공학석사학위논문

The application of *trans*-oxazolidine methyl ester synthons to the stereoselective synthesis of potential aminopeptidase inhibitors

잠재적인 아미노펩티다아제 억제제의 입체선택적인 합성을 위한 트랜스-옥사졸리딘 메틸 에스터 신톤의 적용

2015年 8月

서울대학교 대학원
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The application of *trans*-oxazolidine mehtyl ester synthons to the stereoselective synthesis of potential aminopeptidase inhibitors

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Abstract

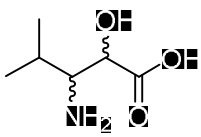
Aminopeptidases are enzymes that catalyze the hydrolytic cleavage of peptides from the N-terminus of amino acid or peptide substrates. It is widely distributed over the human, the animal and the plants, and are essential materials for protein maturation, activation and regulation of (non-)hormonal peptides.

Aminopeptidase inhibitors suppress aminopeptidases' activity so that prevent undesired replication of viruses or cells such as tumor. Ubenimex, commercial name of Bestatin, is one of aminopeptidase inhibitor which is marketed as treatment of acute myelocytic leukemia. Several stereoselective total syntheses of bestatin and its derivatives such as 2-thiolbestatin or bestatin thioamide have been reported.

Most of bestatin analogs which have been reported contain aryl group at the N-terminus, but in this thesis, aryl group is substituted with isobutyl group or isopropyl group. Synthesis of new bestatin derivatives have been studied with two kinds of chiral synthons from D-leucine and D-valine. The precursors for corresponding β-amino-α-hydroxy acids were prepared via intramolecular conjugate addition between phenylsulfonylnitromethane and *N*-hydroxymethyl protected α-amino aldehydes. Bestatin derivatives which contain isobutyl group,

(2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoyl-L-leucine or isopropyl group, (2*S*,3*R*)-3-amino-2-hydroxy-4-methylpentanoyl-L-leucine are synthesized with peptide coupling between corresponding β-amino-α-hydroxy acids and L-Leu-OMe.

Lapstatin, 3-amino-2-hydroxy-4-methylpentanoyl-valine, is one of aminopeptidase inhibitors which has similar vicinal amino alcohol structure to synthesized bestatin derivatives.



3-amino-2-hydroxy-4-methylpentanoic acid

But, lapstatin has not been fully identified its stereochemistry of the vicinal amino alcohol at the *N*-terminal amino acid residue, while the structure of bestatin derivatives were well established. Employing the developed synthetic method, lapstatin derivatives are also synthesized from corresponding β-amino-α-hydroxy acids in order to confirm its stereochemistry.

Key word : Aminopeptidase inhibitor, β-amino-α-hydroxy acids, peptide bond formation, bestatin derivatives, lapstatin derivatives

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific optical rotation
aq.	aqueous
Bn	benzyl
Boc	*t*-butoxycarbonyl
Br	broad
Bu	butyl
calcd	calculated
conc.	concentrated
δ	chemical shift, ppm
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
eq.	equivalent
EDC-HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

EtOAc	ethylacetate
g	gram(s)
GC	gas chromatography
Hz	hertz
HOBt	hydroxybenzotriazole
HRMS	high resolution mass spectrum
IR	infrared (spectrum)
^{i}Pr	iso-propyl
J	coupling constant(s)
m	multiplet
M	mole(s)/liter
Me	methyl
MC	methylene chloride
min	minute(s)
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
n	normal
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million

q	quartet
quant.	quantitative
rt.	Room temperature
s	singlet
t	tertiary
^{t}Bu	tert-butyl
TFA	trifluoroacrtic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
UV	ultraviolet spectrum

1. Introduction

1.1. Aminopeptidase inhibitors

Aminopeptidases play an important role in tissues, organs and cells. In case of solid tumors such as cancer, aminopeptidases help their angiogenesis and metastasis.[1]

Aminopeptidase inhibitors are used as anti-tumor drugs that improve immunomodulation of human[2] and it has been also widely studied in medicine, pharmacy and chemistry because it prevents replication of solid tumor by selective binding to activate sites of aminopeptidase block hydrolytic cleavage of peptides (Figure 1).[3]

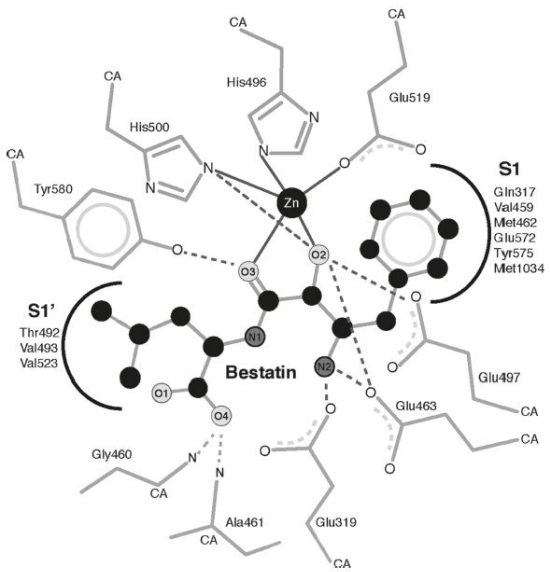


Figure 1. Schematic of bestatin binding to the active site of peptide.

Many studies about aminopeptidase inhibitors have been reported, and bestatin is one of them. Bestatin, commercial name is Ubenimex, not only shows effects on immunomodulation as an aminopeptidase inhibitor but is also used in the treatment of acute myelocytic leukemia.

Bestatin can be synthesized with two kinds of amino acids, D-phenylalanine and L-leucine, which substituents are binding into activation site of aminopeptidase. Furthermore, bestatin has *threo*-β-amino-α-hydroxy acid moiety, and it interacts with zinc ion which also interacts with adjacent α-amino acid.[3] Several stereoselective total syntheses of its derivatives (Figure 2)[4a, 4b] are reported for structure-activity relationship.

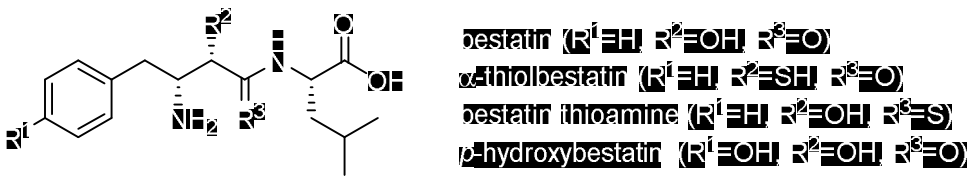


Figure 2. The structure of bestatin and its derivatives.

In the biological activity of aminopeptidase inhibitors including bestatin, the stereochemistry of its hydroxy and amino group is important.[5a, 5b]

Many other bestatin derivatives substitute aryl group on N-terminus, but there are no derivatives that substitute alkyl group on N-terminus. The synthesis of new bestatin analogs are introduced with isobutyl group and isopropyl group on N-terminus, and employing the

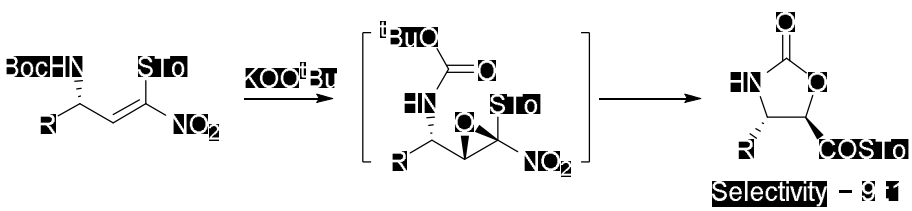
developed synthetic method, lapstatin analogs are also introduced which has unidentified stereochemistry of the vicinal amino alcohol at the *N*-terminal amino acid residue.

1.2. Reported synthetic method for *threo*-β-amino-α-hydroxy acid

As mentioned in previous section, the stereochemistry of hydroxy and amino group are important on aminopeptidase inhibitor. Accordingly, there are many examples have been reported for the stereoselective synthesis of *threo*-β-amino-α-hydroxy acid.

1.2.1. Nucleophilic epoxidation of 1-arythio-1-nitroalkenes

In this method, *trans*-oxazolidinone which is precursor of *threo*-β-amino-α-hydroxy acid is obtained with high selectivity by using potassium *tert*-butylperoxide as the epoxidation reagents (Scheme 1)[6].



Scheme 1. Nucleophilic epoxidation to form *trans*-oxazolidinone.

Starting alkenes, 1-arylthio-l-nitroalkenes which substitute methyl, benzyl and phenyl group on R group are synthesized with corresponding Boc protected α-amino aldehyde.

Epoxidation of 1-arylthio-l-nitroalkenes with peroxide reagent,

diastereoisomeric mixture of *cis*- and *trans*- oxazolidinones are formed instead of corresponding oxiranes which are intermediate because the carbamate group is enough nucleophilic to attack the oxirane when *tert*-butyl cation on *N*-Boc group is removed.

The stereoselectivity of this reaction might be decided by allylic strain. When *tert*-butylperoxide anion do nucleophilic attack to alkene, it approach from less hindered allylic hydrogen position (Figure 3) to form *trans*-oxazolidinone mainly via *anti*-oxirane intermediate.

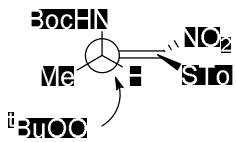


Figure 3. Nucleophilic attack of *tert*-butylperoxide anion.

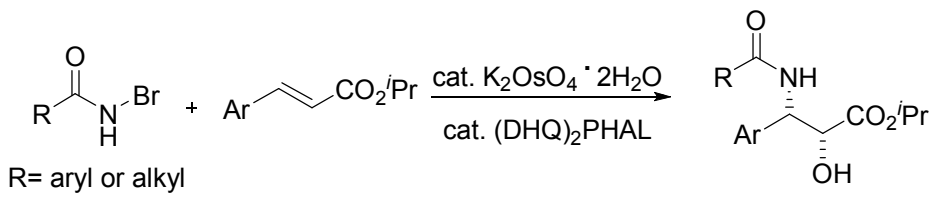
Even if this reaction method is simple and can afford to apply other kinds of *trans*-oxazolidinone synthon, purification and isolation of final product from the diastereoisomeric mixture of *cis*- and *trans*-oxazolidinones is very difficult.

1.2.2. Asymmetric aminohydroxylation of olefins

The asymmetric aminohydroxylation which is reported by Sharpless group is a useful synthetic method for enantiomerically enriched vicinal

amino alcohols.[7]

This reaction method allow excellent stereospecific *syn*-selective conversion of olefins to protected β-aminoalcohols by osmium catalyst and chiral ligands based on cinchona alkaloids. Sulfonamides, carbamates, or aminoheterocycles have been used as nitrogen sources, and *N*-bromocarboxamide is also used as nitrogen sources recently (Scheme 2).



Scheme 2. Asymmetric aminohydroxylation of olefins.

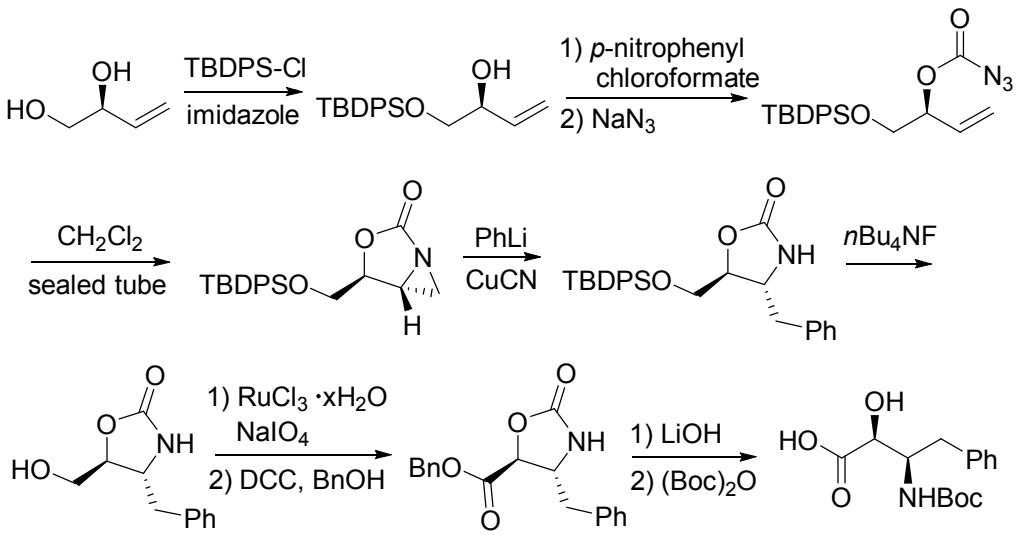
The highest regioselectivity (23:1) is obtained when the olefin is a kind of cinnamate, but relatively low regioselectivity (1.3:1) is obtained when olefin is styrene and its derivatives (2.5:1). Moreover, if nonconjugated olefins are used, not only regioselectivity but also reaction yield one low.

1.2.3. Acylnitrene route to vicinal amino alcohols

The synthetic method of vicinal amino alcohols with acylnitrene aziridination followed by aziridine opening is introduced as a versatile

method for these kind of molecules.[8]

At first, allylic alcohol is converted to an azidoformate and thermally cyclized to a bicyclic aziridine (Scheme 3). Then, the aziridine is readily opened using phenyl anion with the desired organocuprate reagent. The benzyl protected carboxylic acid form of oxazolidinone is synthesized via deprotection and oxidation, followed by oxazolidinone ring opening to form β-amino-α-hydroxy acid.



Scheme 3. Acylnitrene aziridination/aziridine opening method.

Although this synthetic method can be used as vicinal amino alcohol moiety of bestatin and its analogs, overall yield is too low (0.04%) and reaction steps are too many (10 steps).

2. Background for the stereoselective synthesis of aminopeptidase inhibitor

2.1. *N,O*-Acetal lactols derived from α-amino acids

The family of α-amino acids is one of the useful chiral compounds that occur in nature or utilize in asymmetric syntheses of biologically active compounds.[9] As the derivative of α-amino acid, *N*-protected α-amino aldehydes are the important chiral synthons for α-amino acid moiety synthesis. However, the aldehydes have a chemically and configurationally labile proton at α-position. The labile proton causes the difficulty of purification and often gives poor result in asymmetric synthesis. Some *N*-protected α-amino aldehydes **1-4 (Figure 4)** have been reported as the substrates for the sufficient asymmetric syntheses methods of nitrogen containing natural products. Several limitations still exist even though these aldehydes are chemically and configurationally stable. [10a-10d]

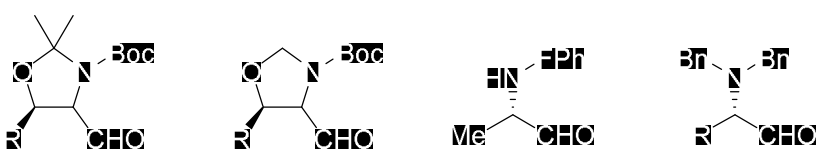
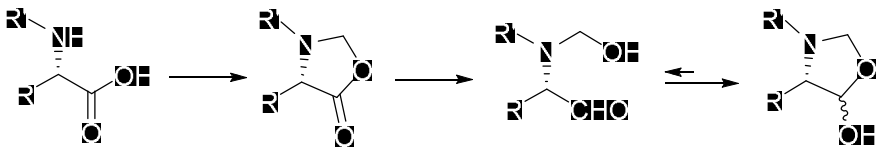


Figure 4. Reported *N*-protected α-amino aldehydes.

N-Hydroxymethyl group was introduced for resolving problems that are acidity of α-proton in the aldehyde and racemization.[11] *N*-Hydroxymethyl group leads aldehyde into the equilibrium states via the formation of hemiacetal lactol (Scheme 4).



Scheme 4. The synthetic pathway with *N*-Hydroxymethyl group.

N,O-Acetal lactols can be synthesized with commercially available *N*-protected α-amino acids in two steps; *N*-hydroxymethyl group are introduced to the *N*-protected α-amino acids, and the reduction of oxazolidinones to the hemiacetal form of α-amino aldehydes which are *N,O*-Acetal lactols.

2.2. Stereoselective synthesis of *threo*-β-amino-α-hydroxy acids

The effective application of the stable α-amino aldehyde has been found in many bioactive natural compound such as alkaloids, peptide enzyme inhibitors, and sympathomimetic amines.[12] As I mentioned before, stereoselective synthesis of the β-amino-α-hydroxy acids

moiety is important for biologically active compounds, and α-amino aldehyde which are *N,O*-acetal lactols can be used as effective precursors for it.

Therefore, effective synthesis of *threo*-β-amino-α-hydroxy acid moiety is developed in previous study.[13] Among its procedure, synthetic method of *trans*-oxazolidine methyl esters can be used as chiral synthon of bestatin, (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA) (Figure 5).

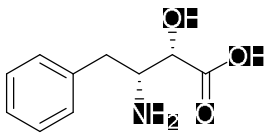


Figure 5. (2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutanoic acid.

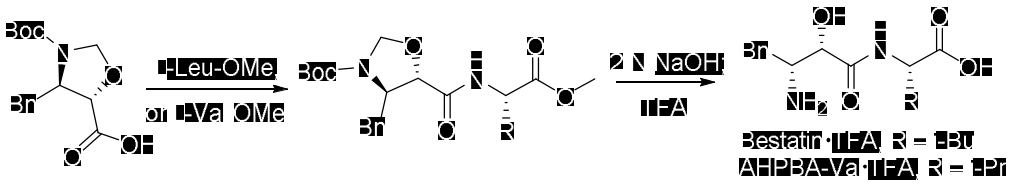
The three tandem reactions which is the nitro-aldol reaction, the dehydration reaction, and the intramolecular conjugate addition reaction of configurationally stable α-amino aldehyde are introduced for the synthesis of *threo*-β-amino-α-hydroxy acids (Scheme 5).

Scheme 5. The synthetic pathway for *threo*-β-amino-α-hydroxy acids.

Henry reaction has been attempted with phenylsulfonylnitromethane. Several amine bases such as TEA, DMAP, pyridine, *N*-

methylmorpholine, and DBU are tested for this reaction, the desired *trans*-oxazolidine product was obtained with DMAP.

In order to confirm whether *trans*-oxazolidine methyl esters is useful chiral synthon of bestatin, bestatin and its analog, AHPBA-Val, was synthesized (Scheme 6). [13]



Scheme 6. Syntheses of bestatin and its potent derivative, AHPBA-Val.

A simple peptide coupling of free carboxylic acid, produced via basic hydrolysis of *trans*-oxazolidine methyl ester, with L-leucine methyl ester (L-Leu-OMe) or L-Valine methyl ester (L-Val-OMe), and then the following hydrolysis gave bestatin or AHPBA-Val as its TFA salt in high yield.

2.3. Synthetic plans for derivatives of aminopeptidase inhibitors

Not only natural substrates aminopeptidase inhibitors (Figure 6) but also synthetic small molecules aminopeptidase inhibitors (Figure 7)[14] are associated with various physiological or pathological functions.

Natural substrates aminopeptidase inhibitors have being found for a long time, and synthetic small molecules aminopeptidase inhibitors are inspired by the structure of natural substrates aminopeptidase inhibitors.

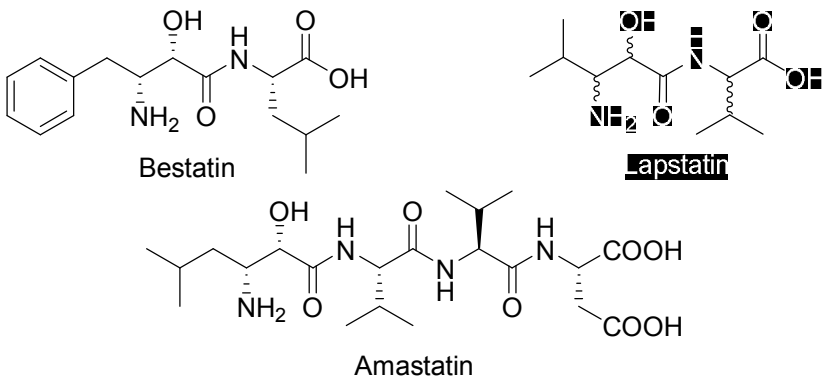


Figure 6. Natural substrates aminopeptidase inhibitors.

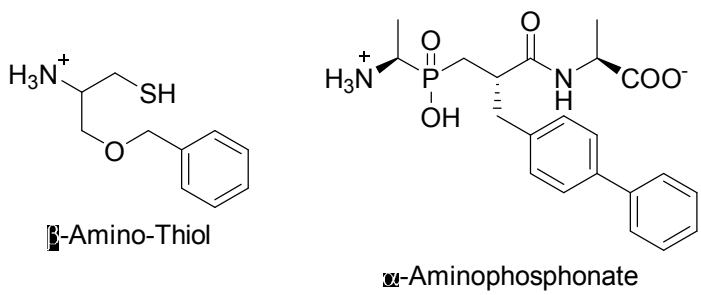


Figure 7. Synthetic small molecules aminopeptidase inhibitors.

Among natural substrates aminopeptidase inhibitors, bestatin was discovered at 1976.[15] Bestatin has been extensively studied due to its multiple effects on the immune system, and it has been used to treat acute myelocytic leukemia under a trade name of Ubenimex. Bestatin contains β-amino-α-hydroxy acids moiety, and its stereochemistry is

important to biological activity like any other aminopeptidase inhibitors. We found that stereoselective synthesis of β-amino-α-hydroxy acids can be possible through *trans*-oxazolidine derivative which is *N,O*-acetal lactols from α-amino acids.

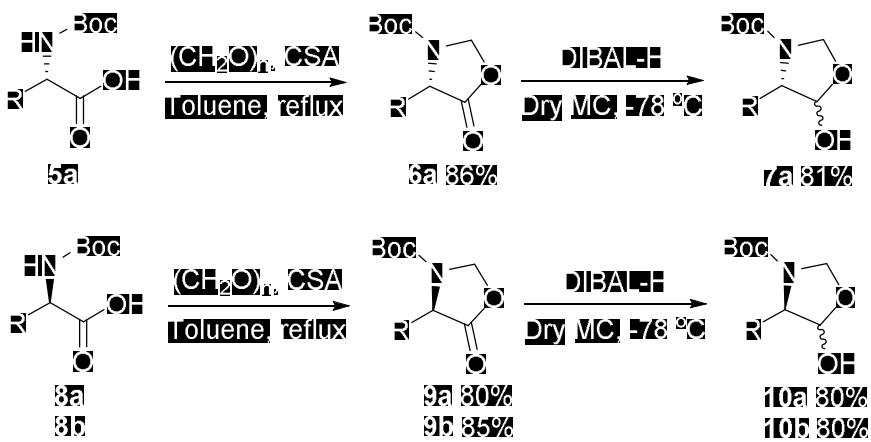
So, we planned to substitute benzyl group on N-terminus with alkyl groups, isobutyl and isopropyl, which are present in amastatin or lapstatin. The precursors for corresponding β-amino-α-hydroxy acids were prepared via the intramolecular conjugate addition between phenylsulfonylnitromethane and *N*-hydroxymethyl protected α-amino aldehydes. Several stereoselective total syntheses of its derivatives are reported, but there are no report about isobutyl and isopropyl group substitute on N-terminus have been reported.

Furthermore, employing the developed synthetic method, we also planned to synthesize lapstatin derivatives. Lapstatin has β-amino-α-hydroxy moiety similar to bestatin, but its stereochemistry of β-amino-α-hydroxy moiety is still not identified. Four kinds of lapstatin derivatives are being synthesized in order to confirm its stereochemistry.

3. Result and Discussion

3.1. Preparation of lactols from α-amino acids

The key strategy for the synthesis of bestatin derivatives and lapstatin derivatives is how to prepare the *threo*-β-amino-α-hydroxy acids moiety.[16] Commercially available Boc protected amino acids **5** and **8** are readily converted to oxazolidinone with paraformaldehyde and the catalytic amount of (±)-10-camphorsulfonic acid (CSA) under dean-stock condition (Scheme 7). The synthesized lactones **6** and **9** are reduced to lactols **7** and **10** by dropwise addition of DIBAL-H in dry MC at -78℃.

