

**Synthesis of novel 1,3,4-oxadiazole-derived  
 $\alpha$ -aminophosphonates/ $\alpha$ -aminophosphonic acids and evaluation of their in  
vitro antiviral activity against the avian coronavirus infectious bronchitis  
virus**

Shaima Hkiri, Marwa Mekni-Toujani, Elvan Üstün, Karim Hosni, Abdeljelil Ghran, Soufiane  
Touil, Ali Samarat and David Sémeril

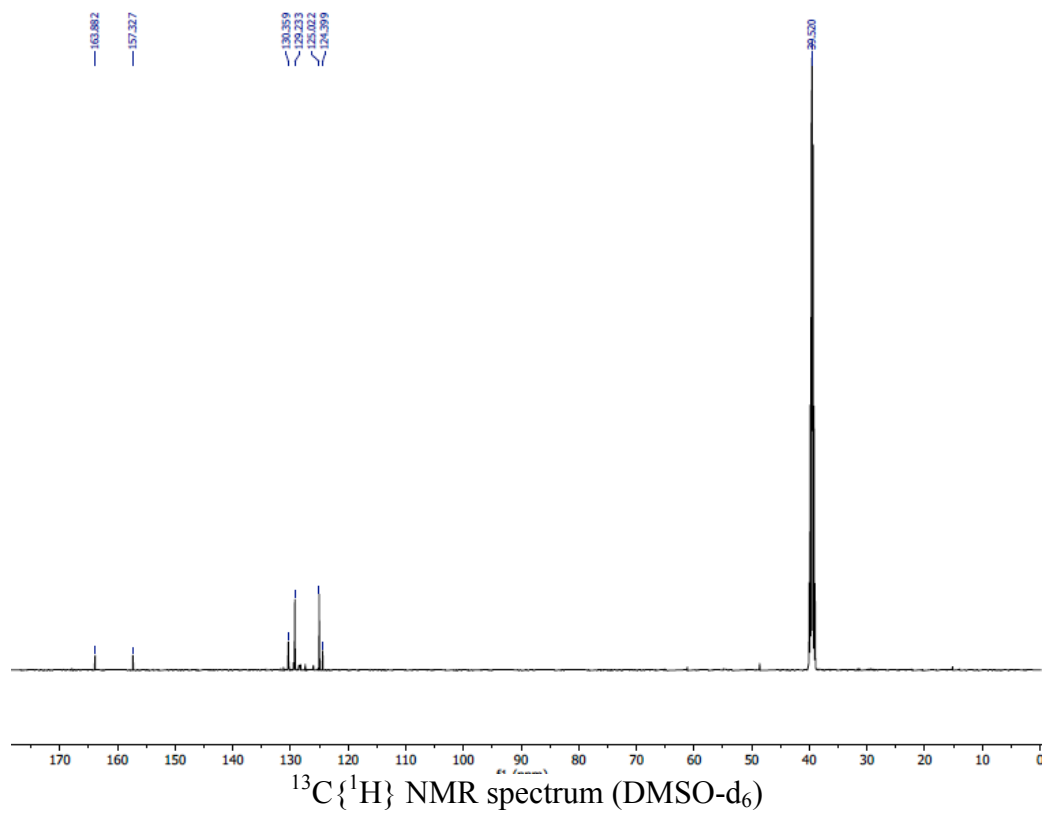
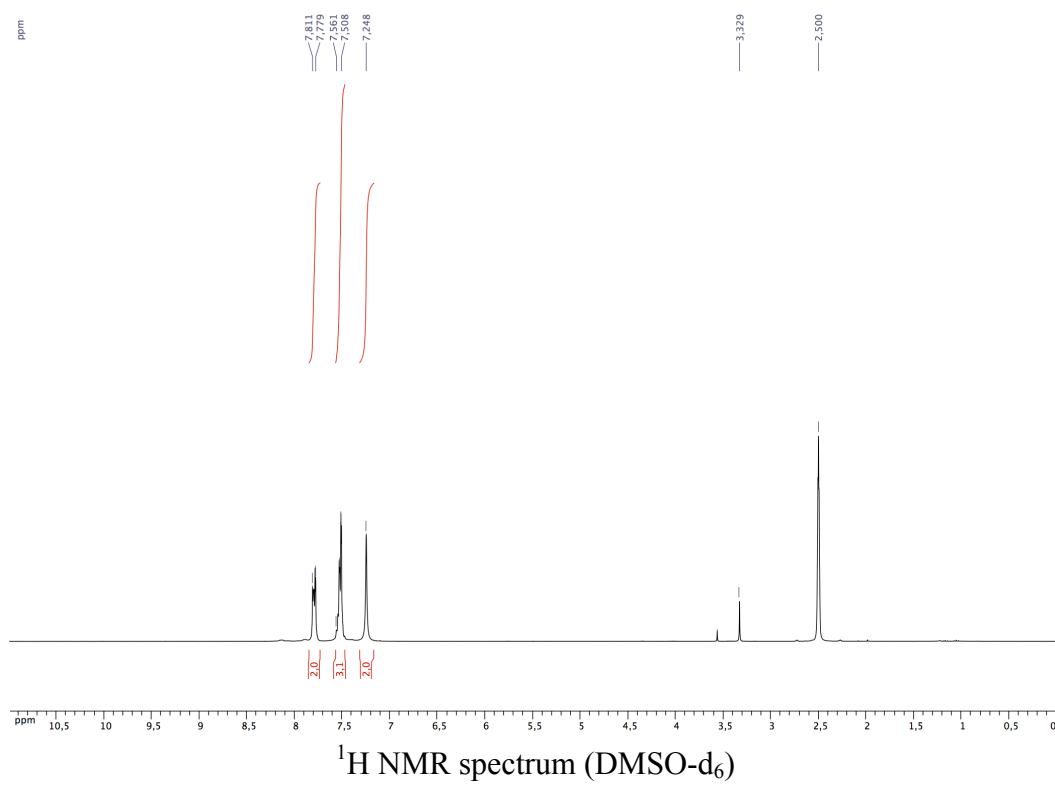
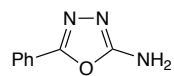
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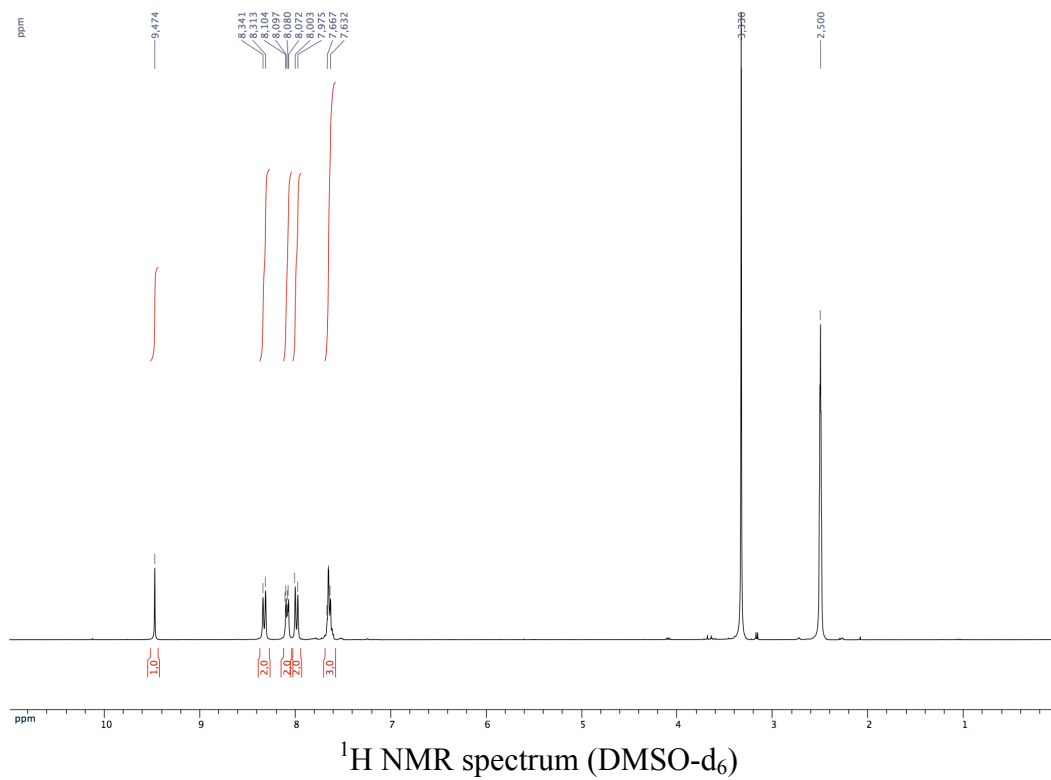
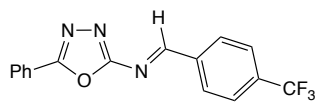
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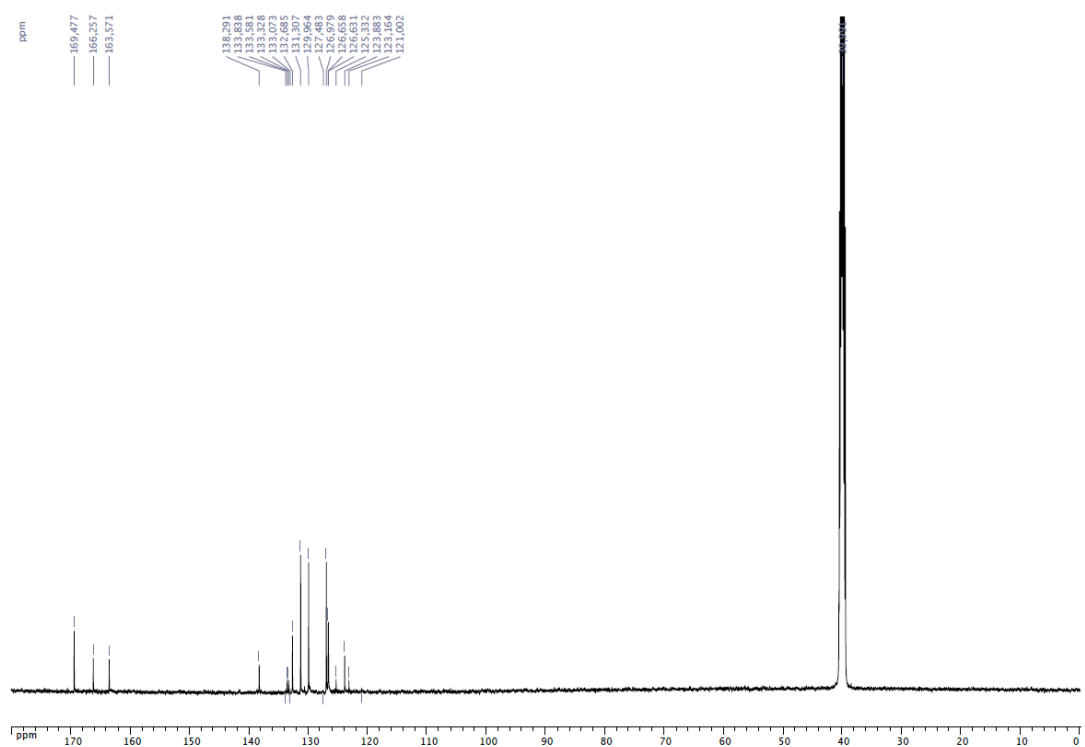
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# Characterising data of 2-amino-5-phenyl-1,3,4-oxadiazole (1)

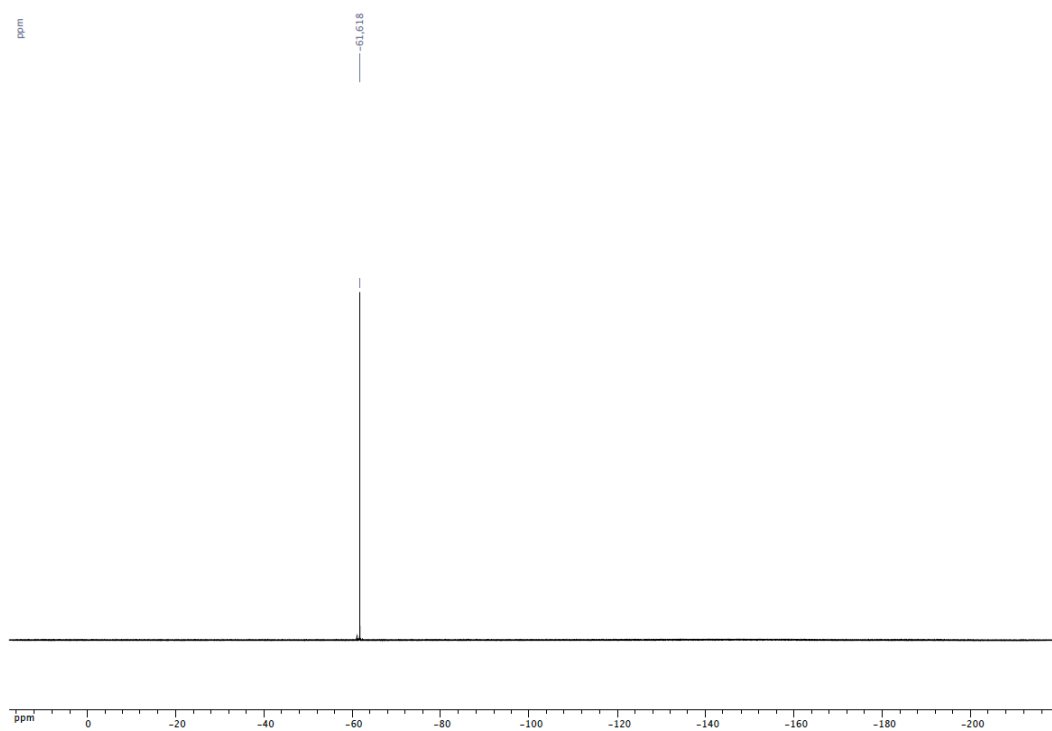


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N-(5-phenyl-1,3,4-oxadiazol-2-yl)methanimine (2a)**



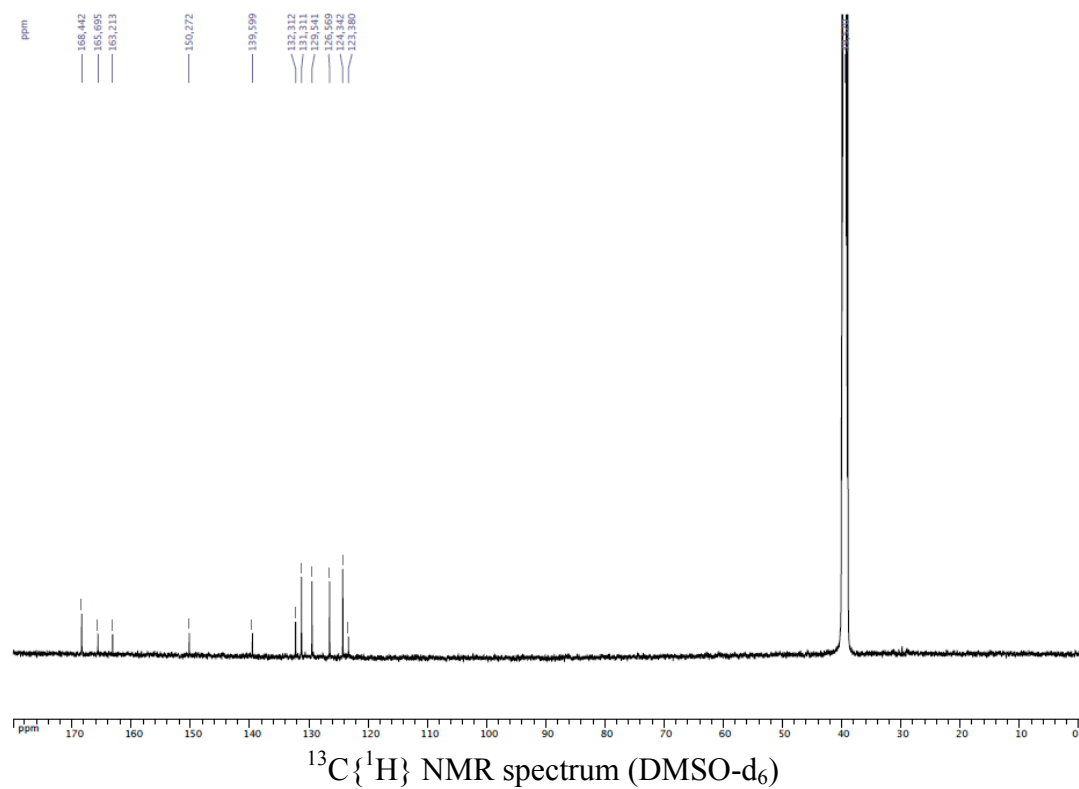
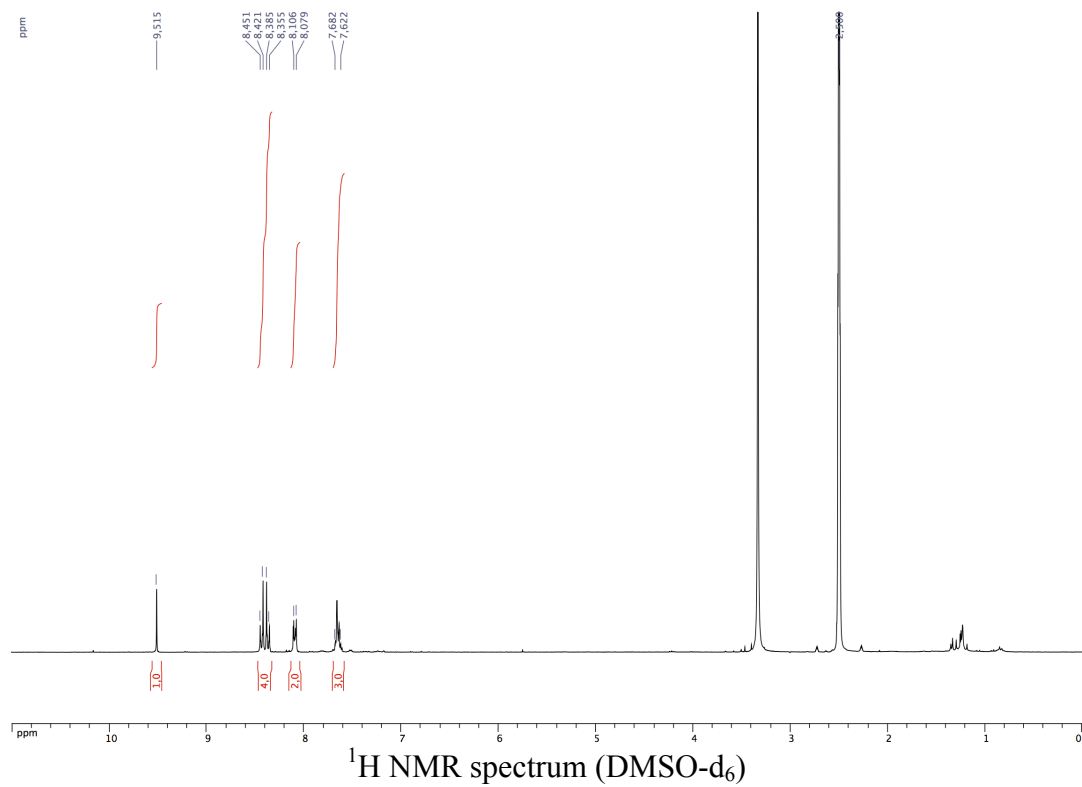
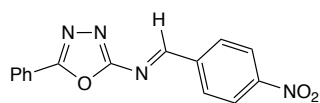


$^{13}\text{C}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

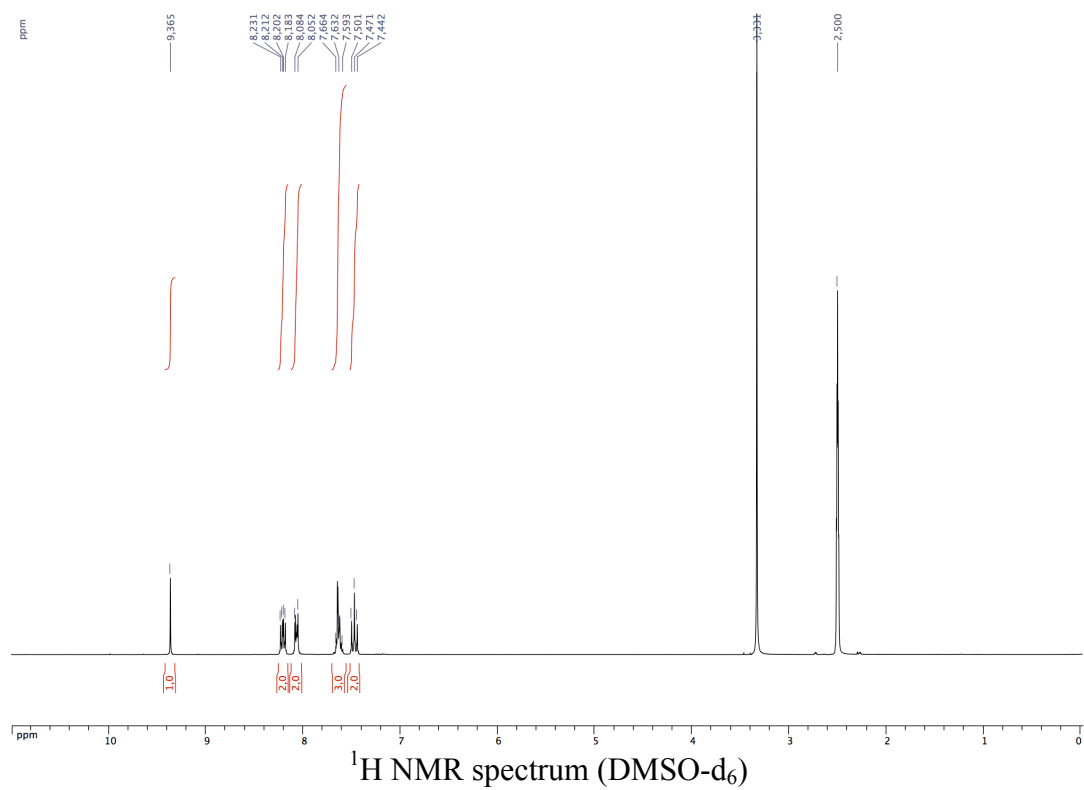
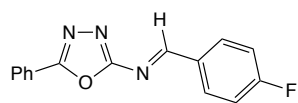


