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Supplementary Information

3-Substituted 2-isocyanopyridines as versatile convertible isocyanides for peptidomimetic design

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TABLE OF CONTENTS

GENERAL CONSIDERATIONS

Unless stated otherwise, all commercial materials were used without further purification. Anhydrous tetrahydrofuran was obtained using a PureSolv Innovative Technology system. Anhydrous dichloromethane was obtained by storing under argon atmosphere on activated 4 Å molecular sieves for 24 hours prior to use. Non-commercial starting materials were prepared based on literature procedures and are described below. ^{1}H and ^{13}C NMR spectra were recorded using different spectrometers. A Bruker Avance II 500 spectrometer was used at 500 MHz (^{1}H NMR) and 126 MHz (^{13}C NMR) at ambient temperature. To obtain spectra at 250 MHz (^{1}H NMR) and 63 MHz (^{13}C NMR), the Bruker Avance DRX 250 was used. The chemical shifts were reported in delta (δ) units in parts per million (ppm) relative to the signal of the deuterated solvent. For the $CDCl_3$, the singlet in ^{1}H NMR was calibrated at 7.26 ppm and the ^{13}C NMR at the central line of the triplet at 77.0 ppm. When recording in MeOD or DMSO-d_6, the calibration was performed at 3.31 ppm and 2.50 ppm for the ^{1}H NMR and 49.00 ppm and 39.50 ppm for the ^{13}C NMR, respectively. The assignments were made using one dimensional (1D) ^{1}H and ^{13}C spectra and two-dimensional (2D) HSQC, HMBC and COSY spectra. Multiplicities were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination thereof. The corresponding coupling constants (*J* values) were reported in Hertz (Hz). Analytical RP-HPLC were performed on an VWR-Hitachi Chromaster HPLC with a Chromolith HighResolution RP-18C column from Merck (150 mm X 4.6 mm, 1.1 μm, 150 Å) or a Chromolith HighResolution RP-18C column from Merck (50 mm X 4.6 mm, 1.1 μm, 150 Å). The analysis performed on the columns is specified as HPLC-1 and HPLC-2, respectively. The flow rate was 3 ml/min and the UV detection was done at 214 nm. The solvent system consisted of 0.1% TFA in ultrapure water (A) and 0.1% TFA in acetonitrile (B) with a gradient from 3% B to 100% B over a 4 minutes runtime for the column with a length of 50 mm and 5 min for the column with a length of 150 mm. Mass spectra were recorded with a LC-MS triplequadrupole system. HPLC unit was a Waters 600 system combined to a Waters 2487 UV detector at 215 nm and as stationary phase a Vydac MS RP C18-column (150 mm x 2.1 mm, 3 μm, 300 Å). The solvent system was 0.1 % formic acid in water (A) and 0.1 % formic acid in acetonitrile (B) with a gradient going from 3 % to 100 % B over 20 minutes with a flow rate of 0.3 ml/min. The MS unit, coupled to the HPLC system, was a Micromass QTOF-micro system. For the high-resolution mass spectroscopy (HRMS), the same MS system was used with reserpine (2.10^{-3} mg/ml) solution in H_2O:CH_3CN (1:1) as reference. Automated flash chromatography was performed using Grace® Reveleris X2 system equipped with ELSD and UV detector (254 nm or 280 nm). The used normal phase column for the systems were Grace® Silica Flash Cartridges of 40 g with a flow rate of 40 ml/min unless stated otherwise. Semi-preparative HPLC-purifications were done using a Gilson HPLC system with Gilson 322 pump equipped with a Grace® Vydac 150HC C18 (250 mm x 22 mm, 10 μm) column and Waters UV/VIS-156 detector at 214 nm. The same solvent system is used as for the analytical RP-HPLC with a flow rate of 20 ml/min. Melting points were recorded on a Büchi B-540 and are uncorrected. The transamidations were performed in sealed microwave vials for a reaction volume of 0.5 ml – 2 ml (Figure S1) equipped with a triangle stirring bar. Unless otherwise stated classical heating in an oil bath was performed.

Figure S1. Reaction vial (0.5 ml – 2 ml) used for the transamidation reactions.

OPTIMIZATION DATA OF THE ISOCYANIDE SYNTHESIS

General Procedure for the synthesis with $POCl_3$

The reactions with $POCl_3$ were performed according to a literature procedure.[1] To a flame-dried round-bottom flask charged with 3-substituted-2-formamidopyridine **2** (1 equiv, 5 mmol) in anhydrous CH_2Cl_2 (15 ml), Et_3N was added. The mixture was cooled to -78 °C. $POCl_3$ was added dropwise to the mixture and stirred continued at -78 °C for 1 h. Next, the mixture was allowed to warm up to 0 °C and stirred overnight. The reaction was quenched by adding it to a saturated $NaHCO_3$ solution. The water phase was extracted with CH_2Cl_2. The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by automated flash column chromatography.

General Procedure for the synthesis with $PhPO_2Cl_2$

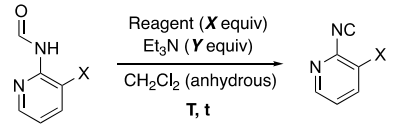
To a flame-dried round-bottom flask charged with 3-substituted-2-formamidopyridine **2** (1 equiv, 5 mmol) in anhydrous CH_2Cl_2 (5 ml), Et_3N (7.2 equiv, 35.9 mmol, 5 ml) was added. The solution was cooled to 0 °C followed by the dropwise addition of $PhPO_2Cl_2$ (1.2 equiv, 6 mmol, 0.9 ml). The mixture was stirred at 0 °C for 30 minutes, allowed to warm up to room temperature and stirring for another 24 hours.

The reaction mixture was added to brine (300 ml) and extracted with EtOAc (3 x 200 ml). The combined organic layers were washed with HCl (1M, 200 ml), $NaHCO_3$ solution (sat., 200 ml) and brine (200 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude mixture was purified by automated flash column chromatography.

Evaluation of the reaction parameters

The 3-substituted 2-isocyanopyrdines **3** were synthesized by the dehydration of its corresponding formamide **2**. Starting from the procedure described in literature for the 6-bromo-2-isocyanopyridine,[1] the isolation of 3-bromo-2-isocyanopyridine **3a**, 3-chloro-2-isocyanopyrinde **3b**, and 2-isocyano-3-methoxypyridine **3c** was possible, yet the purified yields (Table S1, Entry 1, 4 and 7) were very low. ^1H NMR analysis of the crude showed a significant amount of starting material, that could be recycled during the purification. In order to push the reaction towards full conversion, an increased amount of $POCl_3$ and Et_3N was used (Table S1, Entry 2, 5 and 8). In case of the *C3*-ester substituent, full degradation was observed where neither starting material or product could be isolated (Table S1, Entry 10 and 11). Application of $PhPO_2Cl_2$ gave access to the four isocyanides of type **3** with a significant improvement in yield (Table S1, Entry 3, 6, 9 and 12).

Table S1. Synthesis of 3-substituted-2-isocyanopyridines: optimization



2 **3**

Entry	X	**2**	Reagent (***X*** equiv)	Et_3N (***Y*** equiv)	T (°C)	t (h)	Yield **3** (%)[a]
1	Br	**2a**	$POCl_3$ (1.15 equiv)	6	-78 to 0	o.n.	5
2	Br	**2a**	$POCl_3$ (2.3 equiv)	12	-78 to 0	o.n.	19
3	Br	**2a**	$PhPO_2Cl_2$ (1.2 equiv)	7.2	rt	24	53
4	Cl	**2b**	$POCl_3$ (1.15 equiv)	6	-78 to 0	o.n.	4
5	Cl	**2b**	$POCl_3$ (2.3 equiv)	12	-78 to 0	o.n.	22
6	Cl	**2b**	$PhPO_2Cl_2$ (1.2 equiv)	7.2	rt	24	63
7	OMe	**2c**	$POCl_3$ (1.15 equiv)	6	-78 to 0	o.n.	6
8	OMe	**2c**	$POCl_3$ (2.3 equiv)	12	-78 to 0	o.n.	9
9	OMe	**2c**	$PhPO_2Cl_2$ (1.2 equiv)	7.2	rt	24	61
10	COOMe	**2d**	$POCl_3$ (1.15 equiv)	6	-78 to 0	o.n.	0
11	COOMe	**2d**	$POCl_3$ (2.3 equiv)	12	-78 to 0	o.n.	0
12	COOMe	**2d**	$PhPO_2Cl_2$ (1.2 equiv)	7.2	rt	24	55

[a] Isolated yield on a 6 mmol scale.

OPTIMIZATION DATA OF THE UGI REACTION

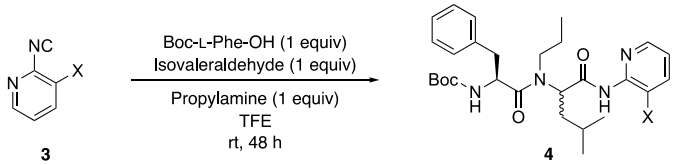
General procedure for the optimization

To a microwave vial was added isovaleraldehyde, propylamine and a solvent. The mixture was stirred for two hours at room temperature. Then Boc-L-Phe-OH and 3-substituted 2-isocyanopyridine **3** (1 equiv, 1 mmol) were added. The vial was sealed with a crimp cap and stirred at the specified temperature and time. The mixture was then allowed to cool down to room temperature, decapped, and concentrated *in vacuo*. HPLC analysis of the crude was recorded and the signals of the isocyanide and Ugi product were integrated to determine the conversion. If the conversion was deemed significant, the crude was purified by automated flash column chromatography.

Initial evaluation of the Ugi reaction with 3-substituted 2-isocyanopyridine 3

The isocyanides **3** were first tested in an Ugi reaction with propylamine, isovaleraldehyde and Boc-L-Phe-OH in a 1:1:1:1 ratio of the different components in TFE at room temperature. For **3a-c**, the desired Ugi product **4a-c** was observed with a conversion of approximately 70% (Table S2, Entry 1-3). For the C^3-ester-substituted isocyanide **3d**, no conversion to the desired Ugi product **4d** was observed and degradation of the isocyanide was observed (Table S2, Entry 4), most likely due to the lack of compatibility with the fluorinated alcohol TFE.

Table S2. Evaluation of the 3-substituted 2-isocyanopyrdine **3** in the Ugi reaction



3 **4**

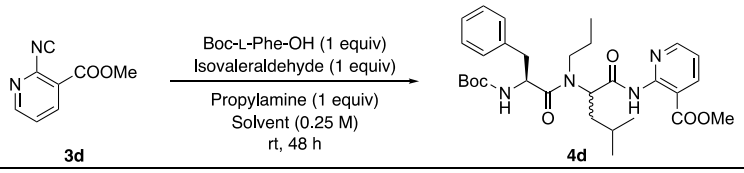
Entry	X	**3**	Conversion (%)[a]	**4**	Yield **4** (%)[b]
1	Br	**3a**	71	**4a**	50
2	Cl	**3b**	74	**4b**	63
3	OMe	**3c**	73	**4c**	38
4	COOMe	**3d**	100	**4d**	0

[a] Conversion determined by HPLC. [b] Isolated yield.

Optimization of the Ugi reaction with methyl 2-isocyanonicotinate 3d

As the methyl 2-isocyanonicotinate **3b** lacked compatibility with TFE as a solvent, a solvent screening was carried out at a concentration of 0.25 M. Here, MeOH (Table S3, Entry 2), *t*BuOH (Table S3, Entry 3) and CH_2Cl_2 (Table S3, Entry 7) showed conversion towards the desired Ugi product **4d**. MeOH showed the lowest amount of product lost during purification and was selected to further study of the reactant ratios (Table S4).

Table S3. Solvent screening

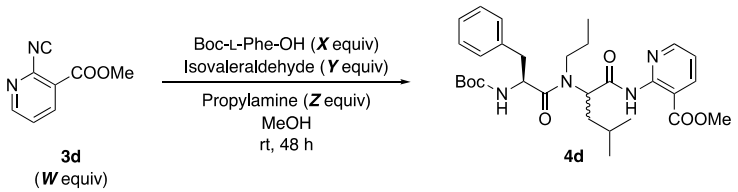


Entry	Solvent	Conversion (%)[a]	Yield **4d** (%)[b]
1	TFE	< 5	ND
2	MeOH	37	17
3	*t*BuOH	42	21
4	Dioxane	8	ND
5	DMF	< 5	ND
6	CH_3CN	10	ND
7	CH_2Cl_2	48	19
8	HFIP	< 5	ND
9	THF	14	ND
10	*t*BuOAc	10	ND

[a] Conversion of **3d** to **4d** determined by HPLC. [b] Isolated yield. ND = not determined

In an effort to improve the conversion and the isolated yield of the Ugi product **4d**, the ratio of the reactants was evaluated (Table S4). By increasing the isovaleraldehyde and propylamine to 2 equivalents, the conversion towards the Ugi product **4d** almost doubled. However only a small increase in isolated yield was observed (Table S4, Entry 1 vs. Entry 6).

Table S4. Evaluation of the reactant ratio

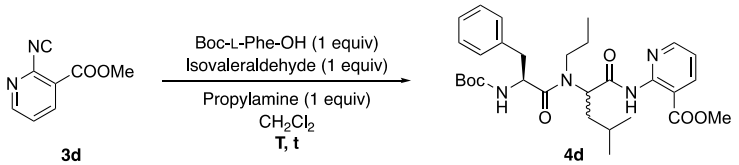


Entry	**3d** (***W*** equiv)	Boc-Phe-OH (***X*** equiv)	Isovaleraldehyde (***Y*** equiv)	Propylamine (***Z*** equiv)	Conversion (%)[a]	Yield **4d** (%)[b]
1	1	1	1	1	37	17
2	1.5	1	1	1	43	13
3	2	1	1	1	47	18
4	1.2	1.5	1	1	45	20
5	1	1	1.2	1.2	51	17
6	1	1	2	2	65	26
7	1	1	4	4	48	16

[a] Conversion determined by HPLC. [b] Isolated yield.

As the effect of the reactant ratios on the isolated yield remained limited, the temperature and heat source were evaluated. However, as MeOH is a nucleophilic solvent, the formed amide bond might be cleaved due to the heating. This compelled us to change to a non-nucleophilic solvent that performed well in the previous solvent screening, CH_2Cl_2 (Table S3, Entry 7). Heating the reaction mixture to 110 °C for 30 minutes significantly increased the conversion toward the Ugi product **4d** (Table S5, Entry 1 vs 2 and 3). Increasing the reaction time to 1 hour, did not significantly improve the conversion and showed no difference in conversion (Table S5, Entry 3 and 4). Comparison of microwave heating and classical heating revealed equal results (Table S5, Entry 2 and 3).

Table S5. Evaluation of effect of heating and the heat source



Entry	T (°C)	Heat source	t (h)	Conversion (%)[a]	Yield **4d** (%)[b]
1	rt	-	48	37	17
2	110	MW	0.5	72	41
3	110	Oil bath	0.5	74	ND
4	110	Oil bath	1	78	40

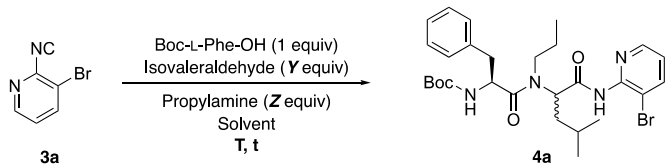
[a] Conversion determined by HPLC. [b] Isolated yield. ND = not determined

The best conditions (Table S5, Entry 2), however, showed not to be transferable to other examples varying the different components in the Ugi reaction.

Optimization of the Ugi reaction with 3-bromo-2-isocyanopyridine 3a, 3-chloro-2-isocyanopyridine 3b and 3-methoxy-2-isocyanopyridine 3c.

From the optimization of the Ugi reaction with the methyl 2-isocyanonicotinate **3d**, a few key conditions were selected in an effort to improve the Ugi reaction with the other three isocyanides **3a-c** (Table S6, S7, and S8). First the ratios of aldehyde and amine to isocyanide and carboxylic acid were evaluated in TFE (Table S6, S7, and S8, Entry 1-3). Here, an increase of 1.2 equivalents of isovaleraldehyde and propylamine showed to significantly increase the conversion and improve the isolated yield to 68% of **4a** (Table S6, Entry 2), 77% **4b** (Table S7, Entry 2) and 66% **4c** (Table S8, Entry 2). In parallel, a solvent screening (Table S6, S7, and S8, Entry 1, 4, and 5) and the effect of heating (Table S6, S7, and S8, Entry 6, and 7) were tested, however, these affected the conversion and yield negatively.

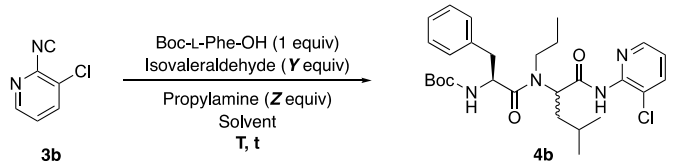
Table S6. Evaluation of the reaction conditions for the Ugi reaction with **3a**



Entry	Isovaleraldehyde (***Y*** equiv)	Propylamine (***Z*** equiv)	Solvent	T (°C)	t (h)	Conversion (%)[a]	Yield **4a** (%)[b]
1	1	1	TFE	rt	48	71	50
2	1.2	1.2	TFE	rt	48	87	68
3	2	2	TFE	rt	48	74	52
4	1	1	CH_2Cl_2	rt	48	29	ND
5	1	1	*t*BuOH	rt	48	14	ND
6	1	1	CH_2Cl_2	100 (MW)	0.5	60	25
7	1	1	CH_2Cl_2	100 (oil bath)	2	57	25

[a] Conversion determined by HPLC. [b] Isolated yield. ND = not determined

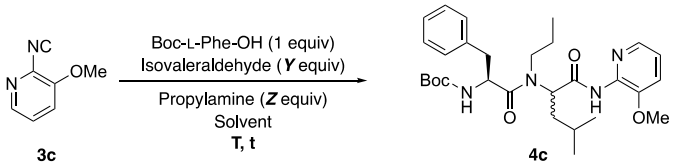
Table S7. Evaluation of the reaction conditions for the Ugi reaction with **3b**



Entry	Isovaleraldehyde (***Y*** equiv)	Propylamine (***Z*** equiv)	Solvent	T (°C)	t (h)	Conversion (%)[a]	Yield **4b** (%)[b]
1	1	1	TFE	rt	48	74	63
2	1.2	1.2	TFE	rt	48	86	77
3	2	2	TFE	rt	48	69	54
4	1	1	CH_2Cl_2	rt	48	16	ND
5	1	1	*t*BuOH	rt	48	6	ND
6	1	1	CH_2Cl_2	100 (MW)	0.5	54	28
7	1	1	CH_2Cl_2	100 (oil bath)	2	64	34

[a] Conversion determined by HPLC. [b] Isolated yield. ND = not determined

Table S8. Evaluation of the reaction conditions for the Ugi reaction with **3c**



Entry	Isovaleraldehyde (***Y*** equiv)	Propylamine (***Z*** equiv)	Solvent	T (°C)	t (h)	Conversion (%)[a]	Yield **4c** (%)[b]
1	1	1	TFE	rt	48	73	38
2	1.2	1.2	TFE	rt	48	91	66
3	2	2	TFE	rt	48	83	64
4	1	1	CH_2Cl_2	rt	48	56	34
5	1	1	*t*BuOH	rt	48	44	23
6	1	1	CH_2Cl_2	100 (MW)	0.5	88	56
7	1	1	CH_2Cl_2	100 (oil bath)	2	85	45

[a] Conversion determined by HPLC. [b] Isolated yield.

OPTIMIZATION DATA OF THE TRANSAMIDATION

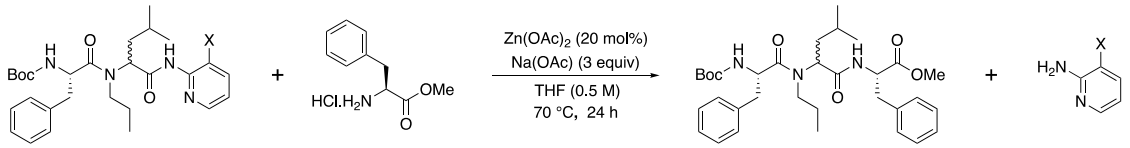
General procedure for the optimization

To a microwave vial was added the Ugi product **4a-c** (1 equiv, 0.25 mmol), H-L-Phe-OMe.HCl (3 equiv, 0.75 mmol, 162 mg), NaOAc (3 equiv, 0.75 mmol, 62 mg), and solvent. The vial was sealed with a crimp cap, and stirred at the specified temperature and time. The mixture was then allowed to cool down to room temperature, decapped, and concentrated *in vacuo*. A known amount of 1,3,5-trimethoxybenzene, between 10 - 15 mg, was added to the crude mixture, which was then dissolved in MeOD. Potential precipitating salts were removed by centrifugation. A ^{1}H NMR of the crude was recorded and signals were integrated in comparison to the internal standard. The mass balance was calculated considering product **9**, the remaining starting material **4a-c** and 3-substituted 2-aminopyridine by-product of the transamidation. Considering experimental and instrumental errors, a total measured mass balance in the 95-105% range was deemed as a successful experiment. Reported values were subsequently recalculated to 100%. HPLC and LC/MS of the sample were subsequently recorded to confirm the formation of the desired peptide compound.

Evaluation of the reaction parameters

As a starting point, the reaction conditions of the transamidation previously developed in our laboratories for nicotinates were evaluated for the 3 pyridine directing groups in **4a-c** (20 mol% $Zn(OAc)_2$, 3 equiv H-L-Phe-OMe.HCl, 3 equiv NaOAc in THF, 70 °C).[2] Here, a very similar NMR yield was observed for all three substituents X (Table S9). Optimization of the transamidation on the Ugi products was carried out on **4b**.

Table S9. Evaluation of the transamidation on the Ugi reaction **4a-c**



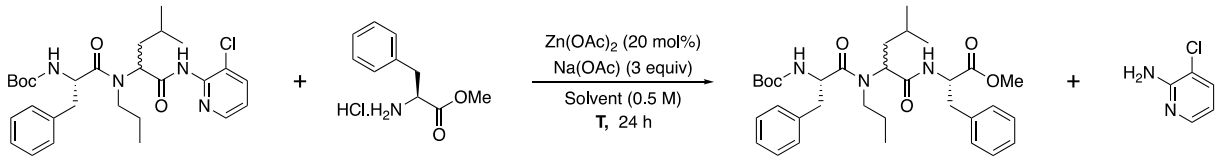
4 (3 equiv) **9**

Entry	X	**4**	Yield **4** (%)[a]	Yield **9** (%)[a]
1	Br	**4a**	53	47
2	Cl	**4b**	53	47
3	OMe	**4c**	56	44

[a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

For the optimization of the transamidation, the solvent was evaluated alongside the temperature (Table S10). As alternative solvent for THF, *t*BuOAc was selected as it was already previously used in the alcoholysis.[3] *t*BuOAc as a solvent resulted in a slightly higher yield (55%) (Table S10, Entry 4).

Table S10. Screening of the solvent for the transamidation of Ugi product **4b**



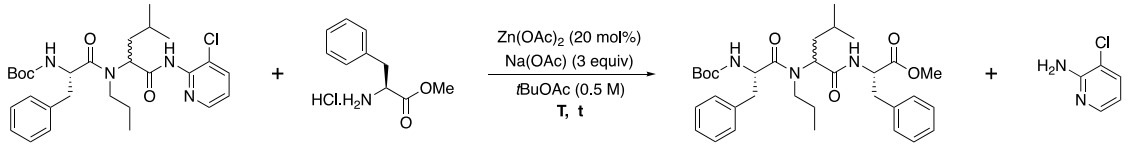
4b (3 equiv) **9**

Entry	Solvent	T (°C)	Yield **4b** (%)[a]	Yield **9** (%)[a]
1	THF	70	53	47
2	THF	85	43	57
3	*t*BuOAc	70	45	55
4	*t*BuOAc	85	30	70

[a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

Finally, the temperature at which the transamidation was carried out was evaluated alongside the reaction time. Here, 85 °C for 48 hours showed an excellent NMR yield of 91% (Table S11, Entry 4).

Table S11. Evaluation of the temperature and reaction time for the transamidation of Ugi product **4b**

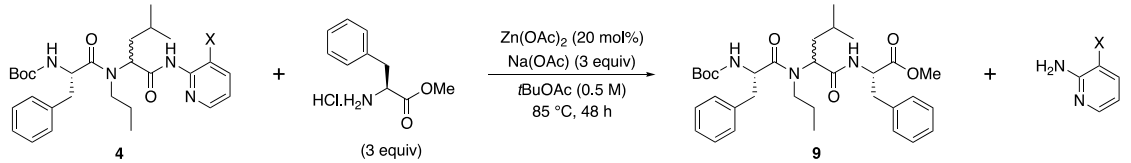


Entry	T (°C)	t (h)	Yield **4b** (%)[a]	Yield **9** (%)[a]
1	70	24	45	55
2	70	48	24	76
3	85	24	30	70
4	85	48	9	91

[a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

Under the optimized conditions, the three substituents X were compared (Table S12). The bromo **4a**, chloro **4b**, and methoxy **4c** showed a similar NMR yield. However, a significant better isolated yield was observed for **9** from the chloro **4b**(Table S12, Entry 2).

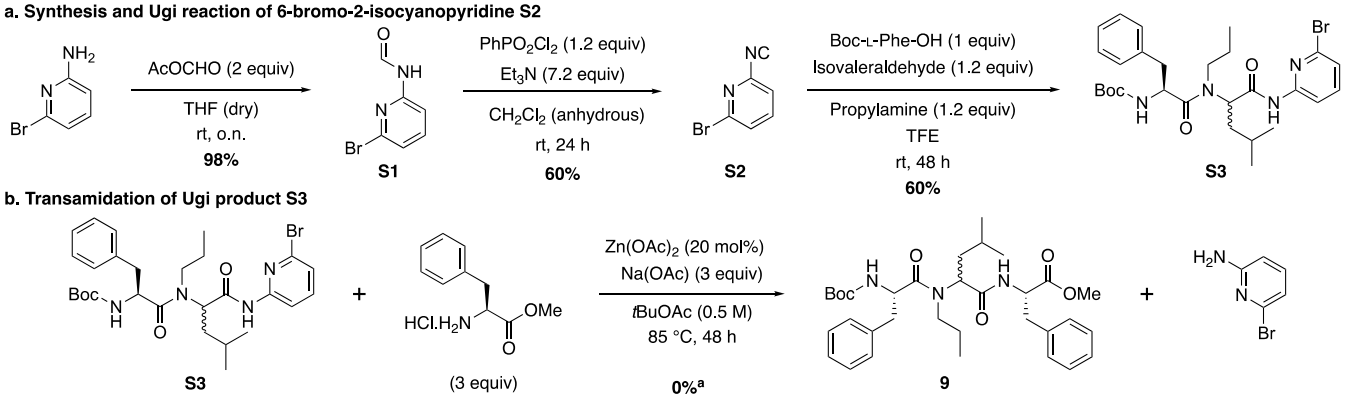
Table S12. Comparison of the different substituents under the optimized conditions for transamidation



Entry	X	**4**	Yield **4** (%)[a]	Yield **9** (%)[a]	Yield **9** (%)[b]
1	Br	**4a**	15	85	60
2	Cl	**4b**	9	91	85
3	OMe	**4c**	10	90	68

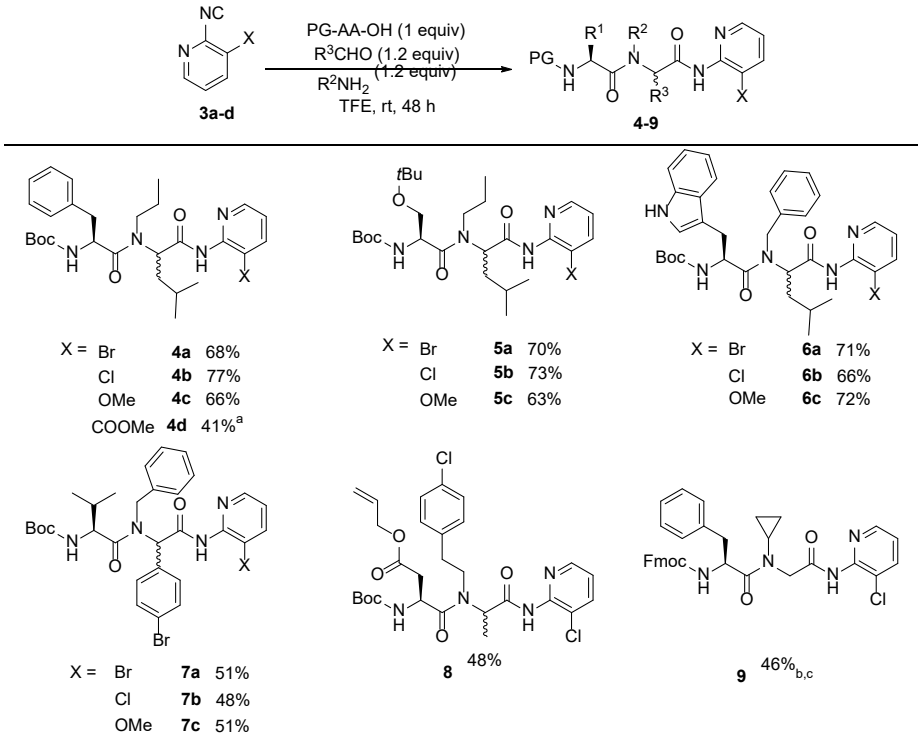
[a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield after column chromatography.

As a proof-of-concept, the 6-bromo-2-isocyanopyridine **S2** previously published by Orru and co-workers[1] was evaluated under the optimized conditions. First, the isocyanide **S2** was obtained in a similar fashion to the 3-substituted 2-isocyanopyridine **3** and subsequently implemented in the Ugi reaction in TFE (Scheme S1a). Next, the Ugi product **S3** was used in a transamidation with H-L-Phe-OMe (3 equiv) as optimized for **4b**. However, after stirring for 48 hours at 85 °C, no conversion of the starting material **S3** was observed and **S3** remained intact (Scheme S1b).

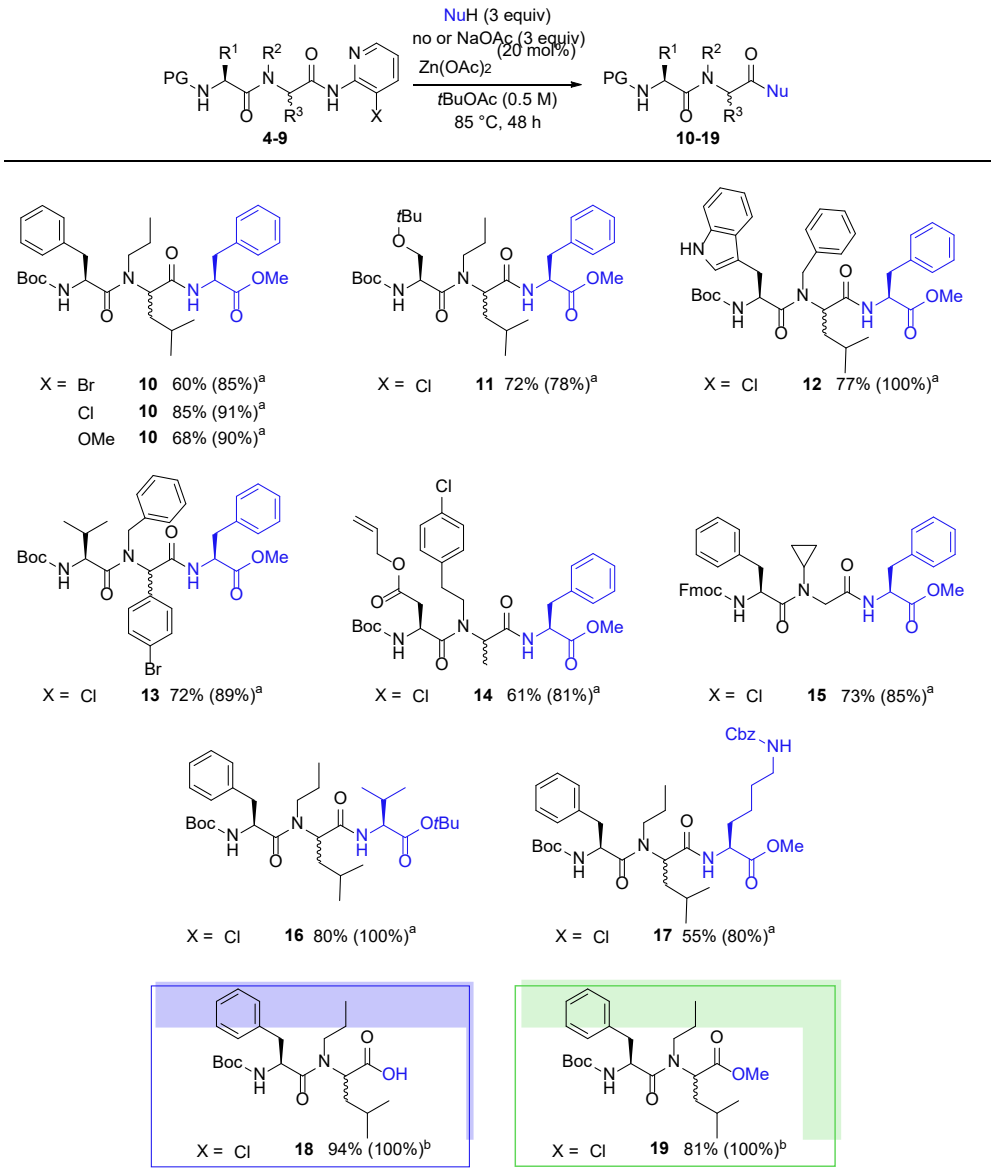


Scheme S1. Evaluation of 6-bromo-2-isocyanopyridine S2 in an Ugi reaction and subsequent transamidation with the Ugi product S3. [a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

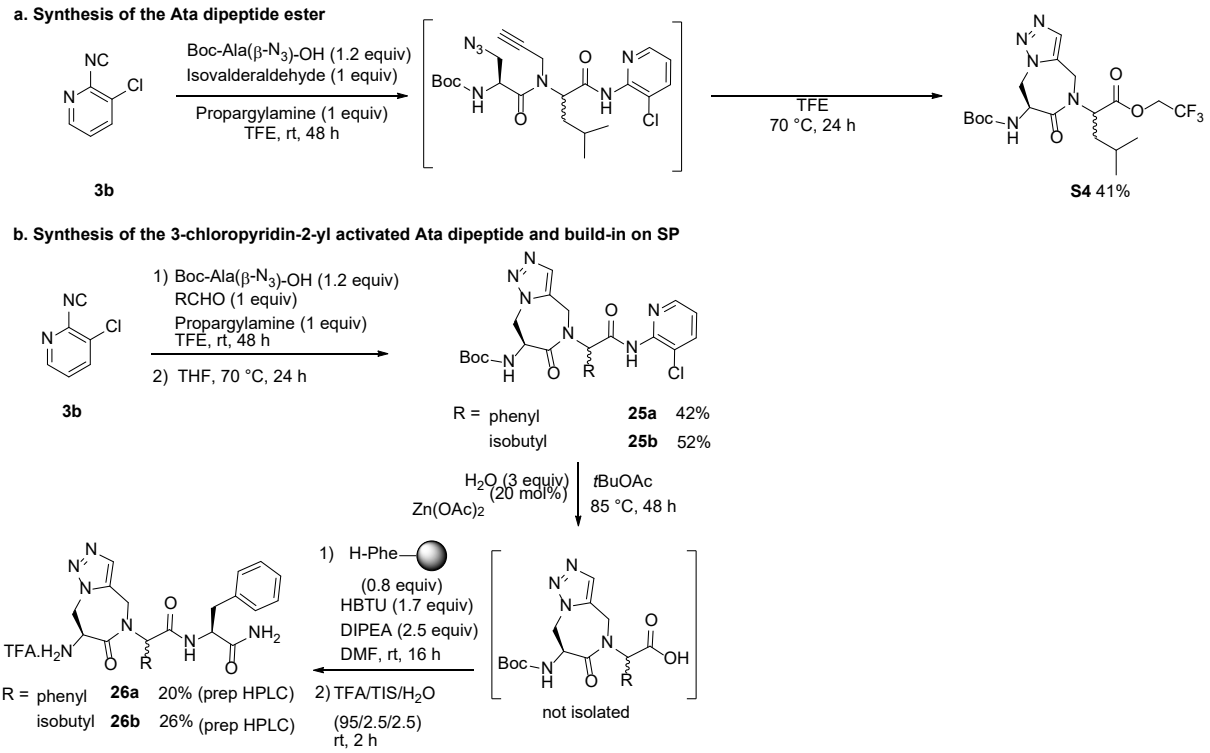
OVERVIEW OF THE SYNTHETIC SCOPE



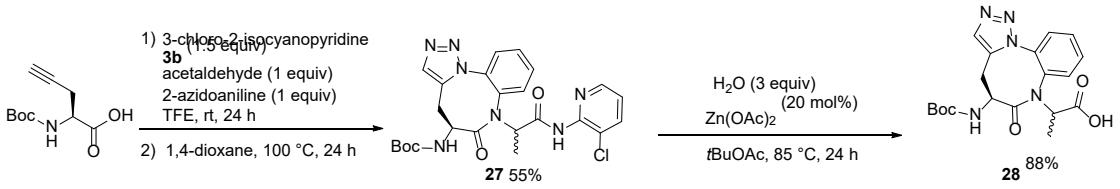
Scheme S2. Use of the isocyanides 3a-d in the Ugi-4CR. [a] CH_2Cl_2 as solvent at 110 °C (μW) for 0.5 h. [b] 3-chloro-2-isocyanopyridine **3b** (1.5 equiv)



Scheme S3. Amide cleavage in Ugi products 4-9. Isolated yield with a 1:1 diastereomeric ratio on 0.25 mmol scale is reported, ^{1}H NMR yield determined with internal standard between brackets. Examples of amide hydrolysis and esterification framed in blue and green, respectively.
[a] NaOAc for *in situ* release of amine from the ammonium salt. [b] no NaOAc used.



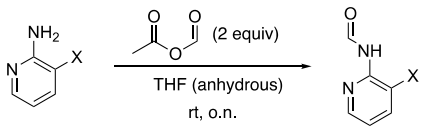
Scheme S4. Synthesis of the Ata-scaffold. (a) synthesis of Ata dipeptide ester S4 in a 1:1 diastereomeric ratio. (b) Application of 3-chloro-2-isocyanopyridine 3b in the synthesis of scaffold 25, in a 1:0.7 and 1:1 diastereomeric ratio for 25a and 25b, respectively, *via* a Ugi-4CR-Huisgen one-pot reaction, followed by amide hydrolysis and its application in SPPS with reported, combined isolated yield for the separated diastereomers.



Scheme S5. Application of 3-chloro-2-isocyanopyridine 3b in the synthesis of scaffold 27 in a 1:1 diastereomeric ratio via a Ugi-4CR-Huisgen one-pot reaction, followed by amide hydrolysis to give the building block 28.

GENERAL PROCEDURES

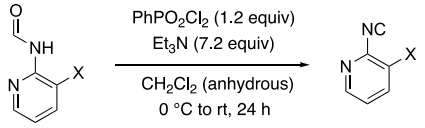
General Procedure A: Synthesis of 3-Substituted-2-Formamidopyridine 2



1 **2**

Unless stated otherwise, formic acid (2.05 equiv, 41 mmol, 1.6 ml) was added dropwise to a flame-dried microwave vial charged with acetic anhydride (2 equiv, 40 mmol, 3.8 ml). The vial was sealed and the mixture was refluxed for 2 hours at 60 °C under argon atmosphere. Into a flame dried 100 ml round-bottom flask, the 2-amino-3-substituted pyridine **1** (1 equiv, 20 mmol) was dissolved in anhydrous THF (50 ml) and cooled to 0 °C. Then the refluxed mixture was allowed to cool down to room temperature and was added dropwise to the 2-amino-3-substituted pyridine solution. The mixture was stirred overnight at room temperature under argon atmosphere. The solvent was removed *in vacuo*.

General Procedure B: Synthesis of 3-Substituted-2-Isocyanopyridine 3

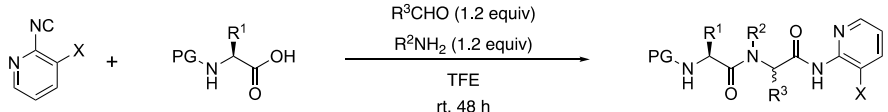


2 **3**

To a flame-dried round-bottom flask charged with 3-substituted-2-formamidopyridine **2** (1 equiv, 5 mmol) in anhydrous CH_2Cl_2 (5 ml), Et_3N (7.2 equiv, 35.9 mmol, 5 ml) was added. The solution was cooled to 0 °C followed by the dropwise addition of $PhPO_2Cl_2$ (1.2 equiv, 6 mmol, 0.9 ml). The mixture was stirred at 0 °C for 30 minutes, allowed to warm up to room temperature and continued to stir for another 24 hours.

The reaction mixture was added to brine (300 ml) and extracted with EtOAc (3 x 200 ml). The combined organic layers were washed with HCl (1 M, 200 ml), $NaHCO_3$ solution (sat., 200 ml) and brine (200 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude mixture was purified by automated flash column chromatography.

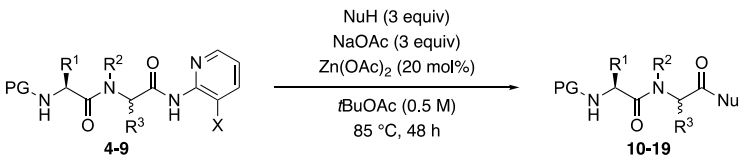
General Procedure C: Synthesis of Ugi Product 4-9



3 **4-9**

Unless stated otherwise, a microwave vial was charged with an aldehyde (1.2 equiv, 1.2 mmol), an amine (1.2 mmol, 1.2 equiv), and trifluoroethanol (4 ml). The mixture was stirred for two hours at room temperature. Then a *N*-protected amino acid (1 equiv, 1 mmol) and 3-substituted-2 isocyanopyridine **3** (1 equiv, 1 mmol) were added. The mixture was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the crude was purified by automated flash column chromatography.

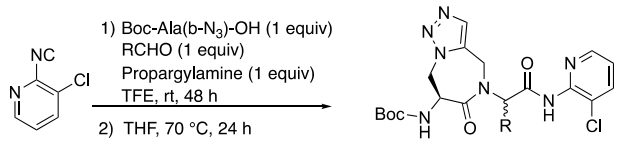
General Procedure D: Cleavage of the Amide 4-9



4-9 **10-19**

Unless stated otherwise, a microwave vial was charged with $Zn(OAc)_2$ (20 mol%, 0.05 mmol, 9 mg), Ugi product **4-9** (1 equiv, 0.25 mmol), nucleophile (3 equiv, 0.75 mmol), NaOAc (3 equiv, 0.75 mmol, 62 mg) and dissolved in *t*BuOAc (0.5 ml). The vial was sealed and stirred at 85 °C for 48 hours. Subsequently, the mixture was concentrated, coated on silica and purified using automated normal phase flash chromatography.

General Procedure E: Synthesis of the Ata Scaffold 25



3b **25**

Into a microwave vial, propargylamine (0.064 ml, 1 mmol, 1 equiv) and aldehyde (1 mmol, 1 equiv) were dissolved in TFE (4 ml). The mixture was stirred for 2 hours at room temperature. Then Boc-L-Ala(β-N_3)-OH (1.2 mmol, 1.2 equiv) and 3-chloro-2-isocyanopyridine **3b** (1 mmol, 1 equiv) were added to the mixture. The resulting mixture was stirred for 48 hours at room temperature. Subsequently the solvent was removed *in vacuo* and the crude reaction mixture was redissolved in THF (4 ml). The mixture was heated at 70 °C and stirred for another 24 hours. The solvent was removed *in vacuo* and the crude was purified by automated flash column chromatography.

General Procedure F: Solid-Phase Peptide Synthesis

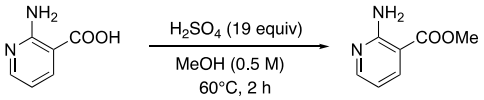
Into an SPPS reactor, the rink amide resin was weighted and swollen in CH_2Cl_2 for twenty minutes under constant shaking. The solvent was removed by filtration and the deprotection of the Fmoc protecting group was achieved by treatment of the resin with a solution of 4-methylpiperidine (20%) in DMF (5 and 15 minutes of shaking). In the meantime, a mixture of Fmoc-AA-OH (0.20 mmol, 2.0 equiv), HBTU (0.20 mmol, 2.0 equiv, 0.076 g) and DIPEA (0.30 mmol, 3.0 equiv, 0.052 ml) was stirred for 15 minutes in DMF (1 ml). The resin was washed with DMF (3x) and CH_2Cl_2 (3x) before the pre-stirred mixture was added. After one hour of shaking, the excess of reagents was removed by filtration and the resin was washed with DMF (3x) and CH_2Cl_2 (3x). The Kaiser test was applied to determine if the peptide coupling was finished. The same deprotection and coupling strategy was applied for the coupling of the following amino acids.

Kaiser test:

For this test, some beats were transferred in a glass tube. Then two droplets of three different solutions were added: a) a solution containing 2.5 g ninhydrin in 50 ml ethanol, b) a solution of 40 g phenol in 10 ml ethanol and c) a solution containing 1 ml 0.001 M aqueous potassium cyanide (KCN) in 49 ml pyridine. The glass tube was heated at 110 ˚C in a salt bath for approximately 5 min. A pale yellow colored mixture indicates less than 1% free amine present on the resin, while a dark blue color reveals that the coupling was incomplete. In that case, the coupling was repeated.

SYNTHETIC PROCEDURES

Synthesis of Methyl 2-aminonicotinate S5

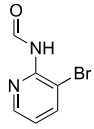


S5

The titled compound was prepared using a slightly adapted literature procedure.[4] A suspension of 2-aminonicotinic acid (500 mg, 3.6 mmol, 1 equiv) in methanol (7 ml) in a microwave vial was cooled to 0 °C. To this, sulfuric acid (95-98%, 3.6 ml, 67 mmol, 19 equiv) was added dropwise. The vial was sealed and the suspension was heated to 60 °C for 2 h. Following, the mixture was allowed to cooled down to room temperature and carefully added to a cold saturated solution of $NaHCO_3$, maintaining at a pH > 8. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The titled compound was isolated as a white solid with 75 % (415 mg, 2.73 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.11 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.61 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.88 (s, 3H) ppm. **^{13}C (126 MHz, $CDCl_3$)** δ 167.6 (C), 159.6 (C), 153.8 (CH), 140.2 (CH), 112.8 (CH), 106.3 (C), 52.1 (CH_3) ppm. **HPLC** $t_{R-HPLC-2}$ = 1.12 min. **HRMS (ESI+)** m/z calc. for $C_7H_9N_2O_2$ $[M+H]^+$: 153.0649, found 153.0659. **m. p.:** 85 °C. The spectroscopic data were in accordance with those previously reported.[4]

Synthesis of 3-Substituted-2-Formamidopyridine 2

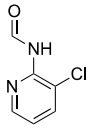
3-Bromo-2-formamidopyridine **2a**



2a

The title compound was prepared following general procedure **A** from formic acid (1.57 ml, 41 mmol, 2.05 equiv), acetic anhydride (3.78 ml, 40.0 mmol, 2 equiv) and 2-amino-3-bromopyridine (3.46 g, 20 mmol, 1 equiv) in anhydrous THF (50 ml). This yielded, after evaporation, the desired compound as a white solid in quantitative yield (4 g, 20 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.50 (d, *J* = 10.9 Hz, 1H), 8.23 (d, *J* = 4.7 Hz, 1H), 8.10 (br s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 6.99-6.94 (m, 1H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.3 (CH), 148.2 (C), 147.2 (CH), 141.6 (CH), 120.8 (CH), 107.0 (C) ppm. **HPLC** $t_{R-HPLC-2}$ = 1.39 min. **HRMS (ESI+)** m/z calcd. for $C_6H_6N_2OBr$ $[M+H;\ ^{79}Br]^+$ = 200.6958, $[M+H;\ ^{81}Br]^+$ = 202.9638 found 200.9654 and 202.9637 in the expected ratio 1:1. **m. p.:** 84 °C. The spectroscopic data were in accordance with those reported for compound with CAS: 1465456-59-0.

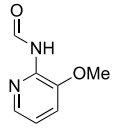
3-Chloro-2-formamidopyridine **2b**



2b

The title compound was prepared following general procedure **A** from formic acid (1.57 ml, 41 mmol, 2.05 equiv), acetic anhydride (3.78 ml, 40 mmol, 2 equiv) and 2-amino-3-chloropyridine (2.57 g, 20 mmol, 1 equiv) in anhydrous THF (50 ml) and. This yielded, after evaporation, the desired compound as a pale-yellow solid in quantitative yield (3.1 g, 20 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.51 (d, *J* = 10.2 Hz, 1H), 8.30-8.05 (m, 2H), 7.69 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.09-7.00 (m, 1H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.2 (CH), 147.4 (C), 146.6 (CH), 138.3 (CH), 120.4 (CH), 117.3 (C) ppm. **HPLC** $t_{R-HPLC-2}$ = 1.34 min. **HRMS (ESI+)** m/z calcd. for $C_6H_5N_2OClNa$ $[M+Na;\ ^{35}Cl]^+$= 178.9983, $[M+Na;\ ^{37}Cl]^+$= 180.9954 found 178.9972 and 180.9911. In the expected ratio 3:1. **m. p.:** 107 °C. The spectroscopic data were in accordance with those reported for compound with CAS: 1700458-38-3

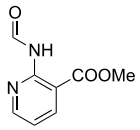
2-Formamido-3-methoxypyridine **2c**



2c

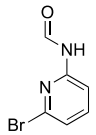
The title compound was prepared following general procedure **A** from formic acid (1.57 ml, 41 mmol, 2.05 equiv), acetic anhydride (3.78 ml, 40 mmol, 2 equiv) and 2-amino-3-methoxypyridine (2.48 g, 20 mmol, 1 equiv) in anhydrous THF (50 ml). This yielded, after evaporation, the desired compound as a brown solid in quantitative yield (3 g, 20 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.46 (d, *J* = 10.0 Hz, 1H), 8.12 (br s, 1H), 7.84 (d, *J* = 4.0 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.00 (dd, *J* = 4.0, 8.1 Hz, 1H), 3.88 (s, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.9 (CH), 142.5 (C), 141.6 (C), 139.1 (CH), 119.6 (CH), 117.6 (CH), 55.9 (CH_3) ppm. **HPLC** $t_{R-HPLC-2}$ = 0.78 min. **HRMS (ESI+)** m/z calcd. for $C_7H_9N_2O_2$ $[M+H]^+$= 153.0659, found 153.0643. **m. p.:** 97 °C. No spectroscopic data are reported in literature.

Methyl 2-formamidonicotinate **2d**


2d

The title compound was prepared following general procedure **A**, from formic acid (1.57 ml, 41.0 mmol, 2.05 equiv), acetic anhydride (3.78 ml, 40.0 mmol, 2 equiv) and methyl 2-aminonicotinate **S5** (3.04 g, 20.0 mmol, 1 equiv) in anhydrous THF (50 ml). This yielded, after evaporation, the desired compound as a white solid in quantitative yield (3.6 g, 20 mmol). **^{1}H NMR (250 Hz, $CDCl_3$)** δ 10.41 (br s, 1H), 9.59 (d, *J* = 10.2 Hz, 1H), 8.34 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.23 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.02 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.87 (s, 3H) ppm. **^{13}C NMR (63 MHz, $CDCl_3$)** δ 166.4 (C), 162.4 (CH), 153.0 (CH), 152.3 (C), 140.6 (CH), 118.9 (CH), 109.2 (C), 52.9 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 1.65 min. **HRMS (ESI+)** m/z calcd. for $C_8H_8N_2O_3Na$ $[M+Na]^+$= 203.0427, found 203.0413. **m. p.:** 77 °C. The spectroscopic data were in accordance with those reported for compound with CAS: 338990-71-9.

6-Bromo-2-formamidopyridine **S1**


S1

The title compound was prepared following general procedure **A** from formic acid (0.32 ml, 8.2 mmol, 2.05 equiv), acetic anhydride (0.75 ml, 8 mmol, 2 equiv) and 2-amino-6-bromopyridine (865 mg, 5 mmol, 1 equiv) in anhydrous THF (50 ml). This yielded, after evaporation, the desired compound as a white solid in 98% (983 mg, 4.88 mmol). **^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers in 1:0.5 ratio)** δ 9.32 (d, *J* = 10.5 Hz, 0.5H), 8.70 (br s, 0.5H), 8.56 (br s, 1H), 8.53 (d, *J* = 1Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.60 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.52 (dd, *J* = 7.8, 7.8 Hz, 0.5H), 7.29-7.23 (m, 1.5H), 6.82 (d, *J* = 7.9 Hz, 0.5H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 162.6 (CH), 159.5 (CH), 150.8 (C), 141.1 (CH), 140.8 (C), 140.7 (CH), 139.5 (C), 124.4 (CH), 123.9 (CH), 113.5 (CH), 109.4 (CH) ppm. **HRMS (ESI+)** m/z calcd. for $C_6H_6N_2OBr$ $[M+H;\ ^{79}Br]^+$ = 200.9658, $[M+H;\ ^{81}Br]^+$ = 202.9638 found 200.9660 and 202.9584 in the expected ratio 1:1. **m. p.:** 143 °C. The spectroscopic data were in accordance with those previously reported.[1]

Synthesis of the 2-Isocyanopyredines 3

3-Bromo-2-isocyanopyridine **3a**


3a

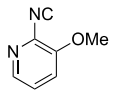
The title compound was prepared following general procedure **B** from 3-bromo-2-formamidopyridine **2a** (2.02 g, 510mmol, 1 equiv), Et_3N (10 ml, 72 mmol, 7.2 equiv) and $PhPO_2Cl_2$ (1.8 ml, 12 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (10 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (EtOAc/CH_2Cl_2 from 1:3 to 0:1), the desired compound as a white solid with 71% (1.3 g, 7.1 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.37 (dd, *J* = 4.7, 1.2 Hz, 1H), 8.00 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.26 (dd, *J* = 8.1, 4.7 Hz, 1H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.2 (C), 148.0 (CH), 142.1 (CH), 139.6 (C), 125.7 (CH), 117.1 (C) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 1.96 min. **HRMS (ESI+)** m/z calcd. for $C_6H_4N_2Br$ $[M+H;\ ^{79}Br]^+$ = 182.9552, $[M+H;\ ^{81}Br]^+$ = 184.9532 found 182.9516 and 184.9534 in the expected ratio 1:1. **Degradation point:** 85 °C. The spectroscopic data were in accordance with those previously reported.[1]

3-Chloro-2-isocyanopyridine **3b**


3b

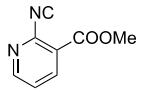
The title compound was prepared following general procedure **B** from 3-chloro-2-formamidopyridine **2b** (1.56 g, 10 mmol, 1 equiv), Et_3N (10 ml, 72 mmol, 7.2 equiv) and $PhPO_2Cl_2$ (1.8 ml, 12 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (10 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (CH_2Cl_2/MeOH from 100:0 to 97:3), the desired compound as a pale-yellow solid with 75% (1.03 g, 7.5 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.43 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.43 (dd, *J* = 8.1, 4.7 Hz, 1H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.0 (C), 147.5 (CH), 138.9 (CH), 138.5 (C), 128.2 (C), 125.6 (CH) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 1.78 min. **HRMS (ESI+)** m/z calcd. for $C_6H_4N_2Cl$ $[M+H;\ ^{35}Cl]^+$ = 39.0058, $[M+H;\ ^{37}Cl]^+$ = 141.0029 found 139.0063 and 141.0031 in the expected ratio 3:1. **Degradation point:** 75 °C. No spectroscopic data are reported in literature.

2-Isocyano-3-methoxypyridine **3c**


3c

The title compound was prepared following general procedure **B** from 3-methoxy-2-formamidopyridine **2c** (1.52 g, 10 mmol, 1 equiv), Et_3N (10 ml, 72 mmol, 7.2 equiv) and $PhPO_2Cl_2$ (1.8 ml, 12 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (10 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (EtOAc/CH_2Cl_2 from 1:1 to 0:1), the desired compound as white solid with 74% (994 mg, 7.4 mmol) yield. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.04 (dd, *J* = 4.0, 2.1 Hz, 1H), 7.46-7.40 (m, 2H), 4.00 (s, 3H) ppm. **^{13}C NMR (63 MHz, CDCl3)** δ 167.3 (C), 150.9 (C), 139.9 (CH), 129.9 (C), 125.7 (CH), 119.9 (CH), 56.0 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 1.64 min. **HRMS (ESI+)** m/z calcd. for $C_7H_7N_2O$ $[M+H]^+$= 135.0553, found 135.0542. **Degradation point:** 95 °C. No spectroscopic data are reported in literature.

Methyl 2-isocyanonicotinate **3d**



3d

The title compound was prepared following general procedure **B** from methyl 2-formamidonicotinate **2d** (0.9 g, 5 mmol, 1 equiv), Et_3N (5 ml, 35.9 mmol, 7.2 equiv) and $PhPO_2Cl_2$ (0.9 ml, 6 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (CH_2Cl_2/EtOAc from 1:0 to 4:1), the desired compound as yellow solid with 55% (447 mg, 2.76 mmol) yield. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.56 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.32 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.90 (s, 3H) ppm. **^{13}C NMR (63 MHz, $CDCl_3$)** δ 168.6 (C), 162.8 (C), 152.4 (CH), 151.7 (C), 140.2 (CH), 124.6 (CH), 122.5 (C), 52.8 (CH_3) ppm. **HPLC** $t_{R-HPLC-2}$ = 1.75 min. **HRMS (ESI+)** m/z calcd. for $C_8H_7N_2O_2$ $[M+H]^+$ = 163.0502, found 163.0479. **Degradation point:** 80 °C. No spectroscopic data are available in literature.

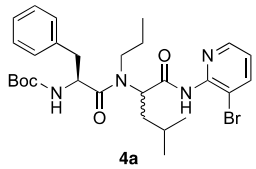
6-Bromo-2-isocyanopyridine **S2**

S2

The title compound was prepared following general procedure **B** from 6-bromo-2-formamidopyridine **S1** (2.02 g, 10 mmol, 1 equiv), Et_3N (10 ml, 35.9 mmol, 7.2 equiv) and $PhPO_2Cl_2$ (1.8 ml, 12 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (10 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (CH_2Cl_2), the desired compound as a white solid with 60% (1.1 g, 6 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.69 (dd, *J* = 8.1, 7.6 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.4 (C), 141.4 (C), 140.7 (CH), 139.5 (C), 129.7 (CH), 120.3 (CH) ppm. **Degradation point:** 86 °C. The spectroscopic data were in accordance with those previously reported.[1]

Synthesis of the Ugi products 4-9

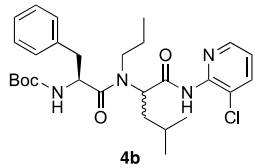
tert-Butyl ((2S)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4a**



4a

The title compound was prepared following general procedure **C** from 3-bromo-2-isocyanopyridine **3a** (183 mg, 1 mmol, 1 equiv), Boc-L-Phe-OH (265 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet Ether/EtOAc from 1:1 to 3:7), the desired compound as a yellow oil with 68% (392 mg, 0.68 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.50 (br s, 0.2H), 9.13 (br s, 0.8H), 9.01 (br s, 0.6H), 8.45 (d, *J* = 4.7 Hz, 0.8H), 8.43 (d, *J* = 4.7 Hz, 1H), 8.41 (dd, *J* = 4.7, 1.6 Hz, 0.2H), 7.91-7.88 (m, 1H), 7.86 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.32-7.16 (m, 8H), 7.09-7.04 (m, 2H), 7.03-7.01 (m, 0.2H), 7.00 (dd, *J* = 7.9, 4.7 Hz, 0.8H), 6.97 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.32 (d, *J* = 8.8 Hz, 1H), 5.27 (d, *J* = 9.2 Hz, 0.8H), 5.17-5.08 (m, 1.2H), 4.99-4.92 (m, 0.8H), 4.98-4.78 (m, 2.2H), 3.48-3.41 (m, 0.2H), 3.31-2.91 (m, 7.8H), 1.95-1.83 (m, 3H), 1.73-1.42 (m, 6.2H), 1.39 (s, 7.2H), 1.37 (s, 9H), 1.30 (s, 1.8H), 1.18-1.09 (m, 0.8H), 0.96-0.88 (m, 12H), 0.84-0.76 (m, 6H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.6 (C), 174.2 (C), 171.8 (C), 169.3 (C), 169.0 (C), 167.6 (C), 156.4 (C), 155.0 (C), 148.9 (C), 148.8 (C), 147.5 (CH), 141.8 (CH), 141.5 (CH), 141.4 (CH), 136.4 (C), 136.2 (C), 129.8 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 122.6 (CH), 121.4 (CH), 121.3 (CH), 112.1 (C), 111.8 (C), 81.1 (C), 80.1 (C), 80.0 (C), 59.3 (CH), 58.2 (CH), 56.6 (CH), 54.0 (CH), 52.3 (CH), 51.2 (CH), 47.8 (CH_2), 46.9 (CH_2), 46.2 (CH_2), 40.4 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 38.3 (CH_2), 36.6 (CH_2), 36.1 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 24.8 (CH), 24.6 (CH), 23.4 (CH_2), 23.3 (CH_2), 23.0 (CH_3), 22.5 (CH_3), 21.9 (CH_3), 21.7 (CH_3), 11.8 (CH_3), 11.4 (CH_3), 11.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 9.78-9.38 (m, 1.6H), 8.44-8.39 (m, 2H), 8.12-8.06 (m, 2H), 7.30-7.04 (m, 12H), 6.86 (br s, 1.6H), 5.13-4.98 (m, 2H), 4.63-4.52 (m, 2H), 3.50-3.33 (m, 2H), 3.25-3.12 (m, 2H), 3.02-2.94 (m, 2H), 2.92-2.82 (m, 2H), 1.86-1.35 (m, 10H), 1.29 (s, 9H), 1.28 (s, 9H), 0.95-0.87 (m, 12H), 0.80 (t, *J* = 7.3 Hz, 6H) ppm. **HPLC** $t_{R-HPLC-2}$ = 3.33 min. **HRMS (ESI+)** m/z calcd. for $C_{28}H_{40}BrN_4O_4$ $[M+H;\ ^{79}Br]^+$ = 575.2227, $[M+H;\ ^{81}Br]^+$ = 577.2212, found 575.2244 and 577.2293 in the expected ratio 1:1. No spectroscopic data are available in literature.

tert-Butyl ((2S)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4b**

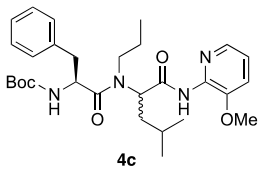


4b

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Phe-OH (265 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 4:1 to 3:2), the desired compound as a yellow oil with 77% (411 mg, 0.77 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.56 (br s, 0.2H), 9.24 (br s, 0.8H), 9.09 (br s, 0.6H), 8.41 (d, *J* = 4.5 Hz, 0.8H), 8.39 (dd, *J* = 4.5 Hz, 1H), 8.36 (dd, *J* = 4.5, 1.4 Hz, 0.2H), 7.73 (dd, *J* = 7.9, 1.4 Hz, 0.8H), 7.72-7.67 (m, 1.2H), 7.32-7.14 (m, 8H), 7.10-7.02 (m, 4H), 5.33-5.26 (m, 1.8H), 5.17-5.05 (m, 1.2H), 5.00-4.93 (m, 0.8H), 4.87-4.64 (m, 2.2H), 3.45-3.37 (m, 0.2H), 3.32-2.91 (m, 7.8H), 1.97-1.81 (m, 3H), 1.73-1.42 (m, 6.2H), 1.39 (s, 7.2H), 1.36 (s, 9H), 1.31 (s, 1.8H), 1.18-1.07 (m, 0.8H), 0.96-0.89 (m, 12H), 0.86-0.76 (m, 6H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.7 (C), 174.3 (C), 171.8 (C), 169.3 (C), 169.0 (C), 167.6 (C), 156.4 (C), 155.1 (C), 148.0 (C), 148.0 (C), 147.8 (C), 146.9 (CH), 138.5 (CH), 138.1 (CH), 138.0 (CH), 136.4 (C), 136.2 (C), 129.8 (CH), 129.4 (CH), 129.4

(CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 122.3 (C), 122.2 (C), 122.0 (C), 121.0 (CH), 120.9 (CH), 81.2 (C), 80.1 (C), 80.0 (C), 59.3 (CH), 58.2 (CH), 56.9 (CH), 52.4 (CH), 52.3 (CH), 51.3 (CH), 47.7 (CH_2), 47.0 (CH_2), 46.1 (CH_2), 40.3 (CH_2), 39.9 (CH_2), 39.4 (CH_2), 38.3 (CH_2), 36.5 (CH_2), 36.2 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 24.8 (CH), 24.6 (CH), 23.4 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 23.0 (CH_3), 22.5 (CH_3), 21.9 (CH_3), 21.6 (CH_3), 11.8 (CH_3), 11.4 (CH_3), 11.3 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 9.81-9.43 (m, 1.6H), 8.40-8.35 (m, 2H), 7.97-7.92 (m, 2H), 7.33-7.14 (m, 12H), 6.88 (br s, 1.6H), 5.13-4.98 (m, 2H), 4.64-4.50 (m, 2H), 3.51-3.33 (m, 2H), 3.26-3.12 (m, 2H), 3.01-2.93 (m, 2H), 2.91-2.83 (m, 2H), 1.87-1.34 (m, 10H), 1.29 (s, 9H), 1.28 (s, 9H), 0.95-0.87 (m, 12H), 0.80 (t, *J* = 7.1 Hz, 6H) ppm. **HPLC** $t_{R-HPLC-2}$ = 3.34 min. **HRMS (ESI+)** m/z calcd. for $C_{28}H_{40}ClN_4O_4$ $[M+H;\ ^{35}Cl]^+$ = 531.2733, $[M+H;\ ^{37}Cl]^+$ = 533.2718, found 531.2745 and 533.2802 in the expected ratio 3:1. No spectroscopic data are available in literature.

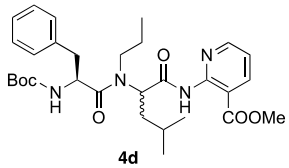
tert-Butyl ((2S)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4c**



4c

The title compound was prepared following general procedure **C** from 2-isocyano-3-methoxypyridine **3c** (134 mg, 1 mmol, 1 equiv), Boc-L-Phe-OH (265 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.0 mmol, 1.0 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 3:7 to 1:9), the desired compound as a colorless oil with 66% (347 mg, 0.66 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.13-8.99 (m, 1H), 8.88-8.75 (m, 1H), 8.09 (d, *J* = 4.6 Hz, 0.9H), 8.07-8.02 (m, 1.1H), 7.31-6.98 (m, 14H), 5.33 (d, *J* = 8.8 Hz, 0.9H), 5.31-5.24 (m, 1H), 5.16-5.05 (m, 2.1H), 4.86-4.75 (m, 2H), 3.91 (s, 2.7H), 3.88 (s, 3H), 3.81 (s, 0.3H), 3.43-3.35 (m, 0.1H), 3.28-3.18 (m, 1.1H), 3.12-2.88 (m, 6.8H), 1.95-1.81 (m, 3H), 1.70-1.44 (m, 6.1H), 1.40 (s, 8.1H), 1.37 (s, 8.1H), 1.31 (s, 0.9H), 1.29 (s, 0.9H), 1.18-1.08 (m, 0.9H), 0.97-0.88 (m, 12H), 0.86-0.74 (m, 6H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.2 (C), 174.0 (C), 168.9 (C), 168.5 (C), 155.0 (C), 154.9 (C), 145.3 (C), 145.0 (C), 142.0 (C), 141.9 (C), 141.2 (C), 139.8 (CH), 139.7 (CH) 136.5 (C), 136.3 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 127.1 (CH), 121.4 (CH), 119.9 (CH), 119.8 (CH), 118.3 (CH), 117.4 (CH), 117.3 (CH), 79.9 (C), 59.4 (CH), 57.5 (CH), 56.7 (CH), 55.8 (CH_3), 53.9 (CH), 52.5 (CH), 52.4 (CH), 51.4 (CH), 47.1 (CH_2), 46.7 (CH_2), 46.1 (CH_2), 41.4 (CH_2), 40.5 (CH_2), 40.1 (CH_2), 39.4 (CH_2), 38.5 (CH_2), 37.0 (CH_2), 36.6 (CH_2), 36.3 (CH_2), 28.4 (CH_3), 28.2 (CH_3), 24.8 (CH), 24.7 (CH), 23.4 (CH_2), 23.1 (CH_2), 23.0 (CH_3), 22.5 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 11.8 (CH_3), 11.5 (CH_3), 11.3 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 9.26-8.86 (m, 1.6H), 7.96-7.92 (m, 2H), 7.45-7.40 (m, 2H), 7.28-7.12 (m, 12H), 6.83 (br s, 1.6H), 5.09-4.99 (m, 2H), 4.64-4.51 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.48-3.30 (m, 2H), 3.21-3.09 (m, 2H), 3.01-2.92 (m, 2H), 2.91-2.82 (m, 2H), 1.86-1.34 (m, 10H), 1.30 (s, 9H), 1.27 (s, 9H), 0.94-0.86 (m, 12H), 0.80 (t, *J* = 7.1 Hz, 6H) ppm. **HPLC** $t_{R-HPLC-2}$ = 2.95 min. **HRMS (ESI+)** m/z calcd. for $C_{29}H_{43}N_4O_5$ $[M+H]^+$ = 527.3228, found 527.3202. No spectroscopic data are available in literature.

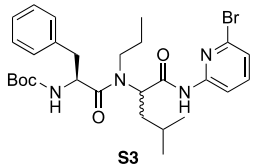
Methyl 2-(2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-phenyl-*N*-propylpropanamido)-4-methylpentanamido)nicotinate **4d**



4d

The title compound was prepared from methyl 2-isocyanonicotinate **3d** (162 mg, 1 mmol, 1 equiv), Boc-L-Phe-OH (265 mg, 1 mmol, 1 equiv), propylamine (0.082 ml, 1 mmol, 1 equiv) and isovaleraldehyde (0.107 ml, 1 mmol, 1 equiv) in dichloromethane (4 ml). The mixture was heated at 110 °C for 0.5 hours by microwave irradiation. This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAC from 1:0 to 13:7) as a pale-yellow oil with 41% (228 mg, 0.41 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 10.94-10.80 (m, 2H), 8.65 (d, *J* = 4.4 Hz, 1H), 8.63 (d, *J* = 4.4 Hz, 0.8H), 8.59 (d, *J* = 4.4 Hz, 0.2H), 8.33-8.27 (m, 1.8H), 8.25 (d, *J* = 7.8 Hz, 0.2H), 7.29-7.16 (m, 8H), 7.13-7.05 (m, 4H), 5.63 (d, *J* = 8.6 Hz, 0.8H), 5.47-5.29 (m, 2.2H), 5.21-5.06 (m, 1H), 4.87-4.75 (m, 1.8H), 4.68-4.62 (m, 0.2H), 3.97 (s, 2.4H), 3.95 (s, 3H), 3.93 (s, 0.6H), 3.33-2.88 (m, 8H), 2.05-1.90 (m, 1.8H), 1.86-1.78 (m, 1H), 1.75-1.42 (m, 5H), 1.37 (s, 7.2H), 1.35 (s, 9H), 1.28-1.23 (m, 2.2H), 1.21 (s, 1.8H), 0.94 (d, *J* = 6.5 Hz, 6H), 0.88 (d, *J* = 6.5 Hz, 6H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers**) δ 173.3 (C), 172.9 (C), 171.6 (C), 169.2 (C), 169.0 (C), 168.2 (C), 167.0 (C), 155.1 (C), 155.0 (C), 153.2 (CH), 153.2 (CH), 152.8 (CH), 152.3 (C), 152.2 (C), 139.9 (CH), 139.7 (CH), 136.9 (C), 136.9 (C), 129.9 (CH), 129.6 (CH), 129.5 (CH), 128.5 (CH), 126.8 (CH), 119.0 (CH), 118.7 (CH), 118.6 (CH), 112.6 (C), 112.3 (C), 80.2 (C), 79.7 (C), 79.7 (C), 60.5 (CH), 58.1 (CH), 56.5 (CH), 56.1 (CH), 54.3 (CH), 53.0 (CH_3), 53.0 (CH_3), 52.8 (CH), 52.4 (CH), 51.8 (CH), 47.6 (CH_2), 47.1 (CH_2), 46.5 (CH_2), 46.2 (CH_2), 41.0 (CH_2), 40.1 (CH_2), 39.8 (CH_2), 39.4 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 36.5 (CH_2), 28.4 (CH_3), 28.1 (CH_3), 24.9 (CH), 24.5 (CH), 23.6 (CH_2), 23.4 (CH_2), 23.1 (CH_3), 23.0 (CH_3), 22.6 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 21.6 (CH_3), 11.7 (CH_3), 11.5 (CH_3), 11.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.31-10.05 (m, 1.6H), 8.58-8.49 (m, 2H), 8.19-8.11 (m, 2H), 7.32-7.12 (m, 12H), 6.85 (br s, 1.6H), 5.11-4.96 (m, 2H), 4.64-4.52 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.48-3.33 (m, 2H), 3.22-3.12 (m, 2H), 3.04-2.94 (m, 2H), 2.91-2.81 (m, 2H), 1.86-1.75 (m, 2H), 1.73-1.35 (m, 8H), 1.29 (s, 18H), 0.94-0.87 (m, 12H), 0.81 (t, *J* = 7.2 Hz, 6H) ppm **HPLC** $t_{R-HPLC-2}$ = 3.29 min. **HRMS (ESI+)** m/z calcd. for $C_{30}H_{42}N_4O_6Na$ $[M+Na]^+$ = 577.2997, found 577.0303. No spectroscopic data are available in literature.

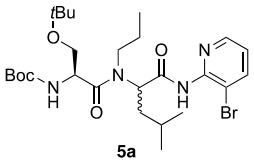
tert-Butyl ((2S)-1-((1-((6-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **S3**



S3

The title compound was prepared following general procedure **C** from 6-bromo-2-isocyanopyridine **S4** (329 mg, 1.8 mmol, 1 equiv), Boc-L-Phe-OH (478 mg, 1.8 mmol, 1 equiv), propylamine (0.18 ml, 2.16 mmol, 1.2 equiv) and isovaleraldehyde (0.23 ml, 2.16 mmol, 1.2 equiv) in trifluoroethanol (7 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet Ether/EtOAc from 1:1 to 3:7), the desired compound as a yellow oil with 65% (678 mg, 1.18 mmol) yield. **^{1}H (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 11.24 (br s, 0.2H), 10.66 (br s, 0.1H), 10.55 (br s, 0.2H), 10.48 (br s, 0.3H), 10.34 (br s, 0.5H), 10.13 (br s, 0.7H), 9.07-7.96 (m, 2H), 7.75-7.69 (m, 2H), 7.39-7.17 (m, 12H), 7.17-7.09 (m, 2H), 5.10-4.98 (m, 1.4H), 4.92-4.79 (m, 0.6H), 4.68-4.58 (m, 0.5H), 4.53-4.37 (m, 1.5H), 3.55-3.44 (m, 0.5H), 3.42-3.25 (m, 1.5H overlap with HDO), 3.18-3.02 (m, 2H), 2.98-2.74 (m, 4H),1.80-1.72 (m, 0.5H), 1.70-1.60 (m, 2.5H), 1.57-1.41 (m, 4H), 1.38 (s, 3H), 1.31 (s, 7H), 1.28 (s, 9H), 0.94-0.67 (m, 20H) ppm. **^{13}C (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 173.5 (C), 173.3 (C), 172.7 (C), 172.1 (C), 171.7 (C), 170.6 (C), 170.6 (C), 168.8 (C), 155.8 (C), 155.3 (C), 155.2 (C), 154.9 (C), 151.8 (C), 151.8 (C), 151.7 (C), 151.5 (C), 141.4 (CH), 141.3 (CH), 141.3 (CH), 138.8 (C), 138.8 (C), 137.6 (C), 137.4 (C), 137.1 (C), 129.6 (CH), 129.4 (CH), 129.2 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 127.7 (CH), 126.5 (CH), 126.4 (CH), 126.3 (CH), 126.0 (CH), 123.5 (CH), 123.3 (CH), 123.2 (CH), 123.1 (CH), 112.8 (CH), 112.6 (CH), 112.5 (CH), 112.3 (CH), 79.2 (C), 78.2 (C), 78.1 (C), 58.2 (CH), 56.2 (CH), 56.1 (CH), 56.0 (CH), 52.6 (CH), 52.4 (CH), 51.6 (CH), 51.5 (CH), 46.3 (CH_2), 46.0 (CH_2), 45.1 (CH_2), 44.8 (CH_2), 37.9 (CH_2), 37.7 (CH_2), 37.4 (CH_2), 37.1 (CH_2), 36.9 (CH_2), 28.2 (CH_3), 28.0 (CH_3), 27.8 (CH_2), 27.7 (CH_2), 24.7 (CH_3), 24.3 (CH_3), 24.2 (CH_3), 22.9 (CH_3), 22.9 (CH_3), 22.8 (CH_3), 22.7 (CH_3), 22.2 (CH), 22.0 (CH), 22.0 (CH), 21.8 (CH_3), 21.7 (CH_3), 21.0 (CH_3), 21.0 (CH_3), 11.5 (CH_3), 11.4 (CH_3), 11.1 (CH_3) ppm. **HPLC** $t_{R-HPLC-2}$ = 3.81 min. **HRMS (ESI+)** m/z calcd. for $C_{28}H_{39}BrN_4O_4Na$ [M+Na; $^{79}Br]^+$ = 597.2047, [M+Na; $^{81}Br]^+$ = 599.2031, found 597.2029 and 599.2009 in the expected ratio 1:1. No spectroscopic data are available in literature.