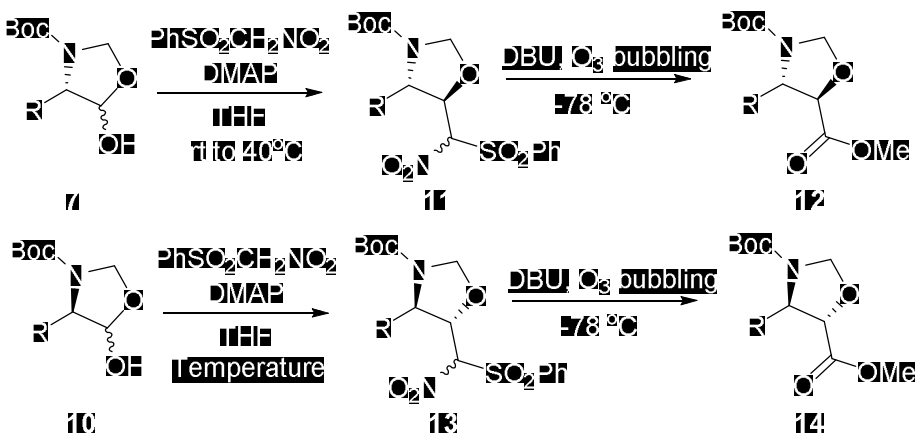


Scheme 7. Preparation of the lactols.

If α-amino acids have L- configuration, only iso-propyl substrates are used for lapstatin derivatives, on the contrary, if α-amino acids have D- configuration, iso-propyl and iso-butyl substrates are used for lapstatin derivatives and bestatin derivatives.

3.2. Preparation of *trans*-oxazolidine derivatives

As our previous research on the *threo*-β-amino-α-hydroxy acid moiety, the protected form of β-amino-α-hydroxy acids is prepared via the three tandem reactions which is the nitro-aldol reaction, the dehydration reaction, and the intramolecular conjugate addition reaction (Scheme 8).



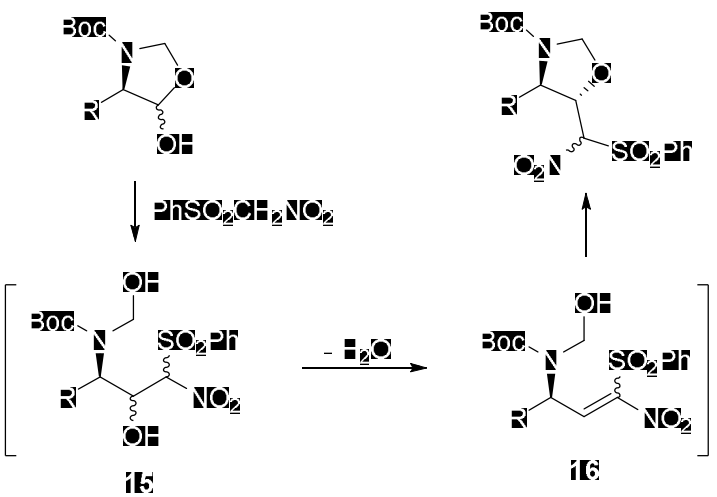
R = i-propyl ( ) **a**, **12a** 59% from **7a**
14a 54% from **10a**

R = i-butyl ( ) **b**, **14b** 72% from **10b**

Scheme 8. Preparation of *trans*-oxazolidine methyl esters.

In case of iso-propyl substrates **7** and **10a**, reaction temperature of phenylsulfonylnitromethane addition is 40℃ due to stability of valine lactol. But, in case of iso-butyl substrates **10b**, reaction is conducted at room temperature. Then, *trans*-oxazolidine methyl esters compounds **12** and **14** are formed via *in-situ* ozonolysis reaction. The stereoselectivity of the *trans*-oxazolidine is more than 20:1 ratio that demonstrated in the previous reports.[17]

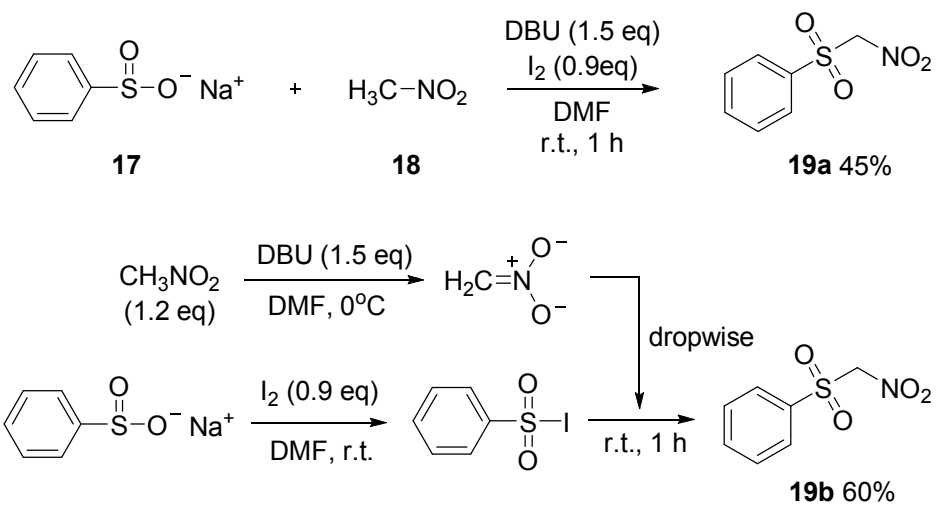
When phenylsulfonylnitromethane is added to *N,O*-acetal lactols, each tandem reaction intermediates **15** and **16** are difficult to isolate because once reaction starts, dehydration and intramolecular conjugate addition reaction is done very fast (Scheme 9).



Scheme 9. Reaction pathway of three tandem reaction.

3.2.1. Synthesis of phenylsulfonylnitromethane

Phenylsulfonylnitromethane is a useful and moderately reactive nitro-source suitable for condensation and alkylation because two electron withdrawing groups are substituted. Phenylsulfonylnitromethane **19** can be synthesized between sodium phenylsulphinate **17** and nitromethane **18**.[18] The mechanism of this reaction is still unknown, whether deprotonated nitromethane or sodium phenylsulphinate reacts with I_2 first. So, I try to separate deprotonation step of nitromethane and I_2 addition step of sodium phenylsulphinate, and then deprotonated nitromethane is added dropwise to benzenesulfonyl iodide (Scheme 10).



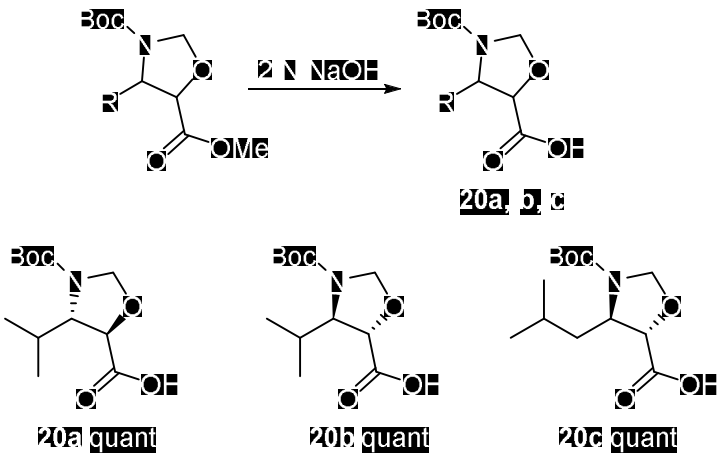
Scheme 10. Synthesis of phenylsulfonylnitromethane.

Two step reaction is little more efficient than one-pot reaction. But when reaction scale is going up, reaction yield is going down.

3.3. Synthesis of bestatin derivatives and lapstatin derivatives

3.3.1. Preparation of Boc protected *threo*-β-amino-α-hydroxy acid moiety

So far, each corresponding *trans*-oxazolidine methyl esters for bestatin derivatives and lapstatin derivatives are obtained. Fully protected methyl ester form of *threo*-β-amino-α-hydroxy acids are hydrolyzed to corresponding Boc protected *threo*-β-amino-α-hydroxy acid moiety **20** in basic condition (Scheme 11).

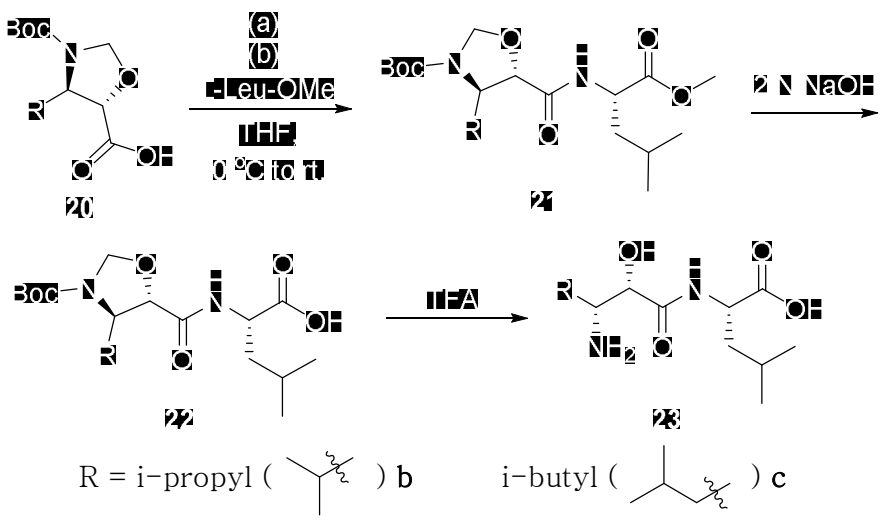


Scheme 11. Boc protected *threo*-β-amino-α-hydroxy acid moiety.

This compounds are key intermediates for bestatin derivatives and lapstatin derivatives because each target derivatives can be derived from these. Once these compounds are coupled with proper protected amino acid moiety, all that remained is to remove the oxazolidine ring and protecting group.

3.3.2. Synthesis of bestatin derivatives

At first, *trans*-oxazolidine carboxylic acid **20b** is reacted with L-Leu-OMe under condition (a) **(Scheme 12)**.



Conditions and yields :

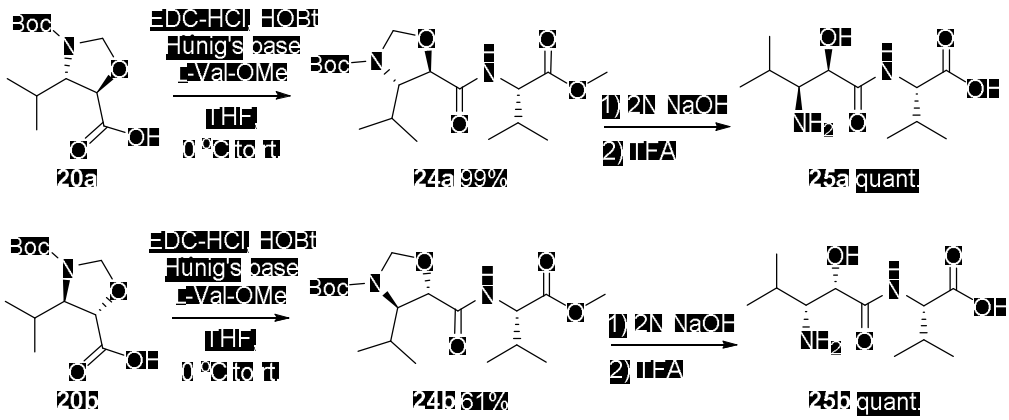
(a) *N*-methyl morpholine, isobutyl chloroformate, 5 hours,
21b : 58%, **22b** : quant., **23b** : quant.

(b) EDC-HCl, HOBt, *N,N*-diisopropylethylamine (Hünig's base), 14 hours,
21b : 76%, **21c** : 74%, **22b,c** : quant. **23b** : quant., **23c** : 95%.

Because c Scheme 12. Synthesis of bestatin derivatives. her peptide coupling reagents, condition (b), and yield is higher than before. Finally, the global deprotection under the sequential basic and acidic hydrolysis conditions produced the desired product **23b** and **23c**.

3.3.3. Synthesis of lapstatin derivatives

We already know that condition (b) is better than (a) for this reaction, *trans*-oxazolidine carboxylic acid **20a** and **20b** is reacted with L-Val-OMe under condition (b) **(Scheme 13)**.



Scheme 13. Synthesis of lapstatin derivatives with L-Val-OMe.

Added to peptide bond formation is successfully carried out with high yield, there are more possibility to modify this final procedures. If

carboxylic acid is protected with t-butyl group instead of methyl group, two step reaction with is removing the oxazolidine ring and protecting group can be done in one step reaction. For this reason, *trans*-oxazolidine carboxylic acid is reacted with D-Val-O^{t}Bu followed by deprotection reaction with TFA. Natural lapstatin which stereochemistry is unidentified has eight possible isomer. We have been obtain four of them and four more stereoisomers are remained to synthesize.

4. Conclusion

Vicinal amino-alcohol structure can be found in many valuable biologically activated natural product. In addition to that, 3-amino-2-hydroxybutanoyl structure can be found in a large number of low-molecular-weight aminopeptidase inhibitors. Because stereochemistry of vicinal amino-alcohol moiety is important in the matter of biologically active compounds, stereoselective synthetic methods have been paying attention. A number of stereoselective synthetic methods for not only vicinal amino-alcohols but also aminopeptidase inhibitors have been reported.

In this thesis, I have applied a novel stereoselective synthesis of *threo*-β-amino-α-hydroxy acids moiety to synthesis of various low-molecular-weight aminopeptidase inhibitor. Starting from commercially available α-amino acids, *N,O*-acetal lactols are formed to make stable intermediates for fully protected methyl ester form of *threo*-β-amino-α-hydroxy acids moiety. After this fully protected compounds are synthesized, three kinds of key intermediates **20a**, **20b**, and **20c** can be obtained via basic hydrolysis.

Two new alkyl substituted bestatin derivatives are synthesized with these intermediates by effective peptide bond coupling reaction. The

new isopropyl and isobutyl analogs of bestatin, **23b** and **23c**, were produced in overall 24% and 35% yields with high stereoselectivity from the corresponding protected α-amino acids in 8 steps, respectively. To the best of our knowledge, it has not been reported that synthesis of isopropyl or isobutyl substituted bestatin analogs.

Employing the developed synthetic method of bestatin derivatives, lapstatin derivatives are also synthesized from corresponding these key intermediates **20a** and **20b**. In this case, some modifications are used. At first, synthesis of phenylsulfonylnitromethane which is important reagent for stereoselective synthesis of the *trans*-oxazolidine is modified to two step reaction with better yield than one-pot reaction which is previous synthetic method, although this modified reaction is not optimized yet. Second, peptide bond coupling reactions are carried out between Boc protected *threo*-β-amino-α-hydroxy acid moieties and D-Val-O^{t}Bu instead of D-Val-OMe. Through this modification, opening of the oxazolidine ring and deprotection of protecting group can be done in one step. The four kinds of lapstatin derivatives are synthesized with high stereoselectivity, but four more stereoisomers of lapstatin which contain *anti*-β-amino-α-hydroxy acid moieties are needed to synthesize in order to confirm stereochemistry of natural lapstatin.

Experimental Details

General procedure.

Materials are obtained from commercial suppliers and are used without further purification. Methylene chloride is distilled in the presence of calcium hydride under N_2 atmosphere immediately prior to use. THF and ether are distilled in the presence of sodium benzophenone ketyl under N_2 atmosphere. Air or moisture sensitive reactions are conducted under N_2 atmosphere using oven-dried glassware and standard syringe/septa techniques. All that glassware, syringe, magnetic stirring bars used in this thesis were prepared by oven-dried. The reactions are monitored with a SiO_2 TLC plate under UV light (254 nm) and/or by visualization with a ninhydrin staining solution. Column chromatography is performed on silica gel 60 (70-230 mesh). Optical rotations are determined at ambient temperature with a digital polarimeter and are the average of ten measurements. ^{1}H and ^{13}C NMR spectra are measured at 400 MHz and 100 MHz, respectively in $CDCl_3$ or MeOH-d_4 unless stated otherwise and data are reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz). Low and high resolution mass spectra were measured by the CI or FAB ionization

method and analyzed by magnetic sector mass analyzer.

Lactone (6, 9)

The Boc protected amino acids was dissolved in ml of toluene then added paraformaldehyde(10 eq.) and (±)-10-camphorsulfonic acid(CSA, 0.1 eq.), The reaction mixture was heated under reflux for about 1 hour with dean-stark apparatus. The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The obtained crude was purified with silica gel column chromatography (8:1 Hexane/EtOAc).

6a : 86%, $[\alpha]_D$ = +108.6 (c = 2.14, $CHCl_3$); white powder, ^1H NMR ($CDCl_3$) δ 1.04 (d, 3H, *J* = 12.4), 1.06 (d, 3H, *J* = 12), 1.49 (s, 9H), 2.33 (s, 1H), 4.16 (s, 1H), 5.11 (d, 1H, *J* = 4.8), 5.57 (s, 1H); ^{13}C NMR δ 17.8, 18.2, 28.2, 31.4, 60.3, 78.6, 82.0, 152.8, 172.2; HRMS (CI) calcd for $C_{11}H_{20}NO_4$ 230.1392 ($[M+H]^+$), found 230.1391

9a : 80%, $[\alpha]_D$ = -108.9 (c = 2.00, $CHCl_3$); white powder, ^1H NMR ($CDCl_3$) δ 1.04 (d, 3H, *J* = 12), 1.06 (d, 3H, *J* = 12), 1.49 (s, 9H), 2.33 (s, 1H), 4.16 (s, 1H), 5.11 (d, 1H, *J* = 4.8), 5.58 (s, 1H); ^{13}C NMR δ 17.8, 18.1, 28.2, 31.4, 60.4, 78.6, 82.0, 153.0, 172.2; HRMS (CI) calcd for $C_{11}H_{20}NO_4$ 230.1392 ($[M+H]^+$), found 230.1388

9b : 85%, $[\alpha]_D$ = +99.6 (c = 1.50, $CHCl_3$); colorless oil, ^1H NMR

($CDCl_3$) δ 0.98 (tr, 6H, *J* = 7.2), 1.49 (s, 9H), 1.66-1.71 (m, 1H), 1.74-1.79 (m, 1H), 1.83-1.88 (m, 1H), 4.28 (tr, 1H, *J* = 6.5), 5.15 (d, 1H, *J* = 4.8), 5.57 (s, 1H); ^{13}C NMR δ 22.4, 22.7, 24.4, 28.2, 39.6, 53.5, 77.5, 81.9, 152.4, 173.1; HRMS (CI) calcd for $C_{12}H_{22}NO_4$ 244.1471 ($[M+H]^+$), found 244.1549

Lactol (7, 10)

To the solution of lactone (**6**, **9**) in dry CH_2Cl_2 (0.1 M conc.) at -78℃, the 1M concentrated solution of DIBAL-H in CH_2Cl_2 (1.5 eq.) added dropwise under N_2 atmosphere and the resulting mixture was stirred for 20 min at -78℃. After the reaction, the mixture was diluted with ethyl acetate and quenched by slowly adding cold MeOH (10 ml). After warming up to room temperature, aqueous sat' solution of Rochelle salt was added excessively and the mixture was stirred for 30min. then, it was extracted with CH_2Cl_2 and aqueous sat' solution of Rochelle salt. The combined organic layers were washed with aqueous sat' solution of Rochelle salt for 2 times to the removal of aluminum salt. The washed organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. Purification was done with silica gel column chromatography (8:1 Hexane/EtOAc). Obtained lactol is mainly exist as α-amino aldehyde.

7a : 81%, colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 7.2), 0.96 (d, 3H, *J* = 6.8), 1.47 (s, 9H), 1.92 (s, 1H), 2.53 (s, 1H), 3.68 (d, 1H, *J* = 4.8), 4.87 (d, 1H, *J* = 3.6), 5.17 (s, 1H), 5.39 (d, 1H, *J* = 3.6) ; ^{13}C NMR δ 18.1, 18.8, 28.3, 29.5, 67.8, 78.6, 80.4, 98.2, 153.5; HRMS (CI) calcd for $C_{11}H_{22}NO_4$ 232.1549 ($[M+H]^+$), found 232.1552

10a : 80%, colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 6.8), 0.96 (d, 3H, *J* = 7.2), 1.47 (s, 9H), 1.93 (s, 1H), 2.52 (d, 1H, *J* = 3.6), 3.69 (d, 1H, *J* = 5.2), 4.87 (d, 1H, *J* = 3.6), 5.18 (s, 1H), 5.39 (d, 1H, *J* = 3.6); ^{13}C NMR δ 18.1, 18.8, 28.3, 29.5, 67.8, 78.6, 80.4, 98.2, 153.5; HRMS (CI) calcd for $C_{11}H_{22}NO_4$ 232.1549 ($[M+H]^+$), found 232.1544

10b : 80%, colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 6H, J = 6.8), 1.27-1.35 (m, 1H), 1.60-1.70 (m, 1H), 2.95 (s, 1H), 3.86-3.89 (m, 1H), 4.88 (d, 1H, J = 3.6), 5.14 (s, 1H), 5.29 (s, 1H); ^{13}C NMR δ 22.3, 23.0, 25.2, 28.4, 40.6, 61.1, 80.4, 100.5, 153.0

trans-Oxazolidine methyl esters (12, 14)

To α-amino aldehyde (**7**, **10**) in THF (1 M conc.) was added phenylsulfonylnitromethane (1.2 eq.) and DMAP (1.5 eq.). The reaction mixture was stirred at room temperature for 3~4 days with vigorous stirring. The reaction mixture was diluted with THF and MeOH and added DBU (3 eq.) at room temperature. Then, the reaction mixture

was cooled to −78 ℃, and ozone was bubbled through over 20~40 min. After quenching the reaction with acetic acid (1 mL), the resulting mixture was warmed up to room temperature. After removing the solvent under reduced pressure, the residue was extracted with EtOAc and aqueous sat' solution of NH_4Cl. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. Purification was done with silica gel column chromatography (8:1 Hexane/EtOAc).

12a : 59% (from **7a**), $[\alpha]_D$ = −2.6 (c = 0.85, $CHCl_3$); colorless oil, ^1H NMR ($CDCl_3$) δ 0.96 (t, 6H, J = 7.2), 1.46 (s, 9H), 2.03 (s, 1H), 3.75 (s, 3H), 3.97 (s, 1H), 4.45 (d, 1H, J = 2.0), 4.82 (d, 1H, J = 3.6), 5.26 (s, 1H); ^{13}C NMR δ 17.9, 18.8, 28.3, 30.9, 52.3, 64.6, 80.0, 80.7, 153.3, 171.8; HRMS (CI) calcd for $C_{13}H_{24}NO_5$ 274.1654 ($[M+H]^+$), found 274.1650

14a : 54% (from **10a**), $[\alpha]_D$ = + 10.5 (c = 0.64, $CHCl_3$); colorless oil; ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, *J* = 7.0), 0.96 (d, 3H, *J* = 7.0), 1.44 (s, 9H), 1.48 (m, 1H), 3.46 (s, 3H), 3.74 (br s, 1H), 4.44 (s, 1H), 4.80 (d, 1H, *J* = 3.2), 5.23 (br s, 1H); ^{13}C NMR δ 17.8, 18.9, 28.3, 31.0, 52.4, 64.6, 76.8, 80.0, 80.8, 153.3, 171.9.; HRMS (CI) calcd for $C_{13}H_{24}NO_5$ 274.1654 ($[M+H]^+$), found 274.1658

14b : 72% (from **10b**), $[\alpha]_D$ = + 5.8 (c = 2.8, $CHCl_3$); colorless oil^1H

NMR ($CDCl_3$) δ 0.99 (d, 3H, *J* = 6.4), 1.01 (d, 3H, *J* = 6.4), 1.44-1.50 (m, 1H), 1.48 (s, 9H), 1.60 (m, 1H), 1.69 (m, 1H), 3.79 (s, 3H), 4.24 (br s, 1H), 4.37 (d, 1H, *J* = 1.6), 4.85 (d, 1H, *J* = 3.6), 5.28 (s, 1H); ^{13}C NMR δ 22.1, 22.8, 25.2, 28.3, 42.2, 52.3, 57.8, 79.0, 79.0, 80.6, 152.8, 171.4.

trans-Oxazolidine carboxylic acid (20)

The methylester (**12**, **14**) was dissolved in THF (2 mL), then was added 2 N NaOH (2 mL). After the reaction mixture was stirred at room temperature for 1 h, it was acidified with 1 N aq. HCl to pH 2~3. The resulting mixture was extracted with EtOAc and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator.

trans-Oxazolidine dipeptide methyl ester for bestatin derivatives (21)

To *trans*-oxazolidine carboxylic acid (**20**) in THF (20 mL) at 0 ℃, HOBt (1.2 eq.) and L-Leu-OMe (1.1 eq.) were added. Then, EDC·HCl (1.2 eq.) and N,N-diisopropylethylamine (2.5 eq.) were added to the reaction mixture. The mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc and saturated aq. solution of NH4Cl. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure.

