

Supporting Information

Synthesis of Tetrasubstituted Phosphorus Analogs of Aspartic Acid as Antiproliferative Agents

Xabier del Corte [†], Aitor Maestro [†], Adrián López-Francés, Francisco Palacios and Javier Vicario ^{*}

Departamento de Química Orgánica I, Centro de Investigación y Estudios Avanzados "Lucio Lascaray", Facultad de Farmacia, University of the Basque Country, UPV/EHU Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain

^{*} Correspondence: javier.vicario@ehu.eus; Tel.: +34 945013891.

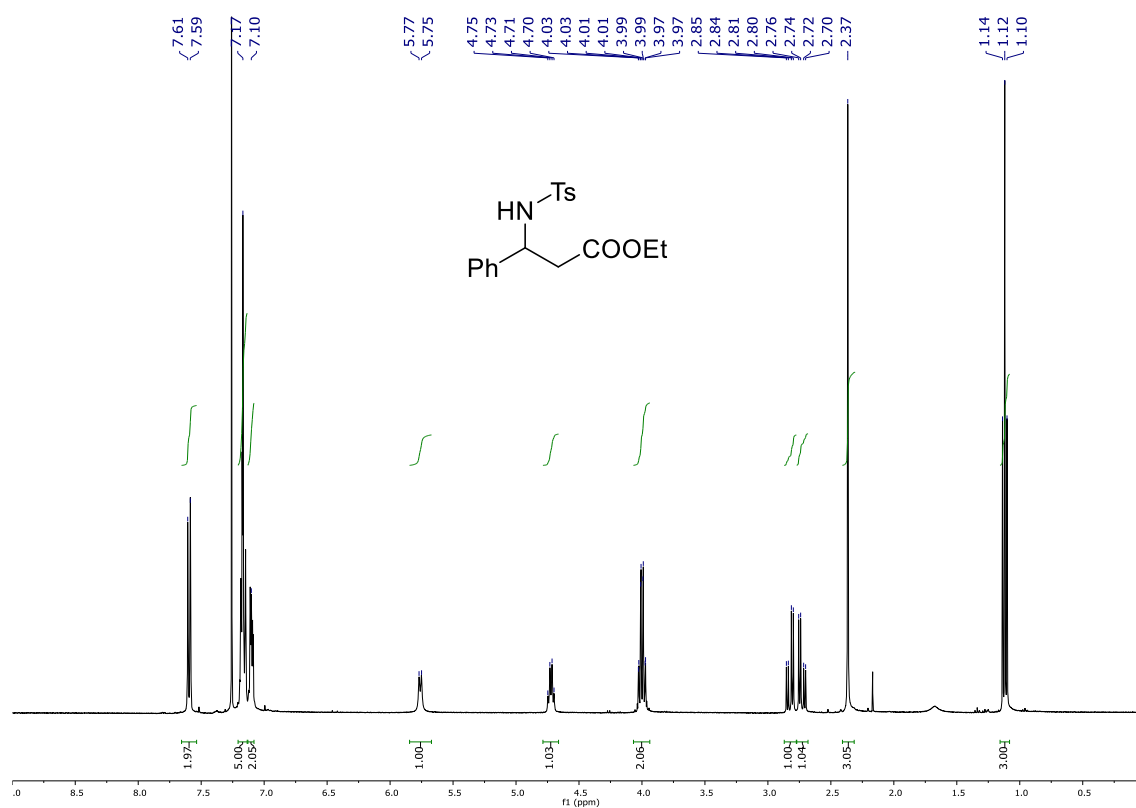
[†] These authors contributed equally to this work.

1. ¹ H NMR and ¹³ C NMR spectra of compounds 5 and 6	S2
2. ¹ H NMR, ¹³ C NMR, ³¹ P NMR and ¹⁹ F NMR spectra of compounds 7	S4
3. ¹ H NMR, ¹³ C NMR, ³¹ P NMR and ¹⁹ F NMR spectra of compounds 12 , 13 and 14	S42
4. ¹ H NMR, ¹³ C NMR and ³¹ P NMR spectra of compound 18	S50
5. 2D NMR spectra of compound 7a	S52

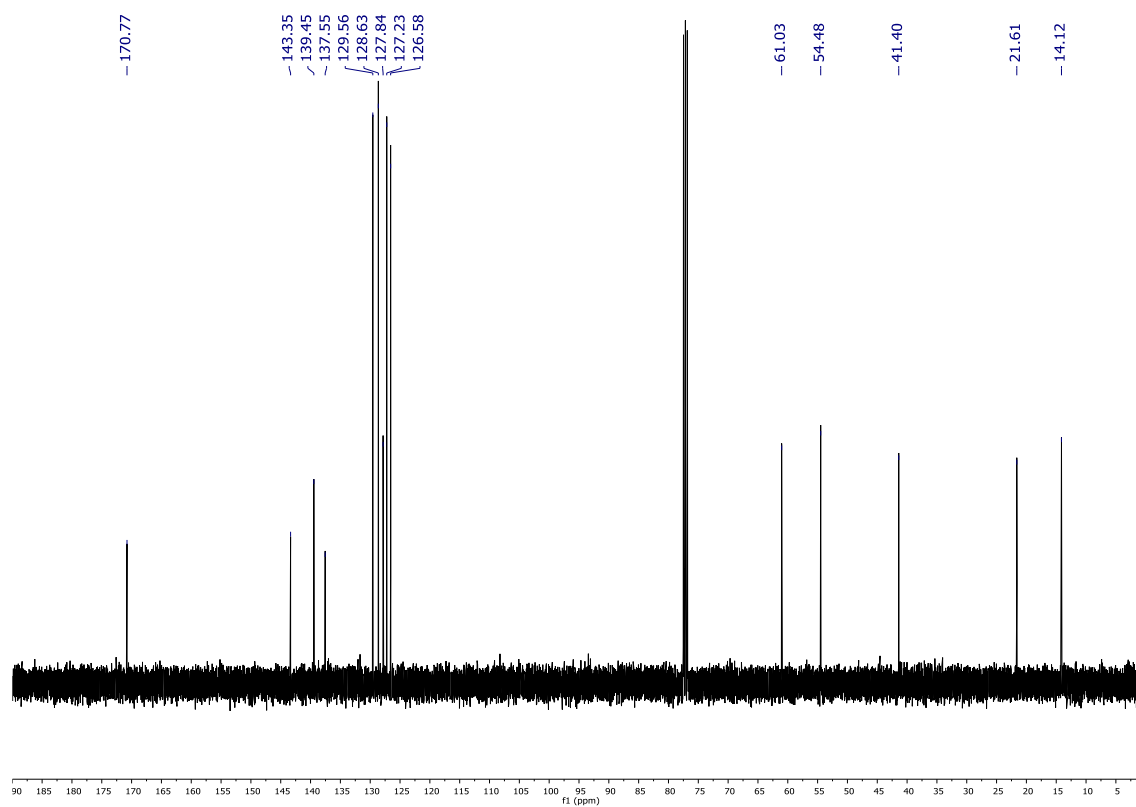
1. ^1H NMR and ^{13}C NMR spectra of compounds 5 and 6

Ethyl 3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate (5).

^1H NMR (400 MHz, CDCl_3)

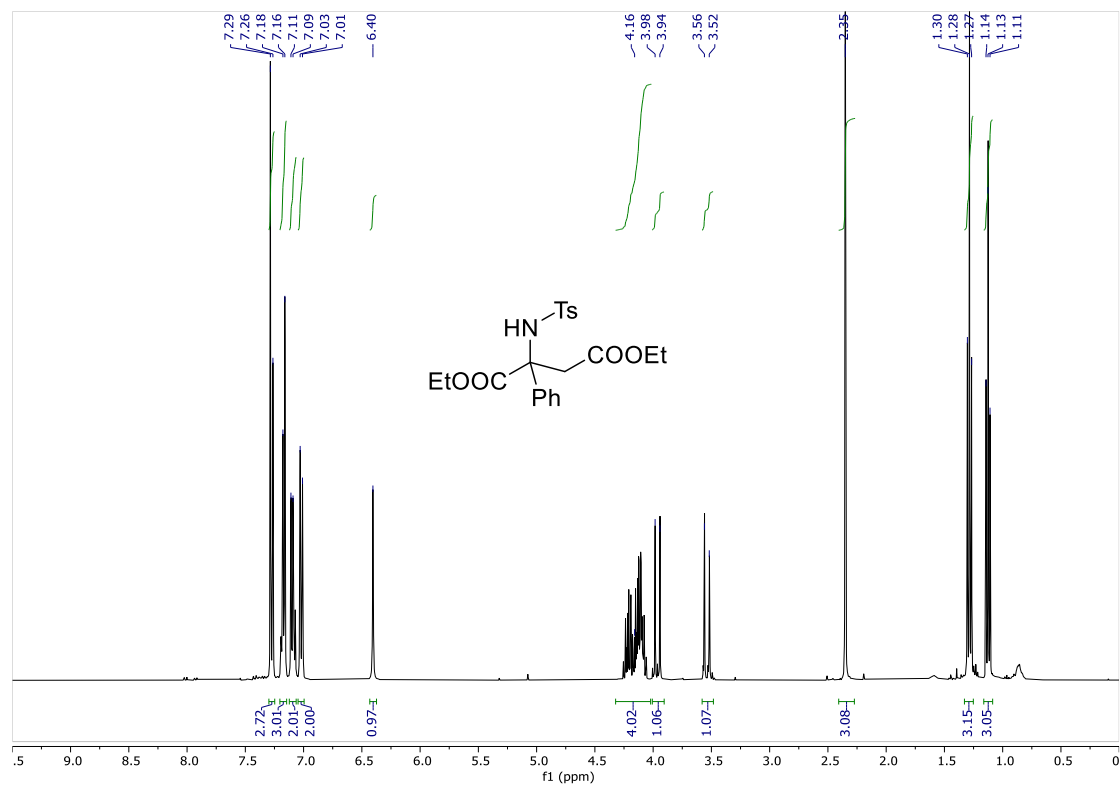


^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

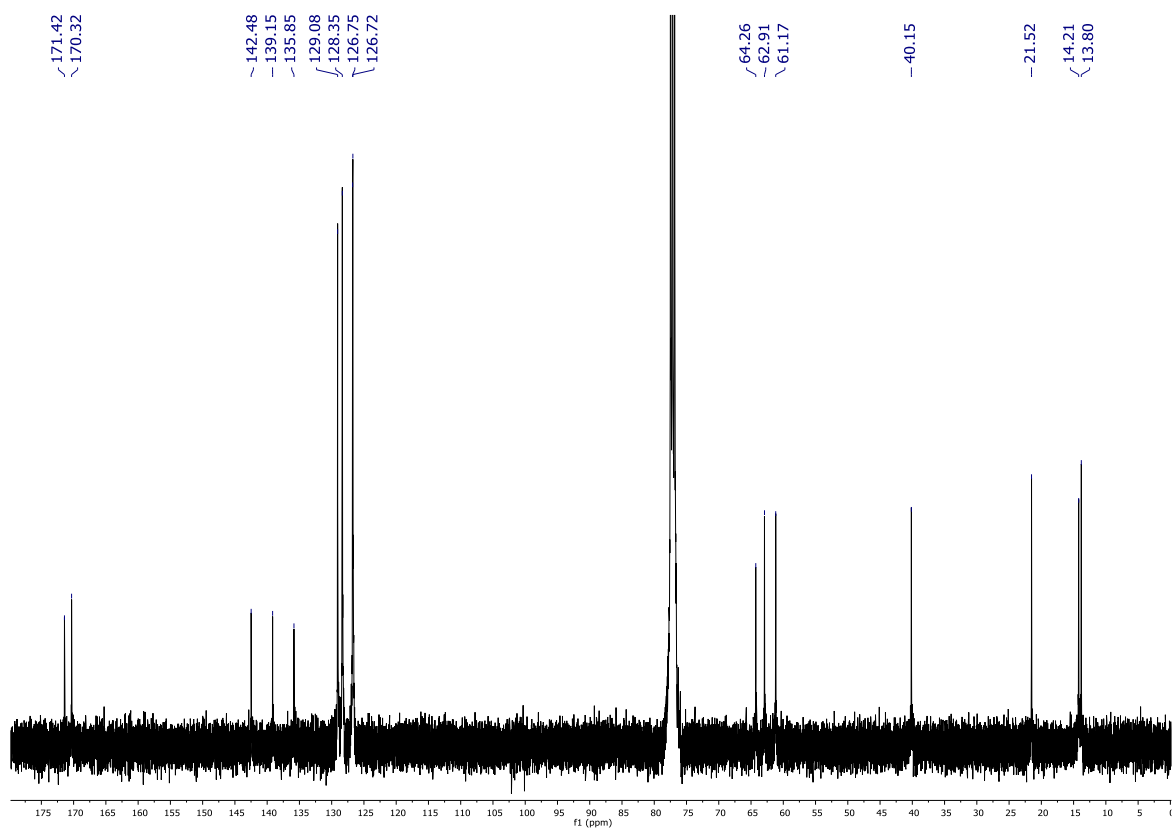


Diethyl 2-((4-methylphenyl)sulfonamido)-2-phenylsuccinate (6).

^1H NMR (400 MHz, CDCl_3)



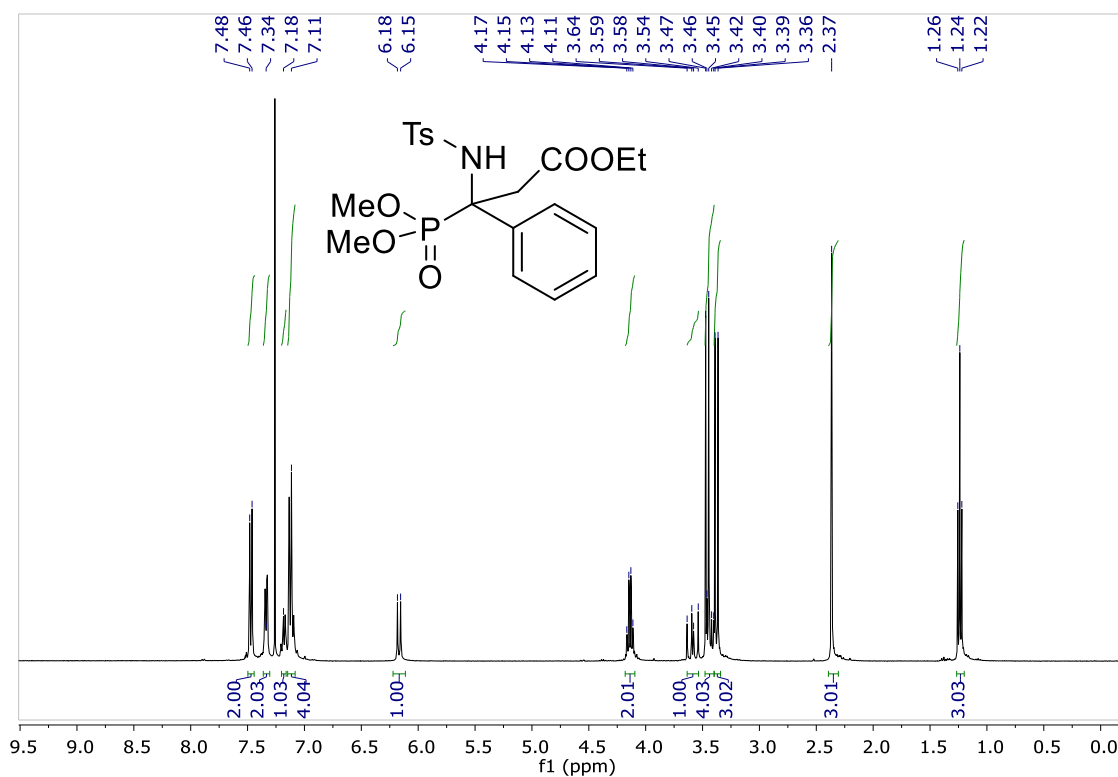
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



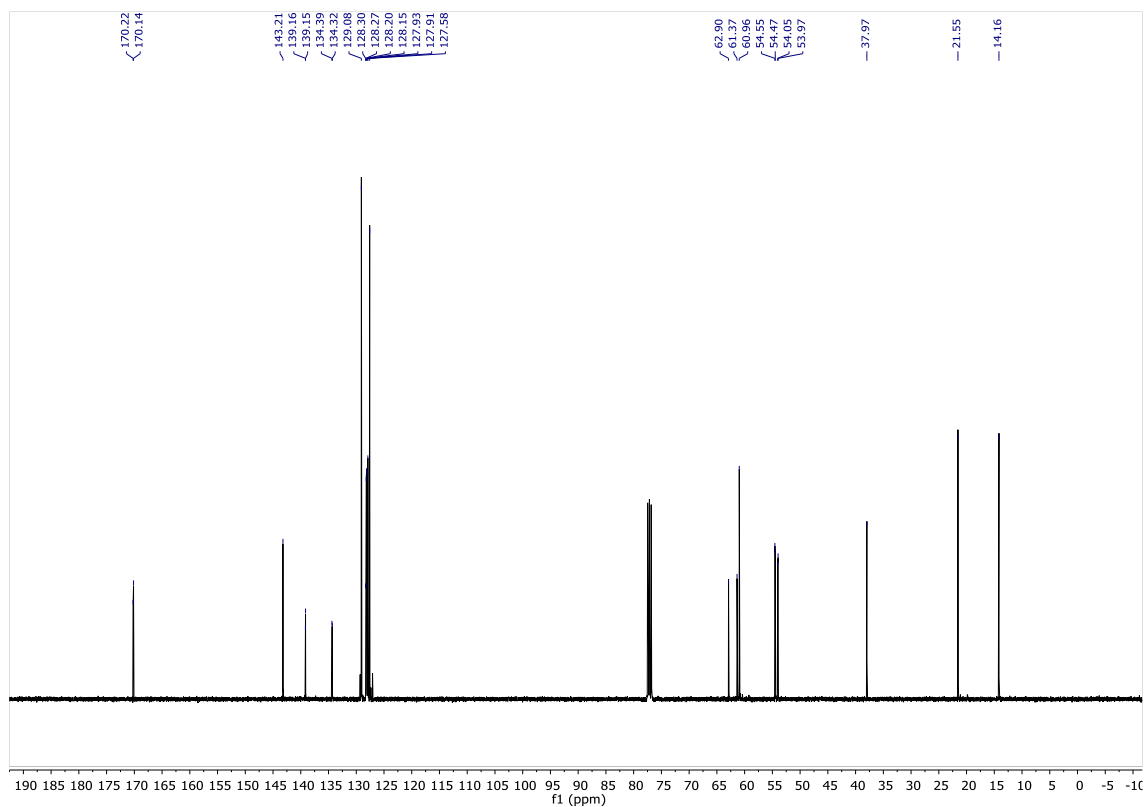
2. ^1H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra of compounds 7

Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate (7a)

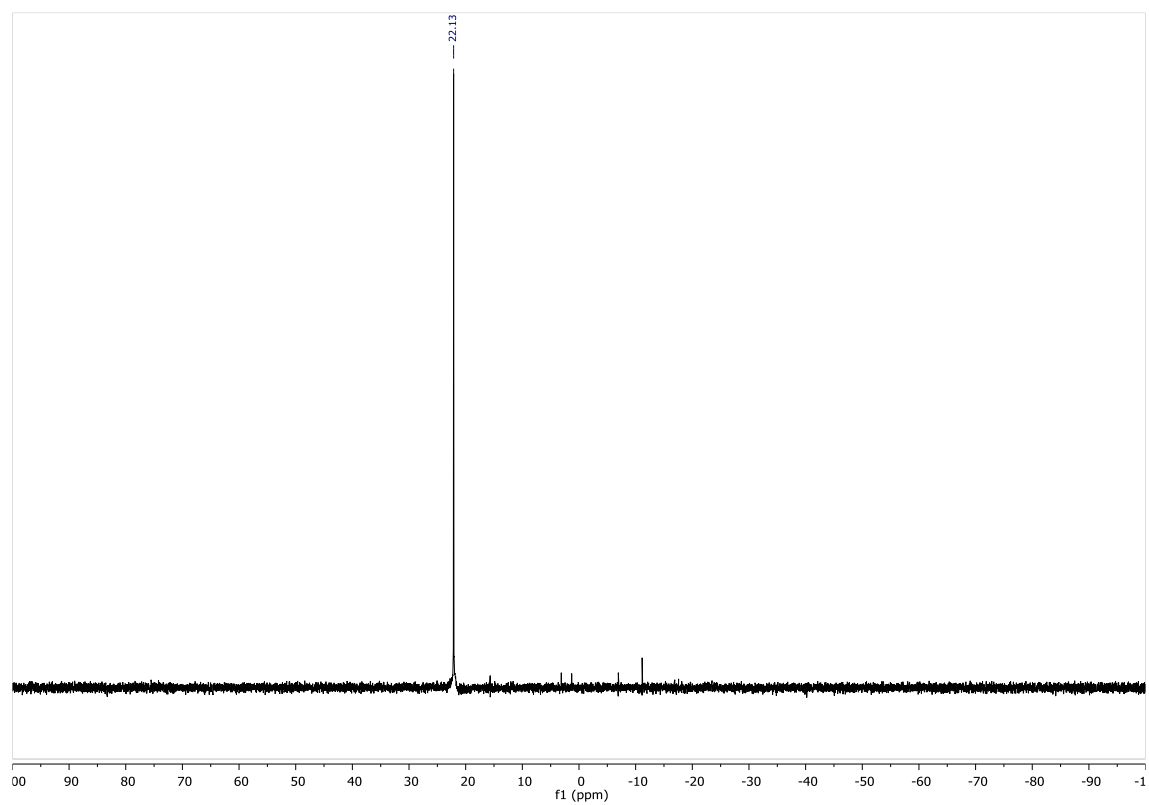
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

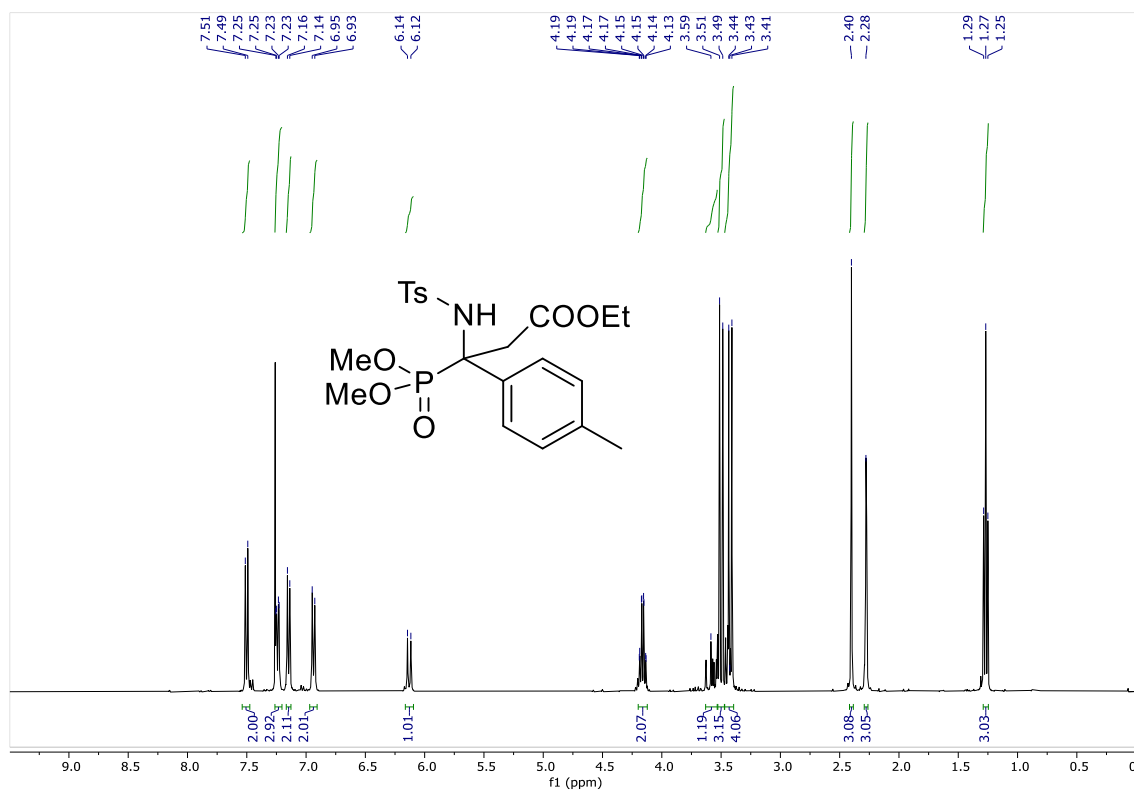


^{31}P NMR (120 MHz, CDCl_3)

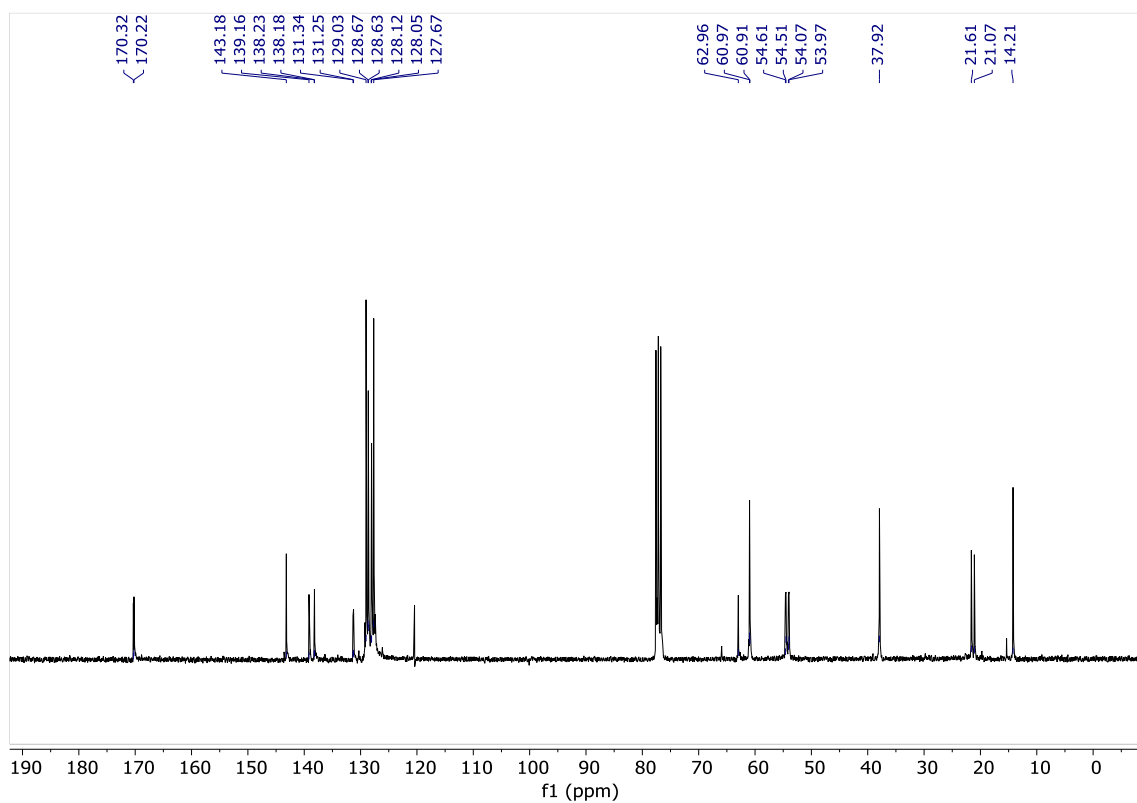


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(p-tolyl)propanoate (7b)

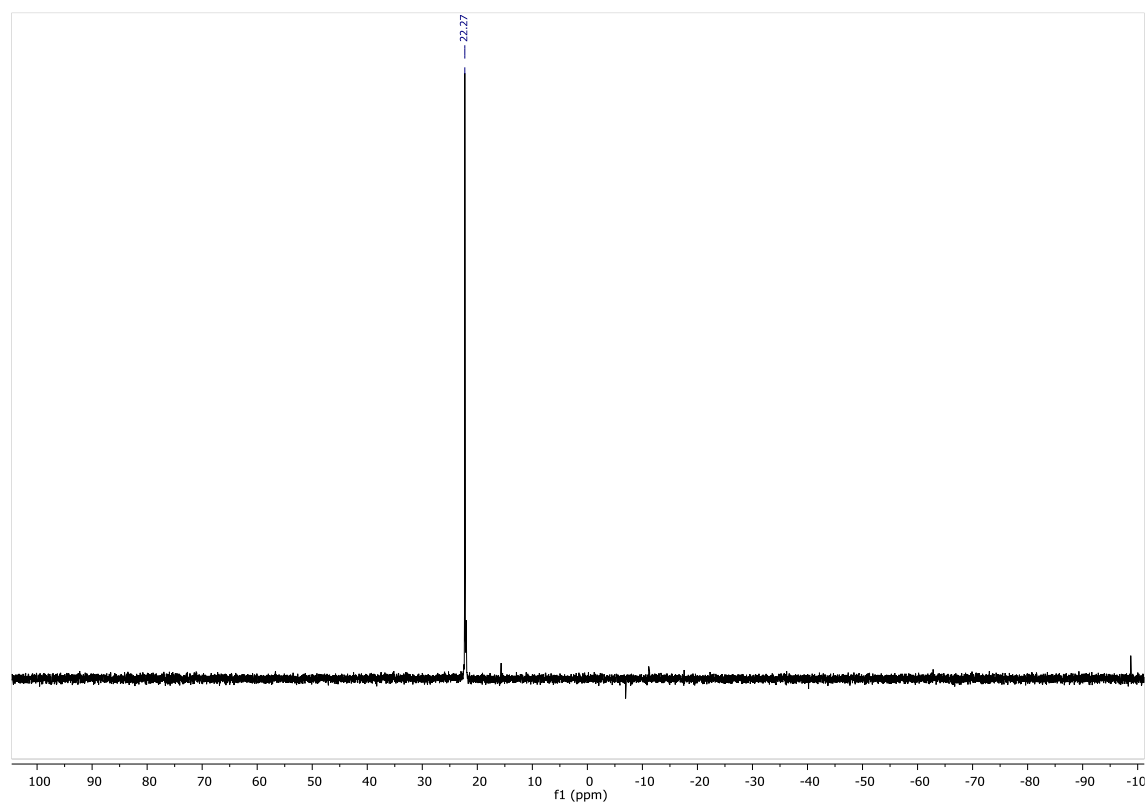
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR [^1H] (75 MHz, CDCl_3)

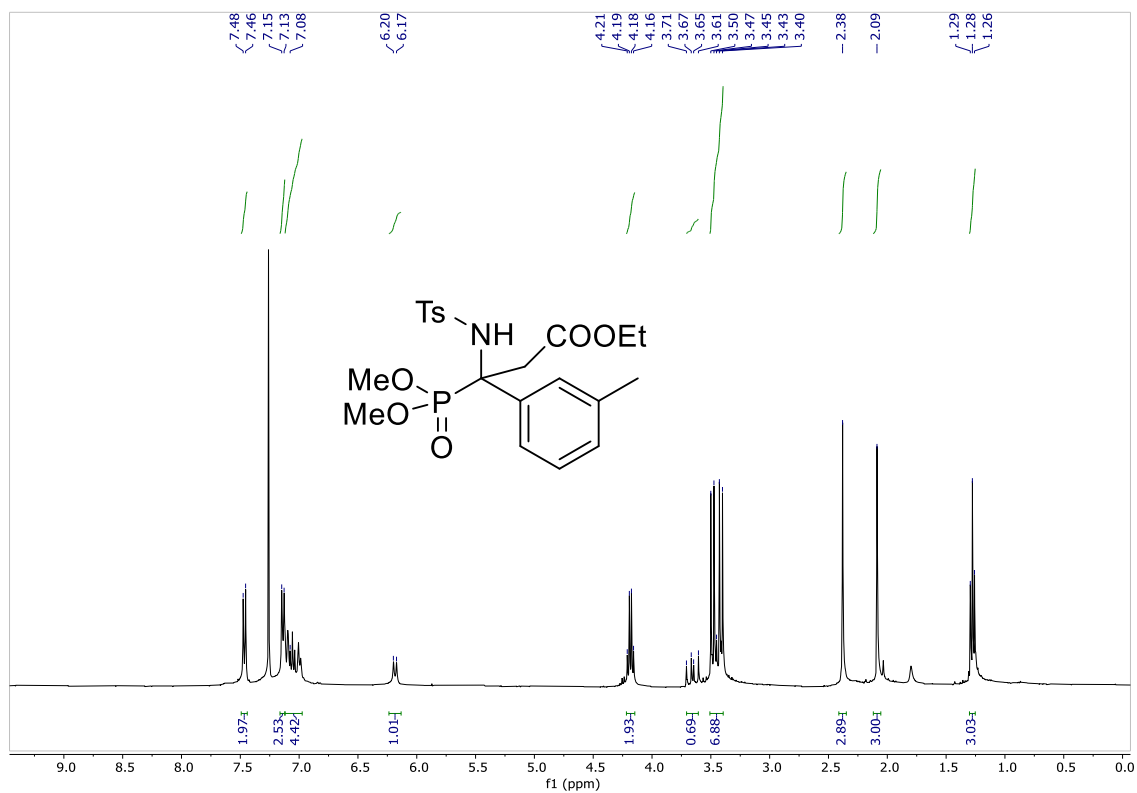


^{31}P NMR (120 MHz, CDCl_3)

