Discovery of GOT1 Inhibitors from a Marine-derived *Aspergillus terreus* that Against Pancreatic Ductal Adenocarcinoma

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ITS sequence of the fungus

CTTCCGGTAGGGTGAACCTGCGGAAGGATCATTACCGAGTGCGGGTCTT
TATGGCCCAACCTCCCACCCGTGACTATTGTACCTTGTTGCTTCGGCGGGCC
CGCCAGCGTTGCTGGCCGCCGGGGGGCGACTCGCCCCCGGGCCCGTGCCC
GCCGGAGACCCCAACATGAACCCTGTTCTGAAAGCTTGCAGTCTGAGTGT
GATTCTTTGCAATCAGTTAAAACTTTCAACAATGGATCTCTTGGTTCCGGCA
TCGATGAAGAACGCAGCGAAATGCGATAACTAATGTGAATTGCAGAATTCA
GTGAATCATCGAGTCTTTGAACGCACATTGCGCCCCCTGGTATTCCGGGGG
GCATGCCTGTCCGAGCGTCATTGCTGCCCTCAAGCCCGGCTTGTGTGTTGG
GCCCTCGTCCCCGGCTCCCGGGGGACGGGCCCGAAAGGCAGCGGCGGC
ACCGCGTCCGGTCCTCGAGCGTATGGGGCTTCGTCTTCCGCTCCGTAGGCC
CGGCCGGCGCCCGCCGACGCATTTATTTGCAACTTGTTTTTTTCCAGGTTGA
CCTCGGATCAGGTAGGGATACCCGCTGAACTTAAGCATATCAATAAGCCGG
GAGGAAG

The optical rotation values for compounds 1−18.

1	$[\alpha]_D^{25}$: −33.5 (c 0.39, MeOH)	10	$[\alpha]_D^{25}$: +129.3 (c 0.67, MeOH)
2	$[\alpha]_D^{25}$: −46.1 (c 0.43, MeOH)	11	$[\alpha]_D^{25}$: +89.1 (c 0.24, MeOH)
3	$[\alpha]_D^{25}$: −31.1 (c 0.33, MeOH)	12	$[\alpha]_D^{25}$: +31.3 (c 0.17, MeOH)
4	$[\alpha]_D^{25}$: +156.1 (c 0.15, MeOH)	13	$[\alpha]_D^{25}$: +112.3 (c 0.35, MeOH)
5	$[\alpha]_D^{25}$: +179.5 (c 0.16, MeOH)	14	$[\alpha]_D^{25}$: +31.2 (c 0.21, MeOH)
6	$[\alpha]_D^{25}$: 0 (c 0.15, MeOH) Plane structure without optical rotation value	15	$[\alpha]_D^{25}$: +56.8 (c 0.18, MeOH)
7	$[\alpha]_D^{25}$: +17.9 (c 0.13, MeOH)	16	$[\alpha]_D^{25}$: +21.1 (c 0.12, MeOH)
8	$[\alpha]_D^{25}$: +115.3 (c 0.51, MeOH)	17	$[\alpha]_D^{25}$: +51.7 (c 0.24, MeOH)
9	$[\alpha]_D^{25}$: +25.1 (c 0.17, MeOH)	18	$[\alpha]_D^{25}$: +112.3 (c 0.81, MeOH)

Figure S1. (A) Position of AH (left) and PLP (right) into the active site of GOT1. (B) Surface representation of GOT1 around the active site pocket. (C) Overlay of GOT1-AH (cyan) and WT GOT1 (magenta) crystal structures. (D) Comparison of the center conformations of core molecules in chain A of GOT1-AH (cyan) and wild-type GOT1 (gray).
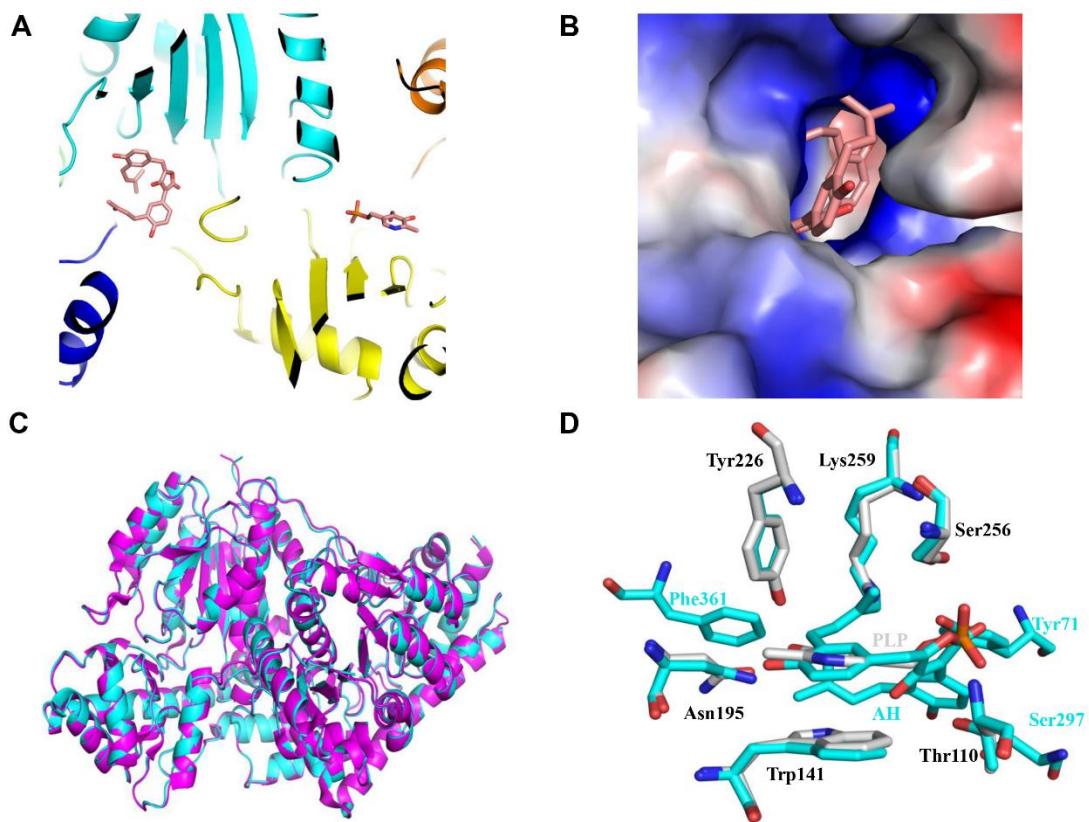
Figure S2. The 2Fo-Fc electron density of PLP bound to chain B is shown as a gray

mesh. The map is contoured at the 1σ level.
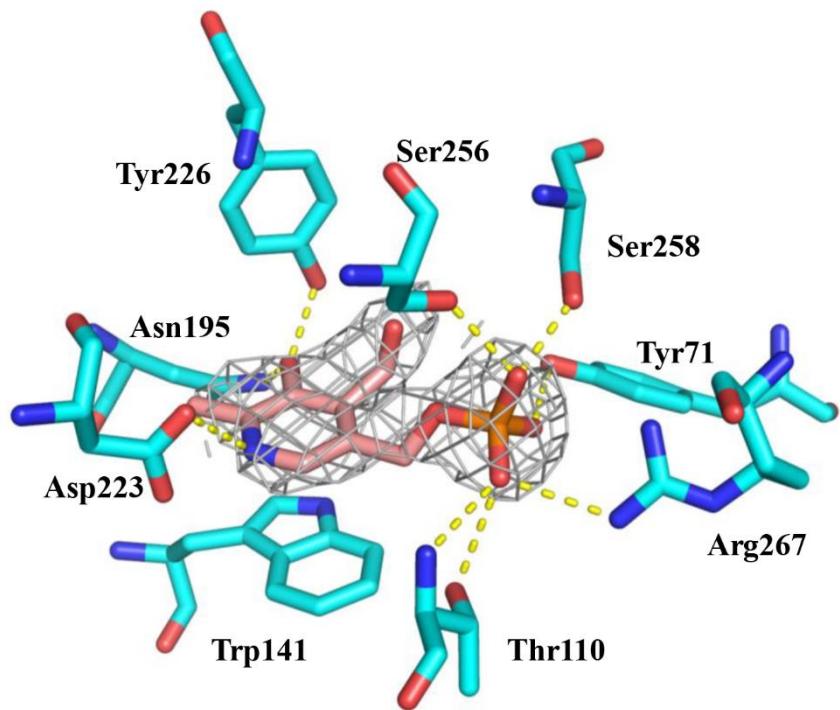
Table S1. Data collection and refinement statistics.

parameter	Enzyme in complex with AH
Resolution (Å)	49.58–2.62 (2.714–2.62)
Space group	P 1 2$_1$ 1
Unit cell dimensions	a=64.87 Å, b=90.42 Å, c=74.05 Å;
	α=90.0°, β =91.87°, γ=90.0°
Unique reflections	25267 (2557)
Multiplicity	2.0 (2.0)
Completeness (%)	97.67 (97.93)
$I/\sigma(I)$	9.34 (2.99)
R-merge[†] (%)	0.07031 (0.2735)
R-work	0.2127 (0.2690)
R-free	0.2661 (0.3291)
Number of non-hydrogen atoms	6,703
Protein residues	820
r.m.s.d.from ideal geometry	
Bonds lengths (Å)	0.002
Angles (°)	0.46
Ramachandran plot (%)	
Favored	96.94
Outliers	0.12
Clashscore	4.51
Average B-factor	29.95
PDB code	6LIG

[†]R-merge = $\Sigma_{hkl} \Sigma_i |I_i(hkl)-<I(hkl)>|/\Sigma_{hkl} \Sigma_i I_i(hkl)$, where $I(hkl)$ is the intensity of reflection hkl, Σ_{hkl} is the sum over all reflections and Σ_i is the sum over i measurements of reflection hkl. Statistics for the highest-resolution shell are shown in parentheses.

Figure S3. ^{1}H NMR spectrum of **1**.