The organic residue was purified by silica gel chromatography (16:1 Hexane/EtOAc).

21b : 76%, $[\alpha]_D$ = -13.7 (c = 0.81, $CHCl_3$); colorless oil; ^1H NMR ($CDCl_3$) δ 0.92 (dd, 6H, *J* = 1.6, 6.4), 0.99 (t, 6H, *J* = 7.0), 1.45 (s, 9H), 1.54-1.61 (m, 2H), 1.63-1.69 (m, 1H), 1.94-1.99 (m, 1H), 3.74 (s, 3H), 4.10 (dd, 1H, *J* = 2.2, 6.6), 4.34 (d, 1H, *J* = 2.8), 4.59-4.65 (m, 1H), 4.74 (d, 1H, *J* = 4.8), 5.31 (br s, 1H), 6.91 (d, 1H, *J* = 8.4); ^{13}C NMR δ 18.7, 18.9, 21.9, 23.0, 25.0, 28.3, 31.5, 41.5, 50.4, 52.5, 64.9, 79.3, 81.0, 153.4, 171.0, 173.0; HRMS (FAB) calcd for $C_{19}H_{35}N_2O_6$ 387.2495 ($[M+H]^+$), found 387.2496.

21c : 74%, $[\alpha]_D$ = -17.4 (c = 0.88, $CHCl_3$); colorless oil; ^1H NMR δ 0.94 (dd, 6H, *J* = 2.8, 6.2), 1.00 (t, 6H, *J* = 6.4), 1.47 (s, 9H), 1.54-1.63 (m, 3H), 1.66-1.77 (m, 2H), 3.76 (s, 3H), 4.22 (d, 1H, *J* = 2.8), 4.38 (dt, 1H, *J* = 2.5, 7.3), 4.61-4.65 (m, 1H), 4.77 (d, 1H, *J* = 4.8), 5.31 (d, 1H, *J* = 3.2), 6.86 (d, 1H, *J* = 8.4); ^{13}C NMR δ 21.9, 22.4, 22.8, 24.9, 25.0, 28.3, 41.4, 42.7, 50.3, 52.3, 57.9, 78.2, 80.9, 81.7, 152.9, 170.4, 172.9; HRMS (CI) calcd for $C_{20}H_{37}N_2O_6$ 401.2652 ($[M+H]^+$), found 401.2651.

trans-Oxazolidine dipeptide carboxylic acid for bestatin derivatives (22)

trans-Oxazolidine dipeptide methyl ester (**21**) in THF (2 mL) at 0 ℃ was added 2 N NaOH (2 mL). After the reaction mixture was stirred at

room temperature for 1 h, it was acidified with 1 N aq. HCl to pH 2~3. The resulting mixture was extracted with EtOAc and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator.

Bestatin derivatives (23)

To *trans*-oxazolidine dipeptide carboxylic acid in CH_2Cl_2 was added trifluoroacetic acid (10 eq.) and the reaction mixture was reacted at room temperature overnight. After the removal of the solvents and acids, the reaction mixture was diluted with water. The aqueous layer was washed with EtOAc three times and then the aqueous layer was condensed under reduced pressure to afford bestatin derivatives **23**.

23b : quant., $[\alpha]_D$ = -28.4 (c = 2.2, H_2O); ^{1}H NMR (MeOH-d_6) δ 0.97 (dd, 6H, *J* = 5.6, 9.2), 1.08 (m, 6H), 1.73 (m, 3H), 2.10 (qt, 1H, *J* = 6.7, 13.4), 3.23 (br s, 1H), 4.37 (s, 2H), 4.42 (m, 1H); ^{13}C NMR (MeOH- d_6) δ 18.5, 19.5, 22.0, 23.2, 26.1, 29.3, 41.3, 52.5, 60.5, 69.6, 174.1, 175.7; HRMS (CI) calcd for $C_{12}H_{25}N_2O_4$ 261.1814 ($[M+H]^+$), found 261.1819.

23c : 95%, $[\alpha]_D$ = -20.4 (c = 2.1, H_2O); ^{1}H NMR (MeOH-d_6) δ 0.98 (m, 12H), 1.50 (m, 1H), 1.63-1.77 (m, 5H), 3.50 (br s, 1H), 4.22 (br s, 1H), 4.43-4.46 (m, 1H); ^{13}C NMR (MeOH- d_6) δ 22.0, 22.3, 22.9, 23.3, 25.2, 26.1, 39.2, 41.3, 52.2, 53.3, 71.1, 173.6, 175.7; HRMS (FAB) calcd for

$C_{13}H_{27}N_2O_4$ 275.1971 ([M+ H]$^+$), found 275.1977.

trans-Oxazolidine dipeptide methyl ester for lapstatin derivatives (24)

To *trans*-oxazolidine carboxylic acid (20) in THF (20 mL) at 0 ℃, HOBt (1.2 eq.) and L-Val-OMe (1.1 eq.) or D-Val-OMe (1.1 eq) were added. Then, EDC·HCl (1.2 eq.) and N,N-diisopropylethylamine (2.5 eq.) were added to the reaction mixture. The mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc and saturated aq. solution of NH4Cl. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The organic residue was purified by silica gel chromatography (16:1 Hexane/EtOAc).

24a : 99%, $[\alpha]_D$ = -0.7 (c = 0.23, $CHCl_3$); colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = 6.8), 0.95 (d, 3H, *J* = 7.2), 0.98 (d, 3H, *J* = 6.8), 0.99 (d, 3H, *J* = 6.8), 1.45 (s, 9H), 2.01 (s, 1H), 2.16-2.23 (m, 1H), 4.11 (s, 1H), 4.37 (d, 1H, *J* = 2.8), 4.50-4.54 (m, 1H), 4.77 (d, 1H, *J* = 4.4), 5.34 (s, 1H), 7.00 (d, 1H, *J* = 9.2); ^{13}C NMR δ 17.7, 18.8, 18.9, 28.2, 31.2, 52.1, 56.8, 64.2, 79.3, 80.8, 153.2, 170.8, 171.7; HRMS (CI) calcd for $C_{18}H_{33}N_2O_6$ 373.2339 ([M+ H]$^+$), found 373.2339.

24b : 61%, $[\alpha]_D$ = -5.5 (c = 0.15, $CHCl_3$); colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 3H, *J* = 6.8), 0.90 (d, 3H, *J* = 6.8), 0.99 (d, 3H, *J* = 10.4), 1.01

(d, 3H, *J* = 10.4), 1.44 (s, 9H), 1.94 (s, 1H), 2.14-2.22 (m, 1H), 4.11 (d, 1H, *J* = 5.6), 4.33 (d, 1H, *J* = 2.4), 4.53-4.57 (m, 1H), 4.75 (d, 1H, *J* = 2.4), 5.39 (s, 1H), 7.99 (d, 1H, *J* = 8.8); ^{13}C NMR δ 17.5, 18.7, 19.1, 28.2, 31.4, 52.2, 56.4, 65.2, 79.2, 80.9, 153.3, 171.0, 171.9; HRMS (CI) calcd for $C_{18}H_{33}N_2O_6$ 373.2339 ($[M+H]^+$), found 373.2334.

Lapstatin derivatives (25) from methyl ester dipeptides.

To *trans*-oxazolidine dipeptide carboxylic acid was added excess trifluoroacetic acid and the reaction mixture was reacted at room temperature overnight. After the removal of the acids, the reaction mixture was diluted with water. The aqueous layer was washed with EtOAc three times and then the aqueous layer was condensed under reduced pressure. The residue was purified by freeze drying to afford lapstatin derivatives **25**.

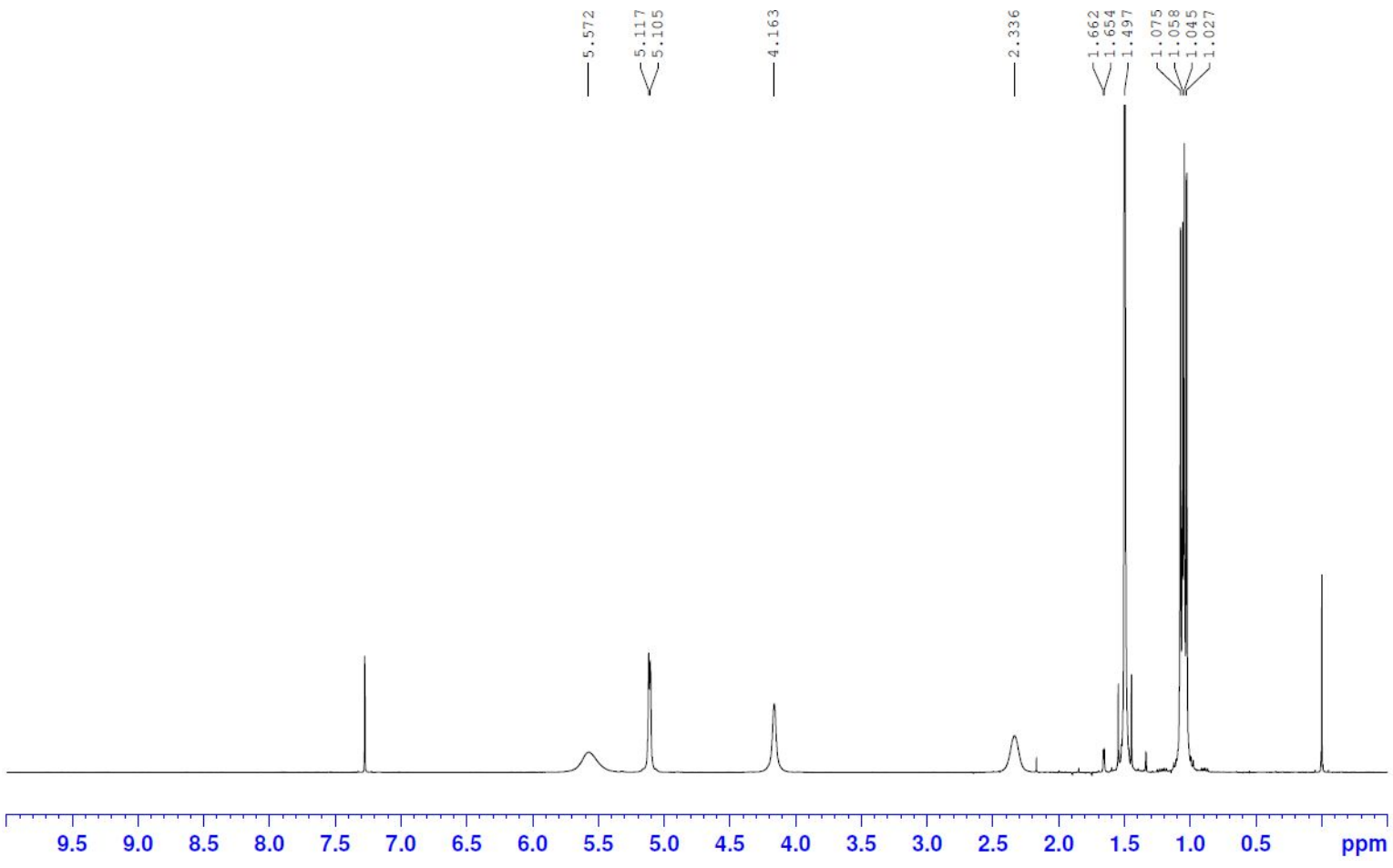
25a : quant., ^{1}H NMR (D_2O) δ 0.85 (dd, 6H, *J* = 6.8, 6.8), 0.94 (d, 6H, *J* = 6.8), 1.91-1.99 (m, 1H), 2.10-2.19 (m, 1H), 3.23-3.26 (m, 1H), 4.21 (d, 1H, *J* = 5.2), 4.40 (d, 1H, *J* = 3.6); ^{13}C NMR (DMSO) δ 18.3, 18.7, 19.4, 19.5, 28.1, 30.8, 57.4, 58.3, 68.7, 171.8, 172.9; HRMS (CI) calcd for $C_{11}H_{23}N_2O_4$ 247.1658 ($[M+H]^+$), found 247.1654.

25b : quant., ^{1}H NMR (D_2O) δ 0.91 (d, 6H, *J* = 6.8), 0.97 (d, 3H, *J* = 6.4), 0.98 (d, 3H, *J* = 6.8), 1.94-2.02 (m, 1H), 2.10-2.19 (m, 1H), 3.27-

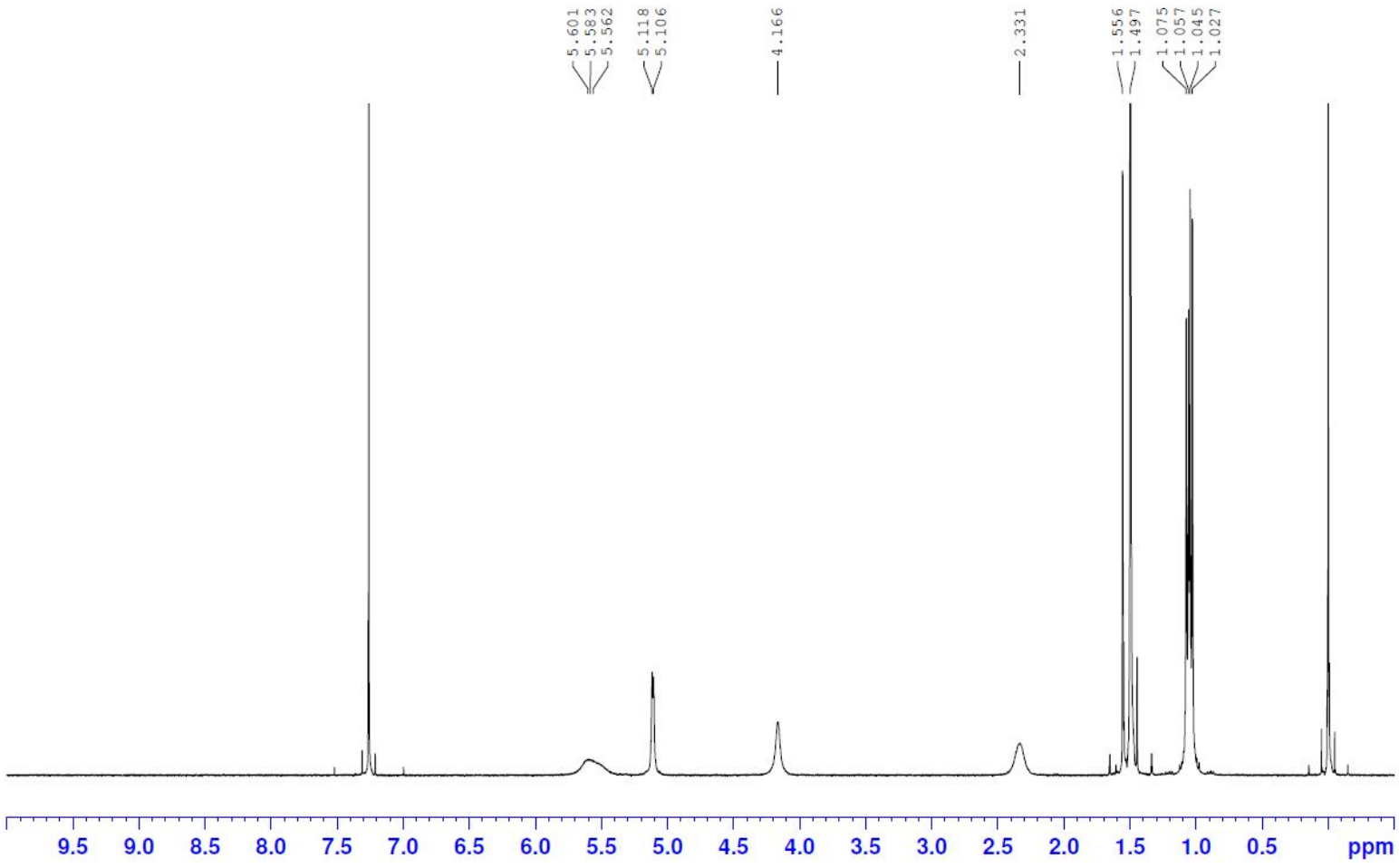
3.29 (m, 1H), 4.15 (d, 1H, J = 6.0), 4.41 (d, 1H, J = 4.4); ^{13}C NMR (DMSO) δ 18.5, 18.6, 19.4, 19.6, 28.0, 30.2, 57.7, 58.4, 68.7, 172.0, 172.8; HRMS (CI) calcd for $C_{11}H_{23}N_2O_4$ 247.1658 ($[M+H]^+$), found 247.1652.

APPENDICES

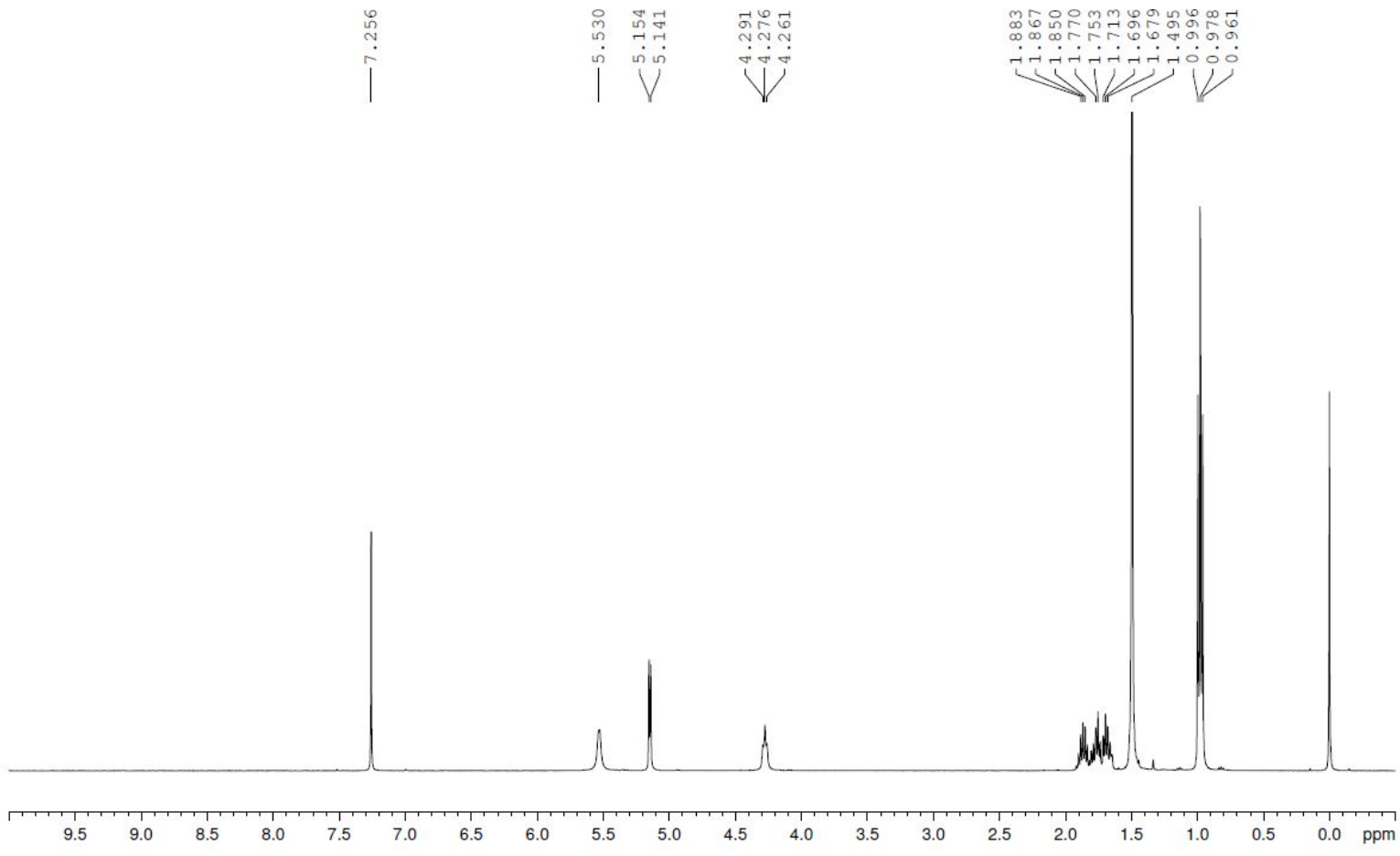
List of ^{1}H NMR Spectra of Selected Compounds



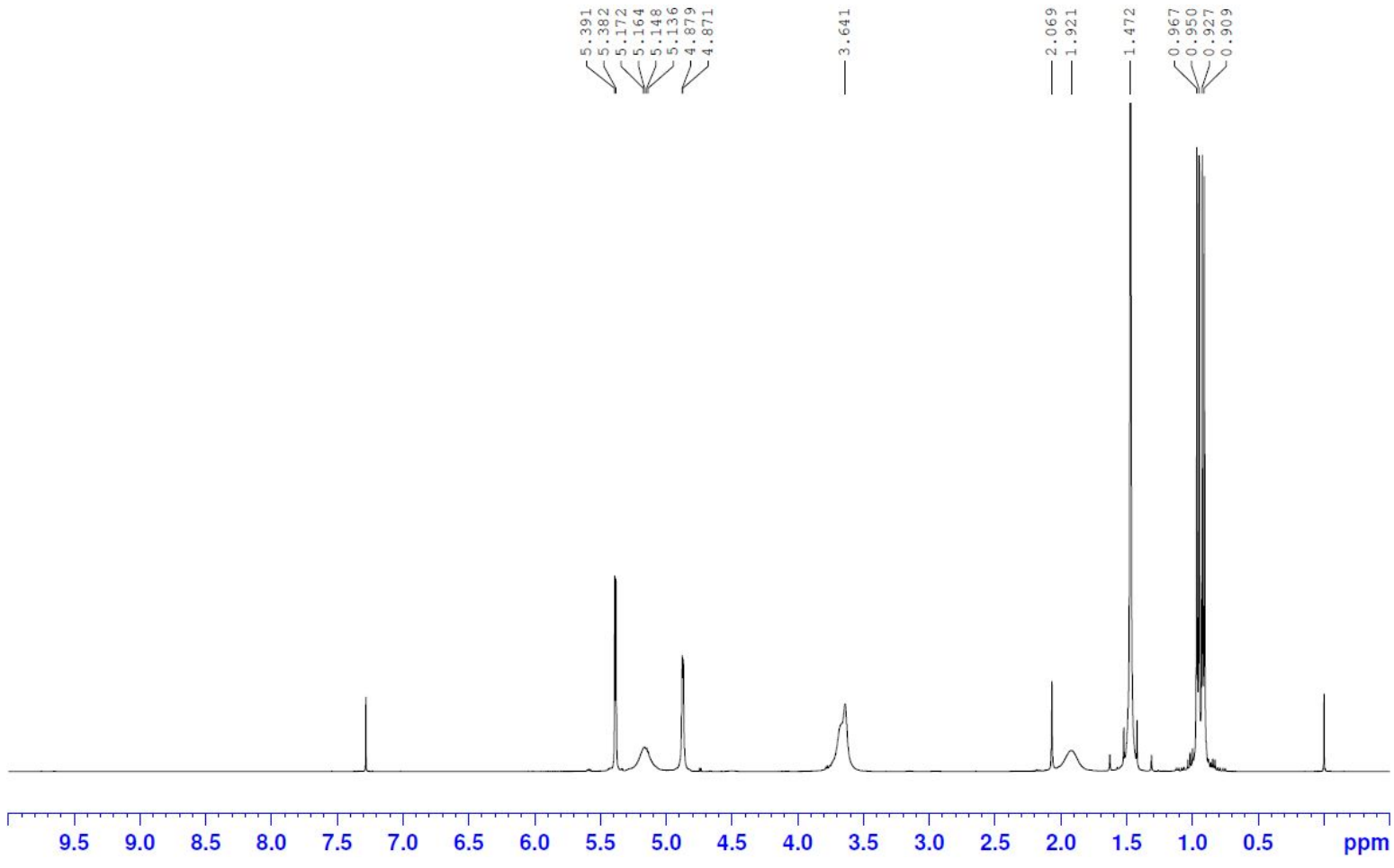
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **6a**