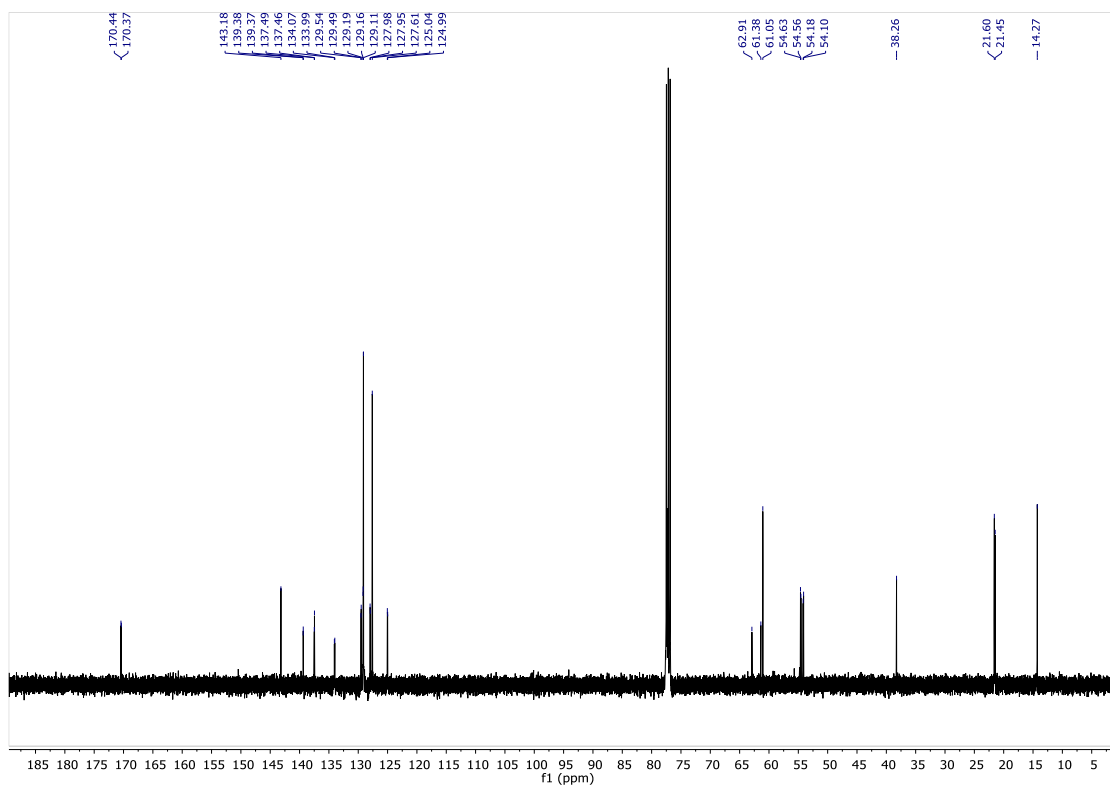


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(m-tolyl)propanoate (7c)

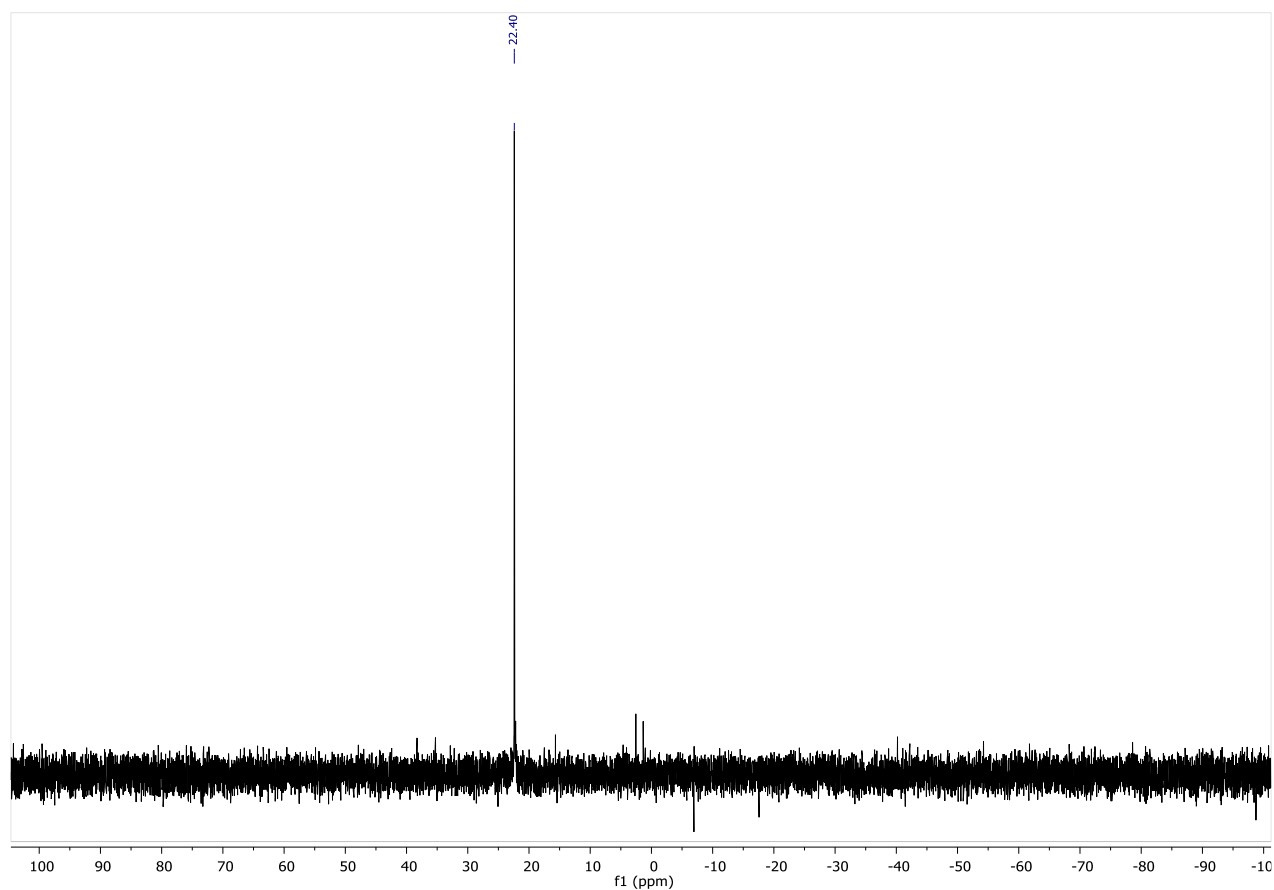
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

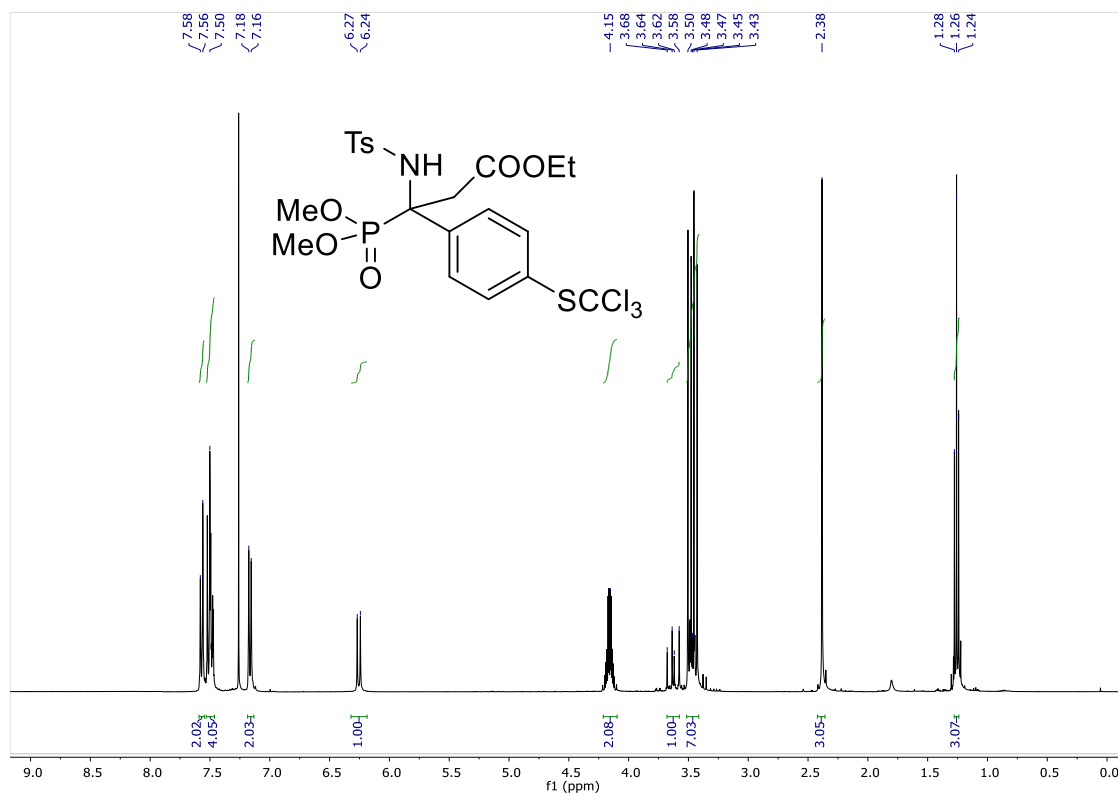


^{31}P NMR (120 MHz, CDCl_3)

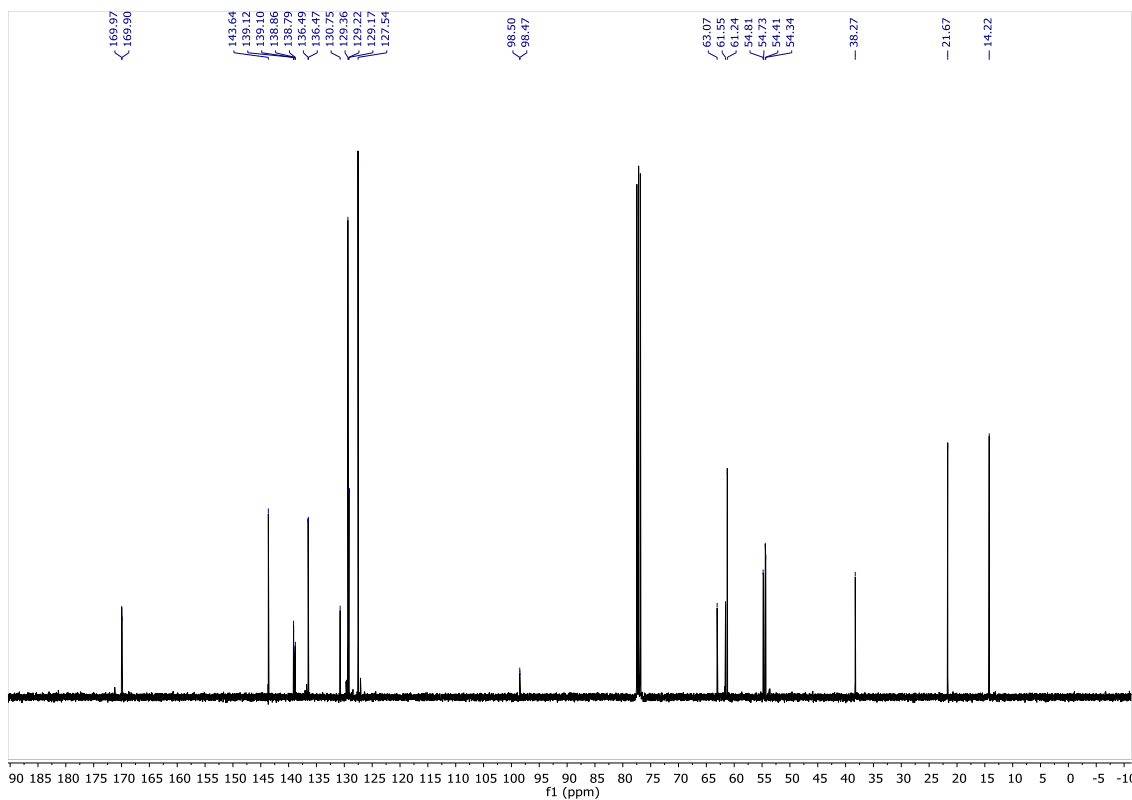


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-((trichloromethyl)thio)phenyl)propanoate (7d)

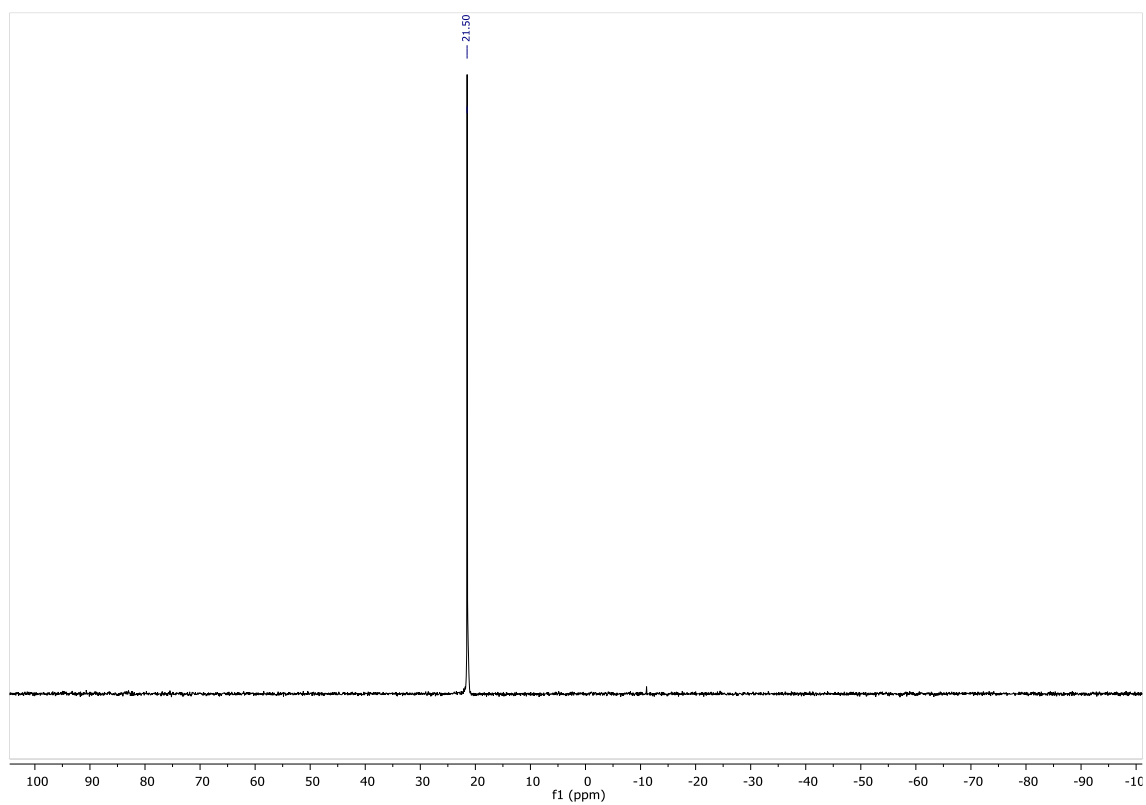
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

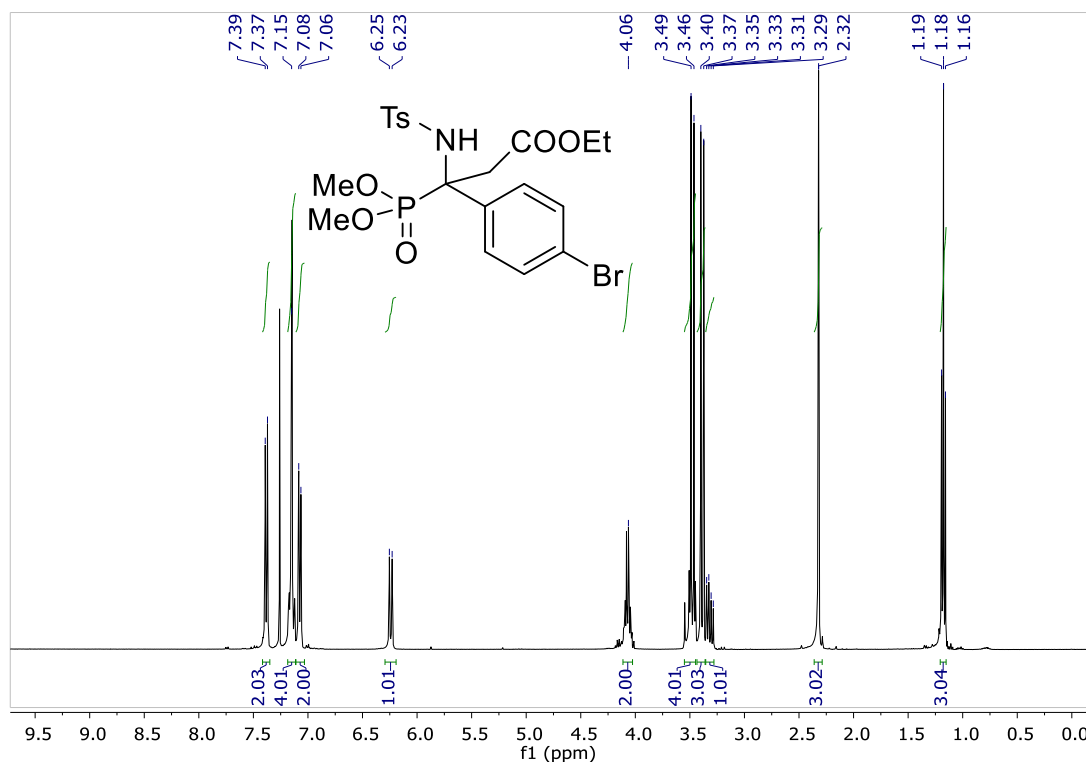


^{31}P NMR (120 MHz, CDCl_3)

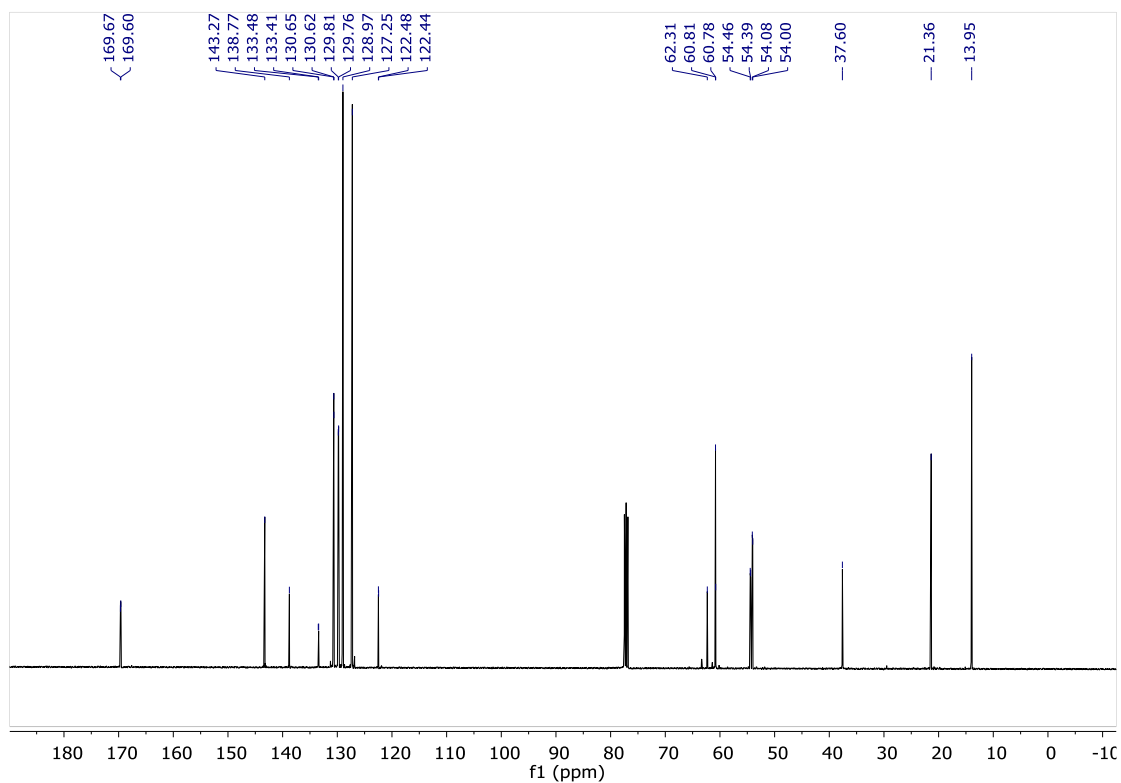


Ethyl 3-(4-bromophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7e)

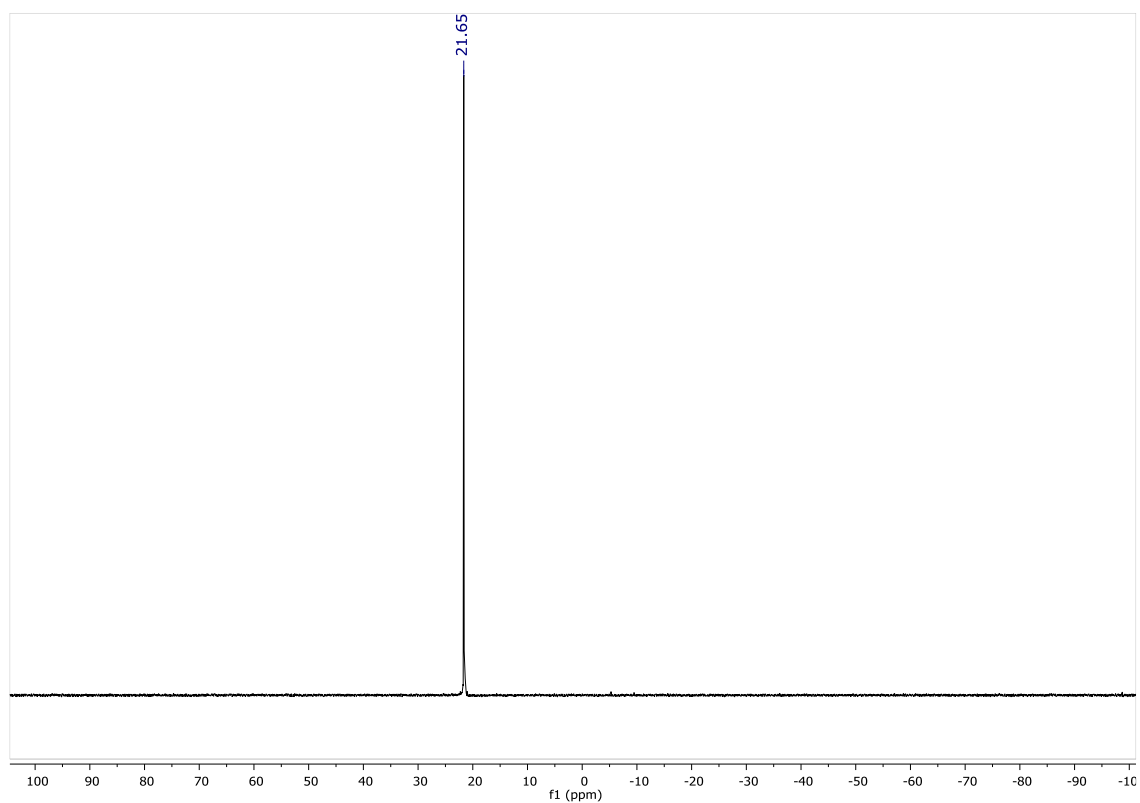
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

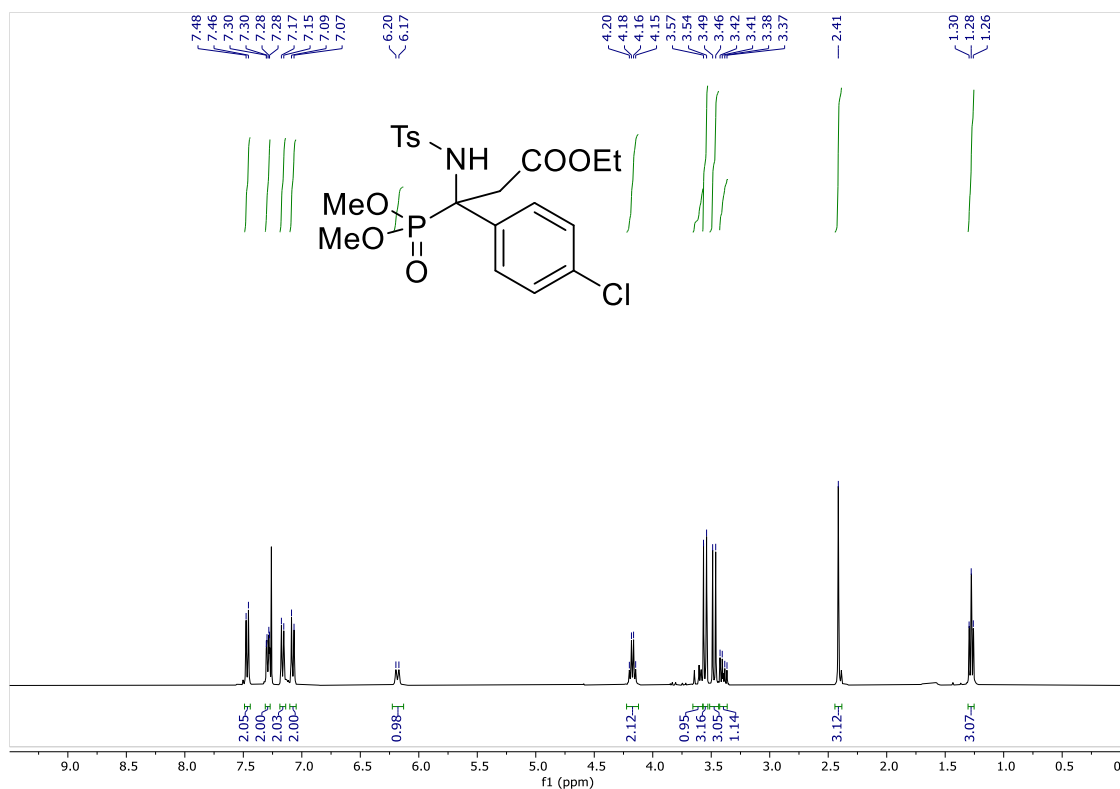


^{31}P NMR (120 MHz, CDCl_3)

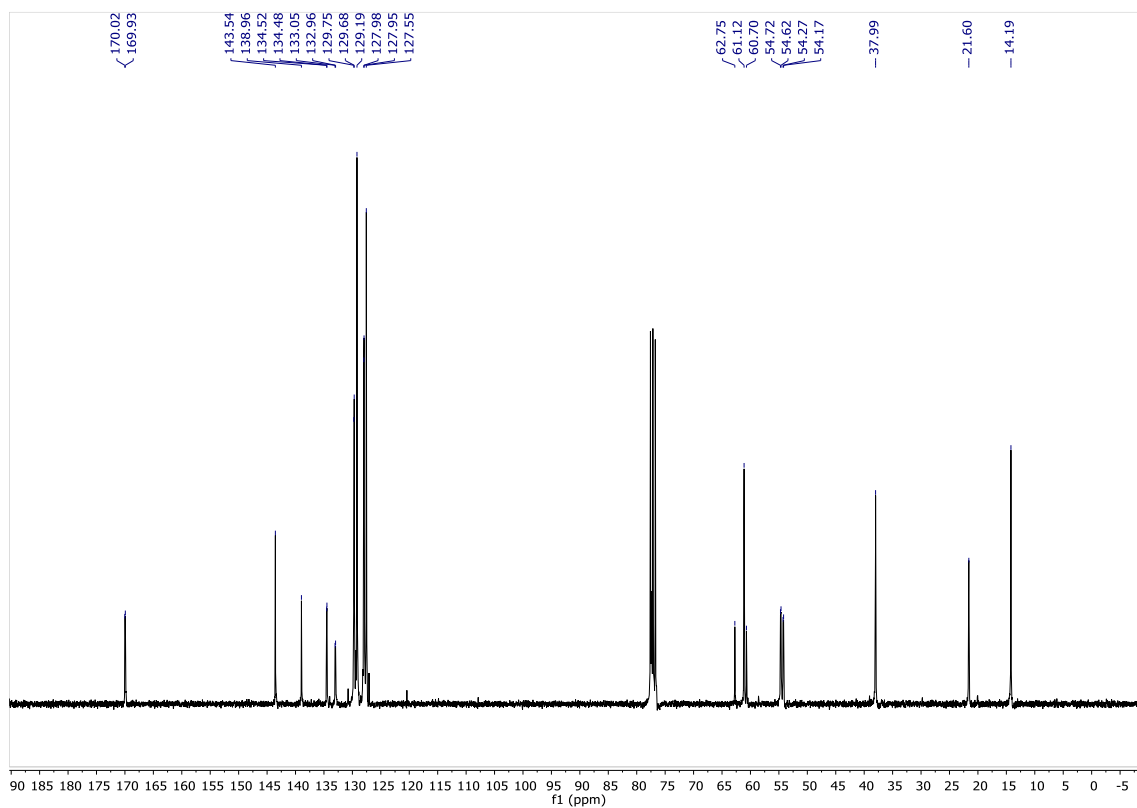


Ethyl 3-(4-chlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7f)

