Supporting Information

Synthesis and Crystal Characteristics Research of Nirmatrelvir

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1.1.1 HRMS

Qualitative Compound Report

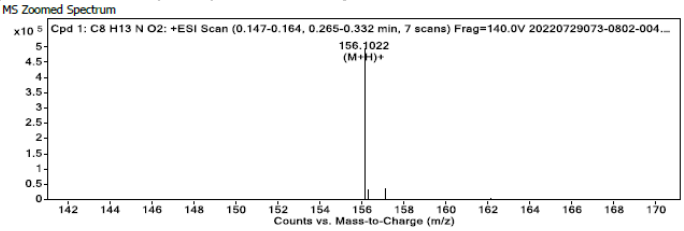
Data File	20220729073-0802-004.d	**Sample Name**	WOK007-8
Sample Type	Sample	**Position**	Vial 9
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220627
AcquiredTime	8/2/2022 10:08:35 AM	**DataFile**	D:\MassHunter\Data\2022-08\2022-08-02\20220729073-0802-004.d

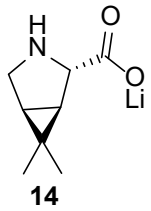
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C8 H13 N O2	0.214	155.095	497975	C8 H13 N O2	155.0946	2.1

Compound Label	RT	Algorithm	Mass
Cpd 1: C8 H13 N O2	0.214	Find By Formula	155.095

MS Zoomed Spectrum





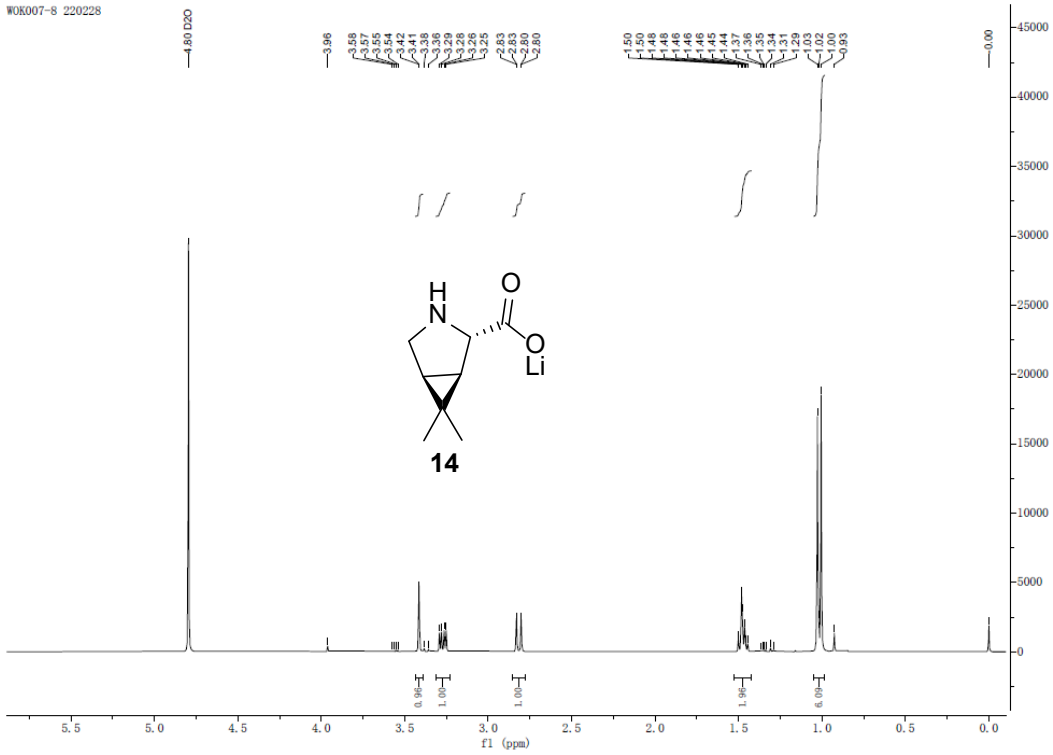
14

MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
156.1022	156.1019	2.09	1	497975	C8 H14 N O2	(M+H)+

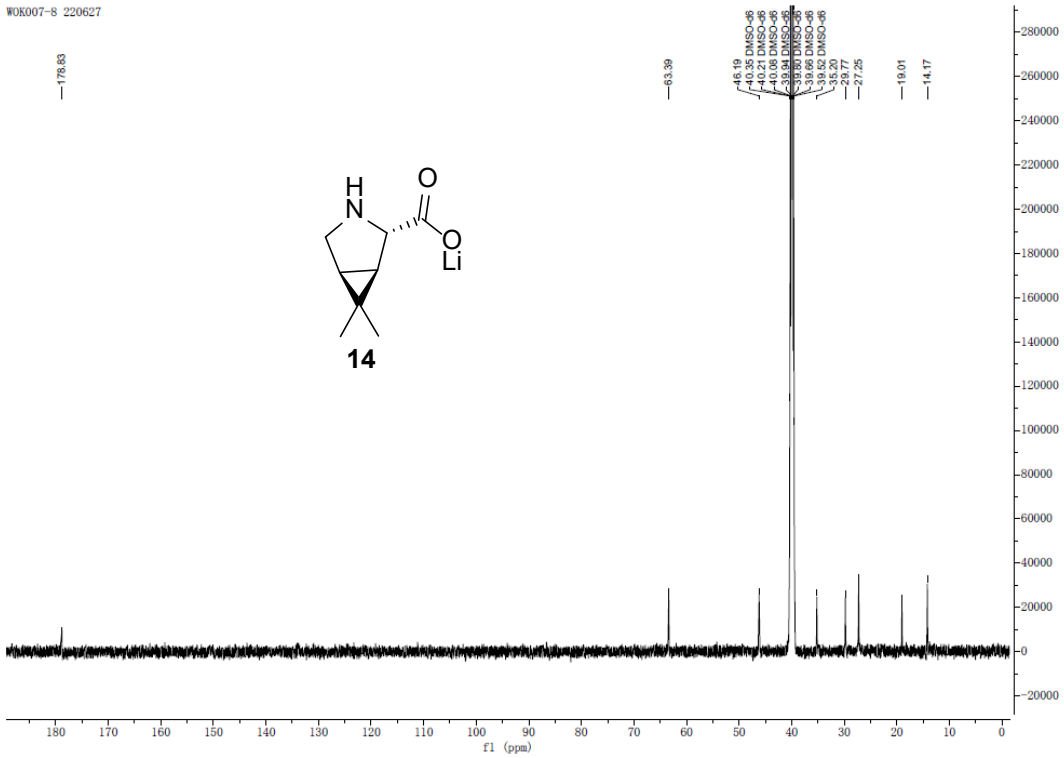
--- End Of Report ---

1.1.2 ^{1}H NMR (D_2O)



14

1.1.3 ^{13}C NMR (DMSO-d6)



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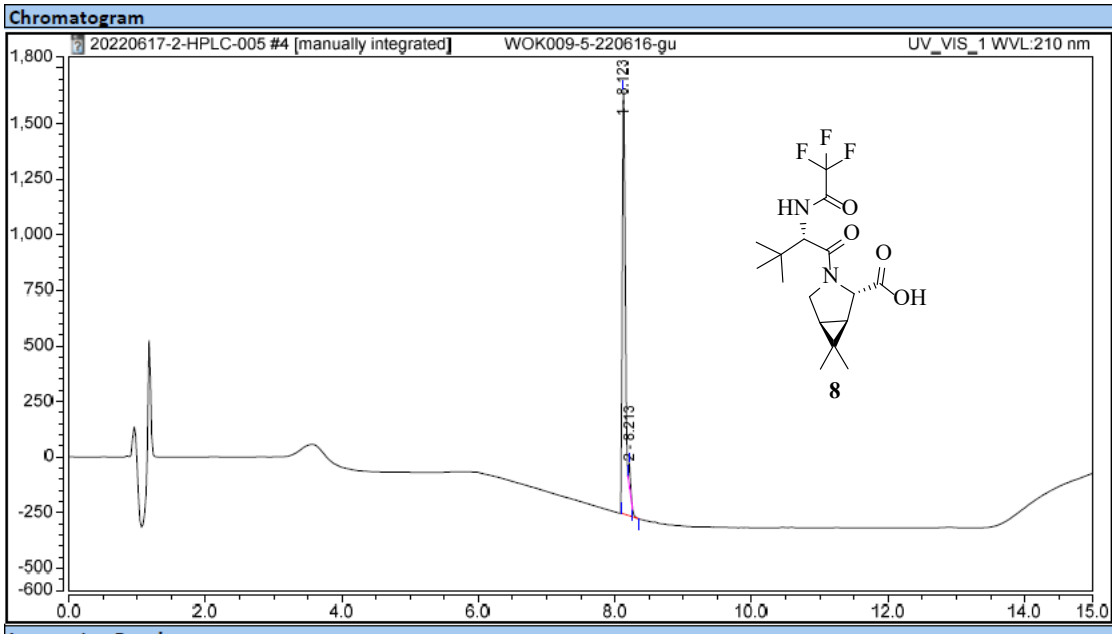
1.2 HPLC, HRMS, and NMR spectra of Compound 8

1.2.1 HPLC



8

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8.123	104.328	1900.607	96.93	94.66	n.a.
2		8.213	3.306	107.239	3.07	5.34	n.a.
Total:			**107.634**	**2007.846**	**100.00**	**100.00**	

1.2.2 HRMS

Qualitative Compound Report

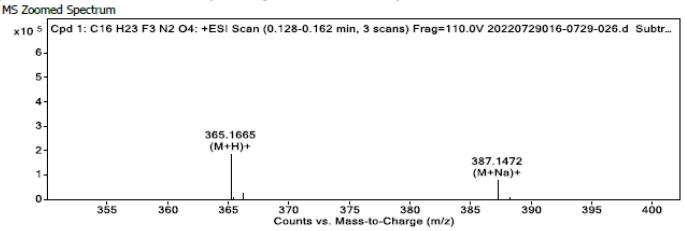
Data File	20220729016-0729-026.d	**Sample Name**	WOK009-5
Sample Type	Sample	**Position**	Vial 86
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220630
AcquiredTime	7/29/2022 2:47:51 PM	**DataFile**	D:\MassHunter\Data\2022-07\2022-07-29\20220729016-0729-026.d

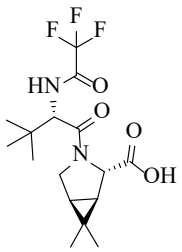
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C16 H23 F3 N2 O4	0.162	364.1591	188669	C16 H23 F3 N2 O4	364.161	-5.11

Compound Label	RT	Algorithm	Mass
Cpd 1: C16 H23 F3 N2 O4	0.162	Find By Formula	364.1591

MS Zoomed Spectrum





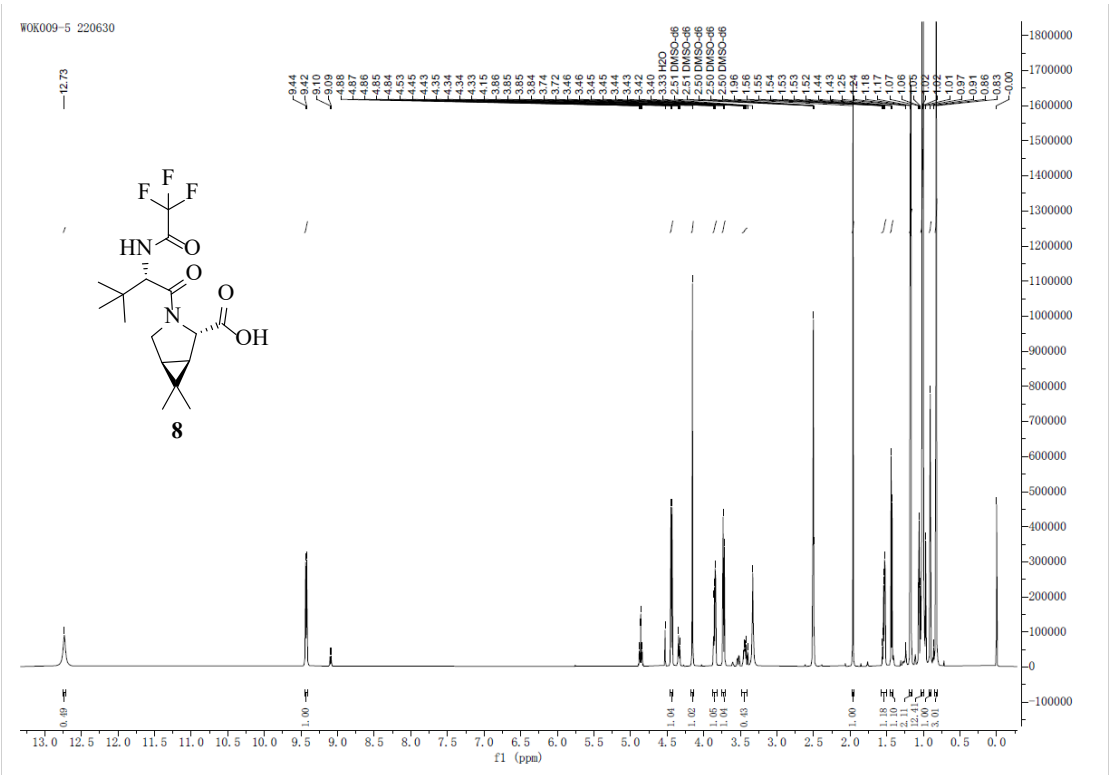
8

MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
365.1665	365.1683	-4.82	1	188669	C16 H24 F3 N2 O4	(M+H)+
387.1472	387.1502	-7.75	1	81677	C16 H23 F3 N2 Na O4	(M+Na)+

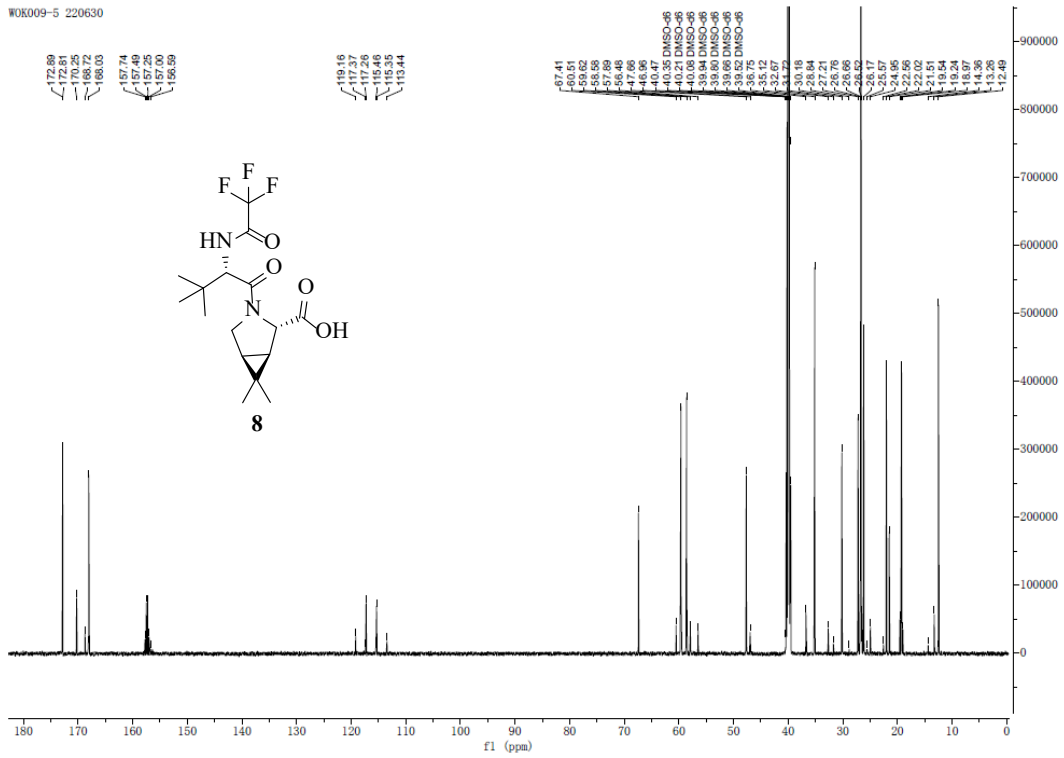
--- End Of Report ---

1.2.3 ^{1}H NMR (DMSO-d6)

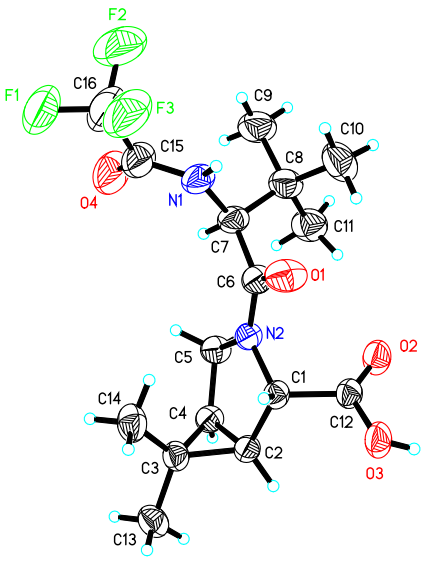


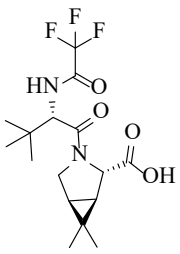
8

1.2.4 ^{13}C NMR (DMSO-d6)



1.2.5 SXRD





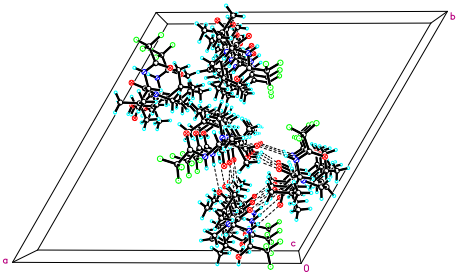


Table 1. Crystal data and structure refinement for cu_d8v22277_0m.