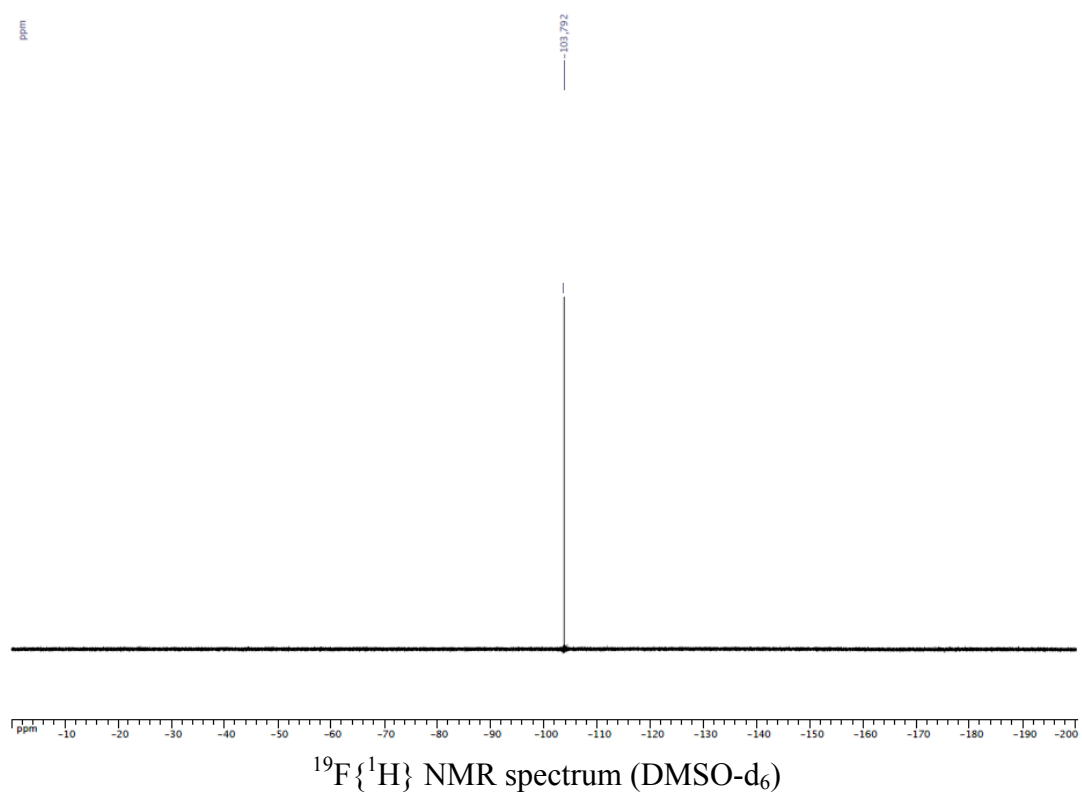
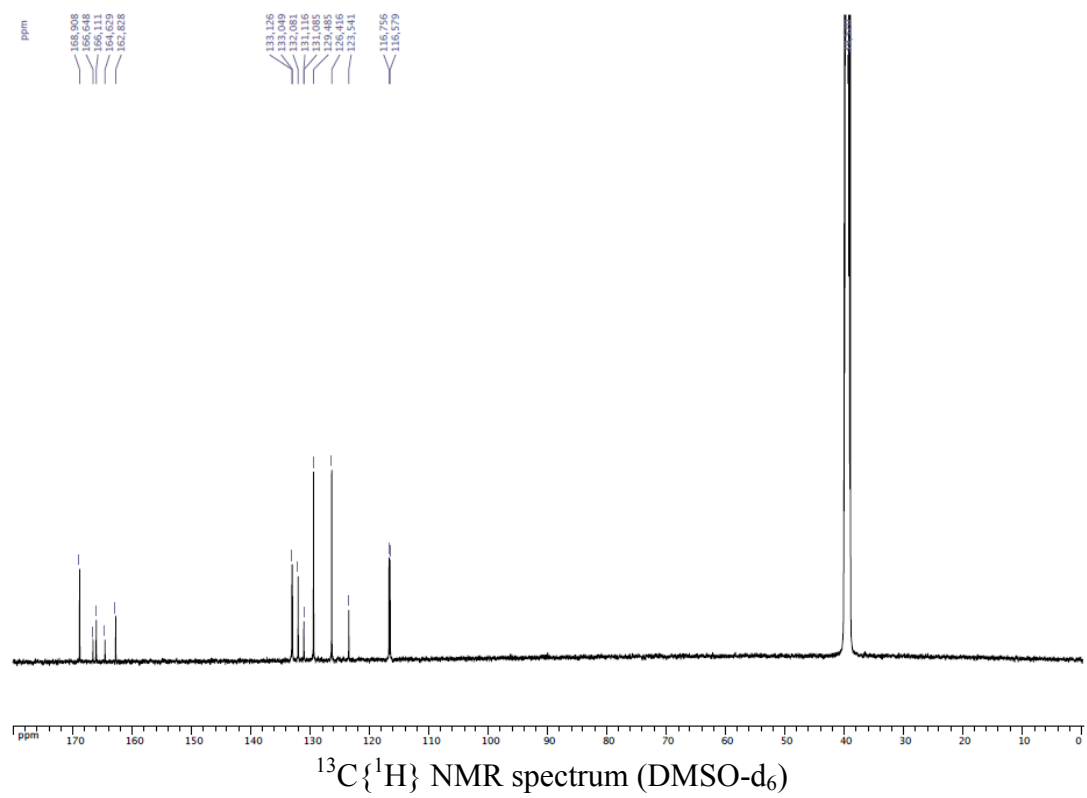
$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

**Characterising data of (*E*)-1-(4-nitrophenyl)-  
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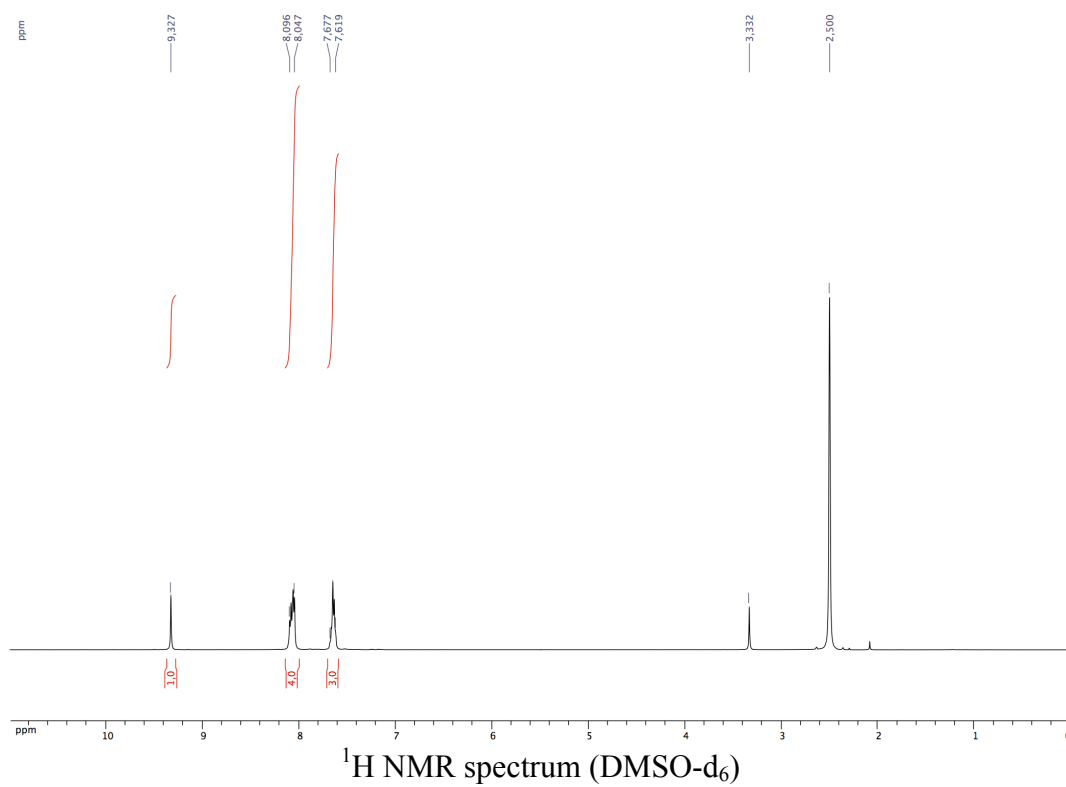
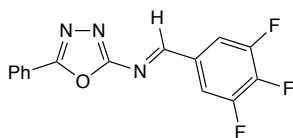
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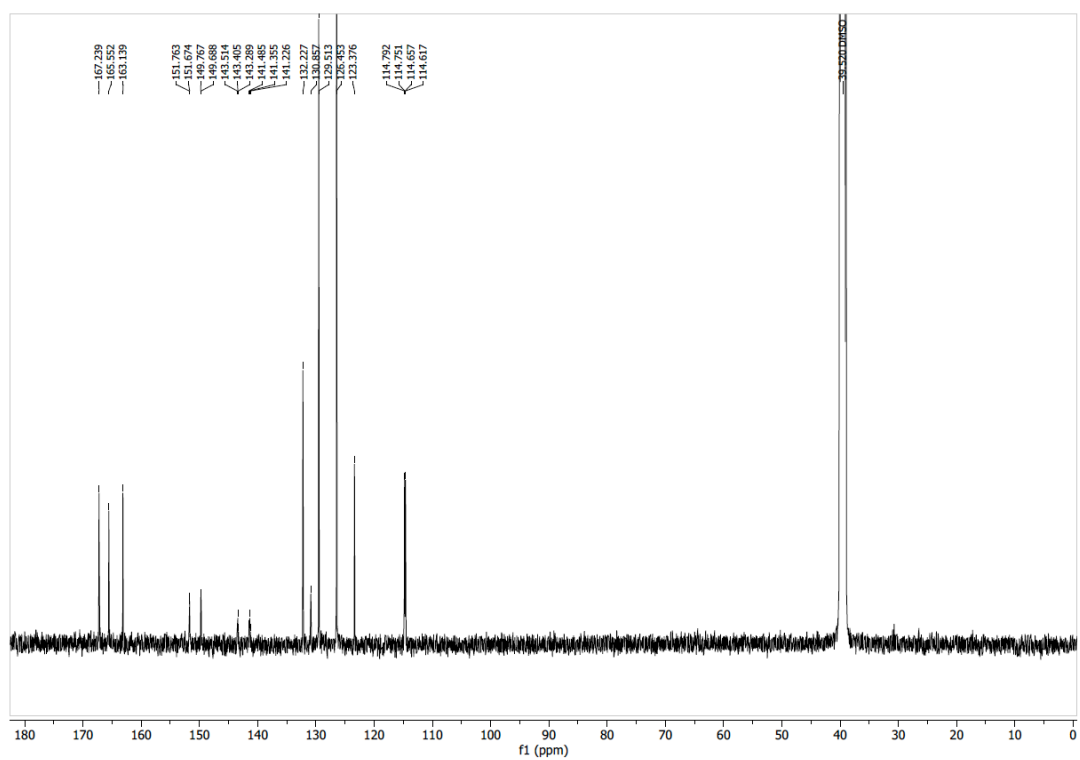




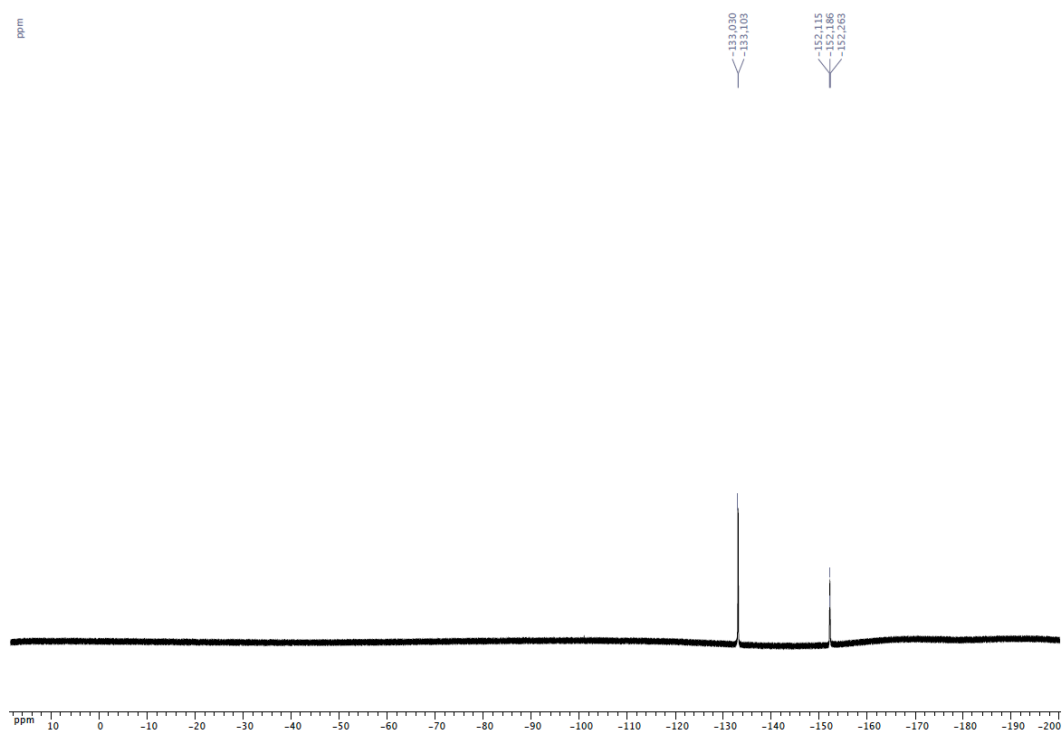


**Characterising data of (*E*)-1-(3,4,5-trifluorophenyl)-  
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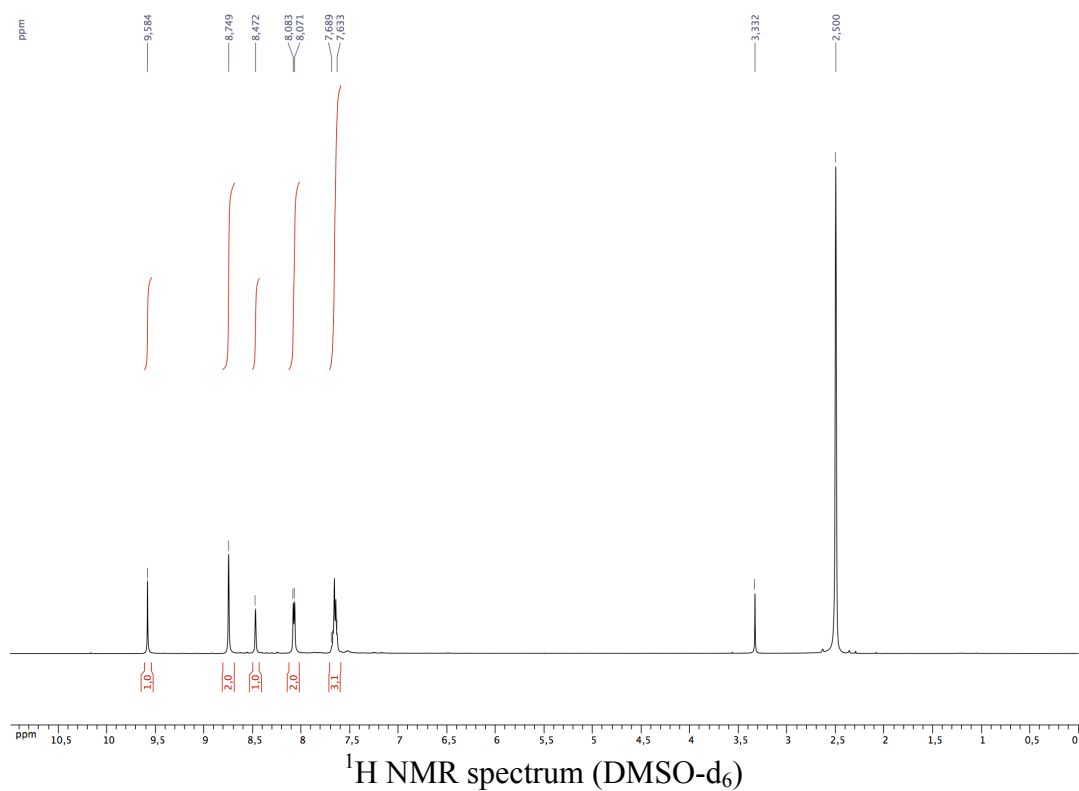
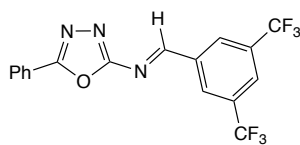


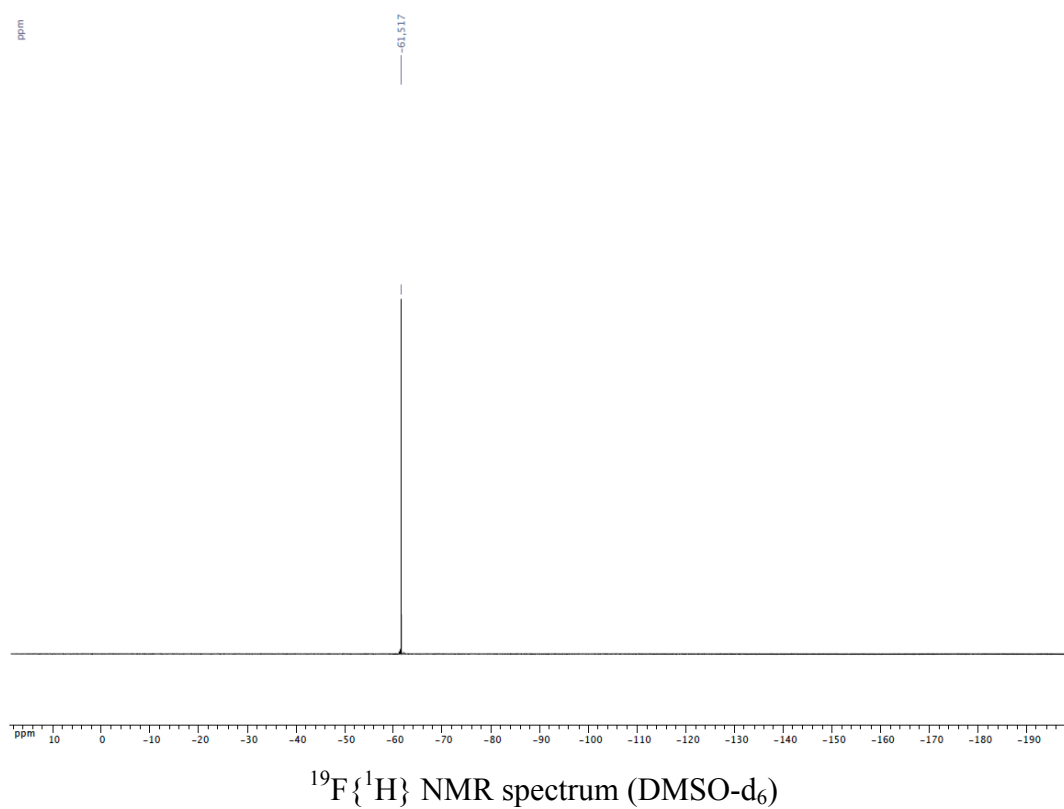
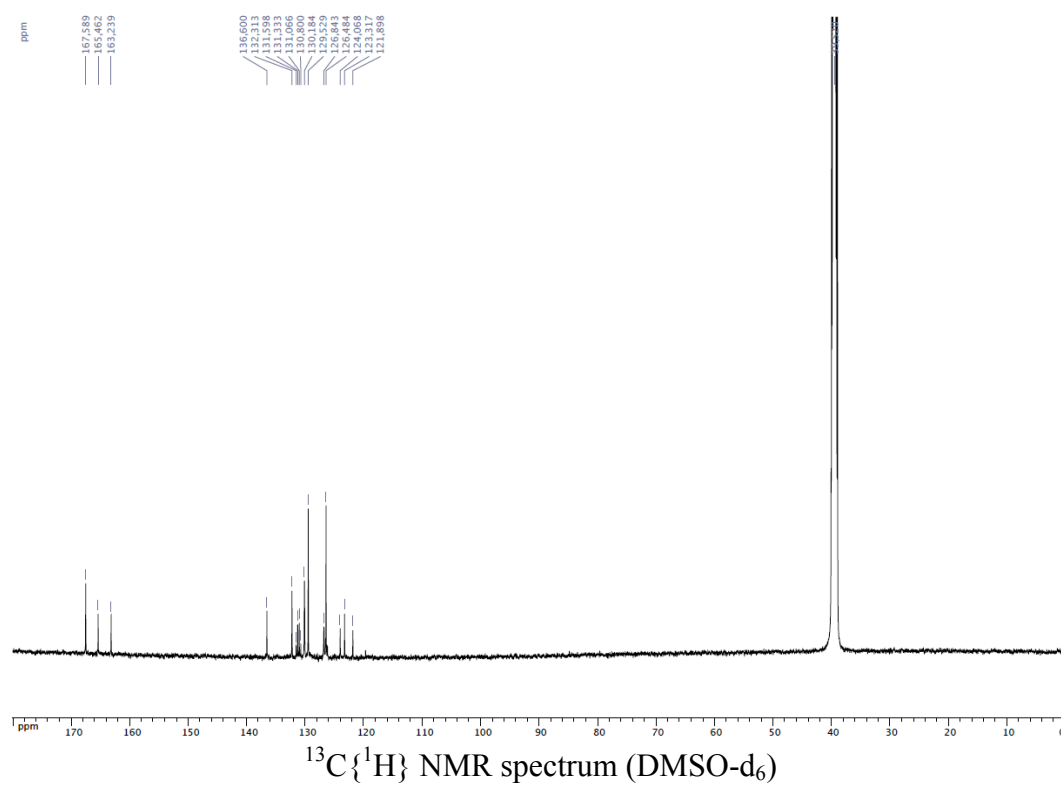
$^{13}\text{C}\{^1\text{H}\}$  NMR spectrum (DMSO-d<sub>6</sub>)



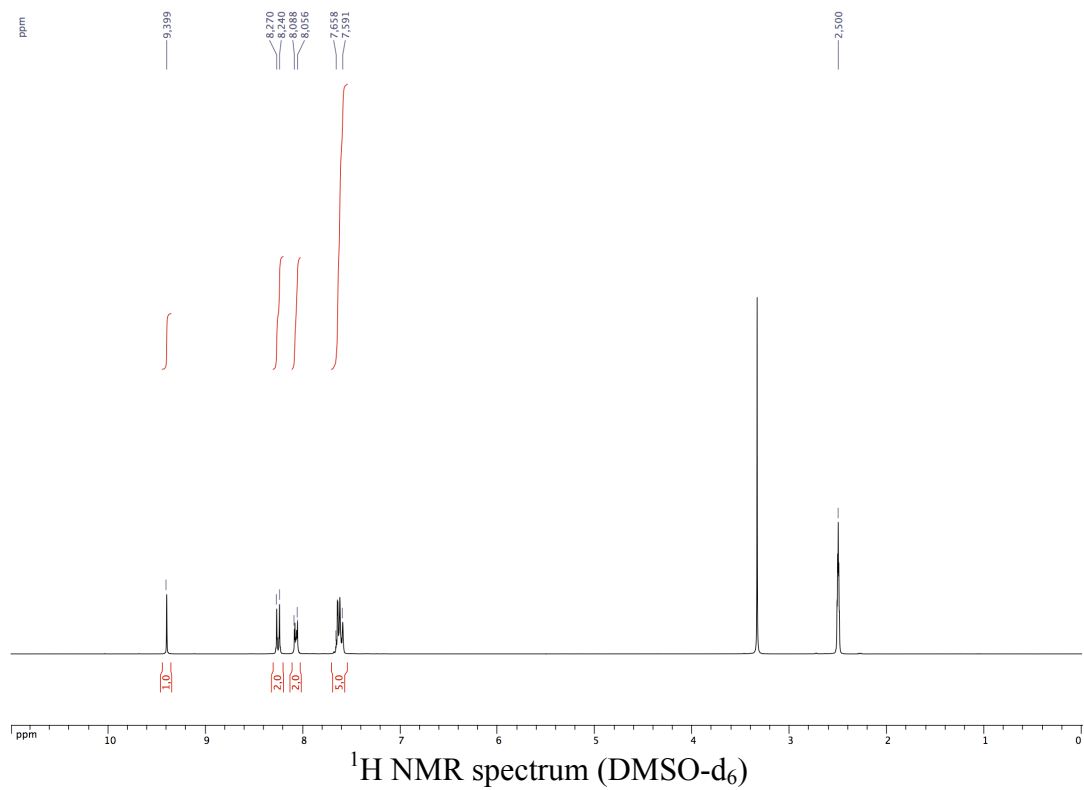
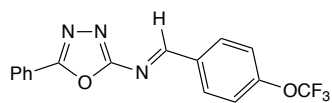
$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO-d<sub>6</sub>)