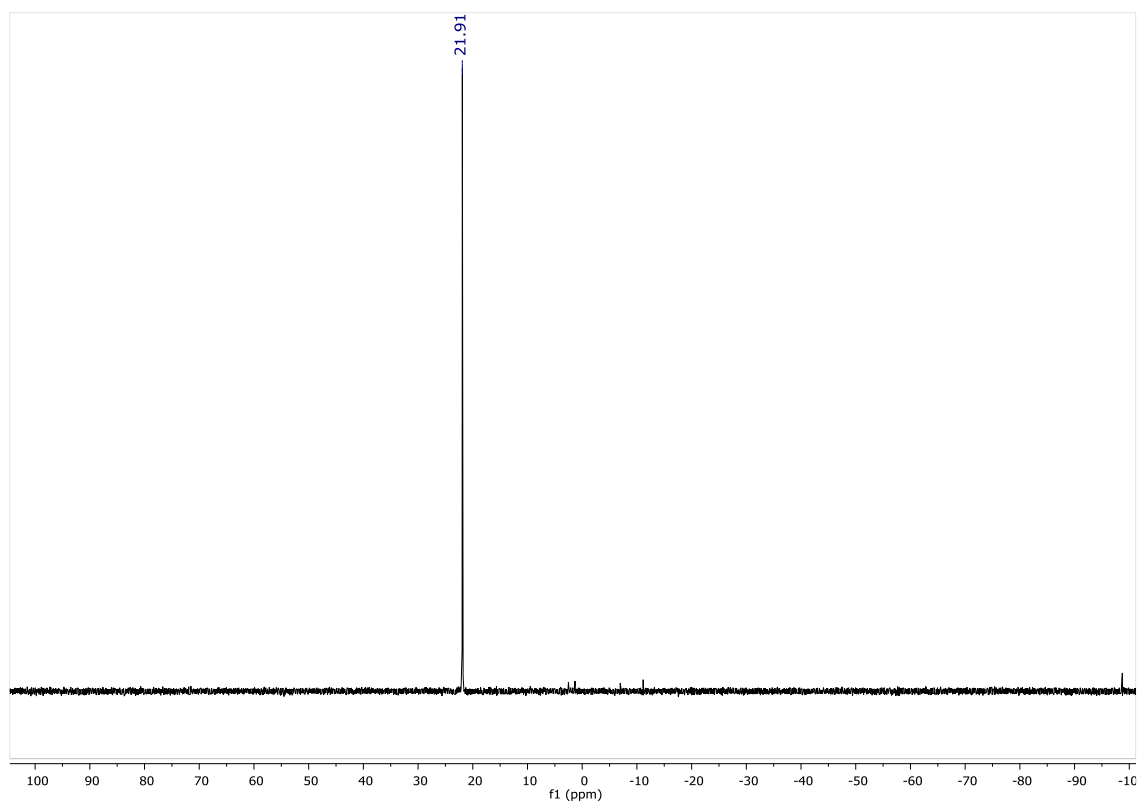
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (75 MHz, CDCl_3)

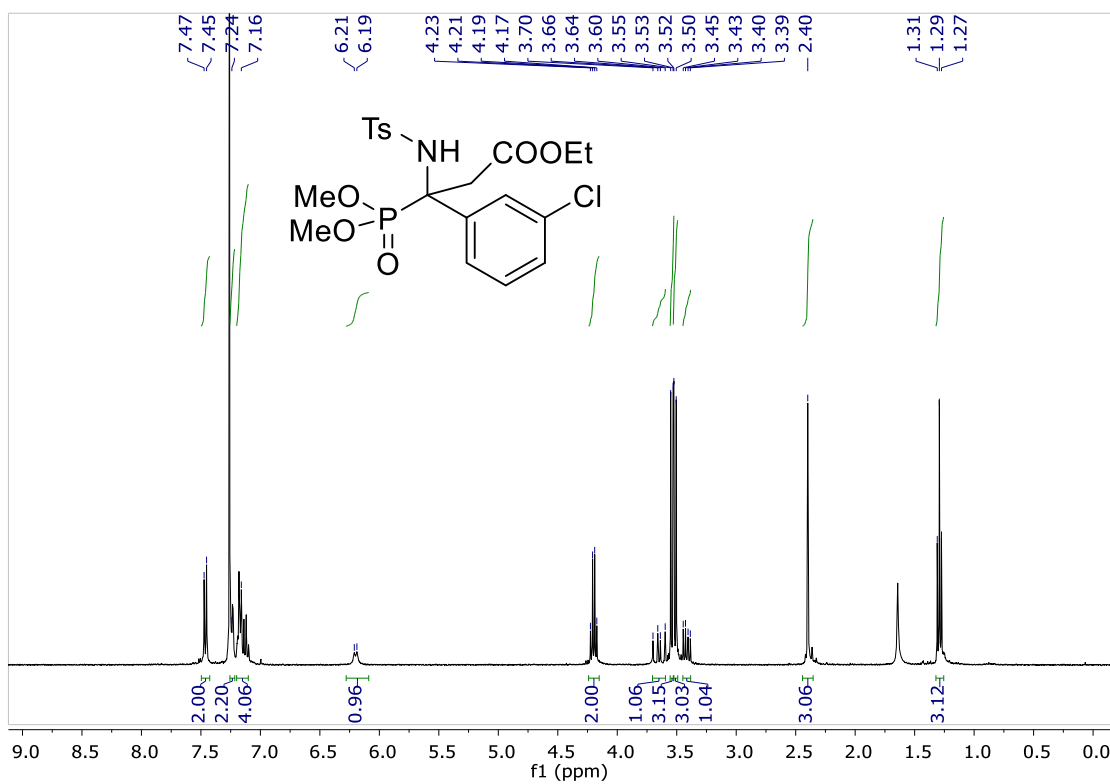


^{31}P NMR (120 MHz, CDCl_3)

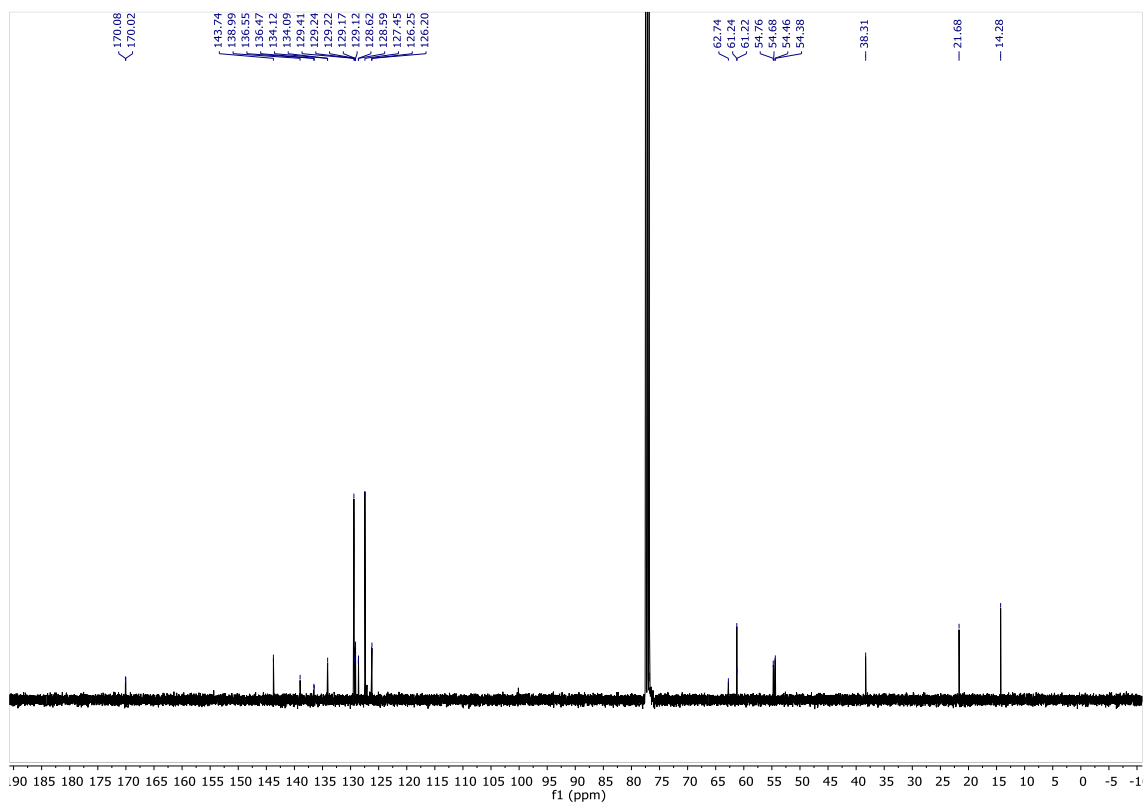


Ethyl 3-(3-chlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7g)

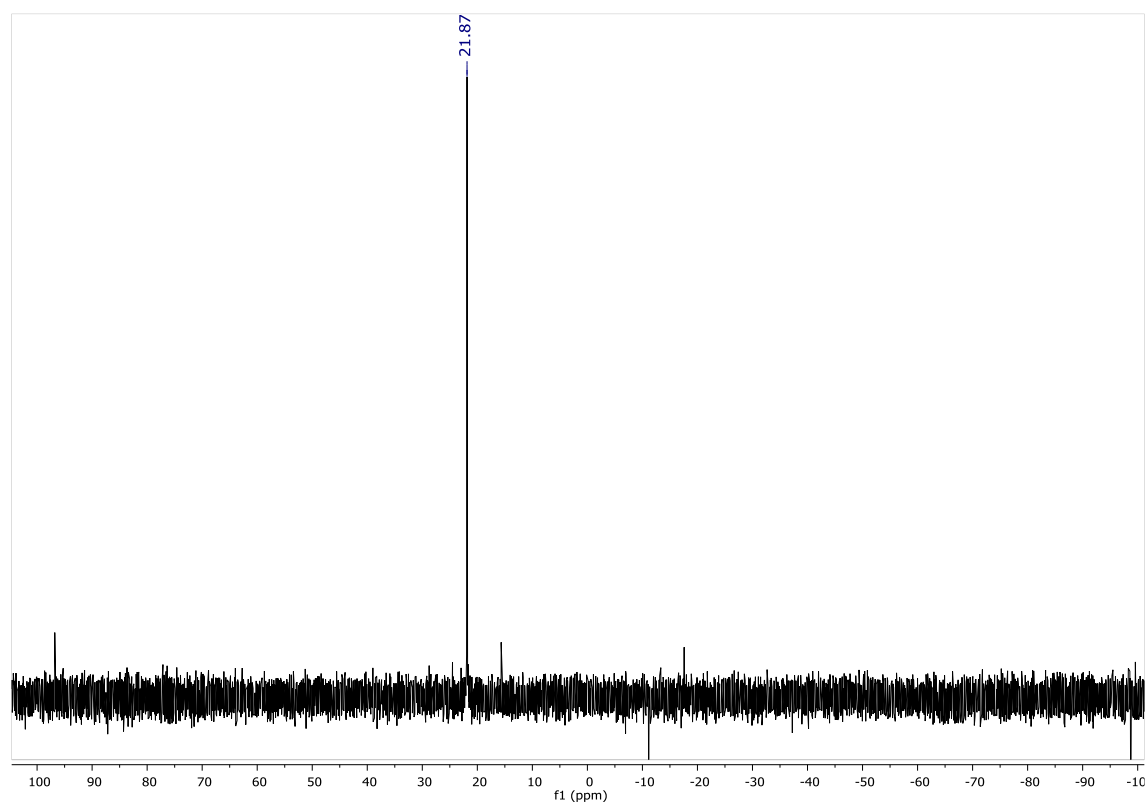
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

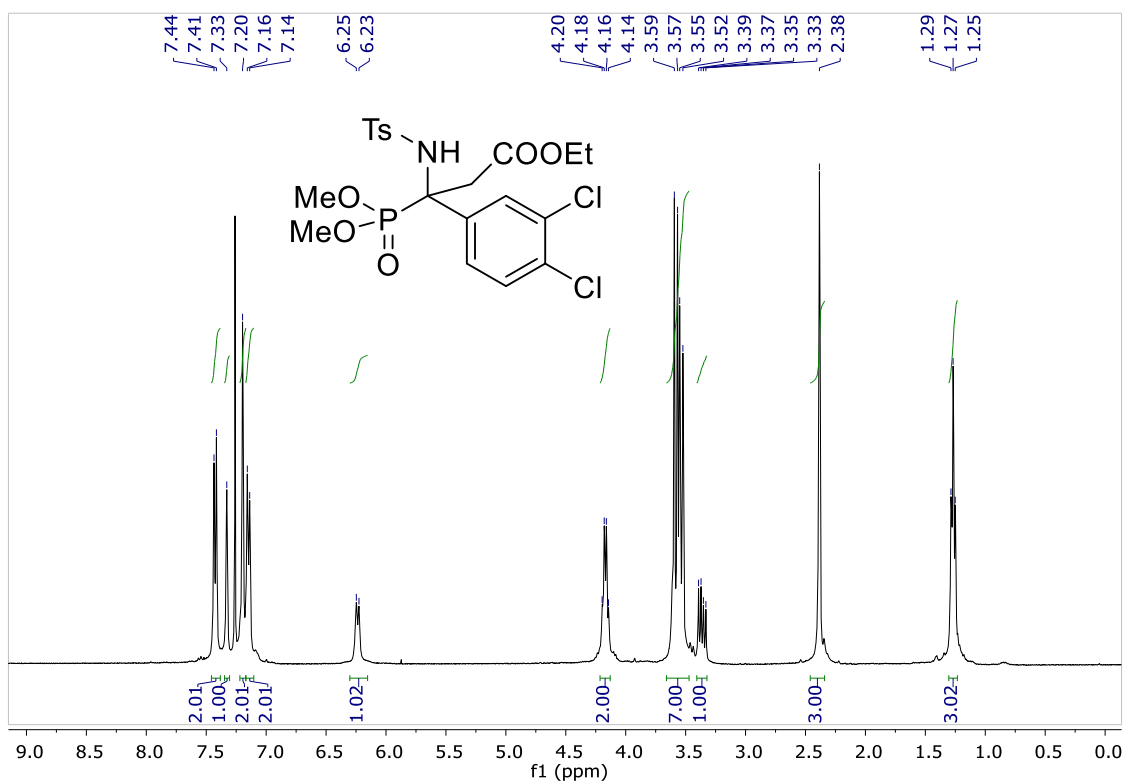


^{31}P NMR (120 MHz, CDCl_3)

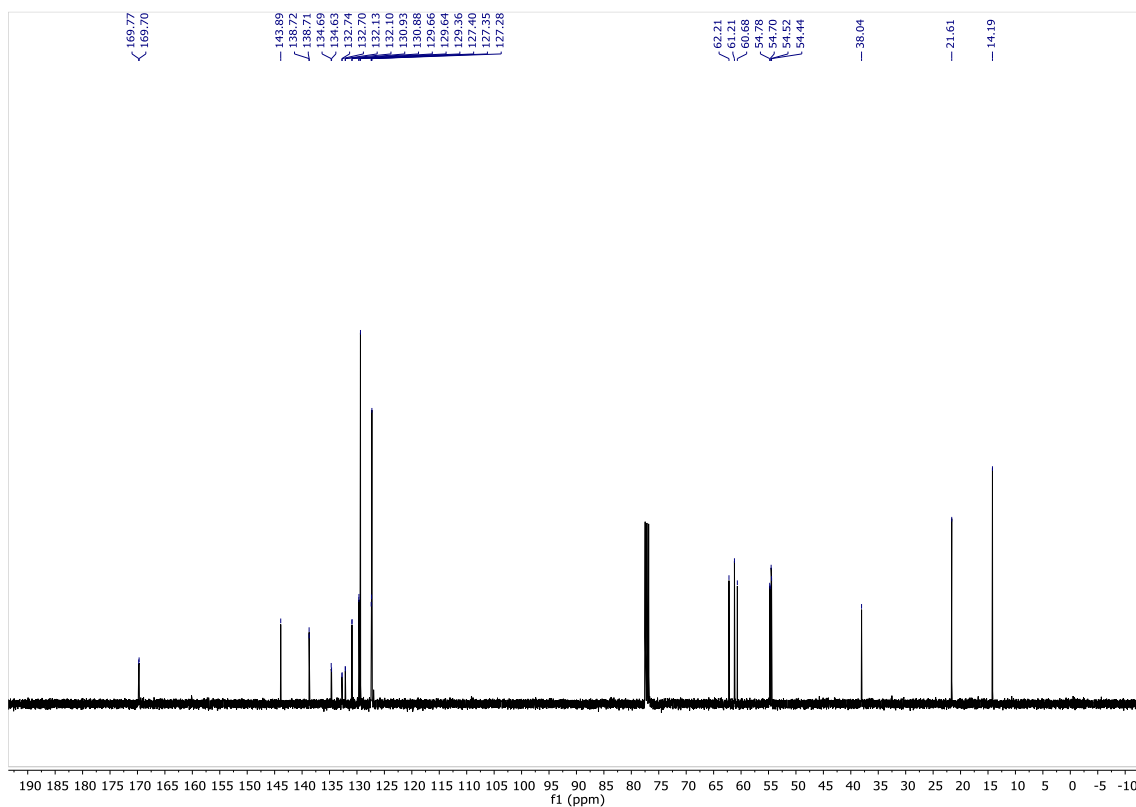


Ethyl 3-(3,4-dichlorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7h)

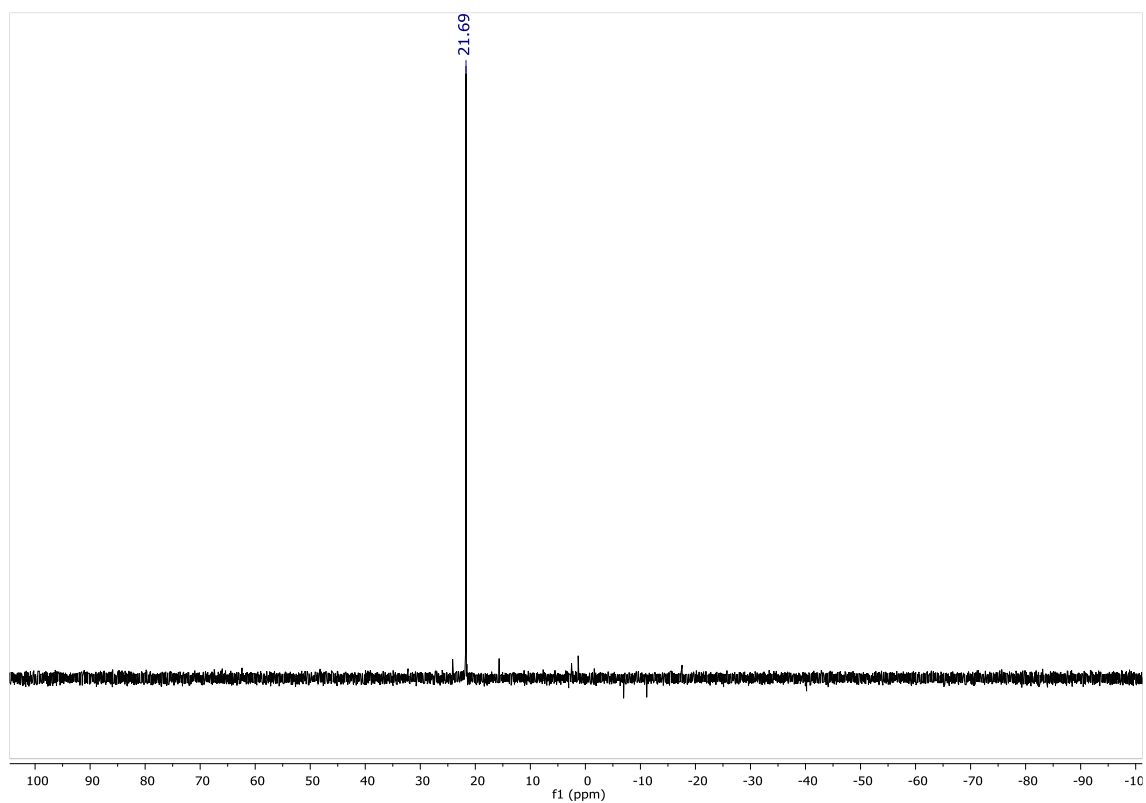
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

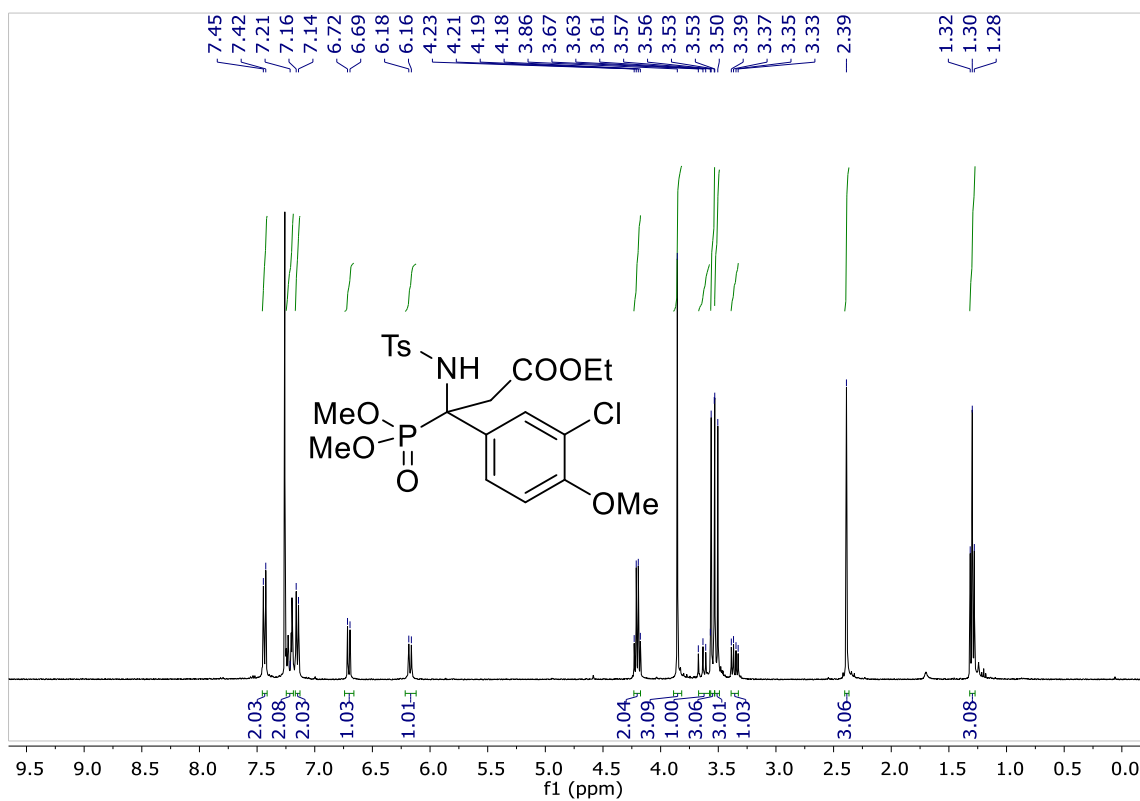


^{31}P NMR (120 MHz, CDCl_3)

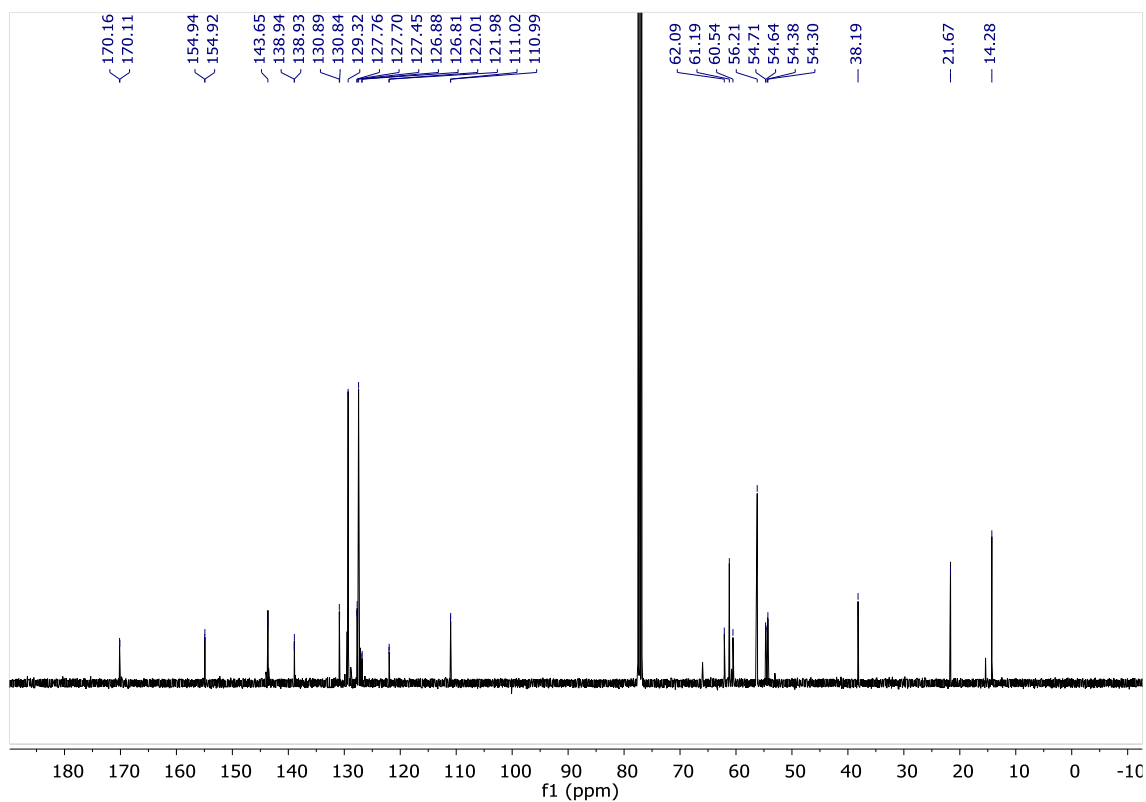


Ethyl 3-(3-chloro-4-methoxyphenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7i)

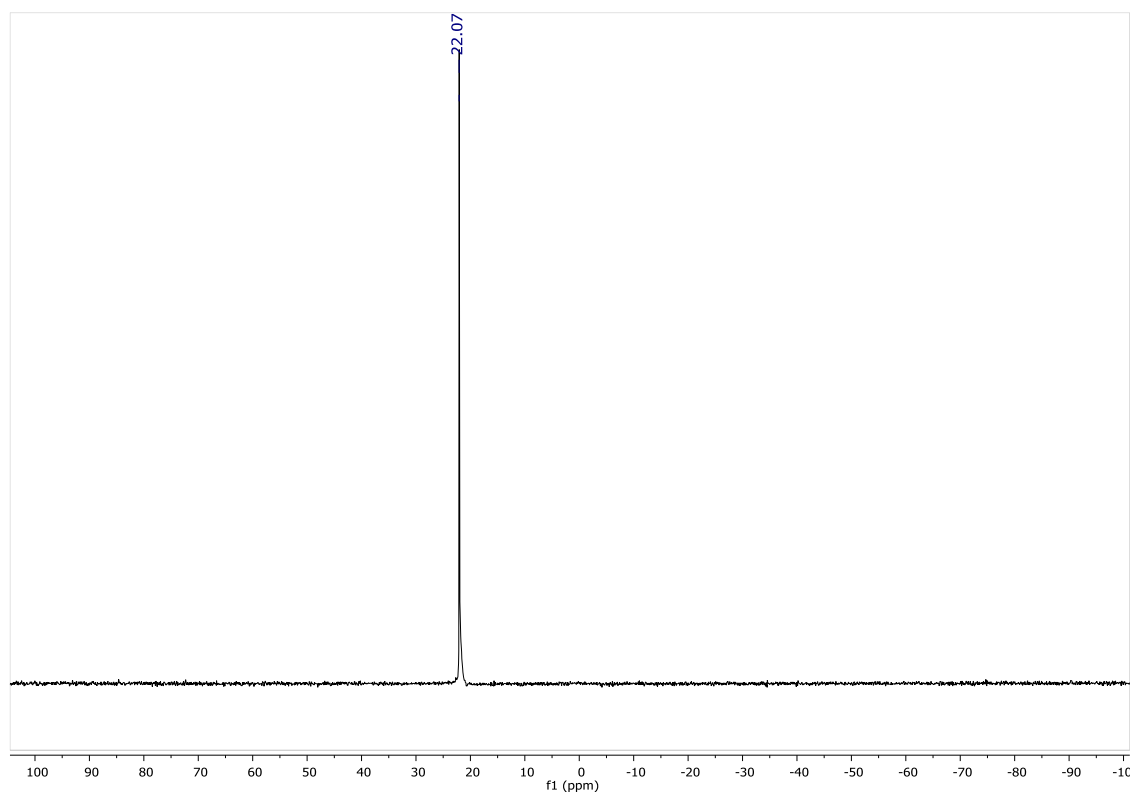
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

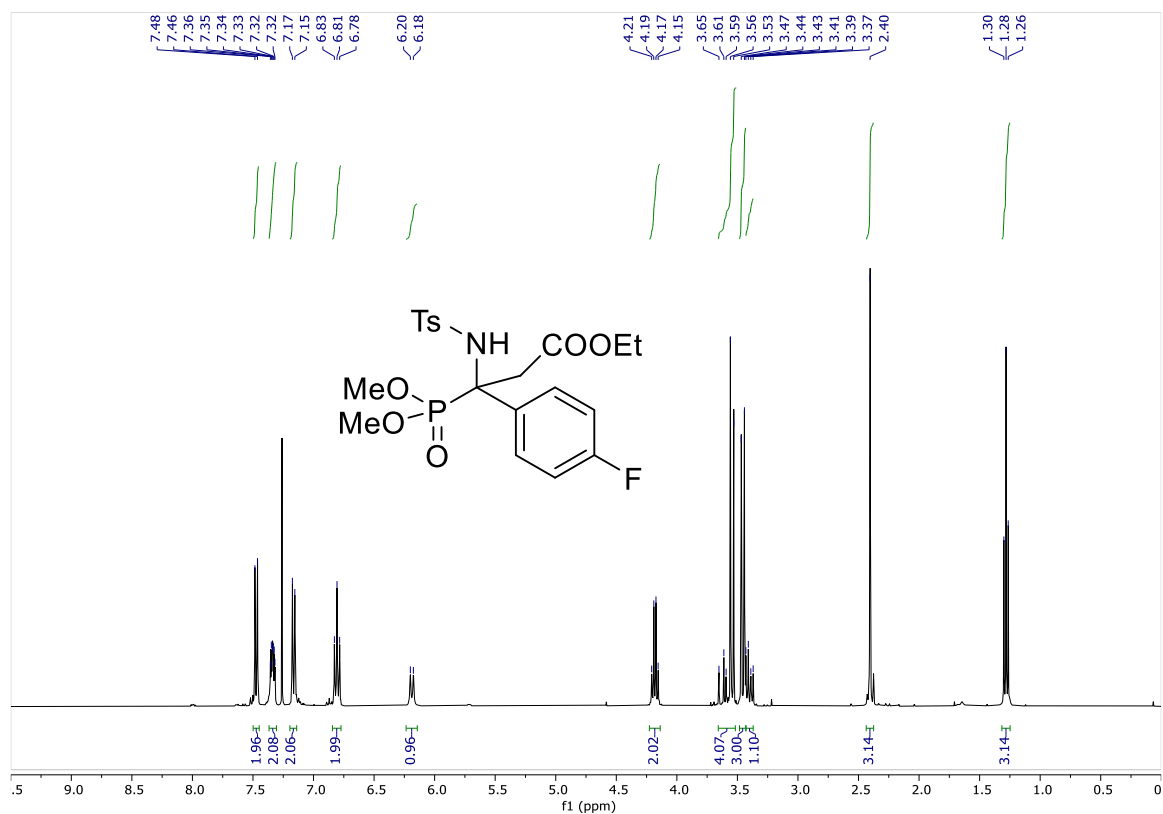


^{31}P NMR (120 MHz, CDCl_3)