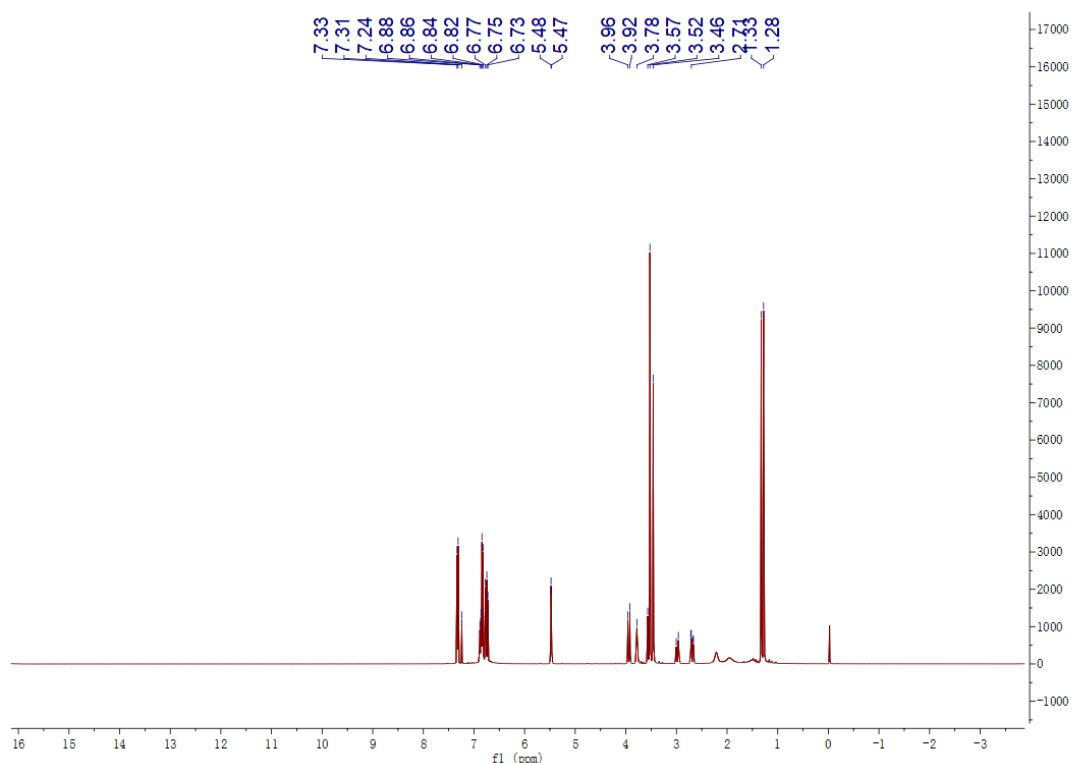
**Figure S4.** ^{13}C NMR spectrum of **1**.
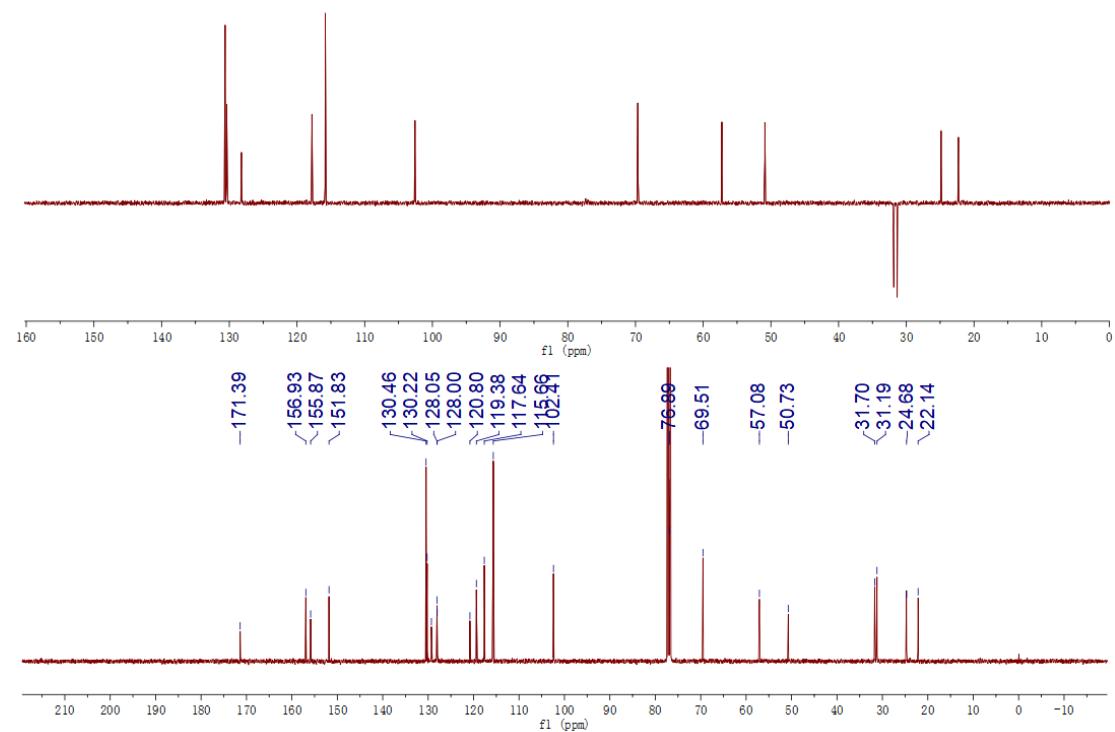
**Figure S5.** ^{1}H NMR spectrum of **2**.
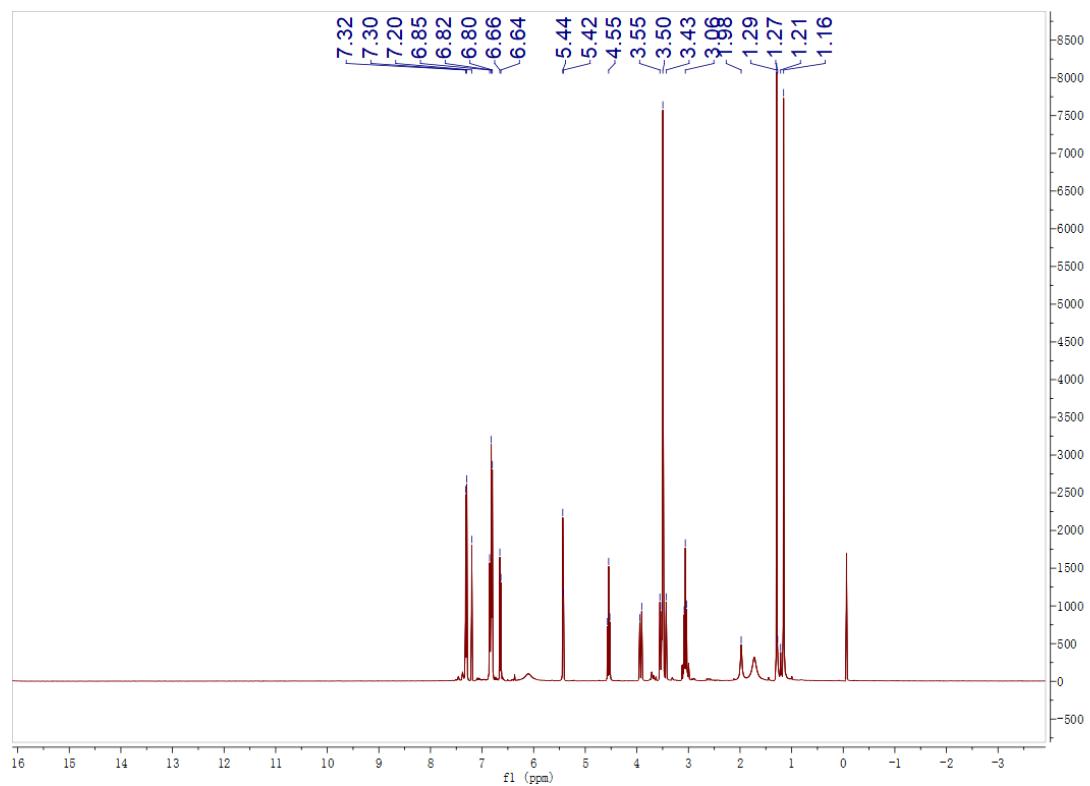
**Figure S6.** ^{13}C NMR spectrum of **2**.
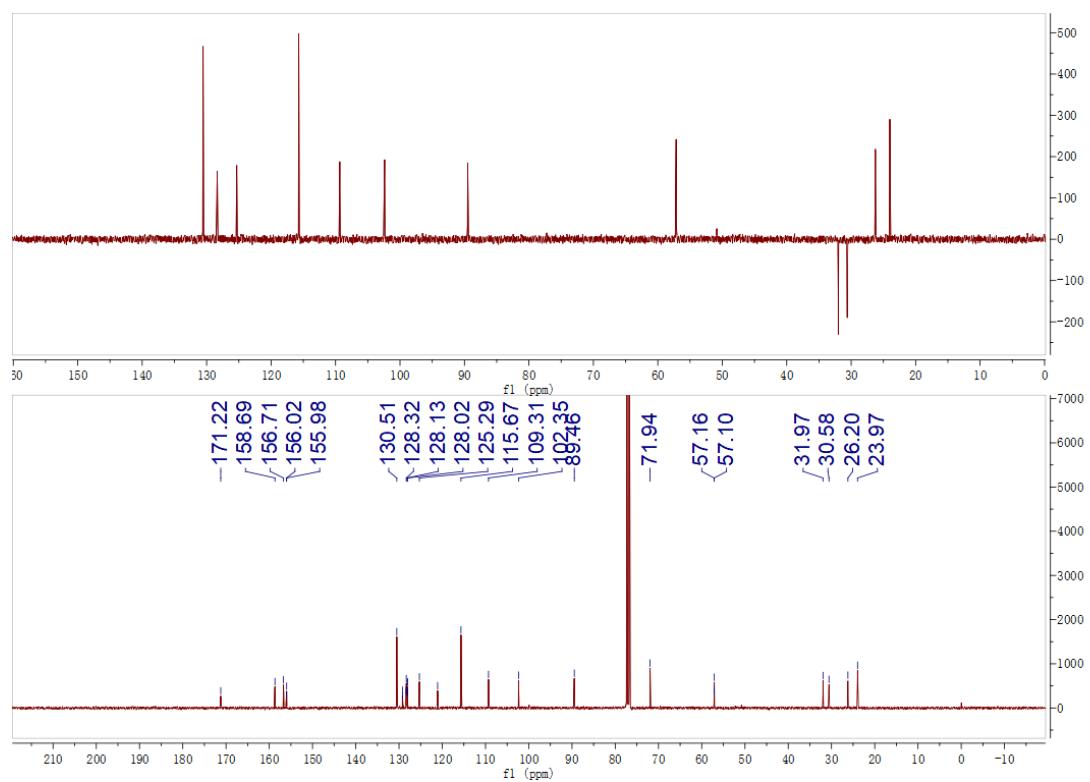
**Figure S7.** ^{1}H NMR spectrum of **3**.
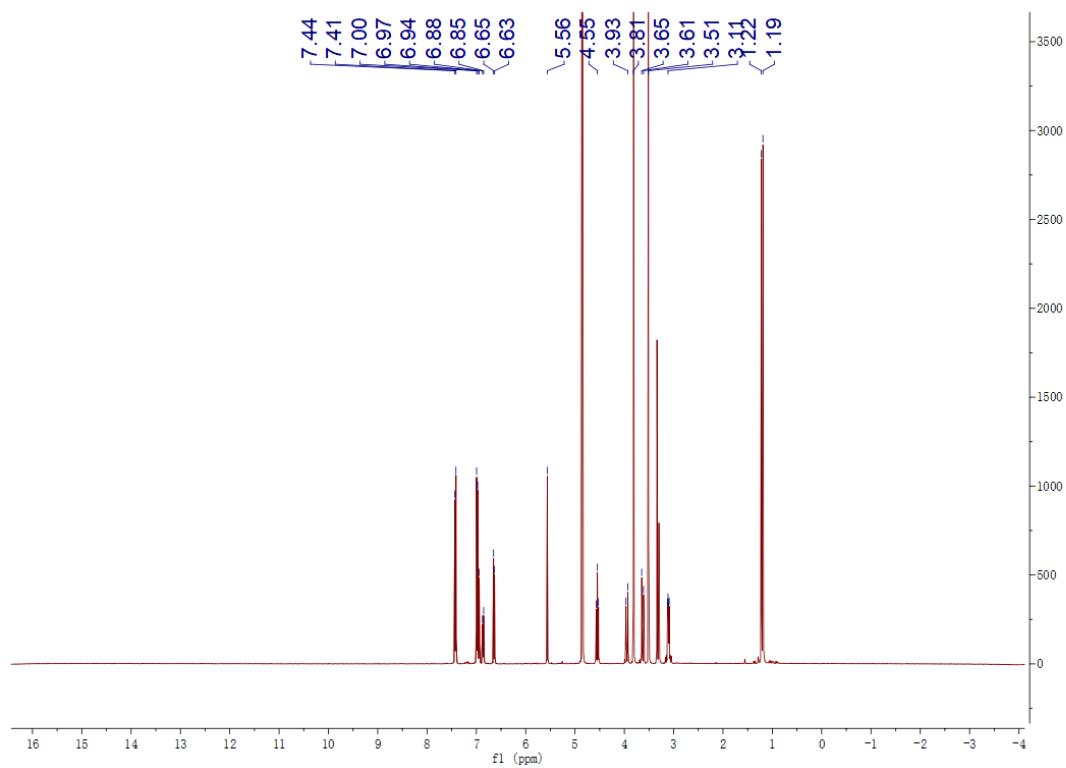
Figure S8. ^{13}C NMR spectrum of **3**.
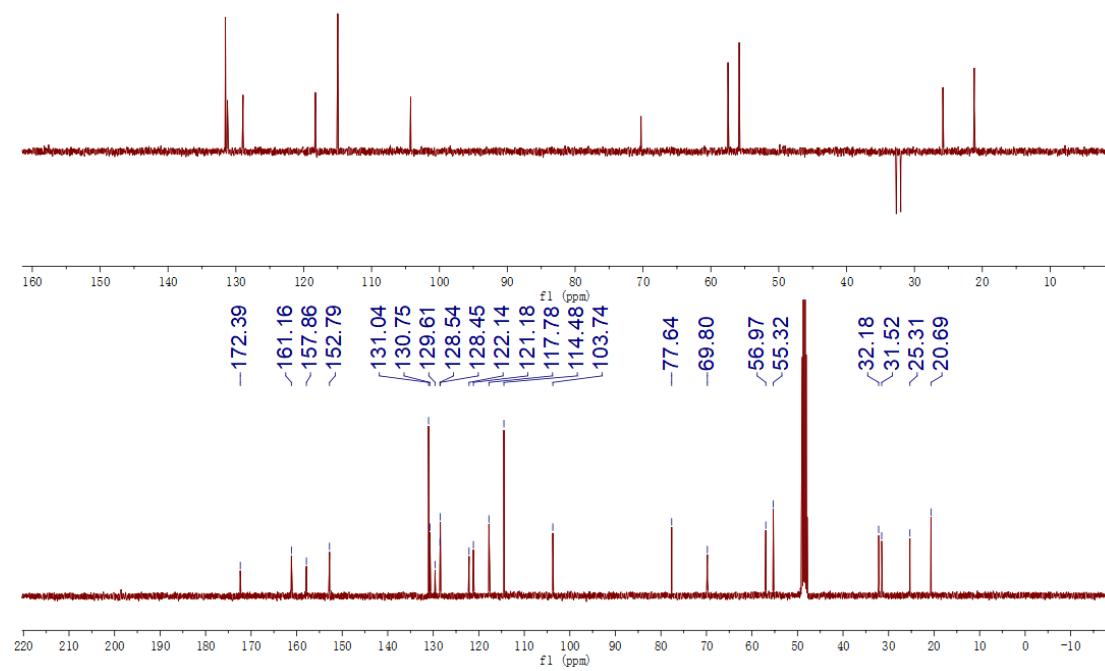
Figure S9. ^{1}H NMR spectrum of **4**.
