Cathepsin-Targeting SARS-CoV-2 Inhibitors: Design, Synthesis, and Biological Activity

Philipp Flury,[a,≠] Julian Breidenbach,[b,≠] Nadine Krüger,[c,≠] Rabea Voget,[b] Laura Schäkel,[b] Yaoyao Si,[b] Vesa Krasniqi,[b] Sara Calistri,[a] Matthias Olfert,[a] Katharina Sylvester,[b] Cheila Rocha,[c] Raphael Ditzinger,[a] Alexander Rasch,[a] Stefan Pöhlmann,[c,d] Thales Kronenberger,[a,e,f] Antti Poso,[a,e] Katharina Rox,[g,h] Stefan A. Laufer,[a] Christa E. Müller,[b] Michael Gütschow,[b,*] and Thanigaimalai Pillaiyar[a,*]

[a]*Institute of Pharmacy, Pharmaceutical/Medicinal Chemistry and Tübingen Center for Academic Drug Discovery, Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany*

[b]*PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical & Medicinal Chemistry, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany*

[c]*Infection Biology Unit, German Primate Center, Leibniz Institute for Primate Research Göttingen, Kellnerweg 4, 37077 Göttingen, Germany*

[d]*Faculty of Biology and Psychology, University Göttingen, Göttingen 37073, Germany*

[e]*School of Pharmacy, University of Eastern Finland, Faculty of Health Sciences, Kuopio 70211, Finland*

[f]*Excellence Cluster "Controlling Microbes to Fight Infections" (CMFI), 72076 Tübingen, Germany*

[g]*Department of Chemical Biology, Helmholtz Centre for Infection Research (HZI), 38124 Braunschweig, Germany*

[h]*German Center for Infection Research (DZIF), Partner Site Hannover-Braunschweig, 38124 Braunschweig, Germany*

[≠] These authors contributed equally.

*Corresponding authors

Prof. Dr. Michael Gütschow: − PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical & Medicinal Chemistry, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany; E-mail: guetschow@uni-bonn.de.

Dr. Thanigaimalai Pillaiyar; − Institute of Pharmacy, Pharmaceutical/Medicinal Chemistry and Tübingen Center for Academic Drug Discovery, Eberhard Karls University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany. E-mail: thanigaimalai.pillaiyar@uni-tuebingen.de.

Table of Content

1. GSH stability data for 11e, 11b, and 9b

GSH stability test 9b

GSH stability test 11b

GSH stability test 11e
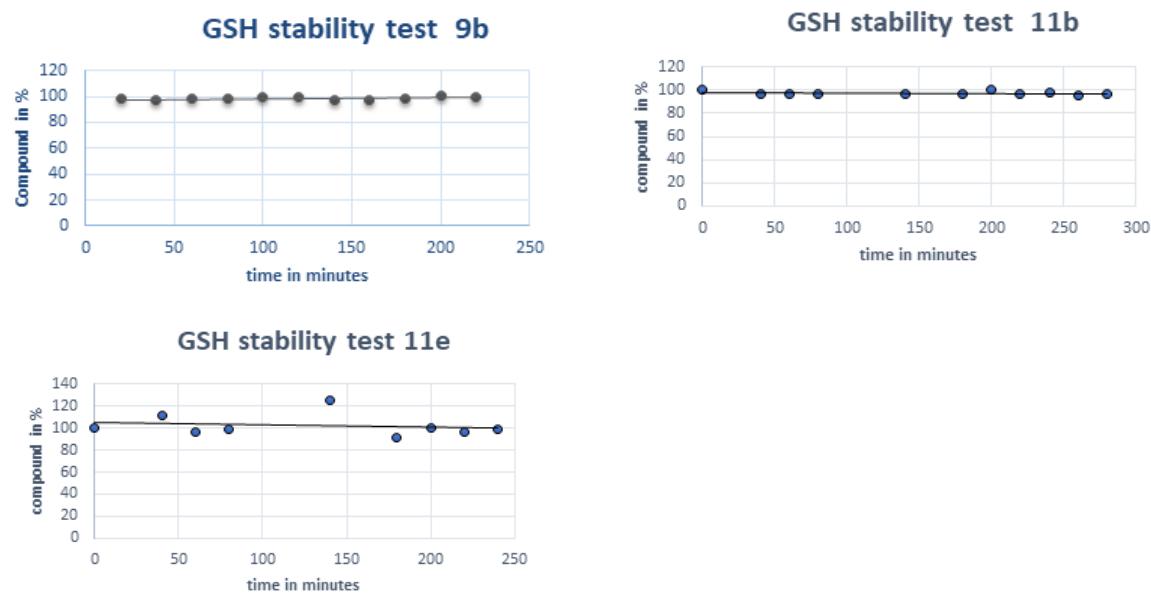
Figure S1: Graphical representation of the GSH studies of **9b**, **11b**, and **11e.**

Table S1: GSH stability data, detected at 280 nm

| 11e			11b			9b		
time (min)	area (mAU*s)	%	time (min)	area (mAU*s)	%	time (min)	area (mAU*s)	%
0	5.1	100	0	58.0	100	0	75.2	100
20	4.0	79	20	54.7	94	20	74.3	99
40	5.7	111	40	56.4	97	40	72.7	97
60	4.9	96	60	56.3	97	60	73.7	98
80	5.0	99	80	56.0	96	80	74.2	99
100	6.5	128	100	58.3	100	100	74.7	99
140	6.4	126	120	60.5	104	120	75.0	100
160	4.0	78	140	56.2	97	140	73.0	97
180	4.7	92	160	58.3	100	160	73.4	98
200	5.1	100	180	56.4	97	180	73.6	98
220	4.9	96	200	58.3	100	200	76.1	101
240	5.0	98	220	56.3	97	220	75.2	100

2. Metabolic stability studies
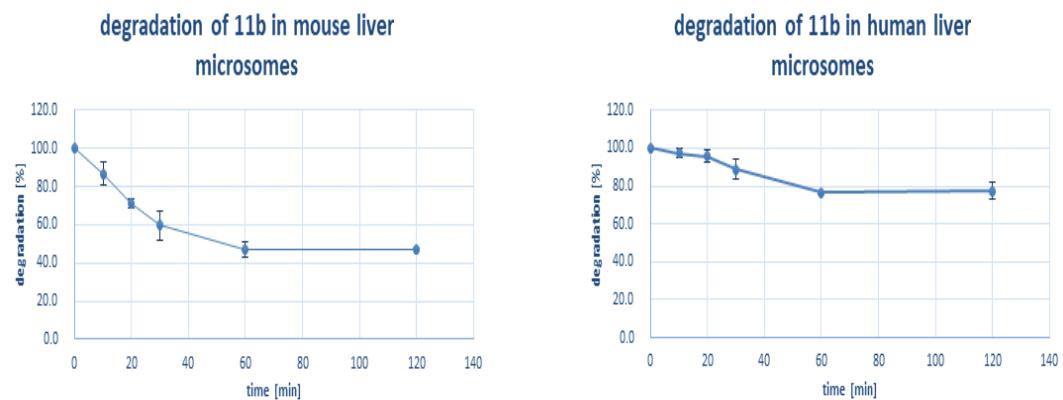
Figure S2: Graphical representation of microsomal metabolic stability studies of **11b.**

Table S2: Microsomal metabolic stability studies of **11b**

time (min)	mouse liver microsomes			human liver microsomes		
	degradation (%)	SD	1/2 SD	degradation (%)	SD	1/2 SD
0	100.0	0.00	0.00	100.0	0.00	0.00
10	86.8	12.7	6.3	97.3	5.2	2.6
20	70.9	5.3	2.6	95.6	6.8	3.4
30	59.5	15.8	7.9	88.9	10.8	5.4
60	47.0	8.5	4.3	76.7	1.51	0.8
120	47.2	1.1	0.5	77.2	8.9	4.4

3. Molecular modeling
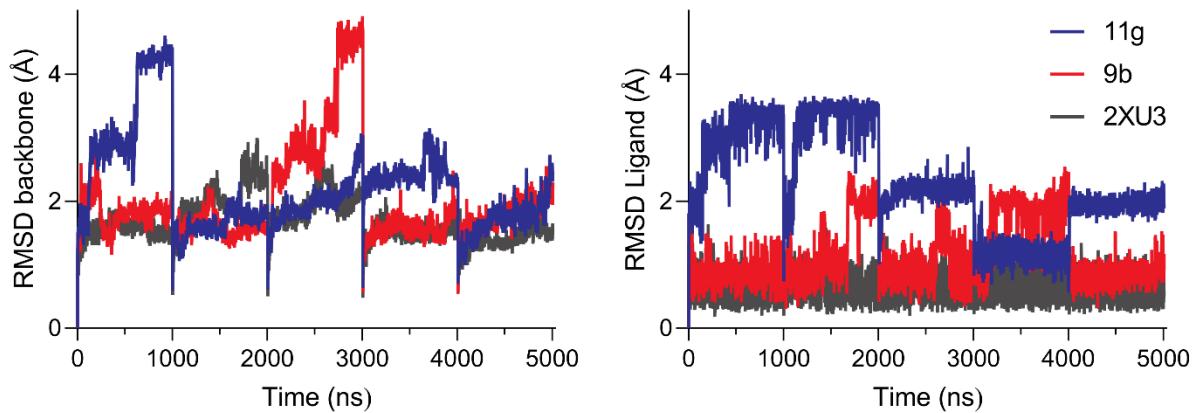
Figure S3: RMSD from the protein's backbone and ligand's heavy atoms along the trajectory time

