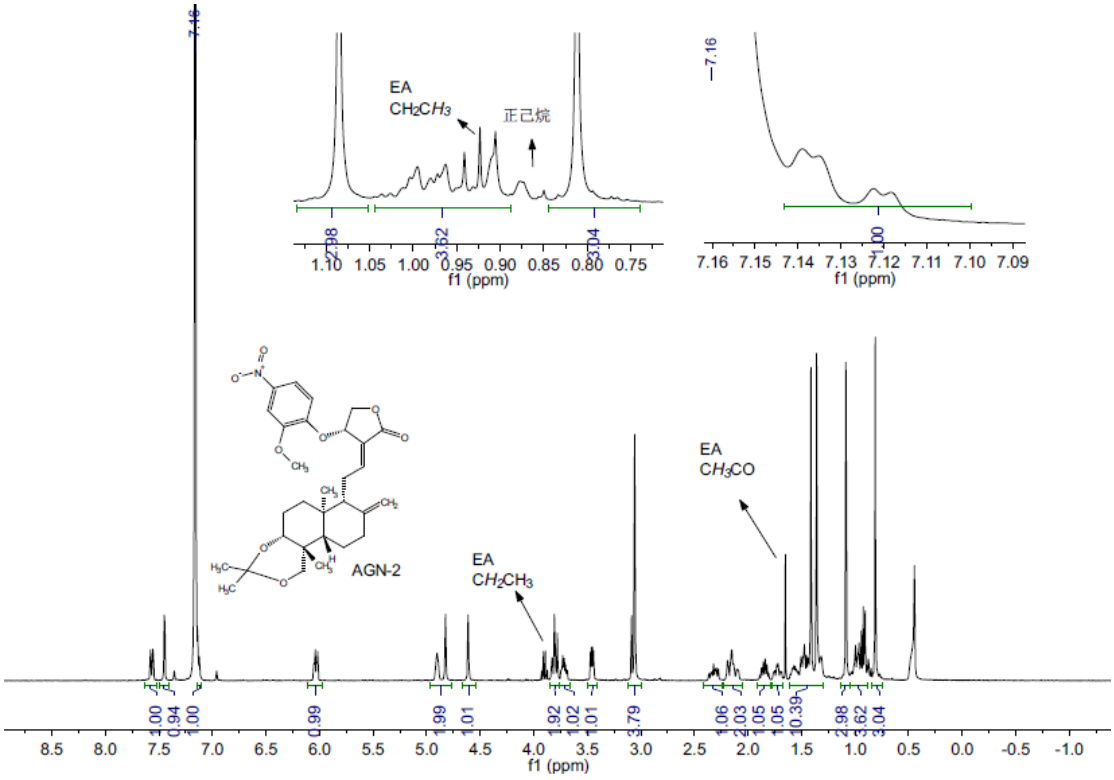
^{1}H NMR of **Compound 11b:**



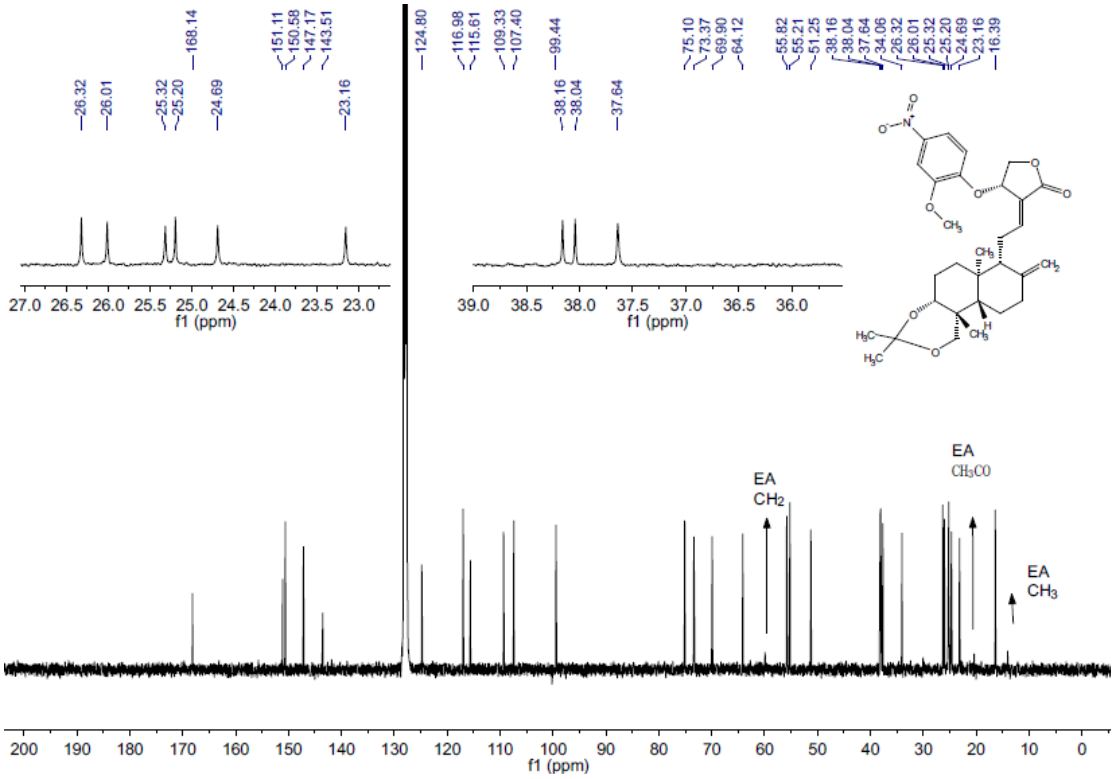
^{13}C NMR of **Compound 11b:**



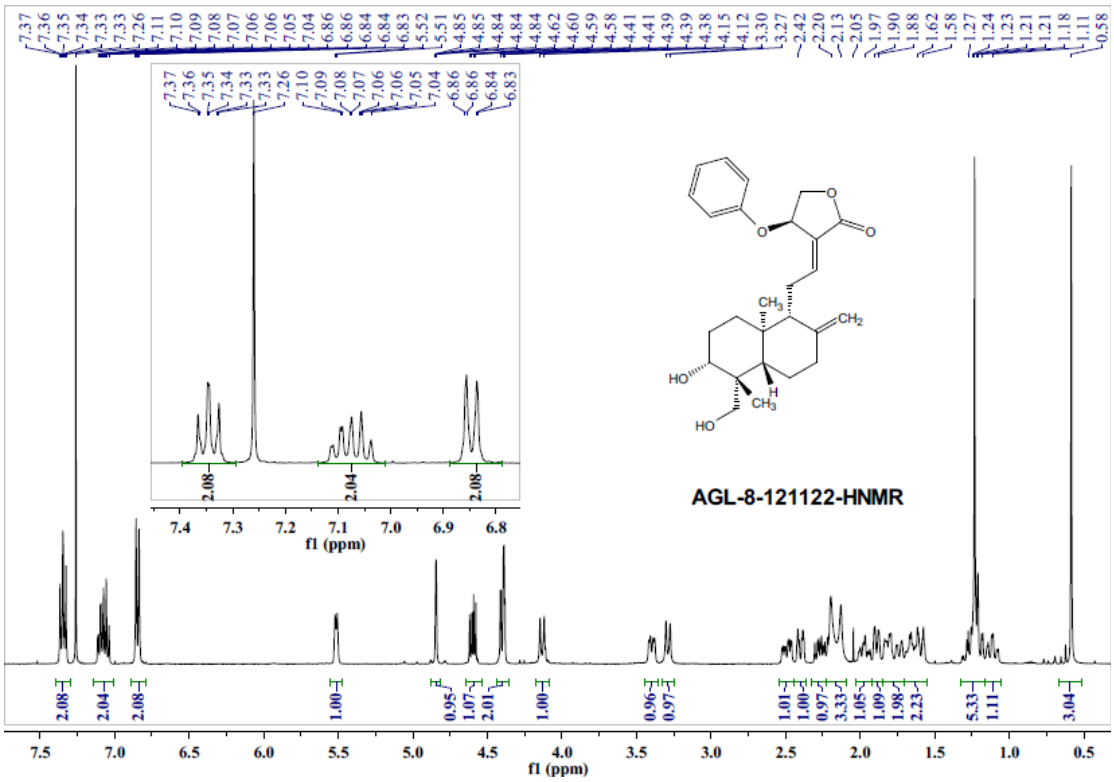
^{1}H NMR of **Compound 11g:**