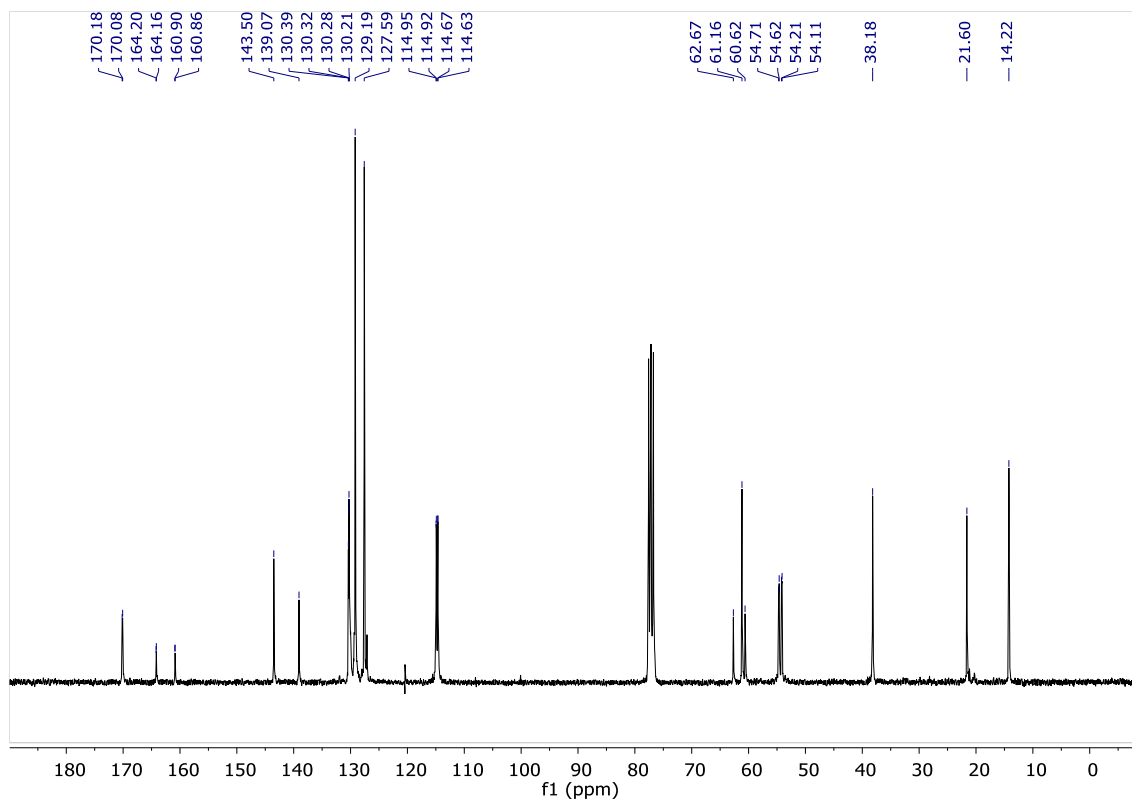


Ethyl 3-(dimethoxyphosphoryl)-3-(4-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (7j)

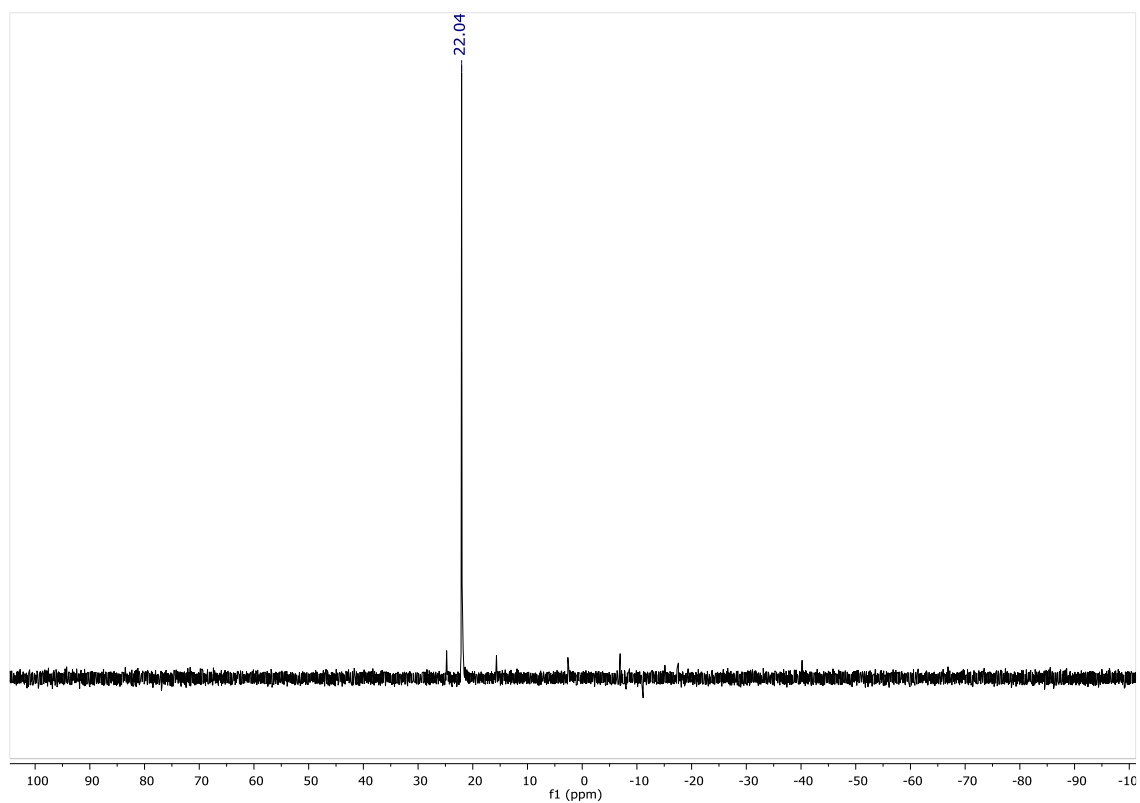
^1H NMR (400 MHz, CDCl_3)



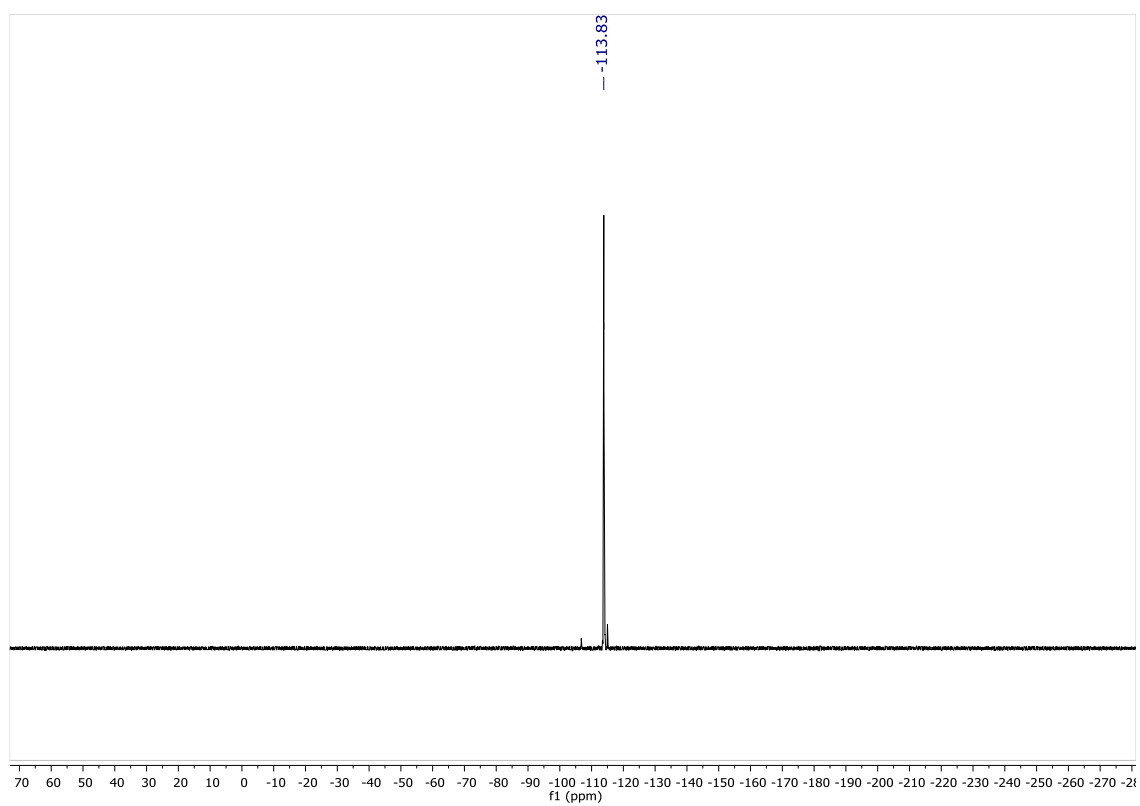
^{13}C NMR $\{^1\text{H}\}$ (75 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

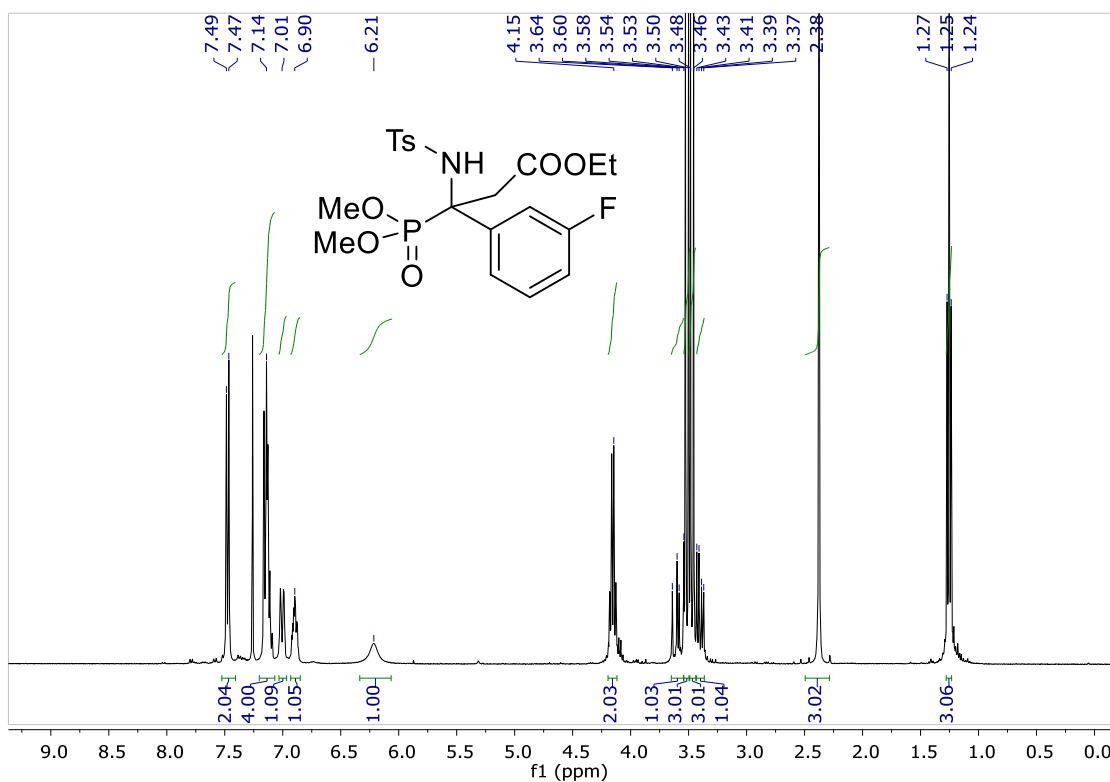


^{19}F NMR (282 MHz, CDCl_3)

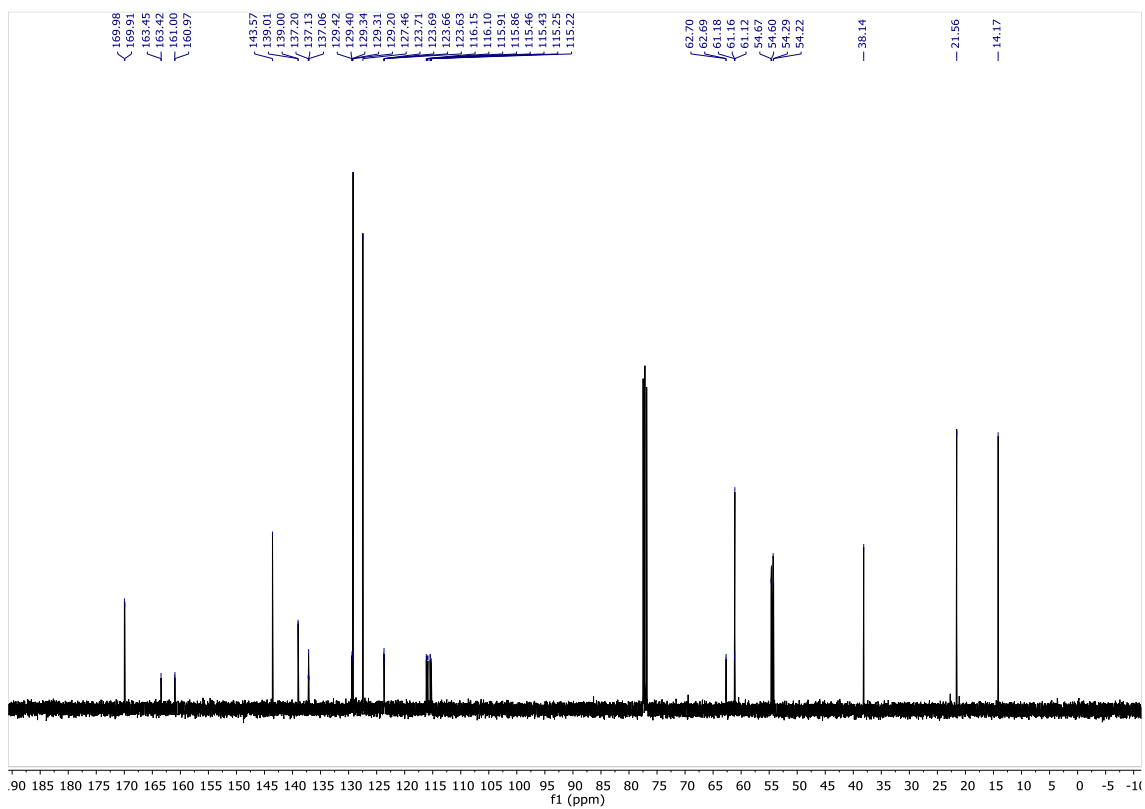


Ethyl 3-(dimethoxyphosphoryl)-3-(3-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (7k)

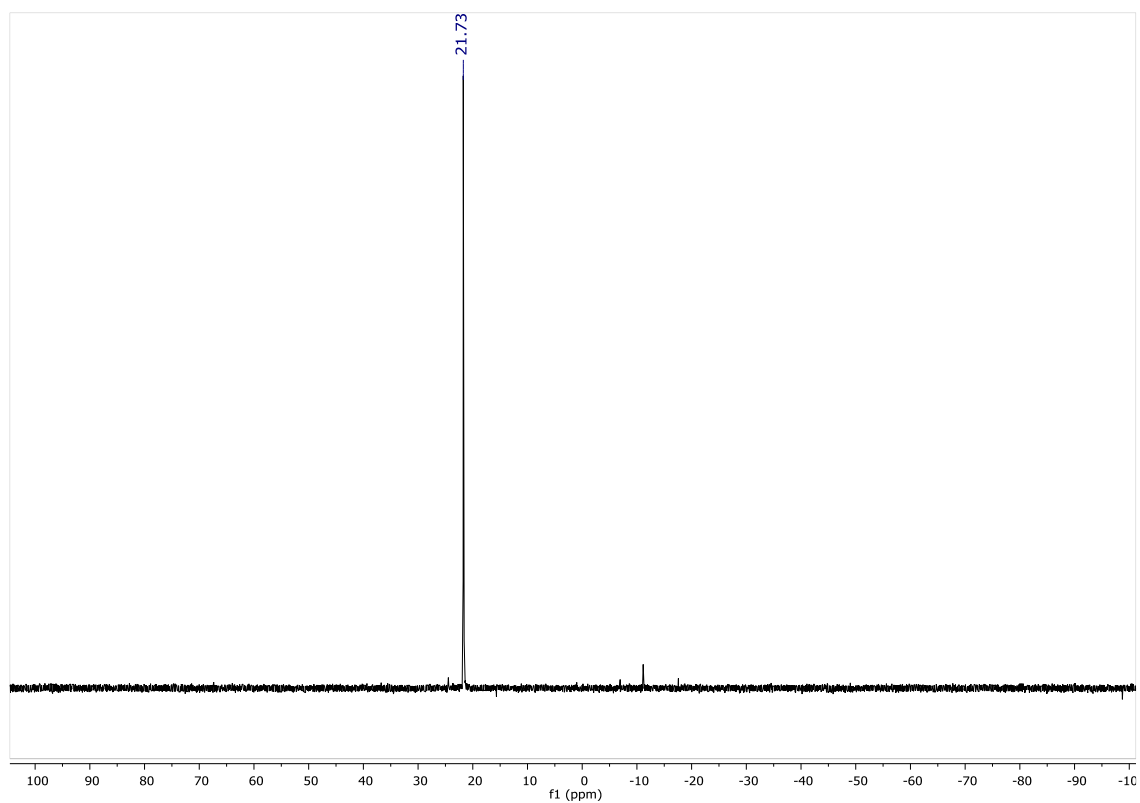
^1H NMR (400 MHz, CDCl_3)



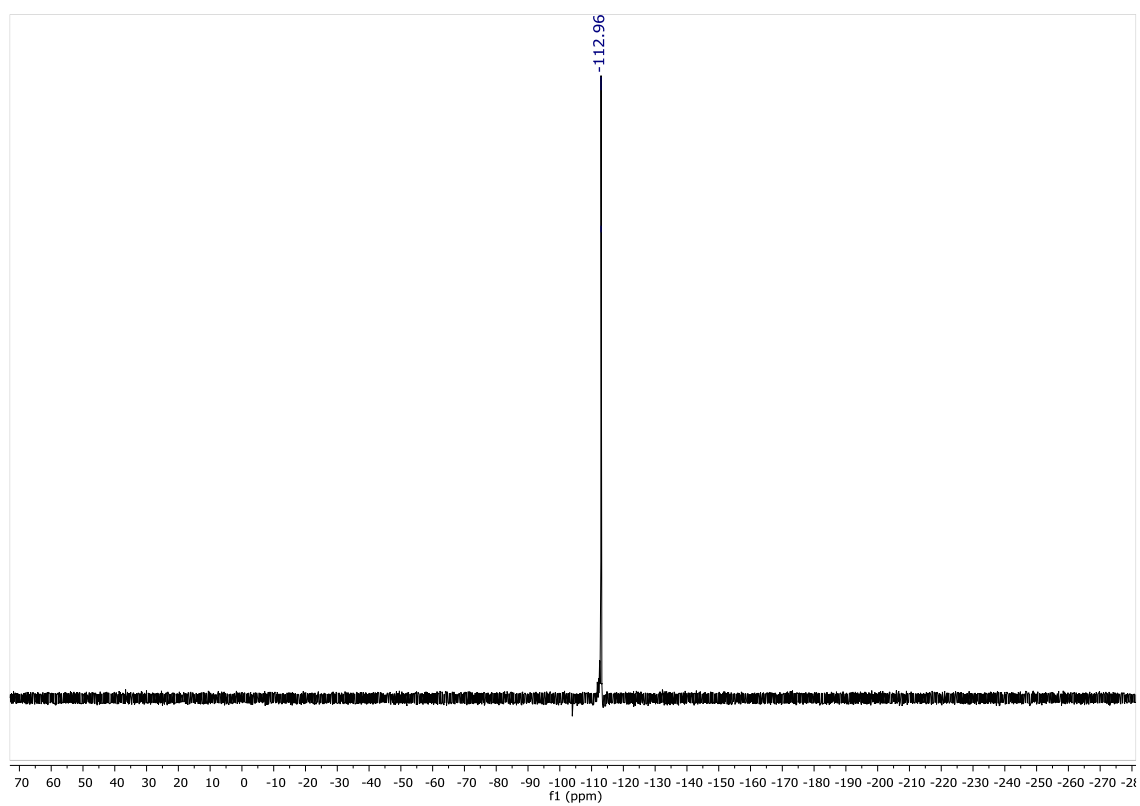
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

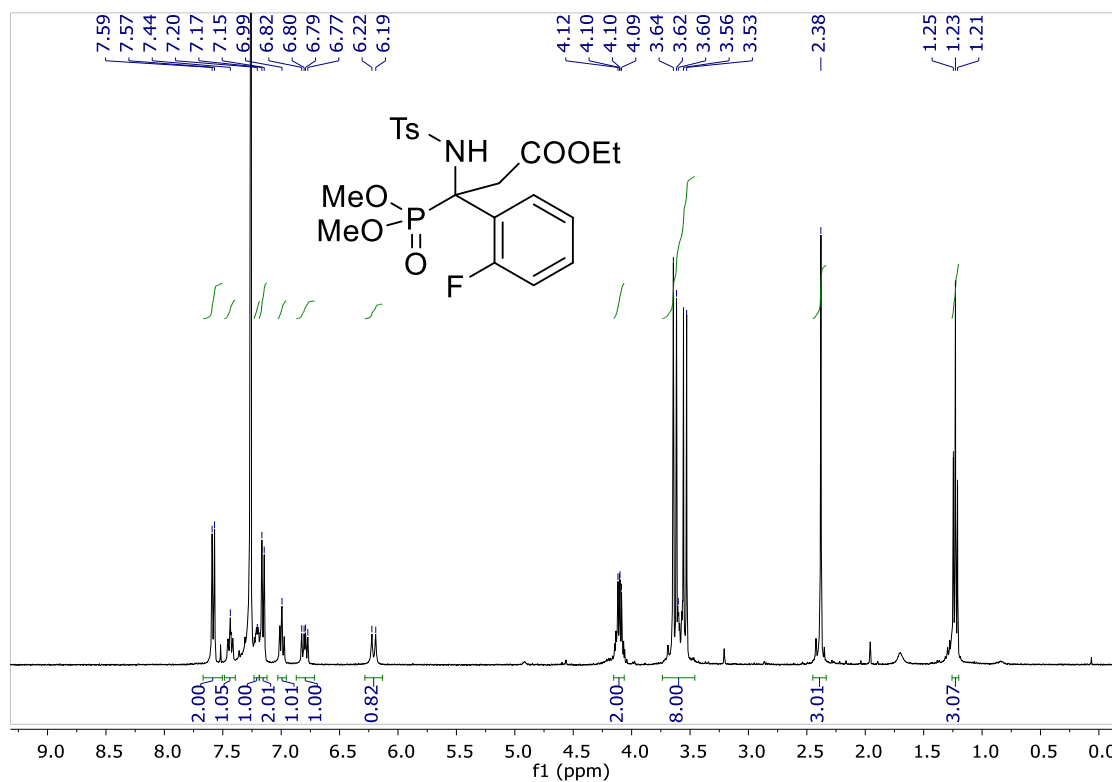


^{19}F NMR (282 MHz, CDCl_3)

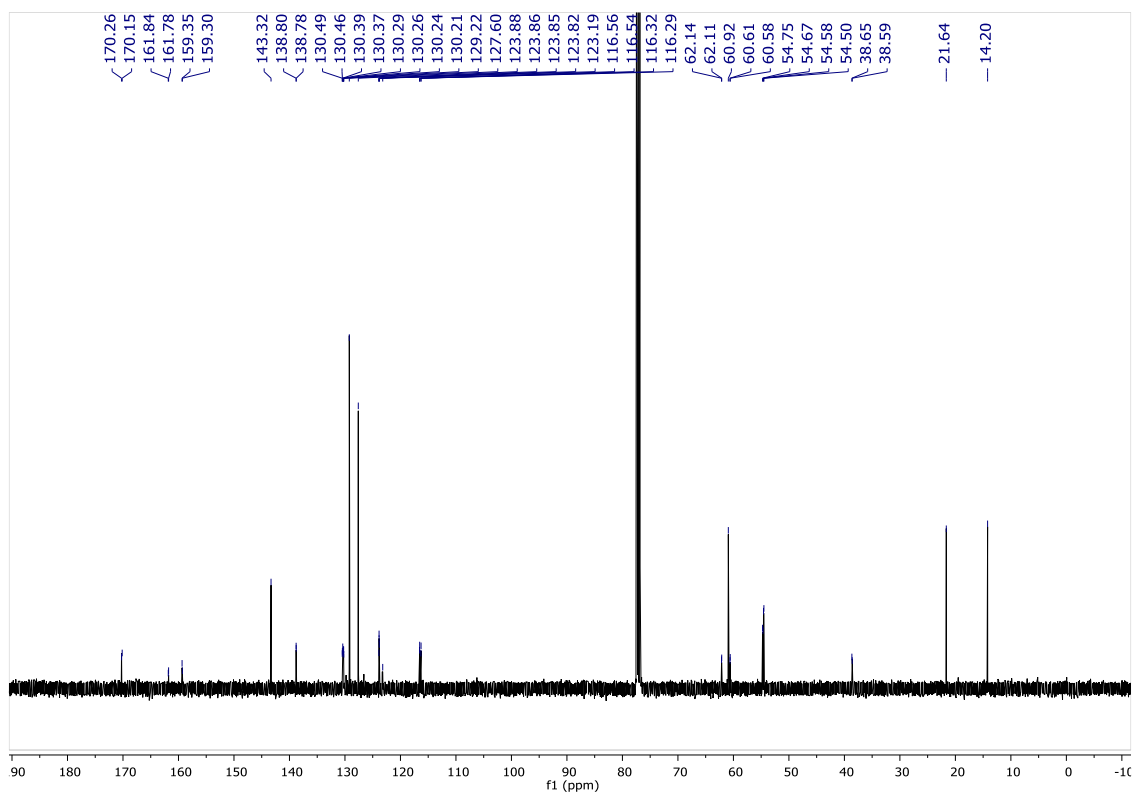


Ethyl 3-(dimethoxyphosphoryl)-3-(2-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (71)

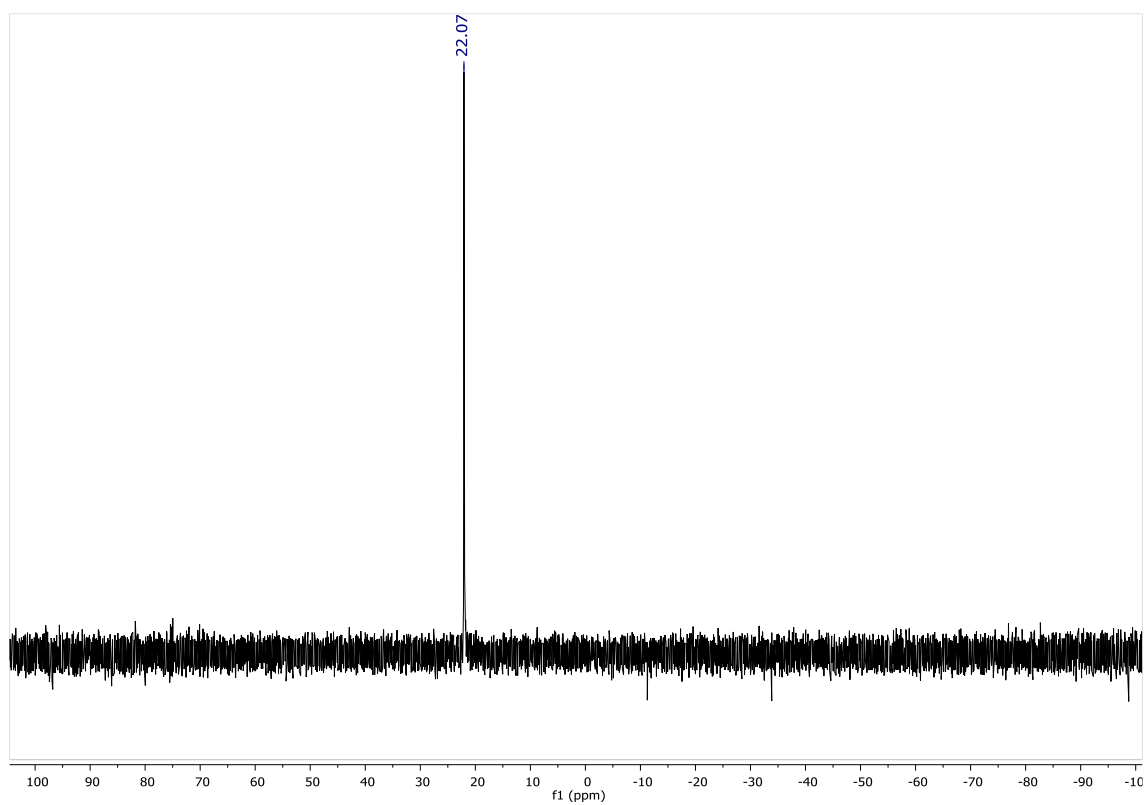
^1H NMR (400 MHz, CDCl_3)



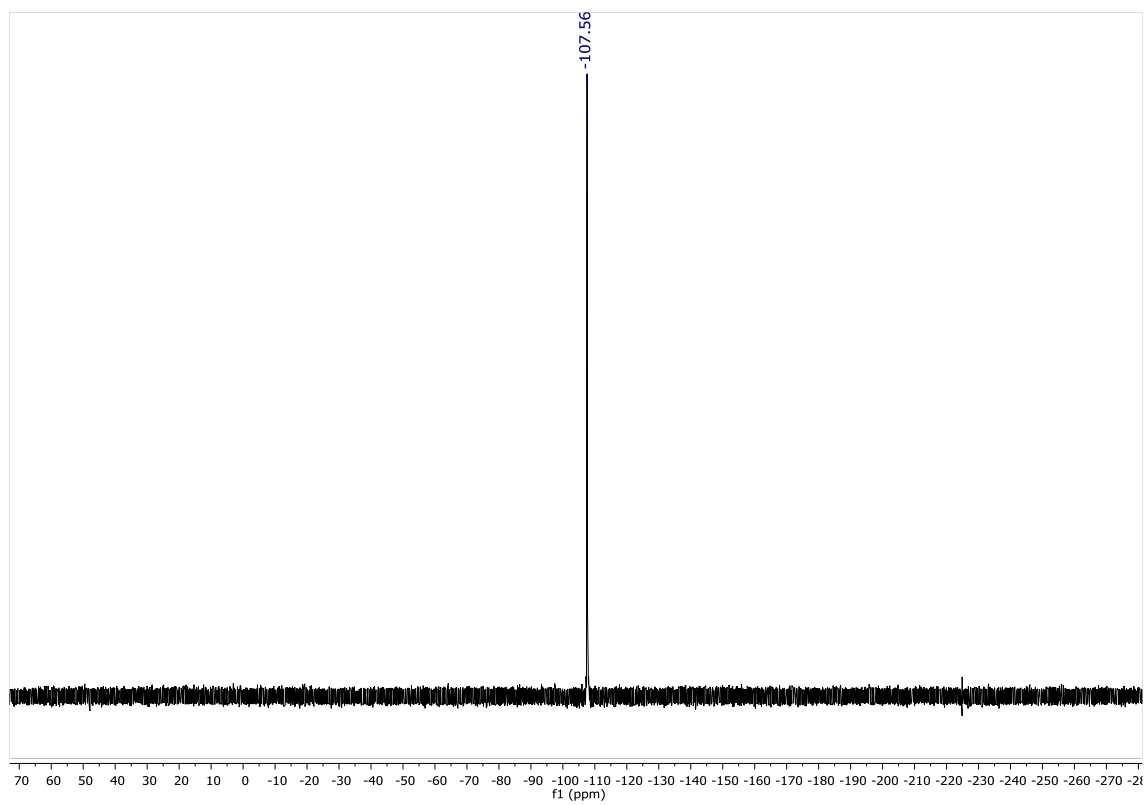
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120MHz, CDCl_3)

