Article

Systematic Modification of the Substitution Pattern of the 7-Hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide Scaffold Enabled the Discovery of New Ligands with High Affinity and Selectivity for the Cannabinoid Type 2 Receptor

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Supplementary Information

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X-Ray crystallographic analysis of compound 51

A single crystal of compound **51** was submitted to X-ray data collection on an Oxford-Diffraction Xcalibur Sapphire 3 diffractometer with a graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at 293 K. The structure was solved by direct methods implemented in SHELXS-97 program [1]. The refinement was carried out by full-matrix anisotropic least-squares on F^2 for all reflections for non-H atoms by means of the SHELXL-97 program [2]. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 2265135. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; (fax: + 44 (0) 1223 336 033; or e- mail: deposit@ccdc.cam.ac.uk).

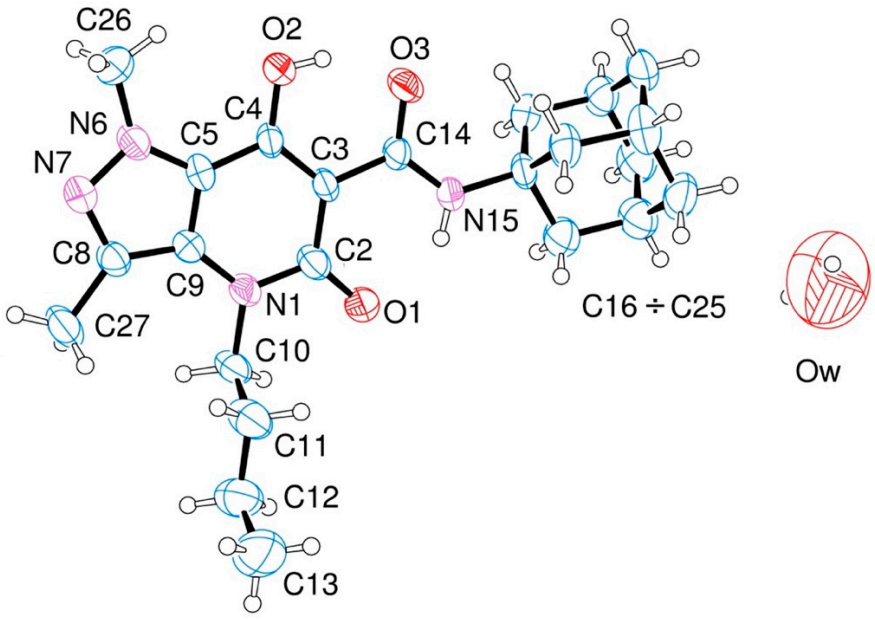
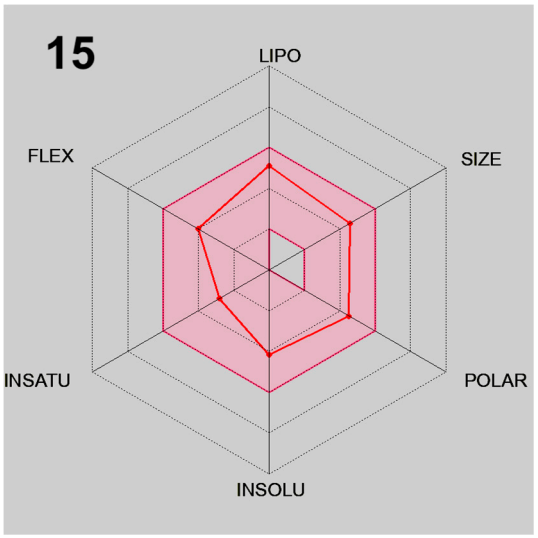


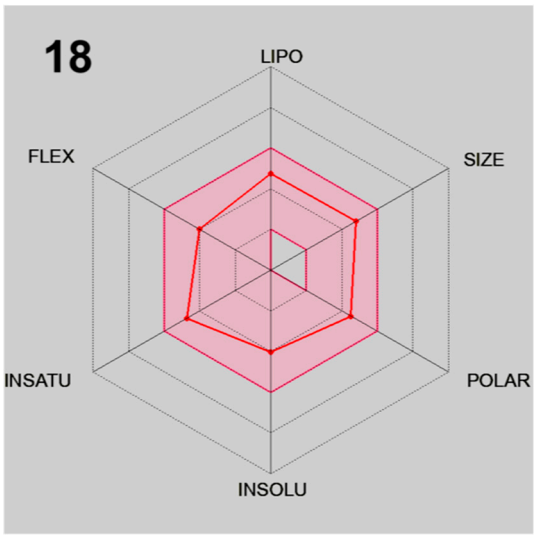
Figure S1. X-ray crystal structure of compound **51**. Ellipsoids enclose 50% probability

References

[1] Sheldrick, G. M. SHELXS-97, Rel. 97-2, A Program for Automatic Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), 1997.

[2] Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst*. **2015**, *C71*, 3-8.





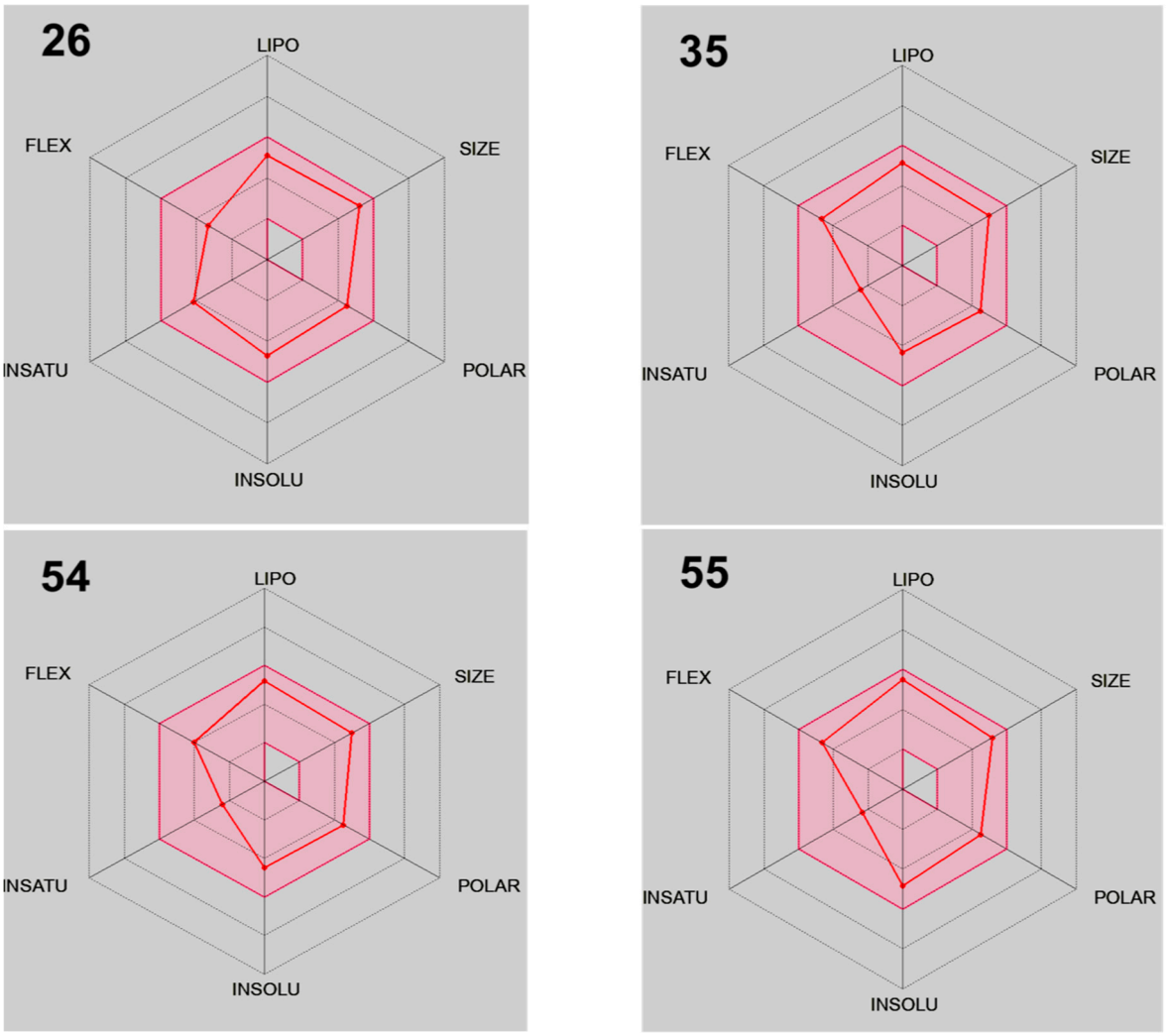


Figure S2. Bioavailability radar plot of selected compounds using the SwissADME software

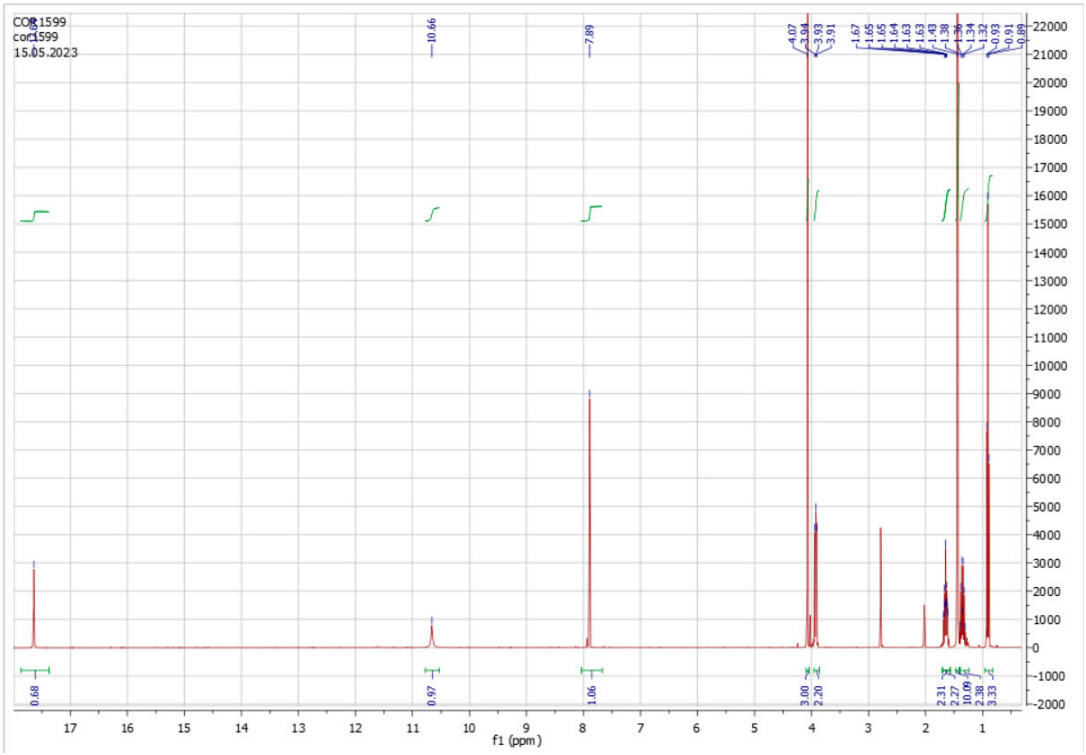


Figure S3. ^{1}H NMR spectrum of compound **13**.

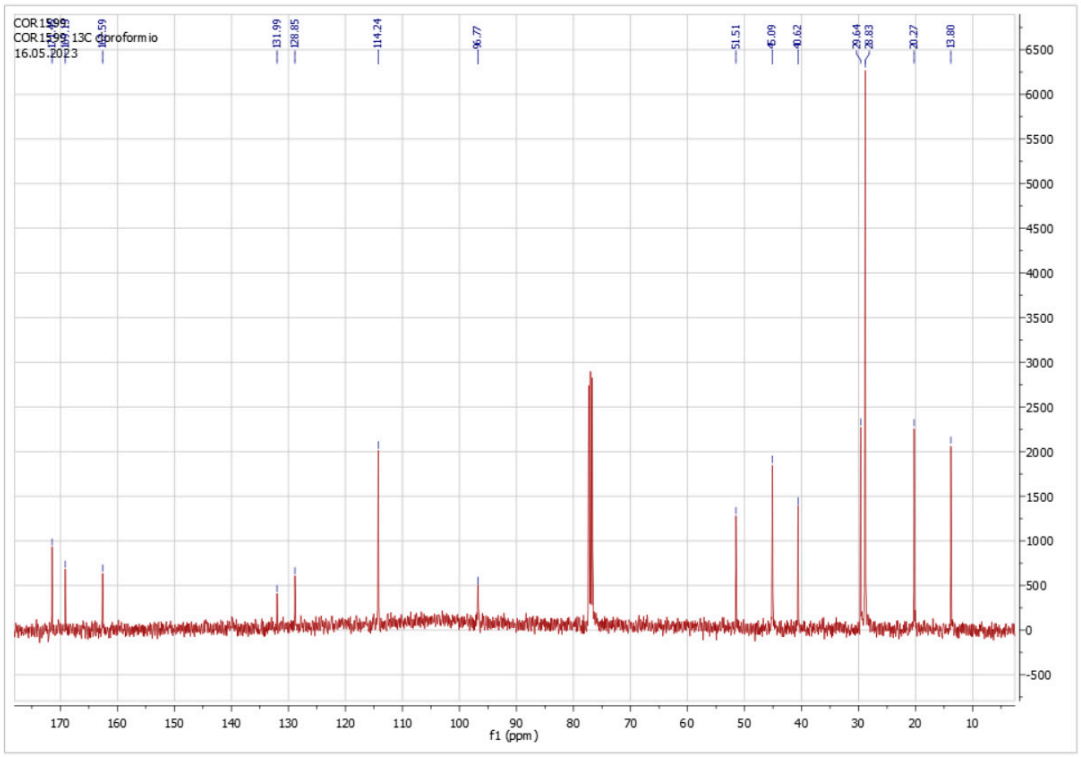


Figure S4. ^{13}C NMR spectrum of compound **13**.

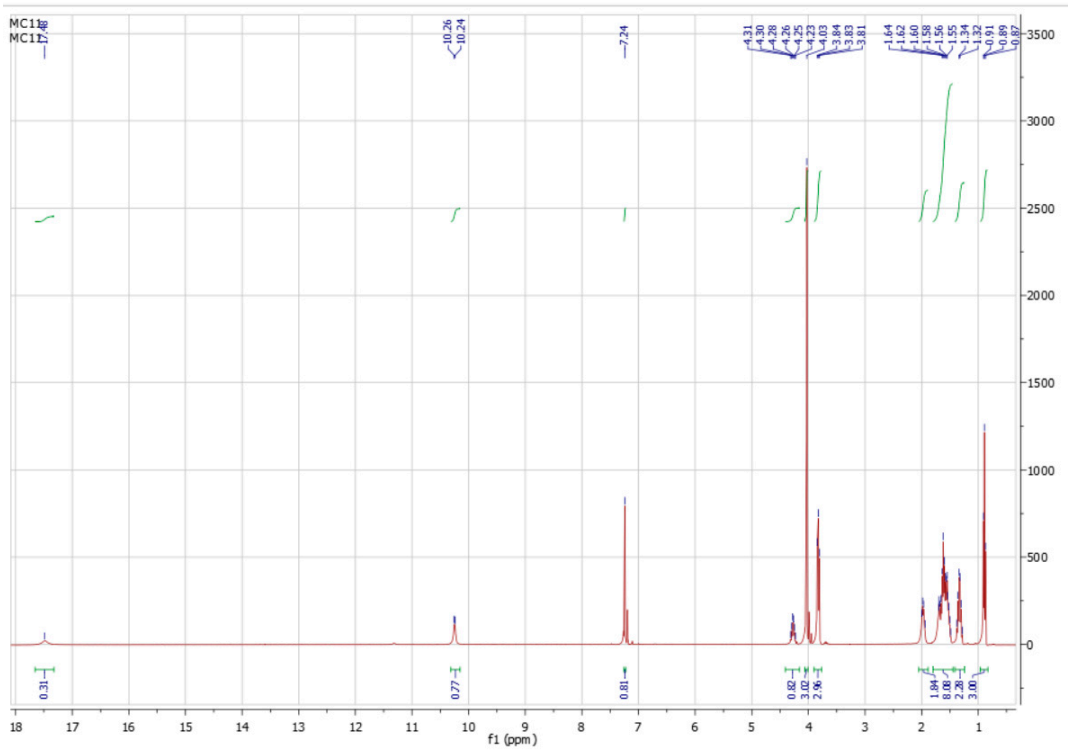


Figure S5. ^{1}H NMR spectrum of compound **14**.