4. ^{1}H and ^{13}C NMR spectra

Figure S4: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of 5-chloropyridin-3-yl (1*H*-indole-2-carbonyl)-*L*-leucyl-*L*-phenylalaninate (**5b**)
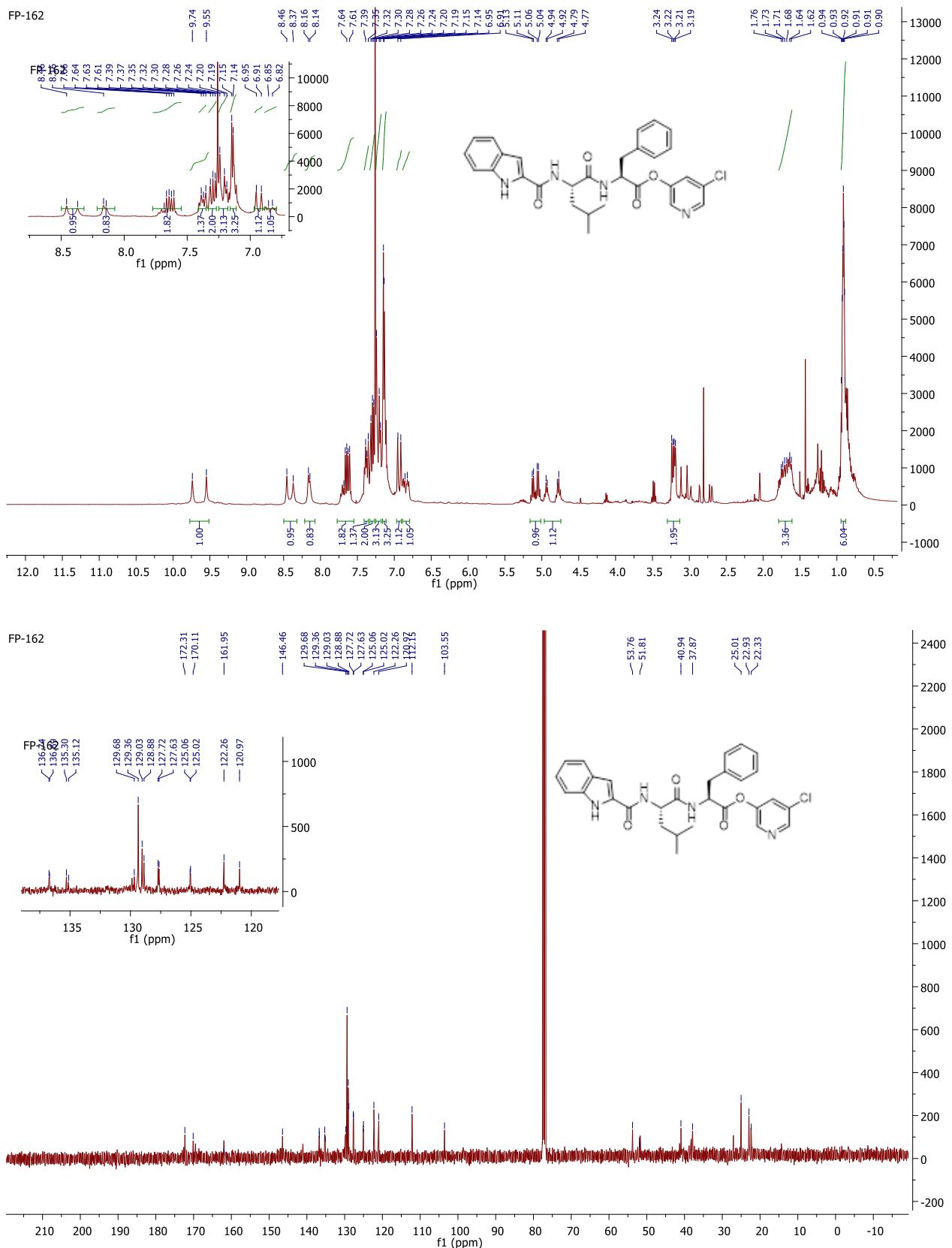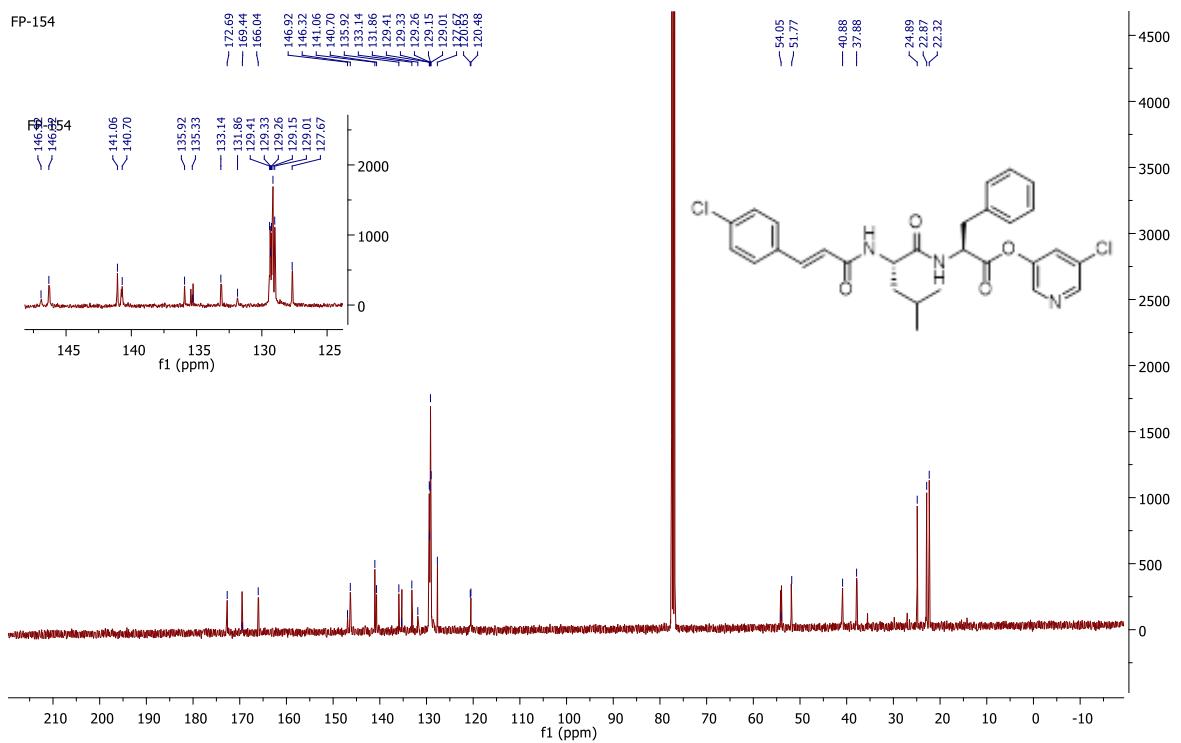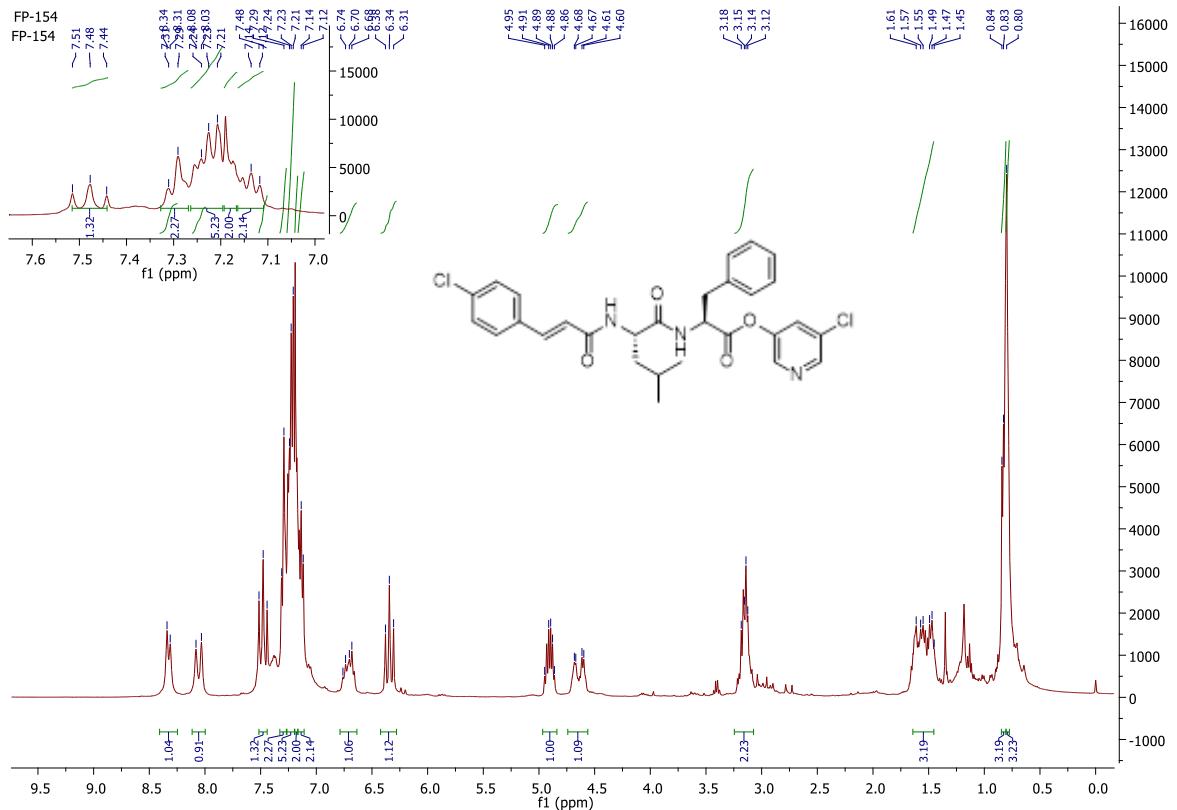
Figure S5: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of 5-chloropyridin-3-yl (-3-(4-chlorophenyl)acryloyl)-*L*-leucyl-*L*-phenylalaninate (**5i**)
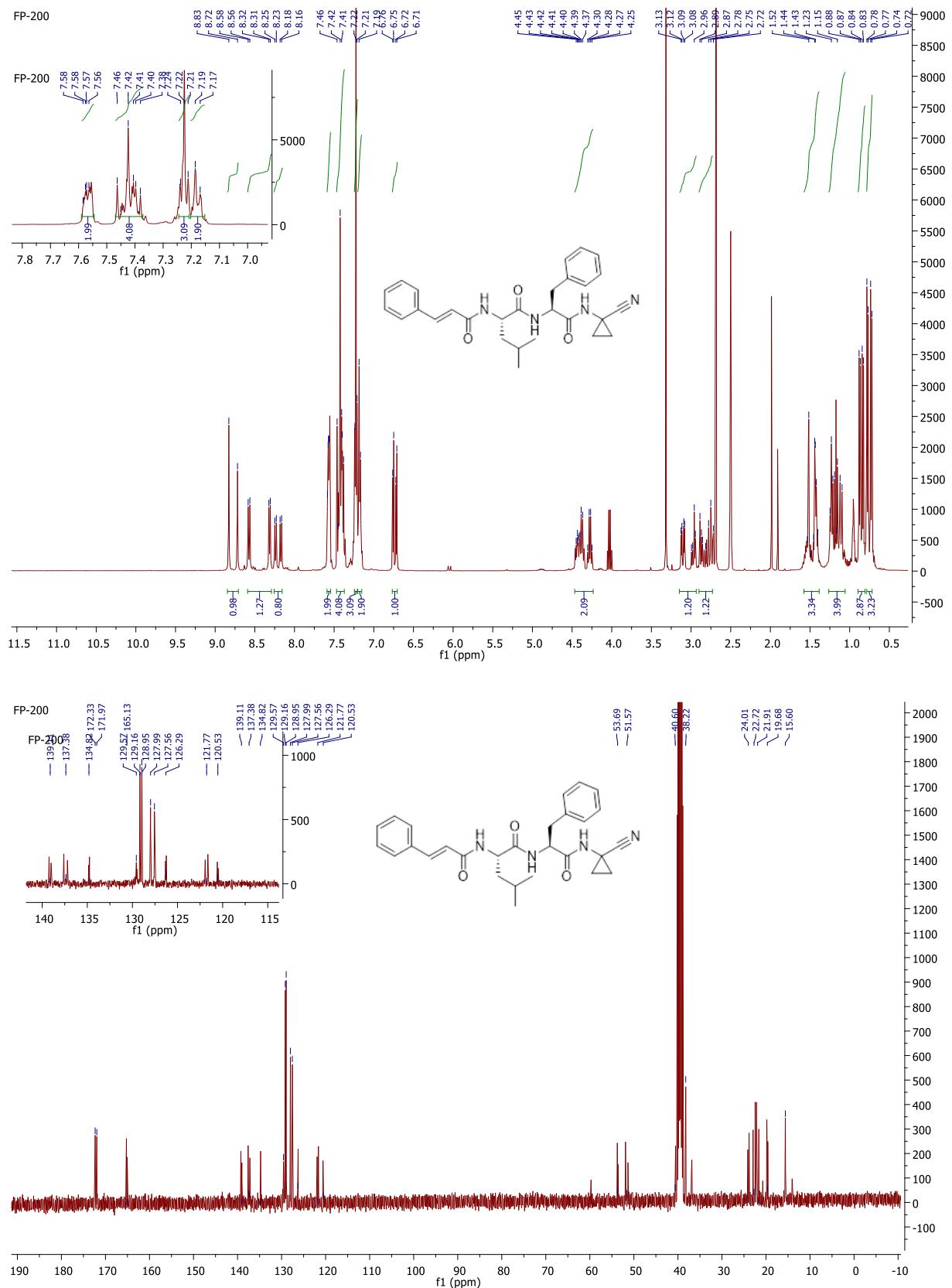
Figure S6: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of (*S*)-2-cinnamamido-*N*-((*S*)-1-((1-cyanocyclopropyl)amino)-1-oxo-3-phenylpropan-2-yl)-4-methylpentanamide (**6**)
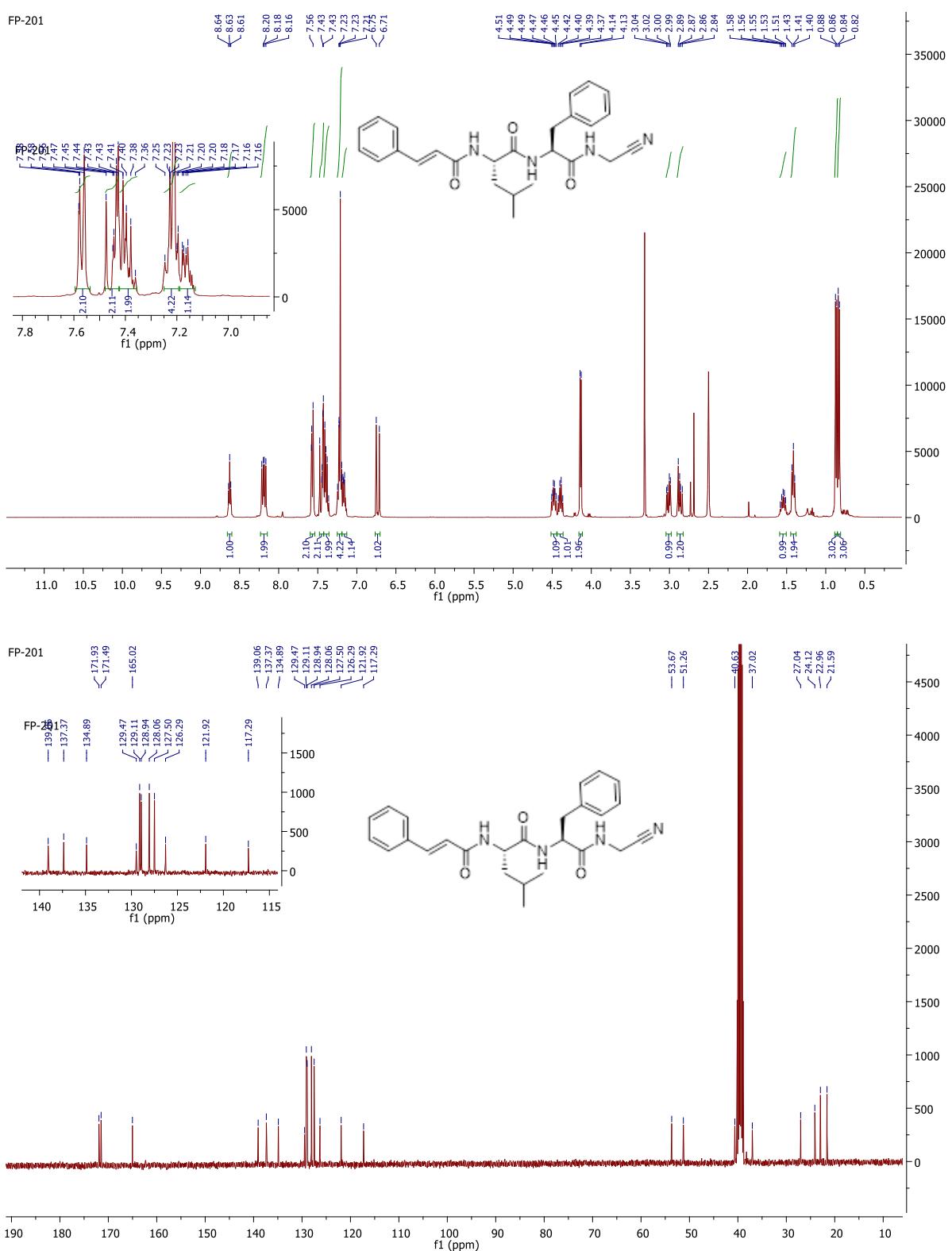
Figure S7: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of (*S*)-2-cinnamamido-*N*-((*S*)-1-((cyanomethyl)amino)-1-oxo-3-phenylpropan-2-yl)-4-methylpentanamide (**7**)
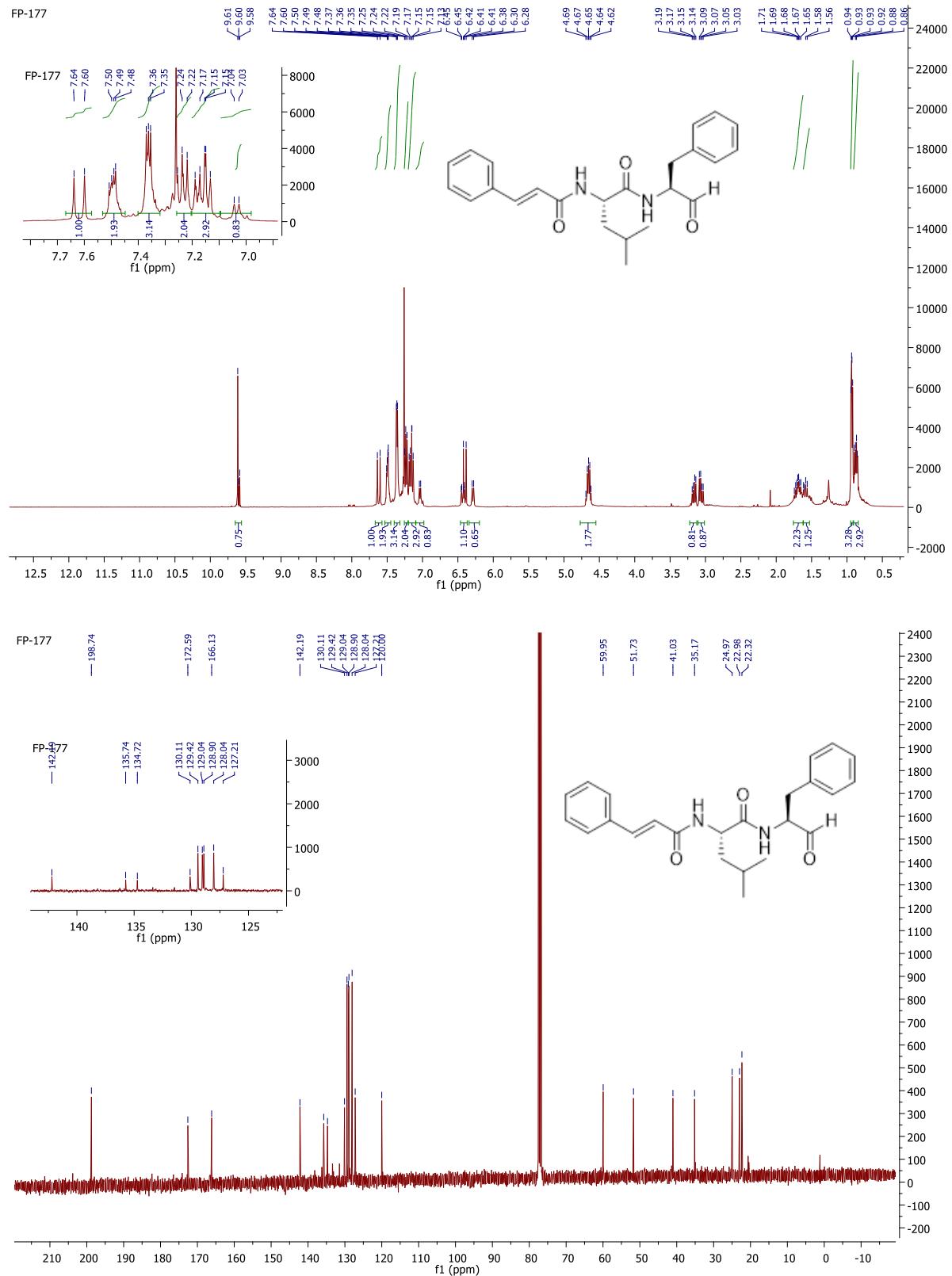