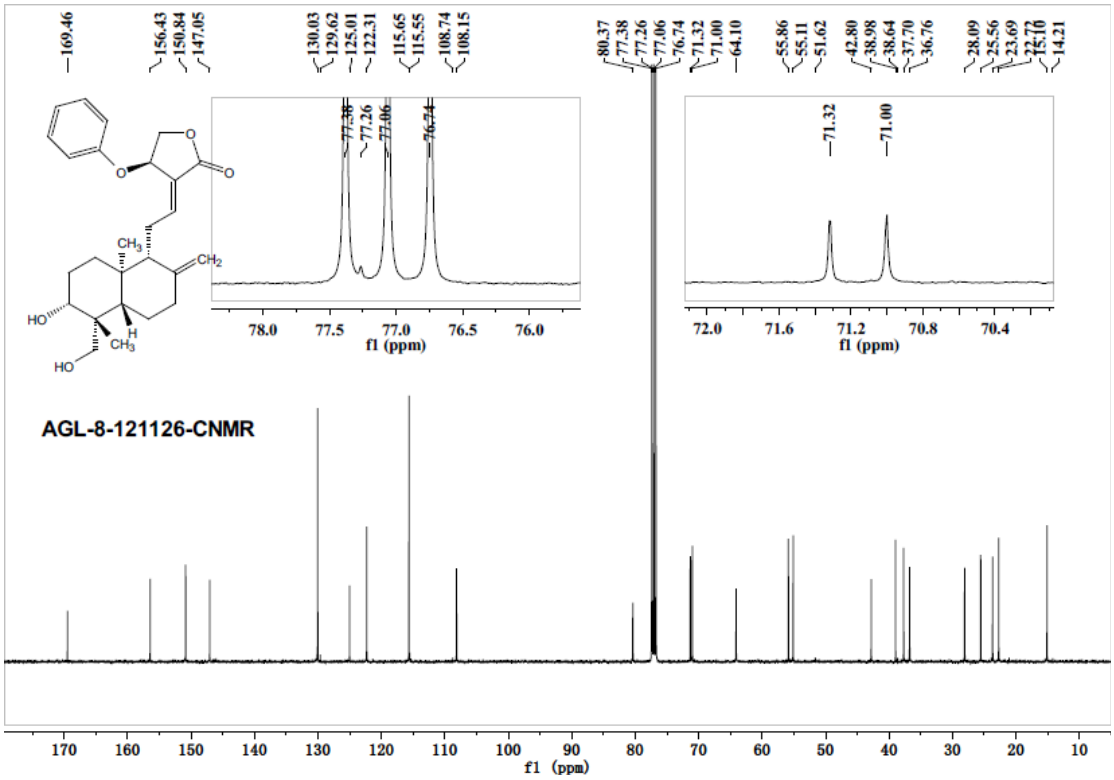
^{13}C NMR of **Compound 11g:**



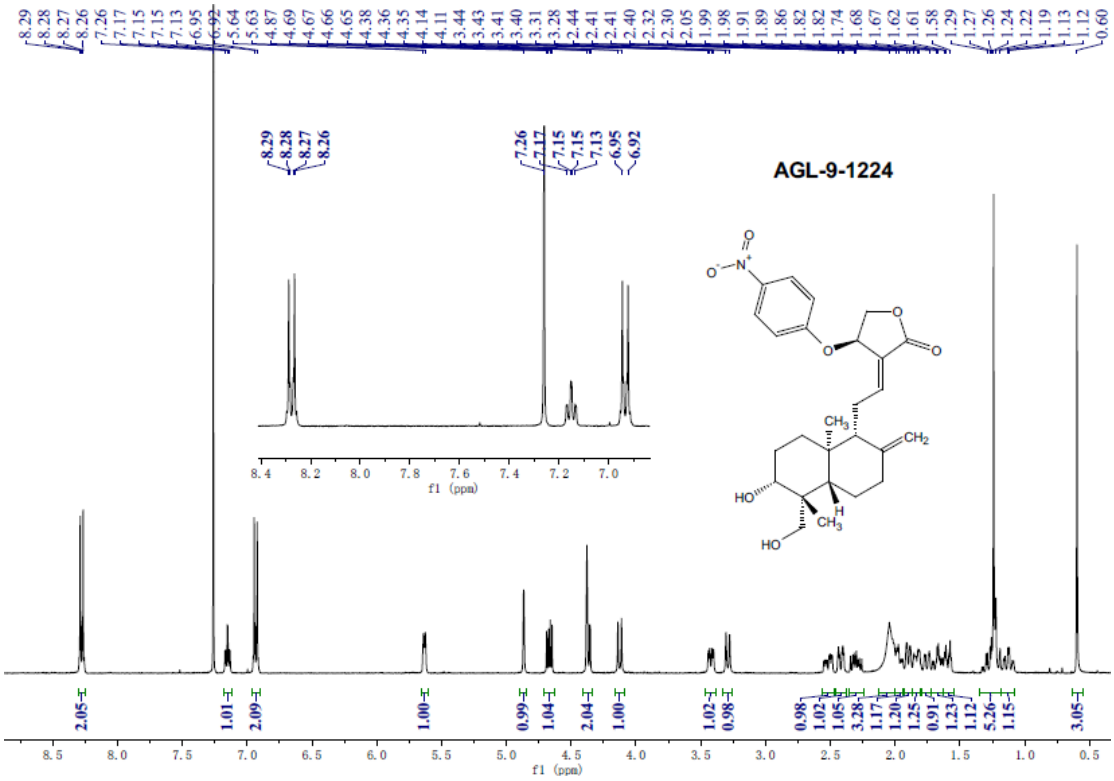
^{1}H NMR of **Compound 12a:**



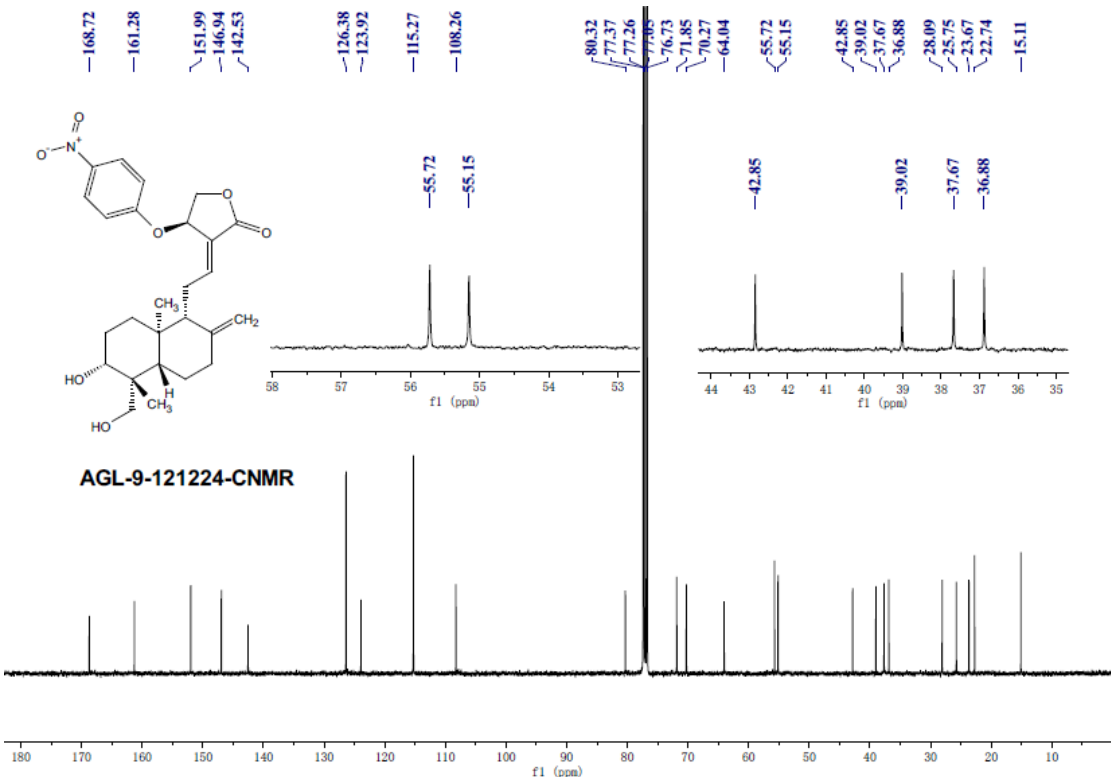
^{13}C NMR of **Compound 12a:**



