Design, Synthesis and Conformational Investigations of Novel Conformationally Restricted α, β-Hybrid Peptides and Hydroxyethylamine Isosteres.

A THESIS TO BE SUBMITTED TO THE

UNIVRSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

By

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CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Design, Synthesis and Conformational Investigations of Novel Conformationally Restricted α, β-Hybrid Peptides and Hydroxyethylamine Isosteres."**, submitted by **Mr. Veera Venkata Ramesh E** for the degree of **Doctor of Philosophy** was carried out by the candidate under my supervision in Organic Chemistry Division, National Chemical Laboratory, Pune, India. Materials obtained from other sources have been duly acknowledged in the thesis.

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Communications Channels ☎ +91 20 25902000 +91 20 25893300 +91 20 25893400 Fax +91 20 25902601 (Director) +91 20 25902660 (Admin.) +91 20 25902639 (Business Development) URL : www.ncl-india.o

DECLARATION

I hereby declare that the thesis entitled **"Design, Synthesis and Conformational Investigations of Novel Conformationally Restricted α, β-Hybrid Peptides and Hydroxyethylamine Isosteres."**, submitted for the Degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work has been carried out at Division of Organic Chemistry, National Chemical Laboratory, Pune under the supervision of Dr. G. J. Sanjayan (Research guide).

Date:
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Veera Venkata Ramesh E
(Research student)

Dedicated to my beloved writer "Chalam"

Acknowledgements

I wish to express my deep sense of gratitude and profound thanks to my research supervisor ***Dr. G. J. Sanjayan*** *for all the advice, guidance, support and encouragement during every stage of this work. He taught me each and every aspect of research, from working table to formulation of ideas to presentation of results. I thank him for giving me enough freedom and valuable suggestions whenever required.*

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I take this opportunity to express my heartfelt gratitude to my teachers Prof. K. Somashekara Rao, Prof. C. Rambabu, and Dr. D. Ramachandran for their encouragement and motivation during my M. Sc, and to my school teachers Mr. Prasad, Mrs. Vimala, Mr. S. Srinivas, Mr. N. Srinivas, Mr. S. Venakataratnam, Mr. Ch. Ramanjaneyulu and Mr. Ch. Adhinarayana. I am deeply indebted to them more than they know.

I would like to thank my past and present labmates Dr. Amol, Dr. Panchami, Dr. Srinivas, Dr. Pranjal, Dr. Arif, Dr. Nilesh, Dr. Kale, Dr. Pinak, Sangram, Roshna, Leena, Divya, Dhananjay, Rakesh, Chetan, Vijayadas, Tukaram, Thorat, Ganesh, Sachin, Sanjeev, Surya Bhai, Shiva, Suresh and Krishna for their cheerful company and support. Heartfelt thanks to Arup and Gowri for being with me during very sensitive phase of life.

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I owe my gratitude to Bangaraju chinnana, Satyam tata, Satyavati mama and their families for timely support and help.

I am deeply indebted to writings of Chalam (Late. Gudipati Venkata Chalam). His philosophical and spiritual writings helped me to keep and cultivate the humanity.

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Heartfelt thanks to my wife Rajani for her unconditional love and affection. Her energetic and cheerful company brought sweetness to my life and fuels me to look forward for better prospects in life. I would also like to thank my parent in-laws, Suresh, Deepa and Bhargav and lovely Abhi for their encouragement and support.

I thank CSIR, New Delhi, for the financial support and Director, N. C. L., for the infra-structural facilities.

Finally, I would like to thank all those who have contributed to the successful realization of this dissertation as well as expressing my apology that I could not mention personally one by one.

Veera Venkata Ramesh E

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Abbreviations

A

Å	Ångström
AA	Amino acid
Ac	Acyl
AcOH	Acetic acid
AcOEt	Ethyl acetate
Aib	Amino isobutyric acid
Ant	Anthranilic acid

B

Boc	tert.- Butyloxycarbonyl
bs	broad singlet (NMR)

C

$CDCl_3$	Chloroform-d
COSY	Correlated spectroscopy

D

d	doublet (NMR)
δ	Chemical shift (NMR)
DCC	*N, N'*-dicyclohexyl-carbodimide
DCM	Dichloromethane
DMF	Dimethyl formamide
DIPEA	Diisopropyl ethylamine
DMSO	Dimethylsulfoxide
4-DMAP	4-dimethyl aminopyridine
DMSO-d_6	Dimethylsulfoxide-d_6

E

ESI	Electron spray ionization
EDC	1-Ethyl-3-(3-dimethylamino -propyl)carbodiimide

G

Gly	Glycine

H

H-bond	Hydrogen bond
HMBC	Hetero Multiple Bond Correlation
HBTU	O-benzotriazol-1-yl-N,N, N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
HSQC	Hetero Nuclear Single Quantum Coherence
Hz	Hertz

L

LC-MS	Liquid chromatography-mass spectrometry

M

MALDI	Matrix-Assisted Laser Desorption Ionization
m	multiplet (NMR)
MS	Molecular Sieves
Me	Methyl

N

NOESY	Nuclear Overhauser and Exchange Spectroscopy

Q

q	quartet (NMR)

P

Ph	Phenyl
Pro	Proline
Pd-C	palladium 10 % on activated carbon

S

s	Singlet (NMR)
$SnCl_2$	Stanous chloride

T

TFA	Trifluroacetic acid
HBTU	O-benzotriazol-1-yl-N,N, N',N'-tetramethyluronium tetrafluoroborate
TEA	Triethyl amine
THF	Tetrahydrofuran
t	triplet (NMR)

ABSTRACT

Name of the Candidate	**Veera Venkata Ramesh E**
Name of the Research Guide	**Dr. G. J. Sanjayan**
Title of the Ph. D. thesis	**Design, Synthesis and Conformational Investigations of Novel Conformationally Restricted α, β-Hybrid Peptides and Hydroxyethylamine Isosteres.**

Chapter 1: The work described in this chapter dwells up on our extensive efforts expended towards understanding the folding pattern observed in Ant (anthranilic acid)-rich synthetic peptides. The results suggest how individual folds of different structural features can "symbiotically" act in stabilizing peptide folding. The folding propensities, unusual hydrogen-bonded networks and their symbiotic stabilizing relationships were extensively investigated by 2D NOESY and by single crystal X-ray diffraction studies.

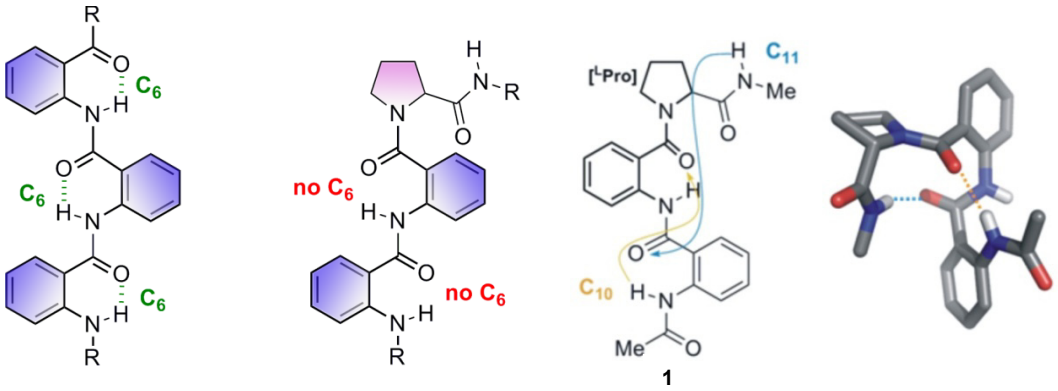


Fig. 1: Molecular structures of Ant oligomers and AcNH-Ant-Ant-^{L}Pro-NHMe **1** with its observed hydrogen-bonding pattern, as deduced from crystal structure.

This part also describes the importance of N- and C-terminal hydrogen-bond donors in stabilizing the entire peptide fold as observed in **1**. Structural investigations of the analogs **2**, **3**, **4** (Fig. 2) lacking H-bond donor at N-terminus and the analog **5** lacking hydrogen-bond donor at C-terminus, suggest unequivocally that N- and C-terminal hydrogen-bond donors are essential for maintaining the doubly folded conformation observed in **1** (Fig. 1). These findings would have a bearing on the fundamental understanding of the importance of individual contributions of non-covalent stabilizing and destabilizing interactions in peptide folding.

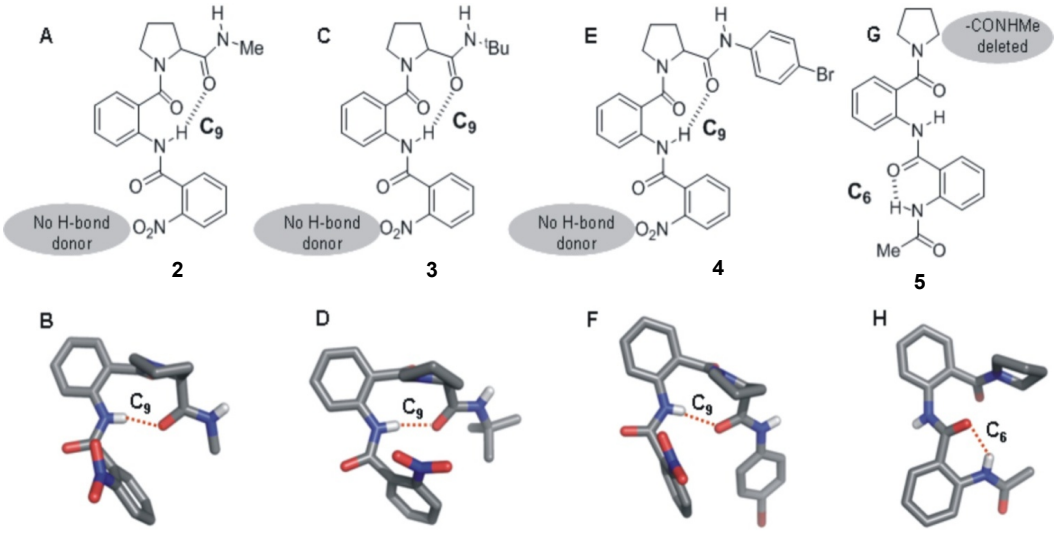


Fig. 2: Molecular and crystal structures of **2** (A,B), **3** (C,D), **4** (E,F) and **5** (G,H), respectively. *Note*: the observed H-bonding pattern has been highlighted in the molecular structures. Structural changes, as compared to **1**, have been highlighted in the molecular structures of **2**-**5**.

[Multifaceted folding in a foldamer featuring highly cooperative folds.
Ramesh, V. V. E.; Priya. G.; Kotmale, A. S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. *Chem. Commun.* **2012**, *48*, 11205-11207]

This part also describes the effect of N-terminal hydrogen-bond donor and acceptor in the C_9 turn (Sanjayan *et. al.*, *J. Am. Chem. Soc.*, **2008**, *130*, 17743-17754) modulations. It has been found that the synthetic peptides lacking hydrogen-bond donor ability at N-terminus display a typical C_9 turn. However, synthetic peptides having OH as hydrogen-bond donor group at N-terminus display a typical C_6-hydrogen-bonding (Fig. 3). It is noteworthy that the hydrogen-bonding observed in **7** is in contrast to twin folded conformation observed for **1** having hydrogen-bond donor as Ac-NH group at N-terminus.

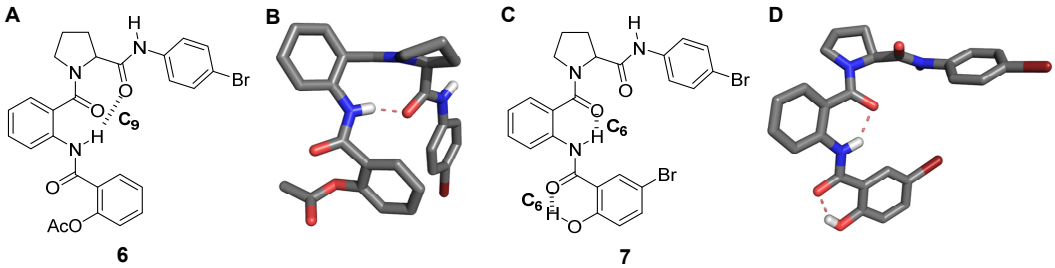


Fig. 3: Molecular and crystal structures of **6** (A,B), and **7** (C,D), respectively.

[Manifestation of remote hydrogen bonding folding interactions in C_9 turn Modulations.
Ramesh, V. V. E.; Kale, S. S.; Kotmale, A. S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. (*Manuscript under preparation*)]

The second part of this chapter describes foldamers featuring $^{L/D}$Pro-Ant-Ant-$^{L/D}$Pro repeating sequences. It has been found that the tetrapeptide building blocks with homochirality sequences **8** and **11** assume a folded structure featuring the typical C_9 turn. Intriguingly, the mixed chirality sequences **9** and **10** have been shown to be devoid of C_9 turn (Fig. 4).

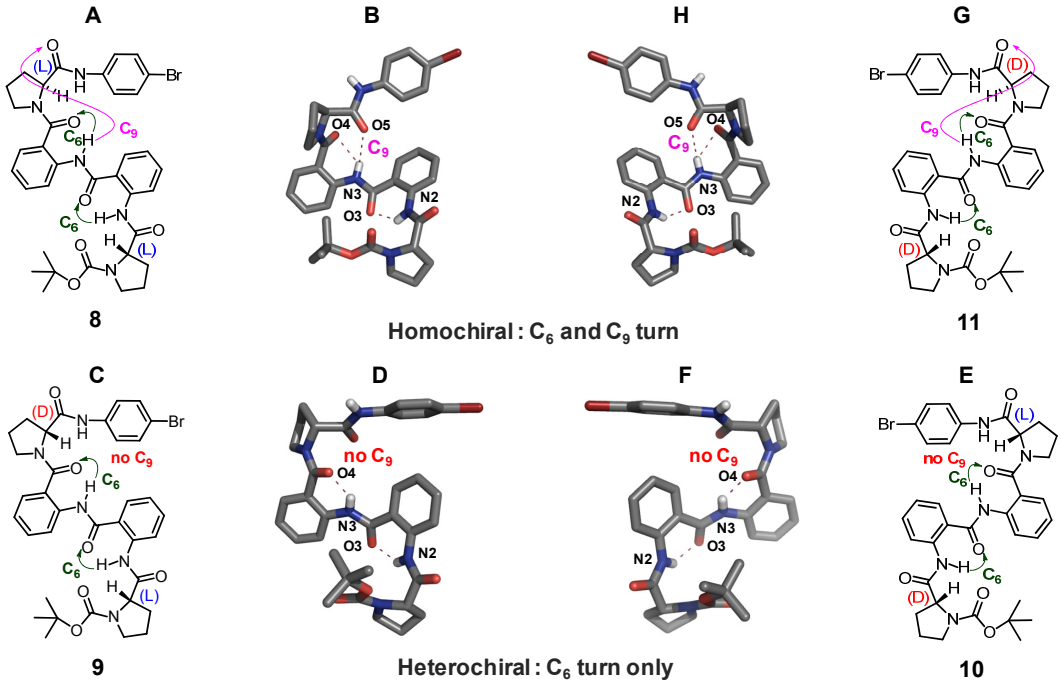


Fig. 4: Molecular and crystal structures of **8** (A,B), **9** (C,D), **10** (E,F) and **11** (G,H), respectively.

[Switching the hydrogen-bonding network of a foldamer motif by backbone chirality alteration.
Ramesh, V. V. E.; Vijayadas, K. N.; Dhokale, S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. (*Manuscript under preparation*)]

Chapter 2: This chapter deals with the design, synthesis and the conformational studies of hybrid peptides using natural and unnatural amino acids.

The first part of this chapter describes about the design, synthesis and conformational studies of foldamers featuring 2-aminomethylbenzoic acid (2-Amb) and proline (Pro) building blocks. These oligomers adopt right-handed helical structural architecture with C_{12} hydrogen-bonding network as evident from *ab initio* molecular modeling and solution-state (NMR) studies.

[Expanding the structural repertoire of β/α Ant-Pro (anthranilic acid-proline) oligomers into γ/α 2-Amb-Pro (2-aminomethyl benzoic acid-proline) oligomers. **Ramesh, V. V. E.**; Priya, G.; Rajamohanan, P. R.; Hoffman, H.-J.; Sanjayan, G. J. *Tetrahedron* **2012**, *68*, 4399-4405. (*Special issue on Chemistry of Foldamers*)]

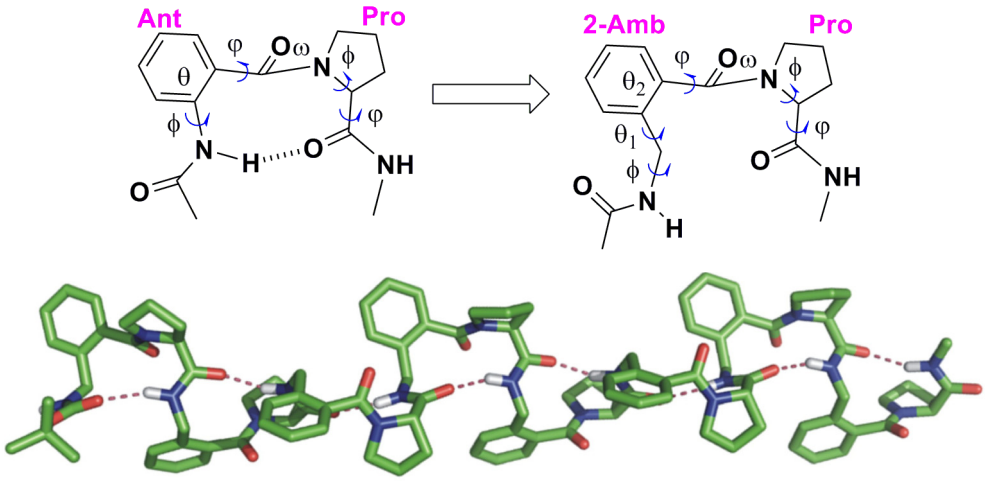


Fig. 5: Design strategy (top) and *ab initio* model (bottom) of -[2-Amb-Pro]$_n$-.

The second part of chapter 2 describes foldamers with Pro-Ant-Aib repeating sequence. Due to the conformational rigidity of the individual amino acid residues, the oligomers made of the tripeptide building block Pro-Ant-Aib assume rigid conformation, as evident from extensive conformational studies carried out in both solid-state (crystal structure) and solution-state (NMR) studies. Synthesis of oligomers, as large as dodecamer has been carried out in the solution-state.

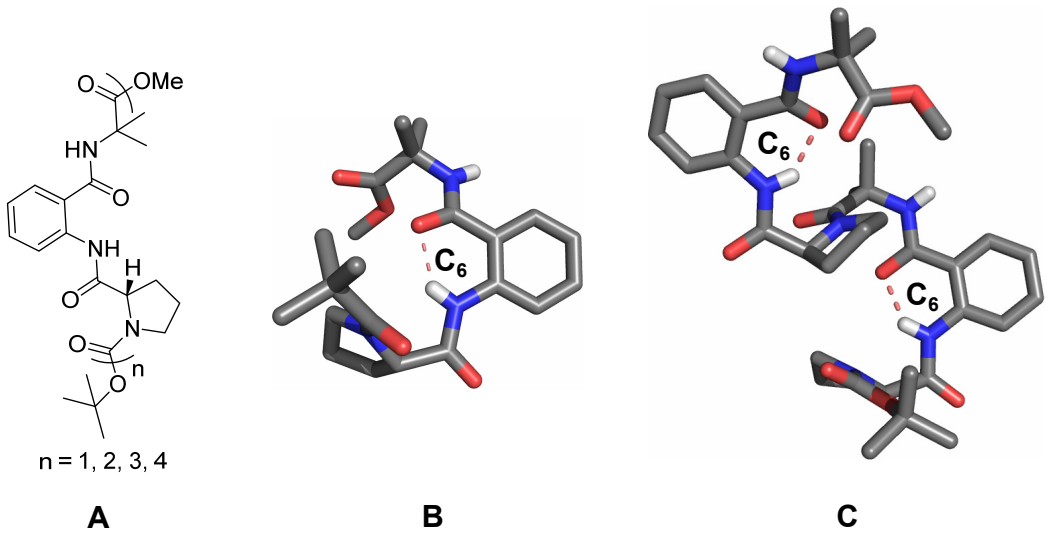
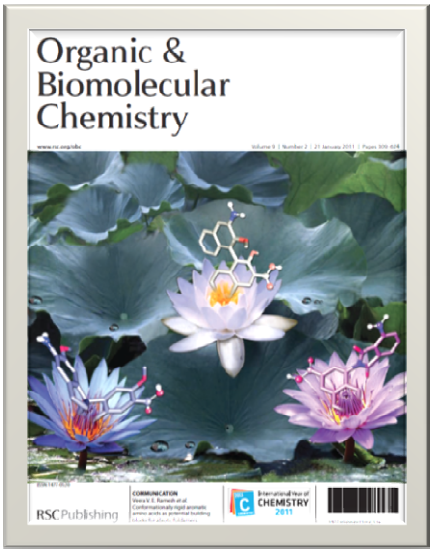


Figure 5: Molecular structure of -(Pro-Ant-Aib)$_n$- oligomers (A), crystal structures of tripeptide (B) and hexapeptide (C).

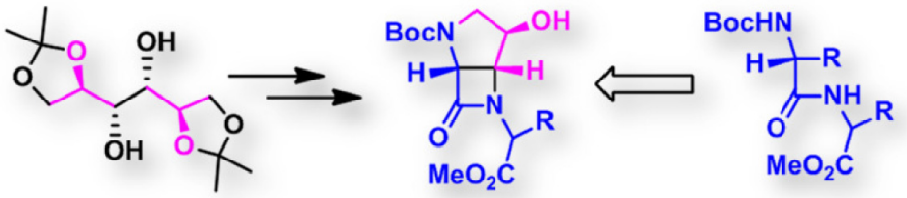
[Carboxamide *vs* sulfonamide in peptide backbone folding: a case study with a synthetic oligomer.
Ramesh, V. V. E.; Kale, S. S.; Kotmale, A. S.; Gawade, R. L.; Puranik, V. G.; Rajamohanan, P. R.; Sanjayan, G. J. *Org. Lett.* **2013**, *Just Accepted*]

Chapter 3: Heterogeneous building blocks, useful for the generation of foldamers with intriguing conformational features are discussed in this chapter. The first part of this chapter discusses the development of conformationally constrained BINOL-based amino acid, featuring carboxyl and amino groups in two dimensions (planes) on the aromatic framework. Such a feature offers the possibility of design and development of conformationally ordered synthetic oligomers with intriguing structural architectures distinct from those classically observed.



[Conformationally Rigid Aromatic Amino acids as Building Blocks for Abiotic Foldamers.
Ramesh, V. V. E.; Roy, A.; Kendhale, A. M.; Prabhakaran, P.; Puranik, V. G. ; Gonnade, R.; Puranik, V. G.; Sanjayan, G. J. *Org. Bimol. Chem.* **2011**, *9,* 367-369. *(Front Cover)*.]

This chapter also describes the development of conformationally restricted bicyclic dipeptide building blocks containing a biomedically important β-lactam core armed with a hydroxyethylamine isostere (HEA) on the backbone.



[Carbohydrate-Derived Conformationally Restricted Bicyclic Dipeptides as Potential Hetero Foldamer Building Blocks.
Ramesh, V. V. E.; Puranik, V. G.; Puranik, V. G.; Sanjayan, G. J. *Tetrahedron: Asymmetry* **2012**, *23*, 1400-1404]

General Remarks

- Unless otherwise stated, all the chemicals and reagents were obtained commercially.
- Required dry solvents and reagents were prepared using the standard procedures.
- All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (kieselgel $60F_{254}$, Merck) with UV, I_2 or ninhydrin solution as the developing reagents in the concerned cases.
- Column chromatographic purifications were done with 100-200 Mesh Silica gel or with Flash silica gel (230-400) mesh in special cases.
- Melting points were determined on a Buchi Melting Point B-540 and are uncorrected.
- IR spectra were recorded in nujol or $CHCl_3$ using Shimadzu FTIR-8400 spectrophotometer.
- NMR spectra were recorded on Ac 200 MHz, AV 400 MHz or DRX-500 MHz Bruker NMR spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities as singlet (s), doublet (d), quartet (q), broad (br), broad singlet (bs) and multiplet (m).
- Elemental analyses were performed on a Elmentar-Vario- EL.
- Electron Scattered Ionization (ESI) Mass Spectrometric measurements were done with API QSTAR Pulsar mass Spectrometer and MALDI-TOF mass spectrometric measurements were done on Voyager-DE STR mass spectrometer.
- *Ab initio* molecular modeling studies were performed employing 6-31G* basis set.
- Single crystal X-ray data were collected on a *Bruker SMART APEX* CCD Area diffractometer.

List of Publications

(1) Conformationally Rigid Aromatic Amino acids as Building Blocks for Abiotic Foldamers. **Ramesh, V. V. E.**; Roy, A.; Vijaydas, K. N.; Kendhale, A. M.; Prabhakaran, P.; Puranik, V. G. ; Gonnade, R.; Puranik, V. G.; Sanjayan, G. J. *Org. Bimol. Chem.* **2011***, 9,* 367-369. *(Front Cover)*

(2) Expanding the structural repertoire of β/α Ant-Pro (anthranilic acid-proline) oligomers into γ/α 2-Amb-Pro (2-aminomethyl benzoic acid-proline) oligomers. **Ramesh, V. V. E.**; Priya, G.; Rajamohanan, P. R.; Hoffman, H.-J.; Sanjayan, G. J. *Tetrahedron* **2012**, *68*, 4399-4405. (*Special issue on Chemistry of Foldamers*)

(3) Carbohydrate-Derived Conformationally Restricted Bicyclic Dipeptides as Potential Hetero Foldamer Building Blocks. **Ramesh, V. V. E.**; Puranik, V. G.; Puranik, V. G.; Sanjayan, G. J. *Tetrahedron: Asymmetry* **2012**, *23*, 1400-1404.

(4) Multifaceted folding in a foldamer featuring highly cooperative folds. **Ramesh, V. V. E.**; Priya. G.; Kotmale, A. S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. *Chem. Commun.* **2012**, *48*, 11205-11207.

(5) Carboxamide *vs* sulfonamide in peptide backbone folding: a case study with a synthetic oligomer. **Ramesh, V. V. E.**; Kale, S. S.; Kotmale, A. S.; Gawade, R. L.; Puranik, V. G.; Rajamohanan, P. R.; Sanjayan, G. J. *Org. Lett.* **2013***, Just Accepted*.

(6) The *Ant-Pro* reverse-turn motif: structural features and conformational characteristics. Thorat, V. H.; Ingole, T. S.; Vijayadas, K. N.; Nair, R. V.; Kale, S. S.; **Ramesh, V. V. E.**; Davis, H. C.; Prabhakaran, P.; Gonnade, R. G.; Gawade, R. L.; Puranik, V. G.; Rajamohanan, P. R.; Sanjayan, G. J. *Eur. J. Org. Chem.* **2013**, *Just Accepted*. (*Special issue on Foldamers***)**

(7) Switching the hydrogen-bonding network of a foldamer motif by backbone chirality alteration. **Ramesh, V. V. E**.; Vijayadas, K. N.; Dhokale, S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. (*Manuscript under preparation*).

(8) Manifestation of remote hydrogen bonding folding interactions in C_9 turn modulations. **Ramesh, V. V. E.**; Kale, S. S.; Kotmale, A. S.; Gonnade, R. G.; Rajamohanan, P. R.; Sanjayan, G. J. (*Manuscript under preparation*).

Chapter 1

Constrained Hybrid Foldamers with a Combination of Natural and Unnatural Amino acids-I

***Part A:** Influence of Multiple Hydrogen-Bonding in Folding*

Part B: Design, Synthesis and Conformational Studies of Oligomers with Proline and Anthranilic acid with Sequence Diversity

Influence of Multiple Hydrogen-Bonding in Folding

1.1 Introduction

Nature has selected the process of folding to control the conformation of its molecular machinery by which biopolymers fold into their characteristic three-dimensional compact structures - quite often mediated by a collection of non-covalent forces such as hydrogen-bonding, van der Waals interactions, π-π interactions, electrostatic interactions etc.[1] Proteins adopt precise three-dimensional conformations through folding in order to carry out chemical functions such as enzyme catalysis, information storage and duplication in nucleic acids, as well as energy capture and conversion.[2] In the folding process, a protein picks out the right conformation, out of billions of other possible conformations. Interestingly, to impart folding Nature, utilize a very limited set of building blocks - e.g. twenty amino acids in proteins and four nucleobases in DNA having a specific abilities not only because they are well suited, but also because they complied with evolutionary constraints.[3] According to LinderstrØm Lang,[4] there are four levels of protein structures namely primary, secondary, tertiary and quaternary. Primary structure represents the sequence of amino acids and secondary structure corresponds to conformation resulting from these sequences (examples are helices, β-sheets and turns).[5] The tertiary structure of peptides and proteins which is responsible for the bioactivity contains many secondary structural elements such as helix, β-sheet and turns.[6] The quaternary structure comprises different peptide strands held together by non-covalent interactions.[7] The peptide backbones undergo folding and defolding, a process governed by molecular recognition and self-assembly.

The relationship between folding and function among proteins has long been one of the important factor that is fascinating the chemical biologist, to understand closely how it's smaller counterpart - a peptide folds.[8] In an attempt to explore the Nature's puzzling events especially the folding mechanism and achieve structures and functions of folded biopolymers matching those of Nature, chemists endeavored in the construction of molecular frameworks with non-natural building blocks, or through the arrangement of natural building blocks into non-natural sequences leading to the flourishing area of ''peptidomimetics''.[9] In

this context, an area of research that has received considerable attention in recent years is foldamers that deals with synthetic oligomers mimicking conformational features of biopolymers.[10]

Before the term ‘‘foldamer’’ was coined, many nucleic acid analogues and peptide analogues had already been successfully designed to mimic the structures and function of their natural counterparts. Typical examples are peptide nucleic acids (PNAs)[11a] and N-substituted oligoglycines (peptoids, Fig. 1.1a).[11b] Contributions by Seebach and Gellman and others from the early 20th century, led the growth of foldamers from its foundation to the present stage.[12] Gellman coined the term foldamer which is defined as “***any oligomer with a strong tendency to adopt a specific compact conformation”***.[13]

1.2 Classification of foldamers

Based on the nature of the backbone, foldamers are classified into different categories: aliphatic and aromatic, biotic and abiotic, and homogeneous and heterogeneous, although the classifications are closely related.

1.2.1 Homogeneous foldamers

To a large extent, the foldamers synthesized at early stages analogous to their biopolymer progenitors are homogeneous foldamers - having homogeneous backbones i.e., monomers of single sub unit. Selected examples for homogeneous biotic foldamers[14-20] having natural and closely related backbones (Fig. 1.1) are: β-,[10a,14] γ-,[15] δ-,[16] peptoid,[11b] oligoureas,[17] azapeptides,[18] aminoxy peptides[19] and hydrazine peptide.[20]

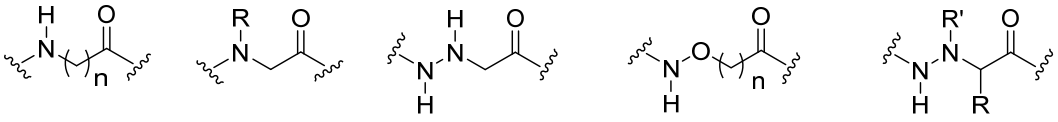


Fig. 1.1: Selected examples of homogeneous biotic foldamers.

Selected examples for homogeneous abiotic foldamers[21-25] having non-natural synthetic backbones (aromatic) (Fig. 1.2) are: oligoamides,[21] oligoureas,[22] pyridine oligoamide,[23] oligo-*m*-phenylethynylenes[24] and oligohydrazides[25] etc.

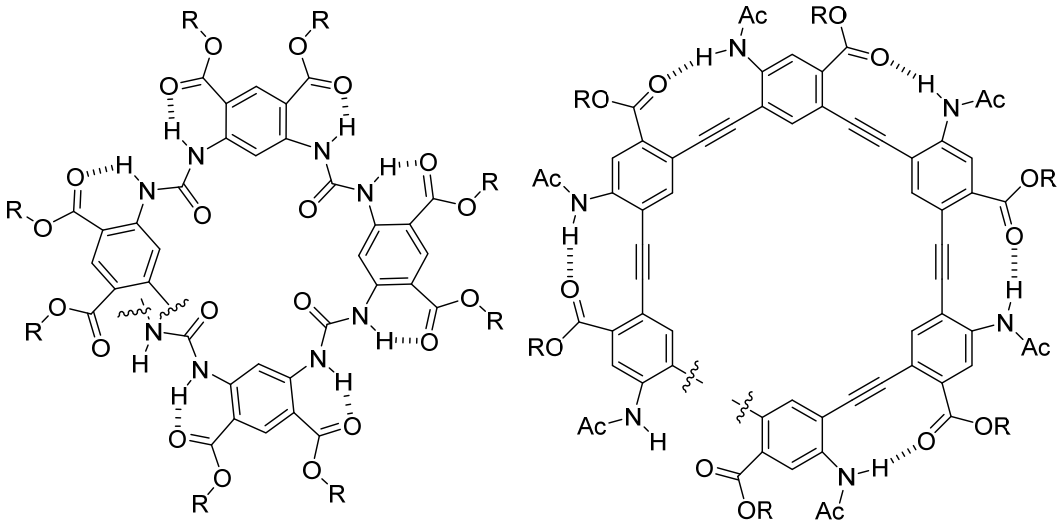


Fig. 1.2: Selected examples of homogeneous abiotic foldamers.

β-peptides (oligomers of β-amino acids) are excellent artificial homogeneous peptides that can mimic protein like secondary structures such as helices, strands, and turns.[26] The self-associating behaviour of β-peptides have widely been investigated, but the construction of higher-order structures with specific morphologies recently came true. Lee *et al.* recently reported highly homogeneous, well-defined, and finite molecular architectures from a peptidic scaffold that is neither cyclic nor amphipilic (Fig. 1.3).[27]

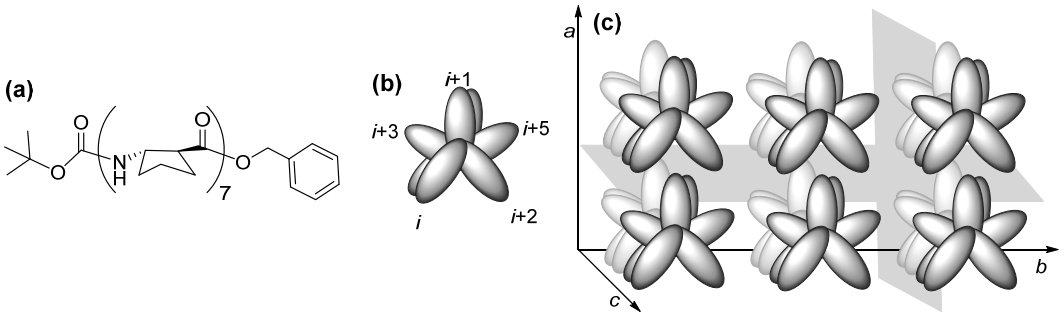


Fig. 1.3: (a) Chemical structure of *trans*-(S,S)-$ACPC_7$ oligomer; (b) cartoon showing the repeating pentad in $ACPC_7$, viewed along the helix axis; (c) schematic representation of possible molecular packing modes of $ACPC_7$ by intermolecular hydrophobic (*ac* and *bc* interfaces) and hydrogen bonding (*ab* interface) interactions during the self assembly process in aqueous solution.[27]

1.2.2 Heterogeneous (hybrid) foldamers

Foldamer synthesis is not limited to homogeneous foldamers. In relative to homogeneous foldamers, due to the innumerable possibilities to augment the

conformational modulation and diversity available for the foldamer design, heterogeneous foldamers (also defined "hybrid") were introduced recently. Hybrid foldamers containing heterogeneous backbones i.e., monomers of more than one sub unit have gained special status mainly because of two reasons. Firstly, hetero foldamers have been proven to be capable of displaying a unique structural architecture, distinctly different from their homo oligomer counterparts.[28] Secondly, by varying the constitutional ratios of the individual amino acid residues, it would be possible to augment the conformational diversity of the oligomers.[29] The superiority of hetero foldamers approach over homo foldamers be well examined by the interesting example reported by Toniolo *et al.*[30a] (Pro-Aib)$_n$ hybrid peptide shows beta-bend ribbon structure having 10-membered hydrogen-bonding network different from their homo foldamers.[30b,31] Several other examples of hybrid foldamers made of alternating aliphatic and aromatic amino acid units showing unconventional periodic structures (described under the appropriate section, *vide infra*).

1.2.2.1 Aliphatic–aliphatic hetero oligomers

Hetero oligomers containing more than one type of aliphatic amino acids in their backbone, for instance oligomers featuring different combinations of α-, constrained β-,[29a,32a-c] γ-, δ-,[32d] α-aminoxy acid,[19a] sugar[33] and β-furanoid sugar[34] *etc.* amino acids. In the literature, ever-increasing number of building blocks available in the armory of foldamer design have been reported (Fig. 1.4).

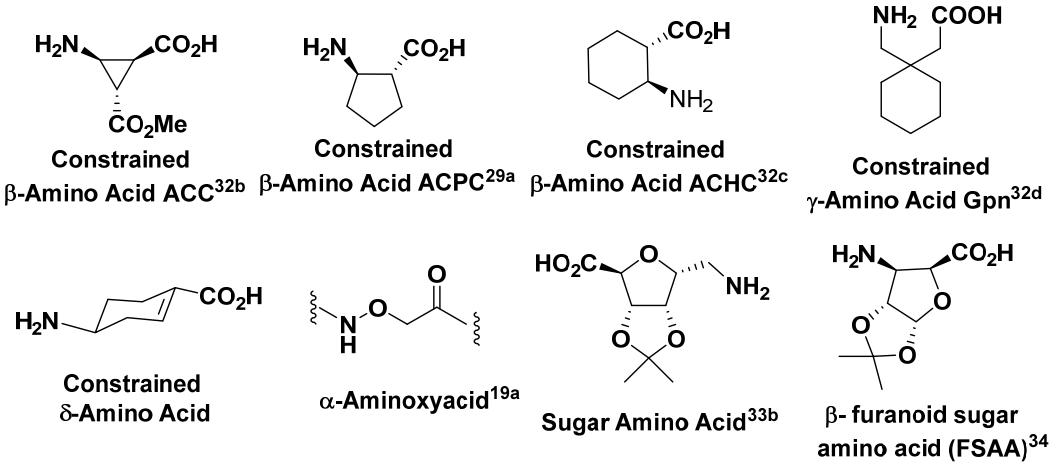


Fig. 1.4: Selected examples of building blocks used for aliphatic heterogeneous foldamer design.

Fig. 1.5 shows an interesting series of turn segments introduced in hairpins, where different length of turns can be achieved by replacing α-amino acid at the *i* + 2 position with homologous amino acids β-, γ- and δ-, reported from the Balaram's group.[35a] The β- [1-aminocyclohexaneacetic acid, β^3-Ac_6c],[35b] γ- [1-(aminomethyl)cyclohexaneacetic acid, Gpn][32d] and δ- [δ-aminovaleric acid, δ-Ava][35c] amino acids were inserted in the α-α segment having conventional β-turn secondary structure (C_{10} turn) to generate C_{11}, C_{12} and C_{13} turns, respectively.

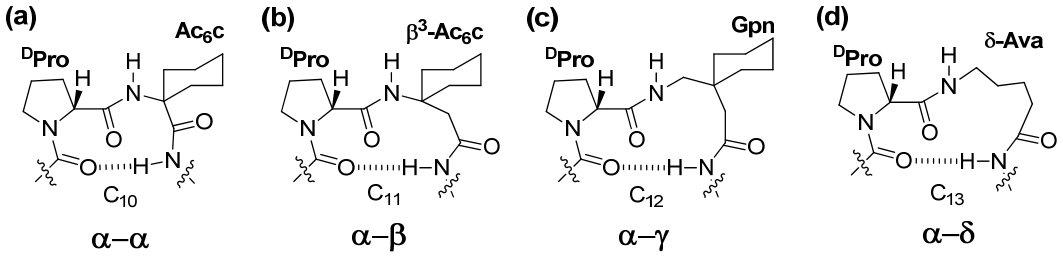


Fig. 1.5: (a) α-α, (b) α-β, (c) α-γ and (d) α-δ segments having C_{10}, C_{11}, C_{12} and C_{13} secondary structures respectively reported by Balaram *et al.* [35a]

In their pioneering work in the field of foldamers, Gellman's group recently reported α/β-[29a,b] and α/γ-[29c] hybrid peptides containing various constitutional ratios of the individual amino acid residues, and these were shown to adopt helical structures with very different hydrogen-bonding patterns (Fig. 1.6).

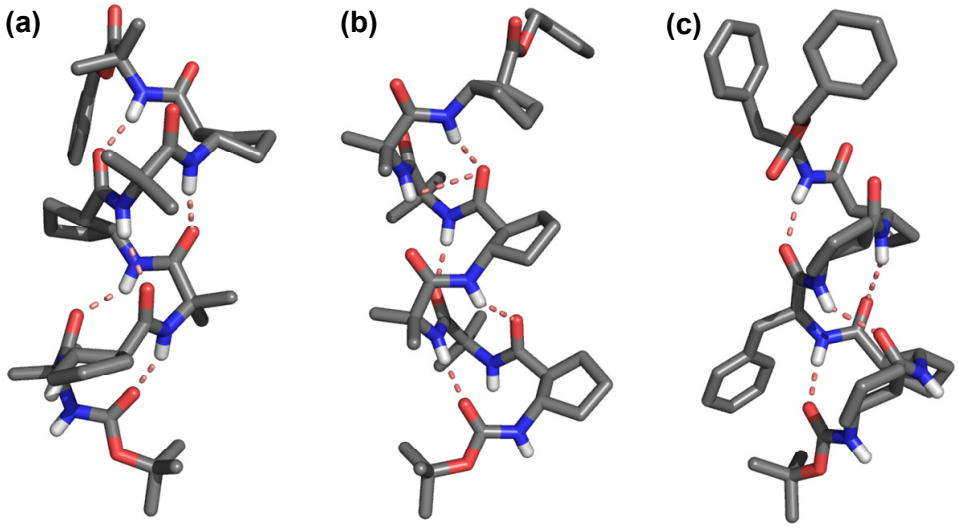


Fig. 1.6: Crystal structures of different helical heterogeneous peptide backbones composed of various constitutional ratios (a) 1:1 (b) 1:2 (c) 1:3 of α/β-hybrid peptides.[29a,b]

Constrained β-amino acids (ACPC,[29a] ACHC[32c]) and 1-(Aminomethyl)-cyclohexaneacetic acid, ''gabapentin'' (Gpn), is a conformationally constrained γ-amino acid,[32d] were extensively investigated by Gellman's and Balaram's group, respectively, in recent years for designing hybrid peptides of diverse secondary structures. Reiser's group developed α/β-peptides displaying 13-helix, which consist of L-alanine and either enantiomer of cis-β-aminocyclopropanecarboxylic acid (β-ACC).[32b] Sugar amino acid (SAA)[33,36a] and *cis*-β-furanoid sugar amino acid (FSAA)[34]-based foldamers demonstrated wide range of well-defined secondary structures. Sharma and Kunwar *et al.* reported several interesting β/γ-hybrid peptides with sugar side chains that adopt 11/13-helix in solution as evident from detailed NMR, CD spectroscopy and molecular dynamics investigations.[36b]

1.2.2.2 Aliphatic–aromatic hetero oligomers

The hetero-concept has proven to be much successful in the case of aliphatic-aromatic oligomers. By careful and proper utilization of non-planar conformation of aliphatic units, and the rigid and predictable conformational features of aromatic frameworks, many secondary structure elements such as helices, sheets and reverse turns along with many other interesting structural architecture were realized.[37] The conformation of hetero foldamers is determined by a combined conformational preference of individual constituent building blocks (residues).

Huc's group reported recently various interesting class of foldamers featuring constitutional ratios of aromatic (8-amino-2-quinoline carboxylic acid) and aliphatic [6-(aminomethyl)-2-pyridinecarboxylic acid] amino acid residues.[38] Sanjayan *et al.* designed and synthesized a novel α/γ-hybrid foldamer consisting of proline (Pro) and 3-amino-5-bromo-2-methoxy benzoic acid (Amb) which forms repeating γ-turn conformation (Fig. 1.7a).[39a] A slight variation in the substitution pattern of aromatic acid from *m*- to *o*-, resulted in α/β-hybrid foldamers displaying a *pseudo* β-turn conformation with 9-membered hydrogen-bonded rings (Fig. 1.7b).[39b] The ααγ-hetero oligomers containing Aib, Pro and 3-amino-4,6-dimethoxybenzoic acid (Adb) display repeat β-turn structure motif (Fig. 1.7c).[39c] These hybrid foldamers adopt a well-defined compact, three-

dimensional architecture, which is governed by a combined conformational restriction imposed by the individual amino acids of which it is composed.[39]

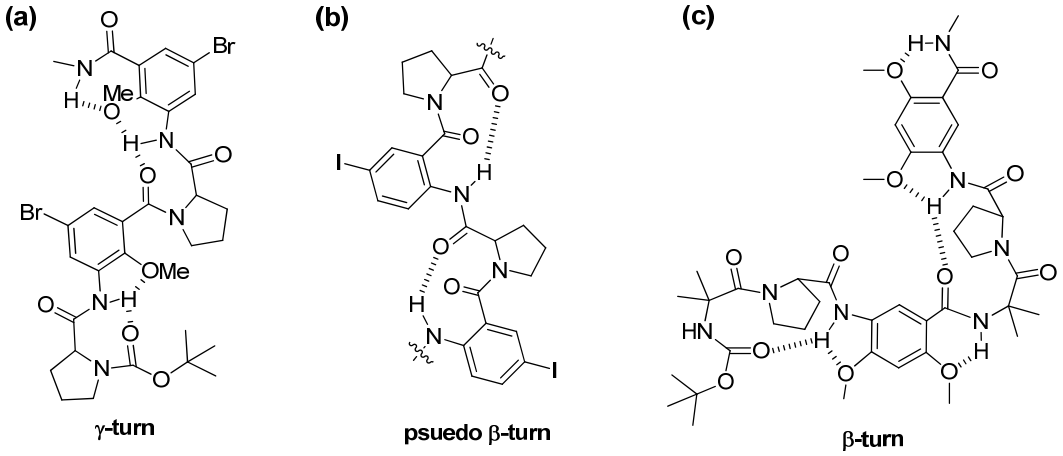


Fig. 1.7: Aliphatic–aromatic hetero foldamers showing (a) γ-turn[39a] (b) *pseudo* β-turn[39b] (c) β-turn[39c] governed by a combined conformational restriction imposed by the individual amino acids.[39]

Inspired by the concept of zippering of DNA double helical strands, hydrogen-bond-mediated duplexes were synthesized because of their potential applications.[40] Extremely stable sequence-specific duplexes were reported in literature comprising glycine and aromatic scaffold stabilized with intramolecular hydrogen-bonding that form complementary strand in aqueous solutions (Fig. 1.8).[40c] In their important contribution, Nowick's group reported sheet mimetics featuring natural and unnatural amino acids.[41] Recently, the crystal structure of a cyclic peptide revealed that two unnatural amino acid units ''Hao'' help in templating the β-sheet formation.[41d]

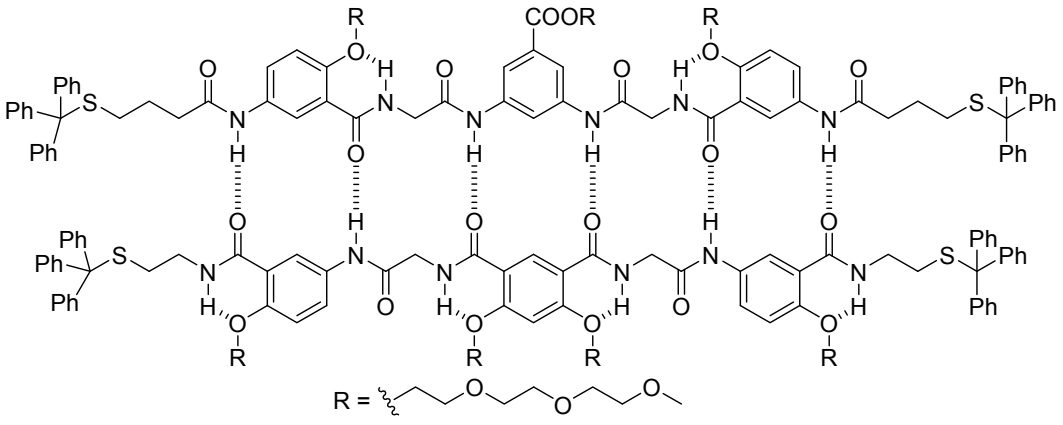


Fig. 1.8: (a) An extremely stable, complementary hydrogen-bonded molecular duplex reported by Gong *et al.*[40c]

A nonpeptidic reverse turn motif reported by Smith *et al.*, involves amino acid-derived alcohol conjoining an aromatic amine which was found to promote parallel sheet structure (Fig. 1.9).[42]

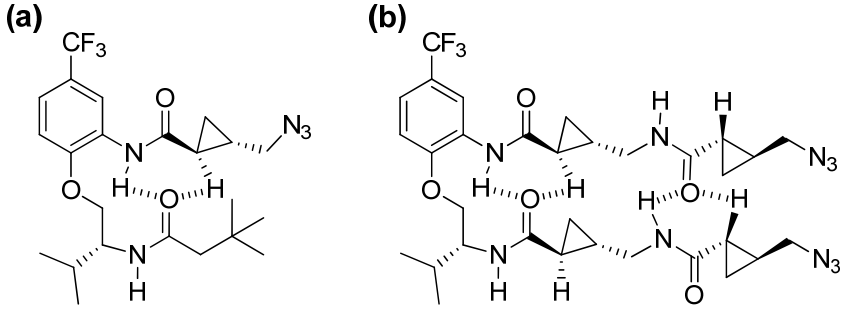


Fig. 1.9: (a) Nonpeptidic reverse turn segment and (b) its hairpin conformation reported by Smith *et al*.[42]

1.2.2.3 Aromatic–aromatic hetero oligomers

Owing to the predictable and stable conformation, foldamers derived exclusively from aromatic backbones have attracted considerable attention and explored to a great extent.[43] For attaining stable conformation from aromatic oligoamides, rotation about the Ar-CONHAr and Ar-NHCOAr bonds have to be restricted. Intramolecular hydrogen-bonding[44,45] and repulsive interactions[46] provide the simple, efficient, and reliable approaches for this restriction.

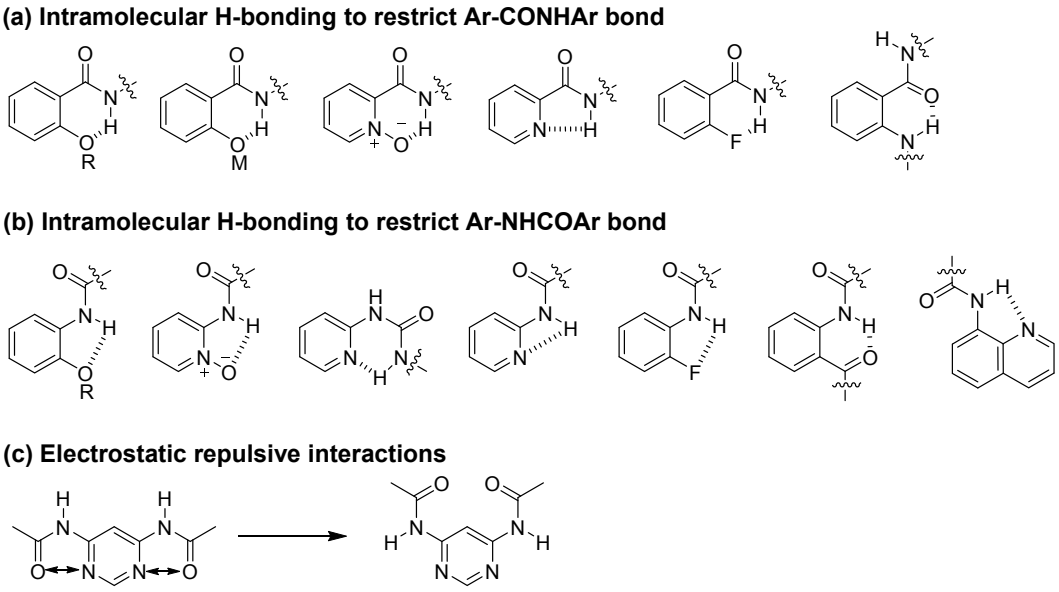


Fig. 1.10: Intramolecular hydrogen-bonding patterns in aromatic amides arresting the rotation anout (a) Ar-CONHAr (b) Ar-NHCOAr bonds and (c) electrostatic repulsive interactions that govern pre-organization.

For folding in oligomers, typical intramolecular hydrogen-bonding patterns have been used to restrict the rotation of the Ar-CONHAr[44] (Fig. 1.10a) and Ar-NHCOAr bond[45] (Fig. 1.10b). Electrostatic repulsion between the proton acceptor (nitrogen) and the amide oxygen atom forces the 2-aminopyridine-derived amides to fold in to helical structures (Fig. 1.10c).[46] These aromatic-aromatic hetero oligomers include oligoamides,[21] oligoureas,[22] pyridine oligoamide,[23] oligo-*m*-phenylethynylenes[24] and oligohydrazides[25] etc.

Several groups[45] have widely used the O…H-N and N…H-N hydrogen-bonding to pre-organize the backbone. Li's group has used the F…H-N hydrogen-bonding approach to pre-organize hetero-aromatic backbones to fold into crescent and helical conformations (Fig. 1.11).[47]

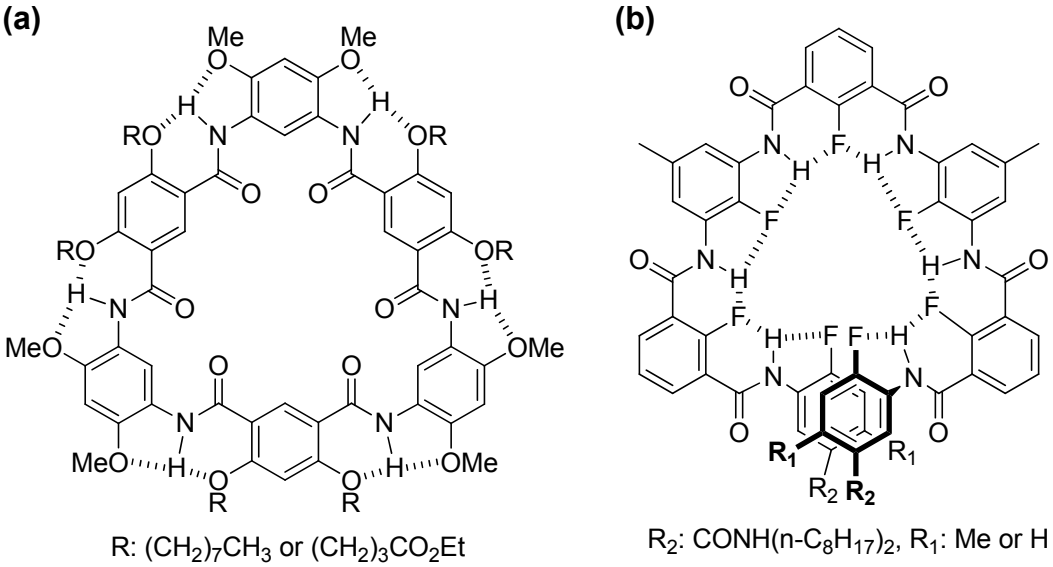


Fig. 1.11: Molecular structure of an aromatic-aromatic hetero foldamer (a) pre-organized with O…H-N hydrogen-bonding[45d] and (b) pre-organized with F…H-N hydrogen-bonding.[47a]

A significant effort has been expended by the Huc group in altering the cavity size of molecular capsules that can accommodate large guest molecules by varying the constitutional ratios of monomers.[48] Aromatic oligoamides composed of 1,8-diazaanthracene unit, instead of a pyridine unit, were shown to enhance its ability to adopt helical conformations that exist preferentially as double helical architecture with enlarged diameter (Fig. 1.12).[48c]

Other aromatic-aromatic reported hetero foldamers are co-facial 1,8-diaryl naphthalene unit,[49a] BINOL unit,[49b] metallofoldamers,[50,51] and stimuli responsive foldamers response to external stimuli such as pH, light, chemical entities.[52]

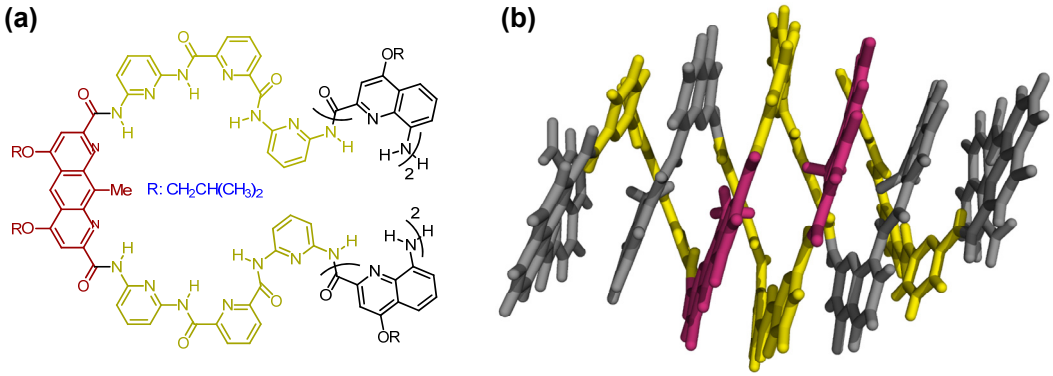


Fig. 1.12: (a) Molecular structure of aromatic hybrid foldamers with quinoline, pyridine and diaza-anthracene monomers and (b) interpenetrating helices with a hetero-sequence reported by Huc *et al.* (diaza-anthracene units are shown in pink color). Selected groups and included solvent molecules are removed for clarity.[48c]

1.3 Applications of foldamers

As mentioned earlier, one of the promising goals in the foldamer research is to mimic the biopolymers both structurally and functionally. Due to their structural tunability and stability, foldamers can be potential candidates for diverse applications.[53] Foldamers find applications as biomimetics,[54] molecular receptors,[55] chemical sensors and actuators[56] and catalysts.[57] Apart from these, foldamers also find extensive applications in material science.[58] The Huc group elegantly demonstrated recently the utility of foldamers as building blocks in developing molecular motors.[59] Termed foldaxanes by analogy with rotaxanes, these structures are formed through a multitude of non-covalent interactions between double-helical foldamers and rod-shaped guest molecules.[59b] The foldaxanes move in a screw-type motion and open up yet another promising application of foldamers in materials science.[60]

1.4 Objective of the present work and design strategy

Hetero oligomers derived from Ant and Pro residues (1:1 amino acid residue ratio) show robust right handed helical structural architectures[39b] - distinctly different from the structural architecture of their homo oligomer counterparts[31,45a] as shown from our group recently. The helical conformational characteristics of the Ant-Pro reverse turn, which assumes a folded pseudo β-turn formed in forward direction of the sequence (1→2 amino acid interactions) involving only two amino acid residues, is in stark contrast to the native β-turns that involve four residues to form hydrogen-bonded network featuring backward

1←4 amino acid interactions. The robustness of this Ant-Pro reverse turn has been proved by carrying out selective structural modulations around the turn segment of the N- and C-terminal amidated peptides, which include altering chiralities of the amino acid residues,[61a] modulating substitution pattern (use of different amino acid residues),[61b] and substituting carboxamides with sulfonamides.[61c]

The work described in this part aspires at investigating the folding propensity of Ant-Ant-Pro tripeptide building block. Logically, it was envisaged that such a building block could feature a "C_6-C_9 mixed" hydrogen-bonding pattern, although the results (*vide infra*) revealed highly unusual folded conformation.

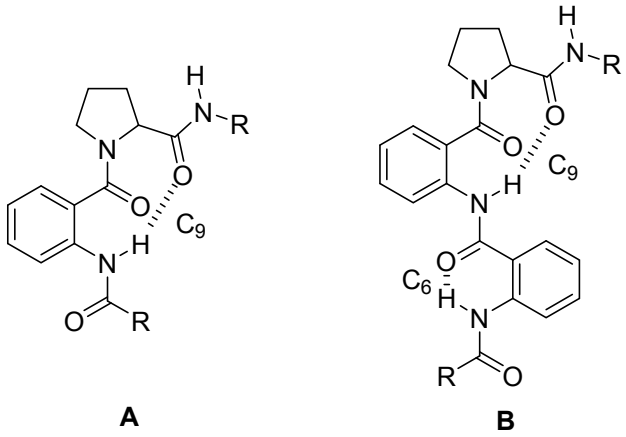
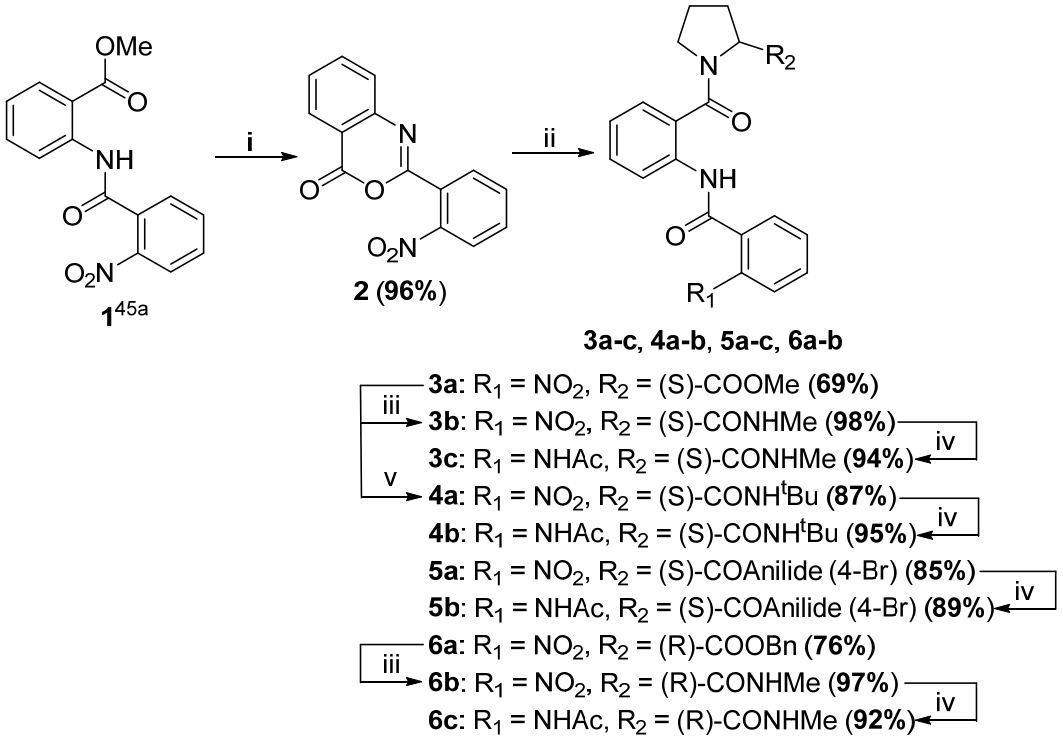


Fig. 1.13: Molecular structure of Ant-Pro with its observed hydrogen-bonding patern (A) and expected conformation of the hybrid foldamer motif Ant-Ant-Pro (B).

1.5 Synthesis

The tripeptides were synthesized as described in Scheme 1.1. Hydrolysis of the ester group of **1**[45a] fallowed by C-terminal activation furnished **2**. The benzoxazinone **2** was subjected to DBU-mediated ring opening by the amines H-^{L}Pro-OMe, H-^{L}Pro-Anilide (4-Br) and H-^{D}Pro-OBn to afford the expected tripeptides **3a**, **5a** and **6a**, respectively, in good yields. The C-terminal methyl amides **3b** and **6b** were accessed readily by direct amidation of the corresponding ester **3a** and **6a** respectively, using saturated methanolic methyl amine. The N-terminal ^{t}butyl amide **4a** was obtained by hydrolysis of ester group of **3a** followed by coupling with ^{t}butyl amine, aided by EDC.HCl. The nitro group of **3b**, **4a** and **6b** were hydrogenated using Pd-C as catalyst, followed by acetylation using acetic

anhydride to furnish the acetyl protected tripeptides **3c**, **4b** and **6c** respectively. The acetyl (4-Br) anilide tripeptide **5b** was obtained by $SnCl_2$ mediated reduction followed by acetyl protection.



Scheme 1.1: Synthesis of peptides **3c**, **4b**, **5b** and **6c**. **Reagents and conditions:** (i) a. aq. $LiOH.H_2O$, MeOH, rt, 12 h; b. Ac_2O, pyridine, DCM, rt, 30 min.; (ii) DBU, DMF, 4 Å molecular sieves, amine [H-^{L}Pro-CO_2Me for **3a**; H-^{L}Pro-$CONHC_6H_4$(4-Br) for **5a** and H-^{D}Pro-CO_2Bn for **6a**], rt, 2 h; (iii) methanolic $MeNH_2$, rt, 5 h; (iv) a. reduction [Pd-C, H_2, 1 atm., rt, 2 h for **3c**, **4b** and **6c** and $SnCl_2.2H_2O$, EtOAc, 50 °C, 2 h for **5b**]; b. Ac_2O, pyridine, DMAP, DCM, rt, 5 h; (v) a. aq. $LiOH.H_2O$, MeOH, rt, 12 h; b. $^{t}BuNH_2$, EDC.HCl, HOBt, DCM, rt, 8 h.

1.6 Conformational analyses

Secondary structural analyses were accomplished by extensive 2D NMR and single crystal X-ray diffraction studies.

1.6.1 Single crystal X-ray diffraction studies

Extensive efforts to crystallize the oligomers resulted in the formation of crystals of **3c** from a solvent mixture of methanol containing few drops of chloroform. The crystallographic studies[62] of **3c** had something startling in the offing. Analysis of the crystal data revealed the presence of an unexpected emergence of a fully folded conformation in **3c**, featuring two unusual folds by toppling the robust 6-membered hydrogen-bonding of Ant oligomers[45a] and 9-membered hydrogen-bonding of Ant-Pro motif.[39b] The molecule surprisingly

adopt a doubly folded conformation featuring two distinctly different folds - one towards the N-terminus with a C_{10}-hydrogen-bonded network, and the other one at the C-terminus displaying a C_{11}-hydrogen-bonded network (Fig. 1.14A, E).

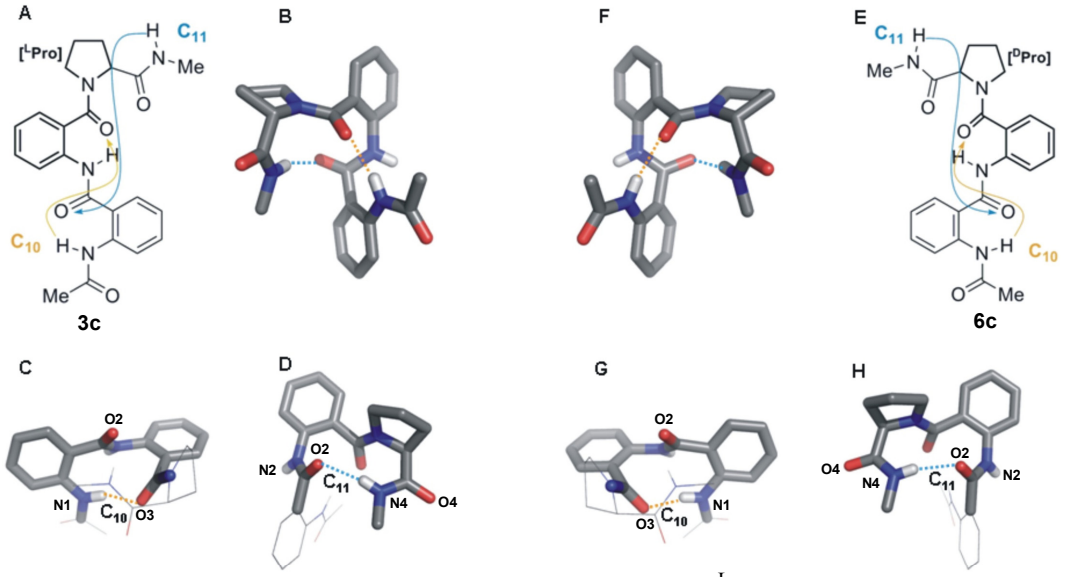


Fig. 1.14: Molecular structure of AcNH-Ant-Ant-^{L}Pro-NHMe **3c** with its observed hydrogen-bonding pattern (A), crystal structure of **3c** (B) and its excerpts (C,D), molecular structure of AcNH-Ant-Ant-^{D}Pro-NHMe **6c** with its observed hydrogen-bonding pattern (E), crystal structure of **6c** (F) and its excerpts (G,H). Note: All hydrogens, except the polar ones, have been deleted for clarity in the crystal structures.

A closer look at the C_{10}-hydrogen-bonded network in the crystal structure of **3c** (Fig. 1.14C) reveals that it involves two consecutive Ant residues, predisposed in an anti-periplanar arrangement, featuring strong hydrogen-bonding [hydrogen-bond geometric parameters: N1-H1N···O3; H1N···O3 = 2.11(2) Å, N1···O3 = 2.977(2) Å, ∠N1-H1N···O3 = 162(2)° and the planarity of the hydrogen bond torsion angle ∠(N1–H1N···O3=C15) = -135.56°]. The C_{11}-hydrogen-bonded network (Fig. 1.14D), on the contrary, involves the C-terminal Ant and Pro residues, aligned in an anti-periplanar arrangement, with a strong hydrogen-bonding [hydrogen-bond geometric parameters: N4-H4N···O2; H4N···O2 = 2.12(2) Å, N4···O2 = 2.948(2) Å, ∠N4-H4N···O2 = 165(2)° and the planarity of the hydrogen bond torsion angle ∠(N4–H4N···O2=C8) = -36.41°]. Exactly similar hydrogen-bonding arrangement is noted in the opposite enantiomer **6c** (Fig. 1.14E-H), which unequivocally precluded any crystal packing effects which could have interfered in the hydrogen-bonding interactions.

Furthermore, neighboring molecules form helical assemblies across the crystallographic two-fold screw axis, dictated exclusively by intermolecular strong N-H···O hydrogen bond engrossing C=O group of the Pro residue and N-H of the Ant moiety [hydrogen-bond geometric parameters: N2-H2N···O4; H2N···O4 = 1.94(2) Å, N2···O4 = 2.783(2)Å, ∠N2-H2N···O4 = 165(2)° and the planarity of the hydrogen bond torsion angle ∠(N2–H2N···O4=C20) = 133.96°] (Fig. 1.15). The aggregation of these helices *via* various weak interactions led to crystal formation.

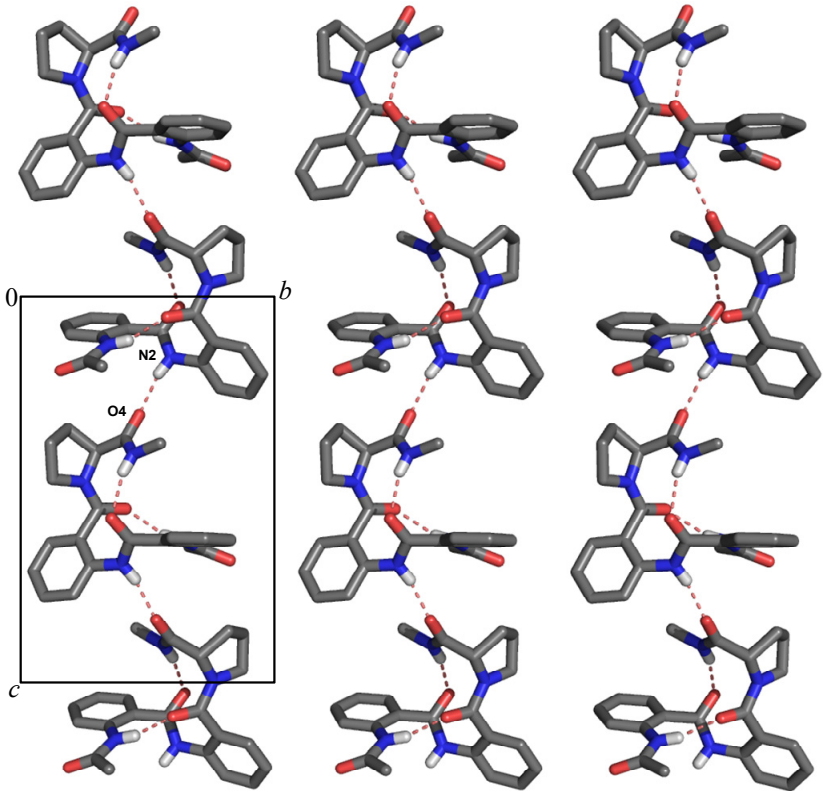


Fig. 1.15: Self-assembly observed in crystals of **3c** displaying helical architecture of molecules linked *via* N-H···O interactions.

1.6.2 NMR studies

We undertook extensive NMR studies to provide insights into the solution-state conformation of the peptide ($CDCl_3$, 500 MHz). The signal assignments were made unambiguously using a combination of two-dimensional COSY, HSQC, HMBC, TOCSY and NOESY experiments. Details of the peak assignments with tables and spectra are provided in the experimental section of this chapter.

The twin-fold observed in the solid-state of **3c** was unambiguously confirmed in its solution-state by the observed characteristic dipolar couplings (nOes) from its 2D NOESY NMR spectra (Fig. 1.16). Analysis of the 2D NOESY data revealed the existence of inter-residual nOe arising from the interaction of C21H of methyl amide with C4H, C5H and C6H of Ant1 residue, suggestive of the prevalence of folded conformation (Fig. 1.16a). Further, the amide NH of Ant2 is found to have nOe with the C14H of Ant2 residue (Fig. 1.16d). Other selected inter-residual nOes that supported the folded conformation were the interactions between C19H of Pro and their respective preceding aromatic proton C11H of Ar2 (Fig. 1.16b) and between the amide NH1 and C22H (Fig. 1.16c).

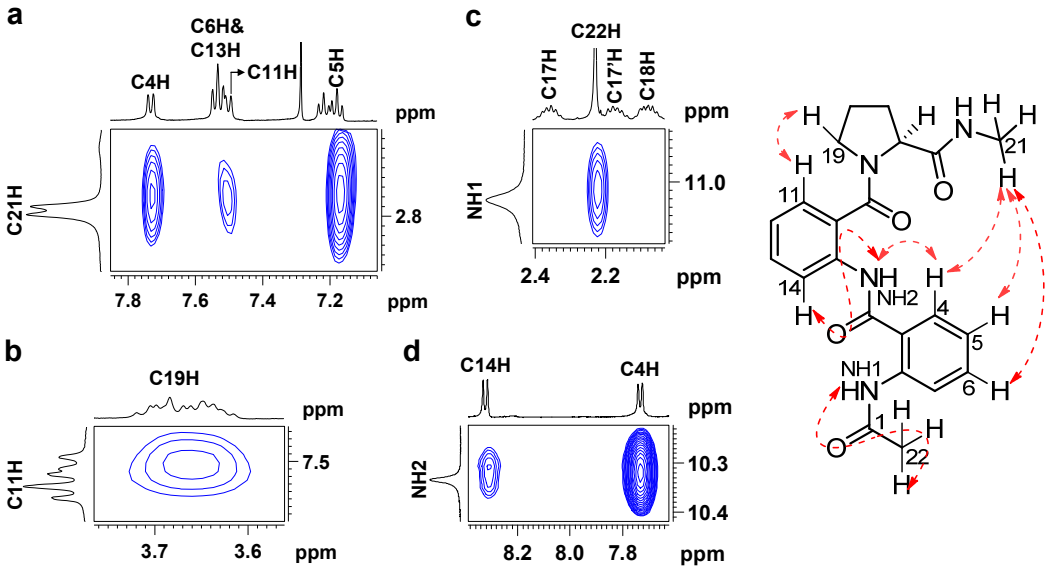


Fig. 1.16: Selected nOe extracts from the 2D NOESY data of **3c** ($CDCl_3$, 500 MHz).

Solvent titration experiments are particularly useful for differentiating the nature of hydrogen bonding interactions (inter *vs* intra) in the solution-state, wherein intermolecular hydrogen bonding interactions (solvent exposed NHs) are relatively more vulnerable to environment effects.[63] Further experimental support for the prevalence of intramolecular hydrogen bonding interactions in tripeptide **3c**, as observed in the solid-state structure of **3c**, came from DMSO-d_6 titration studies of the peptide (Fig. 1.17a). Notably, all the amide NHs of the oligomers showed negligible shift [Δδ (NH1): < 0.39 ppm and Δδ (NH3): < 0.57 ppm] when solutions of **3c** in $CDCl_3$ were titrated gradually with DMSO-d_6 (5 µl on each

addition, totalling ten points). Further, the involvement of strong intra-molecular hydrogen bonding interactions in the **3c** was also substantiated by variable temperature experiments. The amide NHs showed negligible chemical shift difference upon varying the temperature from 268 - 323 K [$(\Delta\delta/\Delta T) < -3$ ppb /deg K for **3c**, Fig. 1.17b]. Thus, the solvent titration and variable temperature studies further supported the involvement of intramolecular hydrogen bonding interactions in the peptide **3c**.

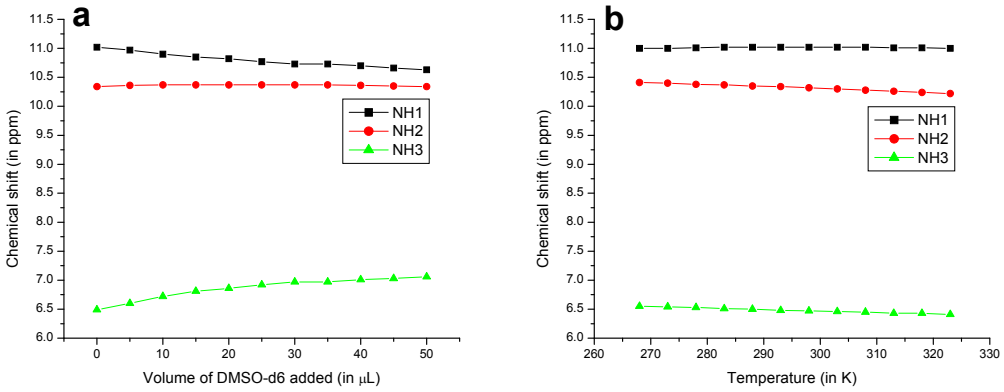


Fig. 1.17: DMSO-d_6 titration and variable temperature plots of the oligopeptide **3c**. (a) DMSO-d_6 titration plot of tripeptide **3c** and (b) variable temperature plot of tripeptide **3c**. *Note*: The assignments of the amide NHs should be from the N-terminal of the peptide, according to the molecular structure given in experimental section.

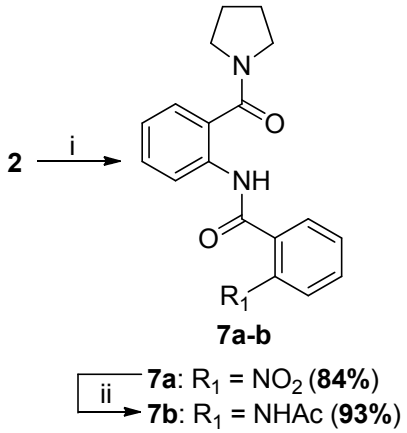
1.7 Role of N- and C-terminal H-bond donors in the twin fold formation

After getting insights into the conformational features of **3c**, we turned our attention to investigate the role of N- and C-terminal hydrogen-bond donors in the twin fold formation. Tripeptides **3b**, **4a** and **5a** (Scheme 1.1), feature a similar backbone structure as that of **3c**, except that they are devoid of the hydrogen-bond donor at the N-terminus. In place of the crucial N-acetyl group that would have otherwise contributed to establish the C_{10}-hydrogen-bonding as in **3c**, the peptides **3b**, **4a** and **5a** possess nitro group - devoid of hydrogen-bond donor ability. The substituents at C-terminus were varied (N-Me in **3b**, N-^{t}Bu in **4a**, and *p*-Br-anilide in **5a**), keeping the N-terminus nitro group constant, in order to gauge the substituent effects. Also, we studied a model tripeptide **7b** (Scheme 1.2) wherein, the Pro in Ant-Ant-Pro sequence was substituted by pyrrolidine, that lacks an amide group at the C-terminus, in order to verify the individual contribution of the

C-terminus hydrogen-bond donor in the stabilization of the entire fold as observed in **3c**.

1.7.1 Synthesis

The benzoxazinone **2** was subjected to DBU-mediated ring opening by pyrrolidine to afford the expected nitro tripeptide **7a**. The nitro group was hydrogenated using Pd-C as catalyst, and acetylated using acetic anhydride furnishing the acetyl protected tripeptide **7b**.



Scheme 1.2: Synthesis of peptide **7b**. **Reagents and conditions:** (i) pyrrolidine, DBU, DMF, 4 Å molecular sieves, rt, 2 h.

1.7.2 Single crystal X-ray diffraction studies

Interestingly, crystal structure studies[62] revealed the emergence of C_9 turn [hydrogen-bond geometric parameters: N1-H1N···O3; H1N···O3 = {1.98(2)-2.14(2) Å}, N1···O3 = {2.809(2)-2.941(3) Å}, ∠N1-H1N···O3 = {165(3)°-171(2)°} and the planarity of the hydrogen bond torsion angle ∠(N1–H1N···O3=C13) = {-144.74°-163.82°}], in the oligopeptides **3b**, **4a** and **5a** (Fig. 1.18B, D and F, respectively) containing nitro group, in place of crucial hydrogen-bond donor at the N-terminus, that would have otherwise contributed to establish the C_{10}-hydrogen-bonding as in **3c**. The crystal structures of **3b**, **4a** and **5a** unequivocally reveals that, due to the lack of hydrogen-bonding donor at the N-terminus, the C_{10}-hydrogen-bonding is absent as observed in **3c**. Surprisingly, deletion of hydrogen-bonding donor at the N-terminus not only caused vanishing of the C_{10}, but also the C_{11} structure.

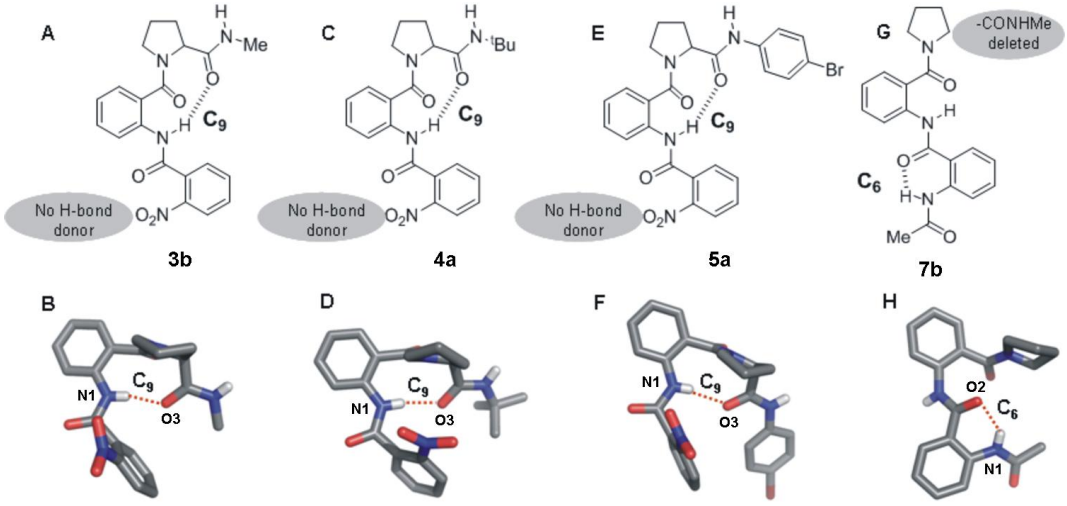


Fig. 1.18: Molecular and crystal structures of **3b** (A,B), **4a** (C,D), **5a** (E,F) and **7b** (G,H), respectively. *Note*: Hydrogen-bonding pattern has been highlighted in the molecular structures. Structural changes, as compared to **3c**, have also been highlighted in the molecular structures.

The crystal structure of **7b** (Fig. 1.18H) astonishingly revealed the absence of not only the C_{11} due to the lack of hydrogen-bond donor (amide group) at the C-terminus, but also the C_{10}-hydrogen-bonded networks. The only hydrogen-bonding observed in this case was the Hamilton-type C_6-bonding [hydrogen-bond geometric parameters: N1-H1N···O2; H1N···O2 = 2.08 Å, N1···O2 = 2.7634(19) Å, ∠N1-H1N···O2 = 134° and the planarity of the hydrogen bond torsion angle ∠(N1–H1N···O2=C8) = -21.20°] - characteristic of consecutive Ant rings.[45a]

This observation unambiguously establishes the role of N- and C-terminus hydrogen-bond donor group in stabilizing the doubly folded conformation observed in **3c** and this work illustrates how multiple hydrogen-bonding of dissimilar structural features can "symbiotically" cause and stabilize peptide folding.[64]

1.7.3 NMR studies

We undertook extensive NMR studies to provide insights into the solution-state conformation of the peptides ($CDCl_3$, 500 MHz). The signal assignments were made unambiguously using a combination of two-dimensional COSY, HSQC, HMBC, TOCSY and NOESY experiments.

Analysis of the crystal structure of **4a** had suggested that the most characteristic nOe that is essential to support the (1→2)-type 9-membered-ring

pseudo β-turn[39b] conformation would be the requirement of a diagnostic long range inter-residual dipolar coupling between C15H of ^{t}butyl group and the aromatic protons of Ar1 [C15H with C20H, C21H and C22H of Ar1, Fig. 1.19a]. Other selected inter-residual nOes that supported this conformation were the interactions between C12H of Pro and NH1 (Fig. 1.19b) and C12H of Pro and C4H of Ar2 (Fig. 1.19c).

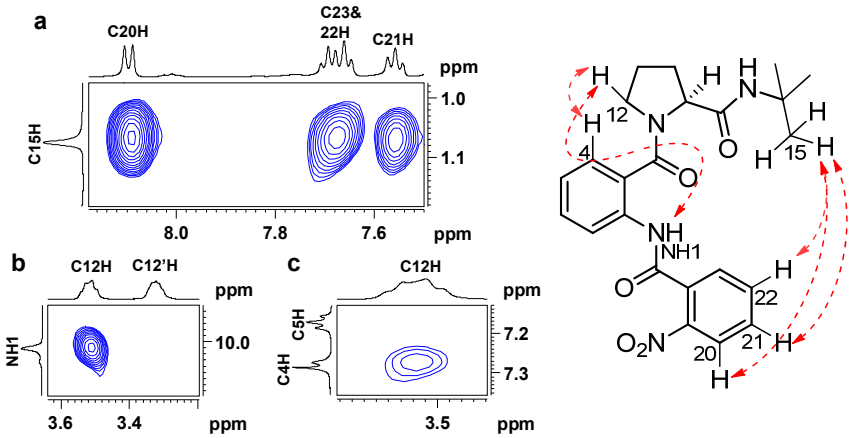


Fig. 1.19: Selected nOe extracts from the 2D NOESY data of **4a** ($CDCl_3$, 500 MHz).

Analysis of the crystal structure of **7b** had suggested that the most characteristic nOe that is essential to support the conformation would be the requirement of a diagnostic long range inter-residual dipolar coupling between NH2 and the aromatic protons C4H of Ar1 and C14H of Ar2 (Fig. 1.20c).

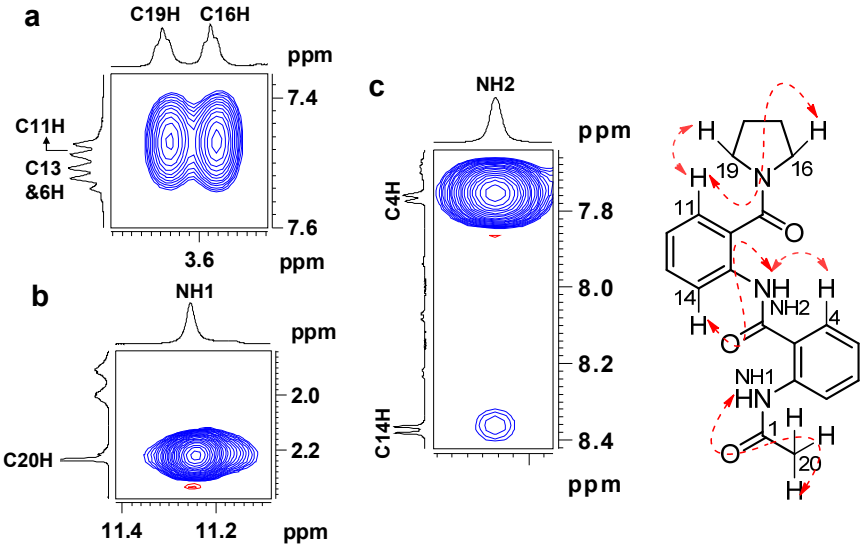


Fig. 1.20: Selected nOe extracts from the 2D NOESY data of **7b** ($CDCl_3$, 500 MHz).

In order to distinguish the hydrogen bonding interactions (inter *vs* intra), we undertook DMSO-d_6 titration, $CDCl_3$ dilution and variable temperature experiments (Fig. 1.21).

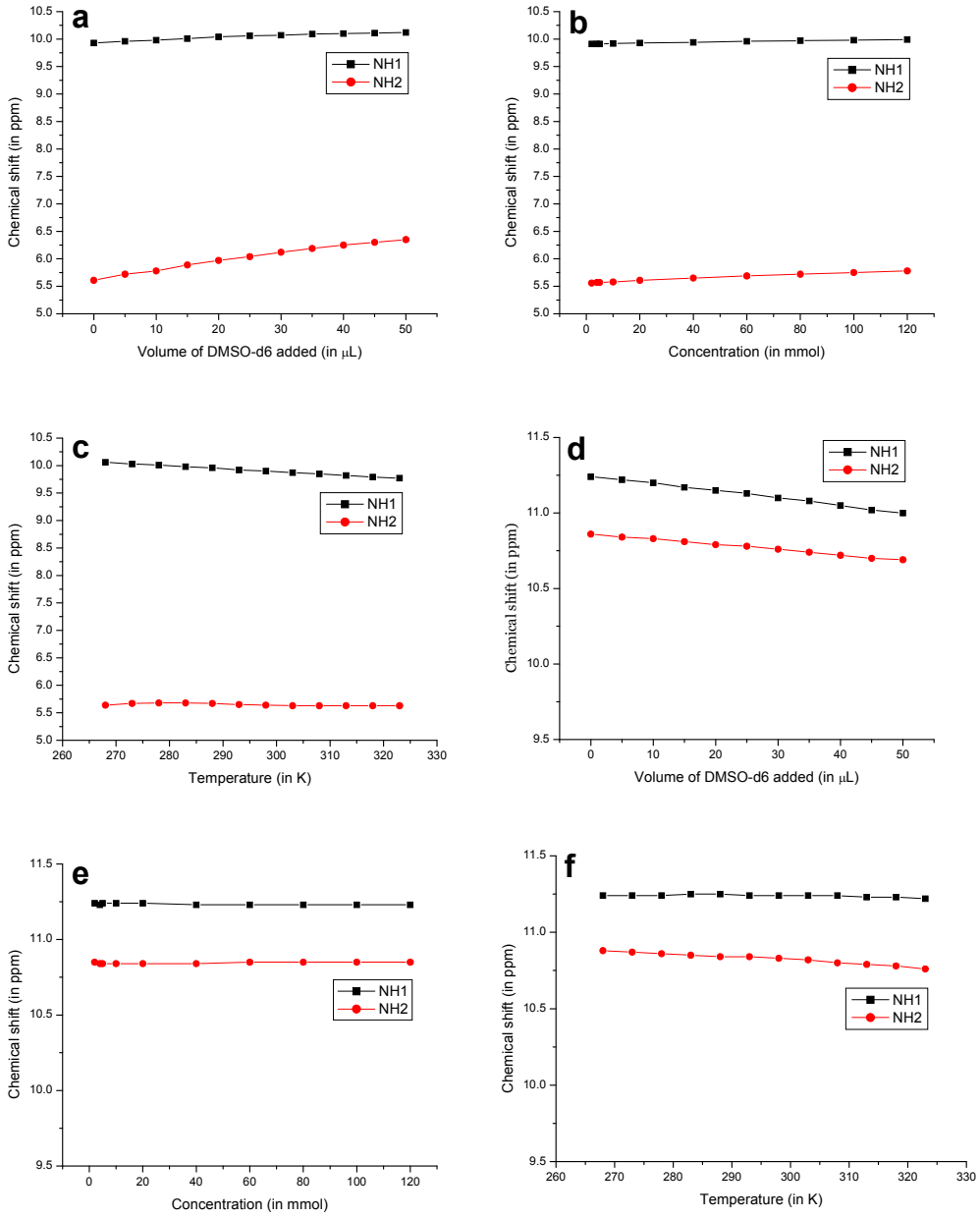


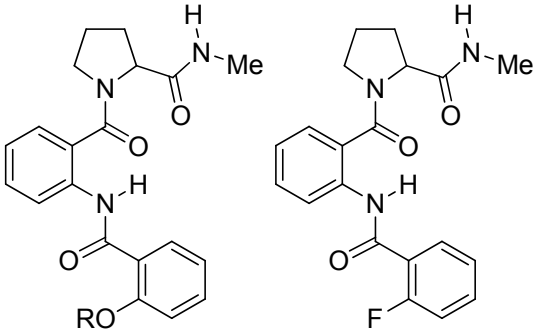
Fig. 1.21: DMSO-d_6 titration, $CDCl_3$ dilution and variable temperature plots of the oligopeptides **4a** and **7b**. (a) DMSO-d_6 titration, (b) $CDCl_3$ dilution and (c) variable temperature plots of tripeptide **4a**; (d) DMSO-d_6 titration, (e) $CDCl_3$ dilution and (f) variable temperature plots of tripeptide **7b**.

Notably, all the amide NHs of the synthetic peptides that are involved in intramolecular hydrogen-bonding showed negligible shifts [$\Delta\delta$ (NH1): < 0.19 ppm

for **4a** and Δδ (NH1): < 0.24 ppm for **7b**] in DMSO-d_6 titration experiment (Fig. 1.21a, d). The same trend was observed in solvent $CDCl_3$ dilution study as well (Fig. 1.21b, e). Further, the amide NHs showed negligible chemical shift difference upon varying the temperature from 268 - 323 K [(Δδ/ΔT) < -6 ppb /deg K for **4a** and -1 ppb /deg K for **7b**] suggesting the involvement of strong intramolecular hydrogen-bonding (Fig. 1.21c, f).

1.8 Effect of N-terminal hydrogen-bond donor and acceptor in the C_9 turn modulations

As part of our ongoing program to investigate the effect of N-terminal hydrogen-bond donor on the C_9-hydrogen-bonding network of the peptides containing constrained β-amino acid (Ant) and α-amino acid (Pro) residues in 2:1 ratio, we recently reported that synthetic peptide **3c**, display an unusual doubly folded conformation by obstructing the robust C_9-hydrogen-bonding of Ant-Pro motif.[64] Continuing the previous work, we designed **8a-8c** and **9** (Fig. 1.22) anticipating that, hydrogen-bond donor and acceptor groups at the N-terminal of the synthetic peptides would have dramatic effect on the stability of the C_9-hydrogen-bonded *pseudo* β-turn.[39b]



8a: R = Ac
8b: R =H
8c: R =Me

9

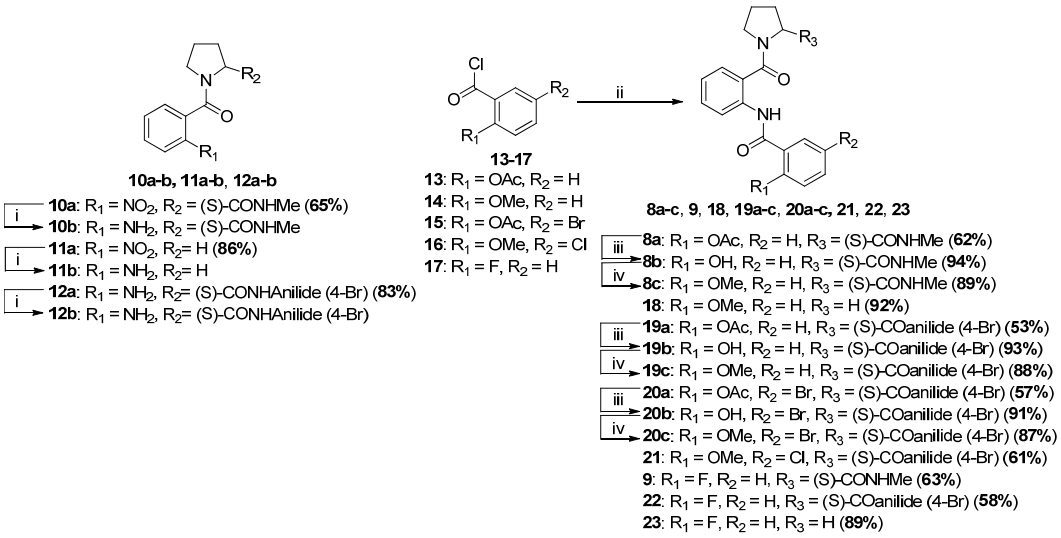
Fig. 1.22: Molecular structure of **8a-8c** and **9**.

In a sequential peptide, *ortho*-hydroxy benzamides are known to form the stronger OH...O hydrogen bond (rather than NH...O), both in the solid state and in so1ution state.[65] Thus, we wanted to investigate the effect of hydrogen-bond donor group (OH), as well as hydrogen-bond acceptor groups (OMe, F)[45,47] at the

N-terminus would have dramatic effect on the stability of the C_9-hydrogen-bonded *pseudo* β-turn.[39b]

1.8.1 Synthesis

Synthesis started with dimers (**10a-12a**), which were obtained by coupling of 2-nitrobezyol chloride with corresponding pyrrolidine amines. The nitro functionality was reduced using Pd-C/H_2 (for **10a** and **11a**) and $SnCl_2$ (for **12a**) to afford corresponding free amine dimers (**10b-12b**). Subsequently, the free amines (**10b-12b**) were coupled with aromatic acid chloride to furnish trimers **8a**, **18**, **19a**, **20a**, **21**, **9**, **22** and **23**. The aromatic acetates **8a**, **19a** and **20a** were subjected for K_2CO_3-mediated hydrolysis to furnish corresponding phenol compounds **8b**, **19b** and **20b**. Further, the phenolic OH of compounds **8b**, **19b** and **20b** were protected as a methyl ethers **8c**, **19c** and **20c** using MeI and K_2CO_3 (Scheme 1.3).



Scheme 1.3: Synthesis of oligopeptides **8a-c**, **18**, **19a-c**, **20a-c**, **21**, **9**, **22** and **23**. **Reagents and conditions:** (i) reduction [Pd-C, H_2, 1 atm., rt, 2 h for **10b**, **11b** and $SnCl_2.5H_2O$, EtOAc, 45 °C, 2 h for **12b**]. (ii) a. $(COCl)_2$, DMF, DCM, 0 °C then rt, 3 h; b. amine [**10b** for **8a** and **9**; **11b** for **18** and **23**; **12b** for **19a**, **20a**, **21**, **22**], pyridine, DCM, 0 °C then rt, 5 h. (iii) K_2CO_3, MeOH, rt, 1 h. (iv) MeI, K_2CO_3, Acetone, 45 °C, 8 h.

1.8.2 Single crystal X-ray diffraction studies

Our extensive efforts to crystallize **3a-c** and **4** did not succeed but, we could crystallize the analogues **14a**, **15b**, **13** and **18** (Fig. 1.23). The crystal structure of **19a** (Fig. 1.23B) clearly reveals the typical intramolecular pseudo β-turn [hydrogen-bond geometric parameters: N1-H1N···O5; H1N···O5 = 2.01 Å,

N1···O5 = 2.847(5) Å, ∠N1-H1N···O5 = 158.9° and the planarity of the hydrogen bond torsion angle ∠(N1–H1N···O5=C20) = 140.14°] as anticipated from the previous results.[39b,64]

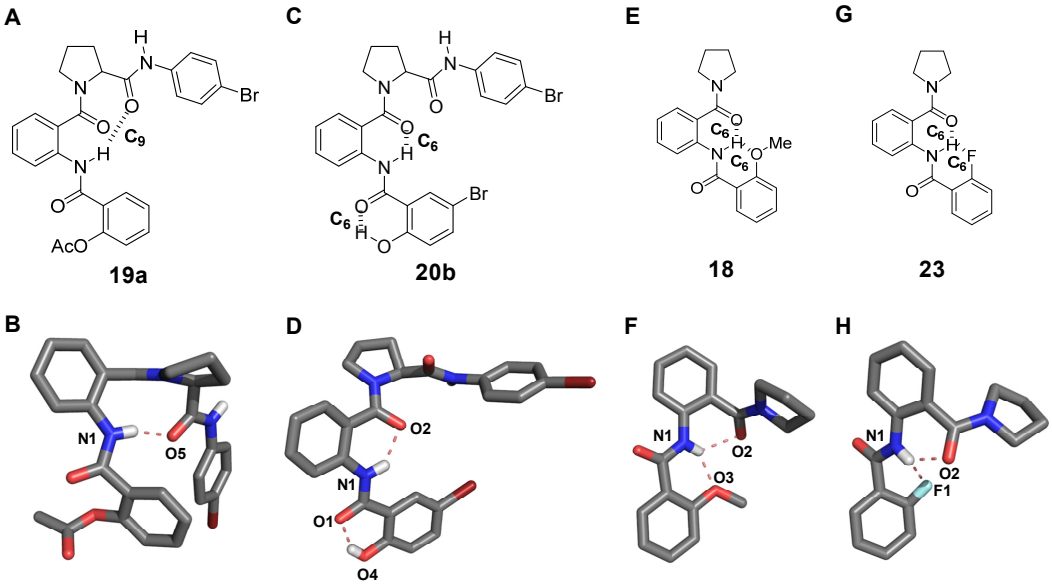


Fig. 1.23: Molecular and crystal structures of **19a** (A,B), **20b** (C,D), **5a** (E,F) and **7b** (G,H), respectively. *Note*: Hydrogen-bonding pattern has been highlighted in the molecular structures.

However, **20b** (Fig. 1.23D) having a free phenolic group at the N-terminus showed 6-membered hydrogen-bonding arising out of the phenolic hydrogen-bonding [hydrogen-bond geometric parameters: O4-H4O···O1; H4O···O1 = 1.92(5) Å, O4···O1 = 2.549(5) Å, ∠O4-H4O···O1 = 147(6)° and the planarity of the hydrogen bond torsion angle ∠(O4-H4O···O1=C1) = 12.74°] and the typical Ant C_6 ineraction [hydrogen-bond geometric parameters: N1-H1N···O2; H1N···O2 = 1.94 Å, N1···O2 = 2.656(5) Å, ∠N1-H1N···O2 = 137.5° and the planarity of the hydrogen bond torsion angle ∠(N1–H1N···O2=C8) = -16.09°]. It is noteworthy that the hydrogen-bonding observed in **20b** is in contrast to twin folded conformation observed for **3c** having hydrogen-bond donor as Ac-NH group at N-terminus.[64] The drastic difference in the conformation of two molecules might be due to the stronger OH...O hydrogen bond (rather than NH...O).[65] Our intense efforts to crystallize the methoxy derivatives **8c**, **19c**, **20c** and **21** and fluoro derivatives **9** and **22** did not meet with success. The analogues **18** and **23** (Fig. 1.23E, G) which are devoid of the C-terminal amides showed

bifurcated hydrogen-bonding involving two successive 6-membered ring hydrogen-bonding networks.

1.8.3 NMR studies

We undertook extensive NMR studies to provide insights into the solution-state conformation of the oligomers ($CDCl_3$, 500 MHz).

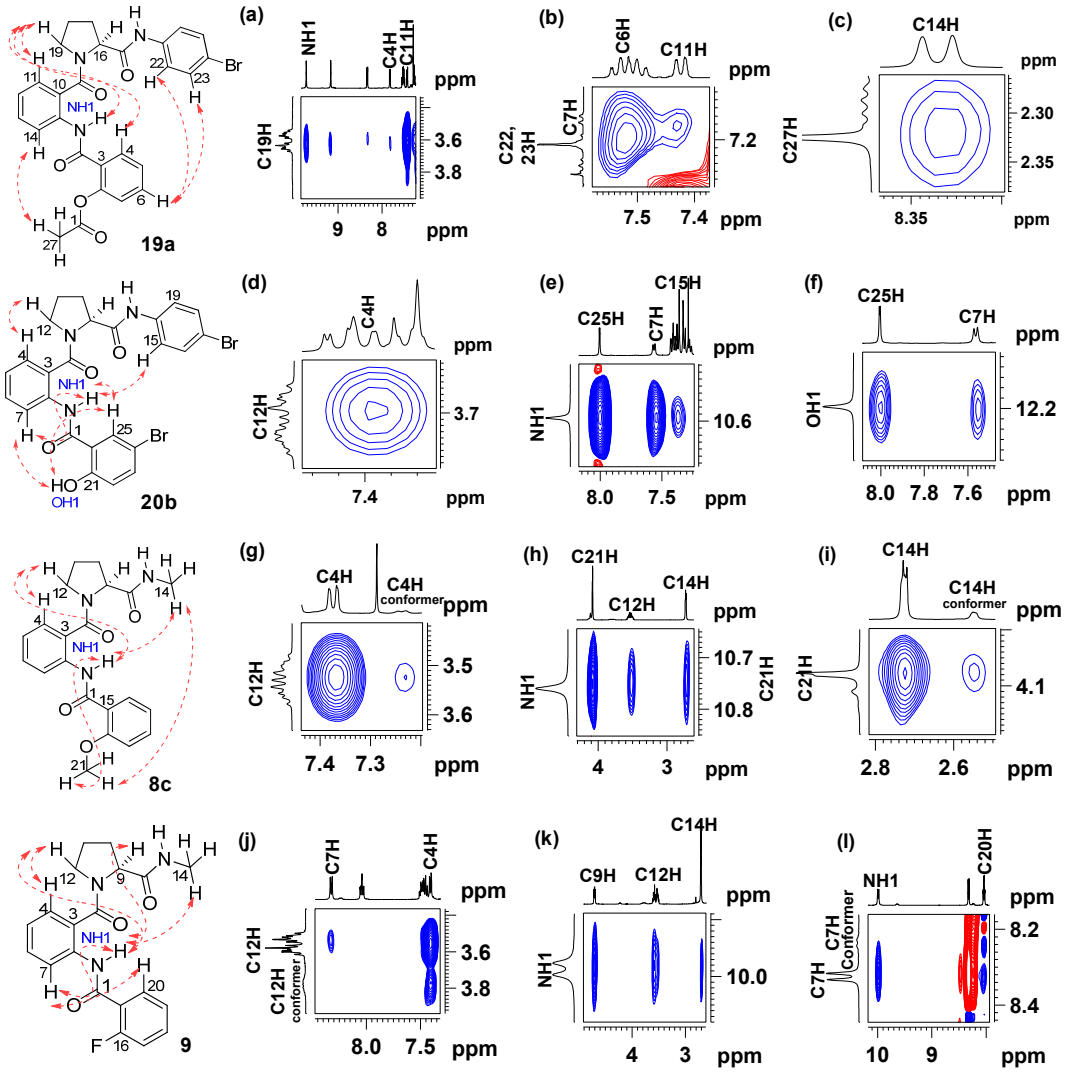


Fig. 1.24: Selected nOe extracts from the 2D NOESY ($CDCl_3$, 500 MHz) of **19a** (a,b,c), **20b** (d,e,f), **8c** (g,h,i) and **9** (j,k,l).

Analysis of the crystal structure of **19a** had suggested that the most characteristic nOe that is essential to support the (1→2)-type 9-membered-ring pseudo β-turn[39b] conformation would be the requirement of a diagnostic long range inter-residual dipolar coupling of C6H of Ar1 with C22H and C23H of Ar3 (Fig. 1.24b). Other selected inter-residual nOes that supported this conformation

were the interactions between C19H of Pro and NH1 (Fig. 1.24a) and C27H of Pro and C14H of Ar2 (Fig. 1.24c).

The hydroxy derivative **20b** showed a long-range nOes between OH1 and C7H (Fig. 1.24f) and NH1 and C15H (Fig. 1.24e). A close analogue **8b** having NHMe instead of *p*-(Br)-anilide, also displayed similar conformation as seen in **20b**, as clearly evident from the 2D NMR study (see Experimental Section).

The crystal structure of **18**, a close analogue of **8c** shows 6-membered bifurcated hydrogen-bonding. The similar conformation has been observed as evident from long-range inter-residual nOes between C21H and NH1 (Fig. 1.24h), C21H and C14H (Fig. 1.24i) and NH1 and C14H (Fig. 1.24h). In case of **9**, we could observe a similar type of nOe pattern as of **8c**. The characteristic nOes that supported its folded conformation are: C12H with C4H (Fig. 1.24j), NH1 with C9H, C12H and C15H (Fig. 1.24k) and C7H with C20H (Fig. 1.24l).

The characteristic hOe that supported the proximity of fluorine with NH1 in **9** is C16F with NH1 (Fig. 1.25a). Other characteristic hOes that supported folded conformation of **9** are C16F with C9H, C12H and C14H (Fig. 1.25b).

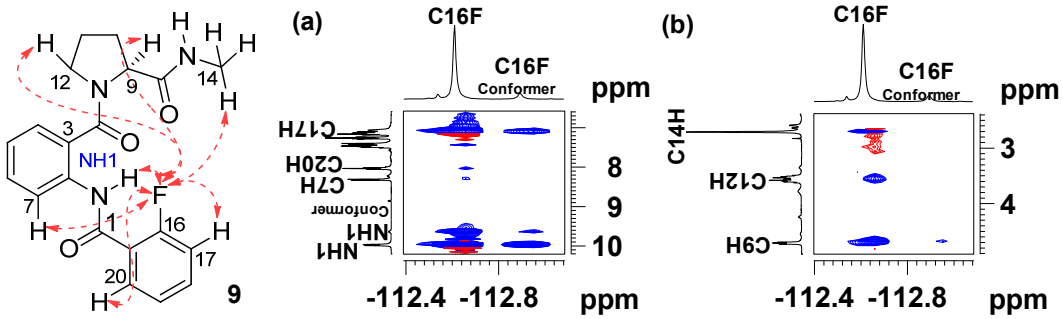


Fig. 1.25: Selected hOe extracts from the 2D HOESY of **9** ($CDCl_3$, 400 MHz).

In order to distinguish the hydrogen bonding interactions (inter *vs* intra), we undertook DMSO-d_6 titration, $CDCl_3$ dilution and variable temperature experiments (Fig. 1.26). Notably, all the amide NHs of the oligopeptides that are involved in intramolecular hydrogen-bonding showed negligible shifts in DMSO-d_6 titration experiment [Δδ (NH1): < -0.06 ppm for **19a**; Δδ (NH1): < 0.18 ppm, Δδ (OH1): < 0.6 ppm for **20b**; Δδ (NH1): < 0.14 ppm for **8c** and Δδ (NH1): < 0.07 ppm for **9**] suggesting the involvement of strong intra-molecular hydrogen-bonding (Fig.1.26a, c, e, g). The same trend was observed in solvent $CDCl_3$ dilution study as well (see Experimental Section).

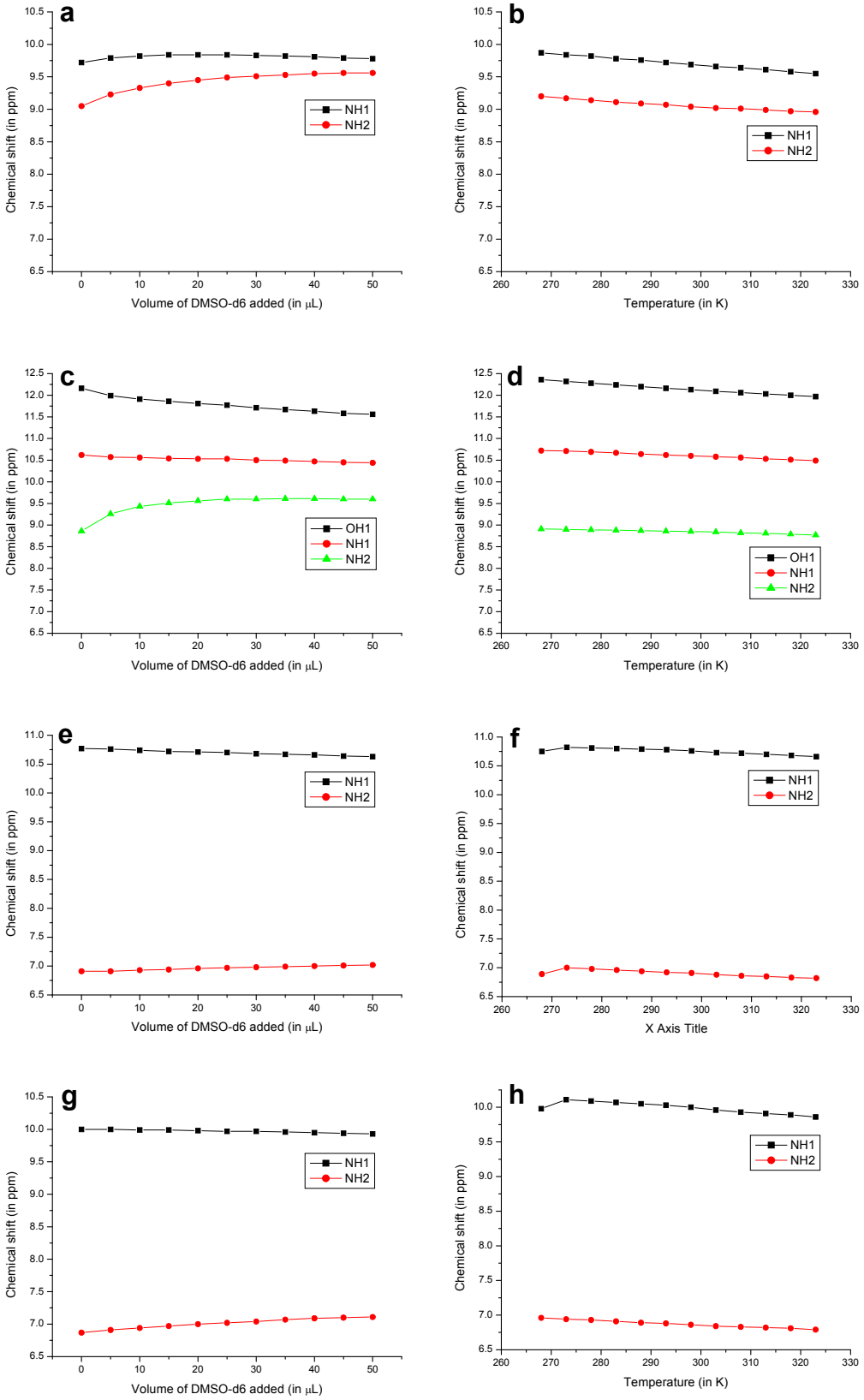


Fig. 1.26: DMSO-d_6 titration and variable temperature plots of the synthetic peptides **19a** (a,b), **20b** (c,d), **8c** (e,f) and **9** (g,h).

The amide NHs showed negligible chemical shift difference upon varying the temperature from 268 - 323 K [(Δδ/ΔT) NH1 = -5.81 ppb /deg K for **19a**; (Δδ/ΔT) NH1 = -4.18, (Δδ/ΔT) OH1 = -7.09 ppb /deg K for **20b**, (Δδ/ΔT) NH1 = -1.63 ppb /deg K for **8c** and (Δδ/ΔT) NH1 = -2.90 ppb /deg K for **9]** suggesting the involvement of strong intra-molecular hydrogen-bonding (Fig.1.26b, d, f, h).

1.9 Conclusion

In conclusion, the robust C_9-hydrogen-bonded *pseudo* β-turn[39b,61] can be modulated by putting hydrogen-bond donor and acceptor groups at the N- and C-terminus of the peptides comprising Ant-Pro motif. Extensive investigations clearly suggest that synthetic peptides lacking hydrogen-bond donor ability at N-terminus display a typical intramolecular 9-membered hydrogen-bonding network. However, oligopeptides having NHAc as hydrogen-bond donor group at N-terminus display a typical fully folded conformation featuring twin-fold. The requirement of each hydrogen-bonded networks as crucial for the formation of such a structural architecture suggests that they work in a cumulative and mutually accommodative manner in helping the peptide adopt a preferred folded conformation.[64] This work illustrates that multiple hydrogen-bondings of dissimilar structural features can "symbiotically" cause and stabilize peptide folding. The structural architecture of these synthetic peptides is in stark contrast to the conformation reported for oligo-anthranilamides, which assume extended sheet structure.[45b] The findings disclosed herein will have the potential to design novel conformationally restricted structures and would help augment the conformational space available for synthetic oligomer design with diverse backbone architectures. The unusual observation with the folding characteristics seen in peptides containing Ant and Pro residues in 2:1 ratios suggests that these residues of constitutional ratios other than 1:1 and 2:1 might give further insights into the folding characteristics of these synthetic oligomers.

Design, Synthesis and Conformational Studies of Oligomers with Proline and Anthranilic acid with Sequence Diversity

1.10 Introduction

In part A, we had elaborate description and our contribution about hybrid peptides containing various constitutional ratios of the individual amino acid residues which have been shown to adopt different secondary structures.[28b,64]

Another strategy useful for backbone conformational modulation is the chirality alteration of backbone amino acid residues.[66] Backbone conformational modulation of -Leu-Leu-Aib-Leu-Leu-Aib- peptides has been elegantly demonstrated by Demizu *et al.* by the appropriate incorporation of the chirality altered amino acid residues in the backbone *de novo* design of myriad of well defined secondary structures.[66b] Indeed, there are several examples which suggest that minute change in the chirality affect the overall conformation of peptides, especially those containing D-Pro residues.[67] Sanjayan *et al.* recently showed that the chirality altered oligomers show well-defined helical conformation featuring 9-membered-ring hydrogen-bonded networks without compromising conformational rigidity, although they differ in the handedness of the helical architectures.[61a]

Herein, the design, synthesis and conformational studies of oligomers having Ant-Pro motif with sequence diversity and chirality alteration are described.

1.11 Objective of the present work

In part A of this chapter 1, we have demonstrated how the competition between different secondary structures and peptides containing Ant and Pro residues with 2:1 constitutional ratio manifest in generating novel secondary structures.[64] The work described herein aims at studying the complexity in folding behaviour by introducing an additional amino acid proline at the N-terminal, forming tetramer building blocks Pro-Ant-Ant-Pro with altering chirality of prolines and investigating their conformational features. [66] It is noteworthy that variation in constitutional ratio very often gives rise to striking hydrogen-bonding patterns.[29,48,64]

1.12 Design strategy

Continuing the previous work, we designed the Pro-Ant-Ant-Pro motif-based foldamers **(**Fig. 1.27) anticipating that the corresponding oligomers would adopt a well-defined, compact, three dimensional structure, governed by a combined conformational restriction imposed by the individual secondary structural preferences of individual amino acid residues on the backbone.

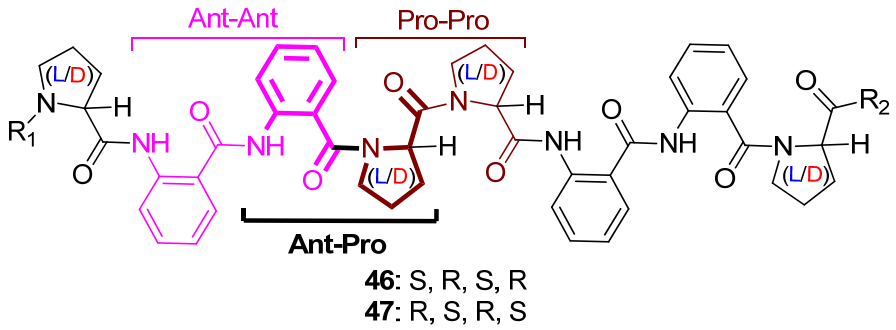
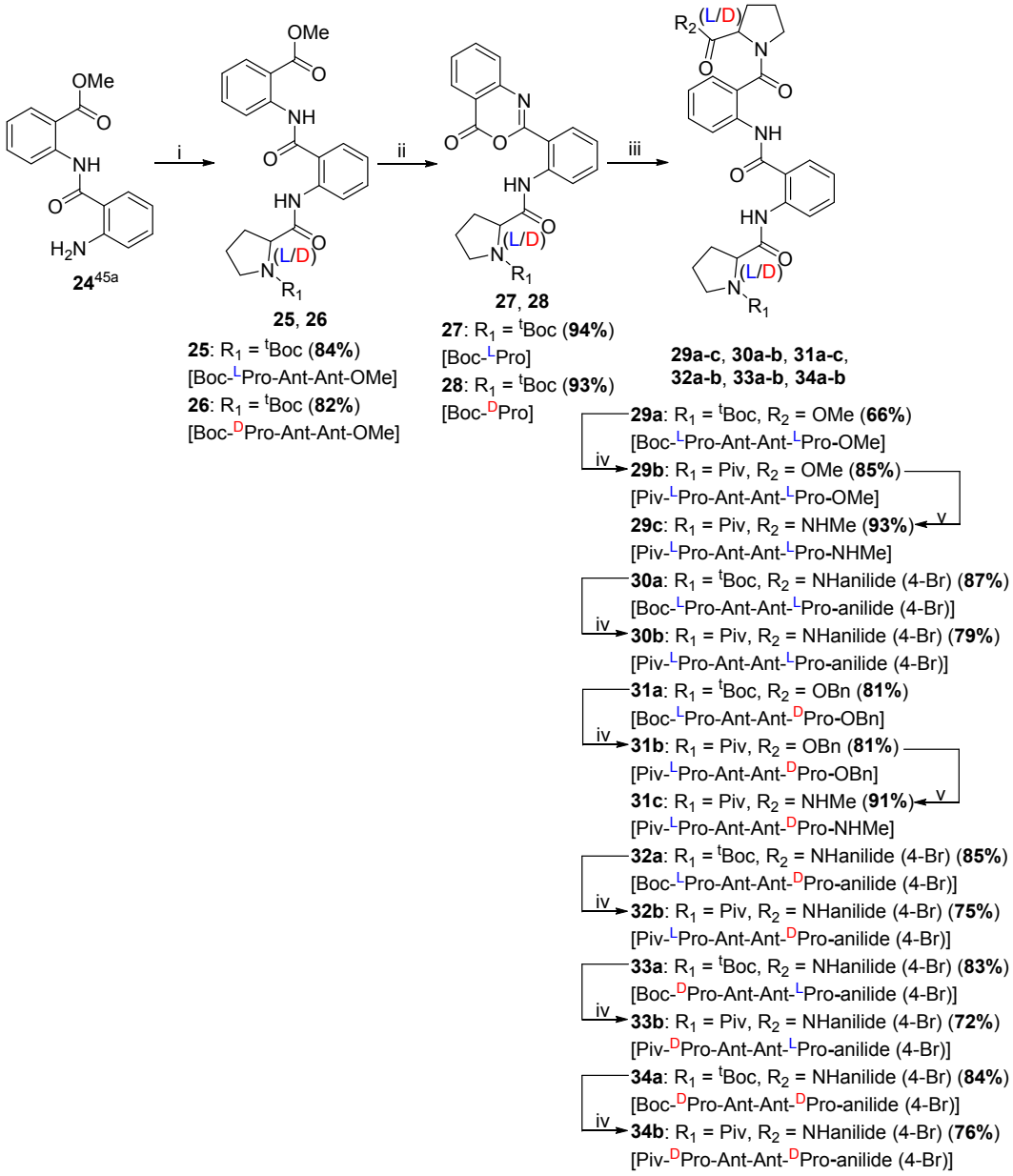


Fig. 1.27: Design principle of the hybrid foldamer (Pro-Ant-Ant-Pro)$_2$.

1.13 Synthesis

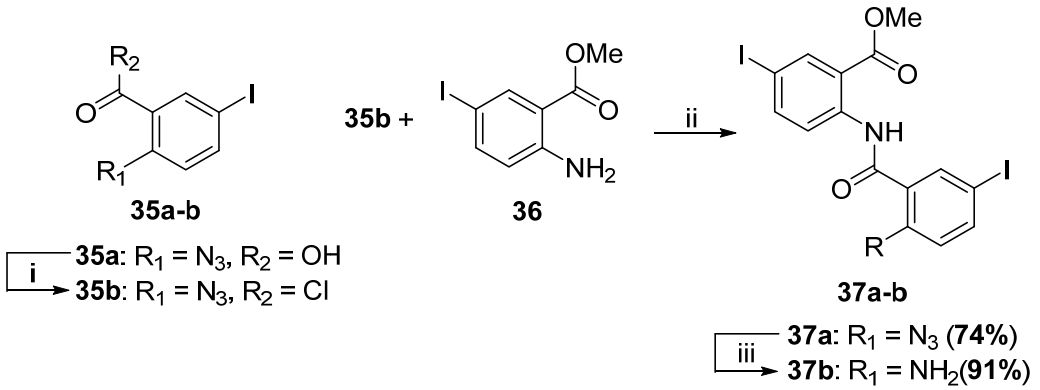
The tetrapeptide building blocks were synthesized as described in Scheme 1.4. The H-Ant-Ant-OMe[45a] **24** was coupled with Boc-$^{(L/D)}$Pro-OH by active ester method to furnish tripeptide **25** and **26.** Hydrolysis of the ester group followed by C-terminal activation furnished benzoxazinones **27** and **28**, respectively, starting from ester **25** and **26**. The benzoxazinone **27** and **28** were subjected to DBU-mediated ring opening by the amines H-^{L}Pro-OMe for **29a**, H-^{L}Pro-anilide (4-Br) for **30a** and **33a**, H-^{D}Pro-OBn for **31a** and H-^{D}Pro-anilide (4-Br) for **32a** and **34a** to afford the expected tetrapeptides in good yields. It is noteworthy that all oligomers having BOC group at the N-termini undergo *cis-trans* isomerizations[68,69] and for the ease of NMR studies, pivaloyl analogues were synthesized from their N-Boc substituted tetrapeptides. The C-terminal methyl amides **29c** and **31c** were accessed readily by direct amidation of the corresponding esters **29b** and **31b** respectively, using saturated methanolic methyl amine (Scheme 1.4).



Scheme 1.4: Synthesis of building blocks **29a-c**, **30a-b**, **31a-c**, **32a-b**, **33a-b** and **34a-b**. **Reagents and conditions:** (i) a. Boc-$^{(L/D)}$Pro-OH, ethylchloroformate, Et_3N, THF, 0 °C, 15 min.; b. **24**, THF, 0 °C then reflux, 8 h; (ii) a. aq. $LiOH.H_2O$, MeOH, rt, 12 h; b. EDC.HCl, HOBt, DCM, 10 min.; (iii) amine [H-^{L}Pro-OMe for **29a**, H-^{L}Pro-anilide (4-Br) for **30a** and **33a**; H-^{D}Pro-OBn for **31a** and H-^{D}Pro-anilide (4-Br) for **32a** and **34a**], DBU, DMF, 4Å MS, 0 °C then rt, 2 h; (vi) a. TFA:DCM (1:1), rt, 1h; b. Piv-Cl, Et_3N, DCM, 0 °C then rt, 5 h; (v) methanolic $MeNH_2$, rt, 5 h.

The iodo functionality has been introduced in the oligomers for the ease of their crystallization and further functionalization, since aryl halides, in particular iodides, can be extensively subjected to substitutional modulation.[70] The

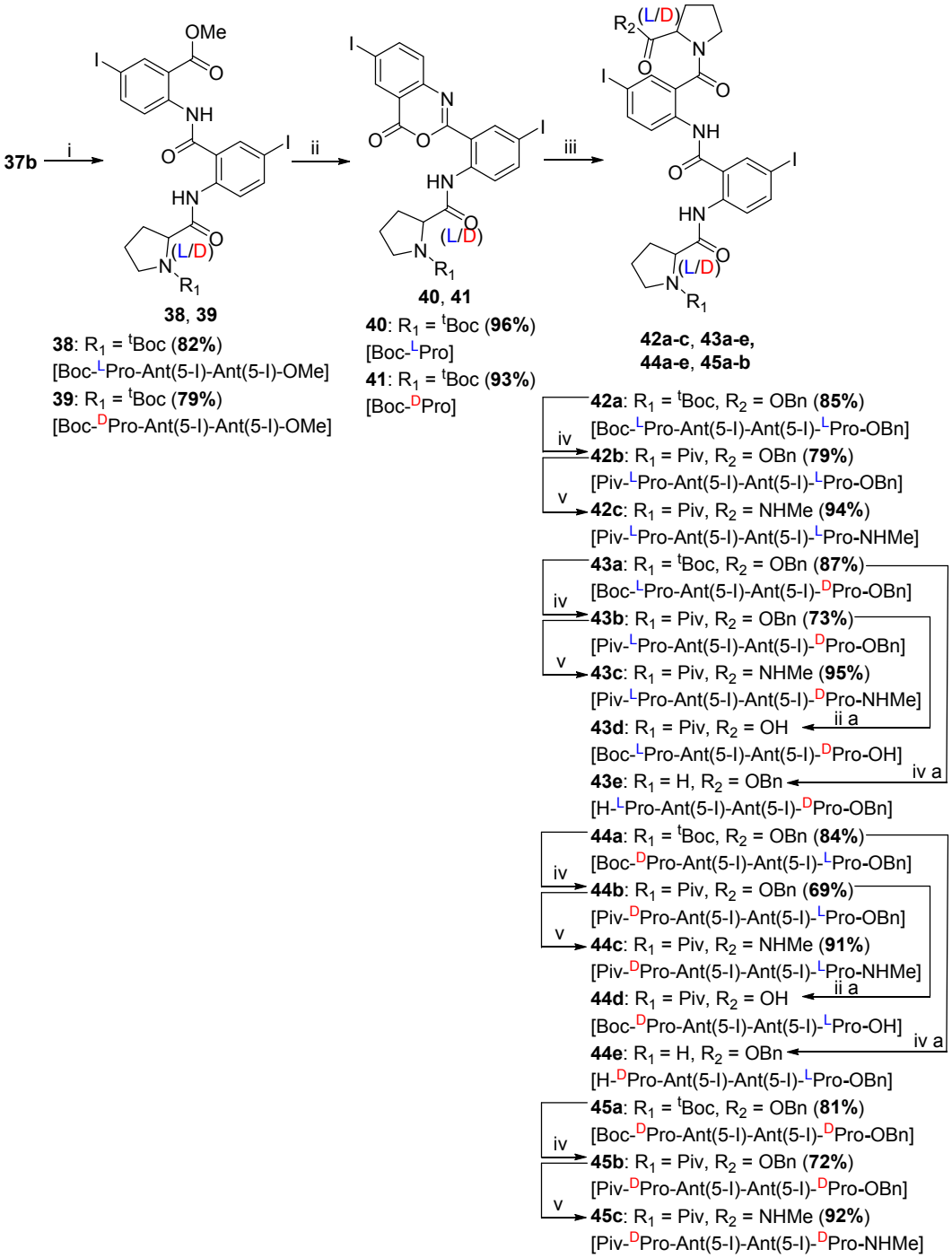
H-Ant(5-I)-Ant(5-I)-OMe dipeptide building block was synthesized as described in Scheme 1.5.



Scheme 1.5: Synthesis of building dipeptide building block **37b**. **Reagents and conditions:** (i) a. $(COCl)_2$, DMF, DCM, 0 °C then rt, 3 h; (ii) pyridine, DCM, 0 °C then rt, 5 h; (iii) $CeCl_3.7H_2O$, NaI, CH_3CN, reflux, 24 h.

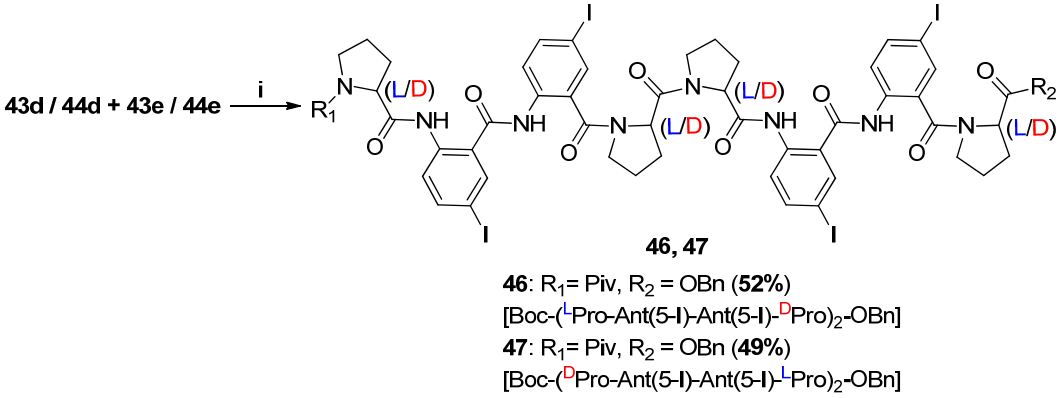
The azido acid **35a** was coupled with 5-iodo methyl anthranilate **36** using the acid chloride strategy furnishing the dipeptide **37a**, which was subsequently reduced using $CeCl_3.7H_2O$/NaI[71] system in acetonitrile to afford the amine dipeptide building block **37b** (Scheme 1.5).

The iodo tetrapeptide building blocks were synthesized as described in Scheme 1.6. The amine dipeptide building block **37b** was coupled with Boc-$^{(L/D)}$Pro-OH by active ester method to furnish tripeptides **38** and **39**. Hydrolysis of the ester group fallowed by C-terminal activation furnished benzoxazinone **40** and **41** respectively, starting from ester **38** and **39**. The benzoxazinone **40** and **41** was subjected to DBU-mediated ring opening by the amines: H-^{L}Pro-OBn for **42a** and **44a** and H-^{D}Pro-OBn for **43a** and **45a**, to afford the expected tetrapeptides in good yields. For the ease of NMR studies, pivaloyl analogues were synthesized from their N-Boc substituted tetrapeptides. The C-terminal methyl amides **42c**, **43c**, **44c** and **45c** were accessed readily by direct amidation of the corresponding esters **42b**, **43b**, **44b** and **45c**, using saturated methanolic methyl amine (Scheme 1.6).



Scheme 1.6: Synthesis of building blocks **42c**, **43c**, **44c** and **45c**. **Reagents and conditions:** (i) a. Boc-$^{(L/D)}$Pro-OH, ethylchloroformate, Et_3N, THF, 0 °C, 15 min.; b. **37b**, THF, 0 °C then reflux, 8 h; (ii) a. aq. $LiOH.H_2O$, MeOH, rt, 12 h; b. EDC.HCl, HOBt, DCM, 10 min.; (iii) amine [H-^{L}Pro-OBn for **42a** and **44a**, H-^{D}Pro-OBn for **43a** and **45a**], DBU, DMF, 4Å MS, 0 °C then rt, 2 h; (iv) a. TFA:DCM (1:1), rt, 1h; b. Piv-Cl, Et_3N, DCM, 0 °C then rt, 5 h; (v) methanolic $MeNH_2$, rt, 5 h.

The octapeptides **46** and **47** were prepared by coupling the corresponding acids with the amines, using EDC.HCl (Scheme 1.7).



Scheme 1.7: Synthesis of oligomers **46** and **47**. **Reagents and conditions:** (i) EDC.HCl, HOBt, DCM, rt, 5 h.

1.14 Conformational analyses

Extensive efforts to crystallize the octamers **46** and **47** to explore their solid-state conformational features did not meet with success, since none of them crystallized, despite best efforts. All oligomers were readily soluble in non-polar solvents suggesting that the backbone amide NHs are strongly solvent shielded, preventing aggregation in solution.[72] Unfortunately, due to chemical shift overlapping, the conformational studies of the octameres **46** and **47** posed considerable challenges. Thus, the conformational investigations of tetrapeptide building blocks were undertaken. The conformational features of tetrapeptides themselves were quite interesting. Secondary structural analyses were accomplished by extensive 2D NMR, single crystal X-ray diffraction and circular dichroism (CD) studies.

1.14.1 Single crystal X-ray diffraction studies

Extensive efforts to crystallize the tetrpeptides resulted in the formation of crystals of **30a**, **32a**, **33a** and **34a**[73] from a solvent mixture of methanol containing few drops of chloroform.

Analysis of the crystal data revealed the presence of a helical conformation with homochiral proline tetramers featuring a combination of C_6- and C_9-hydrogen-bonding networks while the heterochiral tetramers show only C_6-hydrogen-bonding (Fig. 1.28). In the oligomers featuring 1:2:1 constitutional ratio of individual amino acids, the hydrogen-bonding network is seen to be switched

from 9-membered to 6-membered secondary structure by backbone chirality alteration, unlike in the 9-membered ring hydrogen-bonding observed in α/β-hybrid oligomers in 1:1 ratio.[61a]

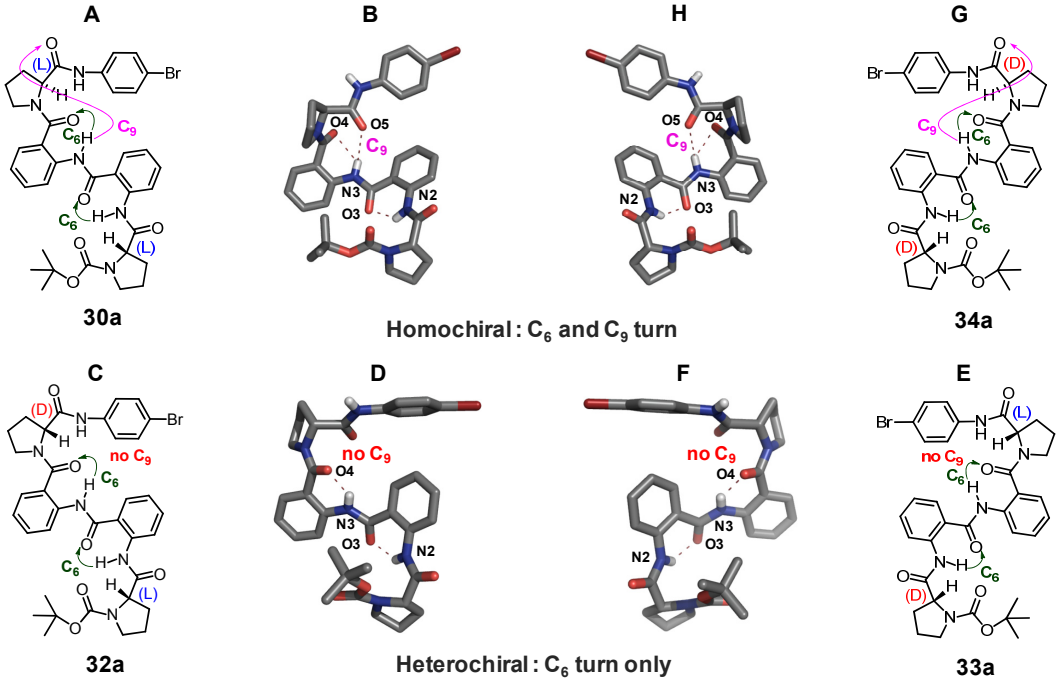


Fig. 1.28: Molecule structure and crystral structures of homochiral tetramers **30a** (A,B) and **34a** (G,H) showing a combination of C_6- and C_9-H-bonding and while the heterochiral tetramers **32a** (C,D) and **33a** (E,F) showing only C_6-H-bonding. *Note*: All hydrogens, except the polar ones, have been deleted for clarity in the crystal structures. The tetramers exist in two conformations in the crystals.

The crystal structures of homochiral tetramers **30a** and **34a** (Fig. 1.28B and H) display a intramolecular C_6-hydrogen-bonding [hydrogen-bond geometric parameters: N2-H2N···O3; H2N···O3 = 1.97 Å, N2···O3 = {2.672(3)-2.674(2) Å}, ∠N2-H2N···O3 = {135.7°-135.9°} and the planarity of the hydrogen bond torsion angle ∠(N2–H2N…O3=C13) = {-11.31°-10.86°}] and typical C_9-hydrogen-bonding [hydrogen-bond geometric parameters: N3-H3N···O5; H3N···O5 = 2.42 Å, N3···O5 = {3.102(2)-3.105(4) Å}, ∠N3-H3N···O5 = 134.4°, and the planarity of the hydrogen bond torsion angle ∠(N3–H3N…O5=C25 = {-133.65°-134.41°}].

The crystal structures of heterochiral tetramers **32a** and **33a** (Fig. 1.28D and F) display a typical intramolecular C_6-hydrogen-bonding [hydrogen-bond geometric parameters: N2-H2N···O3; H2N···O3 = {2.02-2.05 Å}, N2···O3 =

{2.722(2)-2.738(4) Å}, ∠N2-H2N···O3 = {134.5°-135.4°} and the planarity of the hydrogen bond torsion angle ∠(N2–H2N…O3=C13) = {-10.71°-14.95°}; N3-H3N···O4; H3N···O4 = 1.91 Å, N3···O4 = {2.633(2)-2.640(4) Å}, ∠N3-H3N···O4 = {138.7°-138.9°} and the planarity of the hydrogen bond torsion angle ∠(N3–H3N…O4=C20 = {-37.73°-32.98°}].

1.14.2 NMR studies

We undertook extensive NMR studies ($CDCl_3$, 500 MHz) to provide insights into the solution-state conformation of the pivolyl tetramers **30b** and **32b**. The signal assignments were made unambiguously using a combination of two-dimensional COSY, HSQC, HMBC, TOCSY and NOESY experiments. Details of the peak assignments with tables and spectra are provided in the experimental section of this chapter.

Analysis of the crystal structure of **30a** had suggested that the most characteristic nOe that is essential to support the helical conformation of its pivolyl analogue **30b** would be the requirement of a diagnostic long range inter-residual dipolar coupling of C33H of pivolyl group with the protons C24H of Pro2 (Fig. 1.29d) and C27H of Ar3 (Fig. 1.29c) suggesting that both the N- and C-termini are in close proximity due to helicity.

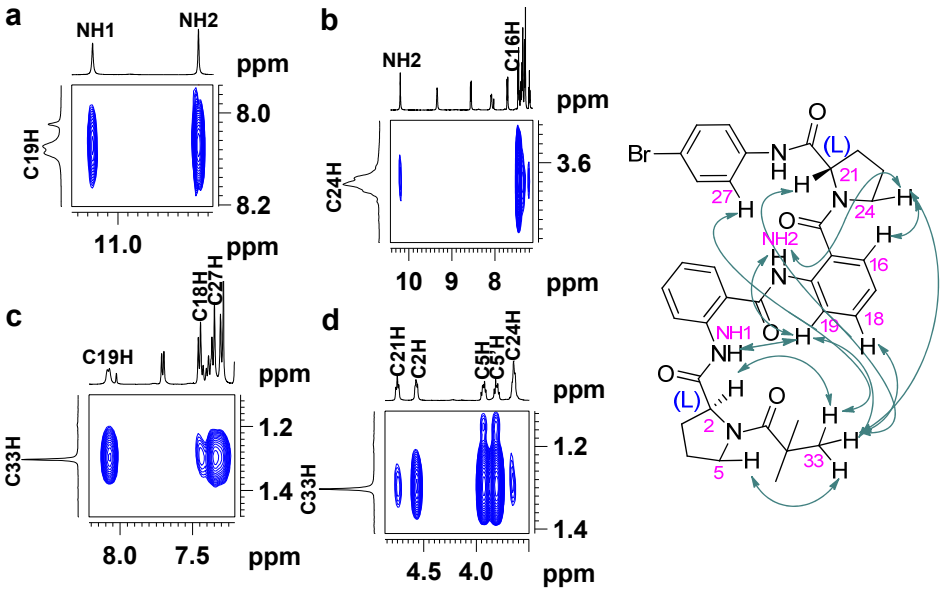


Fig. 1.29: Selected nOe extracts from the 2D NOESY data of **30b** ($CDCl_3$, 500 MHz).

The conformation of heterochiral tetramer **32b** is readily distinguished from its homochiral tetramer **30b** by the typical nOes viz. C9H with C21H and NH3 (see, Fig. 1.30a, b, for typical nOe interactions). The diagnostic long range inter-residual dipolar coupling between C33H of pivolyl group and the protons C24H of Pro2 (Fig. 1.30f) and C27H and C28H of Ar3 (Fig. 1.30d) reveals that both the N- and C-termini are in close proximity due to helicity.

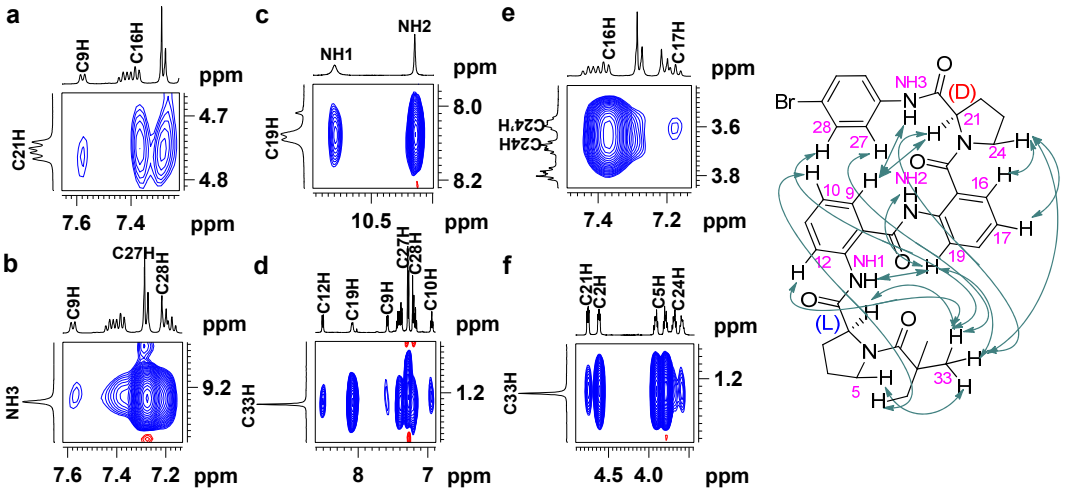


Fig. 1.30: Selected nOe extracts from the 2D NOESY data of **32b** ($CDCl_3$, 500 MHz).

In order to distinguish the hydrogen bonding interactions (inter *vs* intra), we undertook DMSO-d_6 titration, $CDCl_3$ dilution and variable temperature experiments (Fig. 1.31). Notably, all the amide NHs except NH3 of the tetrmers that are involved in intramolecular hydrogen-bonding, showed negligible shifts in DMSO-d_6 titration experiment [Δδ (NH1): < 0.19 ppm and Δδ (NH2): < 0.03 ppm for **30b** and Δδ (NH1): < -0.06 ppm and Δδ (NH2): < -0.04 ppm for **32b**) suggesting the involvement of strong intra-molecular hydrogen-bonding (Fig.1.31a, d). The same trend was observed in solvent $CDCl_3$ dilution study as well [Δδ (NH1): < 0.13 ppm and Δδ (NH2): < -0.01 ppm for **30b** and Δδ (NH1): < -0.06 ppm and Δδ (NH2): < -0.04 ppm for **32b**) (Fig.1.31b, e). Further, the amide NHs showed negligible chemical shift difference upon varying the temperature from 268 - 323 K [(Δδ/ΔT) NH1 = -3.09, (Δδ/ΔT) NH2 = -4.18 ppb /deg K for **30b** and (Δδ/ΔT) NH1 = +1.81, (Δδ/ΔT) NH2 = -3.63 ppb /deg K for **32b]** suggesting the involvement of strong intra-molecular H-bonding (Fig.1.31c, f).

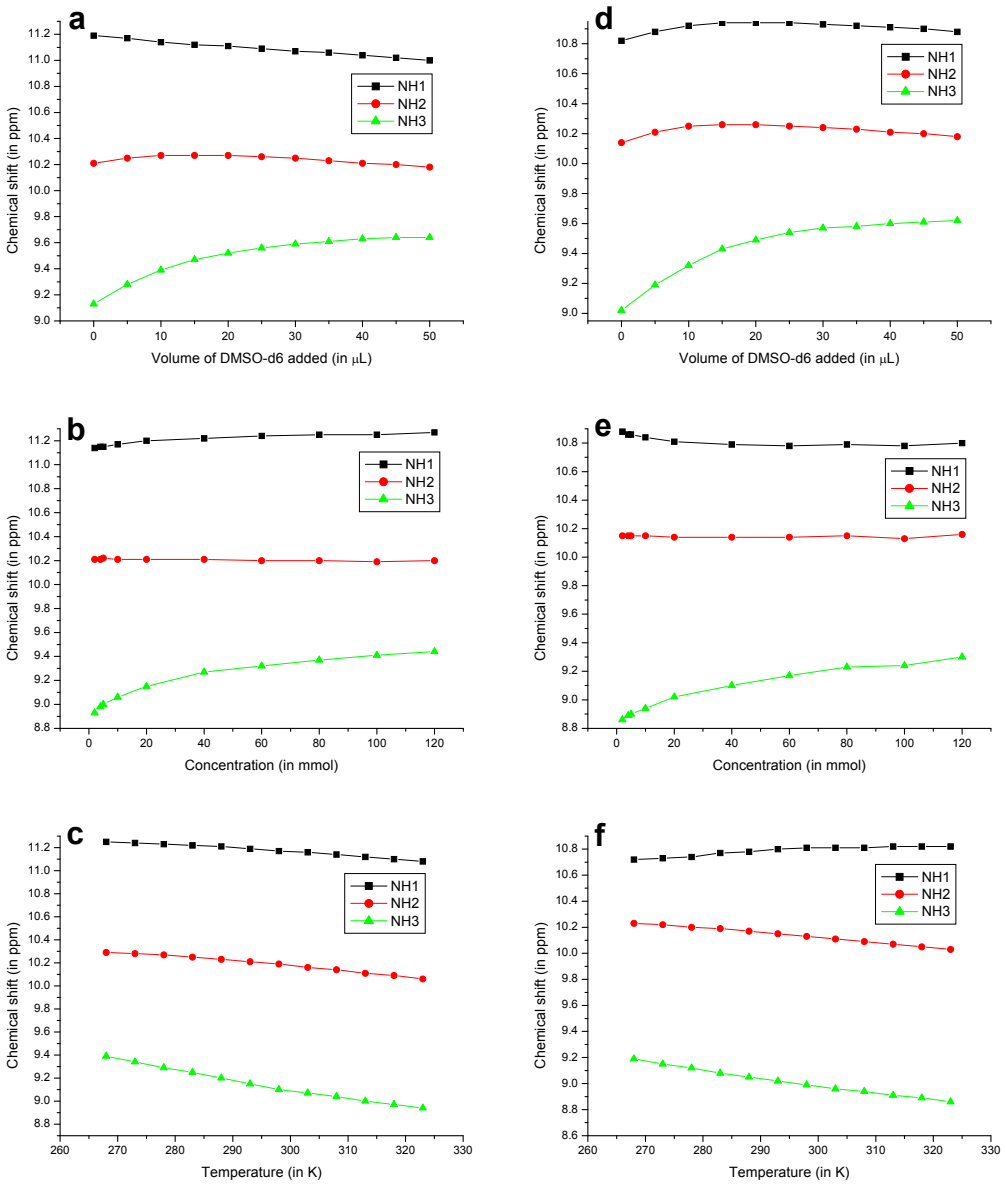


Fig. 1.31: DMSO-d_6 titration, $CDCl_3$ dilution and variable temperature plots of tetrapeptide **30b** (**a**, **b**, **c**) and **32b** (**d**, **e**, **f**).

1.14.3 Circular dichroism (CD) Studies:

Circular dichroism (CD) spectra provide characteristic signature for the conformational features of ordered chiral oligomers. The difference in the chiral and conformational behaviour of tetramers is indeed reflected in the circular dichroism (CD) spectra (Fig. 1.32).[74] The homo chiral LL tetramer **30a**, featuring C_6- and C_9-hydrogen-bonding shows a maxima at 200 nm, zero-crossing at 216 nm and a strong minima at 245 nm which is found to be exact mirror image absorbance observed for DD tetramer **34a**. The hetero chiral LD tetramer **32a** on

the other hand shows entirely different spectral patterns exhibiting maxima at 200 nm and 222 nm, zero-crossing at 230 nm and strong minima at 244 nm. The DL tetramer **33a** shows the exact mirror image of absorbance observed for LD tetramer **32a**. A weak second minima (cotton effect) is observed in **30a** and **32a-34a,** near 300 nm, due to the presence of aromatic groups.[74a]

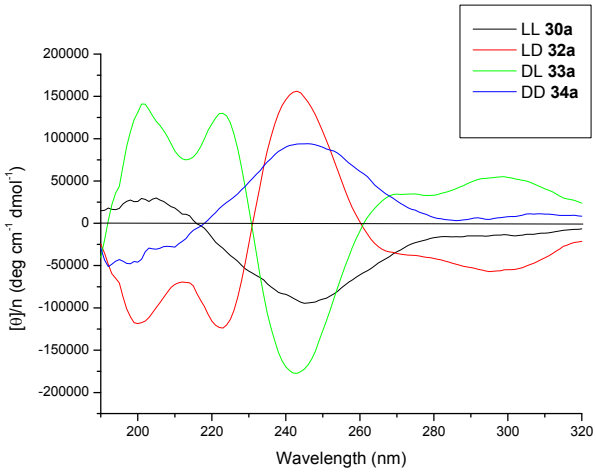


Fig. 1.32: CD absorption spectra (298K) of Pro-Ant tetramers: LL tetrapeptide **30a**, LD tetrapeptide **32a**, DL tetrapeptide **33a** and DD tetrapeptide **34a** in trifluoroethanol. All spectra recorded at 298 K with a concentration 0.02 mM.

1.15 Conclusion

In conclusion, Pro-Ant hetero oligomers featuring of α/β/α foldamer motif in 1:2:1 constitutional ratio of individual amino acids is seen to be switching from 9-membered to 6-membered secondary structure by backbone chirality alteration. The structural architecture of these hetero oligomers is unlike the conformation reported for oligo Pro-Ant motifs, with constitutional ratio 1:1, which assume right-handed helical structural architecture, displaying an unusual (1→2)-type 9-membered-ring pseudo β-turn.[39b,61a] It is noteworthy that the hydrogen bonding observed herein is distinct from the folding characteristics seen in peptide containing Ant and Pro residues in 2:1 ratio.[64] The findings disclosed herein have the potential to design novel conformationally restricted structures using steric and dihedral angle constraints of altering chirality, and would help augment the conformational space available for synthetic oligomer design with diverse backbone structures.

1.16 Experimental Section (Part A)

Single crystal X-ray crystallographic studies:

Crystal Data: X-ray intensity data measurements of all the compounds (**3b**, **3c**, **4a**, **5a**, **6c, 7b** and **19a**) were carried out on a Bruker SMART APEX I CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ωscan width of 0.3° at different settings of φ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data collection was monitored by SMART program (Bruker, 2006).[75]

X-ray intensity data measurements of all the compounds (**18**, **20b** and **23**) was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 100 (2) K. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX 2 program (Bruker, 2006).[75]

All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006).[75] SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms for compounds **3b**, **3c**, **6c**, **18**, **19a** and **23** were located in difference Fourier map and refined isotropically whereas for compounds **4a** and **7b**, they were placed in geometrically idealized positionand constrained to ride on their parent atoms. Most of H-atoms in compound **5a** were located in difference Fourier map and refined isotropically except for the proline H-atoms, which were placed in geometrically idealized position and constrained to ride on their parent atoms. All the hydrogen atoms for compounds **20b** was placed in geometrically idealized position and constrained to ride on their parent atoms except H atom H4A of **20b** was located in difference Fourier map and refined isotropically. Molecular and packing diagrams were generated using ORTEP-32, Mercury-3 and Pymol.[76] Geometrical calculations were performed using SHELXTL (Bruker, 2006) and PLATON.[77]

Crystal data for 3b: Colorless crystals of **3b** were grown by slow evaporation of diethyl ether solution. $C_{20}H_{20}N_4O_5$, M = 396.40, colorless needle, 0.78 x 0.16 x 0.10 mm^3, monoclinic, space group $P2_1$, a = 10.9252(7), b = 8.9395(6), c = 11.2908(7) Å, β = 116.821(2)°, V = 984.09(11) $Å^3$, Z = 2, T = 100(2) K, $2\theta_{max}$ = 57.64°, D_{calc} (g cm^{-3}) = 1.338, $F(000)$ = 416, μ (mm^{-1}) = 0.098, 13960 reflections collected, 4884 unique reflections (R_{int} = 0.0287), 4452 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.927, T_{max} = 0.990, 343 refined parameters, S = 1.054, $R1$ = 0.0386, $wR2$ = 0.0808 (all data R = 0.0443, $wR2$ = 0.0833, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.302, $\Delta\rho_{min}$ = -0.193 ($eÅ^{-3}$).

Crystal data for 3c: Colourless crystals of **3c** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{22}H_{24}N_4O_4$, M = 408.45, colorless plate, 0.31 x 0.21 x 0.16 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.4632(17), b = 11.4185(19), c = 16.753(3) Å, V = 2001.5(6) $Å^3$, Z = 4, T = 133(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.355, $F(000)$ = 864, μ (mm^{-1}) = 0.095, 10141 reflections collected, 3525 unique reflections (R_{int} = 0.0217), 3416 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.971, T_{max} = 0.985, 367 refined parameters, S = 1.117, $R1$ = 0.0340, $wR2$ = 0.0793 (all data R = 0.0354, $wR2$ = 0.0800), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.196, $\Delta\rho_{min}$ = -0.167 ($eÅ^{-3}$).

Crystal data for 4a: Single crystals of **4a** were grown by slow evaporation of $CDCl_3$ solution. $C_{23}H_{26}N_4O_5$, M = 438.48, colorless needle, 0.37 x 0.06 x 0.04 mm^3, orthorhombic, space group $P2_12_12_1$, a = 7.564(3), b = 15.725(7), c = 18.913(8) Å, V = 2249.7(16) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.295, $F(000)$ = 928, μ (mm^{-1}) = 0.093, 16193 reflections collected, 3957 unique reflections (R_{int} = 0.0510), 3787 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.967, T_{max} = 0.997, 365 refined parameters, S = 1.190, $R1$ = 0.0420, $wR2$ = 0.0871 (all data R = 0.0447, $wR2$ = 0.0882, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.197, $\Delta\rho_{min}$ = -0.162 ($eÅ^{-3}$).

Crystal data for 5a: Colorless crystals of **5a** were grown by slow evaporation of a mixture of benzene and chloroform. $C_{25}H_{21}BrN_4O_5$. C_6H_6, M = 615.48, colorless

plate, 0.29 x 0.20 x 0.14 mm^3, monoclinic, space group $P2_1$, a = 9.628(3), b = 11.943(4), c = 12.282(4)Å, β = 91.847(6)°, V = 1411.5(8) $Å^3$, Z = 2, T = 133(2) K, $2\theta_{max}$ = 51.00°, D_{calc} (g cm^{-3}) = 1.448, $F(000)$ = 632, μ (mm^{-1}) = 1.504, 7184 reflections collected, 4873 unique reflections (R_{int} = 0.0215), 4521 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.669, T_{max} = 0.817, 382 refined parameters, 49 restraints applied, S = 1.000, $R1$ = 0.0300, $wR2$ = 0.0717 (all data R = 0.0326, $wR2$ = 0.0730), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.706, $\Delta\rho_{min}$ = -0.307 ($eÅ^{-3}$).

Crystal data for 6c: Colorless crystals of **6c** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{22}H_{24}N_4O_4$, M = 408.45, colorless prism, 0.17 x 0.13 x 0.09 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.4654(8), b = 11.4224(9), c = 16.7268(13) Å, V = 1999.5(3) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.357, $F(000)$ = 864, μ (mm^{-1}) = 0.095, 14600 reflections collected, 3518 unique reflections (R_{int} = 0.0295), 3459 observed ($I > 2\sigma(I)$) reflections multi-scan absorption correction, T_{min} = 0.984, T_{max} = 0.992, 367 refined parameters, S = 1.114, $R1$ = 0.0308, $wR2$ = 0.0700 (all data R = 0.0316, $wR2$ = 0.0704, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.187, $\Delta\rho_{min}$ = -0.165 ($eÅ^{-3}$).

Crystal data for 7b: Colorless crystals of **7b** were grown by slow evaporation a mixture of dichloromethane and acetonitrile. $C_{20}H_{21}N_3O_3$, M = 351.40, colorless needle, 0.61 x 0.20 x 0.09 mm^3, monoclinic, space group $P2_1/c$, a = 21.610(3), b = 8.6706(12), c = 21.210(3) Å, β = 118.719(2)°, V = 3485.2(8) $Å^3$, Z = 8, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.339, $F(000)$ = 1488, μ (mm^{-1}) = 0.092, 17077 reflections collected, 6121 unique reflections (R_{int} = 0.0619), 5518 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.947, T_{max} = 0.992, 480 refined parameters, S = 1.054, $R1$ = 0.0511, $wR2$ = 0.1208 (all data R = 0.0561, $wR2$ = 0.1240, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.343, $\Delta\rho_{min}$ = -0.335 ($eÅ^{-3}$). C18' atoms of the proline moiety in this compound showed positional disorder over two positions (C18' and C18") which have been refined with occupancies 0.6 and 0.4 respectively.

Crystal data for 18: Colorless crystals of **18** were grown by slow evaporation of a mixture of solvents methanol and dichloroethane. $C_{19}H_{20}N_2O_3$, M = 324.37, colorless prism, 0.56 x 0.43 x 0.23 mm^3, orthorhombic, space group *Pbca*, *a* = 10.954(2), *b* = 14.385(3), *c* = 20.452(4) Å, *V* = 3222.7(11) $Å^3$, Z = 8, *T* = 100(2) K, $2\theta_{max}$ = 68.76°, D_{calc} (g cm^{-3}) = 1.337, *F*(*000*) = 1376, μ (mm^{-1}) = 0.091, 46791 reflections collected, 6690 unique reflections (R_{int} = 0.0407), 5713 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.951, T_{max} = 0.979, 218 refined parameters, *S* = 1.042, *R*1 = 0.0374, *wR*2 = 0.1038 (all data *R* = 0.0458, *wR*2 = 0.1114), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.497, $\Delta\rho_{min}$= -0.240 e$Å^{-3}$.