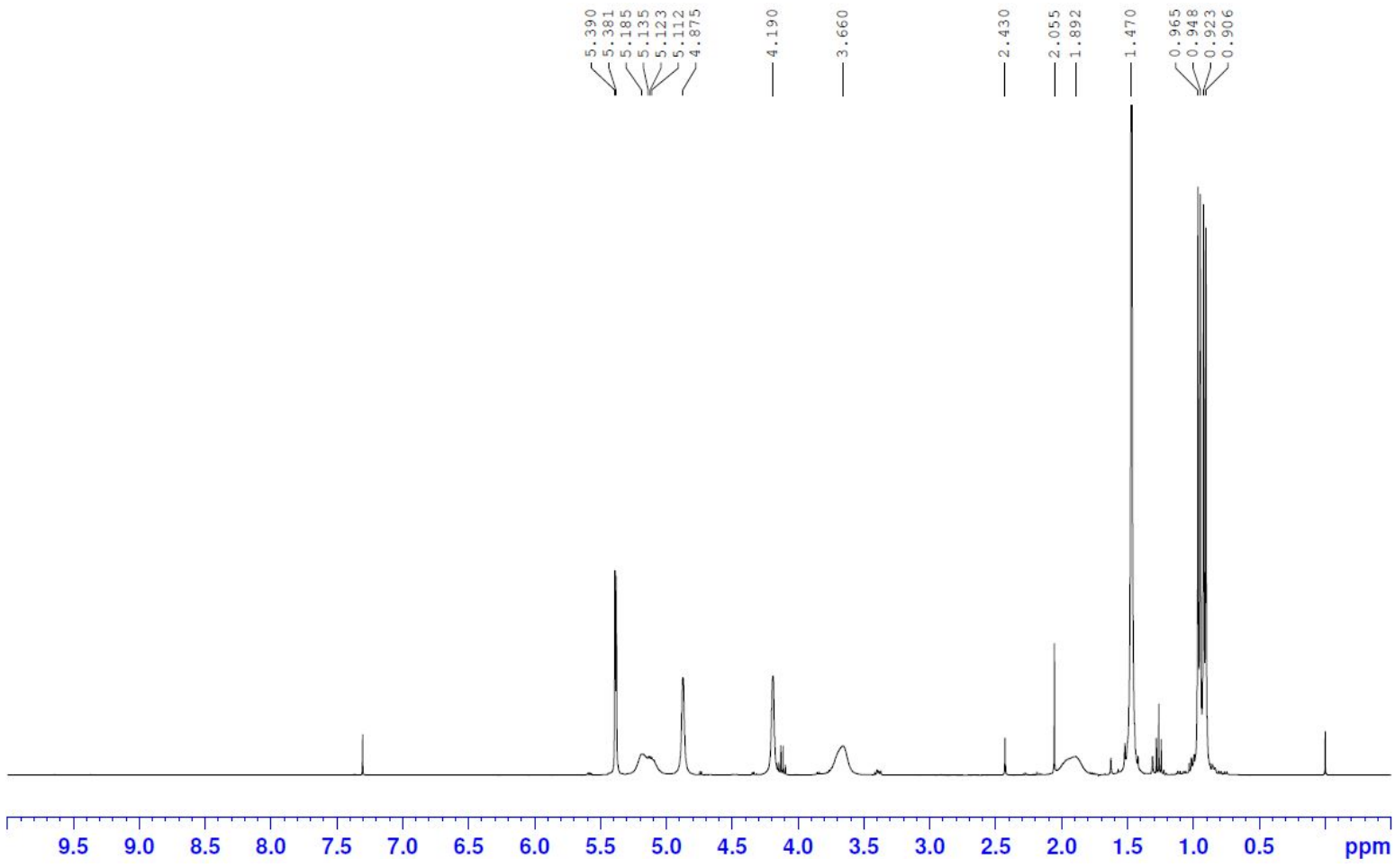
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **9a**



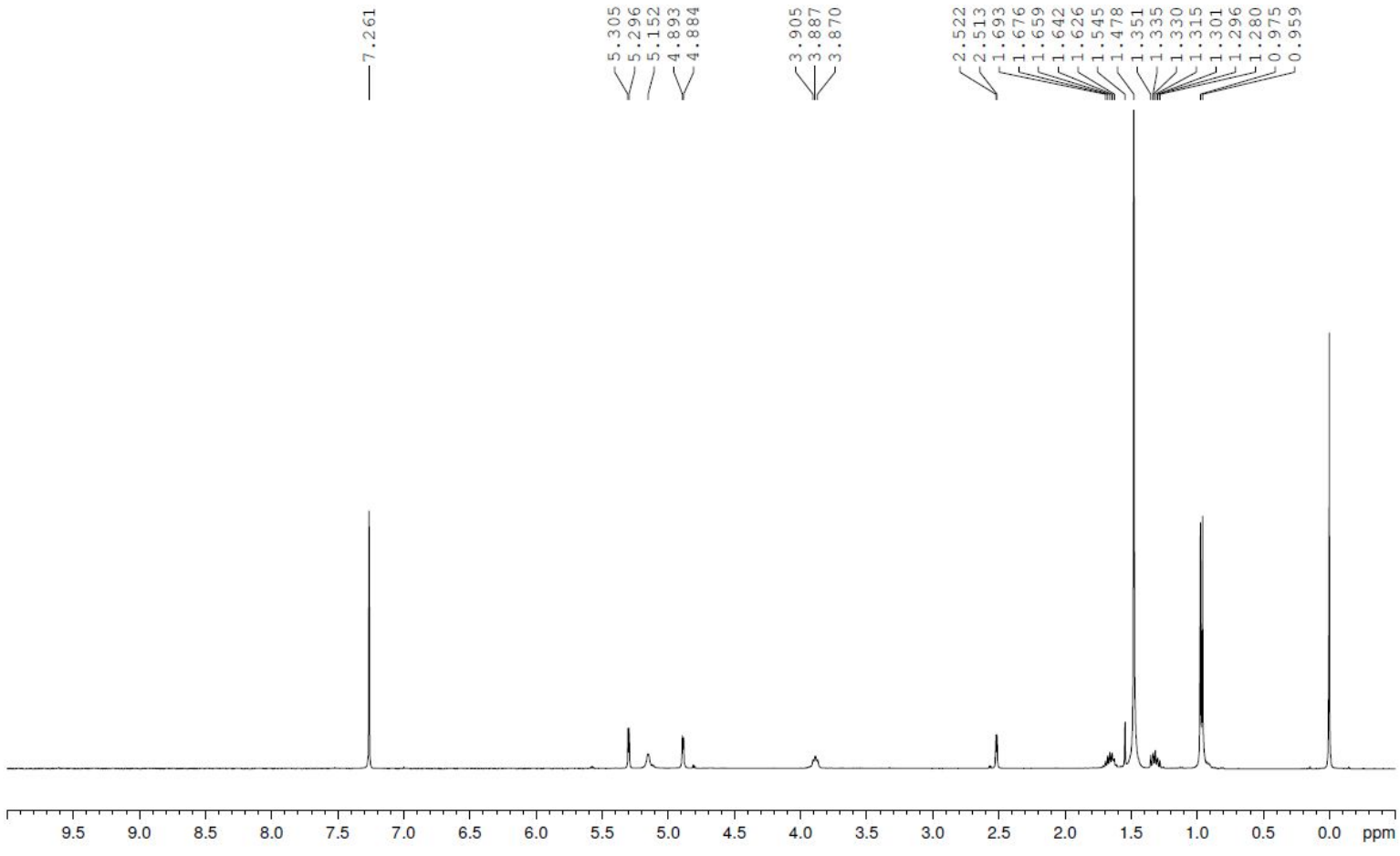
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **9b**



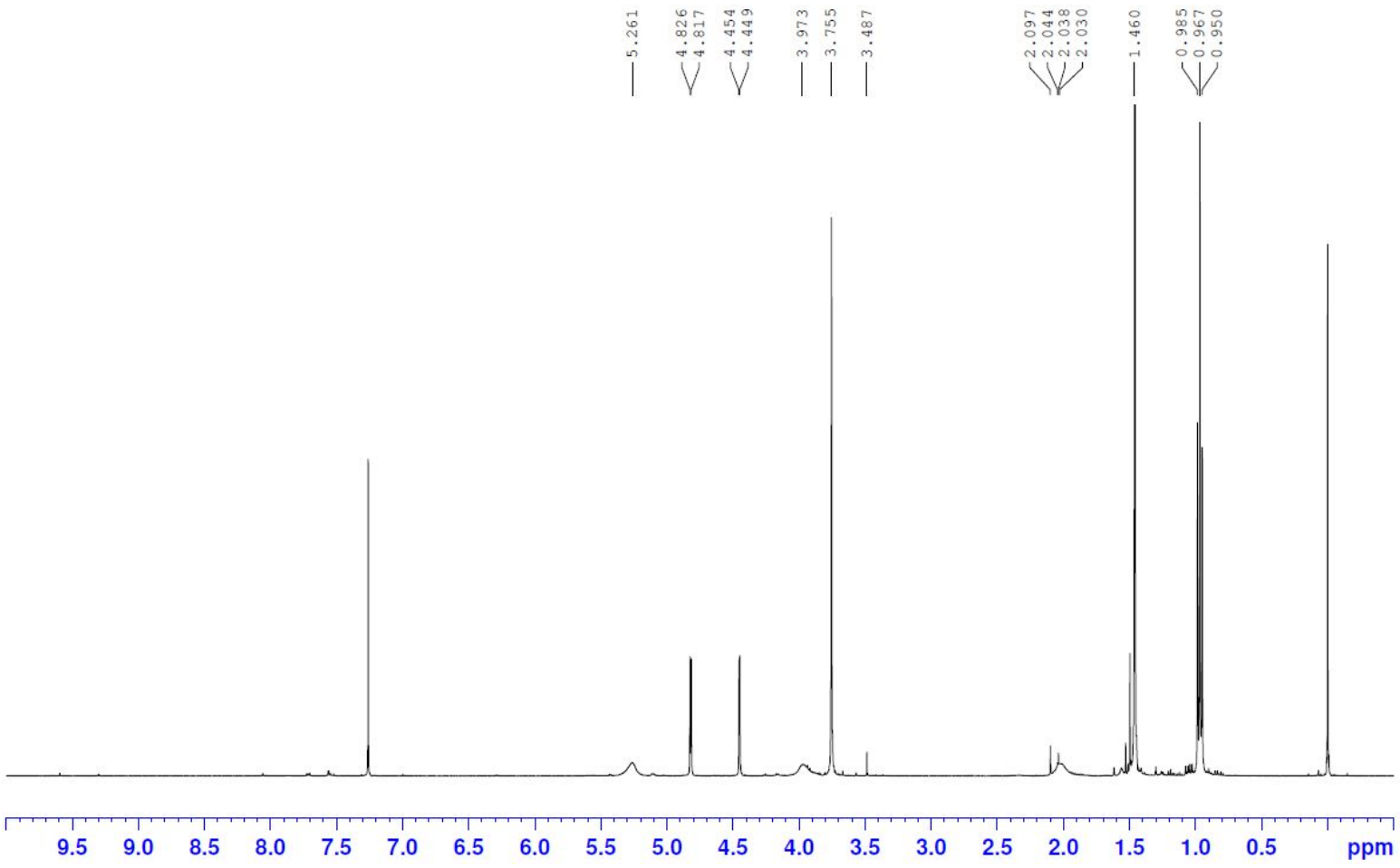
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **7a**



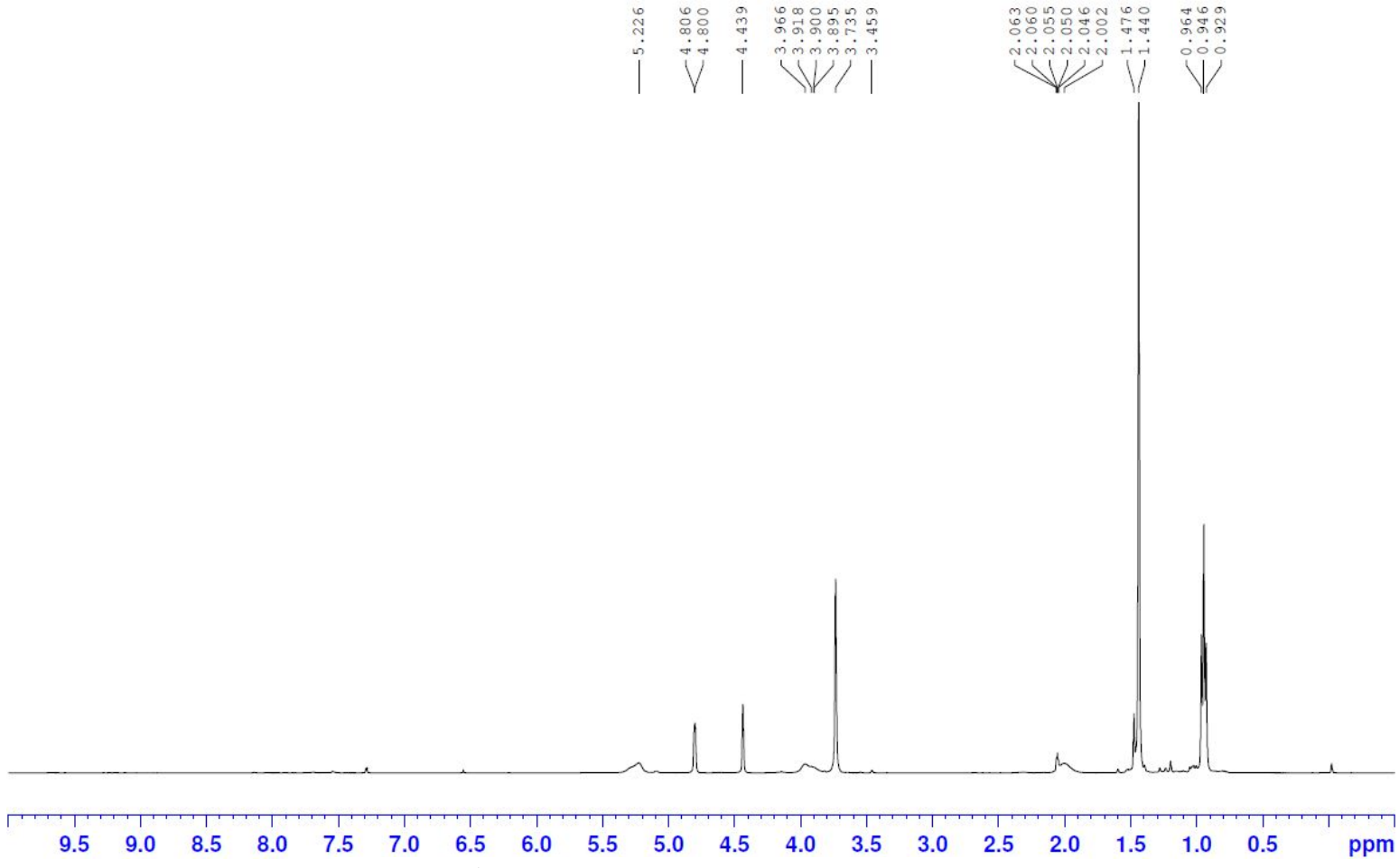
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **10a**



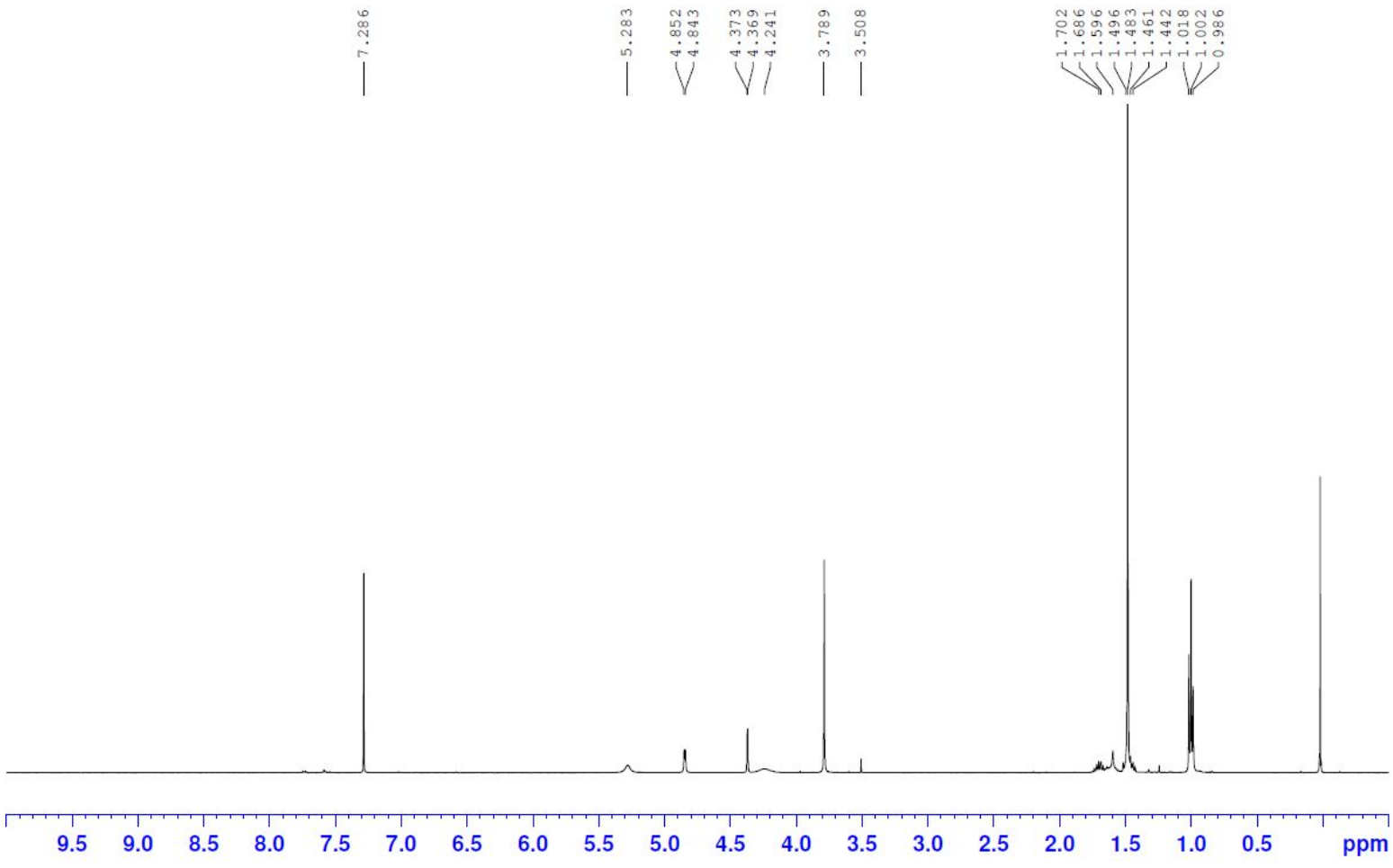
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **10b**



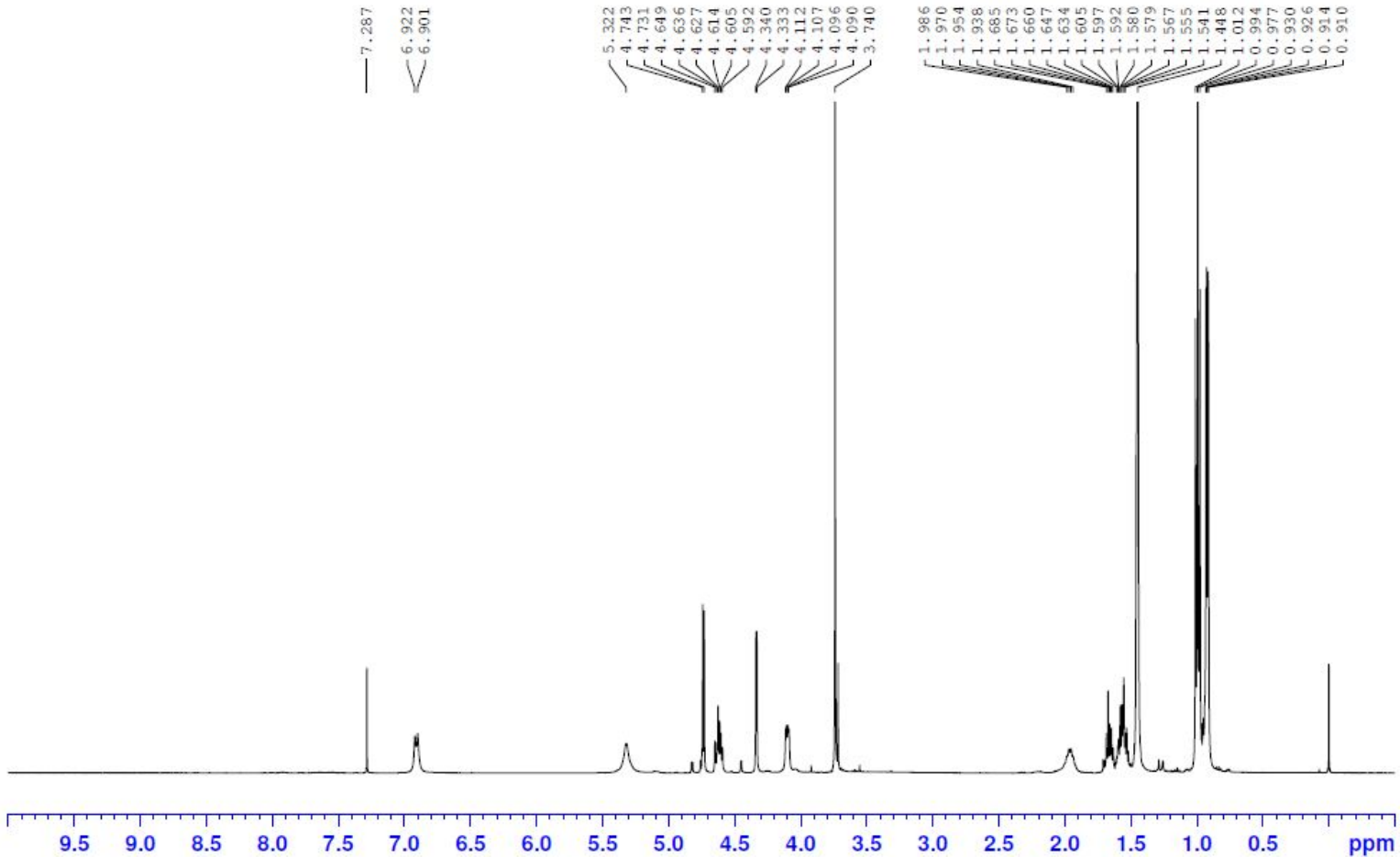
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **12a**