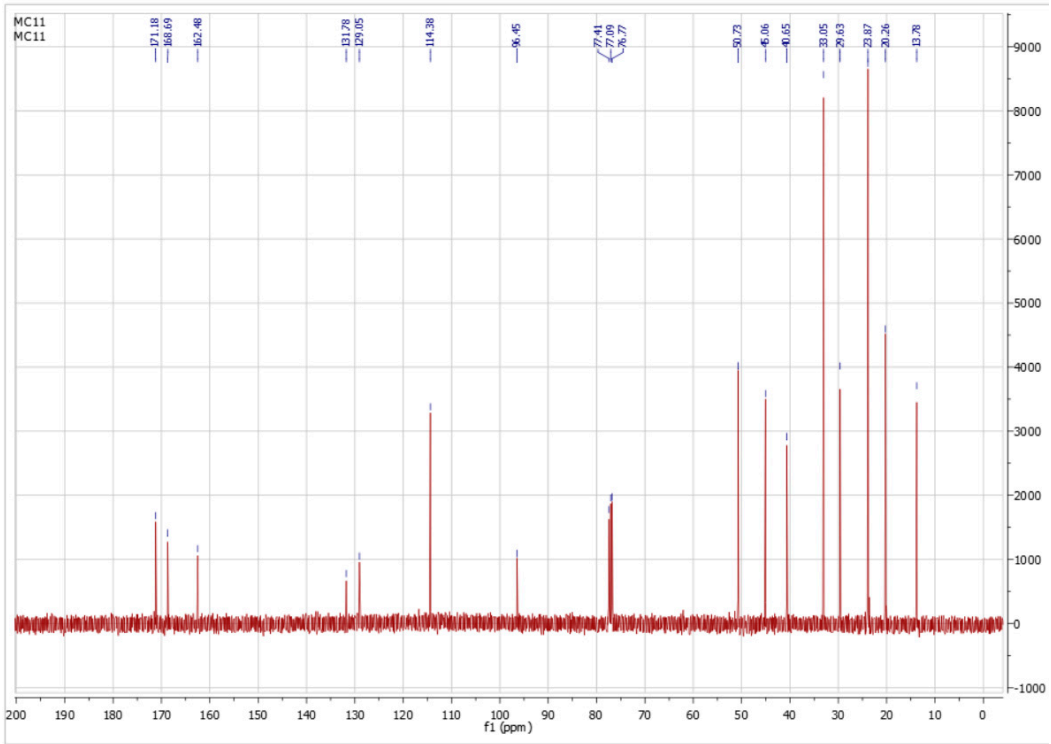
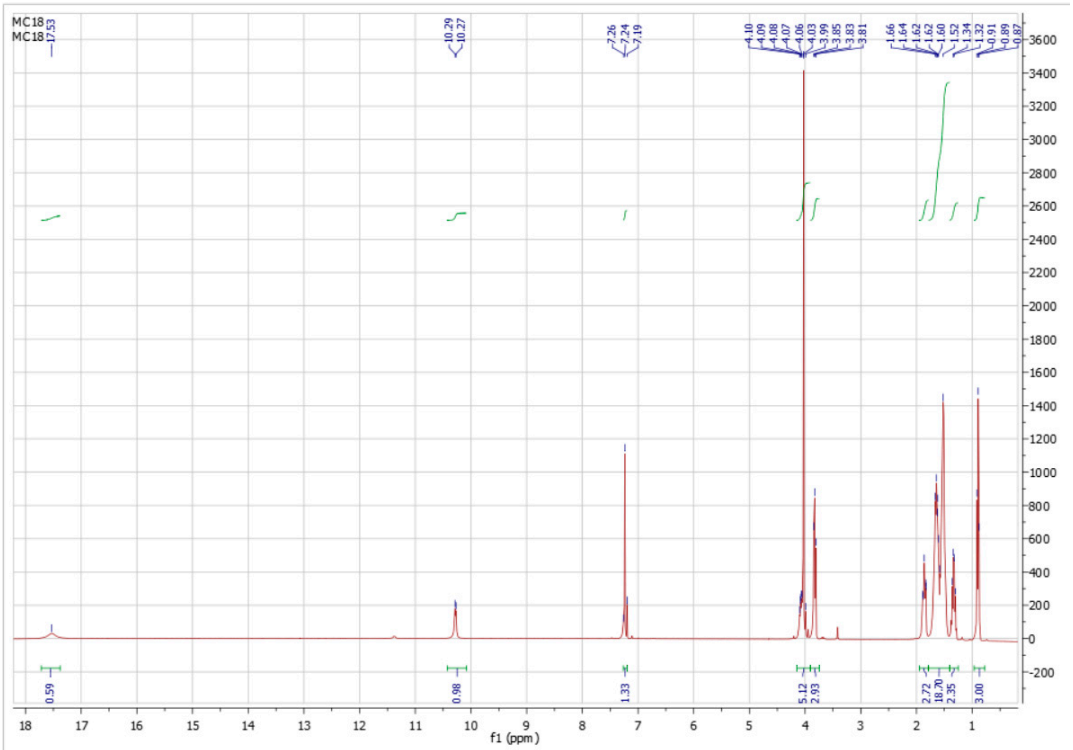


Figure S6. ^{13}C NMR spectrum of compound **14**.



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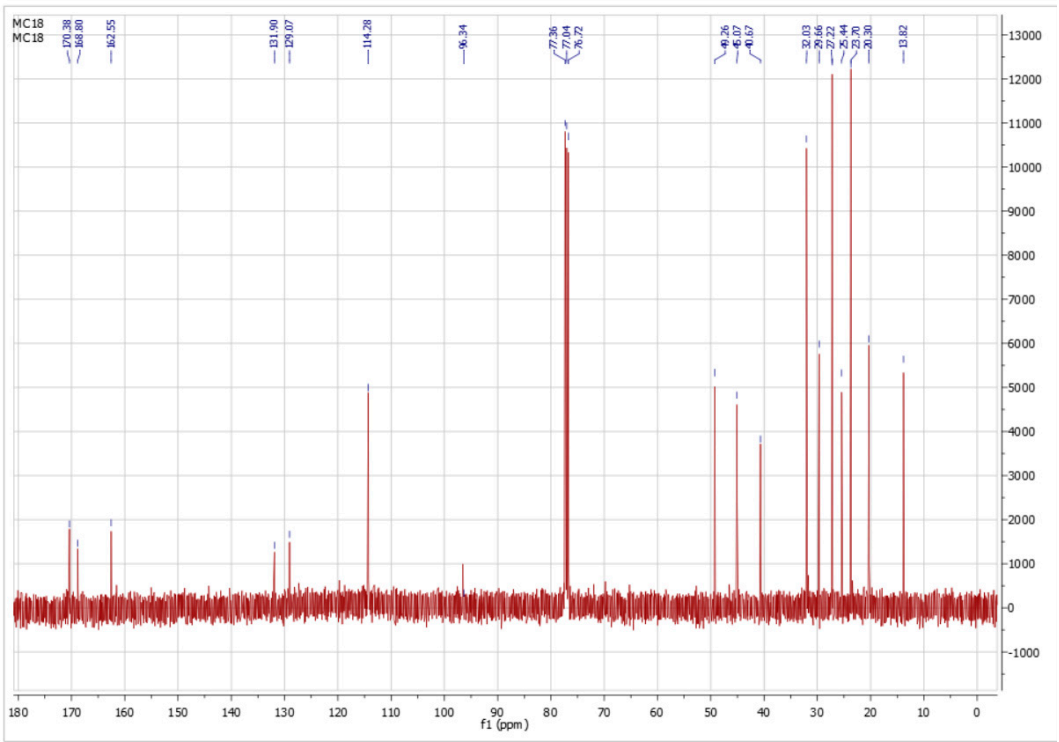

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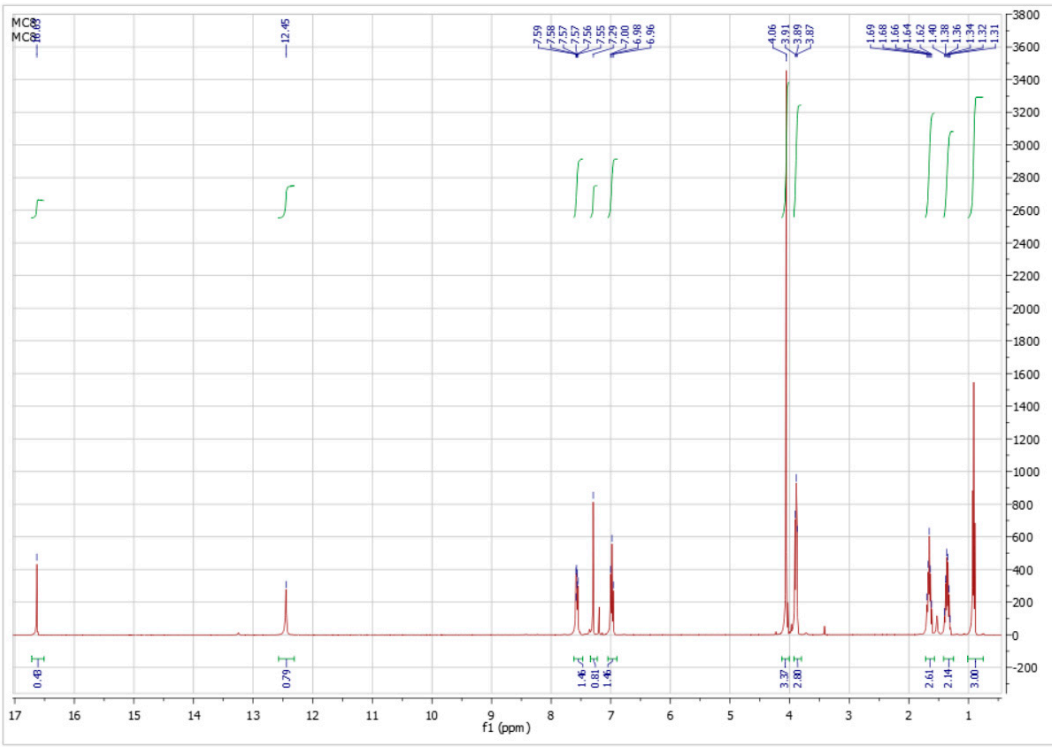


Figure S9. ^{1}H NMR spectrum of compound **16**.

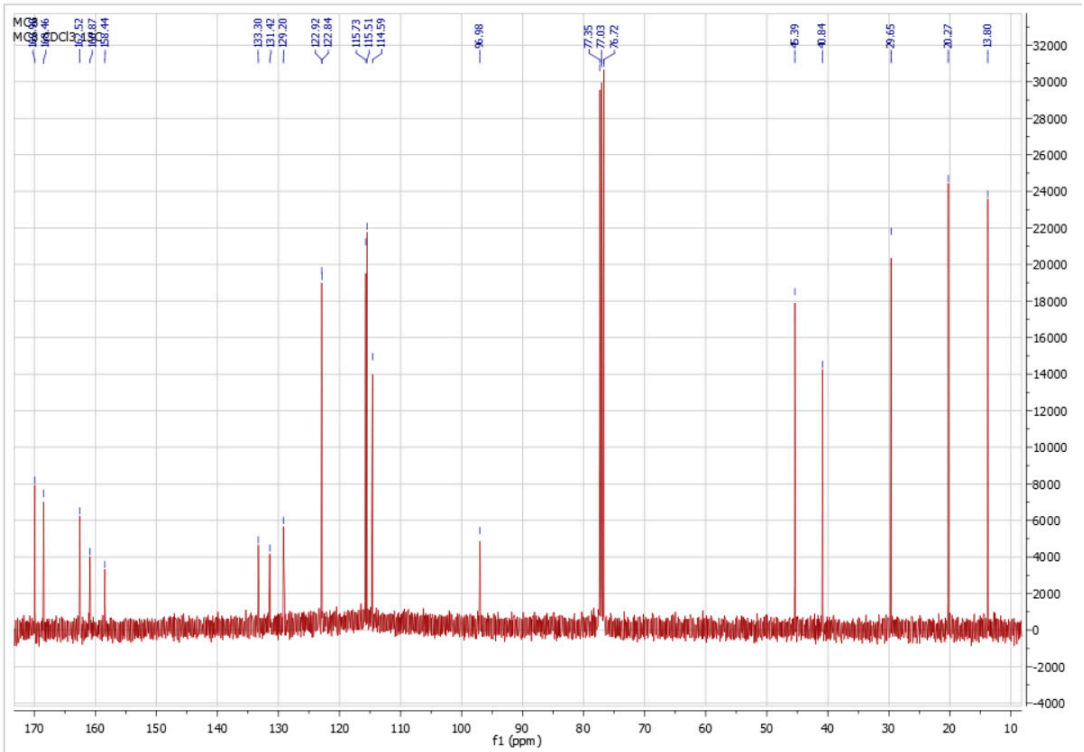
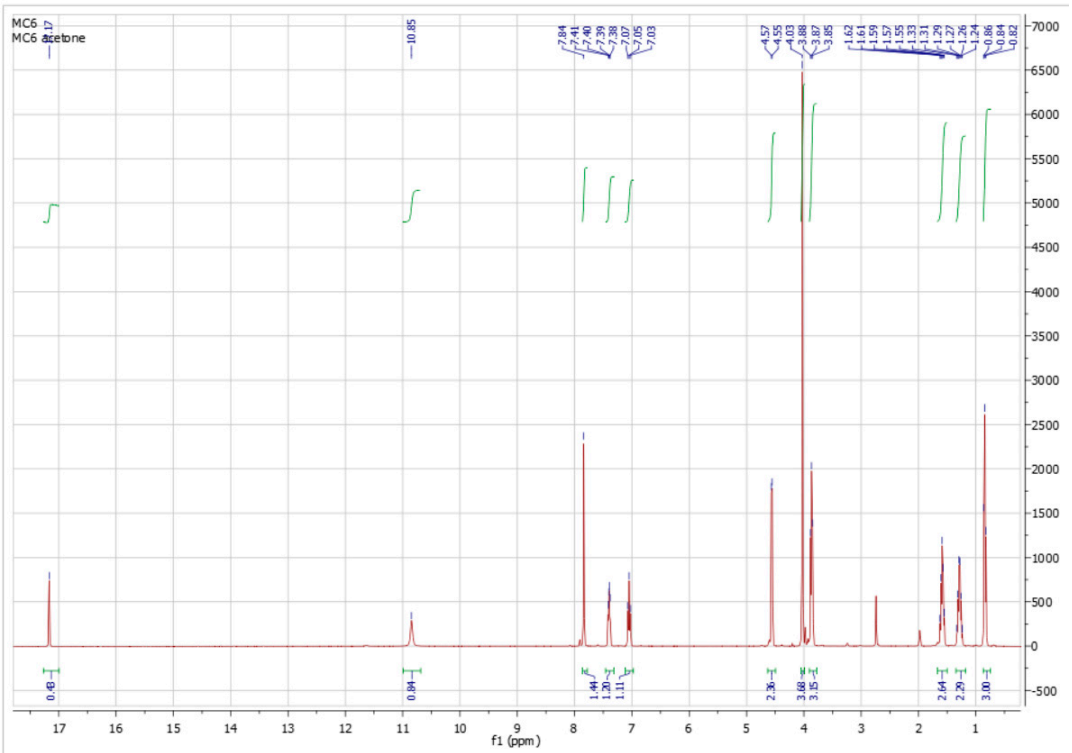


Figure S10. ^{13}C NMR spectrum of compound **16**.