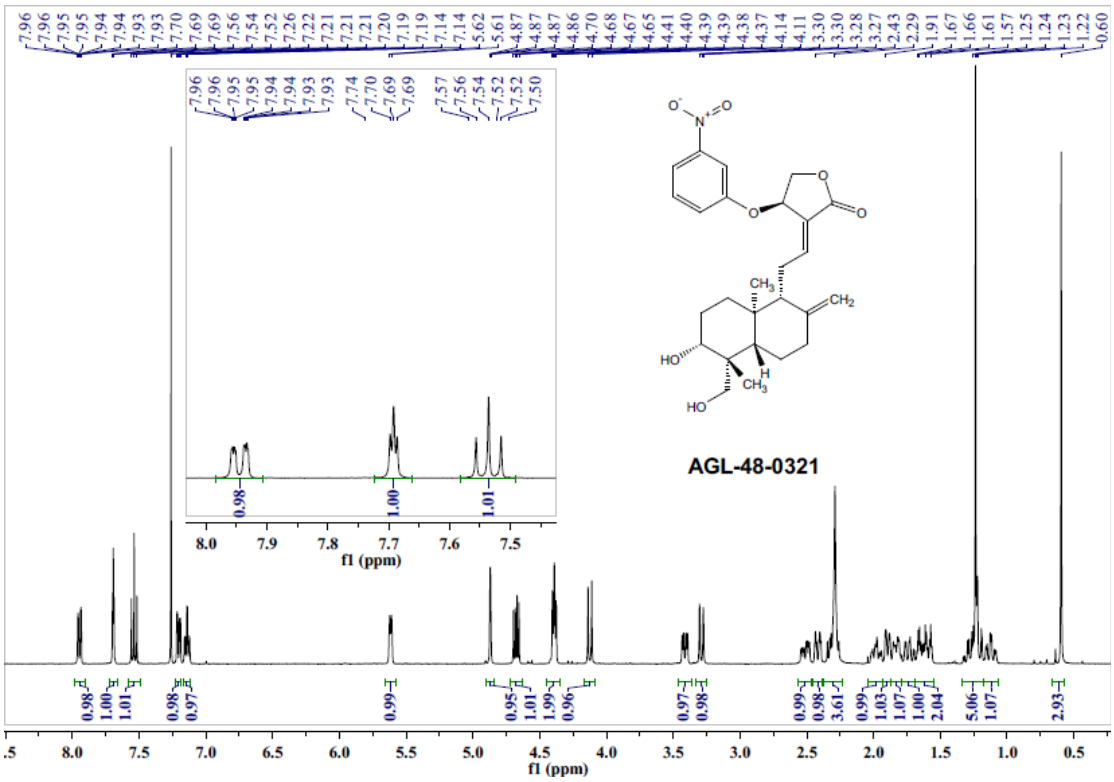
^{1}H NMR of **Compound 12b:**



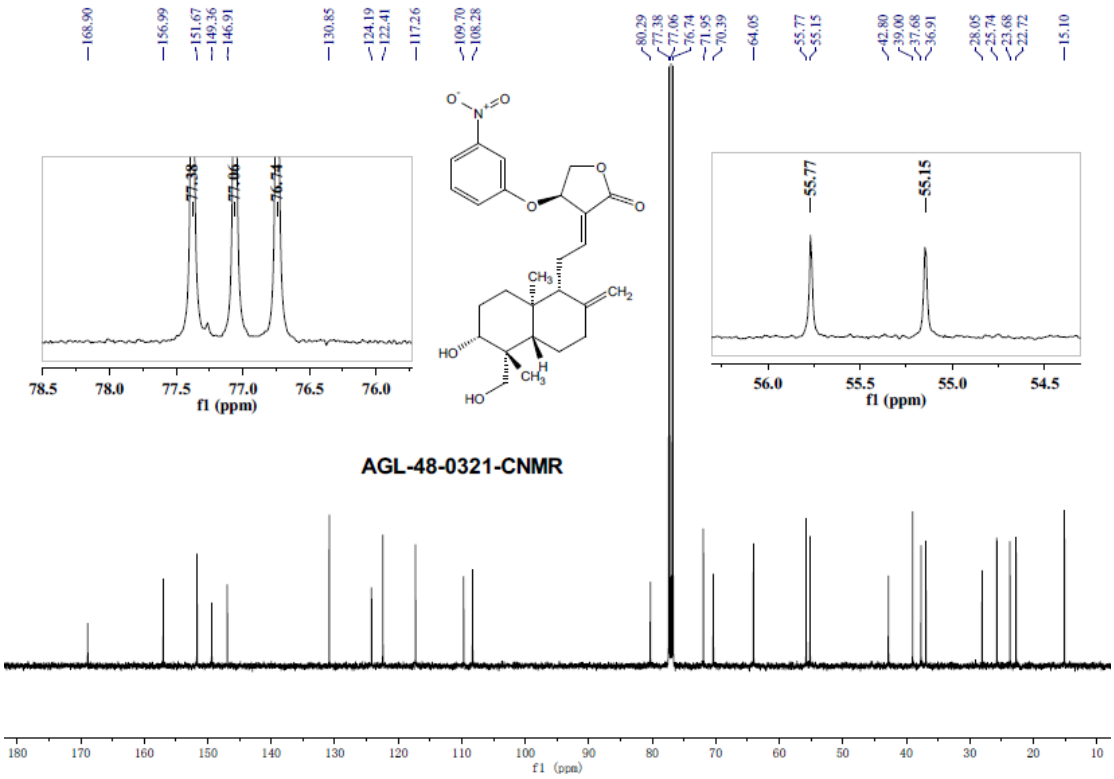
^{13}C NMR of **Compound 12b:**



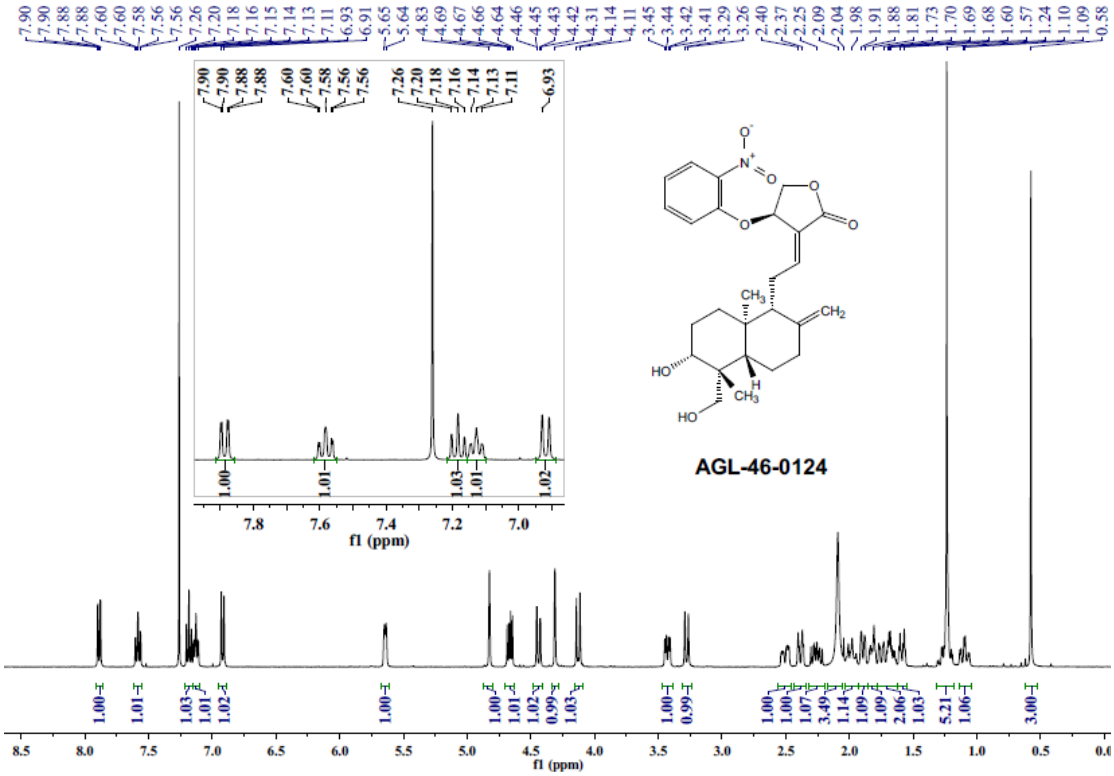
^{1}H NMR of **Compound 12c:**