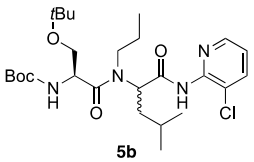
tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate **5a**



5a

The title compound was prepared following general procedure **C** from 3-bromo-2-isocyanopyridine **3a** (183 mg, 1 mmol, 1 equiv), Boc-L-Ser(*t*Bu)-OH (261 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet Ether/EtOAc from 4:1 to 3:2), the desired compound as a yellow oil with 70% (398 mg, 0.70 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.17-9.03 (m, 1.6H), 8.46-8.41 (m, 2H), 7.88-7.86 (m, 1H), 7.86-7.84 (m, 1H), 6.97 (dd, *J* = 8.1, 4.7 Hz, 2H), 5.33 (d, *J* = 8.1 Hz, 1H), 5.30-5.21 (m, 2H), 5.01-4.91 (m, 1H), 4.84-4.73 (m, 2H), 3.67-3.45 (m, 6H), 3.36-3.24 (m, 2H), 2.02-1.94 (m, 1H), 1.91-1.57 (m, 9H), 1.43 (s, 8.1H), 1.40 (s, 9H), 1.32 (s, 0.9H), 1.18 (s, 0.9H), 1.14 (s, 8.1H), 1.08 (s, 0.9H), 1.01 (s, 8.1H), 0.99-0.86 (m, 18H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 174.3 (C), 173.9 (C), 169.7 (C), 169.5 (C), 155.2 (C), 149.1 (C), 148.9 (C), 147.5 (CH), 141.4 (CH), 121.3 (CH), 112.5 (C), 80.1 (C), 73.8 (C), 73.6 (C), 63.6 (CH_2), 63.5 (CH_2), 59.6 (CH), 56.5 (CH), 51.1 (CH), 48.7 (CH_2), 47.0 (CH_2), 36.7 (CH_2), 36.0 (CH_2), 28.4 (CH_3), 27.5 (CH_3), 27.4 (CH_3), 27.2 (CH_3), 24.8 (CH), 24.4 (CH), 23.5 (CH_2), 23.3 (CH_2), 23.3 (CH_3), 23.1 (CH_3), 22.4 (CH_3), 22.2 (CH_3), 11.5 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 9.51-9.36 (m, 1.6H), 8.43-8.38 (m, 2H), 8.09 (d, *J* = 7.8 Hz, 2H), 7.24-7.18 (m, 2H), 6.63 (br s, 1.6H), 5.20-5.14 (m, 1H), 4.98-4.90 (m, 1H), 4.54-4.45 (m, 2H), 3.58-3.29 (m, 8H), 1.87-1.58 (m, 10H), 1.36 (s, 9H), 1.32 (s, 9H), 1.11 (s, 9H), 1.08 (s, 9H), 0.98-0.84 (m, 18H) ppm. **HPLC** $t_{R-HPLC-2}$ = 3.41 min. **HRMS (ESI+)** m/z calcd. for $C_{26}H_{44}BrN_4O_5$ [M+H; $^{79}Br]^+$ = 571.2490, [M+H; $^{81}Br]^+$ = 573.2474, found 571.2503 and 573.2474 in the expected ratio 1:1. No spectroscopic data are available in literature.

tert-Butyl ((2*S*)-3-(*tert*-butoxy)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5b**

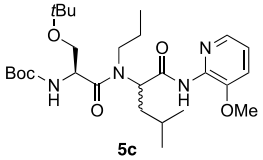


5b

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Ser(*t*Bu)-OH (261 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/ EtOAc from 4:1 to 13:7), the desired compound as a yellow oil with 73% (387 mg, 0.73 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.30 (br s, 1.6H), 8.44-8.39 (m, 2H), 7.77-7.75 (m, 1H), 7.75-7.73 (m, 1H), 7.10 (dd, *J* = 8.1, 4.9 Hz, 2H), 5.35 (d, *J* = 8.1 Hz, 1H), 5.32 (d, *J* = 8.7 Hz, 1H), 5.24-5.17 (m, 1H), 4.99-4.89 (m, 1H), 4.81-4.71 (m, 2H), 3.64-3.55 (m, 3H), 3.54-3.46 (m, 3H), 3.41-3.26 (m, 2H), 2.02-1.94 (m, 1H), 1.92-1.56 (m, 9H), 1.43 (s, 9H), 1.38 (s, 7.8H), 1.32 (s, 1.2H), 1.18 (s, 1.2H), 1.14 (s, 7.8H), 1.05 (s, 0.3H), 1.02 (s, 8.7H), 0.99-0.85 (m, 18H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.6 (C), 174.2 (C), 169.8 (C), 169.7 (C), 155.4 (C), 155.2 (C), 147.8 (C), 147.7 (C), 146.3 (CH), 139.2 (CH), 138.6 (CH), 122.9 (C), 121.2 (CH), 80.2 (C), 73.8 (C), 73.7 (C), 63.4 (CH_2), 63.3 (CH_2), 62.4 (CH_2), 59.7 (CH), 57.1 (CH), 51.2 (CH), 51.1 (CH), 50.3 (CH), 48.9 (CH_2), 47.3 (CH_2), 46.5 (CH_2), 38.7 (CH_2), 36.7 (CH_2), 36.1 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 28.3 (CH_3), 27.5 (CH_3), 27.3 (CH_3), 27.2 (CH_3), 24.8 (CH), 24.5 (CH), 23.4 (CH_2), 23.3 (CH_2), 23.2 (CH_3), 23.0 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 21.7 (CH_3), 11.7 (CH_3), 11.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)**

δ 9.46 (br s, 1.6H), 8.38-8.35 (m, 2H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.32-7.26 (m, 2H), 6.59 (br s, 1.6H), 5.20-5.12 (m, 1H), 4.99-4.90 (m, 1H), 4.54-4.44 (m, 2H), 3.59-3.38 (m, 8H), 1.87-1.57 (m, 10H), 1.36 (s, 9H), 1.33 (s, 9H), 1.11 (s, 9H), 1.09 (s, 9H), 0.98-0.83 (m, 18H) ppm. **HPLC** t_R = 3.39 min. **HRMS (ESI+)** m/z calcd. for $C_{26}H_{44}ClN_4O_5$ $[M+H; {}^{35}Cl]^+$ = 527.2995, $[M+H; {}^{37}Cl]^+$ = 529.2979, found 527.2985 and 529.3007 in the expected ratio 3:1. No spectroscopic data are available in literature.

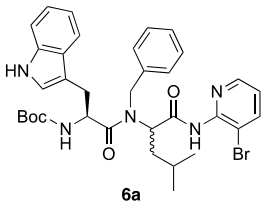
tert-Butyl ((2*S*)-3-*(tert*-butoxy)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5c**



5c

The title compound was prepared following general procedure **C** from 2-isocyano-3-methoxypyridine **3c** (134 mg, 1 mmol, 1 equiv), Boc-L-Ser(*t*Bu)-OH (261 mg, 1 mmol, 1 equiv), propylamine (0.099 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. ether/ EtOAc from 4:1 to 13:7), the desired compound as a pale orange oil with 63% (330 mg, 0.63 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.04-8.86 (m, 2H), 8.08-8.04 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.03-6.98 (m, 2H), 5.33 (d, *J* = 8.0 Hz, 1H), 5.30-5.20 (m, 2H), 5.06-4.96 (m, 1H), 4.83-4.71 (m, 2H), 3.86 (s, 6H), 3.64-3.44 (m, 6H), 3.35-3.22 (m, 2H), 1.99-1.91 (m, 1H), 1.91-1.50 (m, 9H), 1.43 (s, 9H), 1.40 (s, 8.1H), 1.33 (s, 0.9H), 1.17 (s, 0.9H), 1.14 (s, 8.1H), 1.07 (s, 0.9H), 0.99 (s, 8.1H), 0.98-0.84 (m, 18H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.0 (C), 173.6 (C), 169.2 (C), 169.1 (C), 155.1 (C), 145.5 (C), 142.0 (C), 142.0 (C), 139.7 (CH), 121.3 (C), 119.9 (CH), 117.4 (CH), 79.9 (C), 73.6 (C), 63.6 (CH_2), 58.9 (CH), 56.5 (CH), 55.8 (CH_3), 55.7 (CH_3), 51.2 (CH), 51.1 (CH), 48.2 (CH_2), 46.7 (CH_2), 36.9 (CH_2), 36.2 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 27.5 (CH_3), 27.4 (CH_3), 27.2 (CH_3), 24.8 (CH), 24.4 (CH), 23.5 (CH_2), 23.2 (CH_2), 23.2 (CH_3), 23.1 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 21.7 (CH_3), 11.5 (CH_3), 11.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 9.02-8.87 (m, 1.6H), 7.95-7.91 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.22-7.14 (m, 2H), 6.56 (br s, 1.6H), 5.17-5.10 (m, 1H), 5.01-4.93 (m, 1H), 4.55-4.45 (m, 2H), 3.80 (s, 6H), 3.56-3.29 (m, 8H), 1.83-1.55 (m, 10H), 1.36 (s, 9H), 1.32 (s, 9H), 1.11 (s, 9H), 1.06 (s, 9H), 0.96-0.83 (m, 18H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 3.01 min. **HRMS (ESI+)** m/z calcd. for $C_{27}H_{47}N_4O_6$ $[M+H]^+$ = 523.3490, found 523,3474. No spectroscopic data are available in literature.

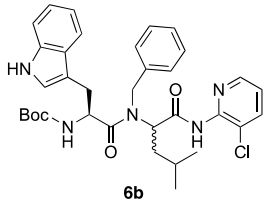
tert-Butyl ((2*S*)-1-(benzyl(1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6a**



6a

The title compound was prepared following general procedure **C** from 3-bromo-2-isocyanopyridine **3a** (183 mg, 1 mmol, 1 equiv), Boc-L-Trp-OH (304 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 11:9 to 7:13), the desired compound as a pale-yellow solid with 71% (470 mg, 0.71 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.61 (br s, 0.2H), 9.30 (br s, 0.8H), 9.16 (br s, 0.2H), 8.93 (br s, 0.8H), 8.51-8.44 (m, 1H), 8.41 (d, *J* = 3.8 Hz, 0.8H), 8.36 (dd, *J* = 4.8, 1.5 Hz, 0.2H), 8.29 (br s, 1H), 8.24-8.19 (m, 1H), 7.96-7.90 (m, 1H), 7.89-7.84 (m, 1H), 7.66 (d, *J* = 7.7 Hz, 0.2H), 7.44 (d, *J* = 7.8 Hz, 0.8H), 7.37-7.29 (m, 1.2H), 7.26-6.95 (m, 17.8H) 6.88-6.86 (m, 1H), 6.83 (br s, 0.8H), 6.78-6.76 (m, 0.2H), 5.43 (d, *J* = 8.4 Hz, 0.2H), 5.40 (d, *J* = 8.4 Hz, 0.8H), 5.22 (d, *J* = 7.4 Hz, 1H), 5.19-5.12 (m, 1H), 5.08-4.95 (m, 1.2H), 4.94-4.90 (m, 0.2H), 4.86 (q, *J* = 7.5 Hz, 0.8H), 4.80 (q, *J* = 7.5 Hz, 0.8H), 4.73-4.60 (m, 1H), 4.44-4.35 (m, 2H), 4.25-4.14 (m, 0.8H), 3.96-3.88 (m, 0.2H), 3.19-3.06 (m, 4H), 2.01-1.94 (m, 1H), 1.93-1.87 (m, 1H), 1.56-1.41 (m, 2H), 1.38 (s, 7.2H), 1.32 (s, 2H), 1.29 (s, 5.8H), 1.07 (s, 1.8H), 1.00 (s, 1.2H) 0.85 (d, *J* = 6.5 Hz, 5.2H), 0.81 (d, *J* = 6.5 Hz, 2H), 0.78 (d, *J* = 6.5 Hz, 5.2H), 0.57 (d, *J* = 6.5 Hz, 0.8H), 0.43 (d, *J* = 6.5 Hz, 0.8) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 175.9 (C), 175.4 (C), 173.4 (C), 168.7 (C), 168.5 (C), 167.6 (C), 156.4 (C), 155.2 (C), 154.9 (C), 154.3 (C), 148.9 (C), 148.8 (C), 147.5 (CH), 147.4 (CH), 141.7 (CH), 141.5 (CH), 138.2 (C), 136.9 (C), 136.3 (C), 136.2 (C), 128.8 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 125.7 (CH), 123.6 (CH), 123.3 (CH), 123.2 (CH), 122.5 (CH), 122.4 (CH), 122.2 (CH), 121.9 (CH), 121.8 (CH), 121.6 (CH), 120.0 (CH), 119.8 (CH), 119.6 (CH), 118.8 (CH), 118.6 (CH), 118.4 (CH), 118.1 (CH), 112.9 (CH), 111.7 (CH), 111.5 (CH), 111.3 (CH), 110.3 (C), 109.9 (C), 81.1 (C), 80.1 (C), 79.8 (C), 59.8 (CH), 58.3 (CH), 57.2 (CH), 53.1 (CH), 52.9 (CH), 52.0 (CH), 51.8 (CH), 50.5 (CH), 49.5 (CH_2), 48.9 (CH_2), 48.2 (CH_2), 47.5 (CH_2), 38.9 (CH_2), 37.2 (CH_2), 36.7 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 27.9 (CH_3) 25.3 (CH), 25.2 (CH), 25.1 (CH), 24.4 (CH_3), 23.1 (CH_3), 23.0 (CH_3), 22.8 (CH_3), 22.7 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 22.3 (CH_3) 21.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.75-10.52 (m, 2H), 9.99-9.56 (m, 2H), 8.43 (br s, 2H), 8.09 (d, *J* = 7.9 Hz, 2H), 7.37-6.96 (m, 20H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.88-6.82 (m, 1H), 5.22-5.07 (m, 2H), 5.02-4.70 (m, 5H), 4.66-4.28 (m, 3H), 3.32-3.15 (m, 1H), 3.08-2.89 (m, 3H), 1.83-1.49 (m, 4H), 1.40-1.16 (m, 18H), 0.90-0.61 (m, 13H), 0.50 (br s, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 173.8 (C), 168.9 (C), 168.7 (C), 154.7 (C), 148.6 (C), 147.0 (CH), 141.4 (CH), 137.8 (C), 137.4 (C), 135.9 (C), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.0 (CH), 126.4 (CH), 125.9 (CH), 123.6 (CH), 122.7 (CH), 120.4 (CH), 117.9 (CH), 116.0 (CH), 110.8 (CH), 109.4 (C), 78.0 (C), 77.9 (C), 58.4 (CH), 56.1 (CH), 51.7 (CH), 47.8 (CH_2), 46.5 (CH_2), 38.1 (CH_2), 37.2 (CH_2), 27.6 (CH_3), 24.1 (CH), 21.9 (CH_3), 21.8 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 3.27 and 3.31 min. **HRMS (ESI+)** m/z calcd. for $C_{34}H_{40}BrN_5O_4Na$ $[M+Na; {}^{79}Br]^+$ = 684.2156, $[M+Na; {}^{81}Br]^+$ = 686.2142, found 684.2153 and 686.2118 in the expected ratio 1:1. No spectroscopic data are available in literature.

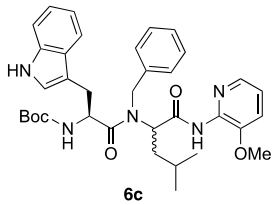
tert-Butyl ((2*S*)-1-(benzyl(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6b**



6b

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Trp-OH (304 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 7:13 to 9:11), the desired compound as a pale-yellow solid with 66% (410 mg, 0.66 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 9.61 (br s, 0.2H), 9.38 (br s, 0.8H), 9.26 (br s, 0.2H), 8.99 (br s, 0.8H), 8.47-8.40 (m, 0.8H), 8.37 (d, *J* = 4.6 Hz, 1H), 8.32-8.28 (m, 1.2H), 8.26-8.17 (m, 1H), 7.74 (d, *J* = 7.9 Hz, 0.8H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.67-7.64 (m, 0.2H), 7.43 (d, *J* = 7.9 Hz, 0.4H), 7.37-7.28 (m, 1.4H), 7.27-6.91 (m, 18.2H), 6.88-6.82 (m, 1.8H), 6.77 (br s, 0.2H), 5.41 (d, *J* = 8.1 Hz, 0.8H), 5.34 (d, *J* = 8.1 Hz, 0.2H), 5.20 (d, *J* = 7.2 Hz, 1H), 5.18-5.12 (m, 1H), 5.05-4.97 (m, 1H), 4.90-4.83 (m, 0.8H), 4.78 (q, *J* = 7.2 Hz, 1H), 4.75-4.68 (m, 1H), 4.66-4.60 (m, 0.2H), 4.45-4.32 (m, 2H), 4.27-4.16 (m, 0.8H), 3.97-3.89 (m, 0.2H), 3.38-3.31 (m, 0.2H), 3.20-3.05 (m, 3.8H), 2.02-1.96 (m, 1.2H), 1.95-1.87 (m, 1.8H), 1.54-1.41 (m, 3H), 1.40-1.33 (m, 7.2H), 1.28 (s, 7.2H), 1.07 (s, 1.8H), 1.00 (s, 1.8H), 0.86 (d, *J* = 6.5 Hz, 4.8H), 0.83-0.76 (m, 6H), 0.56 (d, *J* = 6.5 Hz, 0.6H), 0.44 (d, *J* = 6.5 Hz, 0.6H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 176.0 (C), 175.5 (C), 173.4 (C), 168.6 (C), 168.5 (C), 167.5 (C), 156.5 (C),155.3 (C), 154.9 (C), 154.3 (C), 148.0 (C), 147.9 (C), 146.8 (CH), 146.8 (CH), 146.7 (CH), 138.3 (CH), 138.1 (CH), 136.9 (C), 136.3 (C), 136.2 (C), 128.8 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 125.7 (CH), 123.6 (CH), 123.3 (CH), 123.2 (CH), 122.4 (CH), 122.3 (CH), 121.4 (CH), 121.2 (CH), 120.0 (CH), 119.8 (CH), 118.8 (CH), 118.6, (CH), 111.5 (CH), 111.3 (CH), 110.3 (C), 109.9 (C), 81.1 (C), 80.1 (C), 79.8 (C), 59.7 (CH), 58.3 (CH), 53.1 (CH), 53.0 (CH), 52.0 (CH), 51.8 (CH), 50.6 (CH), 49.5 (CH_2), 48.9 (CH_2), 48.2 (CH_2), 47.3 (CH_2), 38.9 (CH_2), 37.2 (CH_2), 36.7 (CH_2), 31.3 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 27.9 (CH_3), 25.2 (CH), 25.1 (CH), 24.4 (CH), 23.0 (CH_3), 22.8 (CH_3), 22.7 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 21.3 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** 10.76-10.52 (m, 2H), 10.10-9.68 (m, 2H), 8.39 (s, 2H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.37-6.96 (m, 20H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.88-6.82 (m, 1H), 5.20-5.08 (m, 2H), 5.04-4.69 (m, 5H), 4.67-4.28 (m, 3H), 3.32-3.14 (m, 1H), 3.09-2.90 (m, 3H), 1.80-1.51 (m, 6H), 1.42-1.19 (m, 18H), 0.90-0.78 (m, 7H), 0.74-0.47 (m, 5H) ppm. **^{13}C NMR (126 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomers)** δ 173.8 (C), 173.5 (C), 168.9 (C), 168.7 (C), 154.7 (C), 147.5 (C), 146.4 (CH), 138.1 (CH), 137.8 (C), 137.4 (C), 135.9 (C), 127.8 (CH), 127.4 (CH), 127.0 (CH), 126.4 (CH), 125.9 (CH), 125.8 (CH), 123.6 (CH), 122.5 (CH), 120.4 (CH), 117.9 (CH), 110.8 (CH), 109.3 (C), 78.0 (C), 58.4 (CH), 56.1 (CH), 51.7 (CH), 47.7 (CH_2), 46.3 (CH_2), 38.1 (CH_2), 37.3 (CH_2), 27.6 (CH_3), 24.1 (CH), 21.9 (CH_3), 21.8 (CH_3) ppm. **HPLC** $t_{R\ –\ HPLC\text{-}2}$ = 3.27 and 3.30 min. **HRMS (ESI+)** m/z calcd. for $[M+H;\ ^{35}Cl]^+$ = 618.2842, $[M+H;\ ^{37}Cl]^+$ = 620.2831, found 618.2838 and 620.2830 in the expected 3:1 ratio. No spectroscopic data are available in literature.

tert-Butyl ((2*S*)-1-(benzyl(1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6c**

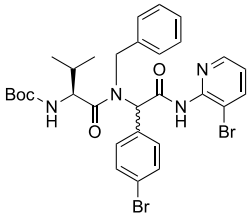


6c

The title compound was prepared following general procedure **C** from 2-isocyano-3-methoxypyridine **6c** (134 mg, 1 mmol, 1 equiv), Boc-L-Trp-OH (304 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and isovaleraldehyde (0.129 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (40 g column, Pet. Ether/EtOAc from 9:11 to 1:3), the desired compound as a pale-yellow solid with 72% (445 mg, 0.72 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 9.10 (br s, 0.6H), 9.00 (br s, 0.2H), 8.69-8.62 (m, 0.8H), 8.42-8.23 (m, 2H), 8.15-8.11 (m, 1H), 8.06-7.97 (m, 1H), 7.46 (d, *J* = 7.7Hz, 0.6H), 7.38-7.29 (m, 2H), 7.28-6.90 (m, 19.4H), 6.89-6.85 (m, 1H), 6.80 (s, 0.2H), 6.76 (s, 0.8H), 5.37 (d, *J* = 8.1 Hz, 0.6H), 5.33-5.26 (m, 0.4H), 5.25-5.12 (m, 2H), 5.10-4.98 (m, 1.2H), 4.89-4.76 (m, 1.6H), 4.72-4.62 (m, 0.2H), 4.61-4.51 (m, 1H), 4.43-4.24 (m, 2H), 4.19 (d, J = 17.8 Hz, 0.2H), 4.04 (d, *J* = 17.8 Hz, 0.8H), 3.93-3.86 (m, 5.4H), 3.81-3.75 (m, 0.6H), 3.20-3.11 (m, 2H), 3.10-3.0 (m, 2H), 2.13-2.01 (m, 1H), 1.97-1.90 (m, 1H), 1.88-1.78 (m, 1H), 1.56-1.45 (m, 0.8H), 1.44-1.35 (m, 7.2H), 1.34-1.24 (m, 9.4H), 1.09 (s, 1.8H), 1.01 (s, 1.8H), 0.87-0.72 (m, 10.8H), 0.58 (d, *J* = 6.2 Hz, 0.6H), 0.45 (d, *J* = 6.2 Hz, 0.6H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 175.6 (C), 175.3 (C), 175.0 (C), 168.3 (C), 168.1 (C), 168.0 (C), 155.0 (C), 154.8 (C), 154.3 (C), 145.9 (C), 145.7 (C), 145.2 (C), 141.8 (C), 141.7 (C), 139.6 (CH), 137.2 (C), 136.9 (C), 136.3 (C), 136.2 (C), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 127.4 (CH), 126.6 (CH), 126.3 (CH), 125.9 (CH), 125.6 (CH), 123.6 (CH), 123.3 (CH), 123.2 (CH), 122.2 (CH), 120.5 (CH), 120.1 (CH), 119.8 (CH), 119.6 (CH), 118.8 (CH), 118.7 (CH), 118.4 (CH), 118.0 (CH), 117.8 (CH), 117.5 (CH), 111.8 (CH), 111.4 (CH), 111.3 (CH), 110.4 (C), 110.2 (C) 80.0 (C), 79.8 (C), 79.7 (C), 58.5 (CH), 57.5 (CH), 57.0 (CH), 55.9 (CH_3), 55.7 (CH_3), 53.2 (CH), 53.0 (CH), 52.1 (CH), 50.8 (CH), 49.2 (CH_2), 48.0 (CH_2), 47.1 (CH_2), 39.0 (CH_2), 37.1 (CH_2), 36.8 (CH_2), 36.6 (CH_2), 31.4 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.0 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 27.9 (CH_3) 27.8 (CH_3) 25.3 (CH), 25.1 (CH), 24.5 (CH), 22.9 (CH_3), 22.8 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 21.6 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.71-10.49 (m, 2H), 9.44-9.09 (m, 2H), 7.93 (s, 2H), 7.40 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.36-6.94 (m, 20H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.86-6.79 (m, 1H), 5.24-4.51 (m, 8H), 4.43 (d, *J* = 17.2 Hz, 1H), 3.84-3.66 (m, 7H), 3.37-3.21 (m, 1H), 3.10-2.85 (m, 3H), 1.80-1.45 (m, 4H), 1.43-1.05 (m, 18H), 0.89-0.75 (m, 8H), 0.73-0.57 (m, 5H), 0.50 (br s, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomers)** δ 173.8 (C), 173.5 (C), 168.5 (C), 168.2 (C), 154.7 (C), 148.0 (C), 140.9 (C), 138.6 (CH), 137.9 (C), 137.4 (C), 135.9 (C), 127.9 (CH), 127.7(CH), 127.3 (CH), 127.0 (CH),

126.4 (CH), 126.3 (CH), 126.0 (CH), 123.6 (CH), 121.3 (CH), 121.2 (CH), 120.4 (CH), 119.1 (CH), 117.9 (CH), 110.8 (CH), 109.4 (C), 78.0 (C), 58.5 (CH), 56.6 (CH), 56.1 (CH), 55.5 (CH_3), 51.7 (CH), 51.0 (CH), 47.8 (CH_2), 47.6 (CH_2), 46.2 (CH_2), 38.5 (CH_2), 37.9 (CH_2), 37.1 (CH_2), 27.6 (CH_3), 24.1 (CH), 21.9 (CH_3), 21.8 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 2.96 min. **HRMS (ESI+)** m/z calcd. for $C_{35}H_{44}N_5O_5$ $[M+H]^+$ = 614.3337, found 614.3344. No spectroscopic data are available in literature.

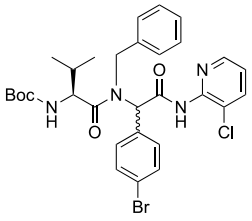
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-bromopyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7a**



7a

The title compound was prepared following general procedure **C** from 3-bromo-2-isocyanopyridine **3a** (183 mg, 1 mmol, 1 equiv), Boc-L-Val-OH (217 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and 4-bromobenzaldehyde (222 mg, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:5 to 7:13), the desired compound as a yellow-brown solid with 51% (343 mg, 0.51 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 8.40 (d, *J* = 4.1 Hz, 1H), 8.32 (d, *J* = 4.1 Hz, 1H), 8.29 (br s, 2H), 7.85-7.82 (m, 0.1H), 7.81-7.77 (m, 1.9H), 7.50-7.45 (m, 2H), 7.37-7.15 (m, 14H), 7.06-7.02 (m, 1.9H), 6.94-6.89 (m, 2H), 6.80-6.78 (m, 0.1H), 6.15 (s, 1H), 5.46 (s, 1H), 5.33 (d, *J* = 9.3 Hz, 1H), 5.17 (d, *J* = 9.3 Hz, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 4.90 (d, *J* = 17.0 Hz, 1H), 4.58-4.48 (m, 3H), 4.41 (dd, *J* = 9.3, 6.9 Hz, 1H), 2.11-2.03 (m, 1H), 1.99-1.92 (m, 1H), 1.45 (s, 8.6H), 1.41 (s, 8.1H), 1.26 (s, 0.4H), 1.21 (s, 0.9H), 0.95-0.88 (m, 9.3H), 0.79 (d, *J* = 6.7 Hz, 2.7H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.7 (C), 174.3 (C), 167.7 (C), 166.2 (C), 156.2 (C), 155.4 (C), 148.4 (C), 148.1 (C), 147.5 (CH), 147.3 (CH), 141.4 (CH), 141.2 (CH), 136.4 (C), 136.2 (C), 133.6 (C), 132.7 (C), 132.3 (CH), 132.0 (CH), 131.8 (CH), 131.6 (CH), 131.5 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.1 (CH), 123.3 (C), 121.2 (CH), 111.2 (C), 110.9 (C), 79.9 (C), 79.6 (C), 66.0 (CH), 63.9 (CH), 56.2 (CH), 56.0 (CH), 51.7 (CH_2), 50.7 (CH_2), 32.3 (CH), 31.3 (CH), 28.4 (CH_3), 28.1 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 19.7 (CH_3), 17.7 (CH_3), 17.5 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.50-9.75 (m, 2H), 8.41 (d, *J* = 3.8 Hz, 2H), 8.07 (d, *J* = 7.9 Hz, 2H), 7.49-6.93 (m, 20H), 6.82 (br s, 2H), 6.34-6.17 (m, 2H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.86 (d, *J* = 16.5 Hz, 1H), 4.69-4.58 (m, 2H), 4.30-4.07 (m, 2H), 2.12-1.92 (m, 2H), 1.50-1.26 (m, 18H), 0.99-0.61 (m, 12H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 3.36 min. **HRMS (ESI+)** m/z calcd. for $C_{30}H_{34}Br_2N_4O_4Na$ $[M+Na;\ ^{79}Br,\ ^{79}Br]^+$ = 695.0839, $[M+Na;\ ^{79}Br,\ ^{81}Br]^+$ = 697.0822 and $[M+Na;\ ^{81}Br,\ ^{81}Br]^+$ = 699.0808, found 695.0828, 697.0778 and 699.0828 in the expected 1:2:1 ratio. No spectroscopic data are available in literature.

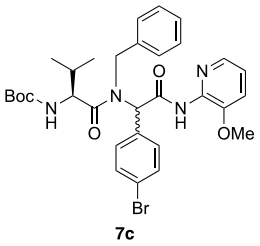
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7b**



7b

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Val-OH (217 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and 4-bromobenzaldehyde (222 mg, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. ETher/EtOAc from 1:5 to 7:13), the desired compound as a yellow-brown solid with 48% (300 mg, 0.48 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 8.41-8.37 (m, 2H), 8.34 (d, *J* = 4.1 Hz, 1H), 8.26 (d, *J* = 4.1 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 0.1H), 7.65-7.62 (m, 1.9H), 7.48-7.44 (m, 2H), 7.34-7.14 (m, 14H), 7.05-6.96 (m, 3.9H), 6.80-6.77 (m, 0.1H), 6.23 (br s, 1H), 5.54 (br s, 1H), 5.38-5.32 (m, 1.1H), 5.18 (d, *J* = 9.4 Hz, 0.9H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.90 (d, *J* = 17.0 Hz, 1H), 4.60-4.47 (m, 3H), 4.41 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.10-2.01 (m, 1H), 1.98-1.91 (m, 1H), 1.45 (s, 8.1H), 1.43 (s, 0.9H), 1.41 (s, 8.1H), 1.21 (br s, 0.9H), 0.95-0.87 (m, 9H), 0.78 (d, *J* = 6.7 Hz, 3H) ppm **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.8 (C), 174.4 (C), 167.8 (C), 166.4 (C), 156.2 (C), 155.5 (C), 147.5 (C), 147.3 (C), 146.8 (CH), 146.6 (CH), 138.6 (C), 138.1 (CH), 137.9 (CH), 136.5 (CH), 136.2 (CH), 133.6 (C), 132.6 (C), 132.3 (CH), 132.0 (CH), 131.8 (CH), 131.6 (CH), 131.4 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 123.2 (C), 120.9 (CH), 120.9 (CH), 79.9 (C), 79.6 (C), 65.9 (CH), 63.8 (CH), 56.3 (CH), 56.1 (CH), 51.7 (CH_2), 50.6 (CH_2), 32.3 (CH), 31.3 (CH), 28.4 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 19.7 (CH_3), 17.7 (CH_3), 17.5 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.57-9.84 (m, 2H), 8.37 (d, *J* = 3.9 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.48-7.23 (m, 10H), 7.18-6.93 (m, 10H), 6.82 (br s, 2H), 6.34-6.18 (m, 2H), 4.98 (d, *J* = 16.8 Hz, 1H), 4.86 (d, *J* = 16.8 Hz, 1H), 4.69-4.53 (m, 2H), 4.30-4.06 (m, 2H), 2.12-1.92 (m, 2H), 1.53-1.25 (m, 18H), 1.00-0.61 (m, 12H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 3.34 min. **HRMS (ESI+)** m/z calcd. for $C_{30}H_{34}BrClN_4O_4Na$ $[M+Na;\ ^{79}Br,\ ^{35}Cl]^+$ = 651.1344, $[M+Na;\ ^{79}Br,\ ^{37}Cl$ or $^{81}Br,\ ^{35}Cl]^+$ = 653.1326 and $[M+Na;\ ^{81}Br,\ ^{37}Cl]^+$ = 655.1314, found 651.1354, 653.1277 and 655.1340 in the 3:4:1 ratio. No spectroscopic data are available in literature.

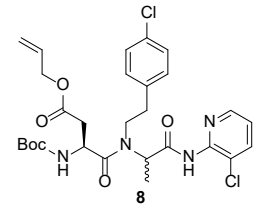
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-methoxypyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7c**



7c

The title compound was prepared following general procedure **C** from 2-isocyano-3-methoxypyridine **3c** (134 mg, 1 mmol, 1 equiv), Boc-L-Val-OH (217 mg, 1 mmol, 1 equiv), benzylamine (0.131 ml, 1.2 mmol, 1.2 equiv) and 4-bromobenzaldehyde (222 mg, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 13:7 to 11:9), the desired compound as a brown solid with 51% (319 mg, 0.51 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers, in a 1:1 ratio and rotamers)** δ 8.34-8.18 (m, 2H), 8.02-7.98 (d, *J* = 4.4Hz, 1H), 7.96-7.90 (m, 1H), 7.46-7.42 (m, 2H), 7.32-7.17 (m, 12H), 7.14-7.11 (m, 4H), 7.05-6.92 (m, 4H), 6.87 (s, 0.2H), 6.82-6.79 (m, 0.2H), 6.55 (br s, 0.8H), 5.70 (br s, 0.8H), 5.36-5.30 (m, 1H), 5.18-5.09 (m, 1.2H), 5.03 (d, *J* = 17.2 Hz, 0.8H), 4.89 (d, *J* = 17.2 Hz, 1H), 4.61-4.47 (m, 3H), 4.41 (dd, *J* = 9.8, 7.1 Hz, 1H), 3.84 (s, 0.6H), 3.81-3.76 (m, 3H), 3.72 (s, 2.4H), 2.10-2.03 (m, 1H), 1.97-1.91 (m, 1H), 1.45 (s, 9H), 1.41 (s, 7.4H), 1.21 (s, 1.6H), 0.98-0.86 (m, 9.6H), 0.77 (d, *J* = 6.7 Hz, 2.4H) ppm **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 174.7 (C), 174.4 (C), 174.0 (C), 168.2 (C), 166.4 (C), 156.0 (C), 155.4 (C), 144.6 (C), 144.2 (C), 141.6 (C), 141.4 (C), 139.5 (CH), 139.2 (CH), 136.9 (C), 136.6 (C), 133.8 (C), 133.3 (C), 132.7 (C), 132.3 (CH), 132.0 (CH), 131.8 (CH), 131.6 (CH), 131.5 (CH), 128.8 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 126.7 (CH), 126.0 (CH), 122.9 (C), 119.7 (CH), 119.6 (CH), 117.2 (CH), 79.8 (C), 79.4 (C), 65.7 (CH), 63.2 (CH), 62.4 (CH), 57.3 (CH), 56.3 (CH), 56.1 (CH), 55.7 (CH_3), 51.4 (CH_2), 50.1 (CH_2), 49.1 (CH_2), 32.9 (CH), 32.4 (CH), 31.5 (CH), 31.1 (CH), 28.4 (CH_3), 28.1 (CH_3), 19.8 (CH_3), 19.7 (CH_3), 17.8 (CH_3), 17.6 (CH_3), 17.5 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.07-9.31 (m, 2H), 7.98-7.91 (m, 2H), 7.50-6.94 (m, 22H), 6.89-6.65 (m, 2H), 6.42-6.18 (m, 2H), 4.96 (d, *J* = 17.3 Hz, 1H), 4.85 (d, *J* = 17.3 Hz, 1H), 4.65-4.54 (m, 2H), 4.29-4.08 (m, 2H), 3.80 (s, 6H), 2.09-1.90 (m, 2H), 1.51-1.25 (m, 18H), 0.98-0.61 (m, 12H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 3.02 min. **HRMS (ESI+)** m/z calcd. for $C_{31}H_{37}BrN_4O_5Na$ [M+Na; $^{79}Br]^+$ = 647.1840 and [M+Na; $^{81}Br]^+$ = 649.1825, found 647.1849 and 649.1851 in the expected 1:1 ratio. No spectroscopic data are available in literature.

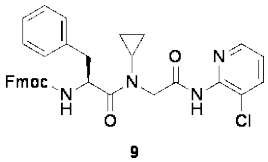
Allyl (3*S*)-3-((tert-butoxycarbonyl)amino)-4-((4-chlorophenethyl)(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoate **8**



8

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Asp(All)-OH (273 mg, 1 mmol, 1 equiv), 2-(4-chlorophenyl)ethylamine (0.168 ml, 1.2 mmol, 1.2 equiv) and acetaldehyde (0.067 ml, 1.2 mmol, 1.2 equiv) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 4:1 to 3:7 over 20 CV), the desired compound as a yellow solid with 48% (283 mg, 0.48 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 10.42 (s, 0.4H), 10.00 (s, 0.2H), 9.94 (s, 0.8H), 9.79 (s, 0.6H), 8.42 (dd, *J* = 4.7, 1.6 Hz, 0.4H), 8.40-8.37 (m, 1.6H), 8.02-7.94 (m, 2H), 7.48 (t, *J* = 9.3 Hz, 2H), 7.40-7.29 (m, 9H), 7.25-7.22 (m, 1H), 5.95-5.83 (m, 2H), 5.35-5.25 (m, 2H), 5.22-5.14 (m, 2H), 5.06-4.86 (m, 4H), 4.58-4.51 (m, 4H), 3.79-3.47 (m, 4H), 3.26-3.02 (m, 2H), 3.00-2.59 (m, 6H), 1.47-1.43 (m, 5.4 H), 1.40 (s, 3.6H), 1.35 (s, 7.2H), 1.33-1.30 (m, 7.2H), 1.28 (d, *J* = 7.0 Hz, 0.6H) ppm **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 171.3 (C), 170.9 (C), 170.6 (C), 170.4 (C), 170.2(C), 170.0 (C), 169.9 (C), 169.9 (C), 169.5 (C), 168.9 (C), 155.3 (C), 155.2 (C), 154.8 (C), 147.9 (C), 147.8 (C), 147.7 (C), 147.0 (CH), 146.9 (CH), 146.8 (CH), 138.9 (CH), 138.8 (CH), 138.6 (CH), 138.6 (C), 137.4 (C), 137.4 (C), 132.6 (CH), 132.5 (CH), 132.5 (CH), 132.4 (CH), 131.2 (C), 130.8 (C), 130.8 (C), 130.6 (CH), 130.4 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 127.3 (C), 126.6 (C), 126.4 (C), 123.6 (CH), 123.3 (CH), 123.1 (CH), 123.0 (CH), 117.7 (CH_2), 117.7 (CH_2), 117.6 (CH_2), 79.1 (C), 78.7 (C), 78.6 (C), 78.6 (C), 64.7 (CH_2), 64.6 (CH_2), 64.6 (CH_2), 64.5 (CH_2), 55.6 (CH), 55.4 (CH), 54.1 (CH), 48.0 (CH), 47.7 (CH), 47.6 (CH), 47.0 (CH_2), 46.6 (CH_2), 46.0 (CH_2), 45.8 (CH_2), 36.6 (CH_2), 36.5 (CH_2), 35.6 (CH_2), 35.4 (CH_2), 33.2 (CH_2), 33.2 (CH_2), 28.1 (CH_3), 28.1 (CH_3), 28.0 (CH_3), 28.0 (CH_3), 16.1 (CH_3), 15.8 (CH_3), 15.0 (CH_3), 14.8 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.16-9.40 (m, 2H), 8.41-8.35 (m, 2H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.38-7.22 (m, 10H), 7.10 (br s, 2H), 5.95-5.84 (m, 2H), 5.33-5.26 (m, 2H), 5.19 (d, *J* = 10.4 Hz, 2H), 5.05-4.88 (m, 4H), 4.55 (d, *J* = 5.4 Hz, 4H), 3.83-3.50 (m, 4H), 3.03-2.75 (m, 6H), 2.71-2.60 (m, 2H), 1.47 (d, *J* = 7.1 Hz, 6H), 1.36 (s, 18H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 2.79 min. **HRMS (ESI+)** m/z calcd. for $C_{28}H_{35}Cl_2N_4O_6$ [M+Na; ^{35}Cl, $^{35}Cl]^+$ = 593.1934, [M+Na; ^{35}Cl, ^{37}Cl or ^{37}Cl, $^{35}Cl]^+$ = 595.1912 and [M+Na; ^{37}Cl, $^{37}Cl]^+$ = 597.1901, found 593.1892, 595.2186 and 597.1978 in the expected 9:6:1 ratio. No spectroscopic data are available in literature.

(9*H*-Fluoren-9-yl)methyl (*S*)-(1-((2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **9**



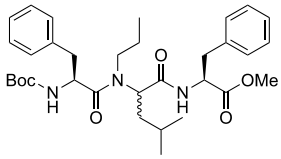
9

The title compound was prepared following general procedure **C** from 3-chloro-2-isocyanopyridine **3b** (208 mg, 1.5 mmol, 1.5 equiv), Fmoc-L-Phe-OH (387 mg, 1 mmol, 1 equiv), cyclopropylamine (0.083 ml, 1.2 mmol, 1.2 equiv) formaldehyde (0.089 ml, 1.2 mmol, 1.2 equiv, 37 wt. % in H_2O) in trifluoroethanol (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 4:1 to 1:1 over 15 CV), the desired compound as a colorless oil with 46% (271 mg, 0.46 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of rotamers)** δ 10.30 (s, 0.1H), 10.25 (s, 0.9H), 8.38 (dd, *J* =4.7, 1.5 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.89-7.83 (m, 3H), 7.65 (dd, *J* = 7.6, 2.7 Hz, 2H), 7.44-7.18 (m, 10H), 5.19-5.12 (m, 0.9H), 5.00-4.94 (m, 0.1H), 4.44 (d, *J*

= 16.7 Hz, 1H), 4.17-4.10 (m, 3H), 4.02 (d, *J* = 16.7 Hz, 0.9H), 3.96 (d, *J* = 16.7 Hz, 0.1H), 3.10 (dd, *J* = 14.1, 3.3 Hz, 0.9 H), 3.04-2.92 (m, 1.1H), 2.80 (dd, *J* = 14.1, 10.6 Hz, 0.9H), 2.66-2.59 (m, 0.1H), 1.09-0.95 (m, 1.8H), 0.86-0.77 (m, 2H), 0.73-0.63 (m, 0.2H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 175.0 (C), 167.7 (C), 156.0 (C), 147.8 (C), 146.8 (CH), 143.75 (C), 143.72 (C), 140.64 (C), 140.63 (C), 138.8 (CH), 138.2 (C), 129.2 (CH), 128.2 (CH), 127.6 (CH), 127.0 (CH), 126.4 (CH), 126.0 (C), 125.34 (CH), 125.30 (CH), 122.9 (CH), 120.1 (CH), 65.7 (CH_2), 53.6 (CH), 50.2 (CH_2), 46.5 (CH), 36.5 (CH_2), 30.3 (CH), 10.0 (CH_2), 8.0 (CH_2) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C)** δ 9.86 (s, 1H), 8.37 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.88-7.78 (m, 3H), 7.66-7.55 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33-7.15 (m, 8H), 5.31-5.06 (m, 1H), 4.40-4.29 (m, 1H), 4.26-4.03 (m, 4H), 3.10-3.01 (m, 1H), 2.93-2.75 (m, 2H), 1.10-0.62 (m, 4H) ppm. **HPLC** $t_{R-HPLC-2}$ = 2.68 min. **HRMS (ESI+)** m/z calcd. for $C_{34}H_{31}ClN_4O_4$ [M+H; ^{35}Cl]$^+$ = 595.2112, [M+H; ^{37}Cl]$^+$ = 597.2101, found 595.2127 and 597.2191 in the expected 3:1 ratio. No spectroscopic data are available in literature.

Cleavage of the amide in the Ugi product 4-9

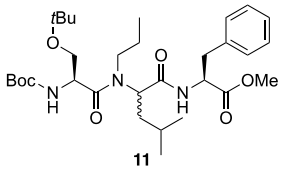
Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-phenylalaninate **10**



10

The title compound was prepared using general procedure **D** from Ugi product **4b** (133 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 15 CV), the desired compound as a white powder in 85% (124 mg, 0.213 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 8.51 (d, *J* = 7.7 Hz, 0.2H), 8.45-8.34 (m, 0.2H), 8.30- 8.19 (m, 0.8H), 8.12 (d, *J* = 7.9 Hz, 0.6H), 7.79-7.71 (m, 0.2H), 7.41-7.35 (m, 0.2H), 7.31-7.10 (m, 21.4H), 6.83-6.75 (m, 0.2H), 6.67 (d, *J* = 7.3 Hz, 0.2H), 6.54 (d, *J* = 8.0 Hz, 0.2H), 5.03-4.83 (m, 1.5H), 4.67-4.41 (m, 3.5H), 4.38-4.30 (m, 0.5H), 4.29-4.19 (m, 0.5H), 3.64-3.52 (m, 6H), 3.26-3.15 (m, 1H), 3.14- 3.01 (m, 3H), 2.96-2.76 (m, 7H), 2.76-2.66 (m, 1H), 1.61-1.46 (m, 1H), 1.43-1.35 (m, 6H), 1.32 (s, 6H), 1.30-1.24 (m, 9H), 1.21-1.12 (m, 4H), 1.04-0.95 (m, 1H), 0.87-0.79 (m, 5H), 0.79-0.68 (m, 11H), 0.67-0.60 (m, 2H), 0.58-0.53 (m, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 172.4 (C), 172.3 (C), 171.8 (C), 171.6 (C), 171.5 (C), 170.1 (C), 155.4 (C), 155.2 (C), 138.1 (C), 137.9 (C), 137.4 (C), 137.1 (C), 136.9 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 126.4 (CH), 126.3 (CH), 78.2 (C), 78.0 (C), 54.4 (CH), 54.3 (CH), 53.6 (CH), 53.4 (CH), 53.3 (CH), 53.1 (CH), 52.5 (CH), 52.3 (CH), 52.5 (CH), 52.3 (CH), 51.8 (CH_3), 51.7 (CH_3), 51.4 (CH_3), 46.2 (CH_2), 45.7 (CH_2), 45.3 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 37.3 (CH_2), 37.1 (CH_2), 36.5 (CH_2), 36.1 (CH_2), 35.9 (CH_2), 28.1 (CH_3), 28.0 (CH_3), 27.7 (CH_3), 24.2 (CH), 24.2 (CH), 23.9 (CH), 23. 8 (CH), 23.0 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.7 (CH_3), 21.6 (CH_3), 11.5 (CH_3), 11.4 (CH_3), 11.2 (CH_3), 11.2 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 8.07-7.55 (m, 2H), 7.34-7.03 (m, 20H), 6.67 (br s, 2H), 4.94-4.71 (m, 1H), 4.67-4.37 (m, 5H), 3.61 (s, 3H), 3.60 (s, 3H), 3.26-3.16 (m, 1H), 3.15-3.10 (m, 3H overlap with HDO), 3.02-2.78 (m, 8H), 1.66-1.49 (m, 1H), 1.44-1.20 (m, 25H), 1.20-1.11 (m, 2H), 0.88-0.62 (m, 18H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 172.0 (C), 172.0 (C), 171.1 (C), 171.0 (C), 170.0 (C), 169.8 (C), 154,7 (C), 154.5 (C), 137.5 (C), 137.1 (C), 136.8 (C), 136.7 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 126.0 (CH), 125.9 (CH), 78.0 (C), 77.9 (C), 55.2 (CH), 54.8 (CH), 53.2 (CH), 52.9 (CH), 51.3 (CH), 51.2 (CH), 51.3 (CH_3), 51.2 (CH_3), 45.7 (CH_2), 38.1 (CH_2), 37.6 (CH_2), 37.3 (CH_2), 36.4 (CH_2), 36.1 (CH_2), 27.7 (CH_3), 23.9 (CH), 23.7 (CH), 22.6 (CH_2), 22.4 (CH_2), 22.0 (CH_3), 21.7 (CH_3), 10.6 (CH_3) ppm. **HRMS (ESI+)** m/z calcd. for $C_{33}H_{47}N_3O_6Na$ [M+Na]$^+$: 604.3357 found 604.3349. No spectroscopic data are available in literature.

Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl)-*N*-propylleucyl-L-phenylalaninate **11**

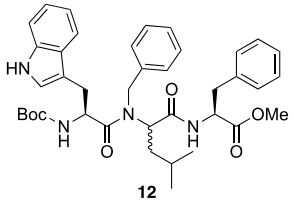


11

The title compound was prepared using general procedure **D** from Ugi product **5b** (132 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 15 CV), the desired compound as a white powder in 72% (104 mg, 0.181 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 8.345-8.22 (m, 0.5H), 8.16 (d, *J* = 7.4 Hz, 0.7H), 8.07 (d, *J* = 7.8 Hz, 0.7H), 7.29-7.17 (m, 10.5H), 7.13 (d, *J* = 7.7 Hz, 0.5H),7.00-6.95 (m, 0.5H), 6.92 (d, *J* = 6.8 Hz, 0.5H), 5.03-4.92 (m, 1H), 4.90-4.78 (m, 1H), 4.64-4.56 (m, 0.5H), 4.56-4.43 (m, 2H), 4.42-4.34 (m, 1H), 4.31-4.24 (m, 0.5H), 3.60-3.56 (m, 6H), 3.47-3.40 (m, 2H), 3.39-3.33 (m, 2H), 3.15-2.98 (m, 5H), 2.95 (m, 3H), 1.68-1.56 (m, 1H), 1.52-1.40 (m, 5H), 1.37 (s, 9.5H), 1.36 (s, 8.5H), 1.33-1.27 (m, 4H), 1.11 (s, 6H), 1.08 (s, 3H), 1.07 (s, 9H), 0.88-0.72 (m, 16H), 0.70-0.62 (m, 2H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 171.9 (C), 171.7 (C), 171.5 (C), 171.4 (C), 170.5 (C), 170.2 (C), 155.3 (C), 155.2 (C), 137.3 (C), 137.2 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.5 (CH), 126.4 (CH), 78.4 (C), 78.1 (C), 72.7 (C), 72.7 (C), 62.4 (CH_2), 62.1 (CH_2), 61.9 (CH_2), 57.6 (CH), 54.8 (CH), 54.2 (CH), 53.6 (CH), 53.5 (CH), 53.3 (CH), 53.1 (CH), 51.8 (CH_3), 51.8 (CH_3), 51.7 (CH_3), 45.8 (CH_2), 45.7 (CH_2), 38.5 (CH_2), 38.1 (CH_2), 37.6 (CH_2), 36.7 (CH_2), 36.5 (CH_2), 36.1 (CH_2), 28.1 (CH_3), 27.2 (CH_3), 27.1 (CH_3), 27.1 (CH_3), 26.9 (CH_3), 24.3 (CH), 24.2 (CH), 23.8 (CH), 23.6 (CH), 23.2 (CH_2), 22.9 (CH_2) 22.8 (CH_2), 22.7 (CH_3), 22.3 (CH_3), 22.0 (CH_3), 21.8 (CH_3), 11.5 (CH_3), 11.4 (CH_3), 11.2 (CH_3), 11.2 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-**

***d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 7.78 (br s, 1H), 7.29-7.23 (m, 4H), 7.22-7.15 (m, 6H), 6.40 (br s, 1H), 4.97-4.4.86 (m, 1H), 4.75-4.33 (m, 5H), 3.60 (s, 6H), 3.52-3.43 (m, 2H), 3.40 (dd, *J* = 8.3, 5.7 Hz, 2H), 3.32-3.24 (m, 1H), 3.24-3.14 (m, 2H), 3.13-3.07 (m, 3H overlap with HDO), 2.94 (dd, *J* = 14.1, 9.0 Hz, 2H), 1.65-1.45 (m, 6H), 1.39 (s, 18H), 1.38-1.28 (m, 4H), 1.13-1.09 (m, 18H), 0.91-0.73 (m, 18H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 171.5 (C), 171.5 (C), 171.0 (C), 170.9 (C), 169.8 (C), 154.5 (C), 136.7 (C), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.0 (CH), 78.2 (C), 72.4 (C), 62.3 (CH_2), 62.1 (CH_2), 56.1 (CH), 54.5 (CH), 53.2 (CH), 52.9 (CH), 52.9 (CH), 51.2 (CH_3), 50.7 (CH_3), 45.6 (CH_2), 45.5 (CH_2), 37.7 (CH_2), 37.3 (CH_2), 36.5 (CH_2), 36.3 (CH_2), 27.8 (CH_3) 26.8 (CH_3), 26.6 (CH_3), 23.9 (CH), 23.5 (CH), 22.4 (CH_2), 22.1 (CH_3), 21.7 (CH_3), 10.7 (CH_3) ppm. **HRMS (ESI+)** m/z calcd. for $C_{31}H_{51}N_3O_7Na$ [M+Na]$^+$: 600.3619 found 604.3621. No spectroscopic data are available in literature.

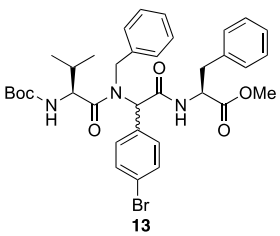
Methyl *N*-benzyl-*N*-((*tert*-butoxycarbonyl)-L-tryptophyl)leucyl-L-phenylalaninate **12**



12

The title compound was prepared using general procedure **D** from Ugi product **6b** (155 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 15 CV), the desired compound as a white powder in 77% (120 mg, 0.193 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 10.95-10.84 (m, 0.4H), 10.82 (br s, 1H), 10.72-10.62 (m, 0.6H), 8.86 (d, *J* = 8.5 Hz, 0.2H), 8.76-8.68 (m, 0.3H), 8.57 (d, *J* = 7.5 Hz, 0.1H), 8.44-8.37 (m, 0.4H), 8.25 (d, *J* = 7.9 Hz, 0.3H), 8.15 (d, *J* = 6.7 Hz, 0.1H), 8.09 (d, *J* = 7.9 Hz, 0.1H), 8.01 (d, *J* = 8.0 Hz, 0.1H), 7.98 (d, *J* = 8.0 Hz, 0.1H), 7.78-7.67 (m, 0.3H), 7.61-7.52 (m, 0.5H), 7.36-7.09 (m, 19.5H), 7.08-7.01 (m, 3H), 7.01-6.97 (m, 2H), 6.97-6.90 (m, 2.5H), 6.89-6.82 (m, 2.5), 6.76-6.66 (m, 0.9H), 6.58 (d, *J* = 7.8 Hz, 0.1H), 6.52 (d, *J* = 7.6 Hz, 0.3H), 6.44 (d, *J* = 7.9 Hz, 0.3H), 6.41-6.32 (m, 0.3H), 6.08 (d, *J* = 9.4 Hz, 0.1H), 5.43-5.15 (m, 0.7H), 5.12-4.98 (m, 0.7H), 4.95-4.84 (m, 1.1H), 4.84-4.57 (m, 2.7H), 4.56-4.26 (m, 3.1H), 4.26-4.15 (m, 1.1H), 4.15-4.06 (m, 0.5H), 4.05-3.98 (m, 0.1H), 3.65 (s, 0.7H), 3.63-3.58 (m, 2H), 3.57-3.51 (m, 2.2H), 3.51-3.46 (m, 0.5H), 3.45-3.40 (m, 0.6H), 3.23-2.98 (m, 4H), 2.97-2.79 (m, 3H), 2.73-2.54 (m, 1H), 1.45-1.40 (m, 2.6H), 1.38 (s, 1.4H), 1.35-1.23 (m, 14H), 1.18-1.00 (m, 2H), 0.88-0.78 (m, 6H), 0.77-0.63 (m, 6H), 0.53-0.51 (m, 1.6H), 0.48-0.45 (m, 0.8H), 0.42-0.40 (m, 0.8H), 0.37-0.34 (m, 0.8H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 174.2 (C), 173.3 (C), 173.0 (C), 171.7 (C), 171.6 (C), 170.2 (C), 169.9 (C), 155.4 (C), 154.9 (C), 147.0 (CH), 139.4 (C), 138.1 (C), 137.4 (C), 137.4 (C), 137.2 (C), 136.0 (C), 135.8 (C), 129.1 (CH), 128.8 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.4 (CH), 126.0 (CH), 125.8 (CH), 124.2 (CH), 124.0 (CH), 121.0 (CH), 120.8 (CH), 120.5 (CH), 118.6 (CH), 118.3 (CH), 118.0 (CH), 111.4 (CH), 111.2 (CH), 111.0 (CH), 110.3 (C), 109.7 (C), 109.6 (C), 78.1 (C), 78.1 (C), 58.1 (CH), 55.2 (CH), 54.2 (CH), 53.8 (CH), 53.3 (CH), 53.2 (CH), 52.9 (CH), 51.9 (CH_3), 51.8 (CH_3), 51.7 (CH_3), 51.6 (CH_3), 51.3 (CH), 51.0 (CH), 47.4 (CH_2), 46.7 (CH_2), 46.3 (CH_2), 38.5 (CH_2), 38.3 (CH_2), 37.8 (CH_2), 37.1 (CH_2), 36.8 (CH_2), 36.7 (CH_2), 36.3 (CH_2), 36.1 (CH_2), 28.2 (CH_3), 28.0 (CH_3), 27.3 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 24.0 (CH_3), 23.7 (CH_3), 23.6 (CH_3), 22.9 (CH_3), 22.7 (CH_3), 22.4 (CH_3), 22.2 (CH), 22.1 (CH_3), 22.0 (CH_3), 22.0 (CH), 20.9 (CH) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 10.74-10.47 (m, 2H), 8.43-8.10 (m, 1H), 8.07-7.77 (m, 2H), 7.65-7.46 (m, 1H), 7.36-6.75 (m, 30H), 5.22-4.90 (m, 1H), 4.88-4.40 (m, 7H), 4.38-4.04 (m, 2H), 3.69-3.44 (m, 6H), 3.06-2.83 (m, 8H overlap with HDO), 1.49-1.17 (m, 18H), 1.12-1.02 (m, 4H), 0.89-0.74 (m, 4H), 0.0.73-0.67 (m, 4H), 0.65-0.37 (m, 6H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 173.4 (C), 173.0 (C), 171.1 (C), 171.0 (C), 169.7 (C), 169.5 (C), 154.7 (C), 154.3 (C), 146.3 (CH), 139.1 (C), 138.2 (CH), 138.1 (CH), 137.6 (C), 137.5 (C), 136.8 (C), 136.7 (C), 135.9 (C), 135.8 (C), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 126.1 (CH), 129.0 (CH), 125.8 (CH), 123.5 (CH), 123.5 (CH), 120.4 (CH), 120.3 (CH), 117.8 (CH), 117.7 (CH), 110.8 (CH), 110.7 (CH), 109.4 (C), 109.3 (C), 78.0 (C), 77.9 (C), 55.6 (CH), 55.1 (CH), 53.4 (CH), 53.2 (CH), 52.8 (CH), 52.7 (CH), 51.9 (CH), 51.7 (CH), 51.3 (CH_3), 51.1 (CH_3), 47.3 (CH_2), 46.9 (CH_2), 38.0 (CH_2), 37.5 (CH_2), 36.6 (CH_2), 36.2 (CH_2), 27.6 (CH_3), 27.2 (CH_2), 27.0 (CH_2), 23.8 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.8 (CH), 21.6 (CH) ppm. **HRMS (ESI+)** m/z calcd. for $C_{39}H_{48}N_4O_6Na$ [M+Na]$^+$: 691.3466 found 691.3470. No spectroscopic data are available in literature.

Methyl (2-((*S*)-*N*-benzyl-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-(4-bromophenyl)acetyl)-L-phenylalaninate **13**

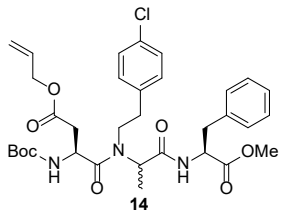


13

The title compound was prepared using general procedure **D** from Ugi product **7b** (132 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 14 CV), the desired compound as a white powder in 72% (104 mg, 0.179 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 9.12-8.91 (m, 1.4H), 8.70-8.52 (m, 0.2H), 8.47-8.34 (m, 0.1H), 8.28-8.06 (m, 0.2H), 7.45-7.35 (m, 2H), 7.34-7.21 (m, 8H), 7.20-7.01 (m, 11H), 6.98-6.86 (m, 7H), 6.79 (br s, 0.4H), 6.72-6.65 (m, 1.6H), 6.39 (br s, 0.5H), 6.33 (br s, 0.2H), 6.25 (br s, 0.6H), 6.20-6.13 (m, 0.4H), 5.92 (br s, 0.1H), 4.96-4.69 (m, 3H), 4.67-4.57 (m, 0.5H), 4.59-4.46 (m, 1H), 4.46-4.36 (m, 1H), 4.35-4.25 (m, 0.7H), 4.24-4.18 (m, 0.2H), 4.17-4.10 (m, 0.2H), 4.06-3.91 (m, 1.4H), 3.67 (s, 0.7H), 3.65 (s, 2H), 3.62 (s, 0.7H), 3.58 (s, 1.9H), 3.54 (s, 0.3H), 3.52 (s, 0.4H), 3.13-2.77 (m, 4H), 2.03-1.78 (m, 2H), 1.46 (s, 5H), 1.43 (s, 3H), 1.40-1.33 (m, 9H), 1.15-1.04 (m, 1H), 0.95-0.87 (m, 2H), 0.86-0.80 (m, 1H), 0.78-0.65 (m, 6H), 0.61-0.55 (m, 0.8H), 0.52-0.45 (m, 2.2H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ

173.9 (C), 173.6 (C), 171.5 (C), 171.5 (C), 169.2 (C), 156.1 (C), 155.5 (C), 138.9 (C), 138.5 (C), 137.1 (C), 137.1 (C), 136.8 (C), 135.2 (C), 134.3 (C), 131.6 (CH), 131.4 (CH), 131.0 (CH), 130.9 (CH), 130.7 (CH), 130.6 (CH), 130.5 (CH), 130.4 (CH), 129.9 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 125.4 (CH), 121.0 (C), 120.9 (C), 78.3 (C), 78.2 (C), 61.4 (CH), 59.2 (CH), 56.3 (CH), 56.0 (CH), 55.8 (CH), 54.1 (CH), 52.9 (CH_3), 52.0 (CH), 51.8 (CH), 48.1 (CH_2), 48.0 (CH_2), 47.7 (CH_2), 36.9 (CH_2), 36.7 (CH_2), 36.2 (CH_2), 30.2 (CH), 30.1 (CH), 29.4 (CH), 28.2 (CH_3), 28.1 (CH_3), 27.6 (CH_2), 26.9 (CH_2), 19.4 (CH), 19.2 (CH_3), 19.1 (CH_3), 18.8 (CH_3), 18.7 (CH_3), 18.6 (CH_3), 17.9 (CH_3), 17.9 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 8.73 (br s, 1H), 8.53 (br s, 1H), 7.45-7.33 (m, 2H), 7.31-7.17 (m, 10H), 7.17-7.06 (m, 8H), 7.06 (m, 8H), 6.46-6.20 (m, 1H), 6.19-609 (m, 1H), 4.87-4.71 (m, 2H), 4.68-4.55 (m, 2H), 4.52 (dd, *J* = 14.3, 7.5 Hz, 1H), 4.48-4.32 (m, 1H), 4.23-4.02 (m, 2H), 3.66-3.56 (m, 6H), 3.12-3.00 (m, 2H overlap with HDO), 3.00-2.84 (m, 2H), 2.09-1.86 (m, 2H), 1.49-1.31 (m, 18H), 0.95-0.57 (m, 12H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 172.9 (C), 172.9 (C), 170.9 (C), 168.6 (C), 154.9(C), 138.0 (C), 136.7 (C), 136.5 (C), 134.6 (C), 131.0 (CH), 130.7 (CH), 130.4 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.2 (CH), 126.0 (CH), 120.7 (C), 78.0 (C), 61.3 (CH), 61.2 (CH), 55.9 (CH), 55.5 (CH), 53.4 (CH), 53.0 (CH), 51.4 (CH), 51.2 (CH), 48.1 (CH_2), 47.4 (CH_2), 36.4 (CH_2), 36.2 (CH_2), 30.1 (CH), 29.3 (CH), 27.8 (CH_3), 27.7 (CH_3), 26.8 (CH_2), 26.7 (CH_2), 18.9 (CH_3), 18.7 (CH), 18.8 (CH_3), 18.5 (CH_3), 17.8 (CH_3), 17.1 (CH_3), 17.0 (CH_3) ppm. **HRMS (ESI+)** m/z calcd. for $C_{35}H_{42}BrN_3O_6Na$ [M+Na; $^{79}Br]^+$ = 702.2149, [M+Na; $^{81}Br]^+$ = 704.2136, found 702.2141 and 704.2127 in the expected ratio 1:1. No spectroscopic data are available in literature.

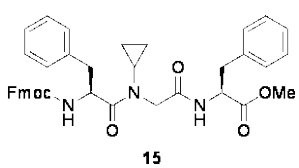
Methyl (6*S*,12*S*)-6-(2-(allyloxy)-2-oxoethyl)-12-benzyl-8-(4-chlorophenethyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **14**



14

The title compound was prepared using general procedure **D** from Ugi product **8** (148 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 7:3 to 1:3 over 15 CV), the desired compound as a white powder in 61% (98 mg, 0.152 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 8.35-8.12 (m, 1H), 8.06 (dd, *J* = 18.5, 7.9 Hz, 1H), 7.46-7.31 (m, 5H), 7.29-6.95 (m, 15H), 5.96-5.84 (m, 2H), 5.36-5.27 (m, 2H), 5.24-5.17 (m, 2H), 4.91-4.47 (m, 10H), 3.62-3.58 (m, 2.4H), 3.56 (s, 0.6H), 3.54 (s, 3H), 3.23-3.01 (m, 3H), 2.99-2.54 (m, 11H), 1.40-1.34 (m, 18H), 1.25-1.06 (m, 6H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 171.8 (C), 171.7 (C), 171.6 (C), 170.9 (C), 170.7 (C), 170.6 (C), 170.6 (C), 170.5 (C), 170.4 (C), 170.2 (C), 170.1 (C), 170.1 (C), 170.0 (C), 155.3 (C), 155.2 (C), 154.7 (C), 138.6 (C), 137.5 (C), 137.3 (C), 137.2 (C), 137.1 (C), 132.6 (CH), 132.5 (CH), 131.1 (C), 130.7 (C), 130.6 (CH), 130.5 (CH), 130.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 126.5 (CH), 126.5 (CH), 126.4 (CH), 117.8 (CH_2), 117.8 (CH_2), 117.7 (CH_2) 117.6 (CH_2), 117.6 (CH_2), 79.0 (C), 78.8 (C), 78.6 (C), 78.6 (C), 78.5 (C), 64.8 (CH_2), 64.7 (CH_2), 64.6 (CH_2), 64.6 (CH_2), 54.9 (CH), 53.6 (CH), 53.4 (CH), 53.1 (CH), 52.8 (CH), 52.0 (CH_3), 51.9 (CH_3), 51.9 (CH_3), 51.8 (CH_3), 47.8 (CH), 47.7 (CH), 47.6 (CH), 47.3 (CH), 47.1 (CH), 46.5 (CH_2), 45.9 (CH_2), 45.6 (CH_2), 36.7 (CH_2), 36.3 (CH_2), 35.4 (CH_2), 33.0 (CH_2), 28.1 (CH_3), 15.8 (CH_3), 15.3 (CH_3), 15.2 (CH_3), 15.0 (CH_3) ppm. NMR-data was acquired at elevated temperature so that most peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 8.01-7.64 (m, 2H), 7.36-7.30 (m, 4H), 7.28-7.14 (m, 14H), 7.10-6.98 (m, 2H), 5.96-5.85 (m, 2H), 5.35-5.32 (m, 1H), 5.31-5.28 (m, 1H), 5.23-5.18 (m, 2H), 4.88-4.74 (m, 3H), 4.69 (q, *J* = 7.0 Hz, 1H), 4.60-4.53 (m, 6H), 3.61 (s, 0.9H), 3.60 (s, 2.1H), 3.57 (s, 3H), 3.46-3.27 (m, 2H), 3.01-2.57 (m, 14H), 1.39 (s, 18H), 1.29-1.17 (m, 6H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers)** δ 171.0 (C), 170.3 (C), 170.2 (C), 170.1 (C), 154.9 (C), 136.7 (C), 132.2 (CH), 132.1 (CH), 130.8 (C), 130.0 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 126.1 (CH), 126.1 (CH), 126.0 (CH), 126.0 (CH), 117.3 (CH_2), 117.3 (CH_2), 78.4 (C), 64.3 (CH_2), 64.3 (CH_2), 64.2 (CH_2), 53.3 (CH), 53.1 (CH), 51.3 (CH), 51.3 (CH), 47.6 (CH), 46.2 (CH_2), 36.5 (CH_2), 36.3 (CH_2), 34.9 (CH_2), 27.8 (CH_3), 14.6 (CH_3). **HPLC** $t_{R\ –\ HPLC\text{-}2}$ = 3.01 min. **HRMS (ESI+)** m/z calcd. for $C_{33}H_{42}ClN_3O_8Na$ [M+Na; $^{35}Cl]^+$ = 666.2558 and [M+Na; $^{37}Cl]^+$ = 667.2590, found 666.2590 and 668.2719 in the expected 3:1 ratio. No spectroscopic data are available in literature.

Methyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*N*-cyclopropylglycyl-L-phenylalaninate **15**

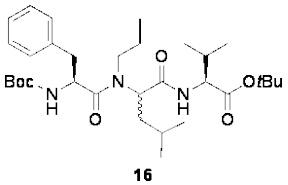


15

The title compound was prepared using general procedure **D** from Ugi product **9** (149 mg, 0.25 mmol, 1 equiv), H-L-Phe-OMe hydrochloric acid salt (162 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 7:3 to 1:4 over 20 CV), the desired compound as a white powder in 73% (118 mg, 0.183 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of rotamers)** δ 8.37 (d, *J* = 7.6 Hz, 0.1H), 8.25 (d, *J* = 7.6 Hz, 0.9H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 7.6, 3.9 Hz, 2H), 7.43-7.37 (m, 2H), 7.35-7.18 (m, 12H), 5.13-5.05 (m, 0.9H), 4.96-4.90 (m, 0.1H), 4.52-4.45 (m, 1H), 4.17-4.08 (m, 3H), 4.04 (d, *J* = 16.4 Hz, 1H), 3.81 (d, *J* = 16.4 Hz, 1H), 3.59 (s, 3H), 3.06-2.99 (m, 2H), 2.91 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.82-2.73 (m, 2H), 0.97-0.84 (m, 2H), 0.75-0.62 (m, 2H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 174.7 (C), 171.8 (C), 168.4 (C), 156.0 (C), 143.7 (C), 140.65 (C), 140.63 (C), 138.1 (C), 137.0 (C), 129.2 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.0 (CH), 126.6 (CH), 126.4 (CH), 125.34 (CH), 125.28 (CH), 120.1 (CH), 65.7 (CH_2), 53.6 (CH), 53.5 (CH), 51.9 (CH_3), 49.4 (CH_2), 46.5 (CH), 36.8 (CH_2), 36.5 (CH_2), 30.1 (CH), 9.8

(CH_2), 7.7 (CH_2) ppm. NMR-data was acquired at elevated temperature so that most peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C)** δ 7.91 (br s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.61 (br s, 2H), 7.48-7.36 (m, 3H), 7.32-7.24 (m, 8H), 7.23-7.17 (m, 4H), 5.13 (br s, 1H), 4.58-4.51 (m, 1H), 4.26-4.12 (m, 3H), 4.03-3.82 (m, 2H), 3.60 (s, 3H), 3.09-2.99 (m, 2H), 2.94 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.88-2.63 (m, 2H), 0.99-0.52 (m, 4H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 2.86 min. **HRMS (ESI+)** m/z calcd. for $C_{39}H_{39}N_3O_6Na$ $[M+Na]^+$ = 668.2737, found 668.2720. No spectroscopic data are available in literature.

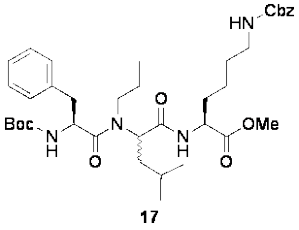
tert-Butyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-valinate **16**



16

The title compound was prepared using general procedure **D** from Ugi product **4b** (148 mg, 0.25 mmol, 1 equiv), H-L-Val-O*t*Bu hydrochloric acid salt (157 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 7:3 to 1:3 over 15 CV), the desired compound as a colorless oil in 80% (115 mg, 0.2 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 8.31 (d, *J* = 8.2 Hz, 0.1H), 8.14 (d, *J* = 8.2 Hz, 0.1H), 8.02 (d, *J* = 9.2 Hz, 0.1H), 7.87-7.80 (m, 1.7H), 7.56-7.51 (m, 0.2H), 7.52 (d, *J* = Hz, 0.3H), 7.32-7.20 (m, 10.7H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.06-4.84 (m, 1.5H), 4.82-4.73 (m, 0.2H), 4.67-4.55 (m, 0.7H), 4.54-4.45 (m, 0.8H), 4.44-4.33 (m, 0.8H), 4.13-4.00 (m, 1H), 3.97-3.89 (m, 1H), 3.35-3.27 (m, 4H overlap with HDO peak), 3.22-2.95 (m, 2H), 2.99-2.78 (m, 4H), 2.02-1.94 (m, 2H), 1.65-1.53 (m, 2H), 1.53-1.42 (m, 2H), 1.39 (s, 7H), 1.38 (s, 8H), 1.37 (s, 8H), 1.31 (s, 7H), 1.30 (s, 6H), 1.24-1.15 (m, 4H), 0.90-0.81 (m, 22H), 0.81-0.70 (m, 8H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 172.7 (C), 172.5 (C), 171.3 (C), 170.7 (C), 170.3 (C), 170.2 (C), 170.1 (C), 169.9 (C), 169.0 (C), 155.8 (C), 155.3 (C), 155.1 (C), 137.8 (C), 137.4 (C), 129.7 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.2 128.1 (CH), 126.4 (CH), 126.3 (CH), 80.6 (C), 80.5 (C), 78.1 (C), 78.1 (C), 58.7 (CH), 58.4 (CH), 58.1 (CH), 55.1 (CH), 55.0 (CH), 52.5 (CH), 52.4 (CH), 45.9 (CH_2), 38.3 (CH_2), 37.9 (CH_2), 37.7 (CH_2), 37.4 (CH_2), 29.8 (CH), 29.6 (CH), 29.5 (CH), 28.1 (CH_3), 28.1 (CH_3), 27.6 (CH_3), 27.6 (CH_3), 27.5 (CH_3), 24.2 (CH), 24.1 (CH), 23.3 (CH_2), 23.0 (CH_3), 22.9 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 18.9 (CH_3), 18.8 (CH_3), 18.6 (CH_3), 18.3 (CH_3), 18.2 (CH_3), 11.5 (CH_3), 11.2 (CH_3), 11.2 (CH_3) ppm. NMR-data was acquired at elevated temperature so that most peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers in a 1:1 ratio)** δ 7.47 (br s, 2H), 7.30-7.16 (m, 10H), 6.62 (br s, 2H), 4.89-4.80 (m, 1H), 4.78-4.66 (m, 1H), 4.63-4.50 (m, 2H), 4.13-4.00 (m, 1H), 4.01 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.47-3.35 (m, 1H), 3.34-3.26 (m, 1H), 3.23-3.01 (m, 5H overlap with HDO peak), 2.98-2.80 (m, 5H), 2.05-1.95 (m, 2H), 1.80-1.65 (m, 2H),1.61-1.43 (m, 4H), 1.42 (s, 9H), 1.40 (s, 9H), 1.32 (s, 18H), 0.91-0.84 (m, 24H), 0.80-0.75 (m, 6H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}1}$ = 4.87 and 4.95 min. HRMS (ESI+) m/z calcd. for $C_{32}H_{53}N_3O_6$ $[M+Na]^+$ =, 589.3832 found 598.3814. No spectroscopic data are available in literature.

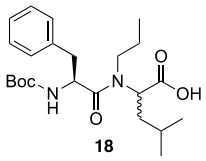
Methyl N^6-((benzyloxy)carbonyl)-N^2-(*N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl)-L-lysinate **17**



17

The title compound was prepared using general procedure **D** from Ugi product **4b** (148 mg, 0.25 mmol, 1 equiv), H-L-Lys(Cbz)-OMe hydrochloric acid salt (248 mg, 0.75 mmol, 3 equiv), NaOAc (62 mg, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (CH_2Cl_2:EtOAc, 9:1 to 1:1 over 30 CV), the desired compound as a colorless oil in 55% (95 mg, 0.138 mmol) yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, mixture of diastereomers in a 1:1 ratio and rotamers)** δ 8.56-8.44 (m, 0.1H), 8.35-8.27 (m, 0.2H), 8.26-8.15 (m, 0.6H), 8.15-8.08 (m, 0.2H), 7.93 (d, *J* = 7.4 Hz, 0.6H), 7.75 (d, *J* = 7.5 Hz, 0.1H), 7.69 (d, *J* = 6.7 Hz, 0.1H), 7.57 (d, *J* = 6.8 Hz, 0.1H), 7.38-7.30 (m, 7H), 7.29-7.16 (m, 13H), 5.08-4.94 (m, 5.5H), 4.78-4.67 (m, 0.1H), 4.66-4.52 (m, 0.8H), 4.51-4.42 (m, 0.8H), 4.41-4.32 (m, 0.8H), 4.27-4.16 (m, 1.4H), 4.15-4.09 (m, 0.6H), 3.67 (br s, 4H), 3.61 (s, 1.6H), 3.59 (s, 1.4H), 3.58 (s, 2H), 3.54 (s, 0.6H), 3.51 (s, 0.4H), 3.50-3.41 (m, 1H), 3.37-3.27 (m, 1H), 3.25-3.03 (m, 1.5H), 3.01-2.92 (m, 4.5H), 2.89-2.77 (m, 4H), 1.72-1.51 (m, 7H), 1.46-1.36 (m, 7H), 1.35 (s, 3H), 1.34-1.32 (m, 2H), 1.31 (s, 6H), 1.30 (s, 7H), 1.27 (s, 2H), 1.26-1.17 (m, 6H), 0.93-0.85 (m, 4H), 0.85-0.80 (m, 7H), 0.79-0.69 (m, 7H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, mixture of diastereomers and rotamers)** δ 172.7 (C), 172.6 (C), 172.4 (C), 172.3 (C), 172.3 (C), 172.2 (C), 172.1 (C), 172.0 (C), 156.0 (C), 156.0 (C), 155.3 (C), 155.3 (C), 137.9 (C), 137.4 (C), 137.2 (C), 137.0 (C), 129.6 (CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 78.2 (C), 78.0 (C), 65.1 (CH_2), 54.5 (CH), 54.3 (CH), 52.1 (CH), 52.1 (CH), 51.9 (CH), 51.7 (CH_3), 51.6 (CH_3), 45.9 (CH_2), 45.4 (CH_2), 38.0 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.1 (CH_3), 28.1 (CH_3), 24.0 (CH), 24.0 (CH), 22.8 (CH_2), 22.8 (CH_3), 22.7 (CH_2), 22.6 (CH_3), 22.5 (CH_2), 11.2 (CH_3), 11.2 (CH_3) ppm. NMR-data was acquired at elevated temperature so that most peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 7.82 (br s, 1H), 7.66 (br s, 1H), 7.38-7.15 (m, 20H), 6.90 (br s, 2H), 6.72 (br s, 2H), 5.05-5.00 (m, 5H), 4.94-4.81 (m, 2H), 4.67-4.49 (m, 3H), 4.28-4.17 (m, 2H), 3.63 (s, 3H), 3.60 (s, 3H), 3.22-3.10 (m, 2H), 3.02-2.97 (m, 6H), 2.96-2.89 (m, 2H), 2.87-2.82 (m, 2H), 1.77-1.61 (m, 10H), 1.48-1.39 (m, 10H), 1.34-1.31 (m, 18H), 0.90-0.83 (m, 10H), 0.81-0.75 (m, 8H) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}1}$ = 4.53 min. **HRMS (ESI+)** m/z calcd. for $C_{38}H_{55}N_4O_8Na$ $[M+Na]^+$ = 719.3996, found 719.3928. No spectroscopic data are available in literature.

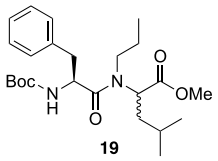
N-((*tert*-Butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucine **18**



18

The title compound was prepared using general procedure **D** from Ugi product **4b** (133 mg, 0.25 mmol, 1 equiv), H_2O (13.5 µl, 0.75 mmol, 3 equiv), and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 14 CV), the desired compound as a white powder in 94% (99 mg, 0.24 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 9.17 (br s, 2H), 7.30-7.17 (m, 10H), 5.88-5.80 (m, 0.2H), 5.77-5.69 (m, 0.2H), 5.53 (d, *J* = 8.4 Hz, 0.8H), 5.44 (d, *J* = 8.4 Hz, 0.8H), 4.83-4.71 (m, 1.6H), 4.68-4.53 (m, 0.6H), 4.46-4.31 (m, 1.8H), 3.41-3.21 (m, 1H), 3.24-3.13 (m, 1H), 3.10-2.84 (m, 6H), 1.97-1.86 (m, 2H), 1.70-1.41 (m, 8H), 1.40-1.23 (m, 18H), 0.94-0.79 (m, 18H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 175.1 (C), 174.7 (C), 174.1 (C), 173.4 (C), 172.6 (C), 172.3 (C), 156.4 (C), 155.5 (C), 155.3 (C), 137.0 (C), 136.4 (C), 136.1 (C), 129.8 (CH), 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 81.3 (C), 81.1 (C), 80.2 (C), 80.0 (C), 59.0 (CH), 58.8 (CH), 58.6 (CH), 58.2 (CH), 57.7 (CH), 54.0 (CH), 52.4 (CH), 52.2 (CH), 51.9 (CH), 51.7 (CH), 50.4 (CH_2), 49.9 (CH_2), 49.1 (CH_2), 46.7 (CH_2), 40.5 (CH_2), 40.3 (CH_2), 39.8 (CH_2), 39.6 (CH_2), 39.1 (CH_2), 38.6 (CH_2), 38.0 (CH_2), 37.8 (CH_2), 28.4 (CH_3), 24.9 (CH), 24.6 (CH), 23.0 (CH_3), 22.9 (CH_3), 22.8 (CH_2), 22.3 (CH_3), 22.1 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 11.7 (CH_3), 11.6 (CH_3), 11.3 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 7.30-7.16 (m, 10H), 6.84-6.39 (m, 2H), 4.68-4.42 (m, 4H), 3.50-3.35 (m, 1H), 3.27-3.13 (m, 2H), 3.10-3.00 (m, 1H), 2.98-2.88 (m, 2H), 2.85-2.75 (m, 2H), 1.81-1.71 (m, 2H), 1.64-1.39 (m, 8H), 1.31 (s, 18H), 0.91-0.80 (m, 18H) ppm **HRMS (ESI+)** m/z calcd. for $C_{23}H_{36}N_2O_5Na$ $[M+Na]^+$ = 443.2516, found 443.2522. No spectroscopic data are available in literature.

Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucinate **19**

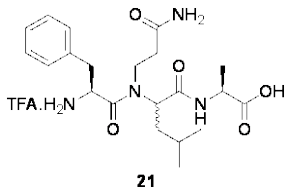


19

The title compound was prepared using general procedure **D** from Ugi product **4b** (133 mg, 0.25 mmol, 1 equiv), MeOH (30.4 µl, 0.75 mmol, 3 equiv), and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether:EtOAc, 100:0 to 50:50 over 14 CV), the desired compound as a white powder in 81% (88 mg, mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in 1:1 ratio and rotamers)** δ 7.29-7.17 (m, 10H), 5.27-5.19 (m, 1.8H), 5.15-5.05 (m, 0.2H), 4.90-4.82 (m, 0.2H), 4.81-4.71 (m, 1.8H), 4.70-4.64 (m, 0.9H), 4.63-4.58 (m, 0.9H), 4.57-4.50 (m, 0.2H), 3.67 (s, 5.4H), 3.63 (s, 0.6H), 3.31-3.22 (m, 0.9H), 3.17-2.95 (m, 4.1H), 2.94-2.79 (m, 3H), 1.88-1.77 (m, 2H), 1.64-1.42 (m, 6H), 1.40-1.33 (m, 18H), 1.29-1.21 (m, 2H), 0.95-0.80 (m, 18H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)** δ 172.8 (C), 172.5 (C), 172.3 (C), 172.1 (C), 171.9 (C), 171.6 (C), 171.4 (C), 155.2 (C), 155.1 (C), 155.0 (C), 154.9 (C), 137.0 (C), 136.8 (C), 136.6 (C), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 80.4 (C), 80.3 (C), 79.8 (C), 79.7 (C), 58.4 (CH), 58.0 (CH), 56.8 (CH), 56.3 (CH), 53.8 (CH), 52.5 (CH), 52.2 (CH), 52.1 (CH), 52.1 (CH), 51.8 (CH), 51.6 (CH), 49.0 (CH_2), 48.3 (CH_2), 46.6 (CH_2), 46.2 (CH_2), 41.0 (CH_2), 40.1 (CH_2), 40.0 (CH_2), 39.7 (CH_2), 39.2 (CH_2), 38.7 (CH_2), 38.2 (CH_2), 38.0 (CH_2), 28.4 (CH_3), 24.8 (CH), 24.6 (CH), 23.2 (CH_3), 23.1 (CH_3), 23.0 (CH_3), 22.8 (CH_3), 22.7 (CH_2), 22.6 (CH_3), 22.4 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.8 (CH_3), 21.4 (CH_3), 11.7 (CH_3), 11.4 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H NMR (500 MHz, DMSO-*d_6*, 80 °C, mixture of diastereomer in 1:1 ratio)** δ 7.32-7.16 (m, 10H), 6.90-6.45 (m, 2H), 4.70-4.37 (m, 4H), 3.59 (s, 6H), 3.53-3.42 (m, 1H), 3.28-3.15 (m, 2H), 3.10-3.00 (m, 1H), 2.98-2.88 (m, 2H), 2.86-2.74 (m, 2H), 1.85-1.72 (m, 2H), 1.64-1.40 (m, 8H), 1.32 (s, 18H), 0.90-0.79 (m, 18H) ppm. **HRMS (ESI+)** m/z calcd. for $C_{24}H_{39}N_2O_5$ $[M+H]^+$ = 435.2853, found 435.2858. No spectroscopic data are available in literature.

On-resin Ugi reaction and transamidation

N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ^4-azaneyl)propanoyl)leucyl-L-alanine **21**



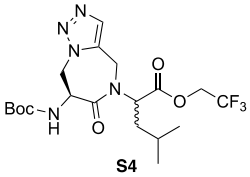
21

The title compound was formed on solid support. First, the resin was preloaded with Fmoc-βAla-OH (93 mg, 0.3 mmol, 3 equiv) following general procedure **F** onto a Rink amide resin (109 mg, 0.1 mmol, 1 equiv, 0.92 mmol/g) using HBTU (113 mg, 0.3 mmol, 3 equiv) and DIPEA (0.087 ml, 0.5 mmol, 5 equiv) in DMF. Following Fmoc deprotection of the resin using solution of a 4-methylpiperidine (20%) in DMF, the Ugi reaction was performed with Boc-L-Phe-OH (106 mg, 0.4 mmol, 4 equiv), 3-chloro-2-isocyanopyridine **3b** (56 mg, 0.4 mmol, 4 equiv) and isovaleraldehyde (0.043 ml, 0.4 mmol, 4 equiv) in TFE/CH_2Cl_2 (1:1) in the SPPS reactor. The mixture was shaken for 48 hours at room temperature. The excess of reagents and solvent were removed by filtration and the resin was washed with DMF (3x) and CH_2Cl_2 (3x). The resin was dried with diethyl ether and transferred in a microwave vial. The transamidation was performed using general procedure **D** by addition of H-L-Ala-O*t*Bu.HCl (91 mg, 0.5 mmol, 5 equiv), NaOAc (41 mg, 0.5 mmol, 5 equiv) and $Zn(OAc)_2$ (4 mg, 0.02 mmol, 20 mol%) in THF (0.5 ml). The mixture was stirred genteelly for 48 h at 90°C. Subsequently, the mixture was transferred to the SPPS reactor with CH_2Cl_2 and the excess of reagents and solvent were removed by filtration and the resin was washed with DMF (3x) and CH_2Cl_2 (3x). Then a mixture of TFA/TIS/H_2O (95/2.5/2.5) was added and the SPOS reactor was shaken for 1 hour at room temperature to cleave the peptide from the resin. Subsequently the cleaved product was obtained *via* filtration and the TFA/TIS/H_2O mixture was removed *in vacuo*. The obtained yellow oil was purified *via* preparative HPLC (AcN + 0.1% TFA /H_2O + 0.1% TFA from 15:85 to 60:40 in 20 minutes) and the title compound was obtained with an overall yield of 22%

(11.5 mg, 0.022 mmol). During purification, the two diastereomers were separated with a yield of 12% (6 mg, 0.012 mmol) for number 1 (white powder) and 10% (5.3 mg, 0.01 mmol for number 2 (colourless oil). **^{1}H (500 MHz, DMSO-*d*$_6$, diastereomer 1, mixture of rotamers)** δ 8.62 (d, *J* = 7.2 Hz, 0.4H), 8.30 (d, *J* = 7.0 Hz, 0.6H), 8.25 (br s, 0.8H), 8.18 (br s, 1.2H), 7.44 (br s, 0.6H), 7.41-7.37 (m, 0.8H), 7.34-7.28 (m, 3.8H), 7.23 (d, *J* = 7.2 Hz, 0.8H), 6.95 (br s, 0.6H), 6.83 (br s, 0.4H), 4.92-4.85 (m, 0.4H), 4.80 (t, *J* = 7.7 Hz, 0.6H), 4.55-4.48 (m, 0.6H), 4.20 (q, *J* = 7.2 Hz, 1H),410 (dd, *J* = 10.7, 4.2 Hz, 0.4H), 3.67-3.60 (m, 0.8H), 3.56-3.48 (m, 1.2H), 340-3.27 (m, 2H), 3.06 (dd, *J* = 13.6, 7.6 Hz, 0.6H), 3.01-2.95 (m, 1.4H), 2.42-2.28 (m, 1H), 2.23-2.15 (m, 0.6H), 2.11-2.02(m, 0.4H), 1.84-1.78 (m, 0.4H), 1.78-1.71 (m, 0.6H), 1.49-1.40 (m, 1H), 1.32-1.28 (m, 3H), 0.92 (d, *J* = 6.3 Hz, 1.6H), 0.89 (d, *J* = 6.4 Hz, 1.6H), 0.83 (d, *J* = 6.3 Hz, 1.4H), 0.78 (d, *J* = 6.7 Hz, 1.4H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 1, mixture of rotamers)** δ 173.8 (C), 173.7 (C), 172.1 (C), 172.0 (C), 169.2 (C), 168.8 (C), 168.5 (C), 168.3 (C), 134.4 (C), 133.8 (C), 129.8 (CH), 129.6 (CH), 128.8 (CH), 128.6 (CH), 127.4 (CH), 127.3 (CH), 57.0 (CH), 55.6 (CH), 51.1 (CH), 49.7 (CH), 47.7 (CH), 47.6 (CH), 40.8 (CH_2), 38.3 (CH_2), 38.2 (CH_2), 37.2 (CH_2), 37.1 (CH_2), 35.6 (CH_2), 33.4 (CH_2), 24.3 (CH), 24.1 (CH), 23.3 (CH_3), 22.5 (CH_3), 21.6 (CH_3), 17.0 (CH_3), 16.8 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H (500 MHz, DMSO-*d*$_6$, 80 °C, diastereomer 1, mixture of rotamers)** δ 8.51-7.99 (m , 2H), 7.91 (br s, 1H), 7.42-7.05 (m, 5H), 6.71 (br s, 1H), 4.85-4.70 (m, 1H), 4.59-4.47 (m, 0.7H), 4.30-4.20 (m, 1H), 4.19-4.12 (m, 0.3H), 3.66-3.49 (m, 2H), 3.46-3.36 (m, 2H, overlap with HDO), 3.15-2.96 (m, 2H overlap with HDO), 2.42-2.32 (m, 1H), 2.30-2.12 (m, 1H), 1.91-1.76 (m, 1H), 1.55-1.38 (m, 2H), 1.30 (d, *J* = 7.4 Hz, 3H), 0.96-0.90 (m, 3H), 0.89-0.80 (m, 3H) ppm. **HPLC** $t_{R-HPLC-1}$ = 2.64 min **HRMS (ESI+)** m/z calcd. for $C_{21}H_{33}N_4O_5$ $[M+H]^+$ = 421.2451, found 421.2424. **m.p.:** 125 °C No spectroscopic data are available in literature. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, diastereomer 2, mixture of rotamers)** δ 8.60-8.56 (m, 0.3H), 8.25 (br s, 1.7H), 8.20 (d, *J* = 7.1 Hz, 1H), 8.11 (br s, 1H), 7.35-7.27 (m, 4.3), 7.26-7.20 (m, 0.7H), 6.95 (br s, 0.7), 6.80 (br s, 0.3H), 4.90 (dd, *J* = 9.5, 6.0 Hz, 0.7H), 4.64 (m, 0.7H), 4.55-4.49 (m, 0.3H), 4.44-4.38(m, 0.3H), 4.25-4.15 (m, 1H), 3.65-3.56 (m, 0.6H), 3.52-3.38 (m, 2.4H overlap with HDO), 3.12-3.03 (m, 1H), 3.00-2.95 (m, 1H), 2.45-2.37 (m, 1H), 2.33-2.25 (m, 1H), 1.67-1.63 (m, 0.3H), 1.60-1.51 (m, 0.7H), 1.51-1.45 (m, 0.3H), 1.45-1.39 (m, 0.7H), 1.32 (d, *J* = 7.4 Hz, 0.7H), 1.26 (d, *J* = 7.2 Hz, 2.3H), 1.25-1.22 (m, 0.3H), 1.17-1.10 (m, 0.7H), 0.95-0.0.91 (m, 1.8H), 0.83 (dd, *J* = 6.8, 4.6 Hz, 4.2H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 2, mixture of rotamers)** δ 173.8 (C),173.7 (C), 172.2 (C), 169.7 (C), 169.5 (C), 134.4 (C), 130.2 (C), 129.6 (C), 128.6 (C), 128.4 (C), 127.4 (C),55.0 (CH), 51.0 (CH), 47.8 (CH), 47.6 (CH), 38.0 (CH2), 37.2 (CH2), 35.6 (CH_2), 24.1 (CH), 23.0 (CH_3), 22.8 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 17.1 (CH_3), 17.0 (CH_3) ppm. NMR-data was acquired at elevated temperature so that peaks arising from hindered rotation coalesced. **^{1}H (500 MHz, DMSO-*d*$_6$, 80 °C, diastereomer 2, mixture of rotamers)** δ 8.35 (br s, 1H), 7.90 (br s, 0.8H), 7.65 (br s, 0.2H), 7.40-7.22 (m, 5H), 7.22-6.40 (m, 2H), 4.82 (dd, *J* = 8.9, 7.4 Hz, 0.8H), 4.63 (dd, *J* = 8.9, 7.2 Hz, 0.8H), 4.47-4.38 (m, 0.4H), 4.33-4.20 (m, 1H), 3.68-3.51 (m, 1H), 3.45-3.36 (m, 1H), 3.10-3.00 (m, 2H overlap with HDO), 2.40-2.23 (m, 2H), 1.80-1.48 (m, 2H), 1.44-1.36 (m, 1H), 1.35-1.24 (m, 4H), 0.93-0.83 (m, 7H) ppm. **HPLC** $t_{R-HPLC-1}$ = 2.82 min, **HRMS (ESI+)** m/z calcd. for $C_{21}H_{33}N_4O_5$ $[M+H]^+$ = 421.2451, found 421.2438. No spectroscopic data are available in literature.

Synthesis of the Ata-scaffold

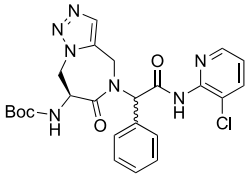
2,2,2-Trifluoroethyl 2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-4-methylpentanoate **S4**



S4

The title compound was prepared following general procedure **E** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Ala(β-N_3)-OH (276 mg, 1.2 mmol, 1.2 equiv), propargylamine (0.064 ml, 1 mmol, 1 equiv) and isovaleraldehyde (0.107 ml, 1 mmol, 1 equiv) in trifluoroethanol (4 ml). Subsequent heating of the reaction mixture was performed in TFE (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:1 to 0:1), the titled compound as a yellow oil with 41% (190 mg, 0.41 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)** δ 7.58 (s, 1H), 7.54 (s, 1H), 5.96-5.92 (m, 2H), 5.46-5.39 (m, 2H), 5.27-5.16 (m, 2H), 5.07-4.97 (m, 2H), 4.87 (d, *J* = 17.6 Hz, 1H), 4.73 (d, *J* = 17.6 Hz, 1H), 4.60-4.38 (m, 5H), 4.23-4.02 (m, 3H), 1.86-1.50 (m, 6H), 1.47 (s, 18H), 1.00 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.82 (d, *J* = 6.2 Hz, 3H), 0.70 (d, *J* = 6.3 Hz, 3H) ppm. . **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers**) δ 170.6 (C), 170.4 (C), 169.9 (C), 169.3 (C), 154.9 (C), 131.6 (C), 131.1 (CH), 130.7 (CH), 122.7 (q, *J* = 277 Hz, CF_3), 122.42 (q, *J* = 277 Hz, CF_3), 81.3 (C), 81.2 (C), 61.1 (q, *J* = 37.0 Hz, CH_2CF_3), 61.0 (q, *J* = 37.0 Hz, CH_2CF_3), 55.6 (CH), 54.9 (CH), 50.5 (CH_2), 50.2 (CH_2), 48.9 (CH), 38.2 (CH_2), 37.6 (CH_2), 37.4 (CH_2), 36.8 (CH_2), 28.4 (CH_3), 25.1 (CH), 25.1 (CH), 23.1 (CH_3), 22.7 (CH_3), 21.5 (CH_3), 21.1 (CH_3) ppm. **HPLC** $t_{R-HPLC-2}$ = 2.76 min, **HRMS (ESI+)** m/z calcd. for $C_{19}H_{29}F_3N_5O_5$ $[M+H]^+$ = 464.2115, found 464.2119. No spectroscopic data are available in literature.

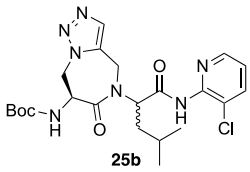
tert-Butyl (*S*)-(5-(2-((3-chloropyridin-2-yl)amino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25a**



25a

The title compound was prepared following general procedure **E** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Ala(β-N_3)-OH (276 mg, 1.2 mmol, 1.2 equiv), propargylamine (0.064 ml, 1 mmol, 1 equiv) and benzaldehyde (0.102 ml, 1 mmol, 1 equiv) in trifluoroethanol (4 ml). Subsequent heating of the reaction mixture was performed in THF (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:1 to 0:1), the desired compound as a brown solid with 42% (215 mg, 0.42 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:0.7 ratio)** δ 8.26-8.19 (m, 2.7H), 8.11 (br s, 0.7H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 0.7H), 7.47-7.41 (m, 4.4H), 7.34-7.25 (m, 4.1H), 7.24-7.19 (m, 2.4H), 7.06-6.97 (m, 1.7H), 6.74 (s, 1H), 6.03-6.00 (m, 1.7H), 5.31-5.25 (m, 1H), 5.21-5.15 (m, 0.7H), 4.99 (dt, *J* = 13.9, 12.8 Hz, 1.7H), 4.86 (d, *J* = 17.8 Hz, 1H), 4.62-4.53 (m, 1.7H), 4.39 (d, *J* = 17.3 Hz, 0.7H), 4.29 (t, *J* = 12.8, 0.7H), 4.19 (t, *J* = 12.8, 1H), 1.48 (s, 15.3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers in a 1:0.7 ratio)** δ 170.8 (C), 170.6 (C), 154.9 (C), 146.7 (C), 146.6 (CH), 138.3 (CH), 133.0 (C), 132.9 (C), 131.6 (CH), 131.4 (C), 130.6 (CH), 129.7 (CH), 129.6 (CH), 129.4 (CH), 129.1 (CH), 121.3 (CH), 81.0 (C), 62.5 (CH), 62.3 (CH), 50.3 (CH_2), 50.2 (CH_2), 49.1 (CH), 38.1 (CH_2), 37.9 (CH_2), 28.4 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 2.35 and 2.43 min. **HRMS (ESI+)** m/z calcd. for $C_{24}H_{27}ClN_7O_4$ [M+H; $^{35}Cl]^+$ =512.1808 and [M+H; $^{37}Cl]^+$ =514.1790, found 512.1806 and 514.1816 in the expected 3:1 ratio. No spectroscopic data are available in literature.

tert-Butyl ((7*S*)-5-(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25b**

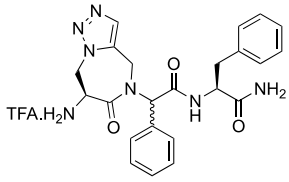


25b

The title compound was prepared following general procedure **E** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1 mmol, 1 equiv), Boc-L-Ala(β-N_3)-OH (276 mg, 1.2 mmol, 1.2 equiv), propargylamine (0.064 ml, 1 mmol, 1 equiv) and isovaleraldehyde (0.107 ml, 1 mmol, 1 equiv) in trifluoroethanol (4 ml). Subsequent heating of the reaction mixture was performed in THF (4 ml). This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:1 to 0:1), the desired compound as a brown solid with 52% (256 mg, 0.52 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)** δ 8.69-8.54 (m, 1.6H), 8.36 (d, *J* = 4.5 Hz, 1H), 8.27 (d, *J* = 4.5 Hz, 1H), 7.76 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.57 (s, 1H), 7.52 (s, 1H), 7.14 (dd, *J* = 8.1, 4.5 Hz, 1H), 7.07 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.21 (d, *J* = 6.2 Hz, 1H), 6.04 (d, *J* = 5.9 Hz, 1H), 5.67 (br s, 2H), 5.27-5.20 (m, 2H), 5.06-4.91 (m, 4H), 4.78 (d, *J* = 17.9 Hz, 1H), 4.68 (d, *J* =17.2 Hz, 1H), 4.25-4.14 (m, 2H), 1.96-1.88 (m, 1H), 1.83-1.75 (m, 2H), 1.67-1.53 (m, 3H), 1.47 (s, 9H), 1.46 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers**) δ 171.1 (C), 170.8 (C), 169.4 (C), 168.2 (C), 155.0 (C), 154.9 (C), 147.1 (C), 146.8 (C), 146.7 (CH), 146.6 (CH), 138.6 (CH), 132.2 (CH), 131.8 (C), 131.0 (CH), 130.9 (C), 123.3 (C), 122.0 (CH), 81.0 (C), 55.9 (CH), 55.4 (CH), 50.3 (CH_2), 49.9 (CH_2), 49.0 (CH), 48.9 (CH), 37.5 (CH_2), 37.3 (CH_2), 36.8 (CH_2), 36.2 (CH_2), 28.4 (CH_3), 25.1 (CH), 25.0 (CH), 23.1 (CH_3), 22.7 (CH_3), 22.1 (CH_3), 21.7 (CH_3) ppm. **HPLC** $t_{R\ -\ HPLC\text{-}2}$ = 2.46 and 2.50 min, **HRMS (ESI+)** m/z calcd. for $C_{22}H_{30}ClN_7O_4Na$ [M+Na; $^{35}Cl]^+$ = 514.1940 and [M+Na; $^{37}Cl]^+$ = 516.1921, found 514.1901 and 516.1900 in the expected 3:1 ratio. No spectroscopic data are available in literature.

Hydrolysis of the Ata-dipeptide 25 and use in SPPS

(*S*)-2-(2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)-3-phenylpropanamide **26a**



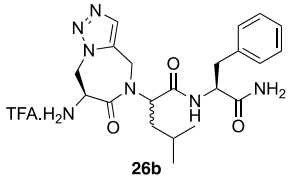
26a

The title compound was obtained by means of a two-step synthesis. The hydrolysis of the amide bond was performed following general procedure **D** from **25a** (61 mg, 0.12 mmol, 1 equiv), H_2O (6.5 µl, 0.36 mmol, 3 equiv) and $Zn(OAc)_2$ (4.4 mg, 0.024 mmol, 20 mol%) in *t*BuOAc (0.24 ml). The mixture was heated at 85 °C for 48 hours. The solvent was removed *in vacuo* and the crude was used without further purification in the subsequent step.

For the coupling of the Ata dipeptide on solid support, the resin was first preloaded with Fmoc-L-Phe-OH (77 mg, 0.2 mmol, 2 equiv) following general procedure **F** onto a Rink amide resin (213 mg, 0.1 mmol, 1 equiv, 0.47 mmol/g) using HBTU (76 mg, 0.2 mmol, 2 equiv) and DIPEA (0.052 ml, 0.3 mmol, 3 equiv) in DMF. Following Fmoc deprotection of the resin using solution of 4-methylpiperidine (20%) in DMF, the crude *N*-Boc protected Ata scaffold (0.12 mmol, 1.2 equiv) was coupled to the resin as described in general procedure **F** with HBTU (57 mg, 0.15 mmol, 1.5 equiv), DIPEA (0.035 ml, 0.2 mmol, 2 equiv) in DMF. The excess of reagents and solvent were removed by filtration and the resin was washed with CH_2Cl_2 (3x). Then a mixture of TFA/TIS/H_2O (95/2.5/2.5) was added and the spps reactor was shaken for 1 hour at room temperature to cleave the peptide from the resin. Subsequently the cleaved product was obtained *via* filtration and the TFA/TIS/H_2O mixture was removed *in vacuo*. The obtained yellow oil was purified *via* preparative HPLC (AcN + 0.1% TFA /H_2O + 0.1% TFA from 3:7 to 7:3 in 20 minutes) and the title compound was obtained as a white solid with 20% (11.1 mg, 0.020 mmol) yield. During purification, the two diastereomers were separated with a yield of 18% for number 1 and 2% for number 2. **^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 1)** δ 8.89-8.79 (m, 3H), 7.59 (s, 1H), 7.26-7.15 (m, 7H), 7.00 (t, *J* = 7.7 Hz, 2H),

6.80 (s, 1H), 6.55 (d, *J* = 7.7 Hz, 2H), 6.31 (s, 1H), 5.34 (dd, *J* = 12.5, 4.1 Hz, 1H), 4.90 (d, *J* = 17.8 Hz, 1H), 4.84 (dd, *J* = 12.8, 4.1 Hz, 1H), 4.78-4.71 (m, 1H), 4.58 (t, *J* = 12.8 Hz, 1H), 4.47 (d, *J* = 17.8 Hz, 1H), 3.04 (dd, *J* = 14.3, 4.1 Hz, 1H), 2.72 (dd, *J* = 14.3, 10.9 Hz, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 1)** δ 172.8 (C), 168.0 (C), 137.8 (C), 134.2 (C), 132.4 (C), 130.4 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 59.8 (CH), 53.8 (CH), 47.4 (CH), 46.9 (CH_2), 37.8 (CH_2), 37.3 (CH_2) ppm. **HPLC (diastereomer 1)** $t_{R\ –\ HPLC\text{-}2}$ = 1.86 min. **HRMS (ESI$^+$)** m/z: calc. for $C_{23}H_{25}ClN_7O_3Na$ $[M+Na]^+$ = 470.1911, found 470.1890 (diastereomer 1). **m. p.:** 178 °C. **^{1}H NMR (500 MHz, DMSO-*d*$_6$, diastereomer 2)** δ 8.76 (br s, 2H), 8.62 (d, *J* = 7.9 Hz, 1H), 7.51 (s, 1H), 7.48-7.38 (m, 4H), 7.34-7.31 (m, 2H), 7.21-7.16 (m, 2H), 7.15-7.11 (m, 3H), 7.01 (br s, 1H), 6.35 (s, 1H), 5.26 (dd, *J* = 12.6, 4.0 Hz, 1H), 4.87 (dd, *J* = 13.0, 4.0 Hz, 1H), 4.60-4.49 (m, 2H), 4.42-4.34 (m, 2H), 2.88 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.70 (dd, *J* = 13.8, 9.0 Hz, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 2)** δ 172.4 (C), 168.0 (C), 167.5 (C), 137.5 (C), 135.0 (C), 132.6 (C), 131.6 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 126.1 (CH), 59.4 (CH), 53.8 (CH), 47.4 (CH), 46.7 (CH_2), 37.3 (CH_2), 37.0 (CH_2) ppm. **HPLC (diastereomer 2)** $t_{R\ –\ HPLC\text{-}2}$ = 1.62 min. **HRMS (ESI$^+$)** m/z: calc. for $C_{23}H_{26}N_7O_3$ $[M+H]^+$ = 448.2092, found 448.2103 (diastereomer 2). **m. p.:** 165 °C. No spectroscopic data are available in literature.

N-((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((S)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)pentanamide **26b**



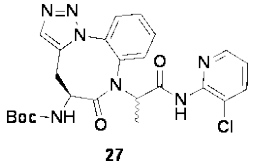
26b

The title compound was obtained by means of a two-step synthesis. The hydrolysis of the amide bond was performed following general procedure **D** from **25b** (59 mg, 0.12 mmol, 1 equiv), H_2O (6.5 µl, 0.36 mmol, 3 equiv) and $Zn(OAc)_2$ (4.4 mg, 0.024 mmol, 20 mol%) in *t*BuOAc (0.24 ml). The mixture was heated at 85 °C for 48 hours. The solvent was removed *in vacuo* and the crude was used without further purification in the subsequent step.

For the coupling of the Ata dipeptide on solid support, the resin was first preloaded with Fmoc-L-Phe-OH (77 mg, 0.2 mmol, 2 equiv) following general procedure **F** onto a Rink amide resin (213 mg, 0.1 mmol, 1 equiv, 0.47 mmol/g) using HBTU (76 mg, 0.2 mmol, 2 equiv) and DIPEA (0.052 ml, 0.3 mmol, 3 equiv) in DMF. Following Fmoc deprotection of the resin using solution of 4-methylpiperidine (20%) in DMF, the crude *N*-Boc protected Ata scaffold (0.12 mmol, 1.2 equiv) was coupled to the resin as described in general procedure **F** with HBTU (57 mg, 0.15 mmol, 1.5 equiv), DIPEA (0.035 ml, 0.2 mmol, 2 equiv) in DMF. The excess of reagents and solvent were removed by filtration and the resin was washed with CH_2Cl_2 (3x). Then a mixture of TFA/TIS/H_2O (95/2.5/2.5) was added and the spps reactor was shaken for 1 hour at room temperature to cleave the peptide from the resin. Subsequently the cleaved product was obtained *via* filtration and the TFA/TIS/H_2O mixture was removed *in vacuo*. The obtained yellow oil was purified *via* preparative HPLC (AcN + 0.1% TFA /H_2O + 0.1% TFA from 3:7 to 7:3 in 20 minutes) and the title compound was obtained with 26% (14.3 mg, 0.026 mmol) yield. During purification, the two diastereomers were separated with a yield of 20% for number 1 (colourless oil) and 6% for number 2 (white powder). **^{1}H NMR (500 MHz, DMSO-*d*$_6$, diastereomer 1)** δ 8.57-8.49 (m, 4H), 7.75 (s, 1H), 7.56 (s, 1H), 7.29-7.23 (m, 4H), 7.22-7.18 (m, 1H), 7.09 (s, 1H), 5.30 (dd, *J* = 12.6, 4.3 Hz, 1H), 5.11 (dd, *J* = 11.8, 3.4 Hz, 1H), 4.98-4.93 (m, 1H), 4.85-4.78 (m, 2H), 4.49-4.43 (m, 1H), 4.35 (t, *J* = 12.6 Hz, 1H), 3.02 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.74 (dd, *J* = 13.5, 11.0 Hz, 1H), 1.47-1.39 (m, 1H), 1.10-1.02 (m, 1H), 0.67 (d, *J* = 5.80 Hz, 3H), 0.47-0.44 (m, 3H), **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 1)** δ 173.0 (C), 170.1 (C), 168.4 (C), 138.0 (C), 133.1 (C), 131.3 (CH), 129.3 (CH), 128.0 (CH), 126.3 (CH), 54.6 (CH), 53.7 (CH), 47.3 (CH), 47.2 (CH_2), 37.9 (CH_2) 37.7 (CH_2), 35.7 (CH_2), 24.2 (CH), 22.4 (CH_3), 20.9 (CH_3). **HPLC** (diastereomer 1) $t_{R\ –\ HPLC\text{-}2}$ = 1.97 min, HRMS (ESI+) m/z: calc. for $C_{21}H_{29}N_7O_3Na$ $[M+Na]^+$ = 450.2224, found 450.2202 (diastereomer 1). **^{1}H NMR (500 MHz, DMSO-*d*$_6$, diastereomer 2)** δ 8.69 (br s, 3H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.54 (s, 1H), 7.33 (s, 1H), 7.18-7.10 (m, 3H), 7.02-6.97 (m, 3H), 5.22 (dd, *J* = 12.5, 4.0 Hz, 1H), 5.11 (dd, *J* = 10.7, 5.3 Hz, 1H), 4.93 (d, *J* = 17.3 Hz, 1H), 4.83 (dd, *J* = 13.0, 4.0 Hz, 1H), 4.73 (d, *J* =17.3 Hz, 1H), 4.34-4.22 (m, 2H), 2.78 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.61 (dd, *J* = 13.9, 8.7 Hz, 1H), 1.79-1.72 (m, 1H), 1.65-1.58 (m, 1H), 1.47-1.40, 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), **^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 2)** δ 172.5 (C), 169.1 (C), 167.7 (C), 137.5 (C), 132.6 (C), 131.5 (CH), 128.8 (CH), 127.9 (CH), 126.1 (CH), 54.5 (CH), 53.5 (CH), 47.3 (CH), 46.7 (CH_2), 37.3 (CH_2) 37.1 (CH_2), 35.3 (CH_2), 24.3 (CH), 23.1 (CH_3), 21.6 (CH_3). **HPLC** (diastereomer 2) $t_{R\ –\ HPLC\text{-}2}$ = 1.56 min, **HRMS (ESI+)** m/z: calc. for $C_{21}H_{30}N_7O_3$ $[M+H]^+$ = 428.2405, found 428.2390 (diastereomer 2). **m. p.:** 138-140 °C. No spectroscopic data are available in literature.

Synthesis of the aminobenzotriazolodiazeocinone scaffold 27 and hydrolysis to the carboxylic acid 28

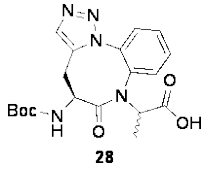
tert-Butyl ((5*S*)-7-(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-5-yl)carbamate **27**



27

The title compound was prepared following general procedure **E** from 3-chloro-2-isocyanopyridine **3b** (139 mg, 1.5 mmol, 1.5 equiv), Boc-L-propargylglycine-OH (213 mg, 1 mmol, 1 equiv), 2-azidoaniline (134 mg, 1 mmol, 1 equiv) and acetaldehyde (0.068 ml, 1 mmol, 1 equiv) in trifluoroethanol (4 ml). Subsequent heating of the reaction mixture was performed in 1,4-dioxane (4 ml) at 100°C. This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:0 to 0:1), the desired compound as a brown solid with 55% (281 mg, 0.55 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)** δ 8.42 (d, *J* = 4.7 Hz, 1H), 8.38 (d, *J* = 4.8 Hz, 1H), 7.83-7.78 (m, 2H), 7.75-7.70 (m, 2H), 7.69-7.66 (m, 2H), 7.61 (s, 1H), 7.55 (s, 1H), 7.18-7.11 (m, 2H), 6.20 (br s, 2H), 5.67-5.59 (m, 2H), 5.09 (br s, 1H), 4.80-4.64 (m, 2H), 4.53 (dd, *J* = 7.8, 6.6 Hz, 1H), 3.54-3.339 (m, 2H), 3.14-3.05 (m, 2H), 1.38 (s, 9H), 1.36 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers**) δ 171.5 (C), 170.6 (C), 167.8 (C), 154.8 (C), 154.7 (C), 147.1 (C), 147.0 (C), 146.2 (CH), 145.5 (CH), 139.1 (CH), 138.7 (CH), 135.7 (C), 135.5 (C), 135.1 (C), 134.9 (C), 133.7 (CH), 133.5 (CH), 132.5 (CH), 132.2 (C), 132.1 (CH), 130.8 (CH), 130.5 (CH), 129.6 (CH), 129.0 (CH), 128.0 (CH), 127.8 (CH), 122.8 (C), 122.8 (C), 121.5 (CH), 121.4 (CH), 80.6 (C), 80.5 (C), 61.4 (CH), 55.0 (CH), 48.6 (CH), 48.3 (CH), 29.0 (CH_2), 28.7 (CH_2), 28.2 (CH_3), 28.1 (CH_3), 13.9 (CH_3), 13.5 (CH_3) ppm. **HRMS (ESI+)** m/z: calc. for $C_{24}H_{27}ClN_7O_4$ $[M+H]^+$ = 512.1813, found 512.1840. No spectroscopic data are reported in literature.

2-((*S*)-5-((*tert*-Butoxycarbonyl)amino)-6-oxo-5,6-dihydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-7(4*H*)-yl)propanoic acid **28**



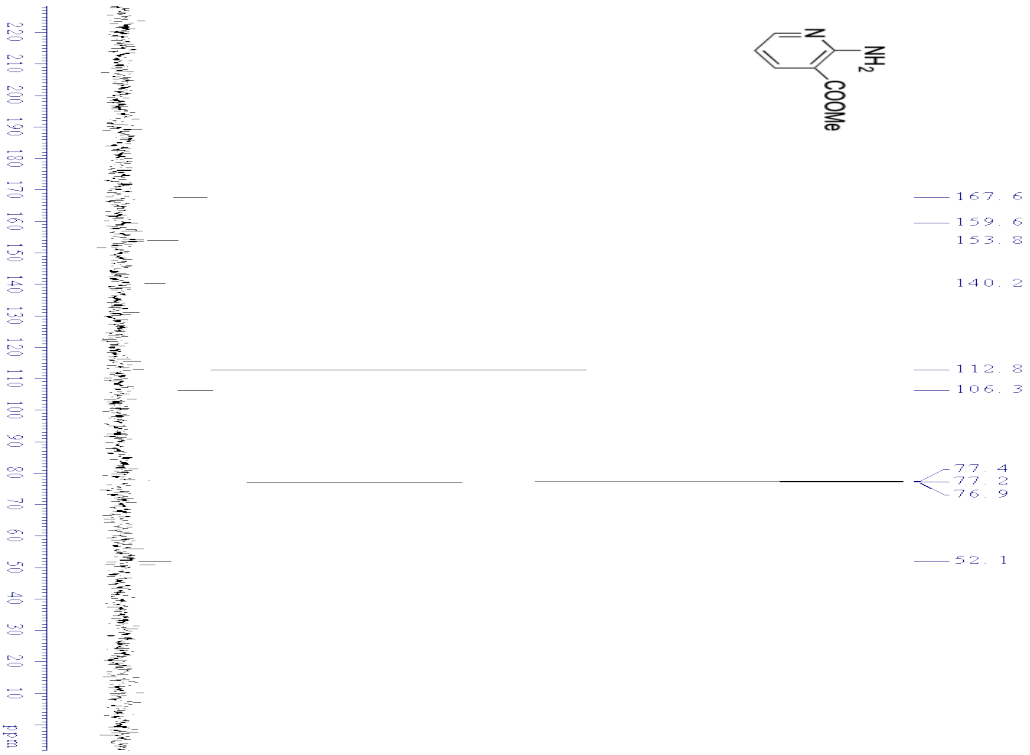
28

The title compound was prepared following general procedure **D** from **27** (128 mg, 0.25 mmol, 1 equiv), H_2O (14 µl, 0.75 mmol, 3 equiv) and $Zn(OAc)_2$ (9 mg, 0.05 mmol, 20 mol%) in *t*BuOAc (0.5 ml). The mixture was heated at 85 °C for 24 hours. This yielded, after Grace Reveleris® X2 Normal Phase silicagel flash chromatography (Pet. Ether/EtOAc from 1:0 to 0:1 with 0.1% AcOH), the desired compound as a brown solid with 88% (89 mg, 0.22 mmol) yield. **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)** δ 9.67 (br s, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.78-7.64 (m, 9H), 5.82-5.73 (m, 2H), 4.76-4.68 (m, 2H), 4.66-4.61 (m, 1H), 4.30-4.23 (m, 1H), 3.53-3.44 (m, 2H), 3.16-3.06 (m, 2H), 1.42 (s, 18H), 1.10 (d, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers**) δ 174.7 (C), 173.6 (C), 170.4 (C), 169.7(C), 154.8 (C), 154.8 (C), 135.5 (C), 135.0 (C), 133.7 (C), 132.5 (CH), 132.3 (CH), 130.7 (CH), 130.5 (CH), 129.1 (CH), 128.8 (CH), 128.0 (CH), 128.0 (CH), 80.6 (C), 80.6 (C), 59.1 (CH), 55.5 (CH), 48.4 (CH), 47.9 (CH), 29.1 (CH_2), 29.0 (CH_2), 28.2 (CH_3), 14.7(CH_3), 13.8 (CH_3) ppm. **HRMS (ESI+)** m/z: calc. for $C_{19}H_{23}N_5O_5Na$ $[M+Na]^+$ = 424.1597, found 424.1550. No spectroscopic data are reported in literature.

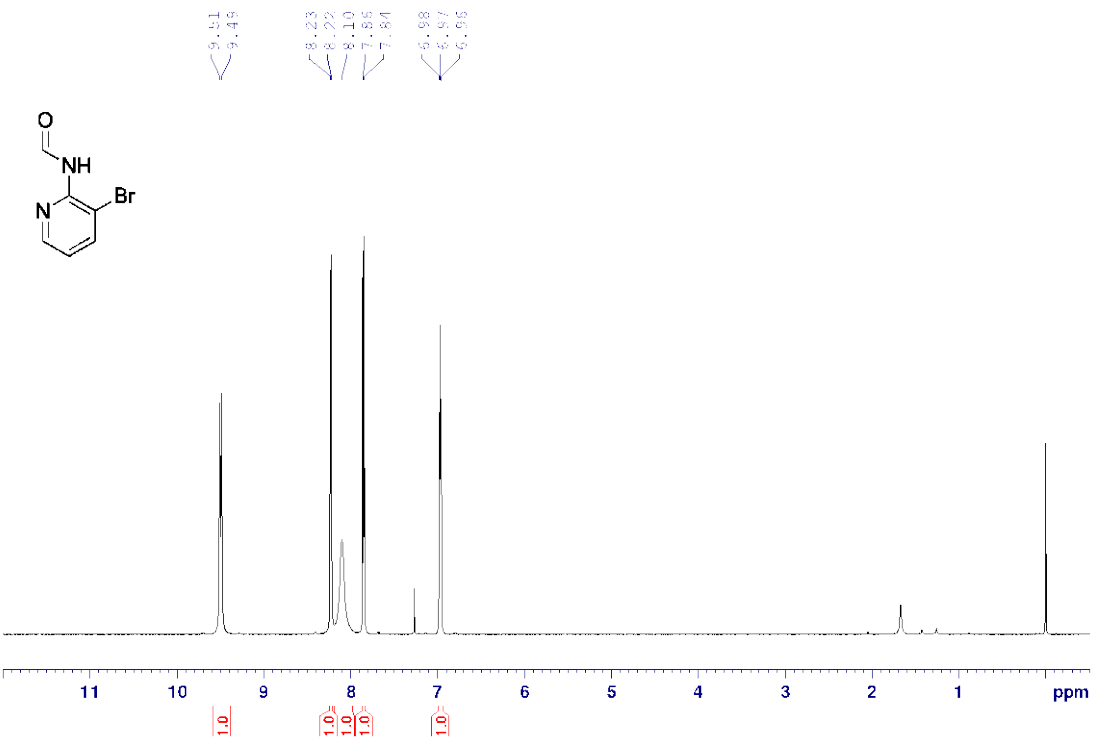
COPIES OF THE NMR SPECTRA

Methyl 2-aminonicotinate **S5 – ^{1}H NMR (500 MHz, $CDCl_3$)**

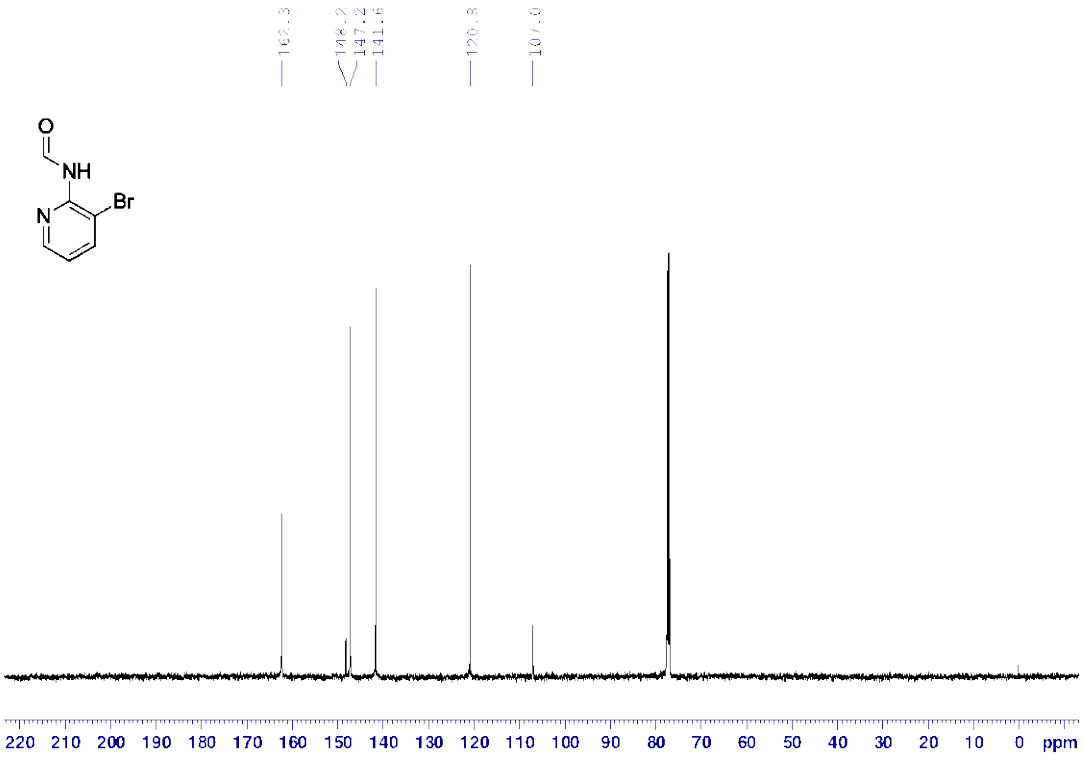
Methyl 2-aminonicotinate **S5 – ^{13}C NMR (126 MHz, $CDCl_3$)**



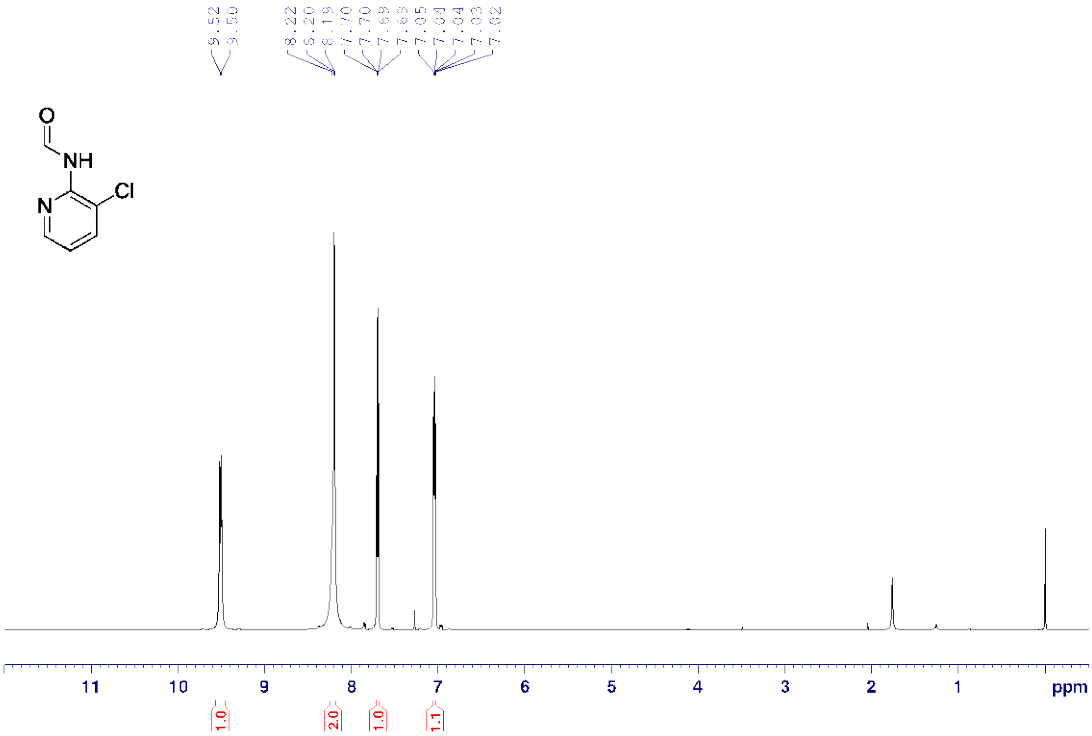
3-Bromo-2-formamidopyridine **2a – ^{1}H NMR (500 MHz, $CDCl_3$)**



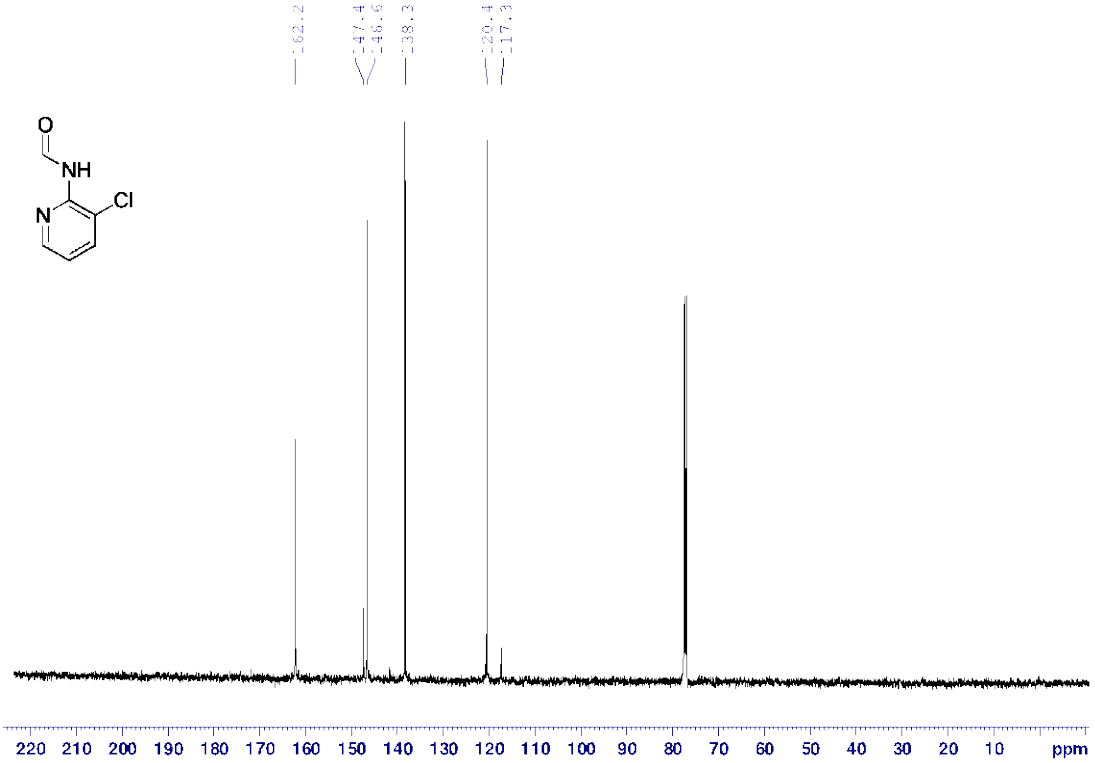
3-Bromo-2-formamidopyridine **2a – ^{13}C NMR (126 MHz, $CDCl_3$)**



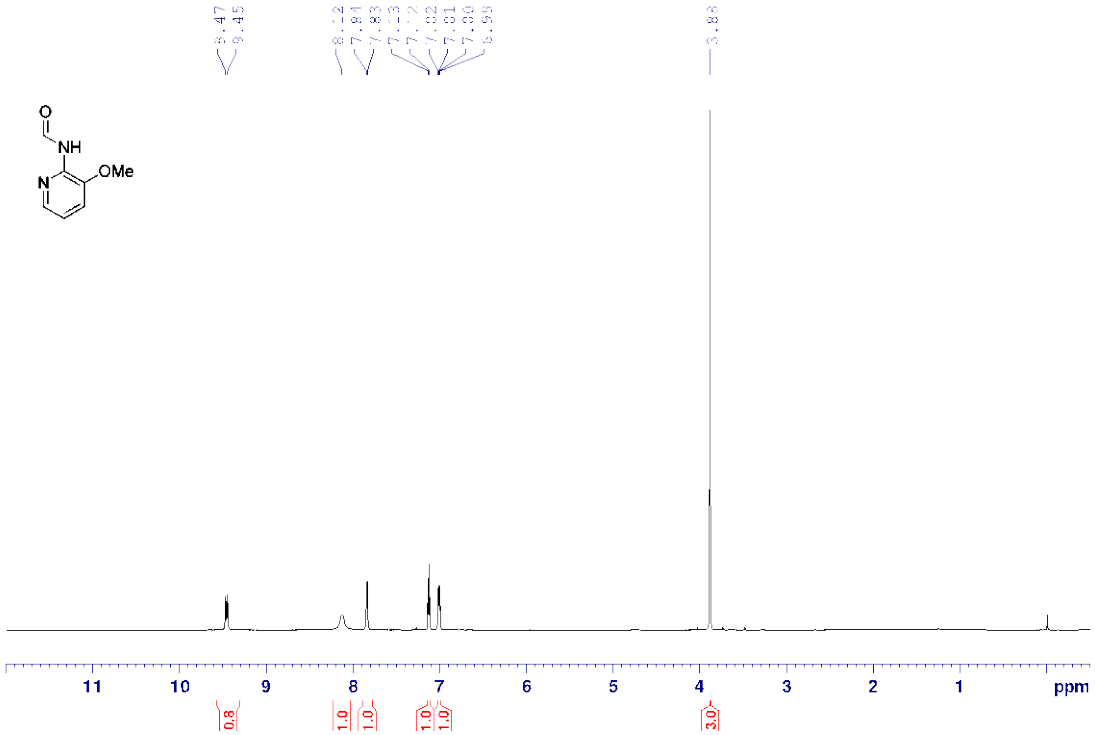
3-Chloro-2-formamidopyridine **2b – ^{1}H NMR (500 MHz, $CDCl_3$)**



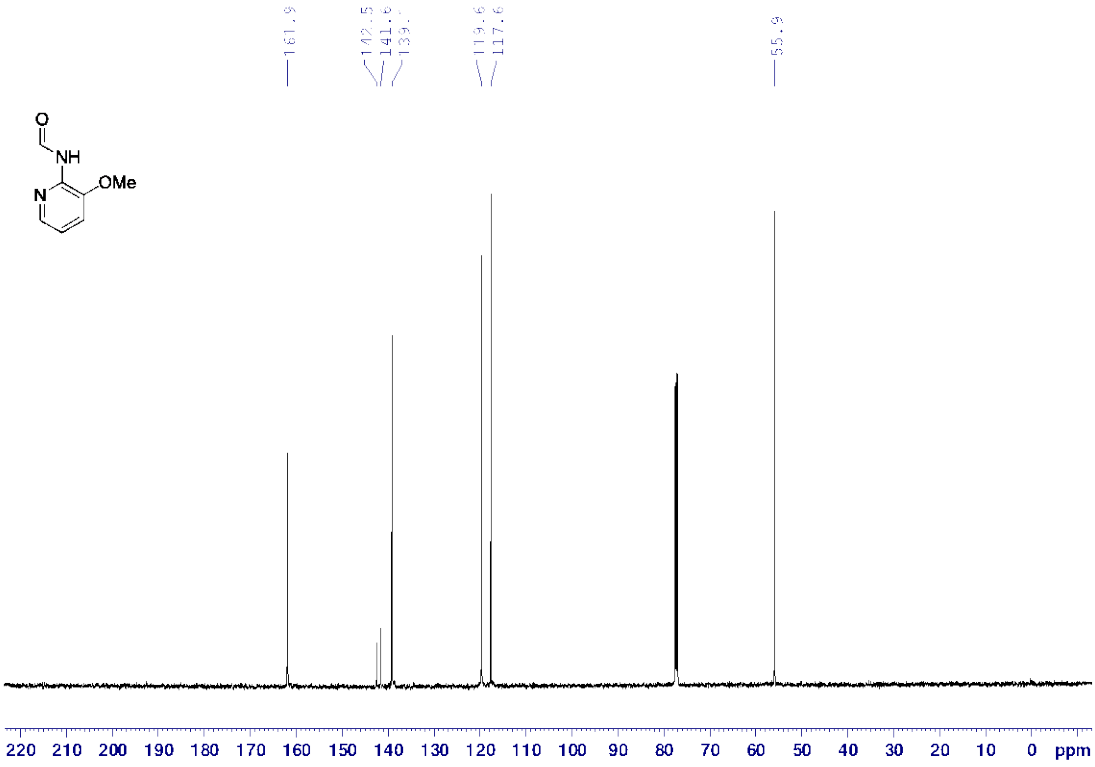
3-Chloro-2-formamidopyridine **2a – ^{13}C NMR (126 MHz, $CDCl_3$)**



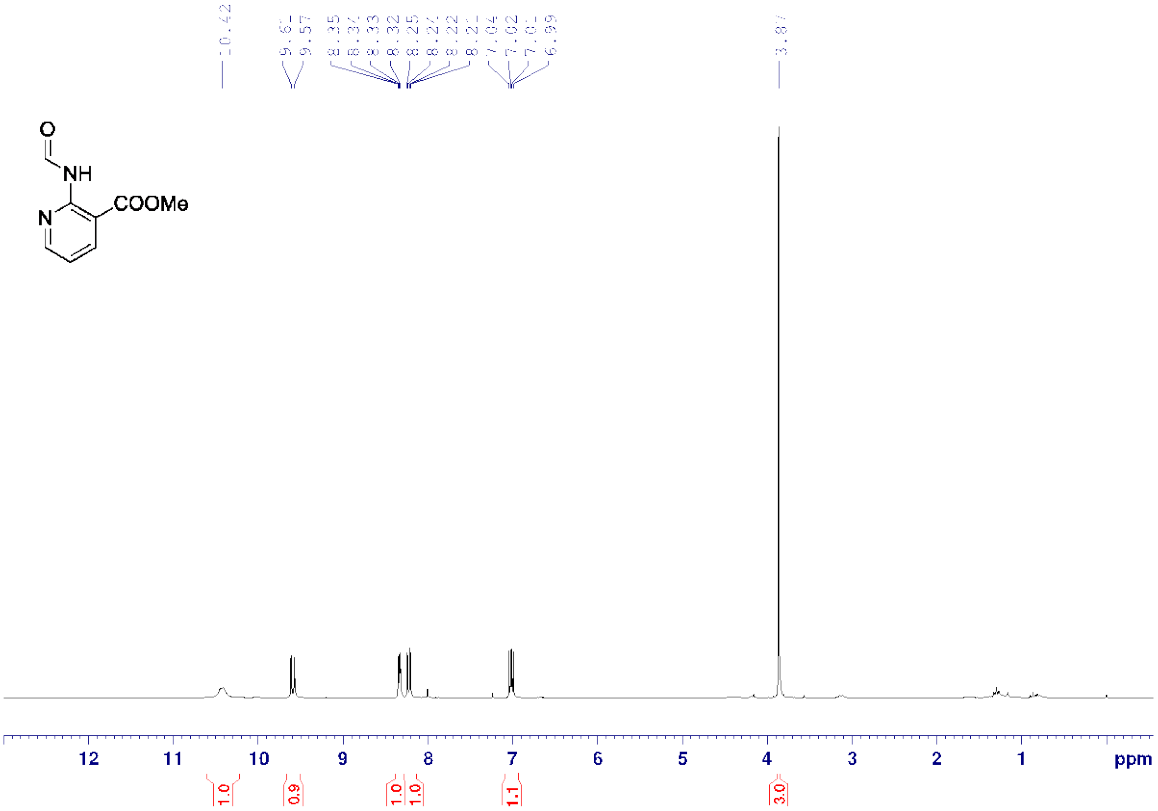
2-Formamido-3-methoxypyridine **2c – ^{1}H NMR (500 MHz, $CDCl_3$)**



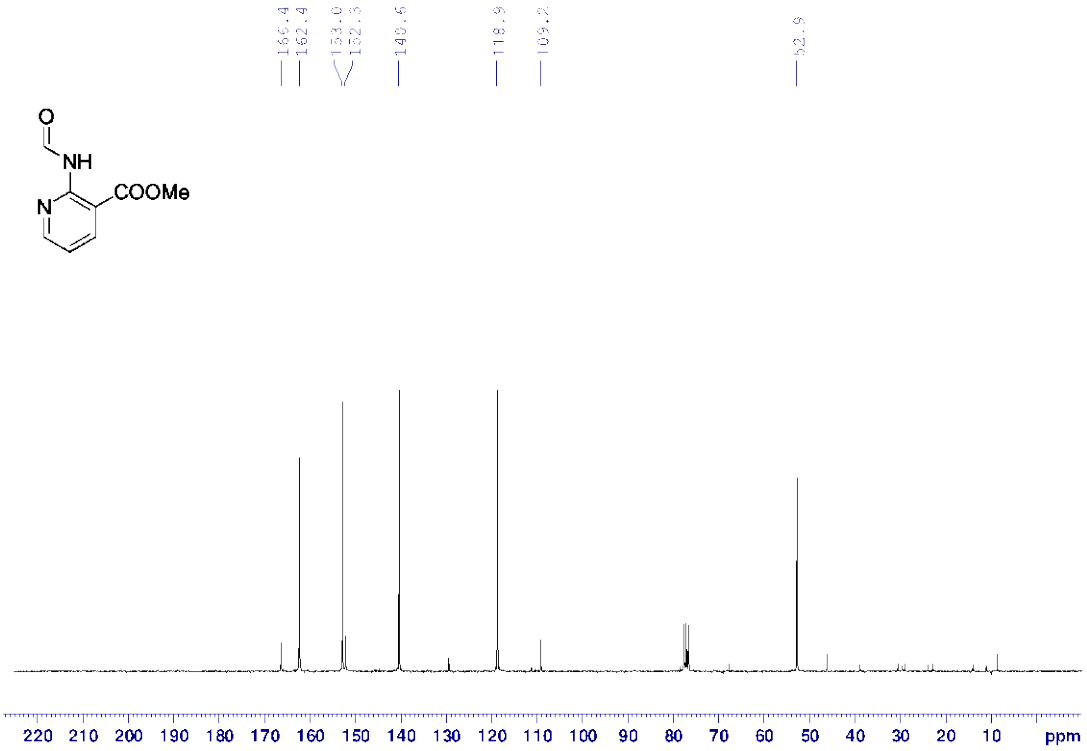
2-Formamido-3-methoxypyridine **2c – ^{13}C NMR (126 MHz, $CDCl_3$)**



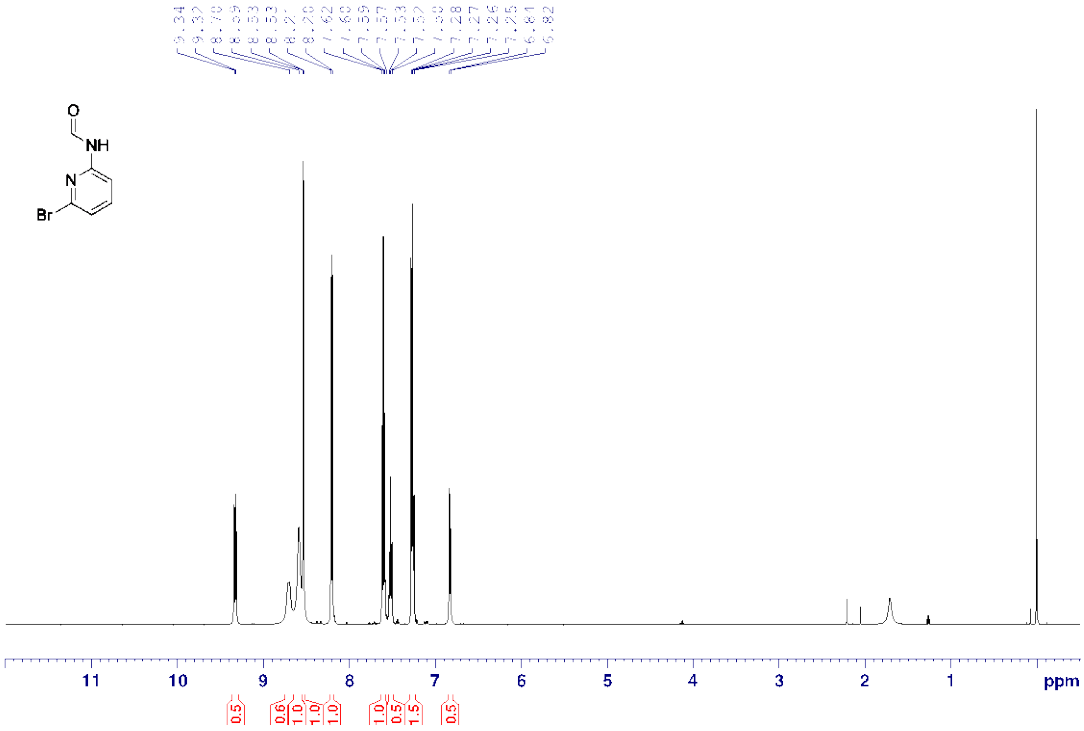
Methyl 2-formamidonicotinate **2d – ^{1}H NMR (250 MHz, $CDCl_3$)**



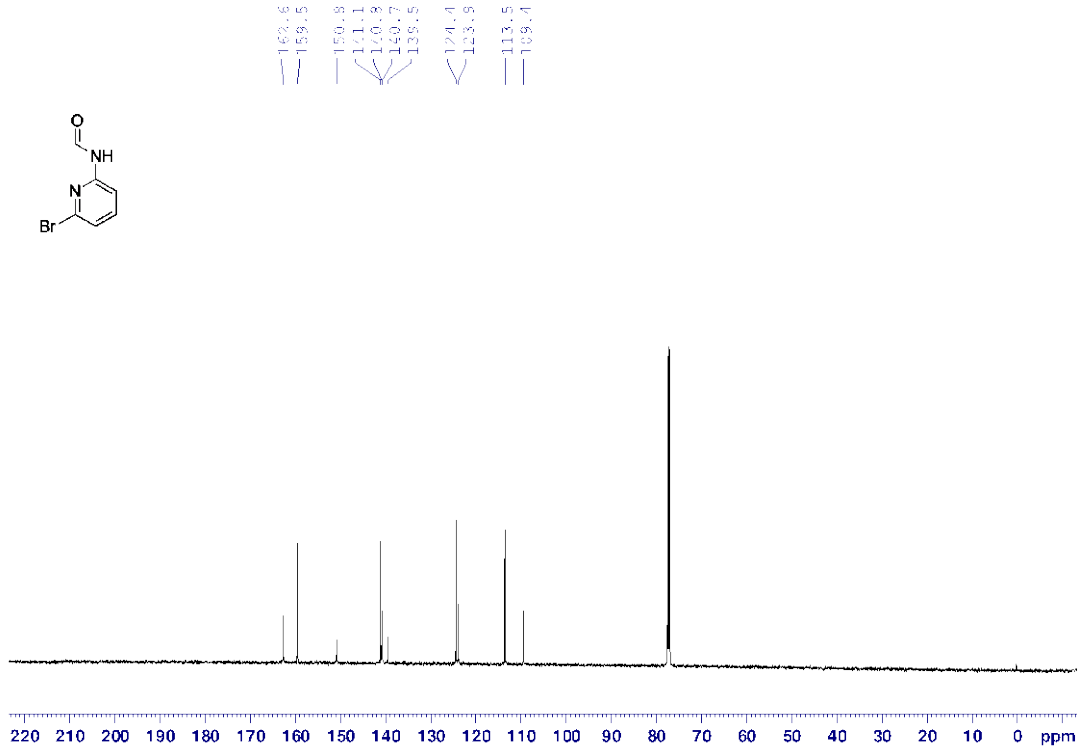
Methyl 2-formamidonicotinate **2d – ^{13}C NMR (63 MHz, $CDCl_3$)**



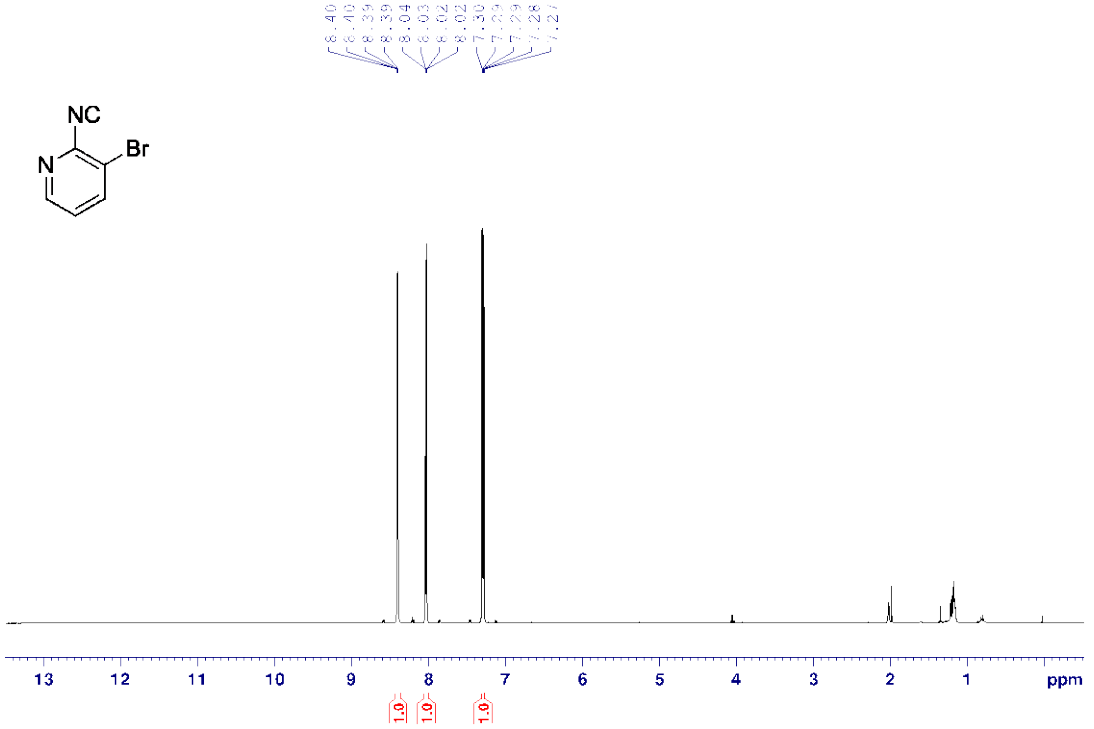
6-Bromo-2-formamidopyridine S1 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers in 1:0.5 ratio)



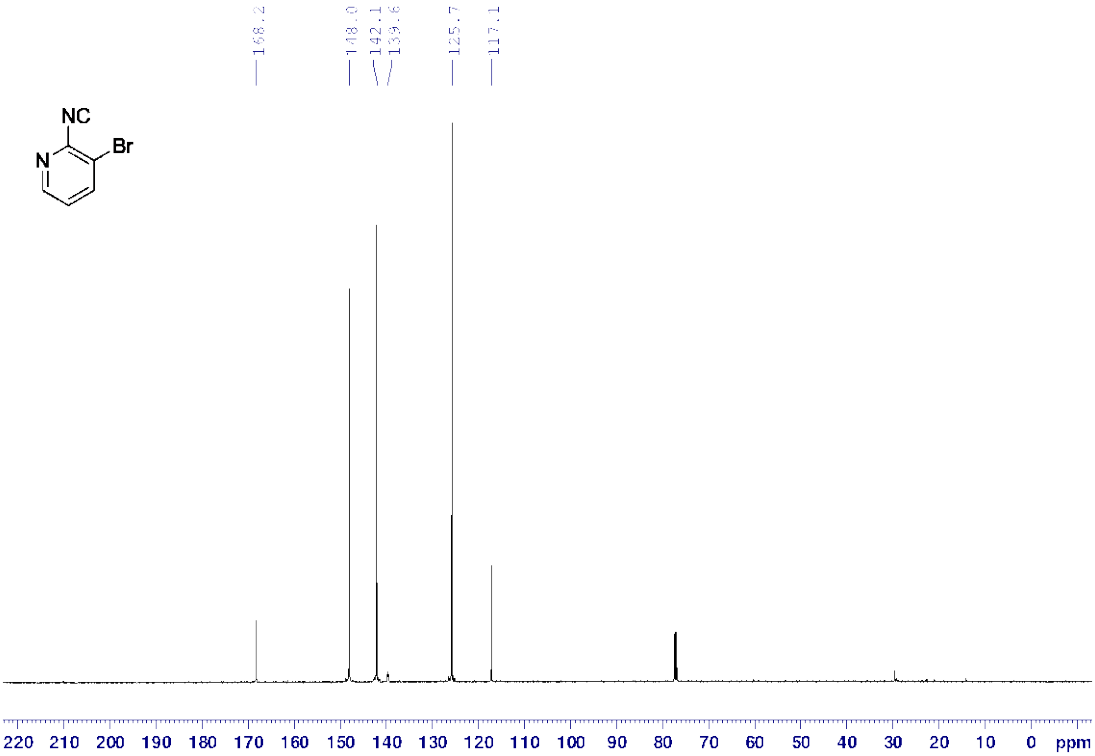
6-Bromo-2-formamidopyridine S1 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)



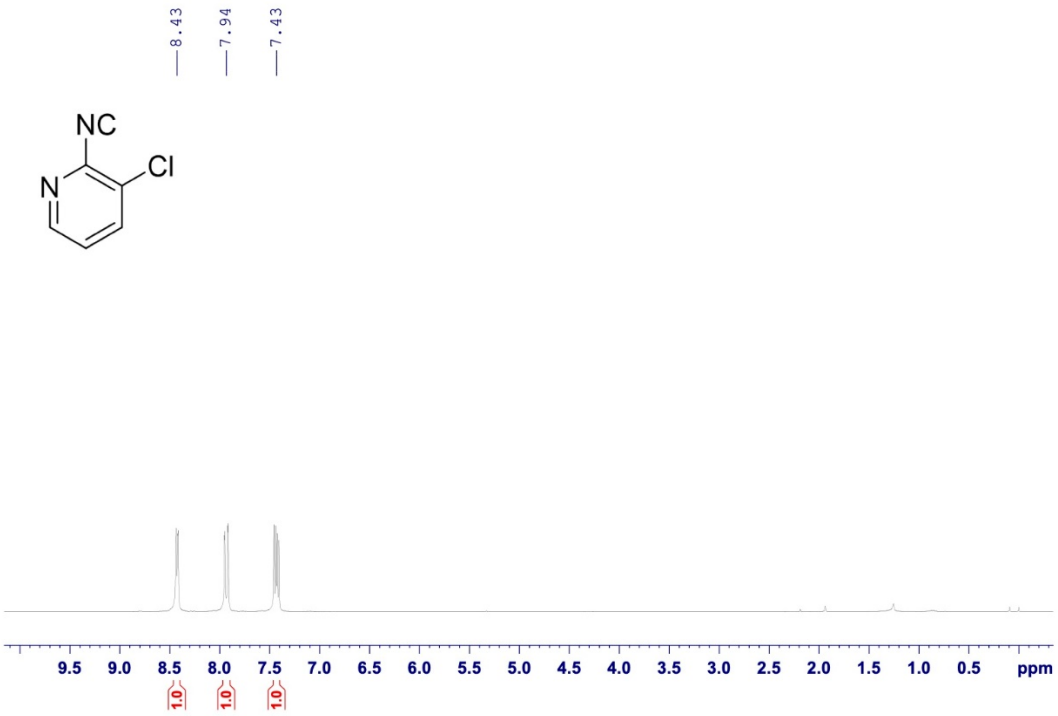
3-Bromo-2-isocyanopyridine **3a – ^{1}H NMR (500 MHz, $CDCl_3$)**



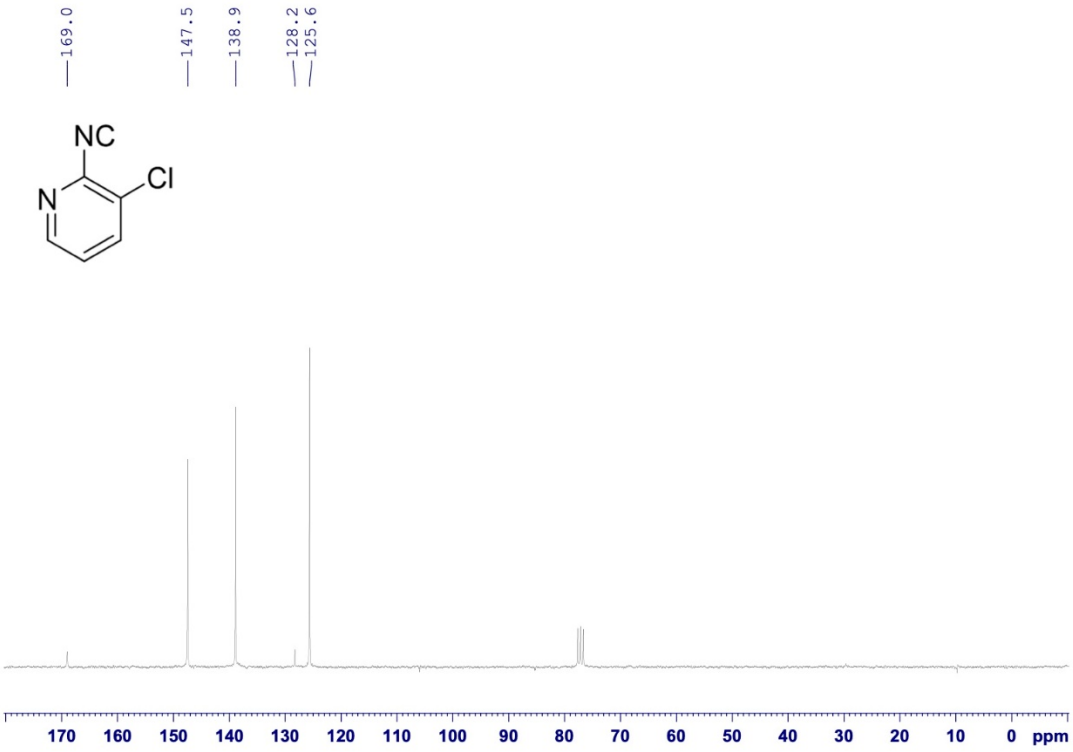
3-Bromo-2-isocyanopyridine **3a – ^{13}C NMR (126 MHz, $CDCl_3$)**



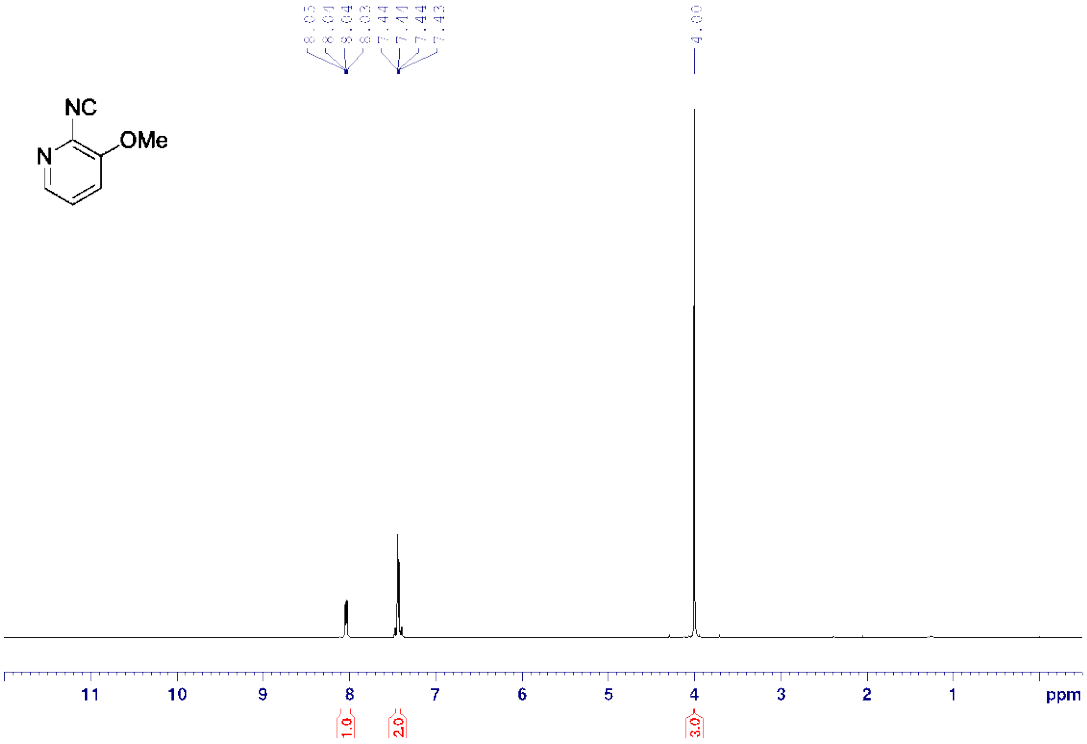
3-Chloro-2-isocyanopyridine **3b – ^{1}H NMR (500 MHz, $CDCl_3$)**



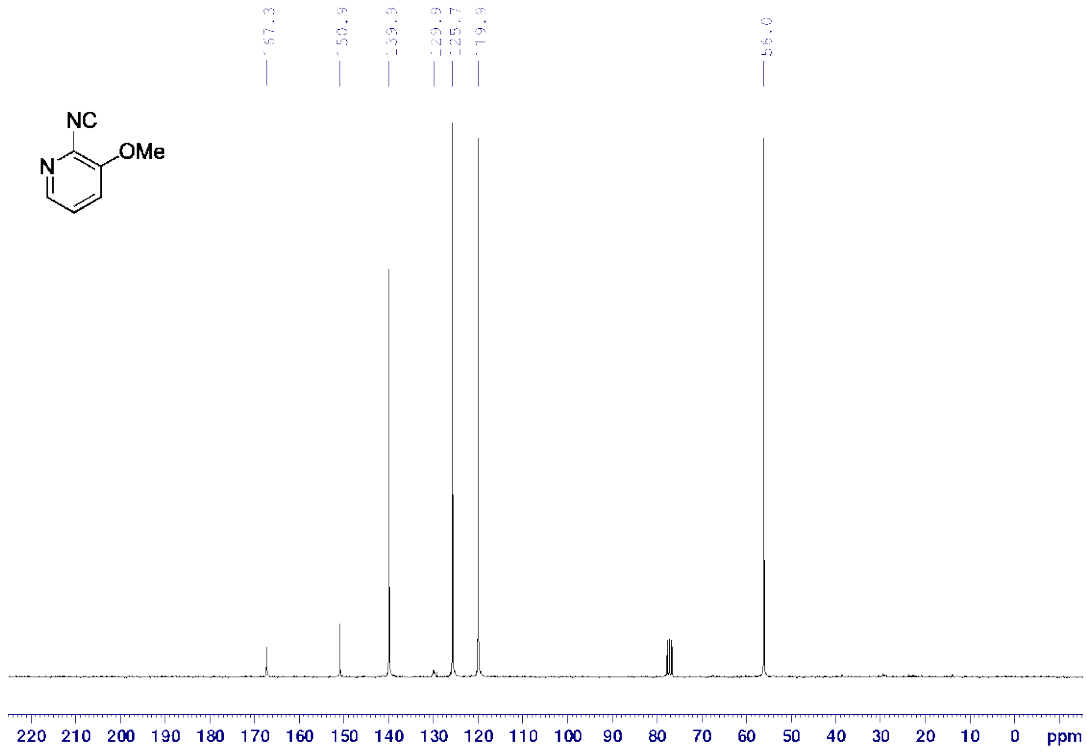
3-Chloro-2-isocyanopyridine **3b – ^{13}C NMR (126 MHz, $CDCl_3$)**



