

Improved Synthesis of Bis (2,2,2-trifluoroethyl) Phosphono Esters

by

Jordan Zaluski

Submitted in Partial Fulfillment of the Requirements

for the Degree of

Master of Science

in the

Chemistry

Program

YOUNGSTOWN STATE UNIVERSITY

August, 2016

Improved Synthesis of Bis (2,2,2-trifluoroethyl) Phosphono Esters

Jordan Zaluski

I hereby release this thesis to the public. I understand that this thesis will be made available from the OhioLINK ETD Center and the Maag Library Circulation Desk for public access. I also authorize the University or other individuals to make copies of this thesis as needed for scholarly research.

Signature:

---

Jordan Zaluski, Student

Date

Approvals:

---

Dr. John A. Jackson, Thesis Advisor

Date

---

Dr. Douglas T Genna, Committee Member

Date

---

Dr. Brian D. Leskiw, Committee Member

Date

---

Dr. Salvatore A. Sanders, Dean of Graduate Studies

Date

## ABSTRACT

The reaction of primary  $\alpha$ -halo esters with potassium bis (2,2,2-trifluoroethyl) phosphite (prepared from bis (2,2,2-trifluoroethyl) phosphite, potassium hexamethyldisilazide, and 18-crown-6 in THF at -78 °C) results in formation of the corresponding bis (2,2,2-trifluoroethyl) phosphono esters in good yield (60-74%). Yields diminish significantly when secondary  $\alpha$ -halo esters are employed (10-12%) due to steric factors. Reaction conditions were applied to primary alkyl halides and  $\alpha$ -halo ketones for the synthesis of bis (2,2,2-trifluoroethyl) alkyl phosphonates and bis (2,2,2-trifluoroethyl) vinyl phosphates respectively.

## ACKNOWLEDGEMENTS

I would like to thank Dr. John A. Jackson for letting me conduct research under his supervision and for broadening my knowledge as a chemist. I would also like to thank Dr. Douglas T Genna, and Dr. Brian D. Leskiw for agreeing to be on my thesis committee and for being mentors to me. I have great appreciation for the chemistry department here at Youngstown State for shaping me into the chemist I am, and for funding. I would also like to thank my family and friends for their support throughout the past two years.

# TABLE OF CONTENTS

Title Page		i
Signature Page		ii
Abstract		iii
Acknowledgements		iv
Table of Contents		v
List of Figures		viii
List of Schemes		xii
List of Tables		xiii
List of Abbreviations		xiv
<b>Chapter 1:</b>	<b>Introduction</b>	1
	Phosphorus in Organic Molecules	1
	Synthetic Applications of Phosponates	2
	Methods to Synthesize Bis (2,2,2-trifluoroethyl) Phosphono Esters	4
	Michaelis-Becker Reactions of Dialkyl Phosphites	5
	Mechanism of the Perkow Reaction	7
	Chemical Properties of Dialkyl Phosphites	9
	Statement of Purpose	10
<b>Chapter 2:</b>	<b>Results and Discussion</b>	11
	Bis (2,2,2-trifluoroethyl) Phosphono Esters	11
	Bis (2,2,2-trifluoroethyl) Phosponates	15
	Bis (2,2,2-trifluoroethyl) Vinyl Phosphates	20

	Summary and Conclusion	28
<b>Chapter 3:</b>	<b>Experimental</b>	29
	Bis (2,2,2-trifluoroethyl) Phosphite (1)	30
	<b>General Procedure For the Synthesis of Methyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) acetate (2)</b>	31
	Ethyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) acetate (3)	32
	Isopropyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) acetate (4)	32
	Tert-butyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) acetate (5)	33
	Methyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) propionate (6)	34
	Ethyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) propionate (7)	35
	Ethyl 2-(bis (2,2,2-trifluoroethyl) phosphoryl) butanoate (8)	35
	<b>General Procedure For Synthesis of Bis (2,2,2-trifluoroethyl) butylphosphonate (9)</b>	36
	Bis (2,2,2-trifluoroethyl) benzylphosphonate (10)	37
	Bis (2,2,2-trifluoroethyl) (3-phenylpropyl) phosphonate (11)	38
	Bis (2,2,2-trifluoroethyl) (4-bromobutyl) phosphonate (12) and Tetrakis (2,2,2-trifluoroethyl) butane-1,4-diylbisphosphonate (13)	39
	1-phenylvinyl bis (2,2,2-trifluoroethyl) phosphate (14)	40
	<b>References</b>	42

## LIST OF FIGURES

<b>Figure 1:</b>	Spatial Arrangements of Organophosphorus Compounds.	1
<b>Figure 2:</b>	Chemical Structures of Select Phosphonates.	1
<b>Figure 3:</b>	Reaction of Primary Alkyl Halides and Sodium Dialkyl Phosphites.	5
<b>Figure 4:</b>	Reactions of $\alpha$ -Halo Ketones and Sodium Dialkyl Phosphites.	7
<b>Figure 5:</b>	Differences in the $^1\text{H}$ NMR Signals of Methine Protons in Compounds <b>7</b> and <b>8</b> .	13
<b>Figure 6:</b>	Expanded $^{13}\text{C}$ NMR Spectra of Compound Ester <b>7</b> .	14
<b>Figure 7:</b>	Expanded COSY Spectrum of Phosphonate <b>9</b> .	16
<b>Figure 8:</b>	Expanded HSQC Spectrum of Phosphonate <b>9</b> .	17
<b>Figure 9:</b>	Expanded $^{13}\text{C}$ NMR Spectrum of Benzyl Phosphonate <b>10</b> .	18
<b>Figure 10:</b>	Overlay of the $^1\text{H}$ NMR Spectra of 1,4-Dibromobutane, Compounds <b>12</b> and <b>13</b> .	19
<b>Figure 11:</b>	Overlay of the $^{13}\text{C}$ NMR Spectra of 1,4-Dibromobutane, Compounds <b>12</b> and <b>13</b> .	19
<b>Figure 12:</b>	Expanded $^1\text{H}$ NMR Spectrum of Vinyl Phosphate <b>14</b> .	21
<b>Figure 13:</b>	Overlay of the $^{13}\text{C}$ NMR Spectra of 2-Chloroacetophenone and Compound <b>14</b> .	22
<b>Figure 14:</b>	$^{31}\text{P}$ NMR Spectrum of the Mixture of Compounds <b>15</b> and <b>16</b> .	23
<b>Figure 15:</b>	Actual and Predicted $^1\text{H}$ NMR Spectra of Compounds <b>15</b> and <b>16</b> .	24
<b>Figure 16:</b>	$^{31}\text{P}$ NMR Spectrum of Vinyl Phosphates <b>17-19</b> .	26
<b>Figure 17:</b>	COSY Spectrum of Compounds <b>17-19</b> .	27
<b>Figure 18:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>1</b>	44

<b>Figure 19:</b>	$^1\text{H}$ NMR Spectrum of Compound 1	45
<b>Figure 20:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 1	46
<b>Figure 21:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 2	47
<b>Figure 22:</b>	$^1\text{H}$ NMR Spectrum of Compound 2	48
<b>Figure 23:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 2	49
<b>Figure 24:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 3	50
<b>Figure 25:</b>	$^1\text{H}$ NMR Spectrum of Compound 3	51
<b>Figure 26:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 3	52
<b>Figure 27:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 4	53
<b>Figure 28:</b>	$^1\text{H}$ NMR Spectrum of Compound 4	54
<b>Figure 29:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 4	55
<b>Figure 30:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 5	56
<b>Figure 31:</b>	$^1\text{H}$ NMR Spectrum of Compound 5	57
<b>Figure 32:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 5	58
<b>Figure 33:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 6	59
<b>Figure 34:</b>	$^1\text{H}$ NMR Spectrum of Compound 6	60
<b>Figure 35:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 6	61
<b>Figure 36:</b>	HSQC NMR Spectrum of Compound 6	62
<b>Figure 37:</b>	$^{31}\text{P}$ NMR Spectrum of Compound 7	63
<b>Figure 38:</b>	$^1\text{H}$ NMR Spectrum of Compound 7	64
<b>Figure 39:</b>	$^{13}\text{C}$ NMR Spectrum of Compound 7	65
<b>Figure 40:</b>	HSQC NMR Spectrum of Compound 7	66
<b>Figure 41:</b>	COSY NMR Spectrum of Compound 7	67



<b>Figure 42:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>8</b>	68
<b>Figure 43:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>8</b>	69
<b>Figure 44:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>8</b>	70
<b>Figure 45:</b>	HSQC NMR Spectrum of Compound <b>8</b>	71
<b>Figure 46:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>9</b>	72
<b>Figure 47:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>9</b>	73
<b>Figure 48:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>9</b>	74
<b>Figure 49:</b>	HSQC NMR Spectrum of Compound <b>9</b>	75
<b>Figure 50:</b>	COSY NMR Spectrum of Compound <b>9</b>	76
<b>Figure 51:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>10</b>	77
<b>Figure 52:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>10</b>	78
<b>Figure 53:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>10</b>	79
<b>Figure 54:</b>	HSQC NMR Spectrum of Compound <b>10</b>	80
<b>Figure 55:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>11</b>	81
<b>Figure 56:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>11</b>	82
<b>Figure 57:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>11</b>	83
<b>Figure 58:</b>	HSQC NMR Spectrum of Compound <b>11</b>	84
<b>Figure 59:</b>	COSY NMR Spectrum of Compound <b>11</b>	85
<b>Figure 60:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>12</b>	86
<b>Figure 61:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>12</b>	87
<b>Figure 62:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>12</b>	88
<b>Figure 63:</b>	HSQC NMR Spectrum of Compound <b>12</b>	89
<b>Figure 64:</b>	COSY NMR Spectrum of Compound <b>12</b>	90

<b>Figure 65:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>13</b>	91
<b>Figure 66:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>13</b>	92
<b>Figure 67:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>13</b>	93
<b>Figure 68:</b>	$^{31}\text{P}$ NMR Spectrum of Compound <b>14</b>	94
<b>Figure 69:</b>	$^1\text{H}$ NMR Spectrum of Compound <b>14</b>	95
<b>Figure 70:</b>	$^{13}\text{C}$ NMR Spectrum of Compound <b>14</b>	96
<b>Figure 71:</b>	HSQC NMR Spectrum of Compound <b>14</b>	97

## LIST OF SCHEMES

<b>Scheme 1:</b>	Formation of the ( <i>E</i> )-Substituted Olefin in the Synthesis of Metachromin V.	2
<b>Scheme 2:</b>	Formation of the ( <i>Z</i> )-Substituted Olefin in the Synthesis of Luffarin L.	3
<b>Scheme 3:</b>	Mechanism of the Michaelis-Abruzov Reaction.	3
<b>Scheme 4:</b>	Still-Gennari Method.	4
<b>Scheme 5:</b>	Oberthür Method.	4
<b>Scheme 6:</b>	Savignac Method.	5
<b>Scheme 7:</b>	Ciszewski-Jackson Method.	5
<b>Scheme 8:</b>	Perkow Mechanism Pathway 1.	8
<b>Scheme 9:</b>	Perkow Mechanism Pathway 2.	8
<b>Scheme 10:</b>	Formation of the 1,2-Epoxyphosphonate.	8
<b>Scheme 11:</b>	Keto-Enol Tautomerization of Dialkyl Phosphite.	9
<b>Scheme 12:</b>	Synthesis of Bis (2,2,2-trifluoroethyl) Vinyl Phosphate <b>14</b> .	20
<b>Scheme 13:</b>	Reaction of 3-Chloro-2-butanone and Potassium Bis (2,2,2-trifluoroethyl) Phosphite.	22
<b>Scheme 14:</b>	Reaction of 2-Bromopropiophenone and Potassium Bis (2,2,2-trifluoroethyl) Phosphite.	25

## LIST OF TABLES

<b>Table 1:</b>	Product Distribution of the Michaelis-Arbuzov Reactions of Trialkyl Phosphites and $\alpha$ -Halo Acetones.	7
<b>Table 2:</b>	$^{31}\text{P}$ and $^{13}\text{C}$ NMR Data of 1,2-Epoxyphosphonates.	9
<b>Table 3:</b>	Synthesis of Primary Bis (2,2,2-trifluoroethyl) Phosphono Esters <b>2-5</b> .	11
<b>Table 4:</b>	Synthesis of Secondary Bis (2,2,2-trifluoroethyl) Phosphono Esters <b>6-8</b> .	12
<b>Table 5:</b>	Synthesis of Bis (2,2,2-trifluoroethyl) Phosphonates <b>9-13</b> .	15
<b>Table 6:</b>	Aromatic $^{13}\text{C}$ NMR Data for Benzyl Phosphonate <b>10</b> .	18

## LIST OF ABBREVIATIONS

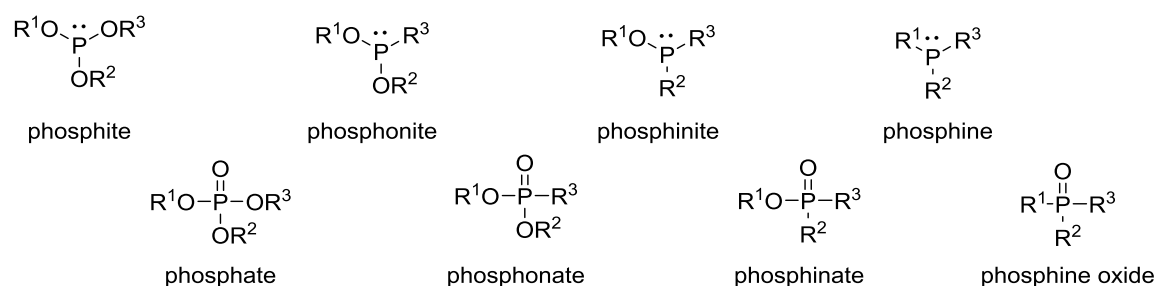
<u>Abbreviation</u>	<u>Description</u>
$^{13}\text{C}$	carbon
$^1\text{H}$	proton
$^{31}\text{P}$	phosphorus
Å	Angstrom
$\text{CDCl}_3$	deuterated chloroform
$\text{CF}_3$	trifluoromethyl
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMSO	dimethyl sulfoxide
$\text{DMSO-d}_6$	deuterated dimethyl sulfoxide
dq	doublet of quartets
equiv	equivalents
EtOAc	ethyl acetate
Hz	hertz
$J$	coupling constant
KHMDS	potassium hexamethyldisilazide
M	molarity
$\text{MgSO}_4$	magnesium sulfate

MHz	megahertz
NMR	nuclear magnetic resonance
PCl <sub>5</sub>	phosphorus pentachloride
PMA	phosphomolybdic acid
ppm	parts per million
PTSA	p-toluenesulfonic acid
R <sub>f</sub>	retention factor
s	singlet
sat.	saturated
SOCl <sub>2</sub>	thionyl chloride
t	triplet
THF	tetrahydrofuran
TMS	tetramethylsilane
UV	ultraviolet

# Chapter 1: Introduction

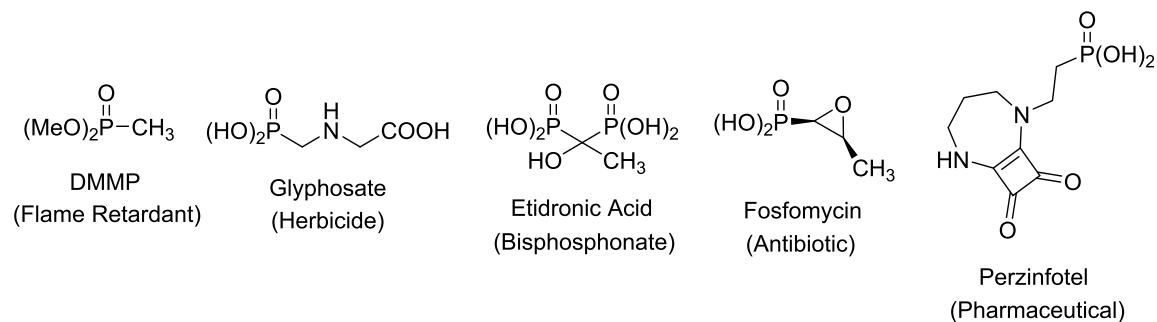
## Part 1: Phosphorus in Organic Molecules

Phosphorus is an element essential to life and organophosphorus compounds have been widely studied. Organophosphorus compounds can be divided into subgroups classified by the oxidation state of phosphorus and the different groups bound to phosphorus (**Figure 1**).



**Figure 1:** Spatial Arrangements of Organophosphorus Compounds.

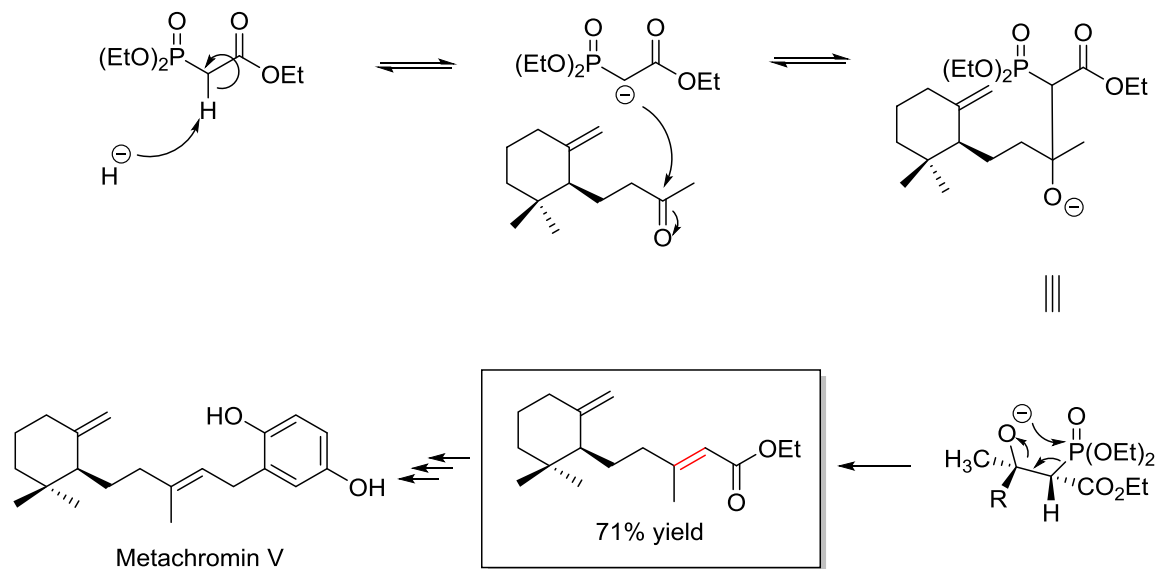
Phosphonates are an important class of organophosphorus compounds which can be found in flame retardants, herbicides, and pharmaceuticals. In addition, bisphosphonates are medicinally active and have been shown to treat osteoporosis.<sup>1-4</sup> Shown in **Figure 2** are the chemical structures of various phosphonates.