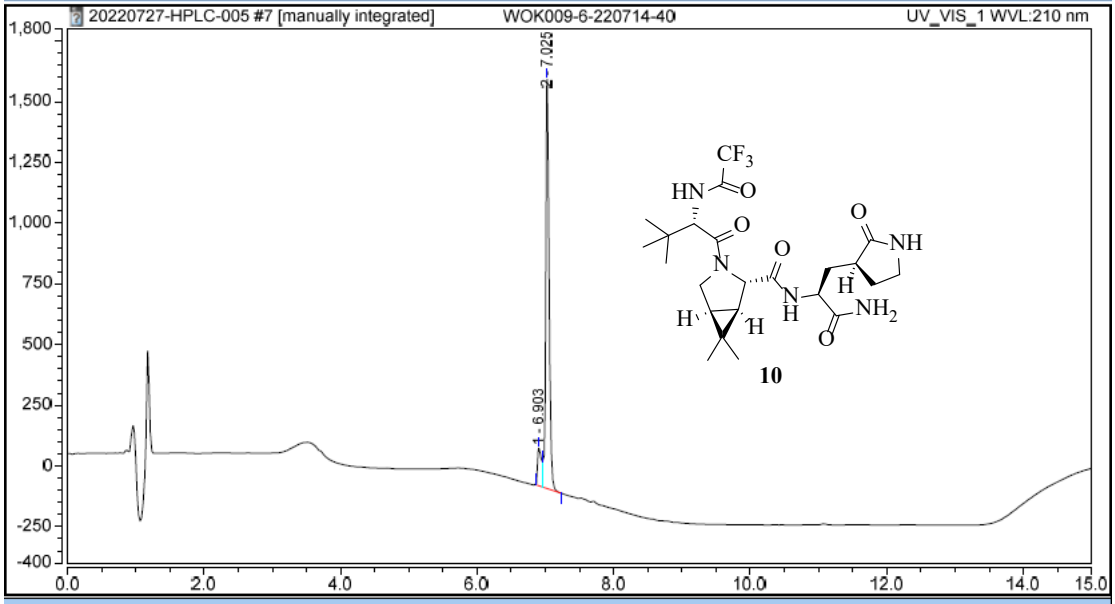
Identification code	cu_d8v22277_0m
Empirical formula	C16.33 H24.33 F3 N2 O4.33

Formula weight	375.04	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Trigonal	
Space group	R 3 :H	
Unit cell dimensions	a = 23.7973(8) Å	a= 90°.
	b = 23.7973(8) Å	b= 90°.
	c = 10.5714(4) Å	g = 120°.
Volume	5184.6(4) $Å^3$	
Z	9	
Density (calculated)	1.081 Mg/m^3	
Absorption coefficient	0.806 mm^{-1}	
F(000)	1782	
Crystal size	0.200 x 0.150 x 0.120 mm^3	
Theta range for data collection	7.061 to 67.388°.	
Index ranges	-26<=h<=28, -28<=k<=25, -12<=l<=12	
Reflections collected	20262	
Independent reflections	4076 [R(int) = 0.0617]	
Completeness to theta = 67.679°	98.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.4876	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4076 / 136 / 300	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0565, wR2 = 0.1578	
R indices (all data)	R1 = 0.0593, wR2 = 0.1635	
Absolute structure parameter	0.02(10)	
Extinction coefficient	0.0107(14)	
Largest diff. peak and hole	0.218 and -0.174 $e.Å^{-3}$	

1.3 HPLC data, HRMS, and NMR of Compound 10

1.3.1.1 HPLC

Chromatogram



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Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.903	9.804	155.015	9.39	8.41	n.a.
2		7.025	94.633	1687.173	90.61	91.59	n.a.
Total:			**104.437**	**1842.188**	**100.00**	**100.00**	

1.3.2 HRMS

Qualitative Compound Report

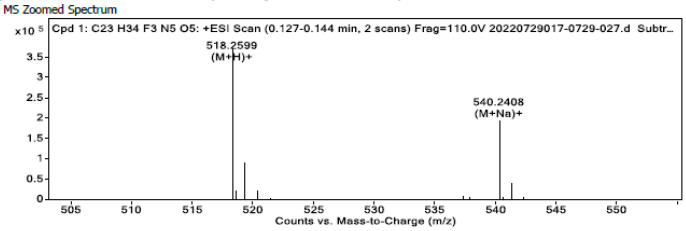
Data File	20220729017-0729-027.d	**Sample Name**	WOK009-6
Sample Type	Sample	**Position**	Vial 87
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220714
AcquiredTime	7/29/2022 2:53:07 PM	**DataFile**	D:\MassHunter\Data\2022-07\2022-07-29\20220729017-0729-027.d

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C23 H34 F3 N5 O5	0.144	517.2525	194751	C23 H34 F3 N5 O5	517.2512	2.43

Compound Label	RT	Algorithm	Mass
Cpd 1: C23 H34 F3 N5 O5	0.144	Find By Formula	517.2525

MS Zoomed Spectrum



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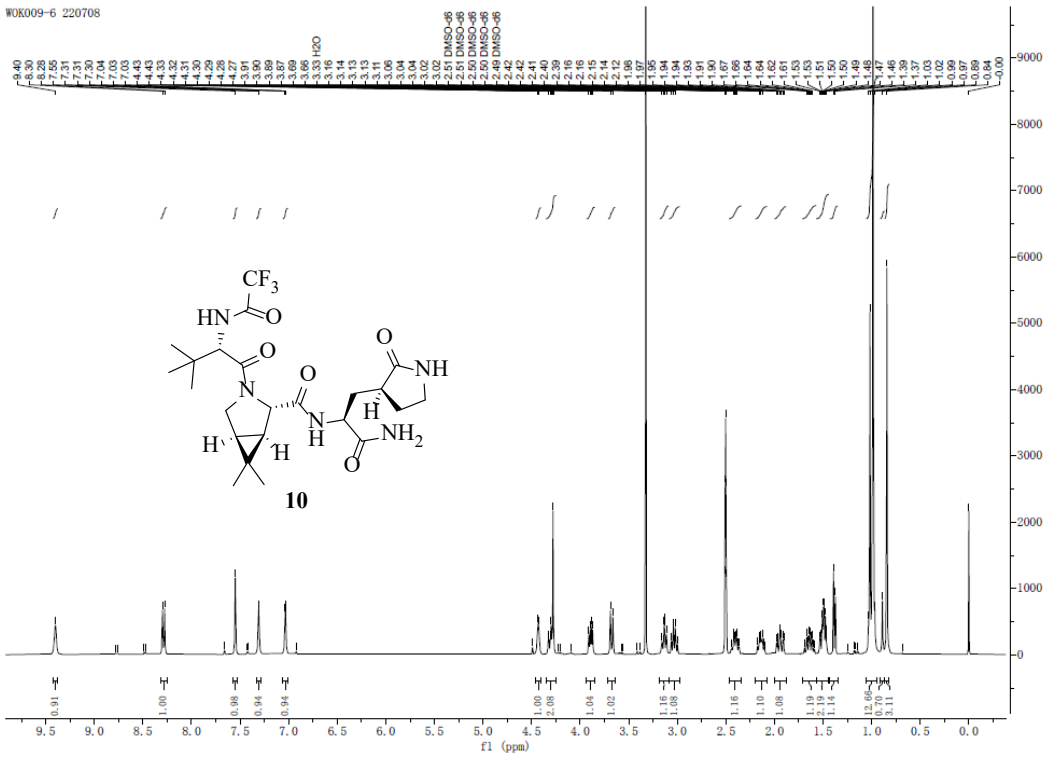
MS Spectrum Peak List

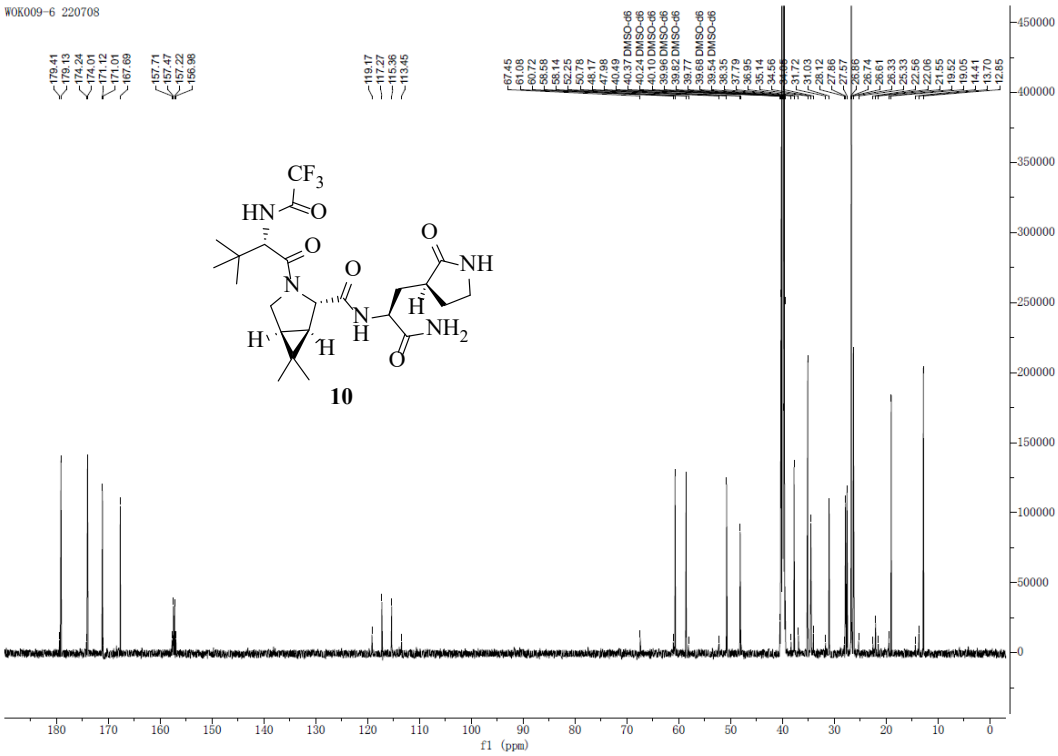
m/z	Calc m/z	Diff(ppm)	Abund	Formula	Ion
518.2599	518.2585	2.7	373635	C23 H35 F3 N5 O5	(M+H)+
540.2408	540.2404	0.67	194751	C23 H34 F3 N5 Na O5	(M+Na)+

--- End Of Report ---

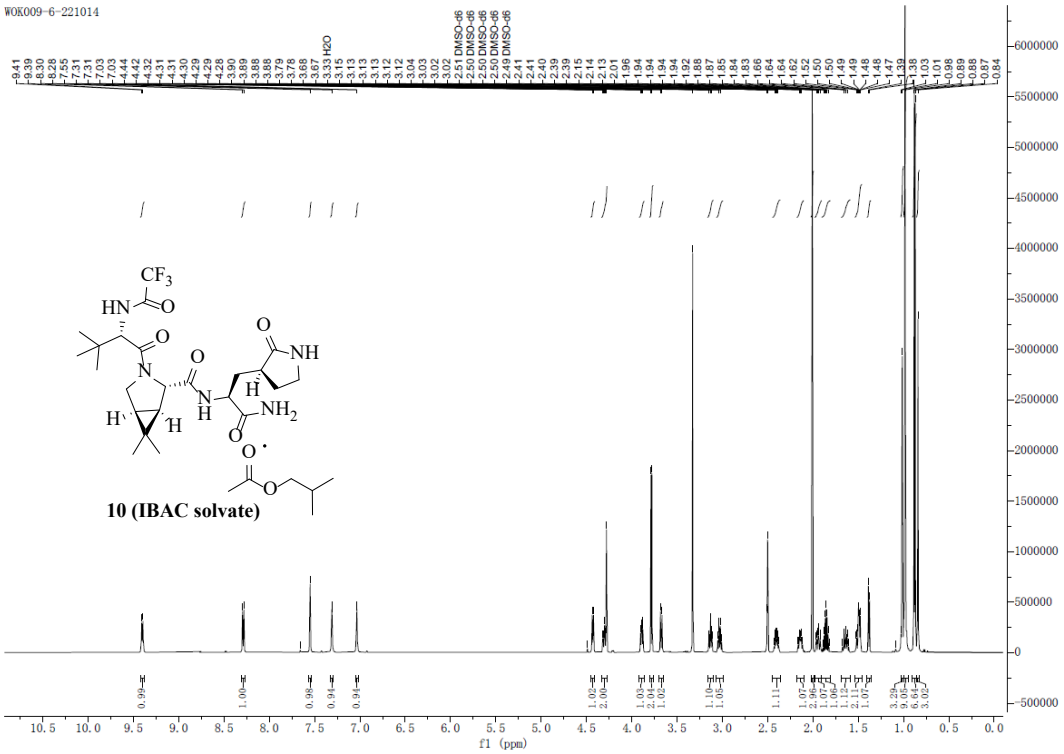
1.3.3 ^{1}H NMR(DMSO-d6)



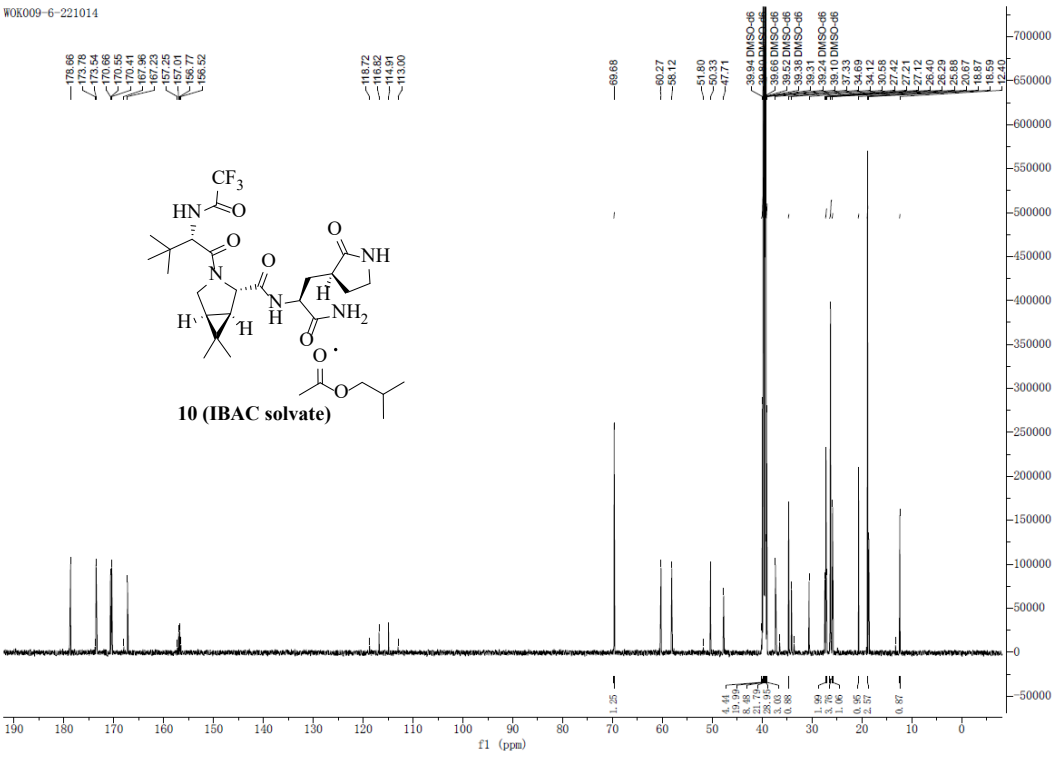
1.3.4 ^{13}C NMR(DMSO-d6)



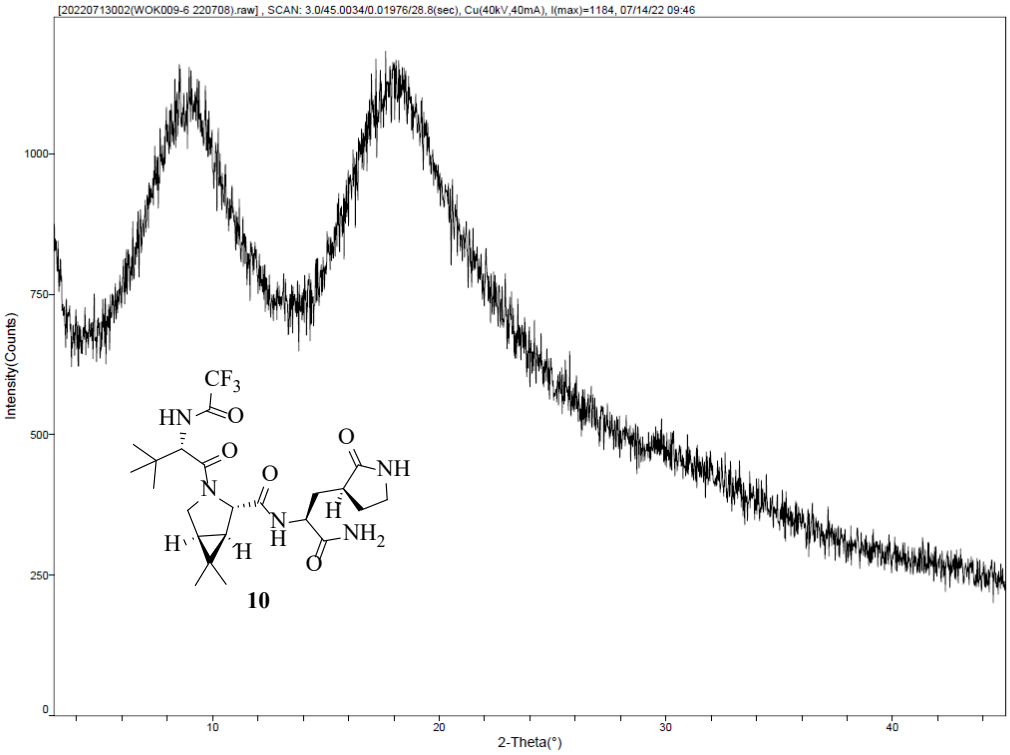
1.3.5 ^{1}H NMR(DMSO-d6)



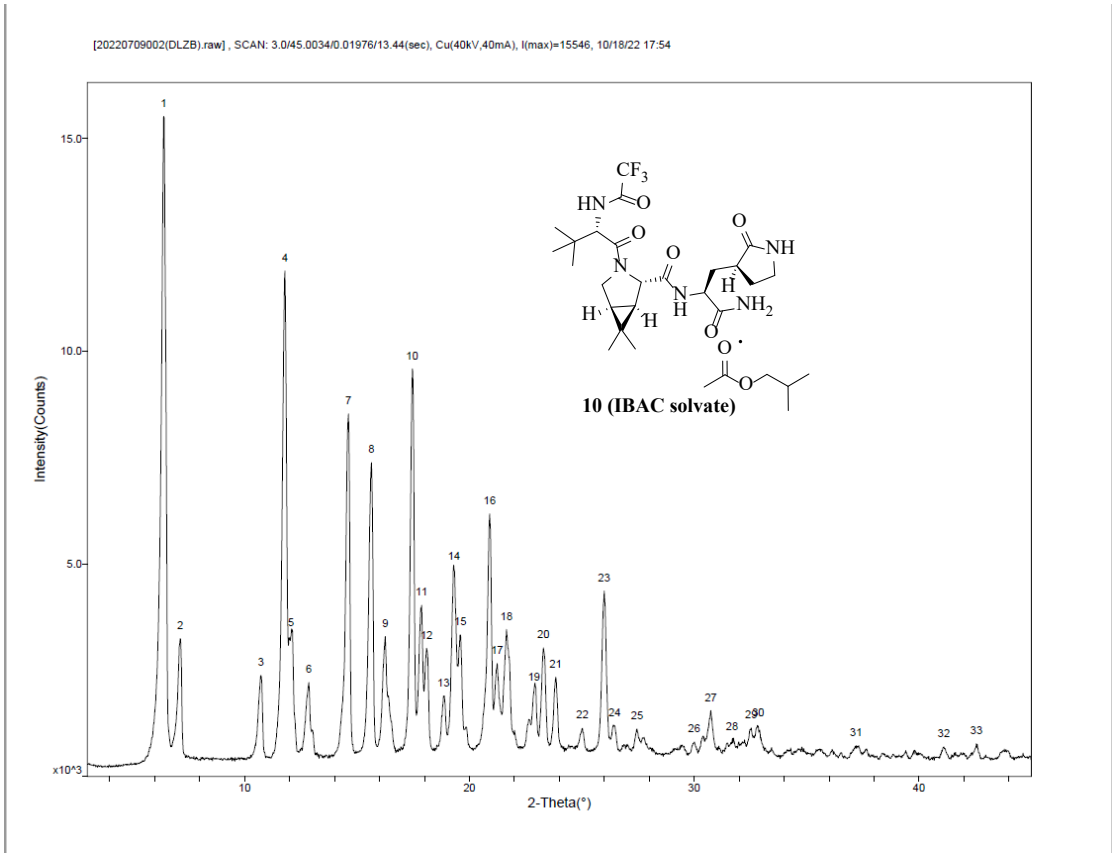
1.3.6 ^{13}C NMR(DMSO-d6)