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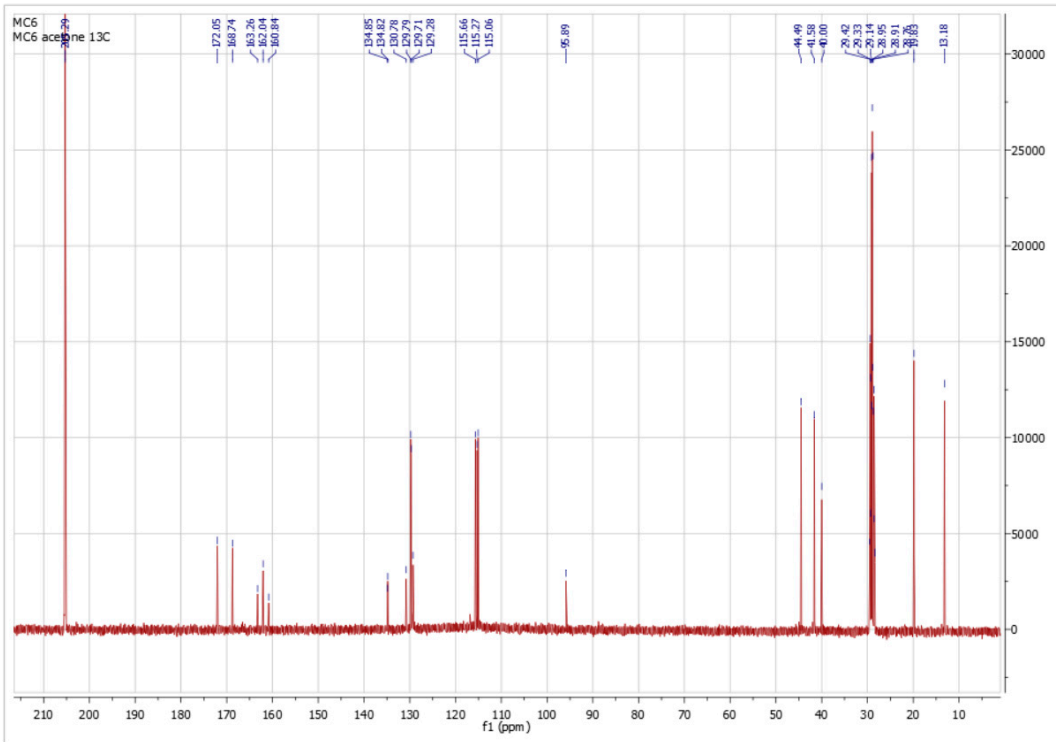


Figure S12. ^{13}C NMR spectrum of compound **17**.

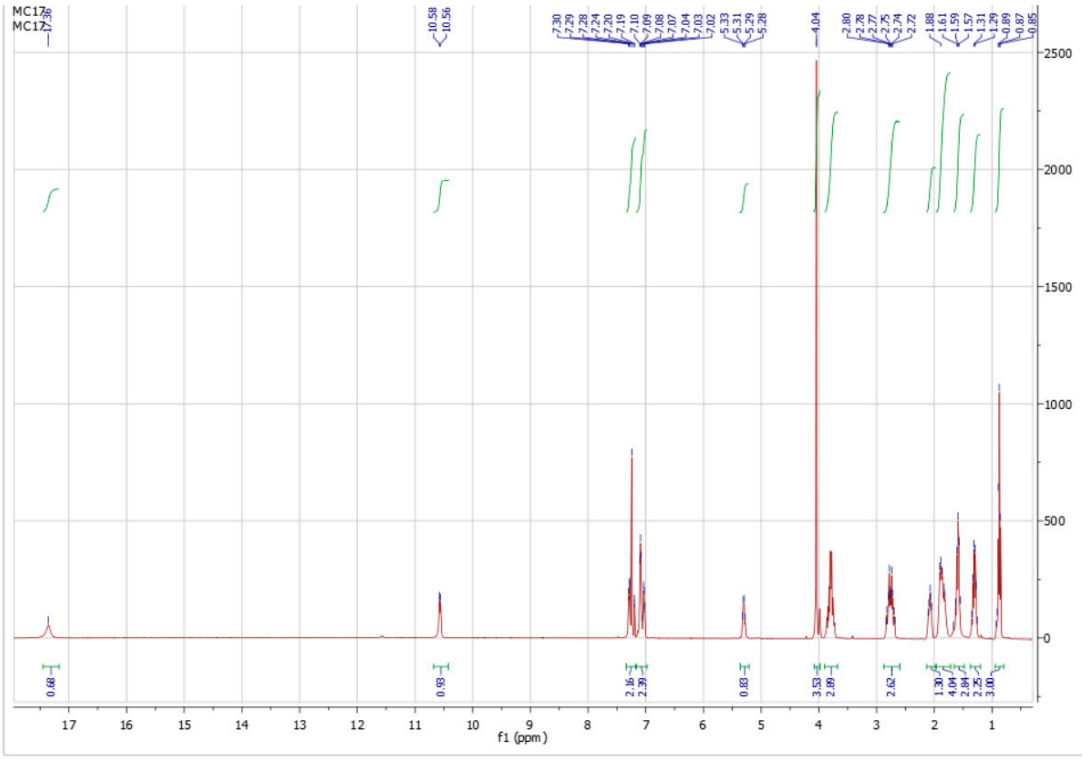
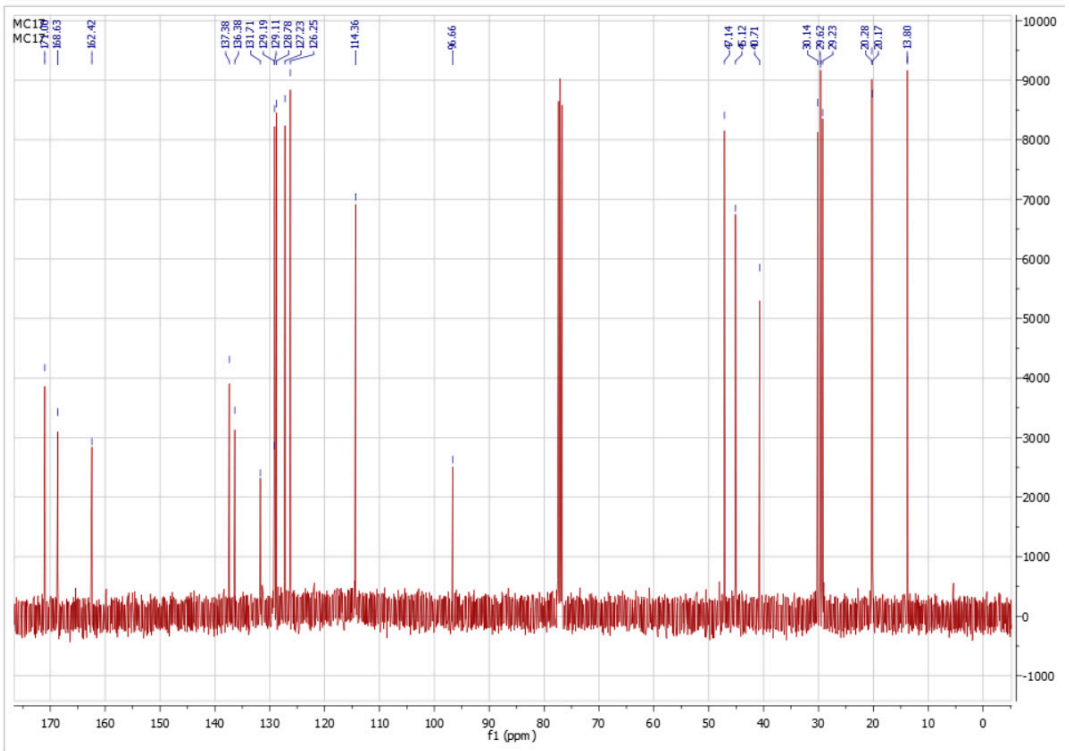


Figure S13. ^{1}H NMR spectrum of compound **18**.



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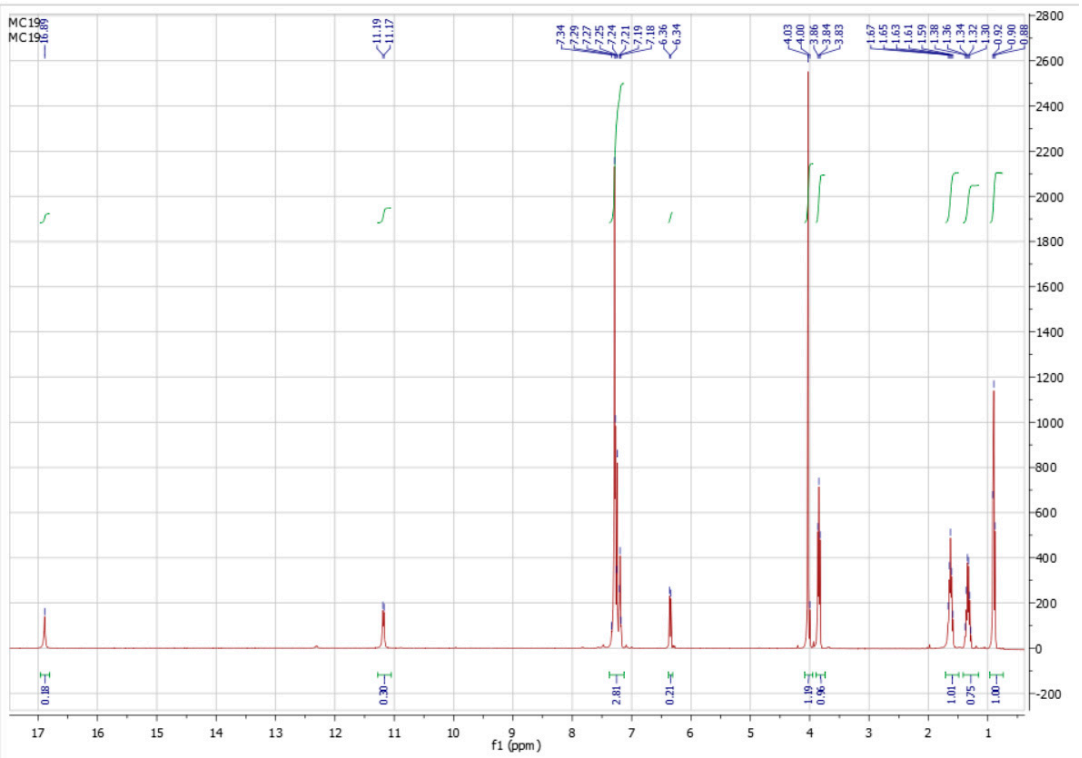

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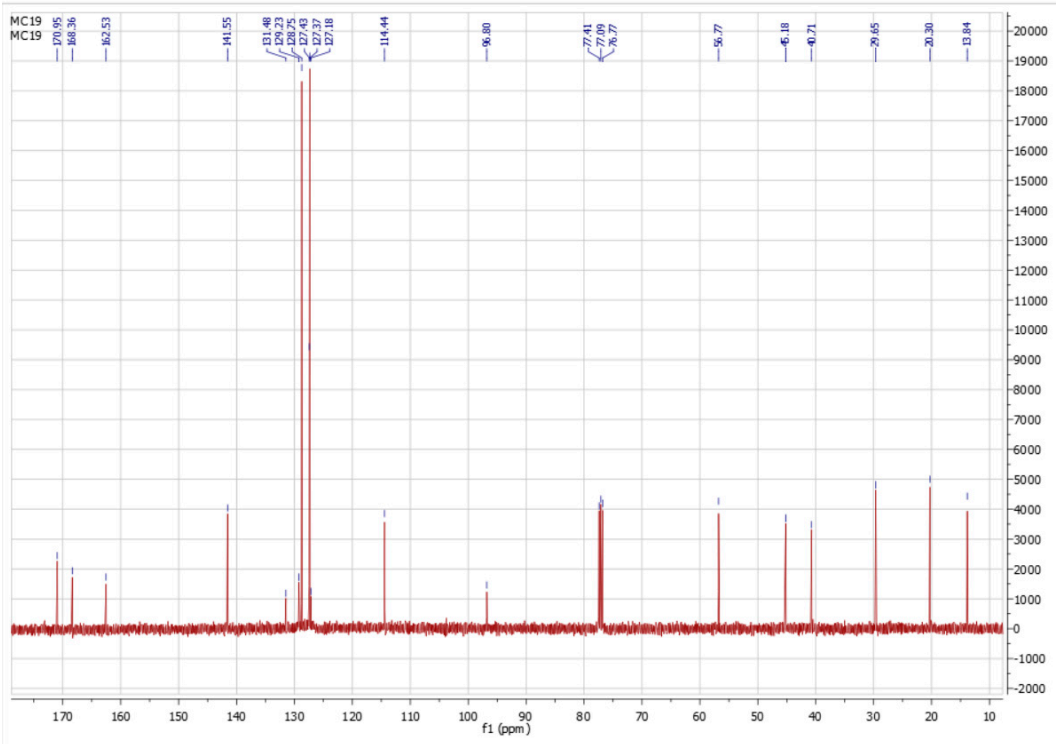

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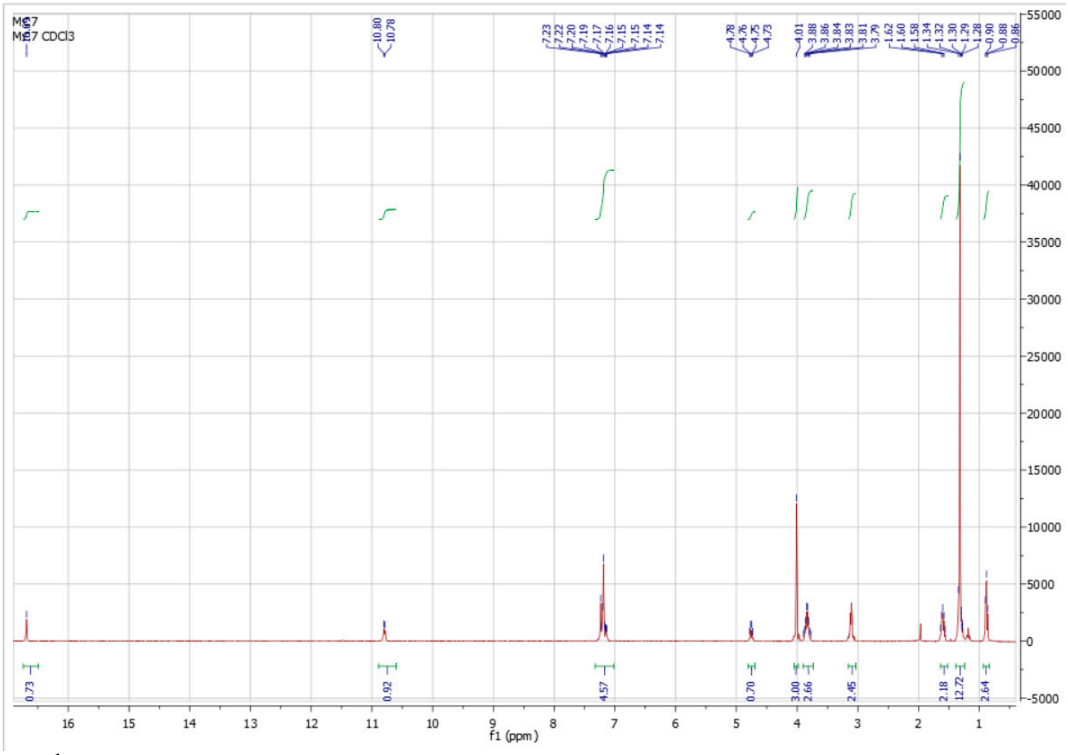