Crystal data for 19a: Colorless crystals of **19a** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{27}H_{24}BrN_3O_5 \cdot CHCl_3$, M = 669.77, colorless plate, 0.47 x 0.22 x 0.06 mm^3, monoclinic, space group *C*2, *a* = 25.393(4), *b* = 10.9662(16), *c* = 23.799(3) Å, β = 119.871(2)°, *V* = 5746.7(14) $Å^3$, Z = 8, *T* = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.548, *F*(*000*) = 2720, μ (mm^{-1}) = 1.753, 20868 reflections collected, 10076 unique reflections (R_{int} = 0.0447), 8967 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.493, T_{max} = 0.902, 741 refined parameters, *S* = 1.095, *R*1 = 0.0566, *wR*2 = 0.1378 (all data *R* = 0.0642, *wR*2 = 0.1437), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 2.514, $\Delta\rho_{min}$= -0.698 e$Å^{-3}$.

Crystal data for 20b: Colorless crystals of **20b** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{25}H_{21}Br_2N_3O_4$, M = 587.27, colorless needle, 0.75 x 0.03 x 0.02 mm^3, monoclinic, space group $P2_1$, *a* = 10.2958(5), *b* = 4.7767(2), *c* = 24.1232(12) Å, β = 99.459(4)°, *V* = 1170.25(9) $Å^3$, Z = 2, *T* = 100(2) K, $2\theta_{max}$ = 56.36°, D_{calc} (g cm^{-3}) = 1.667, *F*(*000*) = 588, μ (mm^{-1}) = 3.502, 14393 reflections collected, 5522 unique reflections (R_{int} = 0.0654), 3957 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.178, T_{max} = 0.933, 312 refined parameters, *S* = 0.991, *R*1 = 0.0490, *wR*2 = 0.0831 (all data *R* = 0.0827, *wR*2 = 0.0931), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.862, $\Delta\rho_{min}$= -0.570 e$Å^{-3}$.

Crystal data for 23: Colorless crystals of **23** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{18}H_{17}FN_2O_2$, M = 312.34, colorless prism, 0.67 x 0.59 x 0.25 mm^3, monoclinic, space group $P2_1/n$, a = 9.7373(3), b = 15.8914(5), c = 9.9621(3) Å, β=100.6800(10)°, V = 1514.83(8) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.370, $F(000)$ = 656, μ (mm^{-1}) = 0.099, 21647 reflections collected, 2660 unique reflections (R_{int} = 0.0240), 2390 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.937, T_{max} = 0.976, 217 refined parameters, S = 1.042, $R1$ = 0.0391, $wR2$ = 0.0929 (all data R = 0.0440, $wR2$ = 0.0972), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.397, $\Delta\rho_{min}$= -0.265 $eÅ^{-3}$. Fluorine atom at the 2-position and H-atom at 6-position of the benzoic acid residue are statistically disordered over two position with occupancies 0.9 and 0.1 respectively and vice versa.

2-(2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 2:

To a solution of the ester **1**[45a] (5 g, 16.6 mmol) in methanol (35 mL), $LiOH·H_2O$ (2.09 g, 49.9 mmol) in water (15 mL) was added at 0 °C and the reaction mixture was stirred for 12 h. After the complete consumption of the starting material, the solvent was evaporated under reduced pressure and the residue was precipitated with the addition of dilute HCl, filtered and washed repeatedly with water. The precipitate (free carboxylic acid) was then dried over P_2O_5 and was carried forward for the next reaction, without any further purification.

A solution containing the crude acid in dry DCM (40 mL) was cooled to 0 °C. The reaction mixture was then treated with acetic anhydride (1.88 mL, 19.9 mmol), pyridine (1.61 mL, 19.9 mmol) and was stirred at 0 °C for 30 min. The reaction mixture was diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solutions. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which on purification by column chromatography (80:20 pet. ether/ethyl acetate, *Rf*: 0.5) afforded **2** as a white solid (4.28 g, 96%). mp: 193-195 °C; IR ($CHCl_3$) ν (cm^{-1}): 3501, 1770, 1635, 1606, 1574, 1531, 1472, 1346, 1216, 770, 669; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.22 (d, J = 7.93 Hz,

1H), 8.17 (d, *J* = 7.93 Hz, 1H), 8.11 (d, *J* = 7.33 Hz, 1H), 8.03 (t, *J* = 7.63 Hz, 1H), 7.97 (t, *J* = 7.33 Hz, 1H), 7.92 (t, *J* = 7.94 Hz, 1H), 7.74-7.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 158.4, 154.7, 148.3, 145.7, 137.4, 133.8, 133.1, 131.3, 129.8, 128.4, 127.2, 125.1, 124.7, 116.8; LC-MS: 268.98 $(M)^+$; Elemental analysis calculated for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44; Found: C, 62.60; H, 3.12; N, 10.32.

General method for the ring opening of 2-(2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 2 with proline amines [H-^{L}Pro-CO_2Me for 3a; H-^{L}Pro-$CONHC_6H_4$(4-Br) for 5a; H-^{D}Pro-CO_2Bn for 6a and pyrrolidine for 7a]:

Representative procedure: To a solution containing the oxazinone **2** (1 equiv), amine (1.1 equiv) and 4Å molecular sieves (0.2 g) in dry DMF at 0 °C, DBU (1.1 equiv) were added. The solution was stirred at room temperature for 2 h. The reaction mixture was quenched with dilute HCl solution and diluted with DCM. The organic layer was repeatedly washed with water followed by brine solution and was dried over anhydrous Na_2SO_4. It was then evaporated under reduced pressure to obtain the crude product which was purified by column chromatography.

(S)-methyl 1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 3a:

The product **3a** was obtained as sticky substance (2.55 g, 69%). $[\alpha]^{24}_{D}$: -44° (*c* = 0.9, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3325, 1740, 1687, 1626, 1597, 1532, 1418, 1349, 1215, 755, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 8.46 (d, *J* = 8.34 Hz, 1H), 8.08 (d, *J* = 7.96 Hz, 1H), 7.69-7.64 (m, 2H), 7.62-7.55 (m, 1H), 7.53-7.47 (m, 1H), 7.43-7.36 (m, 1H), 7.21 (dt, *J* = 0.76 Hz, *J* = 7.45 Hz, 1H), 4.64-4.58 (m, 1H), 3.66-3.54 (m, 1H), 3.58 (s, 3H), 3.50-3.42 (m, 1H), 2.40-2.25 (m, 1H), 2.06-1.85 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.5, 168.3, 164.7, 146.2, 135.4, 133.6, 132.7, 130.8, 130.4, 128.9, 126.5, 125.5, 124.2, 123.9, 122.1, 58.7, 52.2, 49.6, 29.1, 24.8; LC-MS: 420.07 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.57; Found: C, 60.28; H, 5.01; N, 10.41.

General method for C-terminal amidation: Synthesis of 3b and 6b:

***Representative procedure**:* The esters **3a** and **6a** were taken in saturated methanolic methylamine solution and stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to yield pure **3b** and **6b** respectively.

(S)-N-methyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 3b:

The amide **3b** was obtained as a white solid (1.12 g, 98%). mp: 153-155 °C; $[\alpha]^{24}_{D}$: -90° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3346, 1673, 1621, 1590, 1532, 1417, 1350, 1215, 756, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 8.35 (d, *J* = 8.24 Hz, 1H), 8.10 (d, *J* = 8.24 Hz, 1H), 7.71-7.66 (m, 2H), 7.60 (t, *J* = 7.94 Hz, 1H), 7.50 (t, *J* = 7.93 Hz, 1H), 7.33 (t, *J* = 7.63 Hz, 1H), 7.21 (t, *J* = 7.63 Hz, 1H), 6.59 (bs, 1H), 4.60 (t, *J* = 5.50 Hz, 1H), 3.61-3.56 (m, 1H), 3.48-3.43 (m, 1H), 2.55 (s, 3H), 2.24-2.17 (m, 1H), 2.11-2.07 (m, 1H), 1.99-1.93 (m, 1H), 1.91-1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 168.8, 165.5, 146.2, 135.0, 133.6, 132.9, 130.6, 130.2, 129.1, 126.9, 126.3, 124.2, 124.0, 122.4, 60.0, 49.6, 29.4, 25.8, 24.7; LC-MS: 418.99 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13; Found: C, 60.43; H, 4.91; N, 14.31.

General method for N-acetylation: Synthesis of 3c, 4b, 6c and 7b:

***Representative procedure**:* A solution of the tripeptide **3b** in ethyl acetate were subjected to hydrogenolysis using catalytic amount of 10 % Pd-C and H_2 (1 atm). After complete reduction, the reaction mixture was filtered over celite and the filtrate was evaporated under reduced pressure to yield the corresponding free amine, which was subjected to acetylation without further purification.

The free amine obtained thus were taken in dry DCM and cooled to 0 °C. To the reaction mixture, acetic anhydride (1.1 equiv) was added followed by pyridine (1.1 equiv) and catalytic amount of DMAP (0.1 equiv). The reaction mixture was stirred at rt for 5 h. It was then diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was further purified by column chromatography.

(S)-1-(2-(2-acetamidobenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 3c:

The product **3c** was obtained as a white solid (0.86 g, 94%). mp: 225-227 °C; $[\alpha]^{24}_{D}$: -110° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3330, 1702, 1644, 1621, 1603, 1522, 1421, 1215, 759, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.00 (s, 1H), 10.32 (s, 1H), 8.60 (d, *J* = 8.39 Hz, 1H), 8.31 (d, *J* = 8.22 Hz, 1H), 7.72 (d, *J* = 7.40 Hz, 1H), 7.53 (t, *J* = 7.40 Hz, 2H), 7.49 (d, *J* = 8.05 Hz, 1H), 7.22 (t, *J* = 7.57 Hz, 1H), 7.18 (t, *J* = 7.89 Hz, 1H), 6.51 (s, 1H), 4.68 (t, *J* = 7.40 Hz, 1H), 3.70-3.67 (m, 1H), 3.65-3.60 (m, 1H), 2.78 (d, *J* = 4.11 Hz, 3H), 2.37-2.31 (m, 1H), 2.21 (s, 1H), 2.18-2.12 (m, 1H), 2.10-2.03 (m, 1H), 1.86-1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 169.8, 169.0, 167.5, 139.9, 136.5, 132.9, 131.4, 128.0, 127.3, 124.9, 123.7, 123.1, 122.6, 121.6, 120.6, 60.2, 51.0, 28.11, 26.3, 25.3, 25.2; LC-MS: 431.10 $(M+Na)^+$; 447.07 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; Found: C, 64.55; H, 6.09; N, 13.85.

(S)-N-tert-butyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 4a:

To the solution of ester **4a** (1 g, 2.5 mmol) in methanol (15 mL), $LiOH{\cdot}H_2O$ (0.31 g, 7.55 mmol) in water (5 mL) was added at 0 °C and the reaction mixture was stirred for 12 h. After the completion of reaction, the solvent was evaporated under reduced pressure, and the residue was neutralized with dilute HCl solution. The aqueous layer was then extracted with DCM (2 x 25 mL) and evaporated under reduced pressure to obtain the free acid which was then used for the next reaction without further purification.

To a solution of crude acid in dry DCM, tert-butyl amine (0.36 g, 5.0 mmol) was added followed by EDC.HCl (0.58 g, 3.0 mmol), and a catalytic amount of HOBt (0.03 g, 0.2 mmol) at 0 °C. The reaction mixture was then stirred at 15 min at room temperature for 8 h. The reaction mixture was diluted with DCM and washed sequentially with saturated solutions of $NaHCO_3$, $KHSO_4$, water and brine. The organic layer was then dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was purified by column chromatography (eluent: pet. ether/ethyl acetate 30:70, *Rf*: 0.6) to

afford **4a** as a white solid (0.95 g, 87%). mp: 178-180 °C; $[\alpha]^{24}_{D}$: +10° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 1673, 1624, 1589, 1531, 1456, 1421, 1350, 1215, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 8.64 (d, *J* = 8.24 Hz, 1H), 8.11 (d, *J* = 8.24 Hz, 1H), 7.71-7.66 (q, 1H), 7.67 (d, *J* = 7.02 Hz, 1H), 7.58 (t, *J* = 7.94 Hz, 1H), 7.49 (t, *J* = 7.94 Hz, 1H), 7.30 (d, *J* = 7.32 Hz, 1H), 7.19 (t, *J* = 7.33 Hz, 1H), 5.75 (bs, 1H), 4.39-4.35 (m, 1H), 3.56-3.52 (m, 1H), 3.35-3.32 (m, 1H), 2.19-2.18 (m, 1H), 1.97-1.89 (m, 2H), 1.87-1.83 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 168.4, 165.5, 146.0, 135.3, 133.6, 133.4, 130.5, 129.9, 129.3, 126.3, 126.0, 124.1, 123.9, 121.4, 60.4, 51.3, 49.4, 29.6, 28.3, 24.8; LC-MS: 439.09 $(M+H)^+$; 461.14 $(M+Na)^+$; 477.12 $(M+K)^+$; Elemental analysis calculated for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78; Found: C, 62.85; H, 6.15; N, 12.60.

(S)-1-(2-(2-acetamidobenzamido)benzoyl)-N-(tert-butyl)pyrrolidine-2-carboxamide 4b:

The product **4b** was obtained as a white solid (0.73 g, 95%). mp: 115-117 °C; $[\alpha]^{24}_{D}$: -70° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3327, 1682, 1623, 1585, 1519, 1450, 1415, 1298, 1215, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.01 (s, 1H), 10.33 (s, 1H), 8.59 (d, *J* = 8.34 Hz, 1H), 8.30 (d, *J* = 8.21 Hz, 1H), 7.76 (d, *J* = 7.76 Hz, 1H), 7.56-7.37 (m, 4H), 7.21-7.08 (m, 2H), 6.20 (bs, 1H), 4.53 (dd, *J* = 6.45 Hz, 7.46 Hz 1H), 3.62-3.44 (m, 2H), 2.33-1.98 (m, 4H), 2.19 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.9, 169.2, 168.9, 167.5, 139.8, 136.2, 132.8, 131.1, 127.8, 127.4, 125.1, 123.7, 123.0, 122.4, 121.3, 120.3, 60.8, 51.2, 50.7, 28.5, 28.3, 25.2; LC-MS: 473.20 $(M+Na)^+$; Elemental analysis calculated for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44; Found: C, 66.51; H, 6.90 ; N, 12.28.

(S)-N-(4-bromophenyl)-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 5a:

The product **5a** was obtained as white solid (0.51 g, 85%). mp: 210-212 °C; $[\alpha]^{24}_{D}$: +50° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 1677, 1618, 1542, 1534, 1427, 1350, 1218, 771, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 9.11 (s, 1H), 8.68 (d, *J* = 8.24 Hz, 1H), 8.09 (d, *J* = 7.93 Hz, 1H), 7.77 (t, *J* = 7.02 Hz, 1H), 7.67 (d, *J* = 7.01 Hz, 1H), 7.63 (t, *J* = 7.63 Hz, 1H), 7.54 (t, *J* = 7.63 Hz,

1H), 7.31 (d, *J* = 6.71 Hz, 1H), 7.24 (t, *J* = 7.02 Hz, 1H), 7.00 (d, *J* = 7.63 Hz, 1H), 6.66 (d, *J* = 7.32 Hz, 1H), 4.90-4.78 (m, 1H), 3.61-3.59 (m, 1H), 3.42-3.41 (m, 1H), 2.27-2.26 (m, 1H), 2.07-1.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 169.0, 165.7, 146.0, 136.7, 135.1, 133.8, 133.2, 131.0, 130.0, 129.4, 126.0, 125.7, 124.3, 124.3, 121.6, 120.5, 116.0, 60.8, 49.8, 29.8, 24.8; LC-MS: 559.08 $(M+Na)^+$; 561.06 $(M+2+Na)^+$; 574.98 $(M+K)^+$; 576.98 $(M+2+K)^+$; Elemental analysis calculated for $C_{25}H_{21}BrN_4O_5$: C, 55.88; H, 3.94; N, 10.43; Found: C, 56.01; H, 4.11; N, 10.24.

(S)-1-(2-(2-acetamidobenzamido)benzoyl)-N-(4-bromophenyl)pyrrolidine-2-carboxamide 5b:

A solution of the tripeptide **5a** in ethyl acetate was subjected to reduction using $SnCl_2.2H_2O$ (1.1 equiv.), heated at 50 °C. After complete reduction, the reaction mixture was filtered over celite and the filtrate was evaporated under reduced pressure to yield the corresponding free amine, which was subjected to acetylation without further purification.

The free amine obtained thus was taken in dry DCM and cooled to 0 °C. To the reaction mixture, acetic anhydride (1.1 equiv) was added followed by pyridine (1.1 equiv) and catalytic amount of DMAP (0.1 equiv). The reaction mixture was stirred at rt for 5 h. It was then diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solutions. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was further purified by column chromatography to obtain **5b** as a white solid (0.60 g, 89%). mp: 146-148 °C; $[\alpha]^{24}_D$: -200° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3312, 1693, 1658, 1621, 1586, 1519, 1417, 1300, 1215, 759, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.88 (s, 1H), 10.06 (s, 1H), 9.18 (s, 1H), 8.53 (d, *J* = 8.24 Hz, 1H), 8.27 (d, *J* = 8.24 Hz, 1H), 7.68 (d, *J* = 7.63 Hz, 1H), 7.52 (t, *J* = 8.24 Hz, 1H), 7.48 (d, *J* = 7.93 Hz, 1H), 7.44 (d, *J* = 7.63 Hz, 1H), 7.34 (d, *J* = 8.54 Hz, 2H), 7.27 (d, *J* = 8.24 Hz, 2H), 7.22 (t, *J* = 7.32 Hz, 1H), 6.97 (t, *J* = 7.32 Hz, 1H), 4.82-4.80 (m, 1H), 3.67-3.57 (m, 2H), 2.34-2.29 (m, 1H), 2.18 (s, 3H), 2.16-2.15 (m, 1H), 2.08-2.03 (m, 1H), 1.89-1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 169.1, 169.1, 167.6, 139.6, 137.0, 135.9, 132.8, 131.6, 131.3, 127.6, 127.4, 125.4, 124.0, 123.0,

122.8, 121.6, 121.2, 120.6, 120.4, 116.6, 61.0, 50.8, 28.2, 25.2, 25.1; LC-MS: 571.07 $(M+Na)^+$; 573.07 $(M+2+Na)^+$; Elemental analysis calculated for $C_{27}H_{25}BrN_4O_4$: C, 59.02; H, 4.59; N, 10.20; Found: C, 58.88; H, 4.71; N, 10.09.

(R)-benzyl 1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 6a:

The product **6a** was isolated as a white solid (0.93 g, 76%). mp: 122-124 °C; $[\alpha]^{24}_D$: +22° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3336, 1739, 1687, 1626, 1598, 1532, 1420, 1349, 1215, 759, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.39 (s, 1H), 8.41 (d, *J* = 8.21 Hz, 1H), 7.98 (d, *J* = 7.45 Hz, 1H), 7.61-7.55 (m, 2H), 7.52-7.04 (m, 9H), 5.06-4.86 (m, 2H), 4.63-4.57 (m, 1H), 3.70-3.33 (m, 2H), 2.32-2.13 (m, 1H), 2.03-1.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.9, 168.3, 164.7, 146.2, 135.4, 135.2, 133.6, 132.8, 130.8, 130.3, 128.9, 128.4, 128.2, 127.8, 126.4, 125.7, 124.2, 123.9, 122.1, 66.8, 58.8, 49.6, 29.1, 24.8; LC-MS: 496.16 $(M+Na)^+$; Elemental analysis calculated for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87; Found: C, 66.11; H, 5.13; N, 8.68.

(R)-N-methyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 6b:

The product **6b** was isolated as a white solid (0.60 g, 97%). mp: 159-161 °C; $[\alpha]^{24}_D$: +120° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3338, 1671, 1618, 1588, 1534, 1420, 1350, 1216, 756, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.32 (d, *J* = 8.34 Hz, 1H), 8.07 (d, *J* = 7.83 Hz, 1H), 7.69-7.51 (m, 3H), 7.46 (t, *J* = 7.45 Hz, 1H), 7.27-7.24 (m, 1H), 7.19 (t, *J* = 7.20 Hz, 1H), 6.78 (bs, 1H), 4.53-4.49 (m, 1H), 3.71-3.32 (m, 1H), 2.40 (s, 3H), 2.19-2.10 (m, 1H), 1.98-1.78 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.9, 168.7, 165.5, 146.1, 134.9, 133.5, 132.8, 130.5, 130.1, 129.1, 126.9, 126.2, 124.2, 124.0, 122.4, 60.0, 49.6, 29.5, 25.8, 24.6; LC-MS: 418.98 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13; Found: C, 60.75; H, 4.91; N, 13.98.

(R)-1-(2-(2-acetamidobenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 6c:

The product **6c** was isolated as a white solid (0.37 g, 92%). mp: 232-234 °C; $[\alpha]^{24}_D$: +130° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3330, 1701, 1654, 1640, 1618, 1603, 1523, 1424, 1215, 757, 669; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.47 (s, 0.8H), $10.36_{rotamer}$ (s, 0.2H), 10.20 (s, 1H), $8.28_{rotamer}$ (d, *J* = 7.93 Hz, 0.2H),

8.22 (d, *J* = 7.93 Hz, 0.8H), 7.91-7.90$_{rotamer}$ (m, 0.2H), 7.78-7.77 (m, 0.8H), 7.70-7.64 (m, 2H), 7.60-7.59 (m, 1H), 7.55-7.42 (m, 2H), 7.30-7.25 (m, 2H), 7.23-7.16 (m, 1H), 4.32-4.27 (m, 1H), 3.57-3.50 (m, 2H), 2.48-2.48 (m, 3H), 2.19-2.11 (m, 1H), 2.08$_{rotamer}$ (s, 0.7H), 2.06 (s, 2.3H), 1.83-1.80 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 172.7$_{rotamer,}$ 171.9, 168.6, 168.5$_{rotamer}$, 167.1, 166.8$_{rotamer}$, 138.2 $_{rotamer}$, 137.9, 135.0, 134.6$_{rotamer}$, 131.9$_{rotamer}$, 131.7, 131.3$_{rotamer}$, 130.2, 129.9, 128.4, 128.3$_{rotamer}$, 127.7, 126.5$_{rotamer}$, 125.1$_{rotamer}$, 125.0$_{rotamer}$, 124.8, 124.2, 124.1$_{rotamer}$, 123.2, 121.3, 62.6$_{rotamer}$, 60.4, 50.0, 46.7$_{rotamer}$, 31.6$_{rotamer}$, 30.0, 25.8$_{rotamer}$, 25.5, 24.8, 24.6$_{rotamer}$, 24.5, 22.5$_{rotamer}$; LC-MS: 431.13 $(M+Na)^+$; 447.09 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; Found: C, 64.81; H, 6.15; N, 13.53.

2-nitro-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 7a:

The product **7a** was isolated as white solid (0.63 g, 84%). mp: 149-151 °C; IR ($CHCl_3$) ν (cm^{-1}): 3310, 682, 1621, 1594, 1532, 1423, 1348, 1216, 755, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 8.34 (d, *J* = 7.96 Hz, 1H), 8.07 (d, *J* = 7.70 Hz, 1H), 7.76-7.56 (m, 3H), 7.51-7.38 (m, 2H), 7.21-7.13 (m, 1H), 3.59-3.54 (m, 4H), 2.01-1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 164.2, 146.5, 136.0, 133.7, 132.6, 130.8, 130.6, 128.5, 127.3, 125.8, 124.5, 123.7, 123.0, 50.1, 46.2, 26.2, 24.2; LC-MS: 361.92 $(M+Na)^+$; Elemental analysis calculated for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; Found: C, 63.89; H, 4.88; N, 12.49.

2-acetamido-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 7b:

The product **7b** was obtained as a white solid (0.47 g, 93%). mp: 132-134 °C; IR ($CHCl_3$) ν (cm^{-1}): 3290, 1688, 1652, 1621, 1587, 1519, 1449, 1416, 1298, 1216, 754, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.24 (s, 1H), 10.82 (s, 1H), 8.63 (d, *J* = 8.54 Hz, 1H), 8.36 (d, *J* = 8.24 Hz, 1H), 7.77 (dd, *J* = 0.91 Hz, 7.93 Hz, 1H), 7.53-7.48 (m, 2H), 7.48 (dd, *J* = 1.22 Hz, 7.63 Hz, 1H), 7.19 (dt, *J* = 2.14 Hz, 7.33 Hz, 1H), 3.66 (bs, 2H), 3.57 (bs, 2H), 2.22 (s, 3H), 1.99 (bs, 2H), 1.91 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0$_{rotamer}$, 168.7, 167.3, 140.2, 136.9, 133.0, 131.1, 127.9, 127.0, 124.9, 123.3, 123.2, 122.4, 121.5, 120.1, 50.3, 49.2$_{rotamer}$, 46.5, 45.7$_{rotamer}$, 26.4, 26.1$_{rotamer}$, 25.3, 24.2$_{rotamer}$, 24.2; LC-MS: 374.04

$(M+Na)^+$; 390.05 $(M+K)^+$; Elemental analysis calculated for $C_{20}H_{21}N_3O_3$: C, 63.71; H, 5.05; N, 12.38; Found: C, 68.17; H, 5.94; N, 12.15.

(S)-N-methyl-1-(2-nitrobenzoyl)pyrrolidine-2-carboxamide 10a:

To an ice-cold stirred solution of the 2-nitro benzoic acid (1 equiv) in dry DCM was added dry DMF (0.1 equiv) followed by oxalyl chloride (1.1 equiv). The resulting mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure. The residue containing the acid chloride was dissolved in dry DCM and added drop wise to an ice cooled solution of HCl.H-^{L} Pro-OMe (1.1 equiv) and Et_3N (3 equiv) in DCM. The reaction mixture was then stirred at room temperature for 6 h. The reaction mixture was diluted with DCM, and the organic layer was washed sequentially with dil. HCl solution, water, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which was further purified by column chromatography. To a solution of the nitro ester was added saturated methanolic methylamine solution and stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to afford **10a** as a colourless liquid (2.17 g, 65%). $[\alpha]^{24}_D$: -120° (*c* = 1.15, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3338, 3005, 1637, 1529, 1420, 1348, 753; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.24 (d, *J* = 8.21 Hz, 1H), 7.80-7.70 (q, 1H), 7.65 (d, *J* = 8.21 Hz, 1H), 7.49 (dd, *J* = 1.39, 7.45 Hz, 1H), 7.08 (bs, 1H), 4.73 (m, 1H), 3.32-3.11 (m, 2H), 2.88 (dd, *J* = 1.64, 4.80 Hz, 2.7H), $2.79_{rotamer}$ (dd, *J* = 2.02, 4.80 Hz, 0.3H), 2.63-2.39 (m, 1H), 2.17-1.84 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.1, 167.2, 144.6, 134.8, 134.5, 132.9, 130.1, 128.1, 124.8, 60.1, 48.9, 48.7, 28.2, 26.3, 24.5; LC-MS: 300.08 $(M+Na)^+$; Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15; Found: C, 56.05; H, 5.60; N, 14.98.

General method for reduction: Synthesis of 10b and 11b:

Representative procedure: A solution of the dipeptides (**10a** and **11a**) in ethyl acetate were subjected to hydrogenolysis using catalytic amount of 10% Pd-C and H2 (1 atm). After completion of the reaction, the catalyst was filtered over celite and the filtrate was evaporated under reduced pressure to yield the corresponding free amines (**10b** and **11b**) respectively, which were carried forwarded for the next reaction without further purification.

General method for synthesis of 11a and 12a:

***Representative procedure**:* To an ice-cold stirred solution of the 2-nitro benzoic acid (1 equiv) in dry DCM was added dry DMF (0.1 equiv) followed by oxalyl chloride (1.1 equiv). The resulting mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure. The residue containing the acid chloride was dissolved in dry DCM and added drop wise to an ice cooled solution of pyrrolidine (2 equiv) and Et_3N (3 equiv) for **11a** or H-^{L}Pro-anilide (4-Br) (1.1 equiv) and Et_3N (2 equiv) for **12a** in DCM. The reaction mixture was then stirred at room temperature for 6 h. The reaction mixture was diluted with DCM, and the organic layer was washed sequentially with dil. HCl solution, water, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products, which were further purified by column chromatography to afford **11a** and **12a** respectively.

(2-nitrophenyl)(pyrrolidin-1-yl)methanone 11a:

The product **11a** was obtained as a white solid (1.13 g, 86%). mp: 86-88 °C; IR ($CHCl_3$) ν (cm^{-1}): 3444, 2981, 1633, 1531, 1435, 1348, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 8.21 Hz, 1H), 7.74 (t, *J* = 7.45 Hz, 1H), 7.58 (t, *J* = 8.08 Hz, 1H), 7.44 (d, *J* = 7.58 Hz, 1H), 3.71 (t, *J* = 6.69 Hz, 2H), 3.16 (t, *J* = 6.57 Hz, 2H), 2.04-1.81 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.9, 144.7, 134.4, 133.8, 129.5, 127.9, 124.4, 48.0, 45.6, 25.6, 24.3; LC-MS: 242.94 $(M+Na)^+$; Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72; Found: C, 60.15; H, 5.31; N, 12.55.

(S)-N-(4-bromophenyl)-1-(2-nitrobenzoyl)pyrrolidine-2-carboxamide 12a:

The product **12a** was obtained as a white solid (5.34 g, 83%). mp: 200-202 °C; $[\alpha]^{24}_D$: -96° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3318, 3019, 1693, 1631, 1530, 1490, 1216, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.58 (s, 1H), 8.24 (d, *J* = 0.88, 8.21 Hz, 1H), 7.82 (dt, *J* = 1.01, 7.45 Hz, 1H), 7.67-7.55 (m, 2H), 7.43-7.38 (m, 2H), 7.27-7.22 (m, 2H), 4.93 (dd, *J* = 4.93, 7.33 Hz, 1H), 3.47-3.23 (m, 2H), 2.48-2.31 (m, 1H), 2.27-2.18 (m, 1H), 2.13-1.95 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.1, 167.4, 144.8, 137.2, 134.7, 132.6, 131.4, 130.3, 128.1, 124.7, 121.1, 116.3, 61.2, 49.6, 28.8, 24.9; LC-MS: 439.98 $(M+Na)^+$; 441.98

$(M+2+Na)^+$; 455.99 $(M+K)^+$; Anal. Calcd. for $C_{18}H_{16}BrN_3O_4$: C, 51.69; H, 3.86; N, 10.05; Found: C, 51.85; H, 4.03; N, 9.89.

(S)-N-(4-bromophenyl)-1-(2-nitrobenzoyl)pyrrolidine-2-carboxamide 12b:

A solution containing tripeptide **12a** in ethyl acetate was added $SnCl_2.2H_2O$ (1.2 equiv.) and reaction mixture was heated at 45 °C for 2 h. After completion of the reaction, saturated $NaHCO_3$ was added to the reaction mixture and precipitate was filtered over celite and the filtrate was further extracted with ethyl acetate. The organic layer was evaporated under reduced pressure to yield the corresponding free amine **12b**, which was carried forwarded for the next reaction without further purification.

General method for synthesis of 8a, 9, 18, 19a, 20a, 21, 22 and 23:

Representative procedure*:* To an ice-cold stirred solution of the substituted benzoic acid **13** (1.1 equiv) in dry DCM were added dry DMF (0.1 equiv) followed by oxalyl chloride (1.2 equiv). The resulting mixtures were stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure. The residue containing the acid chlorides were dissolved in dry DCM and added drop wise to an ice cooled solution of amine **10b** and Et_3N (2 equiv) in dry DCM and stirred at room temperature for 6 h. The reaction mixtures were diluted with DCM, and the organic layer was washed sequentially with dil. HCl solution, water, saturated $NaHCO_3$ and brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products, which were further purified by column chromatography to obtain **8a**.

(S)-2-((2-(2-(methylcarbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl) phenyl acetate 8a:

The product **8a** was obtained as a white solid (1.80 g, 62%). mp: 132-134 °C; $[\alpha]^{24}_D$: -100° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3453, 3019, 1672, 1626, 1522, 1415, 1216, 756; ^1H NMR (200 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.15 (d, *J* = 8.08 Hz, 1H), 7.78 (dd, *J* = 1.52, 7.71 Hz, 1H), 7.47-7.20 (m, 4H), 7.11-7.05 (m, 2H), 6.69 (d, *J* = 4.42 Hz, 1H), 4.55 (dd, *J* = 1.52, 7.71 Hz, 1H), 3.59-3.39 (m, 2H), 2.56 (d, *J* = 4.80 Hz, 3H), 2.25 (s, 3H), 2.30-2.09 (m, 1H), 2.06-1.84 (m, 2H), 1.77-1.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.6, 169.4, 169.2, 164.1, 148.4, 135.9, 132.1, 130.9, 129.5, 128.0, 127.3, 126.1, 125.9, 123.7, 123.2, 123.0,

60.1, 50.4, 28.3, 26.0, 25.0, 21.0; LC-MS: 432.05 $(M+Na)^+$; 448.08 $(M+K)^+$; Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26; Found: C, 64.71; H, 5.48; N, 10.09.

General method for synthesis of 8b, 19b and 20b:

***Representative procedure**:* To a solution of the acetyl tripeptide **8a** (1 equiv) in dry methanol, ignited K_2CO_3 (1.2 equiv) was added at room temperature and the reaction mixture was stirred for 1 h. After the complete consumption of the starting material, the reaction mixtures were filtered, and the filtrates were evaporated under reduced pressure. The residues obtained were dissolved in DCM and the organic layers were washed sequentially with dilute HCl, water, saturated $NaHCO_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which were then purified by column chromatography to obtain **8b**.

(S)-1-(2-(2-hydroxybenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 8b:

The product **8b** was obtained as a white solid (0.94 g, 94%). mp: 115-117 °C; $[\alpha]^{24}_D$: -166° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3240, 3454, 3019, 1670, 1651, 1623, 1592, 1216, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.09 (s, 1H), 10.60 (s, 1H), 8.27 (t, *J* = 8.24 Hz, 1H), 7.69 (d, *J* = 7.93 Hz, 1H), 7.47 (d, *J* = 6.71 Hz, 1H), 7.42 (t, *J* = 7.63 Hz, 1H), 7.19 (t, *J* = 7.32 Hz, 1H), 6.99 (d, *J* = 8.54 Hz, 1H), 6.89 (t, *J* = 7.32 Hz, 1H), 6.65 (bs, 1H), 4.70 (t, *J* = 6.10 Hz, 1H), 3.69-3.66 (m, 1H), 3.64-3.59 (m, 1H), 2.78 (s, 3H), 2.33-2.29 (m, 1H), 2.19-2.12 (m, 1H), 2.07-2.01 (m, 1H), 1.87-1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5, 169.9, 168.6, 161.6, 136.0, 134.5, 131.3, 127.8, 126.6, 125.1, 124.9, 123.7, 123.0, 119.0, 118.4, 114.8, 60.3, 50.9, 28.2, 26.3, 25.2; LC-MS: 390.05 $(M+Na)^+$; Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44; Found: C, 65.19; H, 5.91; N, 11.25.

General method for synthesis of 8c, 19c and 20c:

***Representative procedure**:* To a solution of hydroxy tripeptide **8b** (1 equiv) in acetone were added MeI (1.5 equiv.) and K_2CO_3 (2 equiv.). After heating at 45 °C for 8 h, the reaction mixtures were filtered, and the filtrates were evaporated under reduced pressure. The residue obtained were taken in DCM, and washed

sequentially with dil. HCl solution, water, saturated $NaHCO_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which were then purified by column chromatography to furnish **8b**.

(S)-1-(2-(2-methoxybenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 8b:

The product **8b** was obtained as viscous liquid (0.46 g, 89%). $[\alpha]^{24}_{D}$: -132° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3323, 3015, 1666, 1583, 1531, 1216, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.74 (s, 0.9H), $10.49_{conformer}$ (s, 0.1H), 8.26 (d, *J* = 8.24 Hz, 2H), 7.51 (t, *J* = 7.63 Hz, 1H), 7.45 (t, *J* = 7.32 Hz, 1H), 7.37 (d, *J* = 7.63 Hz, 1H), $7.23_{conformer}$ (d, *J* = 7.32 Hz, 0.1H), 7.16 (t, *J* = 7.63 Hz, 0.9H), 7.11 (t, *J* = 7.63 Hz, 1H), 7.02 (d, *J* = 8.24 Hz, 1H), 6.91 (bs, 1H), 4.73-4.70 (m, 1H), $4.09_{conformer}$ (s, 0.3H), 4.06 (s, 2.7H), 3.83-$3.74_{conformer}$ (m, 0.2H), 3.56-3.46 (m, 1.8H), 2.71 (d, *J* = 4.58 Hz, 2.7H), $2.53_{conformer}$ (d, *J* = 4.58 Hz, 0.3H), 2.42-2.36 (m, 1H), 2.09-2.02 (m, 1H), 1.99-1.91 (m, 1H), 1.85-1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 171.5, 169.8, 169.1, 163.7, 157.6, 135.8, 133.4, 132.3, 130.6, 130.1, 127.0, 126.4, 123.9, 123.6, 121.2, 121.1, 111.4, 62.5, 59.9, 55.9, 50.2, 46.7, 31.5, 27.9, 26.2, 24.9, 22.8; LC-MS: 404.03 $(M+Na)^+$; 420.04 $(M+K)^+$; Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02; Found: C, 66.30; H, 5.89; N, 10.88.

2-methoxy-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 18:

The product **18** was obtained from acid **14** and amine **11b**, following the procedure for **3a**, as a white solid (0.31 g, 92%). mp: 125-127 °C; IR ($CHCl_3$) ν (cm^{-1}): 3297, 3011, 1660, 1623, 1597, 1421, 1216, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.93 (s, 1H), 8.51 (d, *J* = 8.21 Hz, 2H), 8.30 (dd, *J* = 1.64, 7.71 Hz, 1H), 7.52-7.38 (s, 2H), 7.34 (dd, *J* = 1.01, 7.71 Hz, 1H), 7.14-7.06 (m, 2H), 7.03 (d, *J* = 8.34 Hz, 1H), 4.11 (s, 3H), 3.68 (t, *J* = 6.69 Hz, 2H), 3.40 (t, *J* = 6.57 Hz, 2H), 1.98-1.80 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.2, 163.5, 157.6, 136.0, 133.1, 132.2, 130.0, 127.3, 126.6, 123.1, 121.5, 120.9, 111.3, 55.8, 49.3, 45.7, 26.0, 24.3; LC-MS: 347.09 $(M+Na)^+$; 363.10 $(M+K)^+$; Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64; Found: C, 70.18; H, 6.05; N, 8.81.

(S)-2-((2-(2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl) carbamoyl)phenyl acetate 19a:

The product **19a** was obtained from acid **13** and amine **12b**, following the procedure for **8a**, as a white solid (1.51 g, 53%). mp: 152-154 °C; $[\alpha]^{24}_{D}$: -136° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3320, 3020, 1769, 1682, 1604, 1531, 1216, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 9.15 (s, 1H), 8.33 (d, *J* = 8.54 Hz, 1H), 7.81 (dd, *J* = 1.22, 8.85 Hz, 1H), 7.53-7.47 (m, 2H), 7.41 (dd, *J* = 0.92, 7.63 Hz, 2H), 7.26 (d, *J* = 7.93 Hz, 1H), 7.19-7.17 (m, 5H), 7.14 (d, *J* = 7.93 Hz, 1H), 4.80 (dd, *J* = 5.19, 7.93 Hz, 1H), 3.65-3.60 (m, 1H), 3.57-3.52 (m, 1H), 2.31 (s, 3H), 2.30-2.25 (m, 1H), 2.15-2.07 (m, 1H), 2.06-2.01 (m, 1H), 1.87-1.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.7, 169.4, 169.1, 164.3, 148.4, 137.0, 135.9, 132.1, 131.4, 131.2, 129.6, 128.3, 127.2, 126.1, 125.6, 123.8, 123.2, 122.9, 121.1, 116.4, 60.9, 50.6, 28.2, 25.1, 21.1; LC-MS: 572.06 $(M+Na)^+$; 574.06 $(M+2+Na)^+$; 588.01 $(M+K)^+$; 590.01 $(M+2+K)^+$; Anal. Calcd. for $C_{27}H_{24}BrN_3O_5$: C, 58.92; H, 4.40; N, 7.63; Found: C, 59.10; H, 4.25; N, 7.50.

(S)-N-(4-bromophenyl)-1-(2-(2-hydroxybenzamido)benzoyl)pyrrolidine-2-carboxamide 19b:

The product **19b** was obtained from tripeptide **19a**, following the procedure for **8b**, as a white solid (0.94 g, 93%). mp: 130-132 °C; $[\alpha]^{24}_{D}$: -206° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3318, 3020, 1690, 1648, 1621, 1591, 1531, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.07 (s, 1H), 10.24 (s, 1H), 9.06 (s, 1H), 8.33 (d, *J* = 8.34 Hz, 1H), 7.69 (d, *J* = 7.96 Hz, 1H), 7.56-7.35 (m, 4H), 7.31-7.18 (m, 5H), 7.03 (dd, *J* = 0.88, 8.34 Hz, 1H), 6.79 (t, *J* = 7.83 Hz, 1H), 4.88 (dd, *J* = 5.05, 7.45 Hz, 1H), 3.68 (t, *J* = 11.12 Hz, 1H), 2.48-2.31 (m, 1H), 2.26-1.99 (m, 2H), 1.98-1.74 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.2, 168.9, 168.8, 161.8, 136.8, 135.7, 134.7, 131.6, 131.4, 127.6, 126.5, 125.0, 124.0, 123.2, 121.1, 119.0, 118.5, 116.7, 114.6, 61.0, 51.1, 27.8, 25.2; LC-MS: 530.07 $(M+Na)^+$; 532.16 $(M+2+Na)^+$; 546.16 $(M+K)^+$; 548.16 $(M+2+K)^+$; Anal. Calcd. for $C_{25}H_{22}BrN_3O_4$: C, 59.07; H, 4.36; N, 8.27; Found: C, 58.89; H, 4.51; N, 8.09.

(S)-N-(4-bromophenyl)-1-(2-(2-methoxybenzamido)benzoyl)pyrrolidine-2-carboxamide 19c:

The product **19c** was obtained from tripeptide **19b**, following the procedure for **8c**, as a white solid (0.45 g, 88%). mp: 195-197 °C; $[\alpha]^{24}_{D}$: -192° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3307, 3019, 1695, 1661, 1589, 1526, 1215, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.69 (s, 0.9H), $10.50_{conformer}$ (s, 0.1H), 9.32 (s, 1H), 8.48-$8.44_{conformer}$ (m, 0.1H), 8.30 (d, *J* = 8.07 Hz, 0.9H), 8.23 (dd, *J* = 1.47, 7.82 Hz, 0.9H), $8.05_{conformer}$ (d, *J* = 8.07 Hz, 0.1H), 7.58-$7.54_{conformer}$ (m, 0.2H), 7.52-7.46 (m, 1.8H), 7.38 (d, *J* = 8.56 Hz, 2H), 7.38-7.36 (m, 1H), 7.29 (d, *J* = 9.05 Hz, 2H), 7.20 (t, *J* = 7.58 Hz, 1H), 7.11 (t, *J* = 7.58 Hz, 1H), 7.00-6.98 (m, 0.1H), 6.91 (d, *J* = 8.31 Hz, 1H), 4.88 (dd, *J* = 3.91, 7.82 Hz, 1H), $4.11_{conformer}$ (s, 0.3H), 3.93 (s, 2.7H), 3.84-$3.77_{conformer}$ (m, 0.2H), 3.63-3.53 (m, 1.8H), 2.51-2.46 (m, 1H), 2.15-1.97 (m, 1H), 1.92-1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 170.3, 169.1, 168.9, 163.9, 163.8, 157.5, 137.0, 135.1, 133.4, 132.2, 131.6, 130.8, 126.9, 126.7, 123.9, 123.7, 121.2, 121.1, 116.4, 111.3, 62.6, 60.7, 56.0, 55.7, 50.4, 46.91, 27.5, 27.4, 24.9, 24.5; LC-MS: 544.04 $(M+Na)^+$; 546.04 $(M+2+Na)^+$; 560.07 $(M+2+K)^+$; Anal. Calcd. for $C_{26}H_{24}BrN_3O_4$: C, 59.78; H, 4.63; N, 8.04; Found: C, 59.93; H, 4.50; N, 7.89.

(S)-4-bromo-2-((2-(2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonylphenyl)carbamoyl)phenyl acetate 20a:

The product **20a** was obtained from acid **15** and amine **12b**, following the procedure for **8a**, as a white solid (1.38 g, 57%). mp: 192-193 °C; $[\alpha]^{24}_{D}$: -142° (*c* = 0.56, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3315, 3020, 1765, 1677, 1616, 1591, 1538, 1216, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 9.13 (s, 1H), 8.16 (d, *J* = 8.34 Hz, 1H), 7.81 (dd, *J* = 1.22, 8.85 Hz, 1H), 7.53-7.47 (m, 2H), 7.41 (dd, *J* = 0.92, 7.63 Hz, 2H), 7.78 (d, *J* = 2.15 Hz, 1H), 7.51 (dd, *J* = 2.15, 8.46 Hz, 1H), 7.40 (q, 2H), 7.17-6.96 (m, 4H), 7.02 (d, *J* = 4.29 Hz, 1H), 6.92 (d, *J* = 8.59 Hz, 1H), 4.68-4.68 (m, 1H), 3.62-3.28 (m, 2H), 2.15 (s, 3H), 2.06-1.94 (m, 2H), 1.91-1.64 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.3, 169.0, 169.0, 163.3, 147.2, 136.8, 135.1, 134.6, 132.4, 131.2, 130.9, 130.2, 126.8, 126.1, 124.8, 124.2, 122.6, 120.8, 118.9, 116.2, 60.9, 50.2, 29.0, 25.0, 20.9; LC-MS: 650.09 $(M+Na)^+$; 652.10 $(M+2+Na)^+$; 654.15 $(M+4+Na)^+$; 666.10 $(M+K)^+$; 668.14 $(M+2+K)^+$; 670.15

$(M+4+K)^+$; Anal. Calcd. for $C_{27}H_{23}Br_2N_3O_5$: C, 51.53; H, 3.68; N, 6.68; Found: C, 51.40; H, 3.85; N, 6.50.

(S)-1-(2-(5-bromo-2-hydroxybenzamido)benzoyl)-N-(4-bromophenyl) pyrrolidine-2-carboxamide 20b:

The product **20b** was obtained from tripeptide **20a**, following the procedure for **8b**, as a white solid (0.85 g, 91%). mp: 172-174 °C; $[\alpha]^{24}_D$: -192° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3277, 3020, 1698, 1646, 1591, 1531, 1216, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.18 (s, 1H), 10.57 (s, 1H), 8.90 (s, 1H), 7.99 (d, *J* = 2.14 Hz, 1H), 7.56 (d, *J* = 8.24 Hz, 1H), 7.41 (dt, *J* = 2.14, 8.85 Hz, 2H), 7.36 (d, *J* = 8.85 Hz, 2H), 7.27 (t, *J* = 7.63 Hz, 1H), 7.16 (dt, *J* = 0.61, 7.63 Hz, 1H), 6.86 (d, *J* = 8.85 Hz, 1H), 4.89 (t, *J* = 7.63 Hz, 1H), 3.75-3.70 (m, 1H), 3.69-3.64 (m, 1H), 2.48-2.41 (m, 1H), 2.28-2.21 (m, 1H), 2.15-2.08 (m, 1H), 2.00-1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 169.0, 167.9, 161.0, 137.0, 136.9, 134.3, 131.7, 131.1, 129.4, 127.5, 127.4, 124.8, 124.1, 121.1, 120.3, 116.7, 115.9, 110.4, 61.4, 51.0, 28.1, 25.4; LC-MS: 607.89 $(M+Na)^+$; 609.89 $(M+2+Na)^+$; 611.89 $(M+4+Na)^+$; 625.84 $(M+2+K)^+$; Anal. Calcd. for $C_{25}H_{21}Br_2N_3O_4$: C, 51.13; H, 3.60; N, 7.16; Found: C, 49.95; H, 3.45; N, 6.99.

(S)-1-(2-(5-bromo-2-methoxybenzamido)benzoyl)-N-(4-bromophenyl) pyrrolidine-2-carboxamide 20c:

The product **20c** was obtained from tripeptide **20b**, following the procedure for **8c**, as a white solid (0.44 g, 87%). mp: 189-191 °C; $[\alpha]^{24}_D$: -142° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 3018, 1694, 1662, 1591, 1532, 1216, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.49 (s, 0.9H), $10.35_{conformer}$ (s, 0.1H), 9.12 (s, 1H), 8.45 (bs, 0.1H), 8.16 (d, *J* = 2.65 Hz, 0.9H), 8.15 (d, *J* = 9.60 Hz, 0.9H), 7.91 (d, *J* = 7.33 Hz, 0.1H), 7.46 (dd, *J* = 2.65, 8.84 Hz, 1H), 7.36-7.23 (m, 3H), 7.18-7.04 (m, 4H), 6.84 (d, *J* = 9.22 Hz, 0.1H), 6.65 (d, *J* = 8.84 Hz, 0.9H), 4.74 (dd, *J* = 3.54, 6.82 Hz, 1H), $3.96_{conformer}$ (s, 0.3H), 3.76 (s, 2.7H), 3.17-2.89 (m, 0.2H), 3.57-3.39 (m, 1.8H), 2.38-2.23 (m, 1H), 2.12-1.70 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.9, 169.1, 162.5, 156.4, 136.9, 135.7, 135.4, 134.5, 131.5, 130.8, 126.9, 126.8, 124.0, 123.8, 123.0, 121.1, 116.4, 113.4, 113.2, 60.8, 56.0, 50.3, 27.9, 24.9; LC-MS: 622.11 $(M+Na)^+$; 624.11 $(M+2+Na)^+$; 626.11

$(M+4+Na)^+$; 638.13 $(M+K)^+$; 640.13 $(M+2+K)^+$; Anal. Calcd. for $C_{26}H_{23}Br_2N_3O_4$: C, 51.94; H, 3.86; N, 6.99; Found: C, 52.10; H, 3.69; N, 7.15.

(S)-N-(4-bromophenyl)-1-(2-(5-chloro-2-methoxybenzamido)benzoyl) pyrrolidine -2-carboxamide 21:

The product **21** was obtained from acid **16** and amine **12b**, following the procedure for **8a**, as a white solid (0.35 g, 61%). mp: 199-201 °C; $[\alpha]^{24}_D$: -172° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 3019, 1692, 1665, 1591, 1532, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.57 (s, 0.9H), $10.40_{conformer}$ (s, 0.1H), 9.12 (s, 1H), 8.20 (d, *J* = 8.21 Hz, 1H), 8.09 (d, *J* = 2.65 Hz, 1H), 7.45 (dd, *J* = 2.65, 8.84 Hz, 1H), 7.37-7.27 (m, 3H), 7.24-7.19 (m, 3H), 7.16 (t, *J* = 7.45 Hz, 1H), 6.93 (d, *J* = 8.72 Hz, 0.1H), 6.76 (d, *J* = 8.84 Hz, 0.9H), 4.80 (dd, *J* = 3.54, 6.82 Hz, 1H), $4.02_{conformer}$ (s, 0.3H), 3.84 (s, 2.7H), 3.78-3.70 (m, 0.2H), 3.55-3.49 (m, 1.8H), 2.49-2.33 (m, 1H), 2.14-1.75 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.2, 168.9, 162.5, 156.0, 136.9, 135.5, 132.8, 131.8, 131.6, 130.9, 127.0, 126.4, 124.0, 122.6, 121.1, 116.5, 112.8, 60.8, 56.1, 50.4, 27.5, 24.9; LC-MS: 578.03 $(M+Na)^+$; 580.07 $(M+2+Na)^+$; 594.04 $(M+4+Na)^+$; 596.04 $(M+2+K)^+$; Anal. Calcd. for $C_{26}H_{23}BrClN_3O_4$: C, 56.08; H, 4.16; N, 7.55; Found: C, 55.89; H, 3.99; N, 7.74.

(S)-1-(2-(2-fluorobenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 9:

The product **9** was obtained from acid **17** and amine **10b**, following the procedure for **8a**, as viscous liquid (0.37 g, 63%). $[\alpha]^{24}_D$: -130° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3351, 3017, 1668, 1622, 1597, 1531, 1216, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.98 (d, *J* = 10.38 Hz, 0.9H), $9.63_{conformer}$ (d, *J* = 10.38 Hz, 0.1H), 8.32 (d, *J* = 8.24 Hz, 0.9H), $8.23_{conformer}$ (d, *J* = 8.24 Hz, 0.1H), 8.04 (dt, *J* = 1.53, 7.63 Hz, 1H), 7.50-7.46 (m, 1H), 7.45 (t, *J* = 7.93 Hz, 1H), 7.40 (dt, *J* = 1.22, 7.63 Hz, 1H), 7.26 (dt, *J* = 0.92, 8.54 Hz, 1H), 7.16 (q, 1H), 7.12 (d, *J* = 8.54 Hz, 1H), 7.00 (bs, 1H), 4.70 (dd, *J* = 4.88, 7.93 Hz, 1H), $3.82\text{-}3.70_{conformer}$ (m, 0.2H), 3.60-3.55 (m, 0.9H), 3.53-3.48 (m, 0.9H), 2.70 (d, *J* = 4.27 Hz, 2.7H), $2.57_{conformer}$ (d, *J* = 3.66 Hz, 0.3H), 2.33-2.27 (m, 1H), 2.11-2.04 (m, 1H), 2.03-1.95 (m, 1H), 1.83-1.75 (m, 1H); ^{19}F decoupled ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.96 (s, 0.9H), $9.62_{conformer}$ (s, 0.1H), 8.32 (d, *J* = 8.14 Hz, 0.9H), $8.32_{conformer}$ (bs, 0.1H), 8.04 (d, *J* = 7.63 Hz, 0.9H), $7.99_{conformer}$ (bs, 0.1H), $7.59_{conformer}$ (t, *J* = 7.12

Hz, 0.1H), 7.50-7.40 (m, 2.9H), 7.28-7.23 (m, 1H), 7.17-7.11 (m, 2H), 7.07 (bs, 1H), 4.72 (dd, *J* = 4.58, 7.63 Hz, 0.9H), $4.56_{conformer}$ (bs, 0.1H), $3.77_{conformer}$ (bs, 0.1H), 3.62-3.56 (m, 0.9H), 3.54-3.48 (m, 0.9H), 3.37 (bs, 0.1H), 2.71 (d, *J* = 4.58 Hz, 2.6H), $2.66_{conformer}$ (bs, 0.2H), $2.58_{conformer}$ (bs, 0.2H), 2.31-2.25 (m, 1H), 2.14-2.06 (m, 1H), 2.03-1.93 (m, 1H), 1.83-1.77 (m, 1H); ^{19}F NMR (400 MHz, $CDCl_3$) δ: -112.63 (m, 0.9F), $-112.90_{conformer}$ (m, 0.1F); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.0, 171.5, 169.4, 162.0, 161.2, 159.2, 135.7, 135.1, 133.5, 133.4, 131.6, 130.8, 130.4, 127.3, 126.5, 126.0, 124.6, 124.6, 124.1, 123.8, 123.5, 123.1, 121.8, 121.7, 116.2, 116.0, 62.9, 59.8, 50.4, 46.9, 31.6, 28.0, 26.1, 25.0, 22.6; LC-MS: 392.05 $(M+Na)^+$; Anal. Calcd. for $C_{20}H_{20}FN_3O_3$: C, 65.03; H, 5.46; N, 11.38; Found: C, 64.85; H, 5.61; N, 11.51.

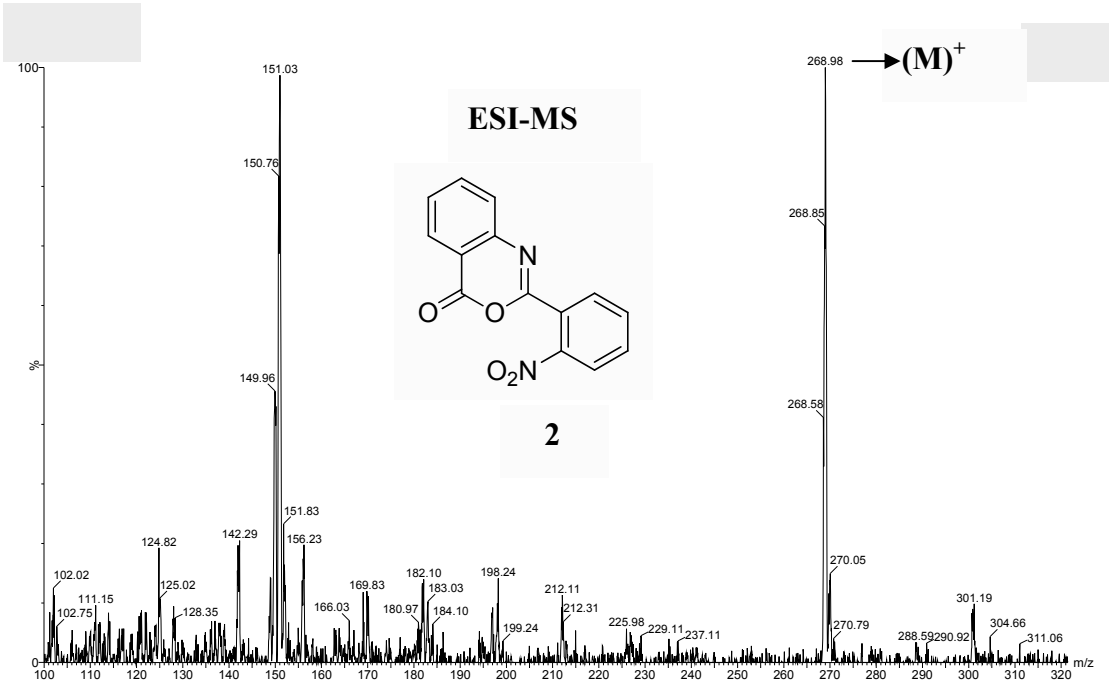
(S)-N-(4-bromophenyl)-1-(2-(2-fluorobenzamido)benzoyl)pyrrolidine-2-carboxamide 22:

The product **22** was obtained from acid **17** and amine **12b**, following the procedure for **8a**, as a white solid (0.30 g, 58%). mp: 139-141 °C; $[\alpha]^{24}_D$: -130° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3312, 3018, 1678, 1615, 1591, 1538, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.72 (d, *J* = 8.59 Hz, 1H), 9.29 (s, 1H), 8.30 (d, *J* = 8.21 Hz, 1H), 7.88 (dt, *J* = 6.19, 7.33 Hz, 1H), 7.42 (q, 2H), 7.16-7.09 (m, 3H), 7.03 (s, 4H), 6.94 (dd, *J* = 8.46, 11.24 Hz, 1H), 4.81 (bs, 1H), 3.61-3.30 (m, 1.8H), $2.96\text{-}2.75_{conformer}$ (m, 0.2H), 2.14-1.89 (m, 3H), 1.84-1.61 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.5, 169.2, 162.6, 157.6, 137.0, 135.2, 133.3, 133.2, 131.4, 131.2, 130.9, 126.8, 126.3, 124.5, 124.5, 124.1, 123.0, 122.4, 122.1, 120.9, 116.2, 115.7, 60.6, 50.3, 28.5, 24.9; LC-MS: 532.07 $(M+Na)^+$; 534.07 $(M+2+Na)^+$; Anal. Calcd. for $C_{25}H_{21}BrFN_3O_3$: C, 58.84; H, 4.15; N, 8.23; Found: C, 59.02; H, 3.98; N, 8.40.

2-fluoro-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 23:

The product **23** was obtained from acid **17** and amine **11b**, following the procedure for **8a**, as a white solid (0.29 g, 89%). mp: 120-122 °C; IR ($CHCl_3$) ν (cm^{-1}): 3337, 3017, 1671, 1623, 1596, 1523, 1216, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.41 (d, *J* = 10.48 Hz, 1H), 8.52 (d, *J* = 8.21 Hz, 1H), 8.14 (dt, *J* = 1.89, 7.83 Hz, 1H), 7.56-7.37 (s, 3H), 7.32 (dd, *J* = 1.01, 7.45 Hz, 1H), 7.24-7.10 (m, 2H), 3.70 (t, *J* = 6.57 Hz, 2H), 3.50 (t, *J* = 6.57 Hz, 2H), 2.03-1.79 (m, 4H);

^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.1, 162.6, 161.6, 161.5, 157.7, 136.2, 133.4, 133.2, 131.5, 130.4, 127.1, 125.8, 124.5, 124.4, 123.2, 122.5, 122.0, 121.7, 116.4, 115.9, 49.7, 46.0, 26.1, 24.1; LC-MS: 335.02 $(M+Na)^+$; 351.23 $(M+K)^+$; Anal. Calcd. for $C_{18}H_{17}FN_2O_2$: C, 69.22; H, 5.49; N, 8.97; Found: C, 69.05; H, 5.65; N, 9.15.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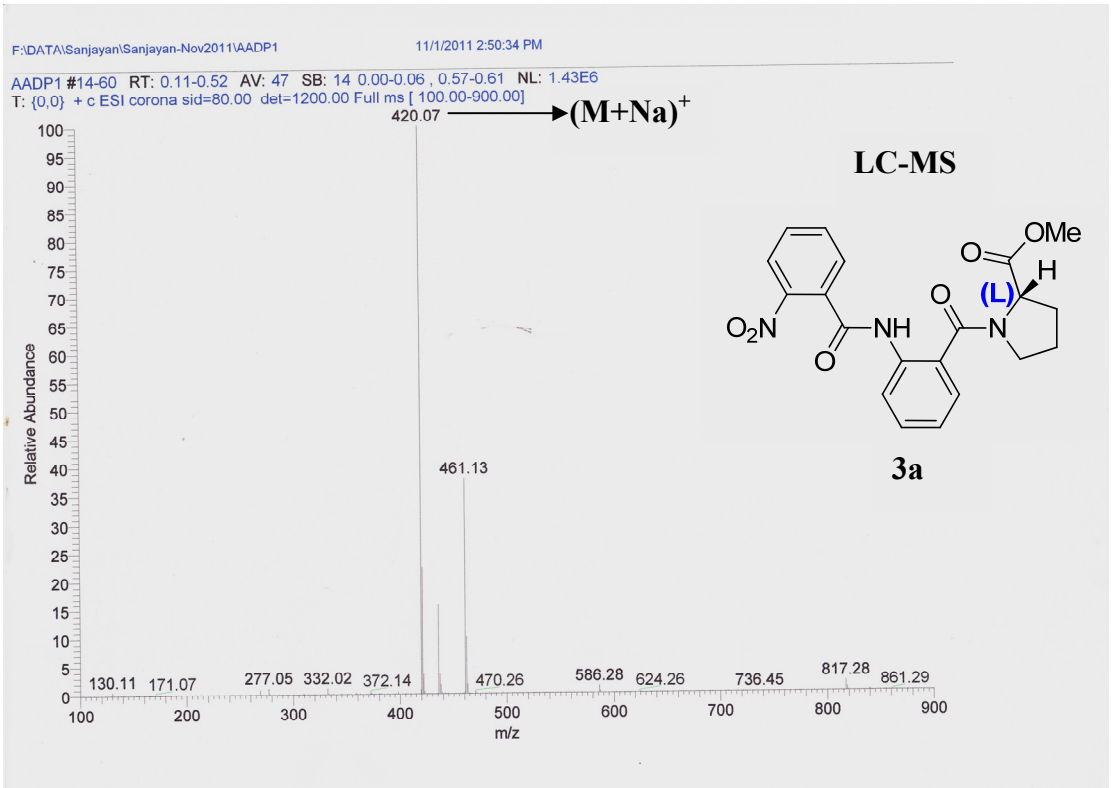
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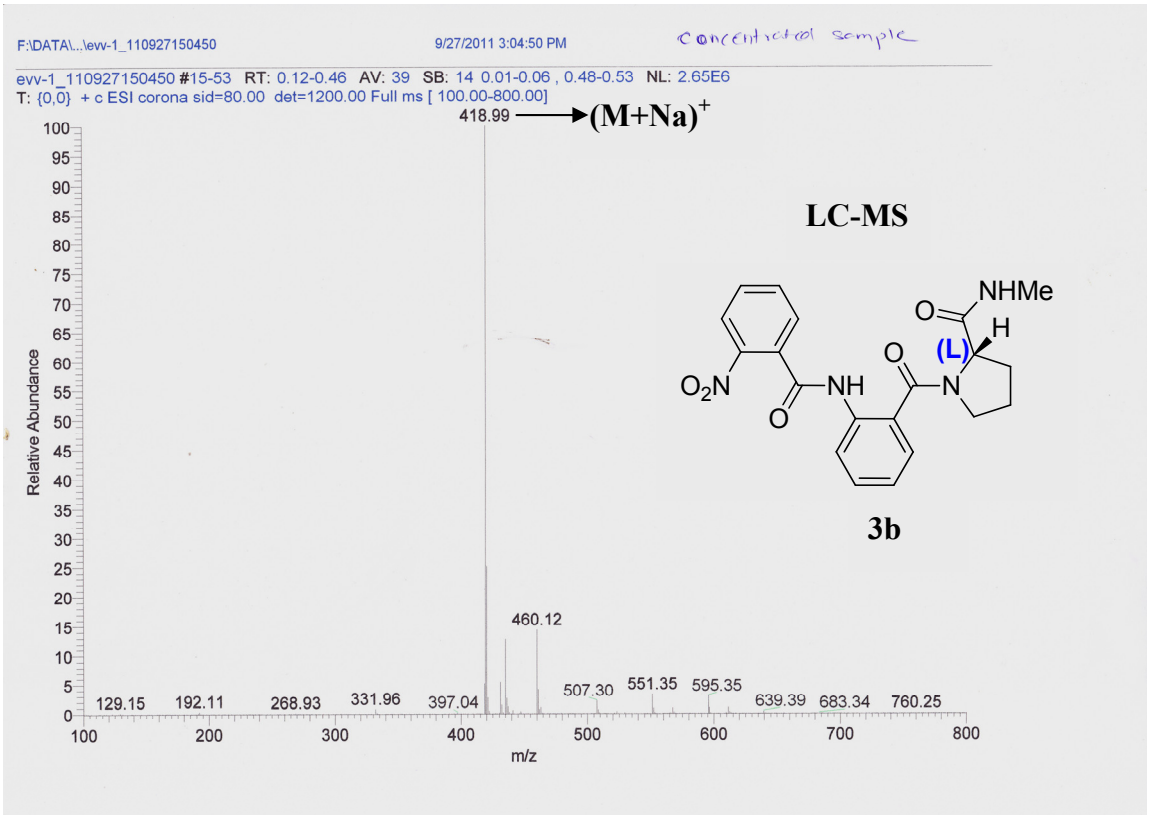
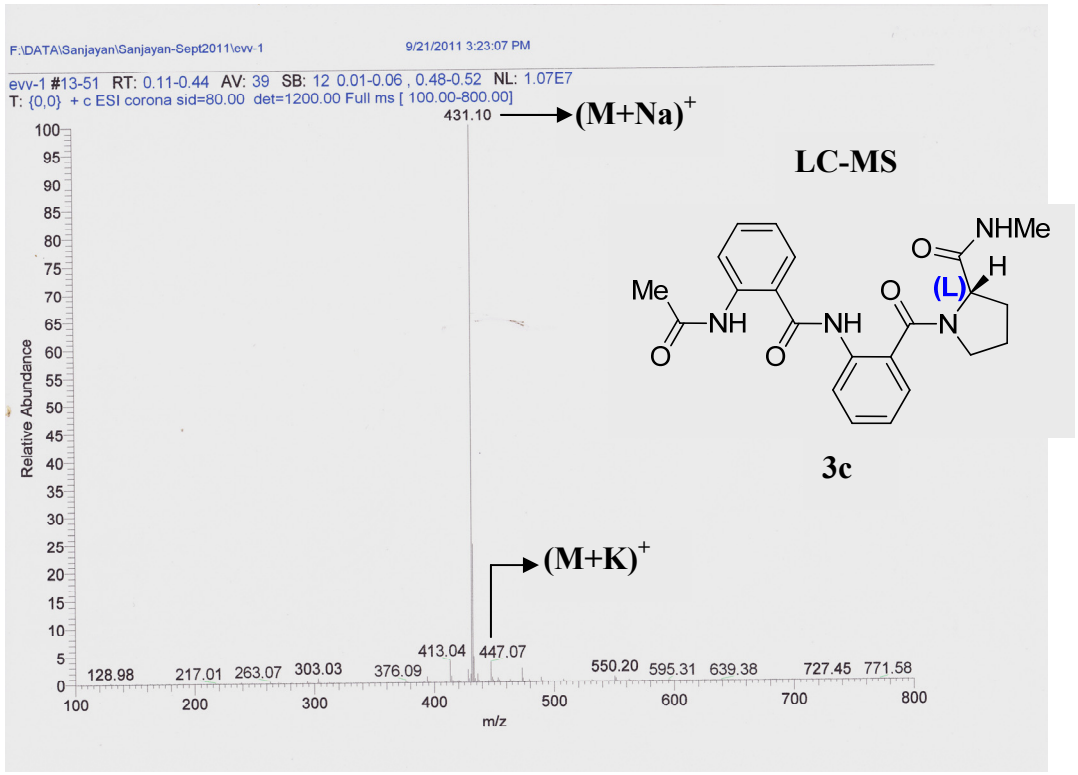
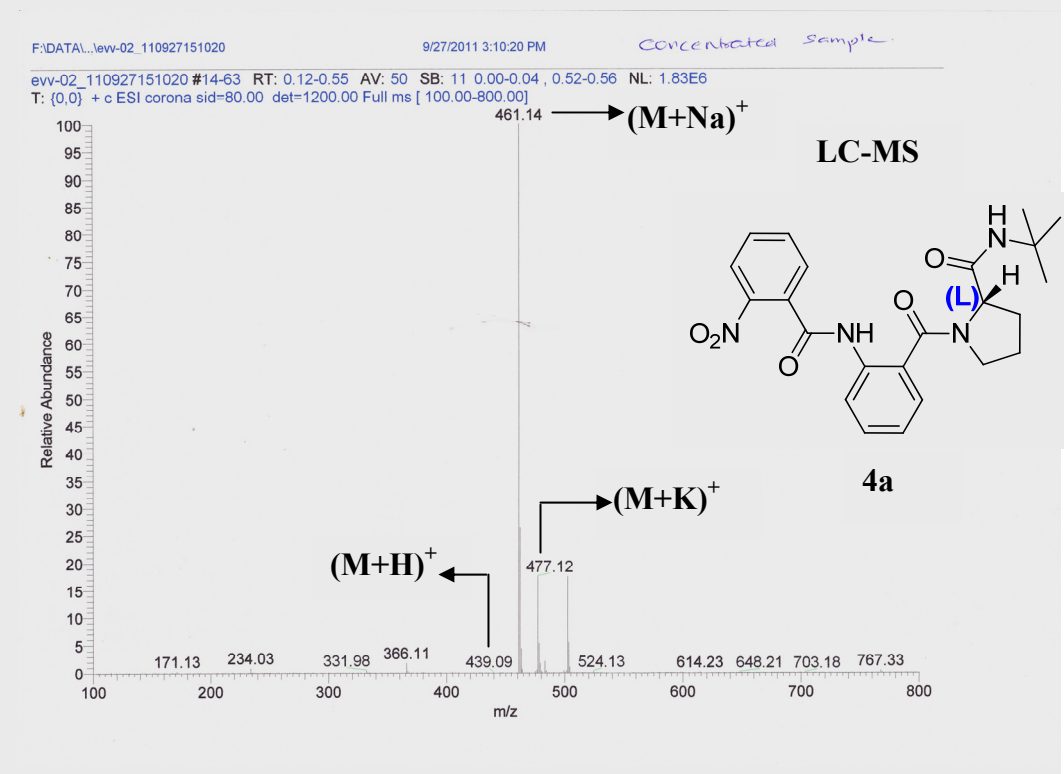
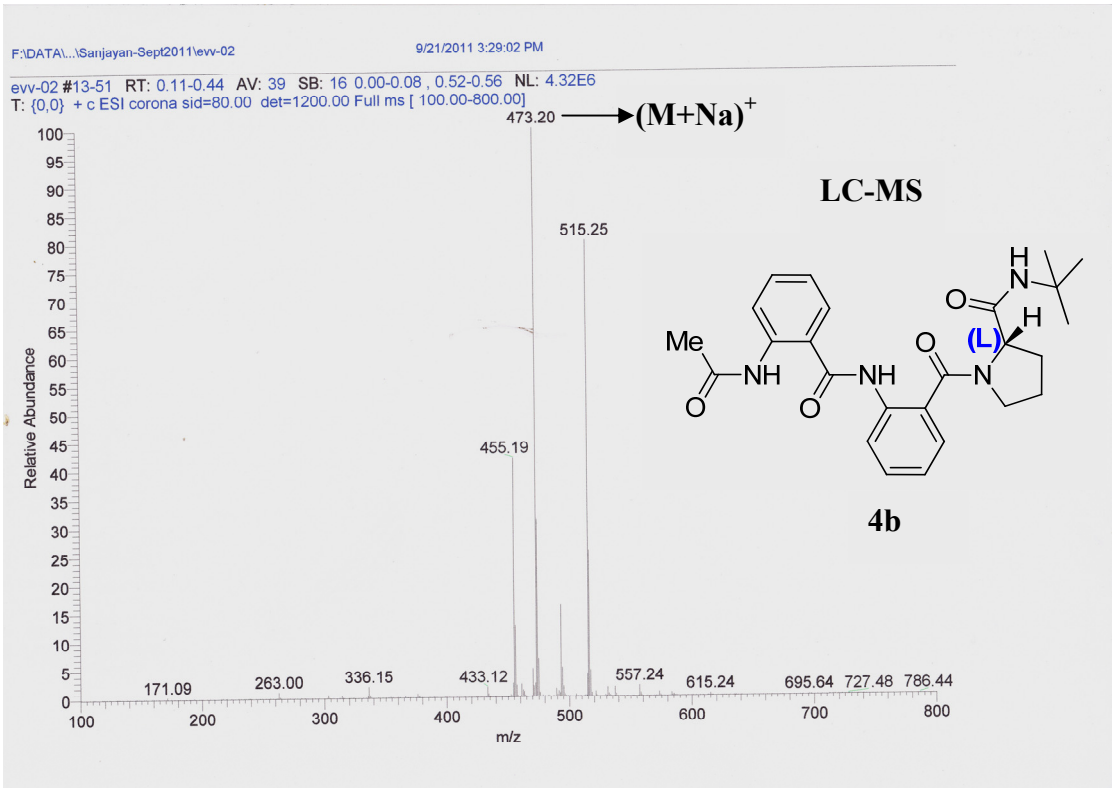
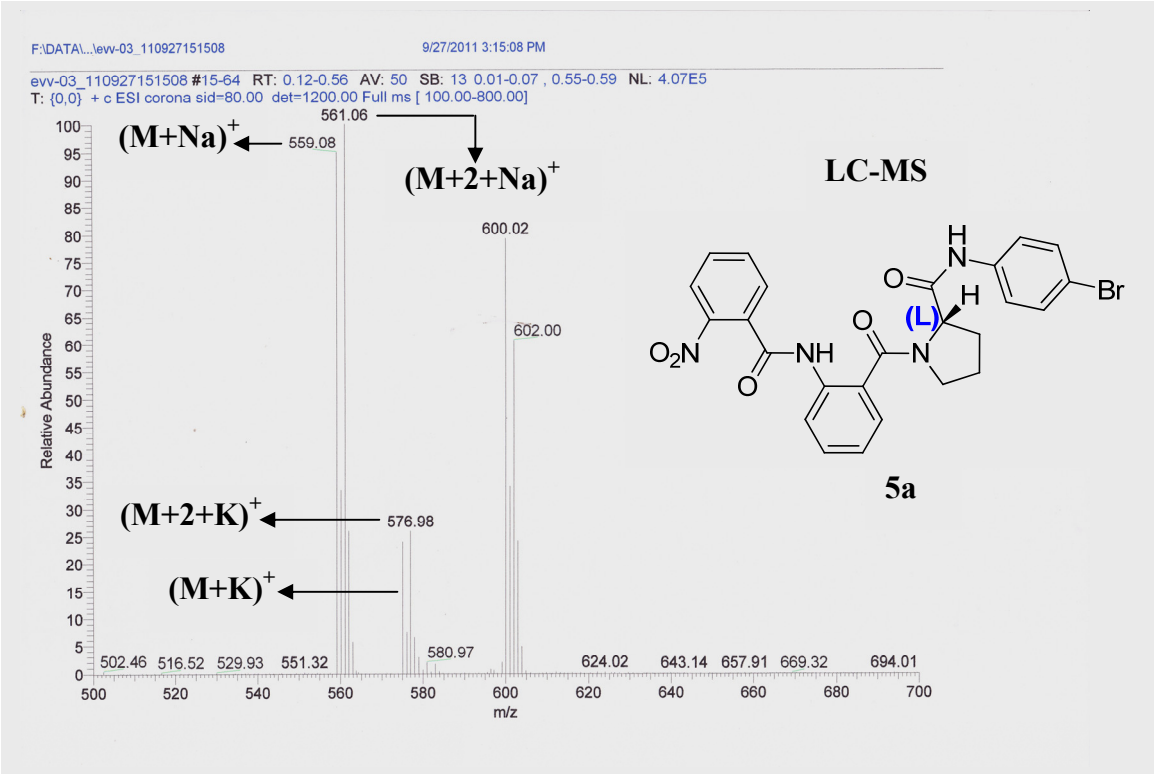
736.45
817.28
861.29
m/z
OMe
O
H
(L)
O
O2N
NH
O
N
3a

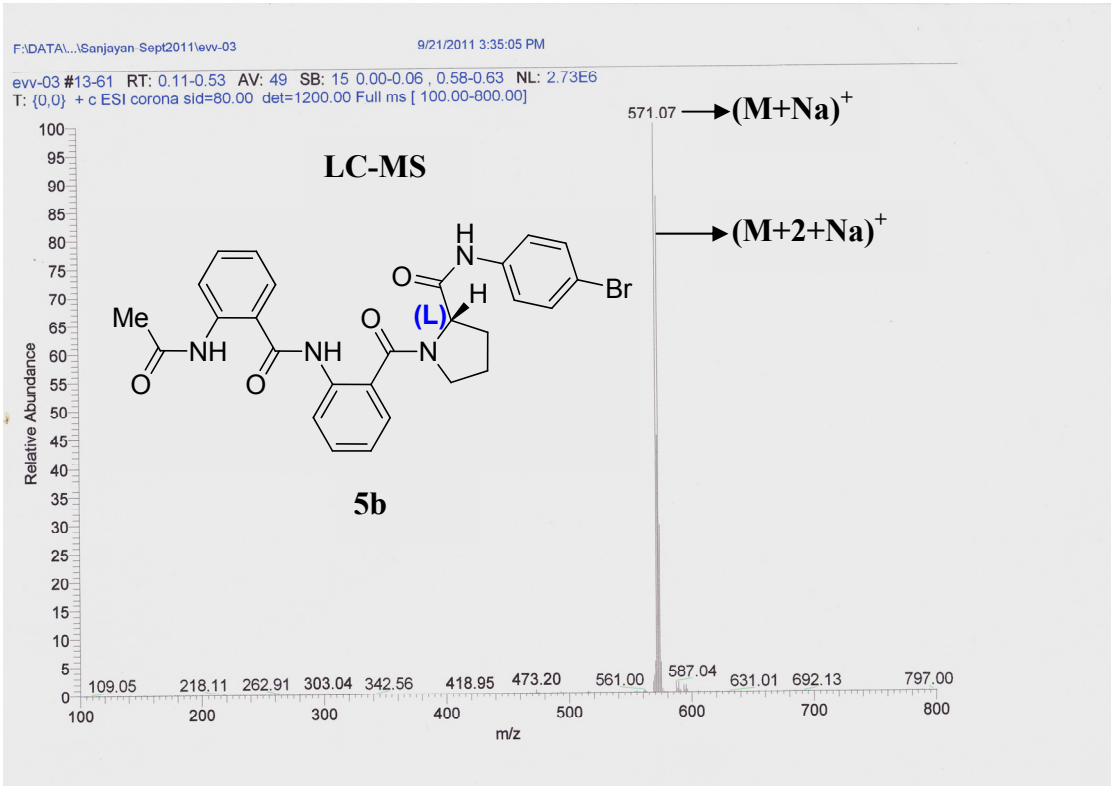

F:\DATA\...\evv-1_110927150450
9/27/2011 3:04:50 PM
concentrated sample
evv-1_110927150450 #15-53 RT: 0.12-0.46 AV: 39 SB: 14 0.01-0.06 , 0.48-0.53 NL: 2.65E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
418.99 (M+Na)+
LC-MS
NHMe
O
H
(L)
O
O2N
NH
O
N
3b
460.12
129.15
192.11
268.93
331.96
397.04
507.30
551.35
595.35
639.39
683.34
760.25
Relative Abundance
m/z

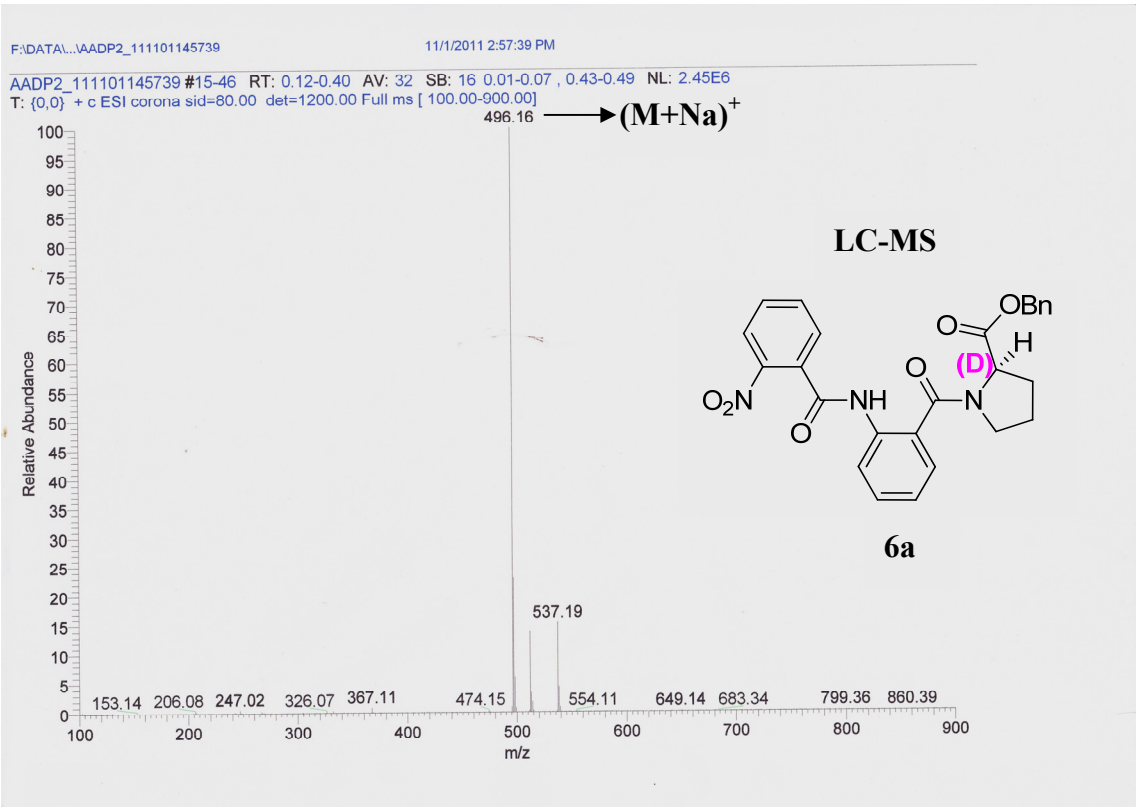

F:\DATA\Sanjayan\Sanjayan-Sept2011\evv-1
9/21/2011 3:23:07 PM
evv-1 #13-51 RT: 0.11-0.44 AV: 39 SB: 12 0.01-0.06 , 0.48-0.52 NL: 1.07E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
431.10 (M+Na)+
LC-MS
NHMe
O
H
Me
NH
O
NH
O
O
(L)
N
3c
(M+K)+
413.04
447.07
128.98
217.01
263.07
303.03
376.09
550.20
595.31
639.38
727.45
771.58
Relative Abundance
m/z

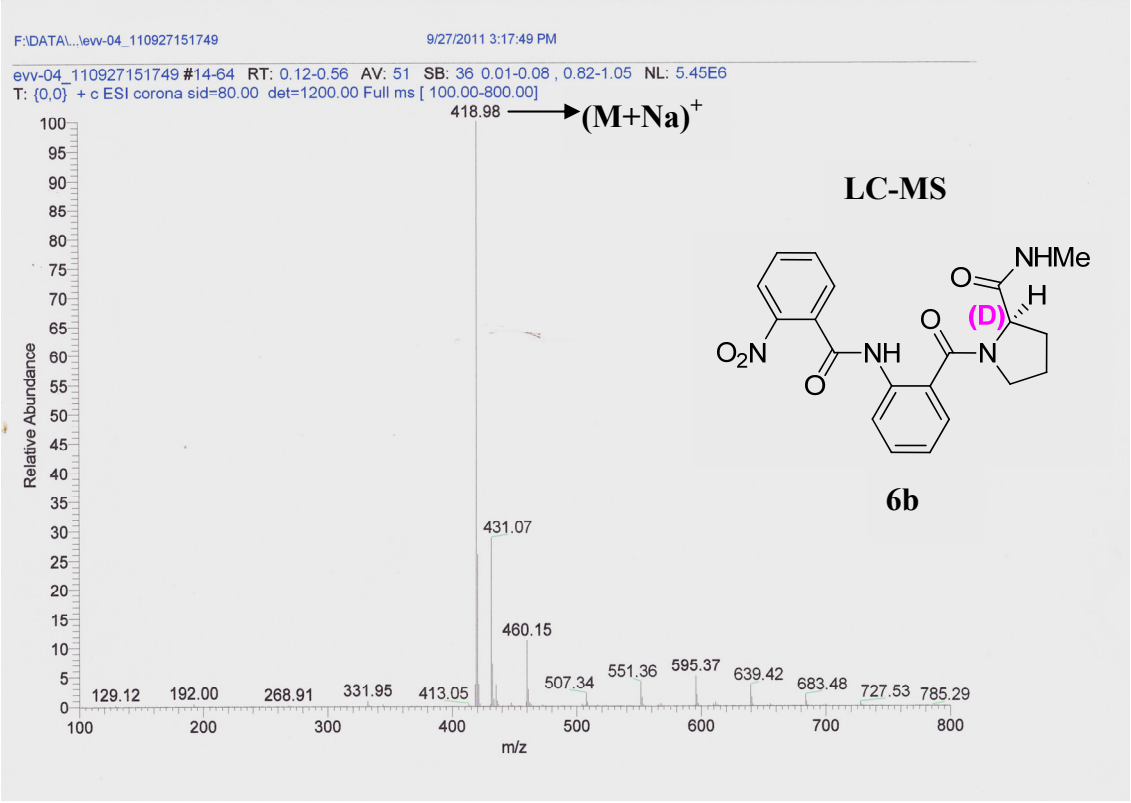

F:\DATA\...\evv-02_110927151020
9/27/2011 3:10:20 PM
Concentrated Sample
evv-02_110927151020 #14-63 RT: 0.12-0.55 AV: 50 SB: 11 0.00-0.04 , 0.52-0.56 NL: 1.83E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
461.14
(M+Na)+
LC-MS
(M+K)+
(M+H)+
477.12
Relative Abundance
m/z
171.13 234.03 331.98 366.11 439.09 524.13 614.23 648.21 703.18 767.33
4a

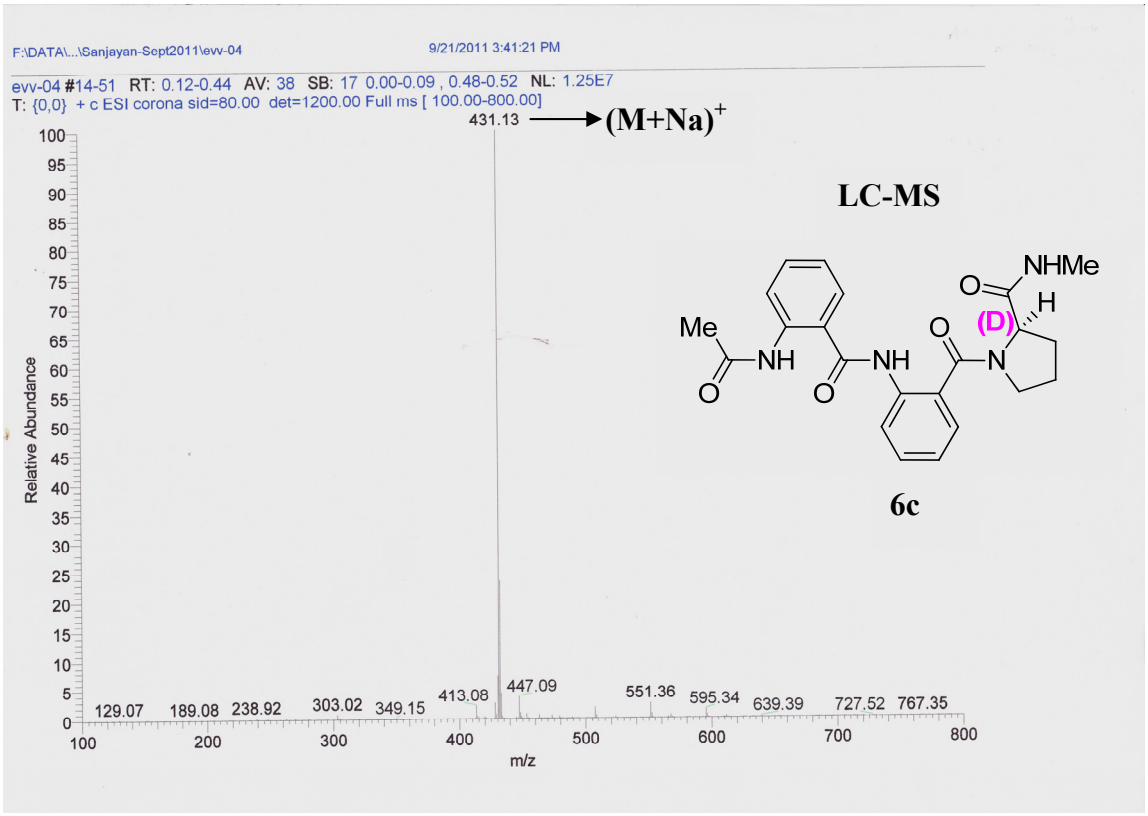

F:\DATA\...\Sanjayan-Sept2011\evv-02
9/21/2011 3:29:02 PM
evv-02 #13-51 RT: 0.11-0.44 AV: 39 SB: 16 0.00-0.08 , 0.52-0.56 NL: 4.32E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
473.20
(M+Na)+
LC-MS
515.25
455.19
Relative Abundance
m/z
171.09 263.00 336.15 433.12 557.24 615.24 695.64 727.48 786.44
4b

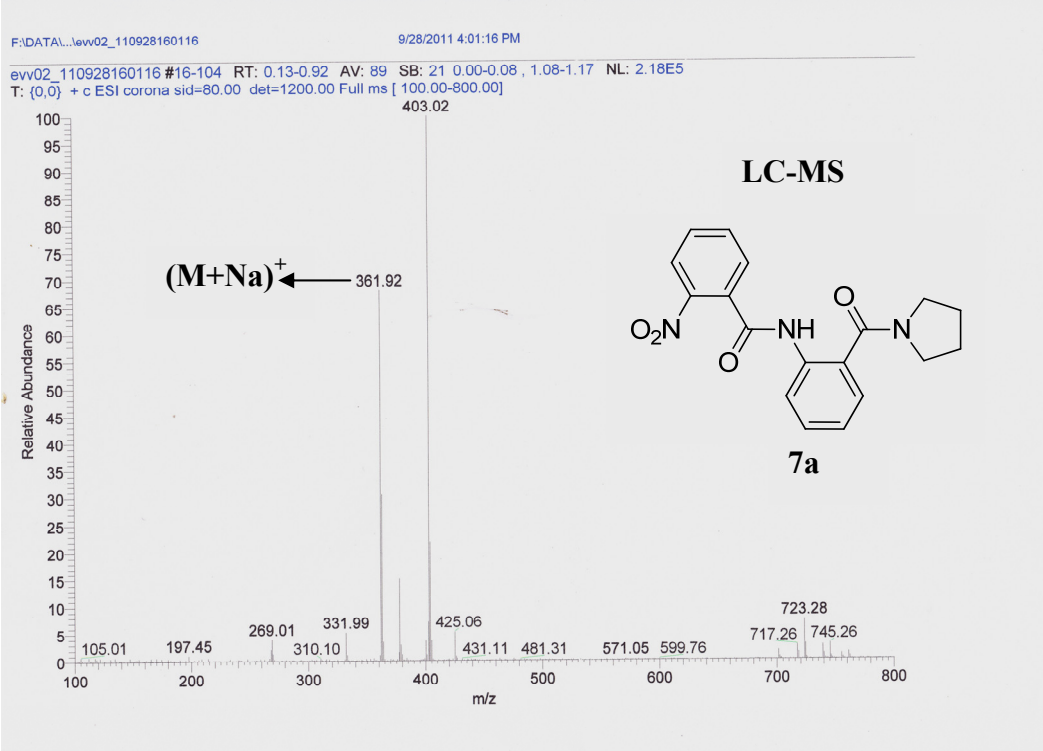

F:\DATA\...\evv-03_110927151508
9/27/2011 3:15:08 PM
evv-03_110927151508 #15-64 RT: 0.12-0.56 AV: 50 SB: 13 0.01-0.07 , 0.55-0.59 NL: 4.07E5
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
(M+Na)+
559.08
561.06
(M+2+Na)+
600.02
602.00
(M+2+K)+
576.98
(M+K)+
580.97
LC-MS
5a
Relative Abundance
m/z

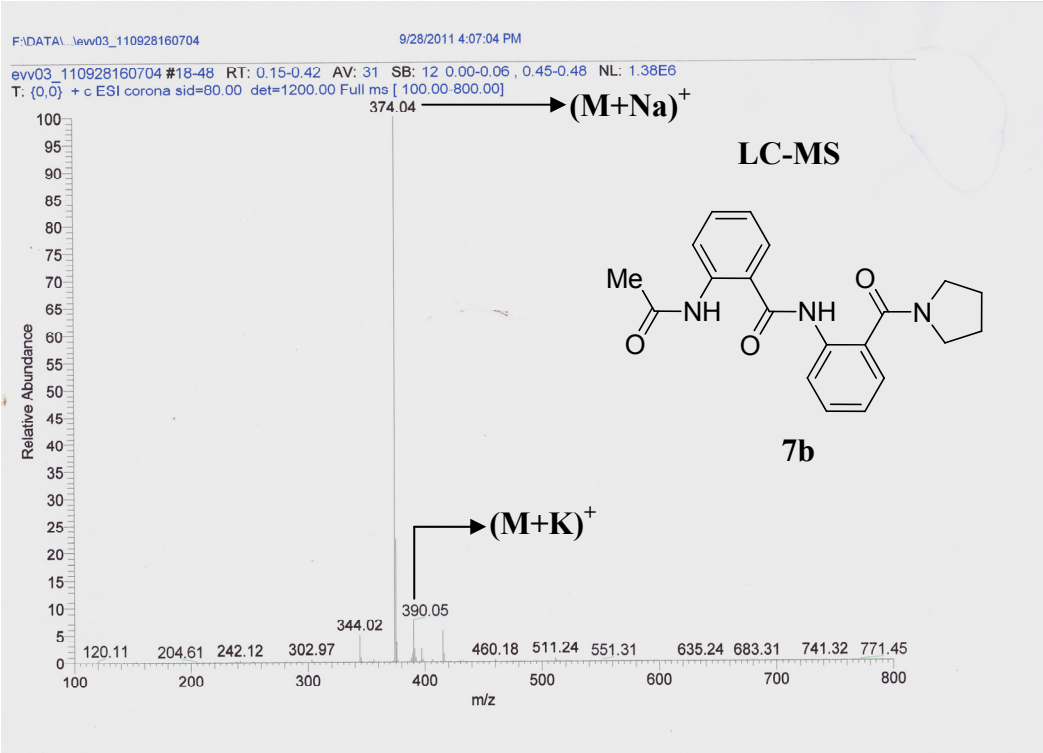

F:\DATA\...\Sanjayan Sept2011\evv-03
9/21/2011 3:35:05 PM
evv-03 #13-61 RT: 0.11-0.53 AV: 49 SB: 15 0.00-0.06 , 0.58-0.63 NL: 2.73E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
571.07
(M+Na)+
(M+2+Na)+
LC-MS
5b
Relative Abundance
m/z

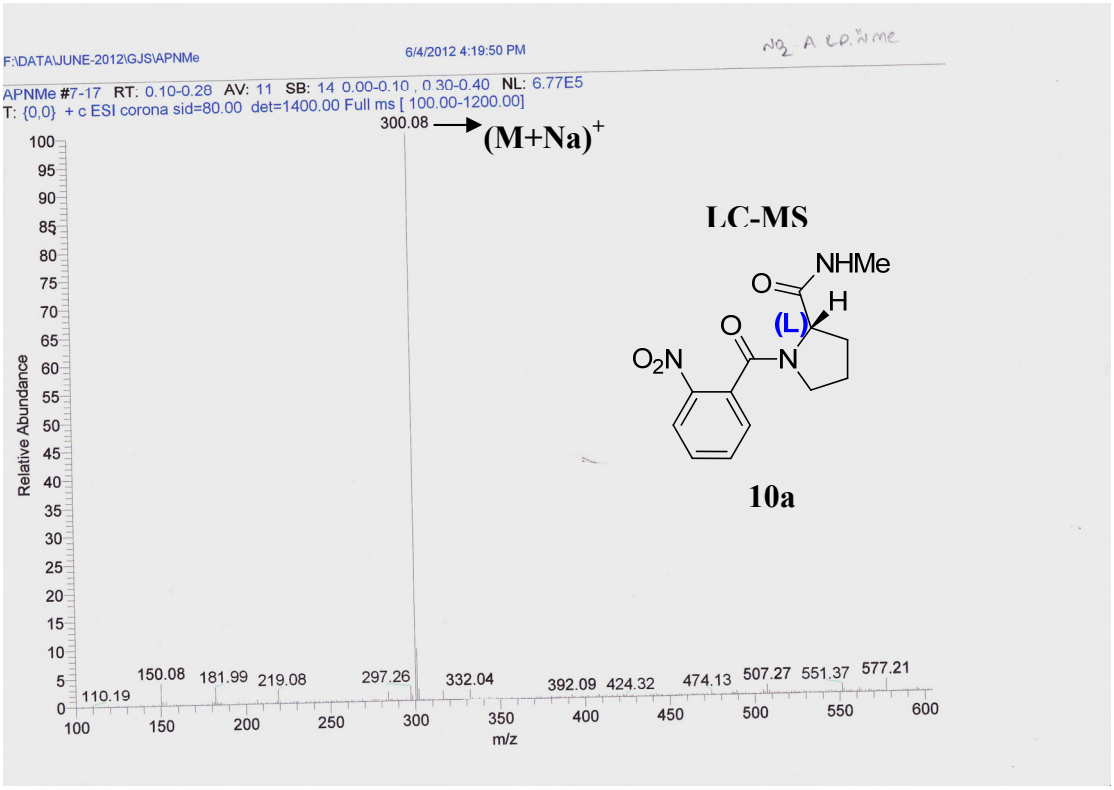

F:\DATA\...\AADP2_111101145739
11/1/2011 2:57:39 PM
AADP2_111101145739 #15-46 RT: 0.12-0.40 AV: 32 SB: 16 0.01-0.07 , 0.43-0.49 NL: 2.45E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
496.16
(M+Na)+
LC-MS
OBn
O
H
(D)
O
O2N
NH
O
N
6a
537.19
153.14 206.08 247.02 326.07 367.11 474.15 554.11 649.14 683.34 799.36 860.39
Relative Abundance
m/z

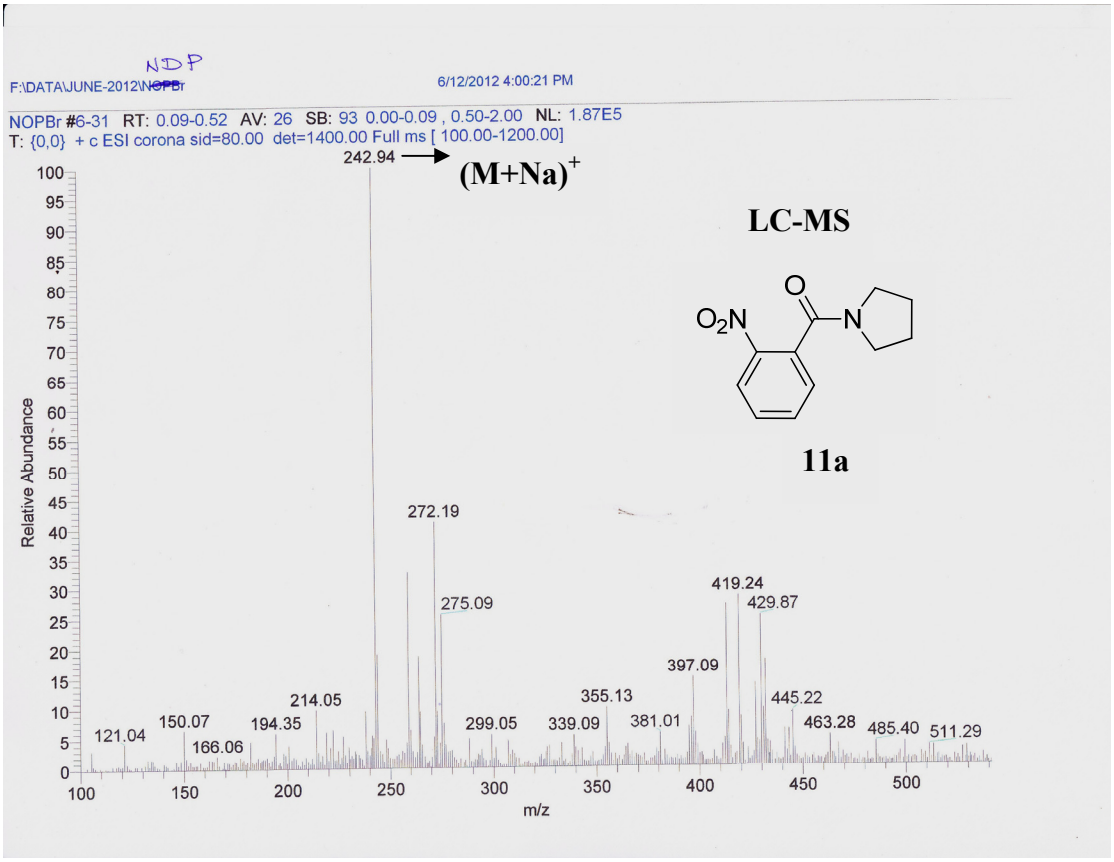

F:\DATA\...\evv-04_110927151749
9/27/2011 3:17:49 PM
evv-04_110927151749 #14-64 RT: 0.12-0.56 AV: 51 SB: 36 0.01-0.08 , 0.82-1.05 NL: 5.45E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
418.98
(M+Na)+
LC-MS
NHMe
O
H
(D)
O
O2N
NH
O
N
6b
431.07
460.15
129.12 192.00 268.91 331.95 413.05 507.34 551.36 595.37 639.42 683.48 727.53 785.29
Relative Abundance
m/z

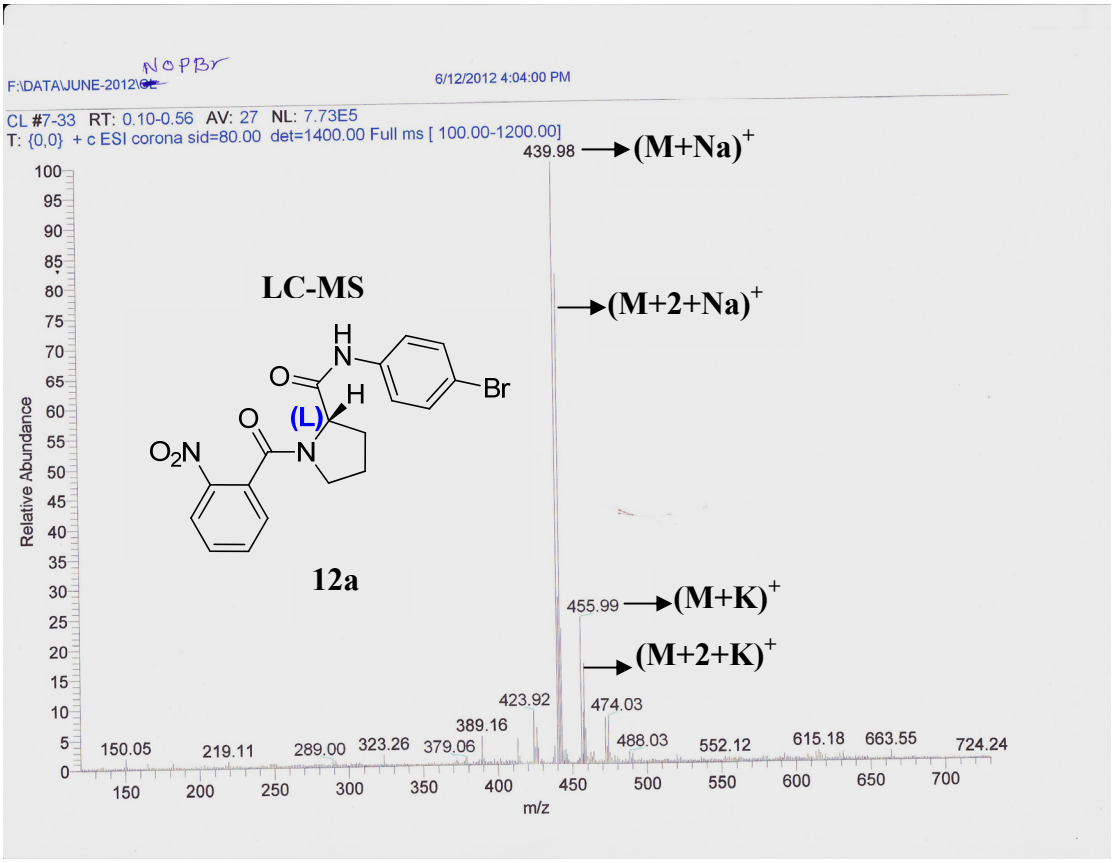

F:\DATA\...\Sanjayan-Sept2011\evv-04
9/21/2011 3:41:21 PM
evv-04 #14-51 RT: 0.12-0.44 AV: 38 SB: 17 0.00-0.09 , 0.48-0.52 NL: 1.25E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
431.13
(M+Na)+
LC-MS
Me
NH
NH
O
NHMe
H
(D)
N
6c
Relative Abundance
m/z
129.07
189.08
238.92
303.02
349.15
413.08
447.09
551.36
595.34
639.39
727.52
767.35

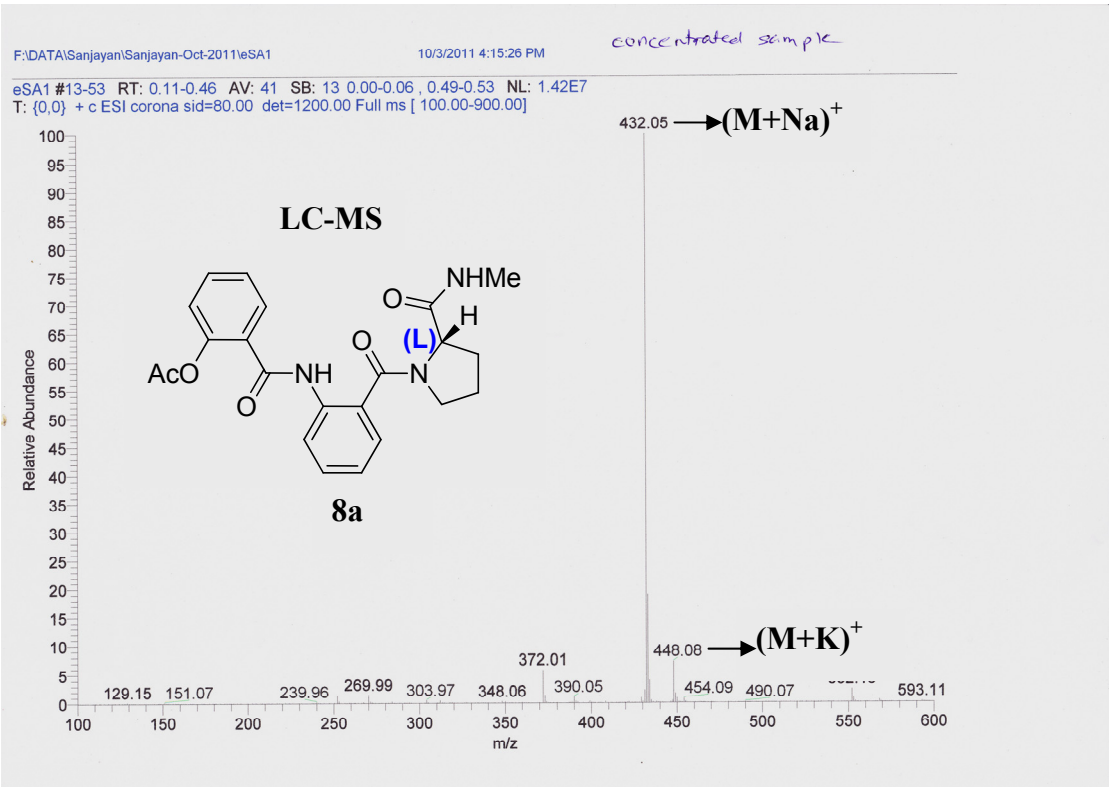

F:\DATA\...\evv02_110928160116
9/28/2011 4:01:16 PM
evv02_110928160116 #16-104 RT: 0.13-0.92 AV: 89 SB: 21 0.00-0.08 , 1.08-1.17 NL: 2.18E5
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
403.02
(M+Na)+
361.92
LC-MS
O2N
NH
O
N
7a
Relative Abundance
m/z
105.01
197.45
269.01
310.10
331.99
425.06
431.11
481.31
571.05
599.76
717.26
723.28
745.26

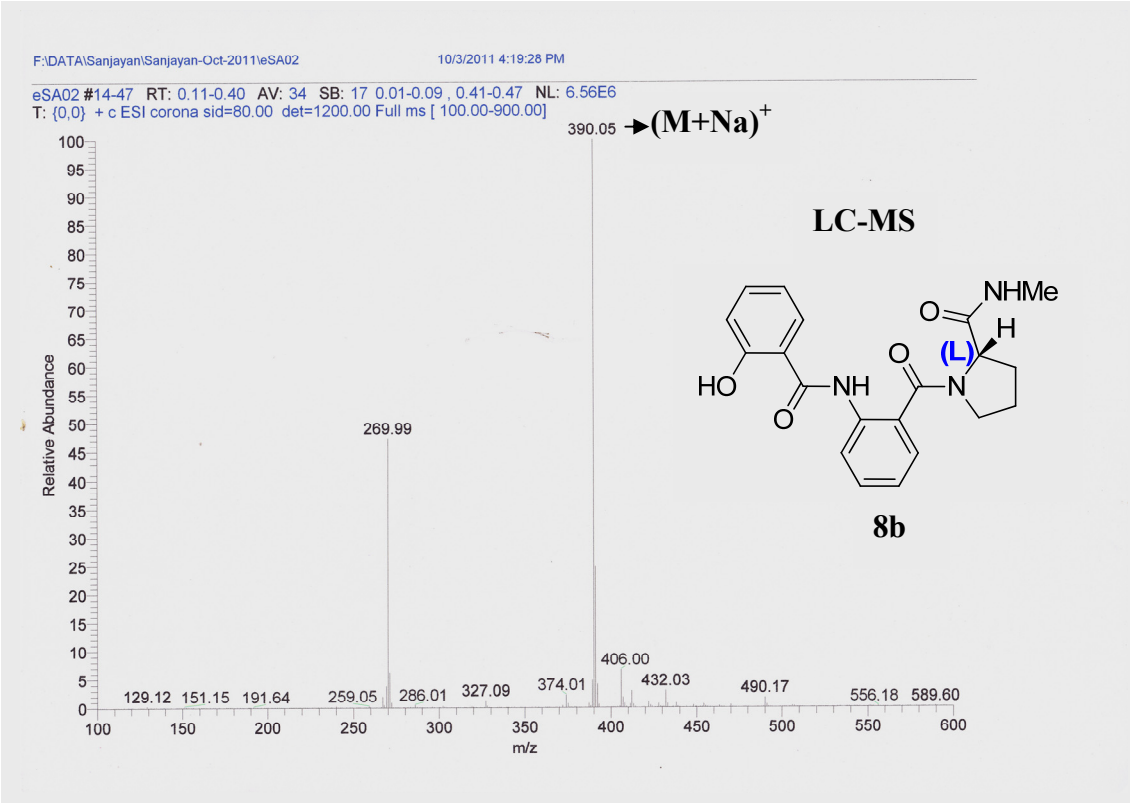

F:\DATA\ ..\evv03_110928160704
9/28/2011 4:07:04 PM
evv03_110928160704 #18-48 RT: 0.15-0.42 AV: 31 SB: 12 0.00-0.06 , 0.45-0.48 NL: 1.38E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
374.04
(M+Na)+
LC-MS
Me
NH
NH
O
N
7b
(M+K)+
390.05
344.02
120.11
204.61
242.12
302.97
460.18
511.24
551.31
635.24
683.31
741.32
771.45
Relative Abundance
m/z

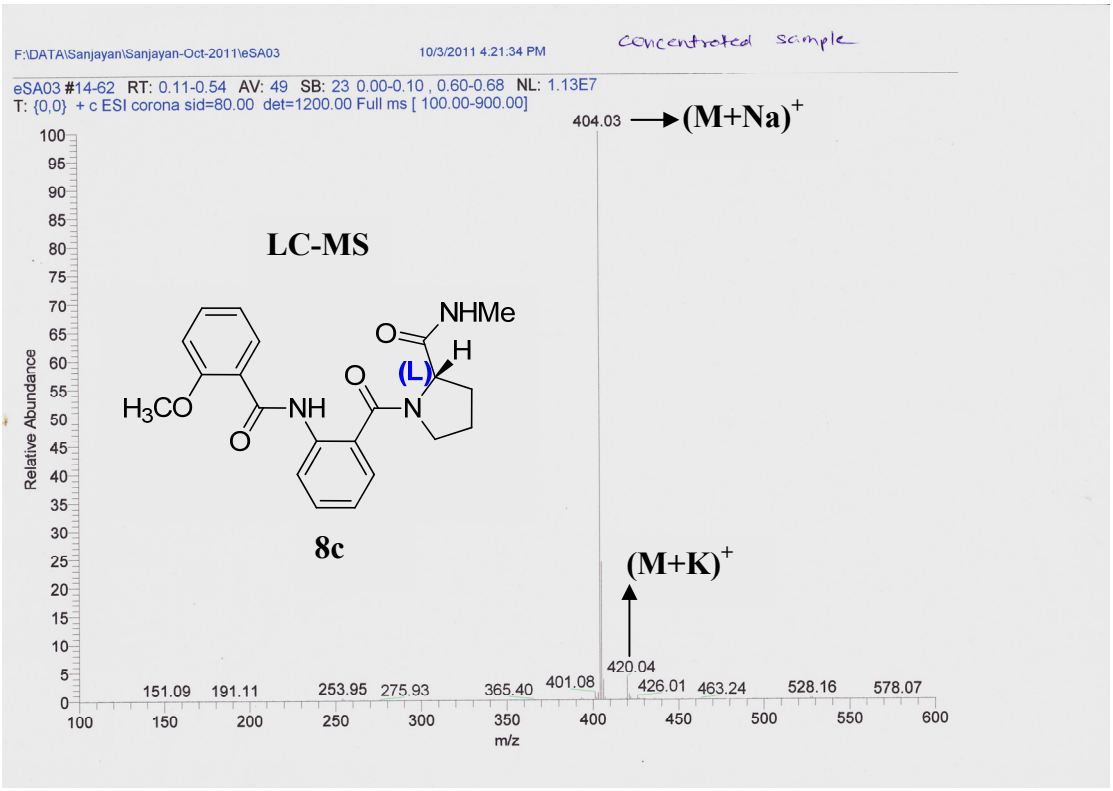

F:\DATA\JUNE-2012\GJS\APNMe
6/4/2012 4:19:50 PM
APNMe #7-17 RT: 0.10-0.28 AV: 11 SB: 14 0.00-0.10 , 0.30-0.40 NL: 6.77E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
300.08
(M+Na)+
LC-MS
NHMe
O
H
O
(L)
O2N
N
10a
110.19
150.08
181.99
219.08
297.26
332.04
392.09
424.32
474.13
507.27
551.37
577.21
Relative Abundance
m/z

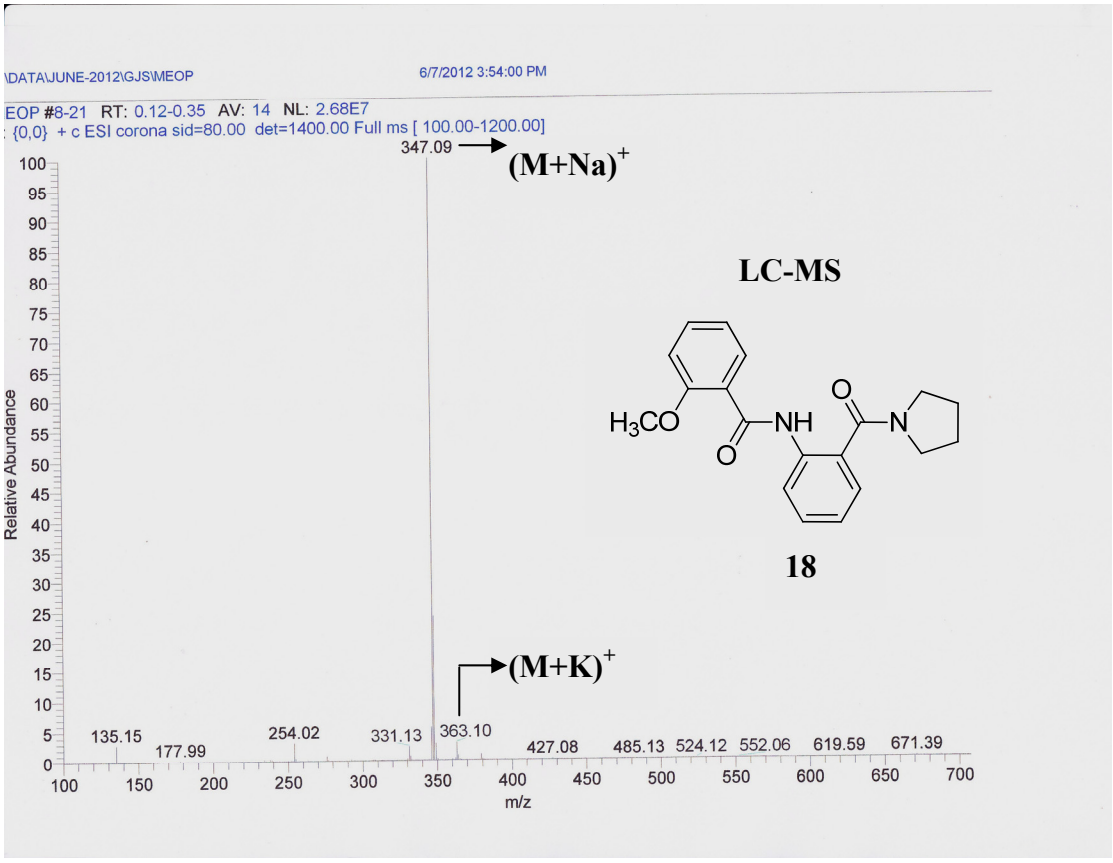

NDP
F:\DATA\JUNE-2012\NOPBr
6/12/2012 4:00:21 PM
NOPBr #6-31 RT: 0.09-0.52 AV: 26 SB: 93 0.00-0.09 , 0.50-2.00 NL: 1.87E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
242.94
(M+Na)+
LC-MS
O2N
O
N
11a
Relative Abundance
m/z
272.19
275.09
419.24
429.87
397.09
355.13
445.22
214.05
150.07
194.35
121.04
166.06
299.05
339.09
381.01
463.28
485.40
511.29

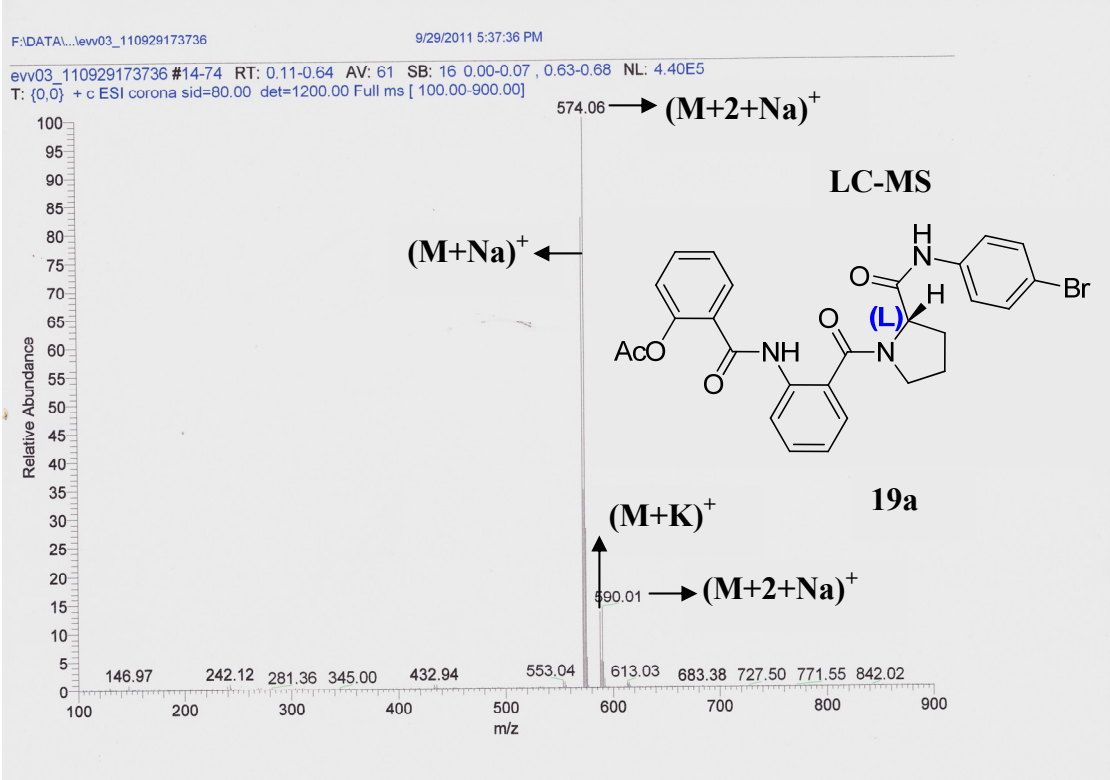

NOPBr
F:\DATA\JUNE-2012\CL
6/12/2012 4:04:00 PM
CL #7-33 RT: 0.10-0.56 AV: 27 NL: 7.73E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
439.98
(M+Na)+
LC-MS
(M+2+Na)+
H
N
O
Br
H
(L)
O
O2N
N
12a
455.99
(M+K)+
(M+2+K)+
Relative Abundance
m/z
423.92
474.03
389.16
488.03
552.12
615.18
663.55
724.24
150.05
219.11
289.00
323.26
379.06

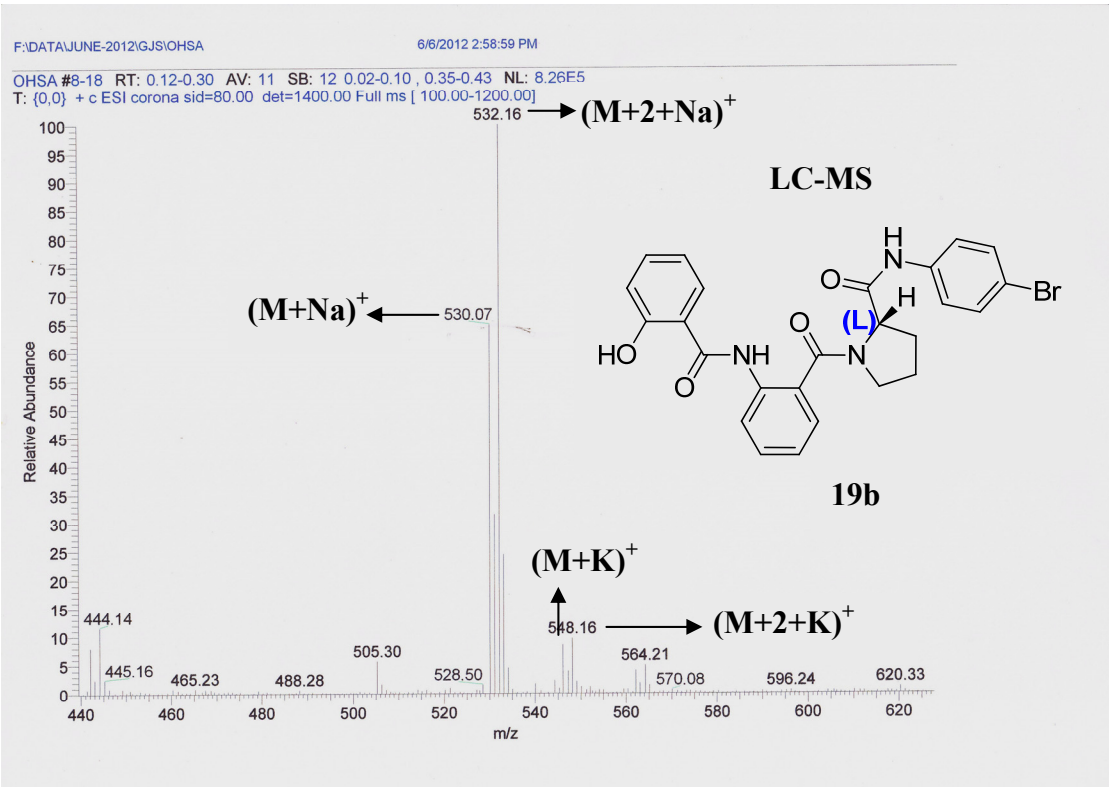

F:\DATA\Sanjayan\Sanjayan-Oct-2011\eSA1
10/3/2011 4:15:26 PM
concentrated sample
eSA1 #13-53 RT: 0.11-0.46 AV: 41 SB: 13 0.00-0.06 , 0.49-0.53 NL: 1.42E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
432.05 (M+Na)+
LC-MS
NHMe
O
H
(L)
AcO
NH
N
8a
448.08 (M+K)+
372.01
Relative Abundance
m/z

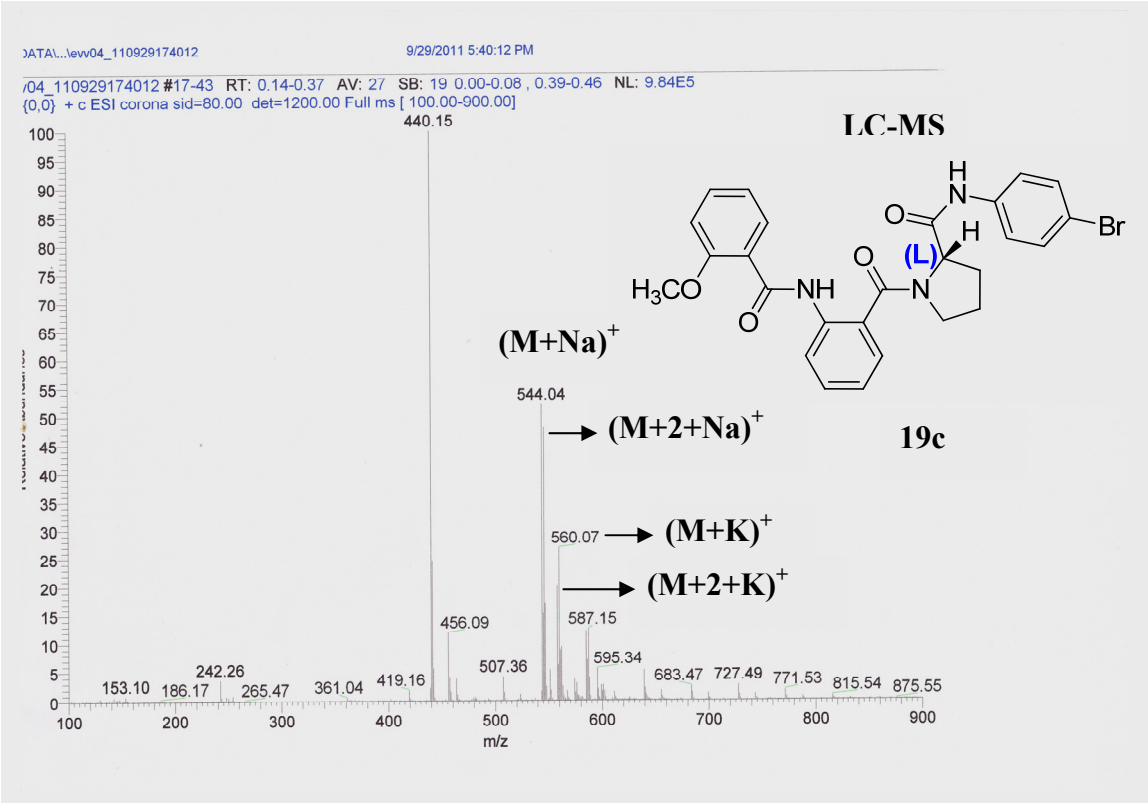

F:\DATA\Sanjayan\Sanjayan-Oct-2011\eSA02
10/3/2011 4:19:28 PM
eSA02 #14-47 RT: 0.11-0.40 AV: 34 SB: 17 0.01-0.09 , 0.41-0.47 NL: 6.56E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
390.05 (M+Na)+
LC-MS
NHMe
HO
NH
N
8b
269.99
406.00
Relative Abundance
m/z

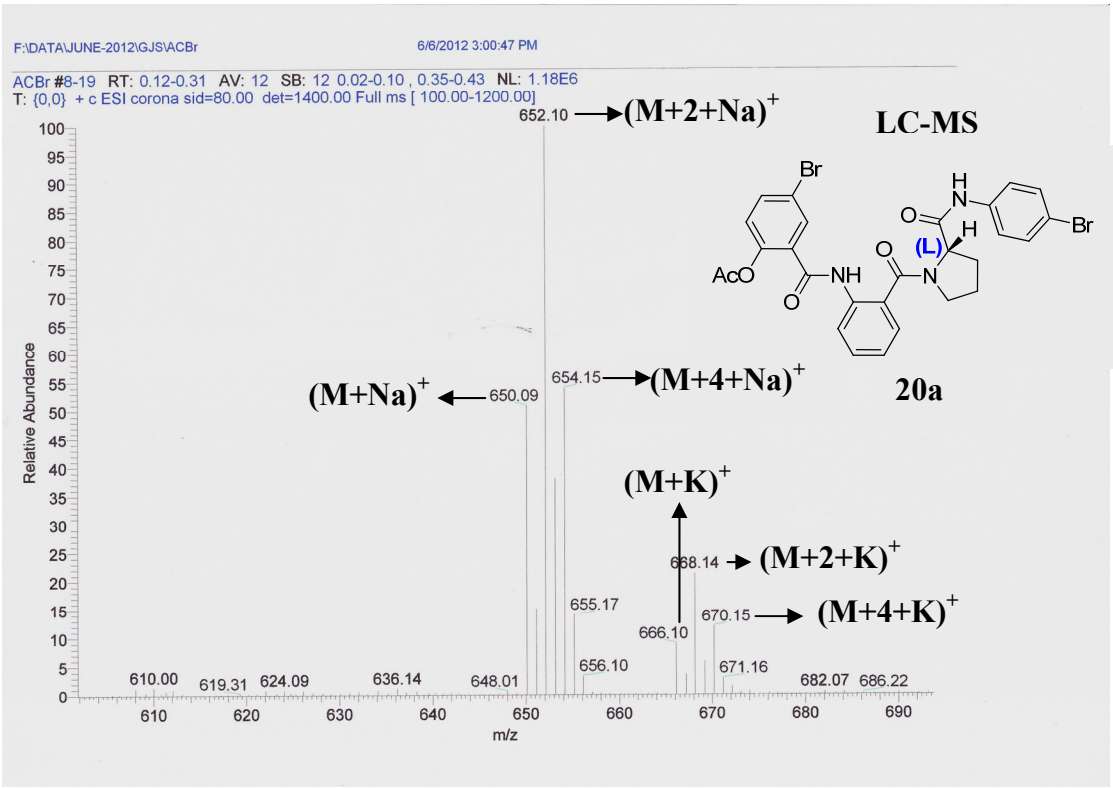

F:\DATA\Sanjayan\Sanjayan-Oct-2011\eSA03
10/3/2011 4.21.34 PM
concentrated sample
eSA03 #14-62 RT: 0.11-0.54 AV: 49 SB: 23 0.00-0.10 , 0.60-0.68 NL: 1.13E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
404.03
(M+Na)+
LC-MS
NHMe
O
H
(L)
H3CO
NH
N
8c
(M+K)+
420.04
Relative Abundance
m/z

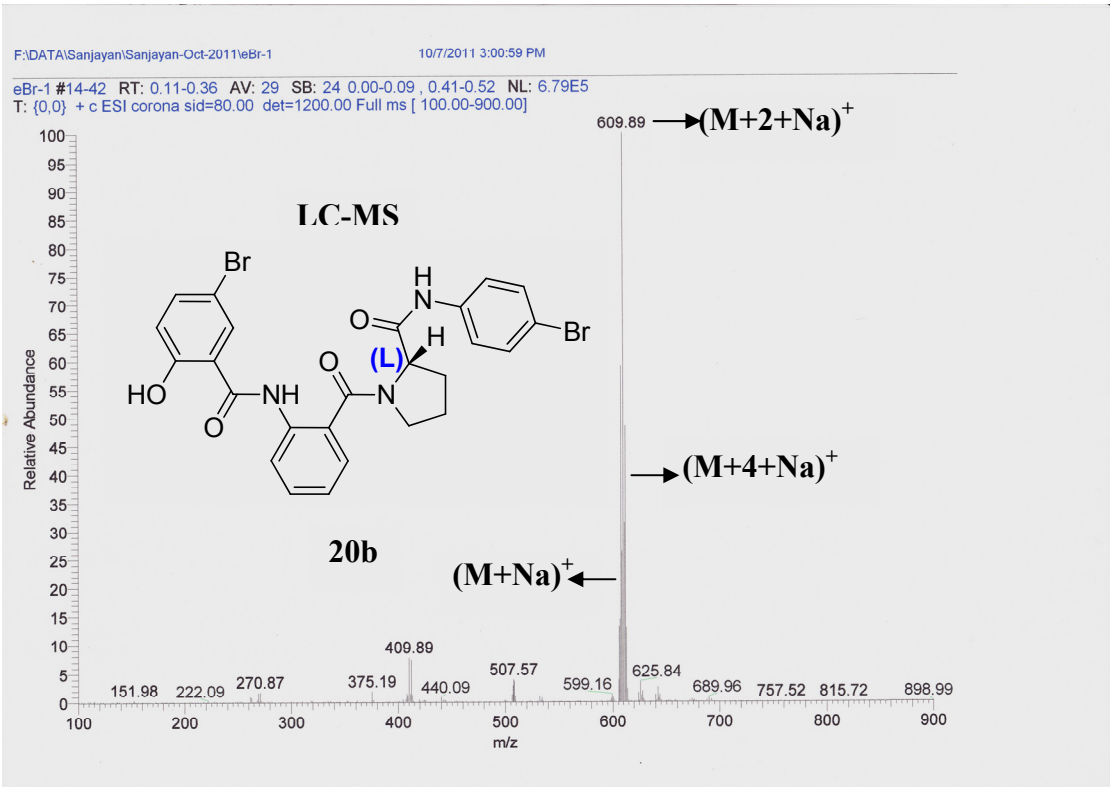

\DATA\JUNE-2012\GJS\MEOP
6/7/2012 3:54:00 PM
EOP #8-21 RT: 0.12-0.35 AV: 14 NL: 2.68E7
{0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
347.09
(M+Na)+
LC-MS
H3CO
NH
O
N
18
(M+K)+
363.10
Relative Abundance
m/z

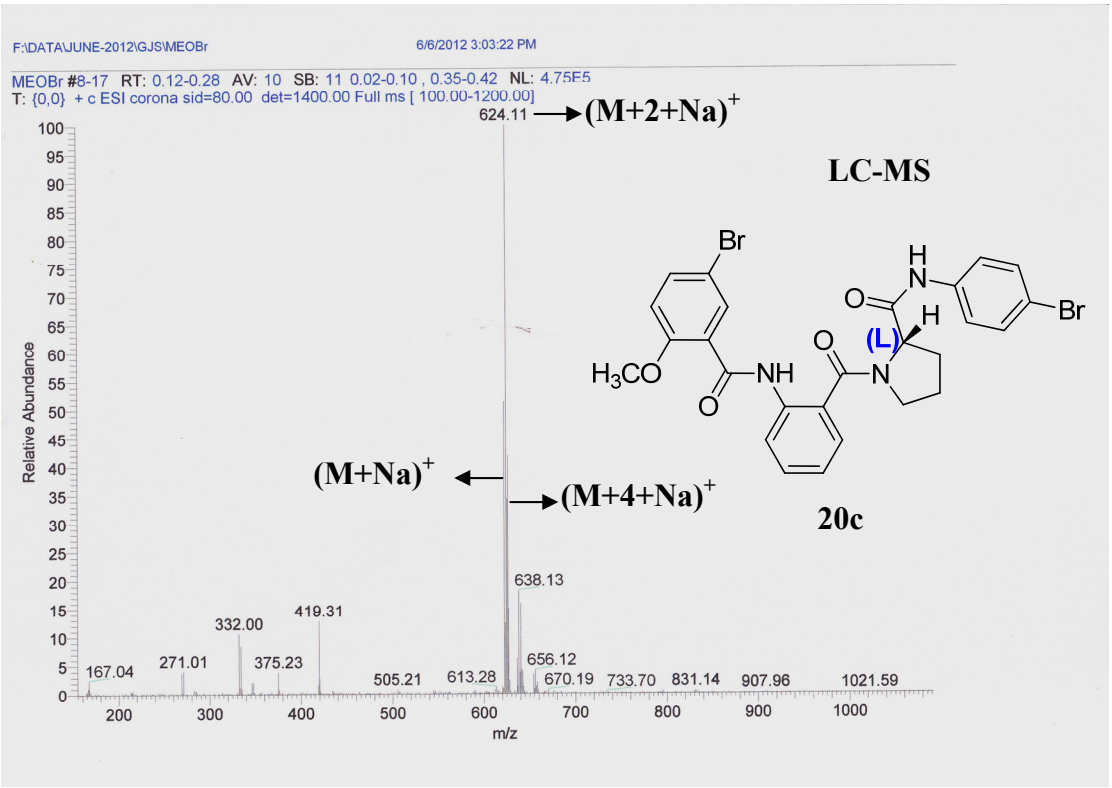

F:\DATA\...\evv03_110929173736
9/29/2011 5:37:36 PM
evv03_110929173736 #14-74 RT: 0.11-0.64 AV: 61 SB: 16 0.00-0.07 , 0.63-0.68 NL: 4.40E5
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
574.06 (M+2+Na)+
LC-MS
(M+Na)+
(M+K)+
590.01 (M+2+Na)+
19a
Relative Abundance
m/z
146.97 242.12 281.36 345.00 432.94 553.04 613.03 683.38 727.50 771.55 842.02

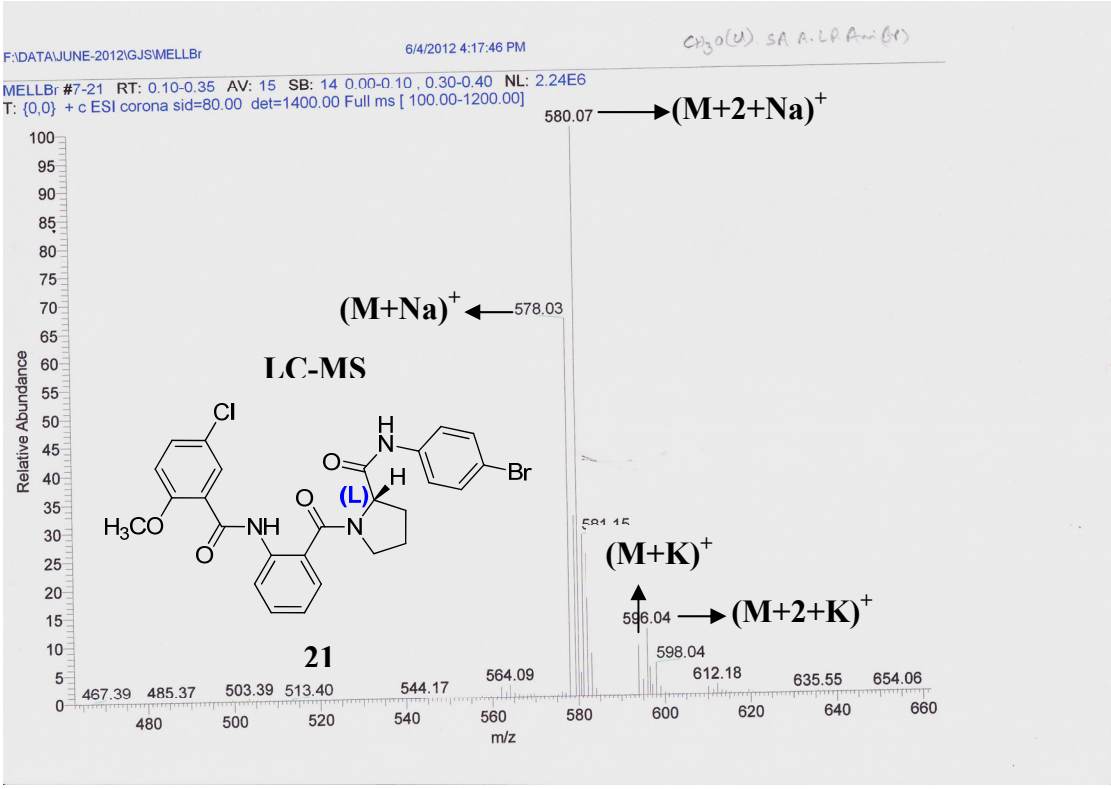

F:\DATA\JUNE-2012\GJS\OHSA
6/6/2012 2:58:59 PM
OHSA #8-18 RT: 0.12-0.30 AV: 11 SB: 12 0.02-0.10 , 0.35-0.43 NL: 8.26E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
532.16 (M+2+Na)+
LC-MS
(M+Na)+ 530.07
19b
(M+K)+
548.16 (M+2+K)+
Relative Abundance
m/z
444.14 445.16 465.23 488.28 505.30 528.50 564.21 570.08 596.24 620.33

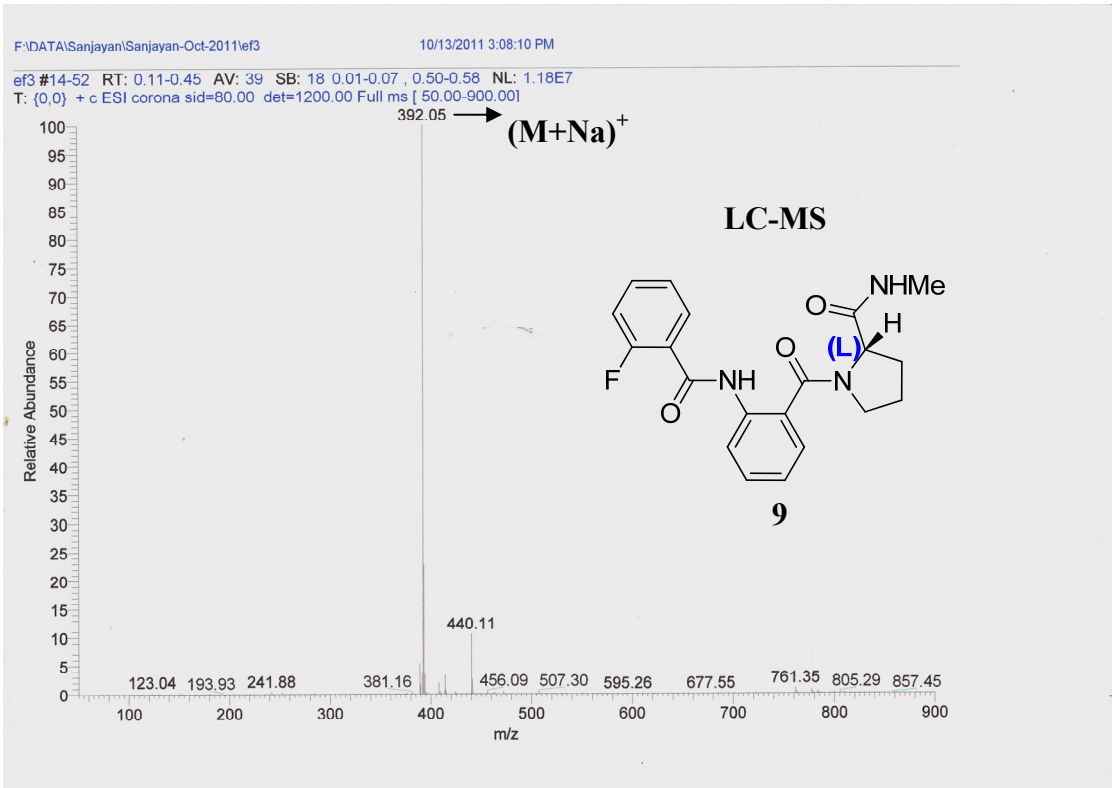

9/29/2011 5:40:12 PM
LC-MS
440.15
(M+Na)+
544.04
(M+2+Na)+
19c
560.07
(M+K)+
(M+2+K)+
456.09
587.15
595.34
507.36
242.26
153.10
186.17
265.47
361.04
419.16
683.47
727.49
771.53
815.54
875.55
m/z

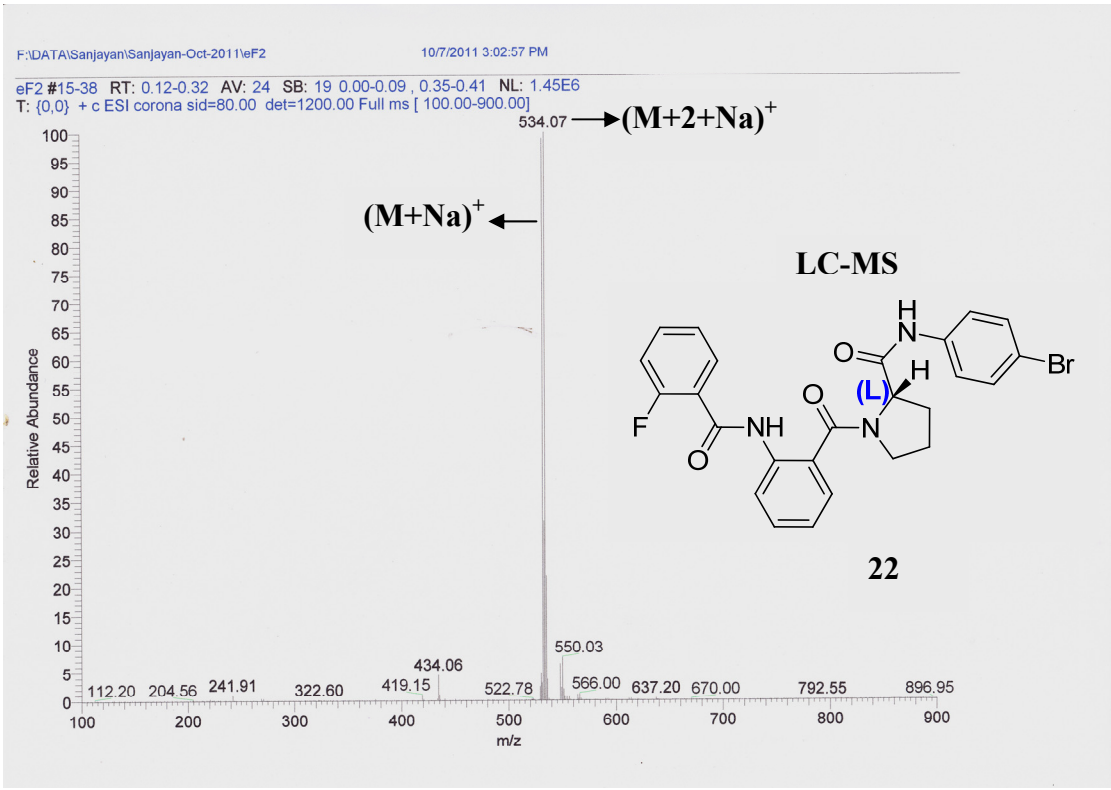

F:\DATA\JUNE-2012\GJS\ACBr
6/6/2012 3:00:47 PM
652.10
(M+2+Na)+
LC-MS
20a
(M+Na)+
650.09
654.15
(M+4+Na)+
(M+K)+
668.14
(M+2+K)+
655.17
666.10
670.15
(M+4+K)+
656.10
671.16
610.00
619.31
624.09
636.14
648.01
682.07
686.22
Relative Abundance
m/z

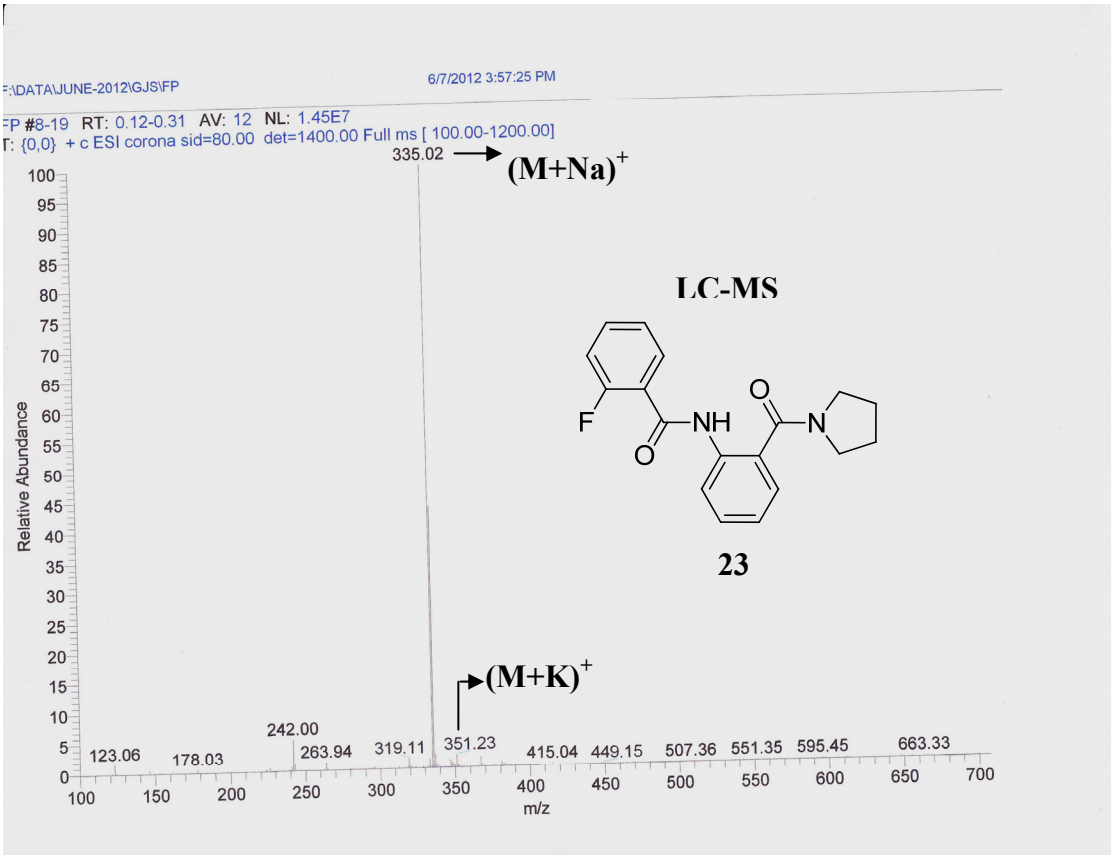

F:\DATA\Sanjayan\Sanjayan-Oct-2011\eBr-1 10/7/2011 3:00:59 PM
eBr-1 #14-42 RT: 0.11-0.36 AV: 29 SB: 24 0.00-0.09 , 0.41-0.52 NL: 6.79E5
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
609.89 (M+2+Na)+
LC-MS
(M+4+Na)+
20b
(M+Na)+
Relative Abundance
m/z


F:\DATA\JUNE-2012\GJS\MEOBr 6/6/2012 3:03:22 PM
MEOBr #8-17 RT: 0.12-0.28 AV: 10 SB: 11 0.02-0.10 , 0.35-0.42 NL: 4.75E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
624.11 (M+2+Na)+
LC-MS
(M+Na)+
(M+4+Na)+
20c
Relative Abundance
m/z

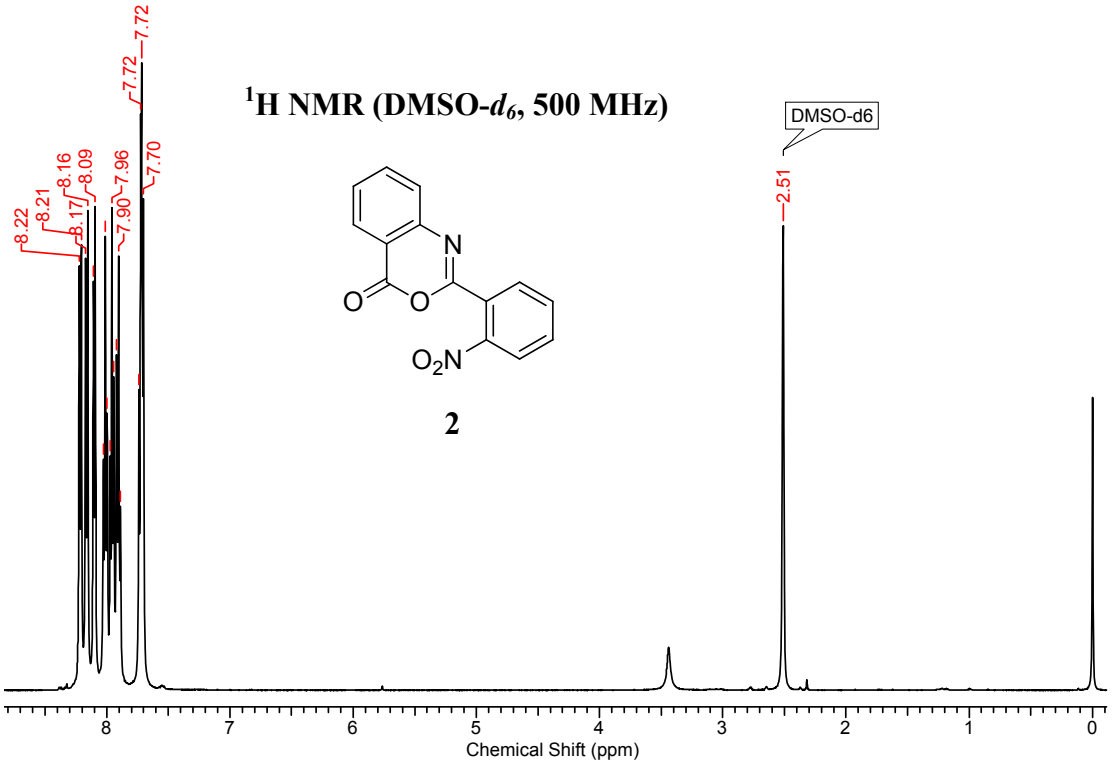

F:\DATA\JUNE-2012\GJS\MELLBr
6/4/2012 4:17:46 PM
MELLBr #7-21 RT: 0.10-0.35 AV: 15 SB: 14 0.00-0.10 , 0.30-0.40 NL: 2.24E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
580.07 (M+2+Na)+
(M+Na)+ 578.03
LC-MS
(M+K)+
596.04 (M+2+K)+
598.04
21
Relative Abundance
m/z


F:\DATA\Sanjayan\Sanjayan-Oct-2011\ef3
10/13/2011 3:08:10 PM
ef3 #14-52 RT: 0.11-0.45 AV: 39 SB: 18 0.01-0.07 , 0.50-0.58 NL: 1.18E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [50.00-900.00]
392.05 (M+Na)+
LC-MS
440.11
9
Relative Abundance
m/z

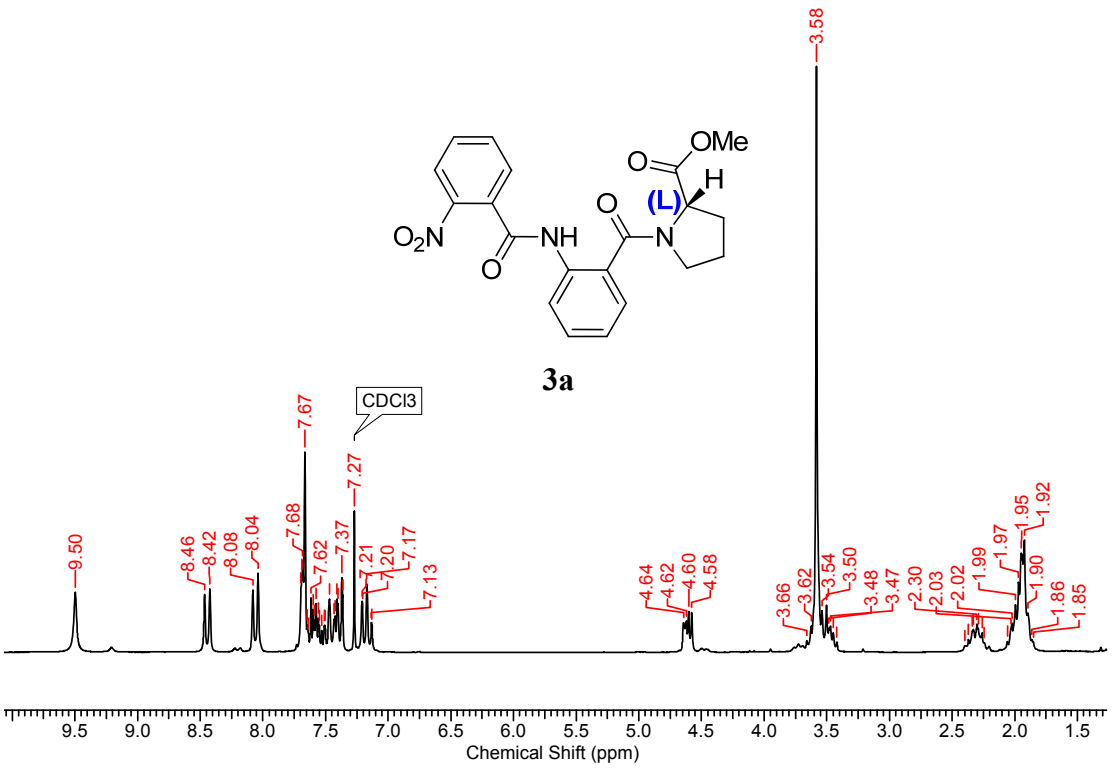

F:\DATA\Sanjayan\Sanjayan-Oct-2011\eF2
10/7/2011 3:02:57 PM
eF2 #15-38 RT: 0.12-0.32 AV: 24 SB: 19 0.00-0.09 , 0.35-0.41 NL: 1.45E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-900.00]
534.07
(M+2+Na)+
(M+Na)+
LC-MS
Relative Abundance
m/z
550.03
434.06
112.20 204.56 241.91 322.60 419.15 522.78 566.00 637.20 670.00 792.55 896.95
22


F:\DATA\JUNE-2012\GJS\FP
6/7/2012 3:57:25 PM
FP #8-19 RT: 0.12-0.31 AV: 12 NL: 1.45E7
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
335.02
(M+Na)+
LC-MS
(M+K)+
Relative Abundance
m/z
242.00
123.06 178.03 263.94 319.11 351.23 415.04 449.15 507.36 551.35 595.45 663.33
23

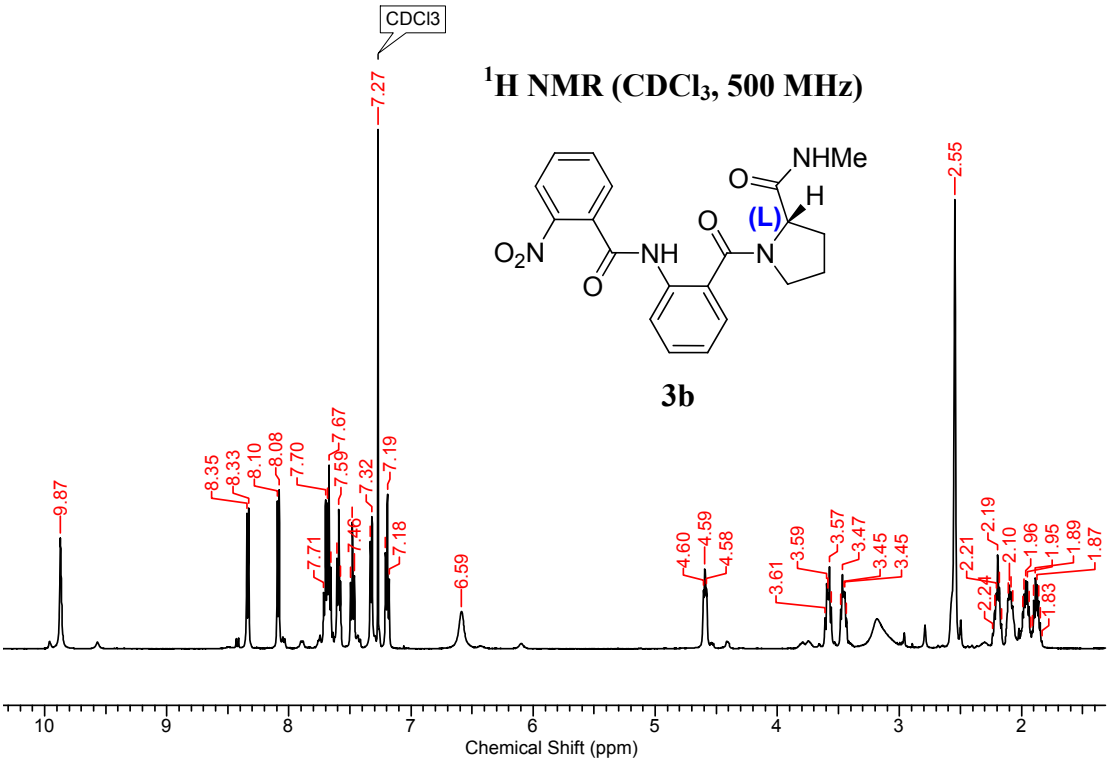
^{1}H NMR (DMSO-d_6, 500 MHz)