Figure S8: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-2-cinnamamido-4-methyl-*N*-((*S*)-1-oxo-3-phenylpropan-2-yl)pentanamide (**9a**)
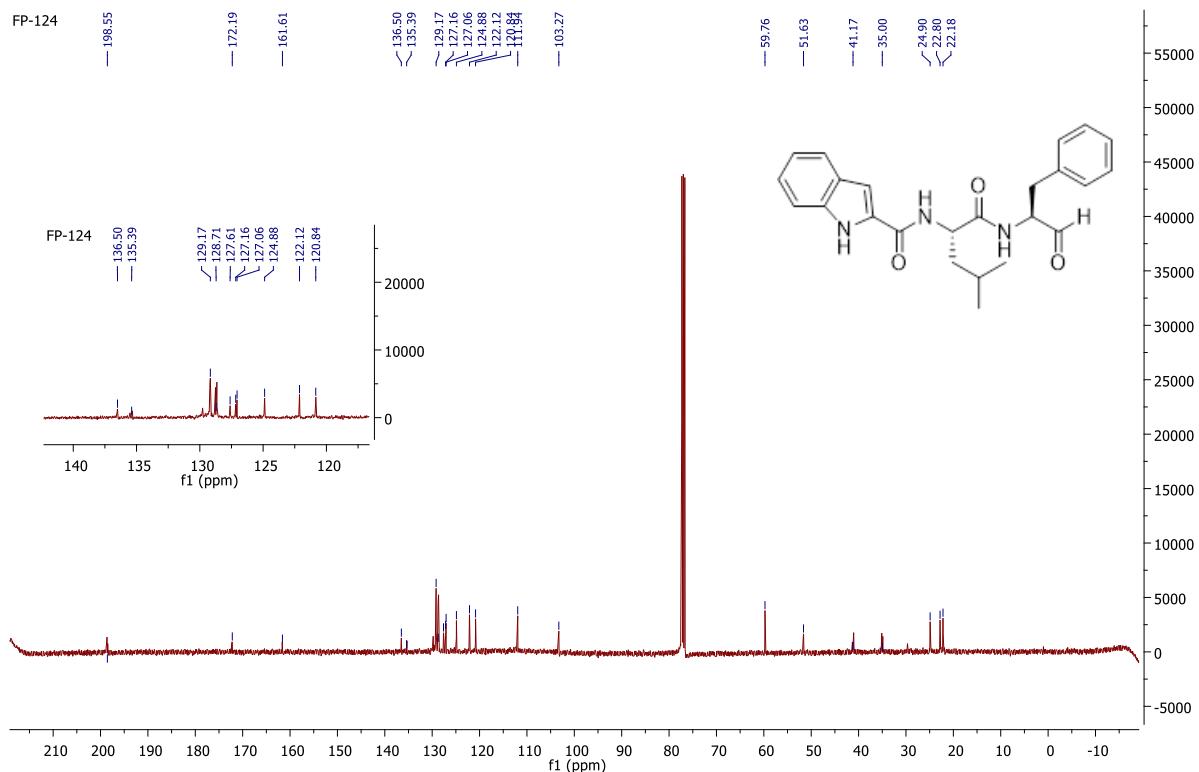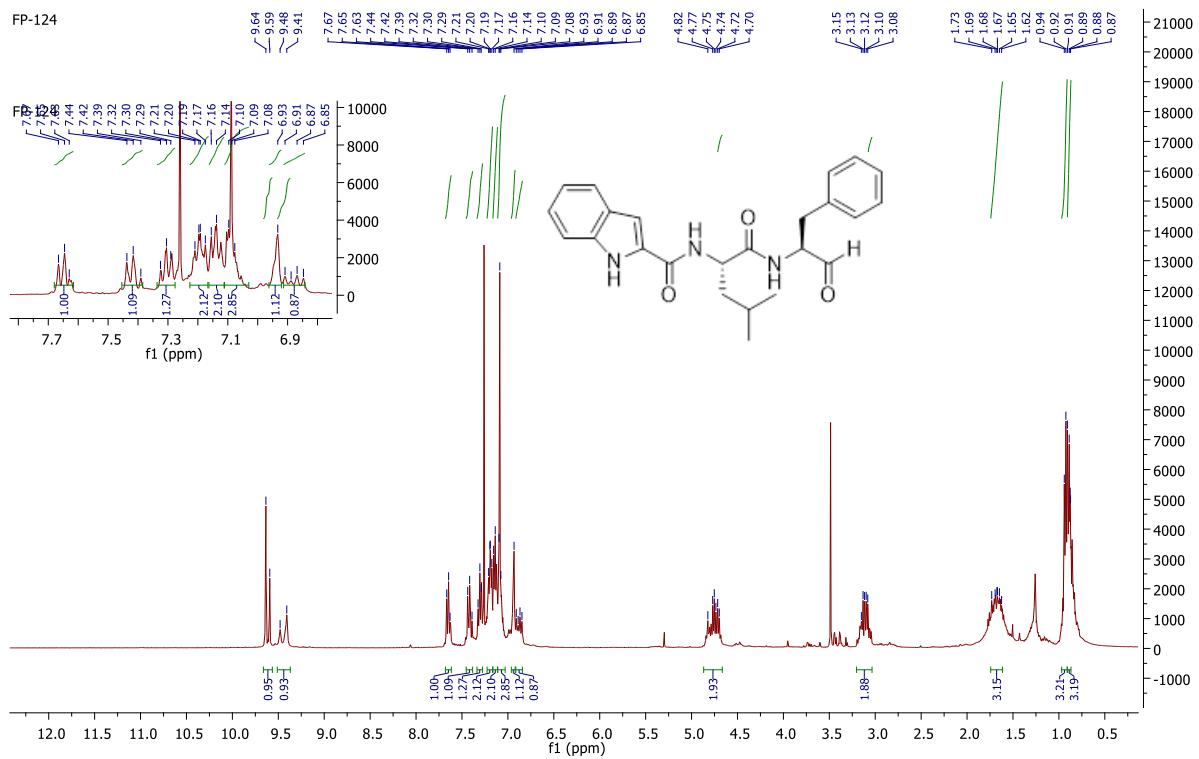
Figure S9: [1]H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of *N*-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-phenylpropan-2-yl)amino)pentan-2-yl)-1*H*-indole-2-carboxamide (**9b**)
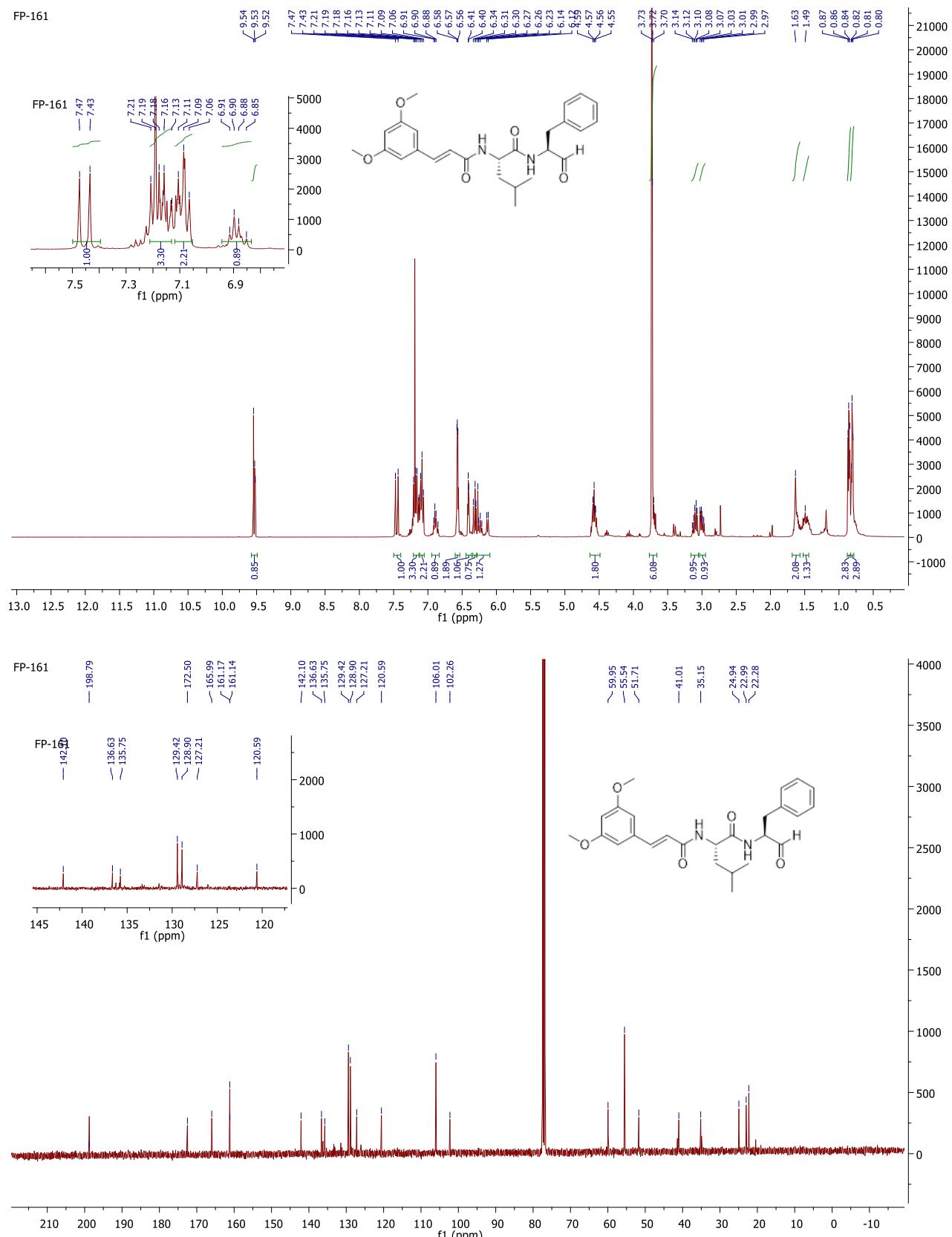
Figure S10: [1]H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-2-(-3-(3,5-dimethoxyphenyl) acrylamido)-4-methyl-*N*-((*S*)-1-oxo-3-phenylpropan-2-yl)pentanamide **(9c)**
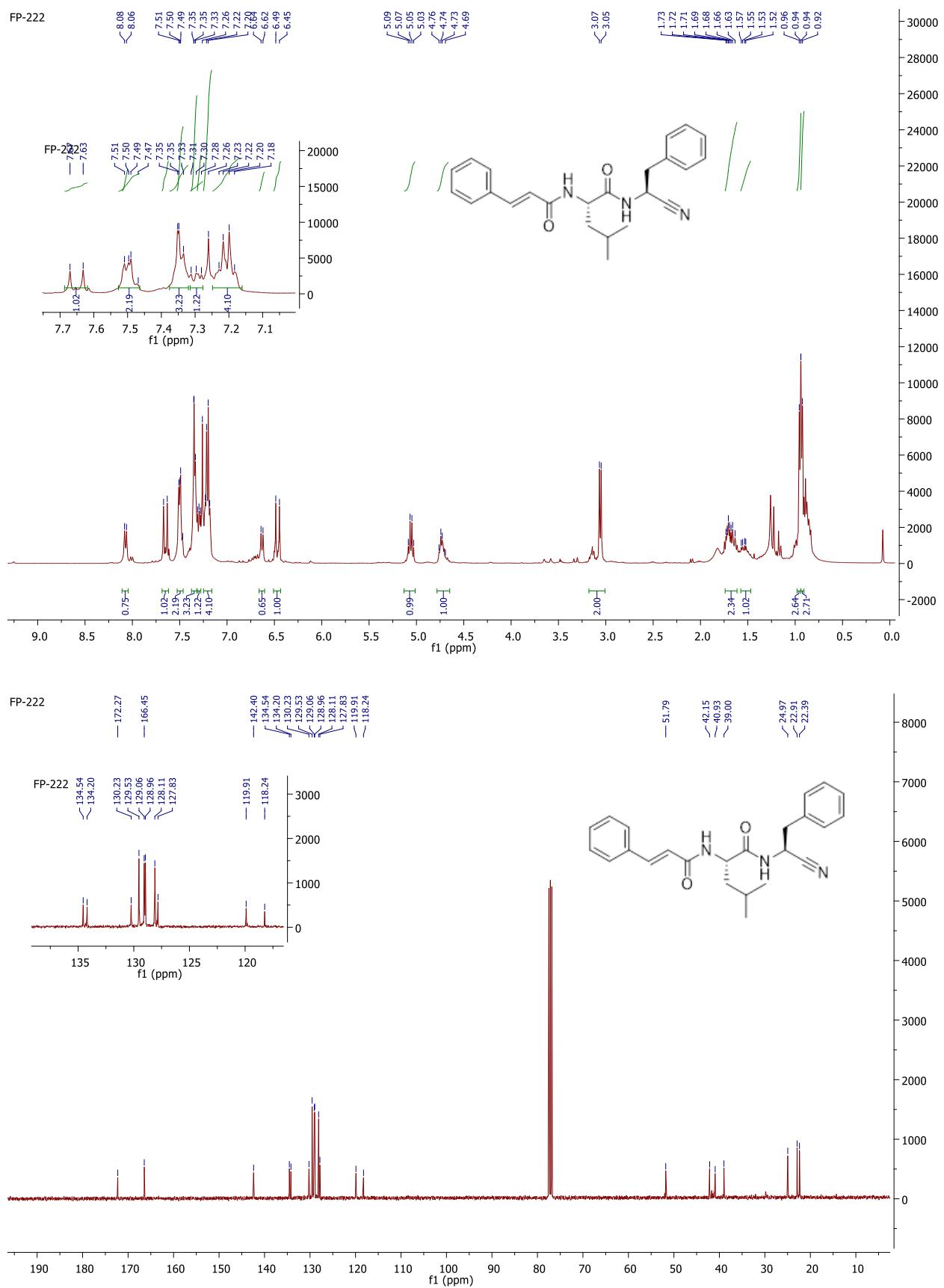
Figure S11: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-2-cinnamamido-*N*-((*S*)-1-cyano-2-phenylethyl)-4-methylpentanamide (**11a**)
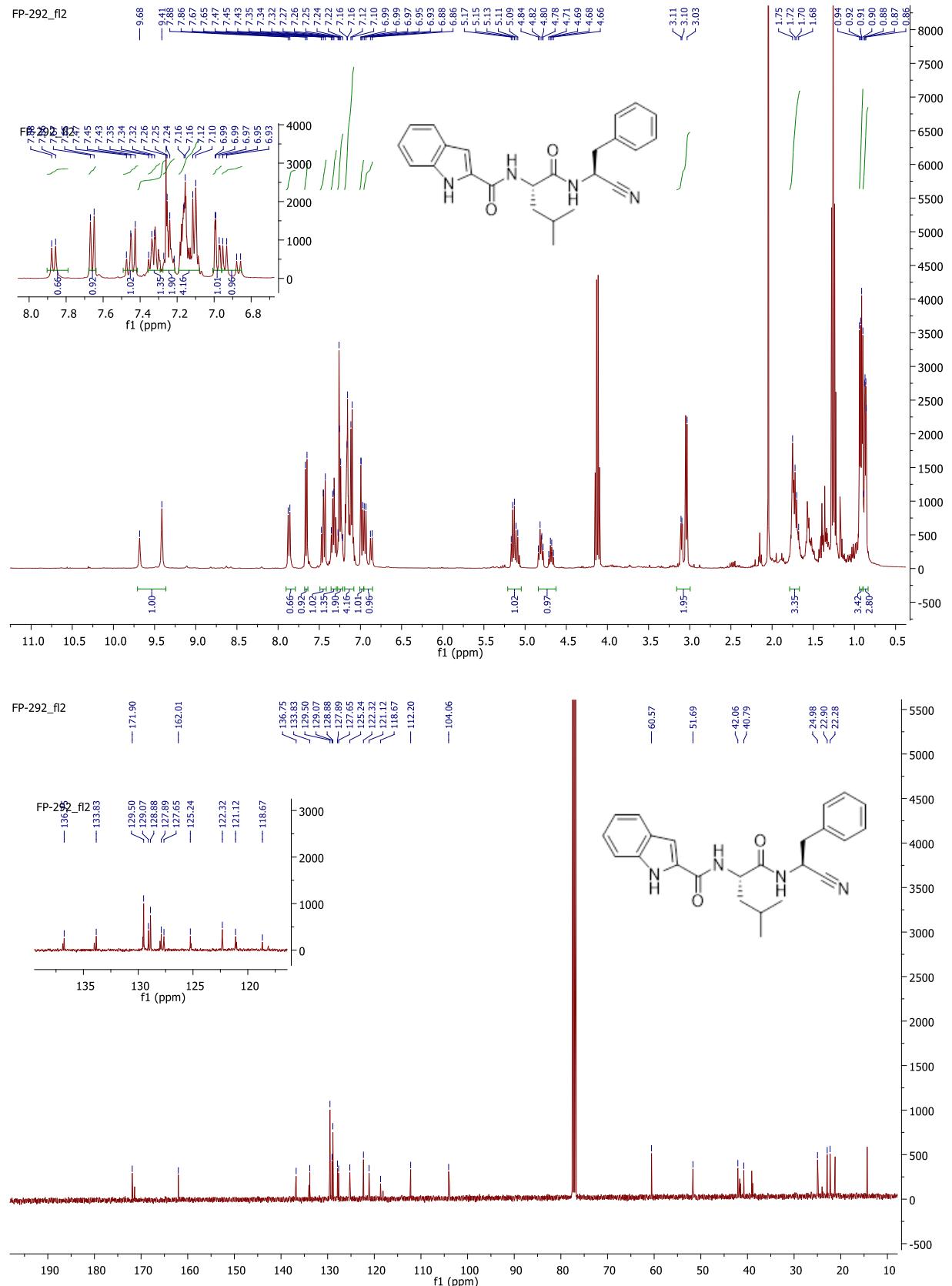
Figure S12: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of *N*-((*S*)-1-(((*S*)-1-cyano-2-phenylethyl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (**11b**)