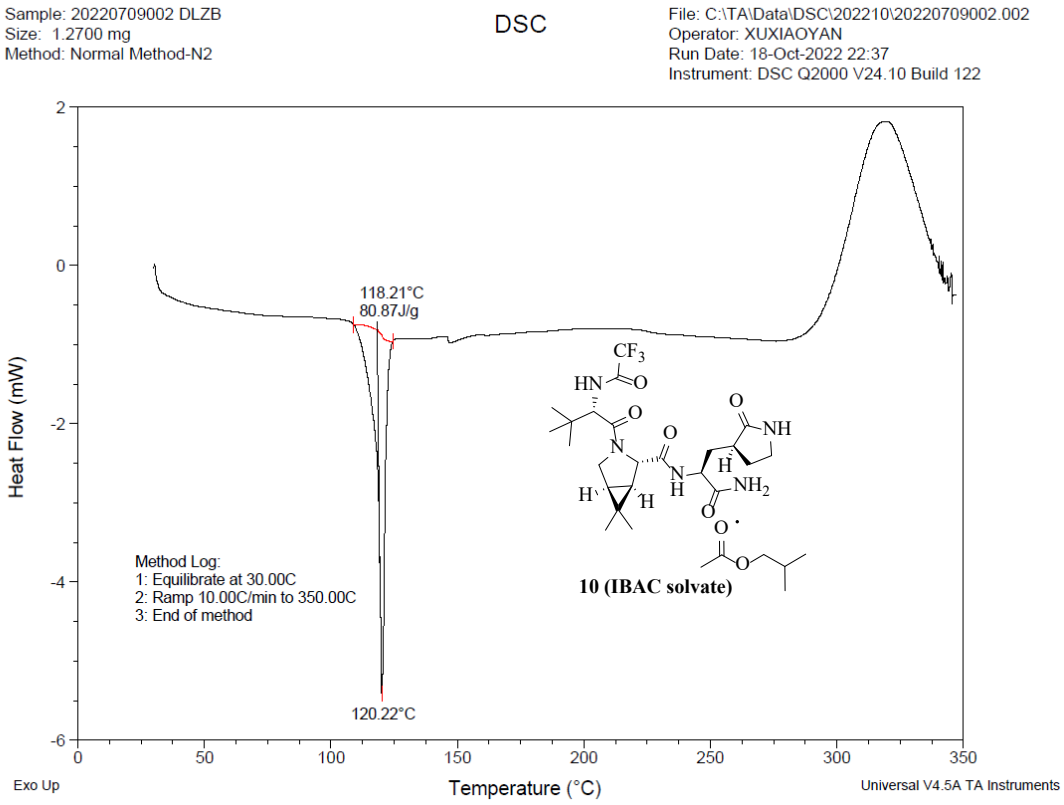
1.3.7 XRPD



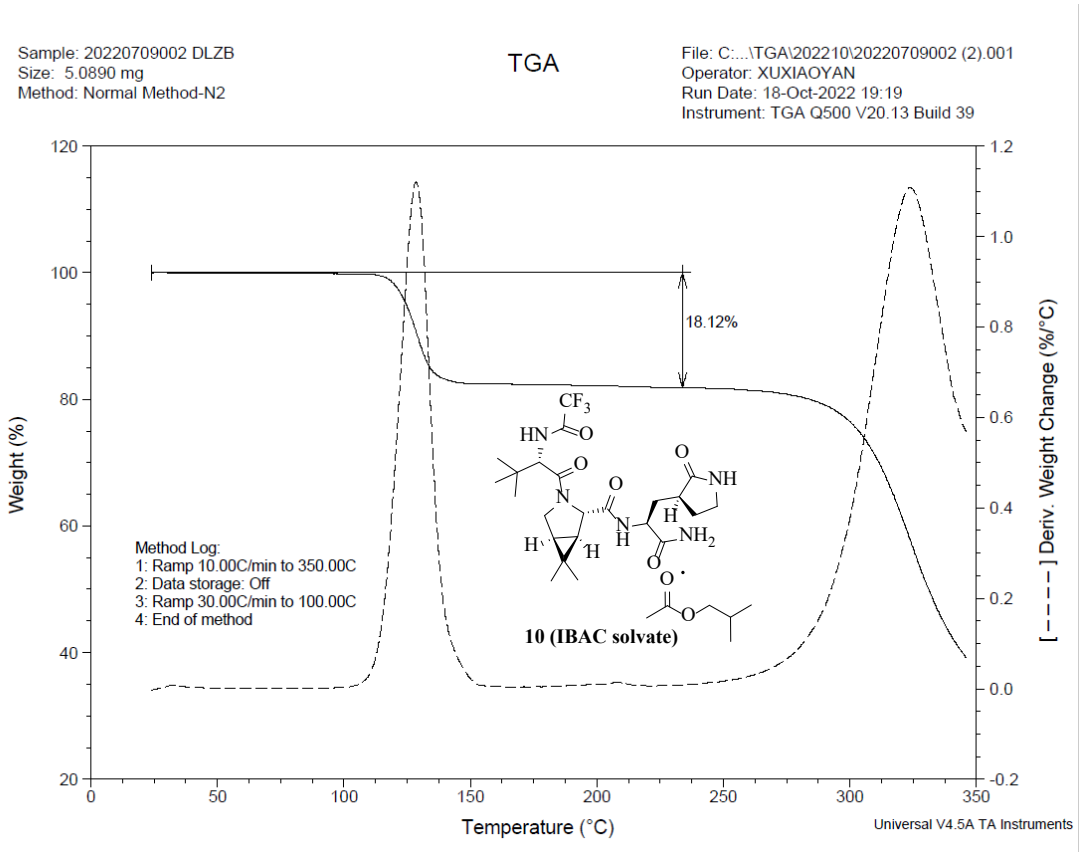
1.3.8 XRPD



1.3.9 DSC



1.3.10 TGA

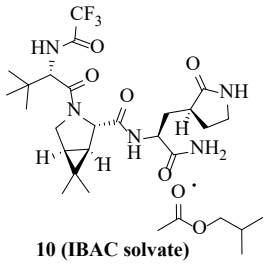


1.3.11 SXRD

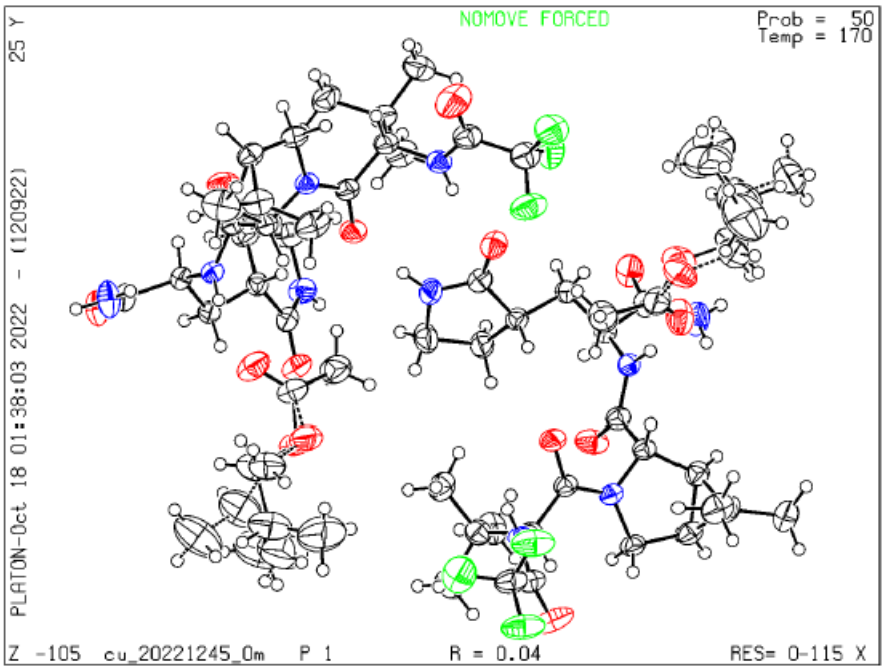
cu_20221245_0m

Table 1 Crystal data and structure refinement for cu_20221245_0m.

Identification code	cu_20221245_0m
Empirical formula	$C_{29}H_{46}F_3N_5O_7$
Formula weight	633.71
Temperature/K	170.00
Crystal system	triclinic
Space group	P1
a/Å	14.6382(13)
b/Å	8.7434(8)
c/Å	14.8811(14)
α/°	90.011(2)
β/°	112.727(4)
γ/°	90.015(3)
Volume/Å^3	1756.7(3)
Z	2
ρ_{calc}g/cm^3	1.198
μ/mm^{-1}	0.811
F(000)	676.0
Crystal size/mm^3	0.15 × 0.13 × 0.12
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.44 to 149.72
Index ranges	-18 ≤ h ≤ 18, -10 ≤ k ≤ 10, -18 ≤ l ≤ 18
Reflections collected	33066
Independent reflections	13052 [R_{int} = 0.0484, R_{sigma} = 0.0519]
Data/restraints/parameters	13052/329/905
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0428, wR_2 = 0.1071
Final R indexes [all data]	R_1 = 0.0488, wR_2 = 0.1148
Largest diff. peak/hole / e Å^{-3}	0.44/-0.20
Flack parameter	0.17(7)



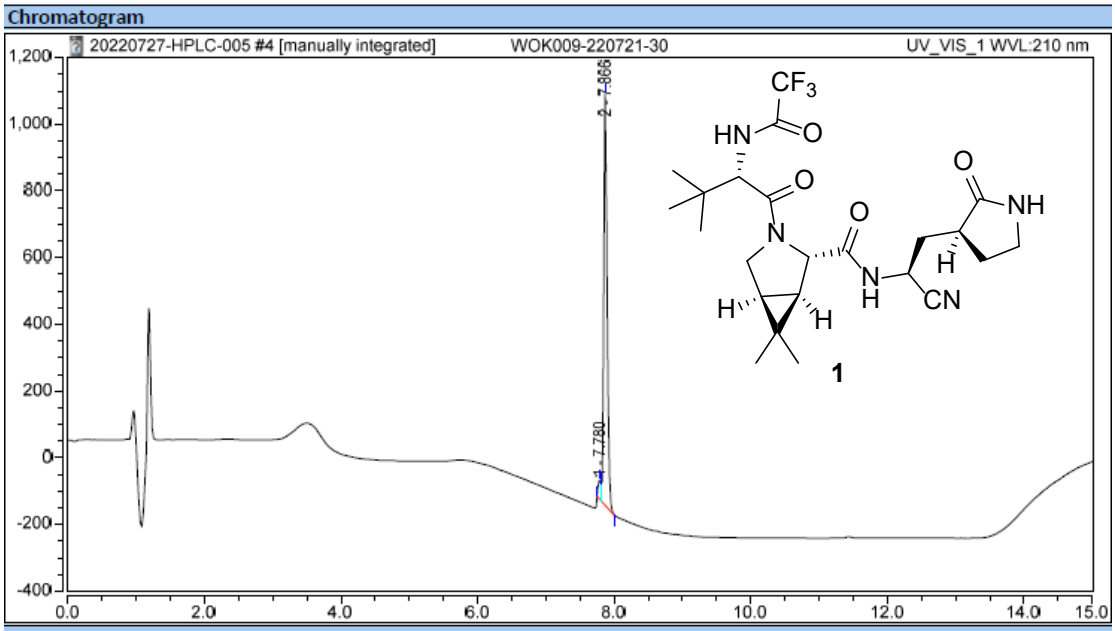
10 (IBAC solvate)



2. HPLC, HRMS, and NMR Spectra of Nirmatrelvir (**1**)

2.1 HPLC, HRMS, NMR of nirmatrelvir (1)

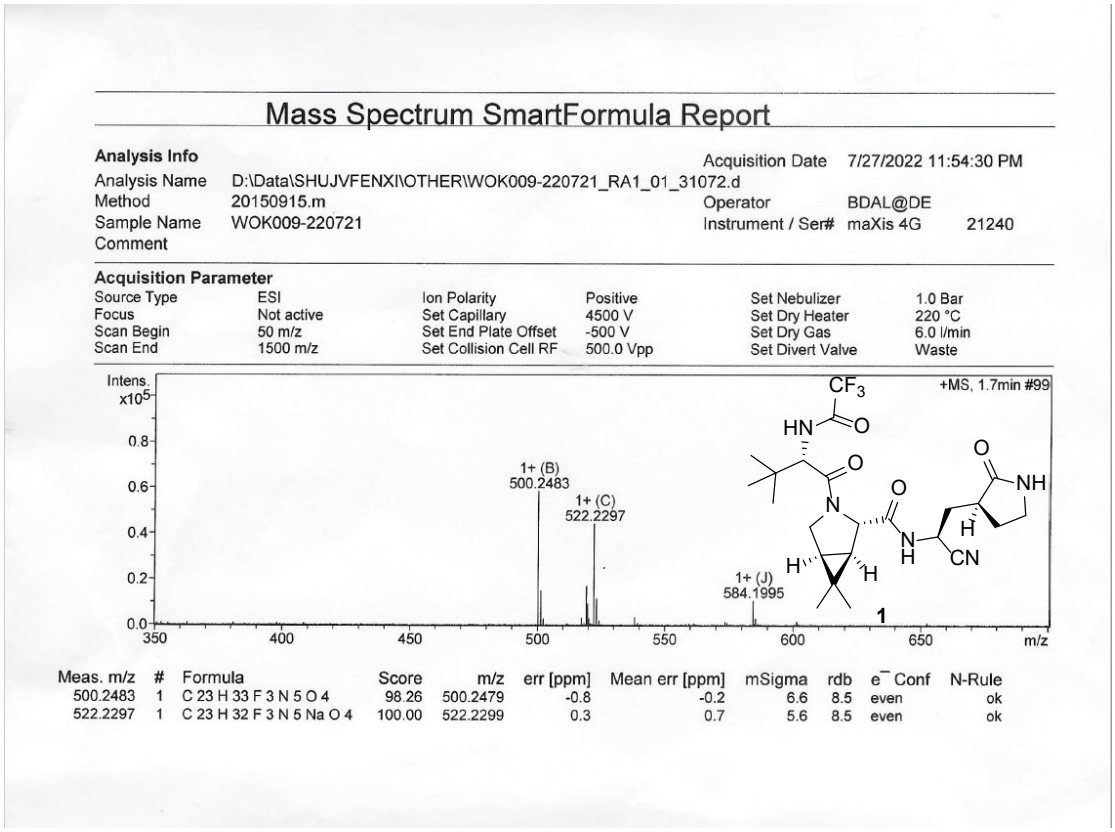
2.1.1 HPLC data



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.780	2.823	55.877	3.97	4.34	n.a.
2		7.866	68.214	1230.999	96.03	95.66	n.a.
Total:			**71.037**	**1286.876**	**100.00**	**100.00**	

2.1.2 HRMS



Mass Spectrum SmartFormula Report

Analysis Info

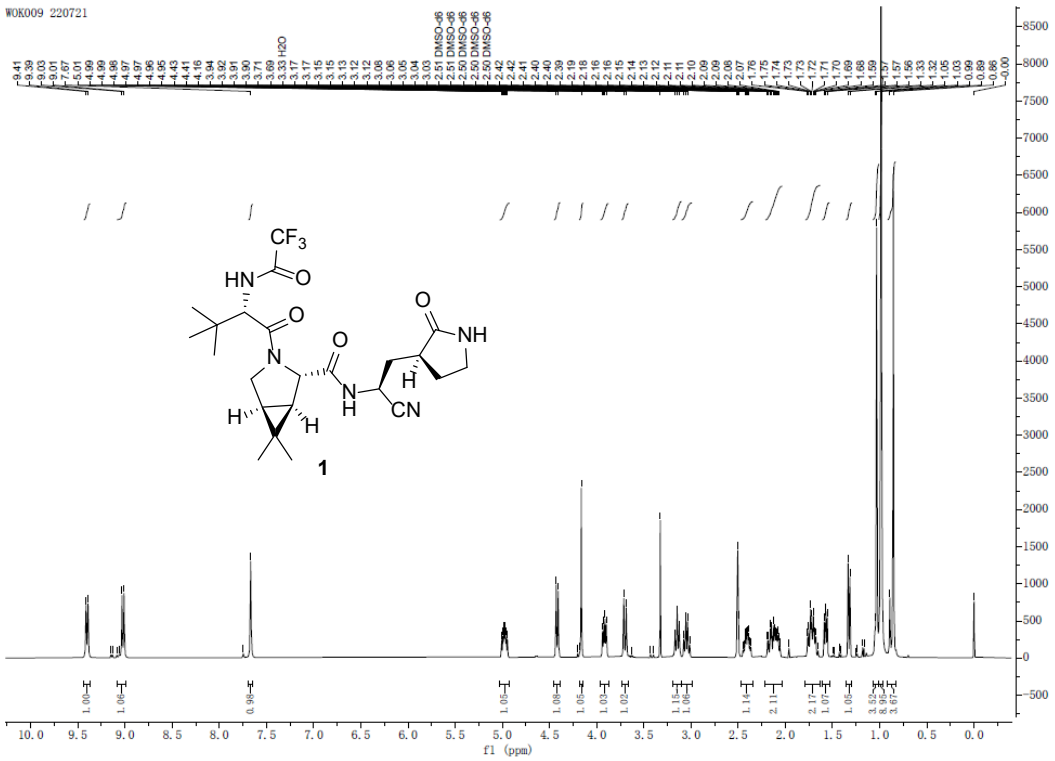
Analysis Name	D:\Data\SHUJVFENXI\OTHER\WOK009-220721_RA1_01_31072.d	Acquisition Date	7/27/2022 11:54:30 PM
Method	20150915.m	Operator	BDAL@DE
Sample Name	WOK009-220721	Instrument / Ser#	maXis 4G 21240
Comment			

Acquisition Parameter

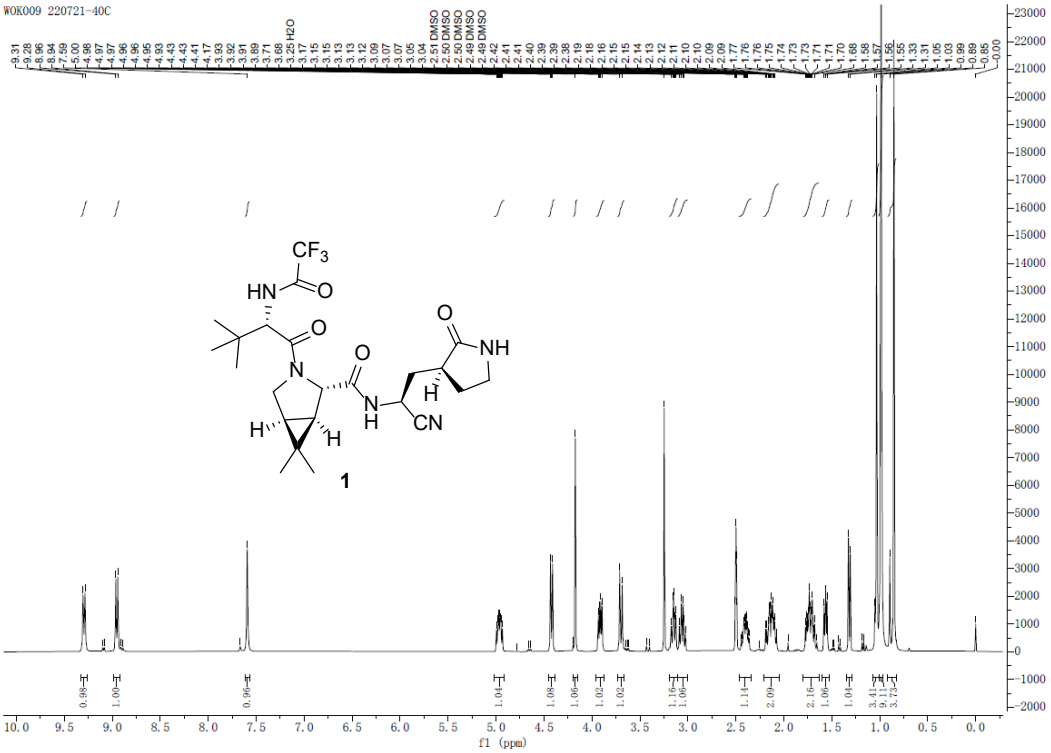
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.0 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	6.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	500.0 Vpp	Set Divert Valve	Waste