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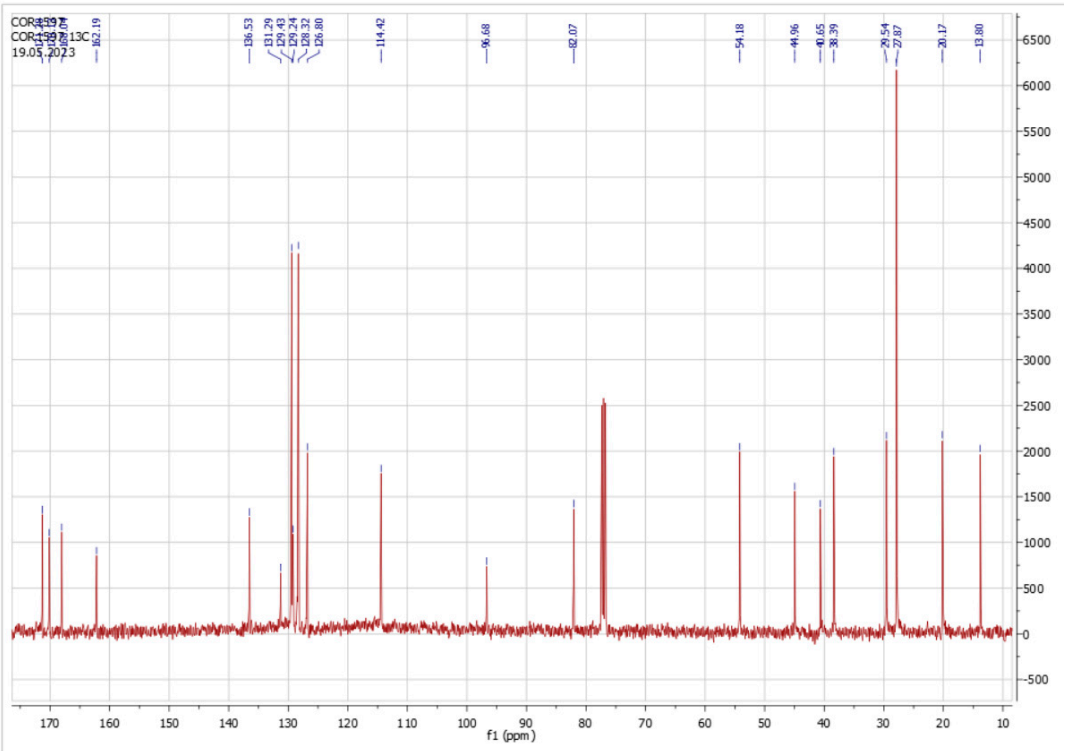
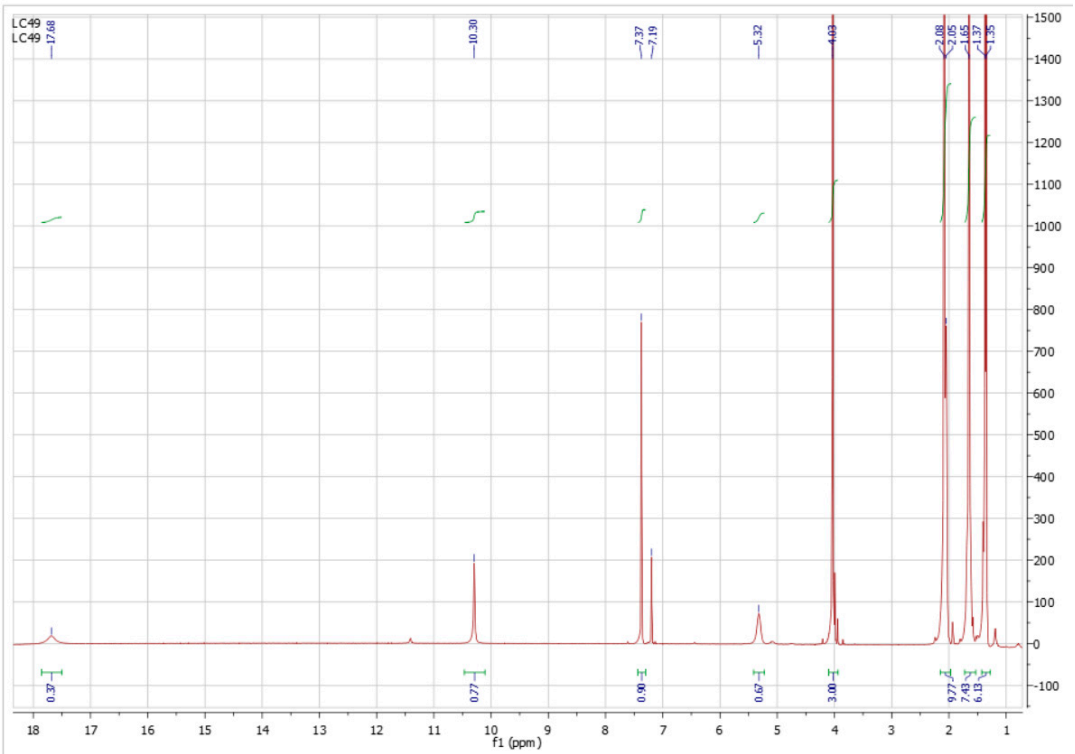


Figure S18. ^{13}C NMR spectrum of compound **20**.



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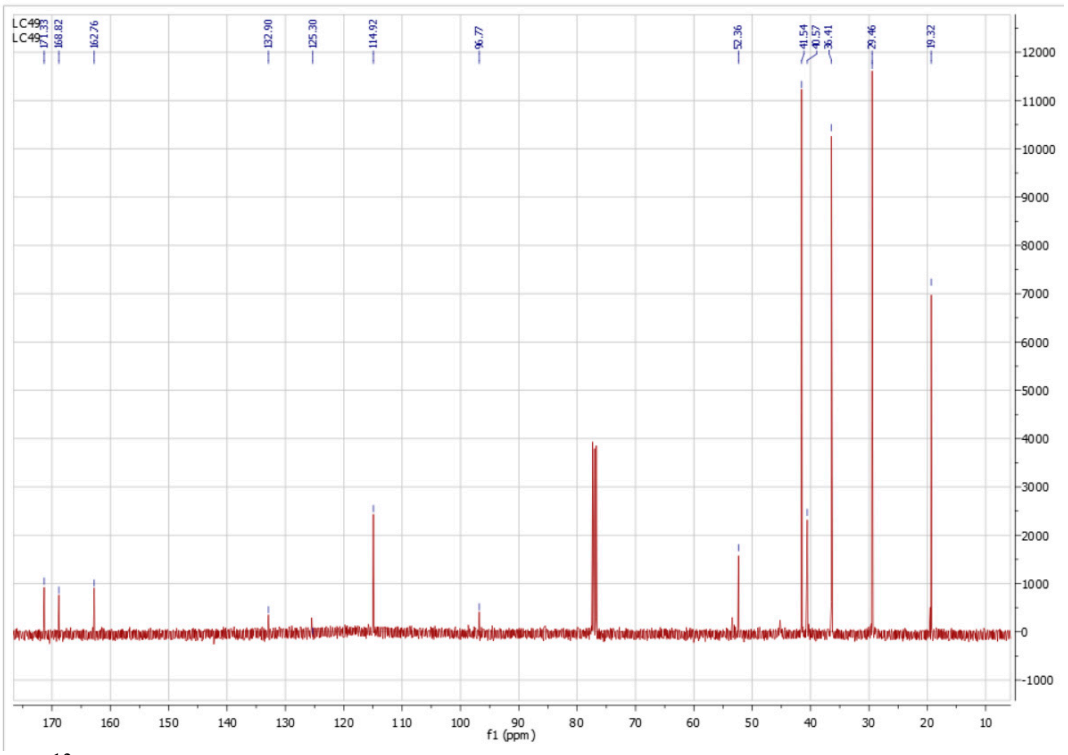

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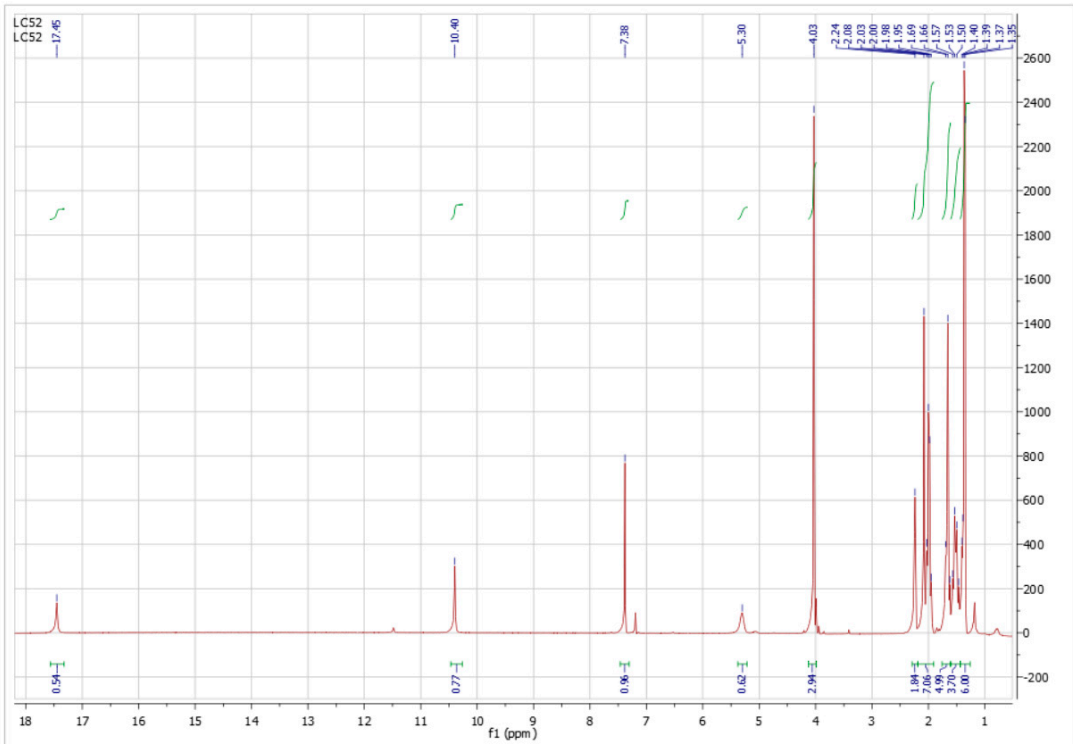


Figure S21. ^{1}H NMR spectrum of compound **22**.

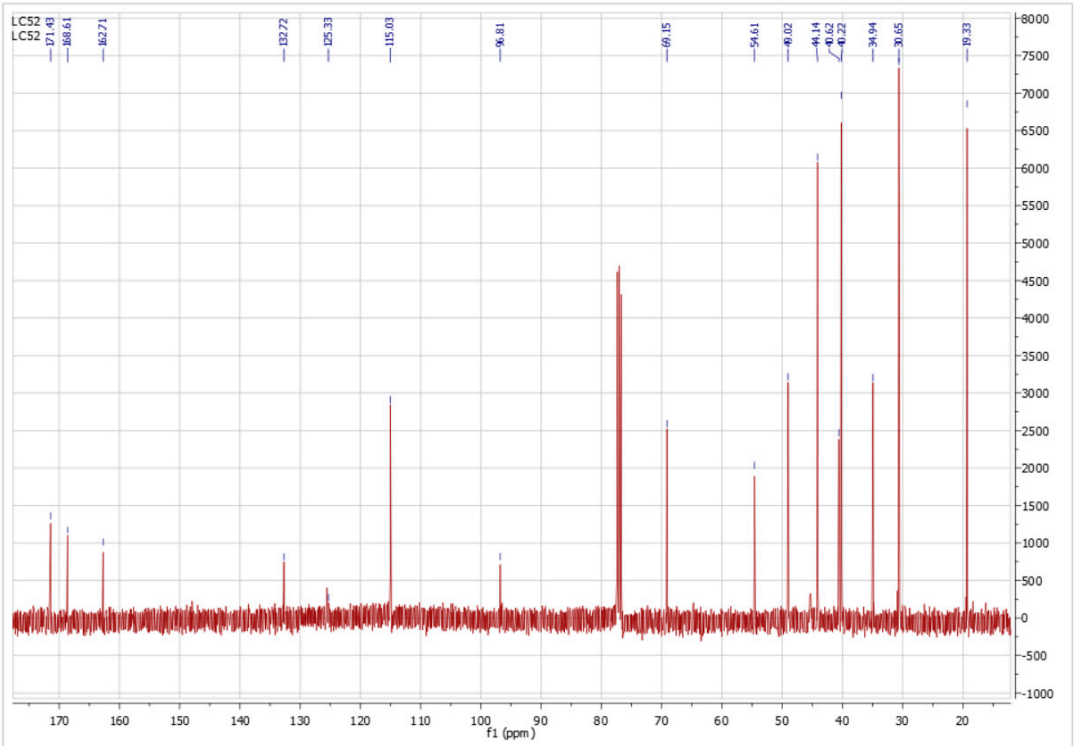
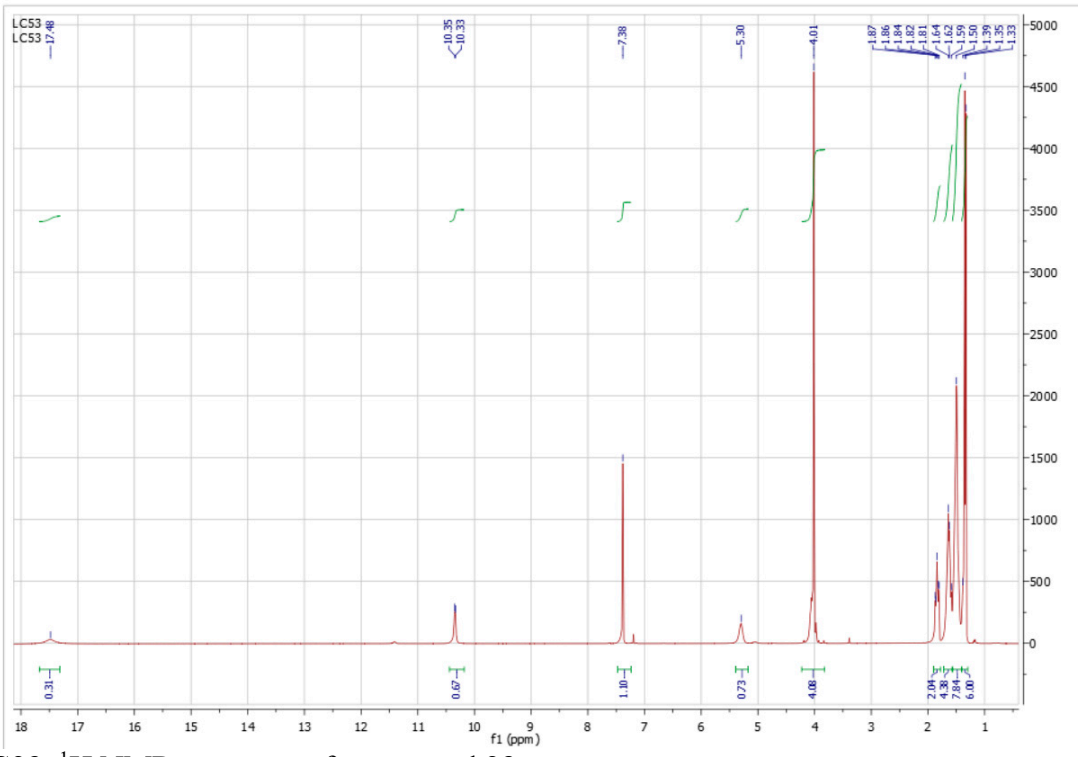


Figure S22. ^{13}C NMR spectrum of compound **22**.



