UNIVERZITA PALACKÉHO V OLOMOUCI

PŘÍRODOVĚDECKÁ FAKULTA

Katedra organické chemie

Vývoj nové metody pro efektivní odstranění hydrazinové funkční skupiny z organických molekul.

Rigorózní práce

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Olomouc 2017

Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Olomouci, 20.3.2017 .....

Mgr. Lenka Kubovičová

Poděkování

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Abstrakt: Předložená rigorózní práce je zaměřena na vývoj nové metody efektivního odstranění hydrazinové skupiny z organických molekul. Práce shrnuje doposud popsané metody jak na pevné fázi, tak i v roztoku. Poté je pozornost věnována syntéze vybraných derivátů hydrazinů podle literárních předpisů nebo s obměnami reakčních podmínek. Vlastní práce se pak zabývá optimalizací reakčních podmínek pro odstranění hydrazinové skupiny ze strukturně diverzních molekul. Tyto výsledky jsou publikovány v mezinárodním impaktovaném časopisu *Organic and Biomolecular Chemistry*.

Klíčová slova: Hydraziny, dehydrazinace, pevná fáze, trimethysilanolát draselný

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The year of presentation:	2017
Abstract:	The submitted Rigorous thesis is focused on the development of a new method for removing a hydrazino group from organic molecules. The rigorous thesis describes overview of already known methods for dehydrazination both in solution and on solid phase. The attention is then concentrated on the synthesis of hydrazino derivatives according to publish procedures or with some modifications. The main part of the work – development and optimization of the dehydrazination reaction follows. Obtained results are published in the international impacted journal *Organic and Biomolecular Chemistry*.
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OBSAH

1. Úvod

Tato rigorózní práce je tvořena třemi hlavními částmi. První část tvoří ucelený úvod do problematiky, komentář a shrnutí k předložené publikaci. Druhá část je tvořena článkem publikovaným v mezinárodním impaktovaném časopise *Organic and Biomolecular Chemistry* a třetí experimentální částí (Supporting Information).

2. Seznámení s tématikou

Tato práce vznikla během vývoje nových derivátů 3-hydroxychinolin-4(1*H*)-onů (3-HQs), skupiny látek, kterou se na našem pracovišti dlouhodobě zabýváme. Tyto látky jsou dusíkatými analogy přírodních flavonů vykazujících řadu biologických aktivit.[1] Také ve skupině 3-HQs již byla objevena řada biologicky aktivních derivátů vykazujících hlavně protinádorovou aktivitu, antivirovou či imunosupresivní.[2-5] Stále však chybí hlubší znalosti o vztahu jejich struktury a biologické aktivity a definice jejich možných molekulárních cílů. Naším úkolem je tedy vývoj nových syntetických metod pro přípravu různě modifikovaných 3-HQs.

Většina syntéz 3-HQs je založená na cyklizačním kroku fenacylesterů kyseliny anthranilové **I** zahříváním v kyselém prostředí – např. v kyselině octové (AcOH), polyfosforečné (PPA) nebo trifluoroctové (TFA), popřípadě zahříváním v *N*-methylpyrrolidonu (NMP) (**Schéma 1**), která byla vyvinuta na našem pracovišti v roce 1995.[6] Tato metoda je univerzální a poskytuje vysoké výtěžky.

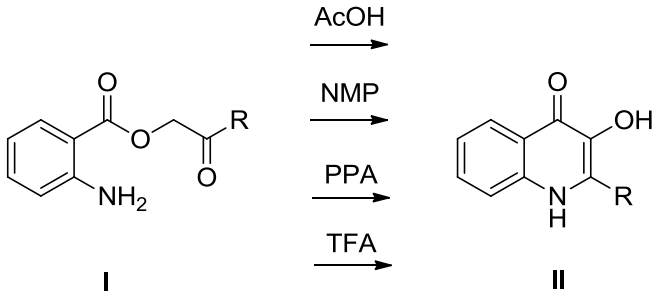

Schéma 1: Cyklizace fenacylesteru na 3-HQ.

Pro efektivnější studium 3-HQs byla vyvinuta také jejich syntéza na pevné fázi.[7] Syntéza na pevné fázi je důležitým nástrojem medicinální chemie. Umožňuje v krátkém

čase současně připravit řadu derivátů. Oproti roztokové chemii přináší velkou časovou úsporu především díky eliminaci čistících a izolačních kroků všech meziproduktů.[8]

Společným problémem doposud připravených derivátů 3-HQs je špatná rozpustnost ve vodě. Má diplomová práce byla proto zaměřená na vhodnou modifikaci aminové skupiny poloze 1 fenacylesteru **III** a jeho následná cyklizace na *N*-substituované 3-HQs **IV** na pevné fázi (**Schéma 2**).

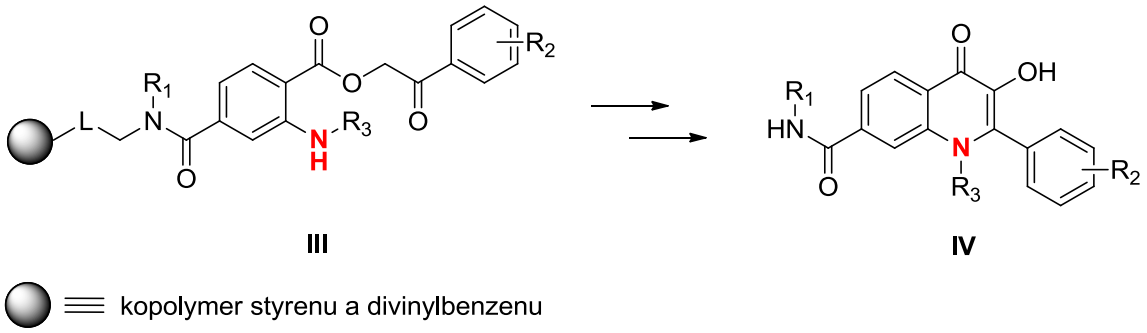

Schéma 2: Obecná příprava cíleného derivátu chinolonu.

Při výstavbě *N*-substituovaného fenacylesteru modifikovaného na dusíku aminovou skupinu bylo pozorováno neobvyklé chování látek **V (Schéma 3)**. Při hydrolýze methylesterové funkce v prostředí trimethylsilanolátu draselného (TMSOK) v tetrahydrofuranu (THF) se odštěpila hydrazinová skupina za vzniku derivátu **IX**, čímž byla znemožněna následná cyklizace na odpovídající produkt **VIII** (**Schéma 3**).

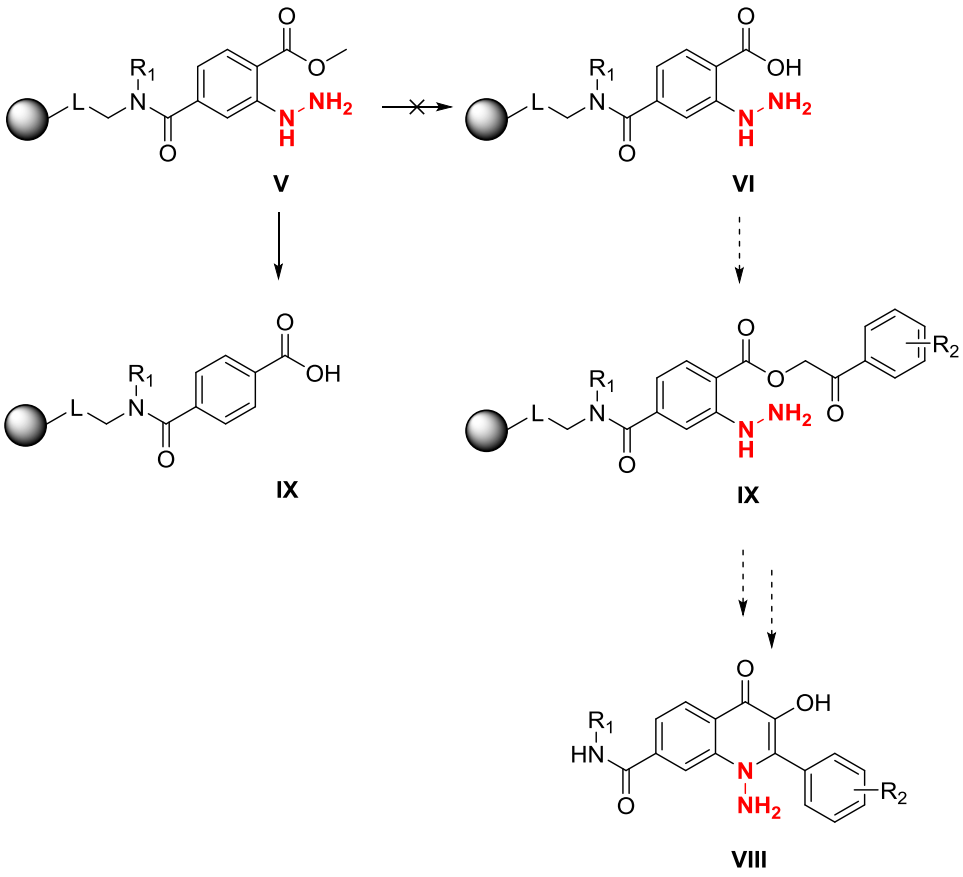

Schéma 3: Odštěpení hydrazinové skupiny za podmínek hydrolýzy esteru.

Vzhledem ke snadnosti (laboratorní teplota, 30 min reakce) a čistotě, s jakou reakce probíhala, jsme se rozhodli touto transformací hlouběji zabývat (**Schéma 4**). Výsledky představuje předložená rigorózní práce.

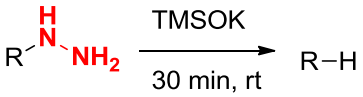

Schéma 4: Obecné schéma dehydrazinace pomocí TMSOK.

Syntéza hydrazinů je prozkoumána už mnoho let.[9] Existuje však málo prací zabývajících se odstraněním hydrazinové skupiny z molekuly. Jsou popsány reakce, které využívají k odstranění hydrazinové skupiny ionty těžkých kovů, hlavně oxidy stříbra a rtuti.[10,11] Evidentní nevýhodou je však toxicita těchto činidel. Podobné problémy přináší i použití síranu mědnatého, kdy je velmi obtížné po reakci odstranit měďnaté ionty, které bývají řadou organických látek komplexovány.[12-15] Metody využívající tato činidla tak nemohou být použity k přípravě látek, které by měly

biologické aplikace. Další popsané metody a jejich nevýhody jsou shrnuty v předkládané publikaci. Naším cílem proto bylo najít nové, mírné podmínky pro odstranění hydrazinové skupiny z organických molekul jak na pevné fázi, tak i v roztoku, které by byli kompatibilní s principy „green“ chemie.

2.1. Komentář k předložené publikaci

Cílem předložené rigorózní práce je v první části syntéza hydrazinových derivátů, které jsou výchozími látkami pro následující dehydrazinační reakce. Další sekce je zaměřena na přípravu monosubstituovaných a disubstituovaných derivátu hydrazinu na pevné fázi. Těchto 12 derivátů hydrazinů je navázaných na Rinkovu pryskyřici s β-alanin-phenylalaninovým linkerem pro lepší monitorování pomocí LC-MS. Poté následuje optimalizace dehydrazinačních podmínek v čase. Nejlepších výsledků pro odstranění hydrazinové skupiny je dosaženo reakcí s 0.2M TMSOK v THF po dobu 30 minut a laboratorní teplotě. Pro monosubstituované hydraziny běží reakce čistě. Naopak, pro *N,N´*- disubstituované hydraziny se reaktivita liší. Hydraziny ochráněné Fmoc skupinou mají nulovou konverzi. Mesylované deriváty reagují, ale s horší čistotou než monosubstituované a acetylované deriváty reagují srovnatelně jako monosubstituované (viz. publikace Tab. 1). Dalším parametrem optimalizace je volba báze, respektive ověření, zda je tato reakce typická pouze pro TMSOK. Z výsledků vyplývá, že štěpit hydraziny je možné i pomocí jiných bází, nicméně pouze použití TMSOK vede ke stoprocentní konverzi a navíc v nejkratším reakčním čas (viz. publikace Tab. 2). Vzhledem k potenciálnímu použití TMSOK v přípravě biologických látek byla optimalizována také koncentrace tohoto činidla. Minimální koncentrace, při které je štěpení stále možné, je 3nM. pH takového roztoku je 7 (viz. publikace Obr. 1).

Vzhledem k tomu, že syntéza na pevné fáze není vždy v organické chemii možná, je další část práce věnována optimalizaci reakčních podmínek v roztoku. Vybraných 12 jednoduchých monosubstituovaných hydrazinů je podrobeno reakci s TMSOK. Koncentrace je snížena na 0.15M roztok TMSOK a reakce jsou provedeny v deuterovaném *N,N*-dimethylformamidu (d_7-DMF) z důvodu současné kvantifikace produktů pomocí ^{1}H NMR. Pro 4 deriváty, které poskytovaly nízký výtěžek, je reakční teplota zvýšena na 70°C. Dehydrazinace běží dobře pro fenylhydrazin a jeho deriváty nesoucí substituenty dodávající elektrony. Naopak, jeho deaktivované deriváty poskytují nižší výtěžky (viz. publikace Tab. 3).

Pro možné uplatnění této metody v „green," chemii je vybráno 8 hydrazinů, které jsou rozpustné ve vodě. Přestože je k dosažení úplné konverze zapotřebí prodloužit reakční čas na 48 hodin (při 15M koncentraci TMSOK ve vodě), reakce poskytují excelentní výtěžky (viz. publikace Tab. 4)

Štěpení hydrazinů pomocí TMSOK je pak podpořeno návrhem mechanismu reakce. Důležitým parametrem je přítomnost vzdušného kyslíku, což bylo experimentálně ověřeno.

2.2. Shrnutí

Tato práce představuje novou metodu efektivního odstranění hydrazinové skupiny z organických molekul, která se dá využít jak na pevné fázi, tak i v roztoku. Reakce probíhá v roztoku TMSOK převážně za krátkých reakčních časů a laboratorní teploty a také splňuje principy „green" chemie.[10,14] V případě, že je štěpení hydrazinu nežádoucí a je nutné použití TMSOK za jiným účelem, je možné hydrazin před štěpením ochránit chránící skupinou (např. Fmoc).

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New (green) methodology for efficient hydrazine cleavage†

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An efficient method for removal of the hydrazine group from (hetero)aromatic substrates has been developed. It can be realized both on a solid support and in solution by synthesis employing a low concentration solution of trimethylsilanolate in tetrahydrofuran or *N,N*-dimethylformamide. For water-soluble substrates, the reaction can be performed in water, highlighting the eco-friendly attributes of this methodology.

Hydrazine chemistry is a part of important areas in organic synthesis.[1] Monosubstituted hydrazines are frequently used intermediates in many synthetic applications, including reactions with carbonyl compounds to produce hydrazones,[2] preparation of indoles by Fisher Indol synthesis,[3] synthesis of aminopyrroles[4] and many others.[2,5] Although hydrazine synthesis is well described,[6] including the chiral species,[7–9] only few methodologies have been reported for dehydrazination reactions, which can be advantageously used for indirect removal of halogens,[10] removal of hydrazine as a protective group in synthetic pathways[10] or labelling of compounds with deuterium.[11]

To the best of our knowledge, the published dehydrazination protocols are mostly based on facile oxidation of hydrazines. The oxidizing agents are typically metallic oxides, very often silver oxide[12] or HgO,[13] which cause complications due to the toxicity of the traces of mercury ions remaining in the synthesized product or the precipitation of metallic silver as well as its salts derived from the treated compounds. Dehydrazination by aqueous copper sulphate was also described.[14,15] In this reaction, the principles of green chemistry are respected, employing a catalytic amount of copper sulphate in water[11] or employing microwave irradiation on supported copper sulphate.[16] The disadvantage of this method is the possible complexation of a substrate by copper ions.

A reaction with nitric oxide in the presence of oxygen in tetrahydrofuran (THF) belongs to the methods that avoid the use of metal ions for removal of hydrazine, but this reaction results in the subsequent formation of azides as co-products.[17]

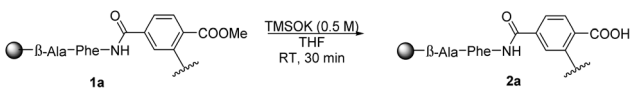
The other oxidative dehydrazination reaction free of metal ions described by Wobus *et al.*[10] is based on dehydrogenation of the hydrazino group to form diazene, followed by spontaneous loss of nitrogen. This reaction is limited to π-deficient (hetero)aromatic systems such as derivatives of pyridazine. Finally hydrazines able to undergo tautomery can be cleaved *via* Wolff–Kishner reduction in strong alkaline solutions. The reaction is limited to heteroaromatic systems able to form hydrazones.[18]

All of these above-mentioned reactions either require oxidizing agents causing potential side reactions or implementing toxicity or they are limited to electron-poor substrates.

Herein, we report a very fast and efficient methodology for dehydrazination of (hetero)aromatic substrates occurring under mild conditions. This protocol can be applied in solution as well as in solid phase organic synthesis (SPOS), which is not limited only to a laboratory scale but can also be applied in commercial drug production.[19]

During our study on the saponification reaction of immobilized ester **1a** using potassium trimethylsilanolate (TMSOK) in THF, we observed not only hydrolysis of the methyl ester group but also removal of the hydrazine moiety as well (Scheme 1).

Realizing the potential application of this result, we decided to study this unusual hydrazine cleavage in detail. For this purpose, we prepared a series of immobilized aromatic and heteroaromatic hydrazines. Their synthesis employed either immobilization of commercially available hydrazines or their direct preparation on a solid support by nucleophilic substitution from the corresponding fluoro derivatives (for details



Scheme 1 Dehydrazination reaction under saponification conditions.

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see the ESI†). Widely used aminomethylene polystyrene with a Rink linker was used as the solid support. For better monitoring of the products by LC/MS, a dipeptide linker (β-Ala-Phe) was introduced before the arylhydrazine moiety.

The hydrazine derivatives selected to be studied in the reaction were monosubstituted arylhydrazines and arylhydrazines protected by using Fmoc, mesyl (Ms) and acetyl groups.

The reaction was carried out in THF, where TMSOK was dissolved at a concentration of 0.2 mol l^{-1}. The reaction time was optimized to 30 min at room temperature (RT).

The results of the complete four step synthesis of derivative **2** are summarized in Table 1. The products were isolated by HPLC purification directly after the reaction, and yields were calculated compared to the initial loading of the resin. The methylester group of compounds **1a**, **1c** and **1d** were hydrolysed and isolated as carboxylic acid **2a**.

These results clearly demonstrate that the monosubstituted (hetero)aromatic hydrazines easily undergo hydrazine cleavage under treatment with TMSOK.

Obviously, once the (hetero)aromatic hydrazine is protected, the dehydrazination does not work properly. No conversion during the treatment with TMSOK was observed in the case of Fmoc protected derivatives **1b**, **1f** and partially **1j**, where also the products of decomposition were observed. Although dehydrazination was observed in the case of mesyl-protected hydrazines **1c** and **1k**, the yields were low because of the formation of a number of side products. In the case of compound **1g** no study of the cleavage was performed because it was possible to prepare the starting material only with very low purity. Surprisingly, when the hydrazine is substituted with an acetyl group, the removal of this moiety proceeds with good conversion as is shown in the case of derivatives **1h** and **1l**. The low reactivity of Fmocylated hydrazines can be advantageously used for selective protection of the hydrazine group against trimethylsilanolate treatment. If hydrazine removal is intended, no protection is necessary. However, if we want to preserve the hydrazine, *e.g.*, during ester hydrolysis mediated by using TMSOK, we can avoid the cleavage by facile Fmoc protection.

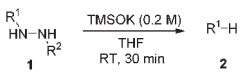
We were also interested in knowing whether TMSOK is the specific base responsible for the cleavage or if it could be replaced by another base. We therefore selected one model compound **1i** and extended the study to a wider range of bases, replacing TMSOK with sodium hydroxide (NaOH), lithium hydroxide (LiOH), sodium *tert*-butoxide (*t*-BuONa), sodium methoxide (MeONa) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 2). At the same time, the influence of the TMSOK concentration on reactivity was studied as well. The reactions were monitored by LC/MS.

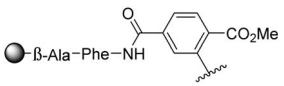
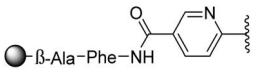
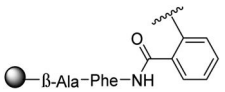
The results indicate that hydrazine can be cleaved from the aromatic compound by treatment with different bases. However, in many cases the remaining starting material decreases the conversion. The best results, requiring the shortest reaction times as well as providing the highest product purities, are achieved using TMSOK.

It is worth highlighting the TMSOK concentration necessary for successful performance of the reaction. The reaction still proceeds satisfactorily with a concentration as low as 3 mM (Fig. 1).

As solid-phase synthesis is not always applicable in organic synthesis, we examined the possibility of hydrazine cleavage in solution as well. Twelve simple (hetero)aromatic hydrazines were chosen as model substrates, including both electron-donating as well as electron-withdrawing substituents (Table 3) in various positions of the aromatic ring, and they were treated with 0.15 M solution of TMSOK in *N*,*N*-dimethylformamide-d_7 (d_7-DMF). d_7-DMF was chosen due to its better solubilization of the selected substrates and a possibility of direct yield determination using ^{1}H NMR by comparison with

Table 1 Synthesis of derivatives **2** *via* dehydrazination of compounds **1**



1	R^1	R^2	2	Yield of 2 [a] (%)
1a		-H	**2a**	20[b]
1b		-Fmoc	**2a**	[c]
1c		-Ms	**2a**	16[b]
1d		-COMe	**2a**	19[b]
1e		-H	**2e**	53
1f		-Fmoc	**2e**	[c]
1g		-Ms	**2e**	[d]
1h		-COMe	**2e**	54
1i		-H	**2i**	58
1j		-Fmoc	**2i**	[c]
1k		-Ms	**2i**	17
1l		-COMe	**2i**	57

[a] Overall yield determined by ^{1}H NMR spectroscopy after HPLC purification and calculated to initial loading of the resin. [b] Product was isolated as a carboxylic acid. [c] Product was not observed. [d] Reaction was not studied because the preparation of **1g** proceeded with very low purity.

Table 2 Optimization of the reaction conditions for derivative **1i** using different bases in THF

Entry	Base	*t* (h)	*c* (mmol)	Conversion[a] (%)
1	NaOH	0.5	500.0	27
2	NaOH	1.5	500.0	70
3	LiOH	0.5	500.0	34
4	LiOH	1.5	500.0	62
5	*t*-BuONa	0.5	500.0	27
6	*t*-BuONa	1.5	500.0	70
7	MeONa	0.5	500.0	9
8	MeONa	1.5	500.0	62
9	DBU	0.5	500.0	36
10	DBU	1.5	500.0	82
11	TMSOK	0.5	200.0	74
12	TMSOK	0.5	100.0	69
13	TMSOK	0.5	50.0	76
14	TMSOK	0.5	25.0	57
15	TMSOK	1.0	12.5	100
16	TMSOK	1.0	6.2	100
17	TMSOK	1.0	3.1	88
18	TMSOK	1.0	1.6	38

[a] Conversion was determined by HPLC with PDA detection.

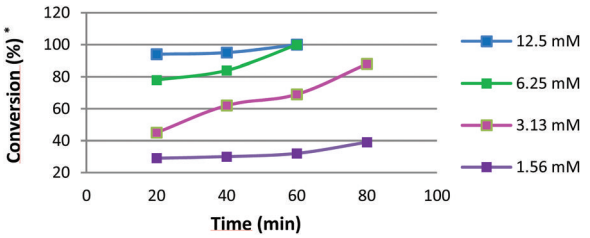
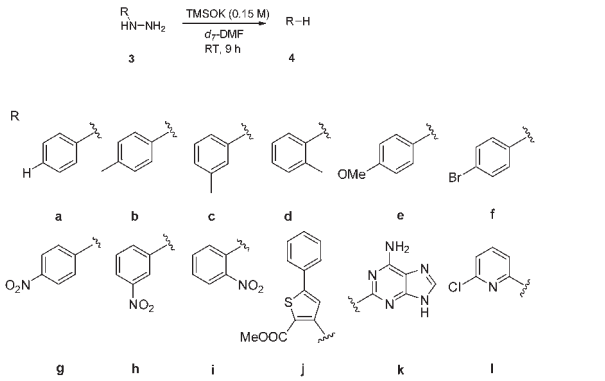


Fig. 1 Optimization of the TMSOK concentration for reaction of **1i**. *Conversion was determined by HPLC with PDA detection.

Table 3 Hydrazine cleavage in solution with the corresponding yields in d_7-DMF



Compound **3**	Yield of **4** [a] (%)	Yield of **4** at 70 °C, 48 h [a] (%)
3a	99	—
3b	95	—
3c	35	70
3d	SM	51
3e	89	—
3f	81	—
3g	55	—
3h	85	—
3i	90	—
3j	69	—
3k	Insoluble	50
3l	42	97

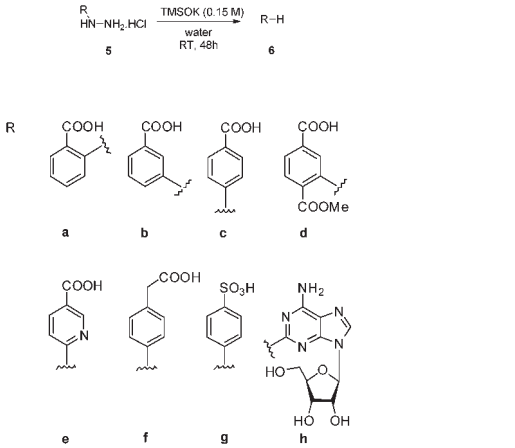
[a] Yield determined by ^{1}H NMR spectroscopy.

the residual solvent signal.[20] The concentration of TMSOK was optimized, and the best results were obtained when the concentration of TMSOK was 0.15 M. For four derivatives the general reaction conditions afforded lower yield, therefore the temperature was increased to 70 °C (Table 4).

The dehydrazination works very well for phenylhydrazine and substrates with electron-donating groups. Lower yields must be expected for substrates bearing electron-withdrawing groups. The good conversion is exemplified by the change in the NMR spectra as shown in Fig. 2 for derivative **3b** (for other crude NMR spectra see the ESI†).

Although THF and DMF are acceptable solvents from their toxicity point of view,[21] water is still the first choice for "green chemistry". We therefore selected another eight water-soluble

Table 4 Hydrazine cleavage in solution with the corresponding yields in water



Entry	Compound **5**	Yield of **6** [a] (%)	Yield of **6** at 70 °C, 48 h [a] (%)
1	**5a**	99	—
2	**5b**	64	—
3	**5c**	77	—
4	**5d**	81	—
5	**5e**	71	—
6	**5f**	90	—
7	**5g**	98	—
8	**5h**	40	89
9	**3k**	49	45

[a] Yield determined by ^{1}H NMR spectroscopy.

substrates **5a–h** and hydrazine **3k** and examined their reactivity under the treatment of 0.15 M solution of TMSOK in water (Table 4). For most substrates the dehydrazination works quantitatively within 48 hours in all cases with excellent yields. For two substrates the temperature had to be increased to achieve higher yields (Table 4).

Finally we tried to suggest a mechanism for hydrazine group removal (Scheme 2).

The reaction of unprotected arylhydrazine $\mathbf{A_H}$ starts probably by dissociation of an acidic NH proton. The possibility of conjugation in the system $\mathbf{C_H}$ is the stimulation for oxidation of intermediate $\mathbf{B_H}$ with air. The air oxidation assistance was proved by performing the experiment under an inert atmosphere, where no reaction was observed. Decomposition of diazene $\mathbf{C_H}$ to hydrocarbon **E** *via* anion **D** is included in other published mechanisms.[11] A similar process can be expected for acetylated hydrazine $\mathbf{A_{Ac}}$, probably when the amide NH proton is removed first. The analogous acetyl diazene $\mathbf{C_{Ac}}$ formed by air oxidation can be then hydrolyzed by trimethylsilanolate to give intermediate **D** again, which is further stabilized by a proton to the final hydrocarbon **E**. The bulky Fmoc and strong electronegative mesyl group analogues of hydrazine $\mathbf{A_{Ac}}$ are probably more resistant to proton removal and/or oxidation because of steric hindrance and/or the increased electron withdrawing effect. The suggested mechanism is probably involved also in cleavage of a hydrazone linker published recently.[22]

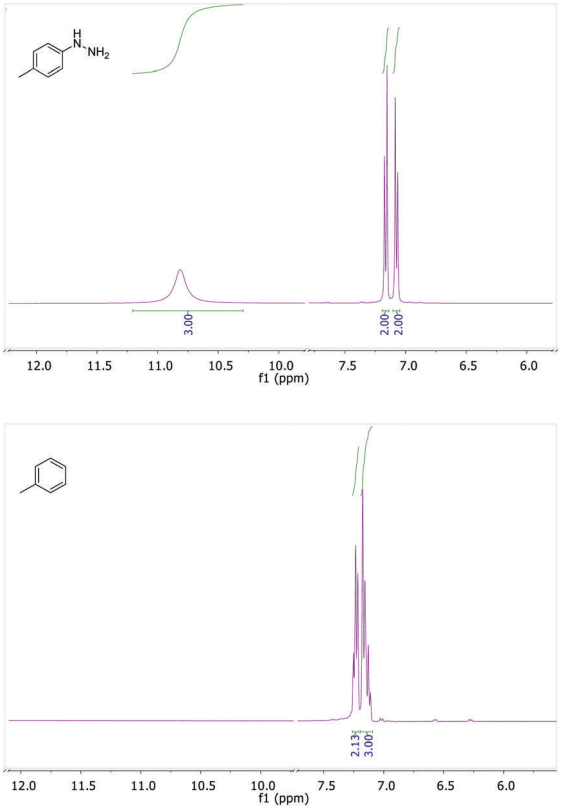
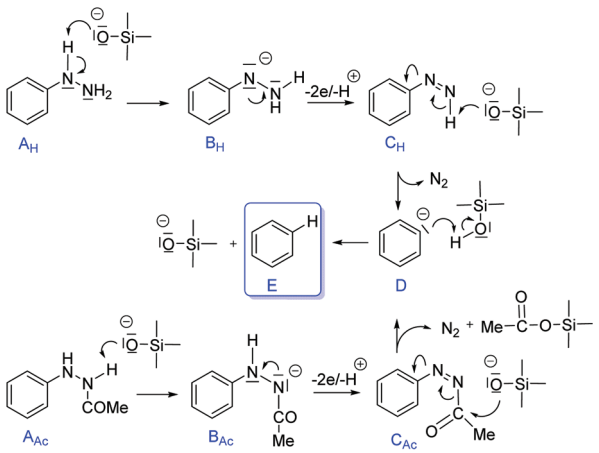


Fig. 2 ^{1}H NMR spectra of starting tolylhydrazine **3b** (upper spectrum) and crude product **4b** after its treatment with TMSOK (lower spectrum) in d_7-DMF.