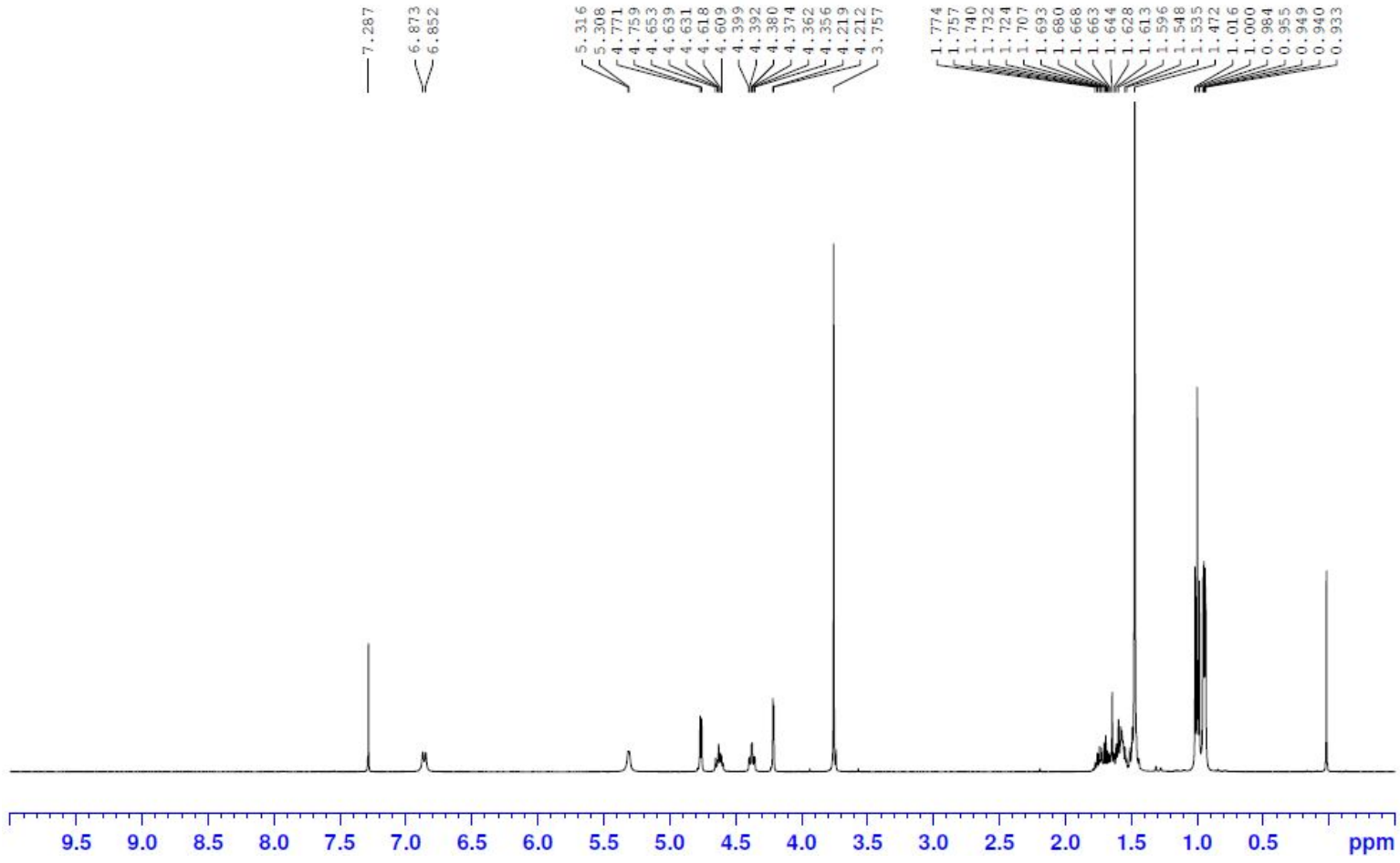
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **14a**



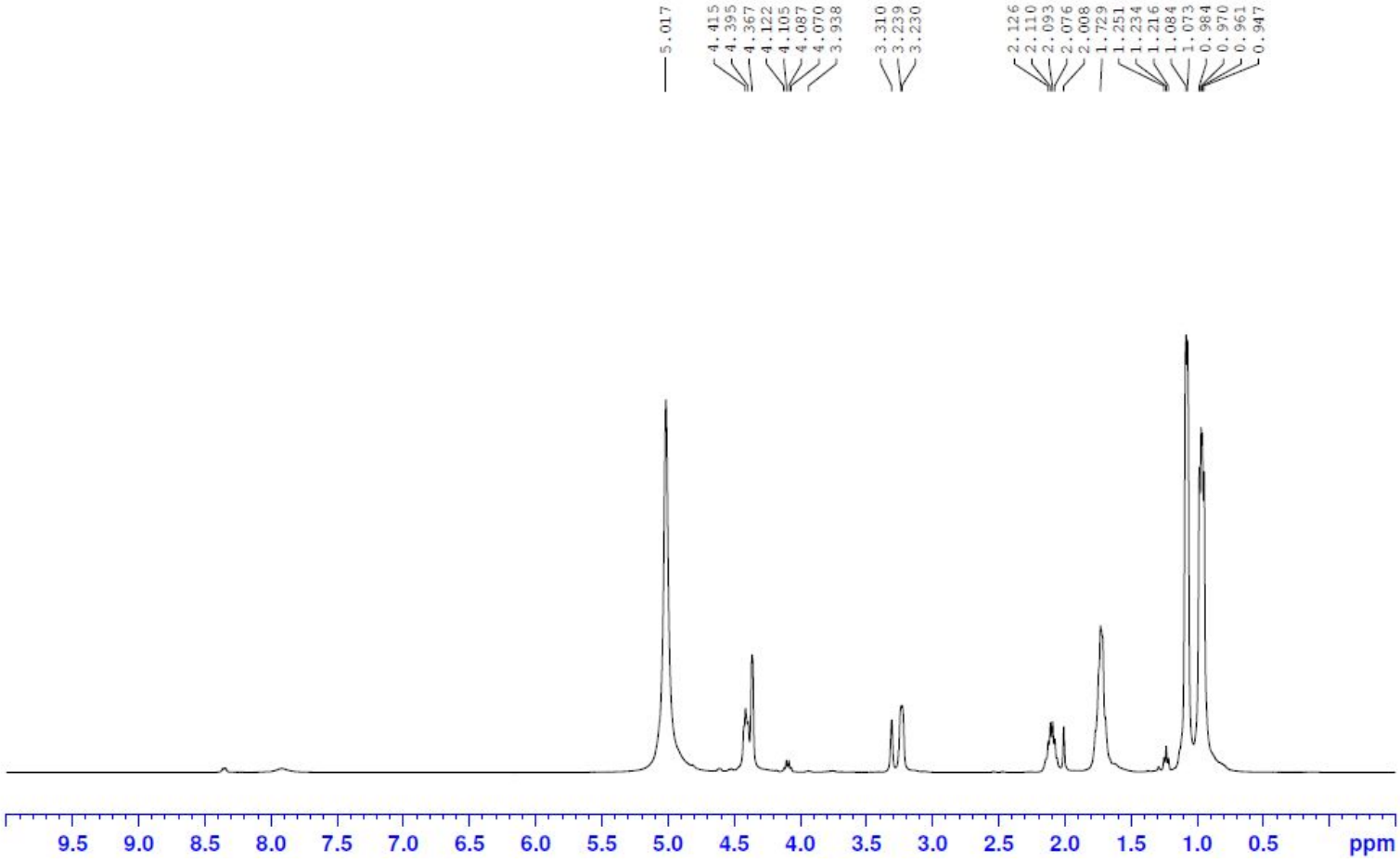
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **14b**



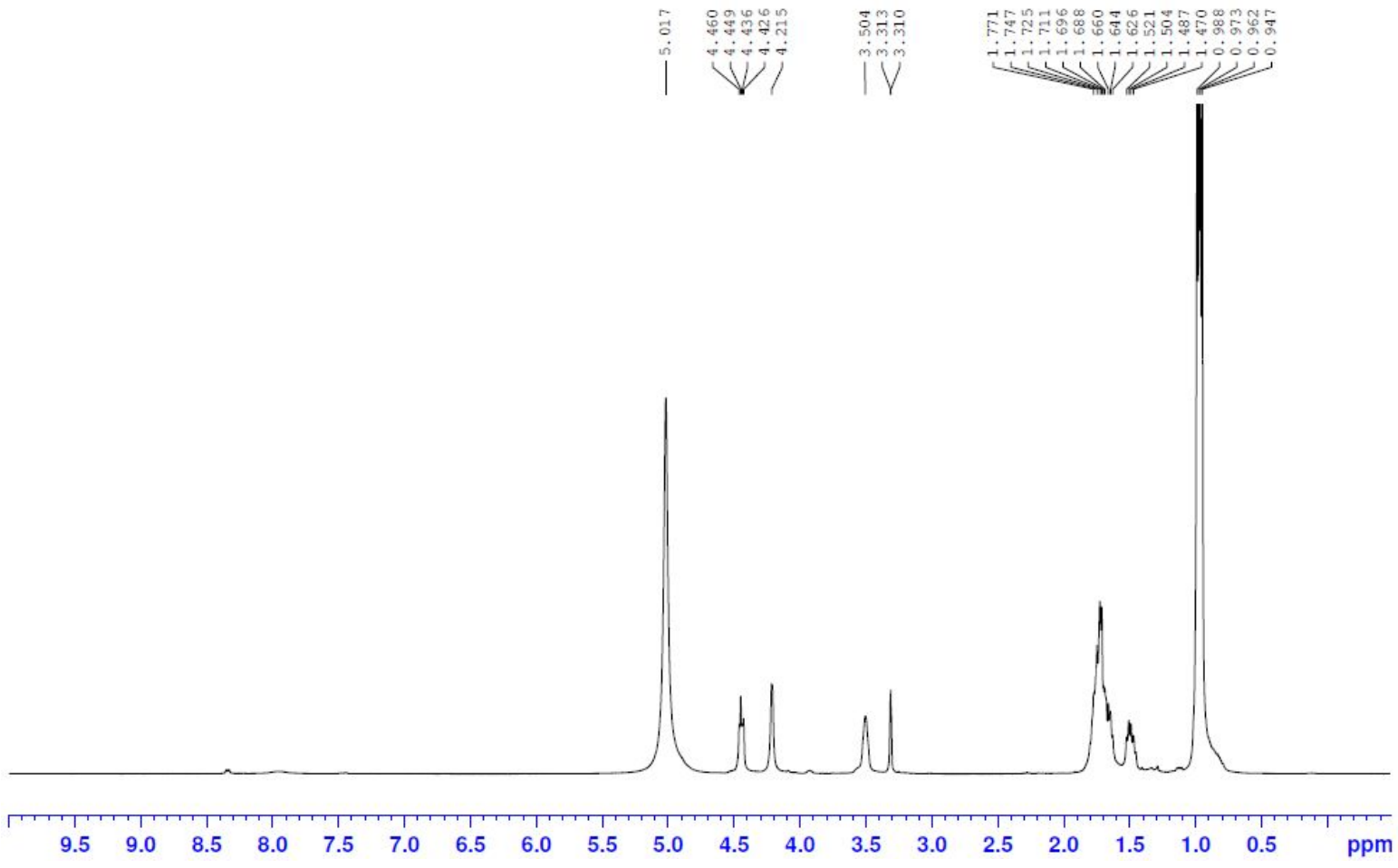
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **21b**



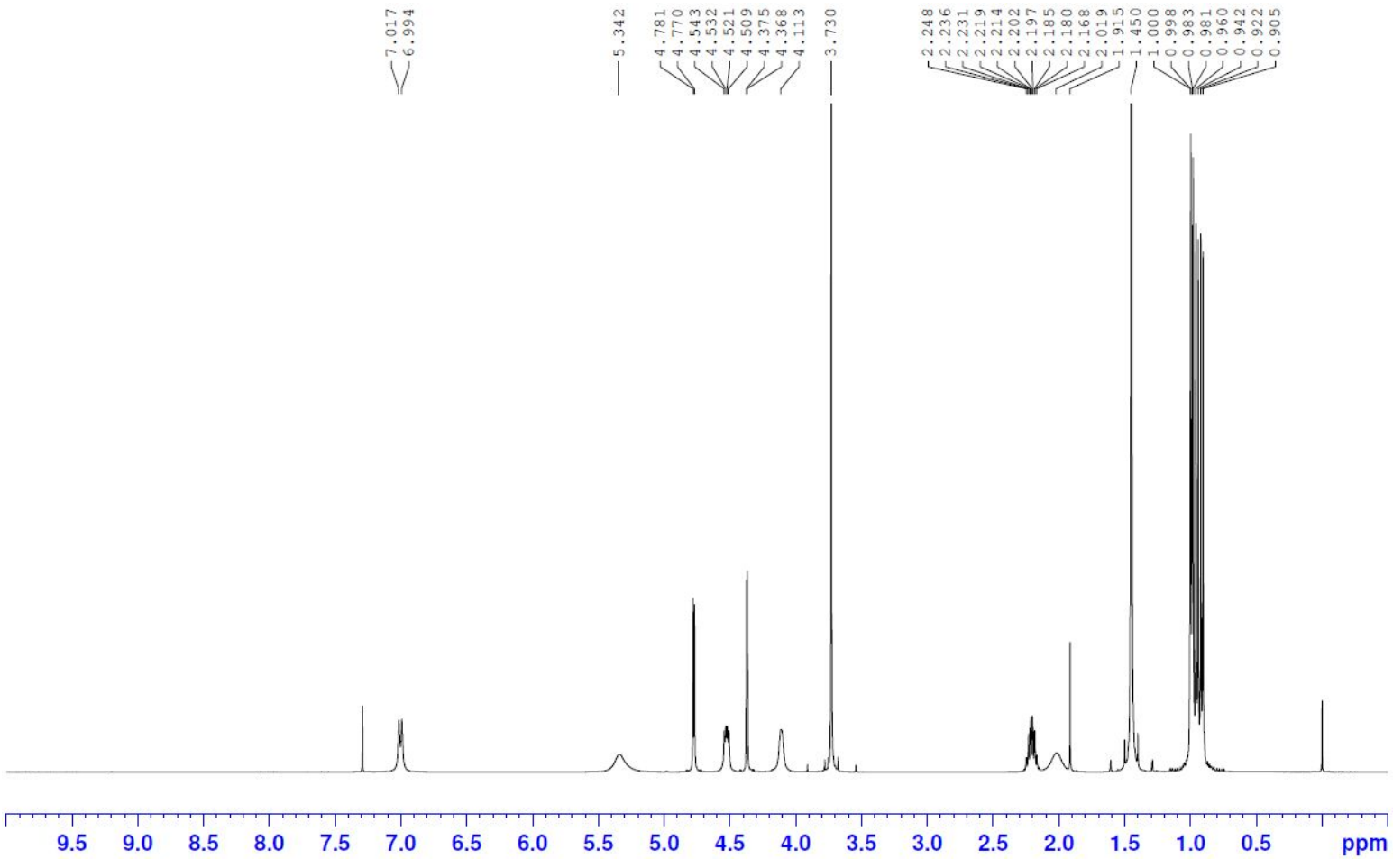
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **21c**



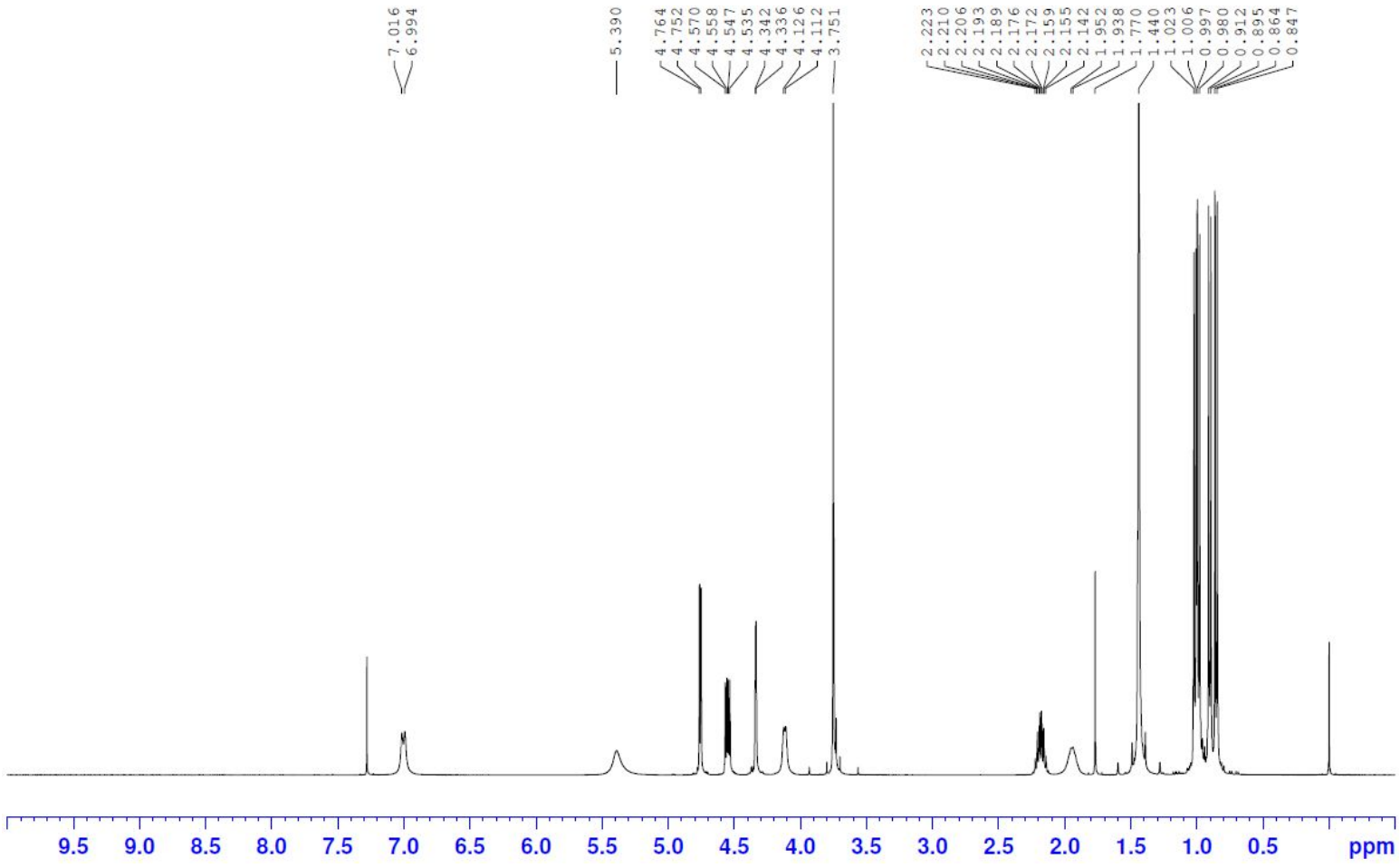
400 MHz ^{1}H NMR Spectrum (MeOH-d_6) of compound **23b**



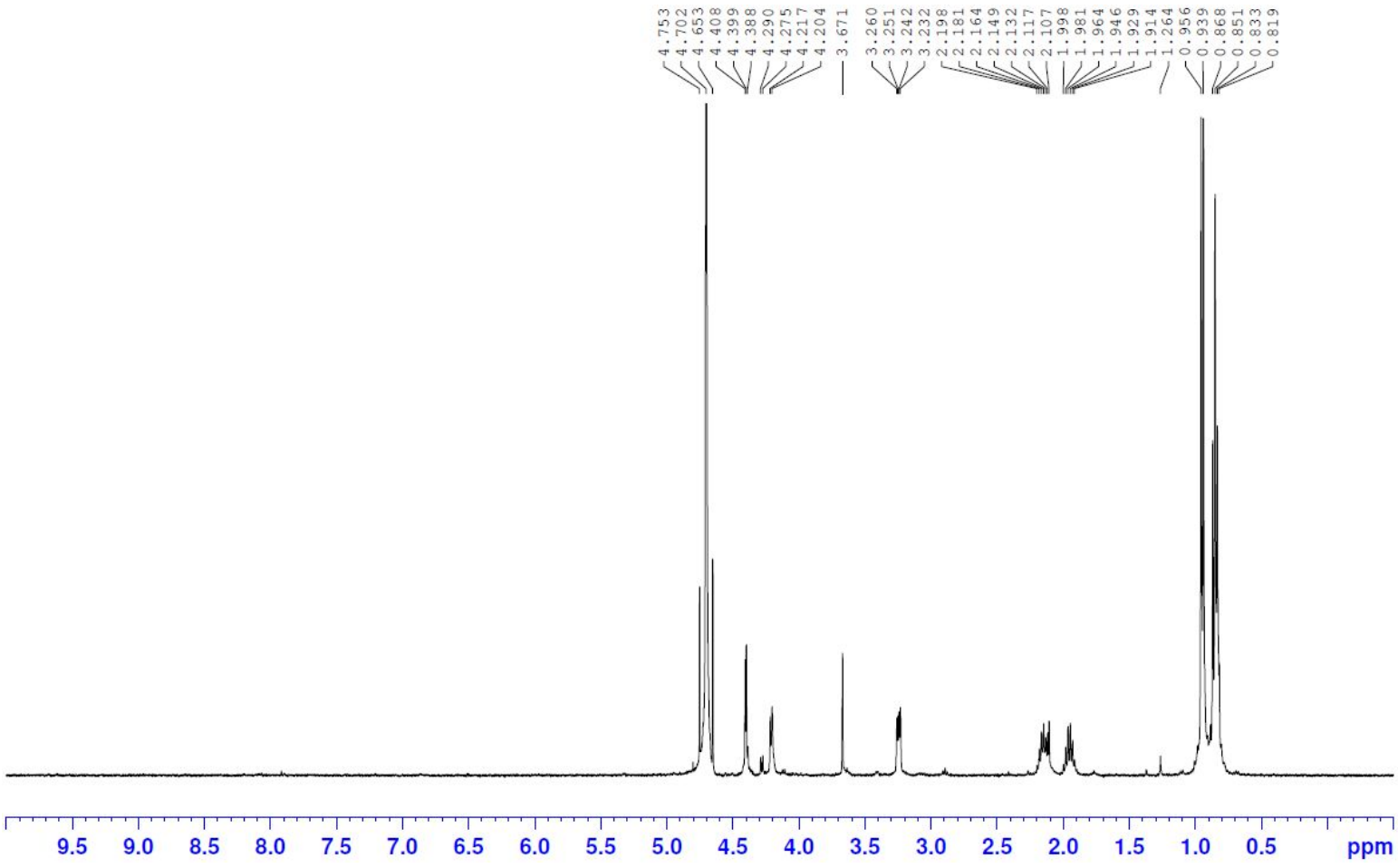
400 MHz ^{1}H NMR Spectrum (MeOH-d_6) of compound **23c**