Meas. m/z	#	Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
500.2483	1	C 23 H 33 F 3 N 5 O 4	98.26	500.2479	-0.8	-0.2	6.6	8.5	even	ok
522.2297	1	C 23 H 32 F 3 N 5 Na O 4	100.00	522.2299	0.3	0.7	5.6	8.5	even	ok

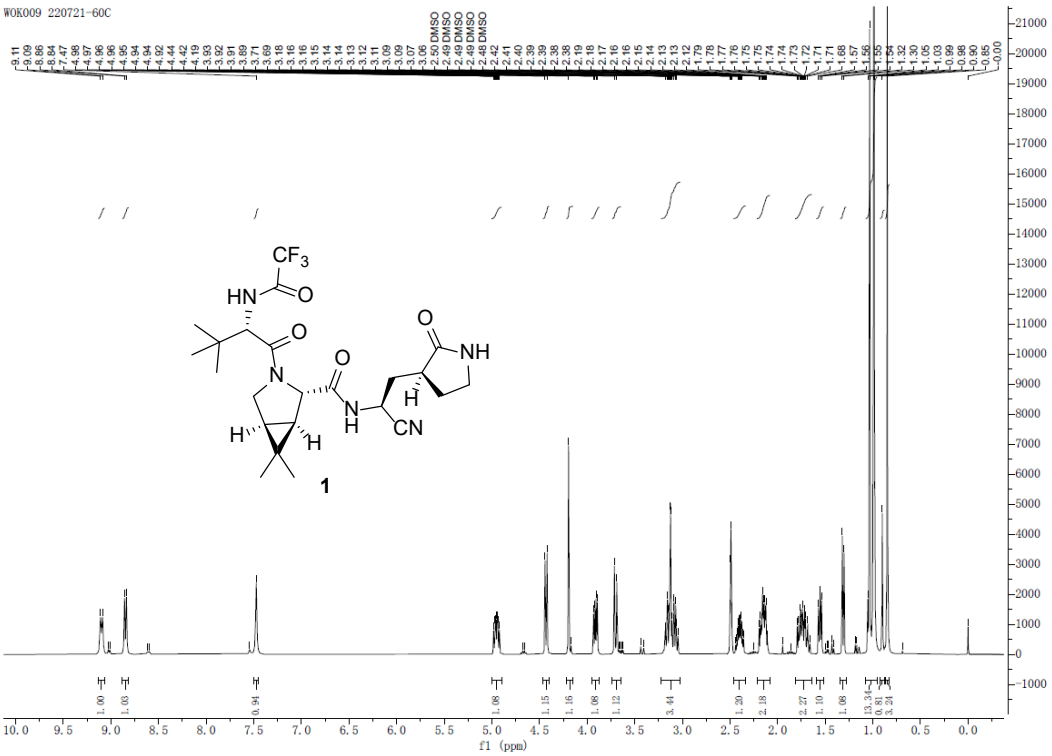
2.1.3 ^{1}H NMR ((DMSO-d6)



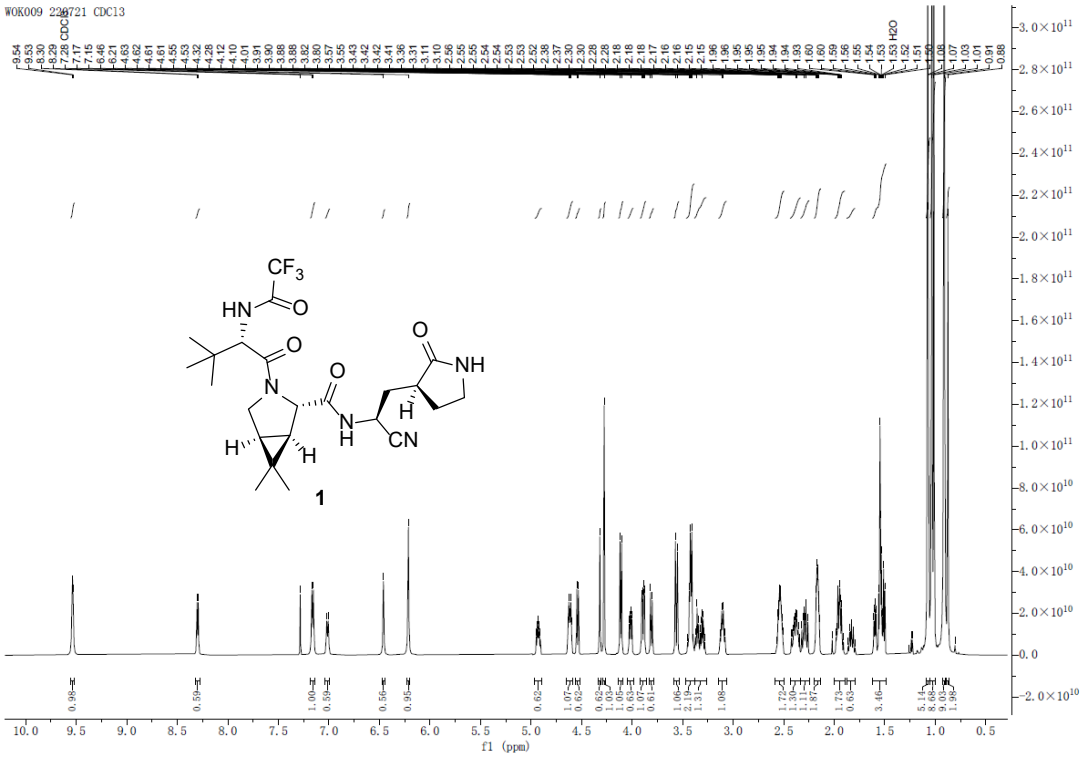
2.1.4 ^{1}H NMR ((DMSO-d6-40℃)



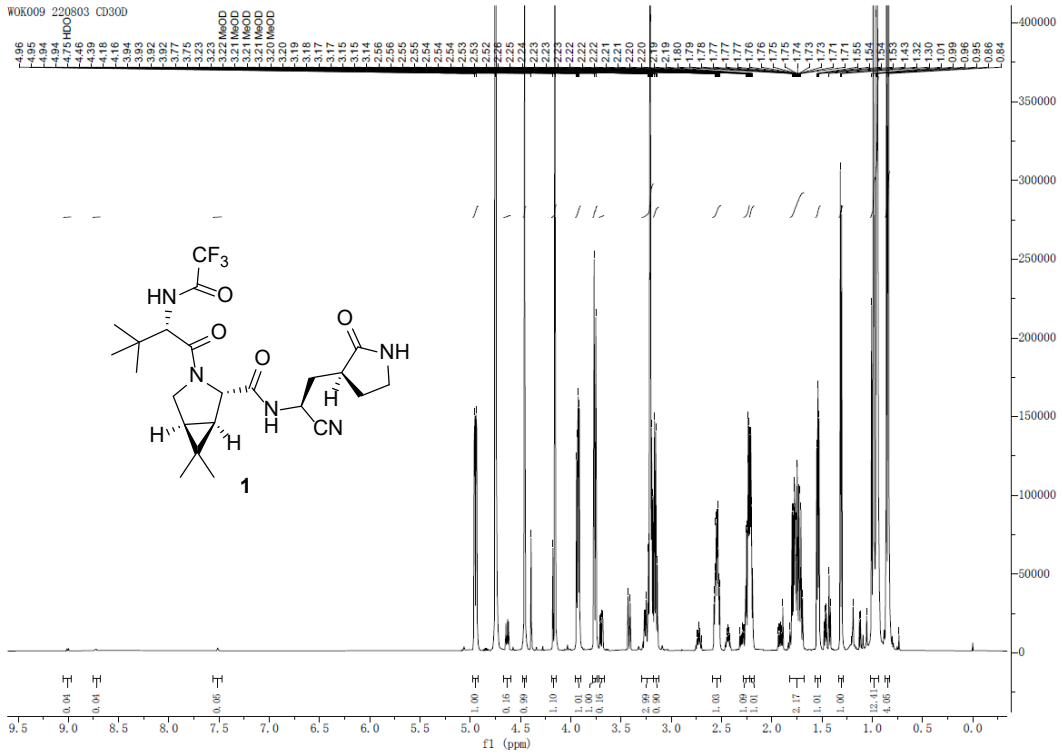
2.1.5 ^{1}H NMR ((DMSO-d6-60℃)



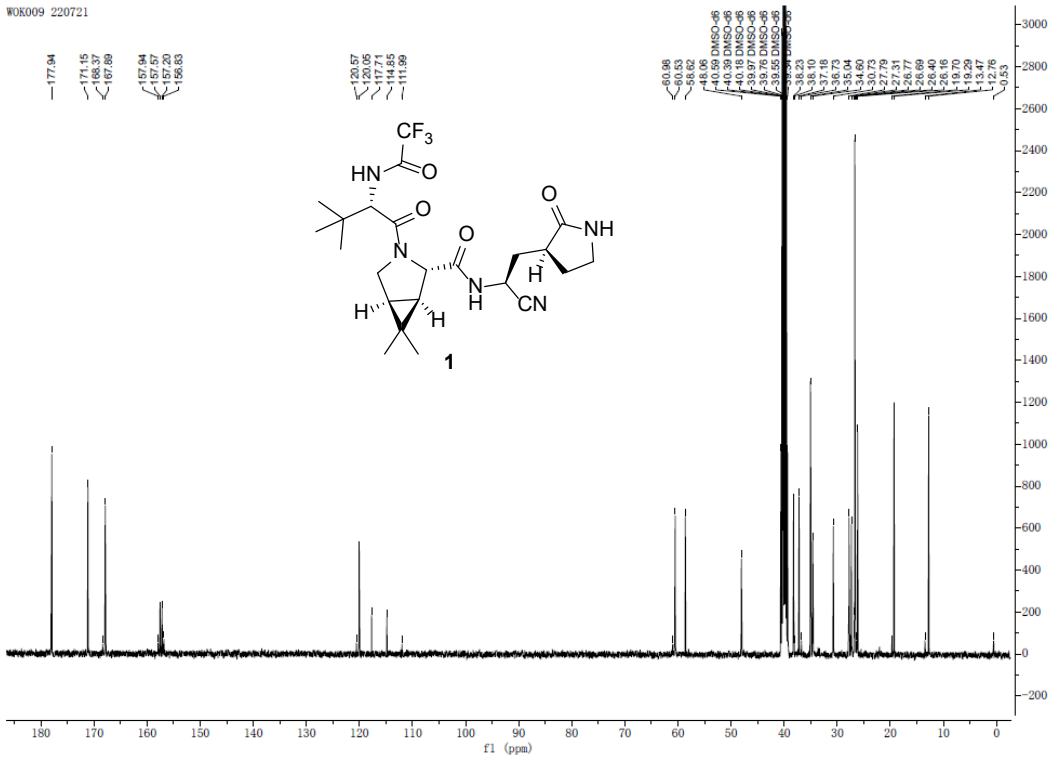
2.1.6 ^{1}H NMR ($CDCl_3$)



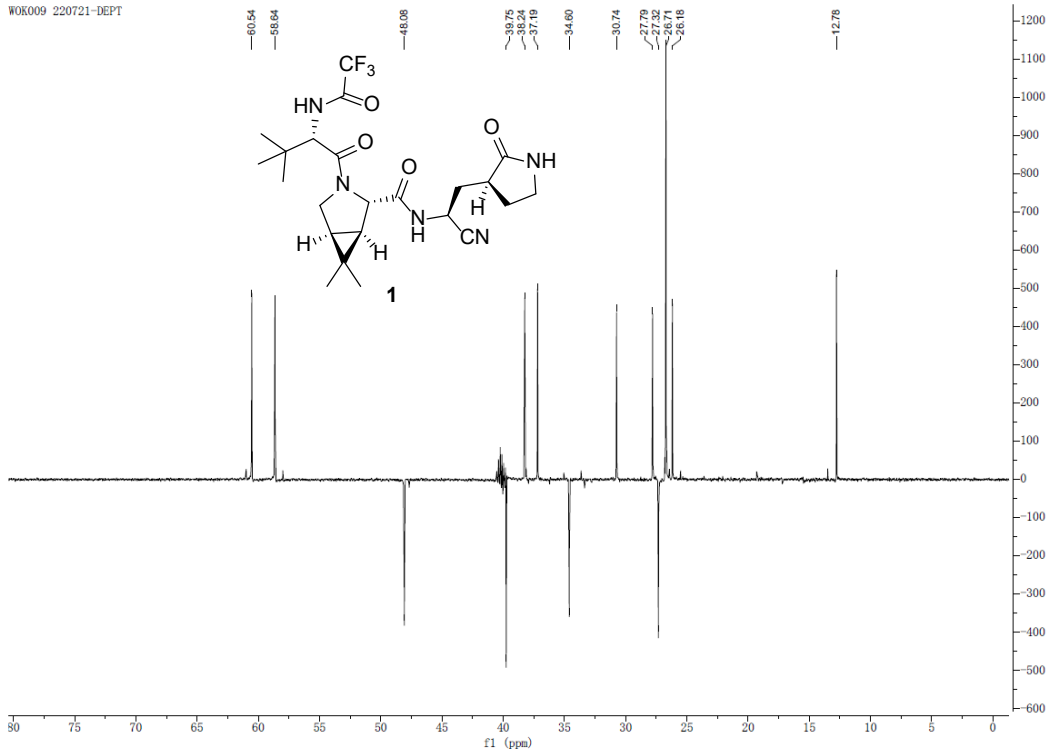
2.1.7 ^{1}H NMR (CD_3OD)



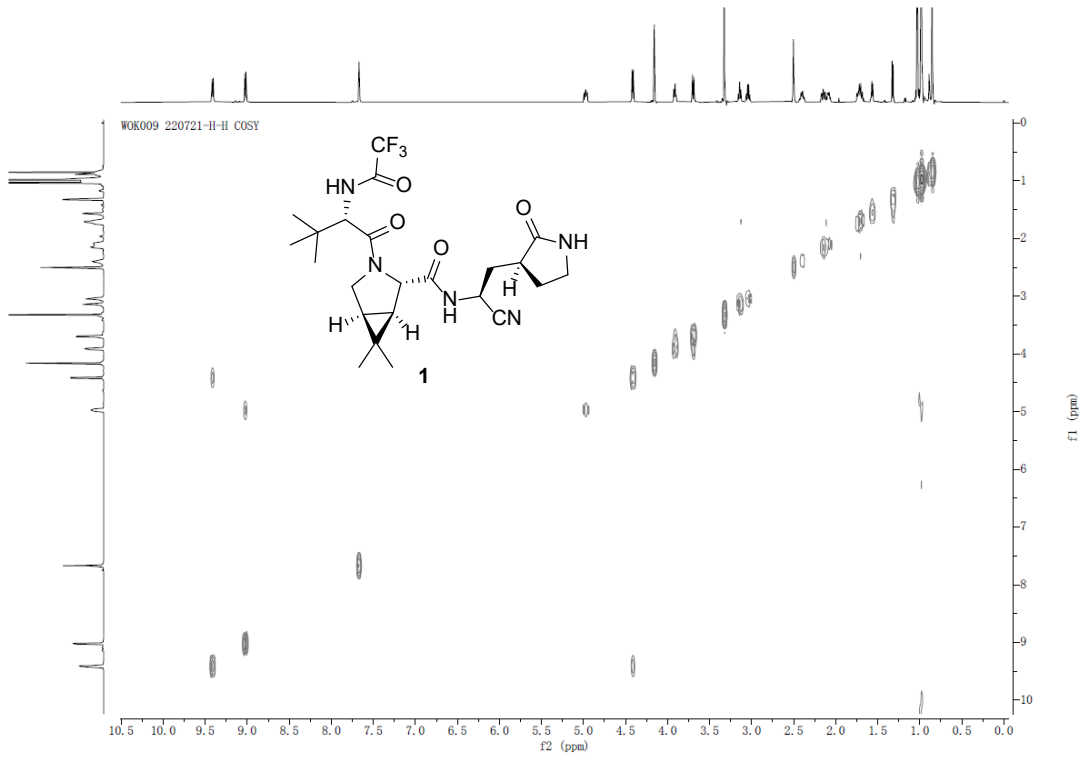
2.1.8 ^{13}C NMR (DMSO-d6)



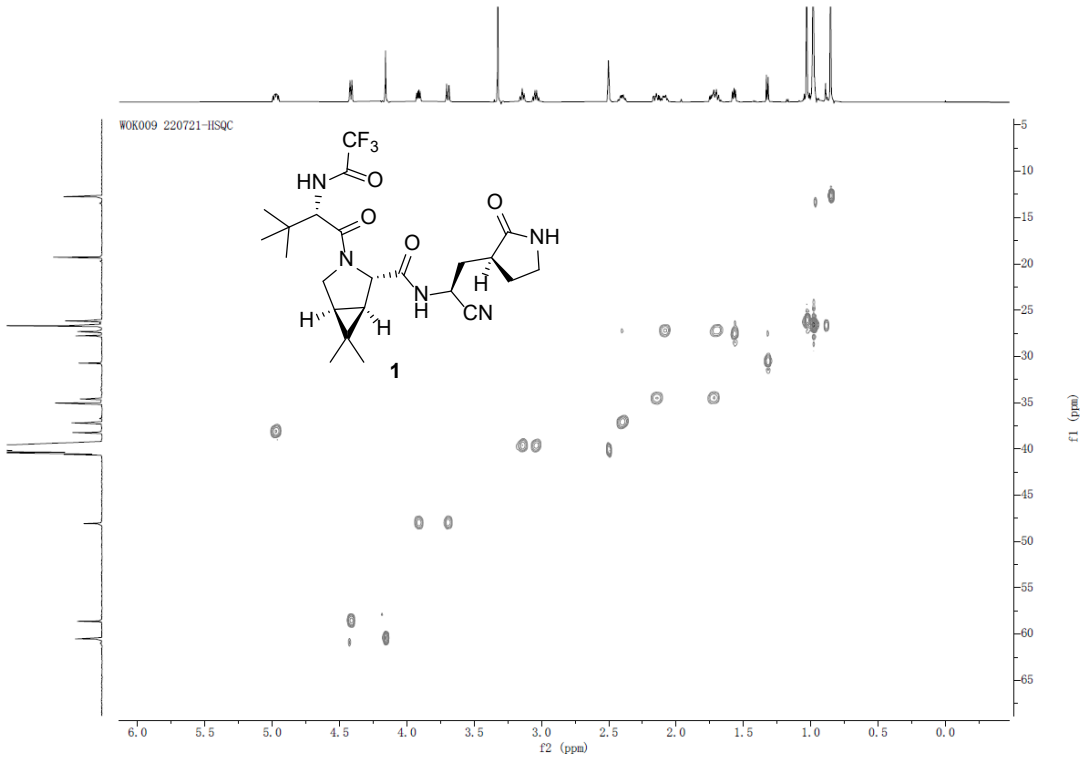
2.1.9 DEPT NMR (DMSO-d6)