Scheme 2 The supposed mechanism of dehydrazination.

In conclusion, we introduced a new methodology for hydrazine cleavage from aromatic substrates. The reaction is wide in scope and usually occurs at RT in acceptable reaction times. The reaction requires only low concentrations of TMSOK in THF or DMF frequently used in chemical research as well as production. Significantly, for water-soluble substrates, the reaction can be successfully performed even in water, which fully respects "green chemistry" principles.

Moreover, such a simple methodology works in solution as well as on a solid support, and thus it is easily applicable in industrial production of active pharmaceutical ingredients *via* both methodologies, where SPOS is also established for commercial production on a kilogram scale in addition to traditional solution-phase synthesis.[18]

Hydrazine removal can be avoided by using a suitable protecting group, and thus the removal of a hydrazine group can be directed.

Acknowledgements

This research project was supported by the Ministry of Education, Youth and Sports of the Czech Republic (project IGA_PrF_2016_020) and by the European Social Fund (CZ.1.07/2.3.00/30.0060 and CZ.1.07/2.3.00/20.0009). The infrastructure of this project (Institute of Molecular and Translation Medicine) was supported by the National Program of Sustainability (project LO1304).

Notes and references

1 A. Roden, Hydrazine, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. Paquette, John Wiley & Sons, New York, 2004.
2 G. D. Byrkit and G. A. Michalek, *Ind. Eng. Chem.*, 1950, **42**(9), 1862.
3 E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2241.
4 M. McLeod, N. Boudreault and Y. Leblanc, *J. Org. Chem.*, 1996, **61**, 1180.
5 L. F. Audrieth and L. H. Diamond, *J. Am. Chem. Soc.*, 1954, **76**, 4869.
6 U. Ragnarsson, *Chem. Soc. Rev.*, 2001, **30**, 205.
7 F. Zhou, F.-M. Liao, J.-S. Yu and J. Zhou, *Synthesis*, 2014, (22), 2983.
8 C.-B. Ji, Y.-L. Liu, X.-L. Zhao, Y.-L. Guo, H.-Y. Wang and J. Zhou, *Org. Biomol. Chem.*, 2014, **10**, 1158.
9 Z.-Q. Qian, F. Zhnou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753.
10 H. El-Kashef, A. A. H. Farghaly, N. Haider and A. Wobus, *Molecules*, 2004, **9**, 849.
11 R. Xia, M.-S. Xie, H.-Y. Niu, R.-G. Qu and H.-M. Guo, *Green Chem.*, 2014, **16**, 1077.
12 R. L. Hardie and R. H. Thomson, *J. Chem. Soc.*, 1957, 2512.
13 J. B. Chattopadhyaya and C. B. Reese, *Synthesis*, 1978, 908.
14 C. Tamborski and E. J. Soloski, *J. Org. Chem.*, 1966, **31**(3), 746.
15 J. M. Birchall, R. N. Haszeldine and A. R. Parkinson, *J. Chem. Soc.*, 1962, 4966.
16 L. D. S. Yadav and R. Kapoor, *J. Org. Chem.*, 2004, **69**(23), 8118.
17 T. Itoh, Y. Matsuya, K. Nagata and A. Oshawa, *Tetrahedron Lett.*, 1997, **38**(23), 4117.

18 A. Unciti-Broceta, M. J. Pineda de las Infantas, M. A. Gallo and A. Espinosa, *Chem. – Eur. J.*, 2007, **13**, 1754.
19 M. Verlander, *Int. J. Pept. Res. Ther.*, 2007, **13**(1–2), 75.
20 G. K. Pierens, A. R. Carroll, R. A. Davis, M. E. Palframan and R. J. Quinn, *J. Nat. Prod.*, 2008, **71**, 810.
21 J. Fowles, R. Boatman, J. Bootman, C. Lewis, D. Margott, E. Rushton, J. von Rooij and M. Banton, *Crit. Rev. Toxicol.*, 2013, **43**(10), 811.
22 S. Okorochenkov, K. Burglova, I. Popa and J. Hlavac, *Org. Lett.*, 2015, **17**(2), 180.

4. Doplňující informace k publikaci

New (green) methodology for efficient hydrazine cleavage

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1. General considerations

LC/MS analyses were performed using UHPLC/MS with an UHPLC chromatograph Acquity with PDA detector and a single quadrupole mass spectrometer (Waters) with an X-Select C18 column at 30 °C and a flow rate of 600 µl/min. The mobile phase consisted of (A) 0.01 M ammonium acetate in water and (B) acetonitrile, with linearly programmed gradient over the course of 2.5 min and then maintains this concentration for 1.5 min. Two methods with various solvent gradients were used for the measurements (change of % A): method 1 (from 80 to 20), method 2 (from 100 to 50). The column was re-equilibrated at 10% B for 1 min. The APCI ionization operated at a discharge current of 5 µA, vaporizer temperature of 350 °C and capillary temperature of 200 °C.

Purity of compounds was determed as ratio of appropriate peak area to sum of areas of all peaks of the mixture. Areas were determined by integration of the peaks from PDA detector response.

Purification was performed using semipreparative HPLC with a Waters 1500 series HPLC equipped with an Autosampler 2707, a Binary HPLC pump 1525, a Waters Photodiode Array Detector 2998 and a Waters Fraction Collector III with a YMC C18 reverse phase column, 20 x 100 mm, with 5 µm particles. The mobile phase consisted of acetonitrile and a 10 mM aqueous ammonium acetate gradient over 6 min.

NMR spectra were measured in DMSO-d_6, water-d_2 DMF-d_7 using JEOL ECX-500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are reported in Hertz (Hz). Acetate salts exhibited singlet at 1.7 – 1.9 ppm in the ^{1}H NMR spectrum and two resonances at 173 and 23 ppm in ^{13}C spectrum.

Solvents and chemicals were purchased from Sigma-Aldrich (Milwaukee, IL, www.sigmaaldrich.com) or Aapptec (USA, http://www.aapptec.com).

Following abbreviations were used: AAL (amino acid linker), DCM (dichloromethane), DIC (*N,N'*-diisopropylcarbodiimide), DIEA (*N,N*-diisopropylethylamine), DMF (*N,N*-dimethylformamide), HOBt (1-hydroxybenzotriazole hydrate), RT (room temperature), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TMSOK (potassium trimethylsilanolate).

Deprotected resin means that resin was treated in mixture of 50% of piperidine in DMF for 20 min at RT to removed Fmoc group.

For the analysis of the product immobilized on the resin following procedure was used: analytical sample of resin (~ 5 mg) was treated with cleavage cocktail 50% TFA in DCM for 15 min at RT. The cleavage cocktail was evaporated by a stream of nitrogen and resin was extracted into 1 mL of 50% MeOH/water and analyzed by LC/MS.

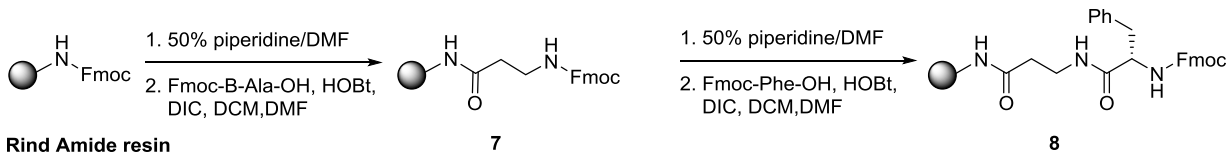
Analysis of preparative sample for full characterization of the compound was done by the same procedure with use of 10 ml of TFA/DCM per 1g of the resin and extraction of the residue to 10 ml of 50% MeOH/water. All compounds after semipreparative HPLC were obtained with purity ≥98% according to the PDA detector.

NMR quantification was determined directly using ^{1}H NMR by comparison with the residual solvent signal[1].

2. Reactions on solid support

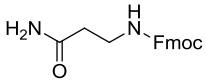
2.1. Synthesis of β-Ala-Phe spacer – resins 7 and 8

Resin 7 and **resin 8** were prepared according to the following scheme:



Resin 7: To the deprotected Rink Amide resin (1 g; 100-200 mash; loading 0.6 mmol/g) solution of an Fmoc-β-Ala (1.24 g; 4 mmol), DIC (0.62 mL; 4 mmol) and HOBt (0.61 g; 4 mmol) in mixture of DMF and DCM (50% vw; 12 mL) was added. Slurry was stirred 1 h at RT. Resin was washed with 3×12 mL DMF and 3×12 mL DCM and used in following steps.

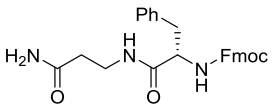
Analysis of the cleaved compound from the resin **7.**



Crude product: LC/MS analysis after cleavage form the resin: MS (ESI) exact mass calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$: 311.13; found: 311.27, t_R = 2.42 min (method 1), purity: 99%.

Resin 8: Attachment of the second amino acid followed the same procedure with use of resin **7** and Fmoc-Phe as the aminoacid. The Fmoc groups were deprotected and the resin was used in following steps.

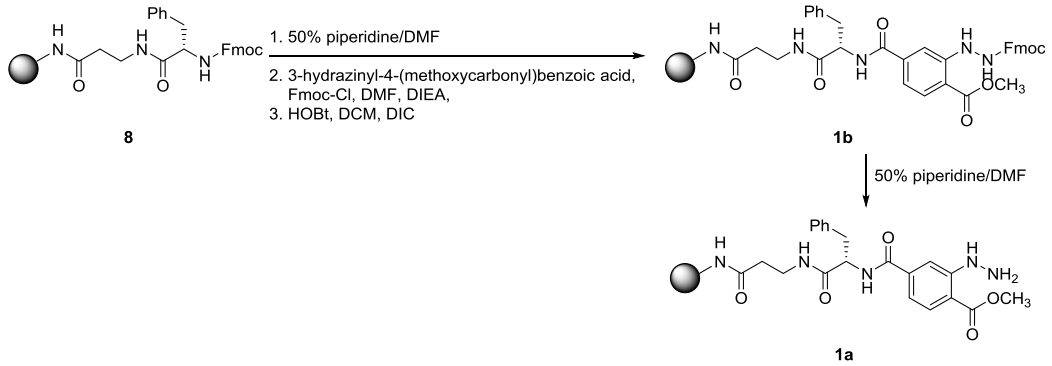
Analysis of the cleaved compound from the resin **8.**



Crude product: LC/MS analysis after cleavage form the resin: MS (ESI) exact mass calcd. for $C_{27}H_{28}N_3O_4$ $[M+H]^+$: 458.20; found: 458.40, t_R = 2.81 min (method 1), purity: 99%.

2.2. Preparation of monosubstituted and Fmocylated hydrazines 1a, 1b, 1e, 1f, 1i, 1j.

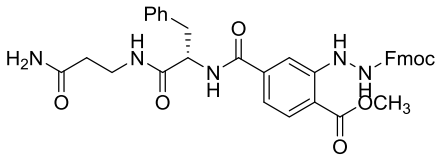
Resin **1a** and resin **1b** were prepared according to the following scheme:



Resin 1b: 3-hydrazinyl-4-(methoxycarbonyl)benzoic acid **5d**[1] (0.55 g; 2.6 mmol), DIEA (1 mL; 2.6 mmol) and Fmoc chloride (0.59 g; 2.3 mmol) were dissolved in DMF (5 mL). After 20 min, solution of HOBt (0.49 g; 3.6 mmol) and DIC (0.52 mL; 4 mmol) in DCM (5 mL) was added. Meanwhile, immobilized peptide **8** (1 g) was deprotected. The resin was washed with 3×12 mL DMF and 3×12 mL

DCM followed by the addition of the prepared solution of the hydrazine. The mixture was stirred for 1 h at RT. Finally, the resin was washed with 3×12 mL DCM and 3×12 mL DMF.

Analysis of the cleaved compound from the resin **1b.**

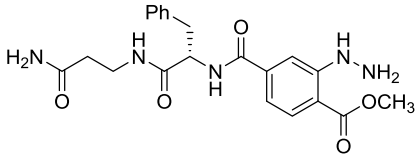


Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{36}H_{36}N_5O_7$ $[M+H]^+$: 650.25; found: 650.27, t_R = 2.88 min, (method 1), purity: 88%.

Pure product: Yield: 41 mg, 48%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.78 (bs, 1H), 8.62 (d, *J* = 8.1 Hz, 1H), 8.12 (t, *J* = 5.6 Hz, 1H), 7.85 (bs, 2H), 7.71 (bs, 2H), 7.43 – 7.26 (m, 8H), 7.19 (t, *J* = 6.5 Hz, 3H), 7.09 (t, *J* = 7.1 Hz, 1H), 6.79 (s, 1H), 4.64 – 4.55 (m, 1H), 4.45 – 4.11 (m, 3H), 3.82 (s, 3H), 3.36 – 3.16 (m, 4H), 3.07 – 2.88 (m, 2H), 2.19 (td, *J* = 7.2, 1.9 Hz, 2H).

Resin 1a: The resin **1b** was deprotected and washed with 3×12 mL DMF and 3×12 mL DCM.

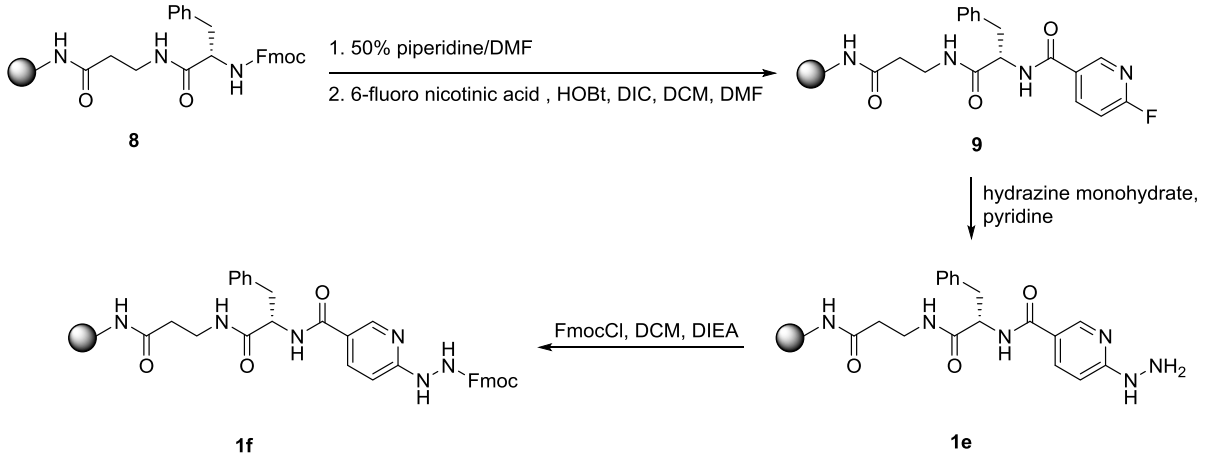
Analysis of the cleaved compound from the resin **1a.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{21}H_{26}N_5O_5$ $[M+H]^+$: 428.19; found: 428.40, t_R = 1.71 min (method 1), purity: 57%.

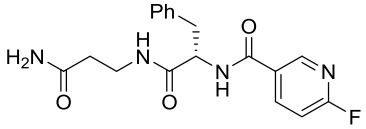
The derivative **1a** was very unstable during purification, therefore its structure was confirmed only by MS analysis and used directly for next reaction.

Resin **1e** and resin **1f** were prepared according to the following scheme:



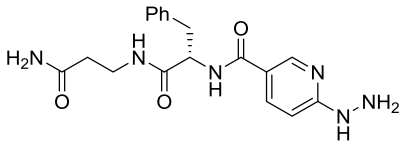
Resin 9: The resin **8** (1 g) was deprotected and washed with 3×12 mL DMF and 3×12 mL DCM. Then, solution of 6-fluoro nicotinic acid (0.43 g; 3 mmol), HOBt (0.46 g; 3.4 mmol) and DIC (0.47 mL; 3.7 mmol) in DMF and DCM (50% vv; 12 mL) was added. The mixture was stirred for 1 h at room temperature. Finally, resin was washed with 3×12 mL DMF, 3×12 mL DCM and used for next step.

Analysis of the cleaved compound from the resin **9.**



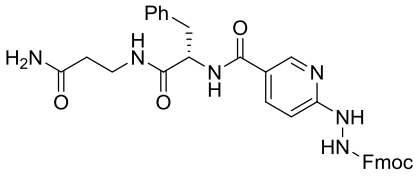
Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{18}H_{20}FN_4O_3$ $[M+H]^+$: 359.14; found: 359.45, t_R = 1.41 min (method 1), purity: 99%.

Resin 1e: The resin **9** (1 g) was stirred in solution of hydrazine monohydrate (0.29 mL; 1 mmol) in pyridine (12 mL) for 48 h at RT. Finally, the resin was washed with 3×12 mL DMF and 3×12 mL DCM.
Analysis of the cleaved compound from the resin **1e.**



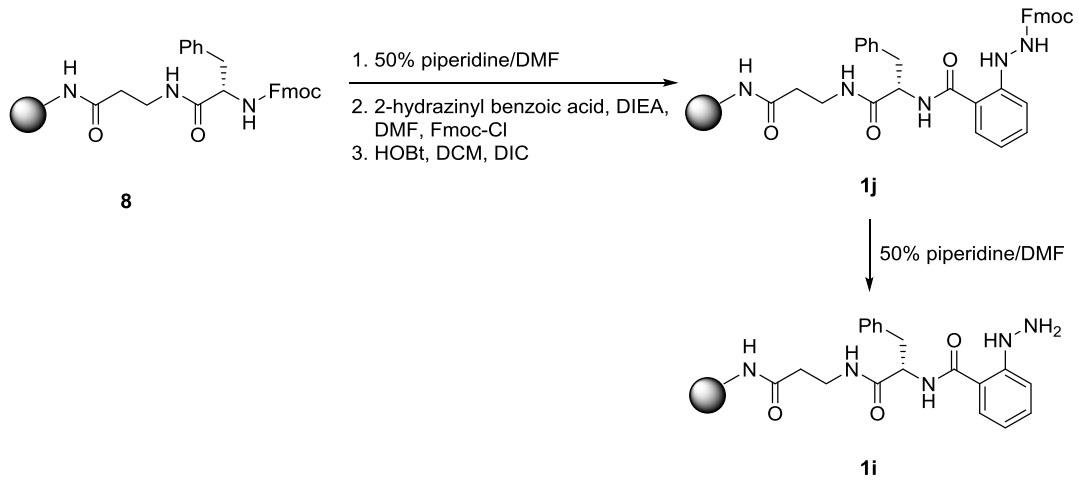
Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{18}H_{23}N_6O_3$ $[M+H]^+$: 371.18; found: 371.40, t_R = 0.98 min (method 1), purity: 61%.
The derivative **1e** was very unstable during purification, therefore its structure was confirmed only by MS analysis and used directly for next reaction.

Resin 1f : The resin **1e** (1 g) was stirred in solution of Fmoc chloride (1.48 g; 5.7 mmol) and DIEA (1.04 mL; 6 mmol) in DCM (12 mL) for 30 min at RT. Then, the resin was washed with 5×12 mL DCM.
Analysis of the cleaved compound from the resin **1f.**



Crude product: LC/MS analysis MS (ESI) exact mass calcd. for $C_{33}H_{33}N_6O_5$ $[M+H]^+$: 593.24; found: 593.22, t_R = 2.55 min, (method 1), purity: 98%.
Pure product: Yield: 59 mg, 44%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.38 (s, 1H), 8.50 (s, 1H), 8.41 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 5.0 Hz, 1H), 7.91 (t, *J* = 9.4 Hz, 3H), 7.75 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 22.2, 5.4 Hz, 6H), 7.24 (t, *J* = 7.6 Hz, 3H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 4.67 – 4.58 (m, 1H), 4.45 – 4.26 (m, 3H), 3.30 – 3.24 (m, 2H), 3.08 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.97 – 2.91 (m, 1H), 2.23 (td, *J* = 9, 6.9 Hz, 2H). ^{13}C NMR (101 MHz) δ 173, 172, 165, 157, 144, 141, 139, 130, 129, 128 (2C), 127 (3C), 126, 121 (2C), 66, 55, 47, 38, 36, 35.

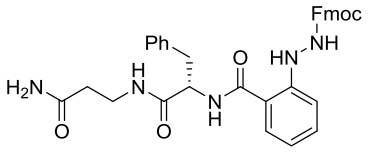
Resin 1i and **resin 1j** were prepared according to the following scheme:



8 → 1j → 1i

Resin 1j: 2-hydrazinyl benzoic acid **5a**[1] (0.4 g; 2.6 mmol), DIEA (1 mL) and Fmoc Chloride (0.59 g; 2.3 mmol) were dissolved in DMF (5 mL). After 20 min, solution of HOBt (0.49 g; 3.6 mmol) and DIC (0.52 mL; 4 mmol) in DCM (5 mL) was added. Meanwhile, immobilized peptide **8** (1 g) was deprotected. The resin was washed with 3×12 mL DMF and 3×12 mL DCM followed by the addition of the prepared solution of the 2-hydrazinylbenzoic acid. The mixture was stirred for 1 h at RT. Finally, the resin was washed with 3×12 mL DCM and 3×12 mL DMF.

Analysis of the cleaved compound from the resin **1j**

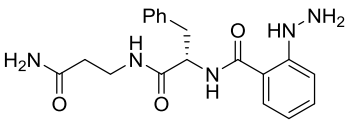


Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{34}H_{34}N_5O_5$ $[M+H]^+$: 592.25; found: 592.22, t_R = 3.03 min (method 1), purity: 99%.

Pure product: Yield: 52 mg, 39%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.31 (s, 1H), 8.82 (s, 1H), 8.47 (d, *J* = 7.1 Hz, 1H), 8.13 (s, 1H), 7.90 (d, *J* = 6.2 Hz, 2H), 7.72 (d, *J* = 6.1 Hz, 2H), 7.60 (d, *J* = 6.3 Hz, 1H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 4H), 7.26 (d, *J* = 7.0 Hz, 2H), 7.16 (d, *J* = 5.9 Hz, 1H), 6.83 (s, 1H), 6.72 (dd, *J* = 38.3, 6.7 Hz, 2H), 4.62 (d, *J* = 1.5 Hz, 1H), 4.48 – 4.18 (m, 3H), 3.30 – 3.24 (m, 2H), 3.06 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.01 – 2.93 (m, 1H), 2.24 (t, *J* = 7.5 Hz, 2H).

Resin 1i: Prepared by defmocation of resin **1j**.

Analysis of the cleaved compound from the resin **1i.**



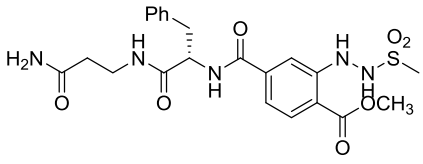
LC/MS analysis: MS (ESI) exact mass calcd. for $C_{19}H_{24}N_5O_3$ $[M+H]^+$: 370.18; found: 370.40, t_R = 1.35 min (method 1), purity: 70%.

The derivative **1i** was very unstable during purification, therefore its structure was confirmed only by MS analysis and used directly for next reaction.

2.3. General Procedure for Preparation of Mesyl Derivatives 1c, 1g and 1k.

Immobilized hydrazine derivatives **1b, 1f, 1j** (1 g) were deprotected, washed with 3×12 mL DMF and 3×12 mL DCM, and then 12 mL of solution of mesyl chloride (0.52 mL; 6 mmol) and pyridine (0.49 mL; 6 mmol) in DCM (12 mL) was added. Slurry was stirred for 3 h at RT. Resin was then washed with 3×12 mL DMF, 3×12 mL DCM.

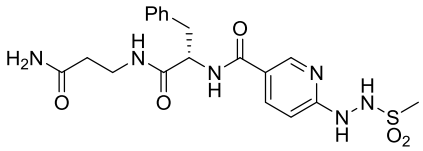
Analysis of the cleaved compound from the resin **1c.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{22}H_{28}N_5O_7S$ $[M+H]^+$: 506.16; found: 506.31, t_R = 1.83 min (method 1), purity: 80%.

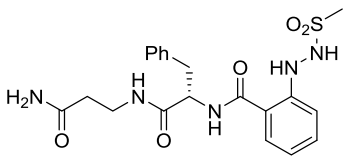
Pure product: Yield: 38 mg, 37%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.15 (s, 1H), 9.03 (s, 1H), 8.64 (d, *J* = 8.5 Hz, 1H), 8.15 (t, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.24 (dd, *J* = 14.1, 6.3 Hz, 3H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 4.67 – 4.60 (m, 1H), 3.86 (s, 3H), 3.29 – 3.24 (m, 2H), 3.06 (dd, *J* = 13.7, 4.2 Hz, 1H), 3.01 (s, 3H), 2.97 (dd, *J* = 13.6, 10.5 Hz, 1H), 2.23 (t, *J* = 7.4 Hz, 2H).

Analysis of the cleaved compound from the resin **1g.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{19}H_{25}N_6O_5S$ $[M+H]^+$: 449.15; found: 449.28, t_R = 1.27 min (method 1), purity: 11%. The compound was not purified and was not used for any other reaction.

Analysis of the cleaved compound from the resin **1k.**



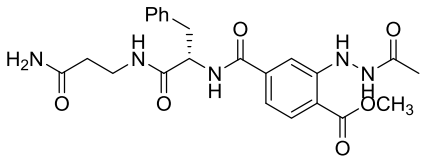
Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{20}H_{26}N_5O_5S$ $[M+H]^+$: 448.16; found: 448.19, t_R = 2.47 min (method 1), purity: 90%.

Pure product: Yield: 35 mg, 39%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.13 (s, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.15 (t, J = 5.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 15.0, 8.0 Hz, 3H), 7.24 (dd, J = 15.9, 8.1 Hz, 3H), 7.16 (t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 6.78 (t, J = 7.3 Hz, 1H), 4.73 – 4.53 (m, 1H), 3.30 – 3.20 (m, 2H), 3.08 (dd, J = 13.7, 4.2 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.94 (d, J = 9.0 Hz, 3H), 2.24 (t, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz) δ 173, 171, 168, 149, 138, 132, 129, 128, 126, 118, 116, 114, 55, 37 (2C), 35 (2C).

2.4. General Procedure for Preparation of Acetyl derivatives 1d, 1h and 1l.

After the deprotection of Fmoc group from the resine **1b, 1f, 1j** (1 g) the slurry was stirred in solution of acetanhydride (0.57 mL; 6 mmol) and DIEA (1.04 mL; 6 mmol) in DMF (12 mL) for 0.5 h at RT. Then, resin was washed with 3×12 mL DMF, 3×12 mL DCM.

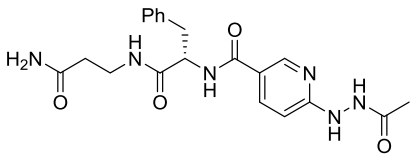
Analysis of the cleaved compound from the resin **1d.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{23}H_{28}N_5O_6$ $[M+H]^+$: 470.20; found: 470.15, t_R = 1.59 min (method 1), purity: 68%.

Pure product: Yield: 42 mg, 42%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.98 (d, J = 2.1 Hz, 1H), 8.87 (d, J = 1.9 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.15 (t, J = 5.6 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.32 (d, J = 7.4 Hz, 3H), 7.28 – 7.23 (m, 3H), 7.19 – 7.13 (m, 2H), 6.84 (s, 1H), 4.63 – 4.56 (m, 1H), 3.85 (s, 3H), 3.31 – 3.23 (m, 2H), 3.06 (dd, J = 13.6, 4.2 Hz, 1H), 2.96 (dd, J = 13.5, 10.7 Hz, 1H), 2.23 (t, J = 7.2 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (101 MHz) δ 173, 171, 169, 167, 166, 151, 140, 139, 131, 129, 128, 126, 116, 112 (2C), 55, 52, 37, 35 (2C), 21.

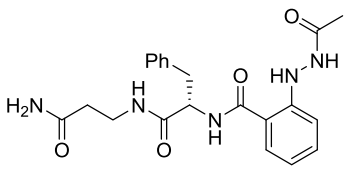
Analysis of the cleaved compound from the resin **1h.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{20}H_{25}N_6O_4$ $[M+H]^+$: 413.13; found: 413.19, t_R = 0.84 min (method 1), purity: 83%.

Pure product: Yield: 39 mg, 44%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.83 (s, 1H), 8.78 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.13 (t, J = 5.6 Hz, 1H), 7.89 (dd, J = 8.8, 2.4 Hz, 1H), 7.38 (s, 1H), 7.33 – 7.30 (m, 2H), 7.25 (d, J = 7.3 Hz, 2H), 7.18 – 7.13 (m, 1H), 6.90 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 4.67 – 4.59 (m, 1H), 3.29 (dt, J = 11.2, 7.1 Hz, 2H), 3.09 (dd, J = 13.6, 4.1 Hz, 1H), 2.94 (dd, J = 13.5, 10.8 Hz, 1H), 2.25 (t, J = 7.4 Hz, 2H), 1.92 (s, 3H). ^{13}C NMR (101 MHz) δ 173, 172, 170, 166, 162, 149, 139, 137, 130, 129, 127, 121, 106, 55, 38, 36, 35, 21.

