

## **Supplementary materials**

# **Carbonic Anhydrase Inhibition with Sulfonamides Incorporating Pyrazole- and Pyridazinecarboxamide Moieties Provides Examples of Isoform-Selective Inhibitors**

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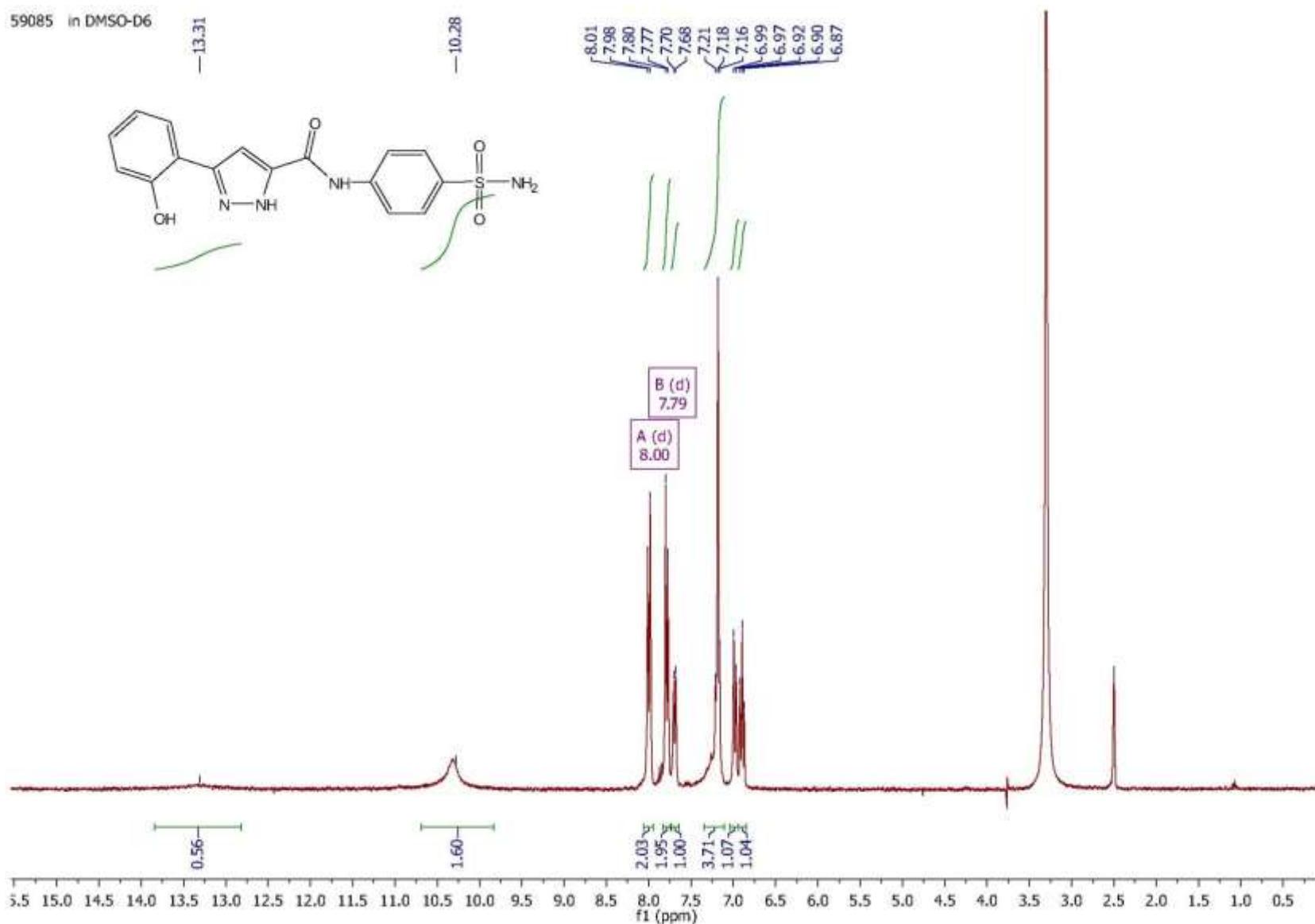
\* Correspondence: geronik@oharm.auth.gr (A.G.); claudiu.supuran@unifi.it (C.T.S.)

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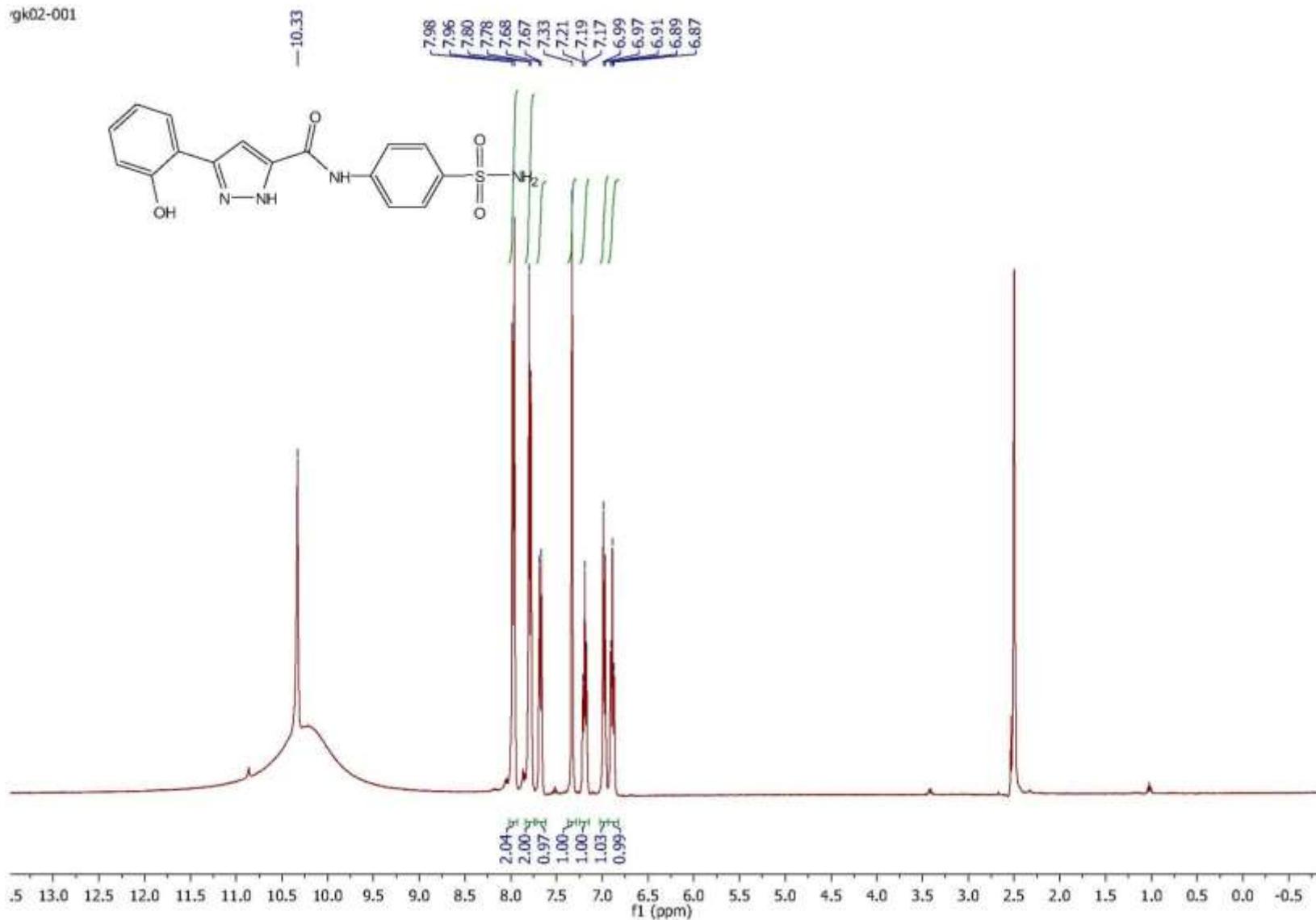
I. $^1\text{H}$ , $^{13}\text{C}$ NMR and LCMS Spectra of Products .....	2
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59085 in DMSO-D6

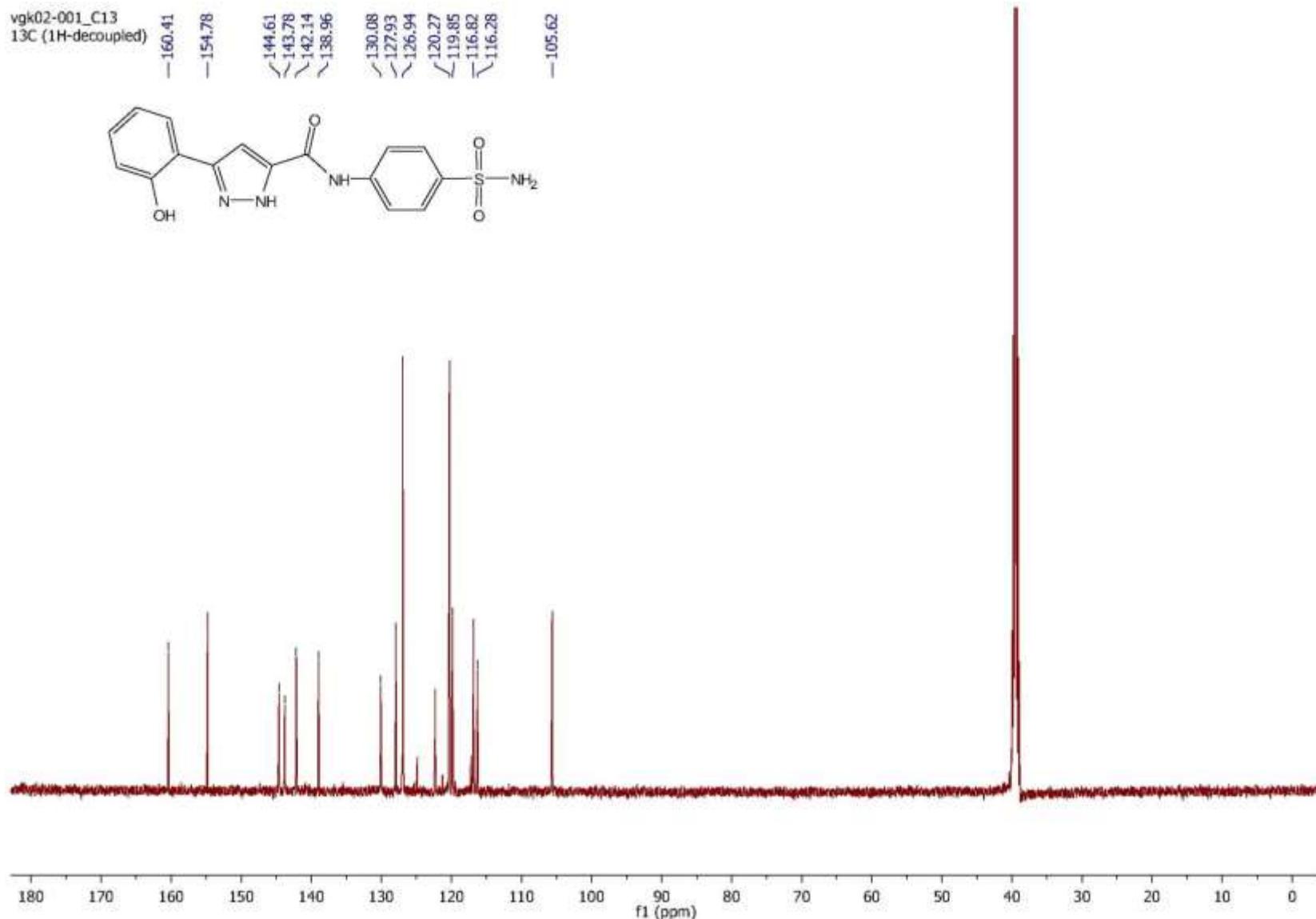


**Figure S1A.**  $^1\text{H}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4a**) in DMSO-*D*6.

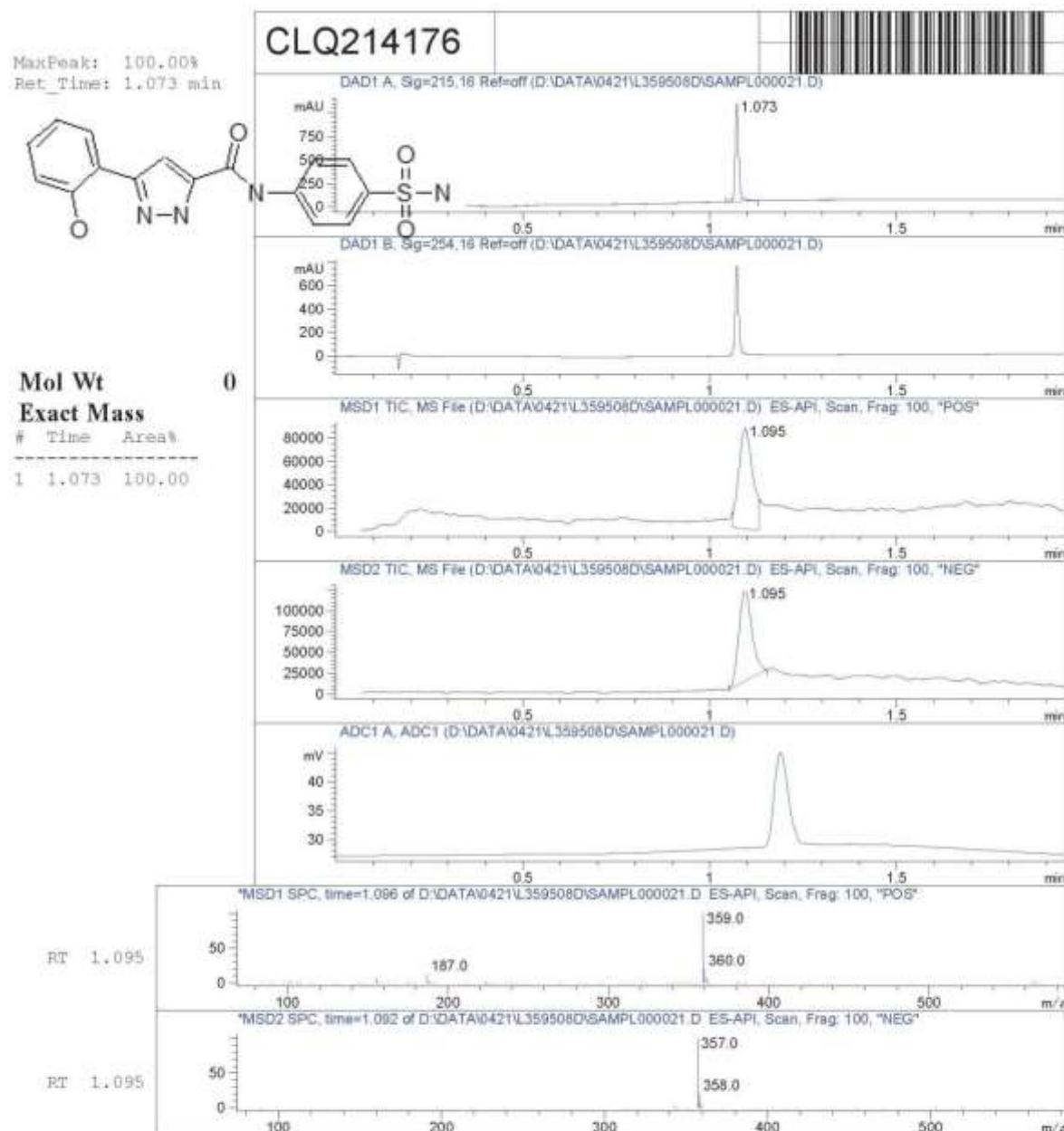
gk02-001



**Figure S1B.** <sup>1</sup>H NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4a**) in DMSO-*D*6.+ 5%CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S1C.** <sup>13</sup>C NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4a**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.



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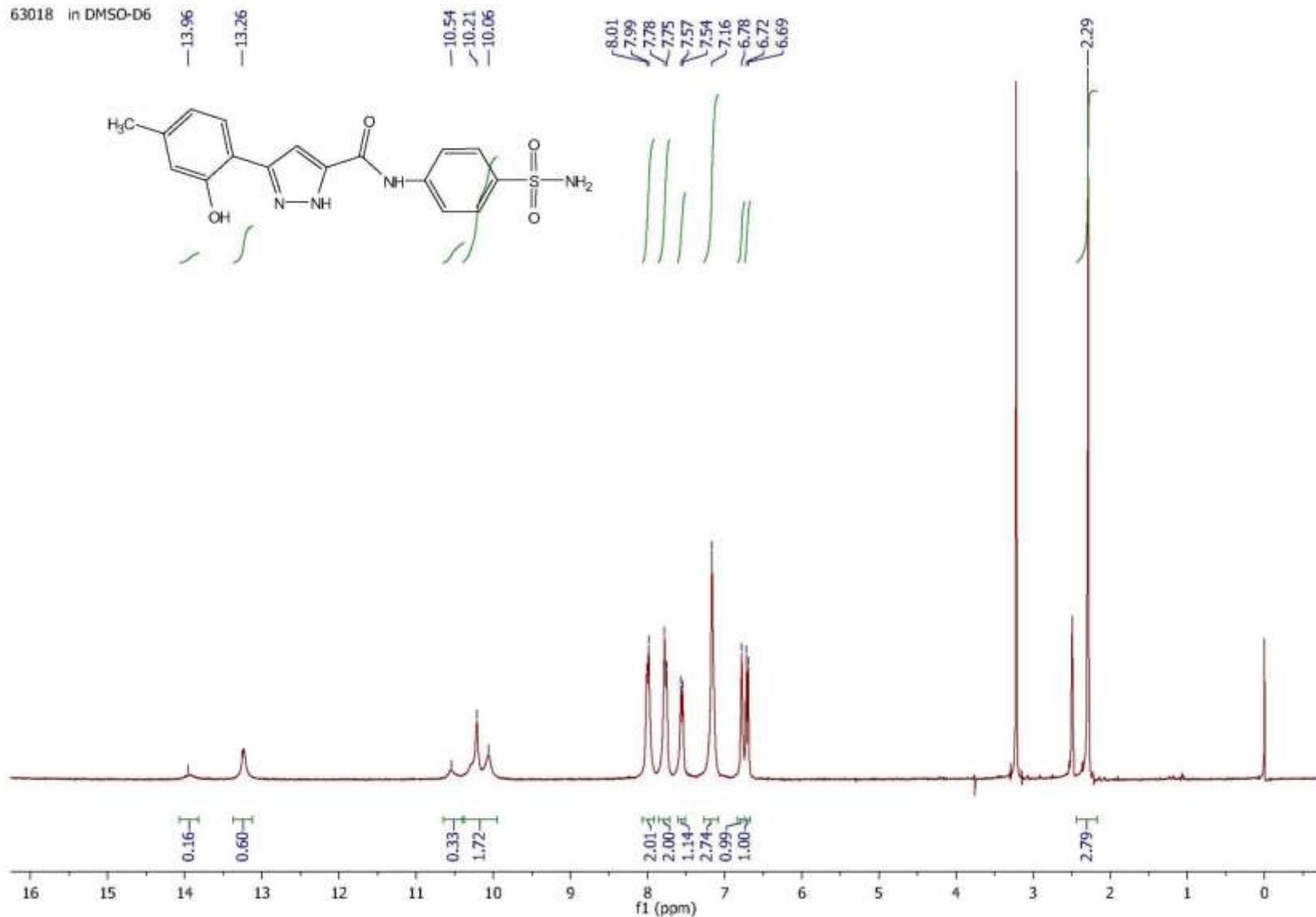
6A

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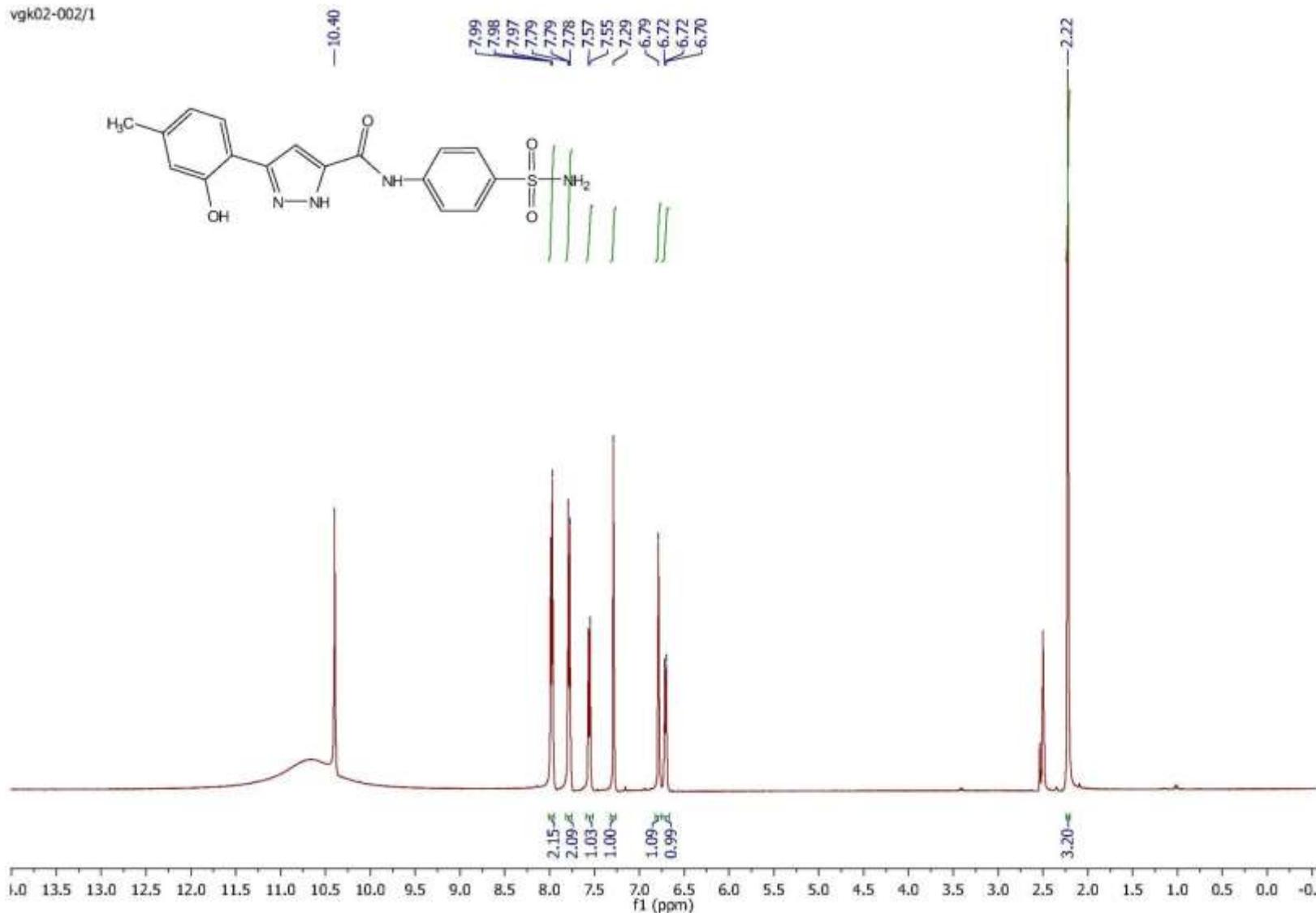
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**Figure S1D.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4a**).



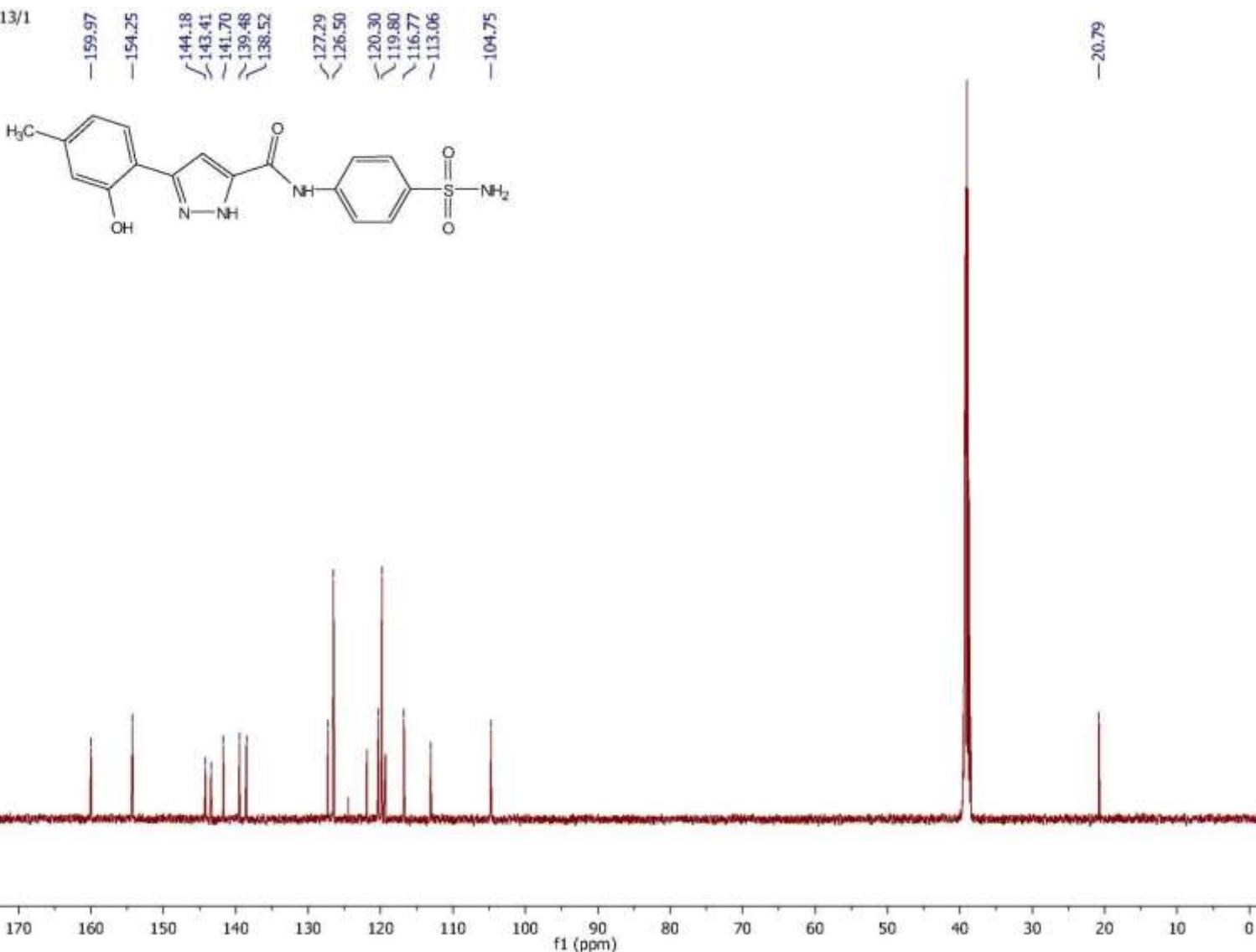
**Figure S2A.**  $^1\text{H}$  NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4b**) in DMSO-*d*6.

vgk02-002/1

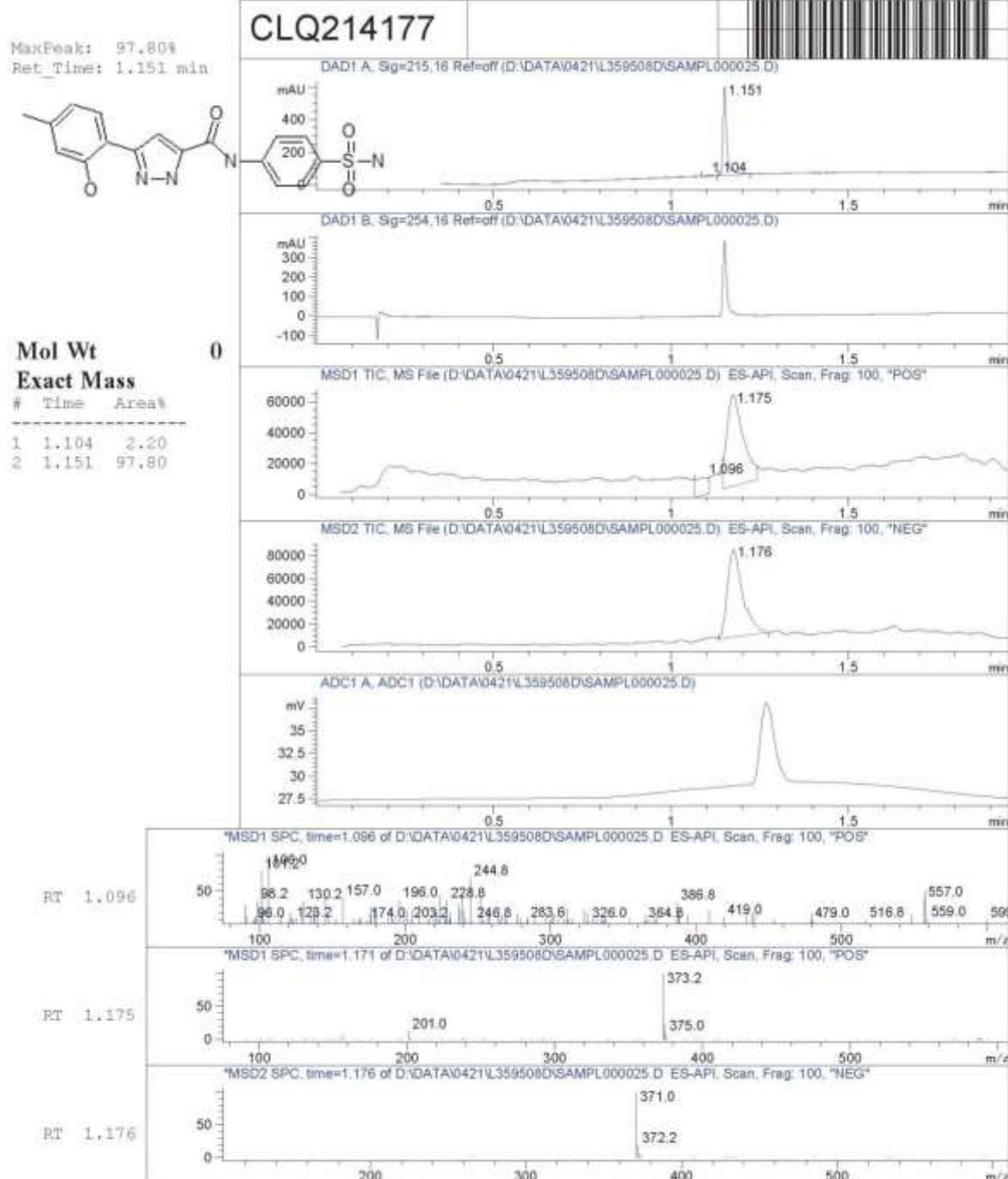


**Figure S2B.** <sup>1</sup>H NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4b**) in DMSO-*d*6.+ 5%CF<sub>3</sub>SO<sub>3</sub>H.