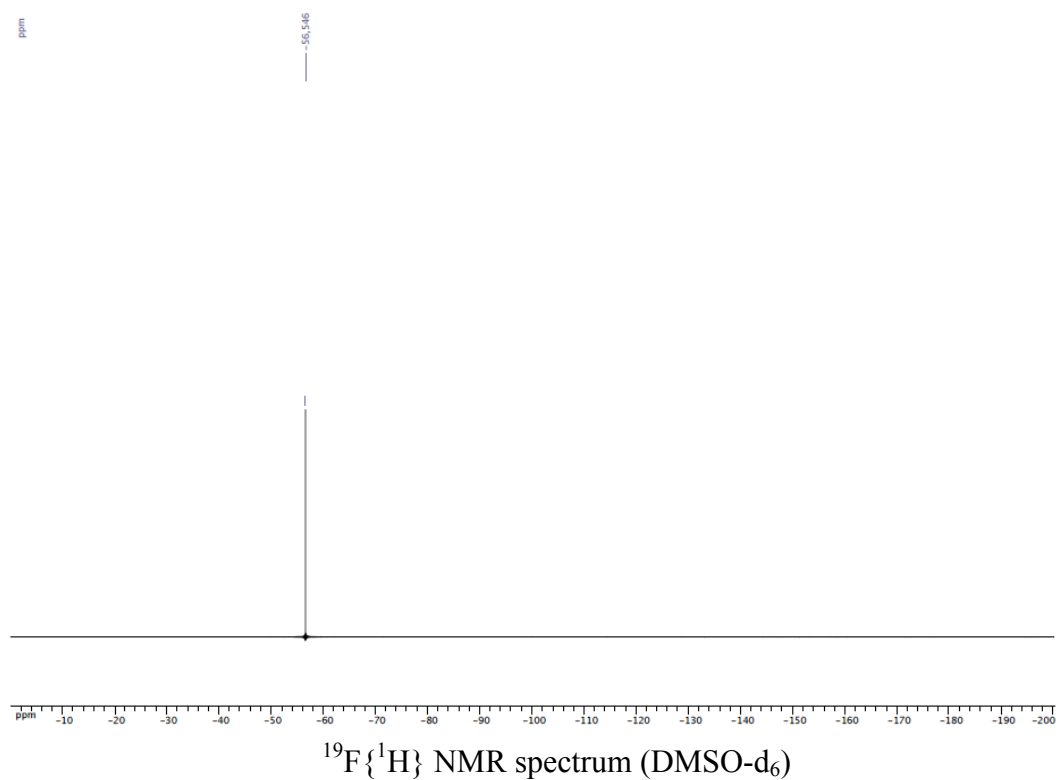
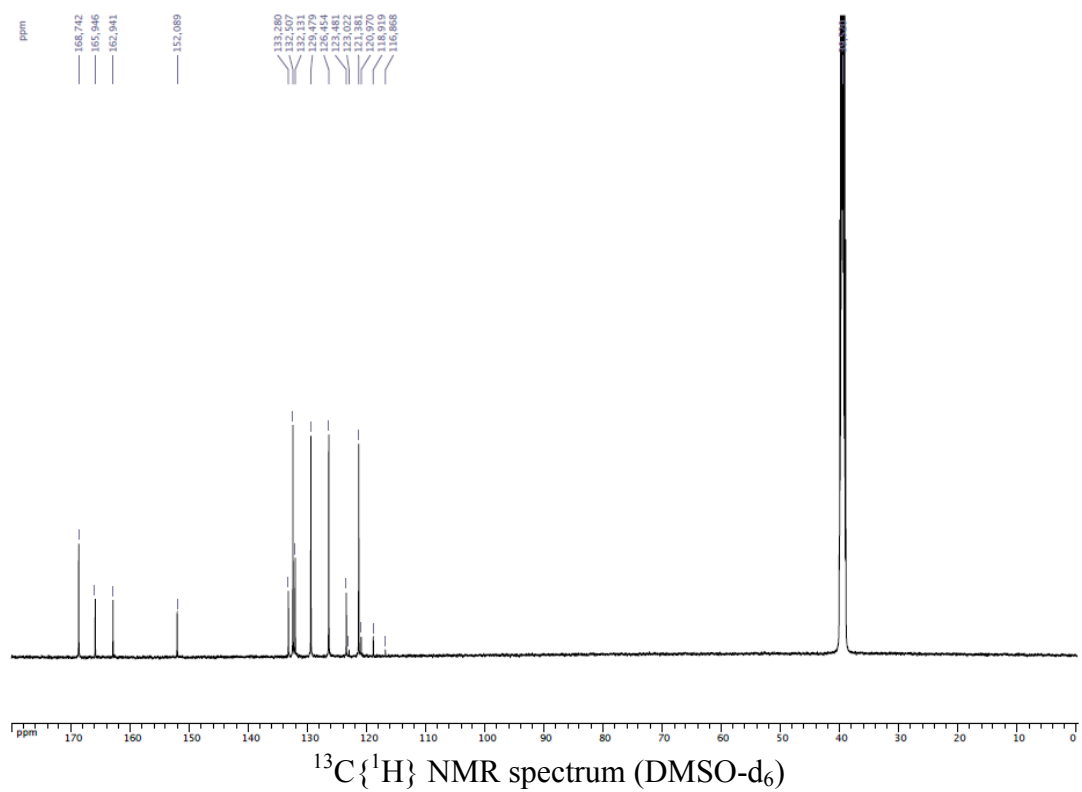
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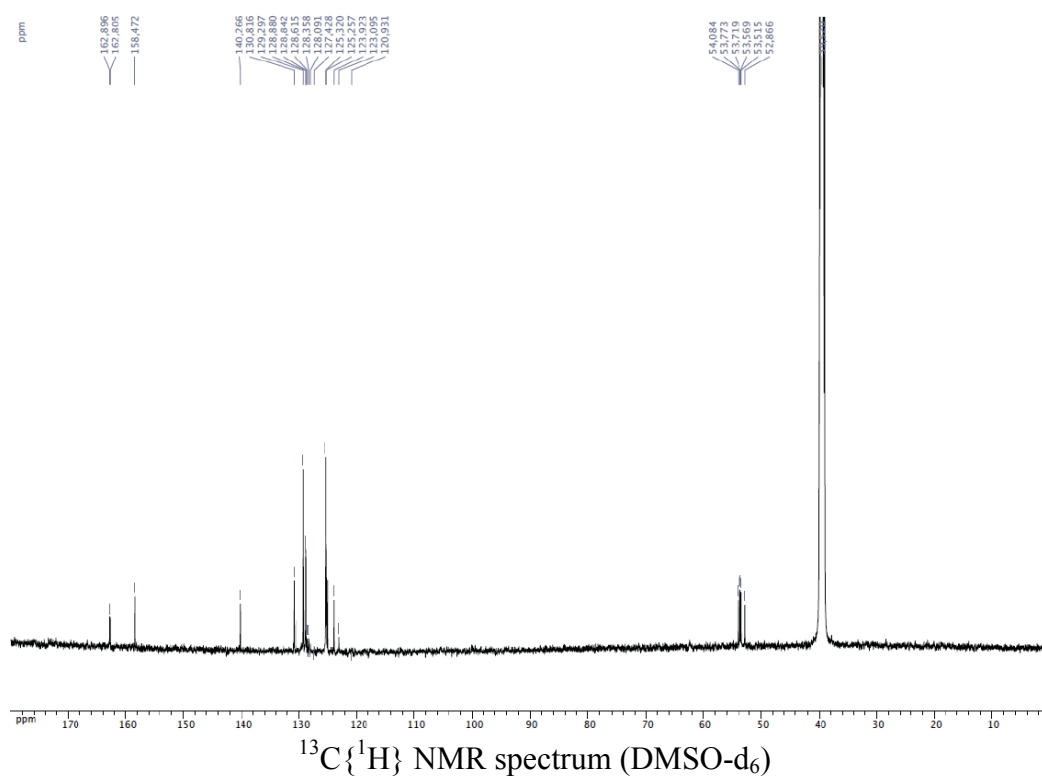
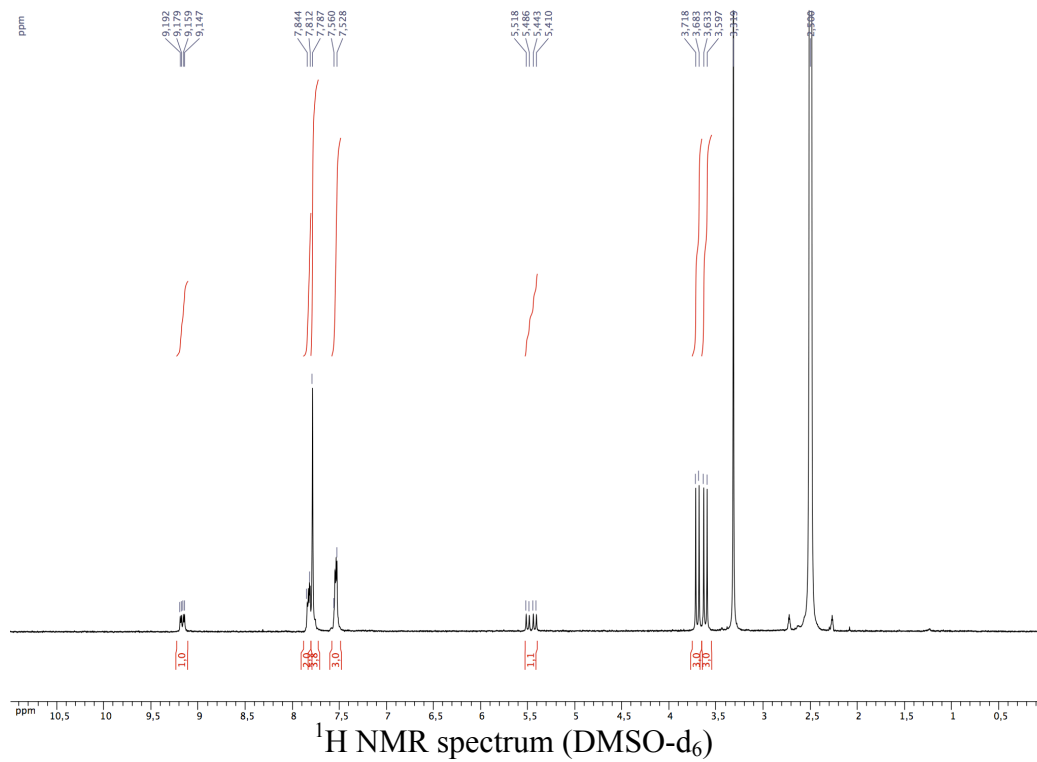
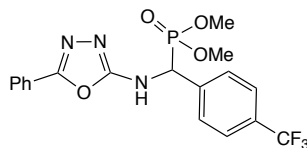


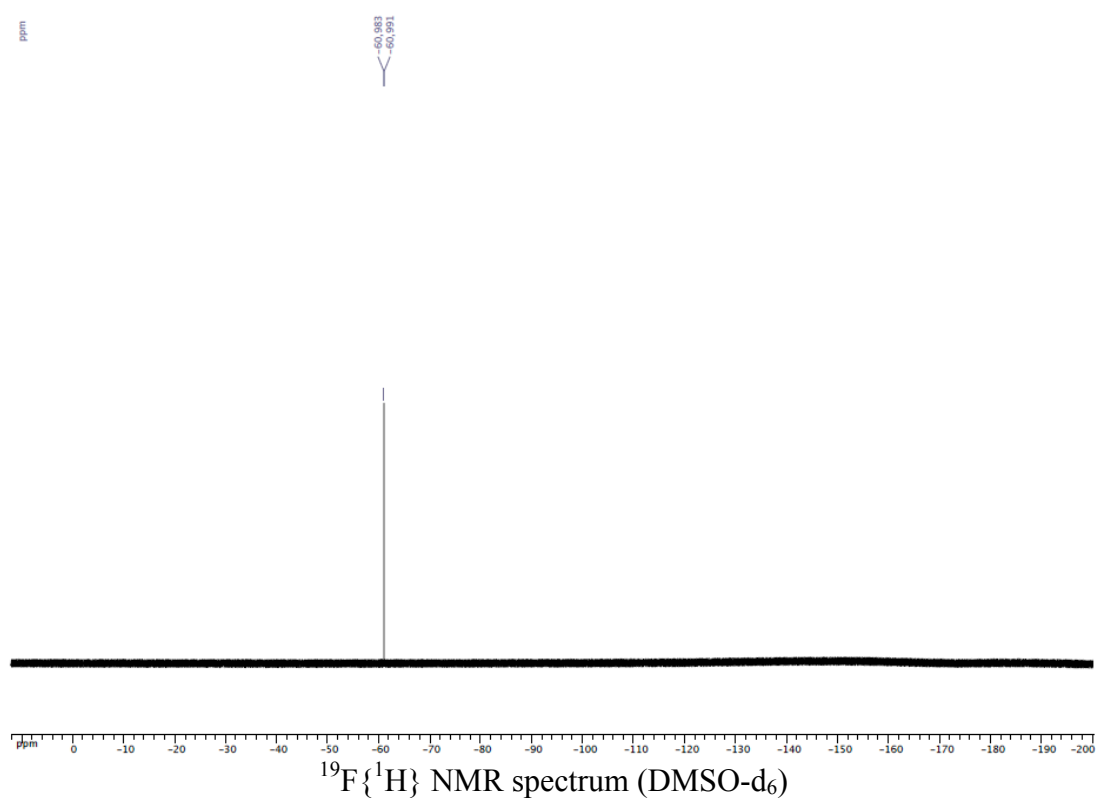
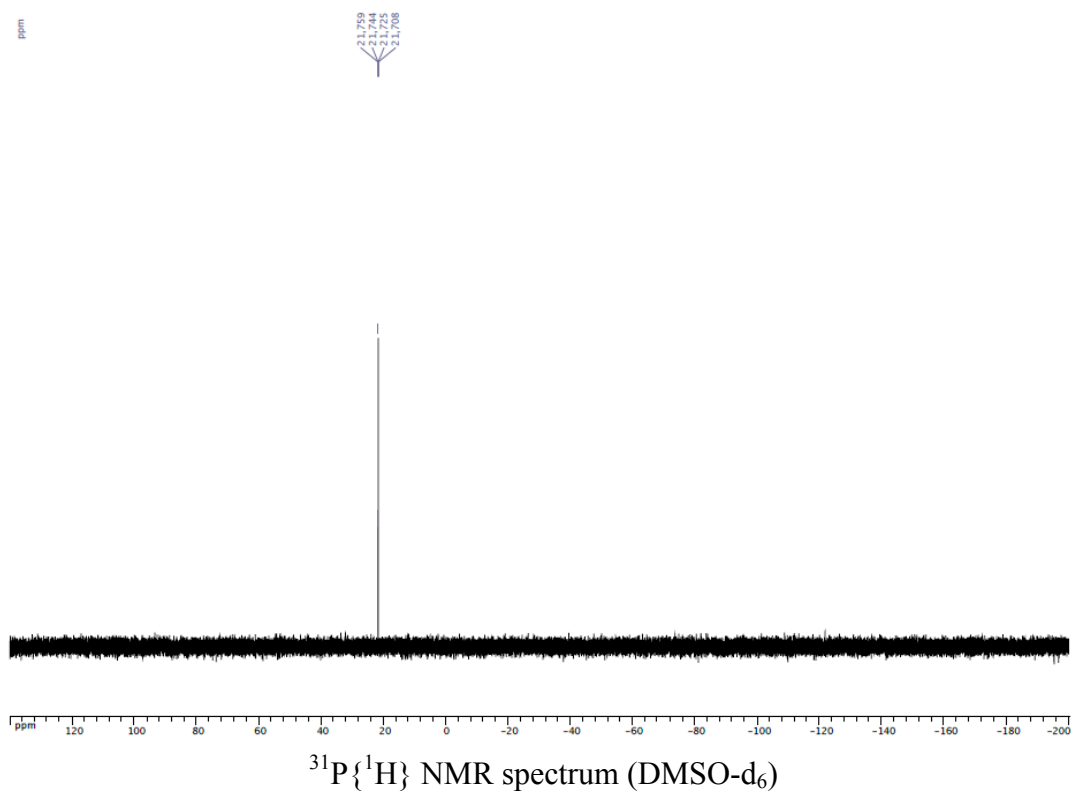
**Characterising data of (*E*)-1-(4-trifluoromethoxyphenyl)-  
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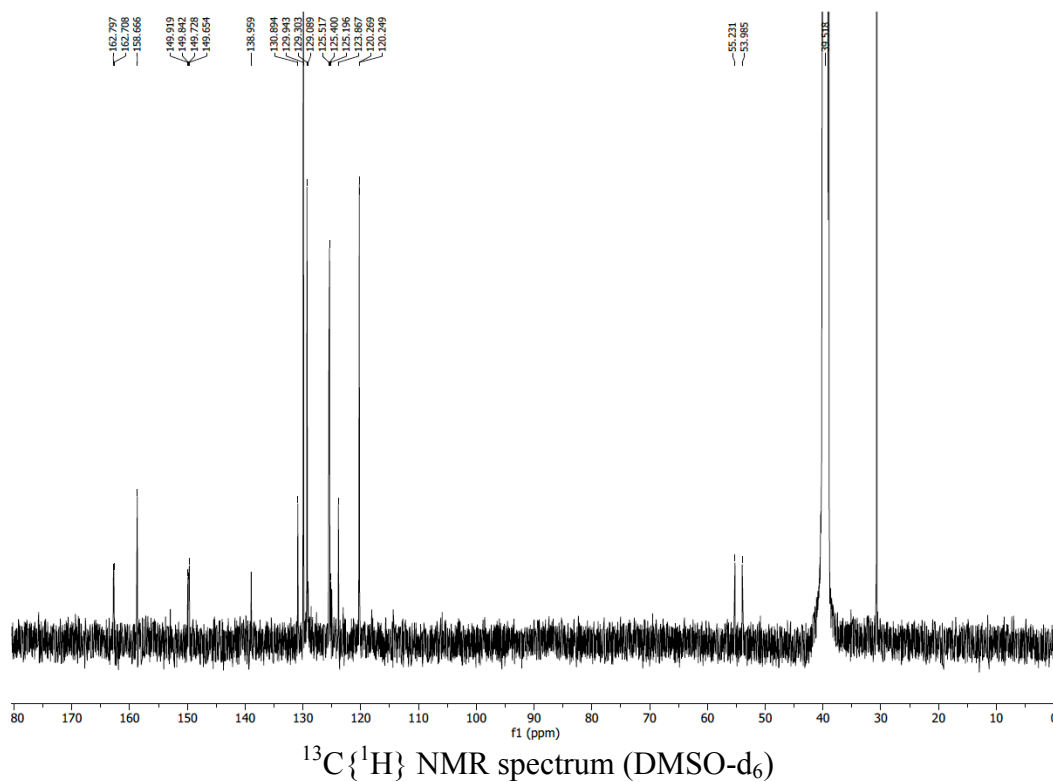
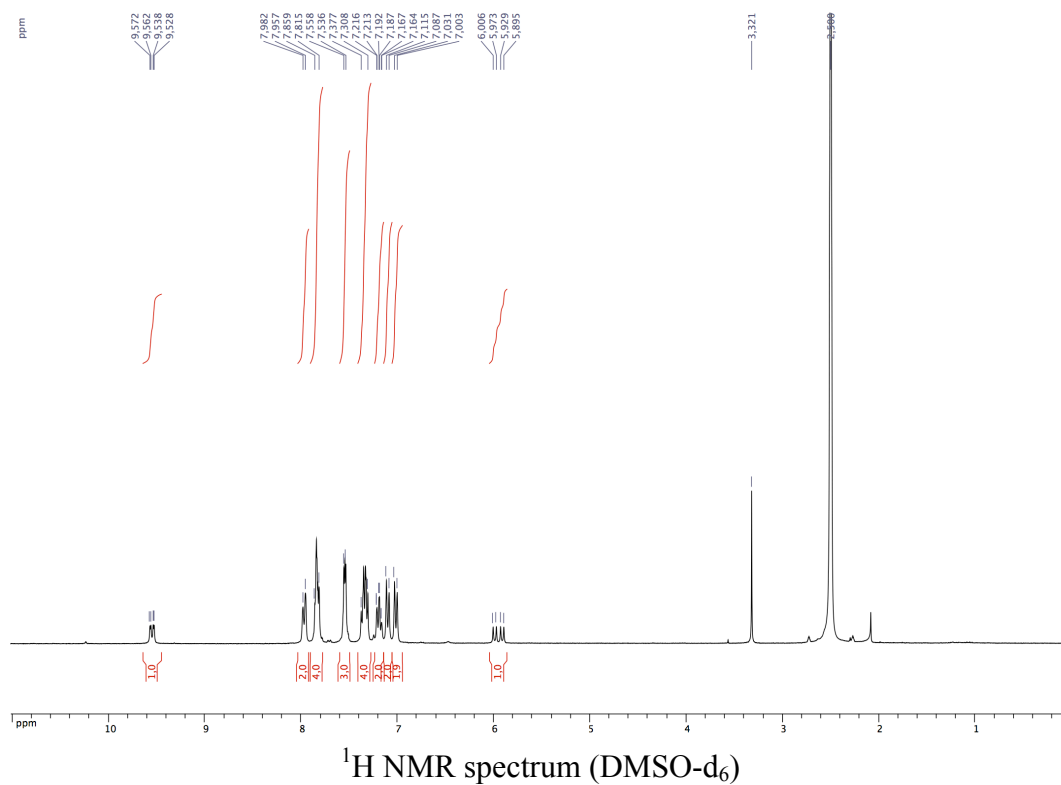
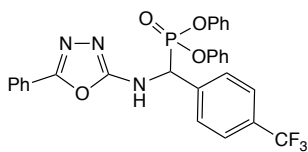
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(4-trifluoromethylphenyl)methyl]phosphonate (3)**

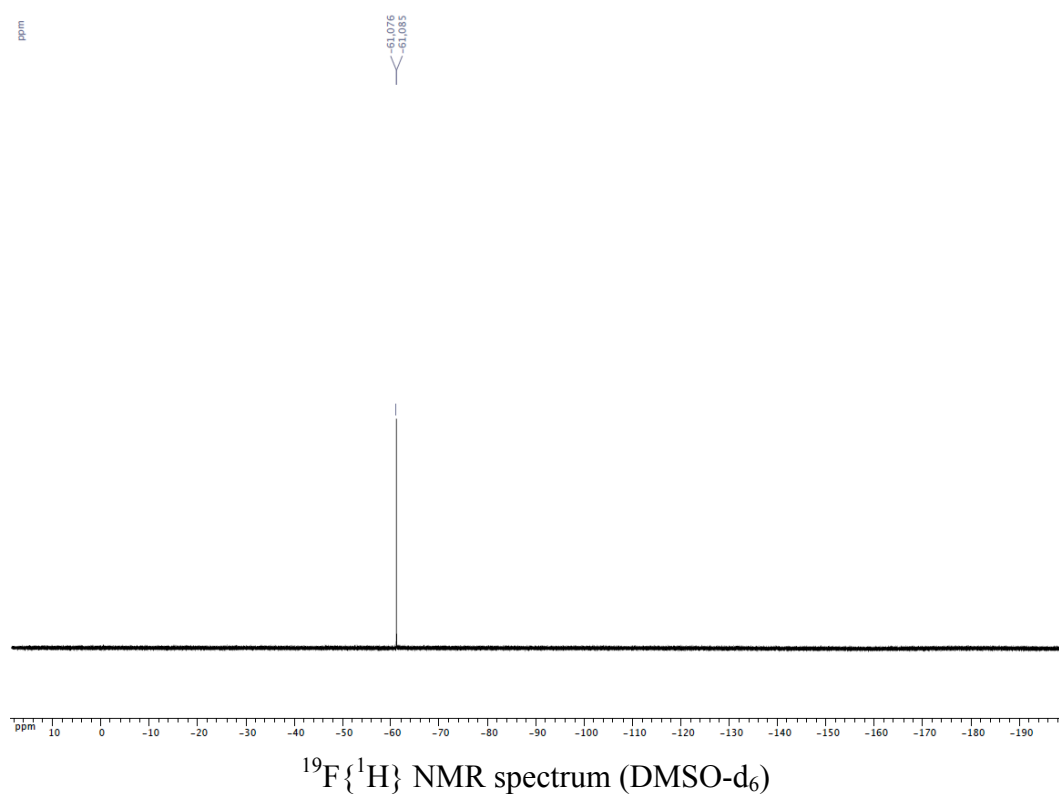
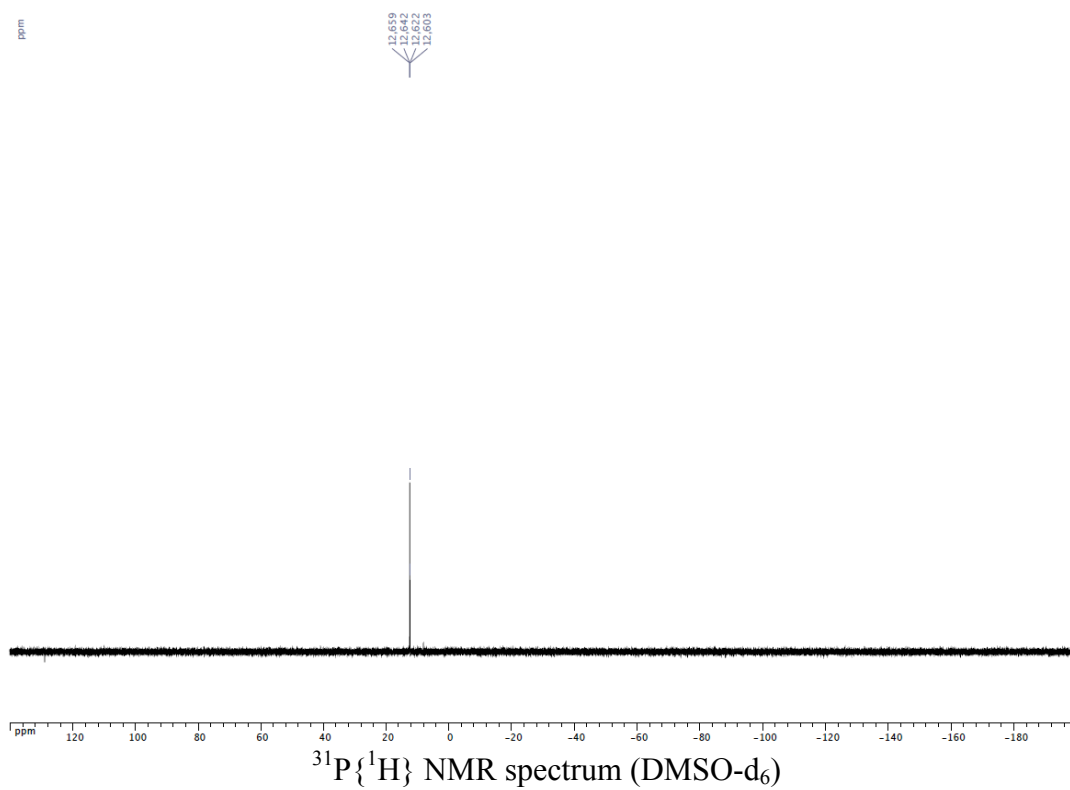