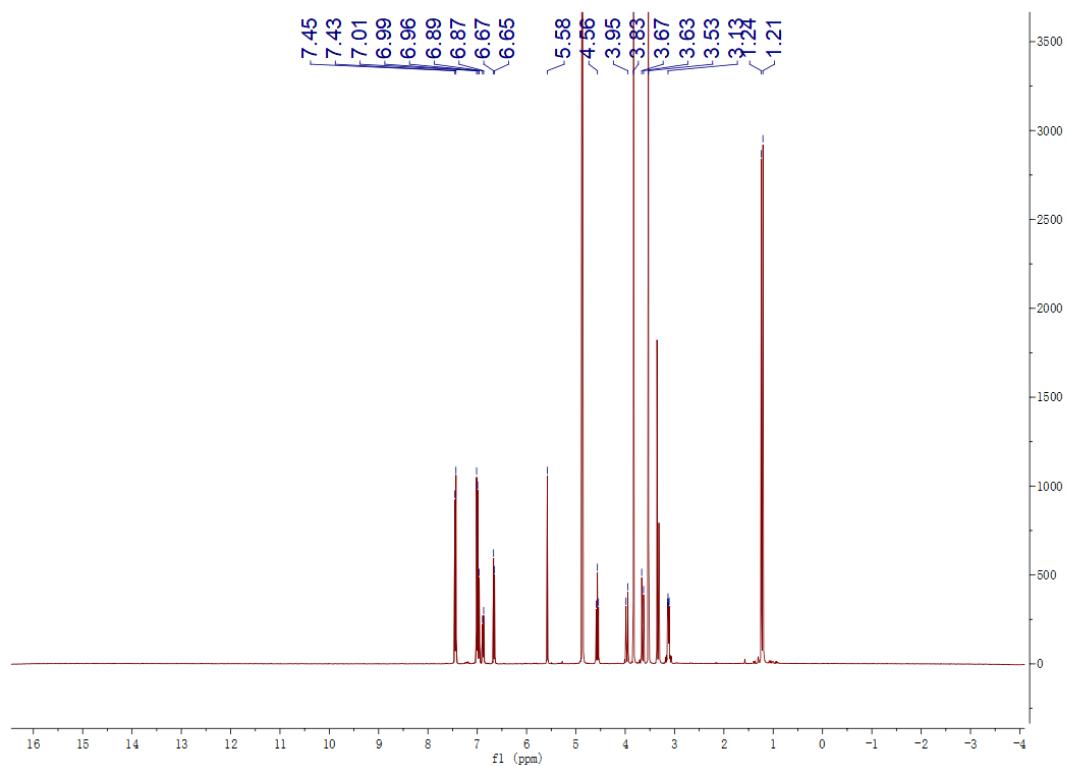
Figure S10. ^{13}C NMR spectrum of **4**.
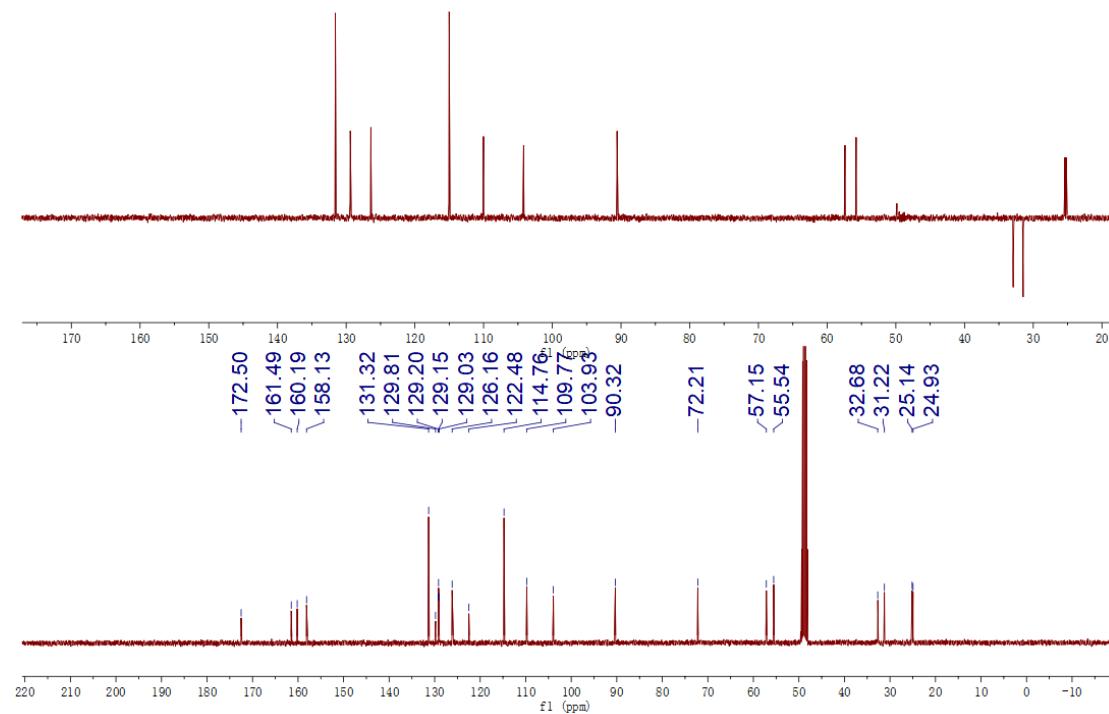
Figure S11. ¹H NMR spectrum of **5**.
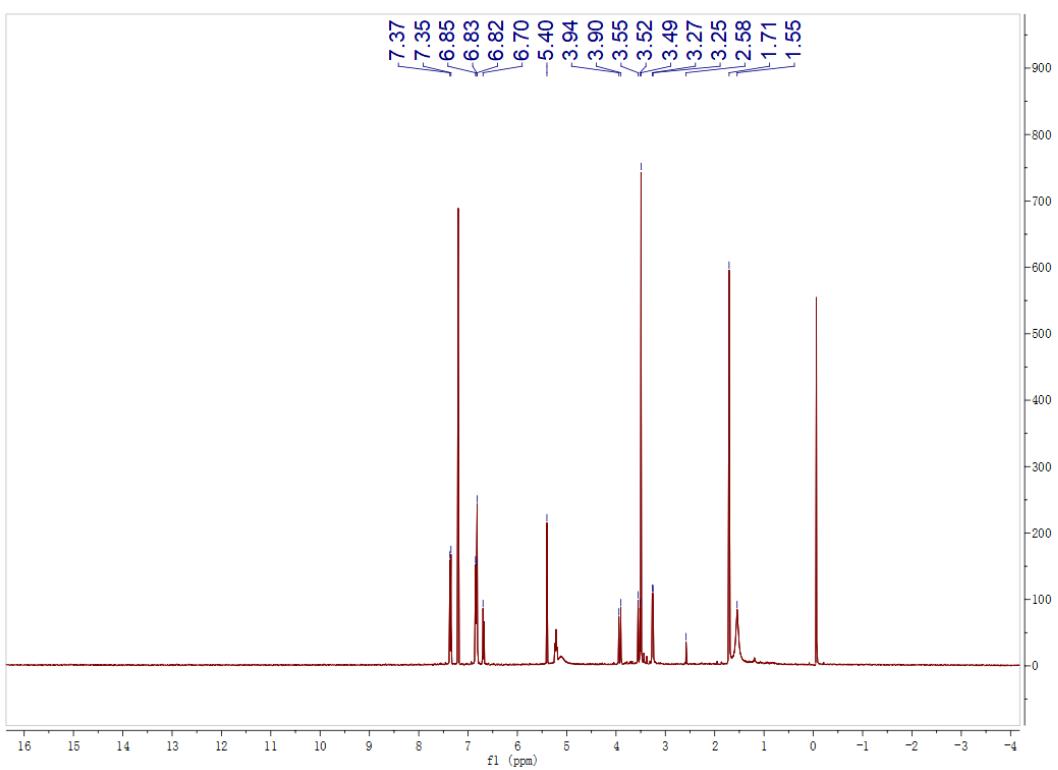
Figure S12. ¹³C NMR spectrum of **5**.
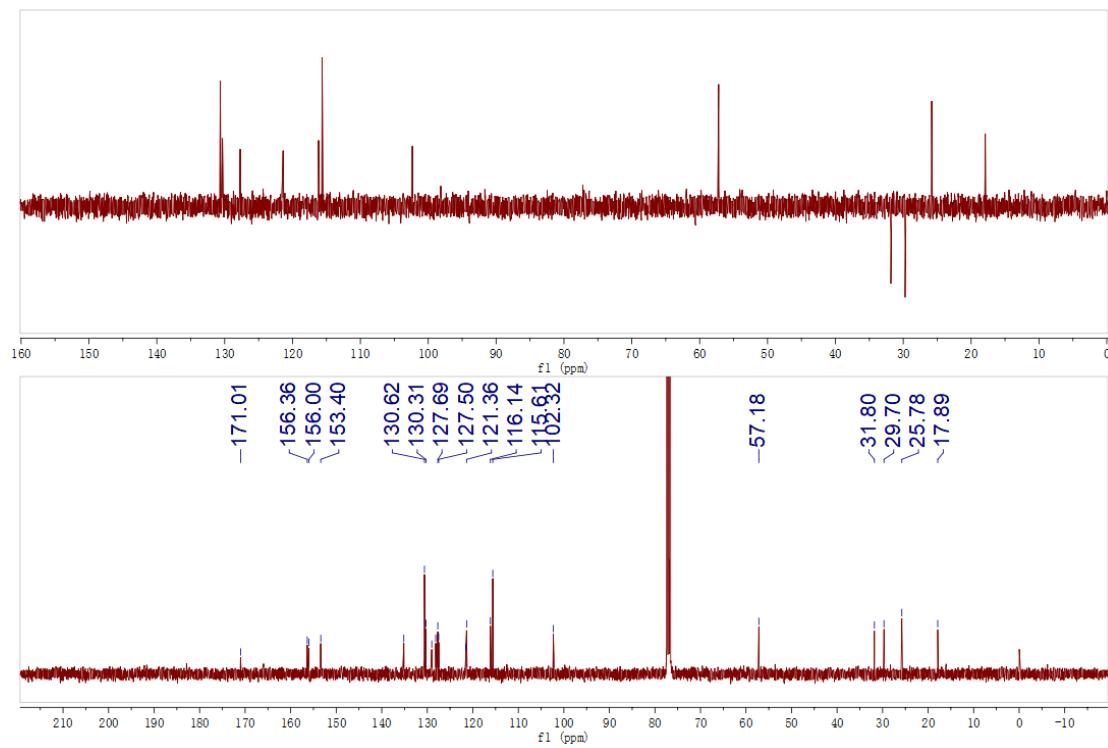
Figure S13. ^{1}H NMR spectrum of **6**.
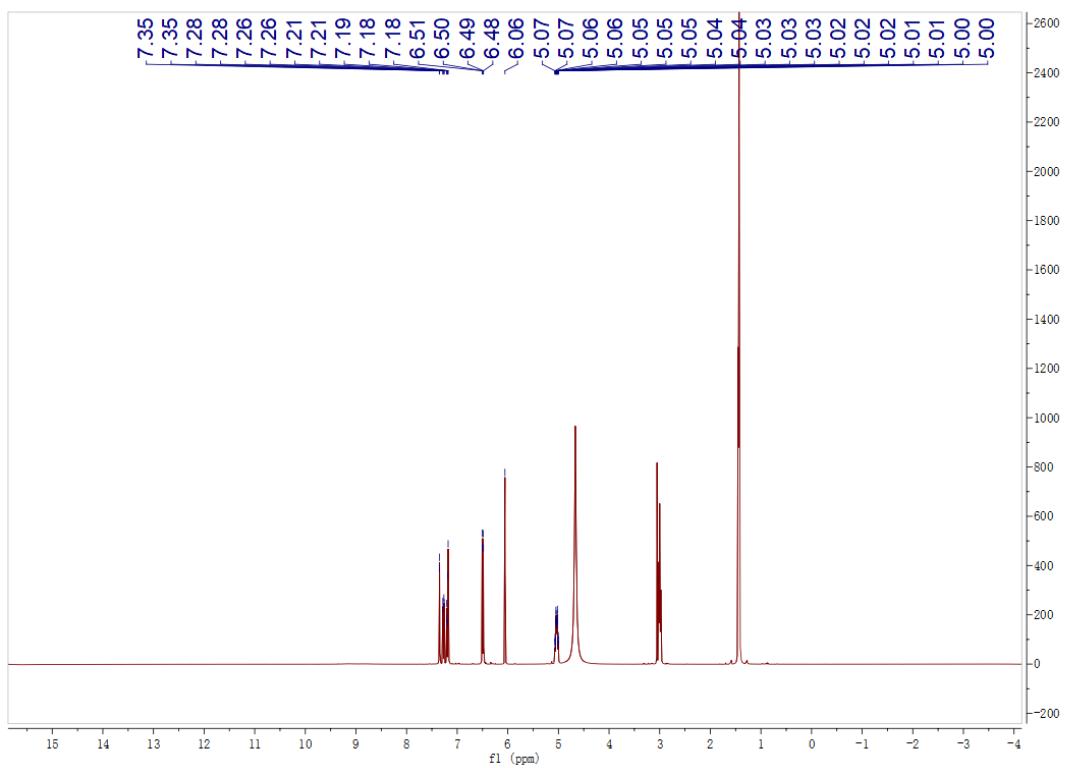
Figure S14. ^{13}C NMR spectrum of **6**.