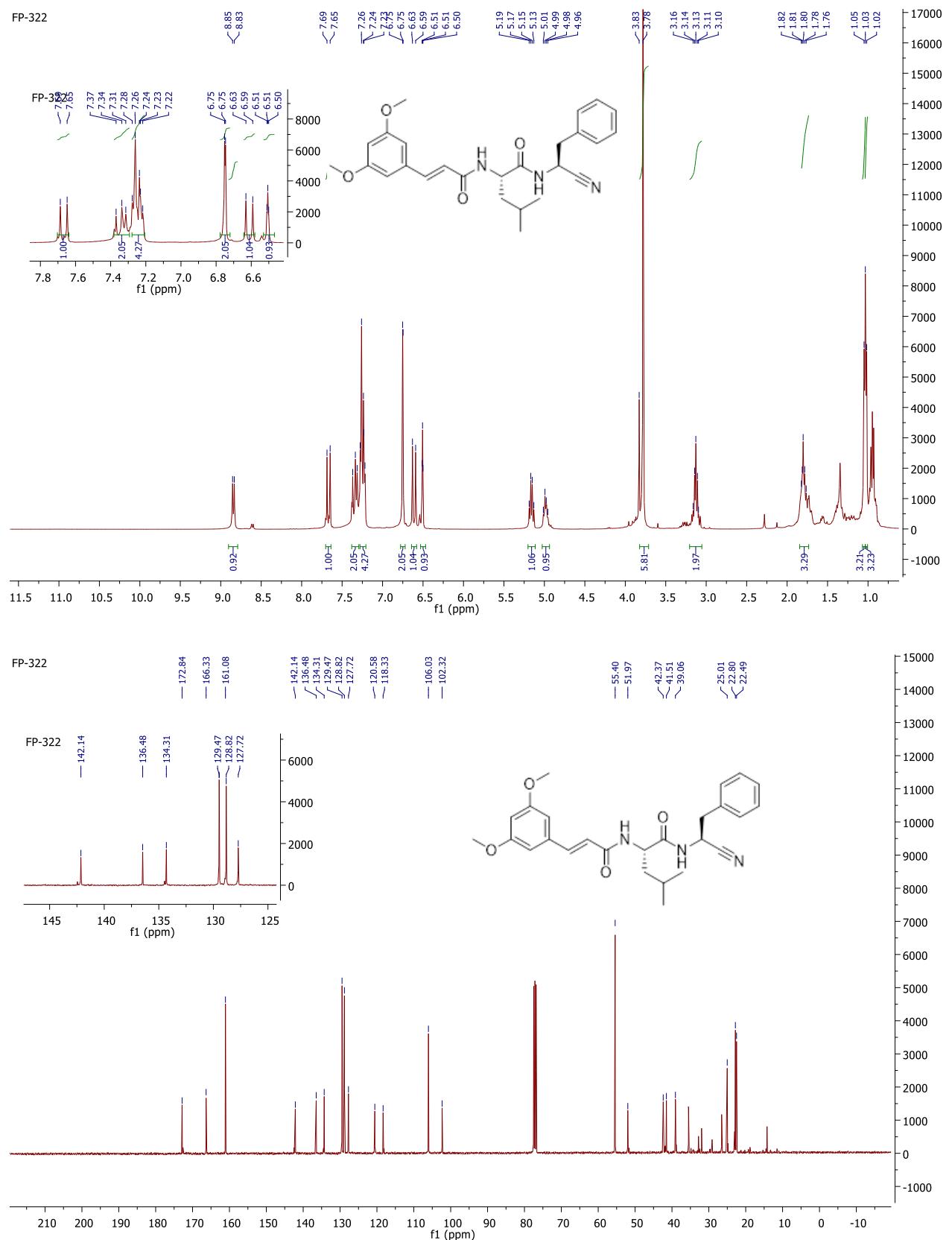
Figure S13: [1]H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-*N*-((*S*)-1-cyano-2-phenylethyl)-2-((*E*)-3-(3,5-dimethoxyphenyl)acrylamido)-4-methylpentanamide (**11c**)
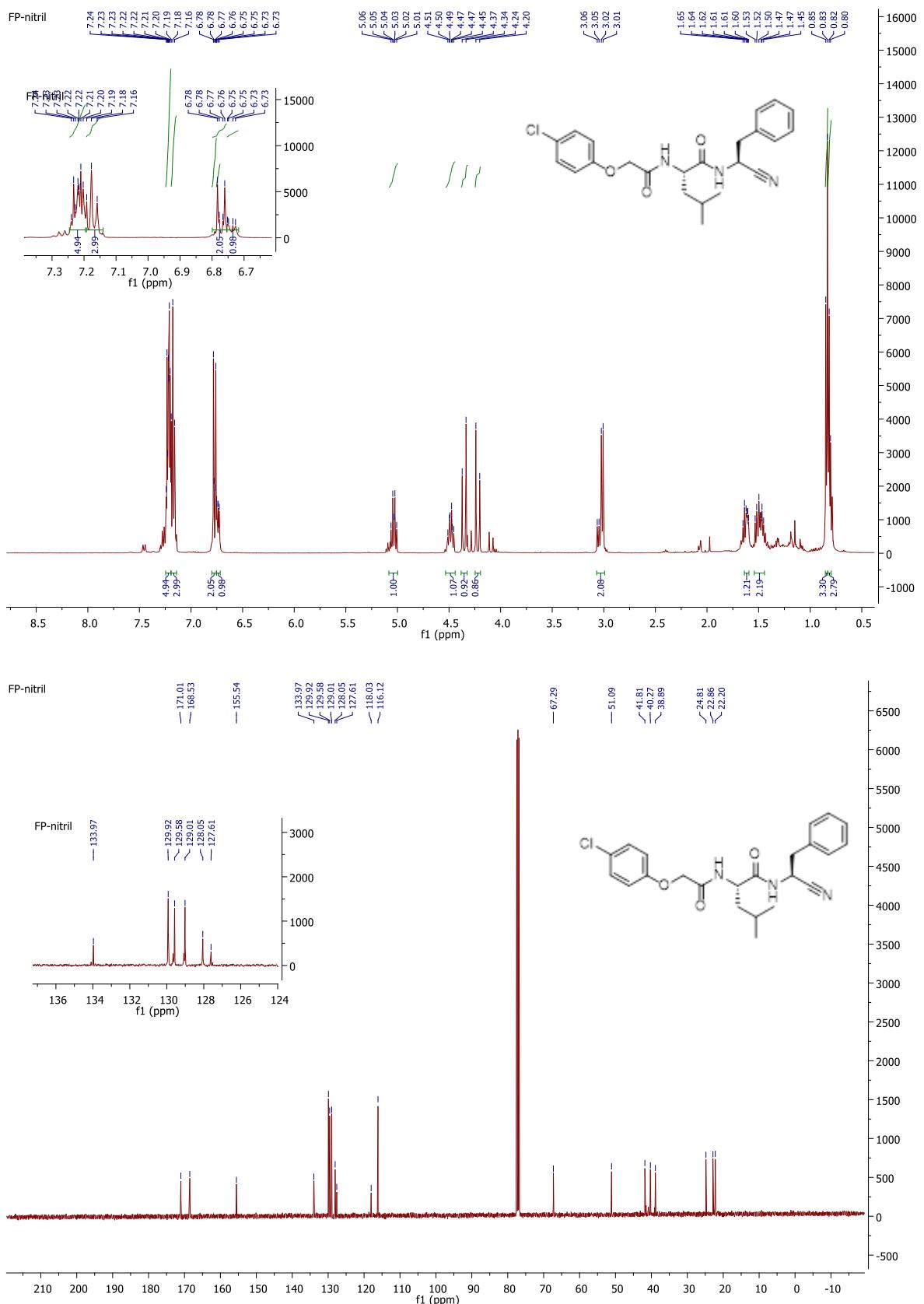
Figure S14: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-2-(2-(4-chlorophenoxy) acetamido)-*N*-((*S*)-1-cyano-2-phenylethyl)-4-methylpentanamide (**11d**)
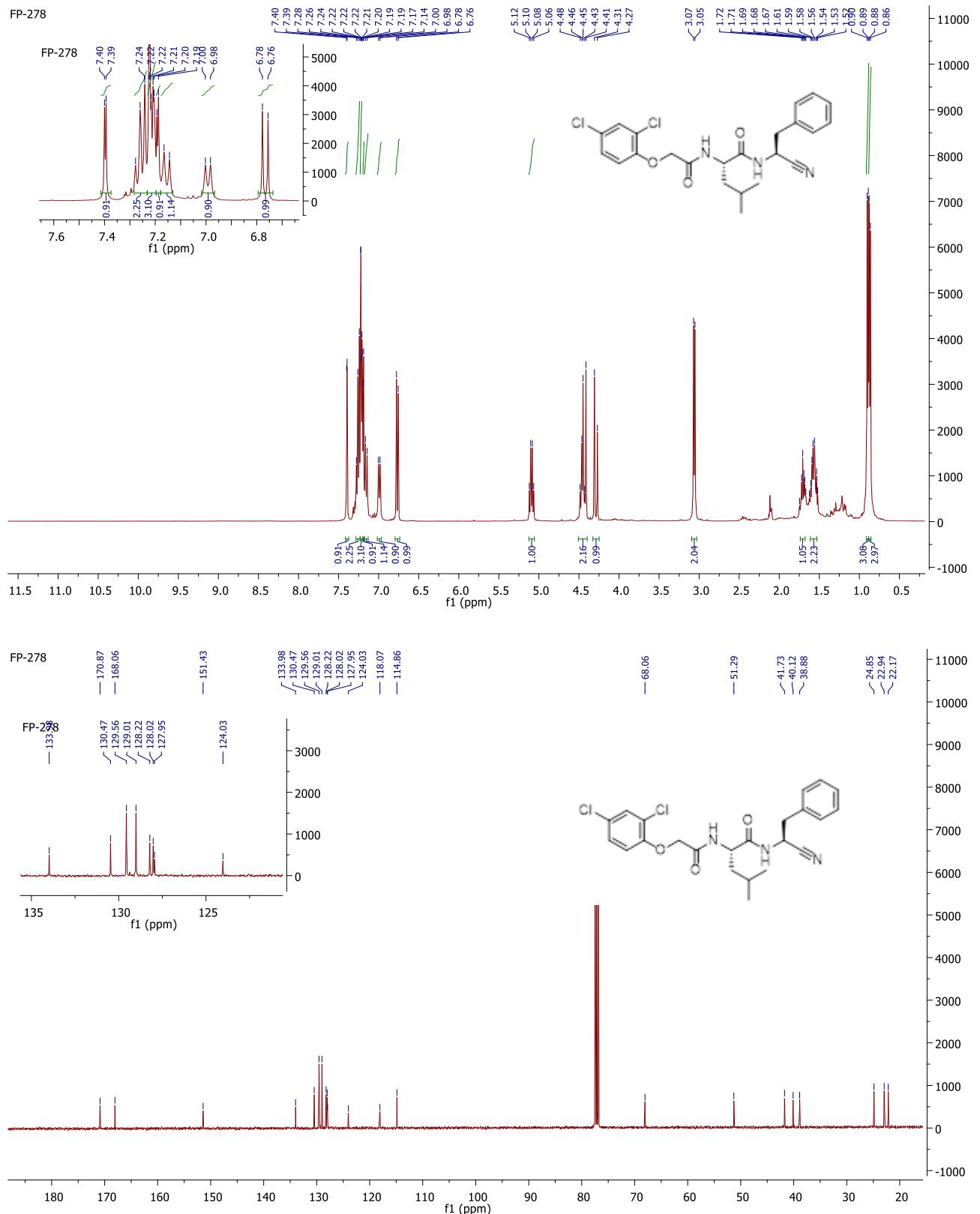
Figure S15: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-*N*-((*S*)-1-cyano-2-phenylethyl)-2-(2-(2,4-dichlorophenoxy)acetamido)-4-methylpentanamide (**11e**)
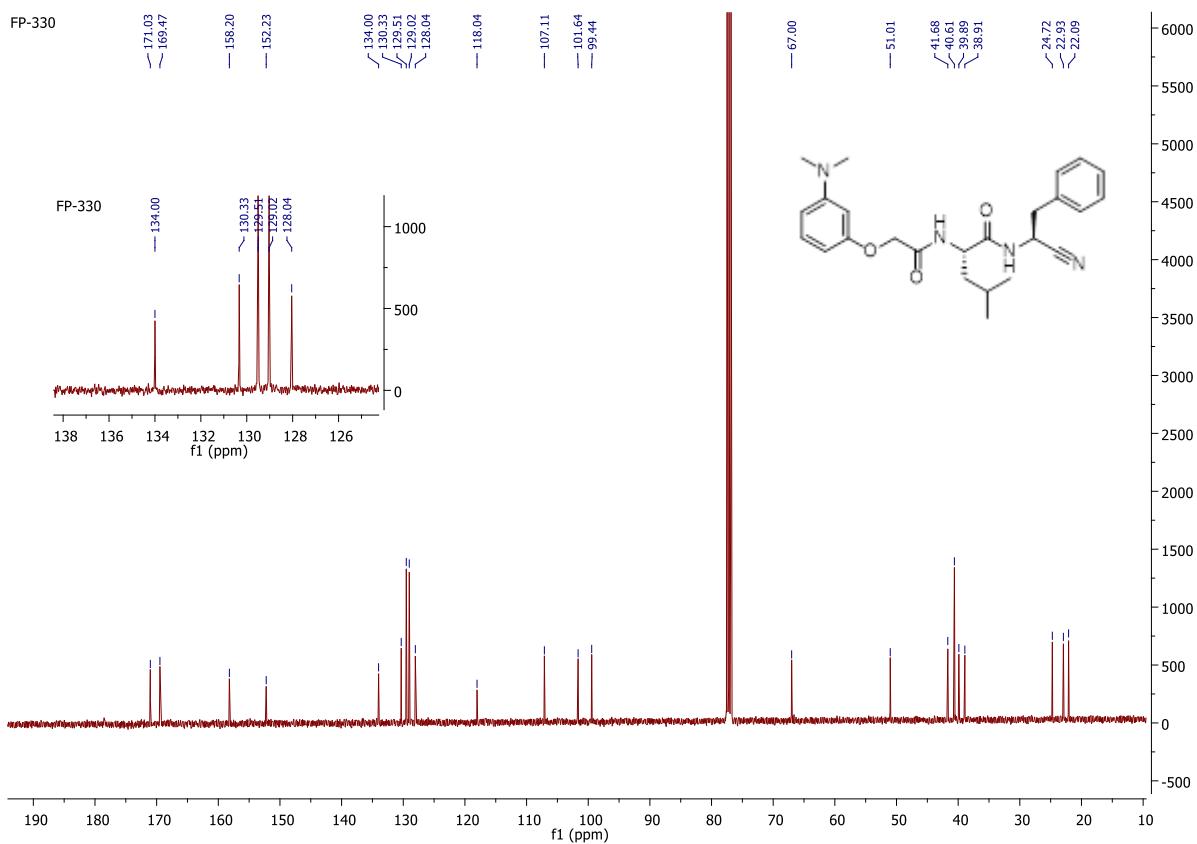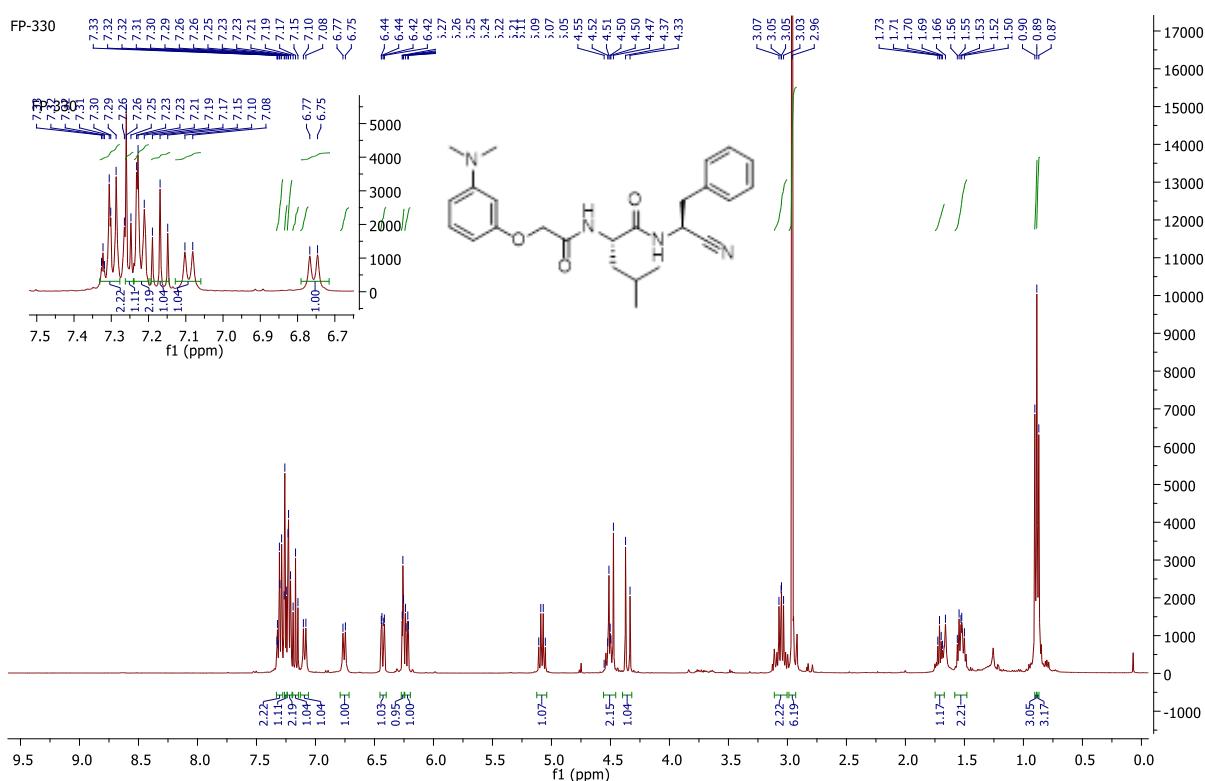
Figure S16: ¹H (400 MHz) & ¹³C (101 MHz) NMR (CDCl₃) spectra of (*S*)-*N*-((*S*)-1-cyano-2-phenylethyl)-2-(2-(3-(dimethylamino)phenoxy)acetamido)-4-methylpentanamide (**11f**)