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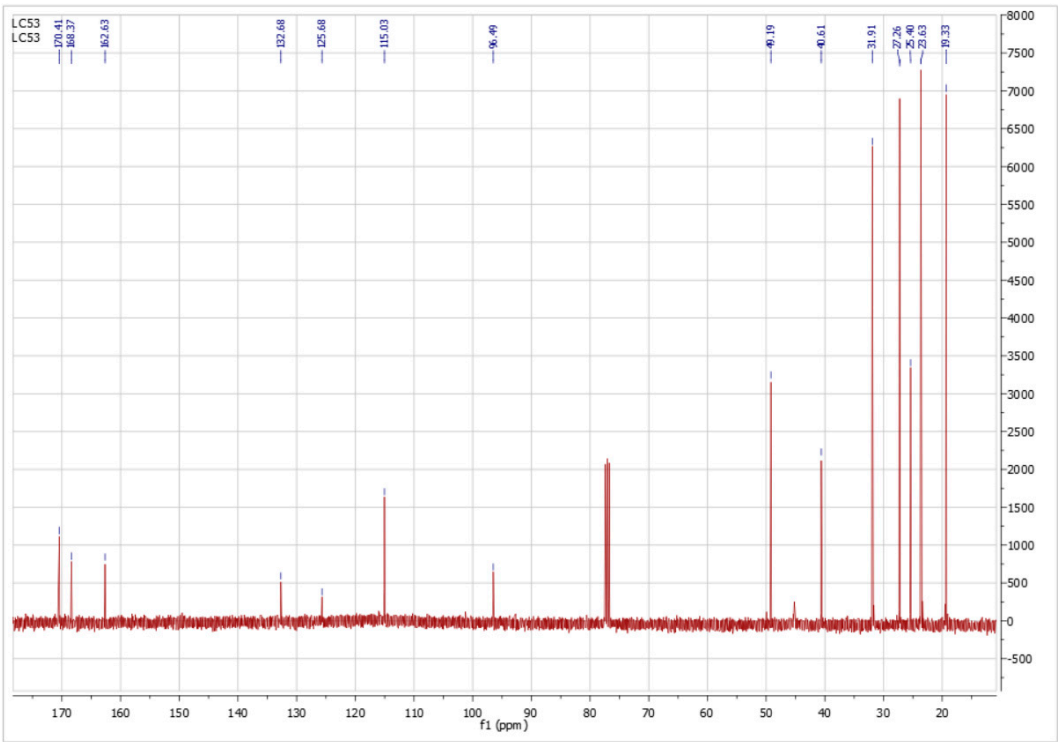

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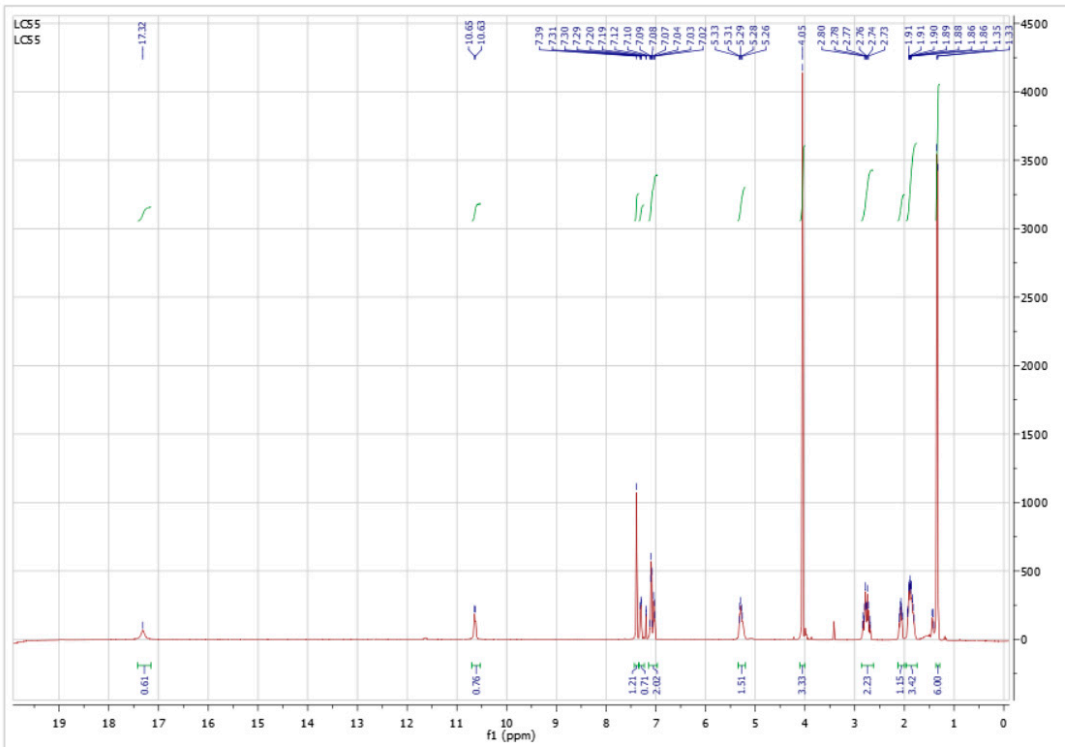
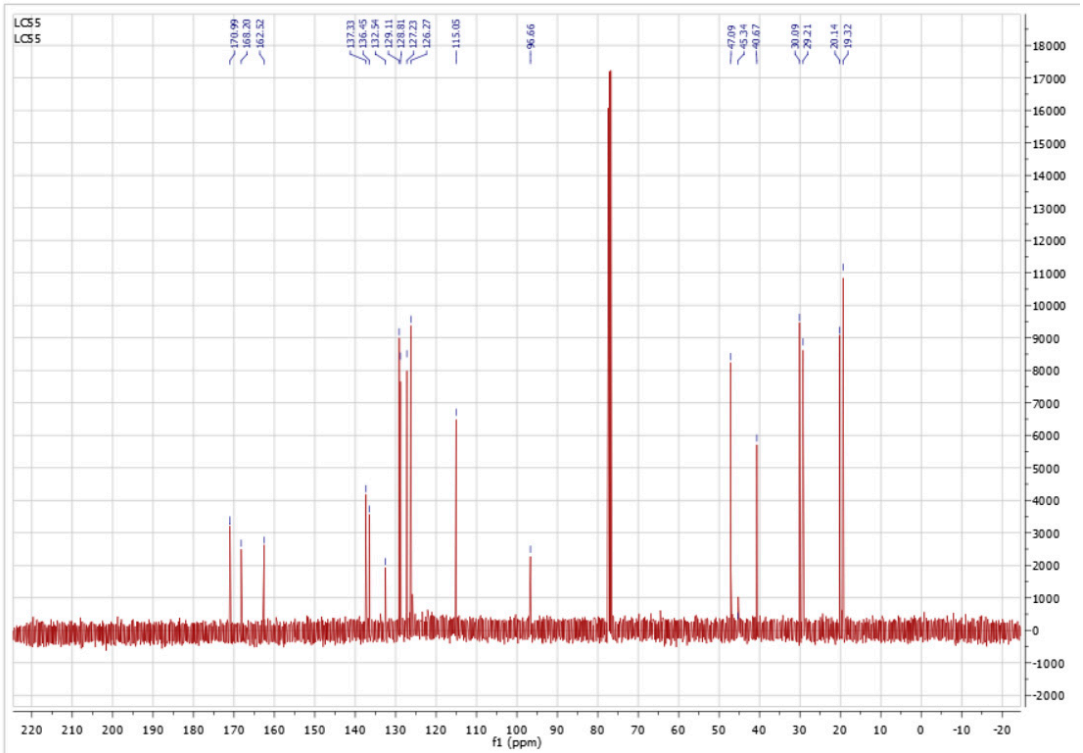


Figure S25. ^{1}H NMR spectrum of compound **24**.



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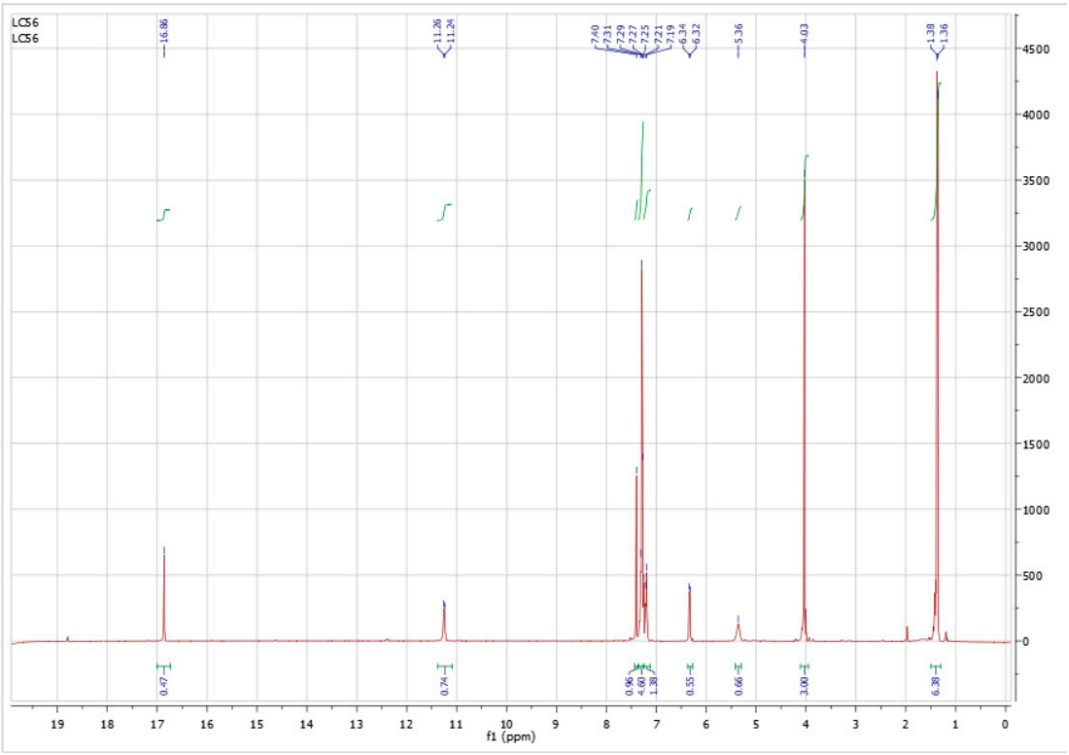
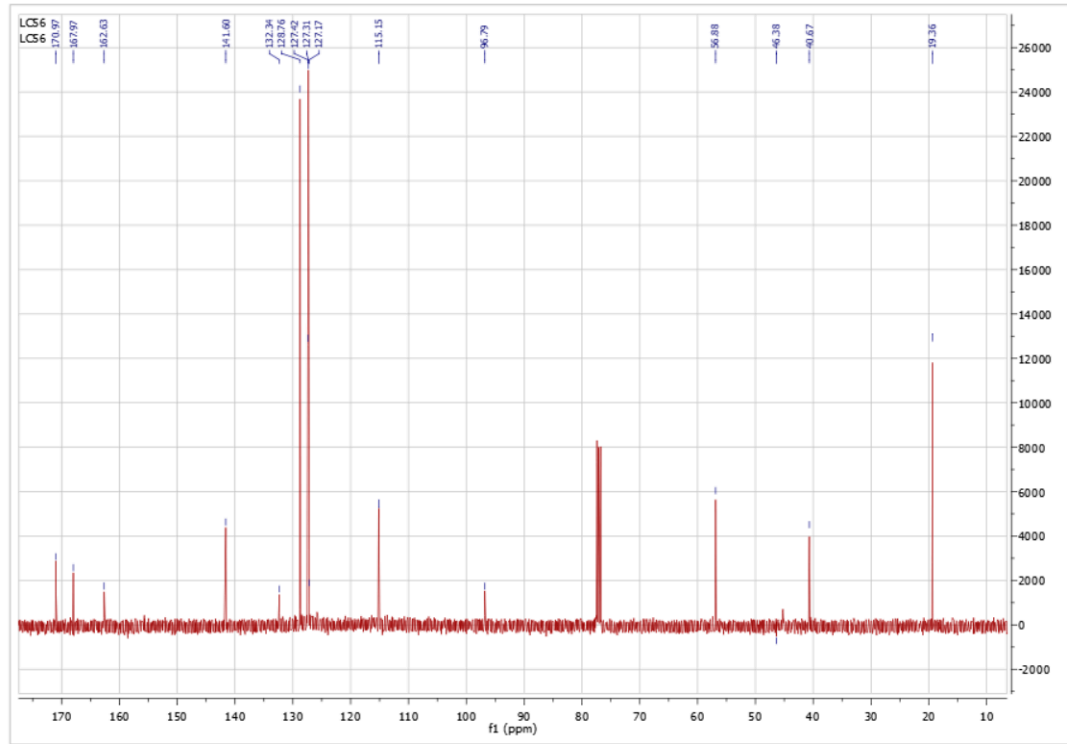


Figure S27. ^{1}H NMR spectrum of compound **25**.



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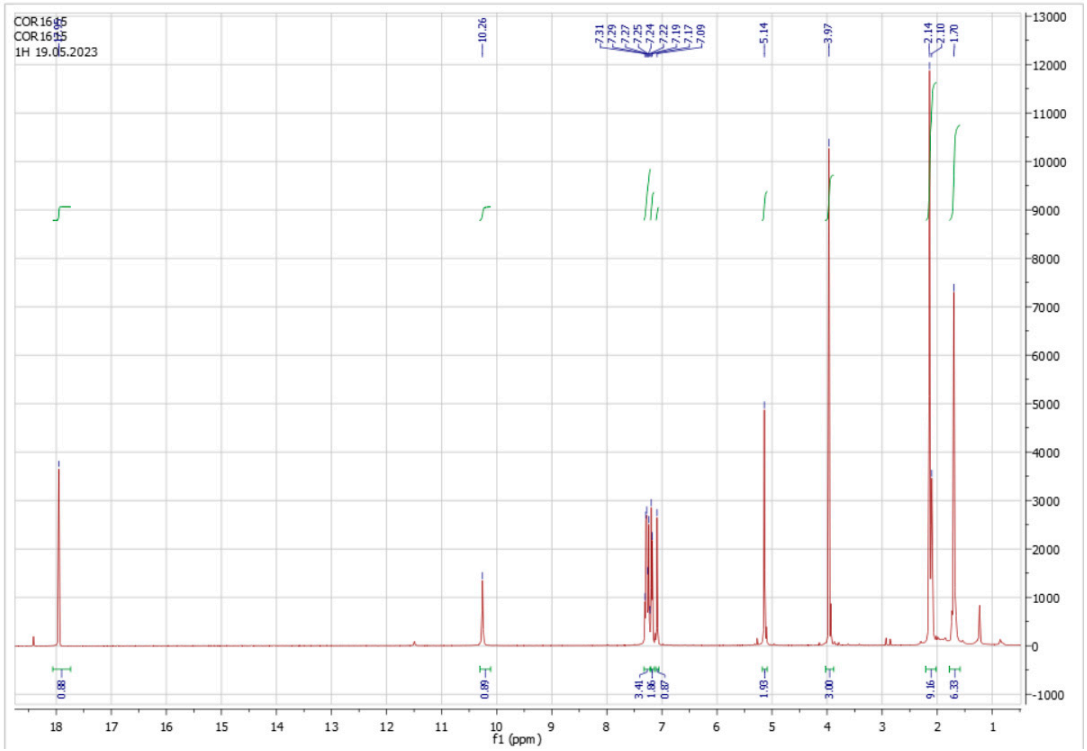


Figure S29. ^{1}H NMR spectrum of compound **26**.

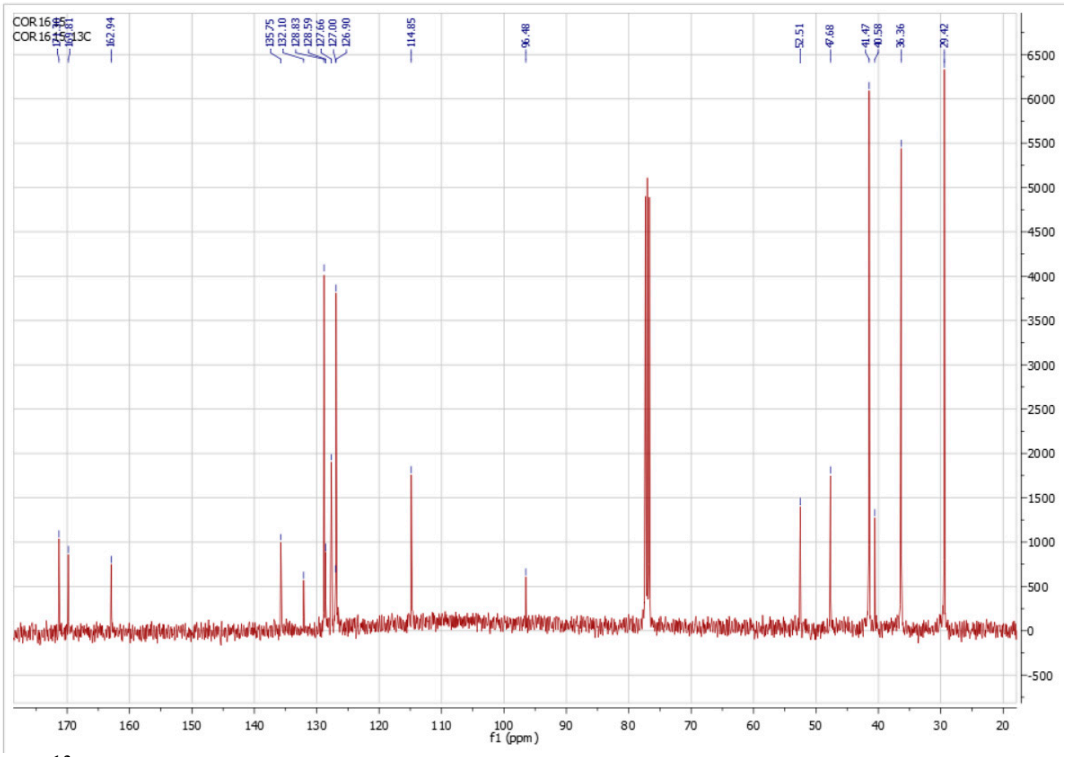


Figure S30. ^{13}C NMR spectrum of compound **26**.