vgk02-002\_C13/1

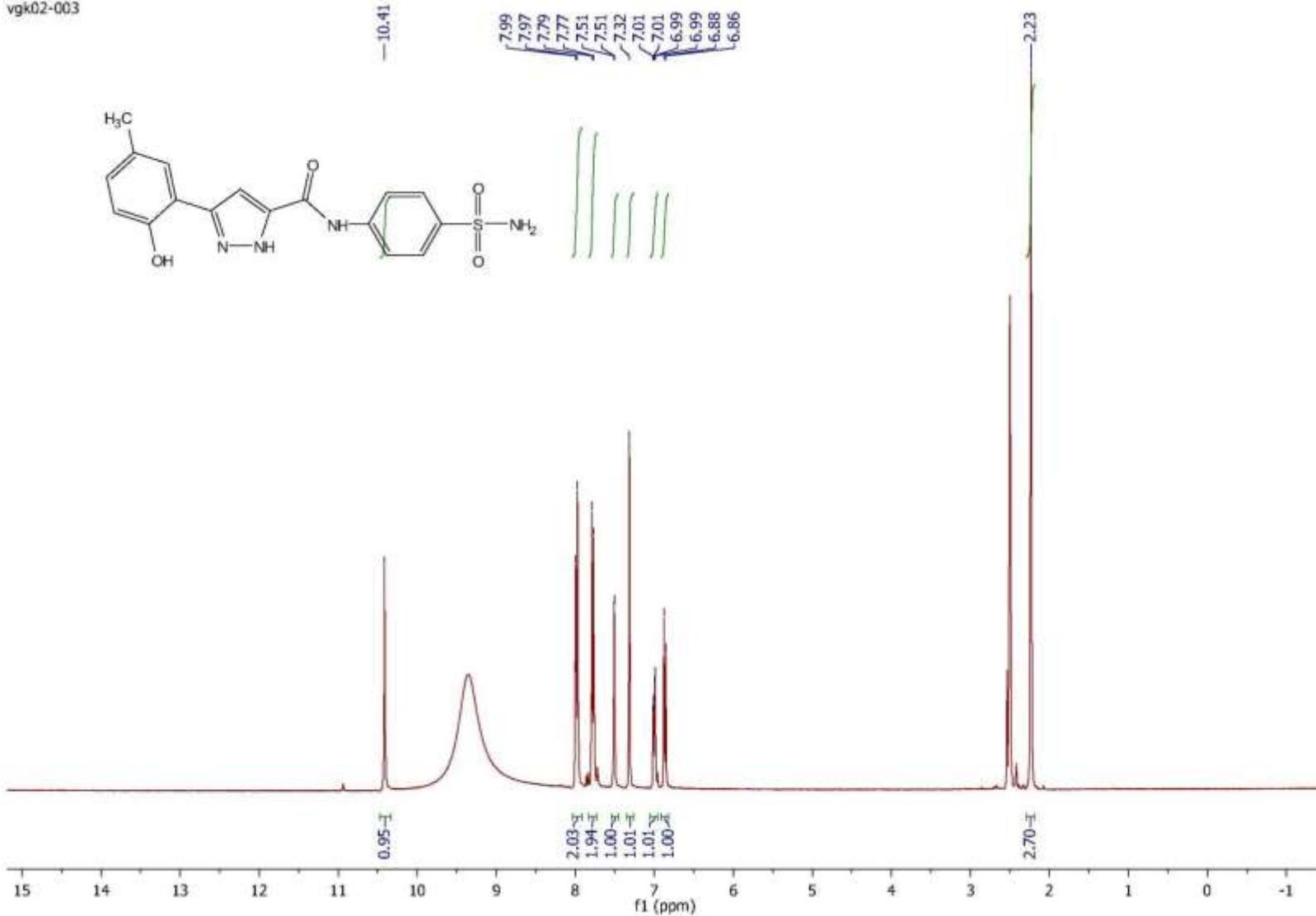


**Figure S2C.** <sup>13</sup>C NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4b**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.

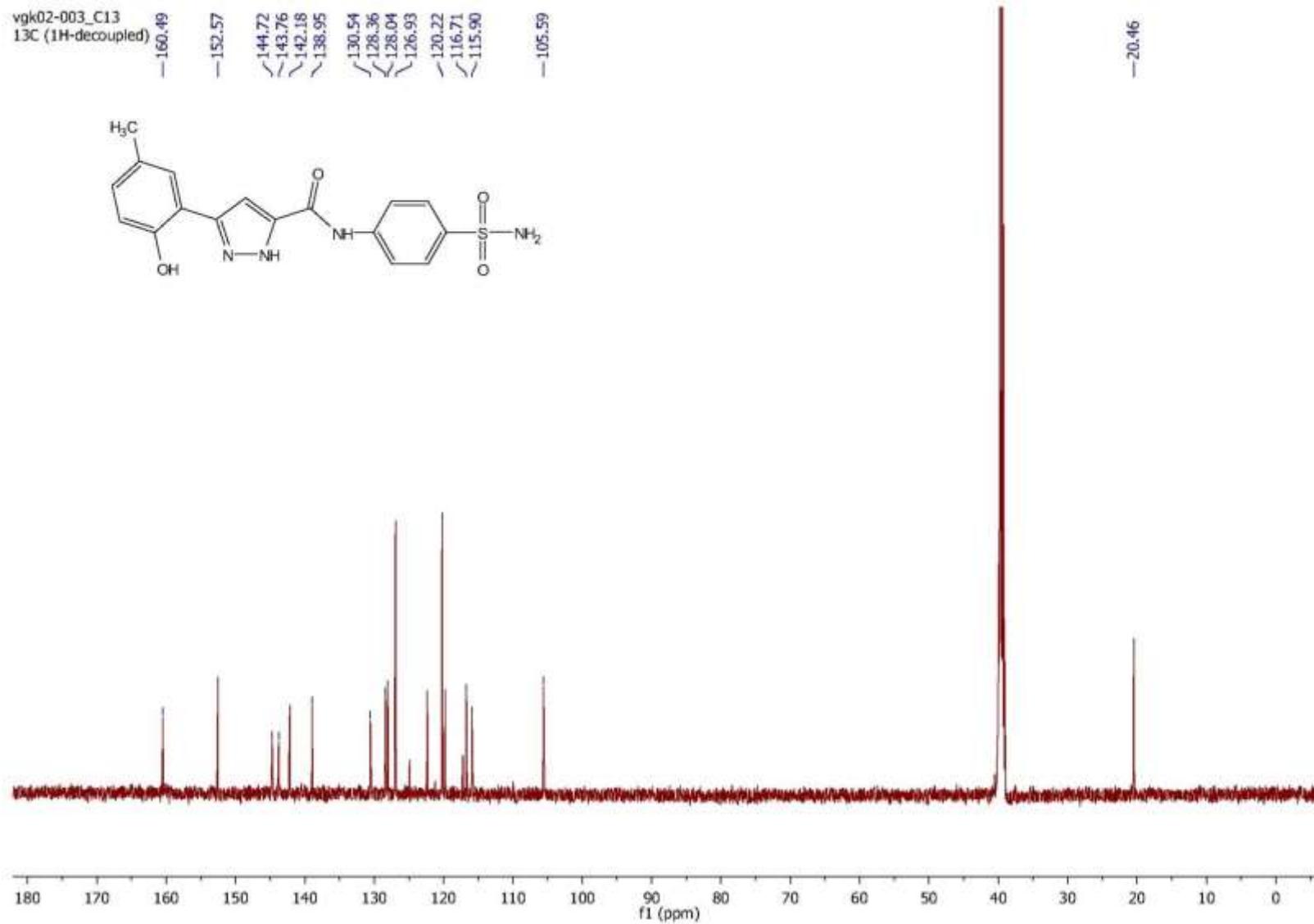


**Figure S2D.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4b**).

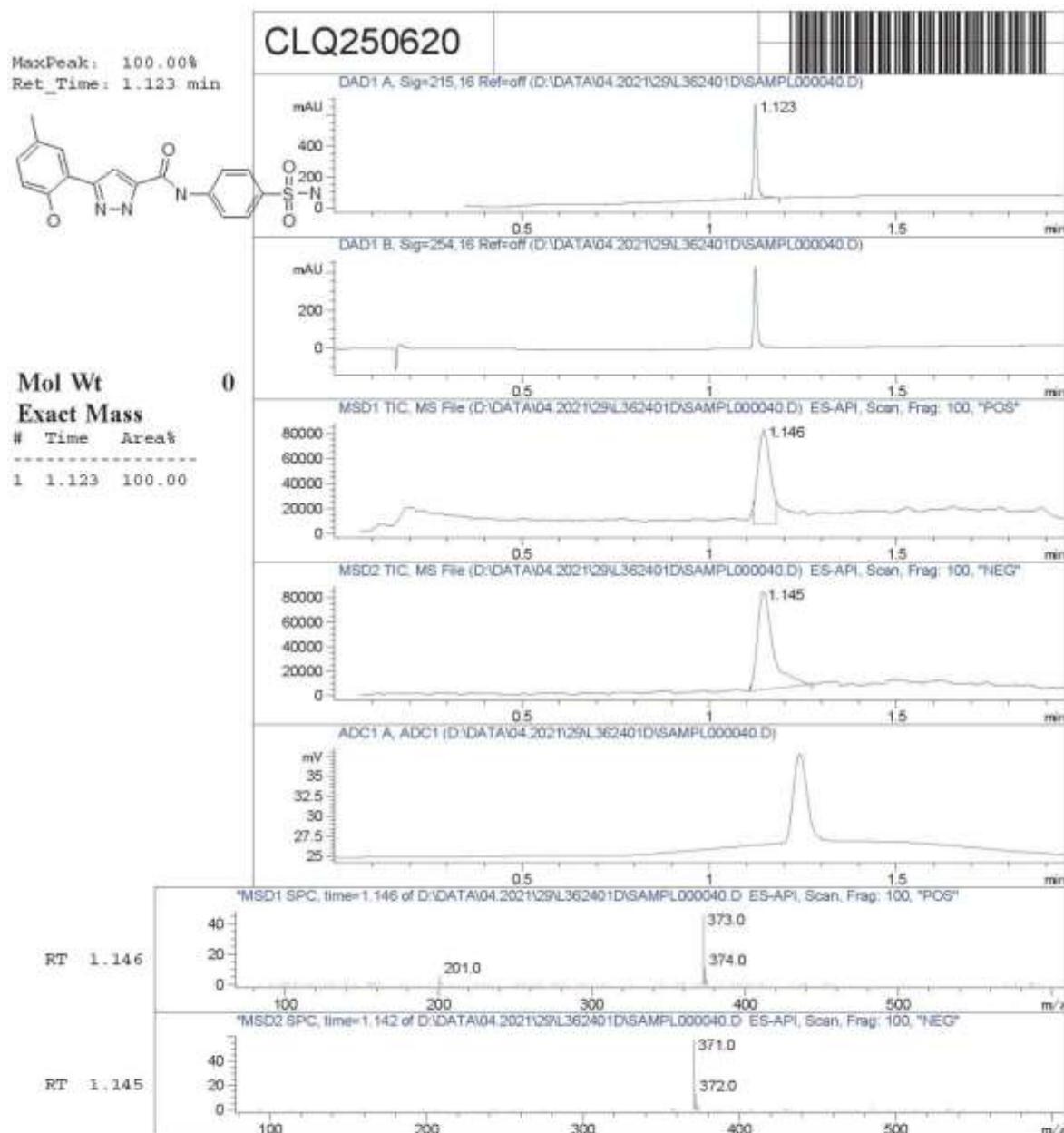
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**Figure S3B.** <sup>1</sup>H NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxy-5-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4c**) in DMSO-*d*6.+ 5%CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S3C.** <sup>13</sup>C NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(2-hydroxy-5-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4c**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.

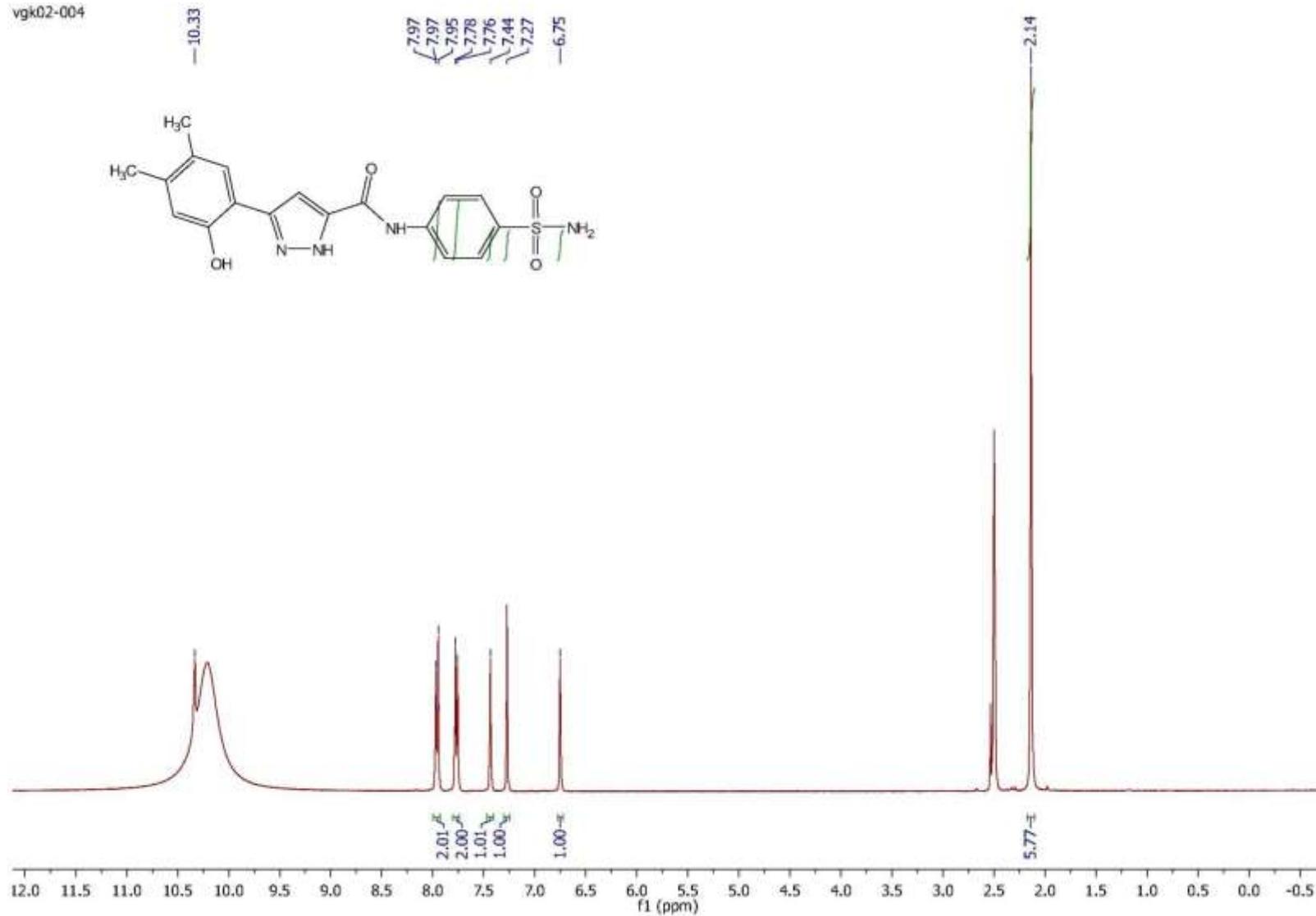


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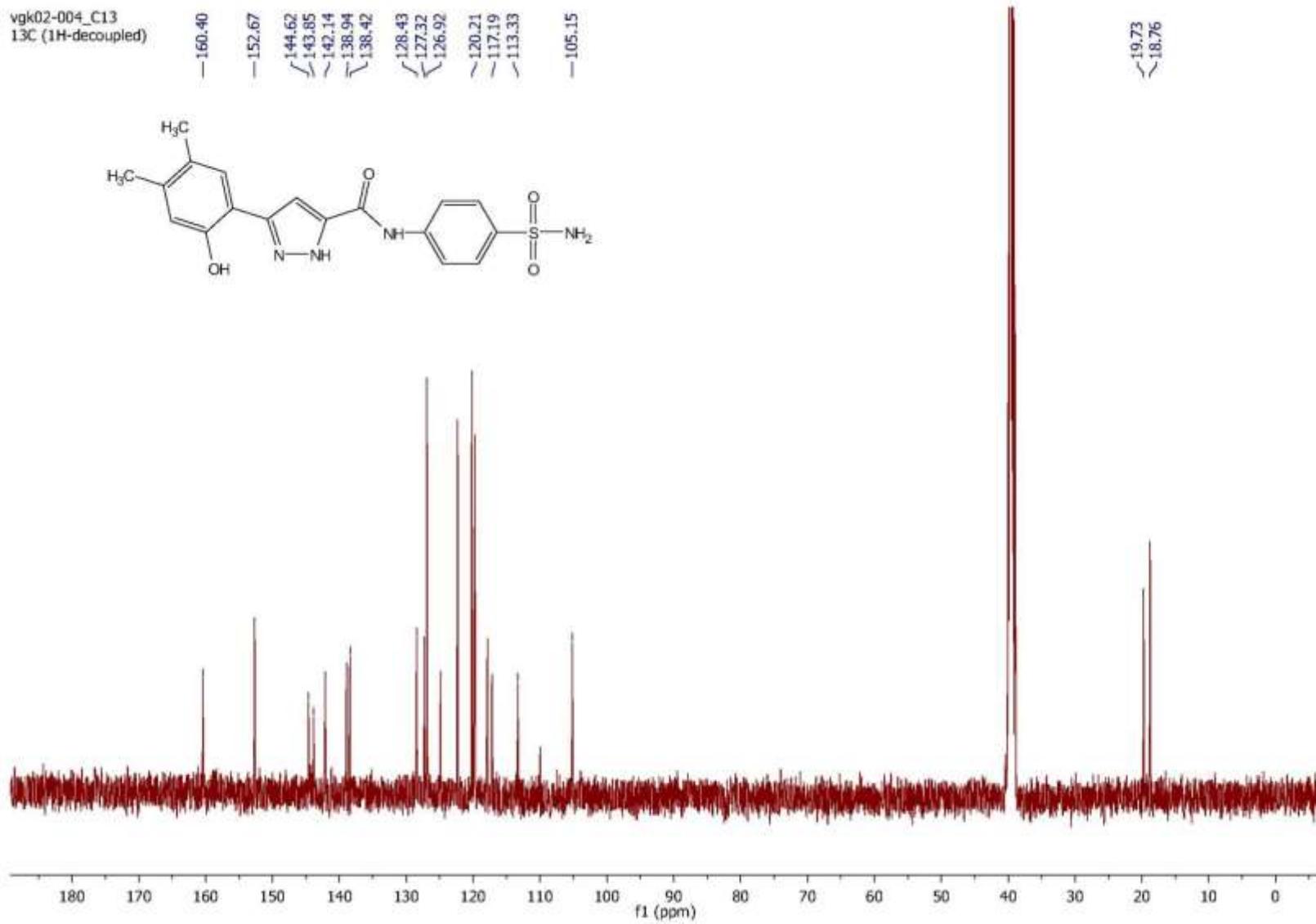
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**Figure S3D.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxy-5-methylphenyl)-1*H*-pyrazole-5-carboxamide (**4c**).

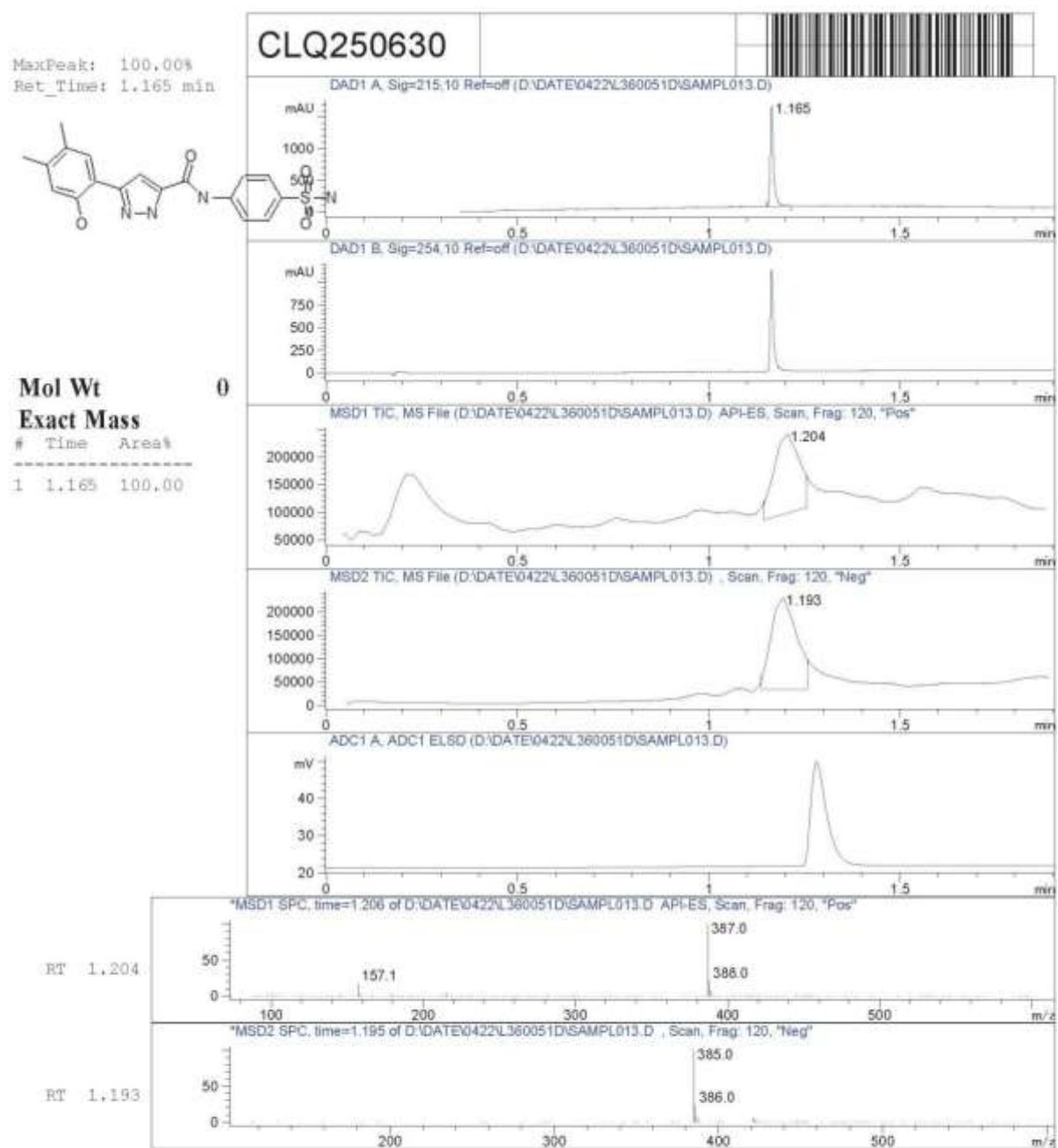
vgk02-004



**Figure S4B.** <sup>1</sup>H NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**4d**) in DMSO-*d*<sub>6</sub>.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S4B.**  $^{13}\text{C}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**4d**) in  $\text{DMSO}-d_6$ .+ 5%  $\text{CF}_3\text{SO}_3\text{H}$ .



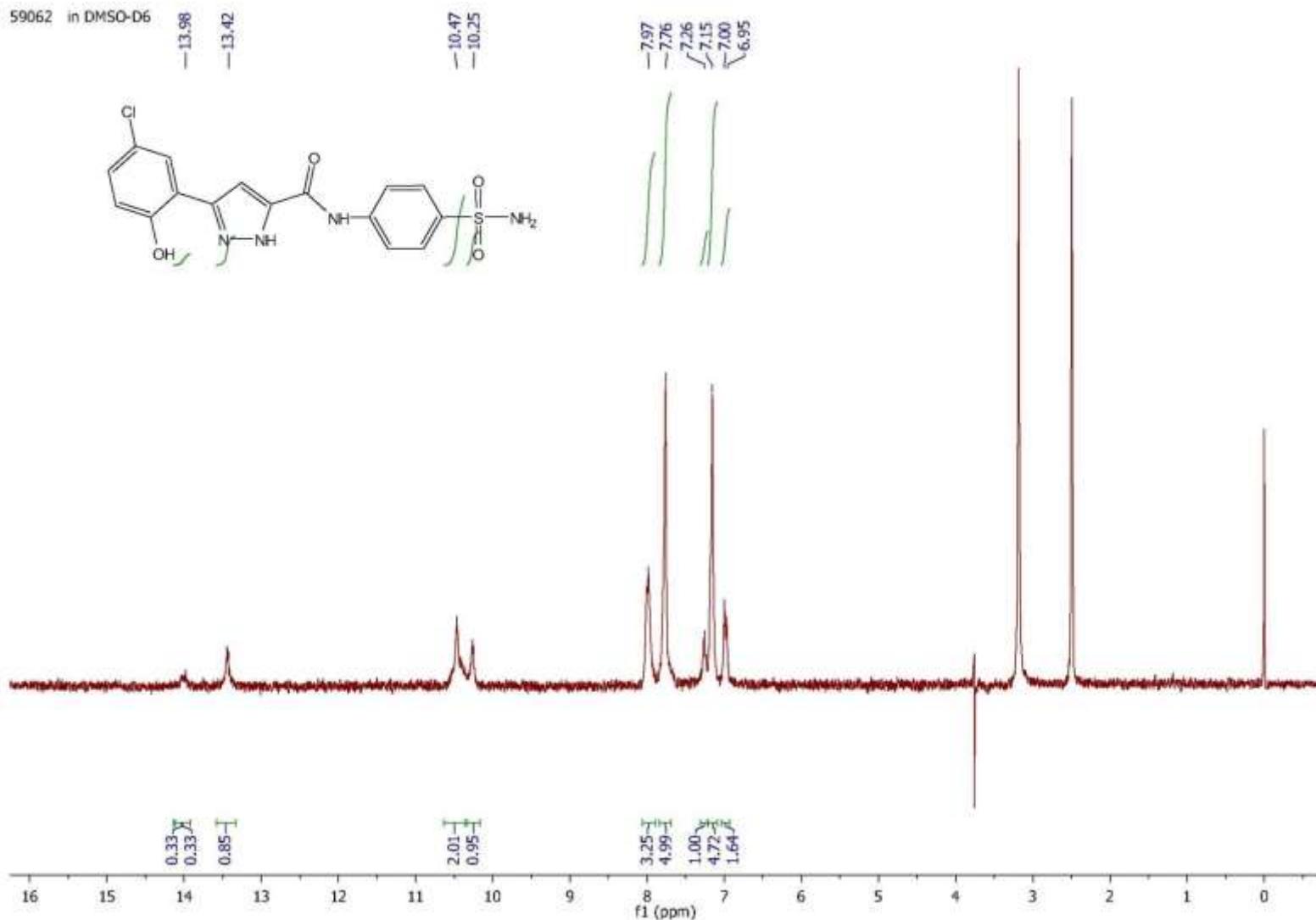
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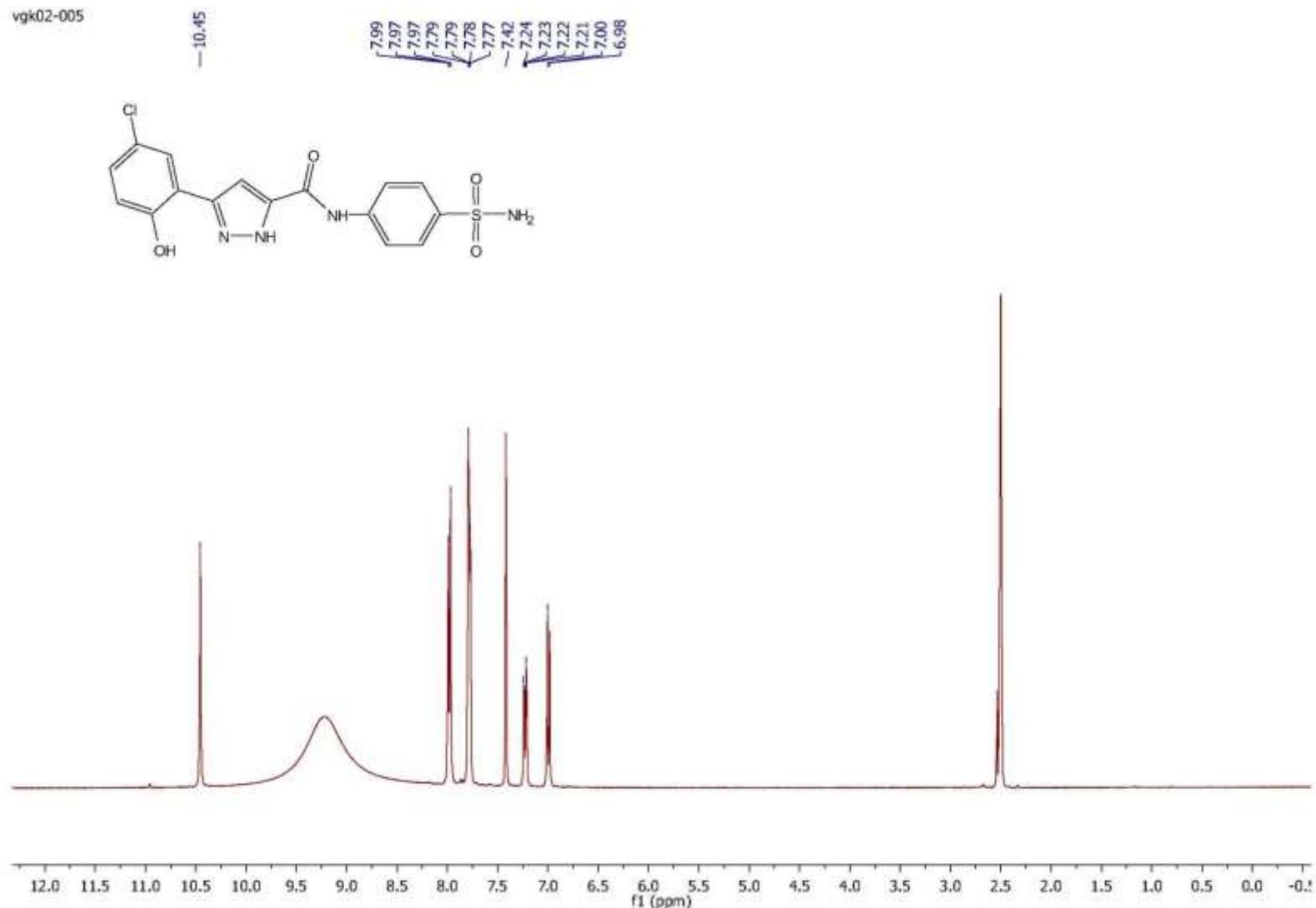
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**Figure S4D.** LCMS spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**4d**).