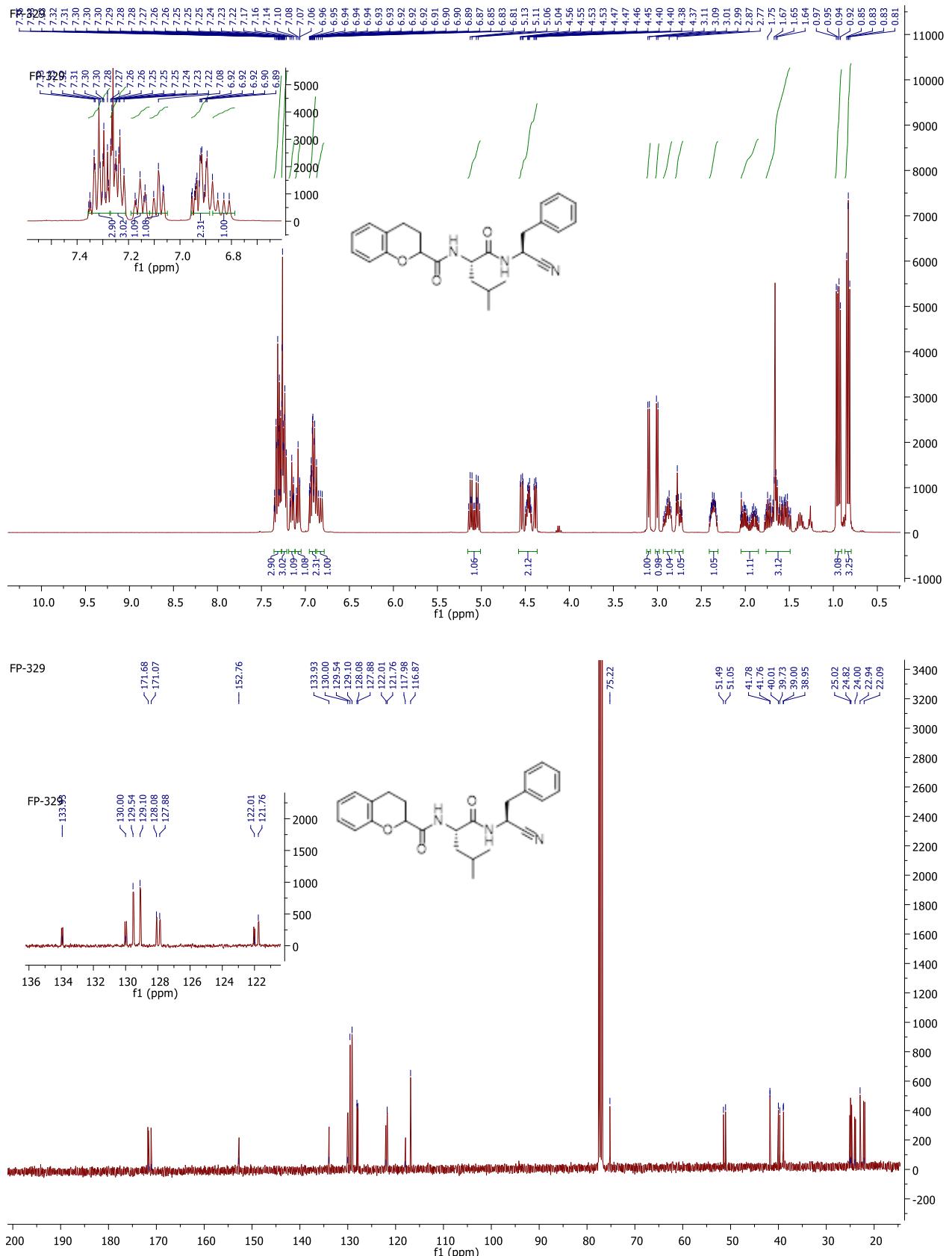
Figure S17: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*R,S*)-*N*-((*S*)-1-(((*S*)-1-cyano-2-phenylethyl)amino)-4-methyl-1-oxopentan-2-yl)chromane-2-carboxamide (**11g**)
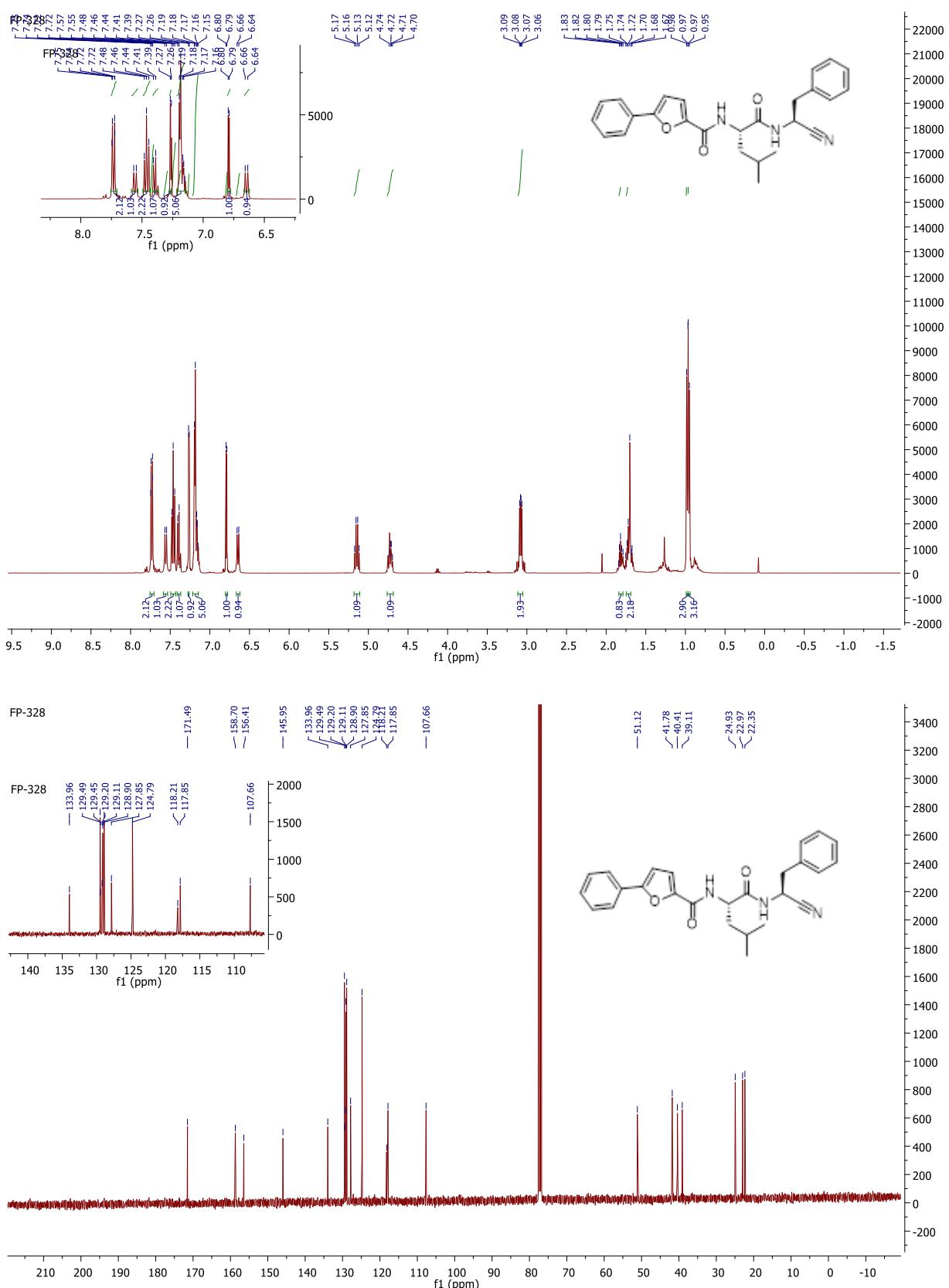
Figure S18: [1]H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of *N*-((*S*)-1-(((*S*)-1-cyano-2-phenylethyl)amino)-4-methyl-1-oxopentan-2-yl)-5-phenylfuran-2-carboxamide (**11h**)
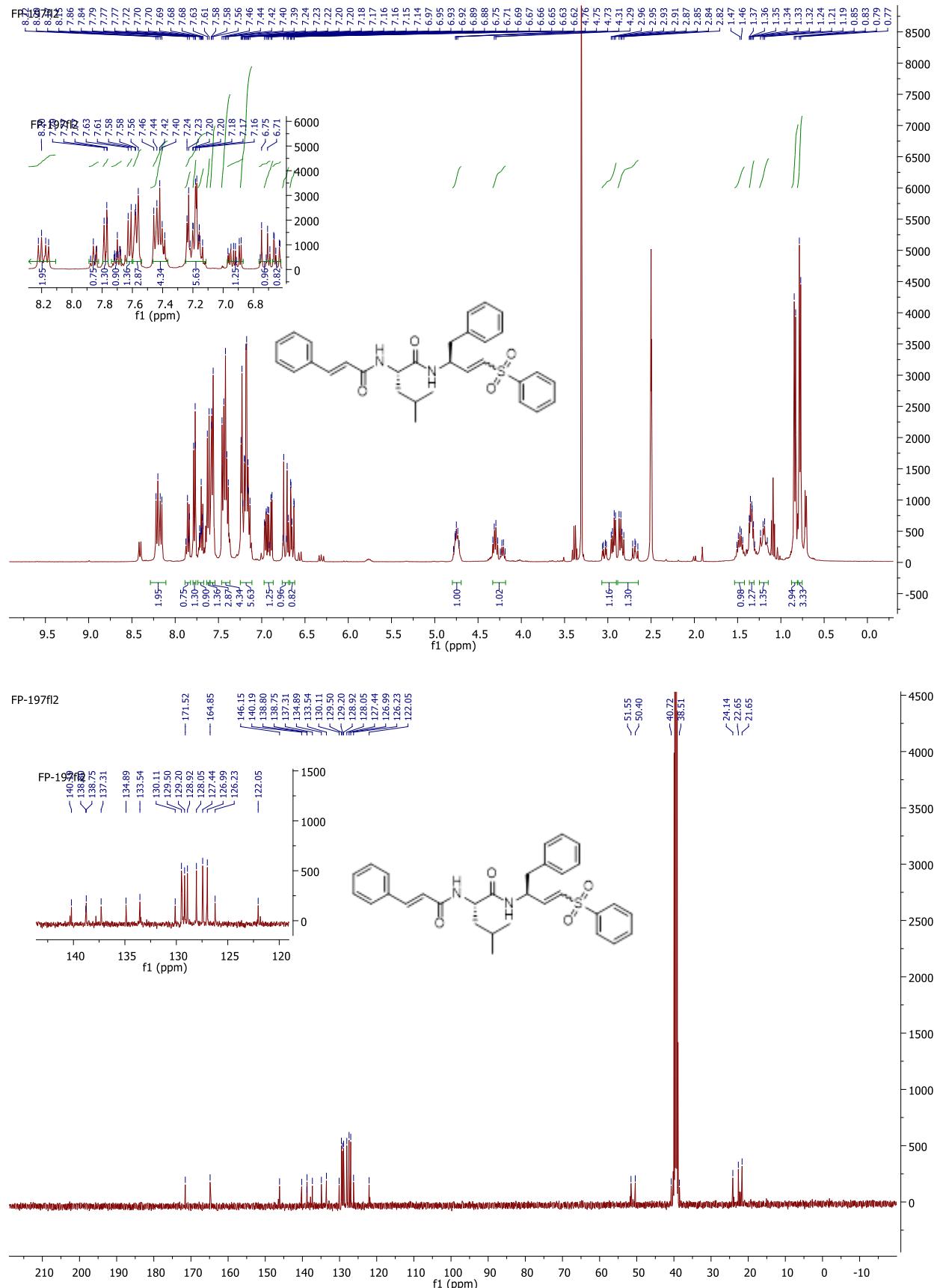
Figure S19: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of (*S*)-2-cinnamamido-4-methyl-*N*-((*S*)-1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)pentanamide (**12a**)
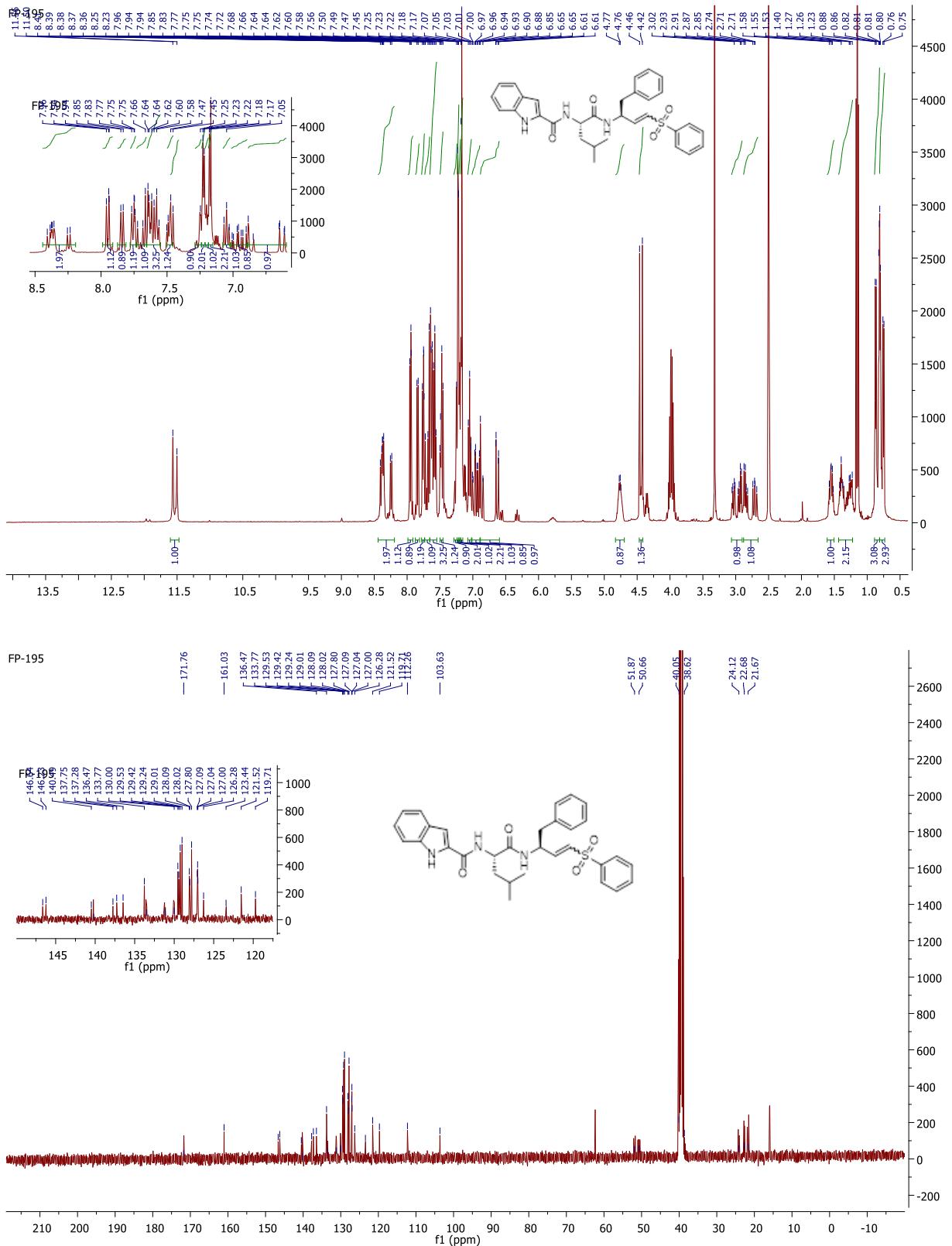
Figure S20: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of N-((S)-4-methyl-1-oxo-1-(((S)-1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)amino)pentan-2-yl)-1H-indole-2-carboxamide (**12b**)