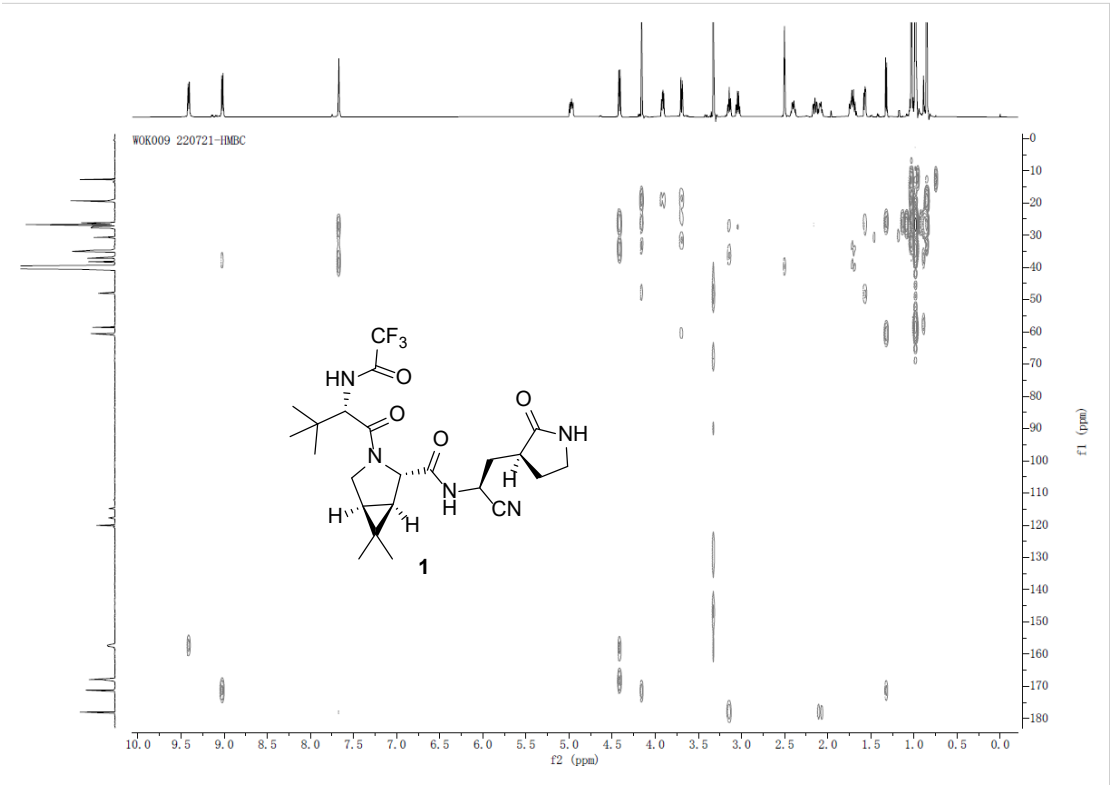
2.1.10 ^{1}H-^{1}H COSY (DMSO-d6)



2.1.11 HSQC (DMSO-d6)

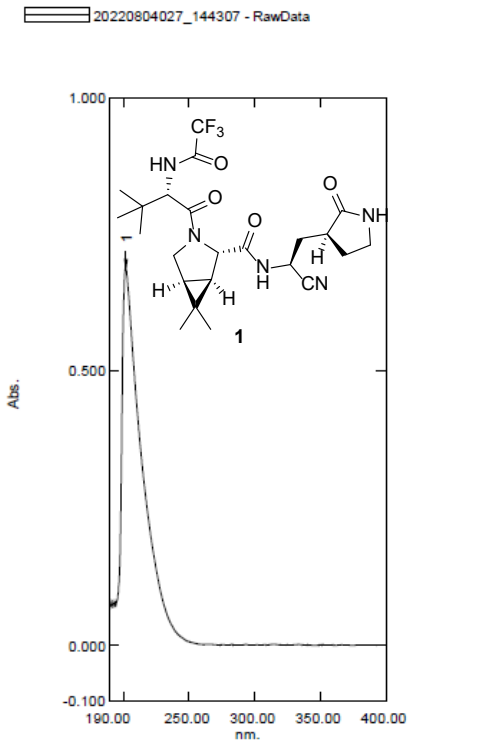


2.1.12 HMBC (DMSO-d6)



2.2 UV, FT-IR (KBr), DSC, TGA, PXRD of Nirmatrelvir (1)

2.2.1 UV



No.	P/V	Wavelength	Abs.	Description
1	T	202.10	0.691	

Software Information
Software Name: UVProbe
Version: 2.52
Mode: LabSolutions

Data Information
Data is: Original
Analyst: hanru
Date/Time: 08/10/2022 02:45:15 PM
Comments:

Instrument Information
Instrument Name: ACQ-3F-010
Instrument Type: UV-2600 Series
Model (S/N): UV-2600 (A11665000543)

[Measurement Properties]
Wavelength Range (nm.): 190.00 to 400.00
Scan Speed: Fast
Sampling Interval: 0.1
Auto Sampling Interval: Disabled
Scan Mode: Auto

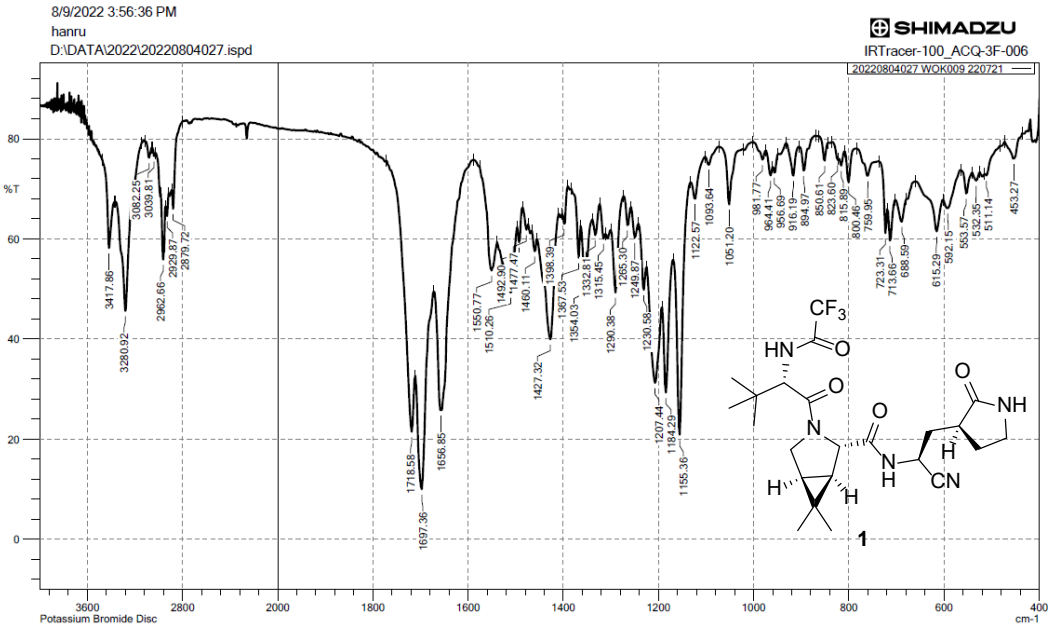
[Instrument Properties]
Instrument Type: UV-2600 Series
Measuring Mode: Absorbance
Slit Width: 2.0
Accumulation time: 0.1 sec.
Light Source Change Wavelength: 313.0 nm
Detector Unit: Direct
S/R Exchange: Normal
Stair Correction: OFF

[Attachment Properties]
Attachment: None

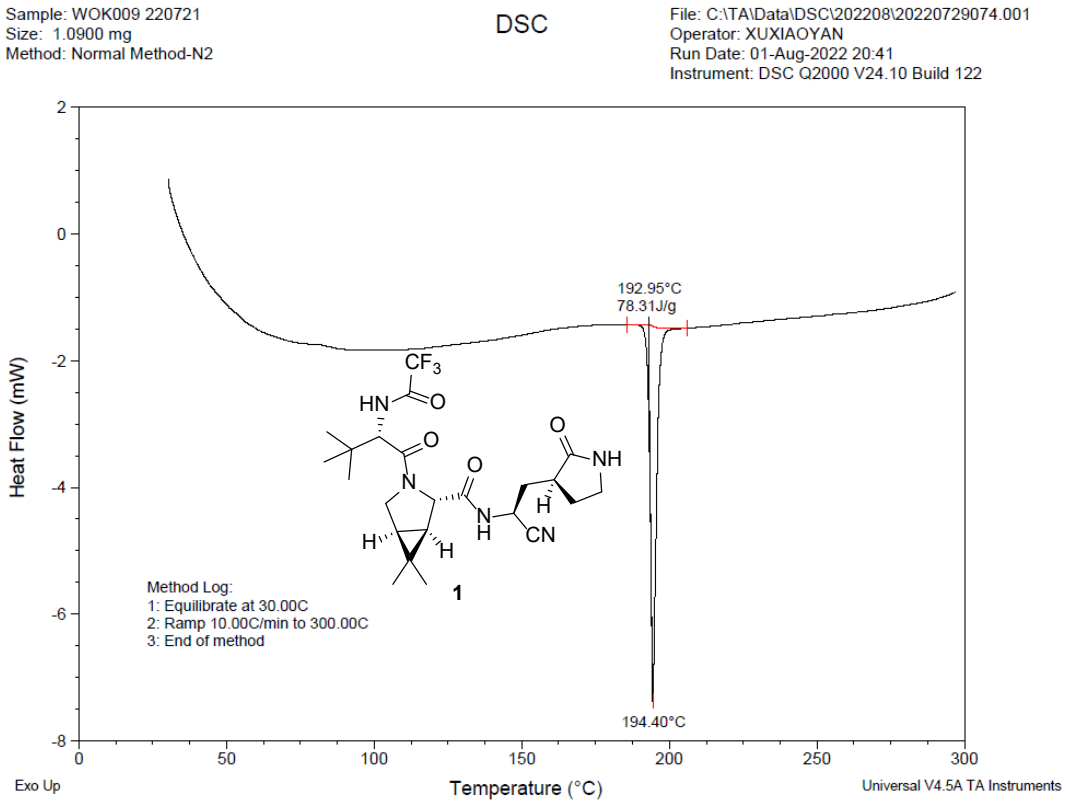
[Operation]
Threshold: 0.0100000
Points: 4
InterPolate: Disabled
Average: Disabled

[Sample Preparation Properties]
Weight: 13.03mg
Volume: 25ml
Dilution: 25
Path Length:
Additional Information: Sample name:WOK009
Lot:220721
No:20220804027
Solvent:Methanol

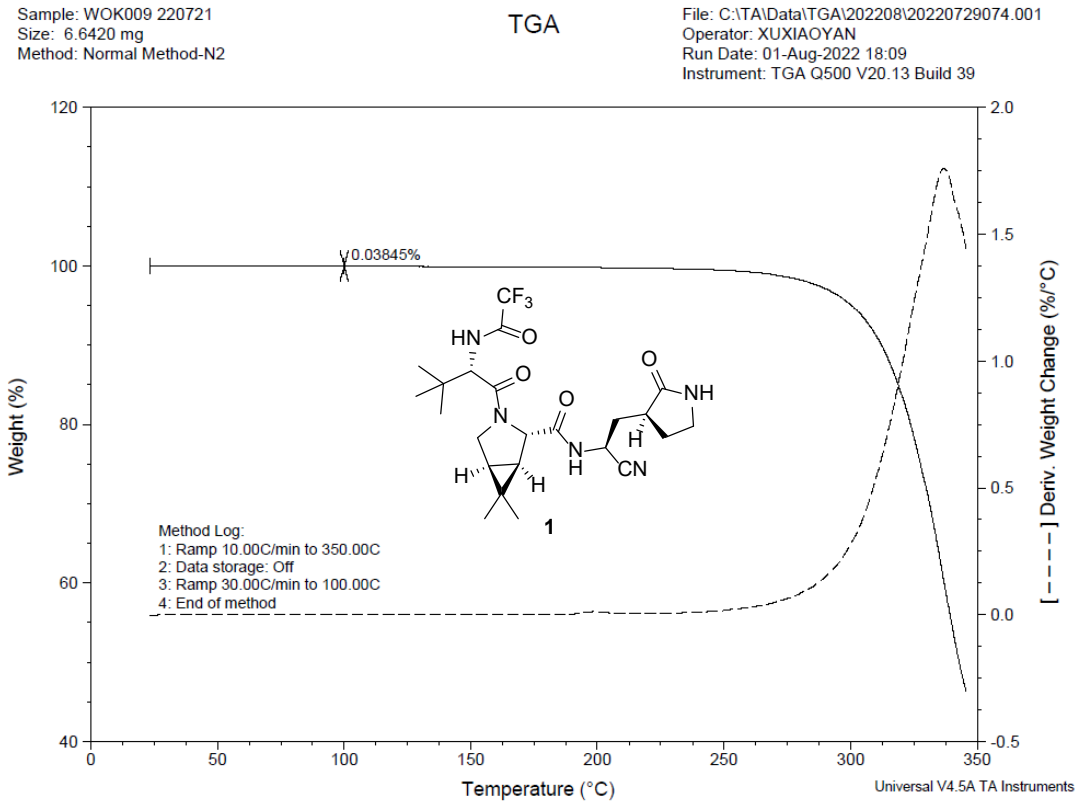
2.2.2 FT-IR (KBr)



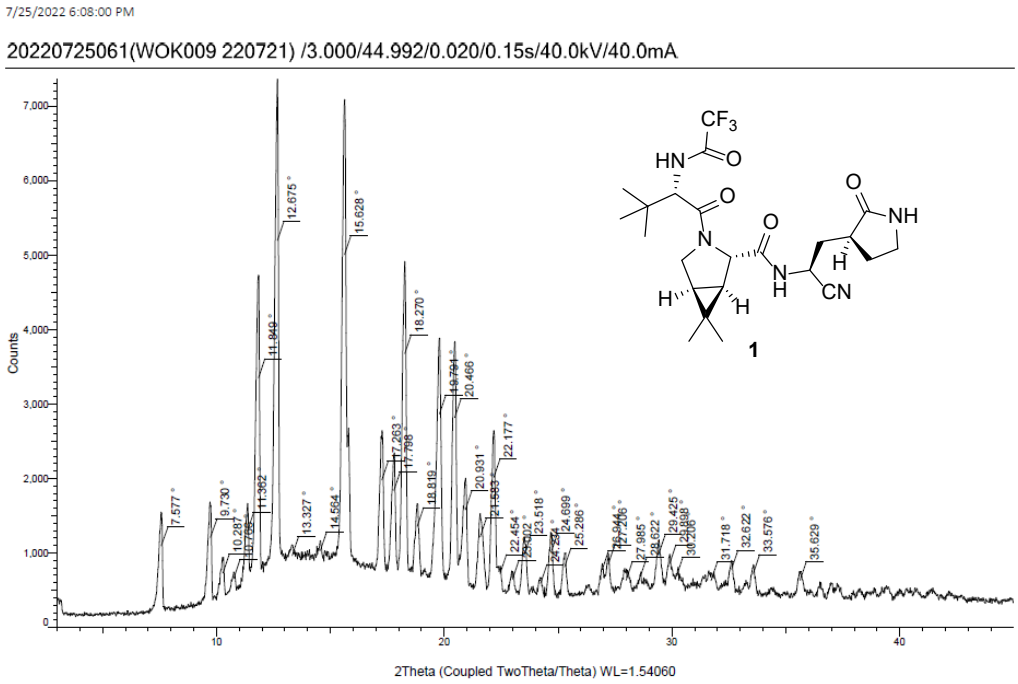
2.2.3 DSC



2.2.4 TGA



2.2.5 XRPD


7/25/2022 6:08:00 PM
20220725061(WOK009 220721) /3.000/44.992/0.020/0.15s/40.0kV/40.0mA
Counts
2Theta (Coupled TwoTheta/Theta) WL=1.54060
1

7/25/2022 6:08:00 PM

20220725061(WOK009 220721)
3.000/44.992/0.020/0.15s/40.0kV/40.0mA

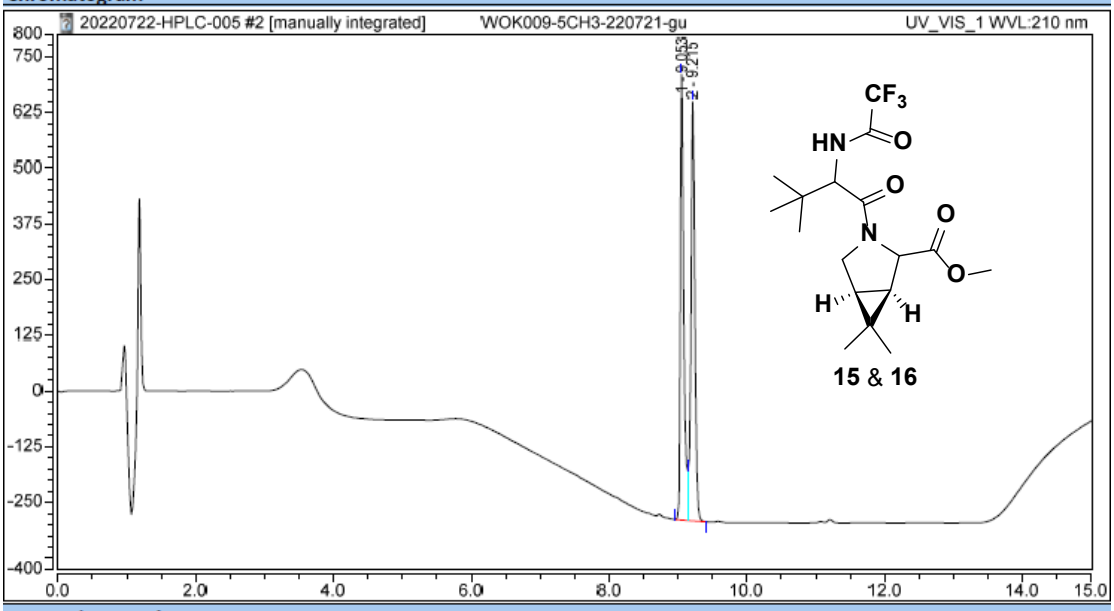
Index	Angle	d Value	Net Intensity	Gross Intensity	Rel. Intensity	FWHM
1	7.577 °	11.65886 Å	869.145	1100.54	19.1%	0.105
2	9.730 °	9.08326 Å	831.810	1207.50	18.3%	0.108
3	10.287 °	8.59259 Å	292.138	729.403	6.4%	0.108
4	10.766 °	8.21069 Å	174.729	660.766	3.8%	0.193
5	11.363 °	7.78127 Å	753.586	1294.71	16.6%	0.105
6	11.849 °	7.46314 Å	2769.60	3351.13	60.8%	0.113
7	12.675 °	6.97841 Å	4553.15	5194.07	100.0%	0.113
8	13.327 °	6.63840 Å	284.646	964.154	6.3%	0.100
9	14.564 °	6.07704 Å	299.374	1032.07	6.6%	0.314
10	15.628 °	5.66574 Å	4248.56	5005.96	93.3%	0.118
11	17.263 °	5.13256 Å	1221.81	1979.35	26.8%	0.108
12	17.798 °	4.97961 Å	1091.26	1838.91	24.0%	0.108
13	18.270 °	4.85203 Å	2942.99	3677.82	64.6%	0.110
14	18.819 °	4.71167 Å	641.644	1356.74	14.1%	0.110
15	19.791 °	4.48225 Å	2199.45	2866.90	48.3%	0.122
16	20.466 °	4.33611 Å	2192.51	2817.42	48.2%	0.113
17	20.931 °	4.24079 Å	990.151	1581.17	21.7%	0.117
18	21.583 °	4.11415 Å	666.637	1214.89	14.6%	0.147
19	22.177 °	4.00523 Å	1498.02	2015.01	32.9%	0.115
20	22.454 °	3.95634 Å	225.152	725.481	4.9%	0.142
21	23.002 °	3.86340 Å	169.267	648.115	3.7%	0.109
22	23.518 °	3.77972 Å	507.188	977.983	11.1%	0.122
23	24.234 °	3.66972 Å	131.138	591.107	2.9%	0.100
24	24.699 °	3.60158 Å	560.629	1008.83	12.3%	0.109
25	25.286 °	3.51938 Å	369.786	812.381	8.1%	0.103
26	26.945 °	3.30637 Å	300.770	777.976	6.6%	0.174
27	27.206 °	3.27515 Å	359.588	848.364	7.9%	0.158
28	27.985 °	3.18572 Å	116.940	633.041	2.6%	0.174
29	28.622 °	3.11628 Å	158.250	688.880	3.5%	0.121
30	29.425 °	3.03302 Å	448.539	991.643	9.9%	0.122
31	29.898 °	2.98612 Å	305.497	853.775	6.7%	0.209
32	30.206 °	2.95635 Å	139.579	689.164	3.1%	0.286
33	31.718 °	2.81883 Å	95.8101	628.206	2.1%	0.266
34	32.622 °	2.74275 Å	279.750	783.028	6.1%	0.105
35	33.576 °	2.66699 Å	262.176	724.289	5.8%	0.120
36	35.629 °	2.51787 Å	209.480	632.959	4.6%	0.150