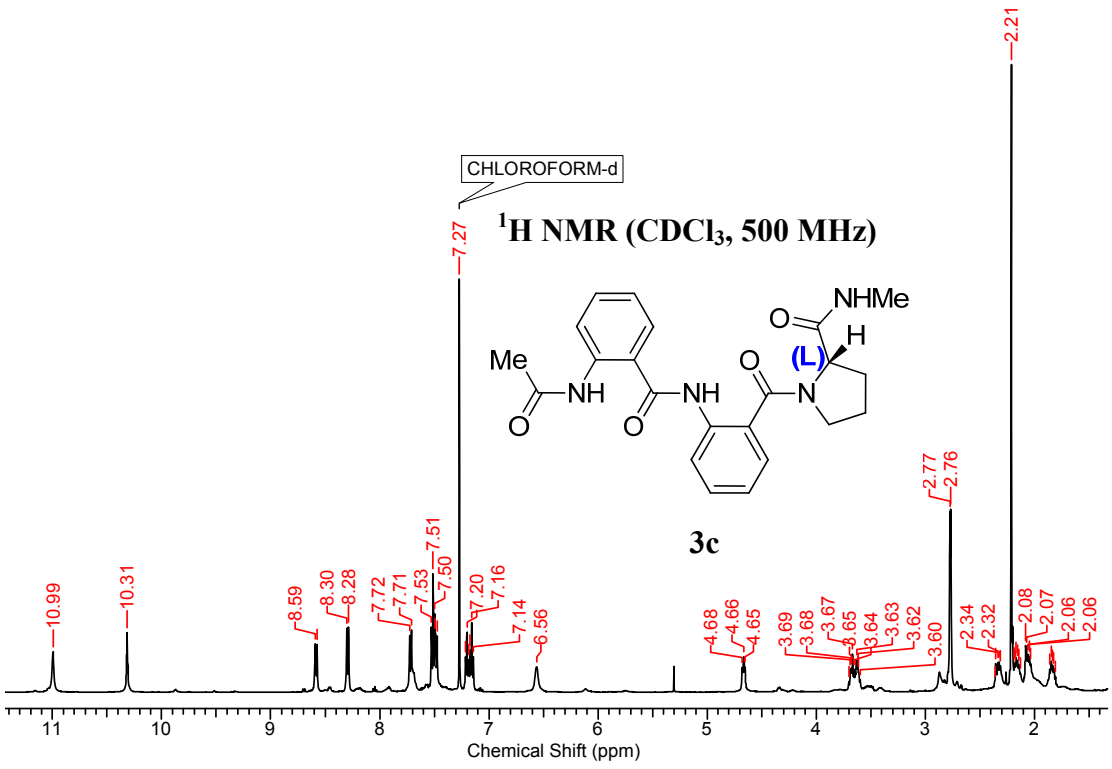


2

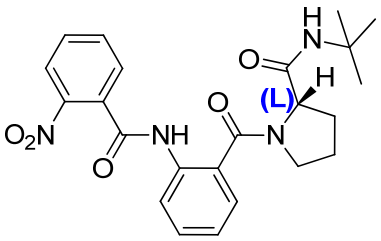


3a


CDCl3
^{1}H NMR (CDCl$_3$, 500 MHz)
NHMe
O
H
(L)
O
O$_2$N
NH
O
N
3b
9.87
8.35
8.33
8.10
8.08
7.70
7.67
7.59
7.46
7.32
7.27
7.19
7.18
7.71
6.59
4.60
4.59
4.58
3.61
3.59
3.57
3.47
3.45
3.45
2.55
2.21
2.24
2.19
2.10
1.96
1.95
1.89
1.87
1.83
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

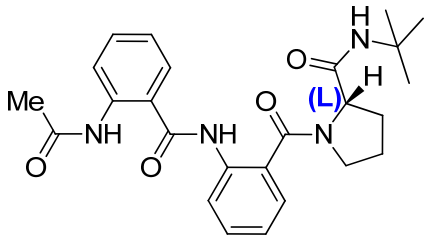

CHLOROFORM-d
^{1}H NMR (CDCl$_3$, 500 MHz)
NHMe
O
H
Me
NH
O
(L)
O
NH
O
N
3c
10.99
10.31
8.59
8.30
8.28
7.72
7.71
7.53
7.51
7.50
7.27
7.20
7.16
7.14
6.56
4.68
4.66
4.65
3.69
3.68
3.67
3.65
3.64
3.63
3.62
3.60
2.77
2.76
2.34
2.32
2.21
2.08
2.07
2.06
2.06
11
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)

^{1}H NMR ($CDCl_3$, 500 MHz)

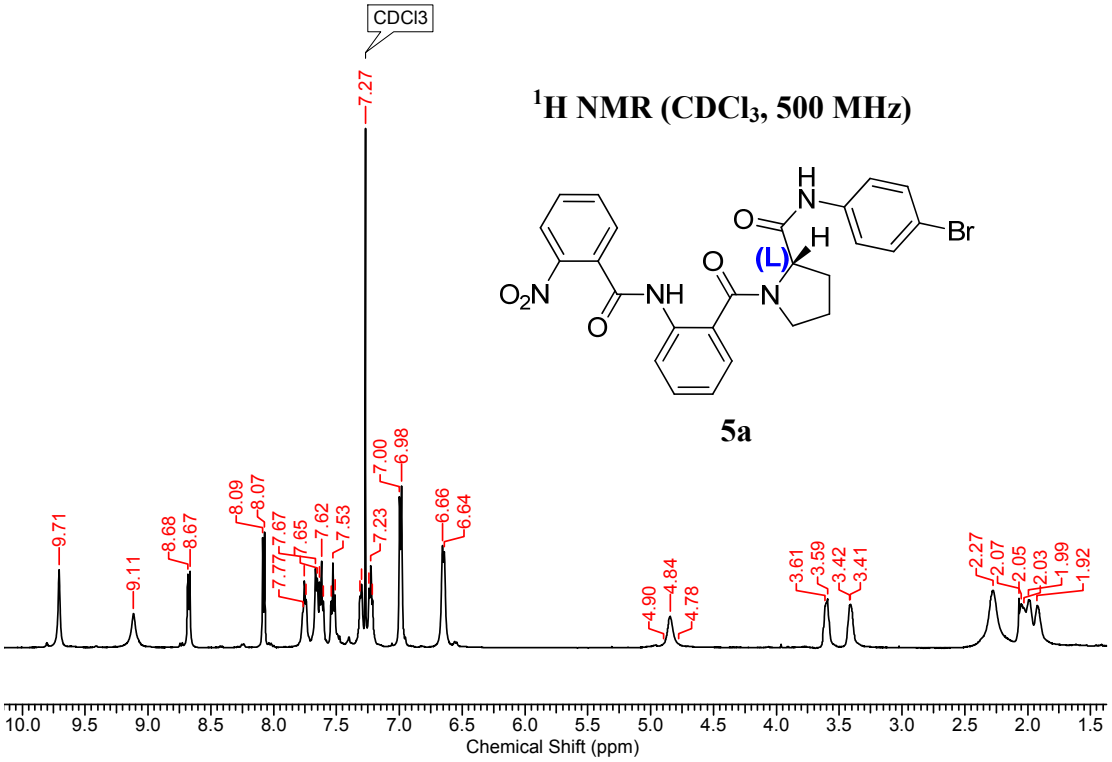


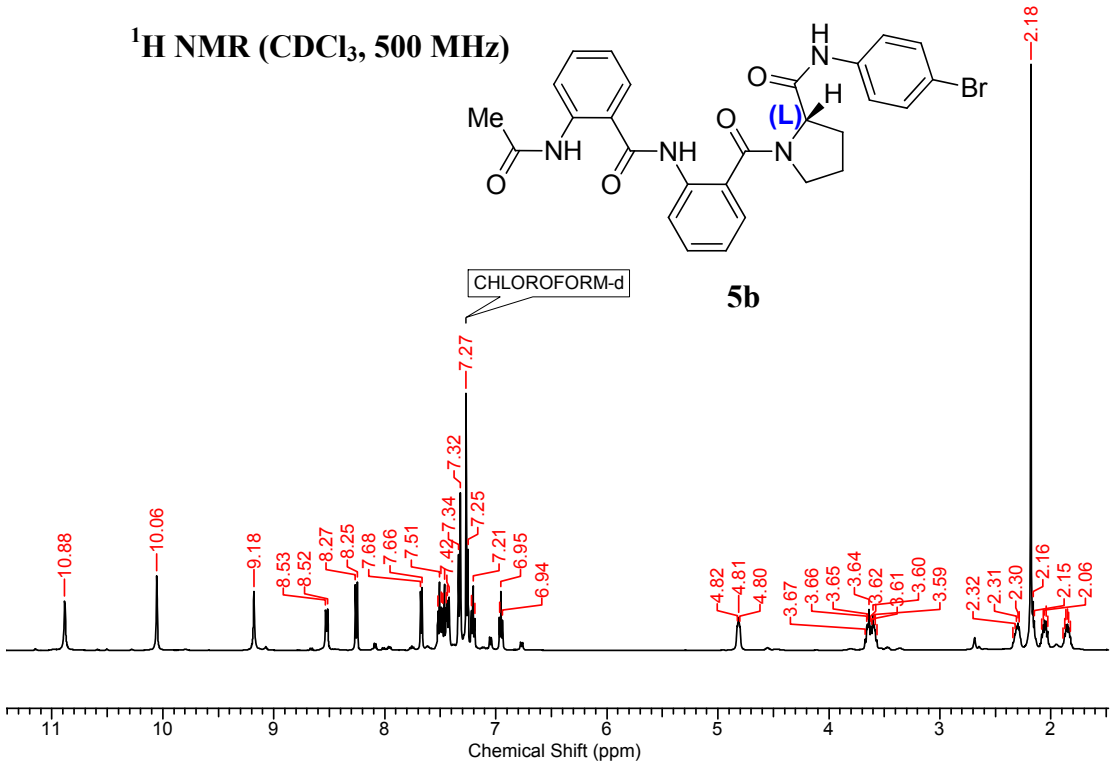
4a

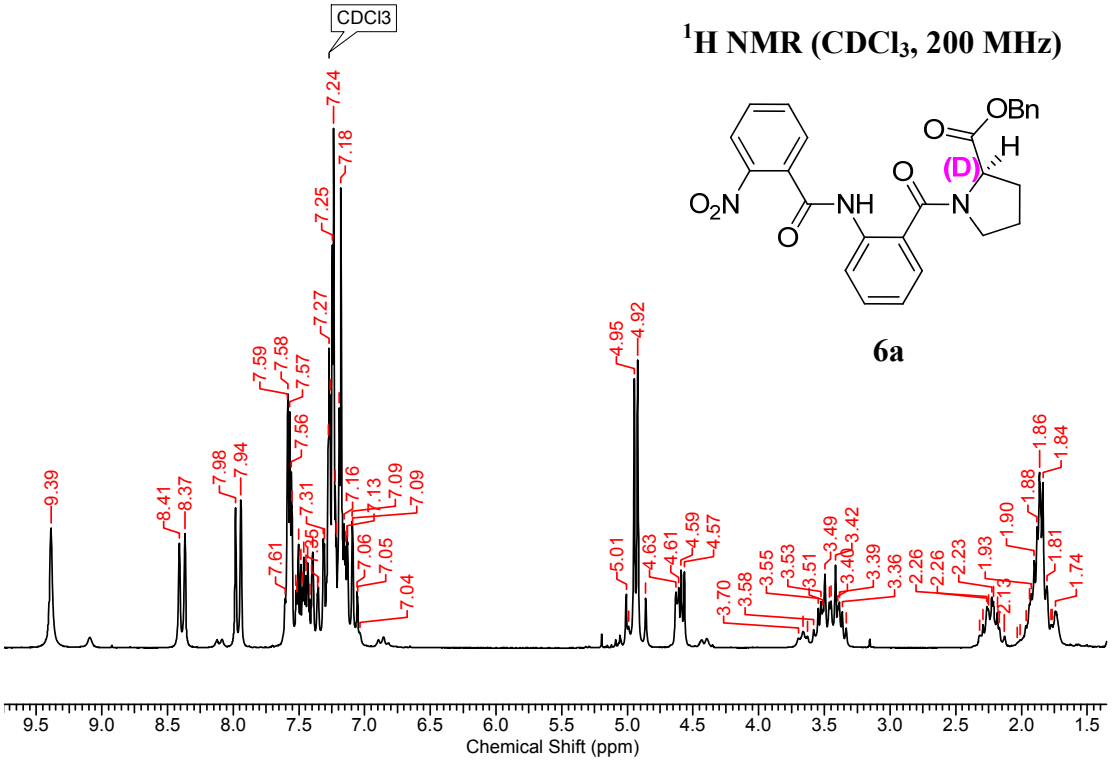
^{1}H NMR ($CDCl_3$, 200 MHz)

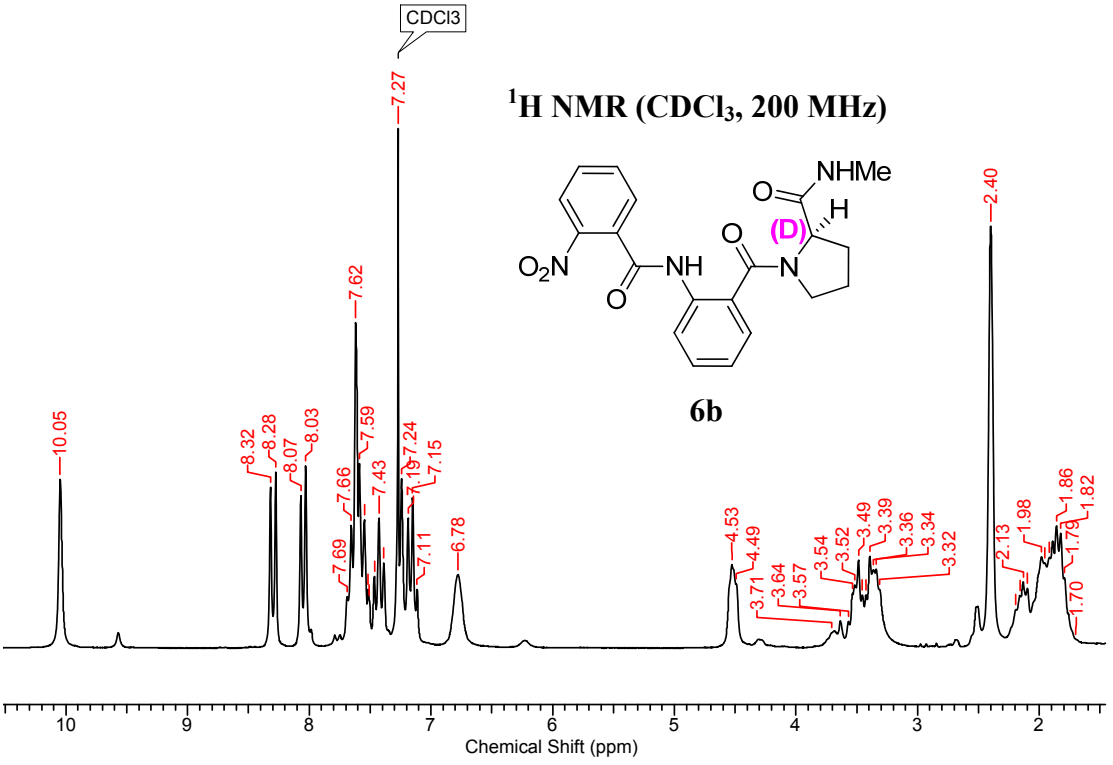


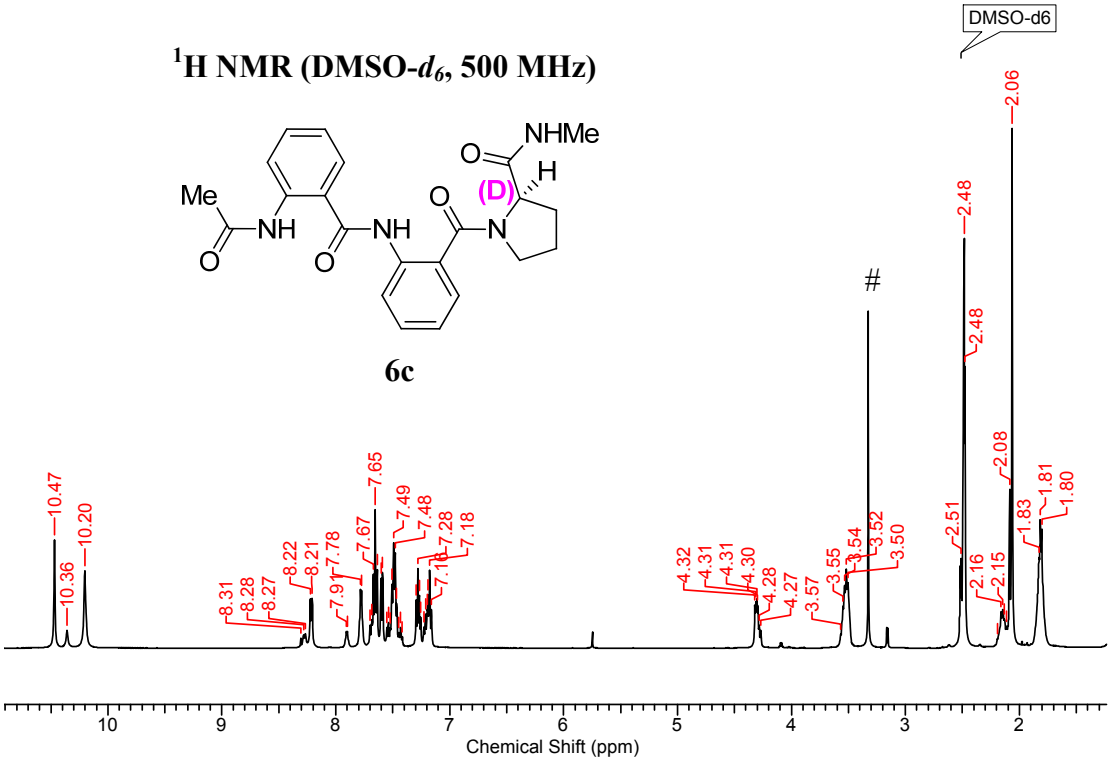
4b


CDCl3
7.27
^{1}H NMR (CDCl$_3$, 500 MHz)
O$_2$N
NH
O
N
(L)
H
O
N
H
Br
5a
9.71
9.11
8.68
8.67
8.09
8.07
7.77
7.67
7.65
7.62
7.53
7.23
7.00
6.98
6.66
6.64
4.90
4.84
4.78
3.61
3.59
3.42
3.41
2.27
2.07
2.05
2.03
1.99
1.92
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
Chemical Shift (ppm)

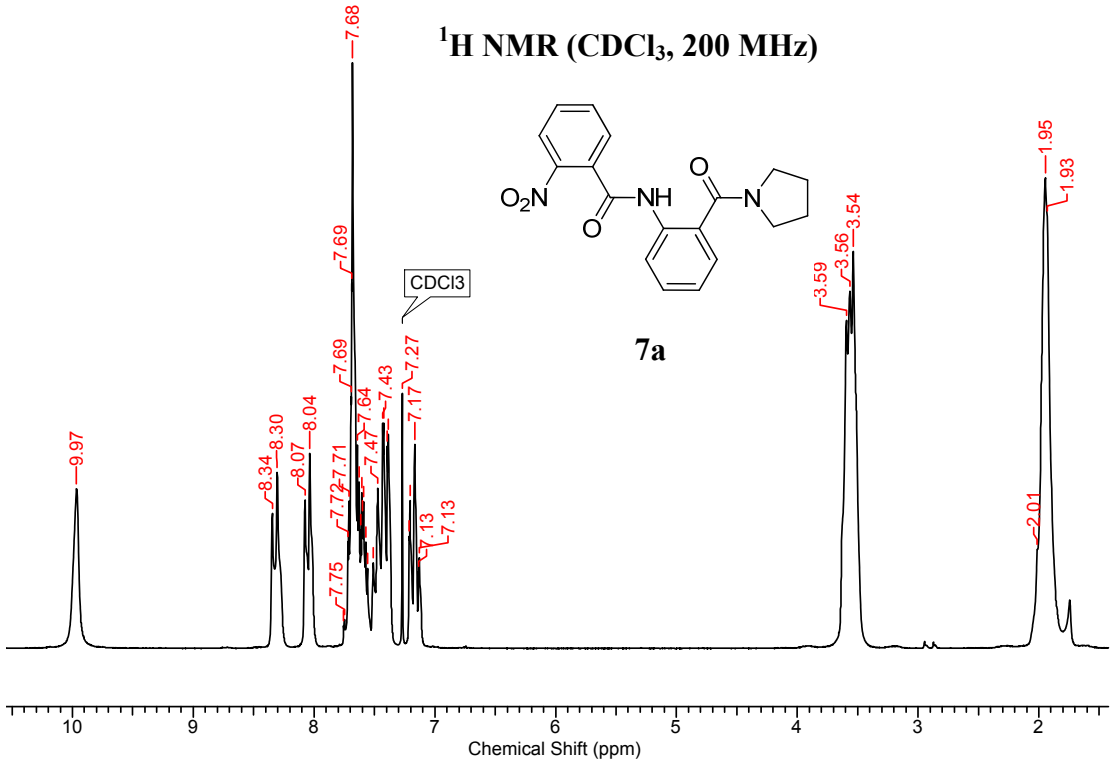

^{1}H NMR (CDCl$_3$, 500 MHz)
Me
NH
O
NH
O
O
N
(L)
H
O
N
H
Br
5b
CHLOROFORM-d
2.18
7.27
7.32
7.34
7.25
7.21
6.95
6.94
10.88
10.06
9.18
8.53
8.52
8.27
8.25
7.68
7.66
7.51
4.82
4.81
4.80
3.67
3.66
3.65
3.64
3.62
3.61
3.60
3.59
2.32
2.31
2.30
2.16
2.15
2.06
11 10 9 8 7 6 5 4 3 2
Chemical Shift (ppm)

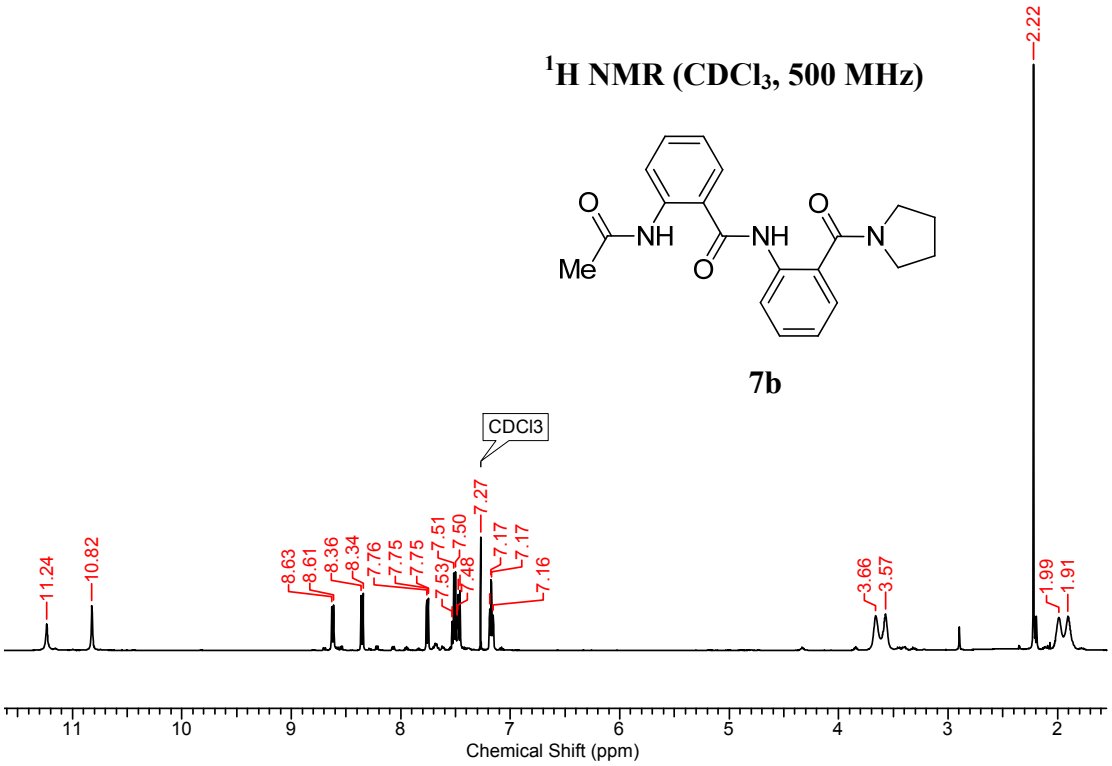

CDCl3
^{1}H NMR (CDCl$_3$, 200 MHz)
OBn
O
H
(D)
O
O$_2$N
NH
O
N
6a
Chemical Shift (ppm)

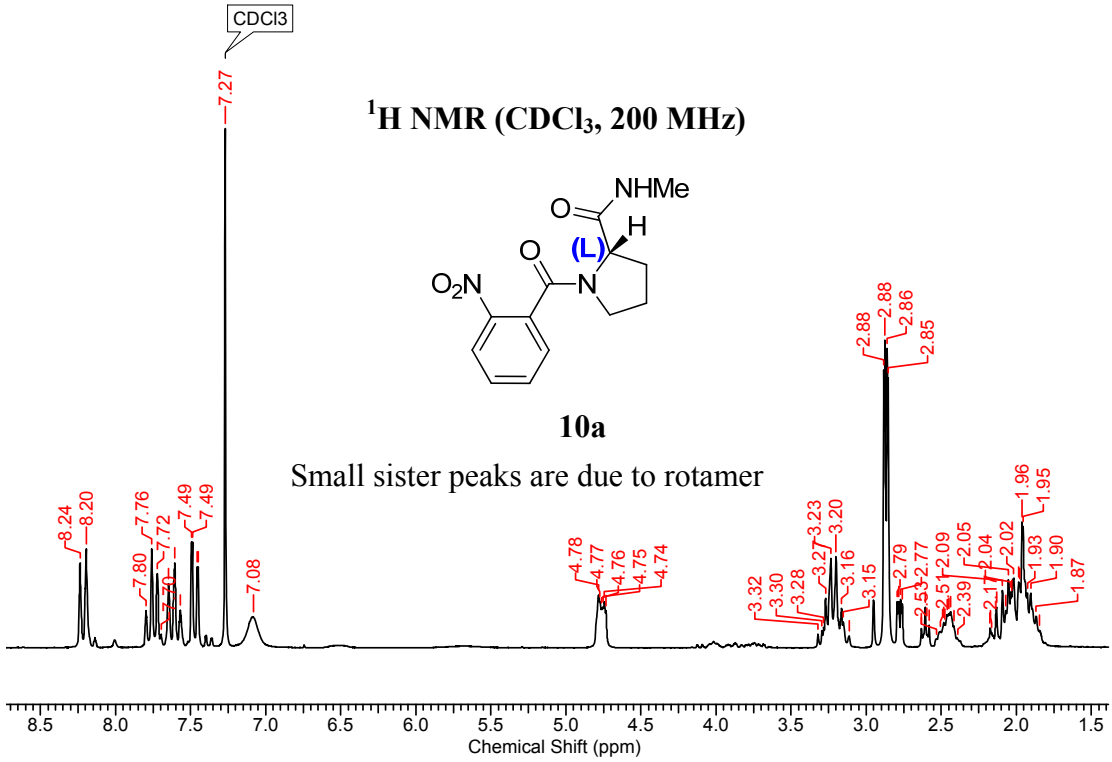

CDCl3
^{1}H NMR (CDCl$_3$, 200 MHz)
NHMe
O
H
(D)
O
O$_2$N
NH
O
N
6b
Chemical Shift (ppm)

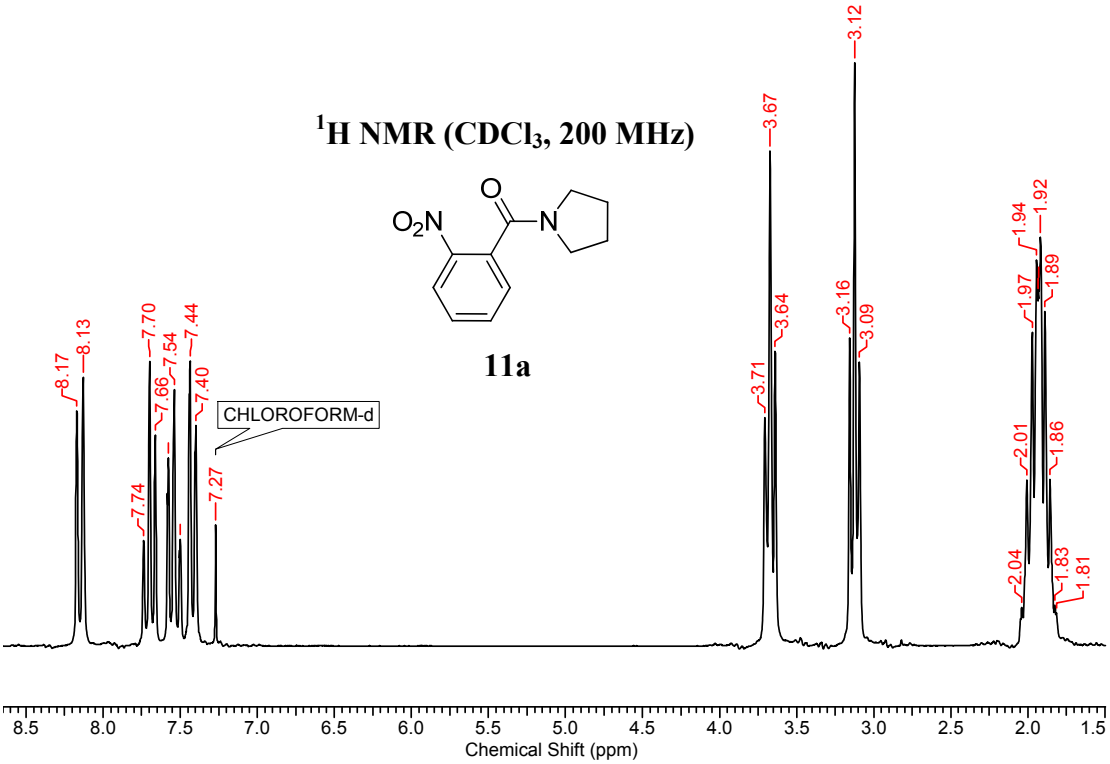


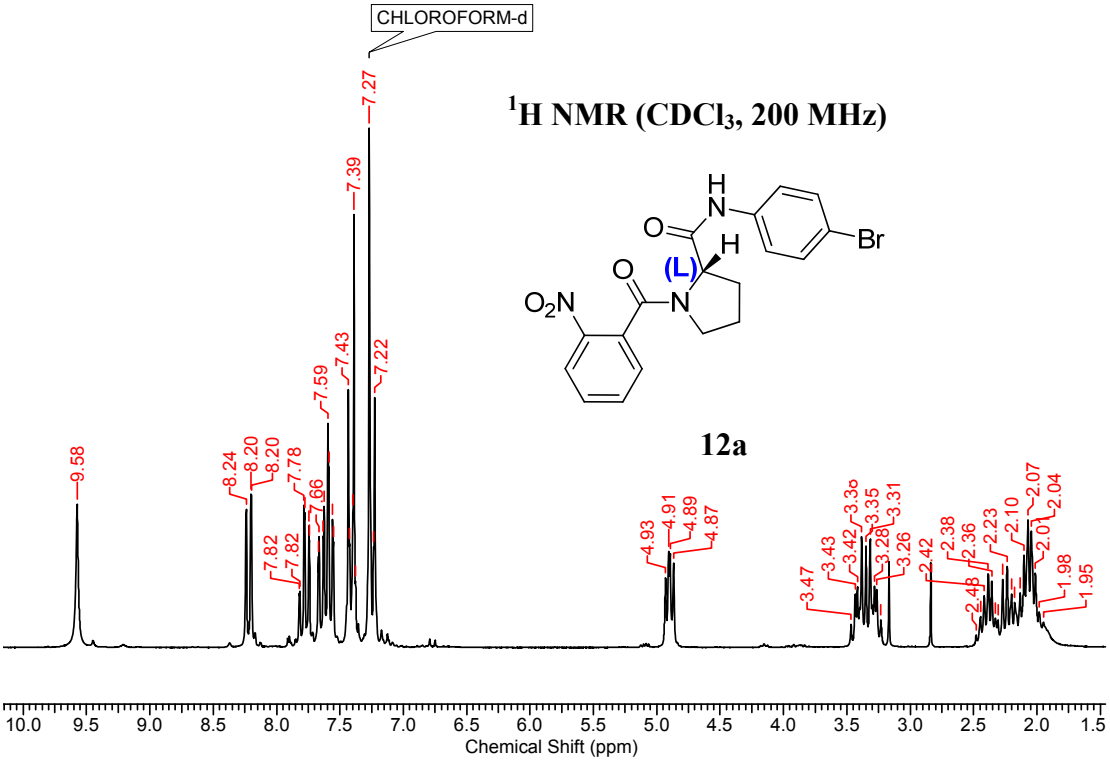
Notes: Small sister peaks are due to rotamer formation in DMSO-d_6. # DMSO-d_6 H_2O

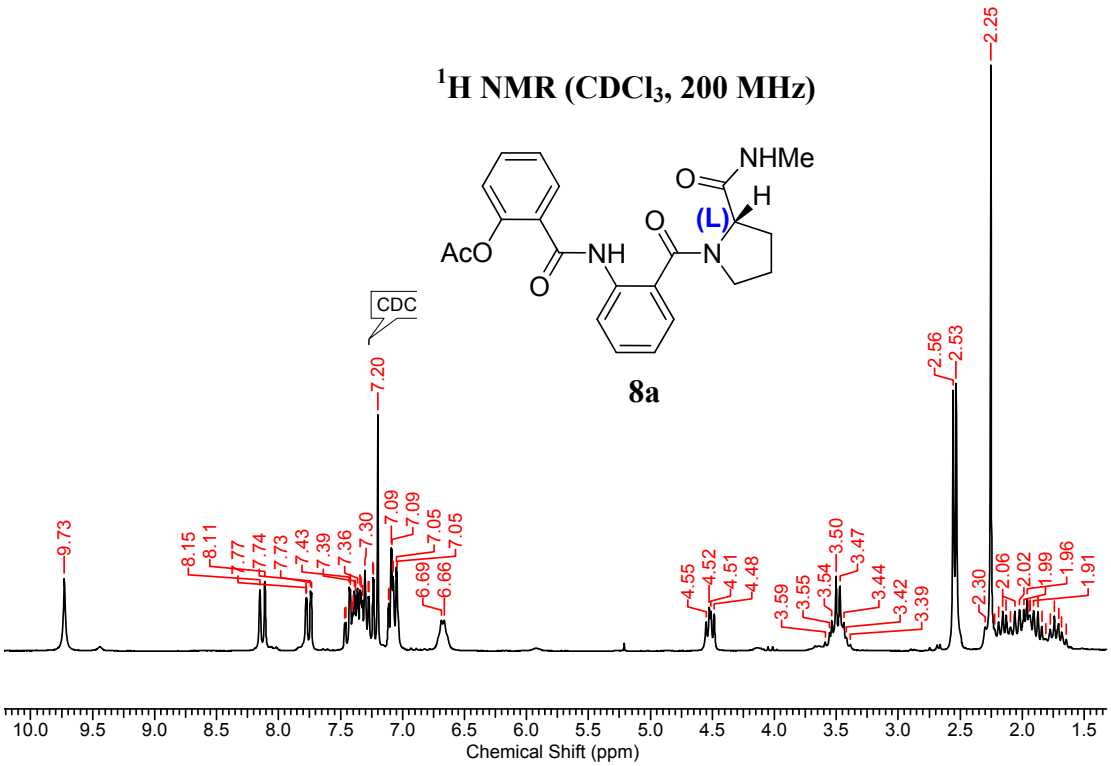


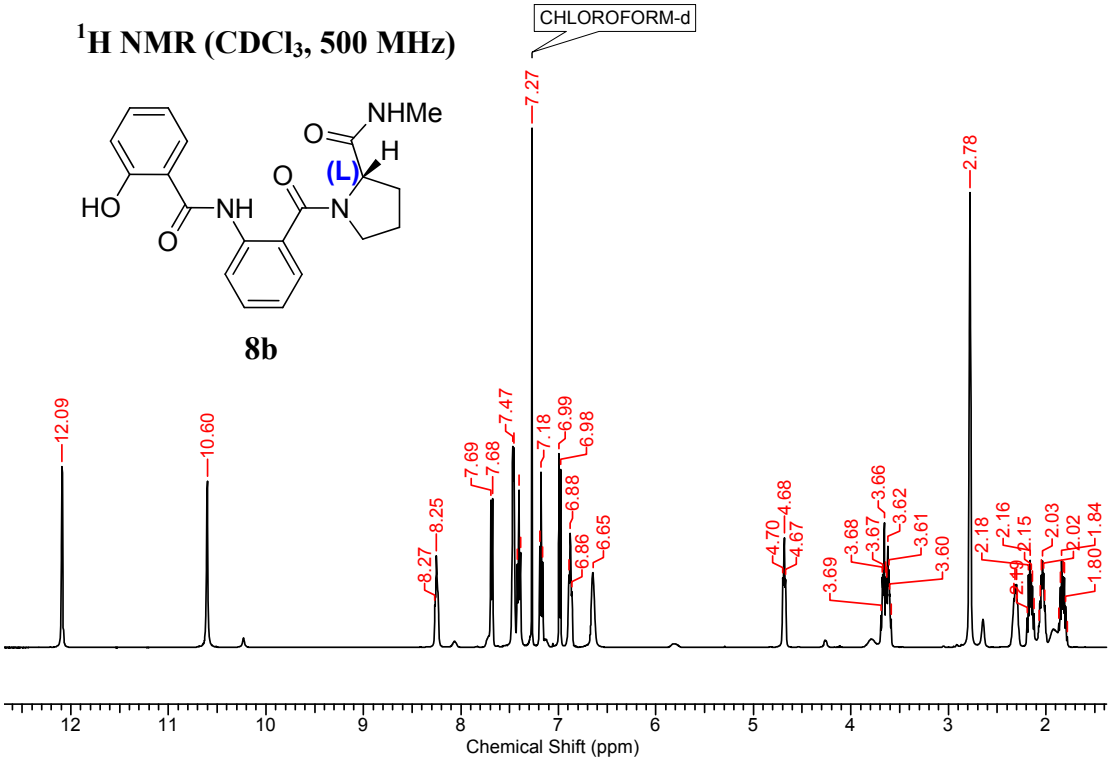

^{1}H NMR ($CDCl_3$, 500 MHz)
Me
NH
NH
N
7b
CDCl3
11.24
10.82
8.63
8.61
8.36
8.34
7.76
7.75
7.75
7.53
7.51
7.50
7.48
7.27
7.17
7.17
7.16
3.66
3.57
2.22
1.99
1.91
Chemical Shift (ppm)


CDCl3
^{1}H NMR ($CDCl_3$, 200 MHz)
NHMe
(L)
O_2N
N
10a
Small sister peaks are due to rotamer
8.24
8.20
7.80
7.76
7.72
7.49
7.49
7.27
7.08
4.78
4.77
4.76
4.75
4.74
3.32
3.30
3.28
3.27
3.23
3.20
3.16
3.15
2.88
2.88
2.86
2.85
2.79
2.77
2.53
2.51
2.09
2.05
2.04
2.02
1.96
1.95
1.93
1.90
1.87
Chemical Shift (ppm)

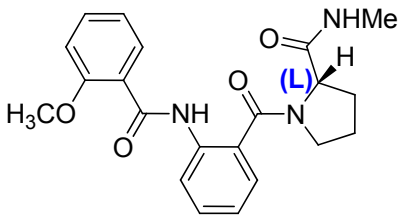

^{1}H NMR (CDCl$_3$, 200 MHz)
11a
CHLOROFORM-d
8.17
8.13
7.74
7.70
7.66
7.54
7.44
7.40
7.27
3.71
3.67
3.64
3.16
3.12
3.09
2.04
2.01
1.97
1.94
1.92
1.89
1.86
1.83
1.81
Chemical Shift (ppm)


CHLOROFORM-d
^{1}H NMR (CDCl$_3$, 200 MHz)
12a
(L)
9.58
8.24
8.20
8.20
7.82
7.82
7.78
7.66
7.59
7.43
7.39
7.27
7.22
4.93
4.91
4.89
4.87
3.47
3.43
3.42
3.35
3.28
3.26
3.31
2.42
2.48
2.38
2.36
2.23
2.10
2.07
2.04
2.01
1.98
1.95
Chemical Shift (ppm)


^{1}H NMR (CDCl$_3$, 200 MHz)
NHMe
O
H
(L)
AcO
NH
N
CDC
8a
Chemical Shift (ppm)


^{1}H NMR (CDCl$_3$, 500 MHz)
CHLOROFORM-d
NHMe
O
H
(L)
HO
NH
N
8b
Chemical Shift (ppm)

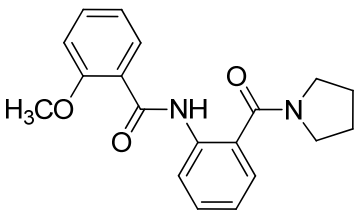
^{1}H NMR ($CDCl_3$, 500 MHz)



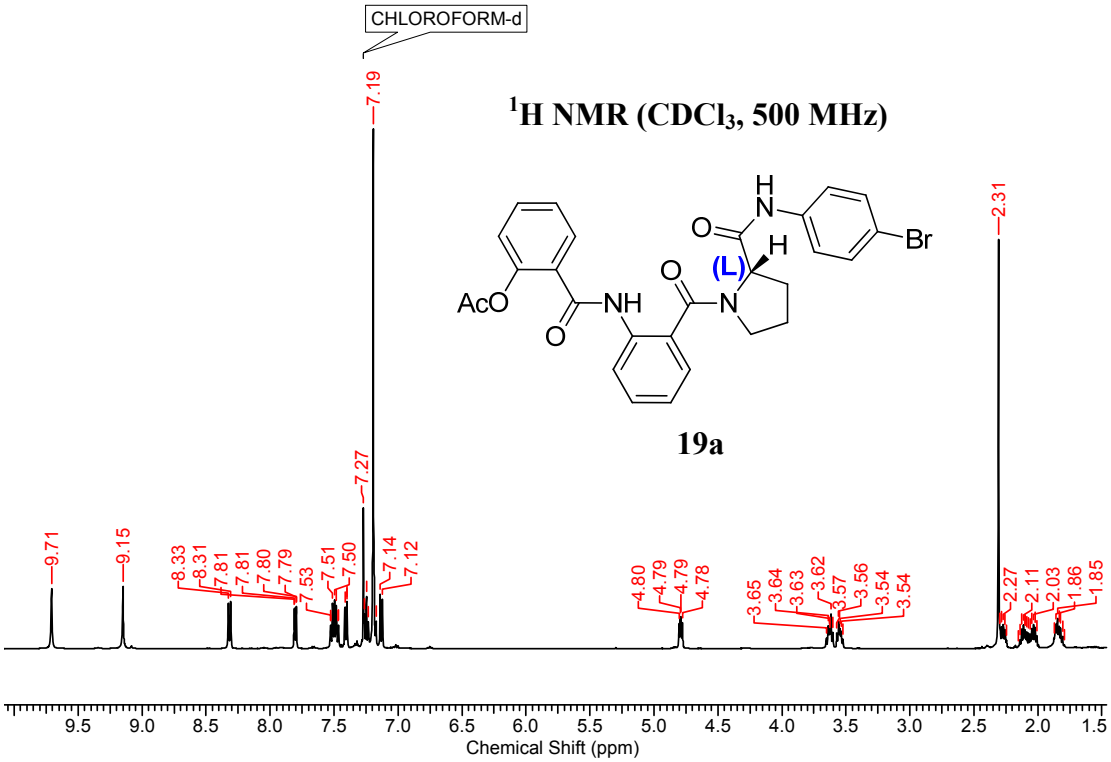
8c

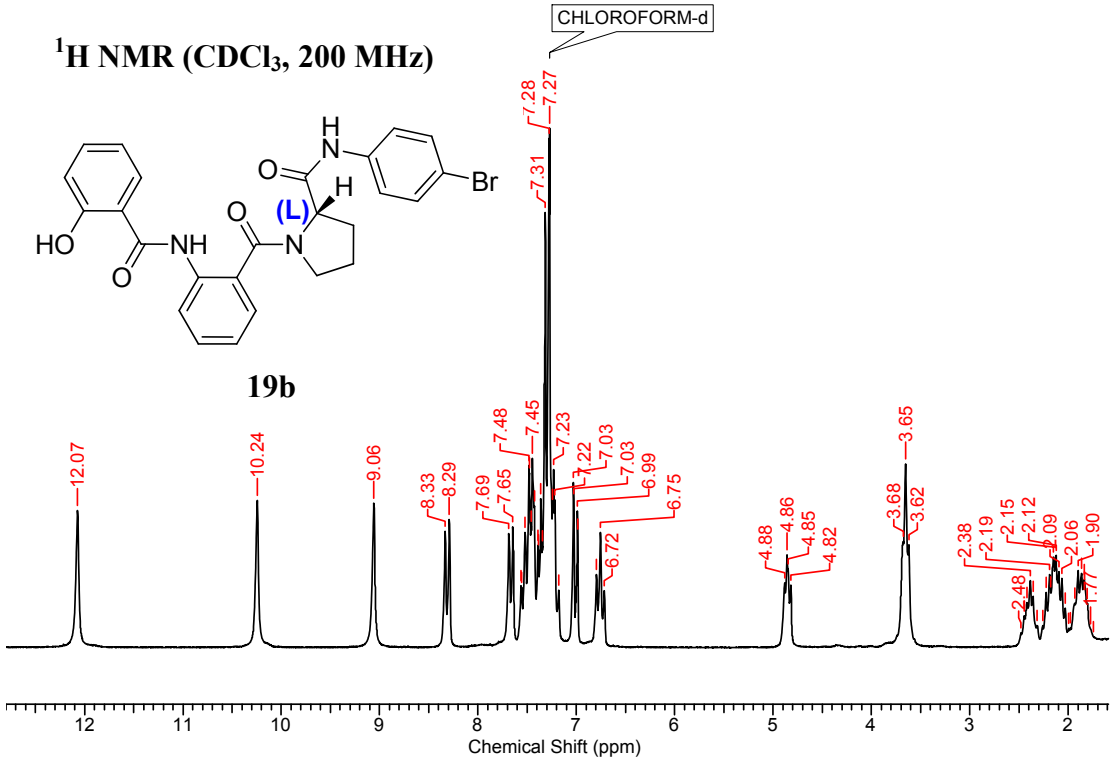
Note: Small sister peaks are due to existence of another conformer (~10%)

^{1}H NMR ($CDCl_3$, 200 MHz)



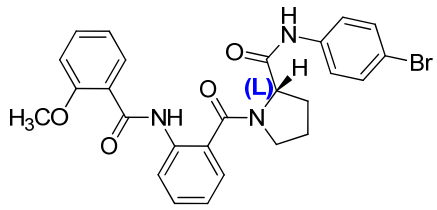
18


CHLOROFORM-d
^{1}H NMR (CDCl$_3$, 500 MHz)
19a
Chemical Shift (ppm)


CHLOROFORM-d
^{1}H NMR (CDCl$_3$, 200 MHz)
19b
Chemical Shift (ppm)

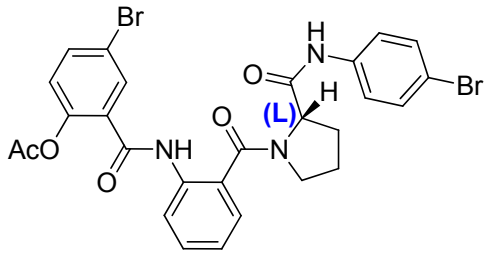
^{1}H NMR ($CDCl_3$, 400 MHz)

Note: Small sister peaks are due to existence of another conformer (~10%)

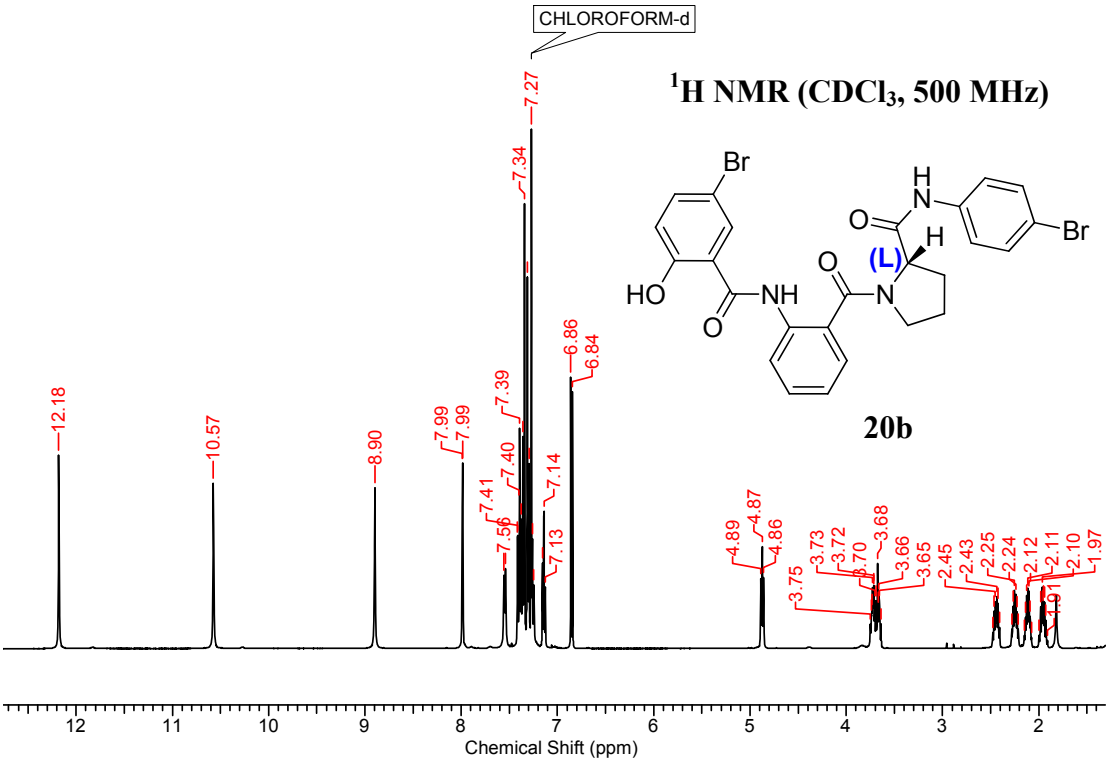


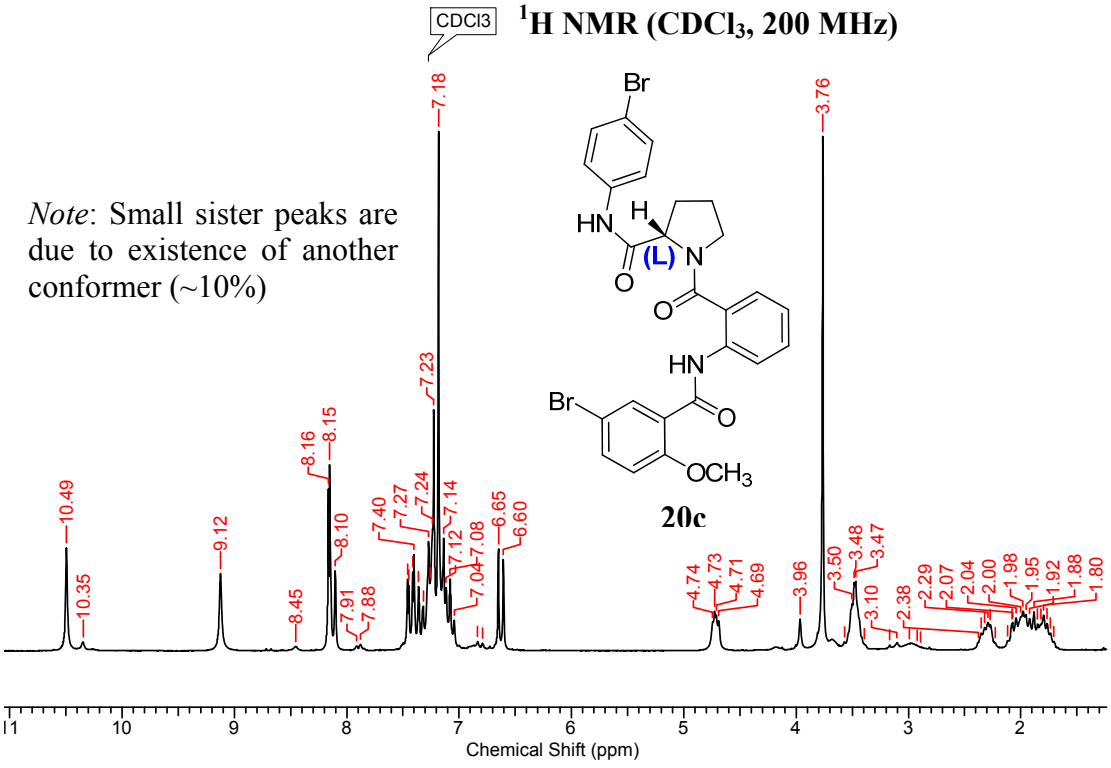
19c

^{1}H NMR ($CDCl_3$, 200 MHz)



20a

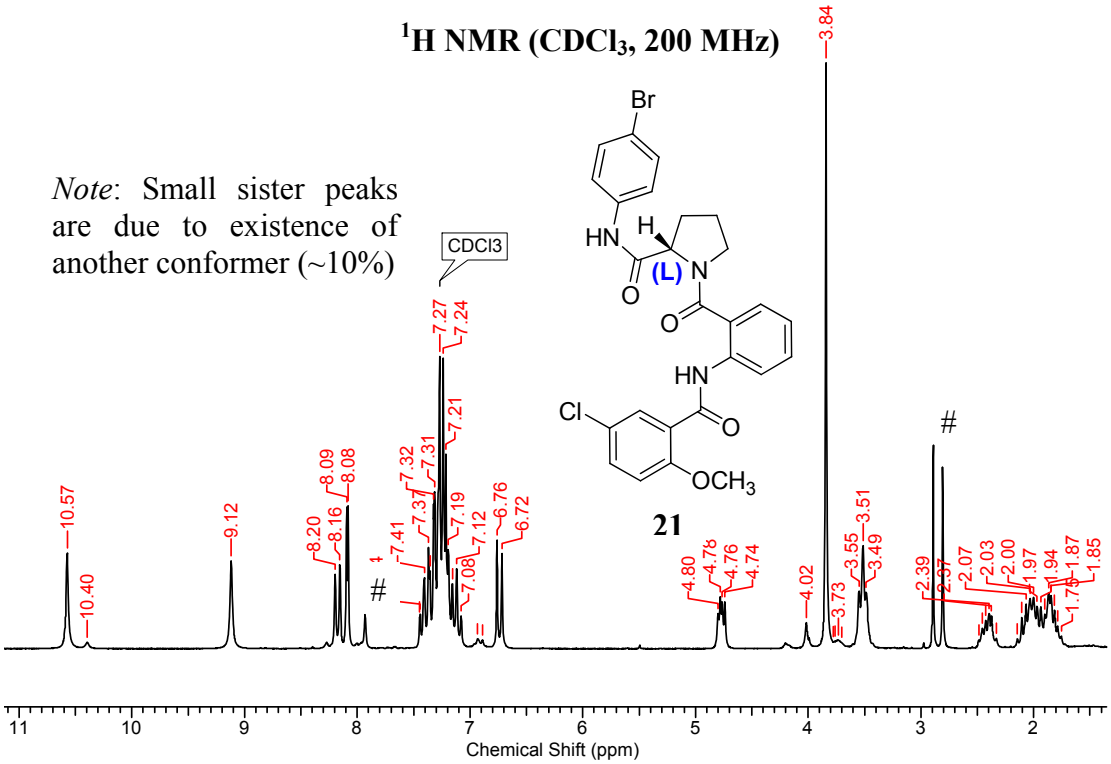




Note: Small sister peaks are due to existence of another conformer (~10%)

^{1}H NMR ($CDCl_3$, 200 MHz)

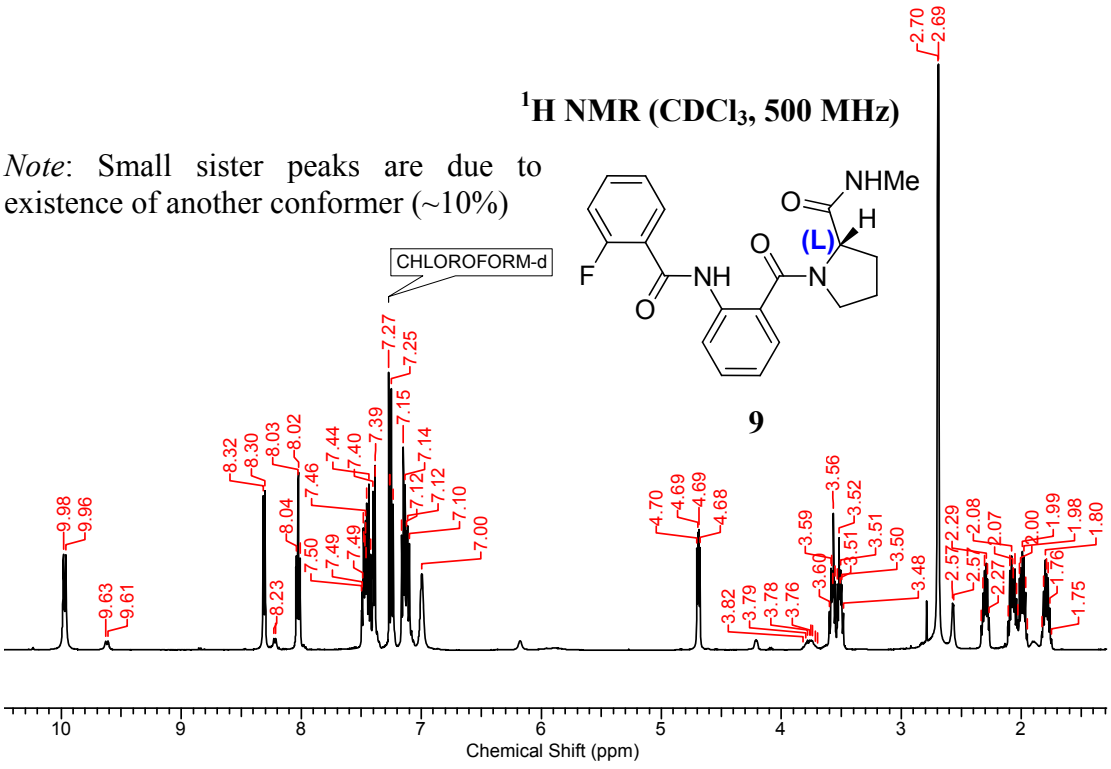
Note: Small sister peaks are due to existence of another conformer (~10%)

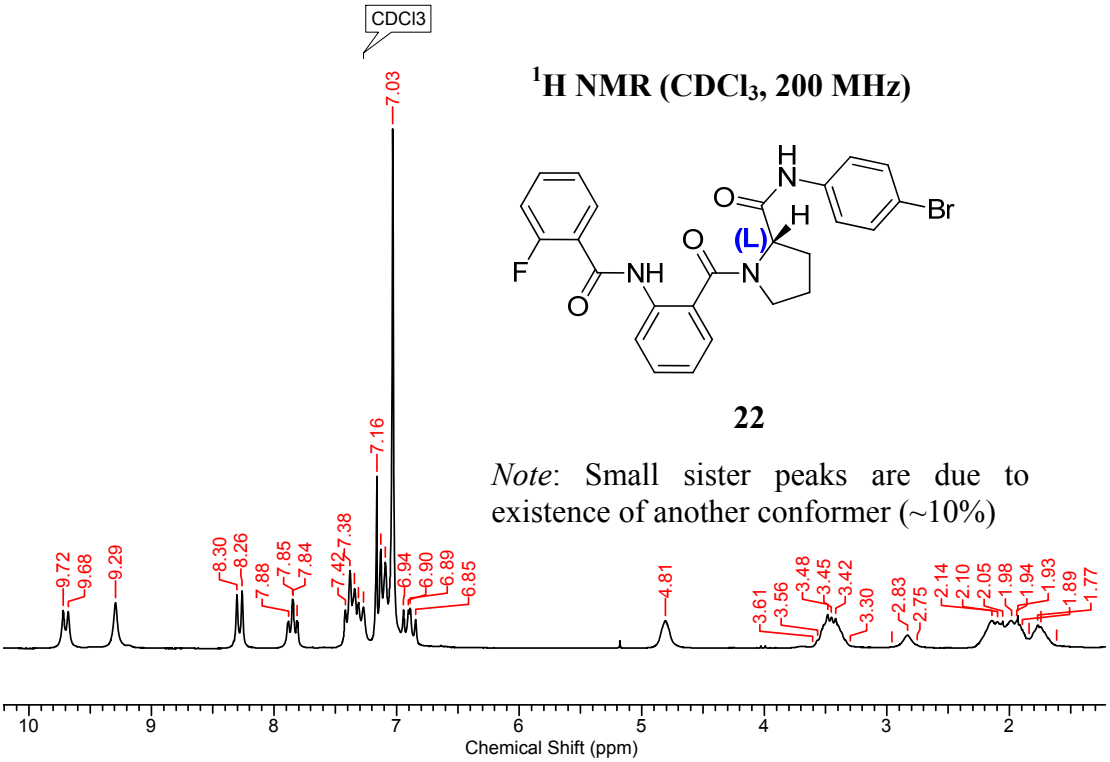


 # DMF

^{1}H NMR ($CDCl_3$, 500 MHz)

Note: Small sister peaks are due to existence of another conformer (~10%)

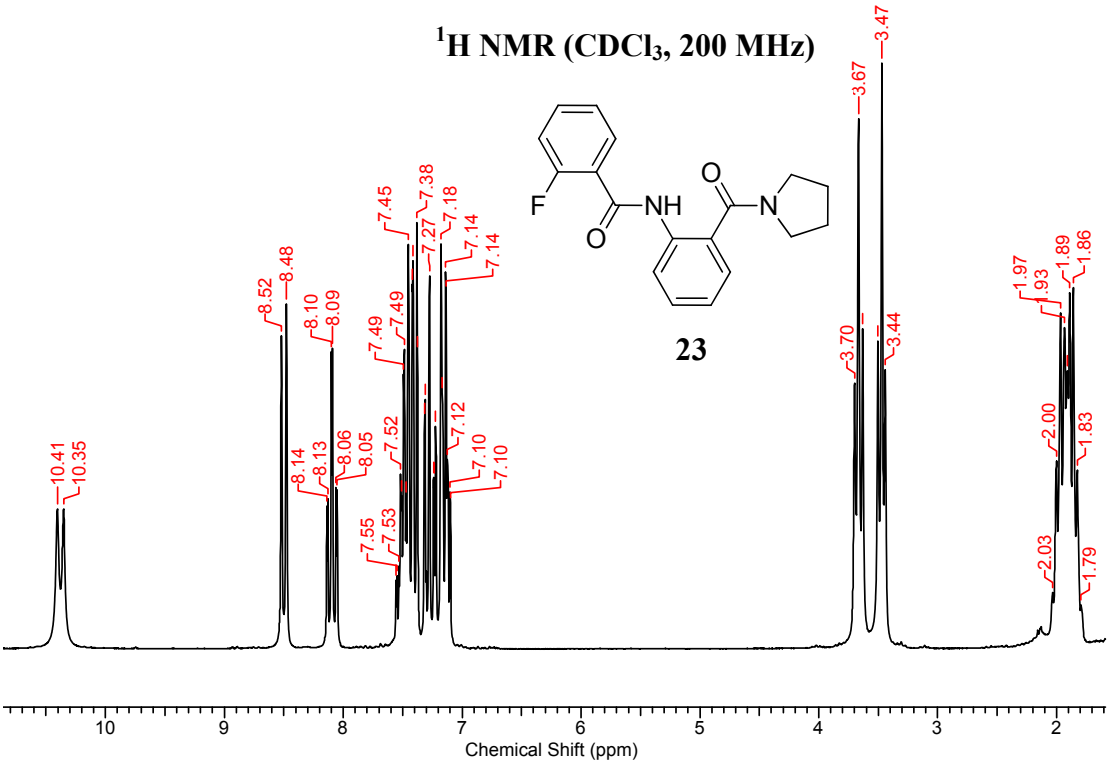




^{1}H NMR ($CDCl_3$, 200 MHz)

22

Note: Small sister peaks are due to existence of another conformer (~10%)

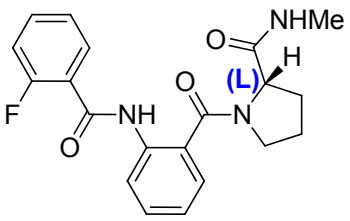


^{1}H NMR ($CDCl_3$, 200 MHz)

23

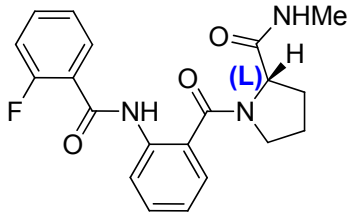
^{19}F decoupled ^{1}H NMR ($CDCl_3$, 400 MHz)

Note: Small sister peaks are due to existence of another conformer (~10%)



4

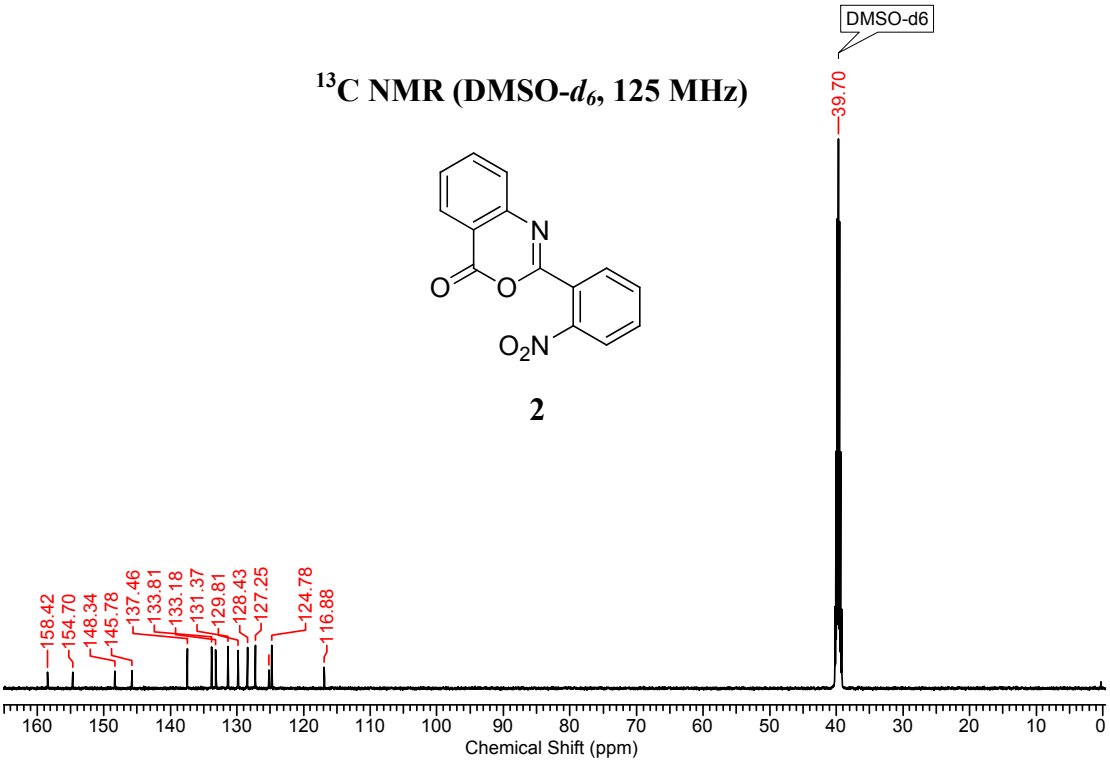
^{19}F NMR ($CDCl_3$, 400 MHz)



4

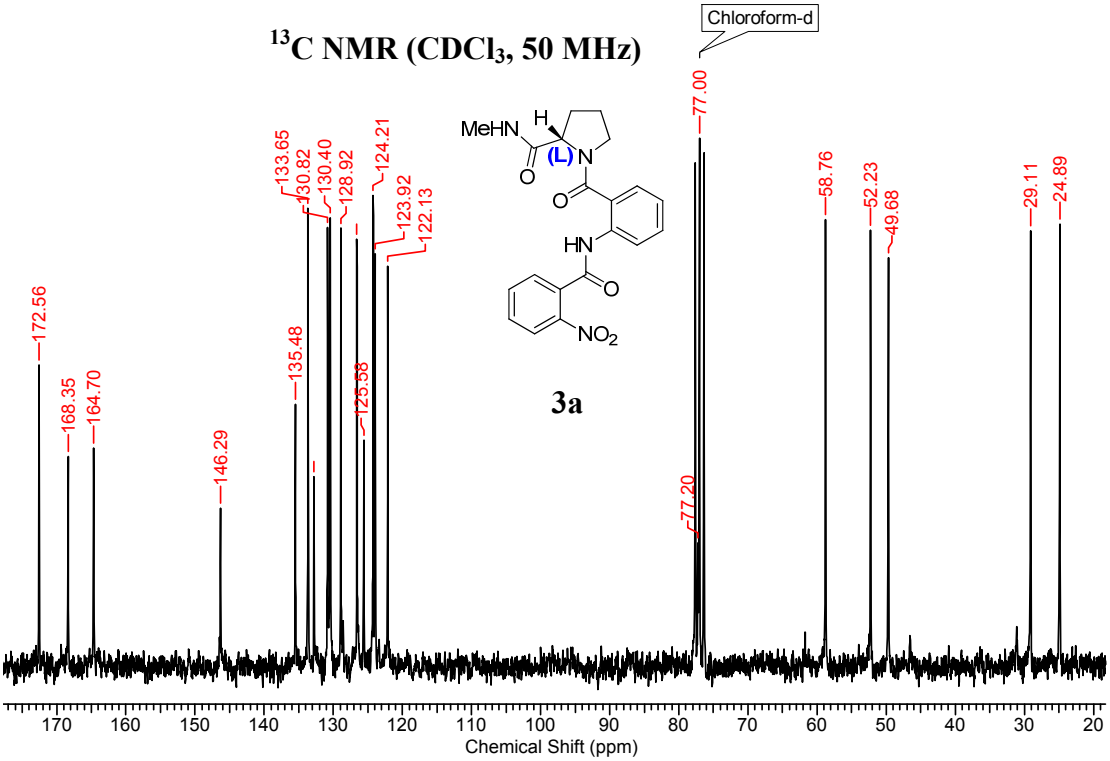
Note: Small sister peak are due to existence of another conformer (~10%)

^{13}C NMR (DMSO-d_6, 125 MHz)



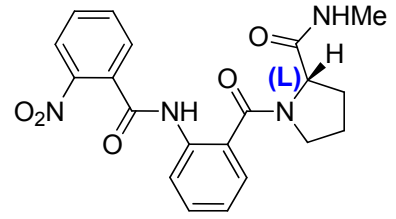
2

^{13}C NMR ($CDCl_3$, 50 MHz)



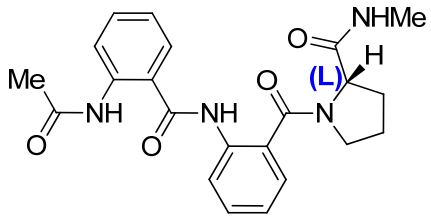
3a

^{13}C NMR ($CDCl_3$, 125 MHz)



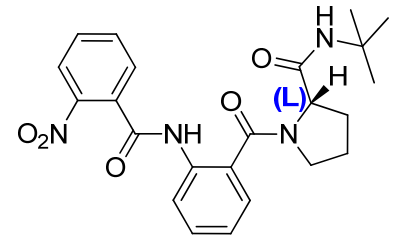
3b

^{13}C NMR ($CDCl_3$, 125 MHz)



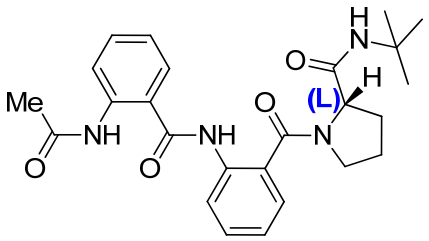
3c

^{13}C NMR ($CDCl_3$, 125 MHz)



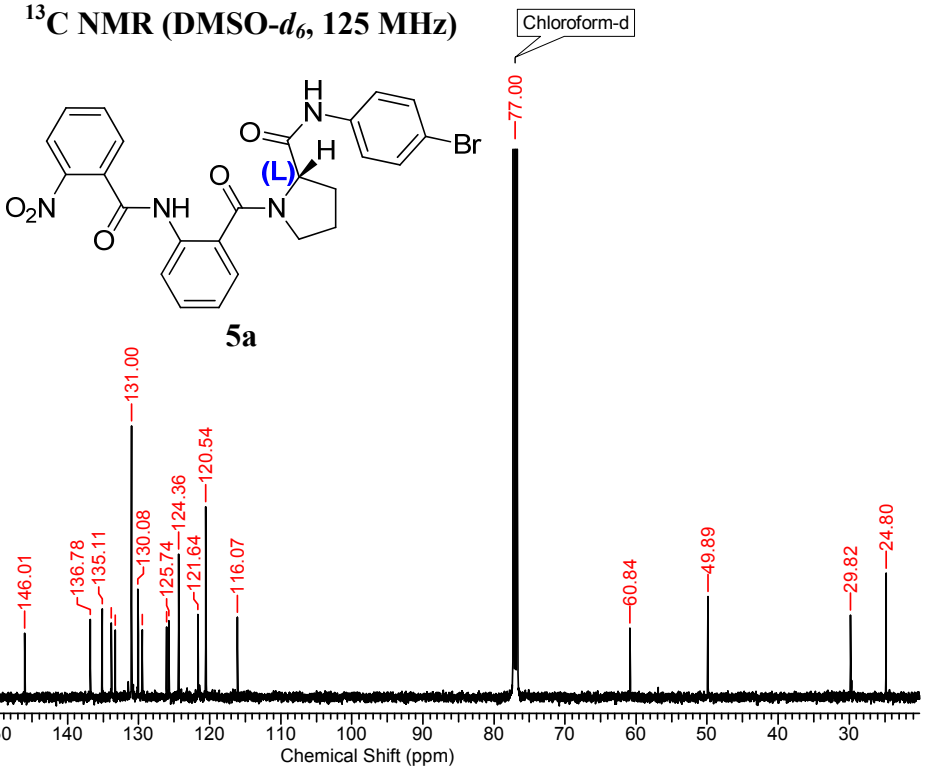
4a

^{13}C NMR ($CDCl_3$, 50 MHz)



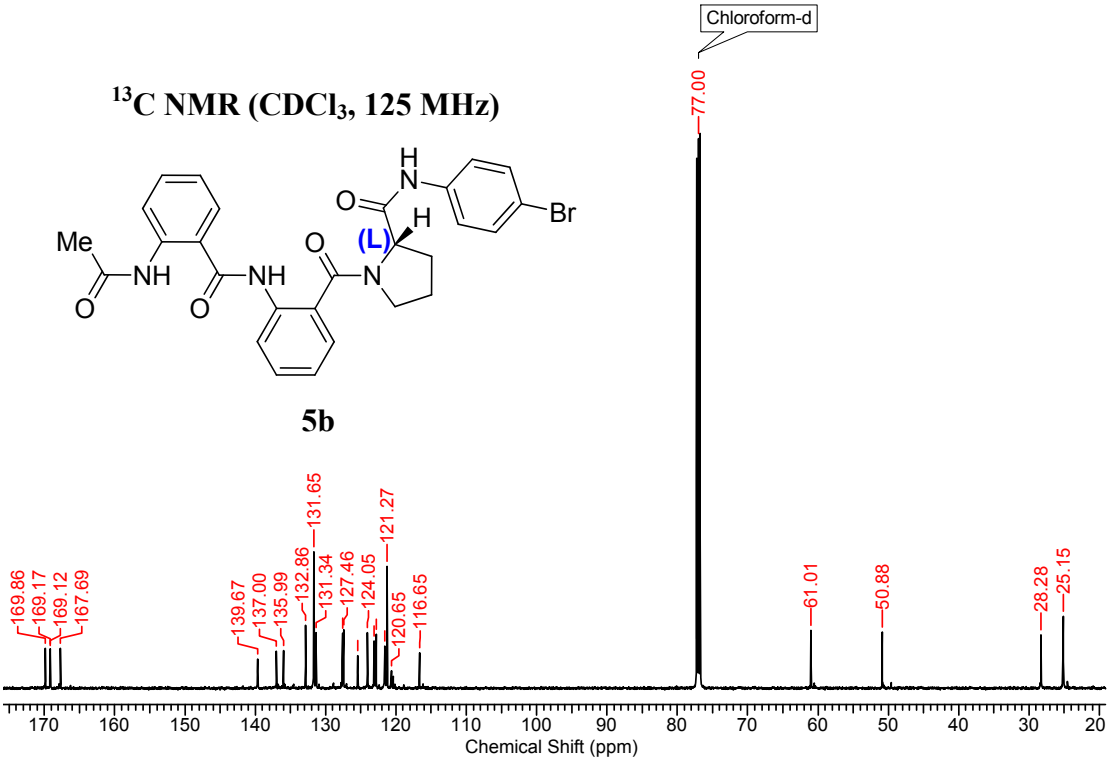
4b

^{13}C NMR (DMSO-d_6, 125 MHz)

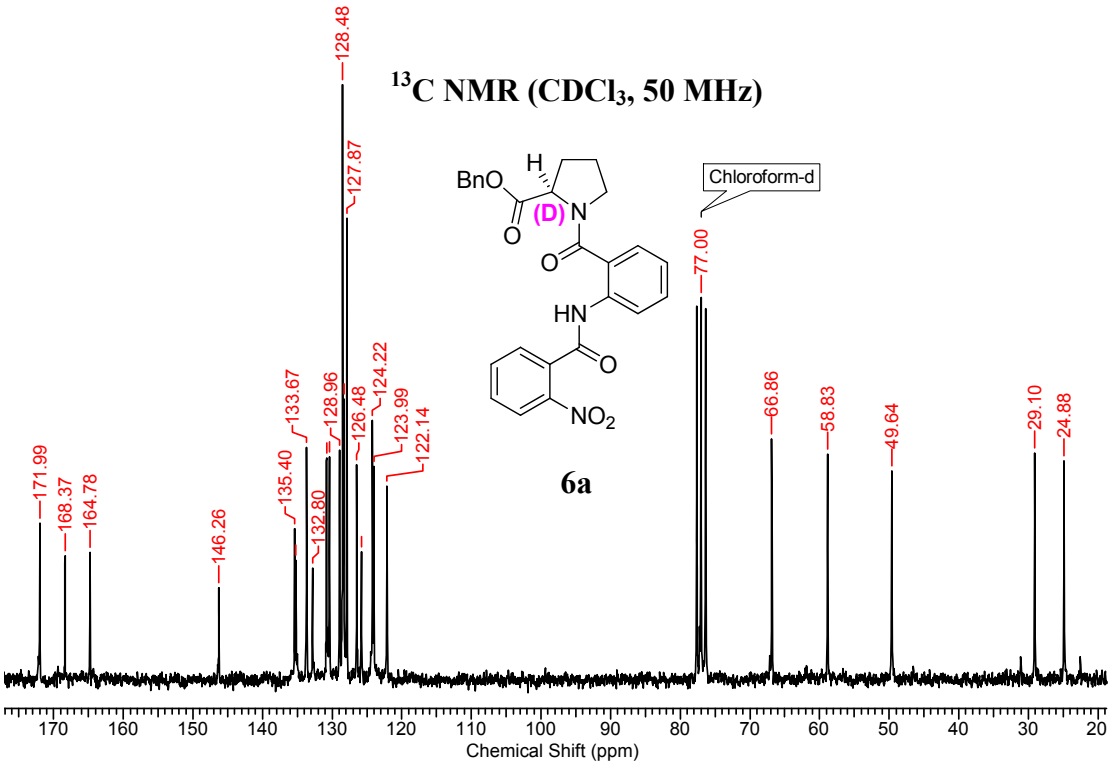


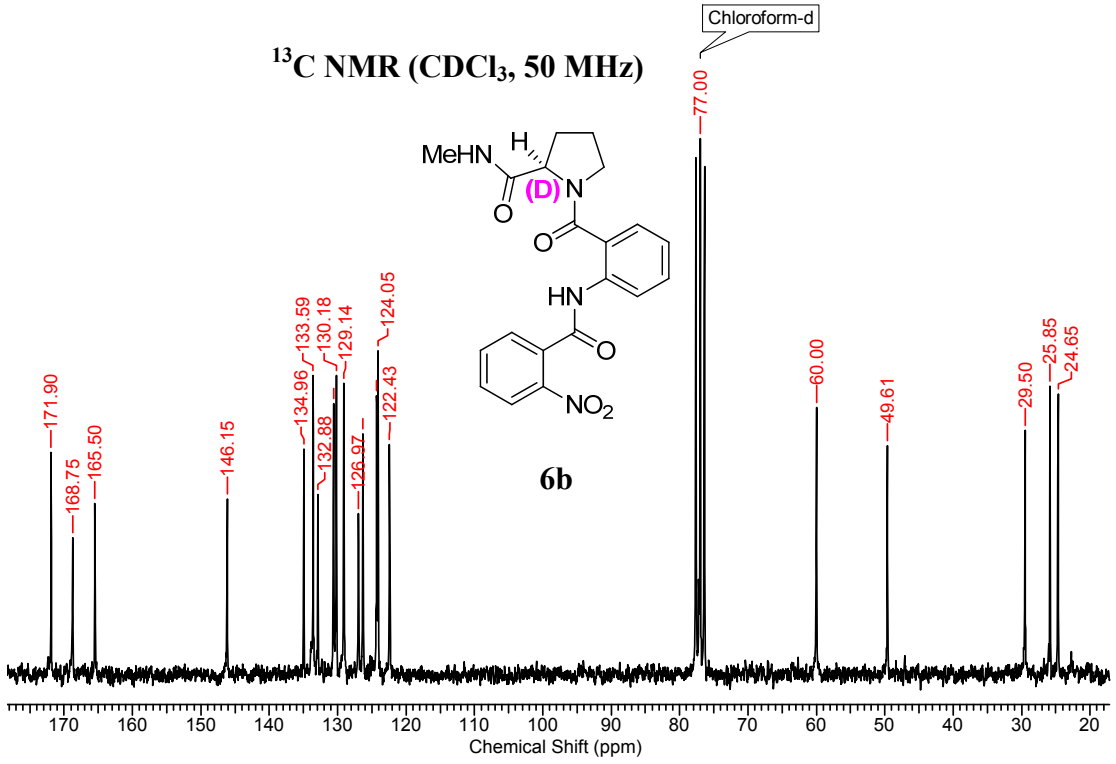
5a

^{13}C NMR ($CDCl_3$, 125 MHz)

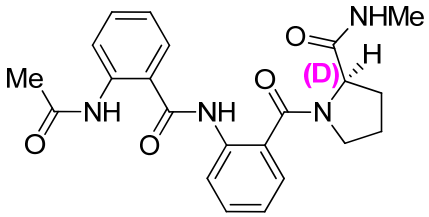


5b


^{13}C NMR ($CDCl_3$, 50 MHz)
BnO
H
(D)
N
O
O
HN
O
NO_2
6a
Chloroform-d
171.99
168.37
164.78
146.26
135.40
133.67
132.80
128.96
128.48
127.87
126.48
124.22
123.99
122.14
77.00
66.86
58.83
49.64
29.10
24.88
Chemical Shift (ppm)


^{13}C NMR ($CDCl_3$, 50 MHz)
MeHN
H
(D)
N
O
O
HN
O
NO_2
6b
Chloroform-d
171.90
168.75
165.50
146.15
134.96
133.59
132.88
130.18
129.14
126.97
124.05
122.43
77.00
60.00
49.61
29.50
25.85
24.65
Chemical Shift (ppm)

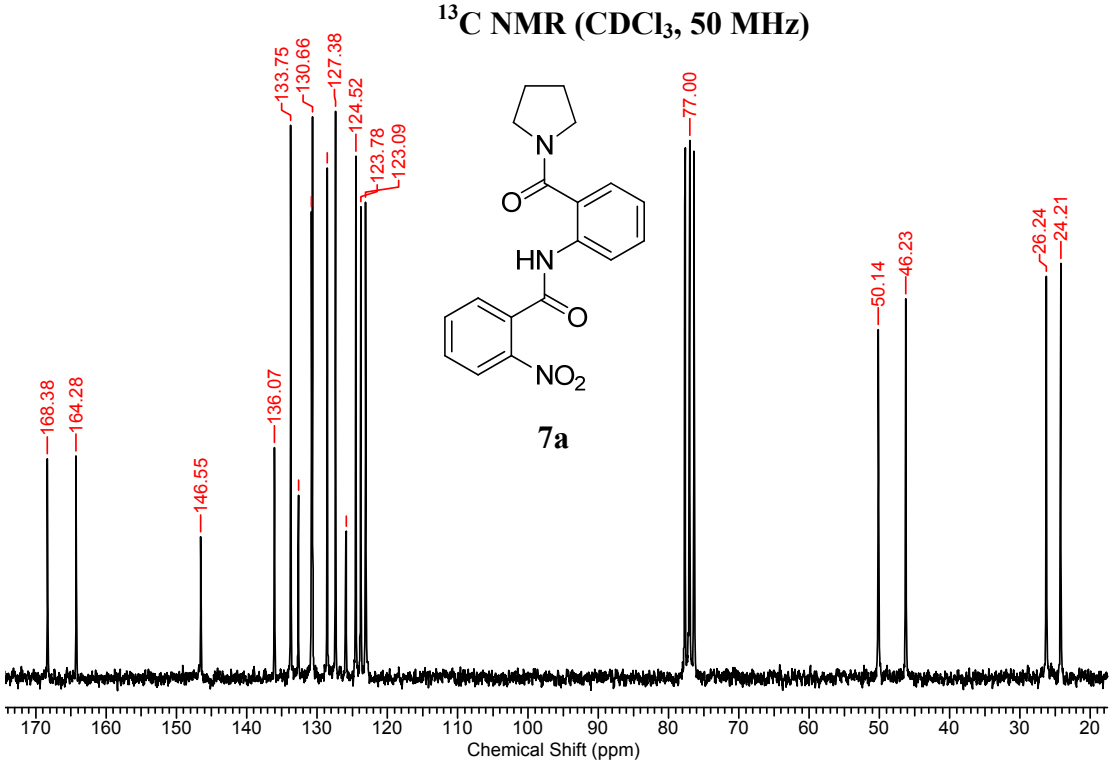
^{13}C NMR (DMSO-d_6, 125 MHz)



6c

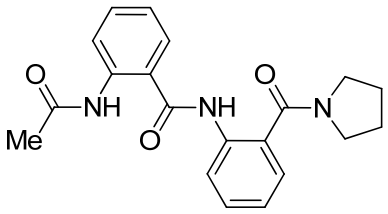
***Note*: The small sister peaks are due to rotamer formation in DMSO-d_6**

^{13}C NMR ($CDCl_3$, 50 MHz)



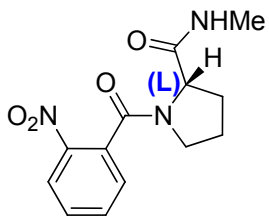
7a

^{13}C NMR ($CDCl_3$, 125 MHz)



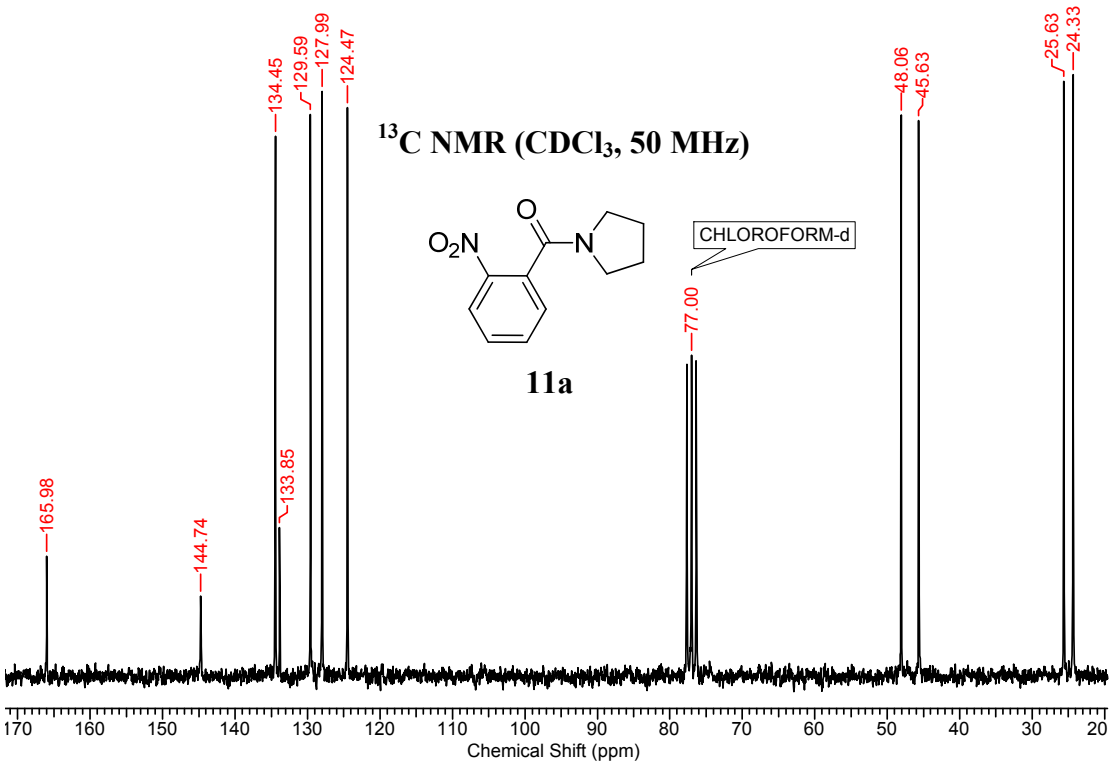
7b

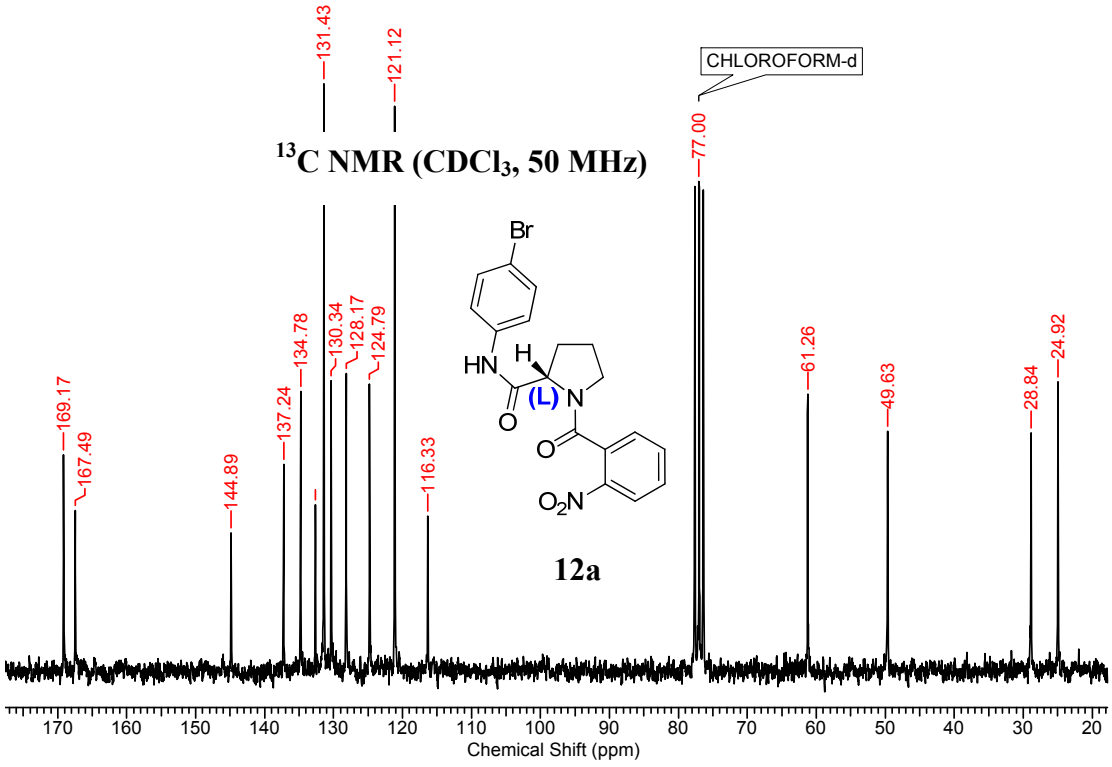
^{13}C NMR ($CDCl_3$, 200 MHz)



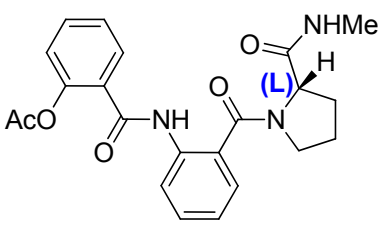
10a

Small sister peaks are due to rotamer


^{13}C NMR ($CDCl_3$, 50 MHz)
11a
CHLOROFORM-d
165.98
144.74
134.45
133.85
129.59
127.99
124.47
77.00
48.06
45.63
25.63
24.33
Chemical Shift (ppm)

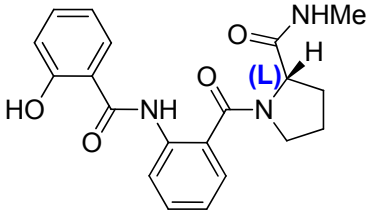

^{13}C NMR ($CDCl_3$, 50 MHz)
12a
CHLOROFORM-d
169.17
167.49
144.89
137.24
134.78
131.43
130.34
128.17
124.79
121.12
116.33
77.00
61.26
49.63
28.84
24.92
Chemical Shift (ppm)

^{13}C NMR ($CDCl_3$, 200 MHz)



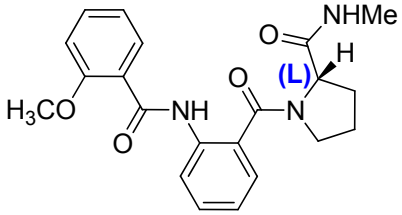
8a

^{13}C NMR ($CDCl_3$, 125 MHz)



8b

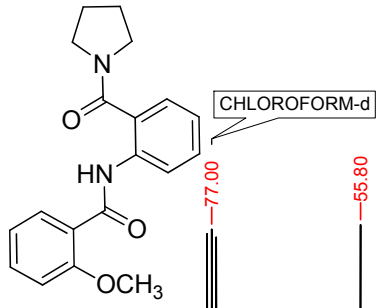
^{13}C NMR ($CDCl_3$, 125 MHz)



8c

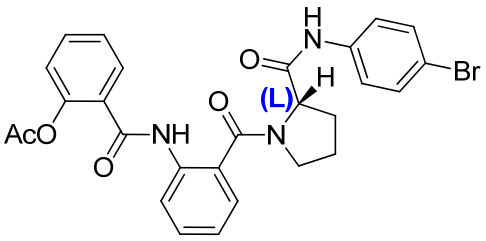
Note: Small sister peaks are due to existence of another conformer (~10%)

^{13}C NMR ($CDCl_3$, 50 MHz)



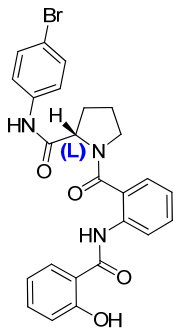
18

^{13}C NMR ($CDCl_3$, 125 MHz)

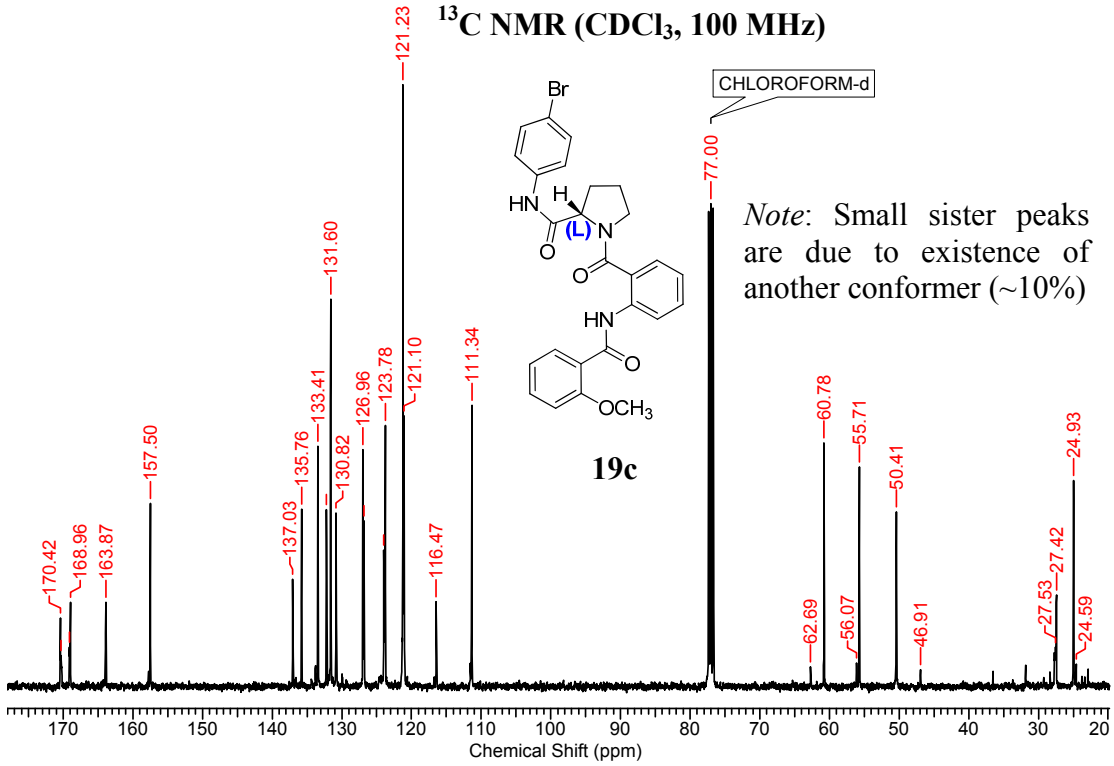


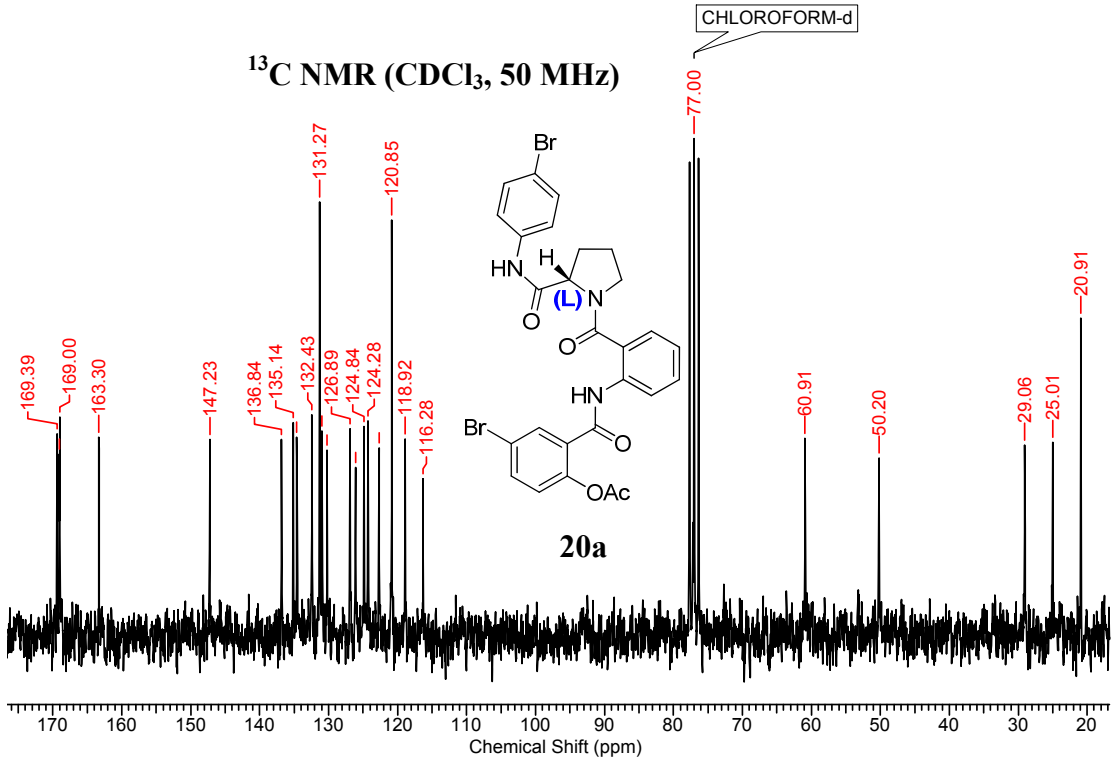
19a

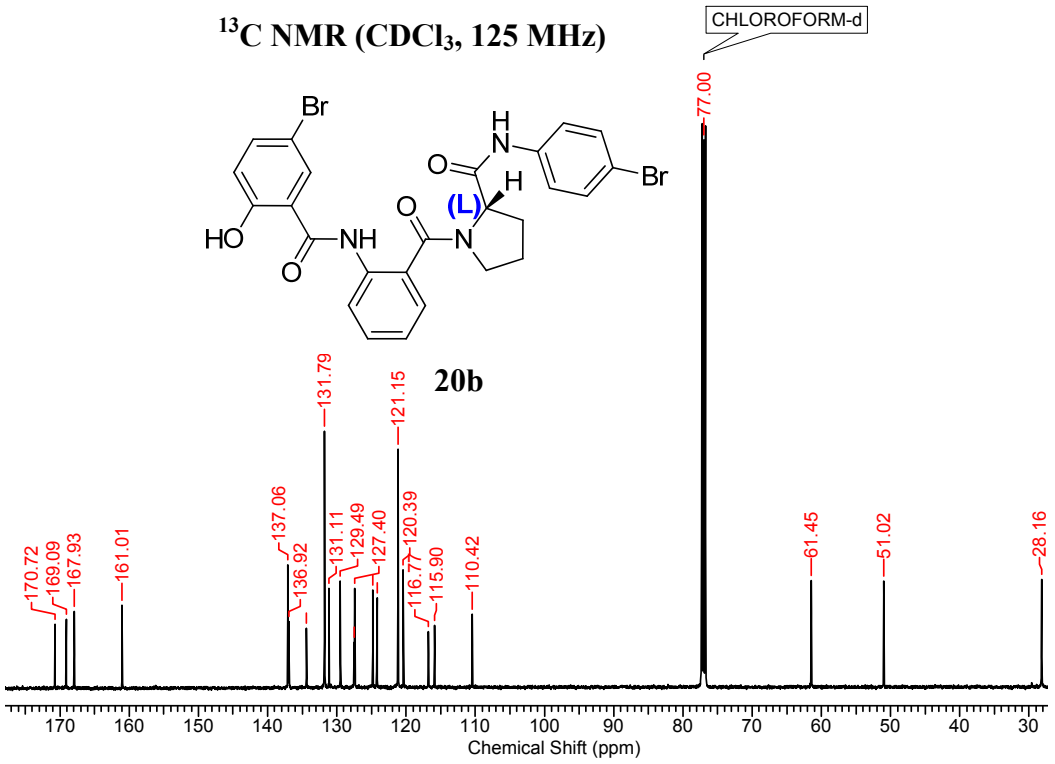
^{13}C NMR ($CDCl_3$, 50 MHz)

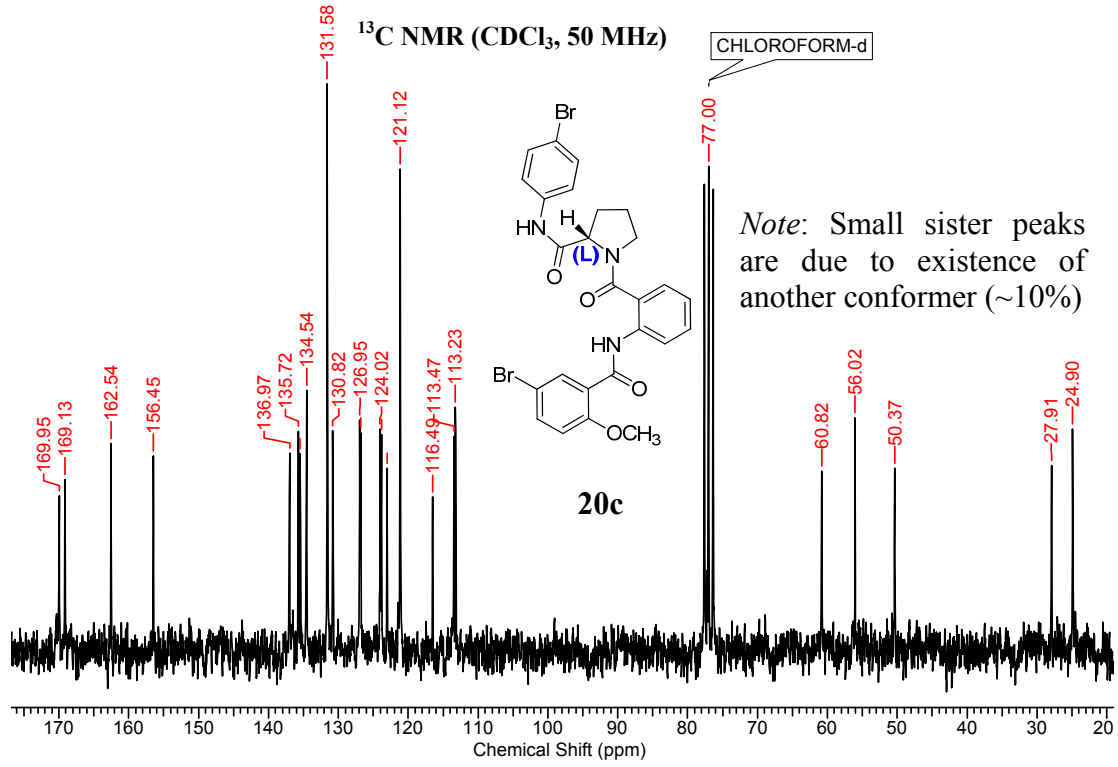


19b


^{13}C NMR ($CDCl_3$, 100 MHz)
CHLOROFORM-d
Br
HN
H
(L)
N
O
HN
O
OCH_3
19c
Note: Small sister peaks are due to existence of another conformer (~10%)
170.42
168.96
163.87
157.50
137.03
135.76
133.41
131.60
130.82
126.96
123.78
121.23
121.10
116.47
111.34
77.00
62.69
60.78
56.07
55.71
50.41
46.91
27.53
27.42
24.93
24.59
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)

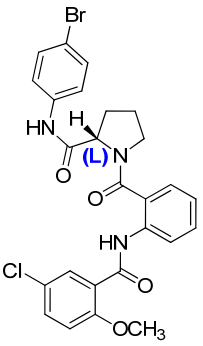

^{13}C NMR ($CDCl_3$, 50 MHz)
CHLOROFORM-d
Br
HN
H
(L)
N
O
HN
O
Br
OAc
20a
169.39
169.00
163.30
147.23
136.84
135.14
132.43
131.27
126.89
124.84
124.28
120.85
118.92
116.28
77.00
60.91
50.20
29.06
25.01
20.91
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)





Note: Small sister peaks are due to existence of another conformer (~10%)

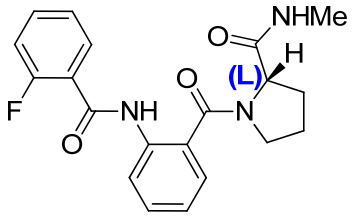
^{13}C NMR ($CDCl_3$, 50 MHz)



21

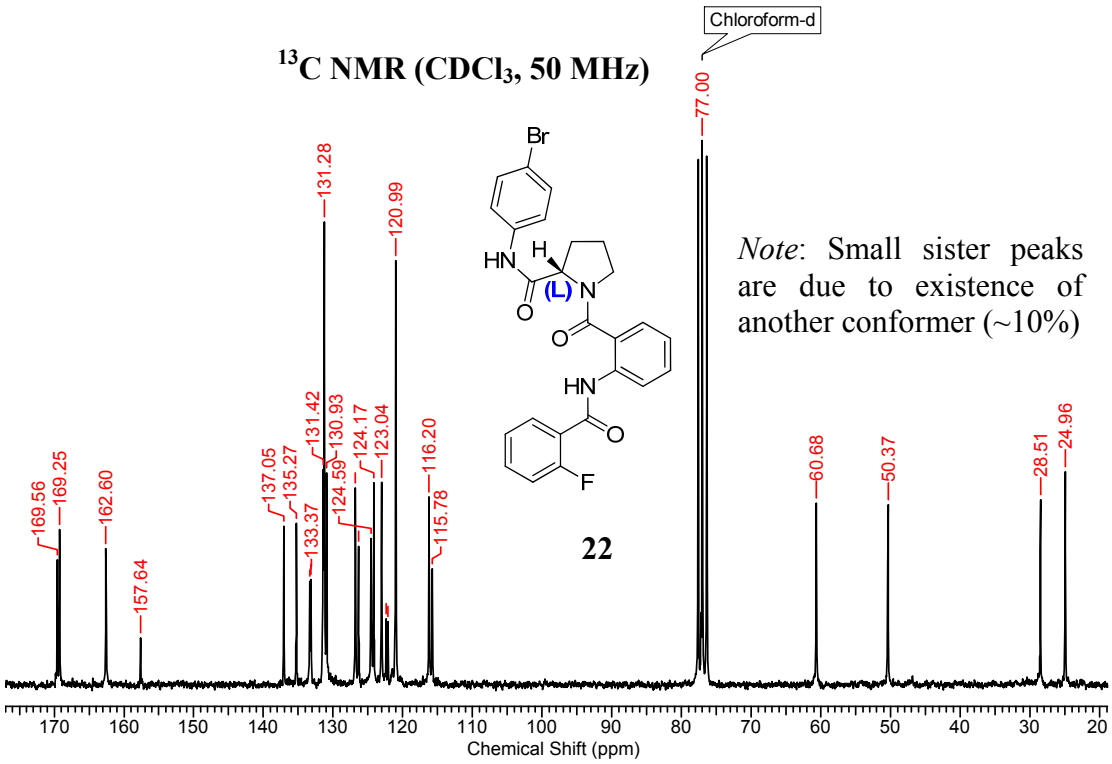
Note: Small sister peaks are due to existence of another conformer (~10%)

^{13}C NMR ($CDCl_3$, 125 MHz)



9

Note: Small sister peaks are due to existence of another conformer (~10%)



Note: Small sister peaks are due to existence of another conformer (~10%)

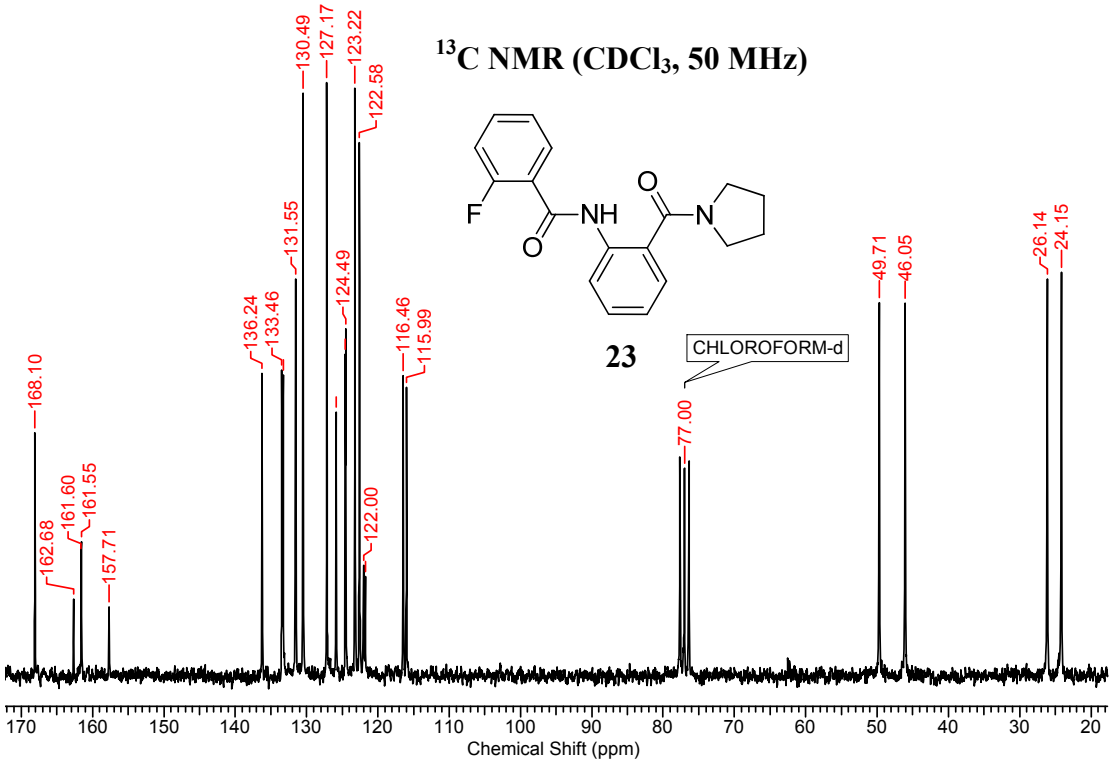
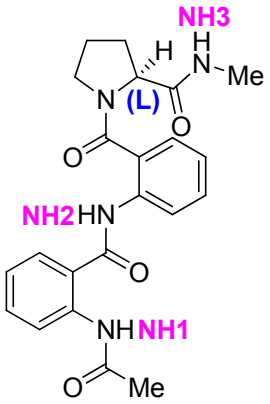


Table 1.1. Titration study of tripeptide 3c in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

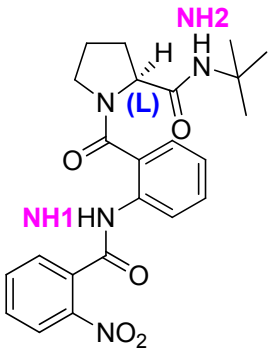
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	11.02	10.34	6.49
5	10.97	10.36	6.60
10	10.90	10.37	6.72
15	10.85	10.37	6.81
20	10.82	10.37	6.86
25	10.77	10.37	6.92
30	10.73	10.37	6.97
35	10.73	10.37	6.97
40	10.70	10.36	7.01
45	10.66	10.35	7.03
50	10.63	10.34	7.06



3c

Table 1.2. Titration study of tripeptide 4a in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

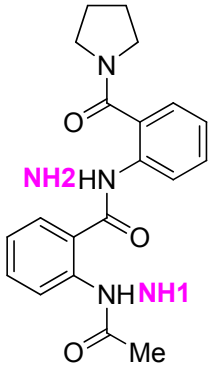
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	9.93	5.61
5	9.96	5.72
10	9.98	5.78
15	10.01	5.89
20	10.04	5.97
25	10.06	6.04
30	10.07	6.12
35	10.09	6.19
40	10.10	6.25
45	10.11	6.30
50	10.12	6.35



4a

Table 1.3. Titration study of tripeptide 7b in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

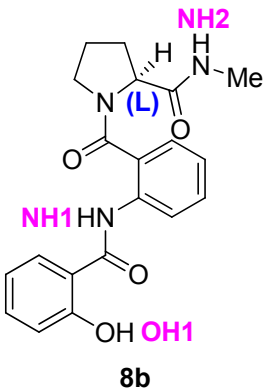
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	11.24	10.86
5	11.22	10.84
10	11.20	10.83
15	11.17	10.81
20	11.15	10.79
25	11.13	10.78
30	11.10	10.76
35	11.08	10.74
40	11.05	10.72
45	11.02	10.70
50	11.00	10.69



7b

Table 1.4. Titration study of tripeptide 8b in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

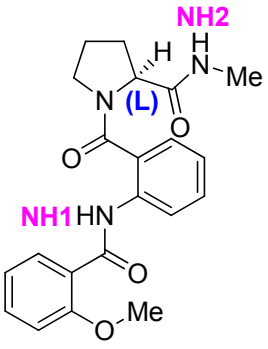
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)		
	OH1	NH1	NH2
0	12.18	10.67	6.54
5	12.09	10.65	6.72
10	12.05	10.64	6.80
15	12.00	10.62	6.87
20	11.96	10.60	6.94
25	11.91	10.58	7.00
30	11.87	10.56	7.03
35	11.82	10.53	7.07
40	11.78	10.51	7.10
45	11.75	10.49	7.11
50	11.71	10.47	7.12



8b

Table 1.5. Titration study of tripeptide 8c in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

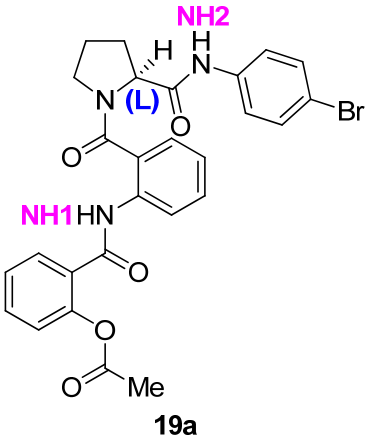
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	10.77	6.91
5	10.76	6.91
10	10.74	6.93
15	10.72	6.94
20	10.71	6.96
25	10.70	6.97
30	10.68	6.98
35	10.67	6.99
40	10.66	7.00
45	10.64	7.01
50	10.63	7.02



8c

Table 1.6. Titration study of tripeptide 19a in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

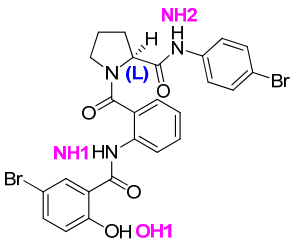
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	9.72	9.05
5	9.79	9.23
10	9.82	9.33
15	9.84	9.40
20	9.84	9.45
25	9.84	9.49
30	9.83	9.51
35	9.82	9.53
40	9.81	9.55
45	9.79	9.56
50	9.78	9.56



19a

Table 1.7. Titration study of tripeptide 20b in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 µl)

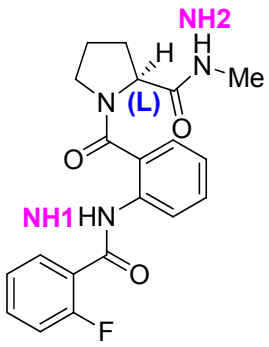
Volume of DMSO-d_6 added (in µL)	Chemical Shift (in ppm)		
	OH1	NH1	NH2
0	12.16	10.62	8.86
5	11.99	10.57	9.26
10	11.91	10.56	9.43
15	11.86	10.54	9.51
20	11.81	10.53	9.56
25	11.77	10.53	9.60
30	11.71	10.50	9.60
35	11.67	10.49	9.61
40	11.63	10.47	9.61
45	11.58	10.45	9.60
50	11.56	10.44	9.60



20b

Table 1.8. Titration study of tripeptide 9 in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 µl)

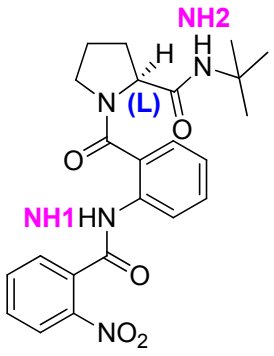
Volume of DMSO-d_6 added (in µL)	Chemical Shift (in ppm)	
	NH1	NH2
0	10.00	6.87
5	10.00	6.91
10	9.99	6.94
15	9.99	6.97
20	9.98	7.00
25	9.97	7.02
30	9.97	7.04
35	9.96	7.07
40	9.95	7.09
45	9.94	7.10
50	9.93	7.11



9

Table 1.9. Dilution study of tripeptide 4a in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

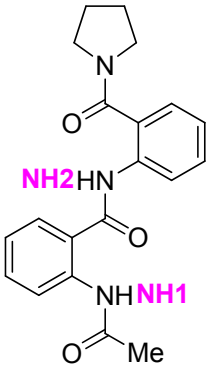
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	9.99	5.78
100	9.98	5.75
80	9.97	5.72
60	9.96	5.69
40	9.94	5.65
20	9.93	5.61
10	9.92	5.58
5	9.91	5.57
4	9.91	5.57
2	9.91	5.56



4a

Table 1.10. Dilution study of tripeptide 7b in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

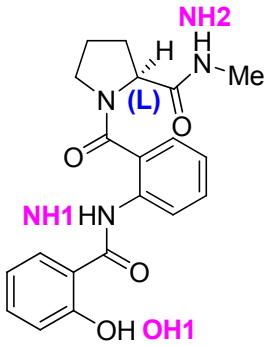
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	11.23	10.85
100	11.23	10.85
80	11.23	10.85
60	11.23	10.85
40	11.23	10.84
20	11.24	10.84
10	11.24	10.84
5	11.24	10.84
4	11.23	10.84
2	11.24	10.85



7b

Table 1.11. Dilution study of tripeptide 8b in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

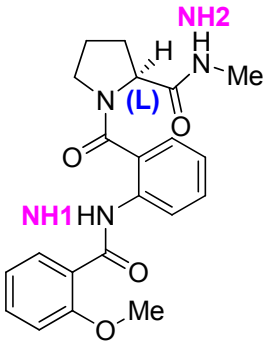
Concentration (in ppm)	Chemical Shift (in ppm)		
	OH1	NH1	NH2
120	12.11	10.62	6.66
100	12.11	10.62	6.66
80	12.12	10.63	6.64
60	12.15	10.65	6.60
40	12.16	10.66	6.57
20	12.18	10.67	6.54
10	12.19	10.68	6.53
5	12.20	10.68	6.52
4	12.20	10.68	6.52
2	12.20	10.69	6.52



8b

Table 1.12. Dilution study of tripeptide 8c in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

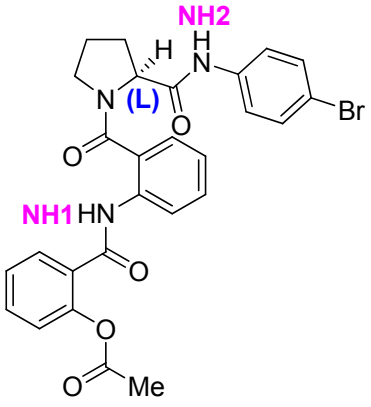
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	10.75	6.93
100	10.74	6.93
80	10.75	6.92
60	10.75	6.91
40	10.76	6.90
20	10.76	6.90
10	10.77	6.90
5	10.77	6.91
4	10.77	6.90
2	10.77	6.90



8c

Table 1.13. Dilution study of tripeptide 19a in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

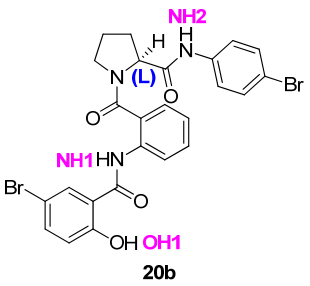
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	9.73	9.18
100	9.73	9.17
80	9.73	9.15
60	9.77	9.17
40	9.75	9.13
20	9.73	9.06
10	9.72	9.03
5	9.72	9.02
4	9.73	9.01
2	9.73	9.01



19a

Table 1.14. Dilution study of tripeptide 20b in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

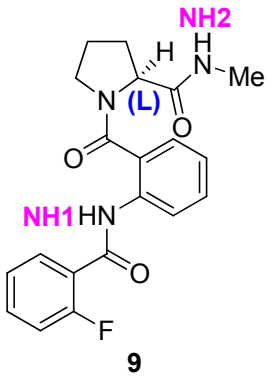
Concentration (in ppm)	Chemical Shift (in ppm)		
	OH1	NH1	NH2
120	12.22	10.60	8.90
100	12.22	10.60	8.91
80	12.22	10.61	8.90
60	12.20	10.62	8.88
40	12.18	10.62	8.87
20	12.13	10.62	8.85
10	12.13	10.62	8.85
5	12.11	10.62	8.85
4	12.10	10.62	8.84
2	12.09	10.62	8.84



20b

Table 1.15. Dilution study of tripeptide 9 in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

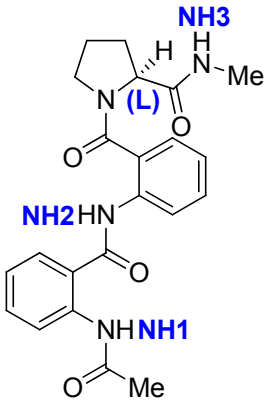
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	9.99	6.93
100	9.99	6.93
80	9.99	6.92
60	9.99	6.89
40	10.00	6.88
20	10.00	6.87
10	10.00	6.86
5	10.00	6.86
4	10.00	6.86
2	10.00	6.86



9

Table 1.16. Temperature variation study of tripeptide 3c (20 mmol, 400 MHz, $CDCl_3$)

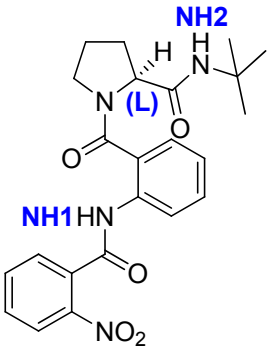
Temperature (in K)	Chemical shift (in ppm)		
	NH1	NH2	NH3
268	11.00	10.41	6.55
273	11.00	10.40	6.54
278	11.01	10.38	6.53
283	11.02	10.37	6.51
288	11.02	10.35	6.50
293	11.02	10.34	6.48
298	11.02	10.32	6.47
303	11.02	10.30	6.46
308	11.02	10.28	6.45
313	11.01	10.26	6.43
318	11.01	10.24	6.43
323	11.00	10.22	6.41



3c

Table 1.17. Temperature variation study of tripeptide 4a (20 mmol, 400 MHz, $CDCl_3$)

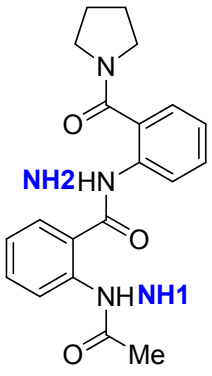
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	10.06	5.66
273	10.03	5.67
278	10.01	5.68
283	9.98	5.68
288	9.96	5.67
293	9.92	5.65
298	9.90	5.64
303	9.87	5.63
308	9.85	5.63
313	9.82	5.63
318	9.79	5.63
323	9.77	5.63



4a

Table 1.18. Temperature variation study of tripeptide 7b (20 mmol, 400 MHz, $CDCl_3$)

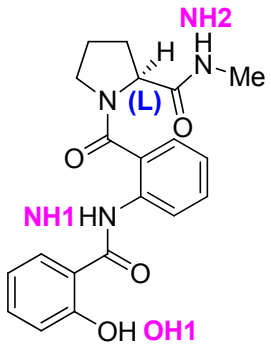
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	11.24	10.88
273	11.24	10.84
278	11.24	10.86
283	11.25	10.85
288	11.25	10.84
293	11.24	10.87
298	11.24	10.83
303	11.24	10.82
308	11.24	10.80
313	11.23	10.79
318	11.23	10.78
323	11.22	10.76



7b

Table 1.19. Temperature variation study of tripeptide 8b (20 mmol, 400 MHz, $CDCl_3$)

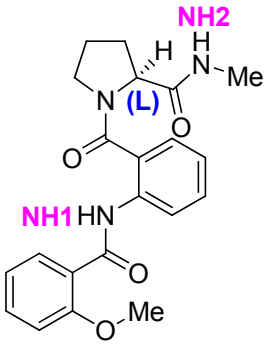
Temperature (in K)	Chemical shift (in ppm)		
	OH1	NH1	NH2
268	12.16	10.65	6.62
273	12.26	10.77	6.61
278	12.24	10.75	6.59
283	12.23	10.73	6.57
288	12.22	10.71	6.56
293	12.20	10.69	6.55
298	12.18	10.67	6.54
303	12.15	10.60	6.51
308	12.12	10.60	6.51
313	12.10	10.57	6.50
318	12.08	10.55	6.48
323	12.06	10.53	6.47



8b

Table 1.20. Temperature variation study of tripeptide 8c (20 mmol, 400 MHz, $CDCl_3$)

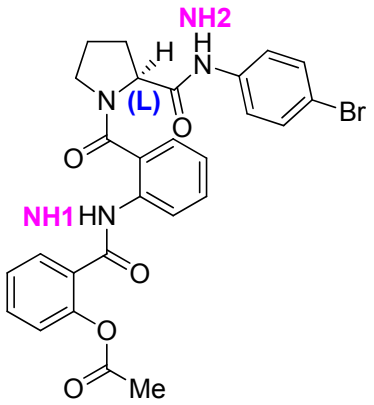
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	10.75	6.89
273	10.82	7.00
278	10.81	6.98
283	10.80	6.96
288	10.79	6.94
293	10.78	6.92
298	10.76	6.91
303	10.73	6.88
308	10.72	6.86
313	10.70	6.85
318	10.68	6.83
323	10.66	6.82



8c

Table 1.21. Temperature variation study of tripeptide 19a (20 mmol, 400 MHz, $CDCl_3$)

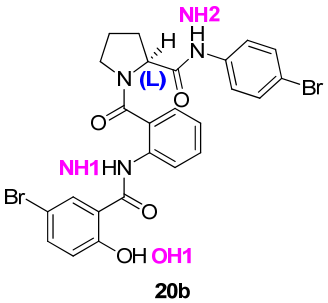
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	9.87	9.20
273	9.84	9.17
278	9.82	9.14
283	9.78	9.11
288	9.76	9.09
293	9.72	9.07
298	9.69	9.04
303	9.66	9.02
308	9.64	9.01
313	9.61	8.99
318	9.58	8.97
323	9.55	8.96



19a

Table 1.22. Temperature variation study of tripeptide 20b (20 mmol, 400 MHz, $CDCl_3$)

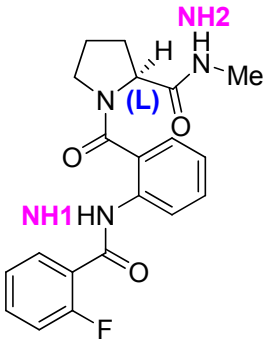
Temperature (in K)	Chemical shift (in ppm)		
	OH1	NH1	NH2
268	12.36	10.72	8.91
273	12.32	10.71	8.90
278	12.28	10.69	8.89
283	12.24	10.67	8.88
288	12.20	10.64	8.87
293	12.16	10.62	8.86
298	12.13	10.60	8.85
303	12.09	10.58	8.84
308	12.06	10.56	8.82
313	12.03	10.53	8.81
318	12.00	10.51	8.79
323	11.97	10.49	8.77



20b

Table 1.23. Temperature variation study of tripeptide 9 (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	9.98	6.96
273	10.11	6.94
278	10.09	6.93
283	10.07	6.91
288	10.05	6.89
293	10.03	6.88
298	10.00	6.86
303	9.96	6.84
308	9.93	6.83
313	9.91	6.82
318	9.89	6.81
323	9.86	6.79



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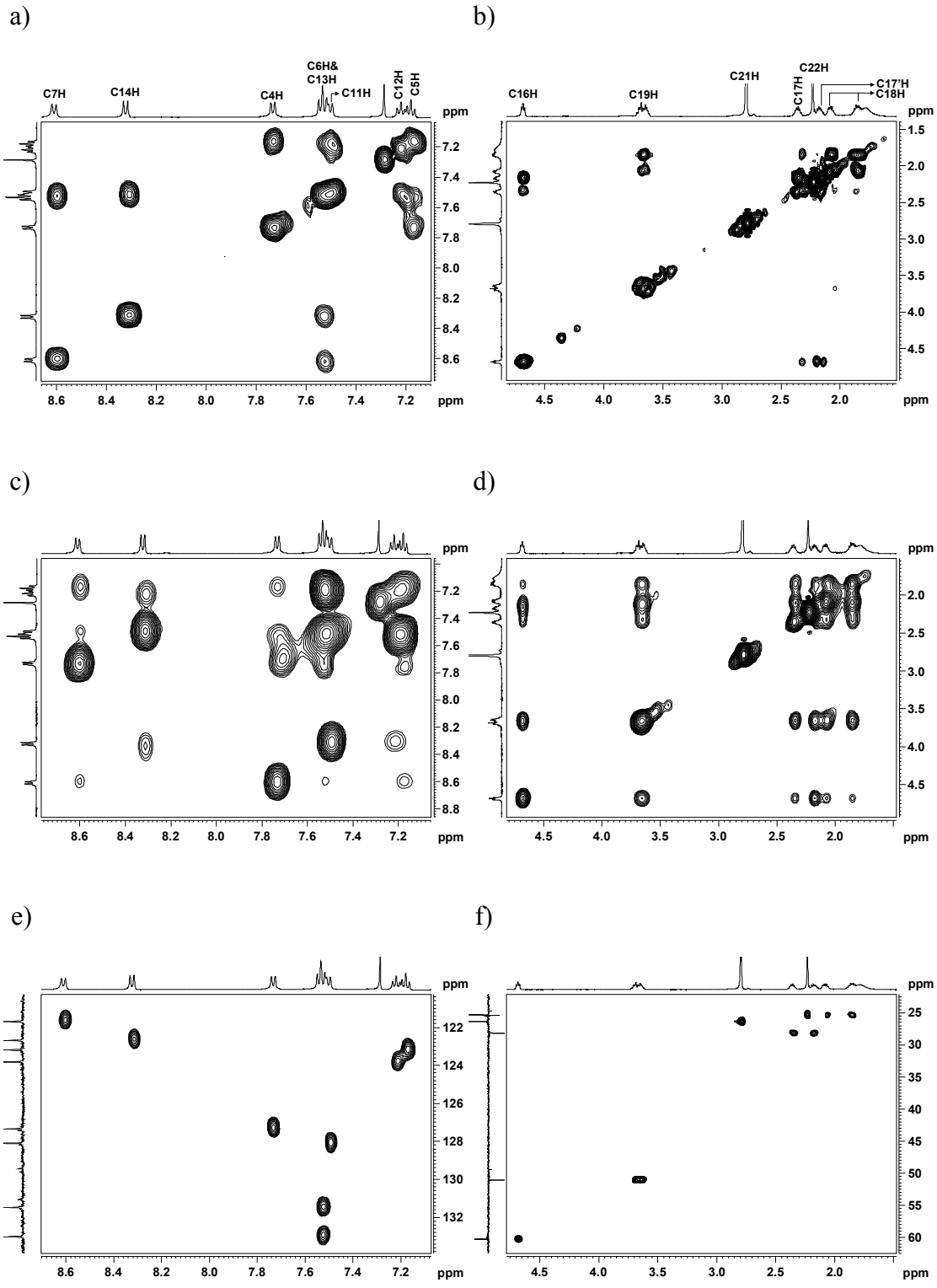


Fig. 1.33: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **3c** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

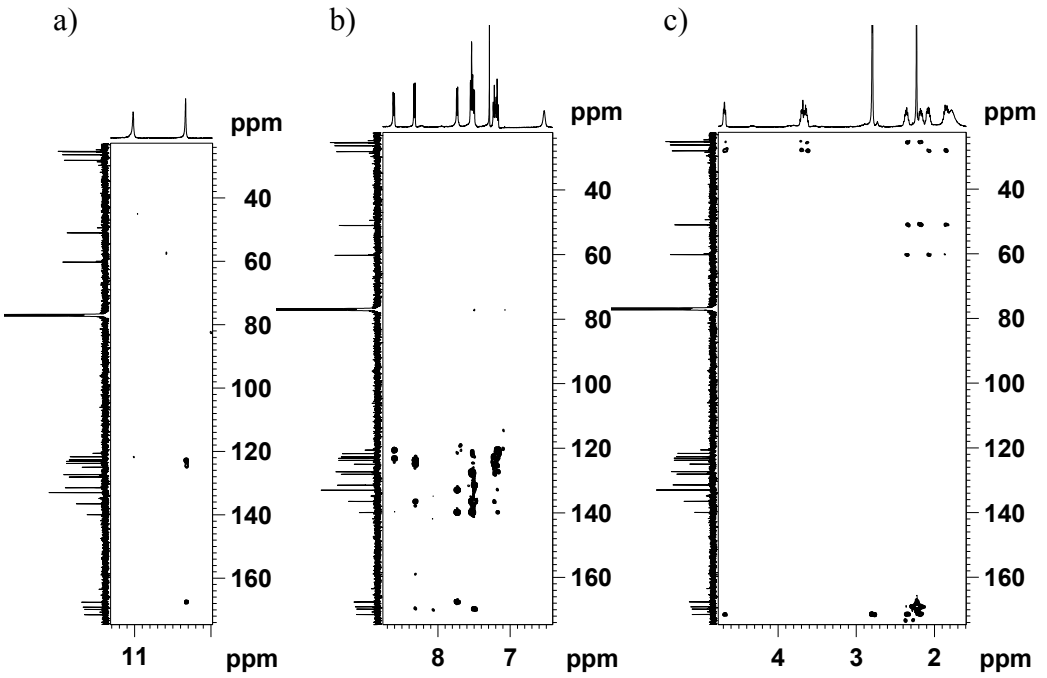


Fig. 1.34: Partial HMBC spectra of tripeptide **3c** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

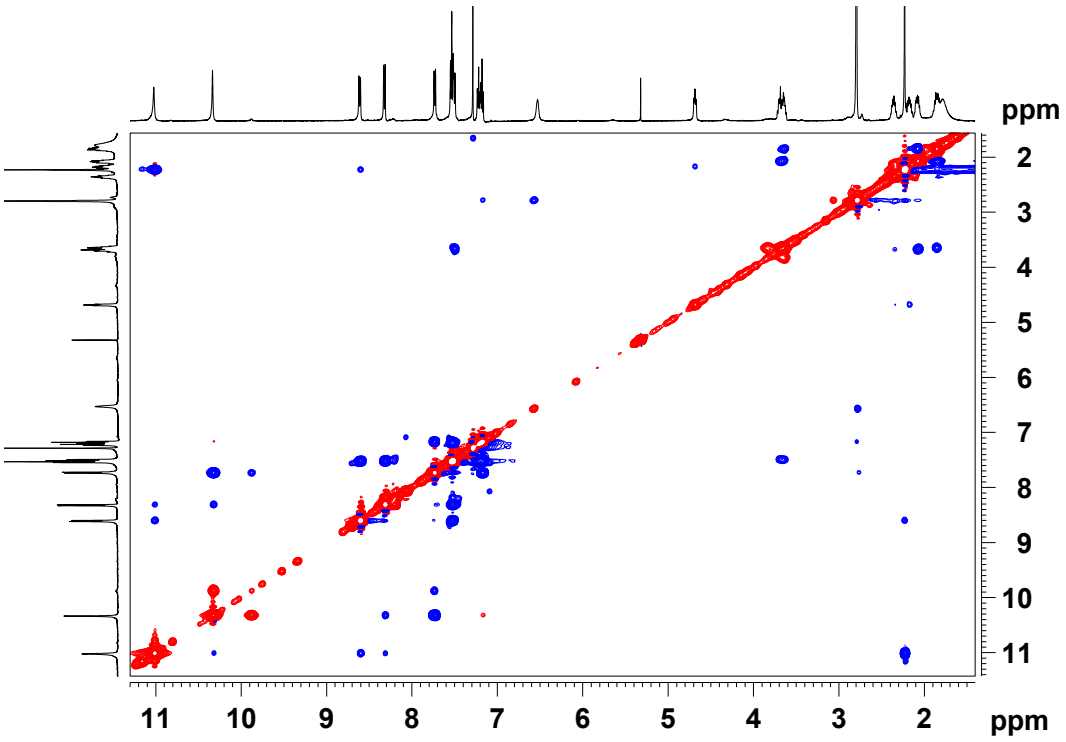


Fig. 1.35: 2D NOESY spectra of tripeptide **3c** (500 MHz, $CDCl_3$).

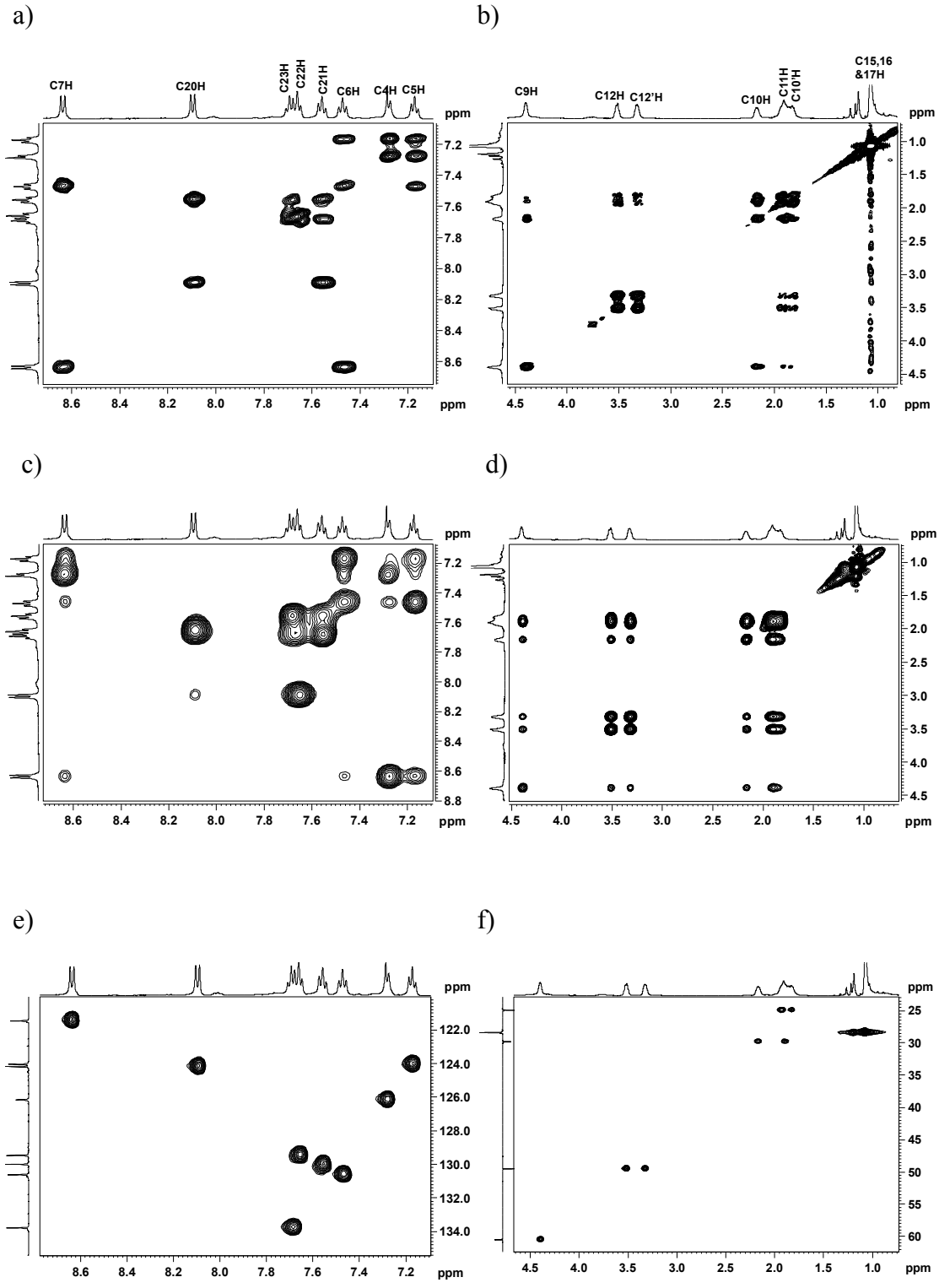


Fig. 1.36: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **4a** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

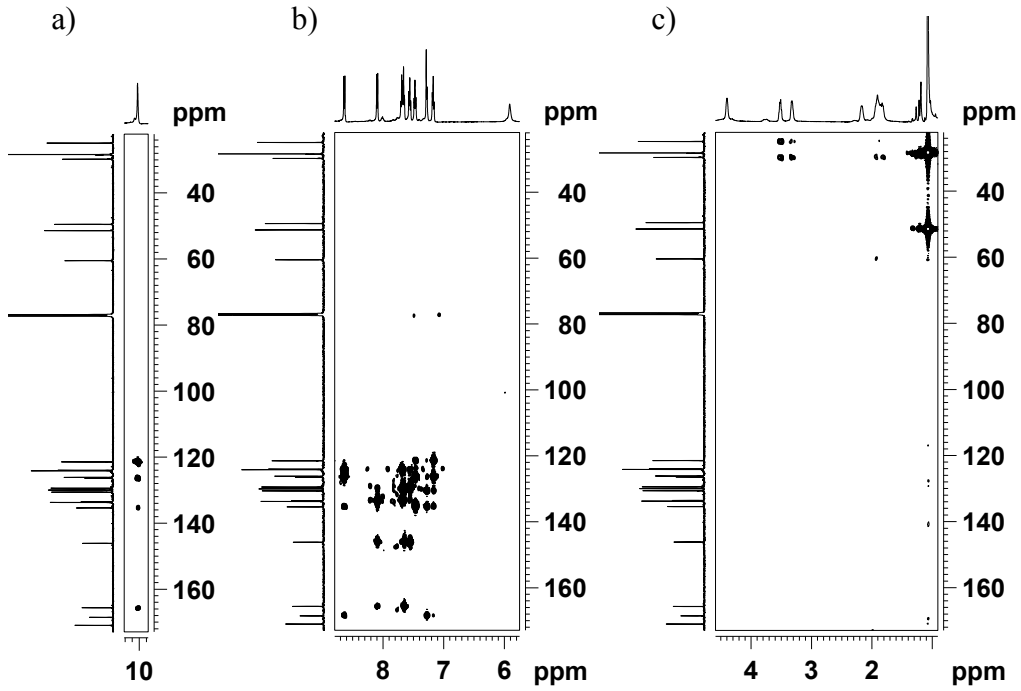


Fig. 1.37: Partial HMBC spectra of tripeptide **4a** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

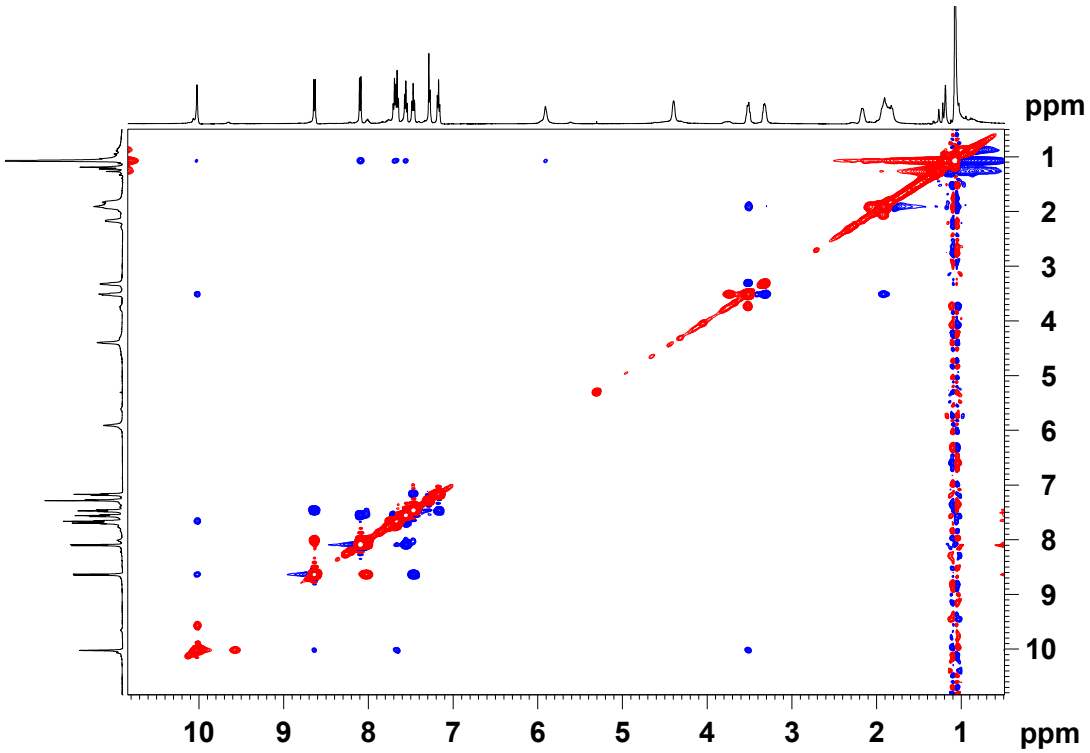


Fig. 1.38: 2D NOESY spectra of tripeptide **4a** (500 MHz, $CDCl_3$).

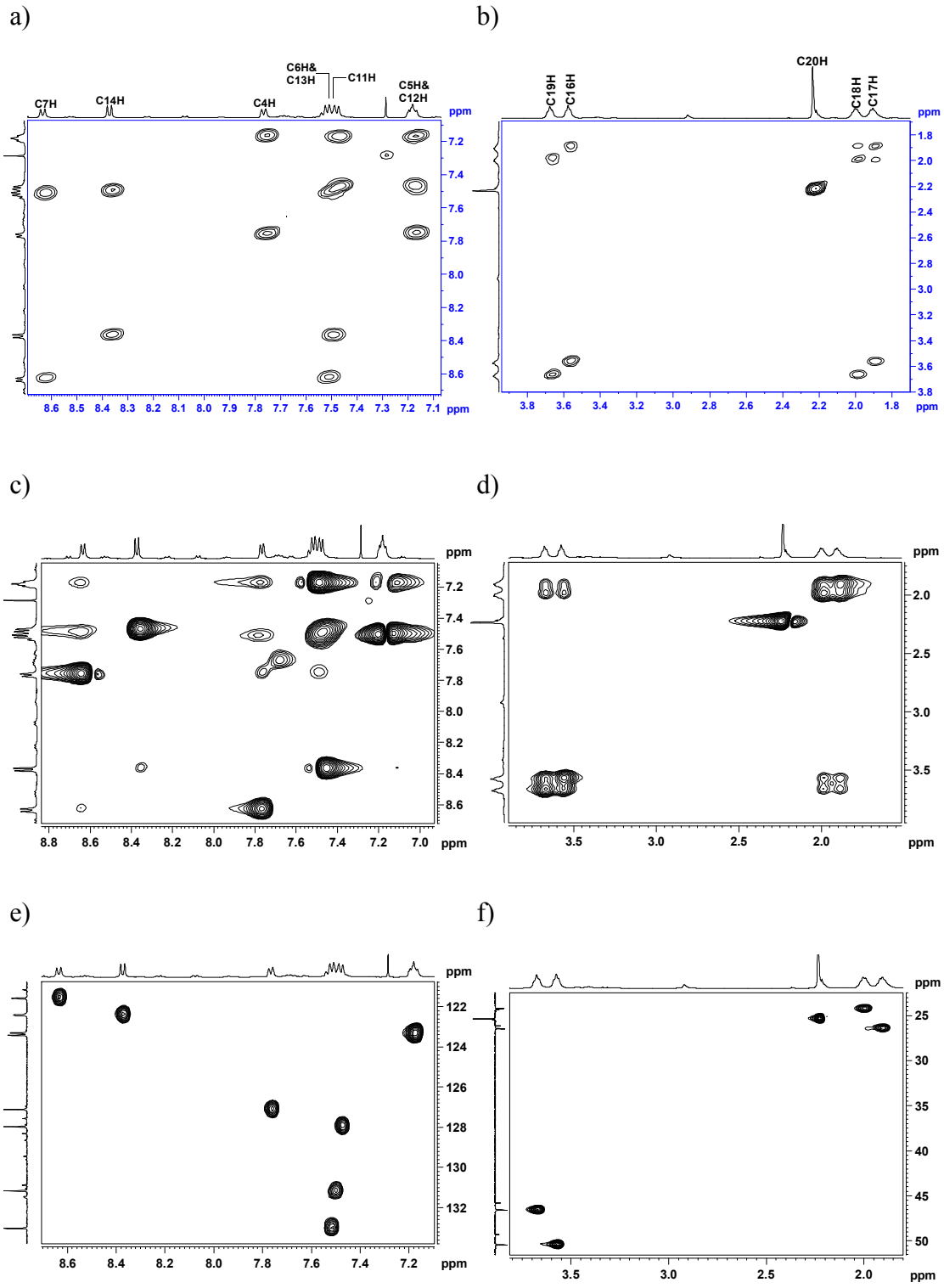


Fig. 1.39: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **7b** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

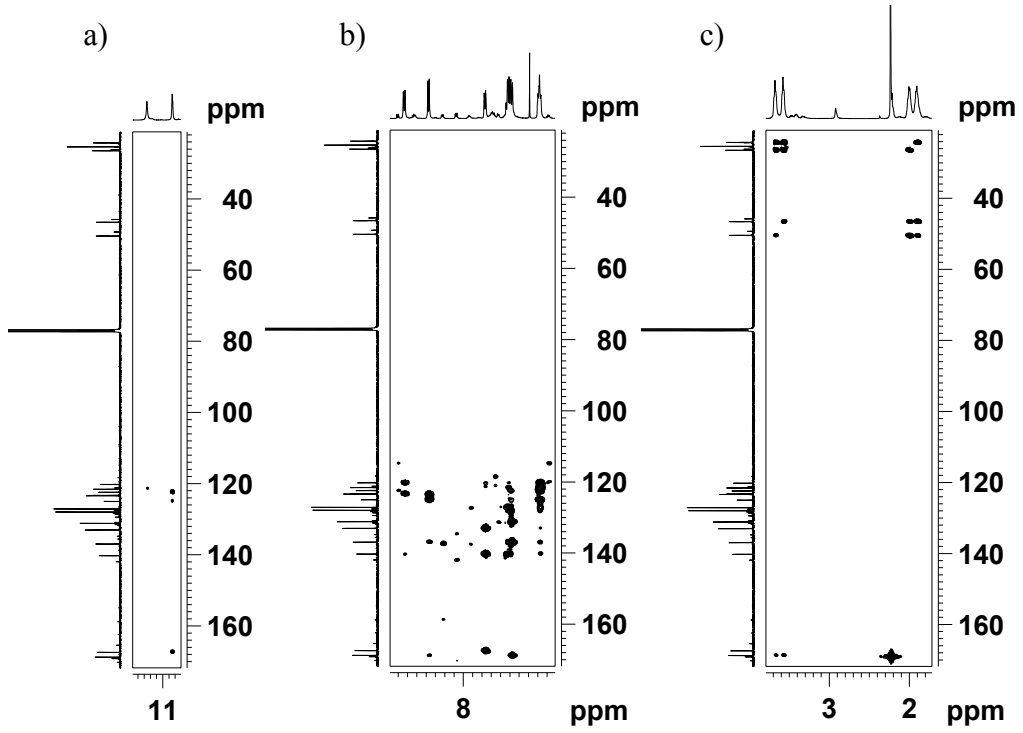


Fig. 1.40: Partial HMBC spectra of tripeptide **7b** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

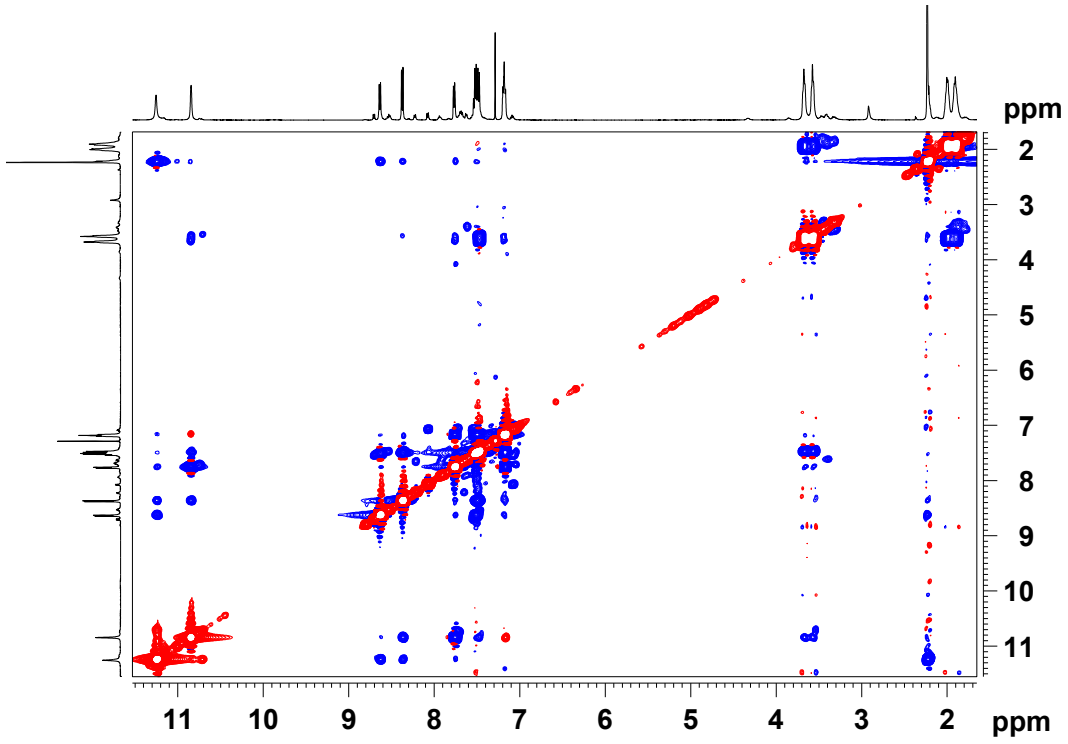


Fig. 1.41: 2D NOESY spectra of tripeptide **7b** (500 MHz, $CDCl_3$).

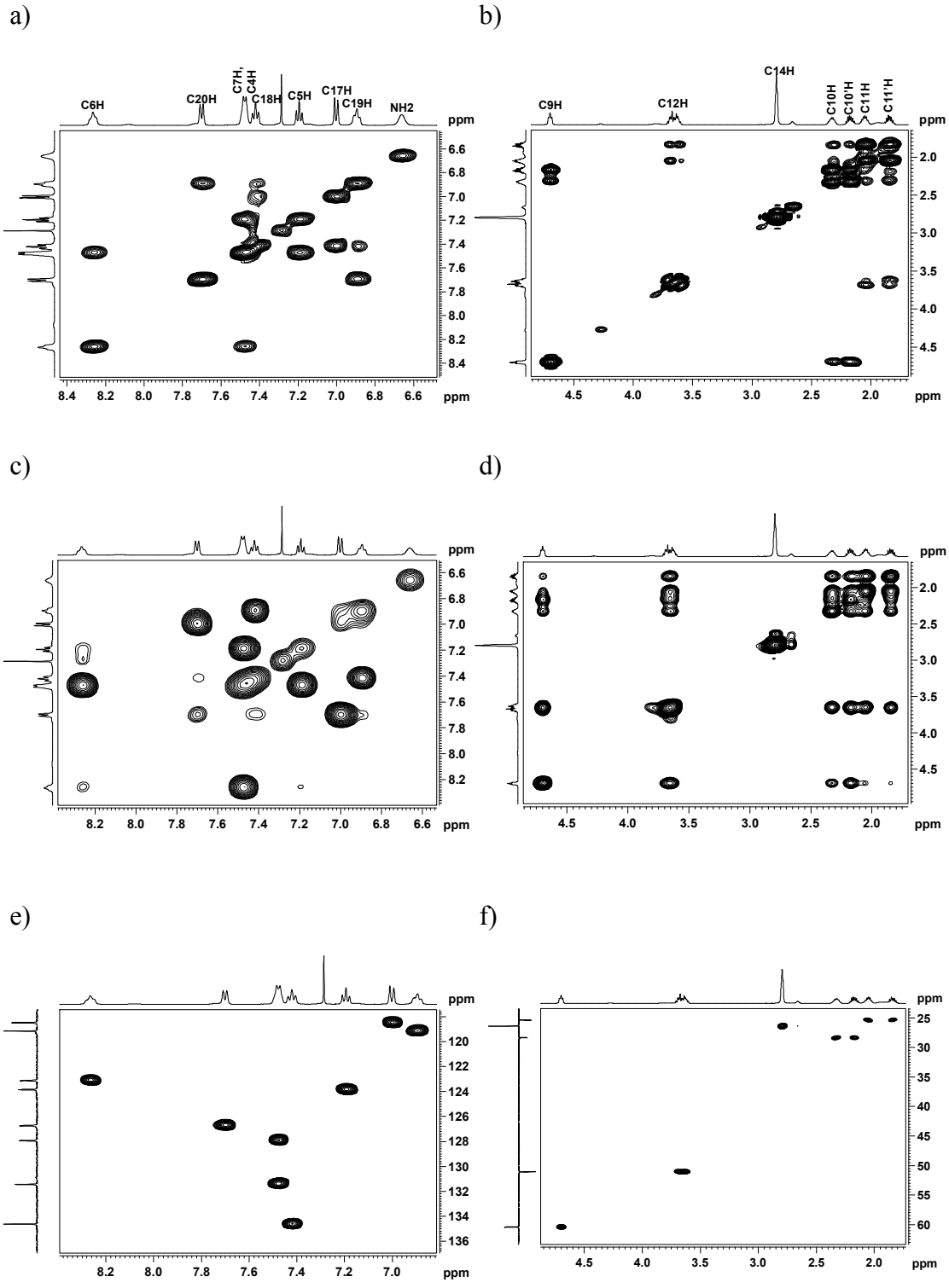


Fig. 1.42: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **8b** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

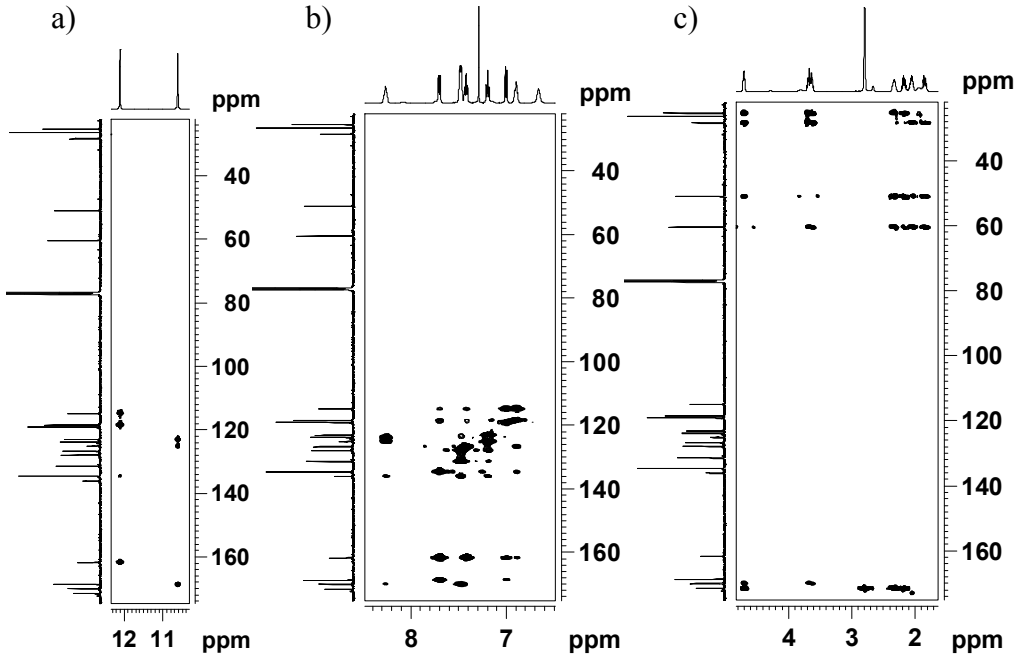


Fig. 1.43: Partial HMBC spectra of tripeptide **8b** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

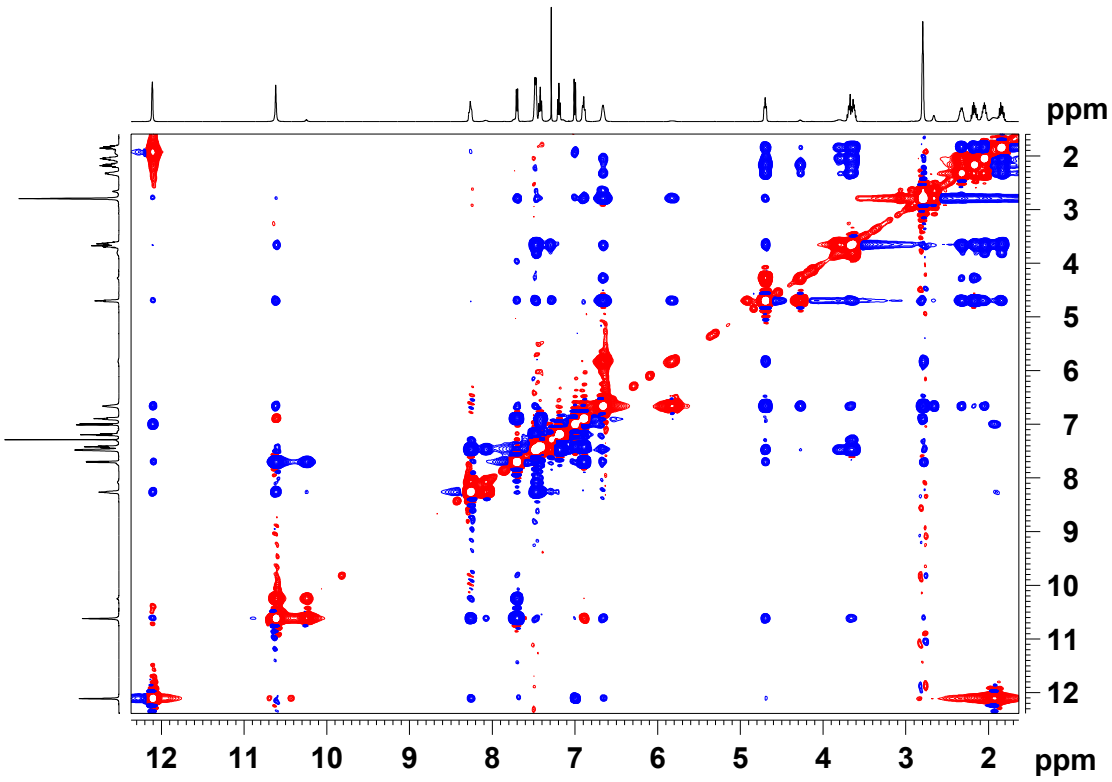


Fig 1.44: 2D NOESY spectra of tripeptide **8b** (500 MHz, $CDCl_3$).