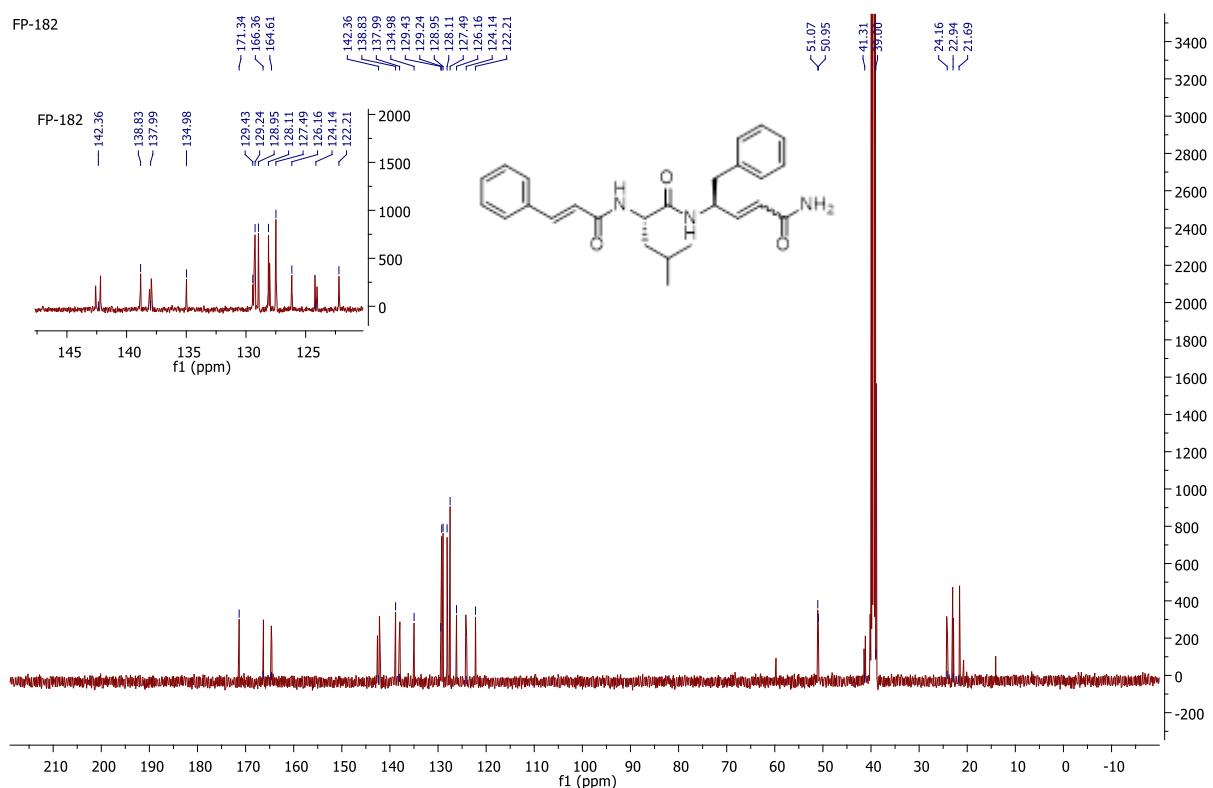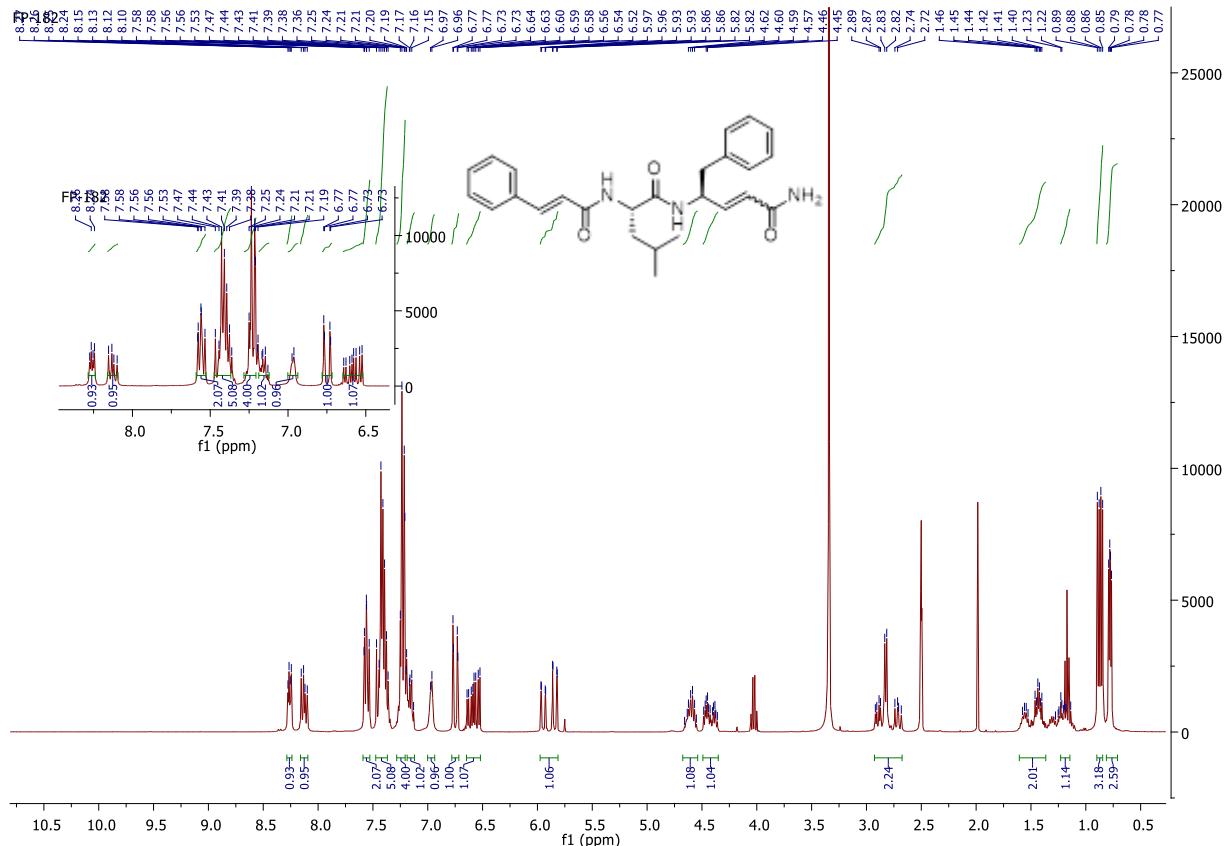
Figure S21: ^1H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of (S)-4-((S)-2-cinnamamido-4-methylpentanamido)-5-phenylpent-2-enamide **(13a)**
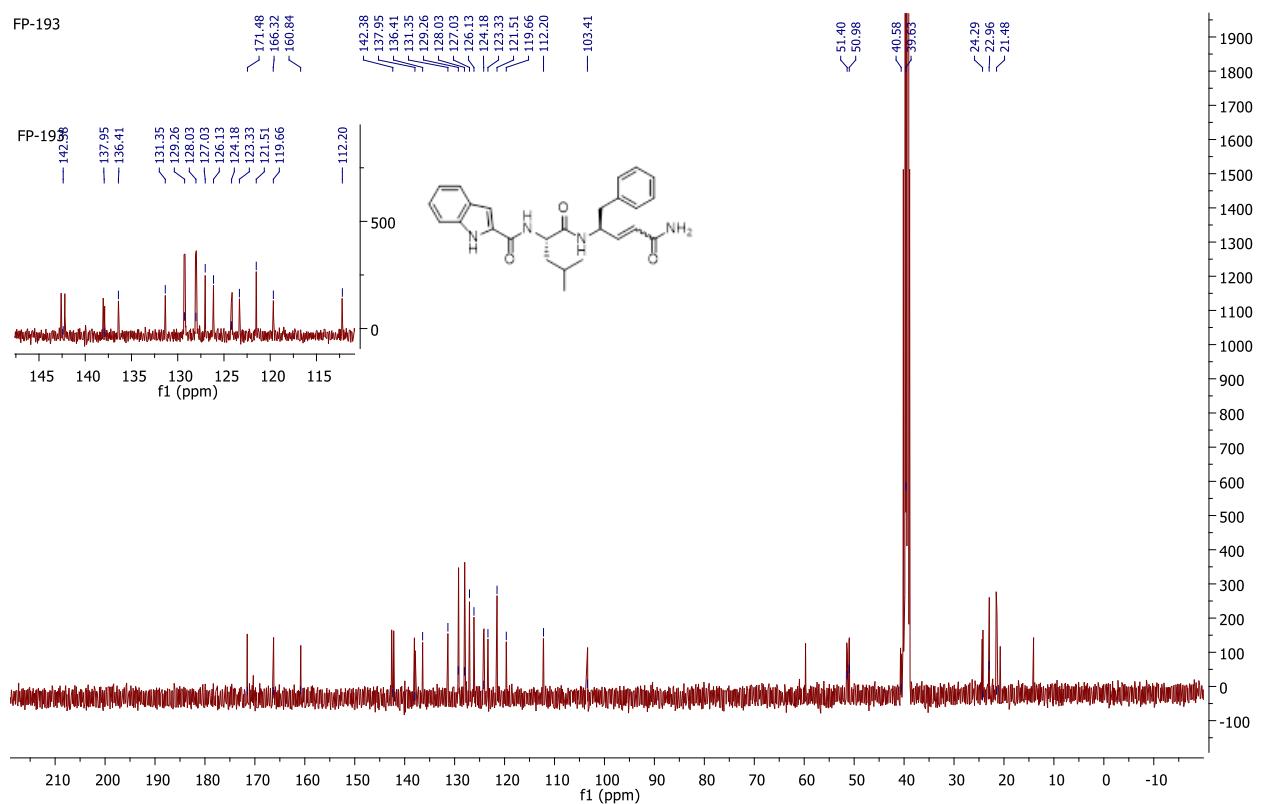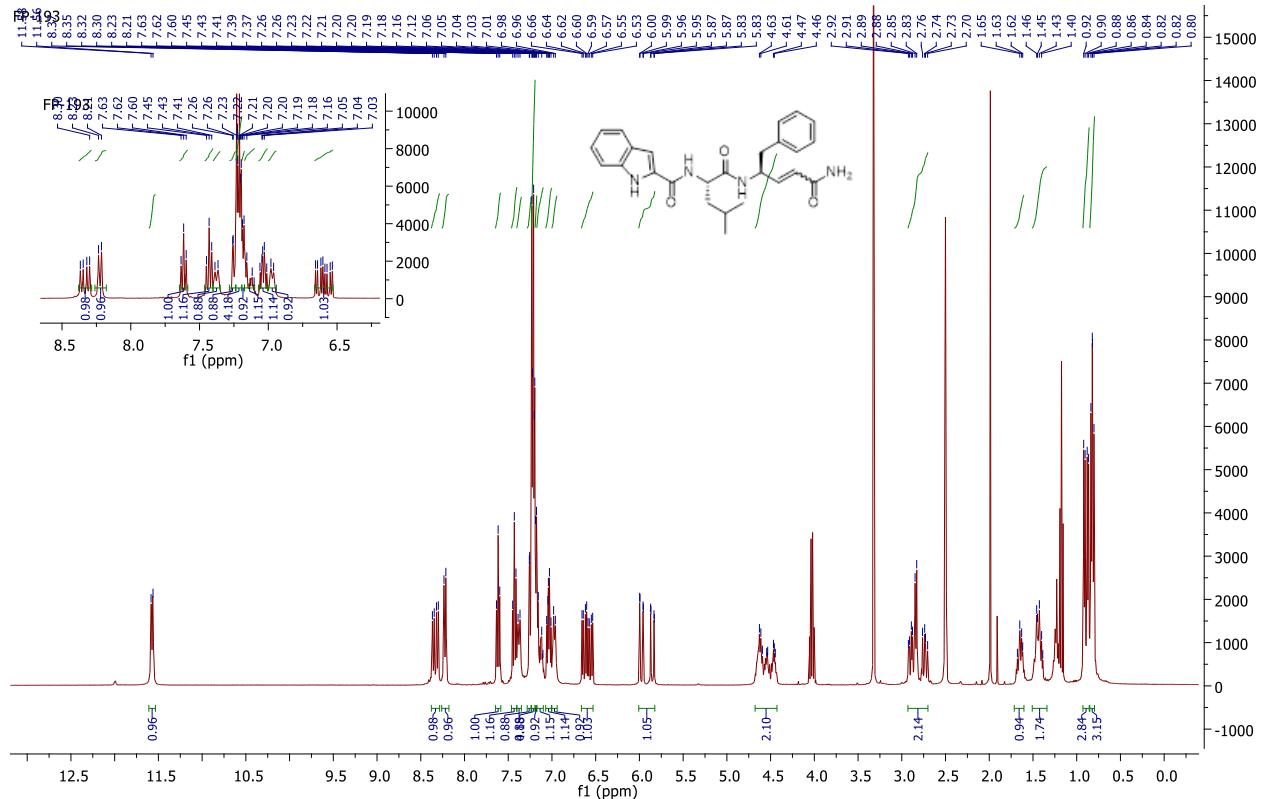
Figure S22: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (DMSO-d_6) spectra of *N*-((*S*)-1-(((*S*)-5-amino-5-oxo-1-phenylpent-3-en-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamid (**13b**)
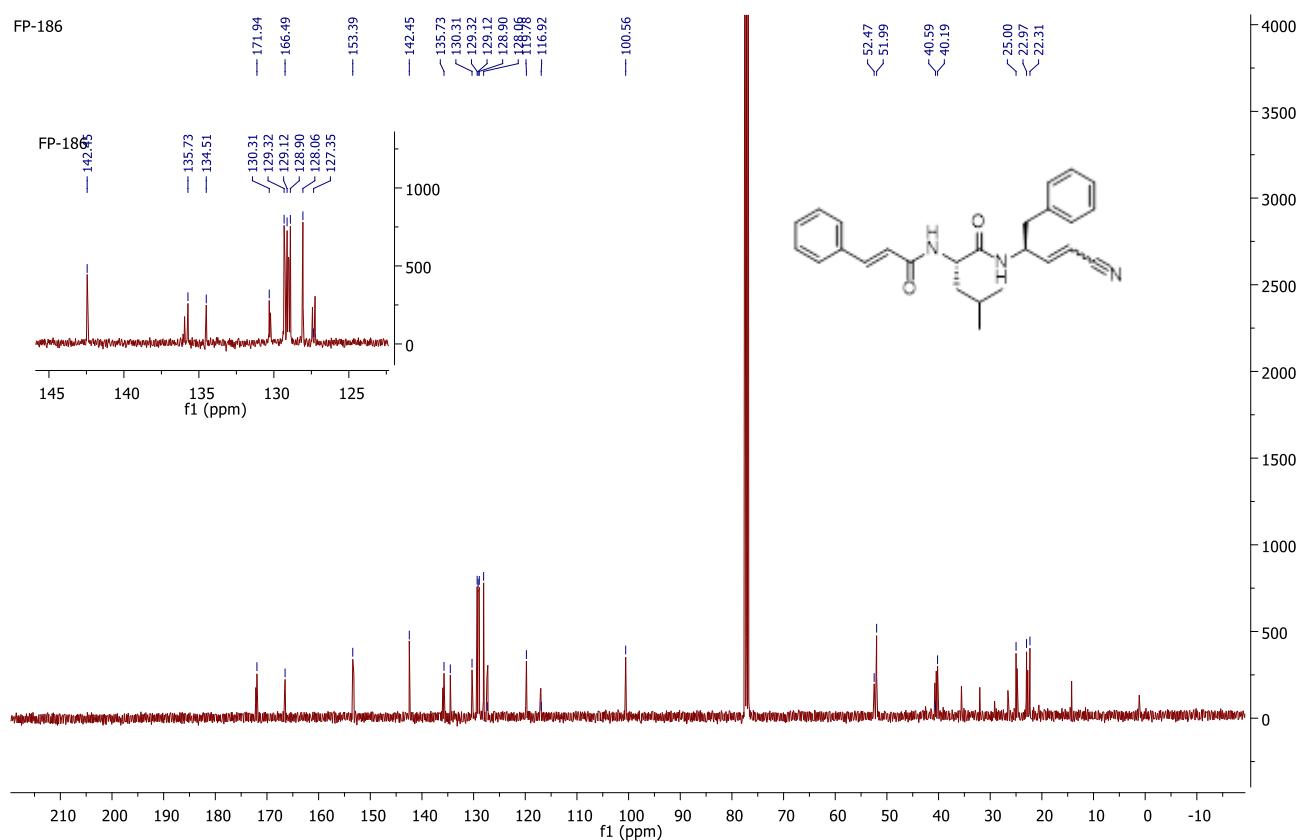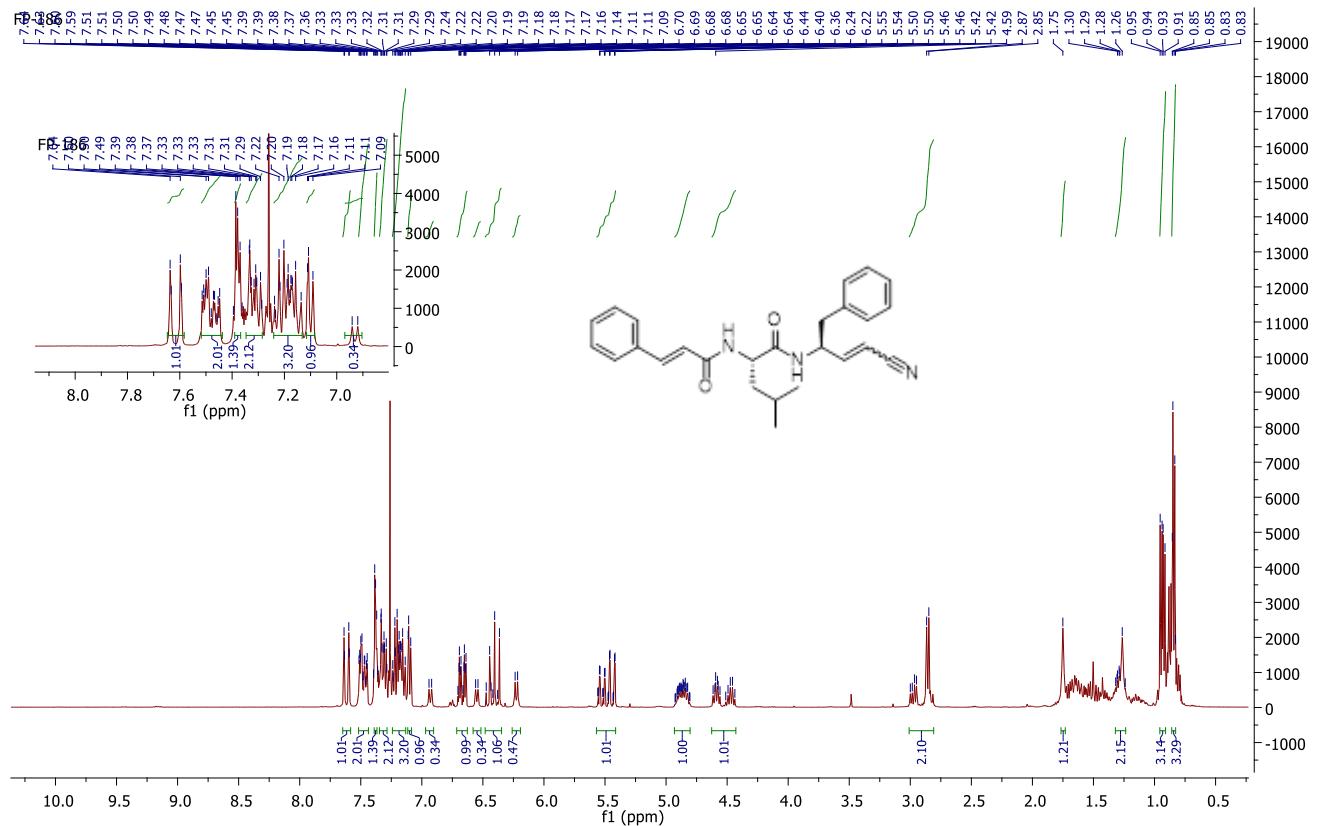
Figure S23: ^{1}H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of (*S*)-2-cinnamamido-*N*-((*S*)-4-cyano-1-phenylbut-3-en-2-yl)-4-methylpentanamide (**14a**)
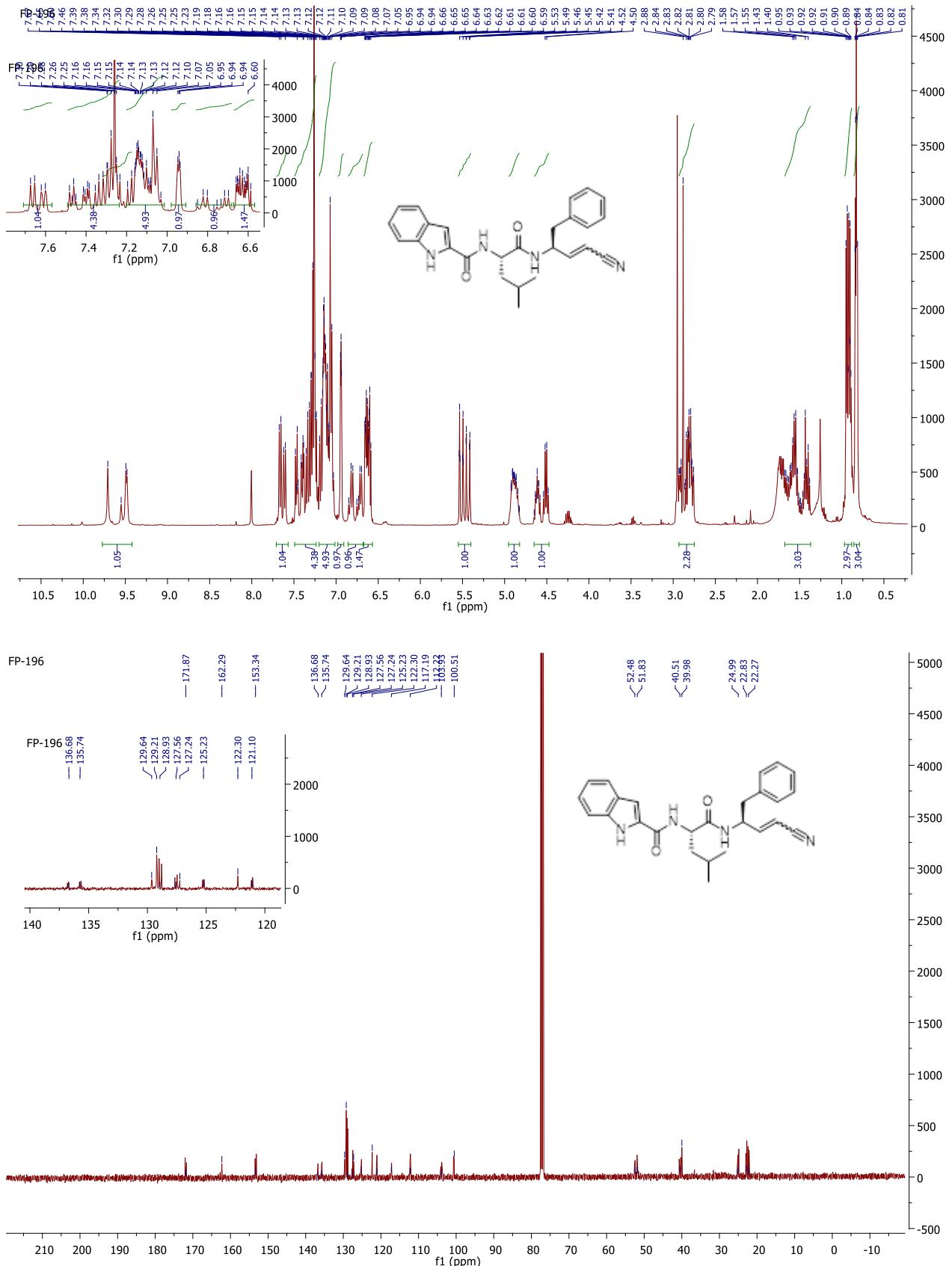
Figure S24: [1]H (400 MHz) & ^{13}C (101 MHz) NMR (CDCl$_3$) spectra of *N*-((*S*)-1-(((*S*)-4-cyano-1-phenylbut-3-en-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (**14b**)