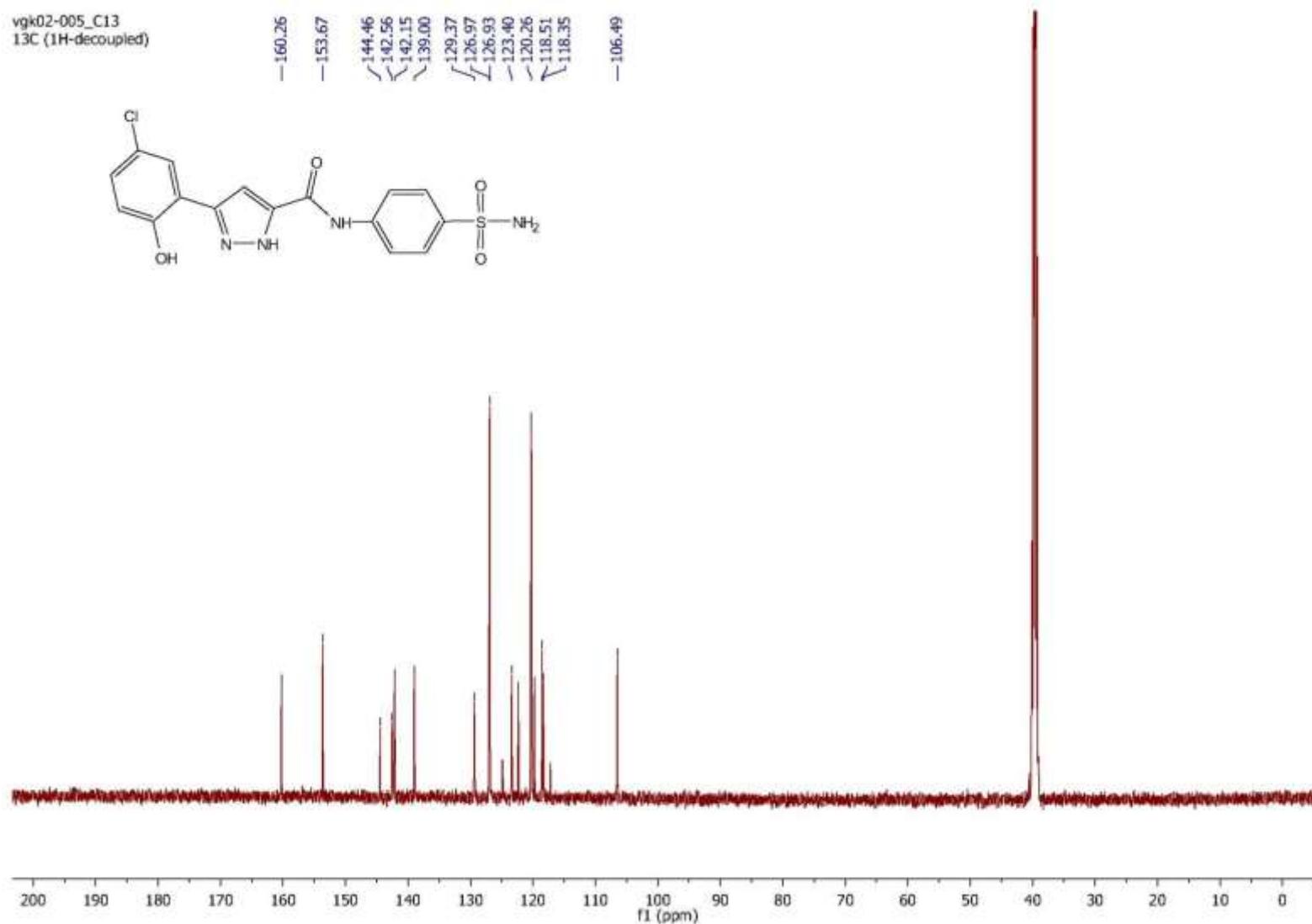
**Figure S5A.**  $^1\text{H}$  NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4f**) in DMSO-*d*6..

vgk02-005

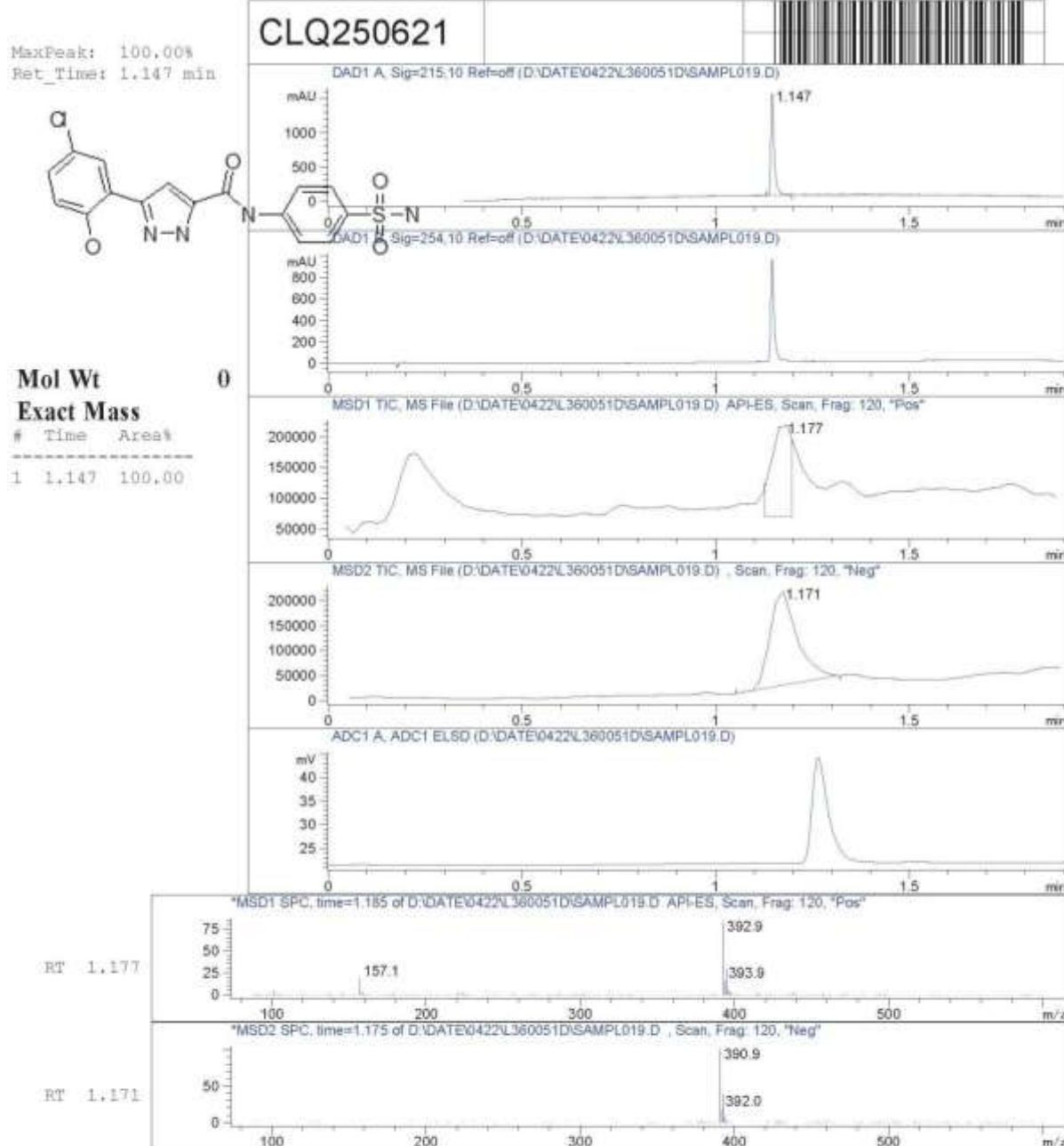


**Figure S5B.**  $^1\text{H}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4f**) in  $\text{DMSO}-d_6$ .+ 5%  $\text{CF}_3\text{SO}_3\text{H}$

vgk02-005\_C13  
13C (1H-decoupled)



**Figure S5C.**  $^{13}\text{C}$ NMR spectrum of *N*-(4-(Aminosulfonyl)phenyl)-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4f**) in  $\text{DMSO}-d_6$ .+ 5%  $\text{CF}_3\text{SO}_3\text{H}$



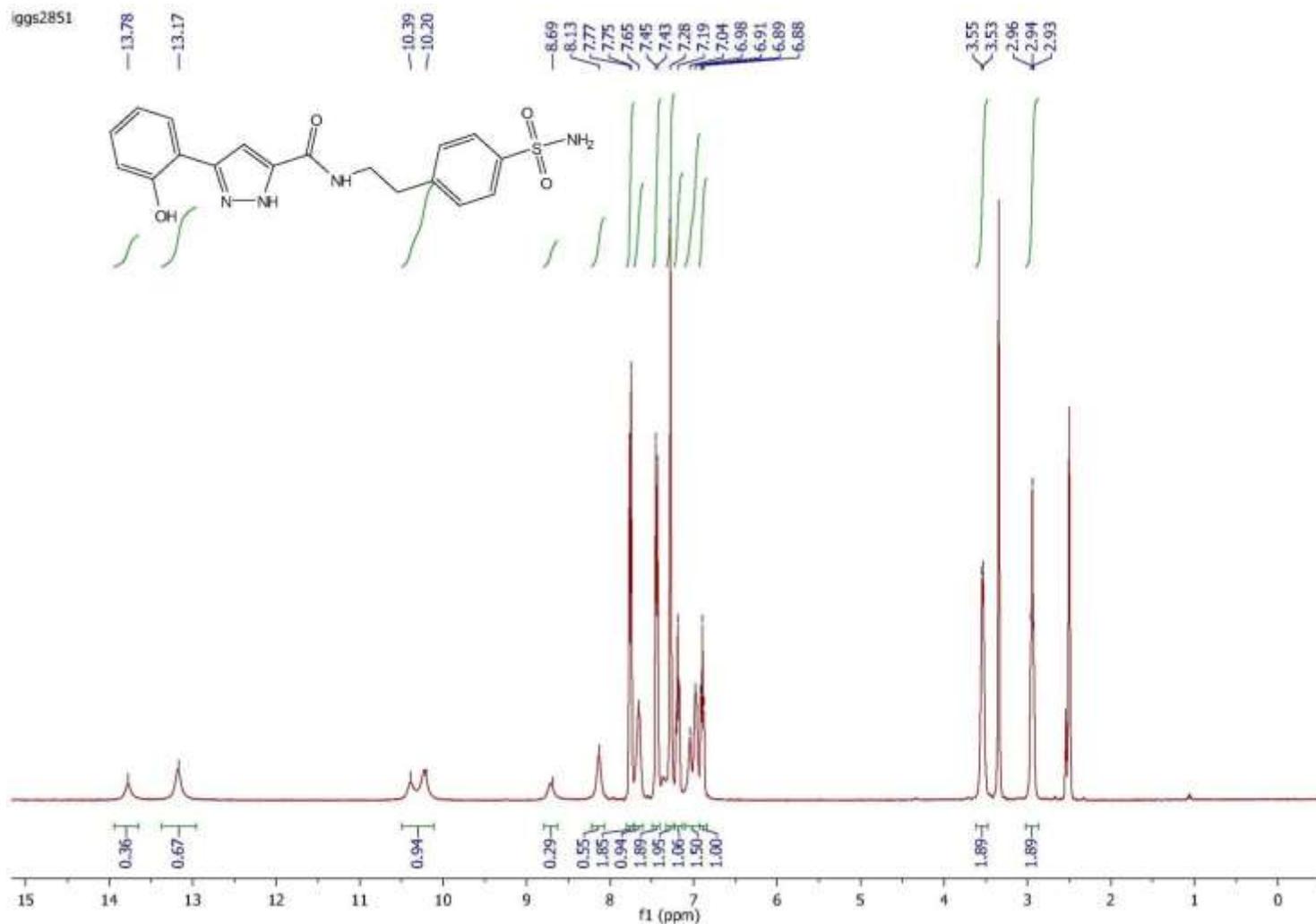
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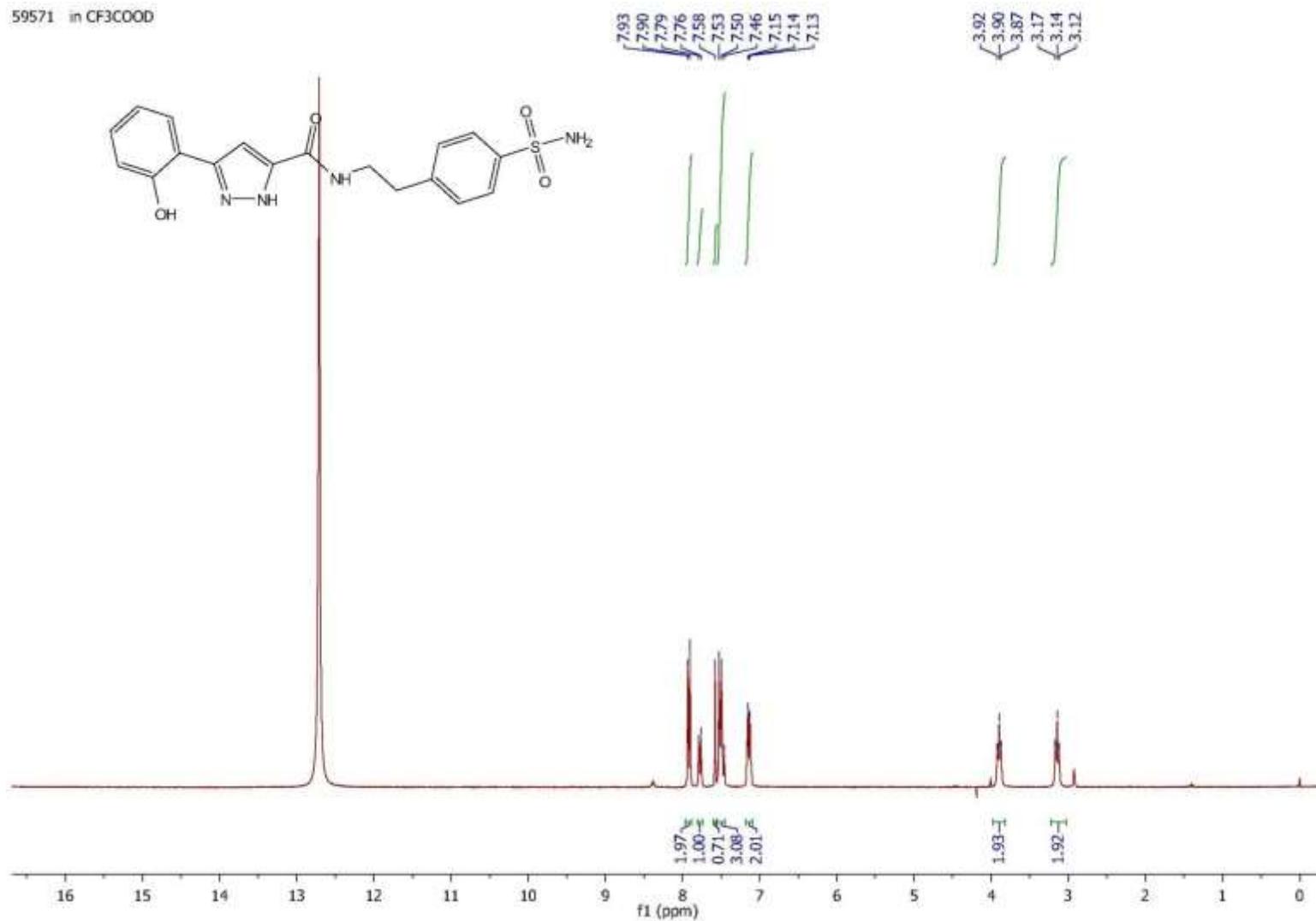
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**Figure S5D.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**4f**).

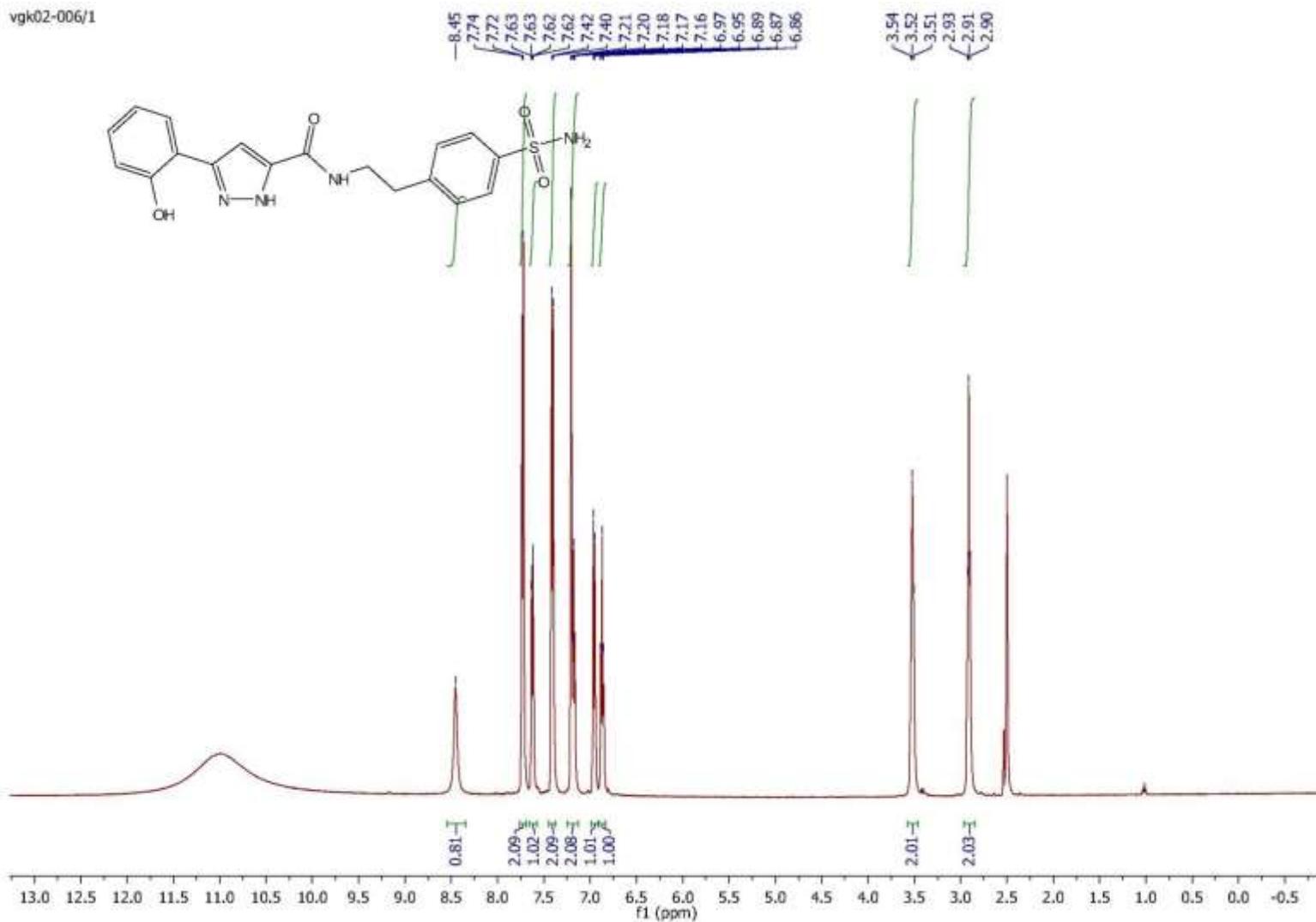


**Figure S6A.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5a**) in DMSO-*d*6.

59571 in CF<sub>3</sub>COOD

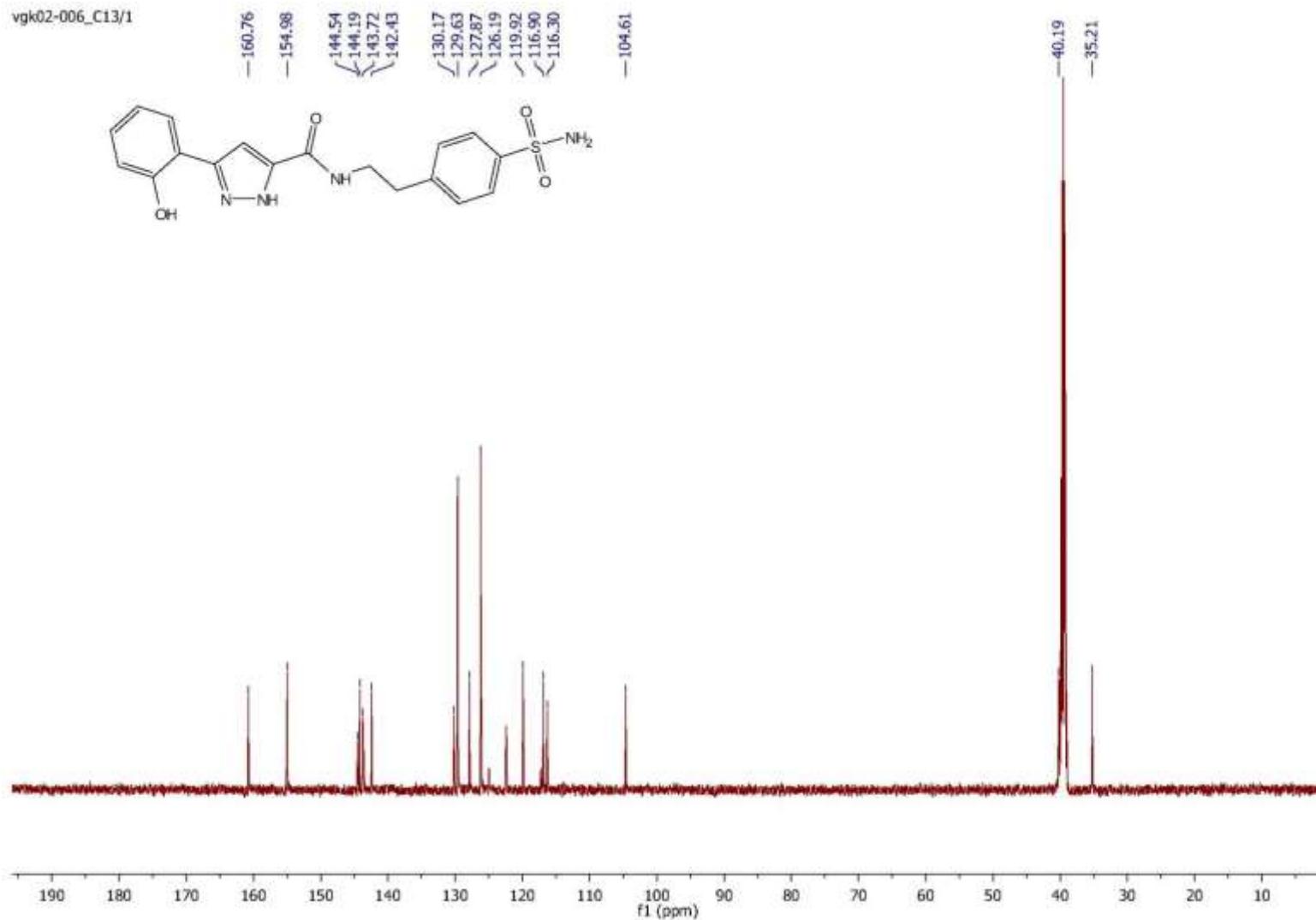


**Figure S6B.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5a**) in CF<sub>3</sub>COOD.

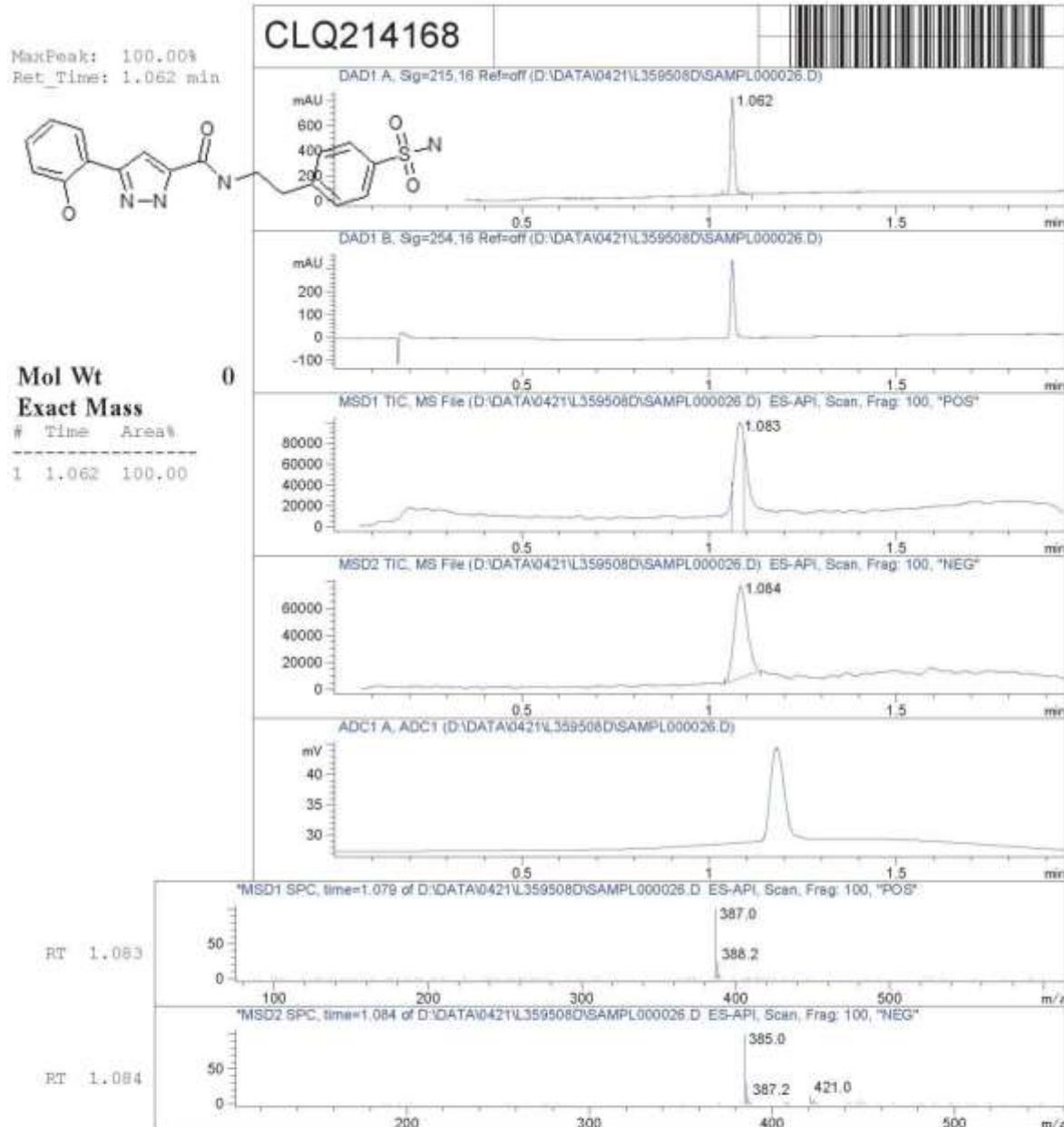


**Figure S6C.**  $^1\text{H}$  NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5a**) in  $\text{DMSO}-d_6 + 5\% \text{CF}_3\text{SO}_3\text{H}$

vgk02-006\_C13/1



**Figure S6D.**  $^{13}\text{C}$  NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5a**) in  $\text{DMSO}-d_6 + 5\% \text{CF}_3\text{SO}_3\text{H}$