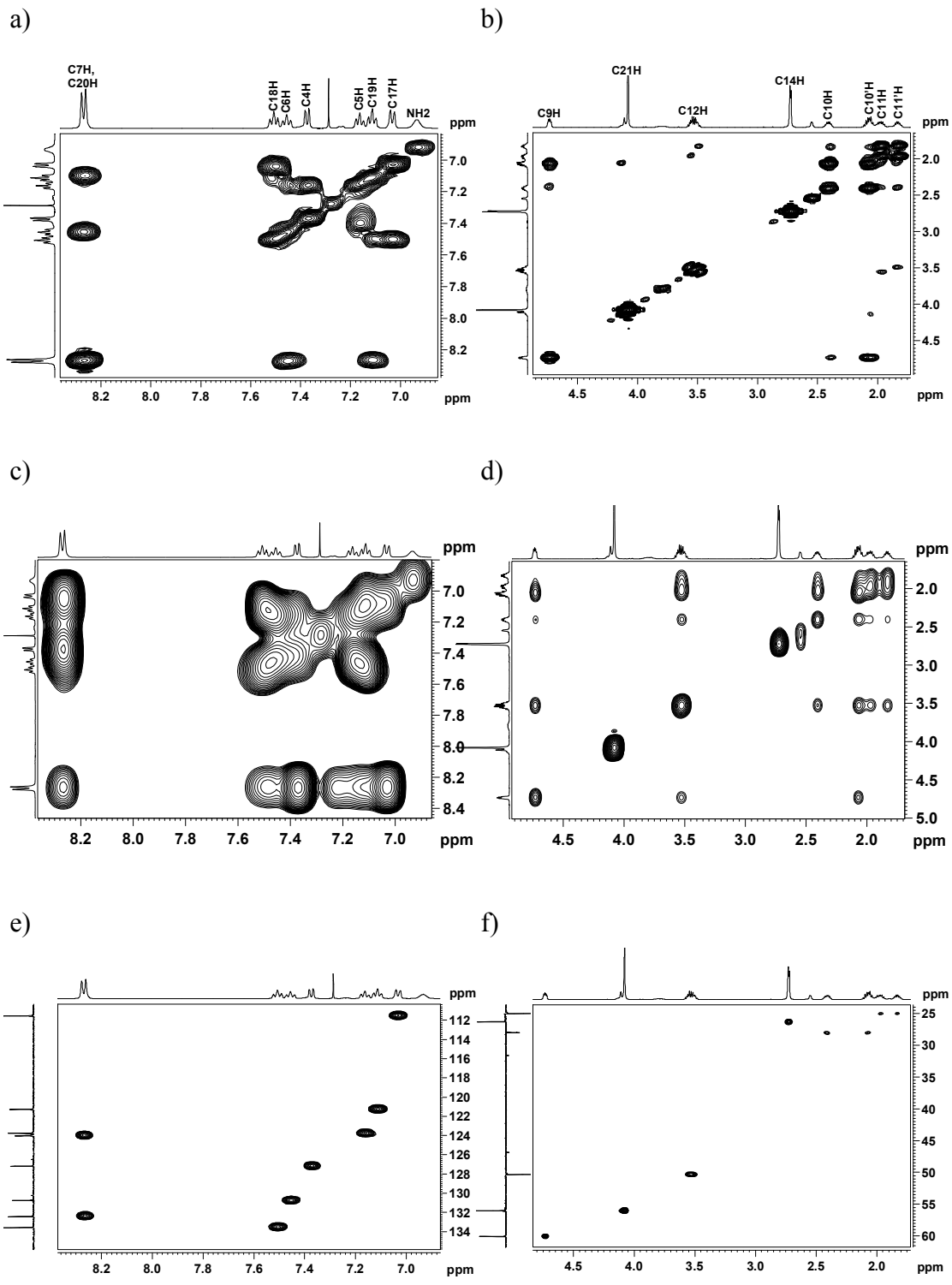


Fig 1.45: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **8c** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

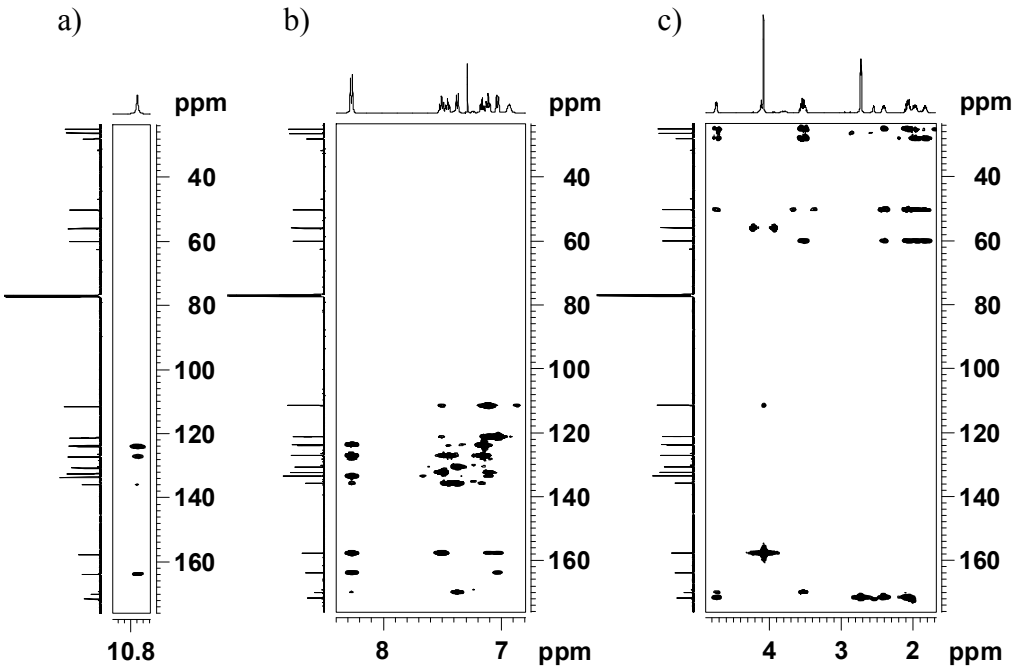


Fig 1.46: Partial HMBC spectra of tripeptide **8c** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

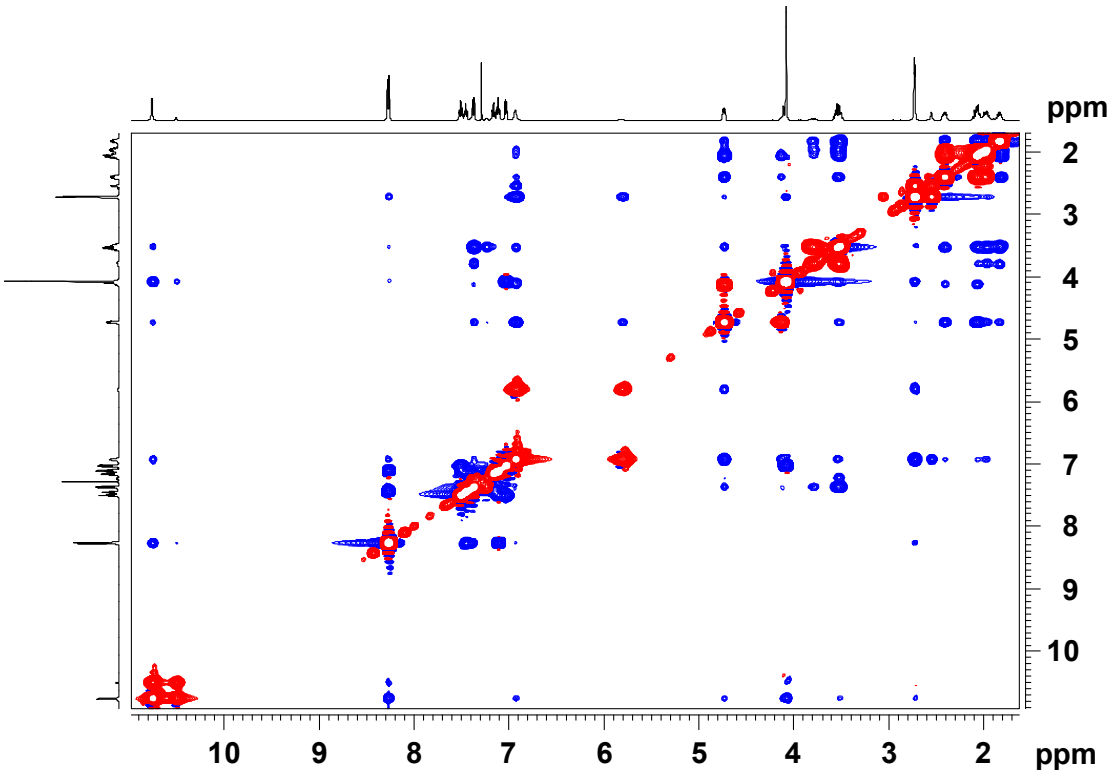


Fig 1.47: 2D NOESY spectra of tripeptide **8c** (500 MHz, $CDCl_3$).

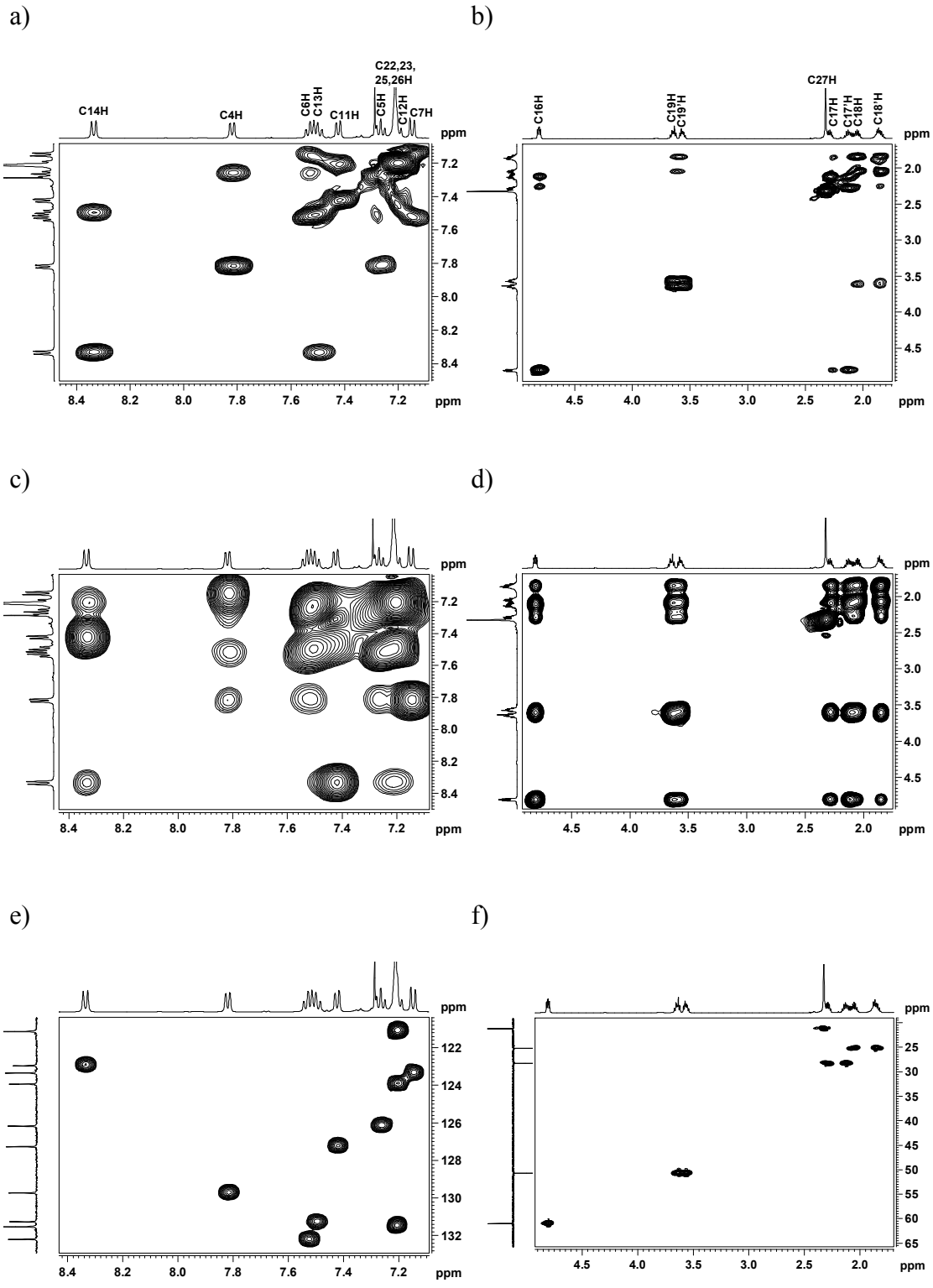


Fig 1.48: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **19a** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

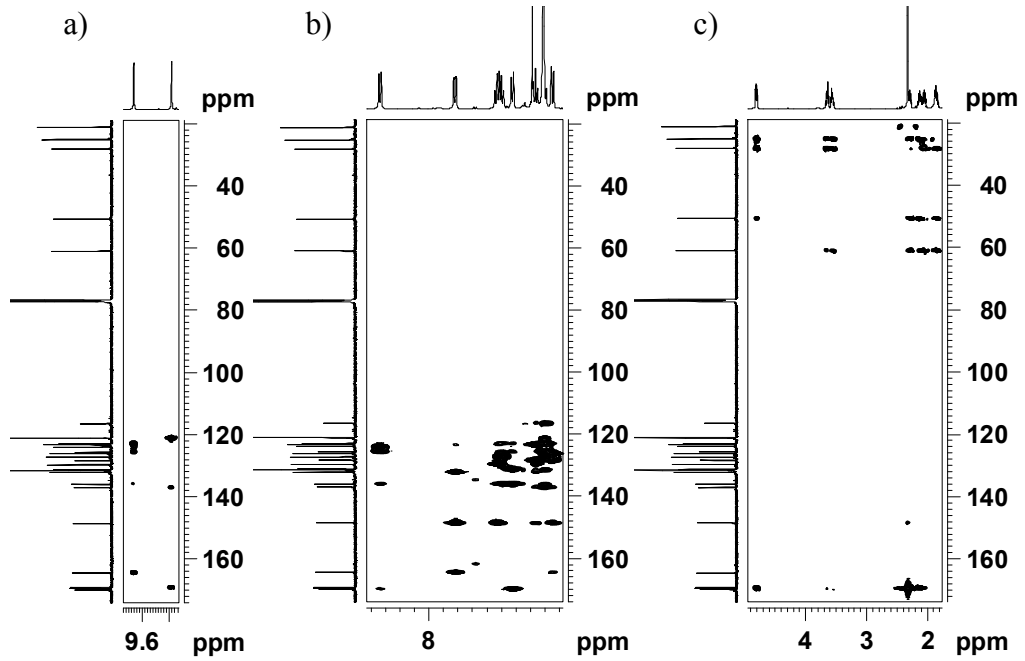


Fig 1.49: Partial HMBC spectra of tripeptide **19a** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

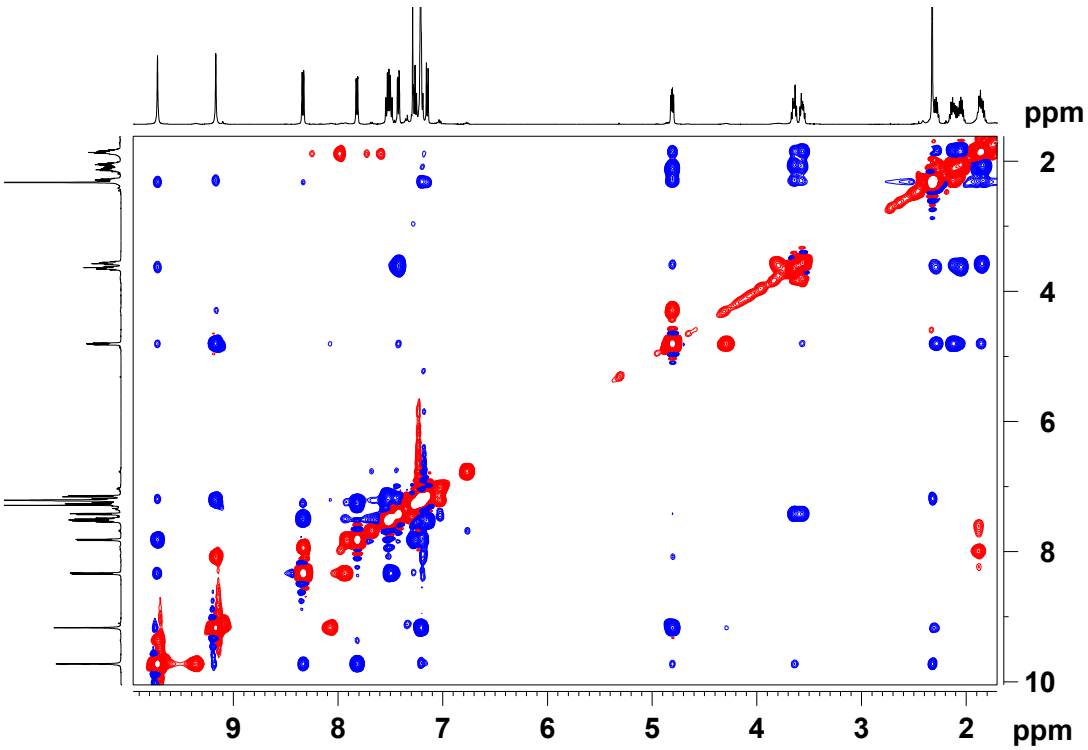


Fig 1.50: 2D NOESY spectra of tripeptide **19a** (500 MHz, $CDCl_3$).

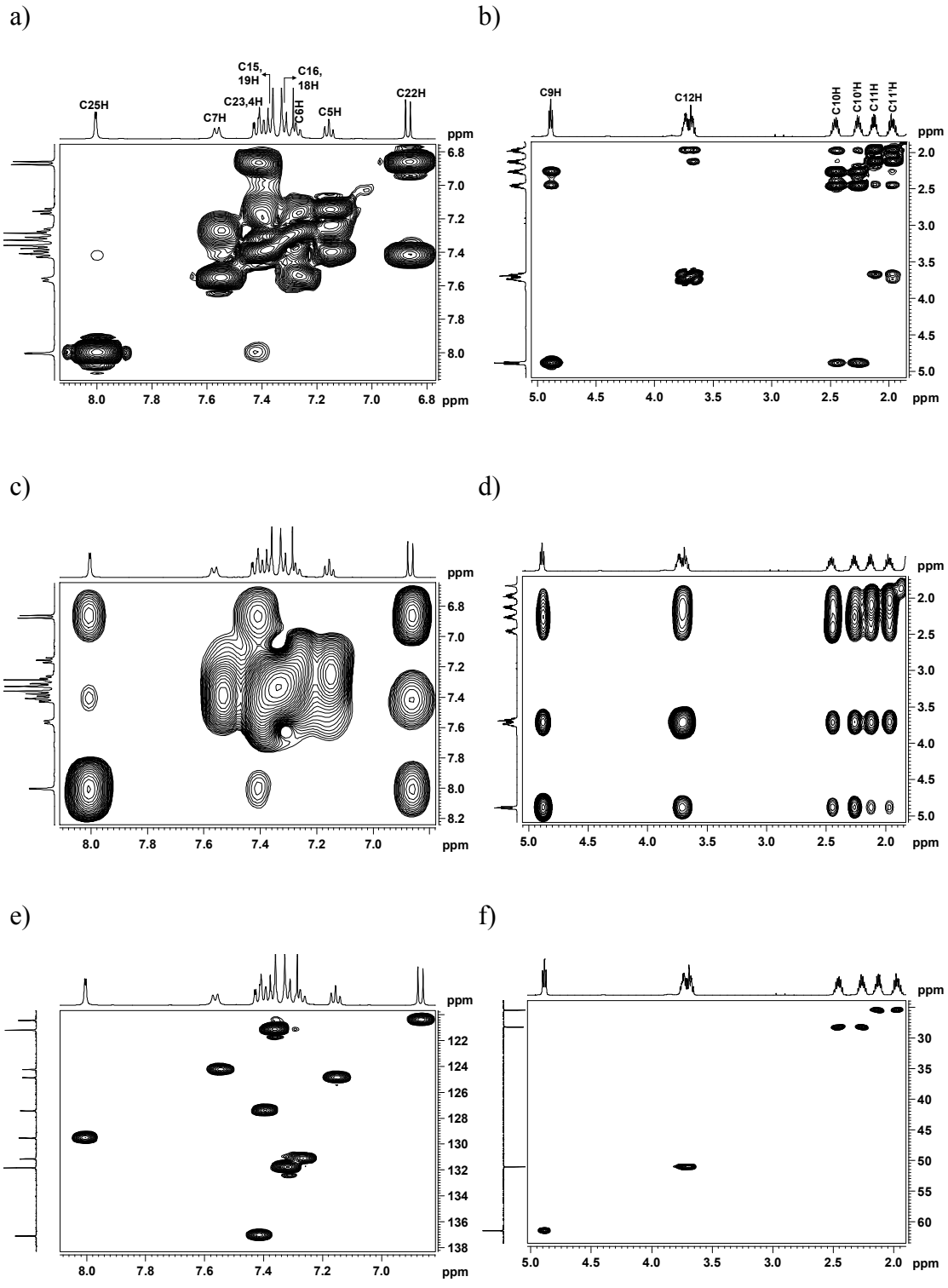


Fig 1.51: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **20b** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

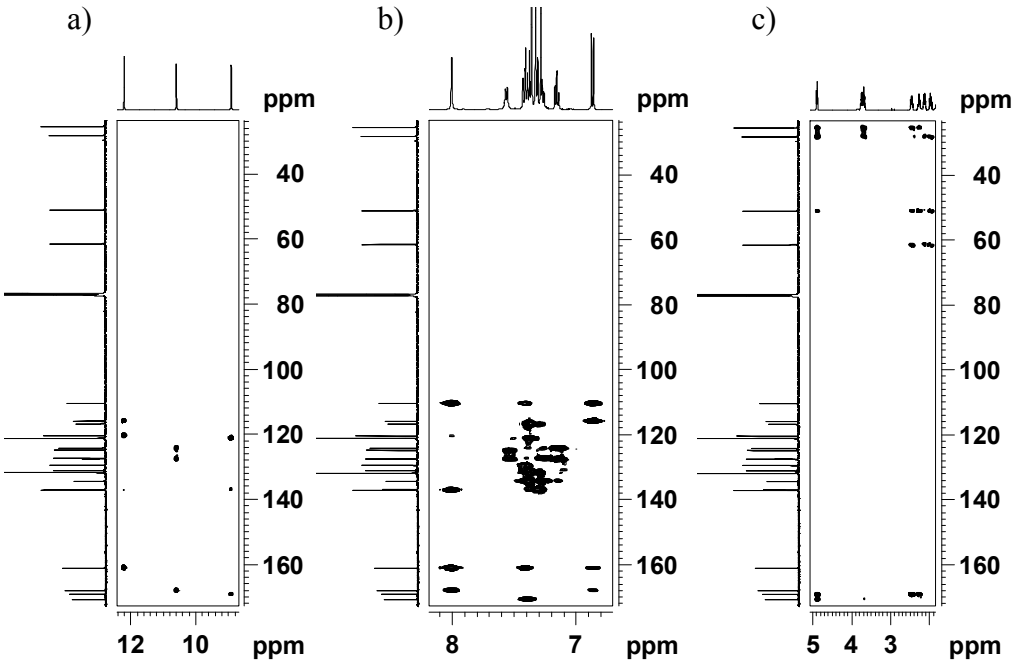


Fig 1.52: Partial HMBC spectra of tripeptide **20b** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

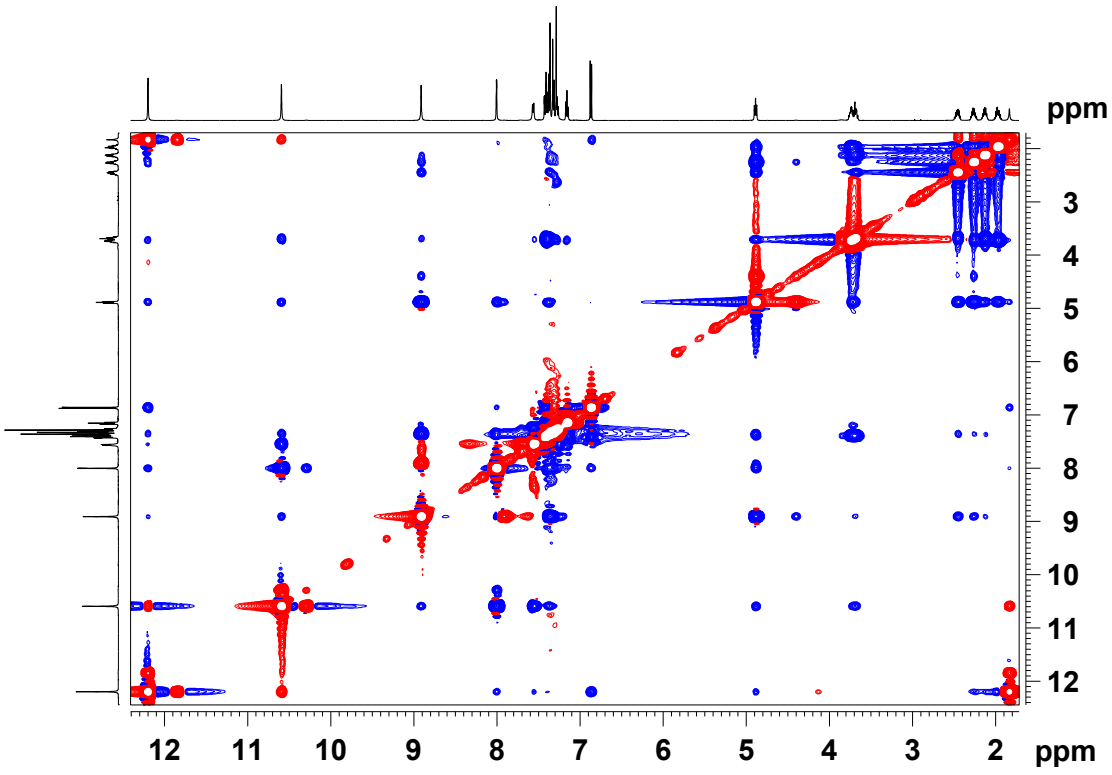


Fig 1.53: 2D NOESY spectra of tripeptide **20b** (500 MHz, $CDCl_3$).

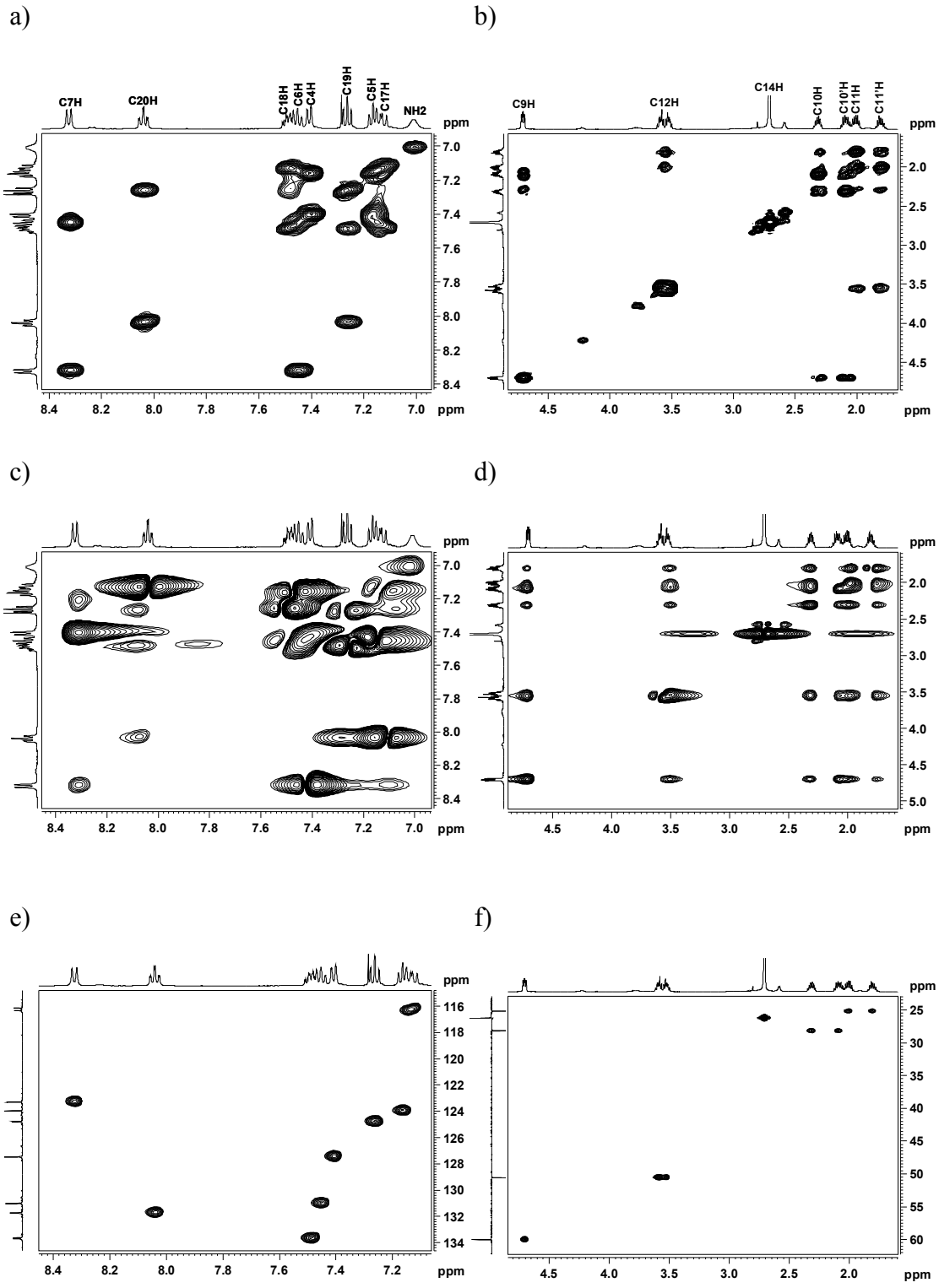


Fig 1.54: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **9** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

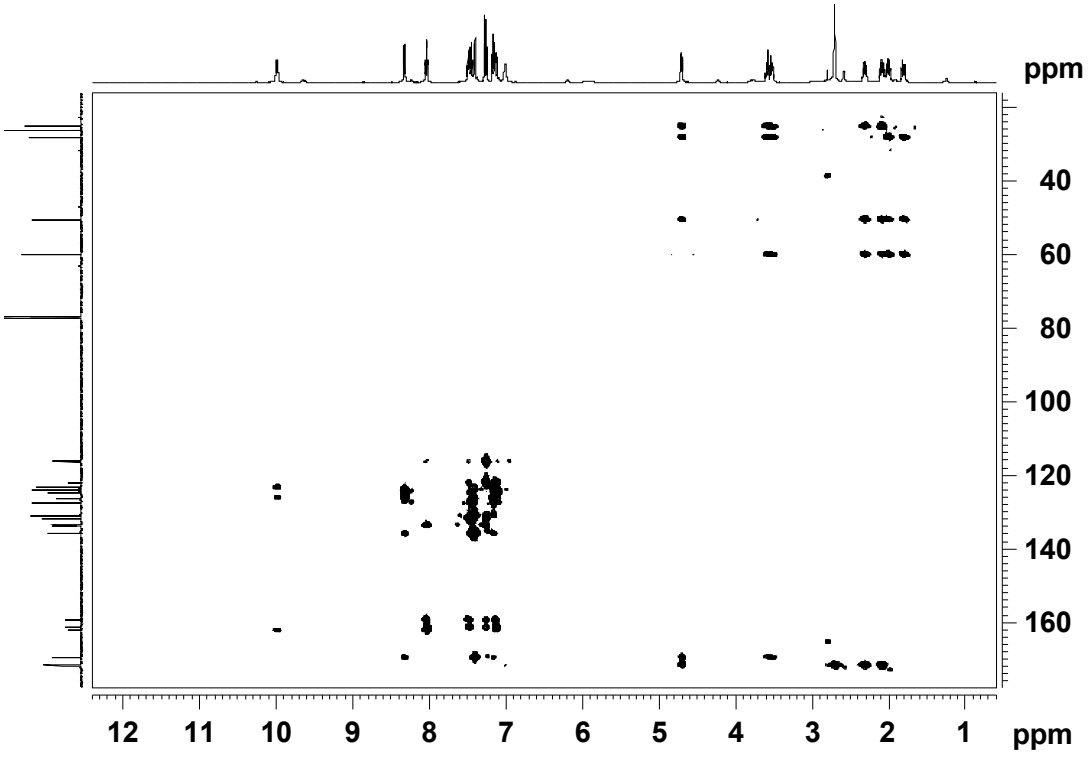


Fig 1.55: Partial HMBC spectra of tripeptide **9** (500 MHz, $CDCl_3$).

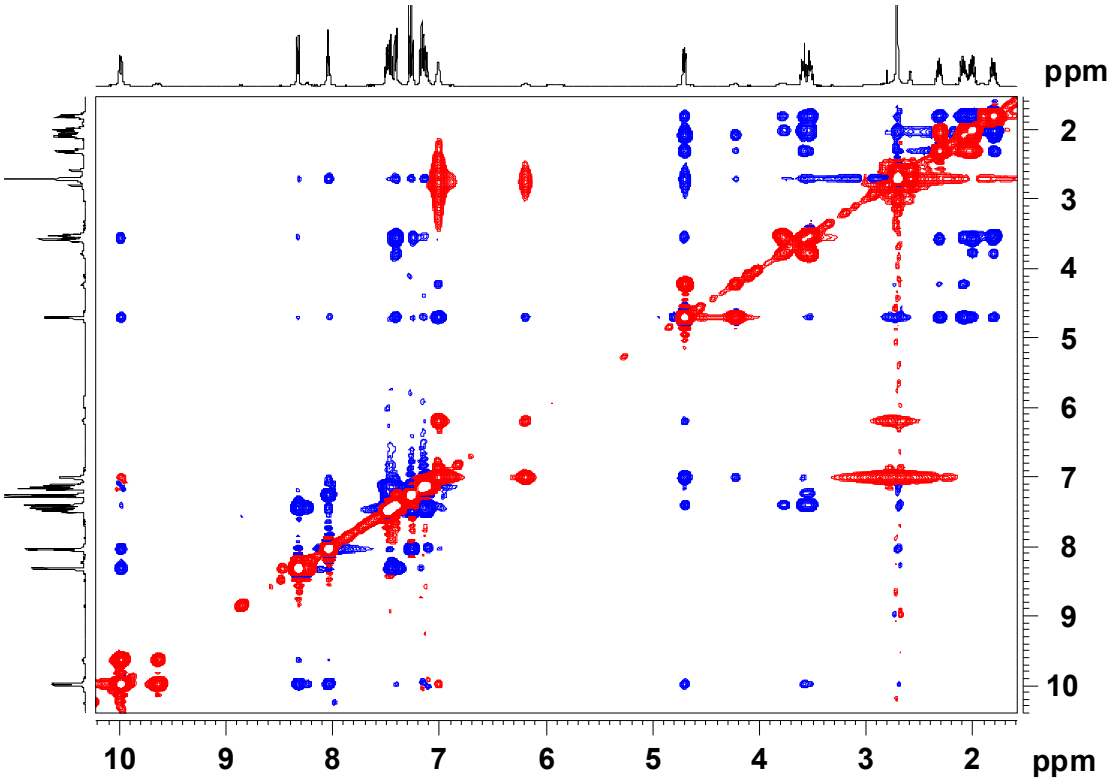


Fig 1.56: 2D NOESY spectra of tripeptide **9** (500 MHz, $CDCl_3$).

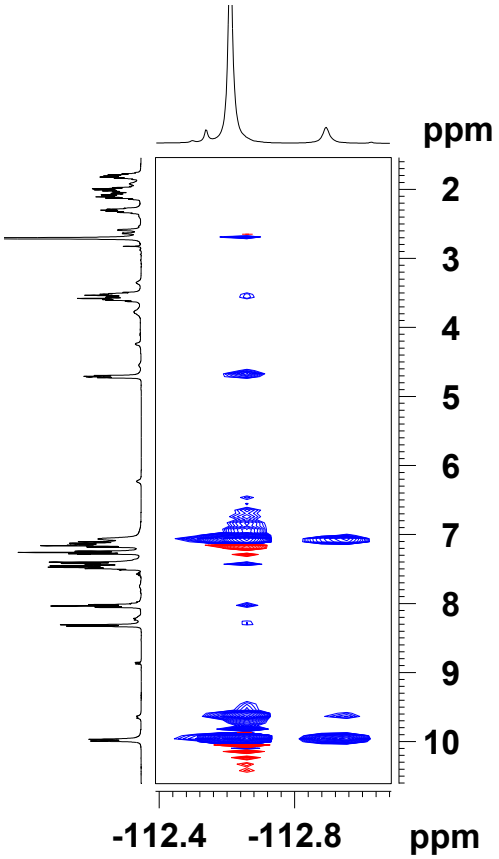


Fig 1.57: 2D HOESY spectra of tripeptide **9** (400 MHz, $CDCl_3$).

1.17 Experimental Section (Part B)

Single crystal X-ray crystallographic studies:

Crystal Data: X-ray intensity data measurements of all the compounds (**30a**, **32a** and **34a**) were carried out on a Bruker SMART APEX I CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.3° at different settings of φ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data collection was monitored by SMART program (Bruker, 2006).[75]

X-ray intensity data measurements of all the compounds (**33a**) was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 100 (2) K. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX 2 program (Bruker, 2006).[75]

All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006).[75] SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms for all the compounds were placed in geometrically idealized position and constrained to ride on their parent atoms. Molecular and packing diagrams were generated using Mercury-3 and Pymol.[76] Geometrical calculations were performed using SHELXTL (Bruker, 2006) and PLATON.[77]

Crystal data for 30a: Colorless crystals of **30a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6 \cdot 0.25(H_2O)$, M = 708.61, colorless prism, 0.28 x 0.16 x 0.10 mm^3, monoclinic, space group $P2_1$, a = 14.1444(14), b = 15.9217(16), c = 16.0940(16) Å, β = 112.638(2)°, V = 3345.2(6) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.407, $F(000)$ = 1472, μ (mm^{-1}) = 1.283, 16915 reflections collected, 11007 unique reflections (R_{int} = 0.0214), 10069 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.715, T_{max} = 0.882, 862 refined parameters, S = 0.962, $R1$ = 0.0316, $wR2$ =

0.0714 (all data R = 0.0360, $wR2$ = 0.0872), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.628, $\Delta\rho_{min}$= - 0.242 eÅ^{-3}.

Crystal data for 32a: Colorless crystals of **32a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6$, M = 704.61, colorless prism, 0.40 x 0.10 x 0.09 mm^3, monoclinic, space group $P2_1$, a = 11.2385(14), b = 9.2310(11), c = 32.800(4) Å, β = 99.779(2)°, V = 3353.3(7) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.396, $F(000)$ = 1464, μ (mm^{-1}) = 1.279, 24538 reflections collected, 11731 unique reflections (R_{int} = 0.0438), 11012 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.629, T_{max} = 0.894, 853 refined parameters, S = 1.051, $R1$ = 0.0402, $wR2$ = 0.0921 (all data R = 0.0438, $wR2$ = 0.0942), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.547, $\Delta\rho_{min}$= -0.319 eÅ^{-3}.

Crystal data for 33a: Colorless crystals of **33a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6$, M = 704.61, colorless prism, 0.70 x 0.11 x 0.09 mm^3, monoclinic, space group $P2_1$, a = 11.2356(6), b = 9.2098(5), c = 32.8244(16) Å, β = 99.779(2)°, V = 3347.3(3) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$ = 52.00°, D_{calc} (g cm^{-3}) = 1.398, $F(000)$ = 1464, μ (mm^{-1}) = 1.281, 41276 reflections collected, 13026 unique reflections (R_{int} = 0.0303), 11766 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.468, T_{max} = 0.893, 853 refined parameters, S = 0.987, $R1$ = 0.0271, $wR2$ = 0.0516 (all data R = 0.0329, $wR2$ = 0.0529), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.418, $\Delta\rho_{min}$= -0.327 eÅ^{-3}.

Crystal data for 34a: Colorless crystals of **34a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6 \cdot 0.25(H_2O)$, M = 708.61, colorless plate, 0.41 x 0.35 x 0.13 mm^3, monoclinic, space group $P2_1$, a = 14.1383(3), b = 15.9256(3), c = 16.0775(4) Å, β = 112.5560(10)°, V = 3343.11(13) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$ = 52.00°, D_{calc} (g cm^{-3}) = 1.400, $F(000)$ = 1464, μ (mm^{-1}) = 1.283, 52660 reflections collected, 13040 unique reflections (R_{int} = 0.0275), 12007 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.621, T_{max} = 0.851, 862 refined parameters, S = 1.044, $R1$ = 0.0265, $wR2$ = 0.0602 (all data R = 0.0310, $wR2$ = 0.0615),

maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.748, $\Delta\rho_{min}$= - 0.477 eÅ^{-3}.

***General method for synthesis of* 25, 26, 38 *and* 39 *using active ester method*:**

(S)-tert-butyl 2-((2-((2-(methoxycarbonyl)phenyl)carbamoyl)phenyl) carbamoyl)pyrrolidine-1-carboxylate 25:

Representative procedure: To a solution of Boc-^{L}Proline (1.1 equiv) in dry THF, TEA (1.2 equiv) was added followed by the addition of ethyl chloroformate (1.2 equiv) dropwise over a period of 10 min. After 15 min, amine **24**[45a] (1 equiv) in THF was added and refluxed for 8 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was washed sequentially with saturated $NaHCO_3$ solution and saturated brine solution. The organic layer was then dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to obtain the crude product which was then purified by column chromatography.

The product **25** was obtained as a white solid (5.24 g, 84%). mp: 92-94 °C; $[\alpha]^{24}_{D}$: -88.84° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3264, 2979, 1690, 1584, 1523, 1271, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.09 (s, 0.55H), $12.05_{rotamer}$ (s, 0.45H), $11.81_{rotamer}$ (s, 0.4H), 11.75 (s, 0.6H), 8.89 (d, *J* = 8.46 Hz, 1H), 8.82-8.71 (m, 1H), 8.11 (dd, *J* = 1.39 Hz, 8.09 Hz, 1H), 7.92 (t, *J* = 7.45 Hz, 1H), 7.68-7.49 (m, 2H), 7.29-7.11 (m, 2H), $4.49\text{-}4.44_{rotamer}$ (m, 0.45H), 4.32-4.26 (m, 0.55H), 3.96 (s, 3H), 3.85-3.74 (m, 1H), 3.65-3.41 (m, 1H), 2.36-2.10 (m, 2H), 2.07-1.87 (m, 2H), $1.45_{rotamer}$ (s, 4H), 1.32 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.7, 168.8, 167.3, 154.8, 154.0, 141.0, 139.8, 134.8, 134.3, 132.9, 130.8, 126.9, 123.1, 123.0, 121.1, 120.5, 115.4, 115.2, 80.0, 62.5, 61.9, 52.4, 46.9, 46.6, 31.4, 30.4, 28.2, 28.1, 24.2, 24.1, 23.7, 23.6; ESI-MS: 468.4953 $(M+H)^+$; 490.3769 $(M+Na)^+$; 506.3938 $(M+K)^+$; Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99; Found: C, 64.35; H, 6.13; N, 9.13.

(R)-tert-butyl 2-((2-((2-(methoxycarbonyl)phenyl)carbamoyl)phenyl) carbamoyl) pyrrolidine-1-carboxylate 26:

The product **26** was obtained was obtained from **24**[1], following the procedure for **25**, as a white solid (1.99 g, 82%). mp: 101-103 °C; $[\alpha]^{24}_{D}$: +188° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3264, 2979, 1690, 1584, 1523, 1271, 756; ^{1}H

NMR (200 MHz, $CDCl_3$) δ: 12.07 (s, 0.6H), $12.04_{rotamer}$ (s, 0.4H), $11.79_{rotamer}$ (s, 0.4H), 11.73 (s, 0.6H), 8.89 (d, *J* = 8.46 Hz, 1H), $8.81_{rotamer}$ (d, *J* = 8.72 Hz, 0.4H), 8.74 (d, *J* = 8.46 Hz, 0.6H), 8.11 (dd, *J* = 1.39, 7.96 Hz, 1H), 7.91 (d, *J* = 7.33 Hz, 1H), 7.67-7.51 (m, 2H), 7.22 (t, *J* = 7.83 Hz, 1H), 7.19 (t, *J* = 6.95 Hz, 1H), $4.48\text{-}4.43_{rotamer}$ (m, 0.4H), 4.32-4.26 (m, 0.6H), 3.95 (s, 3H), 3.83-3.68 (m, 1H), 3.64-3.40 (m, 1H), 2.40-2.10 (m, 2H), 2.06-1.86 (m, 2H), $1.44_{rotamer}$ (s, 4H), 1.31 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.8, 168.9, 167.5, 167.3, 154.1, 141.2, 141.1, 134.9, 134.4, 133.0, 130.9, 127.0, 123.2, 123.0, 121.1, 120.6, 115.4, 115.3, 80.0, 79.9, 62.5, 61.9, 52.5, 46.9, 46.7, 31.4, 30.4, 28.2, 28.1, 24.2, 23.7; LC-MS: 490.16 $(M+Na)^+$; 506.18 $(M+K)^+$; Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99; Found: C, 64.05; H, 6.41; N, 9.15.

***General method for preparation of oxazinones* 27, 28, 40 *and* 41:**

(S)-tert-butyl 2-((2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 27:

Representative procedure: To a solution of the ester **25** (1 equiv) in methanol, $LiOH{\cdot}H_2O$ (3 equiv) in water was added and stirred for 12 h. The solvent was evaporated under reduced pressure and the residue was neutralized with the addition of dilute HCl, filtered and washed repeatedly with water. The precipitate (free carboxylic acid) was then dried over P_2O_5 and was carried forward for the next reaction, without any further purification.

To a solution containing the crude acid in dry DCM, EDC.HCl (1.1 equiv) was added followed by the addition of HOBt (0.2 equiv) and stirred for 10 minutes. It was then diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solutions. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography yielding the product **27**.

The product **27** was obtained as a white solid (3.07 g, 94%). mp: 107-109 °C; $[\alpha]^{24}_D$: +11° (*c* = 1.06, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3240, 1768, 1693, 1681, 1606, 1573, 1519, 759; ^1H NMR (200 MHz, $CDCl_3$) δ: 12.06 (s, 1H), 8.92 (d, *J* = 8.08 Hz, 1H), 8.27 (d, *J* = 7.83 Hz, 2H), 8.08 (d, *J* = 7.33 Hz, 1H), 7.96 (t, *J* = 7.07 Hz, 1H), 7.61 (t, *J* = 7.96 Hz, 2H), 7.25 (t, *J* = 7.71 Hz, 1H), 4.53-4.35 (m,

1H), 3.73-3.53 (m, 2H), 2.45-2.32 (m, 1H), 2.20-2.04 (m, 1H), 1.94-1.87 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 158.3, 157.0, 155.0, 145.5, 139.6, 137.0, 133.8, 129.7, 128.8, 128.5, 127.2, 123.1, 120.8, 116.5, 115.8, 80.6, 62.9, 47.58, 31.8, 28.1, 24.1; ESI-MS: 436.7123 $(M+H)^+$; 458.3249 $(M+Na)^+$; Anal. Calcd. for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65; Found: C, 65.00; H, 5.95; N, 9.81.

(R)-tert-butyl 2-((2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 28:

The compound **28** was obtained from **26**, following the procedure for **27**. White solid (1.60 g, 93%). mp: 115-117 °C; $[\alpha]^{24}_D$: -4° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3242, 3018, 1767, 1686, 1606, 1216, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.06 (s, 1H), 8.91 (d, *J* = 8.08 Hz, 1H), 8.26 (d, *J* = 7.71 Hz, 2H), 8.07 (d, *J* = 6.57 Hz, 1H), 7.96 (t, *J* = 6.95 Hz, 1H), 7.60 (t, *J* = 7.96 Hz, 2H), 7.24 (t, *J* = 7.71 Hz, 1H), 4.53-4.38 (m, 1H), 3.73-3.70 $_{\text{rotamer}}$ (m, 0.8H), 3.64-3.52 (m, 1.2H), 2.48-2.26 (m, 1H), 2.20-2.04 (m, 1H), 1.94-1.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 158.3, 157.0, 155.0, 145.5, 139.5, 137.0, 133.7, 129.6, 128.7, 128.5, 127.1, 123.1, 120.8, 116.5, 115.8, 80.6, 62.9, 47.58, 31.8, 28.1, 24.1; LC-MS: 458.15 $(M+Na)^+$; 490.19 $(M+K)^+$; Anal. Calcd. for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65; Found: C, 66.36; H, 5.92; N, 9.47.

***General method for the ring opening of oxazinone* (27, 28, 40 *and* 41) *with proline amines* [H-^{L}Pro-CO_2Me *for* 29a; H-^{L}Pro-$CONHC_6H_4$(4-Br) *for* 30a, 33a; H-^{D}Pro-CO_2Bn *for* 31a, 43a, 45a; H-^{D}Pro-$CONHC_6H_4$(4-Br) *for* 32a, 34a and H-^{L}Pro-CO_2Bn *for* 42a, 44a]: *Synthesis of* 29a-34a *and* 42a-45a:**

(S)-tert-butyl 2-((2-((2-((S)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 29a:

Representative procedure: To a solution of oxazinone **27** (1 equiv) in dry DMF, amine (1 equiv) was added followed by the addition of 4Å molecular sieves (0.2 g) and DBU (1 equiv). The reaction mixture was stirred at room temperature for 2 h and quenched with saturated $KHSO_4$ solution. The organic layer was repeatedly washed with water, brine solution and dried over anhydrous Na_2SO_4. It was then evaporated under reduced pressure to obtain the crude product which was purified by column chromatography to yield **29a**.

The product **29a** was obtained as a colourless fluffy liquid (1.02 g, 66%). $[\alpha]^{24}_{D}$: -100° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 1747, 1734, 1697, 1683, 1585, 1539, 1521, 1508, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.72 (s, 0.6H), $11.66_{rotamer}$ (s, 0.4H), 10.42 (s, 0.6H), $10.27_{rotamer}$ (s, 0.4H), 8.71 (d, *J* = 8.33 Hz, 1H), 8.56-8.50 (m, 1H), 7.75-7.65 (m, 1H), 7.55-7.41 (m, 3H), 7.20-7.12 (m, 2H), 4.71-4.67 (m, 1H), $4.46\text{-}4.41_{rotamer}$ (m, 0.4H), $4.31\text{-}4.25_{rotamer}$ (m, 0.6H), 3.72 (s, 1.7H), $3.70_{rotamer}$ (s, 1.3H), 3.65-3.40 (m, 4H), 2.33-1.90 (m, 8H), $1.45_{rotamer}$ (s, 3H), 1.33 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.0, 166.9, 139.8, 136.9, 132.9, 131.5, 131.0, 127.5, 127.3, 123.2, 123.0, 122.1, 120.9, 120.3, 80.0, 59.2, 52.3, 50.5, 50.4, 46.7, 31.4, 29.1, 28.2, 25.2, 24.2, 23.7; ESI-MS: 587.7821 $(M+Na)^+$; 603.7756 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{36}N_4O_7$: C, 63.82; H, 6.43; N, 9.92; Found: C, 64.01; H, 6.49; N, 10.05.

General method for the pivolyl protection: Synthesis of* 29b-34b *and* 42b-45b*:

(S)-methyl 1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxylate 29b:

Representative procedure: **29a** was subjected to ^{t}Boc deprotection using TFA to obtain its free amine. To a solution of amine, Et_3N (1.5 equiv) was added followed by the addition of Piv-Cl (1.5 equiv). The reaction mixture was stirred for 5 h and diluted with DCM. It was then washed sequentially with dilute HCl solution, brine, saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was purified by column chromatography affording **29b**.

The product **29b** was obtained as a white solid (0.45 g, 85%). mp: 67-69 °C; $[\alpha]^{24}_{D}$: -41° (*c* = 1.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3321, 1745, 1681, 1622, 1531, 1518, 1415, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.30 (s, 1H), 10.29 (s, 1H), 8.64 (d, *J* = 7.96 Hz, 1H), 8.38 (d, *J* = 8.08 Hz, 1H), 7.70 (dd, *J* = 1.26 Hz, 7.95 Hz, 1H), 7.49-7.40 (m, 3H), 7.18-7.05 (m, 2H), 4.69-4.55 (m, 2H), 3.97-3.72 (m, 2H), 3.67 (s, 3H), 3.62-3.45 (m, 2H), 2.37-1.90 (m, 8H), 1.27 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.2, 172.1, 171.4, 168.8, 167.0, 139.7, 136.6, 132.6, 130.9, 127.4, 127.1, 124.3, 123.2, 122.8, 122.1, 121.3, 120.5, 63.9, 59.1, 52.1, 50.3, 48.4, 38.9, 29.0, 28.7, 27.3, 25.5, 25.0; ESI-MS: 549.5628 $(M+H)^+$;

571.5337 $(M+Na)^+$; 587.5027 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21; Found: C, 65.79; H, 6.45; N, 10.40.

***General method for C-terminal amidation: Synthesis of* 29c, 31c *and* 42c-45c:**

(S)-N-methyl-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxamide 29c:

Representative procedure: The ester **29b** was taken in saturated methanolic methylamine solution and stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to yield pure **29c**.

The product **29c** was obtained as a white solid (0.28 g, 93%). mp: 83-85 °C; $[\alpha]^{24}_D$: -72° (*c* = 1.02, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3321, 1666, 1651, 1519, 1514, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.20 (s, 1H), 10.37 (s, 1H), 8.56 (d, *J* = 8.34 Hz, 1H), 8.14 (d, *J* = 8.08 Hz, 1H), 7.72 (dd, *J* = 1.01 Hz, 7.84 Hz, 1H), 7.49-7.33 (m, 3H), 7.17-7.04 (m, 2H), 6.89-6.86 (d, *J* = 4.80 Hz, 1H), 4.59-4.49 (m, 2H), 3.94-3.57 (m, 4H), 2.73-2.69 (m, 3H), 2.21-1.89 (m, 8H), 1.26 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.2, 171.7, 171.2, 169.8, 169.3, 167.2, 139.3, 135.9, 134.6, 132.5, 130.7, 129.7, 128.0, 127.5, 127.4, 125.7, 123.6, 122.9, 122.7, 121.2, 120.5, 63.8, 60.3, 50.6, 48.4, 38.8, 28.8, 28.6, 27.2, 26.6, 26.0, 25.1; ESI-MS: 548.5326 $(M+H)^+$; 570.5035 $(M+Na)^+$; 586.4995 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{37}N_5O_5$: C, 65.79; H, 6.81; N, 12.79; Found: C, 65.97; H, 7.01; N, 12.64.

(S)-tert-butyl 2-((2-((2-((S)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 30a:

The product **30a** was obtained from **27**, following the procedure for **29a**, as a white solid (0.42 g, 87%). mp: 224-225 °C; $[\alpha]^{24}_D$: -210° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3269, 1693, 1681, 1672, 1587, 1537, 1519, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.55 (s, 0.5H), $11.49_{rotamer}$ (s, 0.5H), 10.06 (s, 1H), 9.32 (s, 1H), 8.66 (q, 1H), 8.42 (d, *J* = 8.21 Hz, 0.5H), $8.22_{rotamer}$ (d, *J* = 8.46 Hz, 0.5H), 7.72 (d, *J* = 6.57 Hz, 1H), 7.51-7.18 (m, 8H), 6.90-6.76 (m, 1H), 4.75 (t, *J* = 5.68 Hz, 1H), $4.40\text{-}4.35_{rotamer}$ (m, 0.45H), 4.30-4.23 (m, 0.55H), 3.76-3.36 (m, 4H), 2.31-1.81 (m, 8H), $1.41_{rotamer}$ (s, 4H), 1.31 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 171.4, 169.6, 169.4, 169.3, 169.3, 167.4, 167.1, 154.8, 154.1, 139.4, 139.3,

137.0, 136.0, 135.7, 132.7, 132.6, 131.4, 130.8, 127.6, 127.2, 126.0, 124.8, 123.9, 123.7, 123.0, 122.4, 121.1, 120.9, 120.4, 116.3, 80.0, 79.9, 62.4, 61.7, 60.9, 50.7, 47.0, 46.6, 31.3, 30.4, 28.9, 28.8, 28.7, 28.2, 28.1, 25.0, 24.1, 23.6; ESI-MS: 726.3931 $(M+Na)^+$; 728.3964 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.82; H, 5.38; N, 10.07.

(S)-N-(4-bromophenyl)-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 30b:

The product **30b** was obtained from **30a**, following the procedure for **29b**, was obtained as a white solid (0.27 g, 79%). mp: 115-117 °C; $[\alpha]^{24}_D$: -169° (*c* = 0.66, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3275, 1697, 1687, 1681, 1602, 1591, 1537, 1519, 759; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.24 (s, 1H), 10.18 (s, 1H), 9.33 (s, 1H), 8.55 (d, *J* = 8.54 Hz, 1H), 8.07 (d, *J* = 6.71 Hz, 1H), 7.70 (d, *J* = 7.63 Hz, 1H), 7.44-7.41 (m, 2H), 7.39-7.33 (m, 3H), 7.29-7.27 (m, 2H), 7.19 (t, *J* = 7.63 Hz, 1H), 6.87 (t, *J* = 7.02 Hz, 1H), 4.75 (t, *J* = 6.41 Hz, 1H), 4.56-4.54 (m, 1H), 3.94-3.89 (m, 1H), 3.81-3.77 (m, 1H), 3.63-3.62 (m, 2H), 2.22-2.08 (m, 3H), 2.07-1.98 (m, 2H), 1.97-1.92 (m, 2H), 1.88-1.83 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.4, 171.2, 169.8, 169.3, 167.5, 162.5, 139.5, 137.1, 135.8, 132.7, 131.6, 130.9, 127.4, 127.4, 126.2, 124.0, 123.2, 122.9, 121.4, 121.2, 120.4, 116.4, 63.9, 61.1, 50.9, 48.6, 38.9, 28.7, 28.6, 28.5, 27.4, 25.7, 25.2; ESI-MS: 710.4007 $(M+Na)^+$; 712.4042 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.96; H, 5.39; N, 10.29.

(S)-tert-butyl 2-((2-((2-((R)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 31a:

The product **31a** was obtained from **27**, following the procedure for **29a**, as a colourless liquid (1.01 g, 81%). $[\alpha]^{24}_D$: +25° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3308, 3016, 2980, 1741, 1691, 1625, 1584, 1216, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ: $11.76_{rotamer}$ (s, 0.4H), 11.74 (s, 0.6H), 10.41 (s, 0.6H), $10.37_{rotamer}$ (s, 0.4H), $8.76_{rotamer}$ (d, *J* = 8.55 Hz, 0.3H), 8.72 (d, *J* = 8.24 Hz, 0.7H), 8.58-8.55 (m, 1H), 7.77 (d, *J* = 7.93 Hz, 0.6H), $7.72_{rotamer}$ (d, *J* = 7.93 Hz, 0.4H), 7.55-7.47 (m, 4H), 7.36-7.32 (m, 5H), 7.18 (d, *J* = 7.63 Hz, 1H), 7.09 (d, *J* = 7.63 Hz, 1H), 5.25-5.17 (m, 2H), 4.76-4.74 (m, 1H), $4.46\text{-}4.44_{rotamer}$ (m, 0.4H), 4.30-4.27 (m, 0.6H), 3.88-3.74 (m, 1H), 3.64 (m, 1.6H), 3.61-3.56 (m, 1H), $3.50\text{-}3.44_{rotamer}$ (m,

0.4H), 2.38-2.25 (m, 2H), 2.23-2.13 (m, 2H), 2.07-1.96 (m, 2H), 1.95-1.91 (m, 1.6H), 1.82-1.74 (m, 0.4H), $1.42_{rotamer}$ (s, 4H), 1.33 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 171.7, 171.6, 169.1, 169.0, 167.1, 167.0, 154.9, 154.1, 139.9, 136.9, 135.4, 132.9, 131.6, 131.1, 128.6, 128.3, 127.9, 127.4, 123.2, 123.0, 122.2, 121.0, 120.8, 120.2, 80.0, 79.8, 66.8, 62.6, 62.6, 62.0, 59.4, 59.3, 50.5, 47.0, 46.7, 31.5, 30.5, 29.1, 28.3, 28.2, 25.2, 25.1, 24.2, 23.7; LC-MS: 663.23 $(M+Na)^+$; 679.30 $(M+K)^+$; Anal. Calcd. for $C_{36}H_{40}N_4O_7$: C, 67.48; H, 6.29; N, 8.74; Found: C, 67.66; H, 6.10; N, 8.89.

(R)-benzyl 1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxylate 31b:

The product **31b** was obtained from **31a**, following the procedure for **29b**, as a colourless liquid (0.51 g, 81%). $[\alpha]^{24}_D$: +8° (*c* = 1.19, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3306, 3013, 1742, 1660, 1548, 1448, 1216, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.42 (s, 1H), 10.35 (s, 1H), 8.72 (d, *J* = 8.34 Hz, 1H), 8.48 (d, *J* = 8.46 Hz, 1H), 7.22 (d, *J* = 7.58 Hz, 1H), 7.52-7.42 (m, 3H), 7.34 (s, 5H), 7.19 (t, *J* = 7.71 Hz, 1H), 7.09 (t, *J* = 7.71 Hz, 1H), 5.17 (s, 2H), 4.78-4.71 (m, 1H), 4.65-4.60 (m, 1H), 4.02-3.92 (m, 1H), 3.86-3.76 (m, 1H), 3.71-3.55 (m, 2H), 2.40-2.22 (m, 1H), 2.18-1.88 (m, 7H), 1.29 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.5, 168.9, 167.0, 139.9, 136.8, 135.4, 132.7, 131.0, 128.5, 128.2, 127.9, 127.5, 127.1, 124.0, 123.1, 122.8, 122.0, 121.3, 120.2, 66.8, 64.1, 59.2, 50.4, 48.4, 39.0, 29.0, 27.4, 25.5, 25.1; LC-MS: 625.34 $(M+H)^+$; 647.34 $(M+Na)^+$; 663.33 $(M+K)^+$; Anal. Calcd. for $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8.97; Found: C, 69.40; H, 6.29; N, 9.13.

(R)-N-methyl-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxamide 31c:

The product **31c** was obtained from **31b,** following the procedure for **29c**, as a white solid (0.32 g, 91%). mp: 115-117 °C; $[\alpha]^{24}_D$: +110° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3326, 3017, 1660, 1610, 1592, 1520, 1216, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.64 (s, 1H), 10.24 (s, 1H), 8.37 (d, *J* = 8.55 Hz, 1H), 7.94 (d, *J* = 7.63 Hz, 1H), 7.67 (d, *J* = 7.63 Hz, 1H), 7.47-7.44 (m, 2H), 7.42 (d, *J* = 7.93 Hz, 1H), 7.20 (t, *J* = 7.63 Hz, 1H), 7.15 (t, *J* = 7.63 Hz, 1H), 6.90 (bs, 1H), 4.60-4.58 (m, 1H), 4.51-4.49 (m, 1H), 3.87-3.83 (m, 1H), 3.76-3.68 (m, 2H), 3.64-3.59

(m, 1H), 2.46 (d, *J* = 4.27 Hz, 3H), 2.26-2.10 (m, 5H), 2.07-2.03 (m, 1H), 2.01-1.94 (m, 1H), 1.92-1.83 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.0, 171.7, 171.6, 169.6, 167.7, 138.1, 136.0, 132.3, 130.7, 127.8, 127.3, 124.0, 123.5, 122.9, 122.6, 63.8, 60.6, 50.4, 48.5, 38.8, 29.0, 28.6, 27.2, 24.9 ; LC-MS: 625.34 $(M+H)^+$; 647.34 $(M+Na)^+$; 663.33 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{37}N_5O_5$: C, 65.79; H, 6.81; N, 12.79; Found: C, 35.62; H, 7.00; N, 12.85.

(S)-tert-butyl 2-((2-((2-((R)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 32a:

The product **32a** was obtained from **27**, following the procedure for **29a**, as a white solid (0.55 g, 85%). mp: 229-231 °C; $[\alpha]^{24}_D$: +54° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3315, 1693, 1681, 1585, 1519, 1514, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.60-11.37 (m, 1H), $10.24_{rotamer}$ (s, 0.1H), 10.13 (s, 0.9H), 9.28 (s, 0.9H), $9.10_{rotamer}$ (s, 0.1H), 8.66-8.59 (m, 1H), 8.26 (d, *J* = 7.96 Hz, 1H), 7.75-7.62 (m, 1H), 7.51-7.14 (m, 8H), 6.95-6.81 (m, 1H), 4.77-4.74 (m, 1H), $4.43-4.38_{rotamer}$ (m, 0.4H), 4.28-4.24 (m, 0.6H), 3.73-3.35 (m, 4H), 2.35-1.88 (m, 8H), $1.47_{rotamer}$ (s, 2H), $1.34_{rotamer}$ (s, 3H), 1.27 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 171.7, 169.6, 169.4, 167.3, 167.3, 154.8, 154.0, 139.3, 139.0, 136.9, 136.1, 135.8, 132.8, 132.5, 131.4, 131.2, 130.9, 127.5, 127.4, 127.2, 125.2, 123.7, 123.1, 122.9, 122.7, 121.3, 121.0, 120.9, 120.4, 116.5, 80.0, 79.8, 62.4, 61.8, 61.0, 58.8, 50.7, 47.0, 46.8, 46.6, 31.3, 30.4, 28.8, 28.3, 28.1, 24.9, 24.2, 23.65; ESI-MS: 726.4358 $(M+Na)^+$; 728.4542 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.54; H, 5.49; N, 9.81.

(R)-N-(4-bromophenyl)-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 32b:

The product **32b** was obtained from **32a**, following the procedure for **29b**, as a white solid (0.29 g, 75%). mp: 169-171 °C; $[\alpha]^{24}_D$: +121° (*c* = 0.7, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3308, 1697, 1681, 1614, 1539, 1519, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.78 (s, 1H), 10.12 (s, 1H), 9.22 (s, 1H), 8.50 (d, *J* = 8.24 Hz, 1H), 8.08 (d, *J* = 7.93 Hz, 1H), 7.57 (d, *J* = 7.63 Hz, 1H), 7.43 (t, *J* = 7.93 Hz, 1H), 7.39 (t, *J* = 7.93 Hz, 1H), 7.27 (d, *J* = 8.54 Hz, 2H), 7.20 (t, *J* = 8.54 Hz, 1H), 7.17 (t, *J* = 7.63 Hz, 1H), 6.94 (t, *J* = 7.63 Hz, 1H), 4.75-4.73 (m, 1H),

4.62-4.59 (m, 1H), 3.92-3.87 (m, 1H), 3.80-3.75 (m, 1H), 3.69-3.64 (m, 1H), 3.59-3.55 (m, 1H), 2.28-2.23 (m, 1H), 2.21-2.16 (m, 2H), 2.13-2.10 (m, 1H), 2.06-1.99 (m, 2H), 1.97-1.92 (m, 1H), 1.88-1.83 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.3, 171.6, 169.8, 169.3, 167.7, 138.7, 136.9, 135.9, 132.3, 131.4, 130.9, 127.4, 125.7, 123.8, 123.1, 121.7, 121.5, 116.4, 63.9, 61.1, 50.7, 48.5, 38.9, 28.7, 27.3, 25.7, 25.0; ESI-MS: 710.5039 $(M+Na)^+$; 712.4886 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.89; H, 5.63; N, 10.33.

(R)-tert-butyl 2-((2-((2-((S)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 33a:

The product **33a** was obtained from **28**, following the procedure for **29a**, as a white solid (0.60 g, 83%). mp: 230-232 °C; $[\alpha]^{24}_D$: -78° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3317, 1691, 1624, 1584, 1410, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $11.58_{rotamer}$ (s, 0.1H), 11.46 (s, 0.5H), $11.31_{rotamer}$ (s, 0.4H), 10.11 (s, 1H), 9.13-8.98 (m, 1H), 8.66 (t, *J* = 7.45 Hz, 1H), 8.30 (d, *J* = 8.34 Hz, 1H), 7.73-7.57 (m, 1H), 7.48-7.42 (m, 3H), 7.36-7.13 (m, 5H), 6.99-6.85 (m, 1H), 4.80-4.76 (m, 1H), 4.47-4.37 (m, 0.6H), $4.28\text{-}4.22_{rotamer}$ (m, 0.4H), 3.71-3.39 (m, 4H), 2.29-1.90 (m, 8H), $1.38_{rotamer}$ (s, 1H), $1.34_{rotamer}$ (s, 4H), 1.28 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.8, 169.9, 169.2, 167.3, 154.8, 154.1, 139.4, 139.0, 136.9, 136.3, 136.0, 132.9, 132.6, 131.5, 131.2, 127.4, 125.0, 123.7, 123.1, 122.7, 122.5, 121.3, 120.4, 116.5, 80.0, 79.8, 64.3, 62.5, 61.8, 61.0, 50.7, 47.0, 46.7, 31.4, 30.5, 28.3, 28.1, 25.0, 24.2, 23.6; LC-MS: 726.31 $(M+Na)^+$; 728.32 $(M+2+Na)^+$; 742.28 $(M+K)^+$; 744.25 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.48; H, 5.31; N, 10.08.

(S)-N-(4-bromophenyl)-1-(2-(2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 33b:

The product **33b** was obtained from **33a**, following the procedure for **29b**, as a white solid (0.28 g, 72%). mp: 140-142 °C; $[\alpha]^{24}_D$: -128° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3279, 3018, 1669, 1614, 1588, 1520, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.82 (s, 1H), 10.14 (s, 1H), 9.31 (s, 1H), 8.52 (d, *J* = 8.34 Hz, 1H), 8.09 (d, *J* = 8.21 Hz, 1H), 7.58 (d, *J* = 7.45 Hz, 1H), 7.43-7.29 (m, 4H),

7.25-7.10 (m, 4H), 6.93 (t, *J* = 7.45 Hz, 1H), 4.75-4.68 (t, *J* = 6.69 Hz, 1H), 4.63-4.57 (m, 1H), 3.94-3.71 (m, 2H), 3.68-3.48 (m, 2H), 2.21-1.78 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.3, 171.5, 169.4, 167.6, 162.4, 138.8, 137.0, 135.8, 132.2, 131.3, 130.8, 127.3, 125.7, 123.7, 123.0, 122.8, 121.5, 121.4, 116.3, 63.9, 61.1, 50.6, 48.5, 38.9, 31.3, 28.9, 28.8, 25.6, 24.9; LC-MS: 710.30 $(M+Na)^+$; 712.30 $(M+2+Na)^+$; 726.30 $(M+K)^+$; 728.29 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.93; H, 5.69; N, 9.99.

(R)-tert-butyl 2-((2-((2-((R)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 34a:

The product **34a** was obtained from **28**, following the procedure for **29a**, as a white solid (0.47 g, 84%). mp: 223-225 °C; $[\alpha]^{24}_D$: +214° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3267, 3019, 1685, 1586, 1522, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.56 (s, 0.5H), $11.44_{rotamer}$ (s, 0.5H), 10.10 (s, 1H), 9.21 (s, 1H), 8.68 (t, *J* = 8.72 Hz, 1H), 8.44 (d, *J* = 8.34 Hz, 0.5H), $8.26_{rotamer}$ (d, *J* = 8.21 Hz, 0.5H), 7.72 (d, *J* = 7.83 Hz, 1H), 7.53-7.42 (m, 3H), 7.33-7.29 (m, 4H), 7.22 (t, *J* = 7.83 Hz, 1H), 6.95-6.84 (m, 1H), 4.81 (dd, *J* = 5.56, 7.07 Hz, 1H), $4.43\text{-}4.36_{rotamer}$ (m, 0.4H), 4.30-4.24 (m, 0.6H), 3.77-3.77 (m, 4H), 2.37-2.02 (m, 5H), 1.96-1.75 (m, 3H), $1.42_{rotamer}$ (s, 4H), 1.32 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.5, 169.9, 169.7, 169.2, 169.1, 167.4, 167.1, 162.5, 154.8, 154.0, 139.6, 137.0, 136.2, 136.0, 132.9, 136.0, 132.9, 132.7, 131.5, 130.9, 127.4, 127.4, 125.7, 124.5, 123.8, 123.6, 123.0, 122.4, 121.2, 121.0, 120.6, 120.4, 116.4, 80.8, 79.9, 62.5, 61.79, 60.9, 50.9, 47.0, 46.7, 31.3, 30.5, 28.3, 28.1, 25.1, 24.2, 23.7; LC-MS: 726.30 $(M+Na)^+$; 728.30 $(M+2+Na)^+$; 742.31 $(M+K)^+$; 744.31 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.84; H, 5.25; N, 10.12.

(R)-N-(4-bromophenyl)-1-(2-(2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 34b:

The product **34b** was obtained from **34a**, following the procedure for **29b**, as a white solid (0.26 g, 76%). mp: 226-228 °C; $[\alpha]^{24}_D$: +156° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3271, 2976, 1684, 1659, 1602, 1415, 1300, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.27 (s, 1H), 10.19 (s, 1H), 9.40 (s, 1H), 8.55 (d, *J* = 8.34 Hz, 1H), 8.06 (d, *J* = 8.46 Hz, 1H), 7.71 (d, *J* = 7.45 Hz, 1H), 7.45-7.36 (m, 2H),

7.31-7.24 (m, 4H), 7.21 (t, *J* = 8.08 Hz, 1H), 6.86 (t, *J* = 7.45 Hz, 1H), 4.74 (t, *J* = 6.69 Hz, 1H), 4.56-4.52 (m, 1H), 3.95-3.73 (m, 2H), 3.65 (t, *J* = 6.1 Hz, 2H), 2.13-1.79 (m, 8H), 1.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.1, 169.5, 167.5, 139.5, 137.1, 135.6, 132.6, 131.4, 130.8, 127.4, 127.3, 126.4, 124.0, 123.1, 122.9, 121.3, 121.1, 120.2, 116.3, 63.9, 61.1, 50.8, 48.5, 38.9, 28.9, 28.7, 27.3, 25.6, 25.1; LC-MS: 710.32 $(M+Na)^+$; 712.34 $(M+2+Na)^+$; 726.29 $(M+K)^+$; 728.30 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 59.89; H, 5.69; N, 9.99.

2-azido-5-iodobenzoic acid 35a:

To a solution of 2-amino-5-iodobenzoic acid (6 g, 22.9 mmol, 1 equiv) in concentrated hydrochloric acid (60 ml) and water (60 ml) was added drop wise a solution of sodium nitrite (1.65 g, 24.0 mmol, 1.05 equiv) in water (30 ml) at a rate such that the temperature of the reaction mixture remained below 5 ^{0}C. After completion of nitrite addition the diazonium solution was filtered (cold sinter) and added drop wise to a solution of sodium azide (1.56 g, 24.0 mmol, 1.05 equiv) and sodium acetate (46.94 g, 572.5 mmol, 25 equiv) in water (60 ml). The yellow solution was stirred for 24 h at room temperature, and then acidified by the addition of concentrated hydrochloric acid to give 2-azido-5-iodobenzoic acid **35a.** The light yellow crystalline solid was filtered through whatmann filter paper and washed several times with water and dried overnight over P_2O_5. Acid which was identified by spectral means and used with out further purification. Yield (6.09 g, 92%); mp: 129-131 °C; IR ($CHCl_3$) ν (cm^{-1}): 3434, 3020, 2120, 1701, 1478, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 2.15 Hz, 1H), 7.92 (dd, *J* = 2.15, 8.46 Hz, 1H), 7.19 (d, *J* = 8.46 Hz, 1H), 3.56 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.3, 141.3, 139.2, 138.9, 126.0, 123.0, 88.9; ESI-MS: 312.2410 $(M+Na)^+$; 328.1911 $(M+K)^+$; Anal. Calcd. for $C_7H_4IN_3O_2$: C, 29.09; H, 1.39; N, 14.54; Found: C, 29.28; H, 1.45; N, 14.45.

Methyl 2-amino-5-iodobenzoate 36:

To a mixture of methyl 2-aminobenzoate (2.5 g, 16.5 mmol, 1 equiv), sodium periodate (3.54 g, 16.5 mmol, 1 equiv) and sodium chloride (1.92 g, 33.1 mmol, 2 equiv) in 120 ml of AcOH:H_2O (9:1) was added potassium iodide (2.74 g, 16.5 mmol, 1 equiv) slowly so that the temperature of the reaction mixture did

not exceed 50 ^{0}C. the reaction mixture was stirred at room temperature for 8 h then poured over ice-cold water. The solid was extracted with dichloromethane, washed sequentially twice with water, saturated $NaHCO_3$, $Na_2S_2O_3$ and saturated brine solution. The organic layer was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to get the crude products, and then purified by column chromatography. (eluent: pet ether/ethyl acetate: 95:5, Rf 0.4) yielded **36** as a white solid (4.37 g, 95%). mp: 81-83 °C; IR ($CHCl_3$) ν (cm^{-1}): 3498, 3379, 1693, 1606, 1294, 1242, 1215, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 2.27 Hz, 1H), 7.51 (dd, *J* = 2.15, 8.72 Hz, 1H), 6.48 (d, *J* = 8.72 Hz, 1H), 5.78 (bs, 2H), 3.87 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.2, 149.7, 142.0, 139.3, 118.6, 112.6, 75.7, 51.6; ESI-MS: 299.3573 $(M+Na)^+$; Anal. Calcd. for $C_8H_8INO_2$: C, 34.68; H, 2.91; N, 5.06; Found: C, 34.75; H, 2.82; N, 5.21.

methyl 2-(2-azido-5-iodobenzamido)-5-iodobenzoate 37a:

A solution of 2-azido-5-iodobenzoic acid **35a** (4.00 g, 13.8 mmol, 1 equiv) and DMF (0.1 mL, 1.3 mmol, 0.1 equiv) in dry DCM (40 mL) was stirred and cooled in an ice bath. Oxalyl chloride (1.32 mL, 15.2 mmol, 1.1 equiv) was added dropwise to the mixture, after the addition the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated in vacuum to obtain the acid chloride as yellow oil. A solution of methyl 2-amino-5-iodobenzoate **36** (3.83 g, 13.8 mmol, 1 equiv) and pyridine (2.23 mL, 27.6 mmol, 2 equiv) in dry DCM (40 mL) was cooled in an ice bath with stirring. A solution of 2-azido-5-iodobenzoyl chloride in DCM (30 mL) was added dropwise for 15 min to the reaction mixture. The mixture was stirred at room temperature for an additional 5 h. The reaction mixture was siluted with DCM, and then washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuum to give crude product. The crude product was recrystallized from AcOEt and pet. ether to obtain the desired compound **37a** as a pale yellow powder (5.62 g, 74%). mp: 159-161 °C; IR ($CHCl_3$) ν (cm^{-1}): 3018, 2129, 1708, 1666, 1504, 769, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.81 (s, 1H), 8.64 (d, *J* = 8.96 Hz, 1H), 8.36 (d, *J* = 2.27 Hz, 1H), 8.25 (d, *J* = 2.14 Hz, 1H), 7.88 (dt, *J* = 2.28, 8.46 Hz, 2H), 7.03 (d, *J* = 8.46 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.8, 162.5, 142.9, 141.1, 140.3, 140.1, 139.3, 137.2, 128.4,

123.0, 120.8, 117.9, 88.3, 85.8, 52.6; ESI-MS: 571.0943 $(M+Na)^+$; Anal. Calcd. for $C_{15}H_{10}I_2N_4O_3$: C, 32.87; H, 1.84; N, 10.22; Found: C, 32.76; H, 1.97; N, 10.15.

Methyl 2-(2-amino-5-iodobenzamido)-5-iodobenzoate 37b:

To a solution of dipeptide **37a** (5.00 g, 9.1 mmol, 1 equiv) in acetonitrile (50 ml) were added $CeCl_3.7H_2O$ (5.10 g, 13.7 mmol, 1.5 equiv) and NaI (12.34 g, 82.2 mmol, 9 equiv),[71] and the resulting mixture was stirred at reflux temperature for 24 h. The solvent was stripped off under reduced pressure; residue was filtered through a sintered funnel and washed sequentially with saturated sodium thiosulphite solution to remove excess iodine and water and dried over night over P_2O_5. The amine **37b**, was used with out further purification (4.35 g, 91%). mp: 170-172 °C; IR ($CHCl_3$) ν (cm^{-1}): 3356, 3016, 2980, 1717, 1626, 1591, 1520, 1454, 1416, 1215, 1159, 1051, 1026; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.04 (s, 1H), 8.19 (d, *J* = 2.02 Hz, 1H), 8.10-8.05 (m, 1H), 7.98 (dd, *J* = 2.15, 8.84 Hz, 1H), 7.87 (dd, *J* = 1.89 Hz, 1H), 7.52 (dd, *J* = 1.90, 8.72 Hz, 1H), 6.68 (d, *J* = 8.71 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.6, 166.2, 149.9, 142.1, 140.8, 139.3, 138.6, 135.8, 124.0, 121.0, 119.7, 116.5, 87.0, 75.29, 52.9; ESI-MS: 425.21 $(M+H)^+$; 447. 23 $(M+Na)^+$; 463.24 $(M+K)^+$. Anal. Calcd. for $C_{15}H_{12}I_2N_2O_3$: C, 34.51; H, 2.32; N, 5.37. Found: C, 34.59; H, 2.20; N, 5.42.

(S)-tert-butyl 2-((4-iodo-2-((4-iodo-2-(methoxycarbonyl)phenyl)carbamoyl) phenyl)carbamoyl)pyrrolidine-1-carboxylate 38:

The product **38** was obtained from **37b**, following the procedure for **25**, as a white solid (2.26 g, 82%). mp: 129-131 °C; $[\alpha]^{24}_D$: -102° (*c* = 0.8, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2359, 1693, 1597, 1570, 1514, 1504, 1215, 767; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.95 (s, 0.6H), $11.90_{rotamer}$ (s, 0.4H), 11.51 (s, 1H), 8.59 (d, *J* = 8.97 Hz, 1H), 8.58 (t, *J* = 8.59 Hz, 1H), 8.39 (d, *J* = 2.14 Hz, 1H), 8.12-8.09 (m, 1H), 7.91-7.80 (m, 2H), $4.47\text{-}4.36_{rotamer}$ (m, 0.45H), 4.20-4.22 (m, 0.55H), 3.99 (s, 3H), 3.78-3.43 (m, 2H), 2.35-2.08 (m, 2H), 2.04-1.88 (m, 2H), $1.43_{rotamer}$ (s, 4H), 1.29 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 171.8, 167.5, 165.8, 153.9, 143.4, 142.9, 141.8, 140.3, 139.4, 135.7, 122.9, 122.4, 117.4, 117.2, 86.1, 85.8, 80.1, 62.5, 61.9, 52.9, 47.0, 46.7, 31.4, 30.3, 28.3, 28.1, 24.2, 23.7; ESI-MS:

742.4921 $(M+Na)^+$; 758.5517 $(M+K)^+$. Anal. Calcd. for $C_{25}H_{27}I_2N_3O_6$: C, 41.74; H, 3.78; N, 5.84; Found: C, 41.79; H, 3.84; N, 5.67.

(R)-tert-butyl 2-((4-iodo-2-((4-iodo-2-(methoxycarbonyl)phenyl)carbamoyl) phenyl)carbamoyl)pyrrolidine-1-carboxylate 39:

The product **39** was obtained from **37b**, following the procedure for **25**, as a white solid (2.17 g, 79%). mp: 108-110 °C; $[\alpha]^{24}_D$: +86° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3254, 1693, 1681, 1597, 1568, 1514, 1504, 1292, 759; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.95 (s, 0.55H), $11.90_{rotamer}$ (s, 0.45H), 11.52 (s, 1H), 8.59 (d, *J* = 8.97 Hz, 1H), 8.57 (t, *J* = 8.72 Hz, 1H), 8.39 (d, *J* = 2.15 Hz, 1H), 8.12-8.09 (m, 1H), 7.91-7.76 (m, 2H), $4.42\text{-}4.36_{rotamer}$ (m, 0.45H), 4.28-4.22 (m, 0.55H), 3.99 (s, 3H), 3.78-3.39 (m, 2H), 2.31-2.05 (m, 2H), 2.02-1.80 (m, 2H),$1.43_{rotamer}$ (s, 4H), 1.29 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.7, 167.5, 167.4, 165.9, 165.8, 154.8, 153.9, 143.4, 142.9, 141.8, 140.3, 139.4, 135.6, 122.9, 122.4, 117.2, 86.2, 85.8, 80.1, 62.5, 61.9, 52.9, 47.0, 46.7, 31.4, 30.3, 28.3, 28.1, 24.2, 23.7; ESI-MS: 742.3020 $(M+Na)^+$; Anal. Calcd for $C_{25}H_{27}I_2N_3O_6$: C, 41.74; H, 3.78; N, 5.84; Found: C, 41.62; H, 3.89; N, 5.93.

(S)-tert-butyl 2-((4-iodo-2-(6-iodo-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl) carbamoyl)pyrrolidine-1-carboxylate 40:

The product **40** was obtained from **38**, following the procedure for **27**, as a white solid (1.64 g, 96%). Mp: 285-287 °C; $[\alpha]^{24}_D$: +20° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 1768, 1687, 1681, 1608, 1597, 1504, 1215, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.82 (s, 1H), 8.67 (d, *J* = 8.46 Hz, 1H), 8.48 (d, *J* = 2.02 Hz, 1H), 8.41 (bs, 1H), 8.17-8.13 (m, 1H), 7.81-7.73 (m, 2H), 4.38-4.20 (m, 1H), 3.81-3.56 (m, 1H), 3.51-3.35 (m, 1H), 2.32-1.73 (m, 4H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.4, 156.4, 156.0, 155.0, 146.1, 144.5, 142.5, 139.2, 137.8, 137.1, 129.0, 122.5, 117.8, 117.2, 93.6, 85.8, 80.8, 62.9, 47.6, 31.7, 28.1, 24.1; ESI-MS: 710.6242 $(M+Na)^+$; Anal. Calcd. For $C_{24}H_{23}I_2N_3O_5$: C, 41.94; H, 3.37; N, 6.11; Found: C, 42.03; H, 3.19; N, 6.30.

(R)-tert-butyl 2-((4-iodo-2-(6-iodo-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl) carbamoyl)pyrrolidine-1-carboxylate 41:

The product **41** was obtained from **39**, following the procedure for **27**, as a white solid (1.60 g, 93%). mp: 282-284 °C; $[\alpha]^{24}_D$: -2° (*c* = 1, $CHCl_3$); IR ($CHCl_3$)

ν (cm^{-1}): 3080, 1776, 1681, 1608, 1573, 1556, 1504, 1386, 771; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.82 (s, 1H), 8.66 (d, *J* = 8.59 Hz, 1H), 8.47 (d, *J* = 2.02 Hz, 1H), 8.41 (bs, 1H), 8.17-8.13 (m, 1H), 7.81-7.73 (m, 2H), 4.40-4.25 (m, 1H), 3.81-3.61 (m, 1H), 3.51-3.39 (m, 1H), 2.47-2.20 (m, 1H), 2.09-1.81(m, 3H), 1.24 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.4, 156.3, 156.0, 155.0, 146.1, 144.4, 142.5, 139.2, 137.8, 137.1, 129.0, 122.5, 117.8, 117.2, 93.5, 85.9, 80.8, 62.9, 47.6, 31.7, 28.1, 24.1; ESI-MS: 710.1471 $(M+Na)^+$; Anal. Calcd. for $C_{24}H_{23}I_2N_3O_5$: C, 41.94; H, 3.37; N, 6.11; Found: C, 41.82; H, 3.42; N, 6.05.

(S)-tert-butyl 2-((2-((2-((S)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)-4-iodophenyl)carbamoyl)-4-iodophenyl)carbamoyl)pyrrolidine-1-carboxylate 42a:

The product **42a** was obtained from **40**, following the procedure for **29a**, as a white solid (0.76 g, 85%). mp: 105-107 °C; $[\alpha]^{24}_D$: -55° (*c* = 0.58, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2929, 1737, 1693, 1681, 1591, 1568, 1504, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.37 (s, 0.5H), $11.28_{rotamer}$ (s, 0.5H), 10.12 (s, 0.5H), $9.93_{rotamer}$ (s, 0.5H), 8.39 (d, *J* = 8.84 Hz, 1H), 7.92-7.80 (m, 2H), 7.71-7.53 (m, 3H), 7.24 (s, 5H), 5.16 (s, 2H), 4.70-4.67 (m, 1H), 4.36-4.14 (m, 1H), 3.68-3.33 (m, 4H), 2.26-1.87 (m, 8H), $1.31_{rotamer}$ (s, 2H), $1.22_{rotamer}$ (s, 2H), 1.18 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.7, 171.4, 166.0, 165.8, 153.9, 141.6, 139.1, 136.2, 135.5, 135.2, 128.5, 128.2, 128.0, 124.6, 124.3, 122.7, 122.1, 114.0, 87.2, 85.6, 80.1, 79.9, 67.3, 62.4, 59.2, 50.0, 47.0, 46.6, 29.5, 29.0, 28.1, 25.1, 24.2, 23.7, 22.5; ESI-MS: 915.4971 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_7$: C, 48.45; H, 4.29; N, 6.28; Found: C, 48.56; H, 4.07; N, 6.12.

(S)-benzyl 1-(5-iodo-2-(5-iodo-2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxylate 42b:

The product **42b** was obtained from **42a**, following the procedure for **29b**, as a white solid (0.46 g, 79%). mp: 127-129 °C; $[\alpha]^{24}_D$: -24° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2976, 1739, 1620, 1593, 1572, 1504, 1383, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.96 (s, 1H), 10.03 (s, 1H), 8.38 (d, *J* = 8.84 Hz, 1H), 7.97 (d, *J* = 1.90 Hz, 1H), 7.91 (d, *J* = 8.59 Hz, 1H), 7.74-7.68 (m, 3H), 7.33 (s, 5H), 5.23 (s, 2H), 4.77-4.71 (m, 1H), 4.55-4.49 (m, 1H), 3.89-3.74 (m, 2H), 3.62-3.56 (m, 2H), 2.36-1.92 (m, 8H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.3, 171.5,

166.9, 166.0, 141.3, 139.4, 138.9, 136.1, 135.7, 135.3, 135.2, 128.5, 128.2, 128.1, 128.0, 124.6, 123.3, 122.7, 87.3, 85.6, 67.3, 63.9, 59.1, 50.0, 48.4, 38.9, 29.5, 29.0, 28.6, 27.2, 25.7, 25.1; ESI-MS: 899.2200 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_6$: C, 49.33; H, 4.37; N, 6.39; Found: C, 49.55; H, 4.32; N, 6.60.

(S)-N-(4-iodo-2-((4-iodo-2-((S)-2-(methylcarbamoyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)-1-pivaloylpyrrolidine-2-carboxamide 42c:

The product **42c** was obtained from **42b**, following the procedure for **29c**, as a white solid (0.30 g, 94%). mp: 190-192 °C; $[\alpha]^{24}_D$: -38° (*c* = 1.18, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3334, 3019, 1674, 1614, 1505, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.47 (s, 1H), 10.44 (s, 1H), 8.40 (d, *J* = 8.84 Hz, 1H), 8.14 (s, 1H), 7.71 (s, 1H), 7.59-7.47 (m, 2H), 7.33-7.09 (m, 1H), 7.03 (bs, 1H), 4.72-4.65 (m, 1H), 4.42-4.42 (m, 1H), 3.83-3.77 (m, 2H), 3.61-3.61 (m, 2H), 2.77 (bs, 3H), 2.12-1.94 (m, 8H), 1.23 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.0, 171.7, 171.2, 167.7, 166.3, 141.1, 141.0, 139.7, 138.9, 136.4, 135.6, 133.9, 131.0, 128.1, 127.0, 126.7, 126.1, 122.8, 120.5, 88.6, 85.6, 64.6, 63.8, 60.6, 50.8, 48.3, 38.6, 29.8, 28.4, 27.1, 25.8, 25.2; LC-MS: 800.23 $(M+H)^+$; 822.25 $(M+Na)^+$; 838.20 $(M+K)^+$; Anal. Calcd for $C_{30}H_{35}I_2N_5O_5$: C, 45.07; H, 4.41; N, 8.76; Found: C, 44.89; H, 4.60; N, 8.76.

(S)-tert-butyl 2-((2-((2-((R)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)-4-iodophenyl)carbamoyl)-4-iodophenyl)carbamoyl)pyrrolidine-1-carboxylate 43a:

The product **43a** was obtained from **40**, following the procedure for **29a**, as a white solid (0.78 g, 87%). mp: 104-106 °C; $[\alpha]^{24}_D$: -30° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2980, 1714, 1687, 1591, 1568, 1504, 1384, 759; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.39 (s, 0.5H), $11.36_{rotamer}$ (s, 0.5H), 10.05 (s, 0.6H), $10.00_{rotamer}$ (s, 0.4H), 8.43 (d, *J* = 8.84 Hz, 1H), 8.13-8.01 (m, 1H), 7.94-7.90 (m, 1H), 7.71-7.68 (m, 3H), 7.30-7.21 (m, 5H), 5.20-5.19 (m, 2H), 4.72-4.62 (m, 1H), 4.34-$4.29_{rotamer}$ (m, 0.4H), 4.21-4.15 (m, 0.6H), 3.65-3.41 (m, 4H), 2.34-1.84 (m, 8H), $1.35_{rotamer}$ (s, 4H), 1.25 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.7, 171.2, 165.7, 153.9, 141.7, 140.9, 139.2, 135.9, 135.6, 135.2, 128.5, 128.3, 128.2, 128.0, 127.4, 126.8, 87.5, 87.1, 80.1, 79.9, 67.4, 65.0, 59.2, 50.1, 47.0, 46.6, 30.3,

29.0, 28.1, 25.0, 23.7; ESI-MS: 915.0897 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_7$: C, 48.45; H, 4.29; N, 6.28; Found: C, 48.52; H, 4.31; N, 6.37.

(R)-benzyl 1-(5-iodo-2-(5-iodo-2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxylate 43b:

The product **43b** was obtained from **43a**, following the procedure for **29b**, as a white solid (0.43 g, 73%). mp: 166-168 °C; $[\alpha]^{24}_D$: +14° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2978, 1747, 1681, 1622, 1591, 1568, 1504, 1217, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.09 (s, 1H), 10.02 (s, 1H), 8.46 (d, *J* = 8.97 Hz, 1H), 8.11 (d, *J* = 9.09 Hz, 1H), 7.95 (d, *J* = 1.89 Hz, 1H), 7.75-7.70 (m, 3H), 7.33 (s, 5H), 5.23 (s, 2H), 4.77-4.70 (m, 1H), 4.59-4.53 (m, 1H), 3.92-3.69 (m, 2H), 3.67-3.51 (m, 2H), 2.37-1.89 (m, 8H), 1.26 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.4, 171.3, 166.8, 165.9, 141.5, 139.5, 139.4, 135.8, 135.7, 135.6, 135.2, 128.5, 128.2, 128.0, 127.0, 124.0, 123.1, 122.2, 86.9, 85.4, 67.4, 64.0, 59.1, 50.0, 48.4, 38.9, 29.5, 29.0, 28.6, 27.3, 25.8, 25.0; ESI-MS: 899.0866 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_6$: C, 49.33; H, 4.37; N, 6.39; Found: C, 49.21; H, 4.21; N, 6.21.

(S)-N-(4-iodo-2-((4-iodo-2-((R)-2-(methylcarbamoyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)-1-pivaloylpyrrolidine-2-carboxamide 43c:

The product **43c** was obtained from **43b**, following the procedure for **29c**, as a white solid (0.21 g, 95%). mp: 162-164 °C; $[\alpha]^{24}_D$: +86° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3323, 1697, 1614, 1573, 1539, 1516, 1506, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.27 (s, 2H), 8.07-7.94 (m, 2H), 7.68-7.68 (m, 3H), 7.49 (d, *J* = 8.59 Hz, 1H), 7.03 (bs, 1H), 4.53 (bs, 1H), 4.45-4.40 (m, 1H), 3.88-3.42 (m, 4H), 2.40 (s, 3H), 2.27-1.76 (m, 8H), 1.16 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.0, 171.5, 171.4, 167.5, 166.6, 140.8, 139.3, 137.3, 136.8, 135.6, 134.9, 130.3, 126.2, 125.2, 124.4, 88.4, 86.4, 63.6, 60.8, 50.0, 48.5, 38.7, 29.5, 28.3, 27.1, 25.9, 24.7; ESI-MS: 822.0094 $(M+Na)^+$; Anal. Calcd. for $C_{30}H_{35}I_2N_5O_5$: C, 45.07; H, 4.41; N, 8.76; Found: C, 44.85; H, 4.33; N, 8.93.

General method for the ester saponification: Synthesis of* 43d *and* 44d*:

(R)-1-(5-iodo-2-(5-iodo-2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxylic acid 43d:

To a solution of **43b** (1 equiv) in methanol, $LiOH.H_2O$ (3 equiv) dissolved in water was added and the reaction mixture was stirred for 12 h. The solvent was

stripped off under reduced pressure and the product was partitioned between dichloromethane and water, repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product quantitatively, which was taken for the next reaction without further purification.

General method for the ^{t}Boc deprotection: Synthesis of* 43e *and* 44e*:

(R)-benzyl 1-(5-iodo-2-(5-iodo-2-((S)-pyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxylate 43e:

A solution containing the tetrapeptide **43a** in dichloromethane was subjected to Boc deprotection using DCM/TFA (50%). After completion of the reaction (1 h), the solvent was stripped off under reduced pressure and the residue was partitioned between dichloromethane and water, and repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product quantitatively, which was taken for the next reaction without further purification.

(R)-tert-butyl 2-((2-((2-((S)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)-4-iodophenyl)carbamoyl)-4-iodophenyl)carbamoyl)pyrrolidine-1-carboxylate 44a:

The product **44a** was obtained from **41**, following the procedure for **29a**, as a white solid (0.76 g, 84%). mp: 97-99 °C; $[\alpha]^{24}_D$: +30° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3292, 1741, 1693, 1591, 1568, 1504, 1384, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.36 (bs, 1H), 10.04 (s, 0.6H), 9.98$_{rotamer}$ (s, 0.4H), 8.41 (d, *J* = 8.84 Hz, 1H), 8.12-7.99 (m, 1H), 7.91-7.88 (m, 1H), 7.68-7.64 (m, 3H), 7.24 (s, 5H), 5.17 (s, 2H), 4.70-4.63 (m, 1H), 4.38-4.26$_{rotamer}$ (m, 0.4H), 4.18-4.12 (m, 0.6H), 3.69-3.34 (m, 4H), 2.36-1.82 (m, 8H), 1.33$_{rotamer}$ (s, 4H), 1.23 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.6, 171.2, 167.1, 165.7, 154.8, 153.9, 141.6, 139.8, 139.5, 139.2, 135.9, 135.8, 135.6, 135.2, 128.5, 128.2, 128.0, 124.4, 122.9, 122.7, 85.6, 80.1, 79.9, 67.4, 62.5, 59.2, 50.1, 46.9, 46.6, 31.3, 30.3, 29.0, 28.1, 25.0, 24.2, 23.7; ESI-MS: 915.4463 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_7$: C, 48.45; H, 4.29; N, 6.28; Found: C, 48.29; H, 4.45; N, 6.12.

(S)-benzyl 1-(5-iodo-2-(5-iodo-2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxylate 44b:

The product **44b** was obtained from **44a**, following the procedure for **29b**, as a white solid (0.40 g, 69%). mp: 162-164 °C; $[\alpha]^{24}_{D}$: -2° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3294, 1739, 1666, 1620, 1591, 1572, 1504, 765; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.02 (s, 1H), 9.94 (s, 1H), 8.40 (d, *J* = 8.85 Hz, 1H), 8.07 (d, *J* = 9.10 Hz, 1H), 7.89 (s, 1H), 7.69-7.65 (m, 3H), 7.27 (s, 5H), 5.17 (s, 2H), 4.70-4.64 (m, 1H), 4.51-4.48 (m, 1H), 3.89-3.642 (m, 2H), 3.61-3.42 (m, 2H), 2.36-1.77 (m, 8H), 1.20 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.4, 171.2, 166.8, 165.9, 141.5, 139.5, 139.3, 135.8, 135.7, 135.6, 135.2, 128.5, 128.2, 128.0, 127.1, 124.0, 123.1, 122.2, 86.9, 85.4, 67.4, 64.0, 59.1, 50.0, 48.4, 38.9, 29.5, 29.0, 28.7, 27.3, 25.6, 25.0; ESI-MS: 899.2367 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_6$: C, 49.33; H, 4.37; N, 6.39; Found: C, 49.41; H, 4.41; N, 6.18.

(R)-N-(4-iodo-2-((4-iodo-2-((S)-2-(methylcarbamoyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)-1-pivaloylpyrrolidine-2-carboxamide 44c:

The product **44c** was obtained from **44b**, following the procedure for **29c**, as a white solid (0.16 g, 91%). mp: 158-160 °C; $[\alpha]^{24}_{D}$: -79° (*c* = 1.06, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3319, 1714, 1666, 1620, 1504, 1384, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.24 (s, 1H), 10.20 (s, 1H), 8.03 (d, *J* = 8.72 Hz, 1H), 7.89 (s, 1H), 7.67-7.62 (m, 3H), 7.43 (d, *J* = 8.33 Hz, 1H), 6.89 (bs, 1H), 4.49-4.44 (m, 1H), 4.41-4.35 (m, 1H), 3.72-3.45 (m, 4H), 2.36 (d, *J* = 3.79 Hz, 3H), 2.10-1.86 (m, 8H), 1.12 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.0, 171.7, 171.3, 167.6, 166.6, 140.8, 139.3, 137.2, 136.8, 135.5, 134.9, 130.3, 126.2, 125.2, 124.4, 88.4, 86.4, 63.6, 60.8, 49.9, 48.5, 38.7, 29.5, 28.3, 27.1, 26.0, 24.7; ESI-MS: 822.3467 $(M+Na)^+$; Anal. Calcd. for $C_{30}H_{35}I_2N_5O_5$: C, 45.07; H, 4.41; N, 8.76; Found: C, 45.18; H, 4.49; N, 8.91.

(R)-tert-butyl 2-((2-((2-((R)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)-4-iodophenyl)carbamoyl)-4-iodophenyl)carbamoyl)pyrrolidine-1-carboxylate 45a:

The product **45a** was obtained from **41**, following the procedure for **29a**, as a white solid (0.70 g, 81%). mp: 75-77 °C; $[\alpha]^{24}_{D}$: +78° (*c* = 0.76, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3246, 1737, 1693, 1681, 1593, 1568, 1504, 1384, 758; ^{1}H NMR

(200 MHz, $CDCl_3$) δ: 11.38 (s, 0.5H), $11.30_{rotamer}$ (s, 0.5H), 10.15 (s, 0.6H), $9.97_{rotamer}$ (s, 0.4H), 8.39 (d, *J* = 8.84 Hz, 1H), 7.93 (s, 1H), 7.84-7.53 (m, 4H), 7.24 (s, 5H), 5.16 (s, 2H), 4.75-4.68 (m, 1H), $4.32\text{-}4.27_{rotamer}$ (s, 0.4H), 4.23-4.13 (s, 0.6H), 3.71-3.33 (m, 4H), 2.29-1.80 (m, 8H), $1.30_{rotamer}$ (s, 4H), 1.21 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.7, 171.3, 167.2, 167.0, 166.3, 166.0, 165.8, 154.7, 153.9, 141.6, 141.4, 139.7, 139.3, 139.3, 139.1, 136.2, 135.5, 135.4, 135.2, 130.2, 128.5, 128.4, 128.2, 127.9, 124.7, 124.4, 122.9, 122.7, 122.3, 122.1, 87.3, 85.7, 85.6, 80.1, 79.9, 67.3, 66.8, 62.4, 61.8, 59.1, 50.0, 49.8, 46.9, 46.6, 31.3, 30.3, 29.5, 29.1, 28.8, 28.2, 28.1, 25.1, 25.0, 24.2, 23.6, 22.8; ESI-MS: 915.4535 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_7$: C, 48.45; H, 4.29; N, 6.28; Found: C, 48.57; H, 4.13; N, 6.39.

(R)-benzyl 1-(5-iodo-2-(5-iodo-2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxylate 45b:

The product **45b** was obtained from **45a**, following the procedure for **29b**, as a white solid (0.42 g, 72%). mp: 93-95 °C; $[\alpha]^{24}_D$: +39° (*c* = 0.4, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3294, 1741, 1666, 1620, 1591, 1572, 1504; ^1H NMR (200 MHz, $CDCl_3$) δ: 10.95 (s, 1H), 10.00 (s, 1H), 8.38 (d, *J* = 8.84 Hz, 1H), 7.96-7.96 (m, 2H), 7.75-7.71 (m, 3H), 7.33 (s, 5H), 5.23 (s, 2H), 4.77-4.71 (m, 1H), 4.54-4.51 (m, 1H), 3.92-3.77 (m, 2H), 3.62 (t, *J* = 6.19 Hz, 2H), 2.40-1.91 (m, 8H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.3, 171.5, 171.5, 166.9, 166.0, 141.3, 139.4, 138.9, 136.1, 135.7, 135.4, 135.2, 128.5, 128.3, 128.0, 124.5, 123.4, 122.8, 87.3, 85.6, 67.4, 63.9, 59.1, 50.0, 48.5, 38.9, 29.1, 28.6, 27.3, 25.6, 25.1; ESI-MS: 899.5955 $(M+Na)^+$; Anal. Calcd. for $C_{36}H_{38}I_2N_4O_6$: C, 49.33; H, 4.37; N, 6.39; Found: C, 49.48; H, 4.19; N, 6.18.

(R)-N-(4-iodo-2-((4-iodo-2-((R)-2-(methylcarbamoyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)-1-pivaloylpyrrolidine-2-carboxamide 45c:

The product **45c** was obtained from **45b**, following the procedure for **29c**, as a white solid (0.25 g, 92%). mp: 149-151 °C; $[\alpha]^{24}_D$: +52° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3362, 1697, 1668, 1614, 1573, 1568, 1506, 758; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.41 (s, 1H), 10.43 (s, 1H), 8.41 (d, *J* = 8.85 Hz, 1H), 8.13 (s, 1H), 7.74 (s, 1H), 7.64-7.53 (m, 2H), 7.30-7.23 (m, 1H), 6.93 (bs, 1H), 4.73-4.66 (m, 1H), 4.45-4.45 (m, 1H), 3.98-3.64 (m, 4H), 2.82 (d, *J* = 4.17 Hz, 3H), 2.17-

1.92 (m, 8H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.1, 171.7, 171.3, 167.9, 166.3, 141.1, 139.6, 139.1, 136.4, 135.8, 134.4, 130.4, 126.0, 123.1, 121.1, 88.4, 85.7, 63.9, 60.7, 50.8, 48.5, 38.8, 29.6, 28.5, 27.2, 25.7, 25.3; ESI-MS: 822.7878 $(M+Na)^+$; Anal. Calcd. for $C_{30}H_{35}I_2N_5O_5$: C, 45.07; H, 4.41; N, 8.76; Found: C, 44.96; H, 4.37; N, 8.55.

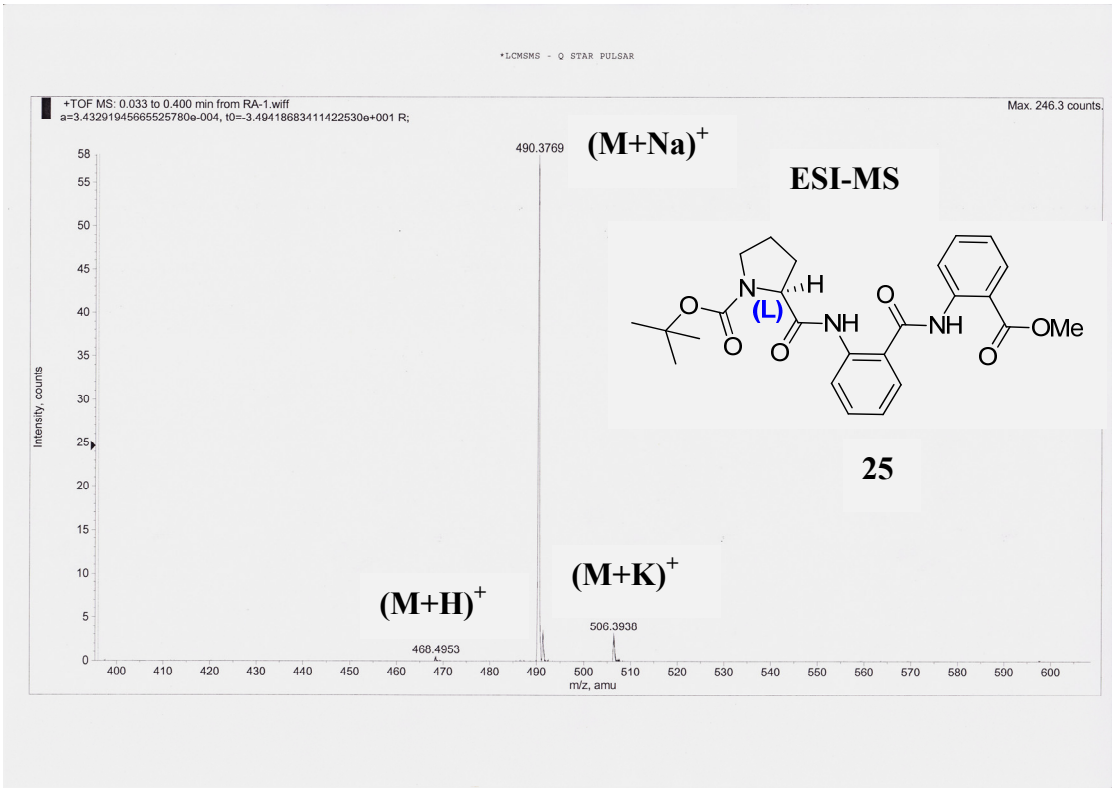
LD octamer methyl ester 46:

To a solution containing the acid **43d** and amine **43e** in dry DCM, EDC.HCl (1.1 equiv) was added followed by the addition of HOBt (0.2 equiv) and stirred for 5 h. It was then diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solutions. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography yielding the product **46** (0.093 g, 52%). mp: 133-135 °C; $[\alpha]^{24}_D$: -26° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3018, 1631, 1620, 1504, 1215, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.37 (s, 1H), 10.04 (s, 1H), 9.55 (s, 1H), 9.23 (s, 1H), 8.33 (d, *J* = 8.84 Hz, 1H), 8.16 (d, *J* = 1.64 Hz, 1H), 8.07 (d, *J* = 8.72 Hz, 1H), 7.93 (d, *J* = 9.35 Hz, 1H), 7.84 (d, *J* = 7.20 Hz, 1H), 7.69-7.55 (m, 6H), 7.23 (s, 5H), 6.76 (d, *J* = 8.46 Hz, 1H), 5.12 (s, 2H), 4.71-4.42 (m, 3H), 3.93 (d, *J* = 5.68 Hz, 1H), 3.79-3.64 (m, 4H), 3.53-3.40 (m, 4H), 2.69-2.56 (m, 1H), 2.40-2.20 (m, 3H), 2.07-1.90 (m, 12H), 1.19 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.4, 171.2, 170.6, 170.4, 167.8, 166.9, 165.9, 163.8, 141.4, 140.9, 139.9, 139.3, 139.1, 136.1, 136.0, 135.9, 135.7, 135.2, 135.2, 128.5, 128.2, 127.9, 127.7, 126.6, 124.7, 123.3, 123.0, 122.2, 88.1, 87.7, 85.9, 67.3, 63.2, 62.0, 59.2, 56.5, 50.1, 50.1, 48.4, 47.3, 38.84, 29.89, 29.06, 28.3, 27.3, 26.1, 25.6, 25.2, 25.0; MALDI-TOF: 1583.1737 $(M+Na)^+$; 1599.1202 $(M+K)^+$; Anal. Calcd. for $C_{60}H_{60}I_4N_8O_{10}$: C, 46.17; H, 3.87; N, 7.18; Found: C, 45.99; H, 4.05; N, 6.99.

DL octamer methyl ester 47:

The product **47** was obtained from **44d** and **44e**, following the procedure for **47**, as a white solid (0.087 g, 49%). mp: 127-129 °C; $[\alpha]^{24}_D$: +50° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3018, 1693, 1631, 1504, 1215, 759; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.47 (s, 1H), 10.14 (s, 1H), 9.65 (s, 1H), 8.96 (s, 1H), 8.44 (d, *J* = 8.84 Hz, 1H), 8.24 (d, *J* = 2.15 Hz, 1H), 8.19 (d, *J* = 8.84 Hz, 1H), 8.01-7.97

(m, 2H), 7.90 (d, J = 1.89 Hz, 1H), 7.79-7.74 (m, 3H), 7.69-7.61 (m, 2H), 7.32 (s, 5H), 6.81 (d, J = 8.46 Hz, 1H), 5.22 (s, 2H), 4.81-4.71 (m, 2H), 4.69-4.61 (m, 2H), 3.86-3.73 (m, 4H), 3.66-3.45 (m, 4H), 2.46-2.25 (m, 3H), 2.21-1.82 (m, 13H), 1.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.4, 171.2, 170.3, 167.8, 167.0, 165.9, 163.8, 141.5, 140.9, 140.0, 139.4, 139.3, 139.2, 136.1, 136.1, 135.9, 135.7, 135.4, 135.2, 135.1, 128.5, 128.2, 128.0, 127.4, 126.5, 124.5, 123.3, 123.1, 122.9, 122.2, 88.1, 87.5, 85.9, 85.8, 67.3, 63.2, 62.0, 59.2, 56.5, 50.2, 50.1, 48.4, 47.3, 38.8, 29.8, 29.0, 28.3, 27.3, 26.1, 25.6, 25.2, 25.0, 23.3; MALDI-TOF: 1583.2034 $(M+Na)^+$; 1599.1112 $(M+K)^+$; Anal. Calcd. for $C_{60}H_{60}I_4N_8O_{10}$: C, 46.17; H, 3.87; N, 7.18; Found: C, 46.33; H, 3.69; N, 7.33.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Max. 246.3 counts.
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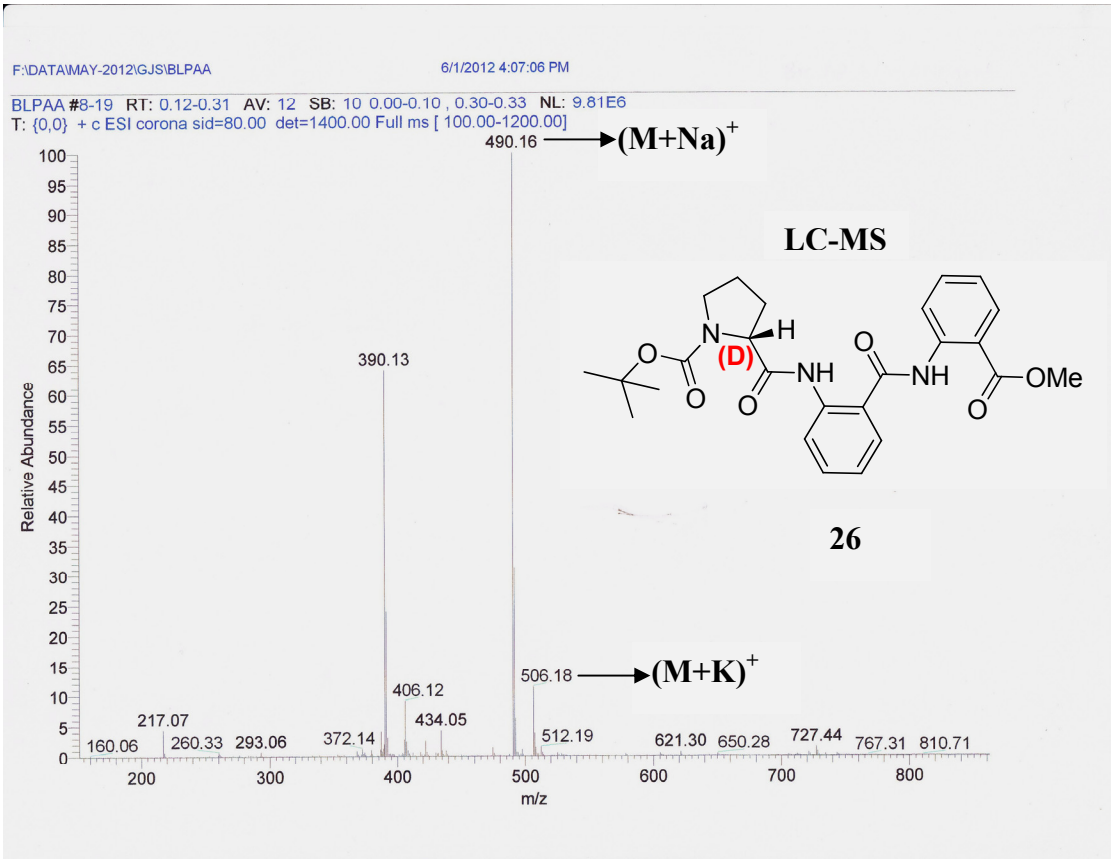
ESI-MS
(L)
25
(M+K)+
(M+H)+
506.3938
468.4953
Intensity, counts
m/z, amu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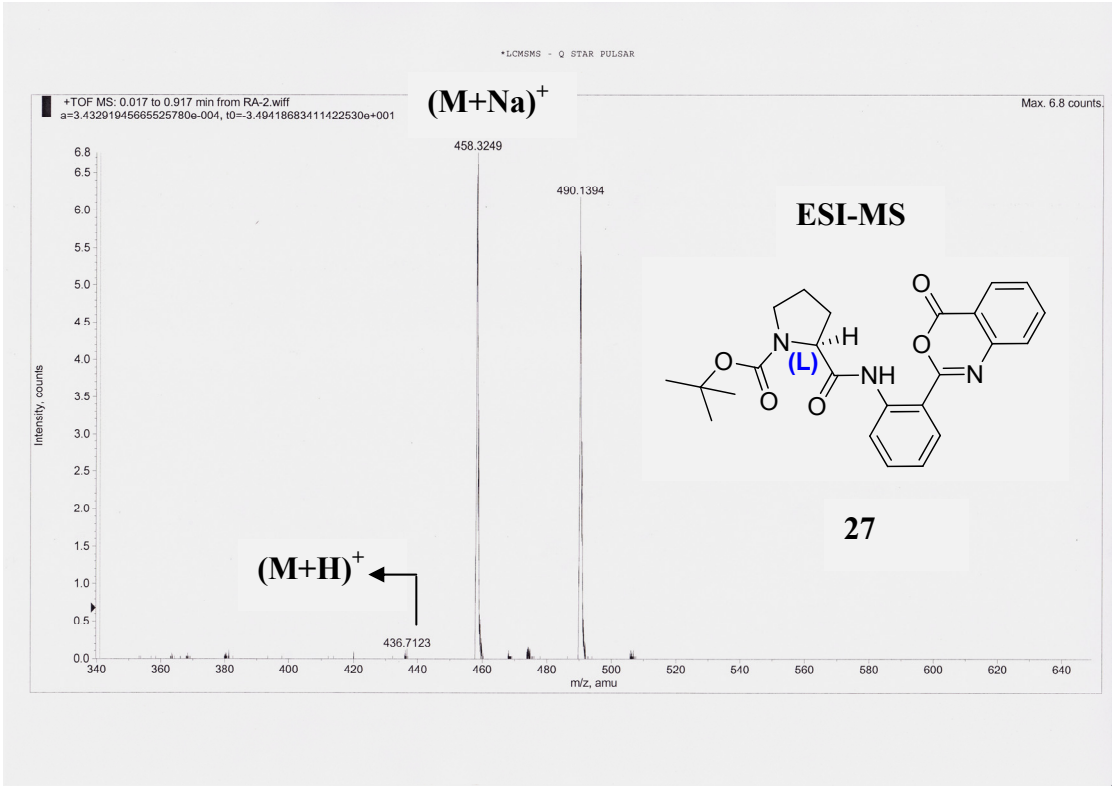
490.16
(M+Na)+
LC-MS
(D)
26
390.13
506.18
(M+K)+
406.12
434.05
217.07
160.06
260.33
293.06
372.14
512.19
621.30
650.28
727.44
767.31
810.71
Relative Abundance
m/z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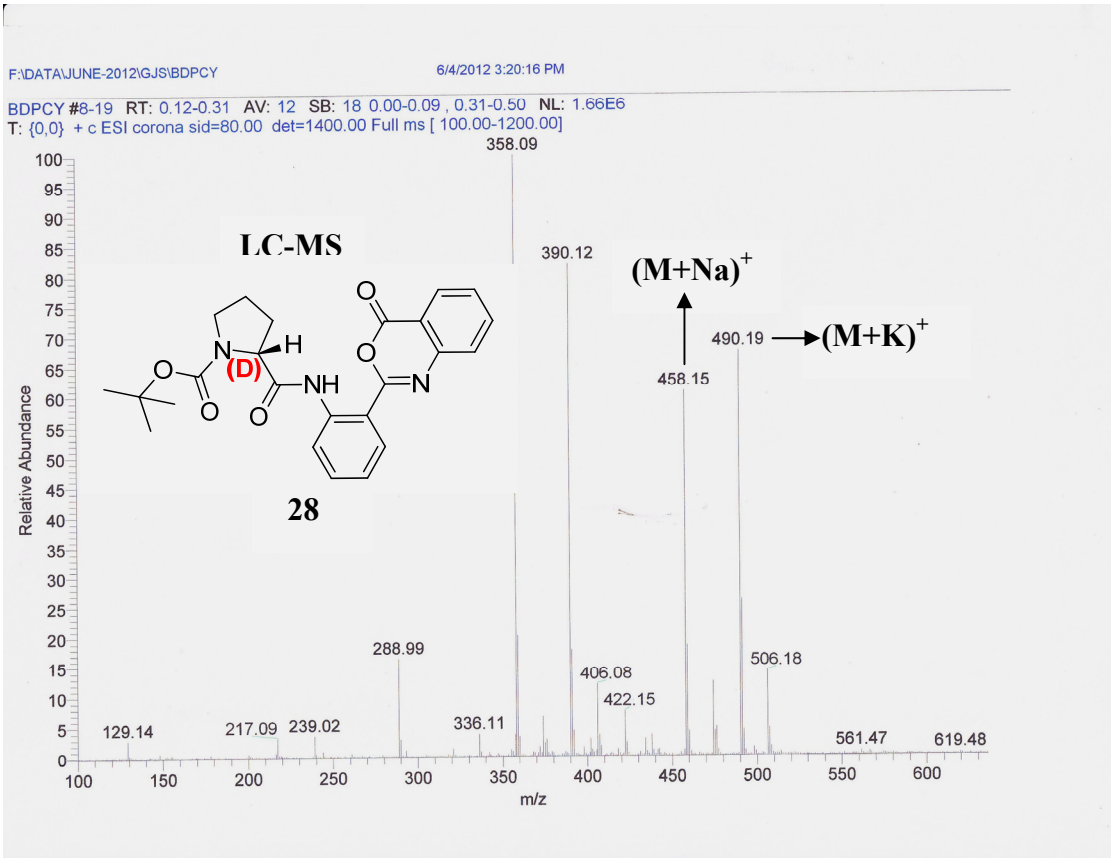
490.1394
ESI-MS
(M+H)+
436.7123
(L)
27
Intensity, counts
m/z, amu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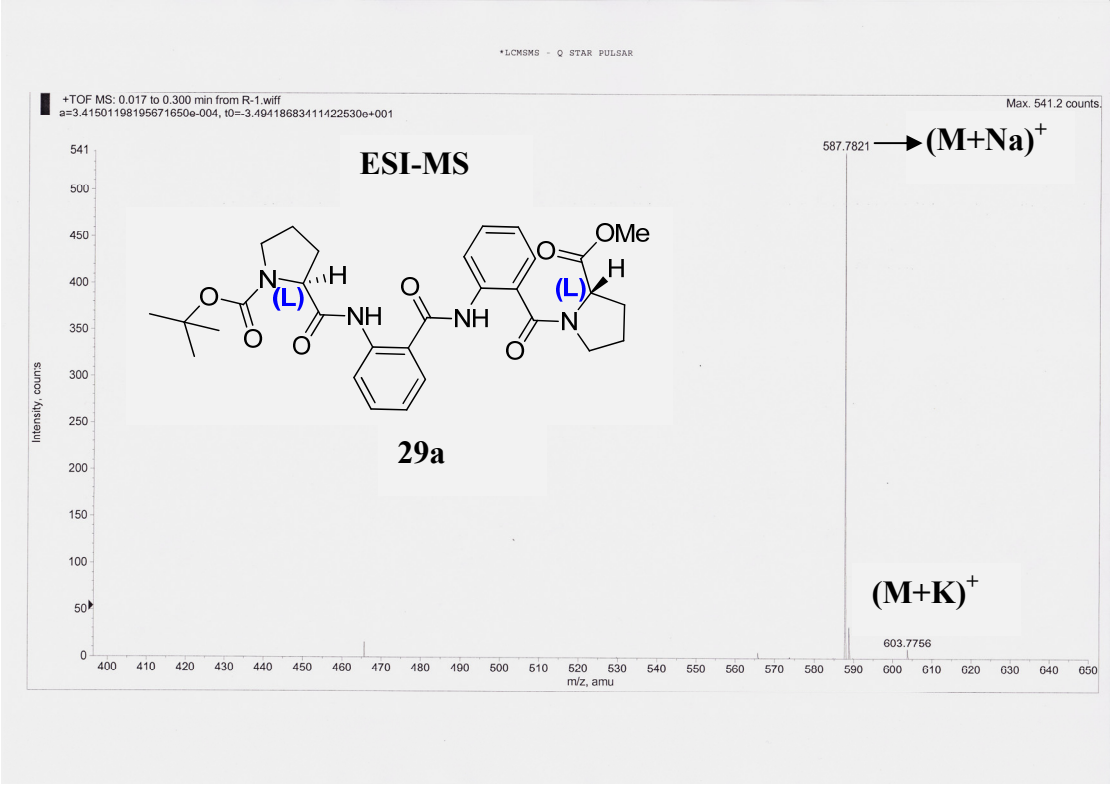
358.09
LC-MS
390.12
(M+Na)+
490.19
(M+K)+
458.15
(D)
28
288.99
406.08
422.15
506.18
129.14
217.09
239.02
336.11
561.47
619.48
Relative Abundance
m/z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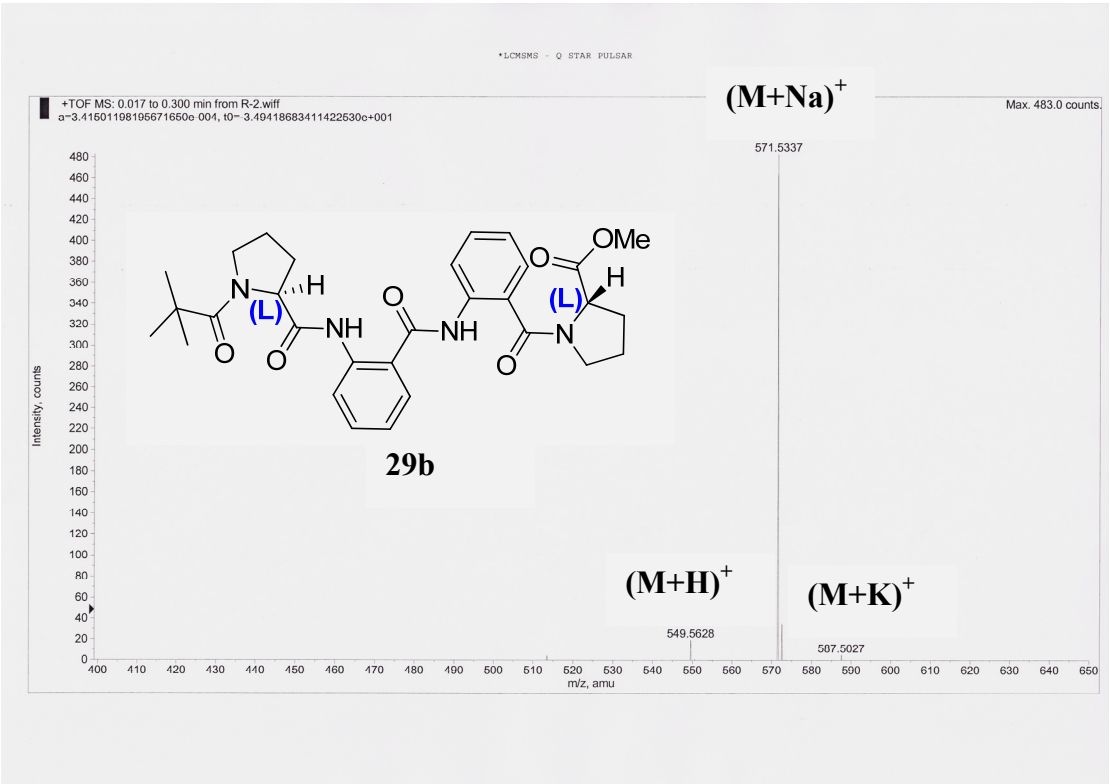
Max. 541.2 counts.
ESI-MS
587.7821
(M+Na)+
OMe
(L)
(L)
29a
(M+K)+
603.7756
Intensity, counts
m/z, amu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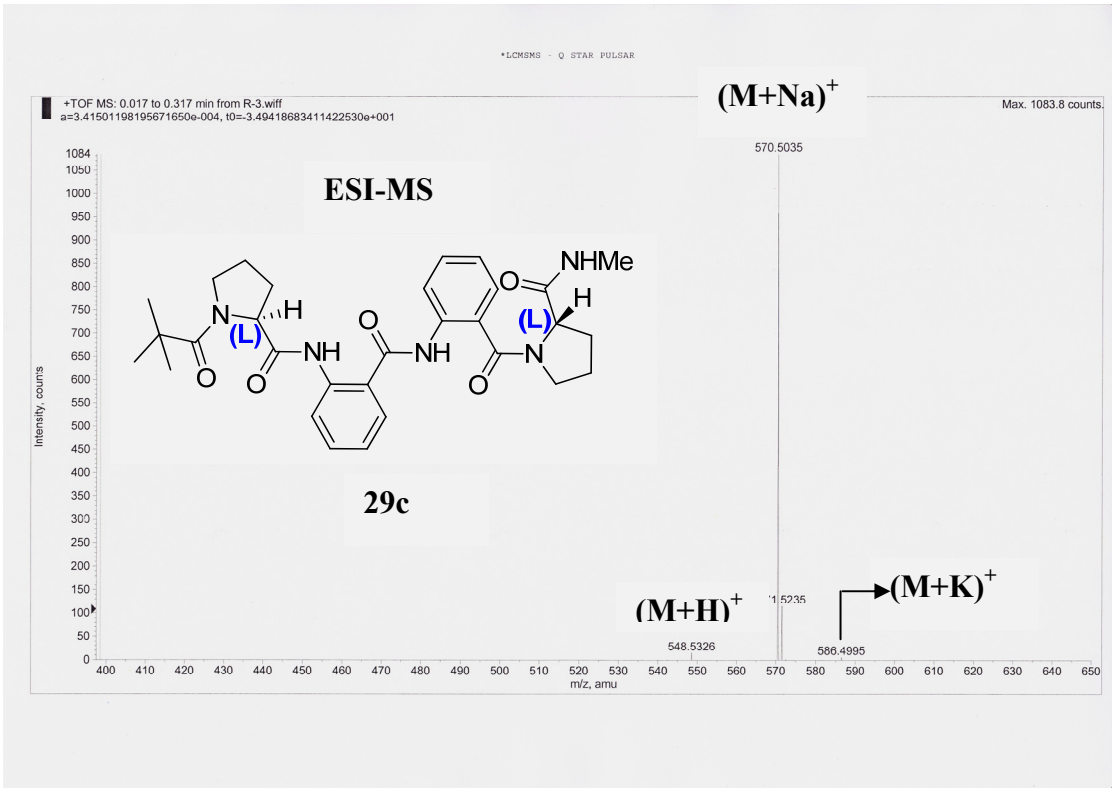
(M+Na)+
Max. 483.0 counts.
571.5337
OMe
(L)
(L)
29b
(M+H)+
549.5628
(M+K)+
587.5027
Intensity, counts
m/z, amu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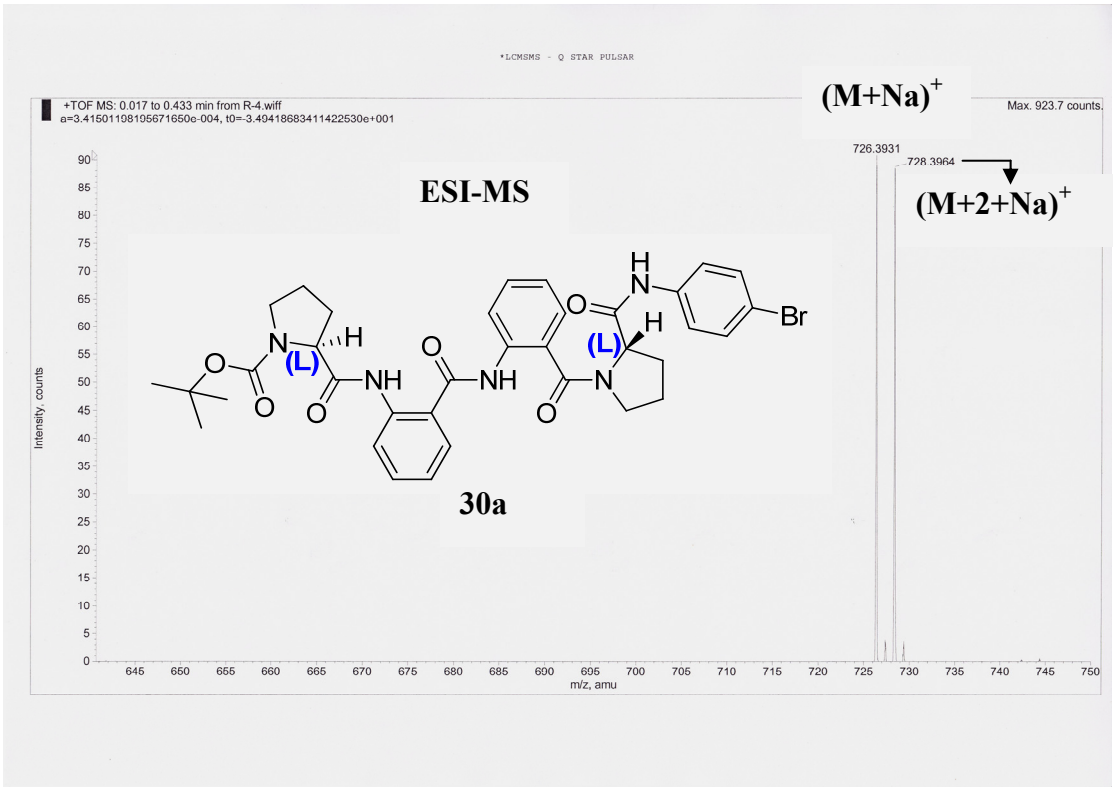
Max. 1083.8 counts.
(M+Na)+
570.5035
ESI-MS
NHMe
(L)
(L)
29c
(M+H)+
548.5326
(M+K)+
586.4995
Intensity, counts
m/z, amu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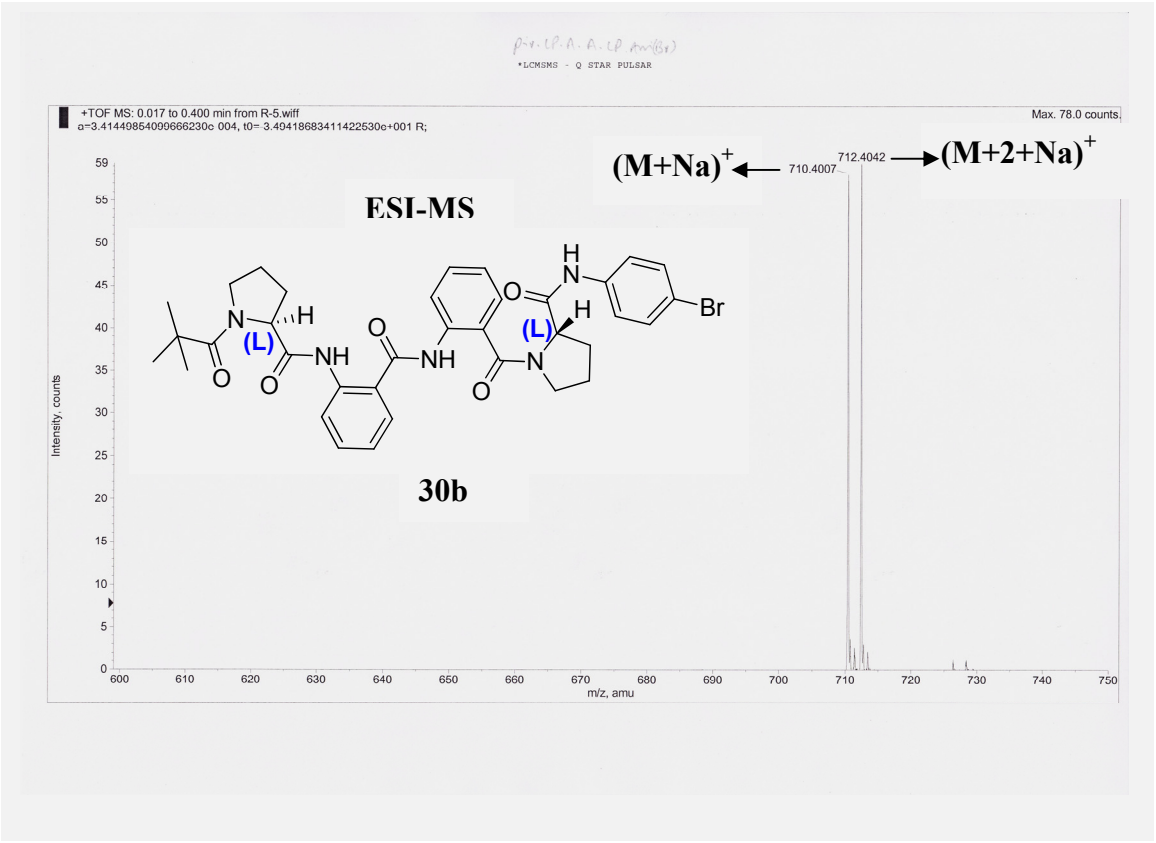
Max. 923.7 counts.
(M+Na)+
726.3931
728.3964
(M+2+Na)+
ESI-MS
Br
(L)
(L)
30a
Intensity, counts
m/z, amu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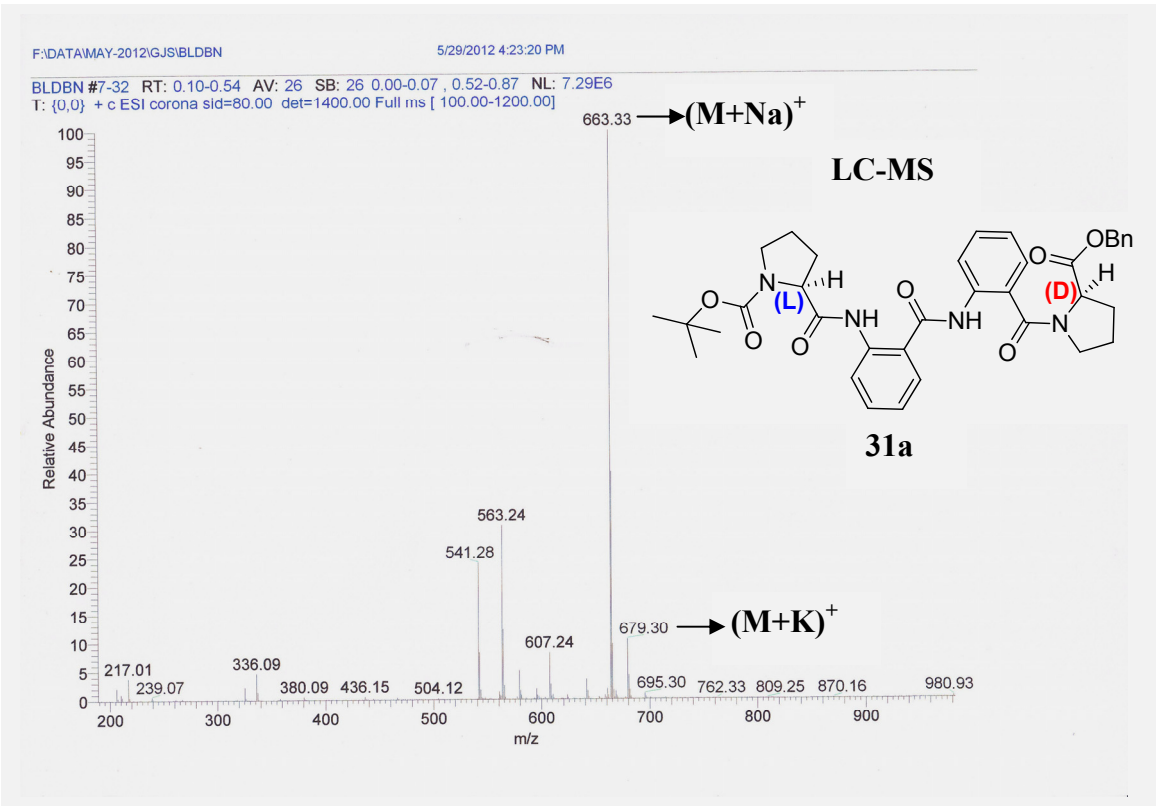
(M+Na)+
710.4007
712.4042
(M+2+Na)+
ESI-MS
30b
Intensity, counts
m/z, amu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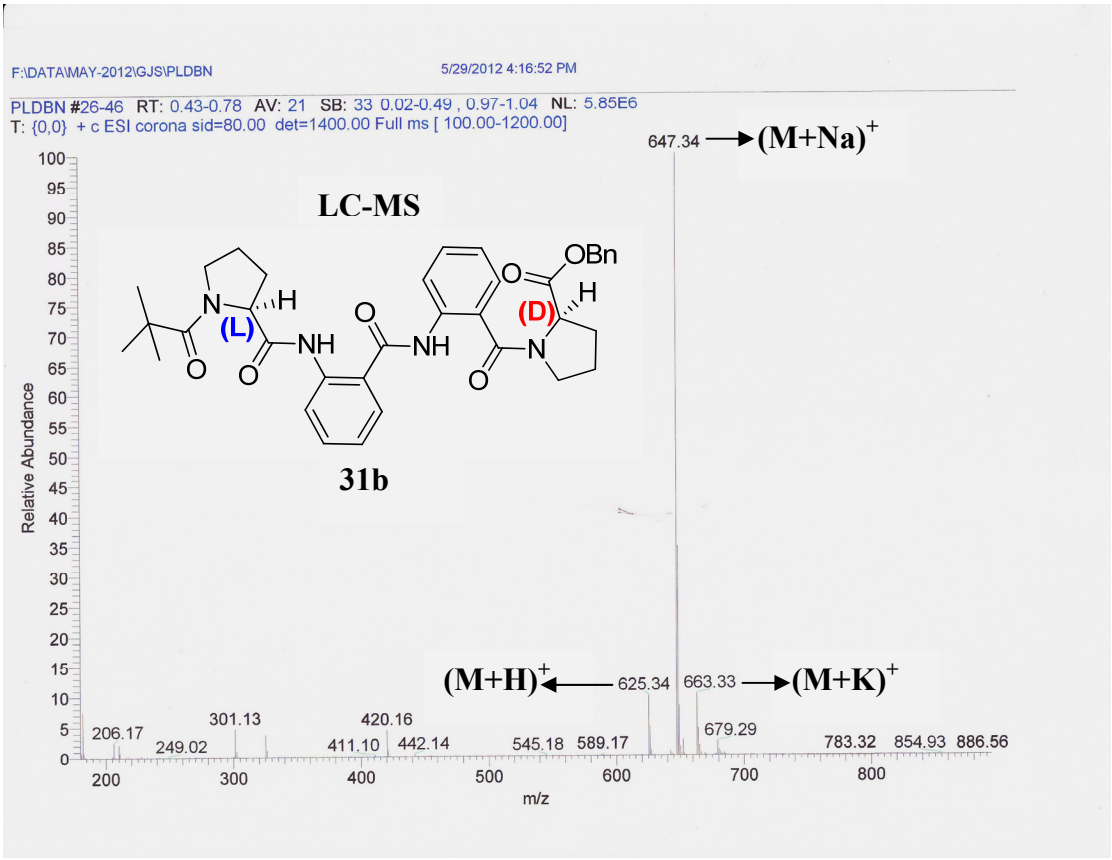
663.33
(M+Na)+
LC-MS
31a
563.24
541.28
679.30
(M+K)+
607.24
217.01
239.07
336.09
380.09
436.15
504.12
695.30
762.33
809.25
870.16
980.93
Relative Abundance
m/z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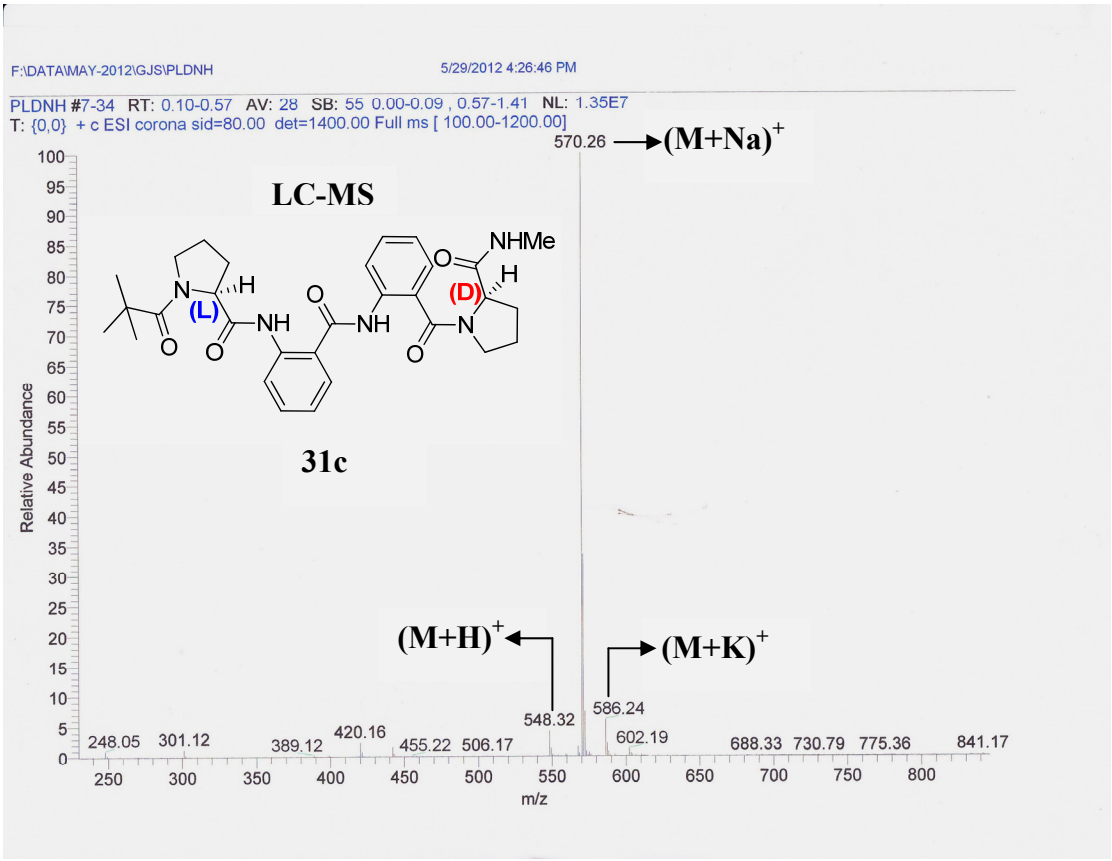
LC-MS
31b
647.34 (M+Na)+
(M+H)+
625.34
663.33 (M+K)+
Relative Abundance
m/z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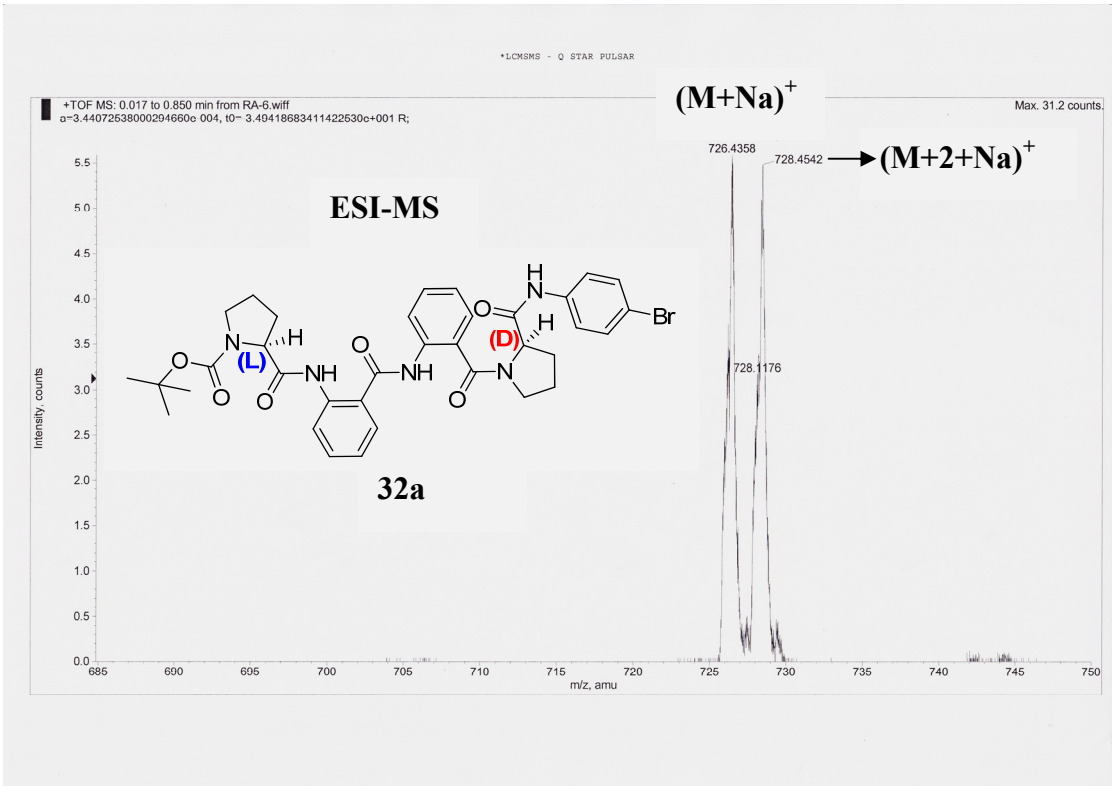
LC-MS
31c
570.26 (M+Na)+
(M+H)+
548.32
586.24 (M+K)+
Relative Abundance
m/z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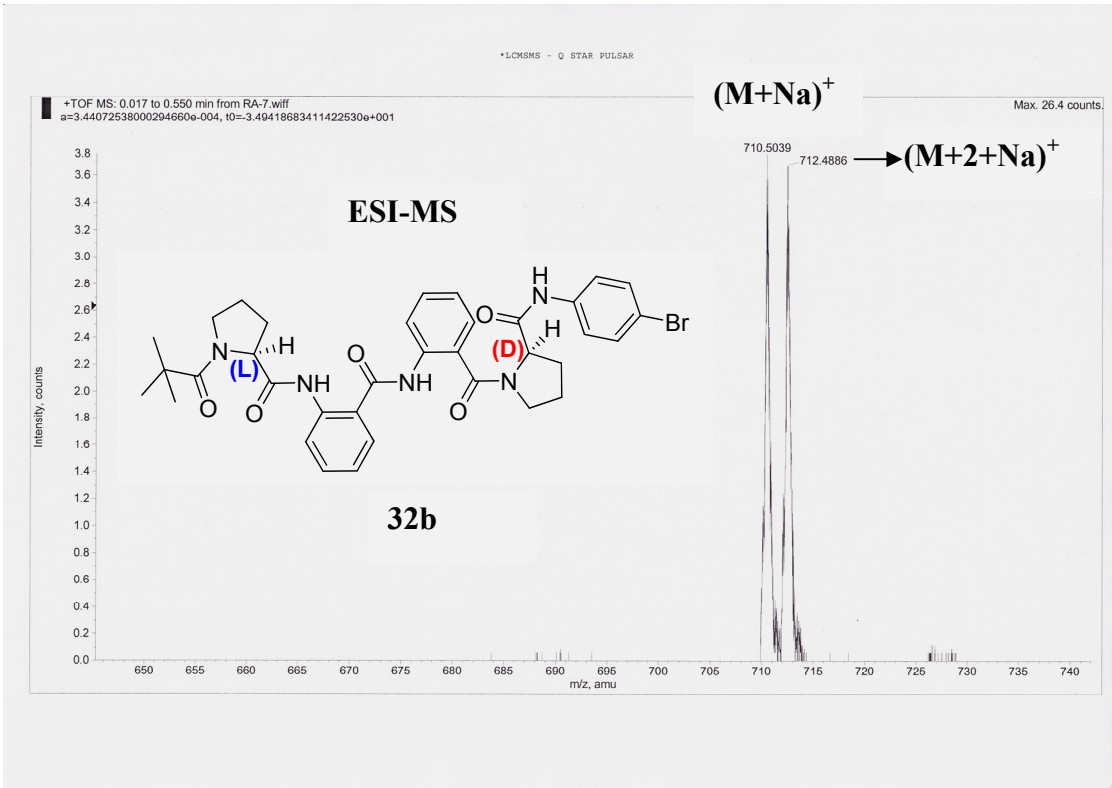
(M+Na)+
726.4358
728.4542
(M+2+Na)+
728.1176
ESI-MS
(L)
(D)
Br
32a
Intensity, counts
m/z, amu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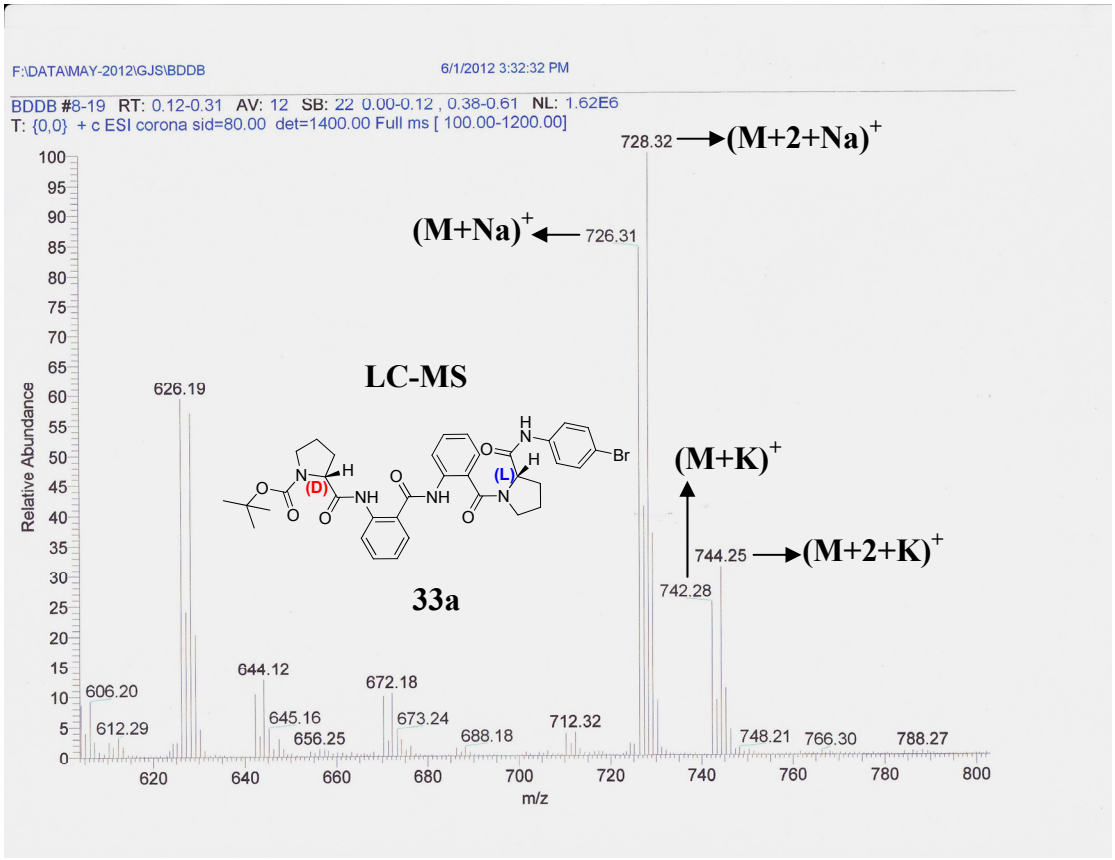
Max. 26.4 counts.
(M+Na)+
710.5039
712.4886
(M+2+Na)+
ESI-MS
(L)
(D)
Br
32b
Intensity, counts
m/z, amu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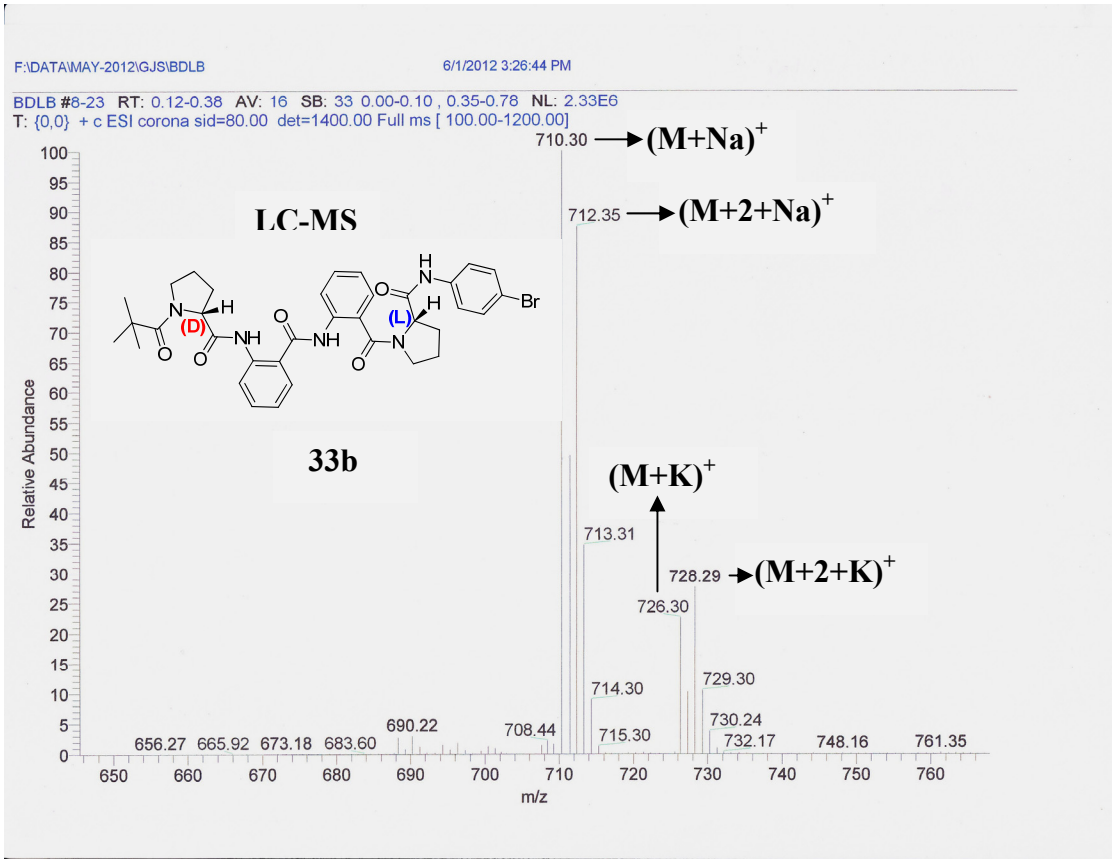
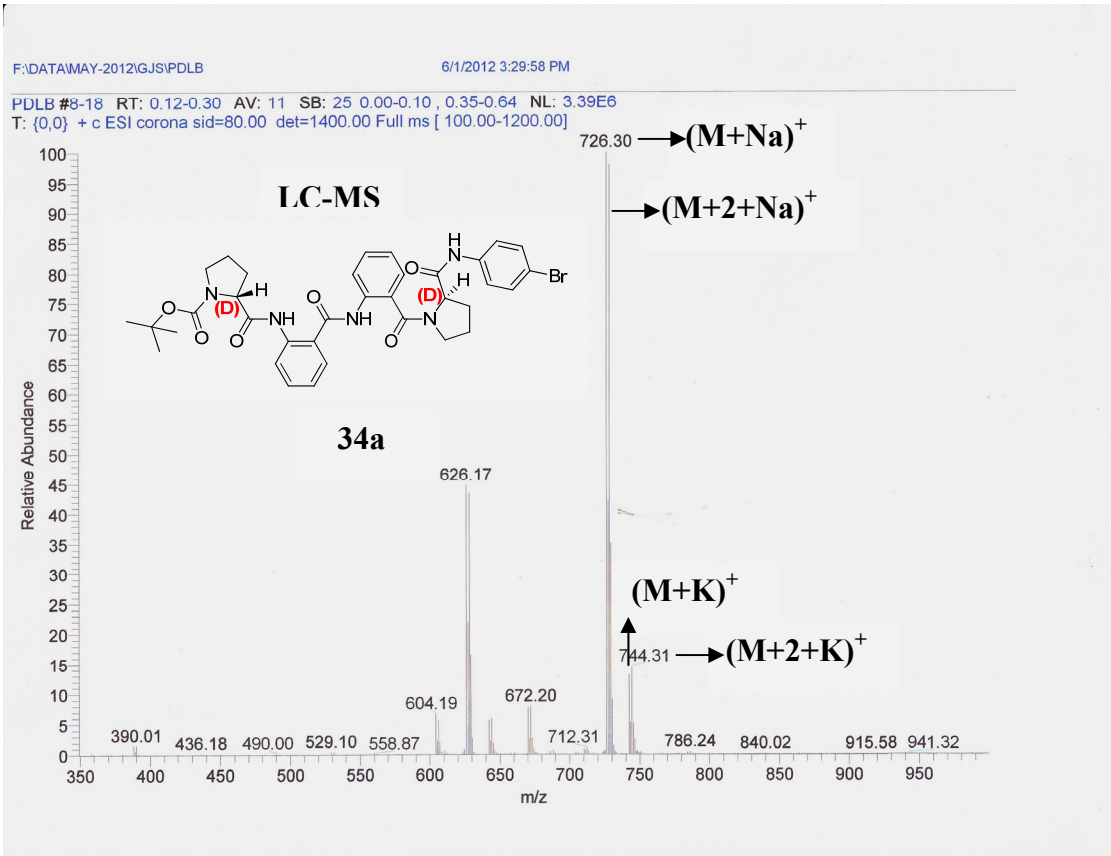
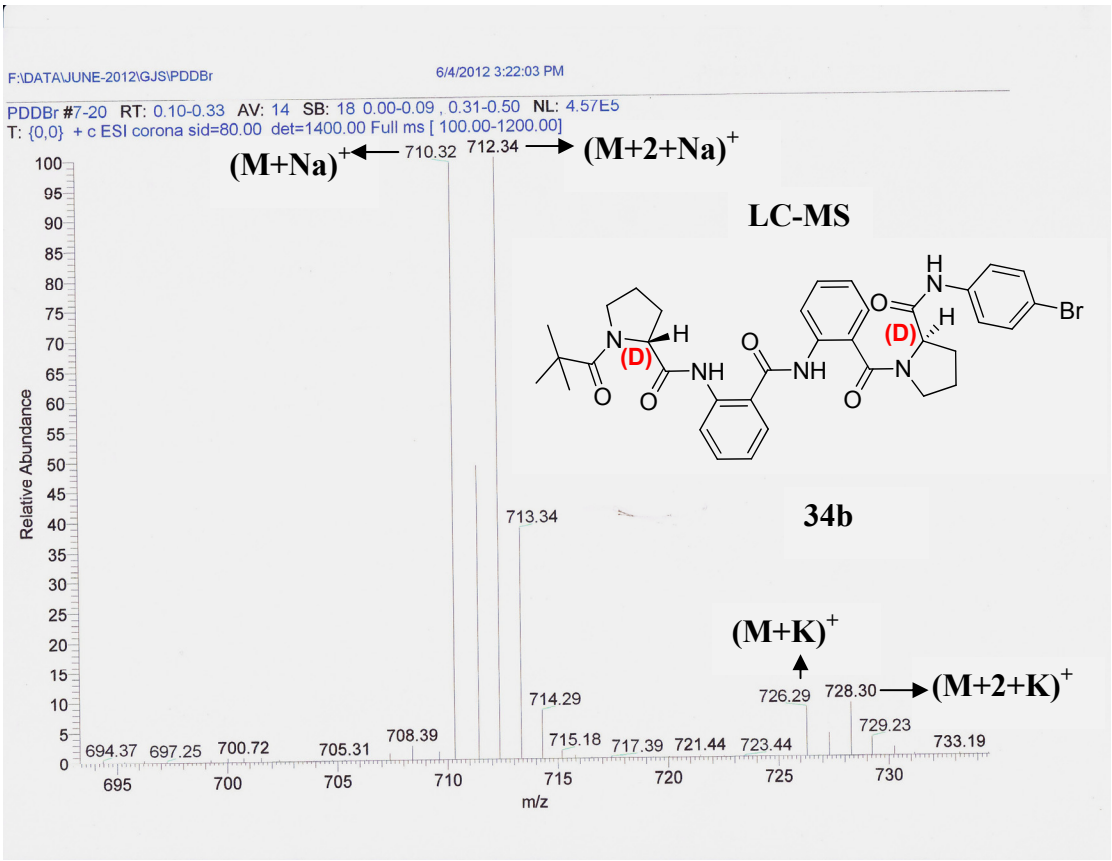
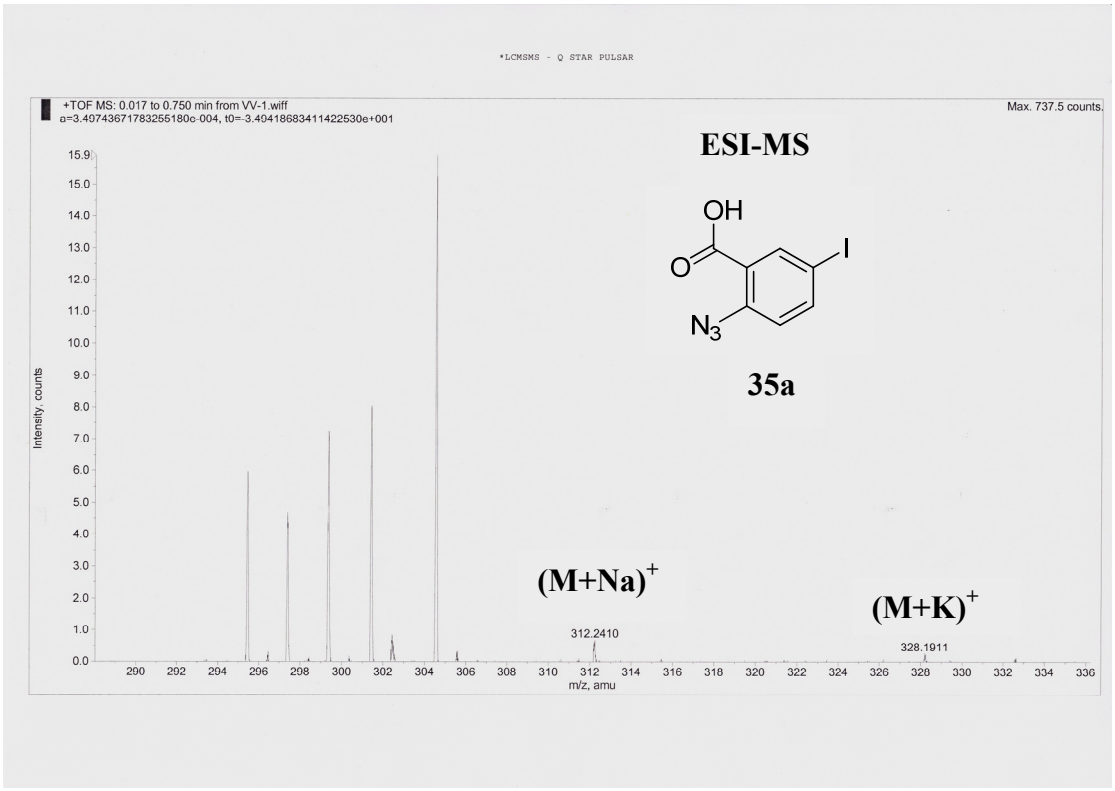
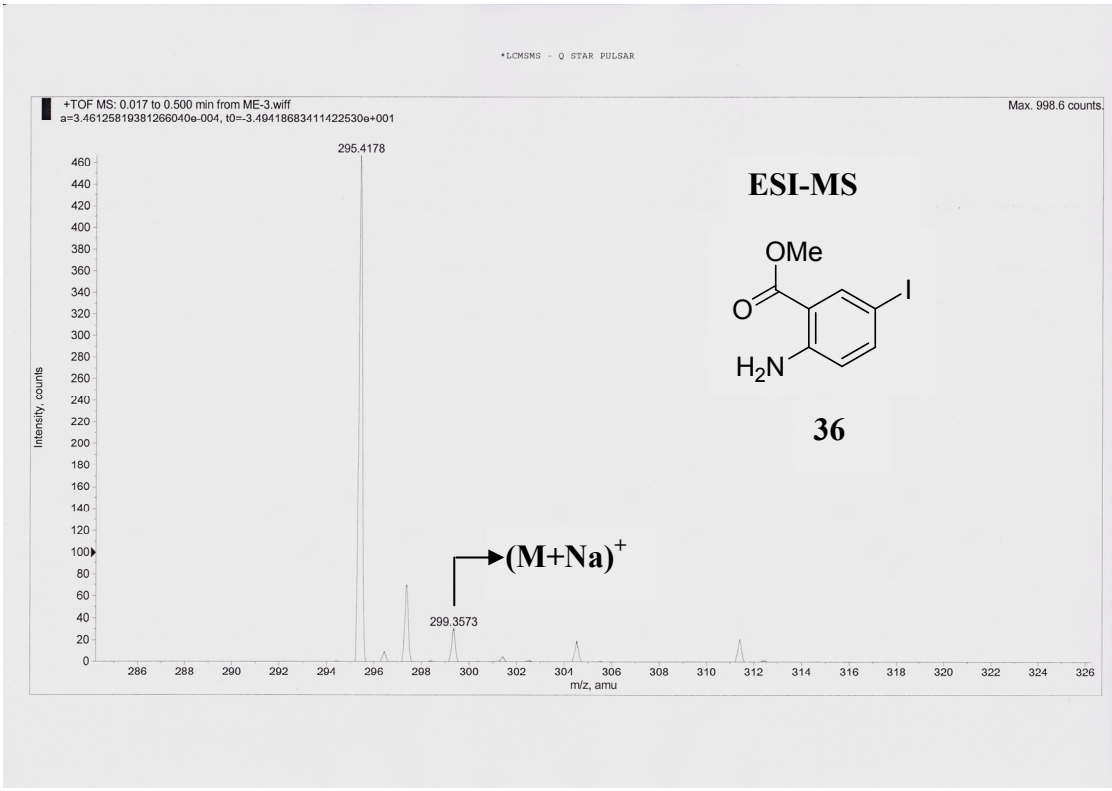
728.32 → (M+2+Na)+
(M+Na)+ ← 726.31
LC-MS
626.19
(M+K)+
744.25 → (M+2+K)+
742.28
33a
644.12
672.18
606.20
645.16
673.24
612.29
656.25
688.18
712.32
748.21
766.30
788.27
Relative Abundance
m/z

