

Supplementary Information

Antibiotic Modulation and Efflux Pump Inhibition by Piperine-Derived Esters and Thiazole Analogs in Multidrug-Resistant *Staphylococcus aureus*

Isabela L. Anesio,^a Helivaldo D. S. Souza,^a Edeltrudes O. Lima,^b Fernando G. Figueiredo,^c Nadghia F. L. Sampaio,^c Henrique D. M. Coutinho,^d José M. Barbosa-Filho,^{*,e} Gabriela F. Fiss^a and Petrônio F. Athayde-Filho^a

^aDepartamento de Química, Universidade Federal da Paraíba, 58051-900 João Pessoa-PB, Brazil

^bDepartamento de Ciências Farmacêuticas, Universidade Federal da Paraíba,
58051-900 João Pessoa-PB, Brazil

^cDepartamento de Microbiologia, Faculdade de Medicina Estácio de Juazeiro do Norte, 63048-080
Juazeiro do Norte-CE, Brazil

^dUniversidade Regional do Cariri (URCA), 63105-010 Crato-CE, Brazil

^ePrograma de Pós-Graduação em Produtos Naturais e Sintéticos Bioativos, Universidade Federal
da Paraíba, 58051-900 João Pessoa-PB, Brazil

*e-mail: jbarbosa@lftf.ufpb.br

Editor handled this article Giovanni Wilson Amarante (Executive)

ORCID

<https://orcid.org/0000-0003-0960-1614>

<https://orcid.org/0000-0002-1708-4066>

<https://orcid.org/0000-0002-9547-0886>

<https://orcid.org/0000-0002-7918-4601>

<https://orcid.org/0000-0003-2378-2570>

<https://orcid.org/0000-0002-6634-4207>

<https://orcid.org/0000-0002-9567-4096>

<https://orcid.org/0000-0001-8156-2272>

<https://orcid.org/0000-0003-0982-8261>

Piperine (7)

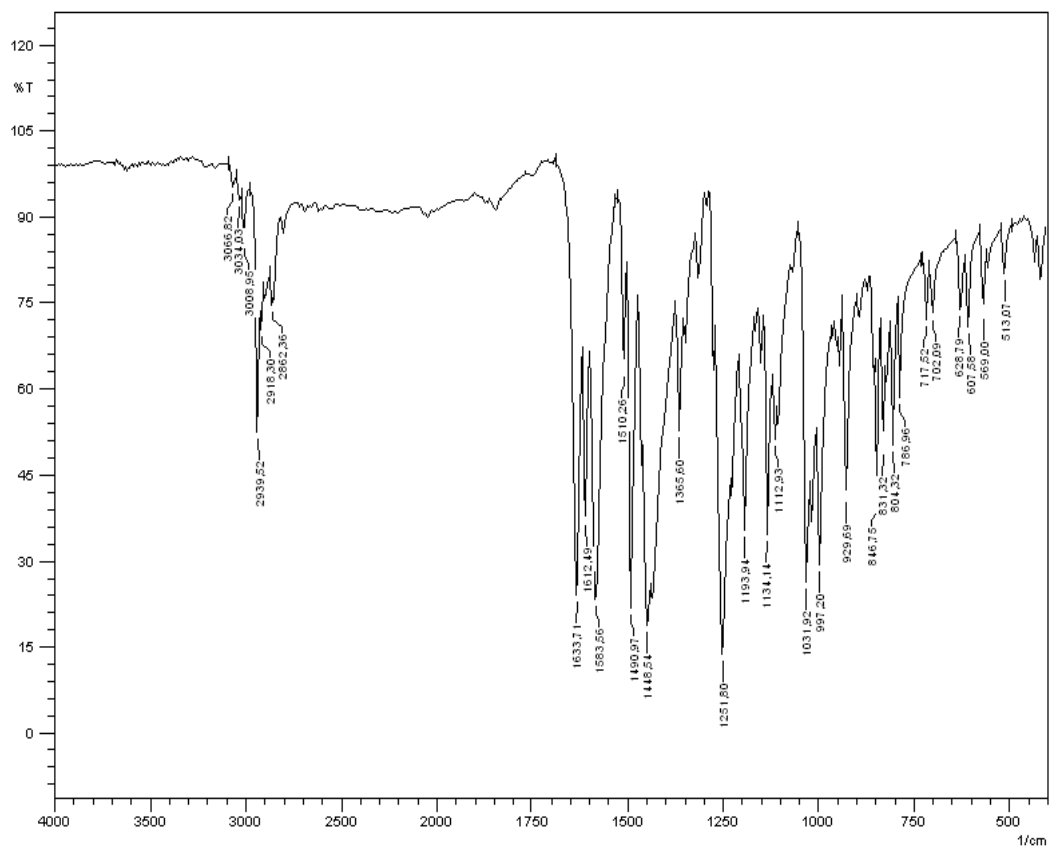


Figure S1. Infrared spectrum (KBr) of piperine.

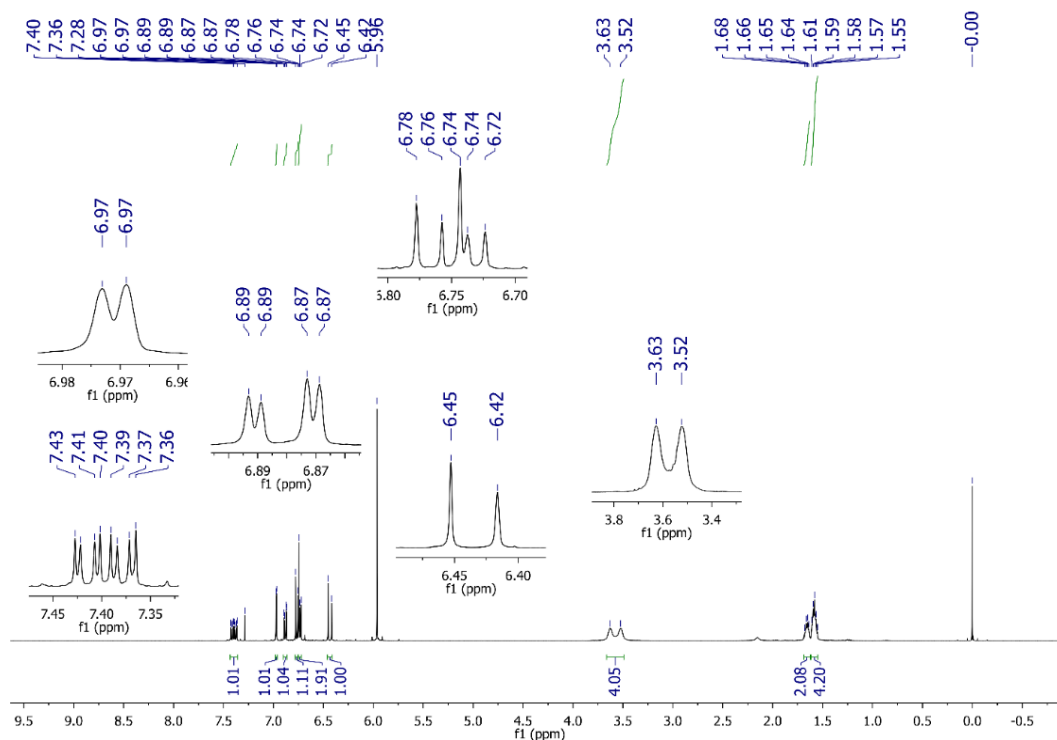


Figure S2. ¹H NMR spectrum (400 MHz, CDCl₃) of piperine (7).

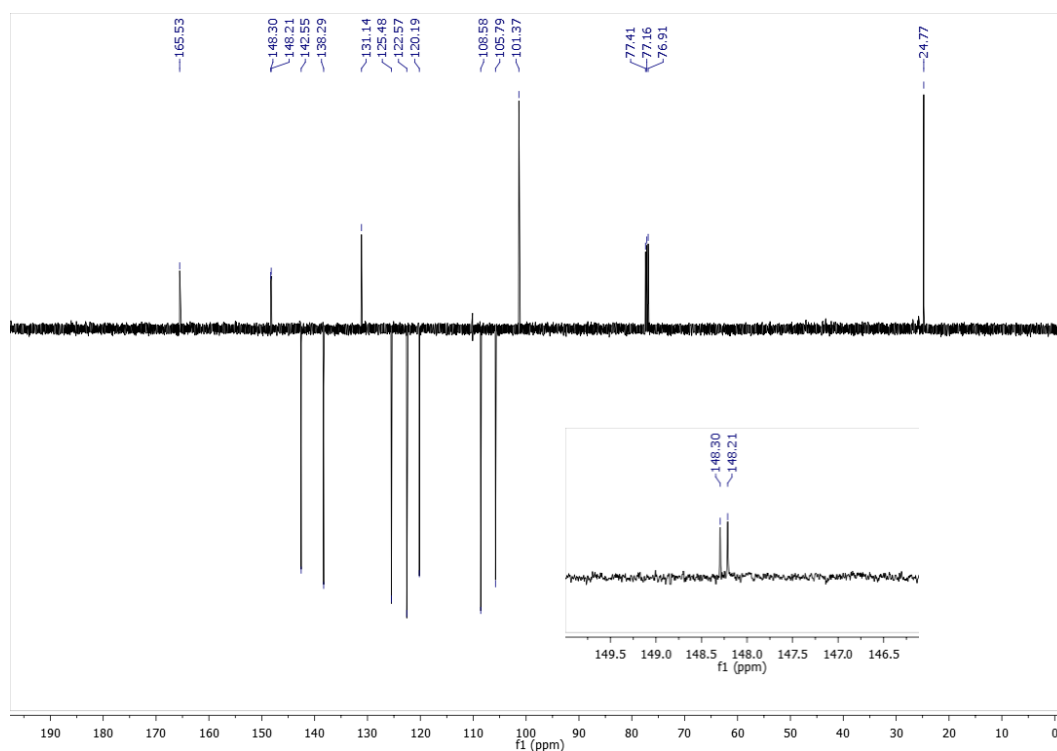


Figure S3. ^{13}C NMR spectrum (126 MHz, CDCl_3) of compound piperine (**7**).

Potassium piperate (**8**)

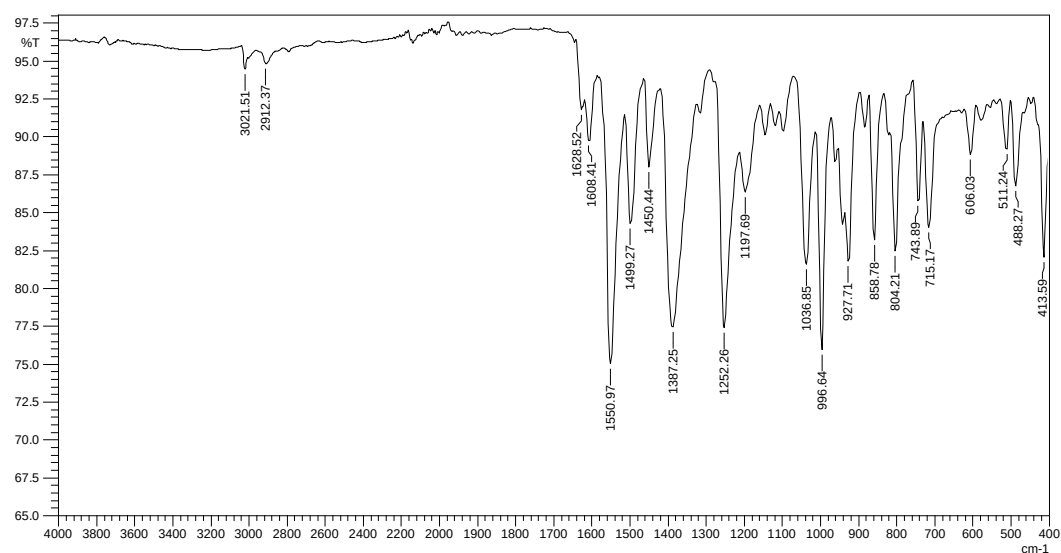


Figure S4. Infrared spectrum (KBr) of potassium piperate.

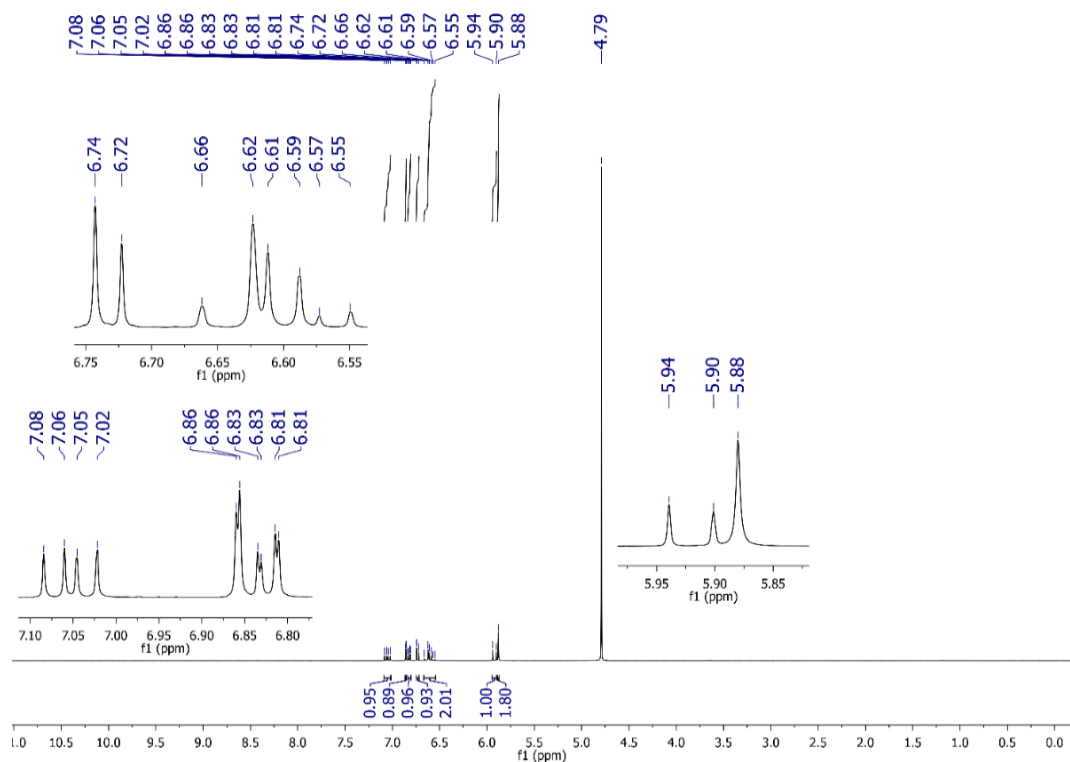


Figure S5. ¹H NMR spectrum (400 MHz, CDCl₃) of potassium piperate (**8**).

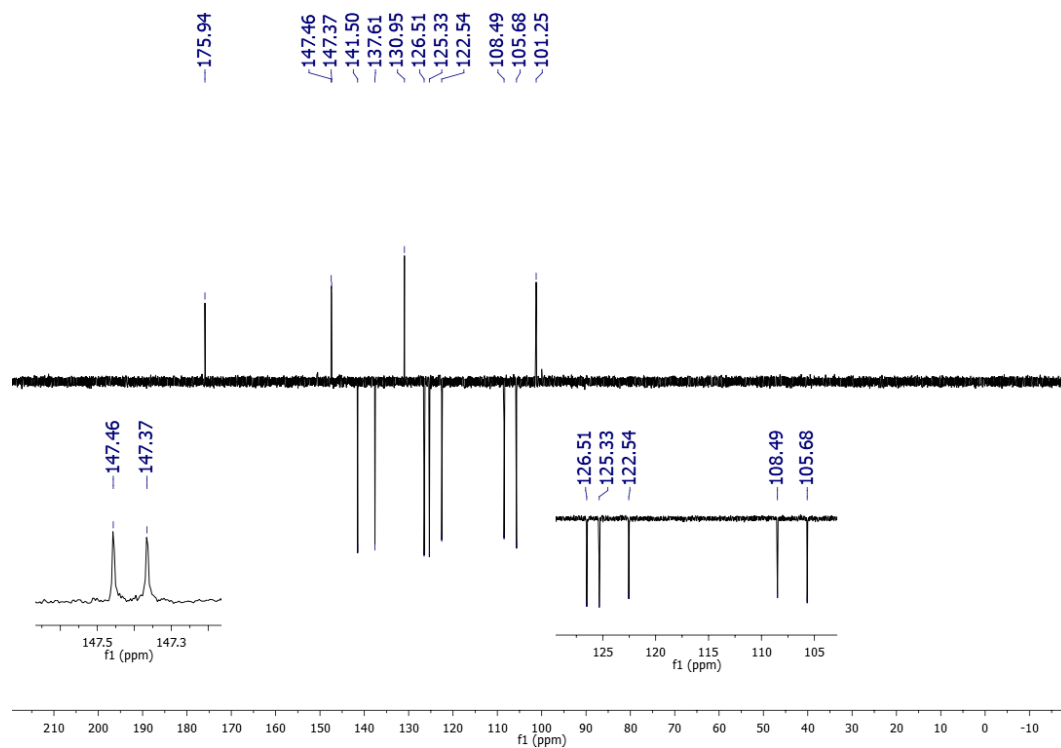


Figure S6. ¹³C NMR spectrum (100 MHz, D₂O) of compound potassium piperate (**8**).

Benzyl alcohols (**10b-10d**)

4-Methylbenzyl alcohol (**10b**)

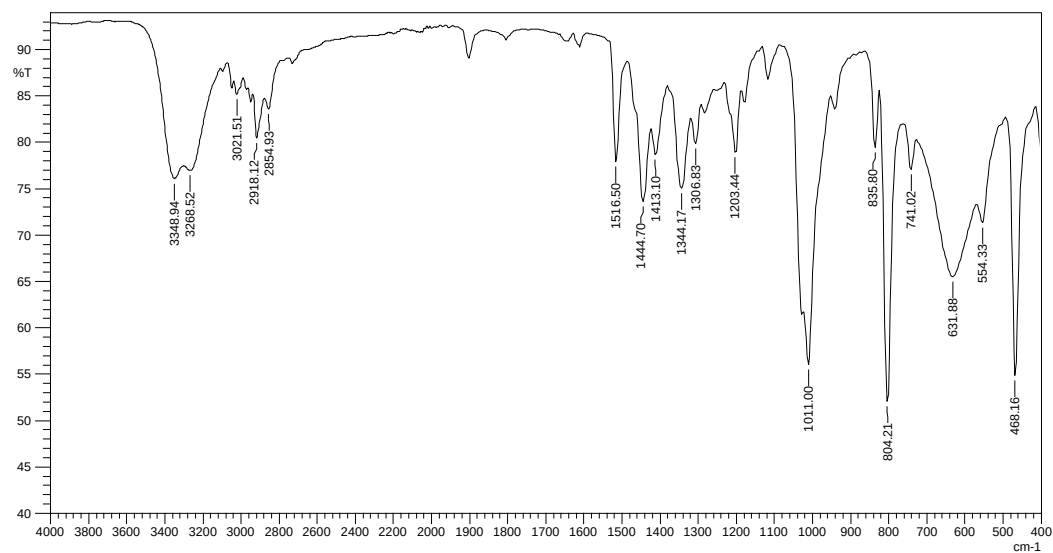


Figure S7. Infrared spectrum (KBr) of the compound **10b**.

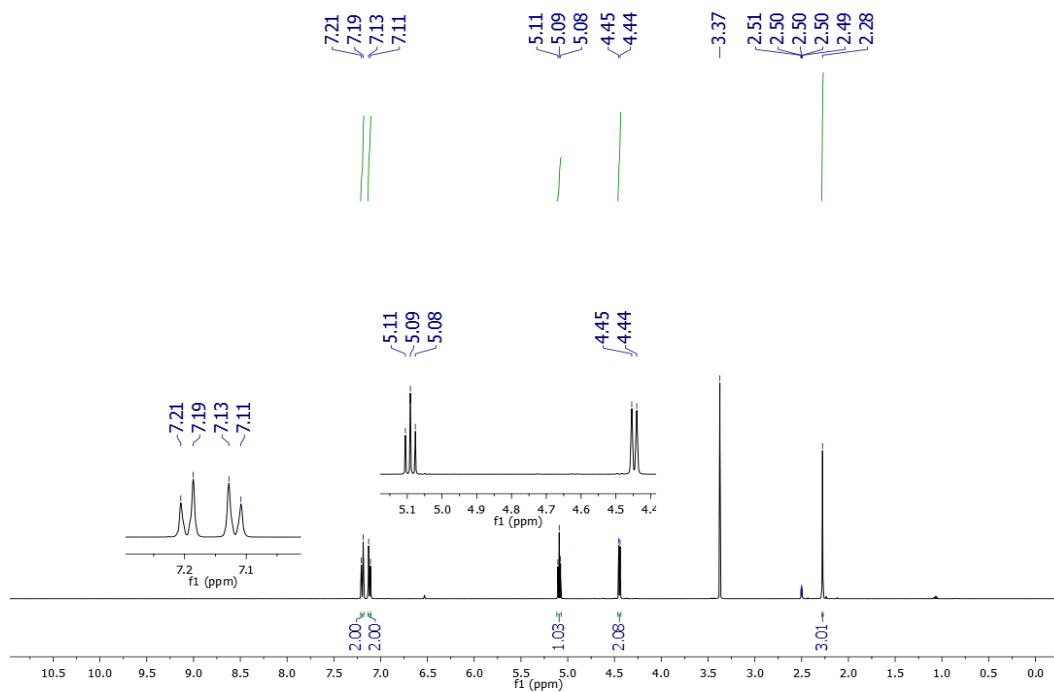


Figure S8. ^1H NMR spectrum (400 MHz, DMSO-d_6) of the compound **10b**.

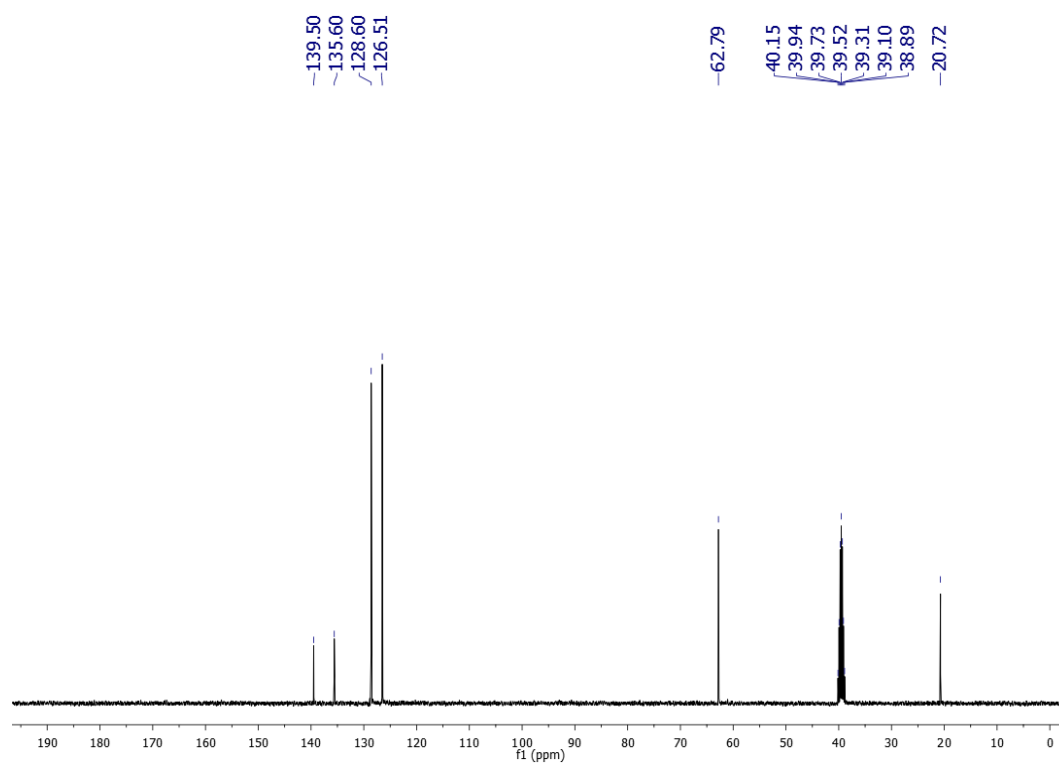


Figure S9. ¹³C NMR spectrum (101 MHz, DMSO-*d*₆) of the compound **10b**.