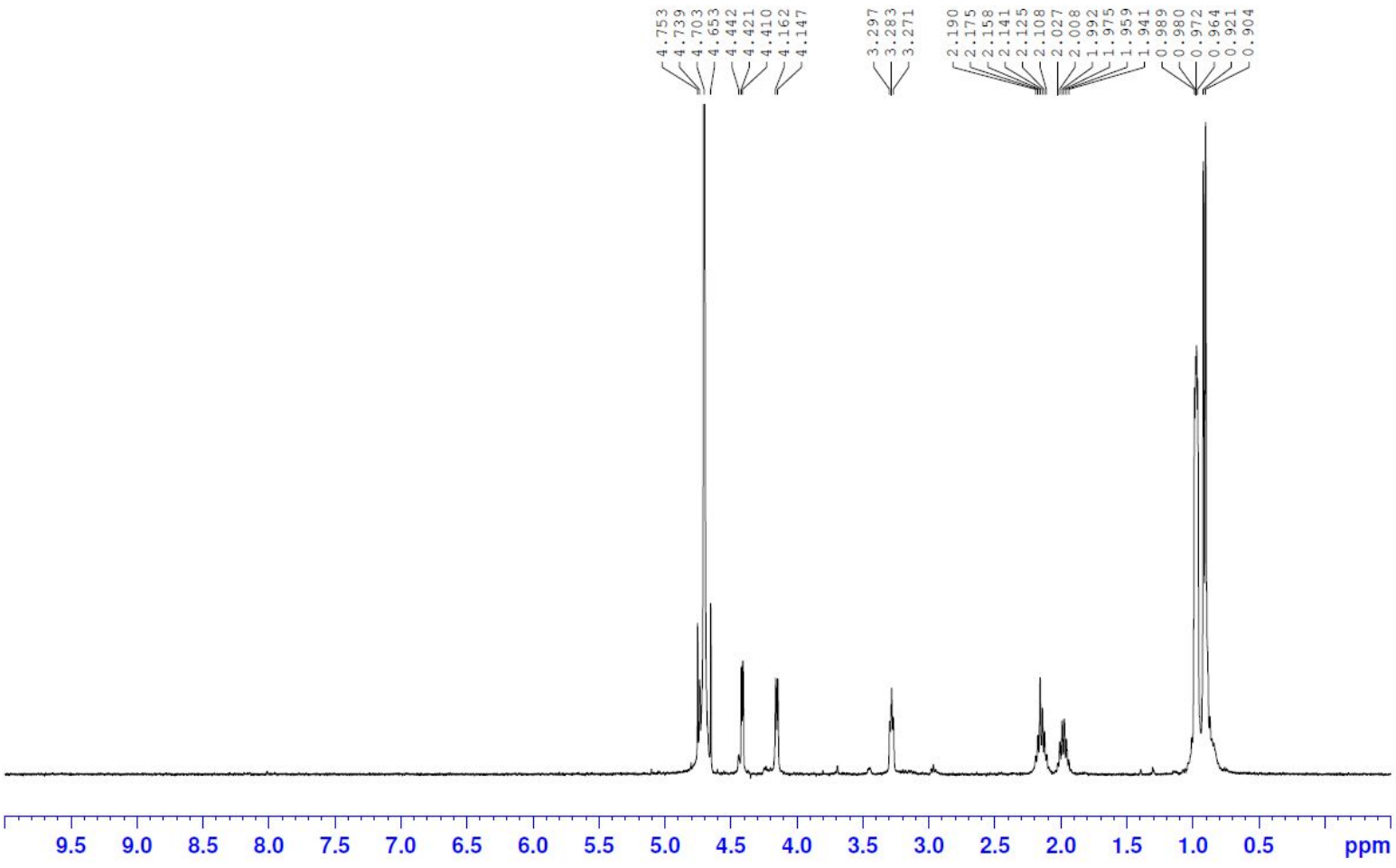
400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **24a**



400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **24b**



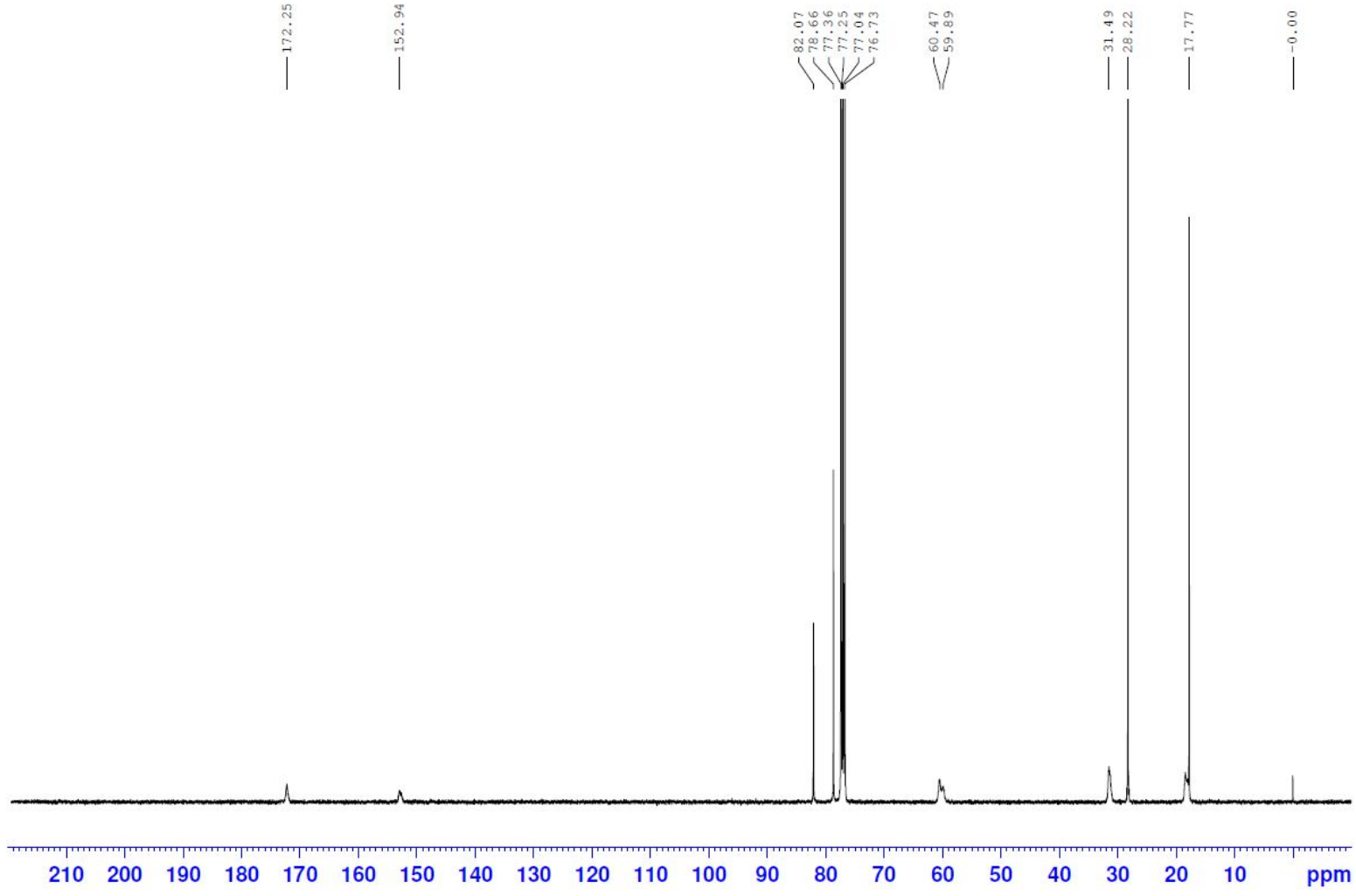
400 MHz ^{1}H NMR Spectrum (D_2O) of compound **25a**



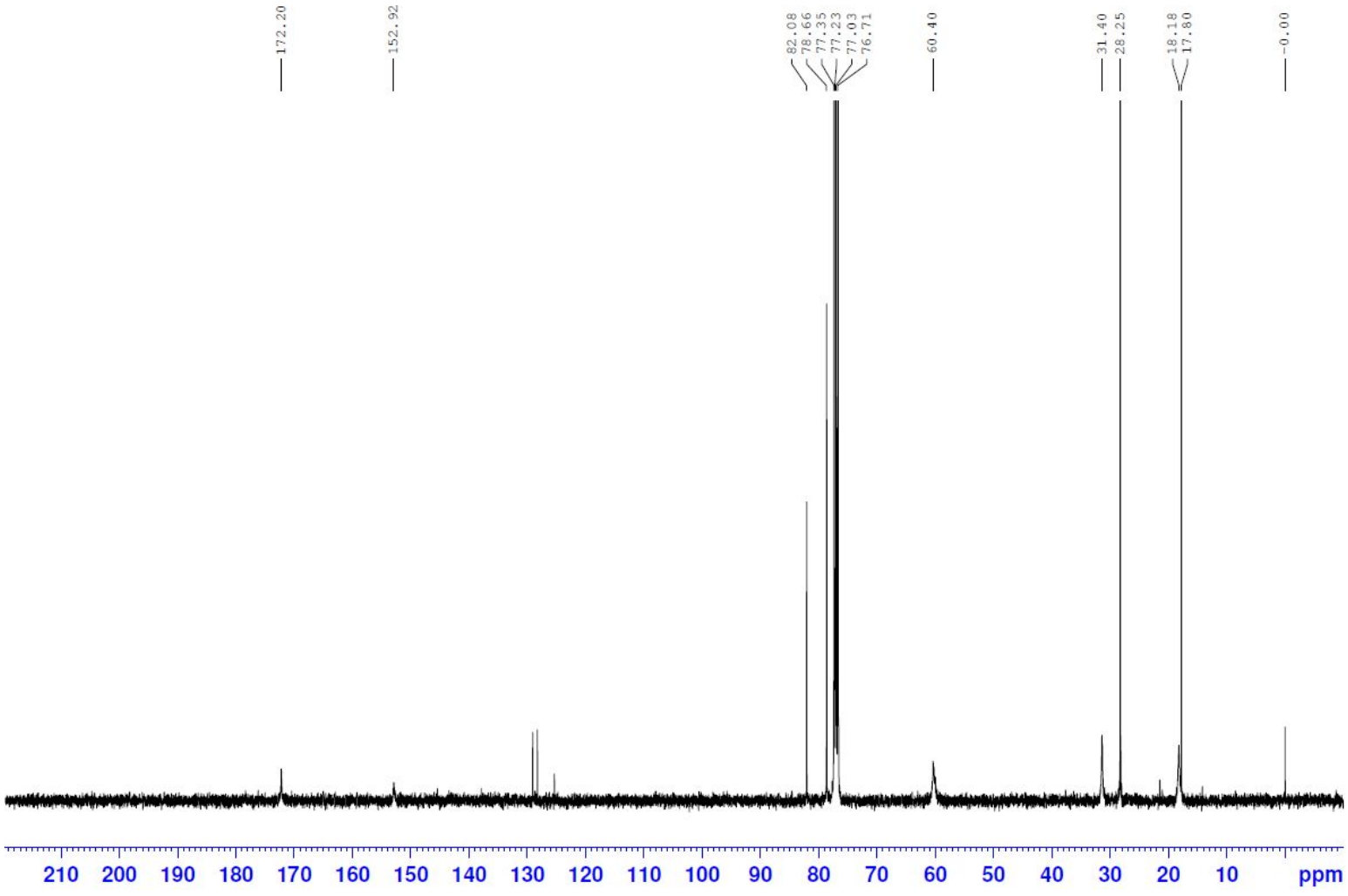
400 MHz ^{1}H NMR Spectrum (D_2O) of compound **25b**

APPENDICES

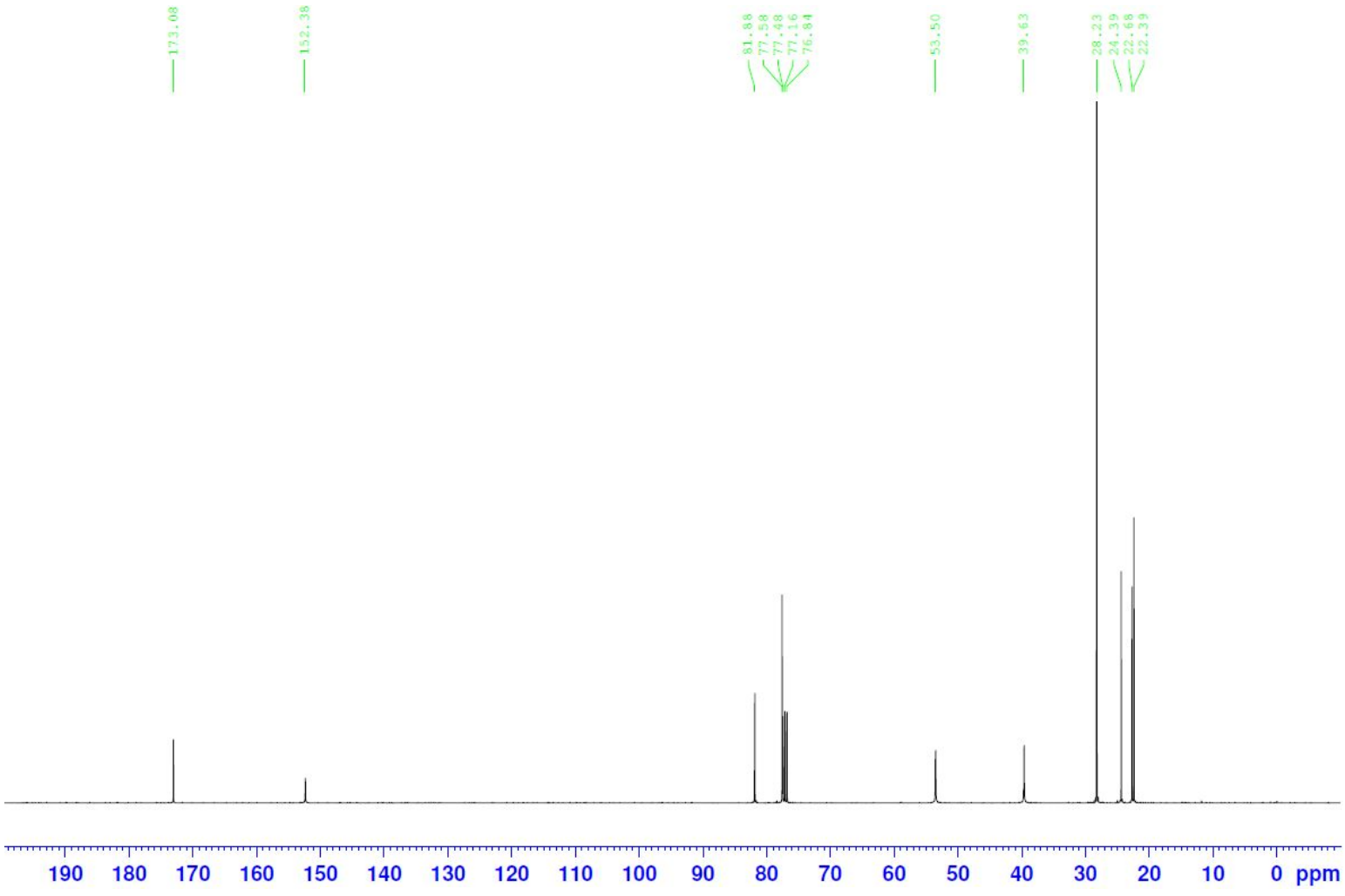
List of ^{13}C NMR Spectra of Selected Compounds



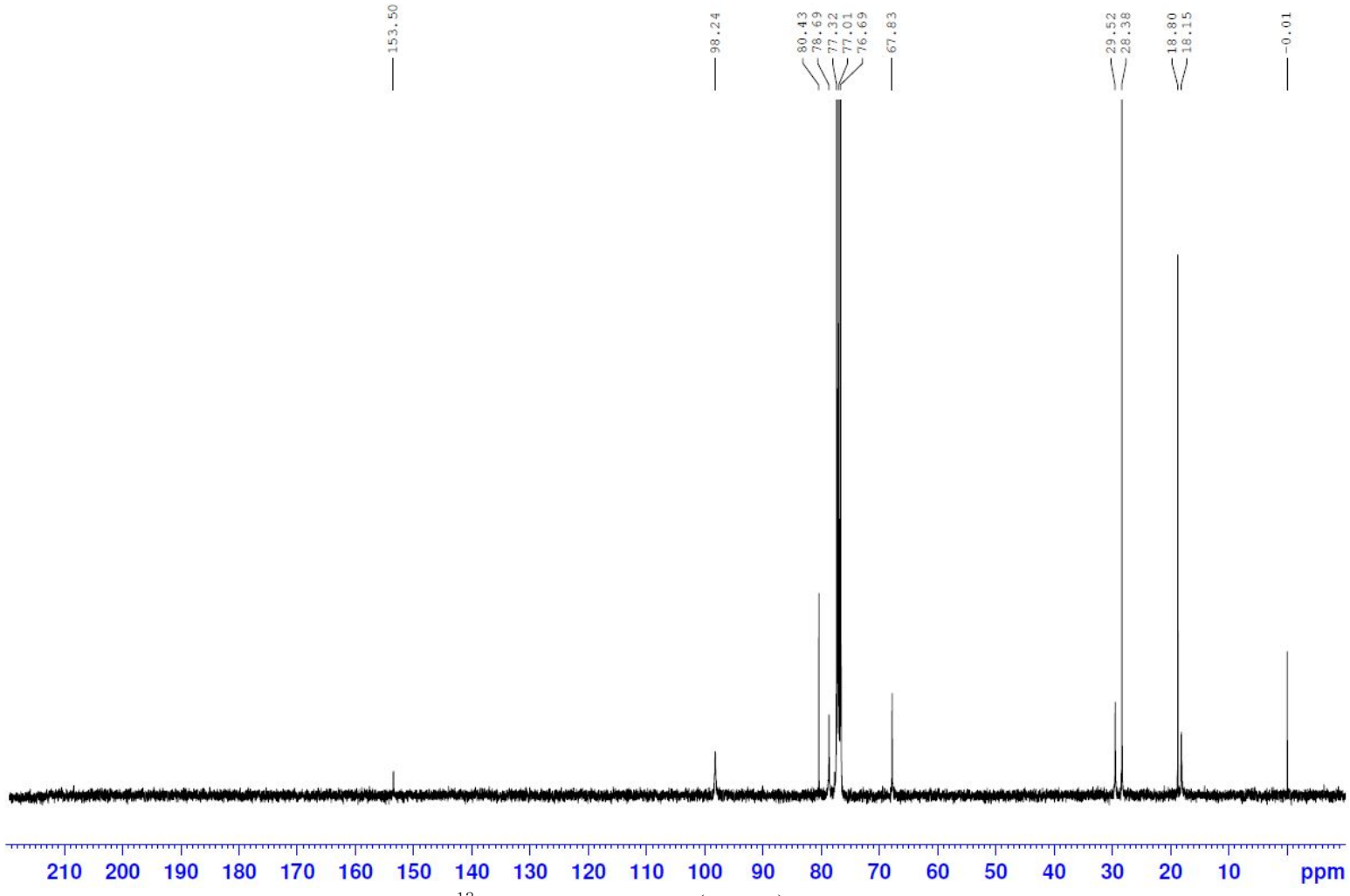
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **6a**



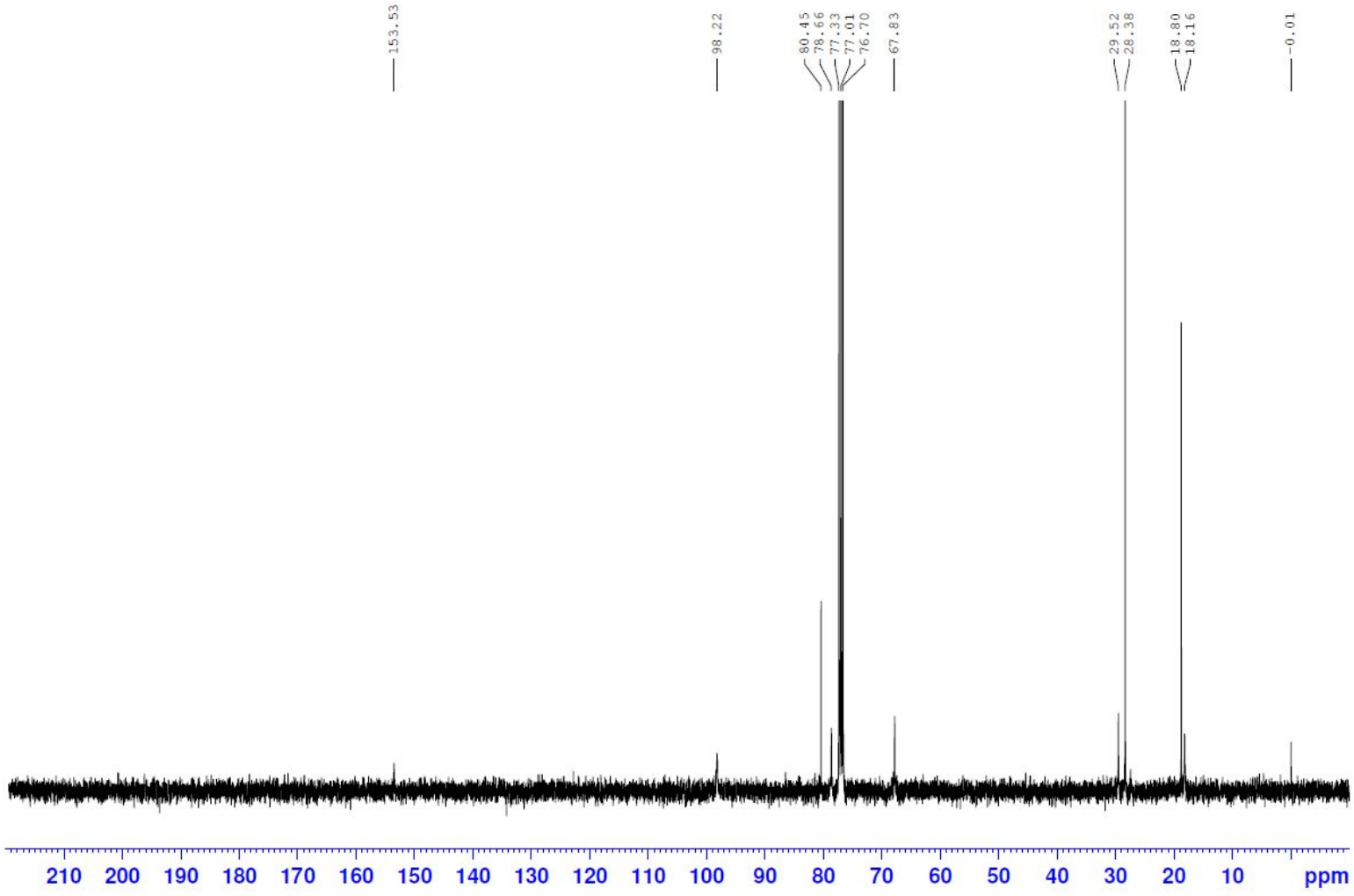
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **9a**