Analysis of the cleaved compound from the resin **1l.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.13; found: 412.37, t_R = 1.53 min, (method 1), purity: 88%.

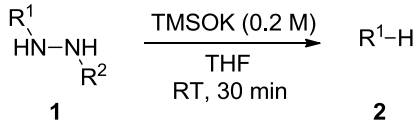
Pure product: Yield: 53 mg, 34%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.79 (d, J = 2.7 Hz, 1H), 8.91 (d, J = 2.5 Hz, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.17 (t, J = 5.7 Hz, 1H), 7.57 (dd, J = 7.9, 1.2 Hz, 1H), 7.34 (d, J = 7.1 Hz, 3H), 7.27 (dd, J = 13.8, 6.4 Hz, 3H), 7.16 (t, J = 7.3 Hz, 1H), 6.78 (dt, J = 15.0, 12.4 Hz, 3H), 4.67 – 4.58 (m, 1H), 3.32 – 3.25 (m, 2H), 3.07 (dd, J = 13.7, 4.3 Hz, 1H), 2.96 (dd, J = 13.7, 10.7 Hz, 1H), 2.24 (t, J = 7.1 Hz, 2H), 1.89

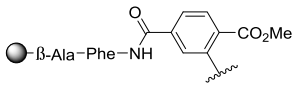
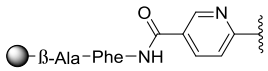
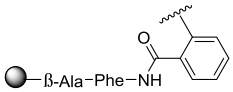
(s, 3H). ^{13}C NMR (101 MHz) δ 173, 172, 169, 168, 150, 139, 132, 129, 128, 126, 117, 116, 113, 55, 37, 35 (2C), 21.

2.5. General procedure for hydrazine cleavage on solid phase

Solution of 0.2 M TMSOK (0.3 g, 2 mmol) in THF (10 mL) was added to the immobilized hydrazine **1a-l** (1 g) which had been swelled in DCM. Slurry was stirred for 0.5 h at RT. Resin was then washed with 3×12 mL DMF, 3×12 mL DCM. Yields are summarized in the following table:

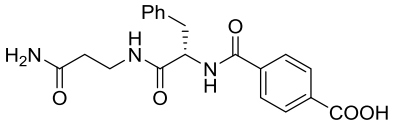
Table 1: Synthesis of derivative **2** via dehydrazination of compounds **1**.



1	R^1	R^2	**2**	Yield of **2** (%)*
1a		-H	**2a**	20**
1b		-Fmoc	**2a**	***
1c		-Ms	**2a**	16**
1d		-COMe	**2a**	19**
1e		-H	**2e**	53
1f		-Fmoc	**2e**	***
1g		-Ms	**2e**	****
1h		-COMe	**2e**	54
1i		-H	**2i**	58
1j		-Fmoc	**2i**	***
1k		-Ms	**2i**	17
1l		-COMe	**2i**	57

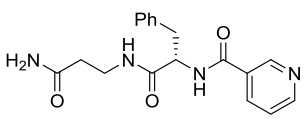
*Yield determined by ^{1}H NMR spectroscopy after HPLC purification.
**Product was isolated as carboxylic acid.
***Product was not observed.
****Reaction was not studied because the preparation of product **1g** proceeded with very low purity.

Analysis of the cleaved compound from the resin **2a.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{20}H_{22}N_3O_5$ $[M+H]^+$: 384.15; found: 384.34, t_R = 2.47 min (method 2). Pure product: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 (d, J = 8.4 Hz, 1H), 8.18 (t, J = 5.6 Hz, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.37 – 7.31 (m, 3H), 7.24 (t, J = 7.6 Hz, 2H), 7.15 (tt, J = 10, 2 Hz, 1H), 6.83 (s, 1H), 4.68 – 4.63 (m, 1H), 3.30 – 3.24 (m, 2H), 3.08 (dd, J = 13.7, 4.3 Hz, 1H), 2.98 (dd, J = 13.6, 10.6 Hz, 1H), 2.54 (s, 1H), 2.24 (J = 7.4 Hz, 2H).^{13}C NMR (126 MHz) δ 173, 172, 171, 166, 139, 136, 129 (2C) , 128, 127, 126, 55, 35 (2C), 21.

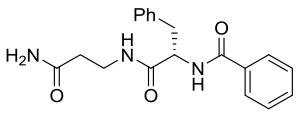
Analysis of the cleaved compound from the resin **2e.**



Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{18}H_{21}N_4O_3$ $[M+H]^+$: 341.15; found: 341.34, t_R = 2.47 min (method 1).

Pure product: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.92 (d, *J* = 2.2 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.16 (t, *J* = 5.7 Hz, 1H), 8.10 (dt, *J* = 4, 2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.33 (d, *J* = 7 Hz, 3H), 7.25 (t, *J* = 10.4 Hz, 2H), 7.18 – 7.13 (m, 1H), 6.84 (s, 1H), 4.70 – 4.63 (m, 1H), 3.31 – 3.24 (m, 2H), 3.11 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.94 (dd, *J* = 13.7, 10.8 Hz, 1H), 2.24 (td, *J* = 7.3, 1.4 Hz, 2H).^{13}C NMR (126 MHz) δ 173, 171, 165, 152, 149, 138, 135, 130, 129, 128, 126, 123, 55, 37, 35(2C).

Analysis of the cleaved compound from the resin **2i.**



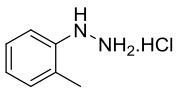
Crude product: LC/MS analysis: MS (ESI) exact mass calcd. for $C_{19}H_{22}N_3O_3$ $[M+H]^+$: 340.13; found: 340.34, t_R = 2.47 min (method 1).
Pure product: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.53 (d, *J* = 8.4 Hz, 1H), 8.11 (t, *J* = 5.7 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 3H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.84 (s, 1H), 4.68 – 4.62 (m, 1H), 3.30 – 3.24 (m, 2H), 3.08 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.97 (dd, *J* = 13.7, 10.7 Hz, 1H), 2.23 (td, *J* = 7.3, 1.4 Hz, 2H).^{13}C NMR (126 MHz) δ 172, 171, 166, 138, 134, 131, 129, 128 (2C), 127, 126, 55, 37, 35 (2C).

3. Reactions in solution

3.1. Preparation of hydrazines in solution

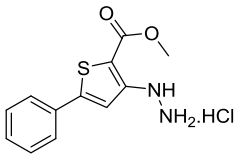
Hydrazines **3a-3c** and **3e – 3i** are commercially available.

2-tolyl hydrazine hydrochloride 3d



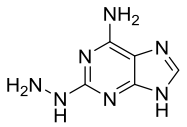
The compound was prepared according to the published procedure[2].
Yield: 1.0 g; 63% of light brown powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_7H_{11}N_2$ $[M+H]^+$: 123.06; found: 123.36, t_R = 1.53 min (method 1), purity: 99%.

Methyl-3-hydrazinyl-5-phenylthiophene-2-carboxylate hydrochloride 3j



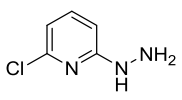
The compound was prepared according to the published procedure[2].
Yield: 0.71 g; 58% of white powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_{12}H_{13}N_2O_2S$ $[M+H]^+$: 249.06; found: 249.26, t_R = 2.93 min (method 1), purity: 86%.

2-hydrazinyl-9*H*-purin 6-amine 3k



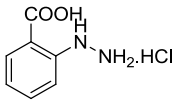
The compound was prepared according to the published procedure[3].
Yield: 1.27 g; 65% of white powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_5H_8N_7$ $[M+H]^+$: 166.08; found: 166.18, t_R = 0.38 min (method 1), purity: 99%.

2-chloro-6-hydrazinyl pyridine 3l



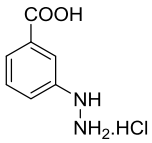
The compound was prepared according to the published procedure[4].
Yield: 1.57 g; 80% of white powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_5H_7ClN_3$ $[M+H]^+$: 144.03; found: 144.57, t_R = 1.28 min (method 1), purity: 95%.

2-hydrazinyl benzoic acid 5a



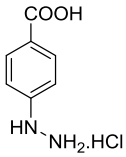
The compound was prepared according to the published procedure[2]. Yield: 1.39 g; 90% of white powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_7H_9N_2O_2$ $[M+H]^+$: 153.06; found: 153.36, t_R = 0.41 min (method 2), purity: 99%.

3-hydrazinyl benzoic acid 5b



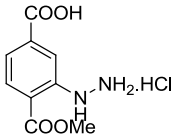
The compound was prepared according to the published procedure[2].
Yield: 1.7 g; 90% of white powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_7H_9N_2O_2$ $[M+H]^+$: 153.06; found: 153.16, t_R = 0.57 min (method 2), purity: 95%.

4-hydrazinyl benzoic acid 5c



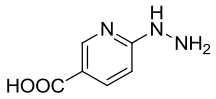
The compound was prepared according to the published procedure[2].
Yield: 1.8 g; 92% of light yellow powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_7H_9N_2O_2$ $[M+H]^+$: 153.06; found: 153.16, t_R = 0.57 min (method 2), purity: 99%.

3-hydrazinyl-4-(methoxycarbonyl)benzoic acid 5d



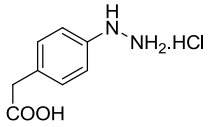
The compound was prepared according to the published procedure[2].
Yield: 2.1 g; 84% of light yellow powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_9H_{11}N_2O_4$ $[M+H]^+$: 210.06; found: 211.20, t_R = 0.94 min (method 2), purity: 99%.

6-hydrazinyl nicotinic acid 5e



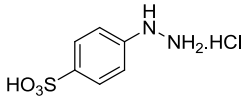
The compound was prepared according to the published procedure[5].
Yield: 1.25 g; 82% of light grey powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_6H_8N_3O_2$ $[M+H]^+$: 154.05; found: 154.16 t_R = 0.51 min (method 2), purity: 91%.

4-hydrazinyl phenylacetic acid 5f



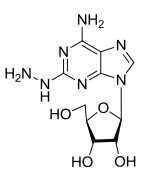
The compound was prepared according to the published procedure[2].
Yield: 1.38 g; 89% of light brown powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_8H_{11}N_2O_2$ $[M+H]^+$: 167.08; found: 167.30, t_R = 0.36 min (method 2), purity: 98%.

4-hydrazinyl sulphanilic acid 5g



The compound was prepared according to the published procedure[2].
Yield: 1.19 g; 92% of light yellow powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_6H_9N_2O_3S$ $[M+H]^+$: 189.03; found:189.05, t_R = 0.47 min (method 2) purity: 91%.

2-hydrazinyl adenosine 5h



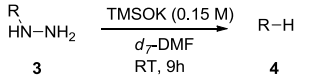
The compound was prepared according to the published procedure[6].
Yield: 1.58 g; 80% of light yellow powder. LC/MS analysis: MS (ESI) exact mass calcd. for $C_{10}H_{16}N_7O_4$ $[M+H]^+$: 298.12; found:298.24, t_R = 2.49 min (method 2) purity: 98%.

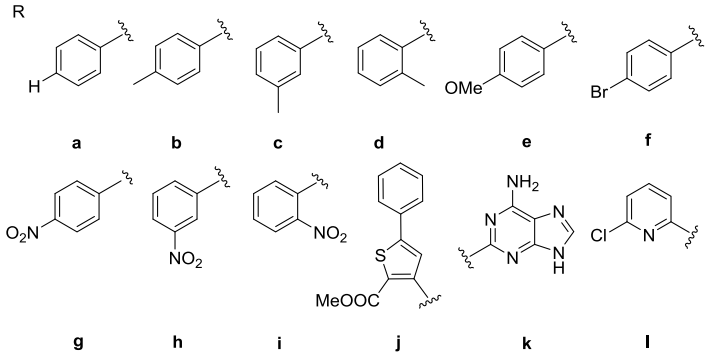
3.2. General procedure for hydrazines cleavage in solution

A/ Cleavage of compounds insoluble in water

Solution of 0.15 M TMSOK (0.02 g, 0.15 mmol) in d_7-DMF (1 mL) was added to the hydrazines **3a-l** (0.02 g). Slurry was stirred for 9 h at RT. Final solution was then analyzed by ^{1}H NMR. The NMR spectra of crude compounds are placed in chapter 9. The yields are summarized in the following table:

Table 2: Hydrazine cleavage in solution with corresponding yields in d_7-DMF.





Compound **3**	Product **4**	Yield of **4** (%)*	Yield of **4** at 70 °C for 48 h (%)*
3a	**4a**	99	-
3b	**4b**	95	-
3c	**4b**	35	70
3d	**4b**	SM	51
3e	**4e**	89	-
3f	**4f**	81	-
3g	**4g**	55	-
3h	**4g**	85	-
3i	**4g**	90	-
3j	**4j**	69	-
3k	**4k**	insoluble	50
3l	**4l**	42	97

*Yield determined by ^{1}H NMR spectroscopy.

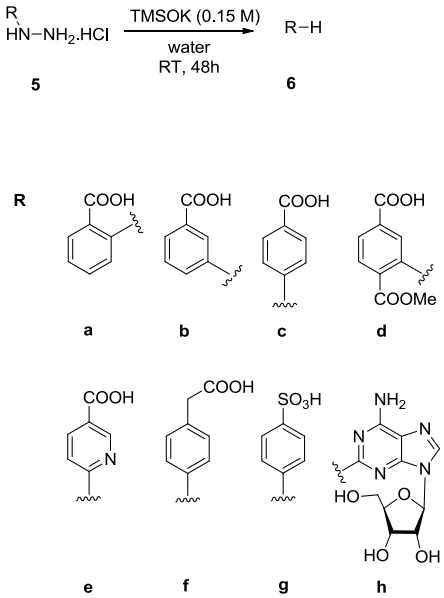
^{1}H NMR data of all final products (**4a**[7], **4b**[8], **4e**[9], **4f**[10], **4g**[11], **4j**[12], **4k**[13],**4l**[14]) are in accordance with published data.

B/ Cleavage of compounds soluble in water

Solution of 0.15 M TMSOK (0.02 g, 0.15 mmol) in water (1 mL) was added to the hydrazine **5a-h** and **3k** (0.02 g). Slurry was stirred for 48 h at RT. Final solution was lyophilized to dryness, residue was dissolved in deuterium oxide and analyzed by ^{1}H NMR. The NMR spectra of crude compounds are placed in chapter 9.

^{1}H NMR data of all final products (**6a**[15]**, 6d**[16]**, 6e**[17], **6f**[18]**, 6g**[19]**,6h**[20]**, 4k**[13]) are in accordance with published data

Table 3: Hydrazine cleavage in solution with corresponding yields in D_2O.



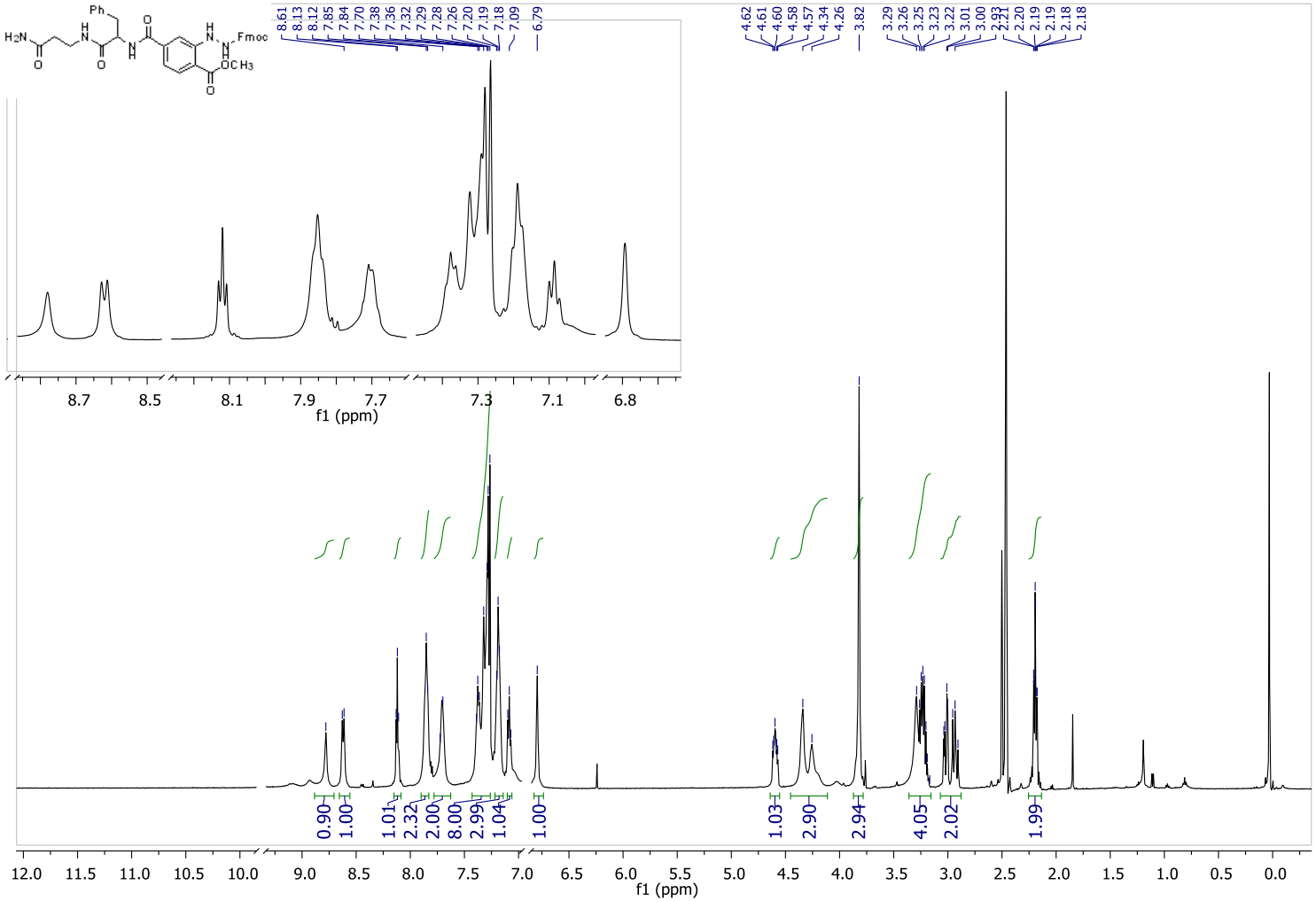
Entry	Compound **5**	Product **6**	Yield of **6a-h** (%)*	Yield of **6(R)** at 70 °C for 48 h (%)*
1	**5a**	**6a**	99	-
2	**5b**	**6a**	64	-
3	**5c**	**6a**	77	-
4	**5d**	**6d**	81	-
5	**5e**	**6e**	71	-
6	**5f**	**6f**	90	-
7	**5g**	**6g**	98	-
8	**5h**	**6h**	40	89
9	**3k**	**4k**	49	45

*Yield determined by ^{1}H NMR spectroscopy.

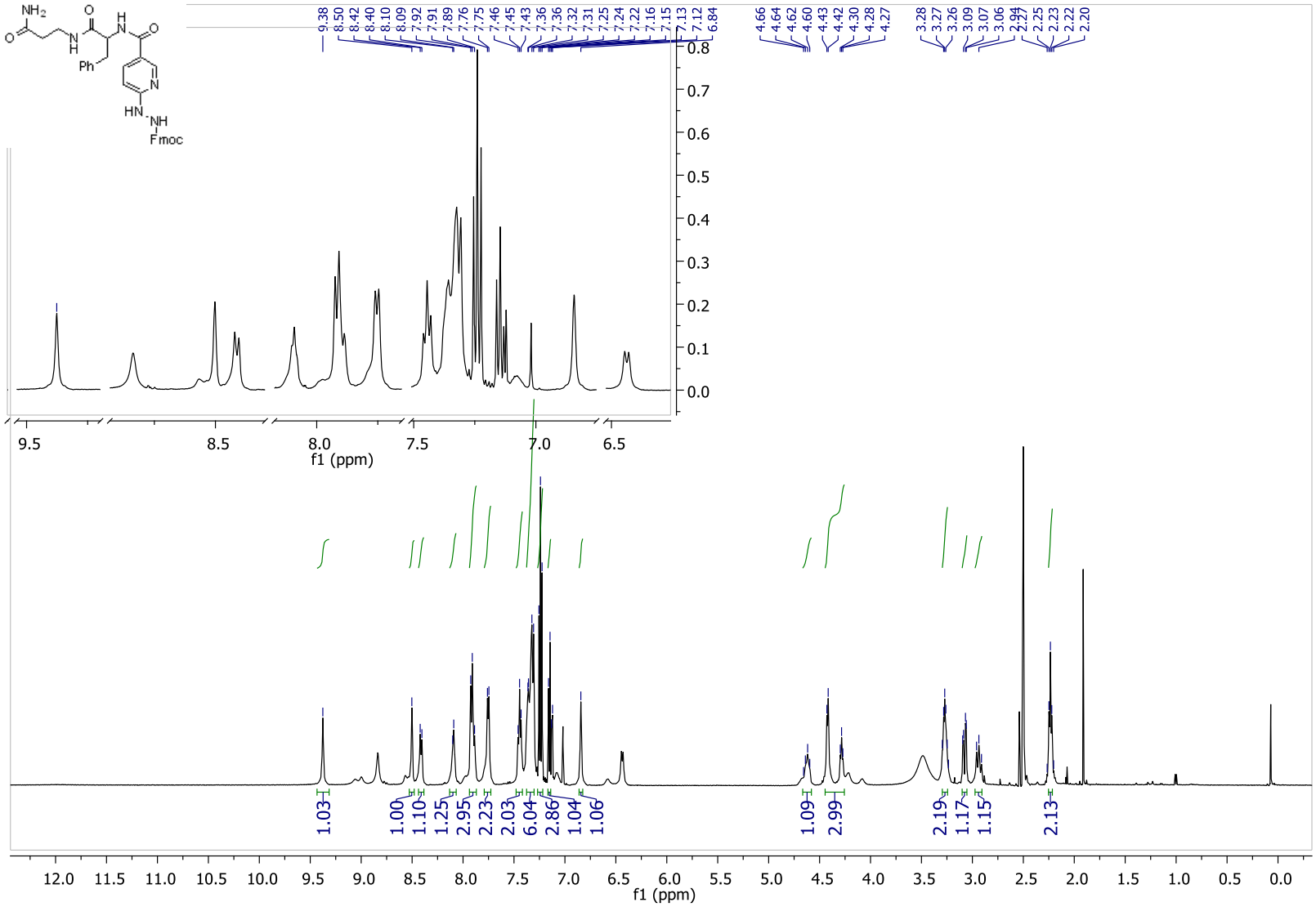
4. NMR spectra

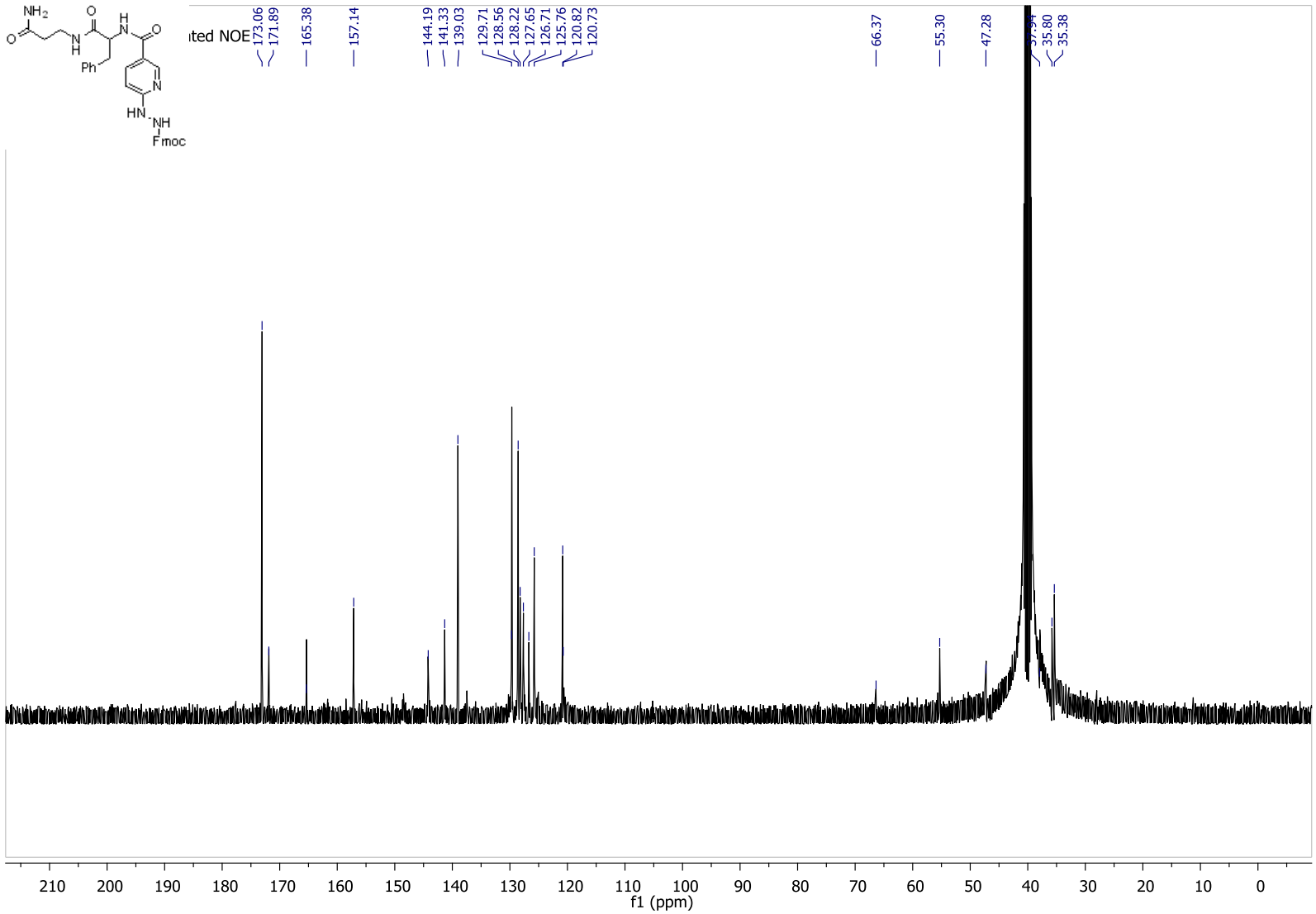
4.1. NMR spectra of products from solid-phase synthesis isolated by HPLC