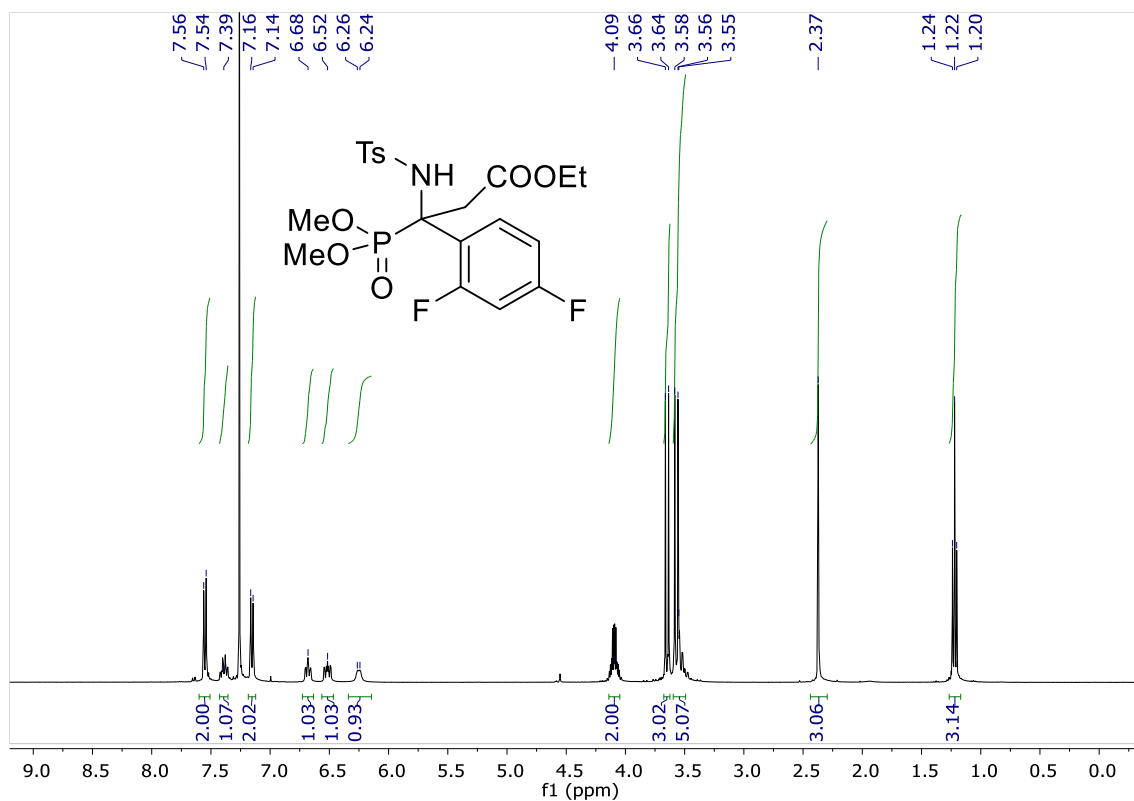


^{19}F NMR (282 MHz, CDCl_3)

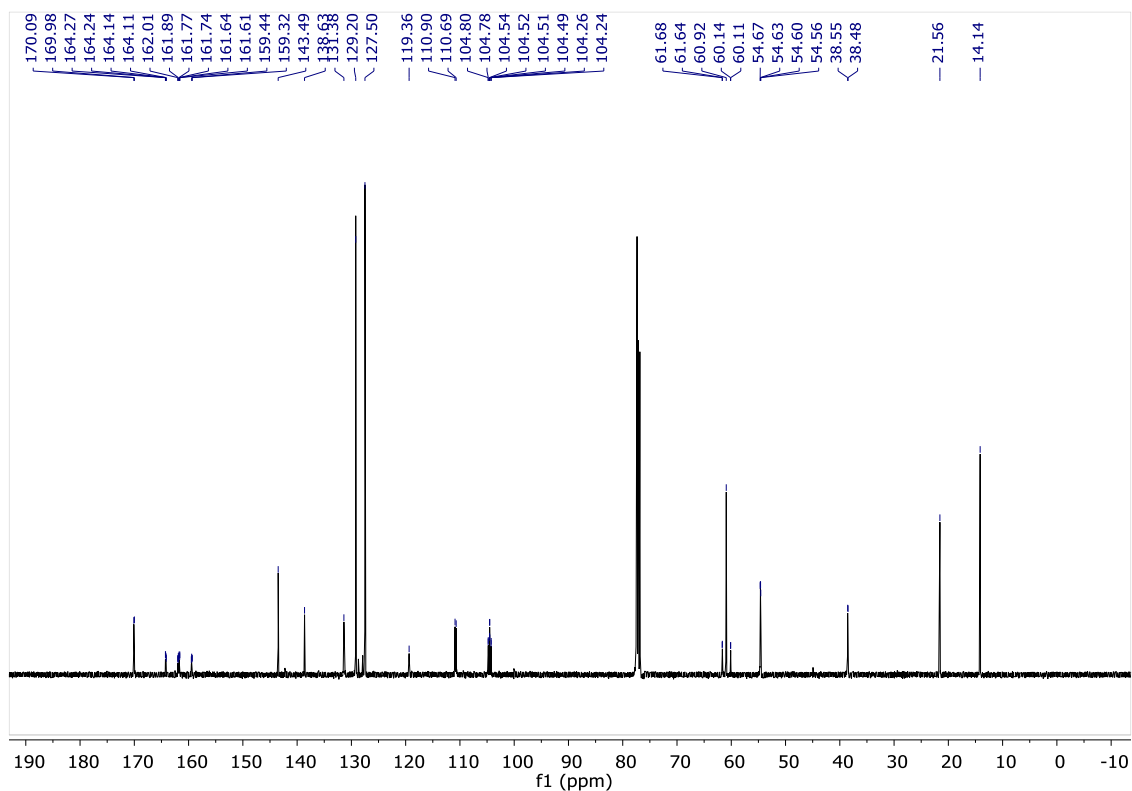


Ethyl 3-(2,4-difluorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7m)

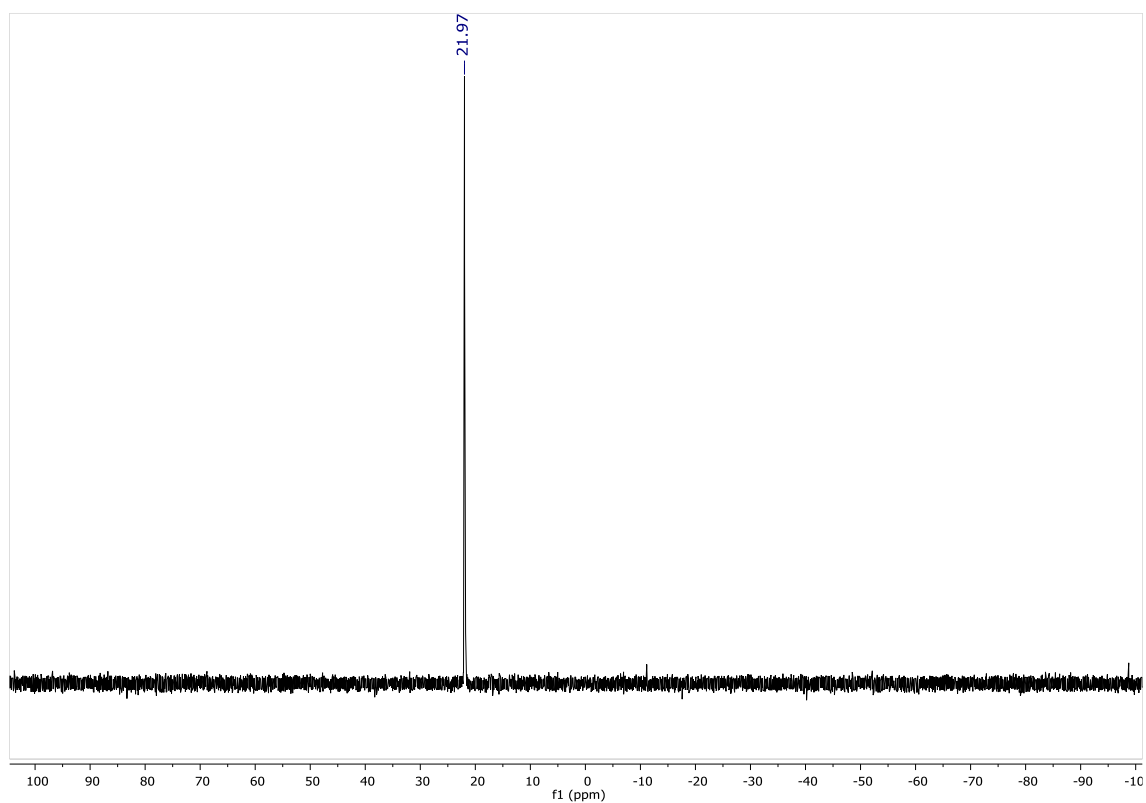
^1H NMR (400 MHz, CDCl_3)



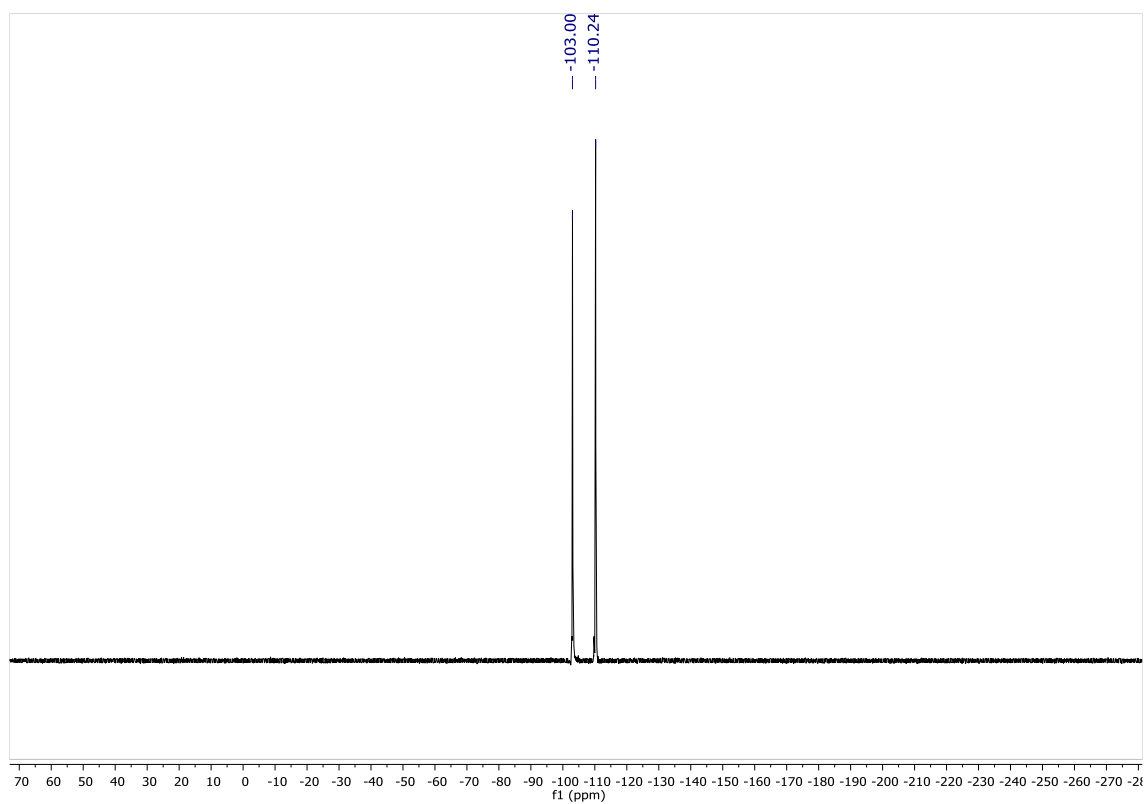
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

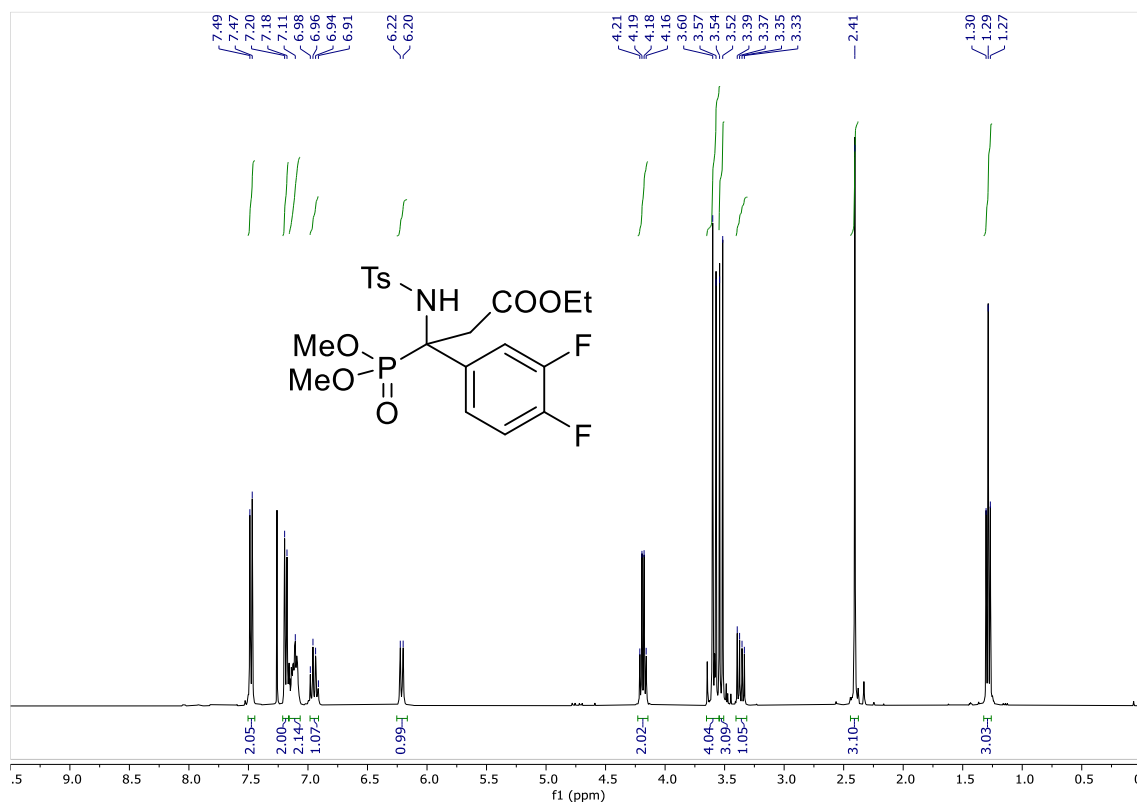


^{19}F NMR (282 MHz, CDCl_3)

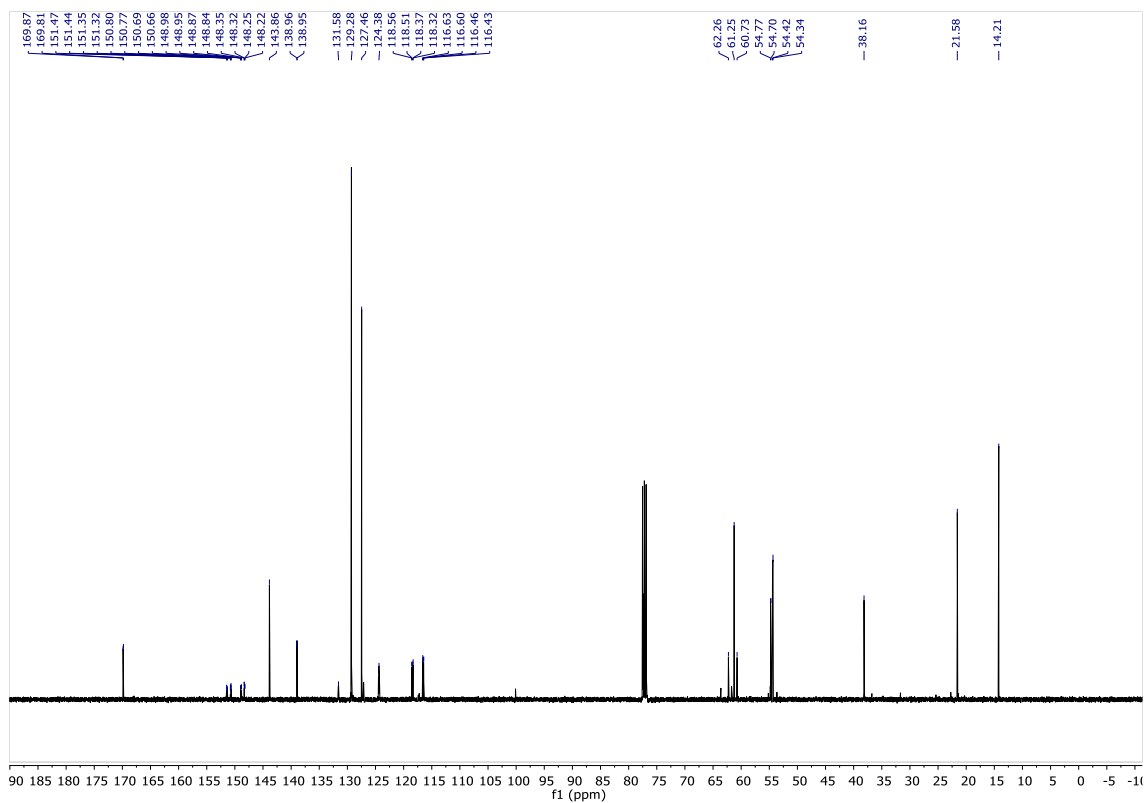


Ethyl 3-(3,4-difluorophenyl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7n)

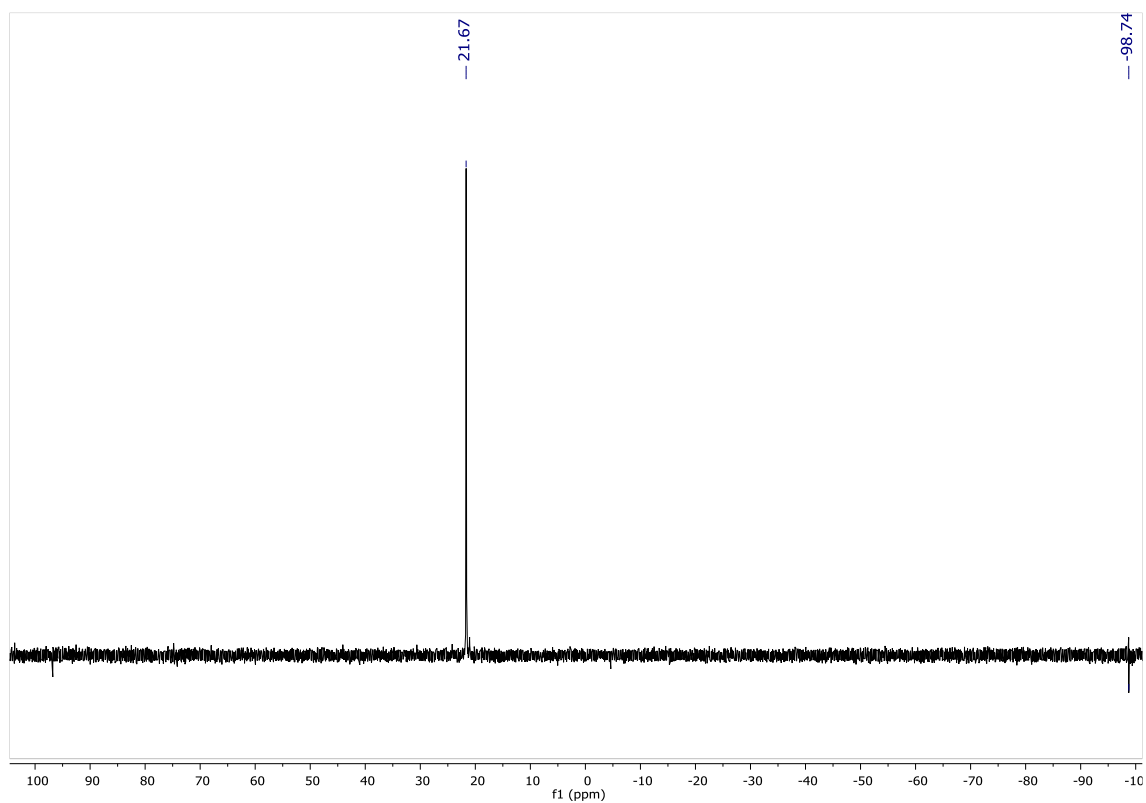
^1H NMR (400 MHz, CDCl_3)



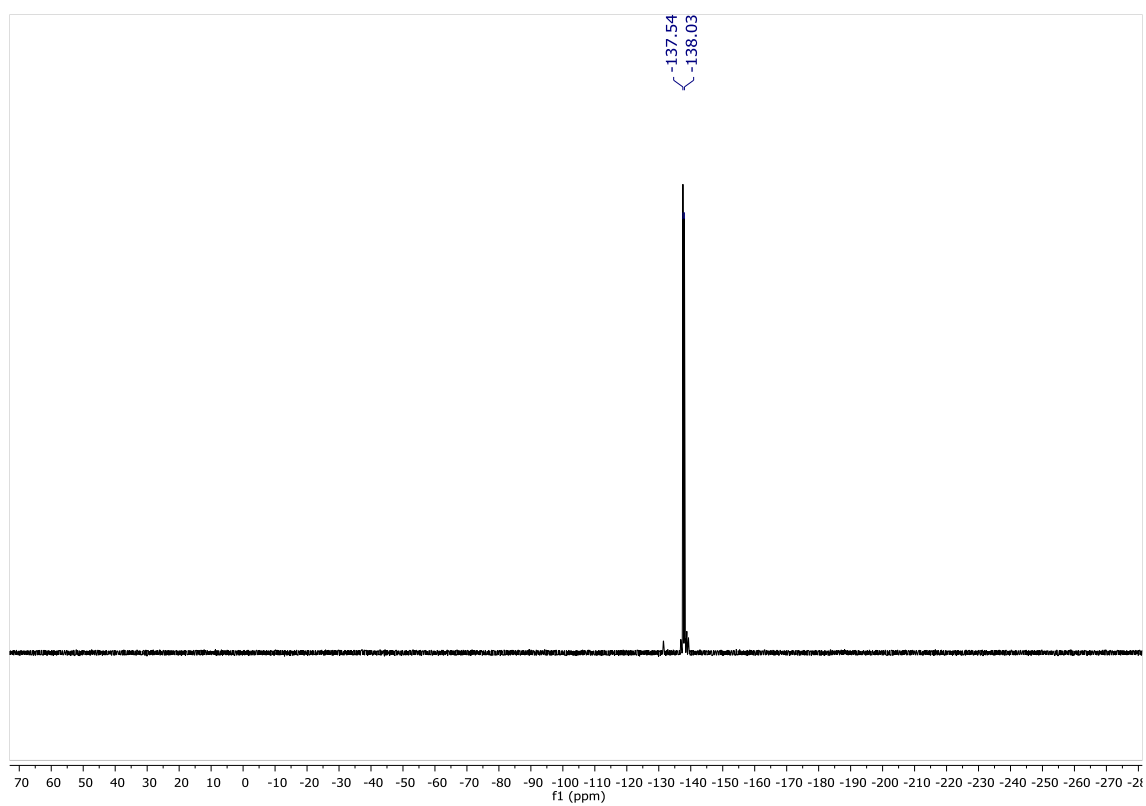
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

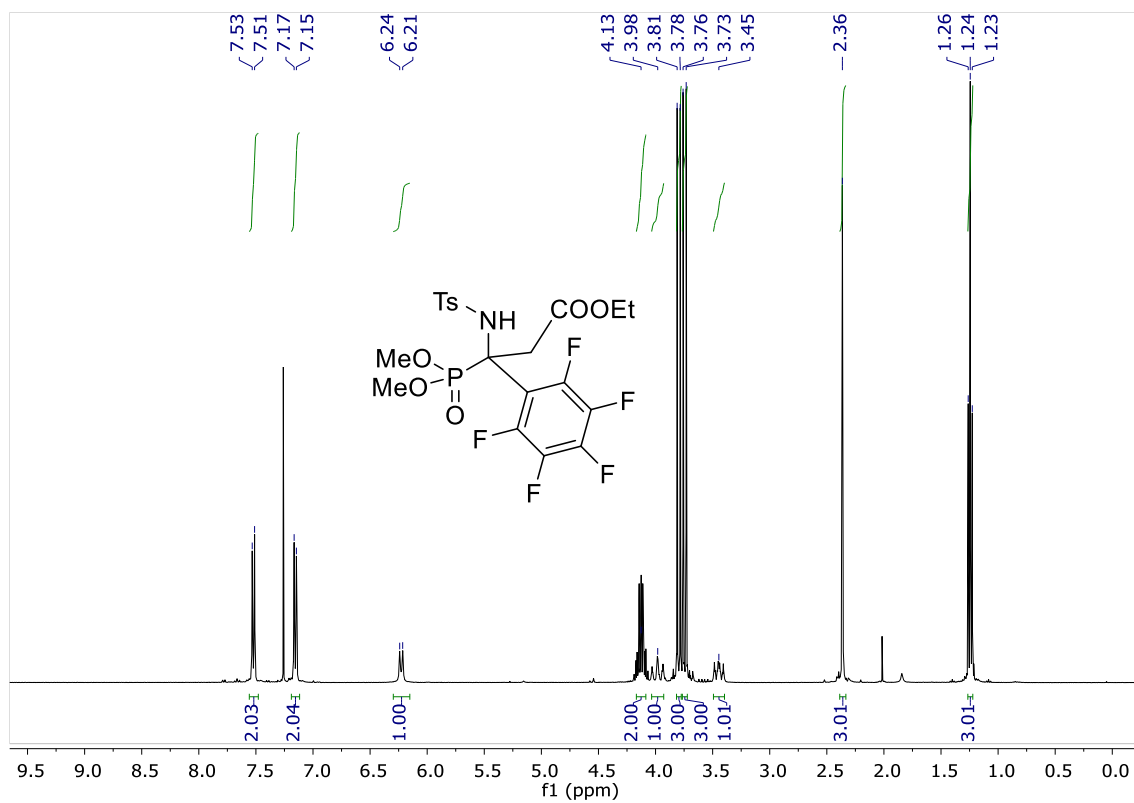


^{19}F NMR (282 MHz, CDCl_3)

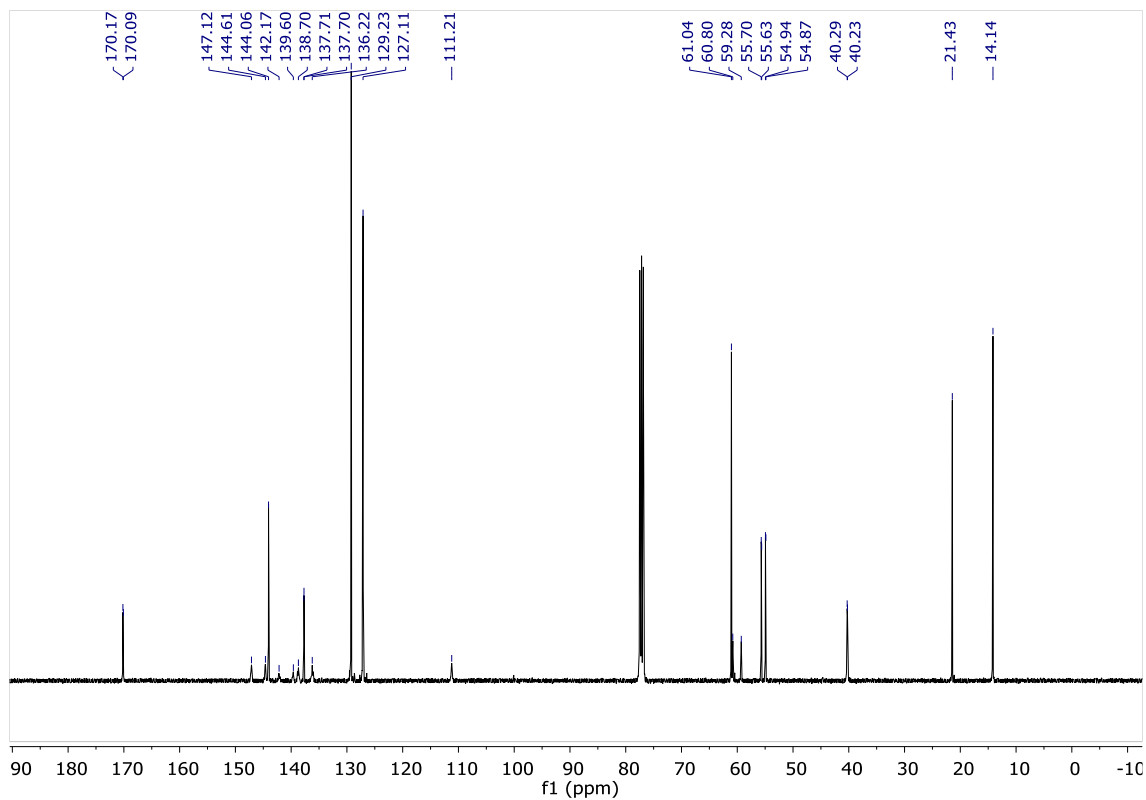


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(perfluorophenyl)propanoate (7o)

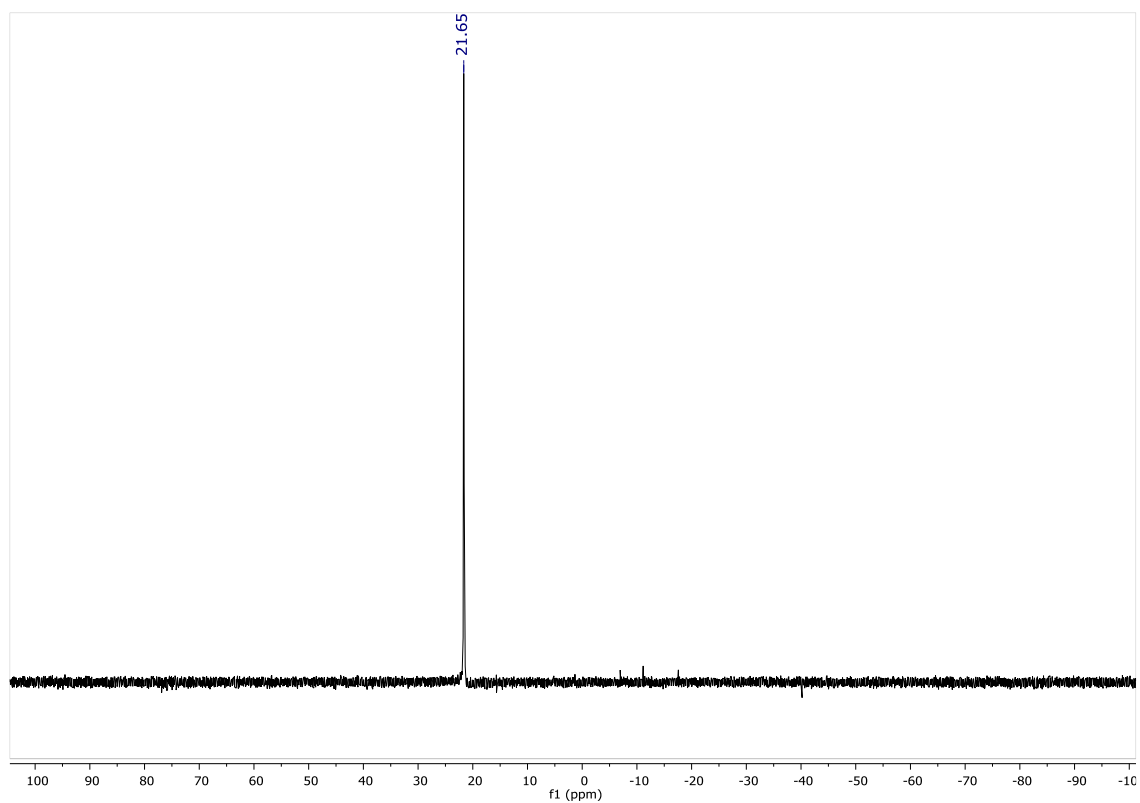
^1H NMR (400 MHz, CDCl_3)