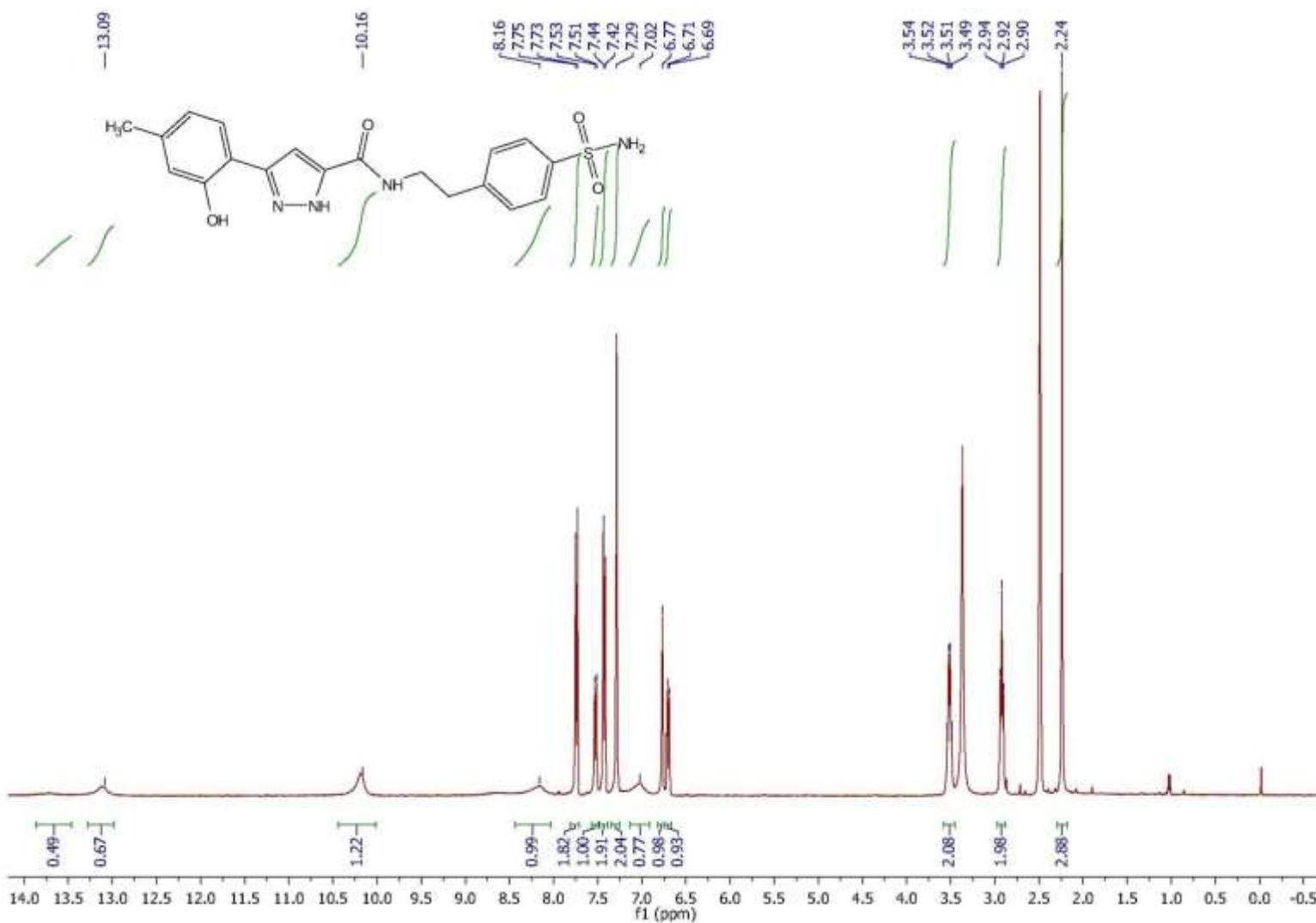


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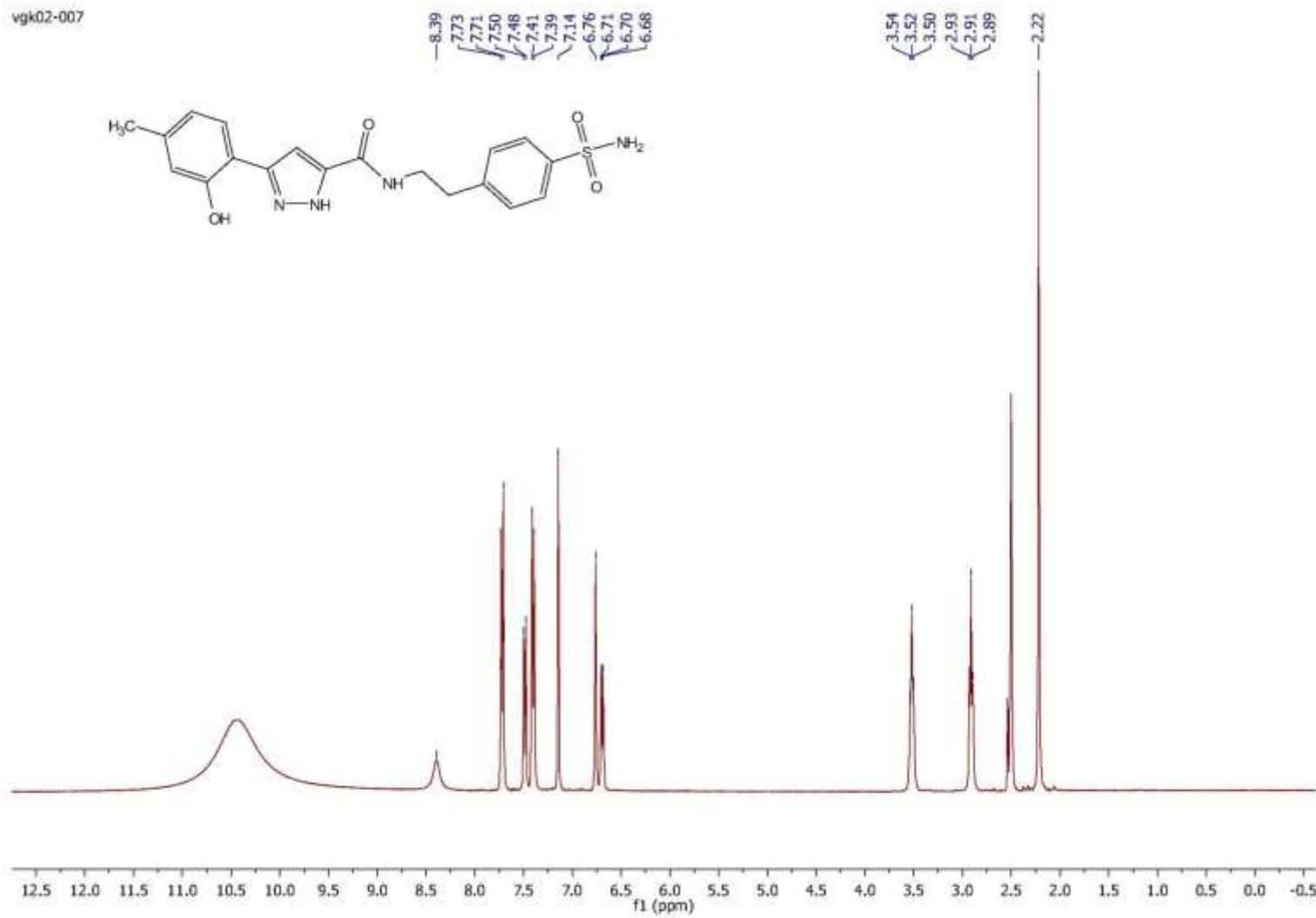
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**Figure S6F.** LCMS spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5a**).

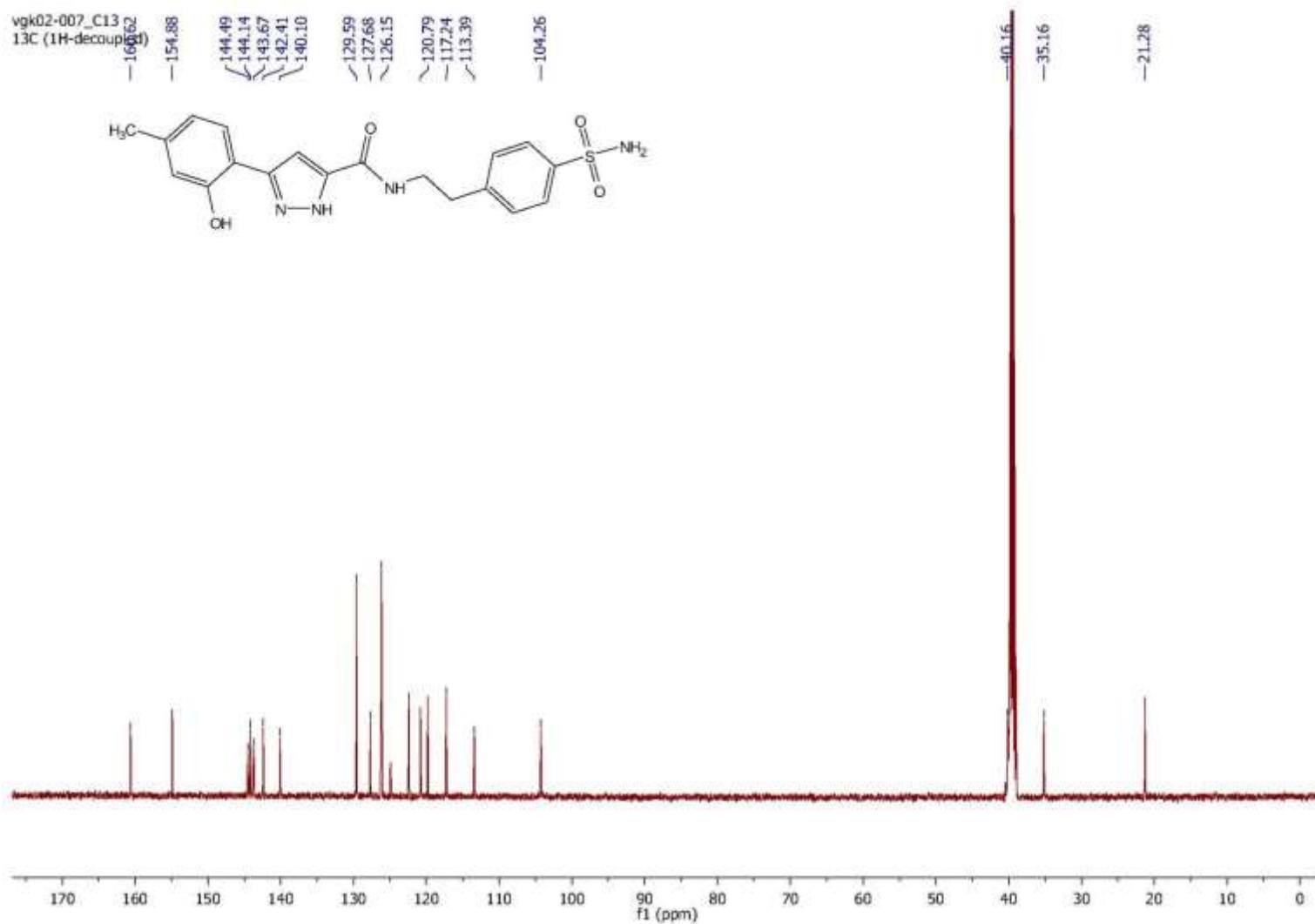


**Figure S7A.**  $^1\text{H}$  NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**5b**) in  $\text{DMSO}-d_6$ .

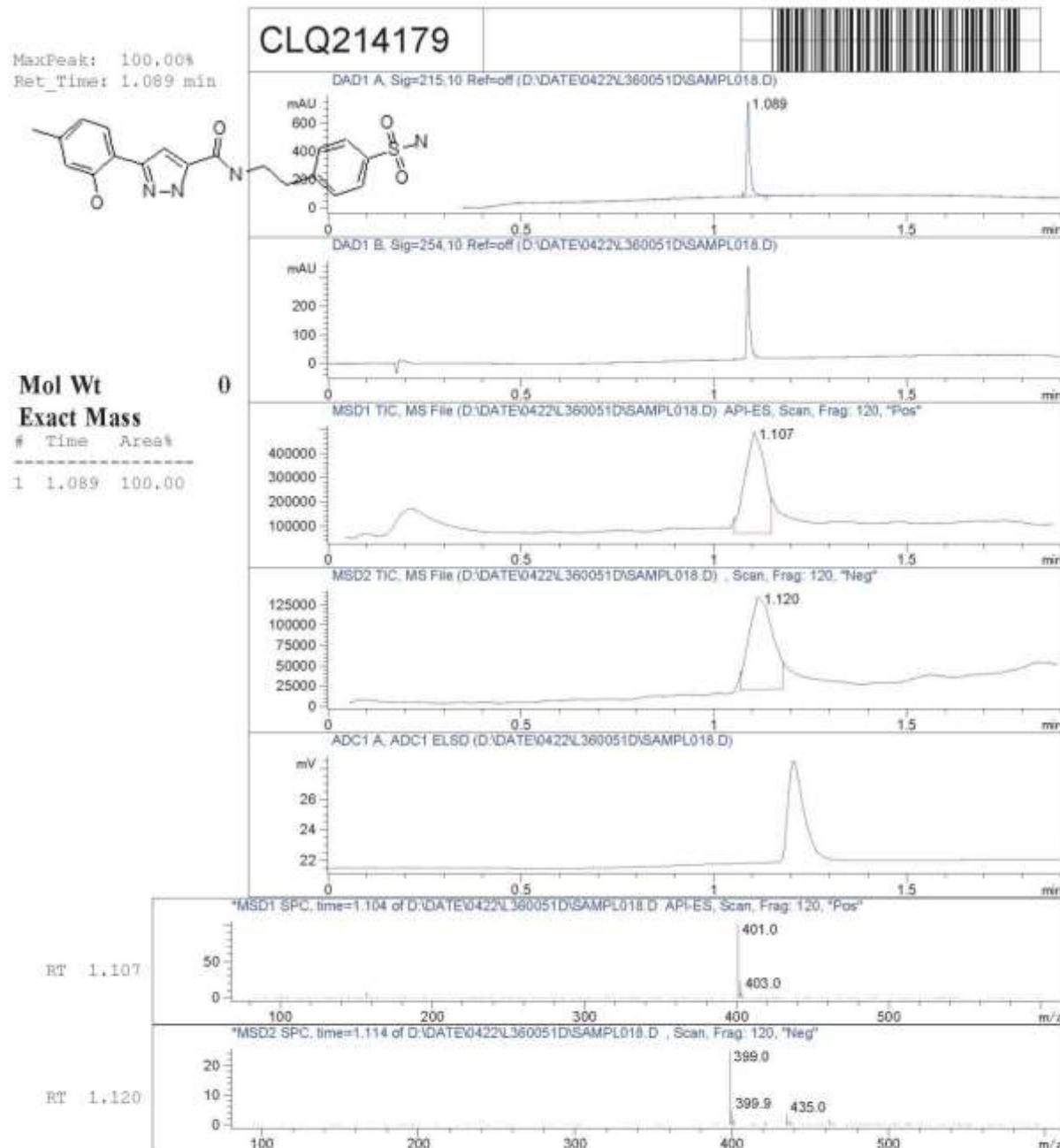
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**Figure S7B.** <sup>1</sup>H NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**5b**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S7C.** <sup>13</sup>C NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**5b**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.



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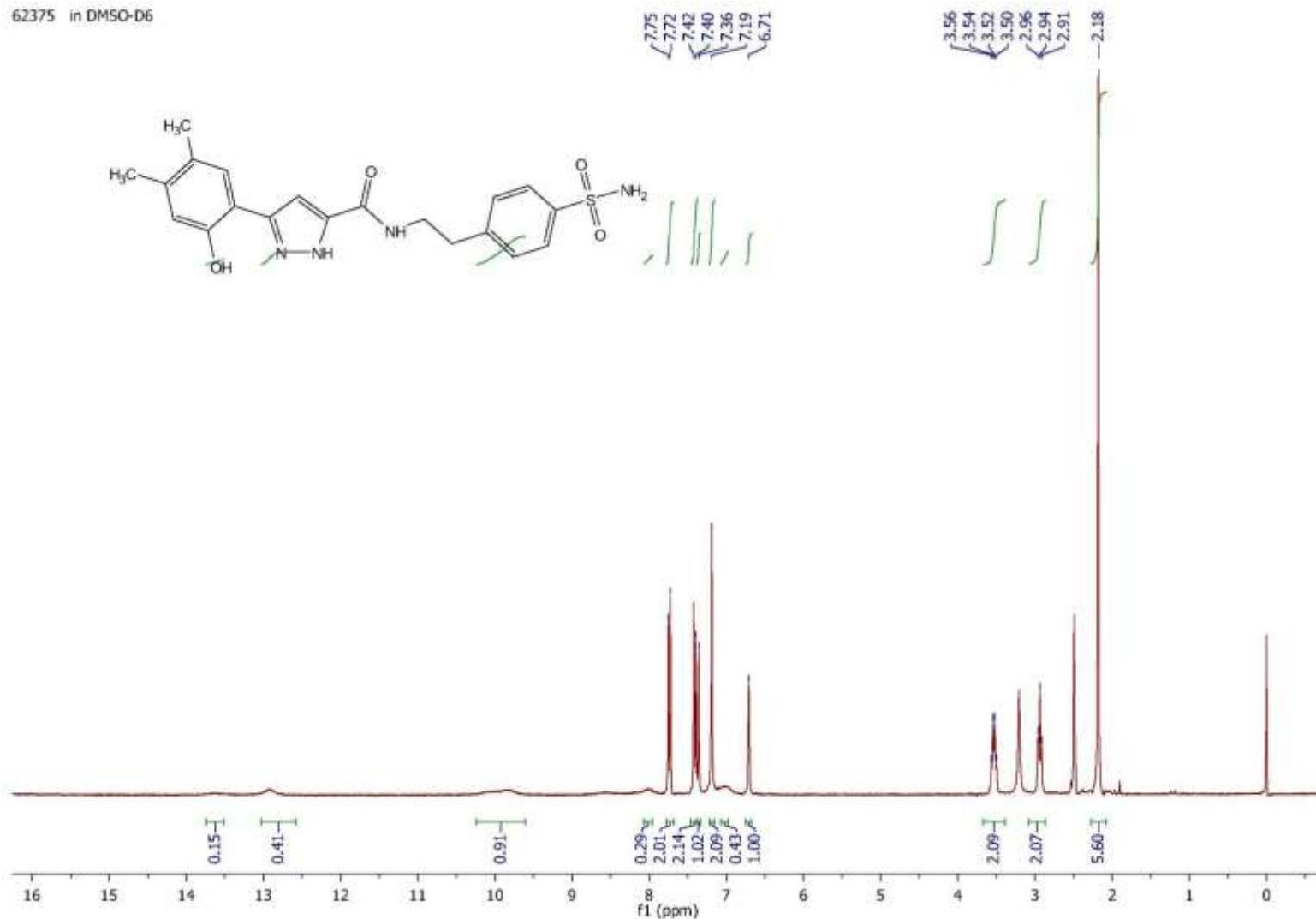
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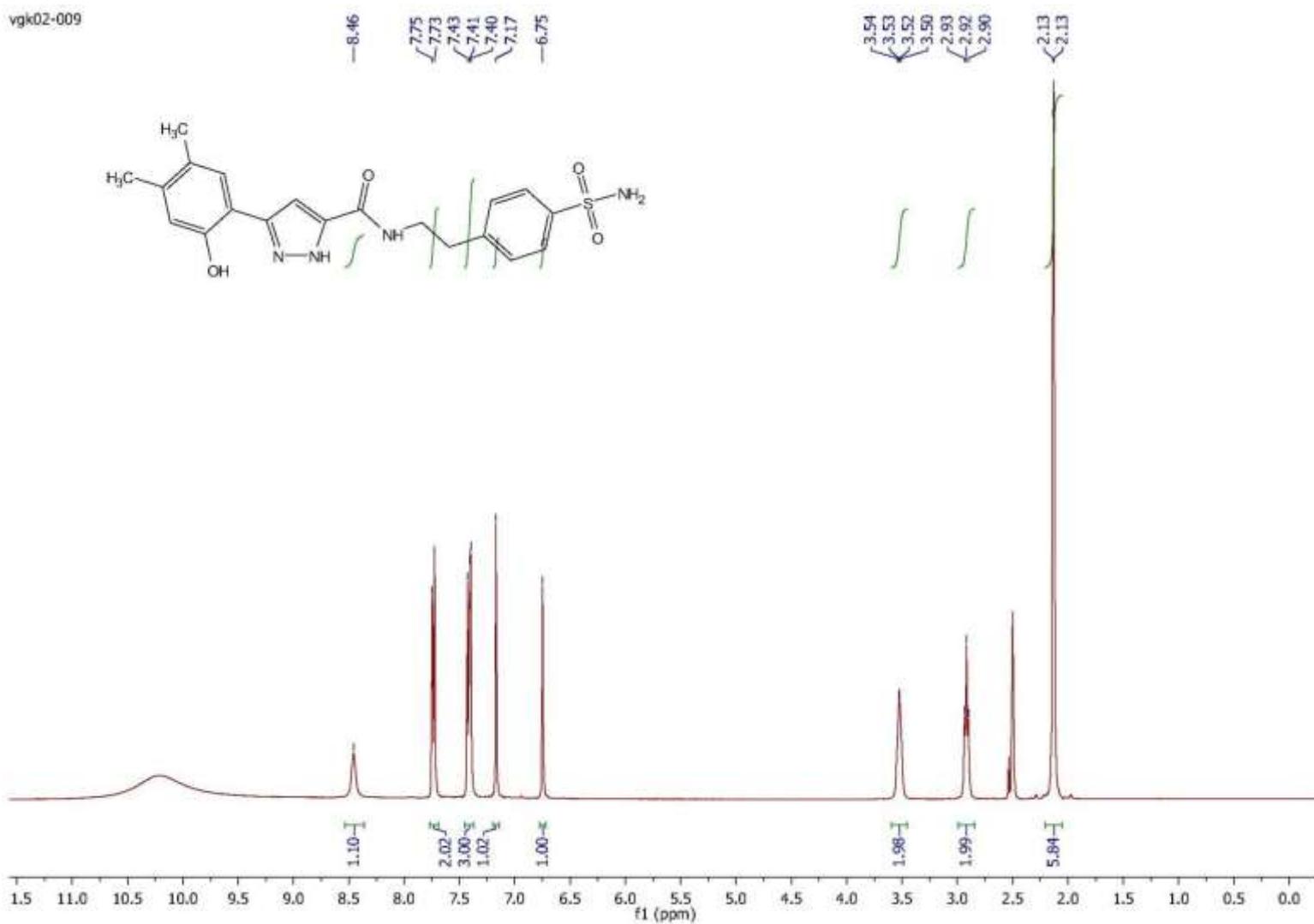
**Figure S7D.** LCMS spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-4-methylphenyl)-1*H*-pyrazole-5-carboxamide (**5b**).

62375 in DMSO-D6

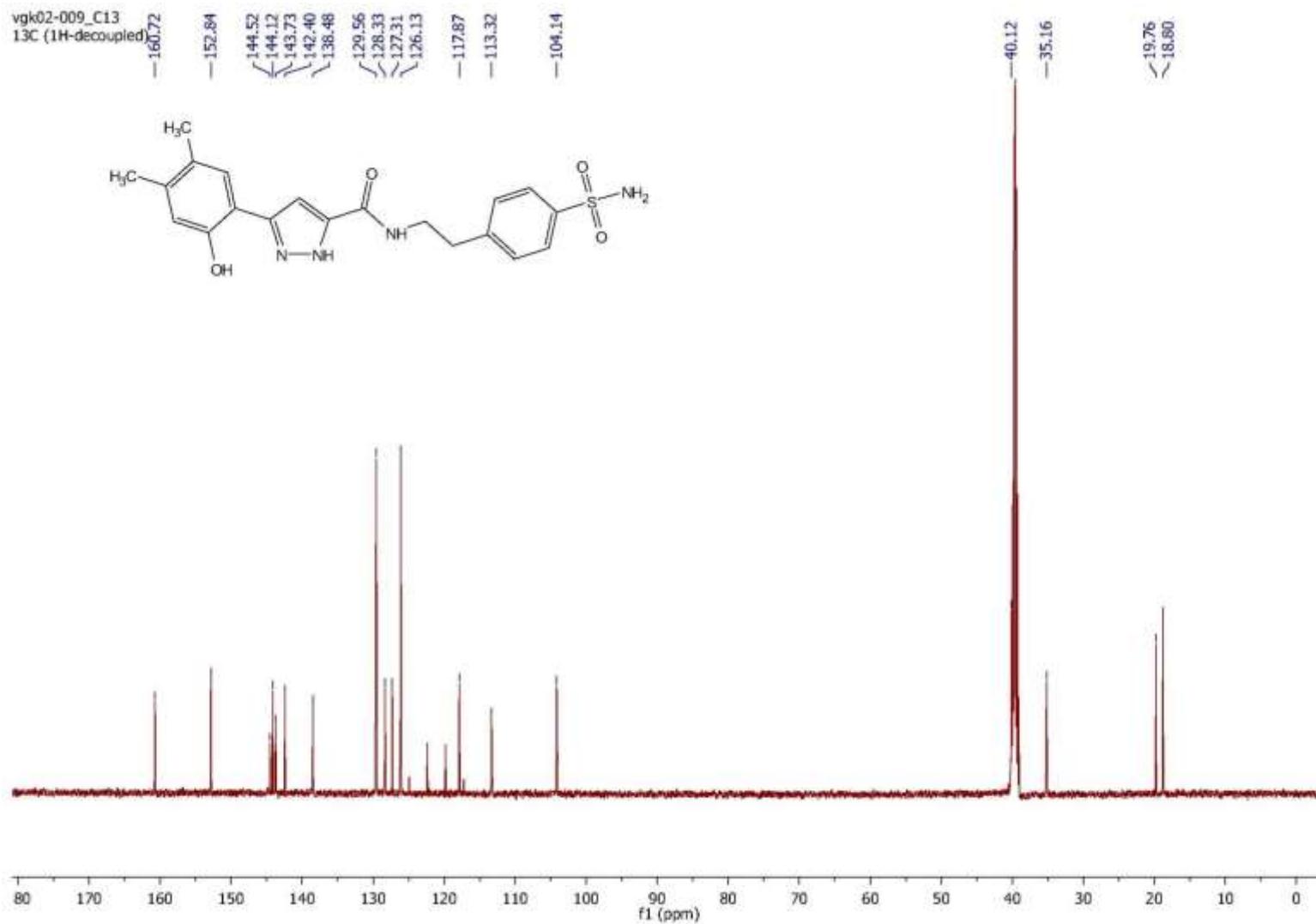


**Figure S8A.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5d**) in DMSO-*d*6.

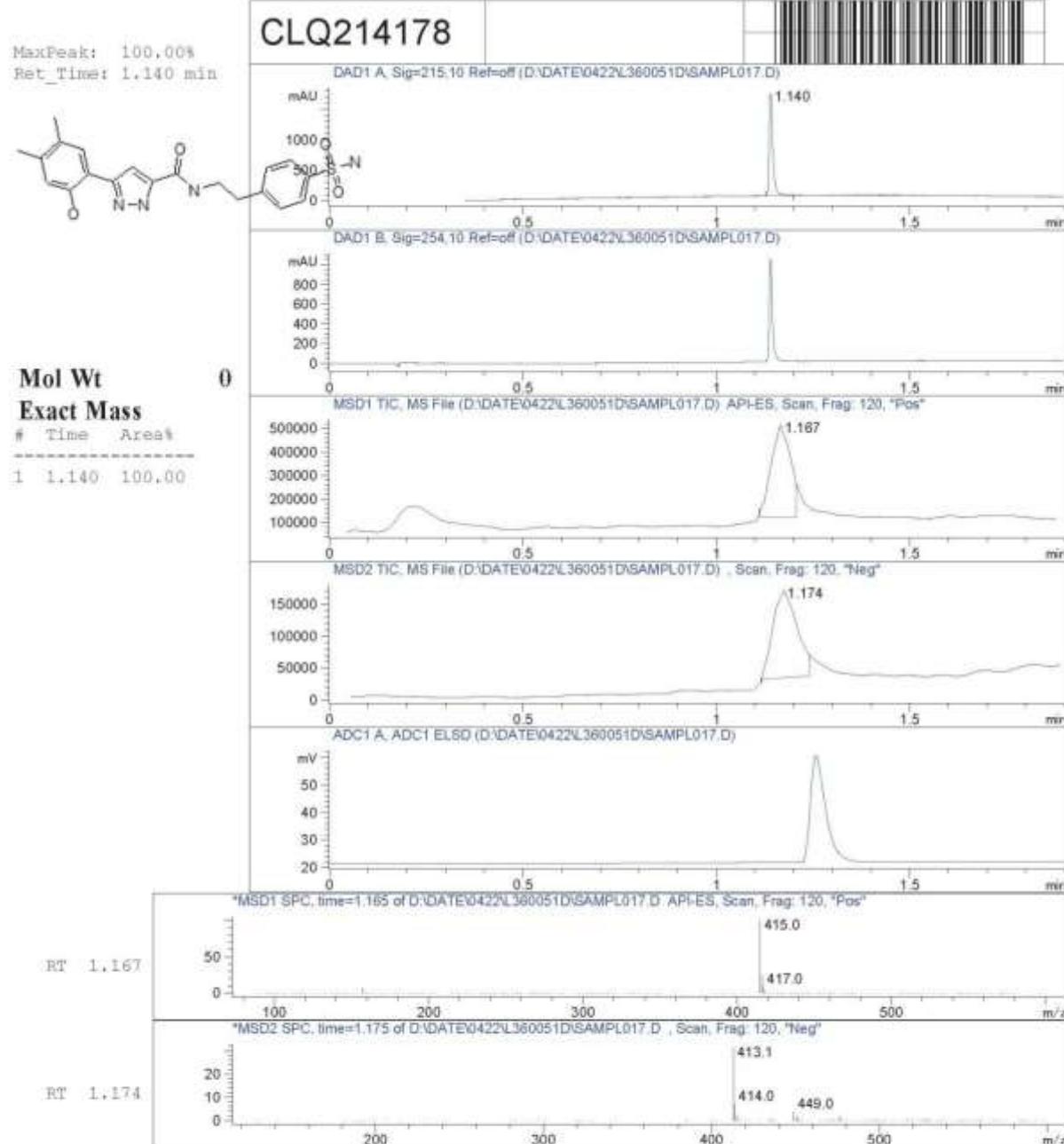
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**Figure S8B.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5d**) in DMSO-*d*6.+ 5%CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S8C.** <sup>13</sup>C NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5d**) in DMSO-*d*6.+ 5%CF<sub>3</sub>SO<sub>3</sub>H.