Product released from the resin 1b

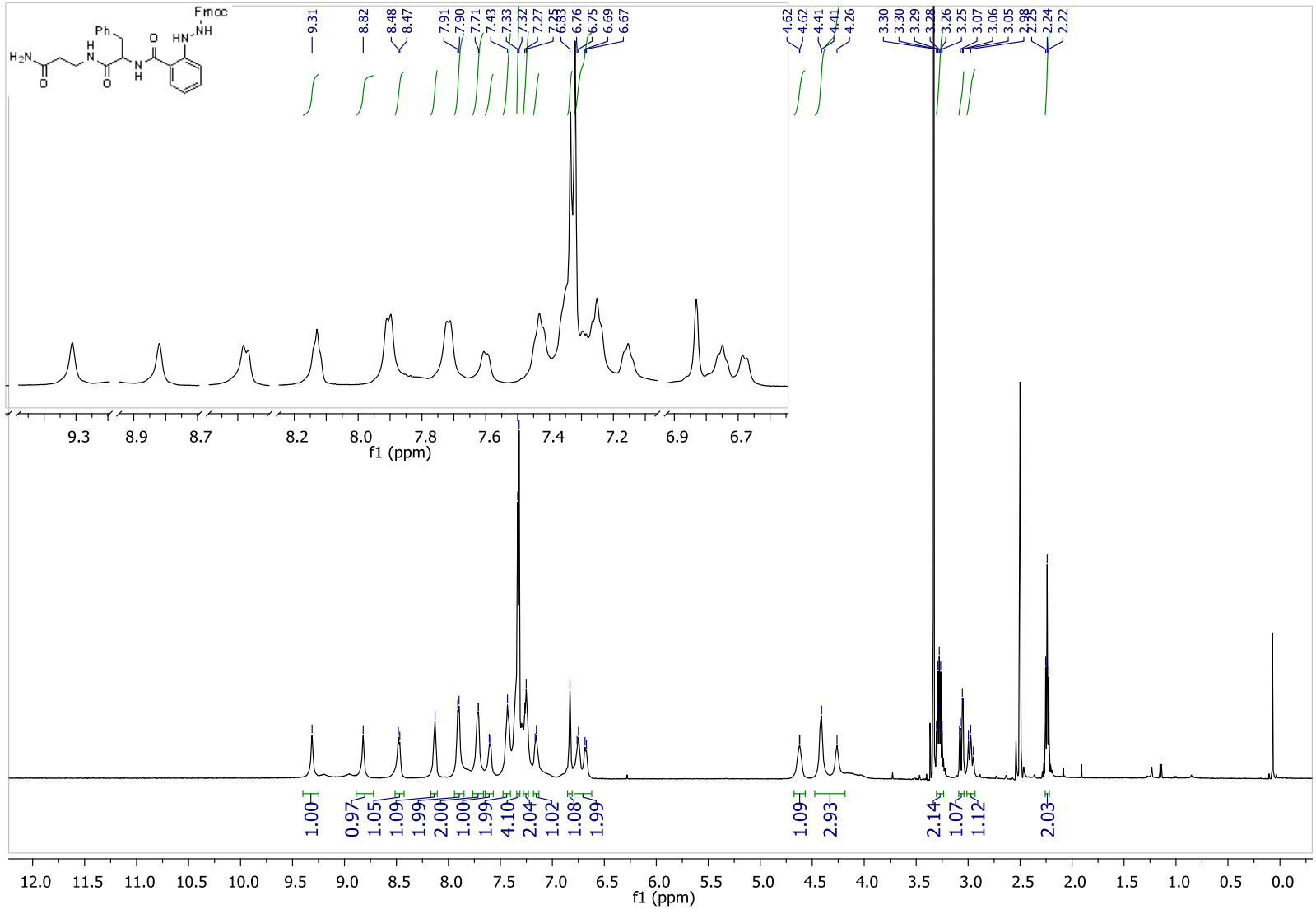


Product released from the resin 1f

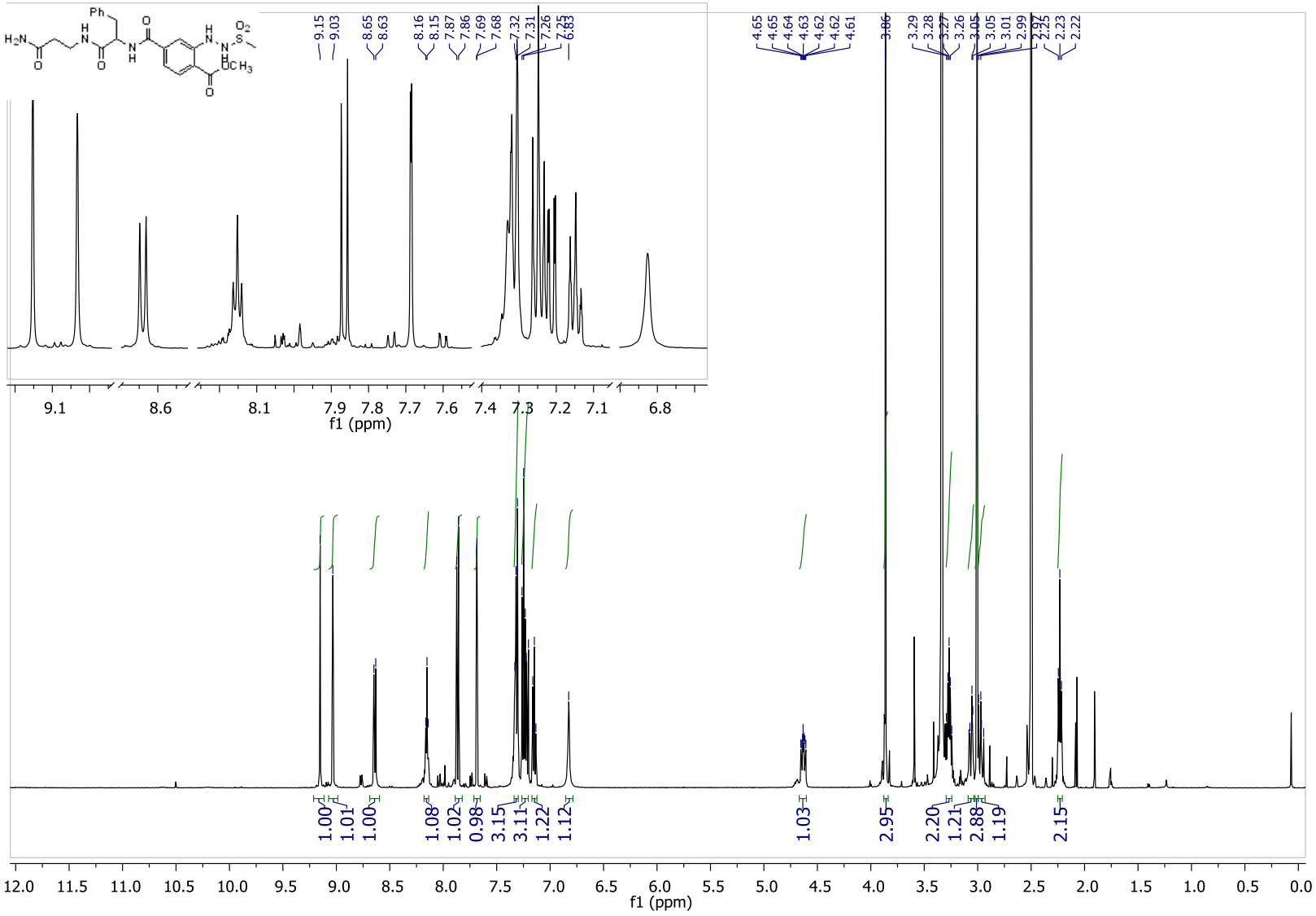



ited NOE
173.06
171.89
165.38
157.14
144.19
141.33
139.03
129.71
128.56
128.22
127.65
126.71
125.76
120.82
120.73
66.37
55.30
47.28
37.94
35.80
35.38
f1 (ppm)

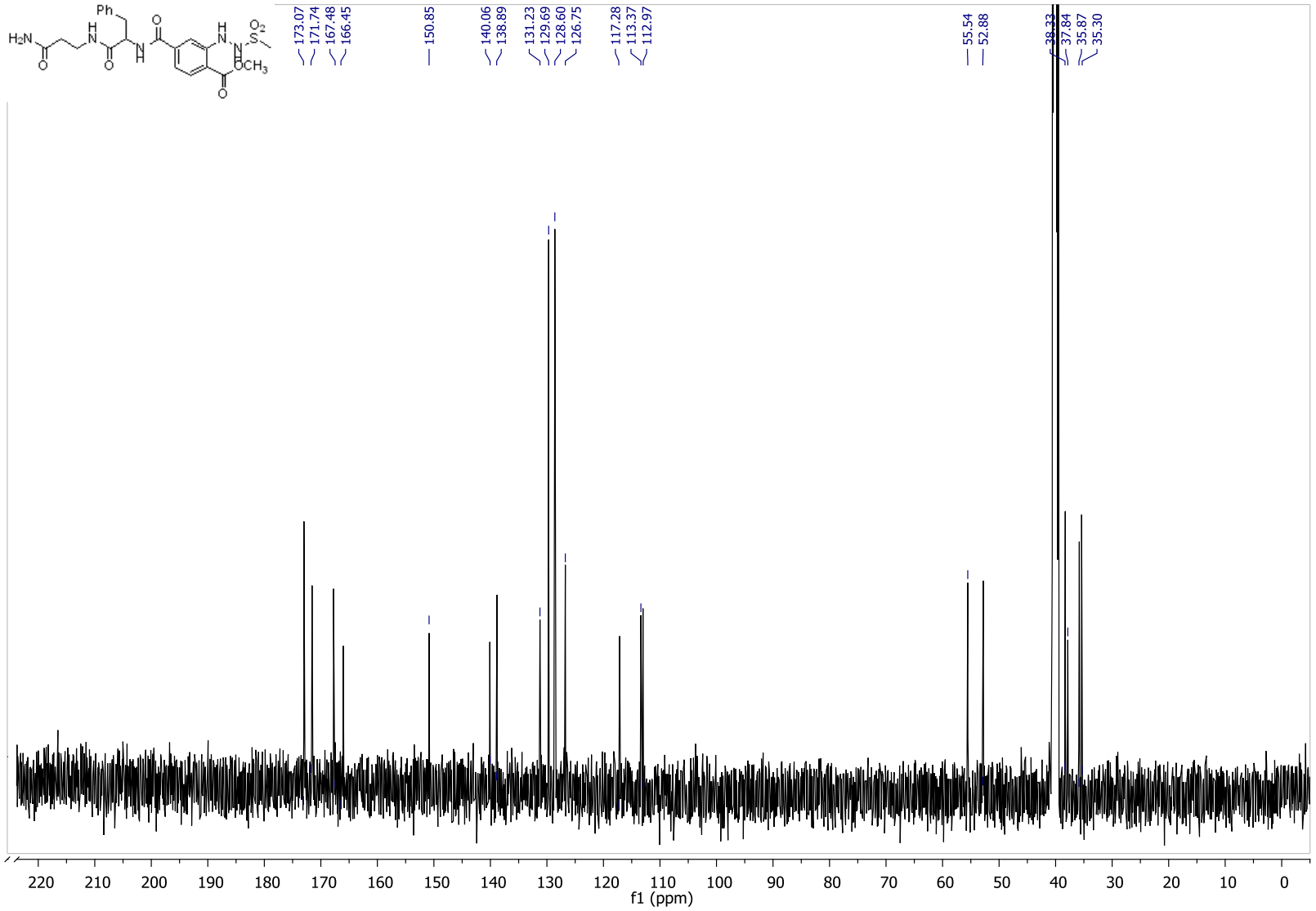
Product released from the resin 1j



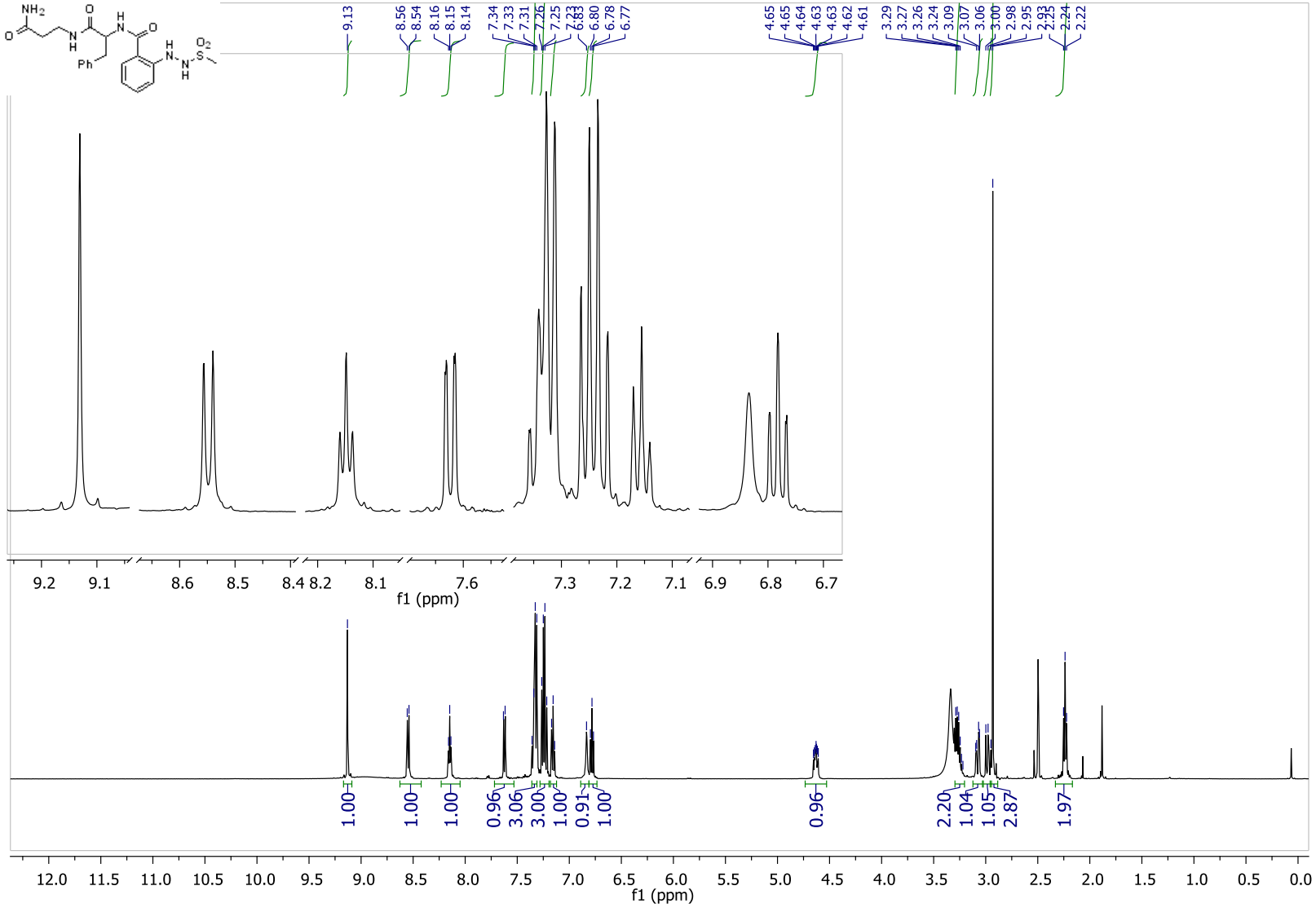
Product released from the resin 1c

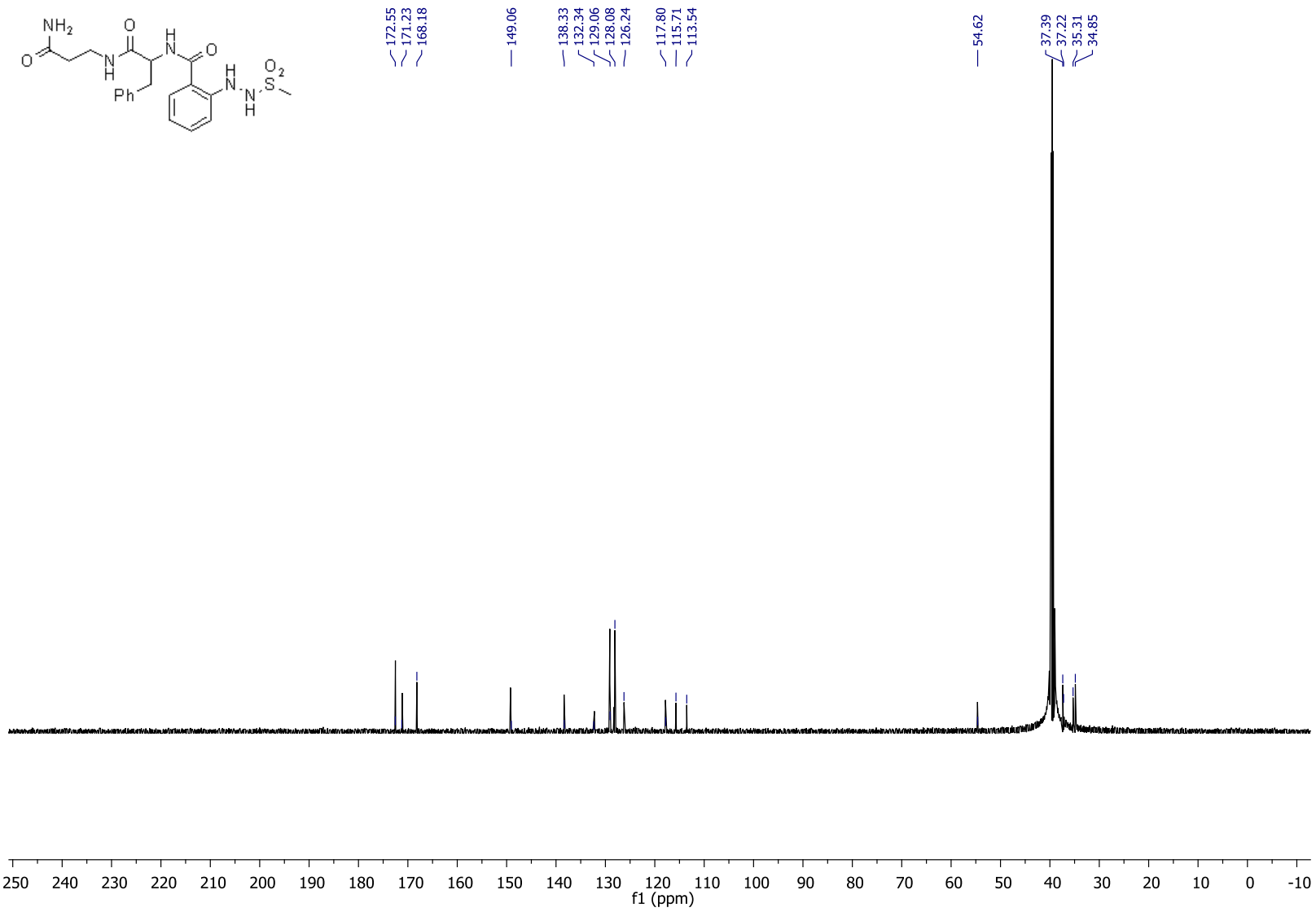


34


Ph
H_2N
O
O
O
O
O
H
N
H
N
H
N
O
O_2
S
CH_3
O
173.07
171.74
167.48
166.45
150.85
140.06
138.89
131.23
129.69
128.60
126.75
117.28
113.37
112.97
55.54
52.88
38.33
37.84
35.87
35.30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

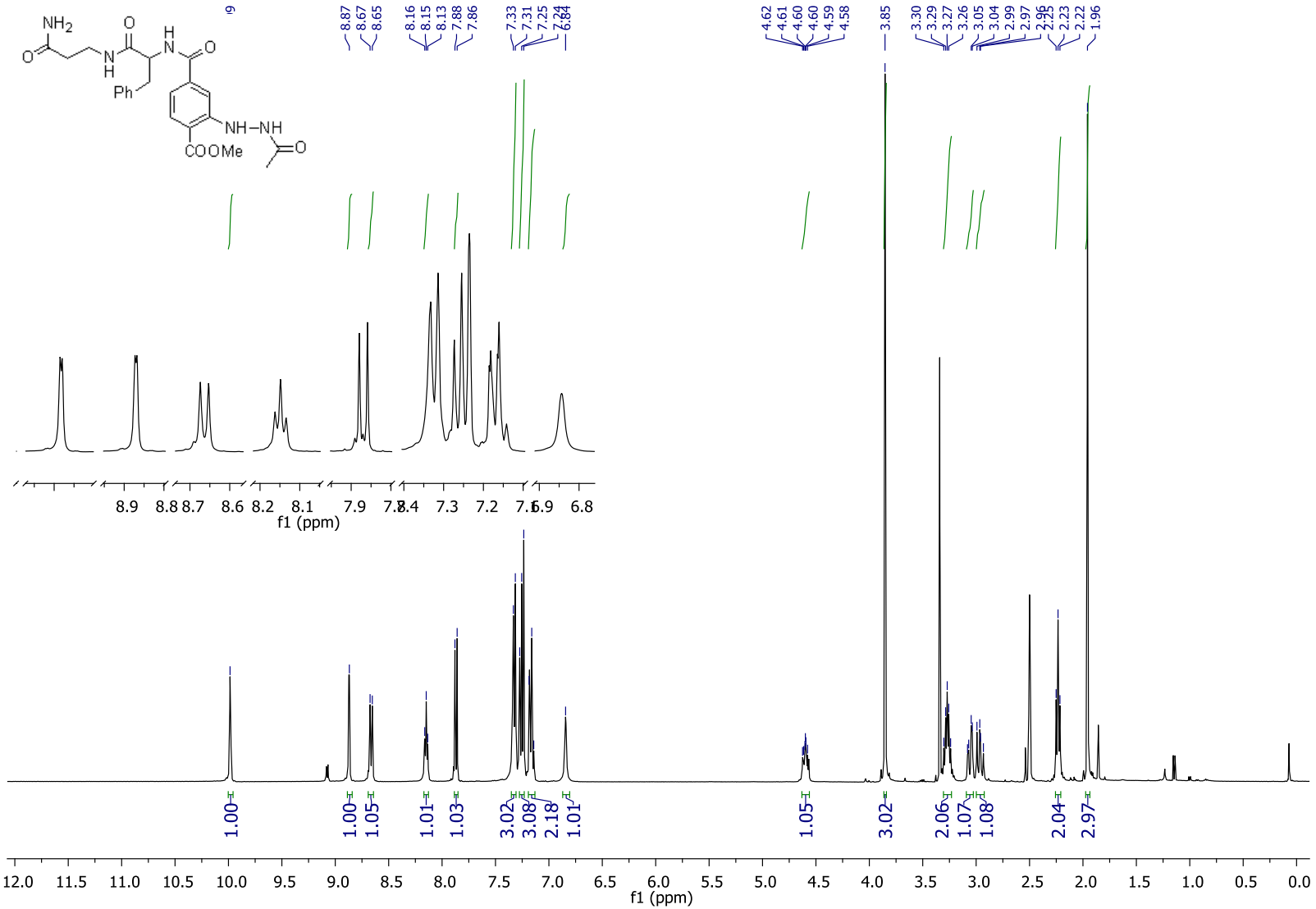
Product released from the resin 1k




NH2
O
O
N
H
H
N
O
Ph
H
N
N
O2
S
172.55
171.23
168.18
149.06
138.33
132.34
129.06
128.08
126.24
117.80
115.71
113.54
54.62
37.39
37.22
35.31
34.85
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

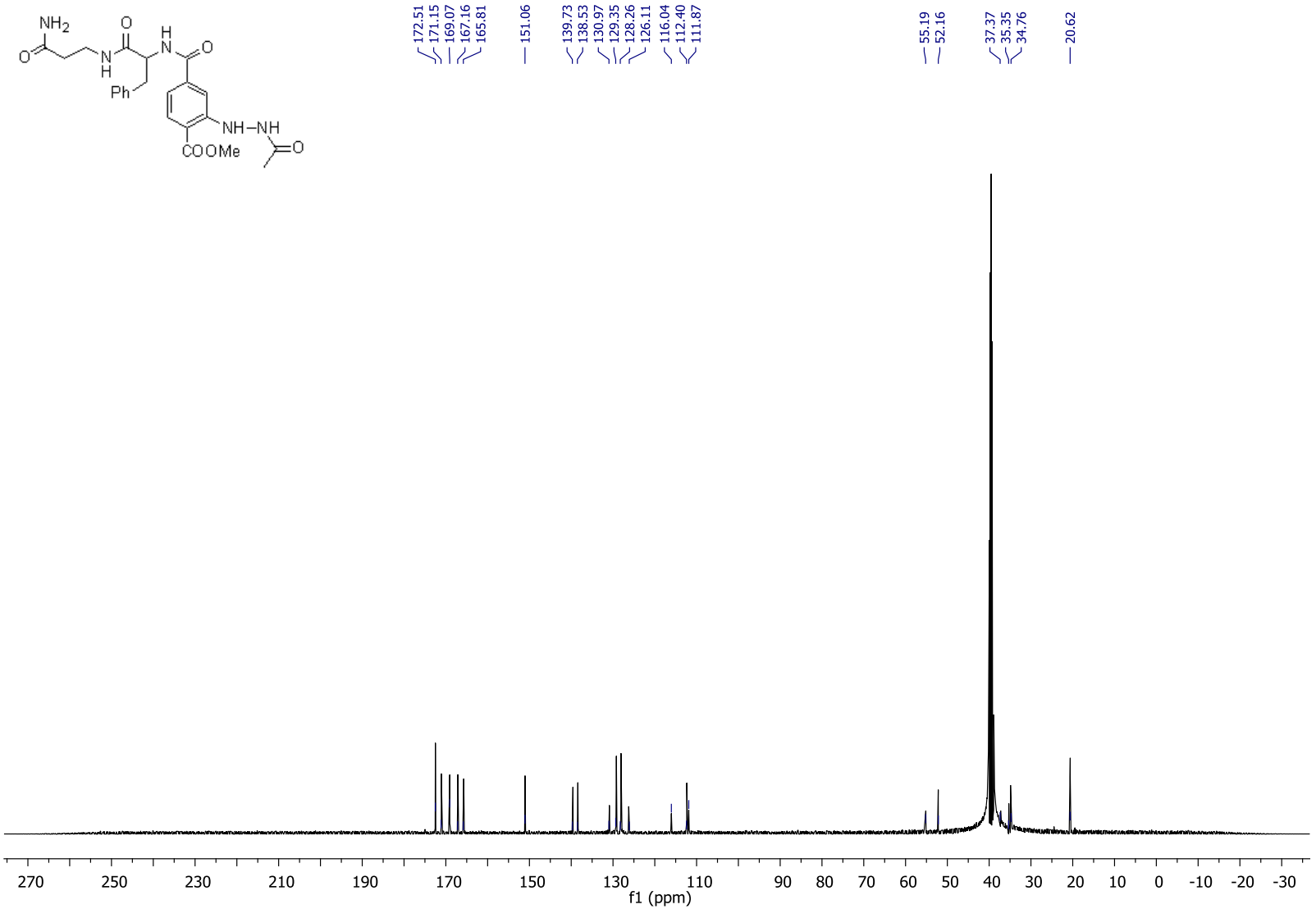
36

Product released from the resin 1d

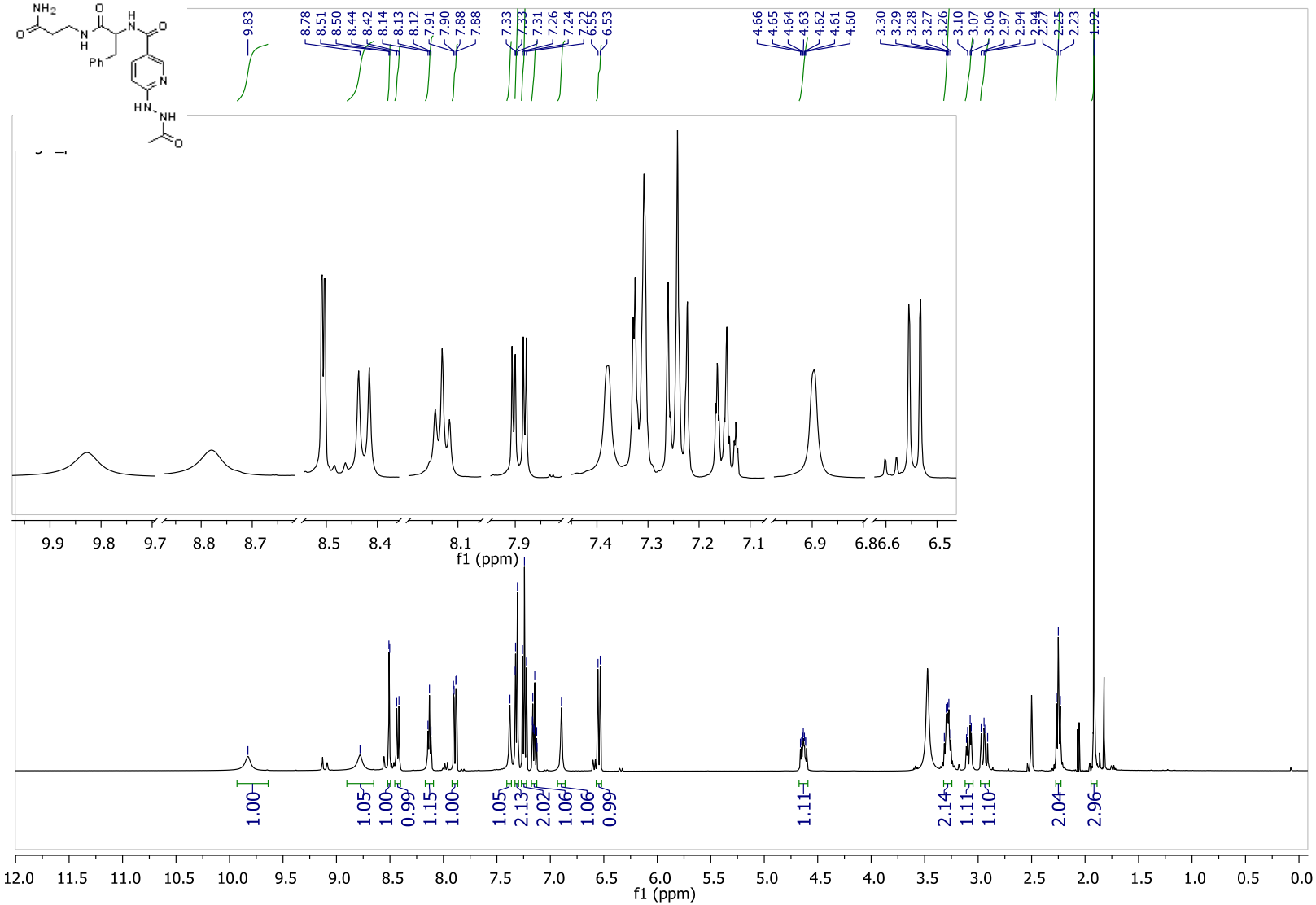


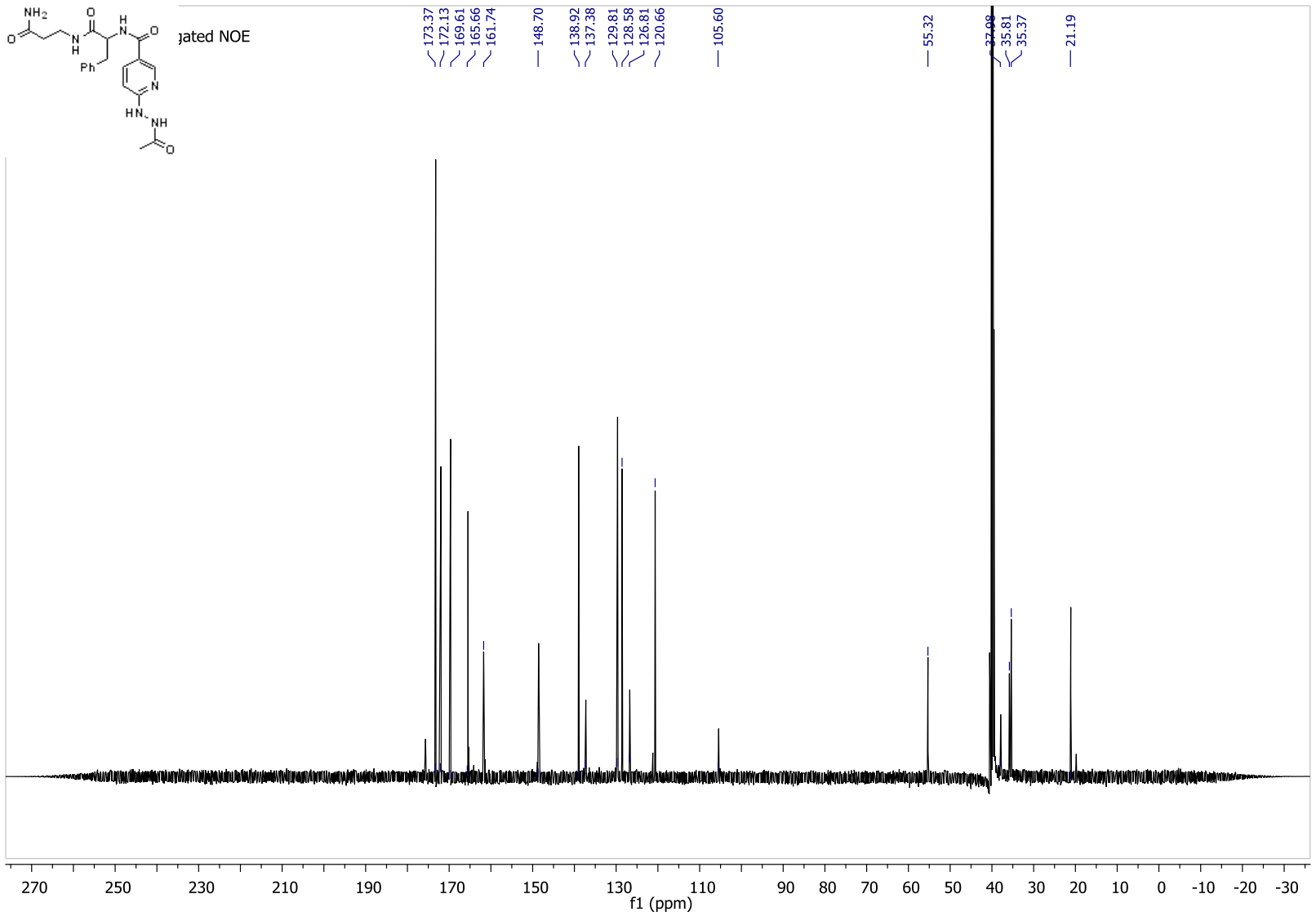
37

38


NH2
O
O
N
H
H
N
O
Ph
NH–NH
COOMe
O
172.51
171.15
169.07
167.16
165.81
151.06
139.73
138.53
130.97
129.35
128.26
126.11
116.04
112.40
111.87
55.19
52.16
37.37
35.35
34.76
20.62
270
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