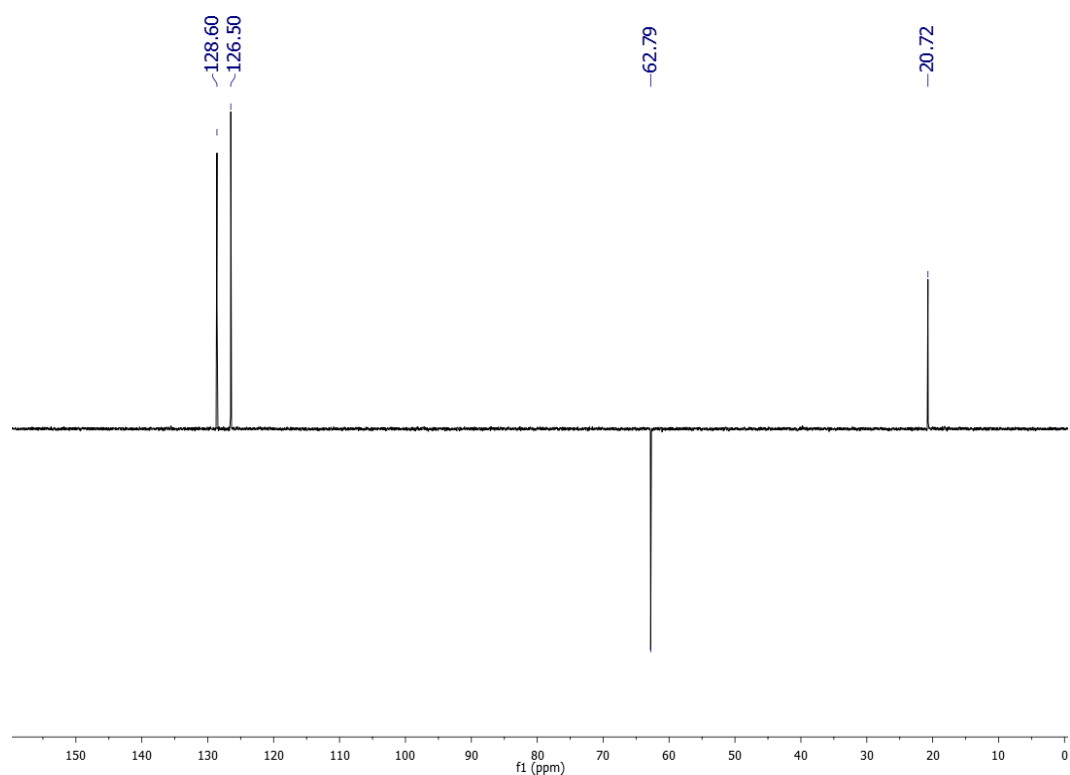


Figure S10. ¹³C DEPT 135 NMR spectrum (101 MHz, DMSO-*d*₆) of the compound **10b**.

4-Bromobenzyl alcohol (**10c**)

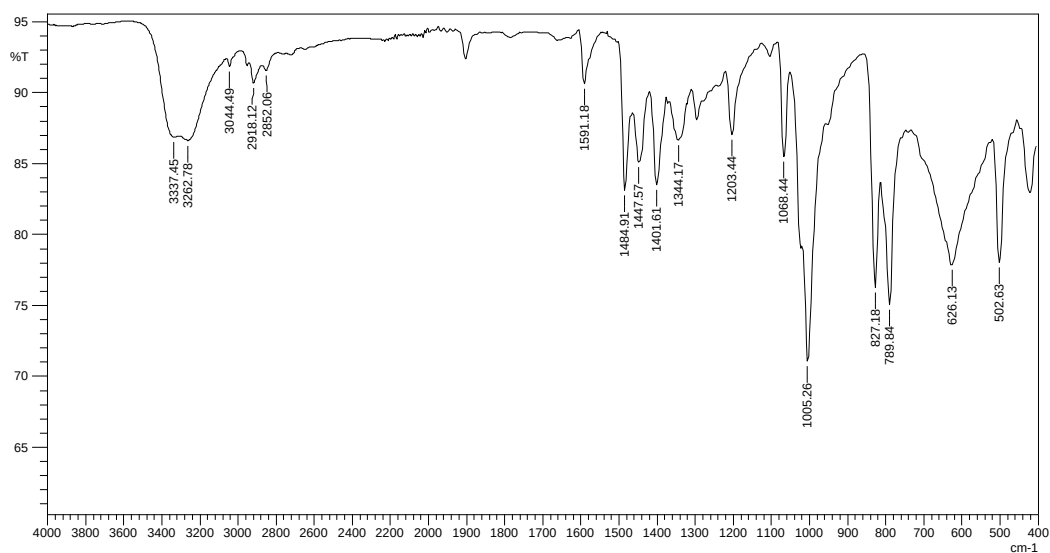


Figure S11. Infrared spectrum (KBr) of the compound **10c**.

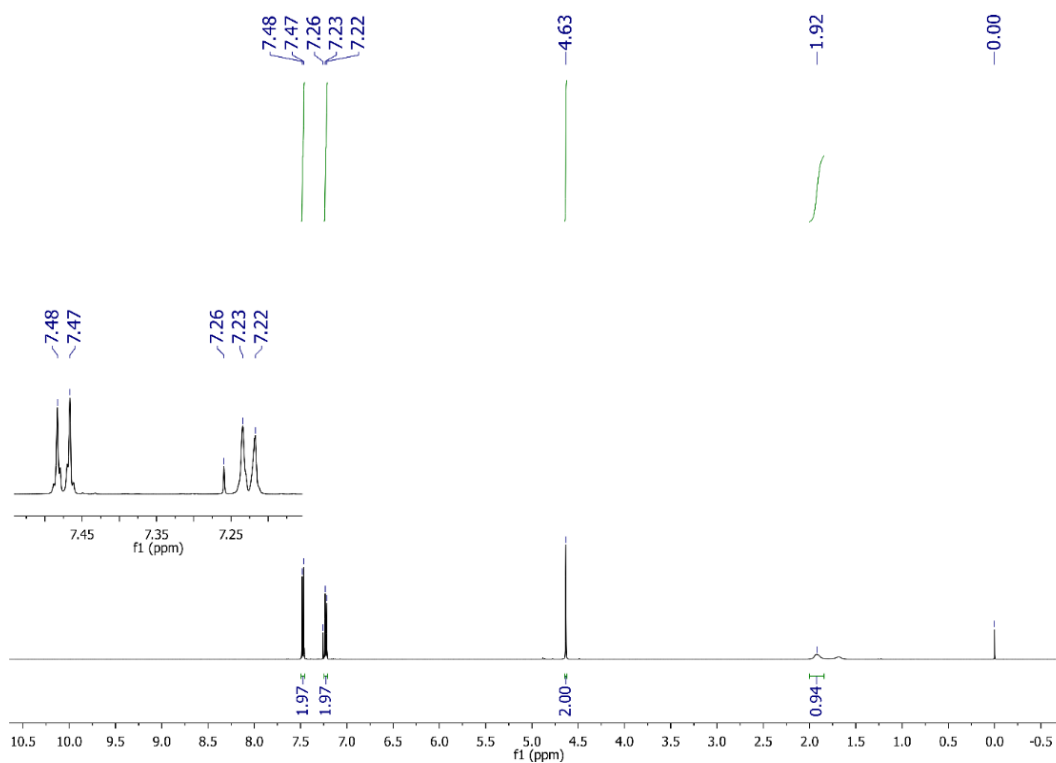


Figure S12. ^1H NMR spectrum (500 MHz, CDCl_3) of the compound **10c**.

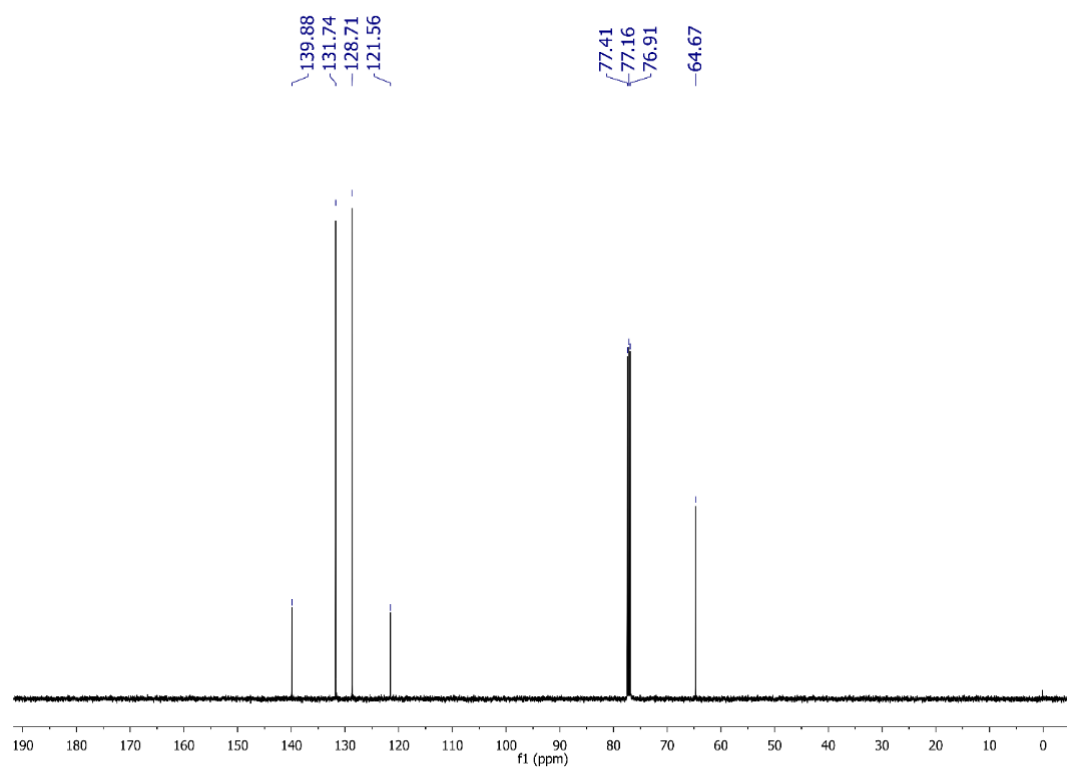


Figure S13. ¹³C NMR spectrum (126 MHz, CDCl₃) of the compound **10c**.

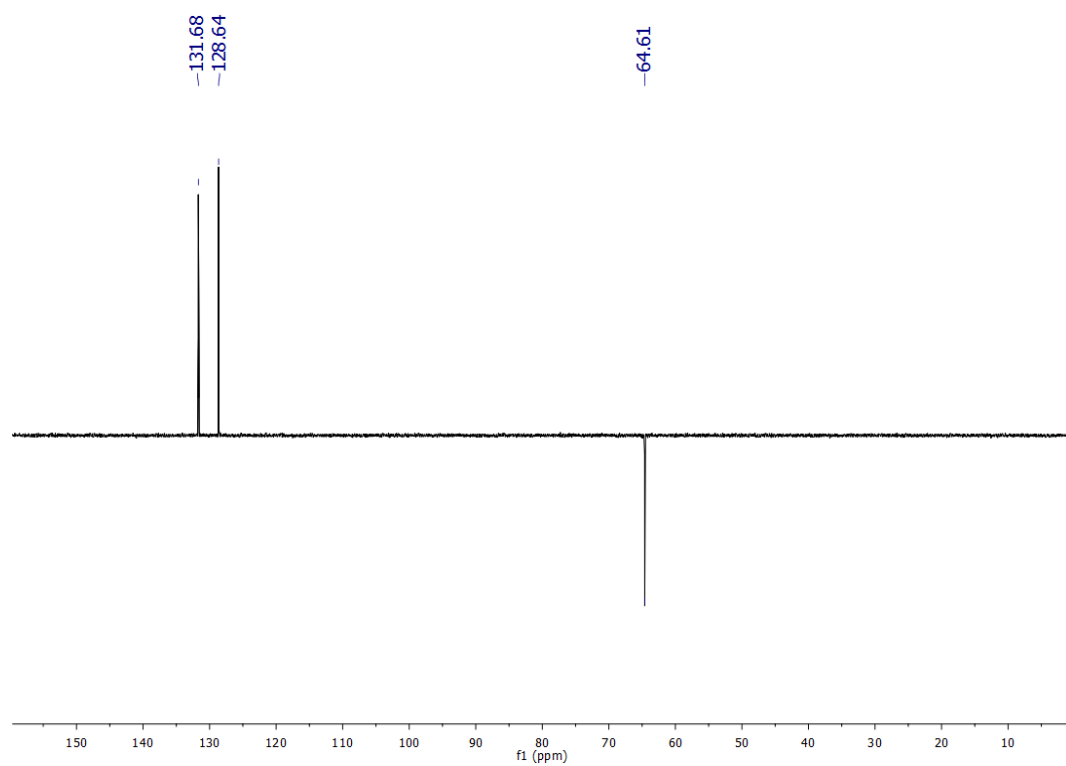


Figure S14. ¹³C DEPT 135 NMR spectrum (126 MHz, CDCl₃) of the compound **10c**.

3-Nitrobenzyl alcohol (**10d**)

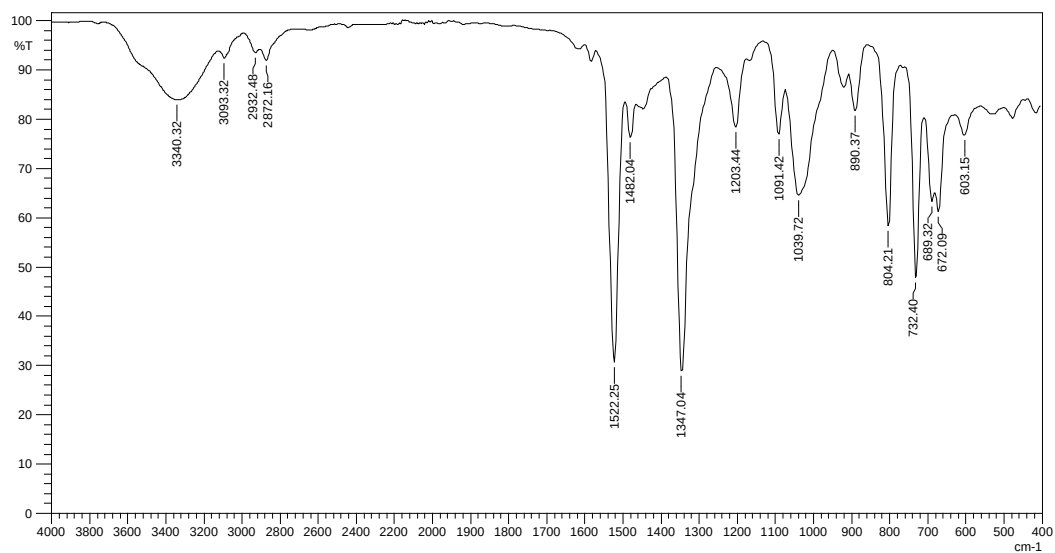


Figure S15. Infrared spectrum (KBr) of the compound **10d**.

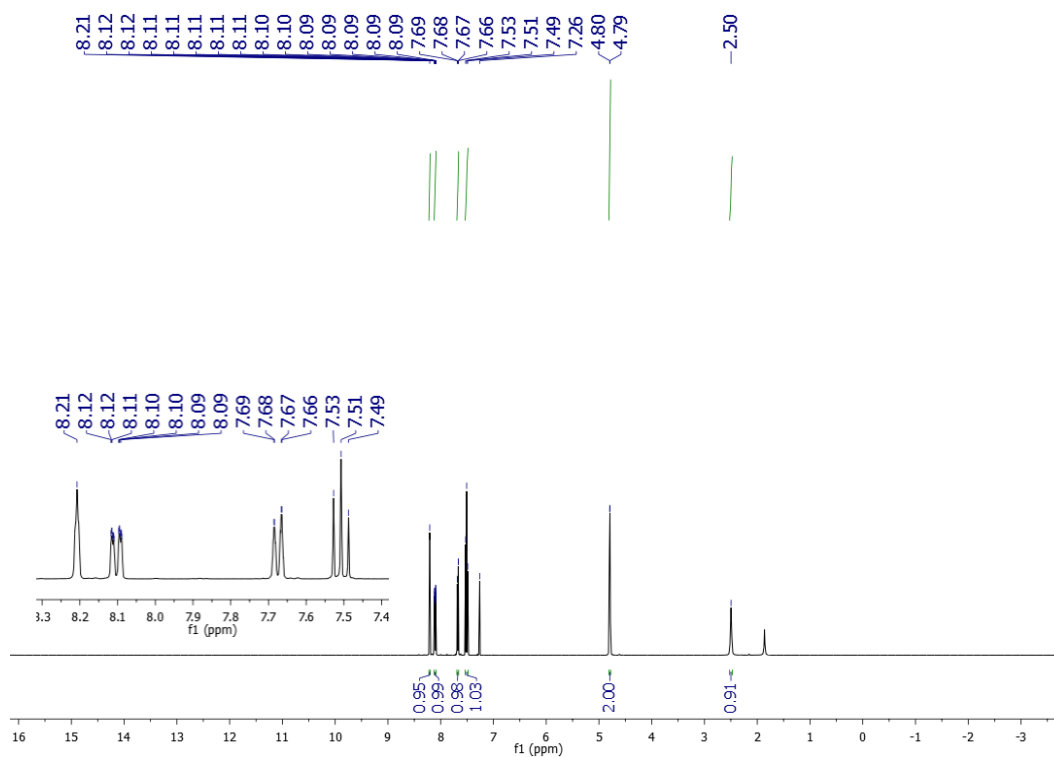


Figure S16. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **10d**.

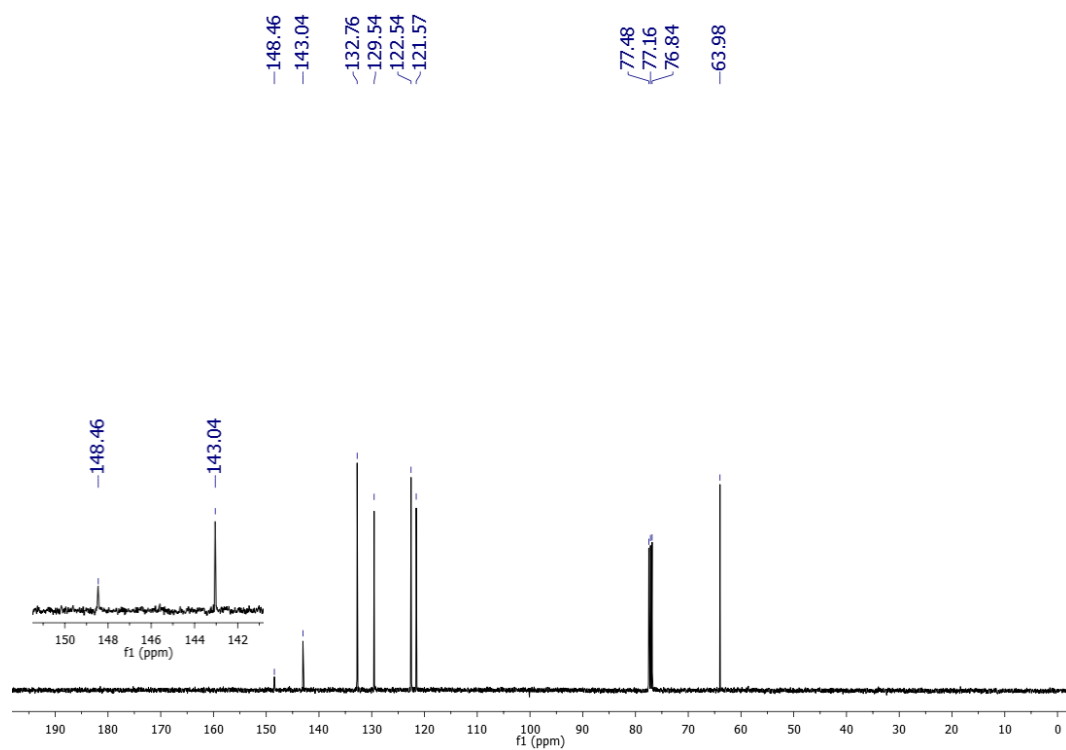


Figure S17. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **10d**.

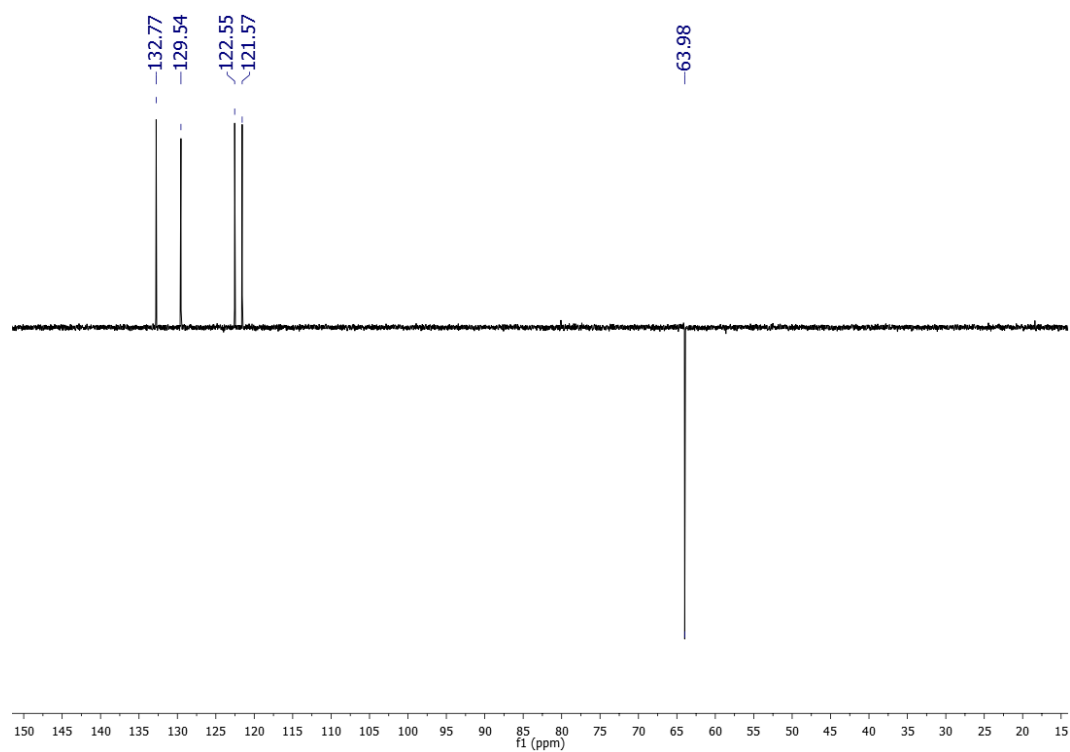


Figure S18. ¹³C DEPT 135 NMR spectrum (101 MHz, DMSO-*d*₆) of the compound **10d**.

Final compounds (**12a-12d**)

Benzyl piperate (**12a**)

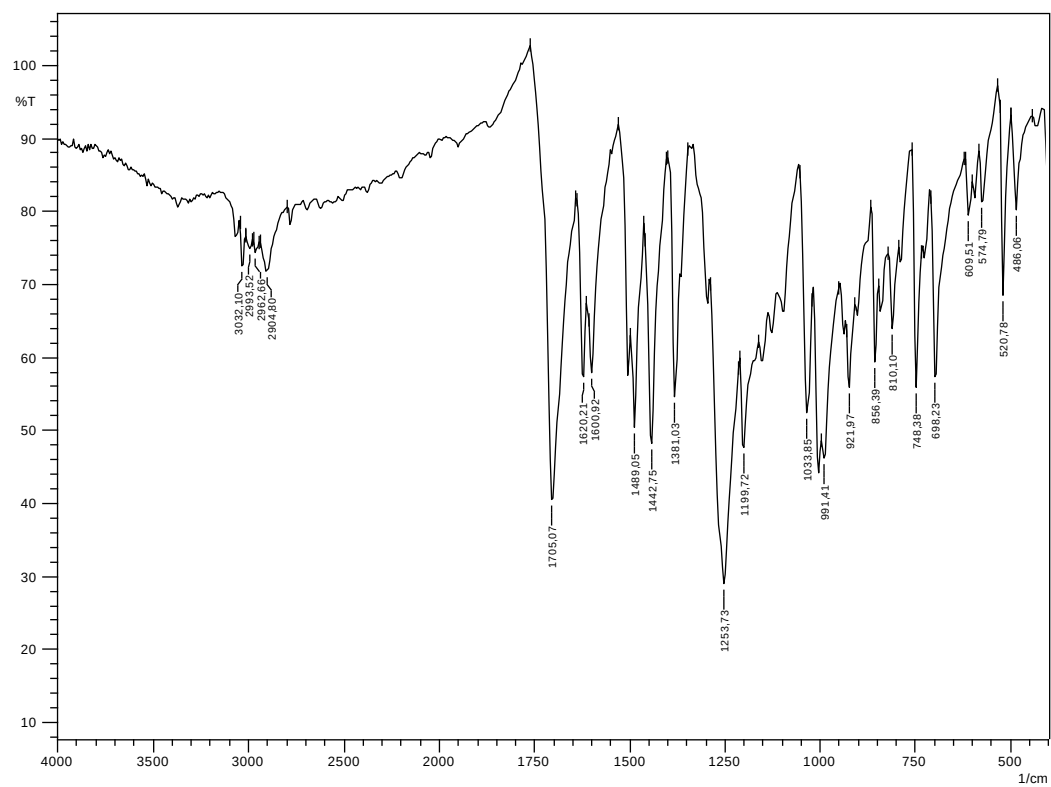


Figure S19. Infrared spectrum (KBr) of compound **12a**.