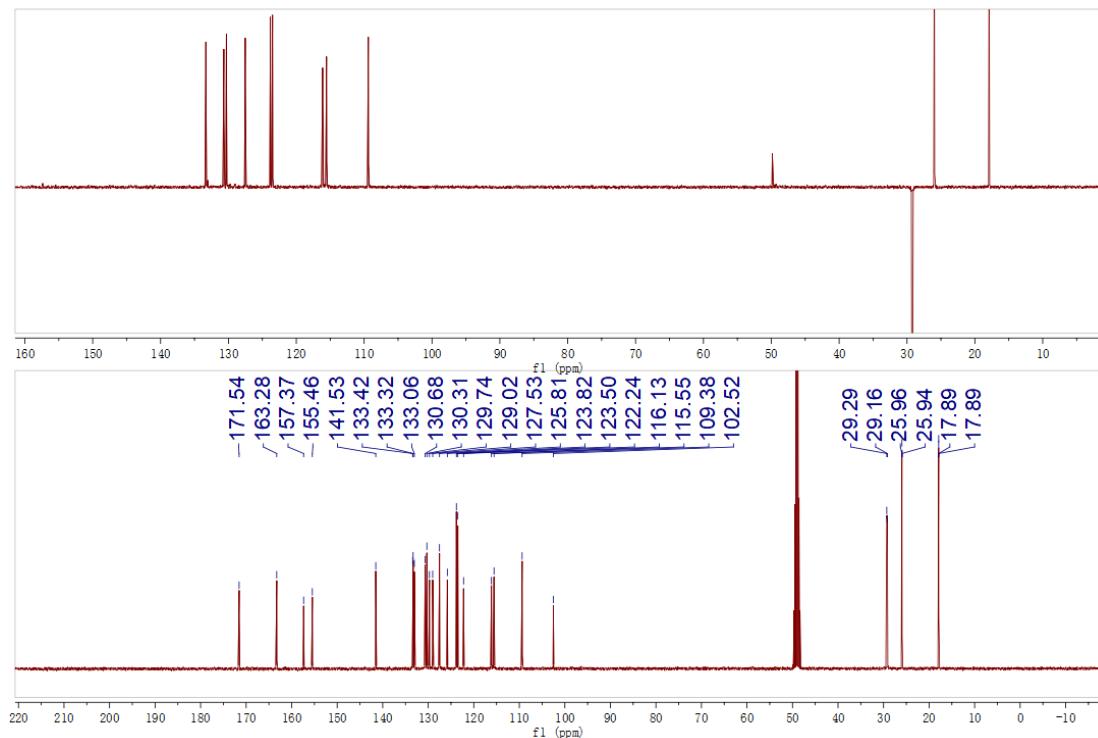
Figure S15. ^{1}H NMR spectrum of **7**.
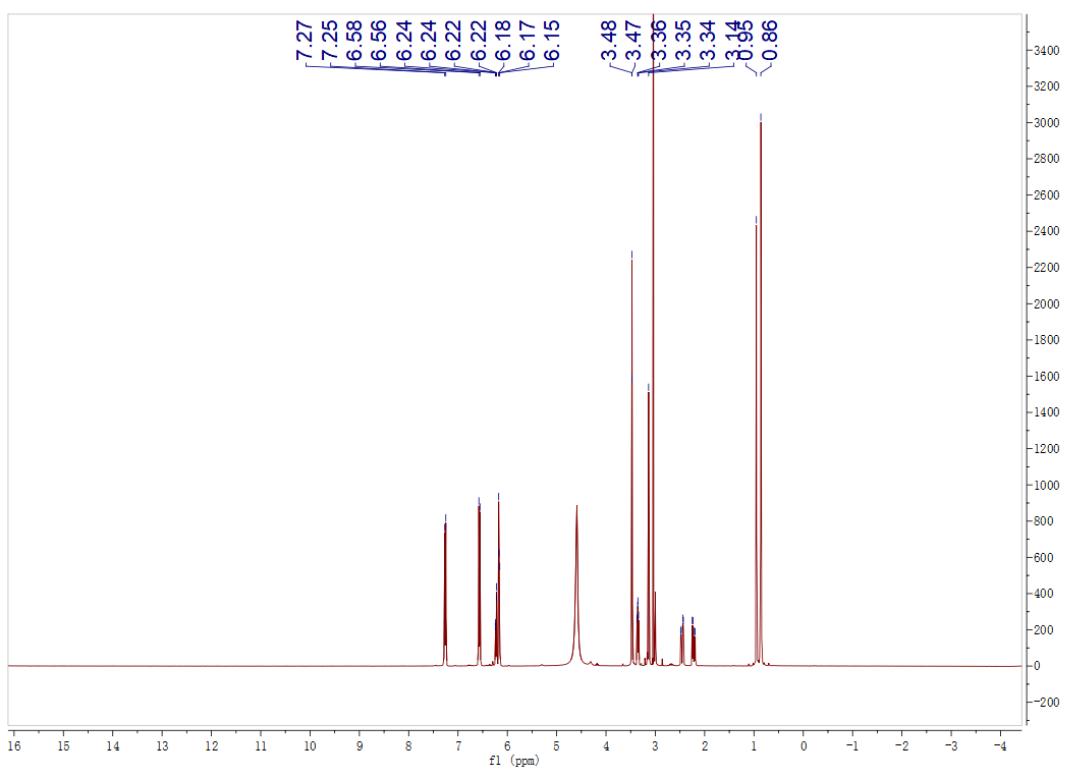
Figure S16. ^{13}C NMR spectrum of **7**.
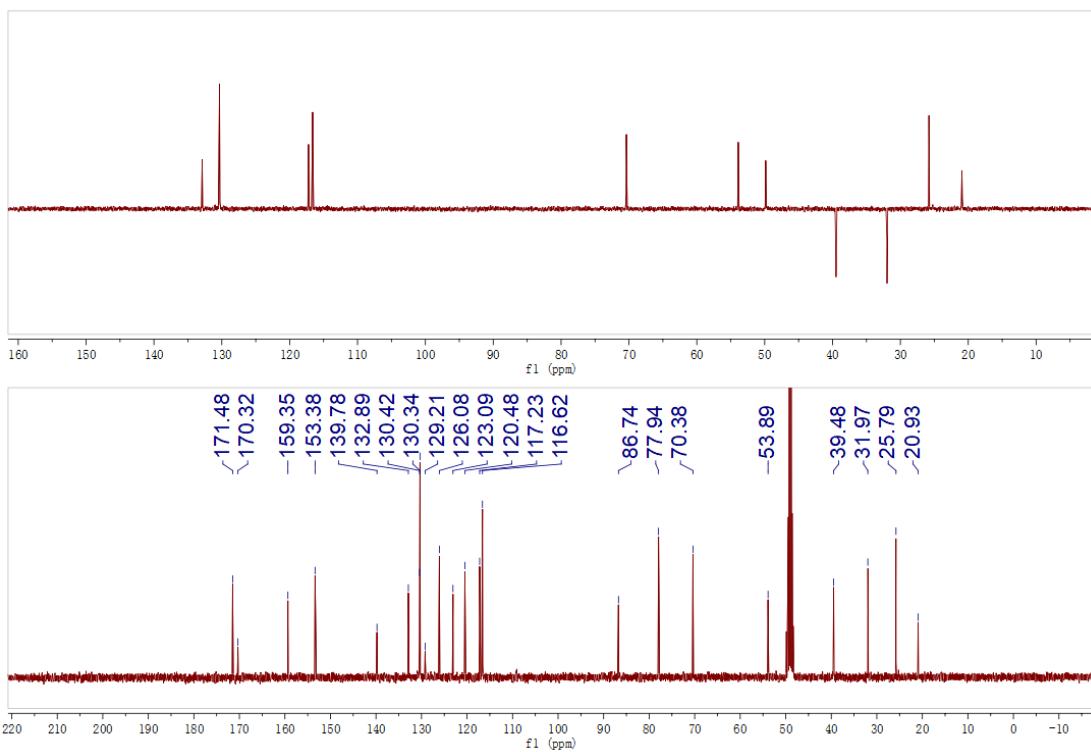
Figure S17. ^{1}H NMR spectrum of **8**.
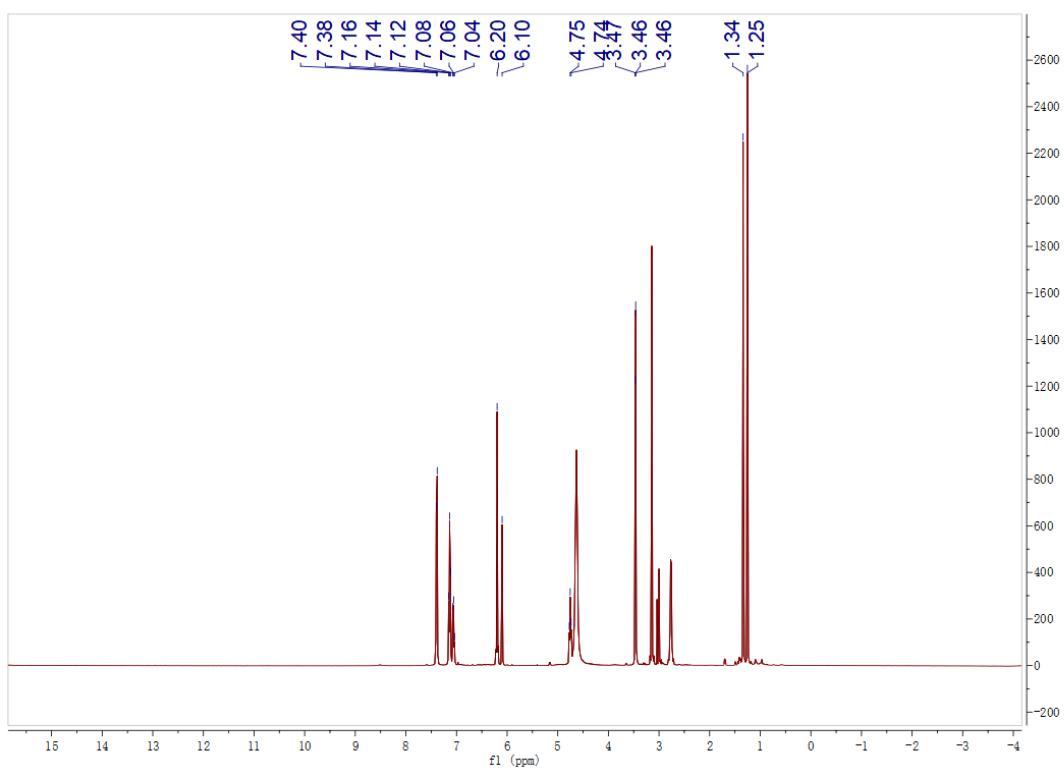
Figure S18. ^{13}C NMR spectrum of **8**.
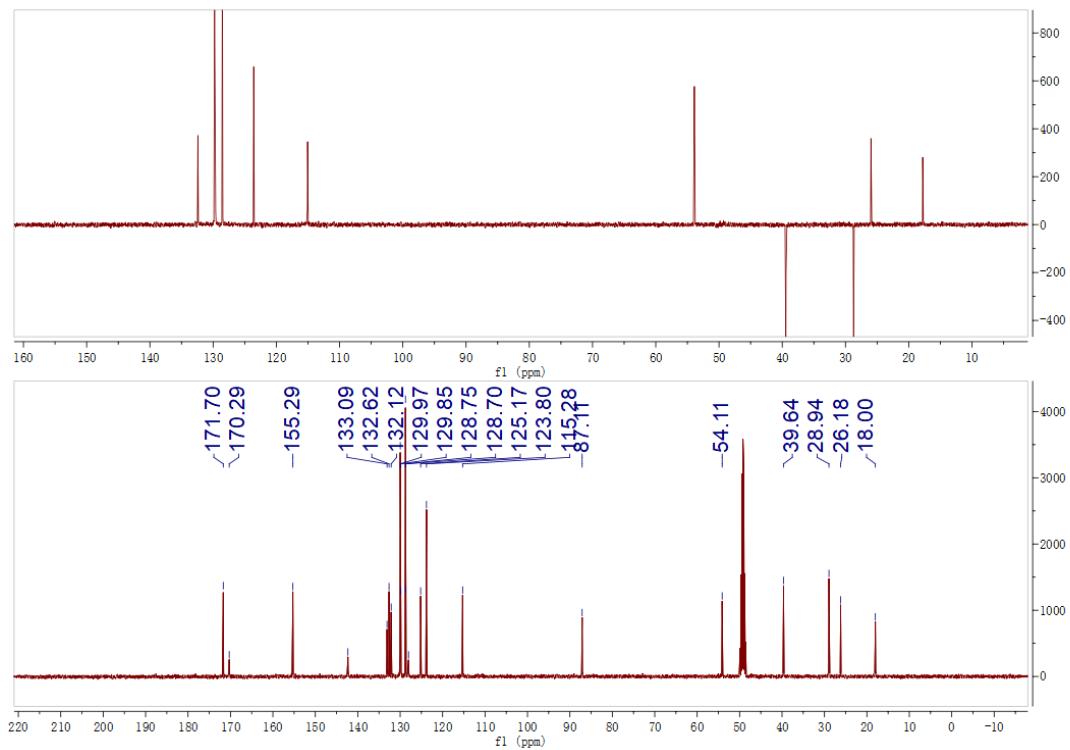
Figure S19. ¹H NMR spectrum of **9**.
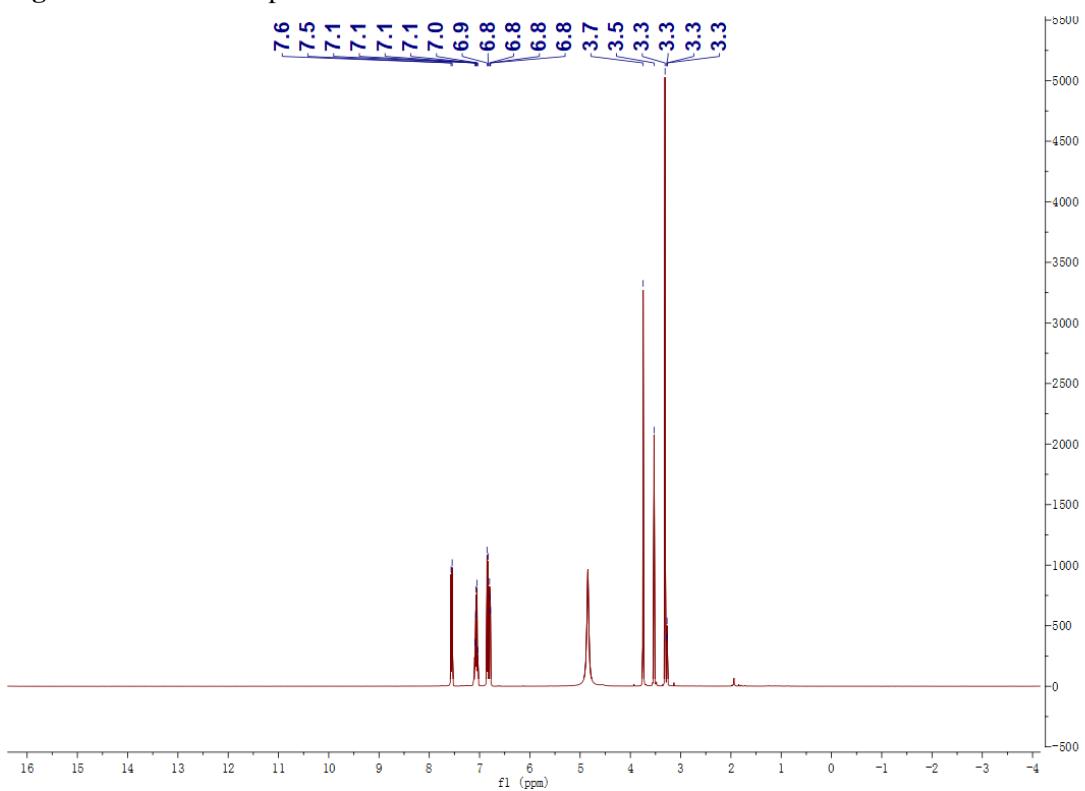
Figure S20. ¹³C NMR spectrum of **9**.