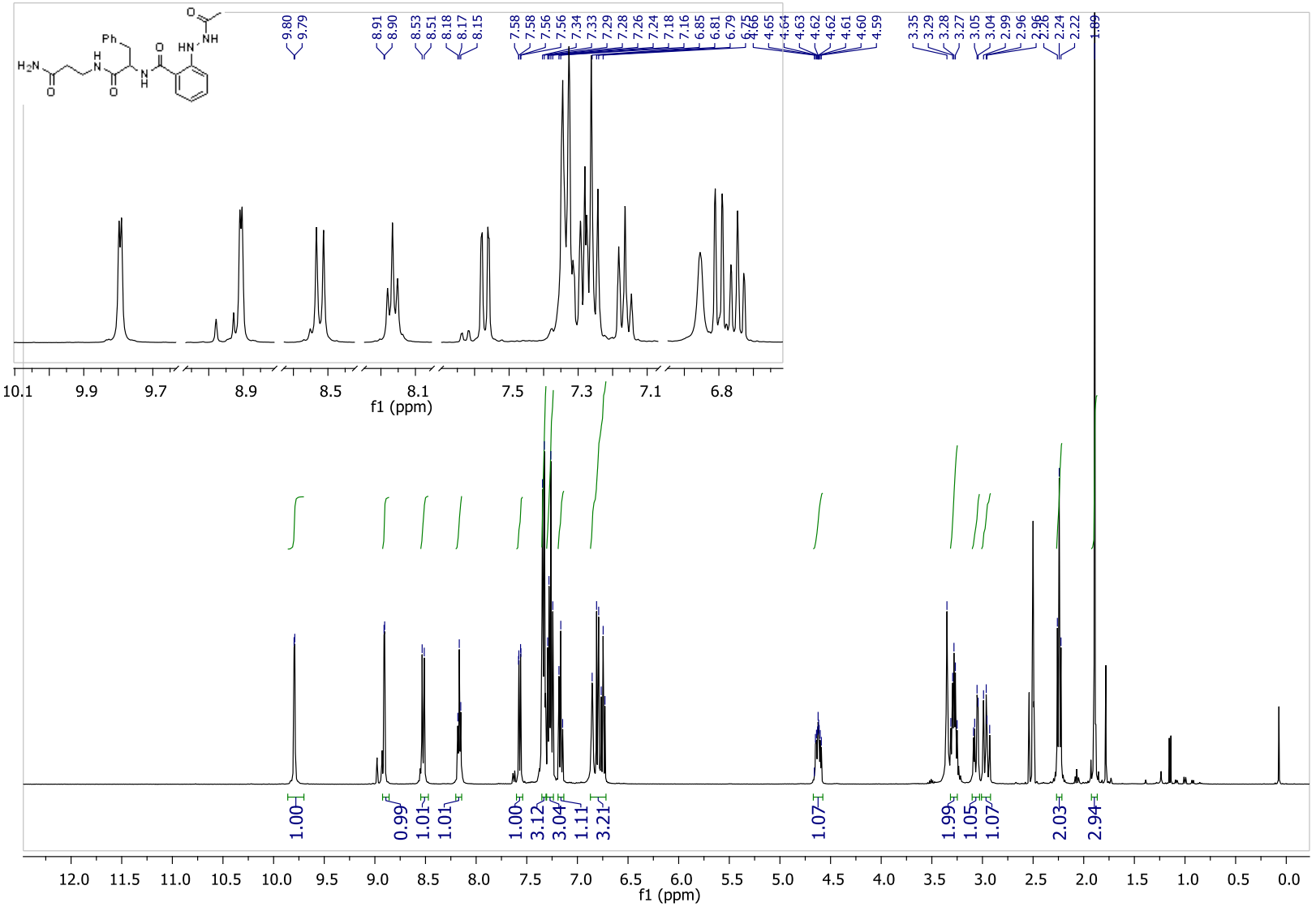
Product released from the resin 1h



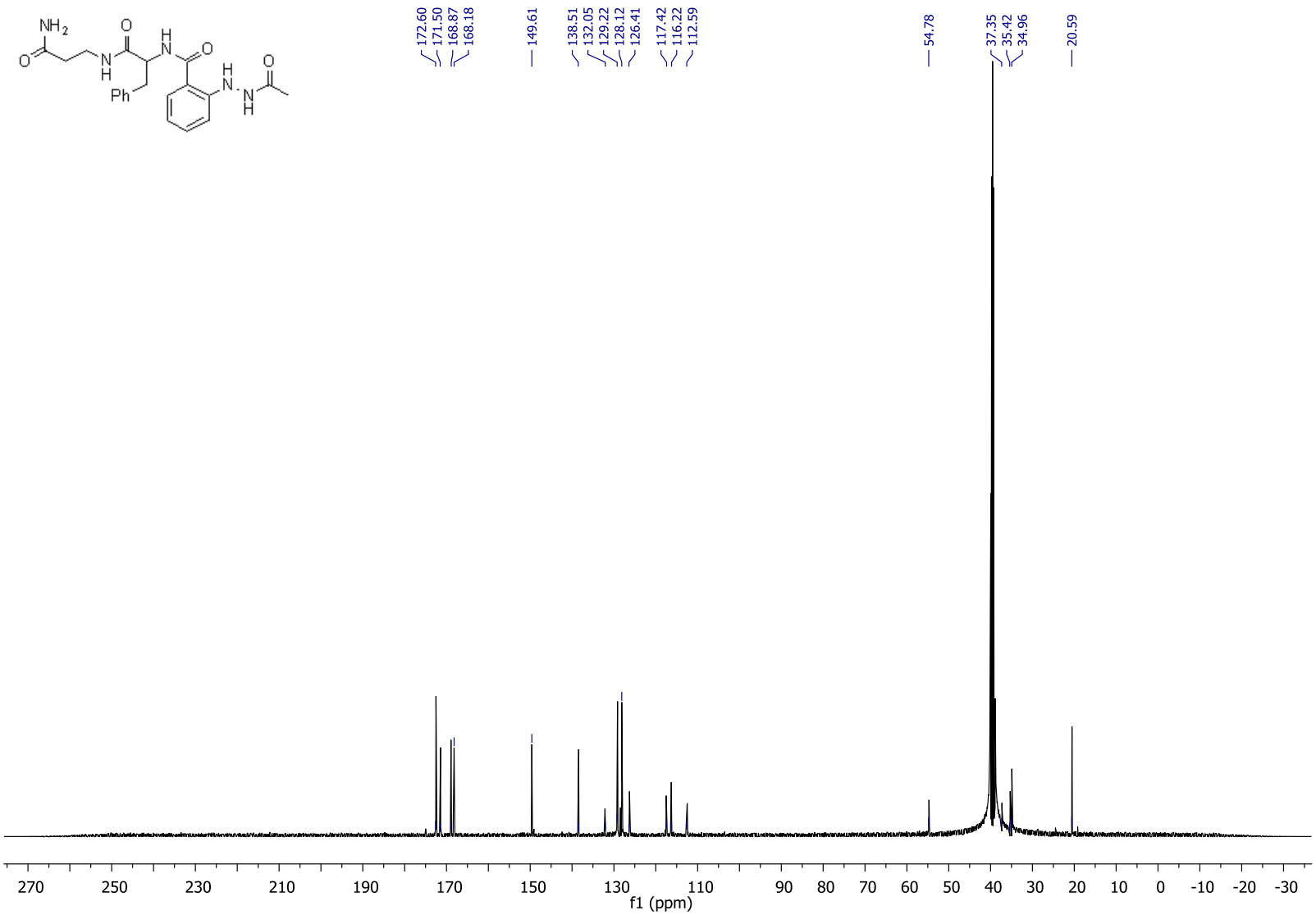

gated NOE
173.37
172.13
169.61
165.66
161.74
148.70
138.92
137.38
129.81
128.58
126.81
120.66
105.60
55.32
37.08
35.81
35.37
21.19
270
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

40

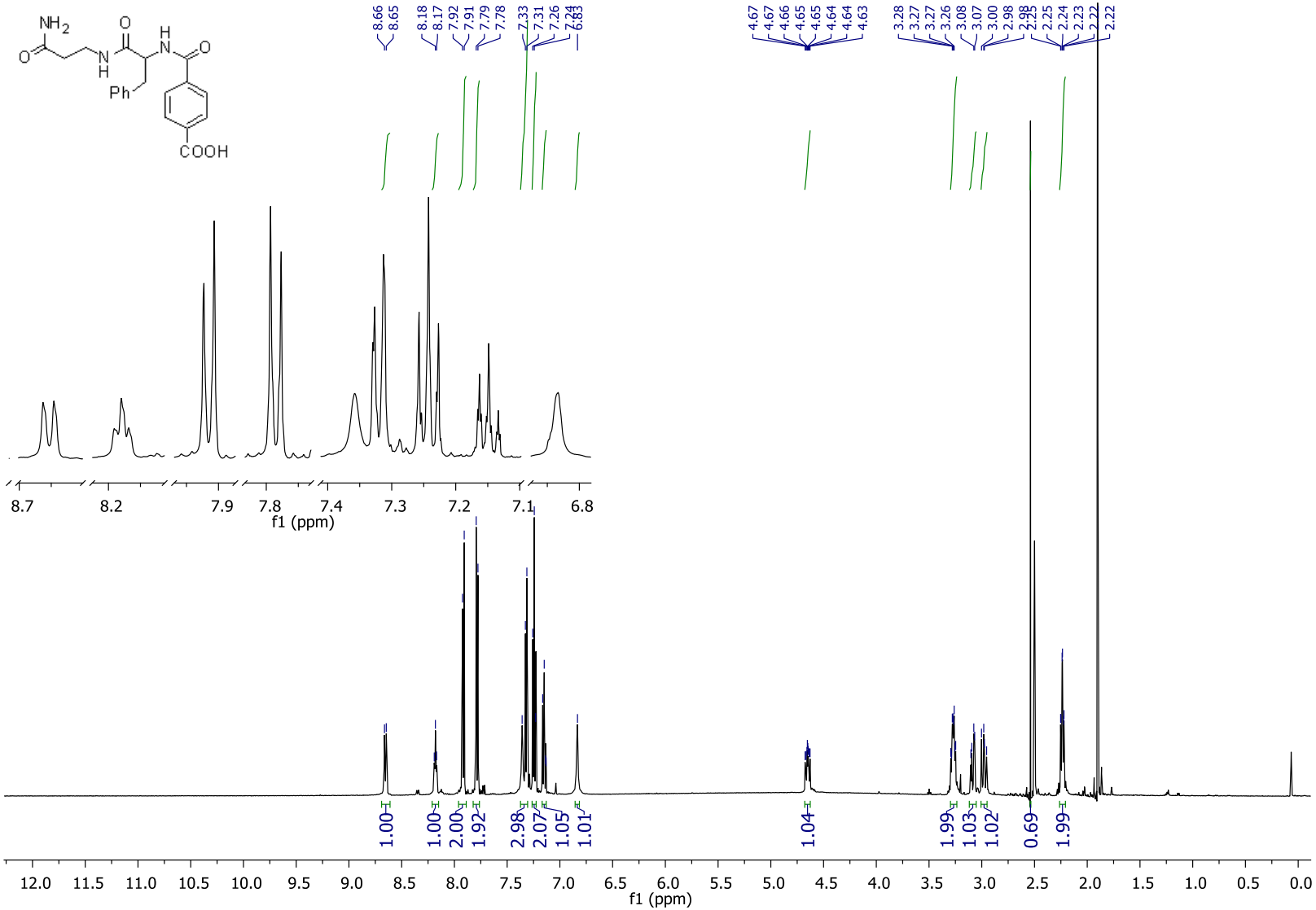
Product released from the resin 1l



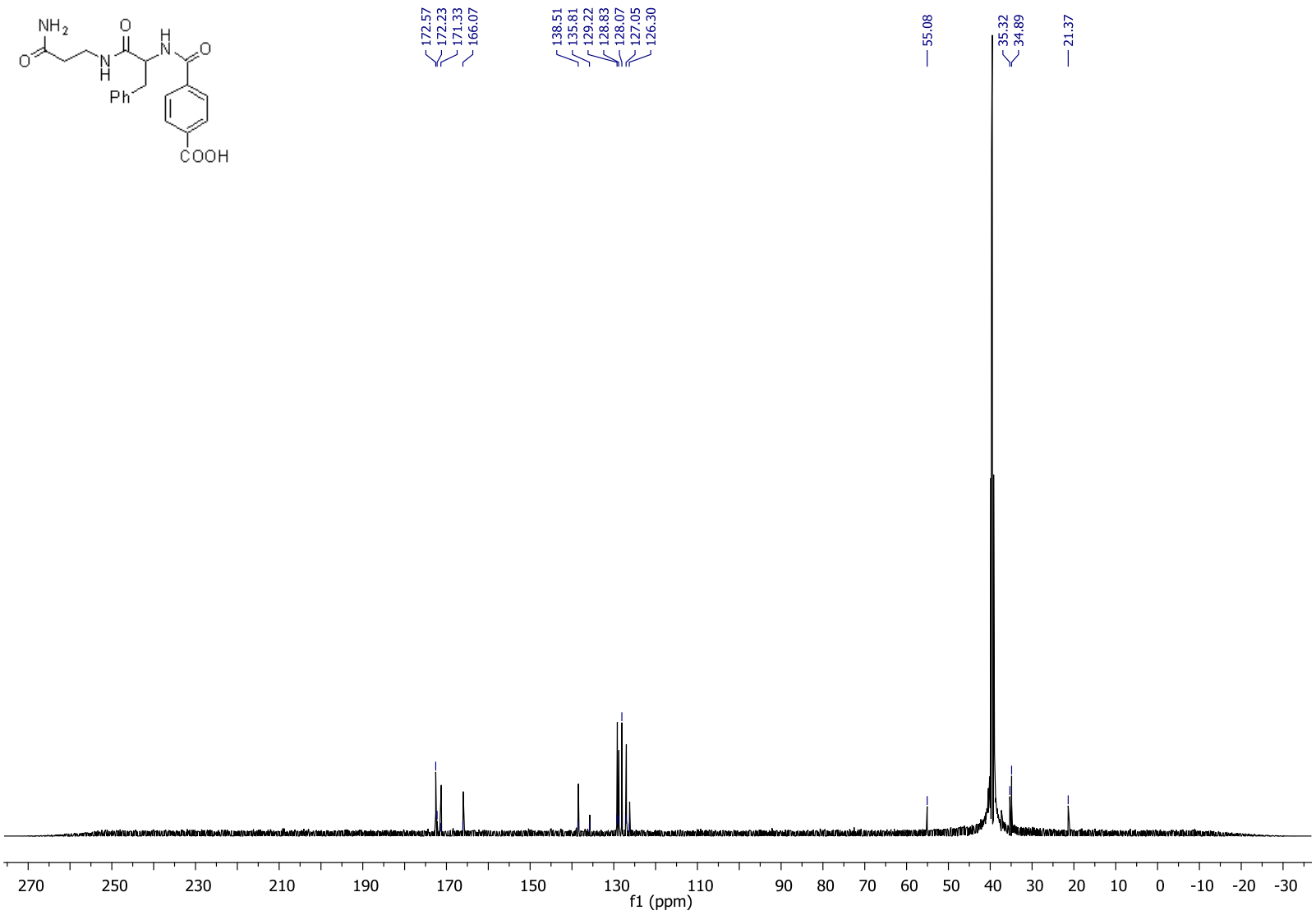
42


172.60
171.50
168.87
168.18
149.61
138.51
132.05
129.22
128.12
126.41
117.42
116.22
112.59
54.78
37.35
35.42
34.96
20.59
270 250 230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

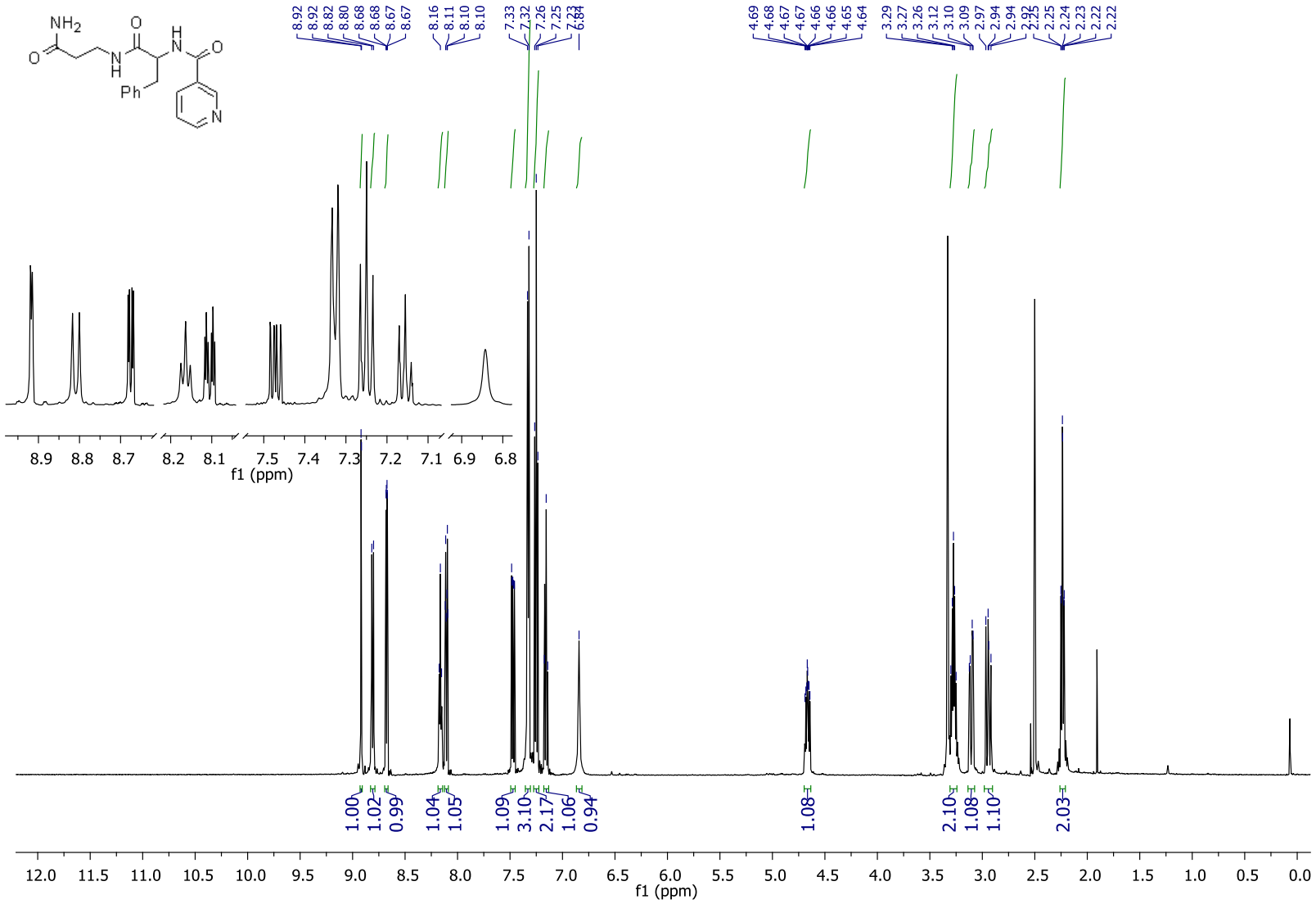
Product released from the resin 2a



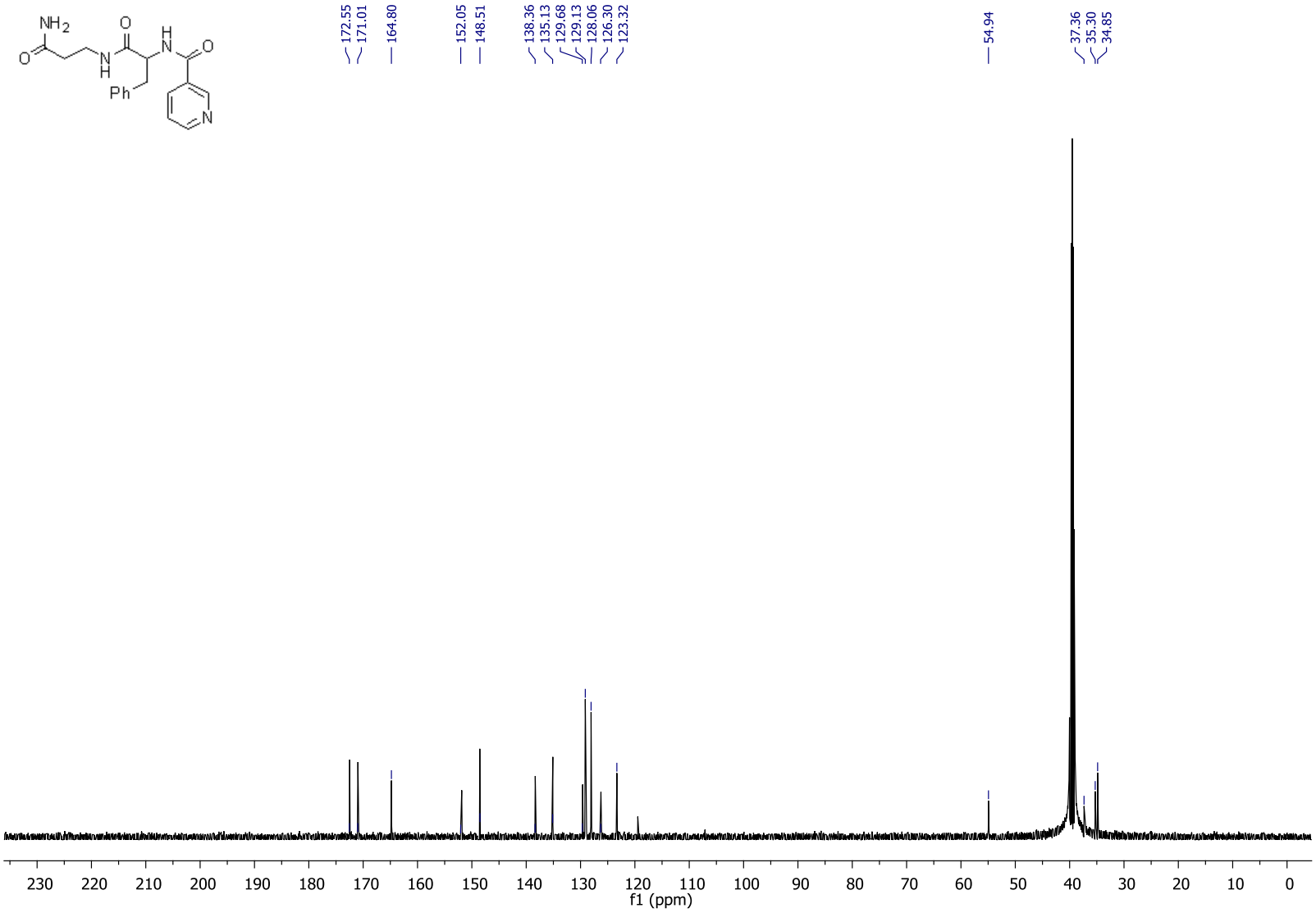
44


NH2
O
O
N
H
H
N
O
Ph
COOH
172.57
172.23
171.33
166.07
138.51
135.81
129.22
128.83
128.07
127.05
126.30
55.08
35.32
34.89
21.37
270 250 230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

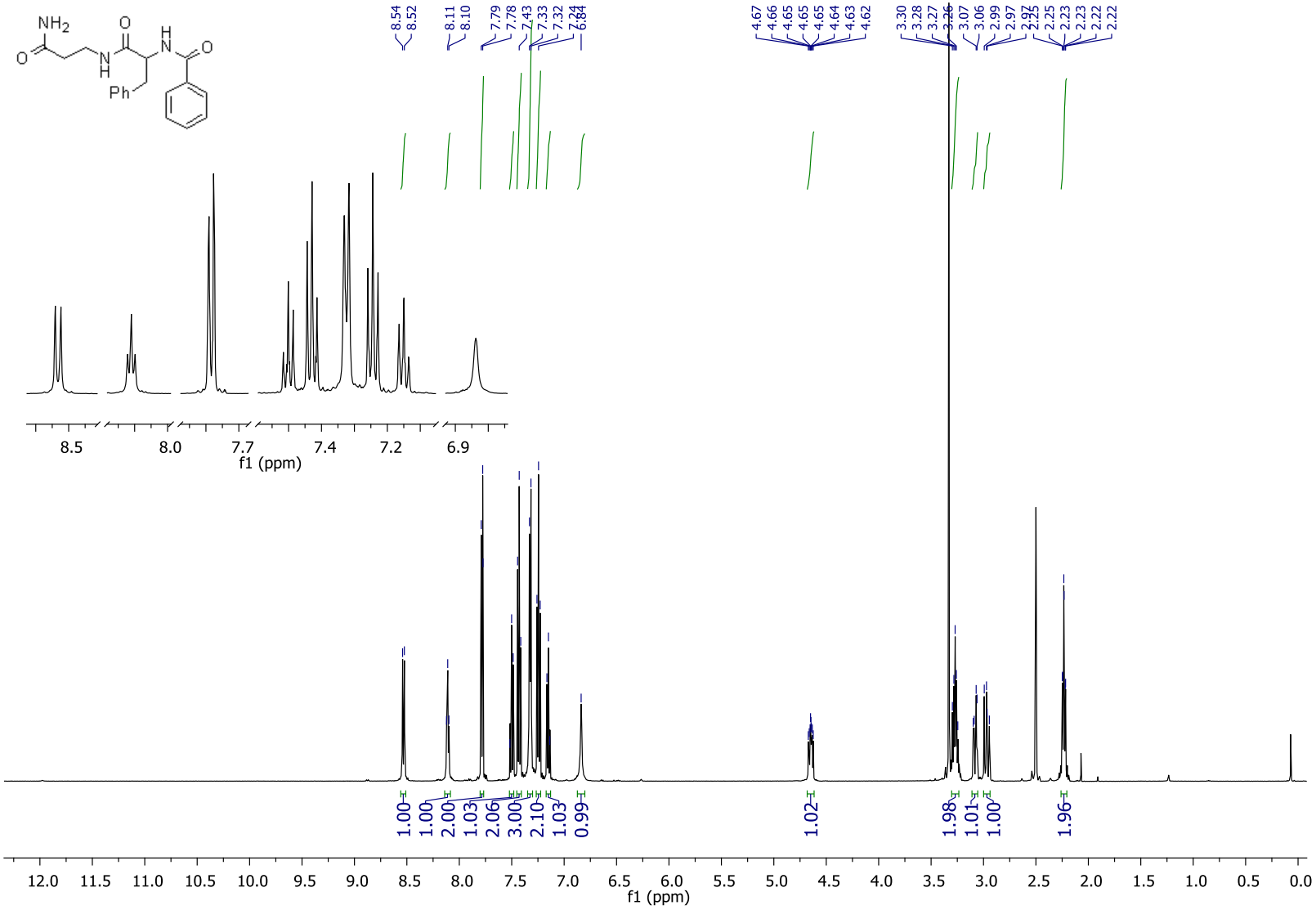
Product released from the resin 2b



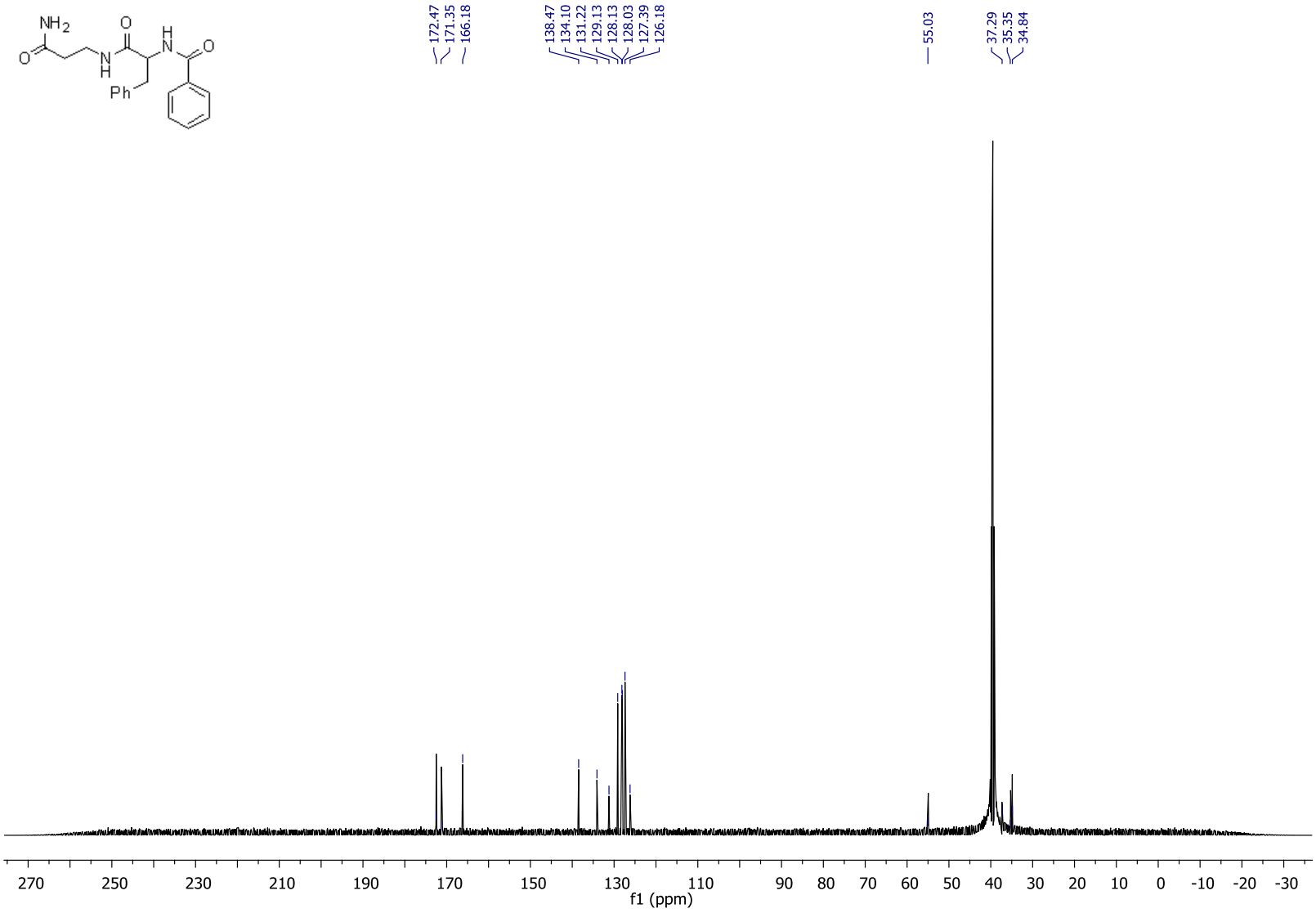
46


NH2
O
O
N
H
H
N
O
Ph
N
172.55
171.01
164.80
152.05
148.51
138.36
135.13
129.68
129.13
128.06
126.30
123.32
54.94
37.36
35.30
34.85
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Product released from the resin 2c