**Figure 2:** Chemical Structures of Select Phosphonates.

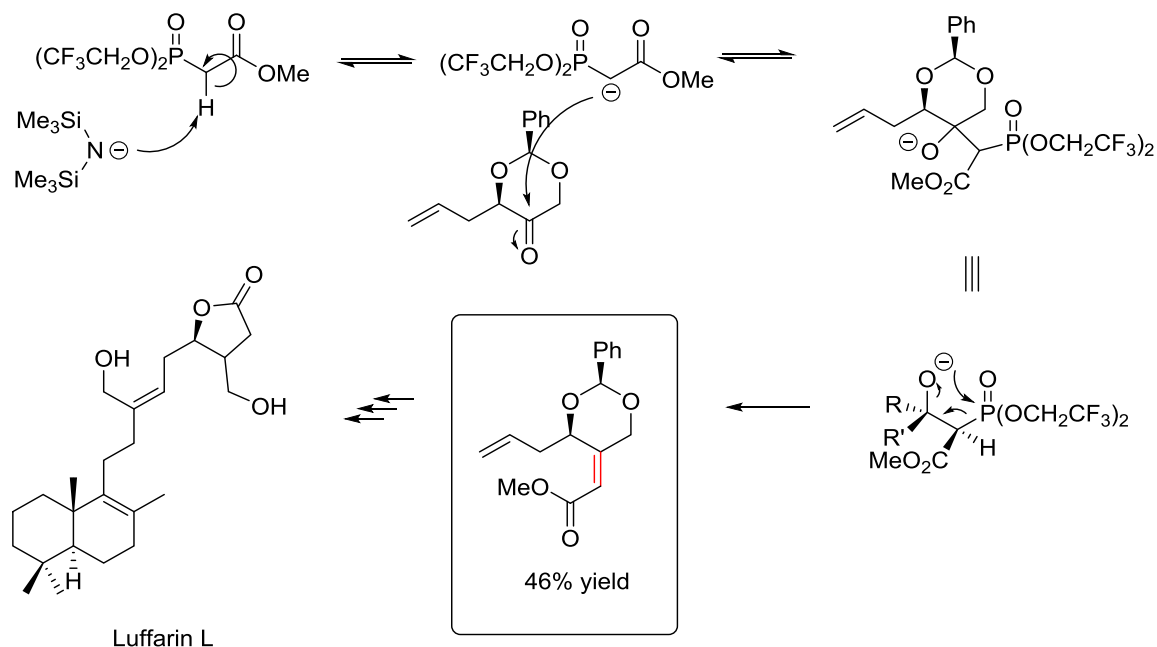
## Part 2: Synthetic Application of Phosphonates

Besides their biological and medicinal importance, phosphonates serve as useful synthetic reagents found in many natural product syntheses.<sup>5-6</sup> The Horner-Wadsworth-Emmons (HWE) condensation is a popular reaction that couples a phosphono ester to an aldehyde or ketone resulting in the formation of either an (*E*) or (*Z*)-substituted olefin. The (*E*)-substituted olefin is the thermodynamically favored product, but Still and Gennari demonstrated that the kinetic product, the (*Z*)-substituted olefin, is highly favored when bis (2,2,2-trifluoroethyl) phosphono esters are used.<sup>3</sup> **Schemes 1** and **2** demonstrate mechanistically how the (*E*)-substituted and (*Z*)-substituted olefins form during the HWE condensations found in the natural product syntheses of Metachromin V<sup>5</sup> and Luffarin L<sup>6</sup> respectively.



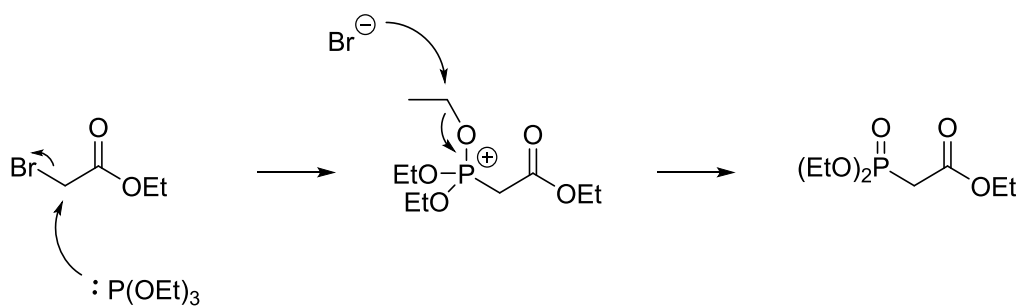
**Scheme 1:** Formation of the (*E*)-Substituted Olefin in the Synthesis of Metachromin V.





**Scheme 2:** Formation of the (*Z*)-Substituted Olefin in the Synthesis of Luffarin L.

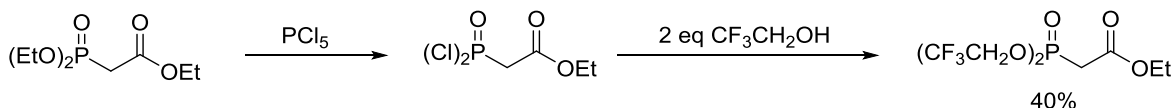
The Michaelis-Arbuzov reaction (**Scheme 3**) traditionally is used to synthesize phosphono esters where a trialkyl phosphite is coupled to an  $\alpha$ -halo ester.<sup>7</sup> Tris (2,2,2-trifluoroethyl) phosphite is non-nucleophilic, thus the Michaelis-Arbuzov reaction cannot be utilized to synthesize bis (2,2,2-trifluoroethyl) phosphono esters.



**Scheme 3:** Mechanism of the Michaelis-Arbuzov Reaction.

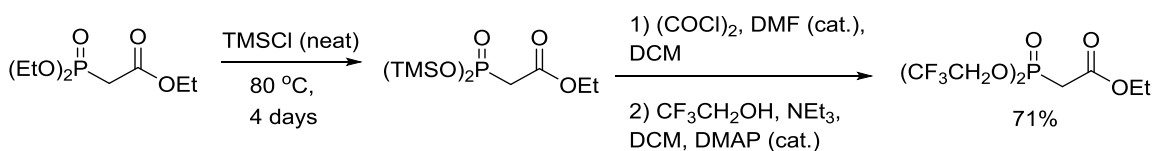
### Part 3: Methods to Synthesize Bis (2,2,2-trifluoroethyl) Phosphono Esters

Still and Gennari showed the exchange of the ethyl groups with chlorines was achieved when phosphorus pentachloride is added. Following the treatment of the phosphoric dichloride with trifluoroethanol, the bis (2,2,2-trifluoroethyl) phosphono ester can be successfully synthesized at 40% yield as shown in **Scheme 4**.<sup>8</sup>



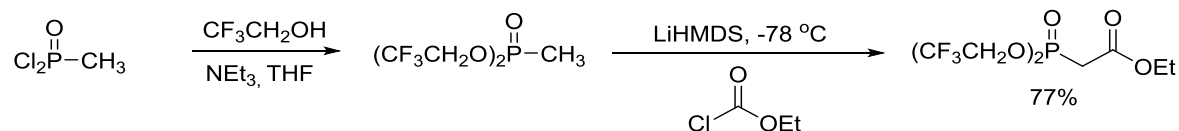
**Scheme 4:** Still-Gennari Method.

Oberthür utilizes a similar pathway (**Scheme 5**) where the treatment of diethyl phosphono ester with trimethylsilyl chloride over the course of 4 days results in the exchange of ethyl groups with trimethylsilyl groups. The trimethylsilyl groups are then further exchanged with chlorines after oxalyl chloride was added. Finally following the addition of trifluoroethanol to the phosphonic dichloride, the desired phosphono ester can be synthesized at 71% yield.<sup>9</sup>



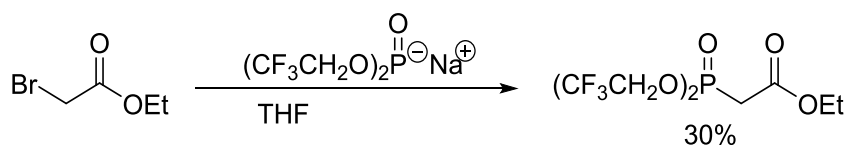
**Scheme 5:** Oberthür Method.

Savignac demonstrated the reaction of methyl phosphonic dichloride with trifluoroethanol generates bis (2,2,2-trifluoroethyl) methylphosphonate. This phosphonate can then be deprotonated, and the subsequent acylation of the carbanion with ethyl chloroformate yields the bis (2,2,2-trifluoroethyl) phosphono ester at 77% yield as depicted in **Scheme 6**.<sup>10</sup>



**Scheme 6:** Savignac Method.

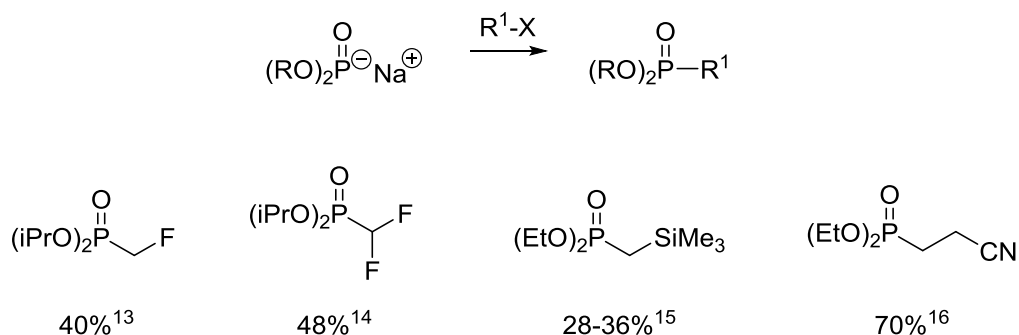
Ciszewski and Jackson used a Michaelis-Becker reaction where bis (2,2,2-trifluoroethyl) phosphite anion acts as a nucleophile after being generated by the deprotonation of the phosphite with sodium hydride. Sodium bis (2,2,2-trifluoroethyl) phosphite then attacks the  $\alpha$ -halo ester generating the desired phosphono ester at 30% yield in one pot as depicted in **Scheme 7**.<sup>11</sup>



**Scheme 7:** Ciszewski-Jackson Method.

#### Part 4: Michaelis-Becker Reactions of Dialkyl Phosphites

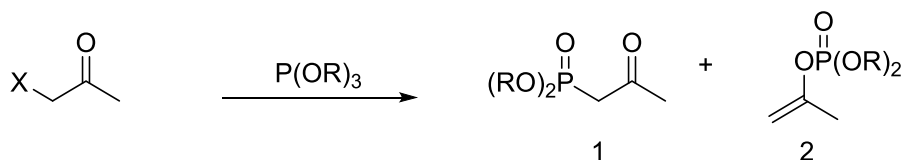
The Michaelis-Becker reaction utilizes dialkyl phosphites not trialkyl phosphites as in the Michaelis-Arbuzov reaction. **Figure 3** summarizes Michaelis-Becker reactions between dialkyl phosphites and simple alkyl halides in the presence of sodium to synthesize alkyl phosphonates.<sup>12-16</sup> Secondary and tertiary halides do not react with



**Figure 3:** Reaction of Primary Alkyl Halides and Sodium Dialkyl Phosphites.

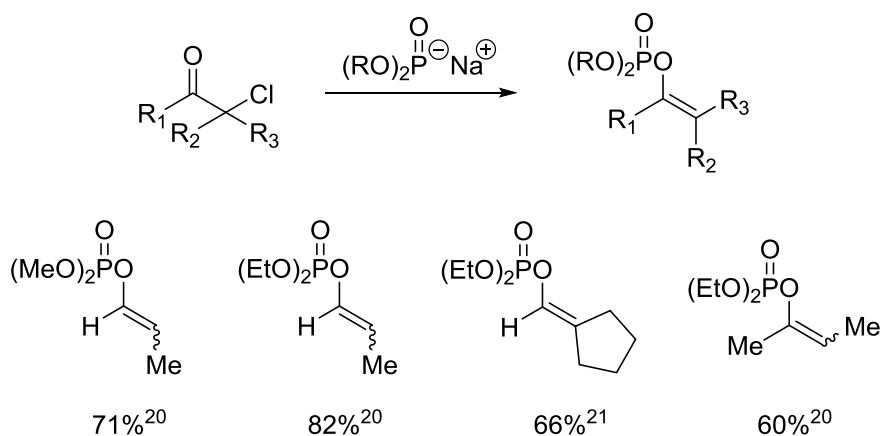
dialkyl phosphites anions under Michaelis-Becker conditions, yet it has been shown that diaryl phosphites in the presence of DBU and acetonitrile can react with trityl bromide and the corresponding phosphonate can be successfully synthesized in good yields.<sup>17</sup>

As previously seen in **Scheme 7**,  $\alpha$ -halo esters can react with dialkyl phosphites under basic conditions to make dialkyl phosphono esters. However the Michaelis-Arbuzov method is more commonly used to synthesize dialkyl phosphono esters since it is higher yielding. As in the Michaelis-Arbuzov reaction, when  $\alpha$ -halo ketones are exposed to Michaelis-Becker conditions, it is possible to form at least two products. The main product observed could be either a  $\beta$ -ketophosphonate or vinyl phosphate depending on the substrate. This was first noticed by Perkow when the reaction between  $\alpha$ -halo aldehydes and trialkyl phosphites gave a rearranged product.<sup>18</sup> Shown in **Table 1**,<sup>12,19</sup> the vinyl phosphate product seems to be highly favored when  $\alpha$ -chloroacetone is the substrate. The phosphonate product is observed at a lower percentage when  $\alpha$ -bromoacetone is used, except when triisopropyl phosphite is employed. The highest percentage of phosphonate product is seen when  $\alpha$ -iodoacetone is used.<sup>18</sup>  $\alpha$ -Halo ketones under Michaelis-Becker conditions are quite reactive and form vinyl phosphate products in moderate to high yield as seen in **Figure 4**.<sup>12,20-21</sup>



R	X	Yield	% Prod. 1	% Prod. 2
Me	Cl	71%	5%	95%
Me	Br	71%	45%	55%
Et	Cl	60%	6%	94%
Et	Br	66%	20%	80%
Et	I	82%	90%	10%
<i>i</i> -Pr	Cl	70%	6%	94%
<i>i</i> -Pr	Br	78%	79%	21%

**Table 1:** Product Distribution of the Michaelis-Arbuzov Reactions of Trialkyl Phosphites and  $\alpha$ -Halo Acetones.

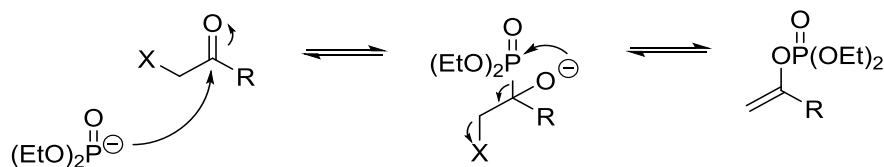


**Figure 4:** Reactions of  $\alpha$ -Halo Ketones and Sodium Dialkyl Phosphites.

### Part 5: The Mechanism of the Perkow Reaction

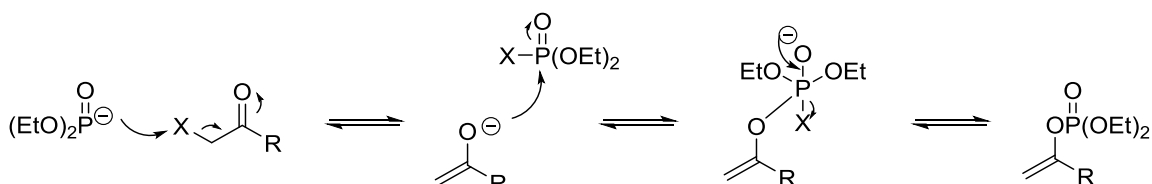
There are two plausible mechanisms to account for the formation of the vinyl phosphate product under Michaelis-Becker conditions. Perkow mechanism pathway 1 (**Scheme 8**) the phosphite anion does a nucleophilic addition to the carbonyl carbon.<sup>12,23-</sup>

<sup>25</sup> After a subsequent rearrangement the vinyl phosphate product forms.



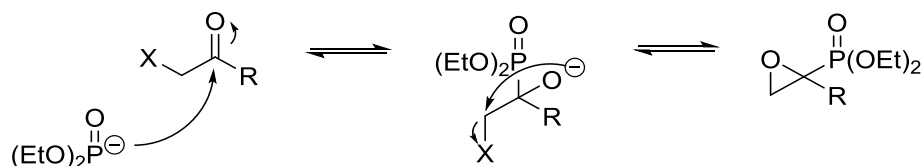
**Scheme 8:** Perkow Mechanism Pathway 1.

In Perkow mechanism pathway 2 (**Scheme 9**) the dialkyl phosphite anion attacks the halogen directly causing the formation of an enolate.<sup>12,25-27</sup> Next the enolate attacks the generated phosphorohalidate, and in a subsequent step the halogen is displaced resulting in the vinyl phosphate product.

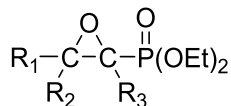


**Scheme 9:** Perkow Mechanism Pathway 2.

One difference between the two reaction pathways is the formation of the 1,2-epoxyphosphonate which can only be formed during Perkow reaction pathway 1.<sup>22</sup> In **Scheme 10** the 1,2-epoxyphosphonate can form when the enolate directly attacks the carbon bearing the halogen instead of the phosphorus.<sup>31</sup>P and <sup>13</sup>C NMR data for 1,2-epoxyphosphonates is assembled in **Table 2**.<sup>28</sup>



**Scheme 10:** Formation of the 1,2-Epoxyphosphonate.

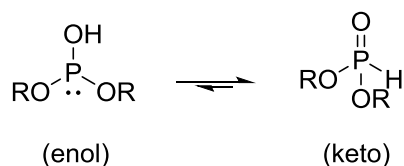


Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	<sup>31</sup> P (ppm)	<sup>1</sup> J <sub>C-P</sub> (Hz)	<sup>2</sup> J <sub>C-P</sub> (Hz)
A	<i>n</i> -Pr	Me	H	19.53 (s)	56.78 (d, <i>J</i> = (202 Hz))	62.88 (s)
B	<i>n</i> -Pr	Ph	H	18.18 (s)	58.38 (d, <i>J</i> = (198 Hz))	65.70 (d, <i>J</i> = 1 Hz)
C	Ph	<i>n</i> Bu	Me	20.87 (s)	62.21 (d, <i>J</i> = (197 Hz))	66.11 (s)
D	<i>n</i> -Pr	Me	Me	23.54 (s)	60.56 (d, <i>J</i> = (196 Hz))	65.78 (d, <i>J</i> = 4 Hz)

**Table 2:** <sup>31</sup>P and <sup>13</sup>C NMR Data of 1,2-Epoxyphosphonates.

### Part 6: Chemical Properties of Dialkyl Phosphites

The dialkyl phosphite starting material for Michaelis-Becker reactions is classified as a phosphite not a phosphonate. **Scheme 11** shows the keto-enol tautomerization of this molecule. IR and NMR experiments confirm the absence of an OH peak and the presence of a phosphoryl peak around 2400 cm<sup>-1</sup> and P-H bond around 1260 cm<sup>-1</sup> suggesting the keto form is the dominate species found in solution.<sup>29</sup>



**Scheme 11:** Keto-Enol Tautomerization of Dialkyl Phosphite.

Bis (2,2,2-trifluoroethyl) phosphite can be synthesized at 82% yield by the protocol reported by Gibbs.<sup>30</sup> The characteristic peak in <sup>1</sup>H NMR is a 1H doublet at 6.9 ppm with a proton-phosphorus coupling constant of 755 Hz.

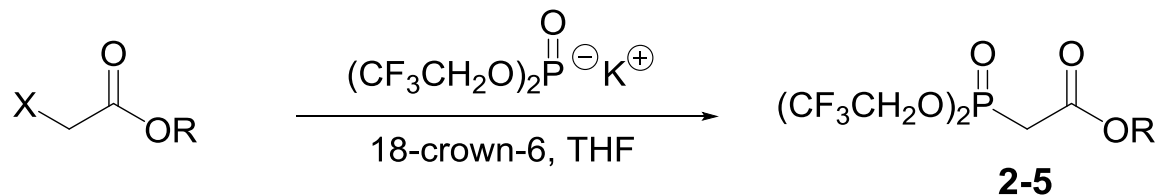
### **Statement of Purpose**

The Ciszewski-Jackson method to synthesize bis (2,2,2-trifluoroethyl) phosphono esters is the most promising approach since this method is the shortest synthesis and uses non-hazardous reagents compared to the other methods. I propose to alter base conditions by using potassium hexamethyldisilazide in the presence of 18-crown-6 to generate potassium bis (2,2,2-trifluoroethyl) phosphite in situ at -78 °C. The generated phosphite anion should be more nucleophilic since the potassium cation would be chelated by the crown ether.