3. Analytical spectra of 15 & 16, 18, 22, 23, 2 in intermediates or Nirmatrelvir

3.1 HPLC data, HRMS, and NMR of Compound 15&16 (compounds 15 and 16 are not separated)

3.1.1 HPLC

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.053	56.878	1000.418	48.38	51.56	n.a.
2		9.215	60.681	939.897	51.62	48.44	n.a.
Total:			117.559	1940.315	100.00	100.00	

3.1.2 HRMS

Qualitative Compound Report

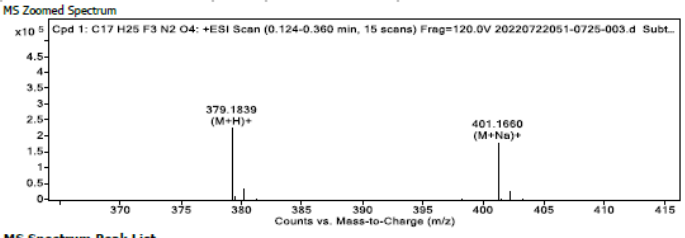
Data File	20220722051-0725-003.d	**Sample Name**	WOK009-5CH3
Sample Type	Sample	**Position**	Vial 2
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220721
AcquiredTime	7/25/2022 11:04:59 AM	**DataFile**	D:\MassHunter\Data\2022-07\2022-07-25\20220722051-0725-003.d

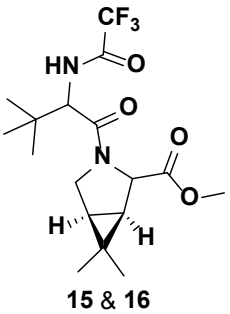
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C17 H25 F3 N2 O4	0.174	378.1767	225276	C17 H25 F3 N2 O4	378.1766	0.15

Compound Label	RT	Algorithm	Mass
Cpd 1: C17 H25 F3 N2 O4	0.174	Find By Formula	378.1767

MS Zoomed Spectrum



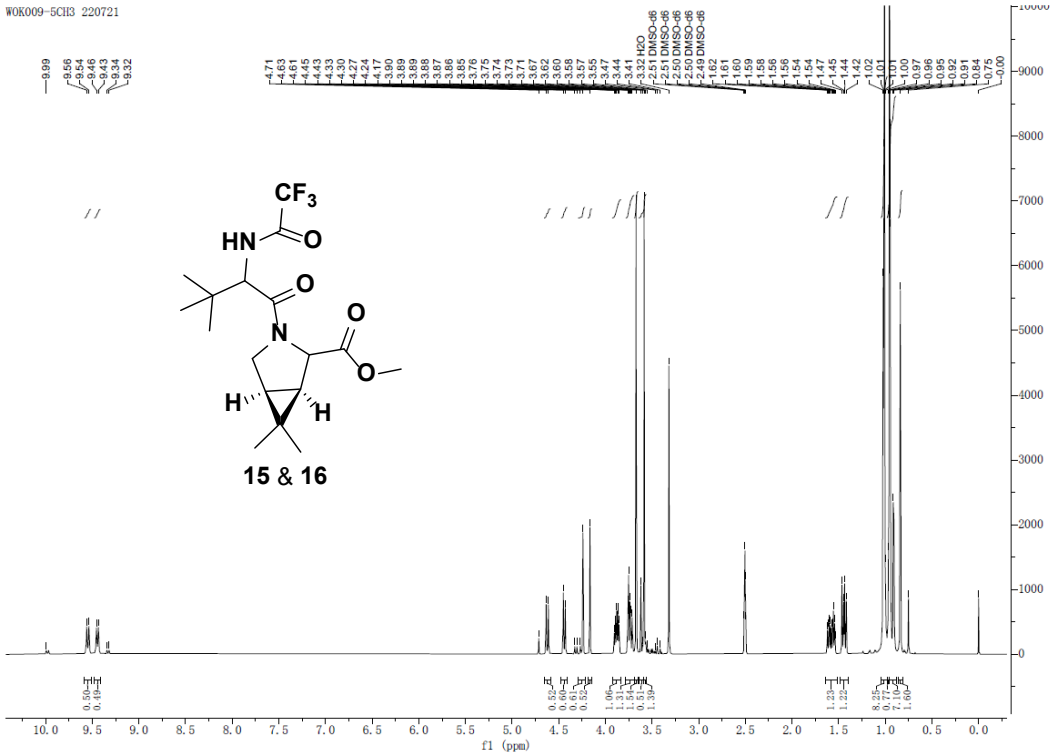


MS Spectrum Peak List

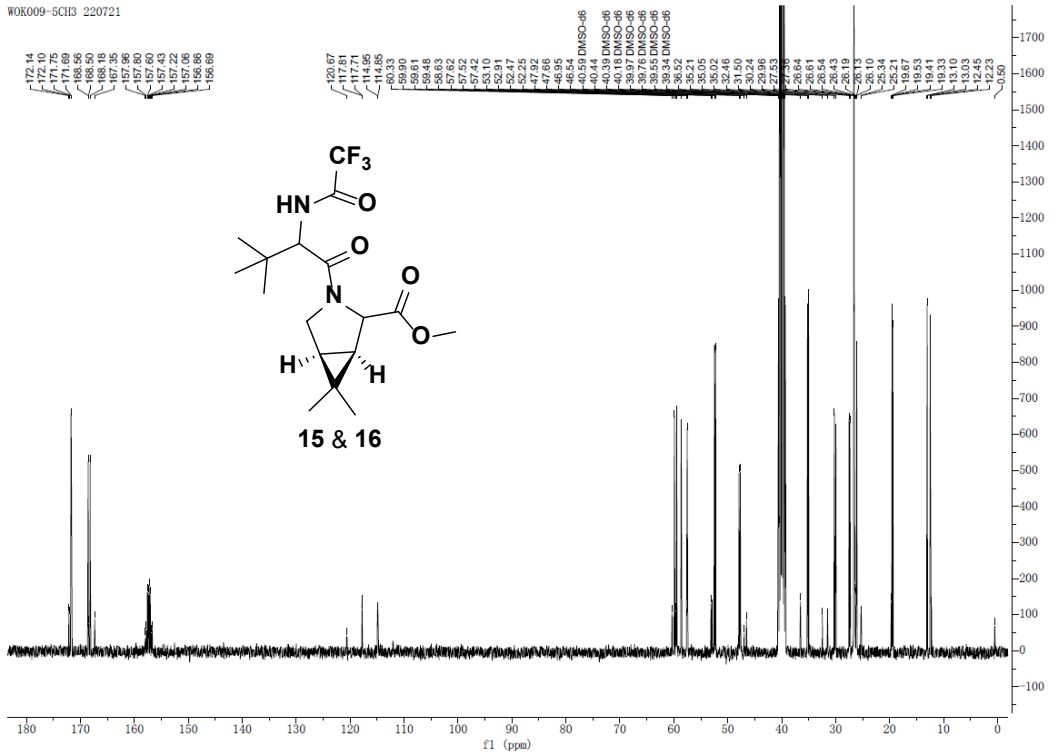
m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
379.1839	379.1839	-0.02	1	225276	C17 H26 F3 N2 O4	(M+H)+
401.166	401.1659	0.45	1	180210	C17 H25 F3 N2 Na O4	(M+Na)+

--- End Of Report ---

3.1.3 ^{1}H NMR (DMSO-d6)

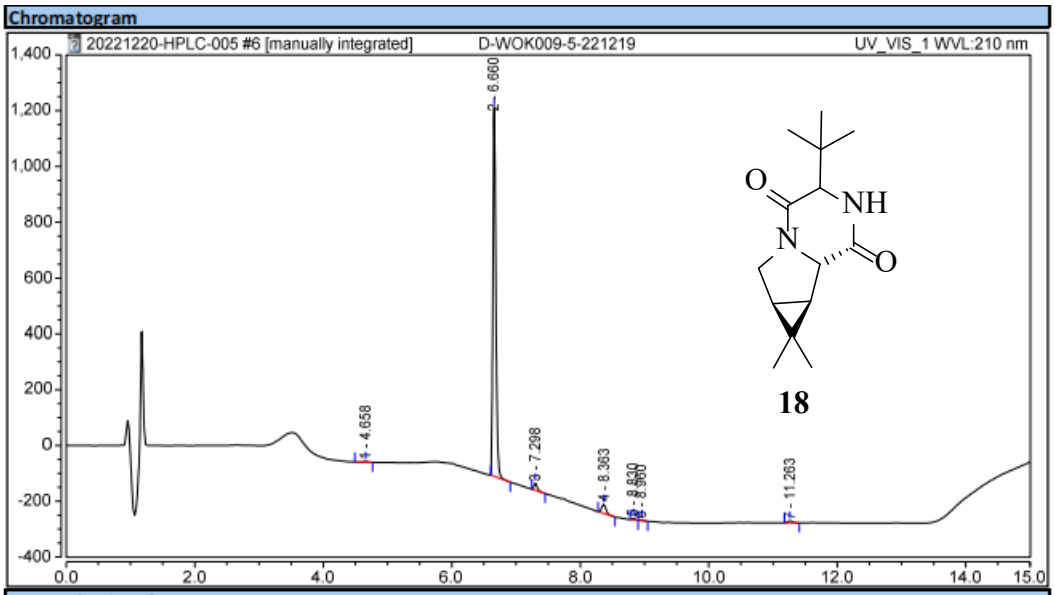


3.1.4 ^{13}C NMR (DMSO-d6)



3.2 HPLC data, HRMS, and NMR of Compound 18

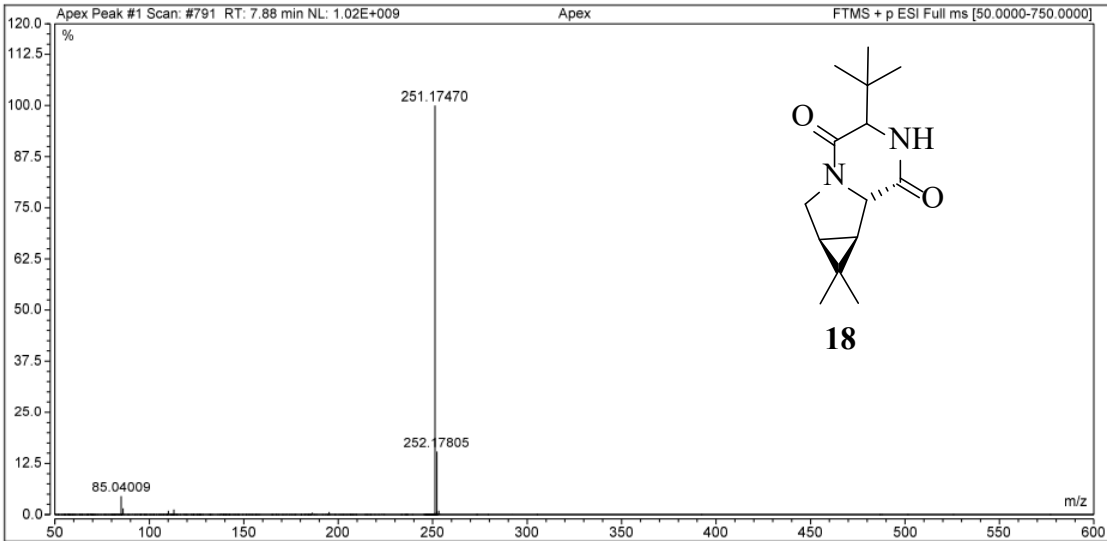
3.2.1 HPLC data



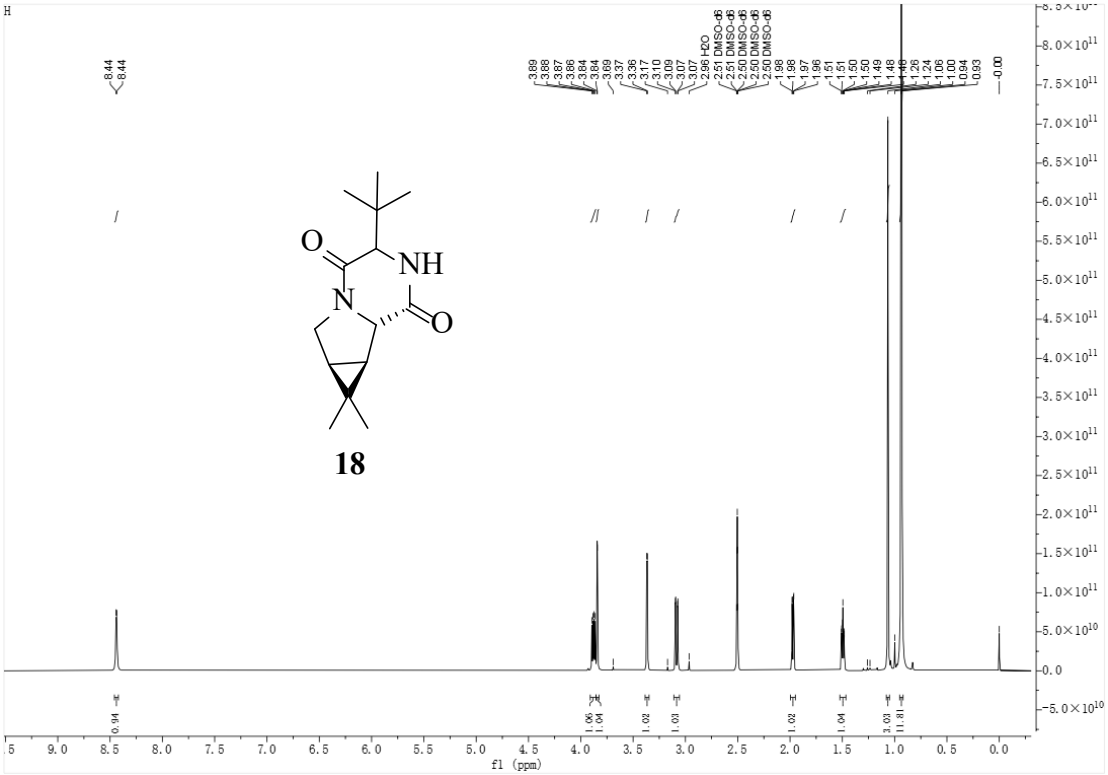
Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.658	0.221	3.552	0.29	0.25	n.a.
2		6.660	70.191	1320.703	93.14	94.40	n.a.
3		7.298	1.385	25.848	1.84	1.85	n.a.
4		8.363	2.447	32.018	3.25	2.29	n.a.
5		8.830	0.303	5.840	0.40	0.42	n.a.
6		8.960	0.277	4.490	0.37	0.32	n.a.
7		11.263	0.537	6.667	0.71	0.48	n.a.
Total:			**75.362**	**1399.119**	**100.00**	**100.00**	

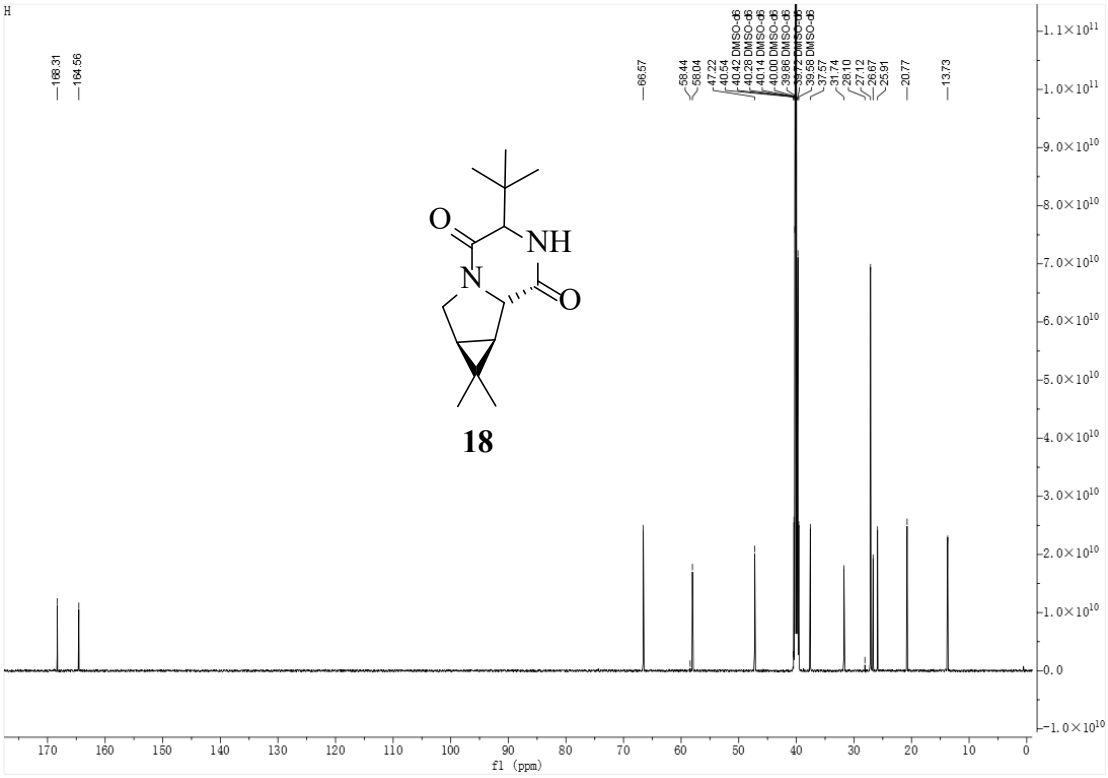
3.2.2 HRMS



3.2.3 ^{1}H NMR (DMSO-d6)

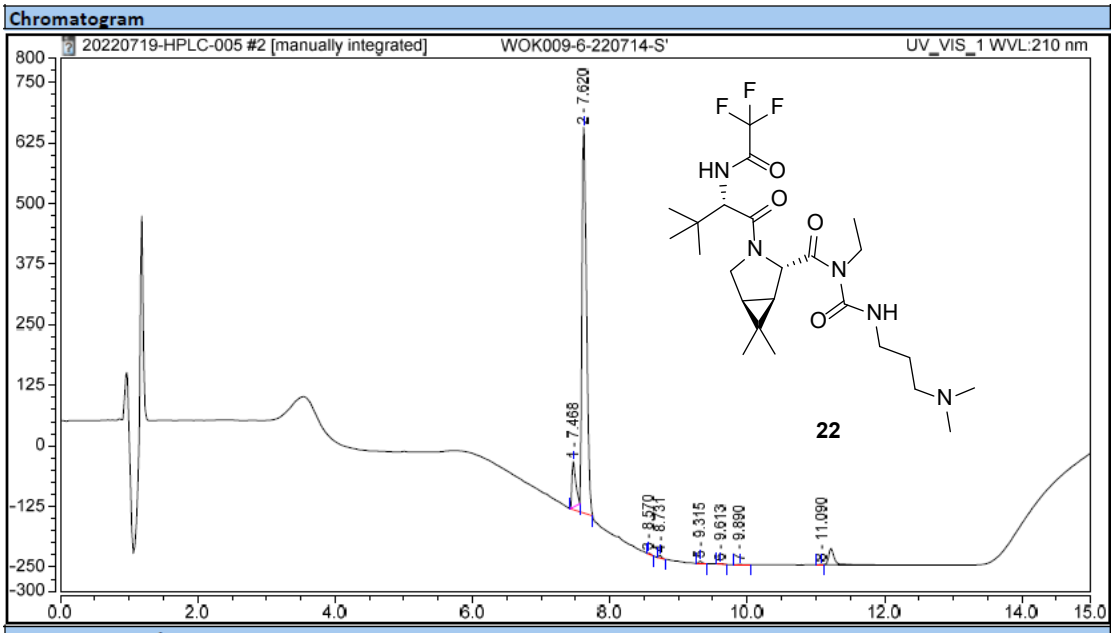


3.2.4 ^{13}C NMR (DMSO-d6)