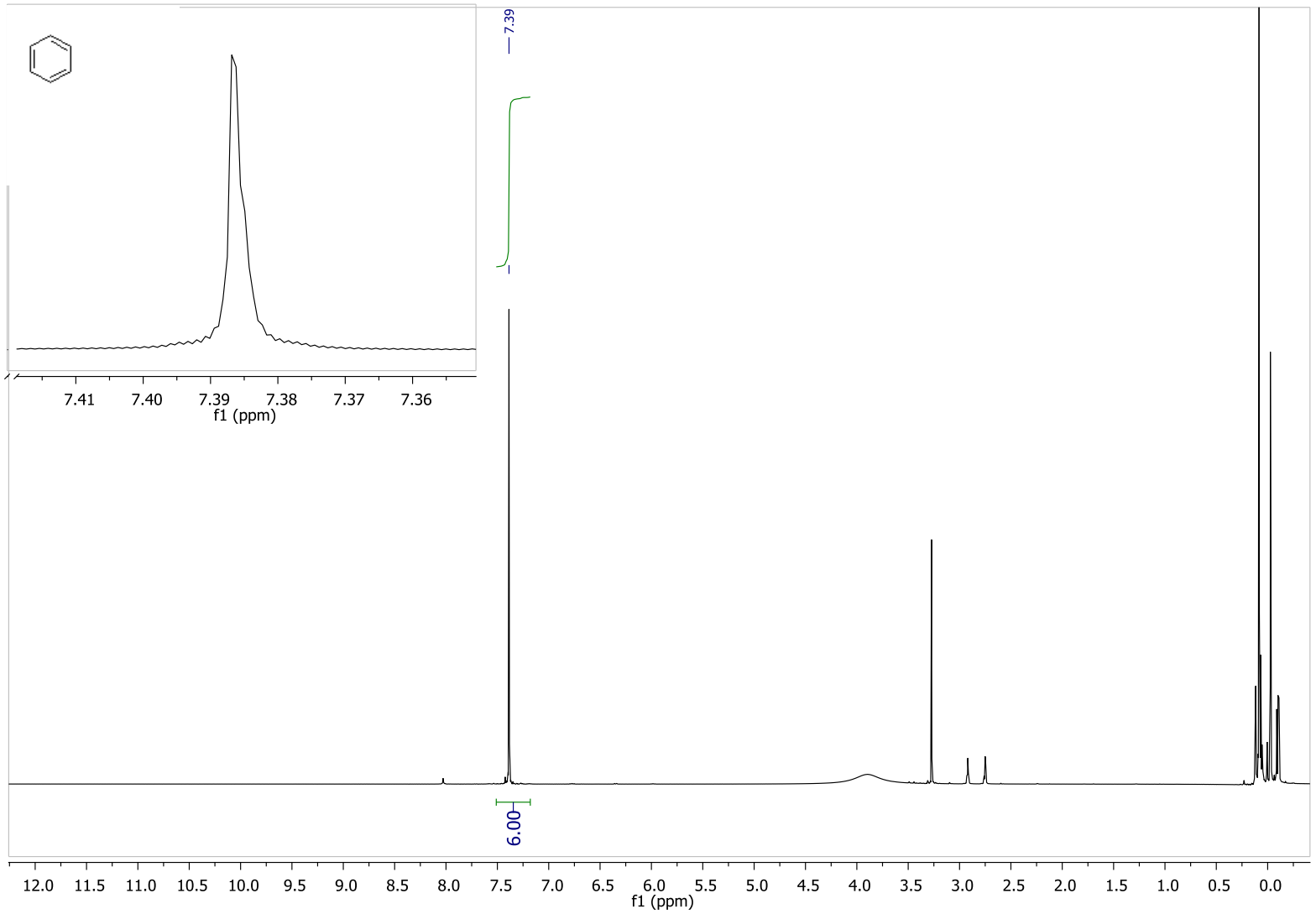


48


NH2
O
N
H
O
H
N
O
Ph
172.47
171.35
166.18
138.47
134.10
131.22
129.13
128.13
128.03
127.39
126.18
55.03
37.29
35.35
34.84
270
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

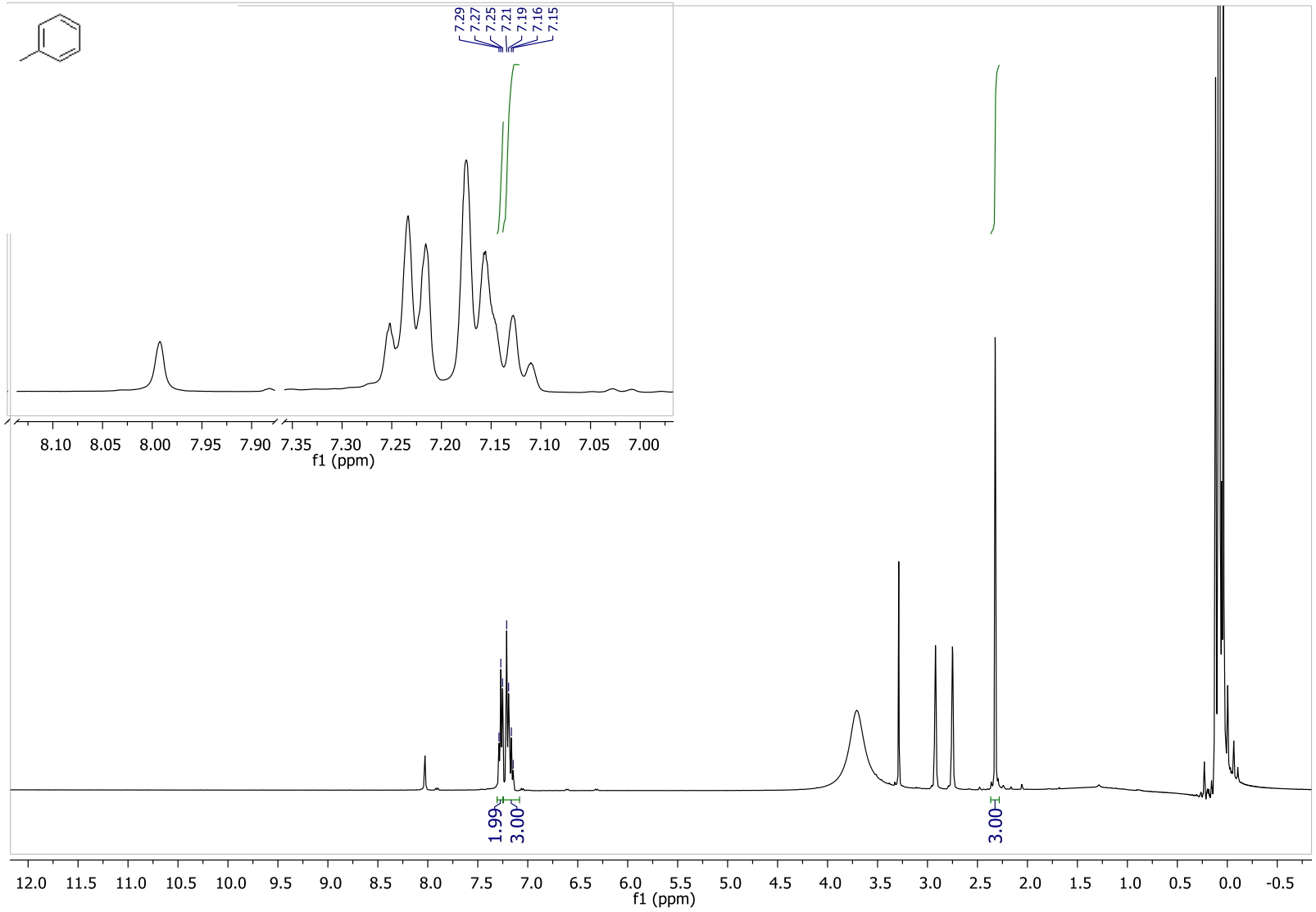
4.2. NMR spectra of crude products of hydrazine cleavage in solution

4a

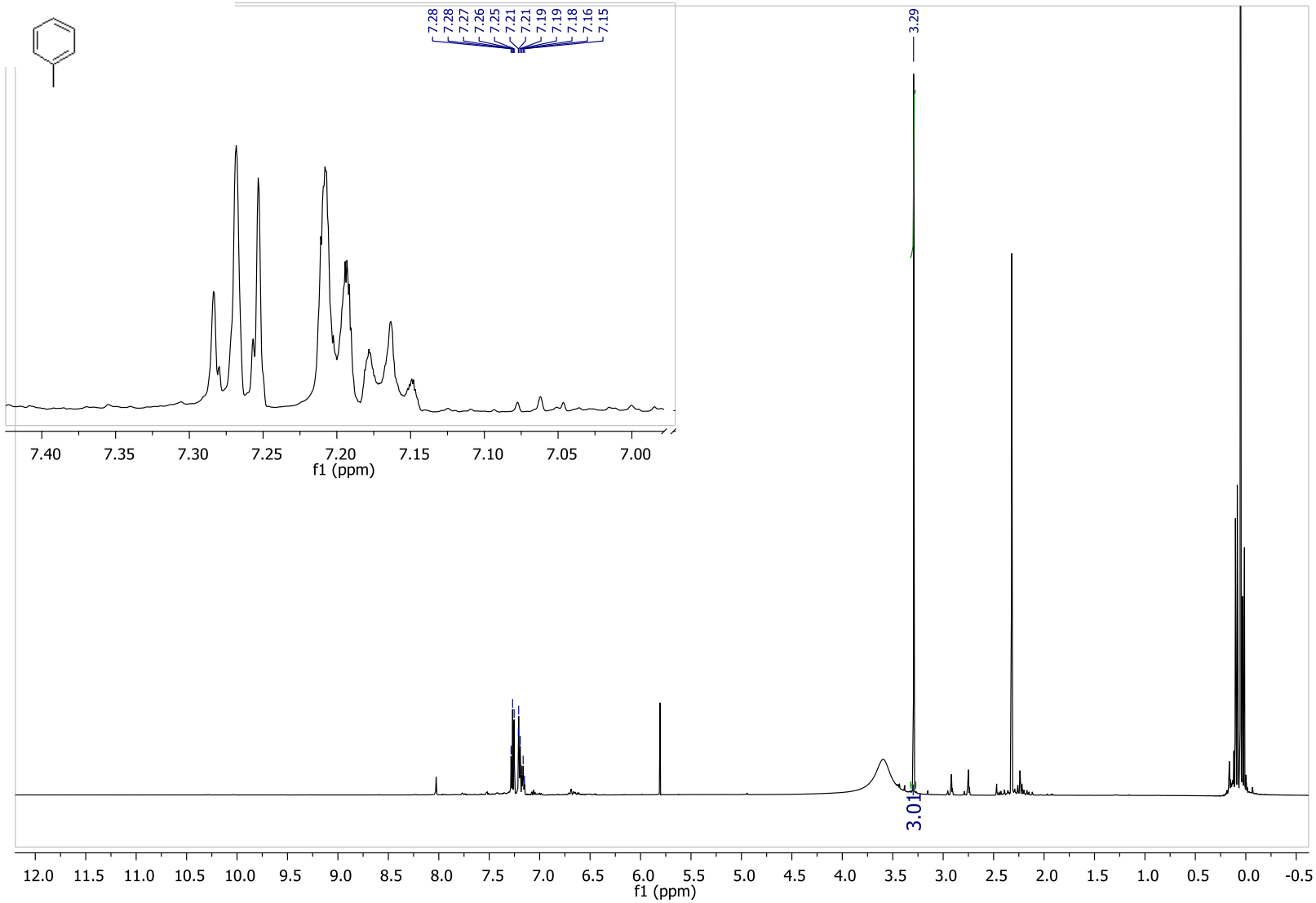


49

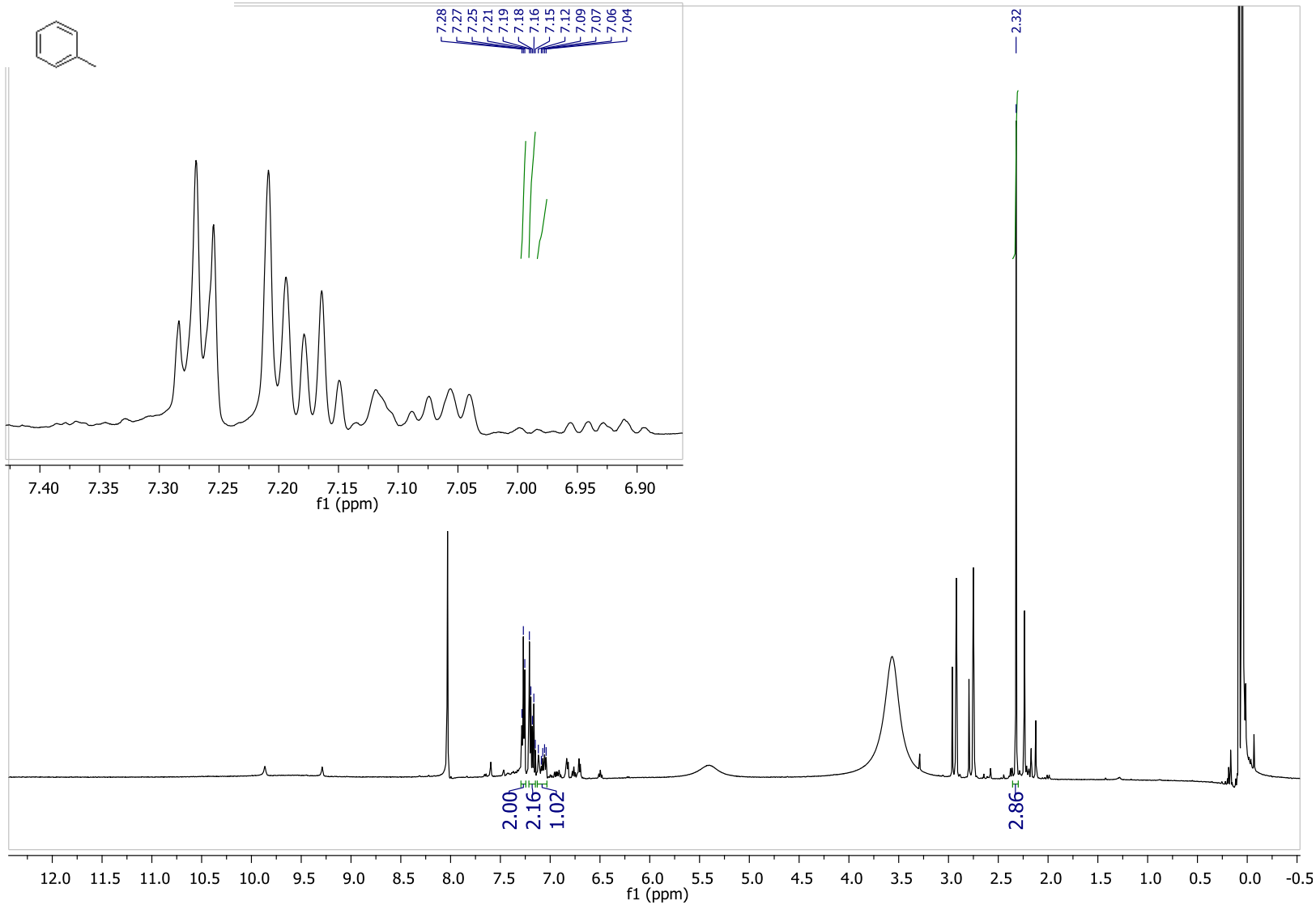
4b prepared from from 3b



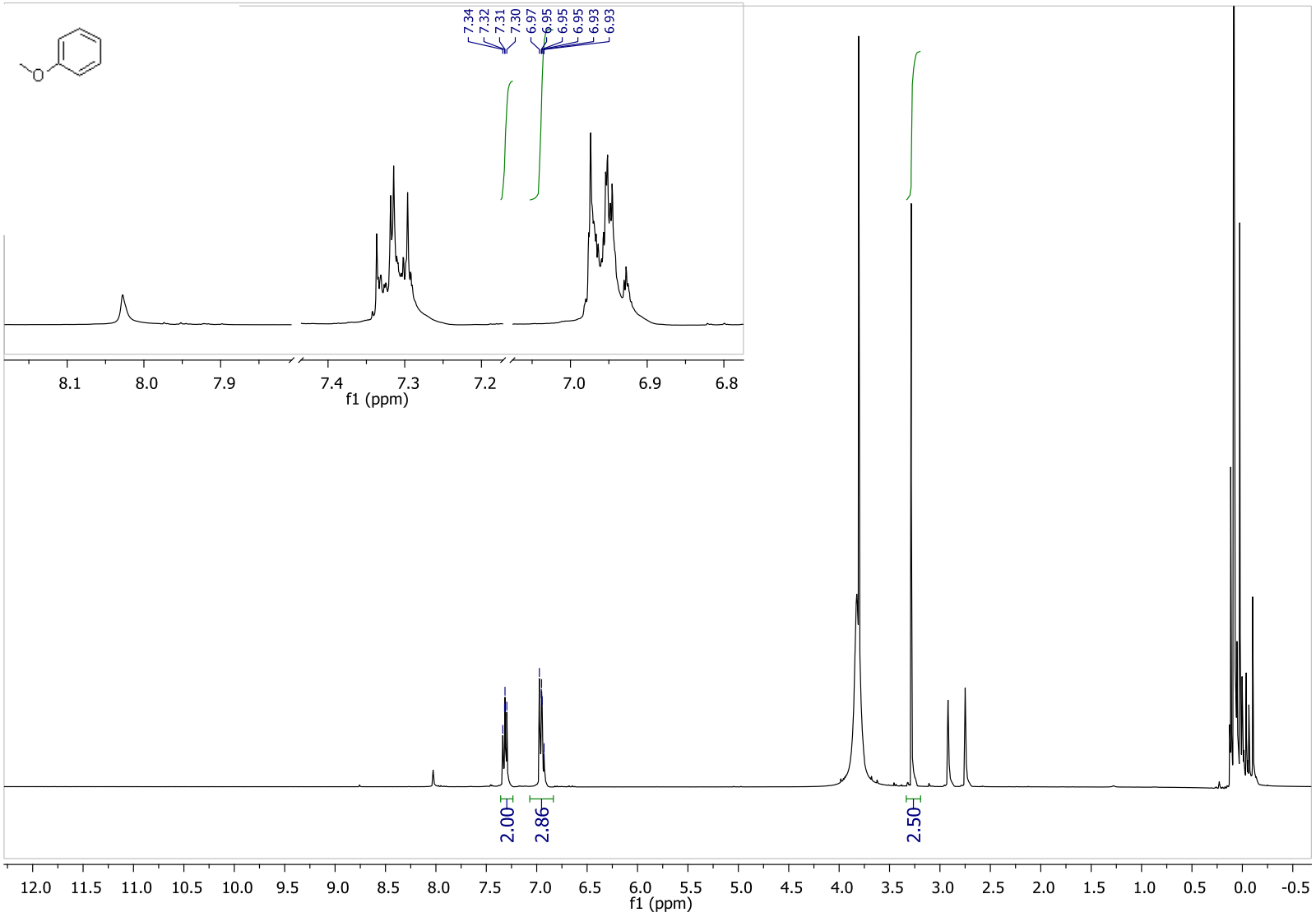
4b prepared from 3c under heating



4b prepared from 3d under heating

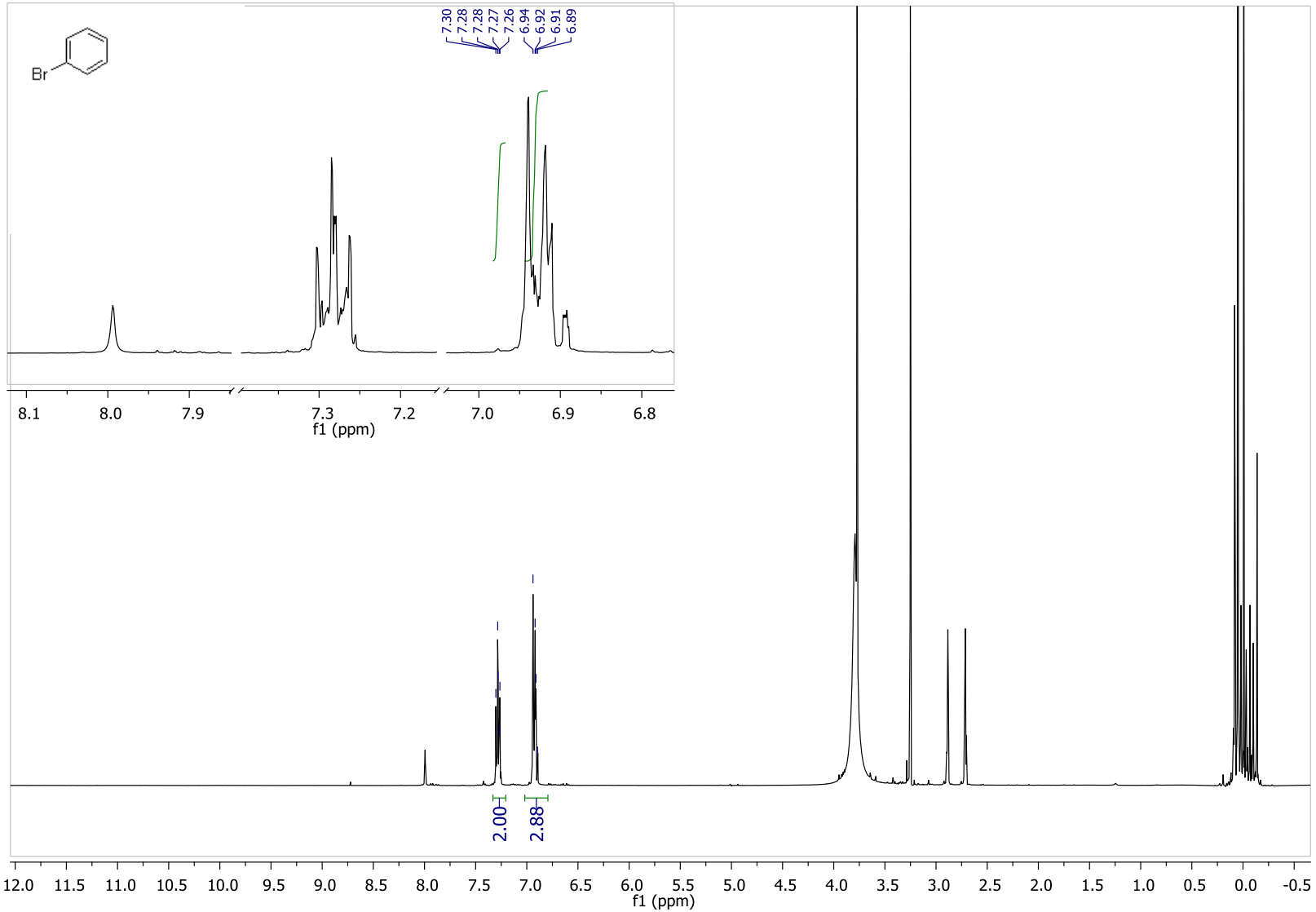


4e

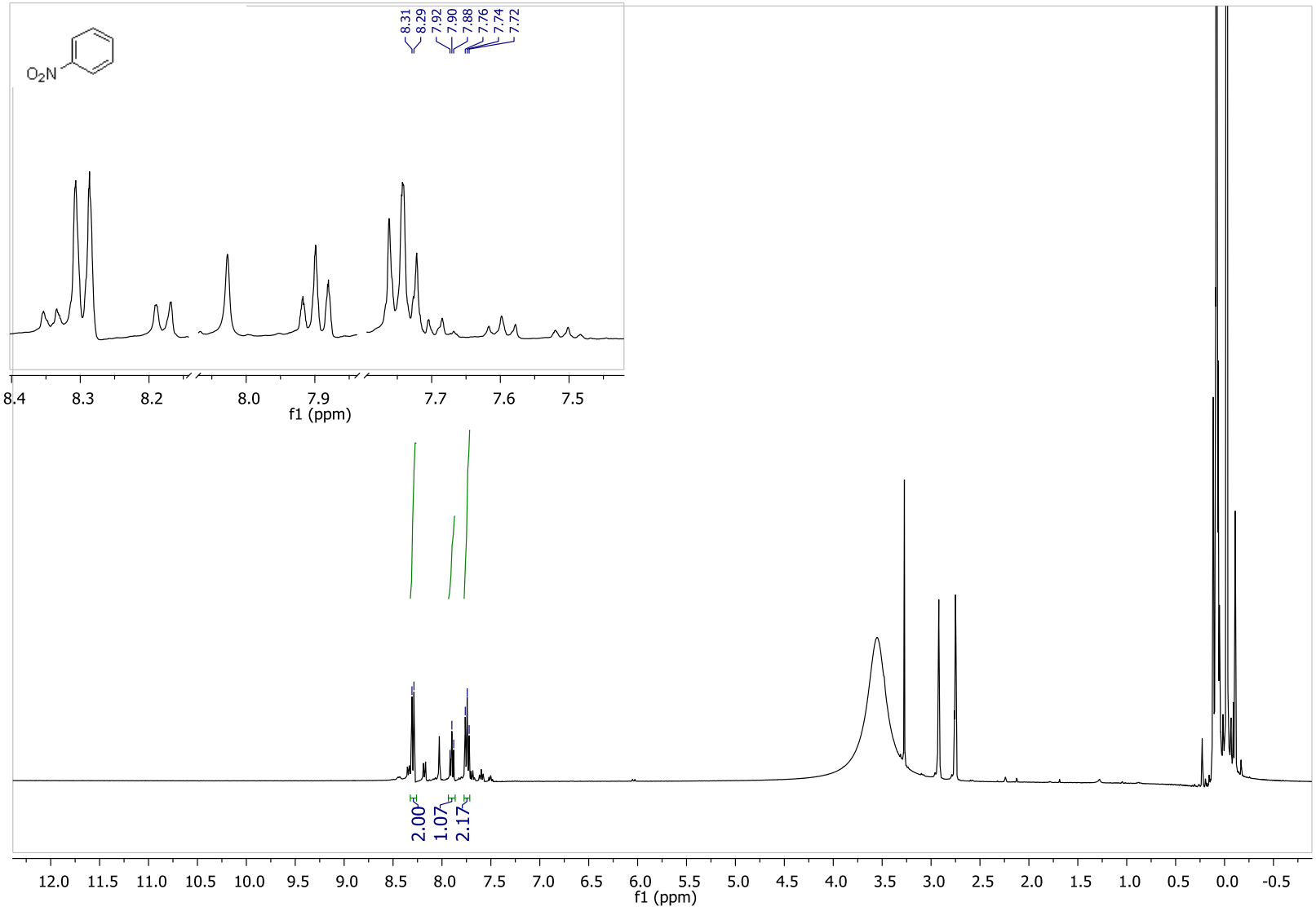

7.34
7.32
7.31
7.30
6.97
6.95
6.95
6.95
6.93
6.93
8.1
8.0
7.9
7.4
7.3
7.2
7.0
6.9
6.8
f1 (ppm)
2.00
2.86
2.50
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