5. HPLC traces

Compound 5b
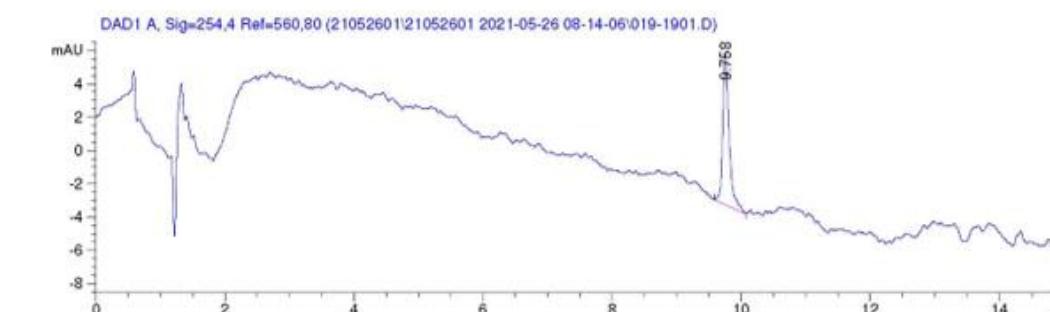
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Dilution:                      :       1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width      Area        Height     Area
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 1    9.758 BB    0.1016    62.32738    9.13607 100.0000

Totals :                    62.32738    9.13607
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Compound 5i
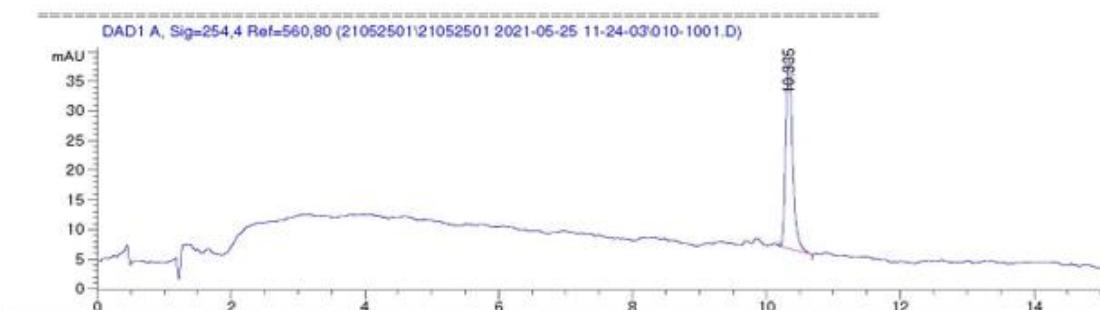
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Dilution:                      :       1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area        Height     Area
 #    [min]        [min]    [mAU*s]       [mAU]        %
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 1   10.335 BB    0.1091   227.98138   31.99082 100.0000

Totals :                   227.98138   31.99082
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Compound 6
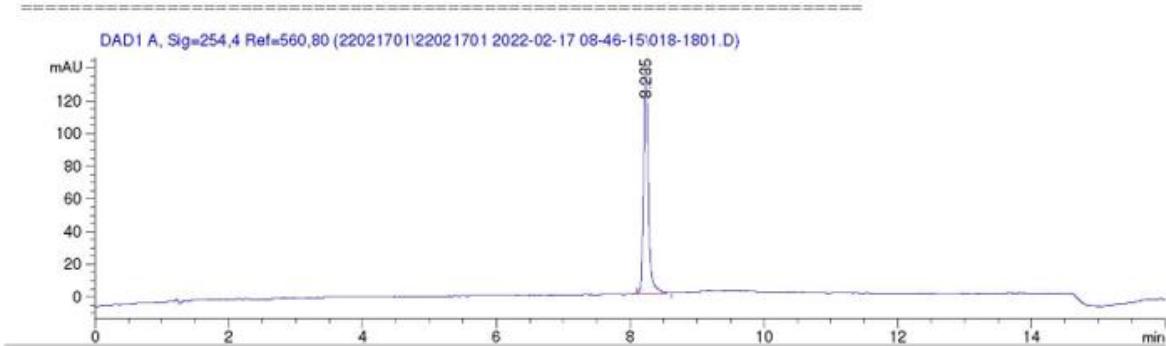
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Dilution:                       :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area        Height     Area
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 1   8.235 BB   0.0764   685.66992   137.08678 100.0000

Totals :                 685.66992   137.08678
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Compound 7
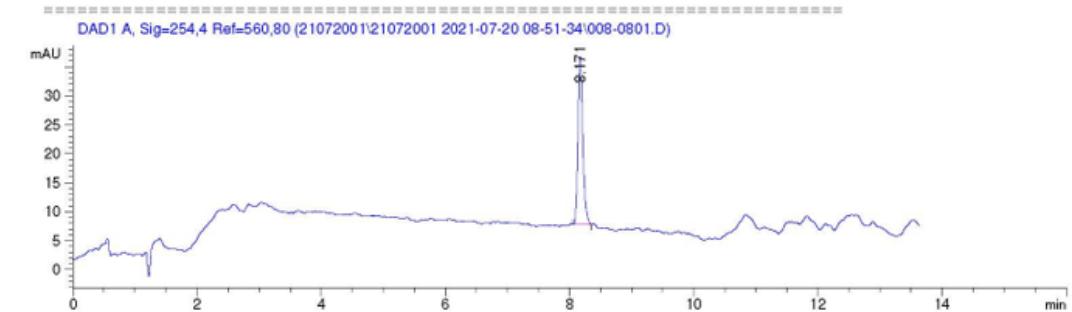
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Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area        Height     Area
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 1   8.171 BB   0.0832   157.33136    29.05354 100.0000

Totals :                 157.33136    29.05354
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Compound 9a

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Dilution:                      :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area       Height     Area
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----|-------|----|-------|----------|----------|--------|
  1   8.644 BB   0.0888  320.96643   54.44330  81.0659
  2   8.965 BB   0.1338   74.96609    9.12502  18.9341

Totals :                 395.93252   63.56832
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Compound 9b