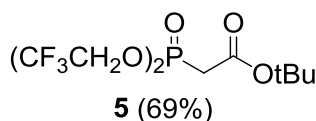
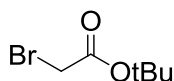
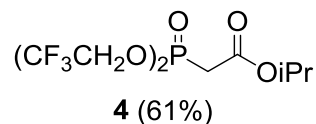
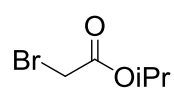
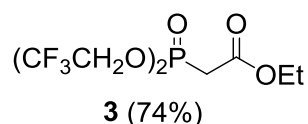
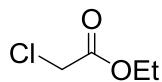
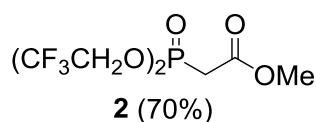
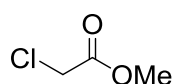
## Chapter 2: Results/Discussion

### Part 1: Bis (2,2,2-trifluoroethyl) Phosphono Esters



#### STARTING MATERIAL

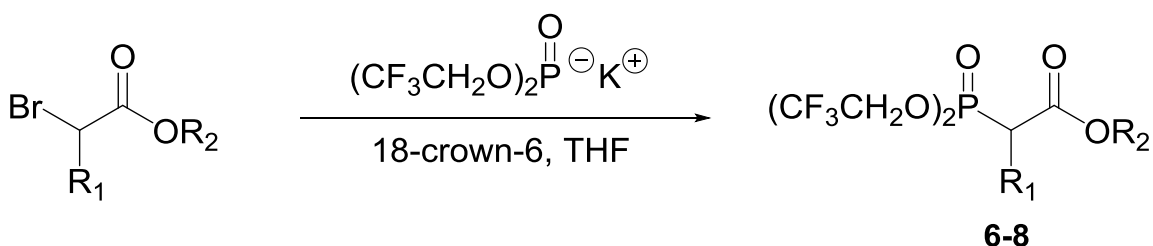
#### PRODUCT (YIELD)



**Table 3:** Synthesis of Primary Bis (2,2,2-trifluoroethyl) Phosphono Esters **2-5**.

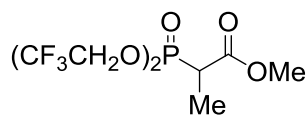
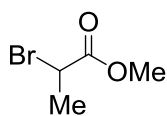
Four bis (2,2,2-trifluoroethyl) phosphono esters (**Table 3**) were successfully synthesized in good yield (60-74%) when primary  $\alpha$ -halo esters were used as reaction substrates. Phosphono esters **2-5** have  $^{31}\text{P}$  NMR signals between 22-23 ppm. The  $^1\text{H}$  NMR spectra shows a characteristic 2H doublet at 3.1 ppm with a proton-phosphorus coupling constant of 21 Hz corresponding to the methylene protons directly attached to phosphorus. In the  $^{13}\text{C}$  NMR spectra of phosphono esters **2-5**, the carbonyl is observed as a doublet at 163 ppm with a carbon-phosphorus coupling constant of 4 Hz. The  $\text{CF}_3$

group is observed as a doublet of quartets at 122 ppm that has a carbon-phosphorus coupling constant of 8 Hz and a 1 bond carbon-fluorine coupling constant of 277 Hz. The methylene of trifluoroethyl group is observed as another doublet of quartets at 62 ppm with a carbon-phosphorus coupling constant of 5 Hz and a 2 bond carbon-fluorine coupling constant of 38 Hz. The methylene carbon attached to phosphorus appears as a doublet at 33 ppm with a carbon-phosphorus coupling constant of 142 Hz. The groups attached to the oxygen of the ester are observed as singlets since those carbons are too far away to be coupled to either phosphorus or fluorine.

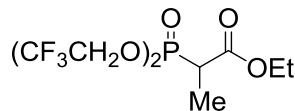
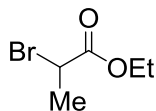


**STARTING MATERIAL**

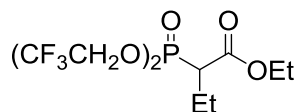
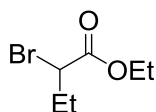
**PRODUCT (YIELD)**



**6 (10%)**



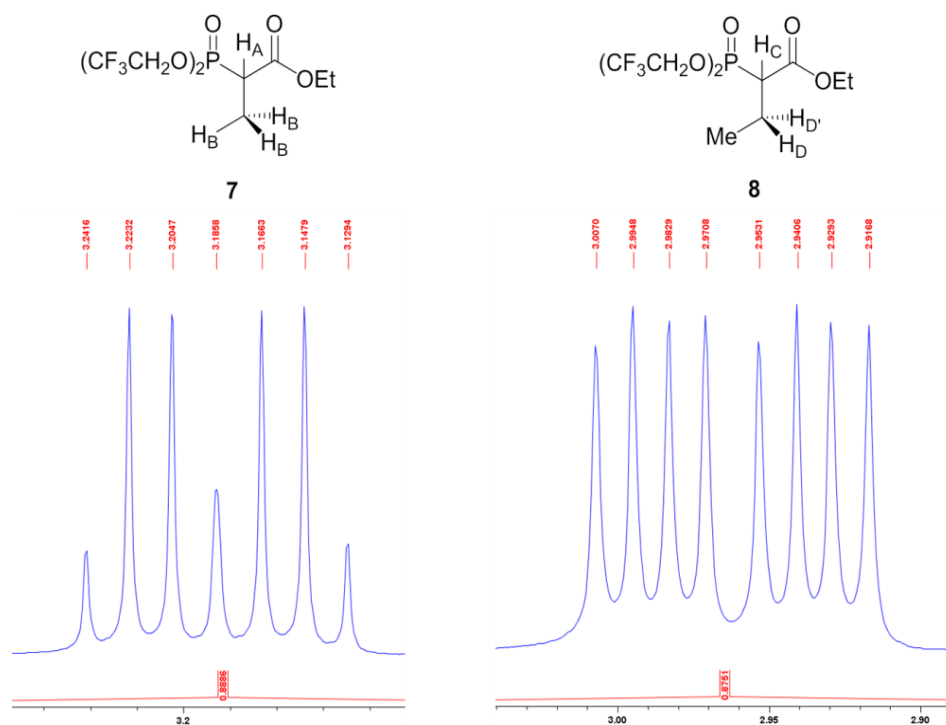
**7 (10%)**



**8 (12%)**

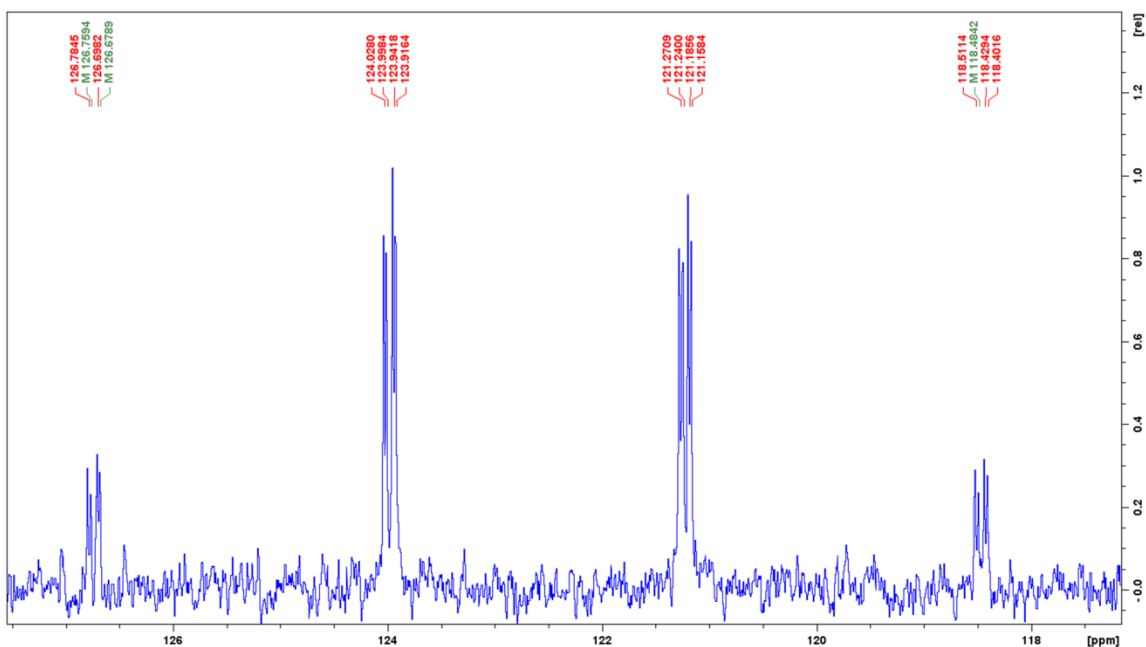
**Table 4:** Synthesis of Secondary Bis (2,2,2-trifluoroethyl) Phosphono Esters **6-8**.

Three secondary phosphono esters **6-8** (Table 4) were synthesized from secondary  $\alpha$ -halo esters at significantly lower yields (10-12%) due to steric hindrance of the starting material. More complicated  $^1\text{H}$  NMR signals are observed for esters **7** and **8** as shown in Figure 5. The proton  $\text{H}_\text{A}$  of compound **7** is observed as a 1H doublet of quartets with a proton-phosphorus coupling constant of 21 Hz and proton-proton coupling constant of 7 Hz. Since the protons of the methyl group are all equivalent, proton  $\text{H}_\text{A}$  is split into a quartet by the methyl group and a doublet by phosphorus. However proton  $\text{H}_\text{C}$  of compound **8** is observed as a 1H doublet of doublet of doublets with a proton-phosphorus coupling constant of 21 Hz and proton-proton coupling constants of 5 and 10 Hz. The methylene protons  $\text{H}_\text{D}$  and  $\text{H}_\text{D}'$  are diastereotopic and each separately split proton  $\text{H}_\text{C}$  into a doublet. Proton  $\text{H}_\text{C}$  is further split into a doublet by phosphorus thus the observed signal.



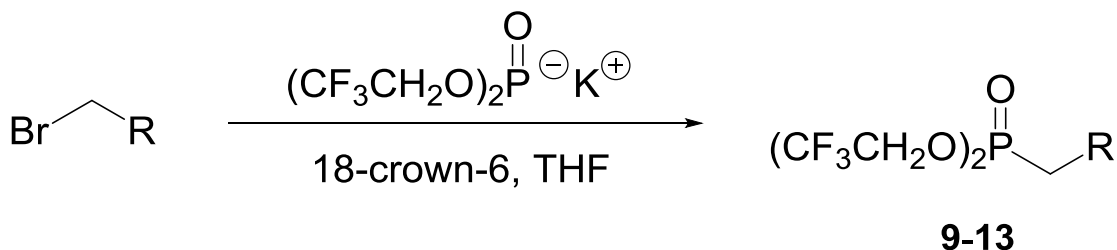
**Figure 5:** Differences in the  $^1\text{H}$  NMR Signals of Methine Protons of Compounds **7** and **8**..

A closer look at the  $^{13}\text{C}$  NMR spectrum of the compound **7** (**Figure 6**) shows that the two trifluoromethyl groups are in different chemical environments which results in the  $\text{CF}_3$  groups to be observed as two different doublet of quartets. One is observed at 122.55 ppm with a carbon-phosphorus coupling of 2.51 Hz, and a carbon-fluorine coupling of 277.50 Hz. The other is observed at 122.63 ppm with a carbon-phosphorus coupling of 2.84 Hz and a carbon-fluorine coupling of 277.52 Hz. This observation in the  $^{13}\text{C}$  NMR spectrum is noticeable since the phosphono ester synthesized is racemic. The (*R*) and (*S*) isomers of the phosphono ester **7** make the trifluoroethyl groups non-equivalent.



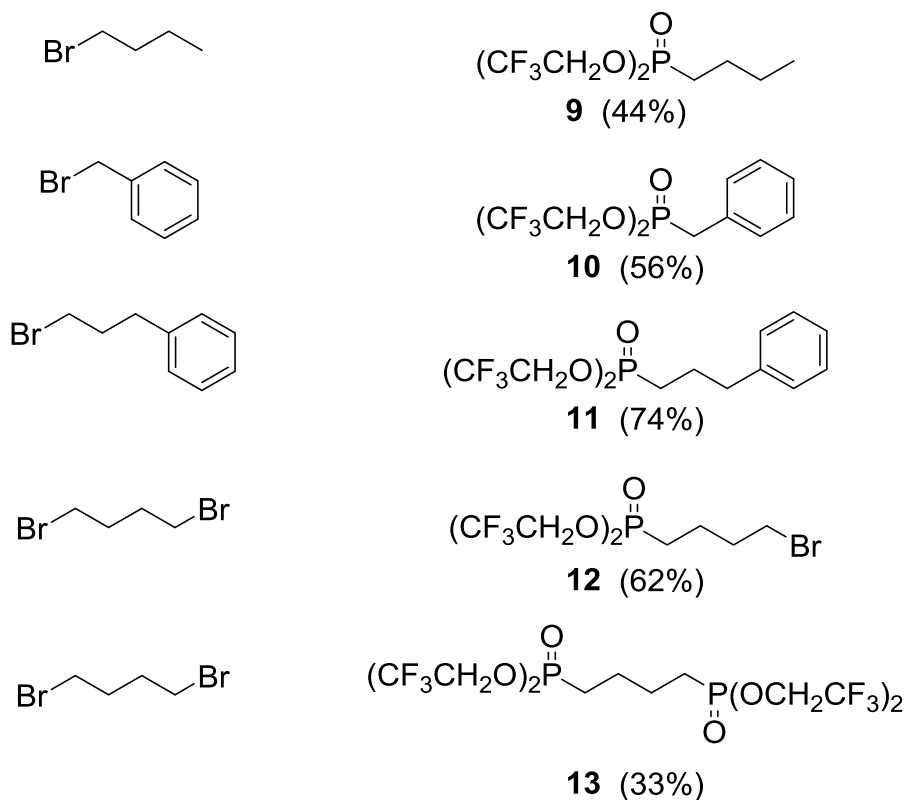
**Figure 6:** Expanded  $^{13}\text{C}$  NMR Spectra of Compound **7**.

## Part 2: Bis (2,2,2-trifluoroethyl) Phosphonates



### STARTING MATERIAL

### PRODUCT (YIELD)

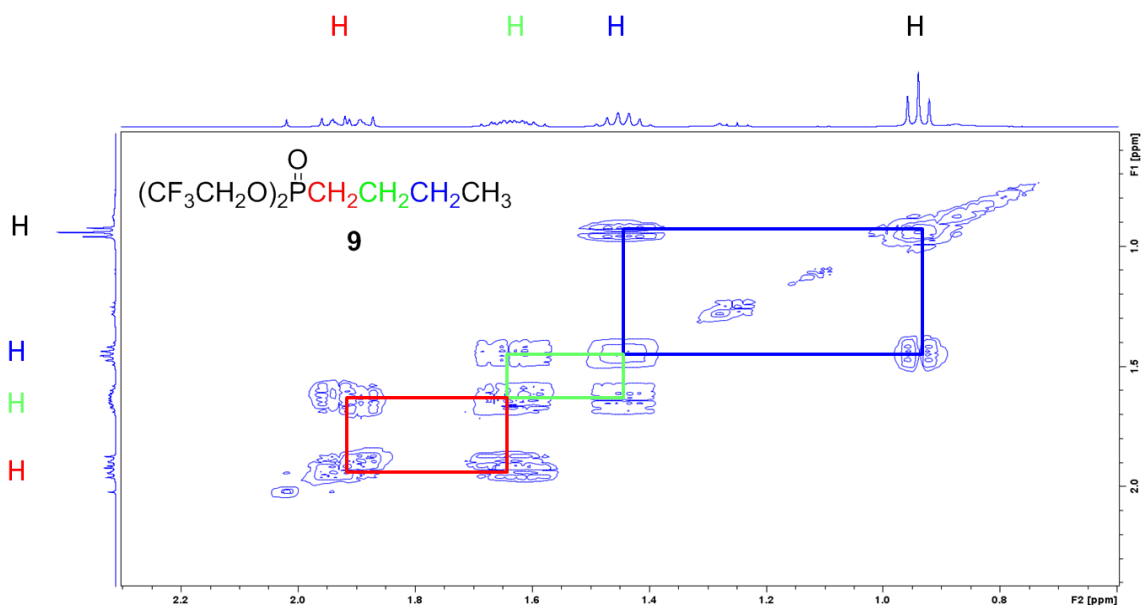


**Table 5:** Synthesis of Bis (2,2,2-trifluoroethyl) Phosphonates **9-13**.

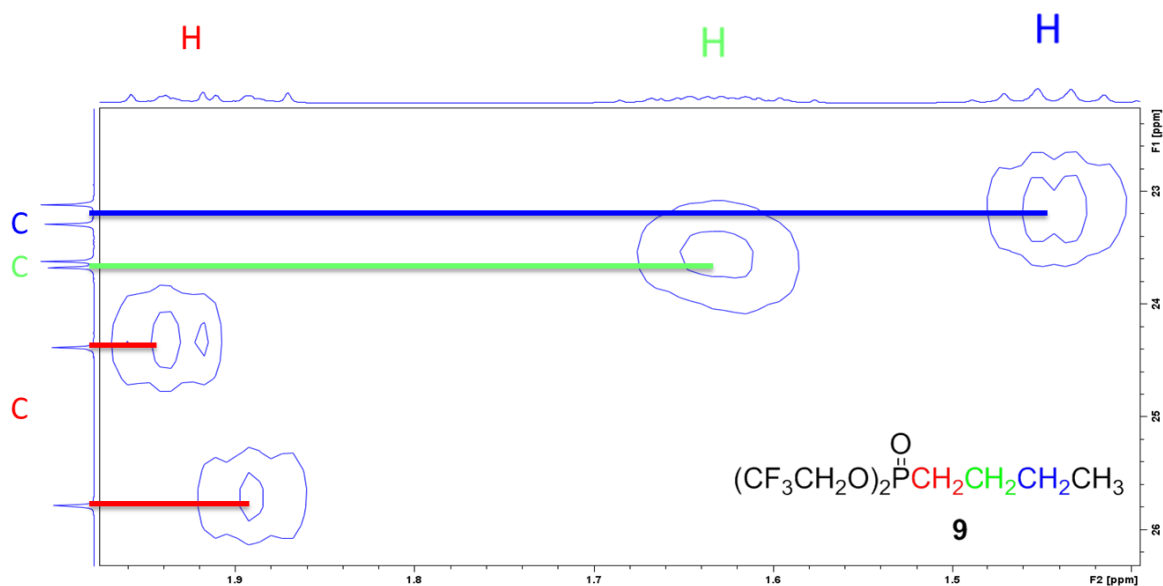
The reaction of primary alkyl and benzyl bromides with potassium bis (2,2,2-trifluoroethyl) phosphite afforded the successful synthesis of four bis (2,2,2-trifluoroethyl) phosphonates and one 1,4-bisphosphonate at moderate to good yields (24-74%). Phosphonate **10** required 2.1 equivalents of potassium bis (2,2,2-trifluoroethyl) phosphite to be added. The reason for this is by increasing the concentration of

nucleophile in the reaction, the rate of the reaction should also increase for  $S_N2$  reactions. Since 5.0 equivalents of 18-crown-6 are needed for every 1.0 equivalents of KHMDS, a total of 10.0 equivalents of 18-crown-6 and 2.0 equivalents of KHMDS were required in the synthesis of phosphonate **10**.

Compounds **9-13** have  $^{31}\text{P}$  NMR shifts between 30-36 ppm. The  $^1\text{H}$  NMR spectra of compounds **9**, **11**, and **13** show overlapping proton signals giving fewer signals than otherwise expected. It was useful to run 2D NMR experiments to help assign the proton and carbon signals of the synthesized bis (2,2,2-trifluoroethyl) phosphonates. With phosphonate **9** it can be assumed the most upfield triplet signal of the  $^1\text{H}$  NMR spectrum corresponds to the protons of the terminal methyl of the alkyl chain. This can be assumed since there is hardly a noticeable shift from starting material. The COSY spectrum (**Figure 7**) was used to identify the remaining proton signals of rest of the molecule. With the identities of the proton signals now known, the HSQC spectrum (**Figure 8**) was used to correlate the proton signals to the appropriate carbon signals.