53

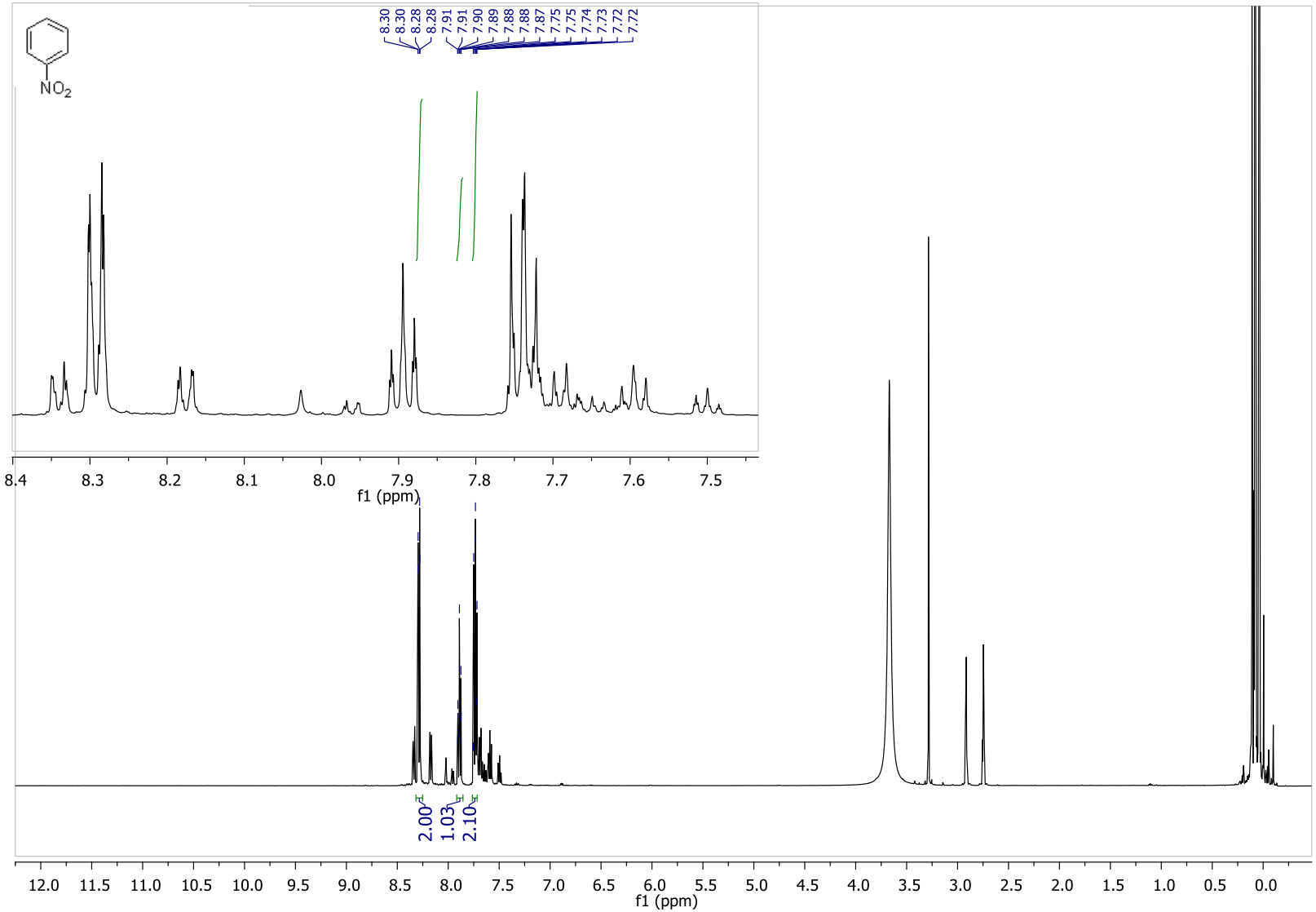
4f


Br
7.30
7.28
7.28
7.27
7.26
6.94
6.92
6.91
6.89
8.1
8.0
7.9
7.3
7.2
7.0
6.9
6.8
f1 (ppm)
2.00
2.88
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

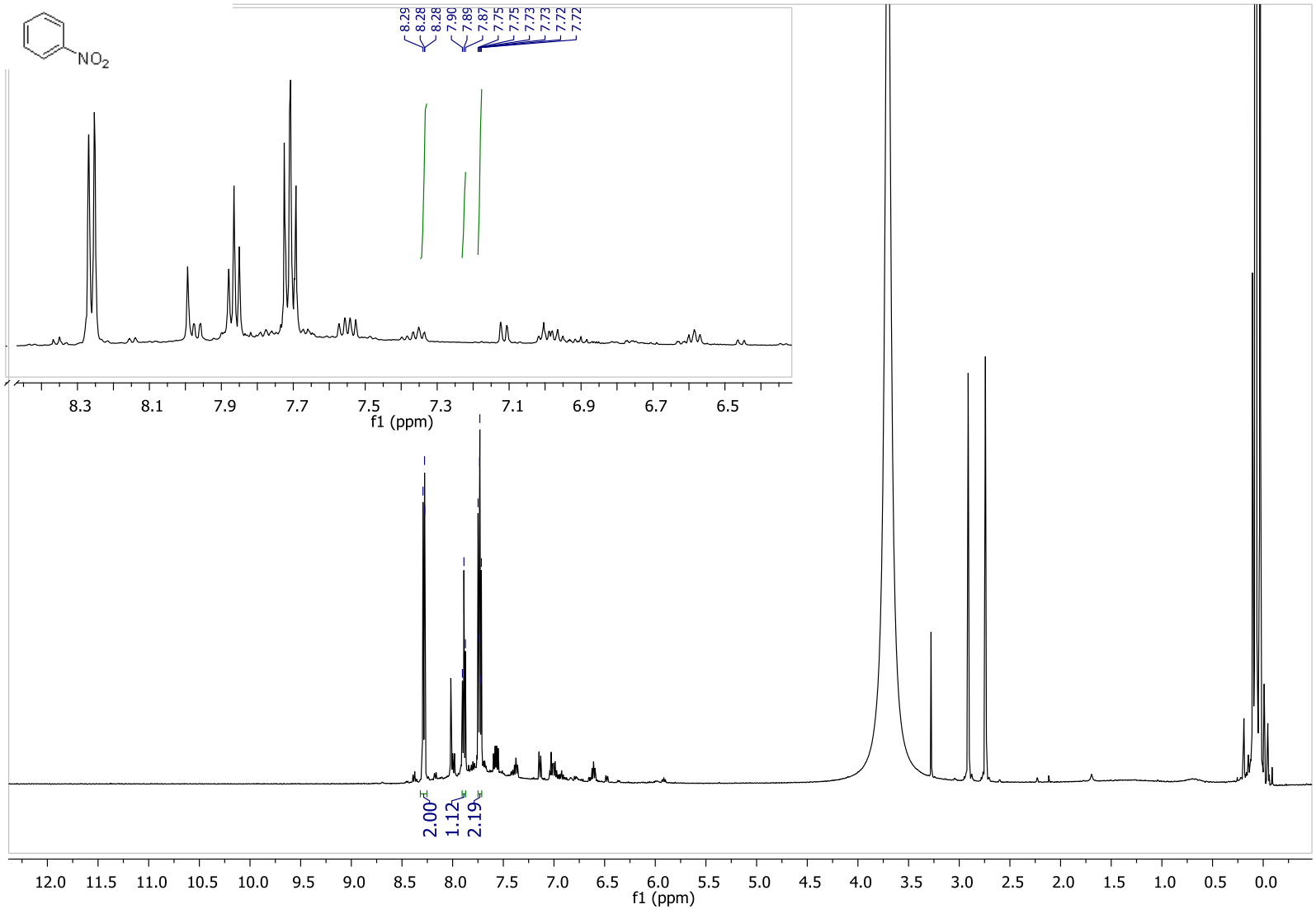
4g prepared from 3g



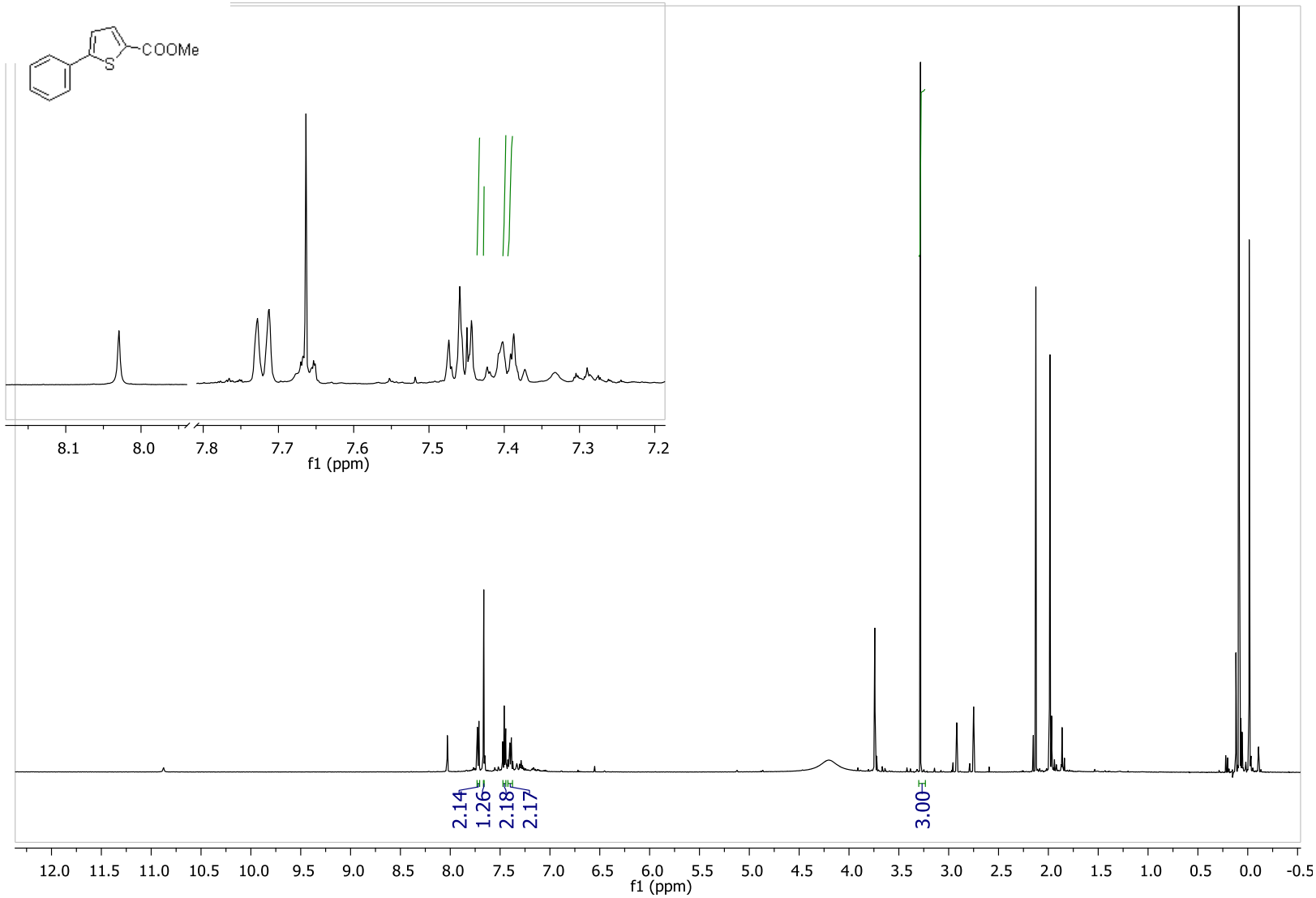
4g prepared from 3h



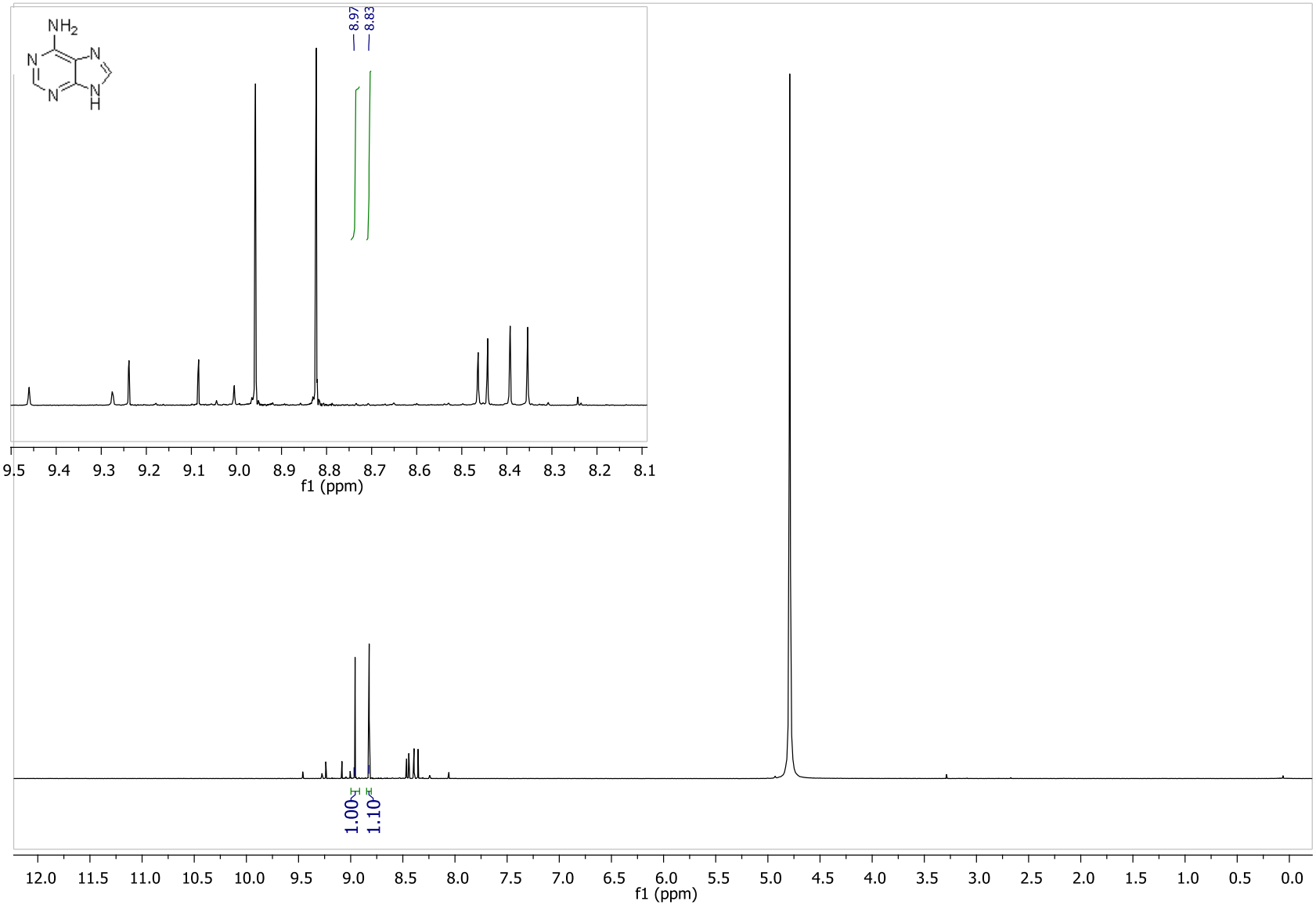
4g prepared from 3i



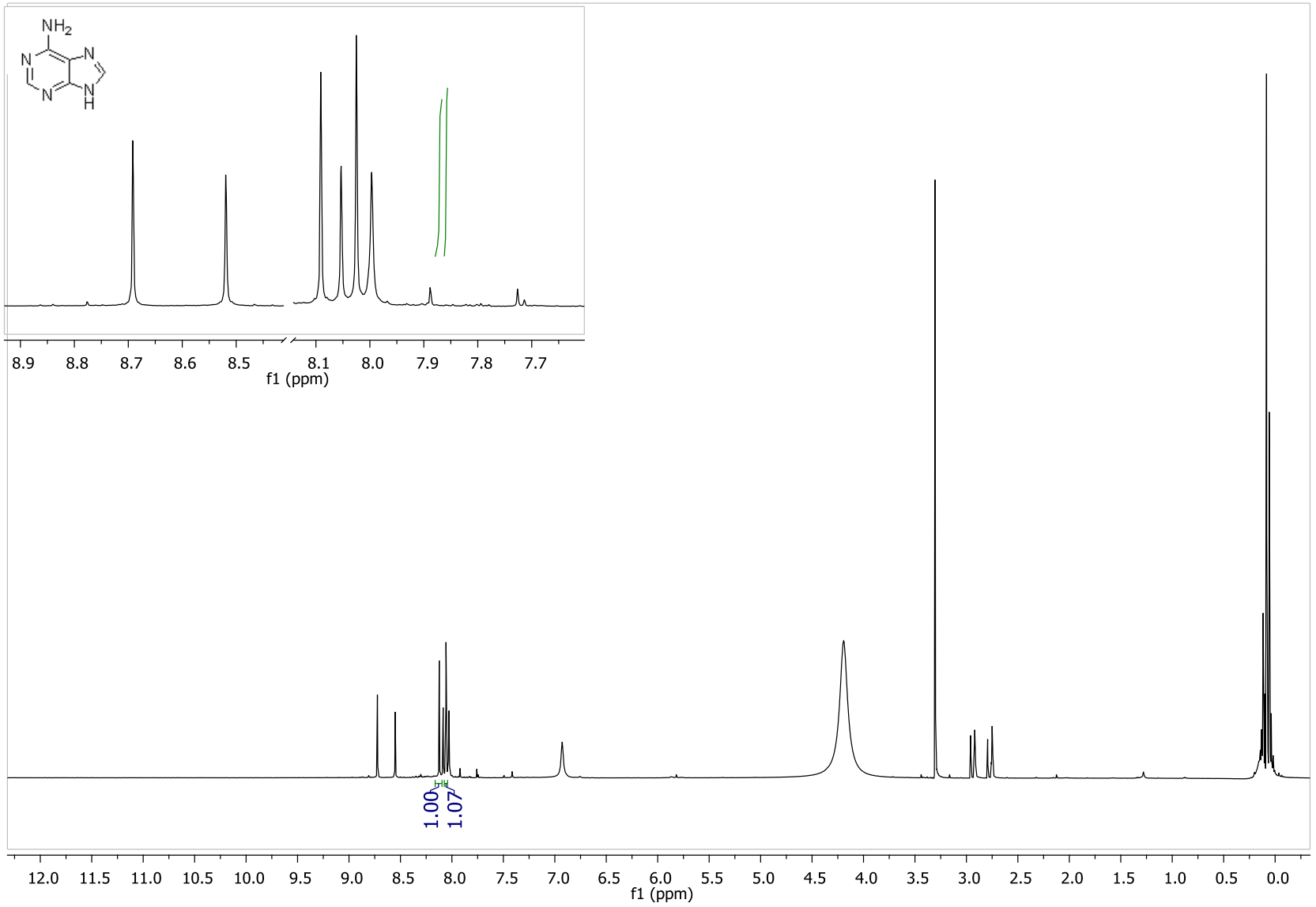
4j


COOMe
S
8.1
8.0
7.8
7.7
7.6
7.5
7.4
7.3
7.2
f1 (ppm)
2.14
1.26
2.18
2.17
3.00
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