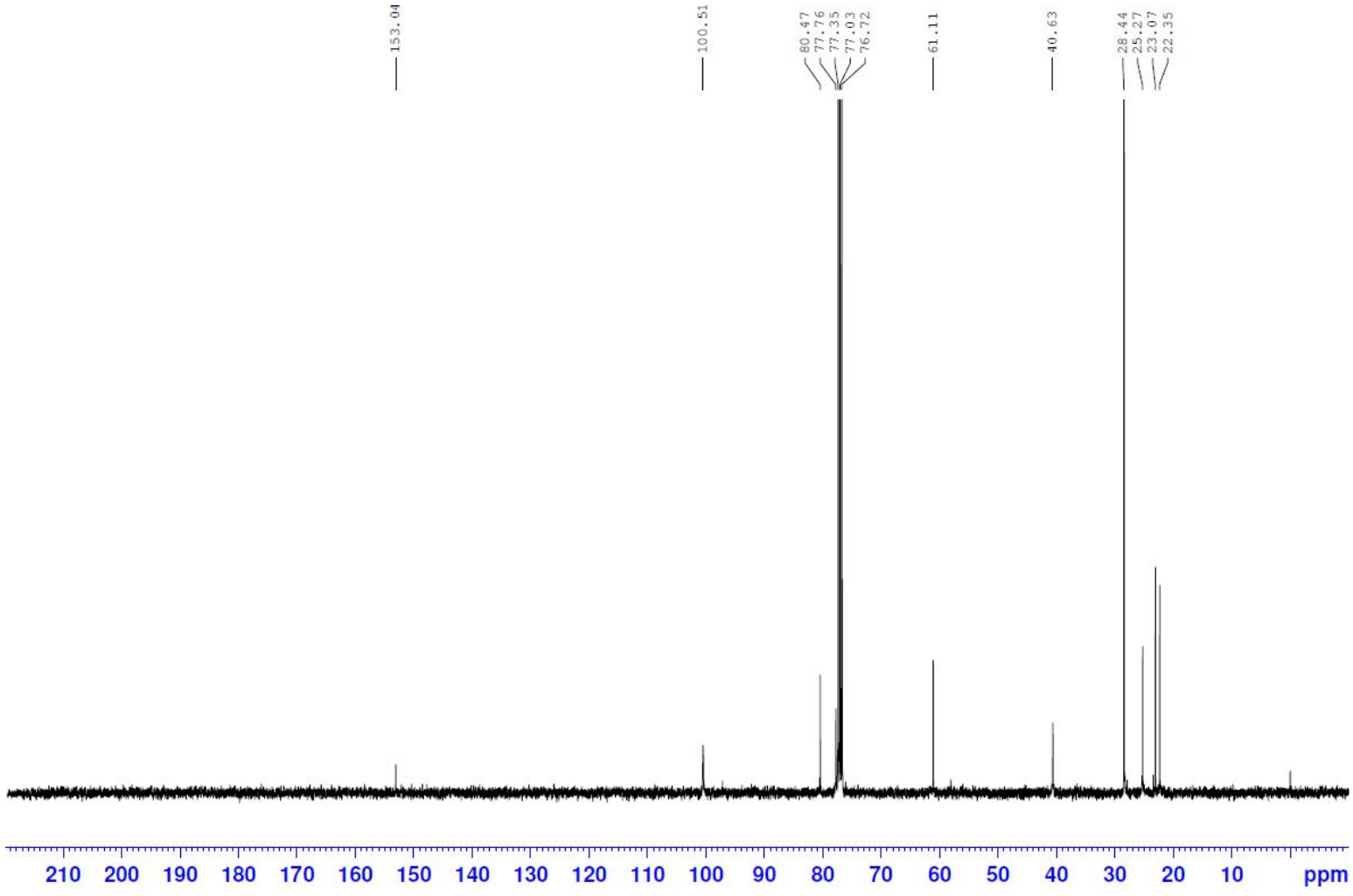
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **9b**



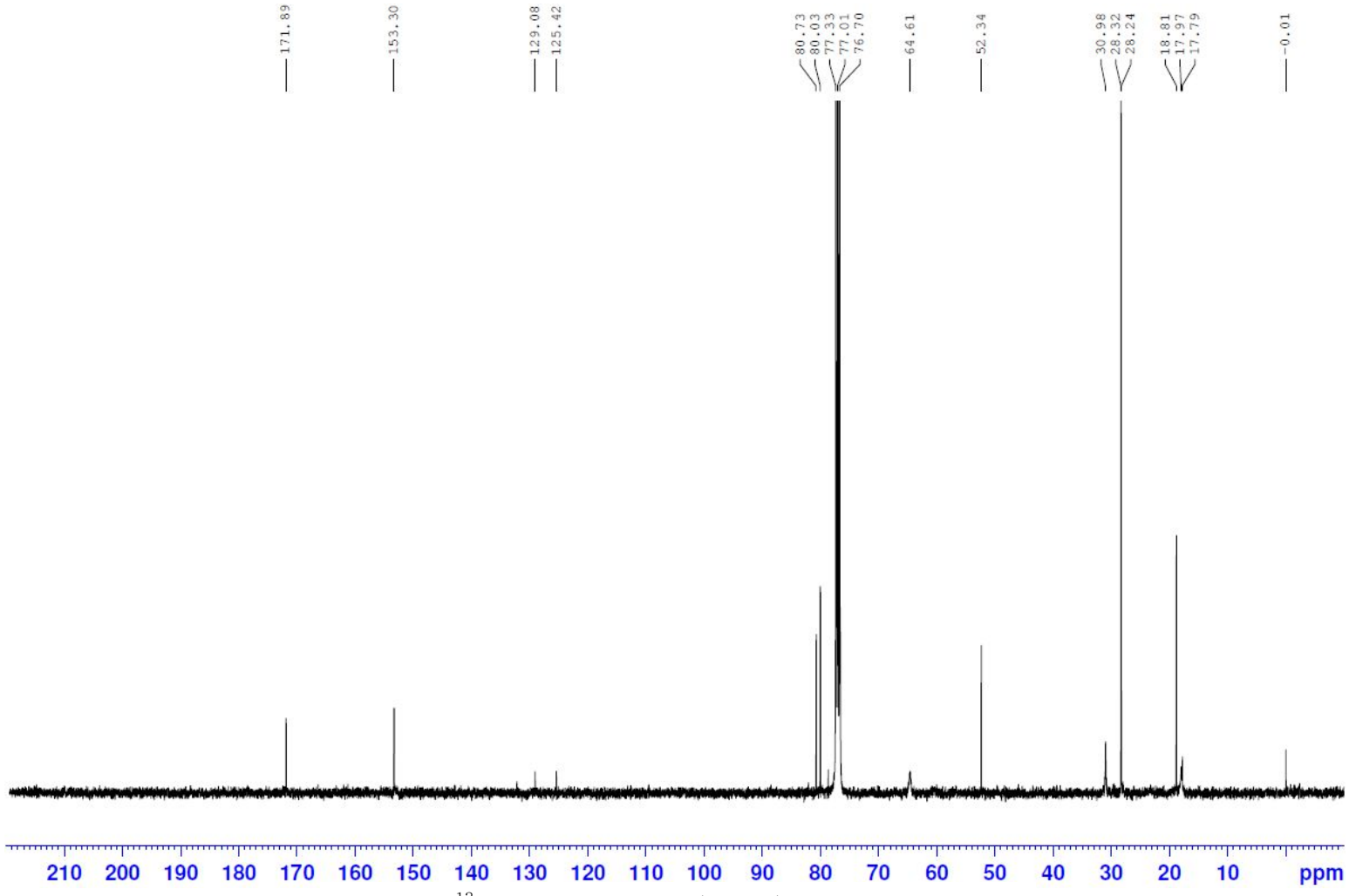
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **7a**



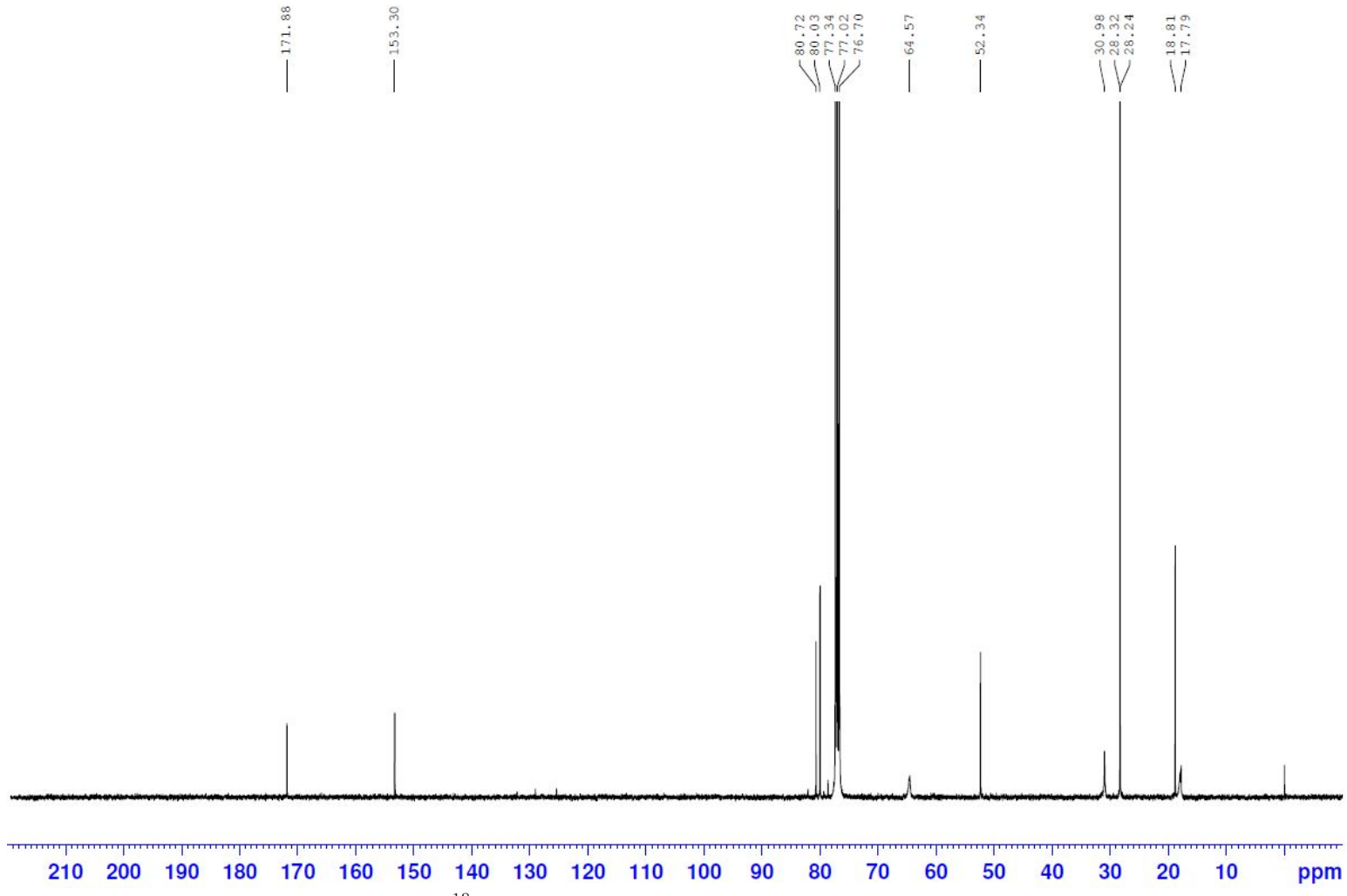
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **10a**



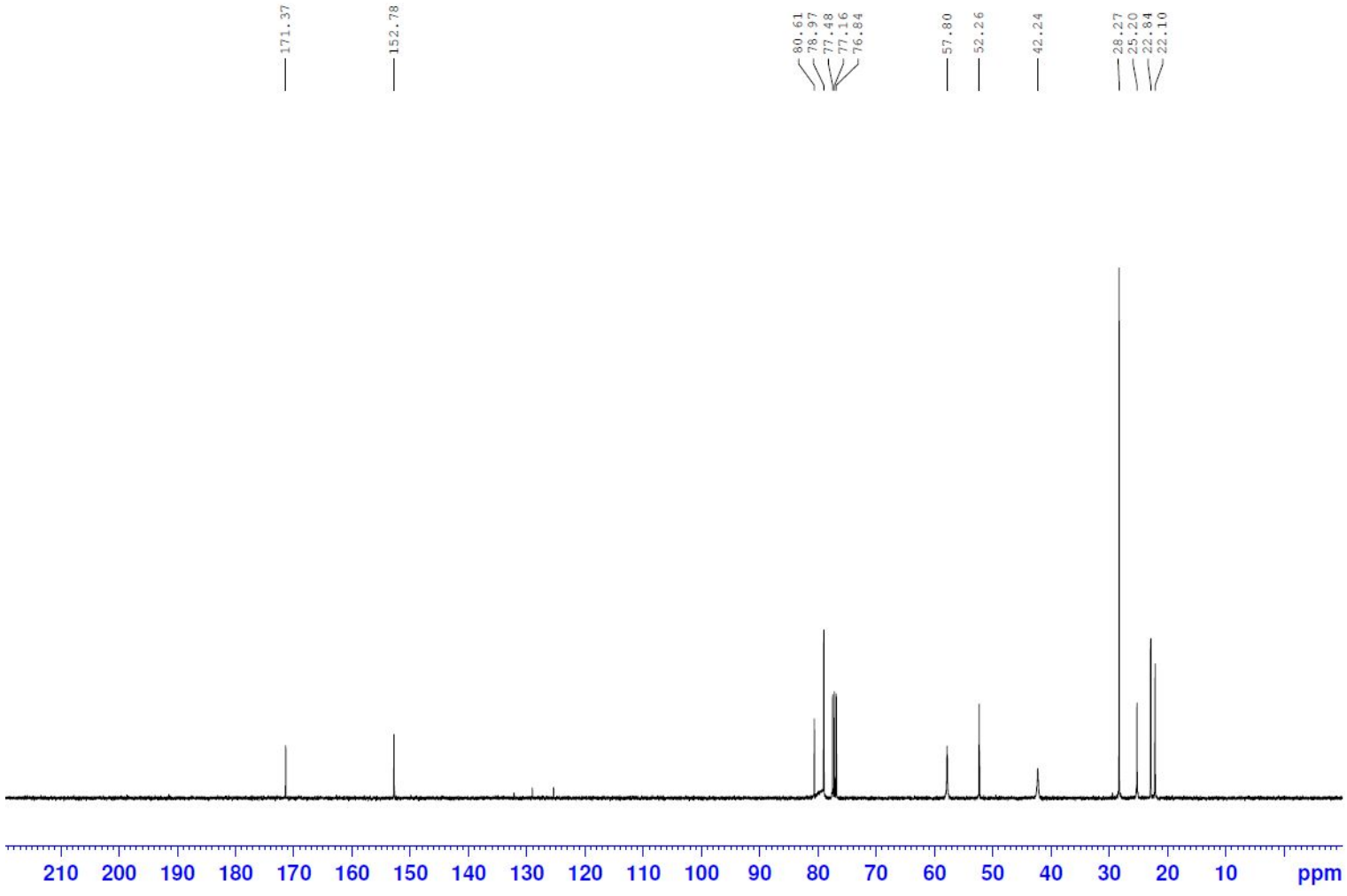
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **10b**



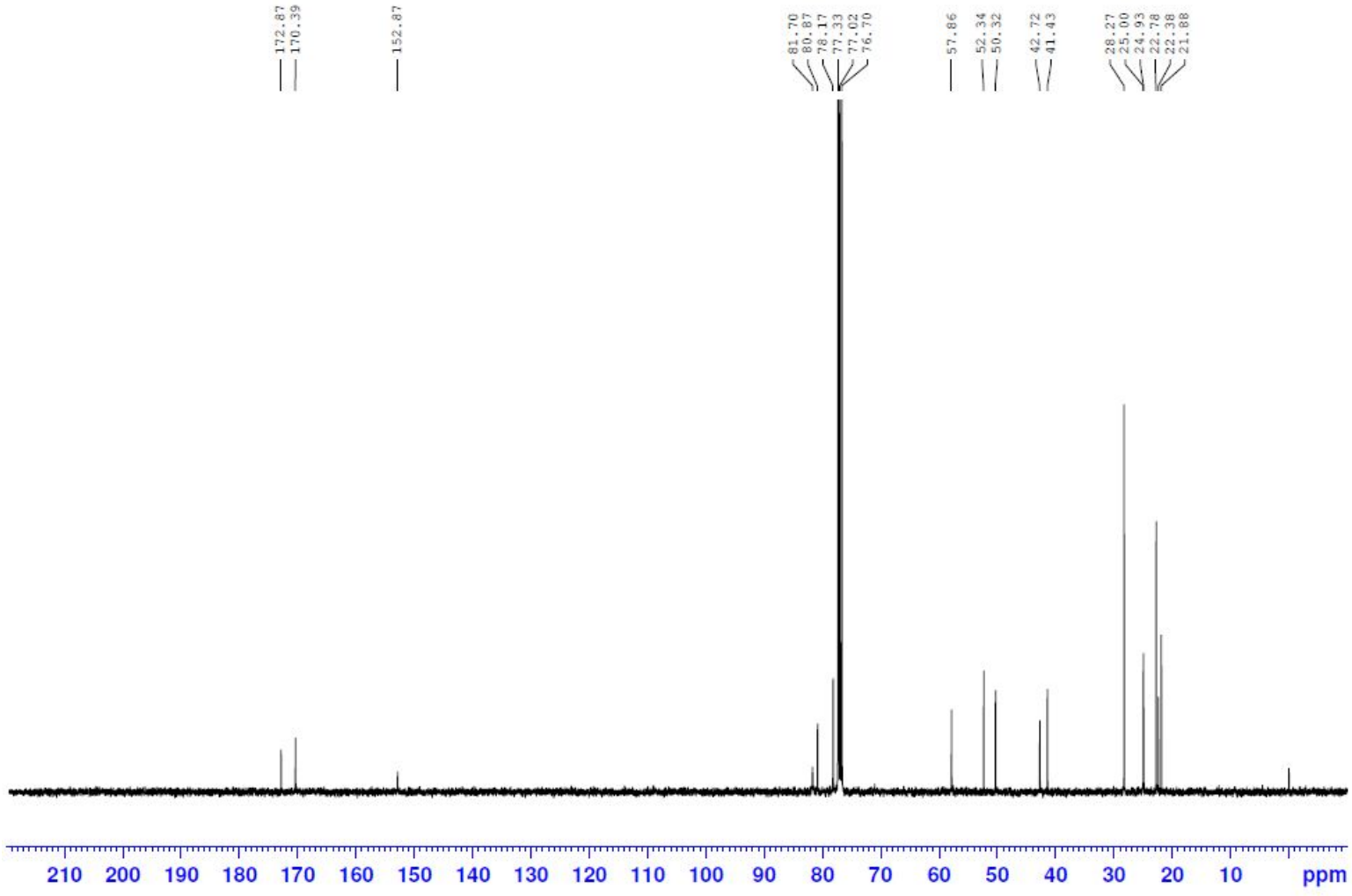
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **12a**



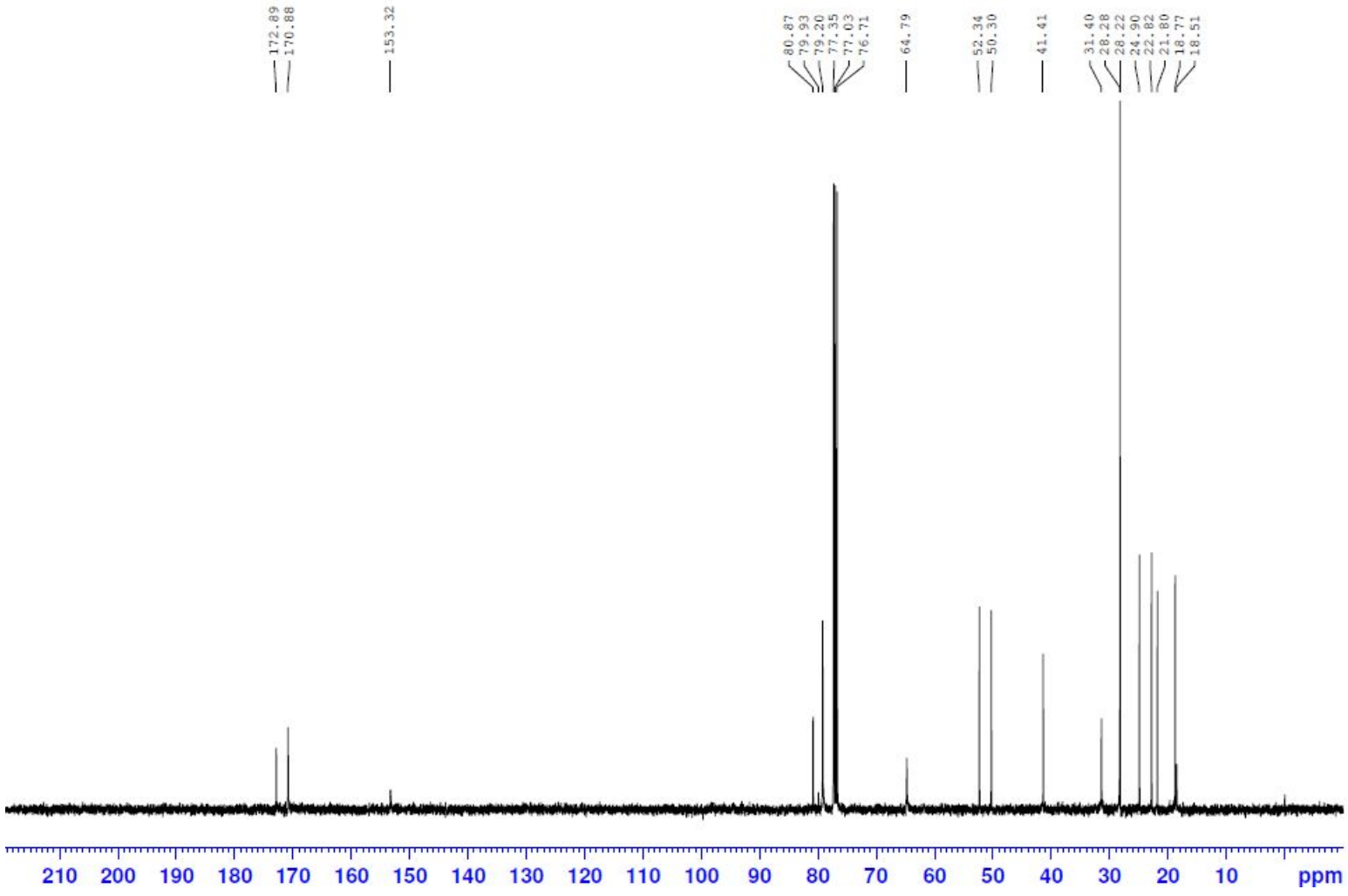
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **14a**



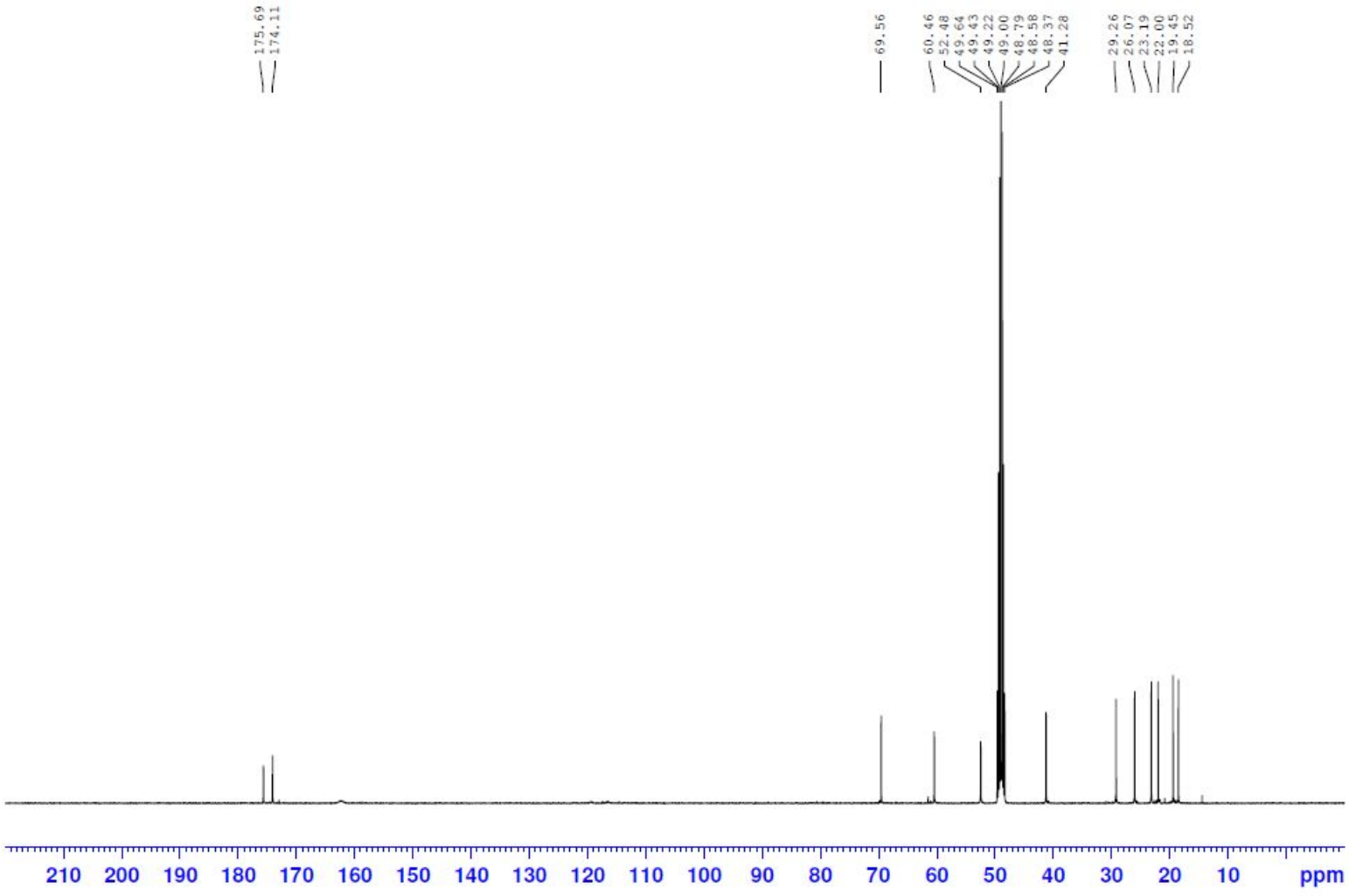
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **14b**