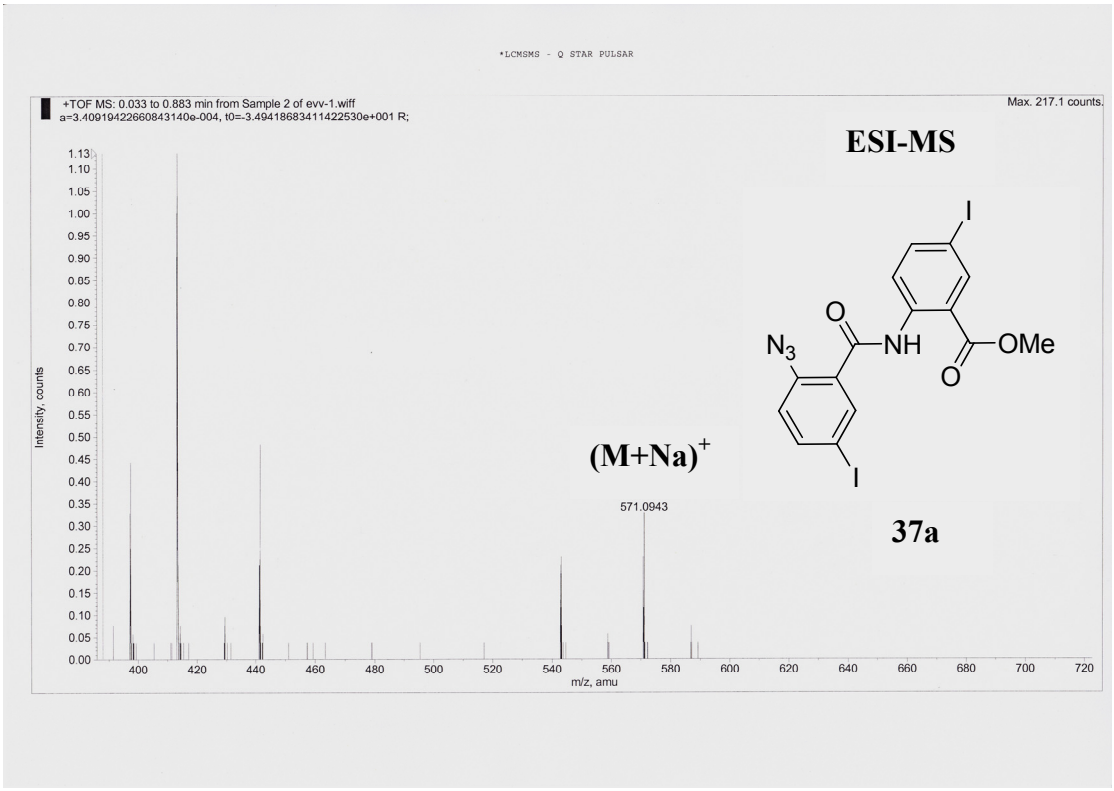

F:\DATA\MAY-2012\GJS\BDLB
6/1/2012 3:26:44 PM
BDLB #8-23 RT: 0.12-0.38 AV: 16 SB: 33 0.00-0.10 , 0.35-0.78 NL: 2.33E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
710.30 → (M+Na)+
712.35 → (M+2+Na)+
LC-MS
33b
(M+K)+
713.31
728.29 → (M+2+K)+
726.30
714.30
729.30
690.22
708.44
715.30
730.24
656.27
665.92
673.18
683.60
732.17
748.16
761.35
Relative Abundance
m/z

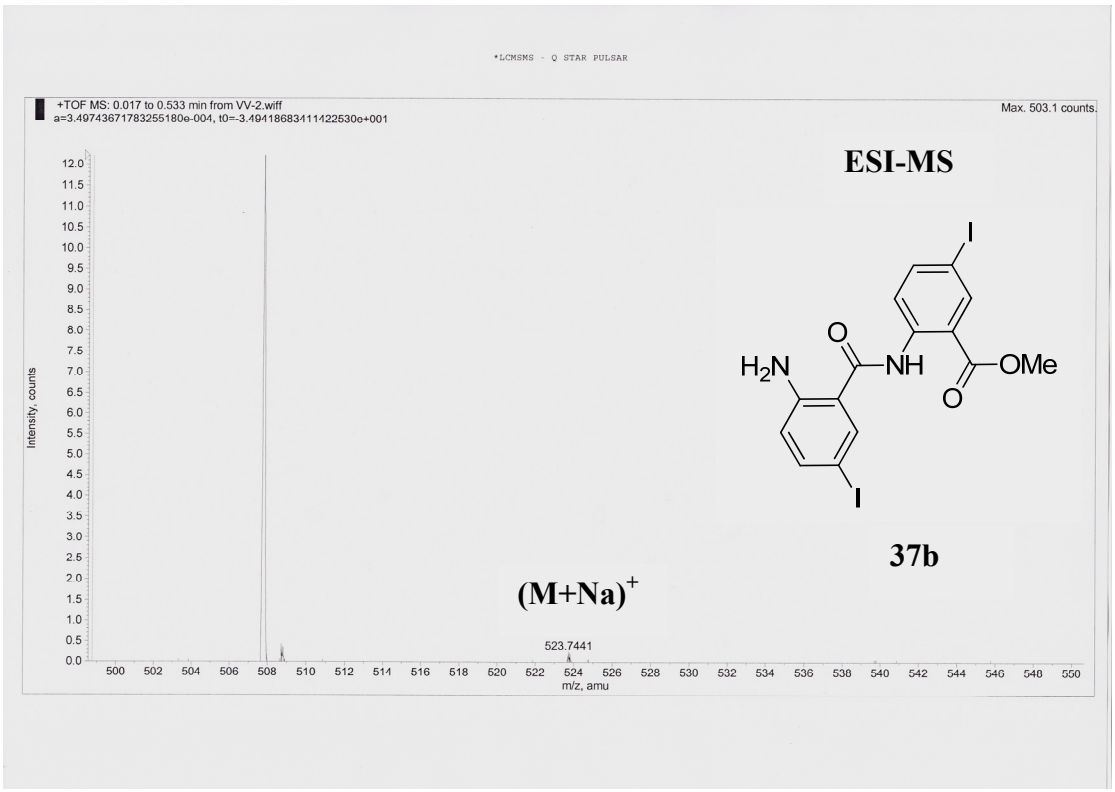

F:\DATA\MAY-2012\GJS\PDLB
6/1/2012 3:29:58 PM
PDLB #8-18 RT: 0.12-0.30 AV: 11 SB: 25 0.00-0.10 , 0.35-0.64 NL: 3.39E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
726.30 (M+Na)+
(M+2+Na)+
34a
626.17
(M+K)+
744.31 (M+2+K)+
604.19
672.20
390.01
436.18
490.00
529.10
558.87
712.31
786.24
840.02
915.58
941.32
Relative Abundance
m/z

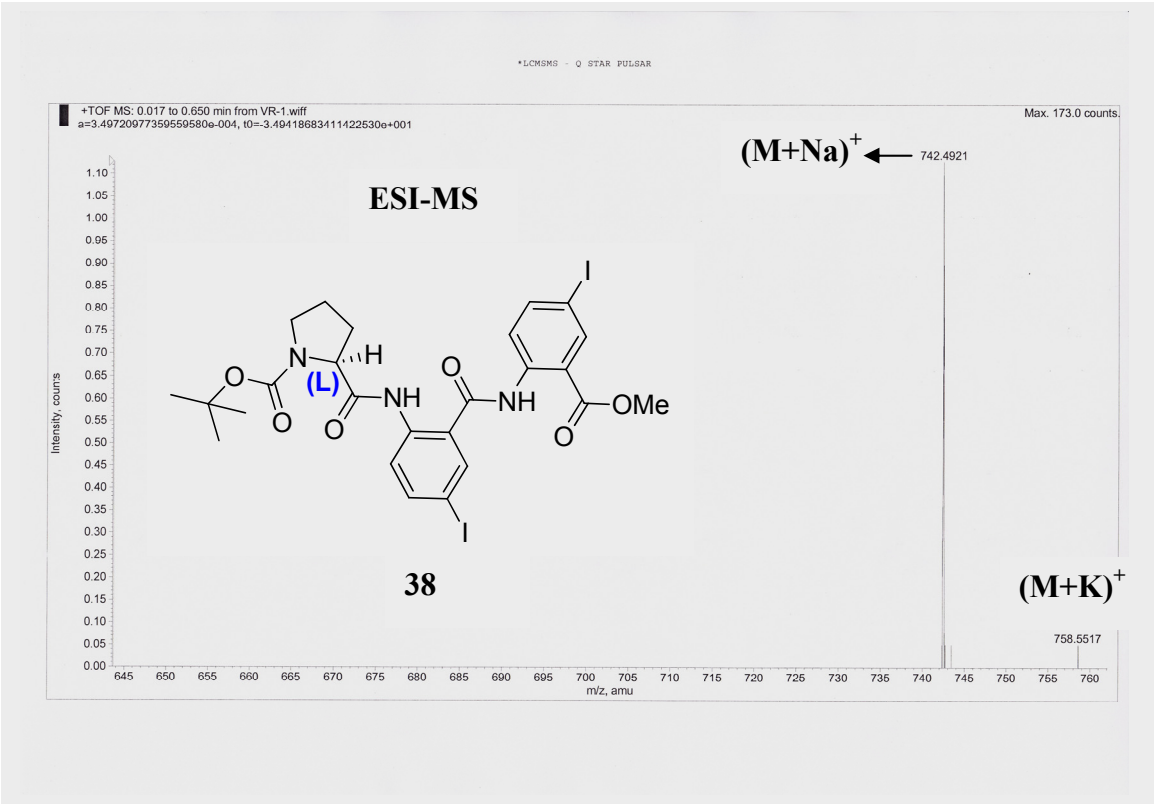

F:\DATA\JUNE-2012\GJS\PDDBr
6/4/2012 3:22:03 PM
PDDBr #7-20 RT: 0.10-0.33 AV: 14 SB: 18 0.00-0.09 , 0.31-0.50 NL: 4.57E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
(M+Na)+
710.32
712.34
(M+2+Na)+
LC-MS
34b
713.34
(M+K)+
714.29
726.29
728.30
(M+2+K)+
729.23
694.37
697.25
700.72
705.31
708.39
715.18
717.39
721.44
723.44
733.19
Relative Abundance
m/z

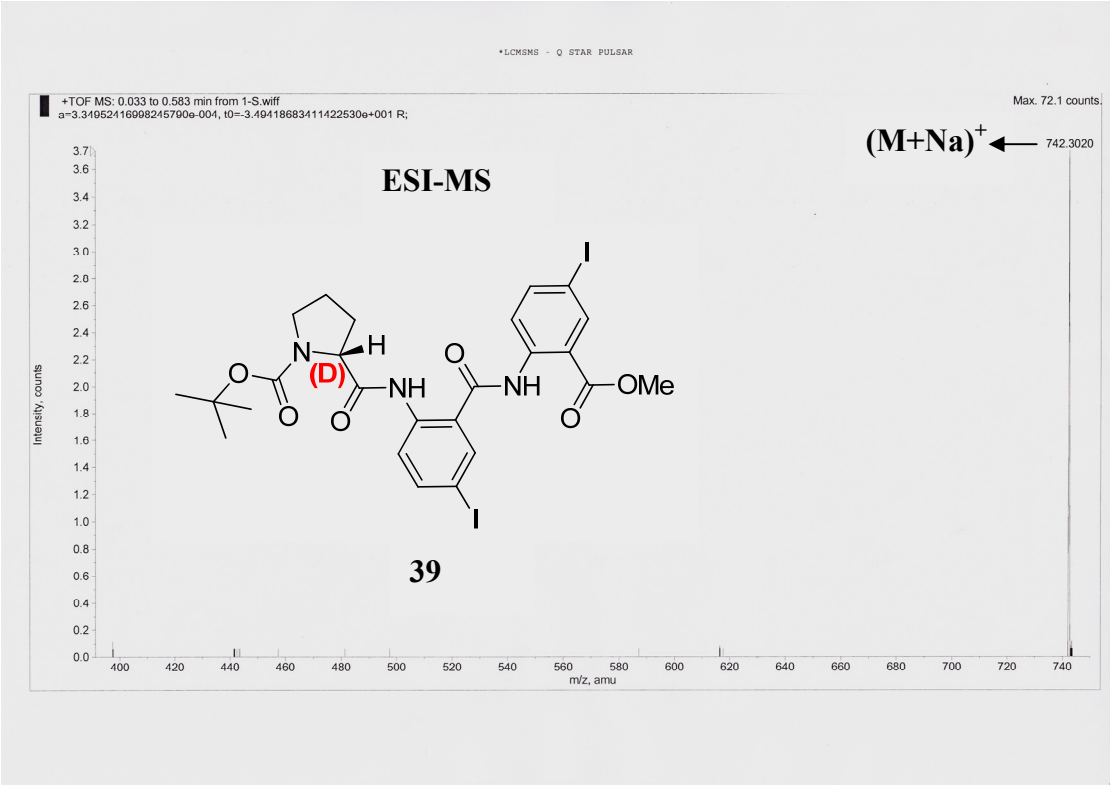

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.750 min from VV-1.wiff
a=3.407436717832551 80c-004, t0=-3.404186834114225 30e+001
Max. 737.5 counts.
ESI-MS
OH
O
I
N3
35a
Intensity, counts
(M+Na)+
312.2410
(M+K)+
328.1911
m/z, amu

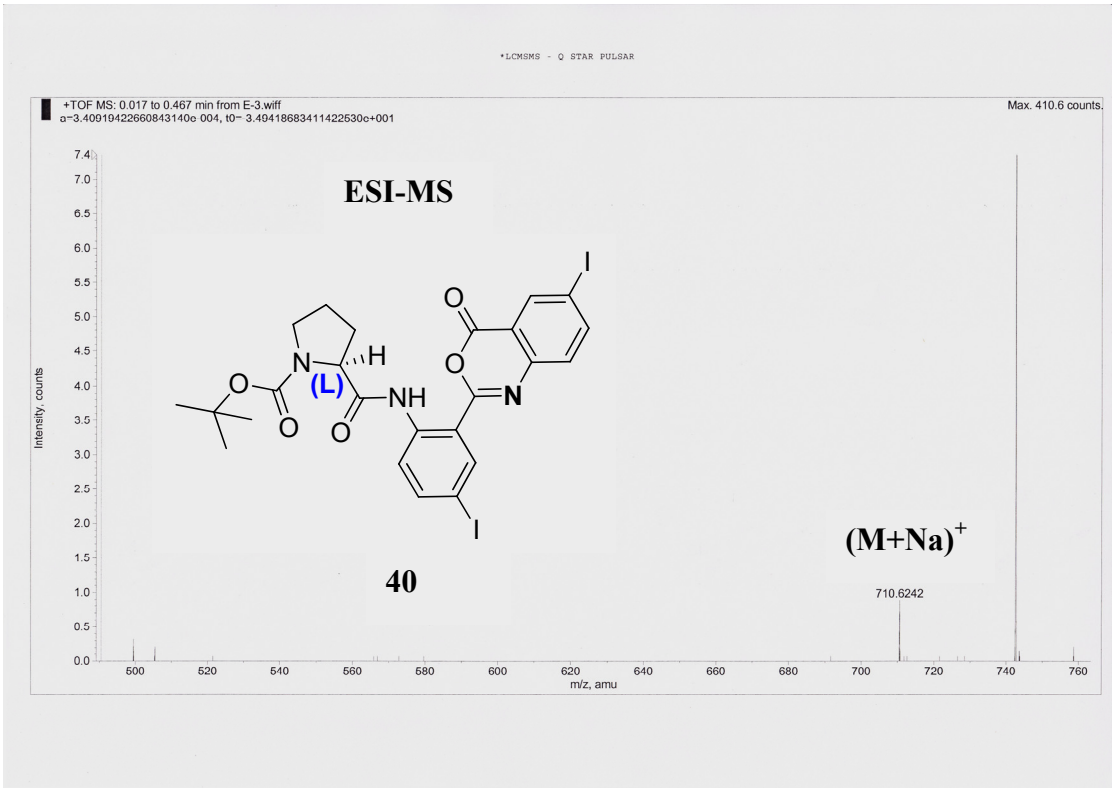

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.500 min from ME-3.wiff
a=3.461258193812660 40e-004, t0=-3.494186834114225 30e+001
Max. 998.6 counts.
295.4178
ESI-MS
OMe
O
I
H2N
36
Intensity, counts
(M+Na)+
299.3573
m/z, amu

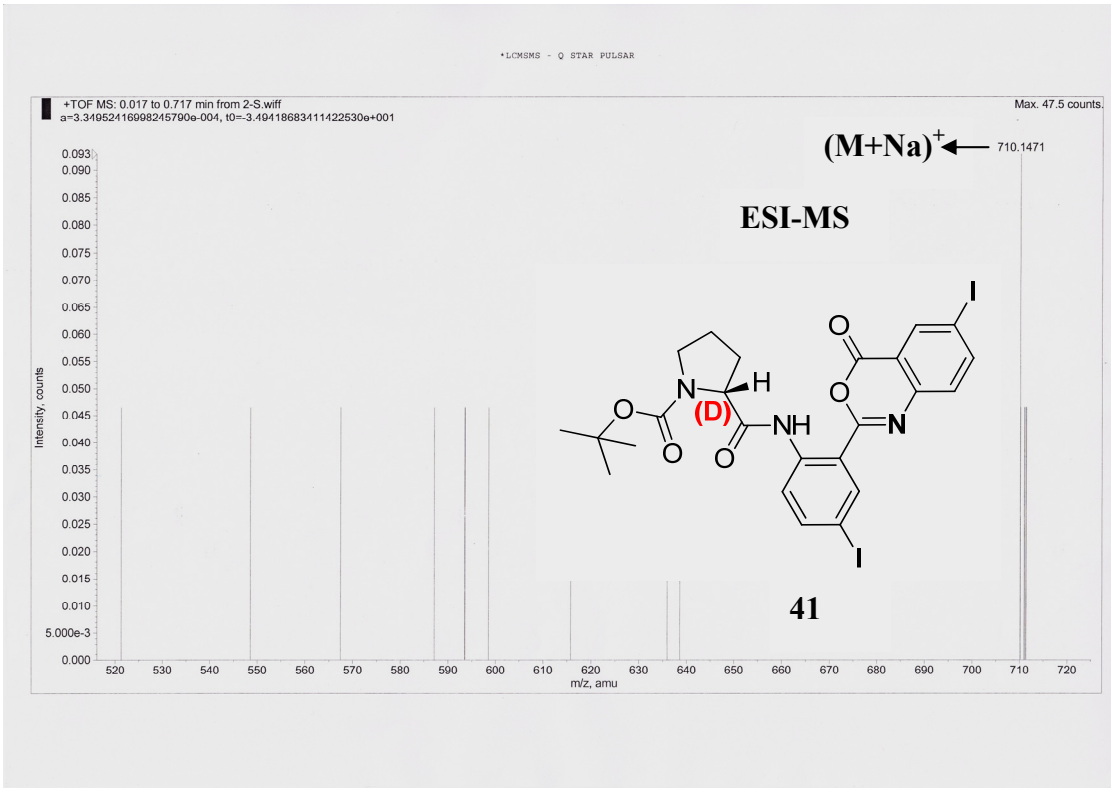

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.883 min from Sample 2 of evv-1.wiff
a=3.40919422660843140e-004, t0=-3.49418683411422530e+001 R;
Max. 217.1 counts.
ESI-MS
Intensity, counts
m/z, amu
(M+Na)+
571.0943
37a

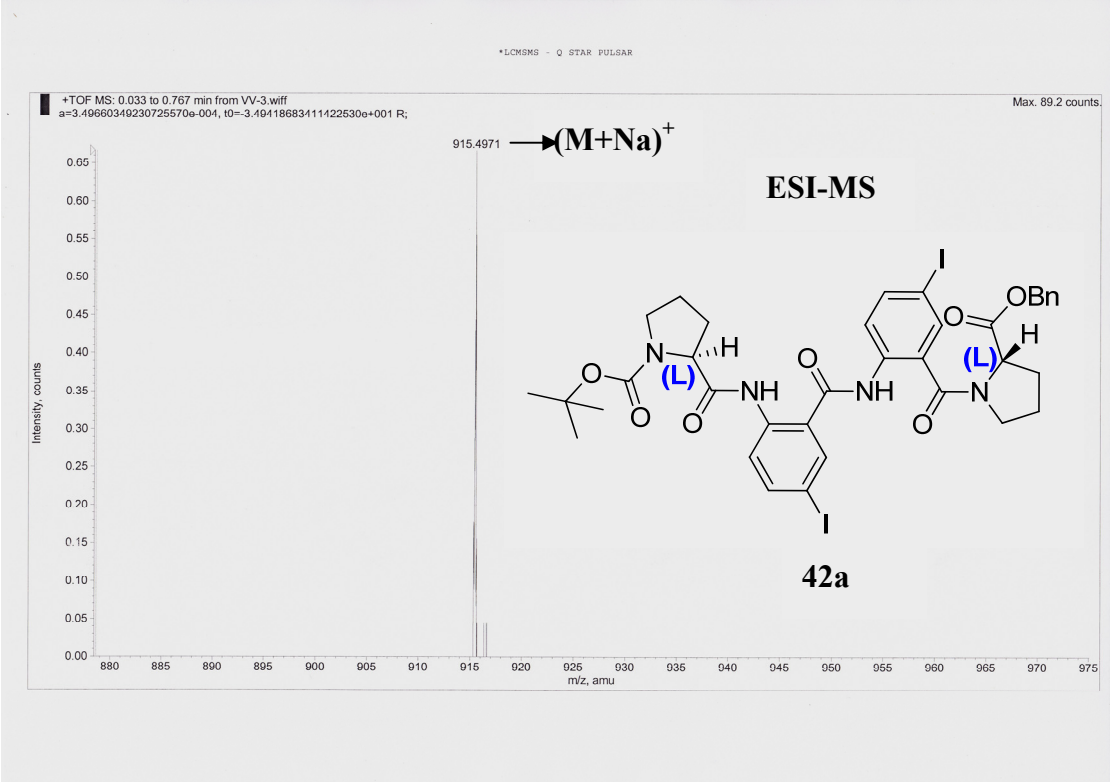

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.533 min from VV-2.wiff
a=3.49743671783255180e-004, t0=-3.49418683411422530e+001
Max. 503.1 counts.
ESI-MS
Intensity, counts
m/z, amu
(M+Na)+
523.7441
37b

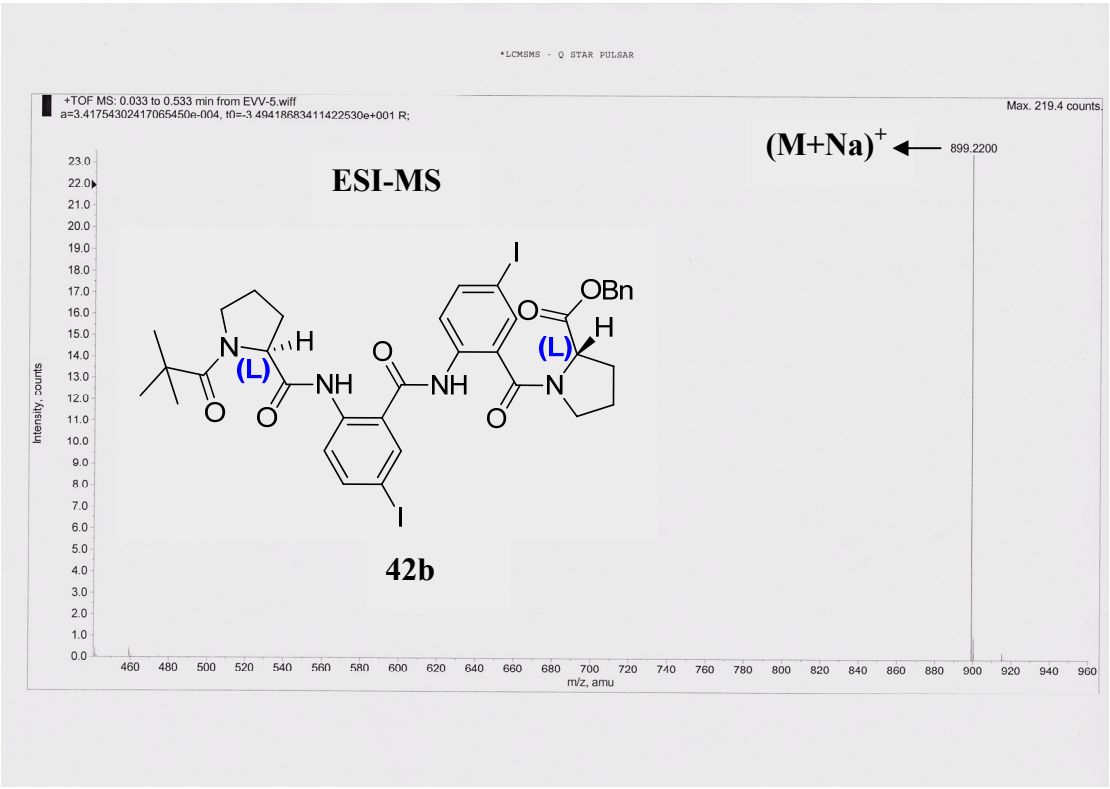

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.650 min from VR-1.wiff
a=3.49720977359559580e-004, t0=-3.49418683411422530e+001
Max. 173.0 counts.
(M+Na)+
742.4921
ESI-MS
(L)
38
(M+K)+
758.5517
Intensity, counts
m/z, amu

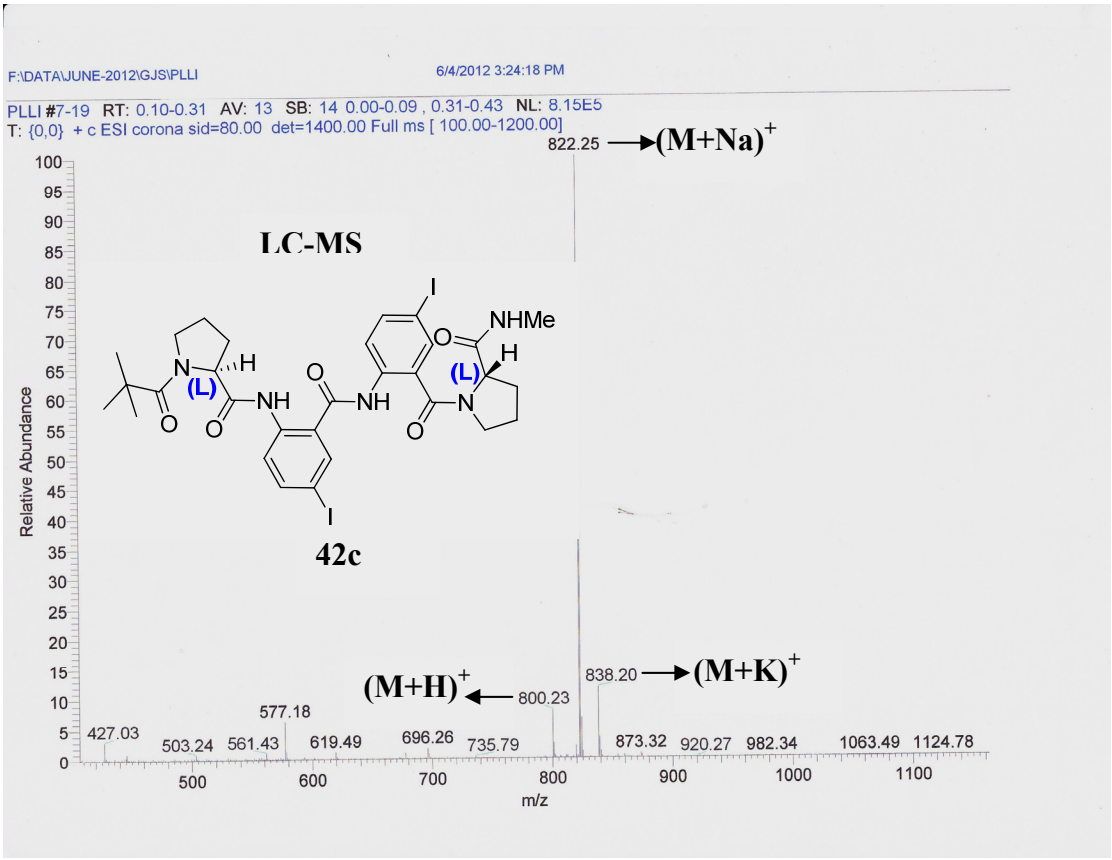

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.583 min from 1-S.wiff
a=3.34952416998245790e-004, t0=-3.49418683411422530e+001 R;
Max. 72.1 counts.
(M+Na)+
742.3020
ESI-MS
(D)
39
Intensity, counts
m/z, amu

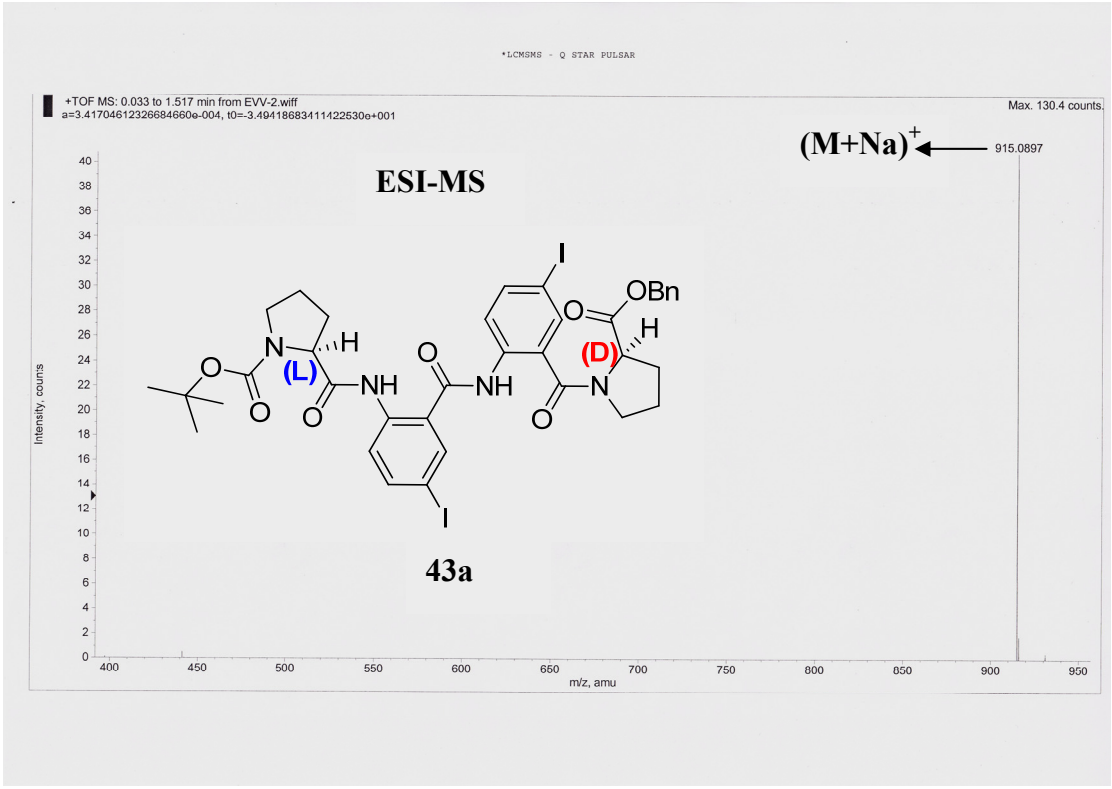

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.467 min from E-3.wiff
a=3.40919422660843140e 004, t0= 3.49418683411422530e+001
Max. 410.6 counts.
ESI-MS
(L)
40
(M+Na)+
710.6242
Intensity, counts
m/z, amu

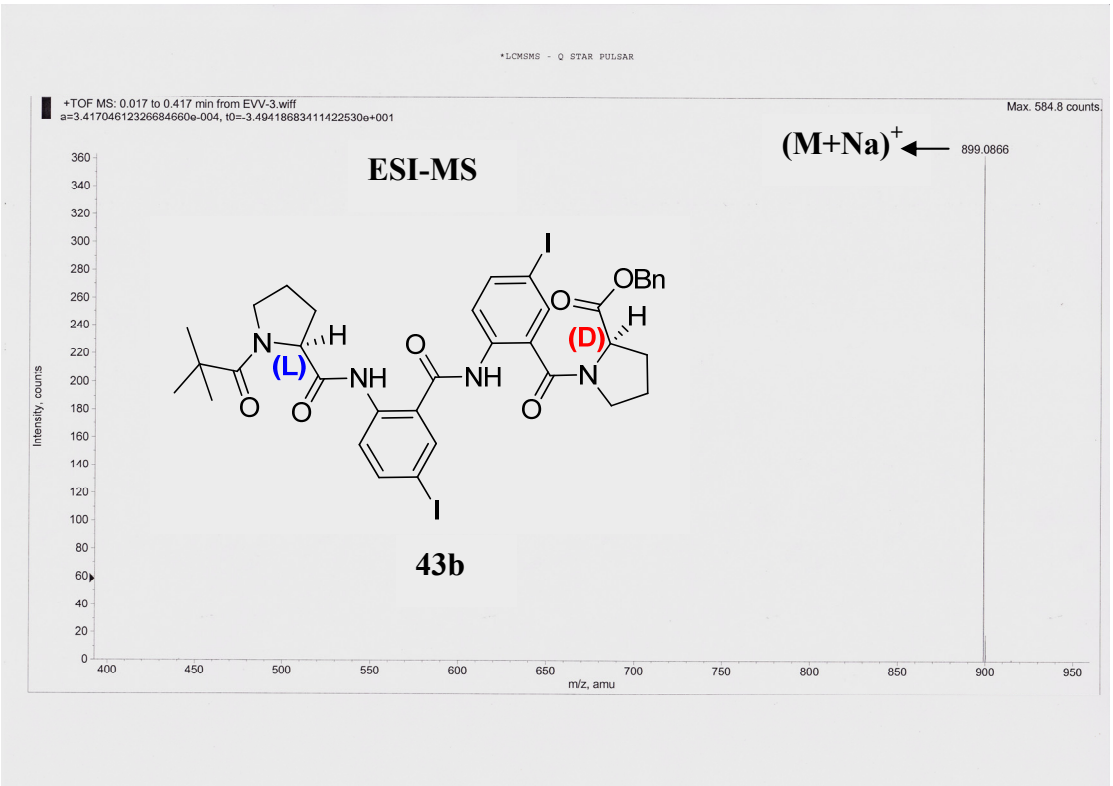

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.717 min from 2-S.wiff
a=3.34952416998245790e-004, t0=-3.49418683411422530e+001
Max. 47.5 counts.
(M+Na)+
710.1471
ESI-MS
(D)
41
Intensity, counts
m/z, amu

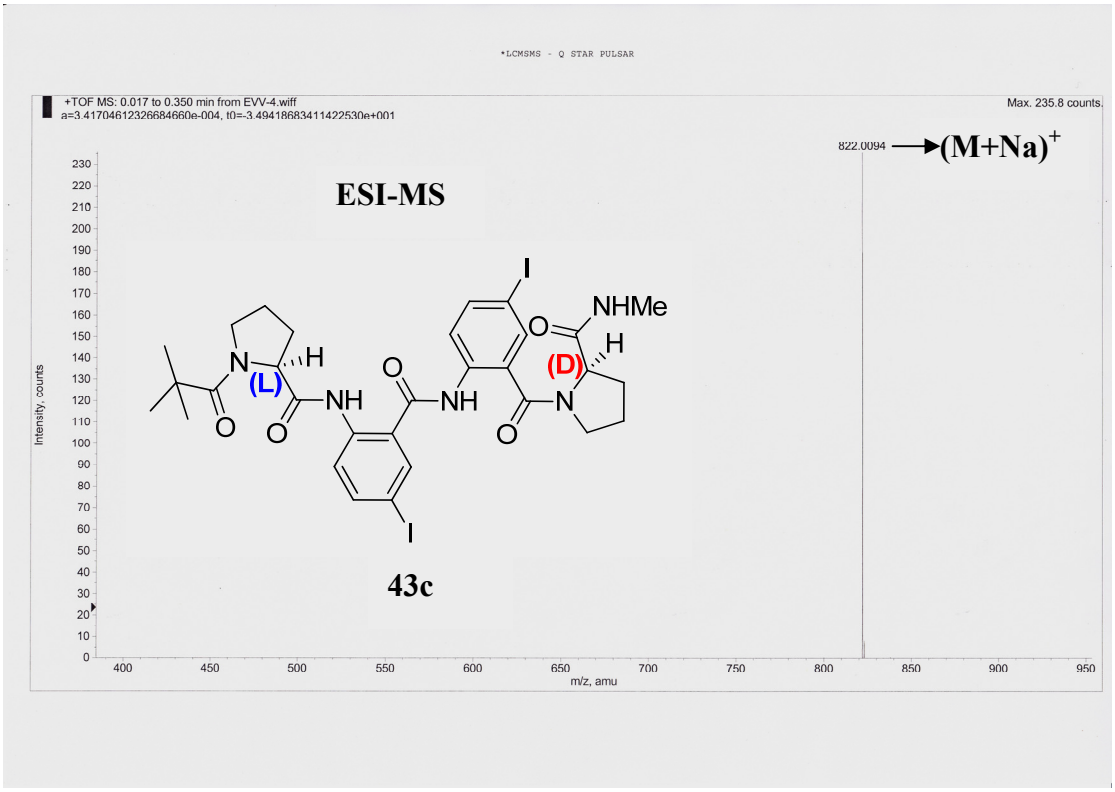

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.767 min from VV-3.wiff
a=3.49660349230725570e-004, t0=-3.49418683411422530e+001 R;
Max. 89.2 counts.
915.4971
(M+Na)+
ESI-MS
Intensity, counts
m/z, amu
OBn
(L)
NH
42a

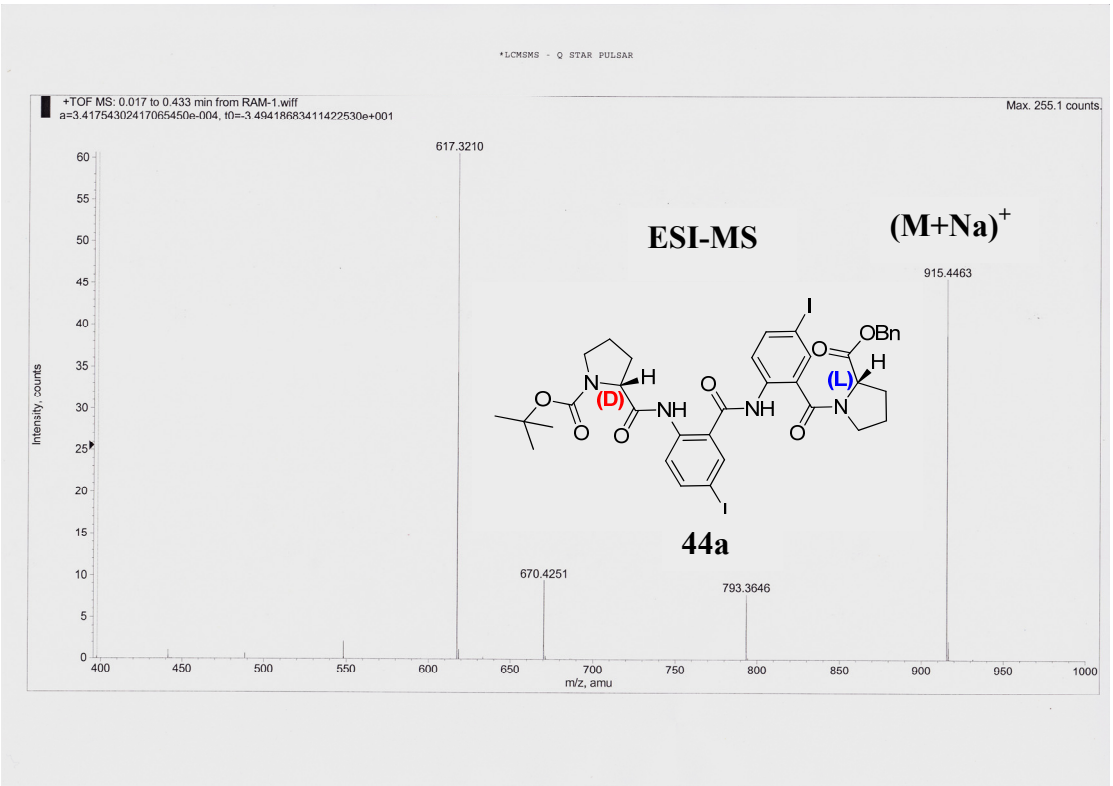

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.533 min from EVV-5.wiff
a=3.41754302417065450e-004, t0=-3.49418683411422530e+001 R;
Max. 219.4 counts.
(M+Na)+
899.2200
ESI-MS
Intensity, counts
m/z, amu
OBn
(L)
NH
42b

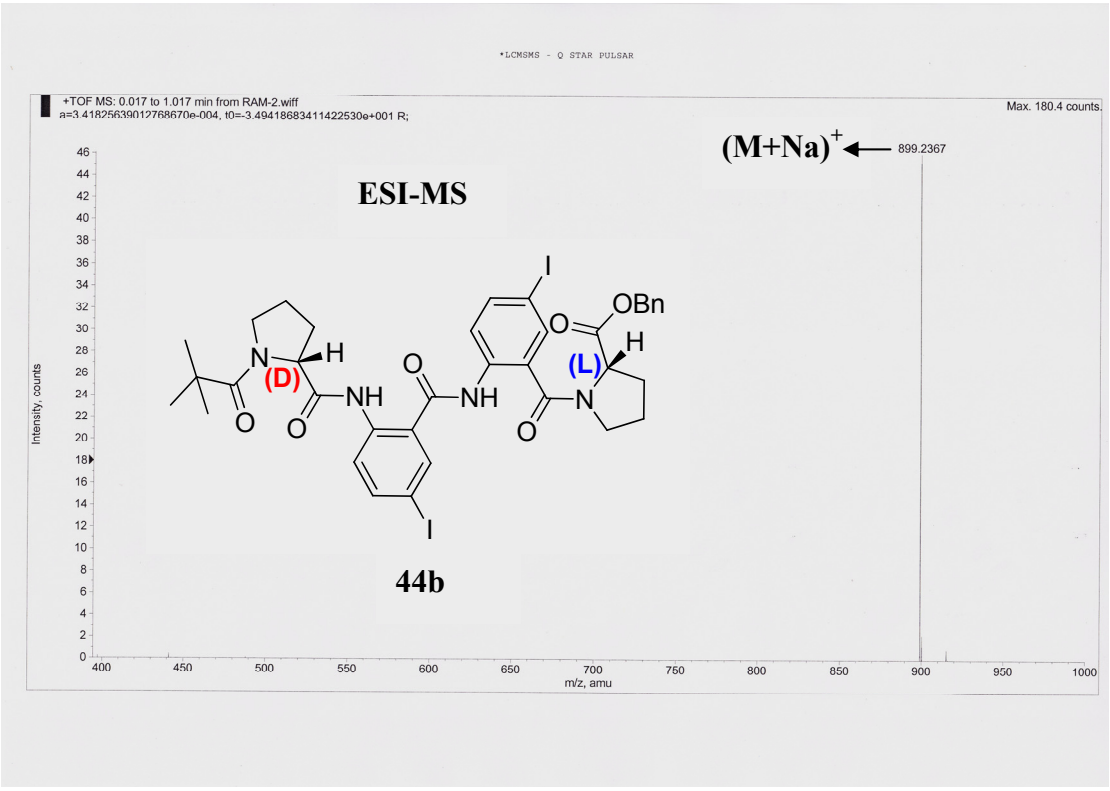

F:\DATA\JUNE-2012\GJS\PLLI
6/4/2012 3:24:18 PM
PLLI #7-19 RT: 0.10-0.31 AV: 13 SB: 14 0.00-0.09 , 0.31-0.43 NL: 8.15E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
822.25 (M+Na)+
LC-MS
NHMe
(L)
(L)
42c
(M+H)+
800.23
838.20 (M+K)+
577.18
427.03
503.24
561.43
619.49
696.26
735.79
873.32
920.27
982.34
1063.49
1124.78
Relative Abundance
m/z

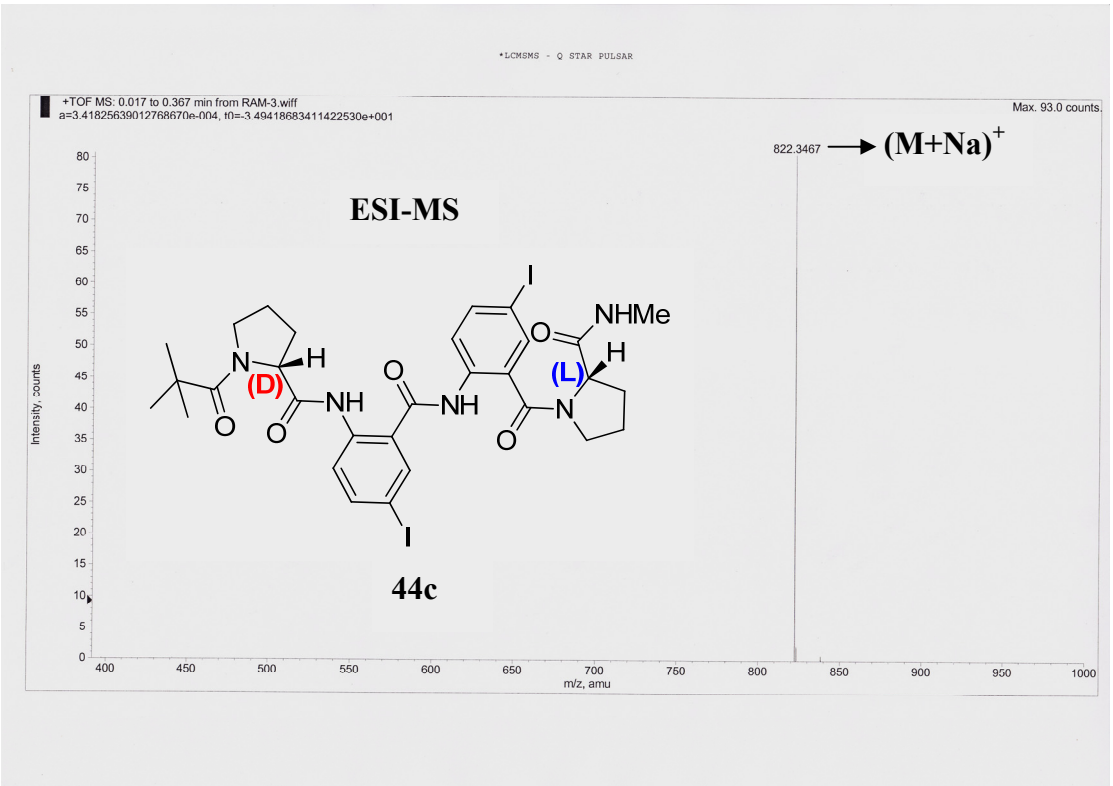

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 1.517 min from EVV-2.wiff
a=3.41704612326684660e-004, t0=-3.49411683411422530e+001
Max. 130.4 counts.
(M+Na)+
915.0897
ESI-MS
OBn
(L)
(D)
43a
Intensity, counts
m/z, amu

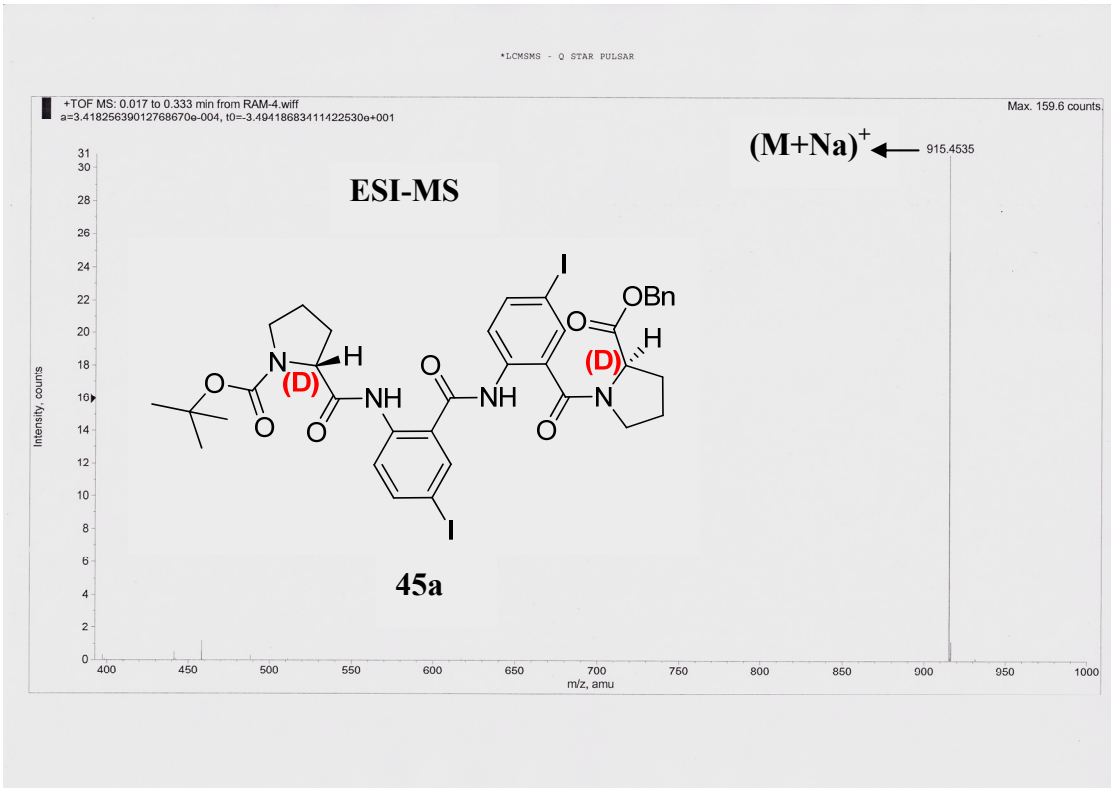

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.417 min from EVV-3.wiff
a=3.41704612326684660e-004, t0=-3.49418683411422530e+001
Max. 584.8 counts.
(M+Na)+
899.0866
ESI-MS
Intensity, counts
m/z, amu
43b

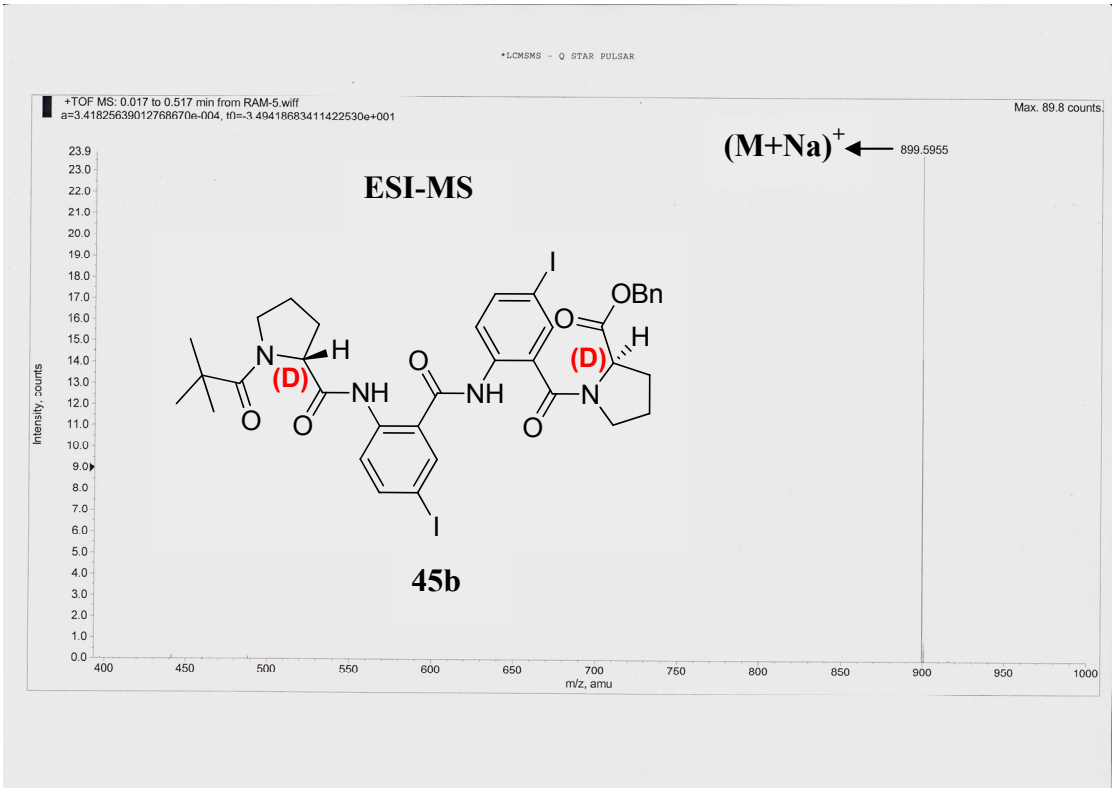

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.350 min from EVV-4.wiff
a=3.41704612326684660e-004, t0=-3.49418683411422530e+001
Max. 235.8 counts.
822.0094
(M+Na)+
ESI-MS
Intensity, counts
m/z, amu
43c

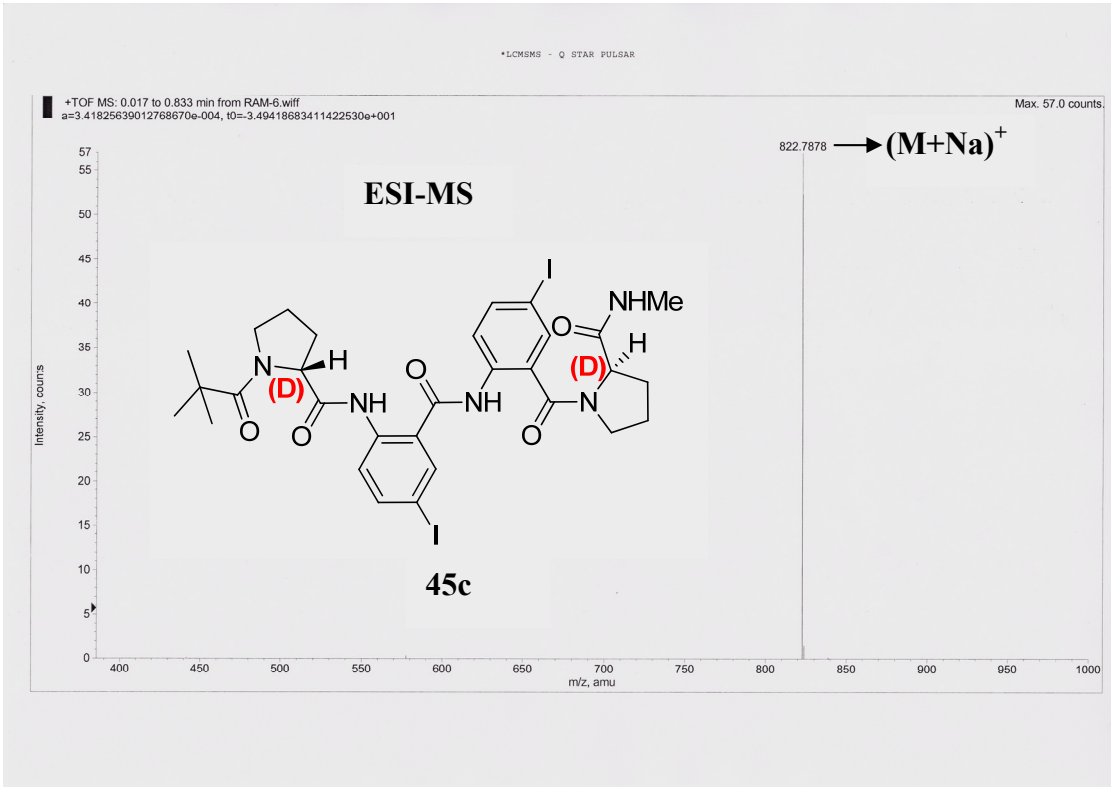

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.433 min from RAM-1.wiff
a=3.417543024170654 50e-004, t0=-3.494186834114225 30e+001
Max. 255.1 counts.
617.3210
ESI-MS
(M+Na)+
915.4463
44a
670.4251
793.3646
Intensity, counts
m/z, amu

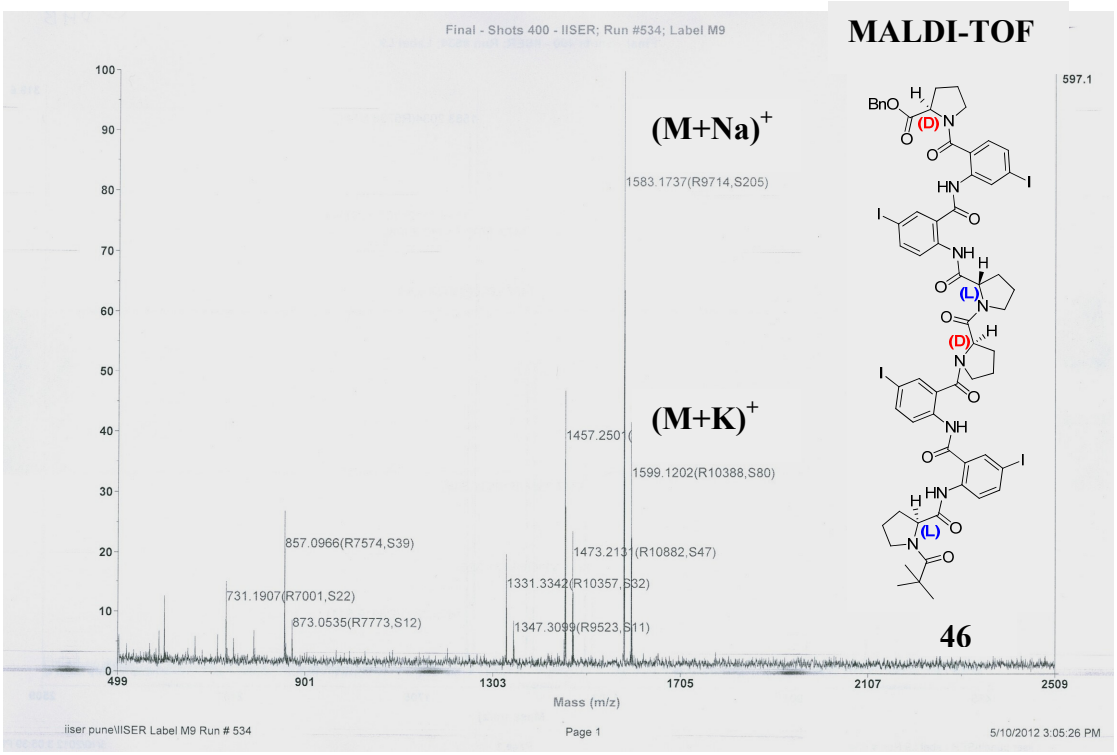

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 1.017 min from RAM-2.wiff
a=3.418256390127686 70e-004, t0=-3.494186834114225 30e+001 R;
Max. 180.4 counts.
(M+Na)+
899.2367
ESI-MS
44b
Intensity, counts
m/z, amu

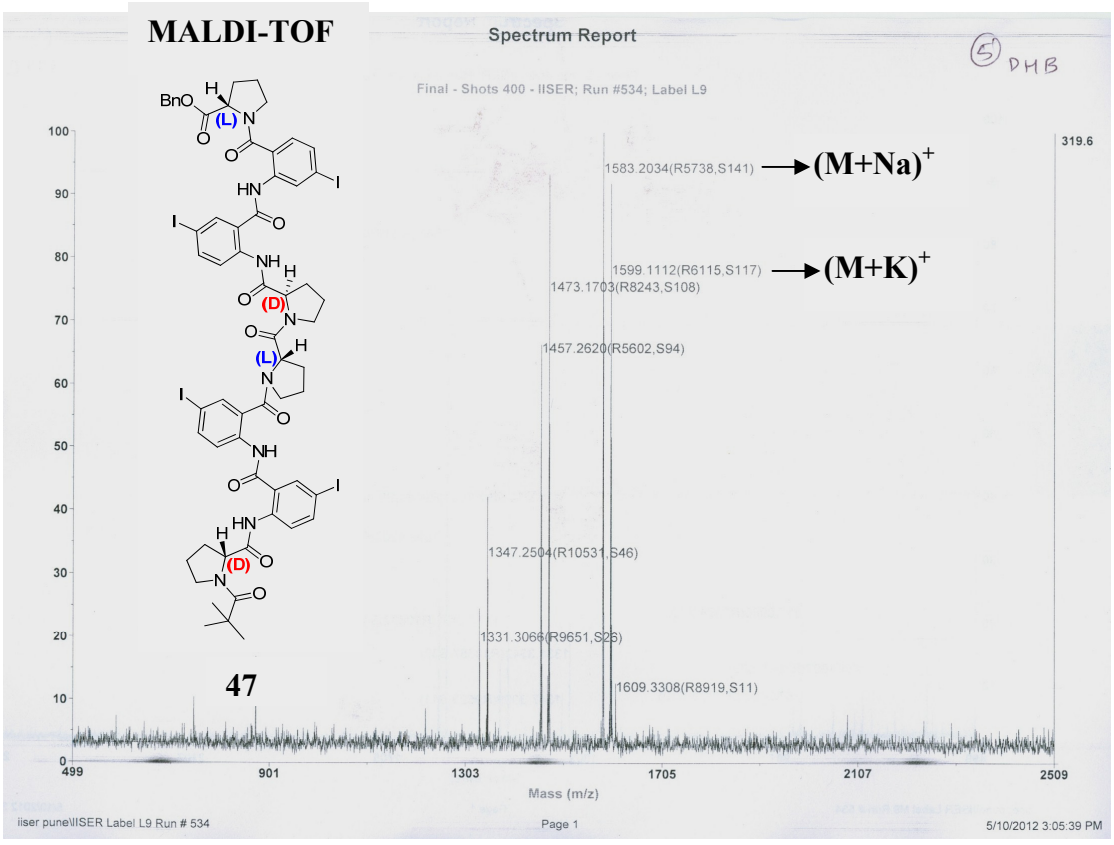

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.367 min from RAM-3.wiff
a=3.418256390127686 70e-004, t0=-3.494186834114225 30e+001
Max. 93.0 counts.
822.3467
(M+Na)+
ESI-MS
Intensity, counts
m/z, amu
44c


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.333 min from RAM-4.wiff
a=3.418256390127686 70e-004, t0=-3.494186834114225 30e+001
Max. 159.6 counts.
915.4535
(M+Na)+
ESI-MS
Intensity, counts
m/z, amu
45a

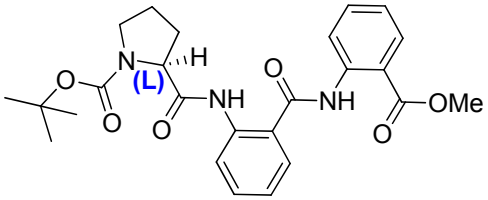

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.517 min from RAM-5.wiff
a=3.41825639012768670e-004, t0=-3.49418683411422530e+001
Max. 89.8 counts.
(M+Na)+
899.5955
ESI-MS
Intensity, counts
m/z, amu
45b


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.833 min from RAM-6.wiff
a=3.41825639012768670e-004, t0=-3.49418683411422530e+001
Max. 57.0 counts.
822.7878
(M+Na)+
ESI-MS
Intensity, counts
m/z, amu
45c


MALDI-TOF
Final - Shots 400 - IISER; Run #534; Label M9
(M+Na)+
1583.1737(R9714,S205)
(M+K)+
1457.2501(
1599.1202(R10388,S80)
857.0966(R7574,S39)
1473.2131(R10882,S47)
731.1907(R7001,S22)
1331.3342(R10357,S32)
873.0535(R7773,S12)
1347.3099(R9523,S11)
597.1
46
Mass (m/z)
iiser pune\IISER Label M9 Run # 534
Page 1
5/10/2012 3:05:26 PM


MALDI-TOF
Spectrum Report
DHB
Final - Shots 400 - IISER; Run #534; Label L9
1583.2034(R5738,S141) → (M+Na)+
1599.1112(R6115,S117) → (M+K)+
1473.1703(R8243,S108)
1457.2620(R5602,S94)
1347.2504(R10531,S46)
1331.3066(R9651,S26)
1609.3308(R8919,S11)
319.6
47
Mass (m/z)
iiser pune\IISER Label L9 Run # 534
Page 1
5/10/2012 3:05:39 PM

^{1}H NMR ($CDCl_3$, 200 MHz)

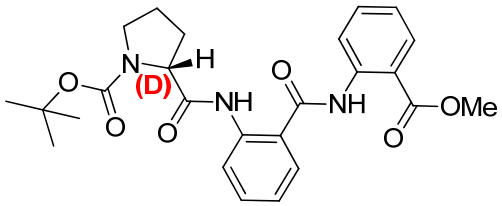


25

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{1}H NMR ($CDCl_3$, 200 MHz)



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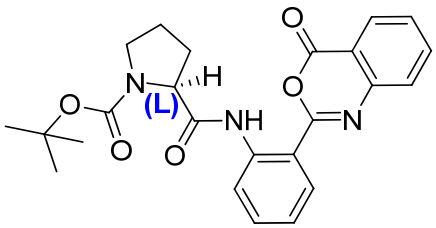
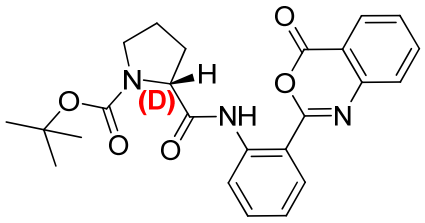
^{1}H NMR ($CDCl_3$, 200 MHz)



27

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

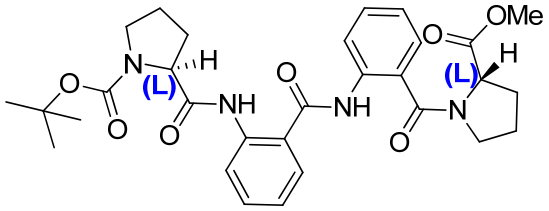
^{1}H NMR ($CDCl_3$, 200 MHz)



28

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

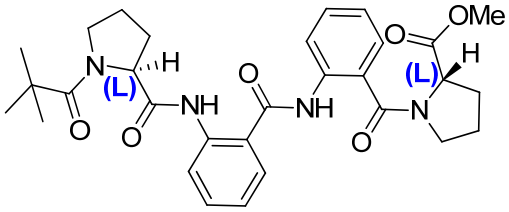
^{1}H NMR ($CDCl_3$, 200 MHz)



29a

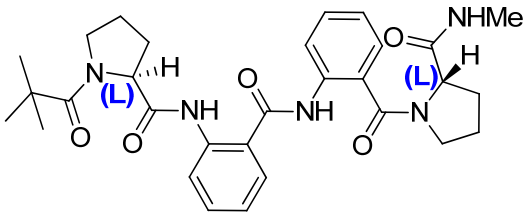
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{1}H NMR ($CDCl_3$, 200 MHz)



29b

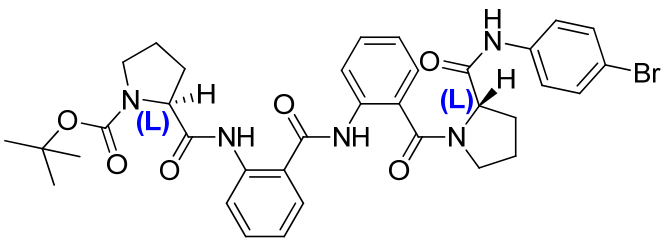
^{1}H NMR ($CDCl_3$, 200 MHz)



29c

 # DMF

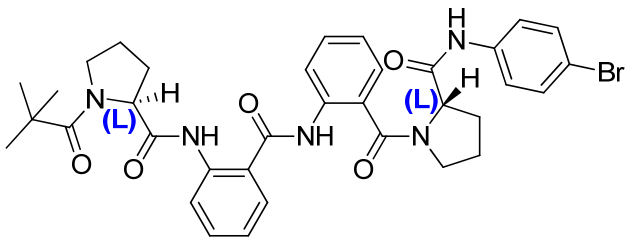
^{1}H NMR ($CDCl_3$, 200 MHz)



30a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

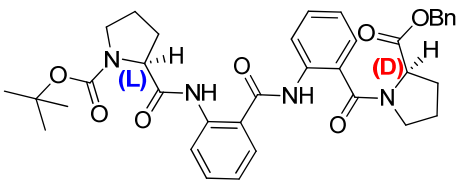
^{1}H NMR ($CDCl_3$, 200 MHz)



30b

 # DMF

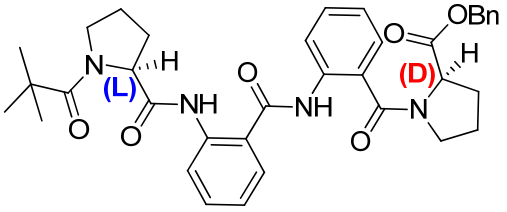
^{1}H NMR ($CDCl_3$, 500 MHz)



31a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

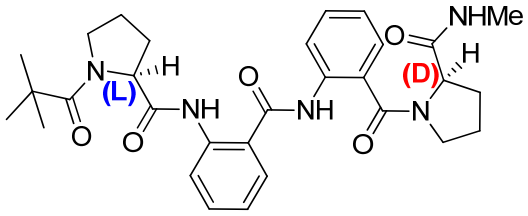
^{1}H NMR ($CDCl_3$, 200 MHz)



31b

 # DMF

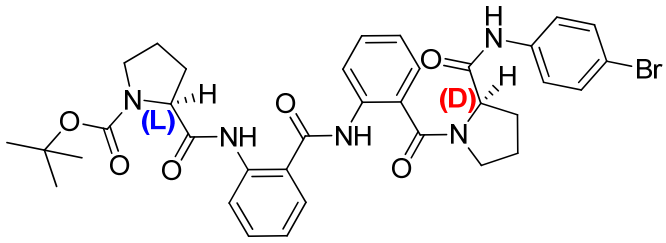
^{1}H NMR ($CDCl_3$, 500 MHz)



31c

 # DMF

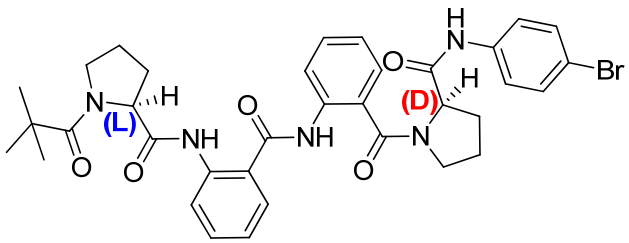
^{1}H NMR ($CDCl_3$, 200 MHz)



NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

32a

^{1}H NMR ($CDCl_3$, 500 MHz)

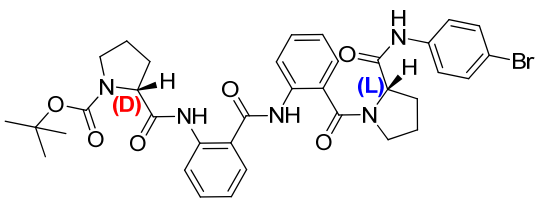


32b

 # DMF

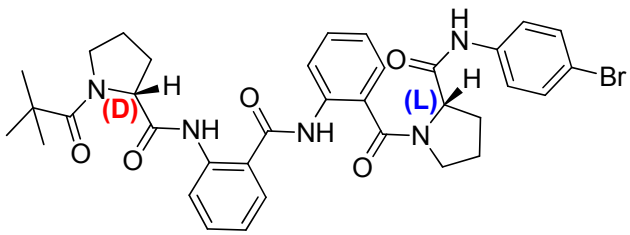
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{1}H NMR ($CDCl_3$, 200 MHz)



33a

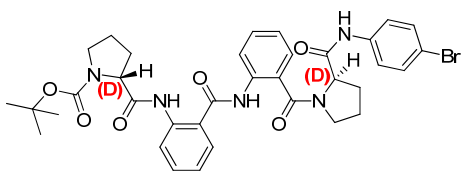
^{1}H NMR ($CDCl_3$, 200 MHz)



33b

DMF

^{1}H NMR ($CDCl_3$, 200 MHz)

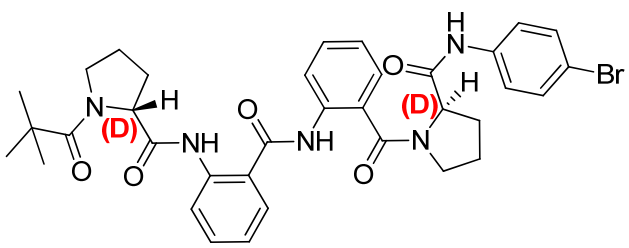


34a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

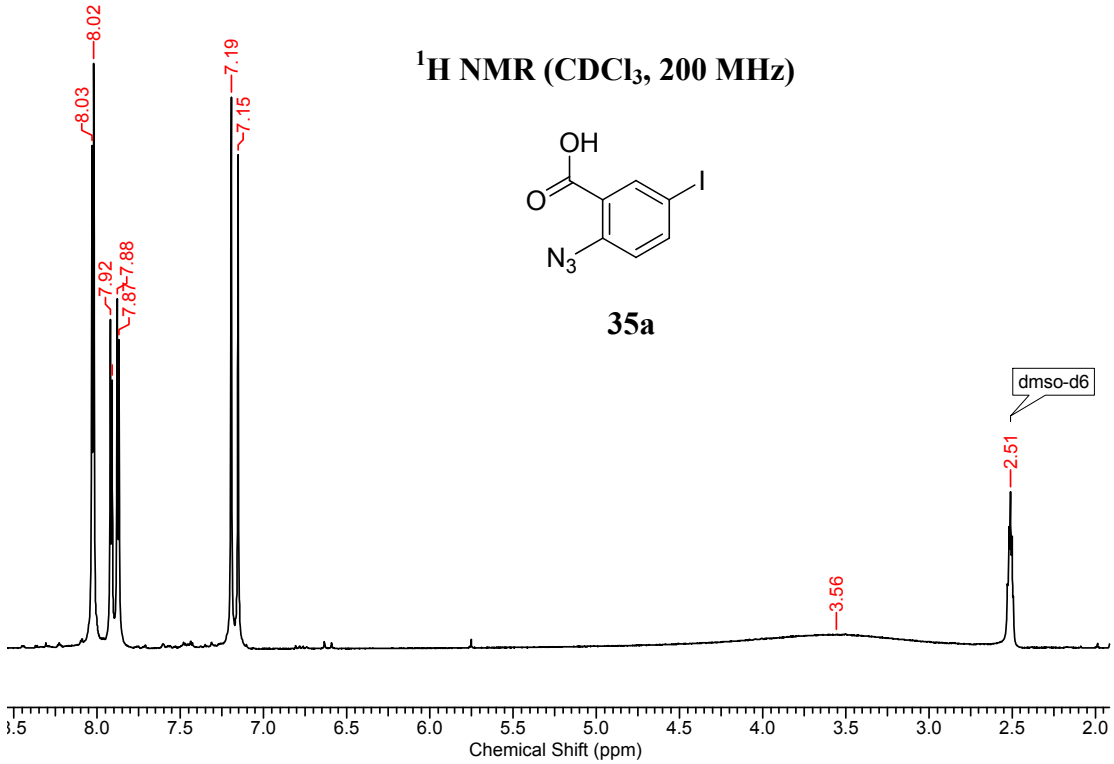
 # DMF

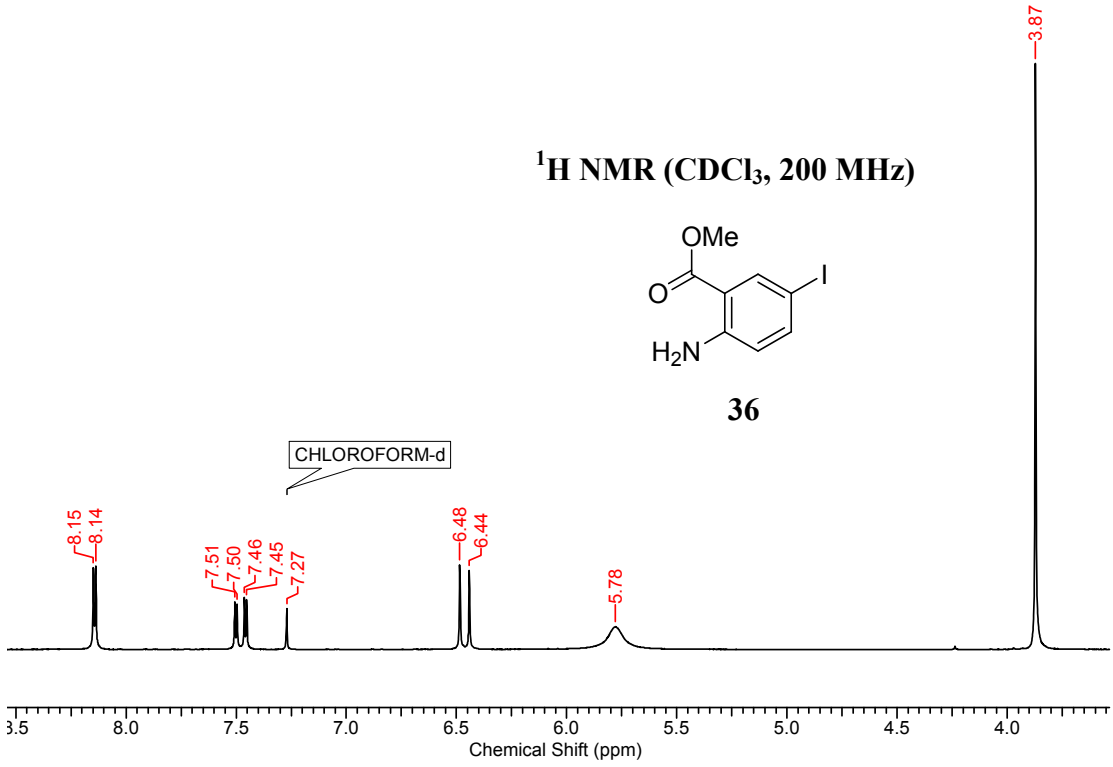
^{1}H NMR ($CDCl_3$, 200 MHz)



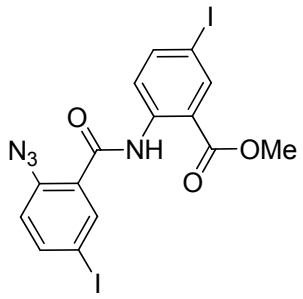
34b

 # DMF


^{1}H NMR (CDCl$_3$, 200 MHz)
OH
O
I
N$_3$
35a
8.02
8.03
7.92
7.88
7.87
7.19
7.15
dmso-d6
2.51
3.56
Chemical Shift (ppm)

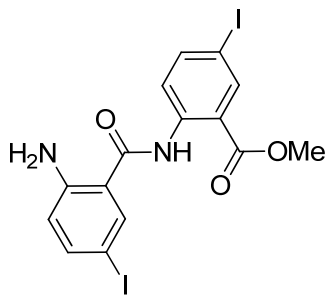

^{1}H NMR (CDCl$_3$, 200 MHz)
OMe
O
I
H$_2$N
36
3.87
CHLOROFORM-d
8.15
8.14
7.51
7.50
7.46
7.45
7.27
6.48
6.44
5.78
Chemical Shift (ppm)

^{1}H NMR ($CDCl_3$, 200 MHz)



37a

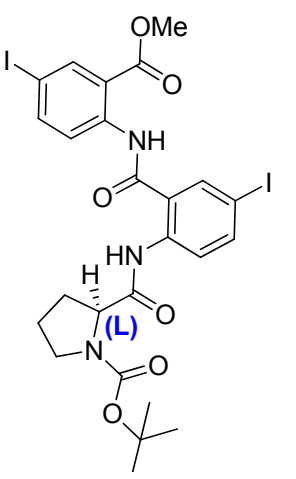
^{1}H NMR ($CDCl_3$, 200 MHz)



37b

^{1}H NMR ($CDCl_3$, 200 MHz)

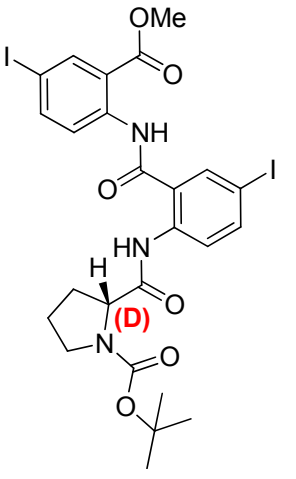
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



38

^{1}H NMR ($CDCl_3$, 200 MHz)

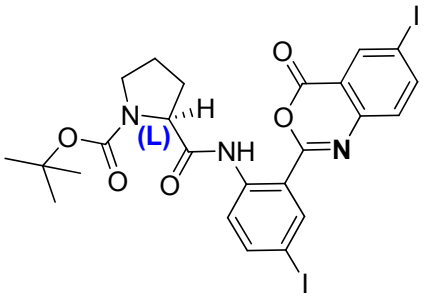
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



39

^{1}H NMR ($CDCl_3$, 200 MHz)

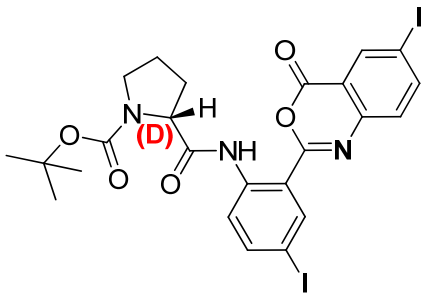
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



40

^{1}H NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

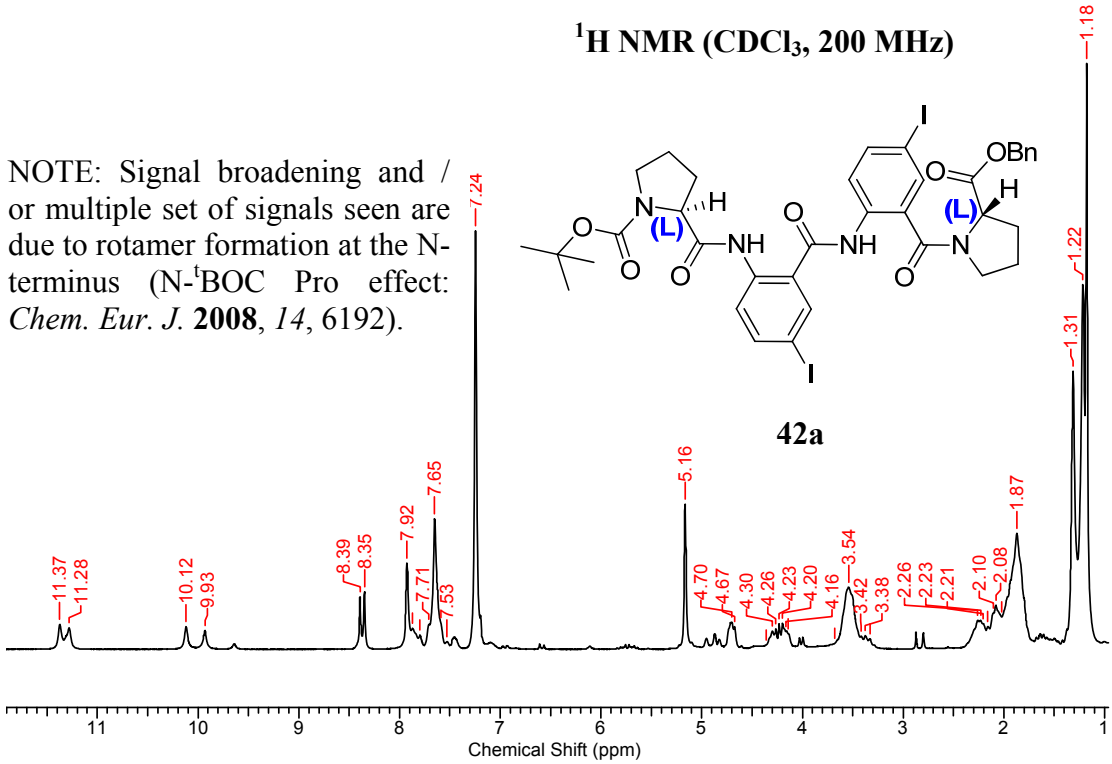


41

DCM

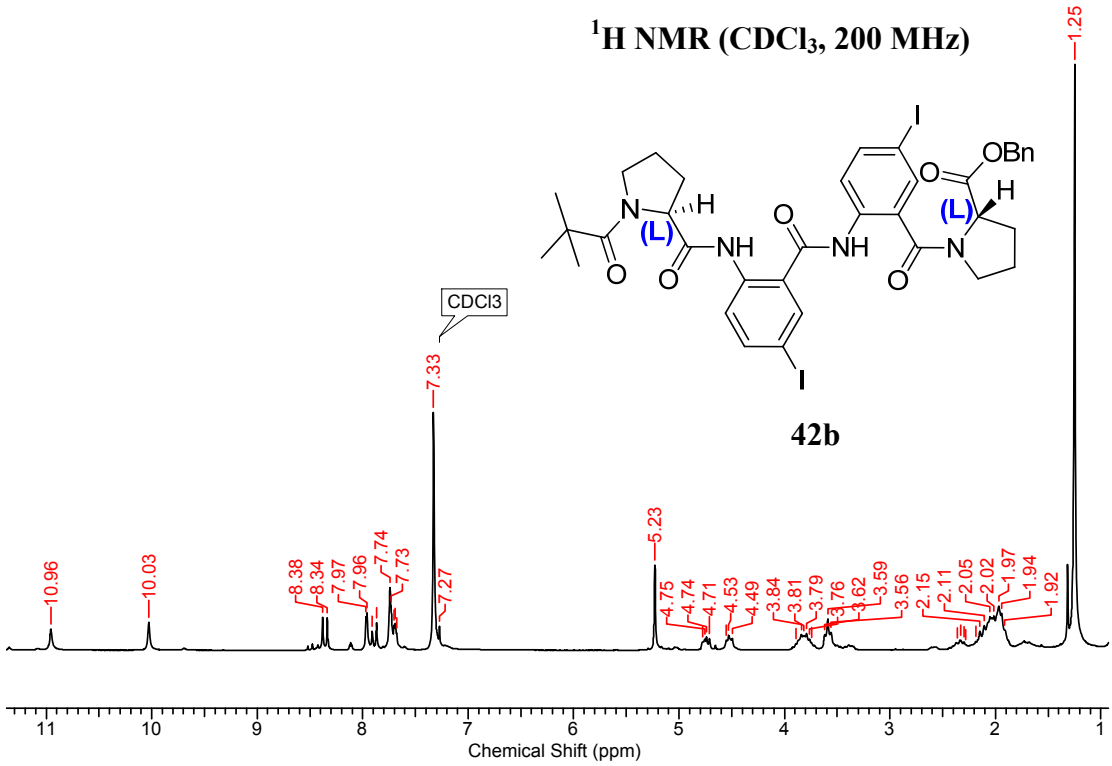
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{1}H NMR ($CDCl_3$, 200 MHz)



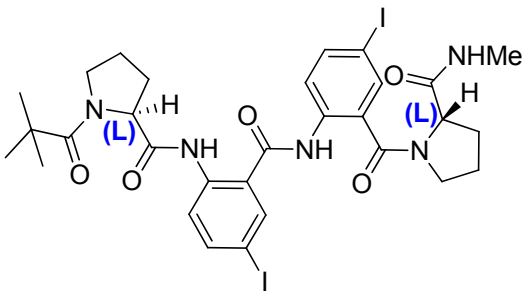
42a

^{1}H NMR ($CDCl_3$, 200 MHz)



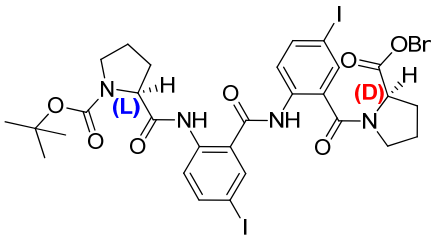
42b

^{1}H NMR ($CDCl_3$, 200 MHz)



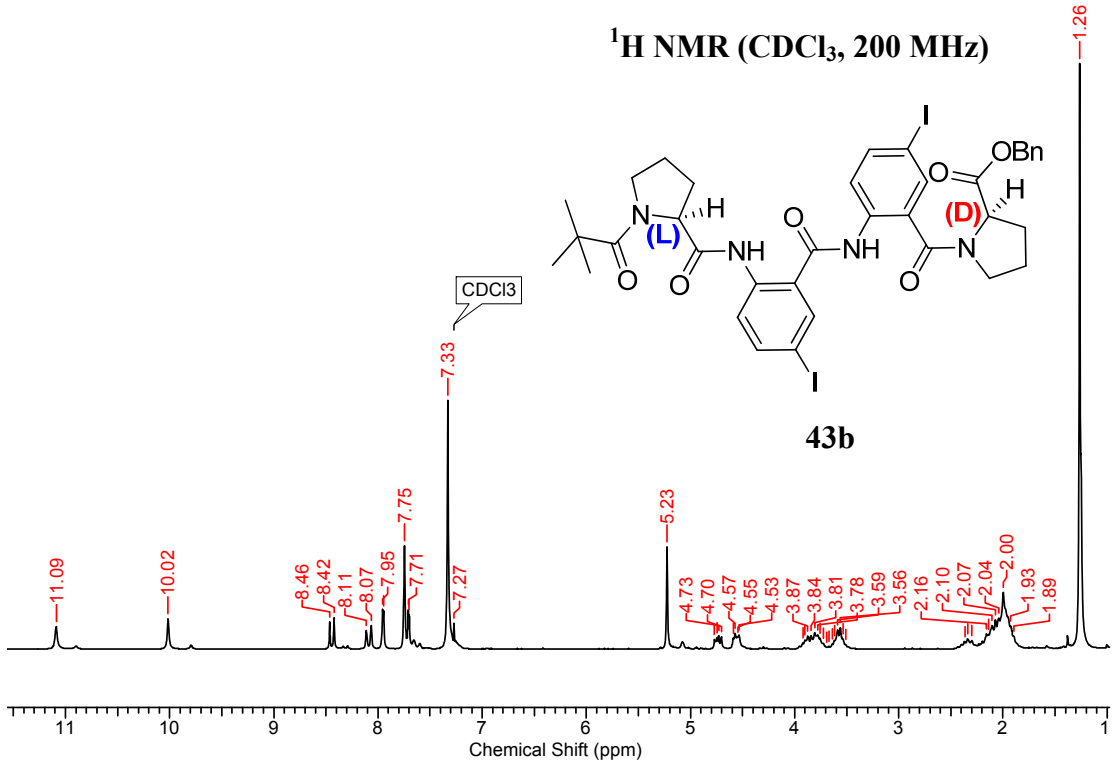
42c

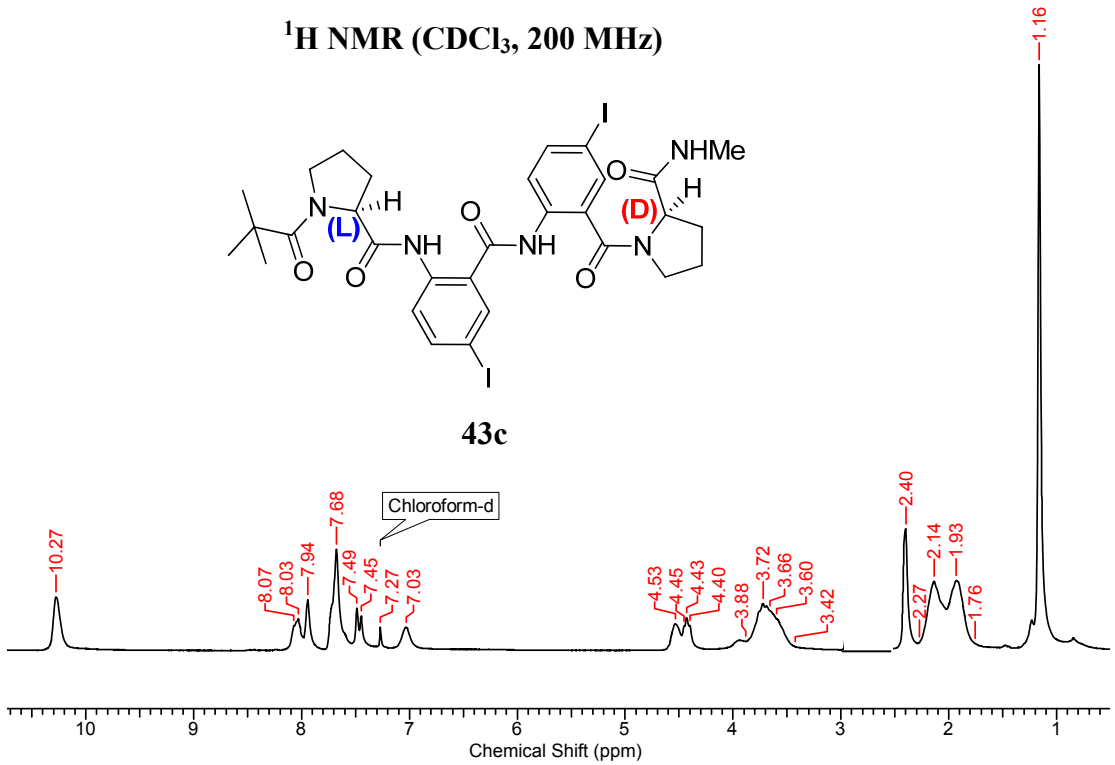
^{1}H NMR ($CDCl_3$, 200 MHz)



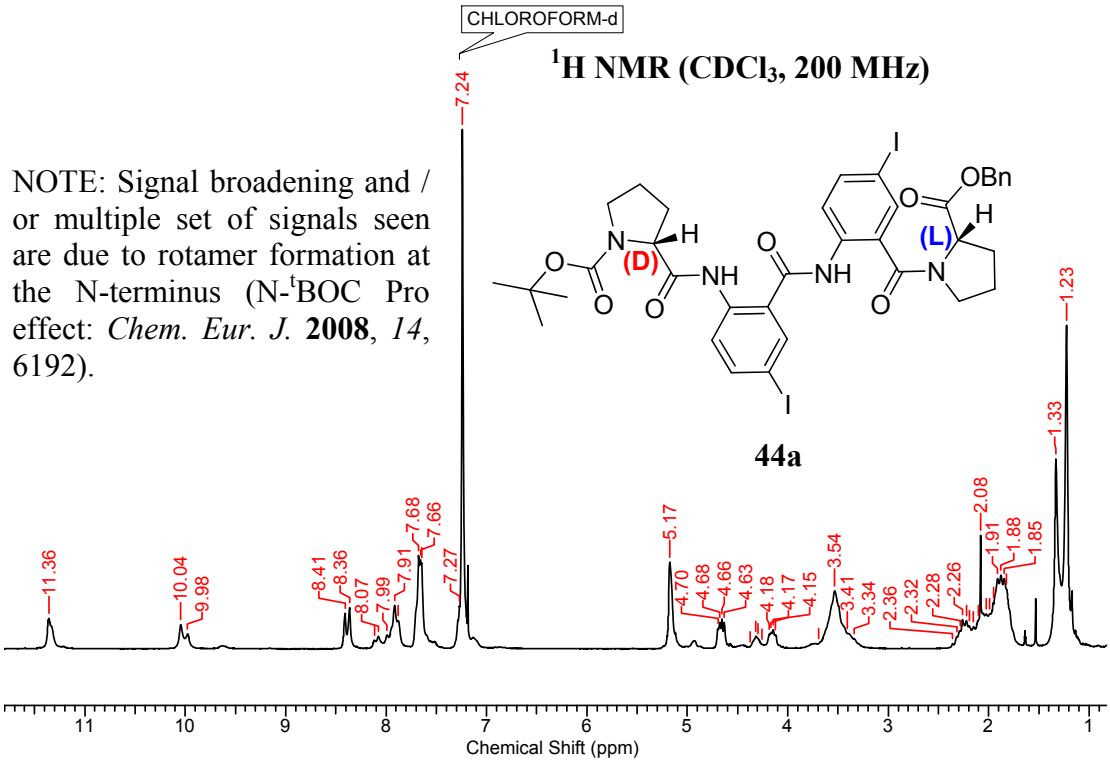
43a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

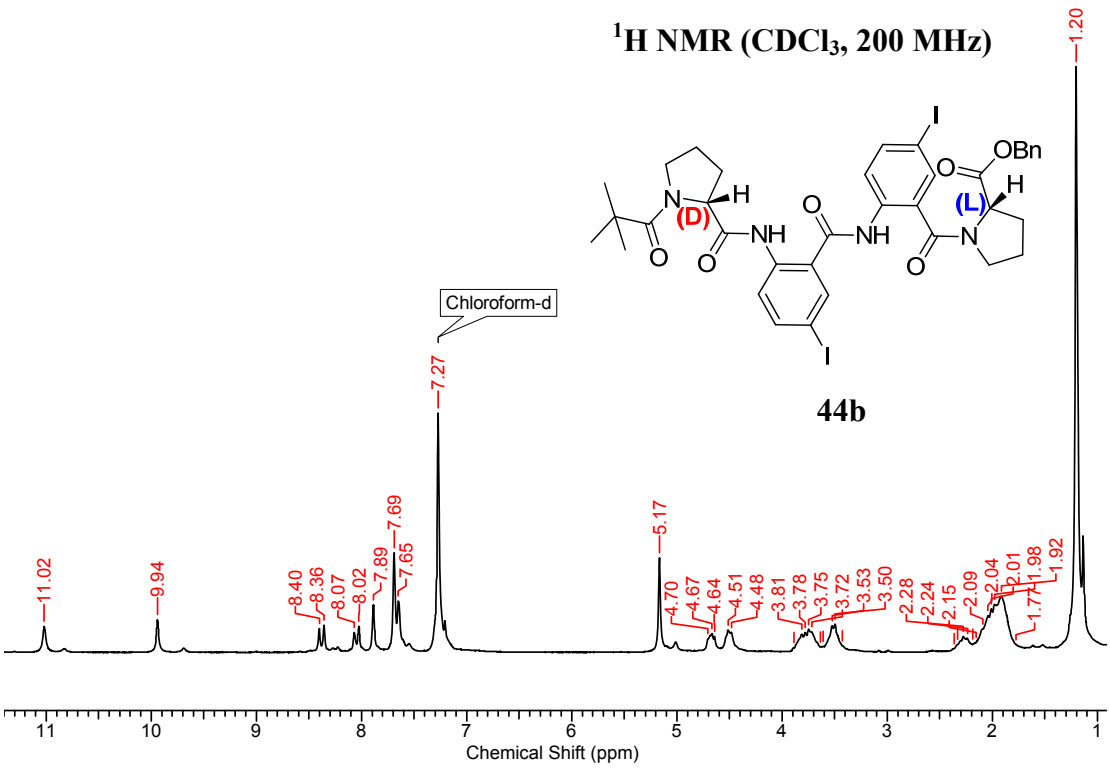

^{1}H NMR (CDCl$_3$, 200 MHz)
CDCl3
43b
Chemical Shift (ppm)


^{1}H NMR (CDCl$_3$, 200 MHz)
Chloroform-d
43c
Chemical Shift (ppm)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

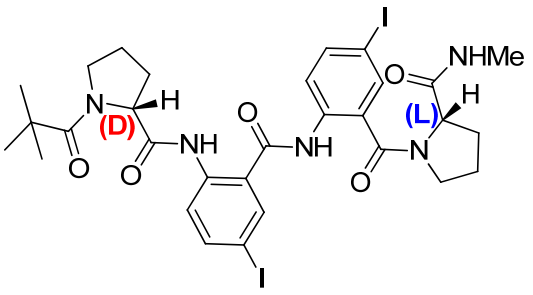


44a



44b

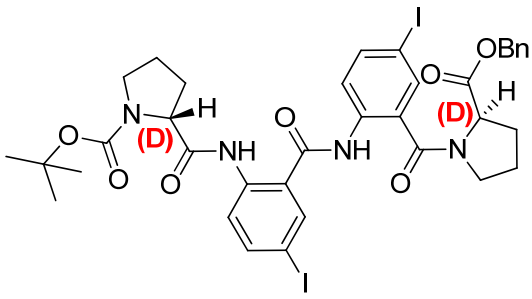
^{1}H NMR ($CDCl_3$, 200 MHz)



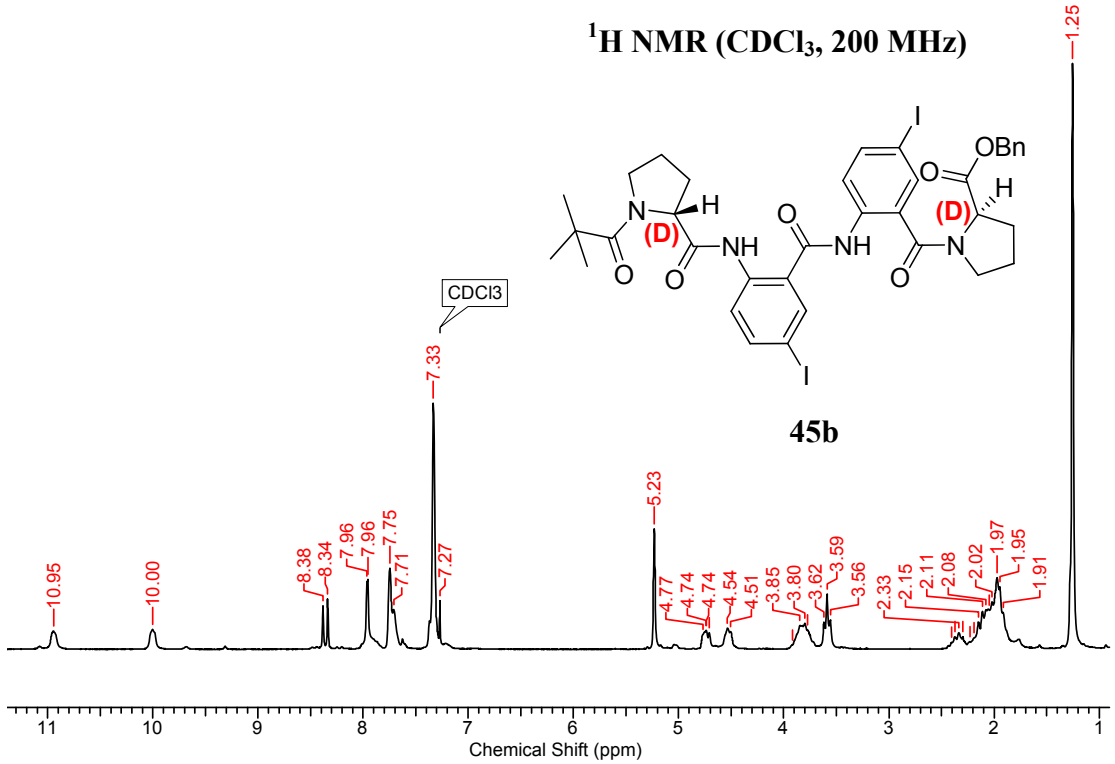
44c

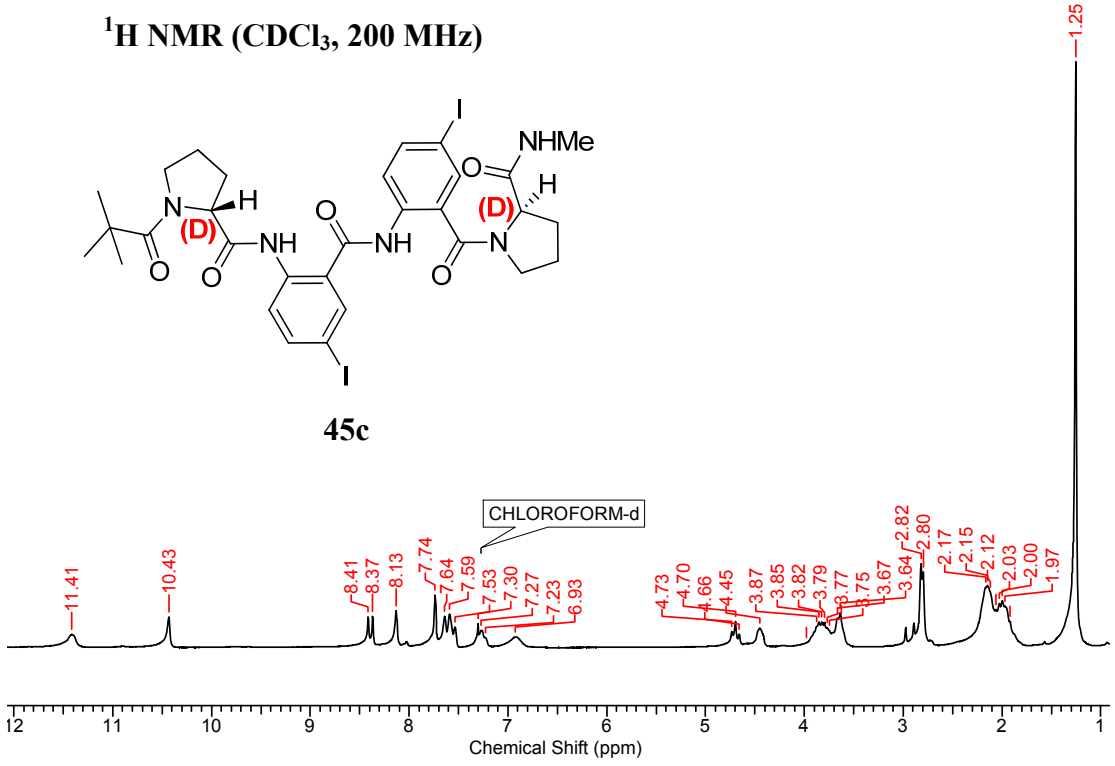
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

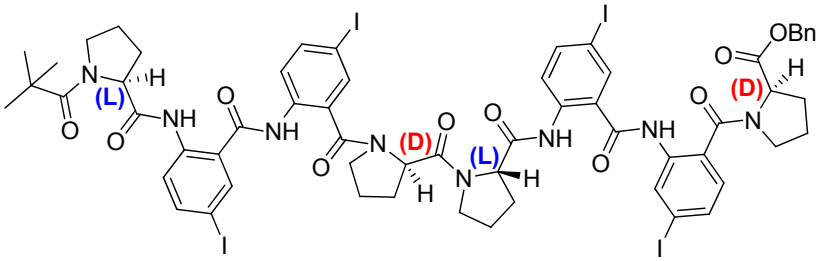
^{1}H NMR ($CDCl_3$, 200 MHz)



45a

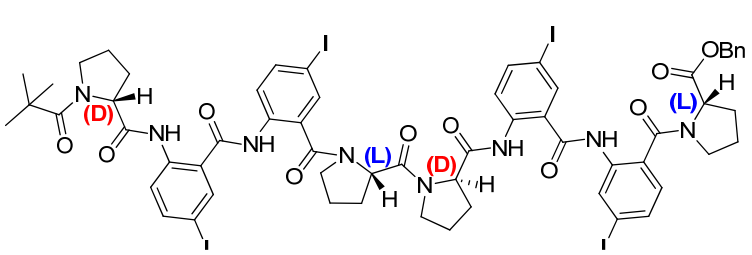

^{1}H NMR (CDCl$_3$, 200 MHz)
CDCl3
45b
Chemical Shift (ppm)


^{1}H NMR (CDCl$_3$, 200 MHz)
CHLOROFORM-d
45c
Chemical Shift (ppm)



46

^{1}H NMR ($CDCl_3$, 200 MHz)

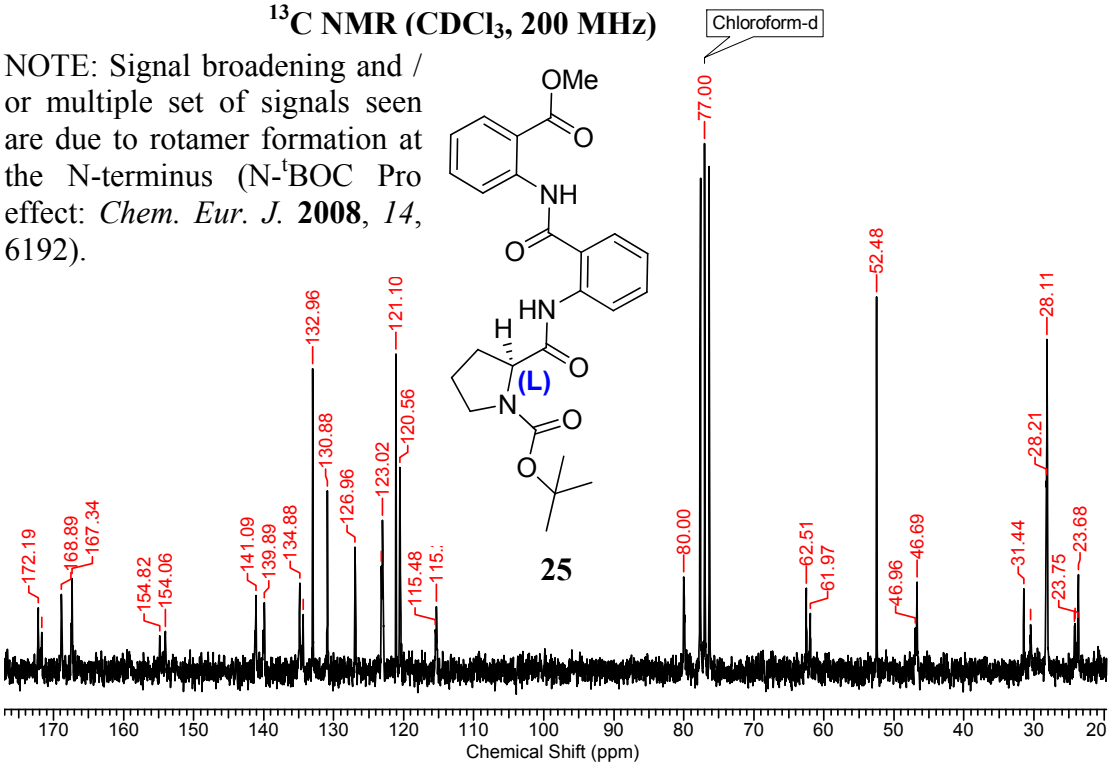


47

^{1}H NMR ($CDCl_3$, 200 MHz)

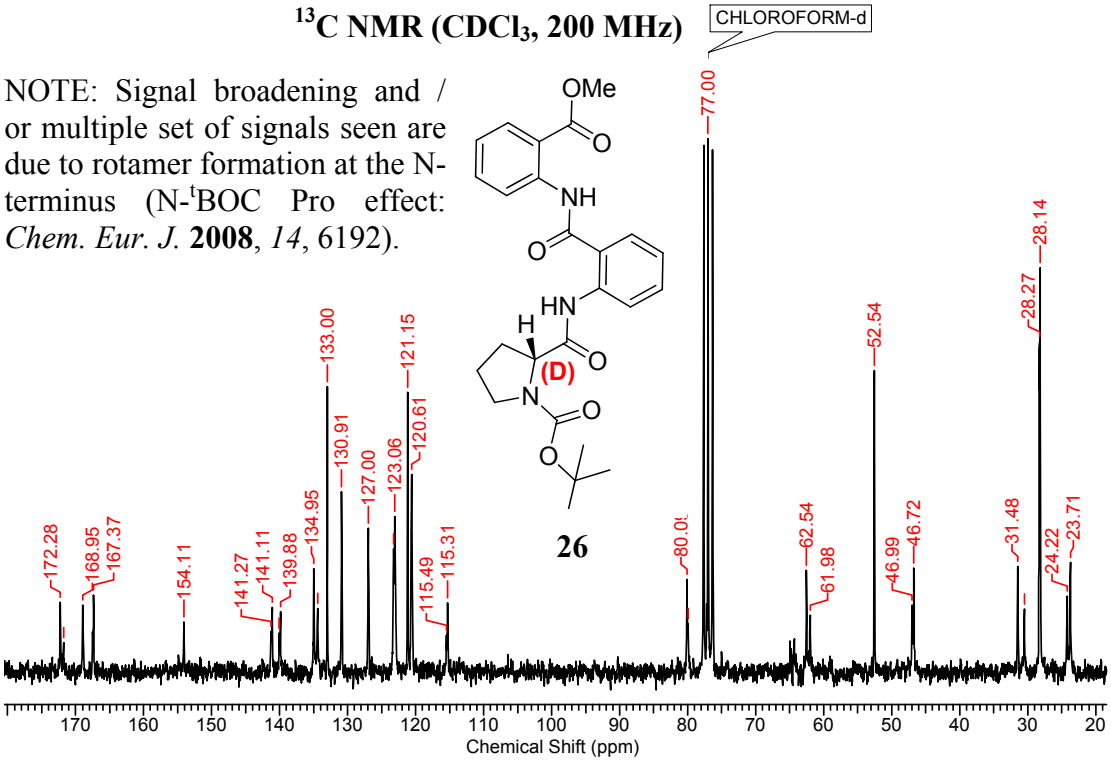
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

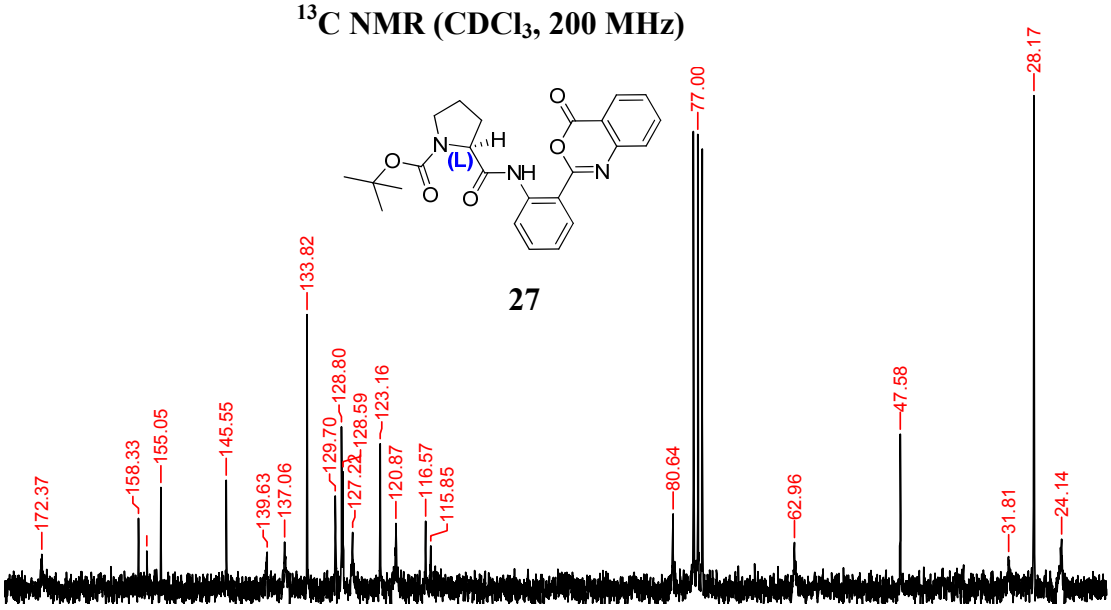


^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



^{13}C NMR ($CDCl_3$, 200 MHz)

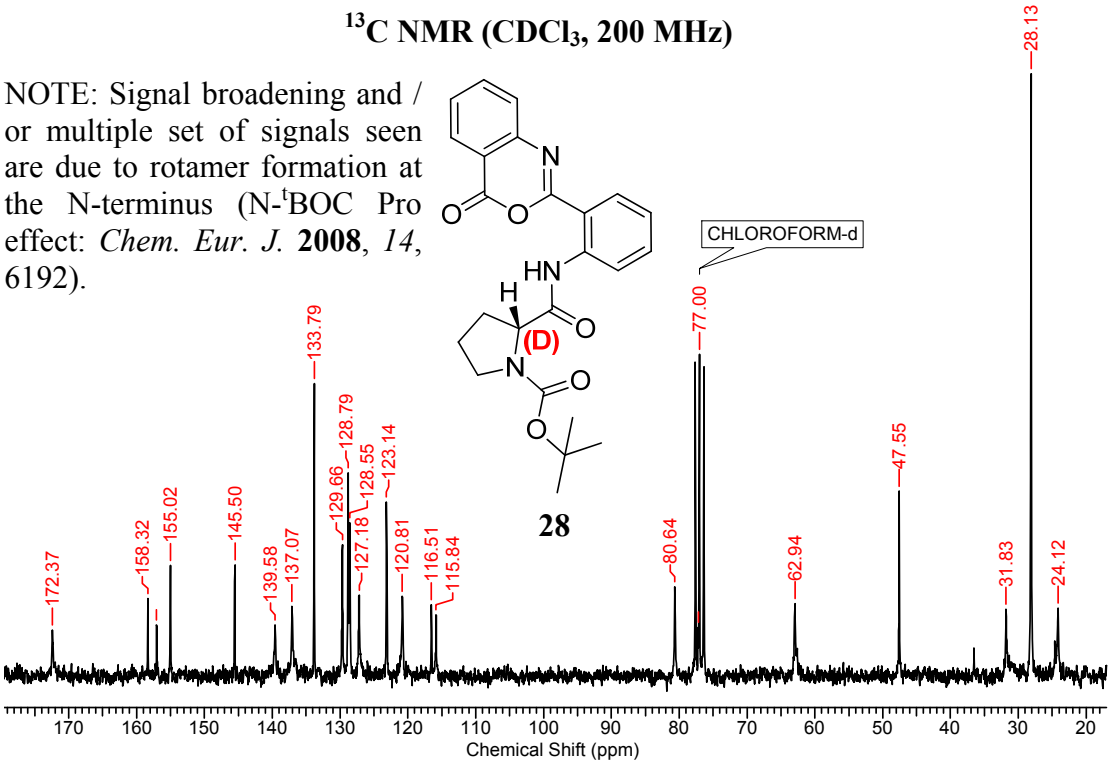


27

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

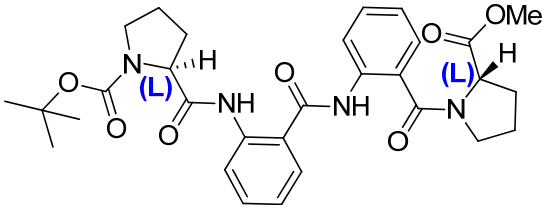
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



28

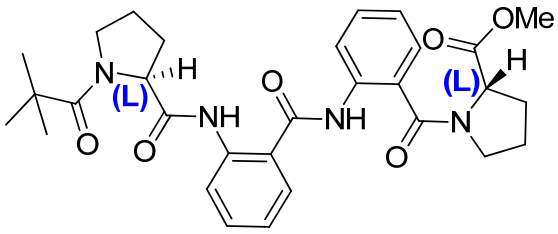
^{13}C NMR ($CDCl_3$, 200 MHz)



29a

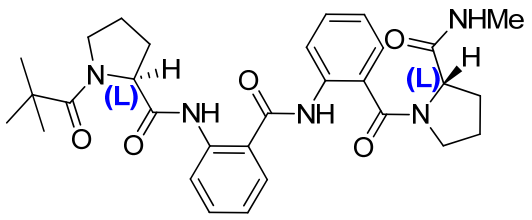
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{13}C NMR ($CDCl_3$, 200 MHz)



29b

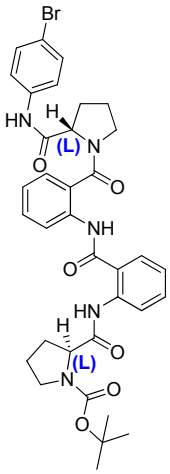
^{13}C NMR ($CDCl_3$, 200 MHz)



29c

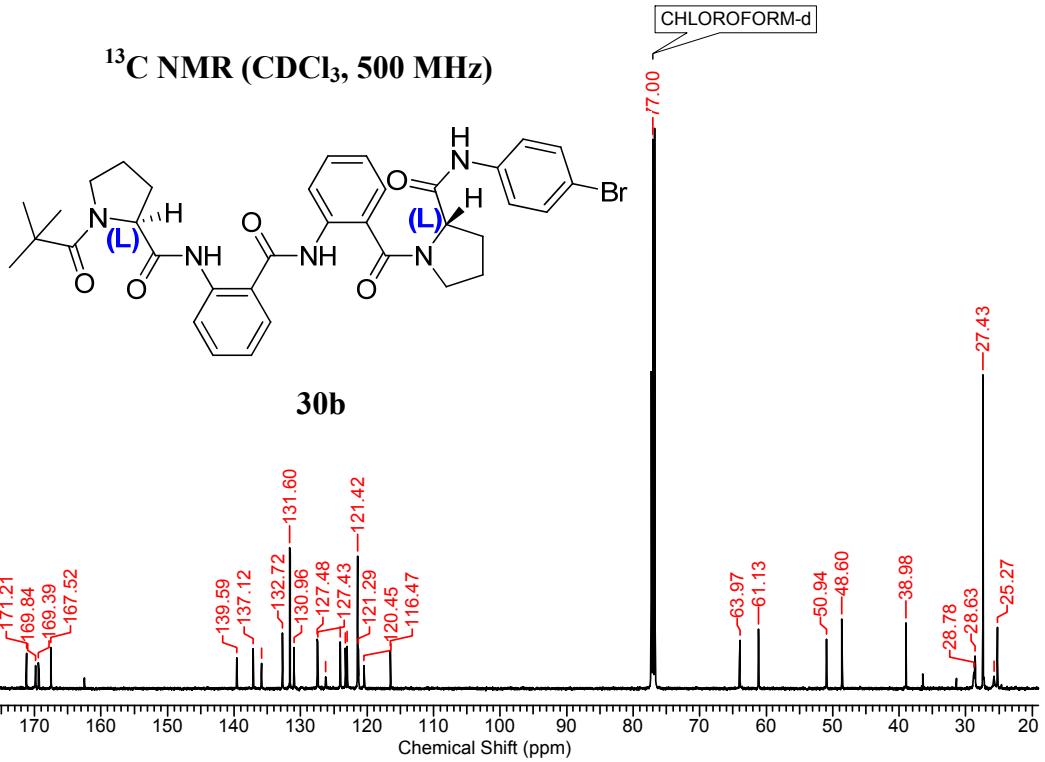
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



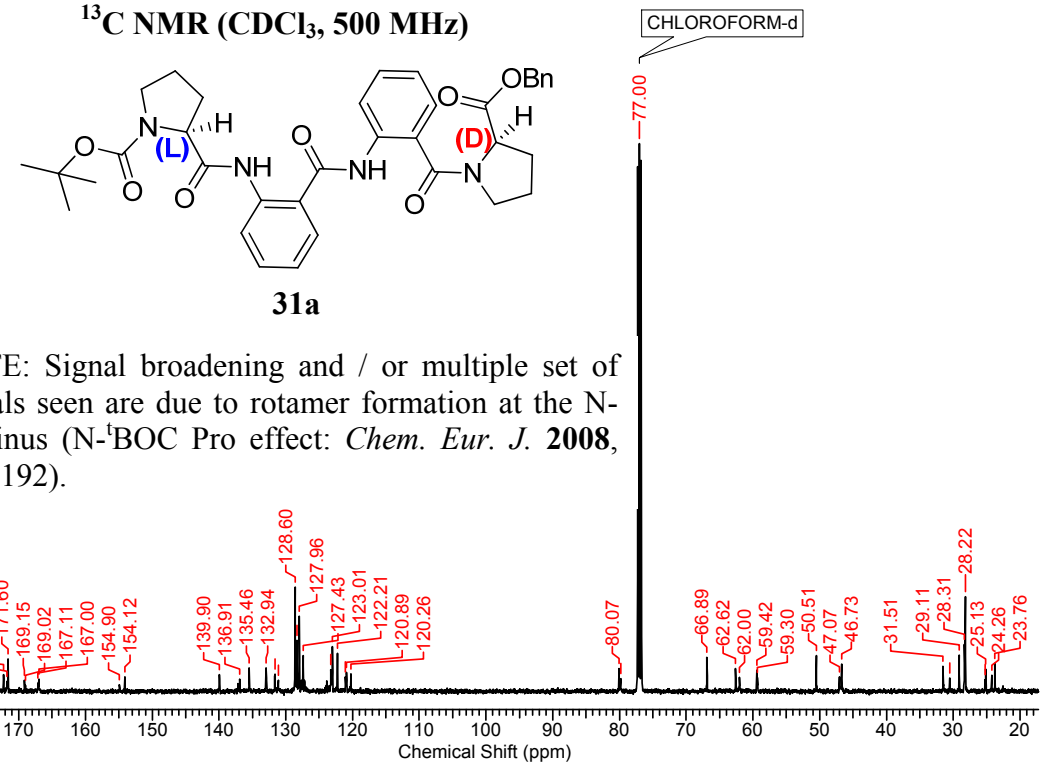
30a

^{13}C NMR ($CDCl_3$, 500 MHz)



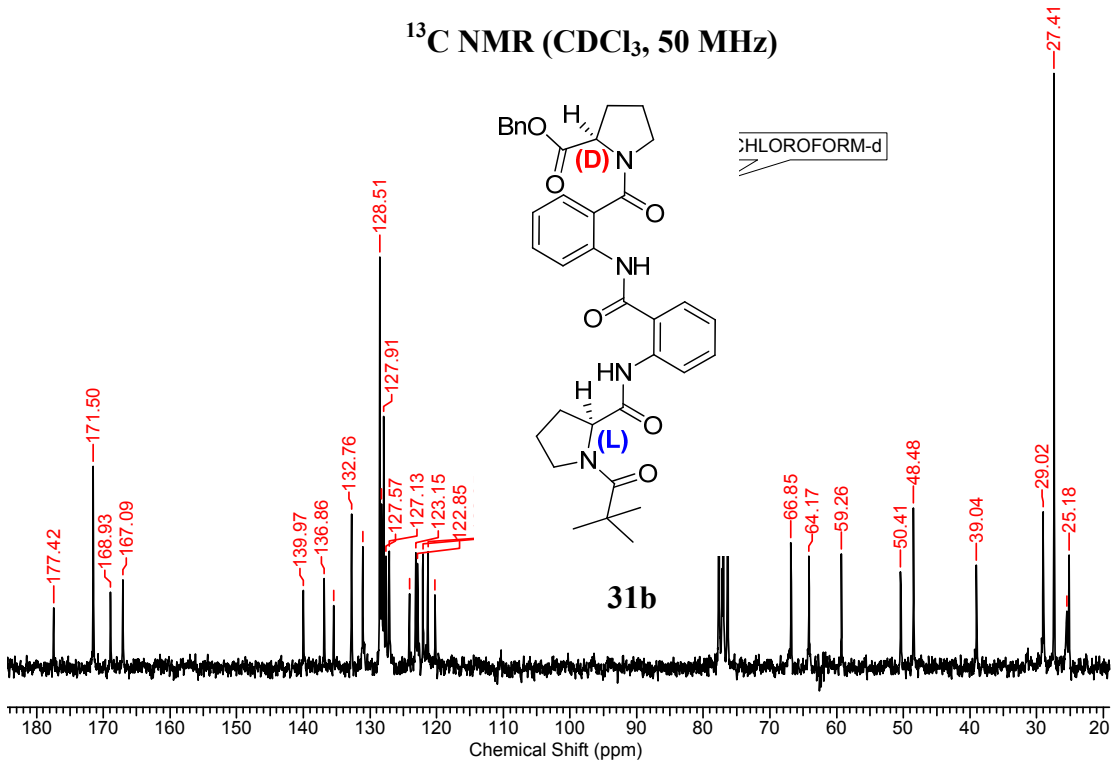
30b

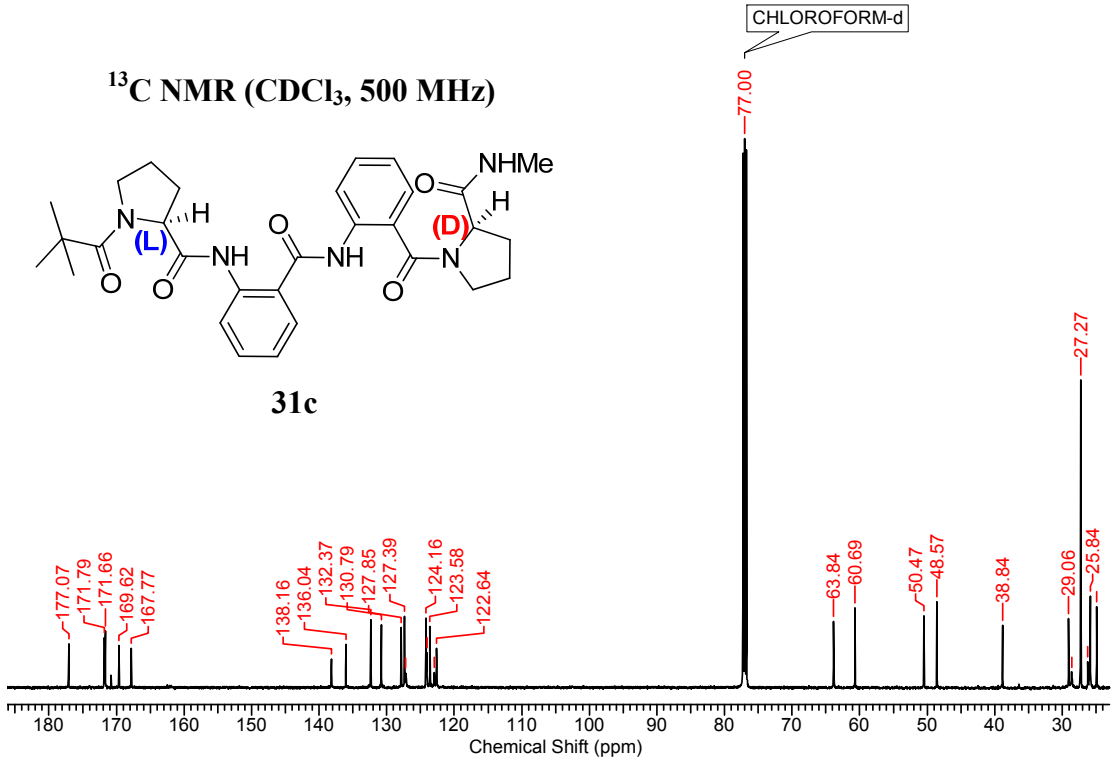
^{13}C NMR ($CDCl_3$, 500 MHz)



31a

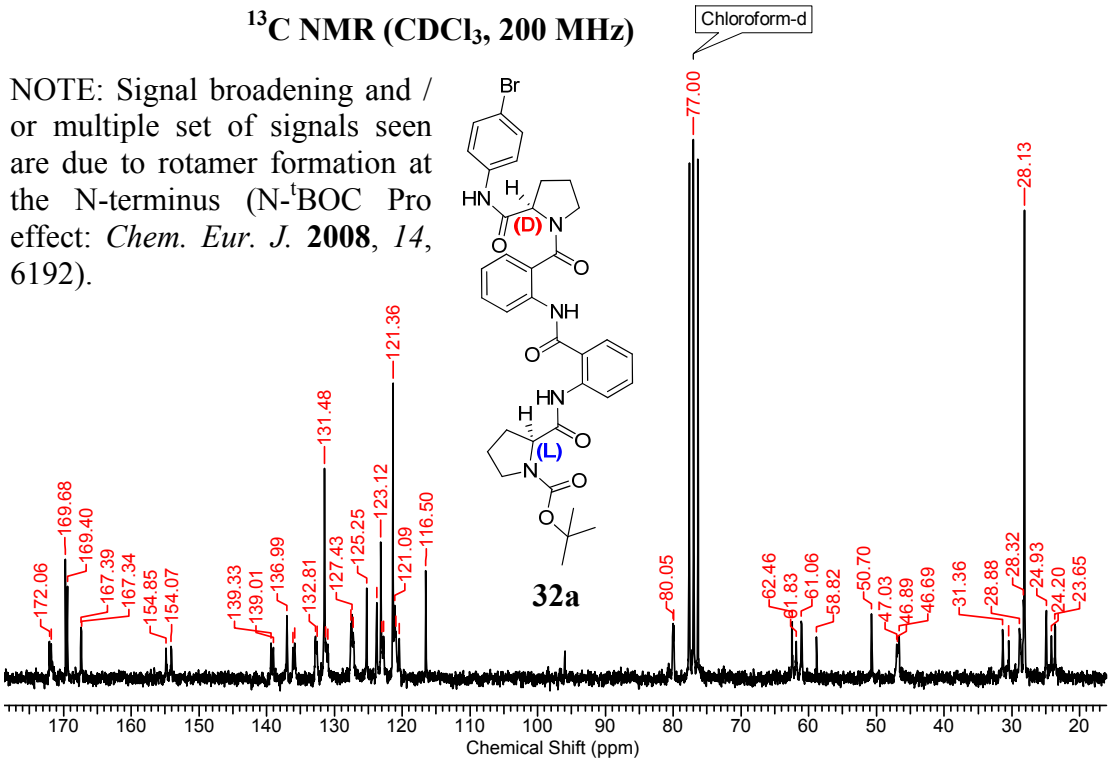
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).


^{13}C NMR ($CDCl_3$, 50 MHz)
BnO
H
(D)
N
O
O
NH
O
HN
H
O
(L)
N
O
CHLOROFORM-d
31b
177.42
171.50
168.93
167.09
139.97
136.86
132.76
128.51
127.91
127.57
127.13
123.15
122.85
66.85
64.17
59.26
50.41
48.48
39.04
29.02
27.41
25.18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)


^{13}C NMR ($CDCl_3$, 500 MHz)
CHLOROFORM-d
N
H
(L)
O
NH
O
NH
O
NHMe
O
H
(D)
N
O
31c
177.07
171.79
171.66
169.62
167.77
138.16
136.04
132.37
130.79
127.85
127.39
124.16
123.58
122.64
77.00
63.84
60.69
50.47
48.57
38.84
29.06
27.27
25.84
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
Chemical Shift (ppm)

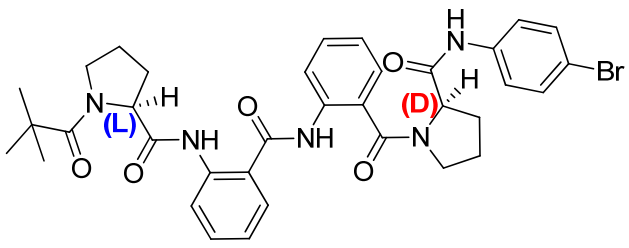
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



32a

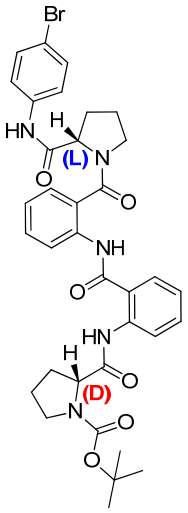
^{13}C NMR ($CDCl_3$, 500 MHz)



32b

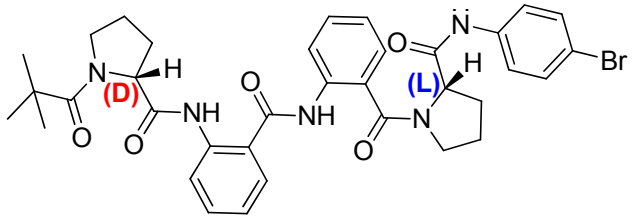
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



33a

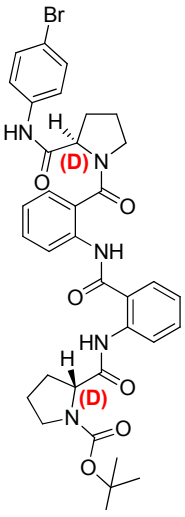
^{13}C NMR ($CDCl_3$, 200 MHz)



33b

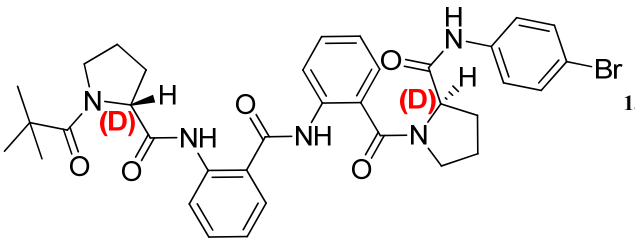
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



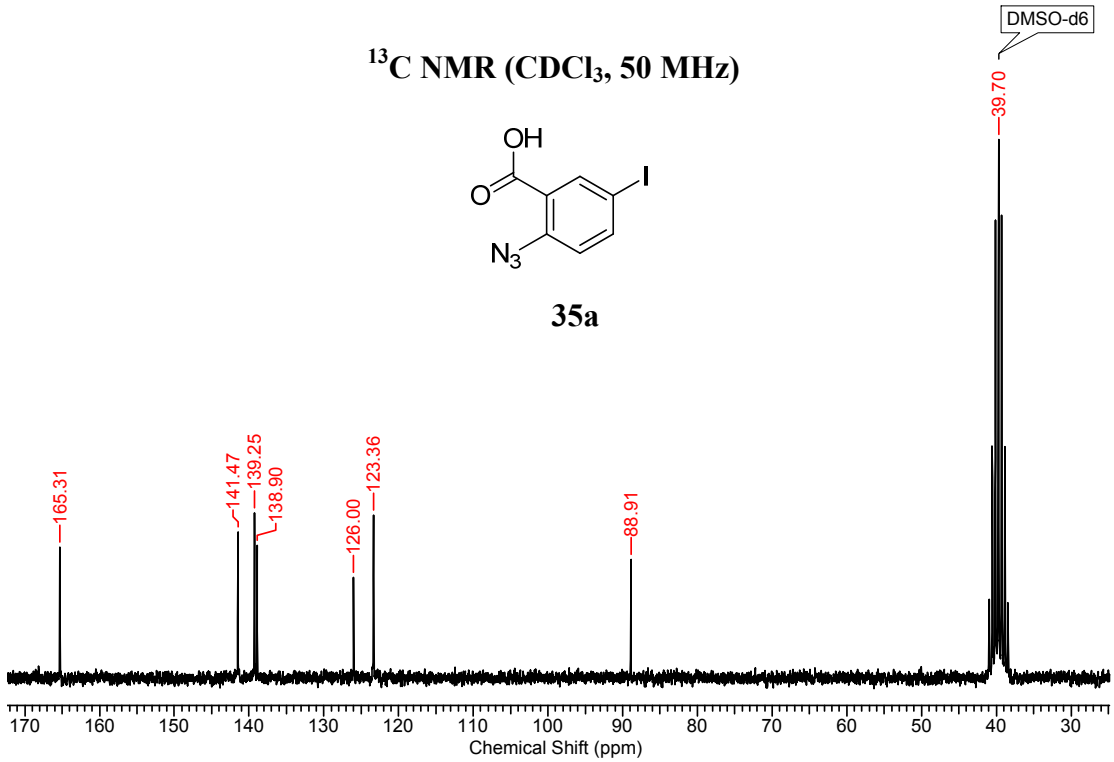
34a

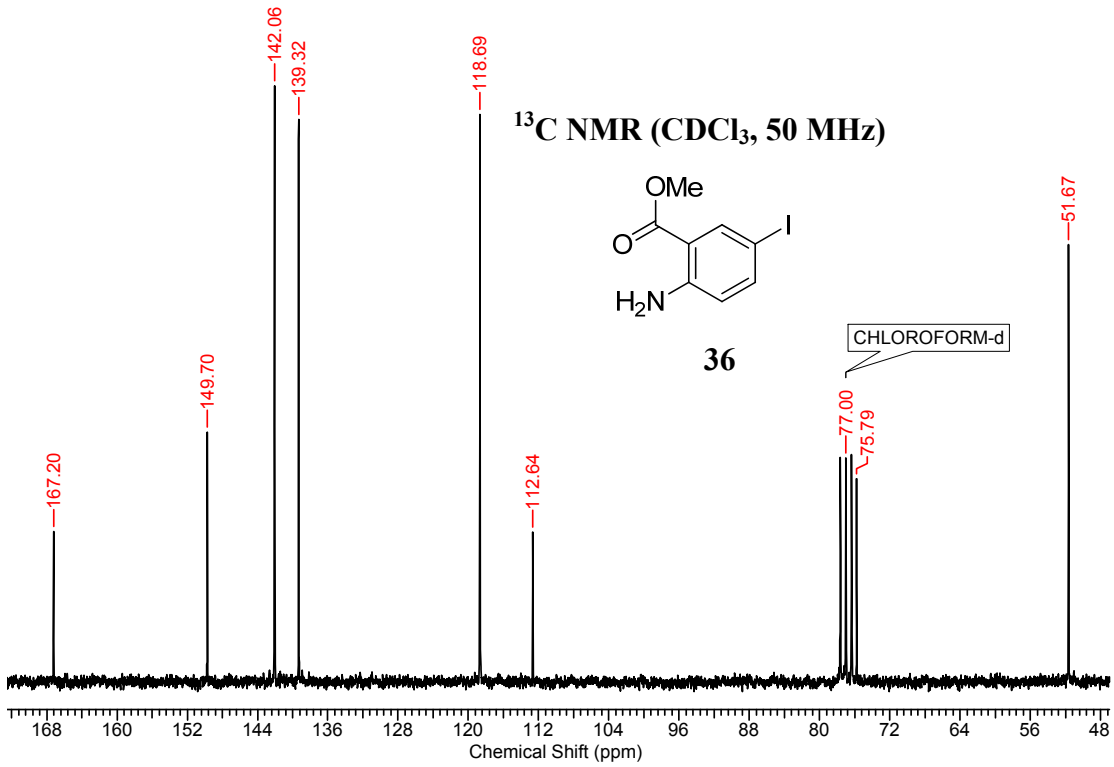
 # DMF



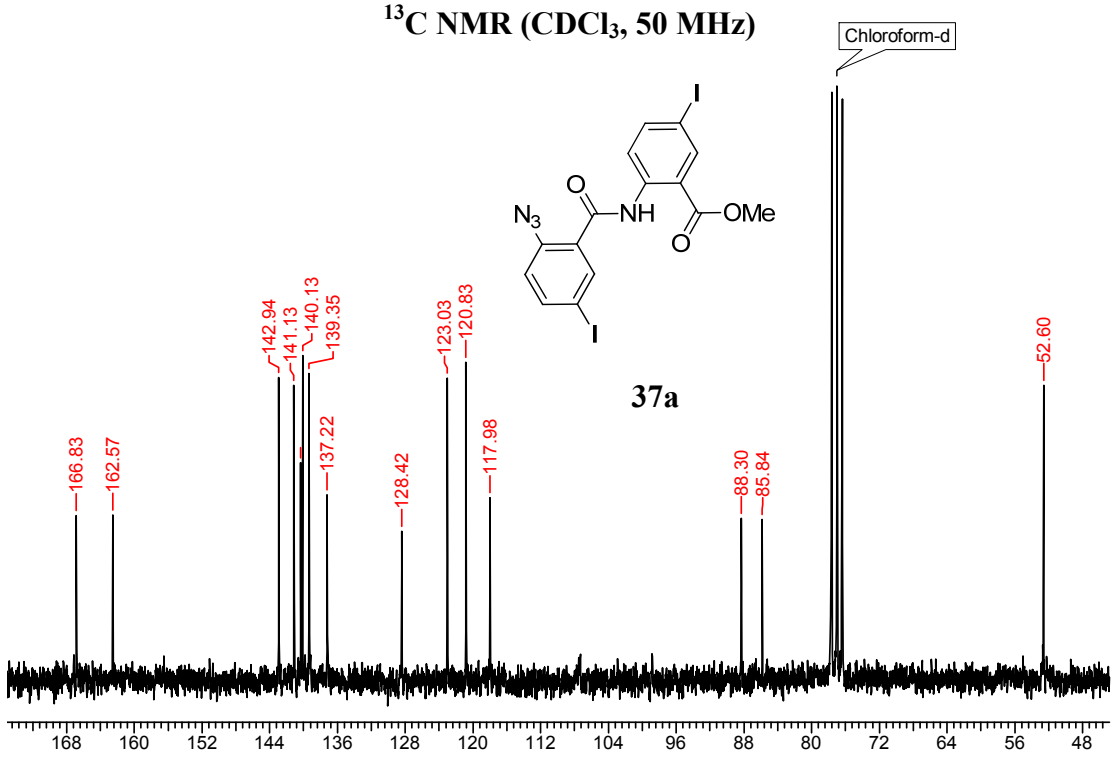
34b

^{13}C NMR ($CDCl_3$, 200 MHz)


^{13}C NMR (CDCl$_3$, 50 MHz)
OH
O
I
N$_3$
35a
DMSO-d6
39.70
165.31
141.47
139.25
138.90
126.00
123.36
88.91
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
Chemical Shift (ppm)

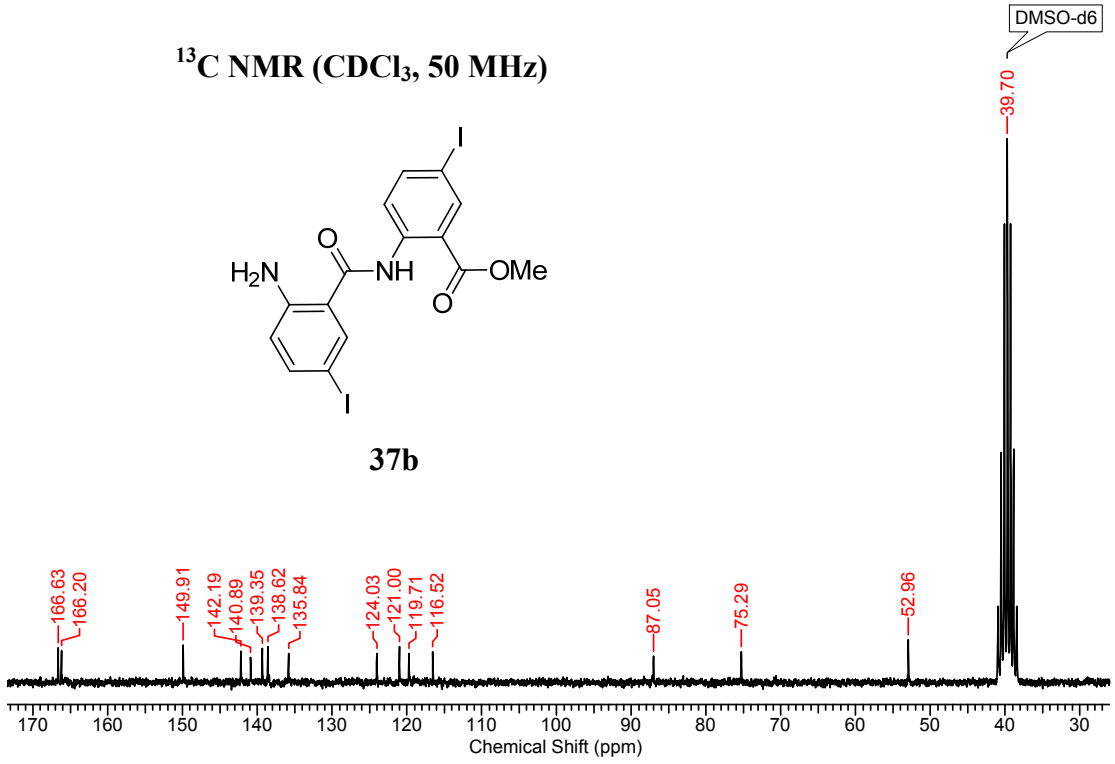

^{13}C NMR (CDCl$_3$, 50 MHz)
OMe
O
I
H$_2$N
36
142.06
139.32
118.69
51.67
CHLOROFORM-d
149.70
77.00
75.79
167.20
112.64
168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48
Chemical Shift (ppm)

^{13}C NMR ($CDCl_3$, 50 MHz)



37a

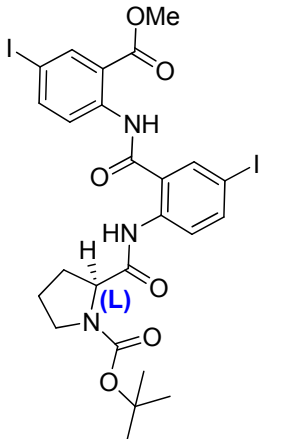
^{13}C NMR ($CDCl_3$, 50 MHz)



37b

^{13}C NMR ($CDCl_3$, 50 MHz)

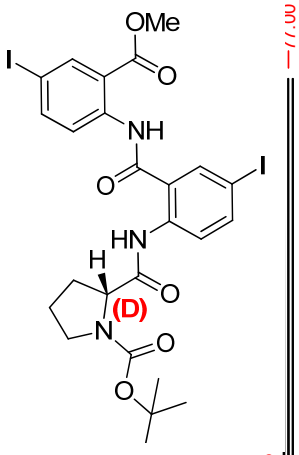
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



38

^{13}C NMR ($CDCl_3$, 50 MHz)

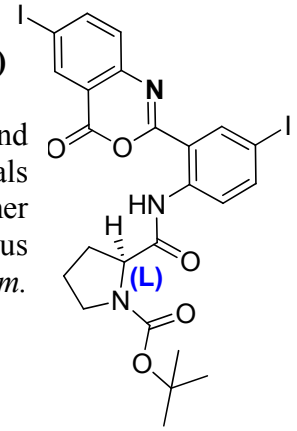
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



39

^{13}C NMR ($CDCl_3$, 50 MHz)

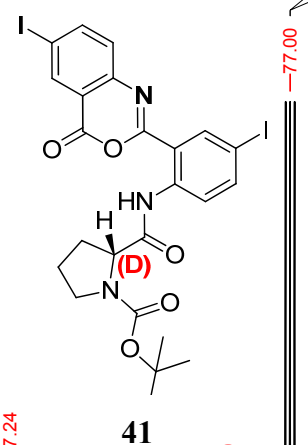
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



40

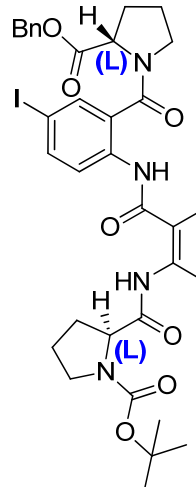
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



41

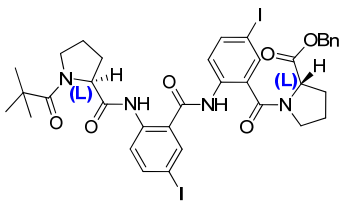
^{13}C NMR ($CDCl_3$, 50 MHz)



42a

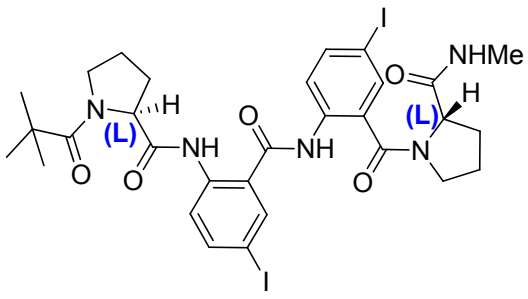
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{13}C NMR ($CDCl_3$, 50 MHz)



42b

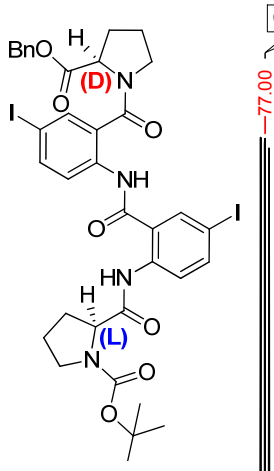
^{13}C NMR ($CDCl_3$, 50 MHz)



42c

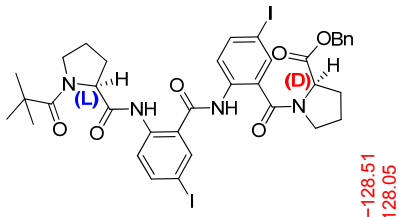
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



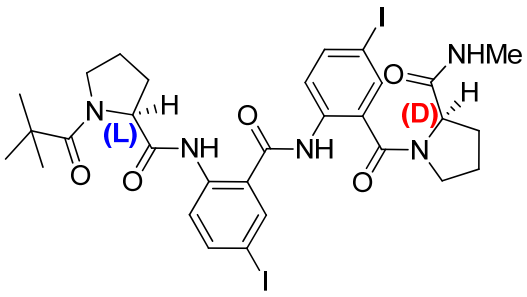
43a

^{13}C NMR ($CDCl_3$, 50 MHz)



43b

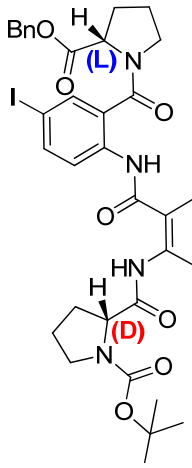
^{13}C NMR ($CDCl_3$, 50 MHz)



43c

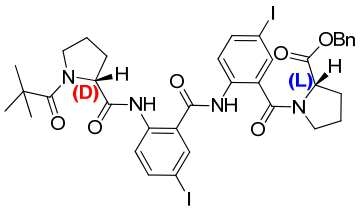
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



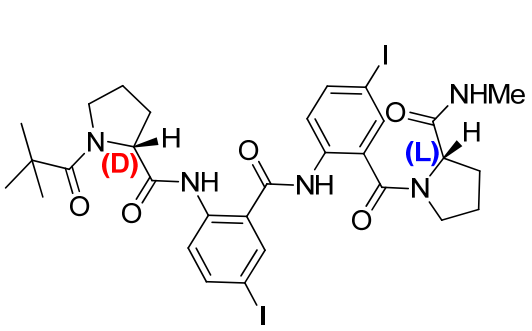
44a

^{13}C NMR ($CDCl_3$, 50 MHz)



44b

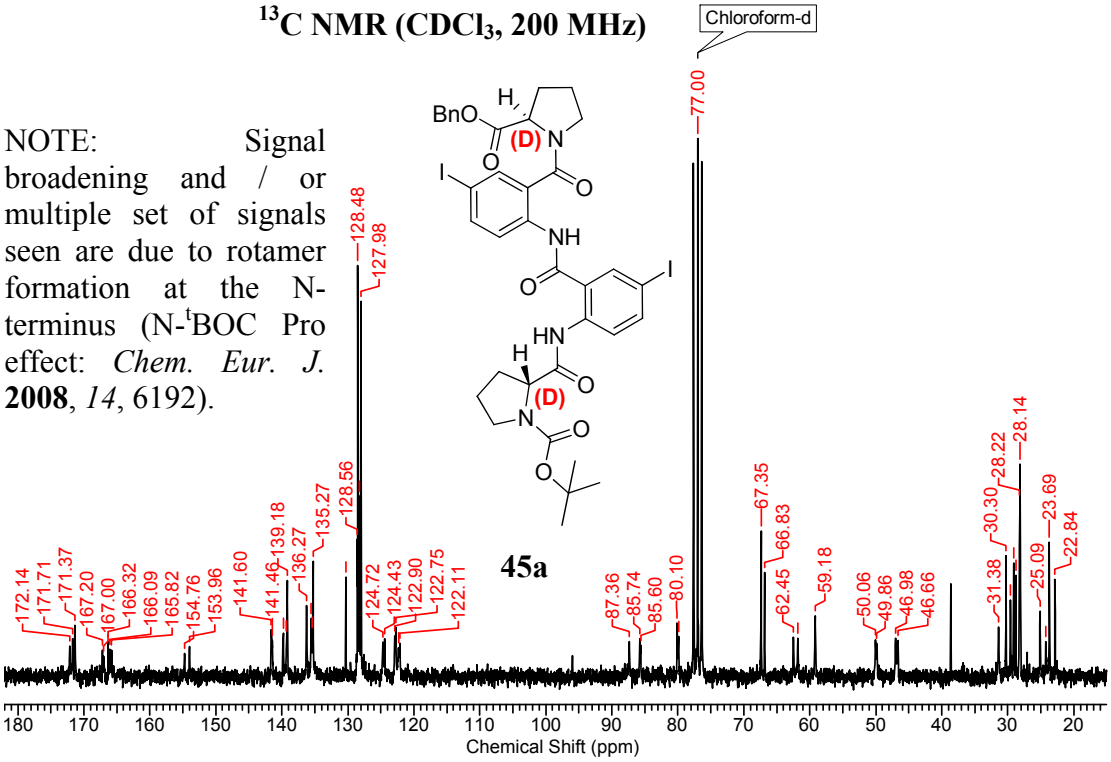
^{13}C NMR ($CDCl_3$, 50 MHz)



44c

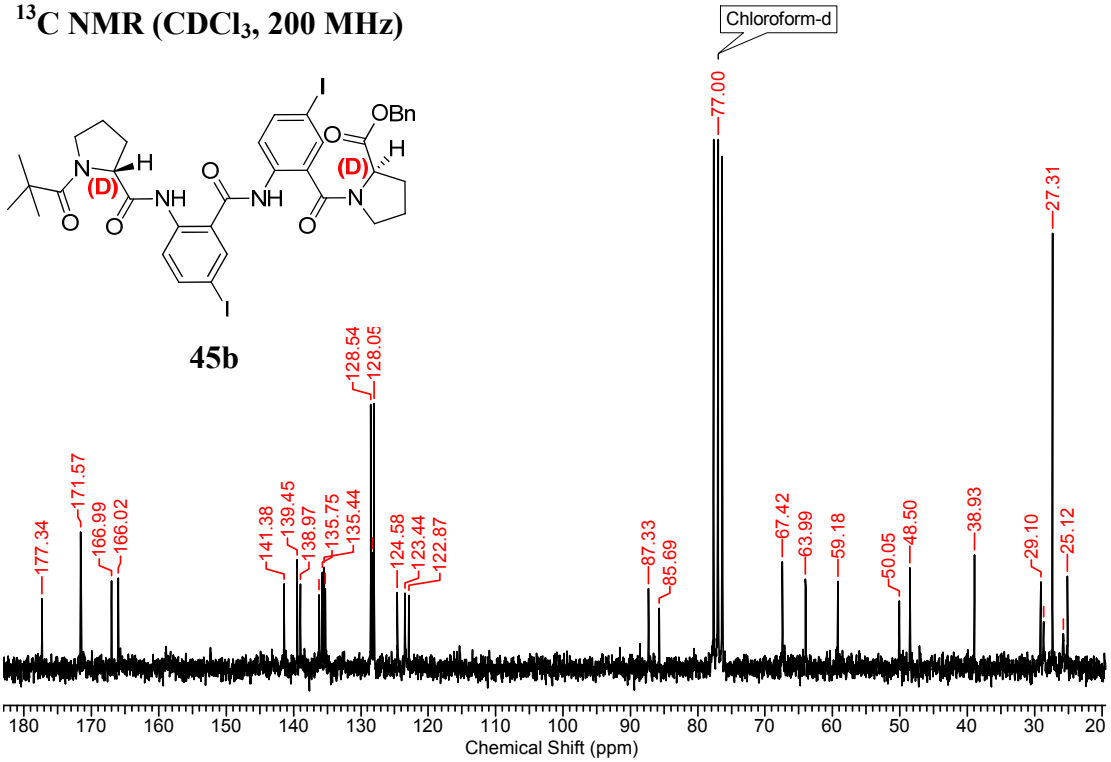
^{13}C NMR ($CDCl_3$, 200 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).