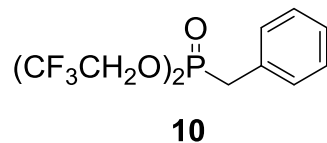


**Figure 7:** Expanded COSY Spectrum of Phosphonate **9**.



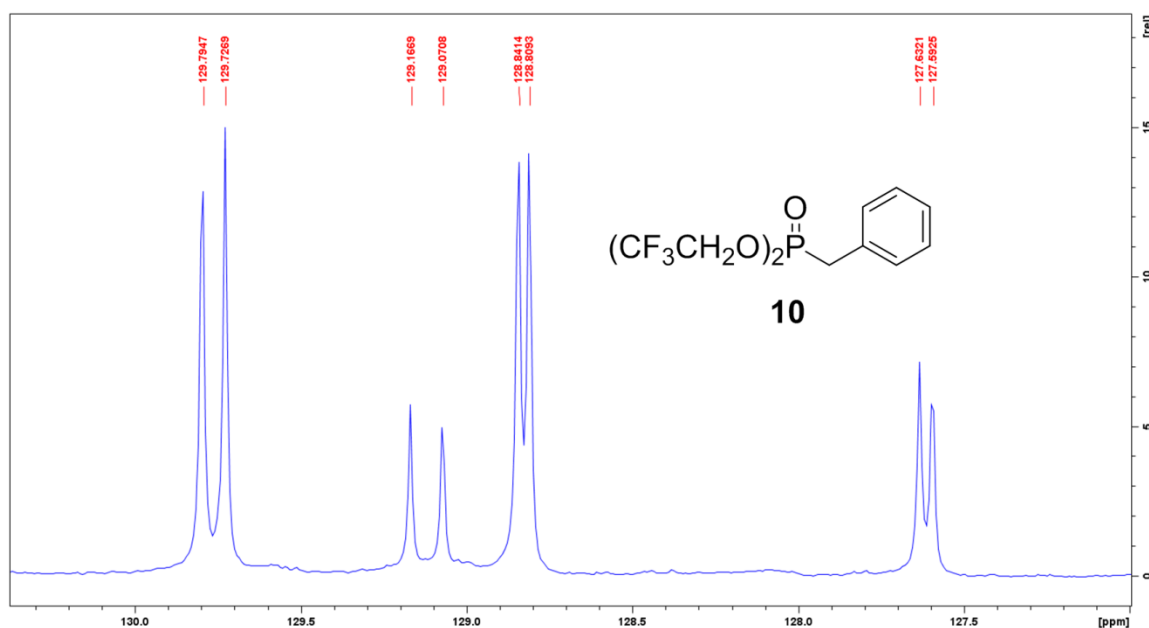
**Figure 8:** Expanded HSQC Spectrum of Phosphonate **9**.

It was shown that when 2 equivalents of bis (2,2,2-trifluoroethyl) phosphite were used, benzyl phosphonate **10** was synthesized at 56% yield, but when only 1 equivalent of potassium bis (2,2,2-trifluoroethyl) phosphite was used the yield dropped to 36%. The product was a white solid with a melting point of 68-72 °C. In the  $^1\text{H}$  NMR spectrum, the methylene protons directly attached to phosphorus are observed as a 2H doublet at 3.2 ppm with a proton-phosphorus coupling constant of 22 Hz. The expanded  $^{13}\text{C}$  NMR spectrum of phosphonate **10** (**Figure 9**) indicates that phosphorus splits all four aromatic carbons of the aromatic ring. **Table 6** summarizes  $^{13}\text{C}$  NMR data in the aromatic region for phosphonate **10**.



Carbon Shift (ppm)	$J_{C-P}$ (Hz)
127.6	3.9
128.8	3.2
129.1	9.6
129.8	6.8

**Table 6:** Aromatic  $^{13}\text{C}$  NMR Data for Benzyl Phosphonate **10**.

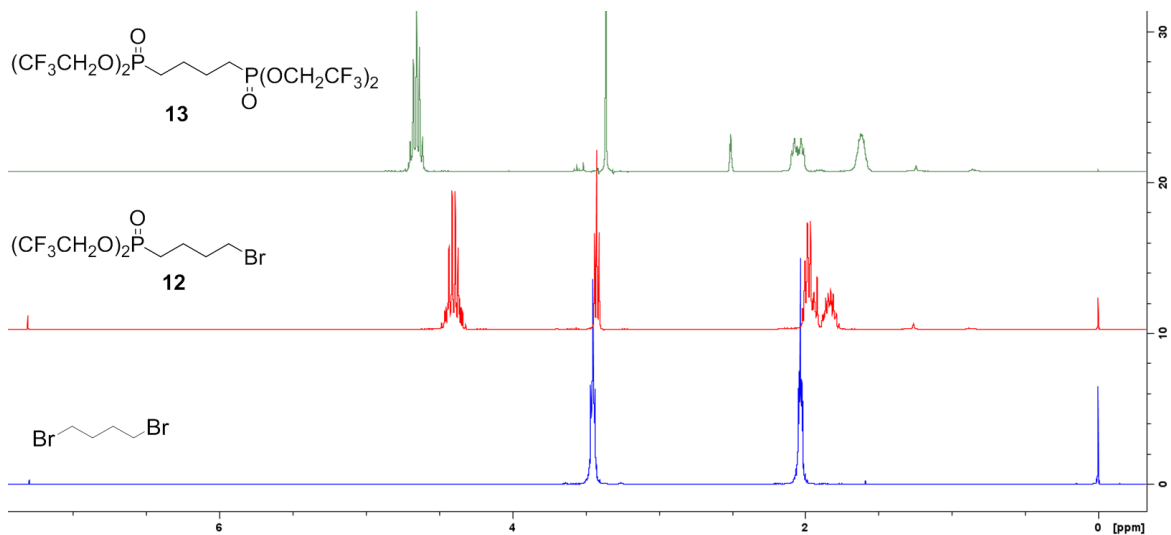


**Figure 9:** Expanded  $^{13}\text{C}$  NMR Spectrum of Alkyl Phosphonate **10**.

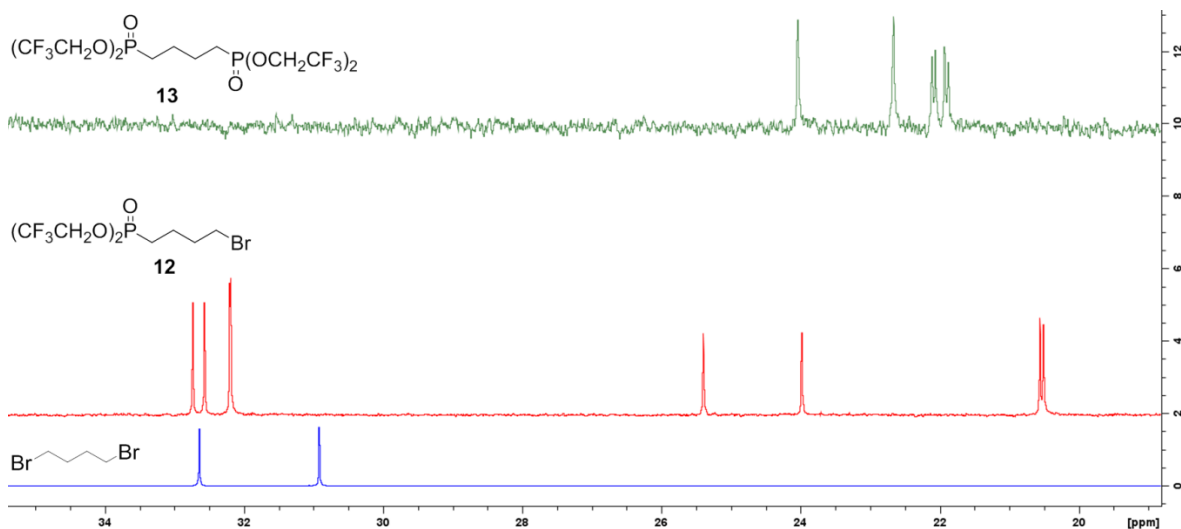
Compounds **12** and **13** were from the same reaction flask and separable by flash column chromatography. The major product (62%) is the mono-substituted alkyl phosphonate **12**, while the 1,4-bisphosphonate **13** was also synthesized at 33% yield. **Figure 10** overlays the  $^1\text{H}$  NMR spectra of the starting material and both compounds. There is conservation of the 2H triplet at 3.45 ppm which is present in the starting material and phosphonate **12**. As bis (2,2,2-trifluoroethyl) phosphite displaces one of the



bromines to make phosphonate **12**, more carbon signals are visible on the  $^{13}\text{C}$  NMR spectrum compared to the two carbon signals seen by the starting material. For bisphosphonate **13**, the beta carbon to the phosphoryl groups is observed as a doublet of doublets since this carbon is being split by both phosphorus's individually. **Figure 11** overlays the  $^{13}\text{C}$  NMR spectra the 1,4-dibromobutane and compounds **12** and **13**.



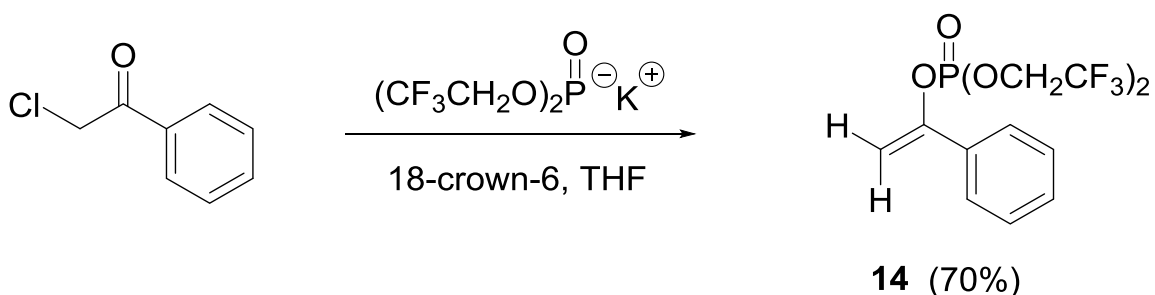
**Figure 10:** Overlay of the  $^1\text{H}$  NMR Spectra of 1,4-Dibromobutane, Compounds **12** and **13**.



**Figure 11:** Overlay of the  $^{13}\text{C}$  NMR Spectra of 1,4-Dibromobutane, Compounds **12** and **13**.

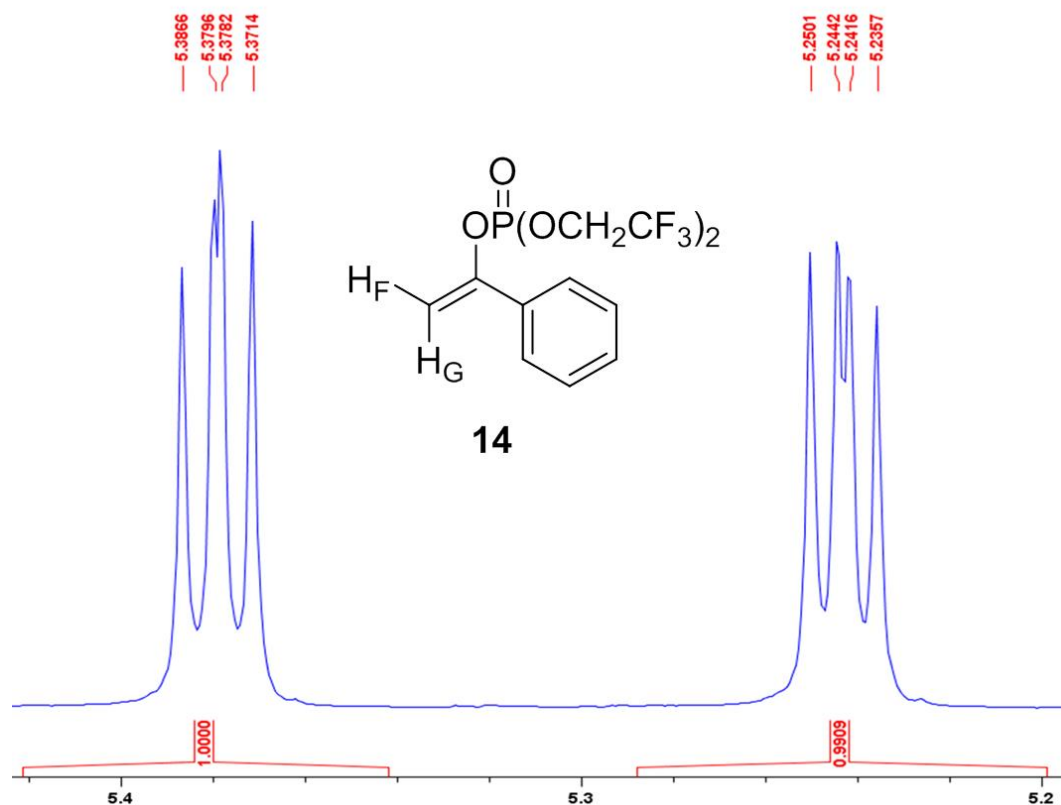
### Part 3: Bis (2,2,2-trifluoroethyl) Vinyl Phosphates

The reaction of  $\alpha$ -halo ketones with potassium bis (2,2,2-trifluoroethyl) phosphite yields bis (2,2,2-trifluoroethyl) vinyl phosphate as the major product and the formation of the (*Z*) isomer was favored when secondary  $\alpha$ -halo ketones were employed as the substrates. Interestingly the  $\beta$ -ketophosphonate product was not observed in any case. The most drastic difference between the vinyl phosphates **14-18** and the phosphono esters **2-8** is the  $^{31}\text{P}$  NMR signals for phosphono esters **2-8** are observed in the range of 23-27 ppm while vinyl phosphates **14-18** are observed between -6 and -7 ppm.



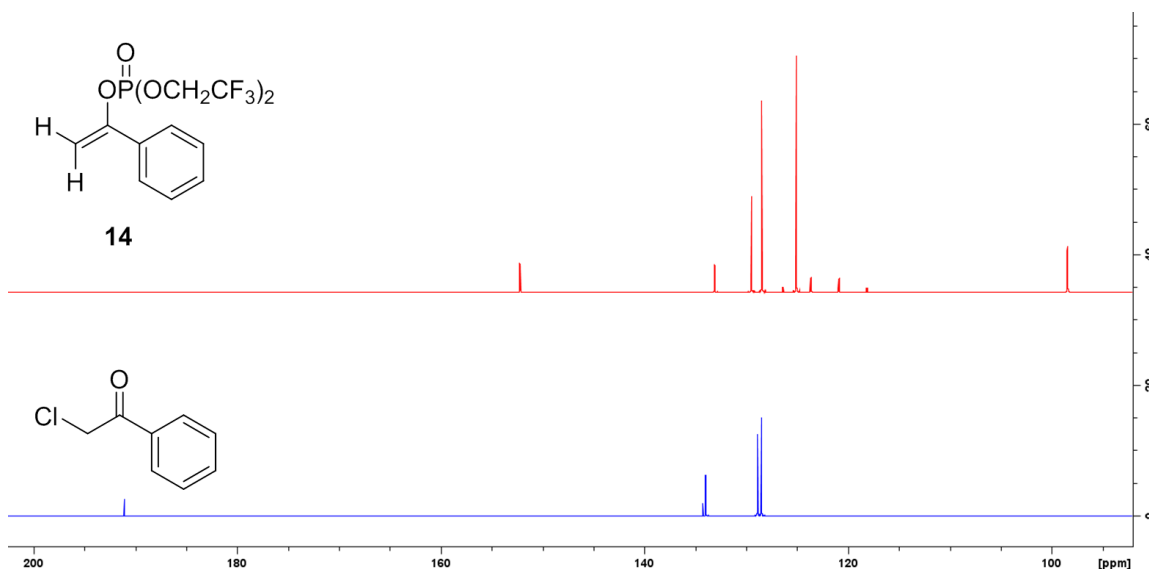
**Scheme 12:** Synthesis of Bis (2,2,2-trifluoroethyl) Vinyl Phosphate **14**.

The reaction of 2-chloroacetophenone with potassium bis (2,2,2-trifluoroethyl) phosphite (**Scheme 12**) yields vinyl phosphate **14** at 70% yield. Inspection of **Figure 12** shows the  $^1\text{H}$  NMR signals at 5.3 and 5.2 ppm are both doublet of doublets. The protons  $\text{H}_F$  and  $\text{H}_G$  will split each other into doublets, while phosphorus splits both into a doublet.

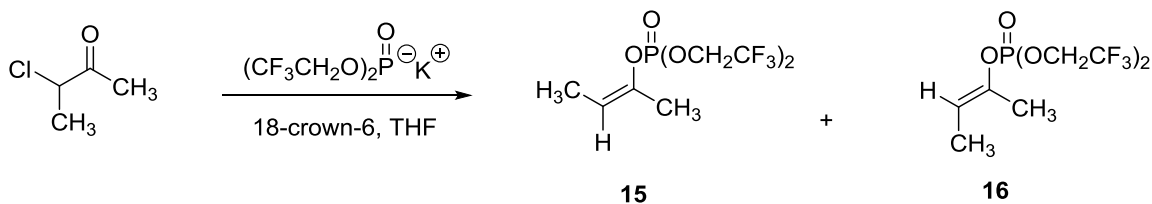


**Figure 12:** Expanded <sup>1</sup>H NMR Spectra of Vinyl Phosphate **14**.

The overlay the <sup>13</sup>C NMR spectra (**Figure 13**) of vinyl phosphate **14** and 2-chloroacetophenone indicates the carbonyl functionality is not present in vinyl phosphate. Also we observe two new carbon signals suggesting two new sp<sup>2</sup> hybridized carbons are present in the vinyl phosphate product. The doublet at 152.2 ppm with a carbon-phosphorus coupling constant of 8.1 Hz can be assigned to the carbon directly bonded to oxygen on the alkene. The other doublet observed at 98.5 ppm with a carbon-phosphorus coupling constant of 4.0 Hz corresponds to the alkene carbon bearing both protons.



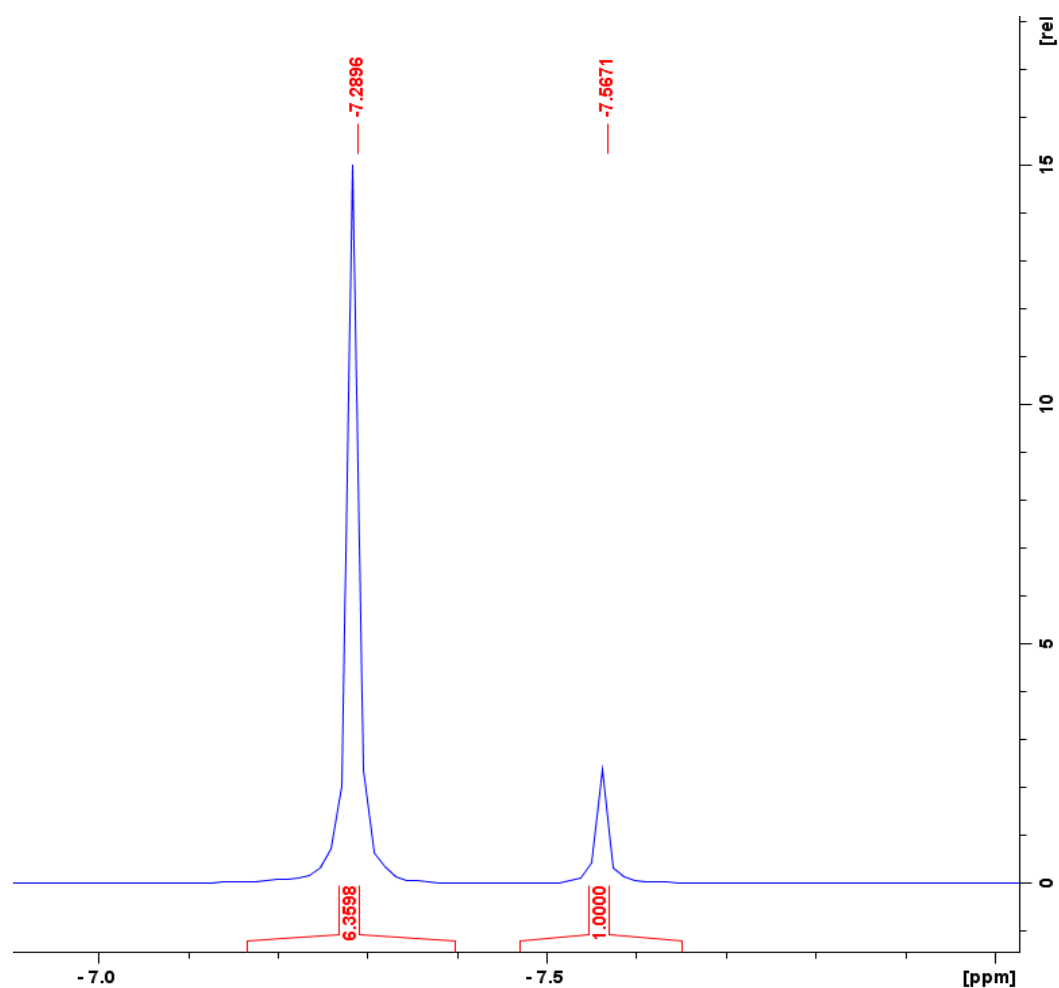
**Figure 13:** Overlay of the  $^{13}\text{C}$  NMR Spectra of 2-Chloroacetophenone and Compound **14**.