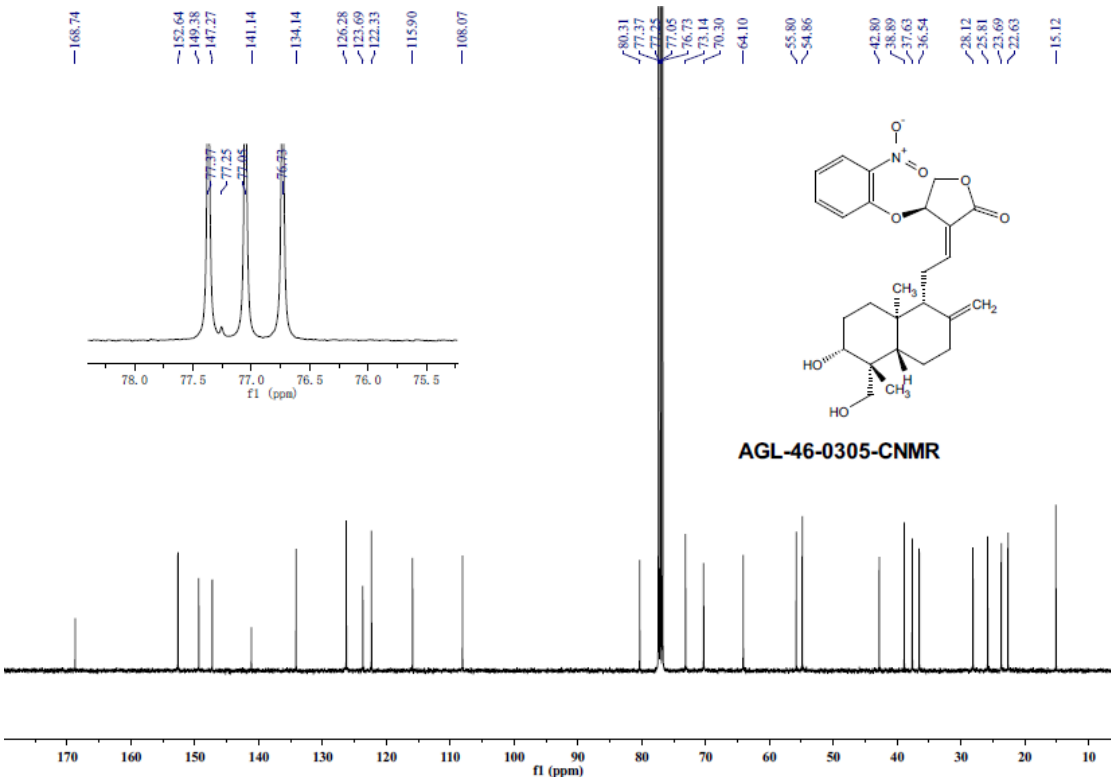
^{13}C NMR of **Compound 12c:**



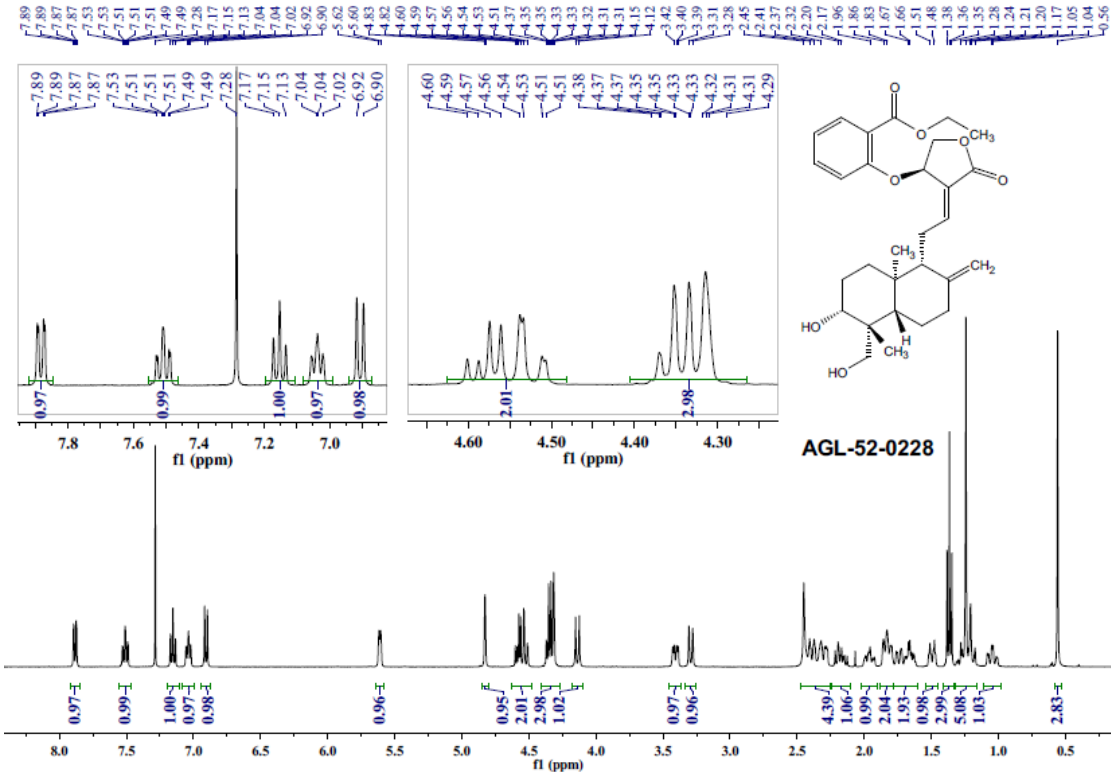
^{1}H NMR of **Compound 12d:**



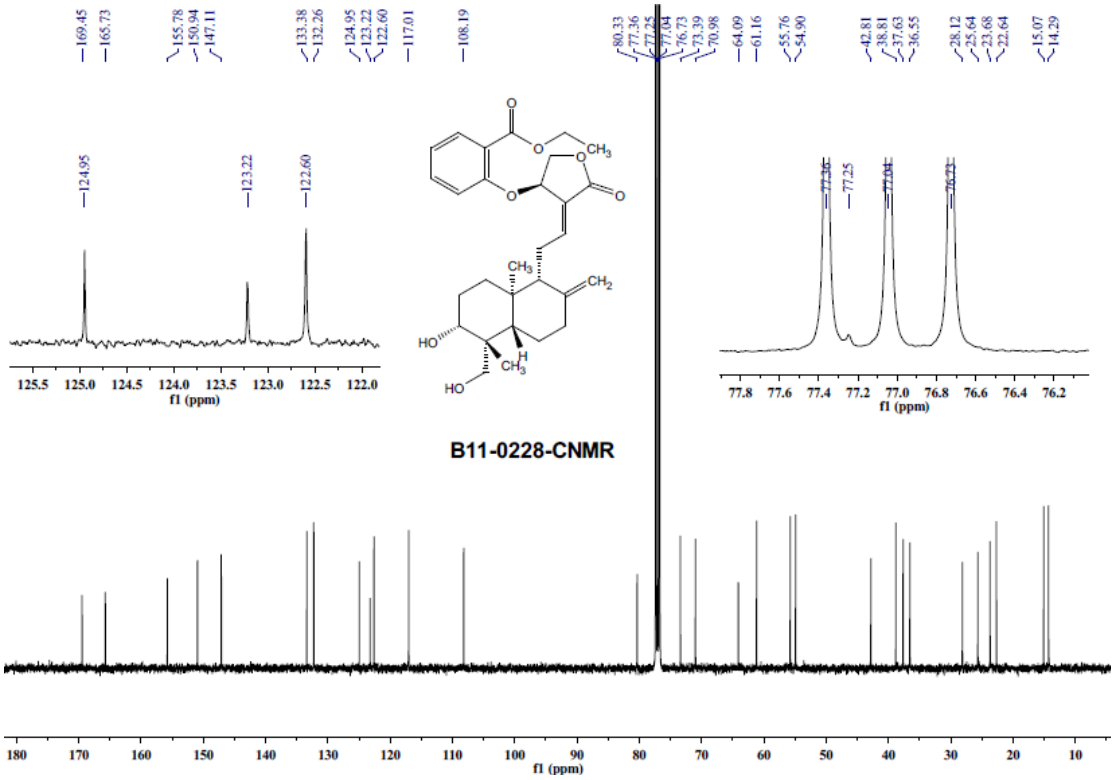
^{13}C NMR of **Compound 12d:**