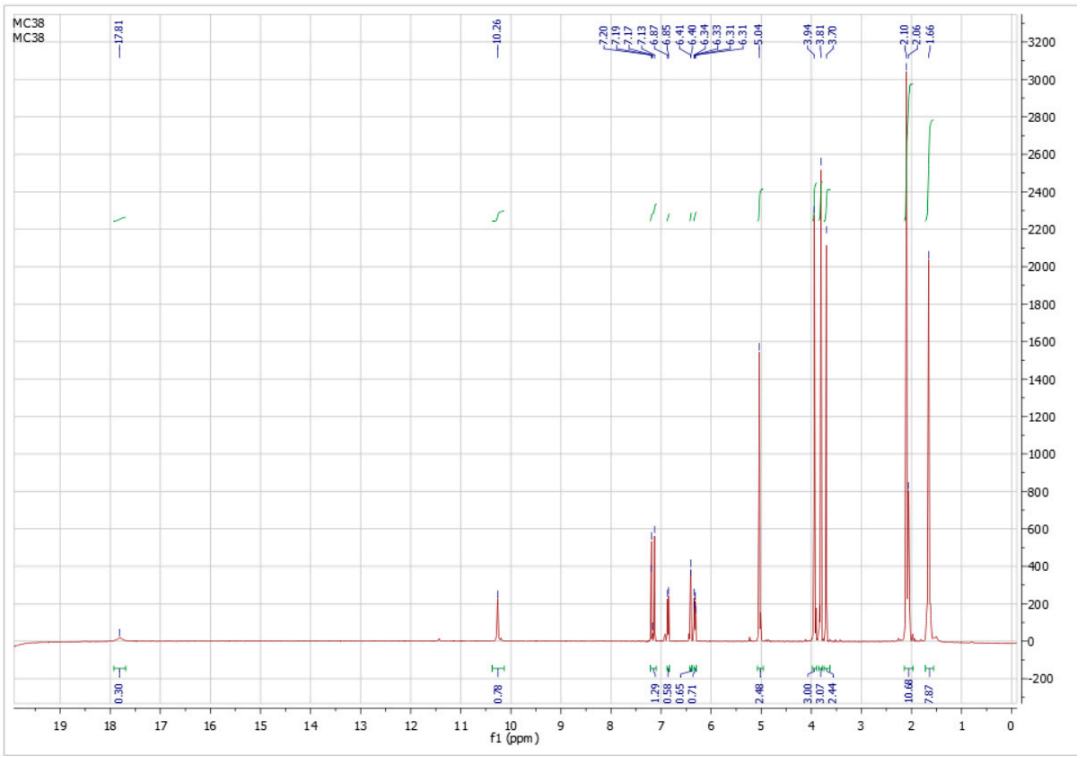


Figure S31. ^{1}H NMR spectrum of compound **27**.

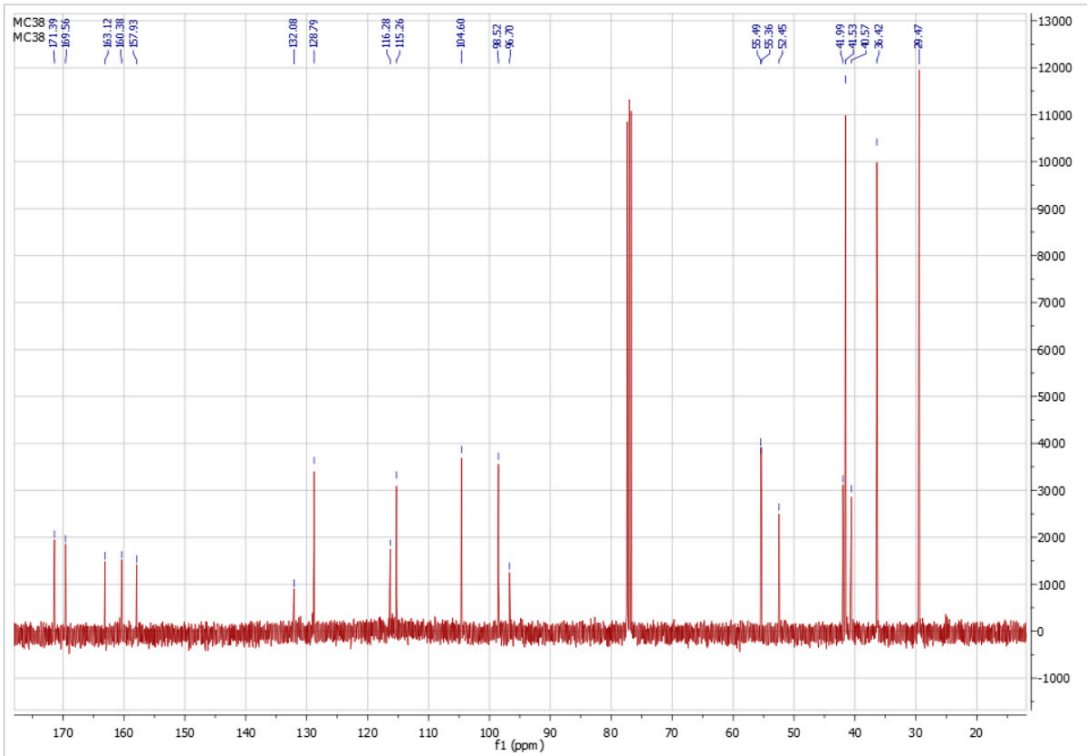


Figure S32. ^{13}C NMR spectrum of compound **27**.

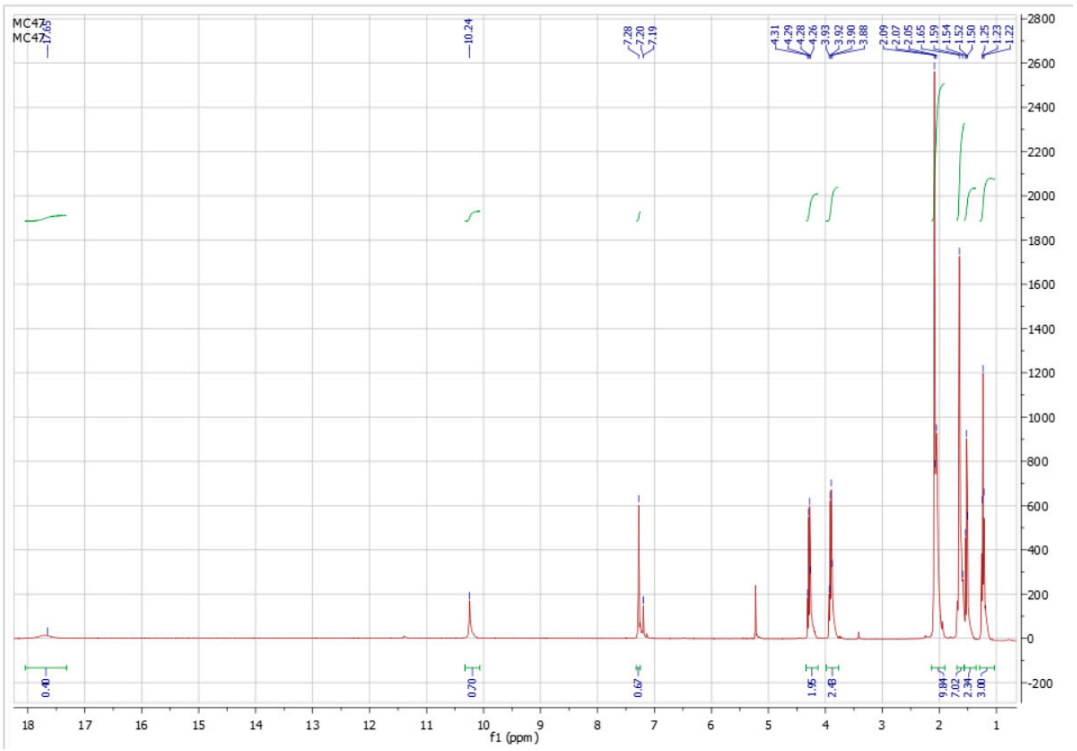
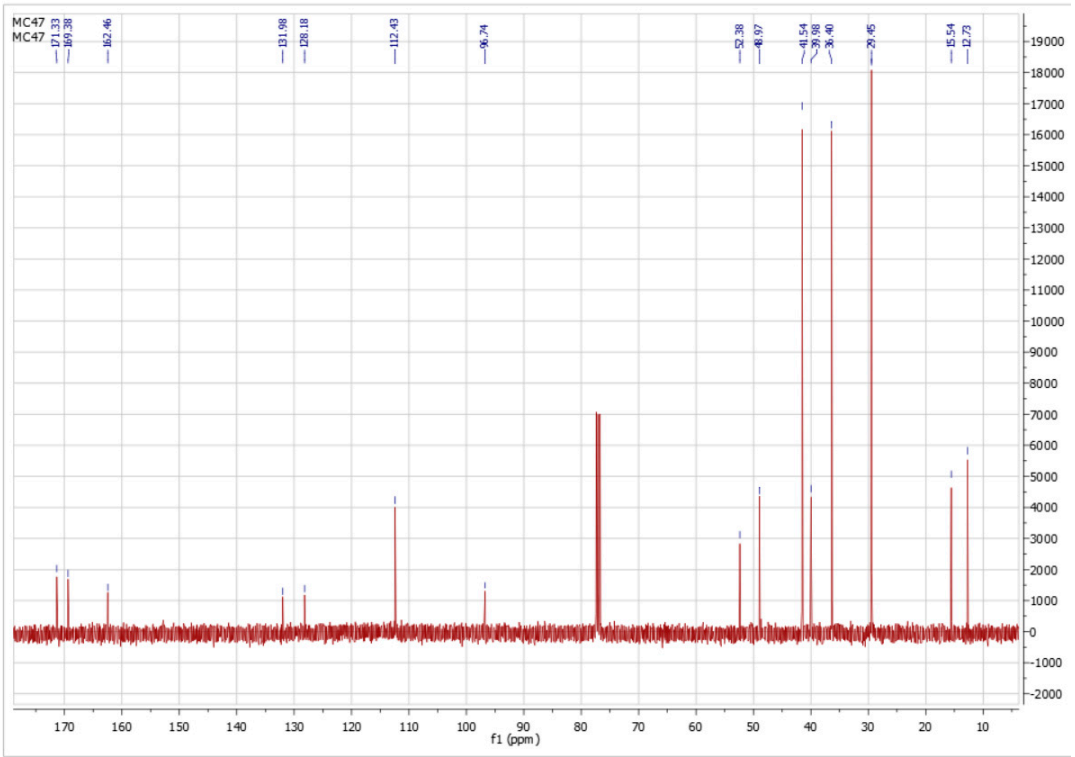


Figure S33. ^{1}H NMR spectrum of compound **33**.



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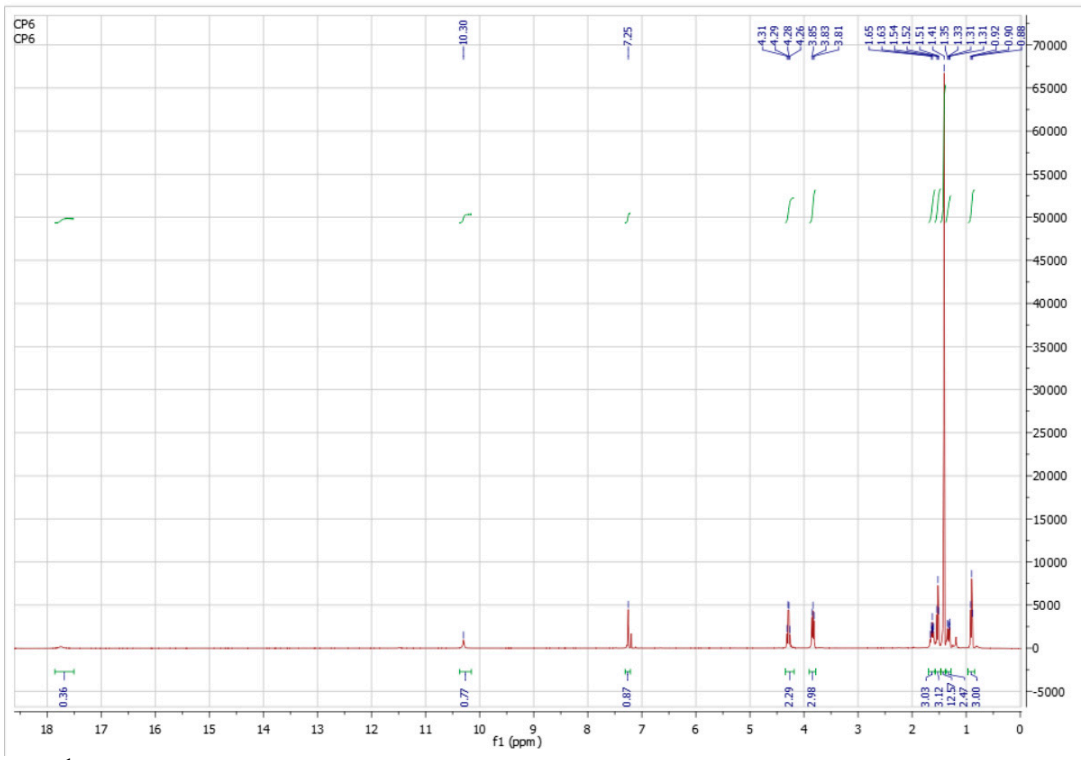

Figure S35. ^{1}H NMR spectrum of compound **34**.

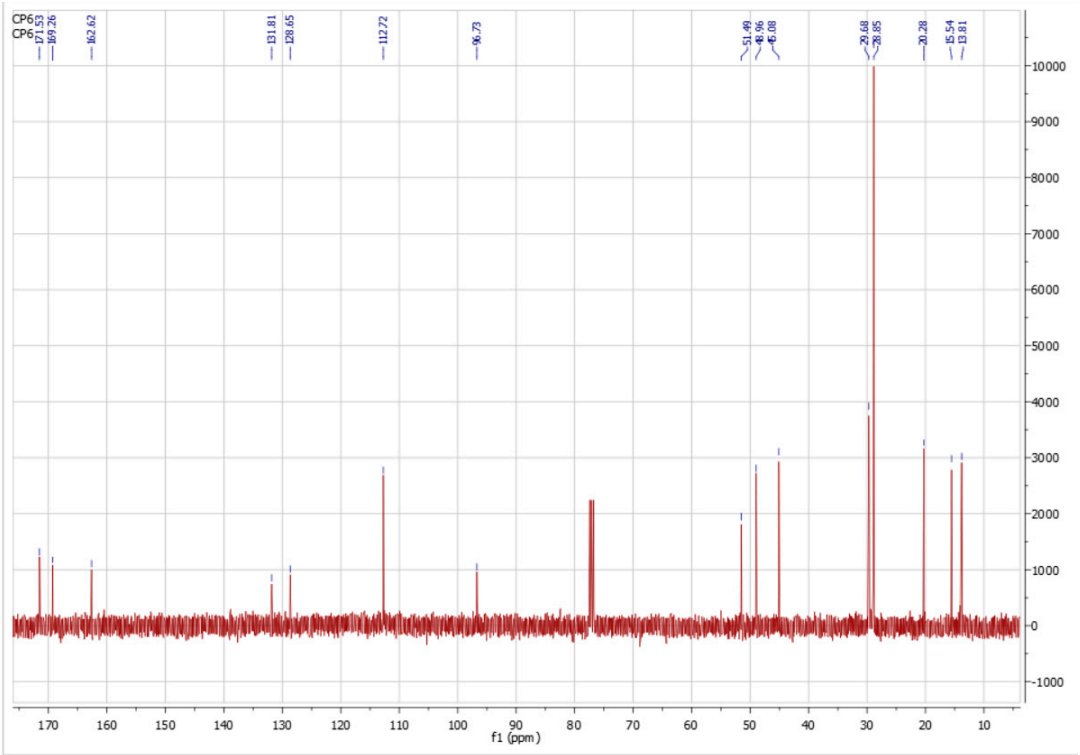

Figure S36. ^{13}C NMR spectrum of compound **34**.