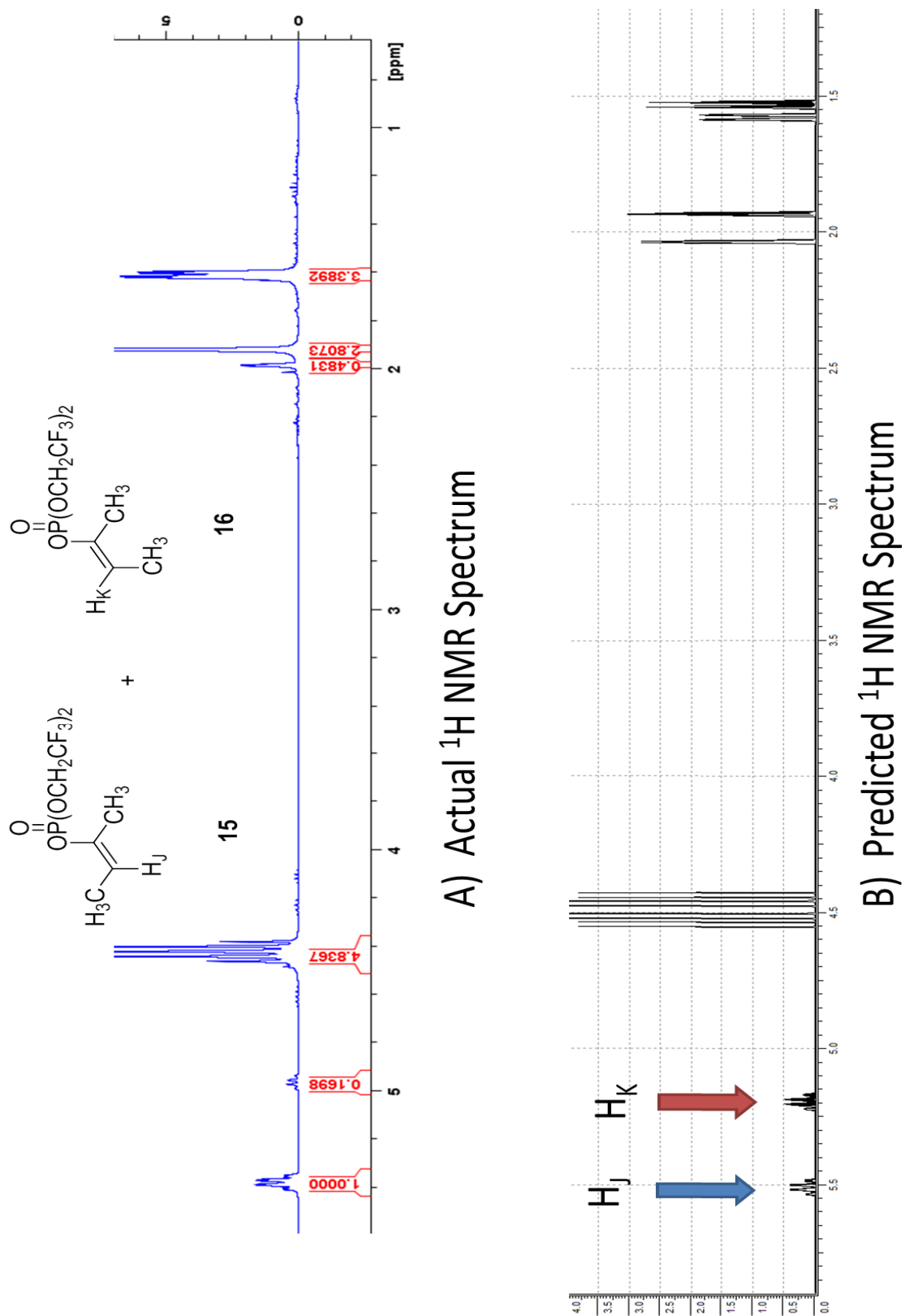
**Scheme 13:** Reaction of 3-Chloro-2-butanone and Potassium Bis (2,2,2-trifluoroethyl) Phosphite.

The reaction of 3-chloro-2-butanone with potassium bis (2,2,2-trifluoroethyl) phosphite (**Scheme 13**) yields a mixture of vinyl phosphates **15** and **16**. Both vinyl phosphates **15** and **16** were modelled in ACD software at a 1 to 1 ratio, and the most downfield proton signal was predicted to be the vinylic proton of vinyl phosphate **15**. That makes vinyl phosphate **15** the (*Z*) isomer. This signal can be found in the actual  $^1\text{H}$  NMR spectrum at 5.38 ppm. This means the proton signal at 4.96 ppm is the vinylic proton of vinyl phosphate **16** which makes that compound the (*E*) isomer. Furthermore integration values of the  $^1\text{H}$  NMR spectrum of compounds **15** and **16** indicate the ratio of (*Z*) to (*E*) isomers is 6:1. Integration of the  $^{31}\text{P}$  NMR peaks (**Figure 14**) is consistent with

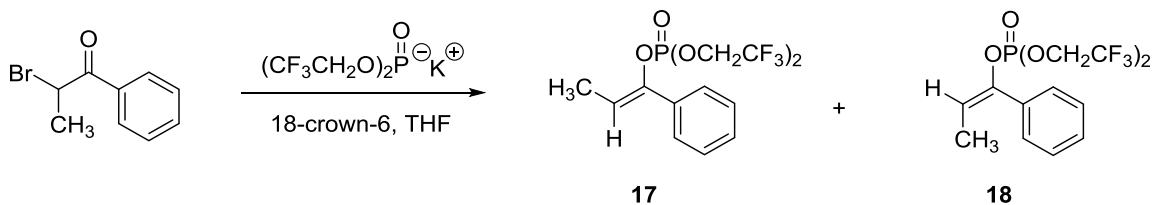
a 6:1 ratio of phosphorus peaks. This suggests the  $^{31}\text{P}$  NMR signal at -7.29 ppm is phosphorus signal associated with vinyl phosphate **15** leaving the other signal at -7.57 ppm to correspond to vinyl phosphate **16**. Since compounds **15** and **16** are inseparable after purification at a combined yield of 66.6%, we cannot accurately assign every proton and carbon signal to their respective protons and carbons. The actual  $^1\text{H}$  NMR spectrum of compounds **15** and **16** match up quite nicely to the predicted spectrum by ACD as shown in **Figure 15**.



**Figure 14:**  $^{31}\text{P}$  NMR Spectrum of the Mixture of Compounds **15** and **16**.



**Figure 15:** Actual and Predicted  $^1\text{H}$  NMR Spectra of Compounds **15** and **16**.



**Scheme 14:** Reaction of 2-bromopropiophenone with Potassium Bis (2,2,2-trifluoroethyl) Phosphite.

The reaction of 2-bromopropiophenone and potassium bis (2,2,2-trifluoroethyl) phosphite (**Scheme 14**) has generated three products after purification according to the  $^{31}\text{P}$  NMR spectrum (**Figure 16**) which account for a combined yield of 43.9%. Both the (*E*) and (*Z*) vinyl phosphates were modelled in ACD software at a 1:1 ratio, and the vinylic proton of compound **18** was predicted to be the most downfield non aromatic proton signal between the two compounds. This means the doublet of quartets signal found at 5.79 ppm in the actual  $^1\text{H}$  NMR spectrum, corresponds the vinylic proton of compound **18**. That makes compound **18** the (*E*) isomer. Similarly the doublet of quartets signal found slightly upfield at 5.71 ppm corresponds to the vinylic proton compound **17** which is the (*Z*) isomer. Integration of these signals indicates the ratio of (*Z*) to (*E*) isomers is 14:1. Integration of the  $^{31}\text{P}$  NMR shifts indicates a 15:1 ratio of phosphorus signals. With this correlation, the  $^{31}\text{P}$  NMR shift of compound **17** is -6.71 ppm, while the  $^{31}\text{P}$  NMR shift of compound **18** is -6.78 ppm.

Unlike compounds **15** and **16**, we can assign some of the observed proton signals for compounds **17** and **18**. Both of the vinylic methyl groups would appear as doublet of doublets since phosphorus and the respective vinylic proton would split those methyl groups into two separate doublets. The COSY spectrum (**Figure 17**) of the mixture of compounds **17-19** suggests the doublet of doublets signal at 1.85 ppm is the methyl group of compound **17**, while the methyl group of compound **18** could be observed at 1.74 ppm.

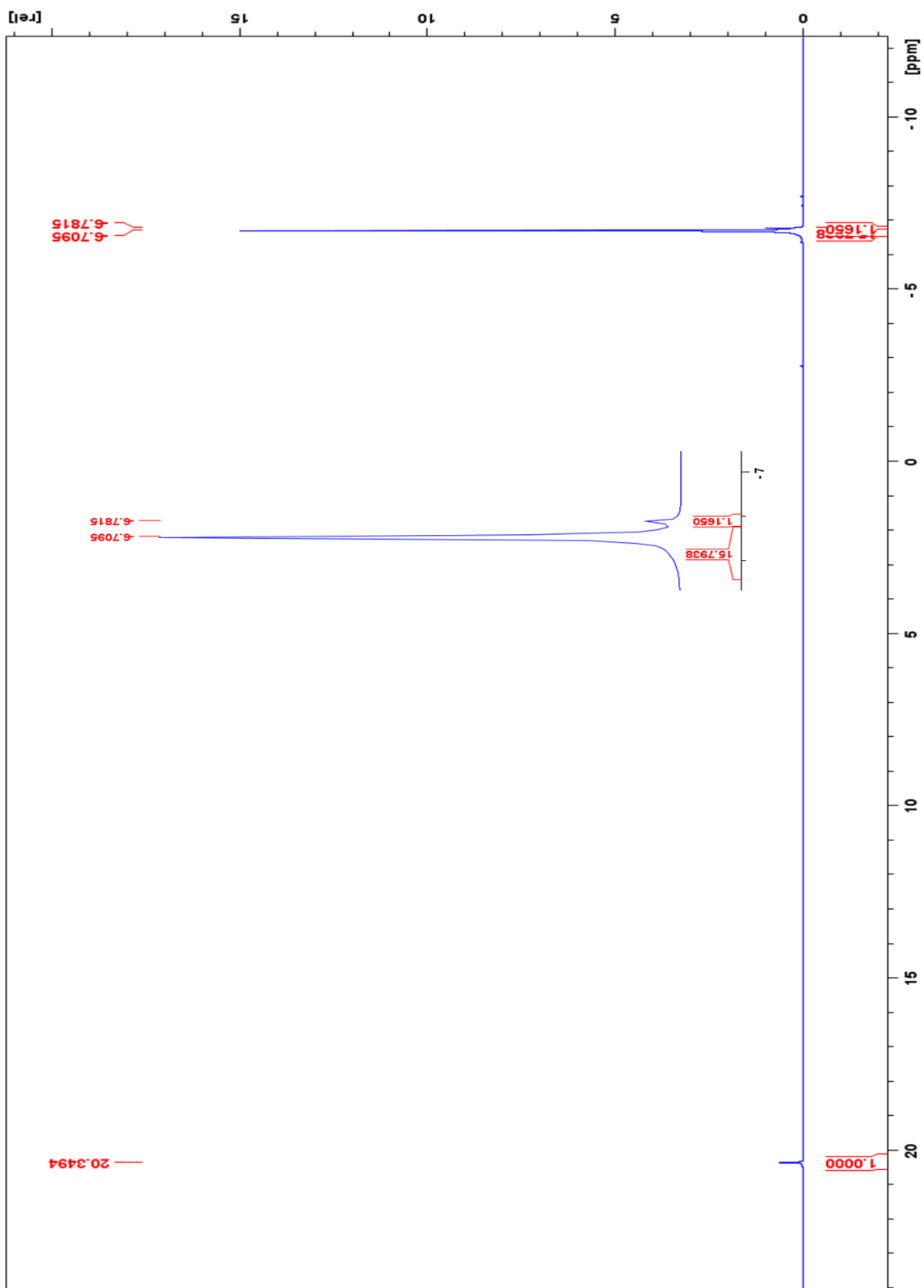
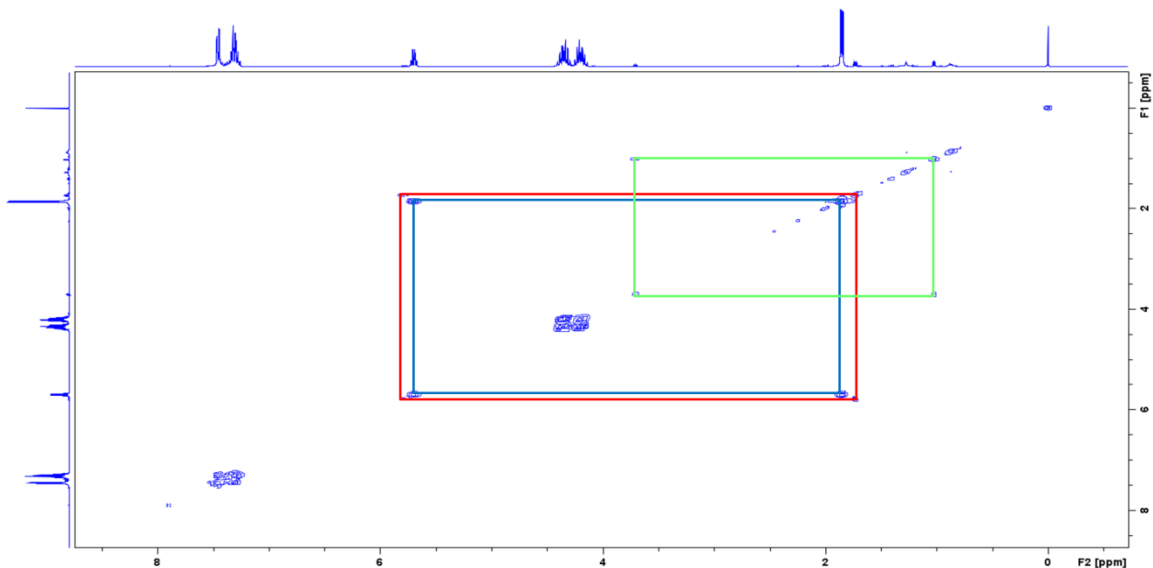


Figure 16:  $^{31}\text{P}$  NMR Spectrum of Compounds 17-19.





**Figure 17:** COSY Spectrum of Compounds **17-19**.

In addition to the vinyl phosphates **17** and **18**, there is evidence that trace amount of 1,2-epoxyphosphonate **19** has also formed during the reaction of 2-bromopropiophenone and potassium bis (2,2,2-trifluoroethyl) phosphite. The remaining  $^{31}\text{P}$  NMR peak at 20.5 ppm is in the expected range of 1,2-epoxyphosphonates (see **Table 2** in the Introduction). Upon closer inspection of the  $^1\text{H}$  NMR spectrum of the mixture of compounds **17-19**, we observe a doublet of doublets signal at 1.03 ppm which could correspond to the methyl of the 1,2-epoxyphosphonate **19**. Also observed is a doublet of quartets signal at 3.71 ppm. This corresponds to the methine proton of the 1,2-epoxyphosphonate. The proton-phosphorus and proton-proton coupling constants are equal, which is why the signal is observed as a doublet of quartets and not a quintet. Furthermore in the  $^{13}\text{C}$  NMR of the mixture of compounds **17**, **18**, and **19**, the carbon signals at 60.1 ppm with a carbon-phosphorus coupling constant of 204 Hz and the singlet at 58.3 ppm are consistent with other 1,2-epoxyphosphonates (see **Table 2** in the Introduction).

Interestingly when 3-chloro-2-butanone and 2-bromopropiophenone were used as reaction substrates, the formation of the (*Z*) isomer was favored over the formation of the (*E*) isomer. Note the ratio of (*Z*) to (*E*) isomers decreases from 14:1 to 6:1 as the phenyl ring is changed to a methyl group.

#### **Part 4: Summary and Conclusion**

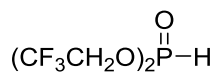
By modifying an the Ciszewski-Jackson method, it has been demonstrated that potassium bis (2,2,2-trifluoroethyl) phosphite in the presence of 5 equivalents of 18-crown-6 can react with primary  $\alpha$ -halo esters yielding the bis (2,2,2-trifluoroethyl) phosphono ester products in good yield (60-74%). Unfortunately reaction conditions are poor for secondary  $\alpha$ -halo esters (10-12% yield) due to steric reasons. The reaction scope was expanded to primary alkyl and primary benzyl bromides resulting in the successful formation of bis (2,2,2-trifluoroethyl) alkyl and benzyl phosphonates at moderate-good yields (24-74%). Upon further investigation of primary and secondary  $\alpha$ -halo ketones, the major products are vinyl phosphates and the  $\beta$ -ketophosphonate product was not observed in any case. In the case of 2-bromopropiophenone, the ratio of (*Z*) to (*E*) isomers is 14:1 and there is evidence of the 1,2-epoxyphosphonate formation. The selectivity of (*Z*) to (*E*) isomers decreased to 6:1 when 3-chloro-2-butanone was used as a reaction substrate suggesting the size of the groups influence the selectivity. Future studies could be taken to see the product distribution of the reaction between potassium bis (2,2,2-trifluoroethyl) phosphite with  $\alpha$ -iodo ketones.

## **Chapter 3: Experimental Section**

### **General Methods**

Dichloromethane was distilled from  $\text{CaH}_2$ , and THF was distilled from sodium benzophenone ketyl. All reagents were ordered from Aldrich and used without purification unless otherwise stated. All reactions were carried out under inert Argon gas atmosphere unless otherwise stated. Flash column chromatography was carried out on Merck grade 9385, 240 – 400 mesh, 60 Å silica. Thin Layer Chromatography (TLC) was performed on aluminium backed plates. The viewing of TLC plates were carried out by UV visualization or PMA stain.

NMR ( $^{31}\text{P}$ ,  $^1\text{H}$ , and  $^{13}\text{C}$ ) spectra were recorded on Bucker, 400 MHz spectrometer using  $\text{CDCl}_3$  as a solvent unless otherwise stated.  $^1\text{H}$  NMR chemical shifts (ppm) reported are relative to the internal standard TMS at 0.00 ppm; while  $^{13}\text{C}$  NMR chemical shifts (ppm) are reported relative to the internal standard  $\text{CDCl}_3$  at 77.00 ppm.  $^{31}\text{P}$  NMR chemical shifts (ppm) are reported relative to the external standard phosphoric acid. Coupling constants are reported in Hz.



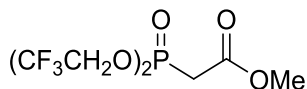
### **Bis (2,2,2-trifluoroethyl) phosphite (1)<sup>29</sup>**

A solution of phosphorus trichloride (43.5 mL, 0.50 mol) in dichloromethane (100 mL) was placed in an oven dried 1L round bottom flask. A reflux condenser and pressure equalizing addition funnel were attached to the round bottom flask. The addition funnel was charged with a solution of 2-methyl-2-propanol (48.0 mL, 0.50 mol) in dichloromethane (100 mL), and then the contents of the addition funnel were added in a dropwise manner to the round bottom flask under argon gas at 0 °C over the course of 30 min. The reaction mixture was allowed to stir for an additional 30 min, then the addition funnel is recharged with a solution of 2,2,2-trifluoroethanol (70.0 mL, 0.96 mol) and dichloromethane (100 mL) and then the contents of the addition funnel were added in a dropwise manner to the round bottom flask under argon gas at 0 °C over the course of 30 min. The reaction mixture was then allowed to stir at RT overnight. The gaseous vapors were then degassed into NaOH (30.2 g, 0.98 mol) in 200 mL of water over the course of 8 hrs. The solvents were removed by rotary evaporation and the crude material was fractionally distilled under reduced pressure yielding phosphite **1** (100.89 g, 0.41 mol, 82.2%) as colorless liquid.

<sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 7.99.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.27 – 4.38 (m, 4H), 6.92 (d, *J* = 755.20 Hz, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 61.41 (dq, *J* = 5.43, 38.37 Hz), 122.28 (dq, *J* = 7.83, 276.87 Hz).



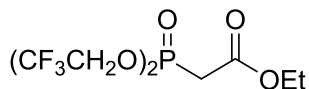
### General Procedure For the Synthesis of Methyl 2-(bis(2,2,2-trifluoroethyl)phosphoryl) acetate (**2**)

To a stirred solution of dried 18-crown-6 (4.53 g, 17.14 mmol), THF (20 mL), and phosphite **1** (0.70 mL, 1.29 mmol), was added KHMDS (9.0 mL, 4.50 mmol, 0.5M in toluene) by syringe in a dropwise manner at -78 °C. After 15 min, methyl chloroacetate (0.30 mL, 3.41 mmol) was added and the reaction mixture was allowed to stir for 4 hr at room temperature. The reaction mixture was diluted with EtOAc (20 mL) and then quenched with sat. ammonium chloride (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried under anhydrous magnesium sulfate. Following filtration, the solvents were removed in vacuo. The crude product was then purified by flash column chromatography (33% EtOAc in hexanes,  $R_f = 0.22$  in 33% EtOAc in hexanes) yielding phosphono ester **2** (766 mg, 2.41 mmol, 70.3%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.00.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.22 (d,  $J = 21.36$  Hz, 2H), 3.76 (s, 3H), 4.46 – 4.54 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.14 (d,  $J = 143.75$  Hz), 52.38, 62.24 (dq,  $J = 5.43, 38.10$  Hz), 122.38 (dq,  $J = 8.43, 277.01$  Hz), 165.06 (d,  $J = 4.38$  Hz).



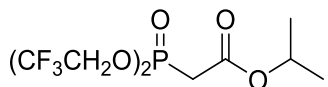
### Ethyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) acetate (**3**)

To stirred solution of 18-crown-6 (4.40 g, 16.65 mmol), THF (20 mL), and bis(2,2,2-trifluoroethyl) phosphite (**1**) (0.55 mL, 3.75 mmol), KHMDS (8.0 mL, 4.00 mmol, 0.5 M in toluene) was added via syringe in a dropwise manner at -78 °C. Ethyl chloroacetate (0.35 mL, 3.30 mmol) was added to the flask after 15 min. The reaction flask was allowed to warm to room temperature and stir for 4 hr. After standard workup procedure, the crude product was then purified by flash column chromatography (2:1-1:1 hexanes:EtOAc,  $R_f = 0.25$  in 2:1 hexanes:EtOAc) yielding phosphono ester **3** (808 mg, 2.43 mmol, 73.4%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.53.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (t,  $J = 7.16$  Hz, 3H), 3.16 (d,  $J = 21.09$  Hz, 2H), 4.23 (q,  $J = 7.15$  Hz, 2H), 4.41 – 4.52 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.40, 33.53 (d,  $J = 143.49$  Hz), 61.92, 62.26 (dq,  $J = 5.52, 38.10$  Hz), 122.38 (dq,  $J = 8.50, 277.10$  Hz), 164.55 (d,  $J = 4.42$  Hz).



### Isopropyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) acetate (**4**)

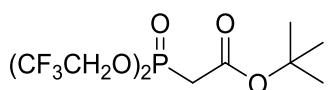
To a stirred solution of 18-crown-6 (4.10 g, 15.51 mmol), THF (30 mL), and phosphite **1** (0.60 mL, 3.77 mmol), was added KHMDS (8.0 mL, 4.00 mmol, 0.5 M in toluene) by syringe in a dropwise manner at -78 °C. The reaction was allowed to stir for 15 min, then isopropyl bromoacetate (0.40 mL, 3.09 mmol) was added to the round

bottom flask. The reaction mixture was allowed to warm to room temperature for 4 hr. After the standard workup procedure, the crude product was then purified by flash column chromatography (9:1-4:1 hexanes:EtOAc,  $R_f = 0.18$  in 2:1 hexanes:EtOAc) yielding phosphono ester **4** (661 mg, 1.91 mmol, 61.7%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.71.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28 (d,  $J = 6.28$  Hz, 6H), 3.13 (d,  $J = 21.09$  Hz, 2H), 4.40 – 4.52 (m, 4H), 5.07 (septet,  $J = 6.28$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.81, 33.69 (d,  $J = 142.38$  Hz), 62.14 (dq,  $J = 5.50, 38.08$  Hz), 69.70, 122.37 (dq,  $J = 8.60, 276.87$  Hz), 163.96 (d,  $J = 4.72$  Hz).



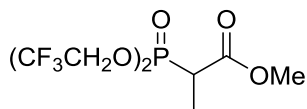
#### **Tert-butyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) acetate (5)**

To a stirred solution of 18-crown-6 (7.18 g, 27.16 mmol), THF (30 mL), bis(2,2,2-trifluoroethyl) phosphite (**1**) (0.95 mL, 5.97 mmol), KHMDS (13.0 mL, 6.50 mmol, 0.5 M in toluene) was added by syringe in a dropwise manner at  $-78$  °C. After 15 min, tert-butyl bromoacetate (0.80 mL, 5.41 mmol) was added to the round bottom flask and the reaction mixture warmed to room temperature over 4 hr. After workup procedure as outlined in the general method, the crude product was then purified by flash column chromatography (6:1-3:1 hexanes:EtOAc,  $R_f = 0.19$  in 3:1 hexanes:EtOAc) yielding phosphono ester **5** (1.345 g, 3.73 mmol, 69.0%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.06.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (s, 9H), 3.08 (d,  $J = 21.05$  Hz, 2H), 4.37 – 4.52 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  27.39, 34.96 (d,  $J = 141.70$  Hz), 62.27 (dq,  $J = 5.39, 38.14$  Hz), 83.00, 122.42 (dq,  $J = 8.52, 277.11$  Hz), 163.46 (d,  $J = 4.95$  Hz).



### **Methyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) propionate (6)**

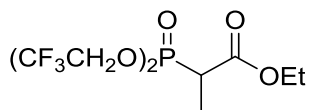
KHMDS (8.0 mL, 4.00 mmol, 0.5M in toluene) was added by syringe to a solution of dried 18-crown-6 (4.20 g, 15.89 mmol), THF (20 mL), and phosphite **1** (0.55 mL, 3.75 mmol) at  $-78$  °C. Following 15 min, methyl 2-bromopropionate (0.35 mL, 3.14 mmol) was added to the reaction flask. The reaction mixture was allowed to warm to room temperature for 4hr. The standard workup protocol was followed, then the crude product was purified by flash column chromatography (9:1-3:2 hexanes:EtOAc,  $R_f = 0.22$  in 1:1 hexanes:EtOAc) yielding phosphono ester **6** (103 mg, 31 mmol, 9.9%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.96.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.48 (dd,  $J = 7.38, 19.31$  Hz, 3H), 3.19 (dq,  $J = 7.57, 22.68$  Hz, 1H), 3.71 (s, 3H), 4.30 – 4.43 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  11.58 (d,  $J = 6.58$  Hz), 39.33 (d,  $J = 141.30$  Hz), 53.02, 62.59 (dq,  $J = 5.71, 38.48$  Hz), 122.40 (dq,  $J = 1.81, 277.66$  Hz), 122.47 (dq,  $J = 2.00, 277.48$  Hz) 168.94 (d,  $J = 2.99$  Hz).





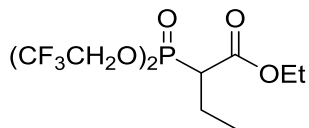
### Ethyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) propionate (7)

KHMDS (7.50 mL, 3.75 mmol, 0.5 M in toluene) was added to a solution of 18-crown-6 (4.10 g, 15.51 mmol), THF (20 mL), and bis (2,2,2-trifluoroethyl) phosphite (**1**) (0.50 mL, 3.41 mmol) by syringe in a dropwise manner at -78 °C. Following 15 min, ethyl 2-bromopropionate (0.40 mL, 3.08 mmol) was added to the round bottom flask and the reaction mixture was allowed to stir for 4 hr at room temperature. Following the standard workup procedure, the crude product was then purified by flash column chromatography (3:1 to 2:1 hexanes:EtOAc,  $R_f = 0.33$  in 1:1 hexanes:EtOAc) yielding ester **7** (112 mg, 0.33 mmol, 10.5%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  27.17.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (t,  $J = 7.16$  Hz, 3H), 1.54 (dd,  $J = 7.40, 19.37$  Hz, 3H), 3.23 (dq,  $J = 7.51, 22.60$  Hz, 1H), 4.23 (q,  $J = 7.13$  Hz, 2H), 4.35 – 4.52 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  11.60 (d,  $J = 6.52$  Hz), 13.97, 39.65 (d,  $J = 140.51$  Hz), 62.24, 62.68 (dq,  $J = 5.81, 38.13$  Hz), 122.55 (dq,  $J = 2.51, 277.50$  Hz), 122.63 (dq,  $J = 2.84, 277.52$  Hz), 168.52 (d,  $J = 3.07$  Hz).



### Ethyl 2-(bis(2,2,2-trifluoroethyl) phosphoryl) butanoate (8)

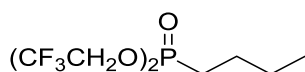
To stirred solution of dried 18-crown-6 (4.50 g, 17.02 mmol), THF (20 mL), and phosphite **1** (0.55 mL, 3.75 mmol) was added KHMDS (8.5 mL, 4.25 mmol, 0.5 M in

toluene) in a dropwise manner by syringe at  $-78\text{ }^{\circ}\text{C}$ . After 15 min, ethyl 2-bromobutyrate (0.50 mL, 3.38 mmol) was added to the flask and after continuous stirring for 4 hr at room temperature the typical workup protocol was followed. The crude product was then purified by flash column chromatography (7:1-4:1 hexanes:EtOAc,  $R_f = 0.14$  in 2:1 hexanes:EtOAc) yielding phosphono ester **8** (168 mg, 0.47 mmol, 13.8%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.13.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.97 (dt,  $J = 0.65, 7.42$  Hz, 3H), 1.23 (t,  $J = 7.14$  Hz, 3H), 1.83 – 2.00 (m, 2H), 2.96 (ddd,  $J = 4.93, 9.57, 21.58$  Hz, 1H), 4.19 (q,  $J = 7.14$  Hz, 2H), 4.27 – 4.41 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.54 (d,  $J = 14.96$  Hz), 13.99, 20.73 (d,  $J = 5.56$  Hz), 47.11 (d,  $J = 137.05$  Hz), 62.09, 62.31 (dq,  $J = 6.72, 37.66$  Hz), 62.66 (dq,  $J = 6.15, 40.66$  Hz), 122.55 (dq,  $J = 2.51, 277.50$  Hz), 122.63 (dq,  $J = 2.84, 277.52$  Hz), 168.03 (d,  $J = 3.50$  Hz).



### General Procedure For the Synthesis of Bis (2,2,2-trifluoroethyl) butylphosphonate (9)

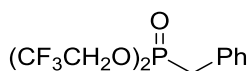
To a solution of 18-crown-6 (2.47 g, 9.34 mmol), THF (20 mL), and bis (2,2,2-trifluoroethyl) phosphite (**1**) (0.35 mL, 2.20 mmol) was added KHMDS (4.50 mL, 2.25 mmol, 0.5 M in toluene) by syringe in a dropwise manner at  $-78\text{ }^{\circ}\text{C}$ . After 15 min, 1-bromobutane (0.20 mL, 2.10 mmol) was added then the reaction mixture was allowed stir for 4 hr at room temperature. The reaction mixture was diluted with ethyl acetate (20

mL) and then quenched with sat. ammonium chloride (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were dried under anhydrous magnesium sulfate. Following filtration, solvents were removed in vacuo, and the crude product was then purified by flash column chromatography (25% EtOAc in hexanes,  $R_f = 0.43$  in 25% EtOAc in hexanes) yielding alkyl phosphonate **9** (251 mg, 0.83 mmol, 44.8%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  36.10.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.93 (t,  $J = 7.30$  Hz, 3H), 1.44 (sextet,  $J = 7.36$  Hz, 2H), 1.57 – 1.68 (m, 2H), 1.87 – 1.96 (m, 2H), 4.29 – 4.45 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  12.91, 23.16 (d,  $J = 17.80$  Hz), 23.58 (d,  $J = 5.70$  Hz), 24.99 (d,  $J = 141.12$  Hz), 61.55 (dq,  $J = 6.05, 37.85$  Hz), 122.55 (dq,  $J = 7.86, 277.24$  Hz).



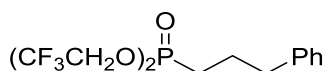
### **Bis (2,2,2-trifluoroethyl) benzylphosphonate (10)**

To a stirred solution of 18-crown-6 (8.93 g, 33.78 mmol), THF (30 mL), and phosphite **1** (1.15 mL, 7.22 mmol) was added KHMDS (15.0 mL, 7.50 mmol, 0.5 M in toluene) by syringe in a dropwise manner at  $-78$  °C. After 15 min, benzyl bromide (0.40 mL, 3.36 mmol) was added to the round bottom flask at  $-78$  °C. After continuous stirring over 4 hr at room temperature the general workup protocol was followed. The crude product was then purified by flash column chromatography (25% EtOAc in hexanes,  $R_f = 0.21$  in 25% EtOAc in hexanes) yielding phosphonate **10** (635 mg, 1.89 mmol, 56.2%) as a white solid (mp =  $68-71$  °C).

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.69.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.29 (d,  $J = 22.25$  Hz, 2H), 4.08 – 4.33 (m, 4H), 7.27 – 7.34 (m, 5H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  33.19 (d,  $J = 139.59$  Hz), 62.15 (dq,  $J = 6.31, 37.89$  Hz), 122.53 (dq,  $J = 7.75, 277.35$  Hz), 127.61 (d,  $J = 3.98$  Hz), 128.83 (d,  $J = 3.23$  Hz), 129.12 (d,  $J = 9.67$  Hz), 129.76 (d,  $J = 6.82$  Hz).



**Bis (2,2,2-trifluoroethyl) (3-phenylpropyl) phosphonate (11)**

KHMDS (8.00 mL, 4.00 mmol, 0.5 M in toluene) was added via syringe in a dropwise manner at  $-78$  °C to a solution of dried 18-crown-6 (4.37 g, 16.53 mmol), THF (30 mL), and phosphite **1** (0.60 mL, 3.77 mmol). After 15 min, 1-bromo-3-phenylpropane (0.50 mL, 3.29 mmol) was added to the flask, and the reaction mixture was allowed stir overnight at room temperature. The general workup procedure was followed and the crude material was then purified by flash column chromatography (3:1 hexanes:EtOAc,  $R_f = 0.38$  in 3:1 hexanes:EtOAc) yielding alkyl phosphonate **11** (892 mg, 2.45 mmol, 74.3%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  35.41.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.77 – 1.96 (m, 4H), 2.64 (t,  $J = 7.30$  Hz, 2H), 4.24 – 4.39 (m, 4H), 7.10 – 7.26 (m, 5H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.32 (d,  $J = 4.96$  Hz), 24.57 (d,  $J = 141.47$  Hz), 35.77 (d,  $J = 17.34$  Hz), 61.57 (dq,  $J = 5.97, 37.70$  Hz), 122.79 (dq,  $J = 7.92, 277.25$  Hz), 126.15, 128.30, 128.40, 140.40.

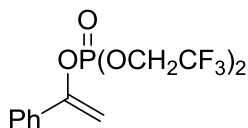


### Bisphosphonate **13**

$^{31}\text{P}$  NMR (DMSO- $d_6$ )  $\delta$  35.05.

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.58 – 1.63 (m, 4H), 2.01 – 2.09 (m, 4H), 4.60 – 4.71 (m, 8H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  20.08 (dd,  $J$  = 5.21, 18.50 Hz), 23.34 (d,  $J$  = 138.28 Hz), 61.15 (dq,  $J$  = 5.57, 36.41 Hz), 123.17 (dq,  $J$  = 8.75, 277.57 Hz).



### **1-phenylvinyl bis (2,2,2-trifluoroethyl) phosphate (14)**

To a stirred solution of 18-crown-6 (4.30 g, 16.27 mmol), THF (30 mL), and phosphite **1** (0.60 mL, 3.77 mmol) was added KHMDS (8.0 mL, 4.00 mmol) by syringe in a dropwise manner at  $-78\text{ }^\circ\text{C}$ . After 15 min, 2-chloroacetophenone (0.50 g, 3.23 mmol, in 5.0 mL of ether) was added to the round bottom flask at  $-78\text{ }^\circ\text{C}$  by syringe. The reaction flask was allowed to warm to room temperature, and after 4 hr the reaction mixture was diluted with EtOAc (20 mL) and quenched with sat. ammonium chloride (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL) then dried under anhydrous magnesium sulfate. Following filtration, the solvents were removed by rotary evaporation, and the crude product was then purified by flash column chromatography (9:1-7:1 hexanes:EtOAc,  $R_f$  = 0.14 in 5:1 hexanes:EtOAc) yielding vinyl phosphate **14** (826 mg, 2.27 mmol, 70.0%) as a yellow syrup.

$^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -7.30.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.35 – 4.53 (m, 4H), 5.24 (dd,  $J$  = 2.36, 3.40 Hz, 1H), 5.38 (dd,  $J$  = 2.76, 3.32 Hz, 1H), 7.38 – 7.40 (m, 3H), 7.54 – 7.56 (m, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  64.16 (dq,  $J$  = 4.48, 38.40 Hz), 98.46 (d,  $J$  = 3.96 Hz), 122.28 (dq,  $J$  = 9.71, 277.27 Hz), 125.10, 128.47, 129.50, 133.11 (d,  $J$  = 6.49 Hz), 152.23 (d,  $J$  = 8.10 Hz).

## References:

1. Rogers, M. J.; Crockett, J. C.; Coxon, F. P.; Monkkonen, J. *Bone*. **2011**, *49*, 34-41.
2. Russell, R. C. *Bone*. **2011**, *49*, 2-19.
3. Cremers, S.; Papapoulos, S. *Bone*. **2011**, *49*, 42-49.
4. Puljula, E.; Turhanen, P.; Vespäläinen, J.; Monteil, M.; Lecouvey, M. *ACS Med. Chem. Lett.* **2015**, *6*, 397-401.
5. Castillo, A.; Silva, L.; Briones, D.; Quilez del Moral, J. F.; Barrero, A. F. *Eur. J. Org. Chem.* **2015**, 3266-3273.
6. Urosa, A.; Marcos, I. S.; Diez, D.; Padron, J. M.; Basabe, P. *J. Org. Chem.* **2015**, *80*, 6447-6455.
7. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.
8. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 41, 4405-4408.
9. Messik, F.; Oberthür, M. *Synthesis*. **2013**, *45*, 167-170.
10. Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Org. Syn.* **1998**, *9*, 88.
11. Ciszewski, G. M.; Jackson, J. A. *Org. Prep. Proced. Int.* **1999**, *31*, 240-243.
12. Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRC Press: Boca Raton, Florida, **2003**.
13. Gryzkiewicz-Trochimowski, E. *Bull. Soc. Chem. Fr.* **1967**, 4289.
14. Bergstrom, D. E.; Shum, P. W. *Tetrahedron Lett.* **1982**, *23*, 2323.
15. Canavan, A. E.; Eaborn, C. *J. Chem. Soc.* **1959**, 3751.
16. Arbuzov, B. A.; Lugovkin, B. P. *Chem. Abstr.* **1951**, *45*, 7002e.