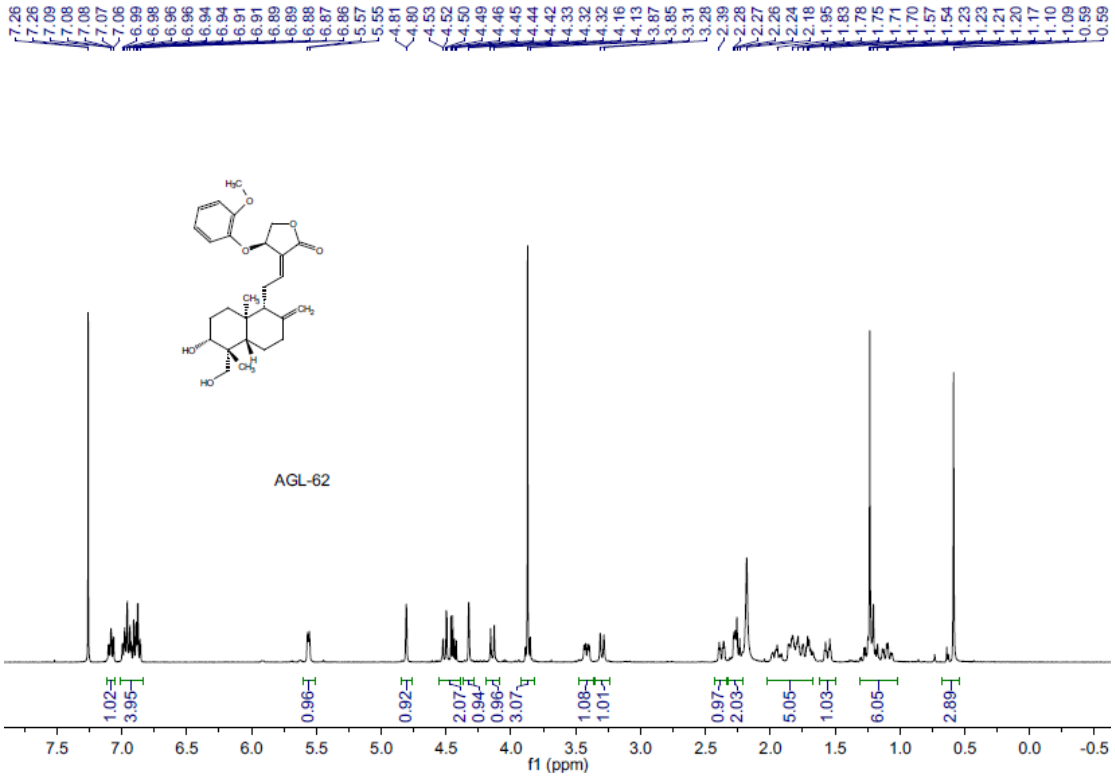
^{1}H NMR of **Compound 12e:**



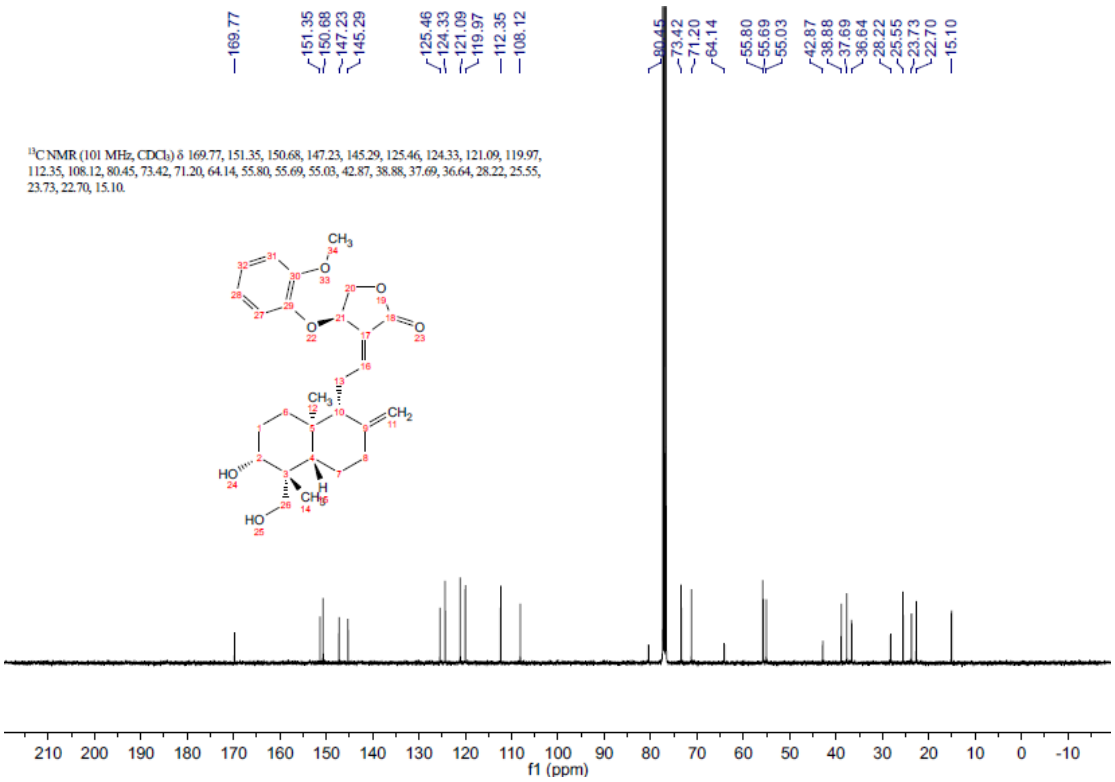
^{13}C NMR of **Compound 12e:**



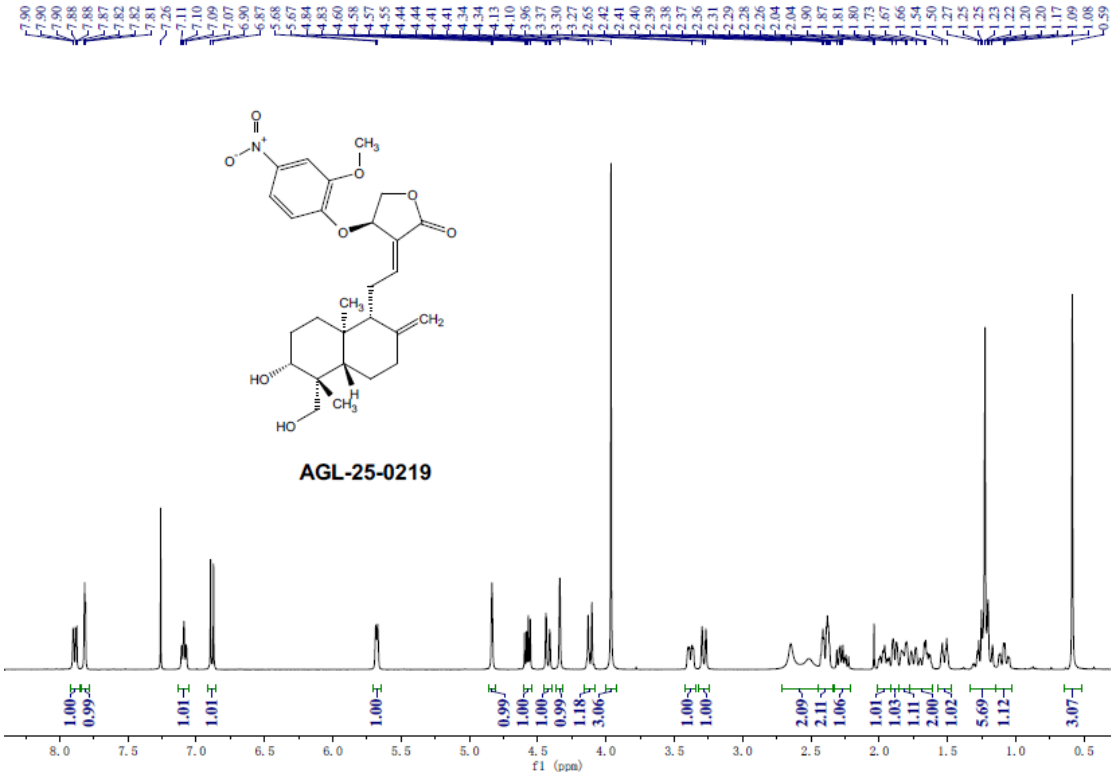
^{1}H NMR of **Compound 12f:**