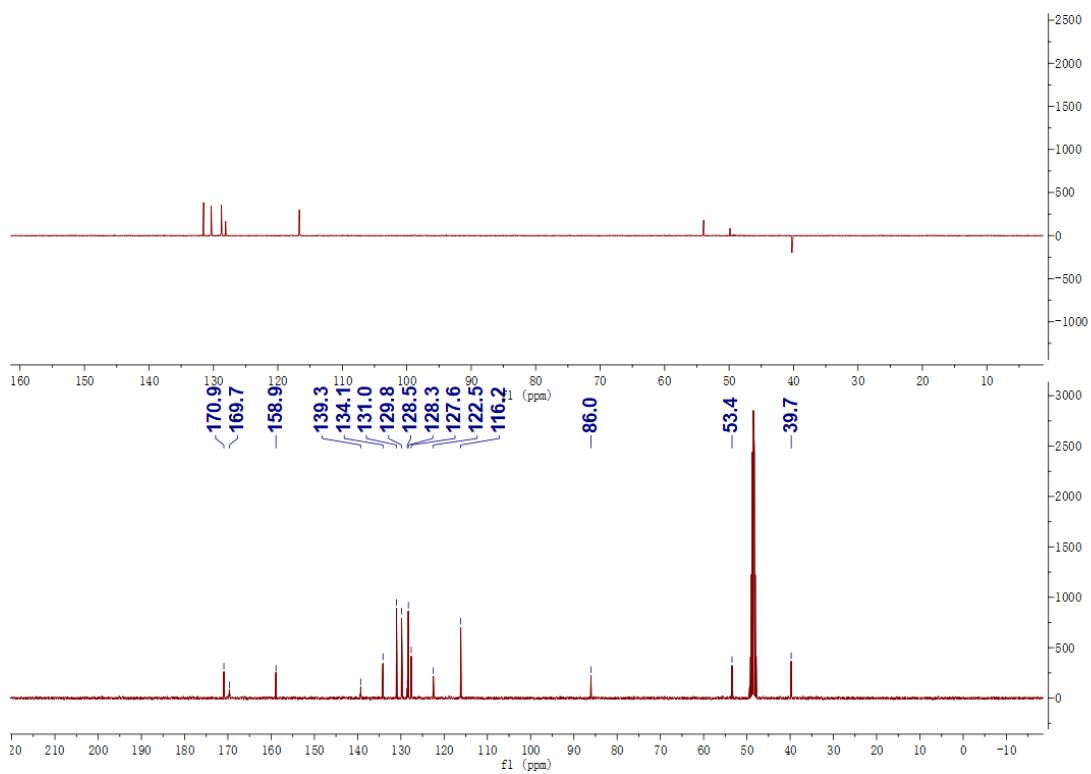
Figure S21. ^{1}H NMR spectrum of **10**.
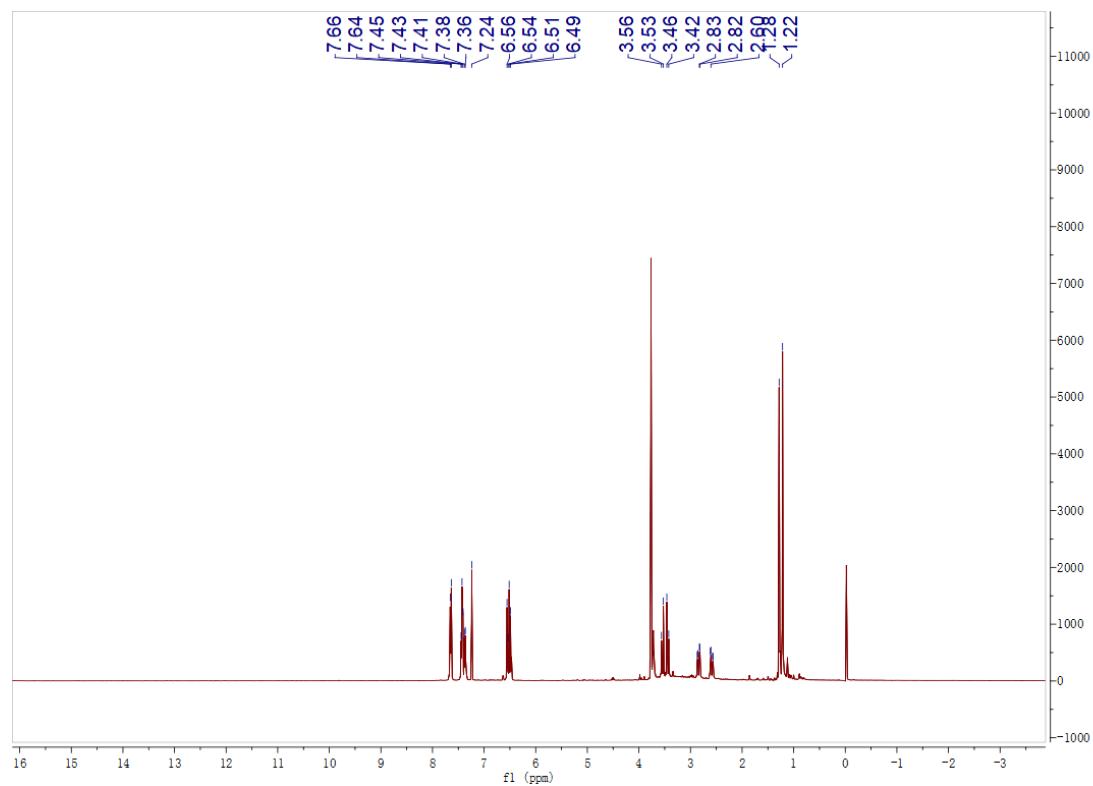
Figure S22. ^{13}C NMR spectrum of **10**.
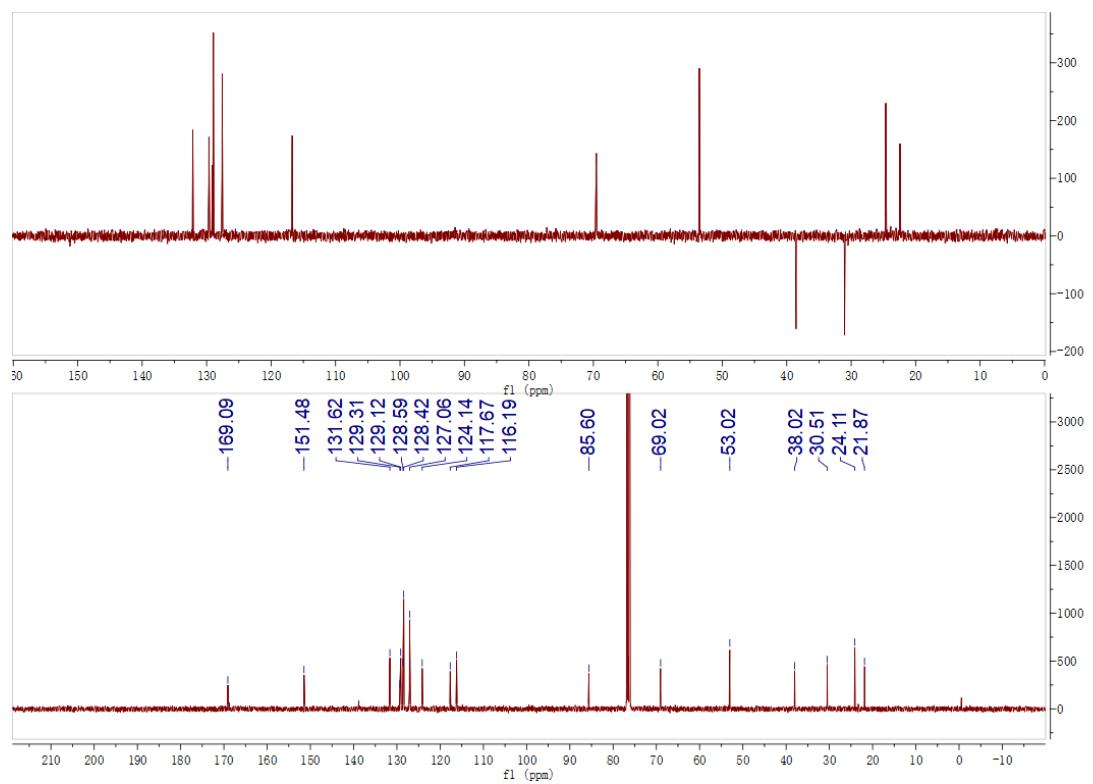
Figure S23. ^{1}H NMR spectrum of **11**.
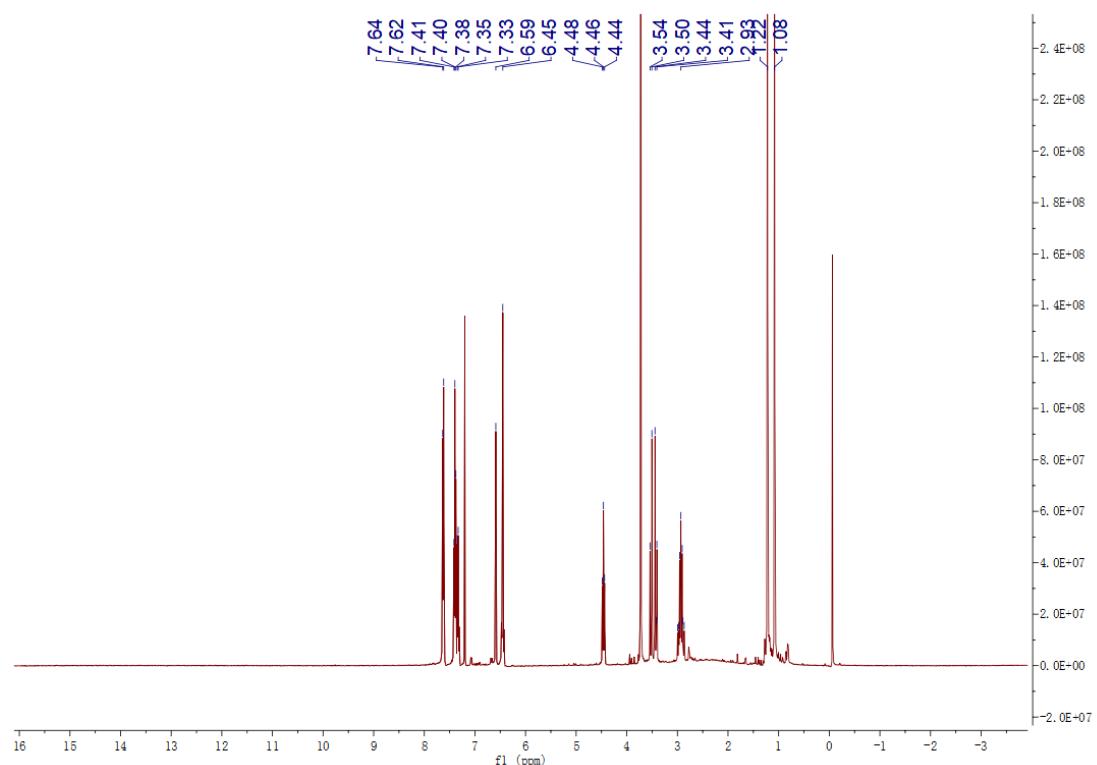
Figure S24. ^{13}C NMR spectrum of **11**.