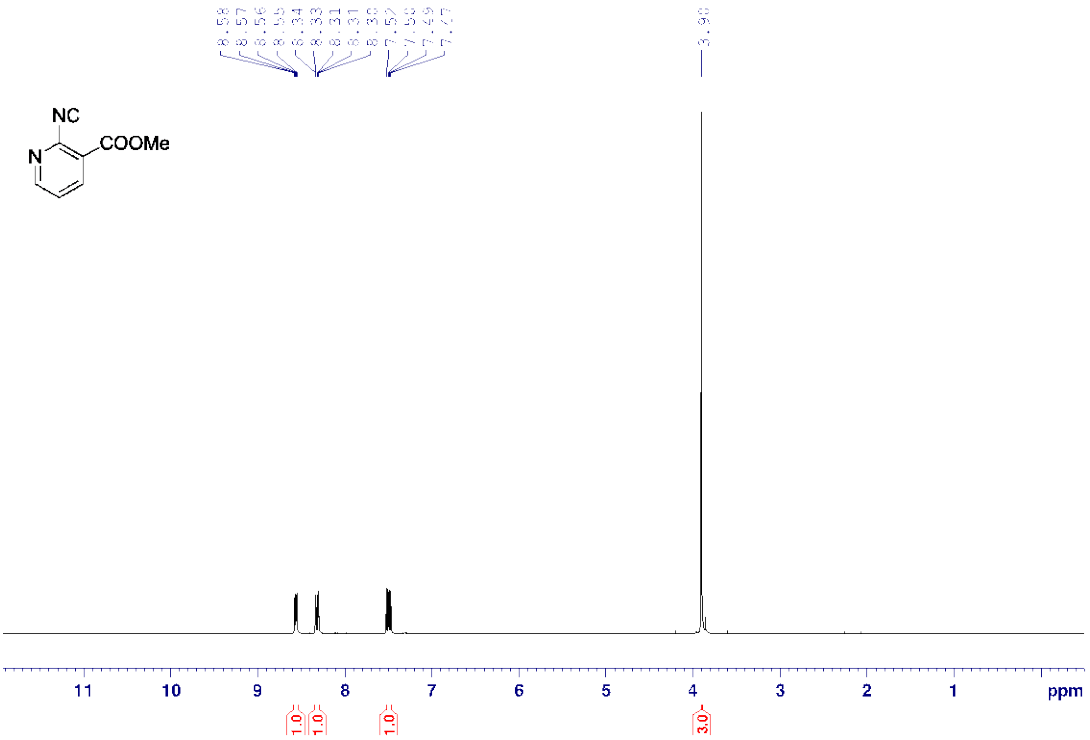
2-Isocyano-3-methoxypyridine **3c – ^{1}H NMR (250 MHz, $CDCl_3$)**



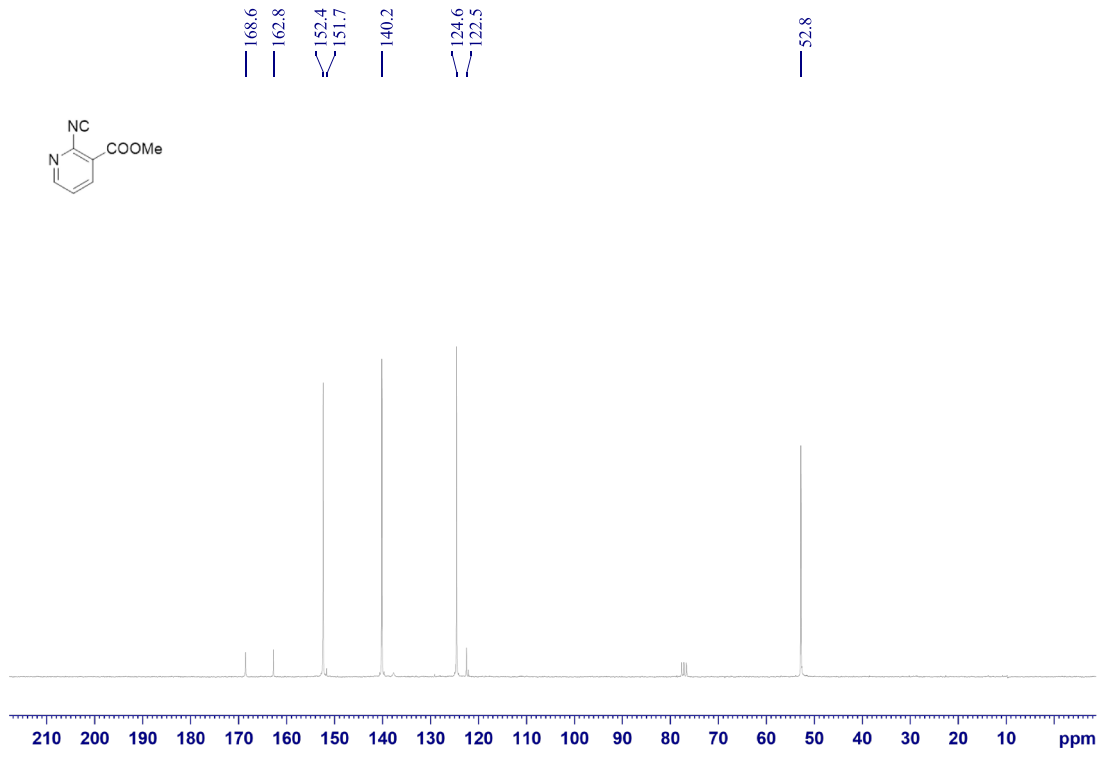
2-Isocyano-3-methoxypyridine **3c – ^{13}C NMR (63 MHz, $CDCl_3$)**



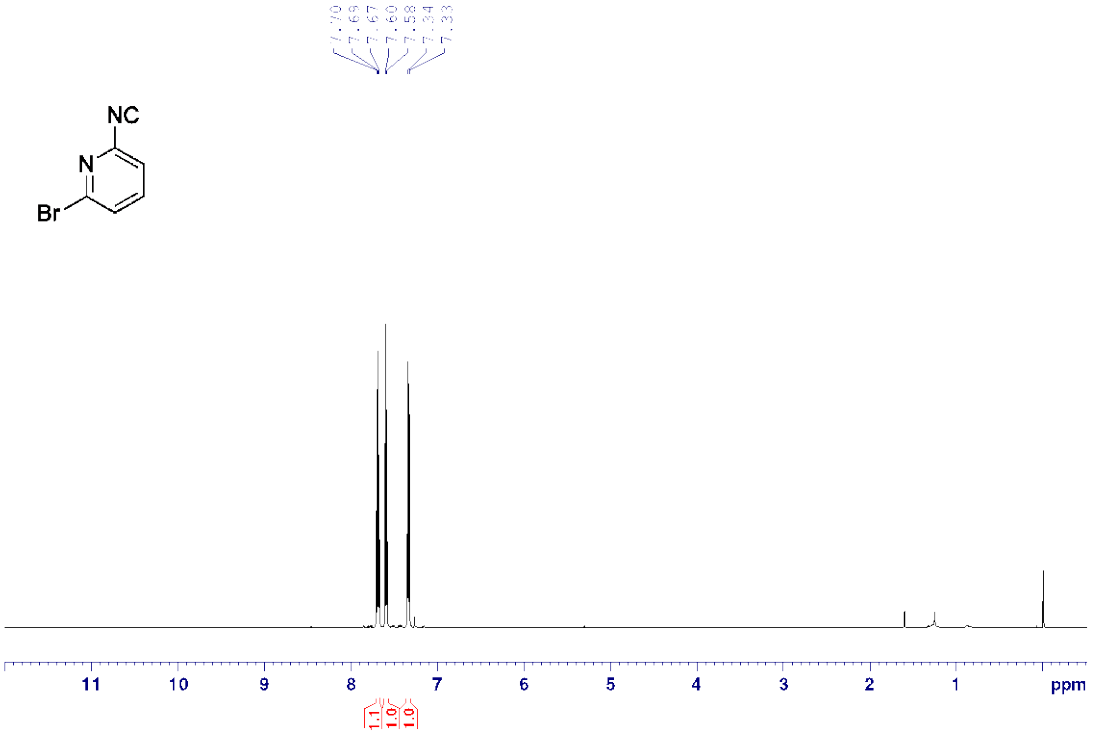
Methyl 2-isocyanonicotinate **3d – ^{1}H NMR (250 MHz, $CDCl_3$)**



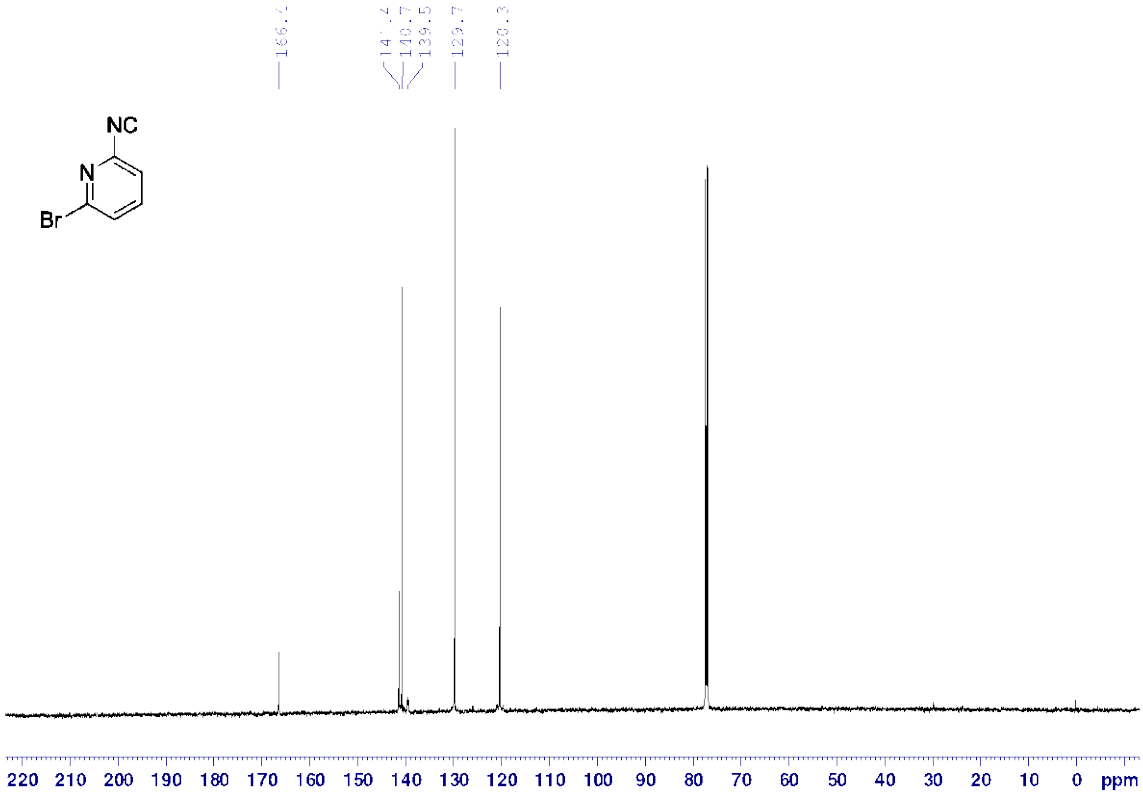
Methyl 2-isocyanonicotinate **3d – ^{13}C NMR (63 MHz, $CDCl_3$)**



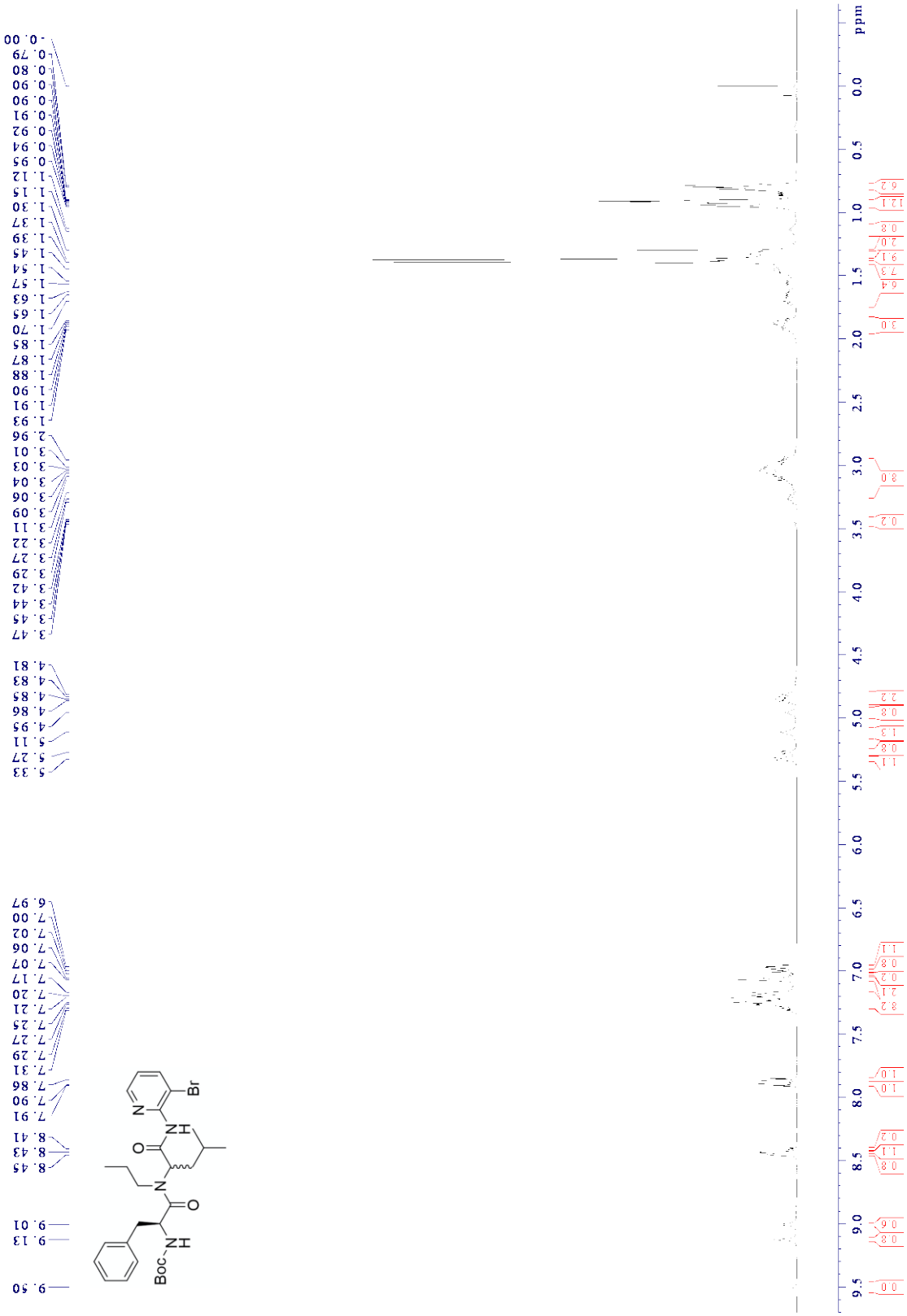
6-Bromo-2-isocyanopyridine **S2 – ^{1}H NMR (500 MHz, $CDCl_3$)**



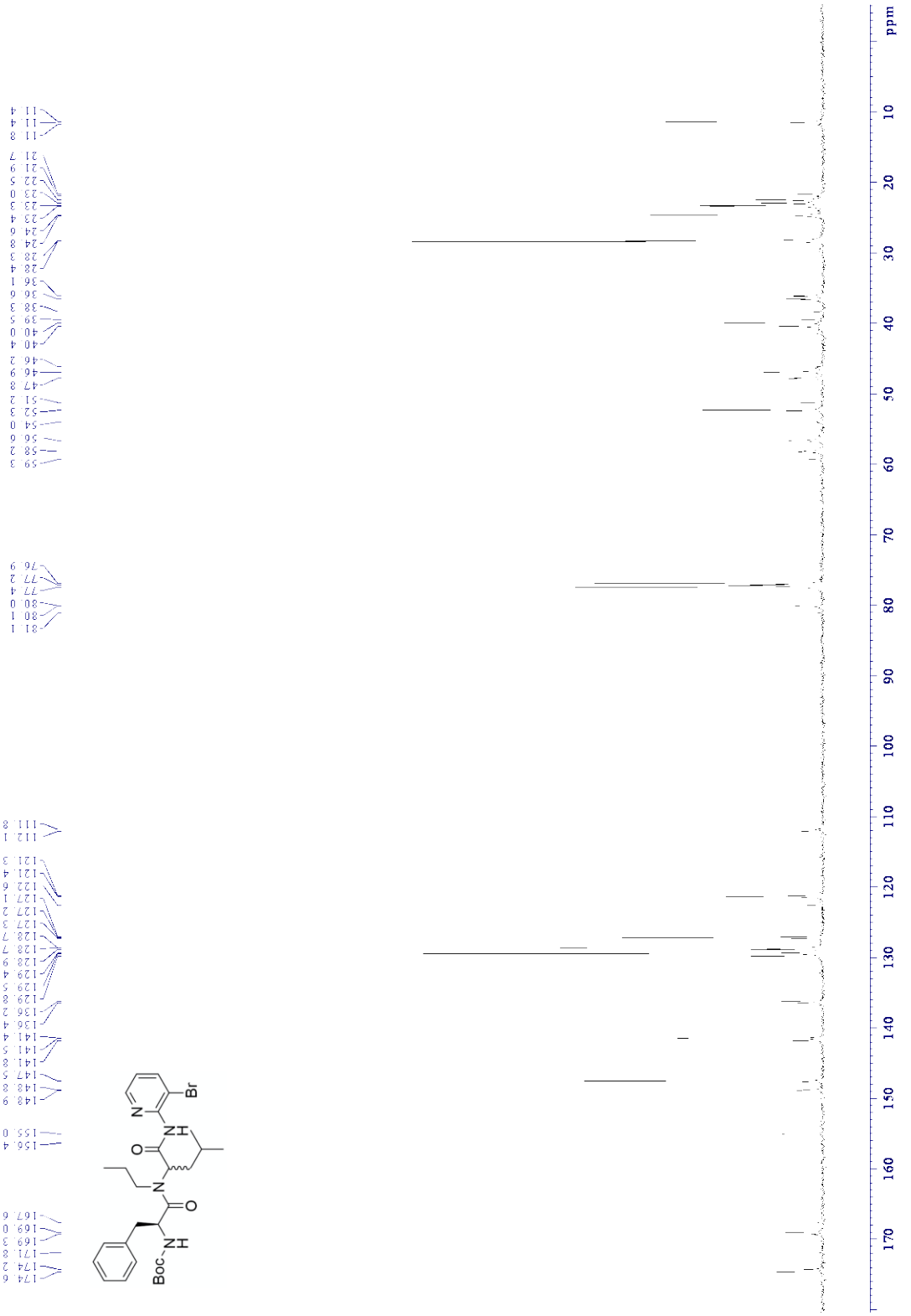
6-Bromo-2-isocyanopyridine **S2 – ^{13}C NMR (126 MHz, $CDCl_3$)**



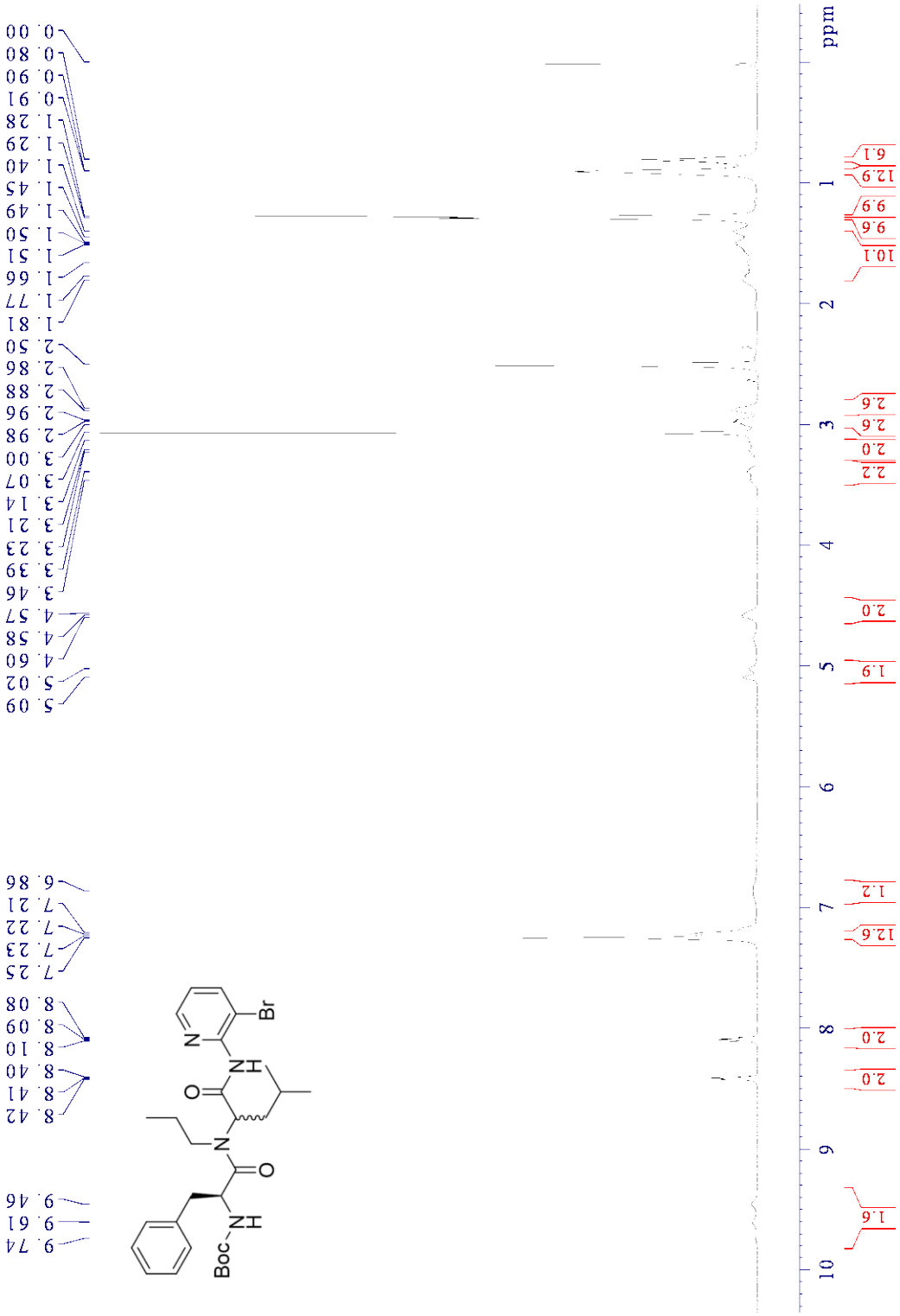
tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4a – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



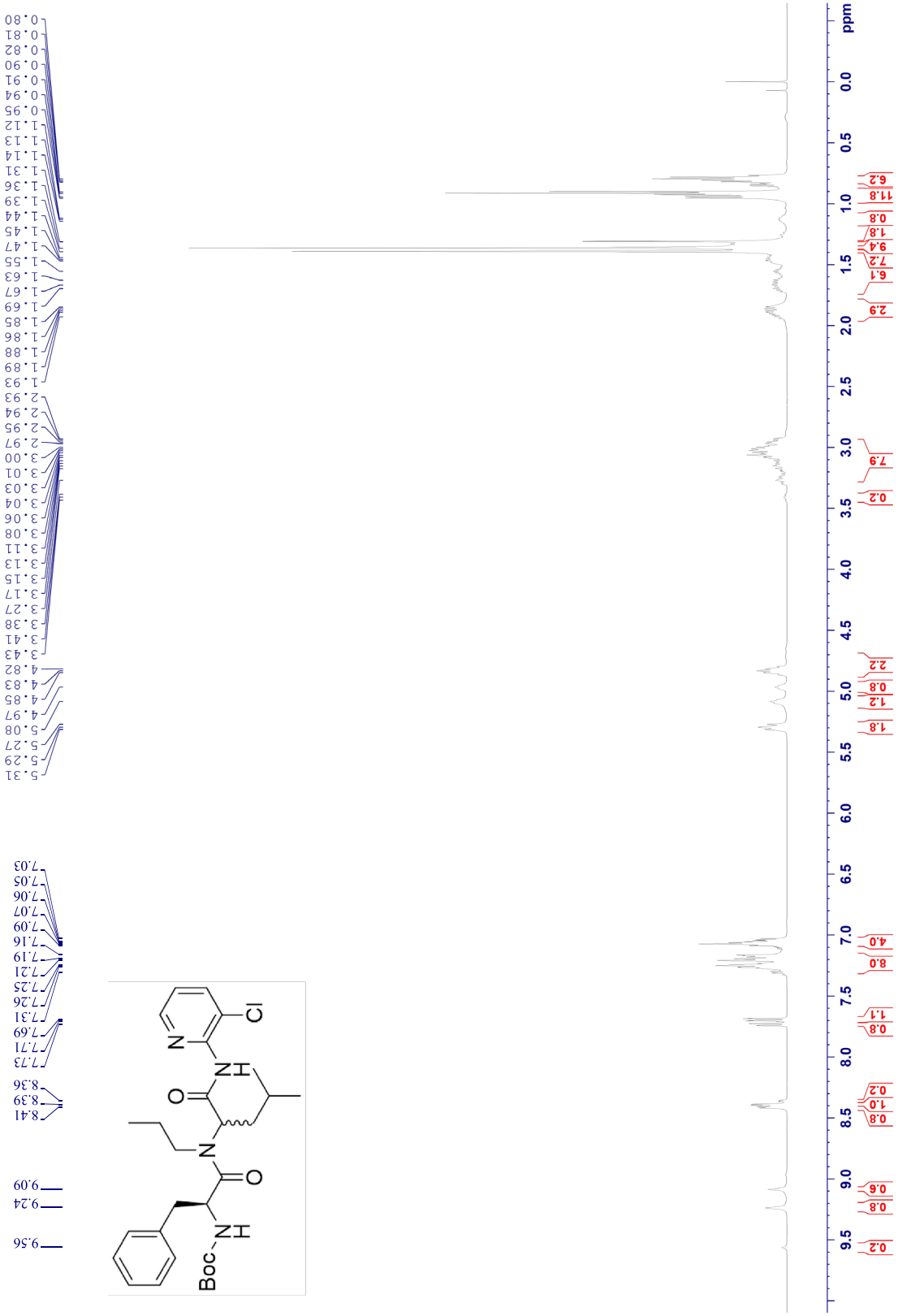
tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4a – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



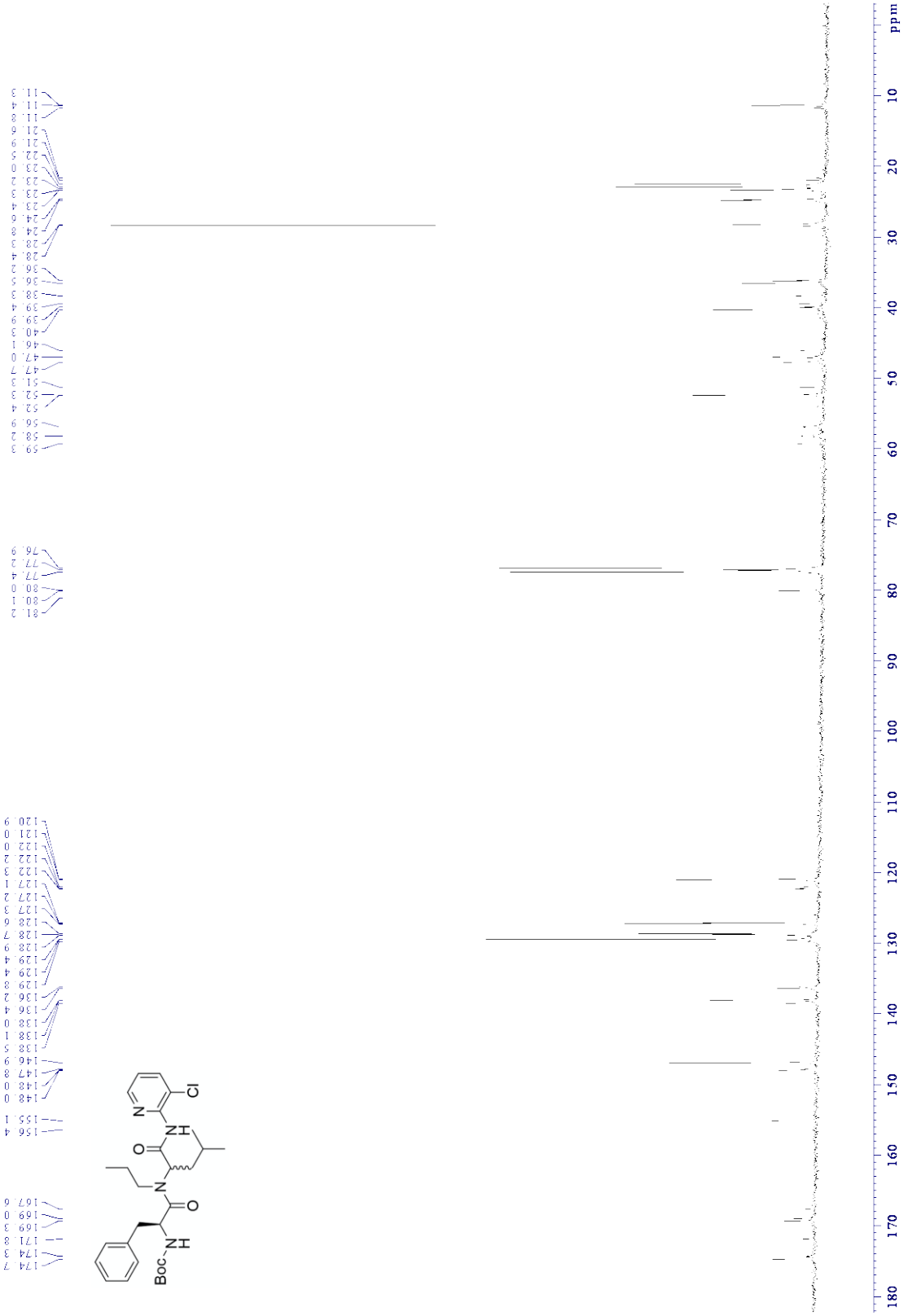
tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4a** – **^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



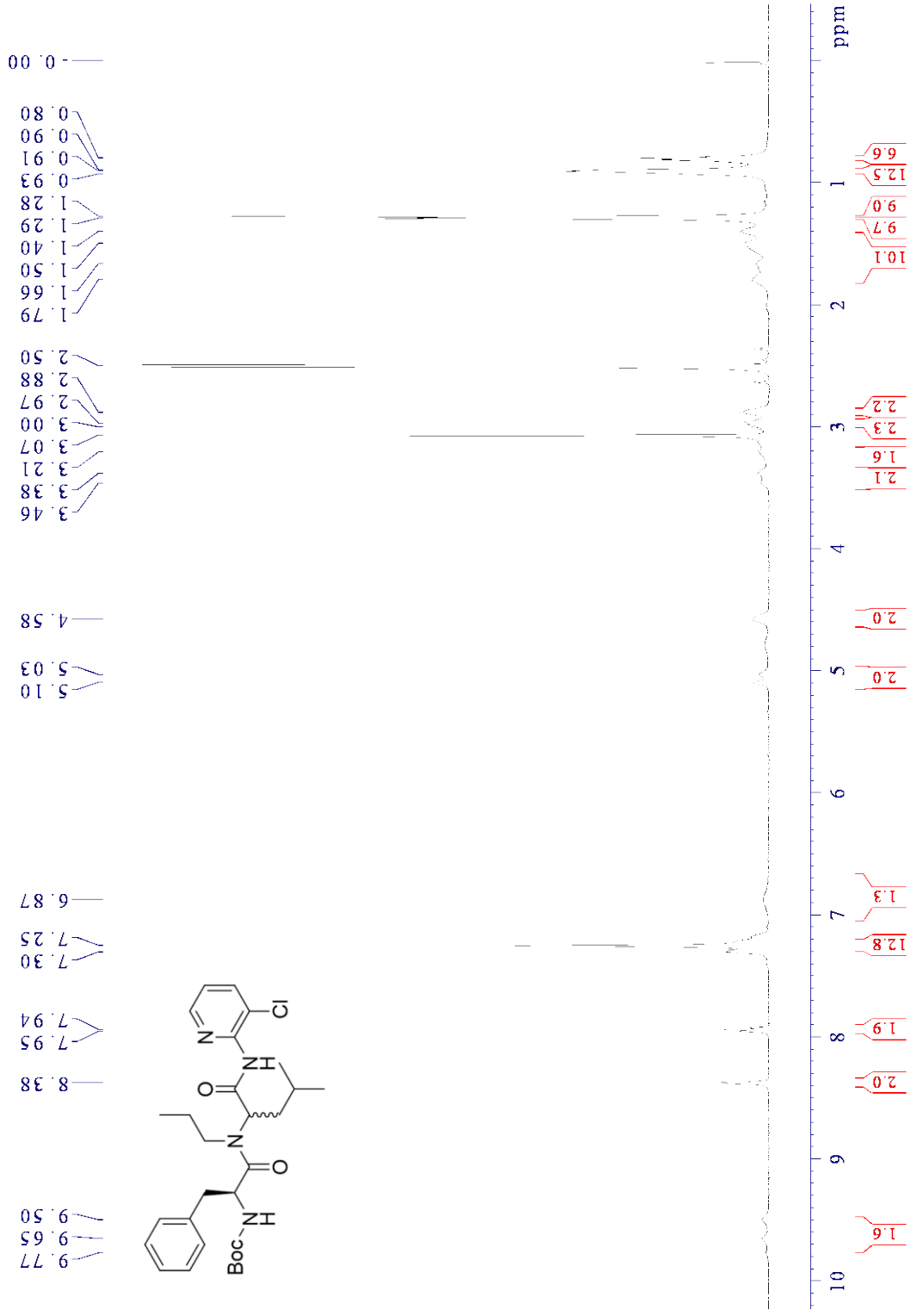
tert-Butyl ((2*S*)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4b** – **^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



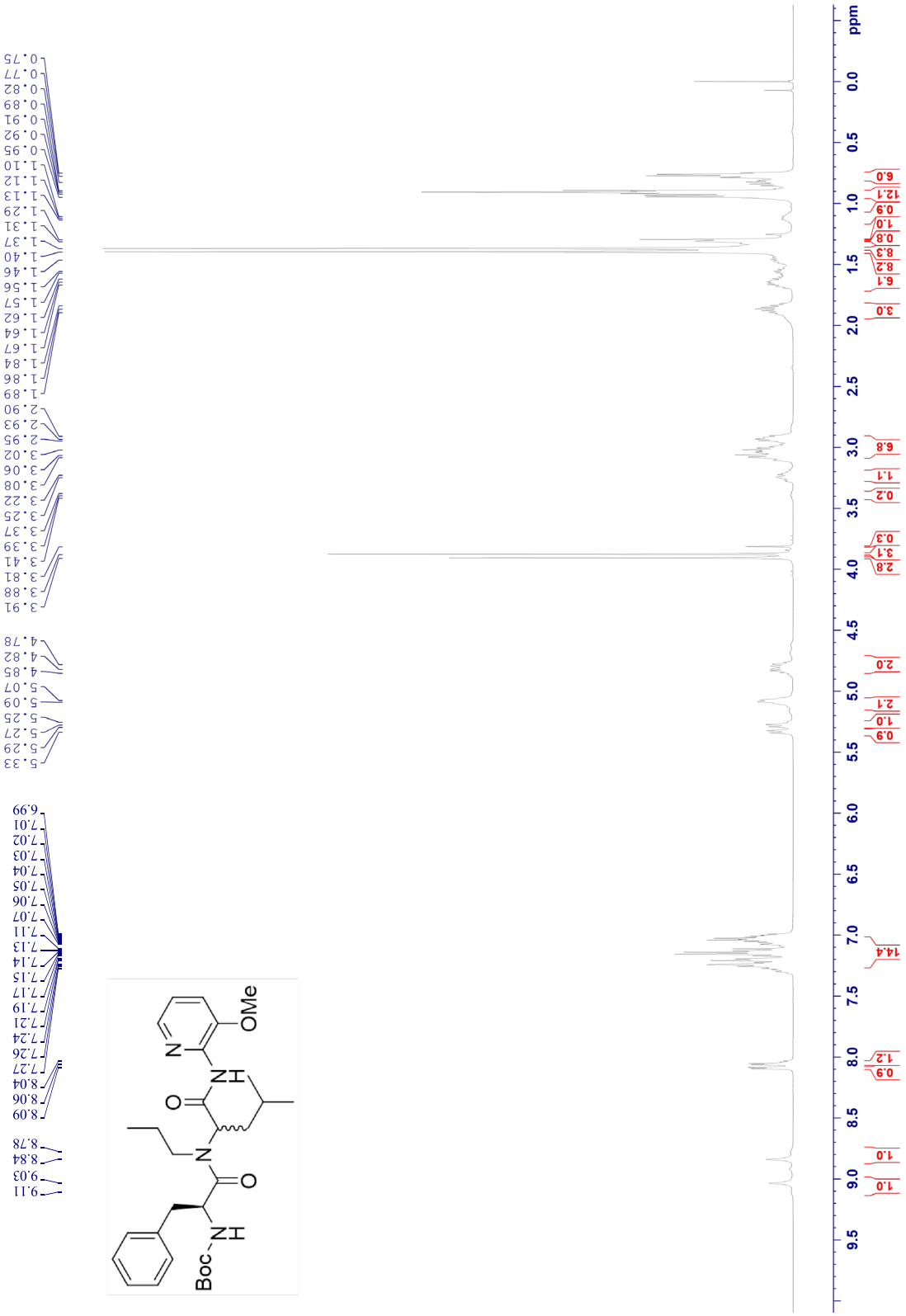
tert-Butyl ((2*S*)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4b** – **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



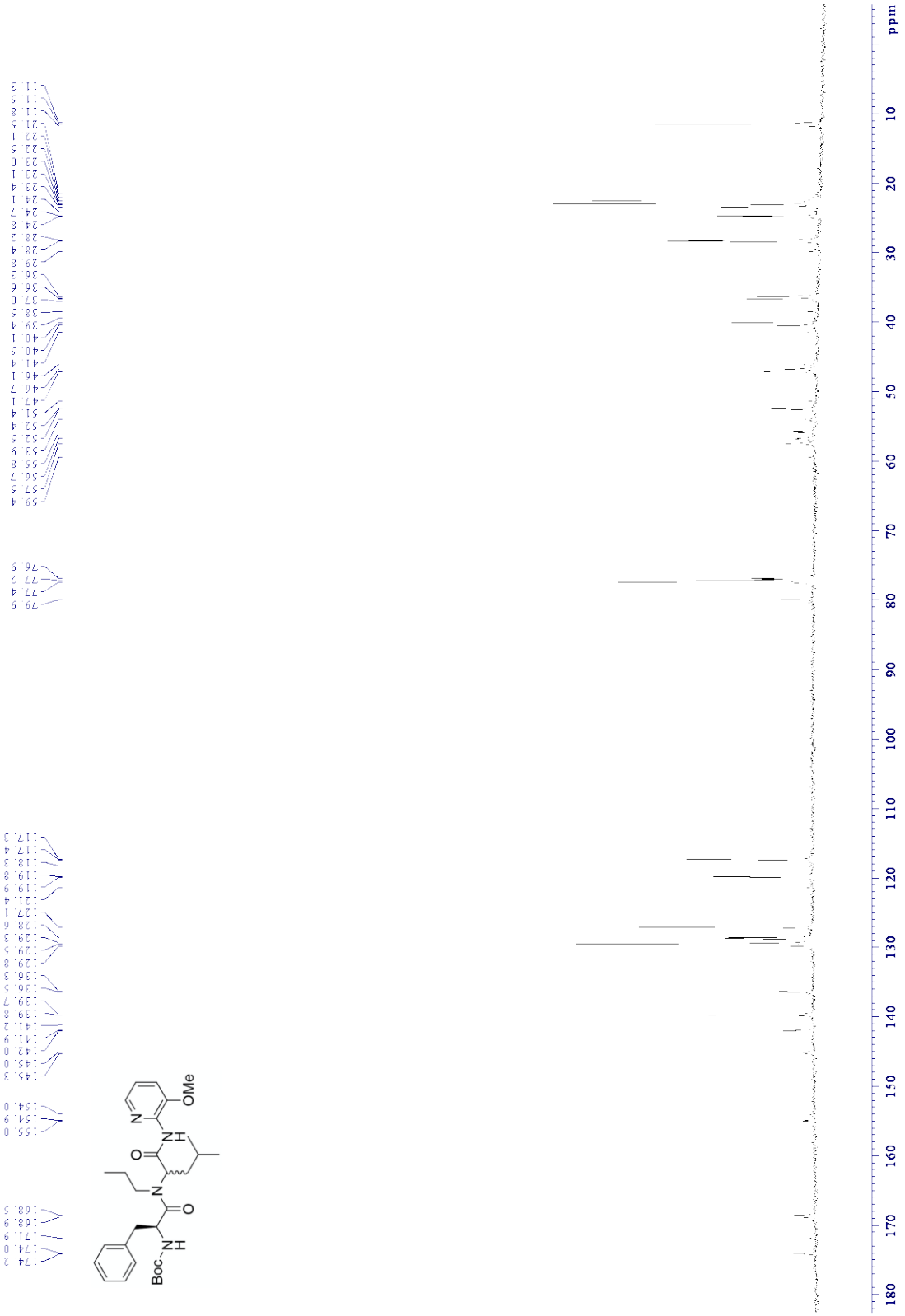
tert-Butyl ((2*S*)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4b** – **^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



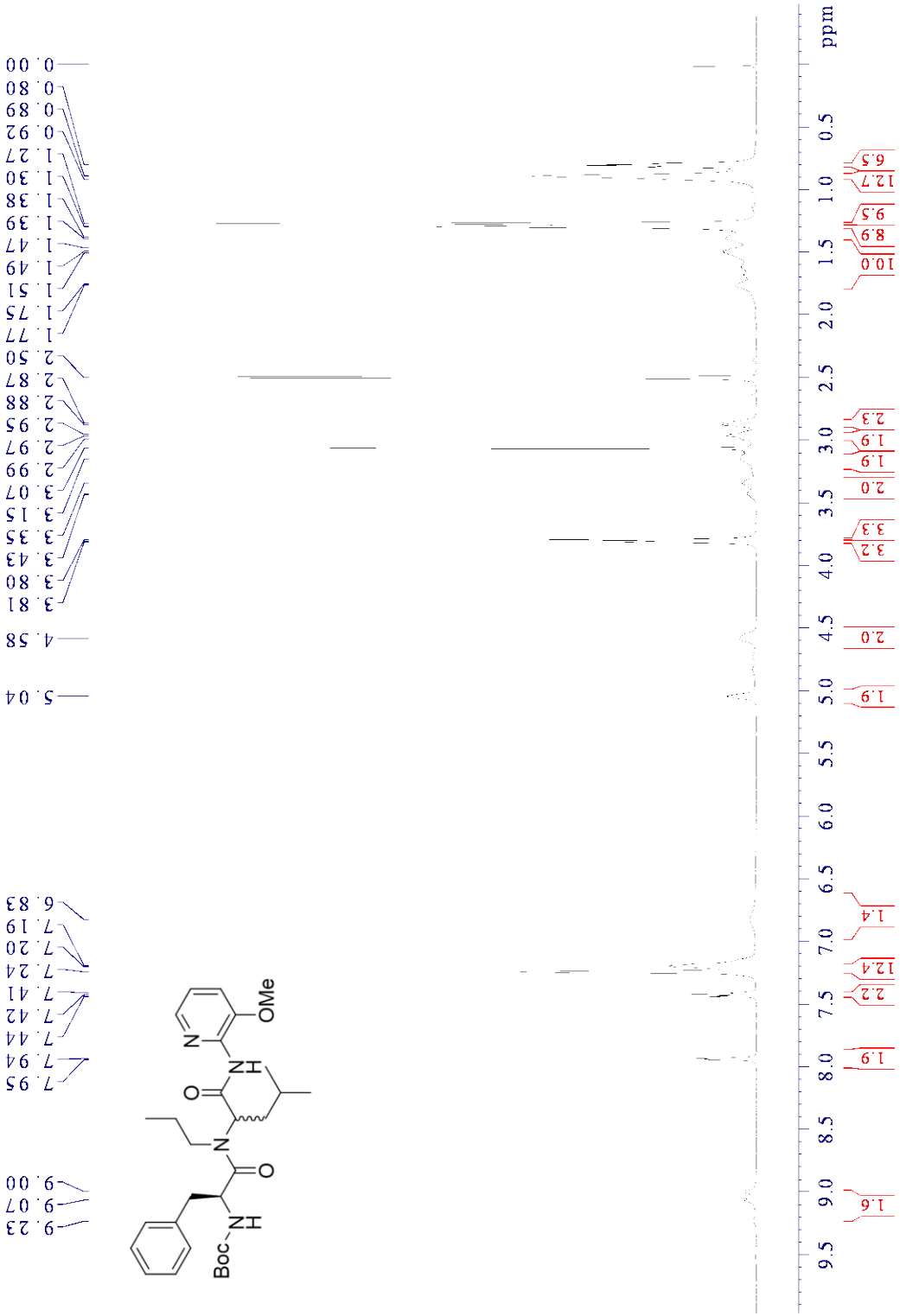
tert-Butyl ((2*S*)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4c – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



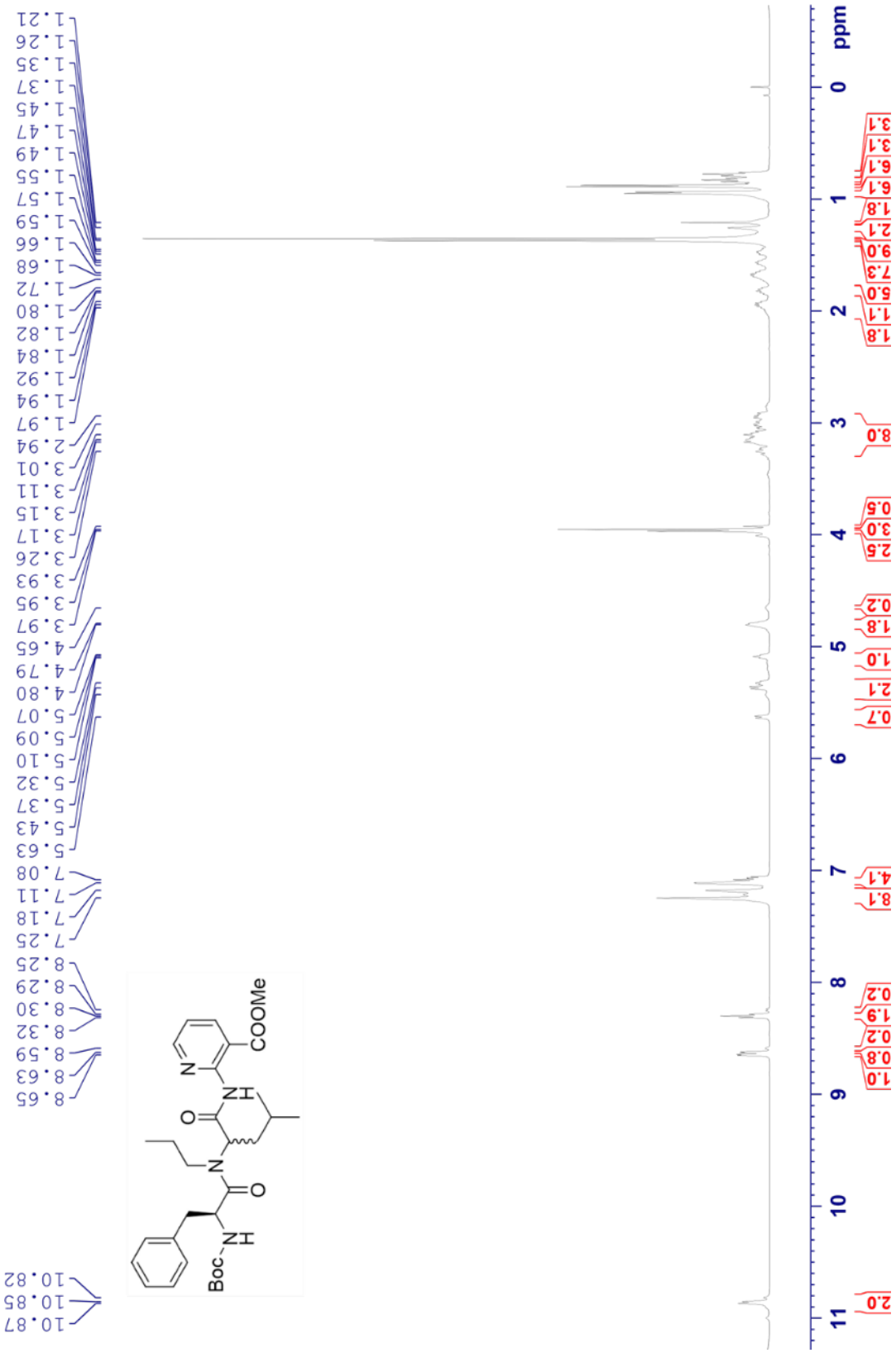
tert-Butyl ((2*S*)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4c – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



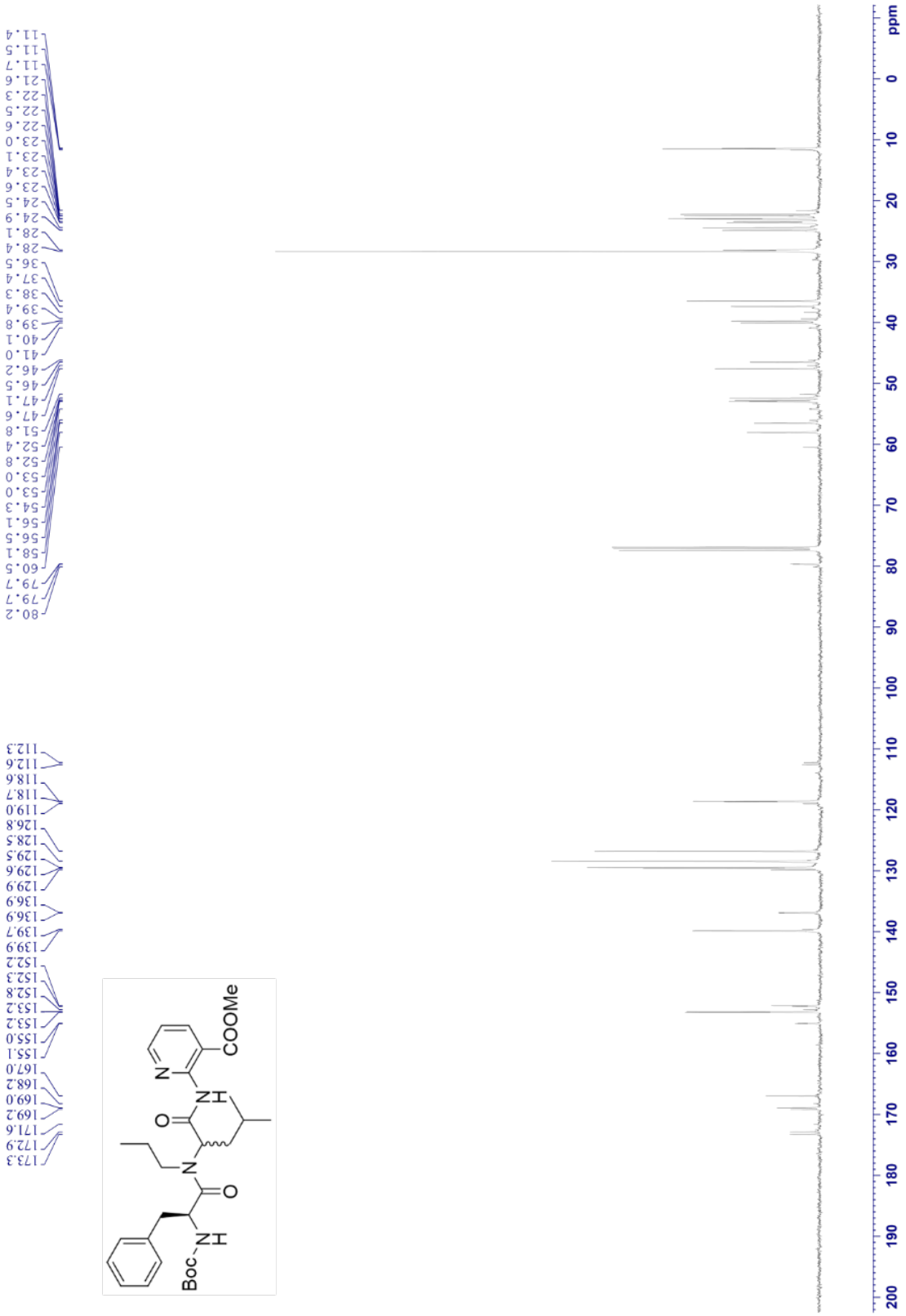
tert-Butyl ((2*S*)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **4c**
– ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



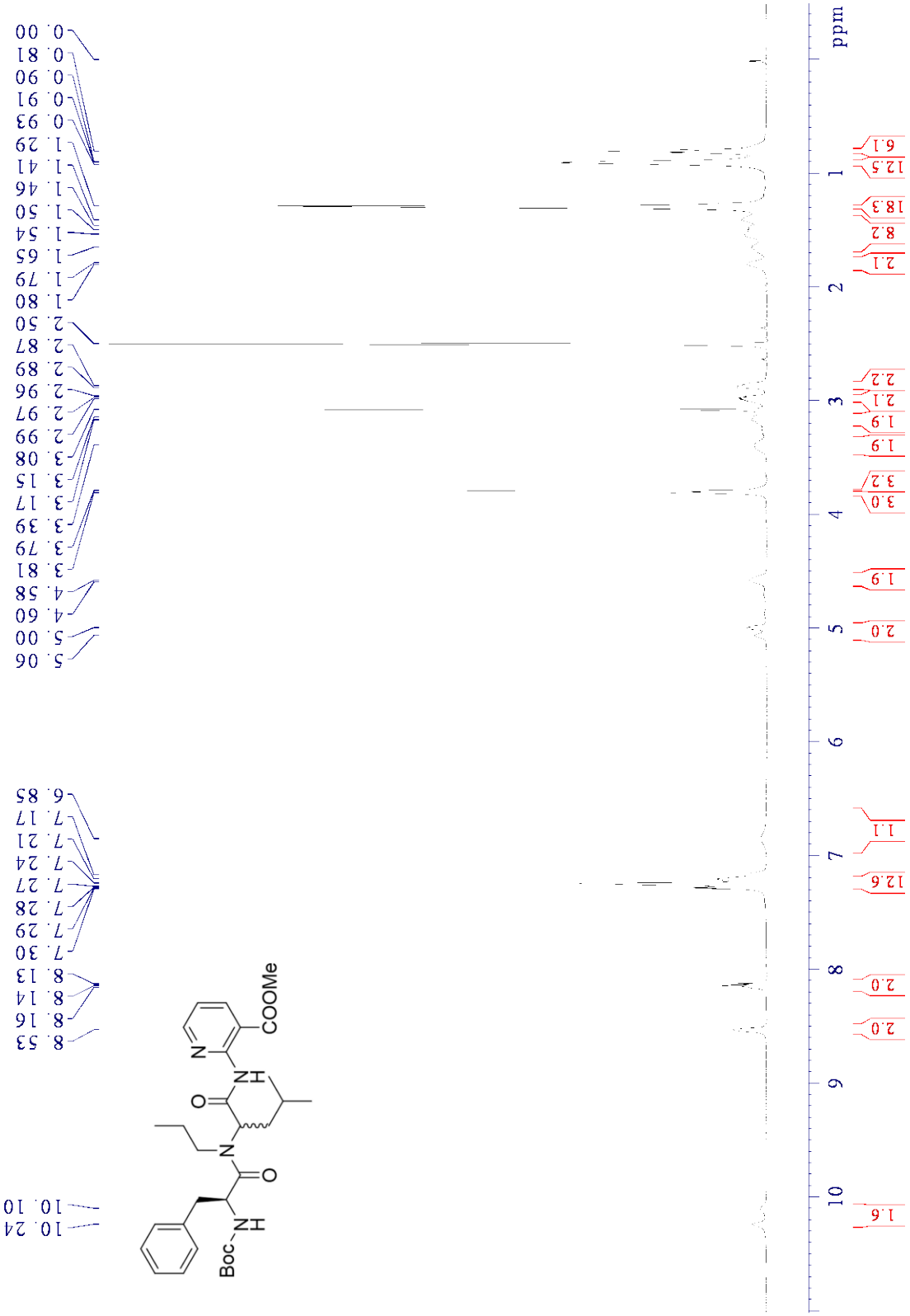
Methyl 2-(2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenyl-*N*-propylpropanamido)-4-methylpentanamido)nicotinate **4d – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



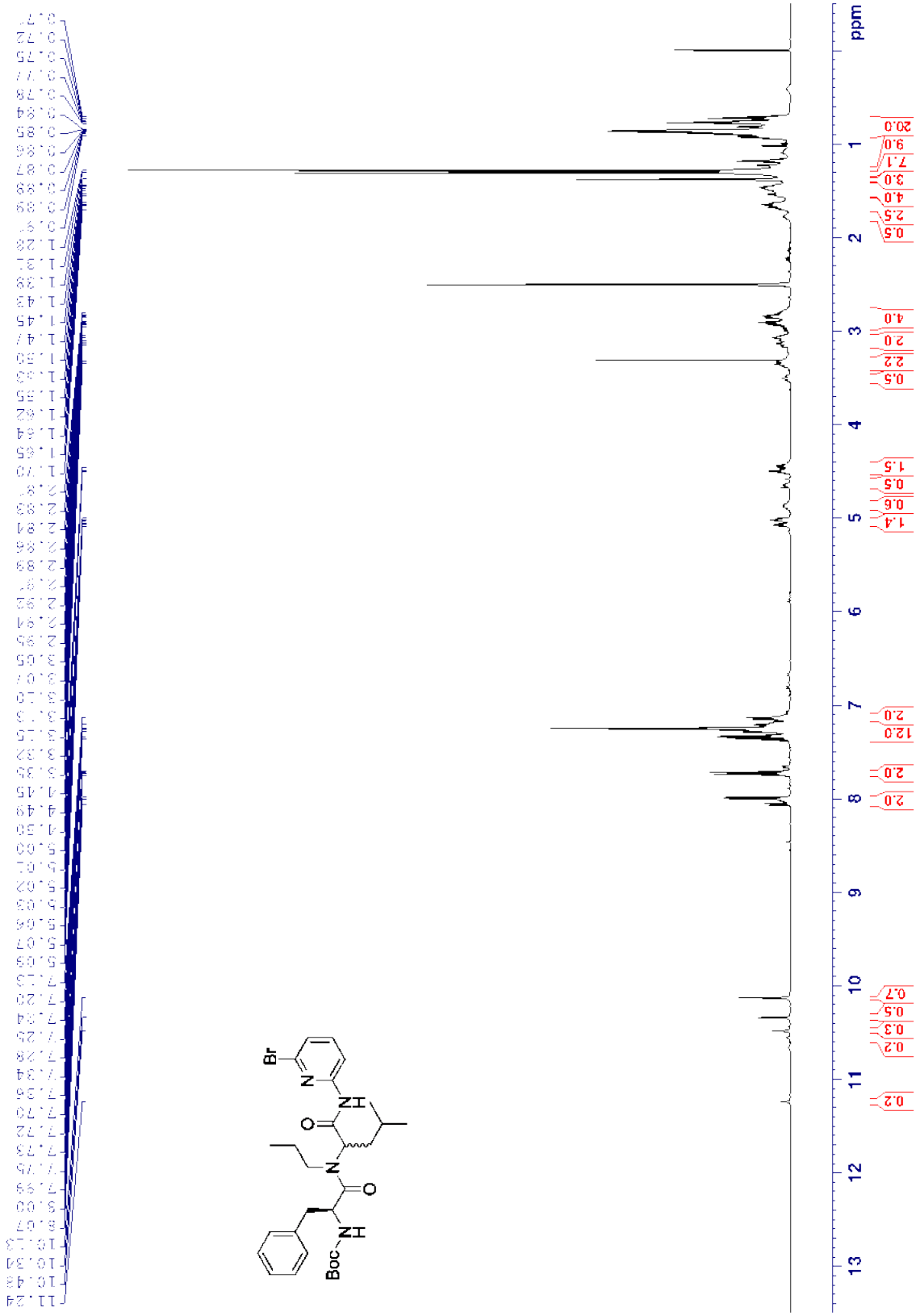
Methyl 2-(2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenyl-*N*-propylpropanamido)-4-methylpentanamido)nicotinate **4d – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



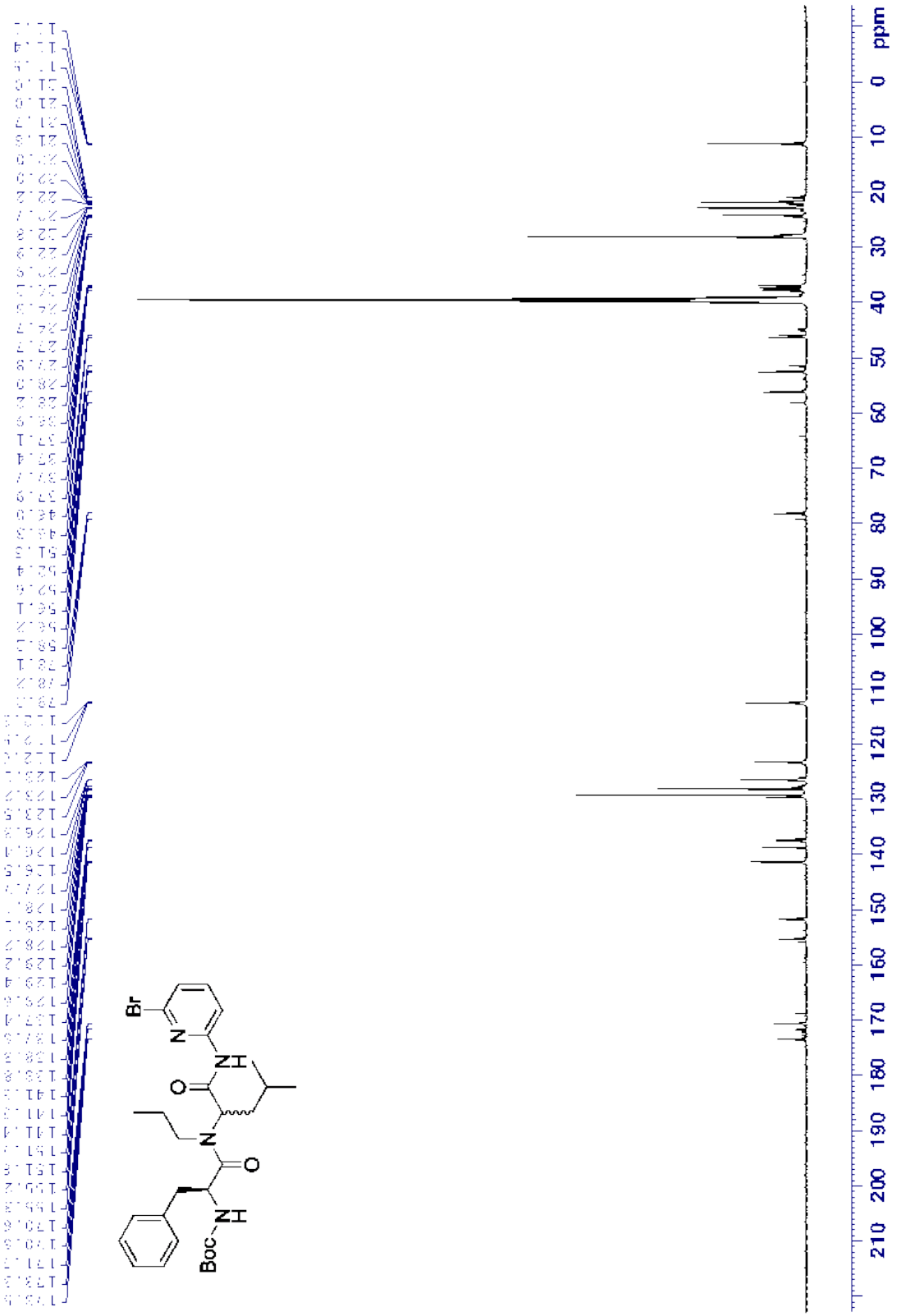
Methyl 2-(2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenyl-*N*-propylpropanamido)-4-methylpentanamido)nicotinate **4d – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



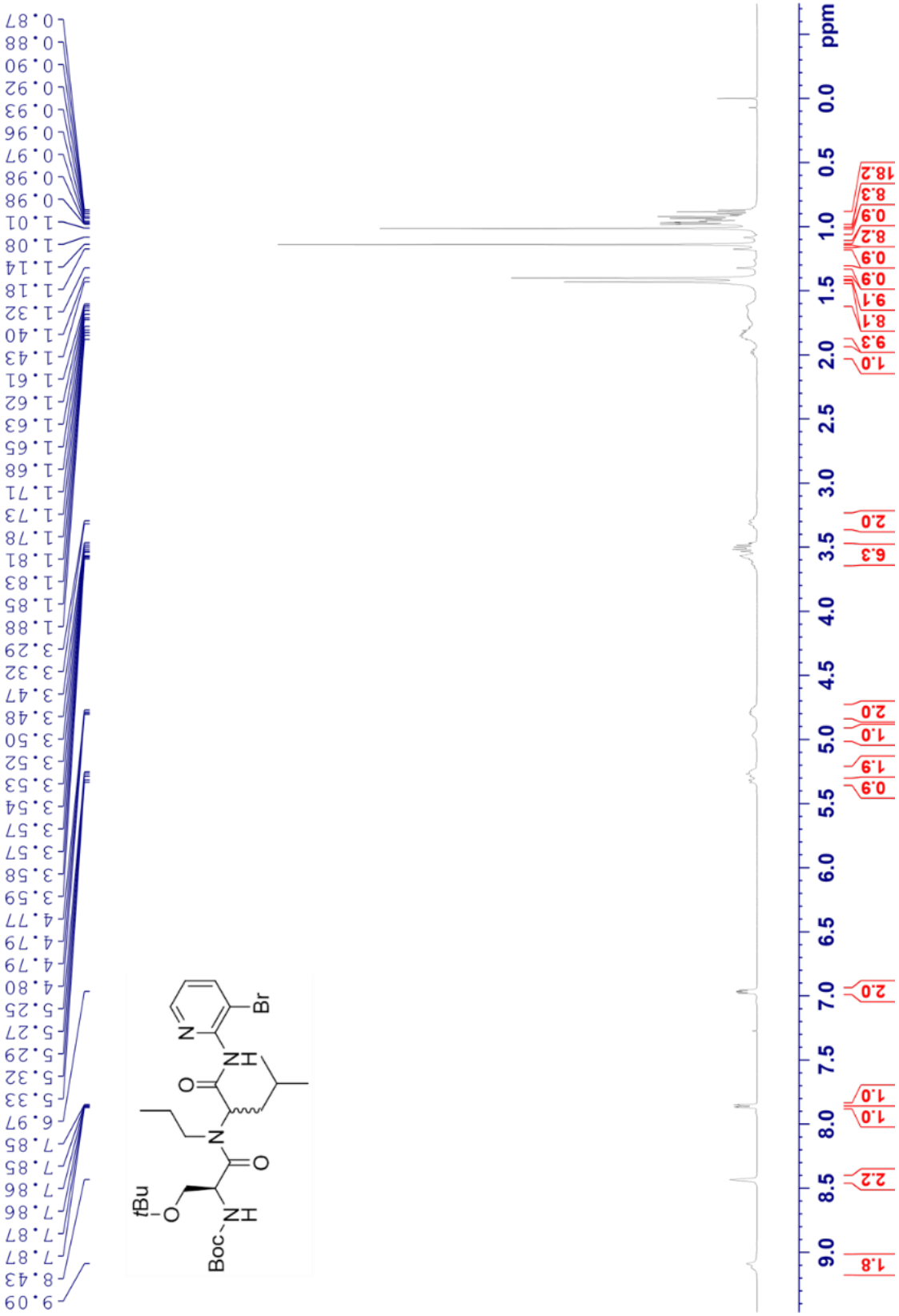
tert-Butyl ((2*S*)-1-((1-((6-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **S3** – **^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



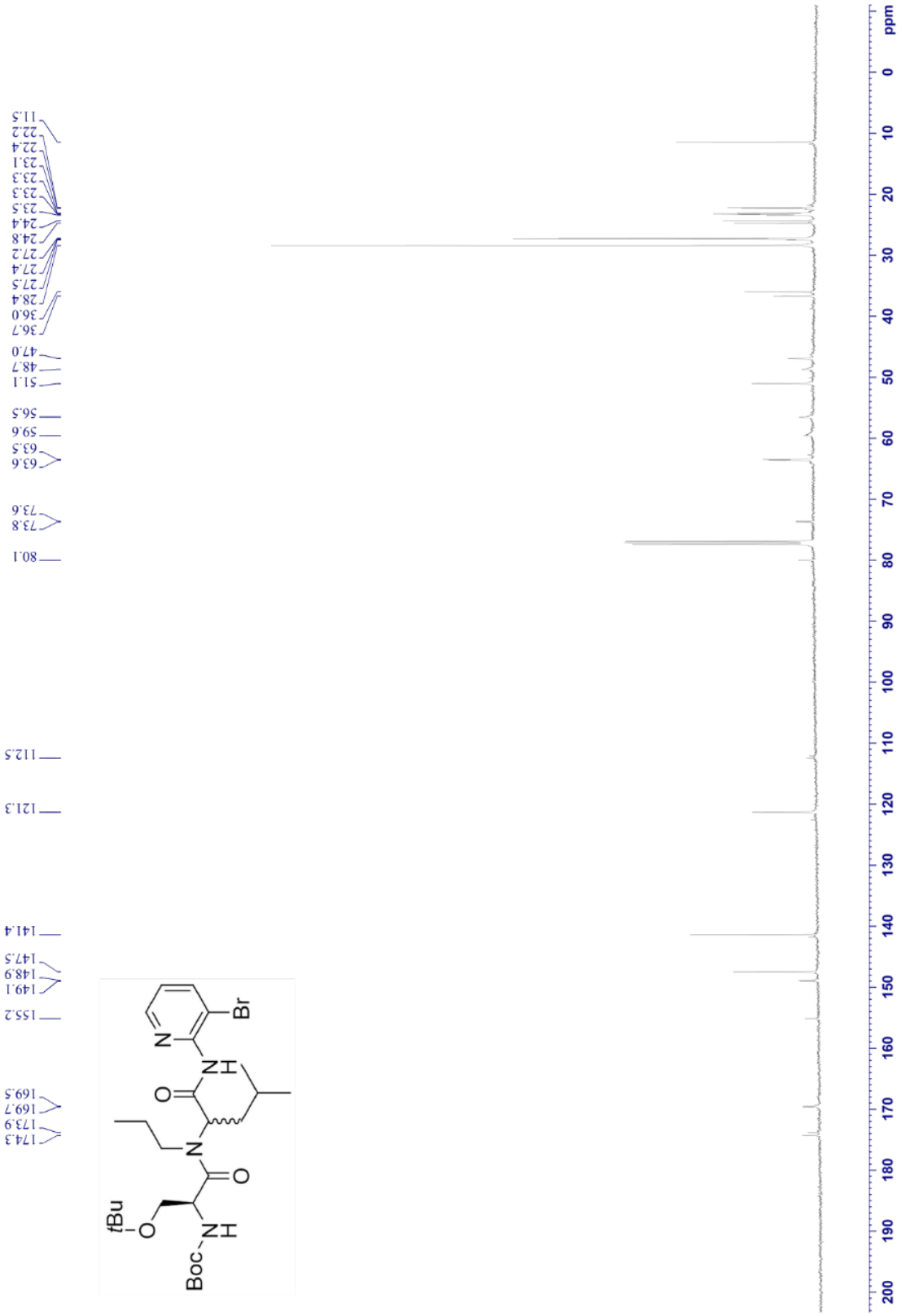
tert-Butyl ((2*S*)-1-((1-((6-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **S3** – **^{13}C NMR (126 MHz,DMSO-d_6, mixture of diastereomers and rotamers)**



tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate **5a – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**

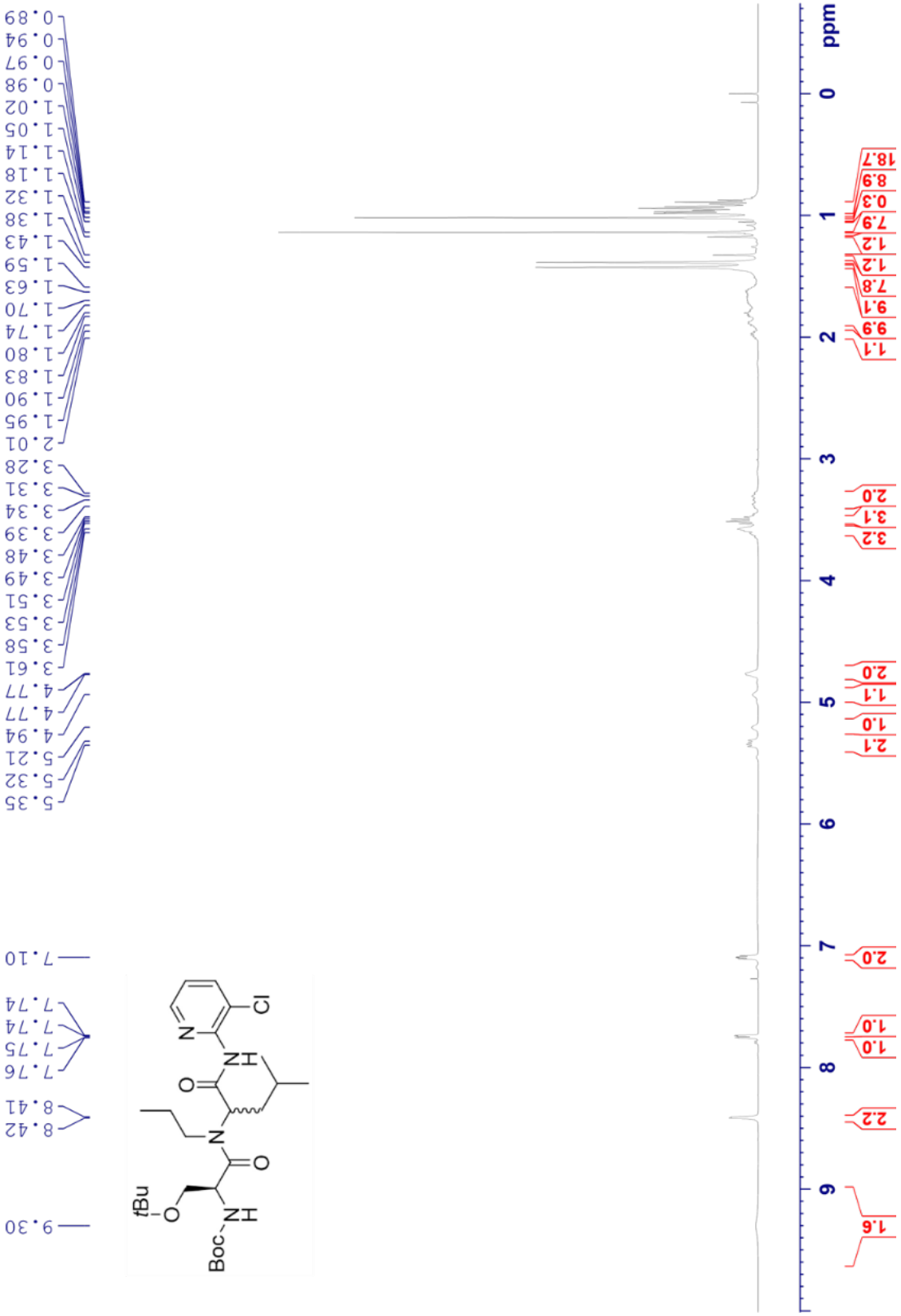


tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate **5a – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**

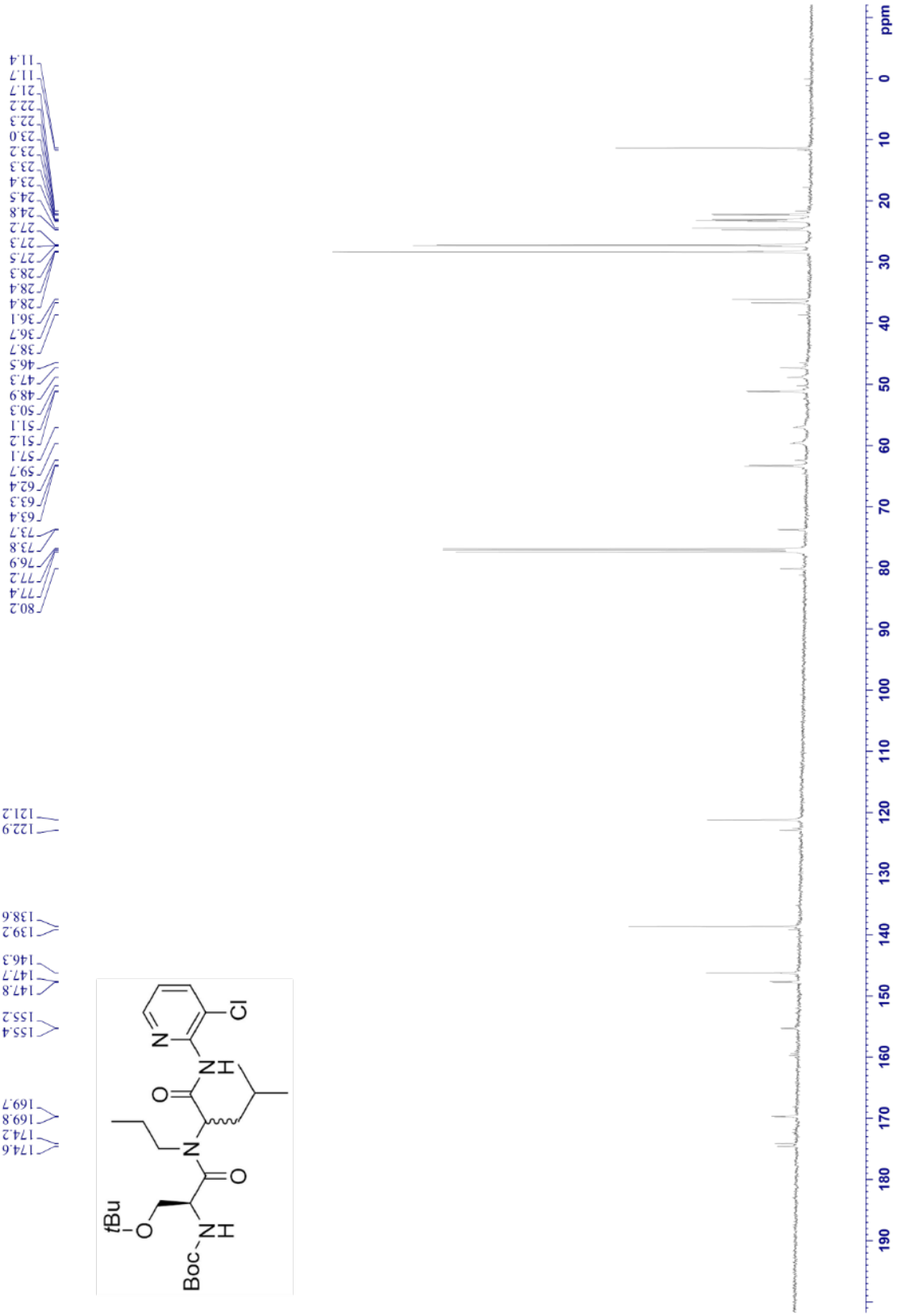


tert-Butyl ((2*S*)-1-((1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate **5a – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**