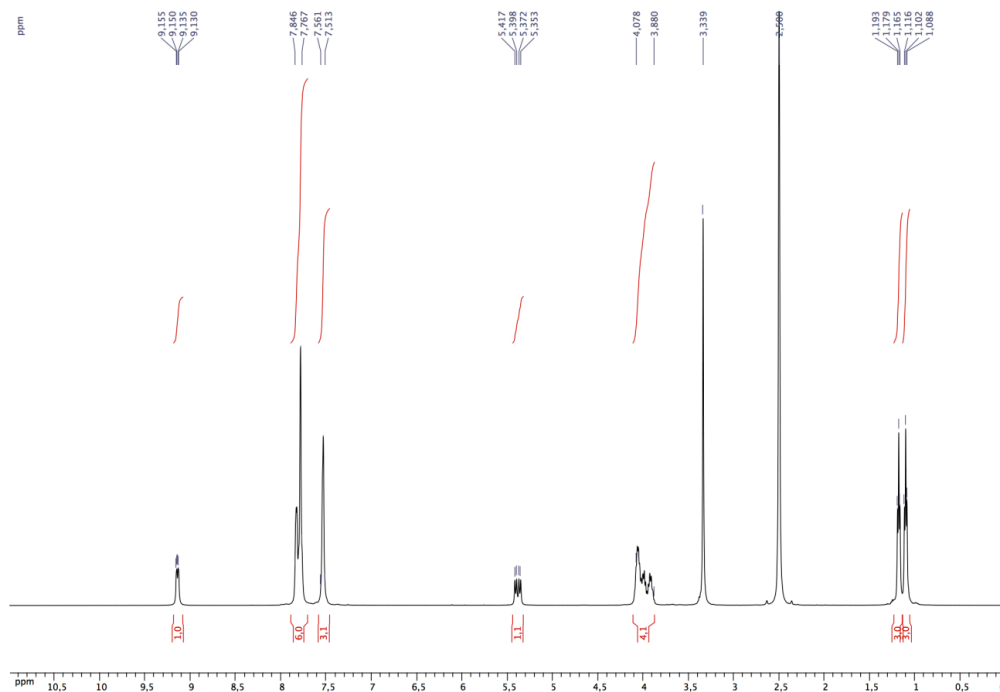
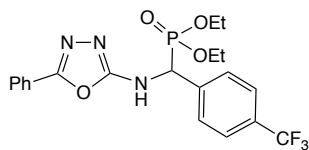


**Characterising data of diphenyl[(5-phenyl-1,3,4-oxodiazol-2-ylamino)  
(4-trifluoromethylphenyl)methyl]phosphonate (4)**

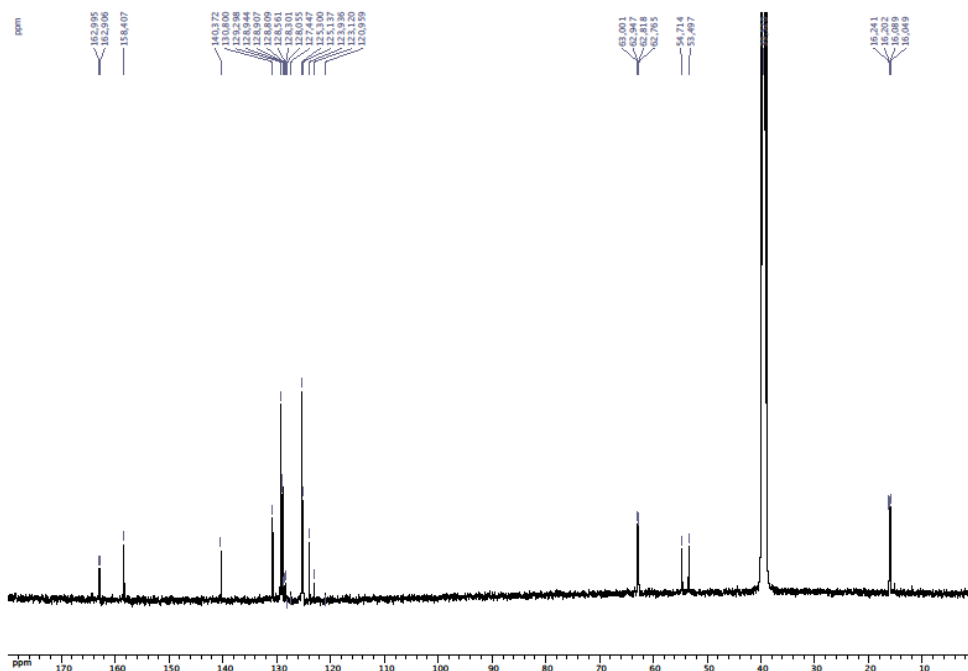




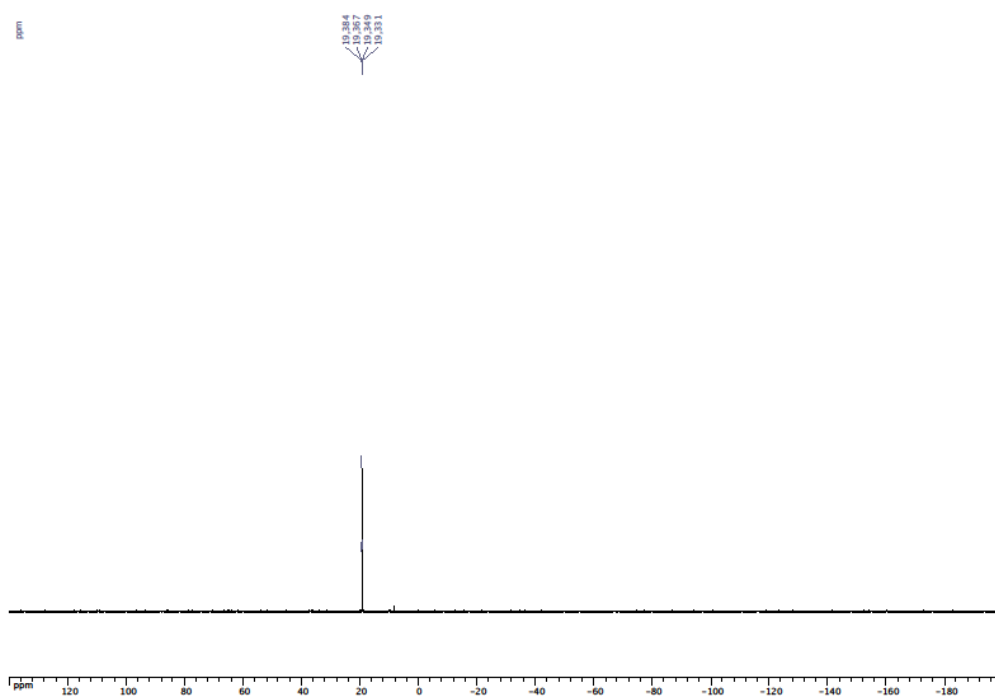
**Characterising data of diethyl[(5-phenyl-1,3,4-oxodiazol-2-ylamino)  
(4-trifluoromethylphenyl)methyl]phosphonate (5a)**



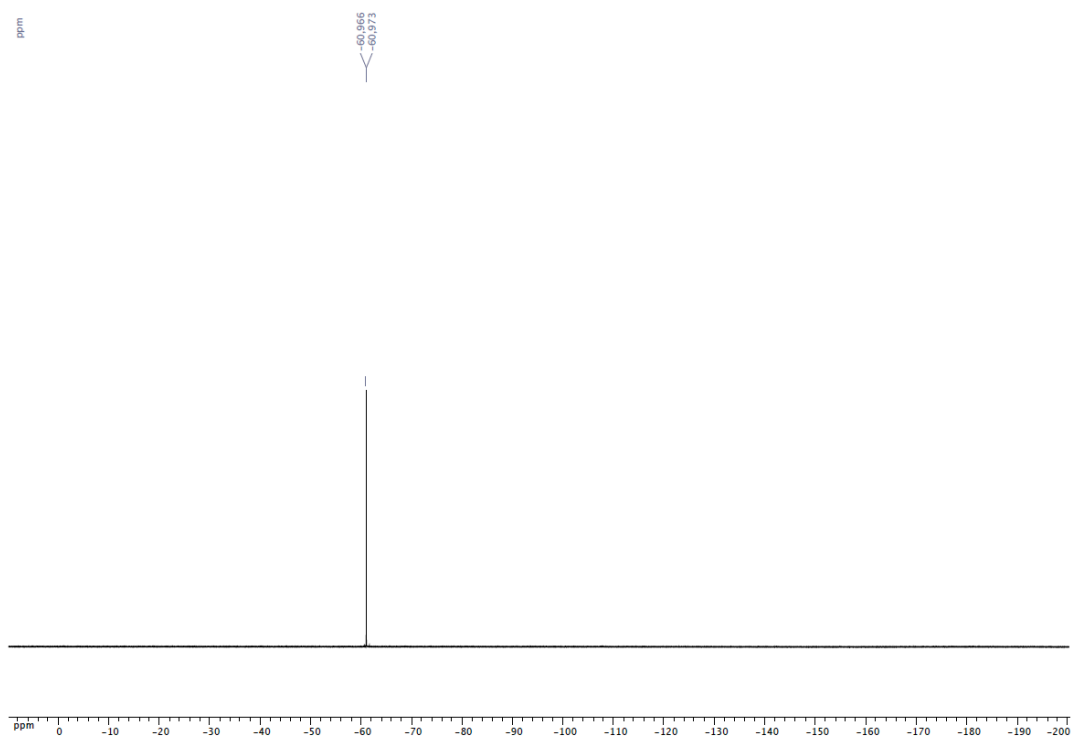
<sup>1</sup>H NMR spectrum (DMSO-d<sub>6</sub>)



<sup>13</sup>C{<sup>1</sup>H} NMR spectrum (DMSO-d<sub>6</sub>)

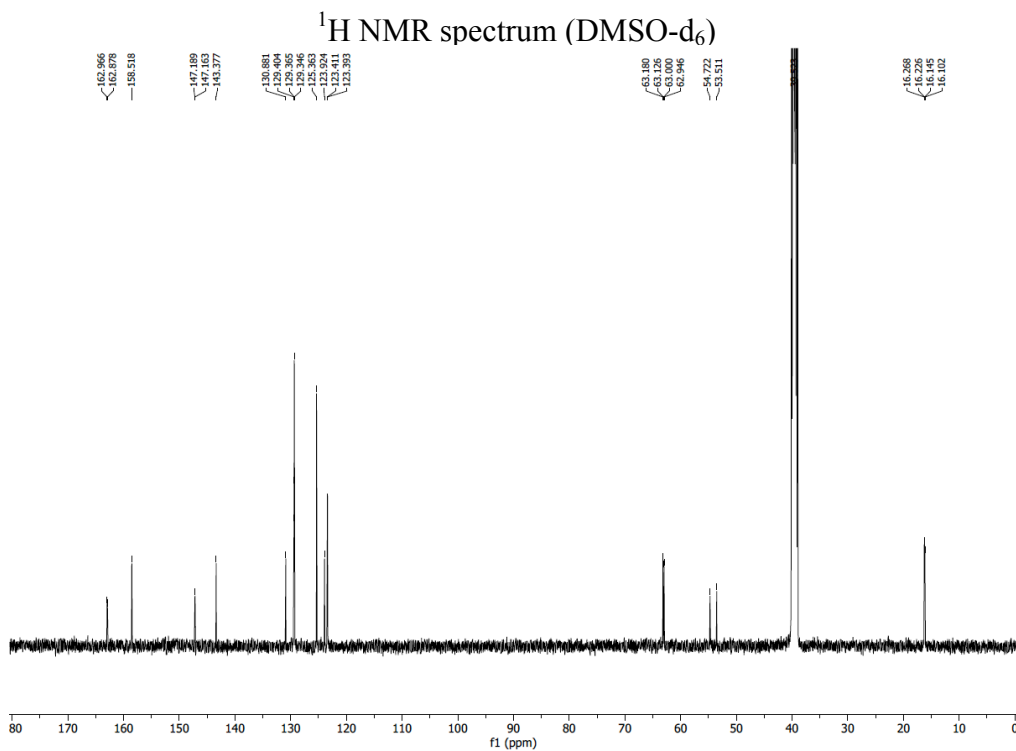
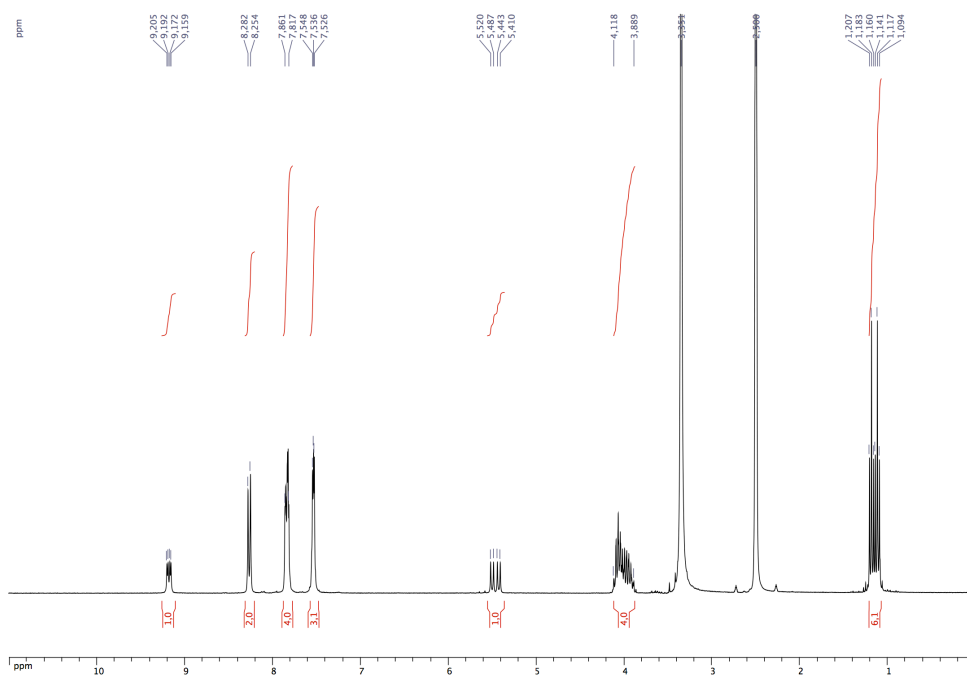
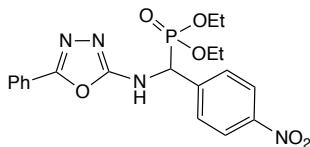


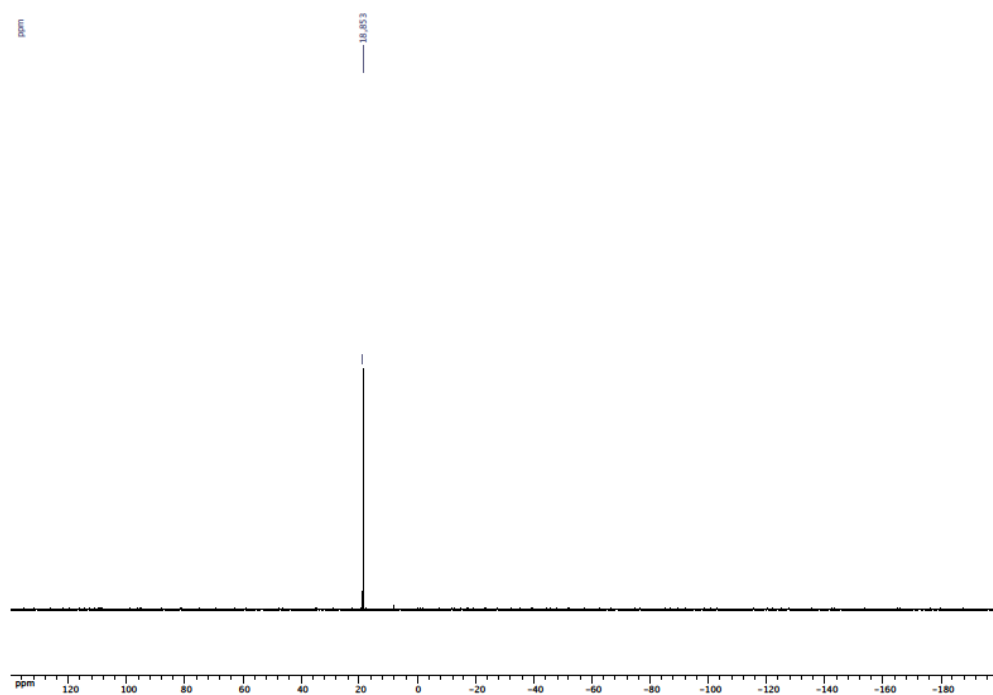
$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )



$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

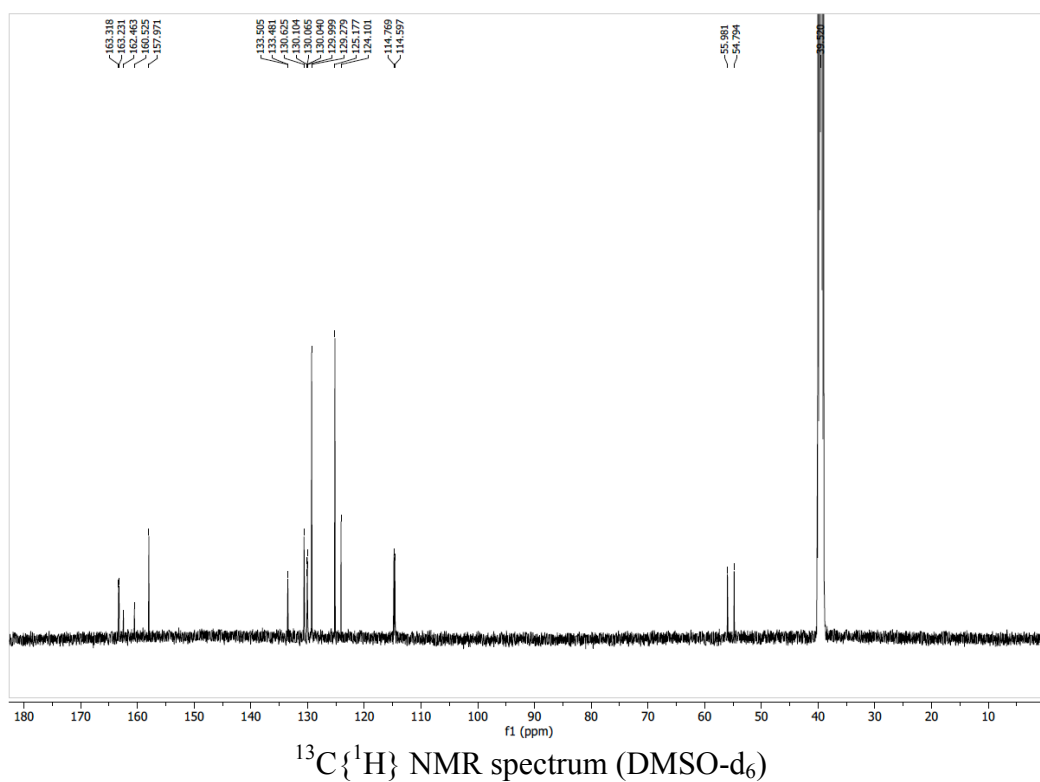
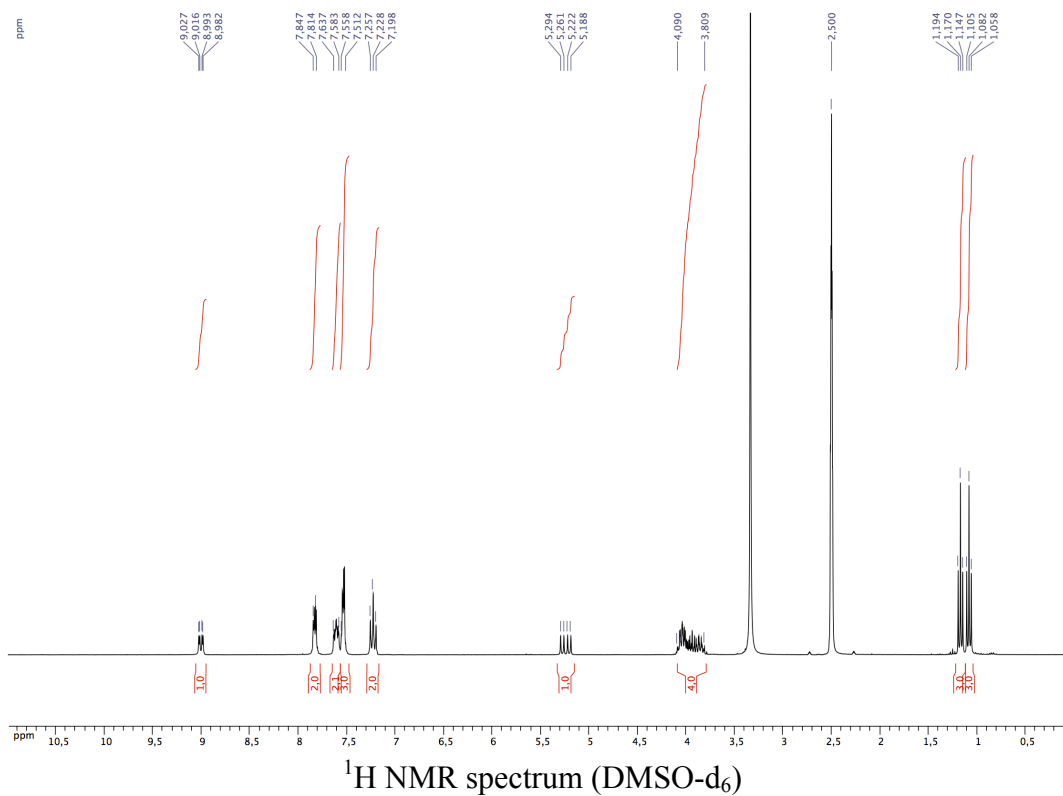
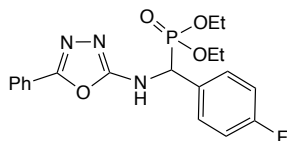
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(4-nitrophenyl)methyl]phosphonate (5b)**