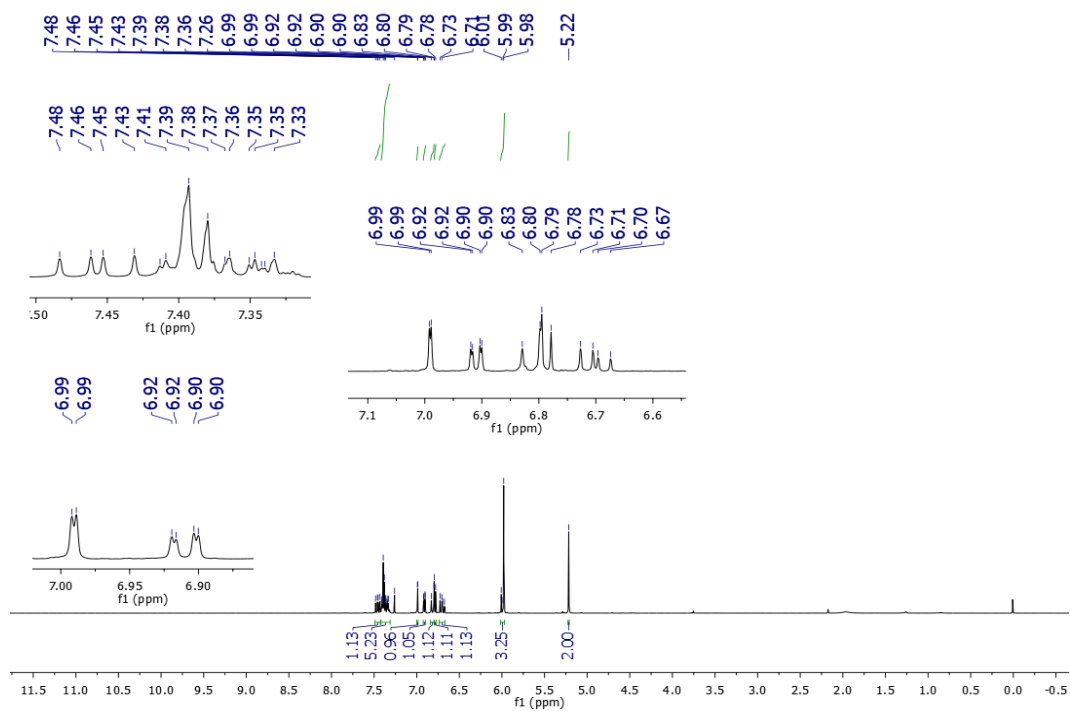


Figure S20. ^1H NMR spectrum (500 MHz, CDCl_3) of compound **12a**.

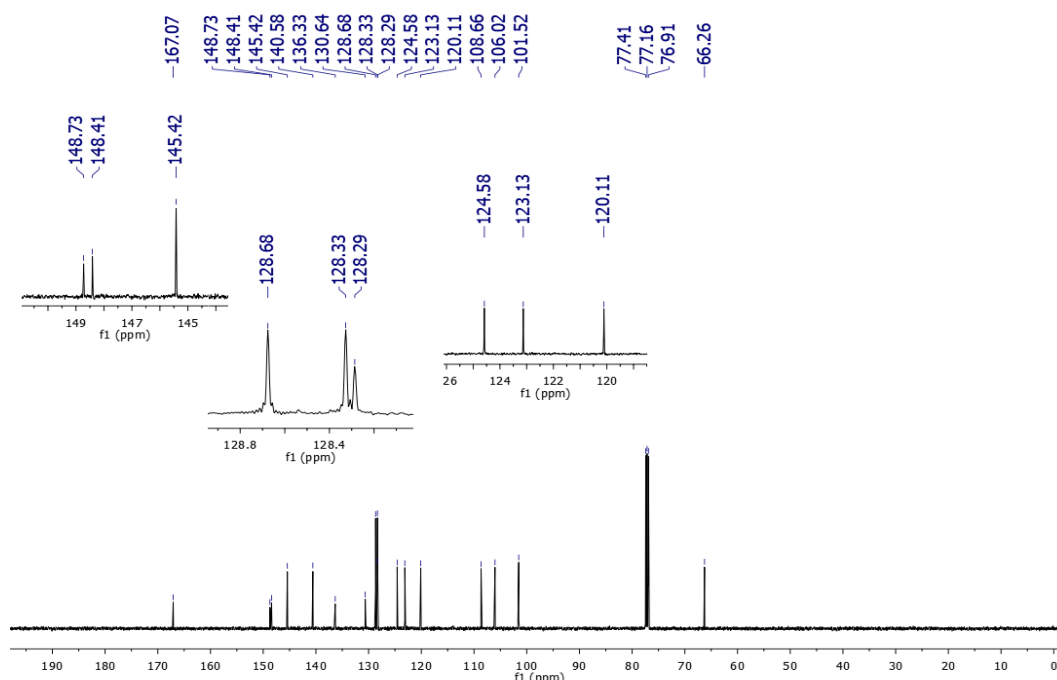


Figure S21. ^{13}C NMR spectrum (101 MHz, CDCl_3) of the compound **12a**.

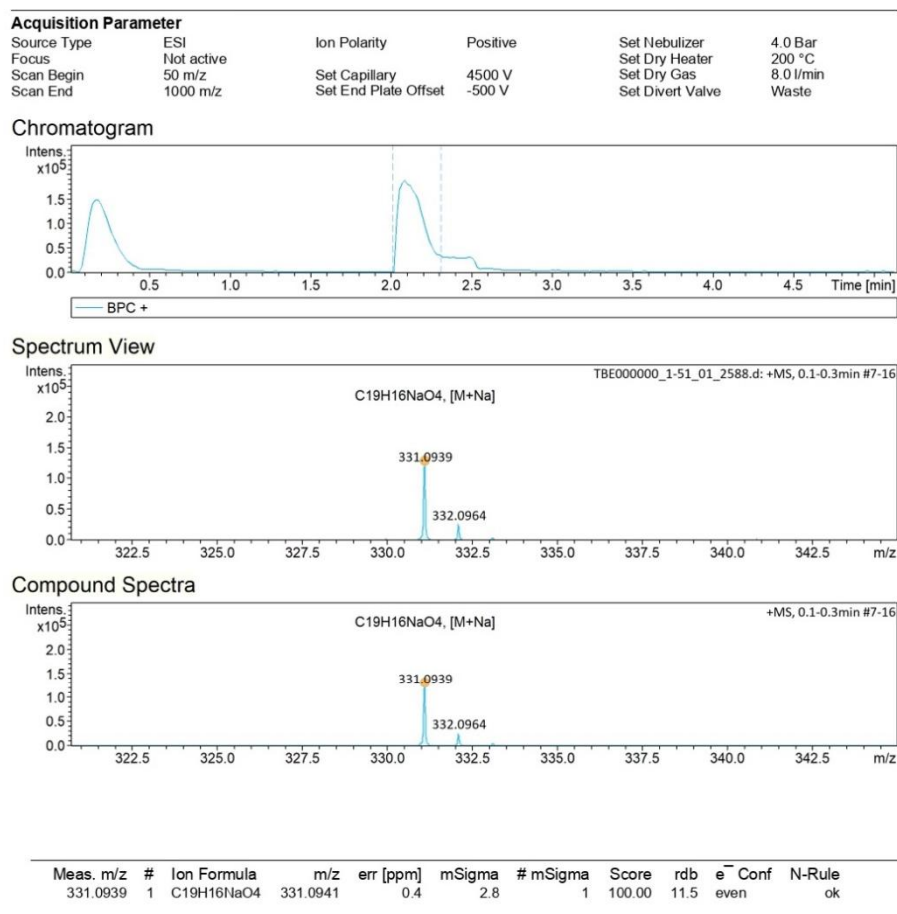


Figure S22. HRMS (ESI) spectrum of the compound **12a**.

4-Methylbenzyl piperate (**12b**)

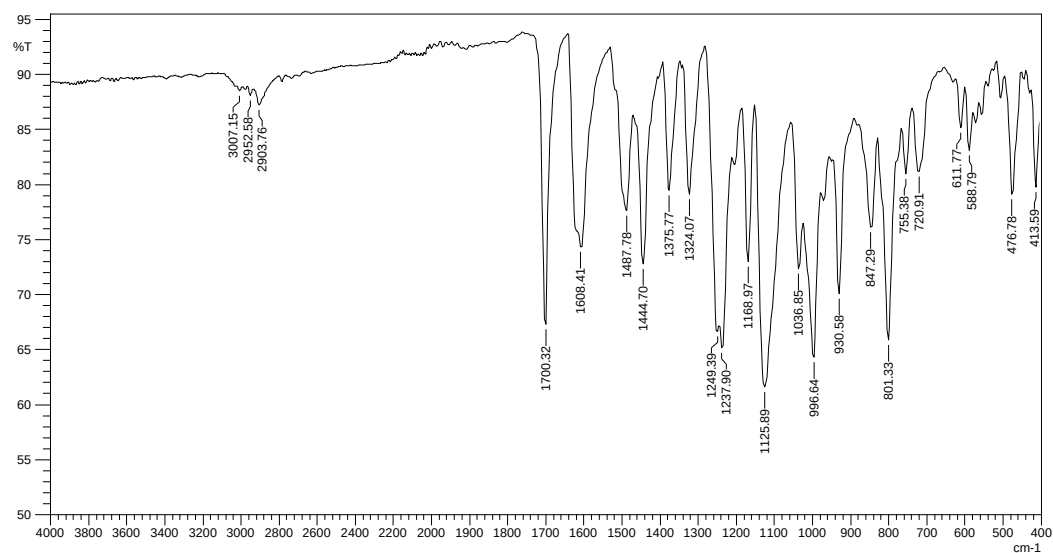


Figure S23. Infrared spectrum (KBr) of compound **12b**.

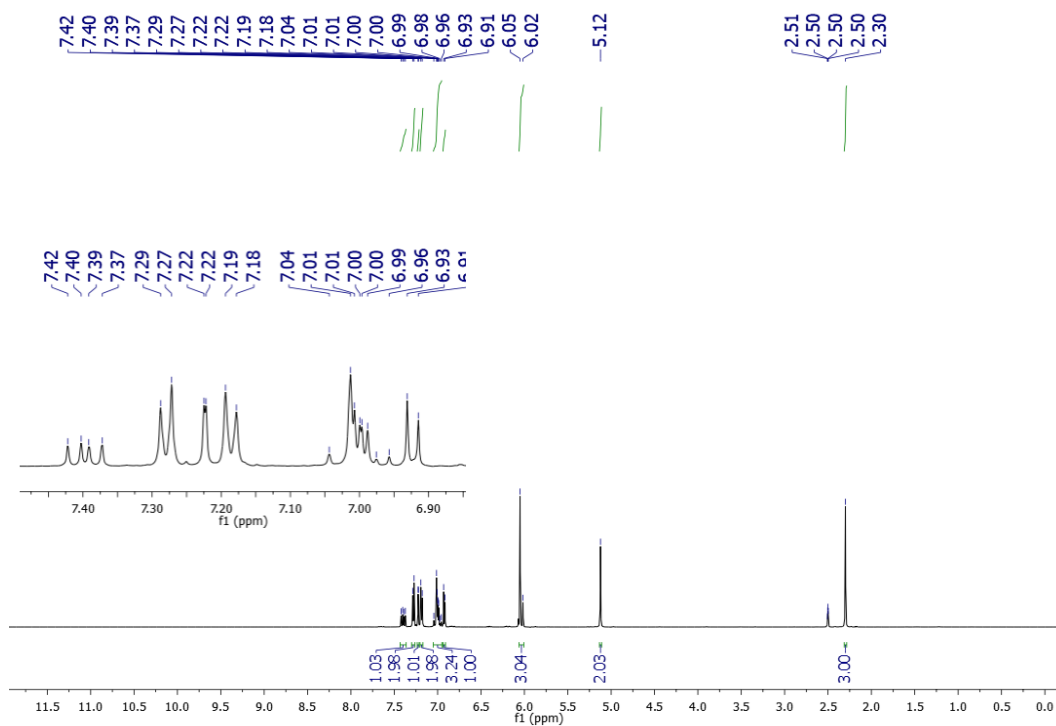


Figure S24. ¹H NMR spectrum (500 MHz, DMSO-*d*₆) of compound **12b**.

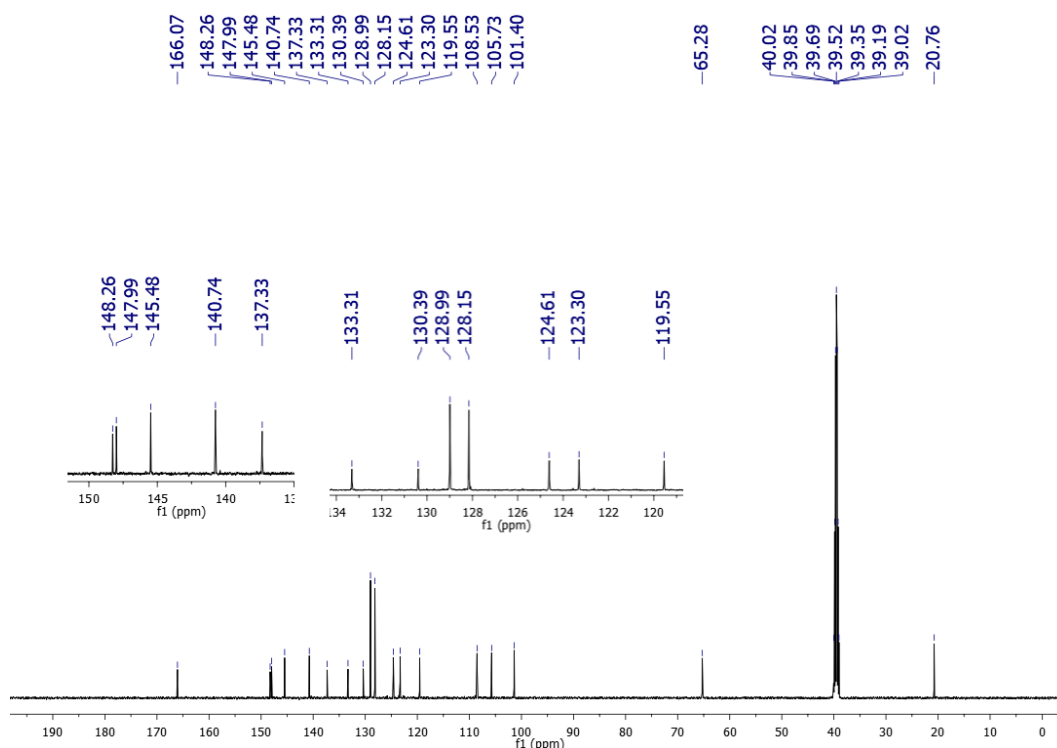


Figure S25. ^{13}C NMR spectrum (125 MHz, $\text{DMSO}-d_6$) of compound **12b**.

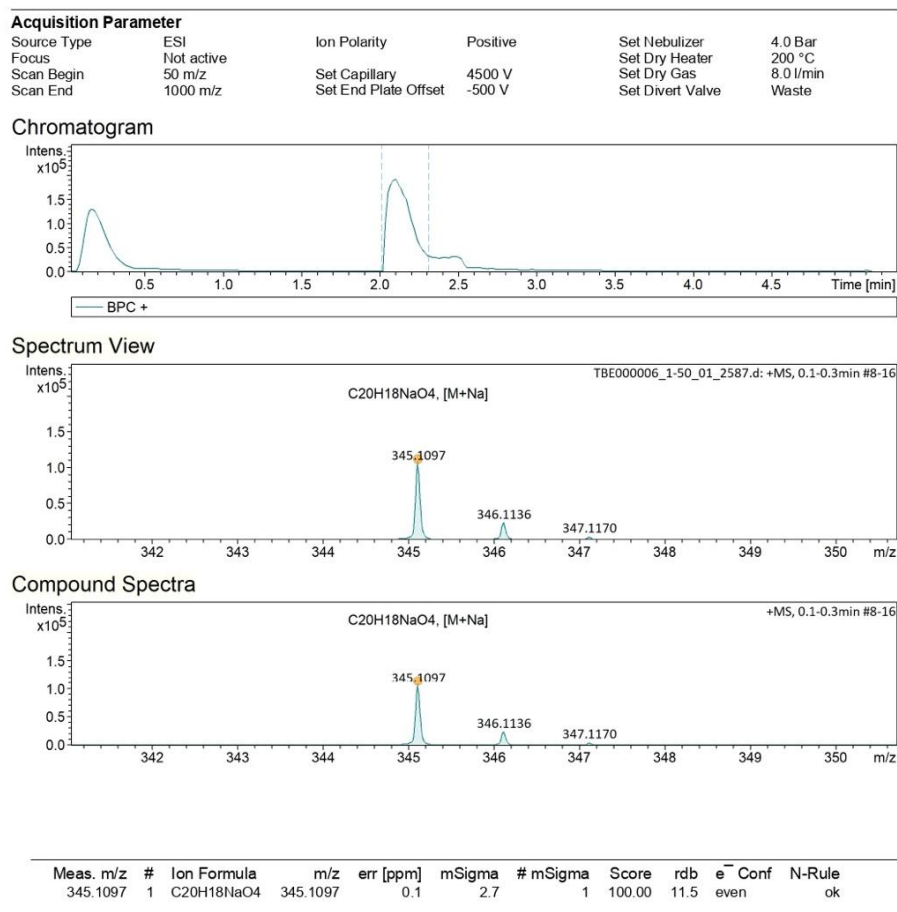


Figure S26. HRMS (ESI) spectrum of the compound **12b**.

4-Bromobenzyl piperate (**12c**)

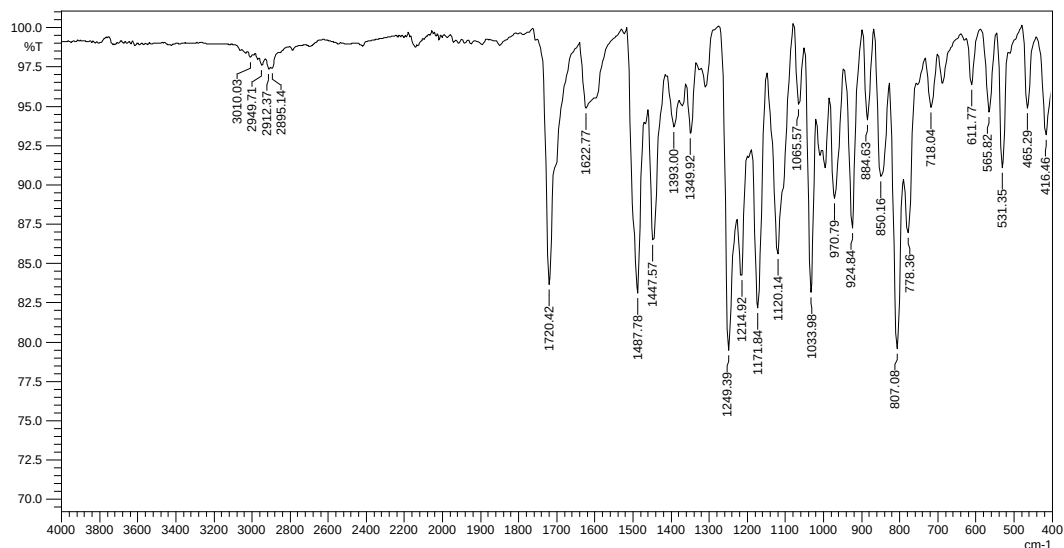


Figure S27. Infrared spectrum (KBr) of compound **12c**.

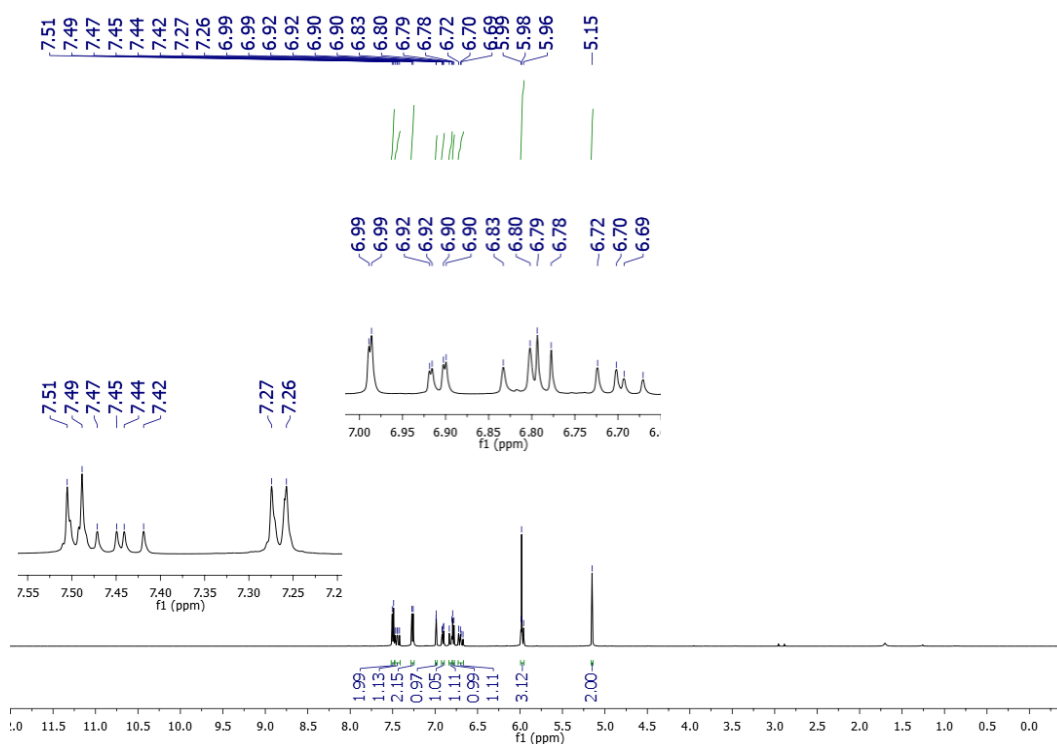


Figure S28. ¹H NMR spectrum (500 MHz, CDCl₃) of compound **12c**.

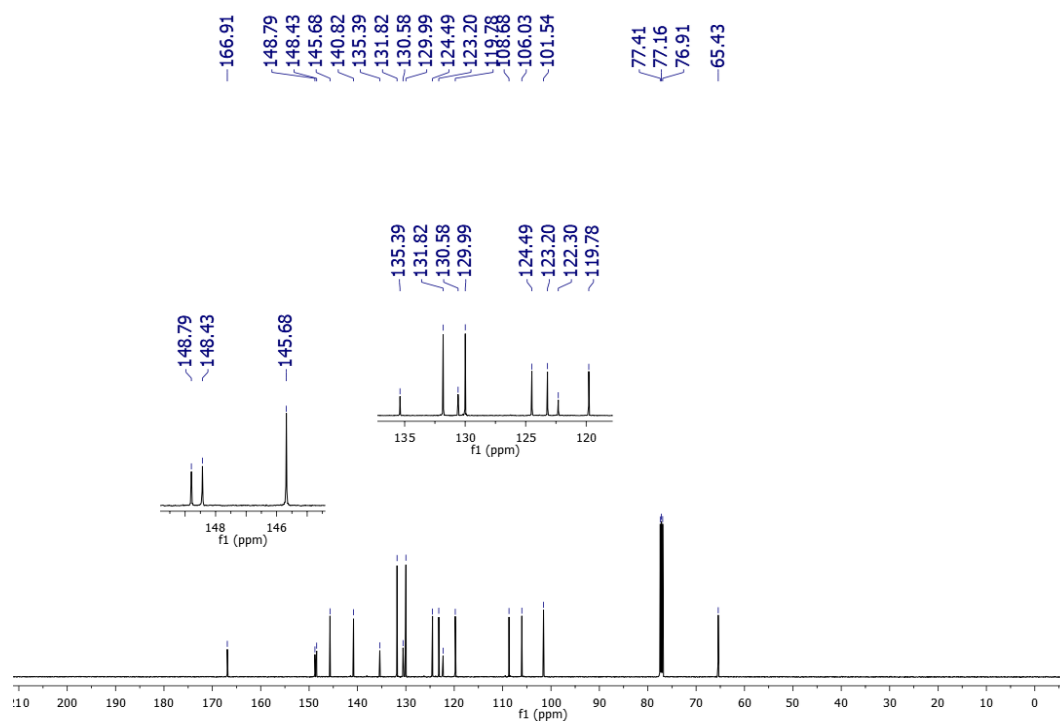


Figure S29. ^{13}C NMR spectrum (125 MHz, CDCl_3) of the compound **12c**.