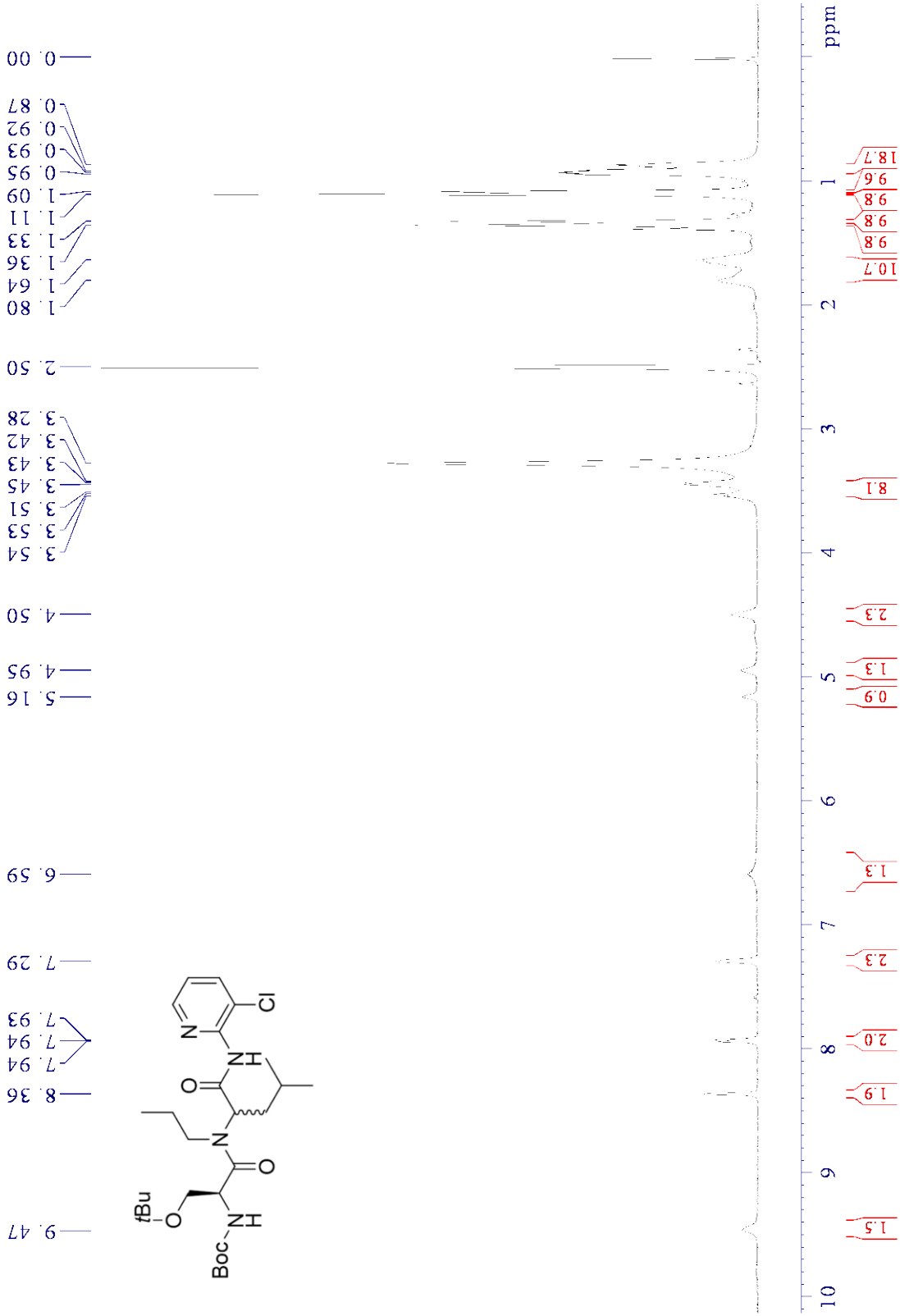
tert-Butyl ((2*S*)-3-(*tert*-butoxy)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5b – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



tert-Butyl ((2*S*)-3-(*tert*-butoxy)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5b – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**

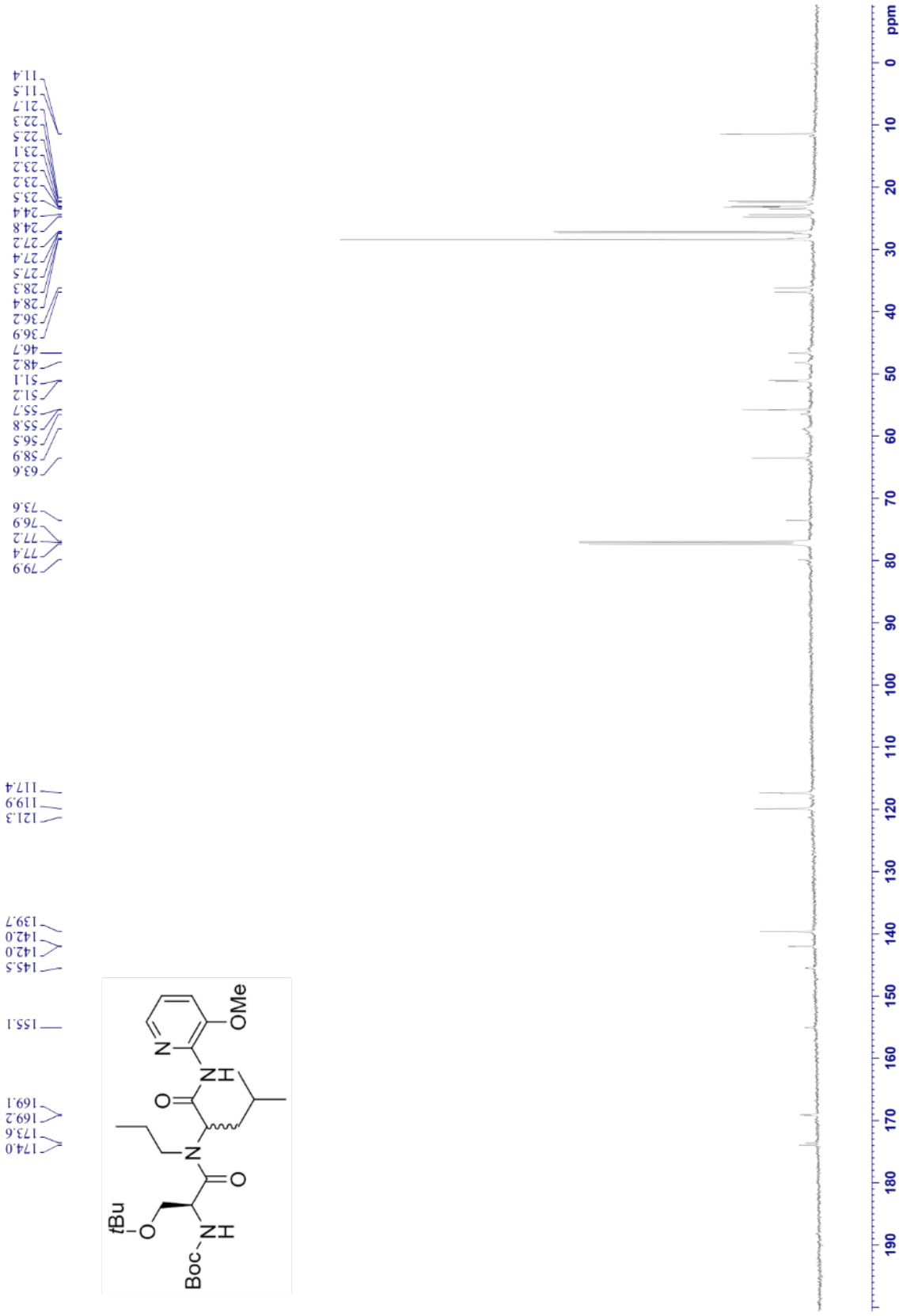


tert-Butyl ((2*S*)-3-(*tert*-butoxy)-1-((1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5b – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**

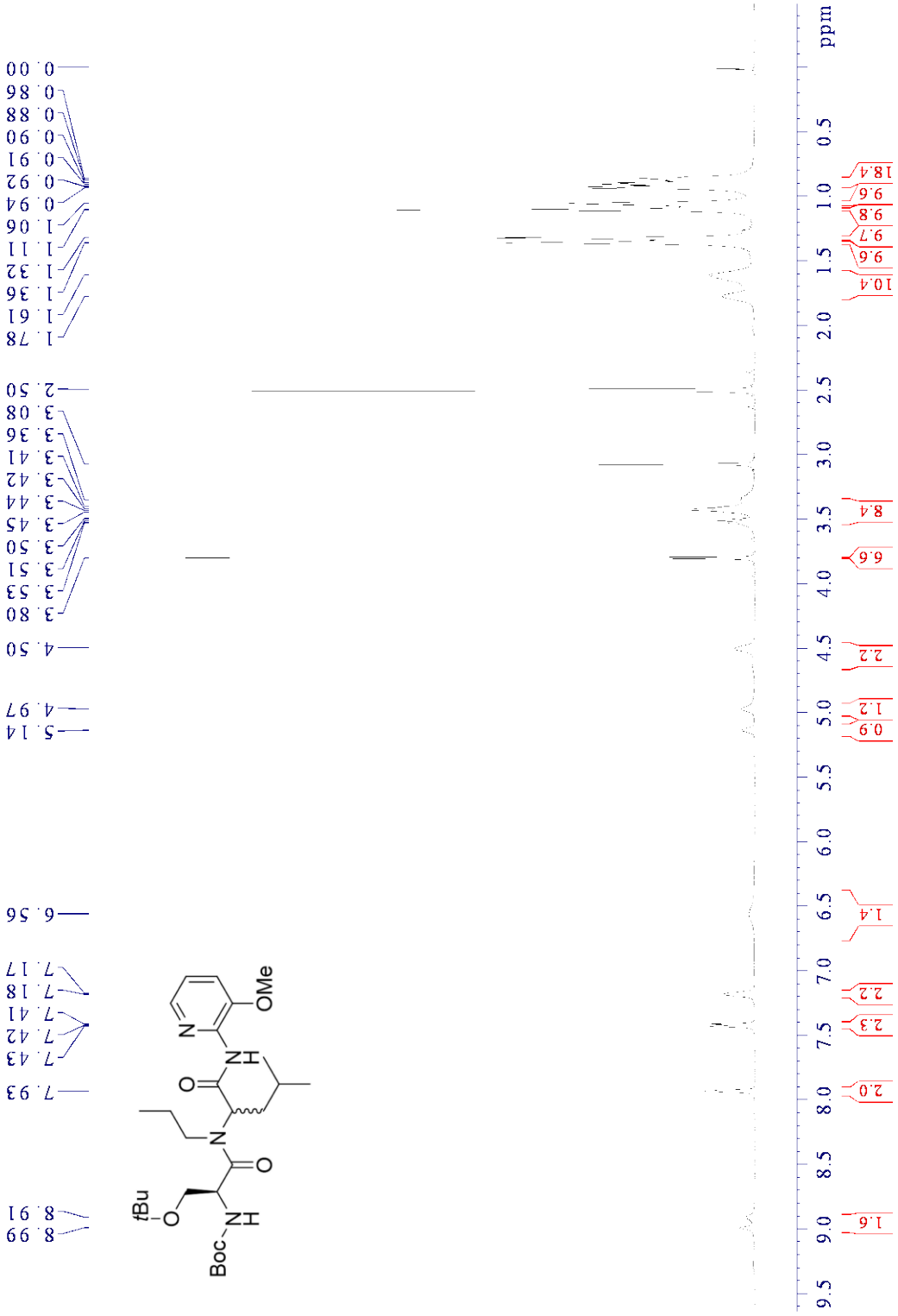


tert-Butyl ((2*S*)-3-*(tert*-butoxy)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5c – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**

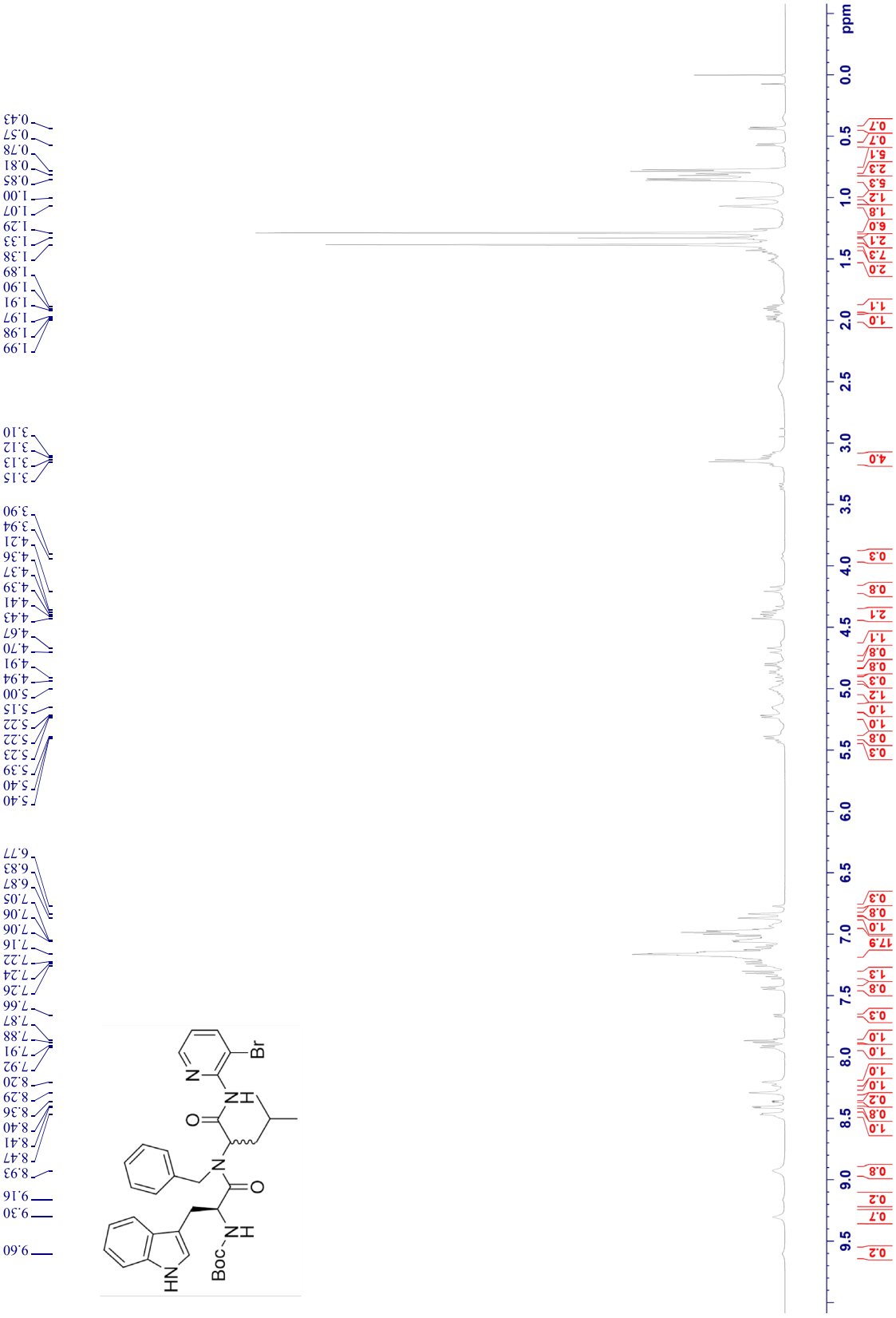
tert-Butyl ((2*S*)-3-*(tert*-butoxy)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5c – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**



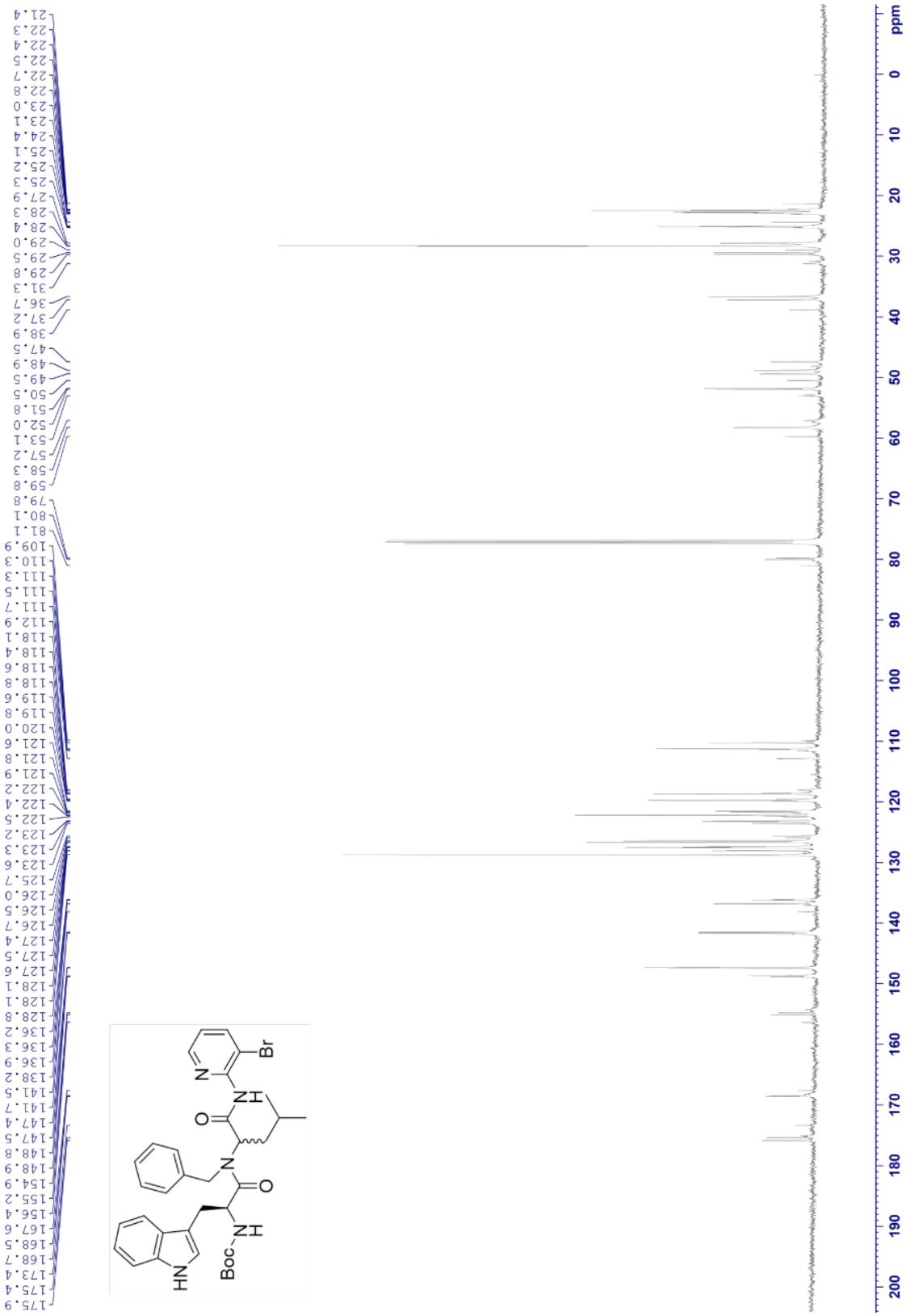
tert-Butyl ((2*S*)-3-*(tert*-butoxy)-1-((1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)(propyl)amino)-1-oxopropan-2-yl)carbamate **5c – ^{1}H NMR (500 MHz,DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



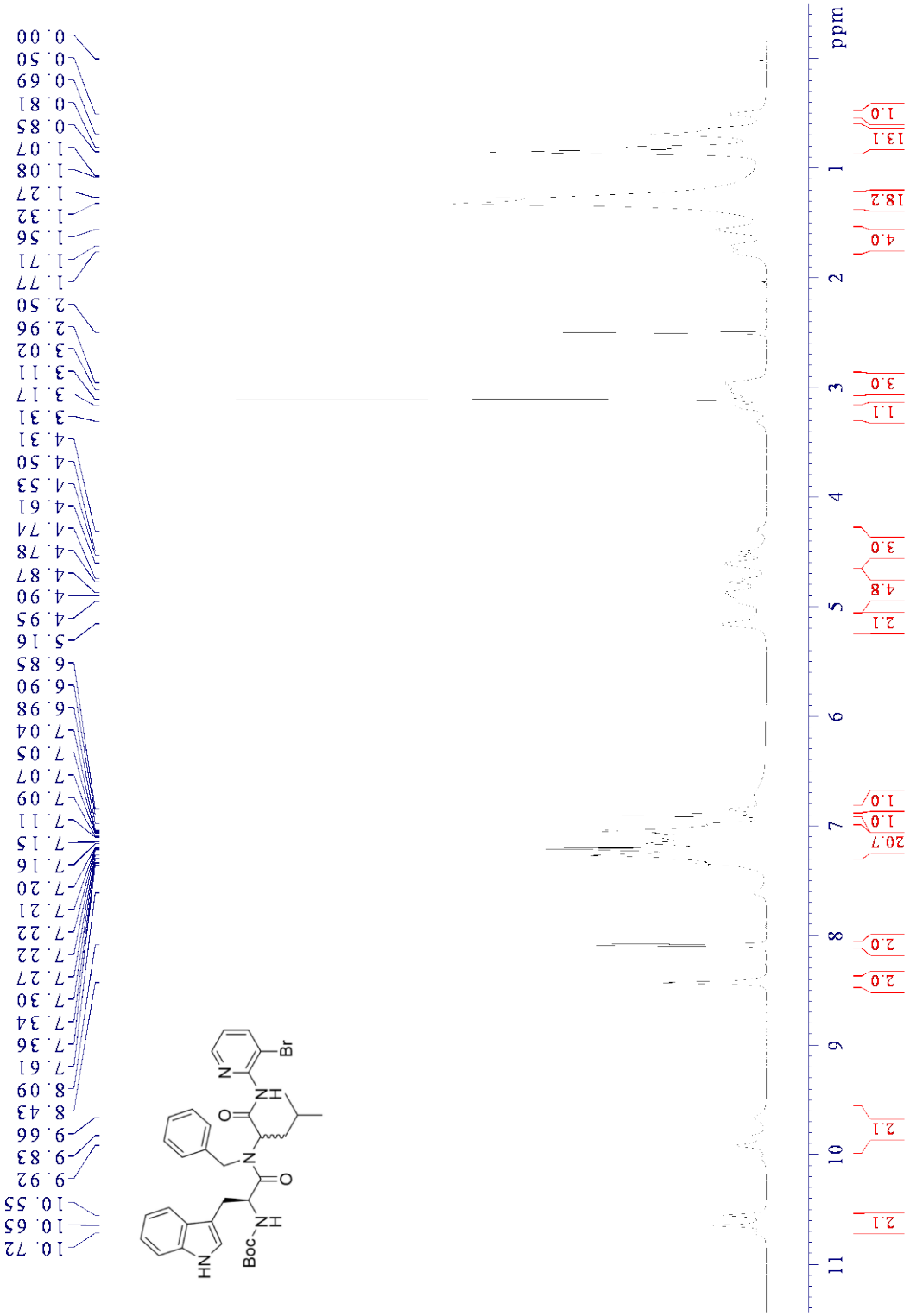
tert-Butyl ((2*S*)-1-(benzyl(1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6a – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



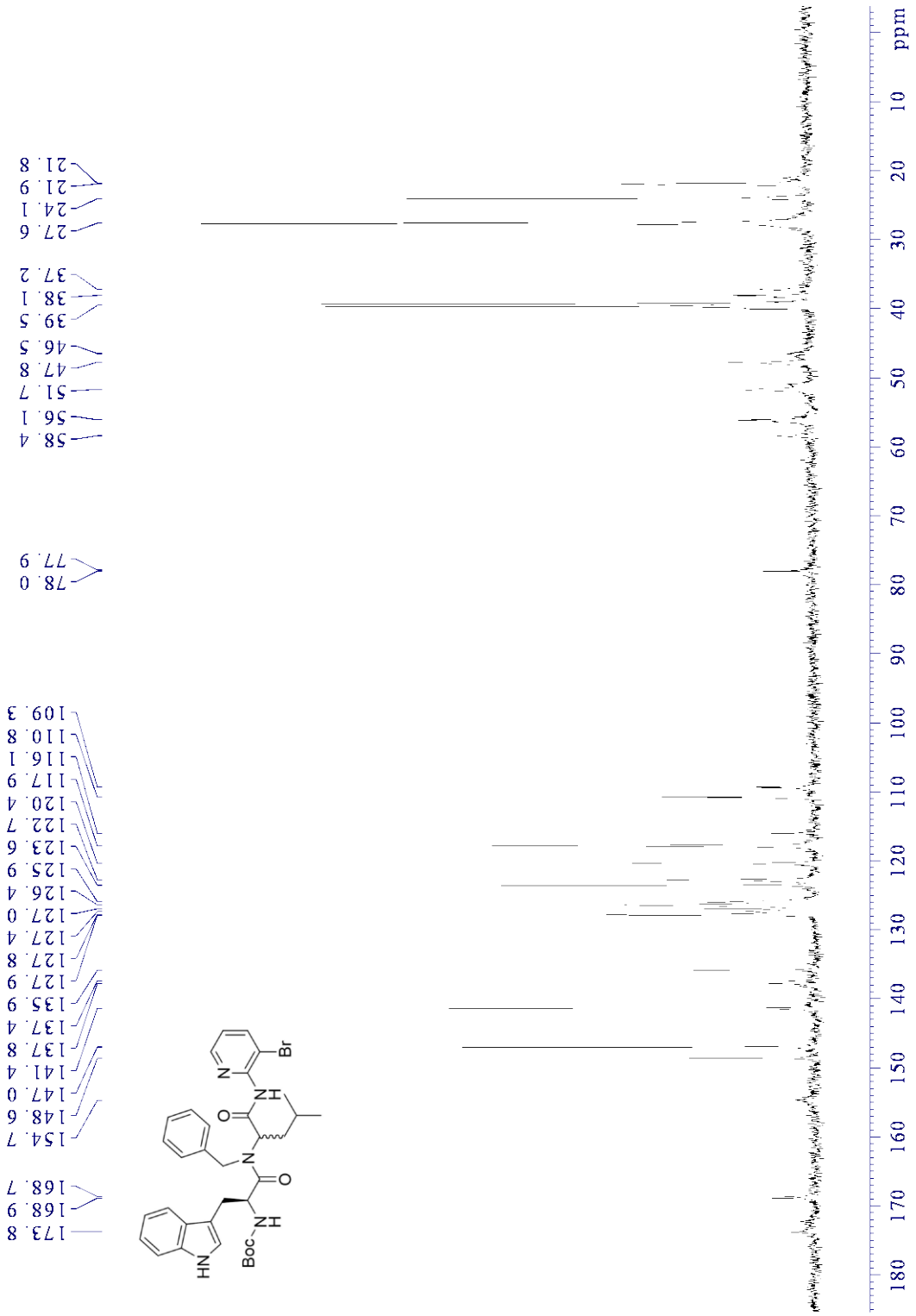
tert-Butyl ((2*S*)-1-(benzyl(1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6a – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



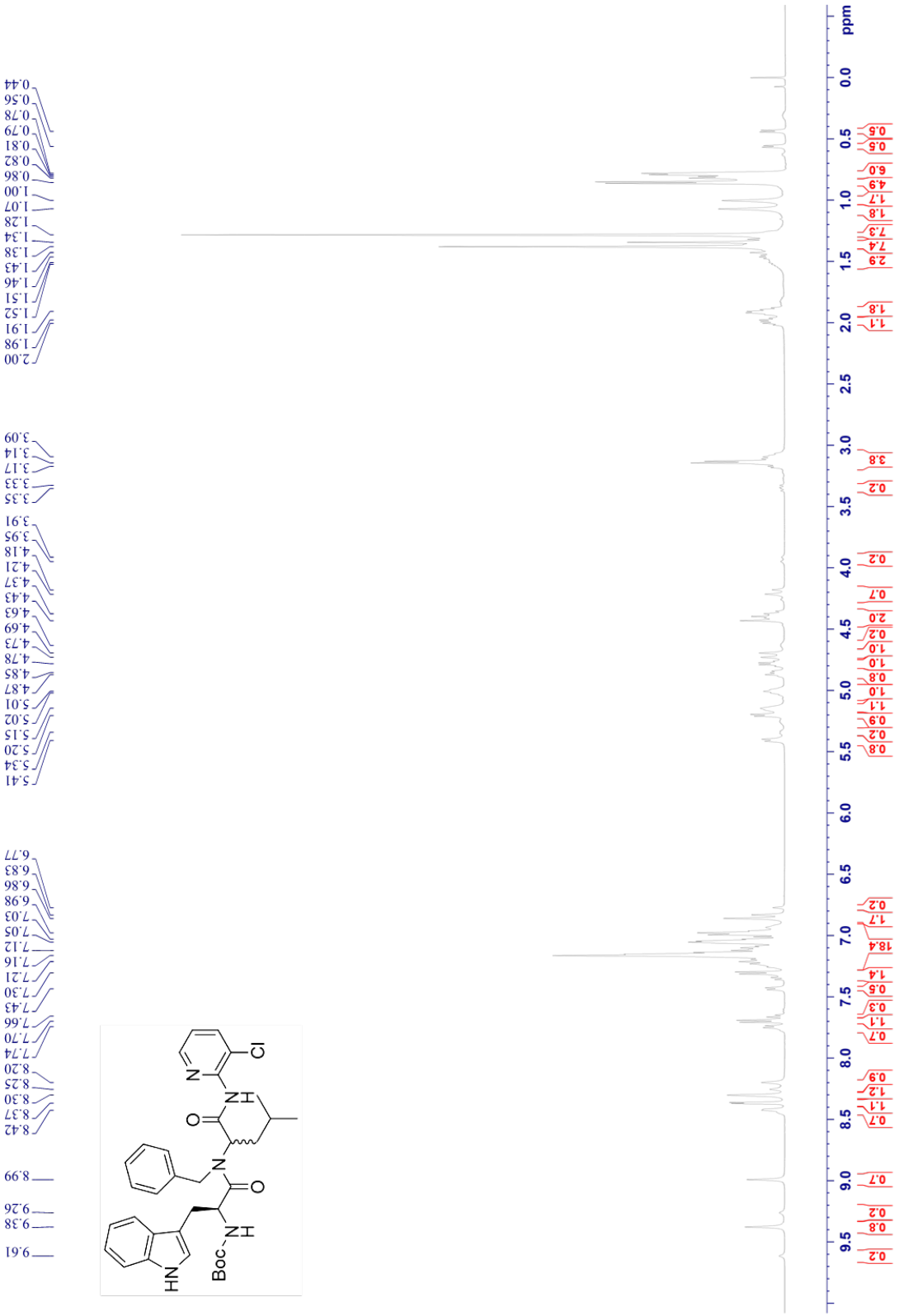
tert-Butyl ((2*S*)-1-(benzyl(1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6a – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



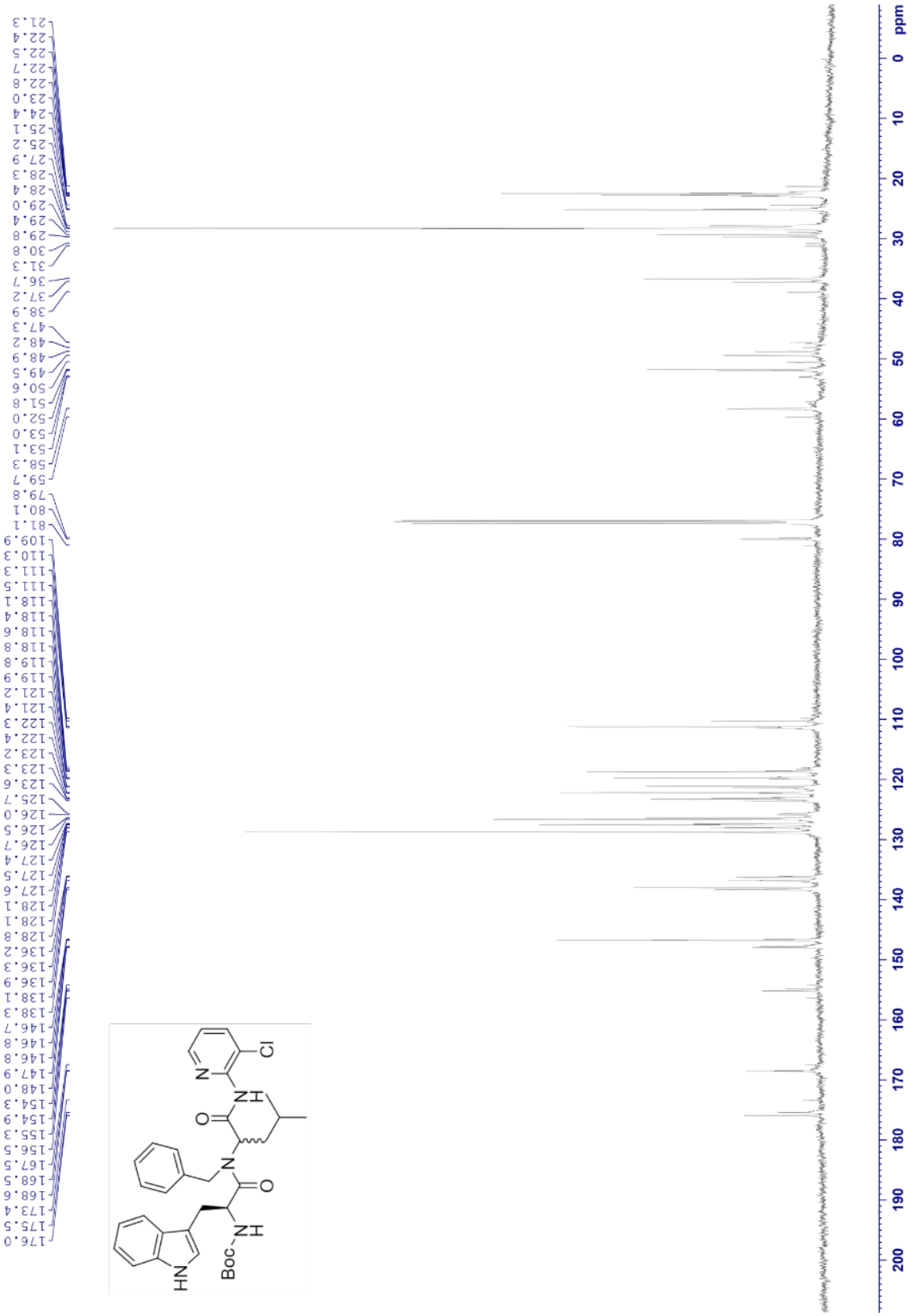
tert-Butyl ((2*S*)-1-(benzyl(1-((3-bromopyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6a – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



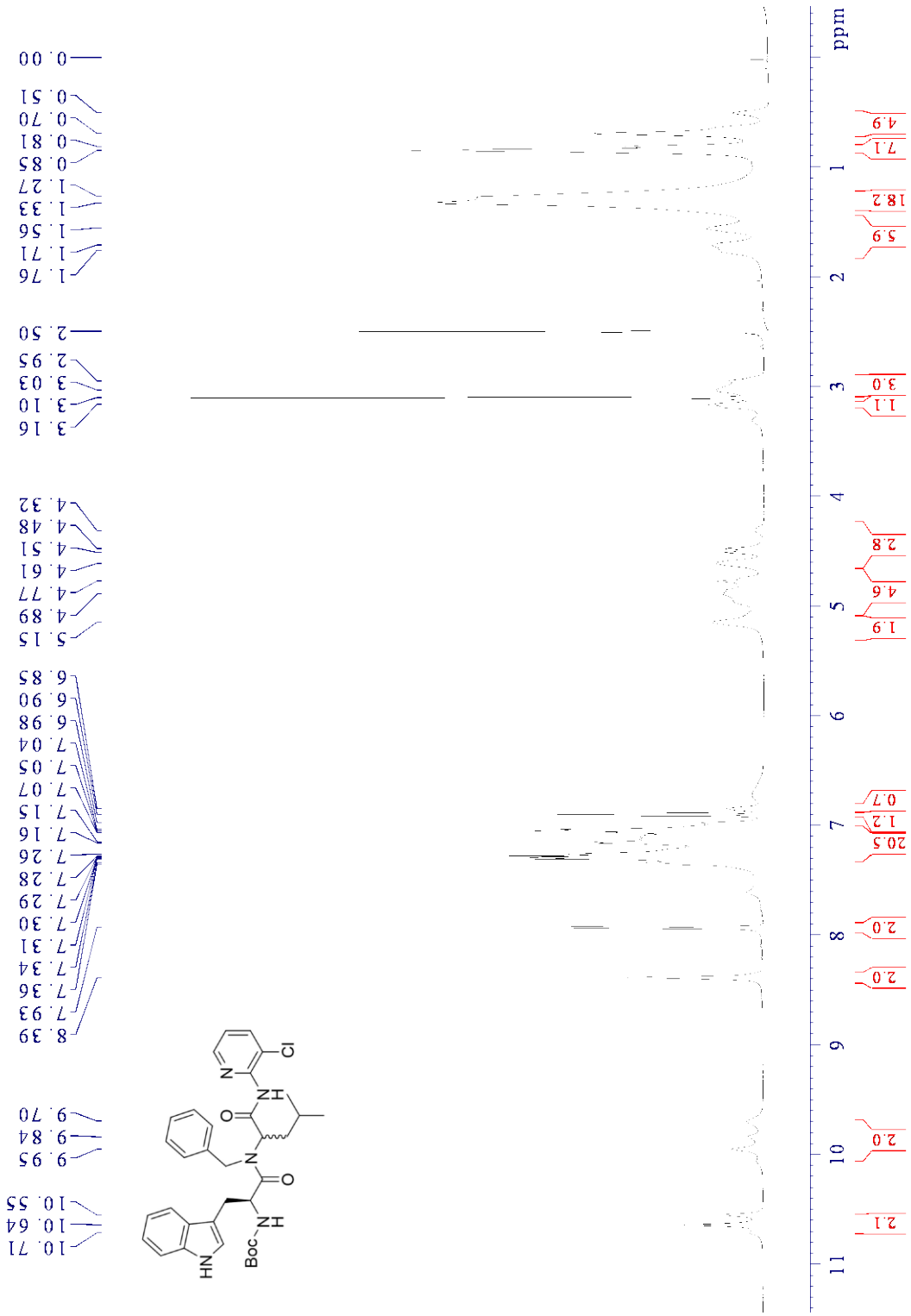
tert-Butyl ((2*S*)-1-(benzyl(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6b – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



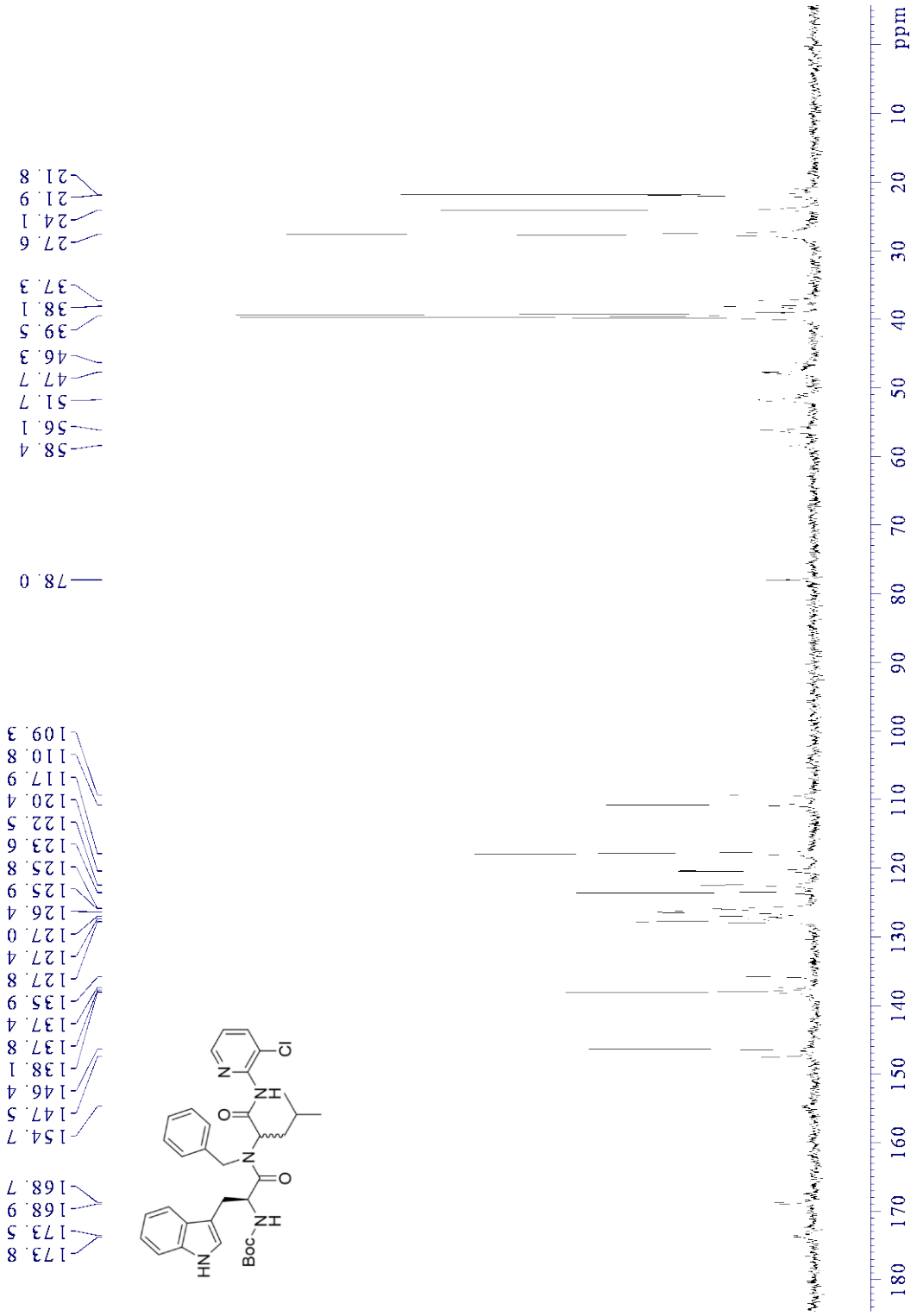
tert-Butyl ((2*S*)-1-(benzyl(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6b – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



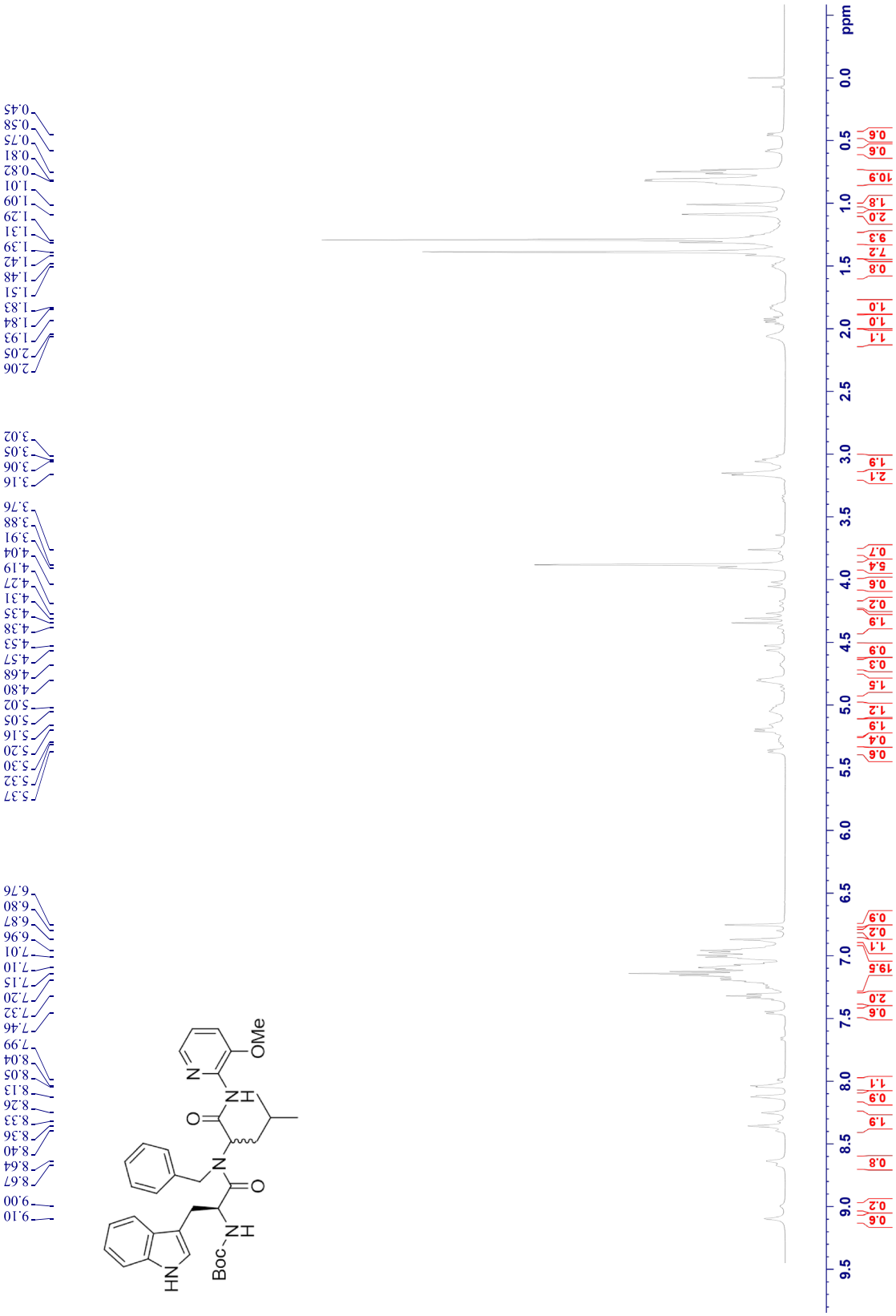
tert-Butyl ((2*S*)-1-(benzyl(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6b – ^{1}H NMR (500 MHz, DMSO-*d*$_6$, 80 °C, mixture of diastereomers in a 1:1 ratio)**



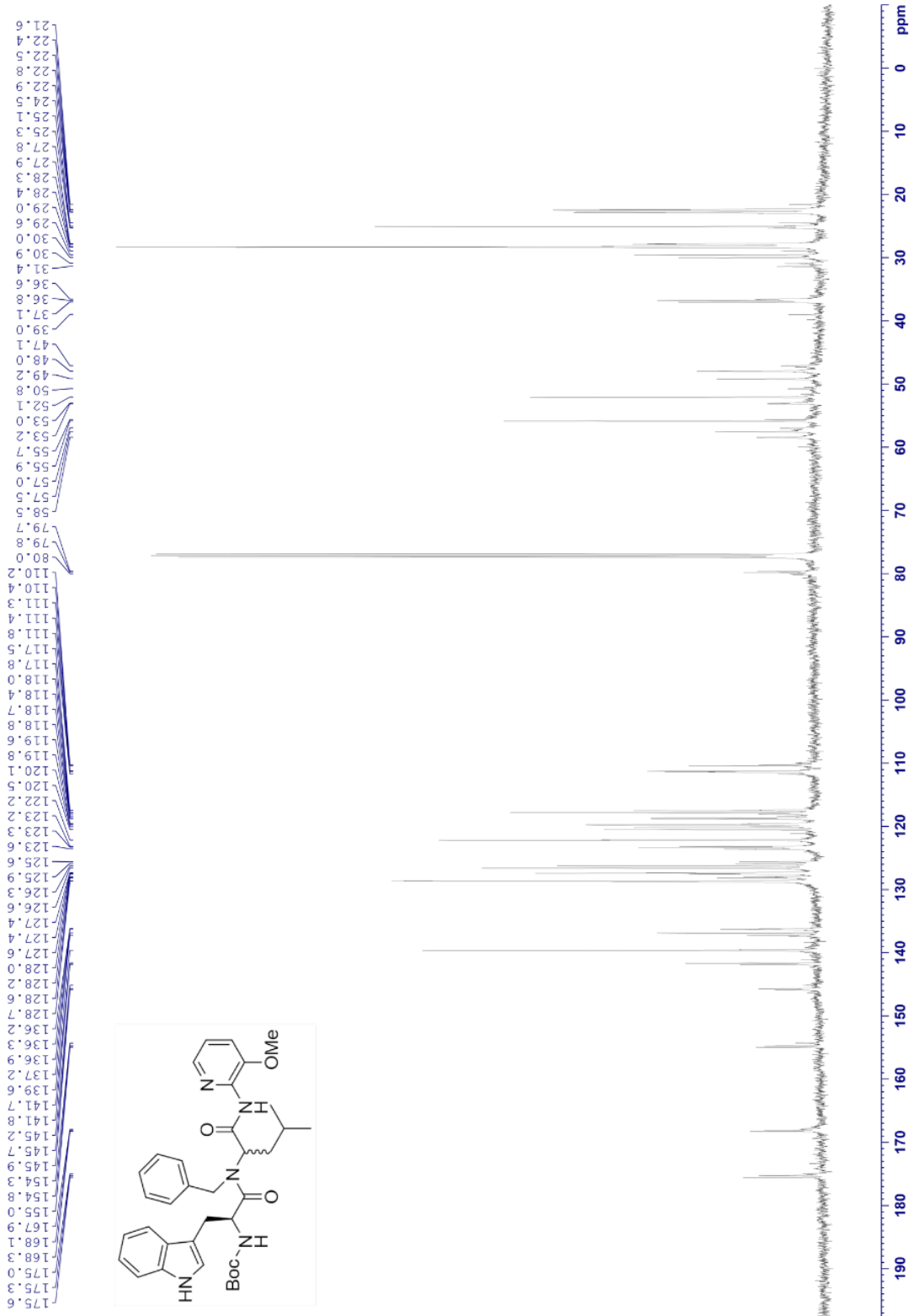
tert-Butyl ((2*S*)-1-(benzyl(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6b – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



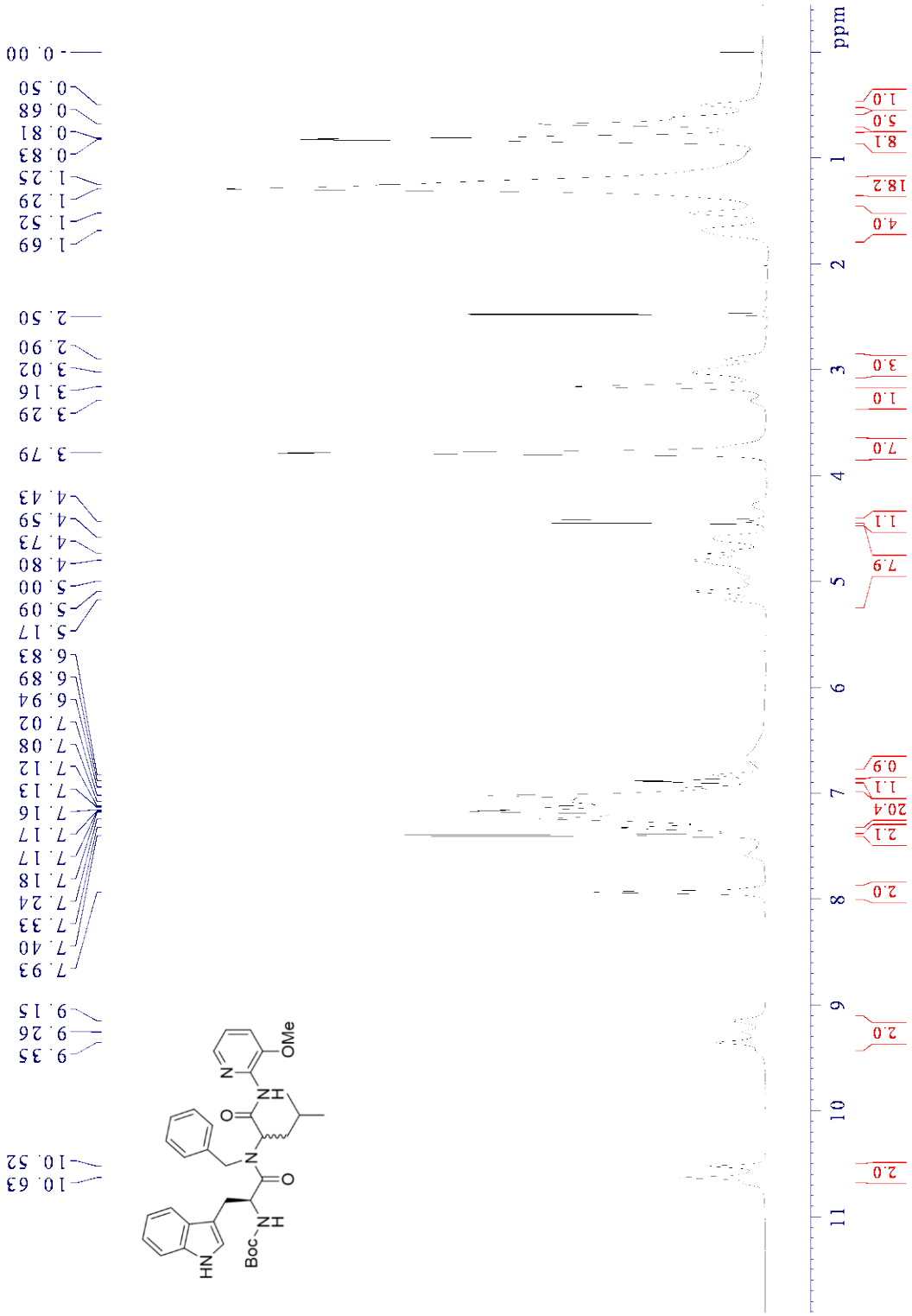
tert-Butyl ((2*S*)-1-(benzyl(1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6c – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



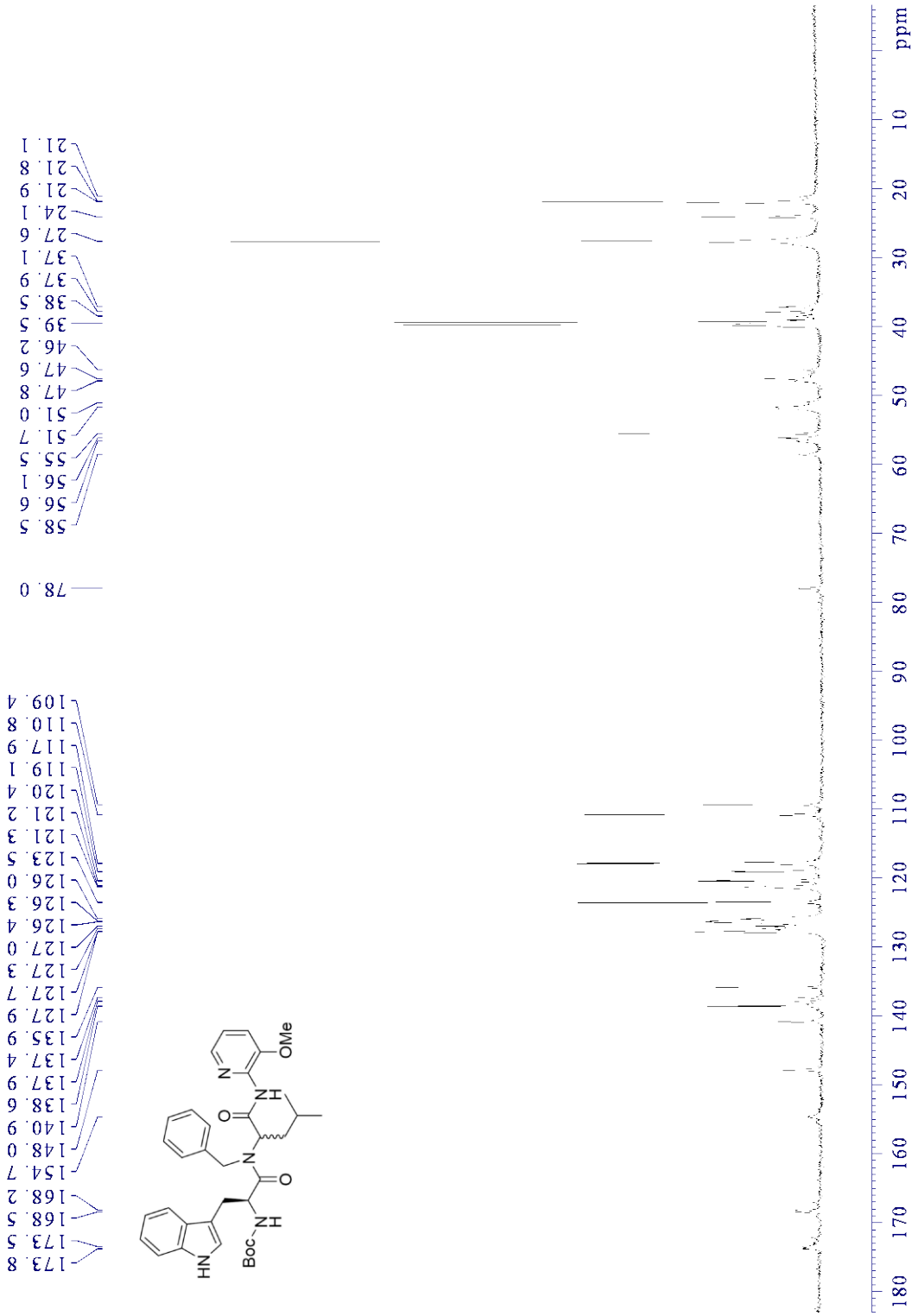
tert-Butyl ((2*S*)-1-(benzyl(1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6c – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**



tert-Butyl ((2*S*)-1-(benzyl(1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6c – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**

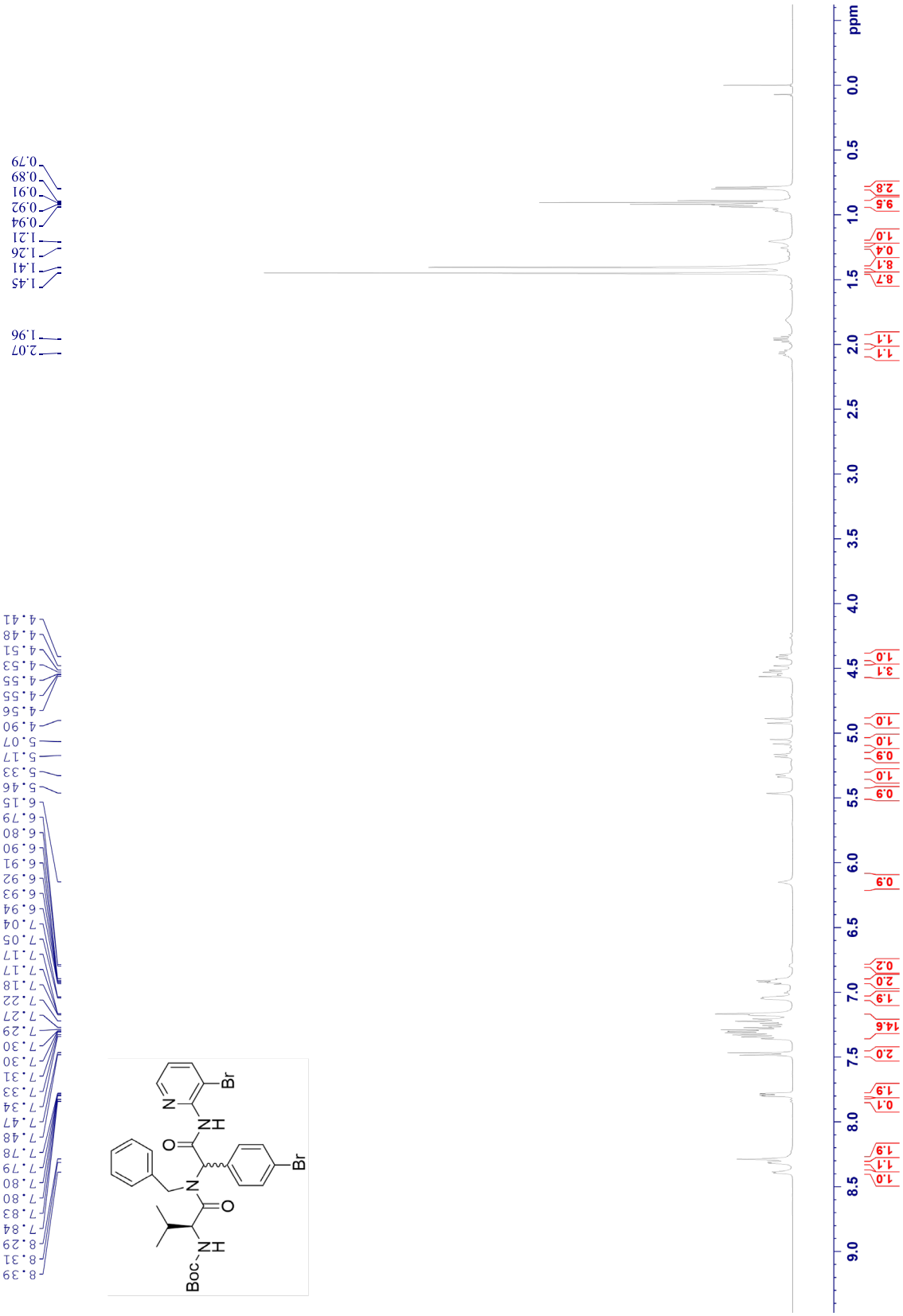


tert-Butyl ((2*S*)-1-(benzyl(1-((3-methoxypyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **6c – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



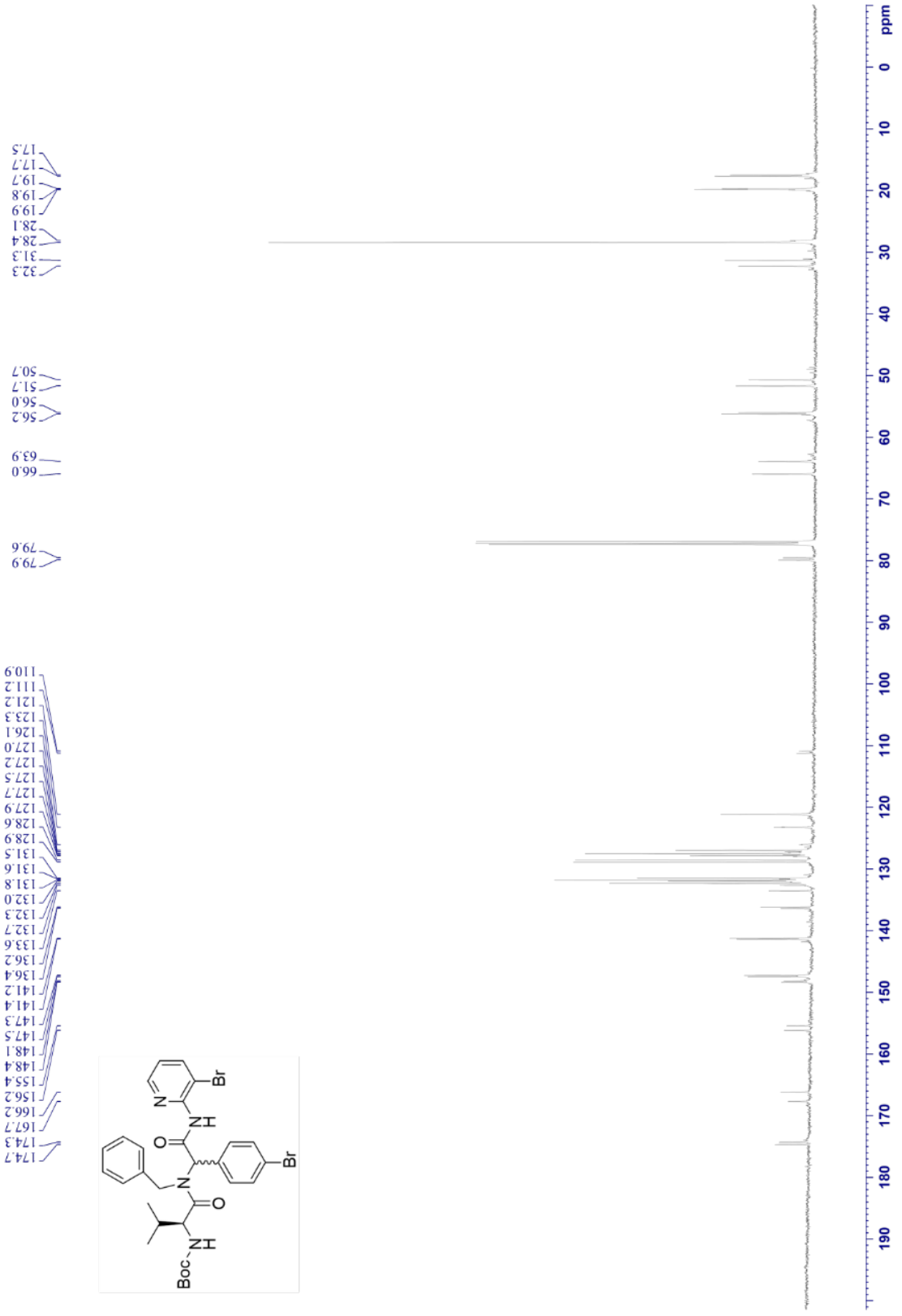
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-bromopyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

7a – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)



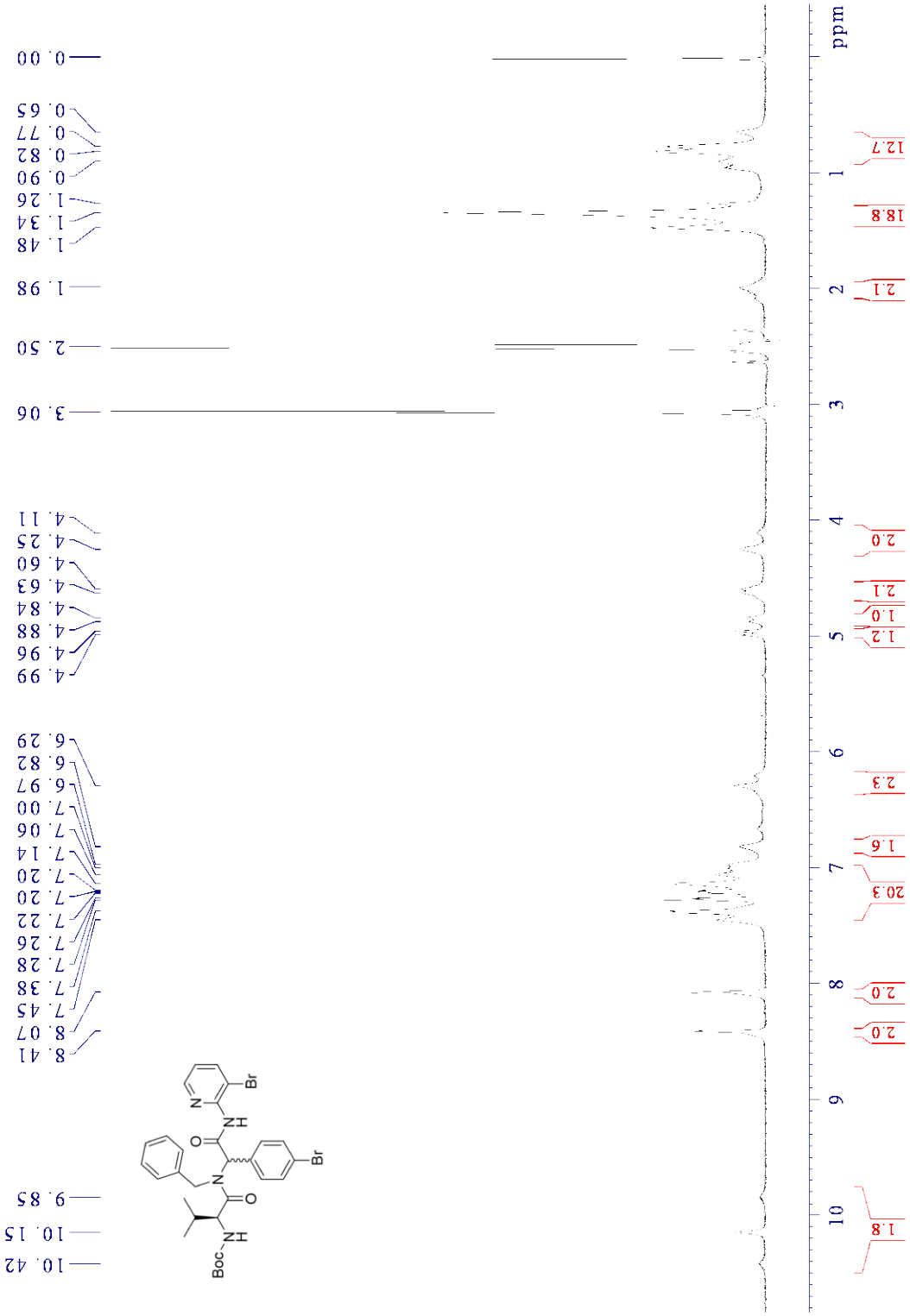
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-bromopyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

7a – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)

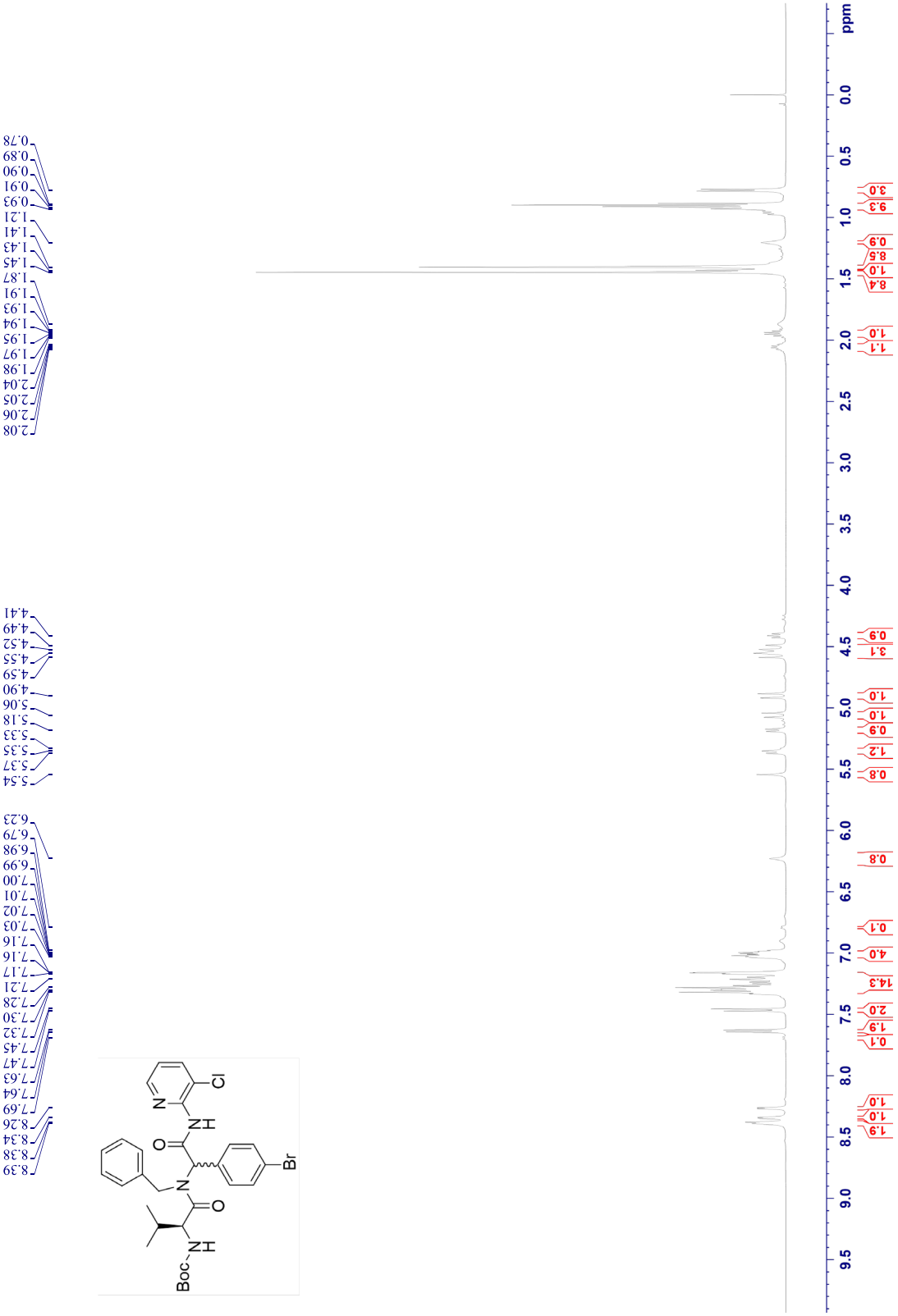


tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-bromopyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

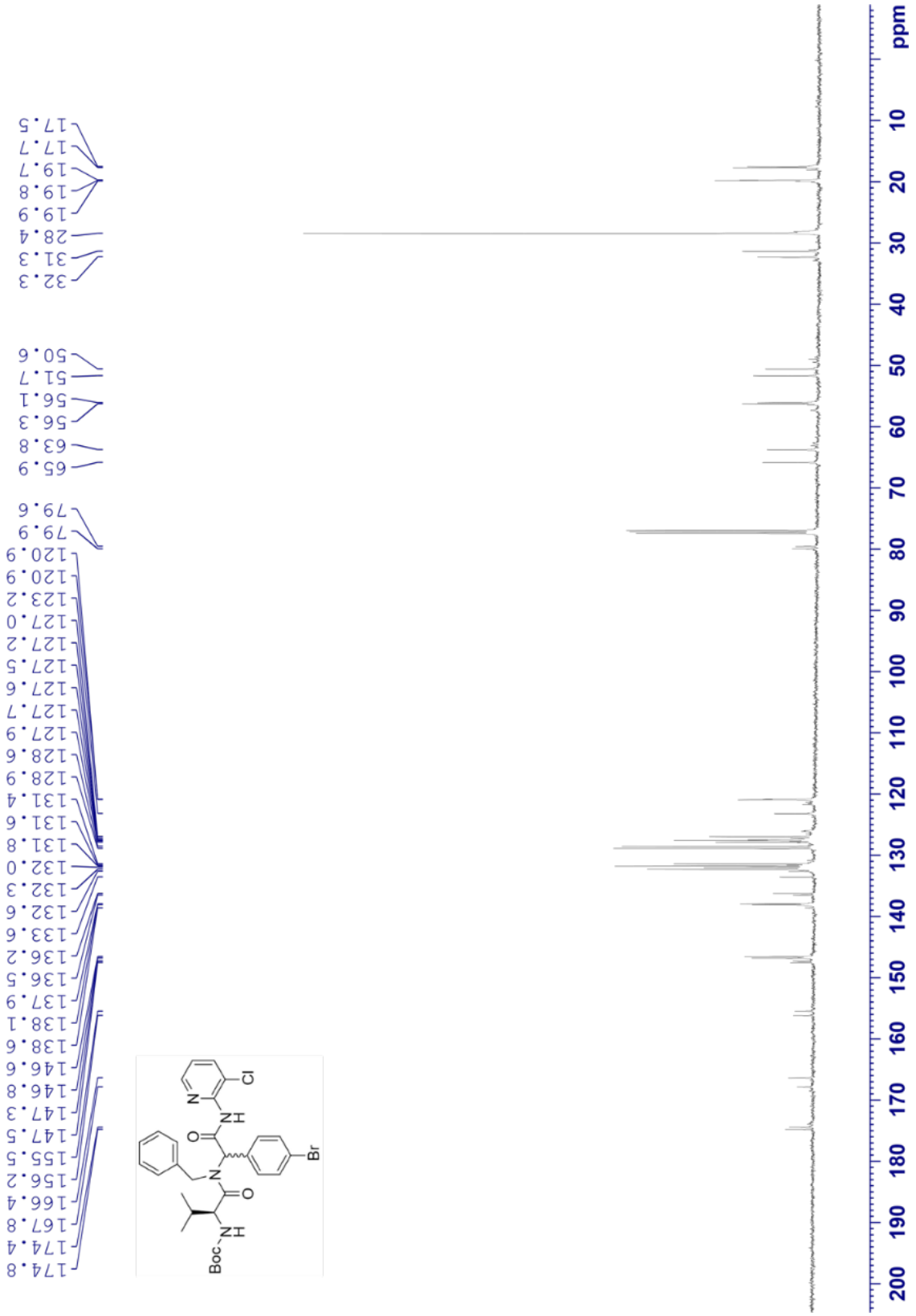
7a – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



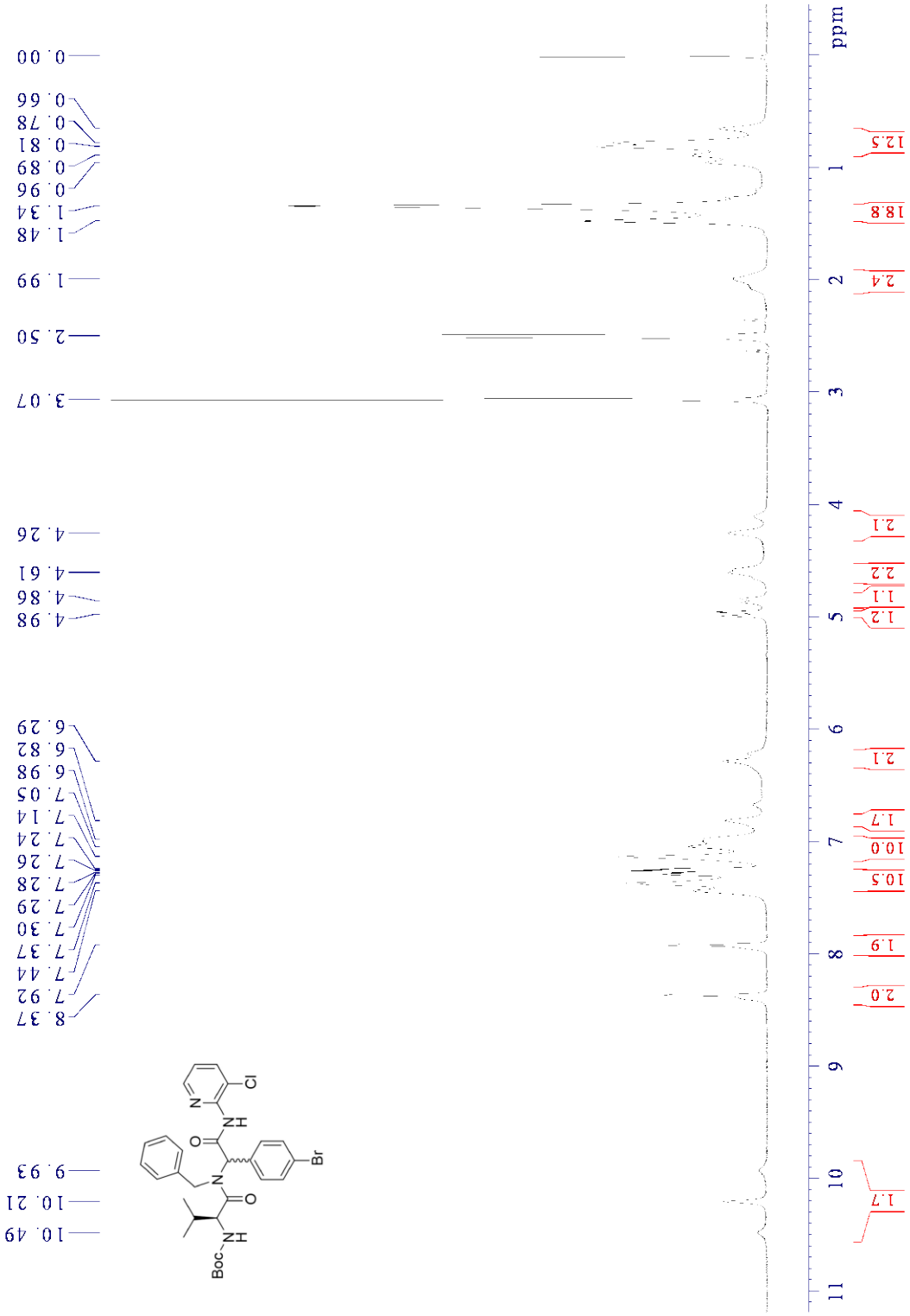
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7b – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)**



tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7b – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)**