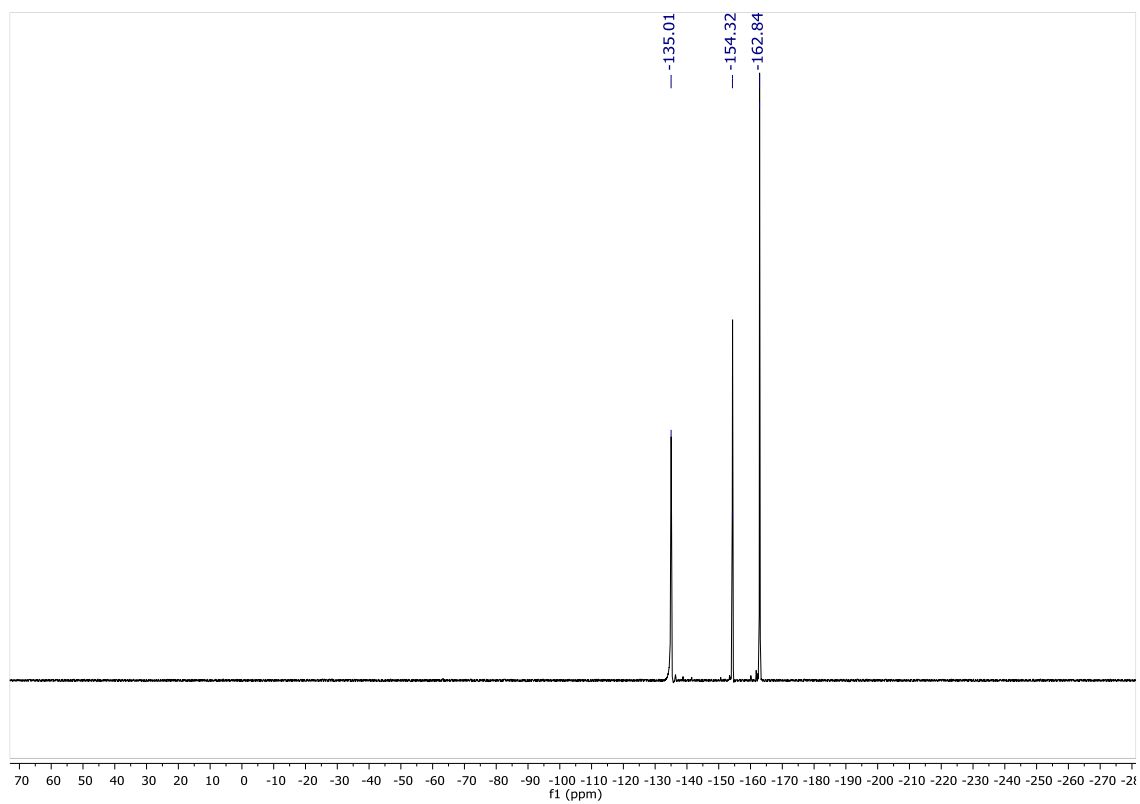
^{13}C NMR [^1H] (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

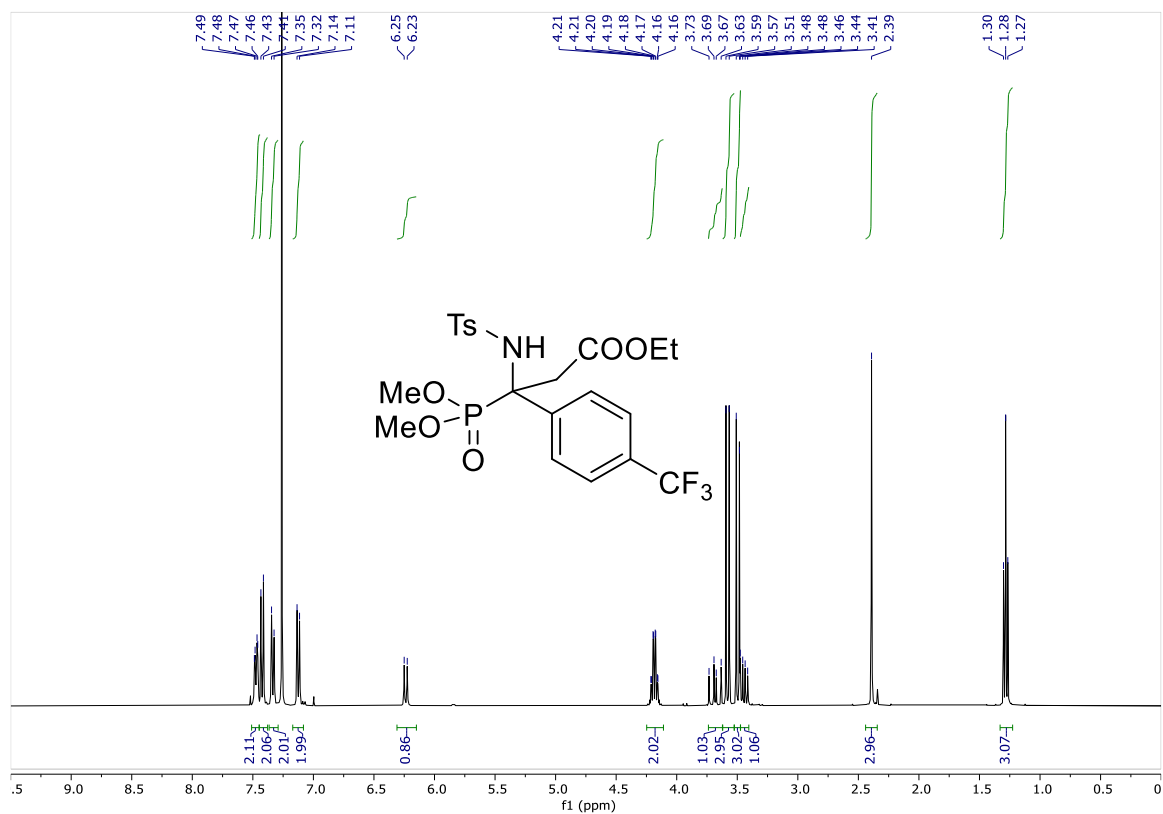


^{19}F NMR (282 MHz, CDCl_3)

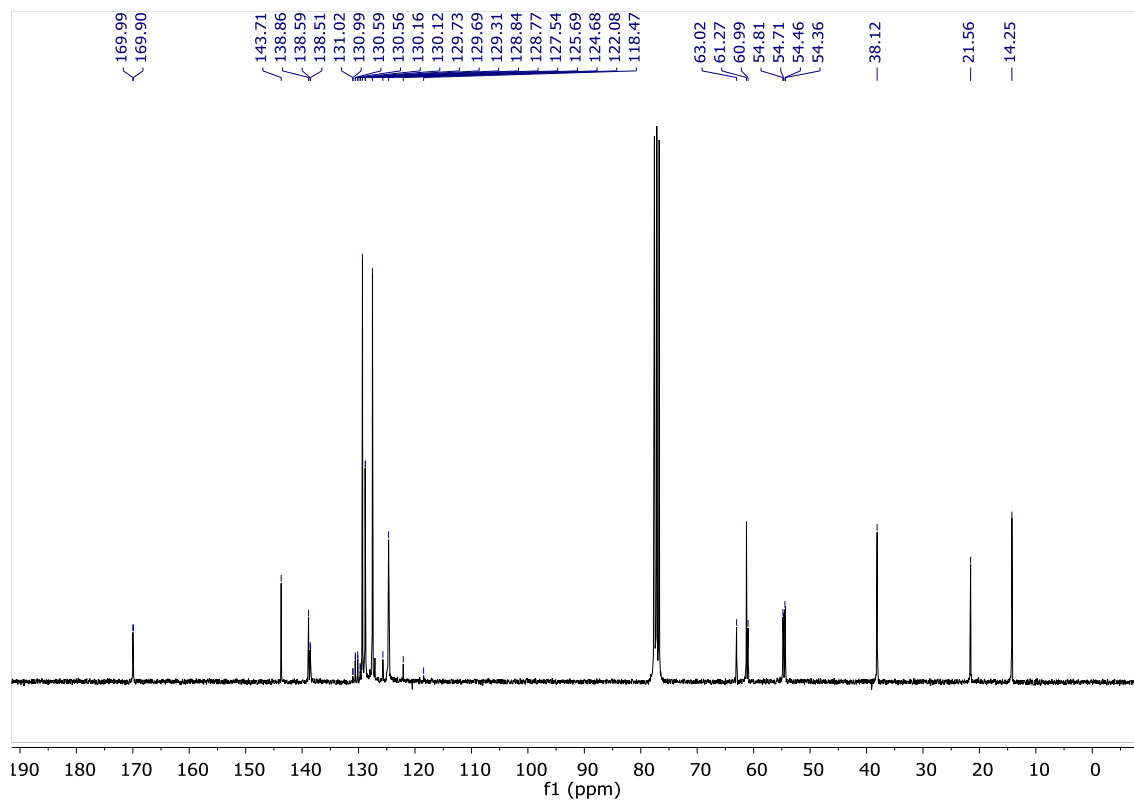


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-(trifluoromethyl)phenyl)propanoate (7p)

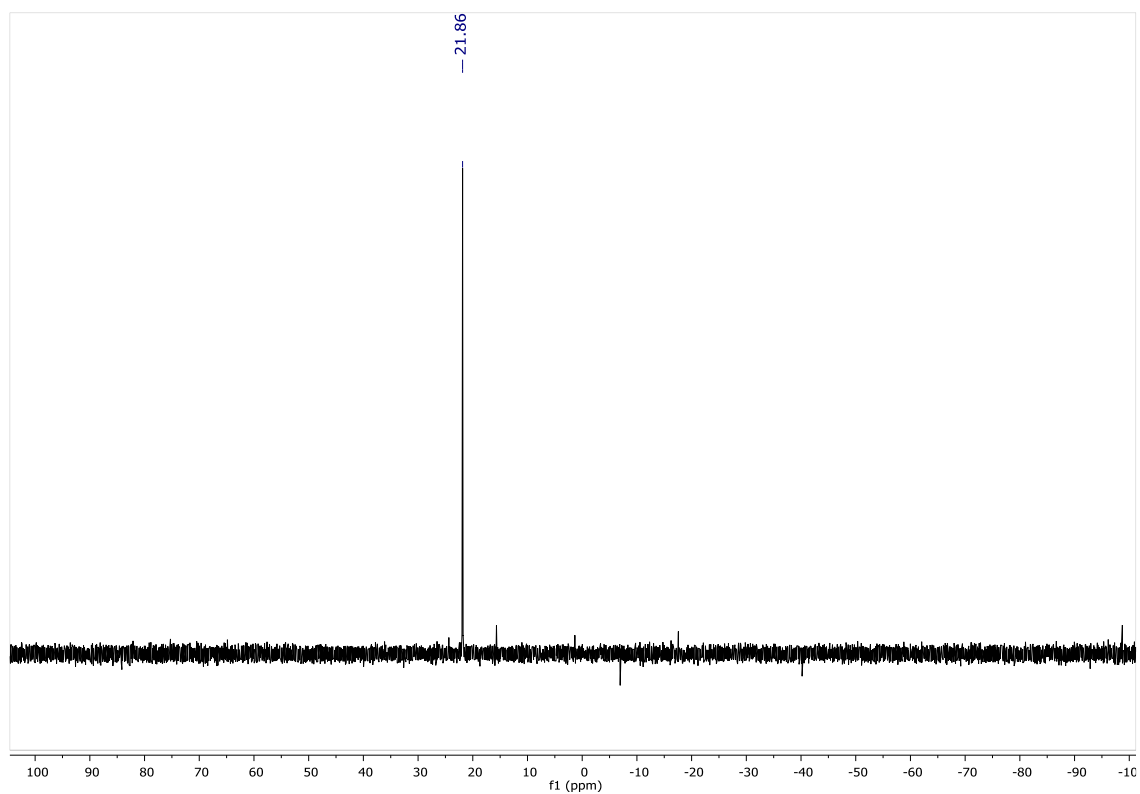
^1H NMR (400 MHz, CDCl_3)



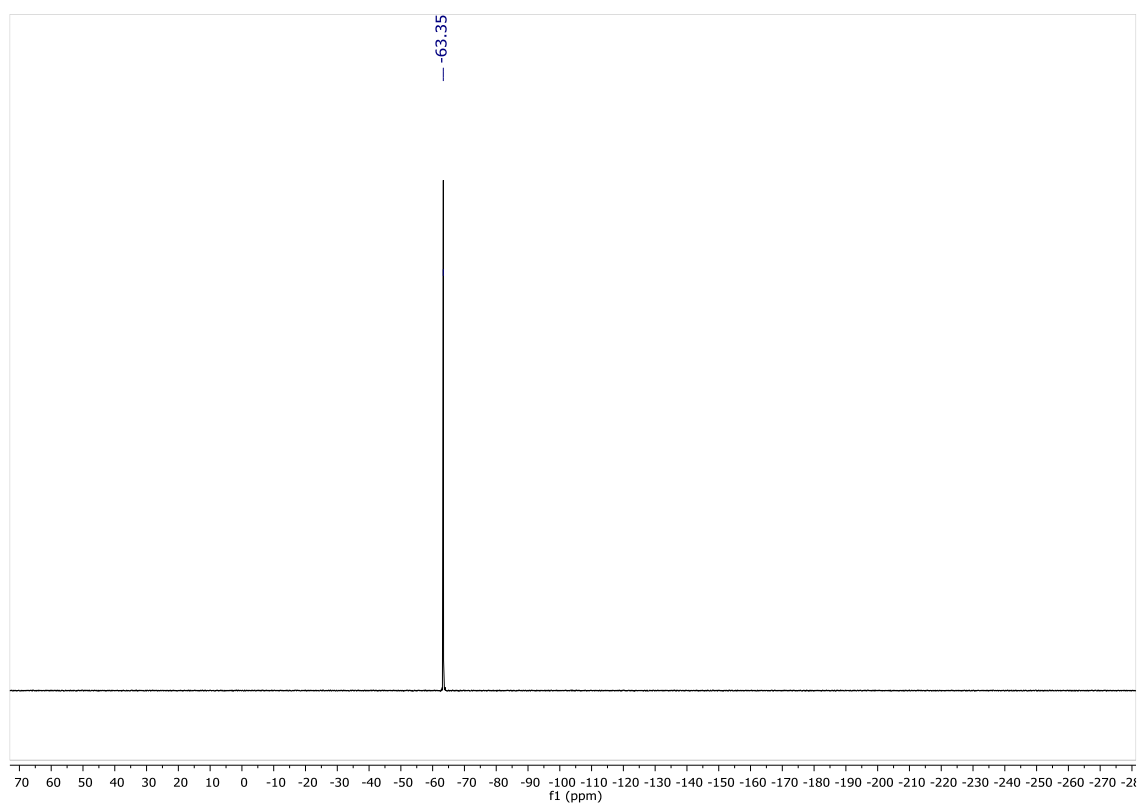
^{13}C NMR [^1H] (75 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

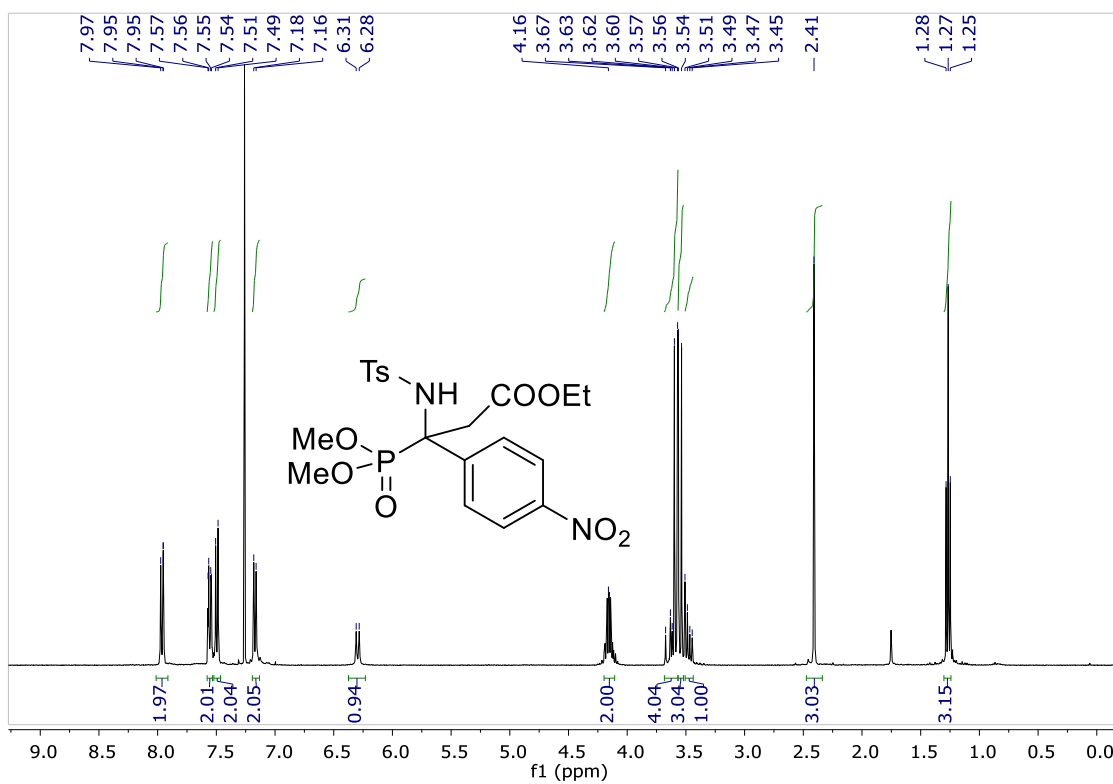


^{19}F NMR (282 MHz, CDCl_3)

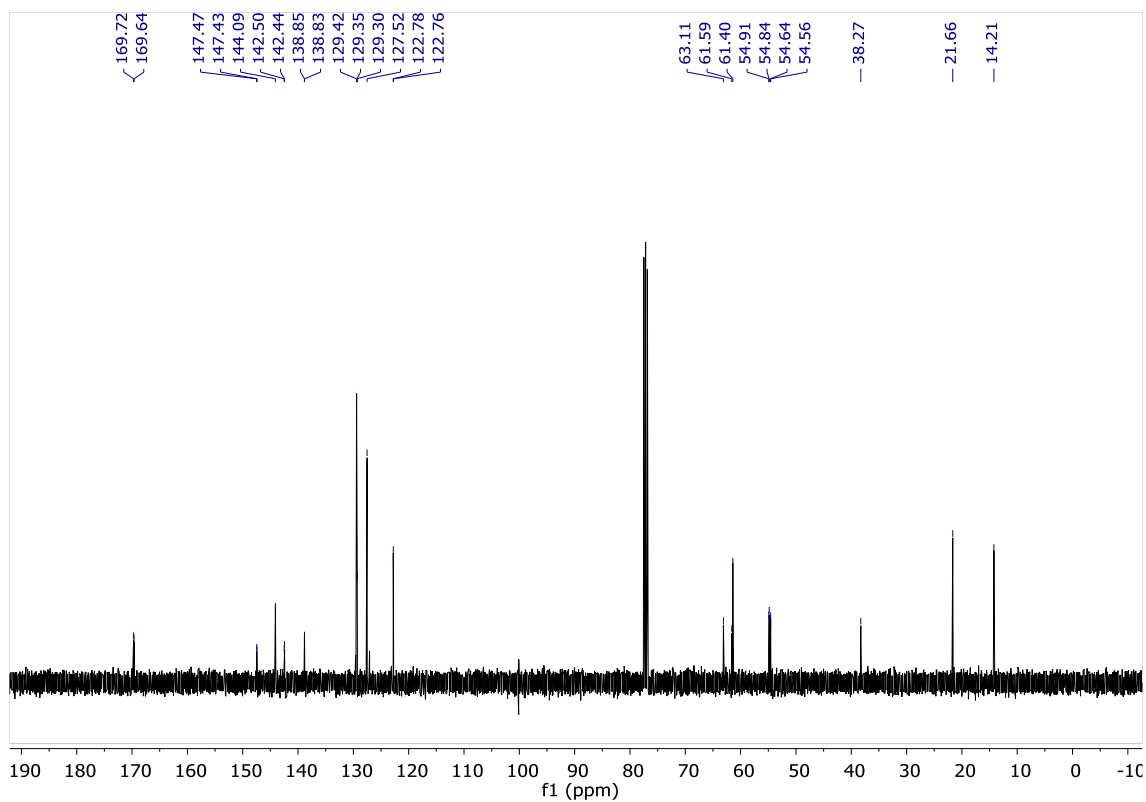


Ethyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-(4-nitrophenyl)propanoate (7q)

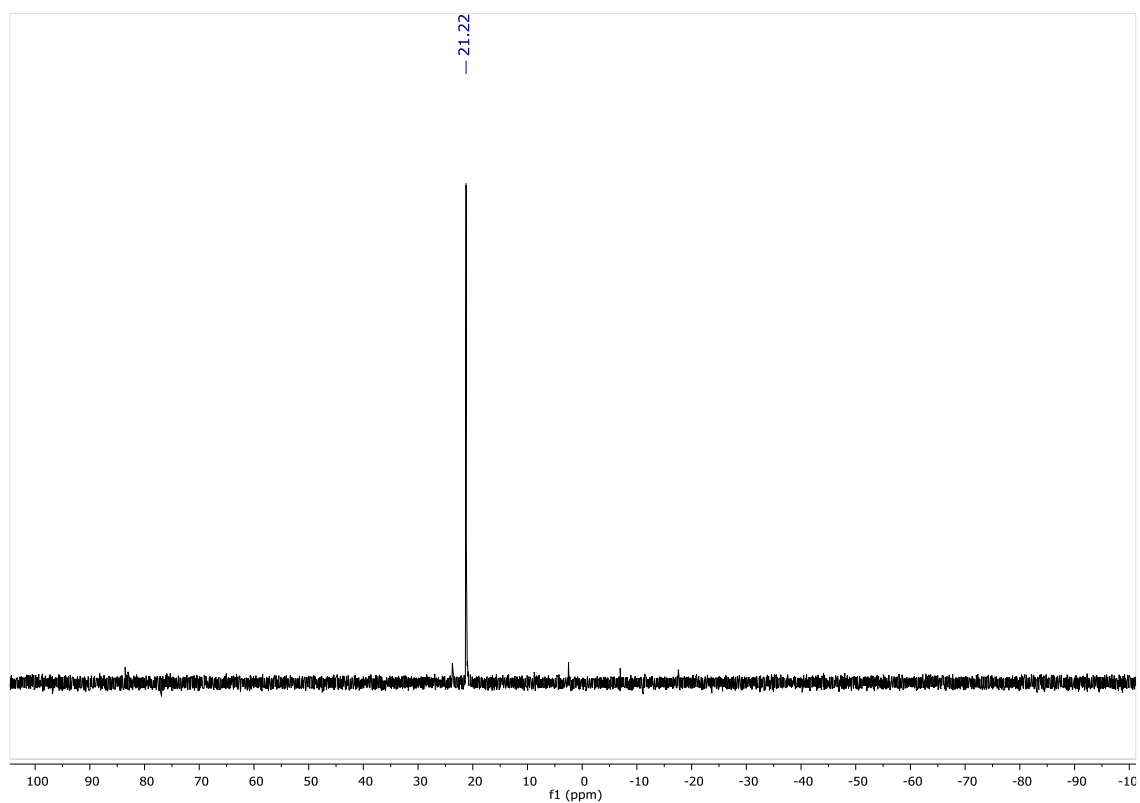
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR [^1H] (101 MHz, CDCl_3)

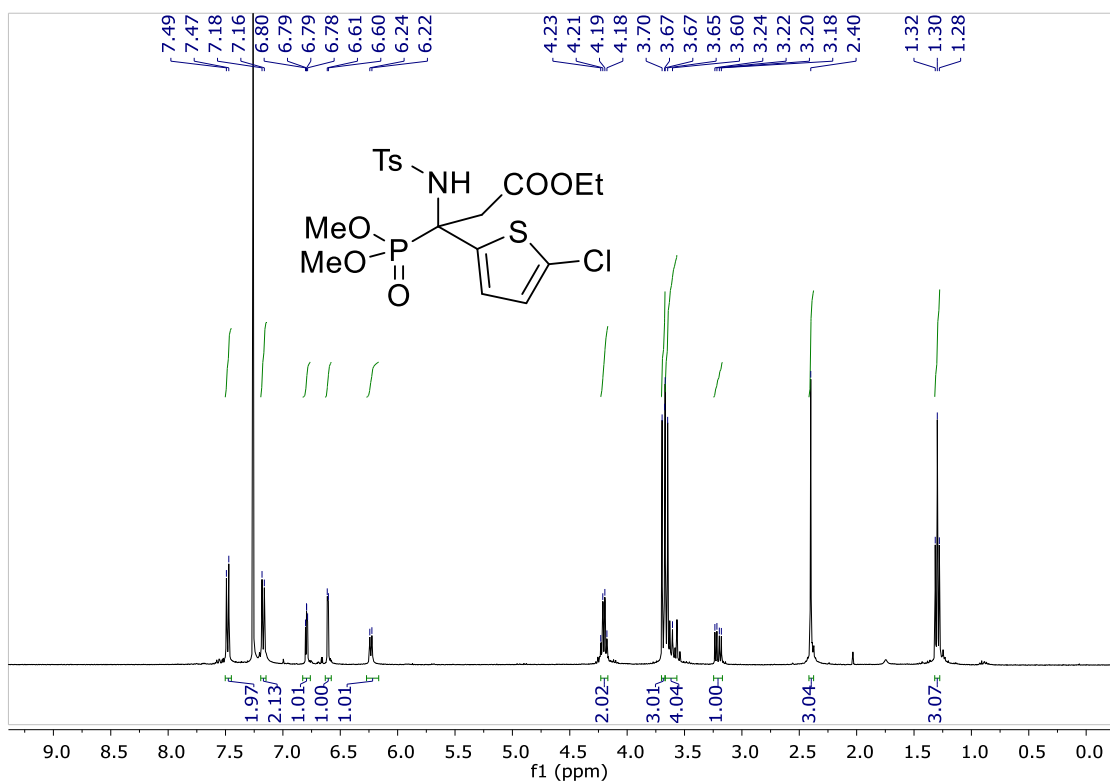


^{31}P NMR (120 MHz, CDCl_3)

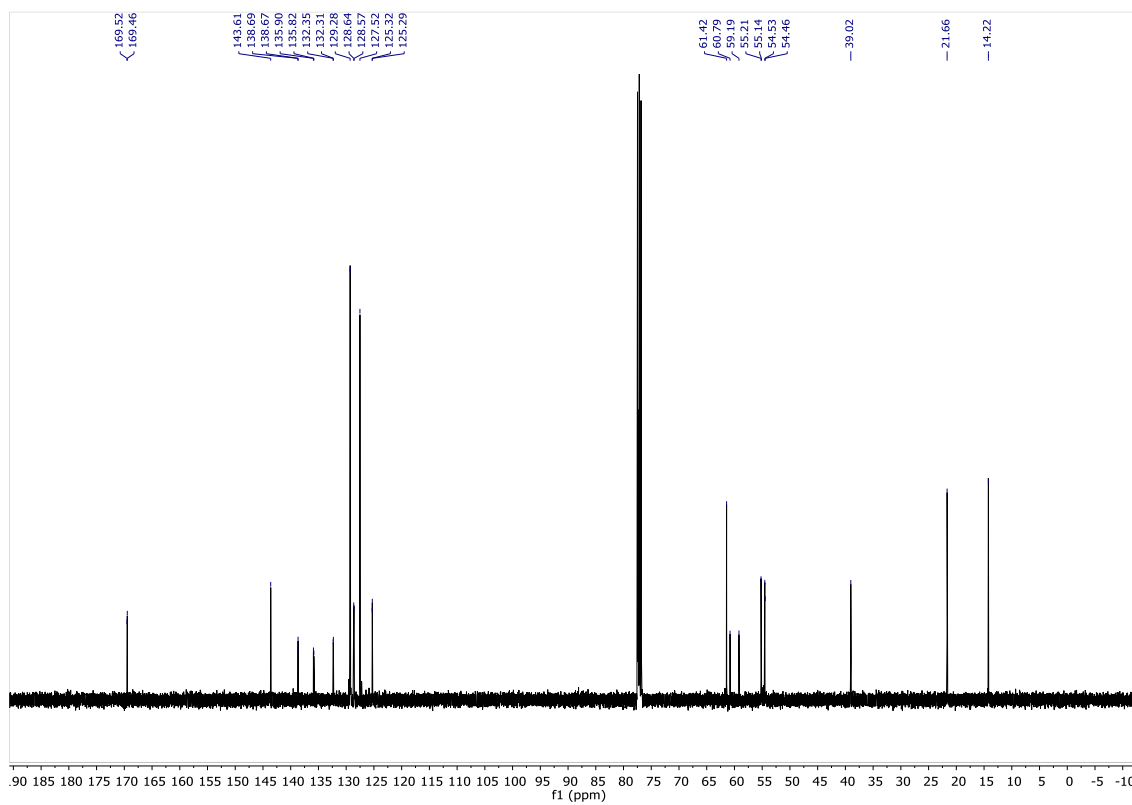


Ethyl 3-(5-chlorothiophen-2-yl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7r)

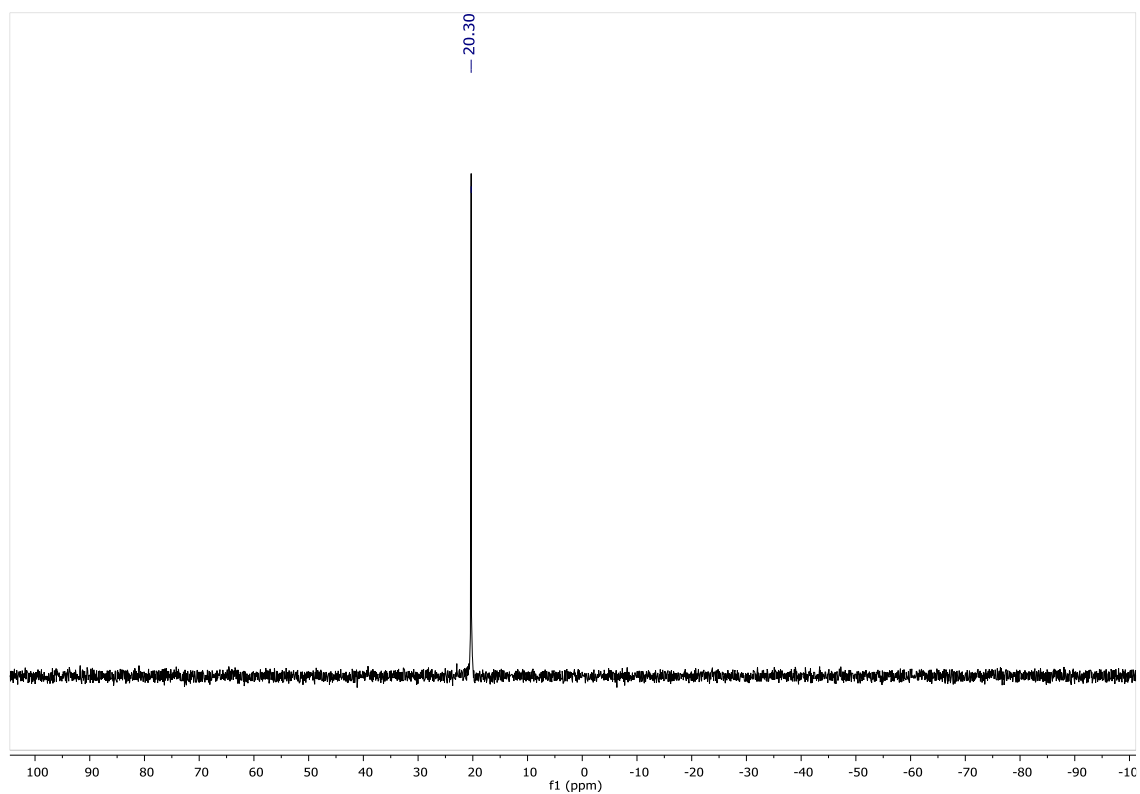
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