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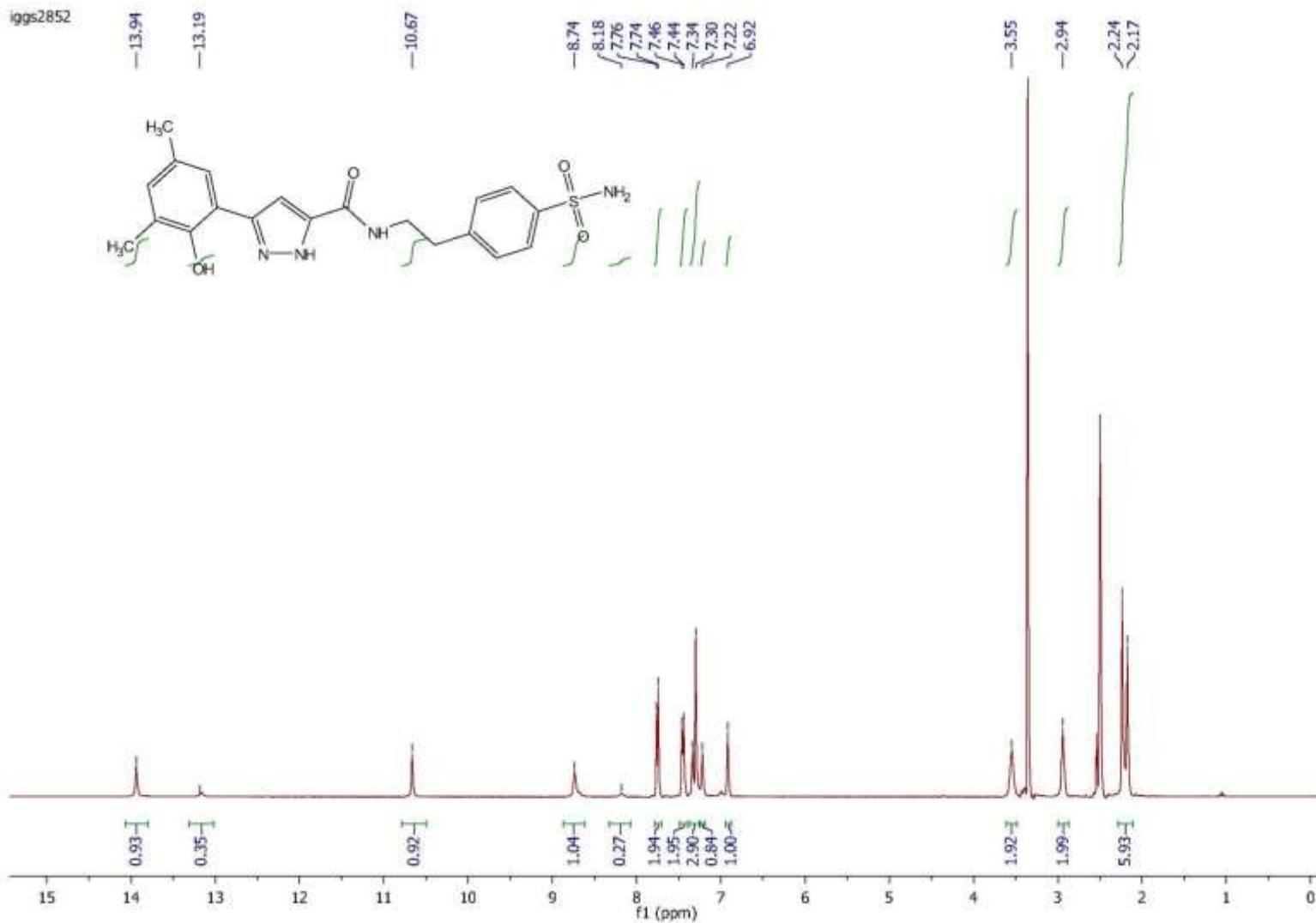
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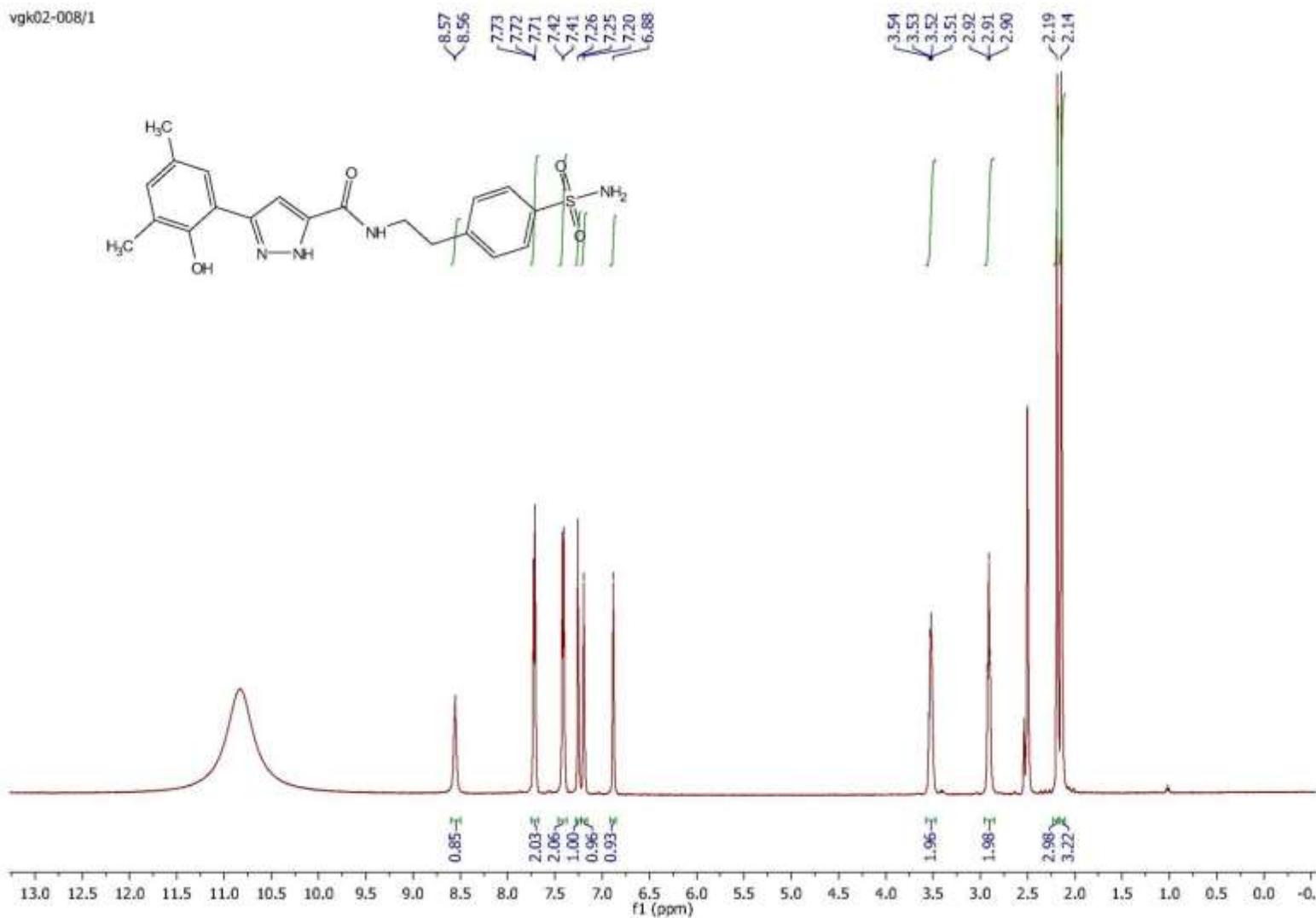
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**Figure S8D.** LCMS spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-4,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5d**).

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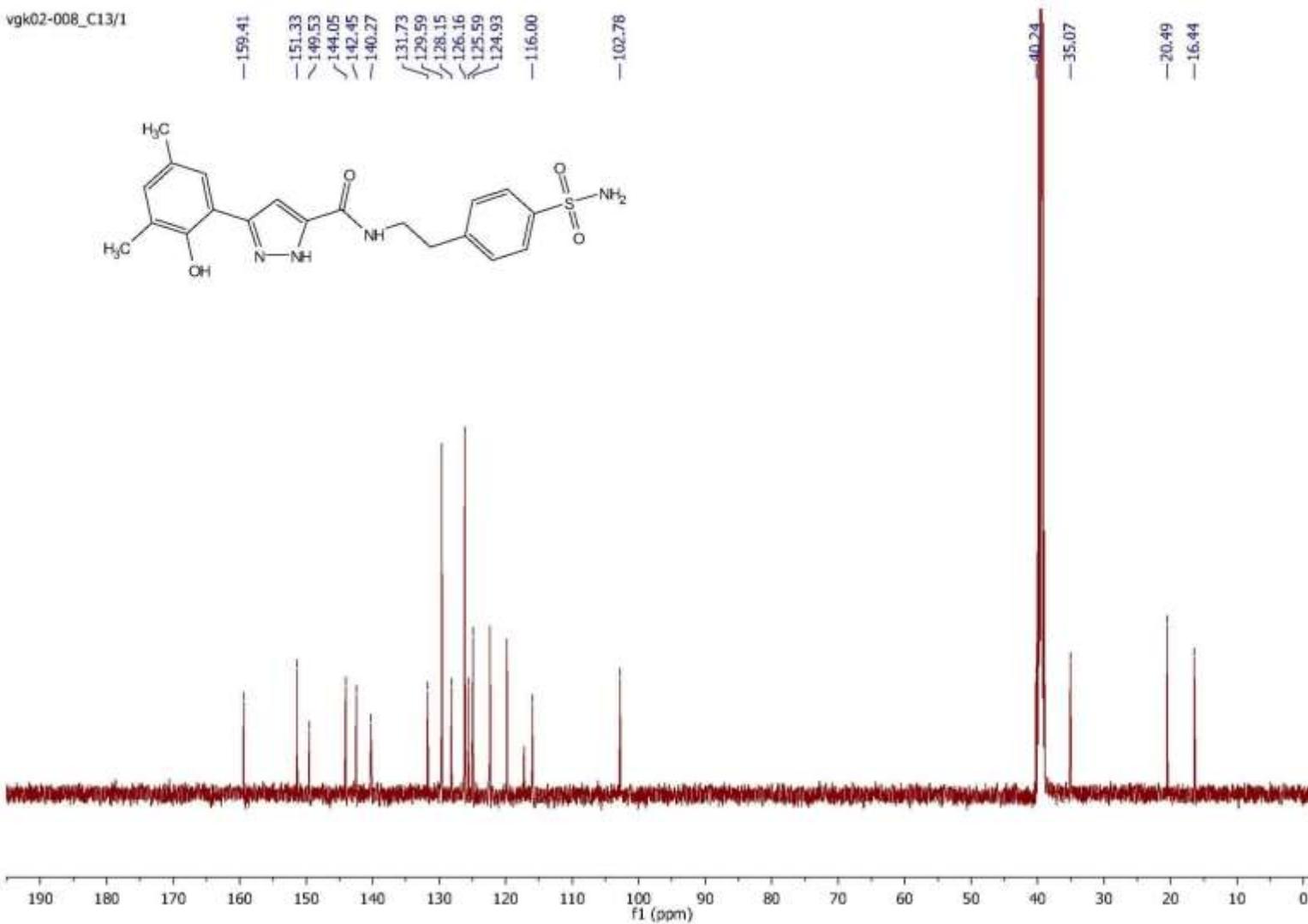


**Figure S9A.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-3,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5e**) in DMSO-*d*6.

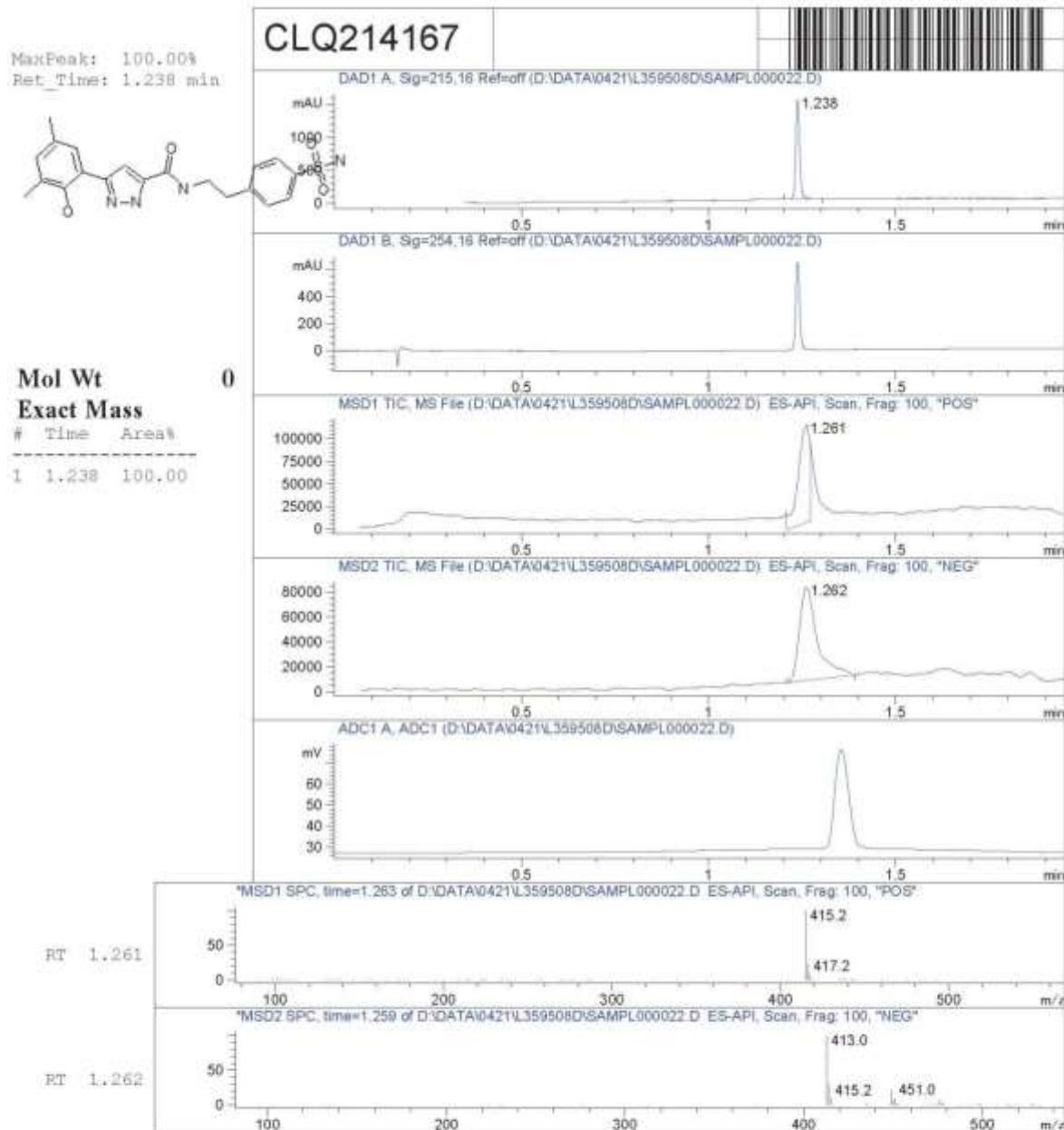


**Figure S9B.**  $^1\text{H}$  NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-3,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5e**) in DMSO-*d*6.+ 5% CF<sub>3</sub>SO<sub>3</sub>H.

vgk02-008\_C13/1



**Figure S9C**  $^{13}\text{C}$  NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(2-hydroxy-3,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5e**) in  $\text{DMSO-}d_6\text{.+5\%CF}_3\text{SO}_3\text{H}$ .



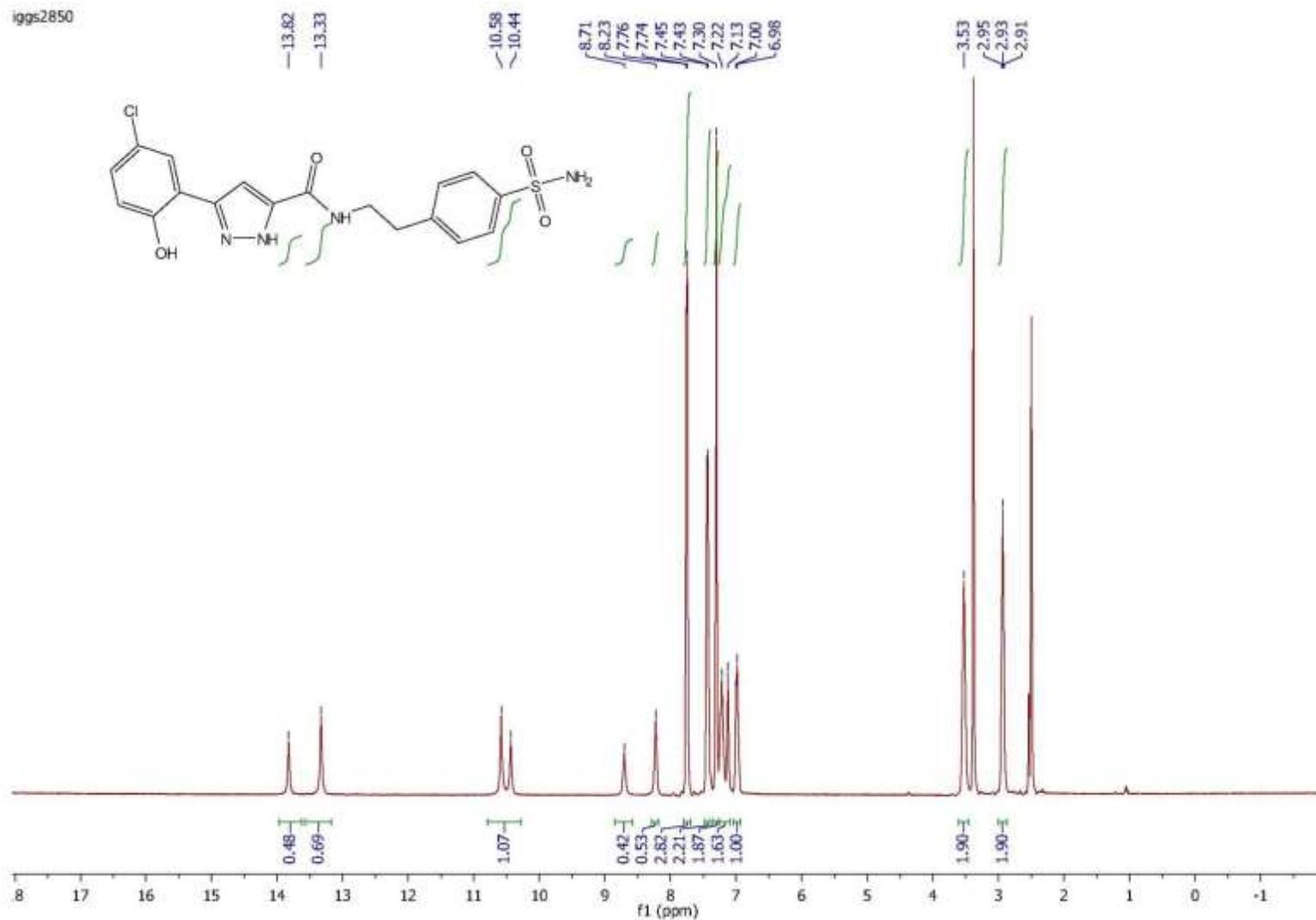
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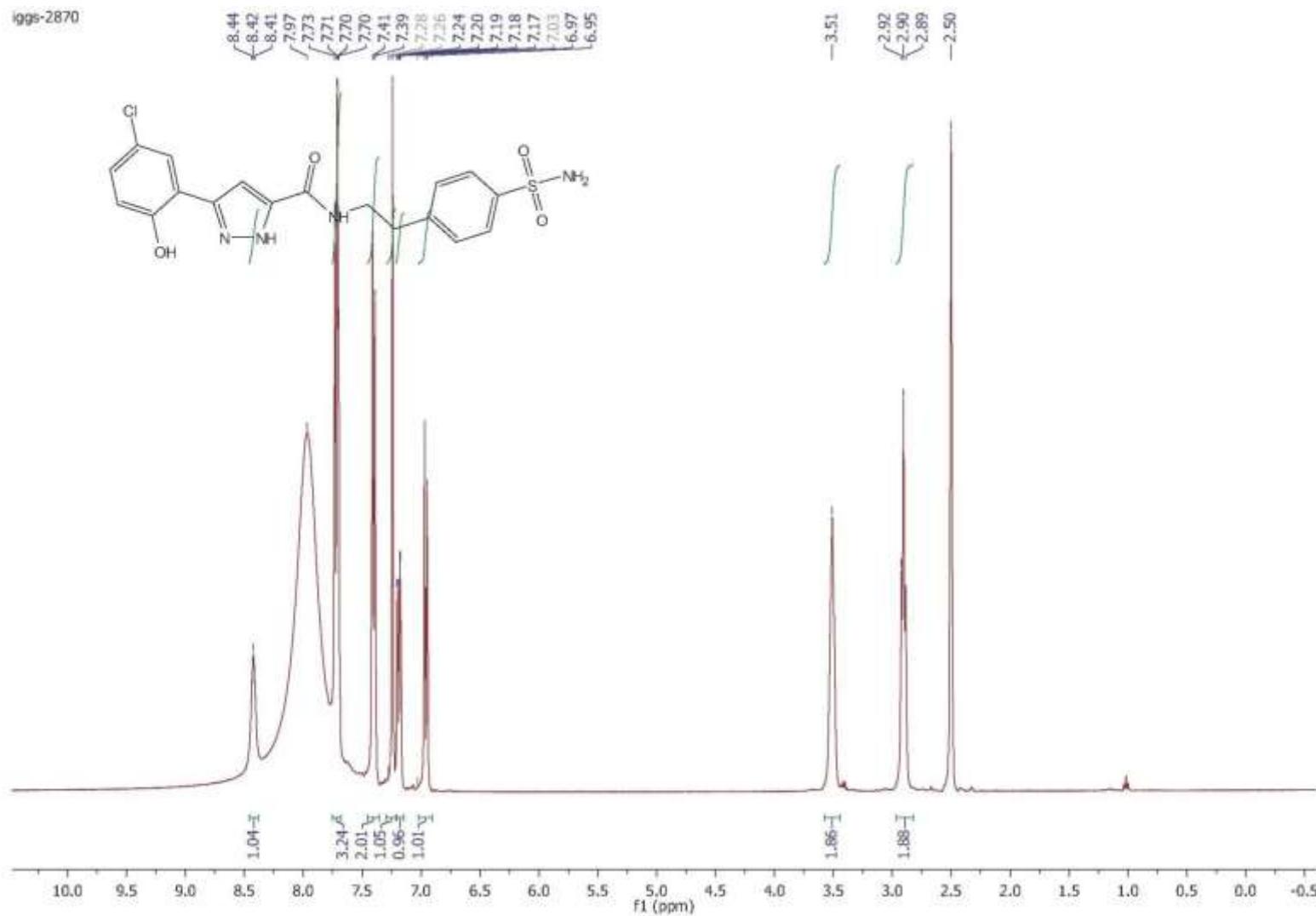
**Figure S9D.** LCMS spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(2-hydroxy-3,5-dimethylphenyl)-1*H*-pyrazole-5-carboxamide (**5e**).

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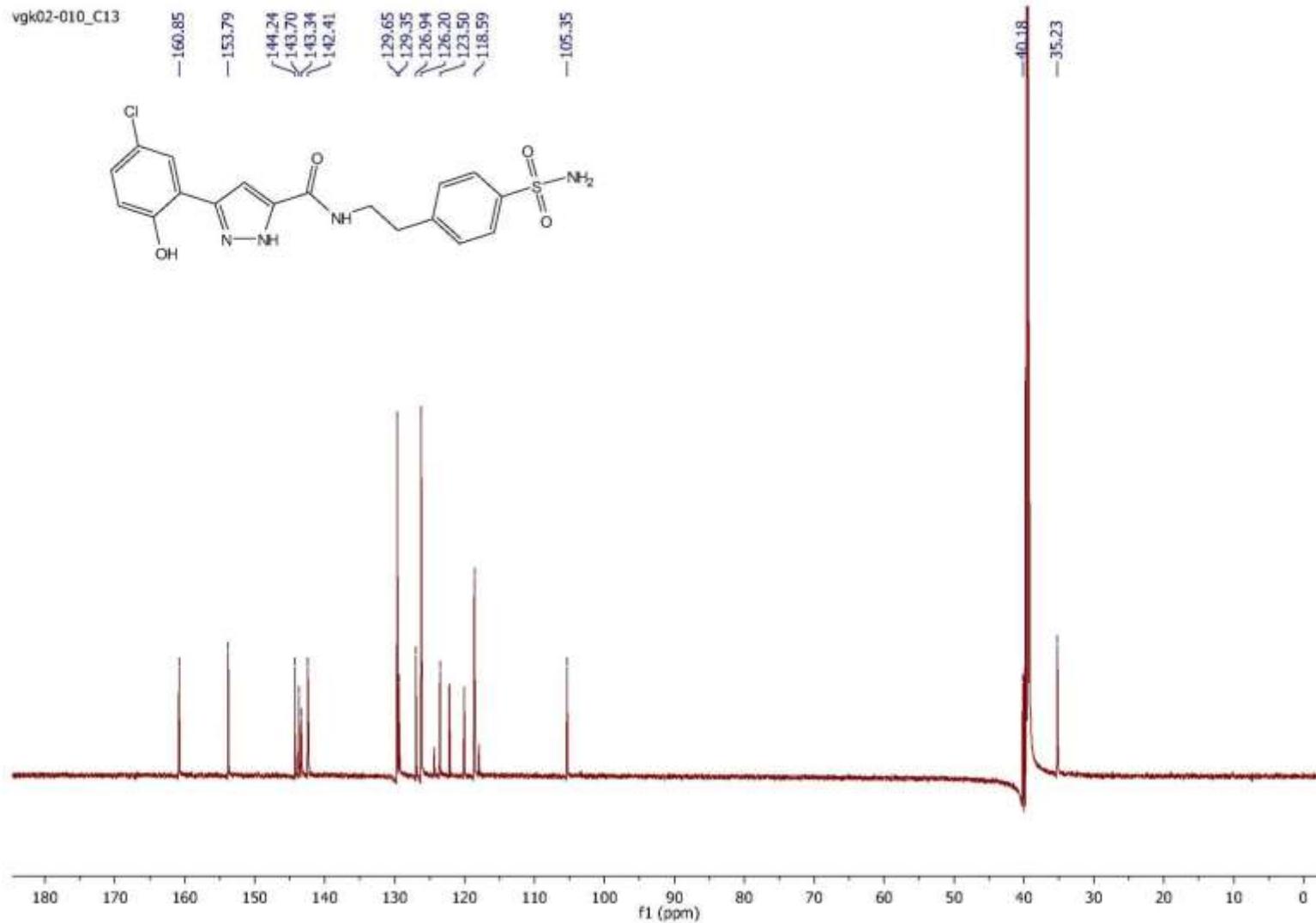


**Figure S10A.** <sup>1</sup>H NMR spectrum of *N*-{2-[4-(Aminosulfonyl)phenyl]ethyl}-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5f**) in DMSO-*d*6.