17. Kers, A.; Stawiński, J.; Dembkowski, L.; Krasweski, A. *Tetrahedron*. **1997**, *53*, 37, 12691-12698.
18. Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607-649.
19. Pudovik, A. N.; Anova, V. P. *Chem. Abstr.* **1956**, *50*.
20. Kossev, K.; Troev, K.; Roundhill, D. M. *Phosphorus, Sulfur, Silicon Rel. Elem.* **1993**, *83*, 1.
21. Arbuzov, B. A.; Vinogradova, V. S.; Polezhaeva, N. A. *Chem. Abstr.* **1959**, *53*, 1180i.
22. Borowitz, I. J.; Firstenberg, S.; Borowitz, G. B.; Schuessler, D. *J. Am. Chem. Soc.* **1972**, *95*, 4, 1623 – 1628.
23. Allen, J. F.; Johnson, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 2871 – 2875.
24. Kharasch, M. S.; Bengelsdorf, I. S. *J. Org. Chem.* **1955**, *20*, 1356 – 1362.
25. Chopard, P. A.; Clark, V. M.; Hudson, R. F.; Kirby, A. J. *Tetrahedron*. **1965**, *21*, 1961 – 1969.
26. Miller, B. *J. Org. Chem.* **1961**, *28*, 4781.
27. Miller, B. *J. Org. Chem.* **1963**, *30*, 345 – 348.
28. Cristau, H.; Mbianda, X. Y.; Geze, A.; Beziat, Y.; Gasc, M. *Journal of Organometallic Chemistry*. **1998**, *571*, 189-193.
29. Doak, G. O.; Freedman, L. D. *Chem. Rev.* **1960**, *60*, 31-44.
30. Gibbs, D. E.; Larsen, C. *Synthesis*. **1984**, 410 – 413.

**Figure 18:**  $^{31}\text{P}$  NMR Spectrum of Compound 1

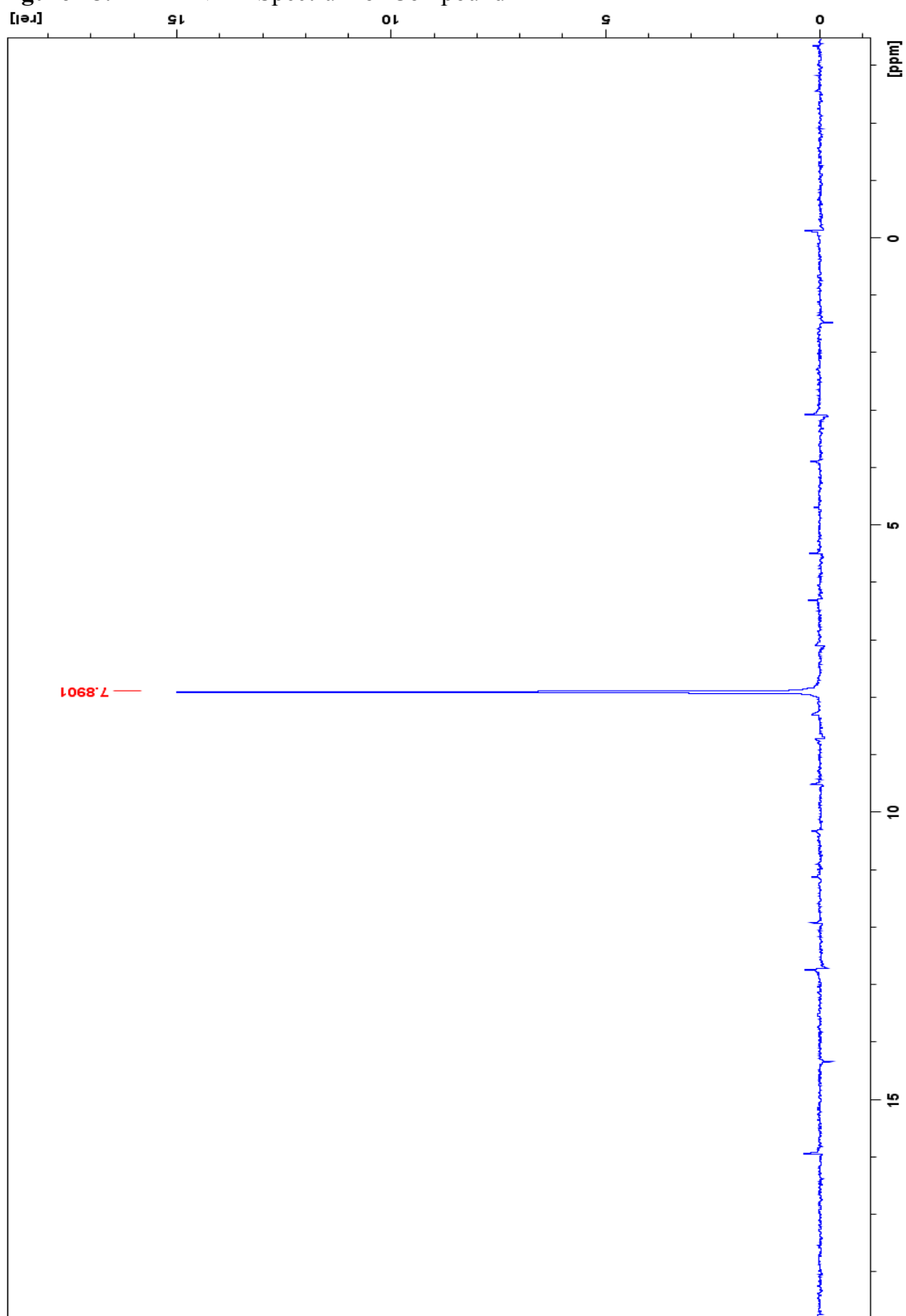


Figure 19:  $^1\text{H}$  NMR Spectrum of Compound 1

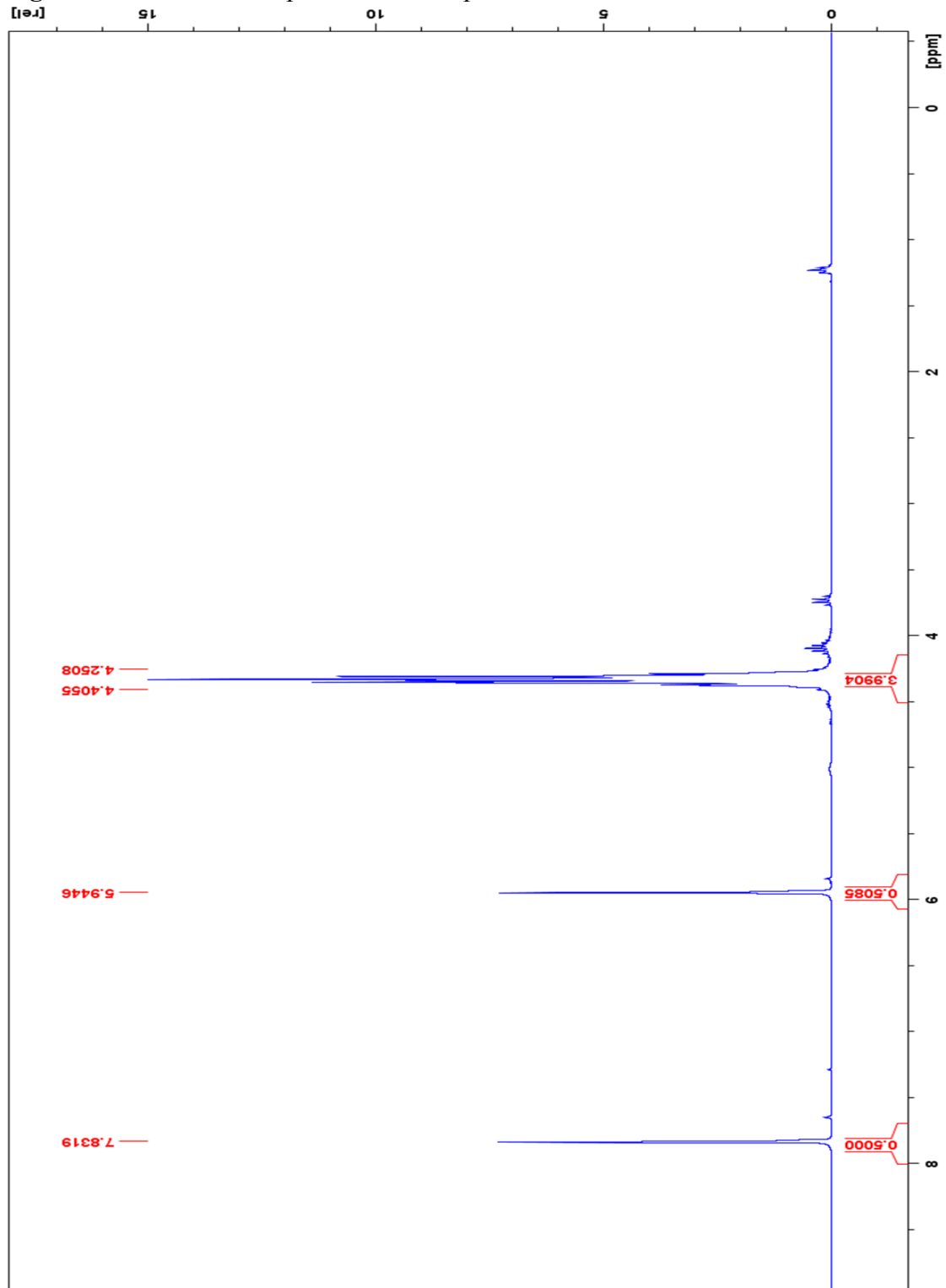
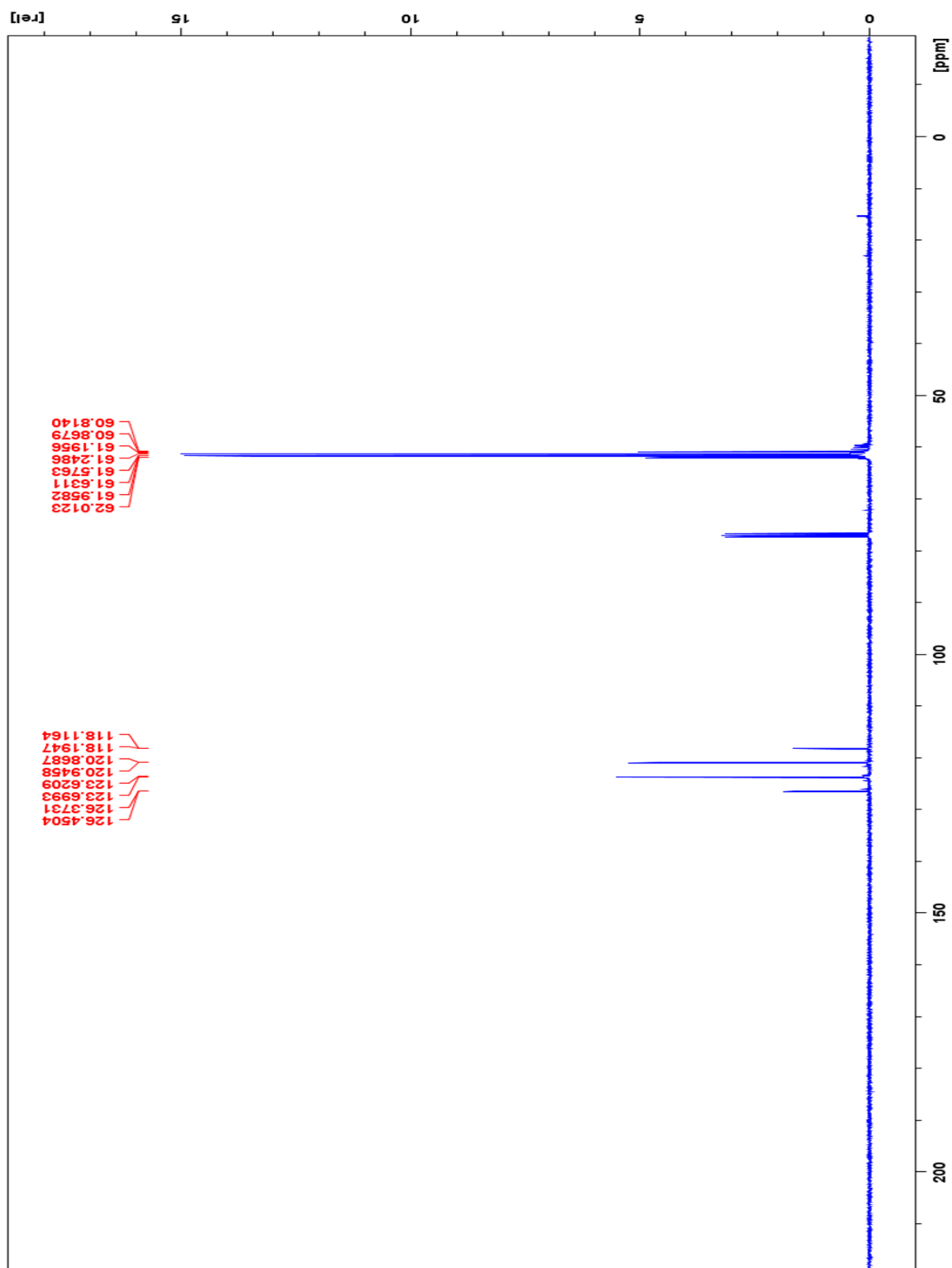