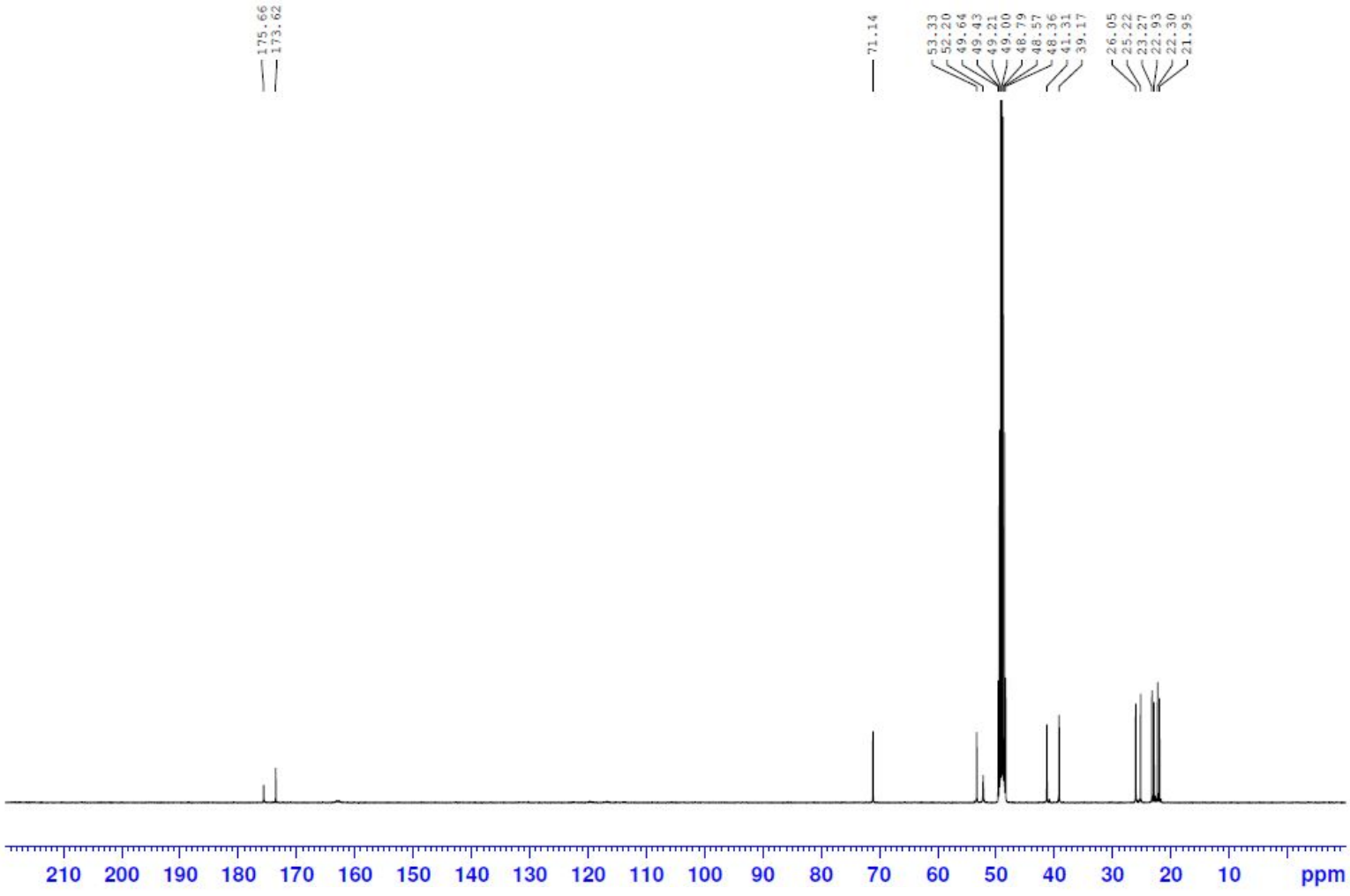
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **21b**



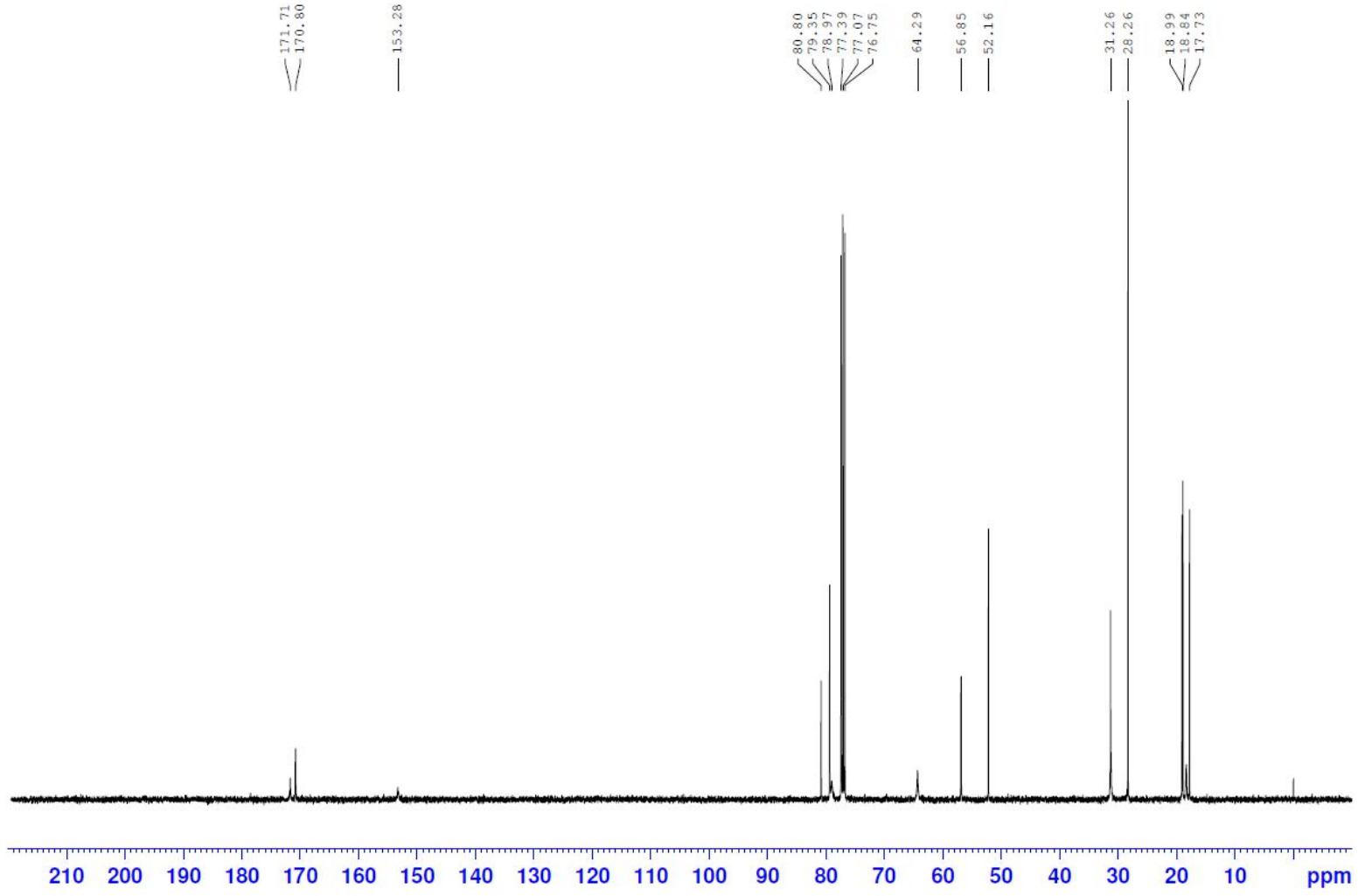
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **21c**



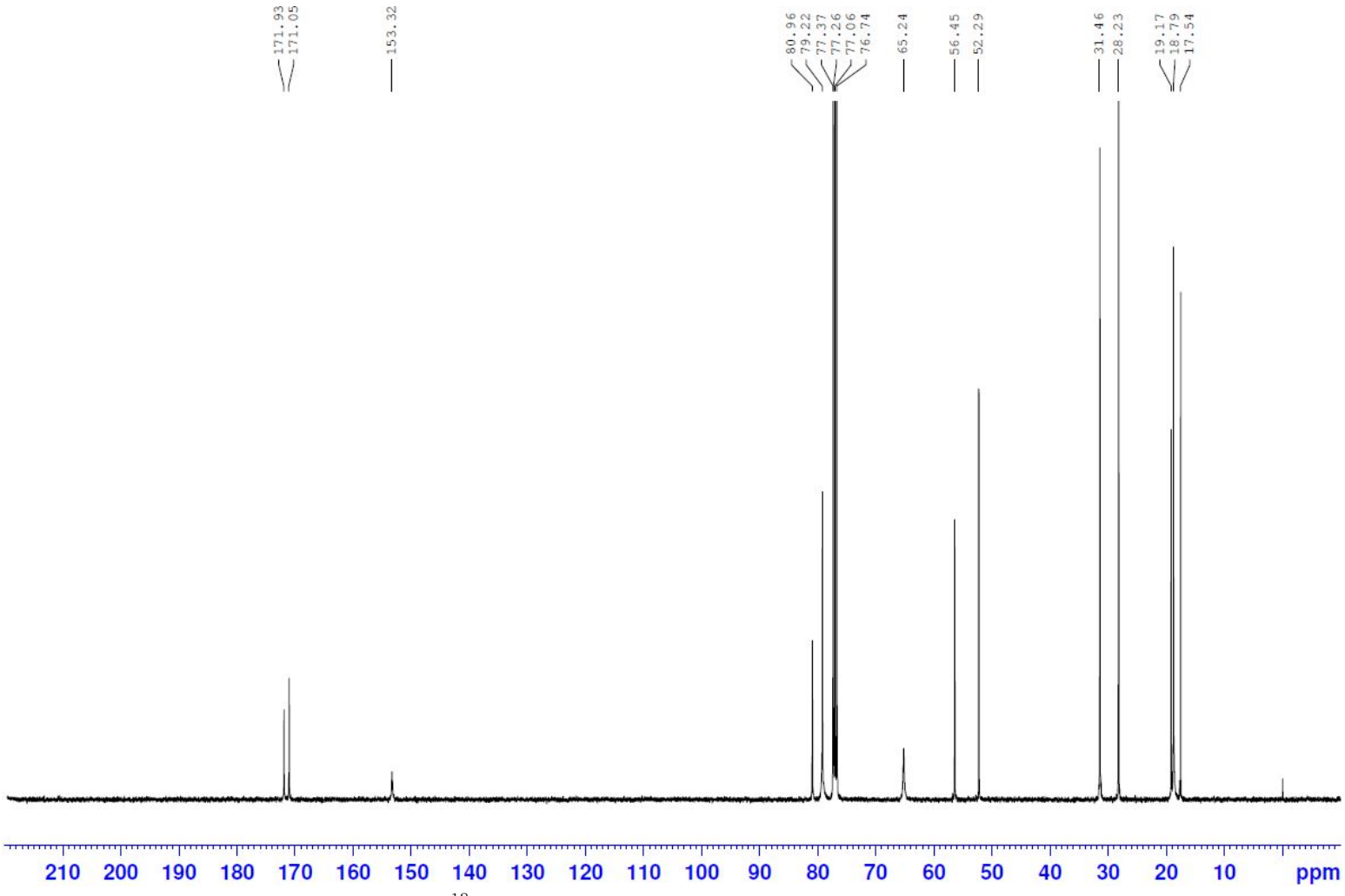
100 MHz ^{13}C NMR Spectrum (MeOH-d_6) of compound **23b**



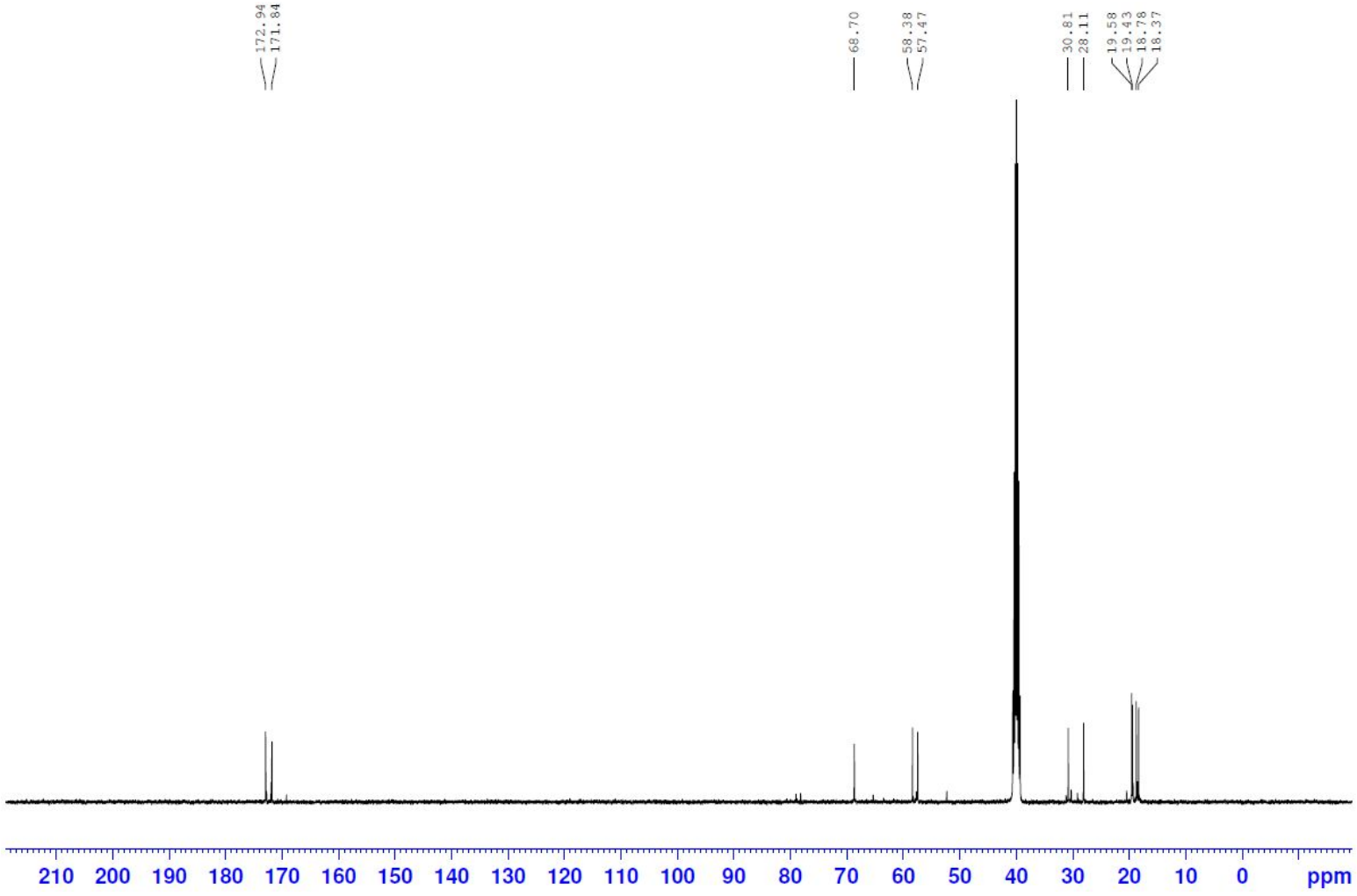
100 MHz ^{13}C NMR Spectrum (MeOH-d_6) of compound **23c**



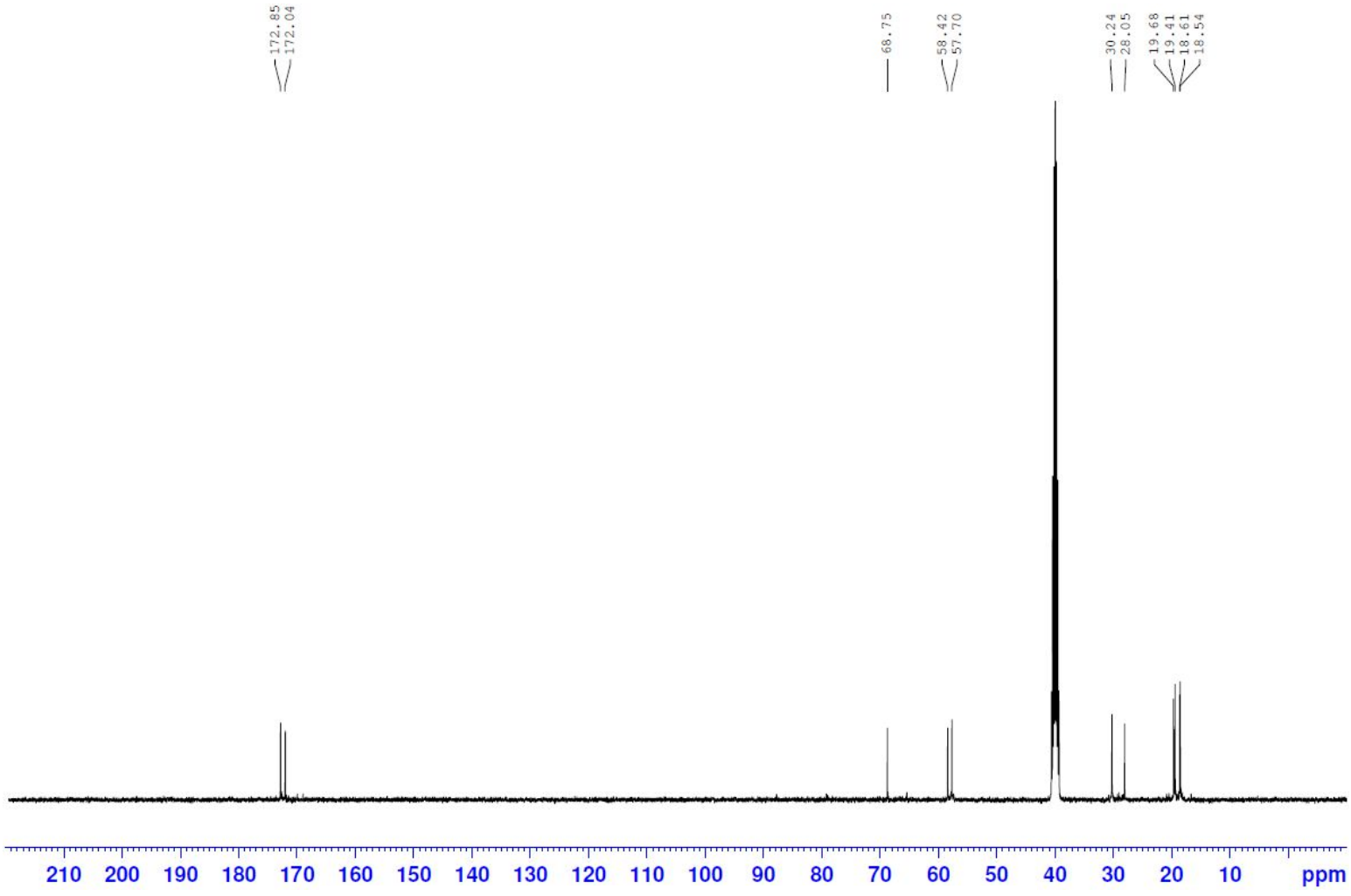
100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **24a**



100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **24b**



100 MHz ^{13}C NMR Spectrum (DMSO) of compound **25a**



100 MHz ^{13}C NMR Spectrum (DMSO) of compound **25b**

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국문 초록

단백질가수분해효소(아미노펩티다아제)는 아미노산이나 펩타이드의 말단의 가수분해를 촉진시키는 효소이다. 사람이나 동물들, 식물들에 널리 분포되어있는 이것은, 단백질의 성장이나 활성화, 호르몬의 제어 등에 필수적인 물질이다.

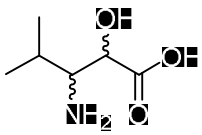
단백질가수분해효소 억제제는 단백질가수분해효소의 활성을 억제하여 종양 등 세포나 바이러스들의 부적절한 복제를 예방한다. Ubenimex라는 상표명으로 알려져있는 bestatin은 그러한 단백질가수분해효소 억제제의 한 종류로, 급성 백혈병 치료제로서 유통되고 있으며, 2-thiolbestatin이나 bestatin thioamide등, bestatin 자체 또는 그 유도체들에 대한 몇 가지 입체선택적인 합성방법이 보고되어 있다.

이미 보고되어있는 몇 가지 유도체들은 N말단에 아릴 그룹을 치환기로 가지고 있는데, 이 논문에서는 아릴 그룹 대신 알킬 그룹인 아이소뷰틸이나 아이소프로필 그룹이 치환된 유도체를 합성하였다. 이 두 가지 새로운 bestatin 유도체는 두 가지 카이랄 신톤인 D-루신과 D-발린으로부터 합성되었는데, 해당되는 β-아미노-α-하이드록시산의 전구체는 페닐설포닐나이트로메테인과 α-아미노 알데하이드의 안정한 구조인 락톨과의 분자 내 콘쥬게이션 첨가반응을 통해 합성되었다.

아이소뷰틸 그룹이 치환된 bestatin 유도체는 (2*S*,3*R*)-3-아미노-2-하이드록시-5-메틸헥사노일-L-루신의 구조를 가지고 있고, 아이소프로필

그룹이 치환된 bestatin 유도체는 (2*S*,3*R*)-3-아미노-2-하이드록시-4-메틸펜타노일-L-루신의 구조를 가지고 있으며, 이것들은 β-아미노-α-하이드록시산과 메틸 보호기가 도입된 L-루신 간의 펩타이드 커플링 반응을 통하여 합성하였다.

아미노펩티다아제 억제제의 한 종류인 lapstatin은 bestatin과 비슷한 이웃자리 아미노 알코올 구조인 3-아미노-2-하이드록시-4-메틸펜타노일-발린의 구조를 가지고 있는 것으로 알려져 있다.



3-amino-2-hydroxy-4-methylpentanoic acid

하지만 모든 입체구조가 완벽하게 밝혀진 bestatin과 다르게 lapstatin은 이웃자리 아미노 알코올의 입체구조가 아직 완벽하게 밝혀지지 않았다. 그리하여 이 논문에서는 새로운 bastatin 유도체들의 합성과 더불어, bestatin의 유도체들을 합성하던 합성법을 응용하여 lapstatin의 유도체들을 합성하고, 합성된 lapstatin 유도체들을 자연계에 존재하는 lapstatin과 비교하여 그것의 입체구조를 밝히고자 한다.

주요어 : 아미노펩티다아제, β-아미노-α-하이드록시산, 펩타이드 결합 형성, bestatin 유도체, lapstatin 유도체.

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