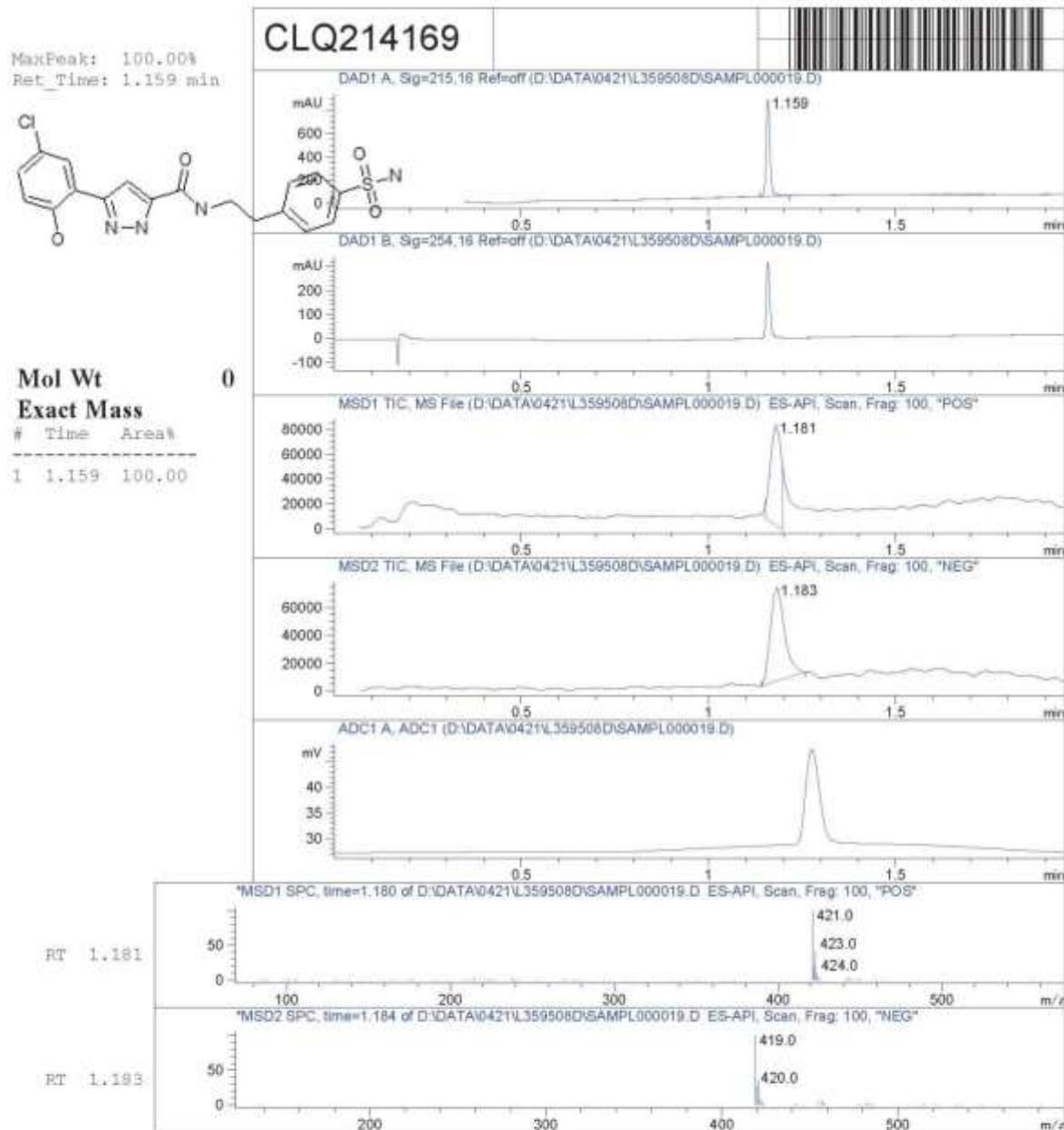
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**Figure S10B.** <sup>1</sup>H NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5f**) in DMSO-*d*6+5% CF<sub>3</sub>SO<sub>3</sub>H.



**Figure S10C.**  $^{13}\text{C}$  NMR spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5f**) in  $\text{DMSO}-d_6 + 5\% \text{CF}_3\text{SO}_3\text{H}$ .



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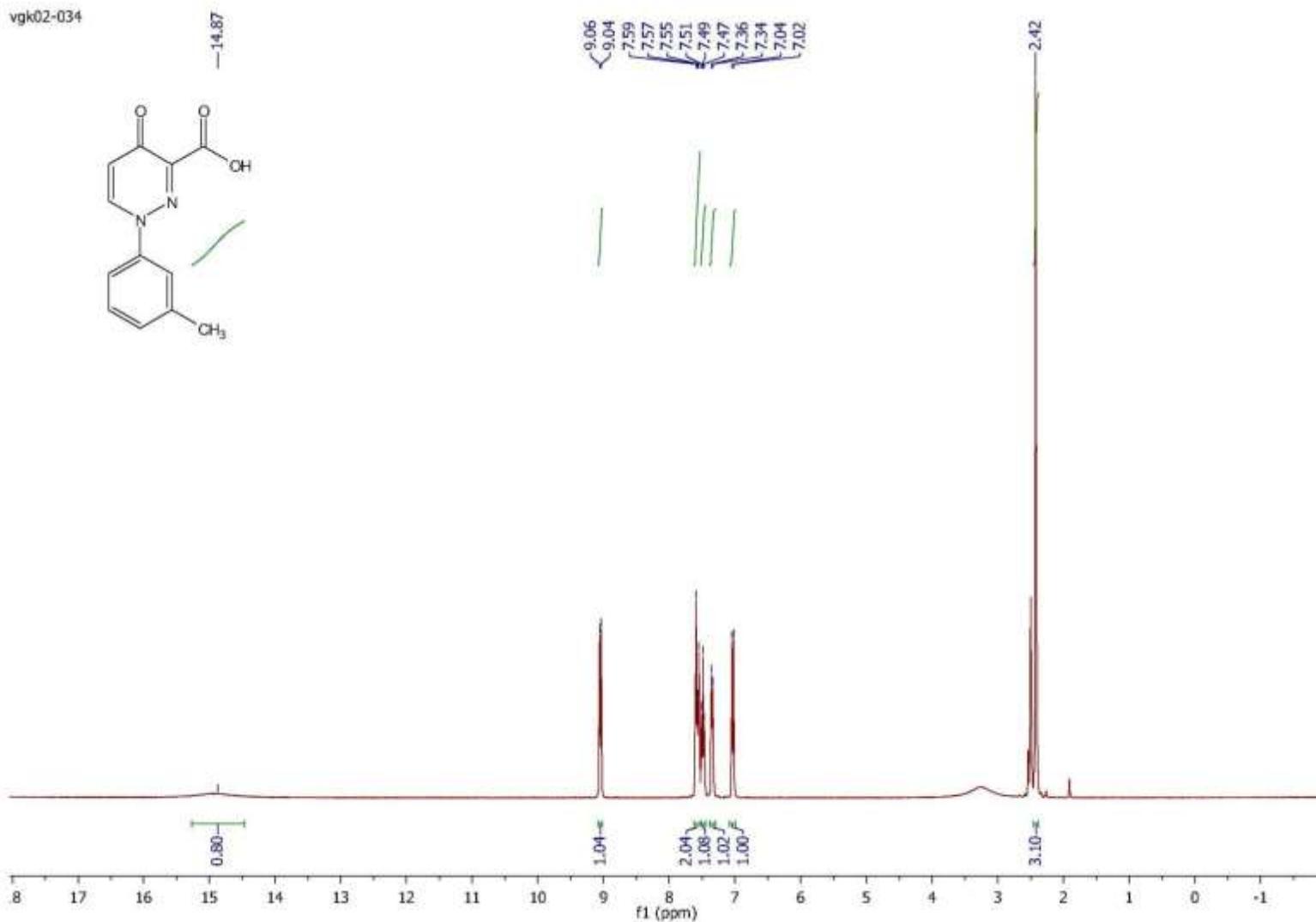
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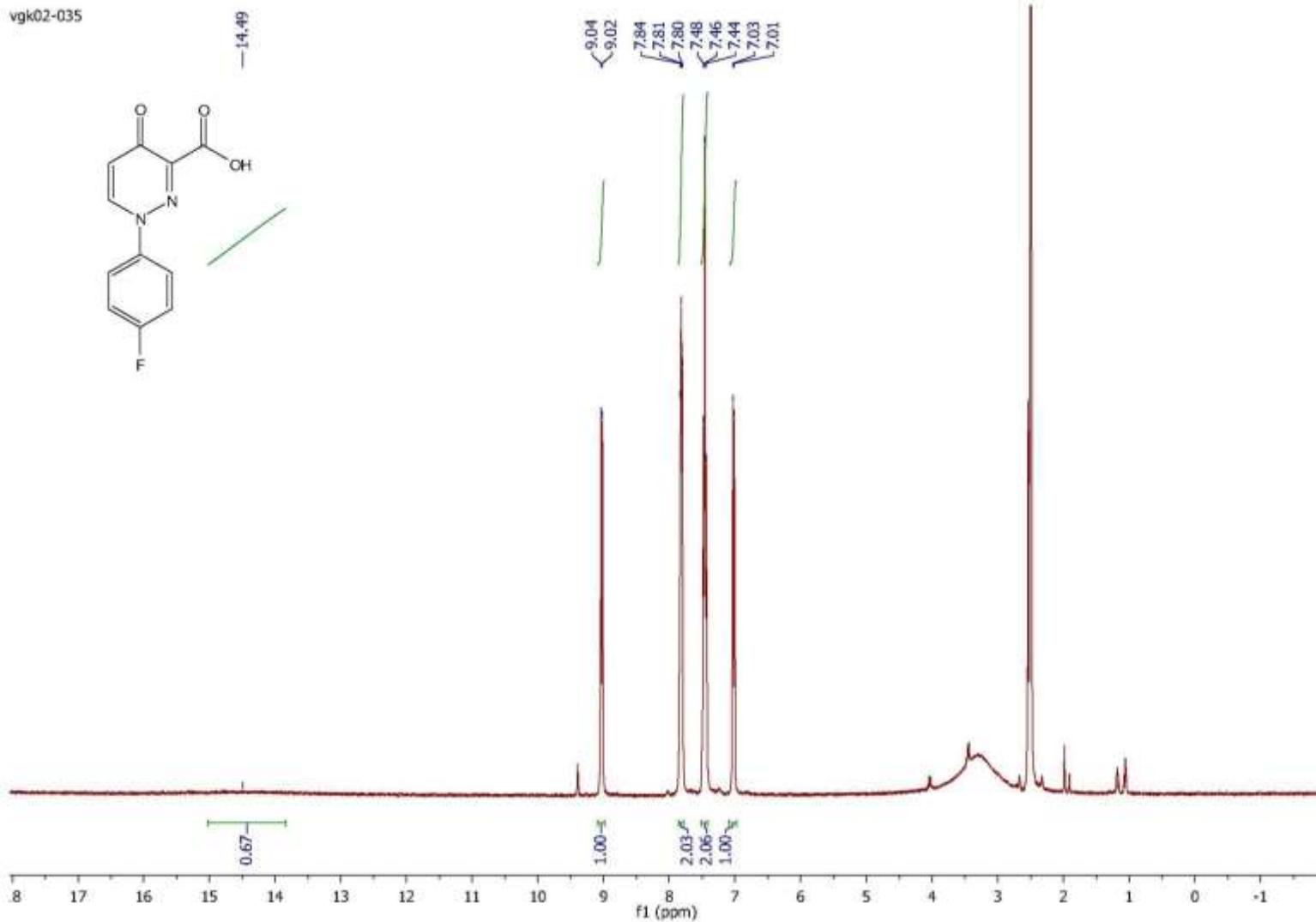
**Figure S10D.** LCMS spectrum of *N*-(2-[4-(Aminosulfonyl)phenyl]ethyl)-3-(5-chloro-2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamide (**5f**).

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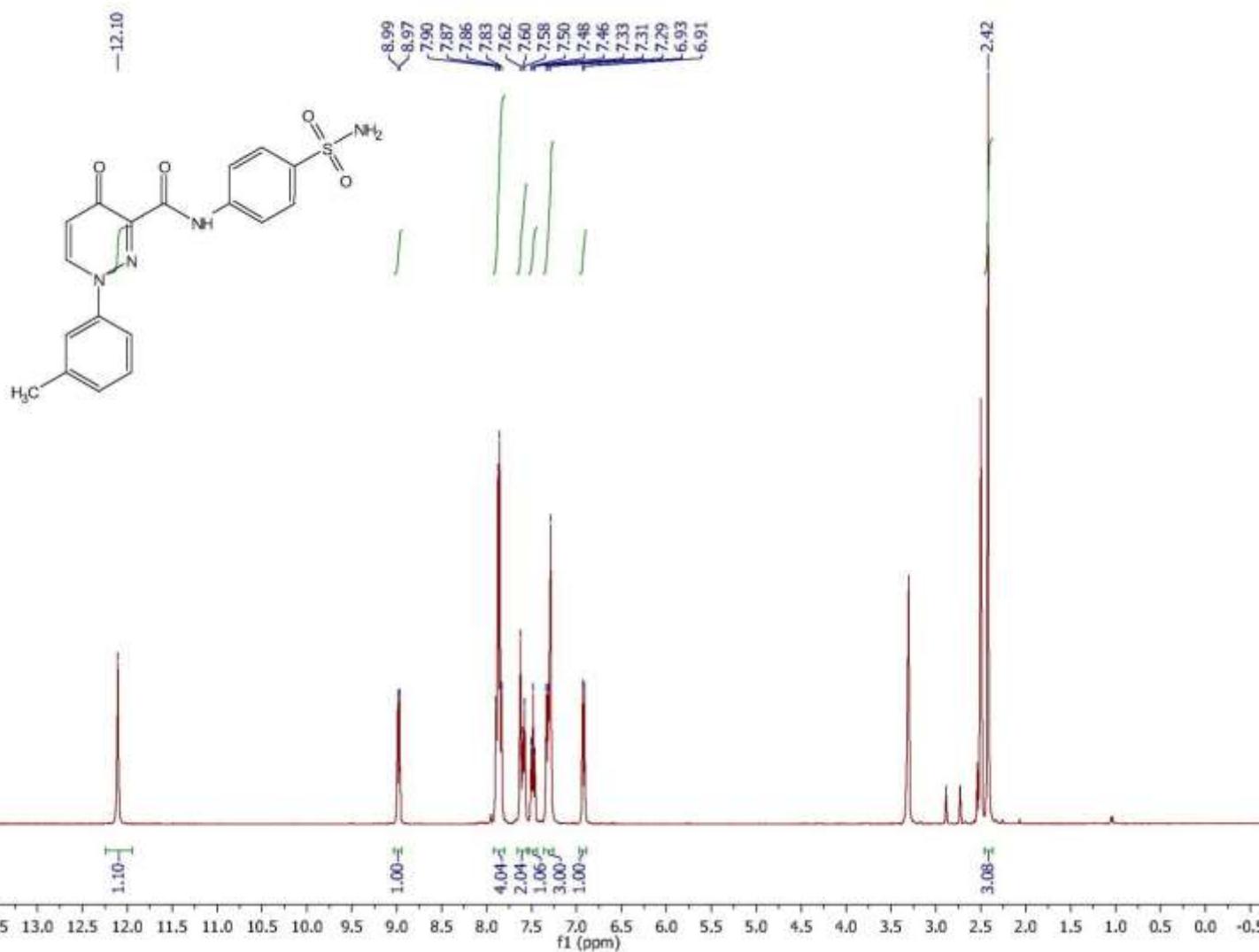
**Figure S11.** <sup>1</sup>H NMR spectrum of *1-(3-Methylphenyl)-4-oxo-1,4-dihydropyridazine-3-carboxylic acid* (**8a**) in DMSO-*d*6.

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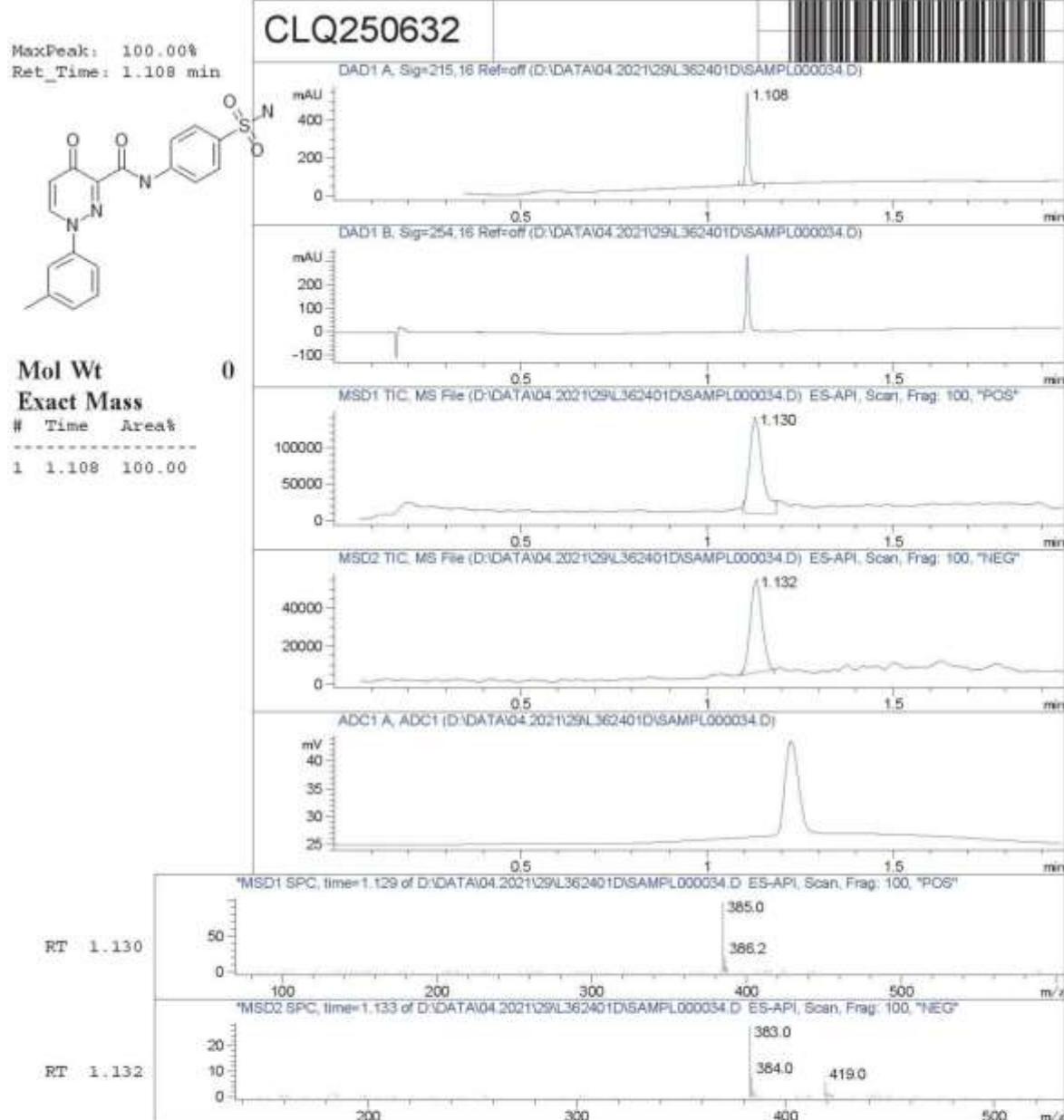


**Figure S12.** <sup>1</sup>H NMR spectrum of 1-(4-Fluorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (**8b**) in DMSO-*d*6.

vgk02-011



**Figure S13A.**  $^1\text{H}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(3-methylphenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10a**) in  $\text{DMSO}-d_6$ .

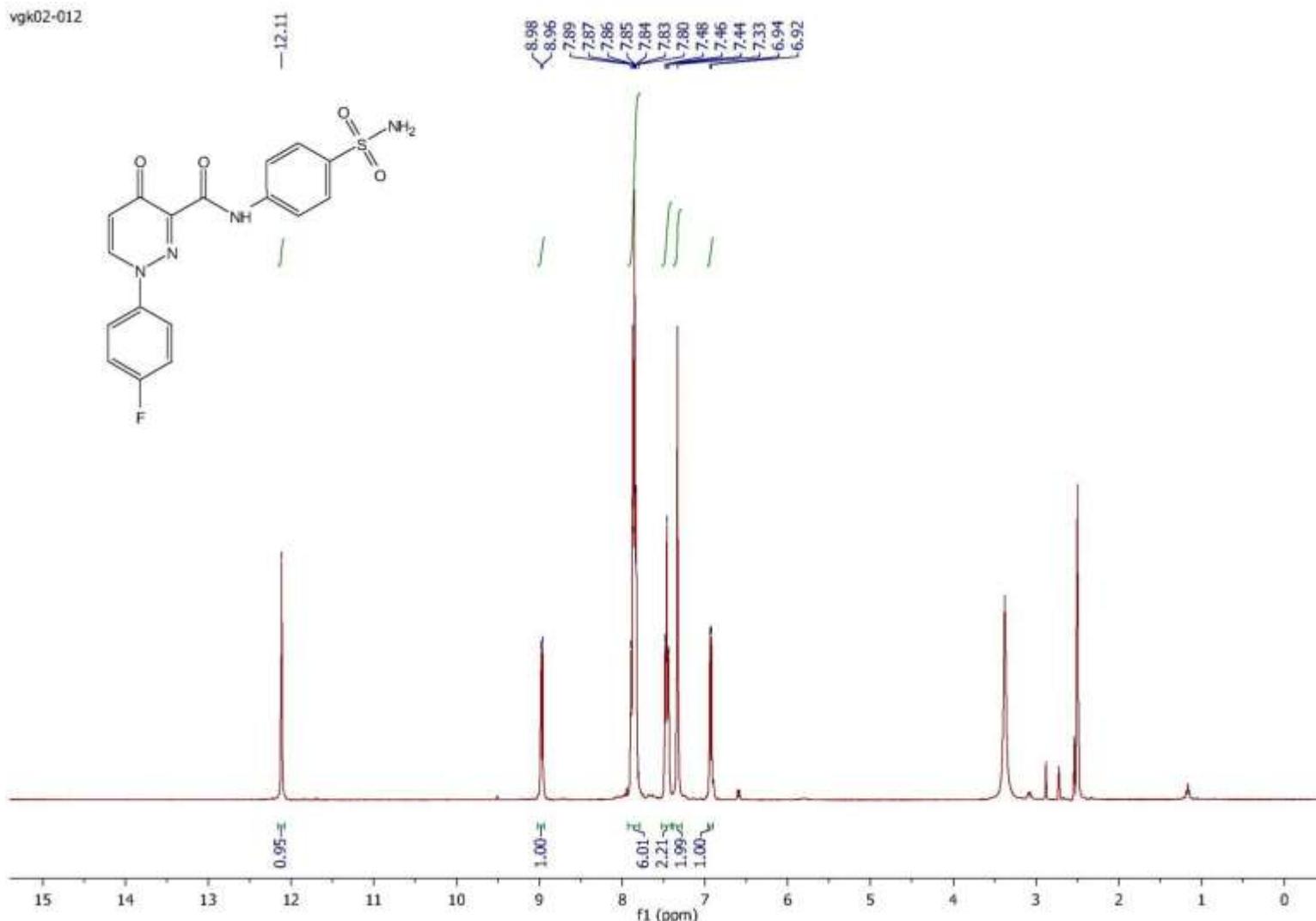


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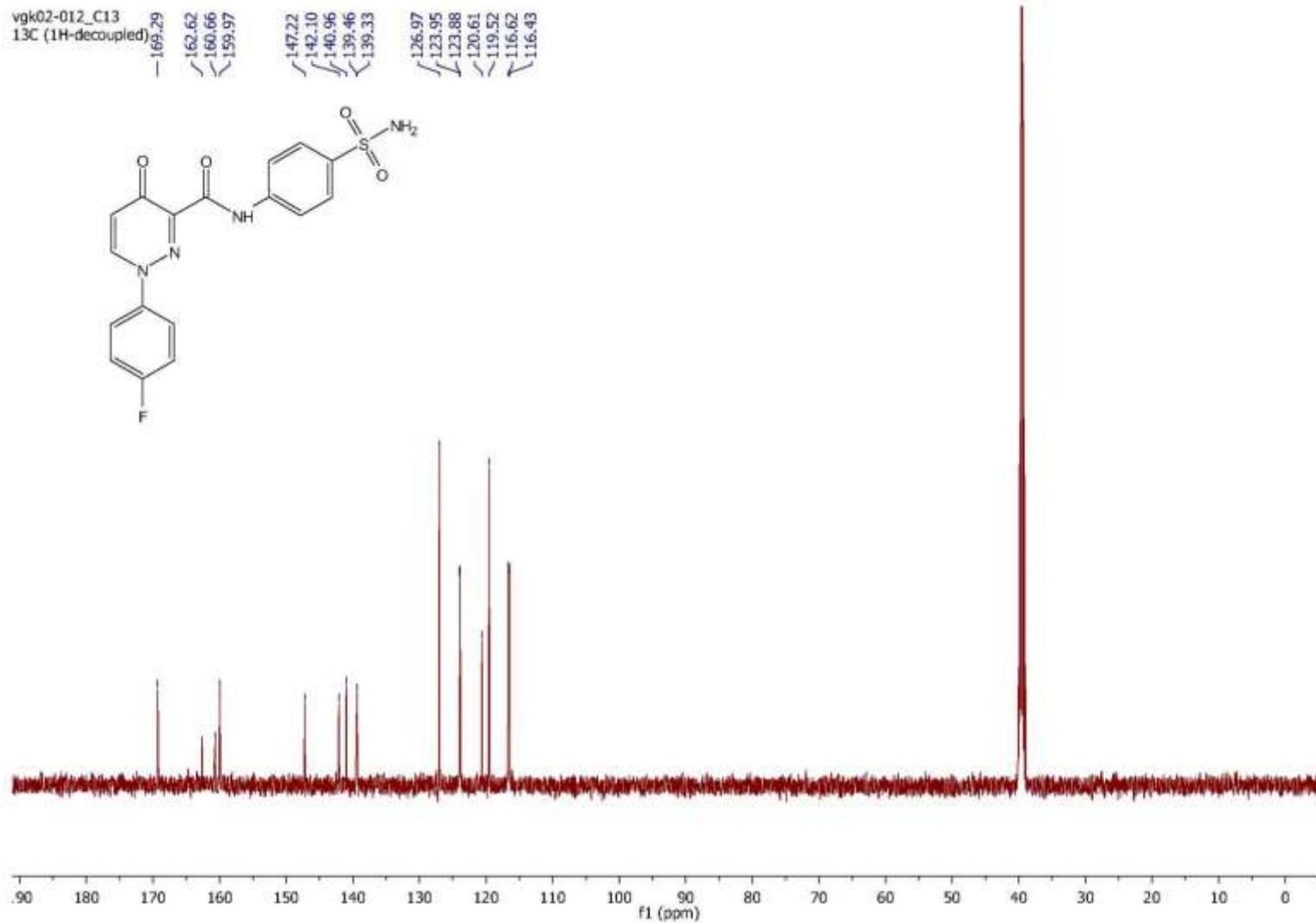
CH P2-D-09 - 4 - Acq. Method C:\CHEM32\-> ->

**Figure S13B.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(3-methylphenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide (**10a**).