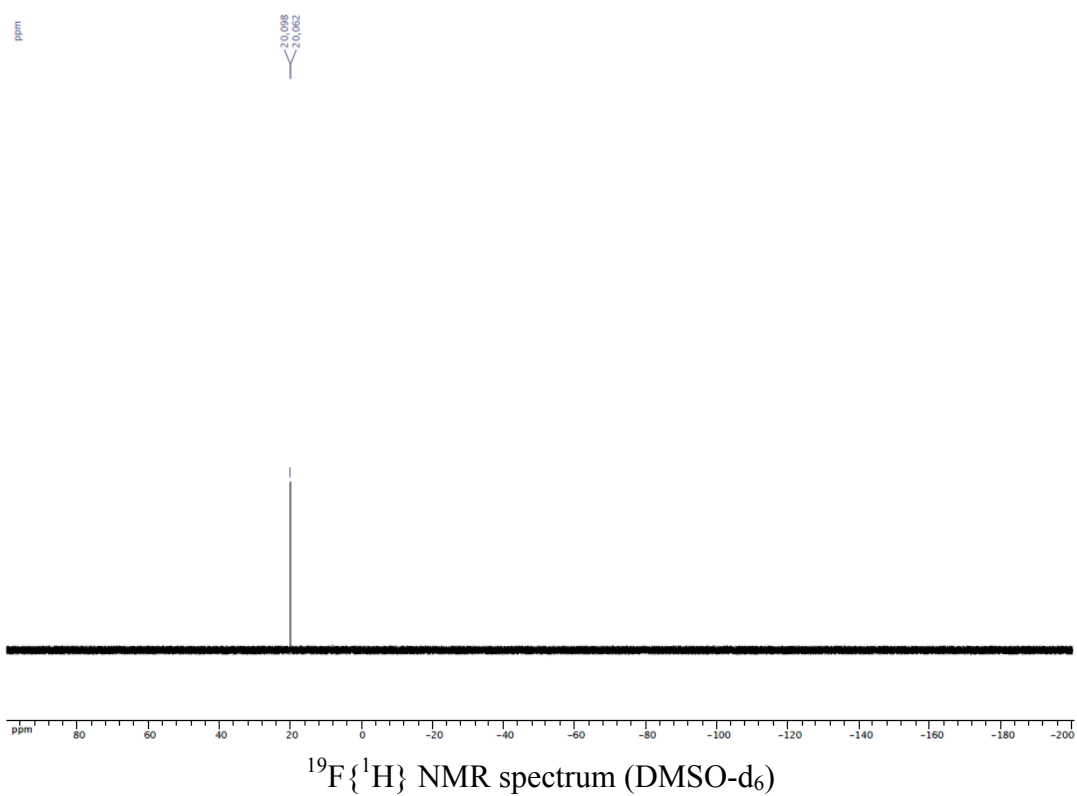
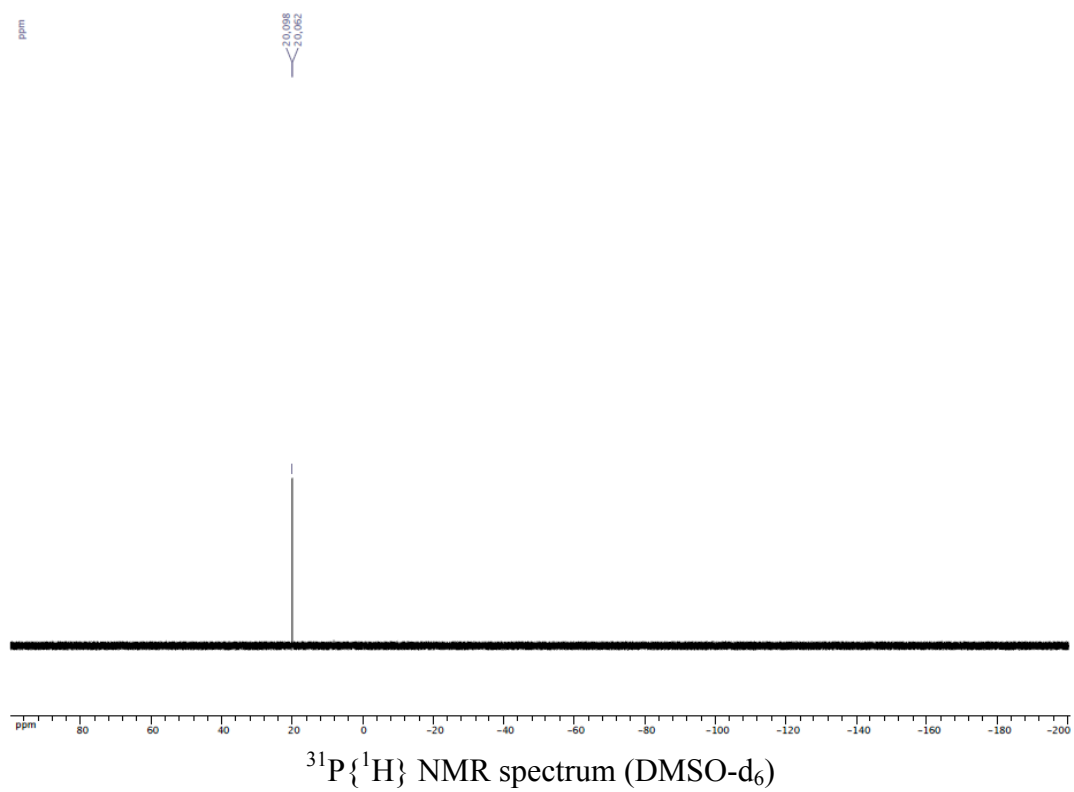




$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO-d}_6$ )

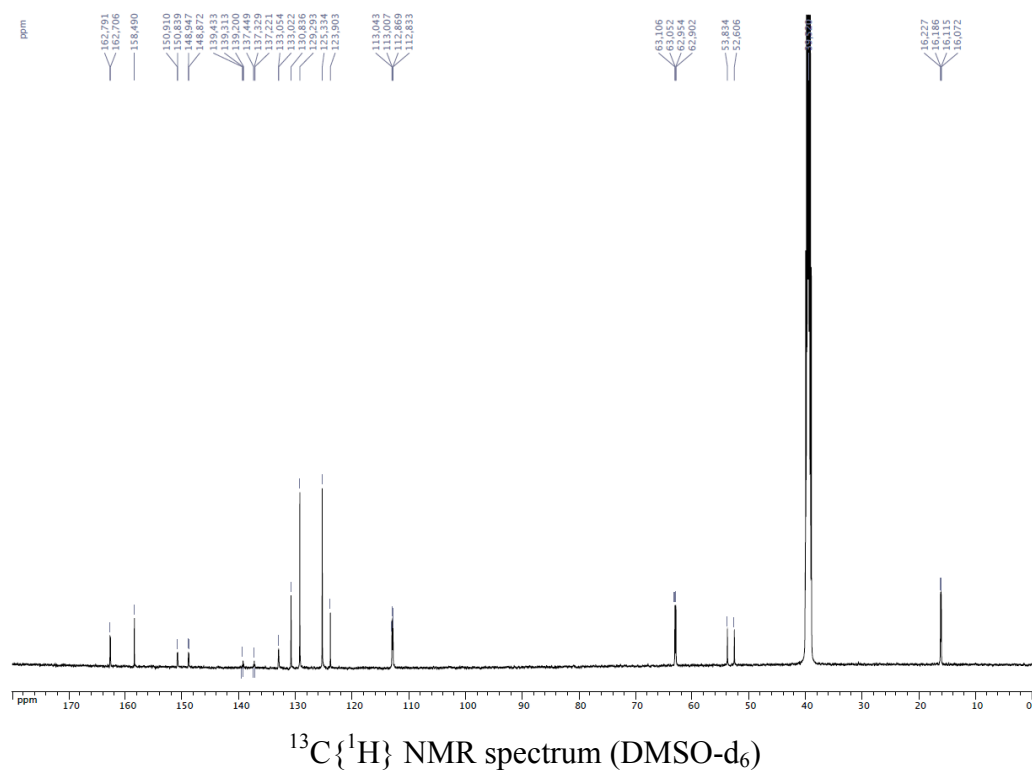
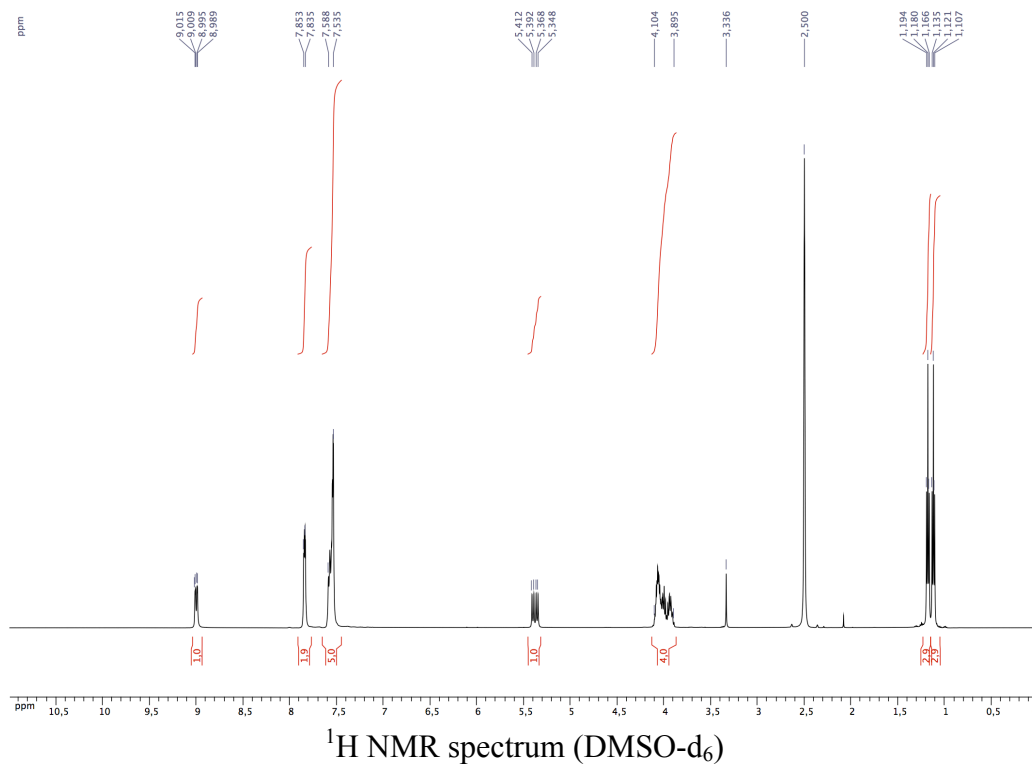
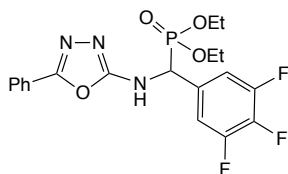
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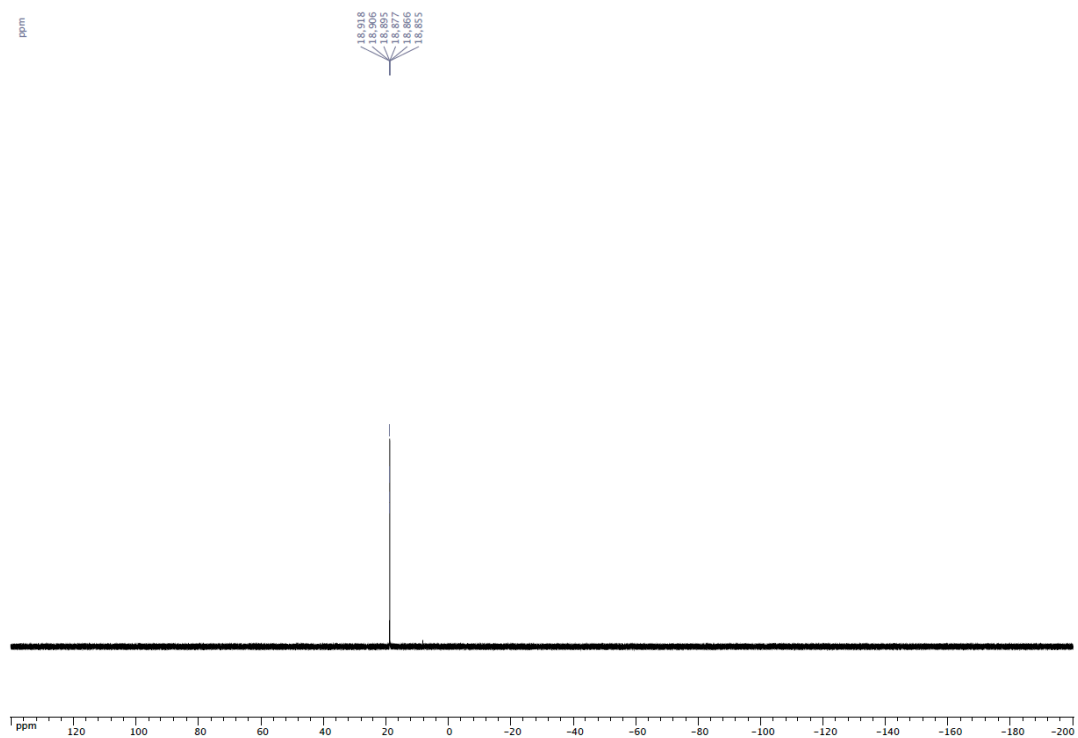




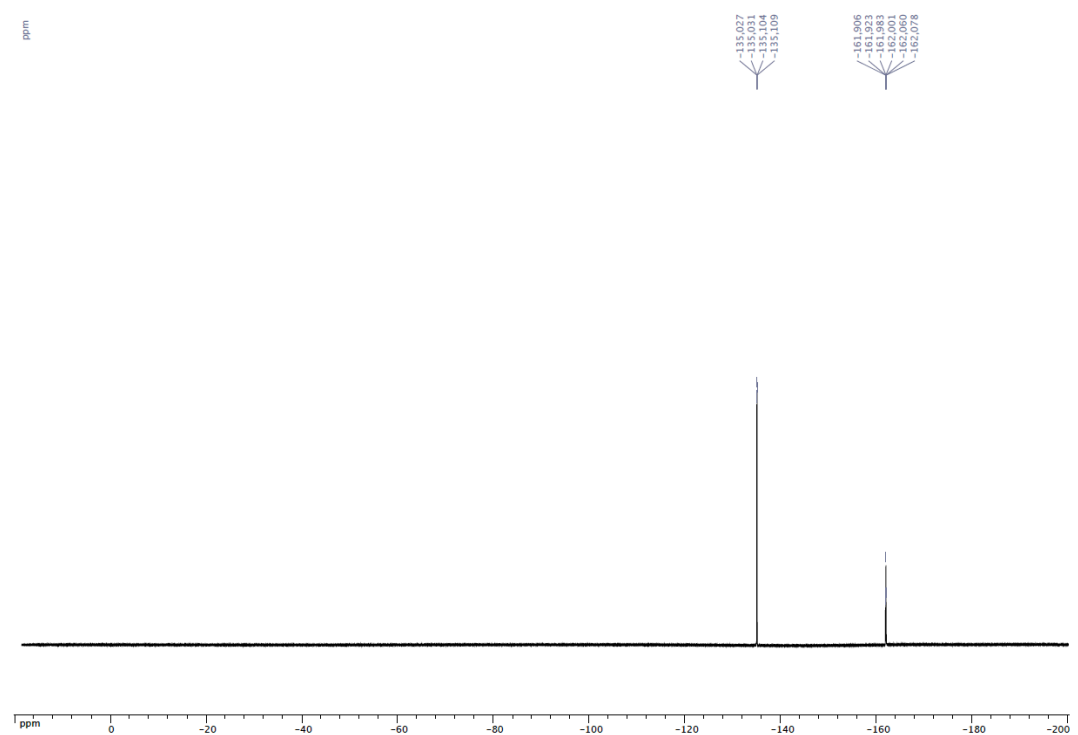


**Characterising data of diethyl[(5-phenyl-1,3,4-oxodiazol-2-ylamino)  
(3,4,5-trifluorophenyl)methyl]phosphonate (5d)**



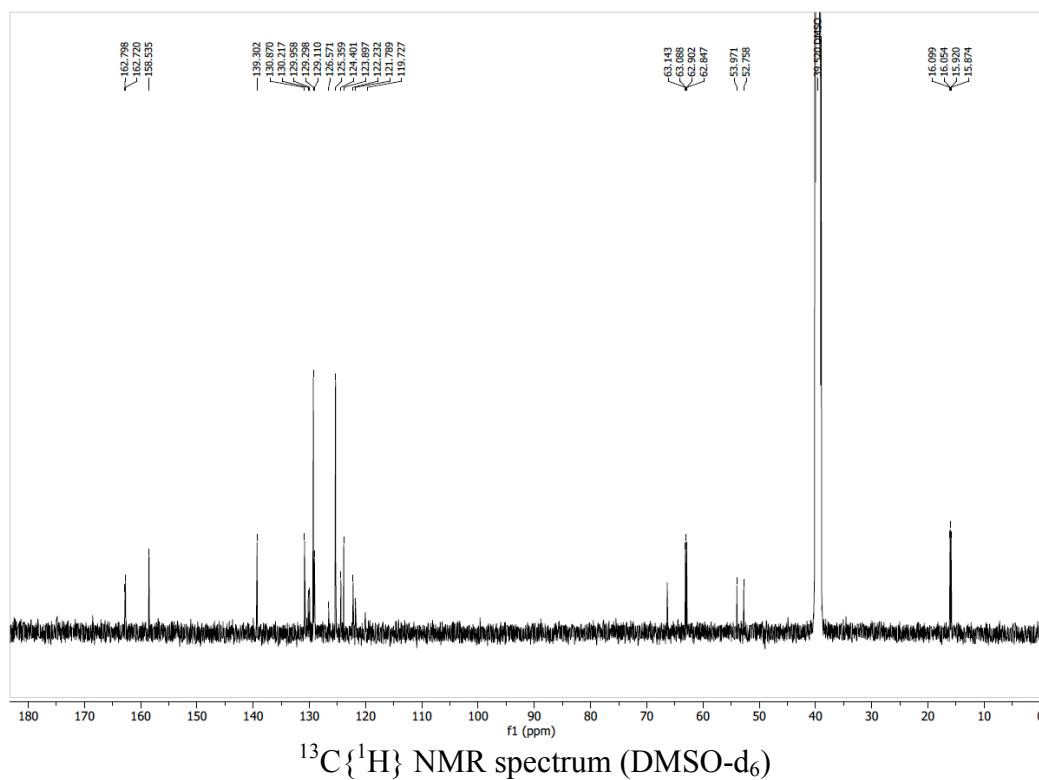
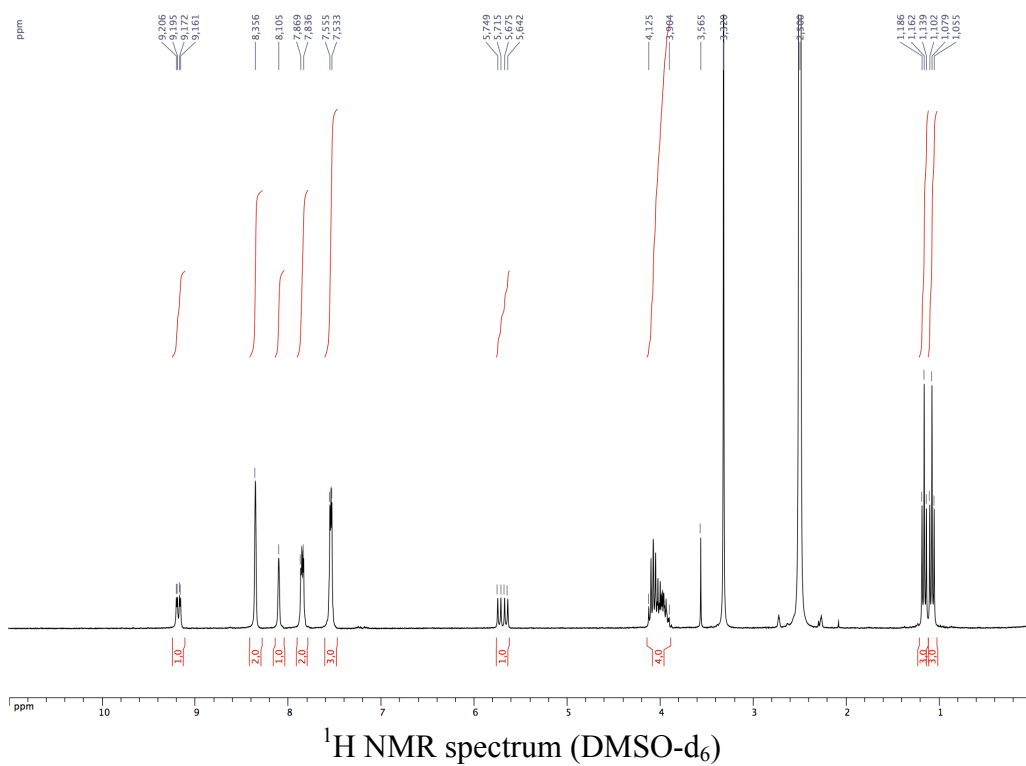
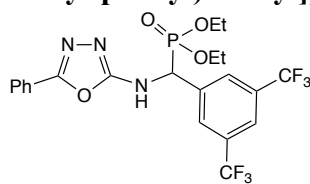