3.3 HPLC data, HRMS, and NMR of Compound 22

3.3.1 HPLC



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.468	5.906	94.227	8.47	10.39	n.a.
2		7.620	62.932	796.255	90.27	87.77	n.a.
3		8.570	0.093	2.072	0.13	0.23	n.a.
4		8.731	0.269	6.070	0.39	0.67	n.a.
5		9.315	0.274	5.229	0.39	0.58	n.a.
6		9.613	0.077	1.081	0.11	0.12	n.a.
7		9.890	0.089	1.102	0.13	0.12	n.a.
8		11.090	0.079	1.139	0.11	0.13	n.a.
Total:			**69.718**	**907.176**	**100.00**	**100.00**	

3.3.2 HRMS

Qualitative Compound Report

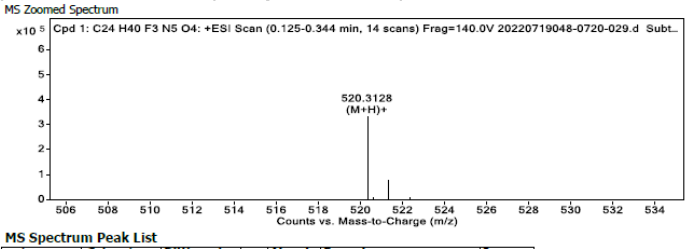
Data File	20220719048-0720-029.d	**Sample Name**	WOK009-6-IMPA
Sample Type	Sample	**Position**	Vial 45
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220714
AcquiredTime	7/20/2022 4:39:30 PM	**DataFile**	D:\MassHunter\Data\2022-07\2022-07-20\20220719048-0720-029.d

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C24 H40 F3 N5 O4	0.193	519.3055	332705	C24 H40 F3 N5 O4	519.3032	4.3

Compound Label	RT	Algorithm	Mass
Cpd 1: C24 H40 F3 N5 O4	0.193	Find By Formula	519.3055

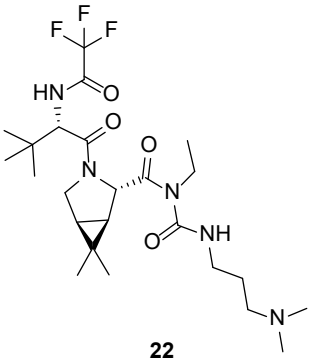
MS Zoomed Spectrum



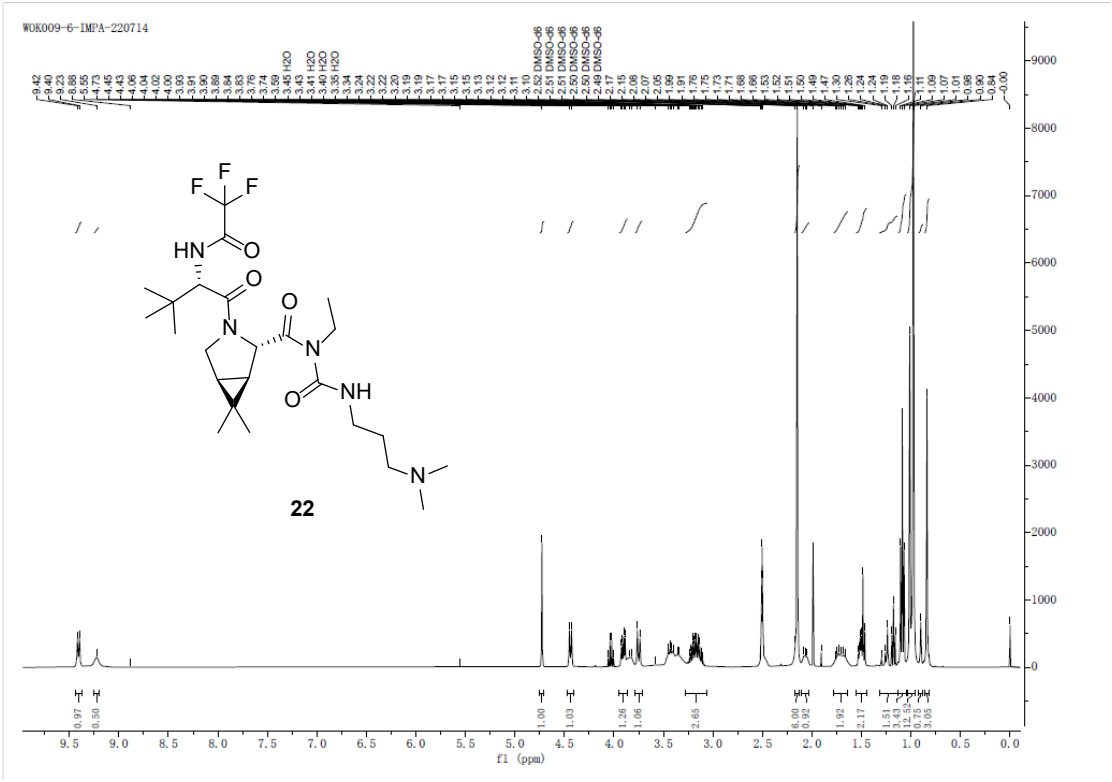
MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
520.3128	520.3105	4.31	1	332705	C24 H41 F3 N5 O4	(M+H)+

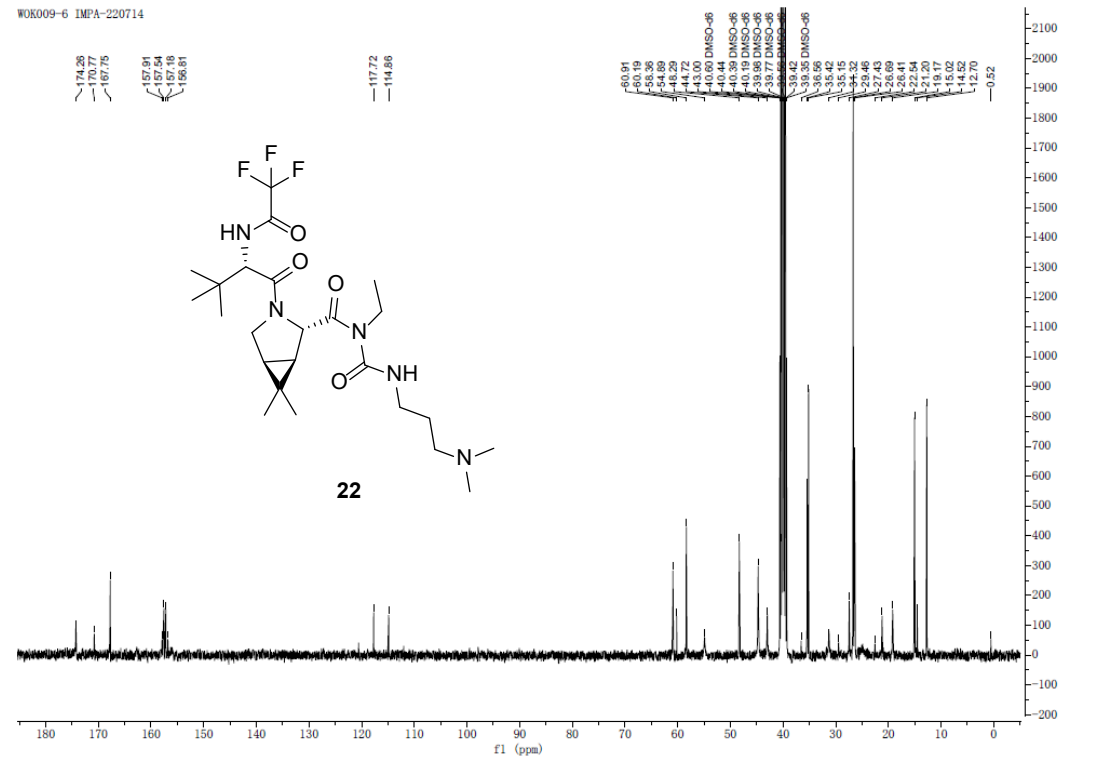
--- End Of Report ---



3.3.3 ^{1}H NMR (DMSO-d6)



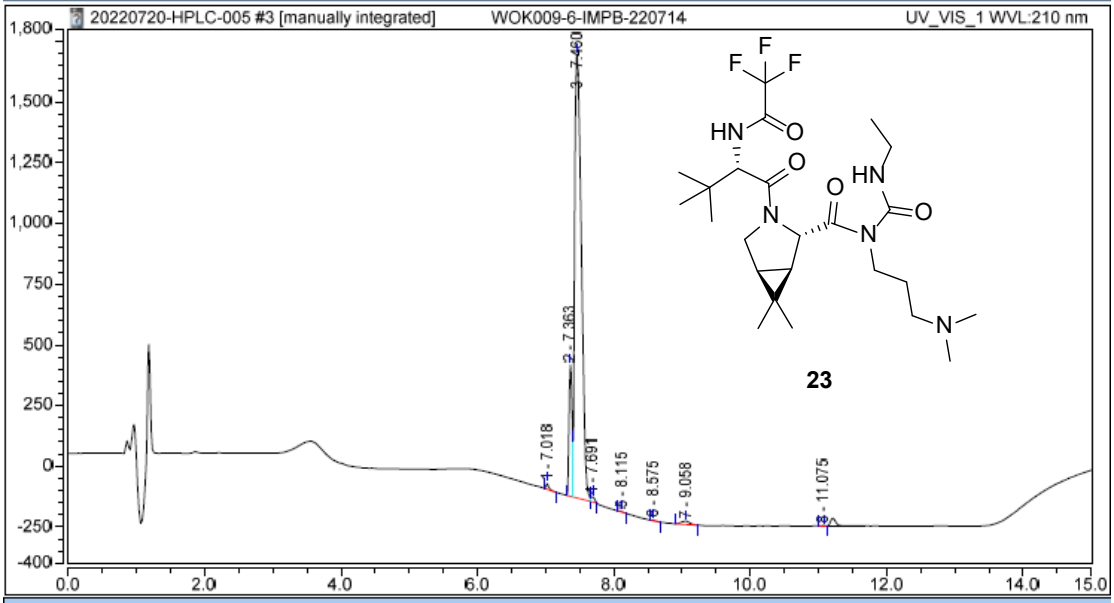
3.3.4 ^{13}C NMR (DMSO-d6)



3.4 HPLC data, HRMS, and NMR of Compound 23

3.4.1 HPLC

Chromatogram



23

Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.018	1.122	24.484	0.47	1.00	n.a.
2		7.363	28.686	541.082	12.07	22.18	n.a.
3		7.460	204.074	1828.964	85.87	74.99	n.a.
4		7.691	1.350	21.913	0.57	0.90	n.a.
5		8.115	0.165	2.521	0.07	0.10	n.a.
6		8.575	0.150	3.114	0.06	0.13	n.a.
7		9.058	1.965	14.816	0.83	0.61	n.a.
8		11.075	0.146	2.089	0.06	0.09	n.a.
Total:			237.658	2438.985	100.00	100.00	

3.4.2 HRMS

Qualitative Compound Report

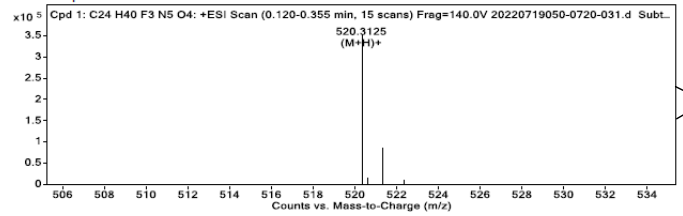
Data File	20220719050-0720-031.d	**Sample Name**	WOK009-6-IMPB
Sample Type	Sample	**Position**	Vial 46
Instrument Name	Instrument 1	**Acq Method**	
DA Method	Default.m	**Comment**	lot:220714
AcquiredTime	7/20/2022 4:48:02 PM	**DataFile**	D:\MassHunter\Data\2022-07\2022-07-20\20220719050-0720-031.d

Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C24 H40 F3 N5 O4	0.187	519.3053	354997	C24 H40 F3 N5 O4	519.3032	3.89

Compound Label	RT	Algorithm	Mass
Cpd 1: C24 H40 F3 N5 O4	0.187	Find By Formula	519.3053

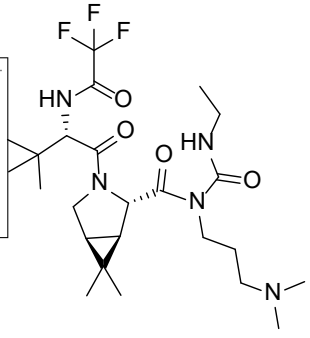
MS Zoomed Spectrum



MS Spectrum Peak List

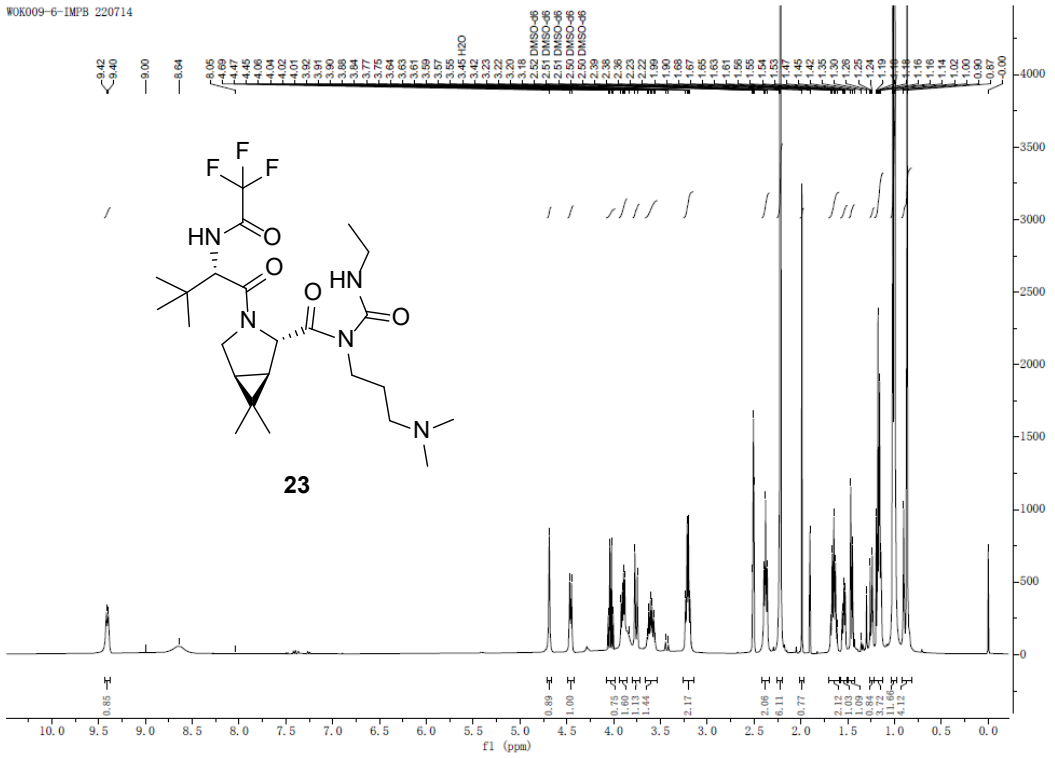
m/z	Calc m/z	Diff(ppm)	Abund	Formula	Ion
520.3125	520.3105	3.9	354997	C24 H41 F3 N5 O4	(M+H)+

--- End Of Report ---

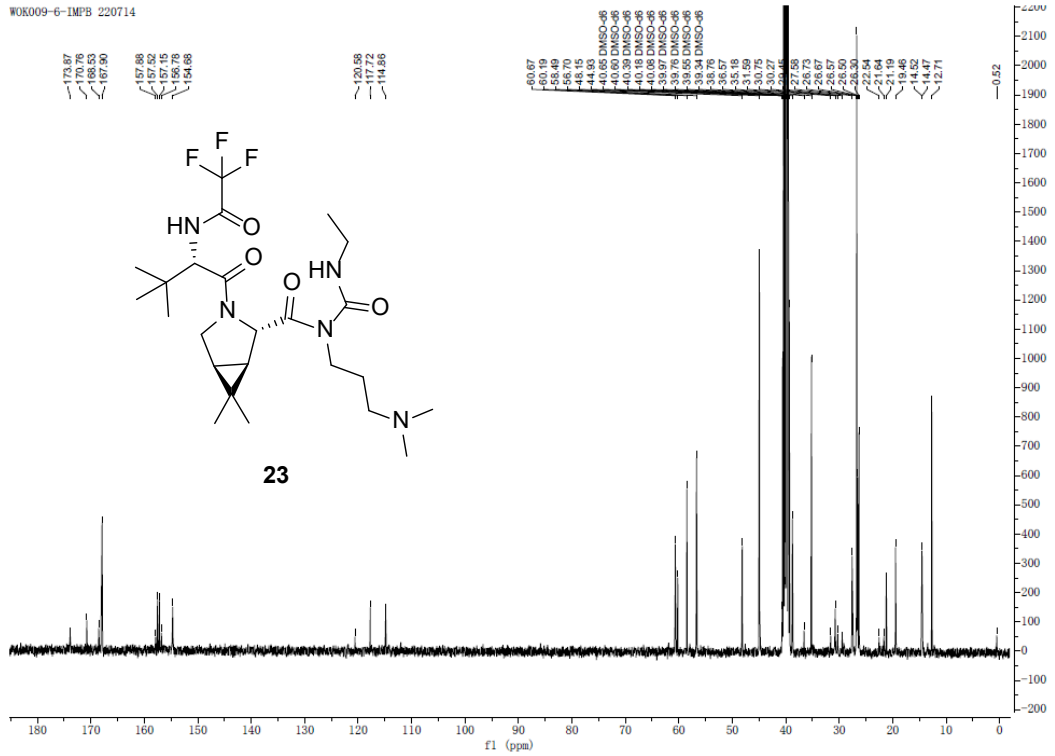


23

3.4.3 ^{1}H NMR (DMSO-d6)

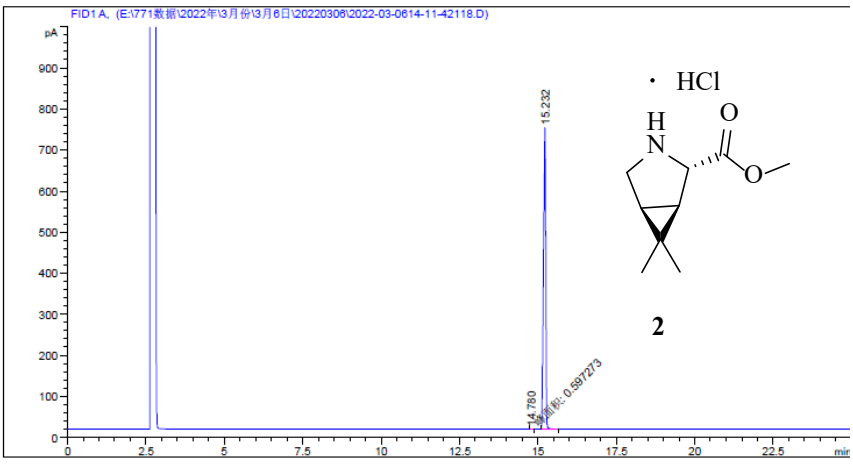


3.4.4 ^{13}C NMR (DMSO-d6)