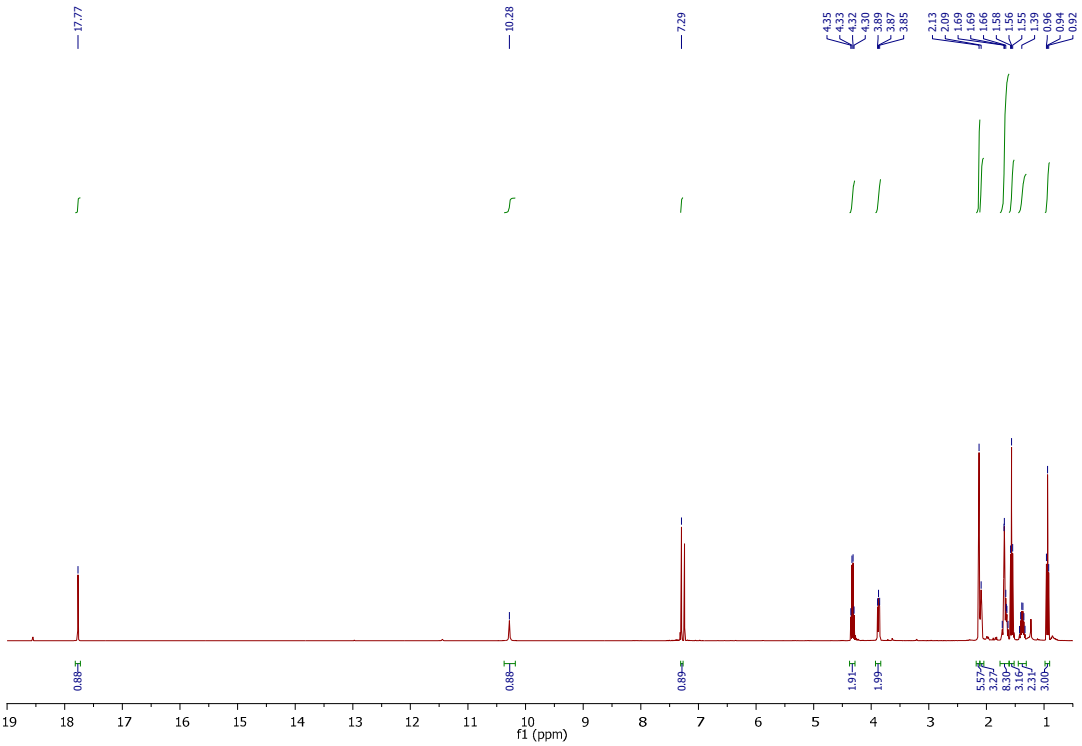

Figure S37. ^{1}H NMR spectrum of compound **35**.

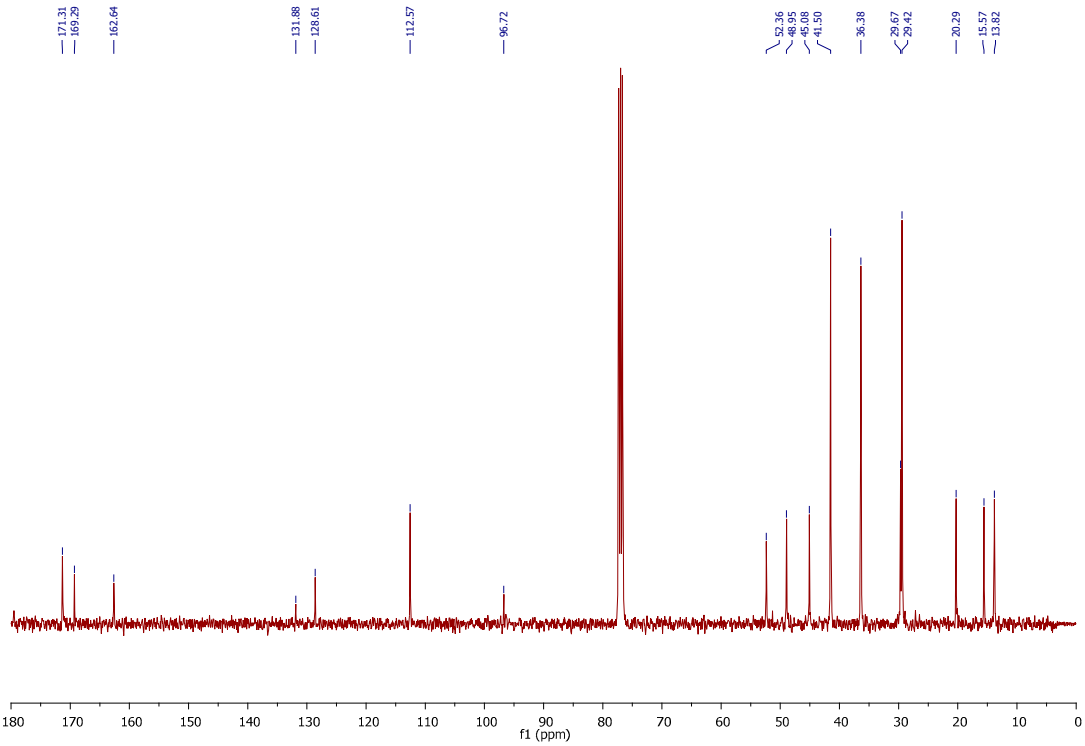

Figure S38. ^{13}C NMR spectrum of compound **35**.

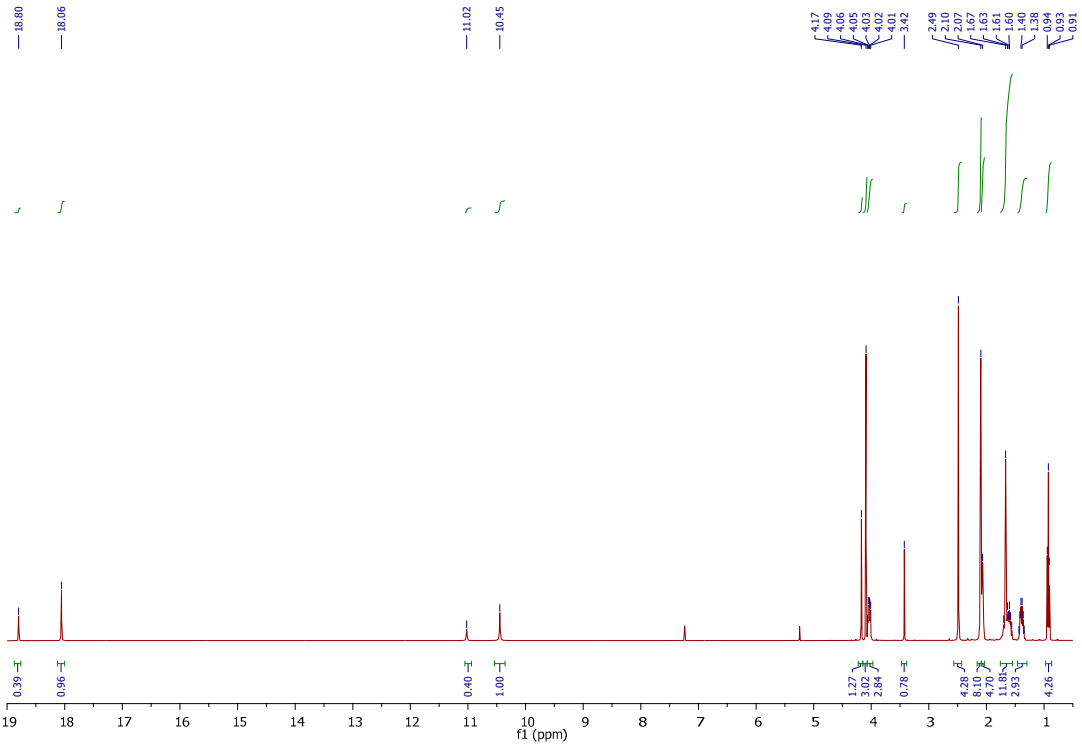

Figure S39. ^{1}H NMR spectrum of compound **51**.

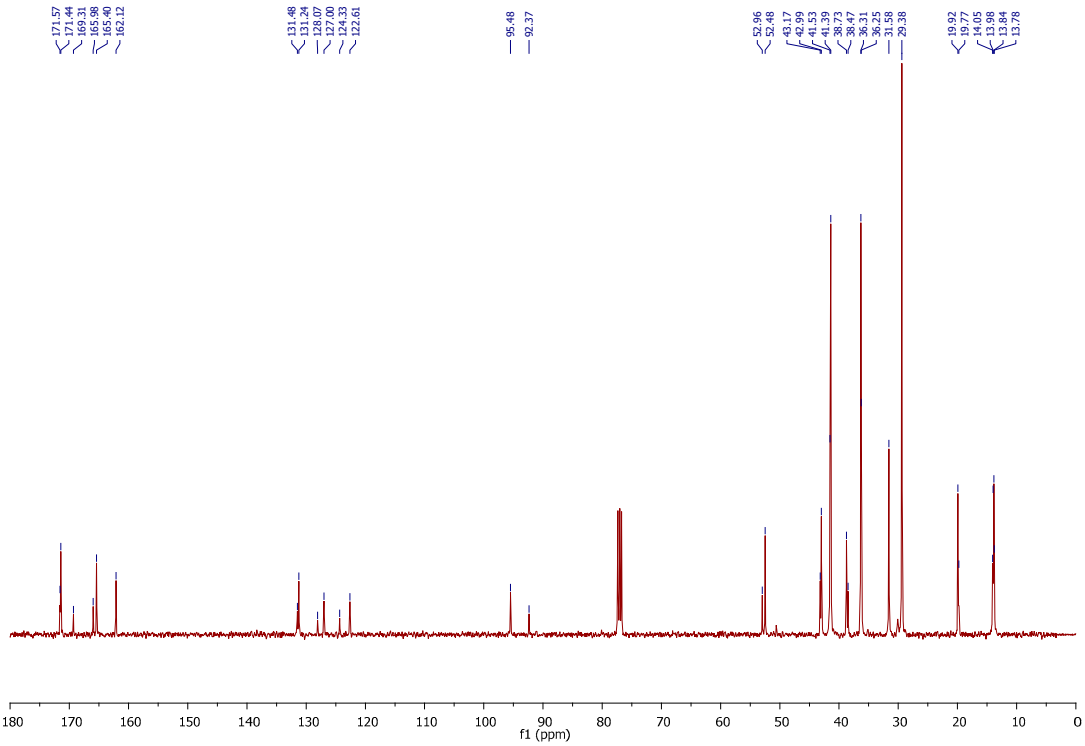

Figure S40. ^{13}C NMR spectrum of compound **51**.

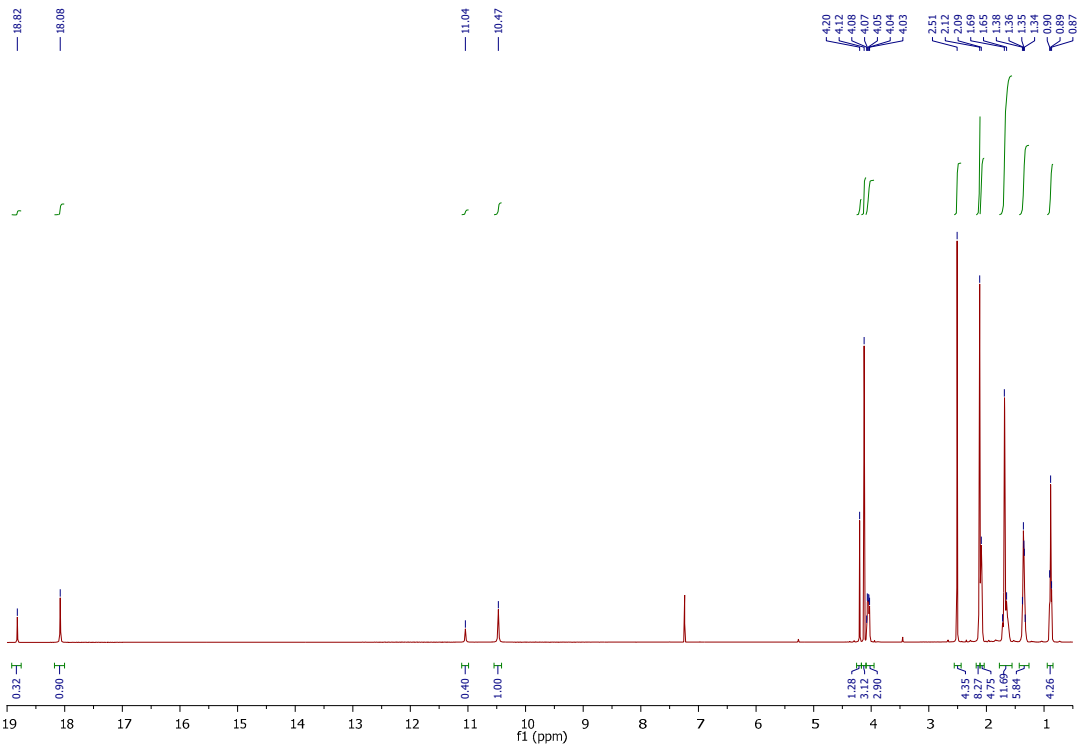

Figure S41. ^{1}H NMR spectrum of compound **52**.

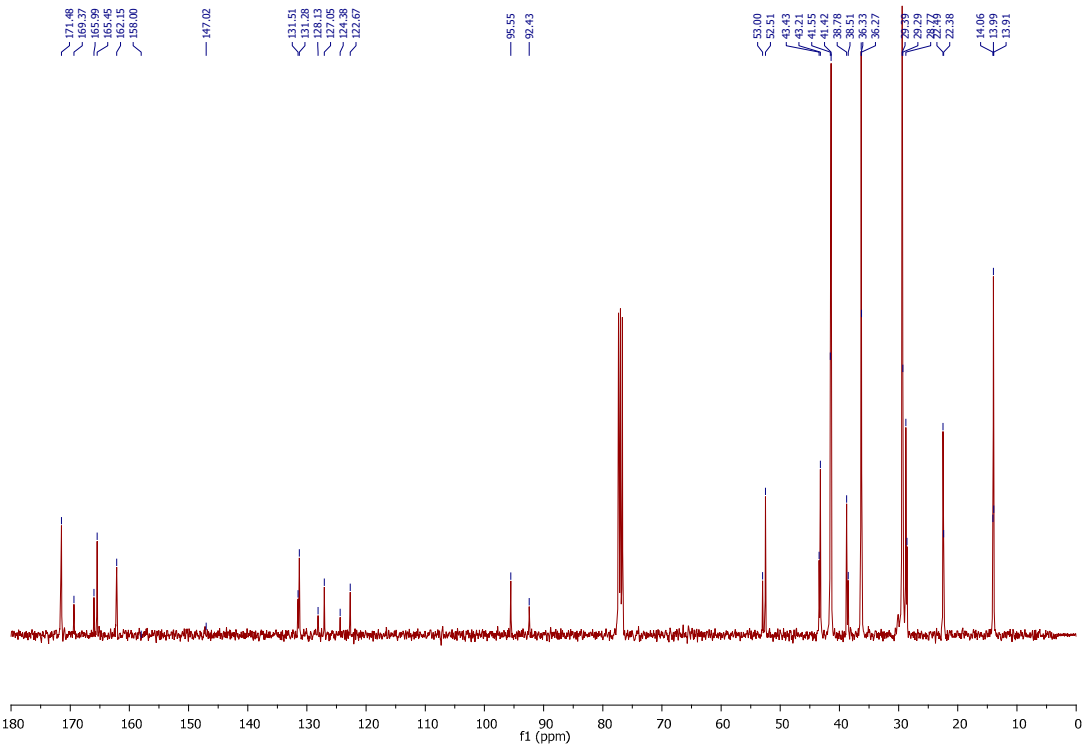

Figure S42. ^{13}C NMR spectrum of compound **52**.