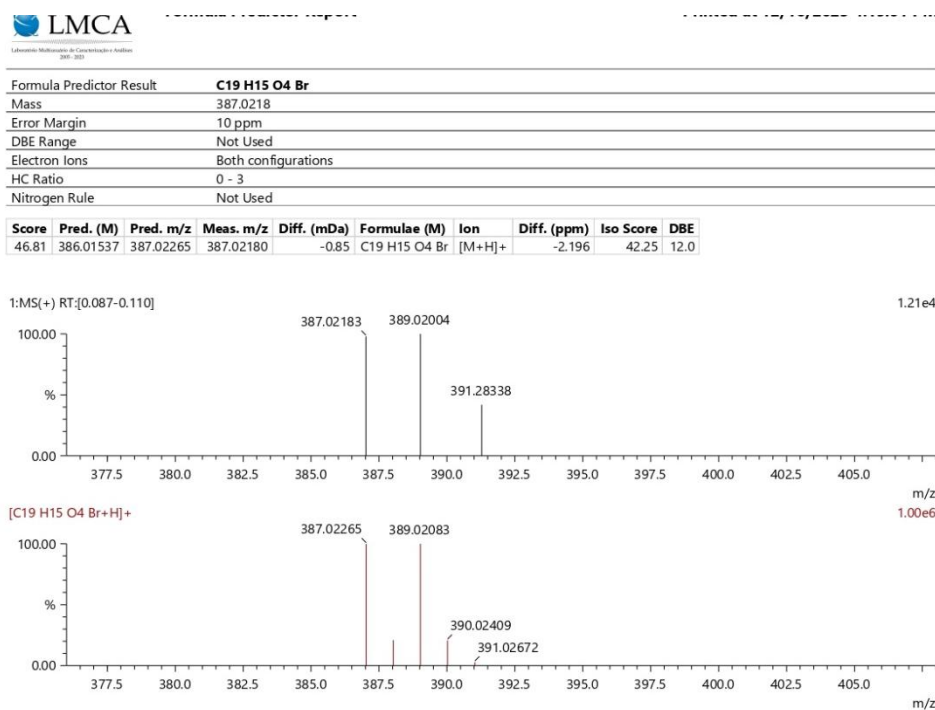


Figure S30. HRMS (ESI) spectrum of the compound **12c**.

3-Nitrobenzyl piperate (**12d**)

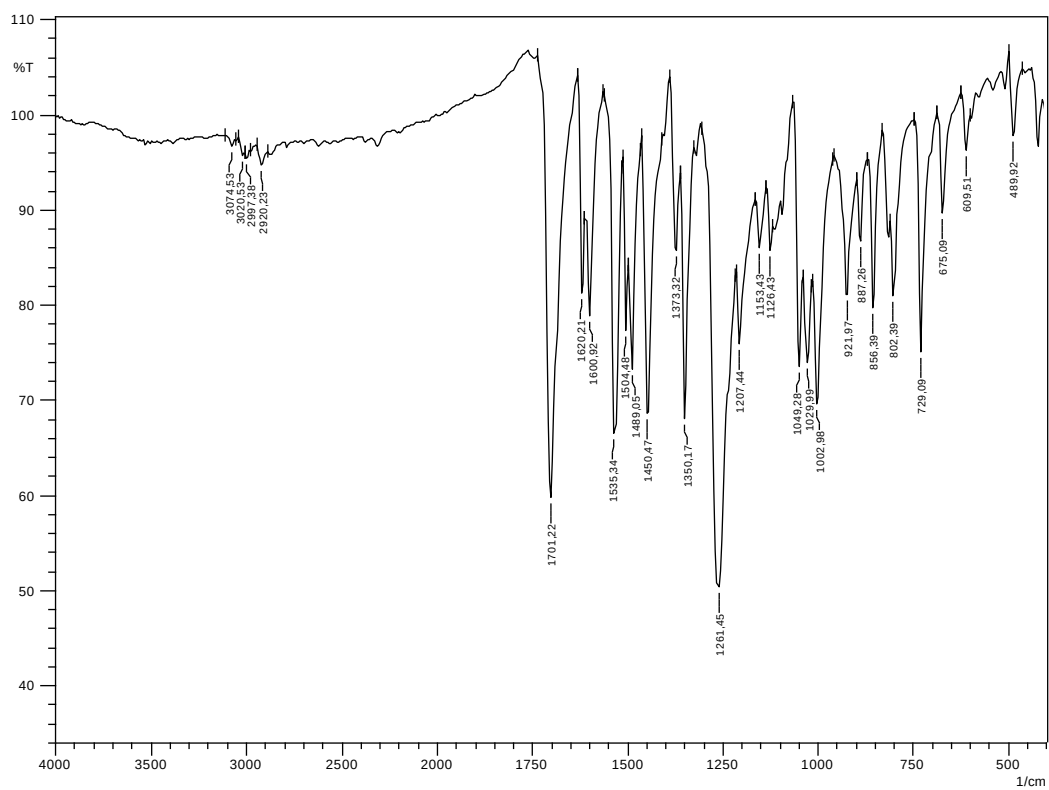


Figure S31. Infrared spectrum (KBr) of compound **12d**.

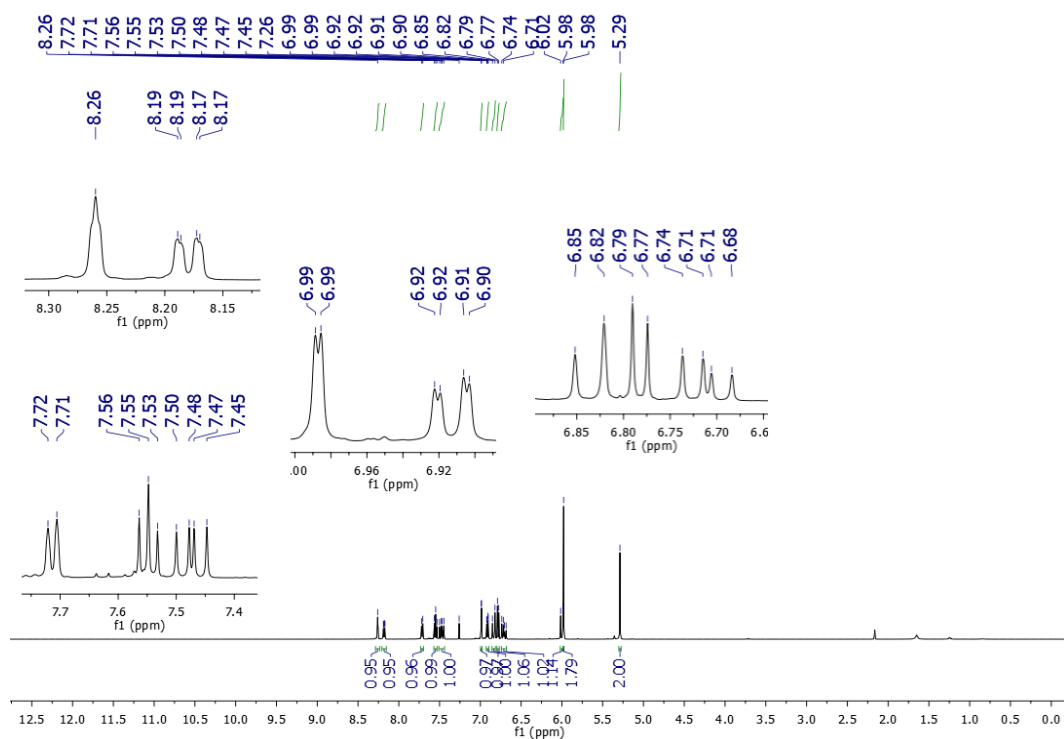


Figure S32. ¹H NMR spectrum (500 MHz, CDCl₃) of compound **12d**.

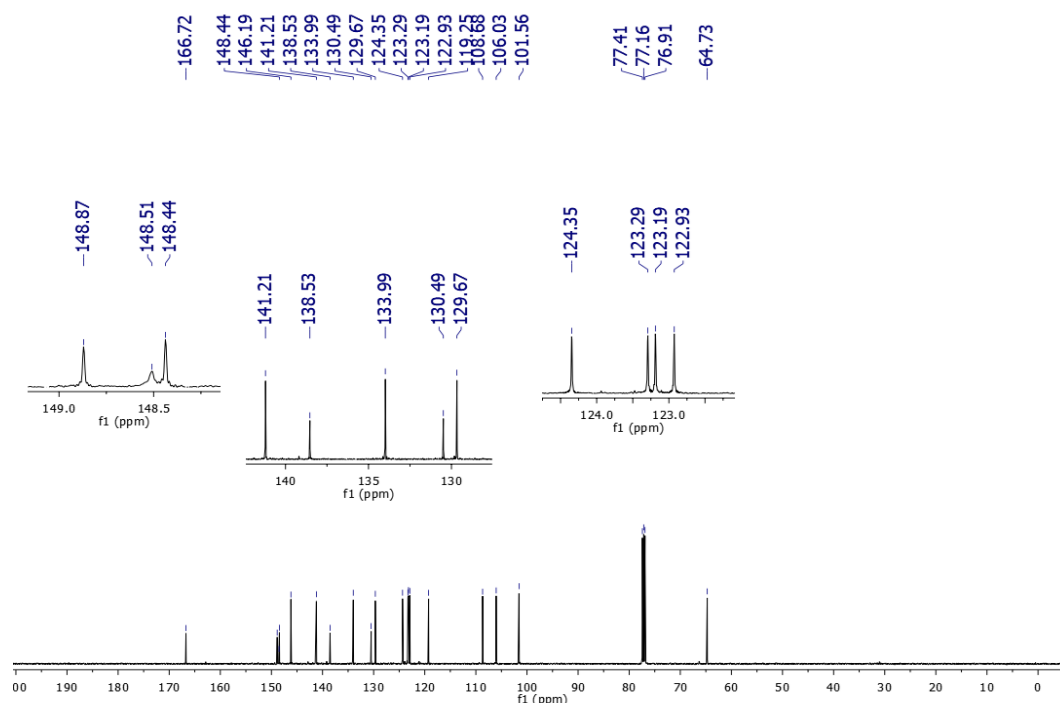


Figure S33. ^{13}C NMR spectrum (125 MHz, CDCl_3) of the compound **12d**.

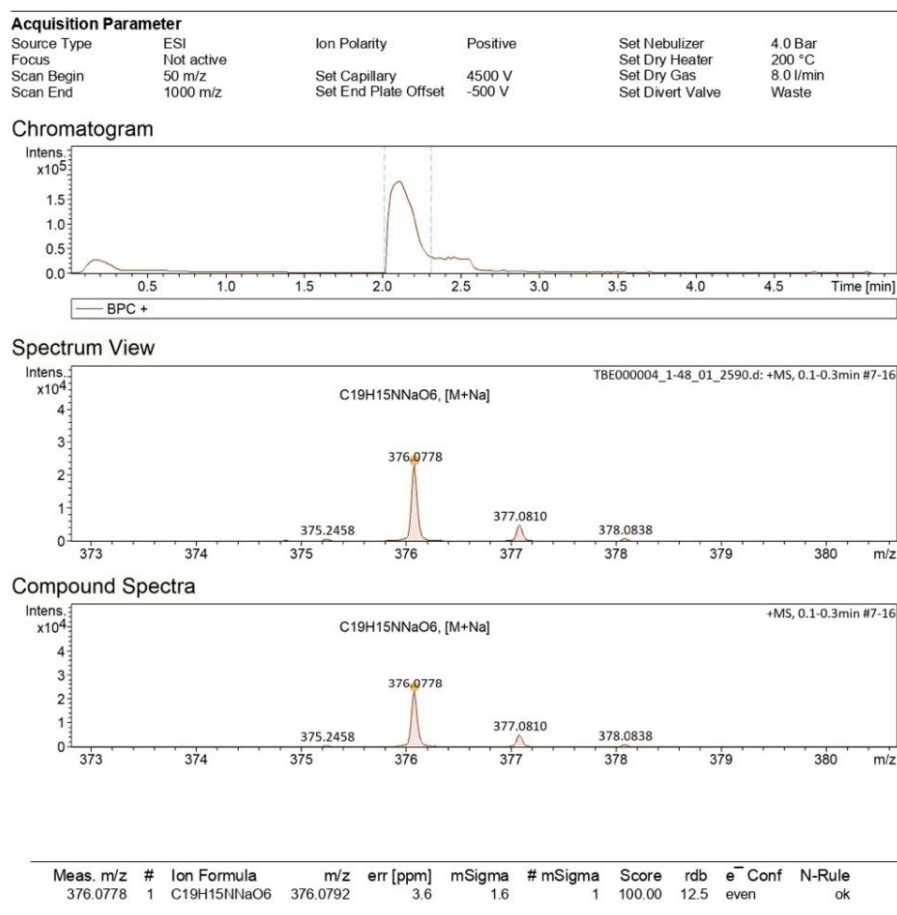


Figure S34. HRMS (ESI) spectrum of the compound **12d**.

General procedure heterocyclic

Bromoacetophenones (**14a-14d**)

2-Bromo-1-phenylethanone (**14a**)

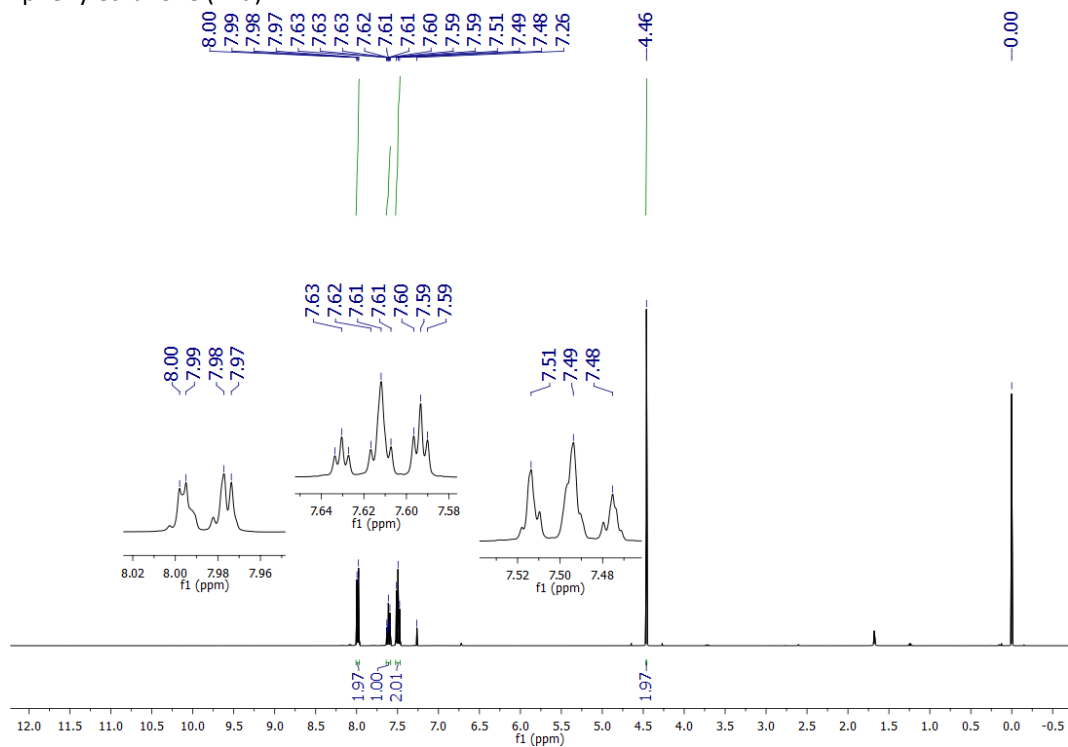


Figure S35. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **14a**.

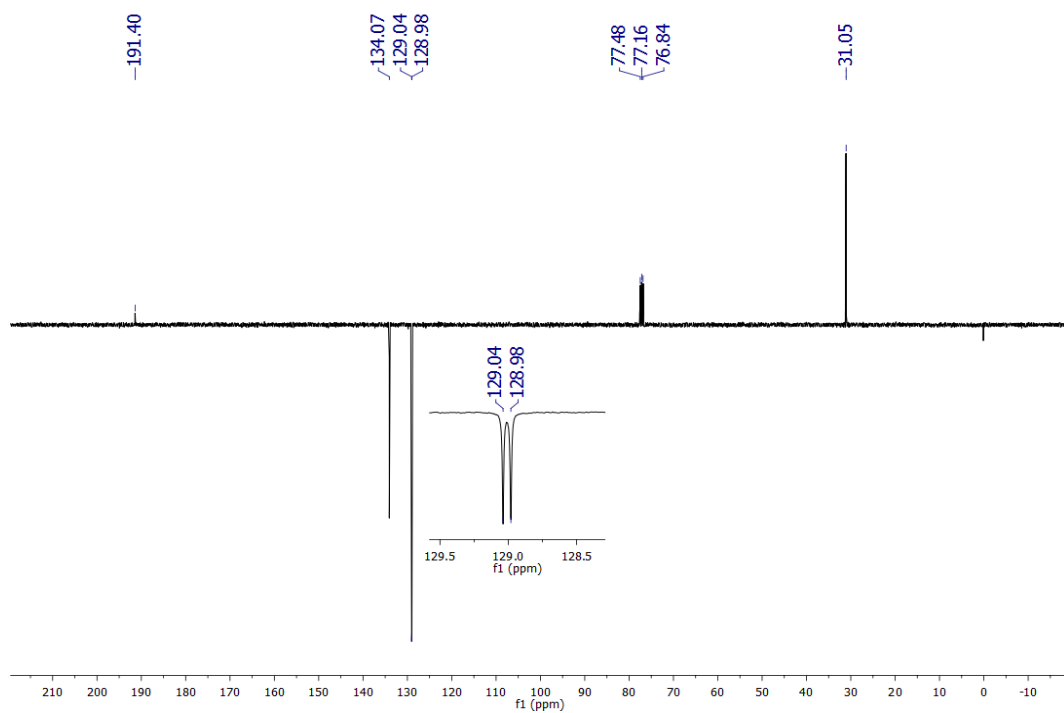


Figure S36. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **14a**.

2-Bromo-1-(4-methylphenyl)ethanone (**14b**)

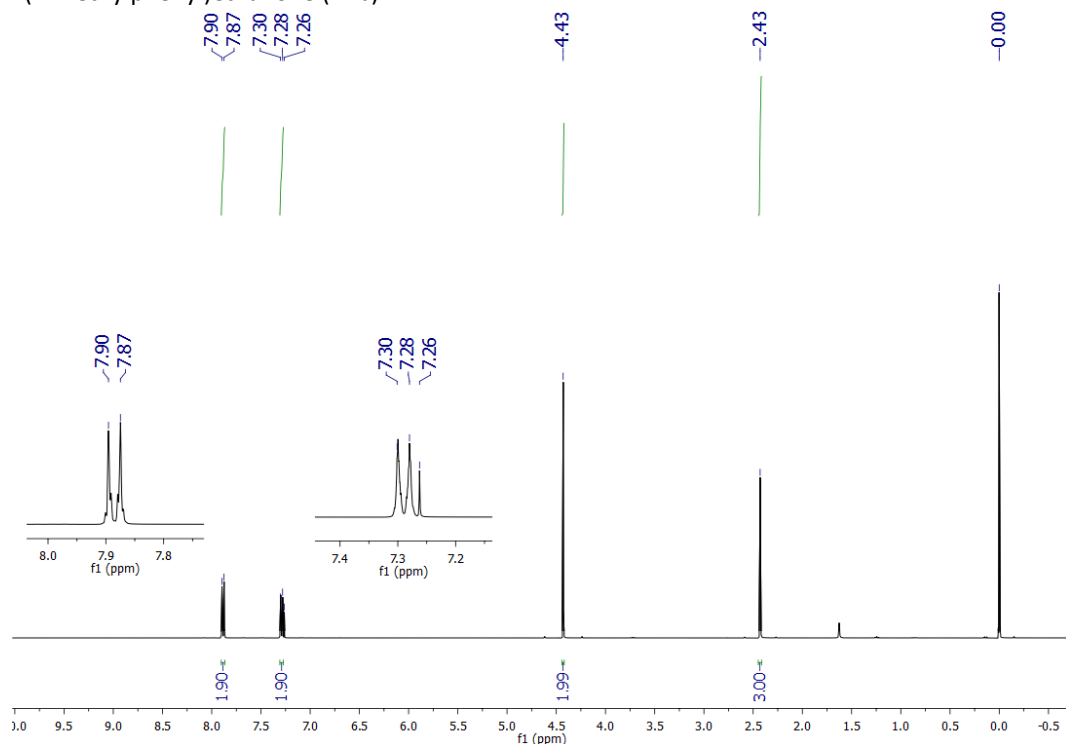


Figure S37. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **14b**.

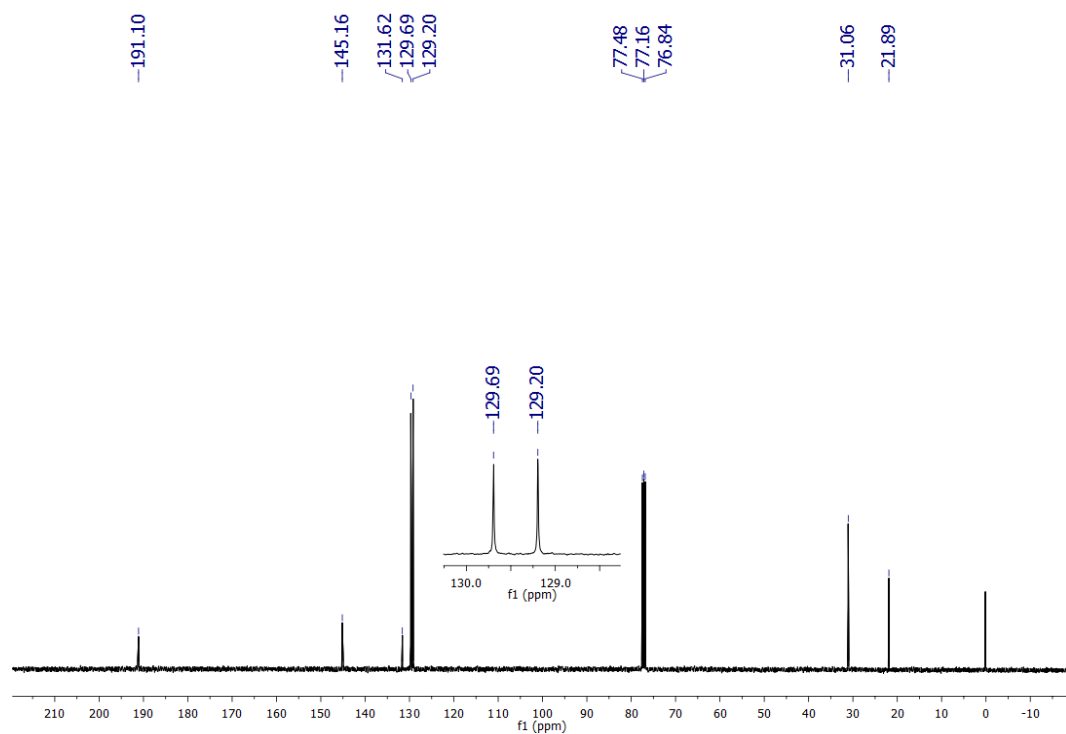


Figure S38. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **14b**.

2-Bromo-1-(4-bromophenyl)ethanone (**14c**)

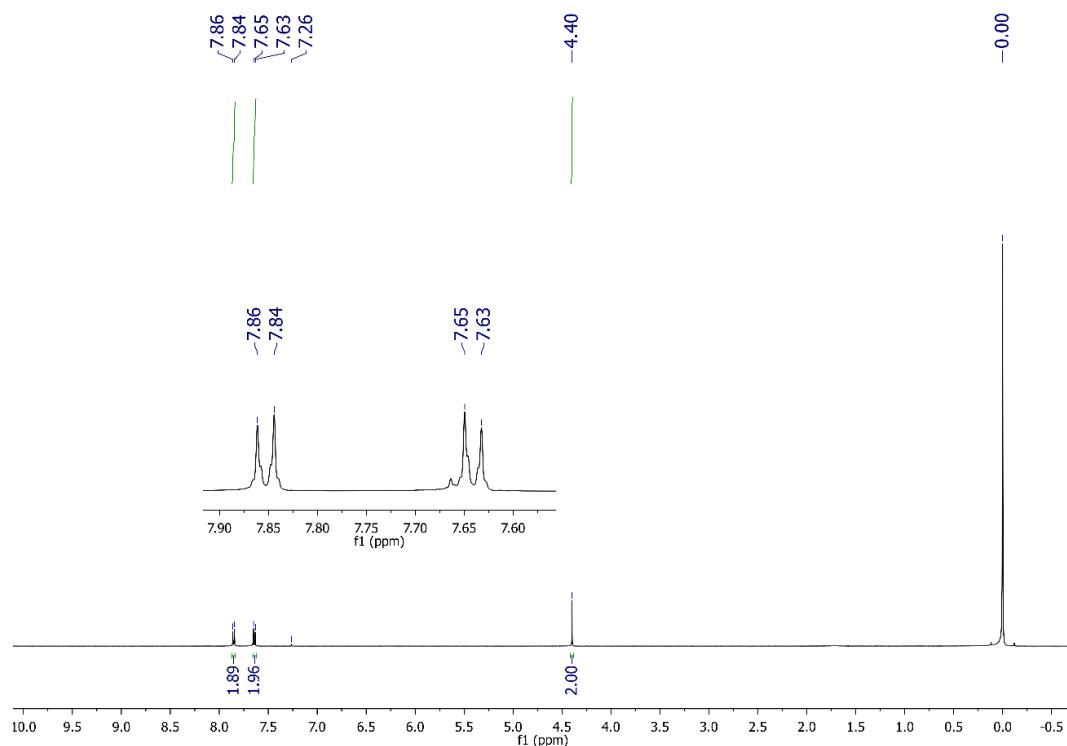


Figure S39. ¹H NMR spectrum (500 MHz, CDCl₃) of compound **14c**.