3.5 purity data of Compound 2

3.5.1 GC (chemical purity)



面积百分比报告

排序 : 信号
乘积因子 : 1.0000
稀释因子 : 1.0000
内标使用乘积因子和稀释因子

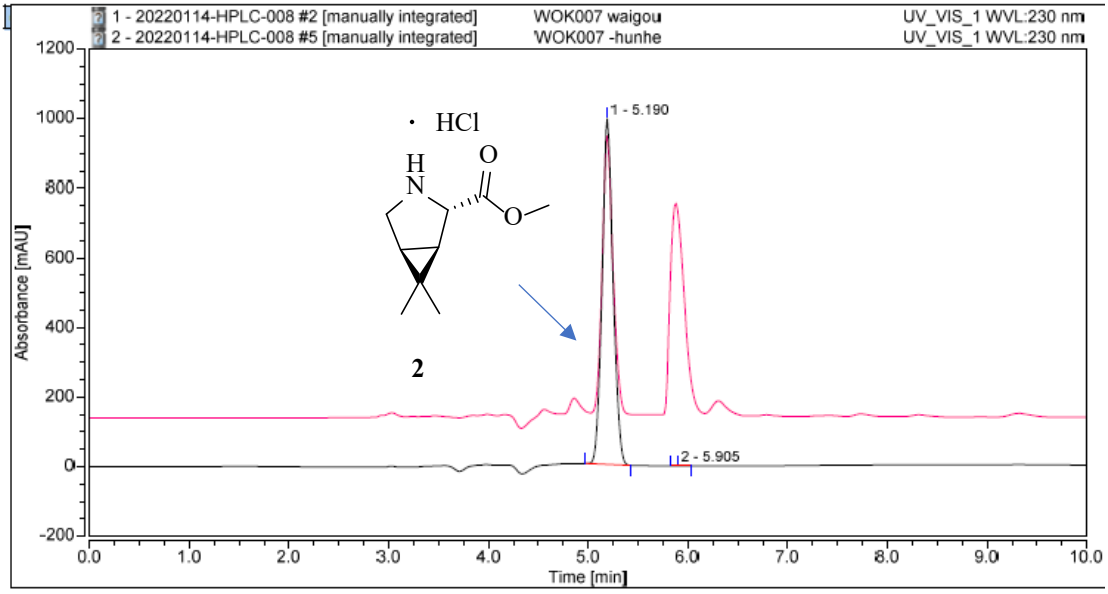
信号 1: FID1 A,

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [pA*s]	峰高 [pA]	峰面积 %
1	14.780	MM	0.0676	5.97273e-1	1.47232e-1	0.01616
2	15.232	BB	0.0737	3696.35474	734.88110	99.98384

总量 : 3696.95201 735.02834

6890 2022/3/6 14:46:04 系统 页 1/2

3.5.2 HPLC (chiral purity)



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.190	126.741	992.882	99.99	99.99	n.a.
2		5.905	0.007	0.079	0.01	0.01	n.a.
Total:			**126.748**	**992.961**	**100.00**	**100.00**	

4 Crystal void and surface calculation of nirmatrelvir

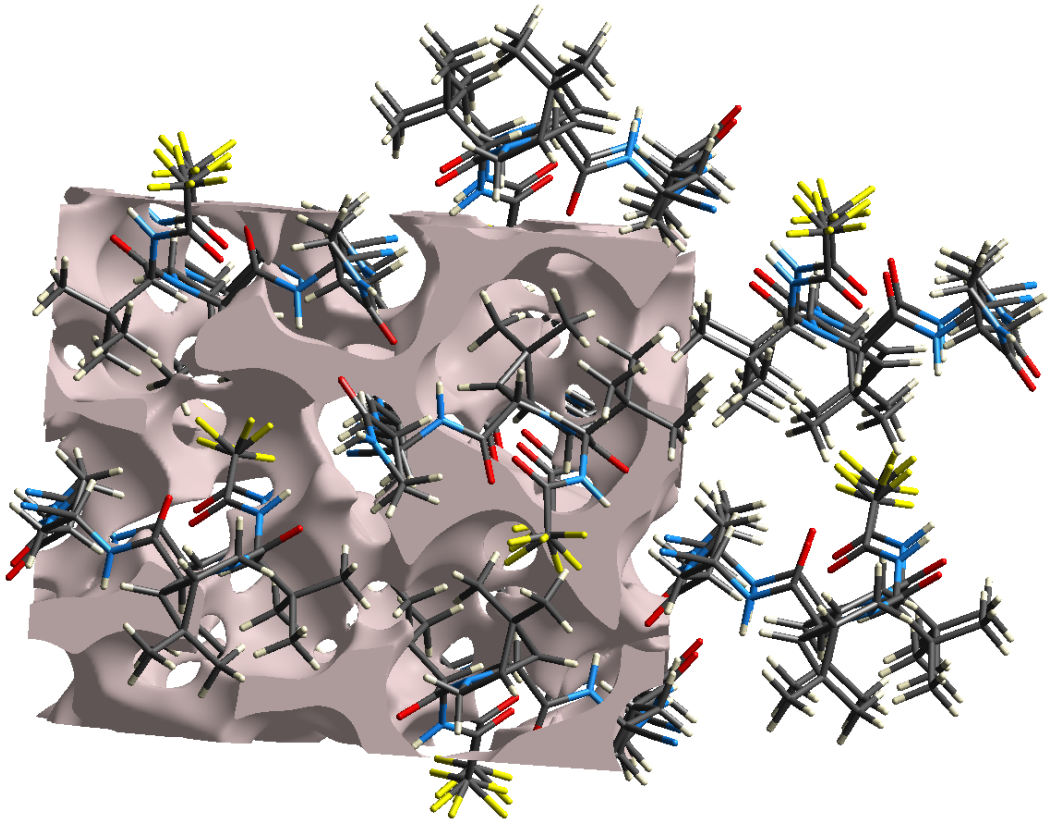


Figure 1. Crystal form A molecular void map

Crystal form A

Type Crystal Voids

Resolution High (Standard)

Isovalue 0.002

Volume 481.04 Å³

Area 1267.06 Å²

Globularity 0.234

Asphericity 0.090

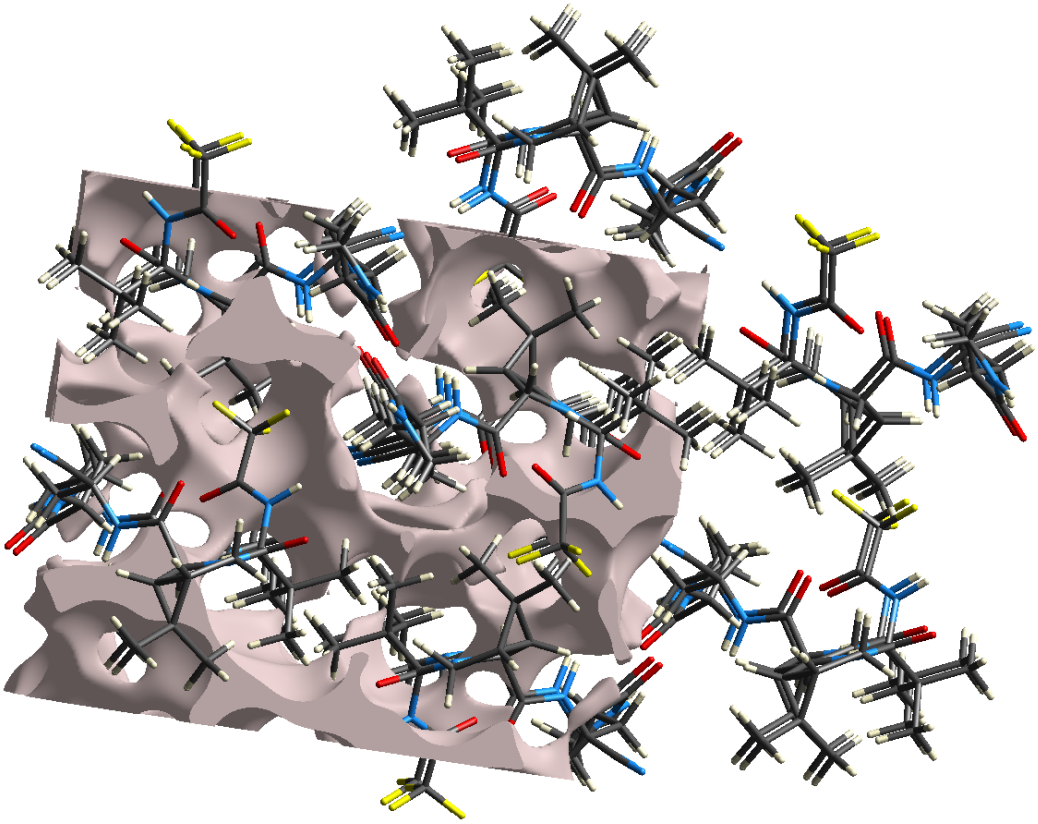


Figure 2. Crystal form B molecular void map

Crystal form B

Type Crystal Voids

Resolution High (Standard)

Isovalue 0.002

Volume 386.86 Å³

Area 1068.44 Å²

Globularity 0.240

Asphericity 0.105

5 Interaction energy calculation of nirmatrelvir

The pairwise intermolecular interaction energy was calculated using CrystalExplorer software (version 17.5) with experimental crystal geometry.1 Considering the uncertainty of hydrogen position by single crystal X-ray diffraction, the hydrogen positions were normalized to standard neutron diffraction values during the calculation. The total intermolecular interaction energy for given molecule, is summed up the electrostatic, polarization, dispersion, and exchange-repulsion components terms with scale factors of 1.057, 0.740, 0.871, and 0.618. The intermolecular interaction is neglected with molecule-molecule distance more than 3.8 Å.

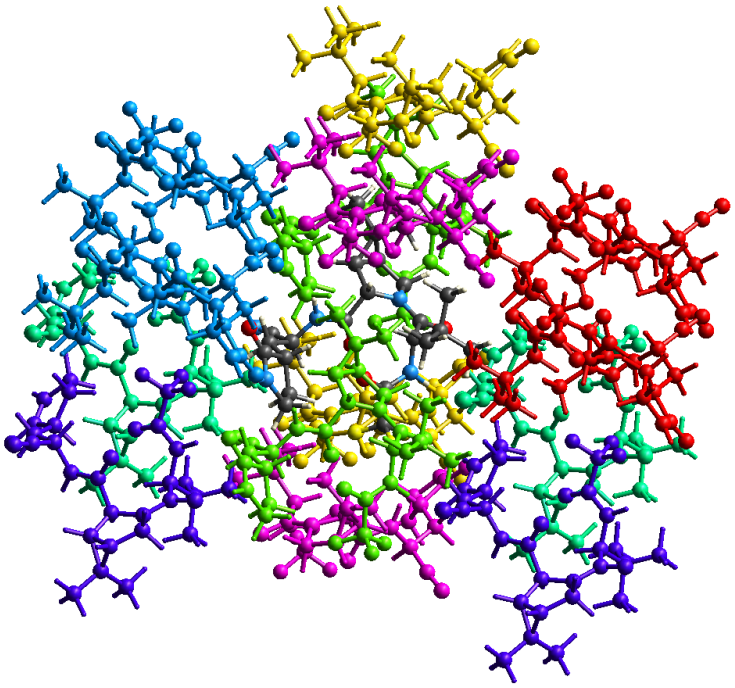
Ref. 1 M. J. Turner, J. J. McKinnon, S. K. Wolff, D. J. Grimwood, P. R. Spackman, D. Jayatilaka and M. A. Spackman, CrystalExplorer17 (2017). University of Western Australia.

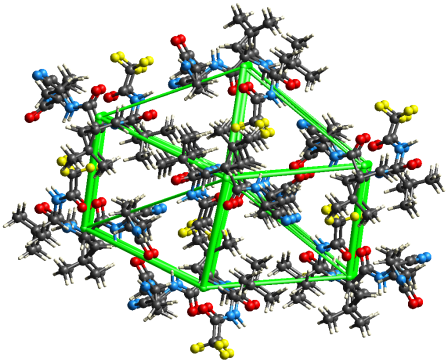
Crystal form A

Interaction Energies (kJ/mol) R is the distance between molecular centroids (mean atomic position) in Å.Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

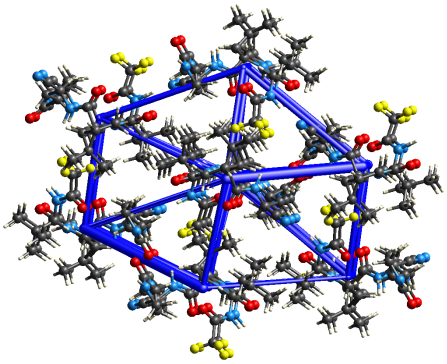
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x+1/2, -y+1/2, -z	11.24	B3LYP/6-31G(d,p)	-7.0	-1.7	-26.9	16.7	-21.8
	2	-x, y+1/2, -z+1/2	10.53	B3LYP/6-31G(d,p)	-3.7	-1.6	-18.7	5.3	-18.1
	2	x, y, z	9.21	B3LYP/6-31G(d,p)	-15.8	-6.4	-52.8	36.2	-45.0
	2	-x+1/2, -y, z+1/2	10.21	B3LYP/6-31G(d,p)	-30.3	-8.9	-18.9	39.9	-30.5
	2	x+1/2, -y+1/2, -z	10.30	B3LYP/6-31G(d,p)	-39.2	-12.2	-29.9	31.7	-56.9
	2	-x+1/2, -y, z+1/2	11.78	B3LYP/6-31G(d,p)	0.4	-0.9	-15.2	4.2	-11.0
	2	-x, y+1/2, -z+1/2	7.79	B3LYP/6-31G(d,p)	-5.2	-3.2	-45.8	16.8	-35.0

Table S1. Intermolecular interaction energies (kJ mol^{-1}) of crystal form A estimated using B3LYP/6-31G (d, p) dispersion-corrected DFT models (nirmatrelvir as the central molecule)

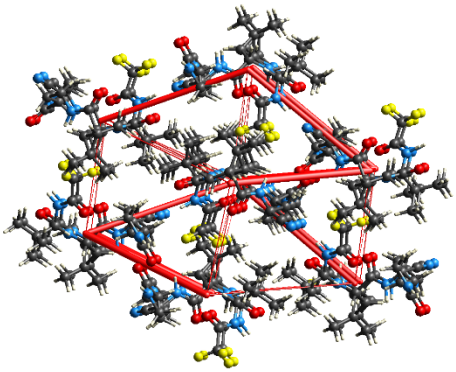




Dispersion Energy



Total Energy



Coulomb Energy

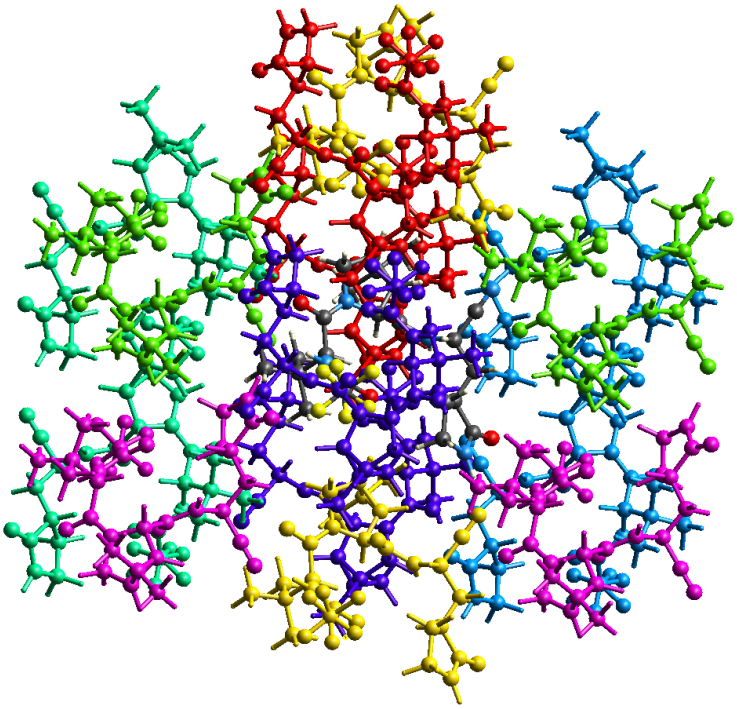
Figure 3. Energy frame diagram

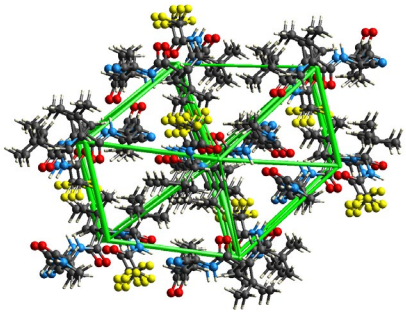
Crystal form B

Interaction Energies (kJ/mol) R is the distance between molecular centroids (mean atomic position) in Å. Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

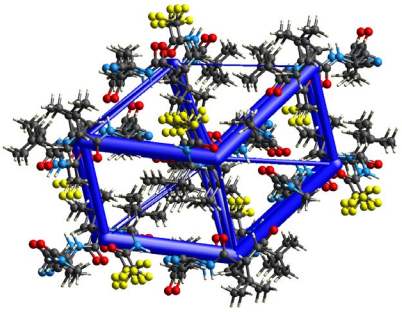
	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	-x, y+1/2, -z+1/2	10.65	B3LYP/6-31G(d,p)	-1.1	-10.0	-18.2	1.2	-23.6
	2	x, y, z	9.69	B3LYP/6-31G(d,p)	-36.8	-16.2	-41.6	23.5	-72.6
	2	-x+1/2, -y, z+1/2	9.84	B3LYP/6-31G(d,p)	-65.8	-28.8	-28.7	24.2	-100.9
	2	x+1/2, -y+1/2, -z	11.74	B3LYP/6-31G(d,p)	7.0	-4.5	-18.6	4.5	-9.3
	2	x+1/2, -y+1/2, -z	10.75	B3LYP/6-31G(d,p)	-9.8	-6.8	-27.5	19.1	-27.5
	2	-x, y+1/2, -z+1/2	7.85	B3LYP/6-31G(d,p)	-11.8	-27.4	-43.4	11.9	-63.1
	2	-x+1/2, -y, z+1/2	11.79	B3LYP/6-31G(d,p)	-13.8	-9.6	-16.8	2.3	-34.9

Table S2. Intermolecular interaction energies (kJ mol^{-1}) of crystal form B estimated using B3LYP/6-31G (d, p) dispersion-corrected DFT models (nirmatrelvir as the central molecule)

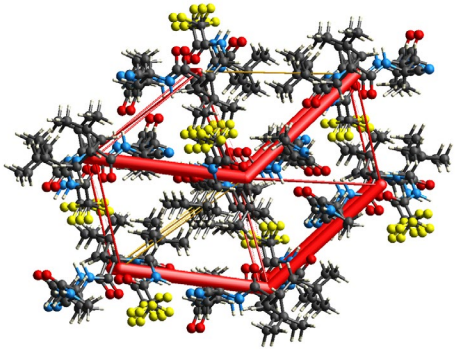




Dispersion Energy



Total Energy



Coulomb Energy

Figure 4. Energy frame diagram