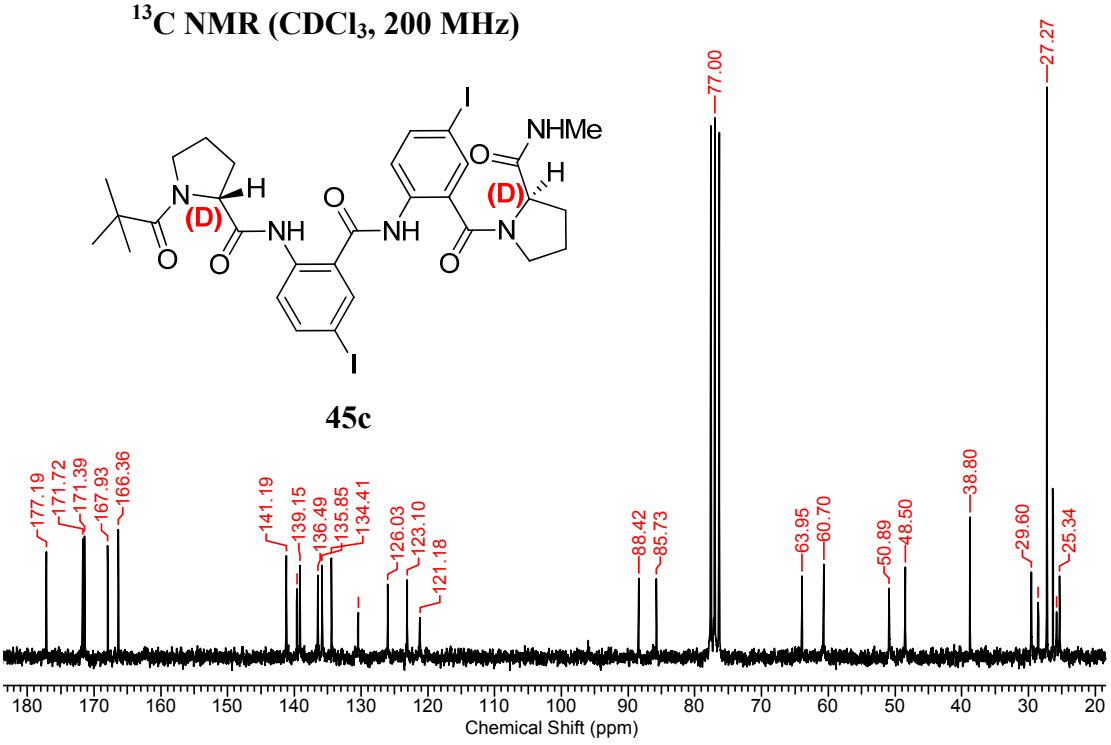
45a

^{13}C NMR ($CDCl_3$, 200 MHz)



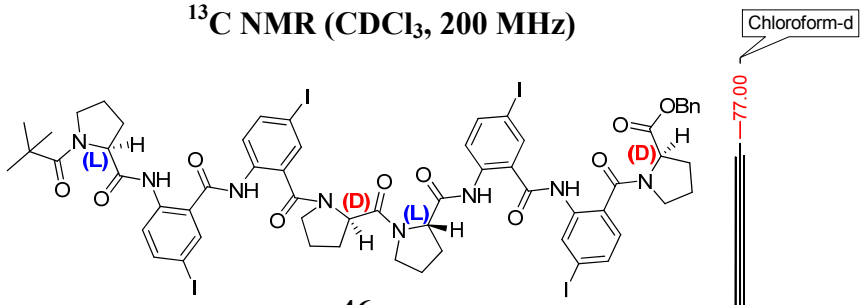
45b

^{13}C NMR ($CDCl_3$, 200 MHz)

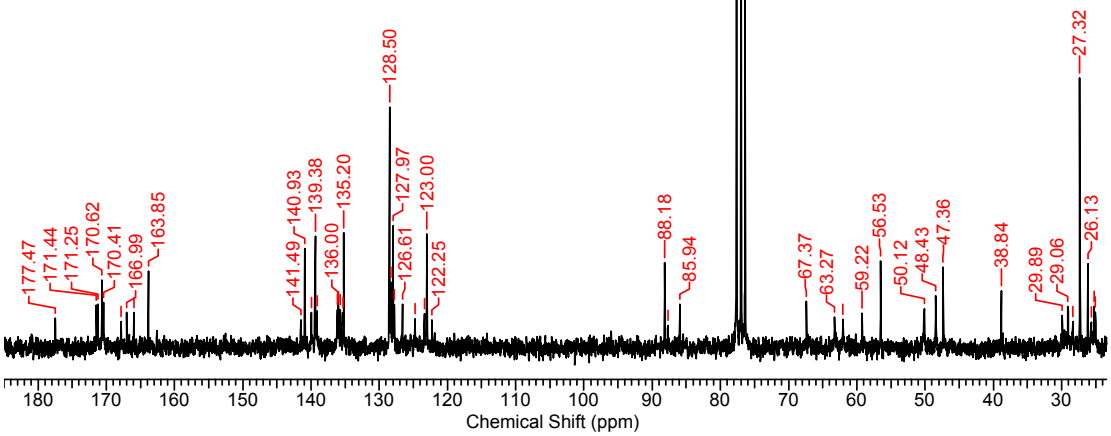


45c

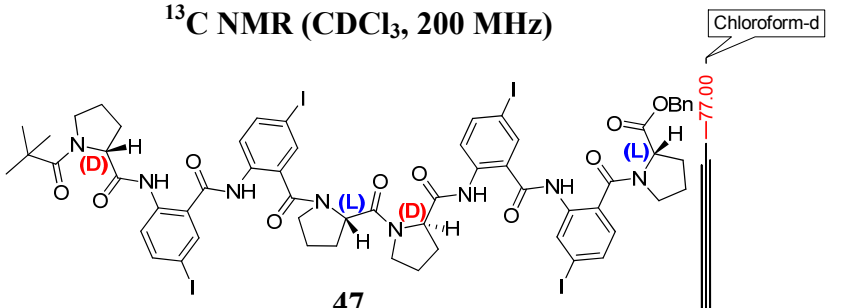
^{13}C NMR ($CDCl_3$, 200 MHz)



46



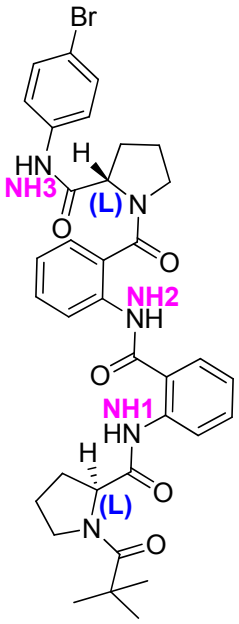
^{13}C NMR ($CDCl_3$, 200 MHz)



47

Table 1.24. Titration study of tetrapeptide 30b in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 µl)

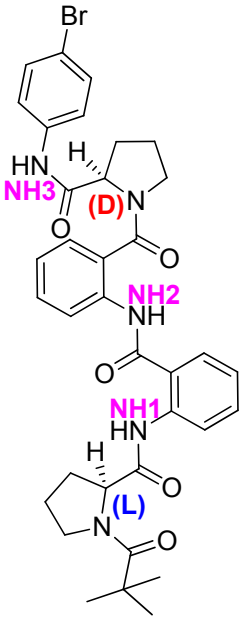
Volume of DMSO-d_6 added (in µL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	11.19	10.21	9.13
5	1.17	10.25	9.28
10	11.14	10.27	9.39
15	11.12	10.27	9.47
20	11.11	10.27	9.52
25	11.09	10.26	9.56
30	11.07	10.25	9.59
35	11.06	10.23	9.61
40	11.04	10.21	9.63
45	11.02	10.20	9.64
50	11.00	10.18	9.64



30b

Table 1.25. Titration study of tetrapeptide 32b in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 µl)

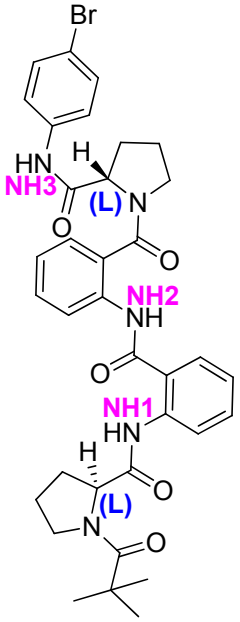
Volume of DMSO-d_6 added (in µL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	10.82	10.14	9.02
5	10.88	10.21	9.19
10	10.92	10.25	9.32
15	10.94	10.26	9.43
20	10.94	10.26	9.49
25	10.94	10.25	9.54
30	10.93	10.24	9.57
35	10.92	10.23	9.58
40	10.91	10.21	9.60
45	10.90	10.20	9.61
50	10.88	10.18	9.62



32b

Table 1.26. Dilution study of tetrapeptide 30b in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

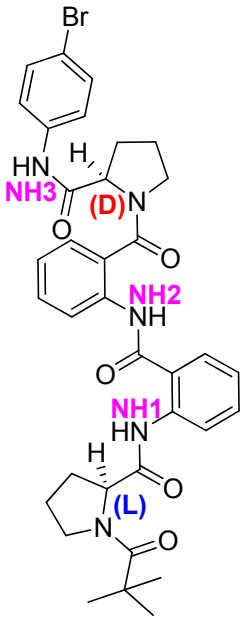
Concentration (in ppm)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
120	11.27	10.20	9.44
100	11.25	10.19	9.41
80	11.25	10.20	9.37
60	11.24	10.20	9.32
40	11.22	10.21	9.27
20	11.20	10.21	9.15
10	11.17	10.21	9.06
5	11.15	10.22	9.00
4	11.15	10.21	8.98
2	11.14	10.21	8.93



30b

Table 1.27. Dilution study of tetrapeptide 32b in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

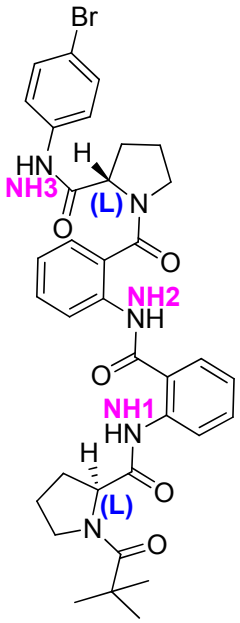
Concentration (in ppm)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
120	10.80	10.16	9.30
100	10.78	10.13	9.24
80	10.79	10.15	9.23
60	10.78	10.14	9.17
40	10.79	10.14	9.10
20	10.81	10.14	9.02
10	10.84	10.15	8.94
5	10.86	10.15	8.90
4	10.86	10.15	8.89
2	10.88	10.15	8.86



32b

Table 1.28. Variable Temperature study of tetrapeptide 30b (20 mmol, 400 MHz, $CDCl_3$)

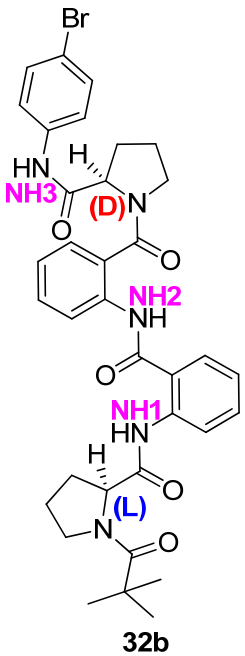
Temperature (in K)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
268	11.25	10.29	9.39
273	11.24	10.27	9.34
278	11.23	10.27	9.29
283	11.22	10.25	9.25
288	11.21	10.23	9.20
293	11.19	10.21	9.15
298	11.17	10.19	9.10
303	11.16	10.16	9.07
308	11.14	10.14	9.04
313	11.12	10.11	9.00
318	11.10	10.09	8.97
323	11.08	10.06	8.94



30b

Table 1.29. Variable Temperature study of tetrapeptide 32b (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
268	10.72	10.23	9.19
273	10.73	10.22	9.15
278	10.74	10.20	9.12
283	10.77	10.19	9.08
288	10.78	10.17	9.05
293	10.80	10.15	9.02
298	10.81	10.13	8.99
303	10.81	10.11	8.96
308	10.81	10.09	8.94
313	10.82	10.07	8.91
318	10.82	10.05	8.89
323	10.82	10.03	8.86



32b

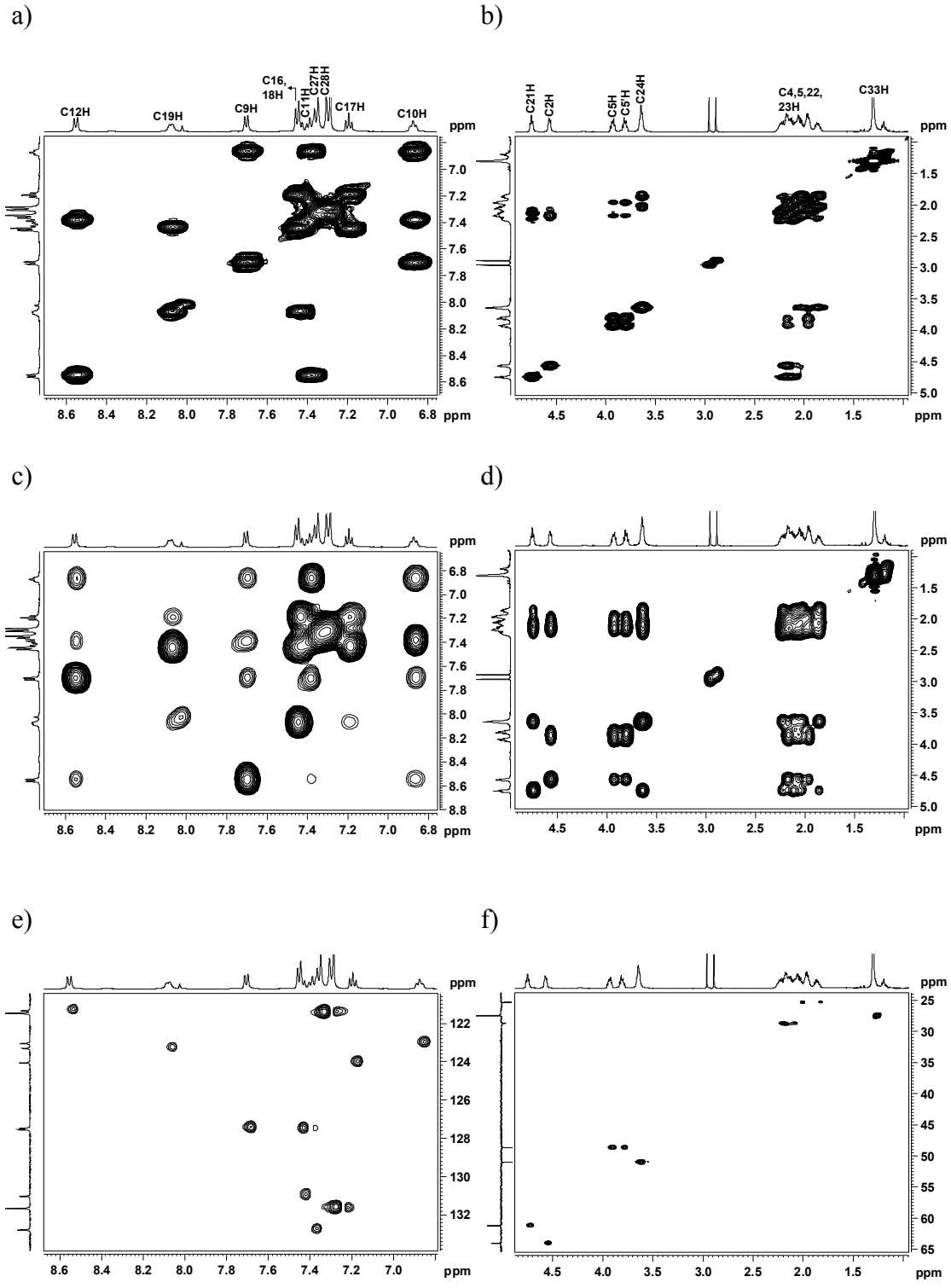


Fig. 1.58: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tetrapeptide **30b** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

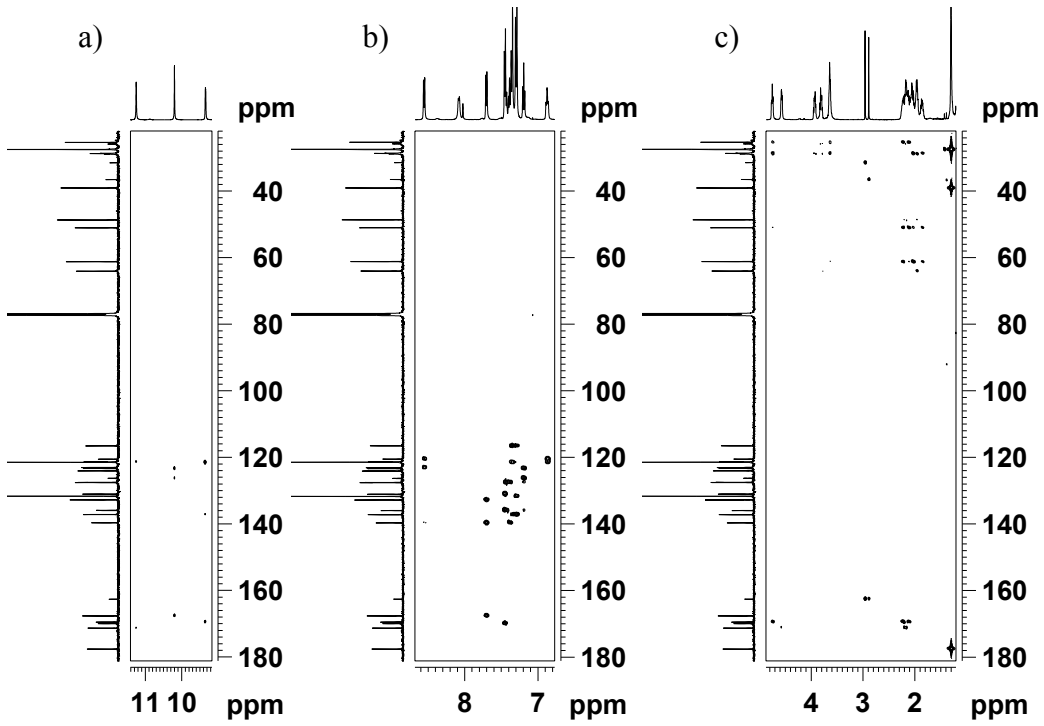


Fig. 1.59: Partial HMBC spectra of tetrapeptide **30b** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

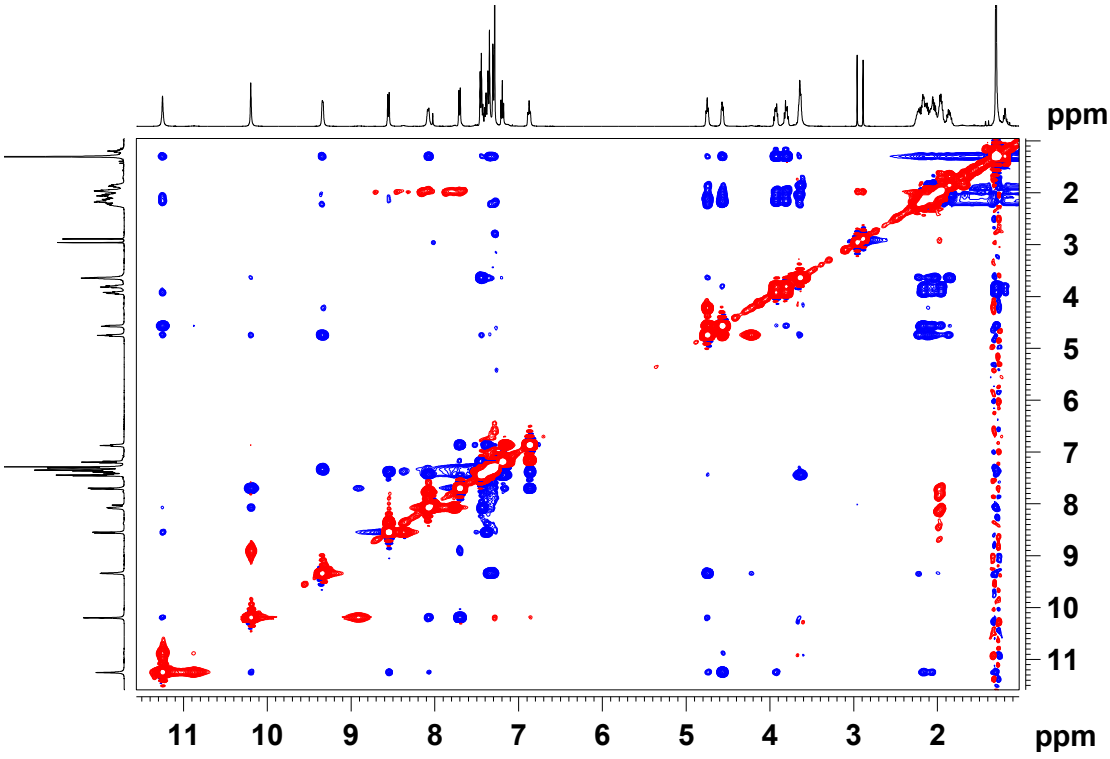


Fig. 1.60: 2D NOESY spectra of tetrapeptide **30b** (500 MHz, $CDCl_3$).

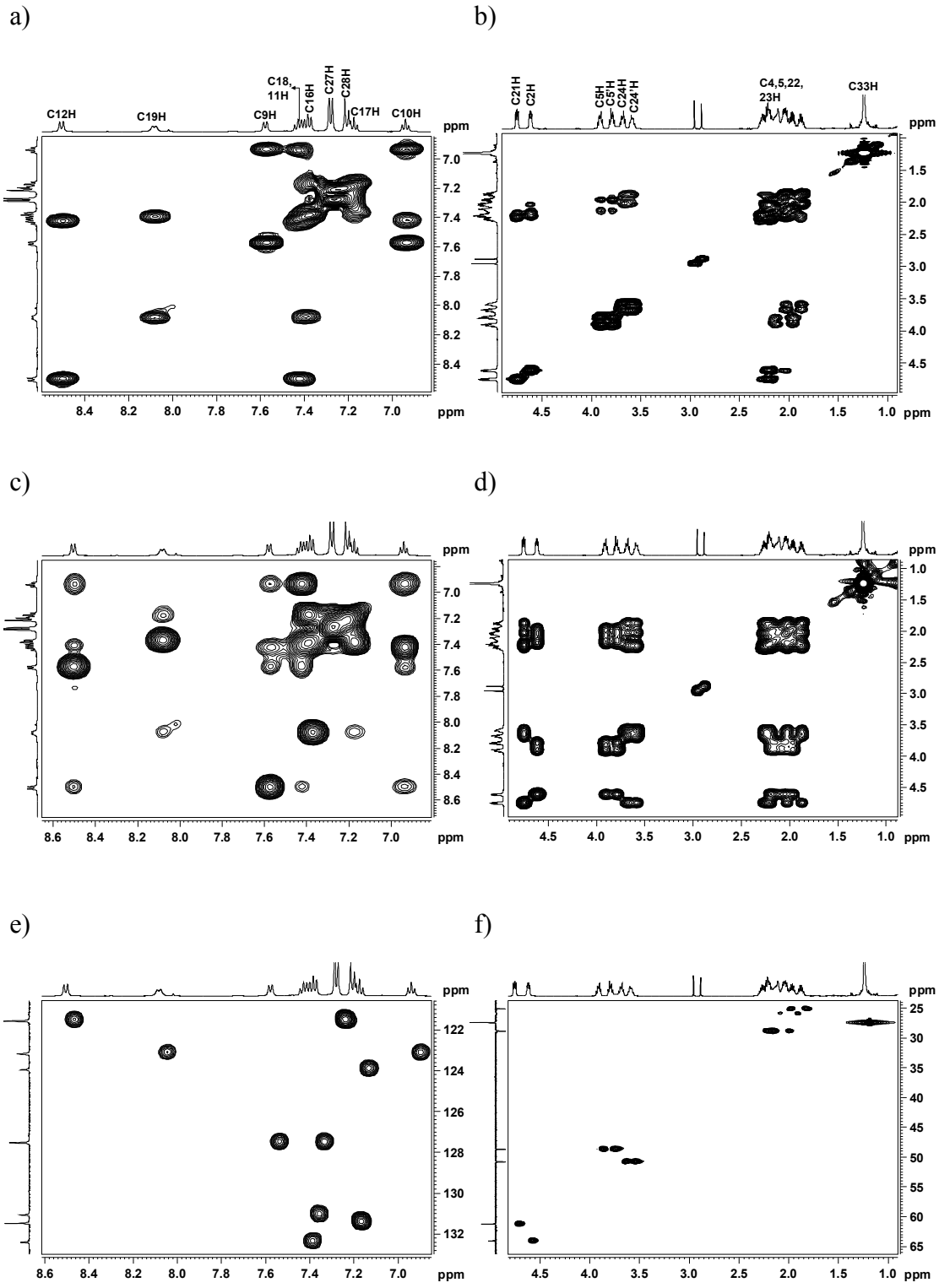


Fig. 1.61: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tetrapeptide **32b** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

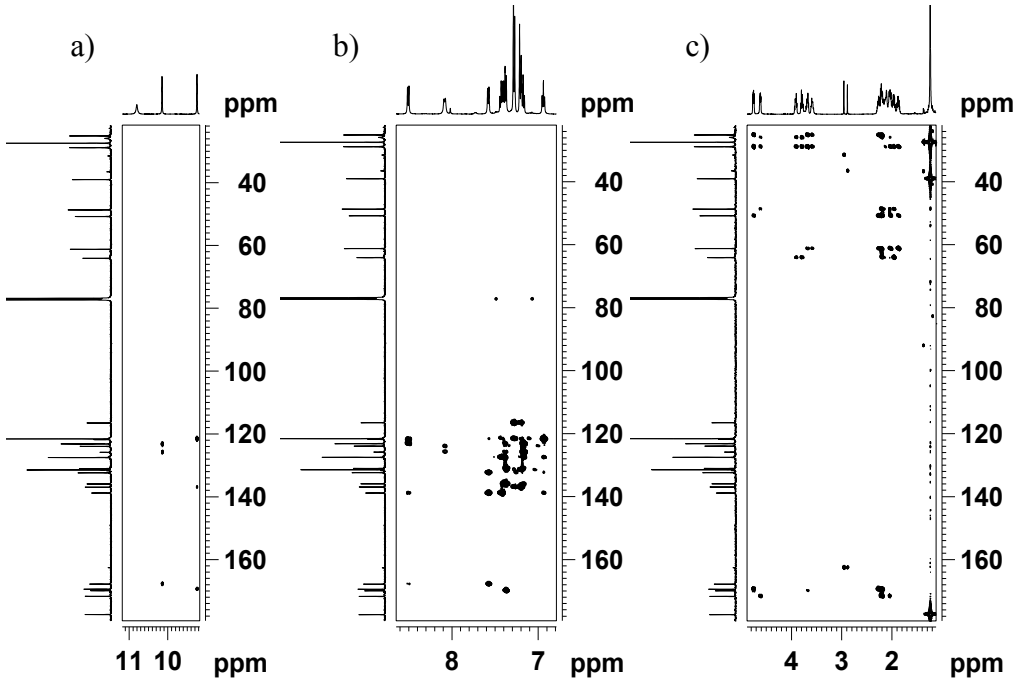


Fig. 1.62: Partial HMBC spectra of tetrapeptide **32b** (500 MHz, $CDCl_3$). For better view, amide (a), aromatic (b) and aliphatic (c) regions are given separately.

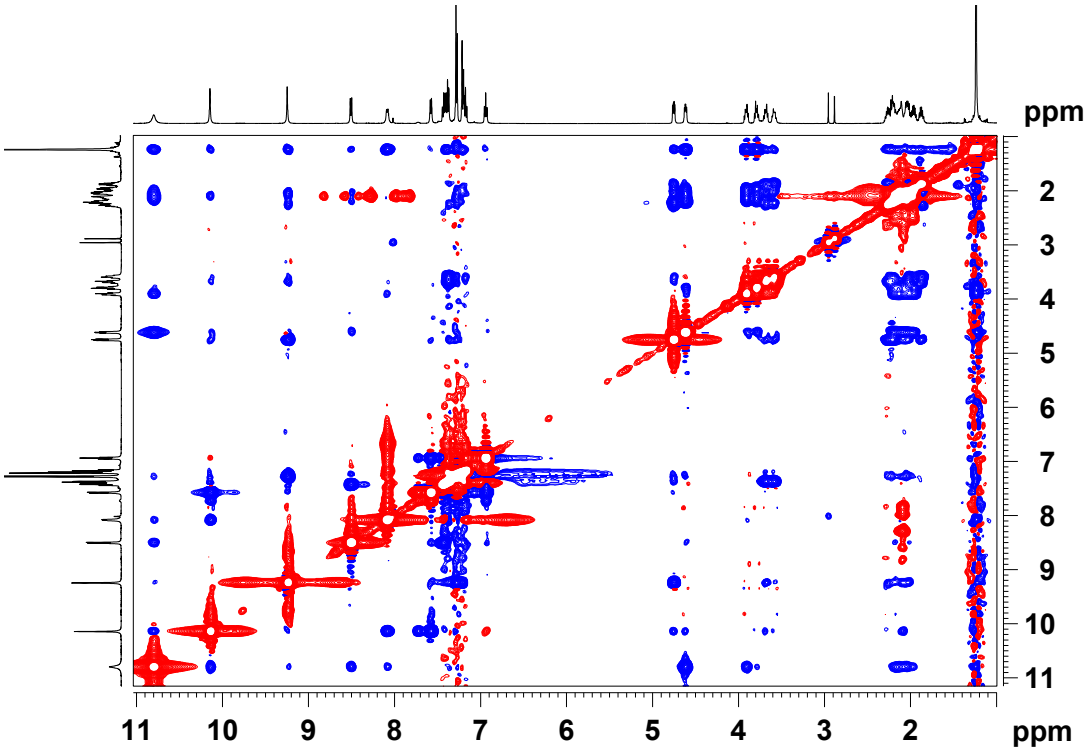


Fig. 1.63: 2D NOESY spectra of tetrapeptide **32b** (500 MHz, $CDCl_3$).

1.18 Reference and notes

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Chapter 2

Constrained Hybrid Foldamers with a Combination of Natural and Unnatural Amino acids-II

Part A: ***Helical Hybrid Foldamer with C_{12} Hydrogen-bonding: Design, Synthesis and Conformational Studies of Oligomers with γ/α 2-Amb-Pro Repeating Sequence***

Part B: ***Conformational Features of Oligomers Derived from Pro-Ant-Aib Repeats***

Helical Hybrid Foldamer with C_{12} Hydrogen-bonding: Design, Synthesis and Conformational Studies of Oligomers with γ/α 2-Amb-Pro Repeating Sequence

2.1 Introduction

In chapter 1, we had elaborate description about the hetrogeneous foldamers and our contribution to aliphatic-aromatic hybrid foldamers. Herein, the design, synthesis and conformational studies of hybrid oligomers based on α-, β- and γ-amino acids are described. The first part of this chapter deals with expanding the structural repertoire of β/α Ant-Pro (anthranilic acid-proline) oligomers into γ/α 2-Amb-Pro (2-aminomethyl benzoic acid-proline) oligomers. In the second part, conformational features of oligomers derived from Pro-Ant-Aib repeats are detailed.

Although the quest in foldamer chemistry started with modification of native peptides with their functionalized homologated amino acid residues (β-, γ- and δ-), diverse classes of backbones with varying combinations of amino acid residues have been developed and reported later leading to conformationally diverse secondary architectures.[1-3] The conventional β-turn secondary structure (C_{10} turn) with an α-α segment can be expanded to C_{11}, C_{12}, and C_{13} turns with homologated amino acids such as β-, γ- and δ-amino acids, as elegantly demonstrated by Balaram's group.[1] Oligomers constructed from combinations of α- and β-amino acid residues ('α/β-peptides') are the among most widely studied foldamers.[2] Recently, several research groups have shown that the oligomers containing both α- and γ-amino acid residues in a 1:1 alternating pattern adopt helical secondary structures.[3] Computational surveys by Hofmann *et al.* identified that a number of possible helical secondary structures available to the unsubstituted α/γ-peptide.[3g] The Gellman group[4a,b] and Balaram group[4c] recently reported that, α/γ-hybrid peptides containing various constitutional ratios of the individual amino acid residues adopt helical structures with very different hydrogen-bonding patterns.

2.2 Objective of the present work

The folding behaviour of short α/γ-peptides containing a 1:1 α/γ backbone pattern was described by several research groups.[3] The conformation of γ-residues incorporated into peptides is described by four torsion angles, θ_1, θ_2, ϕ, φ (Fig. 2.1).[5] The work described herein offers considerable prospects of expanding the structural repertoire of β/α Ant-Pro (anthranilic acid-proline) motif, which has been described earlier to assume right-handed helical architecture displaying robust nine-membered-ring closed network of hydrogen-bonding interactions,[6] into γ/α 2-Amb-Pro (2-aminomethyl benzoic acid-proline) motif.

2.3 Design strategy

It is already known that hybrid oligomers derived from anthranilic acid (Ant; a constrained β-amino acid), and proline (Pro; a constrained α-amino acid), adopt right-handed helical structural architecture, displaying an unusual (1→2)-type 9-membered-ring pseudo β-turn.[5] In this context, it was anticipated that substitution of β-amino acid (Ant) in structure A (Fig. 2.1) with γ-amino acid (2-Amb) (structure B) would provide sufficient steric repulsion between the two rings resulting in oligomers with new structural architectures.

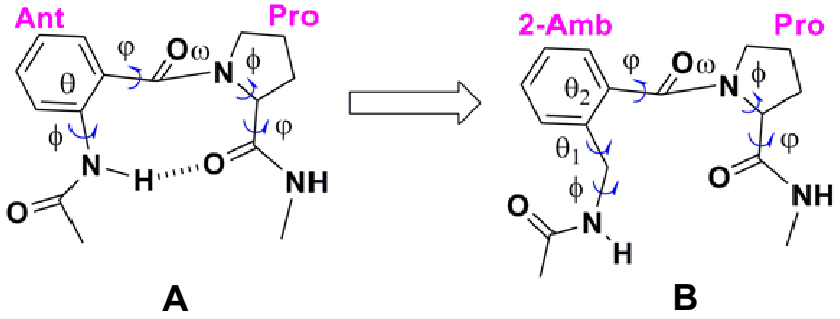
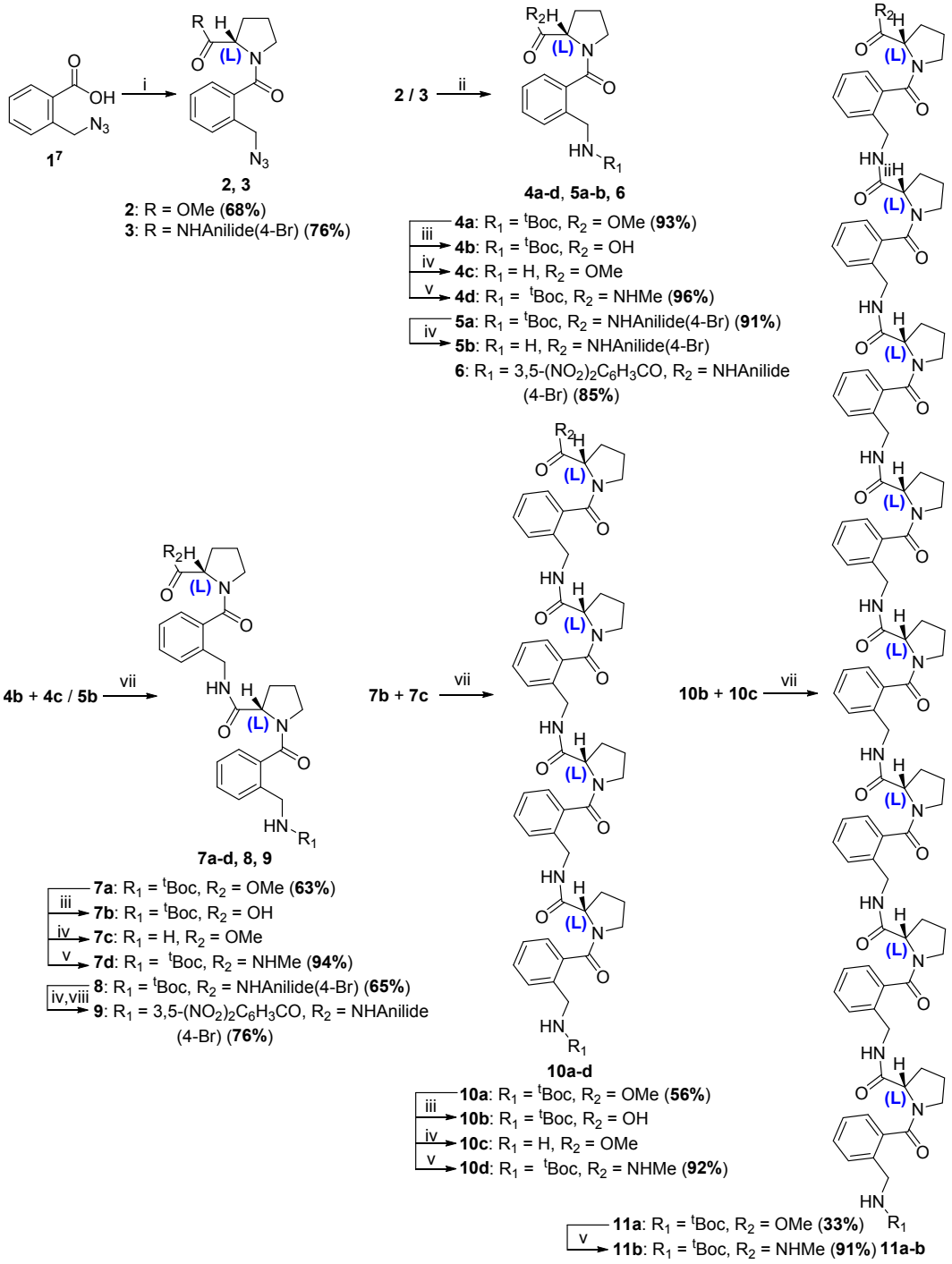


Fig. 2.1: Design principle of the hybrid foldamer 2-Amb-Pro (2-aminomethyl benzoic acid-proline) motif (B).

2.4 Synthesis

The oligomers were assembled as described in Scheme 2.1. 2-(azidomethyl) benzoic acid **1** was synthesized using a literature protocol.[7] The azido acid **1** was then coupled with amines H-^{L}Pro-OMe and H-^{L}Pro-Anilide (4-Br) to afford the expected tripeptides **2** and **3**, respectively, in good yields.



Scheme 2.1: Synthesis of oligomers **4d**, **7d**, **10d** and **11b**. **Reagents and conditions:** (i) a. $(COCl)_2$, DCM, DMF (cat.), 0 °C, then rt, 3 h; b. amine [HCl.H-^{L}Pro-OMe for **2**, H-^{L}Pro-NHanilide(4-Br) for **3**], Et_3N, rt, 6 h; (ii) a. reduction [Pd-C, $CHCl_3$, H_2, 60 psi, EtOAc, rt, 5 h for **4a**; $SnCl_2.2H_2O$, EtOAc, 50 °C, 1 h for **5a** and **6**], b. protection [Boc anhydride, Et_3N, DCM, rt, 5h for **4a** and **5a**; 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, DCM, rt, 5h for **6**]; (iii) aq. $LiOH.H_2O$, MeOH, rt, 12 h; (iv) TFA:DCM (1:1), rt, 1 h; (v) methanolic methylamine, rt, 6 h; (vii) EDC.HCl, HOBt, amine, DCM, rt, 8 h; (viii) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, DCM, rt, 5h.

Tripeptide **2** was subsequently hydrogenated in presence of Boc anhydride to afford the orthogonally protected dipeptide building block **4a**. Reduction of azido group of tripeptide **3** by $SnCl_2.2H_2O$, followed by reaction with the Boc anhydride and 3,5-di nitro benzoyl chloride to afforded protected dipeptide building blocks **5a** and **6** respectively. Repetitive segment doubling of the dipeptide building block **4a** successfully furnished the tetrapeptide **7a**, the octapeptide **10a** and the hexadecapeptide **11a**, in acceptable yields without much synthetic and purification hassles. The C-terminal methyl amides **4d**, **7d**, **10d** and **11b** were accessed readily by direct amidation of the corresponding esters **4a**, **7a**, **10a** and **11a**, respectively, using saturated methanolic methylamine. Dipeptide acid **4b** and dipeptide amine **5b** were coupled to furnish the bromo derivative of tetrapeptide **8**. Deprotection of ^{t}Boc group of **8** by TFA, followed by reaction with the 3,5-di nitro benzoyl chloride to afforded the nitro tetrapeptide **9** (Scheme 2.1).

2.5 Conformational analyses

Extensive efforts to crystallize the oligomers to investigate their solid-state conformational features did not meet with success, since none of them crystallized, despite best efforts. All oligomers were readily soluble in non-polar solvents suggesting that the backbone amide NHs are strongly solvent shielded, preventing aggregation in solution.[8] Secondary structure analyses were accomplished by extensive 2D NMR and HF/6-31G∗ level of *ab initio* MO theory studies.[9]

2.5.1 NMR studies

Unfortunately, due to chemical shift overlapping, the conformational studies of the oligomers posed considerable challenges, though the conformational investigations of the dipeptide **4d** could be undertaken after solvent-induced signal shifts in toluene-d_8, 500 MHz.

The C-terminal amide NH was found to be deshielded (7.39 ppm) in comparison to the solvent exposed N-terminal carbamate NH (6.83 ppm), suggestive of intramolecular hydrogen bonding. The long range observed nOe pattern between C17H *vs* C15H and other nOes (Fig. 2.2) supported the folded conformation, which is in agreement with the molecular modelling studies (*vide infra*).

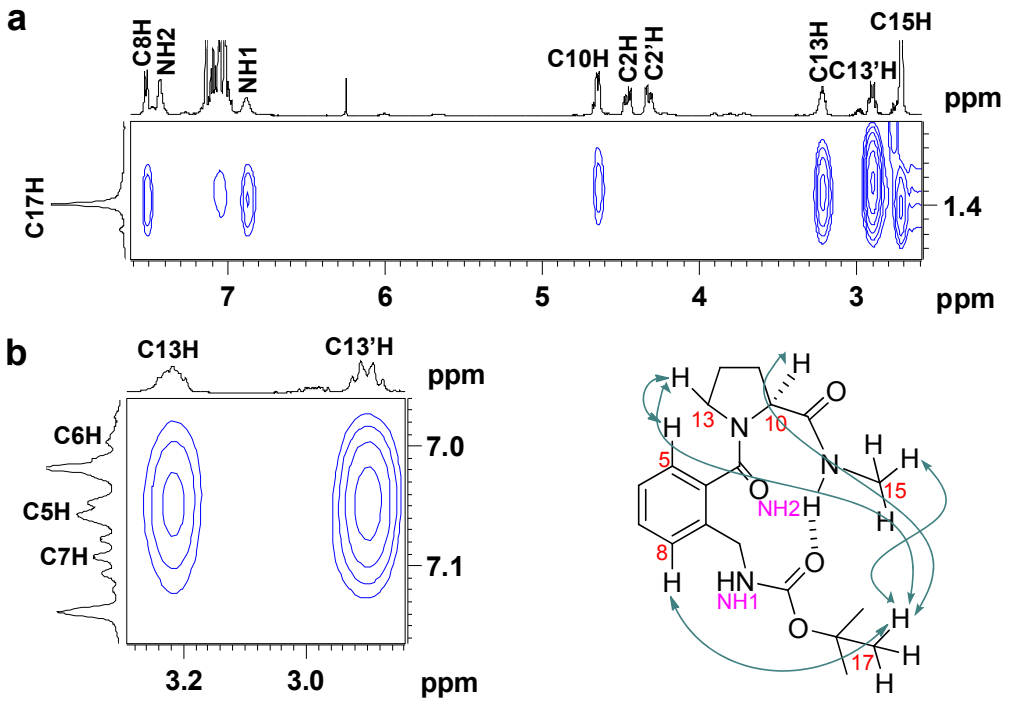


Fig. 2.2: Selected nOe extracts from the 2D NOESY data of **4d** (toluene-d_8, 500 MHz).

2.5.2 Theoretical studies

The difficulty in crystallizing oligomers prompted us to visualize their structural architecture through *ab initio* molecular modelling studies using the HF/6-31G∗ basis set.[9] It should be noted that computational investigations using *ab initio* MO theory continue to be of considerable utility in the structural understanding of synthetic oligomers, in particular structurally rigid oligomers wherein structural/conformational alternatives are limited due to intramolecular stabilizing forces such as hydrogen bonding.[3i,6,10]

Conformational investigations using *ab initio* modelling studies suggested that there are two conformers possible for **4d** retaining similar C_{12} hydrogen-bonding network, although they differ in their hydrogen-bonding distances. Further difference is seen in their positioning of the benzylic methylene, wherein the conformer with short hydrogen-bonding distance (Fig. 2.3, left) has the CH_2 projecting down juxtaposed to the proline ring, though a reverse arrangement is noted for the other conformer (Fig. 2.3, right). Indeed, the dipolar coupling pattern observed in the NMR studies supported the predominance of the former

conformer, although the latter one does exist in negligible amounts (see Experimental Section).

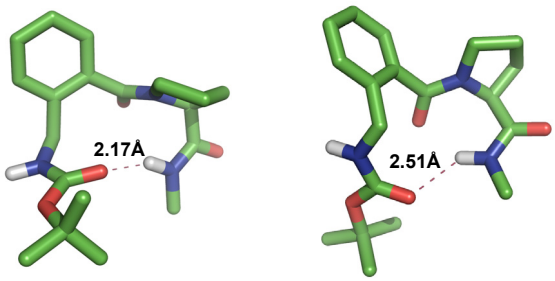


Fig. 2.3: Structural architecture of **4d** at the HF/6-31G* level of *ab initio* MO theory showing two conformers one having strong hydrogen-bonding (left) and another showing relatively weak interaction (right). Hydrogens, other than the polar ones, have been omitted for clarity.

Ab initio molecular modelling studies using the HF/6-31G* basis set clearly revealed the right-handed helical architecture of the large γ/α 2-Amb-Pro oligomers **7d**, **10d** and **11b**, featuring repeating C_{12} hydrogen-bonding networks (Fig. 2.4A-C). The onset of helicity was evident from the tetrameric oligomer **7d** itself (Fig. 2.4A). Except the N-terminus carbamate NH, all backbone amide NHs involve in perfect back-to-back hydrogen-bonding interactions, eventually aiding the oligomer to assume a right-handed helical conformation.

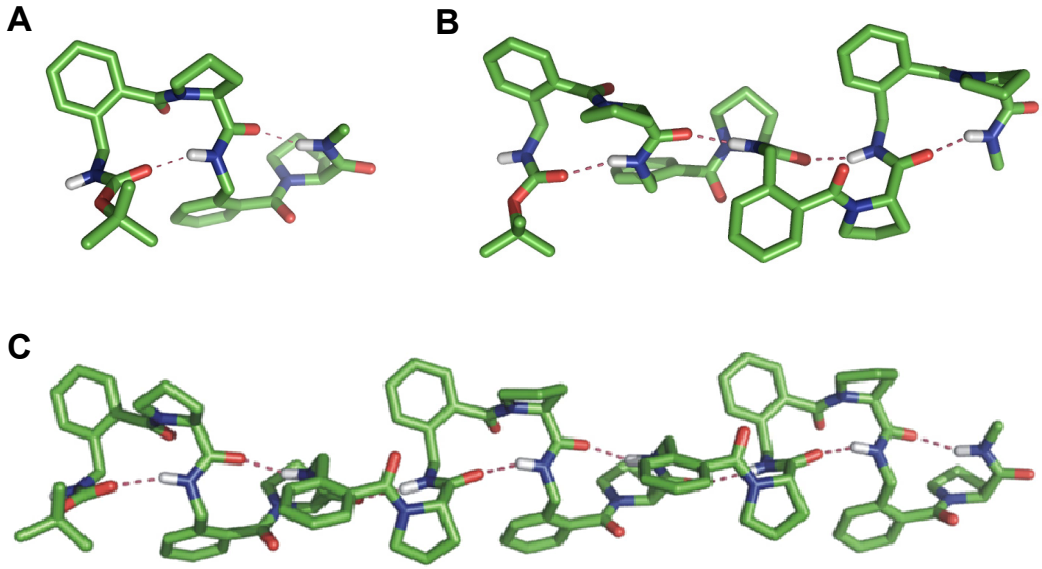


Fig. 2.4: Structural architecture of the tetrapeptide **7d** (A), octapeptide **10d** (B) and hexadecapeptide **11b** (C) at the HF/6-31G* level of *ab initio* MO theory showing right-handed helical conformation with repeating C_{12} hydrogen-bonding networks. Hydrogens, other than the polar ones, have been omitted for clarity.

2.5.3 Circular dichroism (CD) Studies:

Circular dichroism (CD) studies provide characteristic signature for the conformational features of ordered chiral oligomers.[11] The onset of helicity was evident from the octameric oligomer **10d**. The 2-Amb-Pro oligomers octapeptide **10d** and hexadecapeptide **11b** displayed maxima at around 220 nm which is characteristic of right-handed helical conformation, further supporting the theoretical studies (Fig. 2.5).

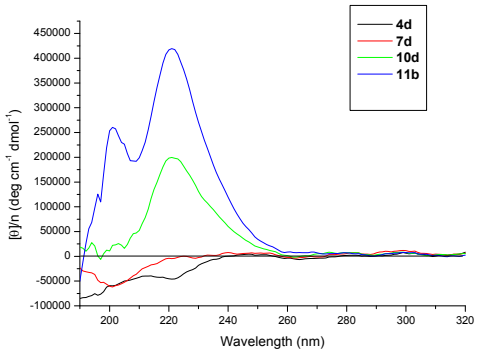


Fig. 2.5: CD absorption spectra of 2-Amb-Pro oligomers: dipeptide **4d**, tetrapeptide **7d**, octapeptide **10d** and hexadecapeptide **11b** in trifluoroethanol. All spectra recorded at 298 K with a concentration 0.01 mM.

2.6 Conclusion

In conclusion, hybrid oligomers comprising 2-Amb-Pro (2-aminomethyl benzoic acid-proline) motifs, repeating at regular intervals, have been shown to be adopting right-handed helical structural architecture, periodically displaying a C_{12} hydrogen-bonding network. The structural architecture of these hybrid oligomers is unlike to the conformation reported for oligo-Ant-Pro amides, which assume right-handed helical architecture displaying robust nine-membered-ring closed network of hydrogen-bonding interactions.[6] Oligomers as large as hexadecamers featuring the conformationally restricted γ/α 2-Amb-Pro motif in repeating sequences have been efficiently assembled using solution-phase Boc strategy, starting from the commercially available *O*-toluic acid. Thus, our study offers considerable prospects of expanding the structural repertoire of β/α Ant-Pro motif in to γ/α 2-Amb-Pro motif, used for the creation of novel synthetic oligomers, whose conformation would be strikingly different from the Ant-Pro oligomers.[6]

Conformational Features of Oligomers Derived from Pro-Ant-Aib Repeats

2.7 Introduction

In chapter 1, we had elaborate description about aliphatic-aromatic hybrid foldamers that adopt a well-defined compact, three-dimensional architecture, which is governed by a combined conformational restriction imposed by the individual amino acids of which it is composed.[5,12]

In a sequential peptide, the alternation of a Pro (proline) residue that disrupts the conventional hydrogen-bonding schemes found in helices and a helix-forming residues such as Aib (γ-amino isobutyric acid) may give rise to a novel helical structure, called the β-bend ribbon spiral.[13] Stabilizing and restoring the 10-membered cyclic hydrogen bond between residue *i* and *i* + 3 defining a β-bend ribbon spiral motif, was achieved by Sanjayan *et al.* using conformationally constrained aliphatic (Aib, Pro) and aromatic amino acid (3-amino-4,6-dimethoxy benzoic acid; Adb) conjugates (Fig. 2.6b). This hybrid foldamers was defined by independent conformational preferences of sub units.[12b]

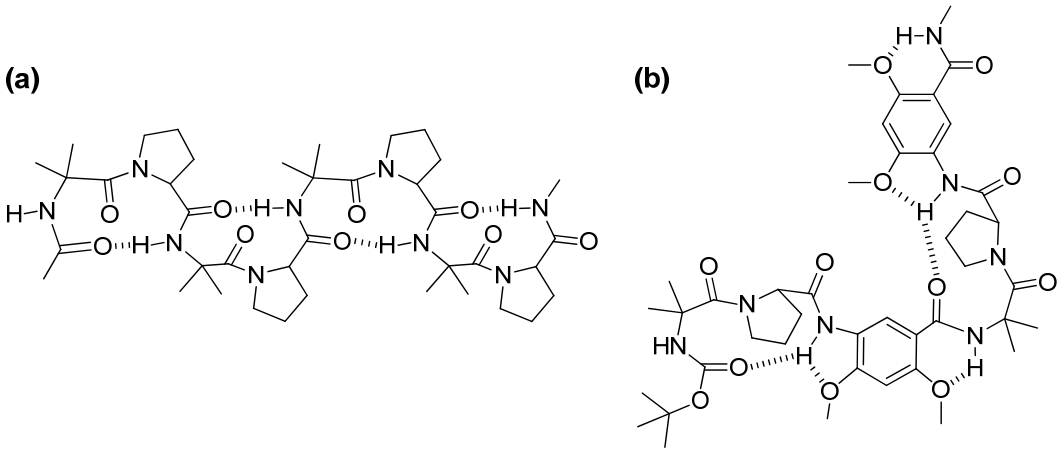


Fig. 2.6: Representation of the (a) β-bend ribbon spiral generated by the repeating -^{L}Pro-Aib- dipeptide unit[13b] (b) Boc-(Aib-Pro-Adb)$_2$-NHMe foldamer having repeat β-turn.[12b] In addition to the N-H…O=C β-turn interaction, C_5 type interaction[13c] is also visible.

2.8 Objective of the present work and design strategy

The work described here in aims at studying the conformational features of oligomers derived from Aib-Pro-Ant repeats, in the context of investigating the influence of substitution pattern on the aromatic nuclei, on the overall structural architecture of the corresponding hybrid foldamers containing -(Aib-^{L}Pro)-

sequences. It is noteworthy that incorporation of constrained amino acids into peptide sequences often causes dramatic conformational flipping.[13c]

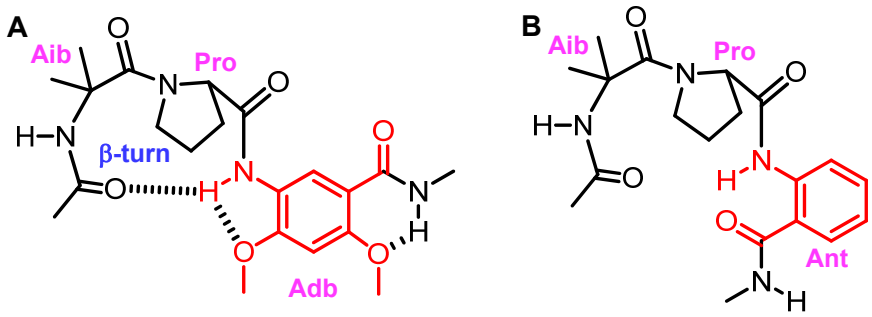


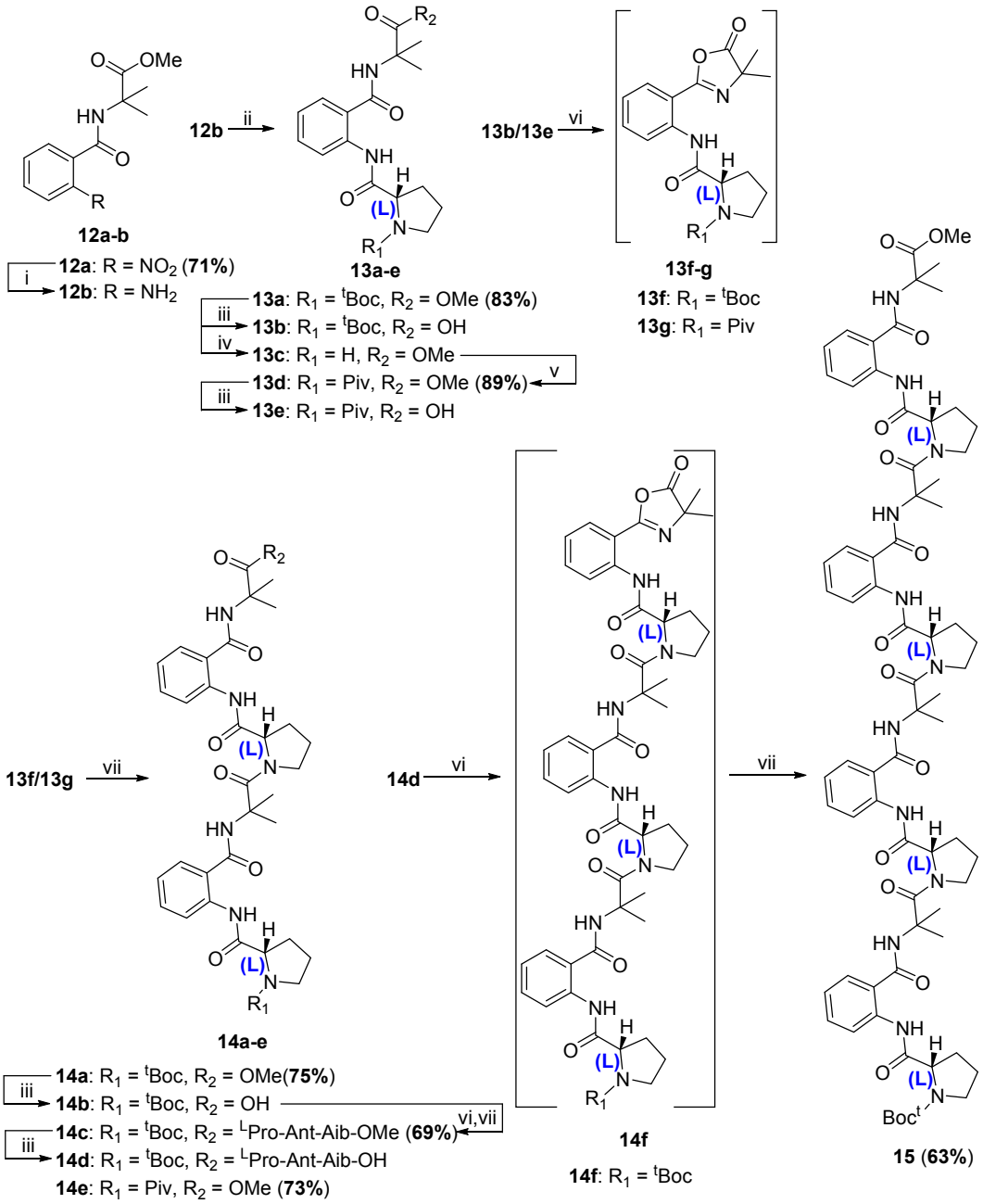
Fig. 2.7: Investigating the influence of substitution pattern on the aromatic nuclei (highlighted by red colour): Aib-Pro-Adb with β-turn **A** (left)[12b] and its analogous structure Aib-Pro-Ant **B** (right; this work).

2.9 Synthesis

Although our initial strategy was to prepare oligomers of Aib-Pro-Ant with Ant at the C-terminal, the facile benzoxazinone formation through intramolecular cyclization yielding benzoxazinone restricted our strategy to start with Boc-Pro-Ant-Aib-OMe. Therefore, we planned the synthesis starting from the tripeptide Boc-Pro-Ant-Aib-OMe **13a** using 'segment doubling strategy'[14] which might furnish the higher oligomers **14a** and **15** using coupling agents.

The oligomers were assembled as described in Scheme 2.2. The synthesis of (Pro-Ant-Aib) oligomers started with 2-nitro benzoic acid which was coupled with hydrochloride salt of Aib methyl ester to afford dipeptide **12a**. The dipeptide **12a** was subjected for reduction of nitro group to amine using Pd-C in presence of H_2 atmosphere at 60 psi. Subsequently, amine was coupled with Boc-^{L}Pro-OH by active ester method to furnish tripeptide **13a** as a building block. Although one would expect a straight forward direct coupling strategy between tripeptide acid **13b** with tripeptide amine **13c** to access the hexapeptide **14a**, the synthesis proved to be trickier owing to the formation of the oxazolone intermediates **13f**,[15] characterized by mass spectrometric analysis. Unfortunately, our repeated attempts to isolate the oxazolone by column chromatography did not succeed. Instead, the in-situ generated oxazolone was carried forward for the next reaction. Thus, hexapeptide **14a** was prepared from DBU mediated nucleophilic opening of oxazolone intermediate **13f** by tripeptide amine **13c**. Our attempts to extend the hexapeptide **14a** to dodecapetide **15** by oxazolone opening failed. The synthesis of

dodecapeptide **15** was achieved by stepwise construction of hexapeptide **14a** to nonapeptide **14c** and further extended to dodecapeptide **15** through oxazolone intermediate.



Scheme 2.2: Synthesis of oligomers **13a**, **14a** and **15**. **Reagents and conditions:** (i) a. Pd-C (cat.), H_2, EtOAc, 60 psi, 5 h; (ii) a. Boc-^{L}Pro-OH, ethylchloroformate, Et_3N, THF, 0 °C, 15 min. b. **12b**, 0 °C, 15 min. then reflux, 8 h; (iii) $LiOH.H_2O$, MeOH, H_2O, rt, 5 h; (iv) TFA:DCM (1:1), rt, 1 h; (v) Piv-Cl, Et_3N, DCM, rt, 5 h; (vi) EDC.HCl, DCM, rt, 15 min.; (vii) **13c**, DBU, 4Å MS, rt, 1 h.

It is noteworthy that all oligomers having BOC group at the N-termini underwent *cis-trans* isomerizations[16] (see Experimental Section) and for the ease of NMR studies, the N-Boc substituted tripeptide **13a** was converted to its pivaloyl analogue **13d**. However, conversion of N-Boc hexapeptide **14a** into its pivaloyl analogue **14e** led to the formation of pivaloyl tripeptide **13d** and pivolyl oxazalone **13g**. Thus, Piv-hexapeptide was synthesized by generation of the pivaloyl oxazolone intermediate **13g** from corresponding acid **13e** and further subjected to the oxazolone opening with the tripeptide amine **13c** aided by DBU in DMF containing 4Å molecular sieves (Scheme 1.2).

2.10 Conformational analyses

Secondary structural analyses were accomplished by extensive 2D NMR, X-ray diffraction.

2.10.1 Single crystal X-ray diffraction studies

Extensive efforts to crystallize the oligomers resulted in crystals of **13d** and **14a**. Investigation of the X-ray diffraction data of **14a**[17] revealed that the (Pro-Ant-Aib) oligomers display Hamilton-type 6-membered intramolecular H-bonding between the amide NH and carbonyl of Ant ring - characteristic of Ant ring (Fig. 2.8D).[18]

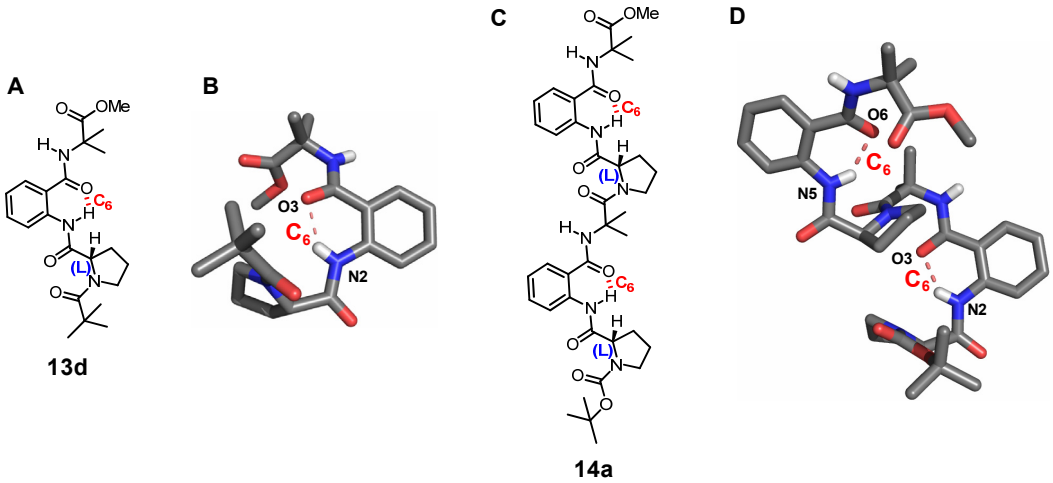


Fig. 2.8: Molecule structure and crystral structures of trimer **13d** (A,B) and hexamer **14a** (C,D) showing C_6 hydrogen-bonding. *Note*: All hydrogens, except the polar ones, have been deleted for clarity.

The crystal structure of hexamer **14a** (Fig. 2.8D) displays intramolecular C_6 hydrogen-bonding [hydrogen-bond geometric parameters: N2-H2N···O3; H2N···O3 = 1.95 Å, N2···O3 = 2.61 Å, ∠N2-H2N···O3 = 133.1° and the

planarity of the hydrogen bond torsion angle ∠(N2–H2N…O3=C13) = -40.9° and N5-H5N···O6; H5N···O6 = 1.95 Å, N5···O6 = 2.65 Å, ∠N5-H5N···O6 = 137.9° and the planarity of the hydrogen bond torsion angle ∠(N5–H5N…O6=C29) = 9.8°]. Although **14a** possesses all the required hydrogen-bonding codes which are essential to help the molecule adopt the C_{10} hydrogen-bonding pattern between H5N…O3 as shown in Fig. 2.8 D, the molecule surprisingly adopts the folded conformation featuring C_6 hydrogen-bonding. The C_6 hydrogen-bonded network in the absence of otherwise stable 10-membered hydrogen-bonding observed herein suggests that it is, presumably, their enhanced stability in such an arrangement which reinforces the folded architecture of **14a**. This aliphatic-aromatic conjugated hybrid foldamer adopts a well-defined, compact, three-dimensional architecture, governed by a combined conformational restriction imposed by the individual amino acids with which they are made of. The conformational feature seen in hexamer **14a**, is similar to its shorter analogue trimer **13d**[17] (Fig. 2.8B) featuring C_6 hydrogen-bonding [hydrogen-bond geometric parameters: N2-H2N···O3; H2N···O3 = 1.89 Å, N2···O3 = 2.63 Å, ∠N2-H2N···O3 = 139.8° and the planarity of the hydrogen bond torsion angle ∠(N2–H2N…O3=C13) = 8.72°].

2.10.2 NMR studies

We undertook extensive NMR ($CDCl_3$, 500 MHz) to provide insights into the solution-state conformation of the pivolyl trimer **13d** and hexamer **14e**. The signal assignments were made unambiguously using a combination of two-dimensional COSY, HSQC, HMBC, TOCSY and NOESY experiments. Details of the peak assignments with tables and spectra are provided in the experimental section of this chapter.

Analysis of the crystal structure of **13d** had suggested that the most characteristic nOe that is quintessential for a folded conformation would be the requirement of a diagnostic long range inter-residual dipolar coupling between C15H of Aib and C5H of Pro (Fig. 2.9b) and C15H of Aib and C20H of pivolyl group (Fig. 2.9c). The selected inter-resiual nOes that support this conformation are shown in Fig. 2.9a.

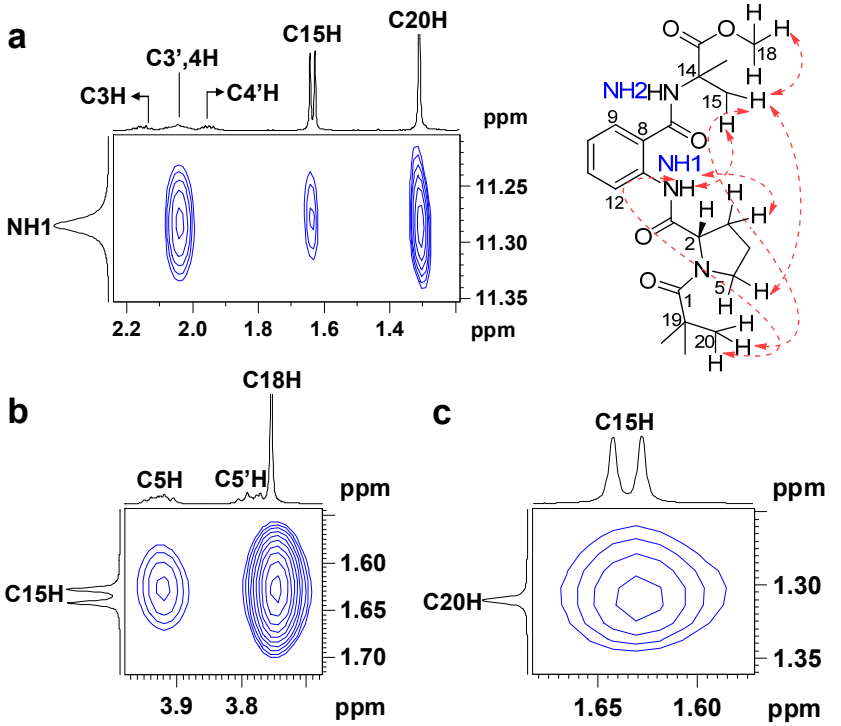


Fig. 2.9: Selected nOe extracts from the 2D NOESY data of **13d** ($CDCl_3$, 500 MHz).

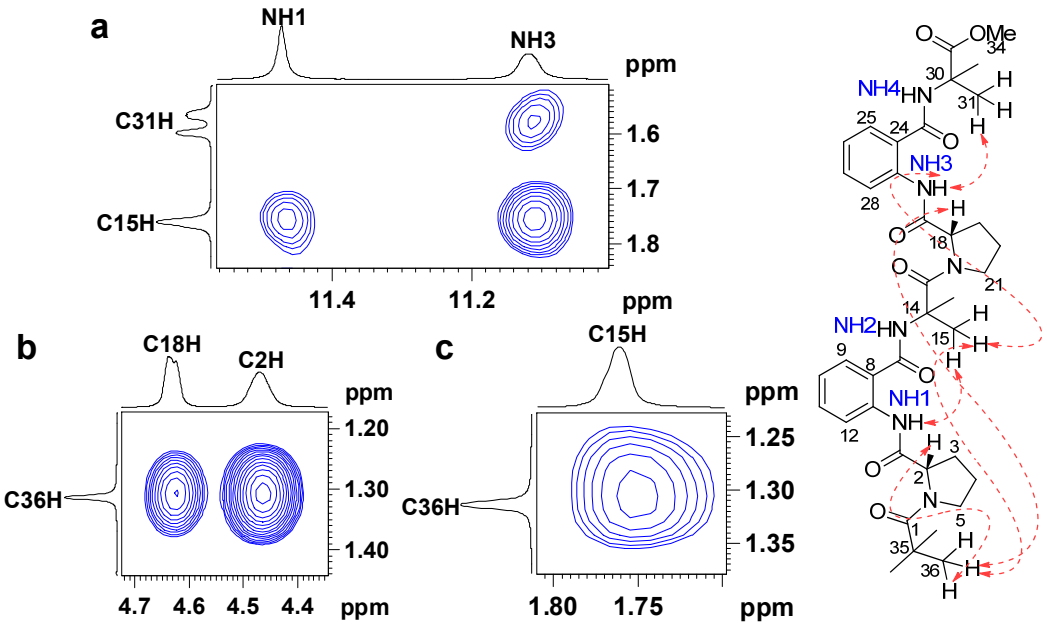


Fig. 2.10: Selected nOe extracts from the 2D NOESY data of **14e** ($CDCl_3$, 500 MHz).

Analysis of the crystal structure of **14a** had suggested that the most characteristic nOe that essential to support a folded conformation the pivolyl

analogue **14e** in solution state, would be the requirement of a diagnostic long range inter-residual dipolar coupling between C36H of pivolyl group and C15H of Aib1 and C18H of Pro2 (Fig. 2.10b, c). Other selected inter-residual nOes that supported this conformation are C15H *vs* NH1 and NH3 (Fig. 2.10a).

2.10.3 Circular Dichroism (CD) Studies:

Circular Dichroism (CD) studies provide characteristic signature for the conformational features of ordered chiral oligomers.[11] The CD spectra of Pro-Ant-Aib oligomers **13a**, **14a** and **15** displayed maxima at about 235 nm, zero crossing at 230 nm and minima at around 211 nm, characteristic of left-handed helical conformation (Fig. 2.11).

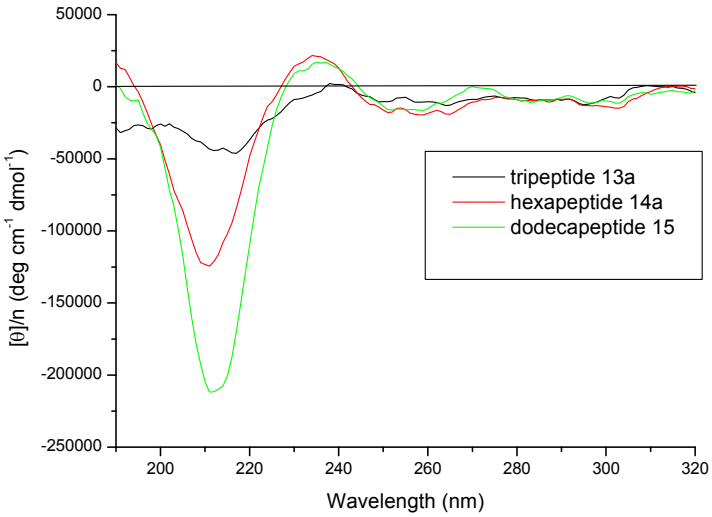


Fig. 2.11: CD absorption spectra of Pro-Ant-Aib oligomers: tripeptide **13a**, hexapeptide **14a** and dodecapeptide **15** in trifluoroethanol. All spectra recorded at 298 K with a concentration 0.01 mM.

2.11 Conclusion

In conclusion, hybrid oligomers comprising Pro-Ant-Aib motifs, repeating at regular intervals, have been shown to be adopting left-handed helical structural architecture, displaying Hamilton-type C_6 hydrogen-bonding network.[17] The structural architecture of these hybrid oligomers is unlike the conformation reported for -(Aib-Pro)- sequence, which assume β-bend ribbon spiral motif displaying robust 10-membered-ring closed network of hydrogen-bonding interactions.[12b,13] This aliphatic-aromatic conjugated hybrid foldamer adopts a

well-defined, compact, three-dimensional architecture, governed by a combined conformational restriction imposed by the individual amino acids with which they are made of. The findings suggest that substitution pattern on aromatic amino acid in constrained aliphatic-aromatic amino acid conjugates would have a *de novo* design of foldamers with distinctive structural architectures.

2.12 Experimental Section (Part A)

***General procedure for the preparation of azido dipeptides* 2 and 3:**

(S)-methyl 1-(2-(azidomethyl)benzoyl)pyrrolidine-2-carboxylate 2:

Representative procedure: To an ice-cold stirred solution of the 2-(azidomethyl) benzoic acid **1**[7] (1 equiv) in dry dichloromethane was added dry DMF (0.1 equiv) followed by oxalyl chloride (1.1 equiv). The resulting mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure and dried. The residue containing the acid chloride was dissolved in dry dichloromethane and added drop wise to an ice cooled solution of HCl.H-^{L}Pro-OMe (1.1 equiv) and Et_3N (2.2 equiv) in dichloromethane. The reaction mixture was then stirred at room temperature for 6 h. The reaction mixture was diluted with dichloromethane, and the organic layer was washed sequentially with dilute HCl solution, water, saturated sodium bicarbonate and saturated brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products, which were then purified by column chromatography.

The product **2** was obtained as a colorless liquid. Yield: 12.96 g (68%); $[\alpha]^{24}_{D}$: -56° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2955, 2100, 1745, 1633, 1600, 1421, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.47-7.41 (m, 4H), 4.77 (q, 1H), 4.66-4.47 (m, 2H), 3.84 (s, 3H), 3.59-3.30 (m, 2H), 2.47-1.86 (m, 4H); ^{13}C (50 MHz, $CDCl_3$) δ: 172.4, 172.2, 168.9, 168.6, 136.1, 135.9, 132.9, 132.7, 130.2, 129.5, 129.4, 129.0, 128.8, 128.0, 127.8, 126.1, 125.9, 125.5, 125.4, 60.8, 58.2, 58.0, 52.1, 52.0, 51.6, 49.1, 48.5, 45.9, 31.1, 30.9, 29.4, 29.33, 24.6, 24.6, 22.7, 22.5; ESI-MS: 311.1485 $(M+Na)^+$; 327.1411 $(M+K)^+$; Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43; Found: C, 58.49; H, 5.41; N, 19.27.

(S)-1-(2-(azidomethyl)benzoyl)-N-(4-bromophenyl)pyrrolidine-2-carboxamide 3:

The product **3** was obtained, following the procedure for **2**, as a white solid. Yield: 1.08 g (76%); mp: 80-82 °C; $[\alpha]^{24}_{D}$: +6° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3316, 2100, 1694, 1620, 1602, 1540, 1434, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 7.44 (bs, 4H), 7.37 (d, *J* = 8.97 Hz, 2H), 7.26 (d, *J* = 8.97 Hz, 2H), 5.01 (dd, *J* = 4.42, 7.45 Hz, 1H), 4.64 (q, 2H), 3.54-3.30 (m, 2H), 2.47-

2.30 (m, 1H), 2.29-2.01 (m, 2H), 1.96-1.80 (m, 1H); ^{13}C (50 MHz, $CDCl_3$) δ: 170.1, 169.4, 137.2, 135.9, 132.5, 131.3, 129.9, 128.6, 126.5, 120.9, 116.1, 60.6, 52.2, 50.2, 28.7, 24.9; LC-MS: 449.99 $(M+Na)^+$; 452.04 $(M+2+Na)^+$; Anal. Calcd. for $C_{19}H_{18}BrN_5O_2$: C, 53.28; H, 4.24; N, 16.35; Found: C, 53.09; H, 4.41; N, 16.54.

(S)-methyl 1-(2-((tert-butoxycarbonylamino)methyl)benzoyl)pyrrolidine-2-carboxylate 4a:

To the solution of azido dipeptide **2** (1 equiv) in ethyl acetate, Boc anhydride (1.2 equiv) and Et_3N (1.5 equiv) were added. The mixture was subjected to hydrogenolysis using 10% Pd-C (cat.) and H_2 (60 psi). After completion of reaction, the reaction mixture was filtered over celite pad. The filtrate on evaporation under reduced pressure yielded crude products, which were then purified by column chromatography.

The product **4a** was obtained as a colourless liquid. Yield: 14.64 g (93%); $[\alpha]^{24}_D$: -2° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3014, 1741, 1703, 1697, 1633, 1516, 1506, 754; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.43-7.12 (m, 4H), 6.12-6.04 (m, 1H), 4.63-4.56 (m, 1H), 4.22 (d, *J* = 6.32 Hz, 2H), 3.75 (s, 2.8H), $3.72_{conformer}$ (s, 0.2H), 3.44-3.24 (m, 2H), 2.31-2.17 (m, 1H), 2.09-1.79 (m, 3H), $1.35_{conformer}$ (s, 0.2H), 1.32 (s, 8.8H); ^{13}C (50 MHz, $CDCl_3$) δ: 172.7, 172.4, 169.9, 169.7, 155.8, 136.6, 136.4, 135.7, 130.2, 129.7, 129.4, 127.0, 125.6, 125.5, 125.4, 78.6, 58.2, 52.3, 52.0, 49.1, 48.5, 42.3, 29.4, 28.2, 24.5; ESI-MS: 363.1542 $(M+H)^+$; 385.0594 $(M+Na)^+$; 401.1011 $(M+K)^+$; Anal. Calcd. for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73; Found: C, 63.13; H, 7.05; N, 7.89.

***General procedure for the C-terminus ester saponification: Synthesis of* 4b, 7b *and* 10b:**

(S)-1-(2-((tert-Butoxycarbonylamino)methyl)benzoyl)pyrrolidine-2-carboxylic acid 4b:

Representative procedure: To a solution of **4a** (1 equiv) in methanol, $LiOH.H_2O$ (2 equiv) dissolved in water was added and the reaction mixture was stirred for 12 h. The solvent was stripped off under reduced pressure and the product was partitioned between dichloromethane and water, repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4

and evaporated under reduced pressure to get the crude products quantitatively, which were taken for the next reaction without further purification.

***General procedure for the N-terminus ^{t}Boc deprotection: Synthesis of* 4c, 5b, 7c *and* 10c:**

(S)-Methyl-1-(2-(aminomethyl)benzoyl)pyrrolidine-2-carboxylate 4c:

Representative procedure: A solution containing the dipeptide **4a** in dichloromethane was subjected to Boc deprotection using DCM/TFA (50%). After completion of the reaction (1 h), the solvent was stripped off under reduced pressure and the residue was partitioned between dichloromethane and water, and repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products quantitatively, which were taken for the next reaction without further purification.

***General procedure for the Boc peptide amide*s 4d, 7d, 10d *and* 11b:**

(S)-tert-butyl 2-(2-(methylcarbamoyl)pyrrolidine-1-carbonyl) benzylcarbamate 4d:

Representative procedure: The esters **4a** was taken in saturated methanolic methylamine solution and stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the products were purified by column chromatography.

The product **4d** was obtained as a sticky colourless liquid. Yield: 0.95 g (96%); $[\alpha]^{24}_{D}$: -40° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2892, 1702, 1674, 1619, 1503, 1424, 1215, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.24-6.97 (m, 5H), 6.12-6.09 (m, 1H), 4.54-4.39 (m, 1H), 4.12-3.88 (m, 2H), 3.21-2.96 (m, 2H), 2.62 (d, *J* = 4.67 Hz, 3H), 2.11-1.56 (m, 4H), 1.17 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.4, 171.7, 171.1, 170.2, 156.0, 136.5, 136.1, 130.4, 129.4, 129.0, 127.2, 125.8, 125.5, 125.3, 78.9, 59.8, 59.1, 49.7, 49.2, 42.2, 29.4, 28.2, 27.8, 26.2, 26.1, 24.7, 24.6; ESI-MS: 384.09 $(M+Na)^{+}$; 400.06 $(M+K)^{+}$; Anal. Calcd. for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 11.63; N, 17.71; Found: 63.14, H, 7.42, N, 11.75.

***General procedure for the preparation of* 5a *and* 6:**

(S)-tert-butyl 2-(2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl) benzylcarbamate 5a:

Representative procedure: To the solution of compound **3** (1 equiv) in ethyl acetate, was subjected to reduction using $SnCl_2.2H_2O$ (1.2 equiv) at 50 °C. After completion of reaction, the reaction mixture was neutralized with sat. $NaHCO_3$, filtered over celite pad. The organic layer was separated which on evaporation under reduced pressure yielded crude products, which were then subjected for Boc protection using Boc anhydride (1.2 equiv) and Et_3N (1.5 equiv) in DCM. After completion of reaction, the reaction mixture was diluted with the DCM and washed sequentially with saturated $KHSO_4$, water and saturated brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products, which were then purified by column chromatography.

The product **5a** was obtained as a sticky colourless liquid. Yield: 0.89 g (91%); mp: 149-151 °C; $[\alpha]^{24}_D$: -24° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3314, 3019, 1690, 1617, 1541, 1490, 1216, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.66 (s, 1H), 7.44 (d, *J* = 6.82 Hz, 1H), 7.36-7.30 (m, 1H), 7.27-7.23 (m, 4H), 7.19-7.12 (m, 2H), 6.10 (bs, 1H), 4.81 (dd, *J* = 3.66, 6.82 Hz, 1H), 4.37-4.10 (m, 2H), 3.41-3.18 (m, 2H), 2.29-1.93 (m, 3H), 1.88-1.74 (m, 1H), $1.36_{conformer}$ (s, 0.3H), 1.31 (s, 8.7H); ^{13}C (50 MHz, $CDCl_3$) δ: 170.7, 169.9, 155.9, 137.2, 136.0, 135.8, 131.4, 130.5, 129.7, 127.4, 125.7, 121.0, 116.3, 79.2, 60.7, 50.1, 42.4, 29.2, 28.3, 24.7; LC-MS: 524.17 $(M+Na)^+$; 526.16 $(M+2+Na)^+$; 540.19 $(M+K)^+$; 542.19 $(M+2+K)^+$; Anal. Calcd. for $C_{24}H_{28}BrN_3O_4$: C, 57.38; H, 5.62; N, 8.36; Found: C, 57.55; H, 5.45; N, 8.19.

(S)-N-(4-bromophenyl)-1-(2-((3,5-dinitrobenzamido)methyl)benzoyl) pyrrolidine-2-carboxamide 6:

The product **6** was obtained, following the procedure for **5a**, as a white solid. Yield: 0.30 g (85%); mp: 160-162 °C; $[\alpha]^{24}_D$: +92° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3306, 3020, 1668, 1617, 1542, 1215, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.54 (s, 1H), 9.36 (t, *J* = 5.18 Hz, 1H), 9.20 (d, *J* = 1.89 Hz, 2H), 8.98 (s, 1H), 7.71 (d, *J* = 6.82 Hz, 1H), 7.60-7.37 (m, 3H), 7.33 (d, *J* = 8.97 Hz, 2H),

7.17 (d, *J* = 8.72 Hz, 2H), 4.80-4.62 (m, 2H), 4.58 (dd, *J* = 4.42, 7.58 Hz, 1H), 3.43-3.30 (m, 1H), 3.24-3.13 (m, 1H), 2.24-2.20 (m, 2H), 1.83-1.73 (m, 2H); ^{13}C (50 Hz, $CDCl_3$) δ: 171.0, 170.0, 162.7, 148.2, 137.5, 136.6, 136.1, 134.7, 132.0, 131.6, 129.8, 128.0, 127.7, 125.4, 121.1, 120.7, 117.0, 60.7, 50.0, 42.3, 30.0, 24.6; LC-MS: 618.17 $(M+Na)^+$; 620.17 $(M+2+Na)^+$; 634.18 $(M+K)^+$; 636.18 $(M+2+K)^+$; Anal. Calcd. for $C_{26}H_{22}BrN_5O_7$: C, 52.36; H, 3.72; N, 11.74; Found: C, 52.19; H, 3.90; N, 11.91.

***General procedure for the preparation of oligomers* 7a, 8, 10a *and* 11a:**

(S)-methyl 1-(2-(((S)-1-(2-((tert-butoxycarbonylamino)methyl)benzoyl) pyrrolidine-2-carboxamido)methyl)benzoyl)pyrrolidine-2-carboxylate 7a:

Representative procedure: To an ice cooled solution of the acid **4b** (1 equiv) in dry dichloromethane, was added the amine **4c** (1 equiv) followed by EDC.HCl (1.1 equiv) and HOBt (0.2 equiv). The reaction mixture was allowed to proceed for 8 h at room temperature and then diluted with dichloromethane. The organic layer was washed sequentially with saturated $KHSO_4$ solution, water, saturated sodium bicarbonate and saturated brine and dried over anhydrous Na_2SO_4. The organic layer was then evaporated under reduced pressure to obtain the crude products, which on purification by column chromatography.

The product **7a** was obtained as a sticky colourless liquid. Yield: 6.30 g (63%); $[\alpha]^{24}_D$: +40° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3352, 1747, 1681, 1631, 1514, 1504, 1427, 771; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.85-7.73 (m, 1H), 7.54-7.14 (m, 8H), 7.02-6.53 (m, 1H), 4.62-4.45 (m, 3H), 4.33-3.98 (m, 3H), 3.82 (s, 2.4H), $3.80_{conformer}$ (s, 0.6H), 3.77-3.56 (m, 1H), 3.48-3.11 (m, 3H), 2.48-1.71 (m, 8H), $1.40_{conformer}$ (s, 1H), 1.36 (s, 8H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.3, 173.1, 171.9, 171.3, 170.2, 169.8, 169.6, 155.9, 136.8, 136.3, 136.2, 135.8, 135.7, 135.6, 134.0, 130.4, 130.4, 130.1, 130.1,129.4, 129.0, 128.7, 127.2, 127.1, 126.9, 125.7, 125.6, 125.5, 125.2, 78.4, 59.6, 59.2, 58.4, 58.3, 52.4, 52.3, 49.4, 49.3, 49.2, 48.9, 42.3, 41.2, 41.1, 40.8, 29.9, 29.4, 29.2, 29.1, 28.2, 24.7, 24.5; ESI-MS: 593.5390 $(M+H)^+$; 615.4870 $(M+Na)^+$; 631.4747 $(M+K)^+$; Anal. Calcd. for $C_{32}H_{40}N_4O_7$: C, 64.85; H, 6.80; N, 9.45; Found: C, 65.01; H, 6.71; N, 9.31.

(S)-methyl 1-(2-(((S)-1-(2-((tert-butoxycarbonylamino)methyl)benzoyl) pyrrolidine-2-carboxamido)methyl)benzoyl)pyrrolidine-2-carboxylate 7d:

The product **7d**, following the procedure for **4d**, as a sticky colourless liquid. Yield: 0.93 g (94%); $[\alpha]^{24}_{D}$: +50° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 1693, 1651, 1633, 1600, 1435, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.56-8.15 (m, 1H), 7.49-7.17 (m, 8H), 6.51 (bs, 1H), 4.52-3.97 (m, 6H), 3.69-3.17 (m, 4H), 2.70-2.62 (m, 3H), 2.16-1.61 (m, 8H), $1.34_{conformer}$ (s, 2H), 1.30 (s, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 173.0, 172.9, 172.3, 171.4, 170.2, 169.8, 169.5, 169.4, 136.4, 136.1, 136.0, 135.9, 135.5, 135.5, 130.4, 129.1, 129.0, 127.1, 126.9, 125.4, 125.3, 78.5, 59.9, 59.5, 59.5, 49.7, 49.5, 42.1, 41.0, 30.0, 28.2, 26.1, 25.9, 24.7, 24.5; ESI-MS: 614.5207 $(M+Na)^+$; 1206.2248 $(2M+Na)^+$; Anal. Calcd. for $C_{32}H_{41}N_5O_6$: C, 64.96; H, 11.84, 16.22; N, 12.72; Found: 64.83, H, 7.13, N, 11.68.

tert-butyl 2-((S)-2-((2-((S)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)benzylcarbamate 8:

The product **8** was obtained from acid **4b** and amine **5b**, following the procedure for **7a**, as a white solid. Yield: 0.57 g (65%); mp: 175-177 °C; $[\alpha]^{24}_{D}$: +6° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3298, 3017, 1675, 1618, 1490, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.82-9.71 (m, 1H), 8.29 (bs, 1H), 7.56 (d, *J* = 7.07 Hz, 1H), 7.49-7.06 (m, 1H), 6.33 (bs, 1H), 4.81-4.69 (m, 1H), 4.66-4.51 (m, 2H), 4.46-4.23 (m, 2H), 4.19-3.99 (m, 1H), 3.94-3.57 (m, 1H), 3.45-3.07 (m, 3H), 2.22-1.72 (m, 8H), 1.39 (s, 9H); ^{13}C (50 MHz, $CDCl_3$) δ: 172.2, 17.9, 170.5, 156.1, 137.4, 136.2, 135.6, 131.4, 130.4, 129.7, 129.3, 127.4, 127.1, 125.8, 125.5, 121.1, 60.9, 59.8, 50.2, 49.6, 42.2, 41.2, 30.0, 29.8, 28.4, 25.0, 24.6; LC-MS: 732.33 $(M+H)^+$; 754.27 $(M+Na)^+$; 756.39 $(M+2+Na)^+$; 770.27 $(M+K)^+$; 772.27 $(M+2+K)^+$; Anal. Calcd. for $C_{37}H_{42}BrN_5O_6$: C, 60.65; H, 5.78; N, 9.56; Found: C, 60.83; H, 5.59; N, 9.73.

(S)-N-(4-bromophenyl)-1-(2-(((S)-1-(2-((3,5-dinitrobenzamido) methyl) benzoyl) pyrrolidine-2-carboxamido) methyl) benzoyl) pyrrolidine-2-carboxamide 9:

A solution containing the tetrapeptide **8** in dichloromethane was subjected to Boc deprotection using DCM/TFA (50%). After completion of the reaction (1 h), the solvent was stripped off under reduced pressure and the residue

was partitioned between dichloromethane and saturated $NaHCO_3$, and repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products quantitatively, which were taken for the next reaction without further purification.

The free amine was dissolved in dichloromethane and cooled to 0 ^{0}C. The residue containing the 3,5-dinitro benzoyl chloride (1.1 equiv) was dissolved in dry dichloromethane was added drop wise to the free amine and Et_3N (1.5 equiv). The reaction mixture was then stirred at room temperature for 6 h. The reaction mixture was diluted with dichloromethane, and the organic layer was washed sequentially with dilute HCl solution, water, saturated sodium bicarbonate and saturated brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products, which were then purified by column chromatography to obtain as a white solid. Yield: 0.25 g (76%); mp: 209-211 °C; $[\alpha]^{24}_D$: +88° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3275, 3019, 1661, 1615, 1599, 1539, 1215, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.84 (bs, 1H), 9.79 (s, 1H), 9.34 (d, *J* = 1.89 Hz, 2H), 9.08 (s, 1H), 8.68 (bs, 1H), 7.66 (d, *J* = 7.20 Hz, 1H), 7.56-7.54 (m, 1H), 7.49-7.10 (m, 10H), 4.79-4.58 (m, 4H), 4.45-4.36 (m, 2H), 3.84-3.61 (m, 1H), 3.47-3.26 (m, 2H), 3.17-3.03 (m, 1H), 2.44-1.66 (m, 8H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.3, 171.3, 170.3, 169.3, 162.6, 162.1, 148.3, 137.9, 137.1, 136.7, 135.8, 135.5, 134.9, 131.8, 131.7, 131.5, 130.9, 129.4, 129.3, 128.1, 127.6, 127.5, 125.6, 125.3, 120.9, 120.6, 116.6, 60.8, 59.6, 50.3, 49.5, 30.5, 30.2, 25.0, 24.5; LC-MS: 826.29 $(M+H)^+$; 828.29 $(M+2+H)^+$; 848.28 $(M+Na)^+$; 850.28 $(M+2+Na)^+$; 864.29 $(M+K)^+$; 866.29 $(M+2+K)^+$; Anal. Calcd. for $C_{39}H_{36}BrN_7O_9$: C, 56.66; H, 4.39; N, 11.86; Found: C, 56.84; H, 4.20; N, 12.04.

Octamer methyl ester 10a:

The product **10a** was obtained from acid **7b** and amine **7c**, following the procedure for **7a**, as a white solid. Yield: 2.19 g (56%); mp: 157-159 °C; $[\alpha]^{24}_D$: +184° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3269, 1747, 1660, 1626, 1427, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.01-8.89 (m, 2H), 8.14-8.08 (m, 1H), 7.57-7.11 (m, 15H), 7.14-6.99 (m, 1H), 6.96-6.70 (m, 1H), 4.76-4.71 (m, 2H), 4.65-4.23 (m,

10H), 3.88 (s, 3H), 3.86-3.14 (m, 8H), 2.25-1.82 (m, 16H),1.45$_{conformer}$ (s, 2H), 1.37 (s, 7H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.9, 173.8, 173.3, 173.3, 173.0, 172.3, 171.4, 169.7, 169.6, 169.5, 169.5, 169.4, 169.1, 168.9, 156.0, 136.9, 136.4, 136.3, 136.2, 136.2, 136.1, 136.0, 135.8, 135.7, 130.6, 130.5, 130.2, 129.1, 129.0, 128.8, 128.6, 127.2, 127.0, 126.9, 126.8, 125.9, 125.7, 125.5, 125.3, 78.6, 78.2, 60.2, 59.5, 59.4, 59.2, 58.5, 52.6, 49.4, 49.3, 42.3, 41.8, 41.7, 41.4, 30.4, 30.1, 29.8, 29.4, 28.3, 24.9, 24.4, 22.6; MALDI-TOF: 1075.1877 $(M+Na)^+$; 1091.1556 $(M+K)^+$; Anal. Calcd. for $C_{58}H_{68}N_8O_{11}$: C, 66.14; H, 6.51; N, 10.64; Found: C, 65.98; H, 6.70; N, 10.55.

Octamer methyl amide 10d:

The product **10d** was obtained from **10a**, following the procedure for **4d**, as a white solid. Yield: 0.55 g (92%); mp: 175-177 °C; $[\alpha]^{24}_D$: +158° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3019, 1659, 1524, 1428, 1215, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.02-8.77 (m, 2H), 7.57-6.98 (m, 18H), 6.89-6.79 (m, 1H), 4.73-3.53 (m, 16H), 3.43-3.08 (m, 4H), 2.87 (d, *J* = 4.55 Hz, 2.7H), 2.76 (d, *J* = 4.80 Hz, 0.3H), 2.45-1.64 (m, 16H), 1.44$_{conformer}$ (s, 3H), 1.36 (s, 6H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.6, 173.4, 172.4, 169.9, 169.7, 169.6, 136.6, 136.5, 136.3, 136.1, 135.9, 135.8, 130.9, 130.7, 129.0, 128.7, 127.3, 127.2, 127.1, 127.0, 126.0, 125.9, 125.6, 125.5, 78.3, 60.0, 59.6, 59.3, 49.8, 49.5, 41.9, 41.8, 41.5, 30.5, 30.4, 30.1, 30.0, 28.4, 26.4, 25.0, 24.6; LC-MS: 1074.58 $(M+Na)^+$; Anal. Calcd. for $C_{58}H_{69}N_9O_{10}$: C, 66.20; H, 6.61; N, 11.98; Found: C, 66.11; H, 6.46; N, 12.16.

Hexadecamer methyl ester 11a:

The product **11a** was obtained from acid **10b** and amine **10c**, following the procedure for **7a**, as a white solid. Yield: 0.46 g (33%); mp: 206-208 °C; $[\alpha]^{24}_D$: +206° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3261, 1737, 1666, 1631, 1573, 1566, 1450, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.24-9.19 (m, 3H), 9.01-8.88 (m, 2H), 8.40-7.98 (m, 1H), 7.47-6.99 (m, 33H), 6.92-6.80 (m, 1H), 4.65-3.87 (m, 24H), 3.78 (s, 3H), 3.70-3.41 (m, 8H), 3.34-2.98 (m, 8H), 2.48-1.52 (m, 32H), 1.34$_{conformer}$ (s, 2H), 1.25 (s, 7H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.9, 173.5, 173.4, 173.4, 173.3, 169.7, 169.4, 169.3, 156.0, 136.9, 136.9, 136.8, 136.8, 136.5, 136.2, 136.1, 136.0, 135.8, 135.8, 130.6, 130.6, 130.5, 130.4, 130.4, 130.4, 129.1, 128.7, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 127.3, 127.2, 127.0, 126.9, 126.9, 126.8,

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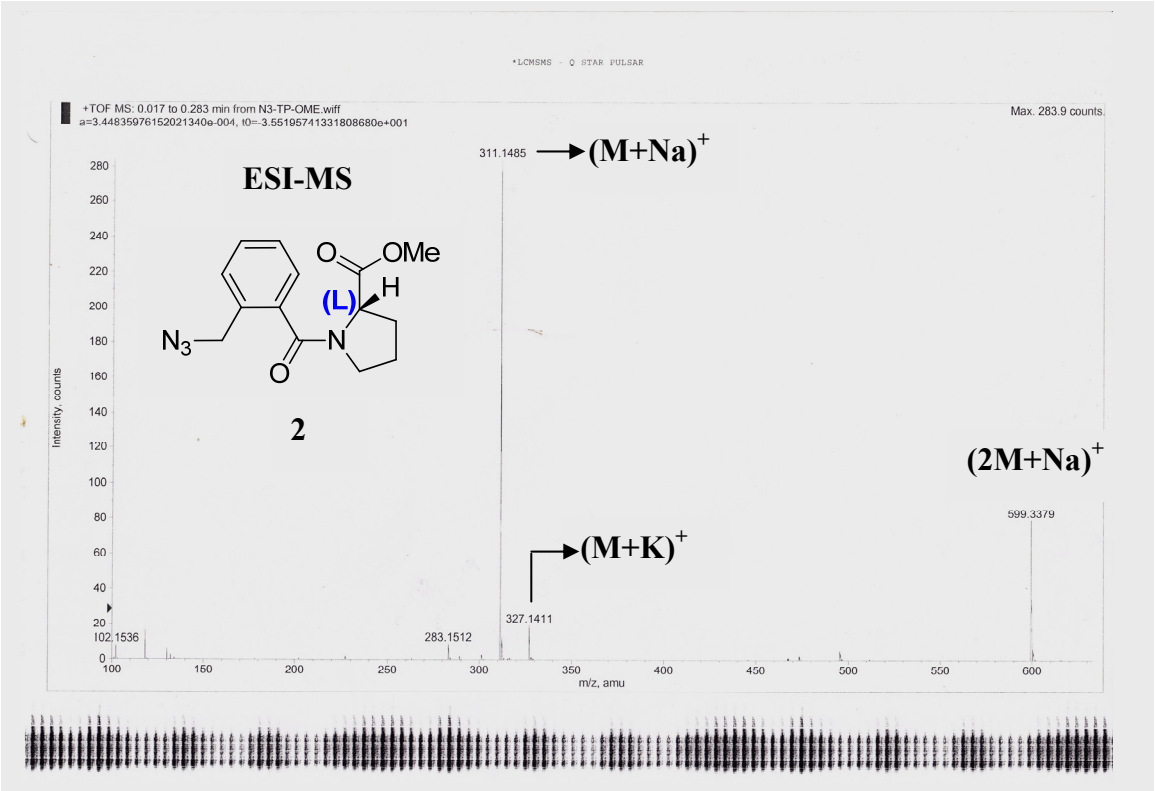
Hexadecamer methyl amide 11b:

The product **11b** was obtained from **11a**, following the procedure for **4d**, as a white solid. Yield: 0.27 g (91%); mp: 228-230 °C; $[\alpha]^{24}_D$: +190° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3020, 1656, 1624, 1563, 1542, 1428, 1215, 756; ^1H NMR (200 MHz, $CDCl_3$) δ: 9.25-8.73 (m, 5H), 7.50-7.37 (m, 7H), 7.28-7.15 (m, 26H), 6.94-6.62 (m, 3H), 4.69-4.32 (m, 22H), 4.09-3.96 (m, 2H), 3.76-3.40 (m, 8H), 3.34-2.99 (m, 8H), 2.80-1.65 (m, 3H), 2.24-1.70 (m, 32H), 1.63-1.27 (m, 9H); ^{13}C (50 MHz, $CDCl_3$) δ: 173.7, 173.6, 173.5, 173.4, 169.5, 169.4, 169.3, 156.2, 155.9, 136.9, 136.7, 136.2, 136.1, 136.0, 135.9, 130.9, 130.7, 130.5, 128.8, 128.8, 130.5, 128.8, 128.8, 128.5, 127.2, 127.1, 126.9, 125.9, 125.7, 78.6, 59.6, 59.2, 49.8, 49.6, 49.5, 42.1, 41.9, 30.6, 30.4, 30.2, 30.1, 28.4, 25.0; MALDI-TOF: 1998.22 $(M+Na)^+$; 2014.37 $(M+K)^+$; Anal. Calcd. for $C_{110}H_{125}N_{17}O_{18}$: C, 66.95; H, 6.38; N, 12.07; Found: C, 67.13; H, 6.19; N, 11.95.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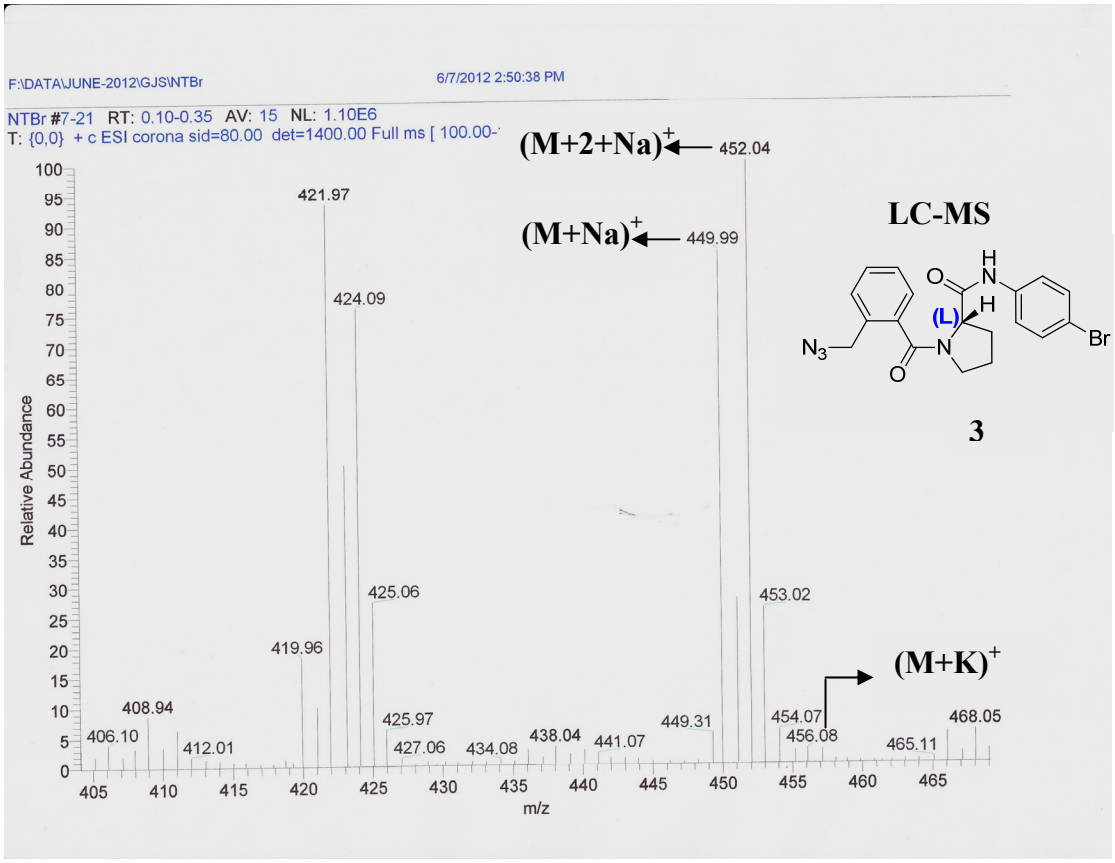
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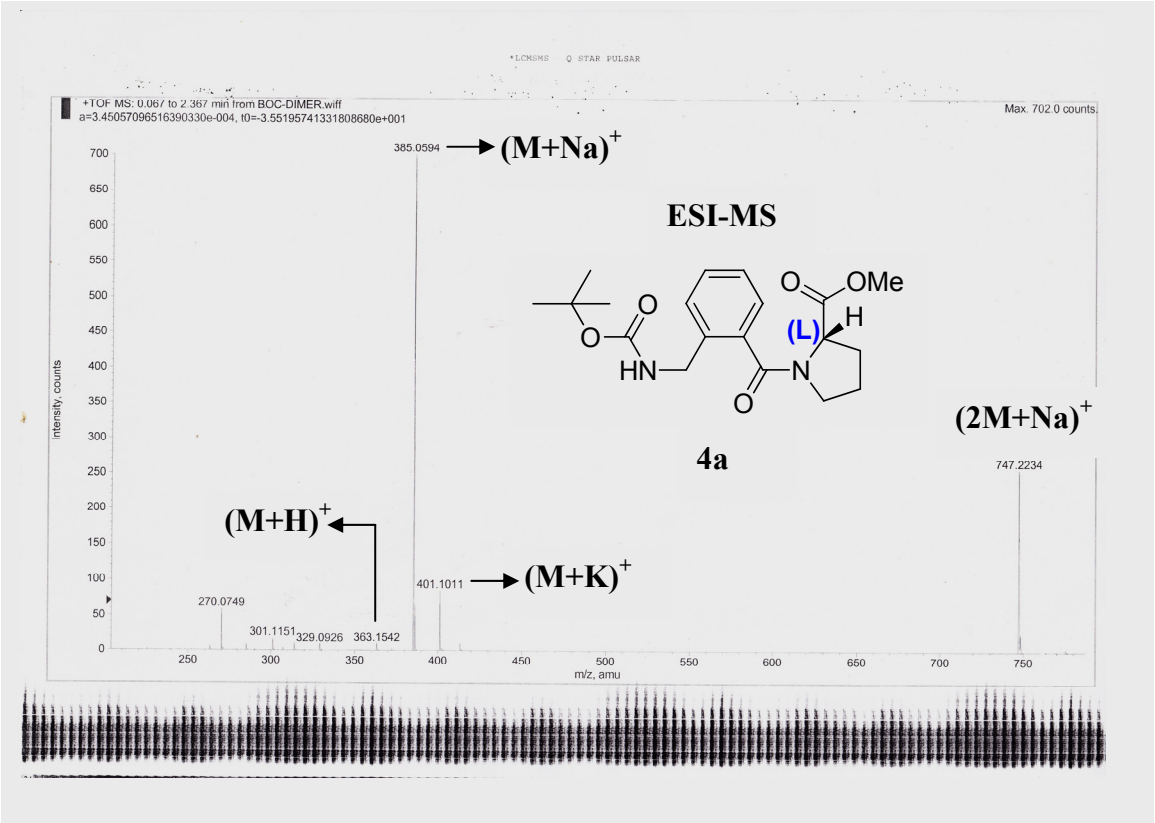
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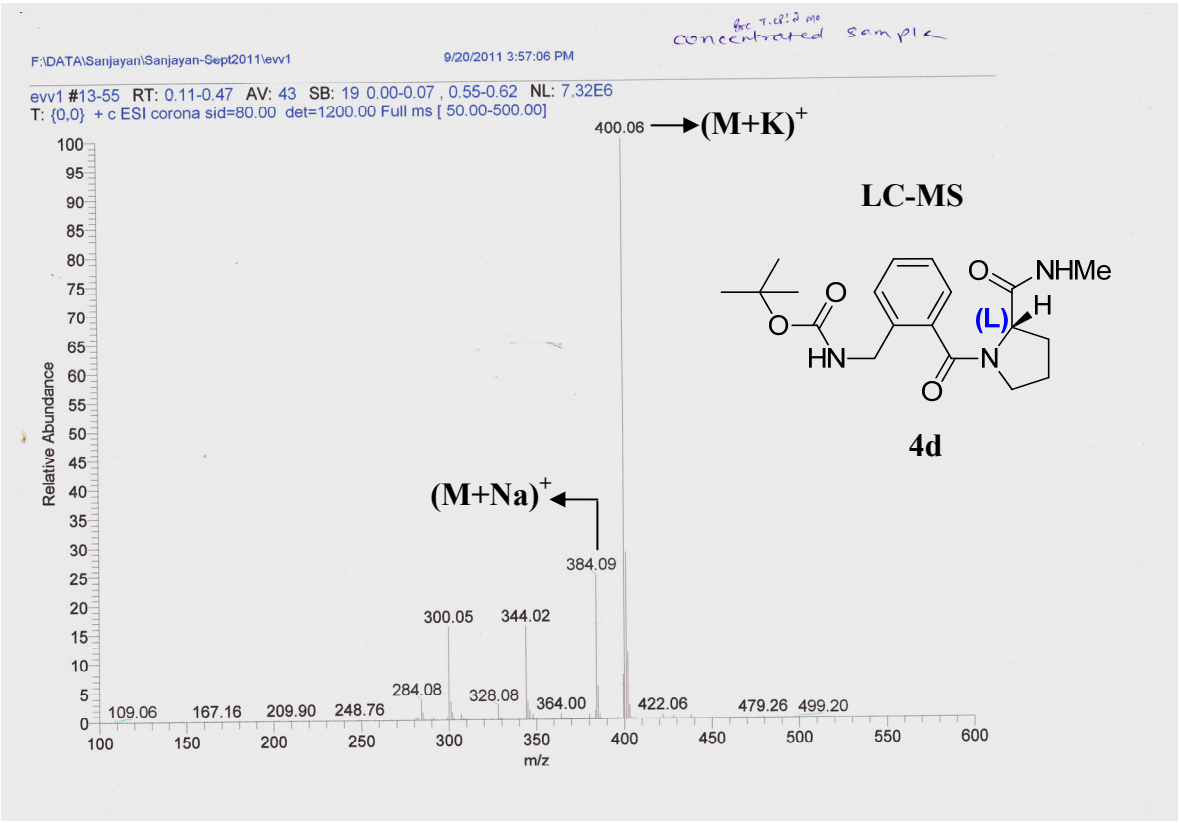
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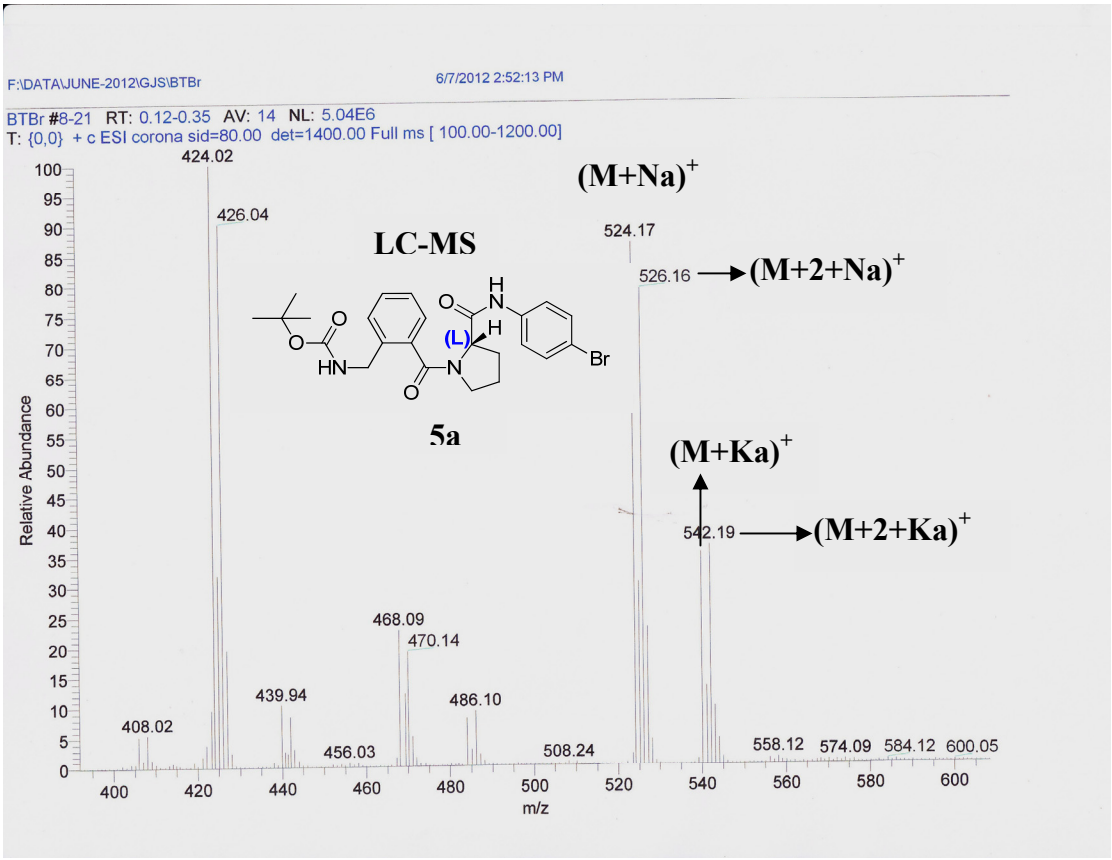
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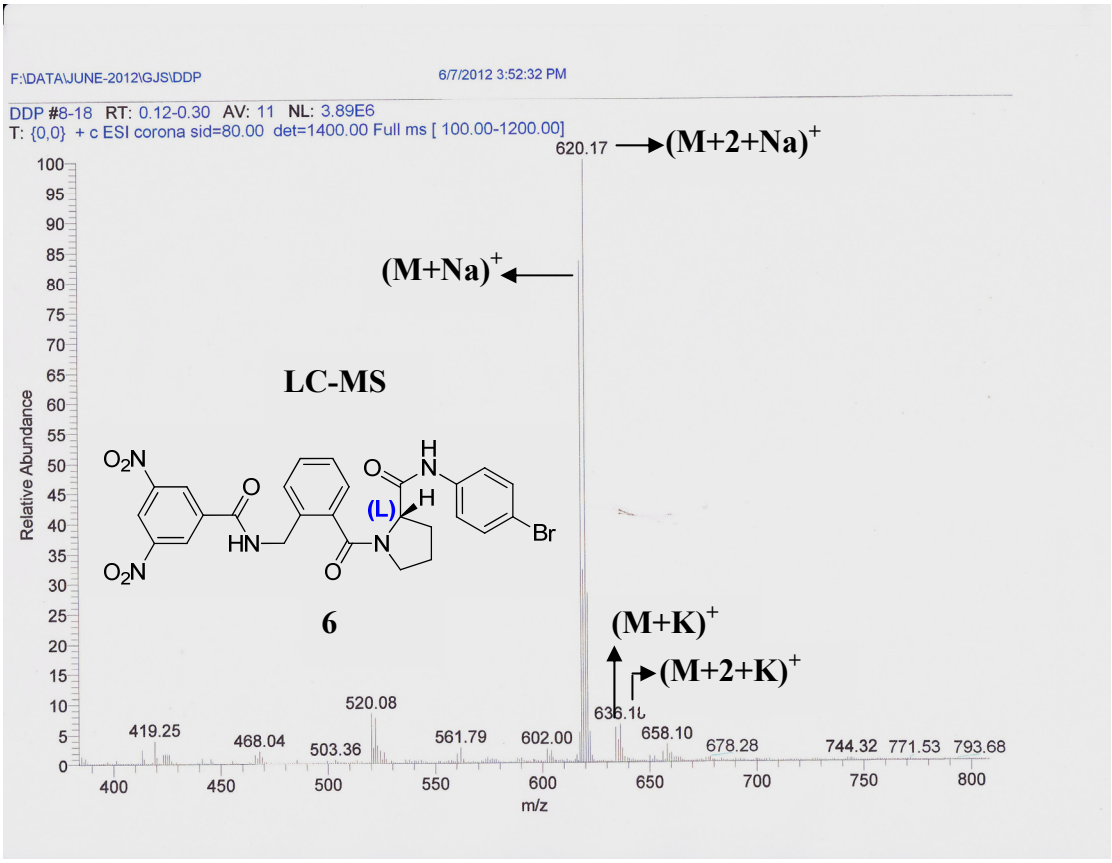
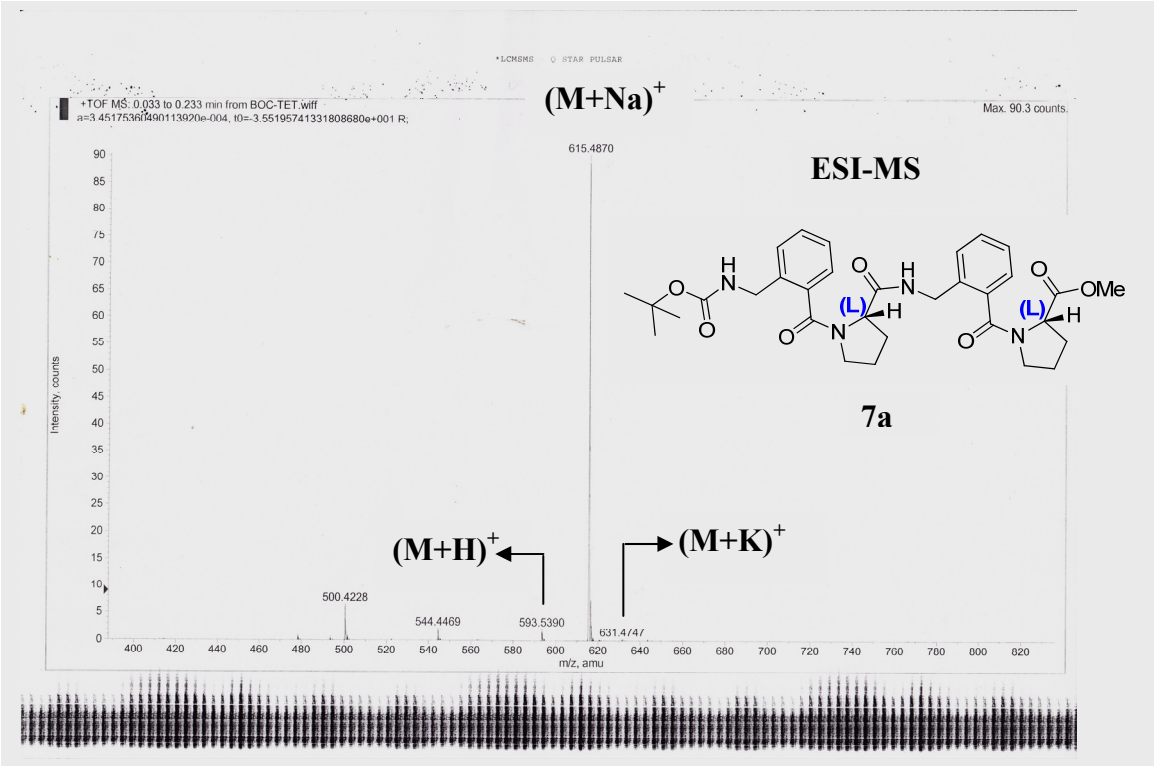
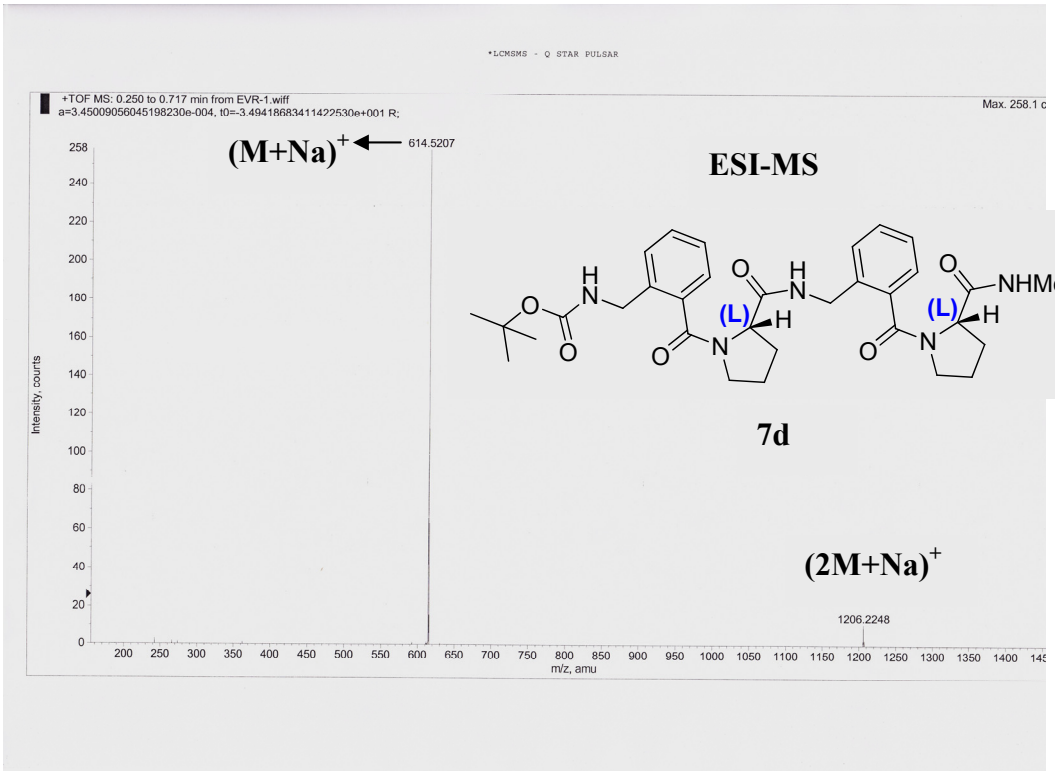
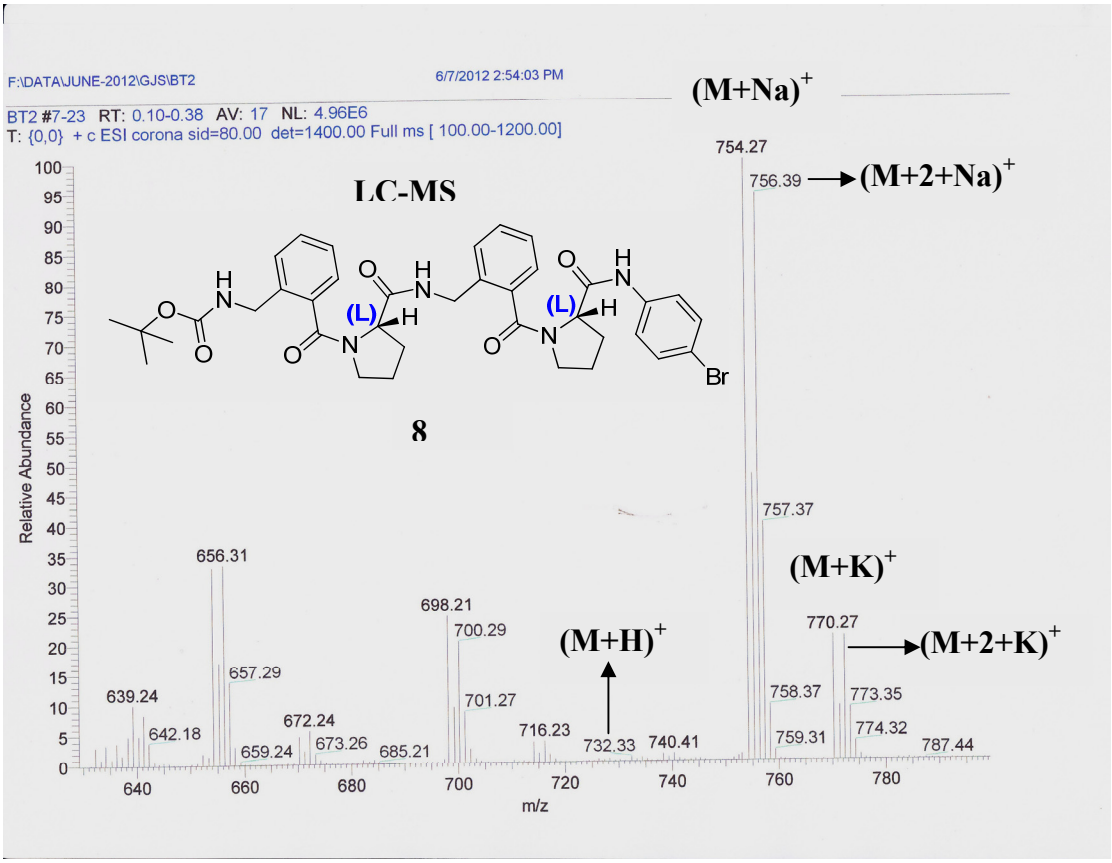
Relative Abundance
m/z


F:\DATA\JUNE-2012\GJS\DDP
6/7/2012 3:52:32 PM
DDP #8-18 RT: 0.12-0.30 AV: 11 NL: 3.89E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
(M+Na)+
(M+2+Na)+
(M+K)+
(M+2+K)+
6
Relative Abundance
m/z


*LCMSMS Q STAR PULSAR
+TOF MS: 0.033 to 0.233 min from BOC-TET.wiff
Max. 90.3 counts.
(M+Na)+
615.4870
ESI-MS
(M+H)+
(M+K)+
500.4228
544.4469
593.5390
631.4747
Intensity, counts
m/z, amu
OMe
(L)
7a


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.250 to 0.717 min from EVR-1.wiff
Max. 258.1 c
(M+Na)+
614.5207
ESI-MS
Intensity, counts
m/z, amu
NHMe
(L)
7d
(2M+Na)+
1206.2248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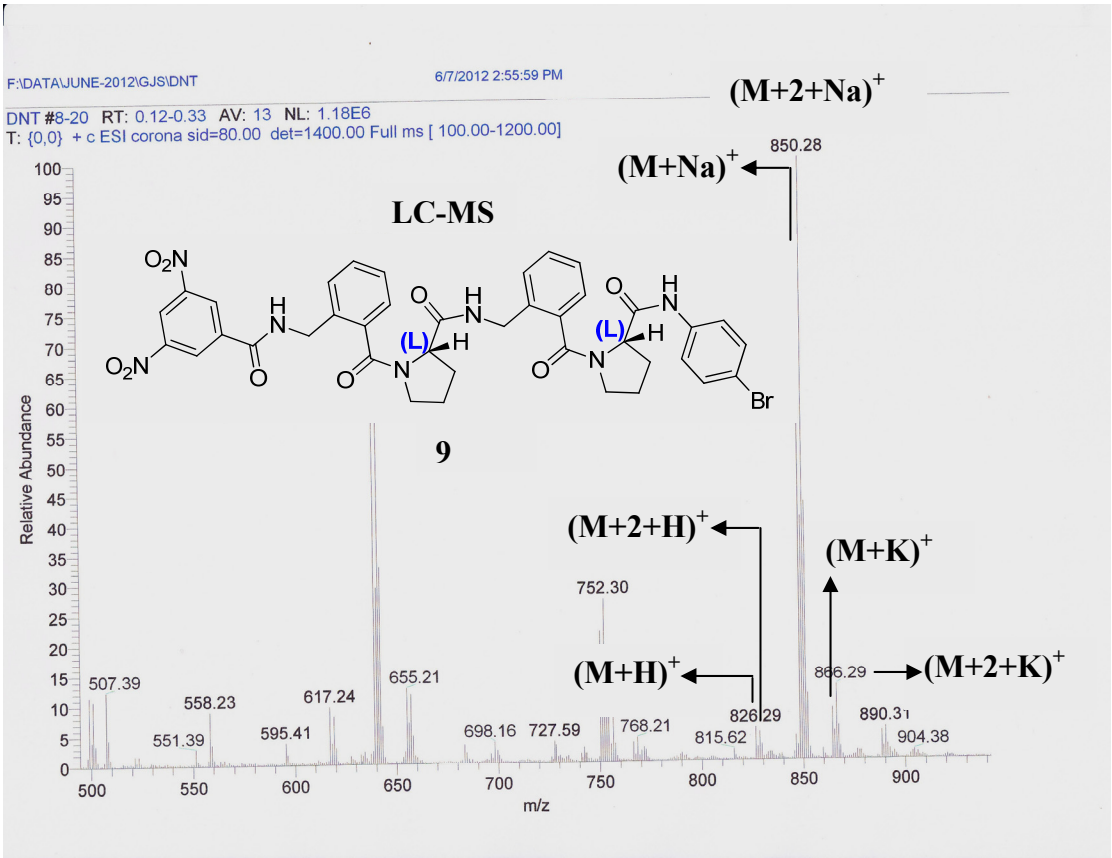
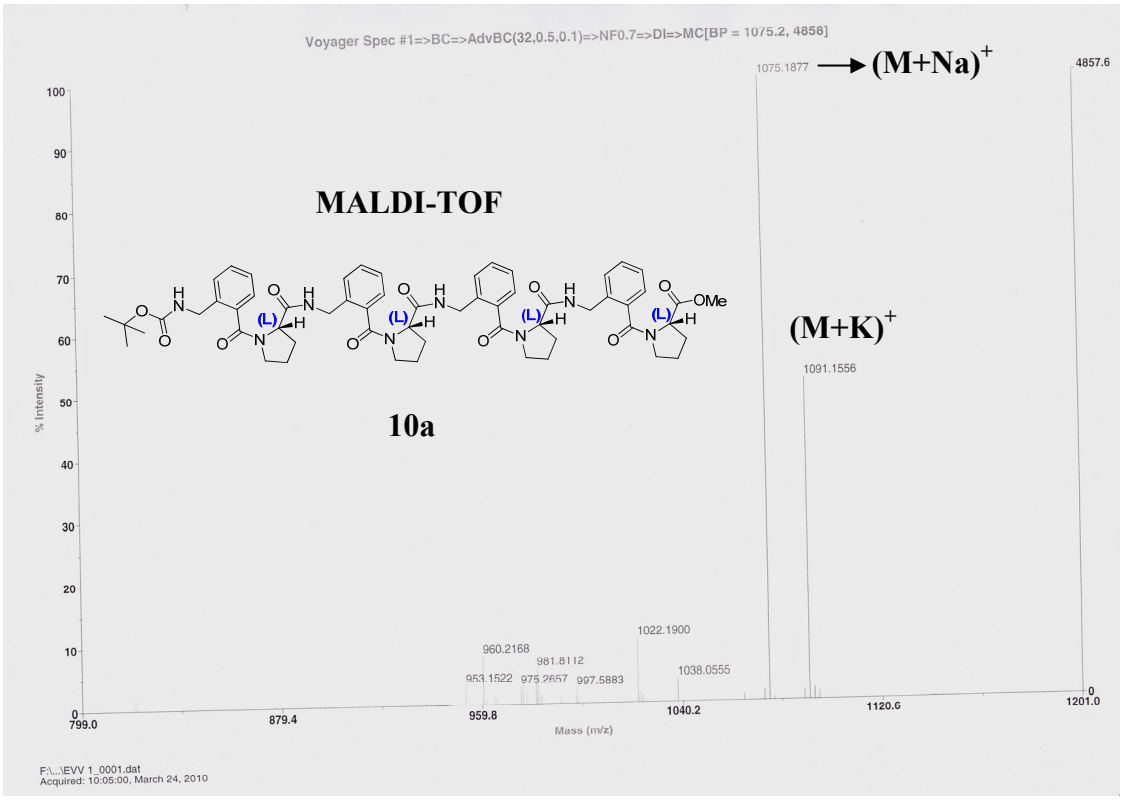
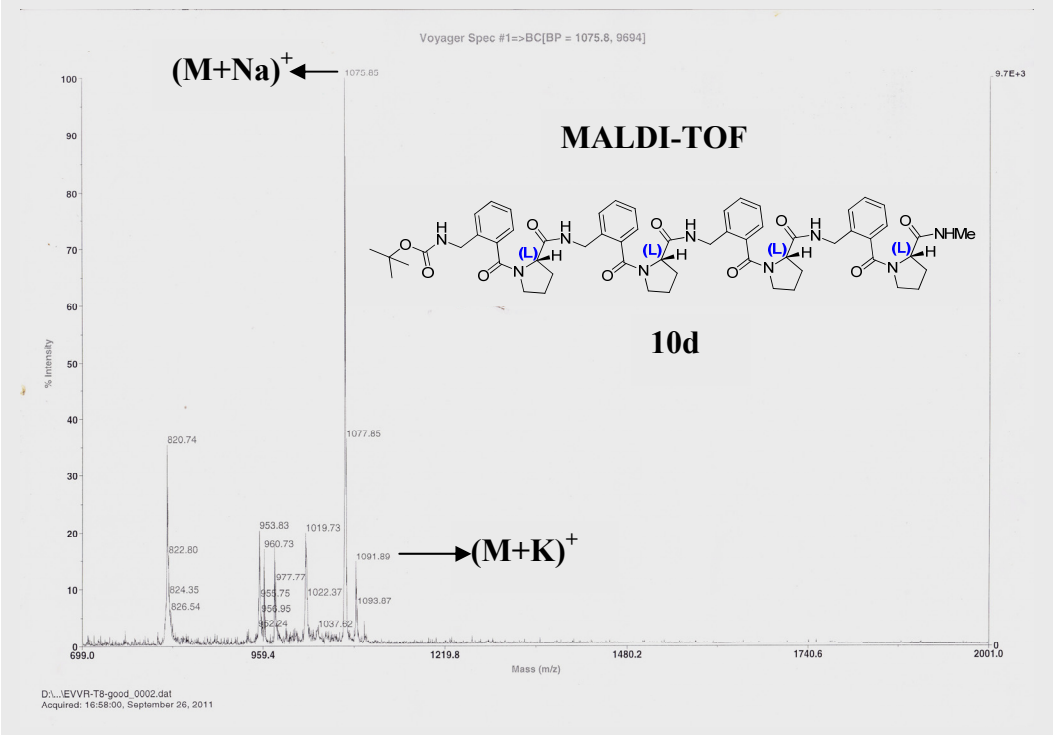
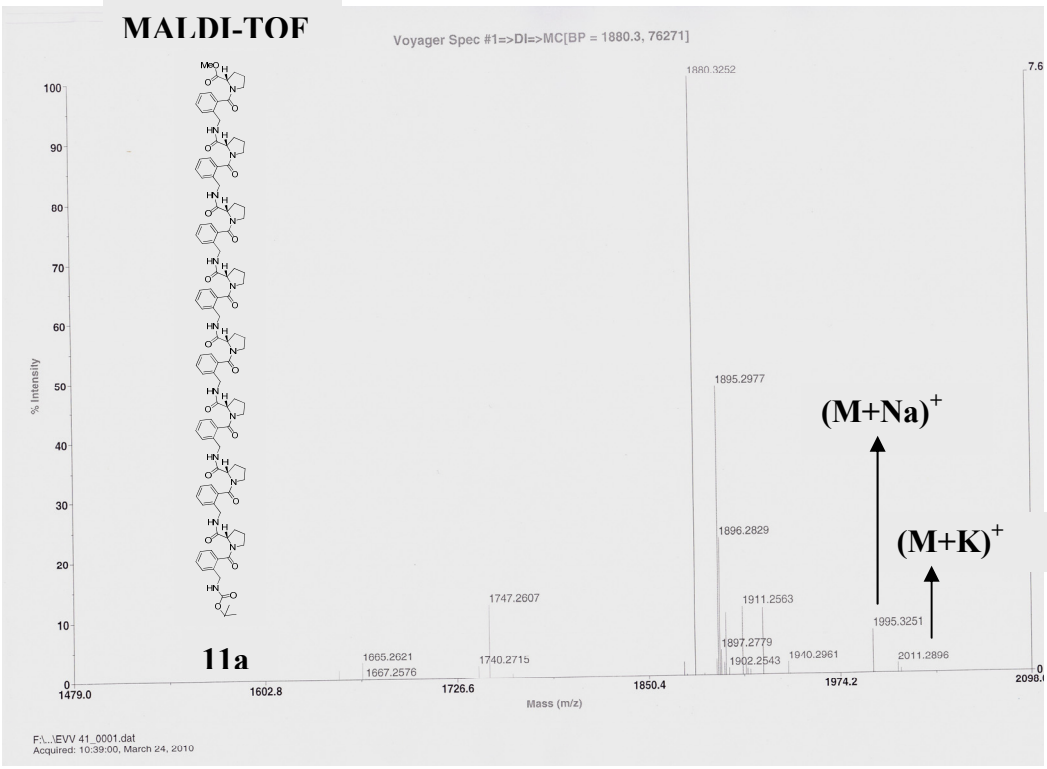
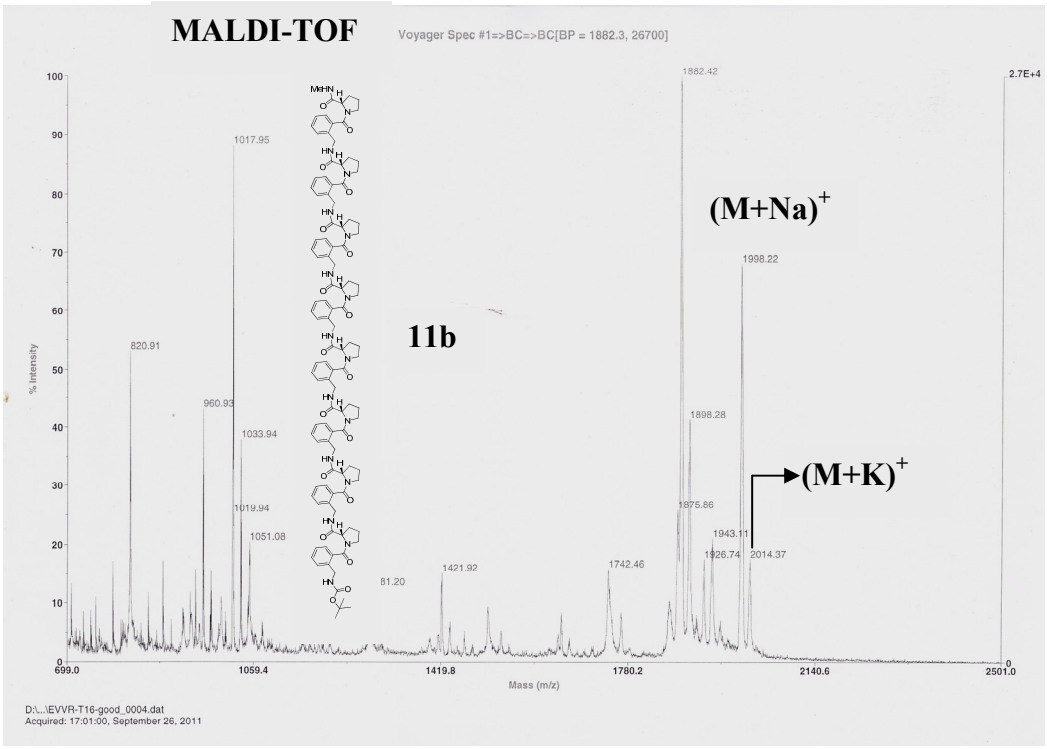
6/7/2012 2:54:03 PM
BT2 #7-23 RT: 0.10-0.38 AV: 17 NL: 4.96E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
8
(M+Na)+
(M+2+Na)+
(M+K)+
(M+H)+
(M+2+K)+
754.27
756.39
757.37
656.31
698.21
700.29
770.27
639.24
657.29
642.18
672.24
673.26
659.24
685.21
701.27
716.23
732.33
740.41
758.37
773.35
759.31
774.32
787.44
Relative Abundance
m/z


F:\DATA\JUNE-2012\GJS\DNT
6/7/2012 2:55:59 PM
DNT #8-20 RT: 0.12-0.33 AV: 13 NL: 1.18E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
9
(M+2+Na)+
(M+Na)+
850.28
(M+2+H)+
(M+K)+
(M+H)+
(M+2+K)+
752.30
866.29
507.39
558.23
617.24
655.21
551.39
595.41
698.16
727.59
768.21
826.29
815.62
890.31
904.38
Relative Abundance
m/z

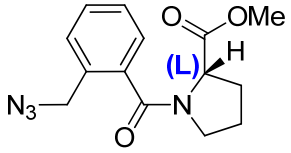

Voyager Spec #1=>BC=>AdvBC(32,0.5,0.1)=>NF0.7=>DI=>MC[BP = 1075.2, 4858]
1075.1877
(M+Na)+
4857.6
MALDI-TOF
(M+K)+
1091.1556
10a
% Intensity
1022.1900
960.2168
981.8112
953.1522
975.2657
997.5883
1038.0555
799.0
879.4
959.8
1040.2
1120.6
1201.0
Mass (m/z)
F:\...\EVV 1_0001.dat
Acquired: 10:05:00, March 24, 2010


Voyager Spec #1=>BC[BP = 1075.8, 9694]
(M+Na)+
1075.85
9.7E+3
MALDI-TOF
10d
% Intensity
820.74
1077.85
953.83
1019.73
960.73
822.80
1091.89
(M+K)+
977.77
824.35
1022.37
826.54
1093.87
699.0
959.4
1219.8
1480.2
1740.6
2001.0
Mass (m/z)
D:\...\EVVR-T8-good_0002.dat
Acquired: 16:58:00, September 26, 2011


MALDI-TOF
Voyager Spec #1=>DI=>MC[BP = 1880.3, 76271]
11a
(M+Na)+
(M+K)+
1880.3252
1895.2977
1896.2829
1747.2607
1911.2563
1995.3251
1897.2779
1902.2543
1940.2961
2011.2896
1665.2621
1667.2576
1740.2715
% Intensity
Mass (m/z)
F:\...\EVV 41_0001.dat
Acquired: 10:39:00, March 24, 2010


MALDI-TOF
Voyager Spec #1=>BC=>BC[BP = 1882.3, 26700]
11b
(M+Na)+
(M+K)+
1882.42
1998.22
1017.95
820.91
960.93
1033.94
1019.94
1051.08
1898.28
1875.86
1943.11
1926.74
2014.37
1421.92
1742.46
81.20
% Intensity
Mass (m/z)
D:\...\EVVR-T16-good_0004.dat
Acquired: 17:01:00, September 26, 2011

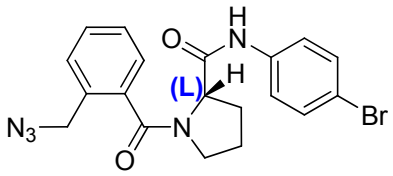
^{1}H NMR (200 MHz, $CDCl_3$)



2

Note: Small sister peaks are due to existence of another conformer in negligible amounts

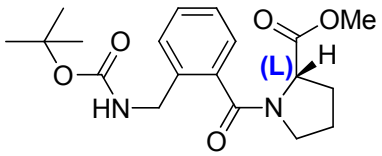
^{1}H NMR (200 MHz, $CDCl_3$)



3

Note: Small sister peaks are due to existence of another conformer in negligible amounts

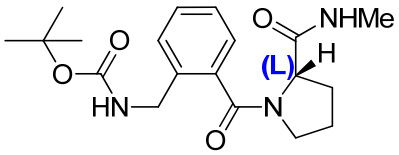
^{1}H NMR (200 MHz, $CDCl_3$)



4a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

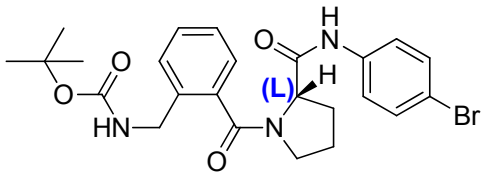
^{1}H NMR (200 MHz, $CDCl_3$)



4d

Note: Small sister peaks are due to existence of another conformer in negligible amounts

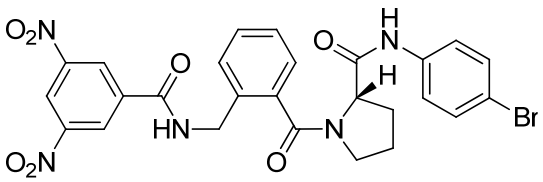
^{1}H NMR (200 MHz, $CDCl_3$)



5a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

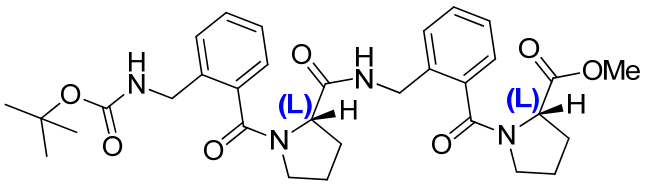
^{1}H NMR (200 MHz, $CDCl_3$)



6

Note: Small sister peaks are due to existence of another conformer in negligible amounts

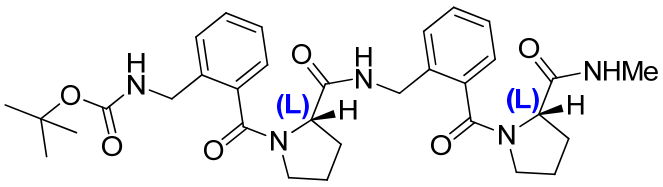
^{1}H NMR (200 MHz, $CDCl_3$)



7a

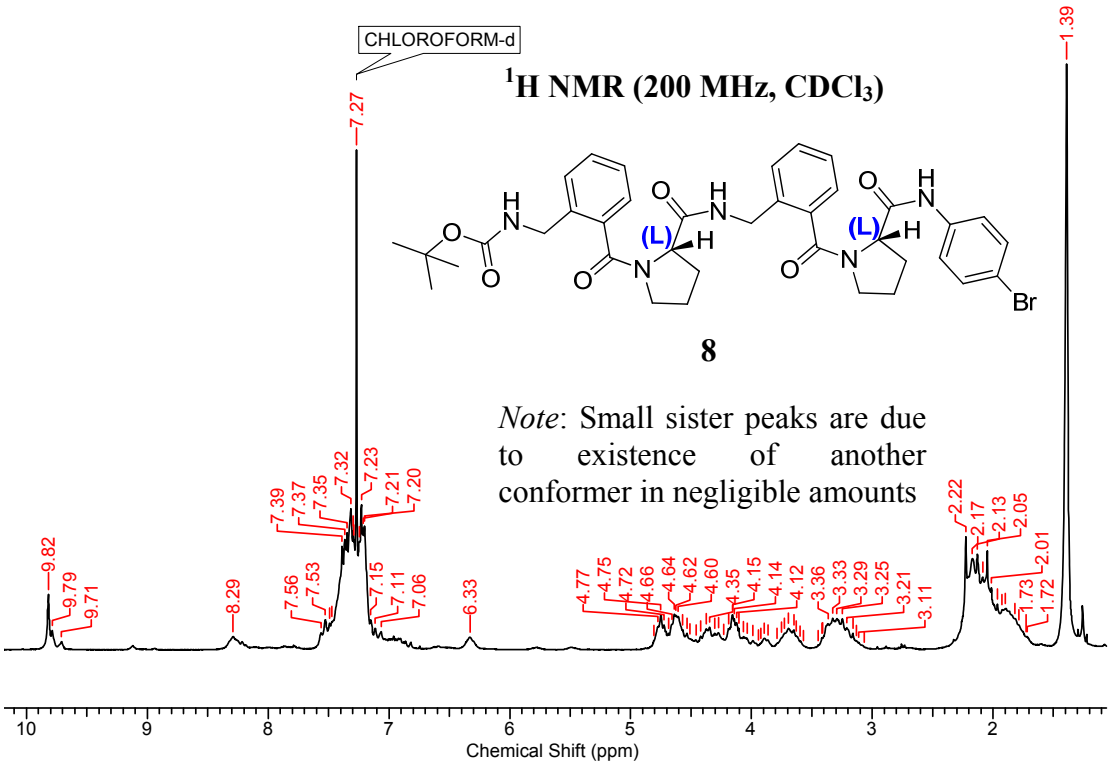
Note: Small sister peaks are due to existence of another conformer in negligible amounts

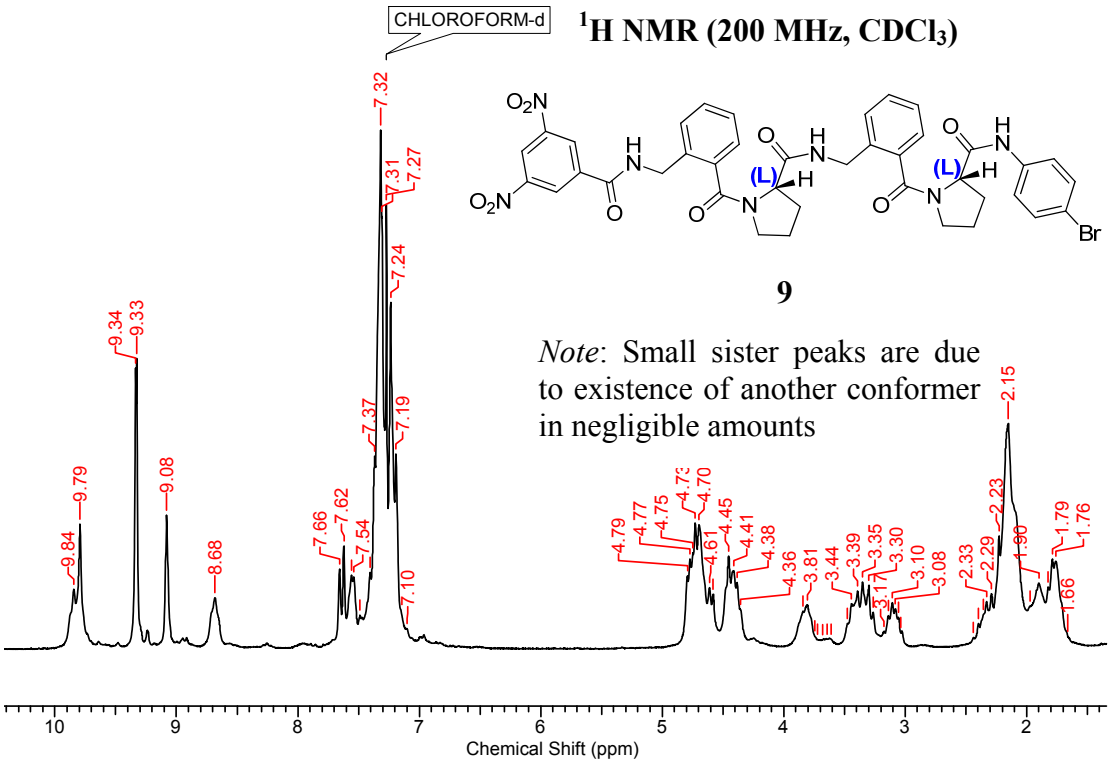
^{1}H NMR (200 MHz, $CDCl_3$)



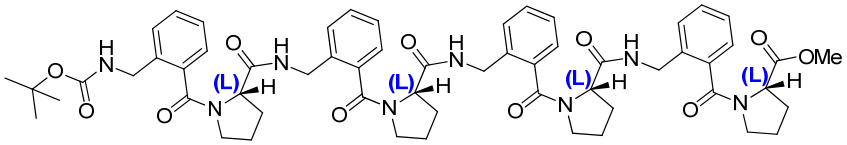
7d

Note: Small sister peaks are due to existence of another conformer in negligible amounts


CHLOROFORM-d
^{1}H NMR (200 MHz, CDCl$_3$)
8
Note: Small sister peaks are due to existence of another conformer in negligible amounts
Chemical Shift (ppm)