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Sorted By              :       Signal
Multiplier:                    :       1.0000
Dilution:                      :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]    [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.134 BV   0.0965   83.99298   13.15737  61.2455
  2   8.444 VV   0.1225   53.14860    5.82108  38.7545

Totals :                 137.14158   18.97845
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Compound 9c

DAD1 A, Sig=254,4 Ref=560,80 (21052601\21052601 2021-05-26 08-15-10\007-0701.D)

Area Percent Report

Sorted By   :   Signal
Multiplier: :   1.0000
Dilution: :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.532	BB	0.1240	47.70889	5.92209	3.7031
2	11.160	VV	0.0917	807.76959	131.46721	62.6978
3	11.430	VB	0.1548	432.87512	43.24741	33.5991

Totals :   1288.35361 180.63671

Compound 11a

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Area Percent Report

Sorted By   :   Signal
Multiplier: :   1.0000
Dilution: :   1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.639	VB	0.0911	268.61740	45.37460	100.0000

Totals :   268.61740   45.37460

Compound 11b

DAD1 A, Sig=254,4 Ref=560,80 (22020201\22020201 2022-02-02 08-51-07\003-0301.D)

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                    Area Percent Report
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Sorted By              :        Signal
Multiplier:                     :     1.0000
Dilution:                       :     1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area        Height      Area
 #    [min]        [min]   [mAU*s]        [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.195 BB   0.0975 1193.95557  194.78198  98.6448
  2   8.981 VB   0.1000   16.40281    2.39228   1.3552

Totals :                1210.35837  197.17426
```

Compound 11c
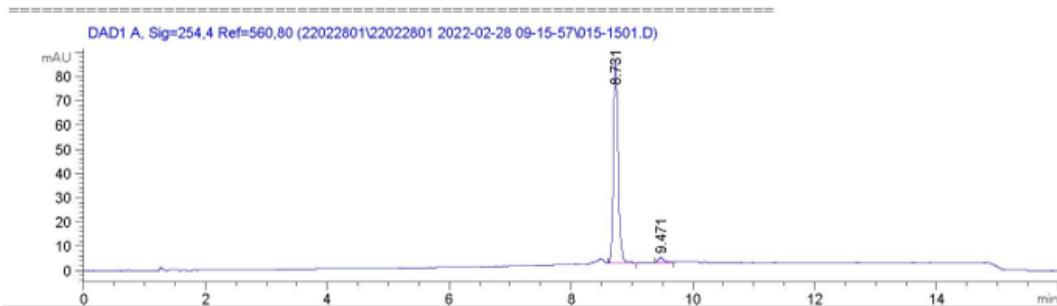
DAD1 A, Sig=254,4 Ref=560,80 (22022801\22022801 2022-02-28 09-15-57\015-1501.D)

```
============================================================
                  Area Percent Report
============================================================

Sorted By              :        Signal
Multiplier:                     :     1.0000
Dilution:                       :     1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area        Height      Area
 #    [min]        [min]   [mAU*s]        [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.731 VB   0.0826  452.26819   84.23004  97.2745
  2   9.471 BB   0.0892   12.67204    2.07576   2.7255

Totals :                 464.94023   86.30580
```

Compound 11d
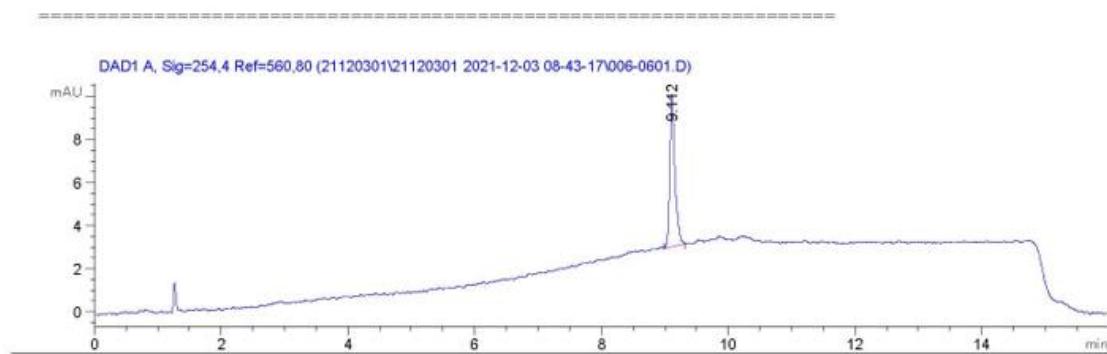

```
========================================================

                    Area Percent Report

========================================================


Sorted By           :        Signal
Multiplier:                  :        1.0000
Dilution:                    :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   9.112 BB    0.0814   39.63363   7.07259 100.0000

Totals :                   39.63363   7.07259
```

Compound 11e
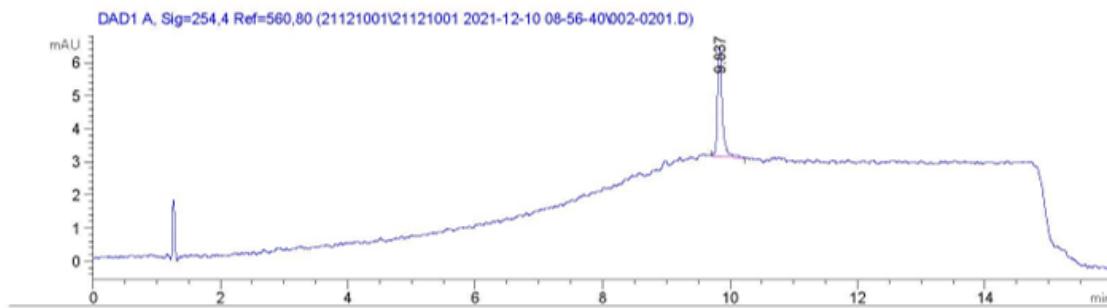

```
========================================================

                    Area Percent Report

========================================================

Sorted By           :        Signal
Multiplier:                  :        1.0000
Dilution:                    :        1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area       Height     Area
  #   [min]        [min]    [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   9.837 BB    0.0764   17.19309   3.31959 100.0000

Totals :                   17.19309   3.31959
```

Compound 11f

```
===============================================================
    DAD1 A, Sig=254,4 Ref=560,80 (22031001\22031001 2022-03-10 08-38-18\016-1601.D)
```



```
===============================================================
                    Area Percent Report
===============================================================

Sorted By              :        Signal
Multiplier:                     :        1.0000
Dilution:                       :        1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area        Height      Area
  #   [min]        [min]   [mAU*s]       [mAU]        %
----|-------|----|-------|----------|-----------|--------|
  1   7.817 BB    0.0885 1216.58289  207.08702   97.1021
  2  10.042 BB    0.1016   36.30735    5.45787    2.8979

Totals :                  1252.89024  212.54489
```

Compound 11g

```
===============================================================
    DAD1 A, Sig=254,4 Ref=560,80 (22031001\22031001 2022-03-10 08-37-05\009-0901.D)
```



```
===============================================================
                    Area Percent Report
===============================================================

Sorted By              :        Signal
Multiplier:                     :        1.0000
Dilution:                       :        1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area        Height      Area
  #   [min]        [min]   [mAU*s]       [mAU]        %
----|-------|----|-------|----------|-----------|--------|
  1   9.116 BV    0.0592   35.36578    9.12228   41.6069
  2   9.175 VB    0.0736   49.63404   10.06014   58.3931

Totals :                    84.99982   19.18242
```

Compound 11h

DAD1 A, Sig=254,4 Ref=560,80 (22030901\22030901 2022-03-09 08-28-50\007-0701.D)

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By              :       Signal
Multiplier:                    :        1.0000
Dilution:                      :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.244 BB   0.0743 1695.46484  339.31561  95.4058
   2  10.255 BB   0.0977   81.64434   12.58922   4.5942

Totals :                  1777.10918  351.90484
```

Compound 12a
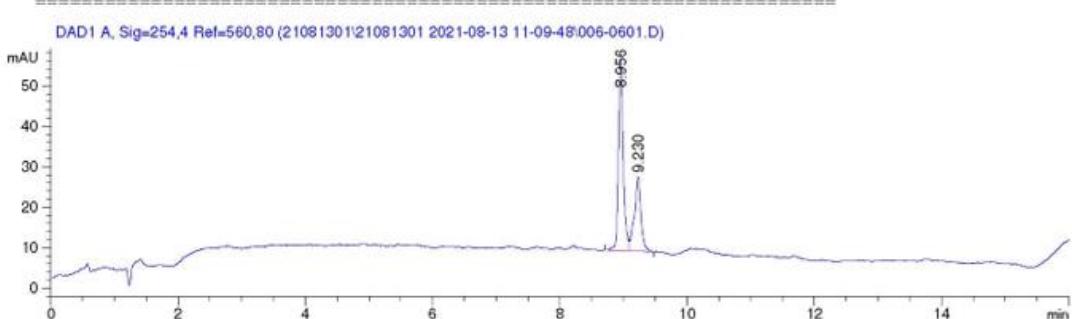
DAD1 A, Sig=254,4 Ref=560,80 (21081301\21081301 2021-08-13 11-09-48\006-0601.D)

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By              :       Signal
Multiplier:                    :        1.0000
Dilution:                      :        1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area       Height     Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.956 BV   0.0795  248.28177   47.12888  65.7967
   2   9.230 VB   0.1003  129.06532   18.30447  34.2033

Totals :                   377.34709   65.43336
```

Compound 12b
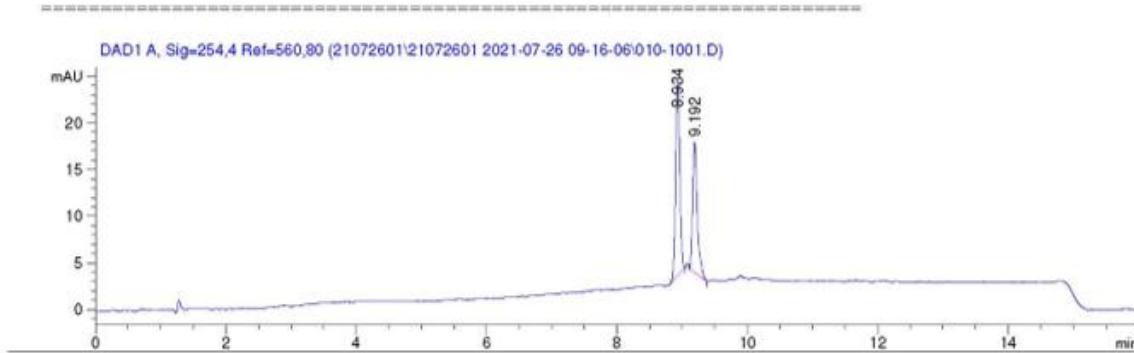
DAD1 A, Sig=254,4 Ref=560,80 (21072601\21072601 2021-07-26 09-16-06\010-1001.D)

```
============================================================
                    Area Percent Report
============================================================

Sorted By          :        Signal
Multiplier:                 :       1.0000
Dilution:                   :       1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area        Height      Area
 #   [min]         [min]    [mAU*s]       [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   8.934 BB    0.0702    94.15446   21.04728   57.7407
  2   9.192 BB    0.0732    68.90974   14.05628   42.2593

Totals :                   163.06419   35.10356
```

Compound 13a
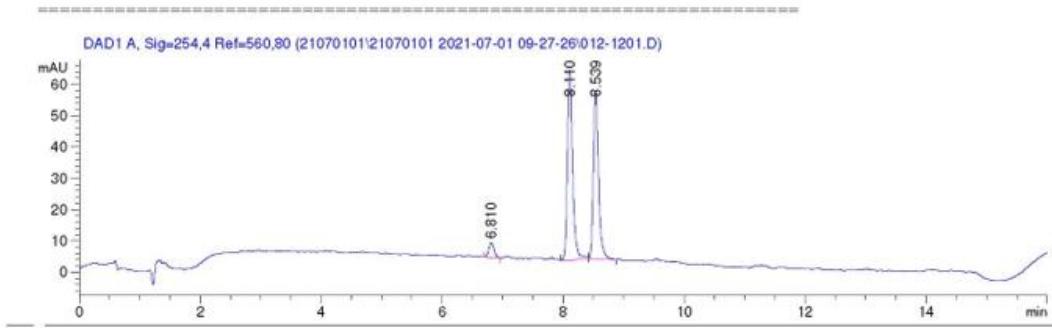
DAD1 A, Sig=254,4 Ref=560,80 (21070101\21070101 2021-07-01 09-27-26\012-1201.D)

```
============================================================
                    Area Percent Report
============================================================

Sorted By          :        Signal
Multiplier:                 :       1.0000
Dilution:                   :       1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width      Area        Height      Area
 #   [min]         [min]    [mAU*s]       [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   6.810 BB    0.0908    27.11792    4.59740    3.8175
  2   8.110 BV    0.0902   365.03259   60.65736   51.3867
  3   8.539 VB    0.0886   318.21301   54.12305   44.7958

Totals :                   710.36353  119.37781
```

Compound 13b
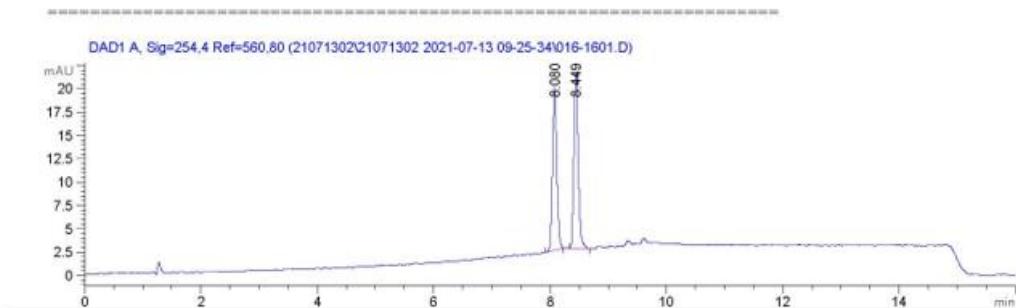

```
DAD1 A, Sig=254,4 Ref=560,80 (21071302\21071302 2021-07-13 09-25-34\016-1601.D)
```

```
============================================================
                     Area Percent Report
============================================================

Sorted By          :        Signal
Multiplier:                :     1.0000
Dilution:                  :     1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area      Height    Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   8.080 BB   0.0775   89.28501   17.49447  48.0036
  2   8.449 BB   0.0778   96.71154   18.85383  51.9964

Totals :                 185.99655   36.34829
```

Compound 14a
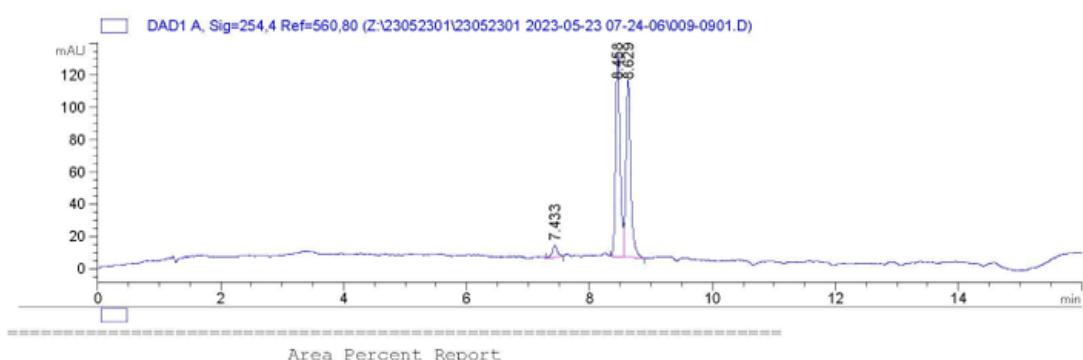

```
DAD1 A, Sig=254,4 Ref=560,80 (Z:\23052301\23052301 2023-05-23 07-24-06\009-0901.D)
```

```
============================================================
                     Area Percent Report
============================================================

Sorted By          :        Signal
Multiplier:                :     1.0000
Dilution:                  :     1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=560,80

Peak RetTime Type  Width     Area      Height    Area
 #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   7.433 BV   0.0867   45.66756    7.75450   3.6275
  2   8.458 BV   0.0738  627.28296  126.57775  49.8266
  3   8.629 VB   0.0796  585.98193  110.93806  46.5459

Totals :                1258.93245  245.27031
```