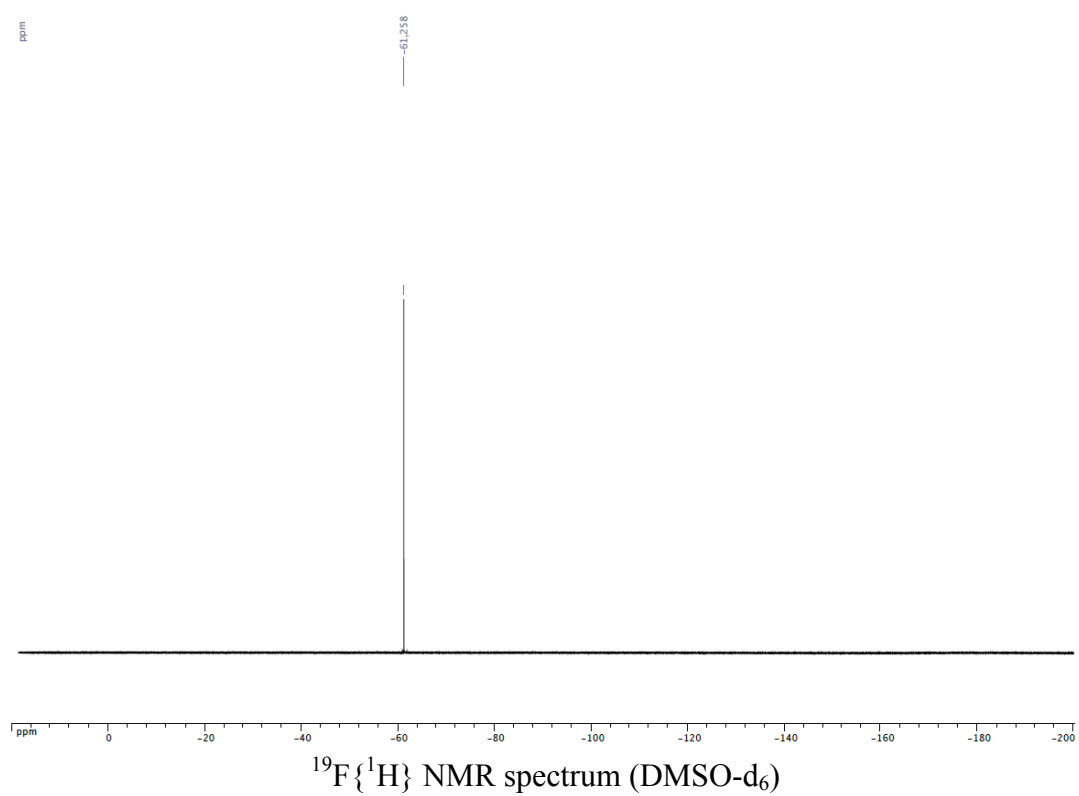
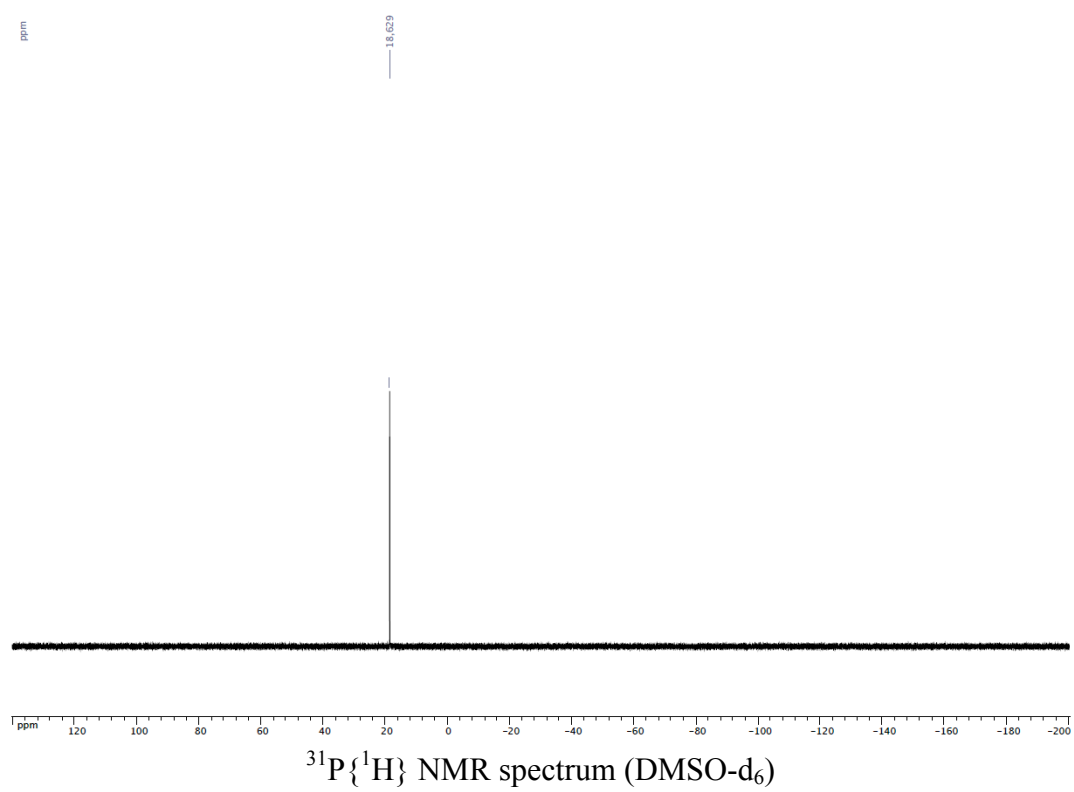
<sup>31</sup>P{<sup>1</sup>H} NMR spectrum (DMSO-d<sub>6</sub>)



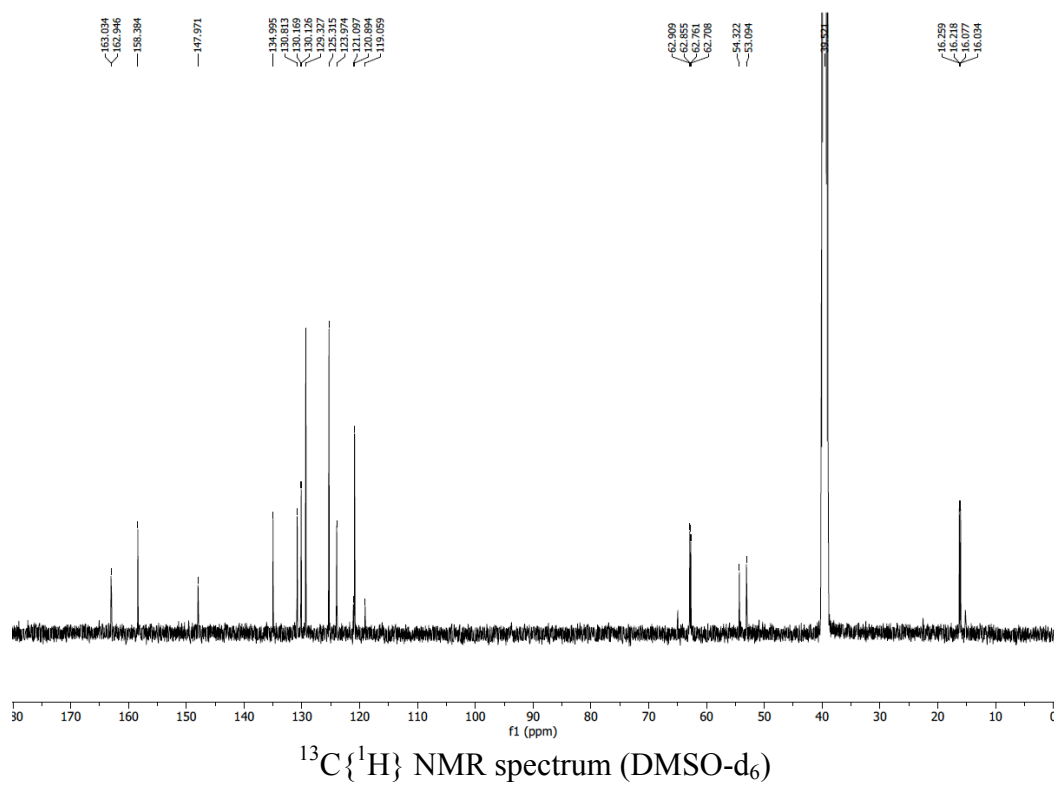
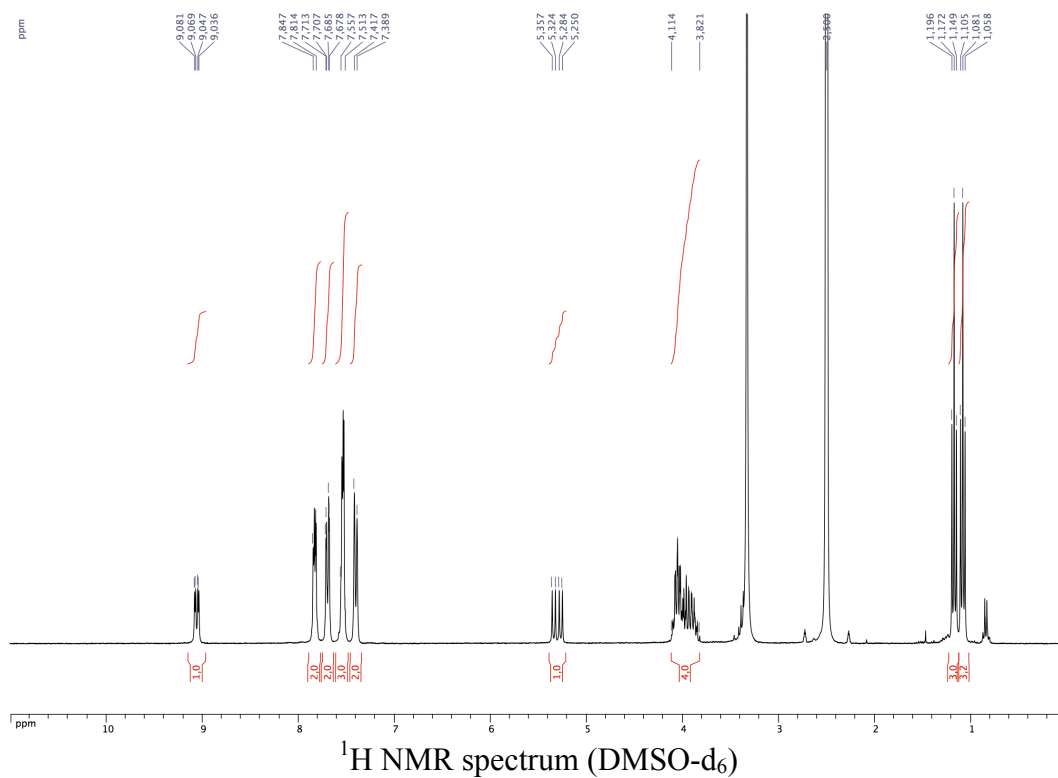
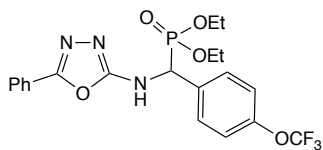
<sup>19</sup>F{<sup>1</sup>H} NMR spectrum (DMSO-d<sub>6</sub>)

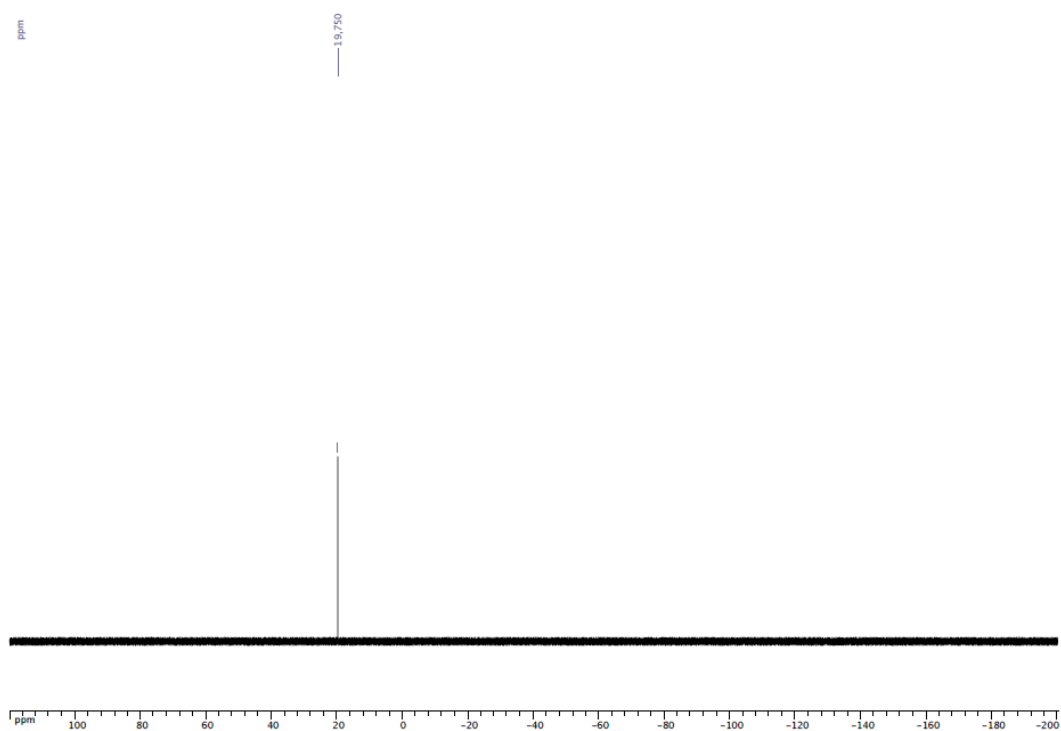
**Characterising data of diethyl[(5-phenyl-1,3,4-oxadiazol-2-ylamino)  
(3,5-bis-trifluoromethyl-phenyl)methyl]phosphonate (5e)**



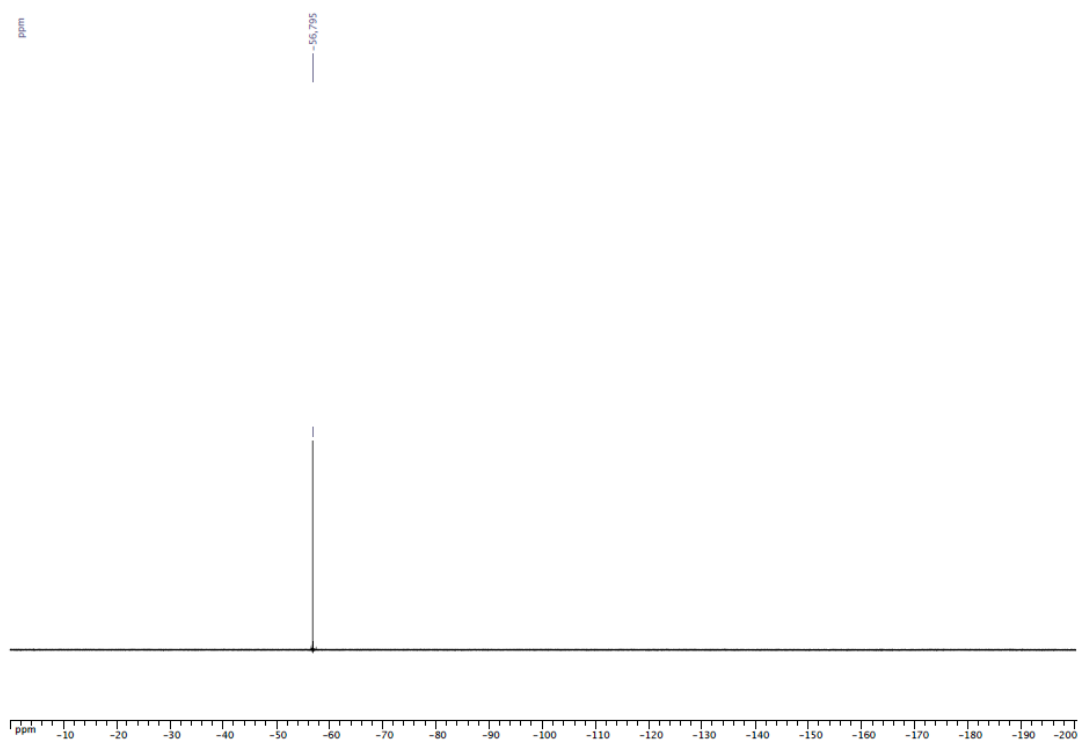


**Characterising data of diethyl[(5-phenyl-1,3,4-oxodiazol-2-ylamino)(4-trifluoromethoxyphenyl)methyl]phosphonate (5f)**



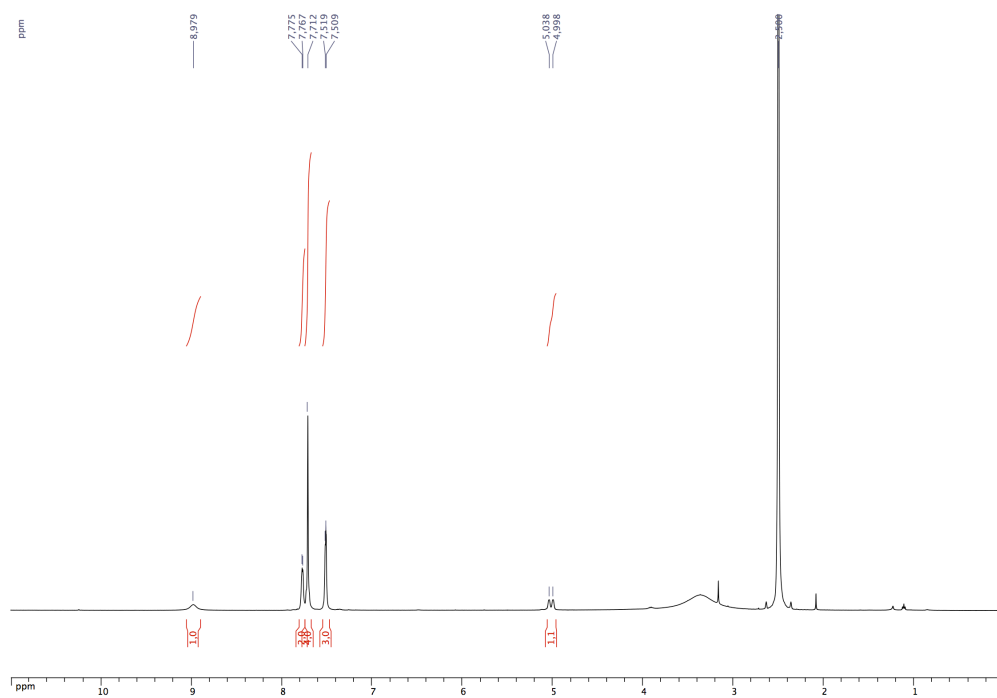
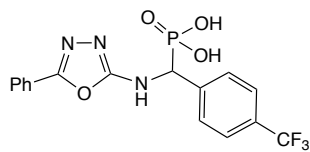


$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

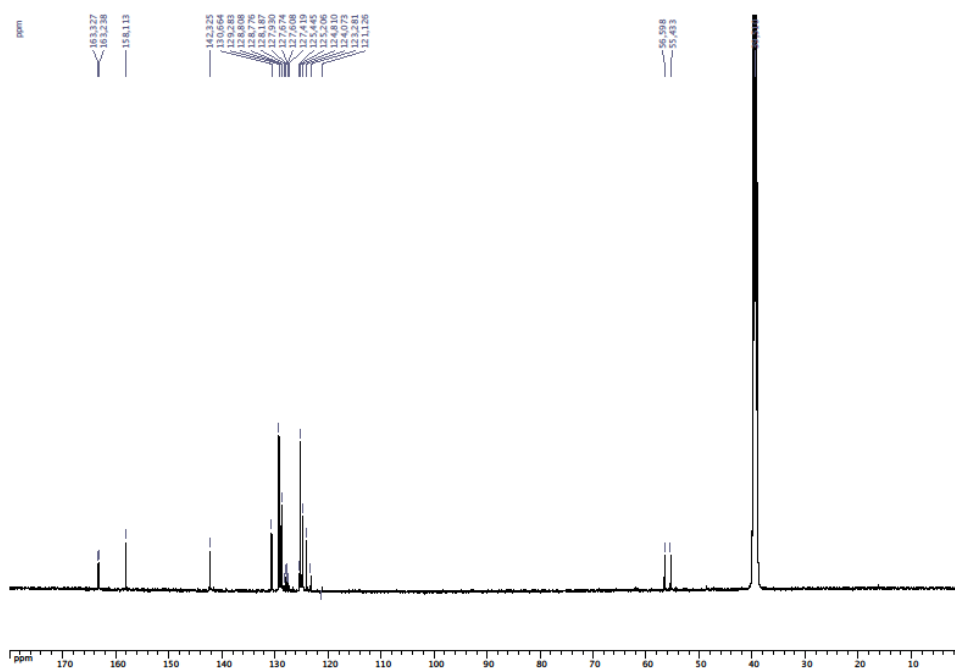


$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

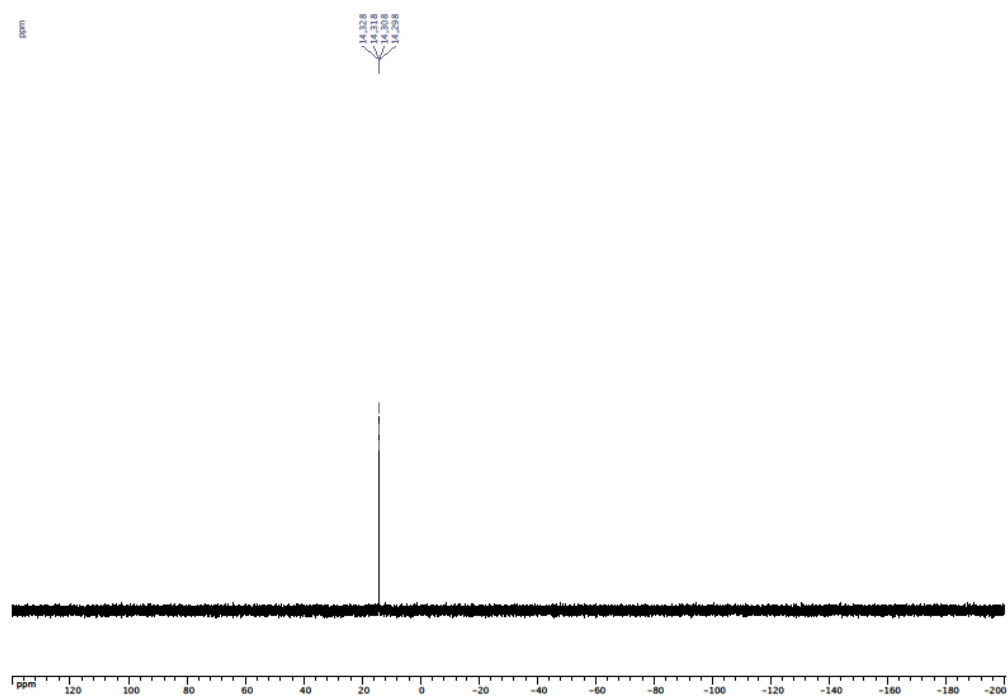
**Characterising data of [(5-phenyl-1,3,4-oxadiazol-2-ylamino) (4-trifluoromethylphenyl) methyl]phosphonic acid (6a)**



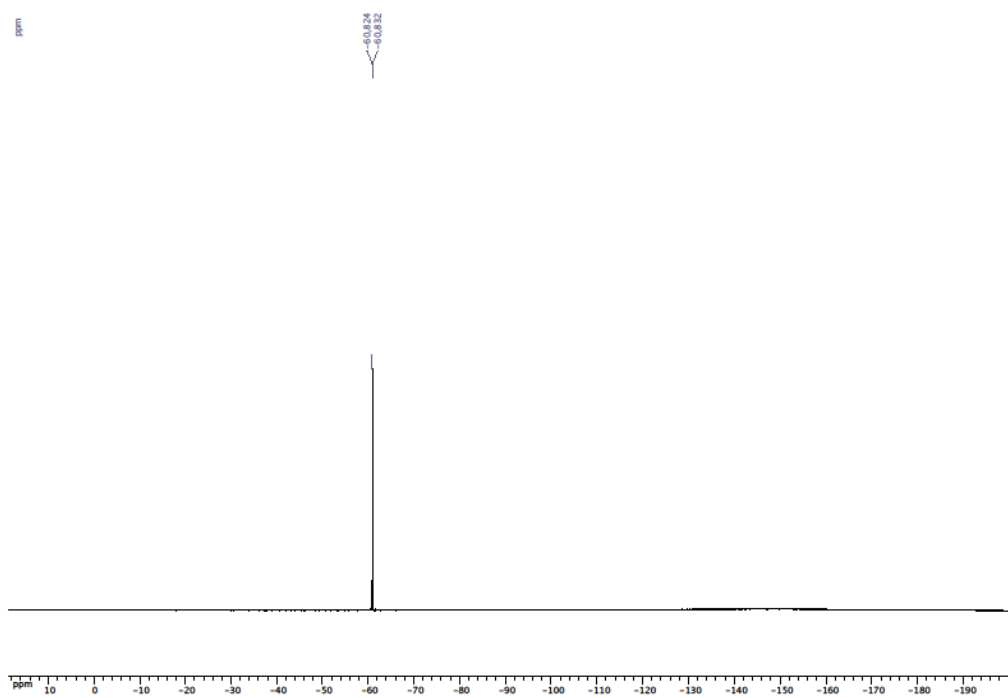
<sup>1</sup>H NMR spectrum (DMSO-d<sub>6</sub>)



<sup>13</sup>C{<sup>1</sup>H} NMR spectrum (DMSO-d<sub>6</sub>)