CHLOROFORM-d
^{1}H NMR (200 MHz, CDCl$_3$)
9
Note: Small sister peaks are due to existence of another conformer in negligible amounts
Chemical Shift (ppm)

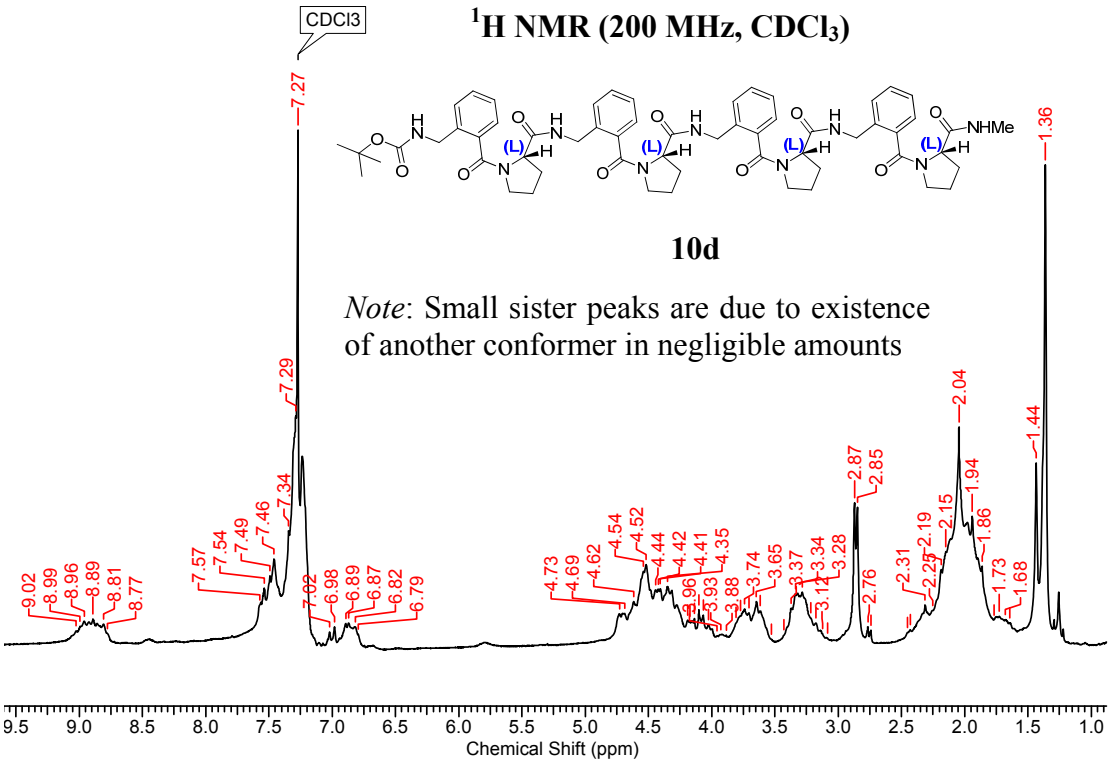
^{1}H NMR (200 MHz, $CDCl_3$)



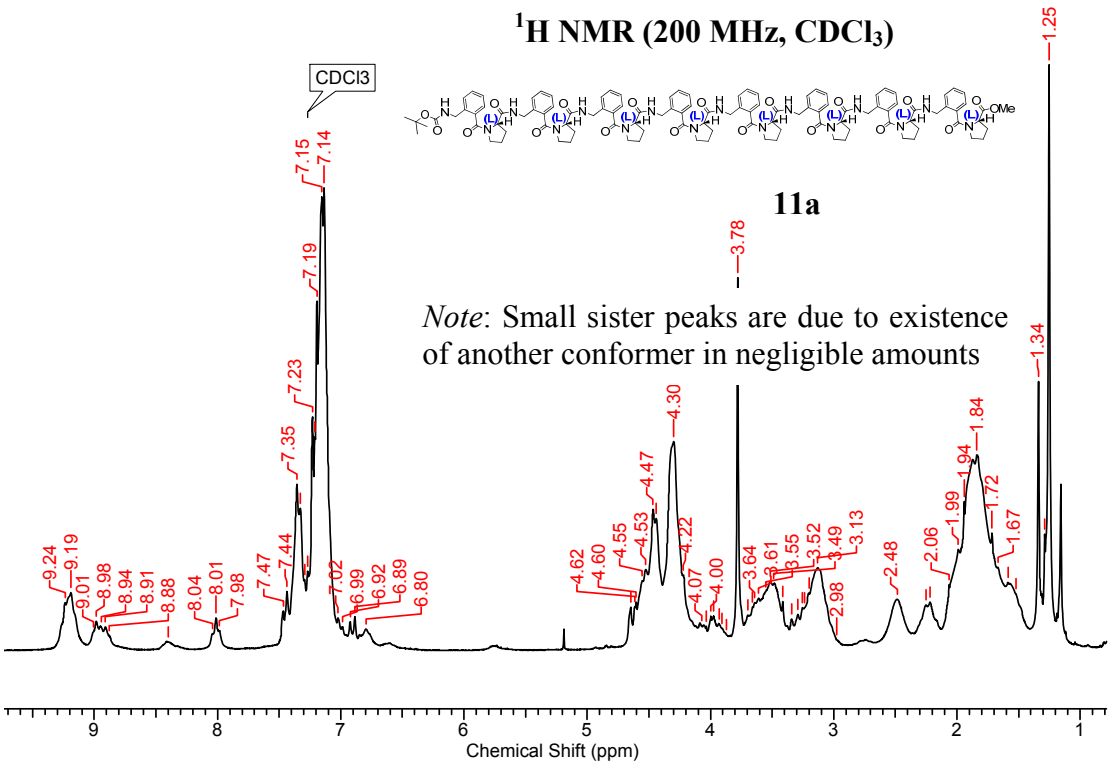
10a

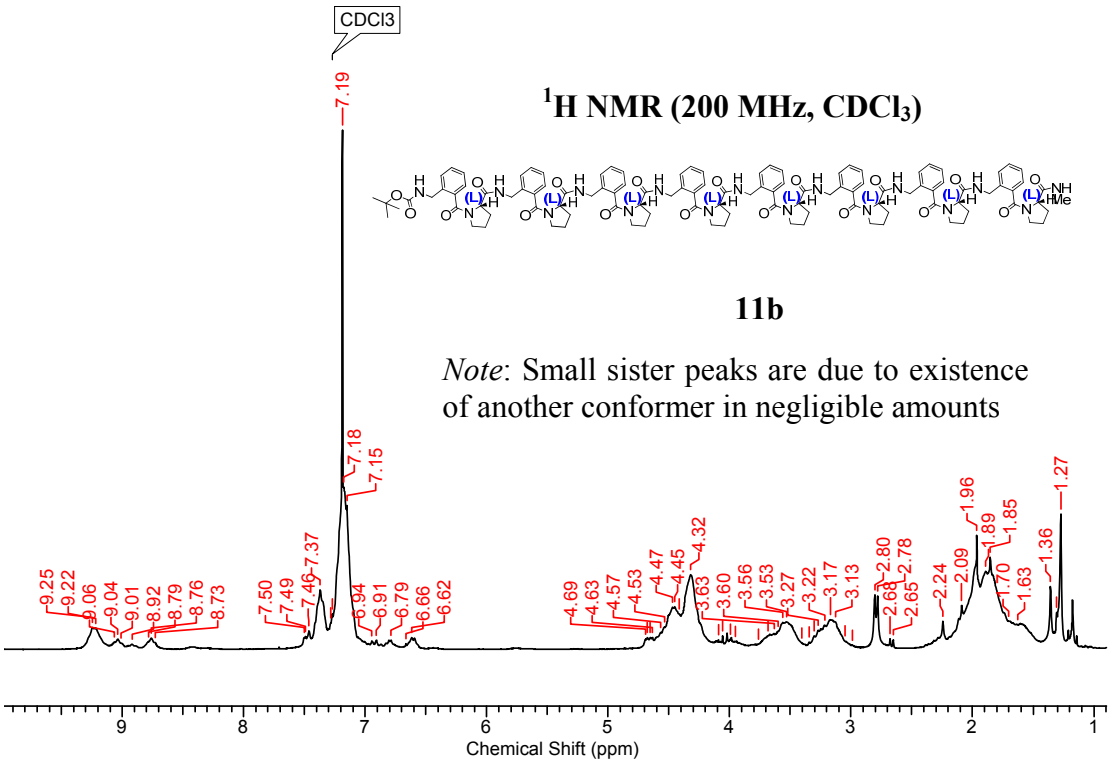
EtOAc

^{1}H NMR (200 MHz, $CDCl_3$)



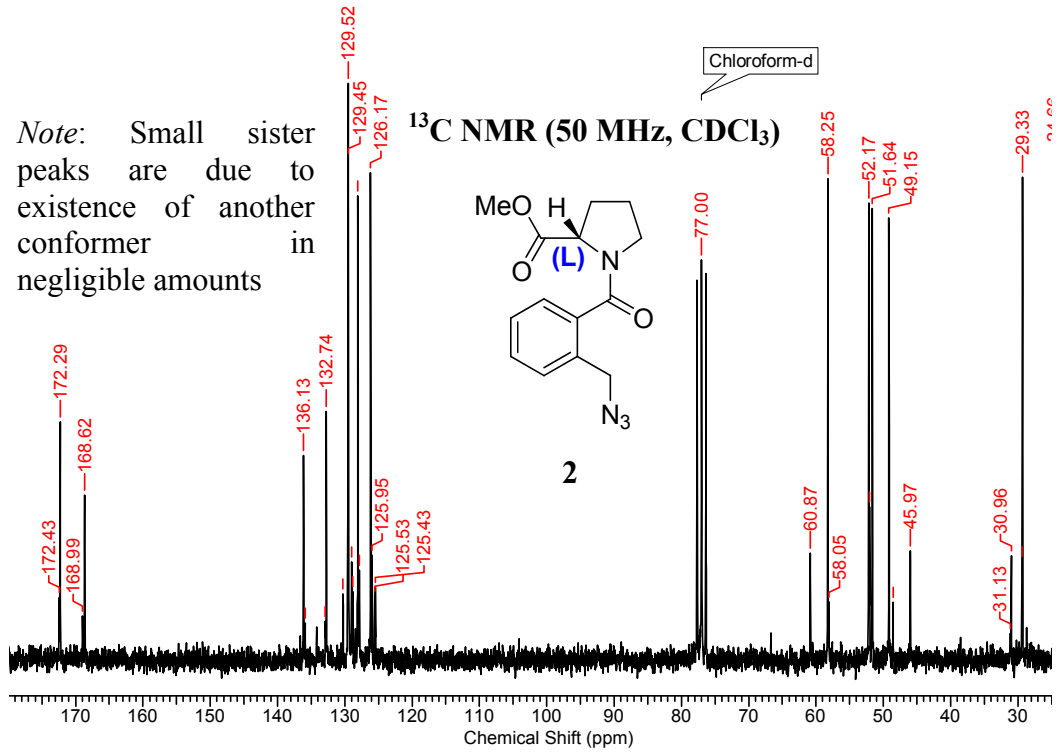
10d


^{1}H NMR (200 MHz, CDCl$_3$)
CDCl3
11a
Note: Small sister peaks are due to existence of another conformer in negligible amounts
Chemical Shift (ppm)


^{1}H NMR (200 MHz, CDCl$_3$)
CDCl3
11b
Note: Small sister peaks are due to existence of another conformer in negligible amounts
Chemical Shift (ppm)

Note: Small sister peaks are due to existence of another conformer in negligible amounts

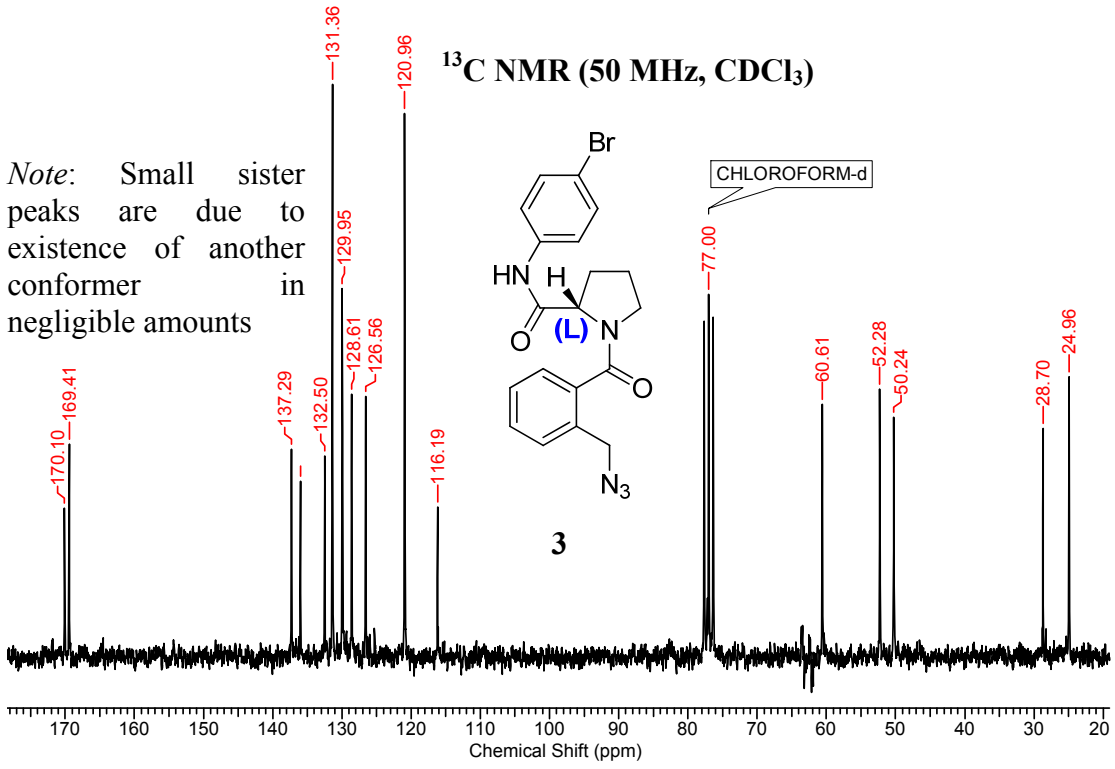
^{13}C NMR (50 MHz, $CDCl_3$)



2

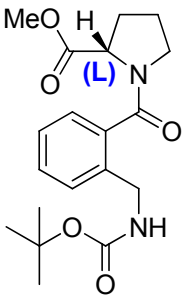
Note: Small sister peaks are due to existence of another conformer in negligible amounts

^{13}C NMR (50 MHz, $CDCl_3$)



3

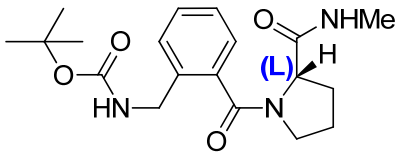
^{13}C NMR (50 MHz, $CDCl_3$)



4a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

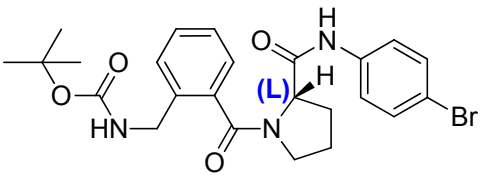
^{13}C NMR (50 MHz, $CDCl_3$)



4d

Note: Small sister peaks are due to existence of another conformer in negligible amounts

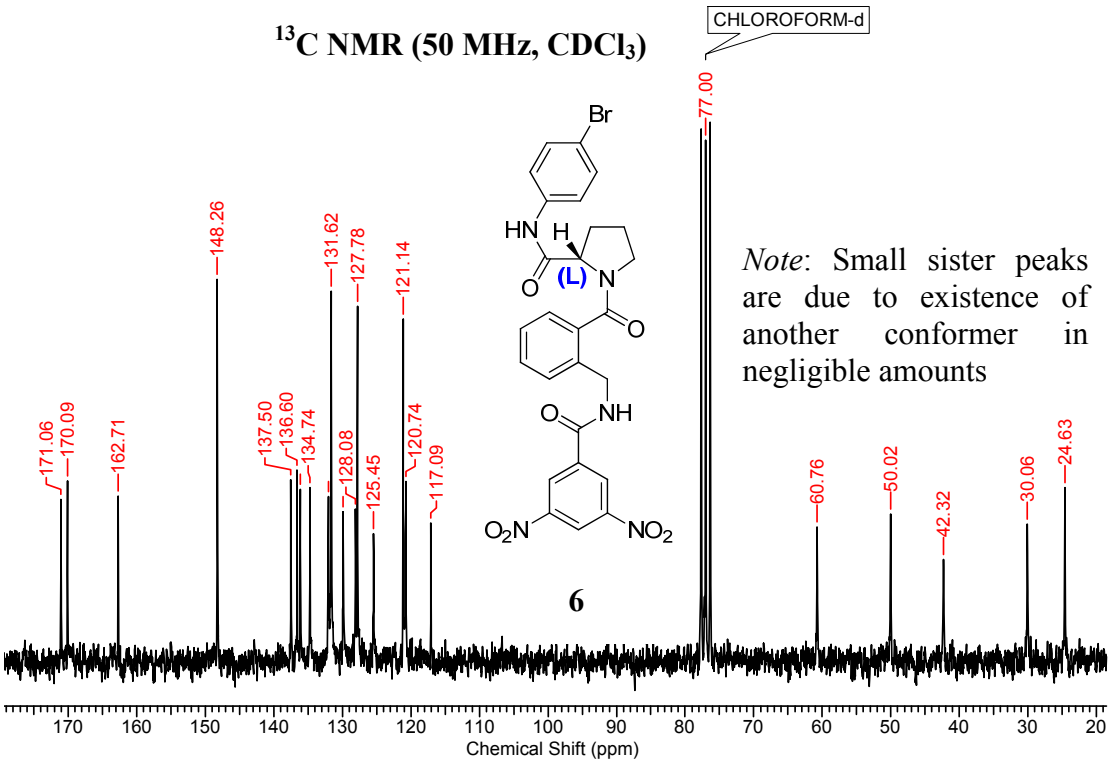
^{13}C NMR (50 MHz, $CDCl_3$)



5a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

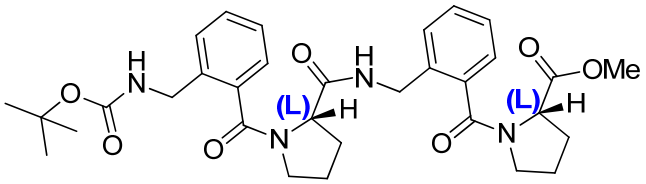
^{13}C NMR (50 MHz, $CDCl_3$)



6

Note: Small sister peaks are due to existence of another conformer in negligible amounts

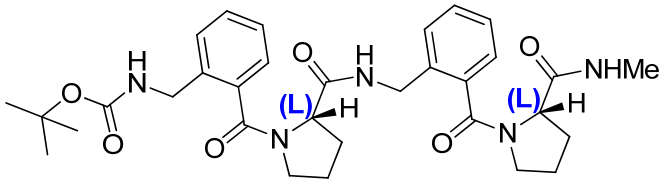
^{13}C NMR (50 MHz, $CDCl_3$)



7a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

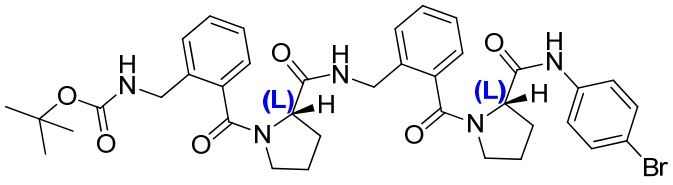
^{13}C NMR (50 MHz, $CDCl_3$)



7d

Note: Small sister peaks are due to existence of another conformer in negligible amounts

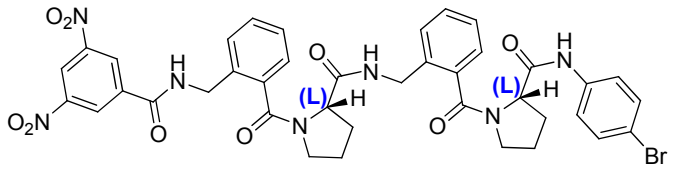
^{13}C NMR (50 MHz, $CDCl_3$)



8

Note: Small sister peaks are due to existence of another conformer in negligible amounts

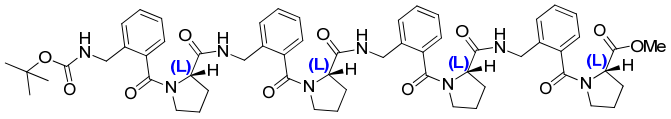
^{13}C NMR (50 MHz, $CDCl_3$)



9

Note: Small sister peaks are due to existence of another conformer in negligible amounts

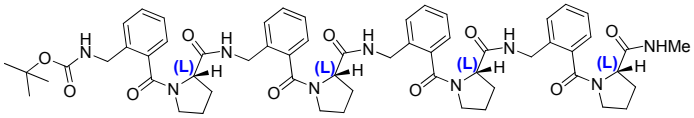
^{13}C NMR (50 MHz, $CDCl_3$)



10a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

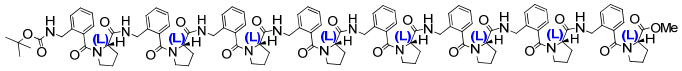
^{13}C NMR (50 MHz, $CDCl_3$)



10d

Note: Small sister peaks are due to existence of another conformer in negligible amounts

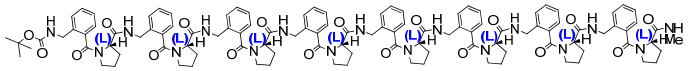
^{13}C NMR (50 MHz, $CDCl_3$)



11a

Note: Small sister peaks are due to existence of another conformer in negligible amounts

^{13}C NMR (50 MHz, $CDCl_3$)



11b

Note: Small sister peaks are due to existence of another conformer in negligible amounts

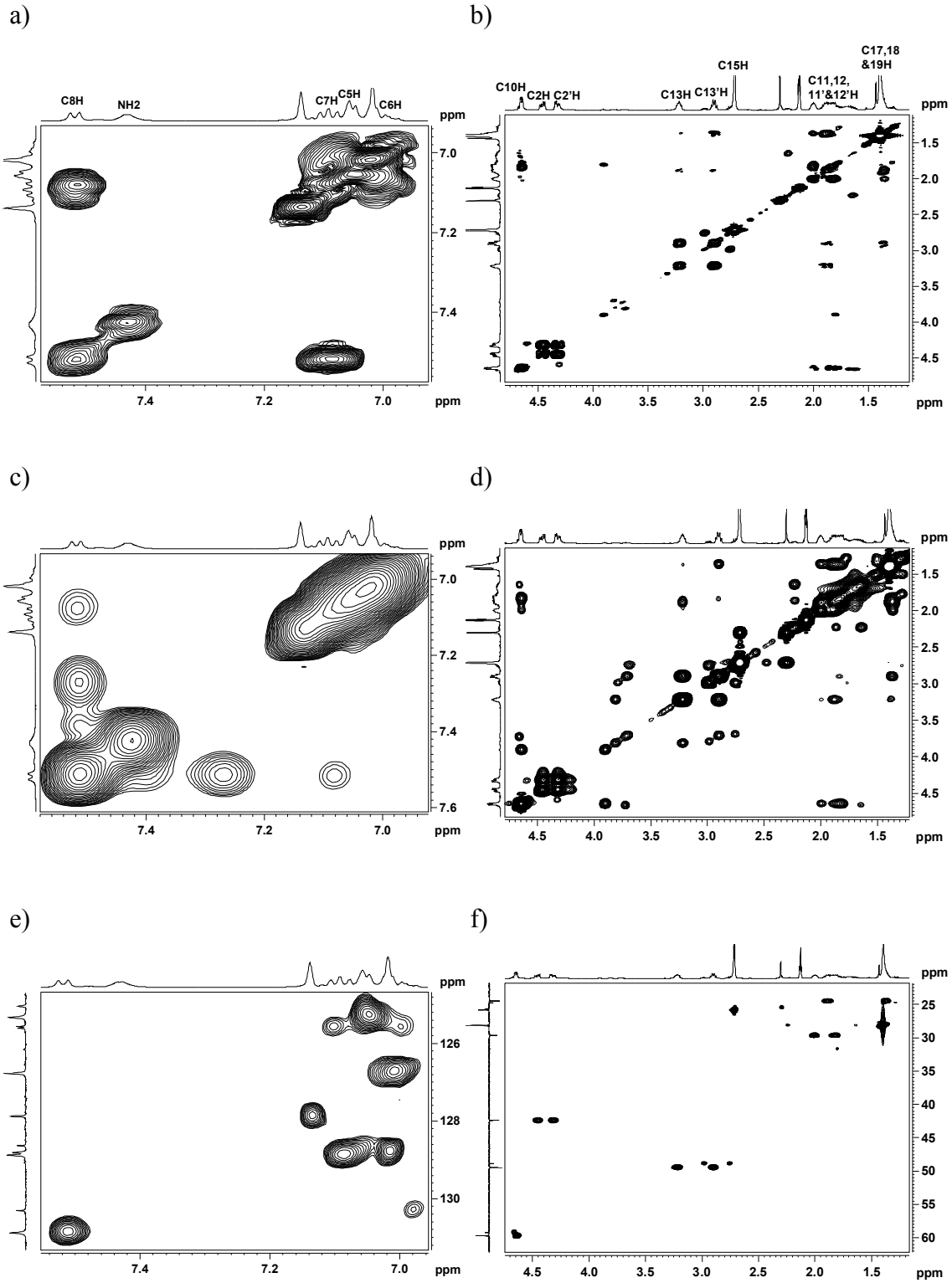


Fig. 2.12: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of dipeptide **4d** (500 MHz, Toluene-d_8). For better view, aromatic and aliphatic regions are given separately.

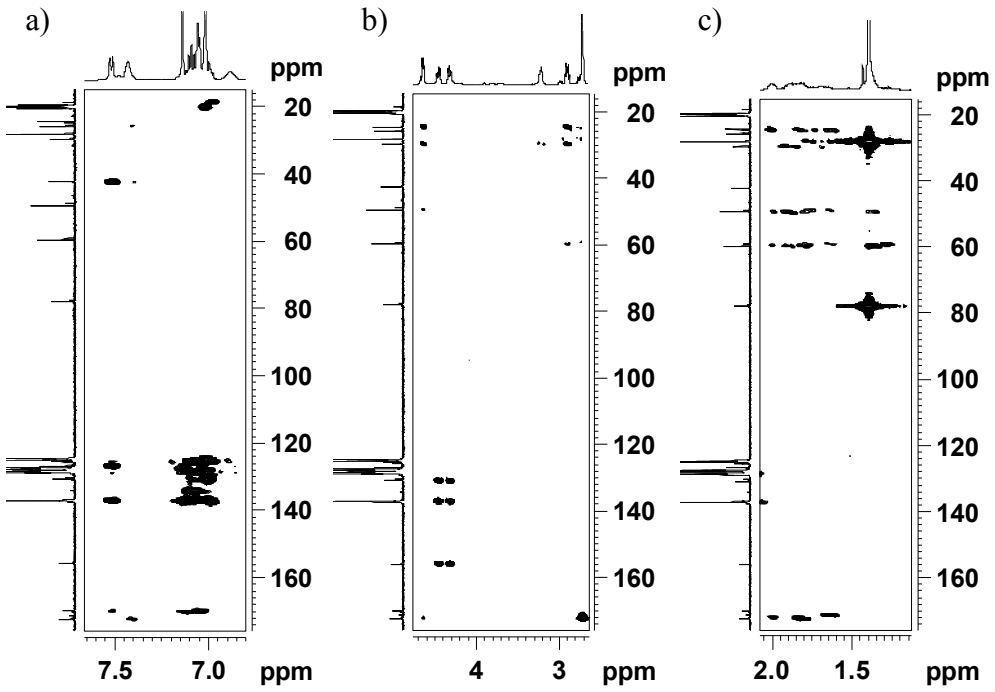


Fig. 2.13: Partial HMBC spectra of tetrapeptide **4d** (500 MHz, Toluene-d_8). For better view, aromatic (a) and aliphatic (b, c) regions are given separately.

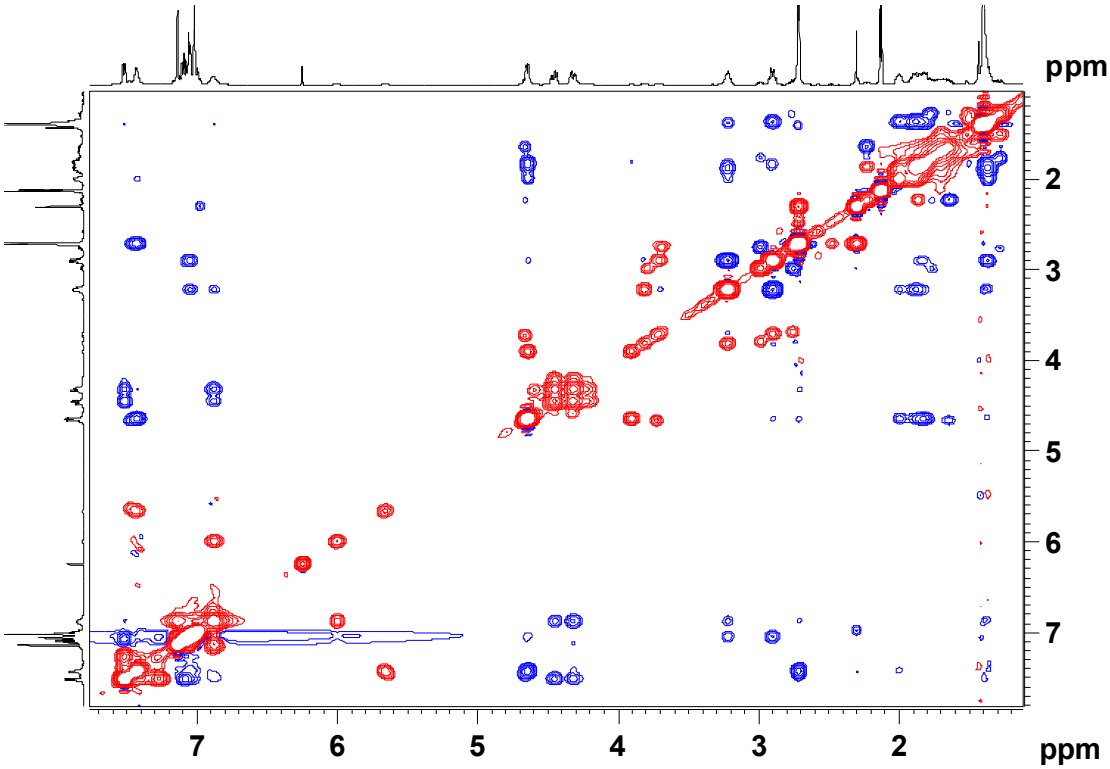


Fig. 2.14: 2D NOESY spectra of tetrapeptide **4d** (500 MHz, Toluene-d_8).

2.13 Experimental Section (Part B)

Single crystal X-ray crystallographic studies:

Crystal Data: Data for the compounds were collected at T = 90(2) K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97

Crystal data for 13d: Single crystals of **13d** were grown by slow evaporation of the solution in chloroform-*d*, colorless needle like crystal of approximate size 0.17 x 0.09 x 0.07 mm^3, was used for data collection. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Multirun data acquisition. Total scans = 4, total frames = 2286, oscillation / frame -0.3º, exposure / frame = 15.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.67 to 25.00°, completeness to θ of 25.00º is 100.0 % SADABS correction applied, $C_{22}H_{31}N_3O_5$, M = 417.50. Crystals belong to monoclinic, space group $P2_12_12_1$, a = 10.2325(5), b = 17.7301(8), c = 12.7057(6) Å, β = 105.974(1)°, V = 2216.10(18) $Å^3$, Z = 4, D_c = 1.251 g/cc, μ (Mo–K_α) = 0.089 mm^{-1}, 20266 reflections measured, 7782 unique [I>2σ(I)], R value 0.0471, wR2 = 0.1219. Largest diff. peak and hole 0.257 and -0.249 e.$Å^{-3}$.

Crystal data for 14a: Single crystals of **14a** were grown by slow evaporation of the solution in chloroform, ethyl acetate, colorless needle like crystal of approximate size 0.40 x 0.15 x 0.07 mm^3, was used for data collection. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Hemisphere data acquisition. Total scans = 3, total frames = 1271, oscillation / frame -0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.52 to 25.00°, completeness to θ of 25.00º is 100.0 % SADABS correction applied, $C_{42}H_{60}N_6O_{12}$, M = 840.96. Crystals belong to orthorhombic, space group $P2_12_12_1$,

a = 11.3088(6), *b* = 15.8114(8), *c* = 25.101(1) Å, V = 4488.3(4) $Å^3$, *Z* = 4, D_c = 1.245 g/cc, μ (Mo–K_α) = 0.092 mm^{-1}, 22600 reflections measured, 7872 unique [I>2σ(I)], R value 0.0464, *R1* = 0.0617, *wR2* = 0.1509. Largest diff. peak and hole 0.887 and -0.301 e.$Å^{-3}$.

methyl 2-methyl-2-(2-nitrobenzamido)propanoate 12a:

To an ice-cold stirred solution of the 2-nitrobenzoic acid (4 g, 23.95 mmol) in dry DCM (40 mL) was added dry DMF (0.18 mL, 2.39 mmol) followed by oxalyl chloride (2.27 mL, 26.34 mmol). The resulting mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure and dried. The residue containing the acid chloride was dissolved in dry DCM (25 mL) and added drop wise to an ice cooled solution of HCl.H-Aib-OMe (3.67 g, 26.34 mmol) and Et_3N (10.10 mL, 71.85 mmol) in DCM (40 mL). The reaction mixture was then stirred at room temperature for 5 h. The reaction mixture was diluted with DCM, and the organic layer was washed sequentially with dil. HCl solution, water, saturated $NaHCO_3$ and brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which on purification by column chromatography (50:50 pet. ether/ethyl acetate, R*f*: 0.5) afforded **12a** as a white solid (4.52 g, 71%). mp: 117-119 °C; IR ($CHCl_3$) ν (cm^{-1}): 3432, 3020, 1735, 1675, 1534, 1512, 1349, 1216, 757, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.03-7.98 (m, 1H), 7.68-7.60 (m, 1H), 7.59-7.53 (m, 1H), 7.59-7.53 (m, 1H), 6.69 (bs, 1H), $3.78_{rotamer}$ (s, 1.2H), 3.77 (s, 1.8H), 1.67 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.8, 165.4, 146.1, 133.6, 132.6, 130.3, 128.6, 124.3, 57.2, 52.7, 24.1; LC-MS: 289.01 $(M+Na)^+$; Elemental analysis calculated for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52; Found: C, 53.94; H, 5.45; N, 10.45.

methyl 2-(2-aminobenzamido)-2-methylpropanoate 12b:

The solution of compound **12a** (3.94 g, 14.81 mmol) in ethyl acetate and methanol (30 mL) respectively, was subjected to hydrogenolysis using 10% Pd-C (0.3 g) and H_2 (60 psi). After completion of reaction, the reaction mixture was filtered over celite pad. The filtrate on evaporation under reduced pressure yielded crude product **12b** quantitatively, which was taken for the next reaction without further purification.

(S)-tert-butyl 2-((2-((1-methoxy-2-methyl-1-oxopropan-2-yl)carbamoyl) phenyl)carbamoyl)pyrrolidine-1-carboxylate 13a:

To a solution of Boc-^{L}Pro-OH (3.50 g, 16.31 mmol) in dry THF (35 mL), was added Et_3N (2.27 mL, 16.31 mmol) under N_2 atmosphere at 0 °C. Subsequently, ethyl chloroformate (1.55 mL, 16.31 mmol) was added drop-wise over a period of 10 min at 0 °C. After 15 min, a solution of **12b** (3.50 g, 14.83 mmol) in dry THF (35 mL) was added. After 15 min at 0 °C, the reaction mixture was refluxed for 8 h. The reaction mixture evaporated under reduced pressure, diluted with DCM (30 mL), and the organic layer was washed sequentially with dil. $KHSO_4$ solution, water and brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which on purification by column chromatography (40:60 pet. ether/ethyl acetate, R*f*: 0.5) afforded **13a** as a white solid (5.30 g, 83%). mp: 148-150 °C; $[\alpha]^{23}_{D}$: -55.28° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3393, 3018, 1735, 1686, 1522, 1446, 1389, 1216, 756, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.44$_{rotamer}$ (s, 0.3H), 11.41 (s, 0.7H), 8.65 (d, *J* = 8.28 Hz, 1H), 7.54-7.42 (m, 2H), 7.10-7.03 (m, 1H), 6.69 (bs, 0.6H), 6.84$_{rotamer}$ (bs, 0.4H), 4.44-4.42$_{rotamer}$ (m, 0.4H), 4.25-4.22 (m, 0.6H), 3.79 (s, 1.7H), 3.77$_{rotamer}$ (s, 1.3H), 3.74-3.68 (m, 0.7H), 3.66-3.61$_{rotamer}$ (m, 0.3H), 3.55-3.48 (m, 0.6H), 3.45-3.38$_{rotamer}$ (m, 0.4H), 2.30-2.21$_{rotamer}$ (m, 0.6H), 2.17-1.85 (m, 3.4H), 1.67 (s, 3H), 1.65 (s, 3H), 1.48$_{rotamer}$ (s, 3.7H), 1.38 (s, 5.3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 174.8, 172.2, 171.7, 168.0, 154.9, 154.0, 139.4, 139.3, 132.8, 132.5, 126.7, 126.6, 122.7, 121.3, 120.9, 120.4, 120.2, 79.9, 62.5, 61.8, 57.1, 56.8, 52.8, 52.7, 46.9, 46.6, 31.4, 30.4, 28.3, 28.2, 24.8, 24.6, 24.3, 24.1, 23.6; LC-MS: 456.17 $(M+Na)^+$; 472.17 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{31}N_3O_6$: C, 60.95; H, 7.21; N, 9.69; Found: C, 61.07; H, 7.12; N, 9.78.

***General method for methyl ester hydrolysis: Synthesis of* 13b, 13e, 14b *and* 14d**

(S)-2-(2-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)benzamido)-2-methylpropanoic acid 13b:

Representative procedure: To the solution of ester **13a** (1.29 g, 2.97 mmol) in methanol, $LiOH{\cdot}H_2O$ (0.37 g, 8.93 mmol) was added in water at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. After complete

consumption of the starting material, the solvent was evaporated under reduced pressure, and the free acid was liberated by treating with saturated $KHSO_4$ solution followed by extraction with DCM (2 x 25 mL). The corresponding crude acid **13b** obtained after evaporation of the solvent under reduced pressure were carried forward for the next reaction, without further purification.

(S)-methyl-2-methyl-2-(2-(pyrrolidine-2-carboxamido)benzamido)propanoate 13c:

A solution containing the tripeptide **13a** (3.60 g, 8.31 mmol) in DCM (10 mL) was subjected to Boc-deprotection using DCM:TFA (50%, 15 mL). After completion of the reaction (1 h), the solvent was stripped off under reduced pressure and the residue was basified with saturated $NaHCO_3$ solution, and then repeatedly extracted with dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product **13c** quantitatively, which was taken for the next reaction without further purification.

(S)-methyl 2-methyl-2-(2-(1-pivaloylpyrrolidine-2-carboxamido)benzamido) propanoate 13d:

A solution containing **13c** (0.76 g, 2.30 mmol) in DCM (8 mL) was cooled to 0 °C, then pivaloyl chloride (0.31 mL, 2.54 mmol) was added followed by the addition of Et_3N (0.38 mL, 2.77 mmol) and stirred at room temperature for 5 h. The reaction mixture was diluted with DCM (20 mL) and washed sequentially with dil. HCl solution, water, saturated $NaHCO_3$ solution and brine. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which on purification by column chromatography (40:60 pet. ether/ethyl acetate, R*f*: 0.45) to afford **13d** as a white solid (0.85 g, 89%). mp: 162-164 °C; $[\alpha]^{23}_D$: -10.74° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 3016, 1735, 1617, 1522, 1509, 1448, 1216, 755, 666; ^1H NMR (500 MHz, $CDCl_3$) δ: 11.26 (s, 1H), 8.63 (d, *J* = 8.55 Hz, 1H), 7.50 (d, *J* = 7.63 Hz, 1H), 7.46 (t, *J* = 8.24 Hz, 1H), 7.07 (t, *J* = 7.33 Hz, 1H), 6.83 (bs, 1H), 4.64-4.61 (m, 1H), 3.95-3.91 (m, 1H), 3.81-3.78 (m, 1H), 3.77 (s, 3H), 2.19-2.13 (m, 1H), 2.10-2.04 (m, 2H), 1.98-1.93 (m, 1H), 1.66 (s, 3H), 1.64 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.4, 174.8, 171.6, 168.1, 139.5, 132.4,

126.7, 122.6, 121.5, 120.1, 64.0, 56.8, 52.6, 48.4, 39.0, 28.9, 27.4, 25.4, 24.8, 24.5; LC-MS: 440.12 $(M+Na)^+$; 456.09 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{31}N_3O_5$: C, 63.29; H, 7.48; N, 10.06; Found: C, 63.44; H, 7.61; N, 9.89.

***General method for oxazolone preparation: Synthesis of* 13f, 13g *and* 14f**

(S)-tert-butyl 2-((2-(4,4-dimethyl-5-oxo-4,5-dihydrooxazol-2-yl)phenyl) carbamoyl)pyrrolidine-1-carboxylate 13f:

Representative procedure: To an ice cooled solution of acid **13b** (1.24 g, 2.97 mmol) in DCM (10 mL), EDC.HCl (0.62 g, 3.27 mmol) was added. The reaction mixture was stirred for 15 min and the reaction progress was monitored by TLC. The reaction mixture was diluted with DCM (10 mL) and washed water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to get the crude product **14a** quantitatively, which was carried forward for the next reaction without further purification. LC-MS: 424.12 $(M+Na)^+$.

(S)-N-(2-(4,4-dimethyl-5-oxo-4,5-dihydrooxazol-2-yl)phenyl)-1-pivaloyl pyrrolidine-2-carboxamide 13g:

The product **13g** was obtained from **13e**, following the procedure for **13f**, as a white solid. LC-MS: 408.07 $(M+Na)^+$.

***General method for oxazolone opening: Synthesis of* 14a, 14e *and* 15**

Boc-Hexamer methyl ester 14a:

***Representative procedure*:** To a solution containing the crude **13f** (1.20 g, 2.99 mmol), amine **13c** (0.99 g, 2.99 mmol) and 4Å MS (0.5 g) in dry DMF (10 mL) was added DBU (0.45 mL, 2.99 mmol) at 0 °C. The solution was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $KHSO_4$ solution and diluted with DCM (20 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which on purification by column chromatography (30:70 pet. ether/ethyl acetate, R*f*: 0.5) afforded **14a** as a white solid (1.65 g, 75%). mp: 164-166 °C; $[\alpha]^{23}_D$: -32.46° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3322, 2982, 1738, 1675, 1586, 1522, 1447, 1160, 754, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.62 (s, 0.6H), $11.57_{rotamer}$ (s, 0.4H), 11.32 (s, 0.6H), $11.18_{rotamer}$ (s, 0.4H), 8.60 (d, *J* = 8.03 Hz, 1H), 8.51-8.44 (m, 1H), 7.93 (bs, 0.6H), $7.69_{rotamer}$ (bs, 0.4H), 7.55-7.51 (m, 2H),

7.42-7.38 (m, 2H), $7.15_{rotamer}$ (bs, 0.4H), 7.08 (bs, 0.6H), 7.05-6.98 (m, 2H), 4.63-4.59 (m, 1H), $4.29\text{-}4.27_{rotamer}$ (m, 0.4H), 4.22-4.19 (m, 0.6H), 3.95-3.93 (m, 1H), 3.72 (s, 2H), $3.70_{rotamer}$ (s, 1H), 3.70-3.60 (m, 2H), 3.50-3.35 (m, 1H), 2.25-1.89 (m, 8H), 1.82-1.76 (m, 6H), 1.60-1.55 (m, 6H), $1.47_{rotamer}$ (s, 3.6H), 1.31 (s, 5.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 173.0, 172.6, 172.1, 171.6, 170.9, 170.7, 168.1, 167.5, 167.3, 154.7, 153.9, 139.4, 139.2, 139.1, 139.0, 132.5, 132.3, 132.2, 126.9, 126.9, 126.7, 123.0, 122.9, 122.6, 121.9, 121.5, 121.1, 120.7, 120.5, 120.3, 120.2, 79.8, 64.1, 62.3, 61.6, 57.8, 57.7, 56.8, 56.7, 52.6, 52.5, 48.5, 46.9, 46.55, 31.3, 30.3, 28.6, 28.3, 28.1, 25.4, 24.7, 24.4, 24.0, 23.6, 23.5, 23.1, 22.9; LC-MS: 757.43 $(M+Na)^+$; 773.3 $(M+K)^+$; Elemental analysis calculated for $C_{38}H_{50}N_6O_9$: C, 62.11; H, 6.86; N, 11.44; Found: C, 61.95; H, 7.01; N, 11.55.

Boc-Nonamer methyl ester 14c:

To an ice cooled solution of acid **14b** (1.12 g, 1.56 mmol) in DCM (10 mL), EDC.HCl (0.33 g, 1.72 mmol) was added. The reaction mixture was stirred for 15 min and the reaction progress was monitored by TLC. The reaction mixture was diluted with DCM (10 mL) and washed water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to get the crude product quantitatively.

To a solution containing the crude product, amine **13c** (0.52 g, 1.56 mmol) and 4Å MS (0.5 g) in dry DMF (5 mL) was added DBU (0.23 mL, 1.56 mmol) at 0 °C. The solution was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $KHSO_4$ solution and diluted with DCM (20 mL). The organic layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product, which on purification by column chromatography (30:70 pet. ether/ethyl acetate, R*f*: 0.5) afforded **14c** as a white solid (1.11 g, 69%). mp: 204-206 °C; $[\alpha]^{23}_D$: -16.94° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3293, 3017, 1733, 1685, 1648, 1522, 1442, 1215, 755, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.62 (s, 0.6H); $11.55_{rotamer}$ (s, 0.4H); 11.47 (s, 0.6H); $11.32_{rotamer}$ (s, 0.4H); 11.20 (s, 0.6H); $11.09_{rotamer}$ (s, 0.4H); 8.61-8.59 (m, 1H); 8.54-8.46 (m, 1H); 8.44-8.39 (m, 1H); 7.97 (bs, 0.6H); $7.76_{rotamer}$ (bs, 0.4H); 7.67-7.57 (m, 2H); 7.54-7.50 (m, 2H); 7.41-7.40 (m, 3H); 7.08-7.01 (m, 4H); 4.61-4.57 (m, 2H); $4.30\text{-}4.30_{rotamer}$ (m, 0.4H); 4.24-4.21 (m, 0.6H); 3.97-3.83 (m, 2H); 3.73

(s, 1.7H); $3.71_{rotamer}$ (s, 1.3H); 3.68-3.64 (m, 3H); 3.53-3.18 (m, 0.7H); $3.44\text{-}3.37_{rotamer}$ (m, 0.3H); 2.27-2.19 (m, 2H); 2.11-1.85 (m, 10H); 1.81-1.76 (m, 6H); 1.72-1.62 (m, 6H); 1.59-1.54 (m, 6H); $1.49_{rotamer}$ (s, 4H); 1.32 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 172.9, 172.6, 172.5, 172.2, 171.6, 170.9, 170.8, 168.2, 167.7, 167.6, 167.4, 154.8, 153.9, 139.5, 139.4, 139.2, 139.0, 132.5, 132.4, 132.2, 127.1, 126.9, 126.8, 123.2, 123.1, 123.0, 122.8, 122.7, 122.2, 122.1, 121.9, 121.5, 121.1, 120.8, 120.3, 120.1, 79.9, 79.8, 64.0, 62.3, 61.7, 57.8, 57.6, 56.8, 52.6, 48.5, 47.0, 46.6, 31.4, 30.4, 28.6, 28.4, 28.2, 25.5, 24.7, 24.4, 24.1, 23.8, 23.7, 23.4, 23.2; MALDI-TOF: 1059.61 $(M+Na)^+$; 1075.59 $(M+K)^+$; Elemental analysis calculated for $C_{54}H_{69}N_9O_{12}$: C, 62.59; H, 6.71; N, 12.17; Found: C, 62.75; H, 6.83; N, 11.99.

Piv-Hexamer methyl ester 14e:

The product **14e** was obtained from oxazolone **13g** opening with amine **13c**, following the procedure for **14a**, as a white solid (0.49 g, 73%). mp: 144-146 °C; $[\alpha]^{23}_D$: -13.64° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3290, 3012, 1738, 1671, 1599, 1522, 1407, 1216, 753, 666; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.46 (s, 1H), 11.10 (s, 1H), 8.58-8.57 (m, 1H), 8.46-8.45 (m, 1H), 7.60 (bs, 1H), 7.53-7.49 (m, 2H), 7.44-7.36 (m, 2H), 7.15-7.12 (m, 1H), 7.06 (dd, *J* = 5.19, 1.52 Hz, 1H), 7.00 (dd, *J* = 3.97, 1.52 Hz, 1H), 4.62-4.61 (m, 1H), 4.45-4.45 (m, 1H), 3.92-3.89 (m, 1H), 3.75-3.72 (m, 1H), 3.72-3.72 (m, 3H), 3.68-3.66 (m, 1H), 2.12-1.88 (m, 8H), 1.75 (s, 6H), 1.58 (s, 3H), 1.55 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.2, 174.8, 172.6, 171.5, 170.9, 168.1, 167.6, 162.4, 139.7, 139.0, 132.4, 127.0, 126.9, 126.7, 123.0, 122.6, 122.1, 121.4, 121.1, 120.0, 64.1, 64.0, 57.7, 56.8, 52.6, 48.4, 39.0, 36.4, 28.7, 27.4, 25.5, 24.8, 24.4, 23.6; LC-MS: 719.49 $(M+H)^+$; 741.49 $(M+Na)^+$; 757.47 $(M+K)^+$; Elemental analysis calculated for $C_{38}H_{50}N_6O_8$: C, 63.49; H, 7.01; N, 11.69; Found: C, 63.64; H, 6.88; N, 11.80.

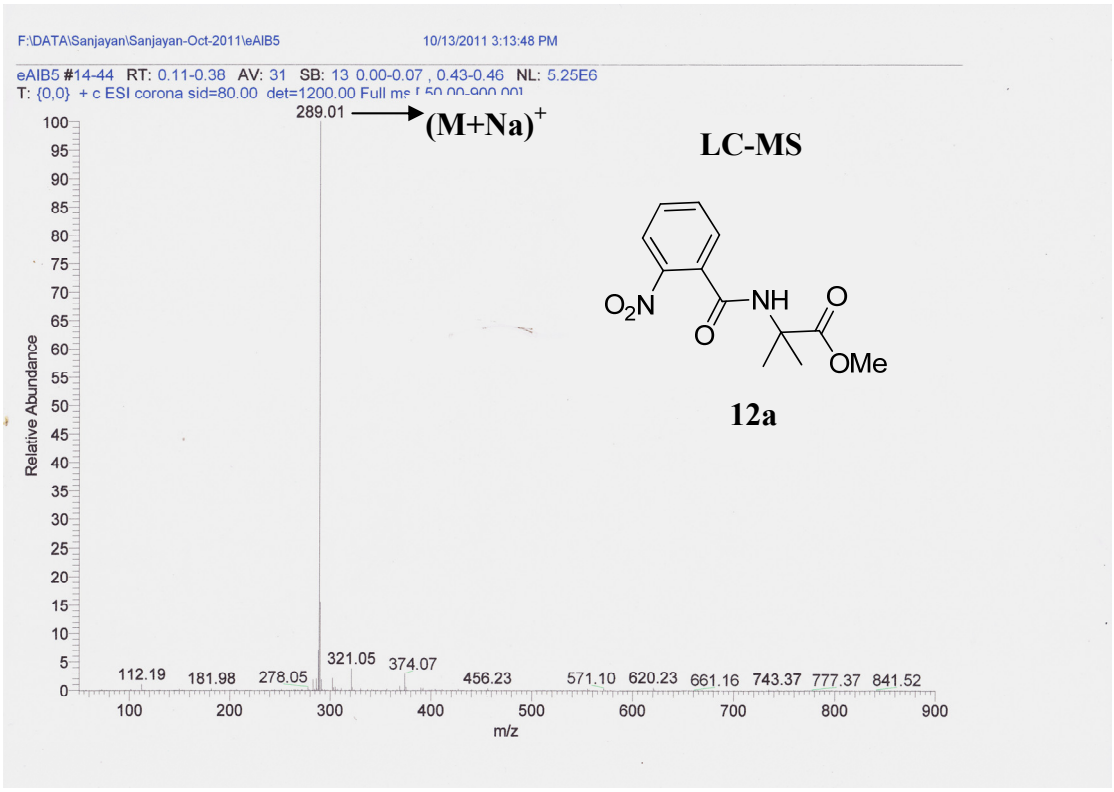
Boc-Nonamer oxazolone 14f:

The product **14f** was obtained from acid **14d**, following the procedure for **14a** as a white solid. LC-MS: 1026.63 $(M+Na)^+$.

Boc-Dodecamer methyl ester 15:

The product **15** was obtained from oxazolone **14f** opening with amine **13c**, following the procedure for **14a**, as a white solid (0.50 g, 63%). mp: 230-232 °C;

$[\alpha]^{23}_{D}$: -1.81° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3333, 3017, 1732, 1675, 1642, 1522, 1447, 1215, 754, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: $11.62_{rotamer}$ (s, 0.4H), 11.60 (s, 0.6H), 11.58 (s, 0.7H), $11.53_{rotamer}$ (s, 0.3H), 11.41 (s, 0.6H), $11.33_{rotamer}$ (s, 0.4H), 11.25 (s, 0.6H), $11.21_{rotamer}$ (s, 0.4H), 8.59-8.57 (d, *J* = 8.78 Hz, 1H), 8.54-8.42 (m, 2H), 8.38-8.37 (m, 0.6H), $8.31\text{-}8.29_{rotamer}$ (m, 0.4H), 7.97 (bs, 0.7H), $7.87_{rotamer}$ (bs, 0.3H), 7.84 (bs, 1H), 7.65-7.59 (m, 2H), 7.54-7.49 (m, 2H), 7.46 (bs, 1H), 7.39-7.29 (m, 2H), 7.10 (bs, 1H), 7.04-7.00 (m, 4H), 4.64-4.62 (m, 1H), 4.55-4.55 (m, 2H), $4.35\text{-}4.32_{rotamer}$ (m, 0.4H), 4.23-4.21 (m, 0.6H), 4.05-4.03 (m, 1H), 3.93-3.93 (m, 2H), 3.72 (s, 3H), 3.67-3.54 (m, 4H), 3.50-3.37 (m, 1H), 2.37-2.16 (m, 2H), 2.09-1.87 (m, 14H), 1.79-1.77 (m, 6H), 1.73-1.71 (m, 6H), 1.69-1.66 (m, 6H), 1.58-1.56 (m, 6H), $1.49_{rotamer}$ (s, 4H), $1.32_{rotamer}$ (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 172.9, 172.7, 172.3, 172.2, 171.0, 168.2, 167.7, 167.6, 154.8, 153.9, 139.5, 139.2, 132.5, 132.4, 127.2, 127.0, 126.9, 126.7, 123.1, 123.0, 122.7, 121.8, 121.1, 120.8, 120.8, 79.9, 79.8, 64.1, 62.3, 57.7, 57.5, 56.7, 52.6, 48.5, 46.6, 28.6, 28.4, 28.2, 25.6, 24.8, 24.5, 24.3, 24.2, 24.1, 24.0, 23.9, 23.7, 23.6; MALDI-TOF: 1360.71 $(M+Na)^+$; 1376.75 $(M+K)^+$; Elemental analysis calculated for $C_{70}H_{88}N_{12}O_{15}$: C, 62.86; H, 6.63; N, 12.57; Found: C, 63.04; H, 6.80; N, 12.39.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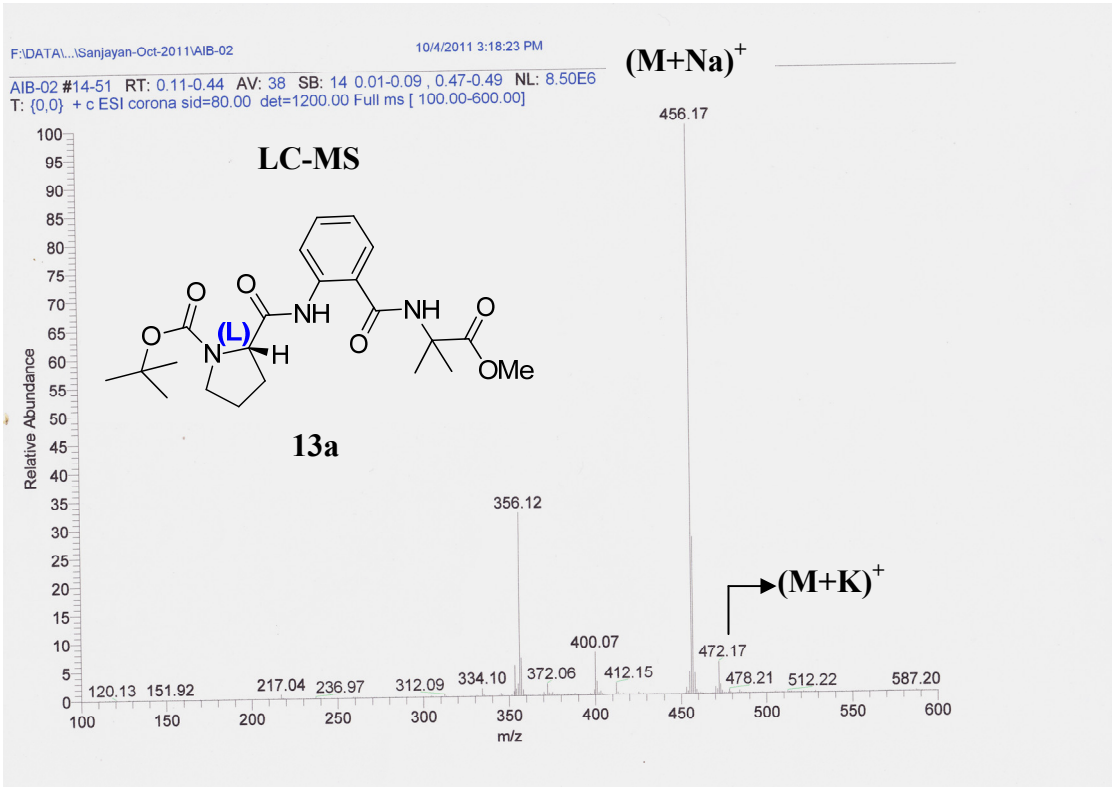
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [50.00-900.00]
289.01
(M+Na)+
LC-MS
O2N
NH
O
OMe
12a
Relative Abundance
m/z
112.19
181.98
278.05
321.05
374.07
456.23
571.10
620.23
661.16
743.37
777.37
841.52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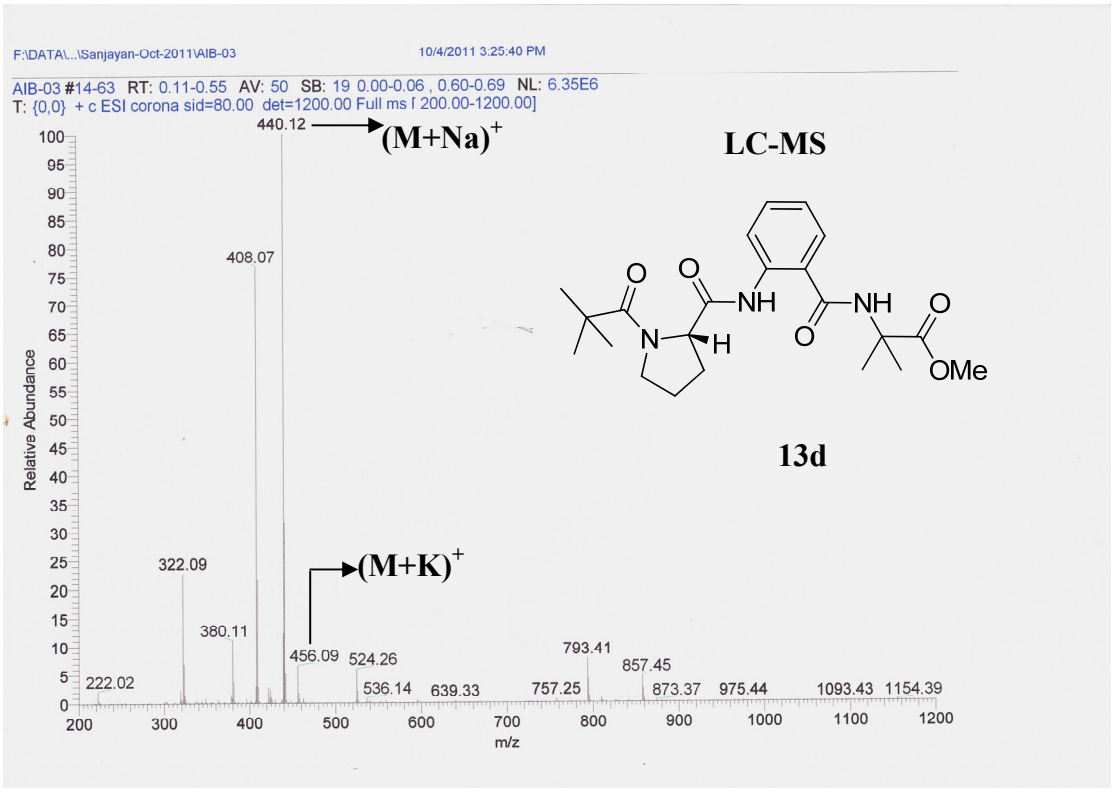
(M+Na)+
456.17
LC-MS
(L)
NH
NH
OMe
13a
356.12
(M+K)+
400.07
472.17
Relative Abundance
m/z
120.13
151.92
217.04
236.97
312.09
334.10
372.06
412.15
478.21
512.22
587.20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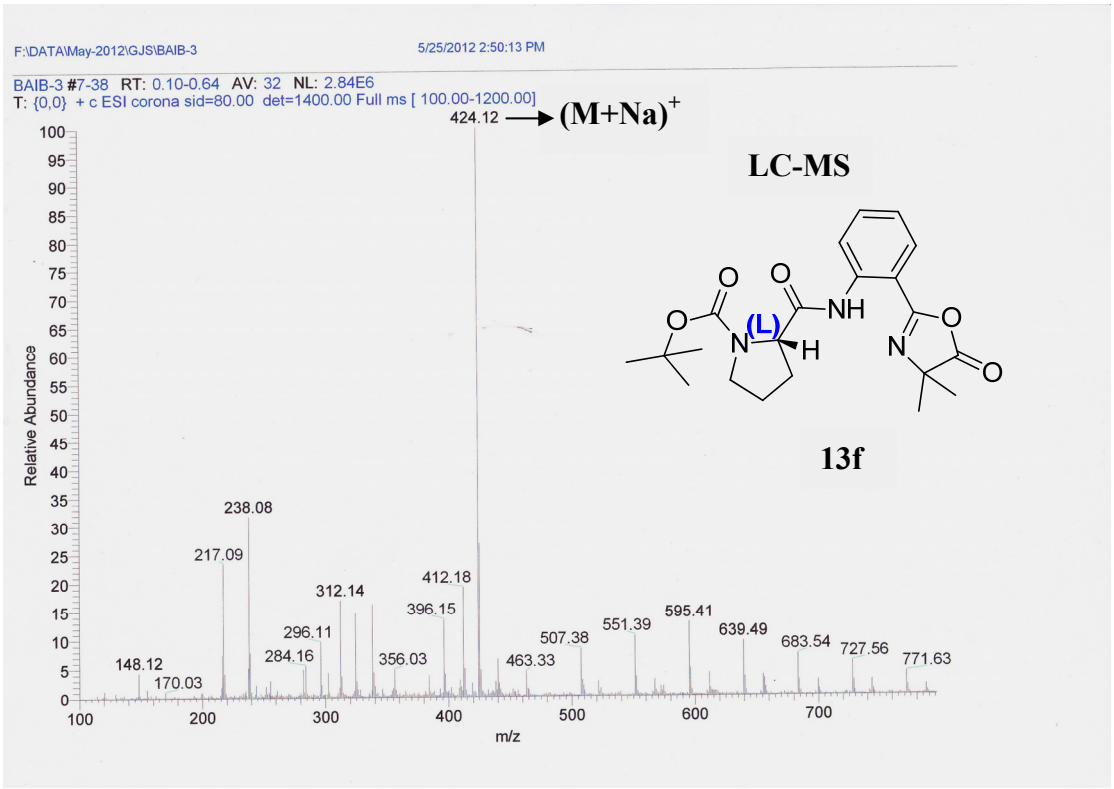
440.12
(M+Na)+
LC-MS
408.07
322.09
(M+K)+
380.11
456.09
524.26
536.14
639.33
757.25
793.41
857.45
873.37
975.44
1093.43
1154.39
222.02
Relative Abundance
m/z
13d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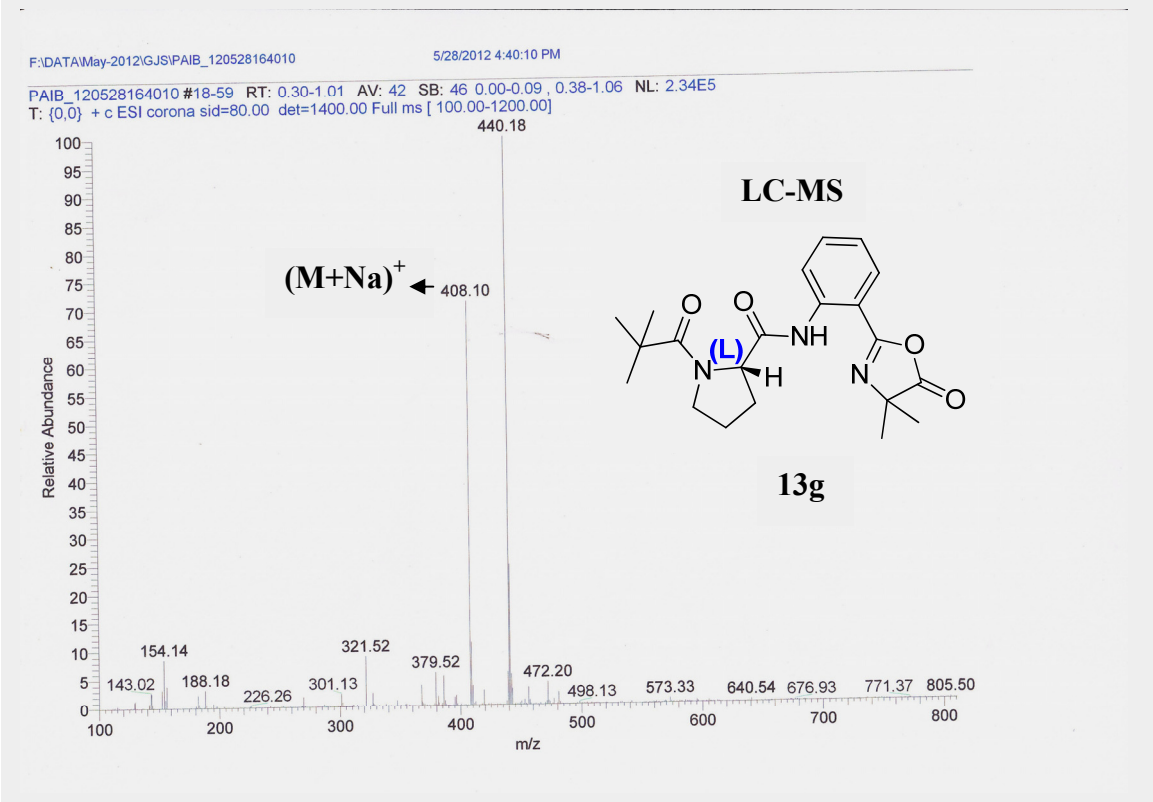
BAIB-3 #7-38 RT: 0.10-0.64 AV: 32 NL: 2.84E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
424.12
(M+Na)+
LC-MS
238.08
217.09
312.14
412.18
396.15
296.11
284.16
356.03
463.33
507.38
551.39
595.41
639.49
683.54
727.56
771.63
148.12
170.03
Relative Abundance
m/z
13f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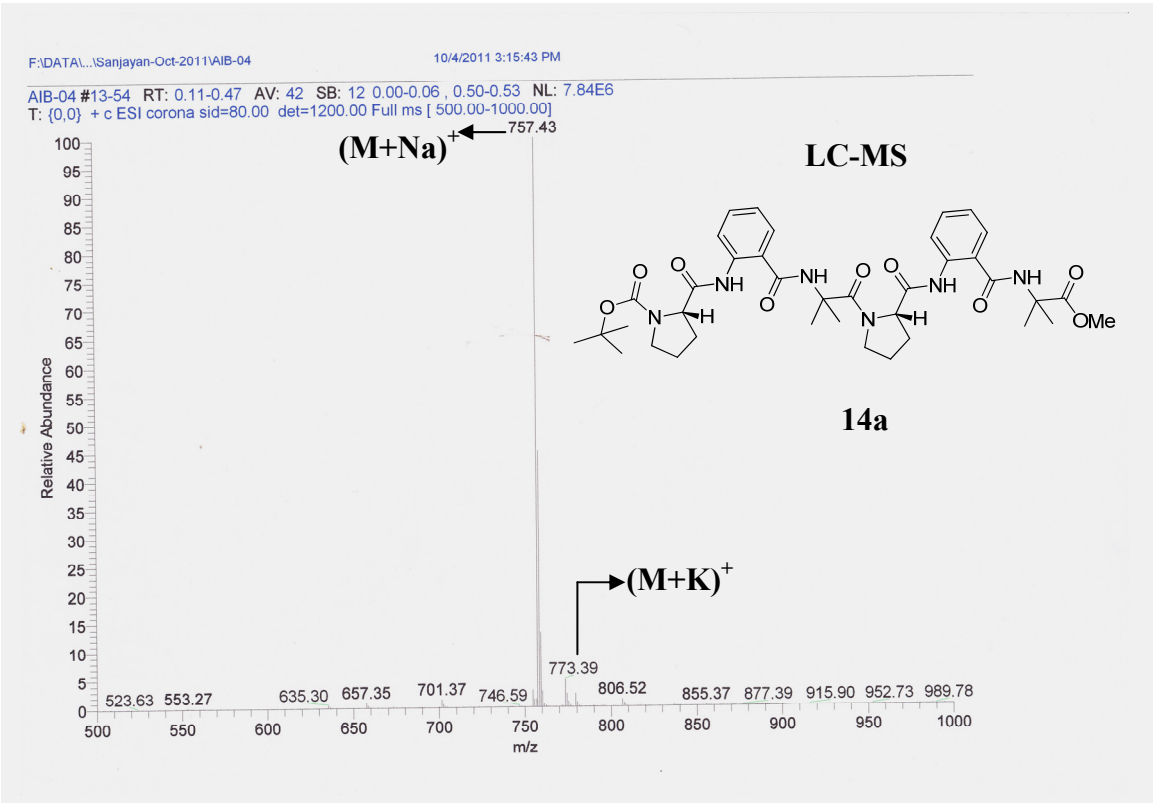
PAIB_120528164010 #18-59 RT: 0.30-1.01 AV: 42 SB: 46 0.00-0.09 , 0.38-1.06 NL: 2.34E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
440.18
LC-MS
(M+Na)+
408.10
(L)
13g
Relative Abundance
m/z
154.14
143.02
188.18
226.26
301.13
321.52
379.52
472.20
498.13
573.33
640.54
676.93
771.37
805.50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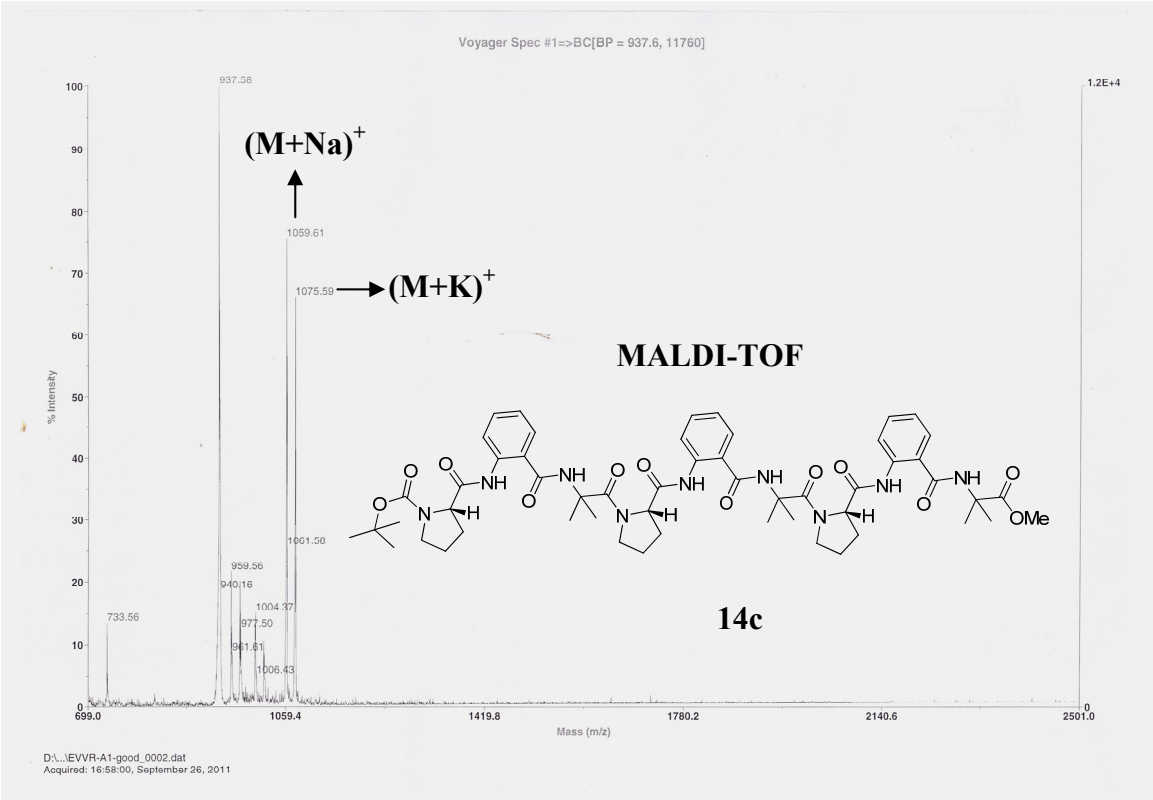
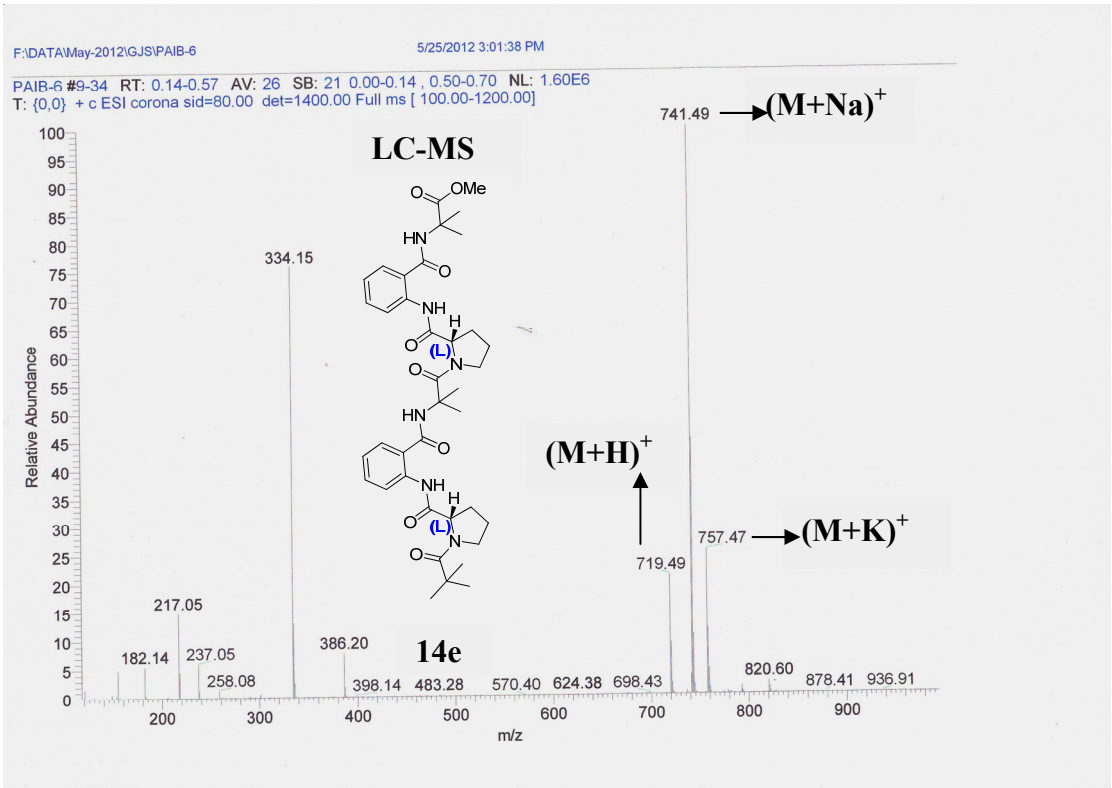
AIB-04 #13-54 RT: 0.11-0.47 AV: 42 SB: 12 0.00-0.06 , 0.50-0.53 NL: 7.84E6
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [500.00-1000.00]
(M+Na)+
757.43
LC-MS
14a
(M+K)+
773.39
Relative Abundance
m/z
523.63
553.27
635.30
657.35
701.37
746.59
806.52
855.37
877.39
915.90
952.73
989.78


Voyager Spec #1=>BC[BP = 937.6, 11760]
(M+Na)+
1059.61
1075.59
(M+K)+
MALDI-TOF
14c
% Intensity
Mass (m/z)
D:\...\EVVR-A1-good_0002.dat
Acquired: 16:58:00, September 26, 2011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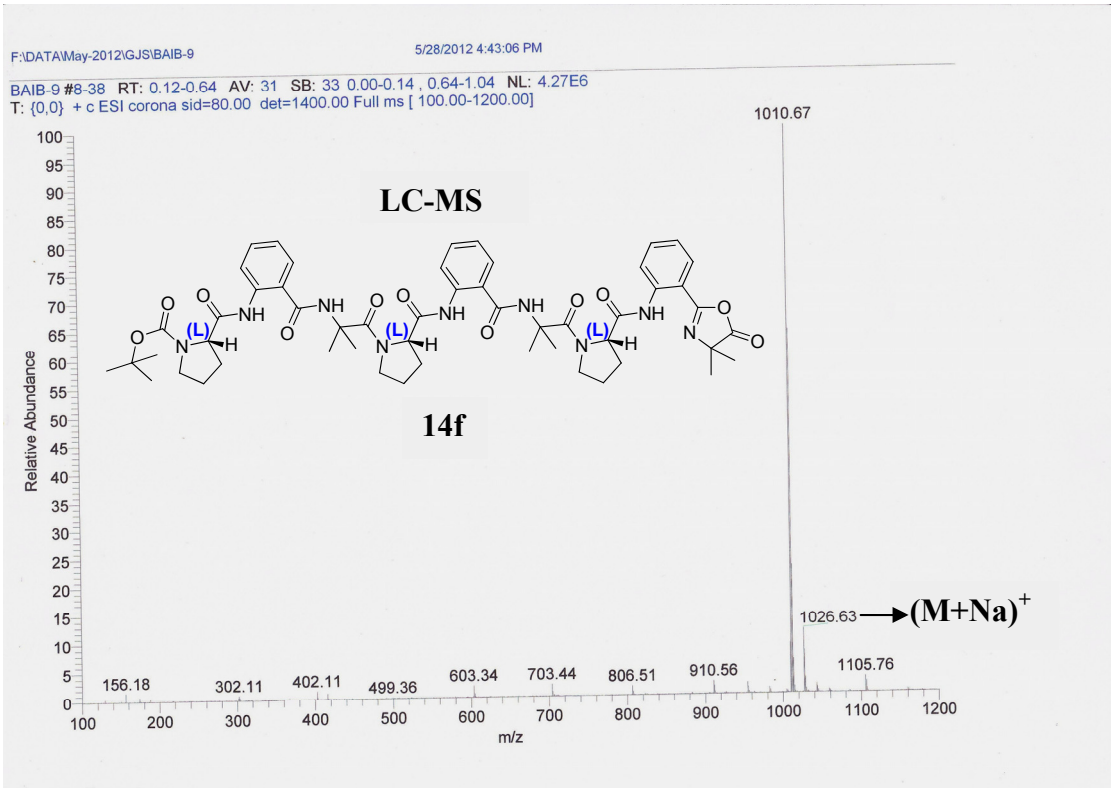
5/25/2012 3:01:38 PM
PAIB-6 #9-34 RT: 0.14-0.57 AV: 26 SB: 21 0.00-0.14 , 0.50-0.70 NL: 1.60E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
741.49 (M+Na)+
334.15
(M+H)+
719.49
757.47 (M+K)+
14e
Relative Abundance
m/z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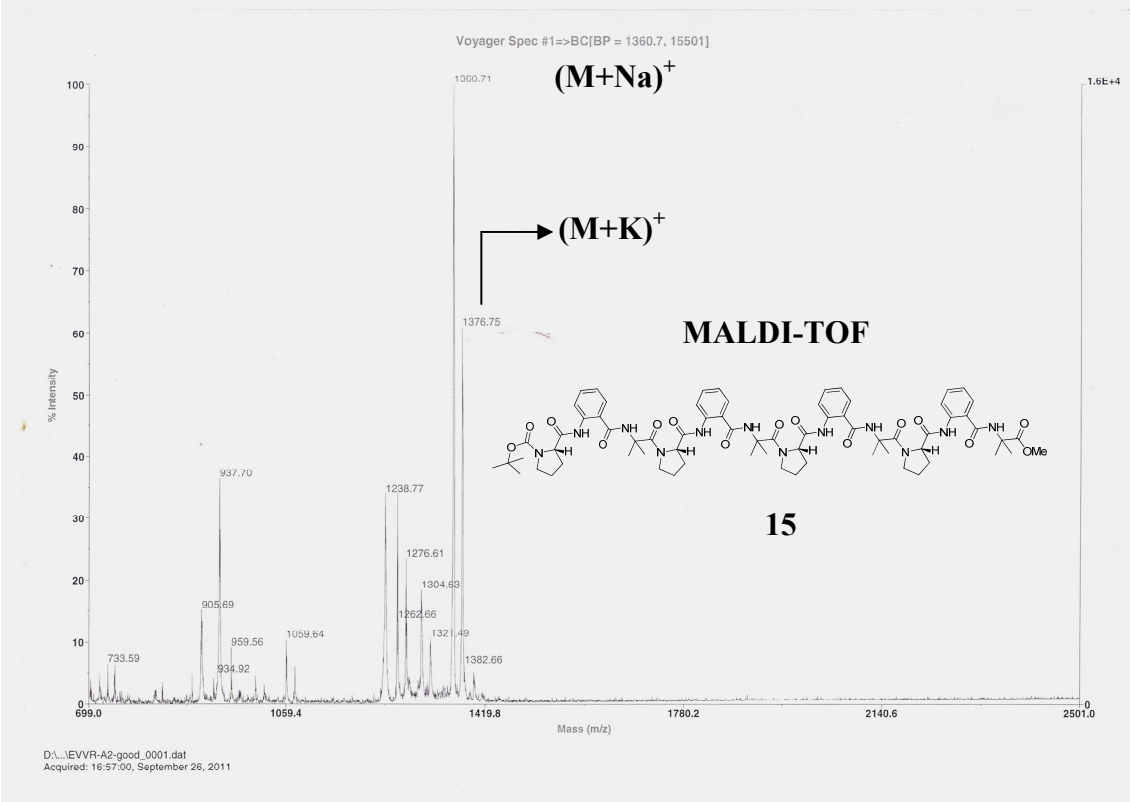
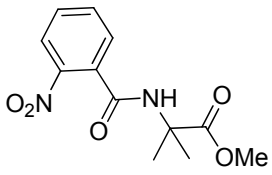
5/28/2012 4:43:06 PM
BAIB-9 #8-38 RT: 0.12-0.64 AV: 31 SB: 33 0.00-0.14 , 0.64-1.04 NL: 4.27E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
14f
1010.67
1026.63
(M+Na)+
1105.76
156.18
302.11
402.11
499.36
603.34
703.44
806.51
910.56
Relative Abundance
m/z

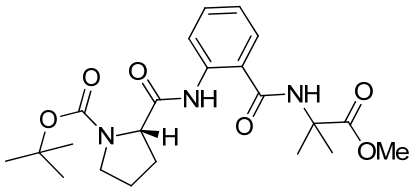

Voyager Spec #1=>BC[BP = 1360.7, 15501]
(M+Na)+
(M+K)+
MALDI-TOF
15
1360.71
1376.75
937.70
1238.77
1276.61
1304.63
905.69
1262.66
959.56
1059.64
733.59
934.92
1382.66
% Intensity
Mass (m/z)
D:\...\EVVR-A2-good_0001.dat
Acquired: 16:57:00, September 26, 2011

^{1}H NMR ($CDCl_3$, 200 MHz)



12a

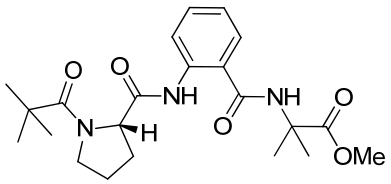
^{1}H NMR ($CDCl_3$, 400 MHz)



13a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

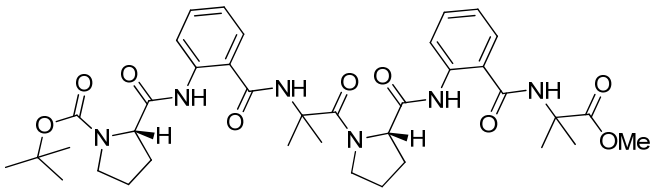
^{1}H NMR ($CDCl_3$, 500 MHz)



13d

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

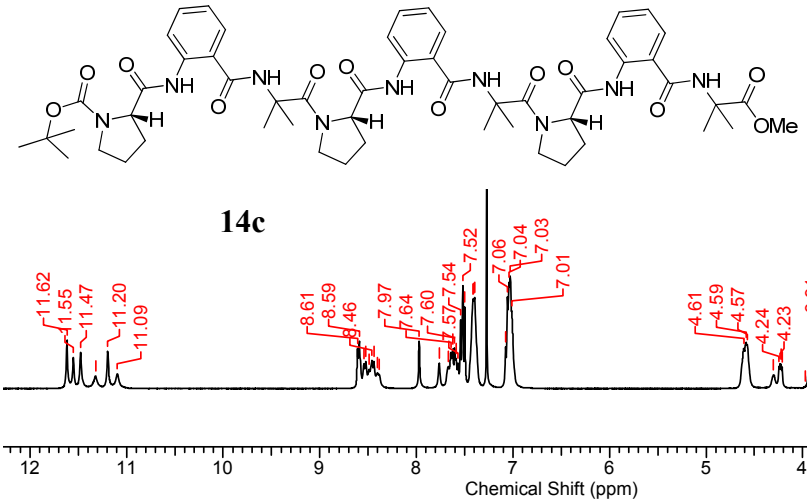
^{1}H NMR ($CDCl_3$, 400 MHz)



14a

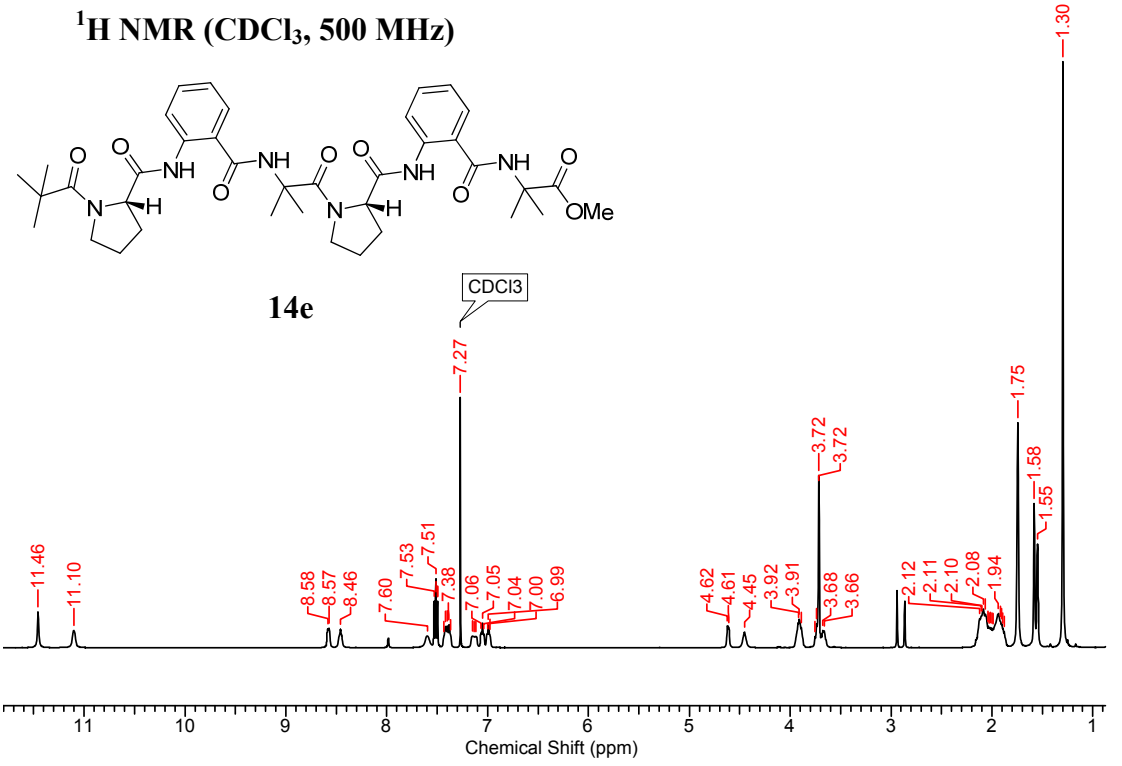
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{1}H NMR ($CDCl_3$, 400 MHz)



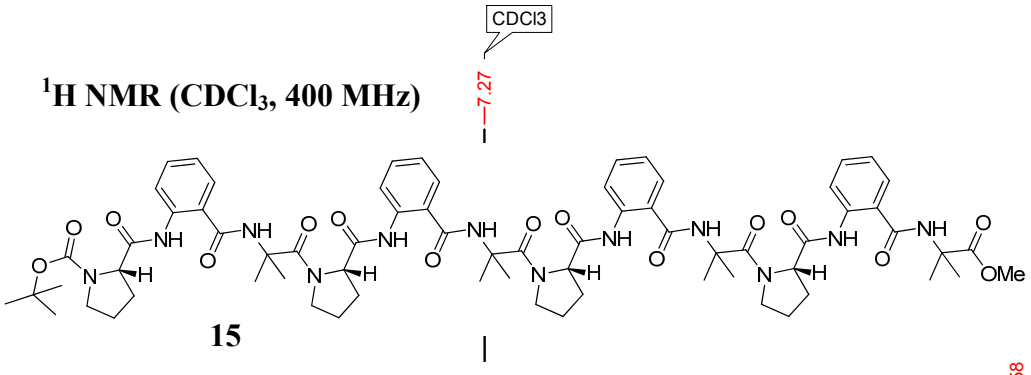
14c

^{1}H NMR ($CDCl_3$, 500 MHz)



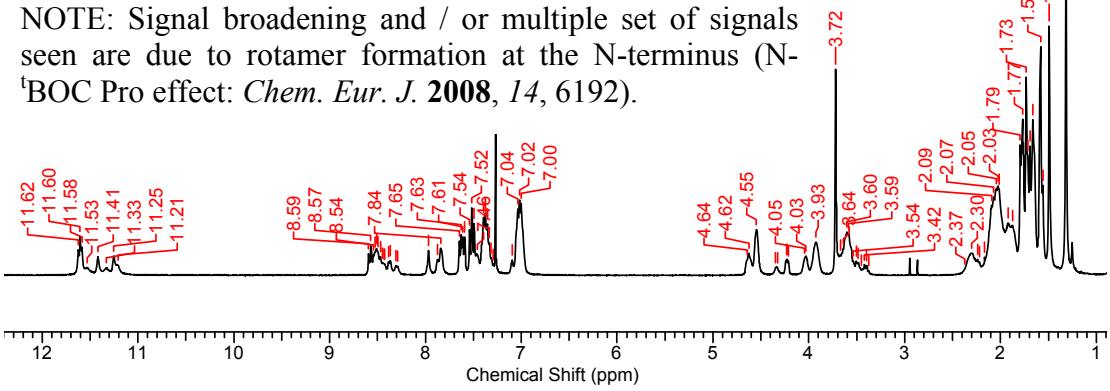
14e

^{1}H NMR ($CDCl_3$, 400 MHz)

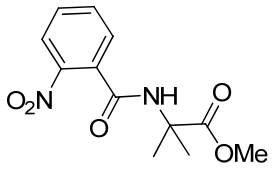


15

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

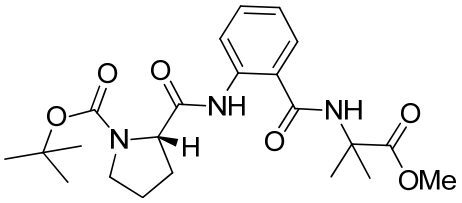


^{13}C NMR ($CDCl_3$, 200 MHz)



12a

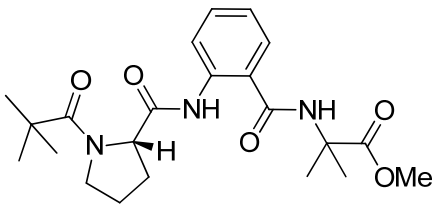
^{13}C NMR ($CDCl_3$, 400 MHz)



13a

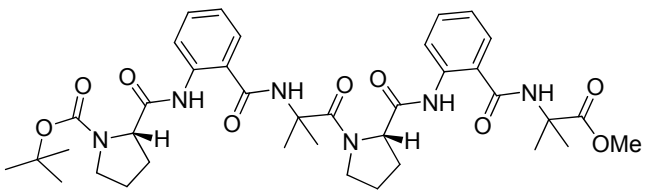
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{13}C NMR ($CDCl_3$, 500 MHz)



13d

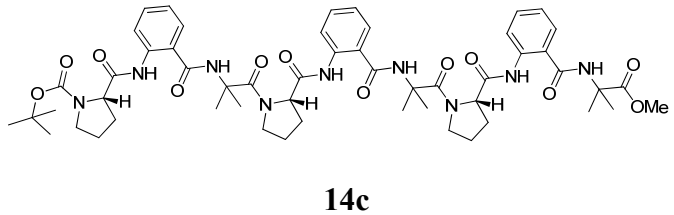
^{13}C NMR ($CDCl_3$, 400 MHz)



14a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

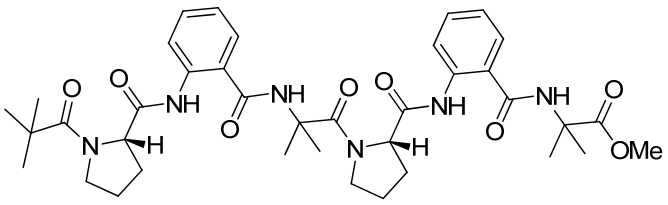
^{13}C NMR ($CDCl_3$, 400 MHz)



14c

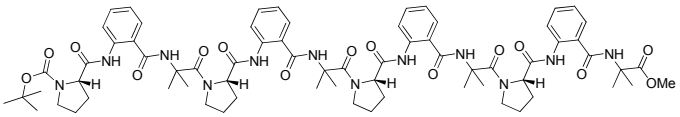
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

^{13}C NMR ($CDCl_3$, 500 MHz)



14e

^{13}C NMR ($CDCl_3$, 400 MHz)

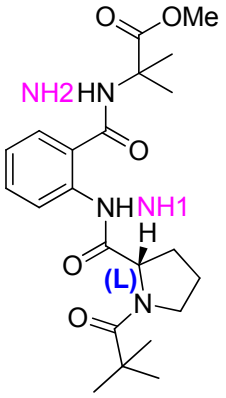


15

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, *14*, 6192).

Table 2.1. Titration study of tripeptide 13d in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

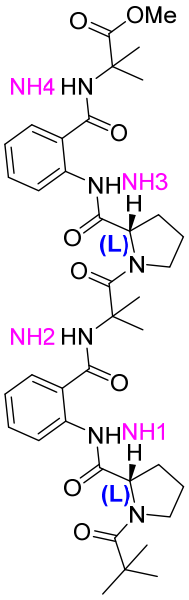
Volume of DMSO-d_6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	11.29	6.80
5	11.28	7.10
10	11.27	7.27
15	11.26	7.37
20	11.25	7.46
25	11.24	7.53
30	11.23	7.59
35	11.22	7.64
40	11.21	7.69
45	11.20	7.73
50	11.18	7.75



13d

Table 2.2. Titration study of hexapeptide 14e in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d_6 (volume of DMSO-d_6 added at each addition = 5 μl)

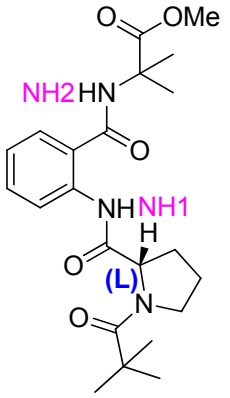
V_{DMSO}-d_6 (in μL)	Chemical Shift (in ppm)			
	NH1	NH3	NH2	NH4
0	11.48	11.18	7.51	6.96
5	11.44	11.11	7.66	7.23
10	11.41	11.05	7.76	7.38
15	11.39	11.01	7.83	7.50
20	11.38	10.99	7.87	7.55
25	11.35	10.95	7.92	7.64
30	11.33	10.92	7.96	7.70
35	11.31	10.90	7.99	7.75
40	11.29	10.88	8.02	7.78
45	11.27	10.86	8.04	7.82
50	11.25	10.84	8.06	7.85



14e

Table 2.3. Dilution study of tripeptide 13d in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

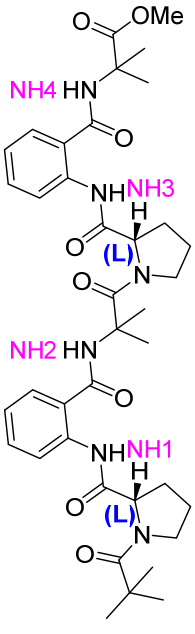
Concentration (in ppm)	Chemical Shift (in ppm)	
	NH1	NH2
120	11.31	6.92
100	11.30	6.89
80	11.30	6.87
60	11.29	6.85
40	11.29	6.82
20	11.29	6.79
10	11.28	6.78
5	11.28	6.77
4	11.28	6.77
2	11.28	6.77



13d

Table 2.4. Dilution study of hexapeptide 14e in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

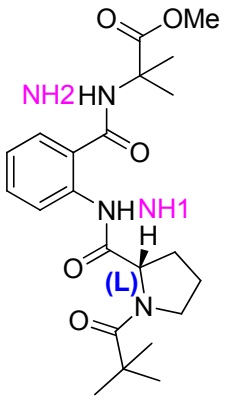
Concentration (in ppm)	Chemical Shift (in ppm)			
	NH1	NH3	NH2	NH4
120	11.46	11.06	7.66	7.24
100	11.46	11.08	7.63	7.20
80	11.47	11.10	7.60	7.15
60	11.47	11.13	7.57	7.09
40	11.47	11.16	7.53	7.03
20	11.48	11.19	7.51	6.97
10	11.48	11.21	7.49	6.93
5	11.48	11.22	7.47	6.92
4	11.48	11.22	7.45	6.91
2	11.48	11.22	7.43	6.91



14e

Table 2.5. Temperature variation study of tripeptide 13d (20 mmol, 400 MHz, $CDCl_3$)

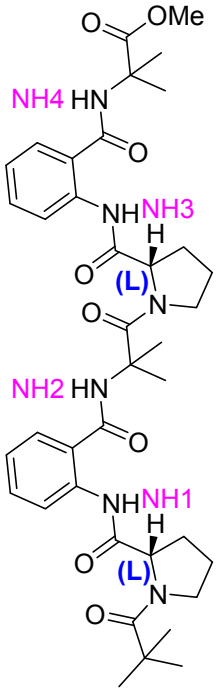
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	11.36	6.84
273	11.34	6.83
278	11.33	6.83
283	11.31	6.82
288	11.29	6.81
293	11.28	6.81
298	11.26	6.81
303	11.24	6.80
308	11.22	6.80
313	11.20	6.80
318	11.18	6.80
323	11.16	6.79



13d

Table 2.6. Temperature variation study of hexapeptide 14e (60 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical shift (in ppm)			
	NH1	NH3	NH2	NH4
268	11.53	11.11	7.59	7.26
273	11.52	11.12	7.58	7.22
278	11.51	11.13	7.57	7.18
283	11.50	11.13	7.57	7.15
288	11.48	11.13	7.57	7.12
293	11.47	11.13	7.57	7.10
298	11.46	11.12	7.58	7.09
303	11.44	11.12	7.58	7.07
308	11.43	11.11	7.58	7.05
313	11.41	11.10	7.58	7.03
318	11.39	11.09	7.58	7.02
323	11.38	11.08	7.58	7.01



14e

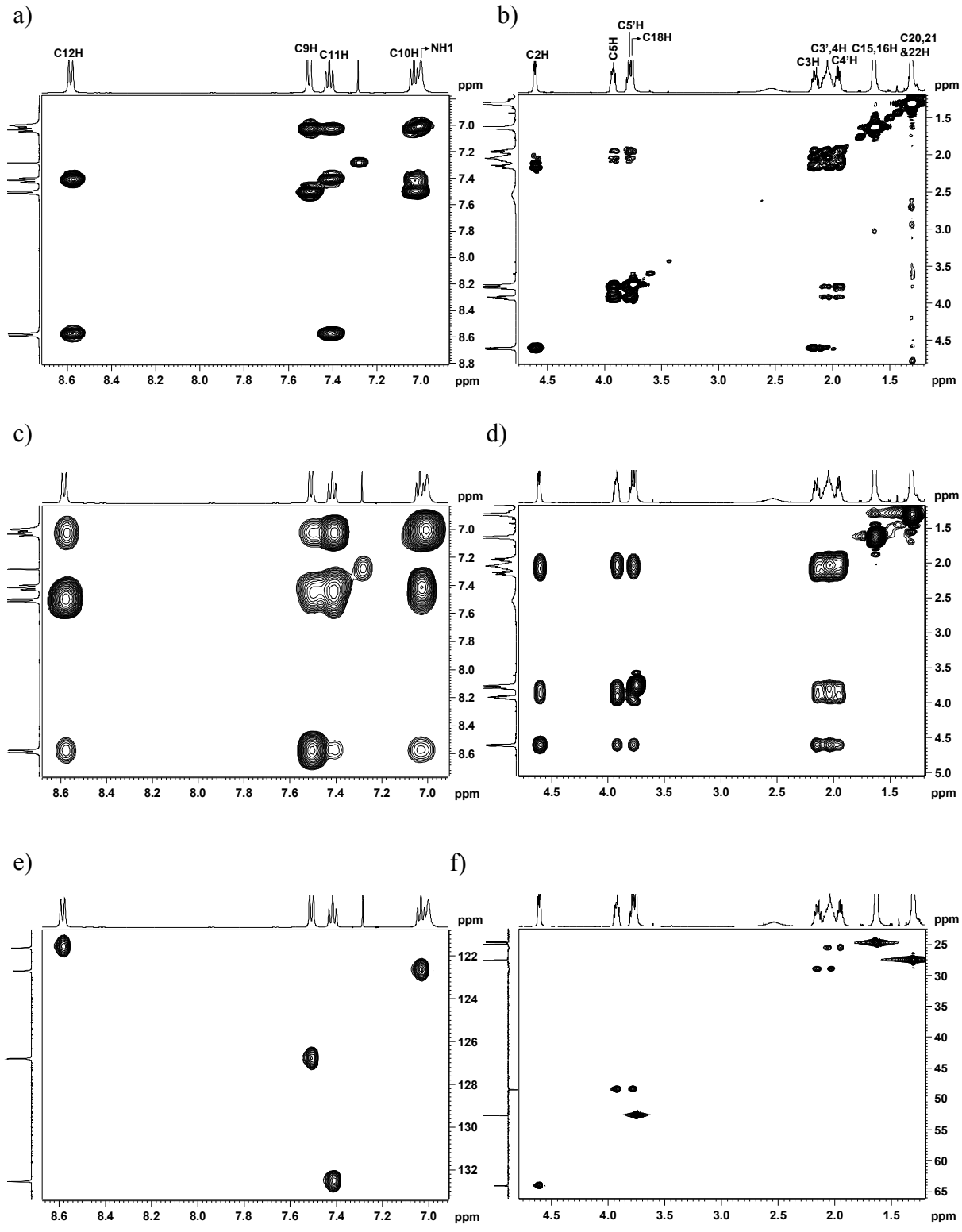


Fig. 2.15: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of tripeptide **13d** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

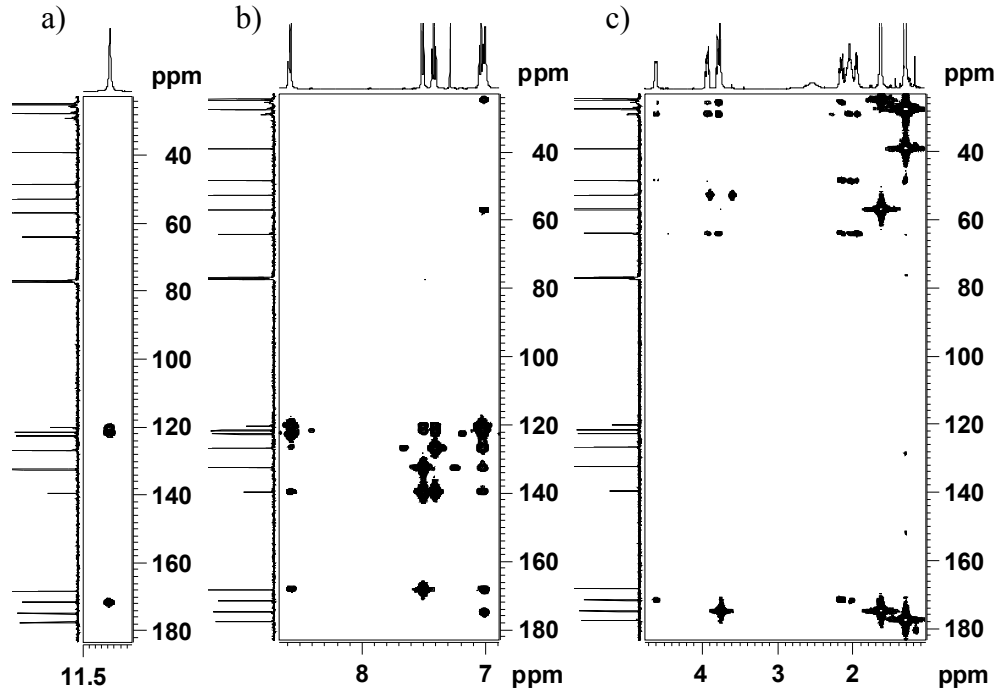


Fig. 2.16: Partial HMBC spectra of tripeptide **13d** (500 MHz, $CDCl_3$). For better view, amide (a) aromatic (b) and aliphatic (c) regions are given separately.

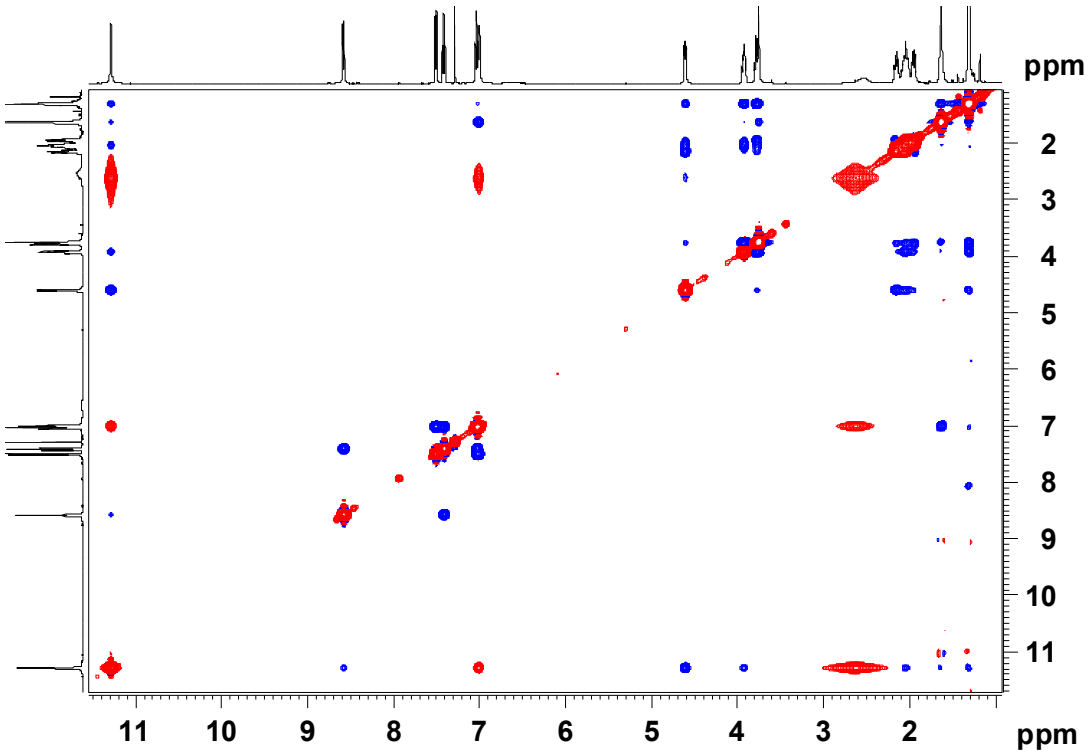


Fig. 2.17: 2D NOESY spectra of tripeptide **13d** (500 MHz, $CDCl_3$).

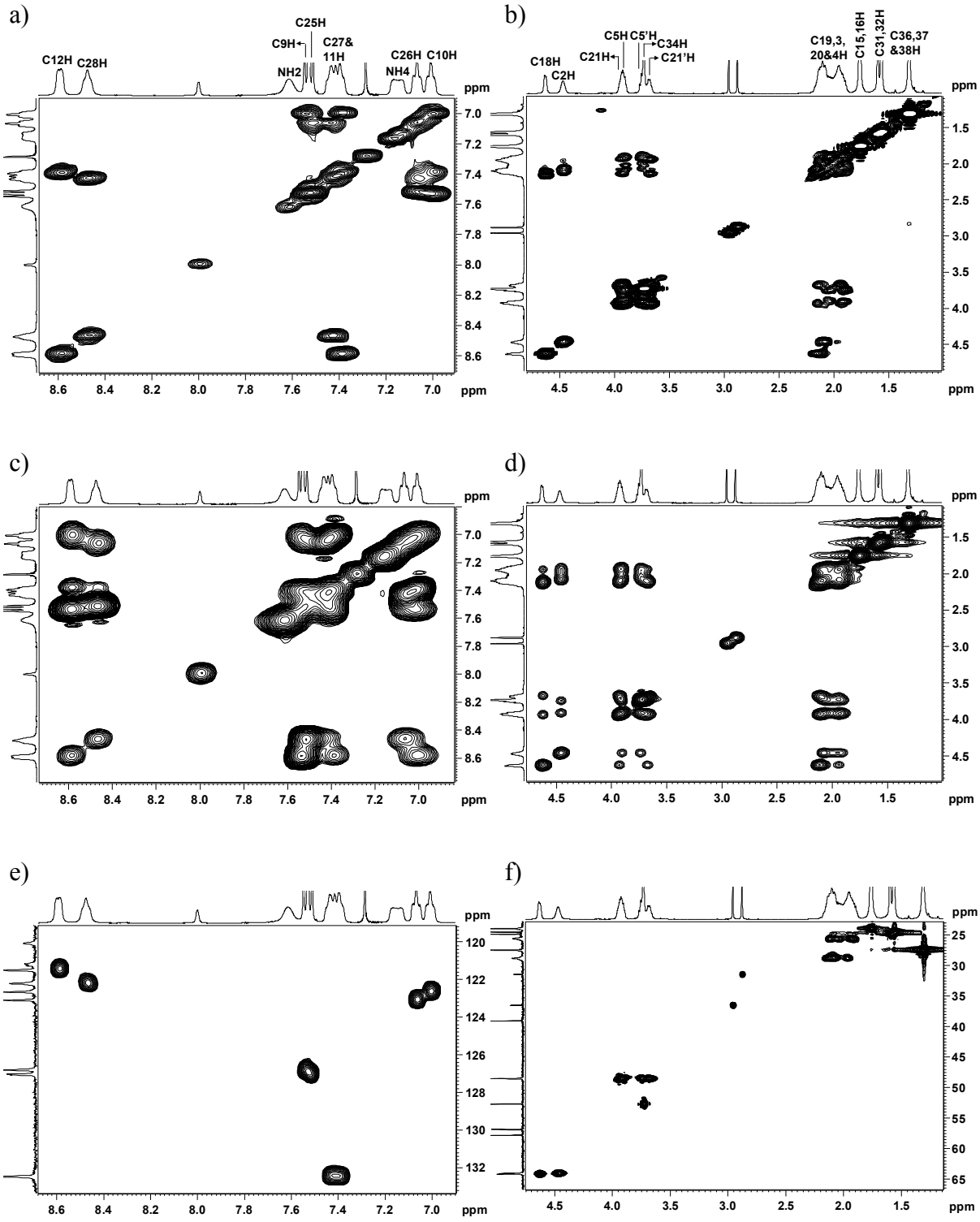


Fig. 2.18: Partial COSY (a, b), TOCSY (c, d) and HSQC (e, f) spectra of hexapeptide **14e** (500 MHz, $CDCl_3$). For better view, aromatic and aliphatic regions are given separately.

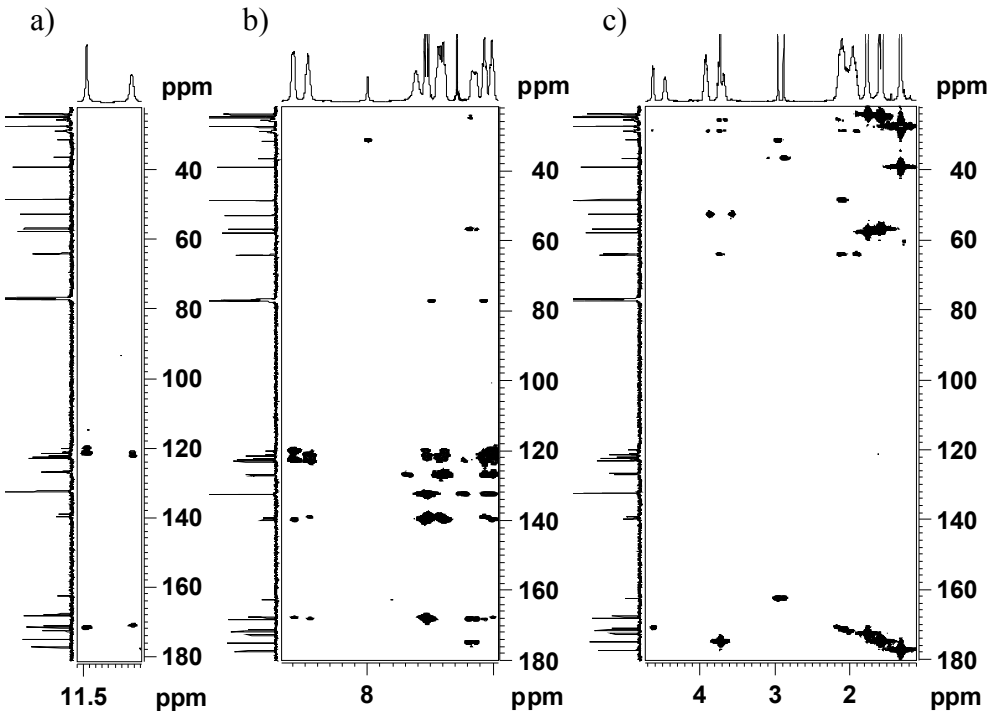


Fig. 2.19: Partial HMBC spectra of hexapeptide **14e** (500 MHz, $CDCl_3$). For better view, amide (a) aromatic (b) and aliphatic (c) regions are given separately.

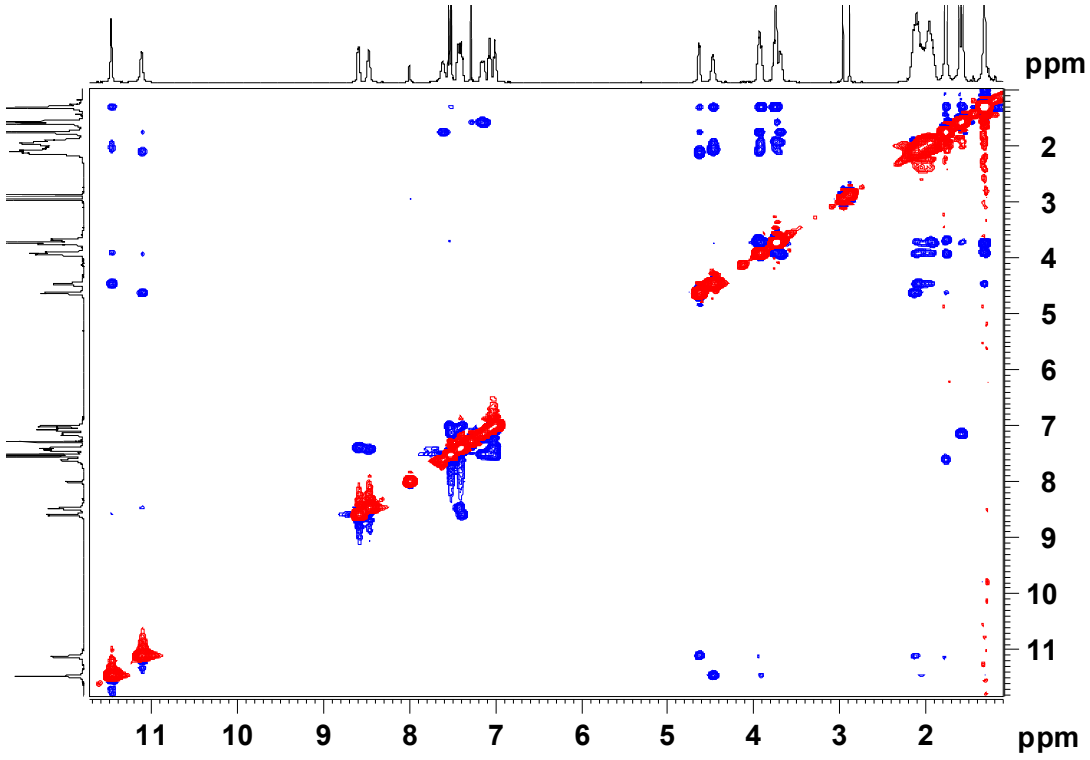


Fig. 2.20: 2D NOESY spectra of hexapeptide **14e** (500 MHz, $CDCl_3$).

2.14 Reference and notes

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Chapter 3

Conformationally Restricted Building Blocks for Foldamers

Part A: ***Conformationally Rigid Aromatic Amino acids as Potential Building Blocks for Abiotic Foldamers***

Part B: β-Lactam-α-Amino acid Conjugated Constrained HEA Isosteres as Building Blocks for Heterogeneous Foldamers

Conformationally Rigid Aromatic Amino acids as Potential Building Blocks for Abiotic Foldamers

3.1 Introduction

In chapter 1, we had discussed the classification of foldamers, in which homogeneous and heterogeneous foldamers were discussed in detail.[1] Based on the nature of the backbone, another way of classification of foldamers are biotic and abiotic foldamers.

3.1.1 Biotic foldamers

Biotic foldamers usually contain bio-inspired aliphatic backbone.[2] These oligomers have attained considerable importance in foldamer chemistry not only because of their conformational resemblance, but also because of their improved pharmacokinetic profiles over biopolymers.[3] Selected examples[4-6] are: β-, γ-, δ-, peptoid, oligoureas, azapeptides, aminoxy peptides, hydrazine peptide and sugar derived peptides.[5,6]

3.1.1.1 Building blocks for biotic foldamers

In addition to homologated amino acids which can mimic the structure and function of α-peptides, various research groups developed diverse classes of conformationally rigid (constrained) aliphatic amino acids including the cyclic β-amino acids such as 2-amino cyclopropanecarboxylic acid (ACC),[7a] 2-amino cyclobutanecarboxylic acid (ACBC),[7b] 2-amino cyclopentane carboxylicacid (ACPC),[7c] 2-amino pyrrolidine-3-carboxyxlic acid (APC),[7c] 2-amino cyclohexanecarboxylic acid (ACHC);[7d] cyclic γ-amino acids like (1R,2R)-2-(aminomethyl)cyclopropanecarboxylic acid, γ-aminobutyric acid (GABA),[7e] 2-((1S,2R)-2-aminocyclohexyl)acetic acid, 1-(Aminomethyl)-cyclohexaneacetic acid, ‘‘gabapentin’’ (Gpn);[7f] cyclic δ-amino acids like (S)-4-aminocyclohex-1-enecarboxylic acid, sugar amino acids (SAA),[5,7g] *cis*-β-furanoid sugar amino acid (FSAA),[6a] and others.[7h] Efforts to further constrain the backbone or ring led to dehydro amino acids,[7i] bicyclic and polycyclic amino acids,[7j] azabicyclo and aminobicyclo amino acids.[7k]

3.1.2 Abiotic foldamers

Abiotic foldamers usually have aromatic backbone displaying folding modes different from those of biopolymers. These classes of oligomers attract

considerable attention mainly because of their predictable conformations and high conformational stability.[8-12] Selected examples are oligoamides,[8] oligoureas,[9] pyridine oligoamide,[10] oligo-*m*-phenylethynylenes[11] and oligohydrazides.[12]

3.1.2.1 Building blocks for abiotic foldamers

The stabilization/rigidification *via* fixed dihedral angles rendered by the aromatic rings in aromatic amino acids, offers considerable advantages. Aromatic amino acids can be widely classified as β-, γ-, δ-amino acids, which differ in the position of NH_2 attached to the carboxylic acid (Fig. 3.1). Aromatic amino acids includes benzenoid and poly-aromatic amino acids, heterocyclic aromatic amino acids[13] having heterocycles like furan, thiophene, pyrrole,[14] imidazole,[14] pyrazole,[15] oxazole,[16] thiazole,[17] pyridine, naphthyrine,[18] indole, phenanthroline[13] and aromatic amino sulfonic acids.[19] Substituents like -OR, -SR, F and N in the aromatic rings facilitate hydrogen-bonding and render additional conformational rigidification to the aromatic amino acid residues.[20] However, amino acids having axial chirality and extended aromatic π-surfaces are limited.[21]

3.2 Objective of the present work

The objective of the work described in this chapter was to design and develop highly conformationally rigid aromatic amino acids as a potential building block for abiotic foldamers, from well-ordered 1,1'-bi-2-naphthols. Although 1,1'-bi-2-naphthols have been used in several applications owing to their interesting atropisomerism,[22] their use in foldamer synthesis as monomeric building block is largely unexplored. Atropisomerism which arises due to the restricted rotation around a single bond connecting the aryl rings, is the phenomenon that is exhibited by variety of biaryl compounds. Such a feature offers the possibility of design and development of conformationally ordered synthetic oligomers with intriguing structural architectures distinct from those classically observed.[23]

3.3 Design strategy

Although there are innumerable unnatural aromatic amino acids[13-19] reported in the literature, aromatic amino acids with two-dimensional orientations of amino and carboxylic groups appended on conformationally rigid framework suitable for foldamer generation have not yet been explored.

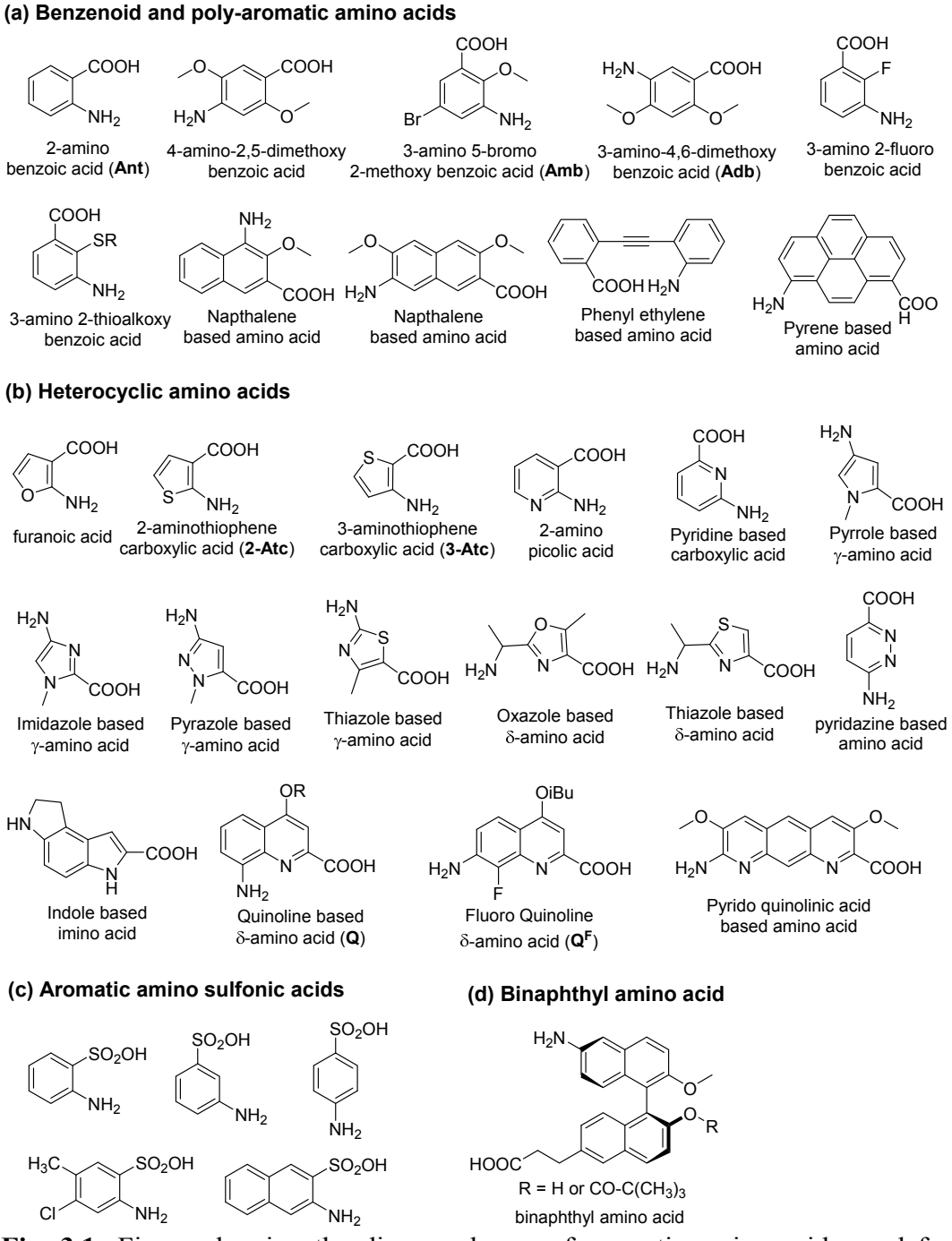


Fig. 3.1: Figure showing the diverse classes of aromatic amino acids used for foldamer design.

1,1'-Bi-2-naphthol scaffold provides rigidity, axial chirality and two extended aromatic π-surfaces. Due to the atropisomerism,[22] naphthyl rings in the 1,1'-bi-2-naphthol are oriented at an angle of nearly 90°.[21] Positioning of the amino and carboxyl groups (chain propagating groups) on a rigid aromatic two-dimensional 1,1'-bi-2-naphthol framework (Fig. 3.2) can be expected to show a marked influence on the overall shape of the oligomers containing such building

blocks. The hydrogen-bonding interactions between amide NHs and methoxy oxygens (OCH_3) on adjacent aromatic rings, were expected to rigidify the oligomeric backbone and thus, could provide an extra stability to secondary structure of the oligomers derived from these building blocks. Furthermore, such a strategy could furnish synthetic oligomers with dazzling structural architectures, distinctly different from those classically observed.[23]

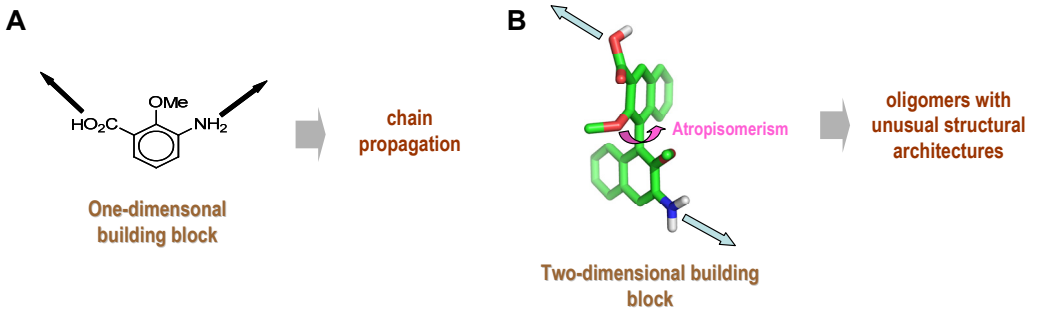
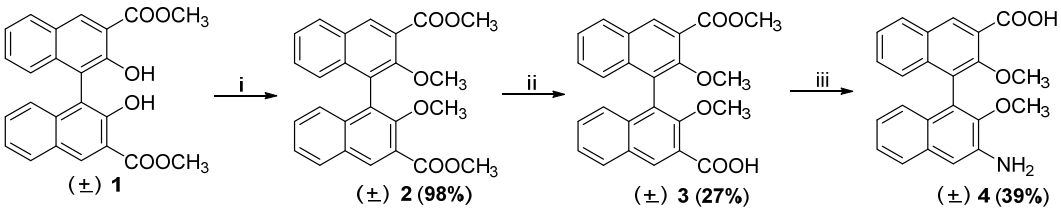


Fig. 3.2: Design strategy of 1,1'-bi-2-naphthol-derived conformationally rigid aromatic amino acid building block. (*Note*: The growth of oligomers takes place two-dimensionally (shown with arrows) with respect to amino and carboxyl groups (chain propagating groups) appended on 1,1'-bi-2-naphthol).

3.4 Synthesis

1,1'-Bi-2-naphthol-based constrained aromatic amino acid **4** was synthesized starting from BINOL ester **1** in overall three steps (Scheme 3.1). The racemic BINOL ester **1** was subjected to *O*-methylation to afford the corresponding bis-ether derivative **2**. Partial hydrolysis of the ester group followed by Curtius rearrangement furnished **4**.



Scheme 3.1: Synthesis of conformationally rigid aromatic amino acid **4**. **Reagents and conditions:** (i) dimethylsulfate, K_2CO_3, acetone, reflux, 5 h; (ii) LiOH (1.3 eq.), H_2O-THF, 0 °C (1 h), then 12 h, rt; (iii) i. $(COCl)_2$, DCM, DMF (cat.), 0 °C, then rt, 3 h, ii. NaN_3, acetone, H_2O, 0 °C, 15 min.; iii. C_6H_6, reflux, 1 h; iv. 10% KOH, reflux, 1 h. *Note*: the isolated yield of **3** based on the recovered starting material, the bis-ester **2**, is 52%.

3.5 Conclusion

In conclusion, this work describes the development of novel aromatic amino acid as potential building blocks for abiotic foldamers. The naphthyl rings bearing carboxylic group and amino group would adopt anti-periplanar conformation, because of restricted rotation of the naphthyl rings. These building blocks would be useful for the construction of oligomers displaying novel molecular architectures with unique conformations, distinctly different from those classically observed.[23]

β-Lactam-α-Amino acid Conjugated Constrained HEA Isosteres as Building Blocks for Heterogeneous Foldamers

3.6 Introduction

In chapter 1, we had discussed the *peptidomimetics*[24] - an area of research which mainly focuses on the development of small molecules which mimic the biological properties of peptides. ''*Peptidomimetic*'' refers to a molecule bearing identifiable resemblance to a peptide that, as a ligand of a biological receptor, can imitate or inhibit the effect of a natural peptide.

Even though many peptides exhibit biological activity,[25] their use as pharmaceutical agents is limited because of their poor bio-availability, low cell permeability and poor *in-vivo* stability owing to their conformational flexibility (resulting in multiple receptor selectivity) and susceptibility towards various proteolytic enzymes (proteases).[26] Peptidomimetics displays enhanced bioavailability and bioselectivity, due to their ability to restrict the conformational flexibility and resist enzymatic degradation.[27] Thus peptidomimetics have emerged flourishing area of research in drug design.[28] Backbone conformational constraints and peptide transition-state isosteres have been used in recent advances in the development of peptidomimetics as therapeutic agents, which would lead to the potent, selective, and proteolytically stable protease inhibitors (PI).[29] Protease inhibitors (PI) are a class of molecules that inhibit the action and function of proteases, through binding *via* a stable complex intermediate.[30] Several heterocyclic scaffolds have also been used for the design of novel protease inhibitors.[31]

3.6.1 Backbone conformational constraints

Imposing backbone conformational restriction is one of the interesting strategies in limiting the number of conformations available to the peptide.[32] Use of these restrictions in biologically active peptides stabilize a biologically active conformation, thereby modulating desirable biological effect.[33] This concept plays an important role in the design of peptidomimetics in the drug development process.

Two basic types of conformational modifications have been used in peptidomimetics to attain pre-organised bioactive conformations. Non-covalent

modification includes incorporation of D-amino acids,[34] N-methyl amino acids[35] and α-methyl amino acids.[32] Covalent modification forming cyclic and polycyclic peptides includes disulfide bridges,[36] *cis*- and *trans*-amide bond mimics[37] and cyclization through amide bonds;[38] all of which are known to occur in nature. For instance, naturally occurring modifications are β-lactams found in the penicillins and cephalosporins.[39] Thus, the incorporation of cyclic structures into peptide backbones has attracted tremendous efforts on the synthesis of enzyme inhibitors, peptide hormones and neuroreceptor ligands. Constrained peptides offer a fascinating challenge to gain insight into molecular recognition processes between peptide ligands and bio-receptors.[24,27a]

3.6.1.1 Dipeptide mimetics

In the early eighties, Freidinger proposed the concept of protected lactam-bridged dipeptides, which was a milestone in the design of conformationally constrained peptides.[40a] These types of compounds, now widely known as Freidinger lactams, have been of great interest to many medicinal and peptide chemists.[40b,c] Freidinger lactams and their hetero-, fused-, unsaturated and homo-analogs, have found various applications in the design of conformationally constrained peptidomimetics in different therapeutic areas.[41] Externally scafolded lactam peptides are among the most efficient and popular β-turn mimics,[42] utilized as renin inhibitors[43] and others.[44]

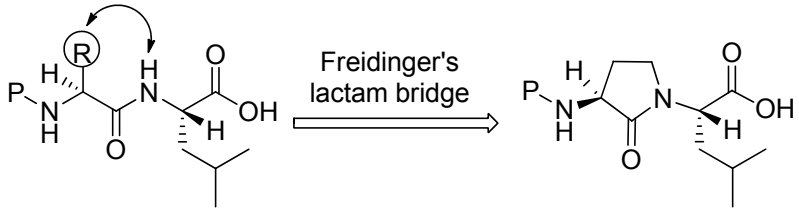


Fig. 3.3: Freidinger's concept of conformationally constrained dipeptides for peptidomimetic design.

3.6.2 Transition-state isosteres

Another strategy that has proved very successful for the design of efficient protease inhibitors is the incorporation of transition-state isosteres into a peptide/peptidomimetic structure. The mechanism of proteolysis by proteases

proteases proceed *via* a tetrahedral transitionstate,[45] which results from nucleophilic attack by a water molecule on the scissile peptide bond carbonyl group. A transition-state isostere is defined as a functional group that can mimic the tetrahedral transition-state of amide bond hydrolysis, but is stable and non hydrolyzable. Usually, dipeptide isosteres are designed to replace two amino acids and are functionalized with an amine and a carboxylate functionality. Among the diverse classes of transition-state isosteres, hydroxyethylamine (HEA) isosteres attract considerable attention in the development of various classes of protease inhibitors.[46] Success of using this moiety as a peptide bond replacement can be readily understood by the number of HEA-based drugs which have been available in the market that includes saquinavir, indinavir, nelfinavir and amprenavir which are the FDA approved protease inhibitors (PIs) (Fig. 3.4). Several other therapeutically significant HEA isosters are known for their potential for treating cancer, Alzheimer's disease and nosocomial infections.[47]

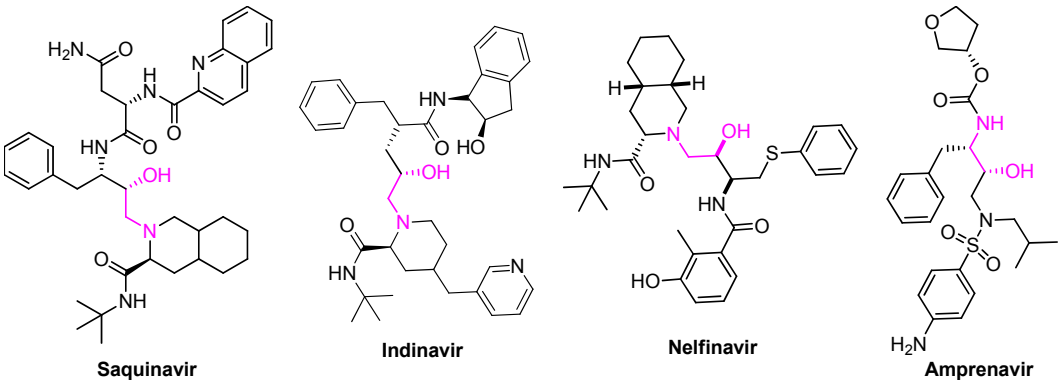


Fig. 3.4: Molecular structures of HEA based HIV protease inhibitors.

3.7 Objective of the present work

In order to attain shape diversity of the oligomer backbone, building blocks with diverse structural architectures are being developed. For instance, Fleet et al.[5] and others[6] have reported a huge repertoire of carbohydrate-based foldamer building blocks. The objective of the work described in this part was to design and develop highly conformationally constrained dipeptide carrying the pharmacologically important HEA-β-lactam-tethered motif as potential building blocks for heterogeneous foldamers, starting from carbohydrate precursors.

3.8 Design strategy

It is already known that conformational restriction has been proven to be an effective and simple tool to improve the druggability, particularly the receptor selectivity, of acyclic/flexible counterparts.[48] The residual flexibility of the peptides can be constrained by incorporating lactam bridges between neighbouring amino acids to stabilize protein secondary structure, as shown by Freidinger[40] and fallowed by others.[42]

Keeping these facts in mind, we designed a set of conformationally constrained sugar derived dipeptide building blocks carrying different α-amino acid residues at the C-terminus (Fig. 3.5). These heterogeneous building blocks feature a biomedically important β-lactam core,[49-51] further constrained with a hydroxyethylamine isostere (HEA) on the backbone. It is noteworthy that HEA isosteres are one of the most important peptide transition-state mimics developed so far, and many drug candidates are known to feature this proteolytically stable peptide bond mimic.[46]

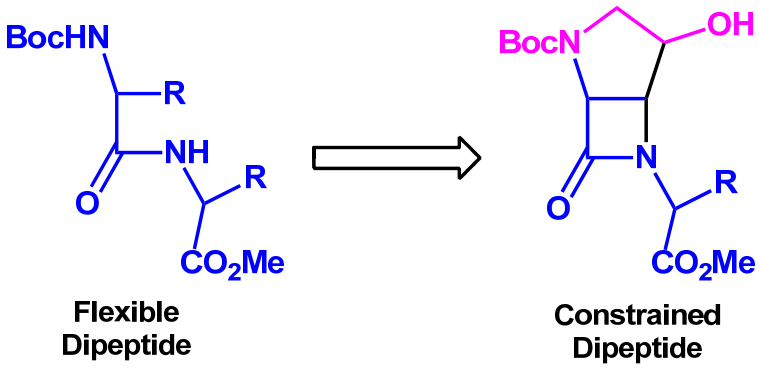
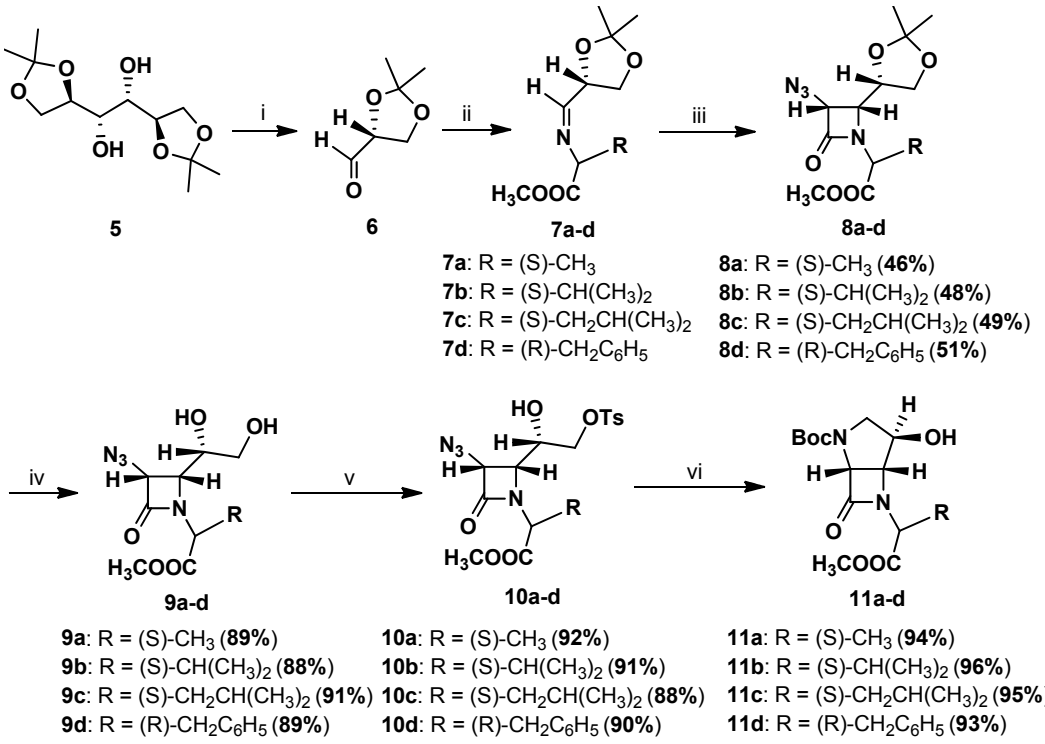


Fig. 3.5: Design strategy of a constrained bicyclic dipeptide heterogeneous foldamer building block with an embedded HEA isostere and a β-lactam core (the dipeptide backbones are highlighted in blue and the HEA moiety in pink).

3.9 Synthesis

The mannitol-derived D-glyceraldehyde **6**[52] was used in the construction of β-lactam **8a-d** via a Staudinger ketene-imine cycloaddition[53] synthetic protocol. The Staudinger synthesis using D-glyceraldehyde not only helped us to access the β-lactam as a single diastereomer, but also furnished a protected *vicinal* glycol, which was amenable to further functional manipulations to effect the second key step of cyclization leading to the formation of the constrained building blocks **11a-d** (Scheme 3.2).



Scheme 3.2: Synthesis of conformationally constrained building blocks **11a-d**. **Reagents and conditions:** (i) $NaIO_4$, H_2O, 0 °C, 30 min.; (ii) R-NH_2, 1,2-dichloroethane-H_2O, rt, 2 h; (iii) potassium azido acetate, triphosgene, Et_3N, DCM, 0 °C, then rt, 15 h; (iv) PTSA, THF:H_2O, reflux, 16 h; (v) tosyl chloride, Bu_2SnO, Et_3N, DCM, rt, 8 h; (vi) Pd-C, H_2, $(Boc)_2O$, 60 psi, 8 h.

The acetonide protected D-glyceraldehyde **6**, readily available from D-mannitol diacetonide **5**[52] by $NaIO_4$-mediated oxidative cleavage, was converted into the aminoacid-conjugated Schiff bases **7a-d**. These Schiff bases **7a-d**, which without purification, were subjected to the standard Staudinger reaction with azidoacetyl chloride, generated *in situ* by reacting potassium azido acetate with triphosgene to furnise azido acetonides **8a-d**. The *cis*-stereochemistry of the β-lactam was readily indicated by the coupling constants (J = 5-6 Hz), which is characteristic of *cis*-β-lactams.[54] Deprotection of azido acetonides **8a-d** cleanly furnished diols **9a-d**, which were then subjected to selective dibutyltin oxide-mediated tosylation[55] to afford the *O*-tosyl derivatives **10a-d** in excellent yields. Azide reduction within **10a-d** with concomitant Boc protection cleanly afforded the cyclized constrained target building blocks **11a-d** in excellent yield (93-96%).

3.10 Conformational analyses

Stereochemical investigations were accomplished by extensive 2D NMR and single crystal X-ray diffraction.

3.10.1 Single crystal X-ray diffraction studies

The dipeptide foldamer building block **11a**, which readily crystallized from chloroform, features a biomedically significant β-lactam fused with a 5-membered pyrrolidine ring. It is noteworthy that the structural architecture of the pyrrolidine ring displaying the hydroxyl group at C5 is reminiscent of a constrained HEA isostere, as noted earlier.[46]

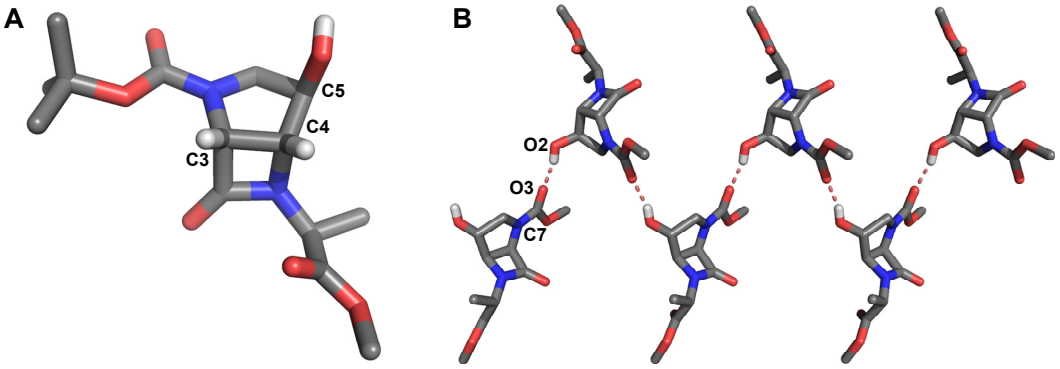


Fig. 3.6: Crystal structure of **11a** (A) and self-assembly aided by the C5 hydroxyl group as the H-bonding donor, and ^{t}Boc carbonyl as H-bonding acceptor (B). Note: Selected hydrogens have been deleted in the crystal structure and ^{t}Boc methyls have been deleted in the self-assembled structure for clarity.

The crystal structure[56] of **11a** (Fig. 3.6A) also clearly established the *cis*-geometry of the C3 and C4 positions of the β-lactam ring. The dipeptide building block **11a** assumes an extended sheet structure in the solid-state, aided by intermolecular hydrogen-bonding interaction between the C5 hydroxyl group of one molecule and the ^{t}Boc carbonyl of another molecule [hydrogen-bond geometric parameters: O2-H2O···O3; H2O···O3 = 1.95 Å, O2···O3 = 2.75 Å, ∠O2-H2O···O3 = 164.2° and the planarity of the hydrogen bond torsion angle ∠(O2–H2O…O3=C7) = -131.6°].

3.10.2 NMR studies

The *cis*-stereochemistry of the β-lactam and constrained bicyclic core was further confirmed by extensive NMR studies ($CDCl_3$, 500 MHz). The most characteristic nOe that is quintessential to support the *cis*-stereochemistry would be the requirement of a diagnostic long range inter-residual dipolar coupling of C4H with C3H and OH (Fig. 3.7a, b).

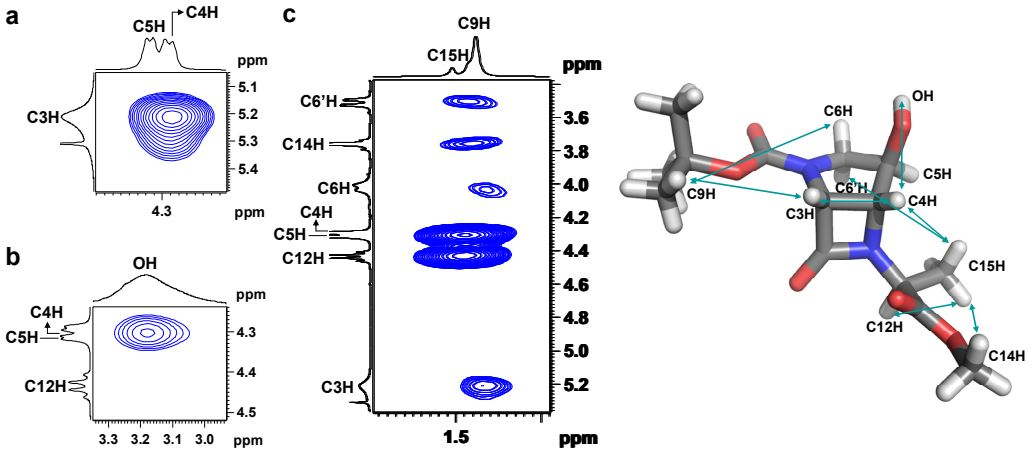


Fig. 3.7: Selected nOe extracts from the 2D NOESY data of **11a** ($CDCl_3$, 500 MHz).

3.11 Conclusion

In conclusion, we have been able to develop β-lactam-α-amino acid-conjugated constrained HEA isostere building blocks derived from readily available carbohydrate precursors through efficient multi-step synthetic protocols. The decoration of these heterogeneous building blocks with biologically relevant moiety such as a rigid fused β-lactam is noteworthy. Oligomers carrying these heterogenous building blocks are expected to show distinctly different conformational preferences, clearly different from their homogenous counterparts.

3.12 Experimental Section (Part A)

Dimethyl-2,2'-dimethoxy-1,1'-naphthalene-3,3'-dicarboxylate 2:

Dimethyl-2,2'-dihydroxy-1,1'-naphthalene-3,3'-dicarboxylate **1** (1 g, 2.48 mmol, 1 equiv.) in acetone (10 mL) was subjected to *O*-methylation using dimethyl sulfate (1.25 g, 9.94 mmol, 4 equiv.) and potassium carbonate (1.71 g, 12.43 mmol, 5 equiv.). After refluxing for 5 h, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The crude product was taken in ethyl acetate and washed sequentially with water and saturated sodium chloride solution. Drying and purification by column chromatography (eluent: 10% EtOAc / Pet. Ether, R_f: 0.4) afforded the diester **2** (1.04 g, 98%). mp: 268-270 °C; IR ($CHCl_3$) ν (cm^{-1}): 3018, 1716, 1593, 1408, 1215; ^1H NMR (200 MHz, $CDCl_3$) δ: 8.56 (s, 2H), 7.99 (d, *J* = 7.33 Hz, 2H), 7.49-7.41 (m, 2H), 7.38-7.30 (m, 2H), 7.17-7.12 (m, 2H), 4.00 (s, 6H), 3.48 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.7, 154.2, 135.5, 133.2, 129.4, 128.9, 128.4, 126.1, 125.4, 125.3, 124.7, 61.8, 52.2; ESI-MS: 431.28 $(M+H)^+$, 453.26 $(M+Na)^+$, 469.24 $(M+K)^+$; Elemental Analysis calculated for $C_{26}H_{22}O_6$: C, 72.55, H, 5.15; Found: C, 72.68; H, 5.03.

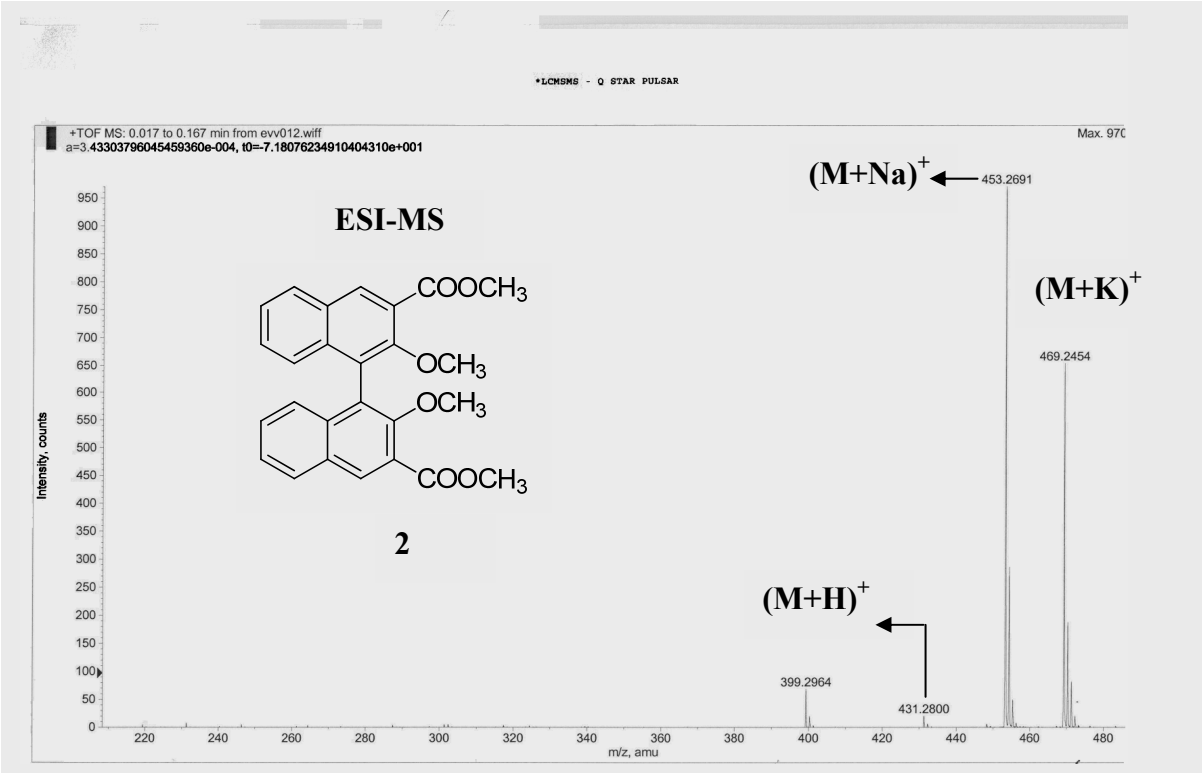
Methyl-2,2'-dimethoxy-1,1'-naphthalene-3-carboxylic acid-3'-dicarboxylate 3:

To a solution of diester **2** (1 g, 2.32 mmol, 1 equiv.) in THF (10 mL) was added a solution of $LiOH.H_2O$ (0.12 g, 3.02 mmol, 1.3 equiv.) in water (10 mL), drop wise at 0 °C. The resulting mixture was then stirred over night at room temperature. The solvent was stripped off completely under reduced pressure. The residue was taken in water, acidified with dil. HCl carefully at 0 °C. The resultant mixture was extracted with ethyl acetate and washed sequentially with water and saturated sodium chloride solution. Drying and concentration of the organic layer under reduced pressure gave the crude product which on column chromatography (eluent: 80% EtOAc/Pet. ether, R_f: 0.5) afforded the desired **3** (0.26 g, 27%). m. p: 144-146 °C; IR ($CHCl_3$) ν (cm^{-1}): 3020, 1731, 1623, 1506, 1217, 771; ^1H NMR (200 MHz, $CDCl_3$) δ: 8.95 (s, 1H), 8.62 (s, 1H), 8.09-8.00 (m, 2H), 7.57-7.47 (m, 2H), 7.46-7.37 (m, 2H), 7.20 (t, *J* = 8.59 Hz, 2H), 4.02 (s, 3H), 3.47 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.5, 166.2, 154.4, 153.5, 136.7, 135.7,

134.2, 130.0, 129.8, 129.5, 129.3, 129.3, 129.0, 126.3, 125.9, 125.4, 125.2, 121.0, 62.5, 62.1, 52.5; ESI-MS: 417.24 $(M+H)^+$, 439.27 $(M+Na)^+$, 455.25 $(M+K)^+$; Elemental Analysis calculated for $C_{25}H_{20}O_6$: C, 72.11; H, 4.84; Found: C, 72.21; H, 4.70.