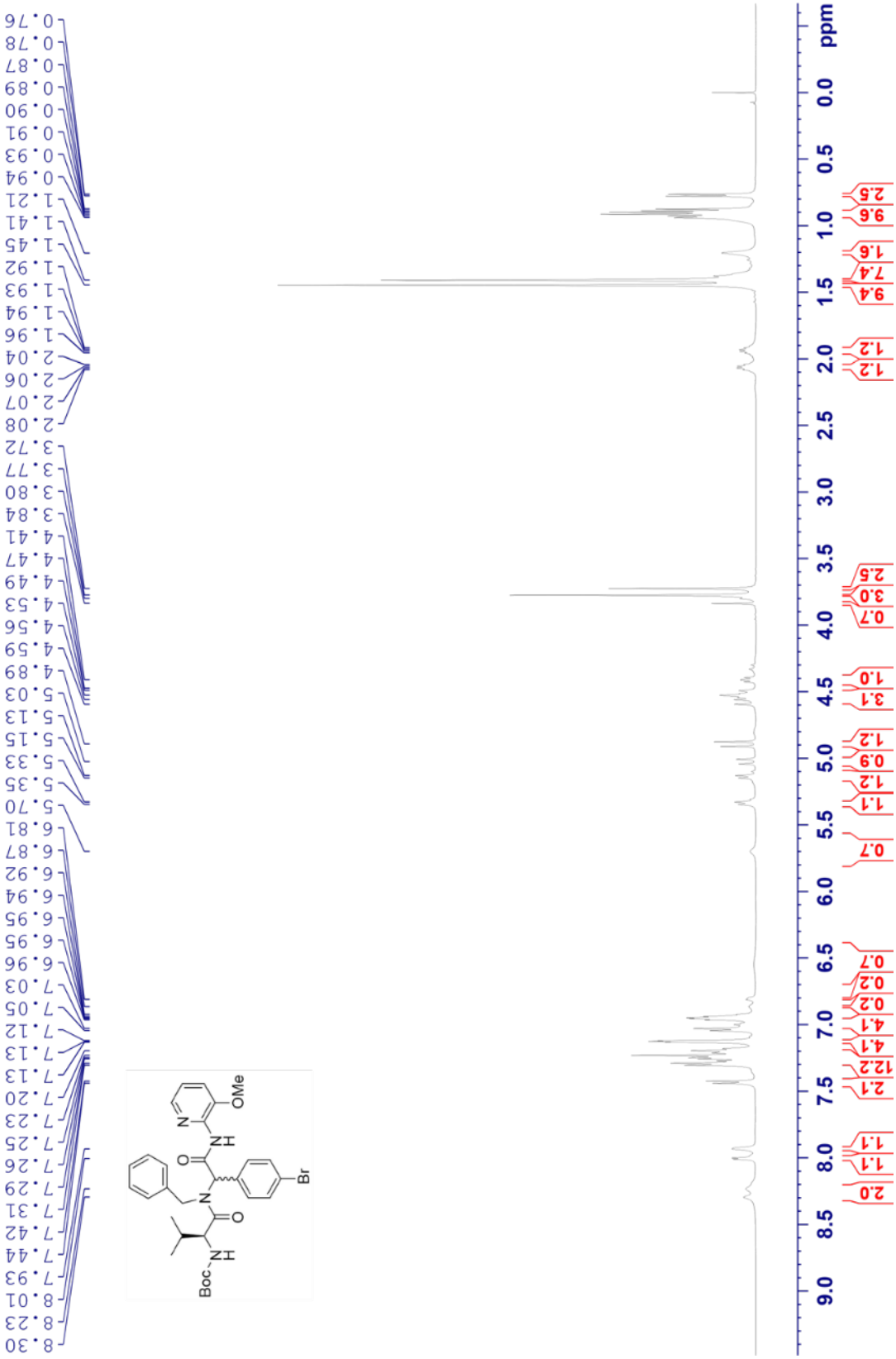


tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate **7b – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



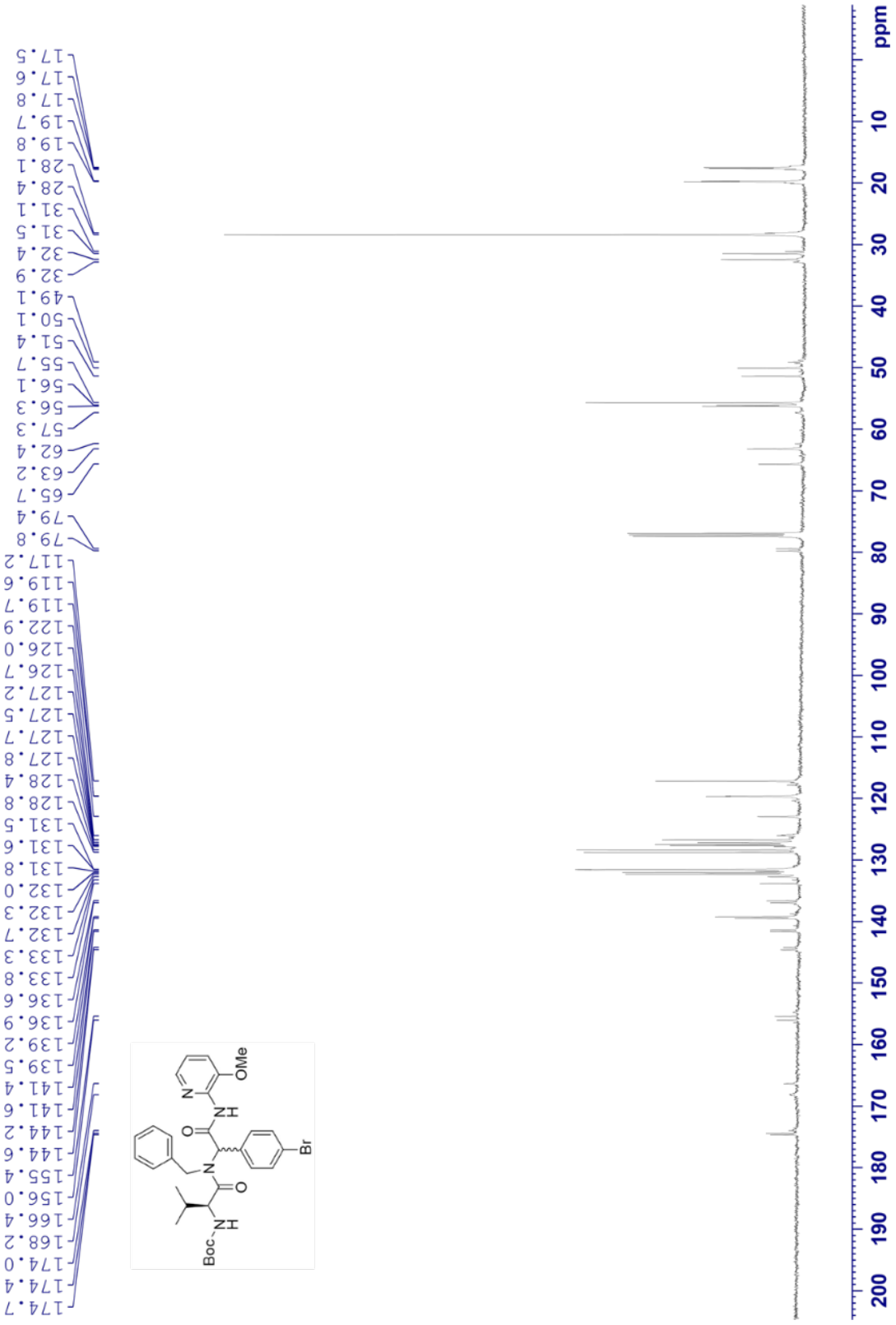
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-methoxypyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

7c – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)



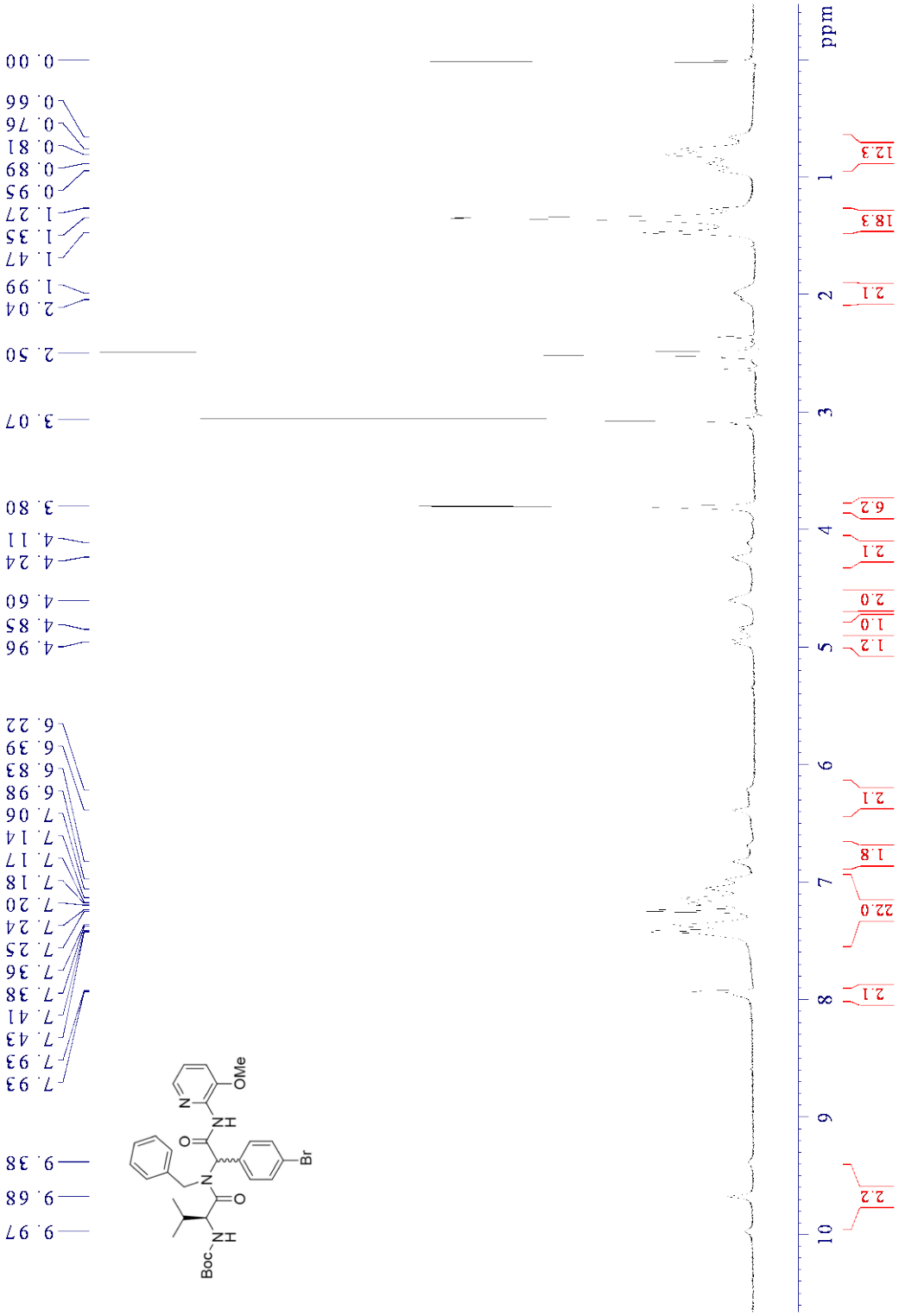
tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-methoxypyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

7c – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)

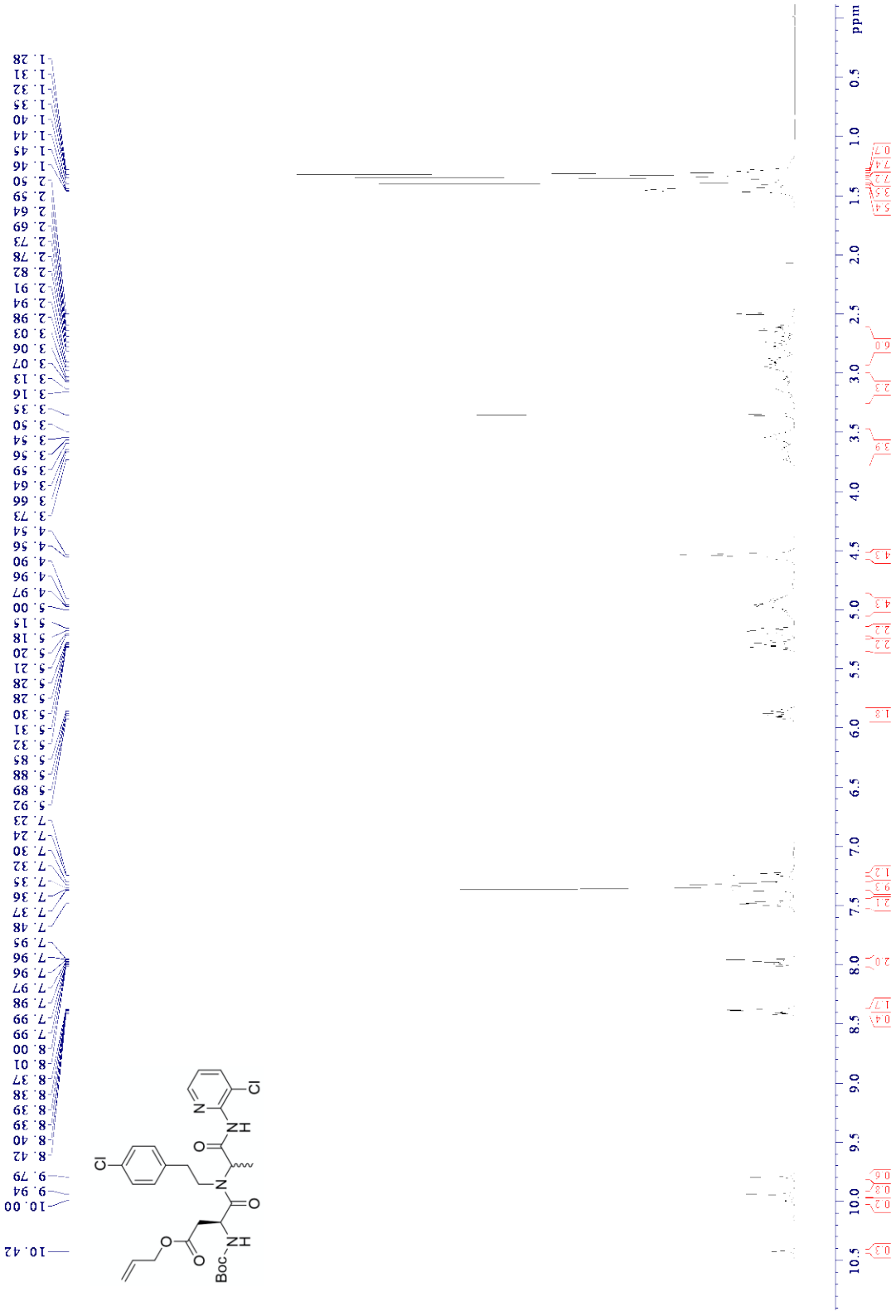


tert-Butyl ((2*S*)-1-((1-(4-bromophenyl)-2-((3-methoxypyridin-2-yl)amino)-2-oxoethyl)(propyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate

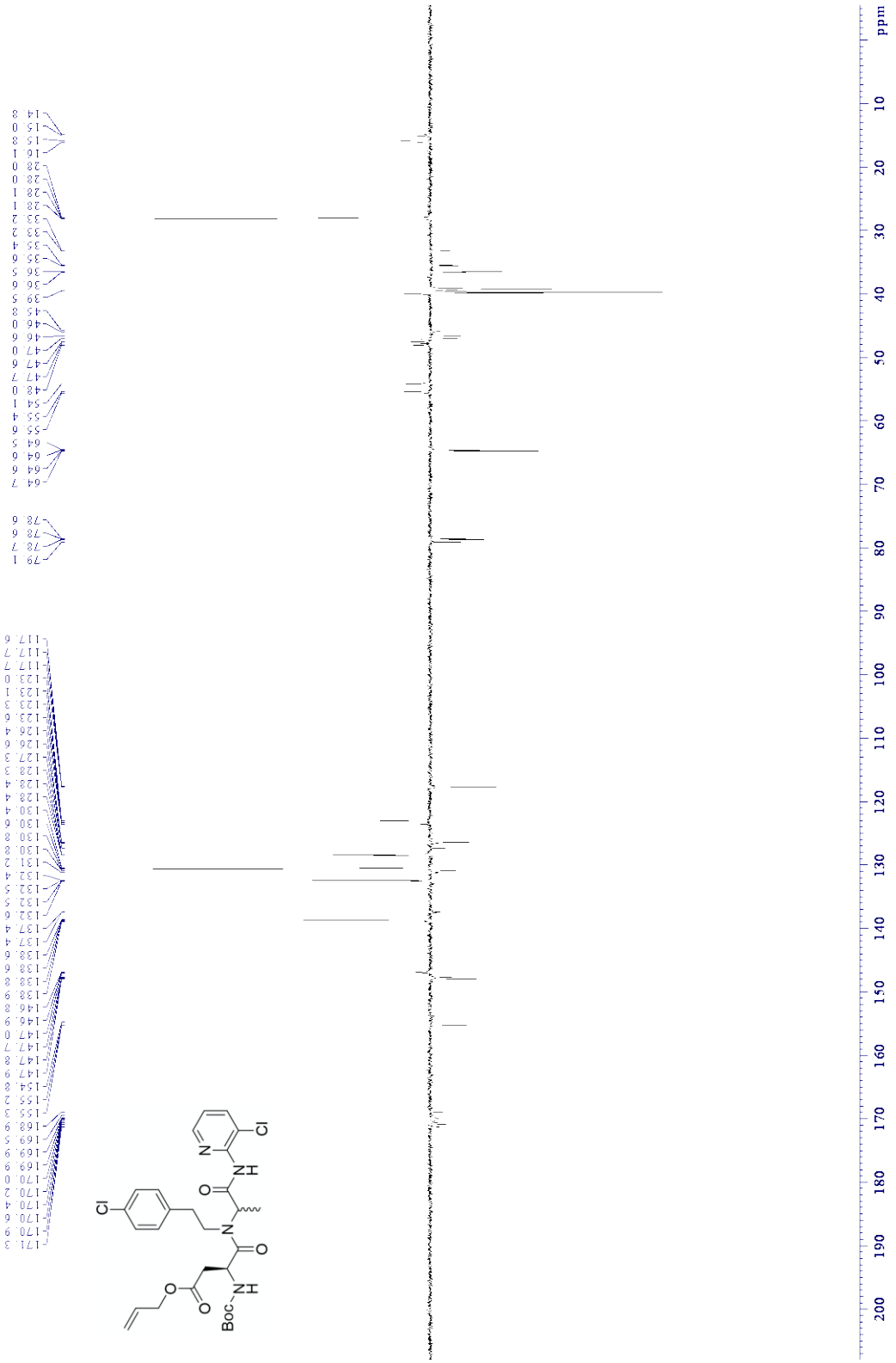
7c – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



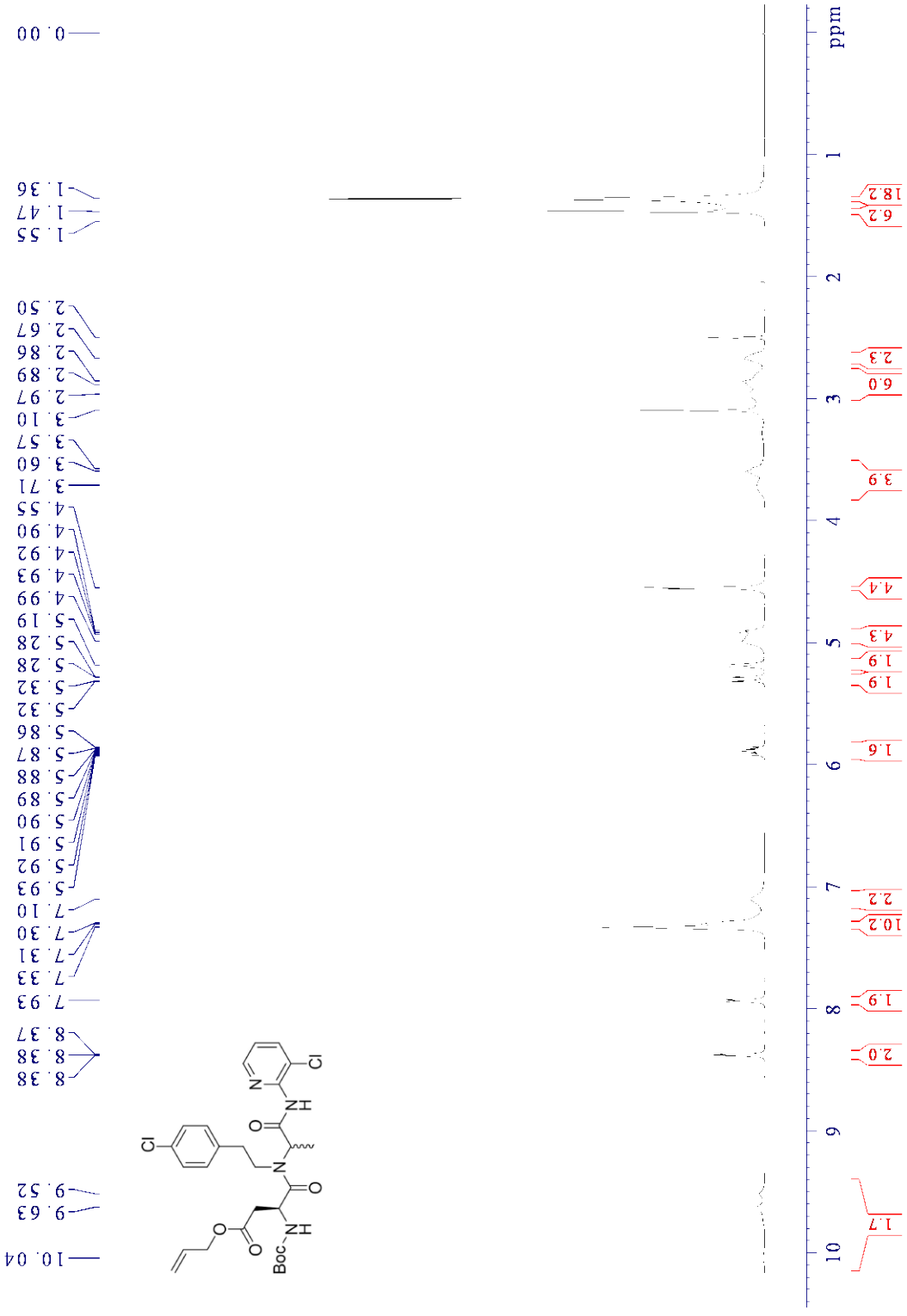
Allyl (3*S*)-3-((tert-butoxycarbonyl)amino)-4-((4-chlorophenethyl)(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoate **8 – ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



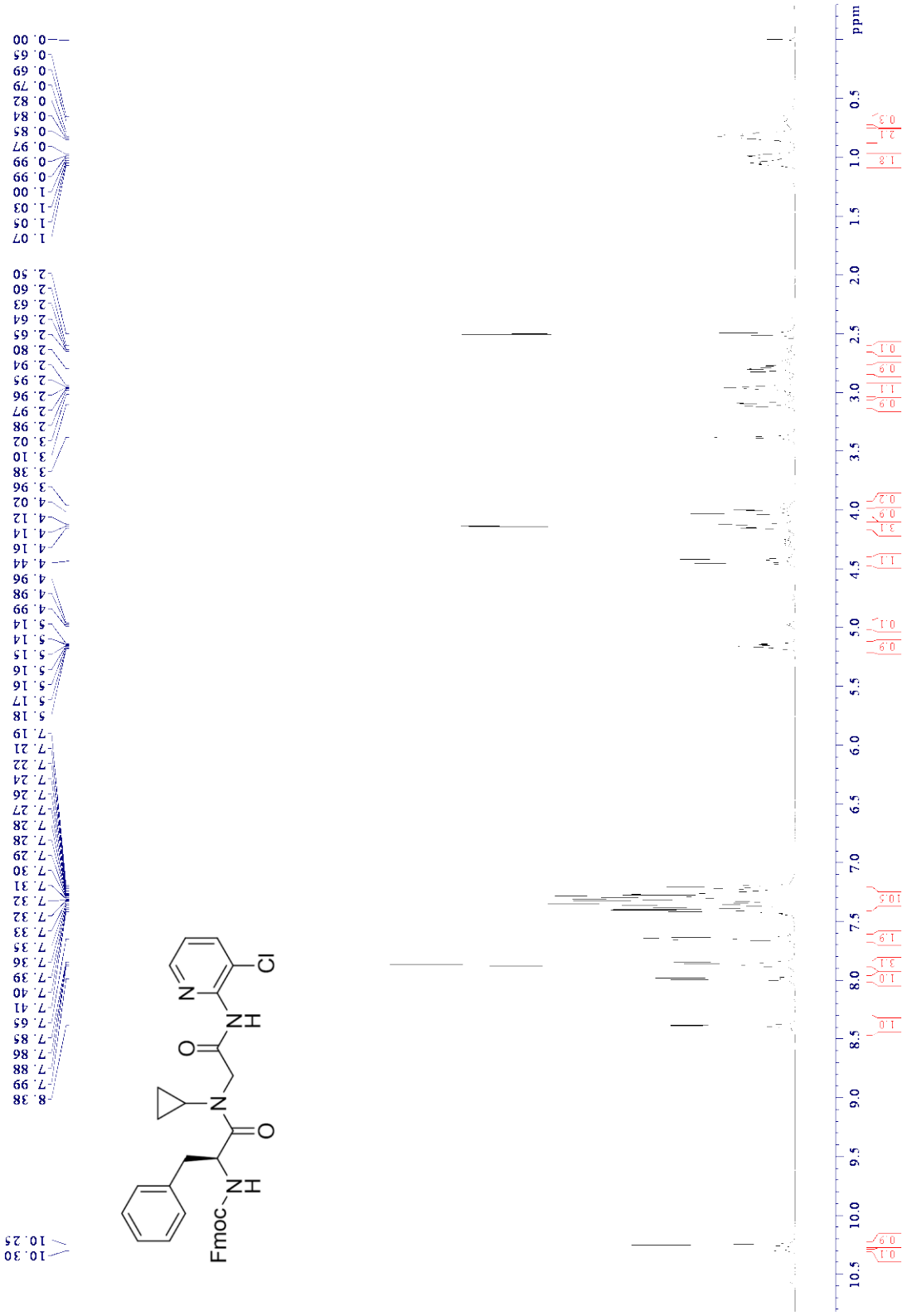
Allyl (3*S*)-3-((tert-butoxycarbonyl)amino)-4-((4-chlorophenethyl)(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoate **8 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



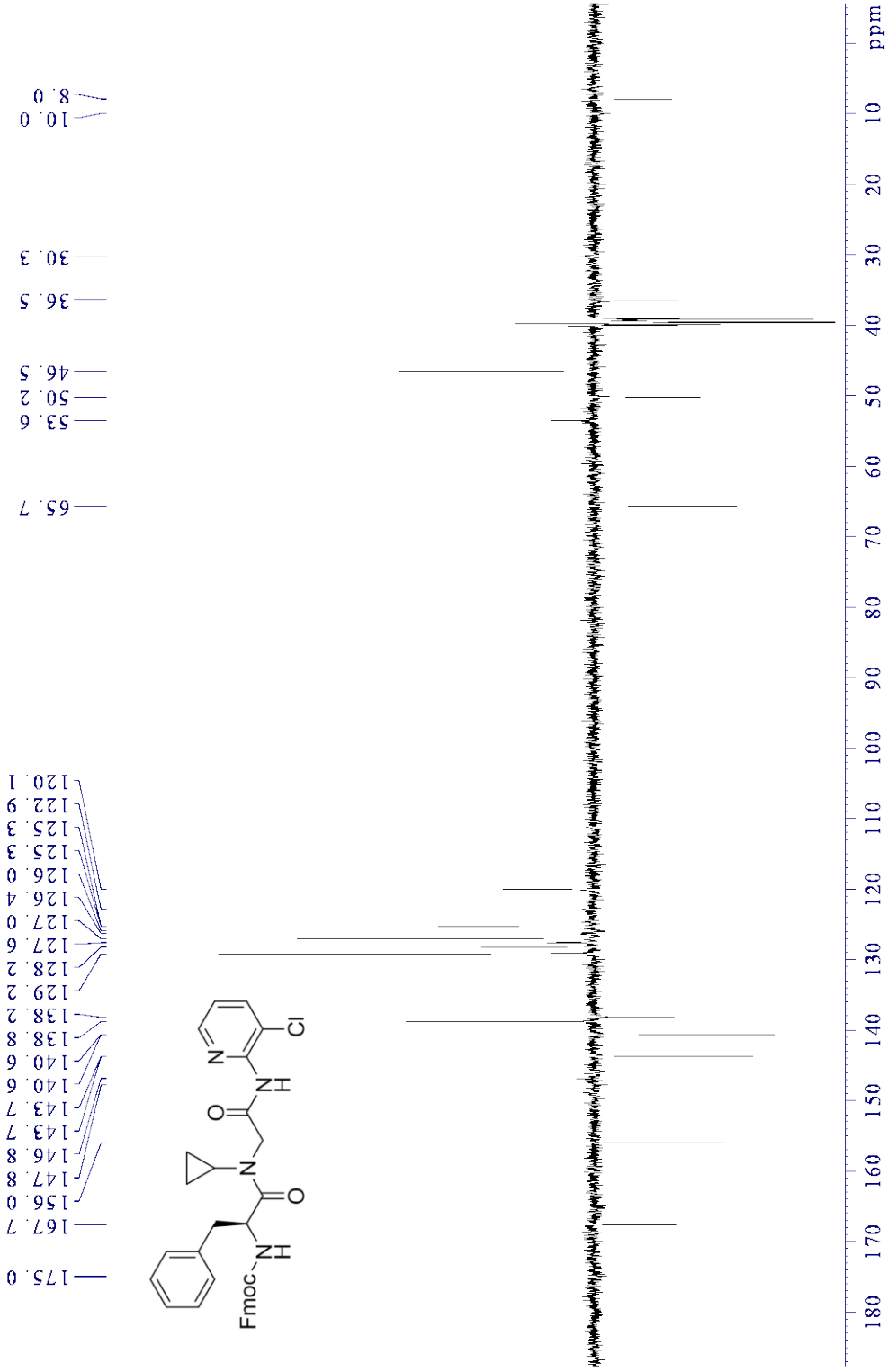
Allyl (3*S*)-3-((tert-butoxycarbonyl)amino)-4-((4-chlorophenethyl)(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-4-oxobutanoate **8 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



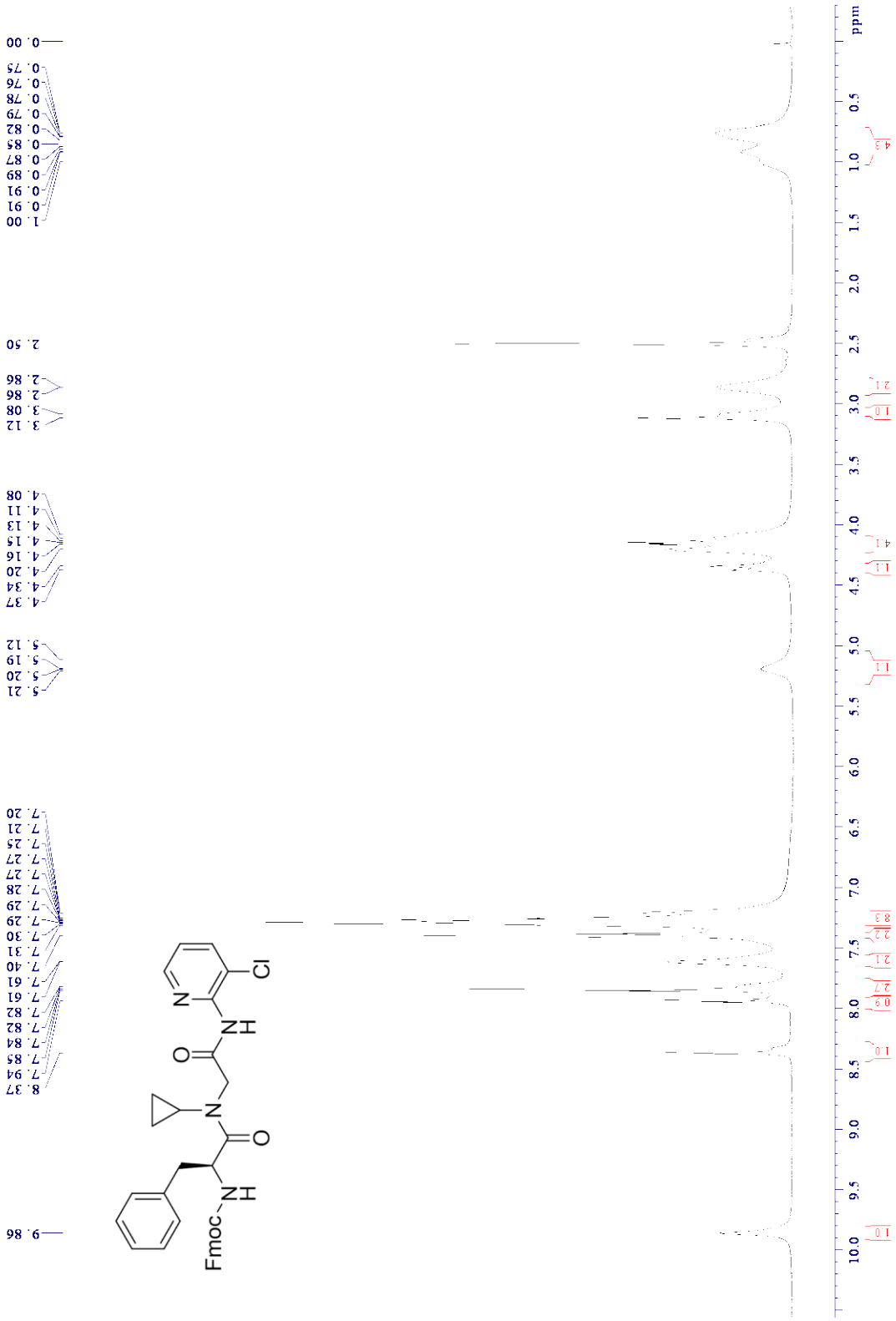
(9*H*-Fluoren-9-yl)methyl (*S*)-(1-((2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **9** – **^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers)**



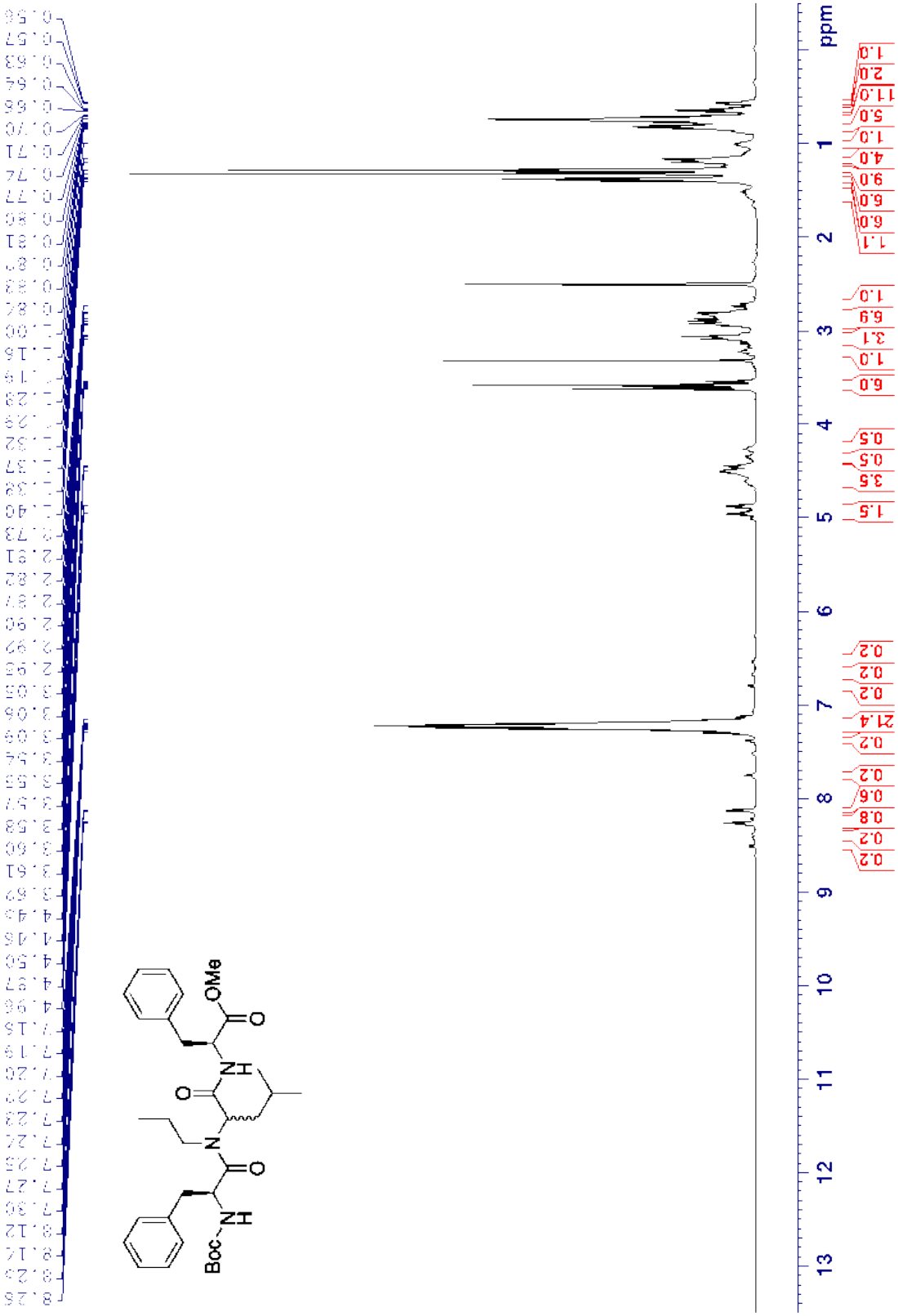
(9*H*-Fluoren-9-yl)methyl (*S*)-(1-((2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **9** – **^{13}C NMR (126 MHz, DMSO-d_6)**



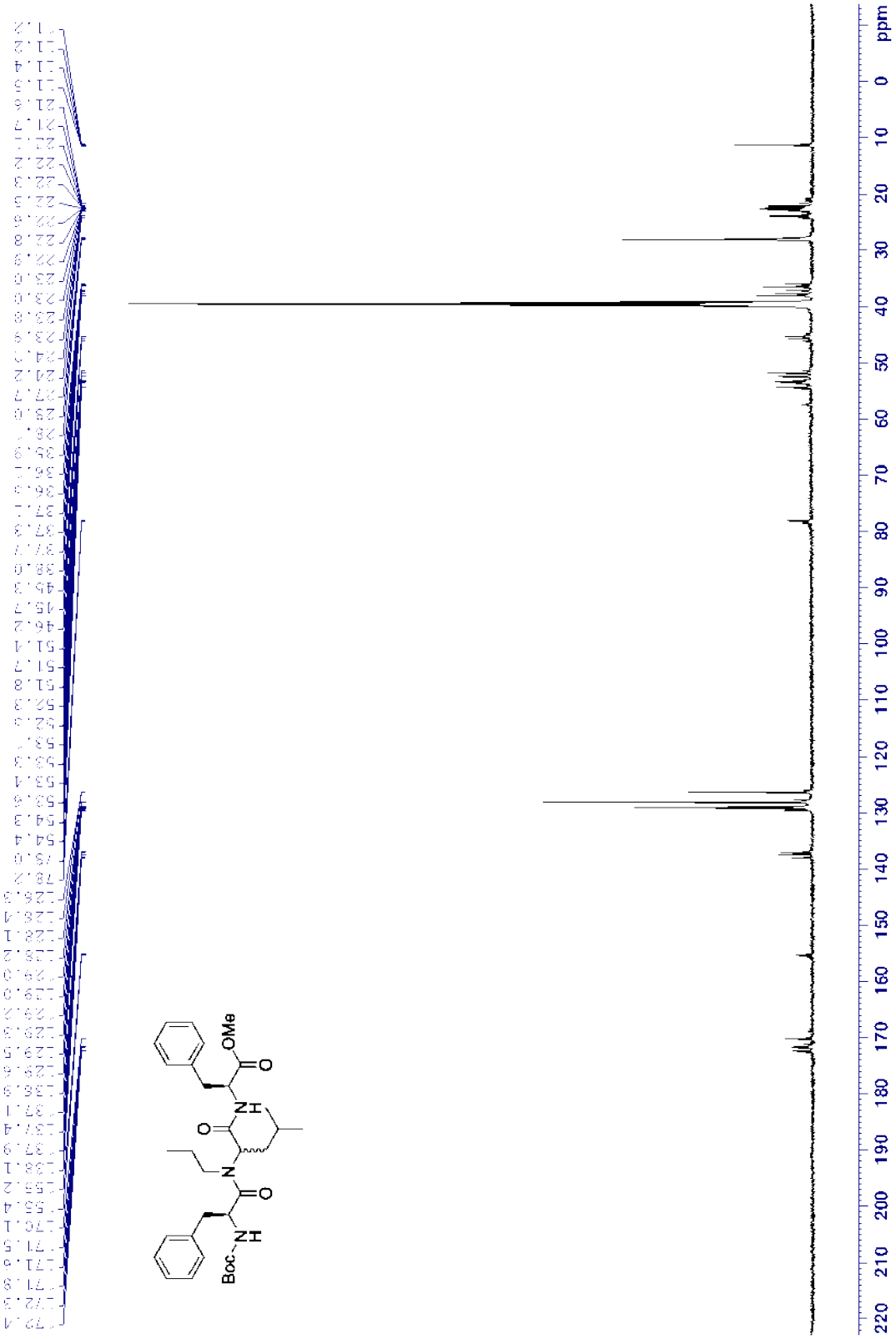
(9*H*-Fluoren-9-yl)methyl (*S*)-(1-((2-((3-chloropyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **9** –
^{1}H NMR (500 MHz, DMSO-d_6, 80 °C)



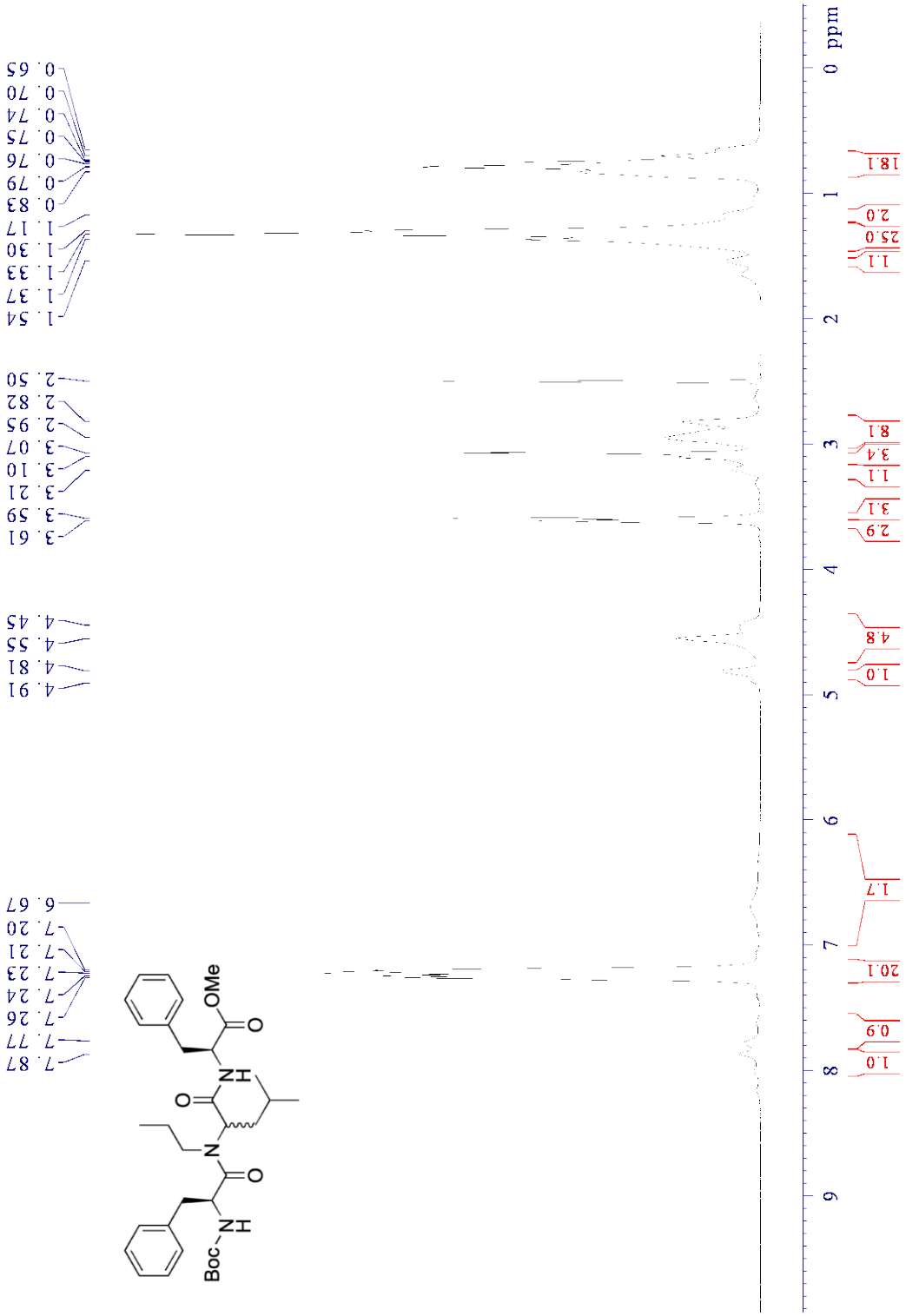
Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-phenylalaninate 10 – ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)



Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-phenylalaninate **10 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**

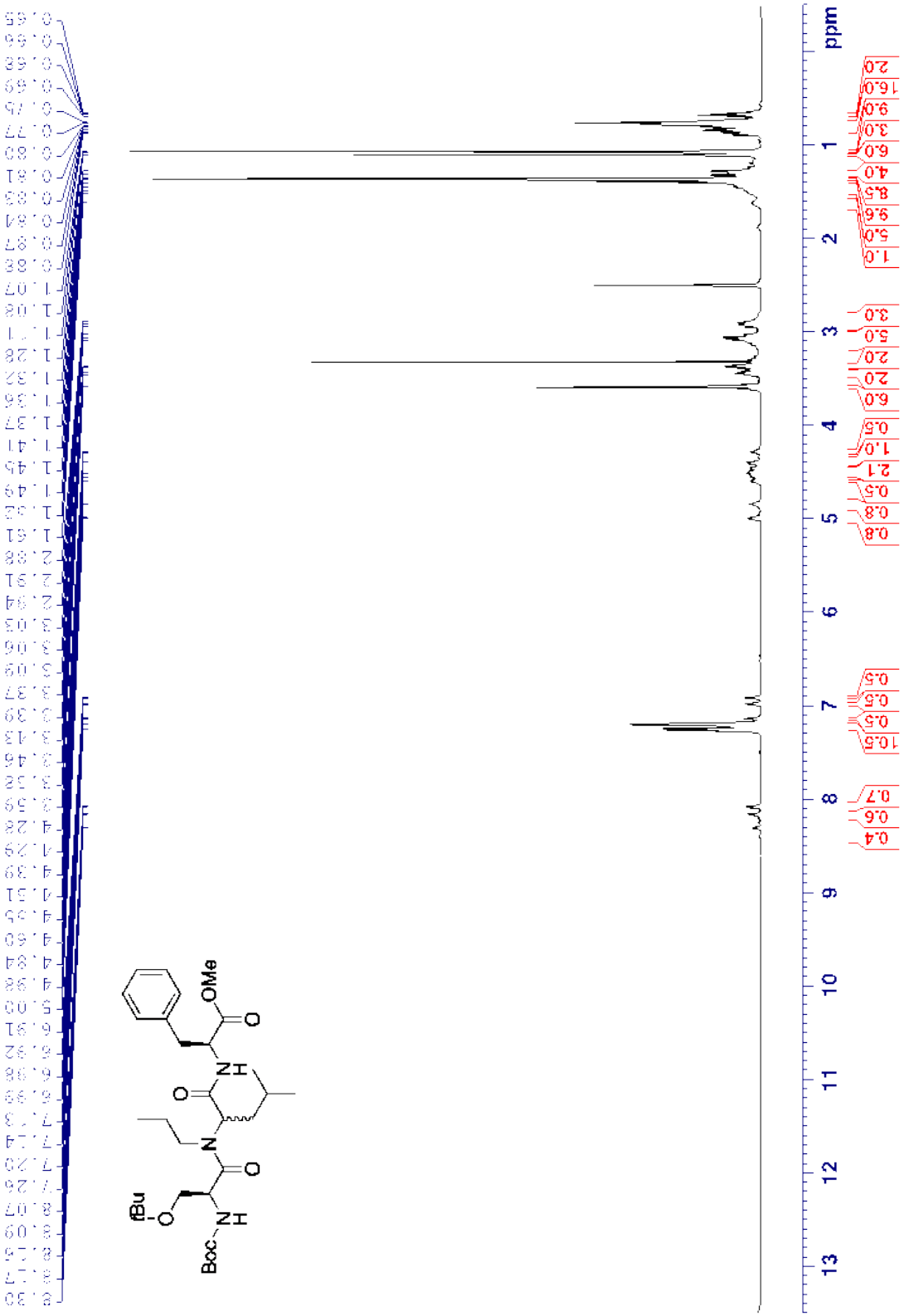


Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-phenylalaninate **10 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**

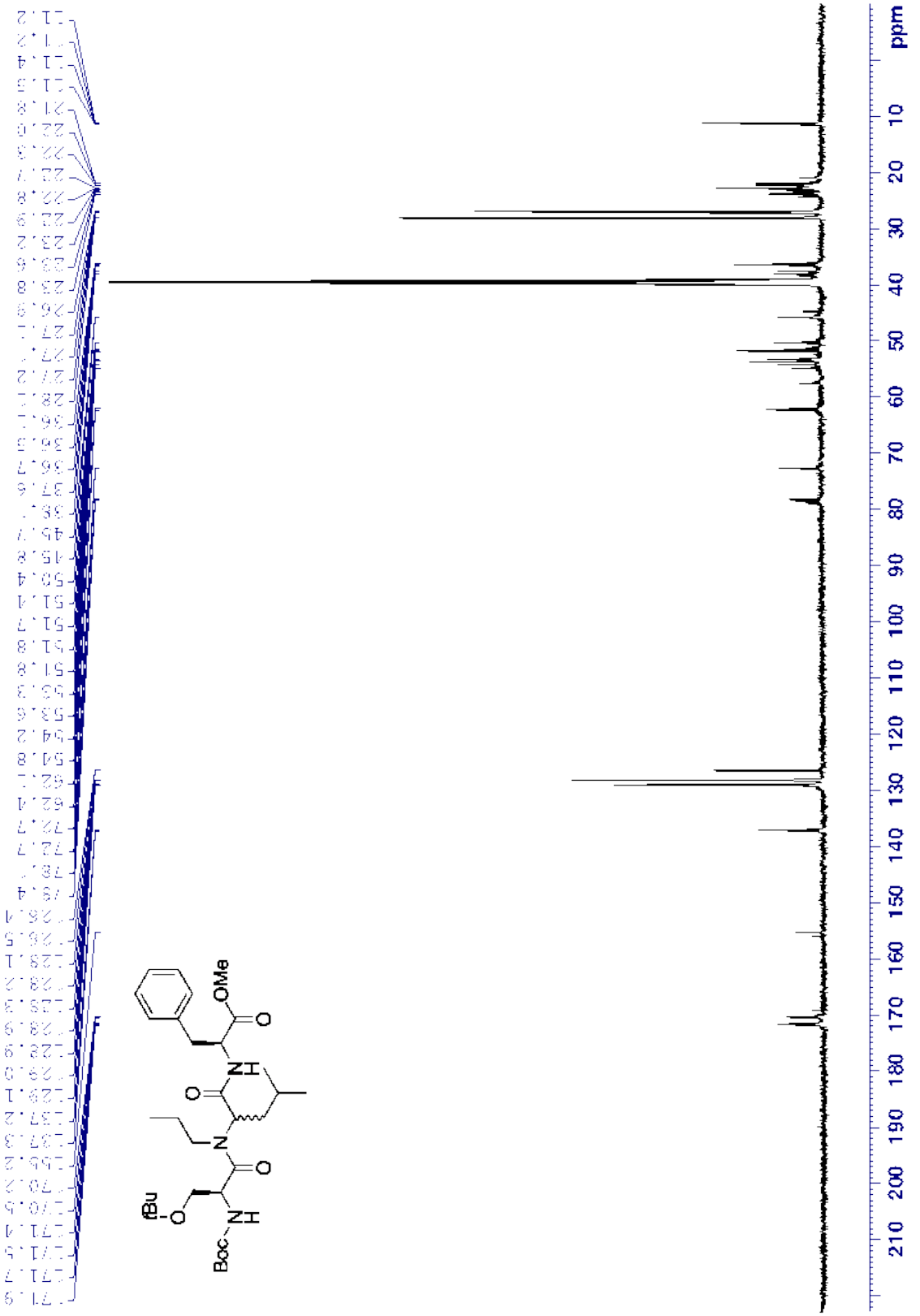


Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-phenylalaninate **10 – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**

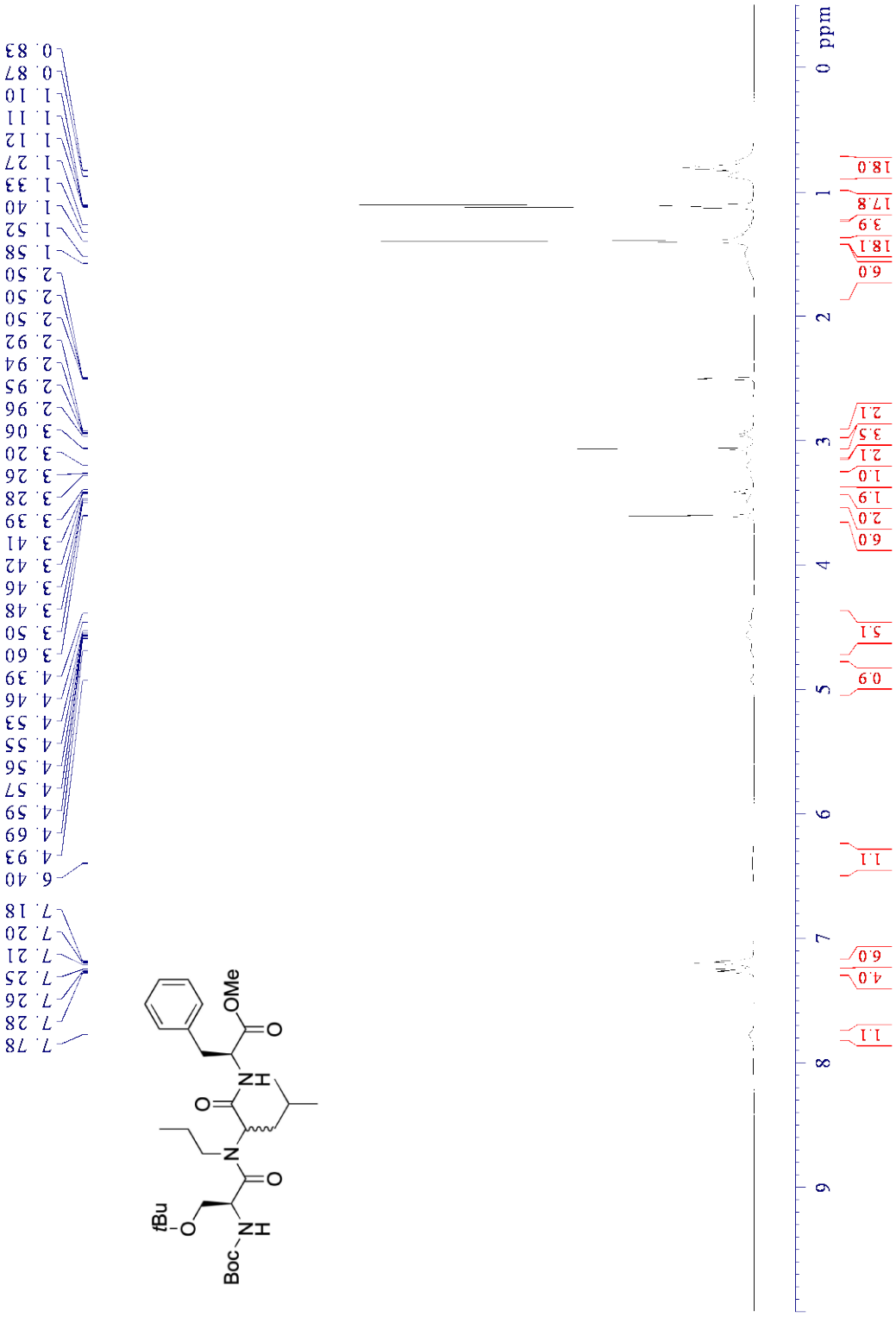
Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl)-*N*-propylleucyl-L-phenylalaninate **11 – ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



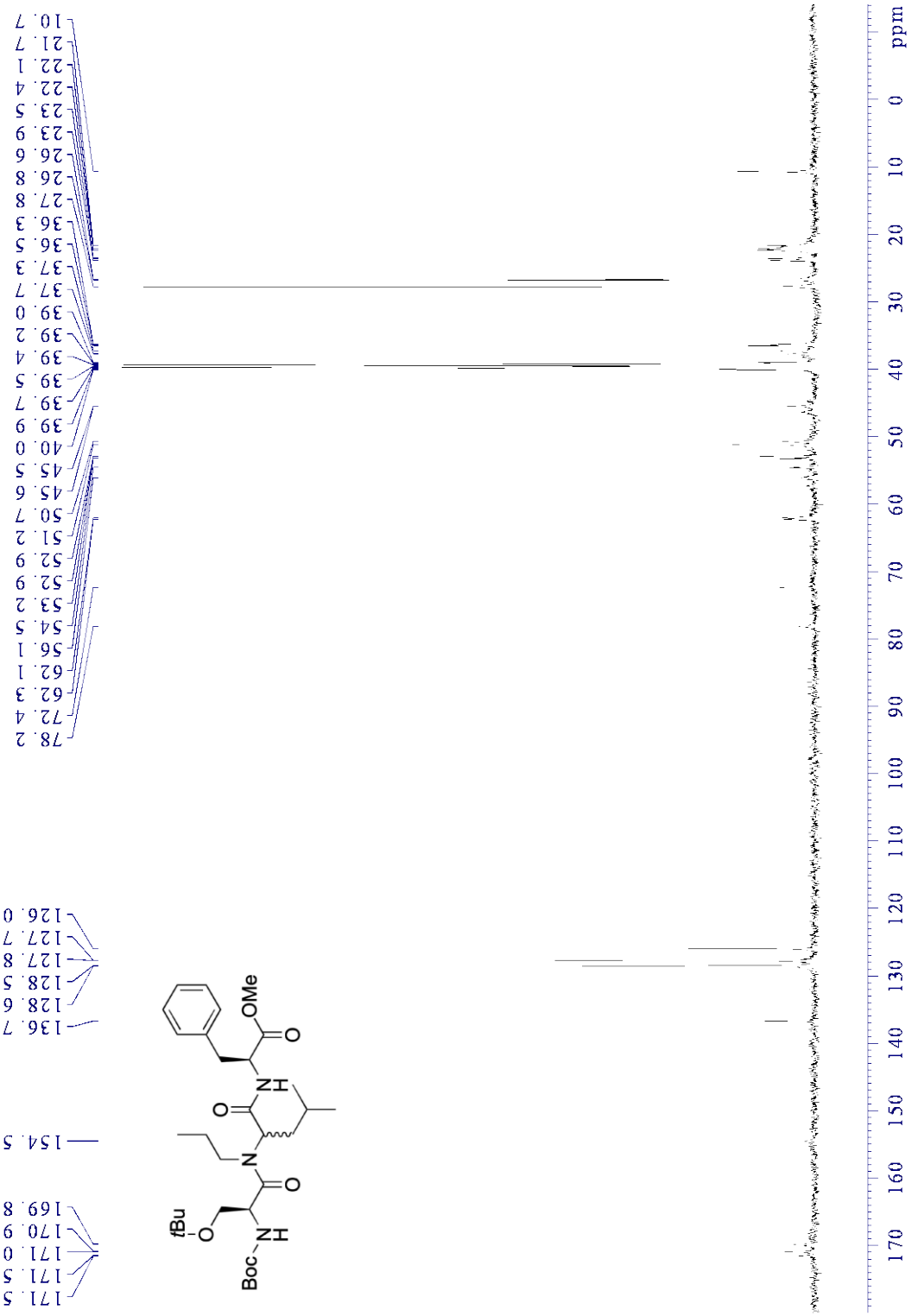
Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl)-*N*-propylleucyl-L-phenylalaninate **11 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



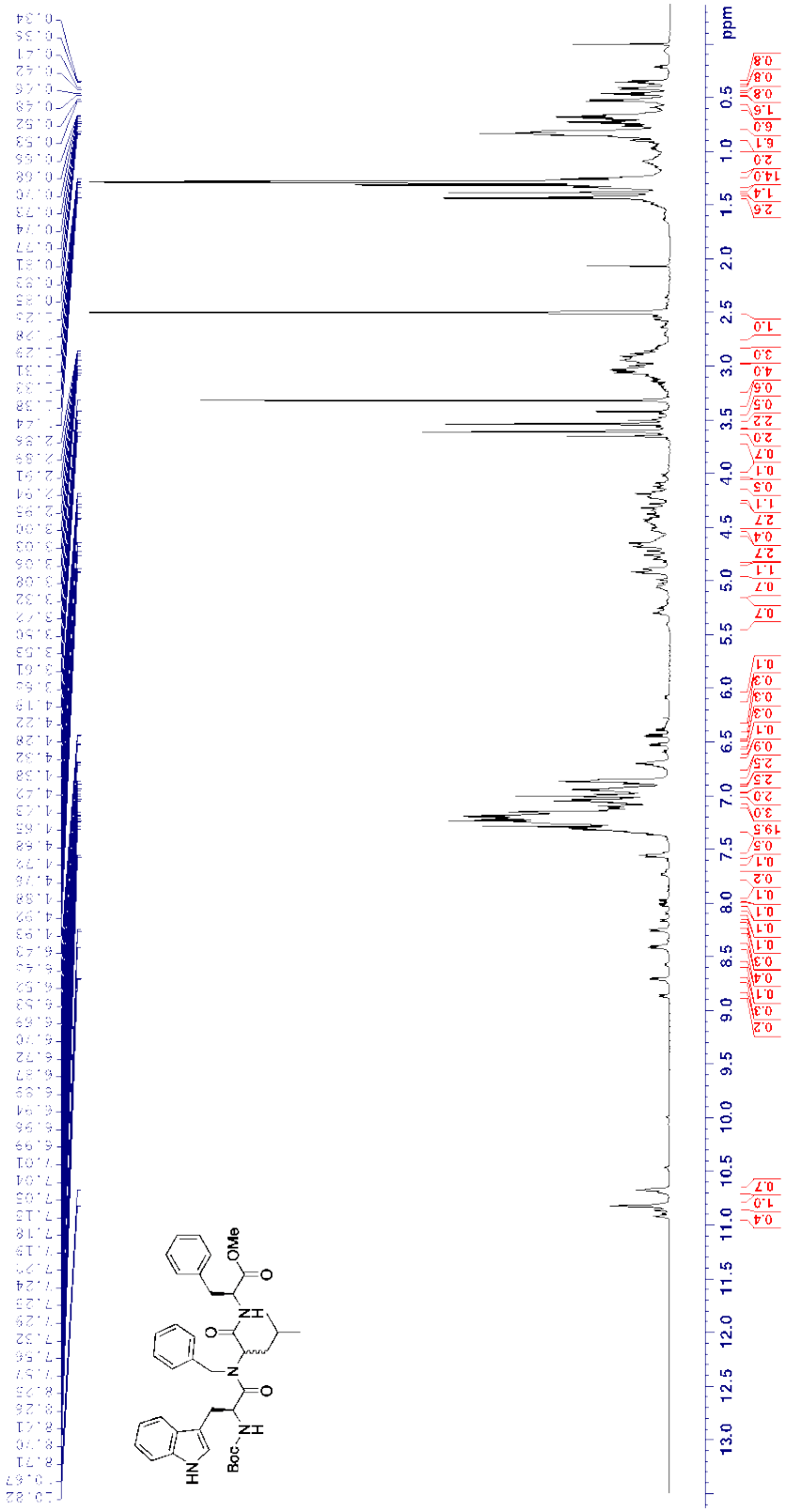
Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl)-*N*-propylleucyl-L-phenylalaninate **11 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



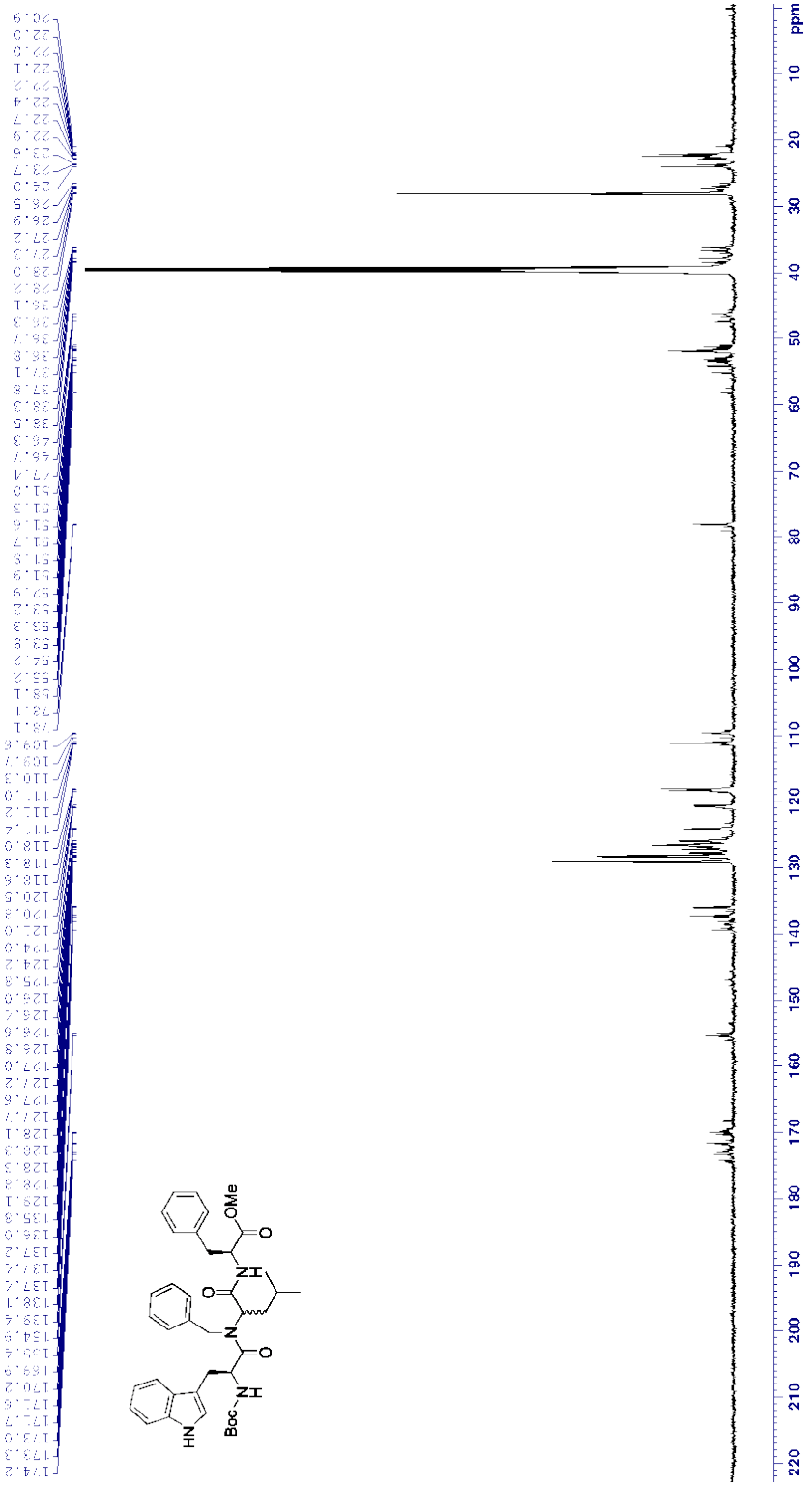
Methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl)-*N*-propylleucyl-L-phenylalaninate **11 – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



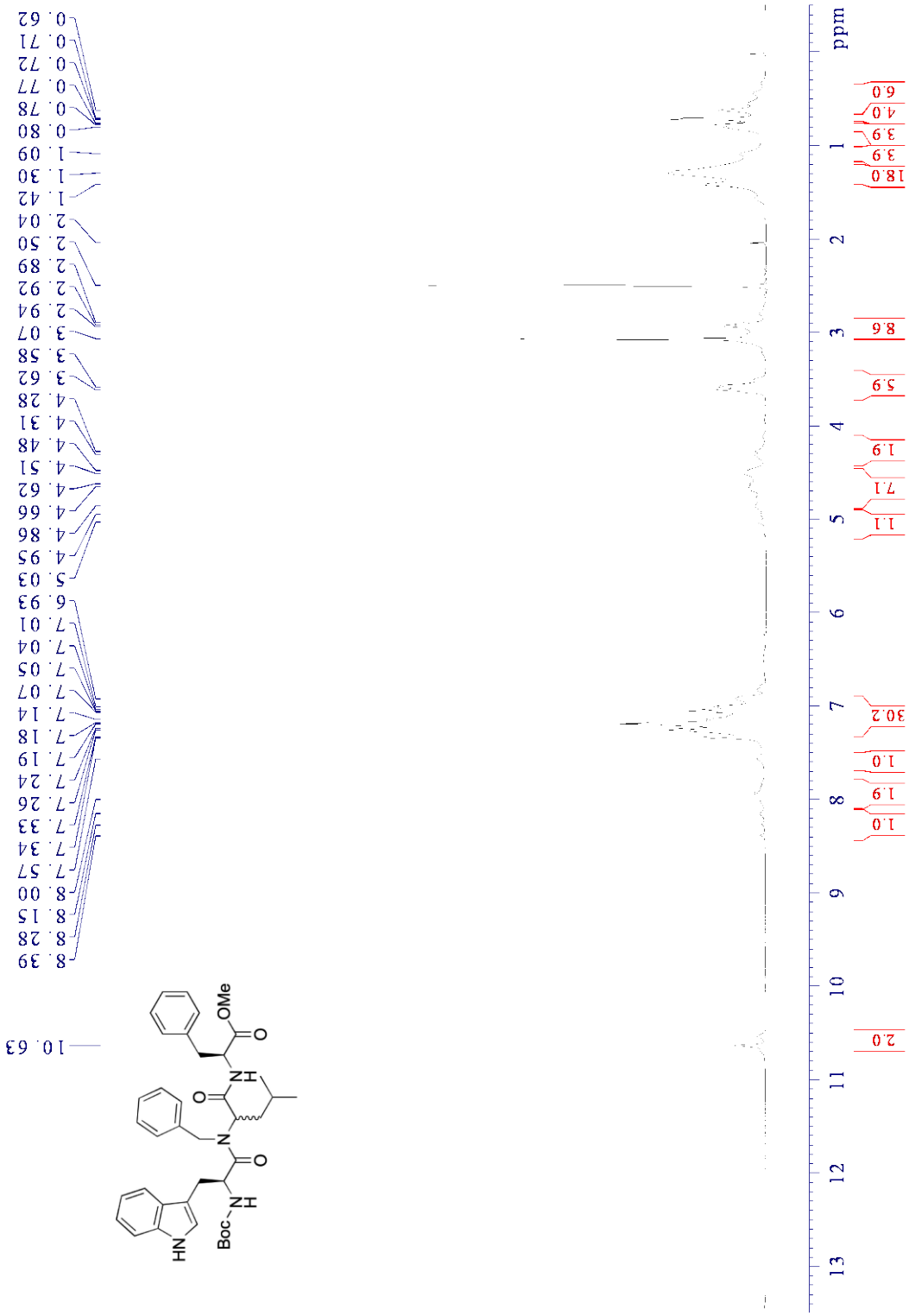
Methyl *N*-benzyl-*N*-((*tert*-butoxycarbonyl)-L-tryptophyl)leucyl-L-phenylalaninate 12 – ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)



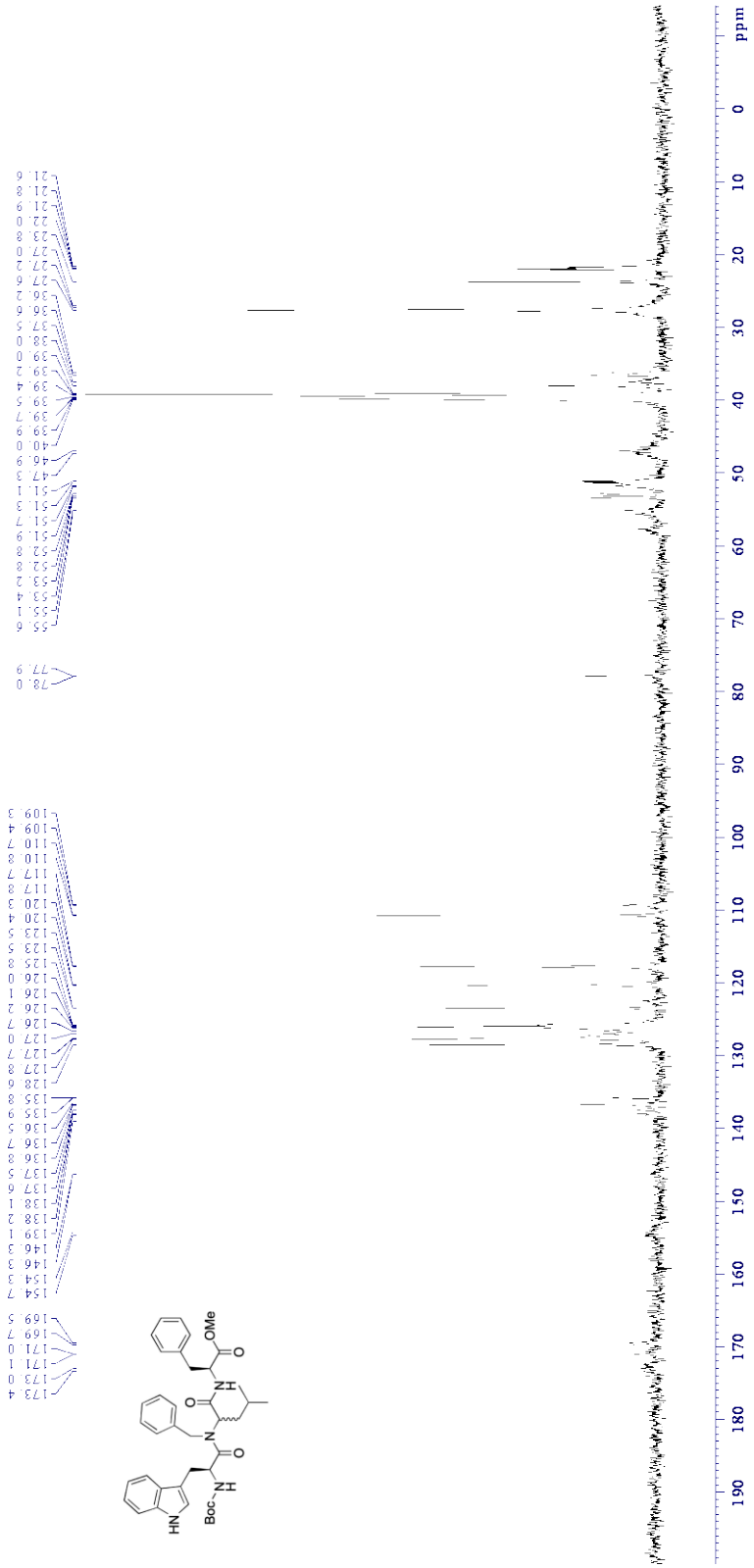
Methyl *N*-benzyl-*N*-((*tert*-butoxycarbonyl)-L-tryptophyl)leucyl-L-phenylalaninate **12 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



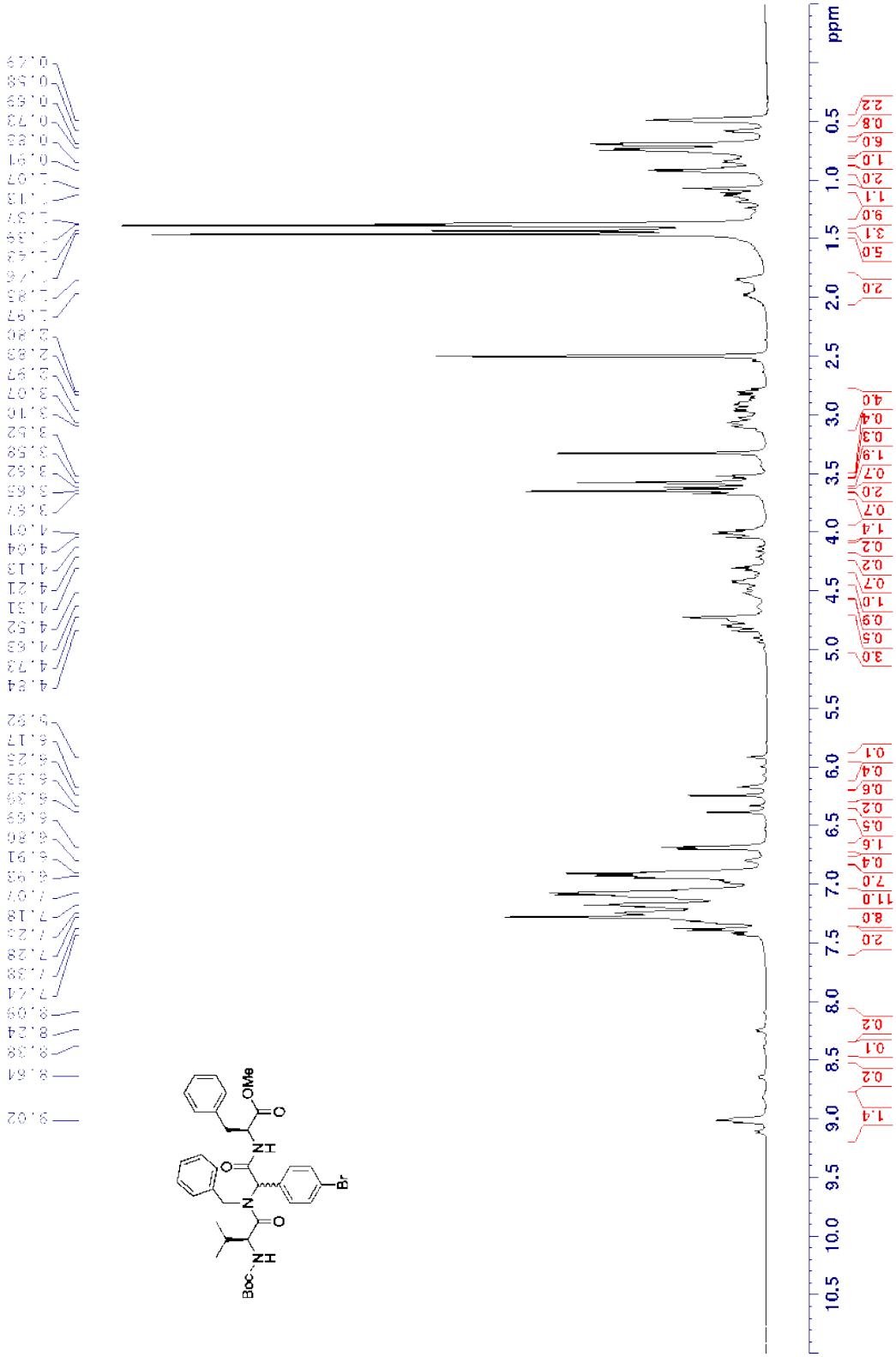
Methyl *N*-benzyl-*N*-((*tert*-butoxycarbonyl)-L-tryptophyl)leucyl-L-phenylalaninate 12 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