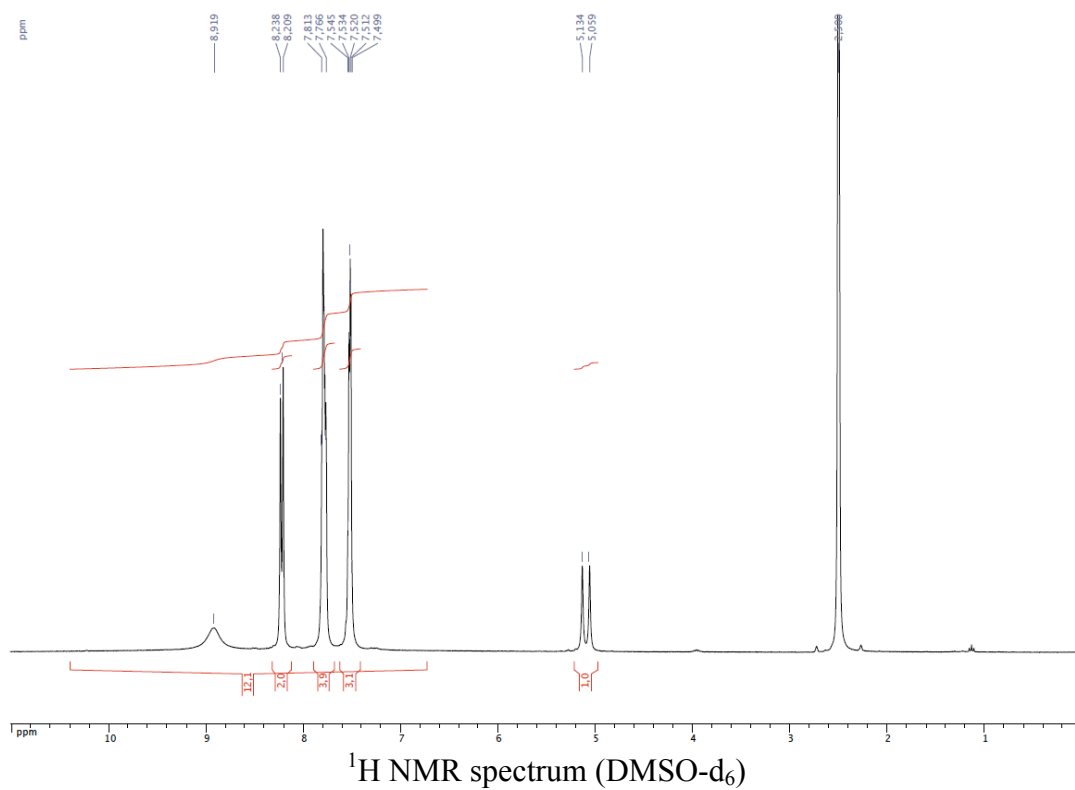
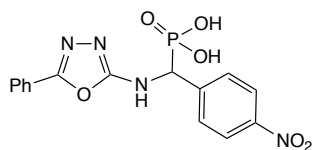
$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

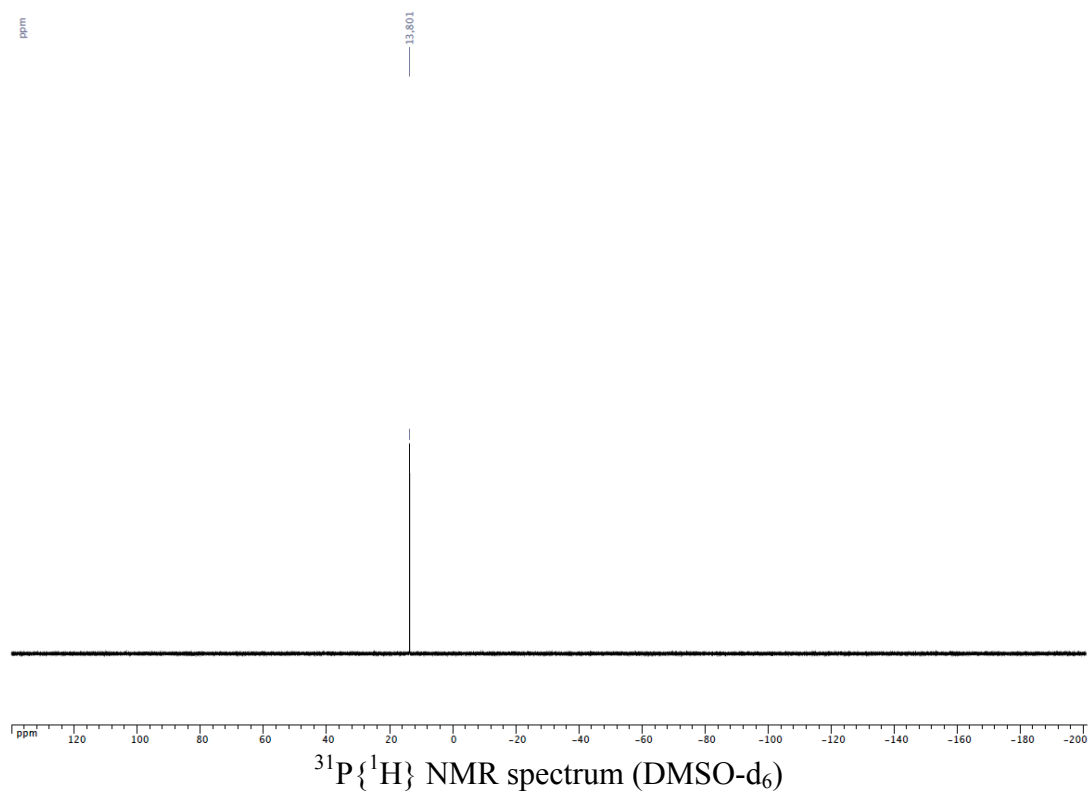
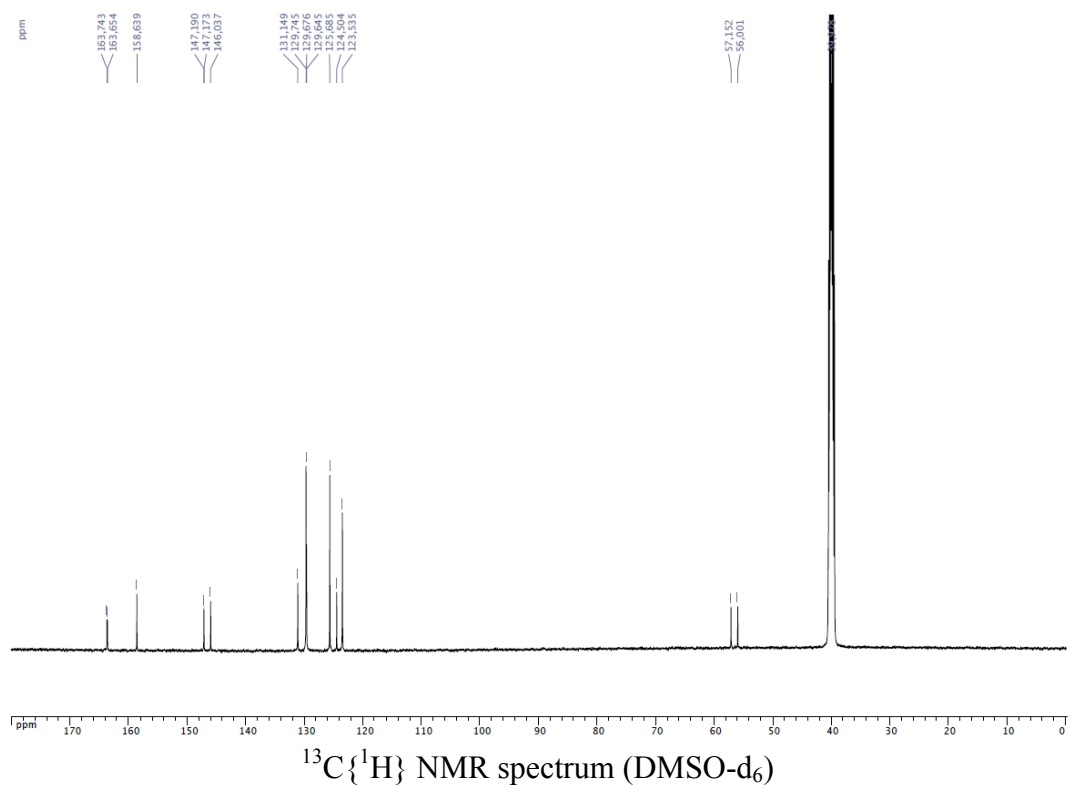


$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

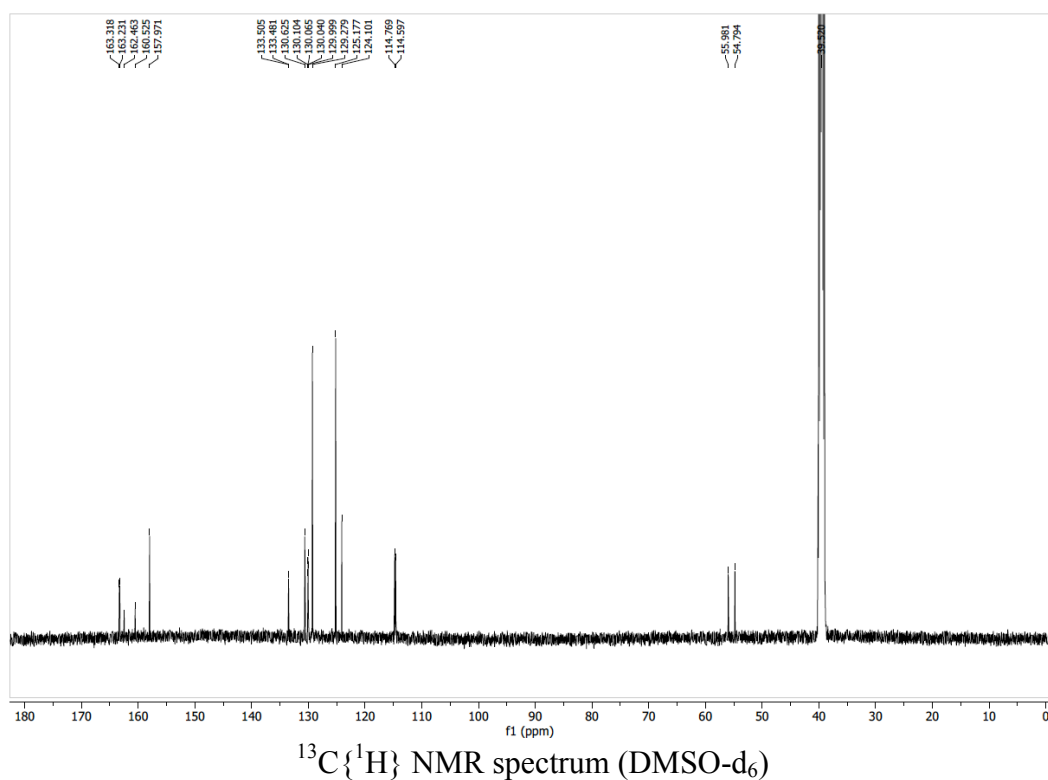
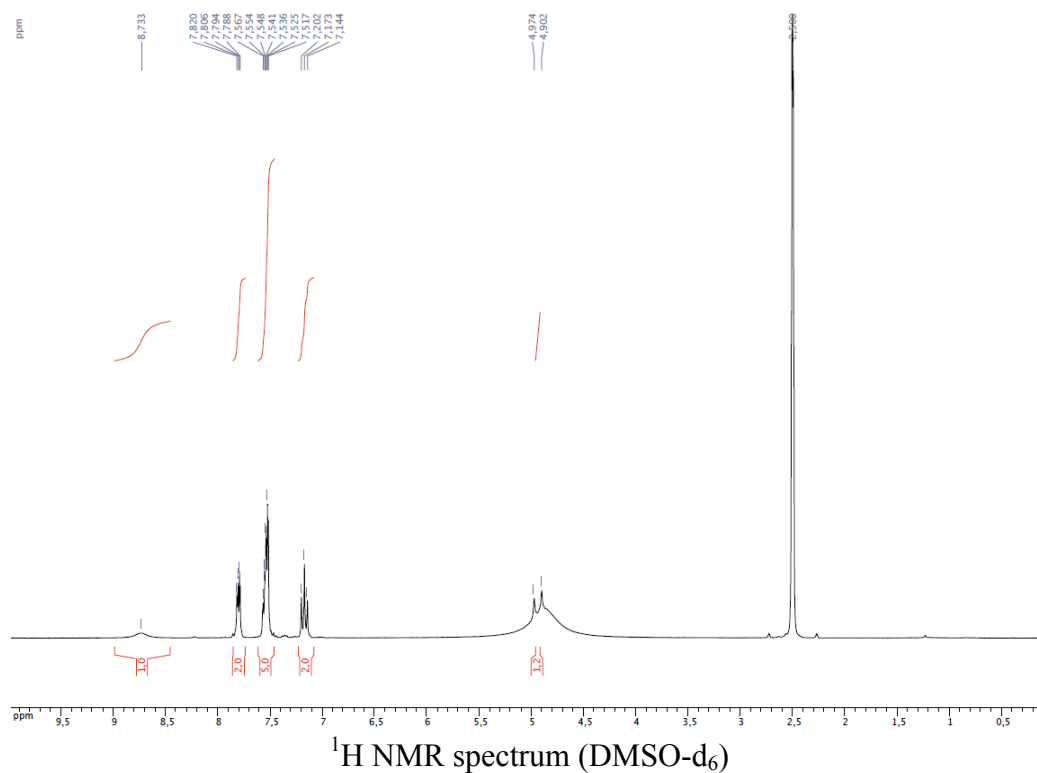
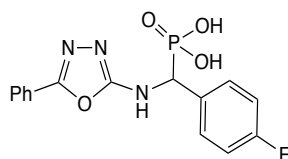


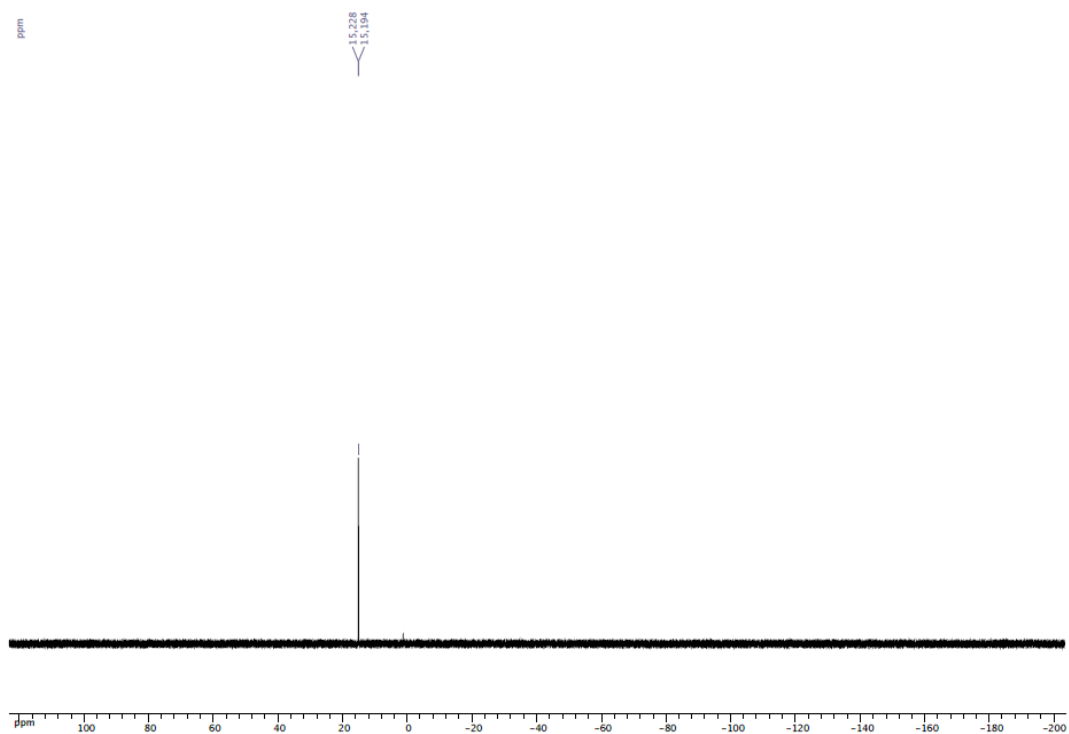
**Characterising data of [(5-phenyl-1,3,4-oxadiazol-2-ylamino)  
(4-nitrophenyl)methyl]phosphonic acid (6b)**



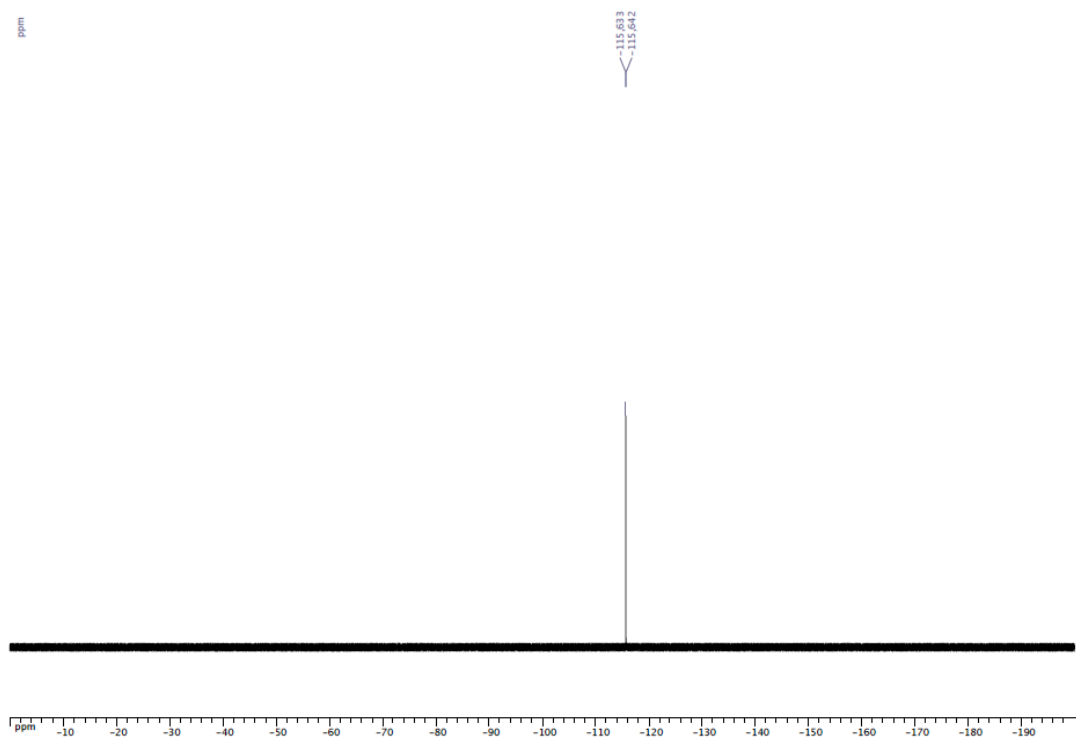


**Characterising data of [(5-phenyl-1,3,4-oxodiazol-2-ylamino)  
(4-fluorophenyl)methyl]phosphonic acid (6c)**



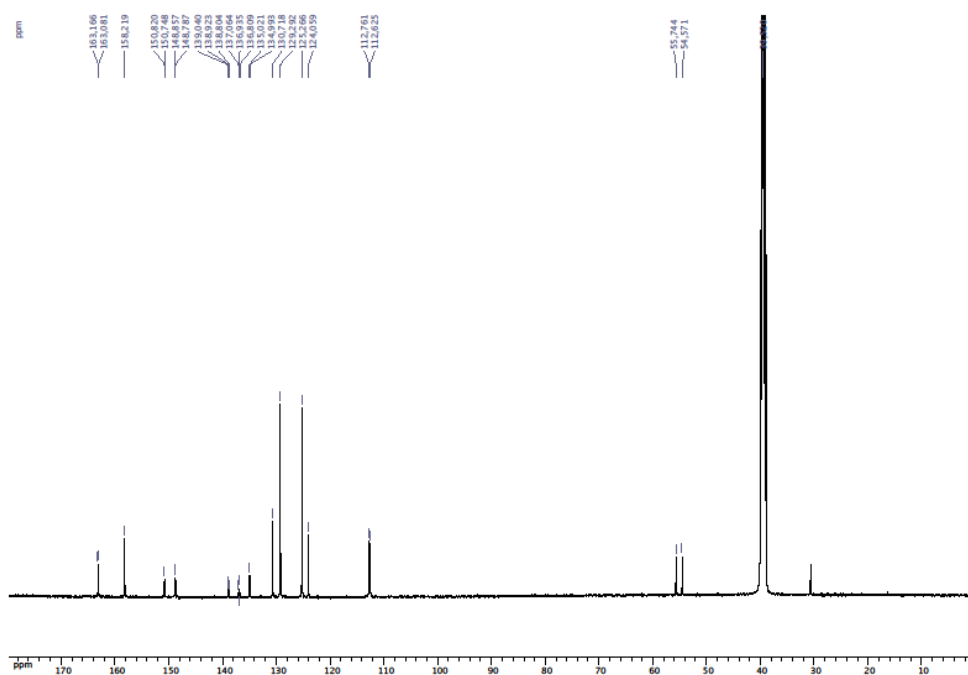
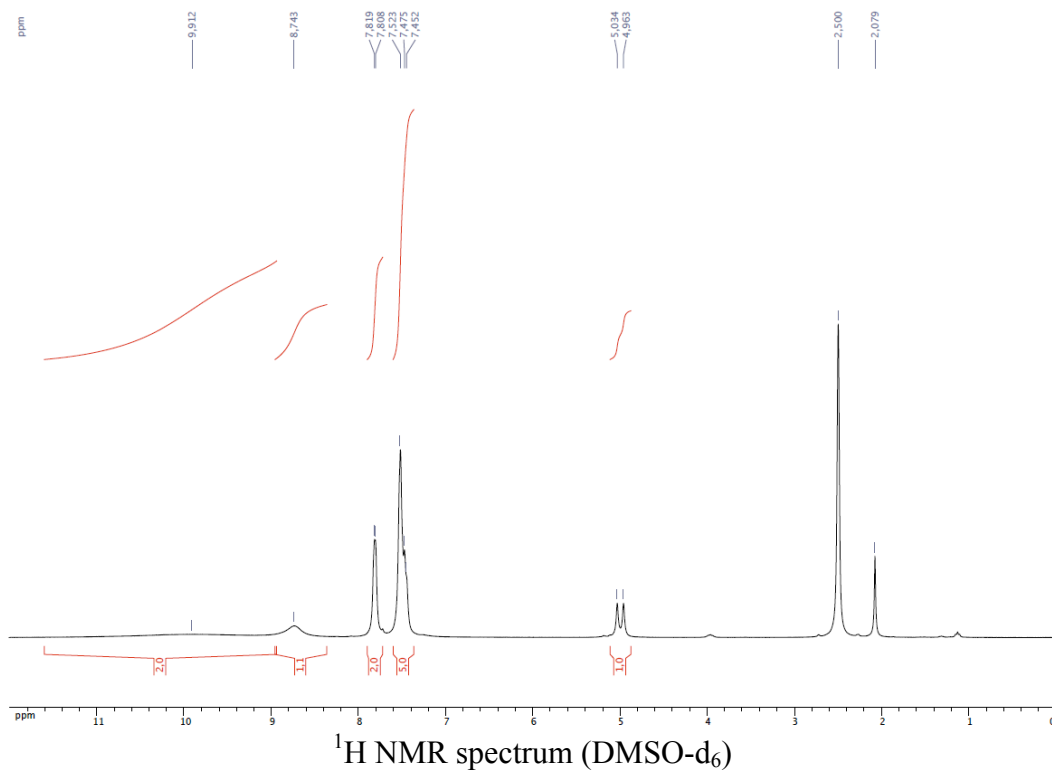
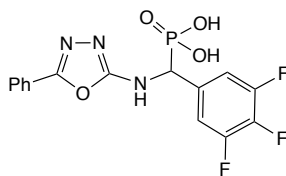