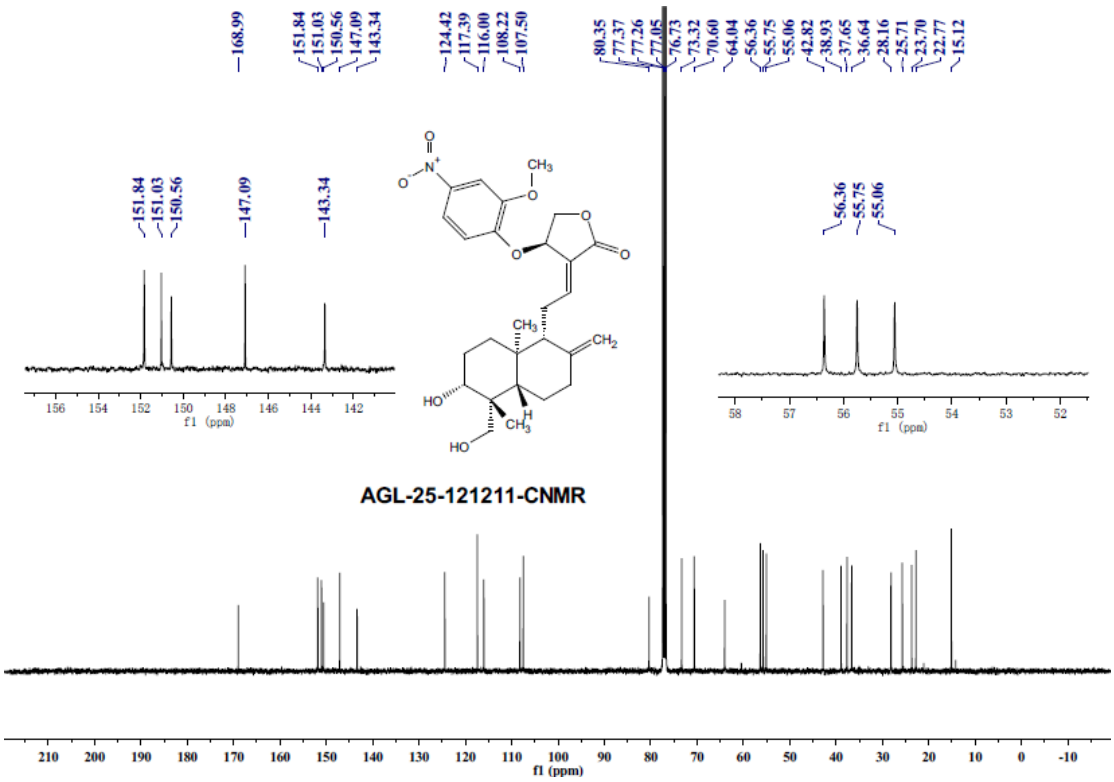
^{13}C NMR of **Compound 12f:**



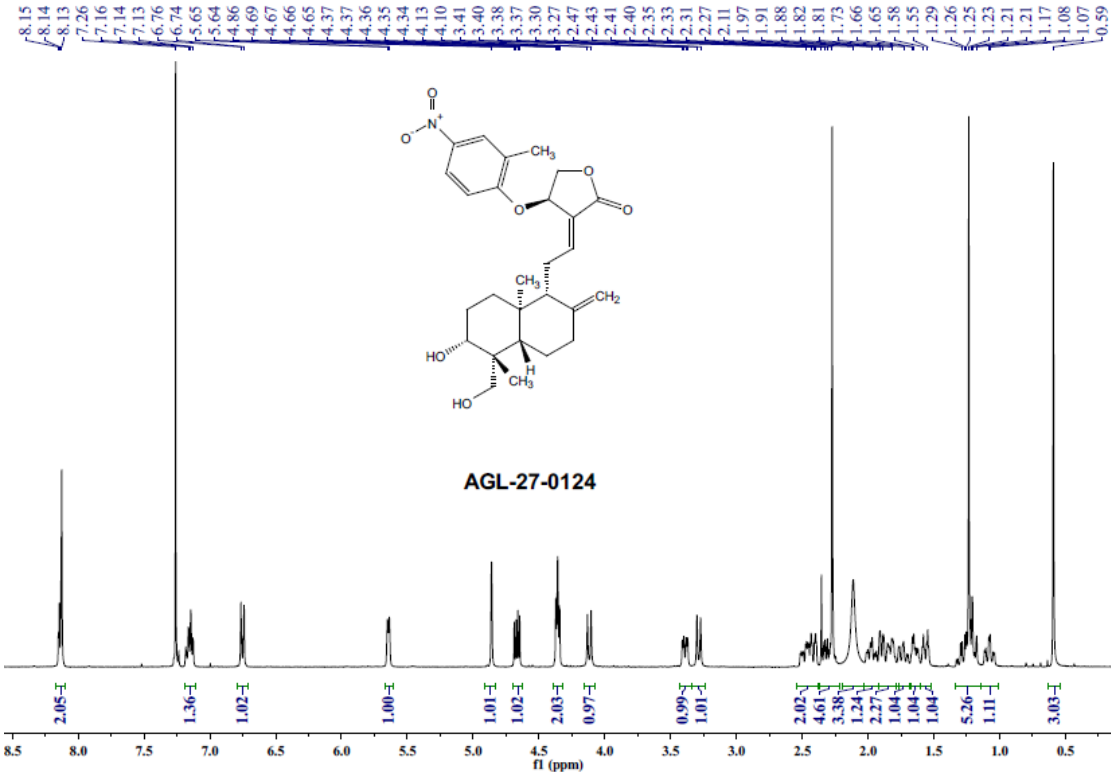
^{1}H NMR of **Compound 12g:**



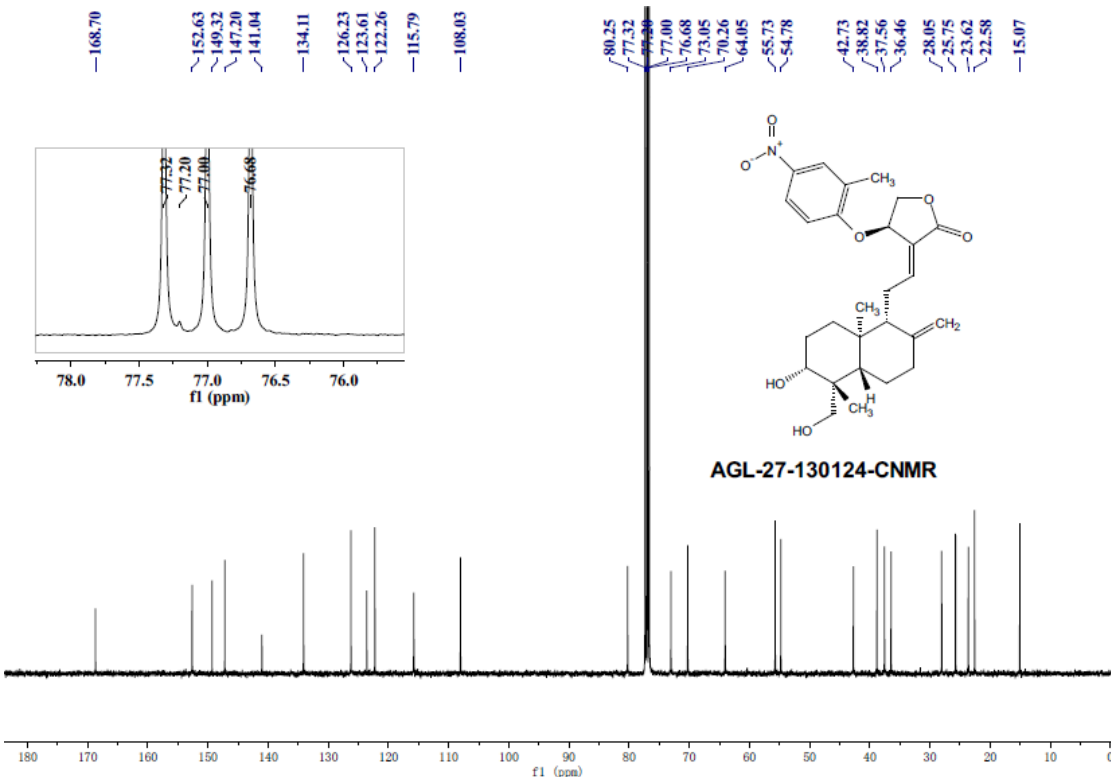
^{13}C NMR of **Compound 12g:**