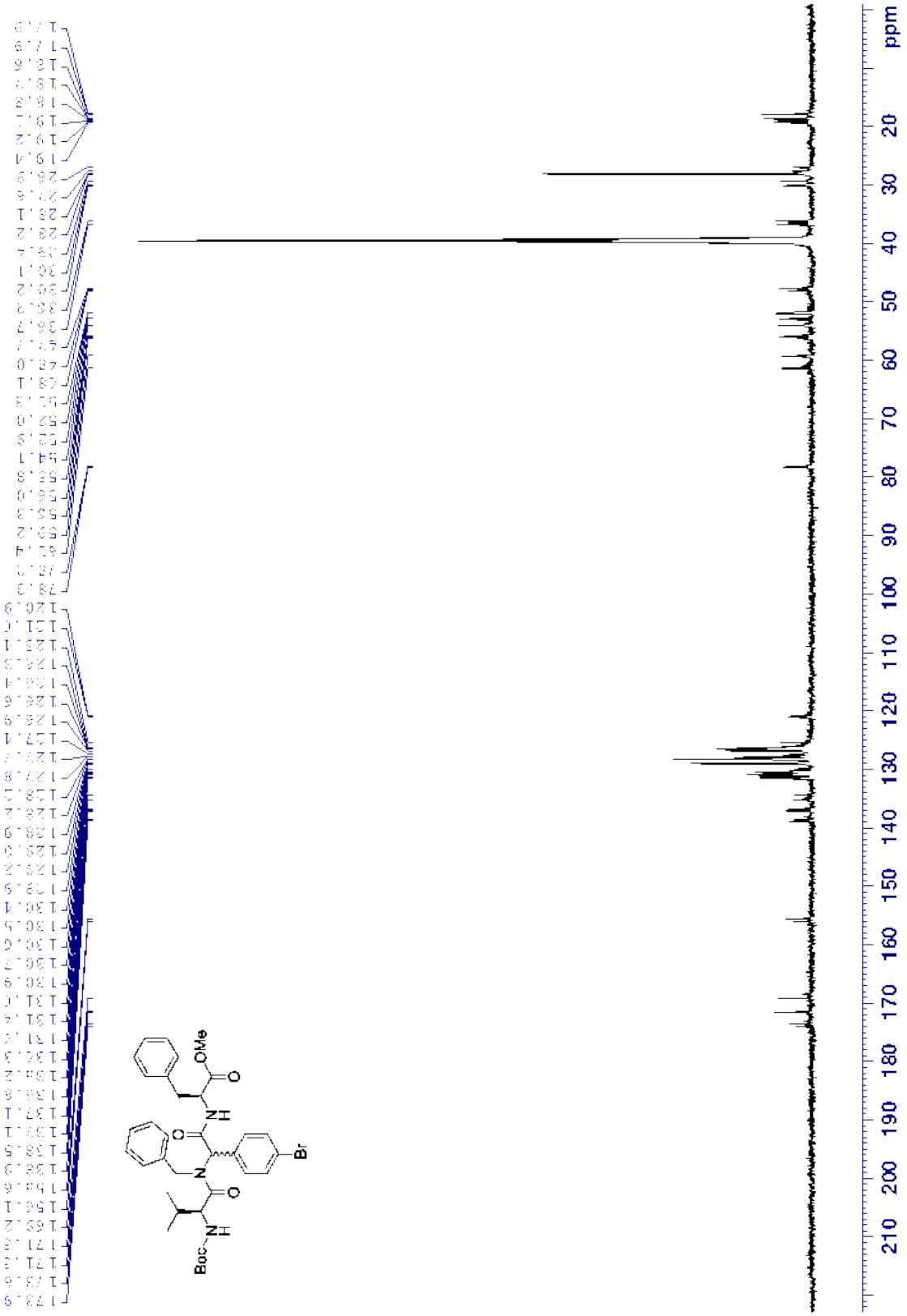
Methyl *N*-benzyl-*N*-((*tert*-butoxycarbonyl)-L-tryptophyl)leucyl-L-phenylalaninate **12 – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



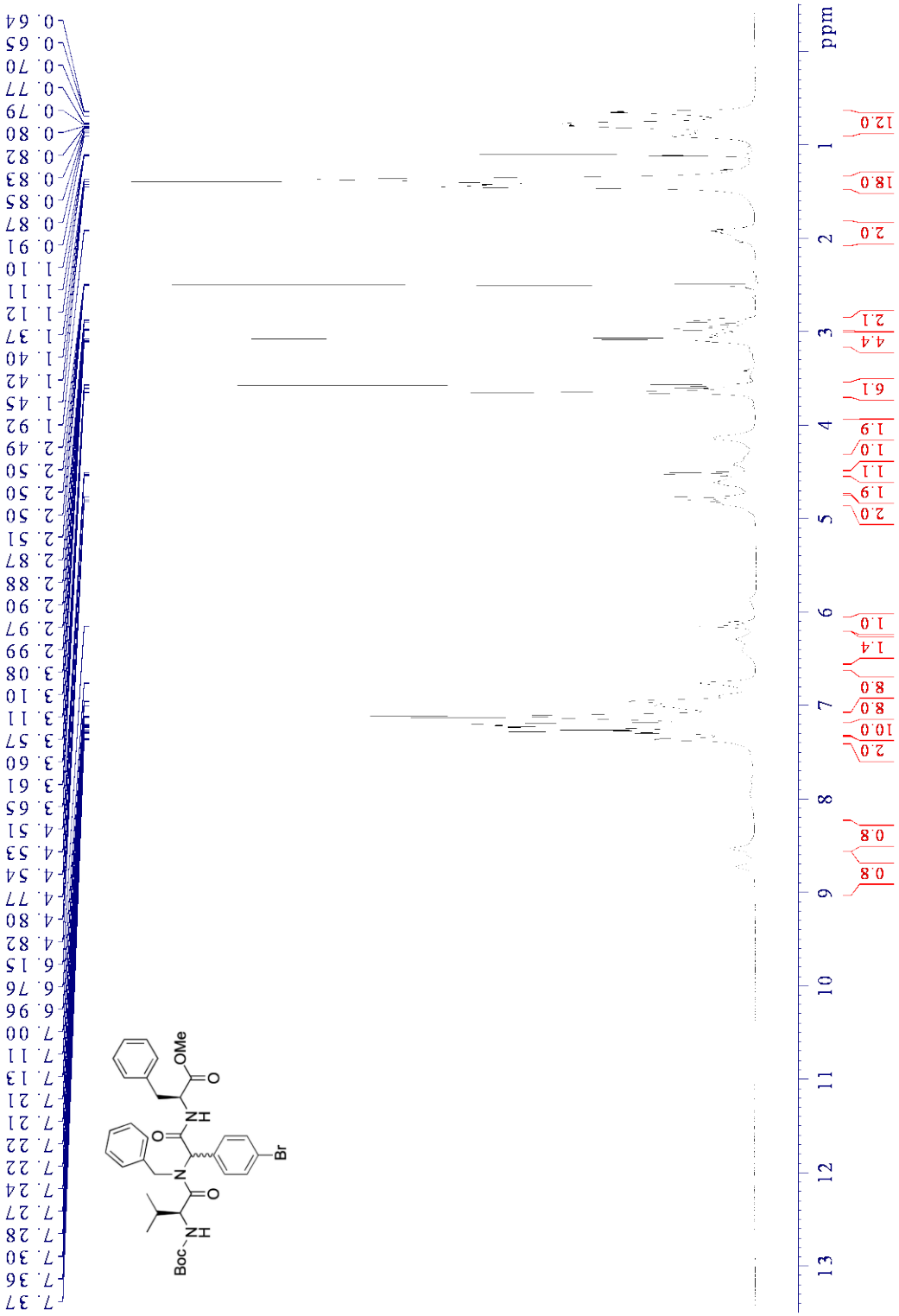
Methyl (2-((S)-*N*-benzyl-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-(4-bromophenyl)acetyl)-L-phenylalaninate **13 – ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



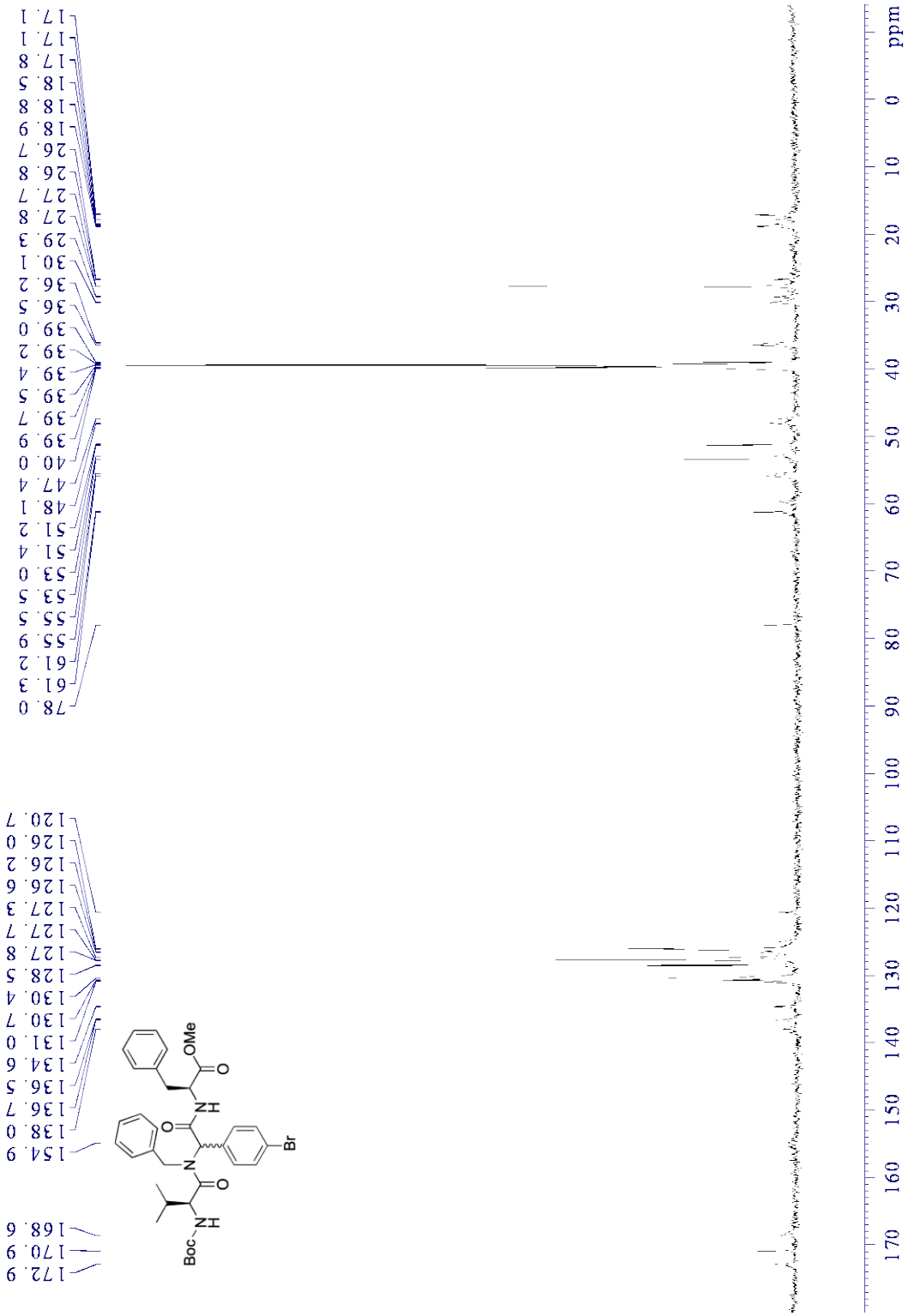
Methyl (2-((S)-*N*-benzyl-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-(4-bromophenyl)acetyl)-L-phenylalaninate **13 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



Methyl (2-((S)-*N*-benzyl-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-(4-bromophenyl)acetyl)-L-phenylalaninate **13 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**

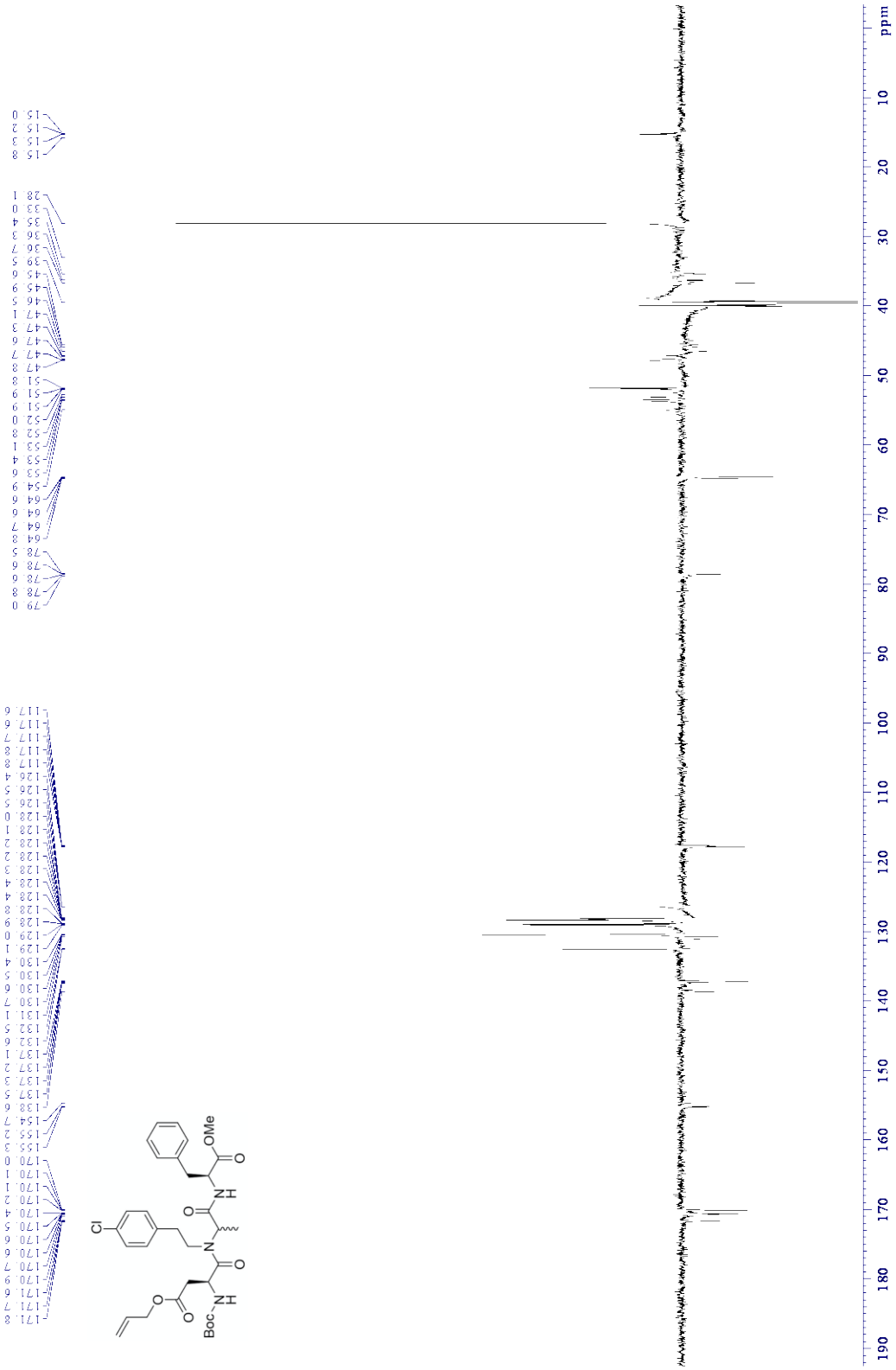


Methyl (2-((S)-*N*-benzyl-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-2-(4-bromophenyl)acetyl)-L-phenylalaninate **13 – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers and rotamers)**

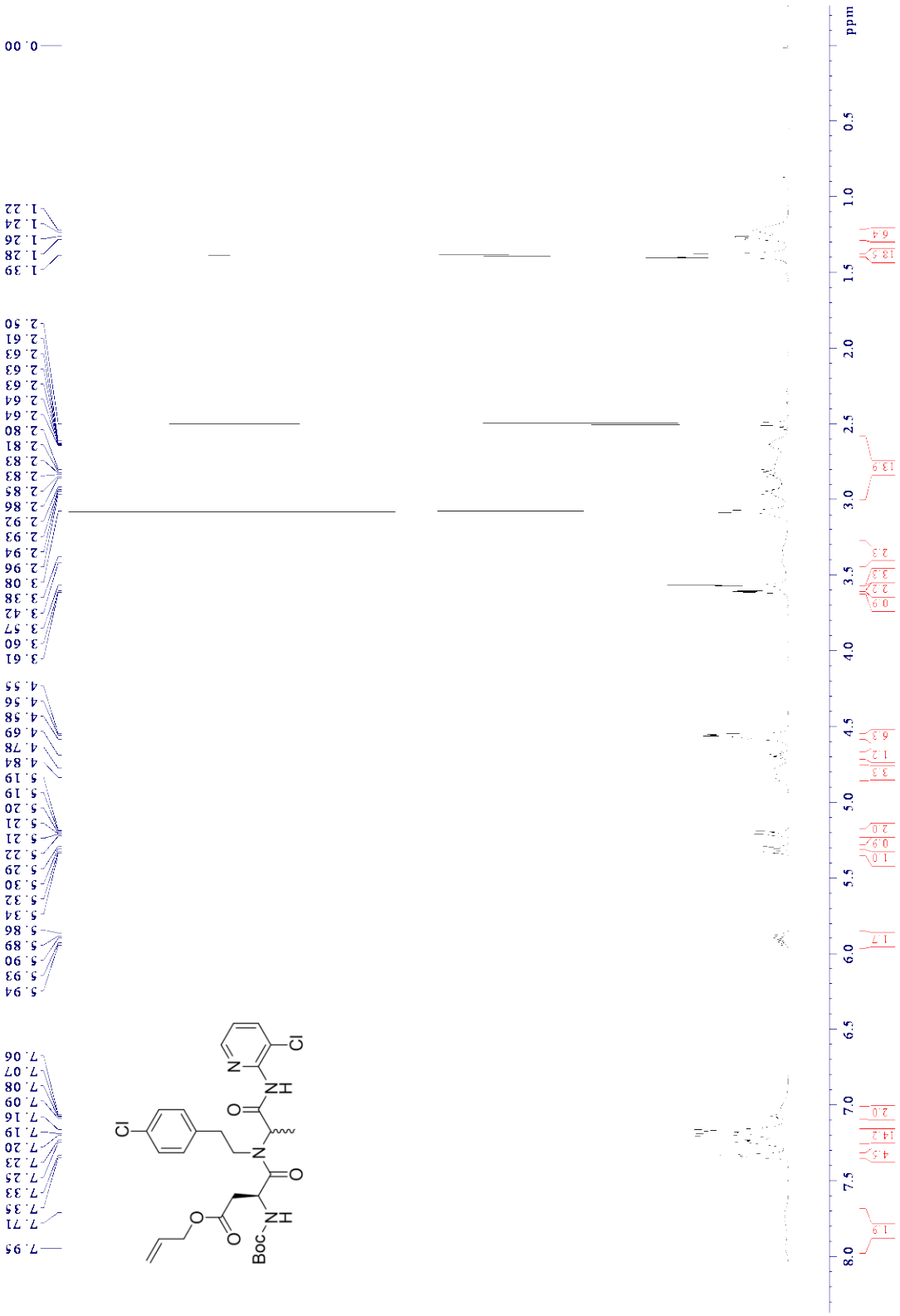


Methyl (6*S*,12*S*)-6-(2-(allyloxy)-2-oxoethyl)-12-benzyl-8-(4-chlorophenethyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **14 - ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**

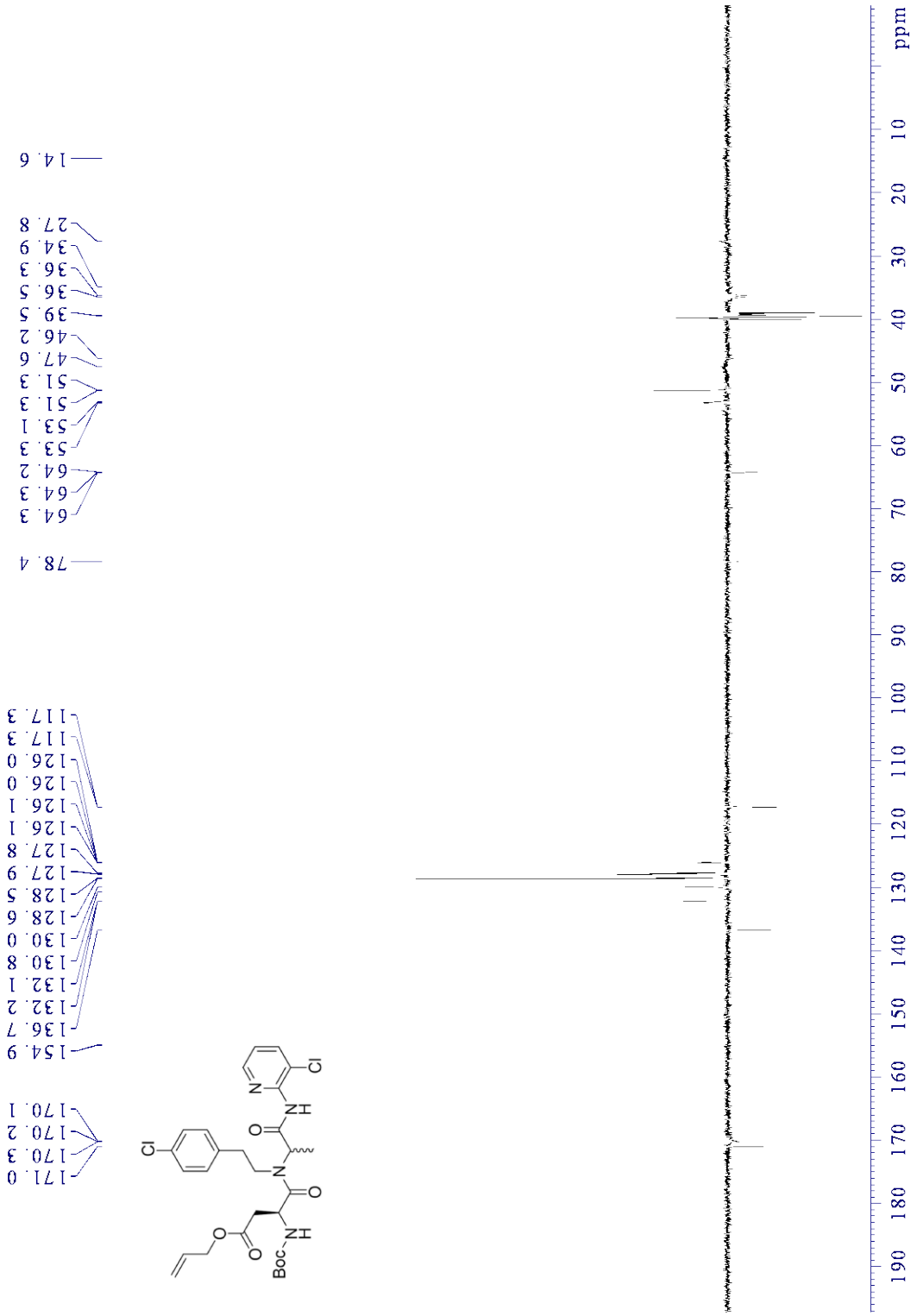
Methyl (6*S*,12*S*)-6-(2-(allyloxy)-2-oxoethyl)-12-benzyl-8-(4-chlorophenethyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **14 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



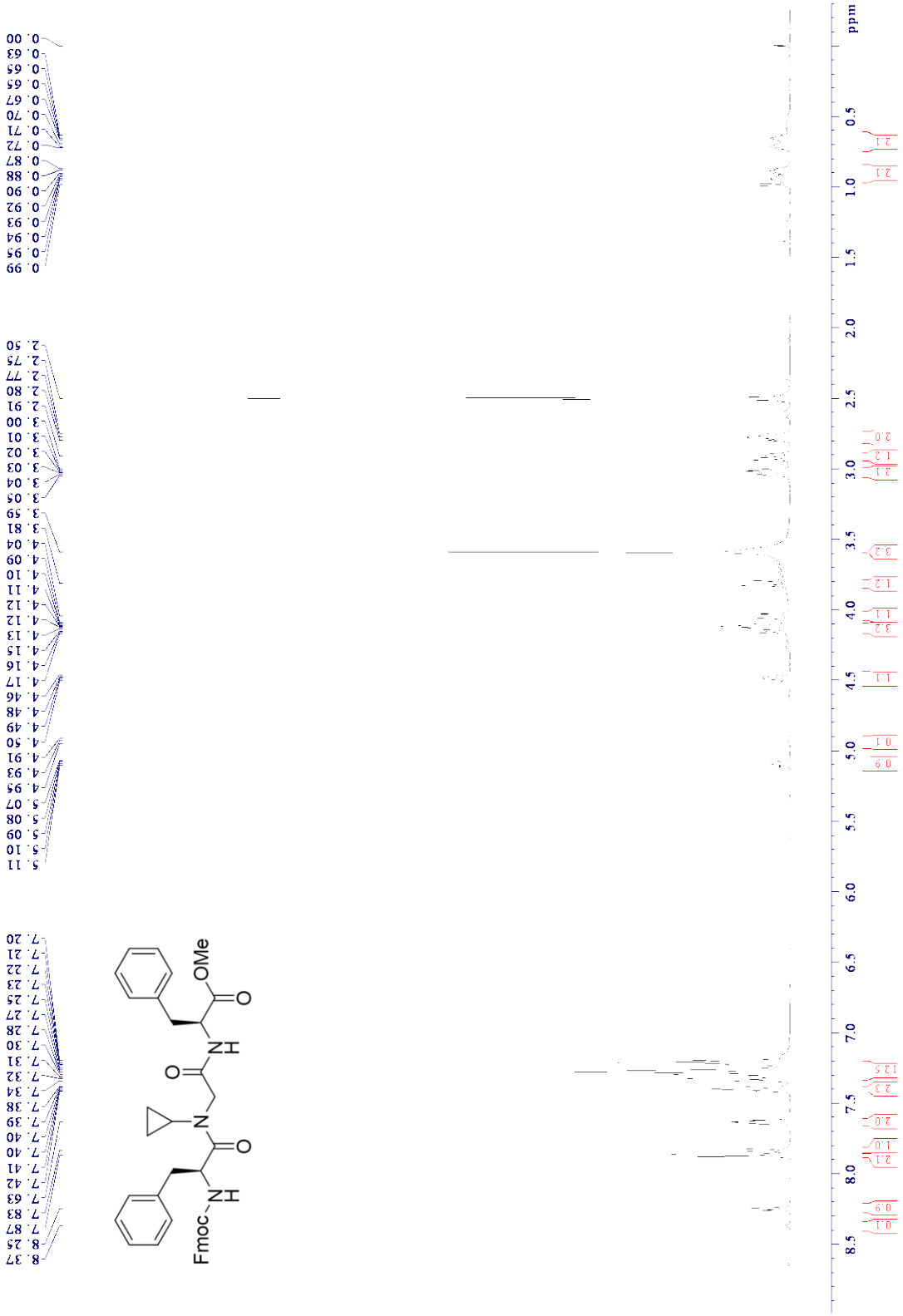
Methyl (6*S*,12*S*)-6-(2-(allyloxy)-2-oxoethyl)-12-benzyl-8-(4-chlorophenethyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **14 - ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



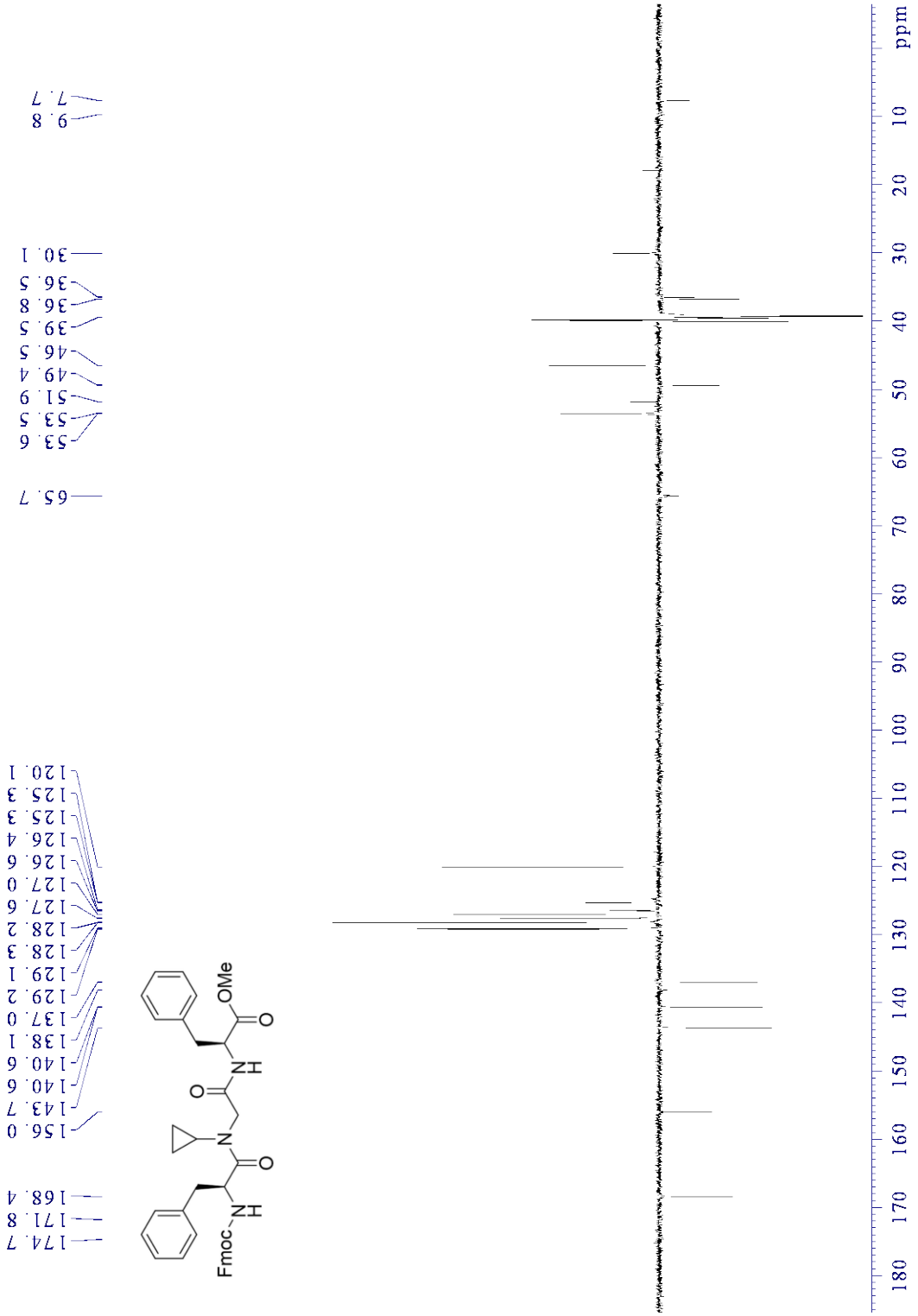
Methyl (6*S*,12*S*)-6-(2-(allyloxy)-2-oxoethyl)-12-benzyl-8-(4-chlorophenethyl)-2,2,9-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **14 – ^{13}C NMR (126 MHz, DMSO-d_6, 80 °C, mixture of diastereomers)**



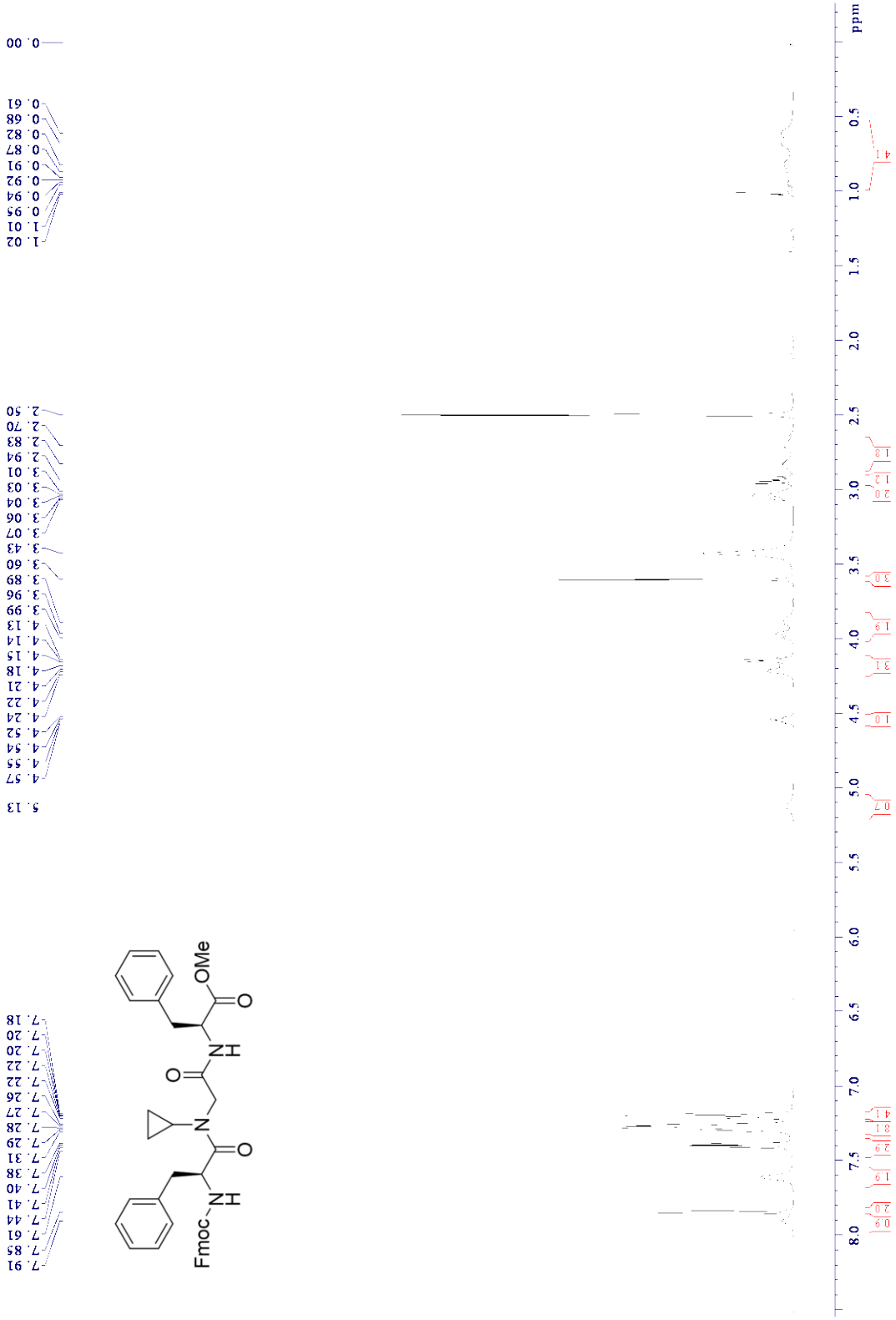
Methyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*N*-cyclopropylglycyl-L-phenylalaninate **15 - ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers)**



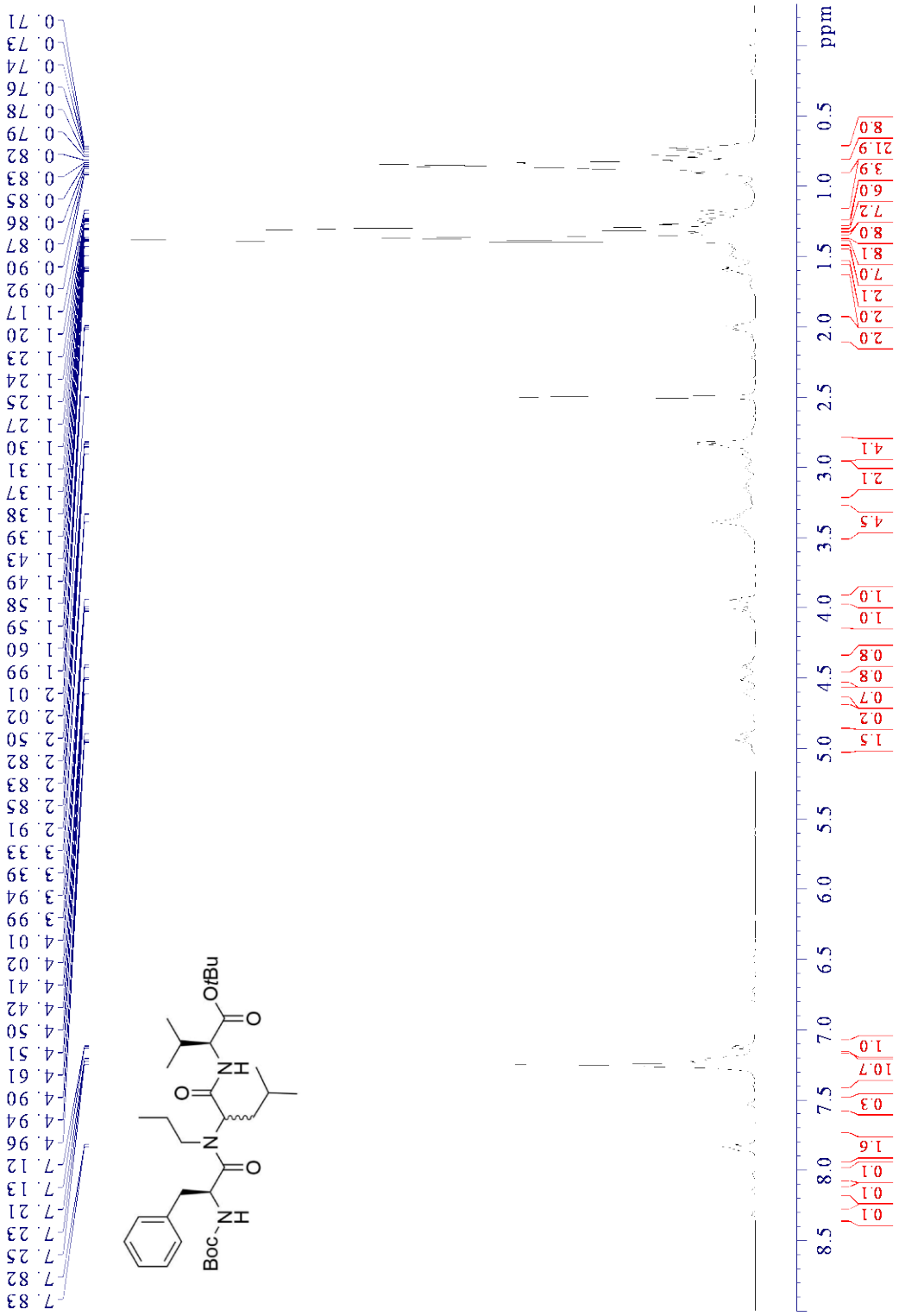
Methyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*N*-cyclopropylglycyl-L-phenylalaninate **15 - ^{13}C NMR (126 MHz, DMSO-d_6)**



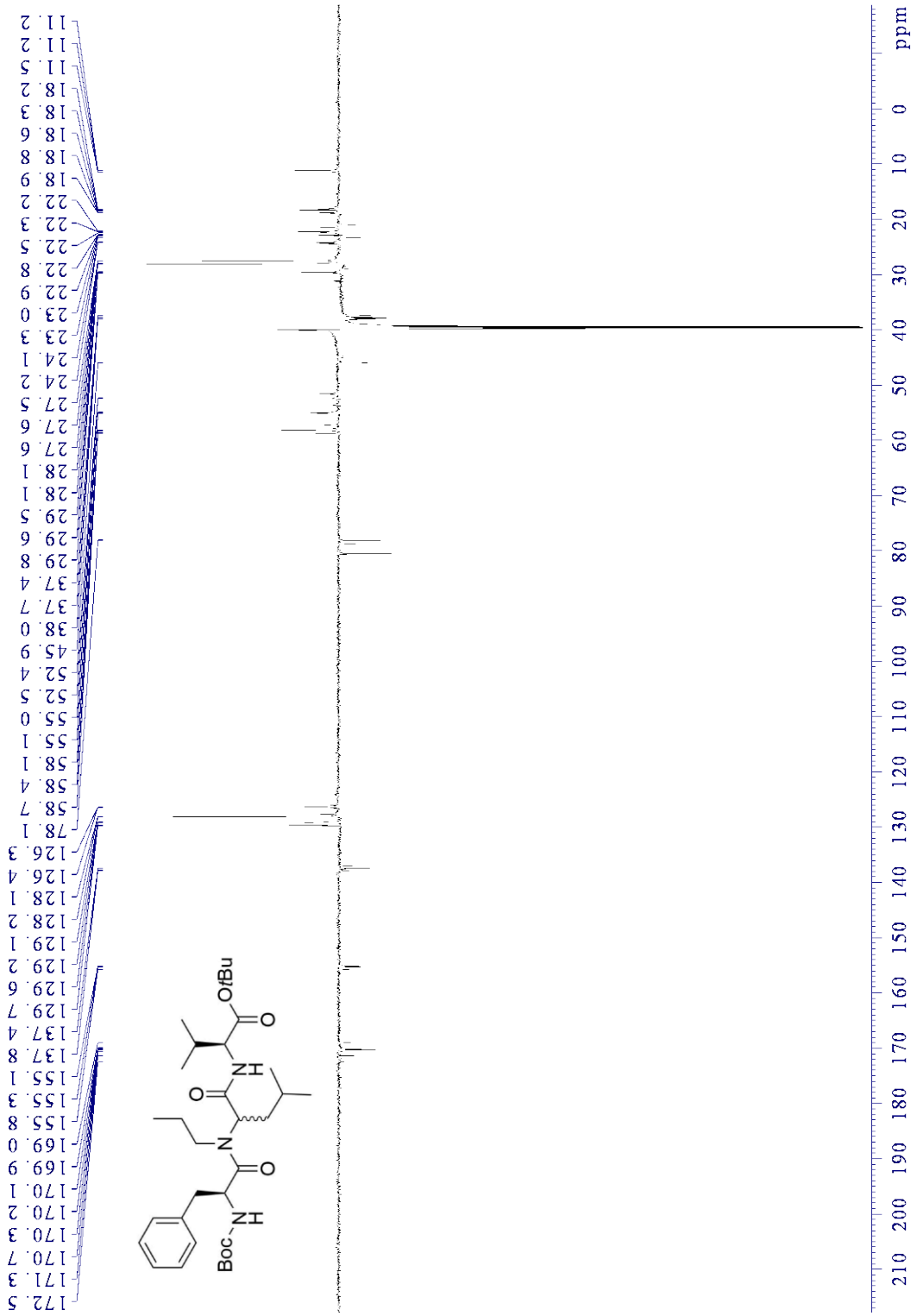
Methyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*N*-cyclopropylglycyl-L-phenylalaninate **15 - ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C)**



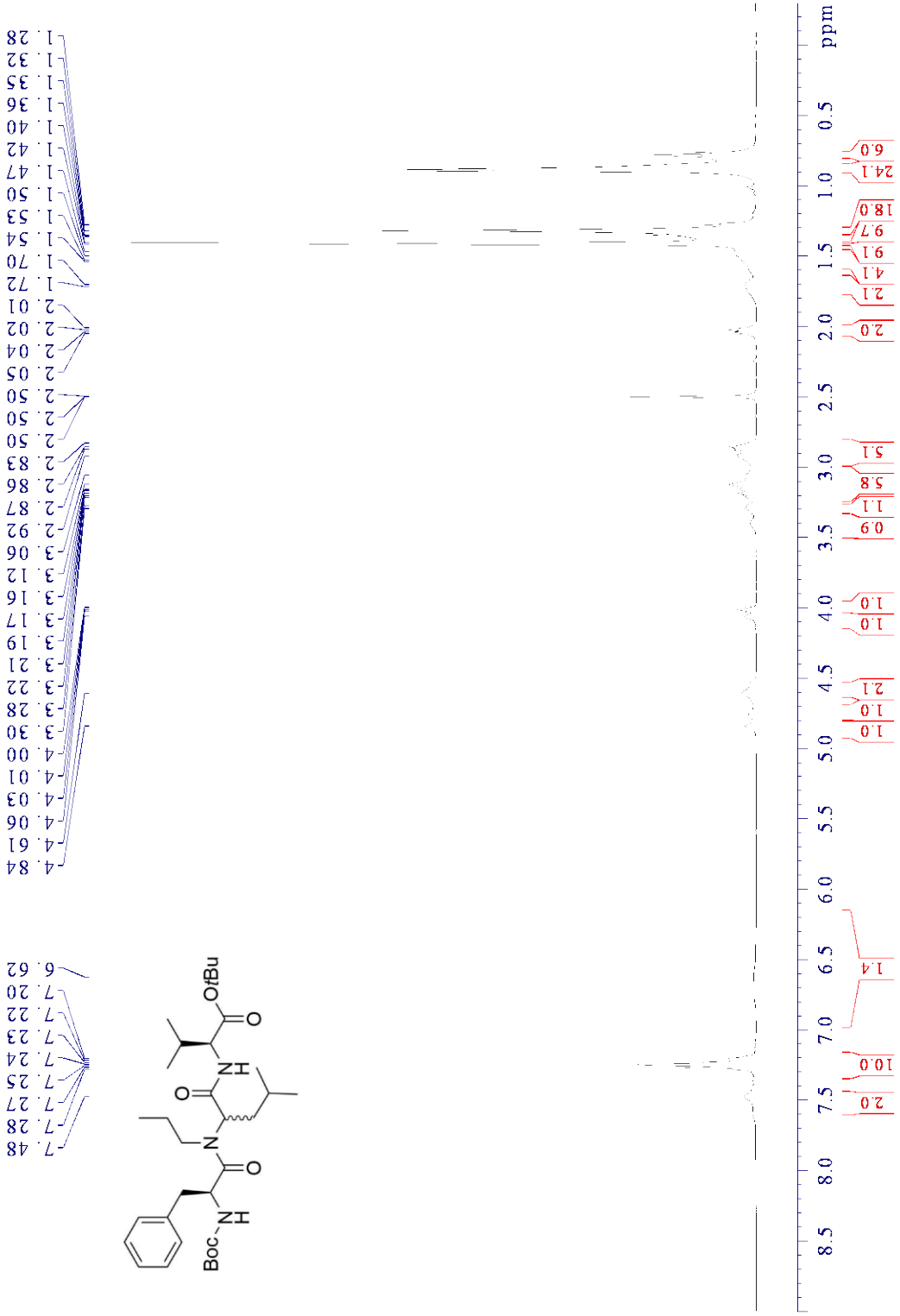
tert-Butyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-valinate 16 - ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)



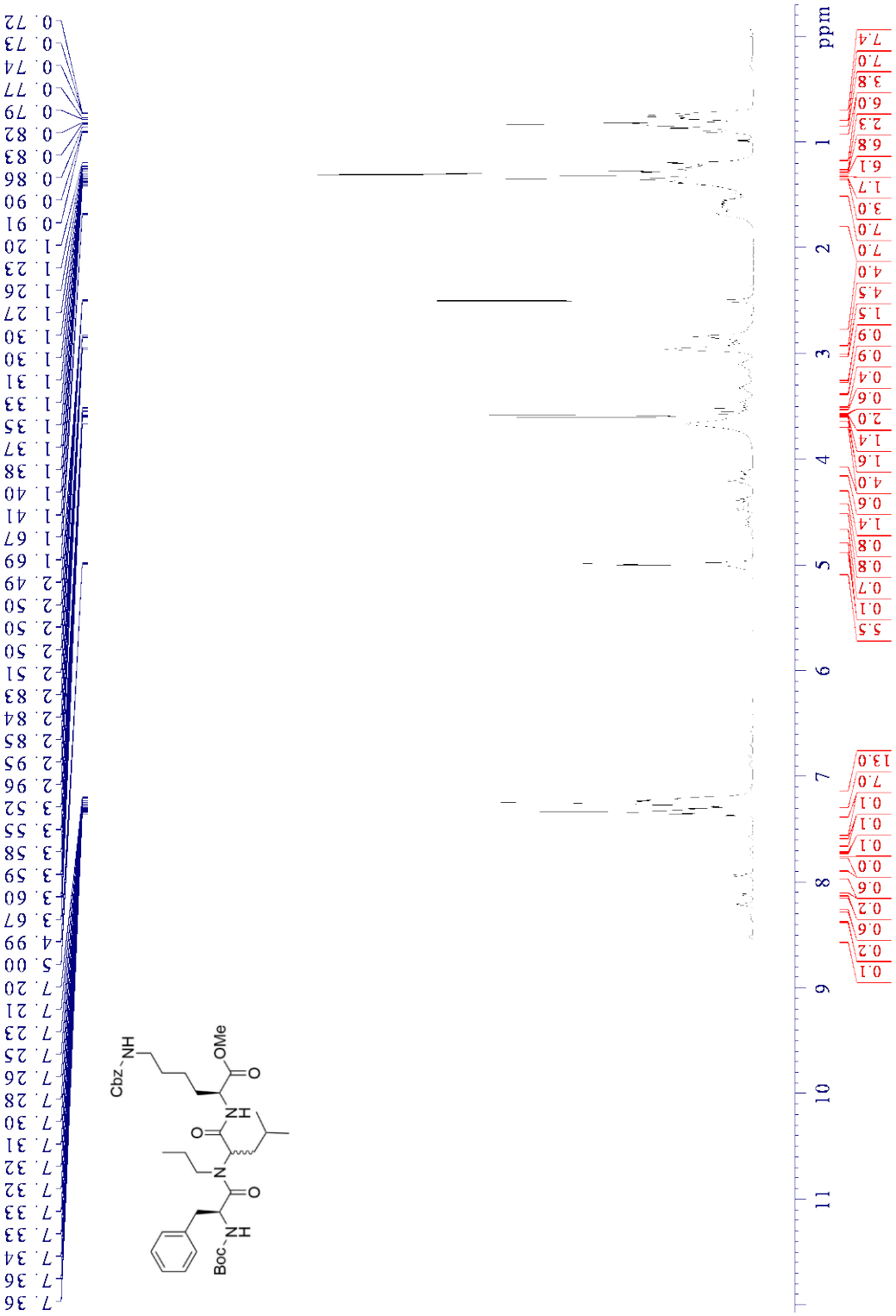
tert-Butyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-valinate **16 – ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers and rotamers)**



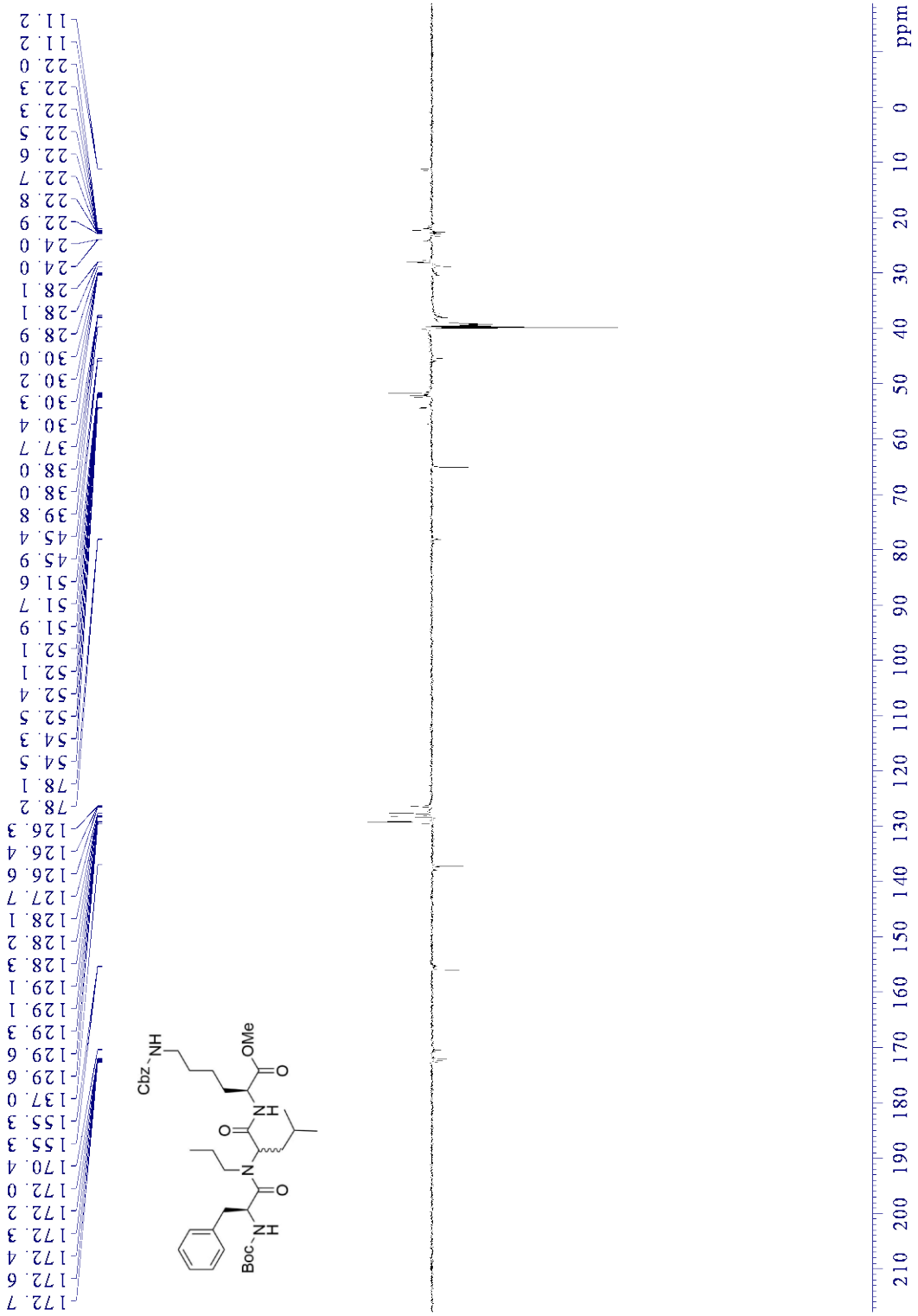
tert-Butyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucyl-L-valinate **16 - ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



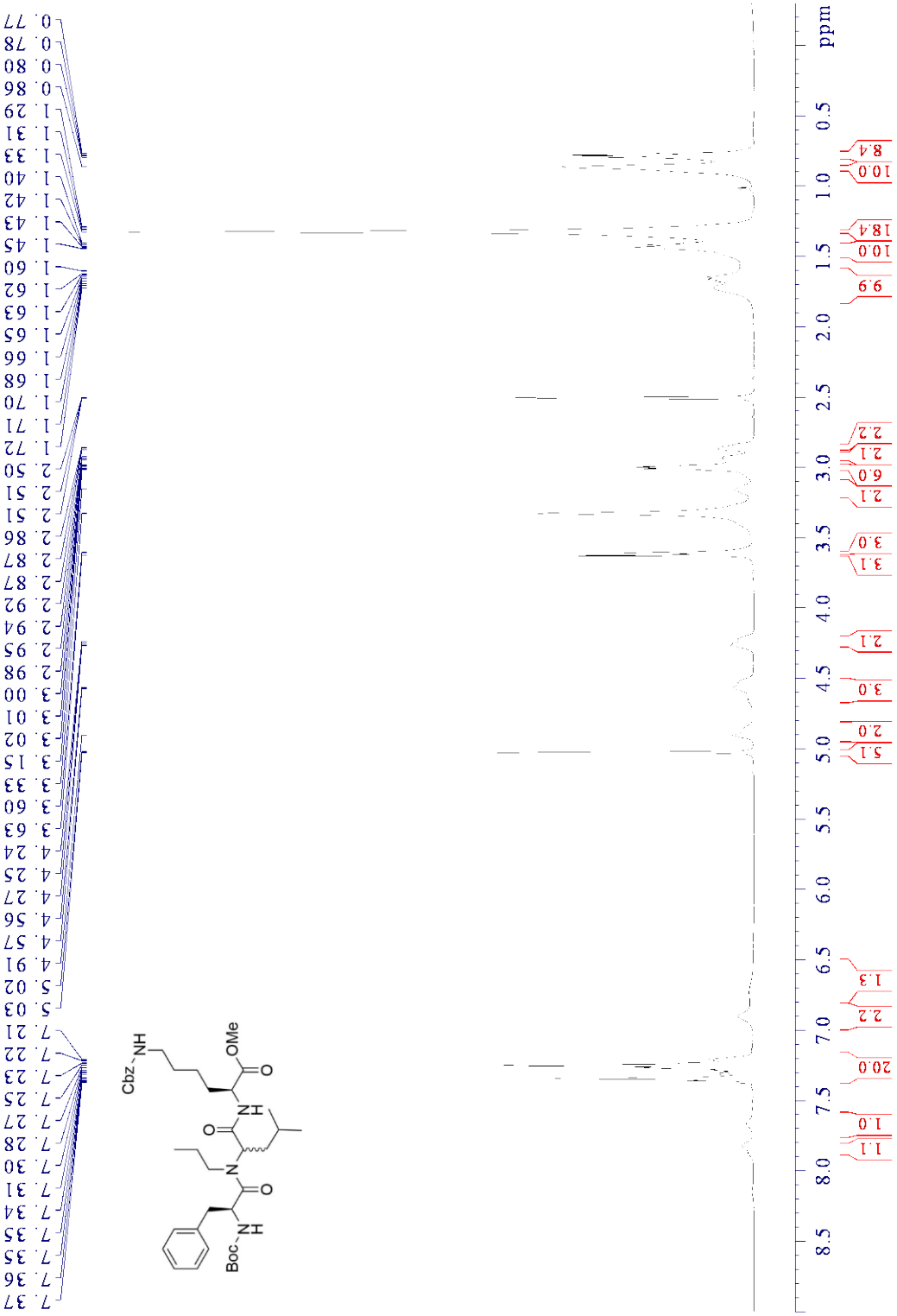
Methyl N^6-((benzyloxy)carbonyl)-N^2-(*N*-((*tert*-butoxycarbonyl)- L -phenylalanyl)-*N*-propylleucyl)-L-lysinate **17 - ^{1}H NMR (500 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



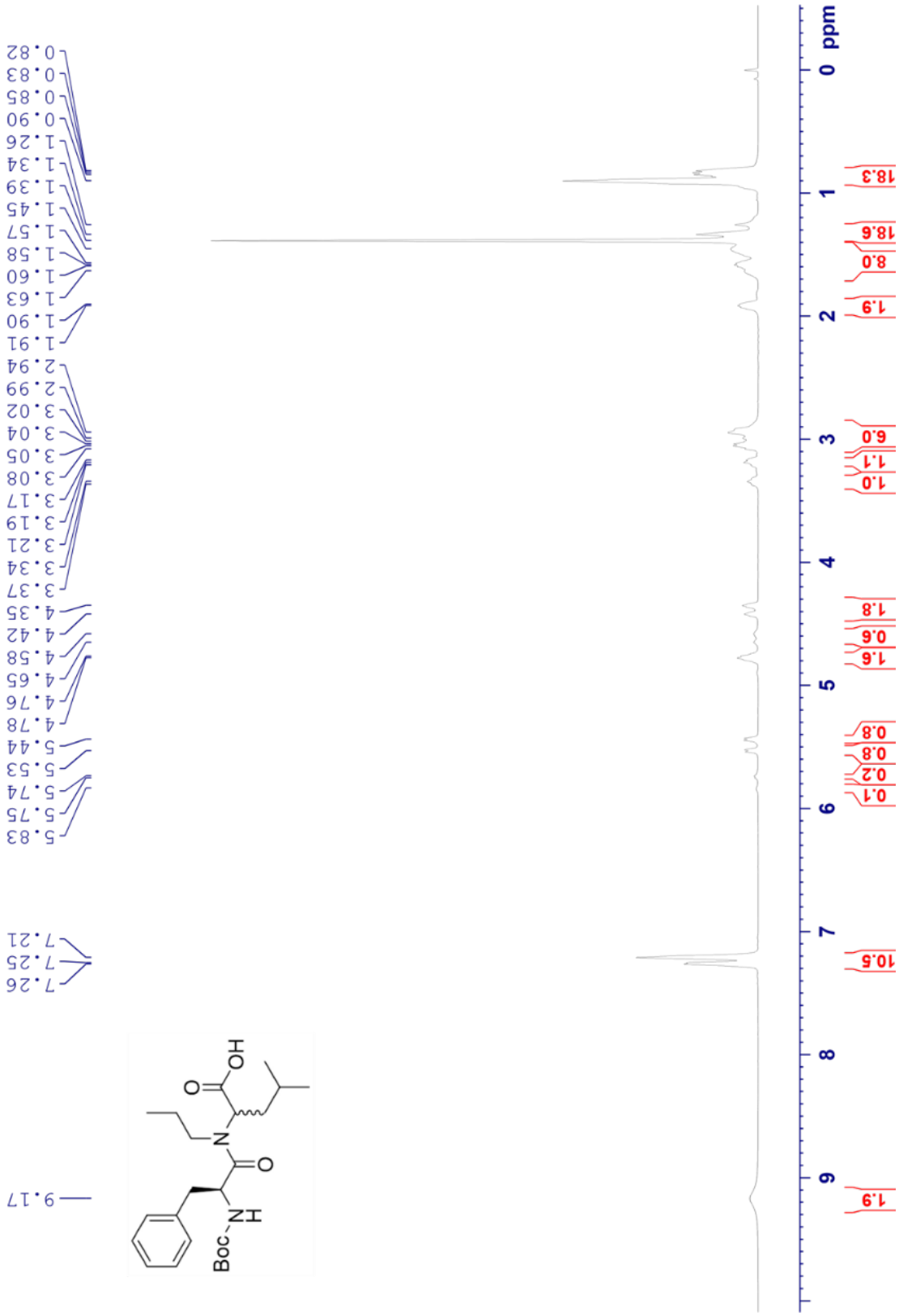
Methyl N^6-((benzyloxy)carbonyl)-N^2-(*N*-((*tert*-butoxycarbonyl)- L -phenylalanyl)-*N*-propylleucyl)-L-lysinate **17 - ^{13}C NMR (126 MHz, DMSO-d_6, mixture of diastereomers in a 1:1 ratio and rotamers)**



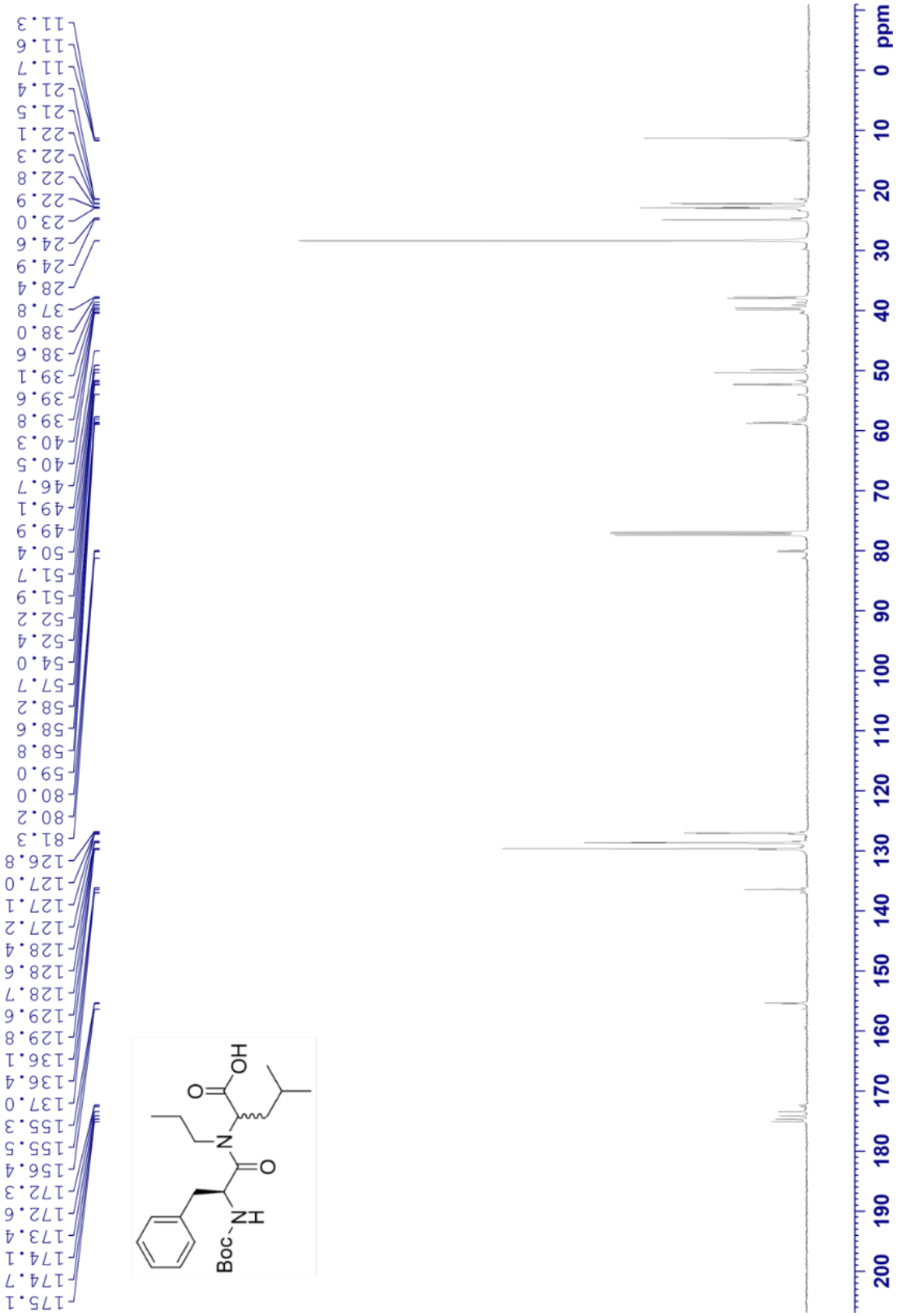
Methyl N^6-((benzyloxy)carbonyl)-N^2-(*N*-((*tert*-butoxycarbonyl)- L -phenylalanyl)-*N*-propylleucyl)-L-lysinate **17 - ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)**



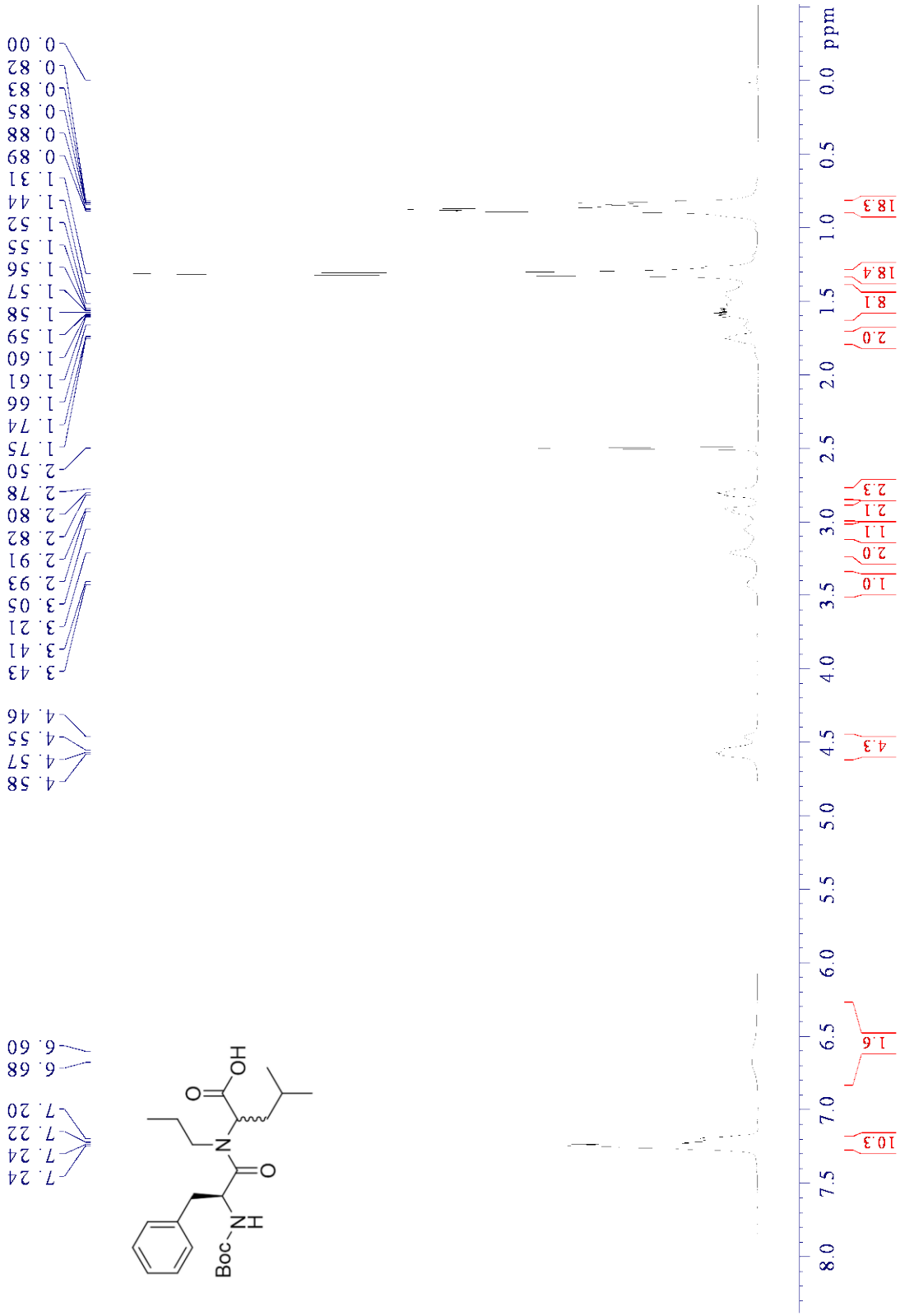
N-((*tert*-Butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucine 18 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)



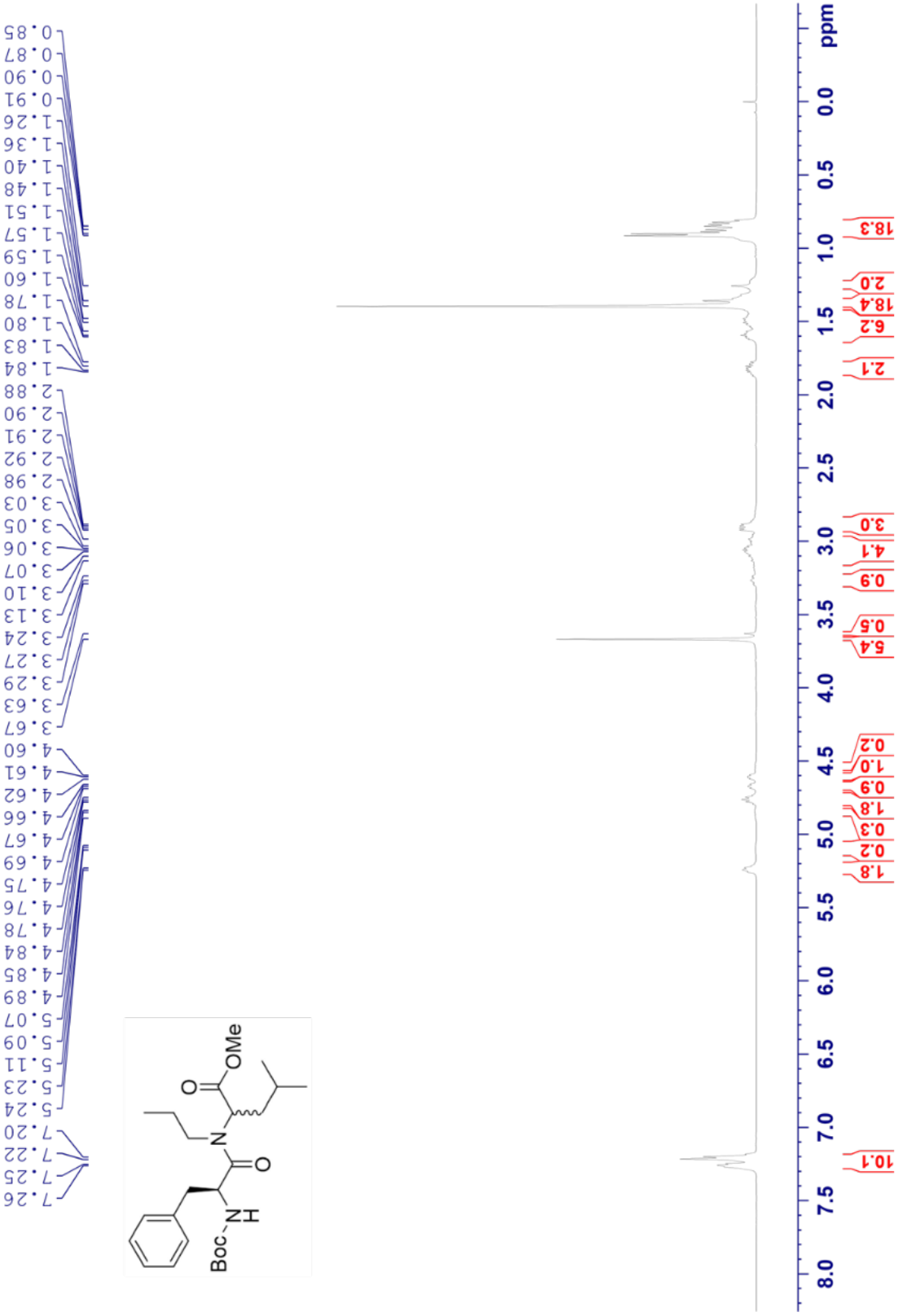
N-((*tert*-Butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucine 14 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)



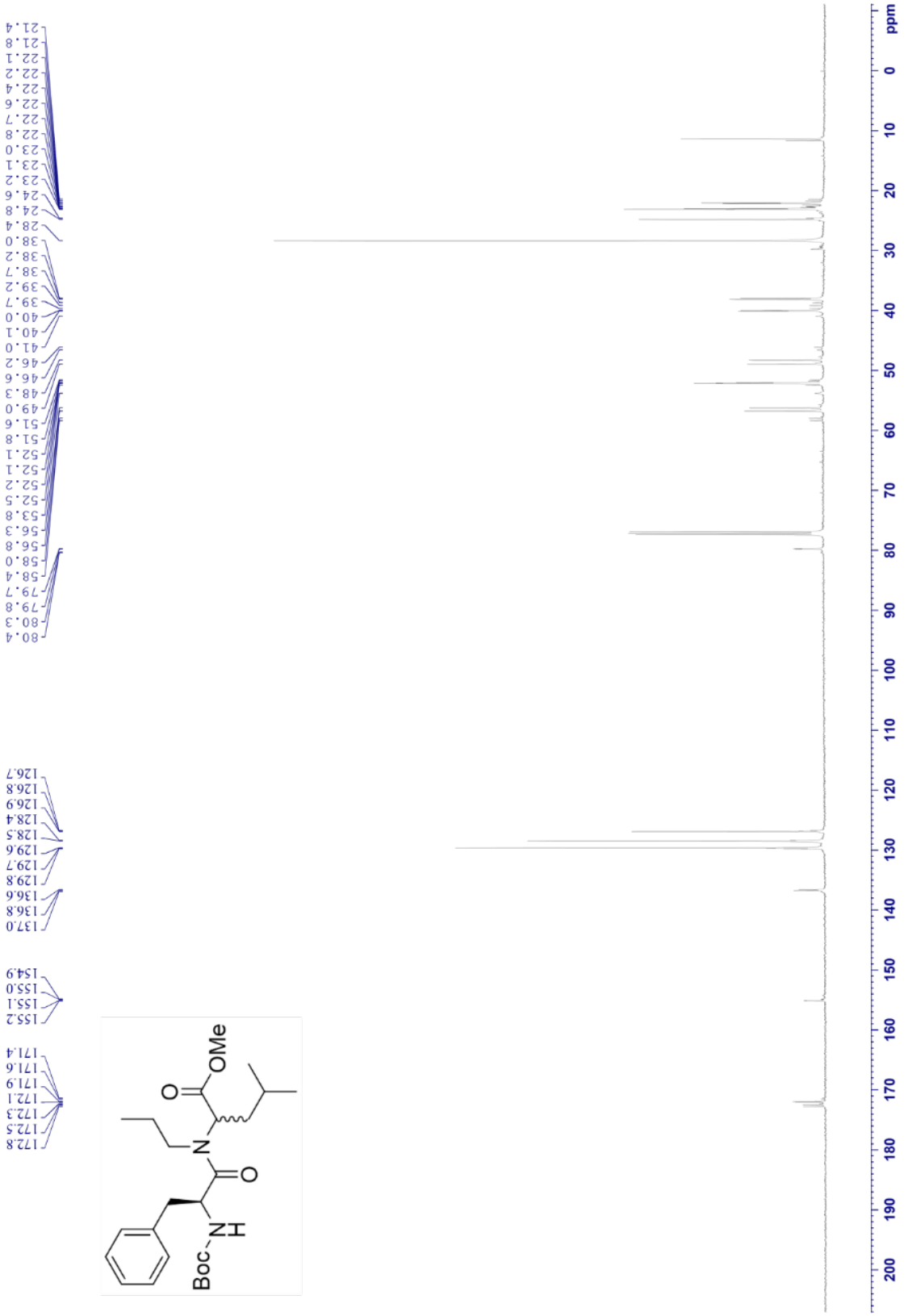
N-((*tert*-Butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucine 18 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



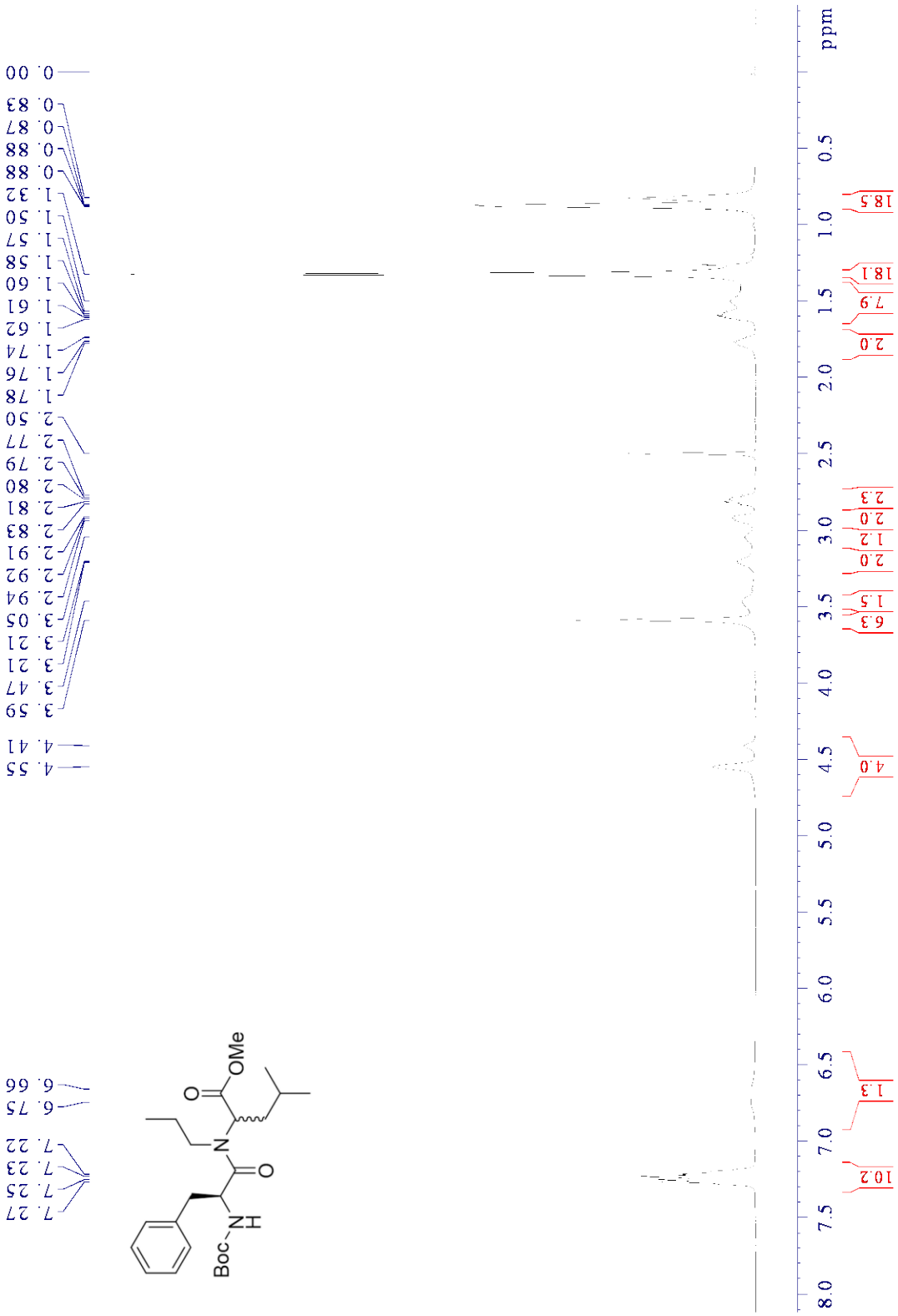
Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucinate 19 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio and rotamers)