4k prepared from 3k in D_2O under room temperature

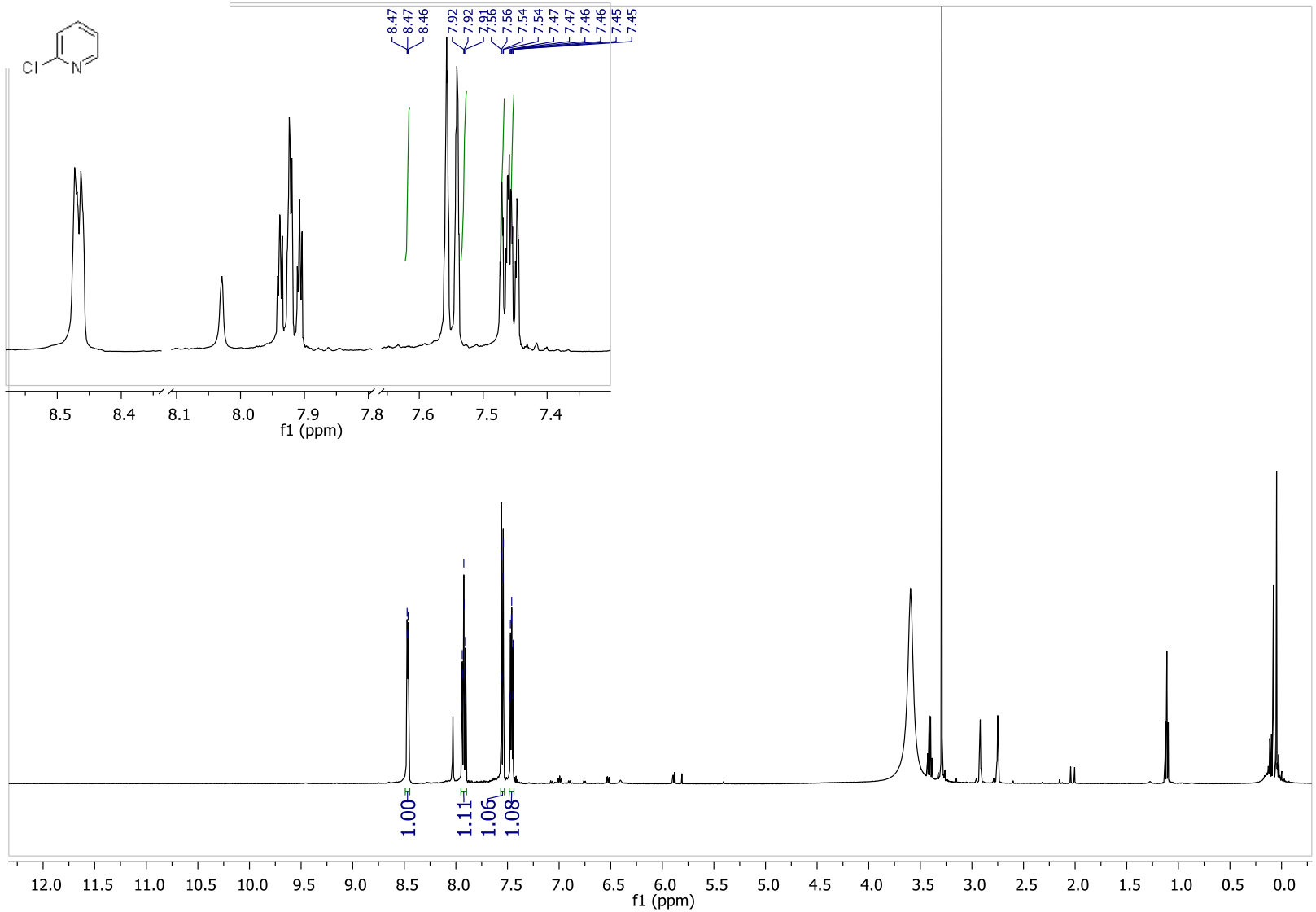


4k prepared from 3k in *d7*-DMF under heating

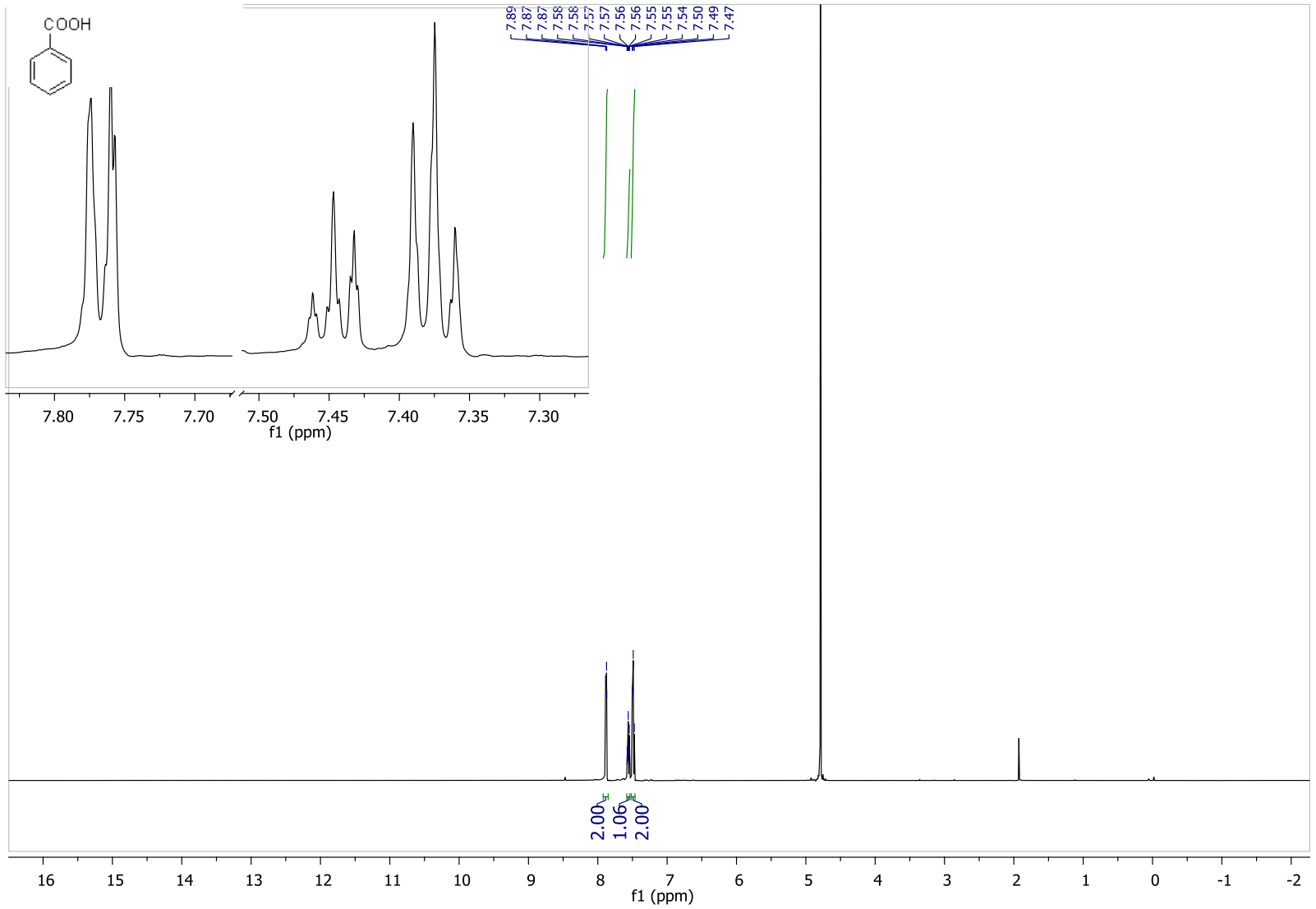


09

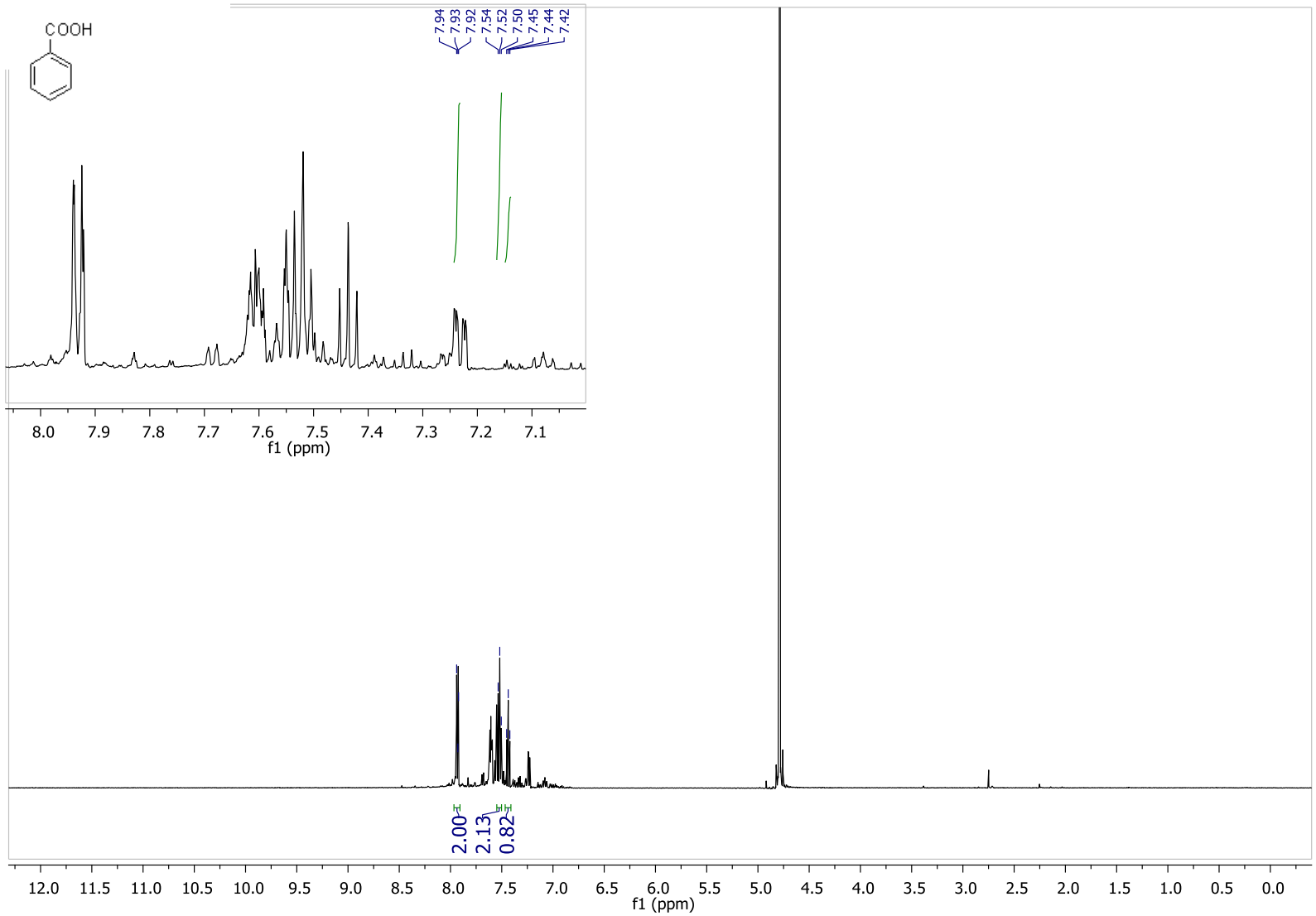
4l prepared from 3l under heating



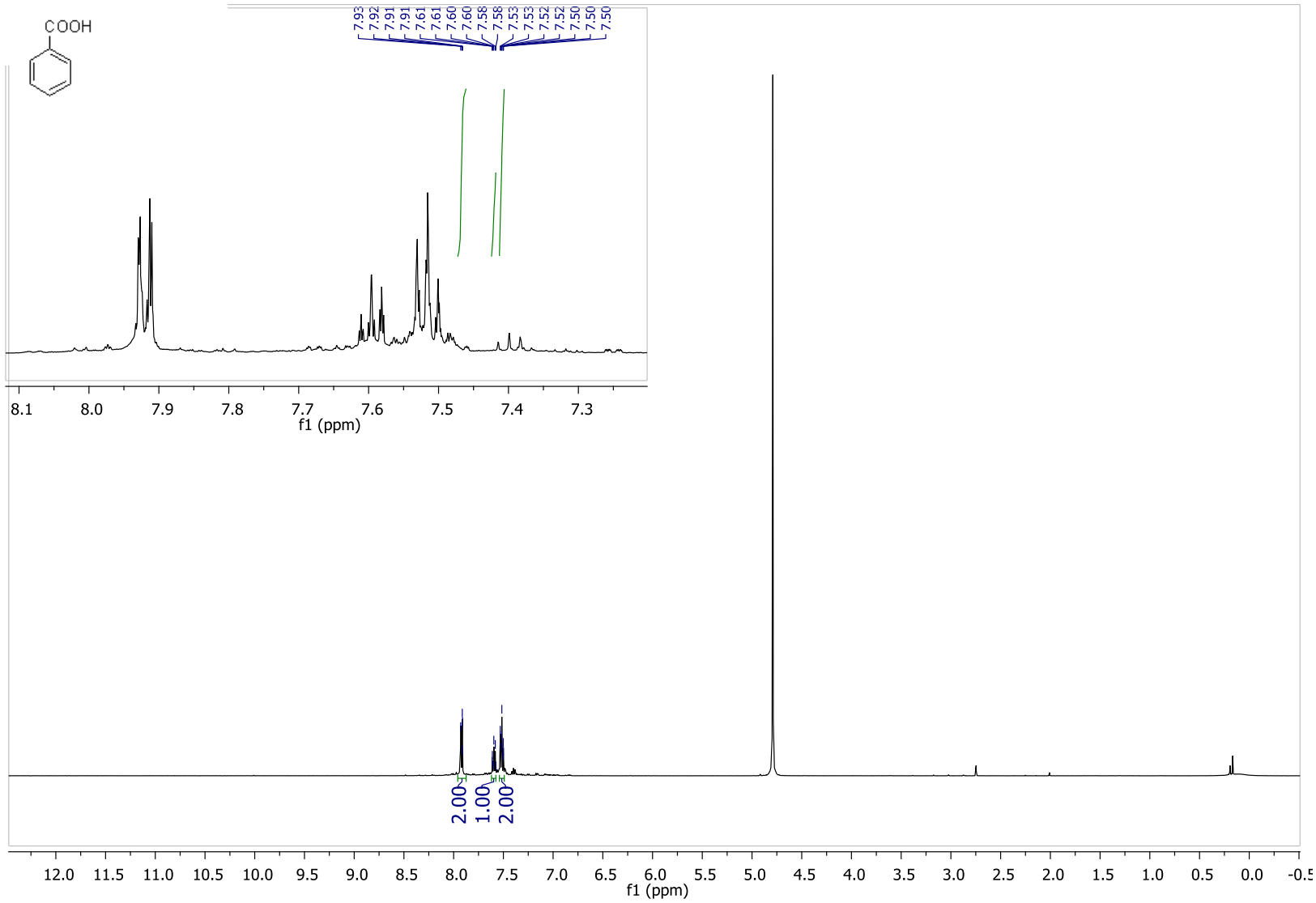
6a prepared from 5a



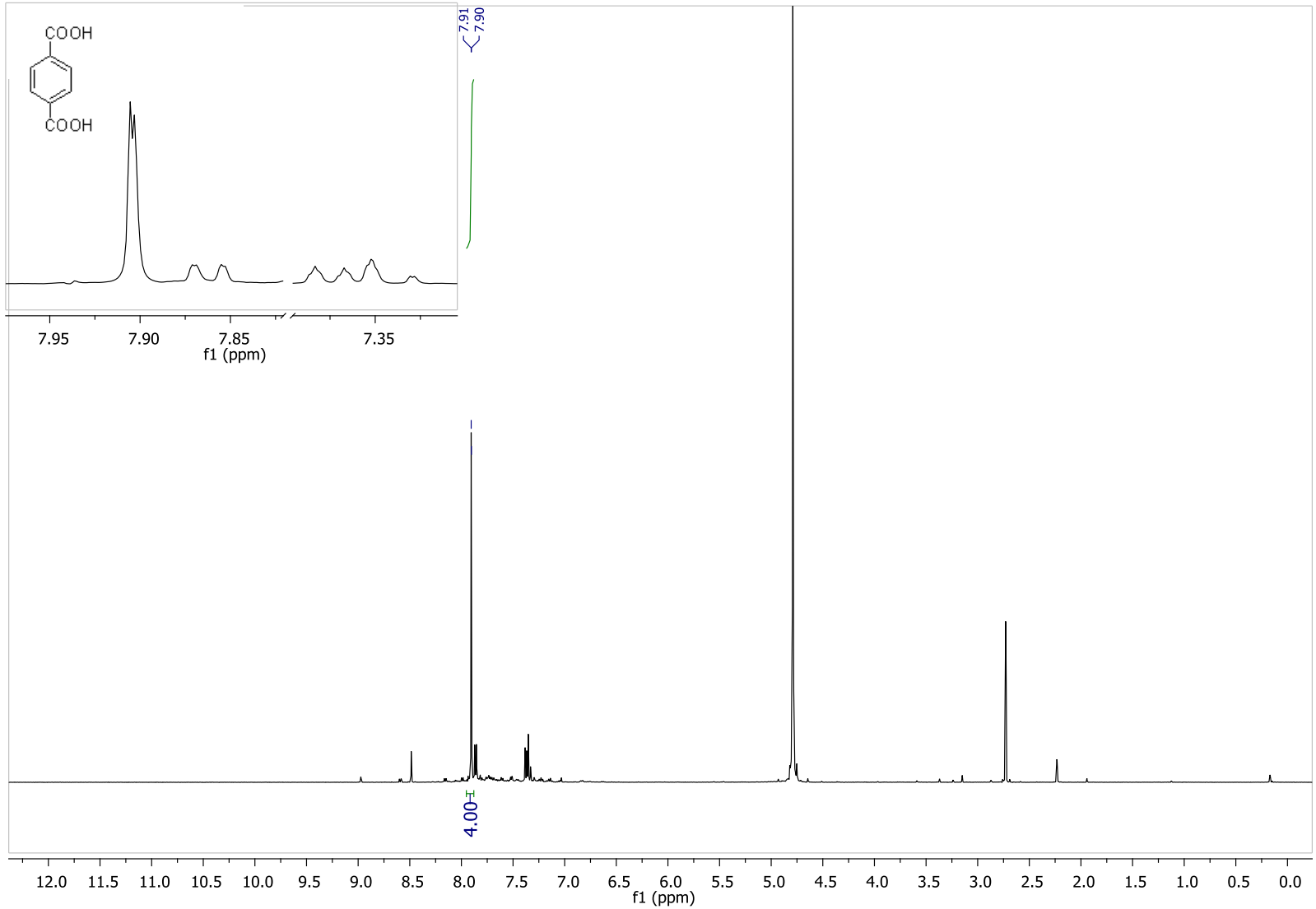
6a prepared from 5b



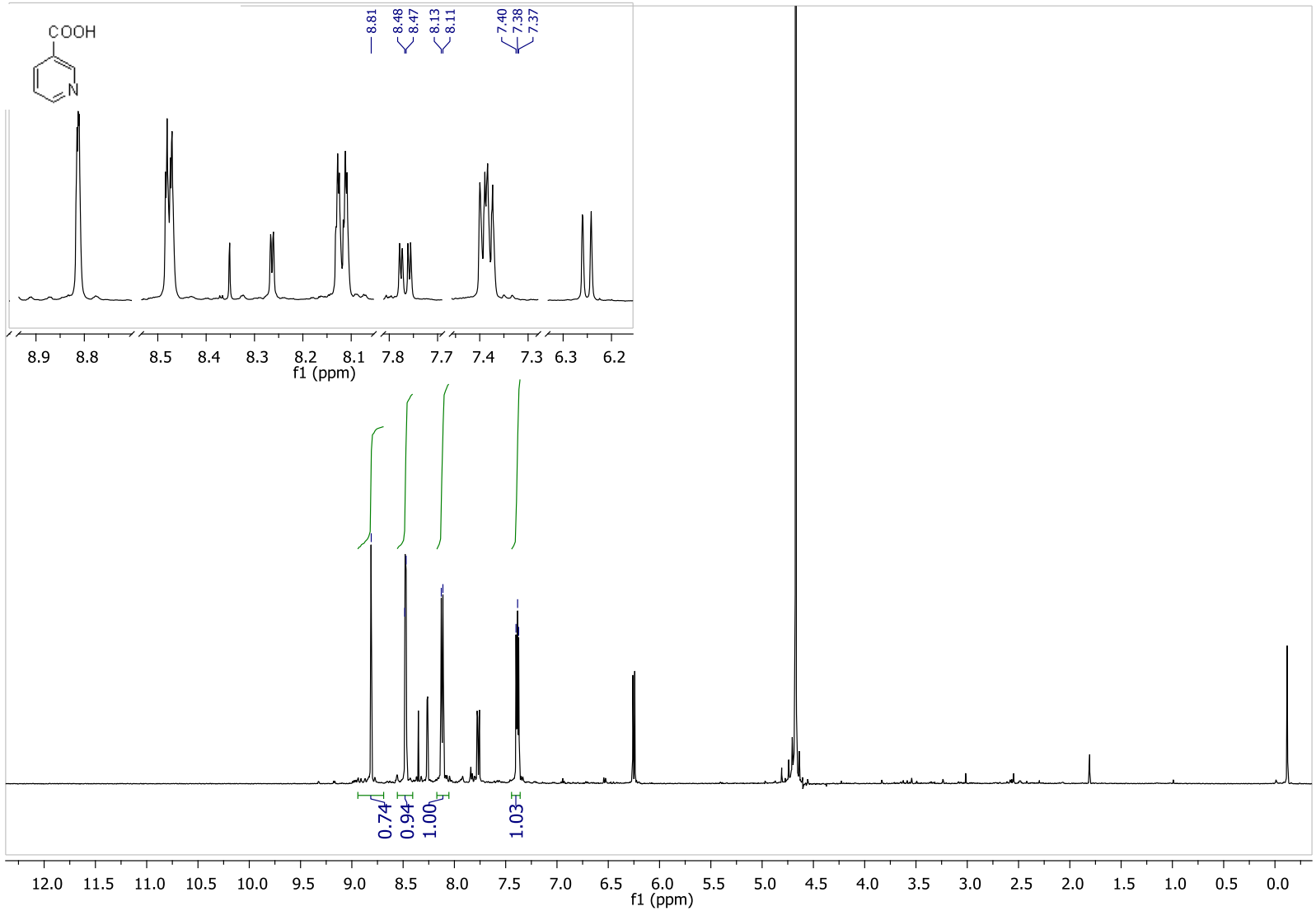
6a prepared from 5c



6d

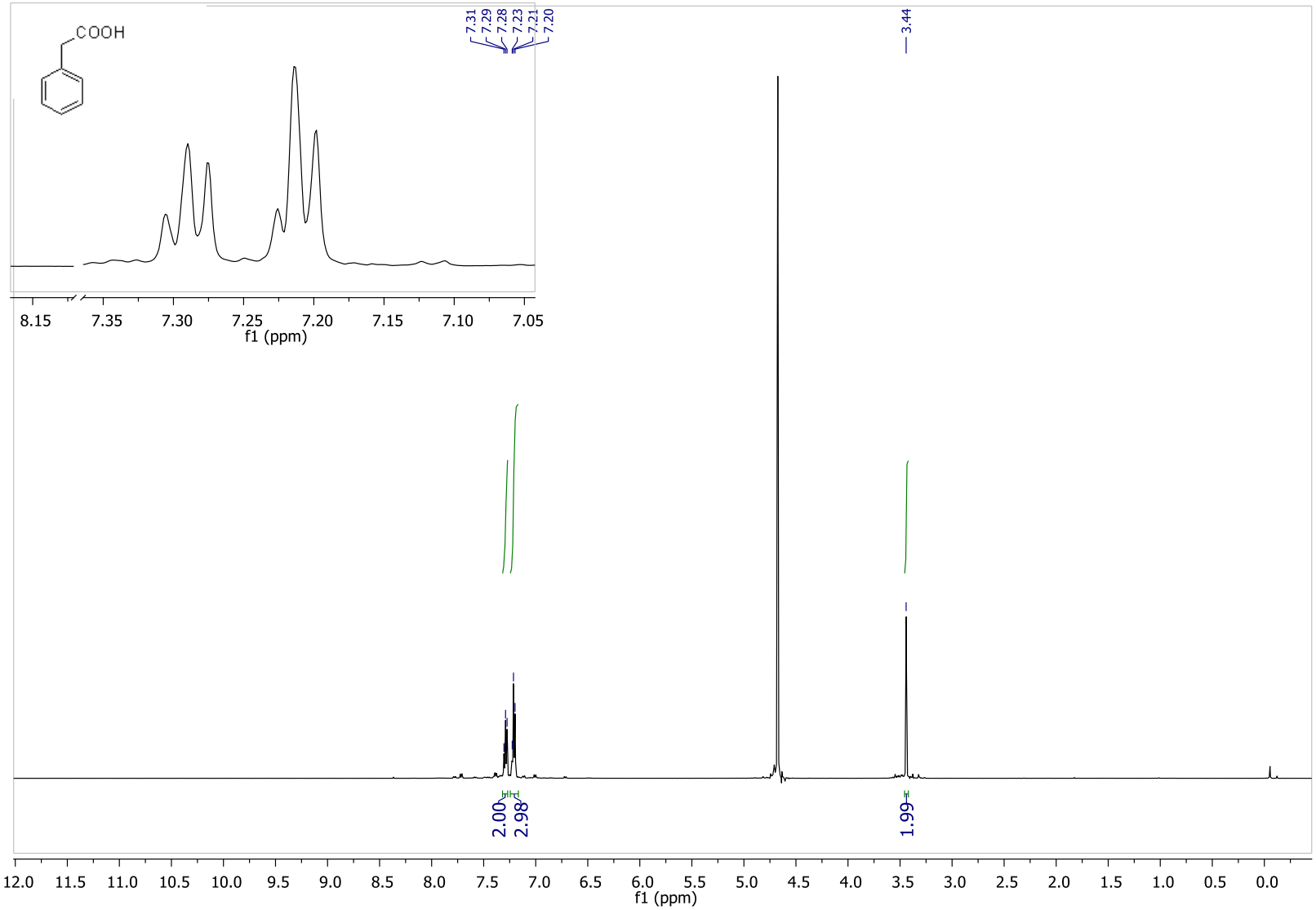

COOH
COOH
7.91
7.90
7.95
7.90
7.85
7.35
f1 (ppm)
4.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

6e

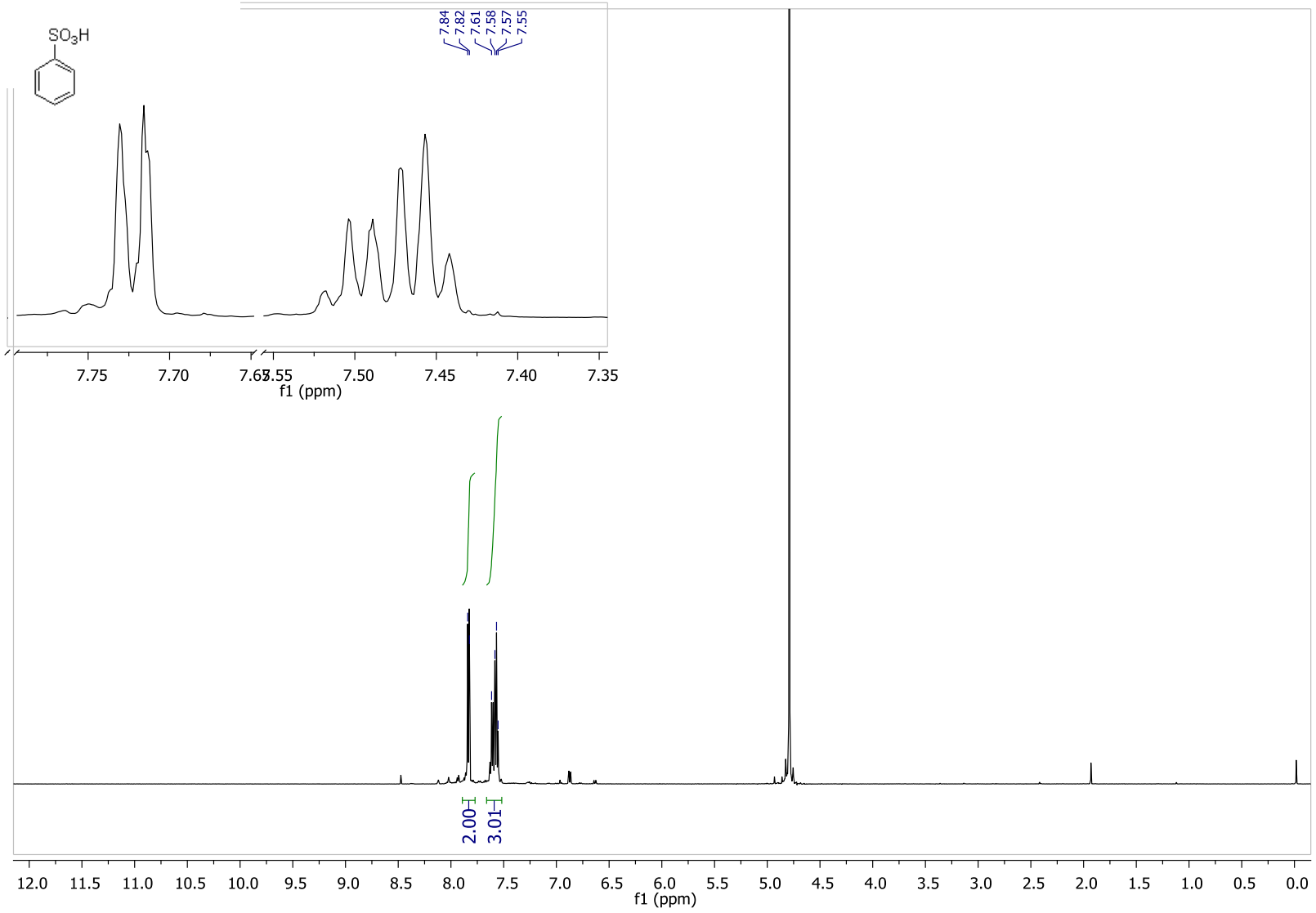

COOH
N
8.81
8.48
8.47
8.13
8.11
7.40
7.38
7.37
8.9 8.8 8.5 8.4 8.3 8.2 8.1 7.8 7.7 7.4 7.3 6.3 6.2
f1 (ppm)
0.74
0.94
1.00
1.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

99

6f

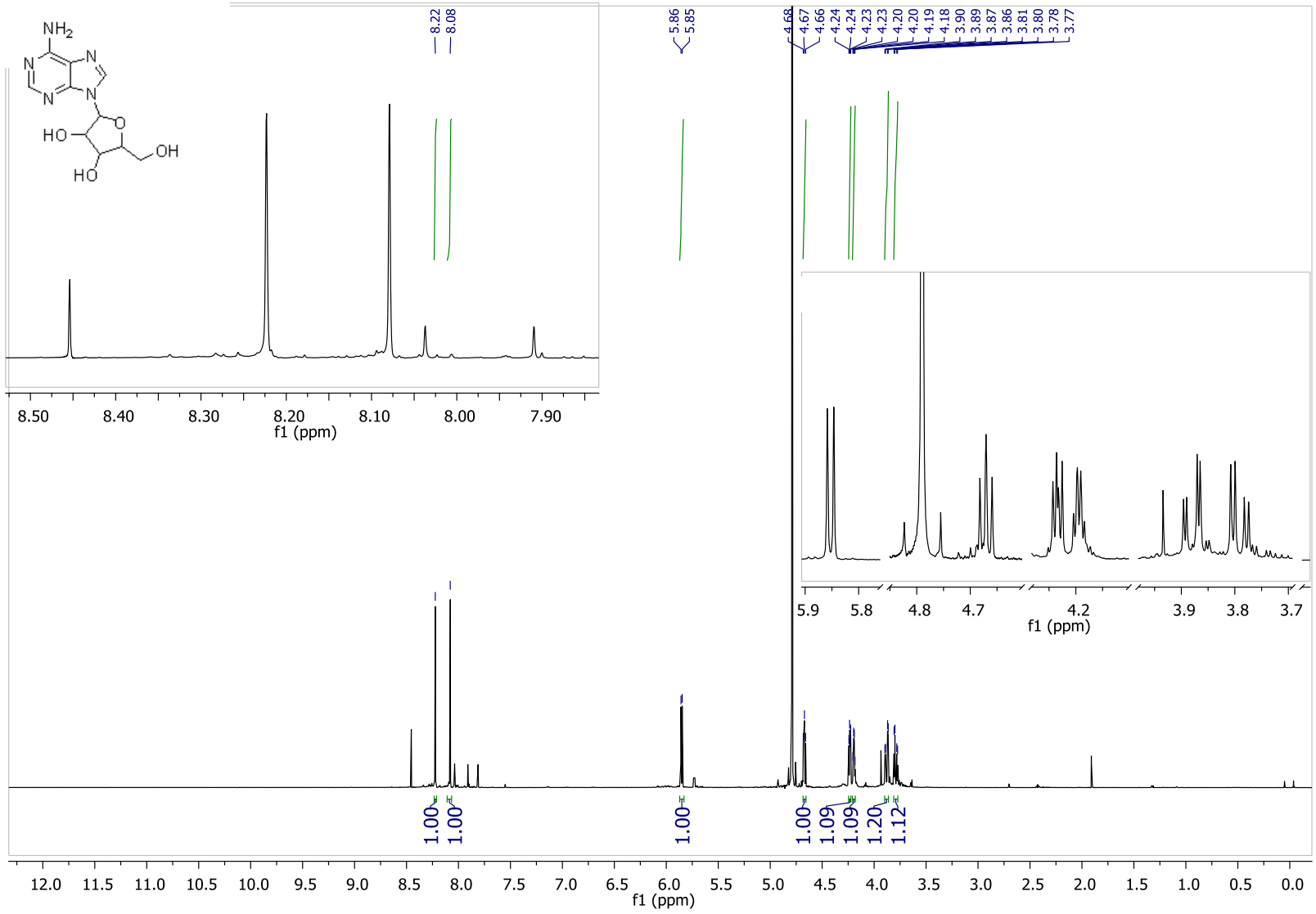

COOH
7.31
7.29
7.28
7.23
7.21
7.20
3.44
8.15
7.35
7.30
7.25
7.20
7.15
7.10
7.05
f1 (ppm)
2.00
2.98
1.99
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

6g


SO3H
7.84
7.82
7.61
7.58
7.57
7.55
7.75
7.70
7.65
7.55
7.50
7.45
7.40
7.35
f1 (ppm)
2.00
3.01
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

89

6h prepared from 5h under heating



5. References

[1] Pierens, G. K. ; Carroll, A. R. ; Davis, R. A. ; Palframan, M. E.; Quinn, R. J. *J. Nad. Prod*., **2008**, 71, 810.

[2] Okorochenkov, S. ; Burglova, K. ; Popa, I. ; Hlavac, J. *Org. Lett.*, **2015**, 17 (2), 180.

[3] Montgomery, J. A.; Holum, L. B. *J. Am. Chem. Soc*., **1957**, 79, 2185.

[4] Hradil, P. *Acta Univ. Palacki. Olomuc., Fac. rer. Nat., Chem.,* **1999**, 38, 13.

[5] Cai, Z. ; Zhou, D.; Lin, Y.; Chen, P. Pub. No. US 2013/0158031A1

[6] Van Tilburg, E.W.; Von Frijtag, J.; Kunzel, D.; De Groote, M.; IJezermna, Ad. P. *J. Med. Chem.*, 2002, 45 (2), 420.

[7] Zhang, Y.; Liao, S. ; Xu, Y. *Tetrahedron Lett.*, **1994**, 35 (26), 4599.

[8] Mallát, T. ; Bodnár, Z. ; Petró, J. *Tetrahedron Lett*., **1991**, 47 (3), 441.

[9] Pyo, A. ; Kim, S. ; Rajesh, M. ; Byeun, K. A. ; Eom, M. S. ; Han, M. S.; Lee, S. *Tetrahedron Lett*., **2013**, 54 (38), 5207.

[10] Relgado-Abad, T. ; Martnez-Ferrer, J. Reig-Lpez, J. ; Mello, R. ; Acerete, R.; Asensio, G. ; Gonzlez-Nez, M. E. RSC Adv., **2014**, 4 (92), 51016.

[11] Manna, S. ; Maity, S. ; Rana, S. ; Agasti, S. ; Maiti, D. *Org. Lett*., **2012**, 14 (7), 1736.

[12] Noguchi, T.; Hasegawa, M.; Tomisawa, K.; Mitsukuchi, M. *Bioorg. Med. Chem*., **2003**, 11 (22), 4729.

[13] Fujii, T.; Ogawa, K.; Saito, T.; Kobayashi, K.; Itaya, T. *Heterocycles*, **1994**, 38 (3), 477.

[14] Sun, Z.; Wang, H.; Wen, K.; Li, Y.; Fan, E. *J. Org. Chem.,* **2011**, 76 (10), 4149.

[15] Seddighi, F. ; Bolourchain, M. *Tetrahedron Lett.*, **1990**, 46 (19), 6869.

[16] Li, Z.; Fang, L. Wang, J. Dong, L. Guo, Y. ; Xie, Y. *Org. process, Res. Rev*., **2015**, 19 (3), 444.

[17] Mirza-Aghayan, M.; Molaee, T.; Boukherroub, R. *Tetrahedron Lett.,* **2014**, 55 (2), 342.

[18] Flakus, H. T. ; Chelmecki, M. *Spectrochim. Acta, Part A,* **2002**, 58 (9), 1867.

[19] Rajab, F. ; Kakeshpour, T.; Saidi, M. R. *Catal. Commun.,* **2013**, 40, 13.

[20] Zhao, H.; Pagano, A.R.; Wang, W.; Shallop, A.; Gaffney, B.L.; Jones, R.A. *J. Org. Chem*., **1997**, 62 (22), 7832.

5. Seznam zkratek

3-HQs	3-hydroxychinolin-4(1H)-on
AcOH	octová kyselina
Fmoc	9-Fluorenylmethoxycarbonyl
NMP	*N*-methylpyrolidon
PPA	polyfosforečná kyselina
rt	laboratorní teplota
TFA	trifluoroctová kyselina
THF	tetrahydrofuran
TMSOK	trimethylsilanolát draselný

6. Literatura

[1] P. Hradil, J. Hlaváč, M. Hajdúch, M. Kolář, R. Večeřová, *Minirew. Med. Chem*., **2009**, 9, 695.

[2] S. Gupta, P. Ghosh, S. Dwivedi, S. Das, *RSC ADV.*, **2014**, 4, 6254.

[3] A. Yahyazadeh, H. Yousefi, *Mol. Biolom. Spectrosc*., **2014**, 117, 696.

[4] S. Loya, A. Rudy, R. Tal, Y. Kashmin, Y. Loya, A. Hizi, *Arch. Biochem Biophys*., **1994**, 309.

[5] P. Krejči, P. Hradil, J. Hlaváč, M. Hajdúch, Patent WO 2008028427.

[6] P. Hradil, J. Jirman, *Collect. Czech. Chem. Commun.,* **1995**, 60, 1357.

[7] M. Soural, V. Krchňák, *J. Comb. Chem.,* **2007**, *9*, 793.

[8] R. B. Merrifield, *J. Am. Chem. Soc.,* **1963**, 14, 2149.

[9]A. Roden, Hydrazine, in Encyclopedia of Reagents for Organic Synthesis, ed. L. Paquette, John Wiley & Sons, New York, **2004**.

[10] R. L. Hardie, R. H. Thomson, *J. Chem. Soc*., **1957**, 2512.

[11] J. B. Chattopadhyaya, C. B. Reese, *Synthesis*., **1978**, 908.

[12] R. Xia, M.-S. Xie, H.-Y. Niu, R.-G. Qu, H.-M. Guo, *Green Chem*., **2014**, 16, 1077.

[13] C. Tamborski, E. J. Soloski, *J. Org. Chem*., **1966**, 31(3), 746.

[14] J. M. Birchall, R. N. Haszeldine, A. R. Parkinson, *J. Chem. Soc*., **1962**, 4966.

[15] L. D. S. Yadav, R. Kapoor, *J. Org. Chem*., **2004**, 69(23), 8118.

[16] A. Unciti-Broceta, M. J. Pineda de las Infantas, M. A. Gallo, A. Espinosa, *Chem. – Eur. J*., **2007**, 13, 1754.