2,2'- dimethoxy-1,1'-naphthalene-3'-amine-3-carboxylic acid 4:

To an ice-cold stirred solution of the mono acid **3** (0.2 g, 0.47 mmol, 1 equiv.) in dry dichloromethane (5 mL), was added two to three drops of dry DMF followed by oxalyl chloride (0.12 mL, 1.43 mmol, 3 equiv.) and the resulting mixture was stirred for 3 h at 0 °C. The solvent and excess oxalyl chloride was removed under reduced pressure. The resultant acid chloride was dissolved in dry acetone (9 mL) and to this solution was added NaN_3 (0.1 g) dissolved in water (0.25 mL). After 15 min. stirring at room temperature, chilled water (18 mL) was added to get an yellow viscous oil. The product was extracted into benzene (20 mL) and the organic layer was dried over an. Na_2SO_4. The benzene solution was refluxed for 1 h until the evolution of gas (N_2) ceased. Then 50% aqueous KOH (10 mL), was added to the benzene solution and reflux was continued for another one hour. The aqueous layer was separated, cooled to 0 °C and neutralized with dilute $KHSO_4$. The reaction mixture was diluted with dichloromethane and washed sequentially with water and saturated sodium chloride solution. Drying and concentration of the organic layer yielded the crude product which on purification by column chromatography (eluent: 80% EtOAc/ Pet. Ether, R_f: 0.3) afforded the desired pure product **4** (0.07 g, 39%); mp: >300 °C; IR ($CHCl_3$) ν (cm^{-1}): 3018, 1733, 1623, 1602, 1506, 1496, 1215, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.96 (s, 1H), 8.10 (d, J = 7.96 Hz, 1H), 7.75 (d, J = 8.21 Hz, 1H), 7.58-7.47 (m, 1H), 7.43-7.38 (m, 1H), 7.34-7.30 (m, 2H), 7.14-6.99 (m, 2H), 6.33 (bs, 2H), 3.49 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 153.3, 147.2, 138.9, 136.5, 135.6, 131.9, 129.9, 129.7, 129.3, 126.2, 126.0, 125.8, 125.5, 123.5, 111.2, 64.2, 60.0; ESI-MS: 374.30 $(M+H)^+$, 396.26 $(M+Na)^+$, 412.24 $(M+K)^+$; Elemental Analysis calculated for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75; Found: C, 73.80; H, 5.26; N, 3.70.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OCH3
OCH3
COOCH3
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(M+H)+
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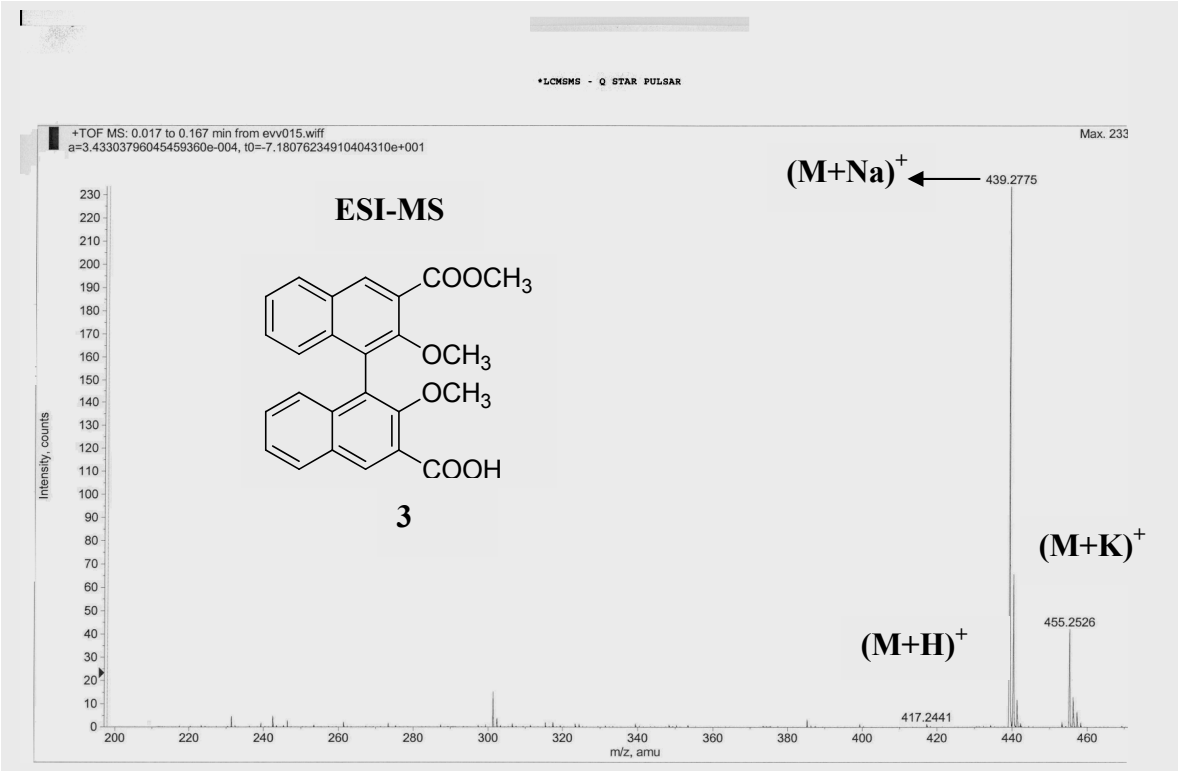
Intensity, counts
m/z, amu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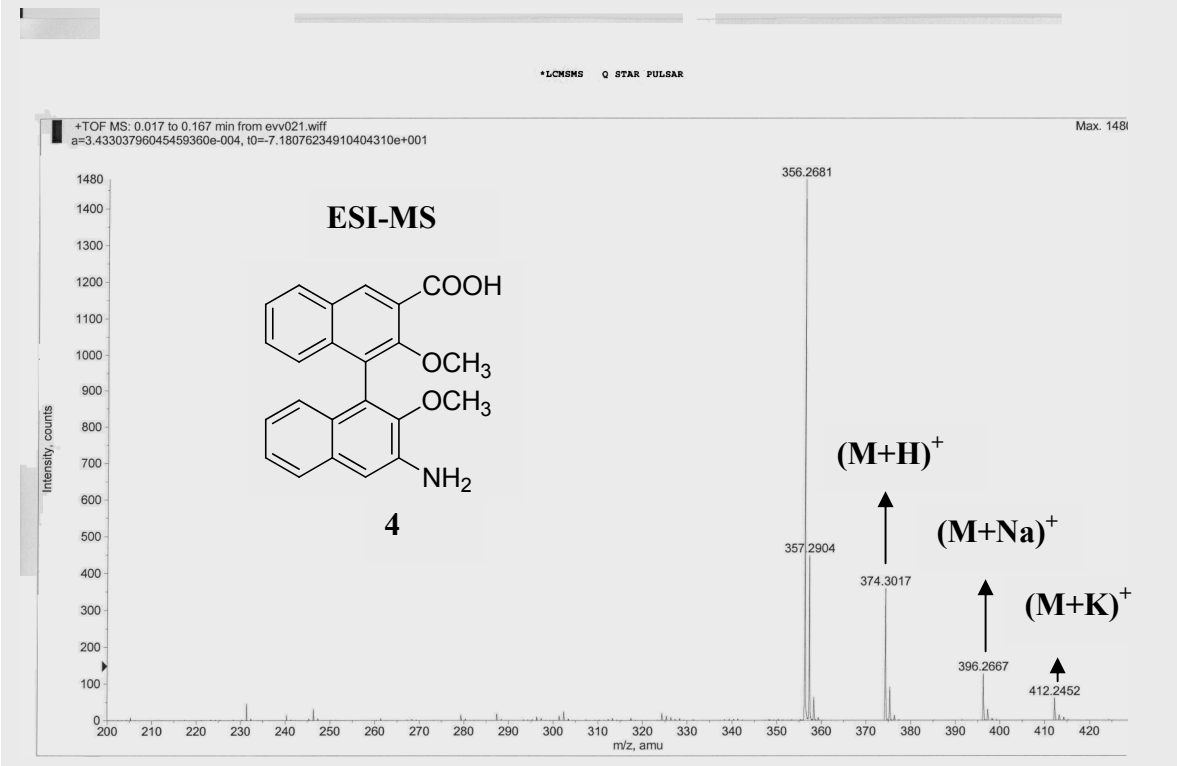
417.2441
Intensity, counts
m/z, amu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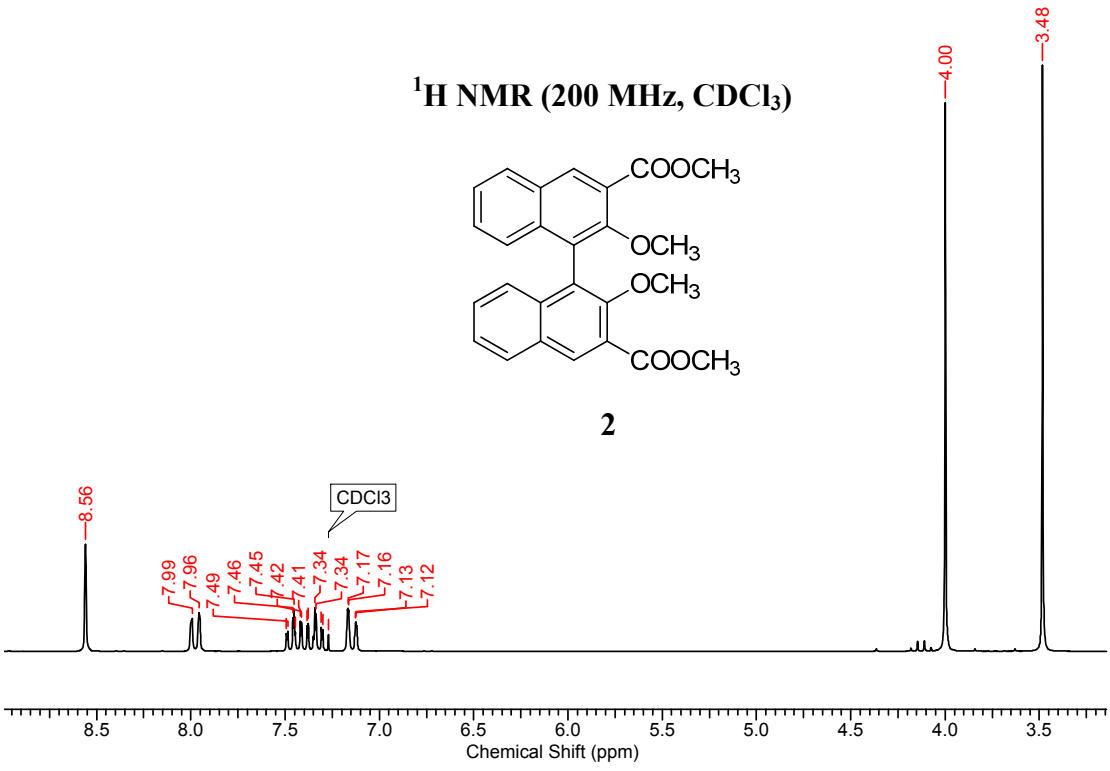
(M+K)+
Intensity, counts
m/z, amu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OCH3
COOCH3
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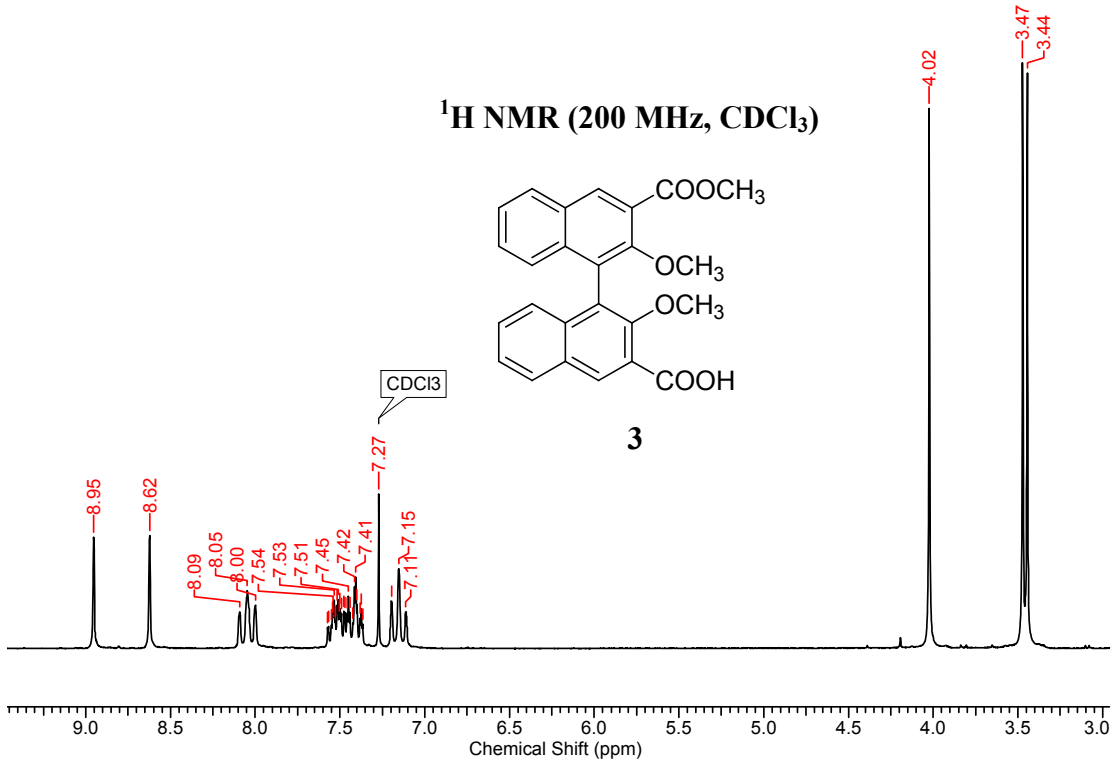
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8.05
8.00
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7.27
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4.02
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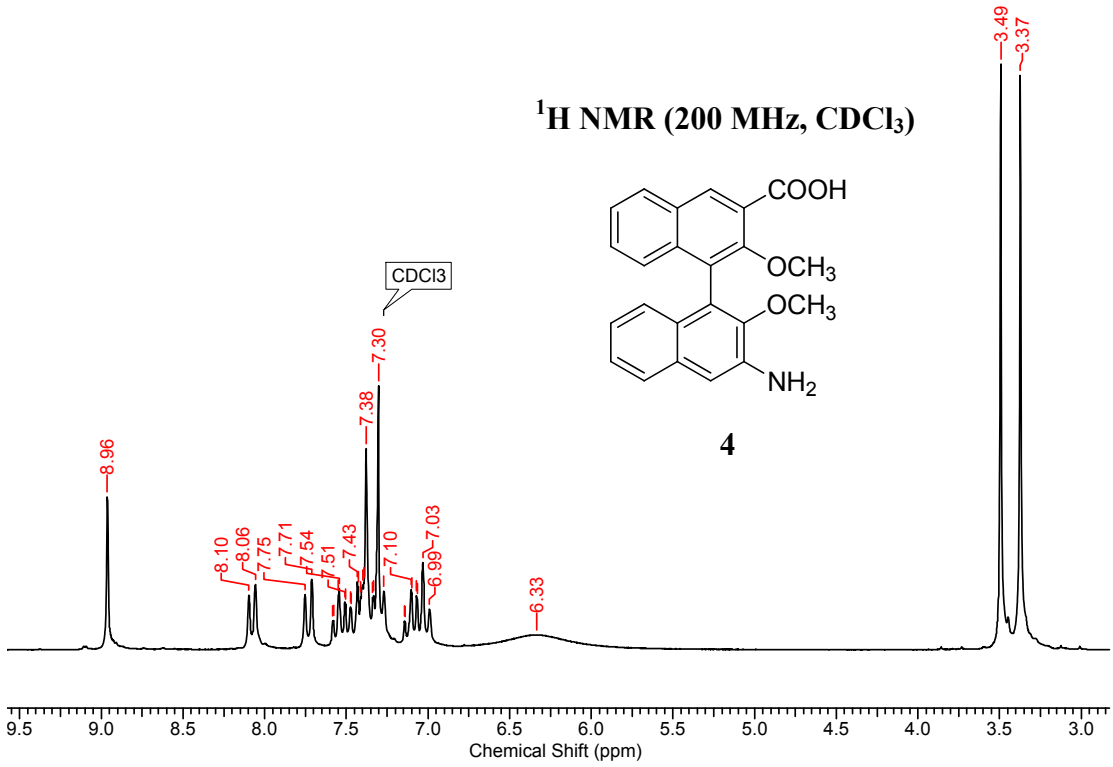
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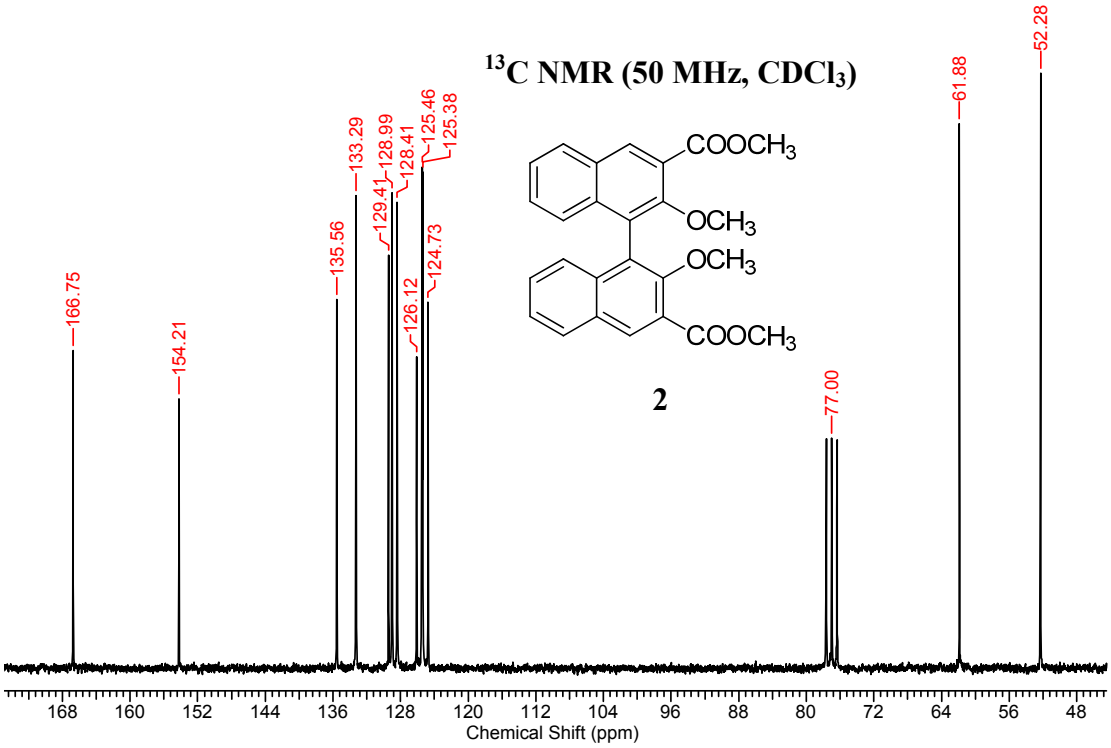
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128.99
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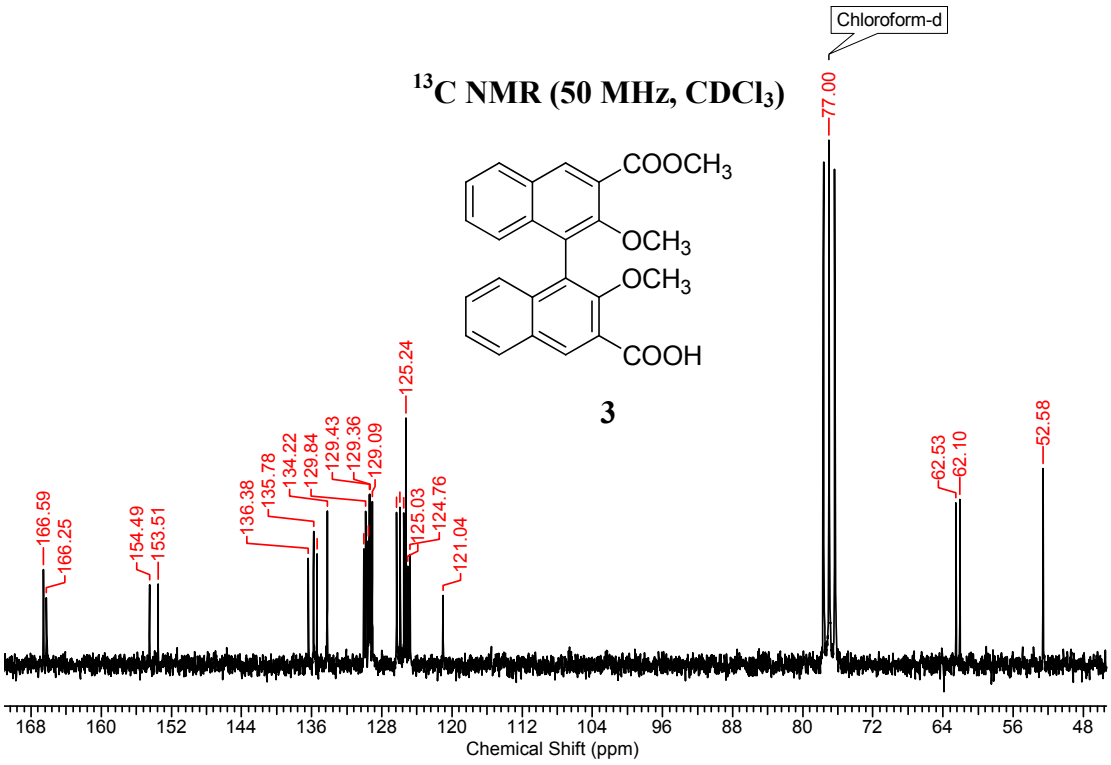
Chemical Shift (ppm)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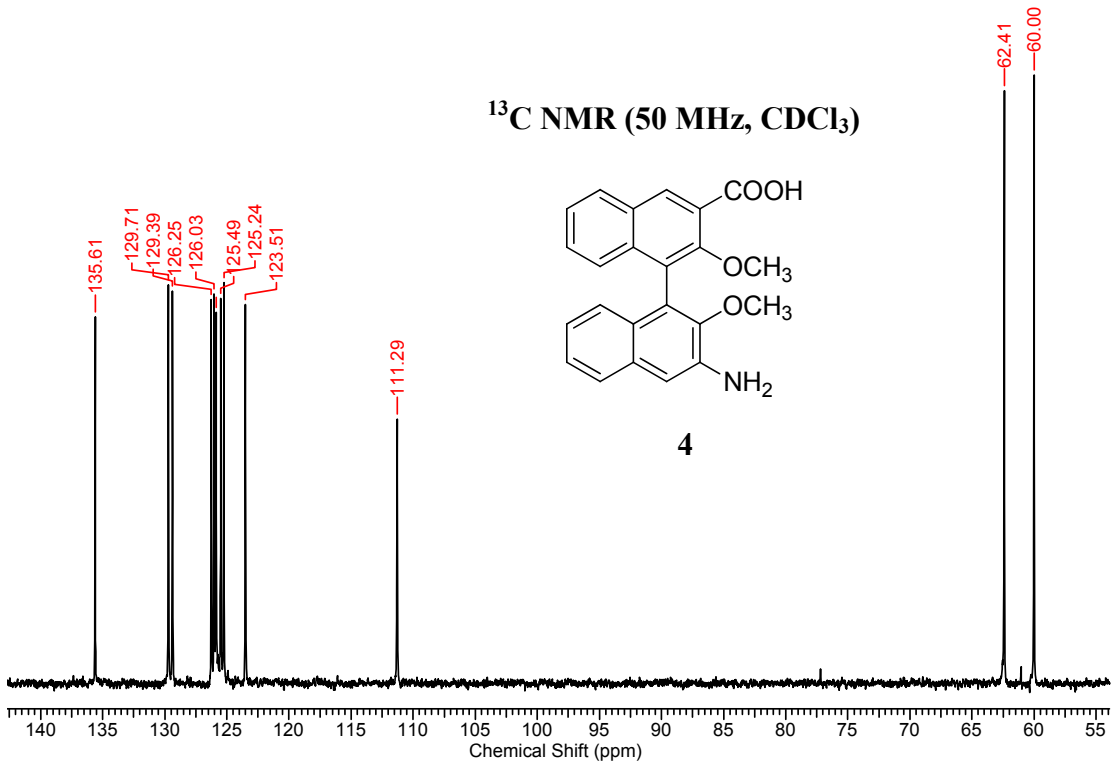
Chemical Shift (ppm)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NH$_2$
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126.03
125.49
125.24
123.51
111.29
62.41
60.00
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55
Chemical Shift (ppm)

3.13 Experimental Section (Part B)

Single crystal X-ray crystallographic studies:

Crystal data of 11a: Single crystals of the compound were grown by slow evaporation of the solution in chloroform. Colourless plate crystal of approximate size 0.37 x 0.25 x 0.10 mm^3, was used for data collection on Bruker SMART APEX CCD diffractometer using MoK_α radiation with fine focus tube with 50kV and 30 mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, hemisphere data acquisition. Total frames = 2424, Oscillation / frame -0.3°, exposure / frame = 10.0 sec / frame, maximum detector swing angle = –30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.30 to 25.00°, completeness to θ of 25.00° is 100.0 %. SADABS correction applied, $C_{14}H_{22}N_2O_6$, M = 314.34. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 9.0692(4), b = 9.942(2), c = 17.6953(5) Å, V = 1595.6(4) $Å^3$, Z = 4, Dc = 1.309 g /cc, μ (MoK_α) = 0.103 mm^{-1}, T = 296(2) K, 15411 reflections measured, 2811 unique [I>2s(I)], R value 0.0497, $wR2$ = 0.1076. Largest diff. peak and hole 0.177 and -0.198 e. $Å^{-3}$. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL) ref was used for structure solution and full matrix least squares refinement on $F2$. Hydrogen atoms were included in the refinement as per the riding model.

(R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 6[54]:

To a chilled solution of $NaIO_4$ (2 equiv) in H_2O, 1,2,5,6-di-isopropylidine-D-mannitol **5** (2 equiv) was added in portions with stirring. After completion of addition, the reaction mixture was stirred for 30 min. The reaction mixture was filtered through sintered funnel to provide an aqueous solution of the crude product **6**, which was used for subsequent reactions without further purification.

General procedure for the preparation of azido β-lactams 8a-d:

Representative procedure: To the cooled filtrate of **6**, a solution of amino ester (1 equiv) in 1, 2-dichloroethane (EDC) was added. The reaction mixture was stirred at room temperature for 2 h. The organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloromethane. The combined organic layer containing the Schiff bases **7a-d** was dried over

anhydrous Na_2SO_4. The solvent was removed under reduced pressure and re-dissolved in dry dichloromethane cooled at 0 °C. Potassium azido acetate (1 equiv) was added to the above mixture, followed by the sequential addition of Et_3N (6 equiv) and a solution of triphosgene (0.8 equiv) in dry dichloromethane. After stirring for 15 h at room temperature, the reaction mixture was diluted with dichloromethane, sequentially washed with water, saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to furnish crude products **8a-d**, which were then purified by column chromatography.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)propanoate 8a:

The product **8a** was obtained as a viscous liquid. Yield: 2.1g (46%); $[\alpha]^{25}_D$: +160° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3392, 2109, 1769, 1382, 1068, 756; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.72 (d, *J* = 5.31 Hz, 1H), 4.41(q, 1H), 4.21-4.12 (m, 2H), 3.93 (dd, *J* = 5.31 Hz, 8.85 Hz, 1H), 3.72 (s, 3H), 3.62 (q, 1H), 1.59 (d, *J* = 7.45 Hz, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.5, 163.9, 109.7, 75.8, 66.3, 63.8, 60.0, 52.3, 51.0, 26.5, 24.9, 16.3; ESI-MS: 299.40 $(M+H)^+$, 321.39 $(M+Na)^+$; Anal. Calcd. for $C_{12}H_{18}N_4O_5$: C, 48.32; H, 6.08; N, 18.78; Found: C, 48.50; H, 5.89; N, 18.62.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-3-methylbutanoate 8b:

The product **8b** was obtained as a viscous liquid. Yield: 2.40 g (48%); $[\alpha]^{25}_D$: +118° (*c* = 1.5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3461, 2110, 1769, 1742, 1675, 1373, 1215, 755; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.69 (d, *J* = 5.31 Hz, 1H), 4.26-4.07 (m, 2H), 3.85-3.73 (m, 2H), 3.71 (s, 3H), 3.62-3.53 (m, 1H), 2.63-2.45 (m, 1H), 1.39 (s, 3H), 1.28 (s, 3H), 1.02 (d, *J* = 6.70 Hz, 3H), 0.96 (d, *J* = 6.82 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.7, 163.8, 109.7, 75.8, 66.3, 63.6, 63.2, 60.8, 51.9, 28.9, 26.5, 24.8, 19.8, 19.7; ESI-MS: 349.12 $(M+Na)^+$, 365.12 $(M+K)^+$; Anal. Calcd. for $C_{14}H_{22}N_4O_5$: C, 51.52; H, 6.79; N, 17.17; Found: C, 51.43; H, 6.61; N, 17.33.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-4-methylpentanoate 8c:

The product **8c** was obtained as a viscous liquid. Yield: 2.56 g (49%); $[\alpha]^{25}_{D}$: +146° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3026, 2118, 1772, 1742, 1372, 1216, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.73 (d, *J* = 5.31 Hz, 1H), 4.36-4.30 (m, 1H), 4.21-4.12 (m, 2H), 3.94-3.87 (m, 1H), 3.71 (s, 3H), 3.63-3.55 (m, 1H), 2.21-2.10 (m, 1H), 1.71-1.51 (m, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 0.94 (d, *J* = 1.14 Hz, 3H), 0.91 (d, *J* = 1.51 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.8, 164.6, 109.7, 75.8, 66.4, 63.7, 60.4, 54.1, 52.3, 38.2, 26.5, 24.9, 24.8, 22.9, 20.7; ESI-MS: 363.30 $(M+Na)^+$, 379.30 $(M+K)^+$; Anal. Calcd. for $C_{15}H_{24}N_4O_5$: C, 52.93; H, 7.11; N, 16.46; Found: C, 53.01; H, 6.99; N, 16.65.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 8d:

The product **8d** was obtained as a viscous liquid. Yield: 2.93 g (51%); $[\alpha]^{25}_{D}$: +170° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3020, 2110, 1771, 1744, 1602, 1422, 1216, 771; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.37-7.19 (m, 5H), 4.65 (dd, *J* = 5.93 Hz, 10.61 Hz, 1H), 4.51 (d, *J* = 5.16 Hz, 1H), 4.10-4.02 (m,1H), 3.81-3.69 (m, 1H) 3.79 (s, 3H), 3.63-3.37 (m, 4H), 1.43 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.7, 163.9, 136.5, 128.6, 128.5, 126.8, 109.6, 75.7, 66.0, 63.3, 59.4, 56.7, 52.5, 34.2, 26.5, 24.7; ESI-MS: 375.22 $(M+H)^+$, 397.19 $(M+Na)^+$, 413.18 $(M+K)^+$; Anal. Calcd. for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.92; N, 14.96; Found: C, 57.57; H, 6.11; N, 15.08.

General procedure for the preparation of dihydroxy β-lactams 9a-d:

Representative procedure: A mixture of azido β-lactams **8a-d** and PTSA (0.33 equiv) in aq. THF was refluxed for 16 h. The reaction mixture was neutralized with $NaHCO_3$. The residue obtained after removing the solvents under reduced pressure was dissolved in ethyl acetate and washed with brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded **9a-d**, which were purified by column chromatography.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)propanoate 9a:

The product **9a** was obtained as a viscous liquid. Yield: 1.53 g (89%); $[\alpha]^{25}_{D}$: +164° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3399, 2117, 1753, 1733, 1654, 1637, 1450, 1412, 1021, 770; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.71 (d, *J* = 5.06 Hz, 1H), 4.38 (q, 1H), 4.01-3.86 (m, 2H), 3.82-3.78 (m, 1H), 3.76 (s, 3H), 3.73-3.70 (m,1H), 3.62-3.54 (m,1H), 2.98 (bs, 1H), 1.64 (d, *J* = 7.46 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 164.5, 70.6, 63.9, 63.7, 59.2, 52.8, 52.7, 16.1; ESI-MS: 259.23 $(M+H)^+$, 281.20 $(M+Na)^+$, 297.20 $(M+K)^+$; Anal. Calcd. for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70; Found: C, 42.02; H, 5.29; N, 21.57.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-3-methylbutanoate 9b:

`The product **9b** was obtained as a viscous liquid. Yield: 1.54 g (88%); $[\alpha]^{25}_{D}$: +100° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3400, 2117, 1743, 1651, 1408, 1020, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.72 (d, *J* = 4.80 Hz, 1H), 3.92-3.80 (m, 4H), 3.74 (s, 3H), 3.74-3.56 (m, 2H), 3.18 (bs, 1H), 2.62-2.44 (m, 1H), 1.02 (d, *J* = 6.57 Hz, 3H), 0.94 (d, *J* = 6.82 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.9, 164.4, 70.9, 64.2, 63.5, 63.4, 59.6, 52.4, 29.5, 19.7, 19.4; ESI-MS: 287.28 $(M+H)^+$, 309.24 $(M+Na)^+$, 325.25 $(M+K)^+$; Anal. Calcd. for $C_{11}H_{18}N_4O_5$: C, 46.15; H, 6.34; N, 19.57; Found: C, 46.29; H, 6.15; N, 19.41.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-4-methylpentanoate 9c:

The product **9c** was obtained as a viscous liquid. Yield: 1.60 g (91%); $[\alpha]^{25}_{D}$: +150° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3444, 2111, 1765, 1755, 1747, 1270, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.70 (d, *J* = 4.67 Hz, 1H), 4.28-4.21 (m, 1H), 3.97-3.91 (m, 2H), 3.86-3.76 (m, 2H), 3.76 (s, 3H), 3.66-3.56 (m, 2H), 2.33-2.14 (m, 1H), 1.73-1.54 (m, 2H), 0.96 (d, *J* = 3.03 Hz, 3H), 0.93 (d, *J* = 2.91 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 164.5, 70.6, 63.8, 63.8, 59.7, 56.0, 52.7, 38.4, 25.1, 22.8, 21.0; ESI-MS: 301.30 $(M+H)^+$, 323.26 $(M+Na)^+$, 339.25 $(M+K)^+$; Anal. Calcd. for $C_{12}H_{20}N_4O_5$: C, 47.99; H, 6.71; N, 18.66; Found: C, 48.15; H, 6.90; N, 18.47.

(R)-methyl 2-((2R,3R)-3-azido-2-((S)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 9d:

The product **9d** was obtained as a viscous liquid. Yield: 1.58 g (89%); $[\alpha]^{25}_{D}$: +118° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 2116, 1764, 1739, 1399, 1215, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35-7.19 (m, 5H), 4.82-4.74 (m, 1H), 4.43 (d, *J* = 5.31 Hz, 1H), 3.83-3.79 (m, 1H), 3.75 (s, 3H), 3.72-3.62 (m, 3H), 3.59-3.39 (m, 2H), 3.37-3.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.7, 165.4, 136.0, 128.6, 128.4, 127.1, 70.8, 63.5, 63.2, 58.3, 56.3, 52.8, 34.5; ESI-MS: 335.15 $(M+H)^+$, 357.15 $(M+Na)^+$, 373.14 $(M+K)^+$; Anal. Calcd. for $C_{15}H_{18}N_4O_5$ **:** C, 53.89; H, 5.43; N, 16.76; Found: C, 54.05; H, 5.30; N, 16.58.

General procedure for the preparation of tosyl β-lactams 10a-d:

Representative procedure: To a solution of the dihydroxy β-lactams **9a-d** (1 equiv) dissolved in dry dichloromethane, dibutyltin oxide (1 equiv) was added and the reaction mixture was stirred for 5 min at room temperature. After cooling the reaction mixture to 0 °C, Et_3N (1.1 equiv) and tosyl chloride (1.05 equiv) were added. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 6 h, diluted with dichloromethane, washed sequentially with water and saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude products **10a-d**, which were then purified by column chromatography.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1-hydroxy-2-(tosyloxy)ethyl)-4-oxoazetidin-1-yl)propanoate 10a:

The product **10a** was obtained as a viscous liquid. Yield: 1.90 g (92%); $[\alpha]^{25}_{D}$: +154° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3400, 2114, 1743, 1652, 1632, 1407, 1176, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 8.34 Hz, 2H), 7.38 (d, *J* = 7.96 Hz, 2H), 4.60 (d, *J* = 4.80 Hz, 1H), 4.30 (q, 1H), 4.09-4.08 (m, 2H), 4.01-3.92 (m, 2H), 3.88-3.84 (m, 1H), 3.74 (s, 3H), 2.43 (s, 3H), 1.62 (d, *J* = 7.45 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.8, 163.9, 145.4, 131.7, 129.6, 127.9, 71.2, 68.4, 63.6, 58.4, 52.8, 52.7, 21.5, 16.0; ESI-MS: 413.41 $(M+H)^+$, 435.41 $(M+Na)^+$, 451.31 $(M+K)^+$; Anal. Calcd. for $C_{16}H_{20}N_4O_7S$: C, 46.60; H, 4.89; N, 13.58; Found: C, 46.79; H, 5.12 ; N, 13.39.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1-hydroxy-2-(tosyloxy)ethyl)-4-oxoazetidin-1-yl)-3-methylbutanoate 10b:

The product **10b** was obtained as a viscous liquid. Yield: 1.82 g (91%); $[\alpha]^{25}_{D}$: +96° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3455, 2114, 1764, 1661, 1359, 1176, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.34 Hz, 2H), 7.37 (d, *J* = 7.96 Hz, 2H), 4.62 (d, *J* = 4.80 Hz, 1H), 4.12-4.06 (m, 2H), 3.95-3.84 (m, 2H), 3.80-3.73 (m, 2H), 3.71(s, 3H), 2.54-2.32 (m, 1H), 2.42 (s, 3H), 0.98 (d, *J* = 6.57 Hz, 3H), 0.91 (d, *J* = 6.69 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.5, 163.9, 145.2, 131.9, 129.8, 127.8, 70.9, 68.8, 63.8, 63.2, 58.6, 52.3, 29.6, 21.4, 19.6, 19.3; ESI-MS: 441.43 $(M+H)^+$, 463.44 $(M+K)^+$; Anal. Calcd. for $C_{18}H_{24}N_4O_7S$: C, 49.08; H, 5.49; N, 12.72; Found: C, 48.92; H, 5.61; N, 12.51.

(S)-methyl 2-((2R,3R)-3-azido-2-((S)-1-hydroxy-2-(tosyloxy)ethyl)-4-oxoazetidin-1-yl)-4-methylpentanoate 10c:

The product **10c** was obtained as a viscous liquid. Yield: 1.72 g (88%); $[\alpha]^{25}_{D}$: +112° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3300, 2116, 1771, 1744, 1599, 1262, 768; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.34 Hz, 2H), 7.39 (d, *J* = 7.96 Hz, 2H), 4.62 (d, *J* = 5.05 Hz, 1H), 4.24-4.16 (m, 1H), 4.12-4.10 (m, 2H), 4.05-3.97 (m, 1H), 3.97 (q, 1H), 3.75 (s, 3H), 3.72-3.66 (m, 1H), 2.45 (s, 3H), 2.29-2.13 (m, 1H), 1.74-1.51 (m, 2H), 0.95 (d, *J* = 1.77 Hz, 3H), 0.92 (d, *J* = 1.39 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 164.1, 145.1, 131.8, 130.0, 127.9, 71.2, 68.5, 63.5, 58.9, 55.9, 52.8, 38.3, 25.0, 22.8, 21.6, 21.0; ESI-MS: 477.15 $(M+Na)^+$; Anal. Calcd. for $C_{19}H_{26}N_4O_7S$: C, 50.21; H, 5.77; N, 12.33; Found: C, 50.35; H, 5.95; N, 12.04.

(R)-methyl 2-((2R,3R)-3-azido-2-((S)-1-hydroxy-2-(tosyloxy)ethyl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 10d:

The product **10d** was obtained as a viscous liquid. Yield: 1.70 g (90%); $[\alpha]^{25}_{D}$: +124° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3420, 2114, 1772, 1764, 1738, 1641, 1216, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.80-7.75 (m, 2H), 7.38-7.20 (m, 7H), 4.80-4.72 (m, 1H), 4.29 (d, *J* = 4.80 Hz, 1H), 4.04- 4.03 (m, 2H), 3.81-3.77 (m, 1H), 3.75 (s, 3H), 3.73-3.70 (m, 2H), 3.43-3.18 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.5, 164.9, 145.2, 135.9, 131.8, 129.8, 128.6, 128.4, 127.8, 127.0, 70.4, 68.4, 63.3, 57.3, 56.1, 52.8, 34.4, 21.4; ESI-MS: 511.39

$(M+Na)^+$, 527.33 $(M+K)^+$; Anal. Calcd. for $C_{22}H_{24}N_4O_7S$: C, 54.09; H, 4.95; N, 11.47; Found: C, 53.91; H, 5.08; N, 11.59.

General procedure for the preparation of the β-lactam foldamer building blocks 11a-d:

Representative procedure: To a solution of **10a-d** (1 equiv) in ethyl acetate, 10% Pd-C, Et_3N (1.2 equiv) and Boc anhydride (1.1 equiv) were added. The reaction mixture was hydrogenated at 60 psi for 4 h. The reaction mixture was filtered over celite pad and washed several times with ethyl acetate. The combined ethyl acetate washings were washed sequentially with saturated $KHSO_4$, and brine solutions and the organic layer was separated and dried over dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get crude **11a-d**, which were then purified by column chromatography.

(1R,4R,5R)-tert-butyl 4-hydroxy-6-((S)-1-methoxy-1-oxopropan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 11a:

The product **11a** was obtained as a white solid. Yield: 0.99 g (94%); mp: 143-145 °C; $[\alpha]^{25}_D$: +180° (*c* = 0.7, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3368, 1752, 1733, 1684, 1655, 1420, 1024; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.20 (bs, 1H), 4.45 (q, 1H), 4.30 (d, *J* = 3.02 Hz, 1H), 4.28 (d, *J* = 3.51 Hz, 1H), 4.02-3.99 (m, 1H), 3.74 (s, 3H), 3.52 (dd, *J* = 3.26 Hz, 13.05 Hz, 1H), 3.16 (bs, 1H), 1.49 (d, *J* = 7.45 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 165.3, 165.3, 154.1, 81.0, 69.8, 67.5, 63.6, 52.6, 52.4, 49.9, 28.2, 16.6; ESI-MS: 315.33 $(M+H)^+$, 337.29 $(M+Na)^+$, 353.28 $(M+K)^+$; Anal. Calcd. for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91; Found: C, 53.57; H, 6.99; N, 9.09.

(1R,4R,5R)-tert-butyl 4-hydroxy-6-((S)-1-methoxy-3-methyl-1-oxobutan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 11b:

The product **11b** was obtained as a white solid. Yield: 1.03 g (96%); mp: 76-78 °C; $[\alpha]^{25}_D$: +110° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 1740, 1697, 1416, 1165, 756; ^1H NMR (200 MHz, $CDCl_3$) δ: 5.12 (bs, 1H), 4.31 (bs, 1H), 4.23 (d, *J* = 3.92 Hz, 1H), 4.02-3.92 (m, 2H), 3.71 (s, 3H), 3.61 (bs, 1H), 3.51 (dd, *J* = 3.54 Hz, 13.01 Hz, 1H), 2.24-2.06 (m, 1H), 1.43 (s, 9H), 0.98 (d, *J* = 6.69 Hz, 3H), 0.92 (d, *J* = 6.70 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.7, 166.0, 153.9, 80.8, 69.2, 67.2, 64.8, 61.5, 52.6, 52.0, 30.0, 28.1, 19.5, 19.1; ESI-MS:

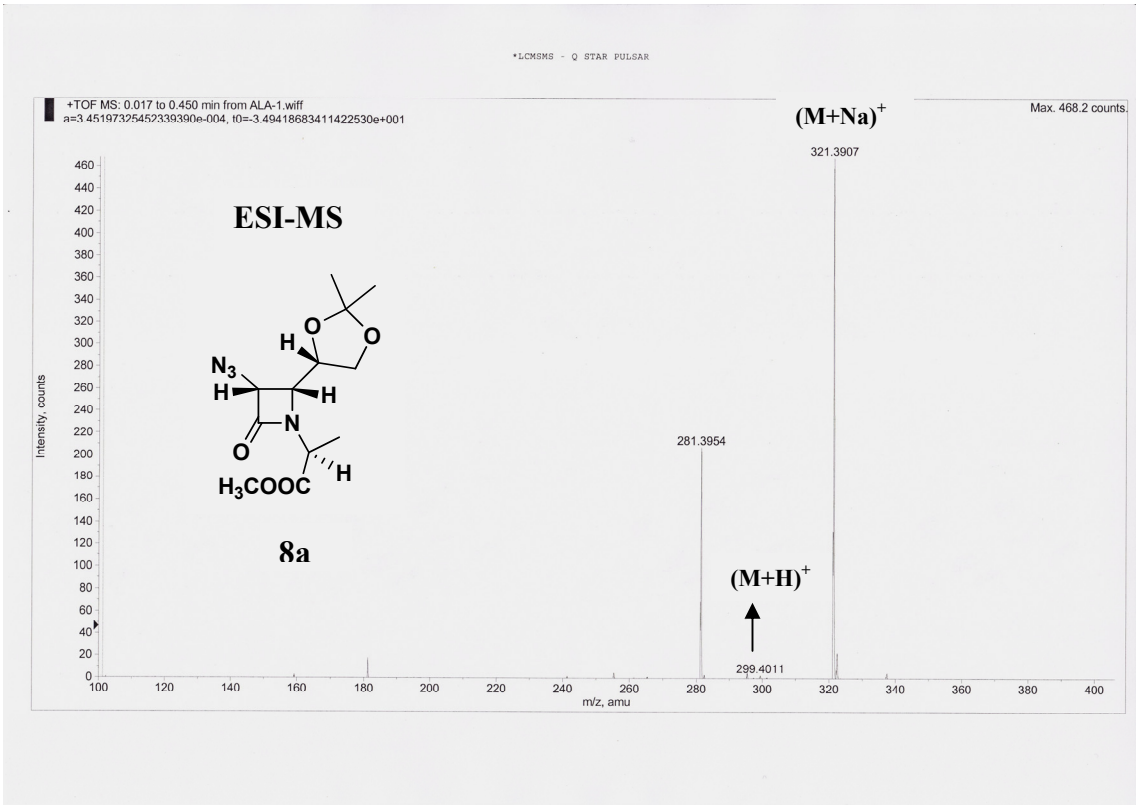
343.54 $(M+H)^+$, 365.47 $(M+Na)^+$, 381.47 $(M+K)^+$; Anal. Calcd. for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18; Found: C, 55.97; H, 7.84; N, 8.28.

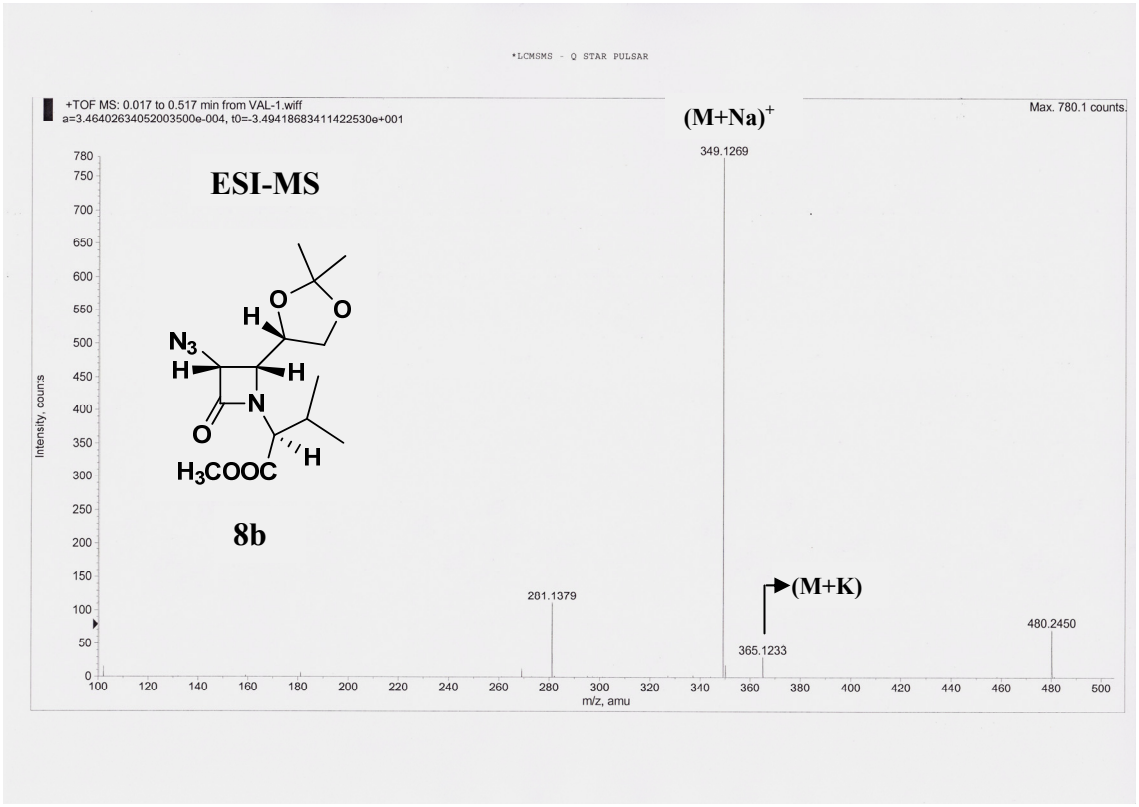
(1R,4R,5R)-tert-butyl 4-hydroxy-6-((S)-1-methoxy-4-methyl-1-oxopentan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 11c:

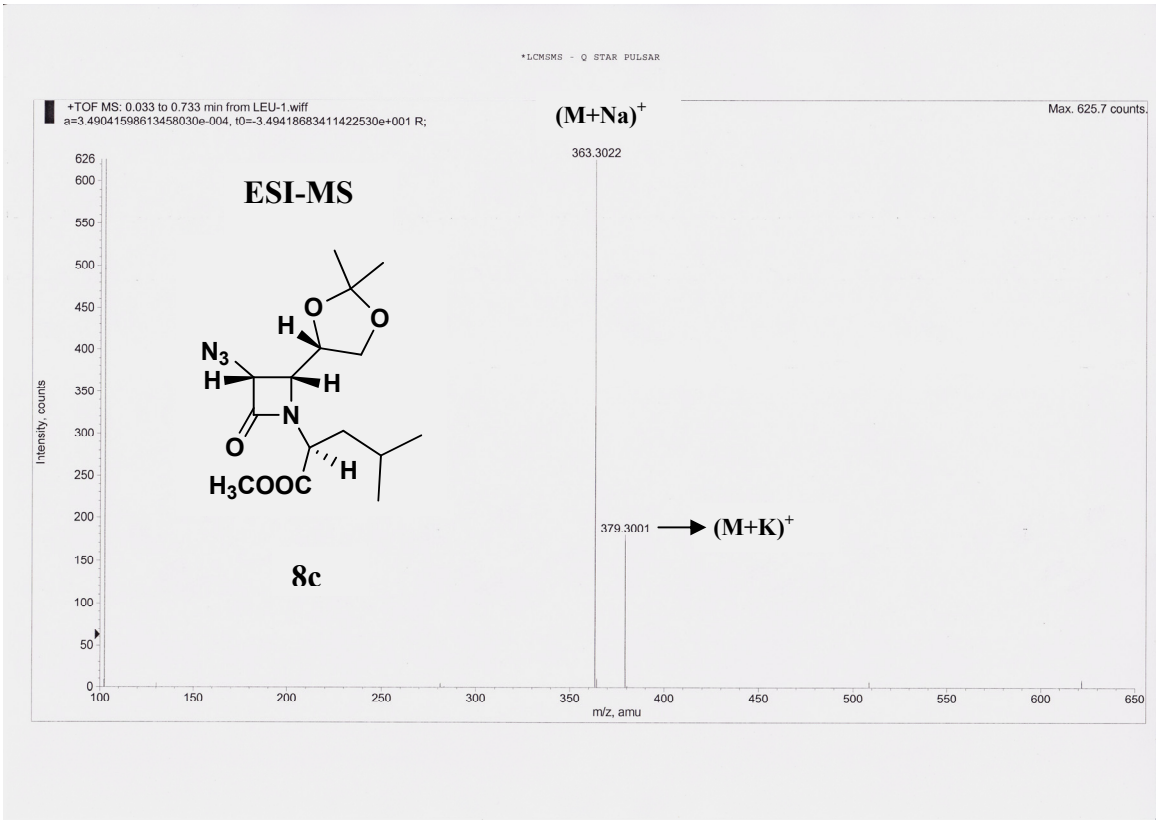
The product **11c** was obtained as a white solid. Yield: 1.03 g (95%); mp: 66-68 °C; $[\alpha]^{25}_D$: +125° (*c* = 0.8, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 1763, 1742, 1685, 1420, 1216, 757; ^1H NMR (200 MHz, $CDCl_3$) δ: 5.24 (bs, 1H), 4.41 (d, *J* = 7.58 Hz, 1H), 4.33-4.27 (m, 2H), 4.07 (d, *J* = 12.89 Hz, 1H), 3.75 (s, 3H), 3.57 (dd, *J* = 3.53 Hz, 13.01 Hz, 1H), 2.49 (bs, 1H), 1.80-1.53 (m, 3H), 1.48 (s, 9H), 0.98 (d, *J* = 0.76 Hz, 3H), 0.94 (d, *J* = 0.69 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.6, 165.8, 153.9, 80.7, 69.1, 67.1, 64.0, 53.0, 52.5, 52.3, 39.0, 28.0, 24.7, 22.5, 21.1; ESI-MS: 379.46 $(M+Na)^+$, 395.46 $(M+K)^+$; Anal. Calcd. for $C_{17}H_{28}N_2O_6$: C, 57.29; H, 7.92; N, 7.86; Found: C, 57.37; H, 7.88; N, 7.74.

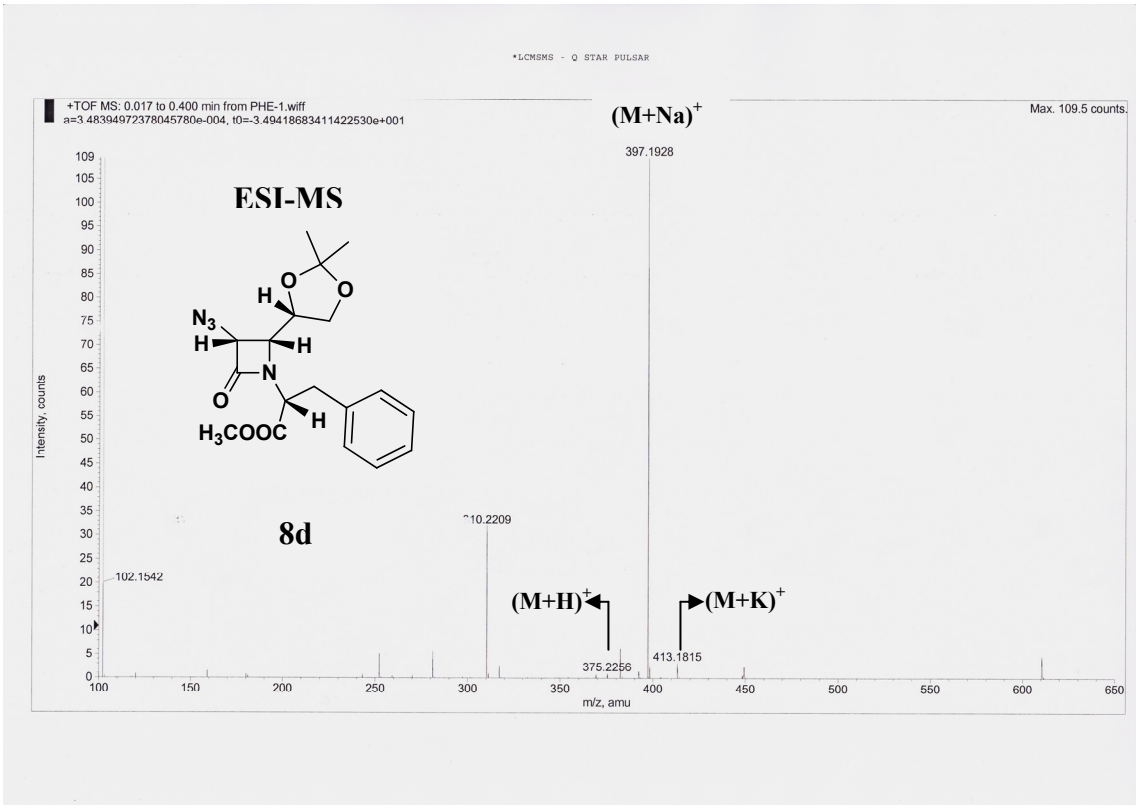
(1R,4R,5R)-tert-butyl 4-hydroxy-6-((R)-1-methoxy-1-oxo-3-phenylpropan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 11d:

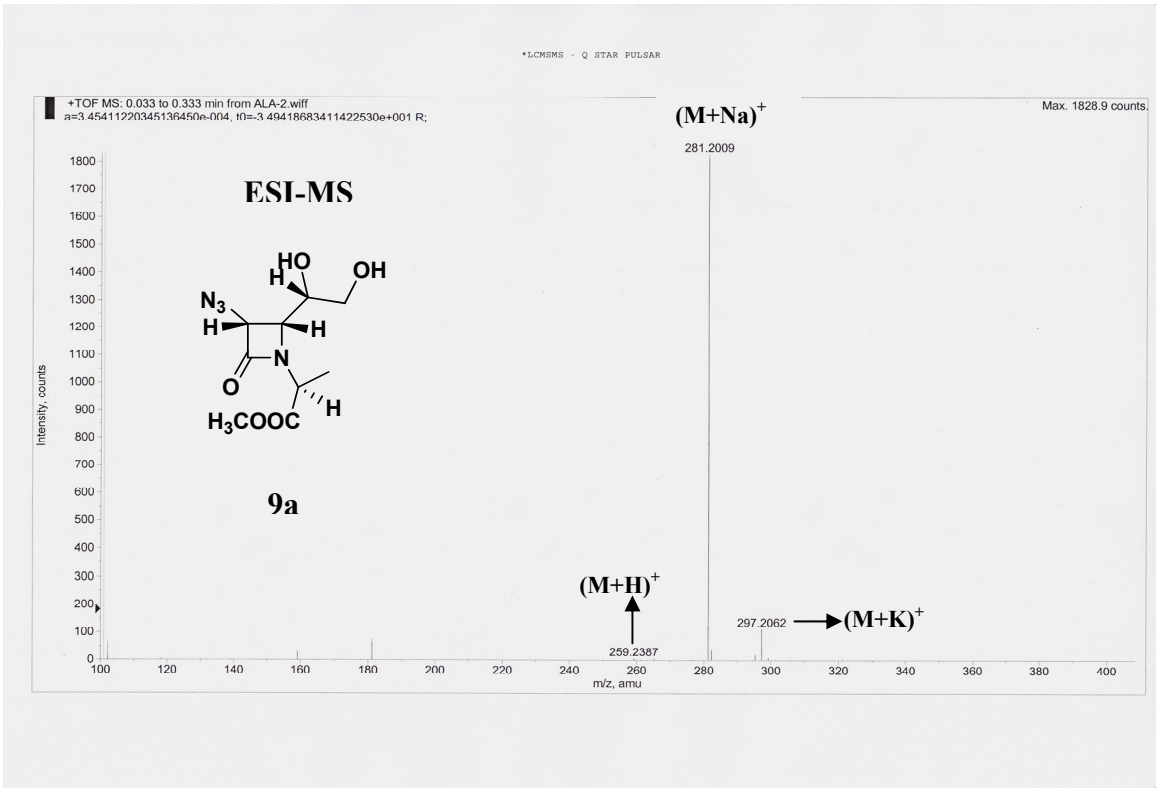
The product **11d** was obtained as a white solid. Yield: 0.94 g (93%); mp: 122-124 °C; $[\alpha]^{25}_D$: +190° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3443, 1764, 1744, 1644, 1216, 772; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.35-7.19 (m, 5H), 5.00 (bs,1H), 4.50-4.42 (m, 1H), 4.05 (d, *J* = 3.28 Hz, 1H), 4.00 (d, *J* = 3.54 Hz, 1H), 3.79-3.74 (m, 1H), 3.74 (s, 3H), 3.37-3.14 (m, 3H), 3.08-3.00 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$,) δ: 170.2, 165.8, 153.9, 136.1, 128.7, 128.4, 127.7, 80.7, 68.9, 67.0, 63.4, 56.4, 52.6, 52.4, 35.0, 28.1; ESI-MS: 413.31 $(M+Na)^+$, 429.31 $(M+K)^+$; Anal. Calcd. for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18; Found: C, 61.38; H, 6.90; N, 6.99.

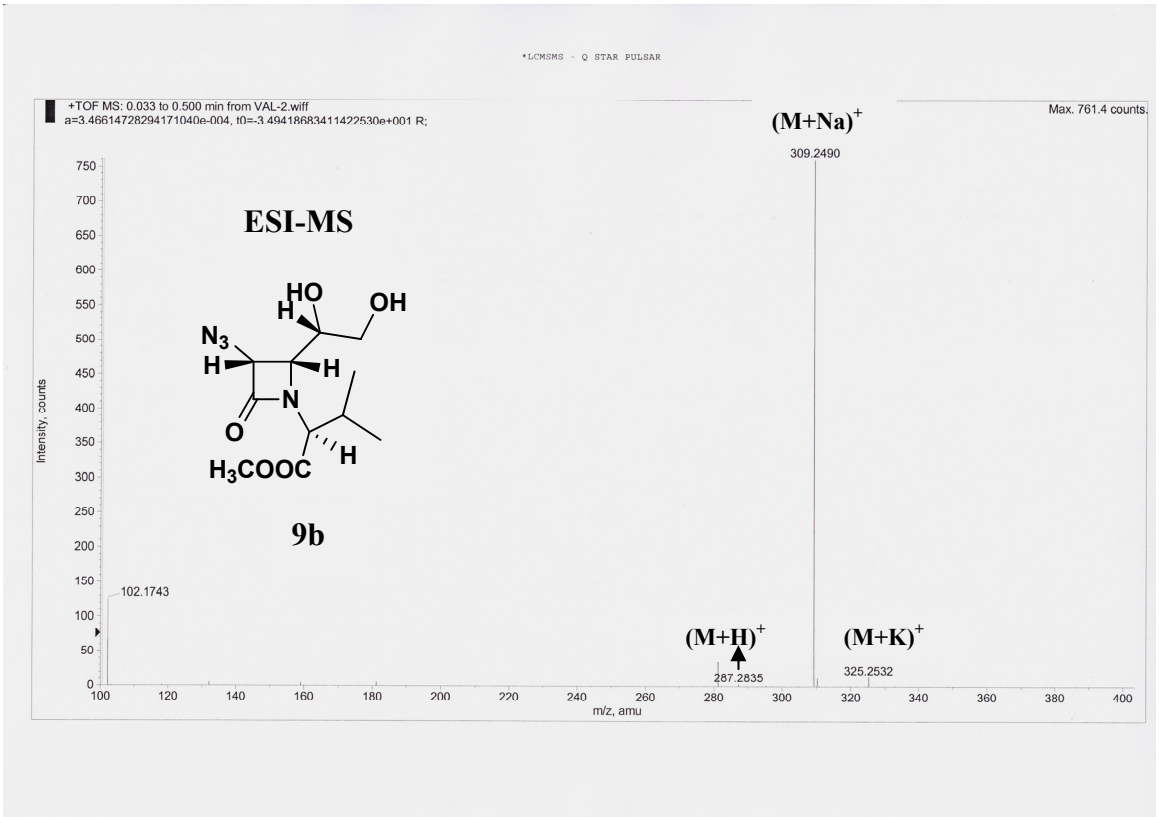

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.450 min from ALA-1.wiff
Max. 468.2 counts.
(M+Na)+
321.3907
ESI-MS
281.3954
(M+H)+
299.4011
8a
Intensity, counts
m/z, amu

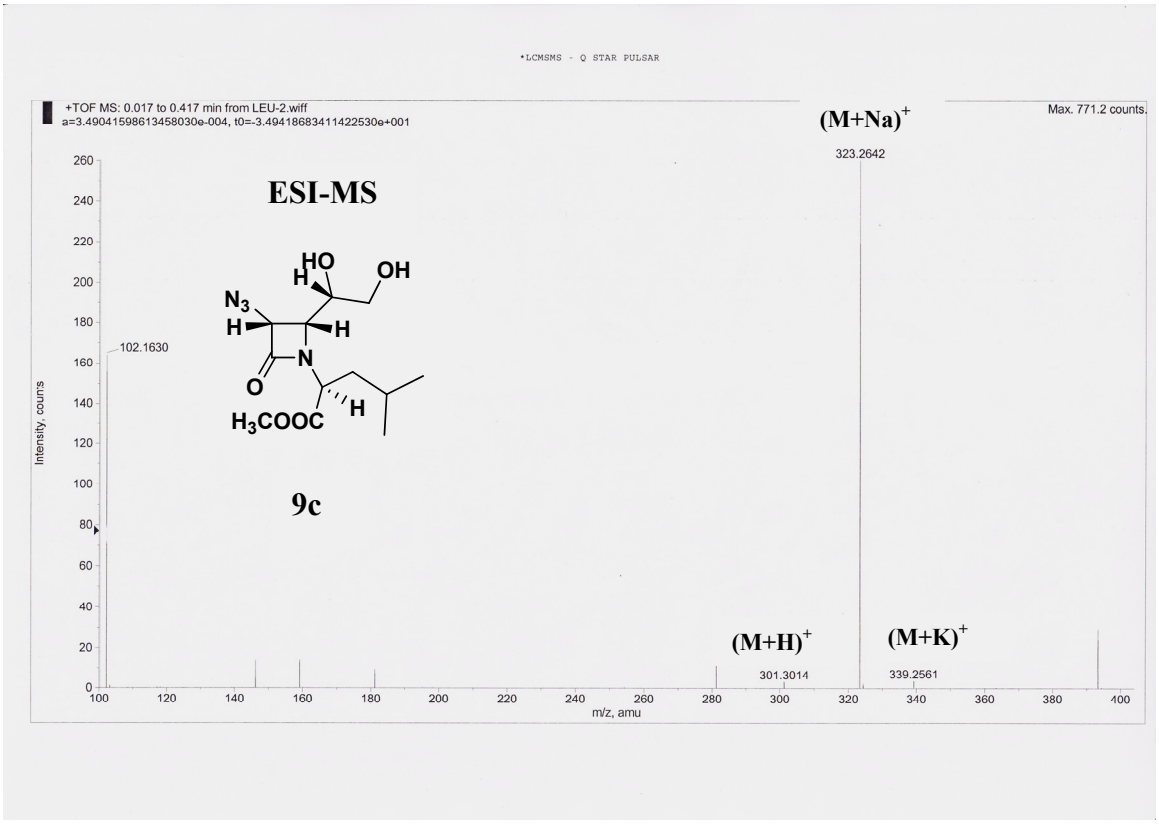

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.517 min from VAL-1.wiff
Max. 780.1 counts.
(M+Na)+
349.1269
ESI-MS
(M+K)
281.1379
365.1233
480.2450
8b
Intensity, counts
m/z, amu

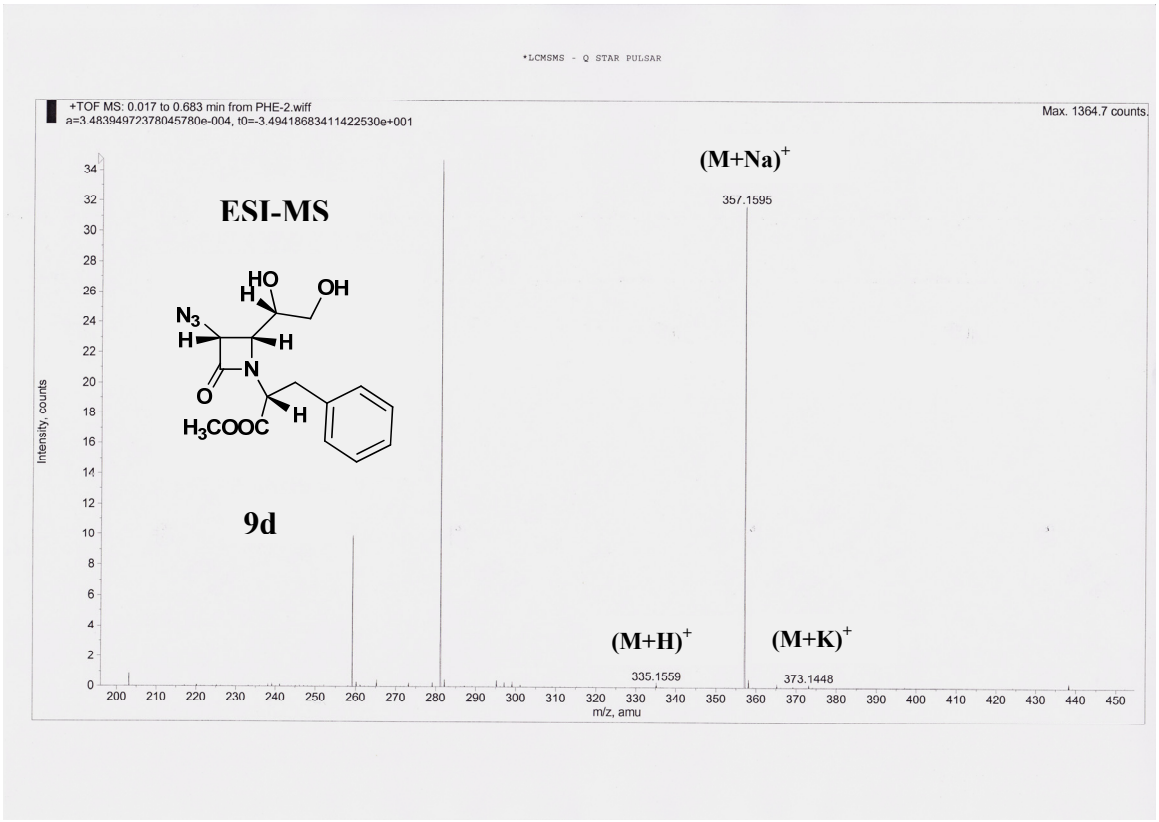

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.733 min from LEU-1.wiff
a=3.490415986134580 30e-004, t0=-3.494186834114225 30e+001 R;
(M+Na)+
Max. 625.7 counts.
363.3022
ESI-MS
379.3001
(M+K)+
8c
Intensity, counts
m/z, amu

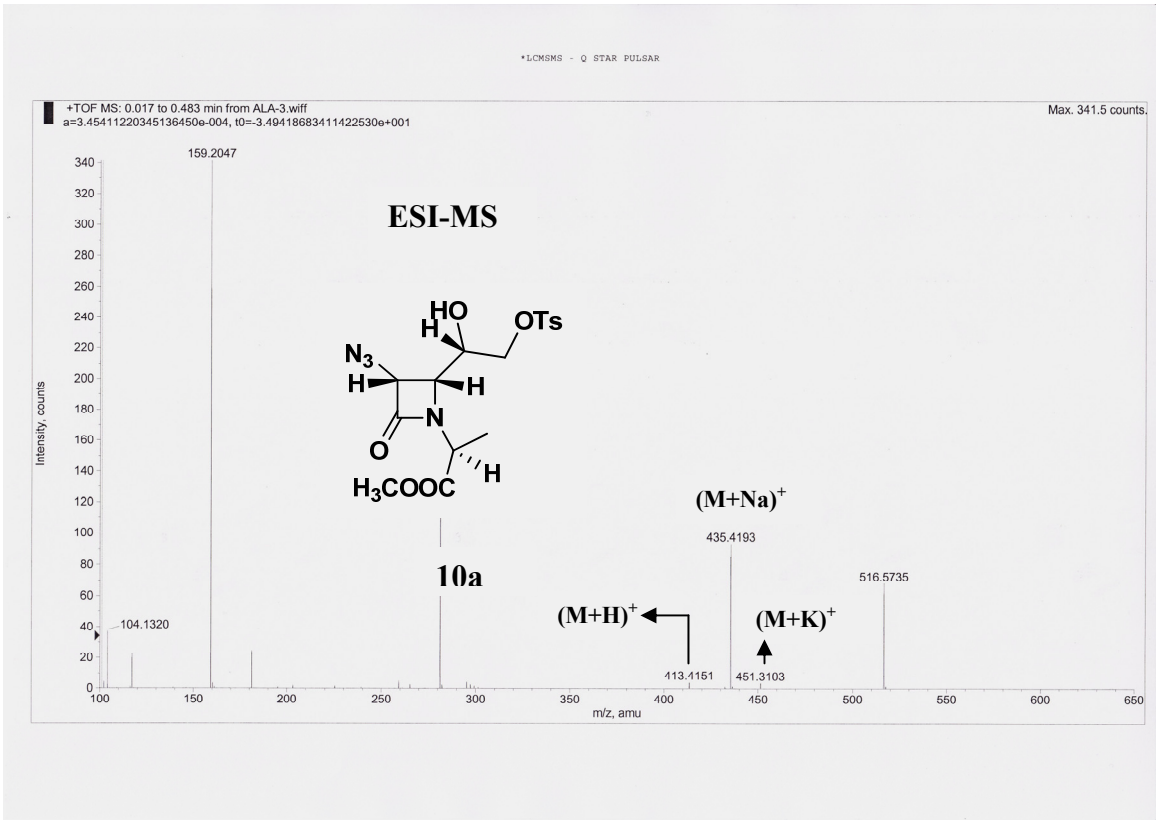

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.400 min from PHE-1.wiff
a=3.483949723780457 80e-004, t0=-3.494186834114225 30e+001
(M+Na)+
Max. 109.5 counts.
397.1928
ESI-MS
210.2209
102.1542
(M+H)+
(M+K)+
375.2256
413.1815
8d
Intensity, counts
m/z, amu

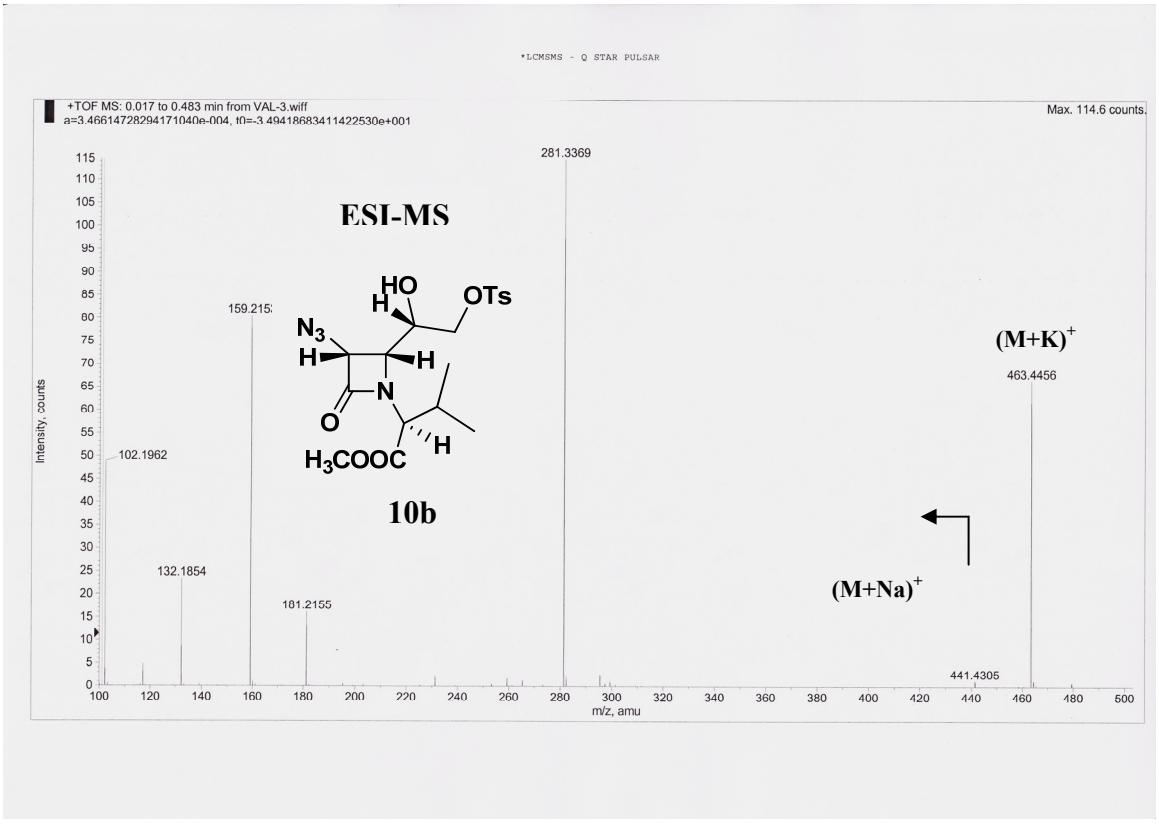

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.333 min from ALA-2.wiff
Max. 1828.9 counts.
(M+Na)+
281.2009
ESI-MS
HO
OH
H
N3
H
H
N
O
H
H3COOC
9a
(M+H)+
259.2387
297.2062
(M+K)+
Intensity, counts
m/z, amu

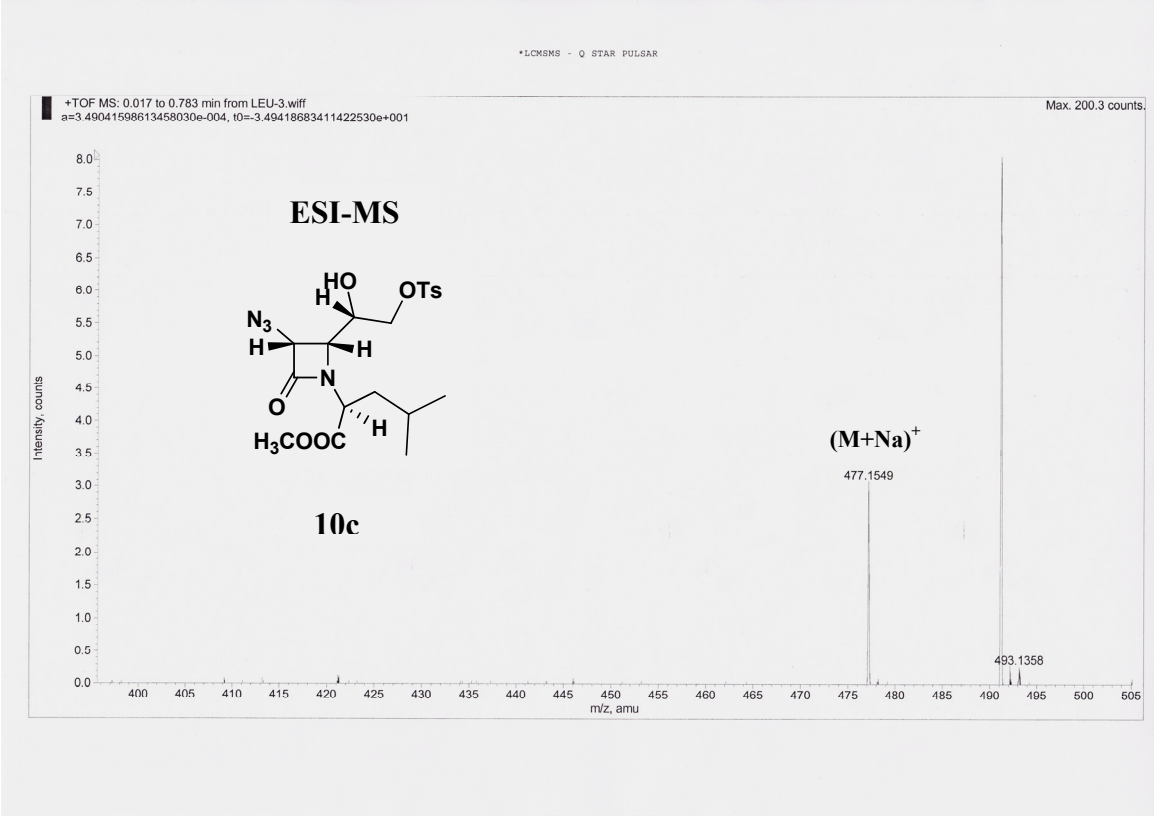

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.500 min from VAL-2.wiff
Max. 761.4 counts.
(M+Na)+
309.2490
ESI-MS
HO
OH
H
N3
H
H
N
O
H
H3COOC
9b
102.1743
(M+H)+
287.2835
(M+K)+
325.2532
Intensity, counts
m/z, amu

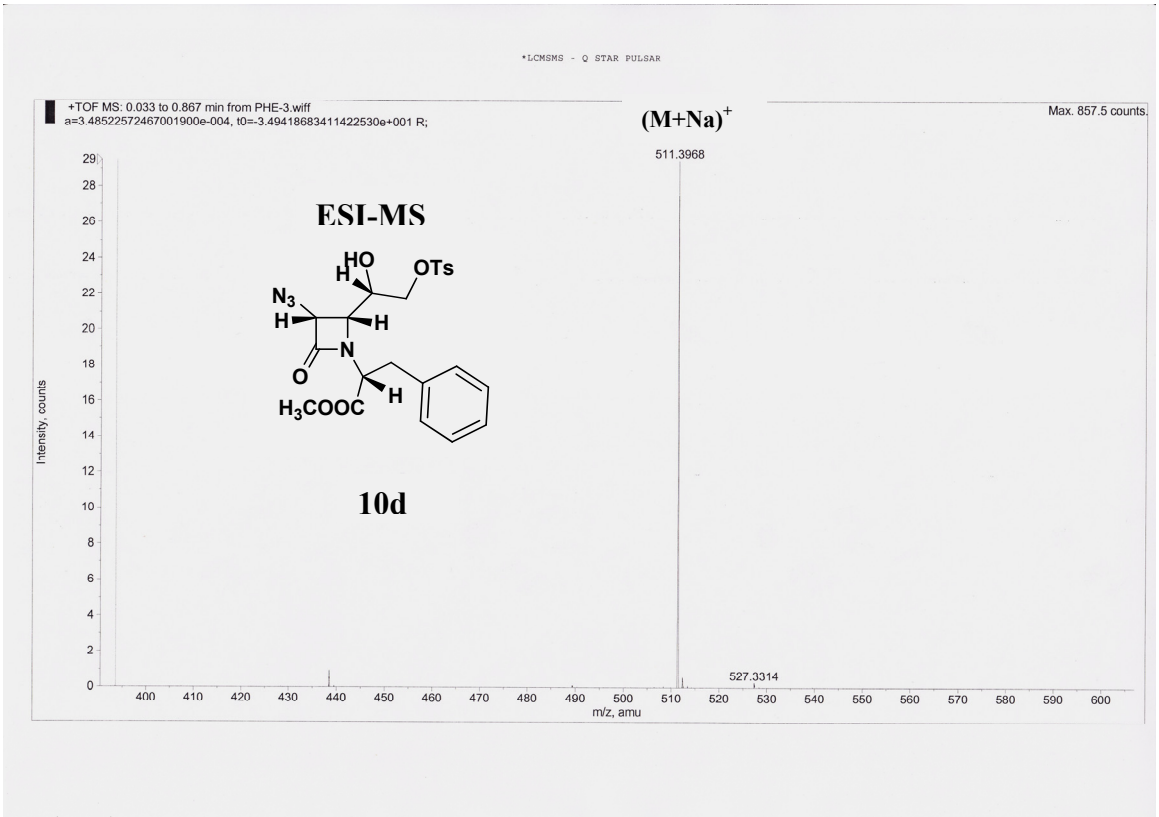

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.417 min from LEU-2.wiff
a=3.49041598613458030e-004, t0=-3.49418683411422530e+001
Max. 771.2 counts.
ESI-MS
(M+Na)+
323.2642
102.1630
(M+H)+
301.3014
(M+K)+
339.2561
Intensity, counts
m/z, amu
9c

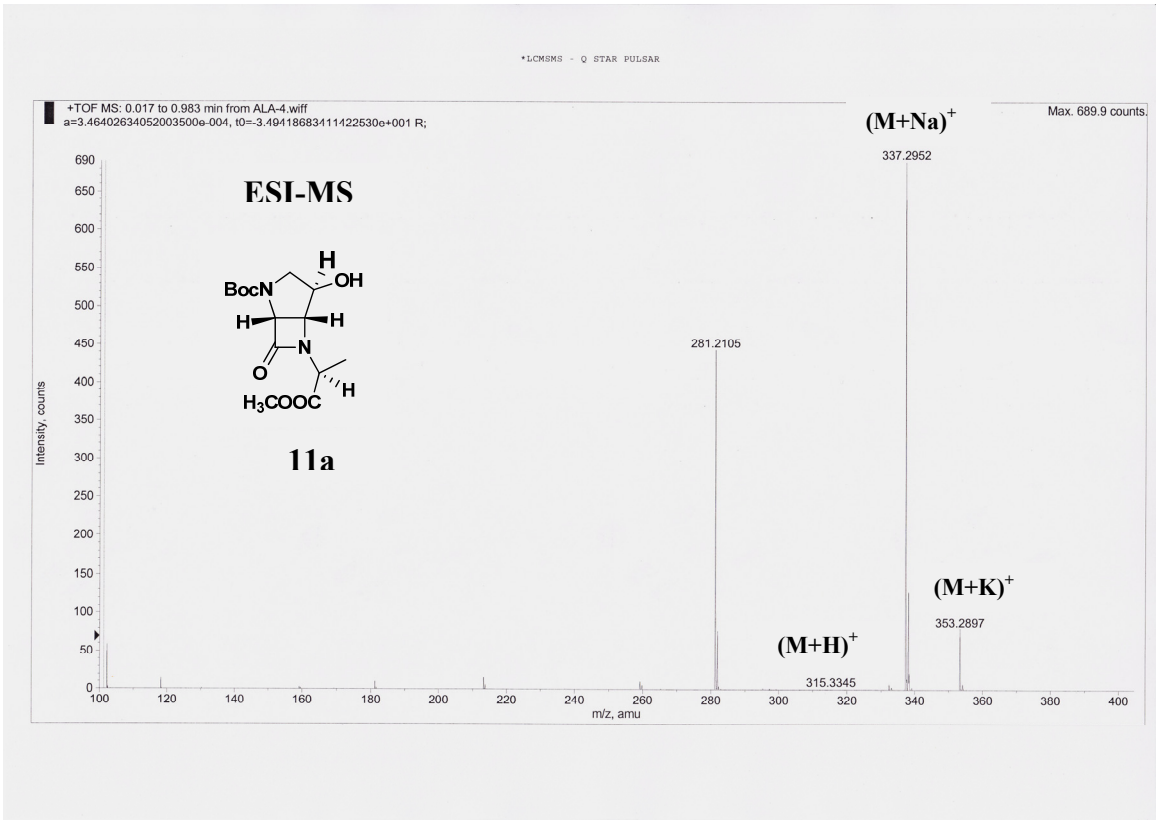

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.683 min from PHE-2.wiff
Max. 1364.7 counts.
ESI-MS
(M+Na)+
357.1595
(M+H)+
335.1559
(M+K)+
373.1448
Intensity, counts
m/z, amu
9d

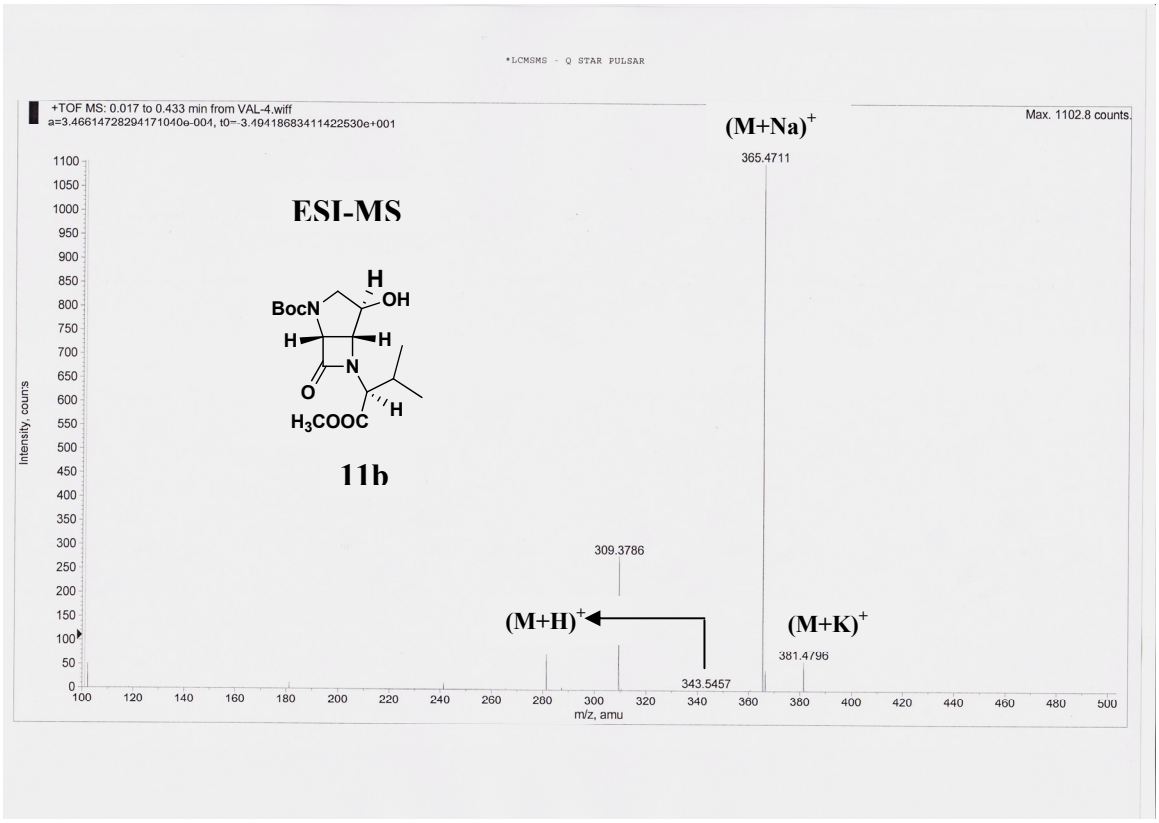

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.483 min from ALA-3.wiff
a=3.45411220345136450e-004, t0=-3.49418683411422530e+001
Max. 341.5 counts.
ESI-MS
159.2047
HO
H
OTs
N3
H
H
N
O
H
H3COOC
10a
(M+Na)+
435.4193
516.5735
(M+H)+
(M+K)+
104.1320
413.4151
451.3103
Intensity counts
m/z, amu

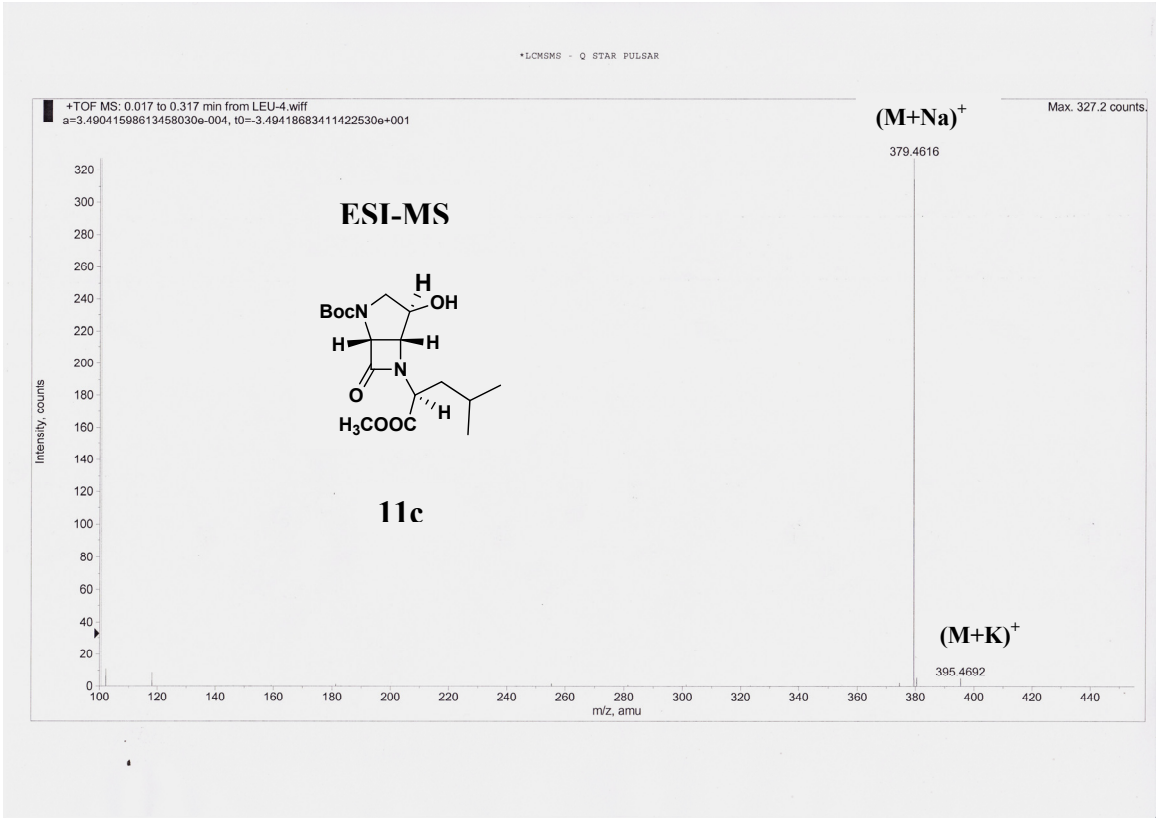

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.483 min from VAL-3.wiff
a=3.46614728294171040e-004, t0=-3.49418683411422530e+001
Max. 114.6 counts.
281.3369
ESI-MS
159.215
HO
H
OTs
N3
H
H
N
O
H
H3COOC
10b
(M+K)+
463.4456
102.1962
132.1854
181.2155
(M+Na)+
441.4305
Intensity, counts
m/z, amu

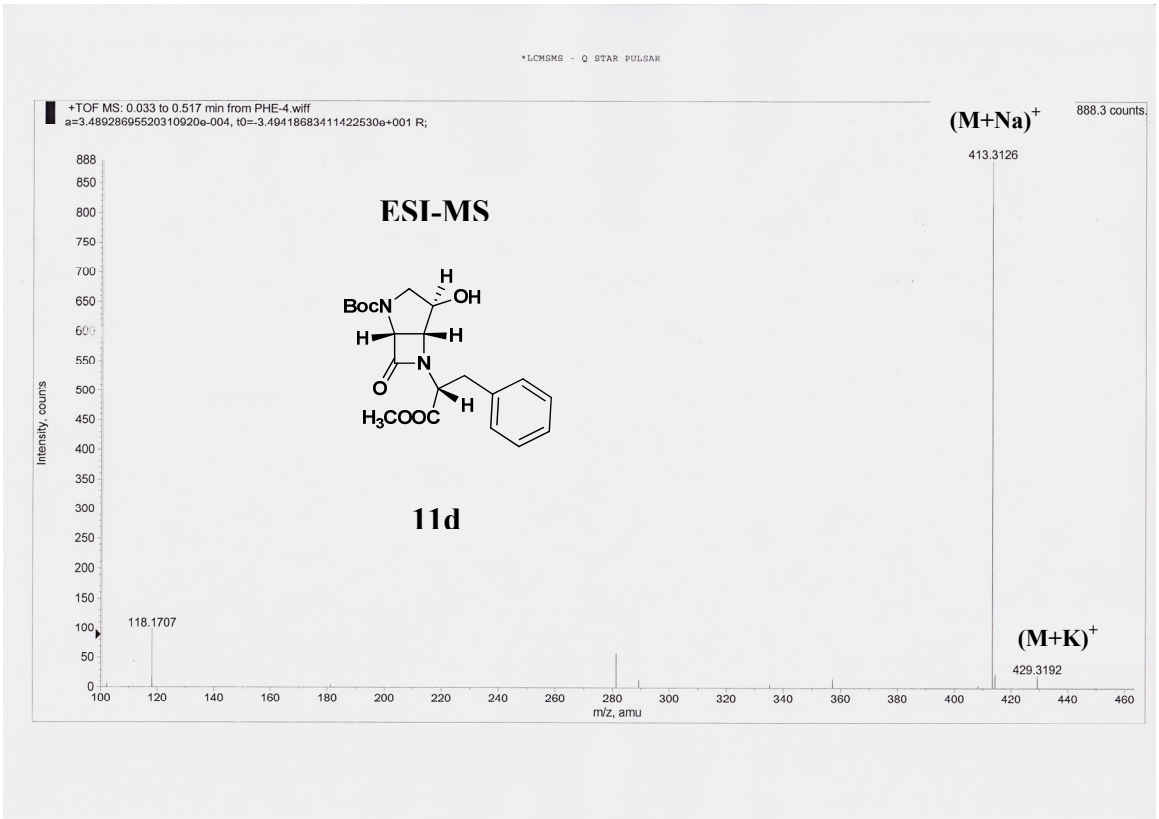

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.783 min from LEU-3.wiff
a=3.49041598613458030e-004, t0=-3.49418683411422530e+001
Max. 200.3 counts.
ESI-MS
HO
H
OTs
N3
H
H
N
O
H3COOC
H
10c
(M+Na)+
477.1549
493.1358
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.867 min from PHE-3.wiff
a=3.48522572467001900e-004, t0=-3.49418683411422530e+001 R;
(M+Na)+
Max. 857.5 counts.
511.3968
ESI-MS
HO
H
OTs
N3
H
H
N
O
H3COOC
H
10d
527.3314
Intensity, counts
m/z, amu

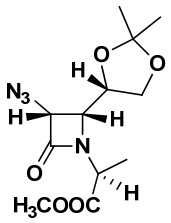

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.983 min from ALA-4.wiff
a=3.46402634052003500e-004, t0=-3.49418683411422530e+001 R;
Max. 689.9 counts.
ESI-MS
11a
(M+Na)+
337.2952
281.2105
(M+K)+
353.2897
(M+H)+
315.3345
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.433 min from VAL-4.wiff
a=3.46614728294171040e-004, t0=-3.49418683411422530e+001
Max. 1102.8 counts.
ESI-MS
11b
(M+Na)+
365.4711
309.3786
(M+H)+
(M+K)+
381.4796
343.5457
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.317 min from LEU-4.wiff
a=3.49041598613458030e-004, t0=-3.49418683411422530e+001
Max. 327.2 counts.
(M+Na)+
379.4616
ESI-MS
BocN
H
OH
H
H
N
O
H3COOC
H
11c
(M+K)+
395.4692
Intensity counts
m/z, amu

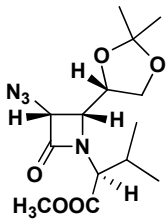

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.033 to 0.517 min from PHE-4.wiff
a=3.48928695520310920e-004, t0=-3.49418683411422530e+001 R;
888.3 counts.
(M+Na)+
413.3126
ESI-MS
BocN
H
OH
H
H
N
O
H3COOC
H
11d
118.1707
(M+K)+
429.3192
Intensity, counts
m/z, amu

^{1}H NMR (200 MHz, $CDCl_3$)

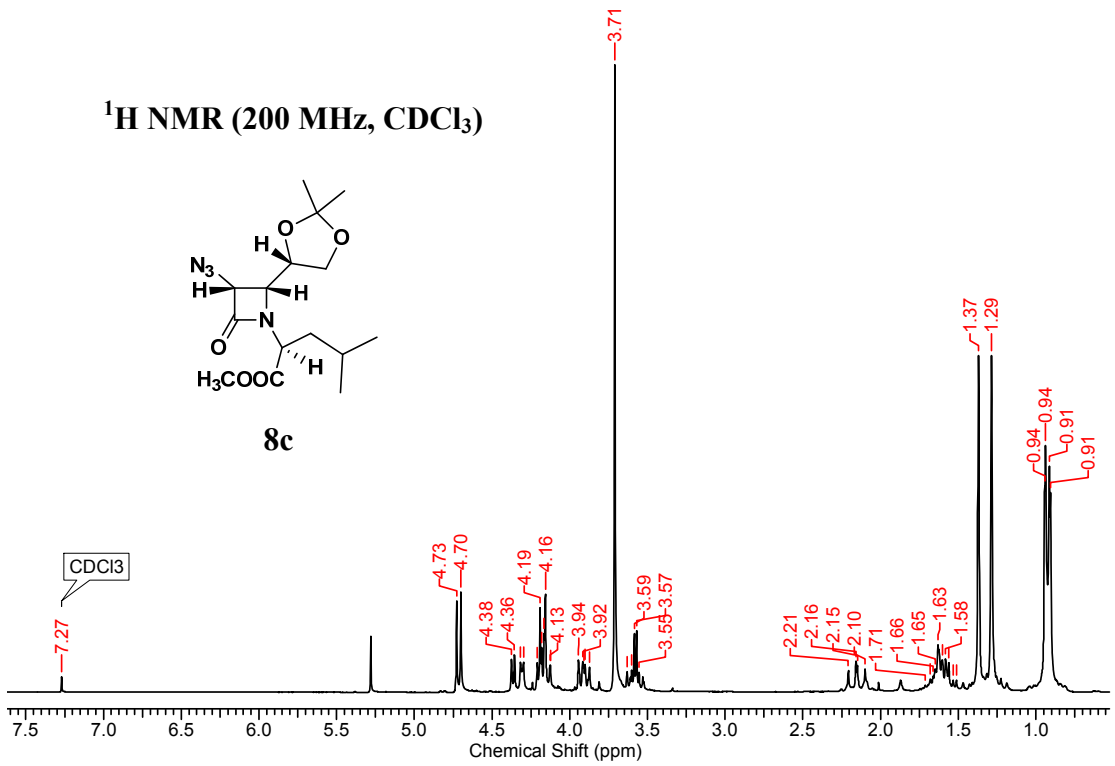


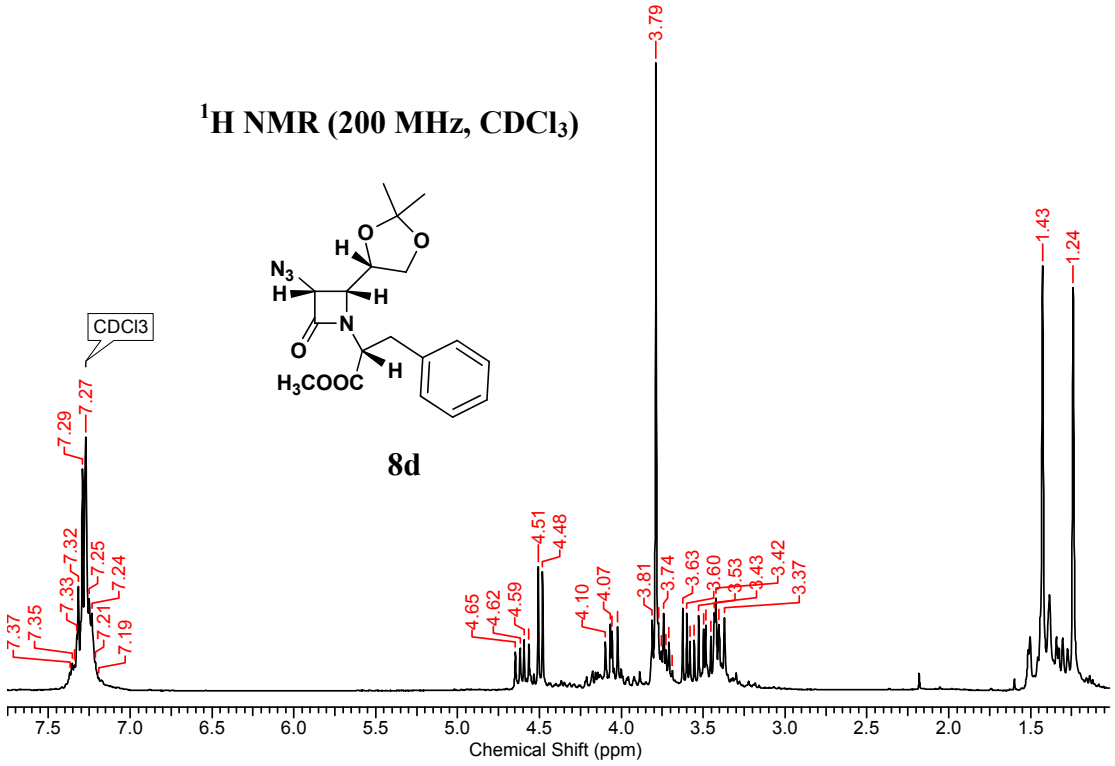
8a

^{1}H NMR (200 MHz, $CDCl_3$)

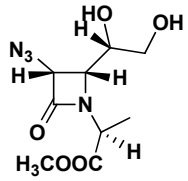


8b


^{1}H NMR (200 MHz, CDCl$_3$)
8c
CDCl3
7.27
4.73
4.70
4.38
4.36
4.19
4.16
4.13
3.94
3.92
3.71
3.59
3.55
3.57
2.21
2.16
2.15
2.10
1.71
1.66
1.65
1.63
1.58
1.37
1.29
0.94
0.94
0.91
0.91
Chemical Shift (ppm)

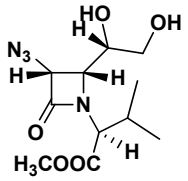

^{1}H NMR (200 MHz, CDCl$_3$)
8d
CDCl3
7.37
7.35
7.33
7.32
7.29
7.27
7.25
7.24
7.21
7.19
4.65
4.62
4.59
4.51
4.48
4.10
4.07
3.81
3.79
3.74
3.63
3.60
3.53
3.43
3.42
3.37
1.43
1.24
Chemical Shift (ppm)

^{1}H NMR (200 MHz, $CDCl_3$)



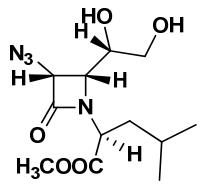
9a

^{1}H NMR (200 MHz, $CDCl_3$)



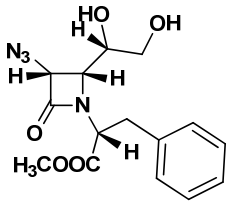
9b

^{1}H NMR (200 MHz, $CDCl_3$)

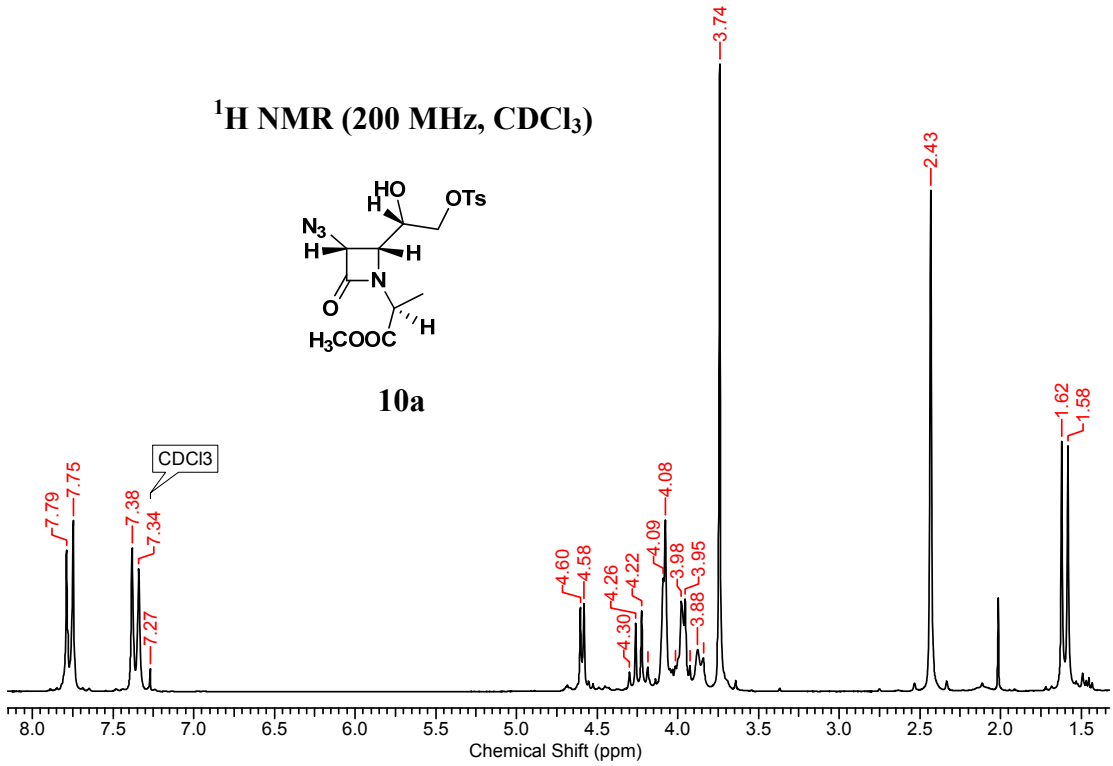


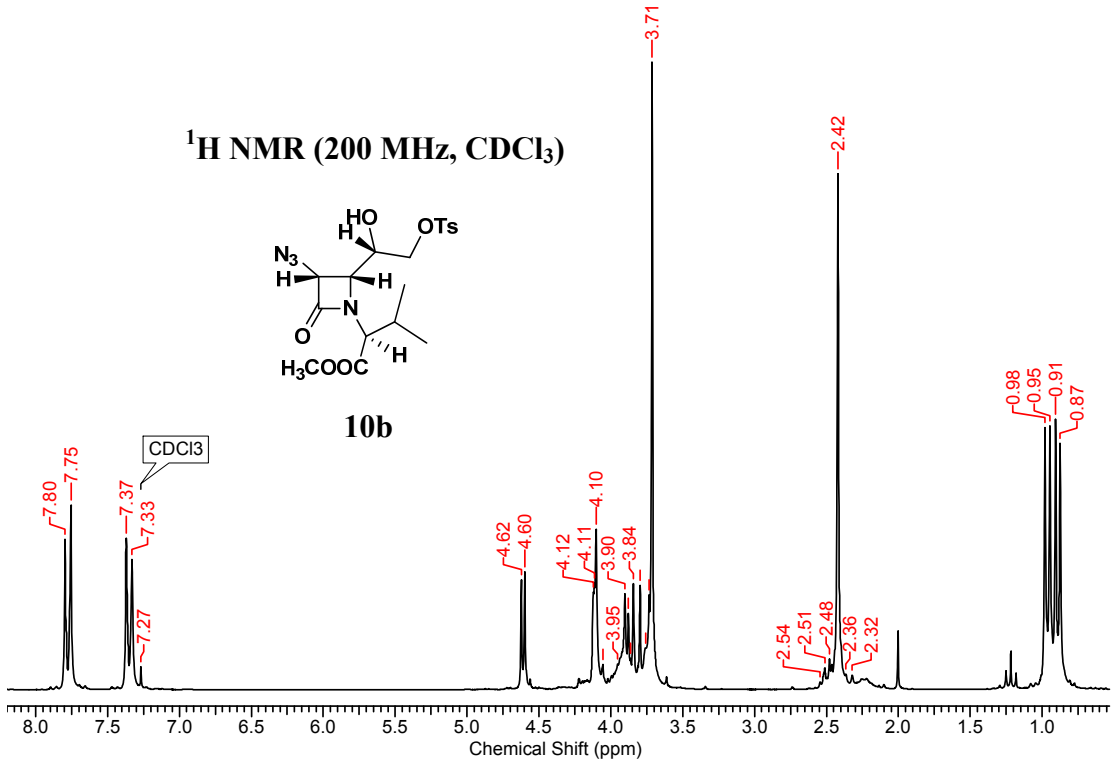
9c

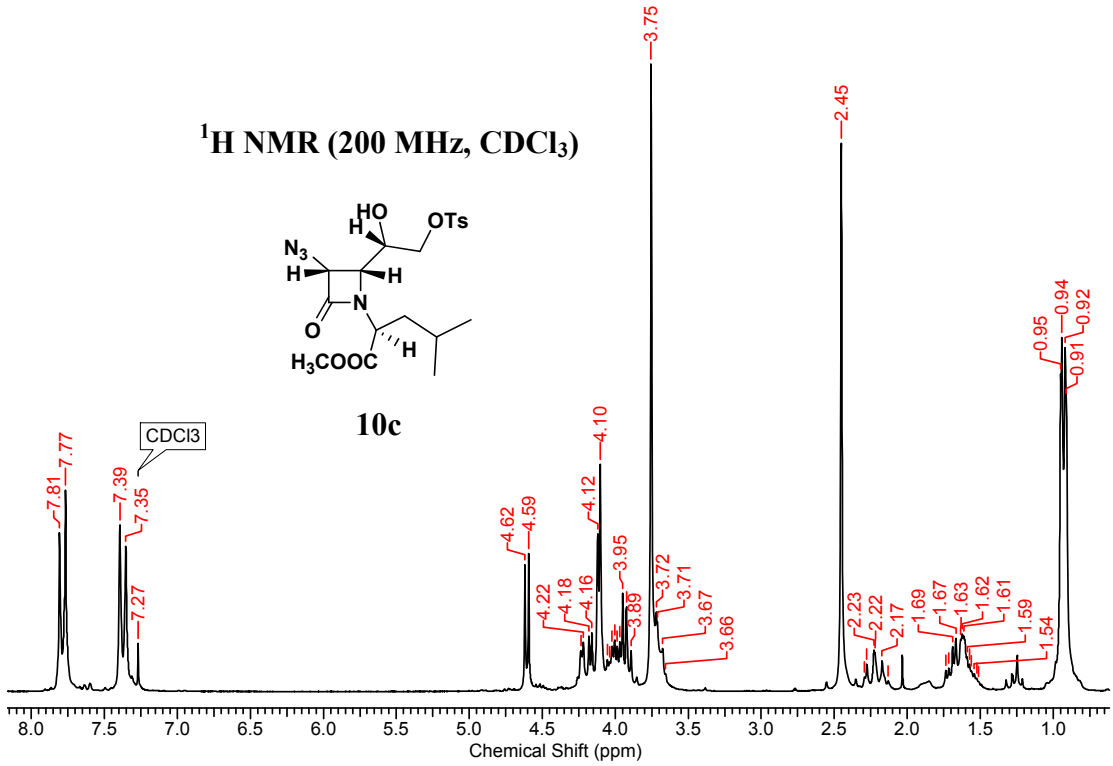
^{1}H NMR (200 MHz, $CDCl_3$)

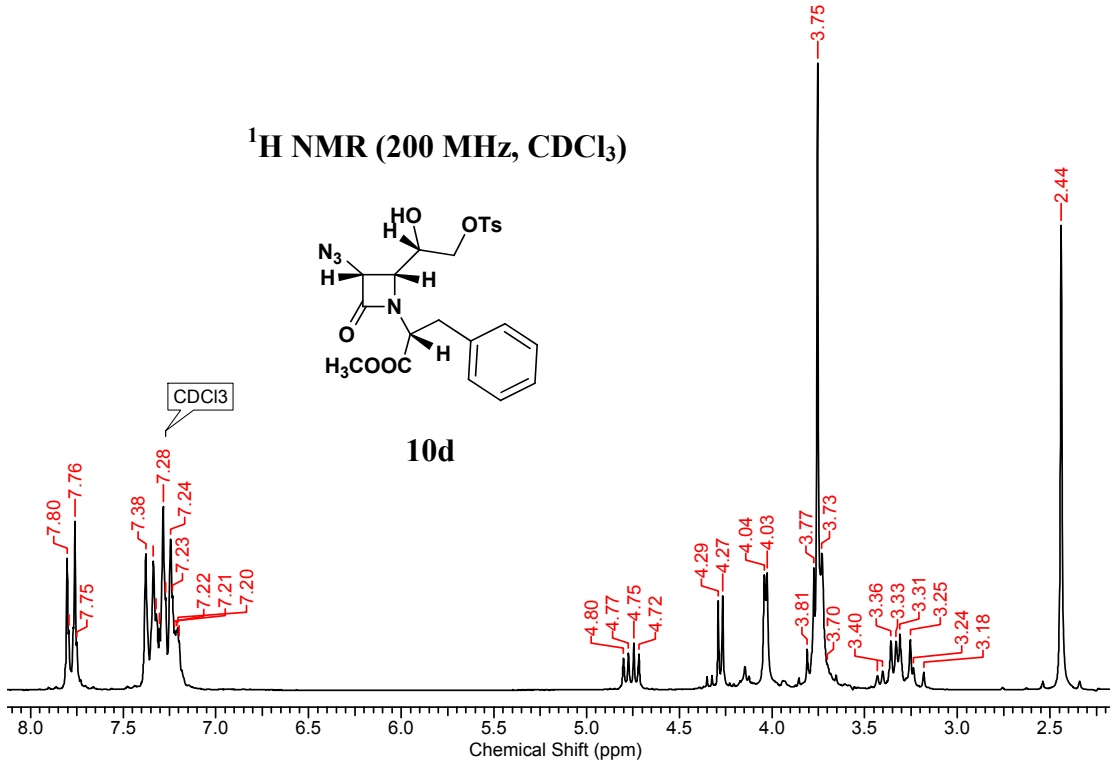


9d

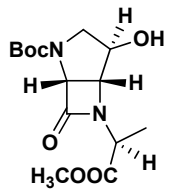

1H NMR (200 MHz, CDCl3)
HO
H
OTs
N3
H
H
N
O
H3COOC
H
10a
CDCl3
7.79
7.75
7.38
7.34
7.27
4.60
4.58
4.26
4.22
4.30
4.09
4.08
3.98
3.95
3.88
3.74
2.43
1.62
1.58
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


1H NMR (200 MHz, CDCl3)
HO
H
OTs
N3
H
H
N
O
H3COOC
H
10b
CDCl3
7.80
7.75
7.37
7.33
7.27
4.62
4.60
4.12
4.11
4.10
3.95
3.90
3.84
3.71
2.54
2.51
2.48
2.42
2.36
2.32
0.98
0.95
0.91
0.87
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
Chemical Shift (ppm)


^{1}H NMR (200 MHz, CDCl$_3$)
HO
H
OTs
N$_3$
H
H
N
O
H$_3$COOC
H
10c
CDCl3
7.81
7.77
7.39
7.35
7.27
4.62
4.59
4.22
4.18
4.16
4.12
4.10
3.95
3.89
3.75
3.72
3.71
3.67
3.66
2.45
2.23
2.22
2.17
1.69
1.67
1.63
1.62
1.61
1.59
1.54
0.95
0.94
0.92
0.91
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
Chemical Shift (ppm)

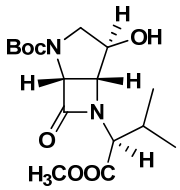

^{1}H NMR (200 MHz, CDCl$_3$)
HO
H
OTs
N$_3$
H
H
N
O
H$_3$COOC
H
10d
CDCl3
7.80
7.76
7.75
7.38
7.28
7.24
7.23
7.22
7.21
7.20
4.80
4.77
4.75
4.72
4.29
4.27
4.04
4.03
3.81
3.77
3.75
3.73
3.70
3.40
3.36
3.33
3.31
3.25
3.24
3.18
2.44
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



11a

^{1}H NMR (200 MHz, $CDCl_3$)



11b

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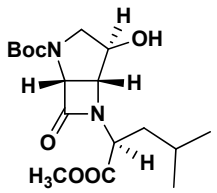
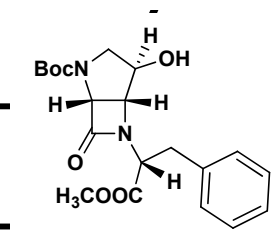
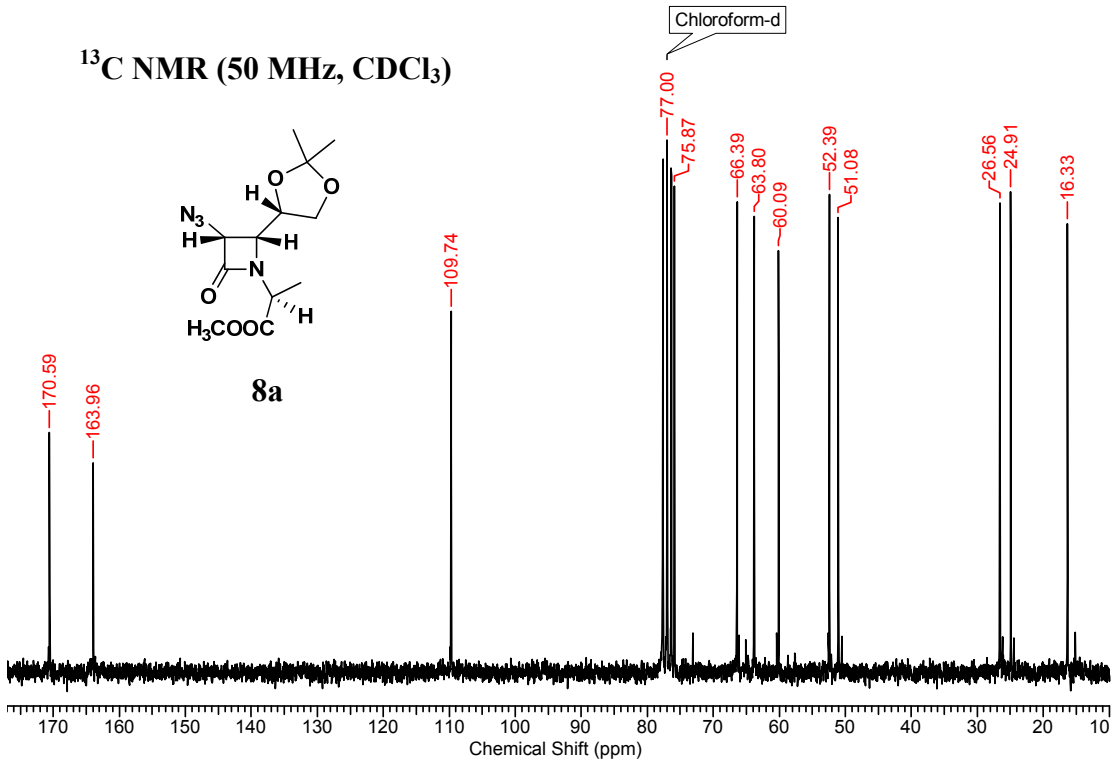


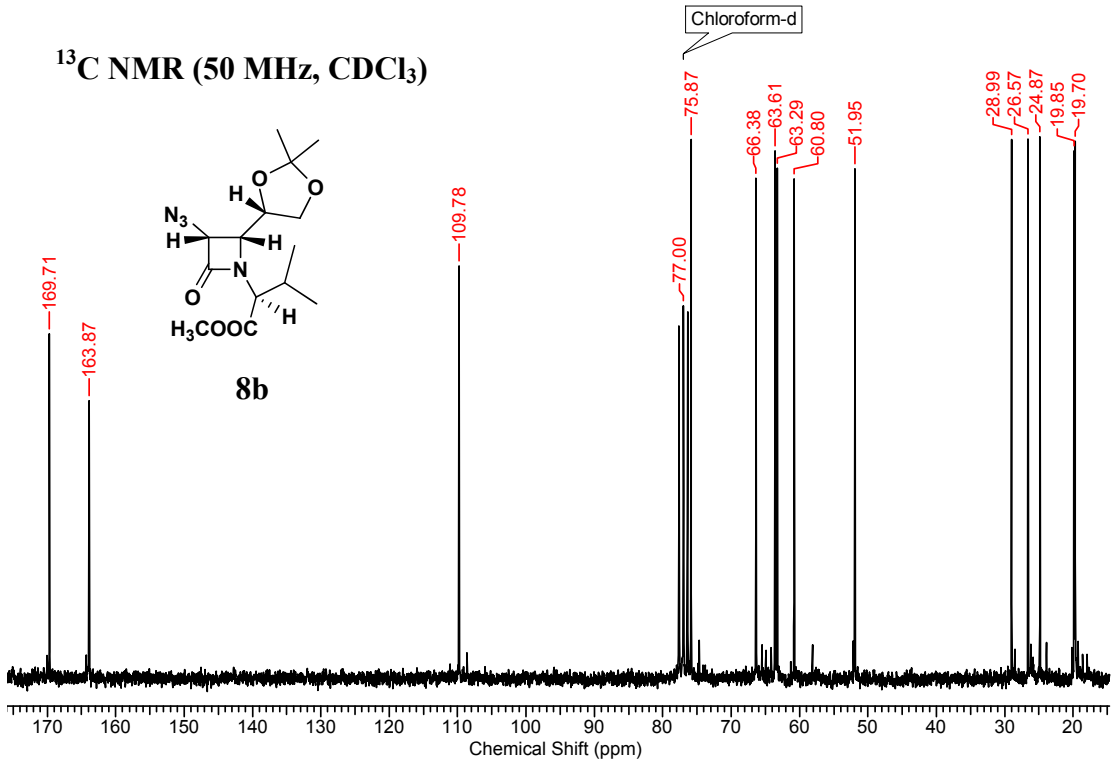
11c

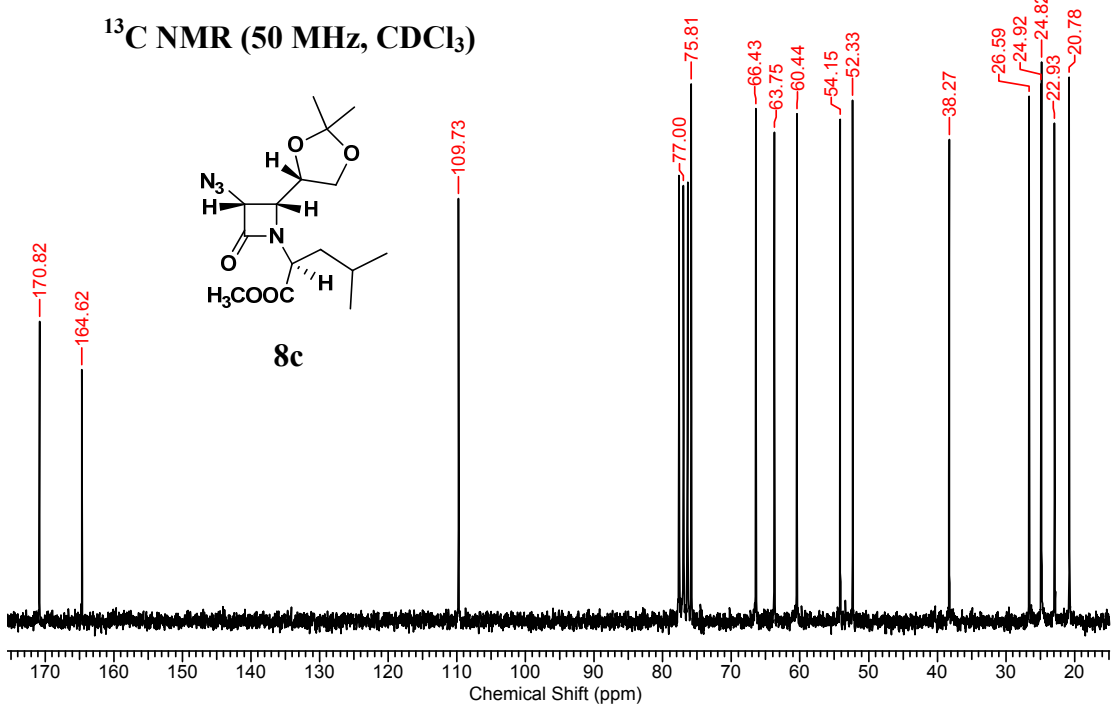
^{1}H NMR (200 MHz, $CDCl_3$)



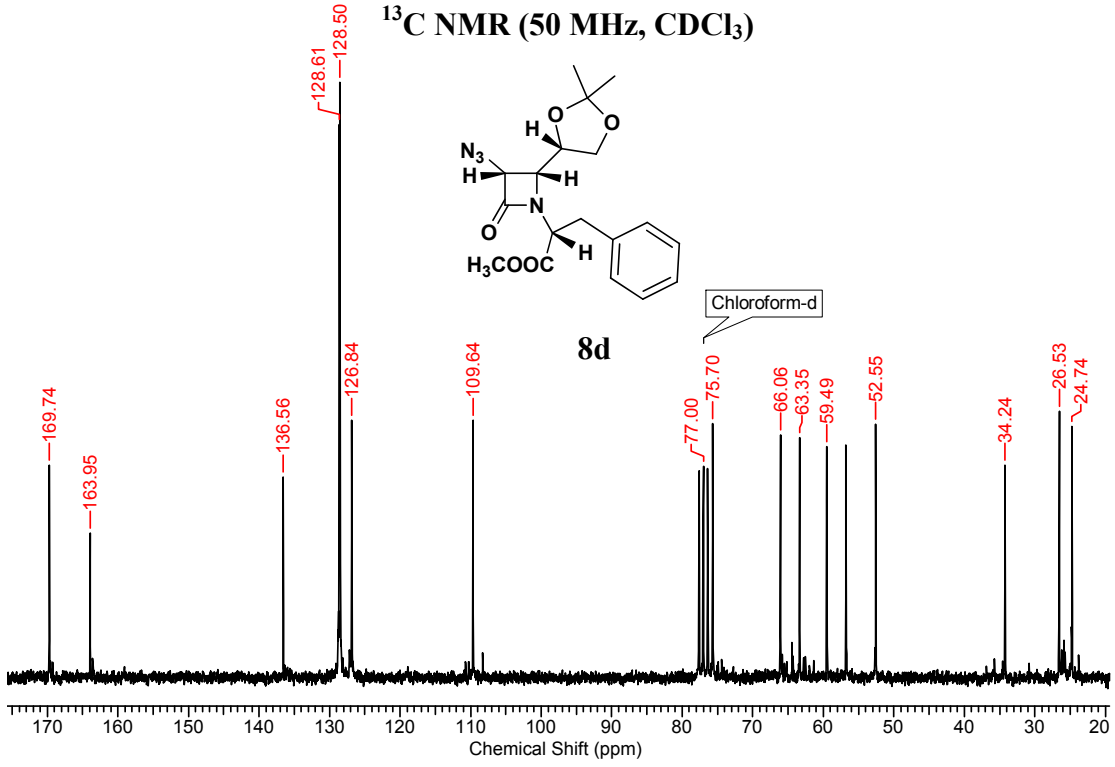
11d


^{13}C NMR (50 MHz, $CDCl_3$)
Chloroform-d
77.00
75.87
66.39
63.80
60.09
52.39
51.08
26.56
24.91
16.33
109.74
170.59
163.96
8a
Chemical Shift (ppm)

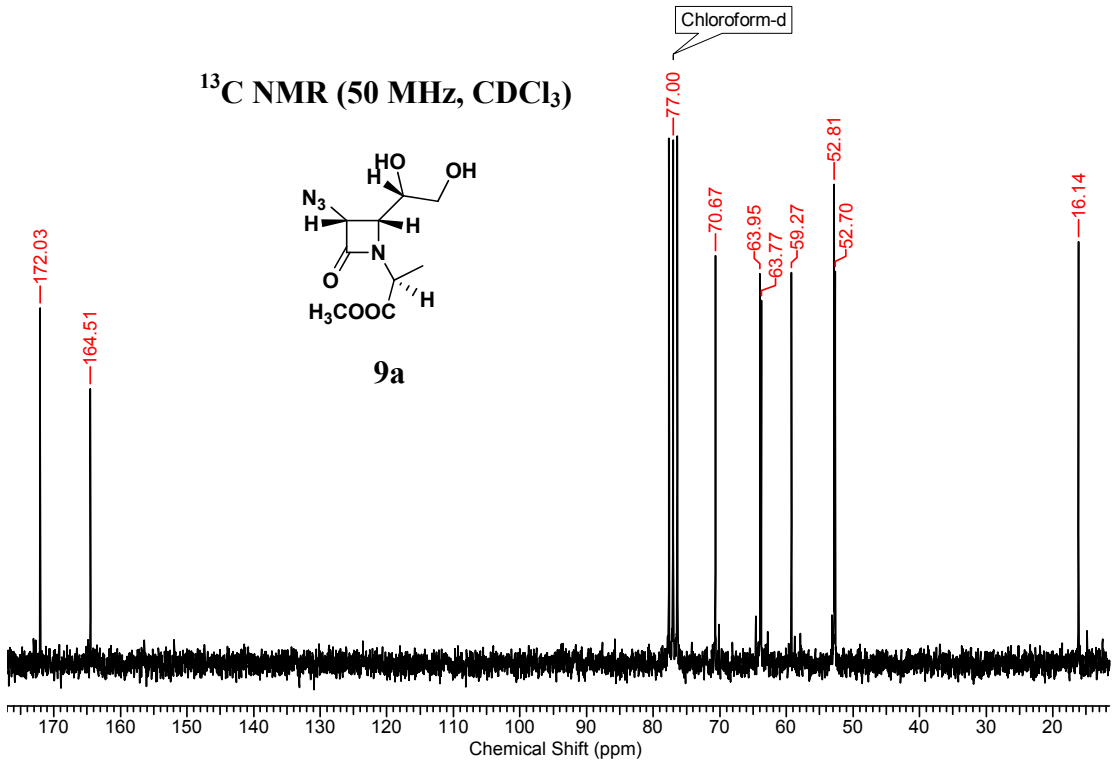

^{13}C NMR (50 MHz, $CDCl_3$)
Chloroform-d
75.87
66.38
63.61
63.29
60.80
51.95
28.99
26.57
24.87
19.85
19.70
109.78
77.00
169.71
163.87
8b
Chemical Shift (ppm)


13C NMR (50 MHz, CDCl3)
170.82
164.62
109.73
77.00
75.81
66.43
63.75
60.44
54.15
52.33
38.27
26.59
24.92
24.82
22.93
20.78
Chemical Shift (ppm)

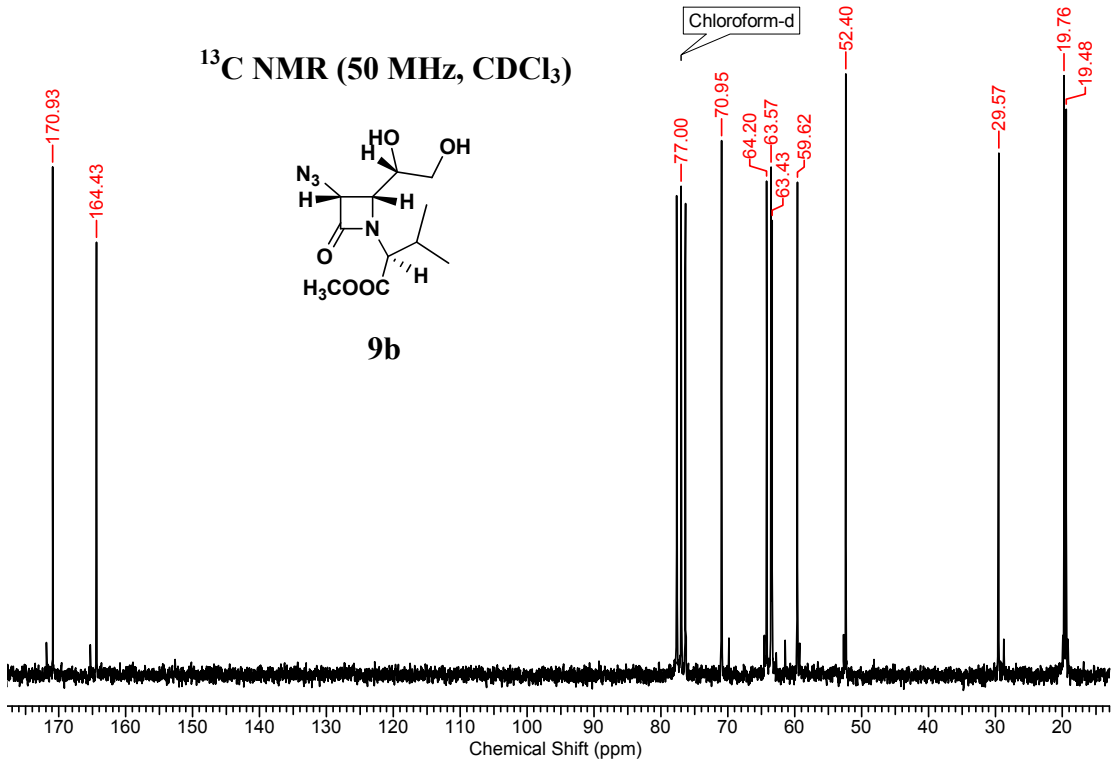
8c


13C NMR (50 MHz, CDCl3)
128.61
128.50
169.74
163.95
136.56
126.84
109.64
77.00
75.70
Chloroform-d
66.06
63.35
59.49
52.55
34.24
26.53
24.74
Chemical Shift (ppm)

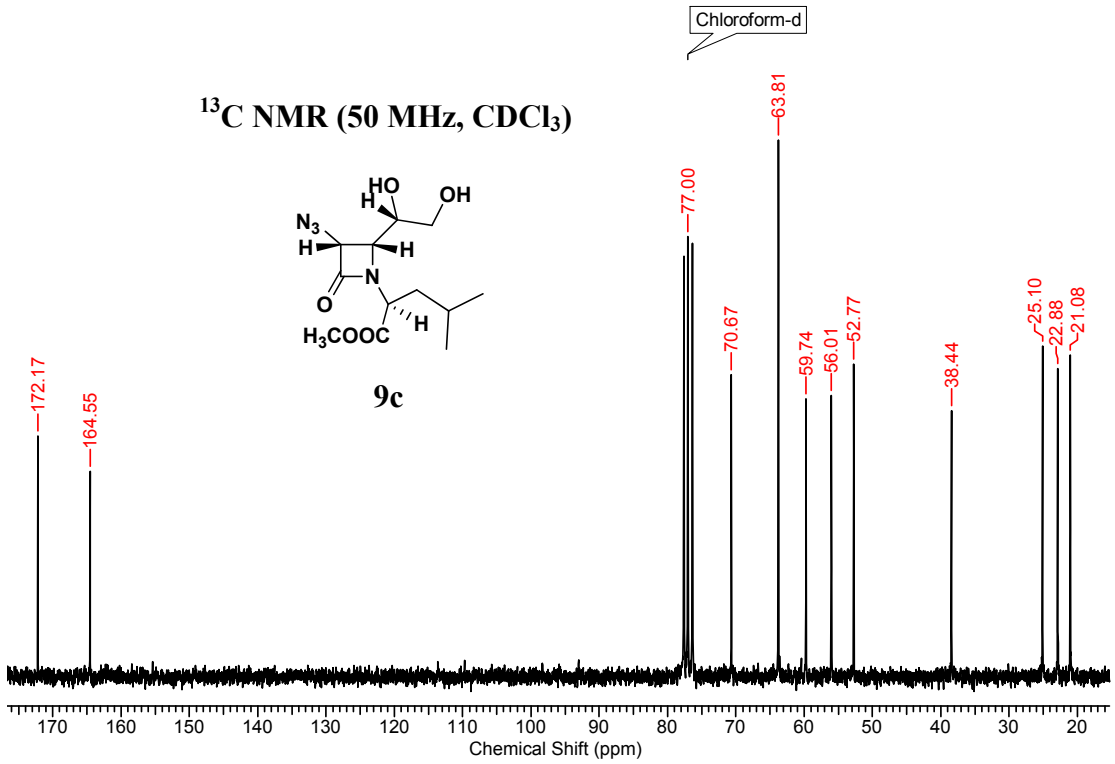
8d


^{13}C NMR (50 MHz, CDCl$_3$)
Chloroform-d
77.00
70.67
63.95
63.77
59.27
52.81
52.70
16.14
172.03
164.51
HO
OH
H
N$_3$
H
H
N
O
H$_3$COOC
H
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

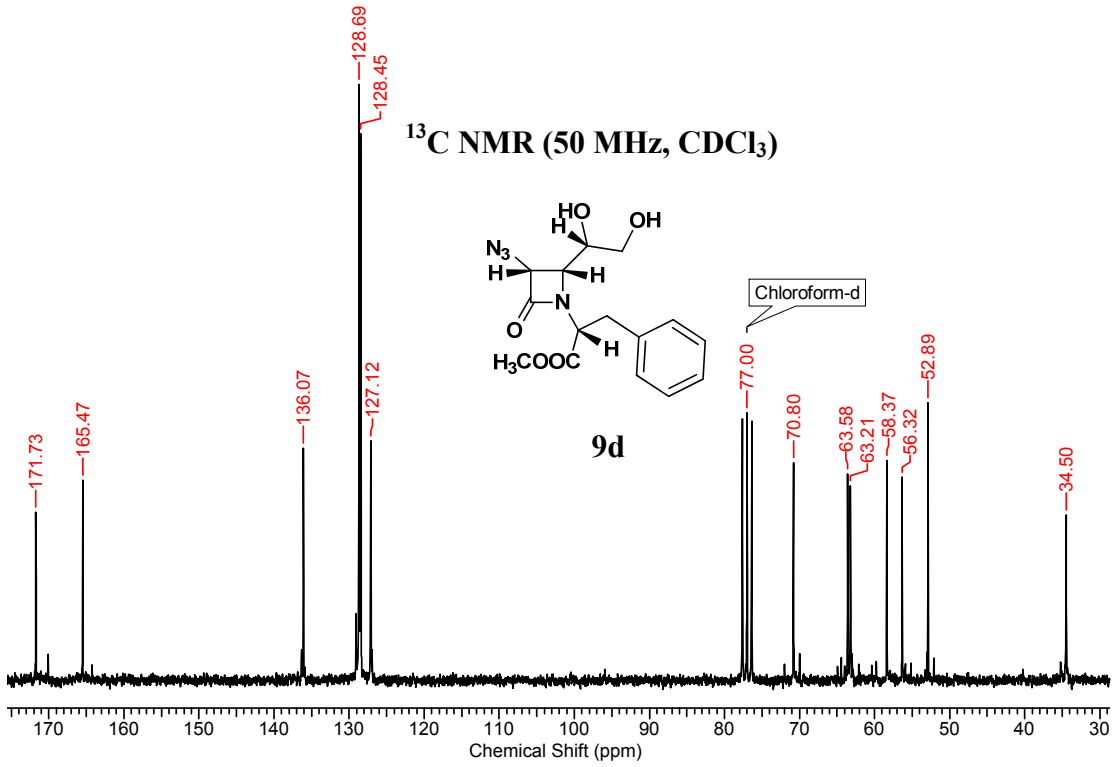
9a


^{13}C NMR (50 MHz, CDCl$_3$)
Chloroform-d
77.00
70.95
64.20
63.57
63.43
59.62
52.40
29.57
19.76
19.48
170.93
164.43
HO
OH
H
N$_3$
H
H
N
O
H$_3$COOC
H
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

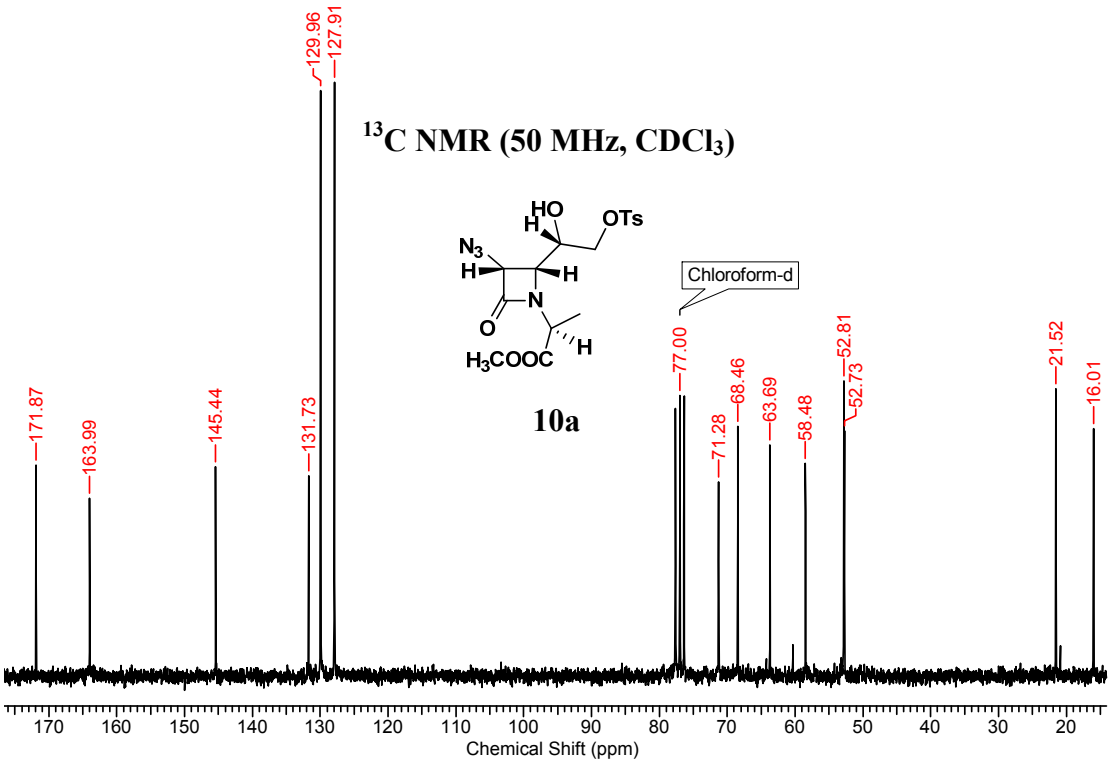
9b

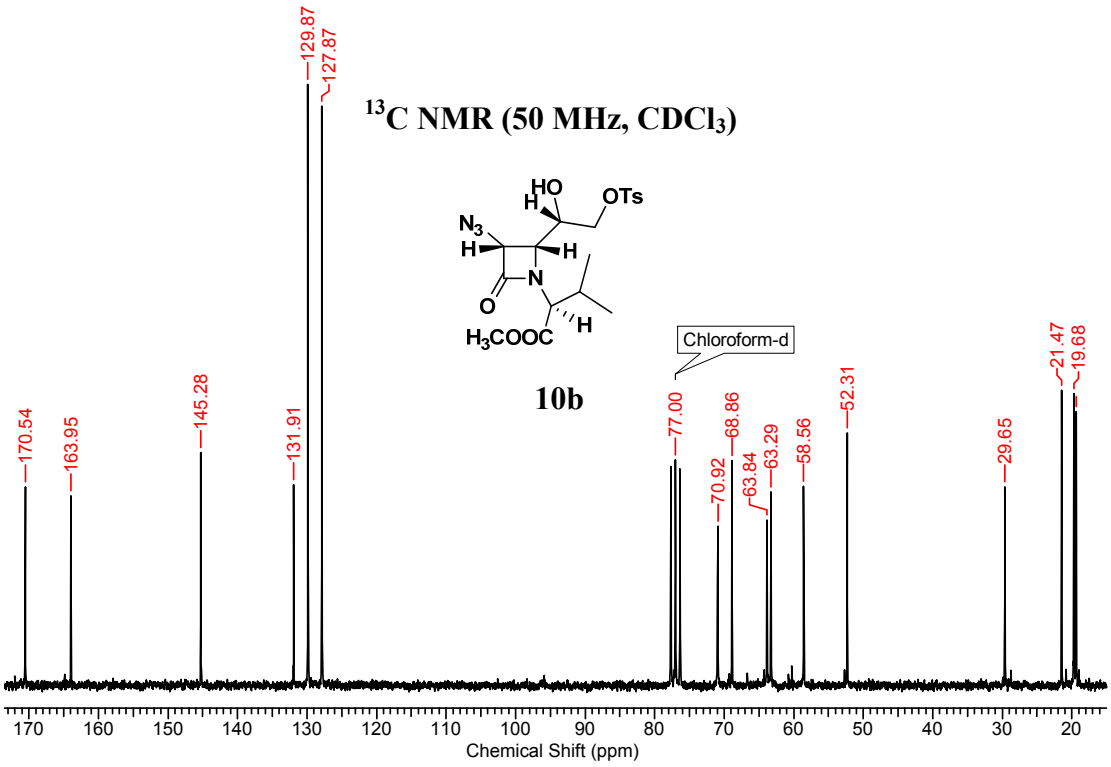

^{13}C NMR (50 MHz, CDCl$_3$)
Chloroform-d
172.17
164.55
77.00
70.67
63.81
59.74
56.01
52.77
38.44
25.10
22.88
21.08
Chemical Shift (ppm)

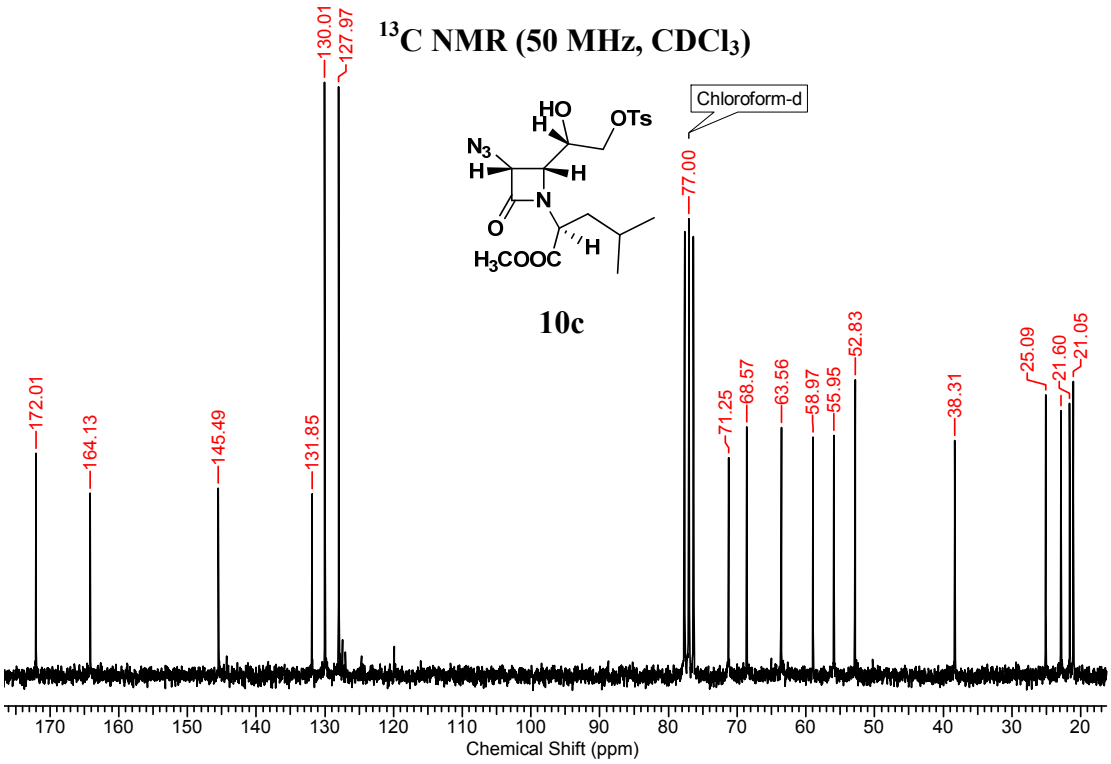
9c

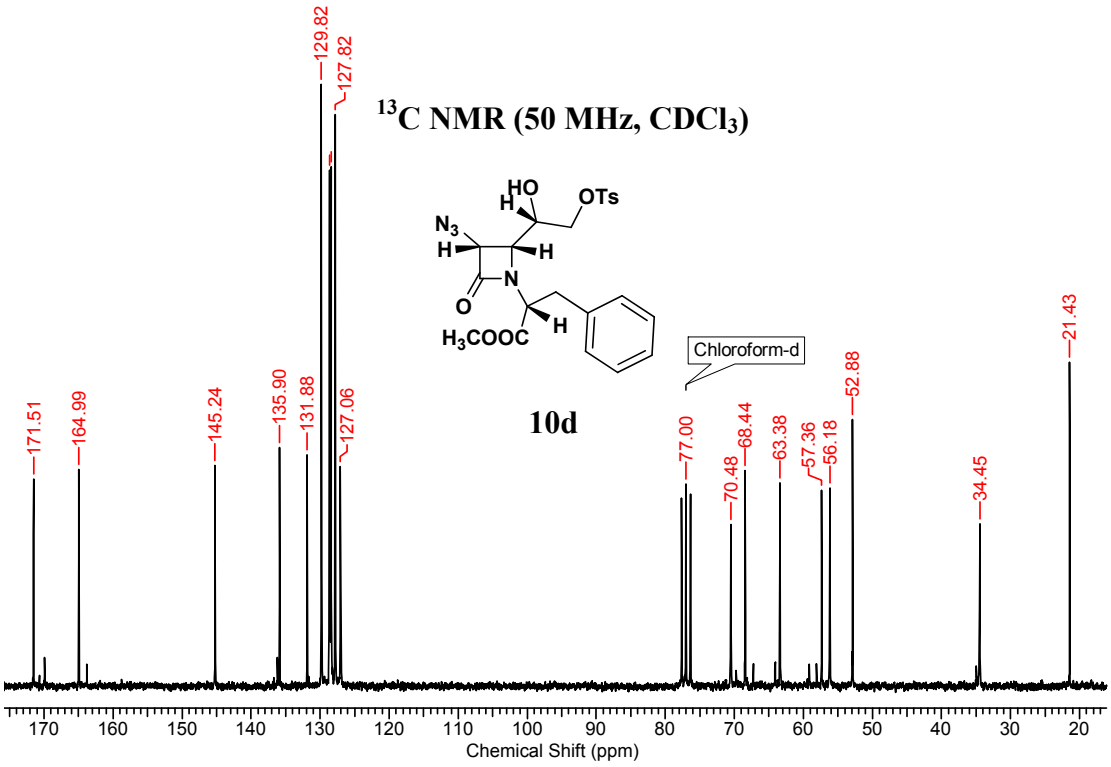

^{13}C NMR (50 MHz, CDCl$_3$)
Chloroform-d
171.73
165.47
136.07
128.69
128.45
127.12
77.00
70.80
63.58
63.21
58.37
56.32
52.89
34.50
Chemical Shift (ppm)

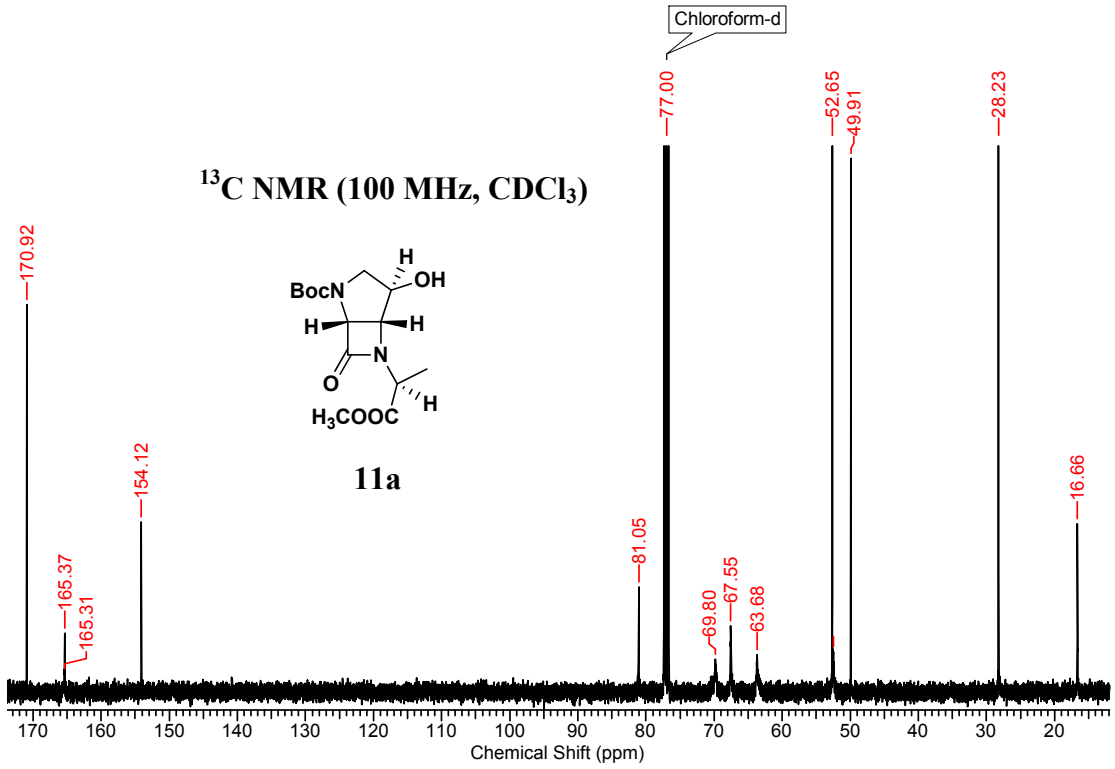
9d

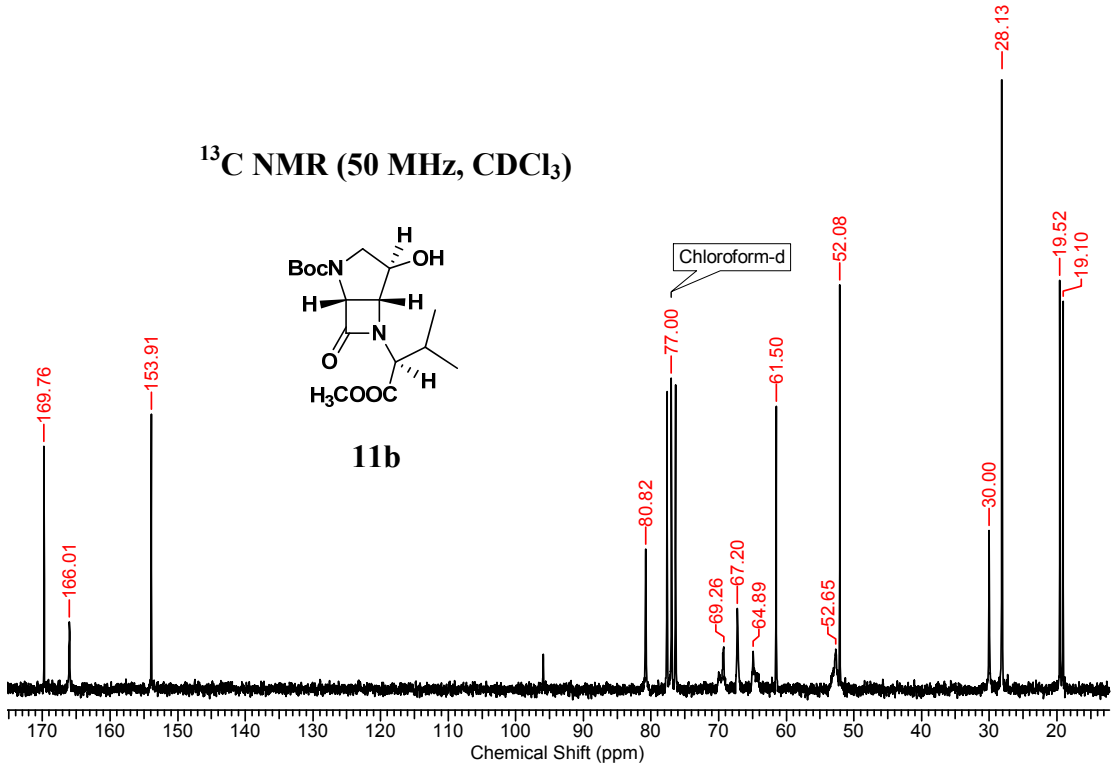

^{13}C NMR (50 MHz, CDCl$_3$)
10a
Chloroform-d
129.96
127.91
171.87
163.99
145.44
131.73
77.00
71.28
68.46
63.69
58.48
52.81
52.73
21.52
16.01
Chemical Shift (ppm)


^{13}C NMR (50 MHz, CDCl$_3$)
10b
Chloroform-d
129.87
127.87
170.54
163.95
145.28
131.91
77.00
70.92
68.86
63.84
63.29
58.56
52.31
29.65
21.47
19.68
Chemical Shift (ppm)

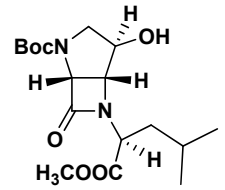

^{13}C NMR (50 MHz, $CDCl_3$)
10c
Chloroform-d
130.01
127.97
77.00
172.01
164.13
145.49
131.85
71.25
68.57
63.56
58.97
55.95
52.83
38.31
25.09
21.60
21.05
Chemical Shift (ppm)


^{13}C NMR (50 MHz, $CDCl_3$)
10d
Chloroform-d
129.82
127.82
171.51
164.99
145.24
135.90
131.88
127.06
77.00
70.48
68.44
63.38
57.36
56.18
52.88
34.45
21.43
Chemical Shift (ppm)


^{13}C NMR (100 MHz, $CDCl_3$)
Chloroform-d
77.00
52.65
49.91
28.23
170.92
154.12
16.66
165.37
165.31
81.05
69.80
67.55
63.68
BocN
OH
H
H
N
O
H_3COOC
11a
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)

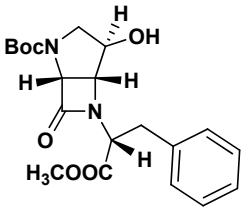

^{13}C NMR (50 MHz, $CDCl_3$)
28.13
19.52
19.10
Chloroform-d
52.08
77.00
61.50
169.76
153.91
80.82
30.00
67.20
69.26
64.89
52.65
166.01
BocN
OH
H
H
N
O
H_3COOC
11b
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)

^{13}C NMR (50 MHz, $CDCl_3$)



11c

^{13}C NMR (50 MHz, $CDCl_3$)



11d

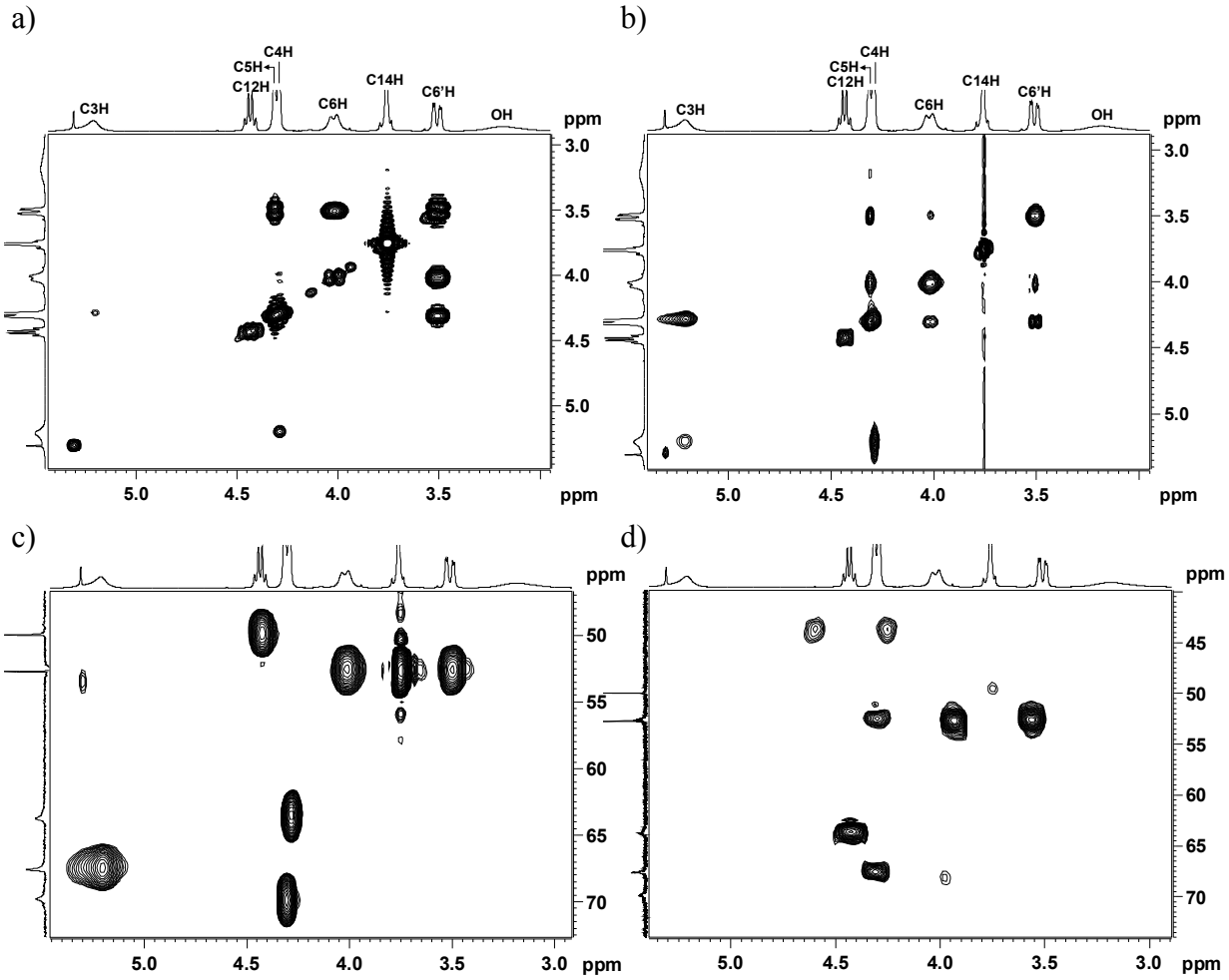


Fig. 3.8: Partial COSY (a), TOCSY (b), HSQC (c) and HMBC (d) spectra of dipeptide building block **11a** (400 MHz, $CDCl_3$). For better view, only ring region is given.

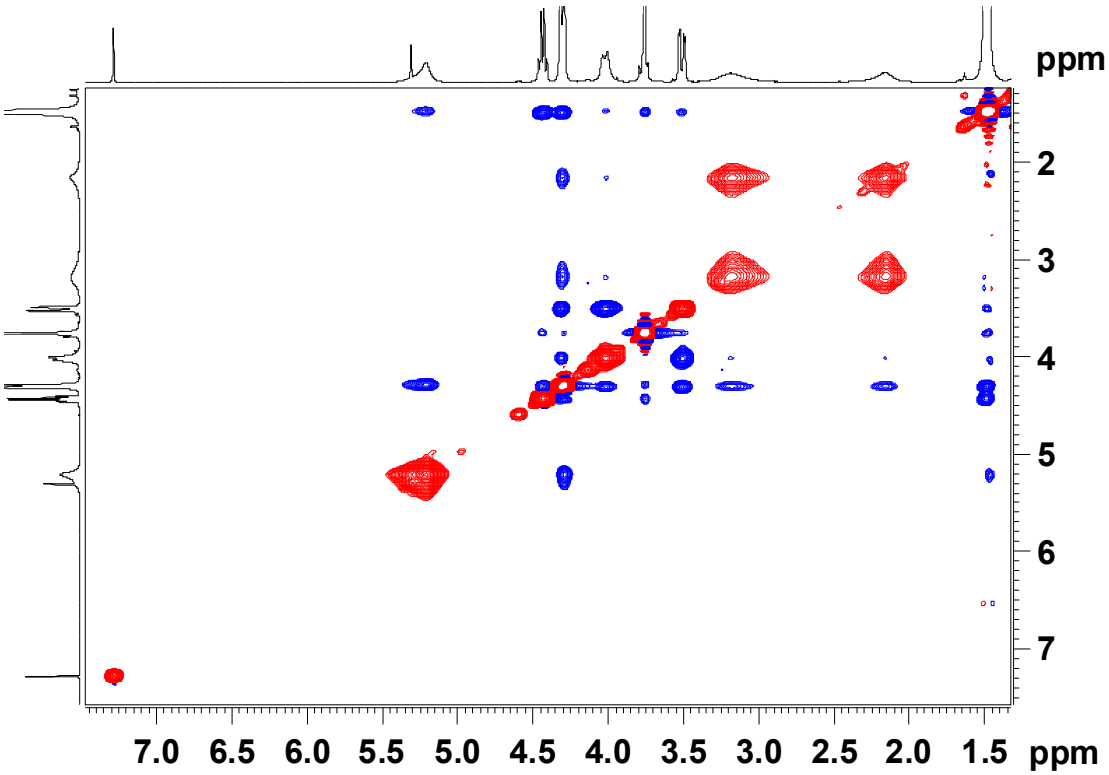


Fig. 3.10: 2D NOESY spectra of dipeptide building block **11a** (400 MHz, $CDCl_3$).

3.14 Reference and notes

(1) See reference no. 14-51 of chapter 1.

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(56) Crystallographic data for **11a** have been deposited with the Cambridge Crystallographic Data Centre: CCDC-878820.

Erratum