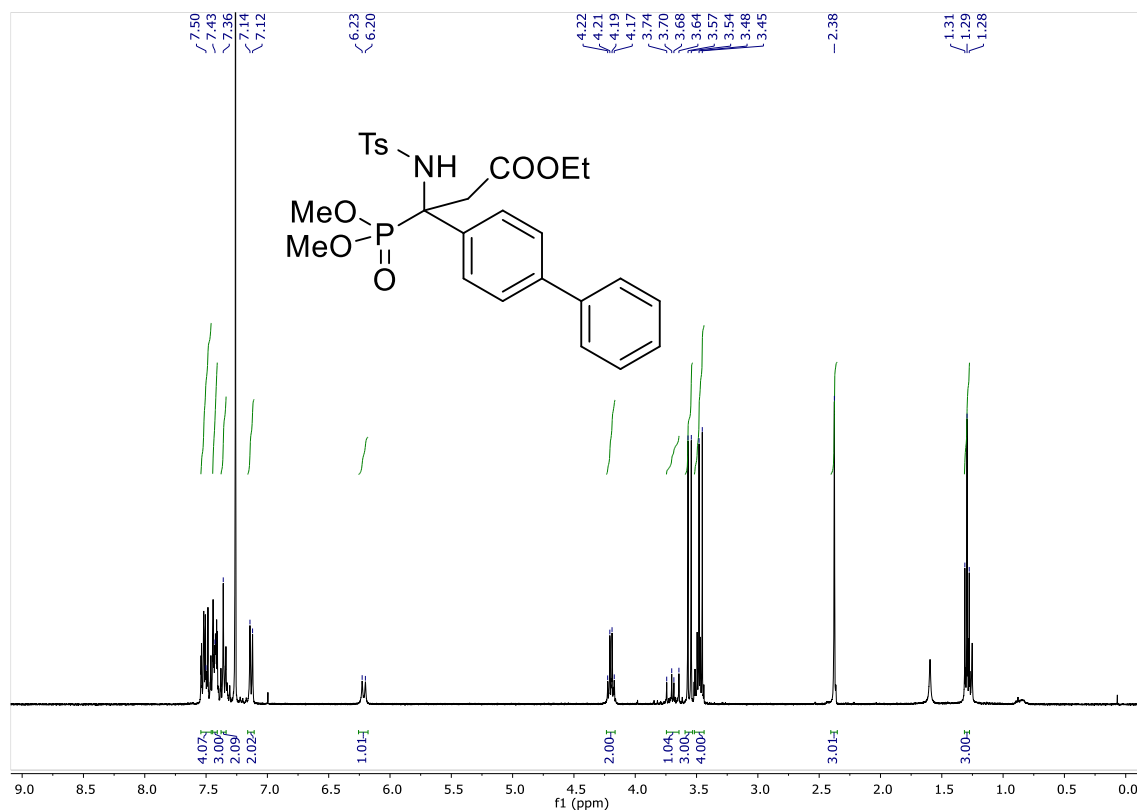


^{31}P NMR (120 MHz, CDCl_3)

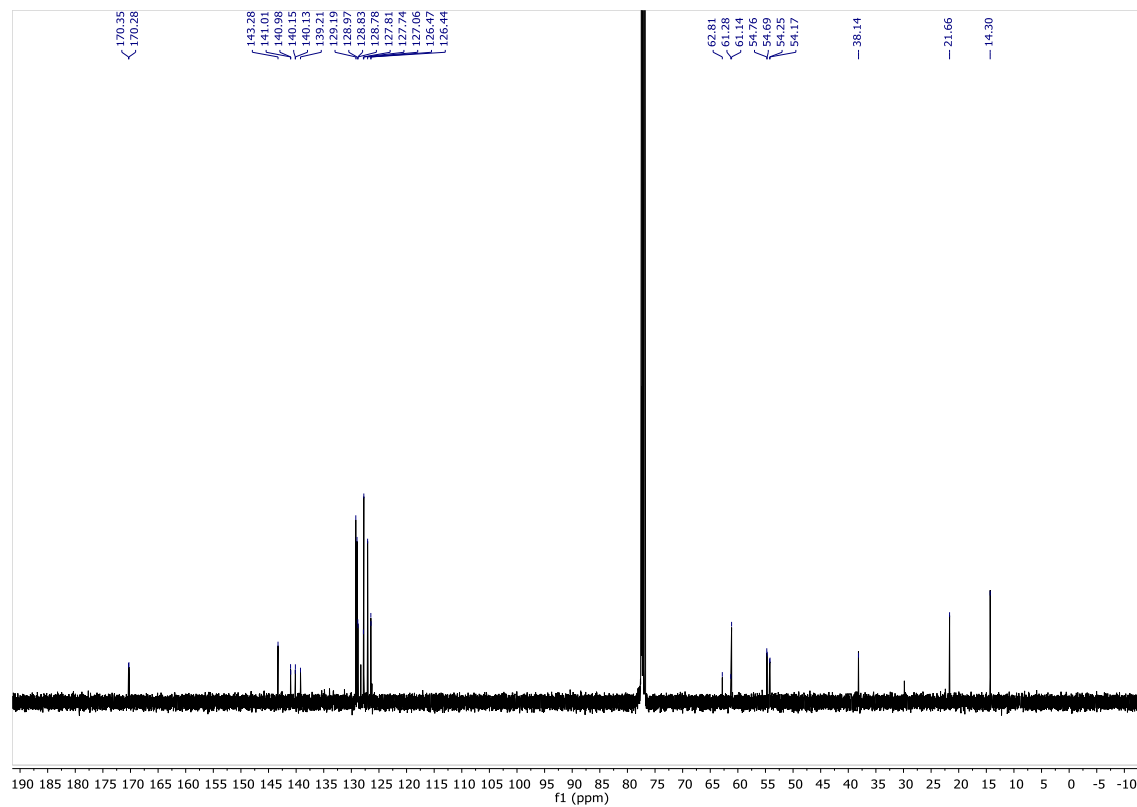


Ethyl 3-([1,1'-biphenyl]-4-yl)-3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)propanoate (7s)

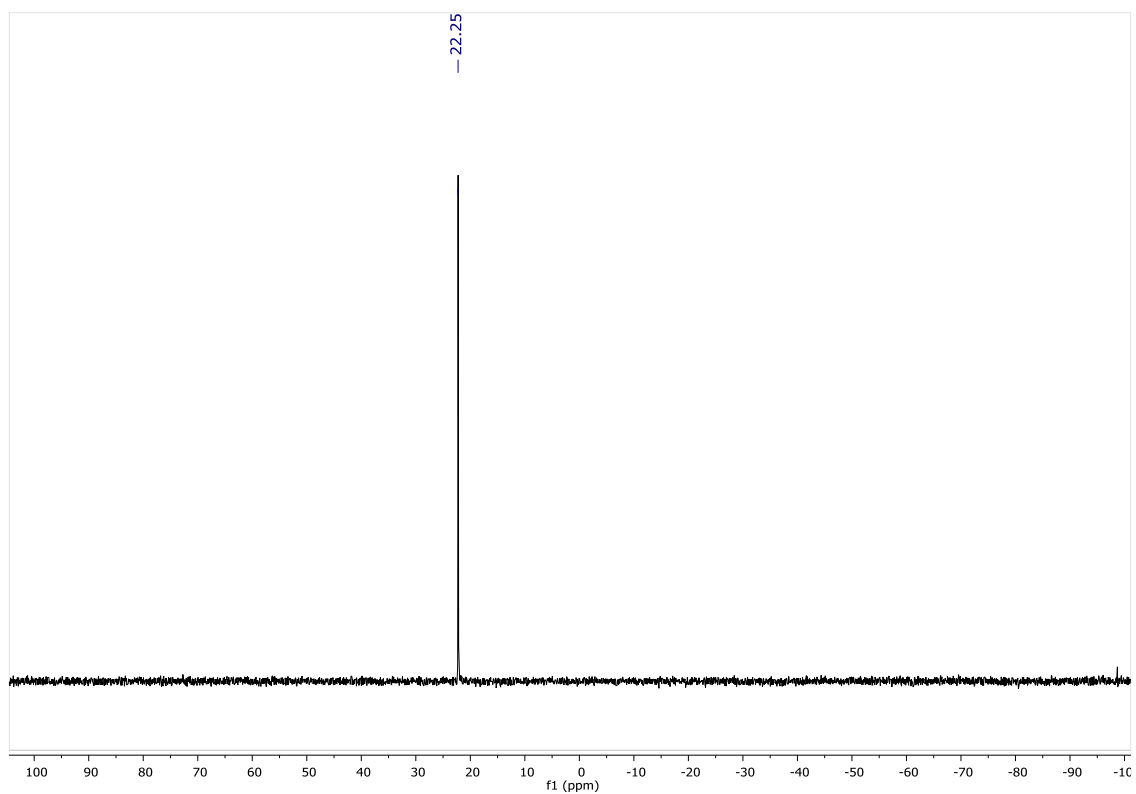
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



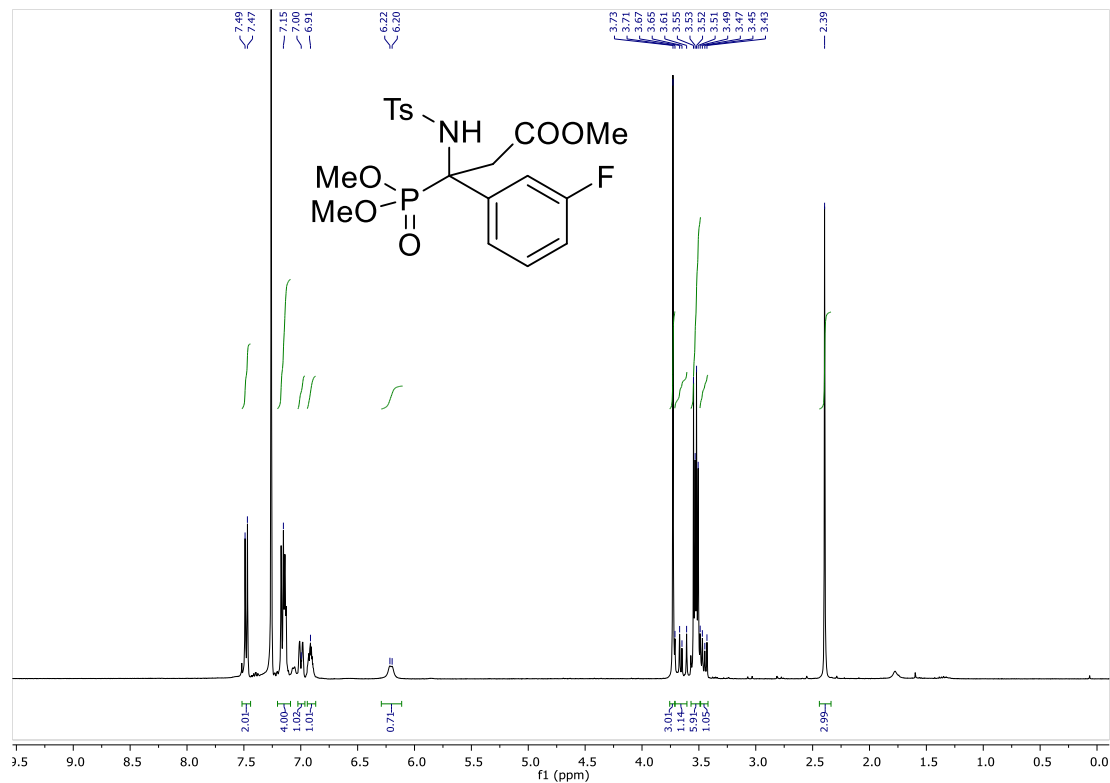
^{31}P NMR (120 MHz, CDCl_3)



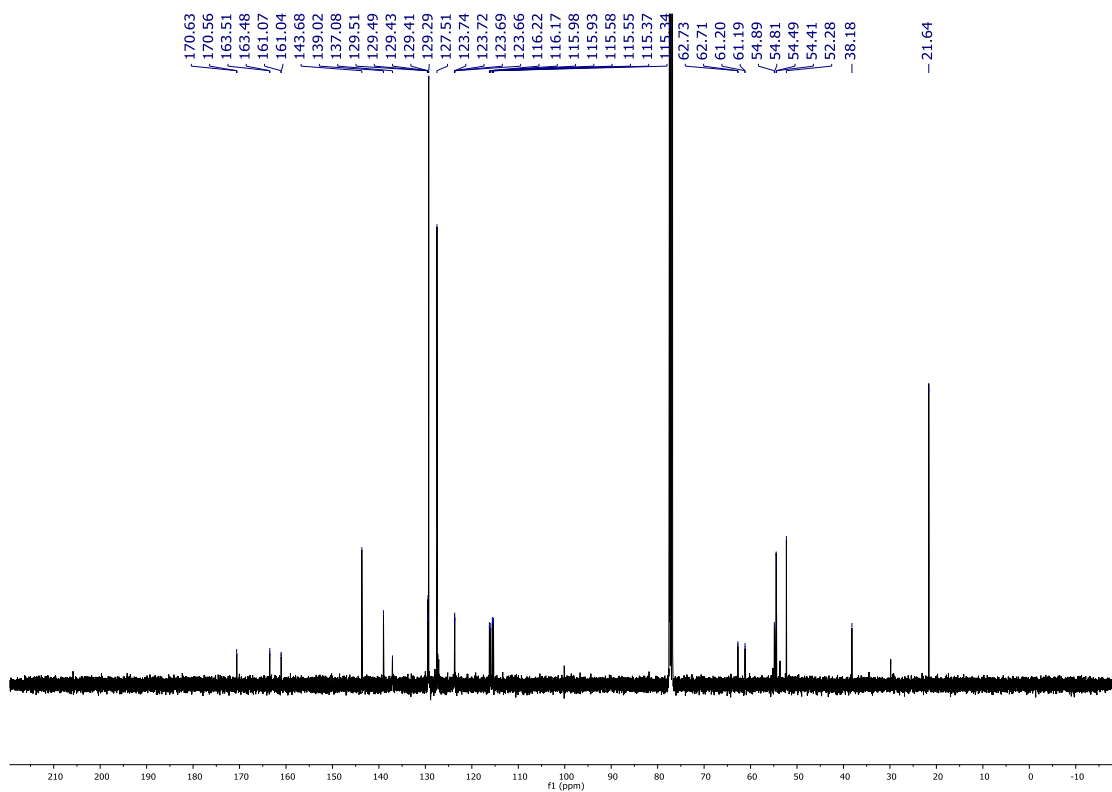
3. ^1H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra of compounds 12, 13 and 14

Methyl 3-(dimethoxyphosphoryl)-3-(3-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (12)

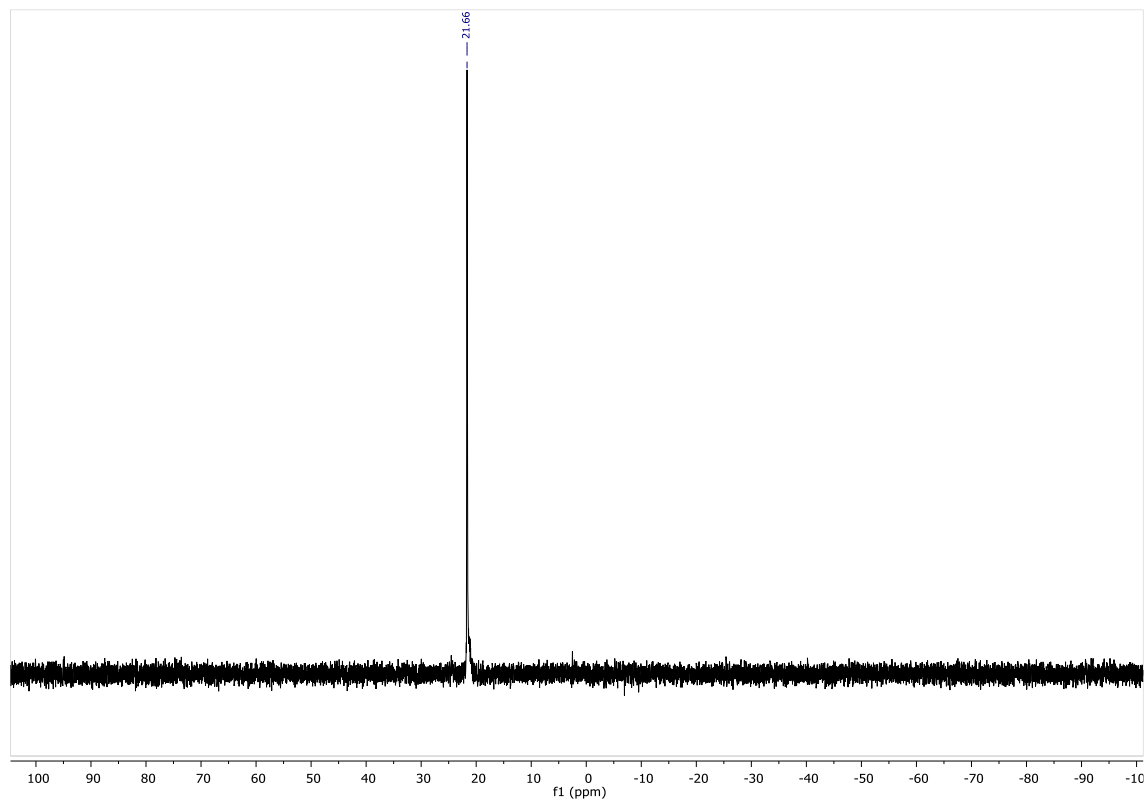
^1H NMR (400 MHz, CDCl_3)



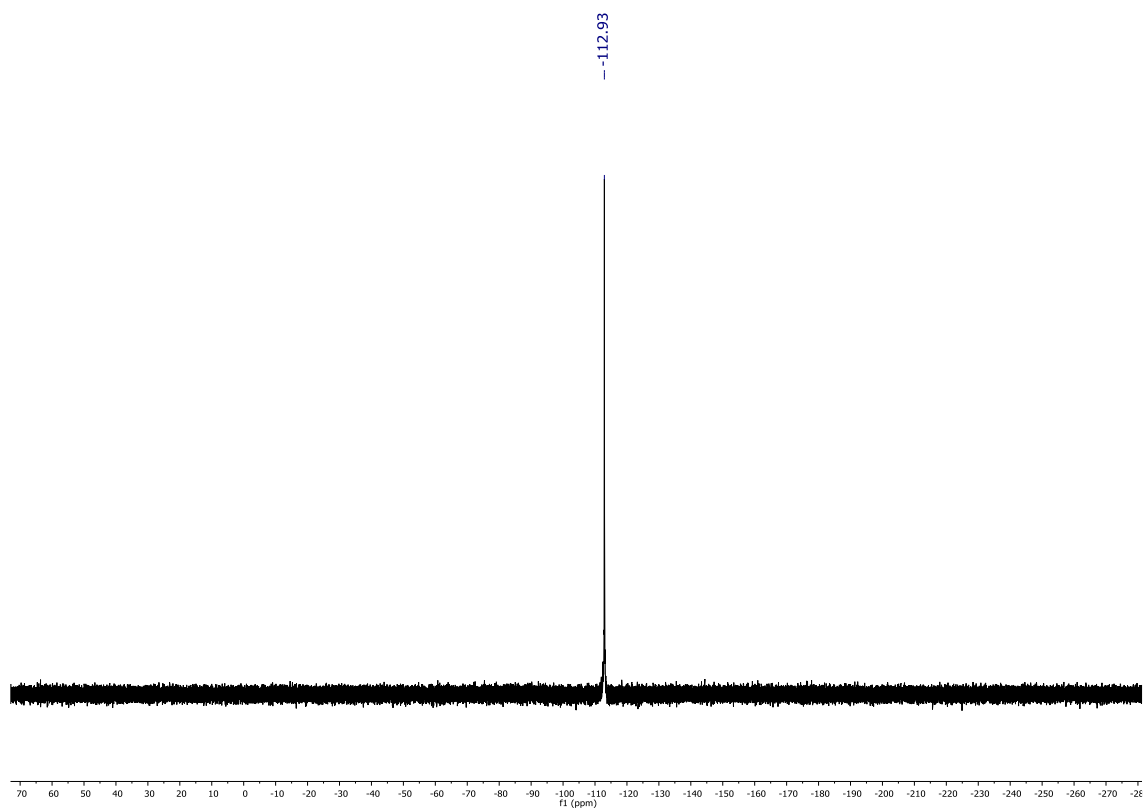
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

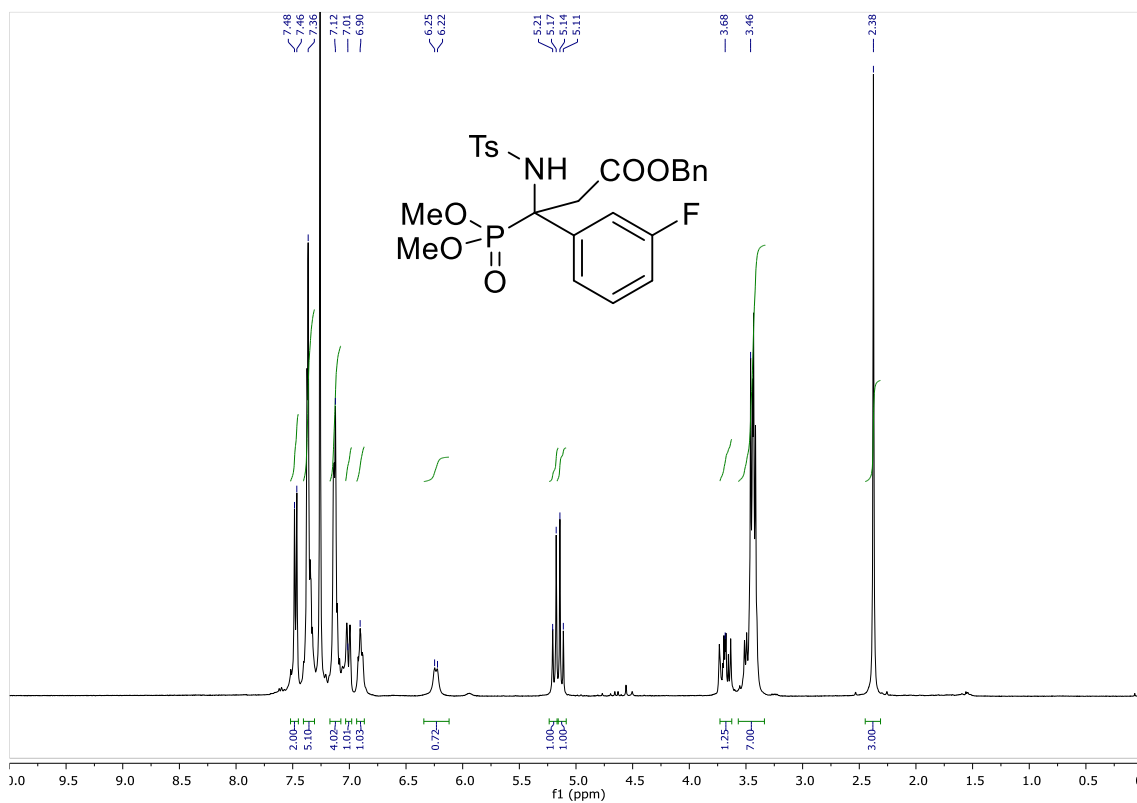


^{19}F NMR (282 MHz, CDCl_3)

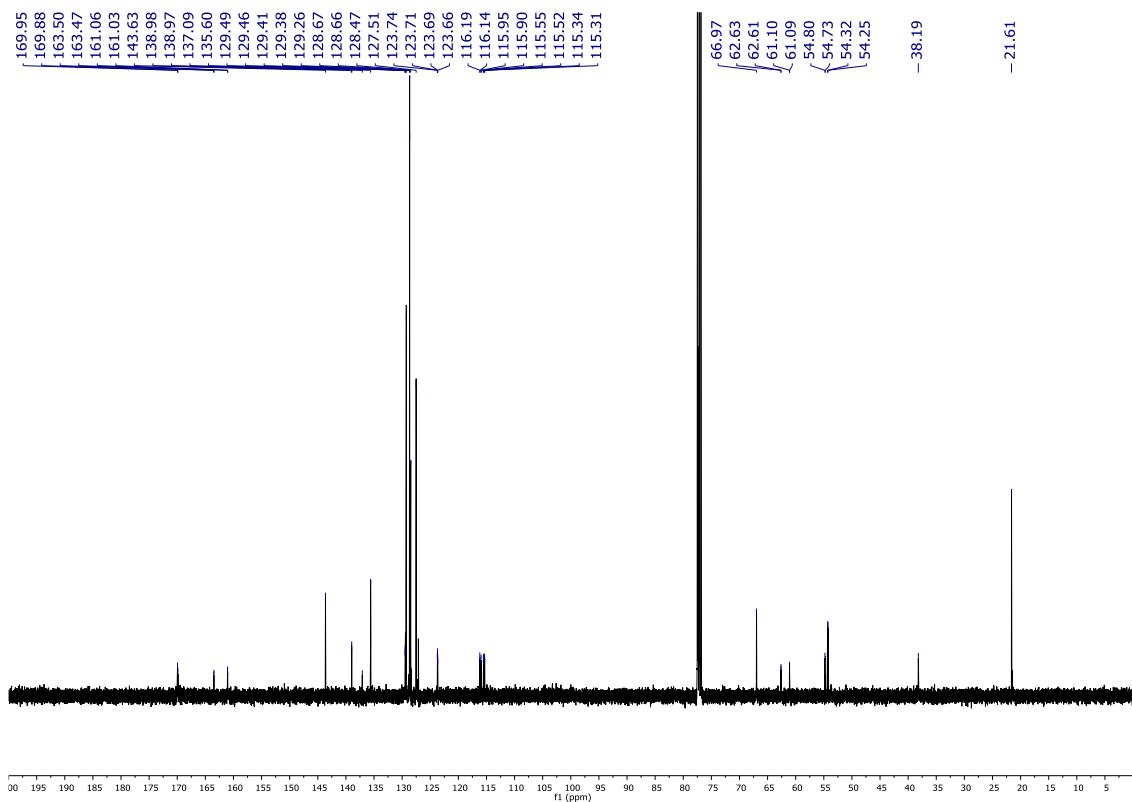


Benzyl 3-(dimethoxyphosphoryl)-3-(3-fluorophenyl)-3-((4-methylphenyl)sulfonamido)propanoate (13a)

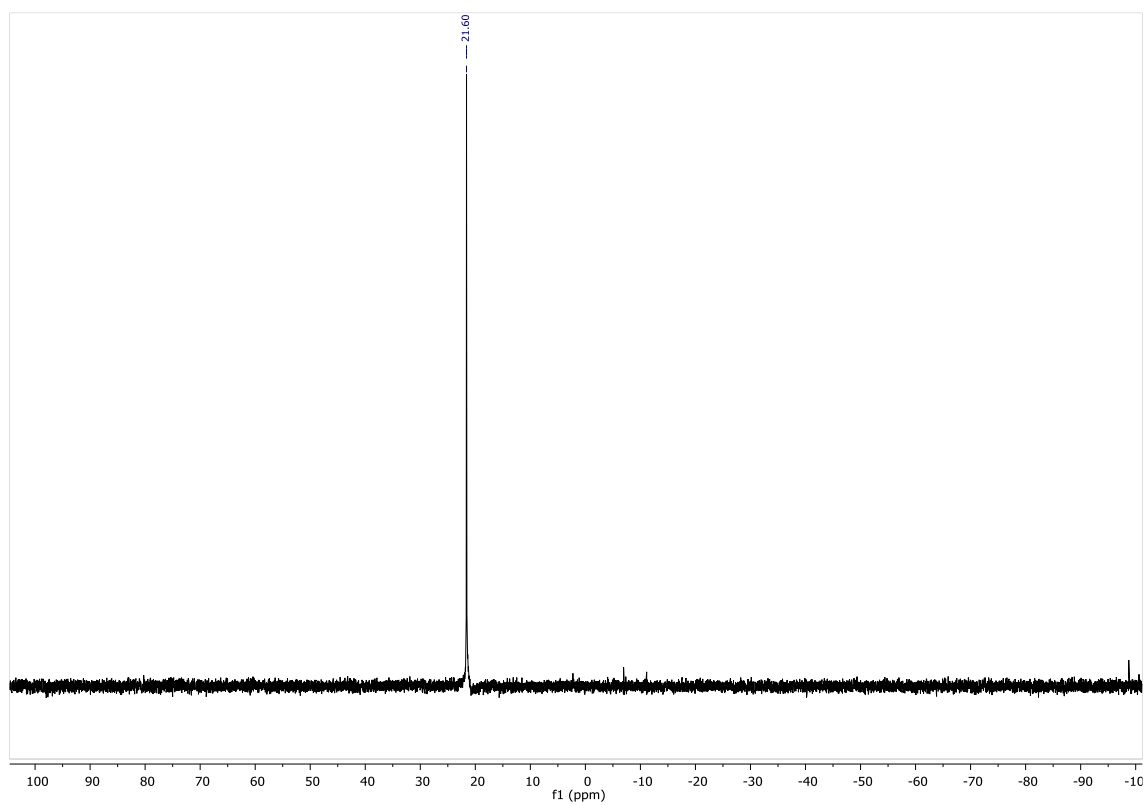
^1H NMR (400 MHz, CDCl_3)



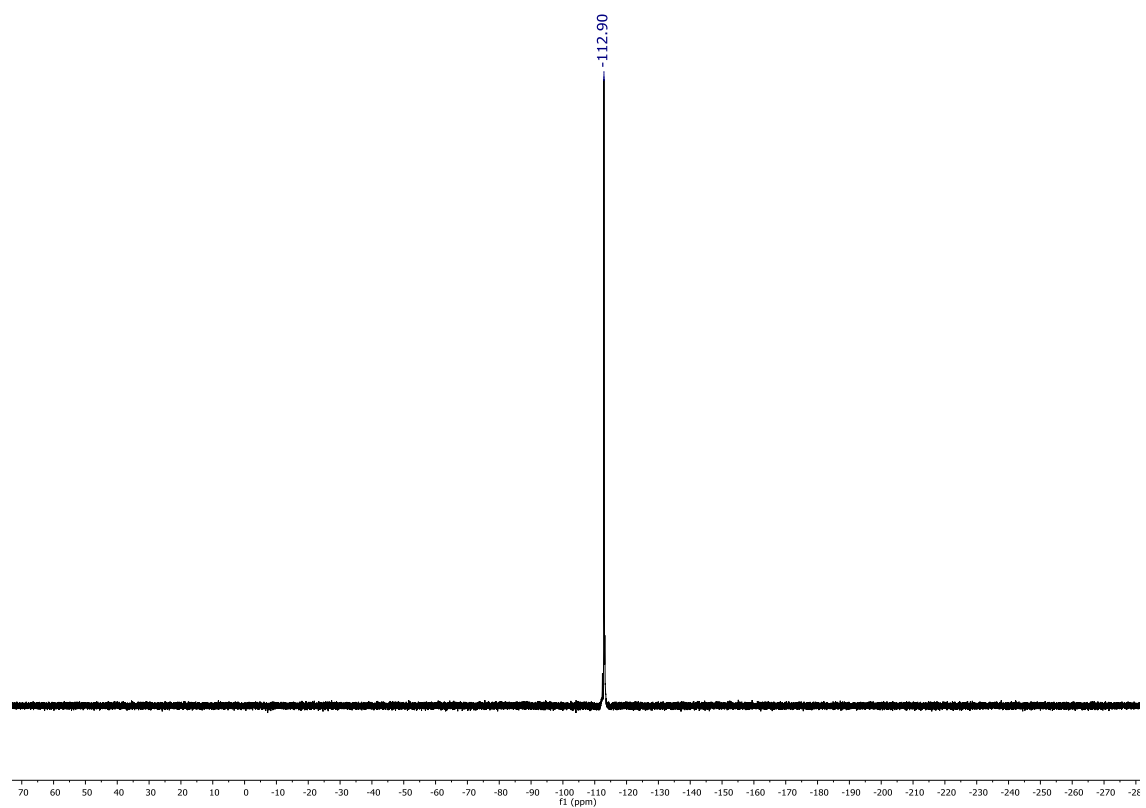
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



^{31}P NMR (120 MHz, CDCl_3)