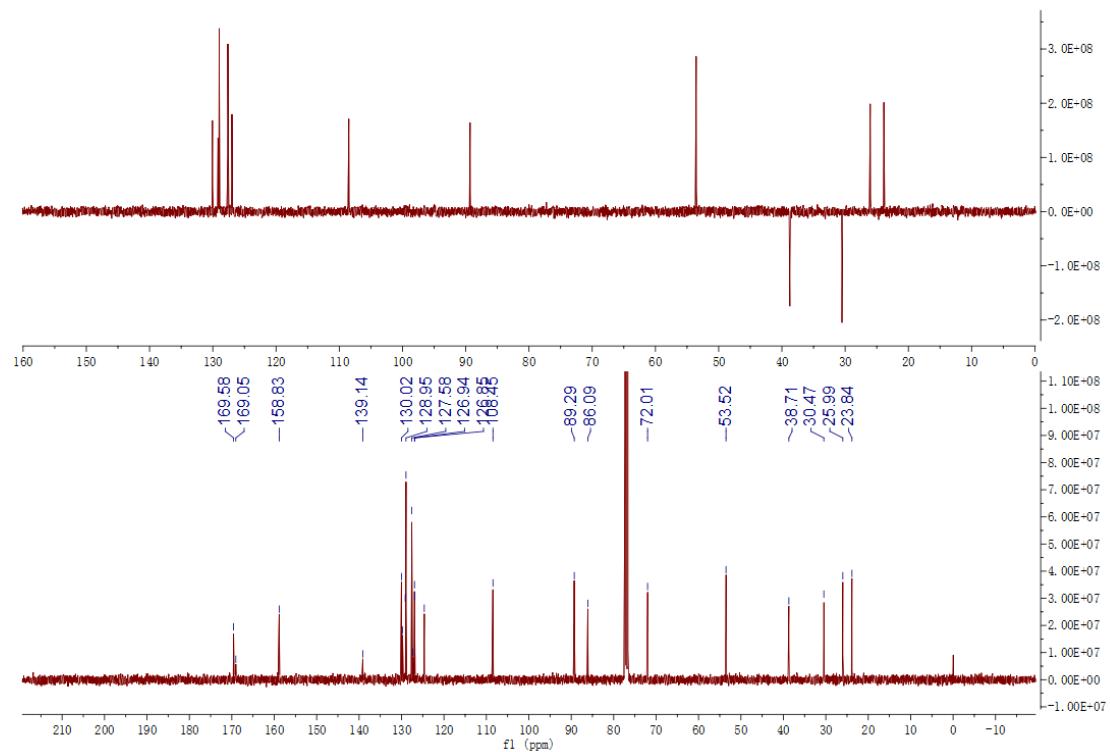
Figure S25. ^{1}H NMR spectrum of **12**.
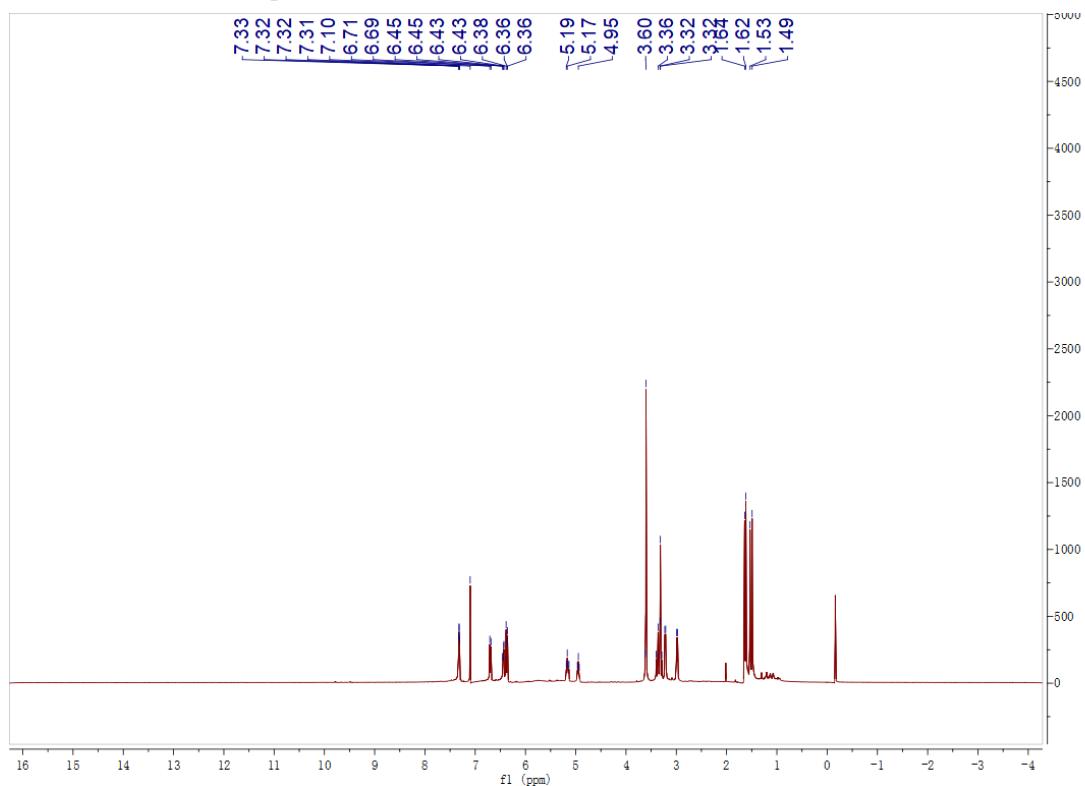
Figure S26. ^{13}C NMR spectrum of **12**.
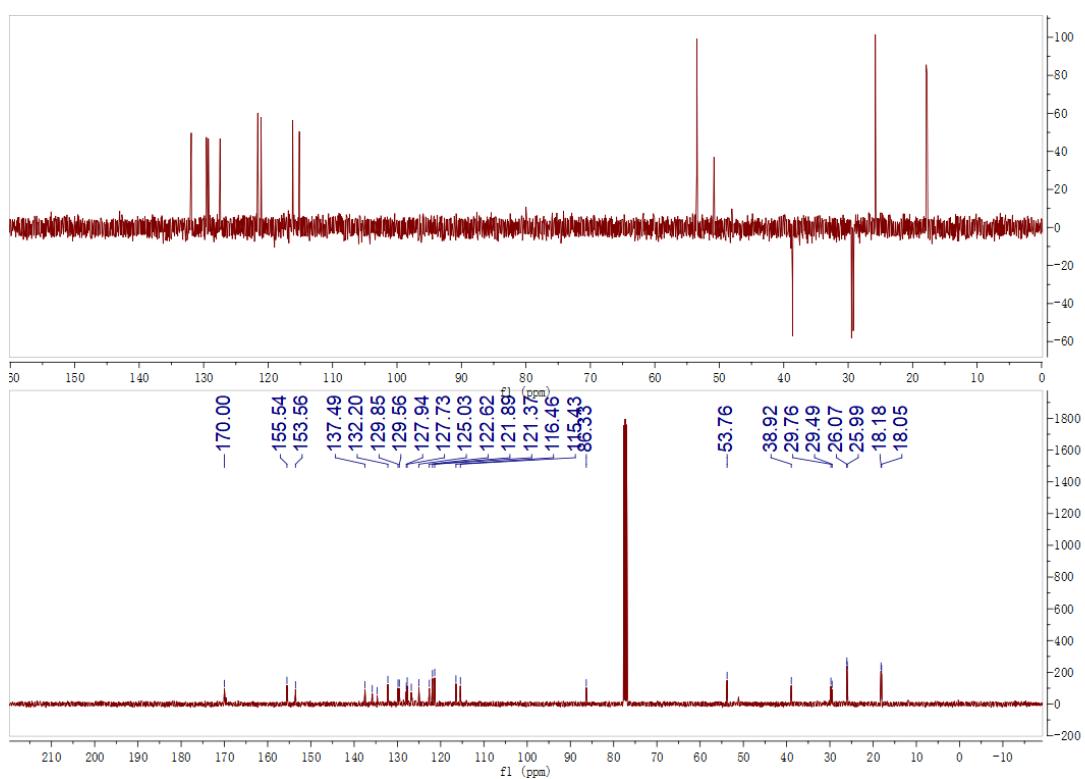
Figure S27. ^{1}H NMR spectrum of **13**.
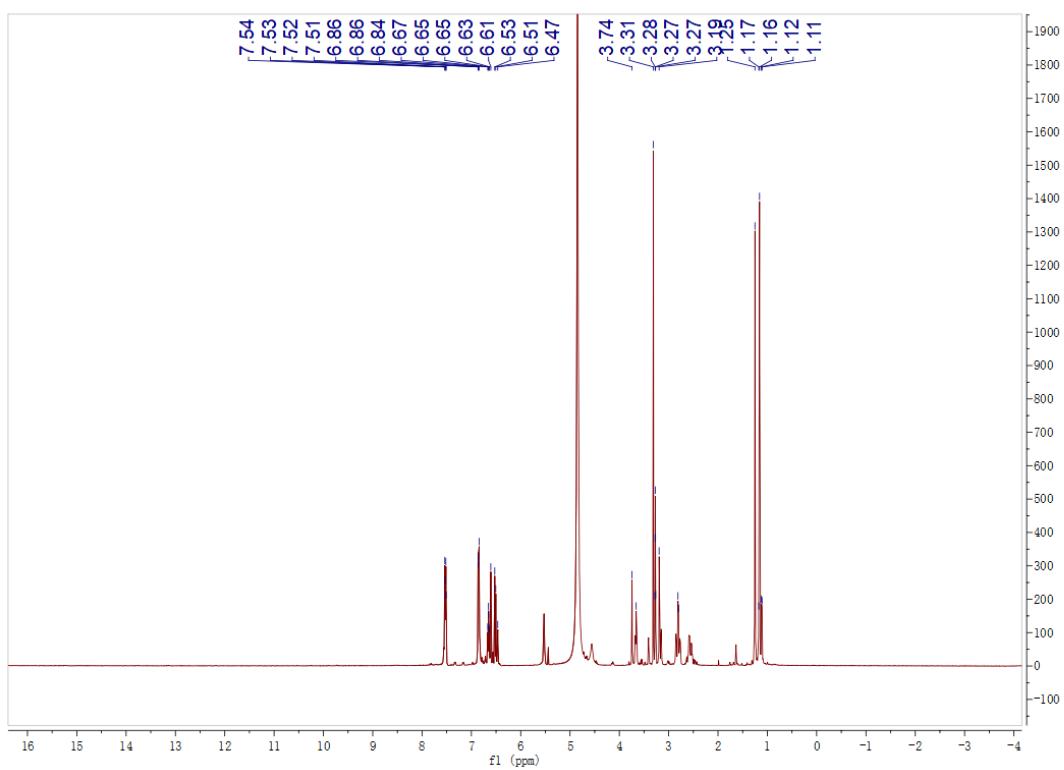
Figure S28. ^{13}C NMR spectrum of **13**.
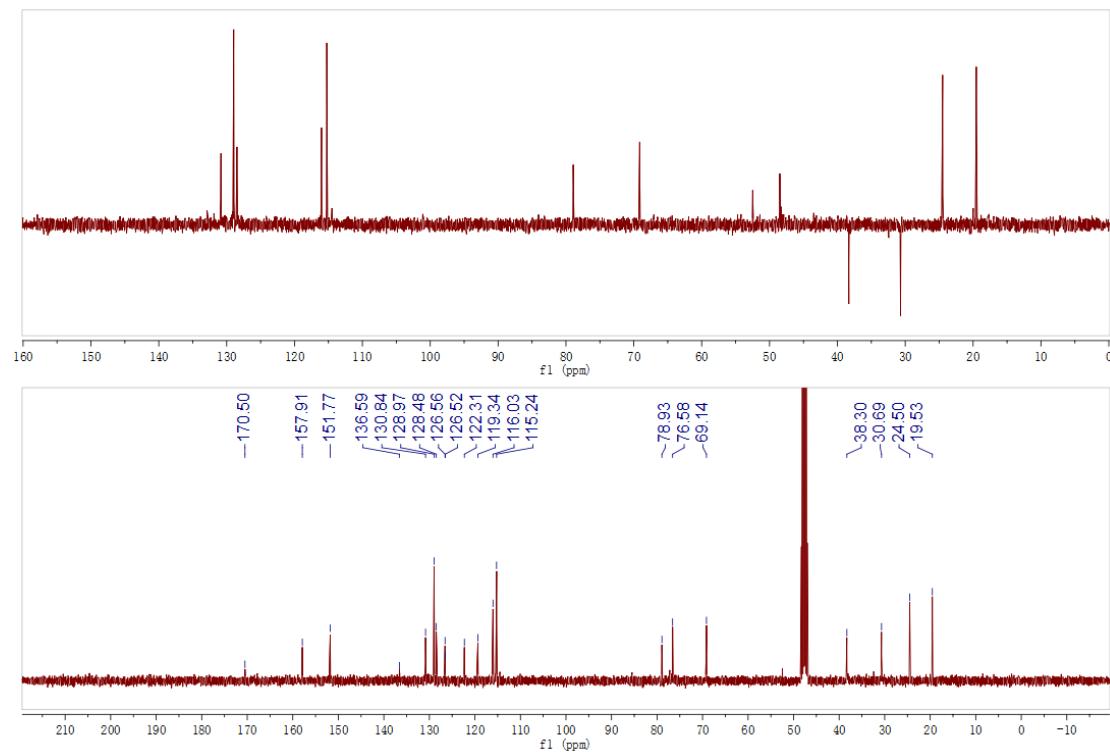
Figure S29. ^{1}H NMR spectrum of **14**.