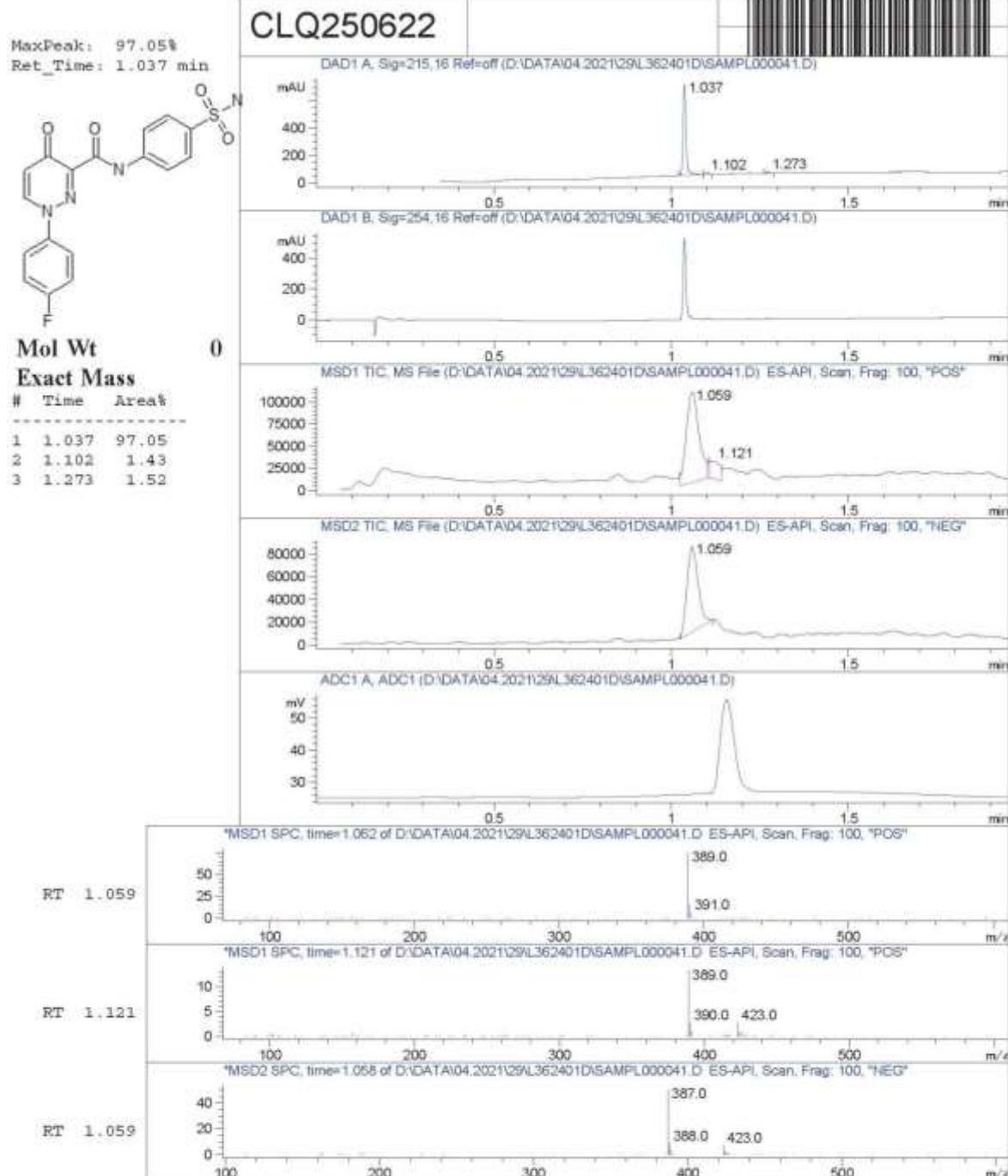
vgk02-012



**Figure S14A.**  $^1\text{H}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-fluorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10b**) in DMSO-*d*6.



**Figure S14B.**  $^{13}\text{C}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-fluorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10b**) in DMSO-*d*6.

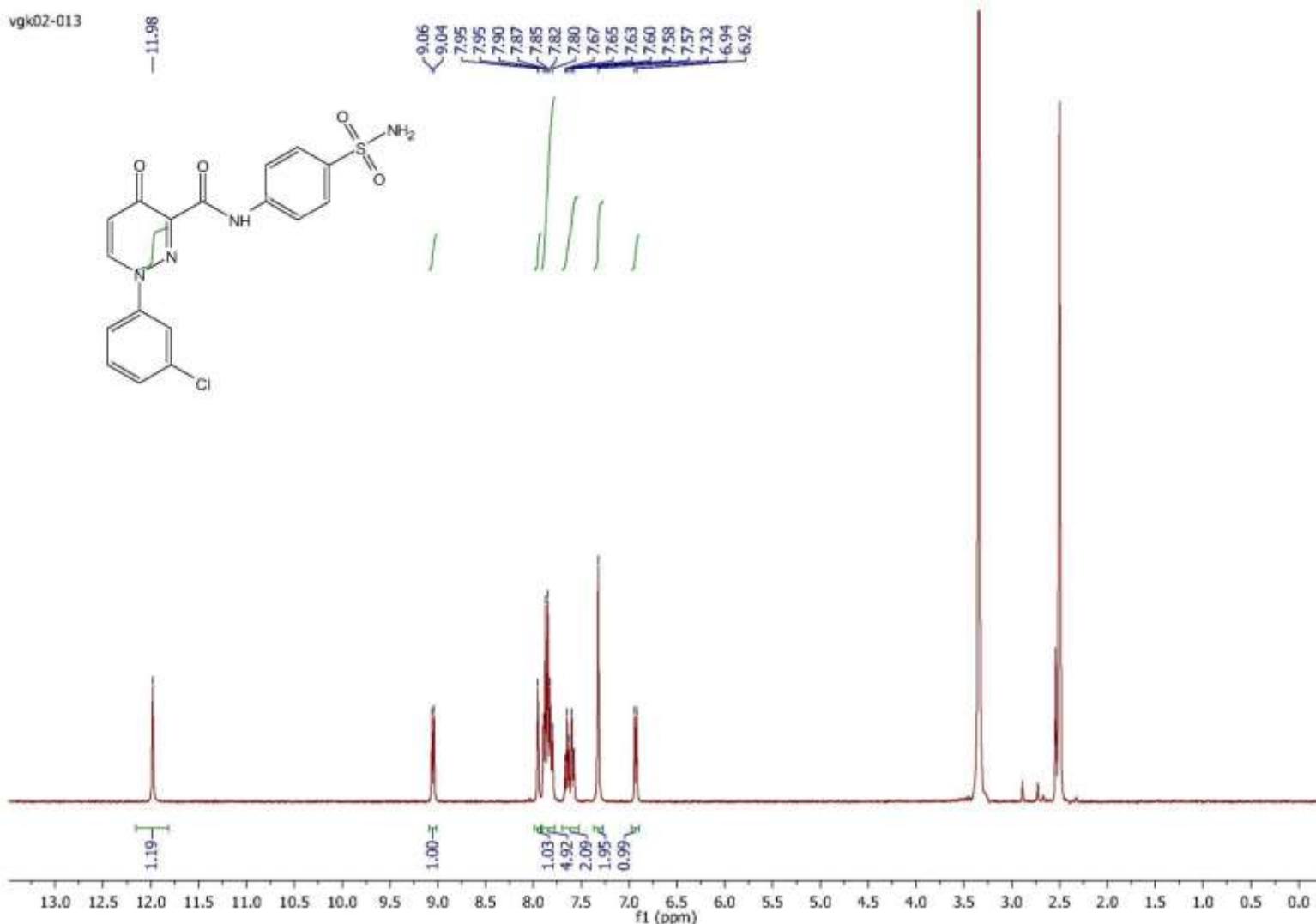


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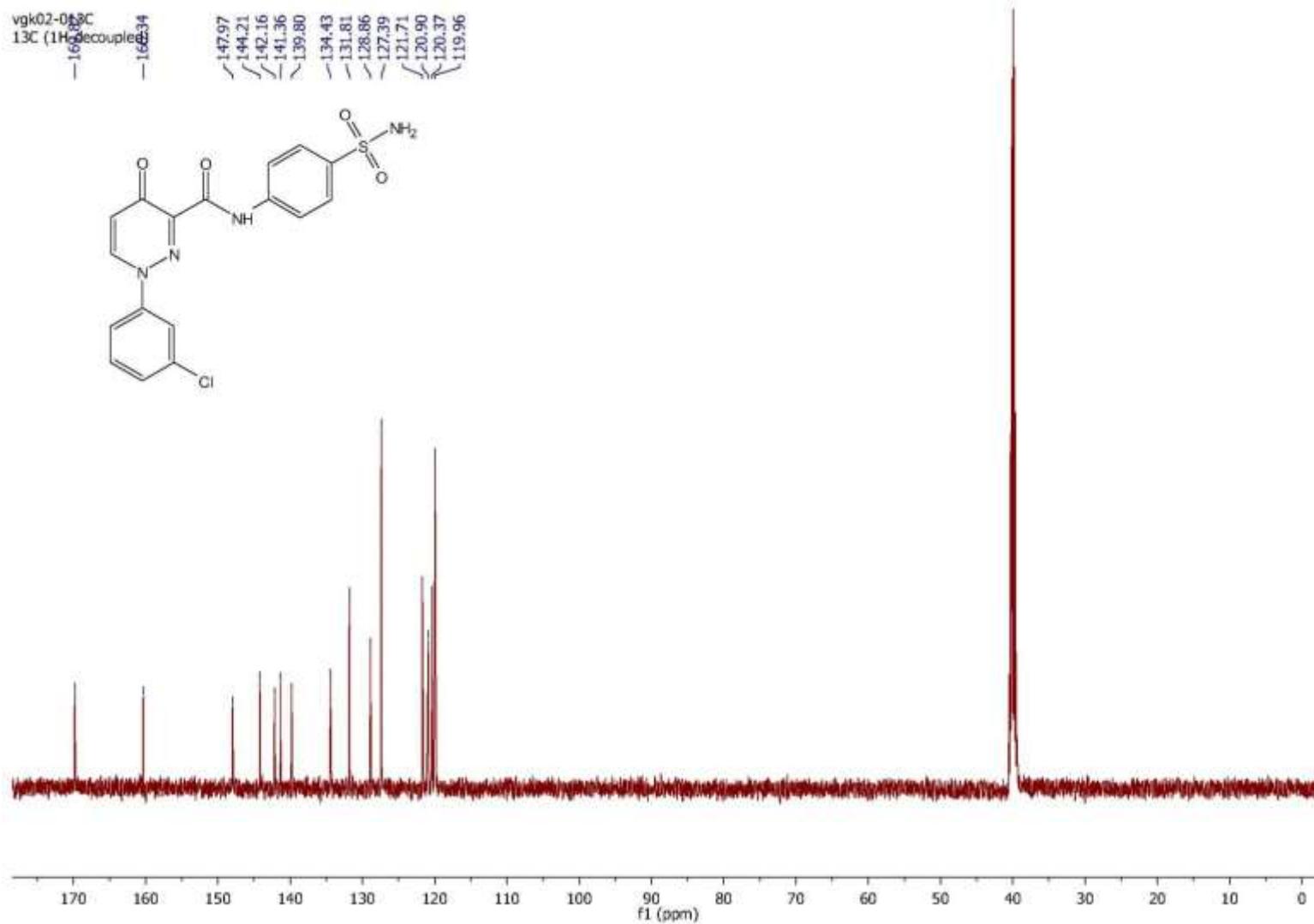
CH P2-E-07 - 4 - Acq. Method C:\CHEM32\-> ->

**Figure S14C.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-fluorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10b**).

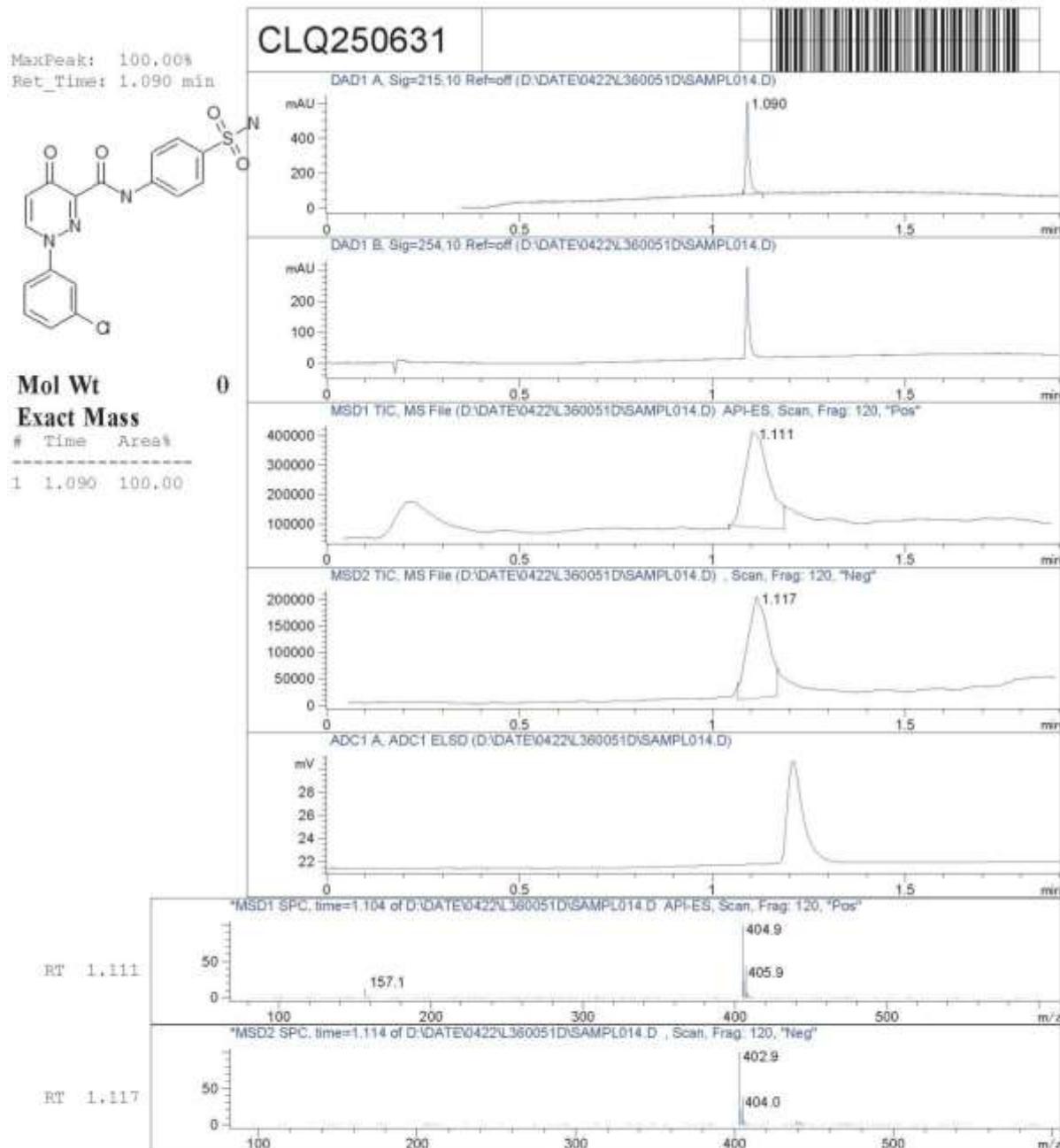
vgk02-013



**Figure S15A.** <sup>1</sup>H NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(3-chlorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10c**) in DMSO-*d*6.



**Figure S15B.**  $^{13}\text{C}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(3-chlorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide (**10c**) in  $\text{DMSO}-d_6$ .



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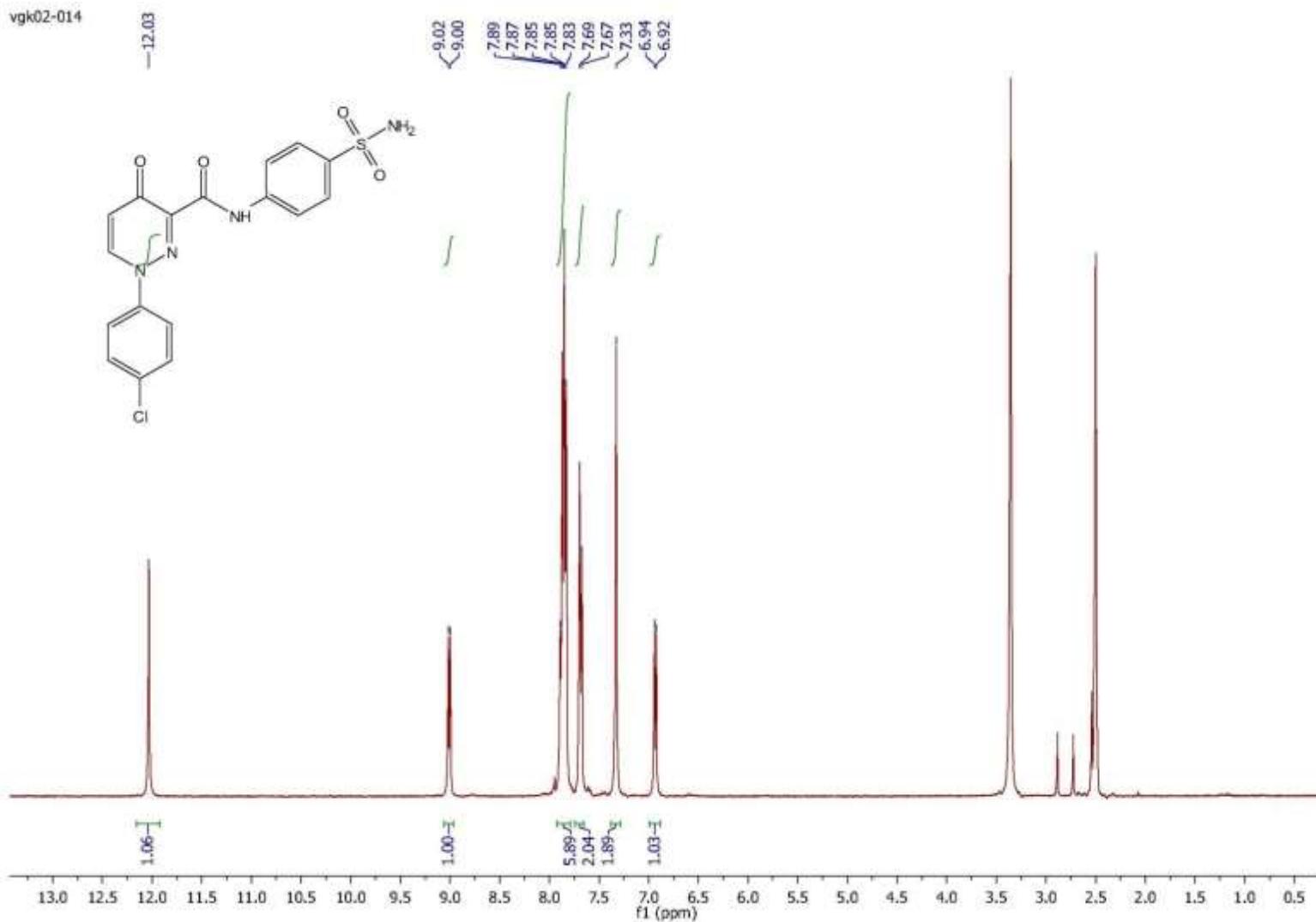
-VI-

Aqc. Method C:\HPCHEM\->

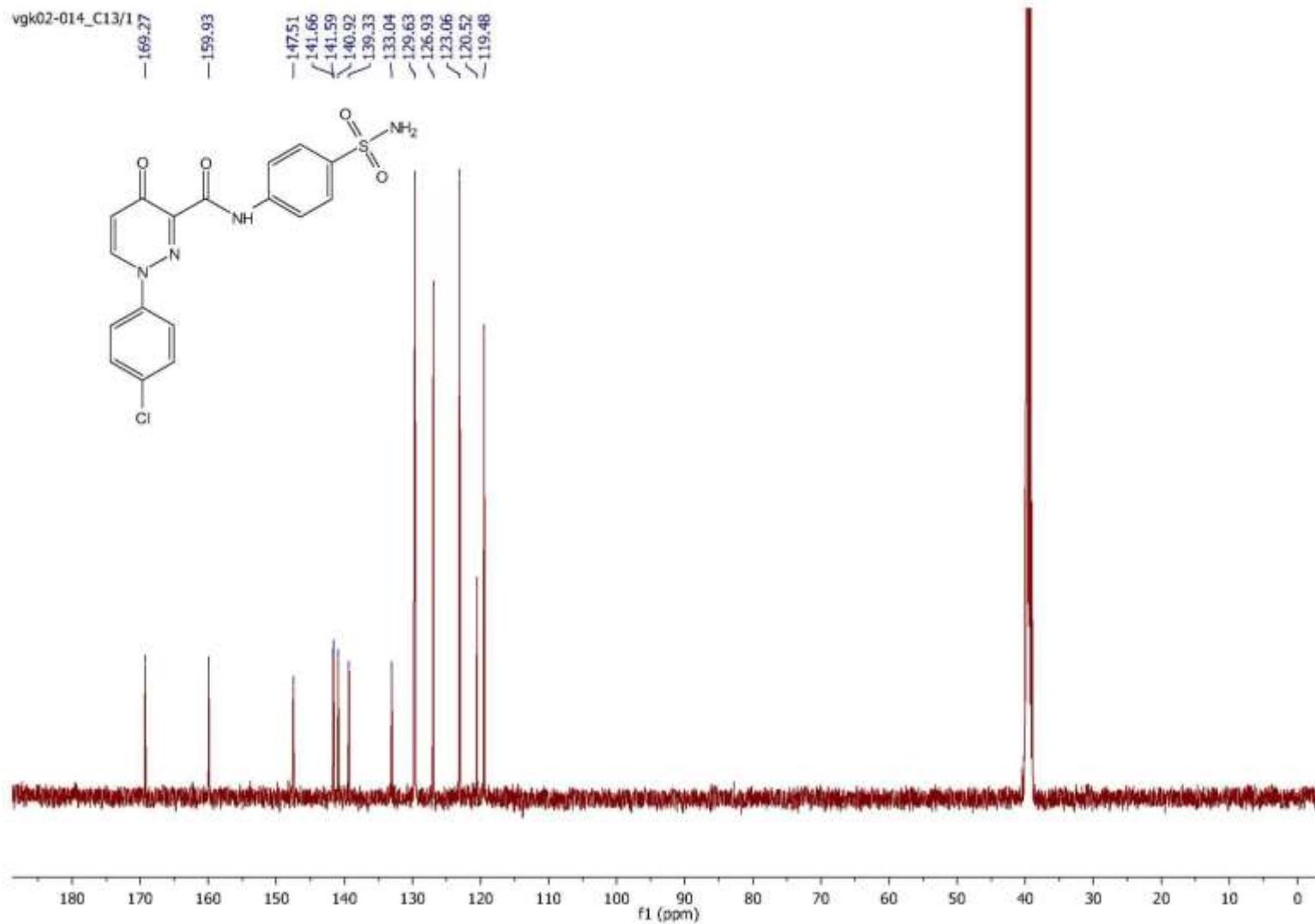
->

**Figure S15C.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(3-chlorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10c**).

vgk02-014

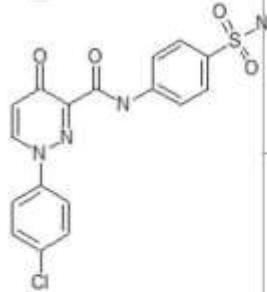


**Figure S16A.**  $^1\text{H}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-chlorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10d**). in  $\text{DMSO}-d_6$ .



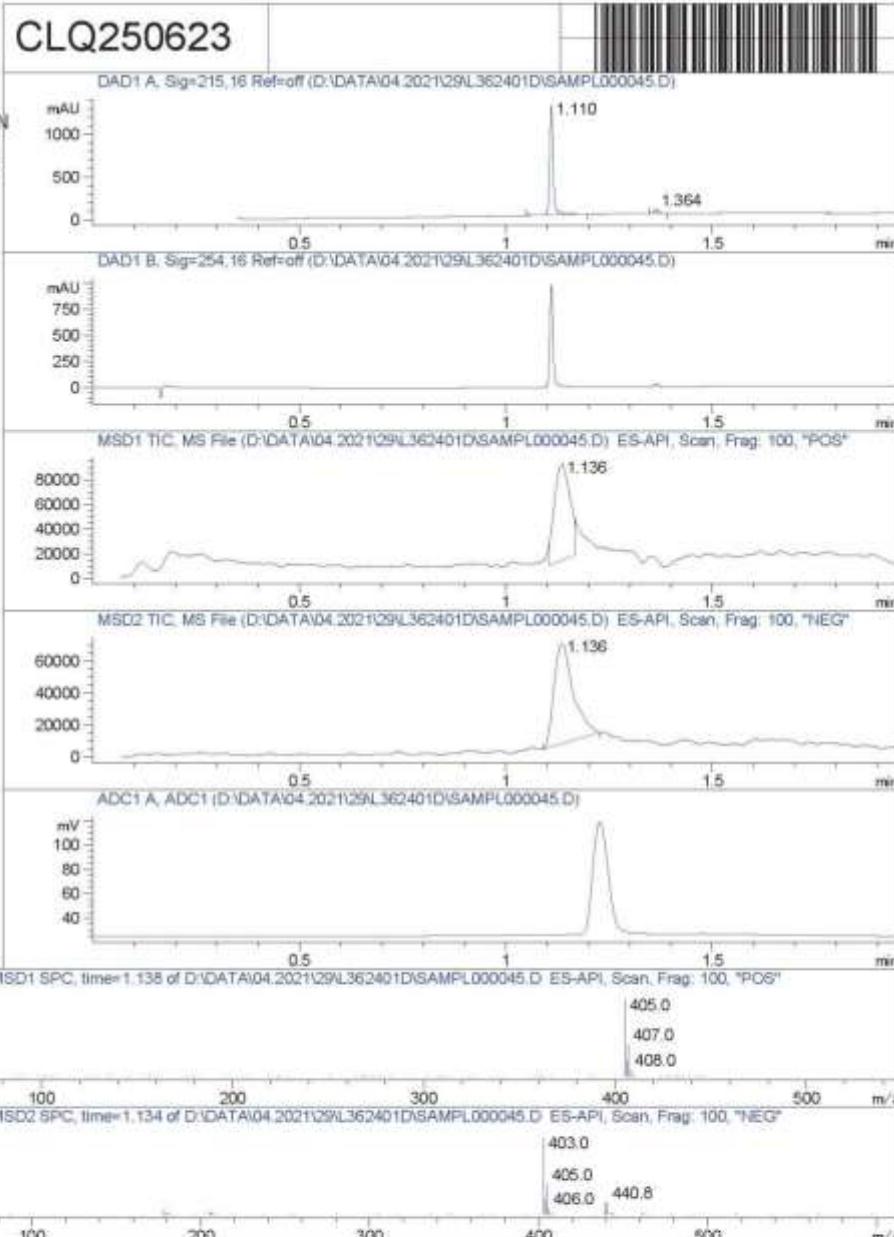
**Figure S16B.**  $^{13}\text{C}$  NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-chlorophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxamide (**10d**). in  $\text{DMSO}-d_6$ .