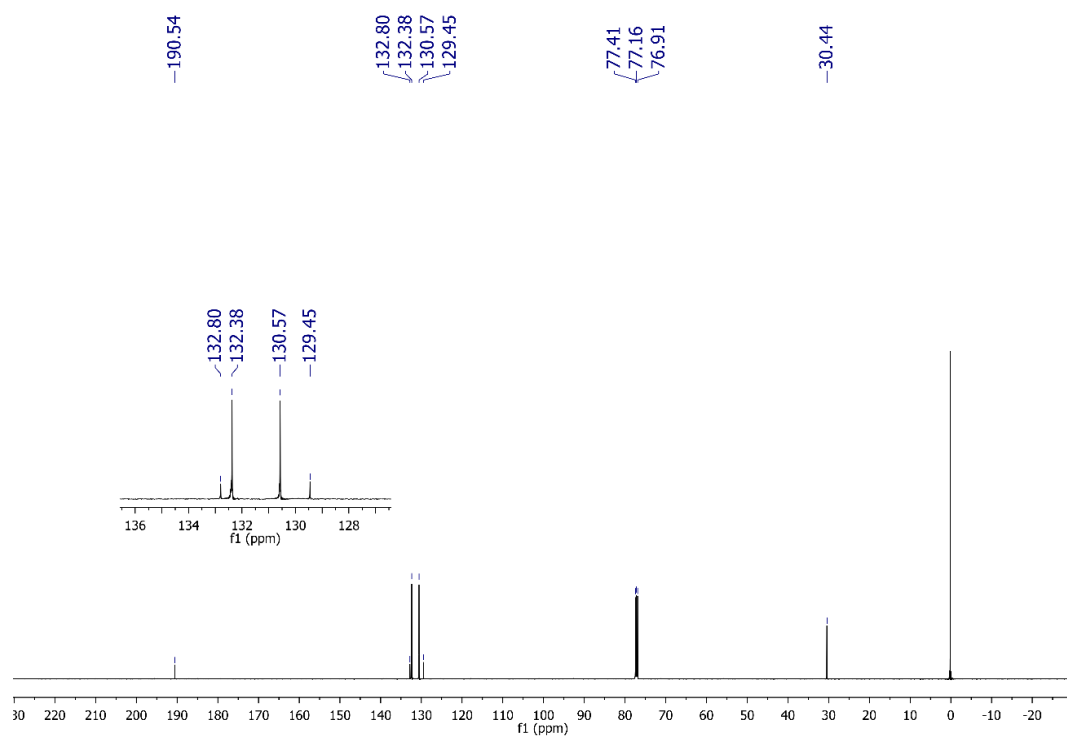


Figure S40. ¹³C NMR spectrum (126 MHz, CDCl₃) of the compound **14c**.

2-Bromo-1-(3-nitrophenyl)ethanone (**14d**)

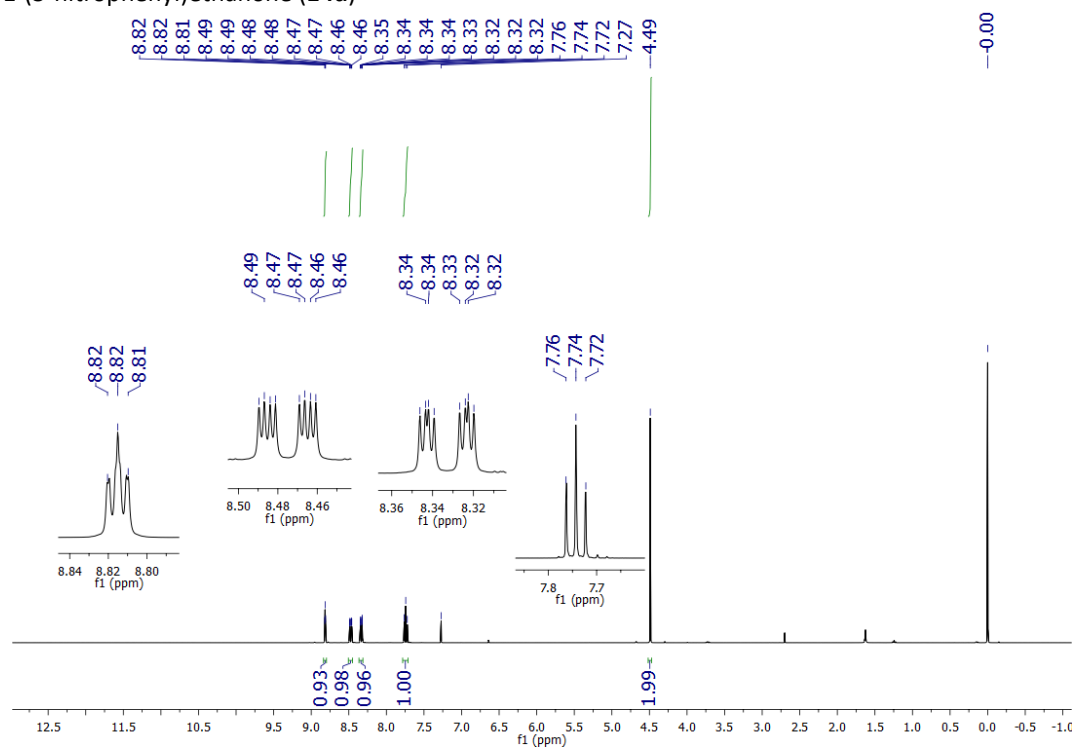


Figure S41. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **14d**.

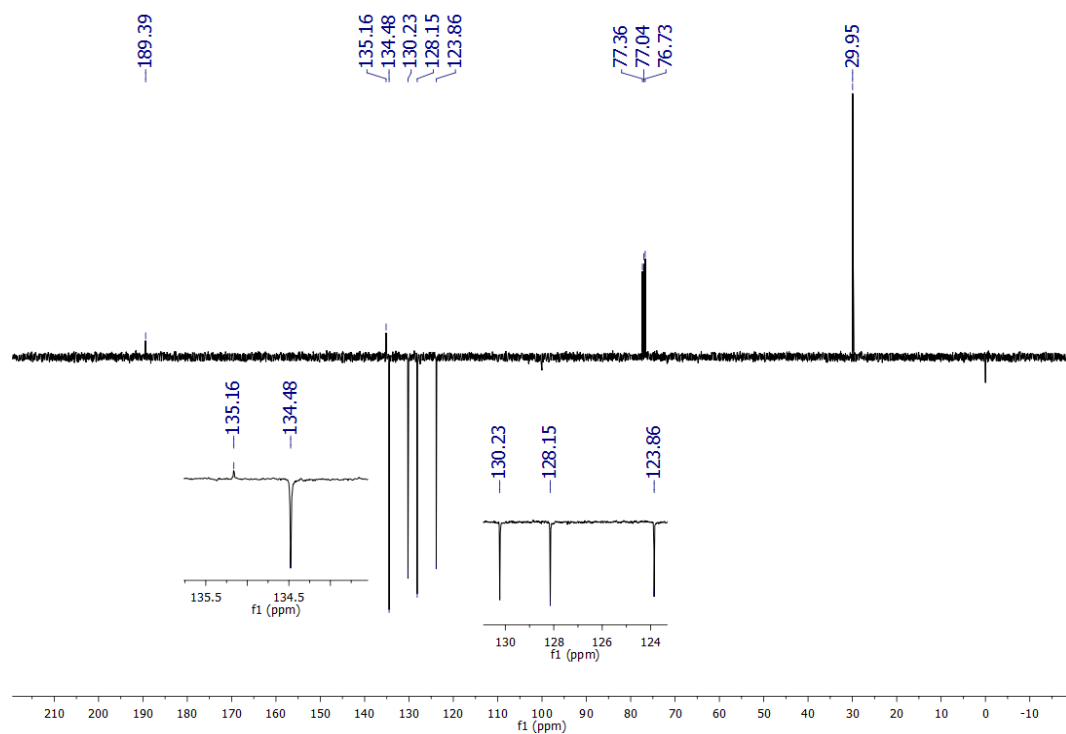


Figure S42. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **14d**.

2-Amino-4-arylthiazoles (**15a-15d**)

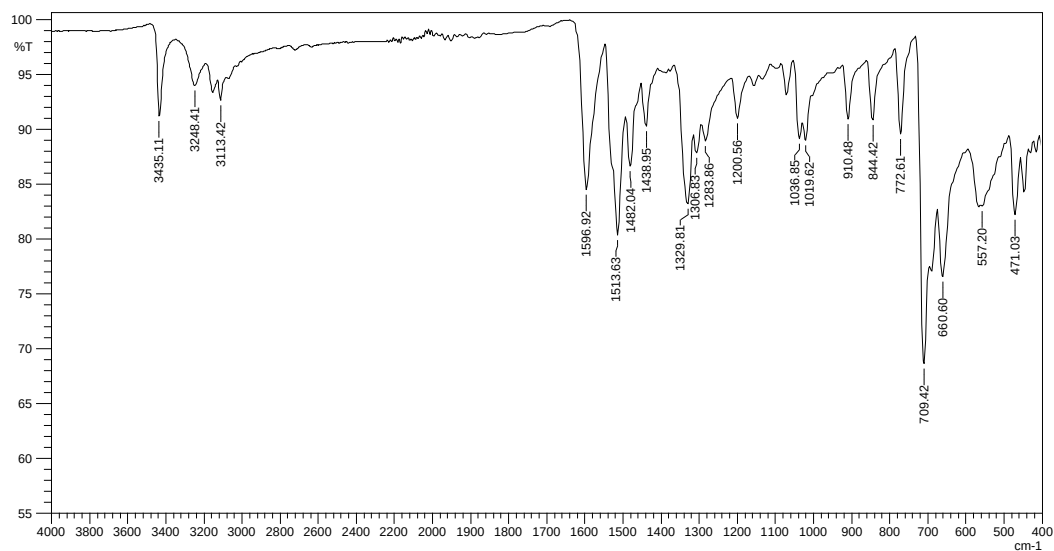


Figure S43. Infrared spectrum (KBr) of compound **15a**.

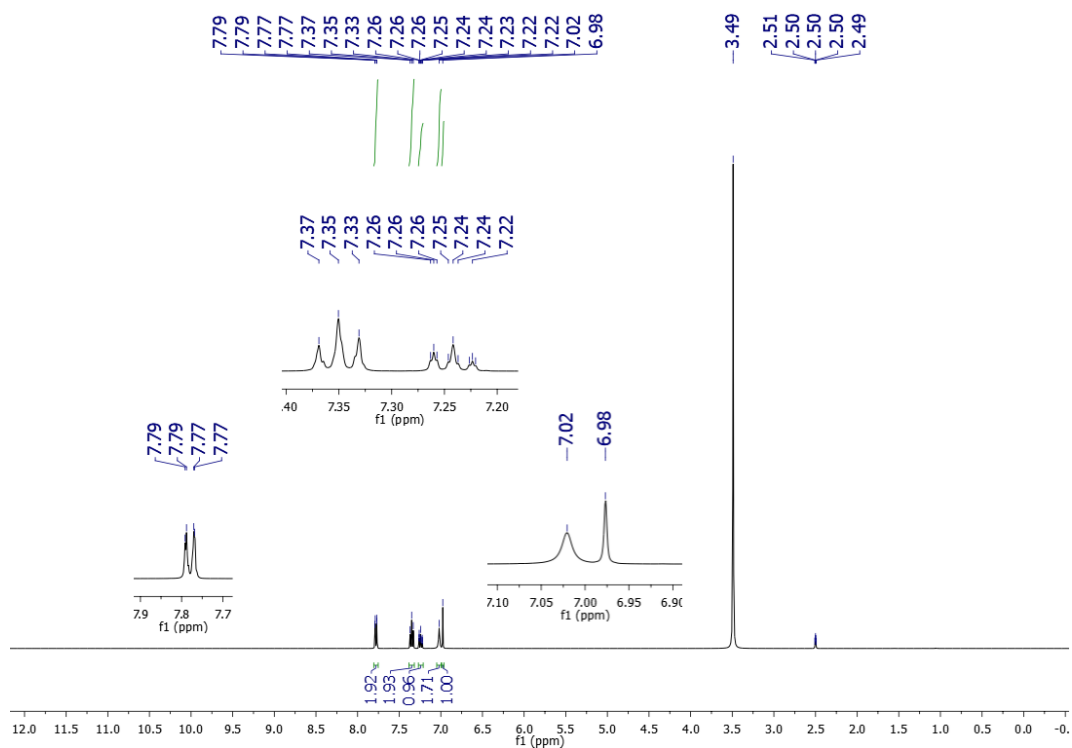


Figure S44. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **15a**.

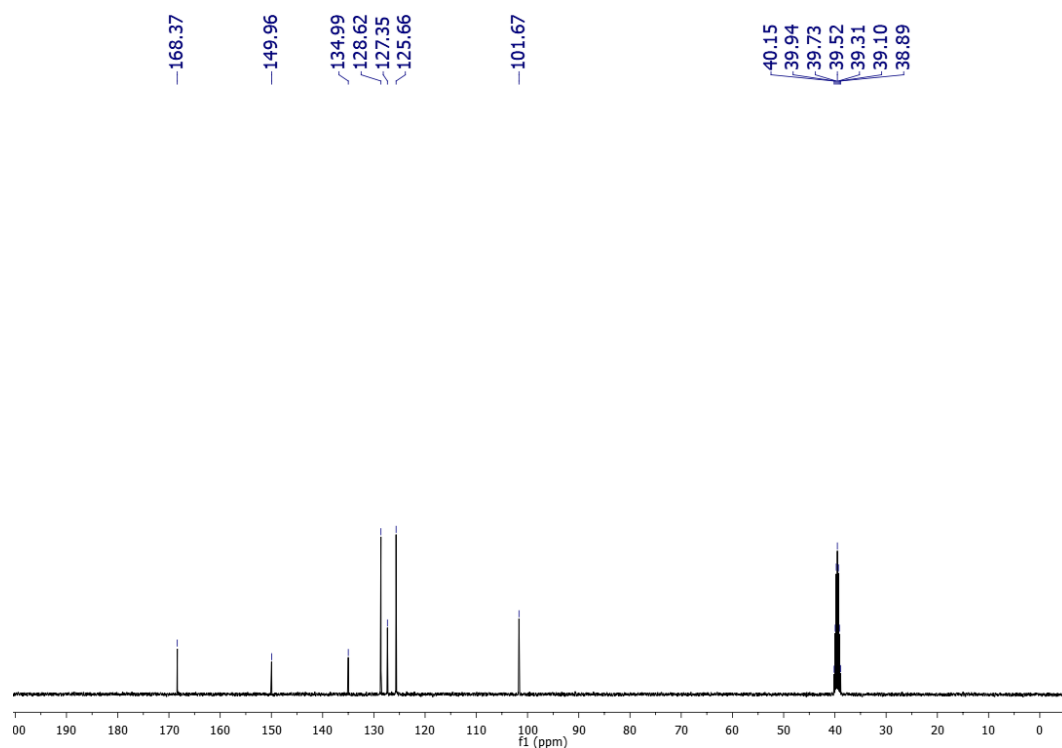


Figure S45. ^{13}C NMR spectrum (100 MHz, $\text{DMSO}-d_6$) of compound **15a**.

4-(*p*-Tolyl)thiazol-2-amine (**15b**)

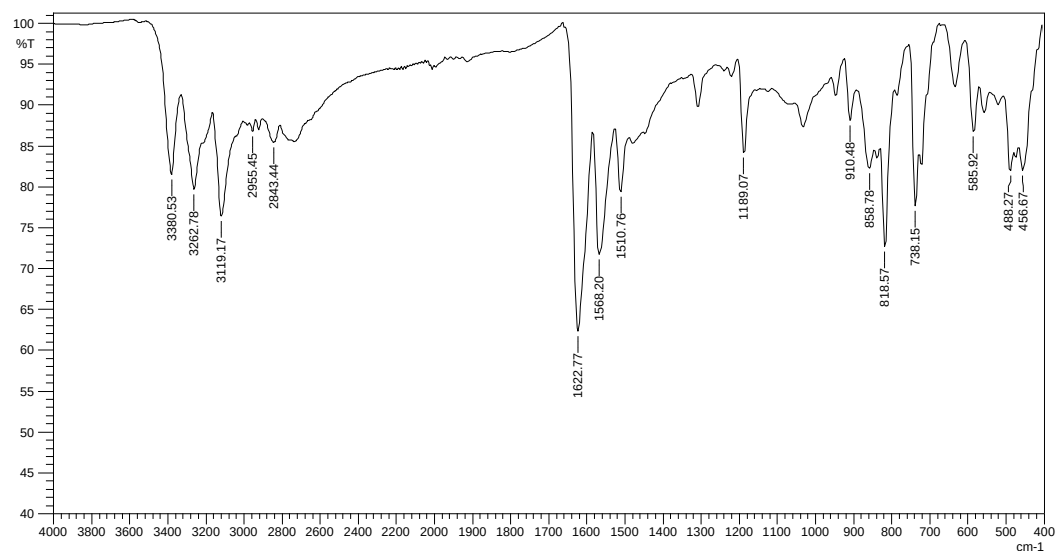


Figure S46. Infrared spectrum (KBr) of compound **15b**.

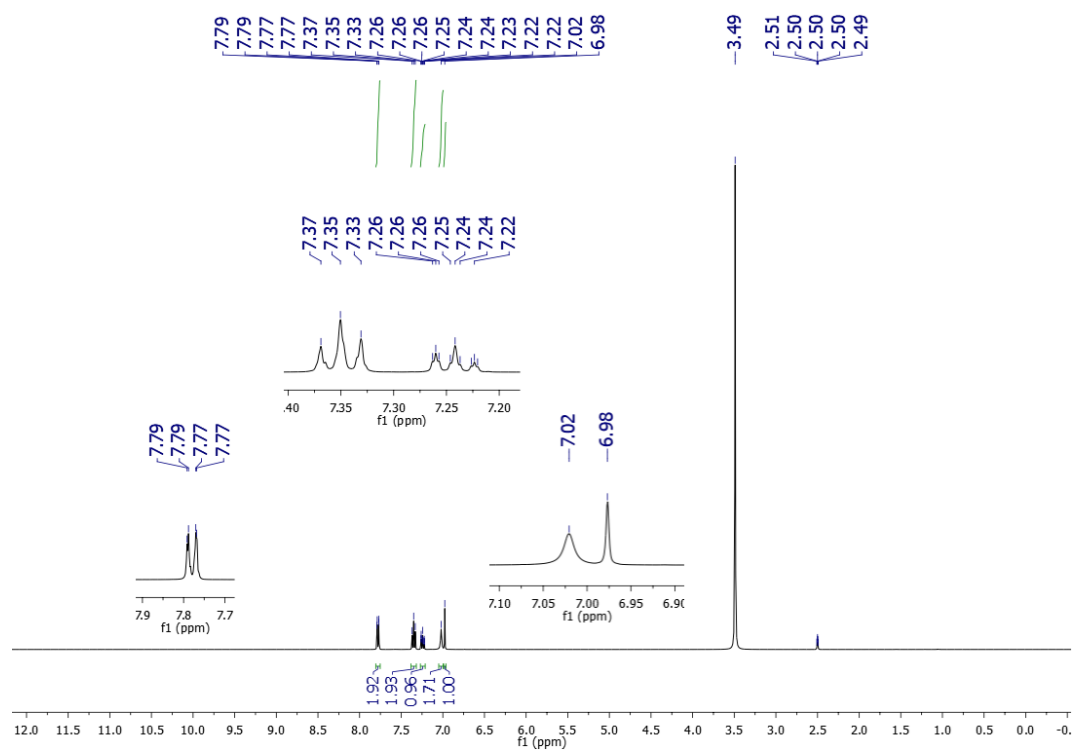


Figure S47. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **15b**.

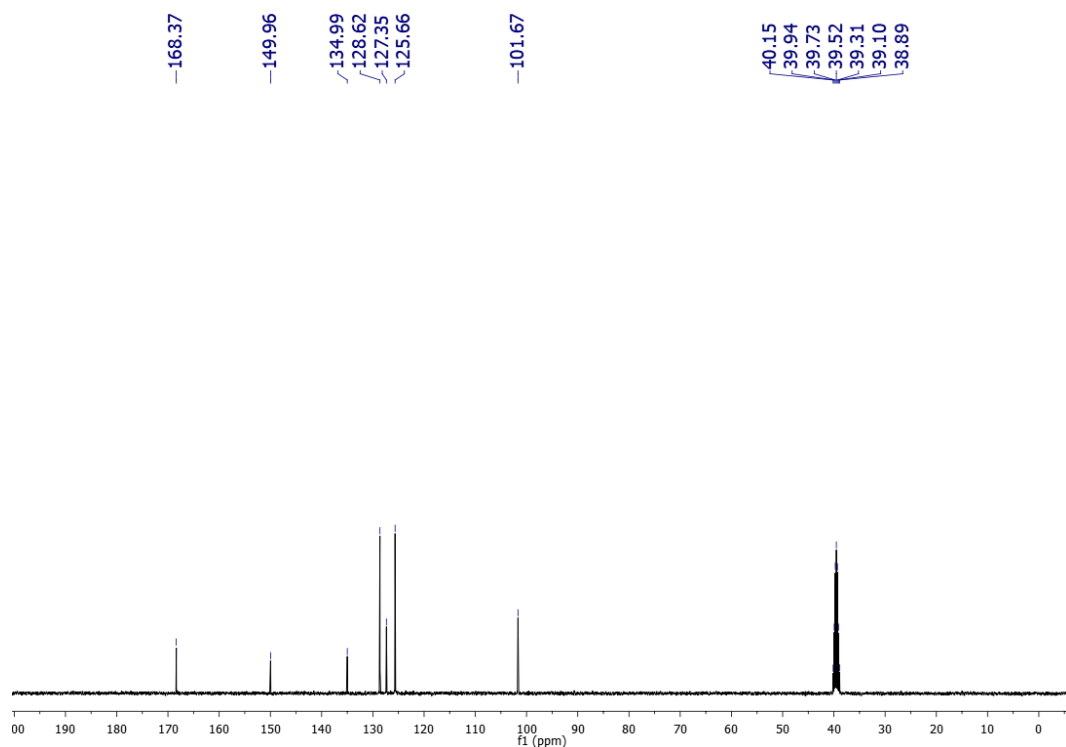


Figure S48. ¹³C NMR spectrum (100 MHz, DMSO-*d*₆) of compound **15b**.

4-(4-Bromophenyl)thiazol-2-amine (**15c**)

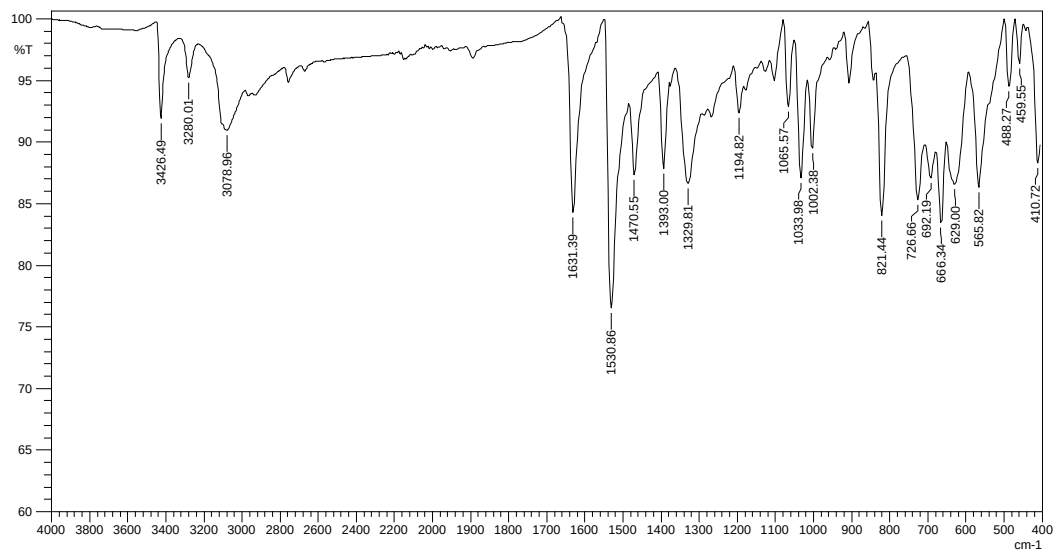


Figure S49. Infrared spectrum (KBr) of compound **15c**.