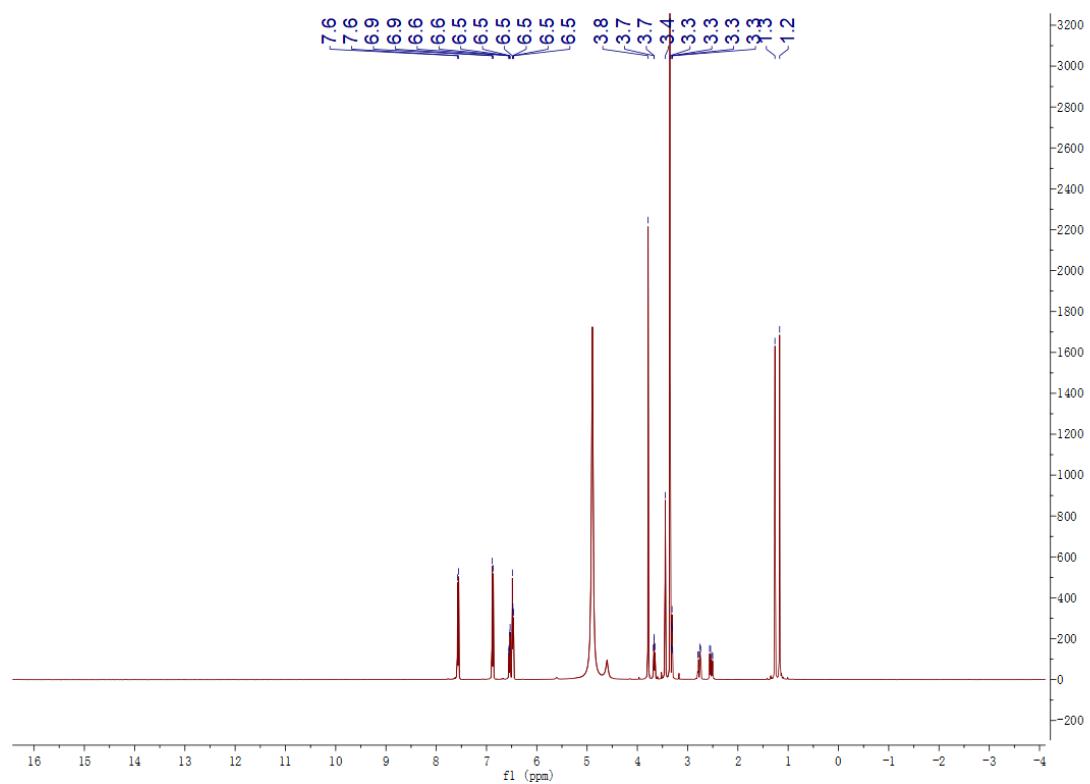
Figure S30. ^{13}C NMR spectrum of **14**.
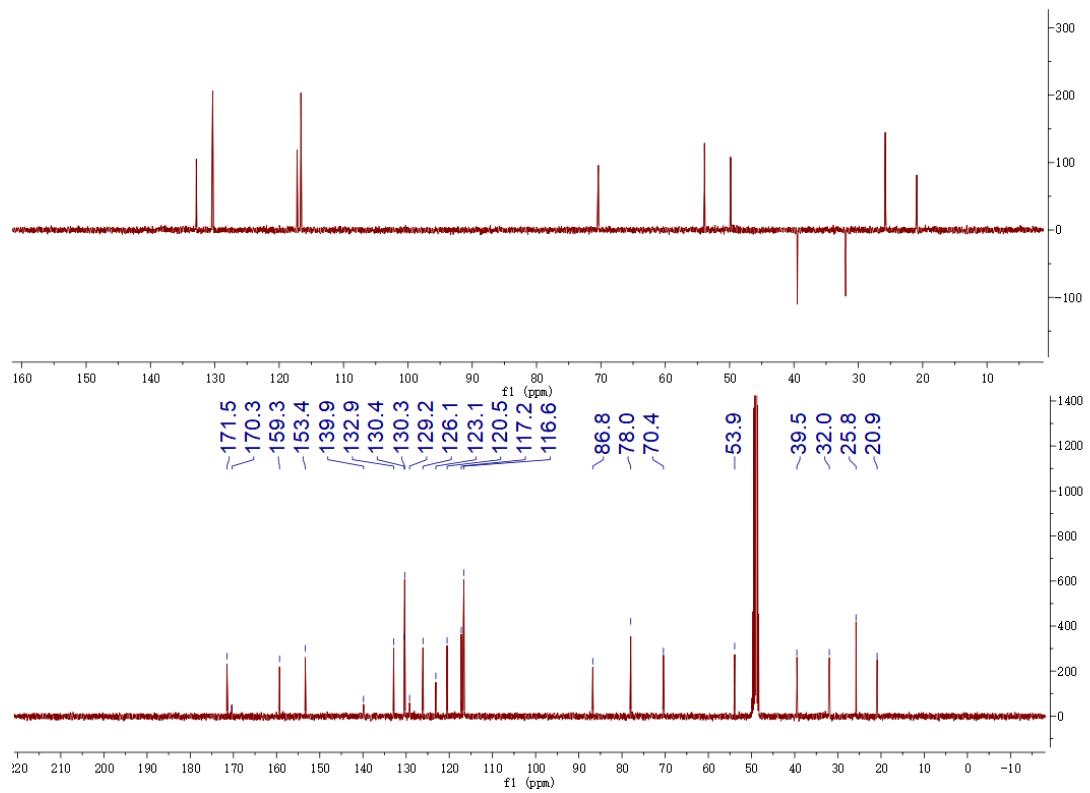
Figure S31. ¹H NMR spectrum of **15**.
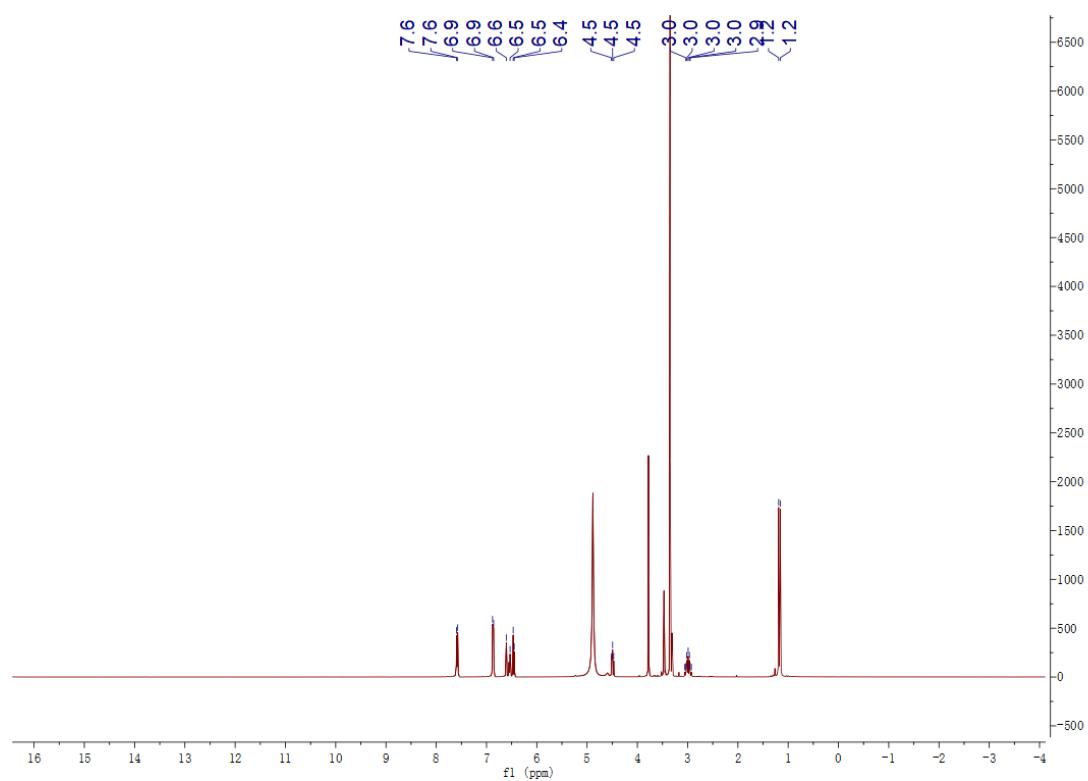
Figure S32. ¹³C NMR spectrum of **15**.
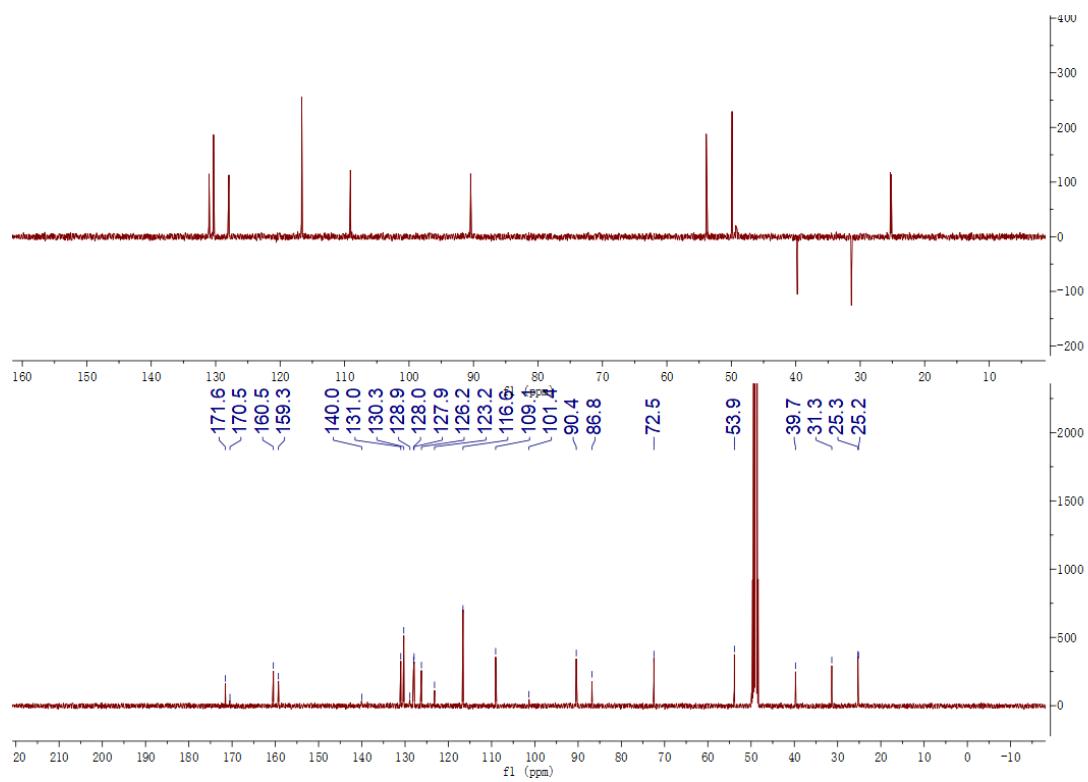
**Figure S33.** ¹H NMR spectrum of **16**.
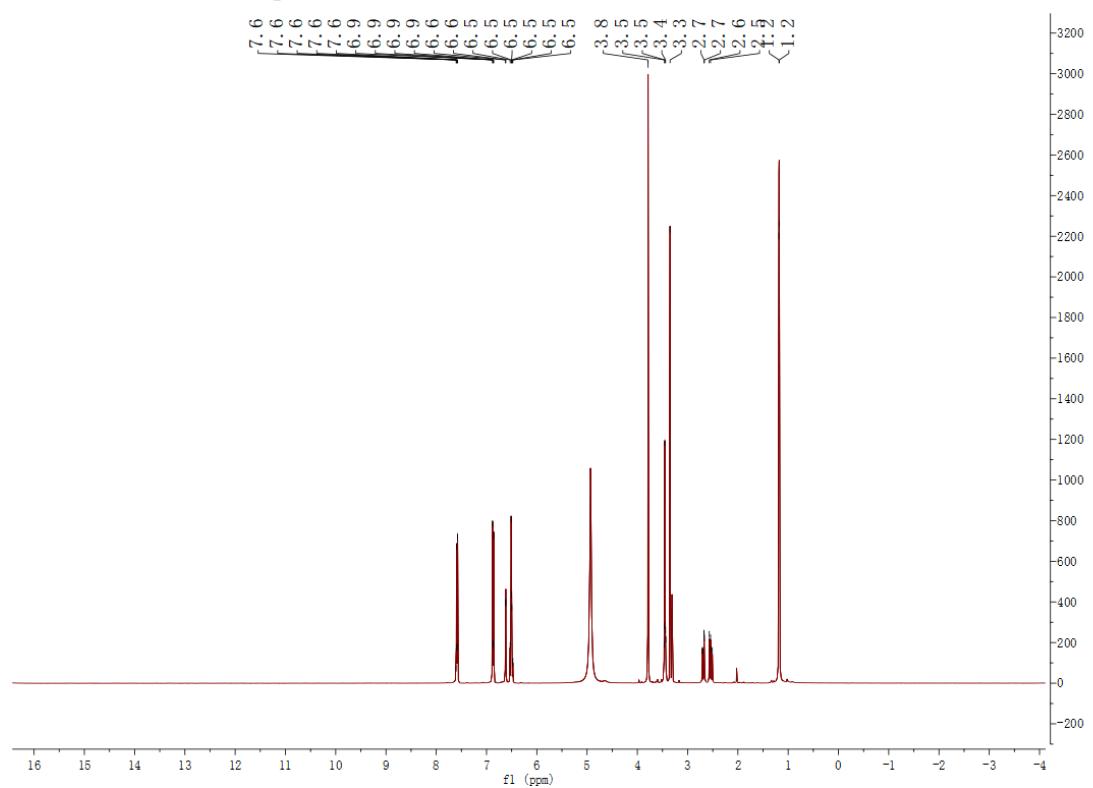
Figure S34. ¹³C NMR spectrum of **16**.