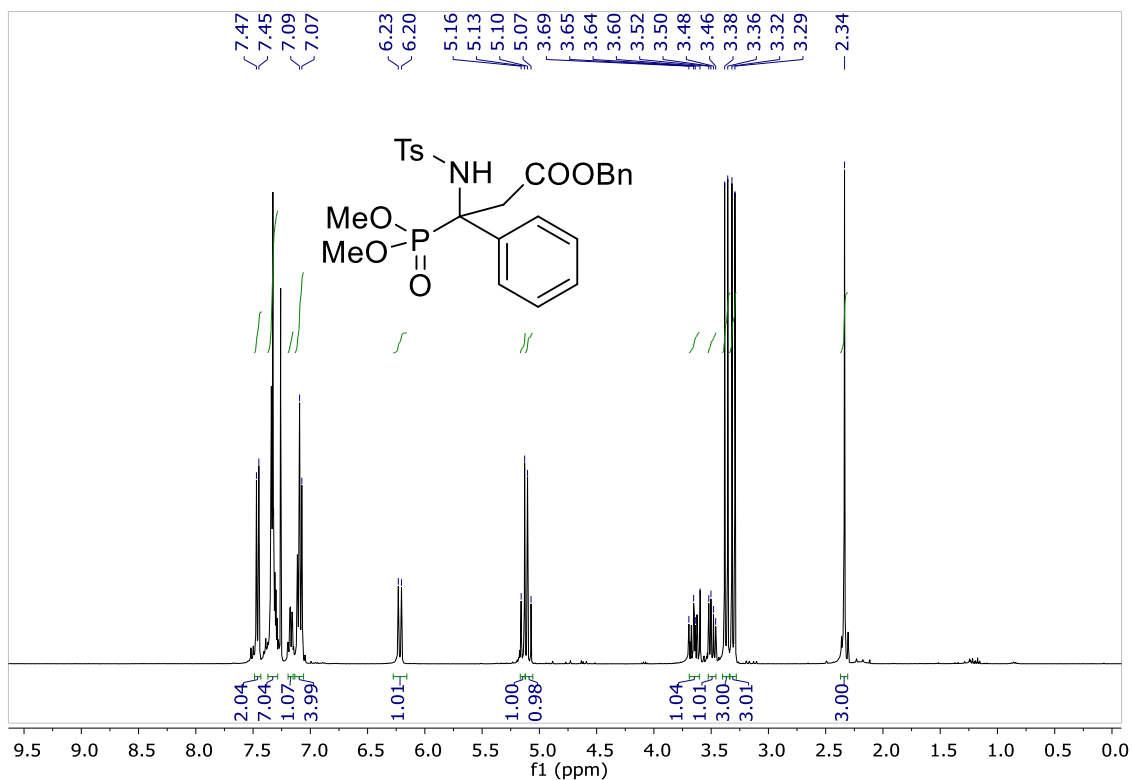


^{19}F NMR (282 MHz, CDCl_3)

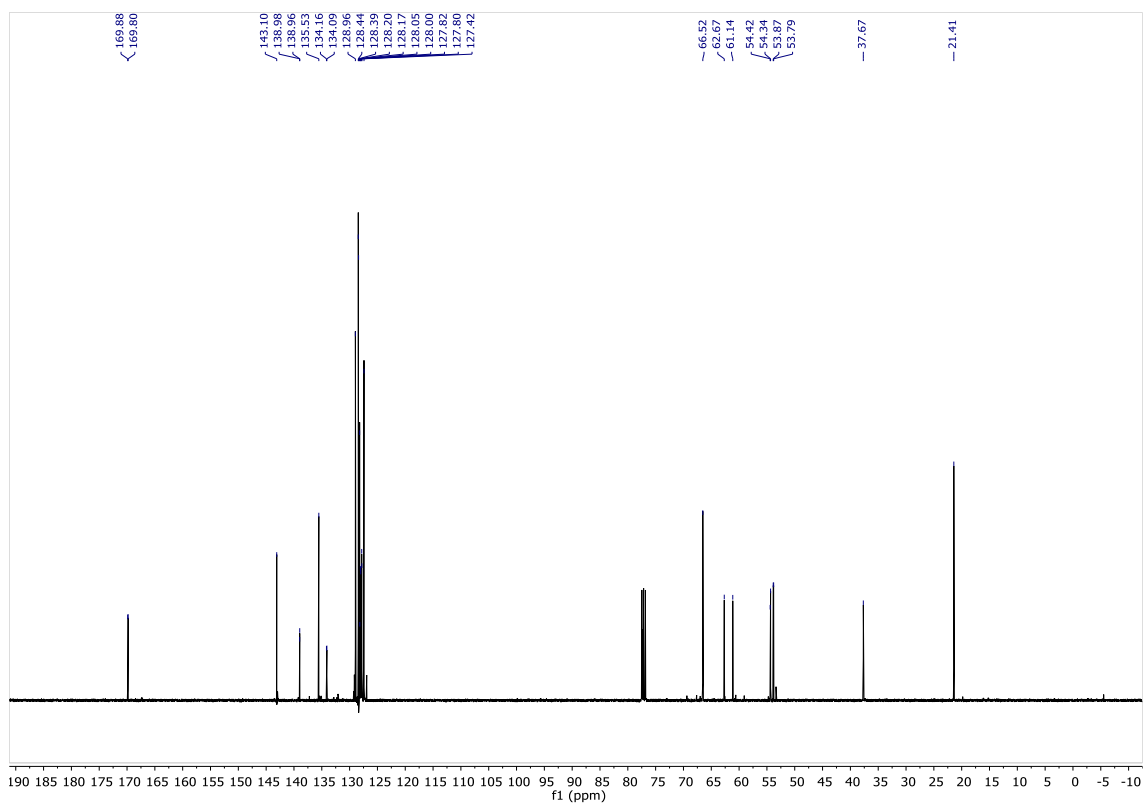


Benzyl 3-(dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate (13b)

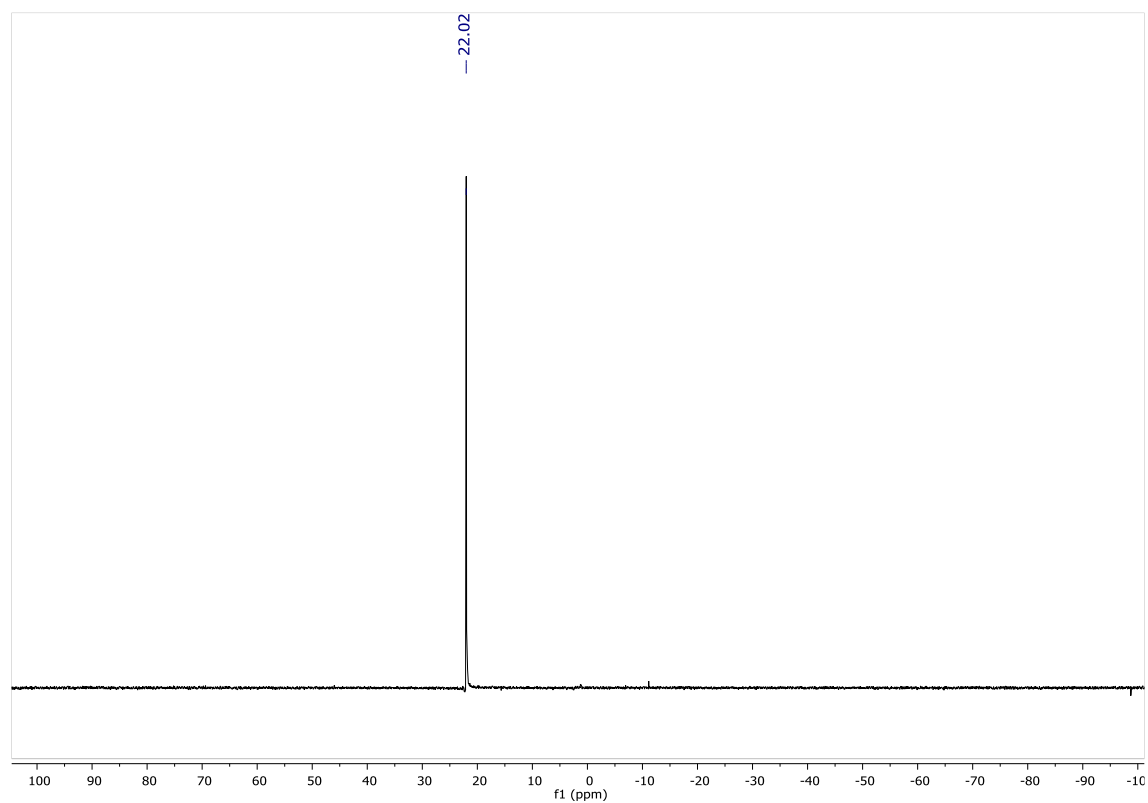
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)

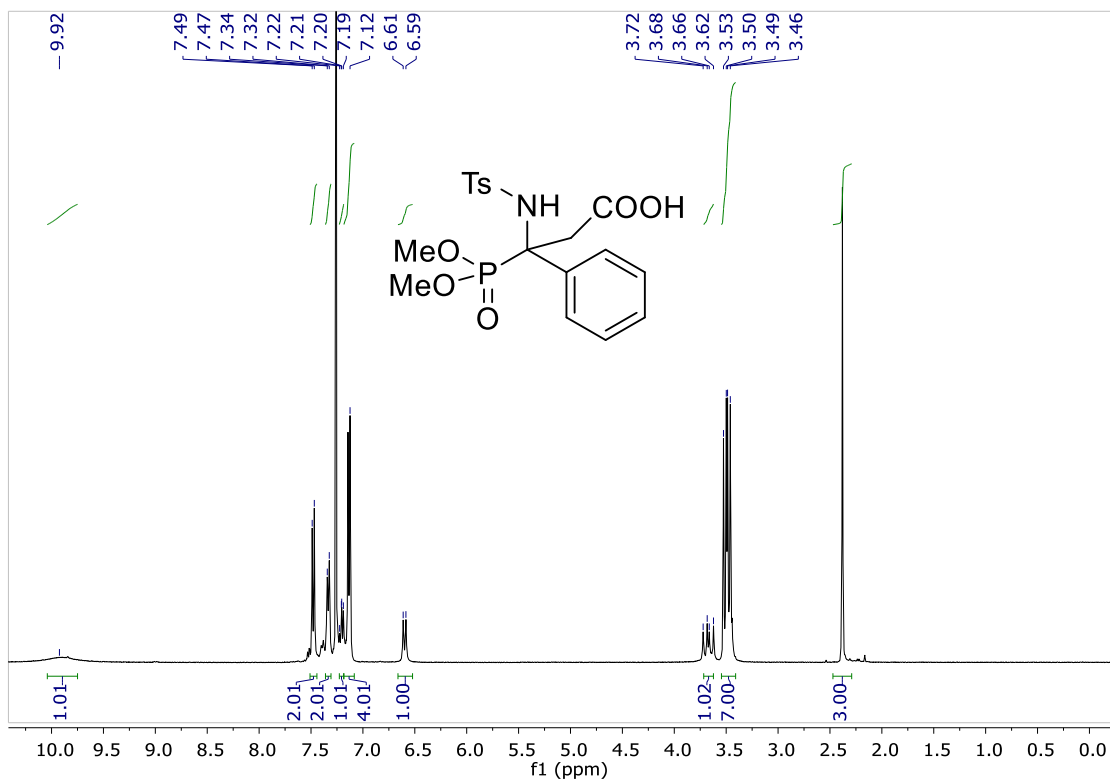


^{31}P NMR (120 MHz, CDCl_3)

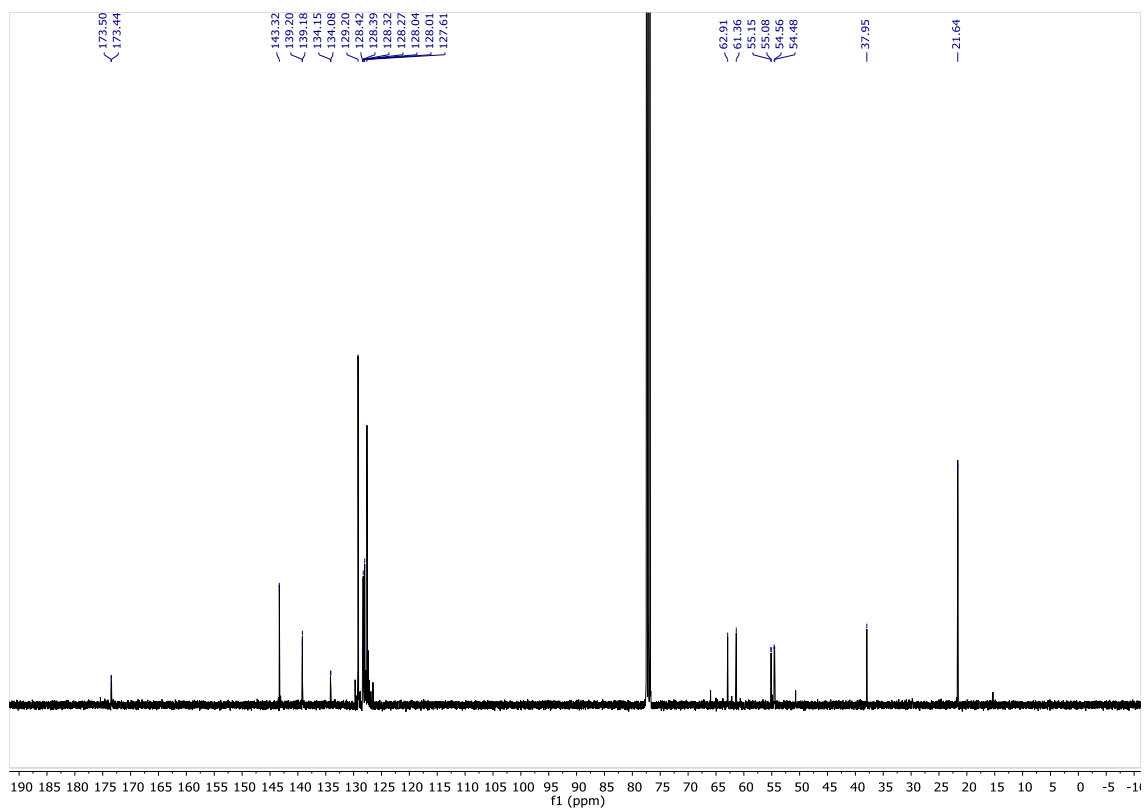


3-(Dimethoxyphosphoryl)-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoic acid (14)

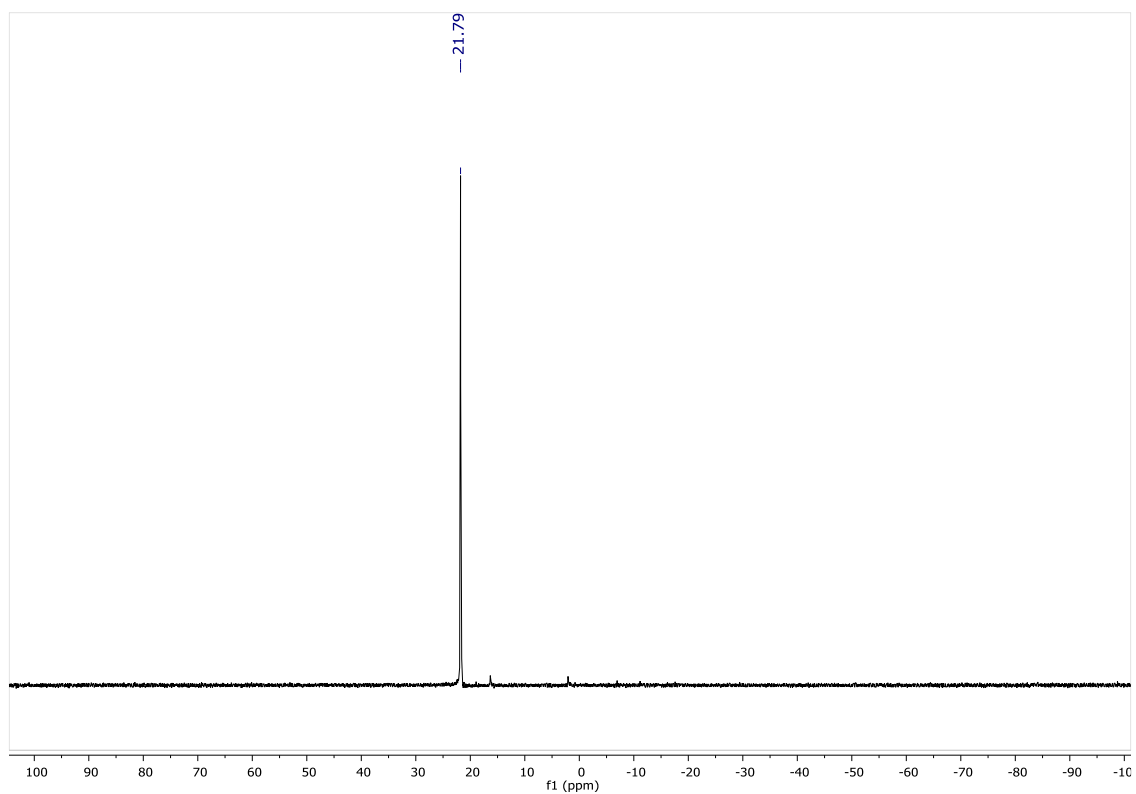
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3)



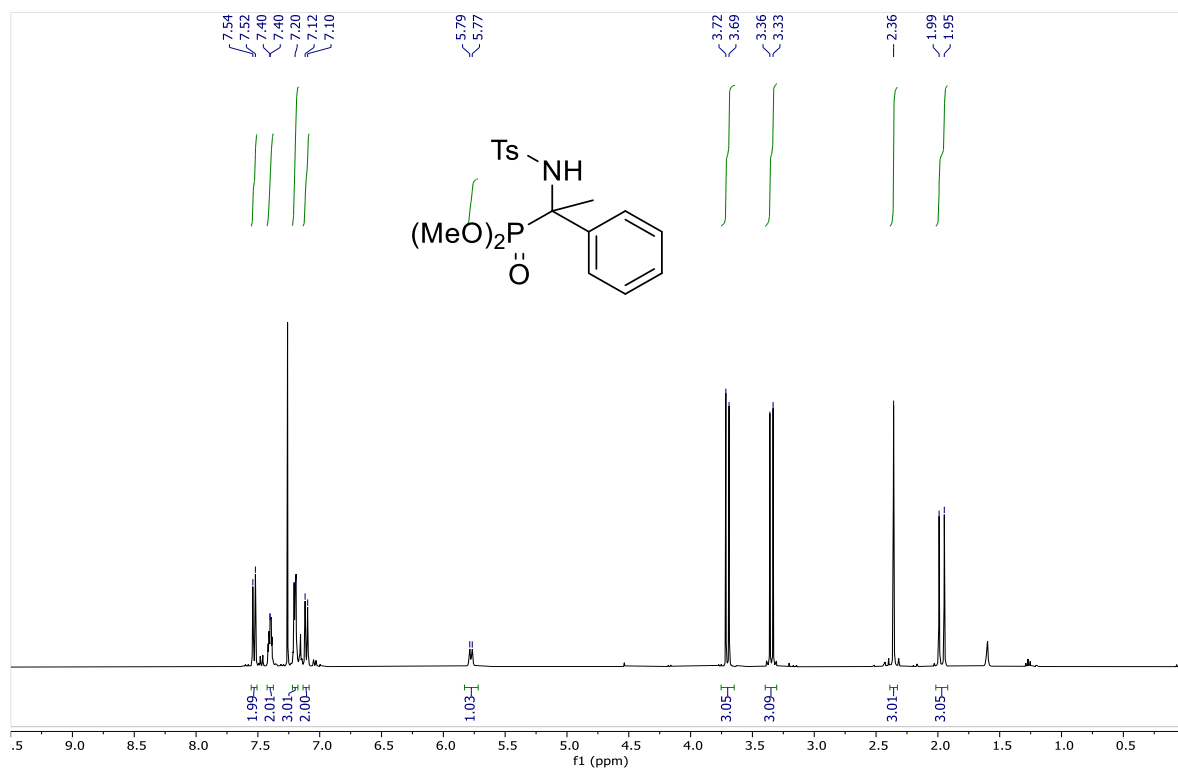
^{31}P NMR (120 MHz, CDCl_3)



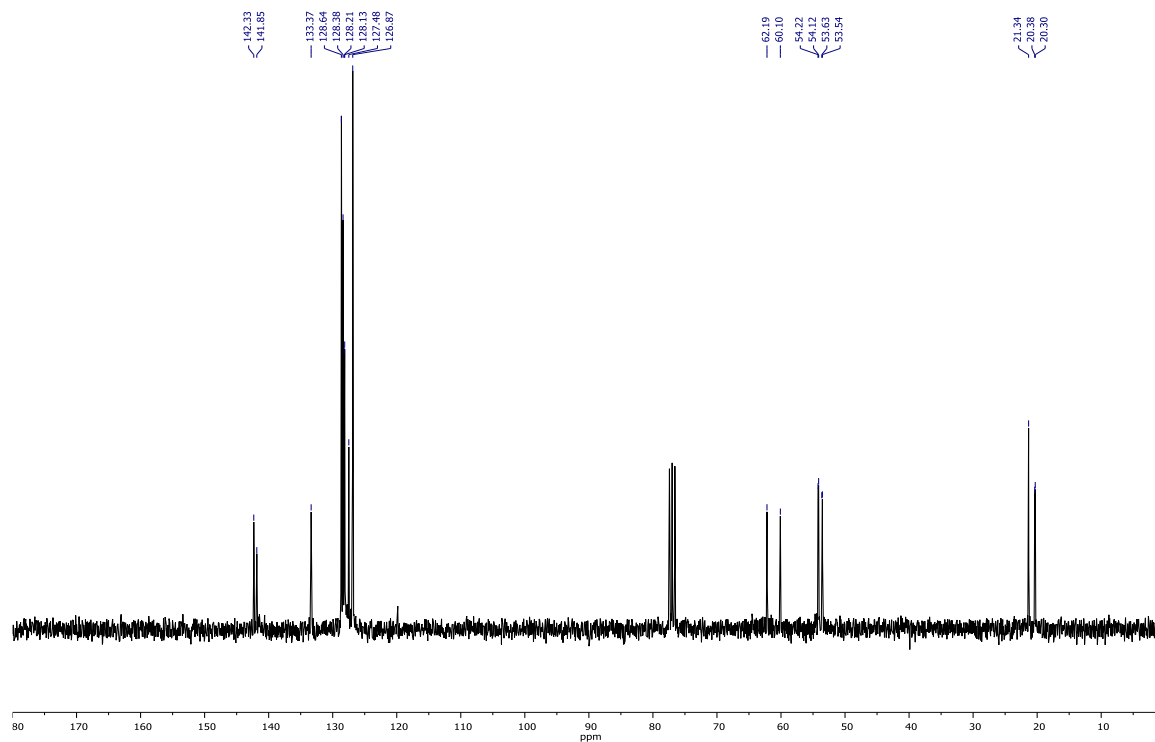
4. ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra of compound 18

Dimethyl (1-((4-methylphenyl)sulfonamido)-1-phenylethyl)phosphonate (18)

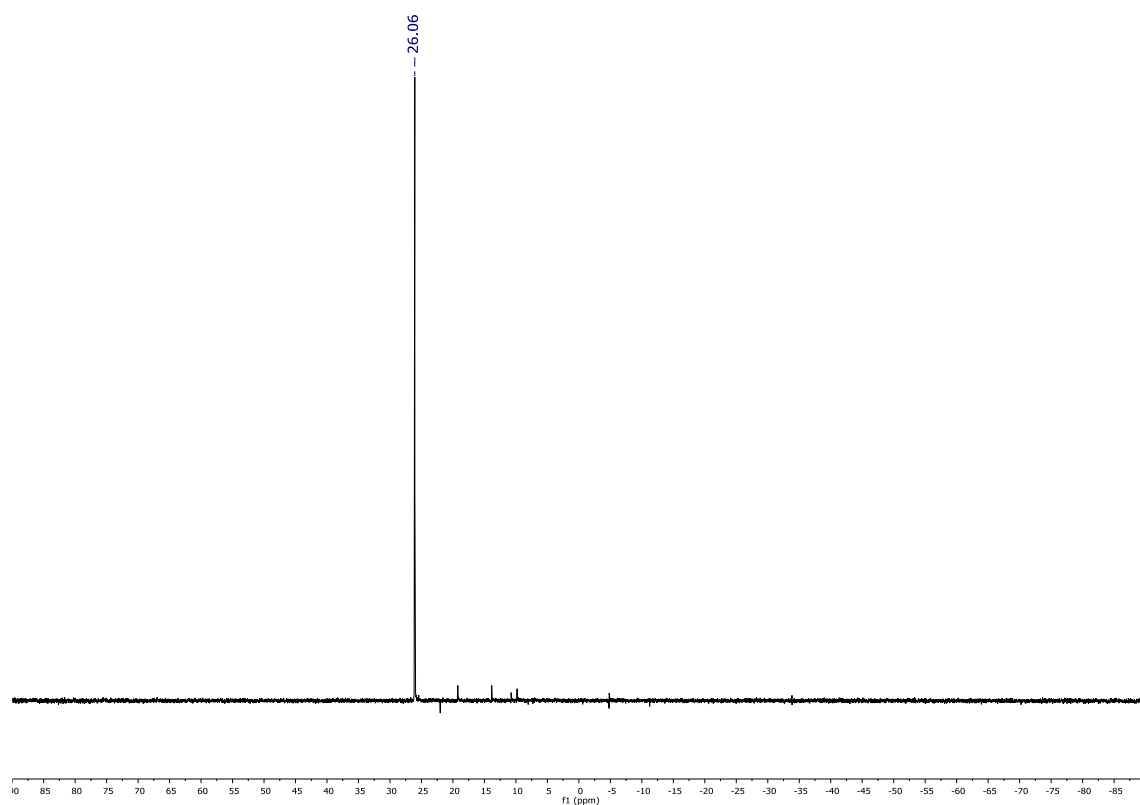
^1H NMR (400 MHz, CDCl_3)



^{13}C NMR [^1H] (75 MHz, CDCl_3)

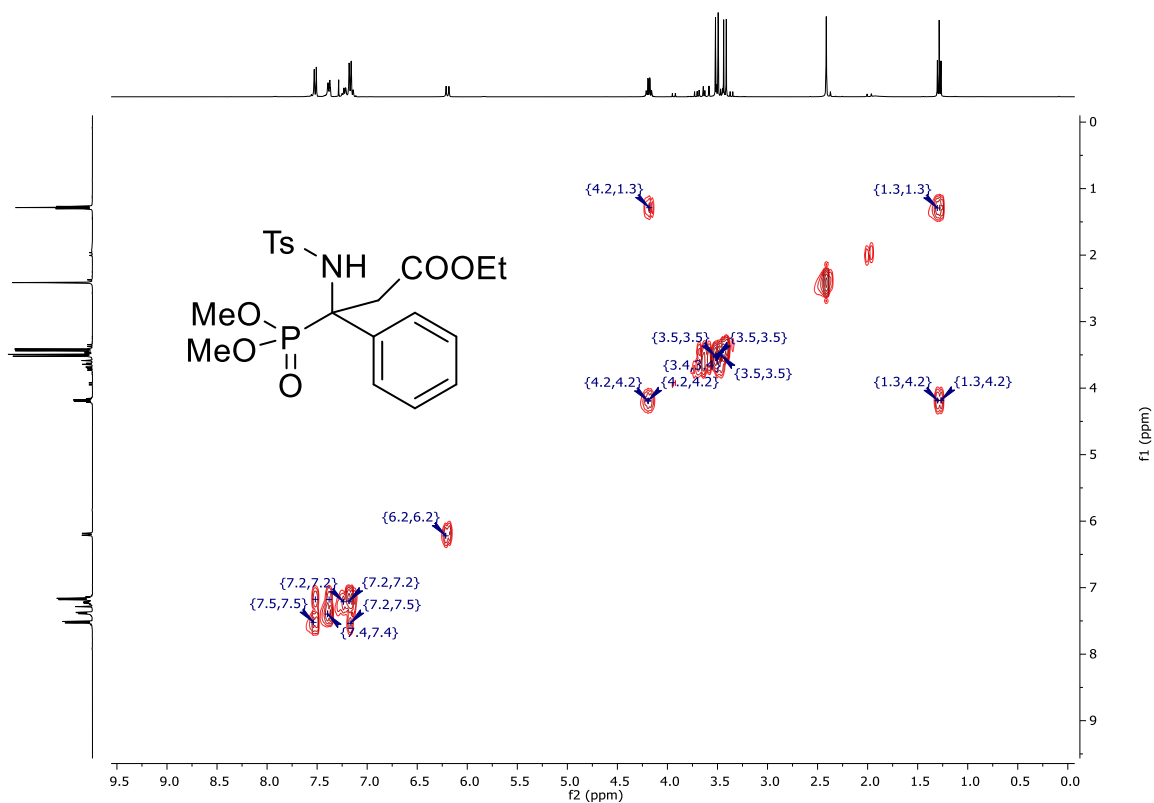


^{31}P NMR (120 MHz, CDCl_3)

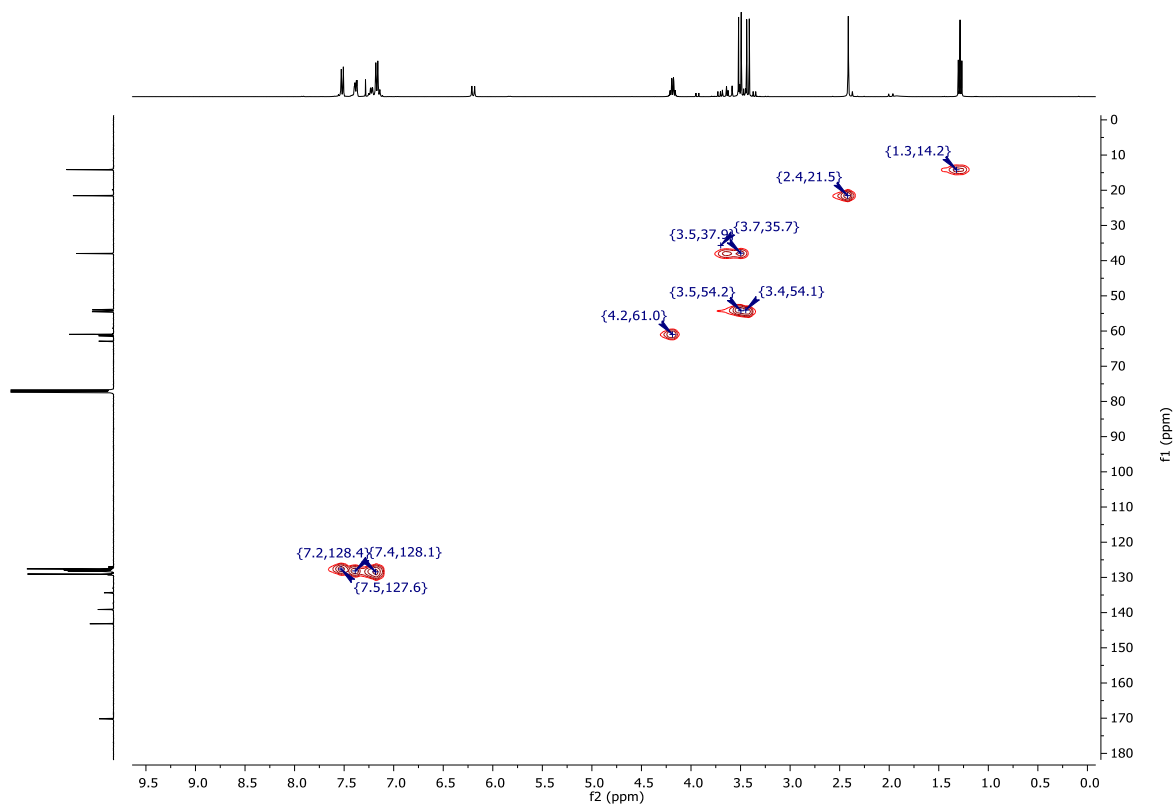


5. 2D NMR spectra of compound 7a

2D-COSY NMR $\{^1\text{H} - ^1\text{H}\}$ (400 MHz, CDCl_3)



2D-HSQC NMR $\{^1\text{H} - ^{13}\text{C}\}$ (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)



2D-HMBC NMR (^1H – ^{13}C) (^1H : 400 MHz, ^{13}C : 101 MHz, CDCl_3)