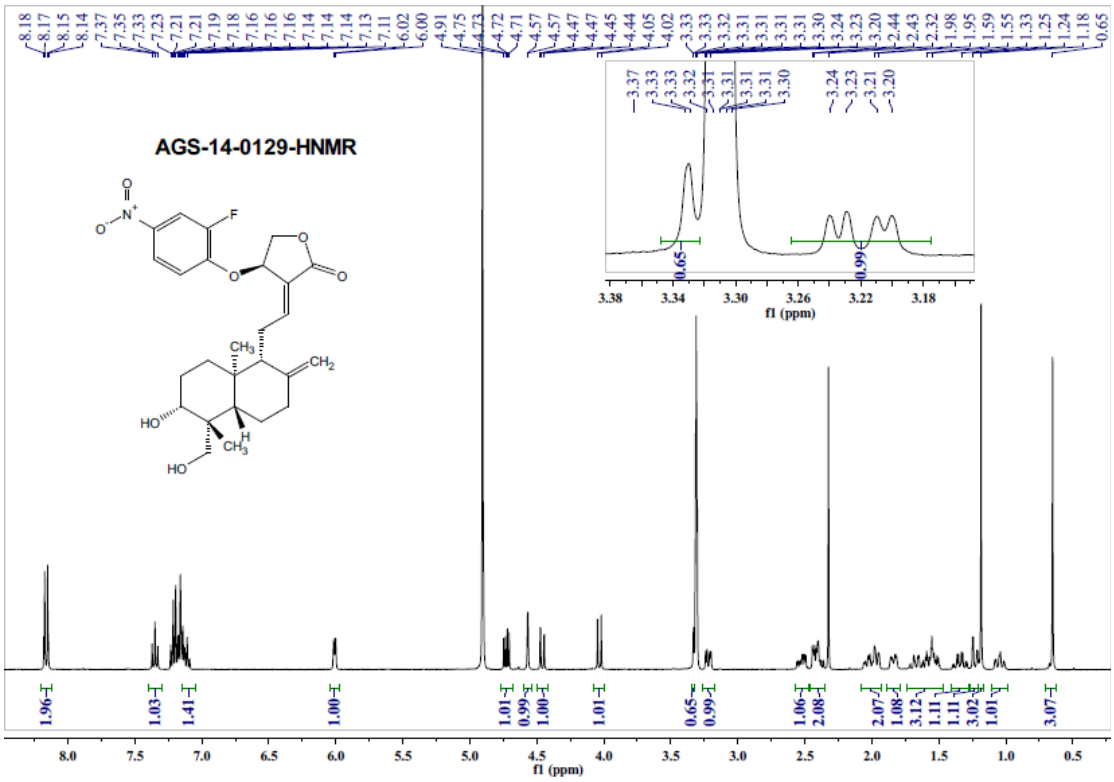
^{1}H NMR of **Compound 12h:**



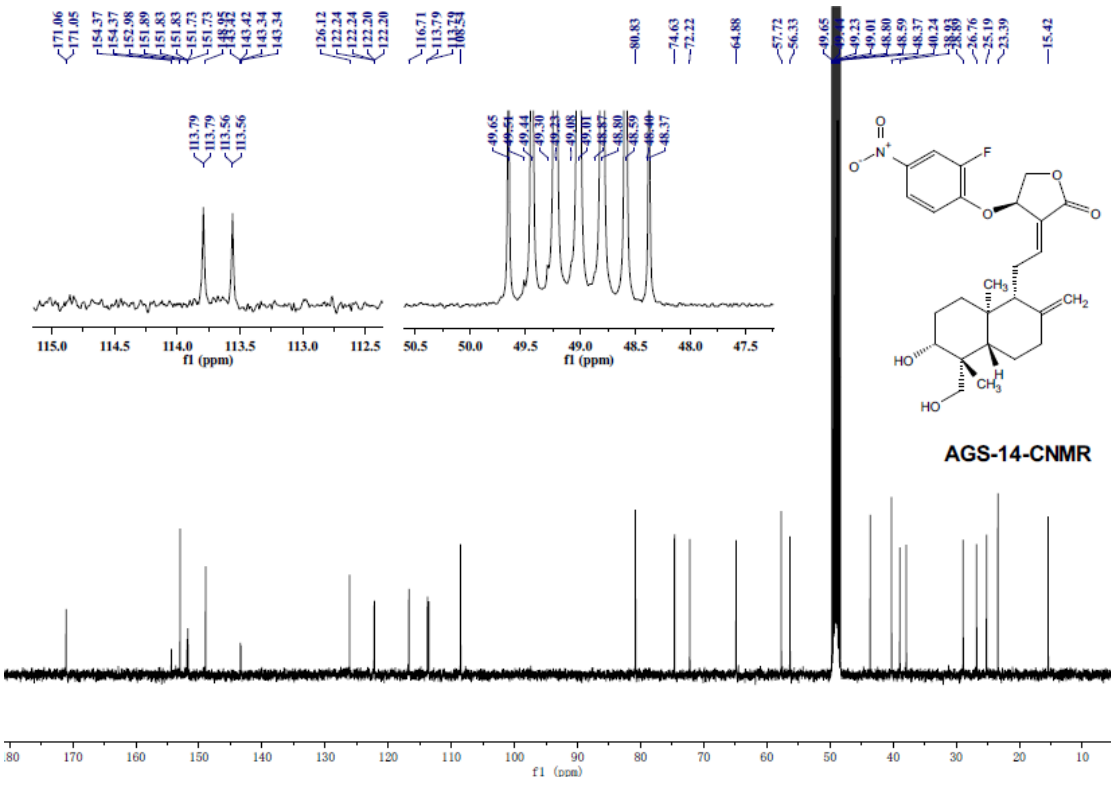
^{13}C NMR of **Compound 12h:**



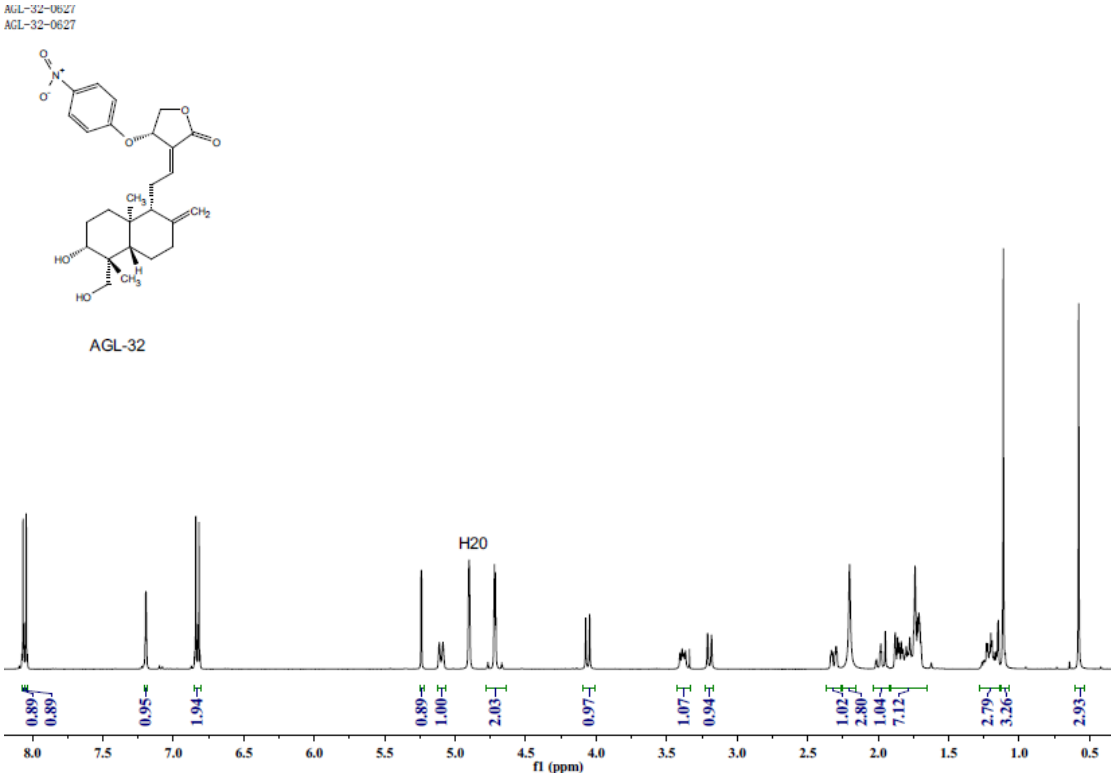
^{1}H NMR of **Compound 12i:**



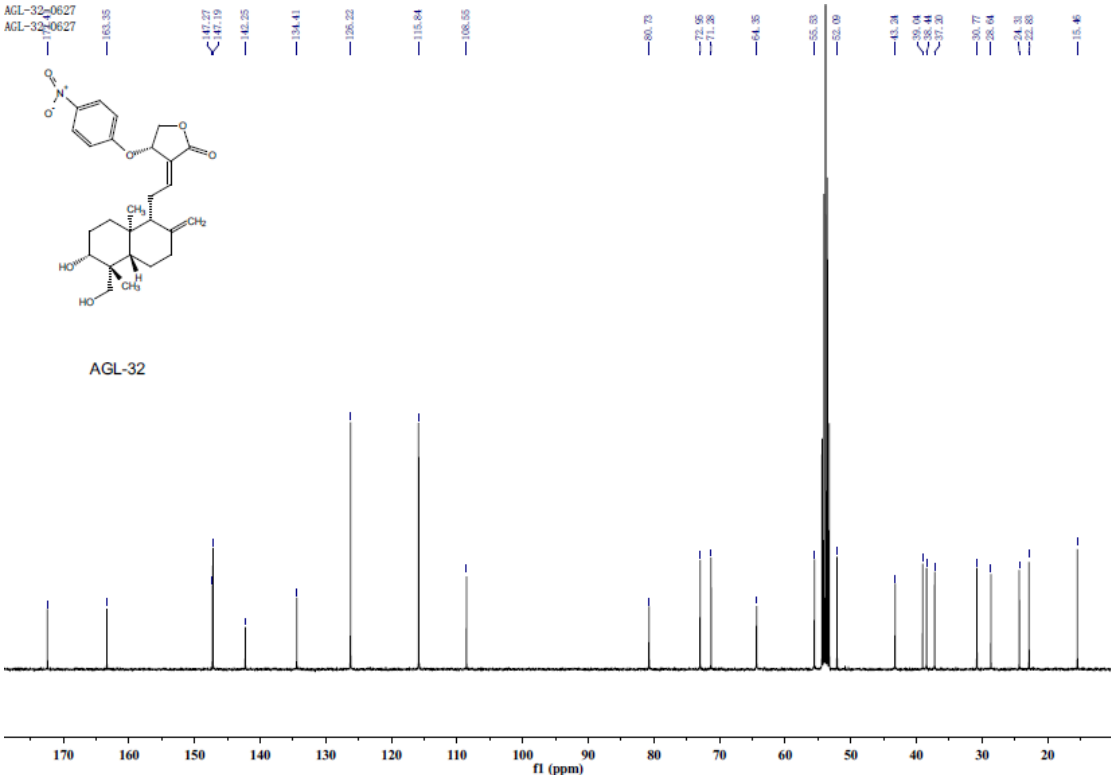