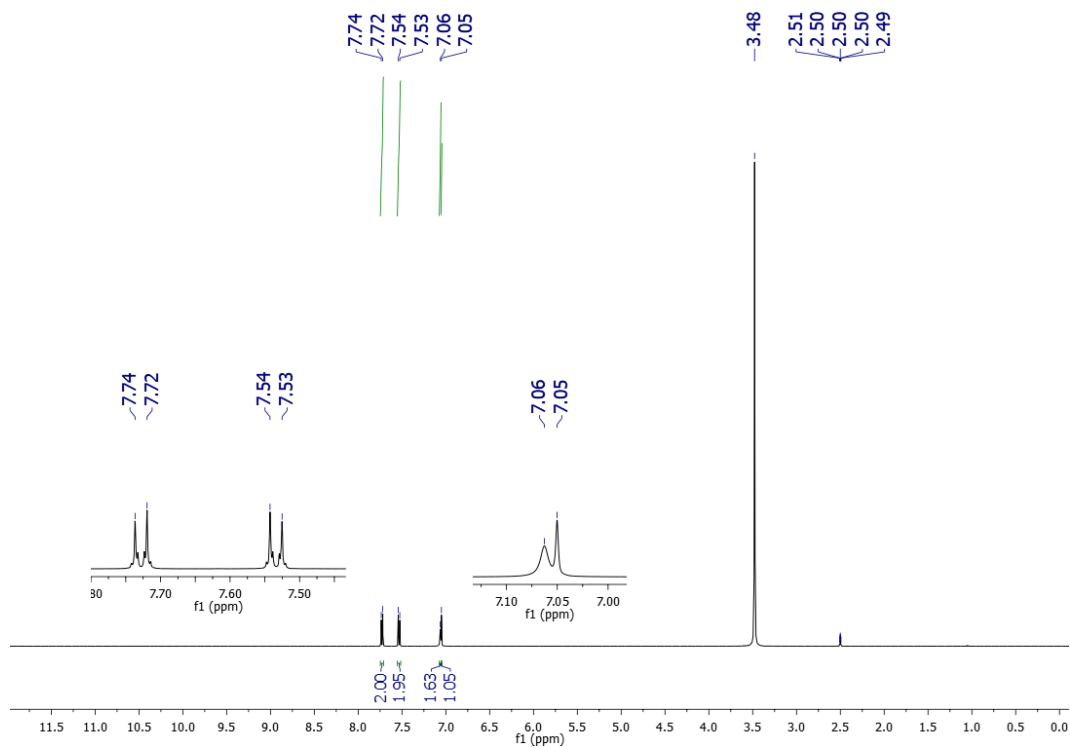


Figure S50. ¹H NMR spectrum (500 MHz, DMSO-*d*₆) of compound **15c**.

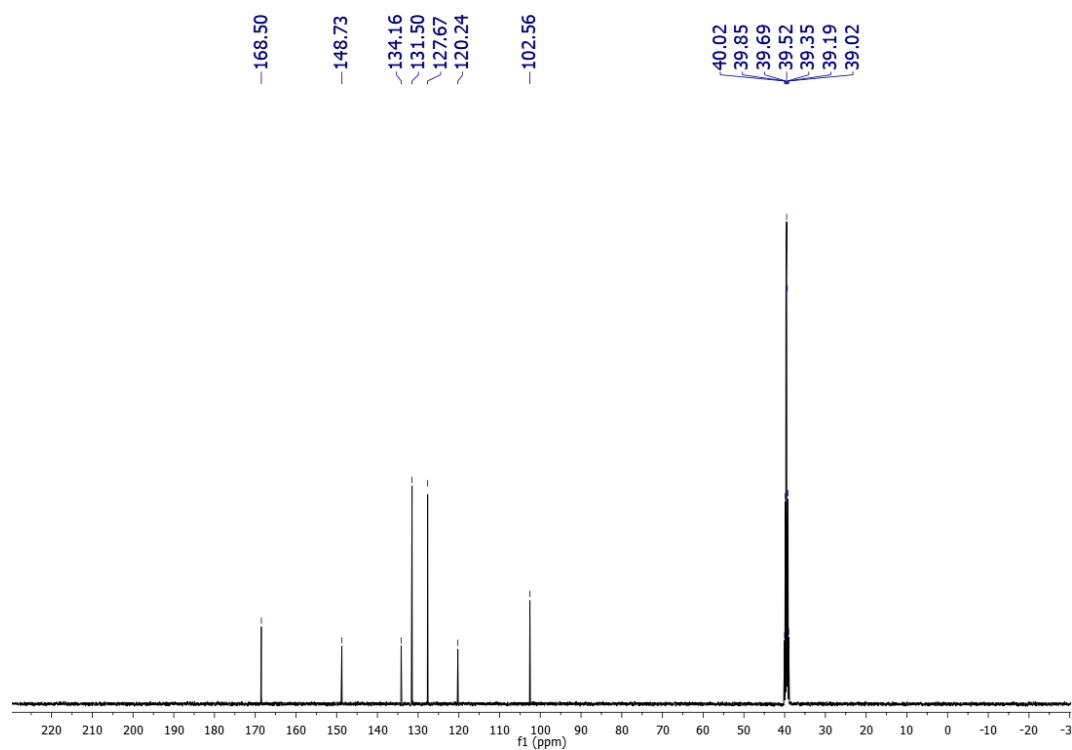


Figure S51. ^{13}C NMR spectrum (125 MHz, $\text{DMSO}-d_6$) of compound **15c**.

4-(3-Nitrophenyl)thiazol-2-amine (15d**)**

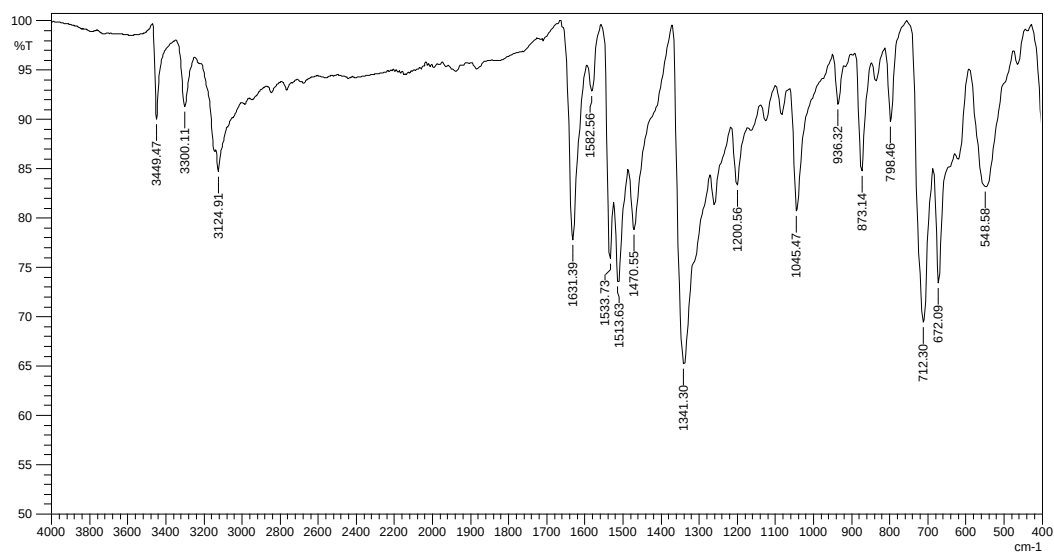


Figure S52. Infrared spectrum (KBr) of compound **15d**.

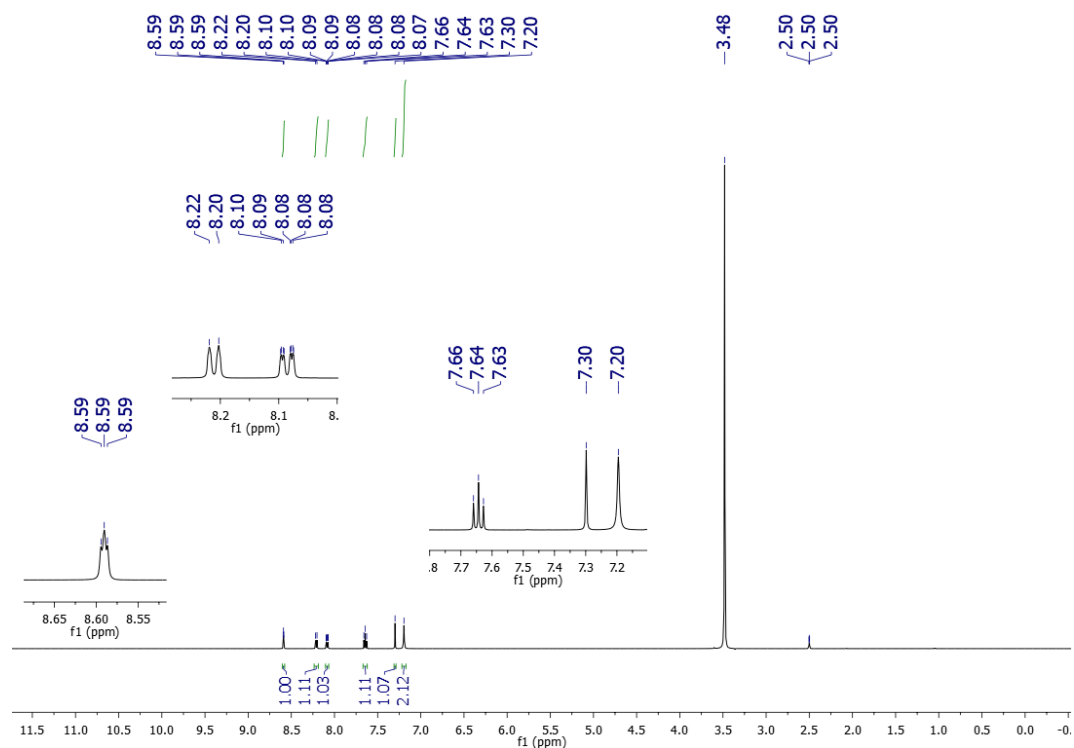


Figure S53. ¹H NMR spectrum (500 MHz, DMSO-*d*₆) of compound **15d**.

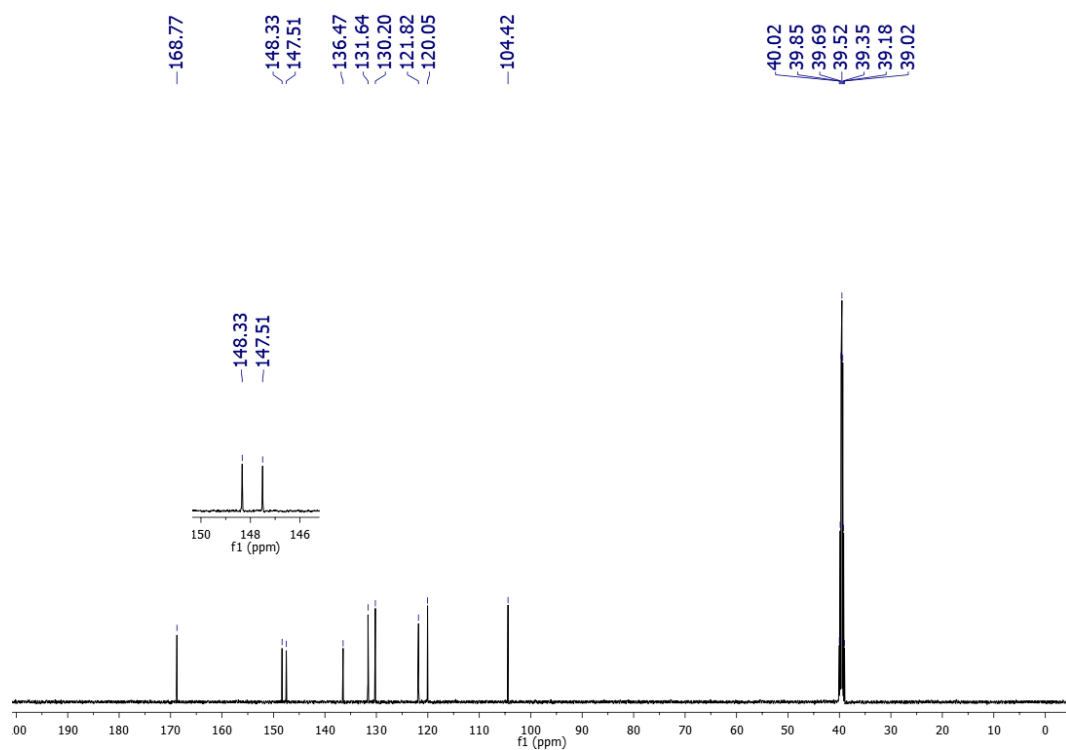


Figure S54. ¹³C NMR spectrum (125 MHz, DMSO-*d*₆) of compound **15d**.

N-(Arylthiazol-2-yl)-2-chloroacetamides (**16a-16d**)

2-Chloro-*N*-(4-phenylthiazol-2-yl)acetamide (**16a**)

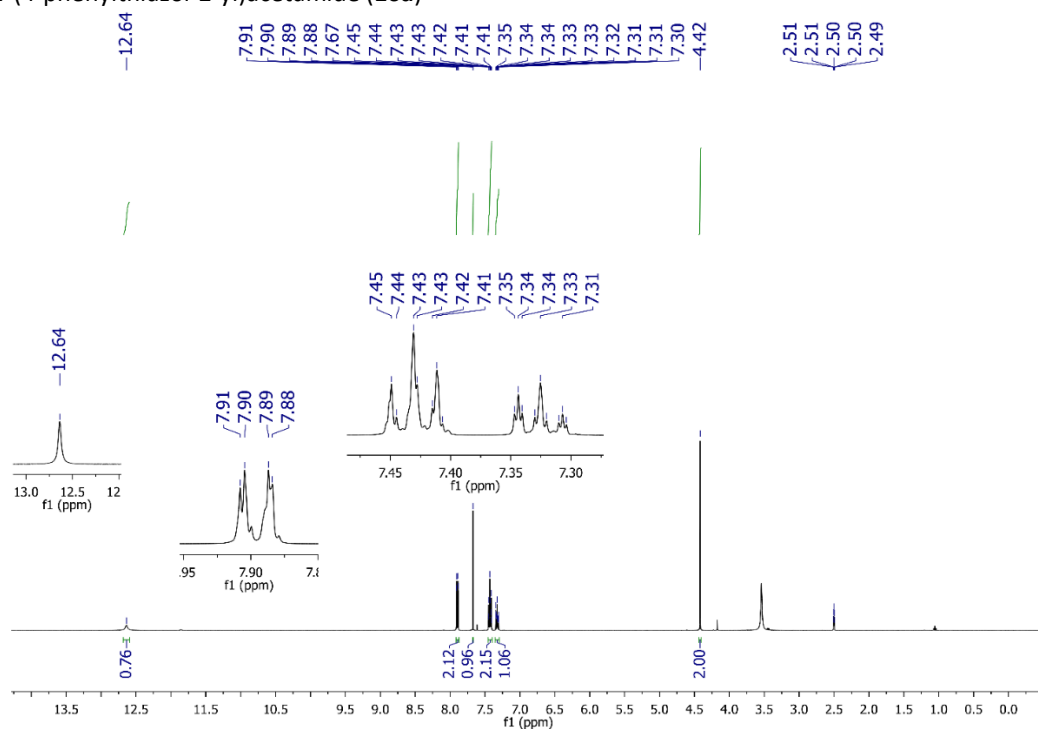


Figure S55. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **16a**.

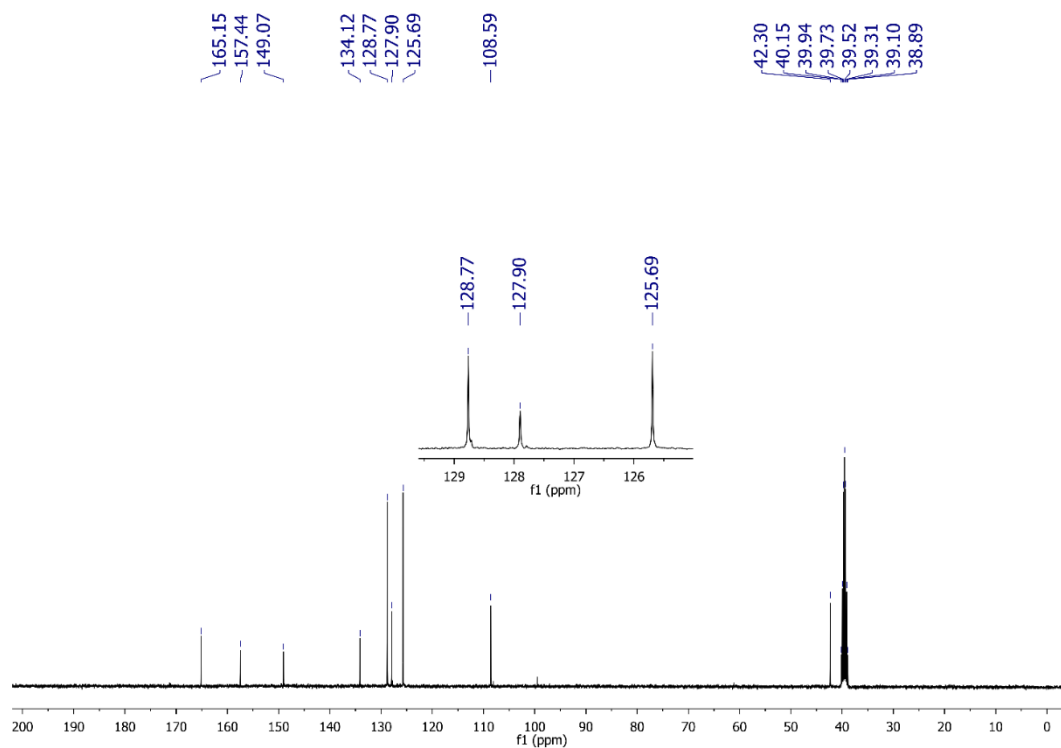


Figure S56. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **16a**.

2-Chloro-*N*-(4-(*p*-tolyl)thiazol-2-yl)acetamide (**16b**)

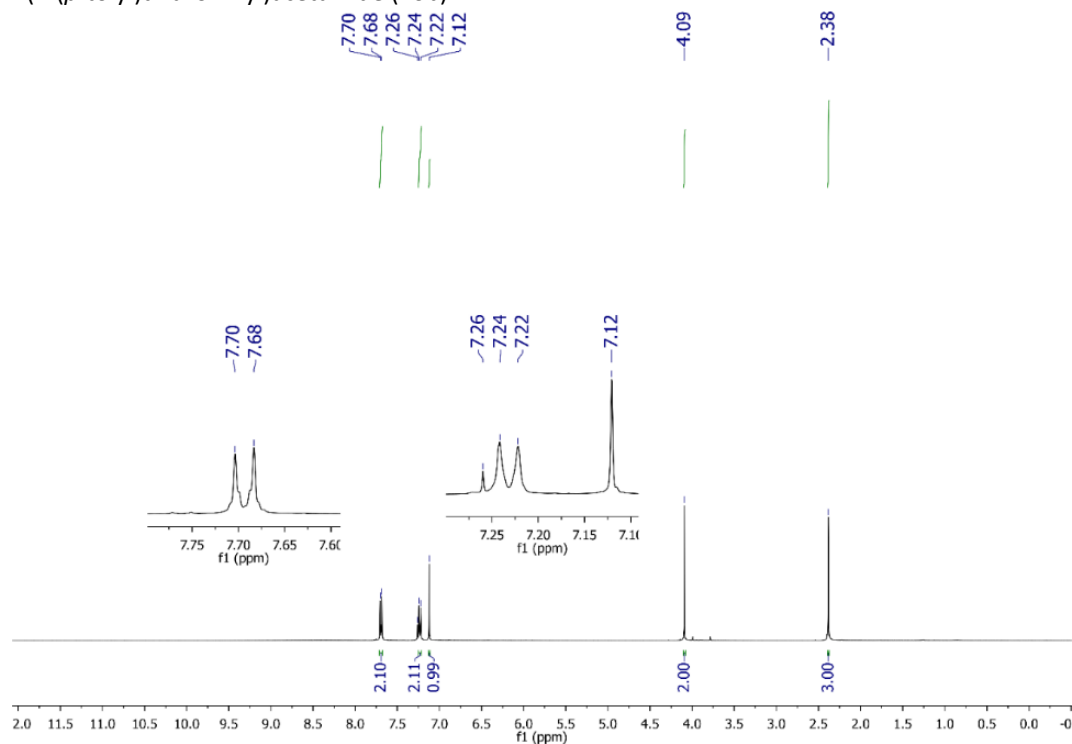


Figure S57. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **16b**.

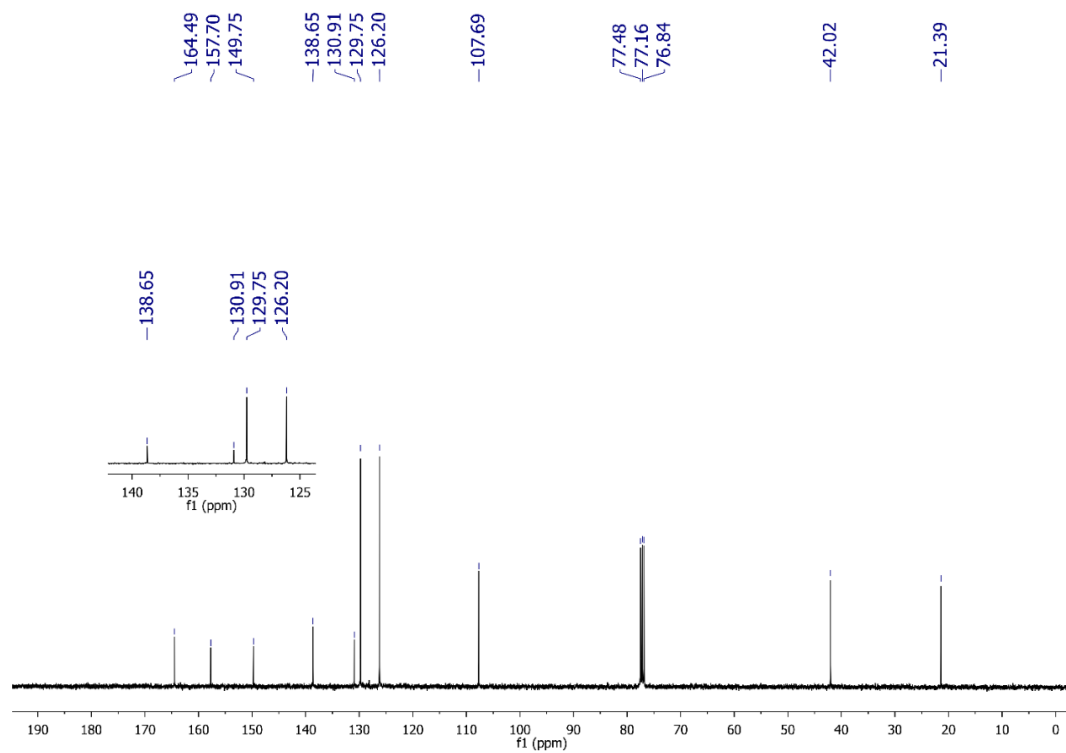


Figure S58. ¹³C NMR spectrum (101 MHz, CDCl₃) of the compound **16b**.