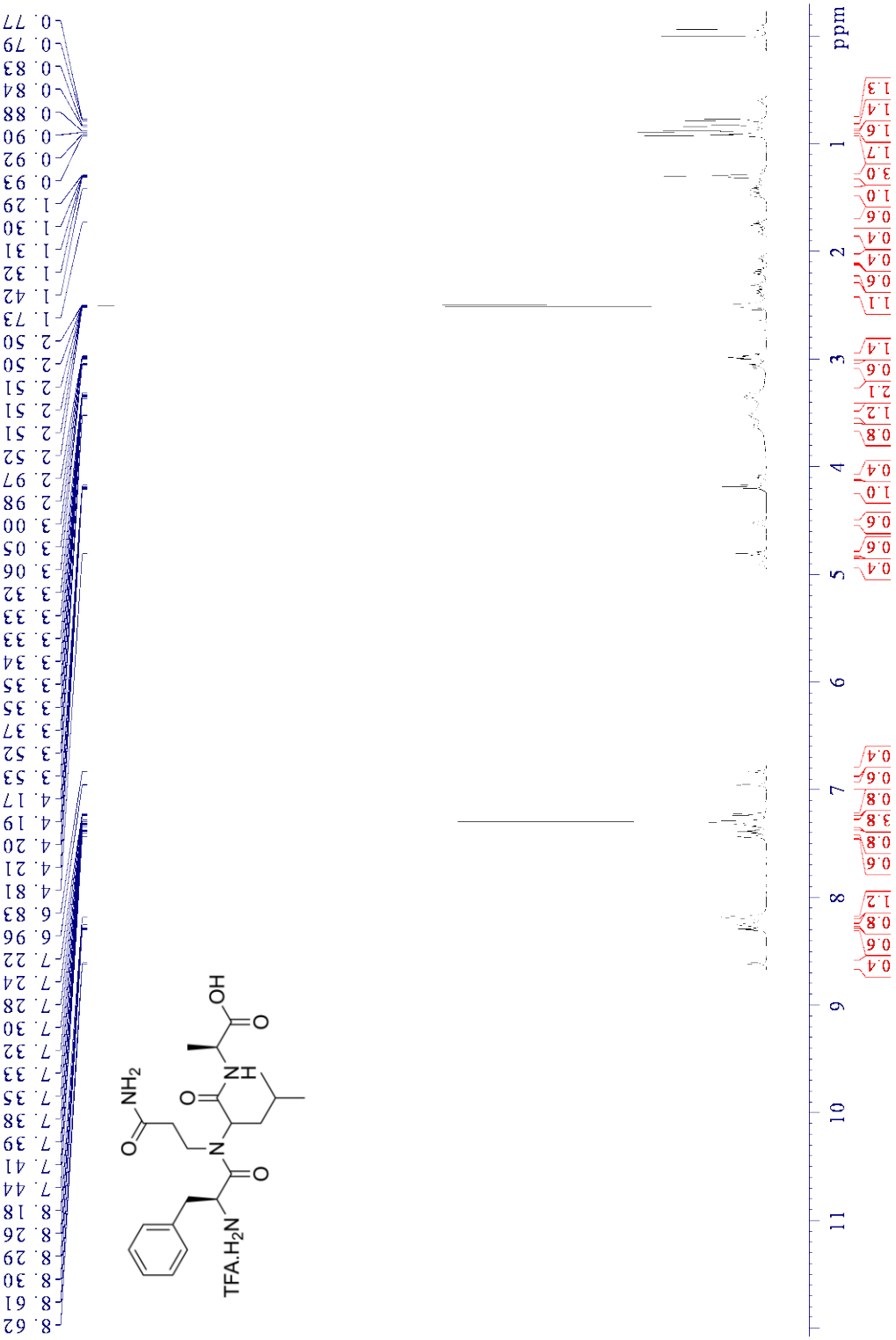
Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucinate 19 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers and rotamers)



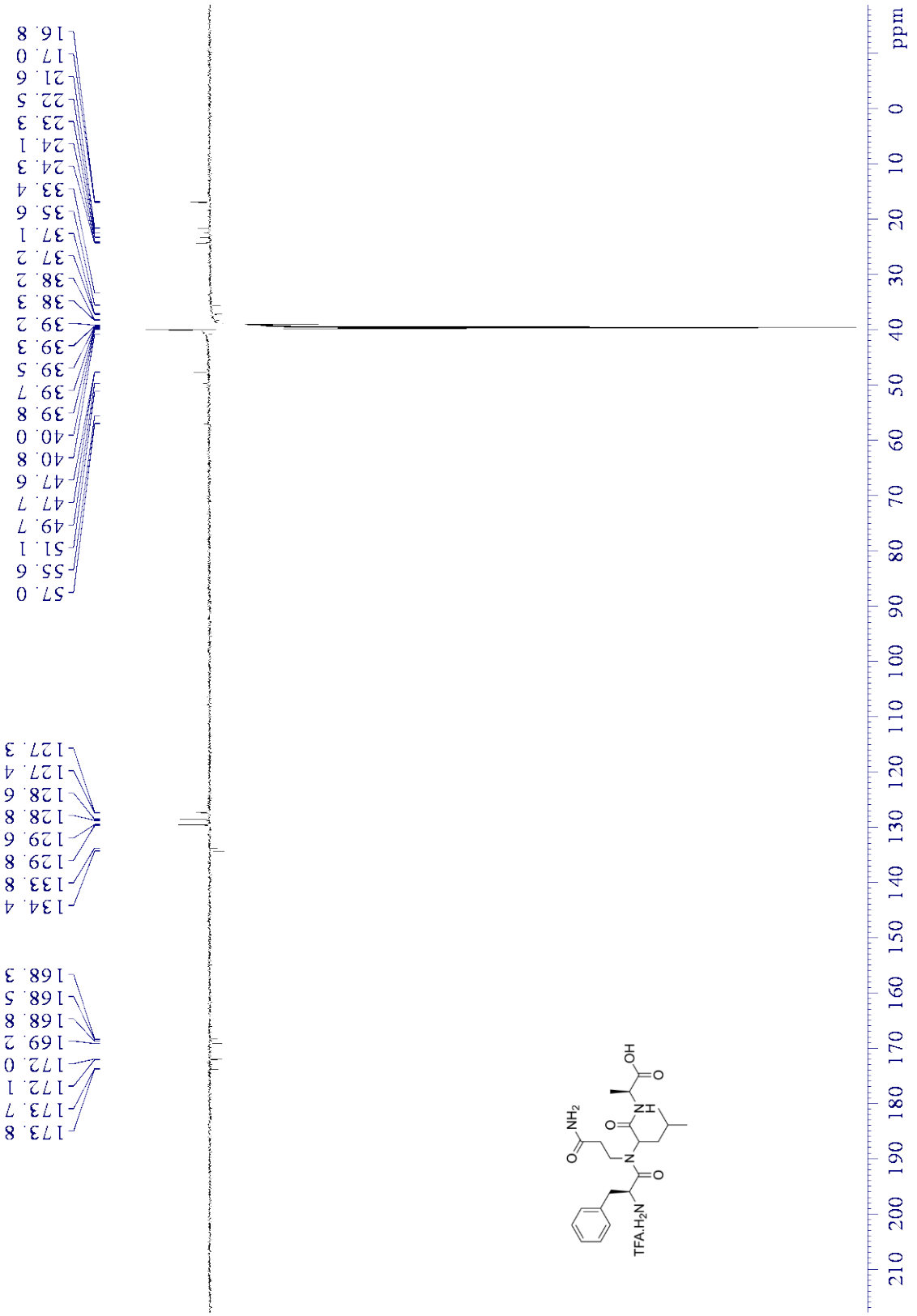
Methyl *N*-((*tert*-butoxycarbonyl)-L-phenylalanyl)-*N*-propylleucinate 19 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, mixture of diastereomers in a 1:1 ratio)



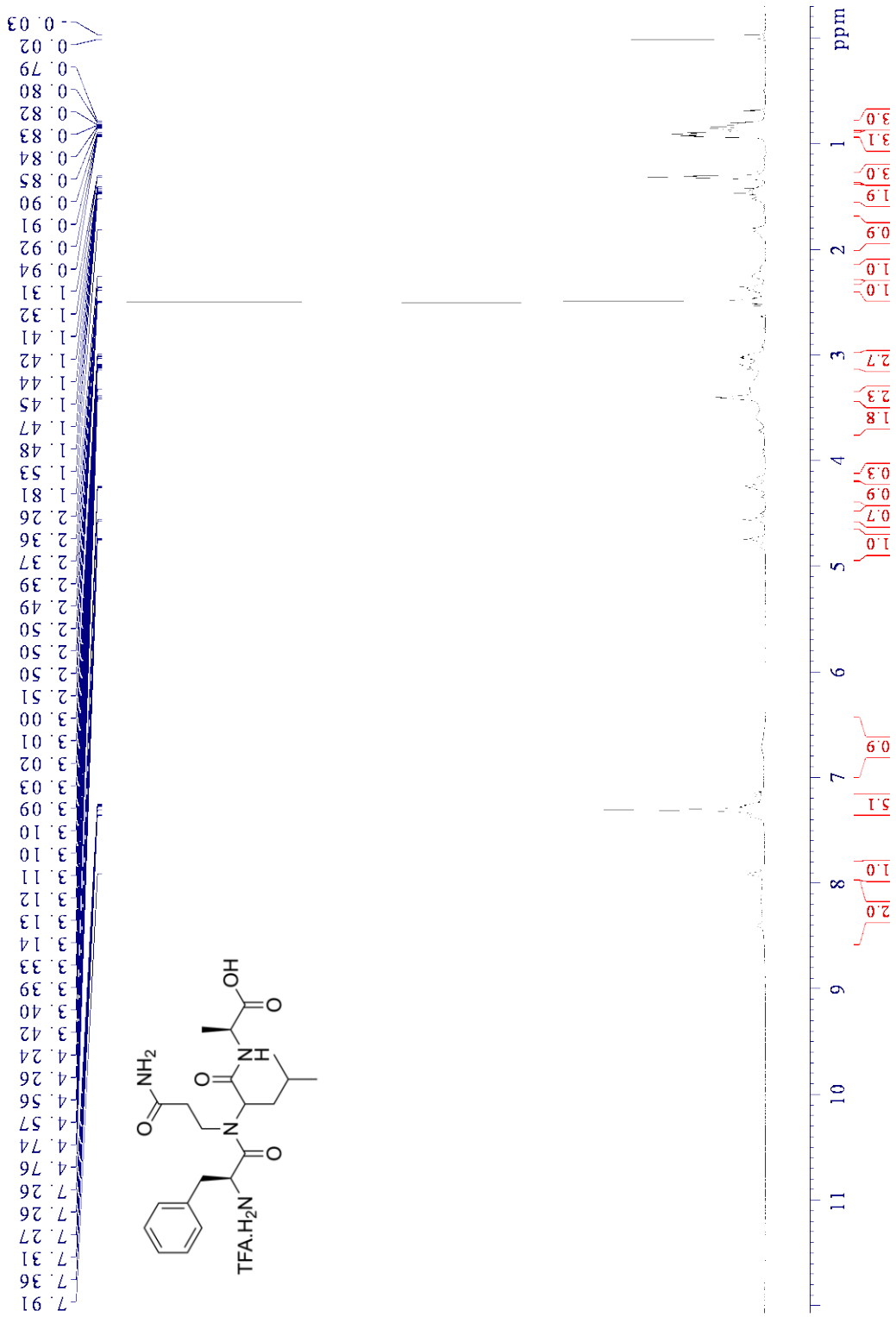
N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 1, mixture of rotamers**)



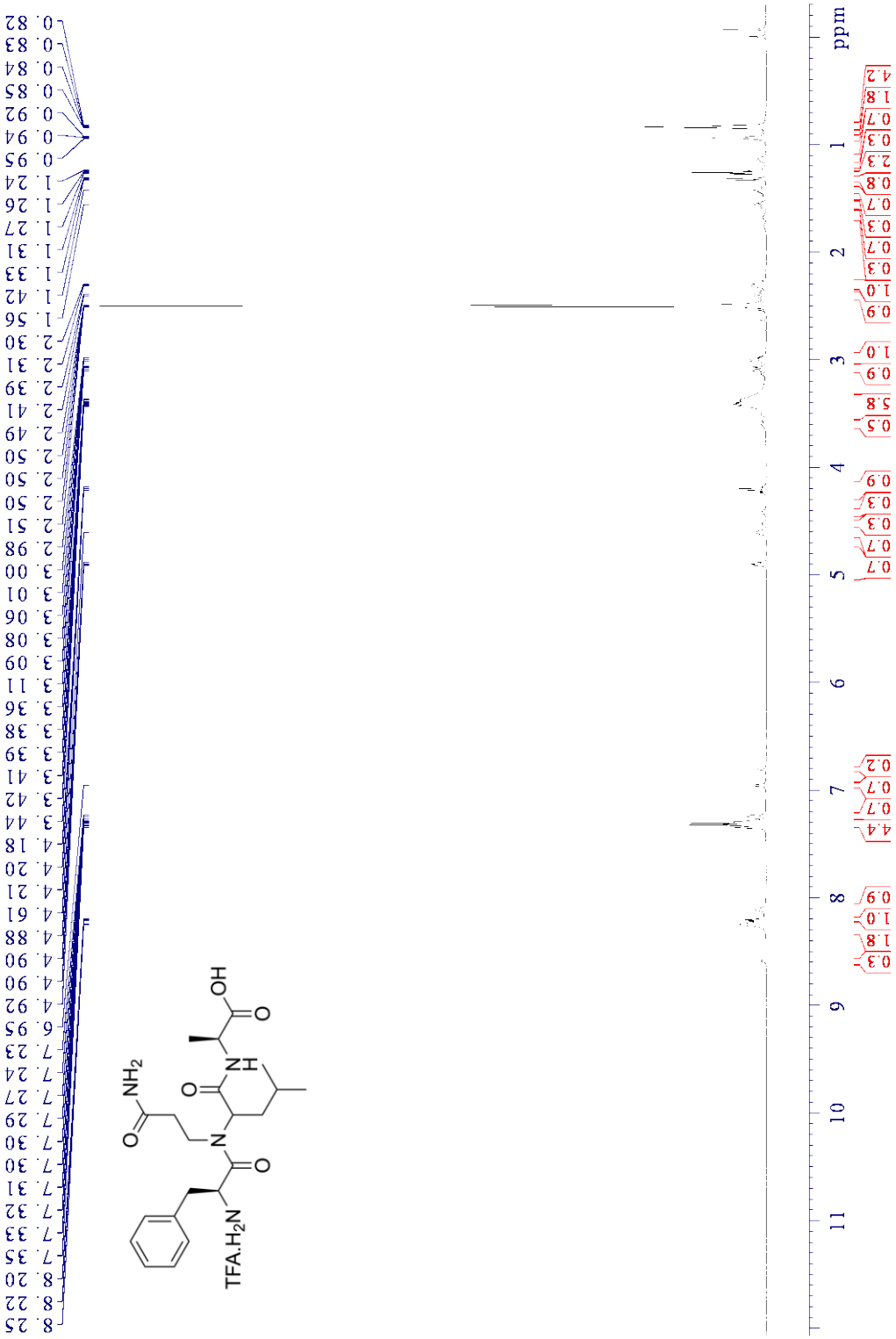
N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{13}C NMR (126 MHz, DMSO-*d*$_6$, diastereomer 1, mixture of rotamers)**



N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, diastereomer 1, mixture of rotamers**)

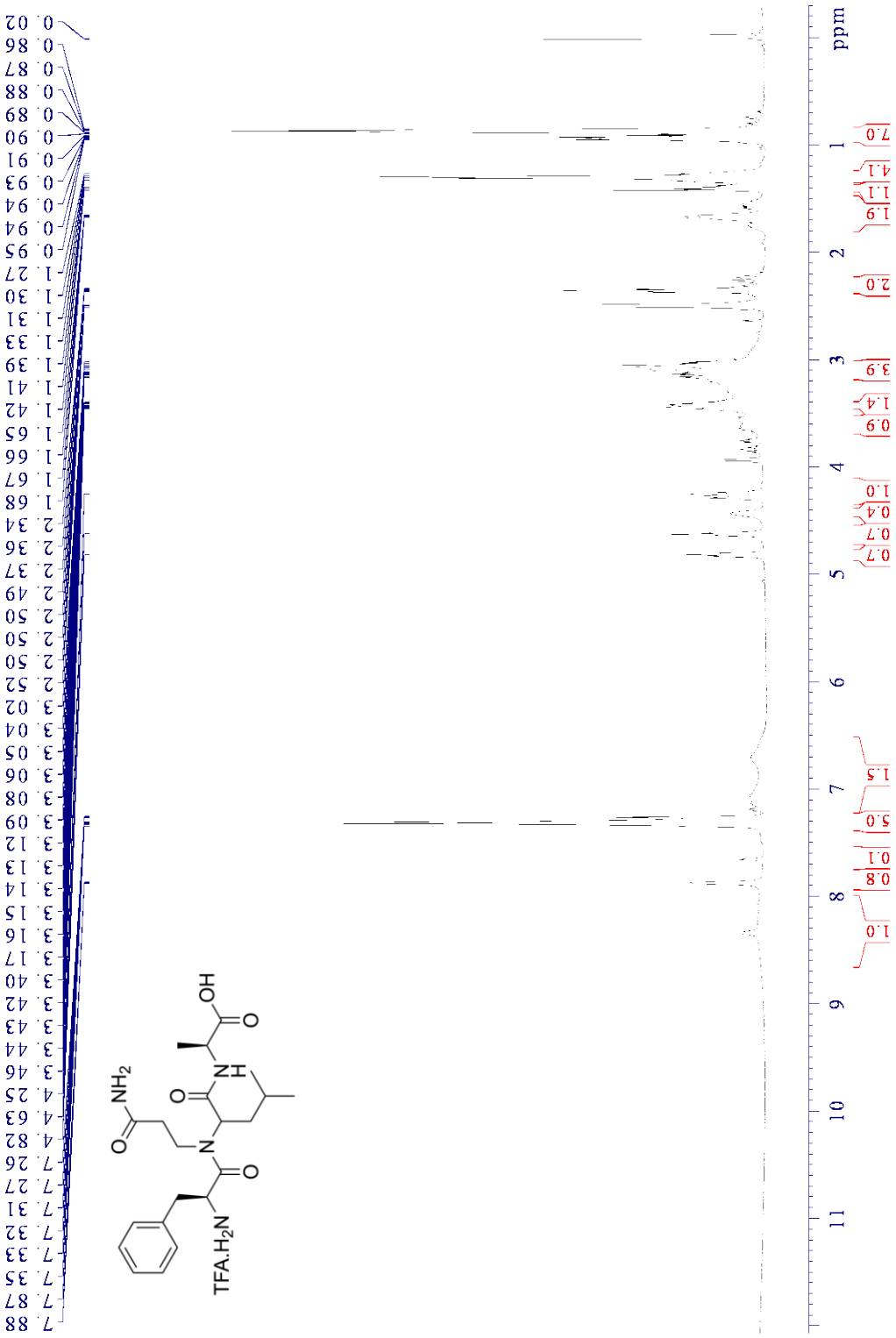


N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 2, mixture of rotamers)**

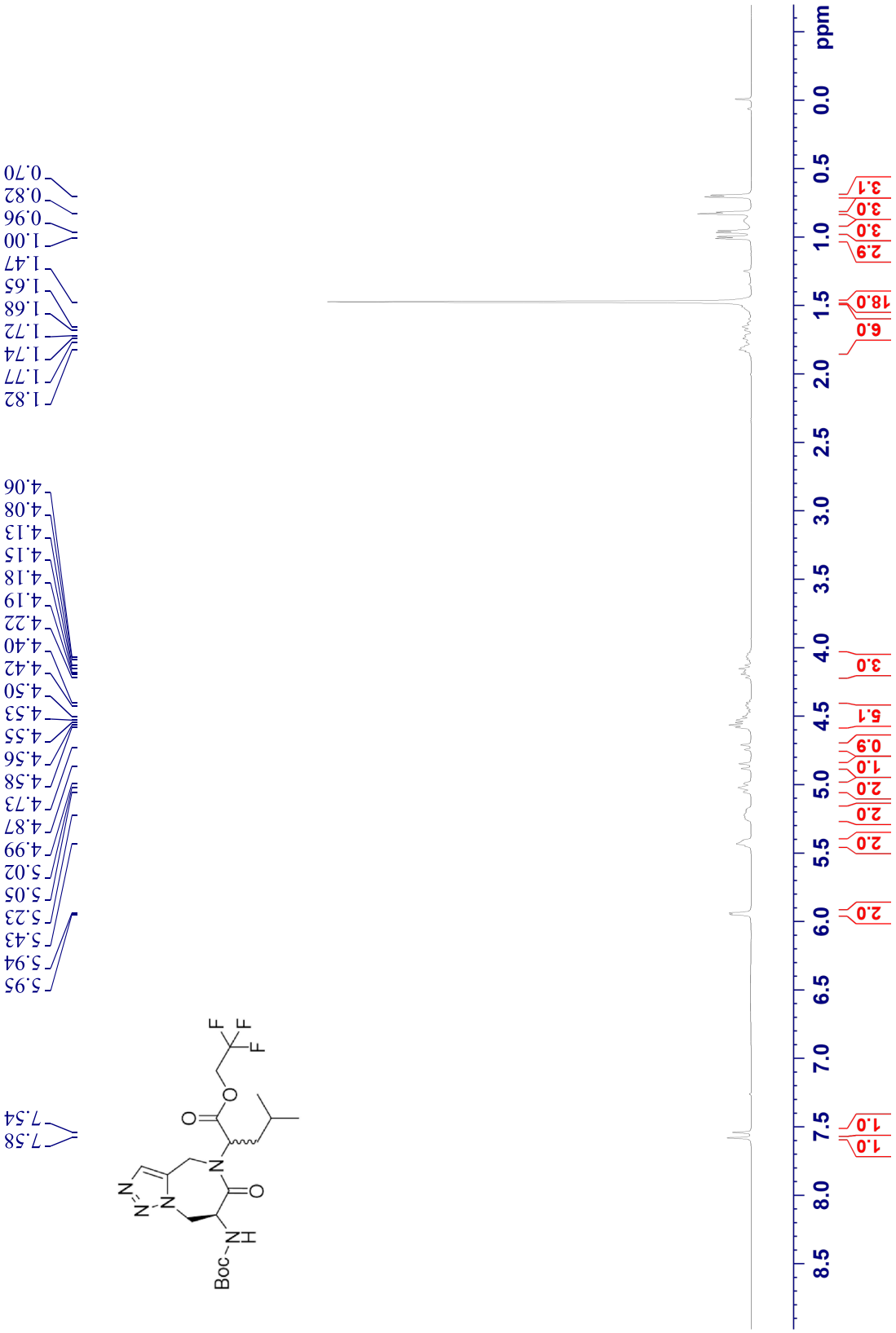


N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{13}C NMR (126 MHz, DMSO-d_6, diastereomer 2, mixture of rotamers)**

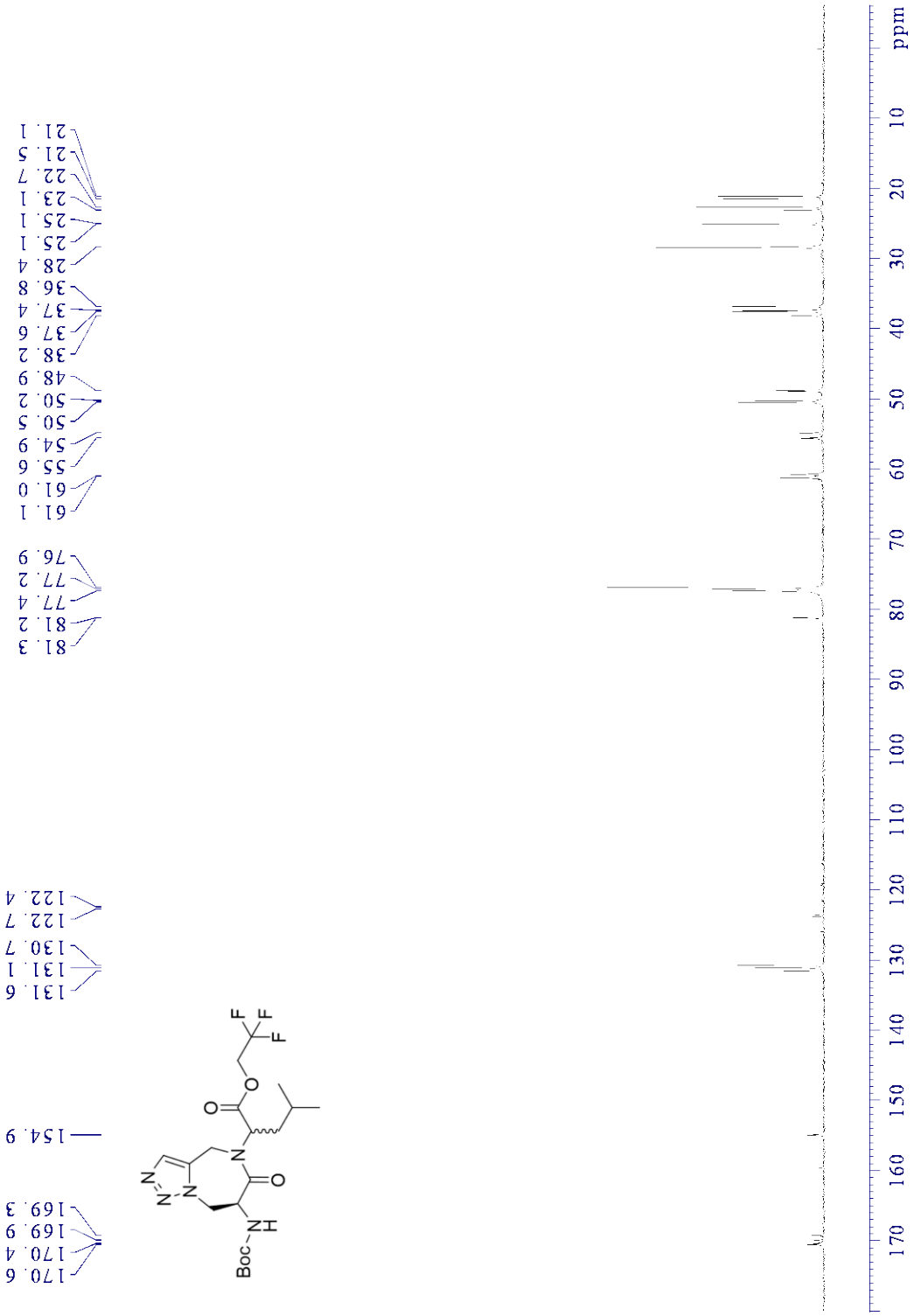
N-(3-amino-3-oxopropyl)-*N*-((*S*)-3-phenyl-2-((2,2,2-trifluoroacetyl)-λ⁴-azaneyl)propanoyl)leucyl-L-alanine **21 – ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C, diastereomer 2**)



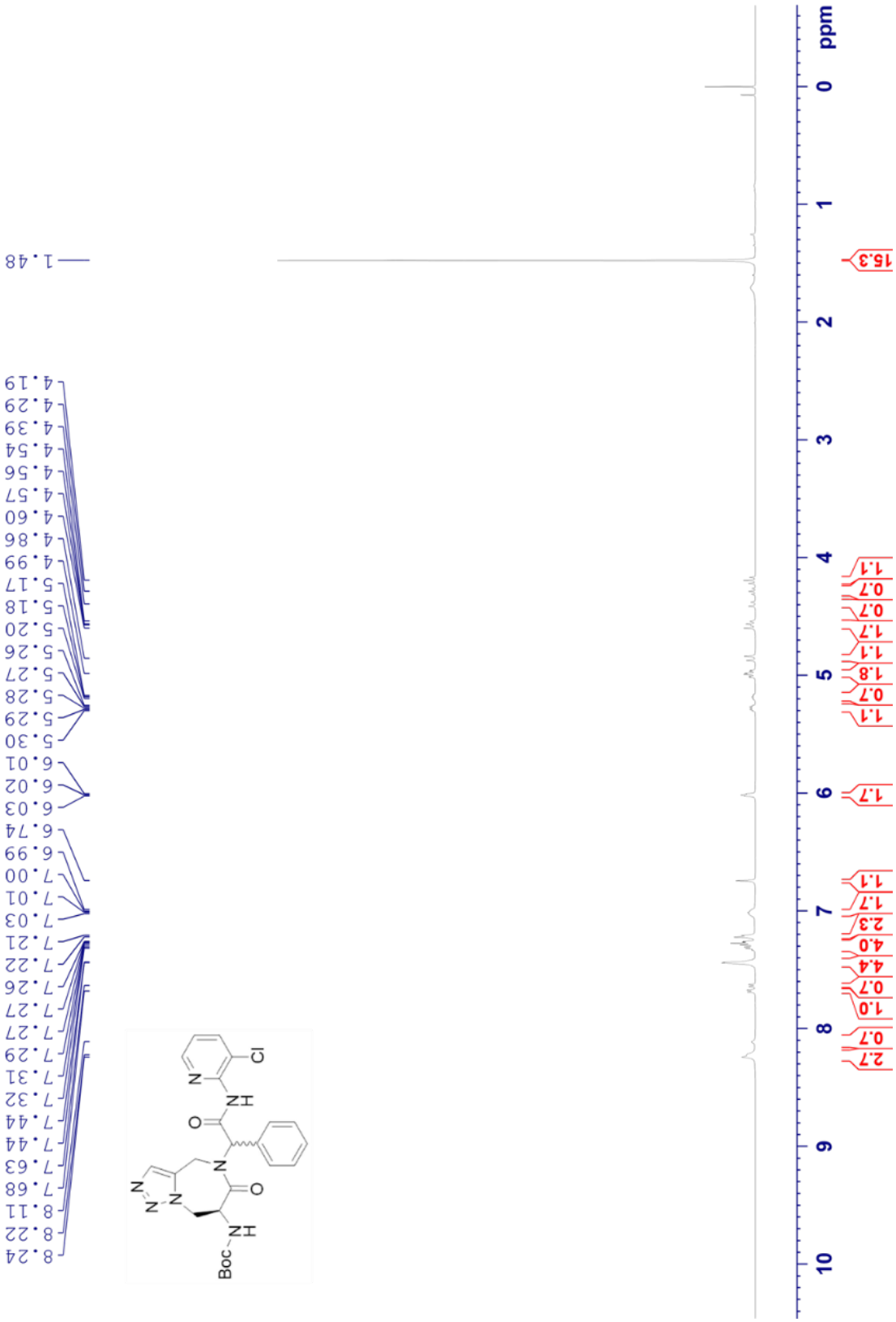
2,2,2-Trifluoroethyl 2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-4-methylpentanoate **S4 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)**



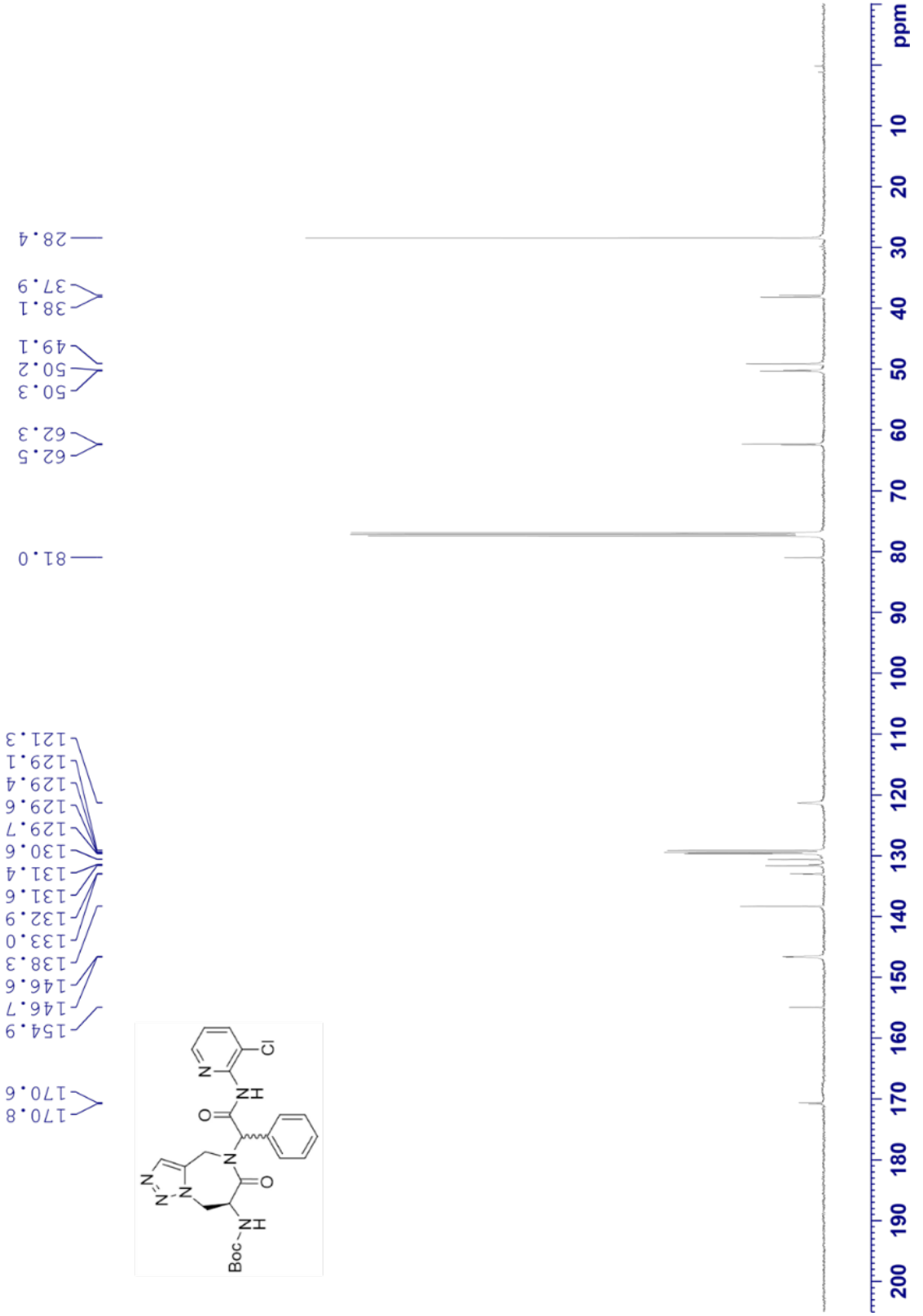
2,2,2-Trifluoroethyl 2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-4-methylpentanoate **S4 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**



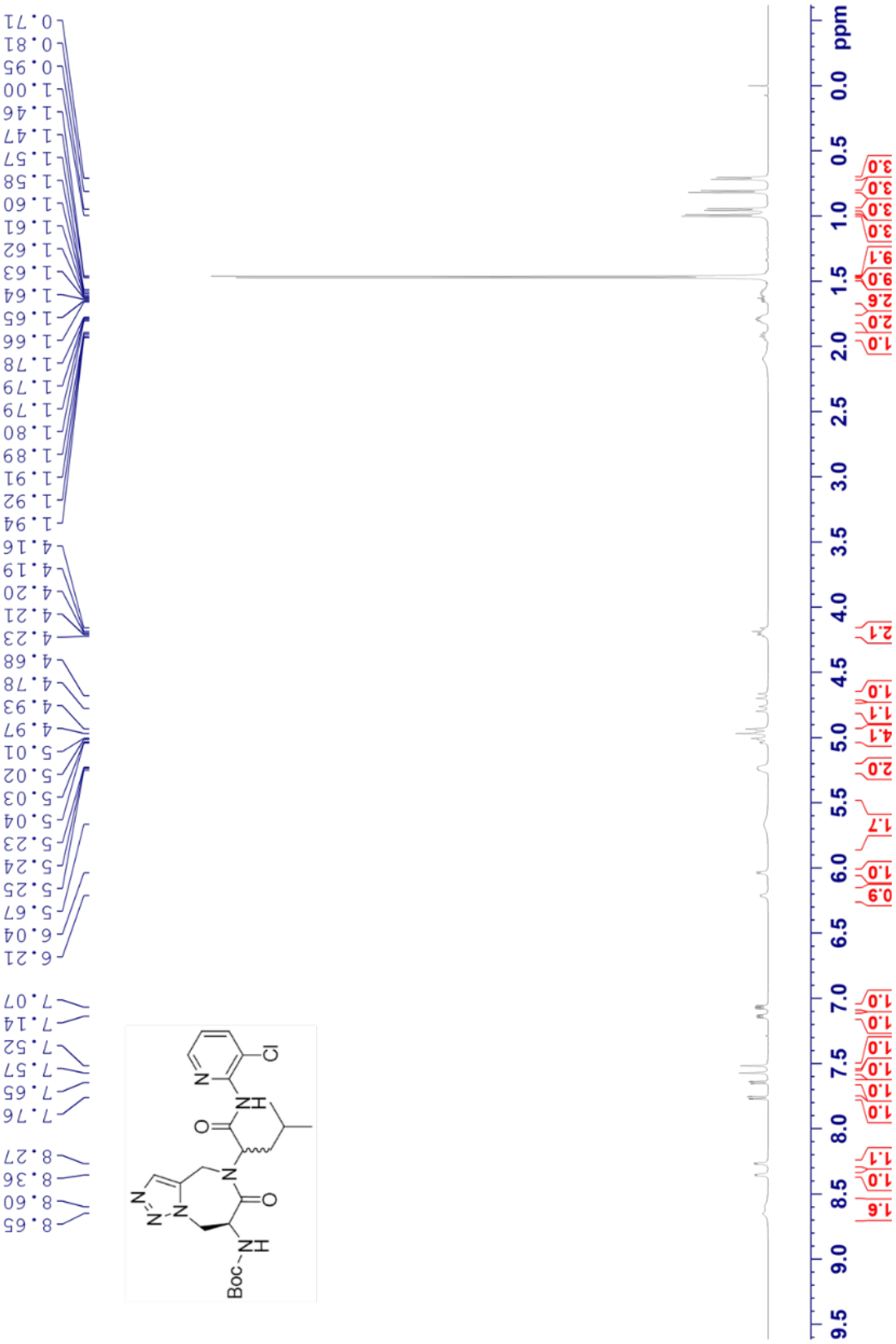
tert-Butyl (S)-(5-(2-((3-chloropyridin-2-yl)amino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25a – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:0.7 ratio)**



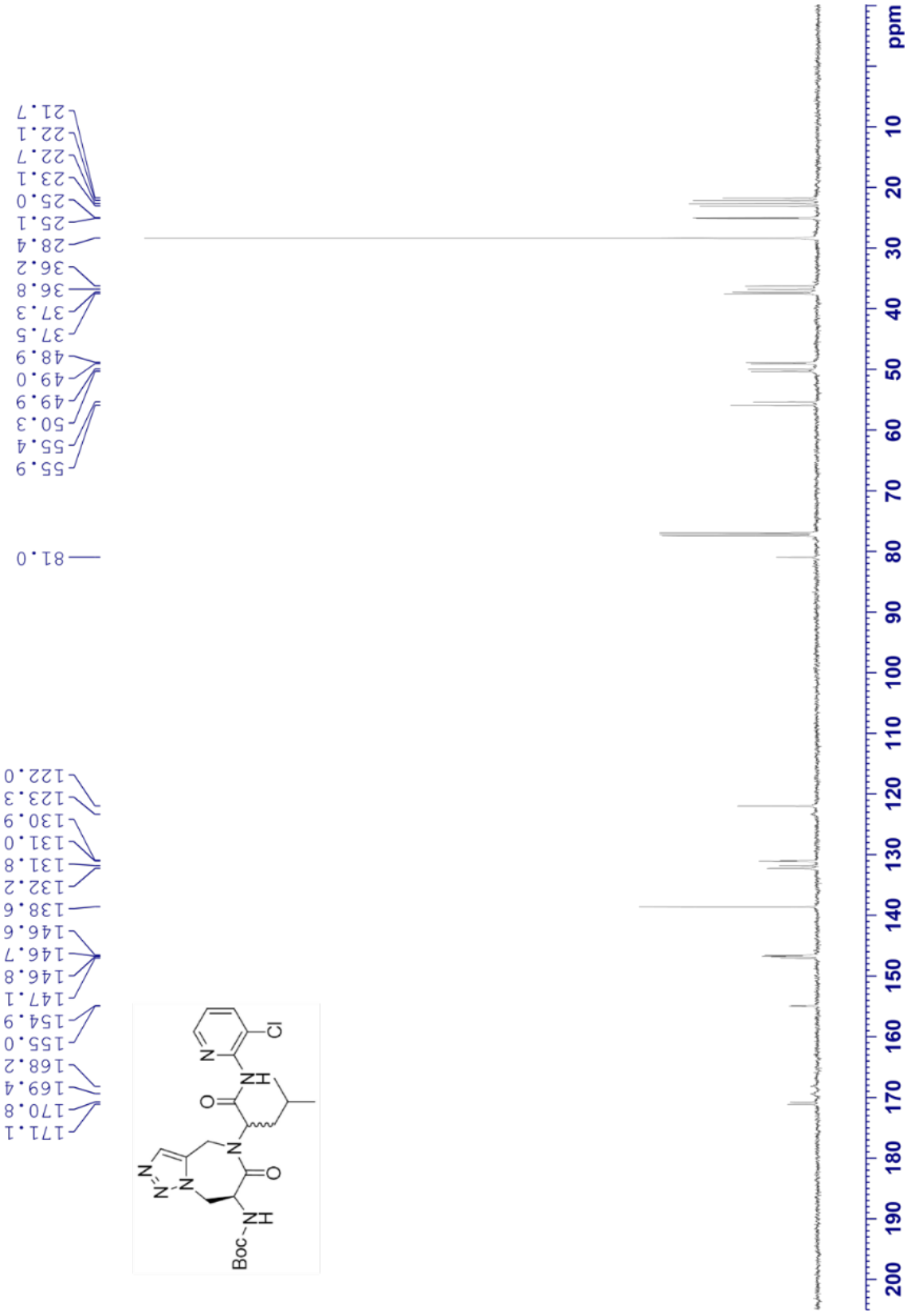
tert-Butyl (S)-(5-(2-((3-chloropyridin-2-yl)amino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25a – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**



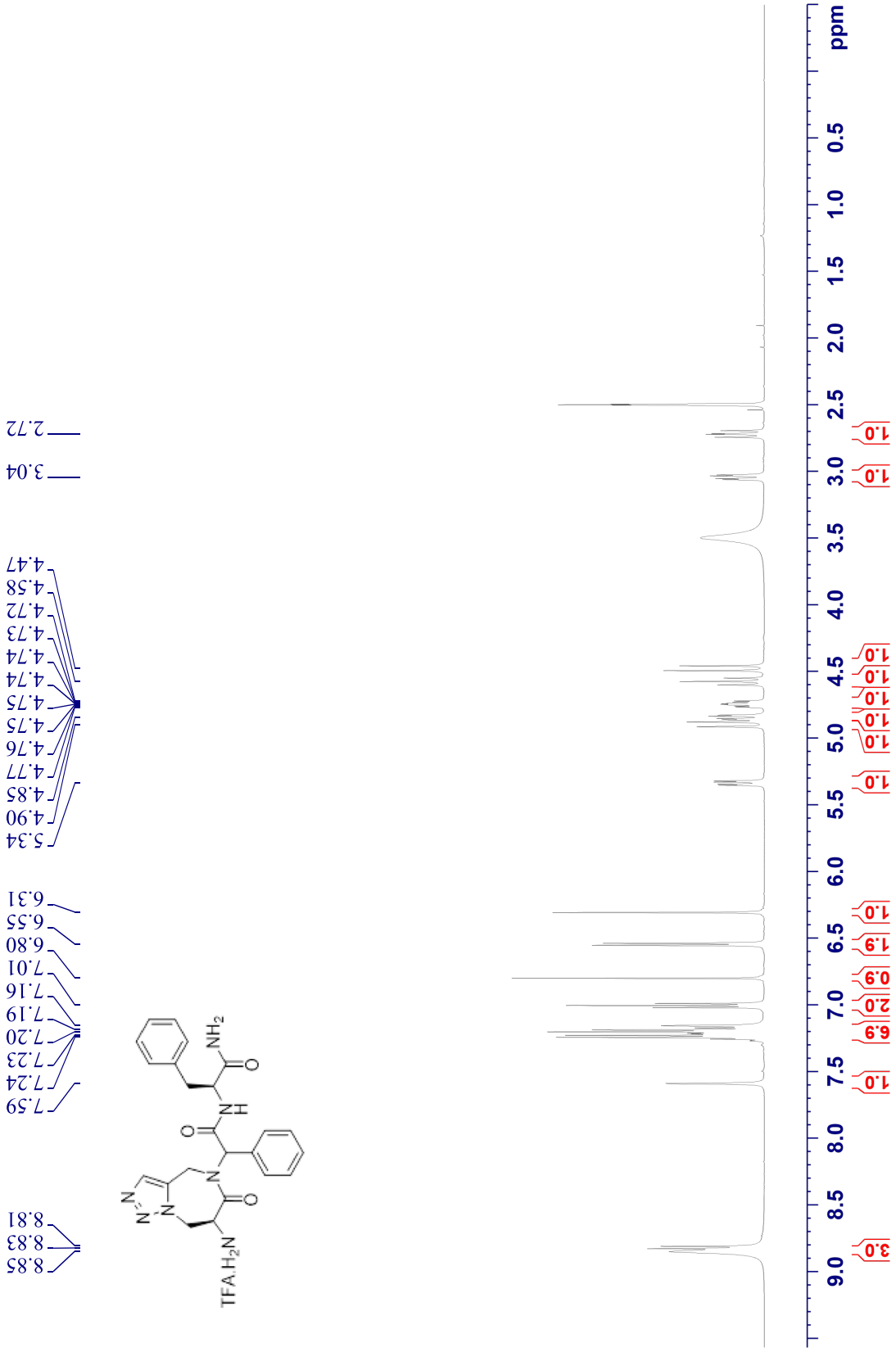
tert-Butyl ((7S)-5-(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25b – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)**



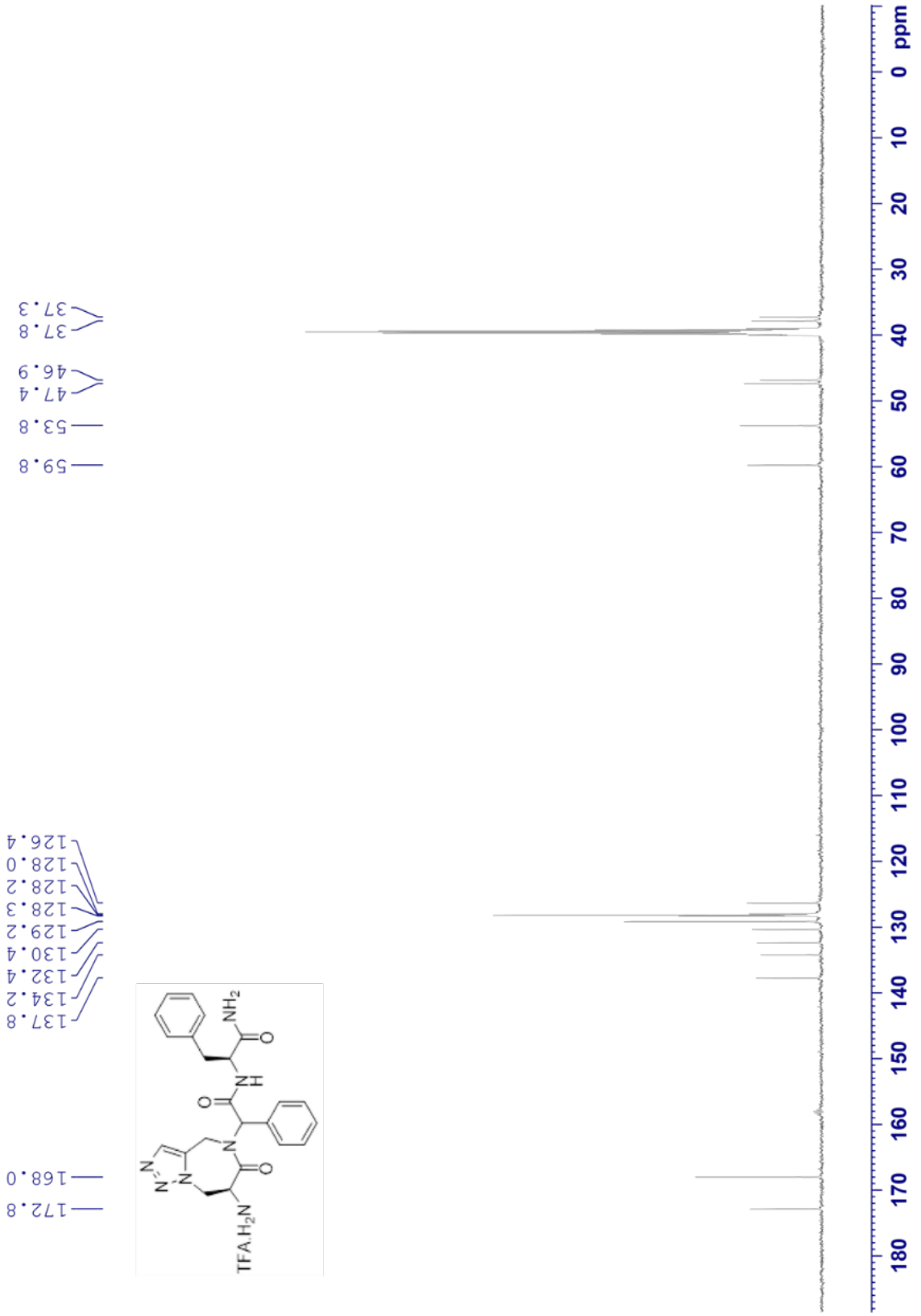
tert-Butyl ((7S)-5-(1-((3-chloropyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate **25b – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**



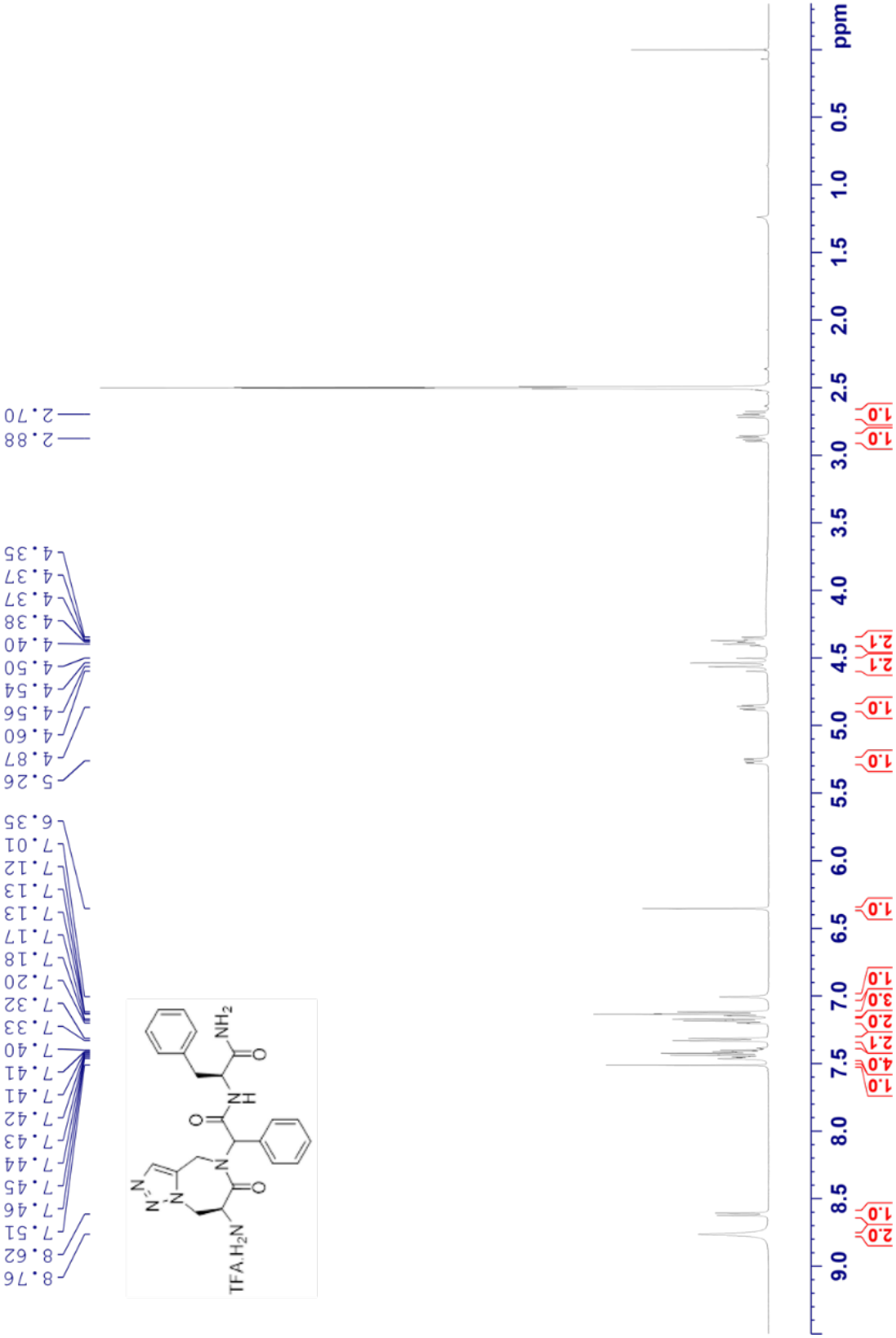
(*S*)-2-(2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)-3-phenylpropanamide **26a – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 1)**



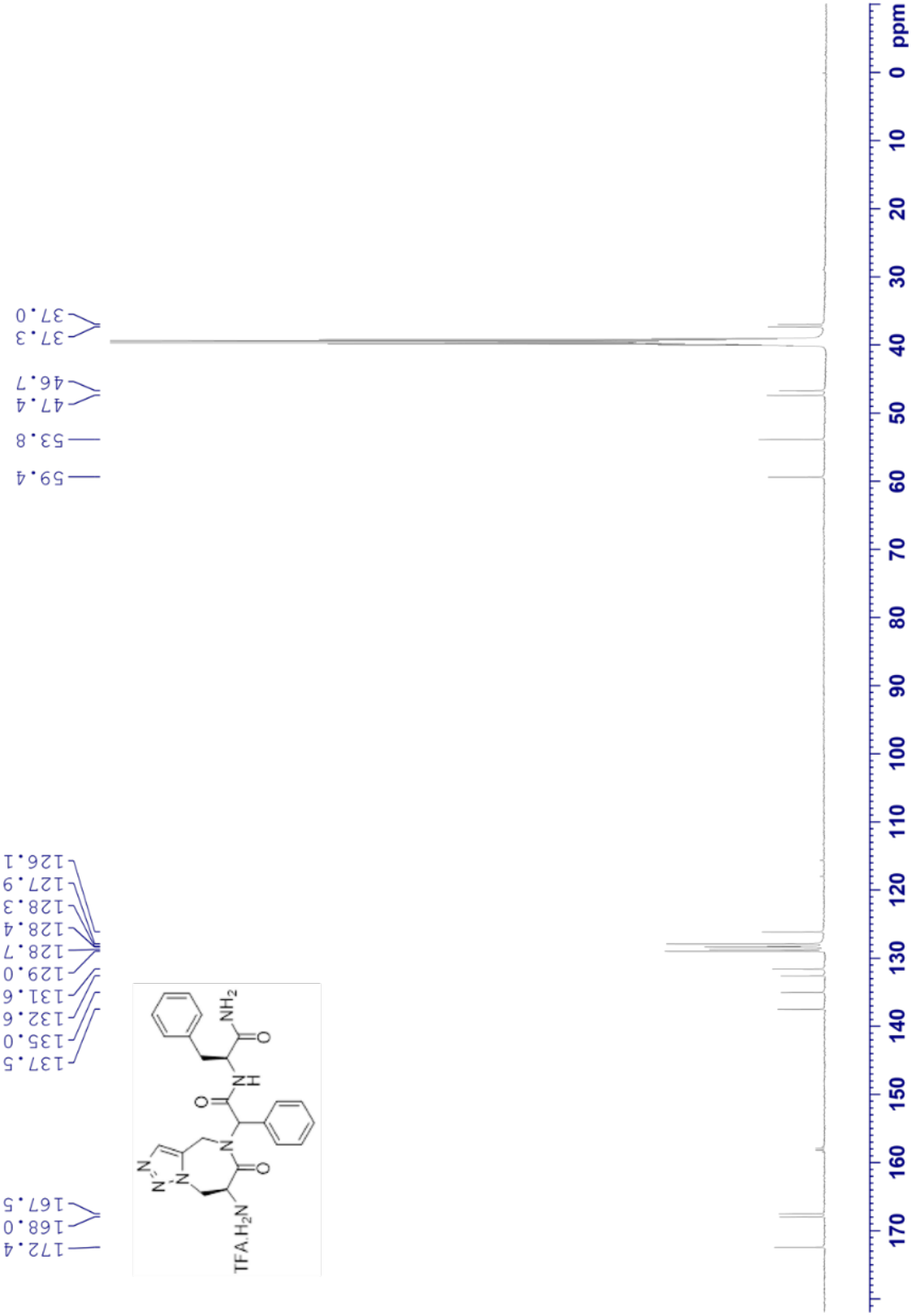
(*S*)-2-(2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)-3-phenylpropanamide **26a – ^{13}C NMR (126 MHz, DMSO-d_6, diastereomer 1)**



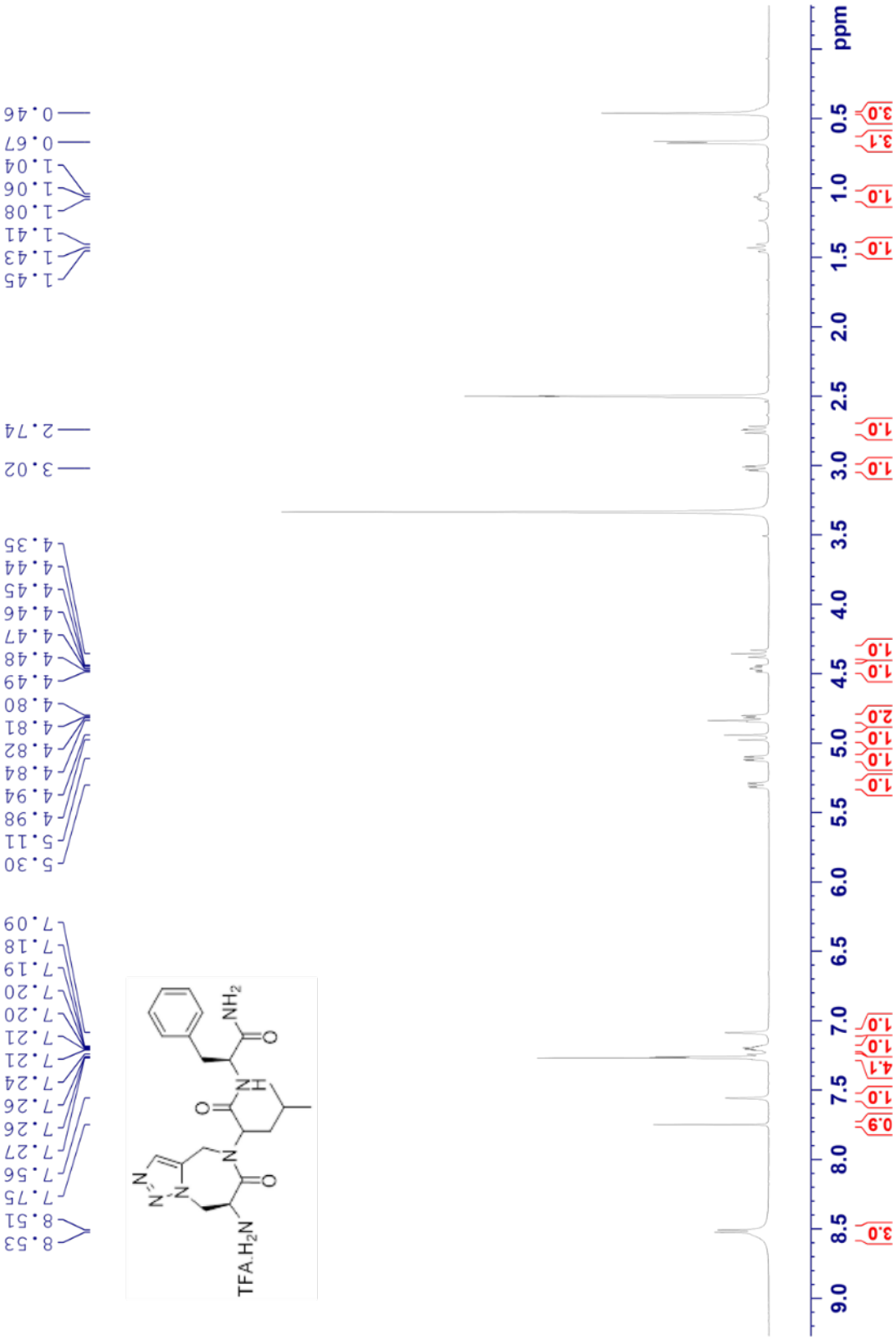
(*S*)-2-(2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)-3-phenylpropanamide **26a – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 2)**



(*S*)-2-(2-((S)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ^4-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)-3-phenylpropanamide **26a – ^{13}C NMR (126 MHz, DMSO-d_6, diastereomer 2)**

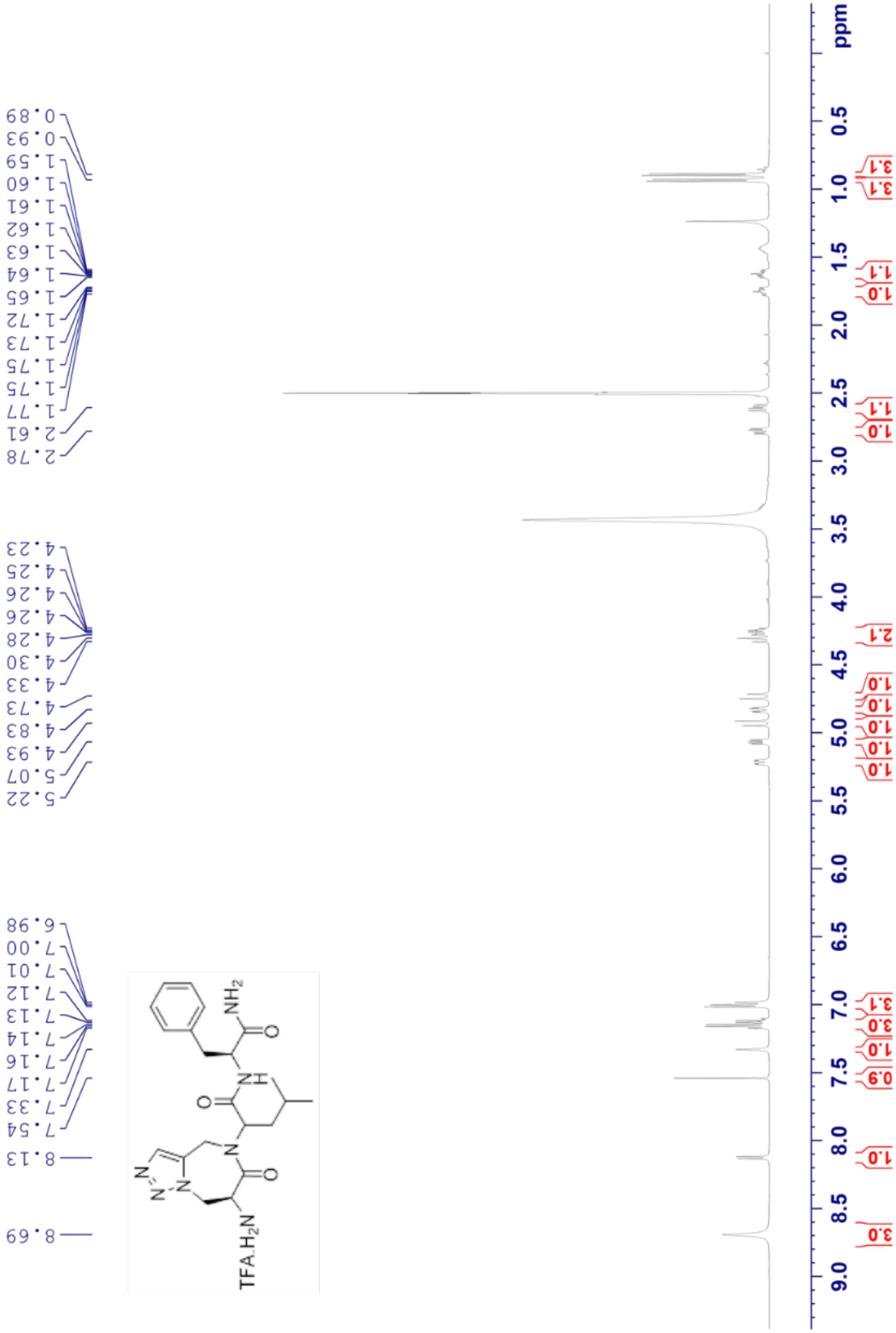


N-((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ⁴-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)pentanamide **26b – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 1)**



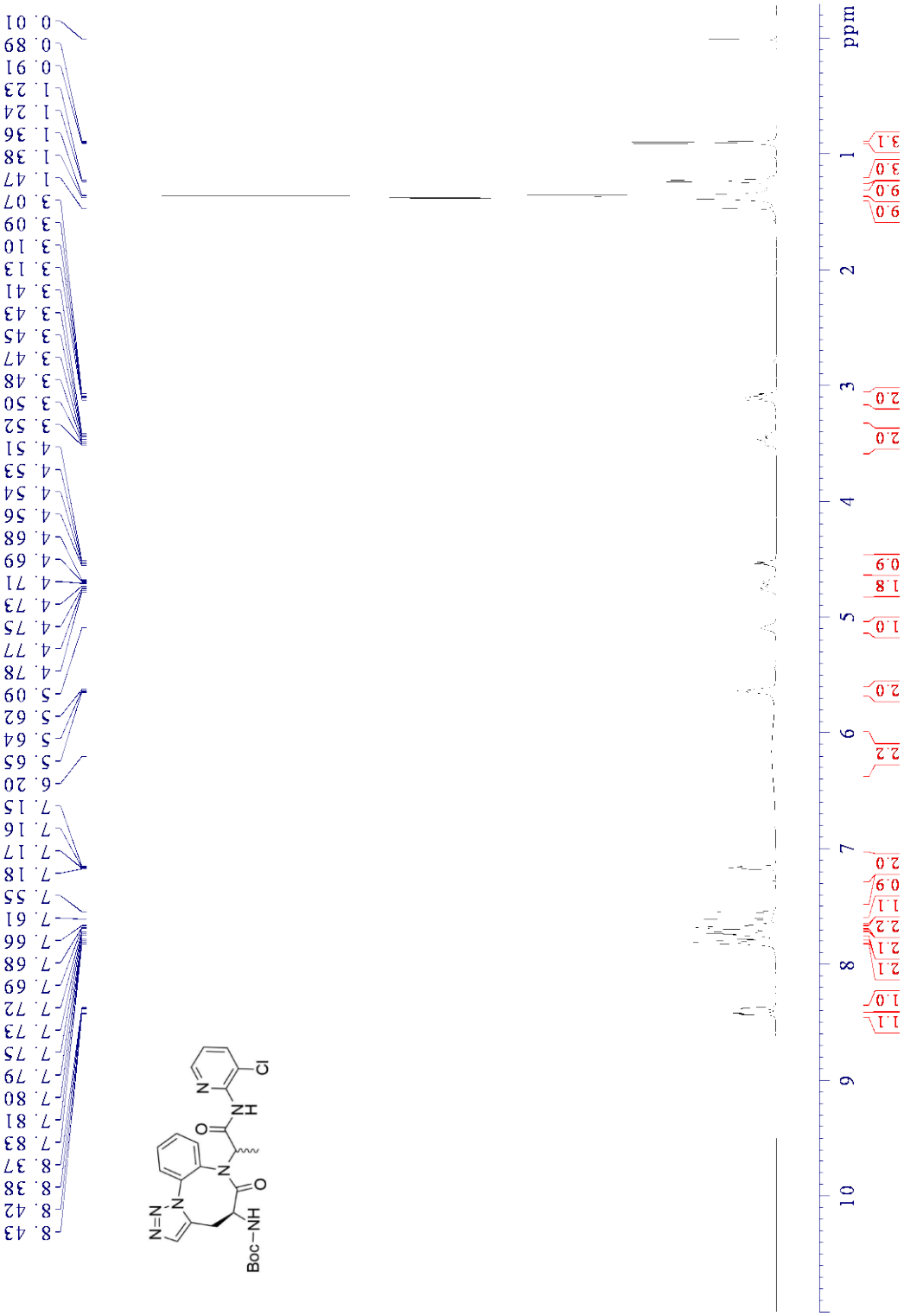
N-((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ⁴-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)pentanamide **26b – ^{13}C NMR (126 MHz, DMSO-d_6, diastereomer 1)**

N-((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ⁴-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)pentanamide **26b – ^{1}H NMR (500 MHz, DMSO-d_6, diastereomer 2)**

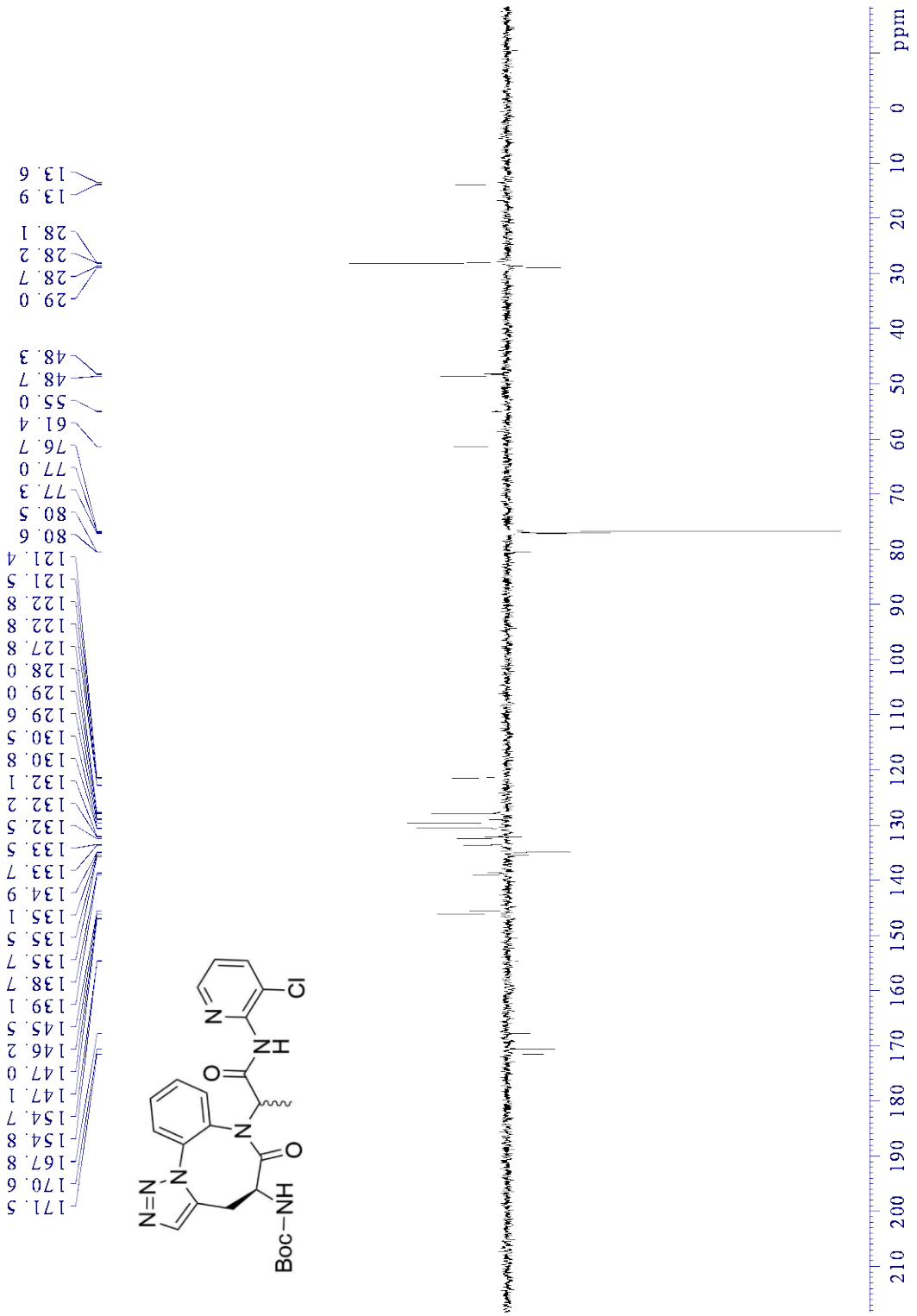


N-((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)-4-methyl-2-((*S*)-6-oxo-7-((2,2,2-trifluoroacetyl)-λ⁴-azanyl)-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)pentanamide **26b – ^{13}C NMR (126 MHz, DMSO-d_6, diastereomer 2)**

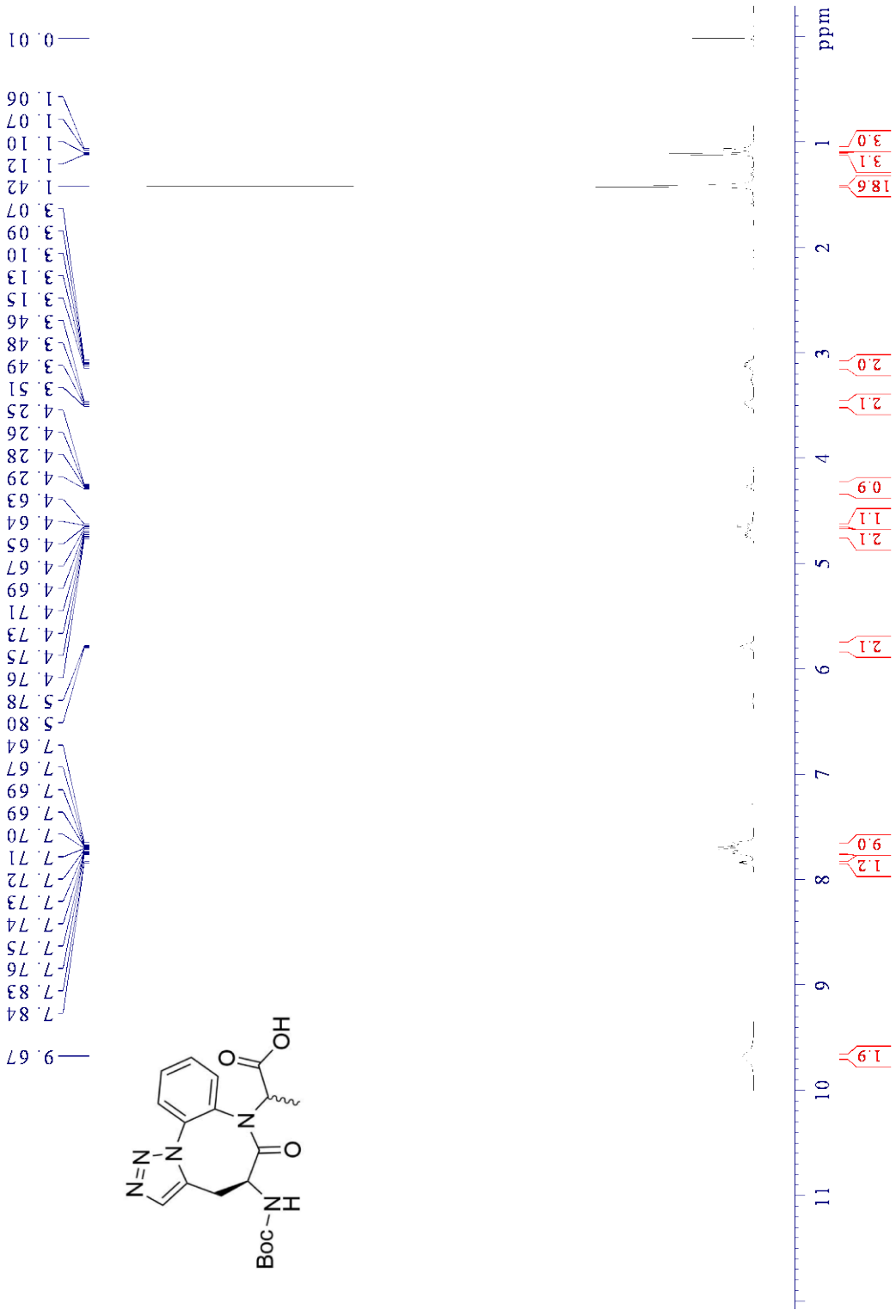
tert-Butyl ((5*S*)-7-(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-5-yl)carbamate **27 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)**



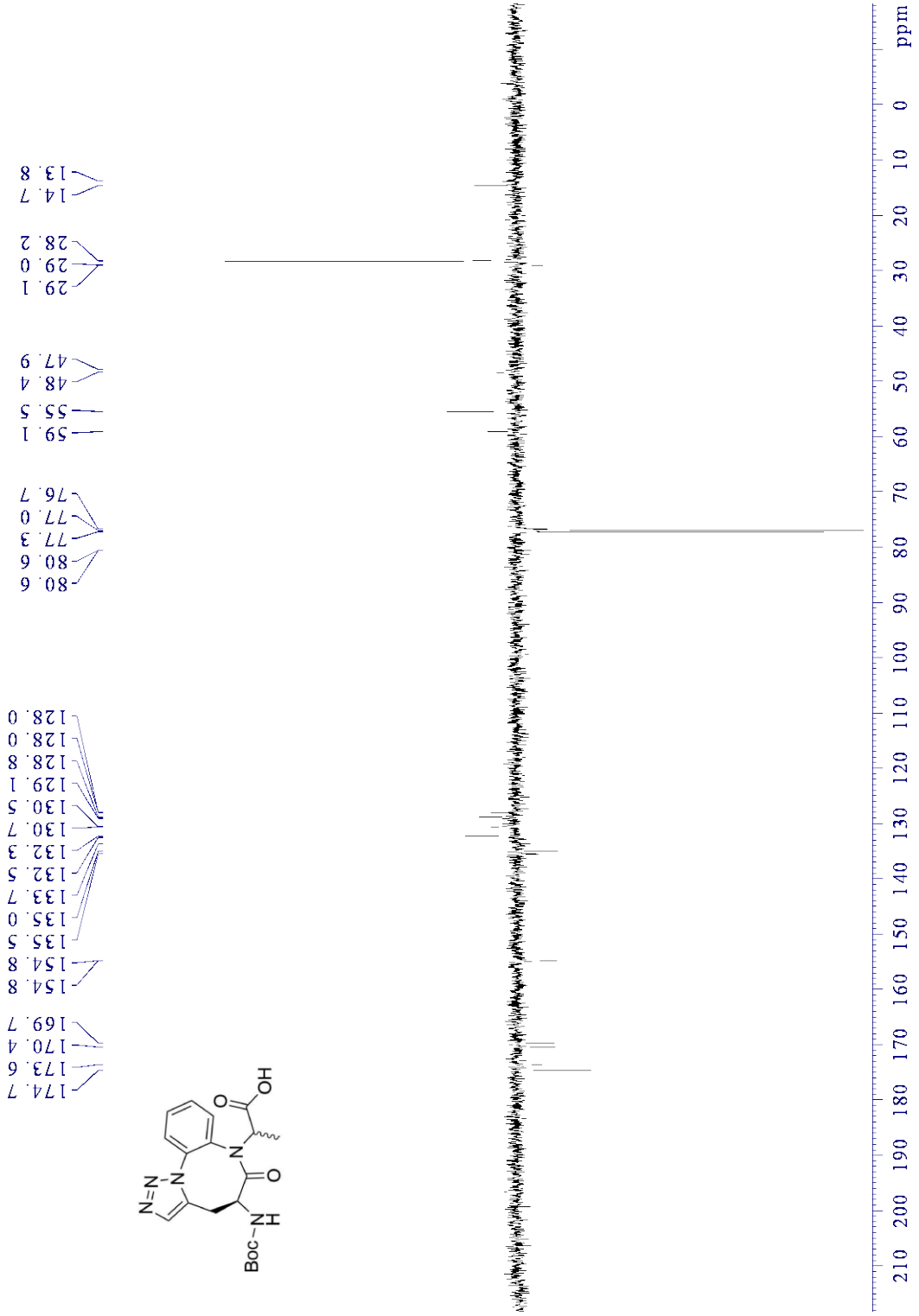
tert-Butyl ((5*S*)-7-(1-((3-chloropyridin-2-yl)amino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-5-yl)carbamate **27 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)**



2-((*S*)-5-((*tert*-Butoxycarbonyl)amino)-6-oxo-5,6-dihydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-7(4*H*)-yl)propanoic acid **28 – ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers in a 1:1 ratio)**



2-((*S*)-5-((*tert*-Butoxycarbonyl)amino)-6-oxo-5,6-dihydrobenzo[b][1,2,3]triazolo[1,5-d][1,4]diazocin-7(4*H*)-yl)propanoic acid **28 – ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)**



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