^{13}C NMR of **Compound 12i:**



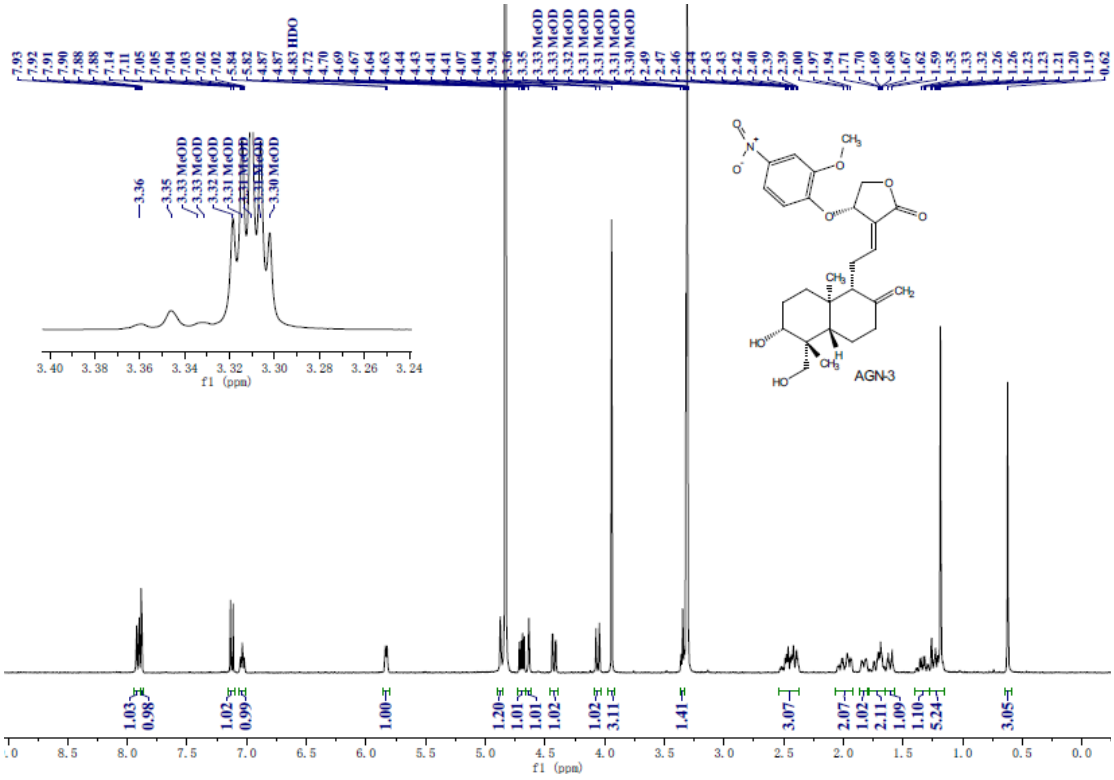
^{1}H NMR of **Compound 13b:**



^{13}C NMR of **Compound 13b:**



^{1}H NMR of **Compound 13g:**



^{13}C NMR of **Compound 13g:**