N-(4-(4-Bromophenyl)thiazol-2-yl)-2-chloroacetamide (**16c**)

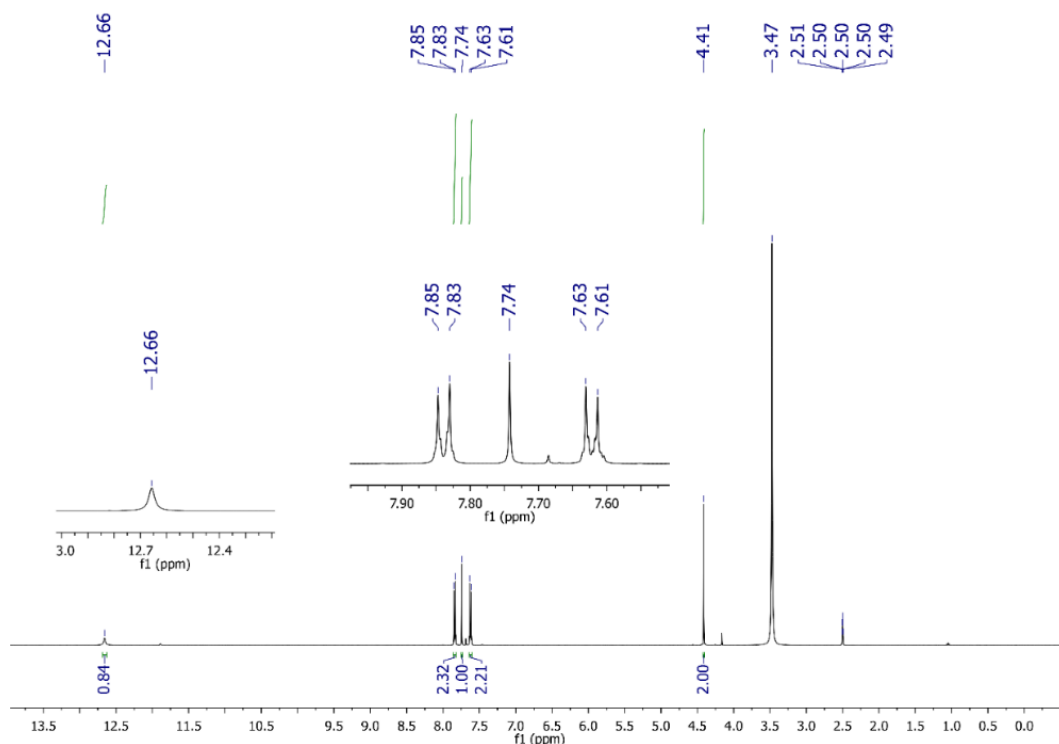


Figure S59. ¹H NMR spectrum (500 MHz, DMSO-*d*₆) of compound **16c**.

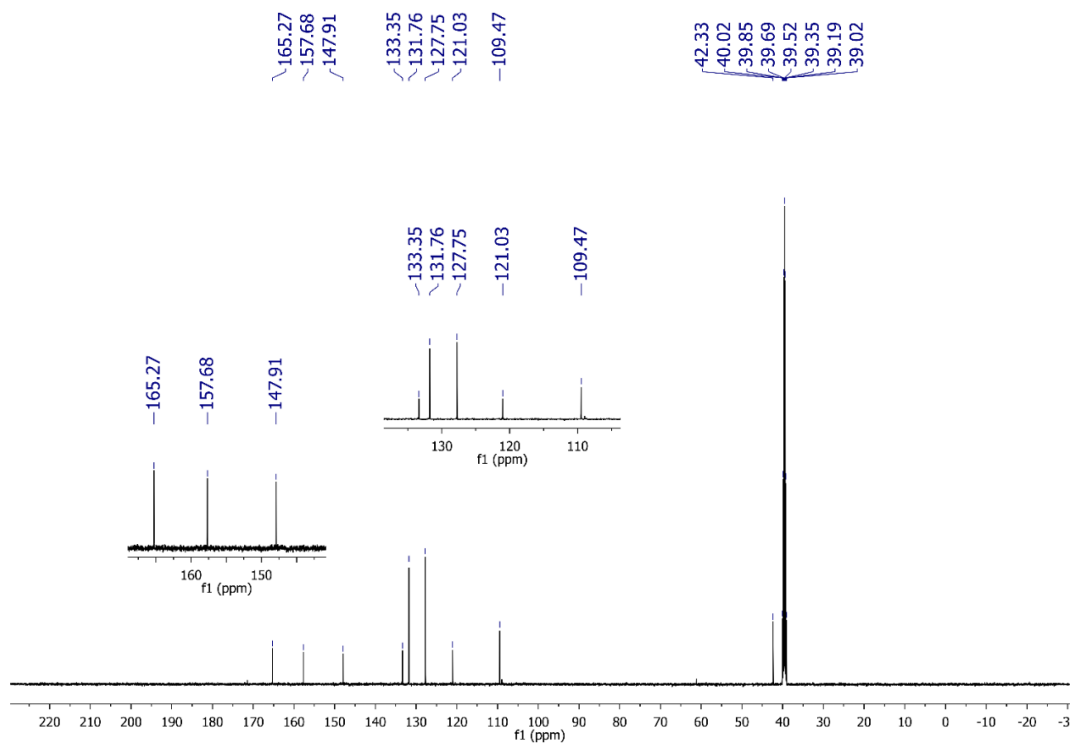


Figure S60. ¹³C NMR spectrum (126 MHz, DMSO-*d*₆) of the compound **16c**.

2-Chloro-*N*-(4-(3-nitrophenyl)thiazol-2-yl)acetamide (**16d**)

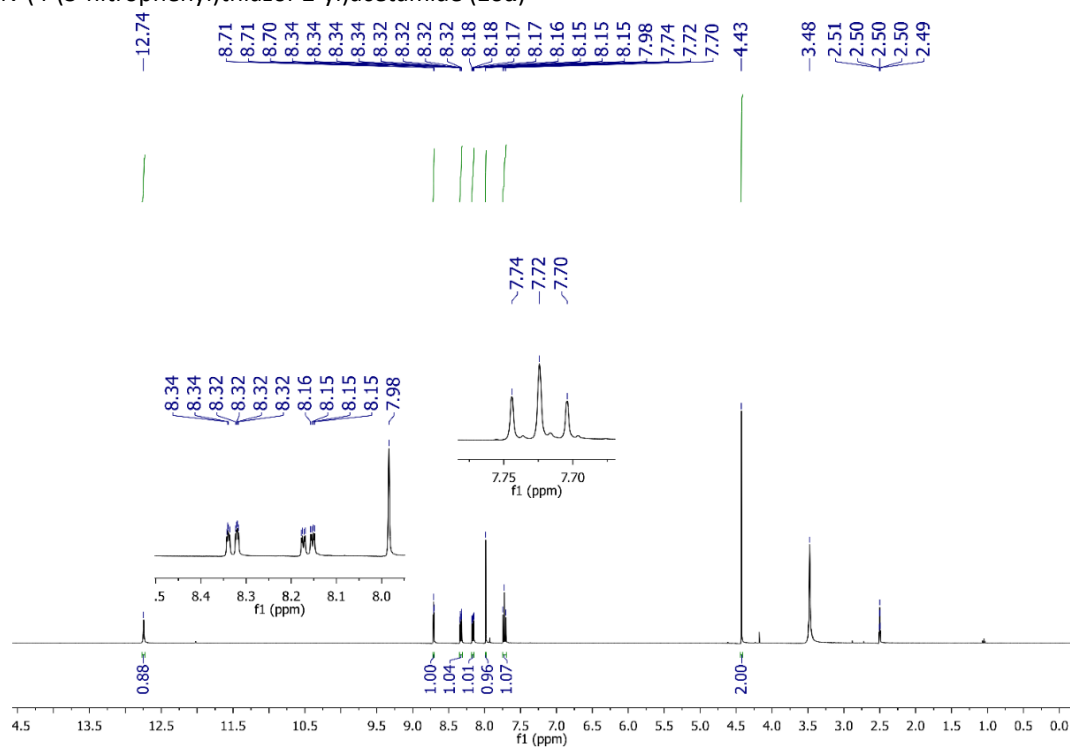


Figure S61. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **16d**.

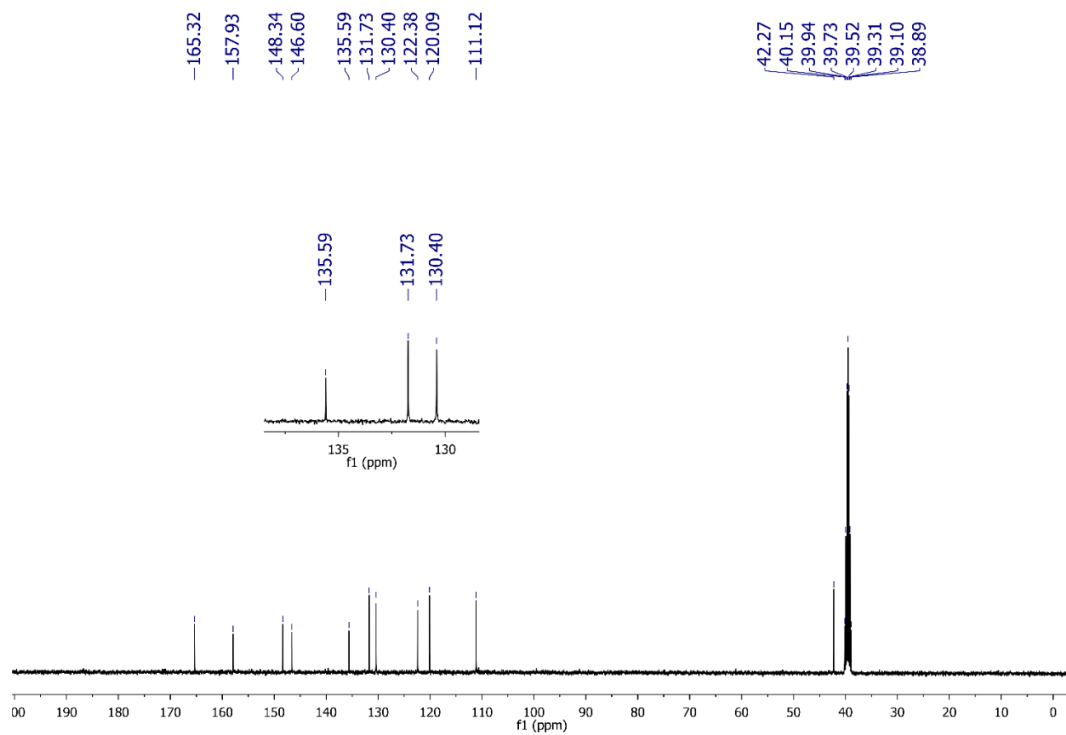


Figure S62. ¹³C NMR spectrum (126 MHz, DMSO-*d*₆) of the compound **16d**.

Final compounds

2-oxo-2-((4-Phenylthiazol-2-yl)amino) piperate (**17a**)

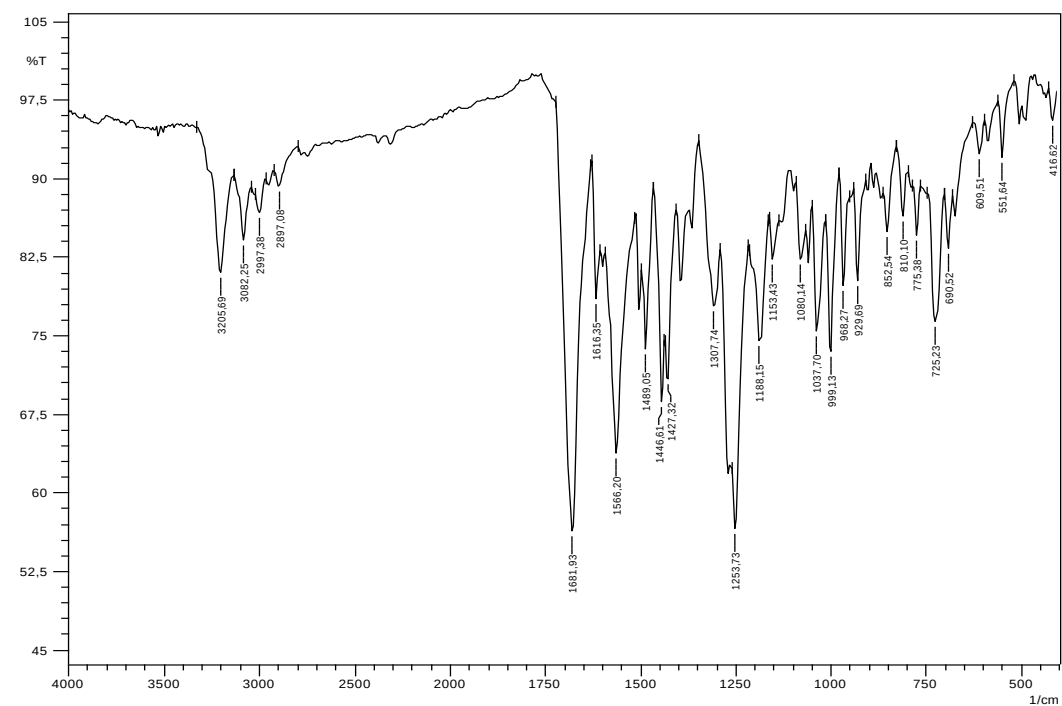


Figure S63. Infrared spectrum (KBr) of compound **17a**.

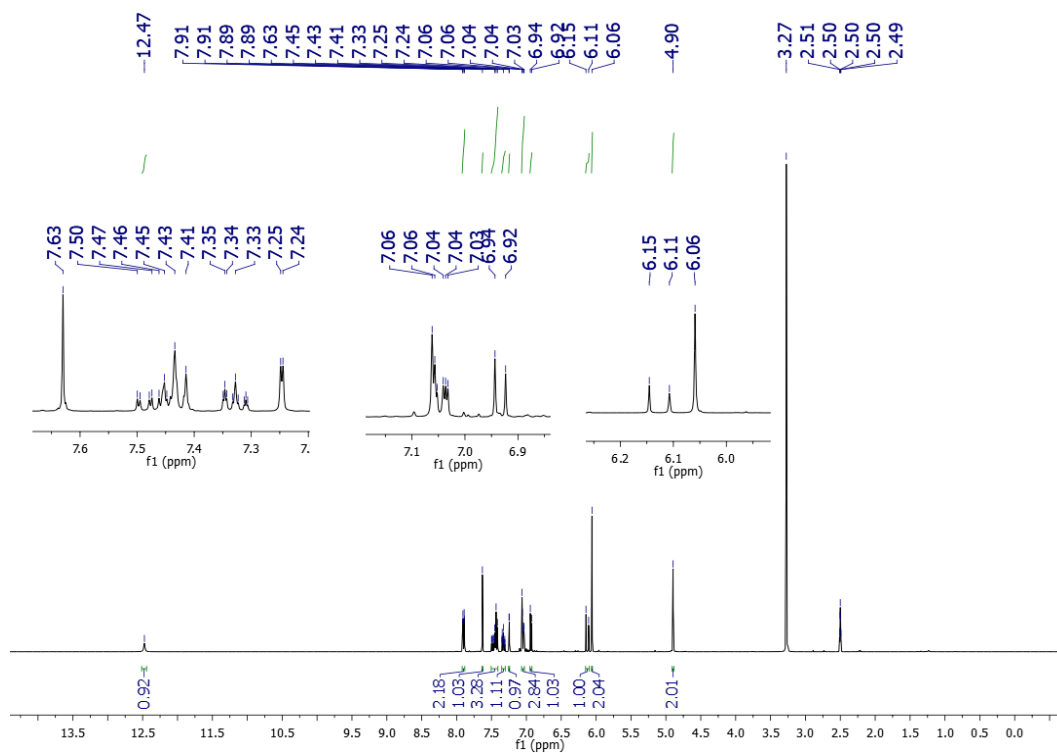


Figure S64. ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of compound **17a**.

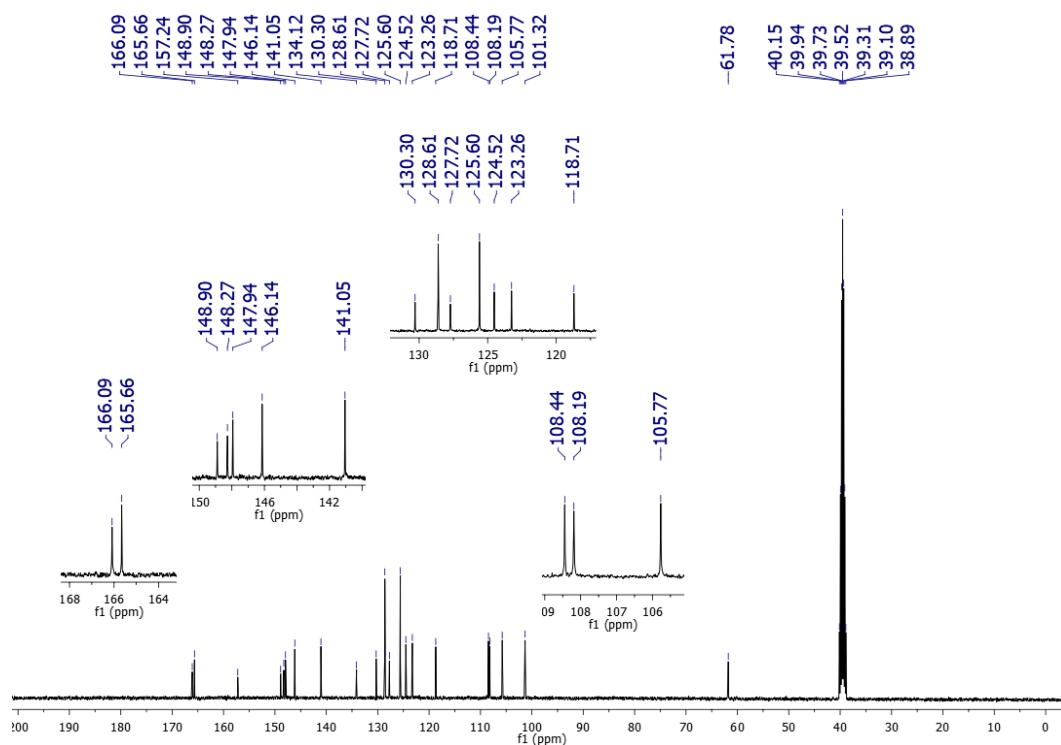


Figure S65. ^{13}C NMR spectrum (100 MHz, $\text{DMSO}-d_6$) of compound **17a**.



Formula Predictor Result		C23 H18 N2 O5 S	
Mass	435.09986		
Error Margin	10 ppm		
DBE Range	Not Used		
Electron Ions	Both configurations		
HC Ratio	0 - 3		
Nitrogen Rule	Not Used		

Score	Pred. (M)	Pred. m/z	Meas. m/z	Diff. (mDa)	Formulae (M)	Ion	Diff. (ppm)	Iso Score	DBE
72.48	434.09364	435.10092	435.09986	-1.06	C23 H18 N2 O5 S	[M+H] ⁺	-2.436	70.99	16.0

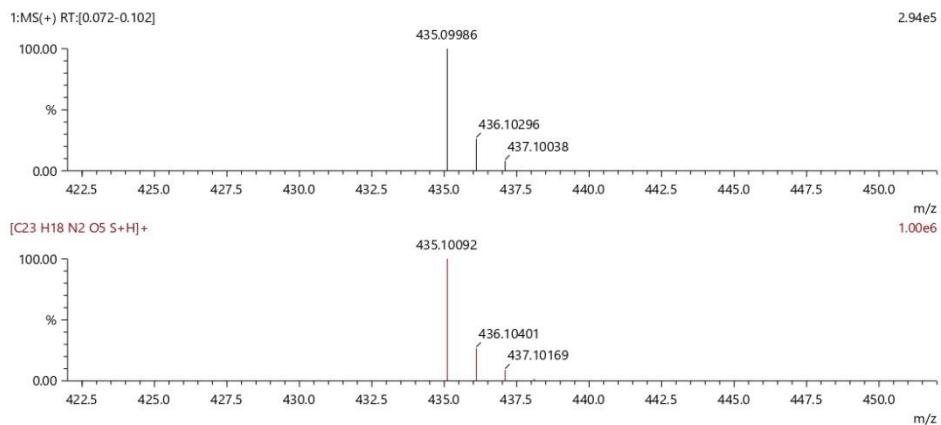


Figure S66. HRMS (ESI) spectrum of the compound **17a**.

2-oxo-2-((4-(*p*-Tolyl)thiazol-2-yl)amino)ethyl piperate (**17b**)

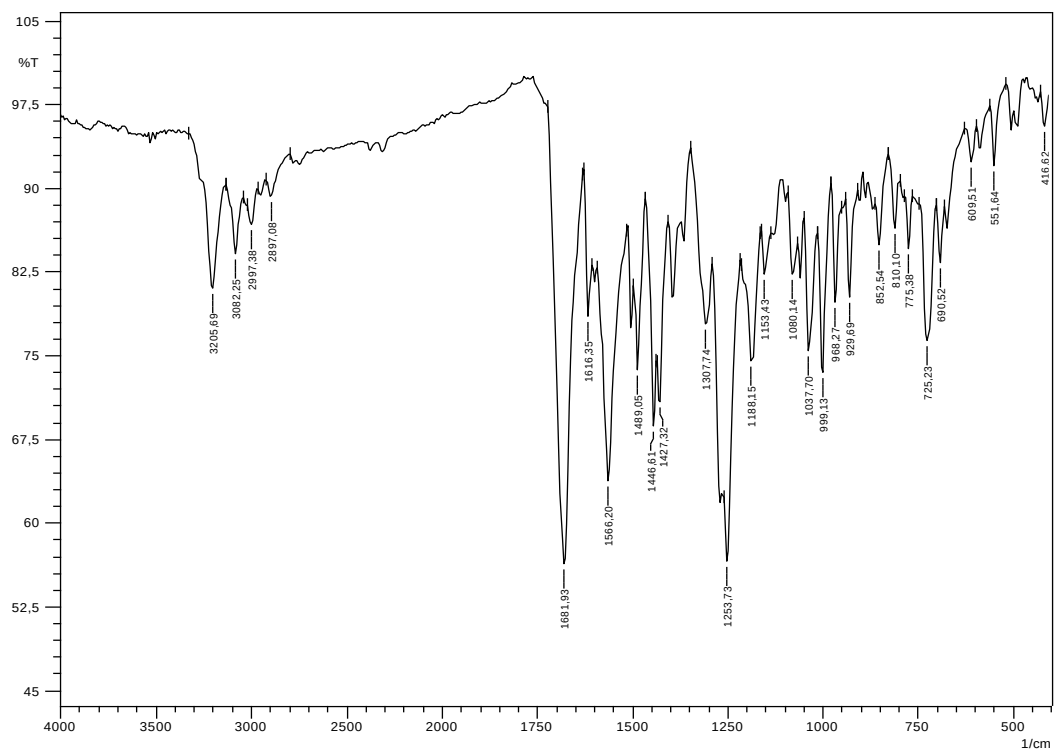


Figure S67. Infrared spectrum (KBr) of compound **17b**.

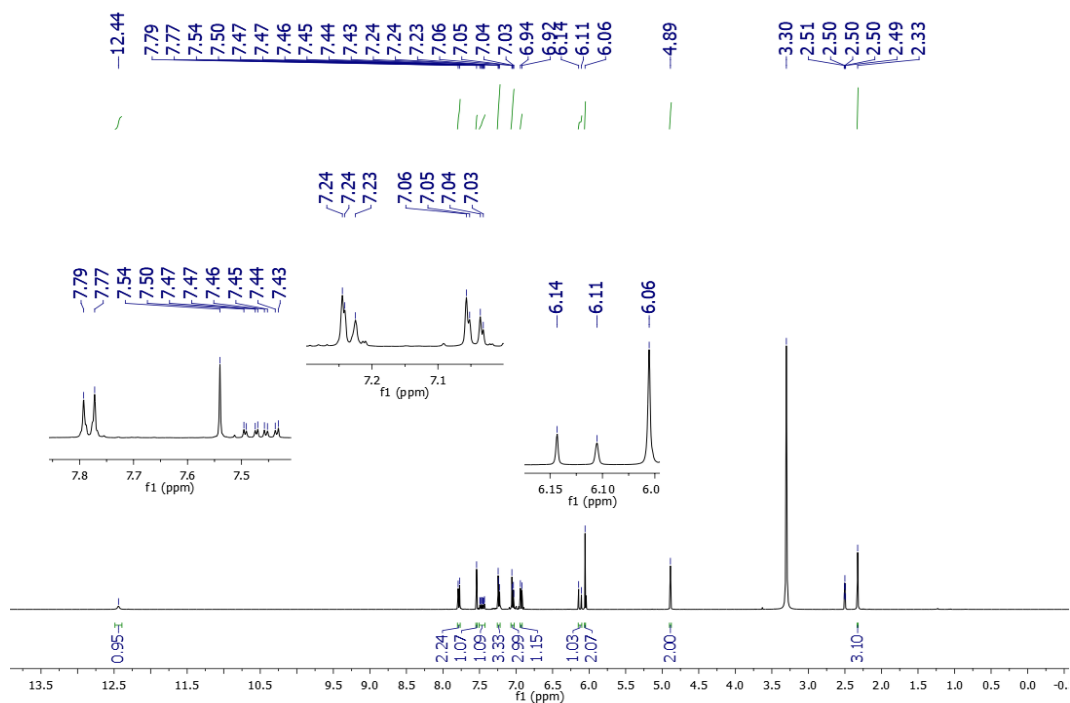


Figure S68. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **17b**.