MaxPeak: 96.22%  
Ret\_Time: 1.110 min



Mol Wt 0  
Exact Mass  
# Time Area%

#	Time	Area%
1	1.110	96.22
2	1.364	3.78

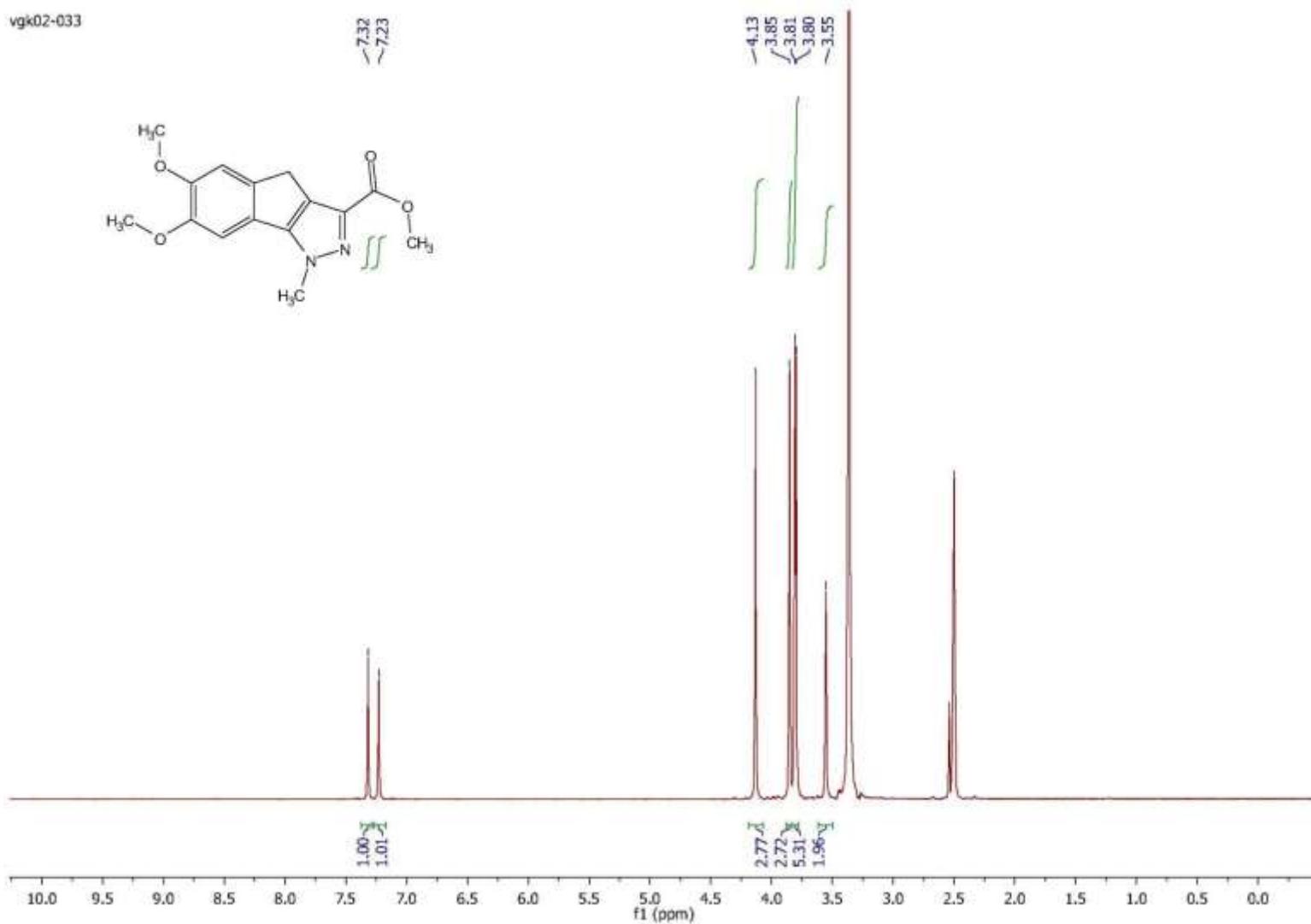


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CH P2-F-02 - 4 - Acq. Method C:\CHEM32\-> ->

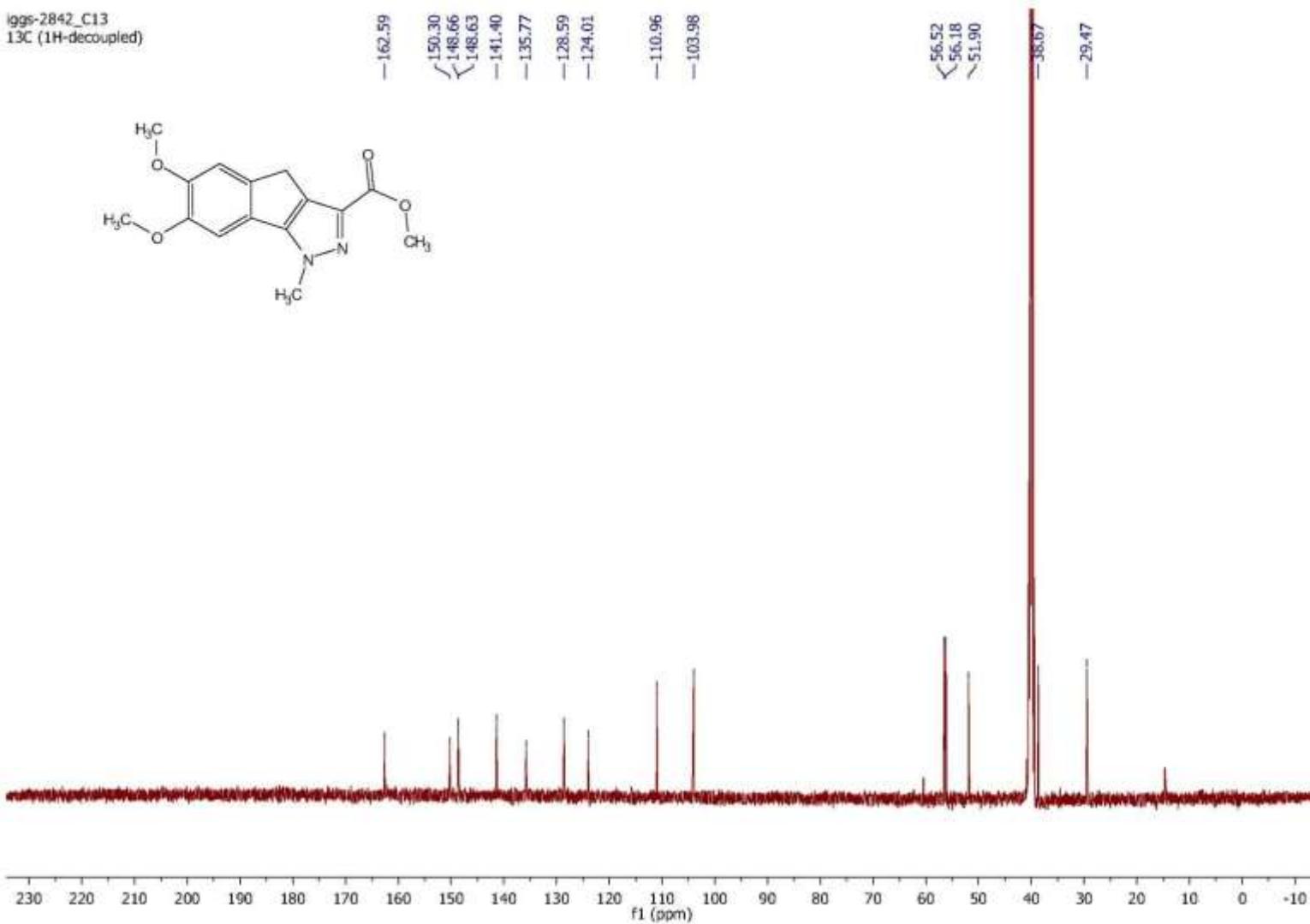
**Figure S16C.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-1-(4-chlorophenyl)-4-oxo-1,4-dihdropyridazine-3-carboxamide (**10d**).

vgk02-033



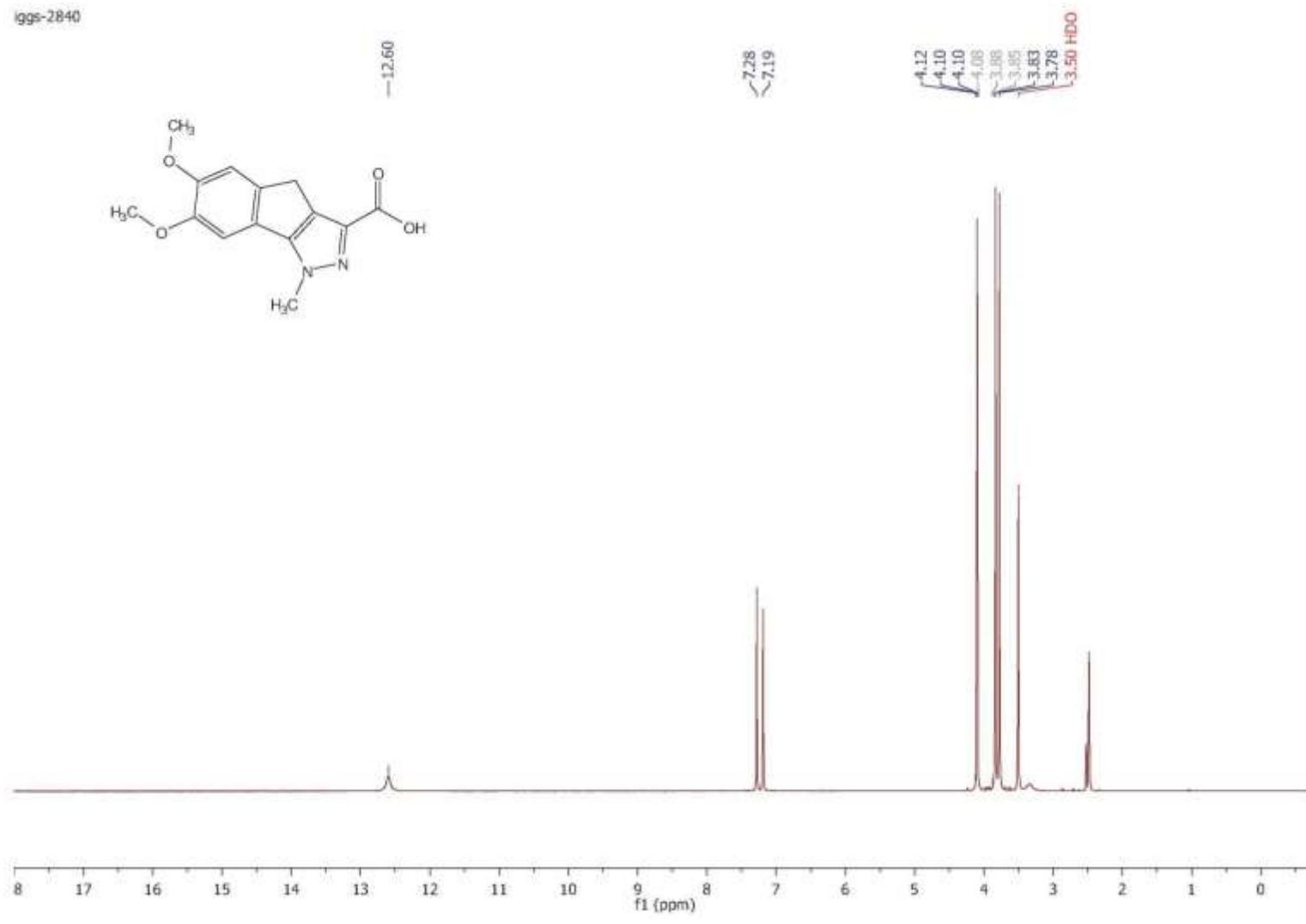
**Figure S17A.** <sup>1</sup>H NMR spectrum of *Methyl 6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxylate (13)* in DMSO-*d*6.

lggs-2842\_C13  
<sup>13</sup>C (1H-decoupled)



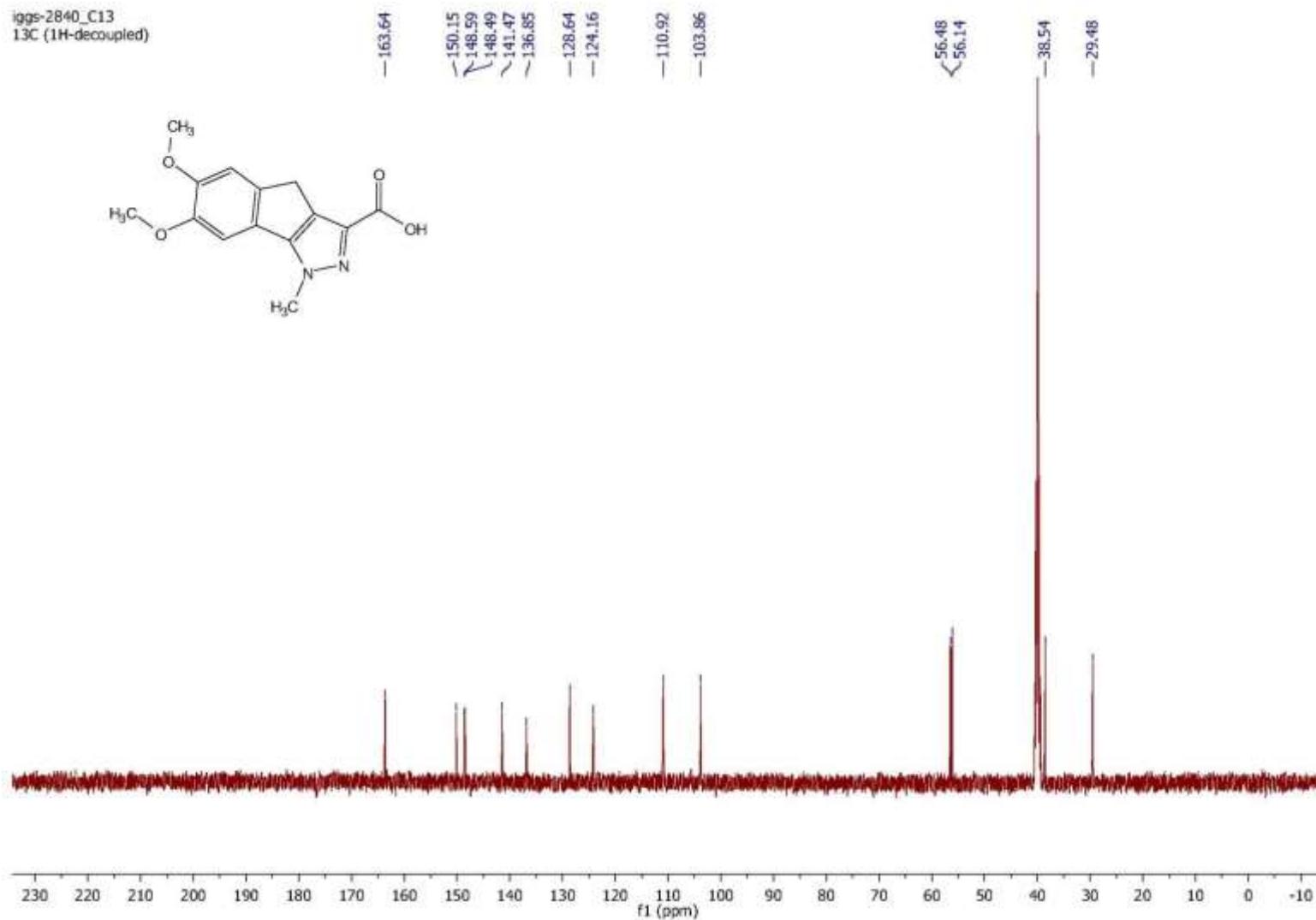
**Figure S17B.** <sup>13</sup>C NMR spectrum of *Methyl 6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxylate (13)* in DMSO-*d*6.

iggs-2840



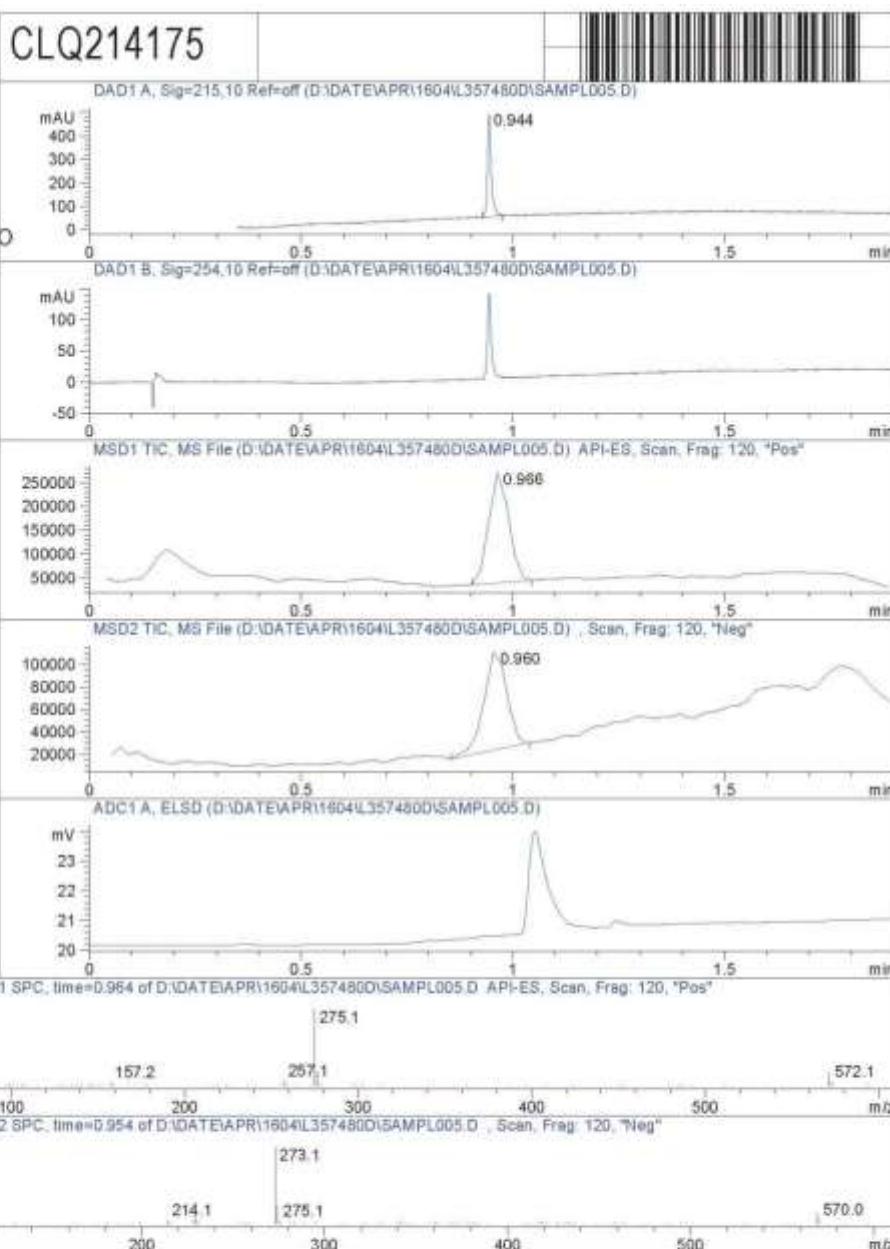
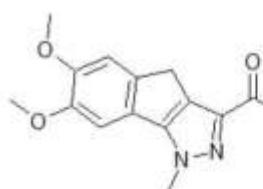
**Figure S18A.** <sup>1</sup>H.NMR spectrum of *6,7-Dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxylic acid* (**14**). in DMSO-*d*6.

iggs-2840\_C13  
13C (1H-decoupled)



**Figure S18B.** <sup>13</sup>C.NMR spectrum of *6,7-Dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxylic acid (14)*. in DMSO-*d*6.

MaxPeak: 100.00%  
Ret\_Time: 0.944 min



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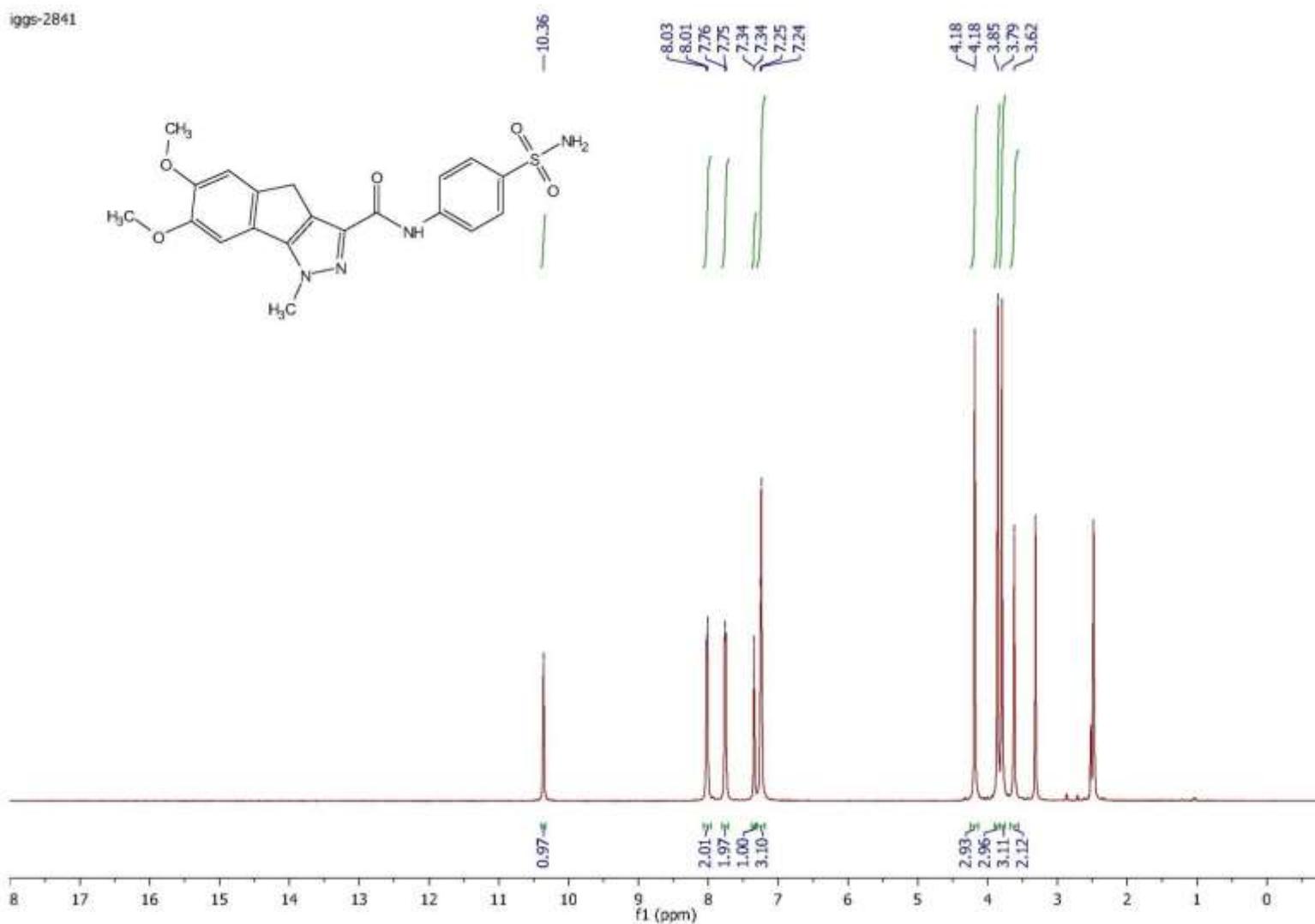
-SL-

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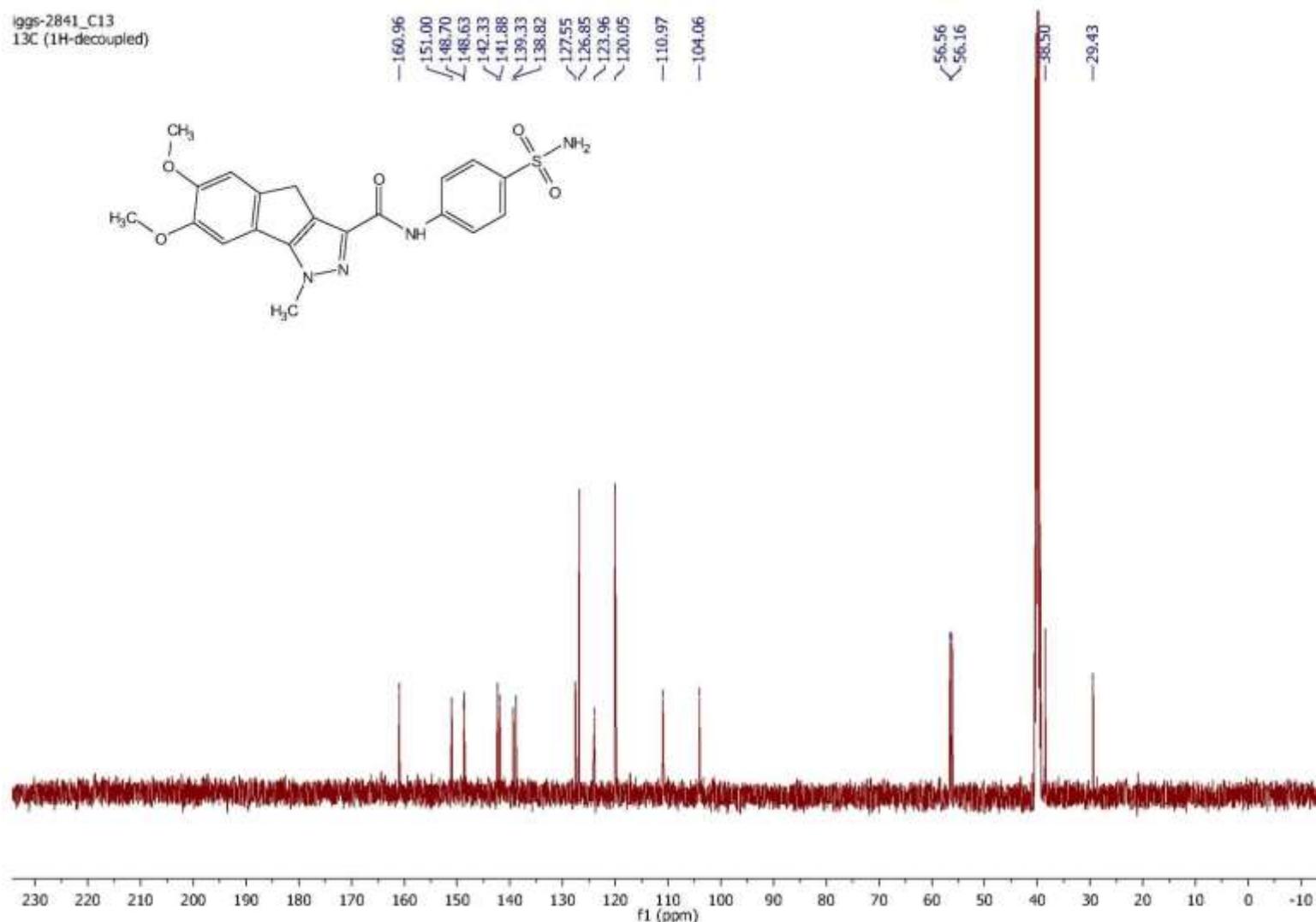
**Figure S18C.** LCMS spectrum of 6,7-Dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxylic acid (**14**).

iggs-2841

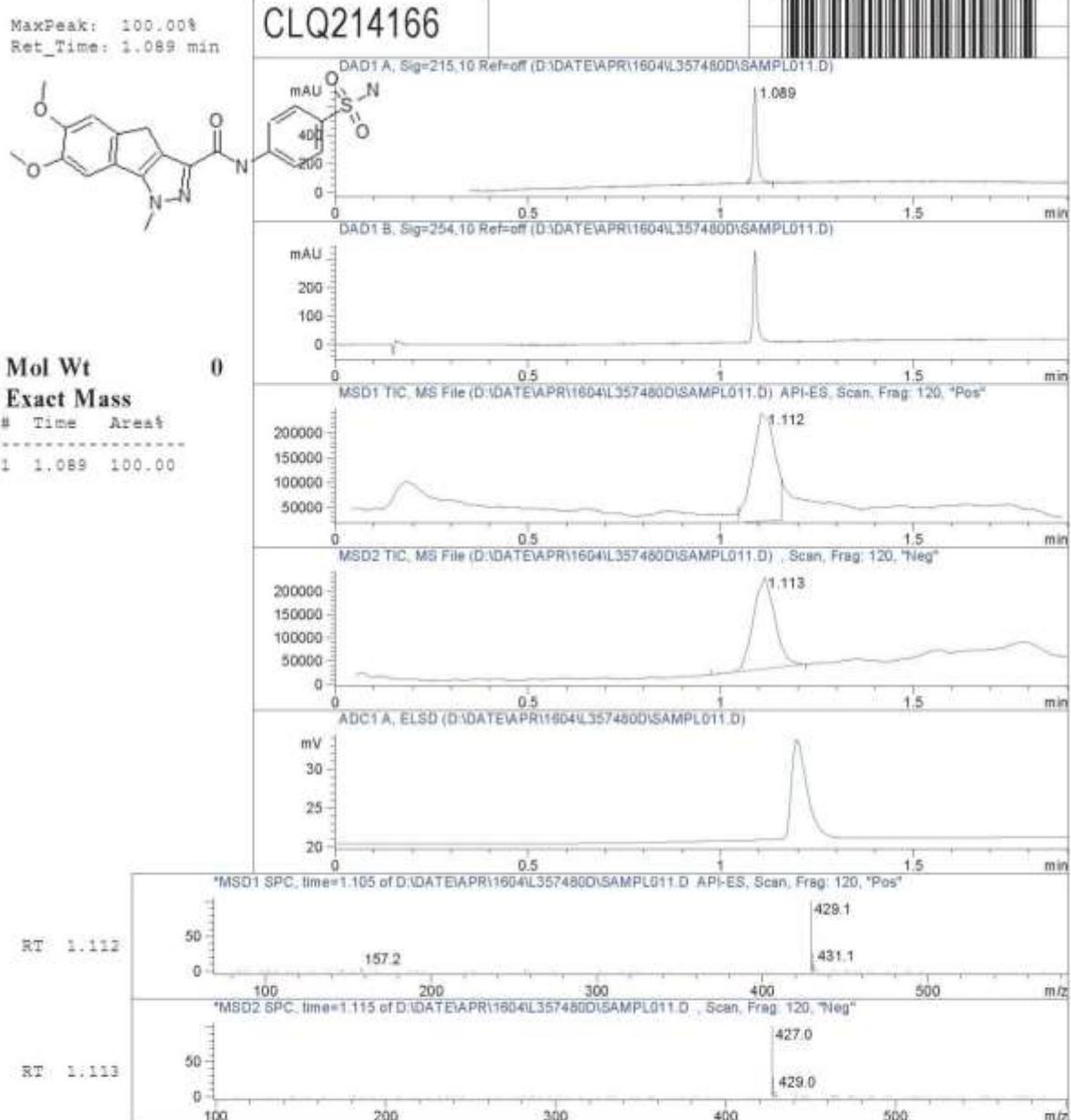


**Figure S19A.** <sup>1</sup>H.NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxamide (**15**) in DMSO-*d*6.

lggs-2841\_C13  
13C (1H-decoupled)



**Figure S19B.** <sup>13</sup>C.NMR spectrum of *N*-[4-(Aminosulfonyl)phenyl]-6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carboxamide (**15**) in DMSO-*d*6.



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**Figure S19C.** LCMS spectrum of *N*-[4-(Aminosulfonyl)phenyl]-6,7-dimethoxy-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxamide (**15**).