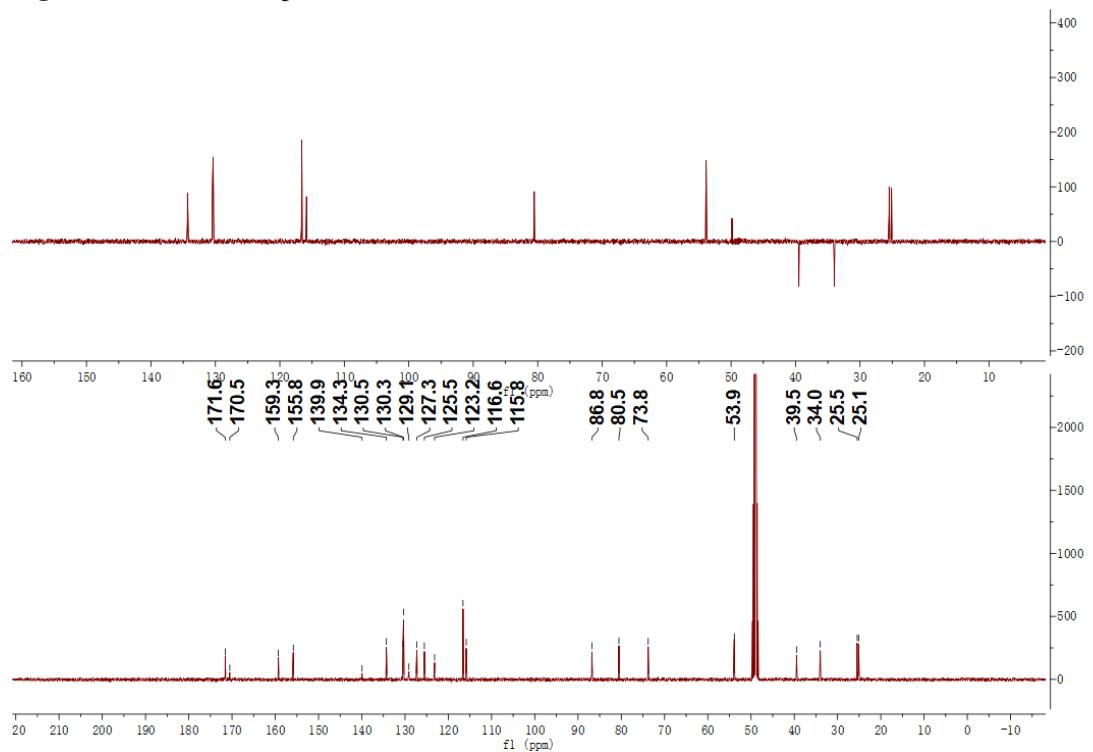
**Figure S35.** ^{13}C NMR spectrum of **17**.
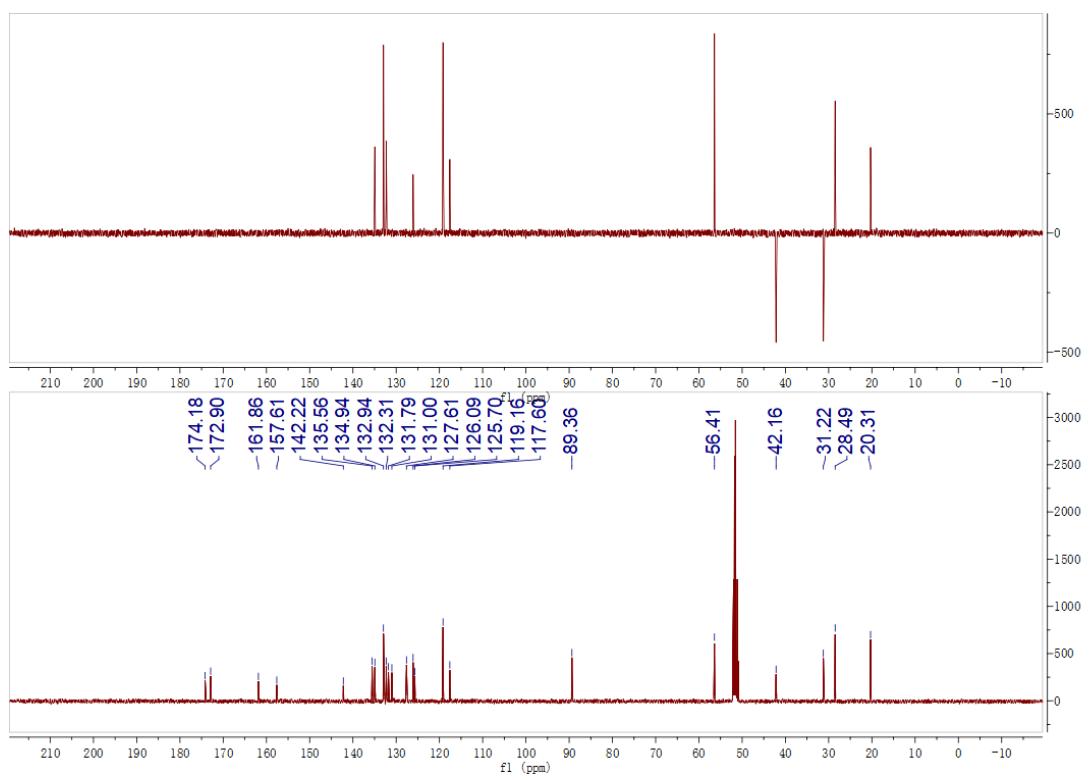
**Figure S36.** ^{1}H NMR spectrum of **18**.
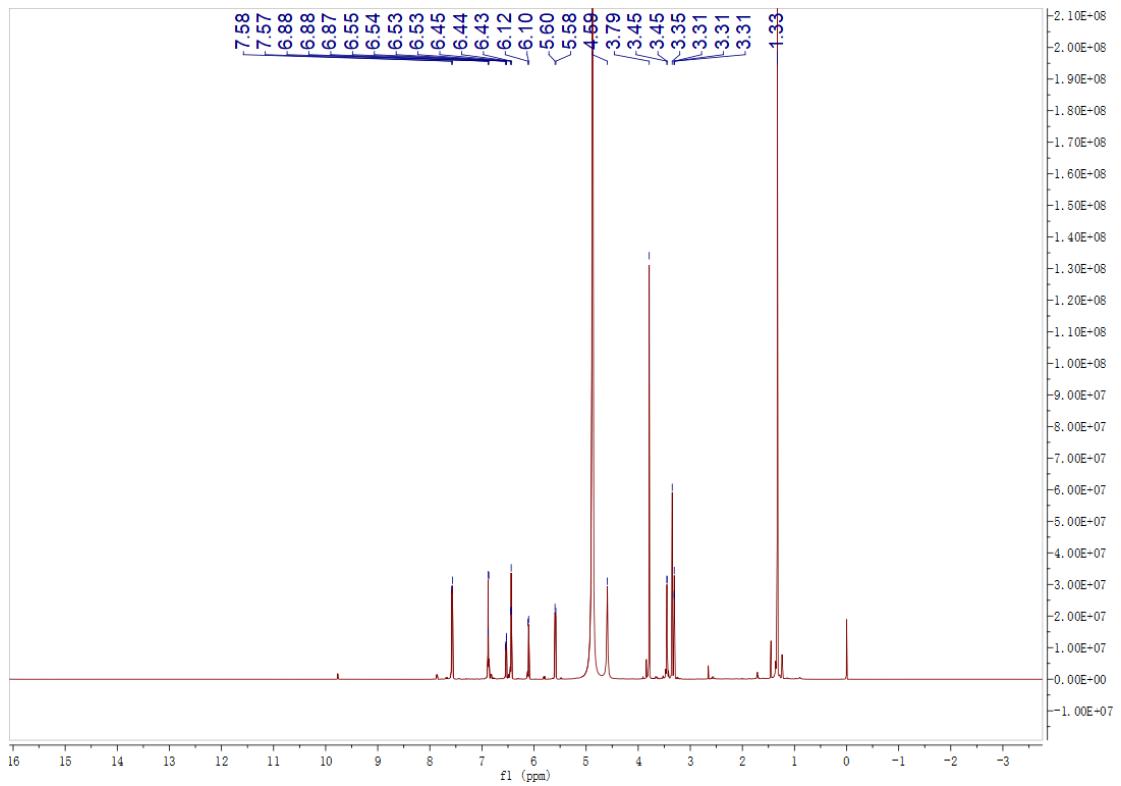
**Figure S37.** ^{13}C NMR spectrum of **18**.
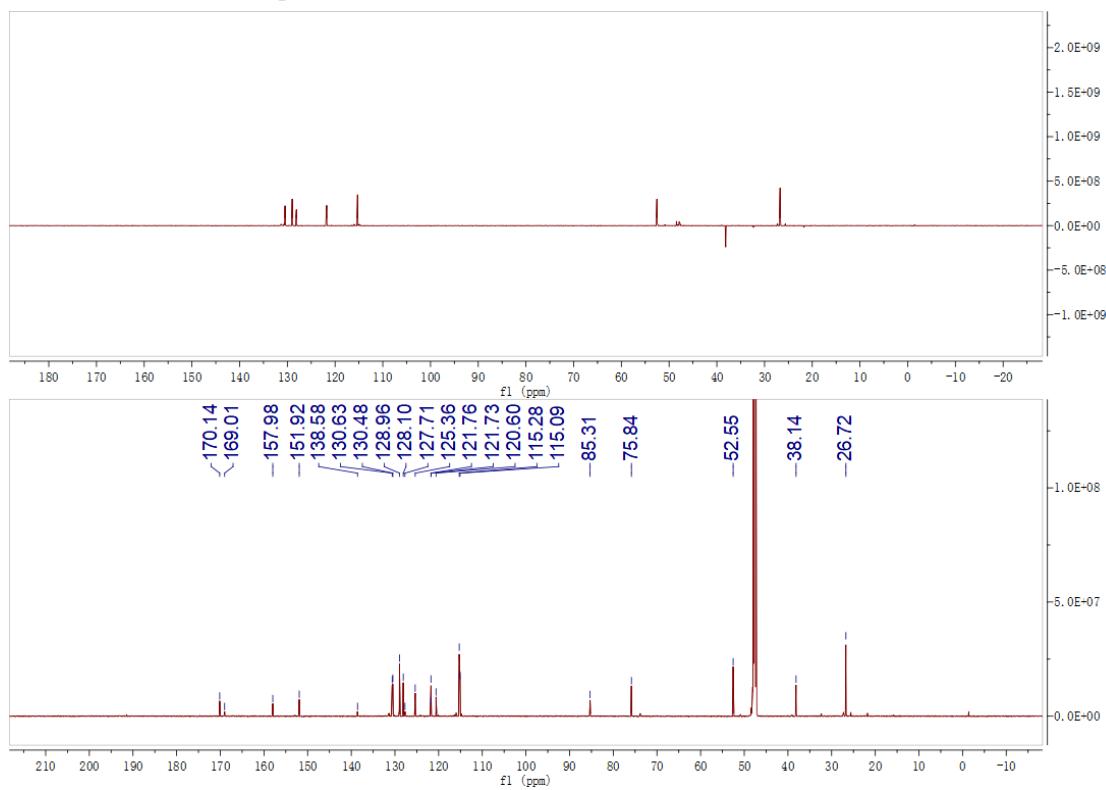
**Figure S38.** HPLC profile for the extract of the culture of *Aspergillus terreus* [MeOH–H$_2$O (20:80 to 80:20, 80 min, v/v, 2.0 mL/min)].
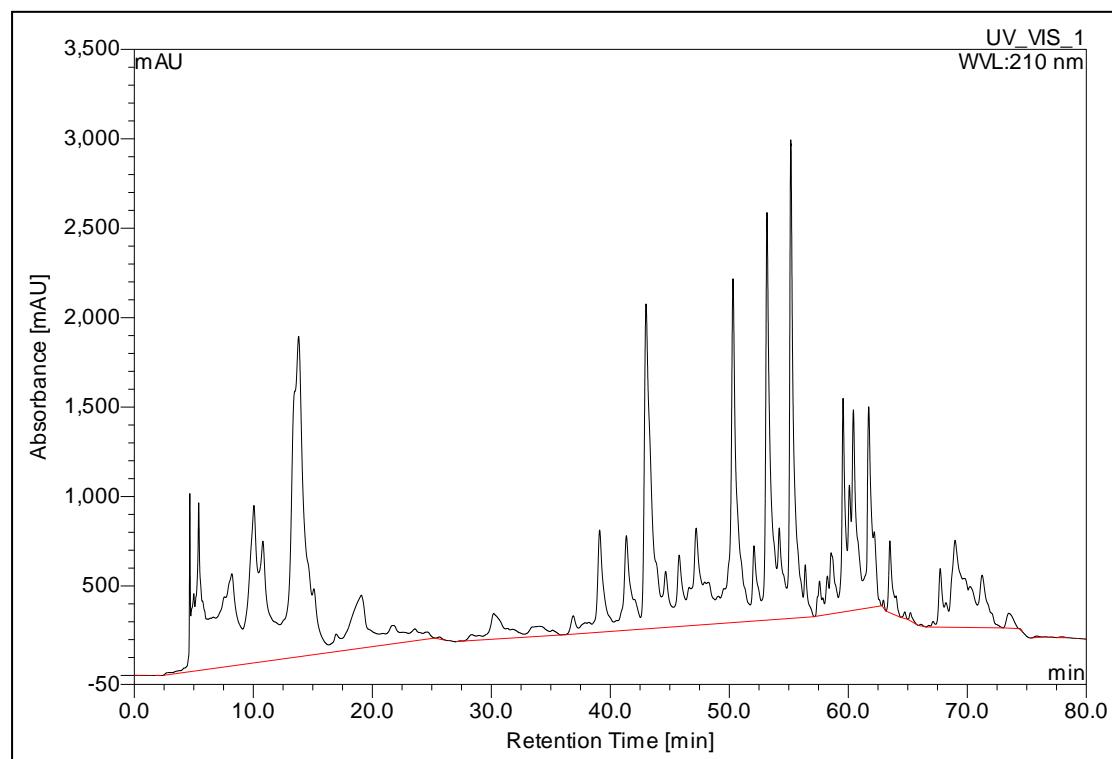
Figure S39. Purity tests of all compounds 1-18.