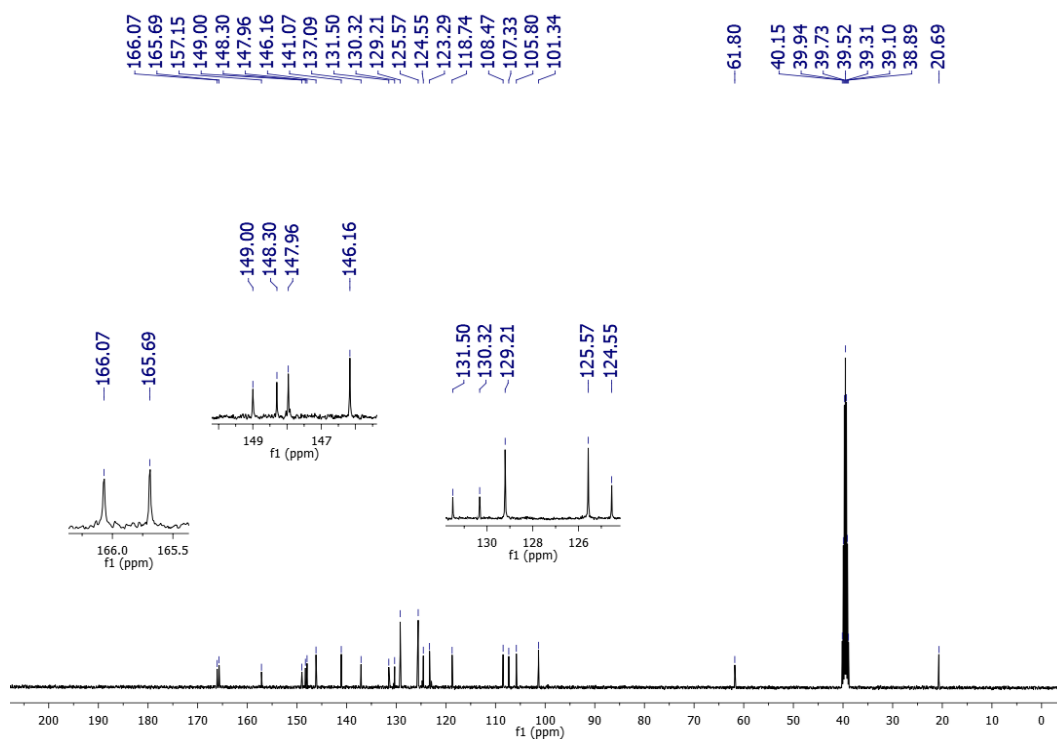


Figure S69. ^{13}C NMR spectrum (100 MHz, $\text{DMSO}-d_6$) of compound **17b**.

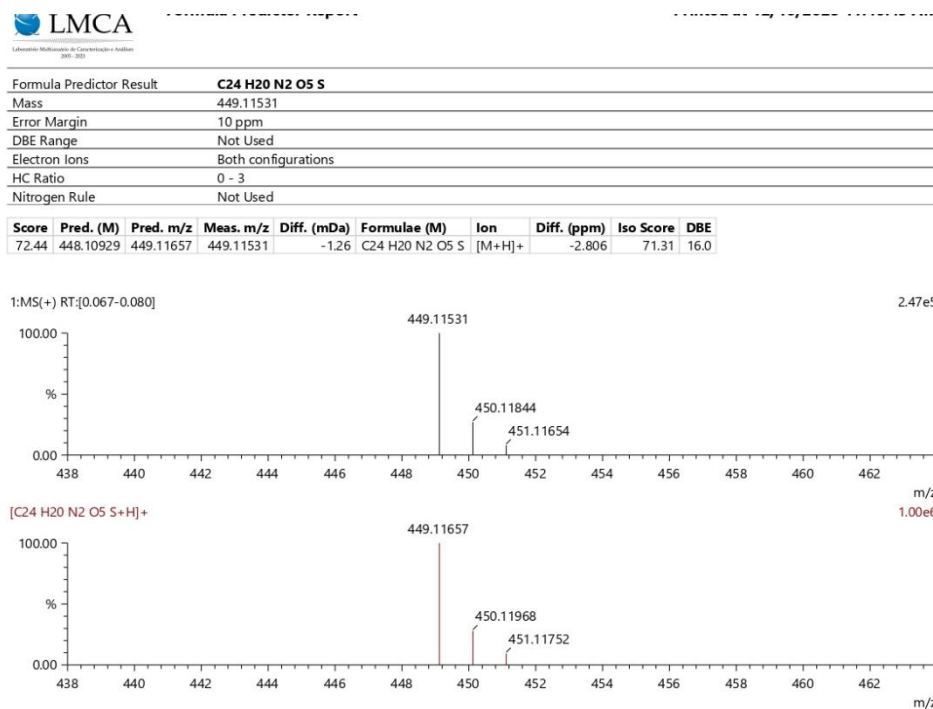


Figure S70. HRMS (ESI) spectrum of the compound **17b**.

2-((4-(4-Bromophenyl)thiazol-2-yl)amino)-2-oxoethyl piperate (**17c**)

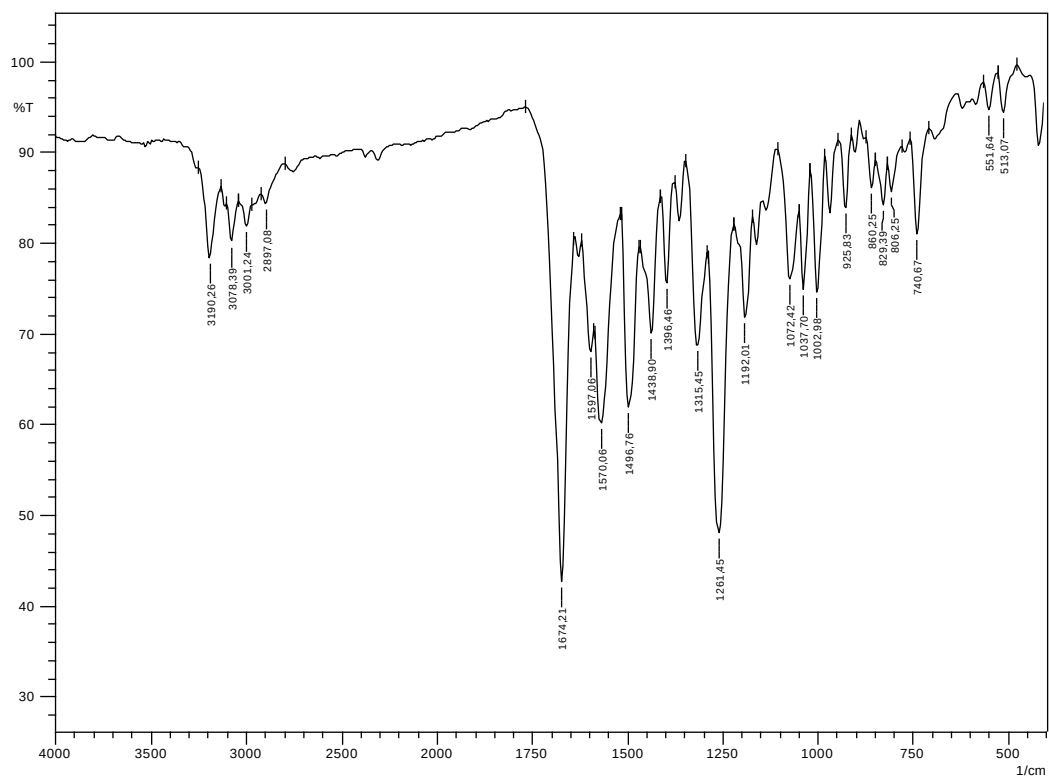


Figure S71. Infrared spectrum (KBr) of compound **17c**.

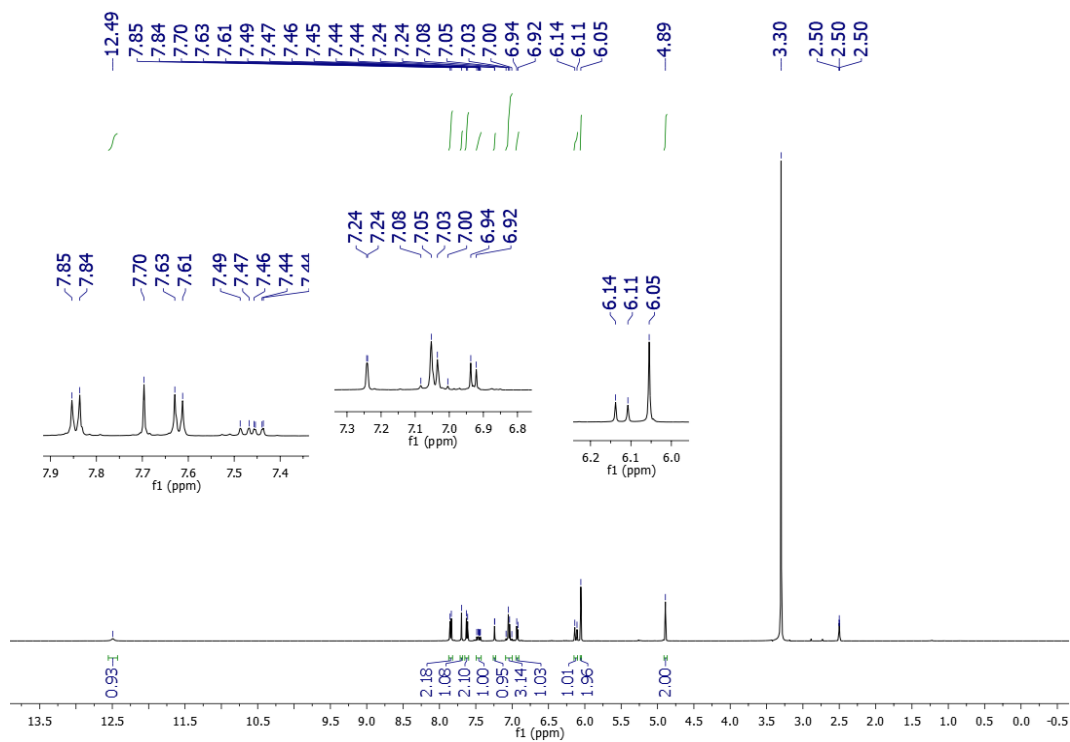


Figure S72. ¹H NMR spectrum (500 MHz, DMSO-*d*₆) of compound **17c**.

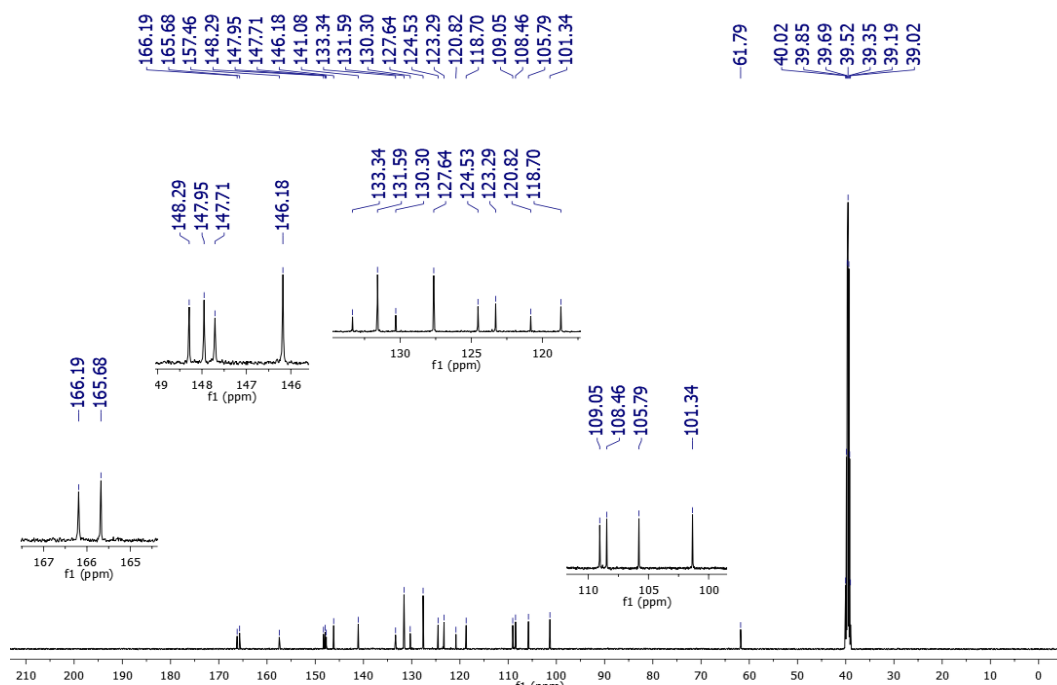


Figure S73. ^{13}C NMR spectrum (125 MHz, $\text{DMSO-}d_6$) of compound **17c**.

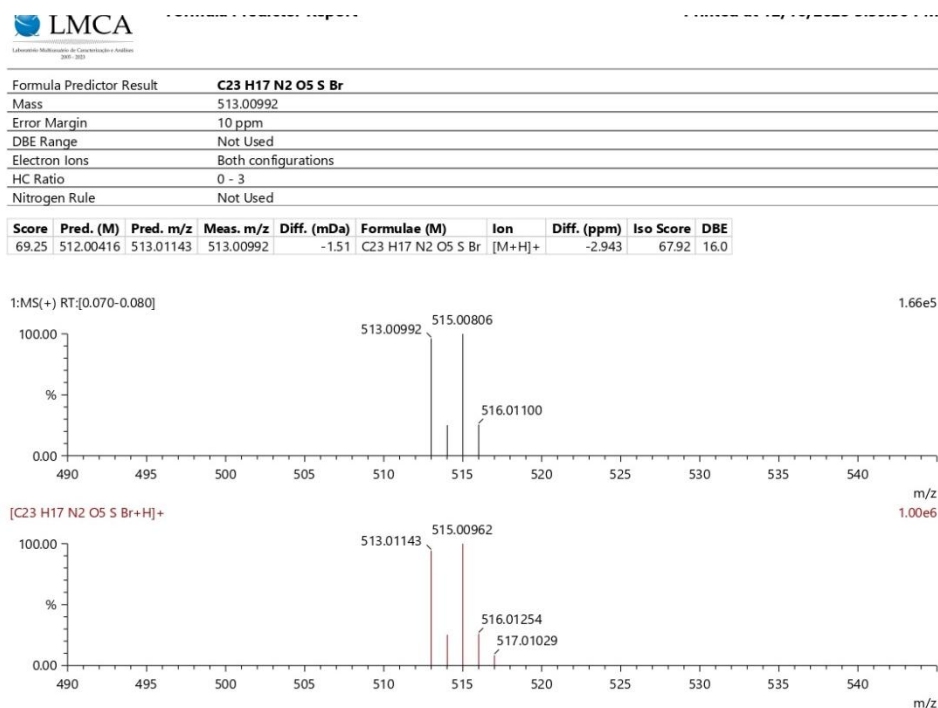


Figure S74. HRMS (ESI) spectrum of the compound **17c**.

2-((4-(3-Nitrophenyl)thiazol-2-yl)amino)-2-oxoethyl piperate (**17d**)

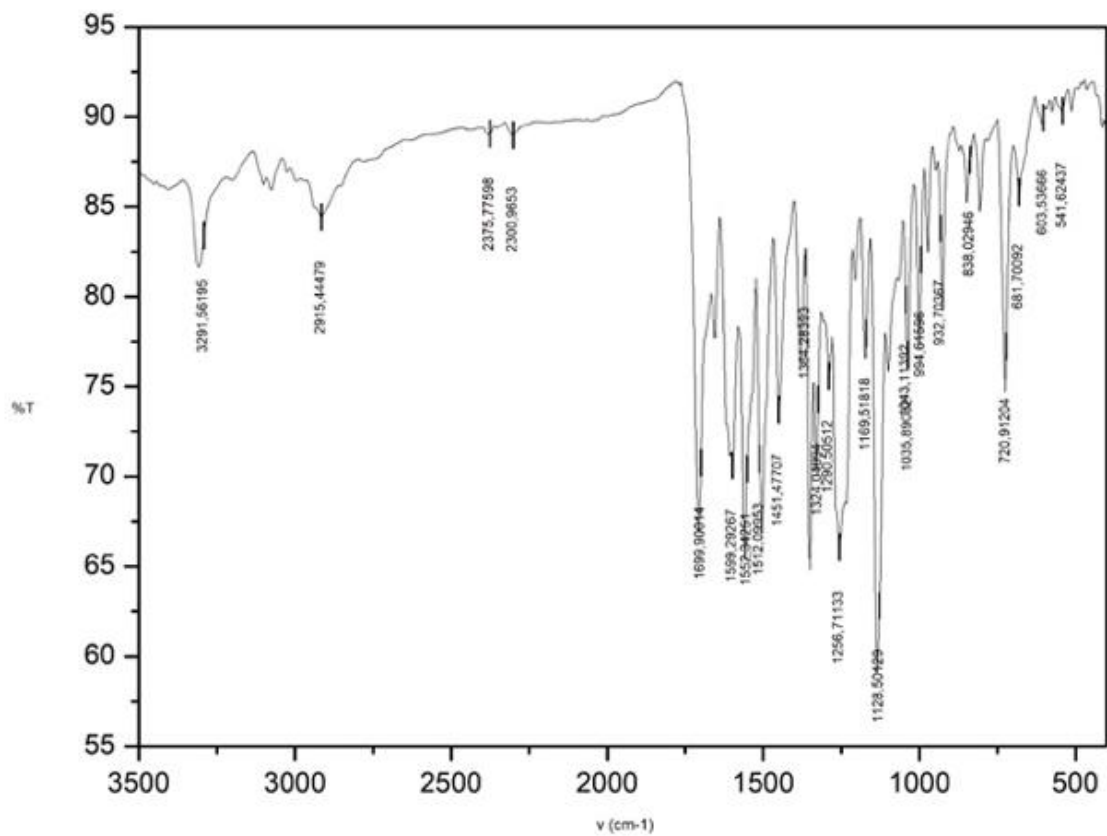


Figure S75. Infrared spectrum (KBr) of compound **17d**.

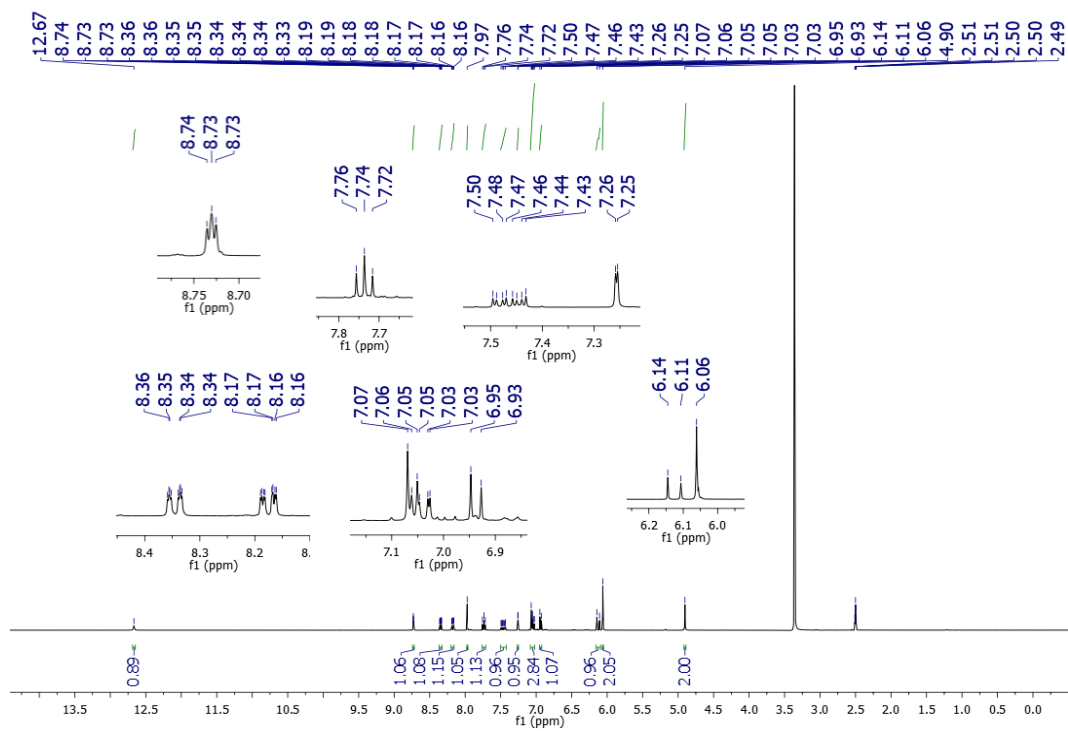


Figure S76. ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **17d**.

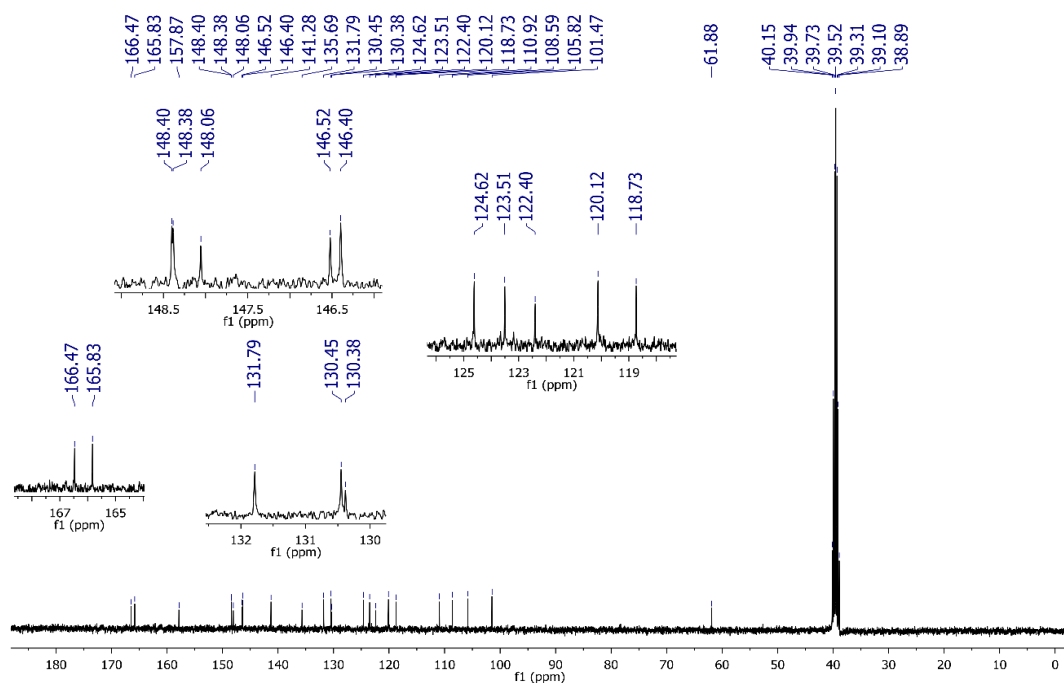


Figure S77. ^{13}C NMR spectrum (125 MHz, $\text{DMSO}-d_6$) of compound **17d**.

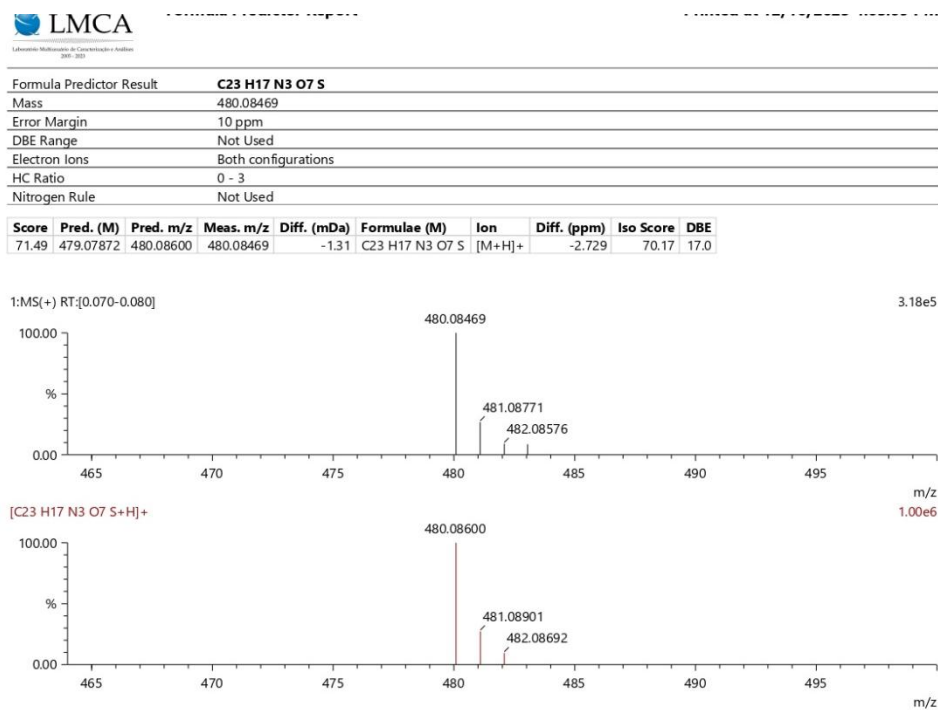


Figure S78. HRMS (ESI) spectrum of the compound **17d**.