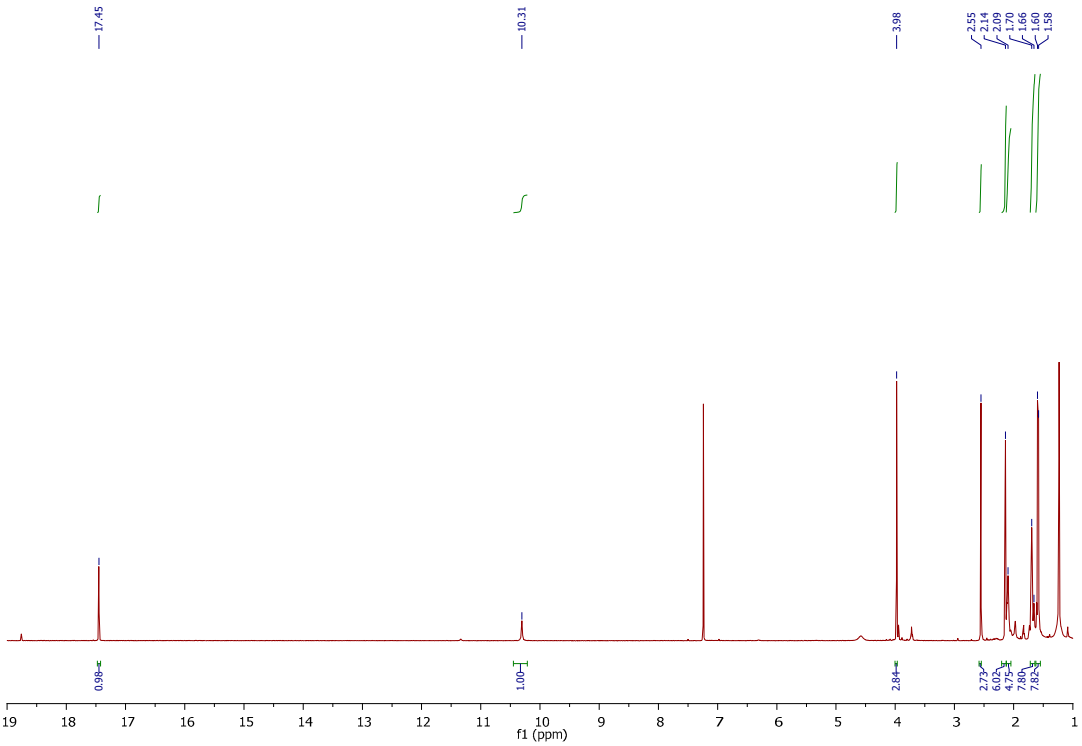

Figure S43. ^{1}H NMR spectrum of compound **53**.

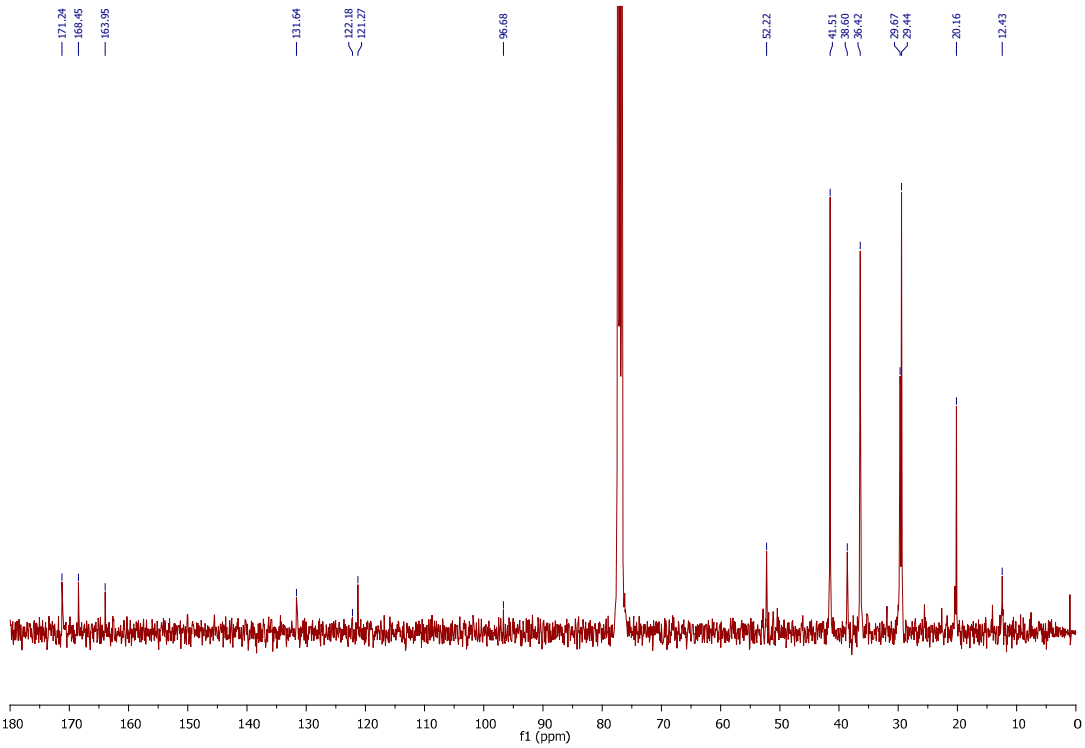

Figure S44. ^{13}C NMR spectrum of compound **53**.

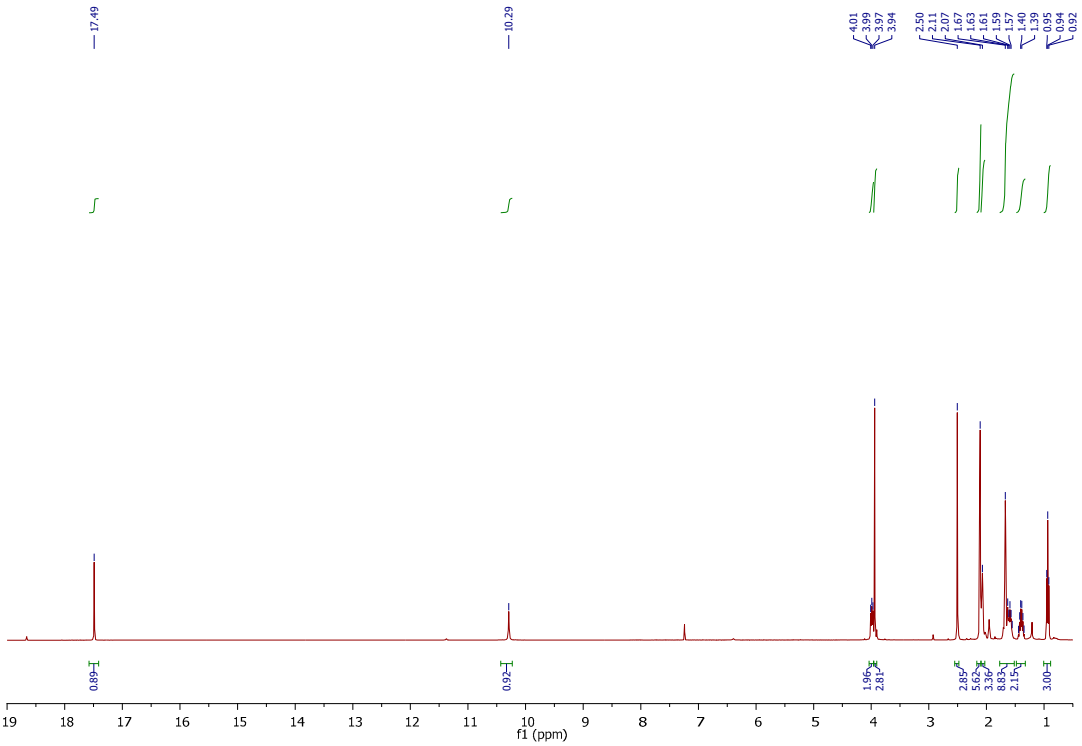

Figure S45. ^{1}H NMR spectrum of compound **54**.

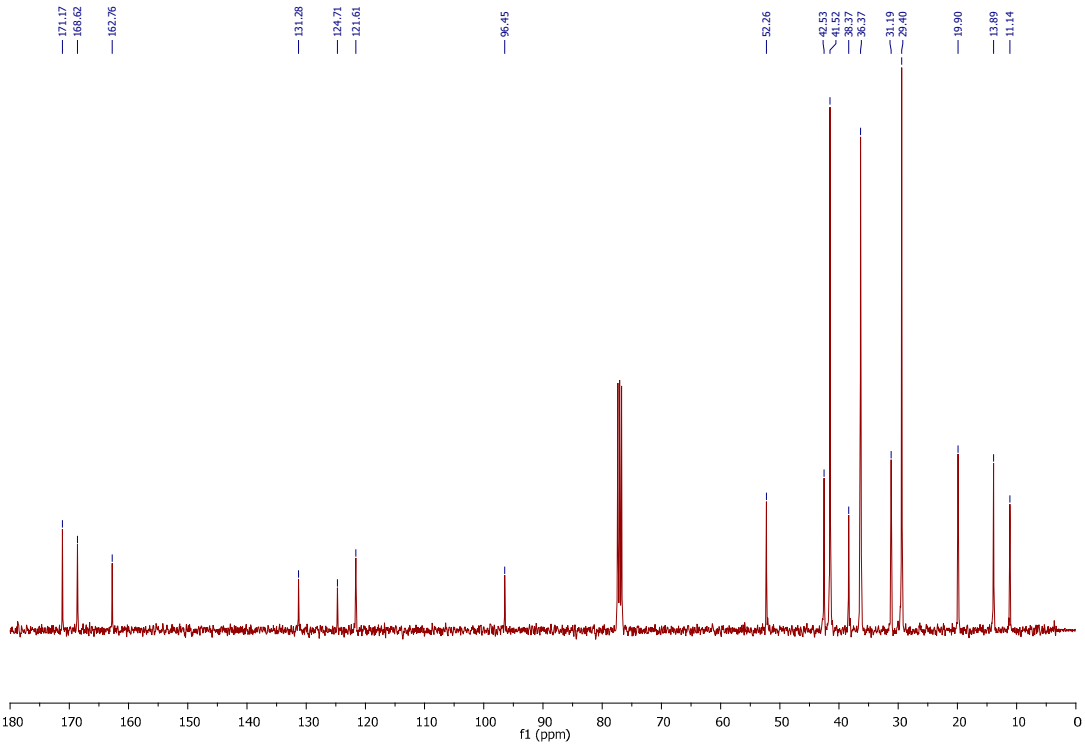

Figure S46. ^{13}C NMR spectrum of compound **54**.

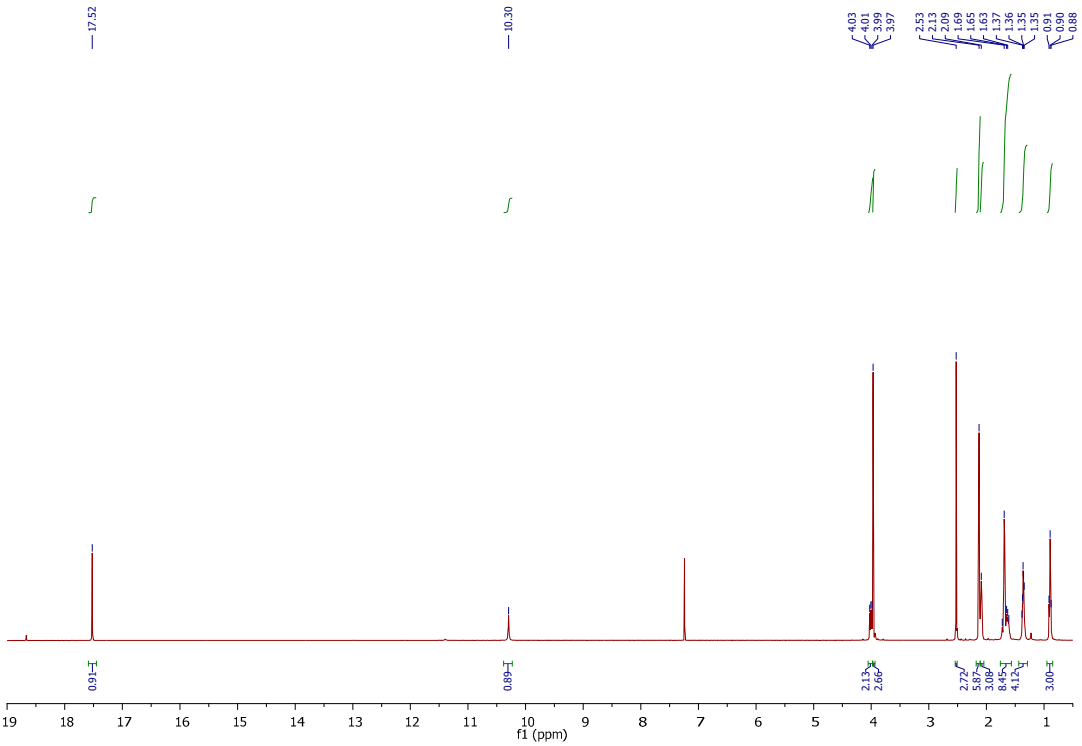

Figure S47. ^{1}H NMR spectrum of compound **55**.

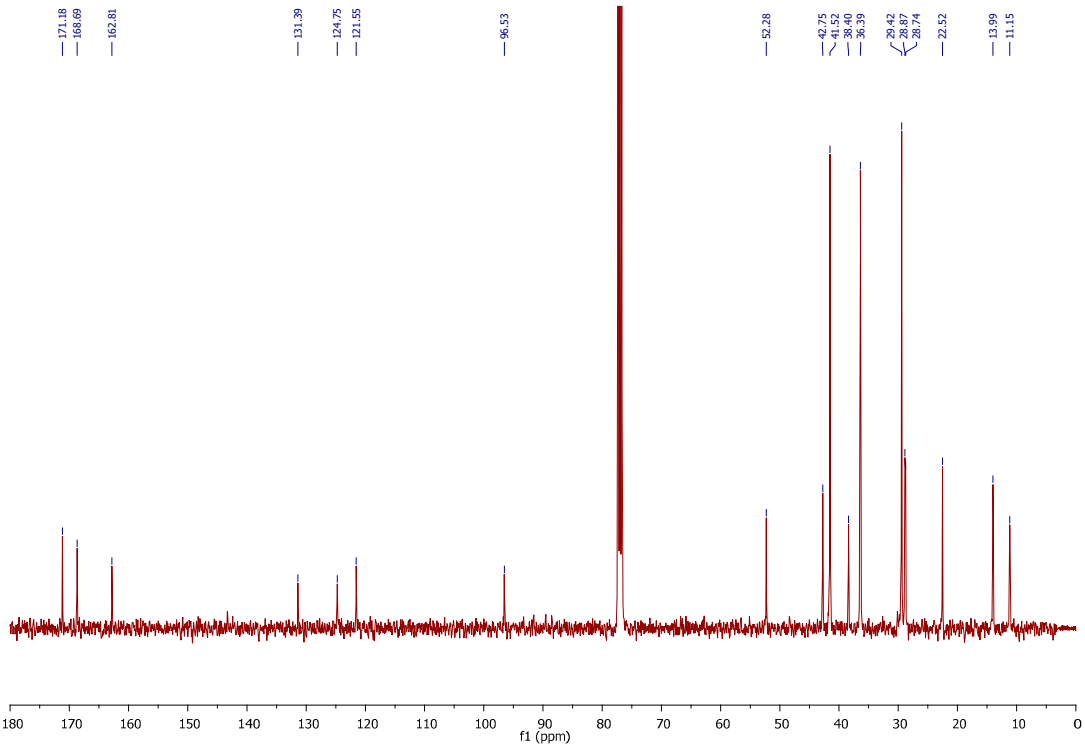

Figure S48. ^{13}C NMR spectrum of compound **55**.

Table S1. Calculated physicochemical and druglike properties of selected compounds

Parameters[a]	Compounds					
	15	**18**	**26**	**35**	**54**	**55**
No. H-bond acceptor	4	4	4	4	4	4
No. H-bond donor	2	2	2	2	2	2
Consensus Log$P_{o/w}$	2.88	2.86	3.11	3.21	3.20	3.53
No. rotatable bond	6	6	5	7	6	7
TPSA[b]	89.15	89.15	89.15	89.15	89.15	89.15
Lipinski's rule violation	No	No	No	No	No	No
PAINS alerts	No	No	No	No	No	No
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55
GI absorption	High	High	High	High	High	High
Lipophilic Ligand Efficiency (LLE)[c]	5.16	4.90	6.21	6.14	5.47	5.15

[a]Properties calculated using the free web tool SwissADME [http://www.swissadme.ch]. [b]TPSA, topological polar surface area. [c]LLE, lipophilic ligand efficiency = pK_{iCB2} – CLogP.