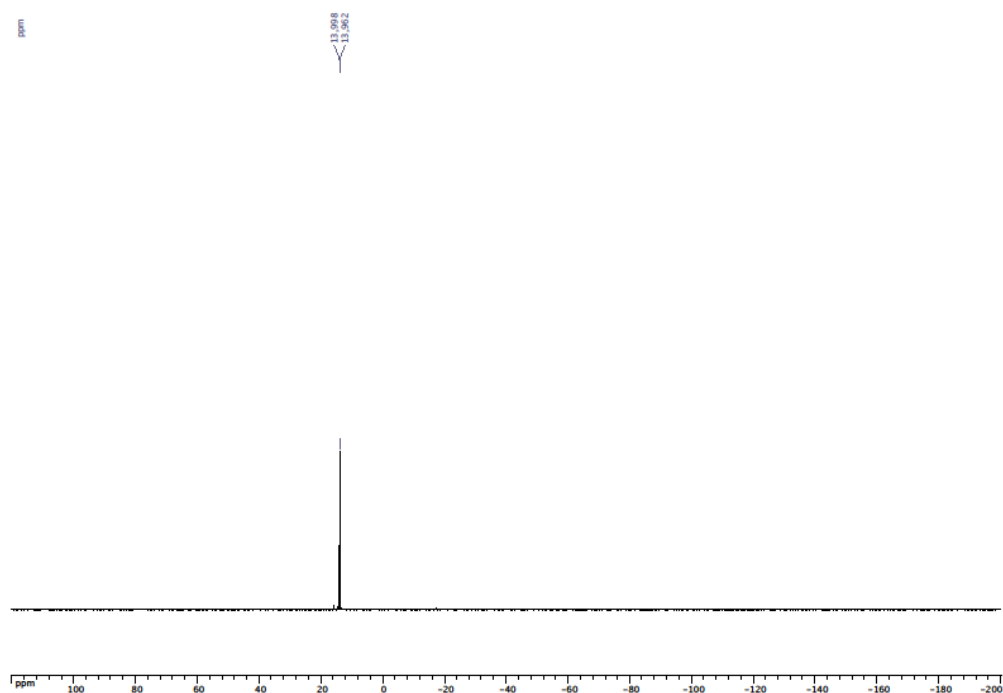
$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )



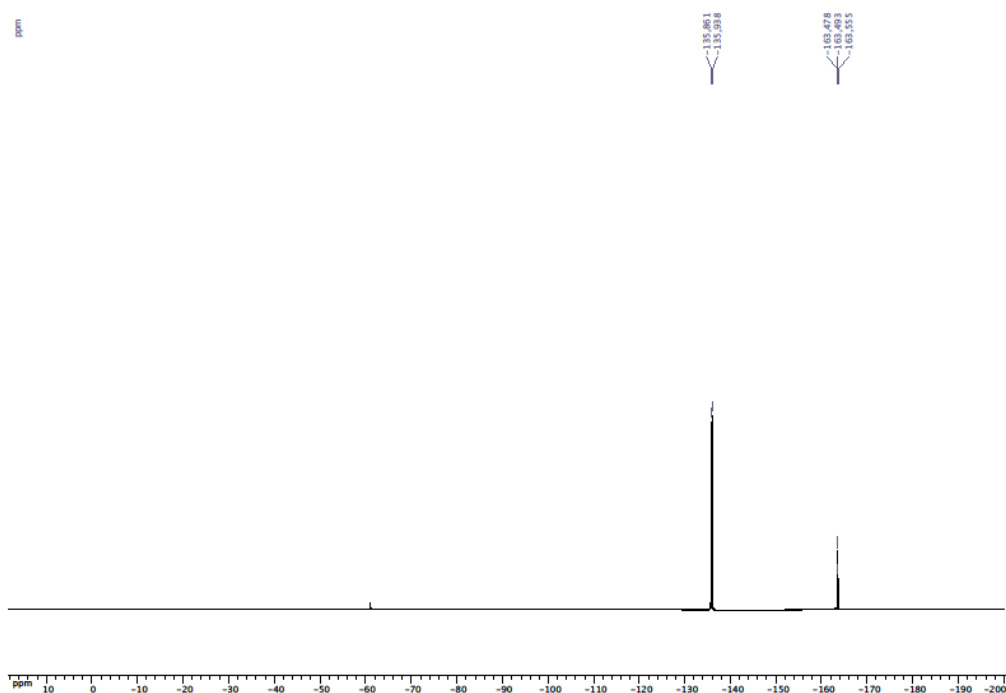
$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

**Characterising data of [(5-phenyl-1,3,4-oxodiazol-2-ylamino)  
(3,4,5-trifluorophenyl)methyl]phosphonic acid (6d)**

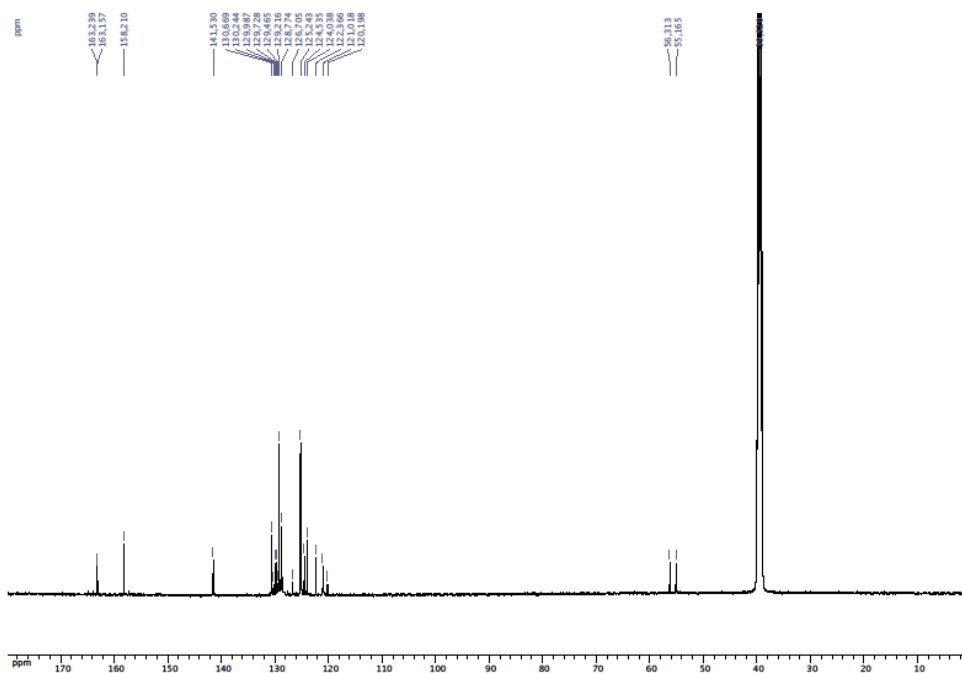


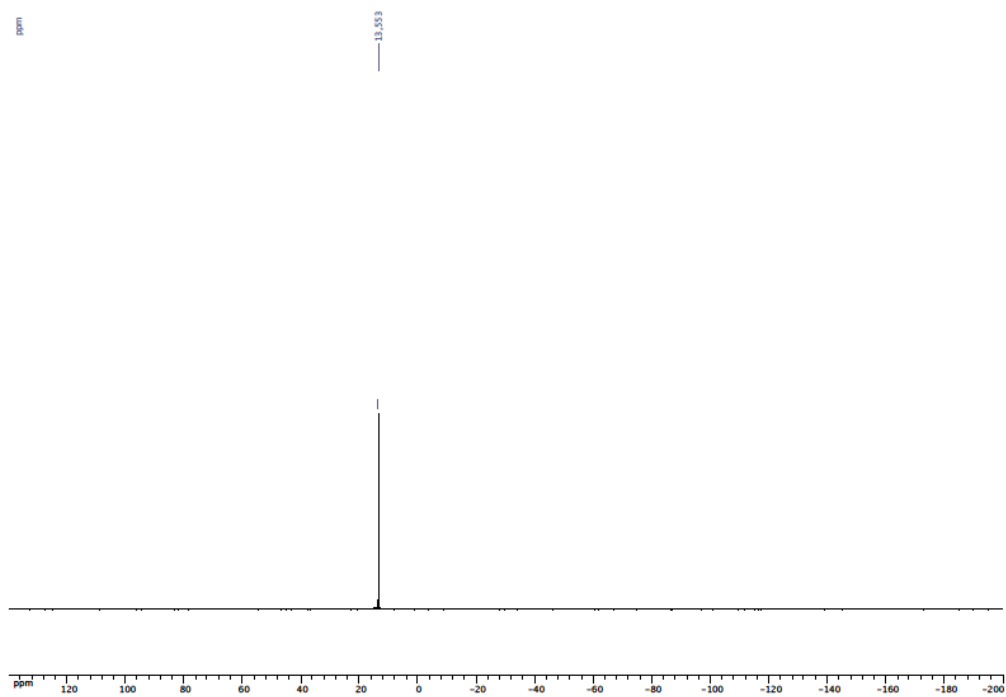


$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

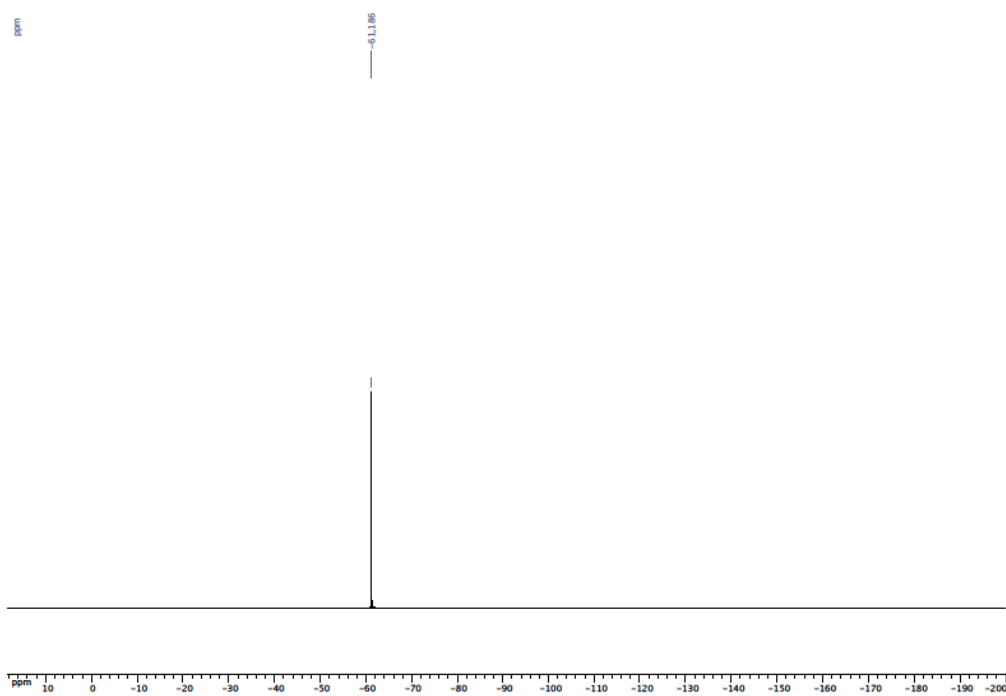


$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

O=P(O)(O)C(c1ccc(C(F)(F)F)c(C(F)(F)F)c1)Nc2nc3ccccc3o2



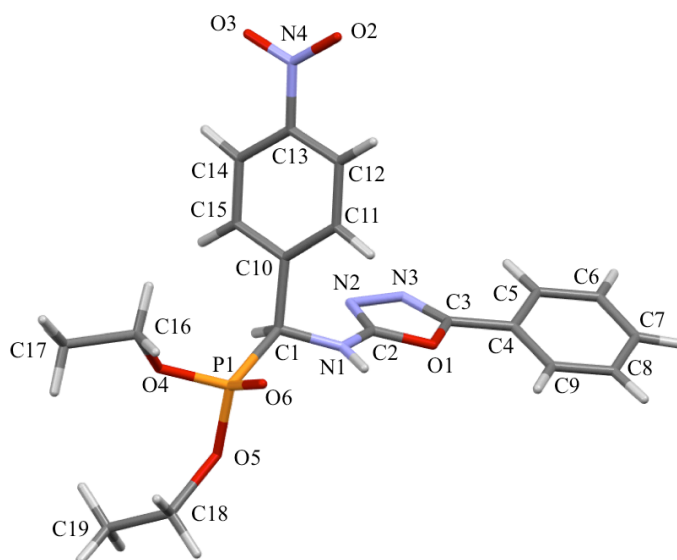
$^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )



$^{19}\text{F}\{^1\text{H}\}$  NMR spectrum (DMSO- $\text{d}_6$ )

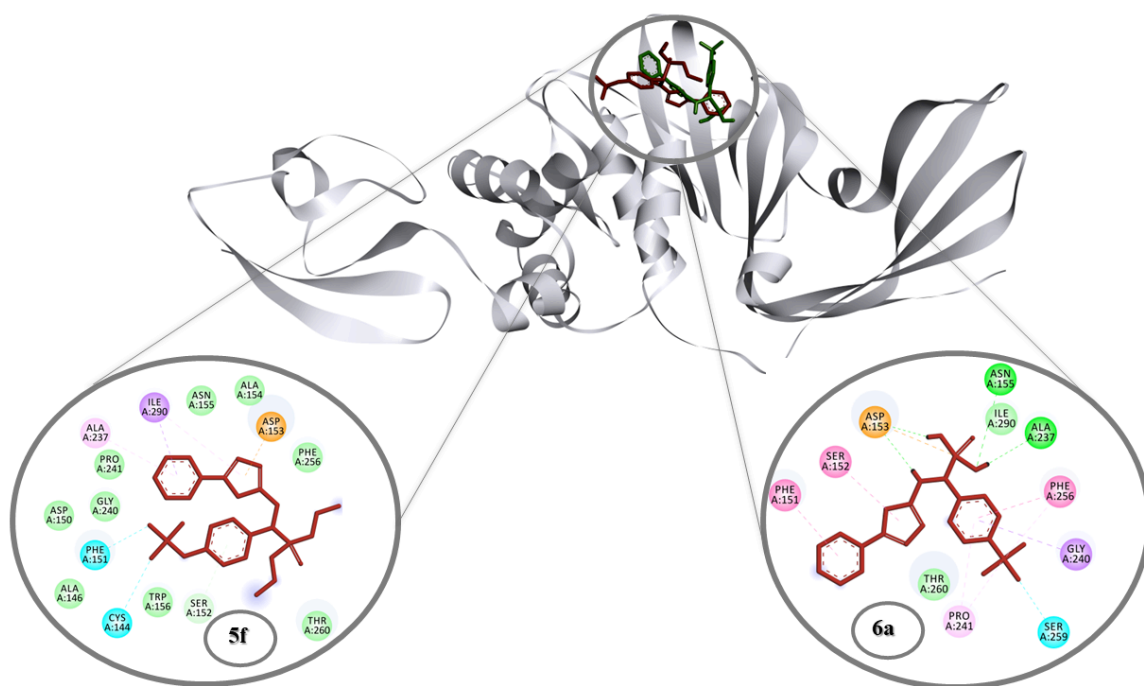


### X-ray structure of 5b

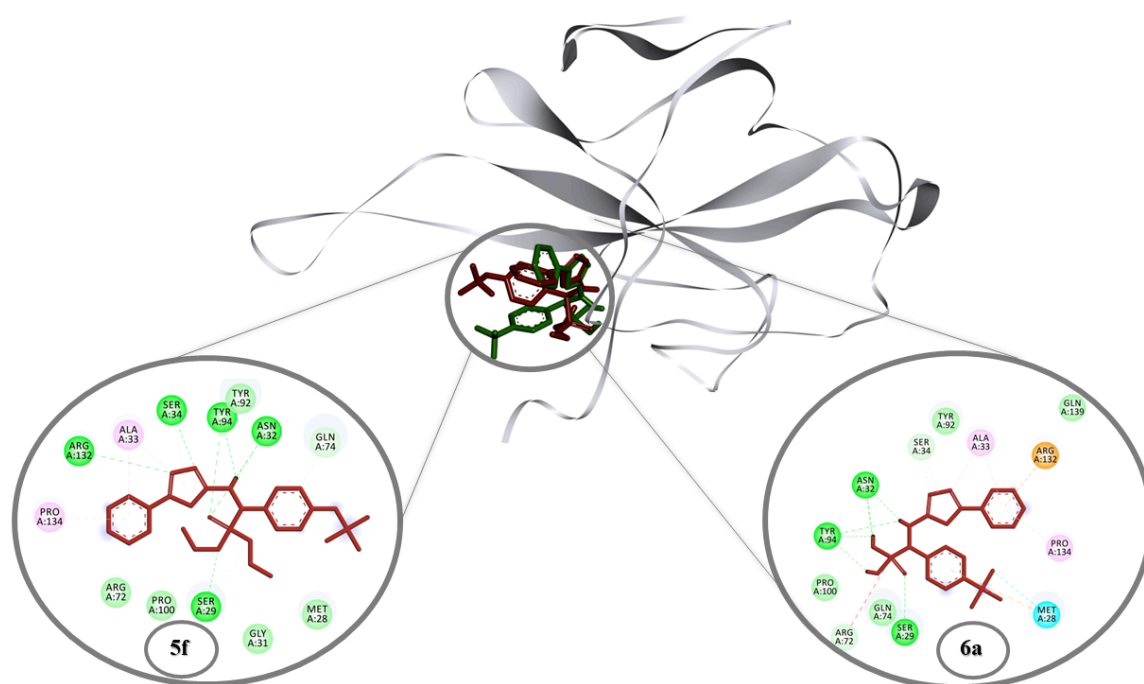


| Lengths (Å)       |                    |                    |
|-------------------|--------------------|--------------------|
| P1 - O6 1.458(3)  | C5 - H5 0.9500     | C15 - H15 0.9500   |
| P1 - O4 1.486(3)  | C6 - C7 1.303(5)   | N4 - O3 1.149(5)   |
| P1 - O5 1.547(3)  | C6 - H6 0.9500     | N4 - O2 1.286(5)   |
| P1 - C1 1.980(4)  | C7 - C8 1.448(6)   | O4 - C16 1.346(5)  |
| C1 - N1 1.351(4)  | C7 - H7 0.9500     | C16 - C17 1.486(6) |
| C1 - C10 1.495(4) | C8 - C9 1.353(5)   | C16 - H16A 0.9900  |
| C1 - H1 1.0000    | C8 - H8 0.9500     | C16 - H16B 0.9900  |
| N1 - C2 1.385(5)  | C9 - H9 0.9500     | C17 - H17A 0.9800  |
| N1 - H1A 0.8800   | C10 - C15 1.307(5) | C17 - H17B 0.9800  |
| C2 - O1 1.267(4)  | C10 - C11 1.468(6) | C17 - H17C 0.9800  |
| C2 - N2 1.286(5)  | C11 - C12 1.353(4) | O5 - C18 1.635(5)  |
| N2 - N3 1.438(4)  | C11 - H11 0.9500   | C18 - C19 1.540(6) |
| N3 - C3 1.214(4)  | C12 - C13 1.293(5) | C18 - H18A 0.9900  |
| C3 - C4 1.409(4)  | C12 - H12 0.9500   | C18 - H18B 0.9900  |
| C3 - O1 1.422(4)  | C13 - N4 1.419(4)  | C19 - H19A 0.9800  |
| C4 - C9 1.320(4)  | C13 - C14 1.445(6) | C19 - H19B 0.9800  |
| C4 - C5 1.472(5)  | C14 - C15 1.349(5) | C19 - H19C 0.9800  |
| C5 - C6 1.341(5)  | C14 - H14 0.9500   |                    |

| Angles (°)               |                          |                         |
|--------------------------|--------------------------|-------------------------|
| O6 - P1 - O4 116.80(16)  | C10 - C1 - H1 108.1      | N3 - C3 - C4 125.4(3)   |
| O6 - P1 - O5 117.93(16)  | P1 - C1 - H1 108.1       | N3 - C3 - O1 114.9(3)   |
| O4 - P1 - O5 92.04(16)   | C1 - N1 - C2 117.2(3)    | C4 - C3 - O1 119.8(3)   |
| O6 - P1 - C1 110.53(18)  | C1 - N1 - H1A 121.4      | C2 - O1 - C3 103.8(3)   |
| O4 - P1 - C1 108.73(16)  | C2 - N1 - H1A 121.4      | C9 - C4 - C3 114.4(3)   |
| O5 - P1 - C1 109.34(15)  | O1 - C2 - N2 109.9(3)    | C9 - C4 - C5 121.9(3)   |
| N1 - C1 - C10 101.4(3)   | O1 - C2 - N1 117.5(3)    | C3 - C4 - C5 123.7(3)   |
| N1 - C1 - P1 113.4(2)    | N2 - C2 - N1 132.5(3)    | C6 - C5 - C4 124.6(3)   |
| C10 - C1 - P1 117.3(2)   | C2 - N2 - N3 110.4(3)    | C6 - C5 - H5 117.7      |
| N1 - C1 - H1 108.1       | C3 - N3 - N2 101.0(3)    | C4 - C5 - H5 117.7      |
| C7 - C6 - C5 113.1(4)    | C11 - C12 - H12 124.8    | C16 - C17 - H17A 109.5  |
| C7 - C6 - H6 123.4       | C12 - C13 - N4 110.3(4)  | C16 - C17 - H17B 109.5  |
| C5 - C6 - H6 123.4       | C12 - C13 - C14 125.2(3) | H17A - C17 - H17B 109.5 |
| C6 - C7 - C8 122.8(3)    | N4 - C13 - C14 124.5(3)  | C16 - C17 - H17C 109.5  |
| C6 - C7 - H7 118.6       | C15 - C14 - C13 124.4(3) | H17A - C17 - H17C 109.5 |
| C8 - C7 - H7 118.6       | C15 - C14 - H14 117.8    | H17B - C17 - H17C 109.5 |
| C9 - C8 - C7 125.1(3)    | C13 - C14 - H14 117.8    | P1 - O5 - C18 125.8(2)  |
| C9 - C8 - H8 117.5       | C10 - C15 - C14 112.3(4) | C19 - C18 - O5 114.9(3) |
| C7 - C8 - H8 117.5       | C10 - C15 - H15 123.9    | C19 - C18 - H18A 108.5  |
| C4 - C9 - C8 112.4(3)    | C14 - C15 - H15 123.9    | O5 - C18 - H18A 108.5   |
| C4 - C9 - H9 123.8       | O3 - N4 - O2 126.1(3)    | C19 - C18 - H18B 108.5  |
| C8 - C9 - H9 123.8       | O3 - N4 - C13 110.1(4)   | O5 - C18 - H18B 108.5   |
| C15 - C10 - C11 122.1(3) | O2 - N4 - C13 123.8(3)   | H18A - C18 - H18B 107.5 |
| C15 - C10 - C1 110.8(3)  | C16 - O4 - P1 114.8(3)   | C18 - C19 - H19A 109.5  |
| C11 - C10 - C1 127.0(3)  | O4 - C16 - C17 102.1(4)  | C18 - C19 - H19B 109.5  |
| C12 - C11 - C10 125.7(3) | O4 - C16 - H16A 111.3    | H19A - C19 - H19B 109.5 |
| C12 - C11 - H11 117.1    | C17 - C16 - H16A 111.3   | C18 - C19 - H19C 109.5  |
| C10 - C11 - H11 117.1    | O4 - C16 - H16B 111.3    | H19A - C19 - H19C 109.5 |
| C13 - C12 - C11 110.4(4) | C17 - C16 - H16B 111.3   | H19B - C19 - H19C 109.5 |
| C13 - C12 - H12 124.8    | H16A - C16 - H16B 109.2  |                         |



Interaction type and interaction residues of **5f** and **6a** with Papain-Like Protease (PDB ID: 4x2z) crystal structure



Interaction type and interaction residues of **5f** and **6a** with N- and C-terminal domain of coronavirus nucleocapsid protein (PDB ID: 2c86) crystal structure