Figure 20:  $^{13}\text{C}$  NMR Spectrum of Compound 1



**Figure 21:**  $^{31}\text{P}$  NMR Spectrum of Compound 2

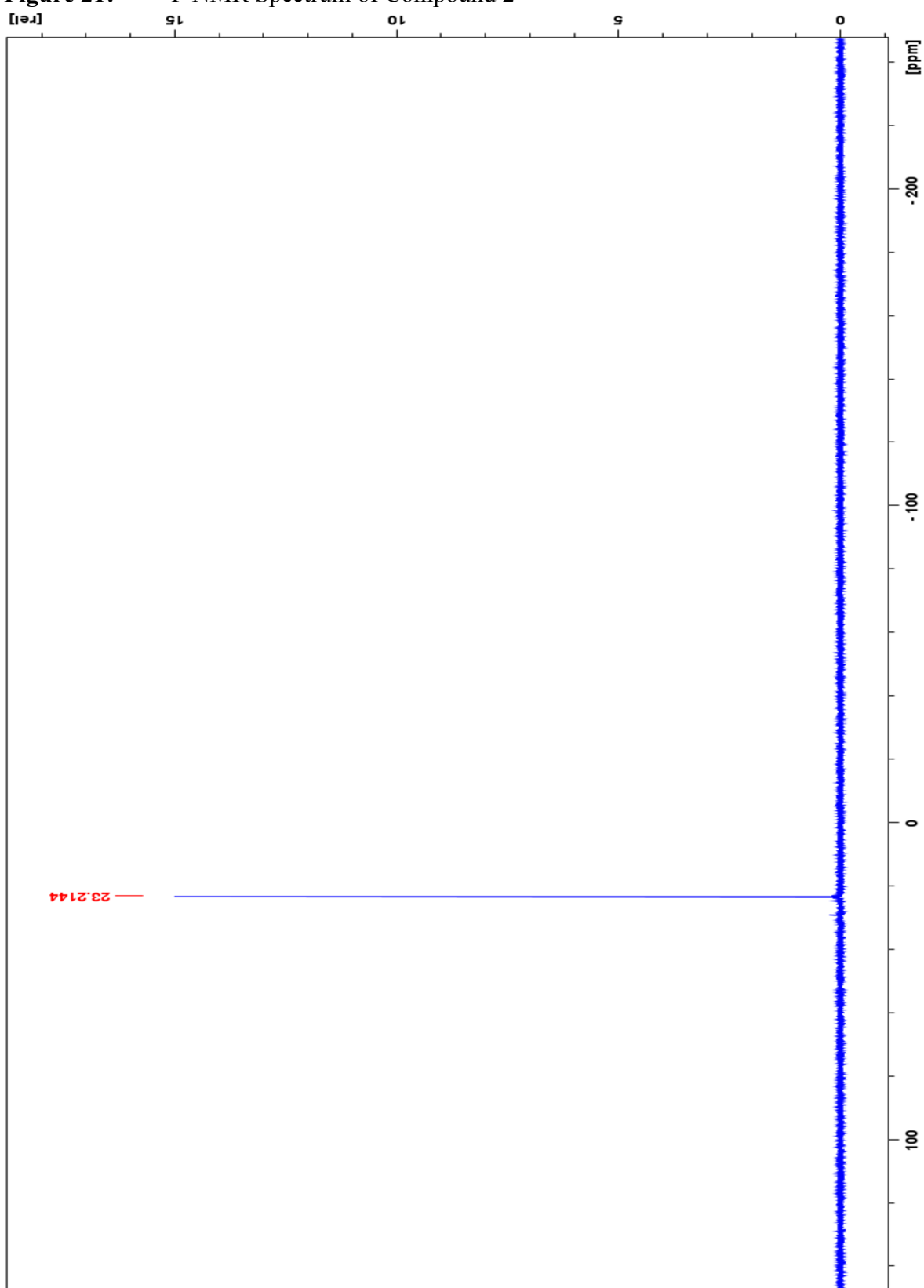


Figure 22:  $^1\text{H}$  NMR Spectrum of Compound 2

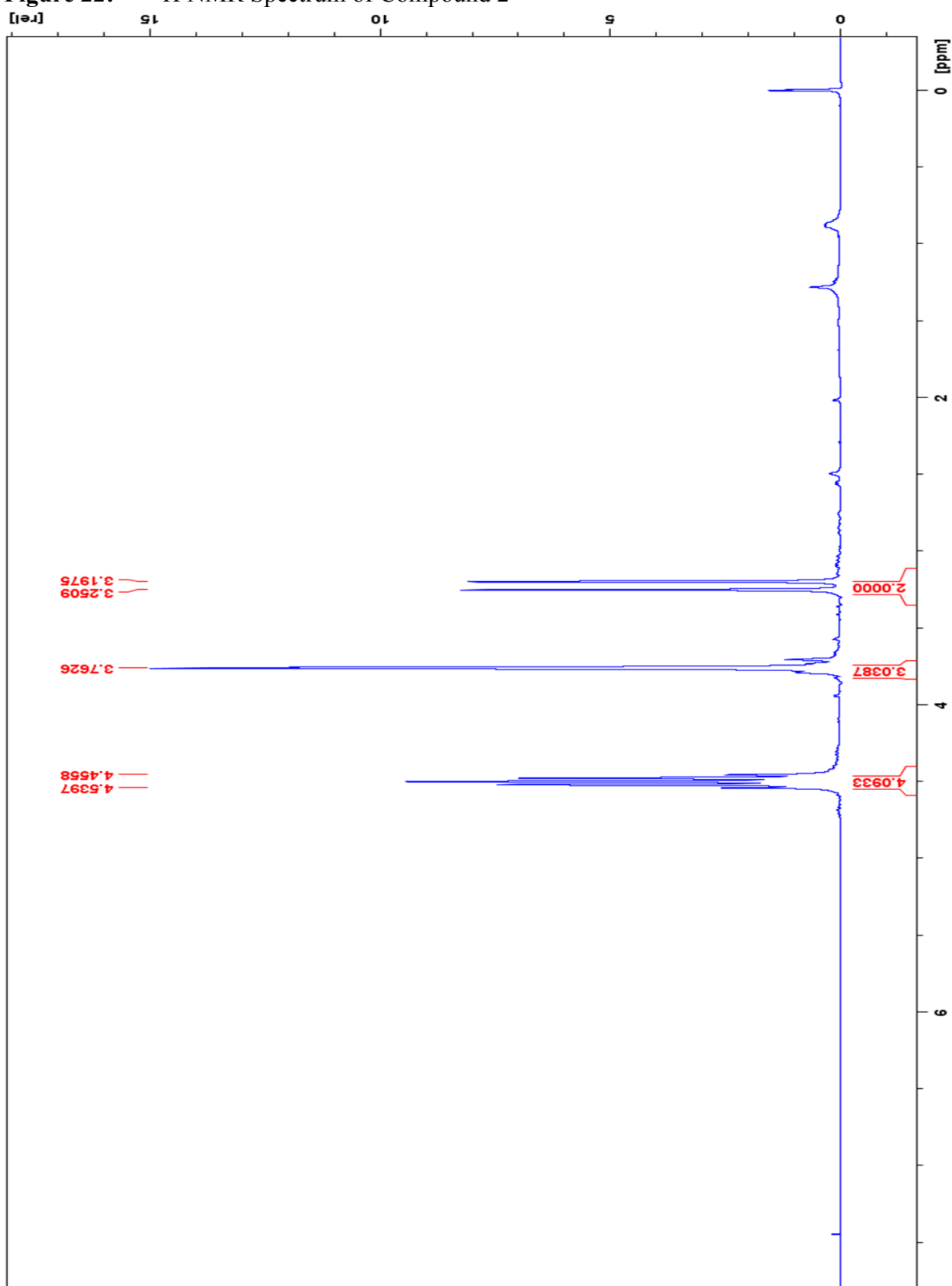
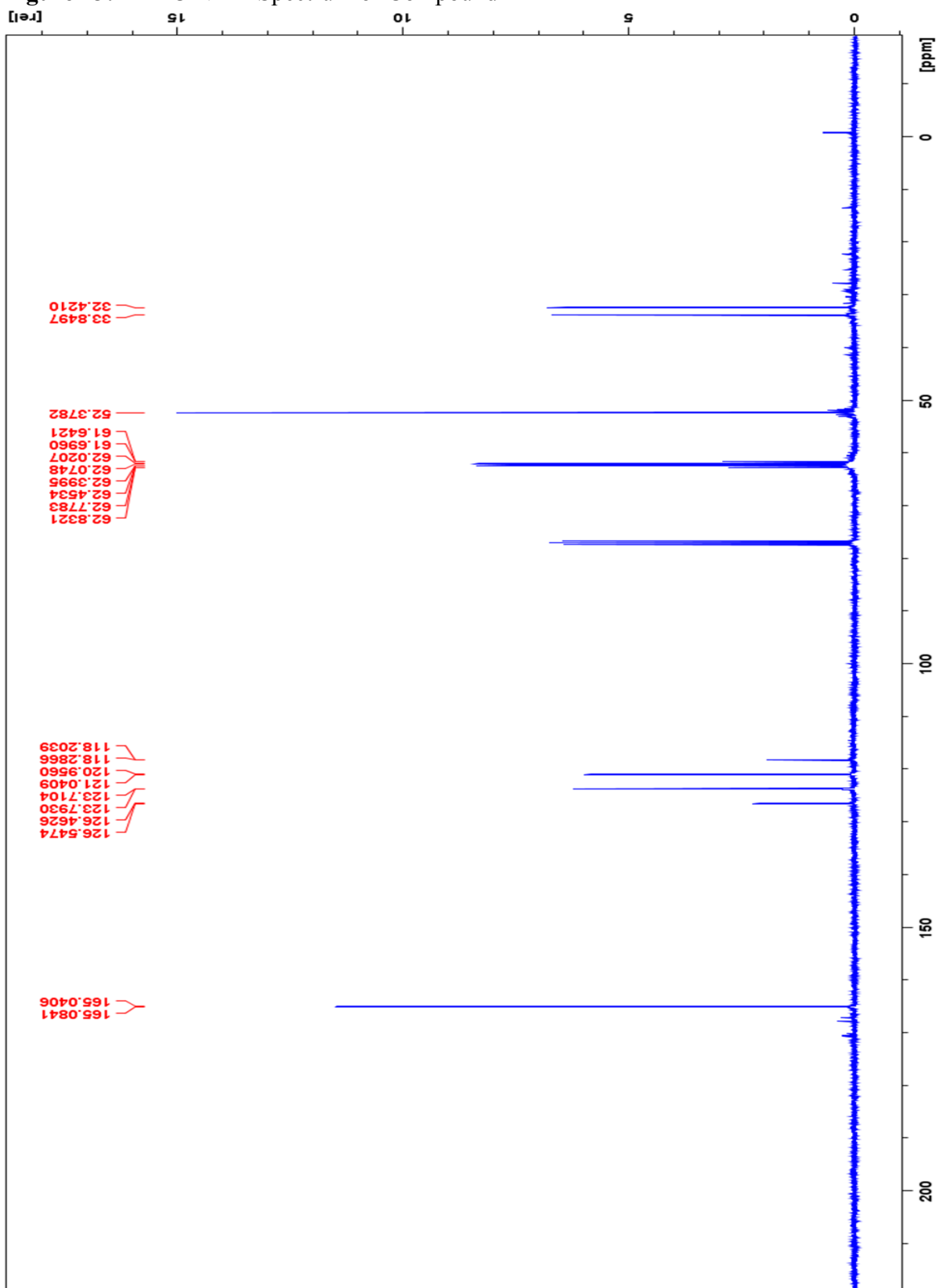


Figure 23:  $^{13}\text{C}$  NMR Spectrum of Compound 2



**Figure 24:**  $^{31}\text{P}$  NMR Spectrum of Compound 3

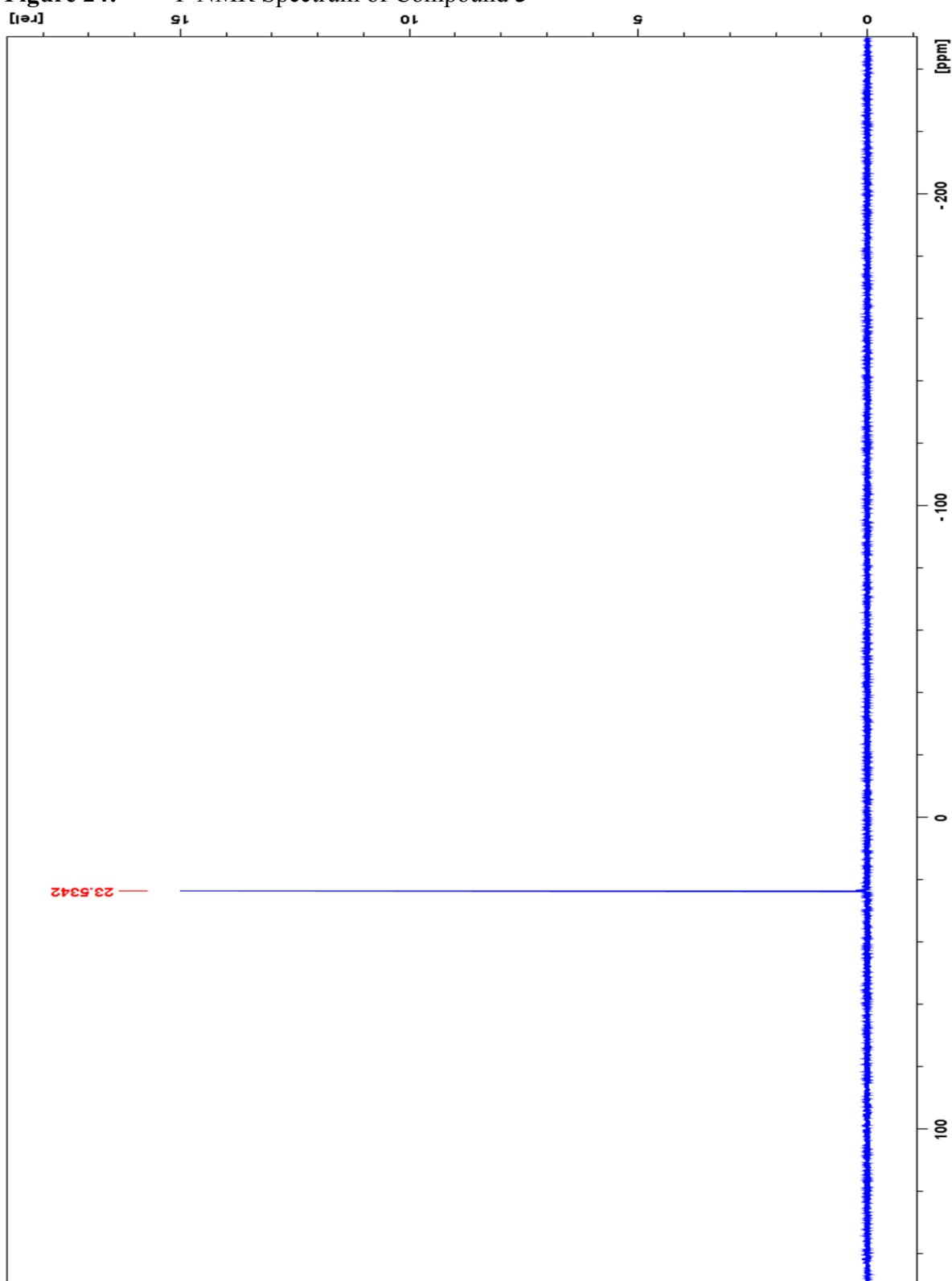




Figure 25:  $^1\text{H}$  NMR Spectrum of Compound 3

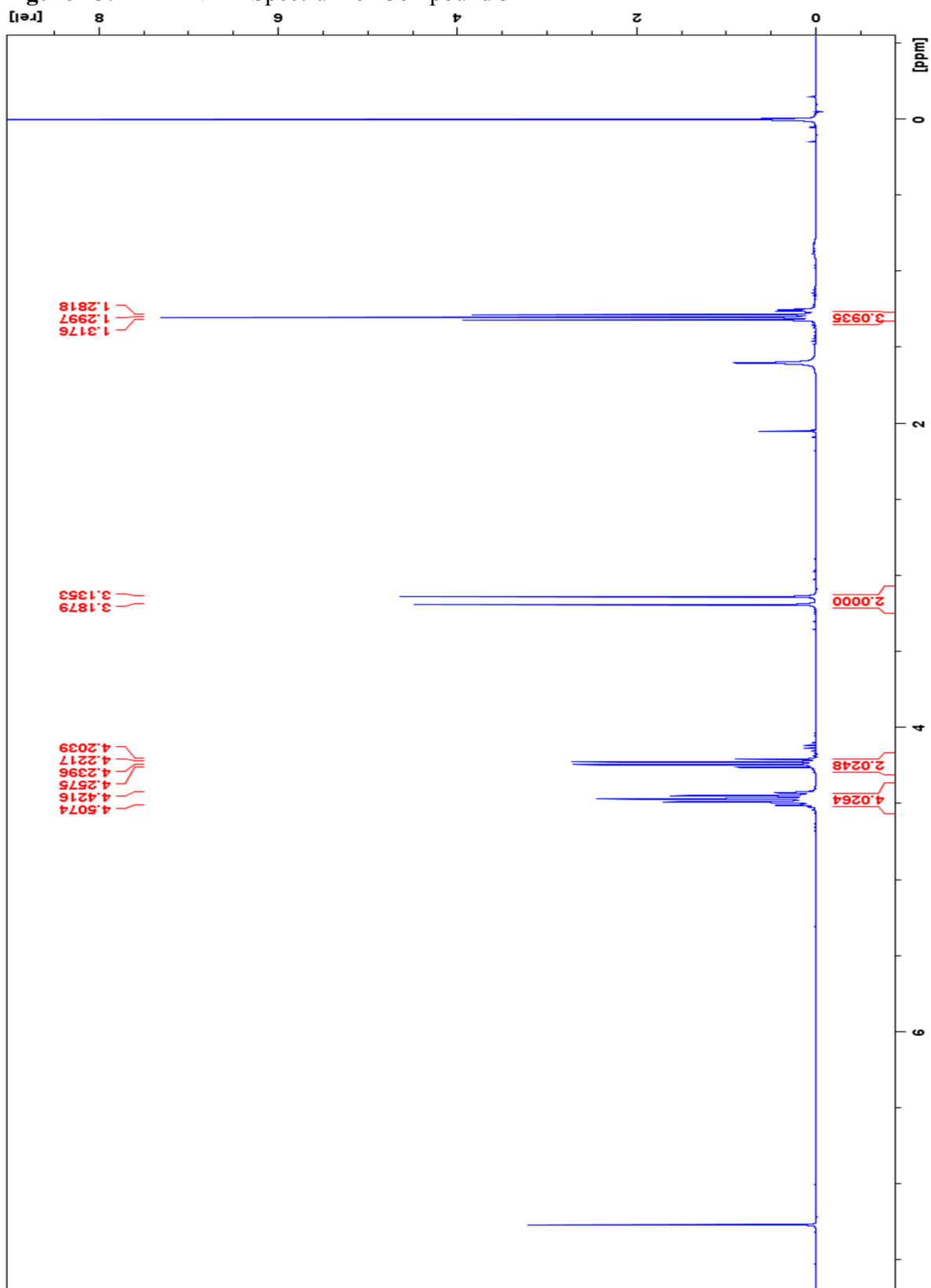


Figure 26:  $^{13}\text{C}$  NMR Spectrum of Compound 3

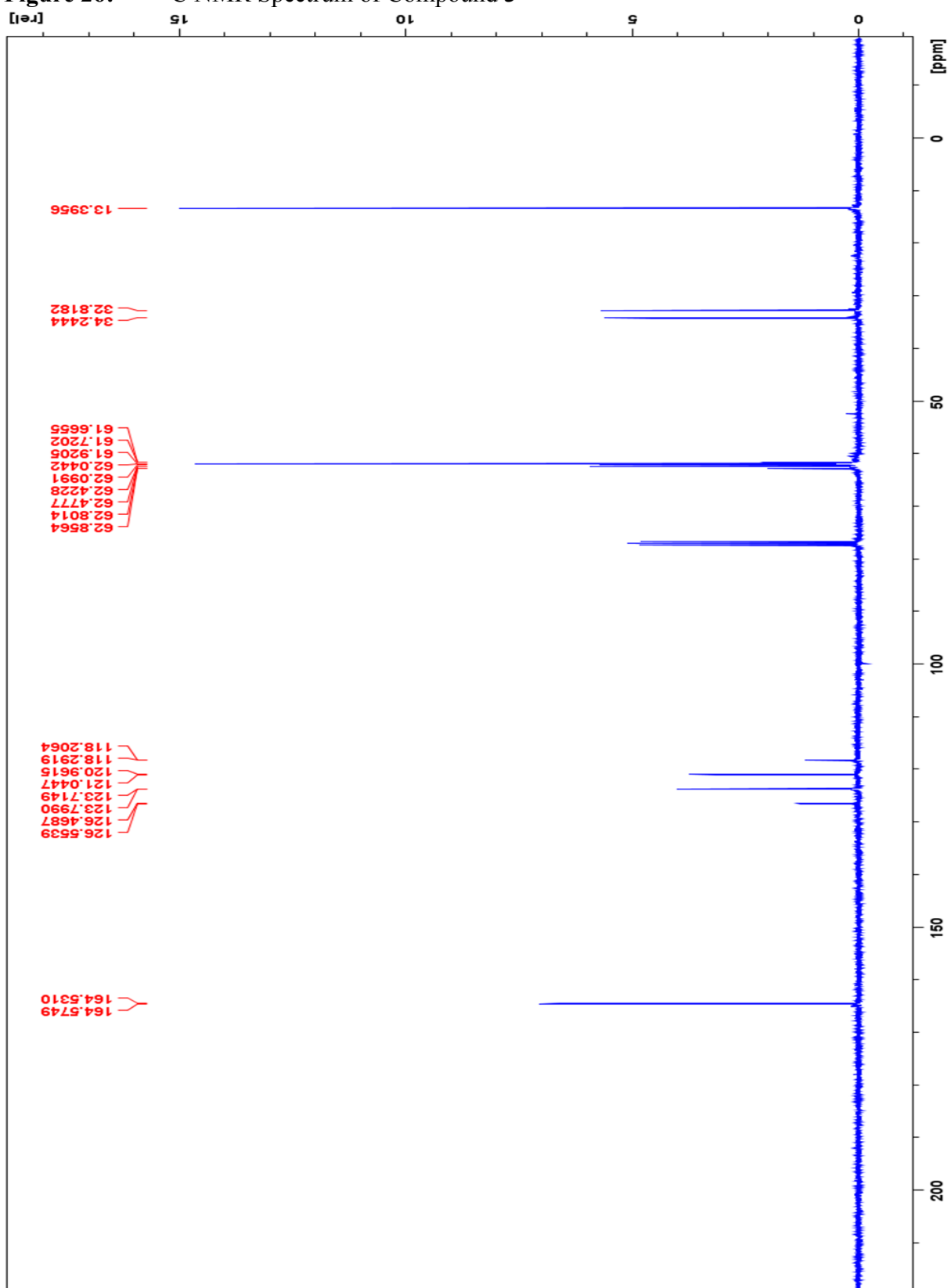


Figure 27:  $^{31}\text{P}$  NMR Spectrum of Compound 4

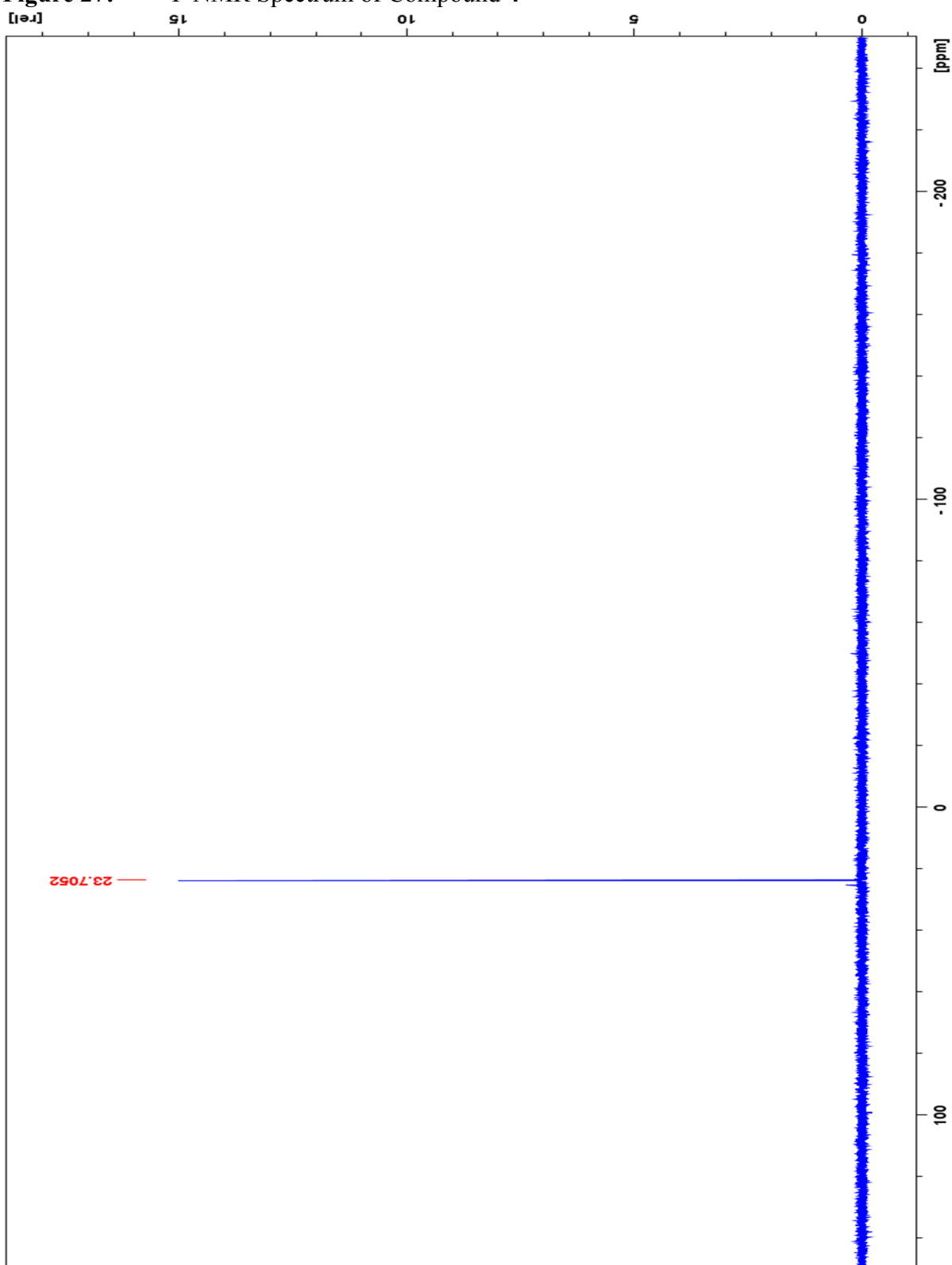


Figure 28:  $^1\text{H}$  NMR Spectrum of Compound 4

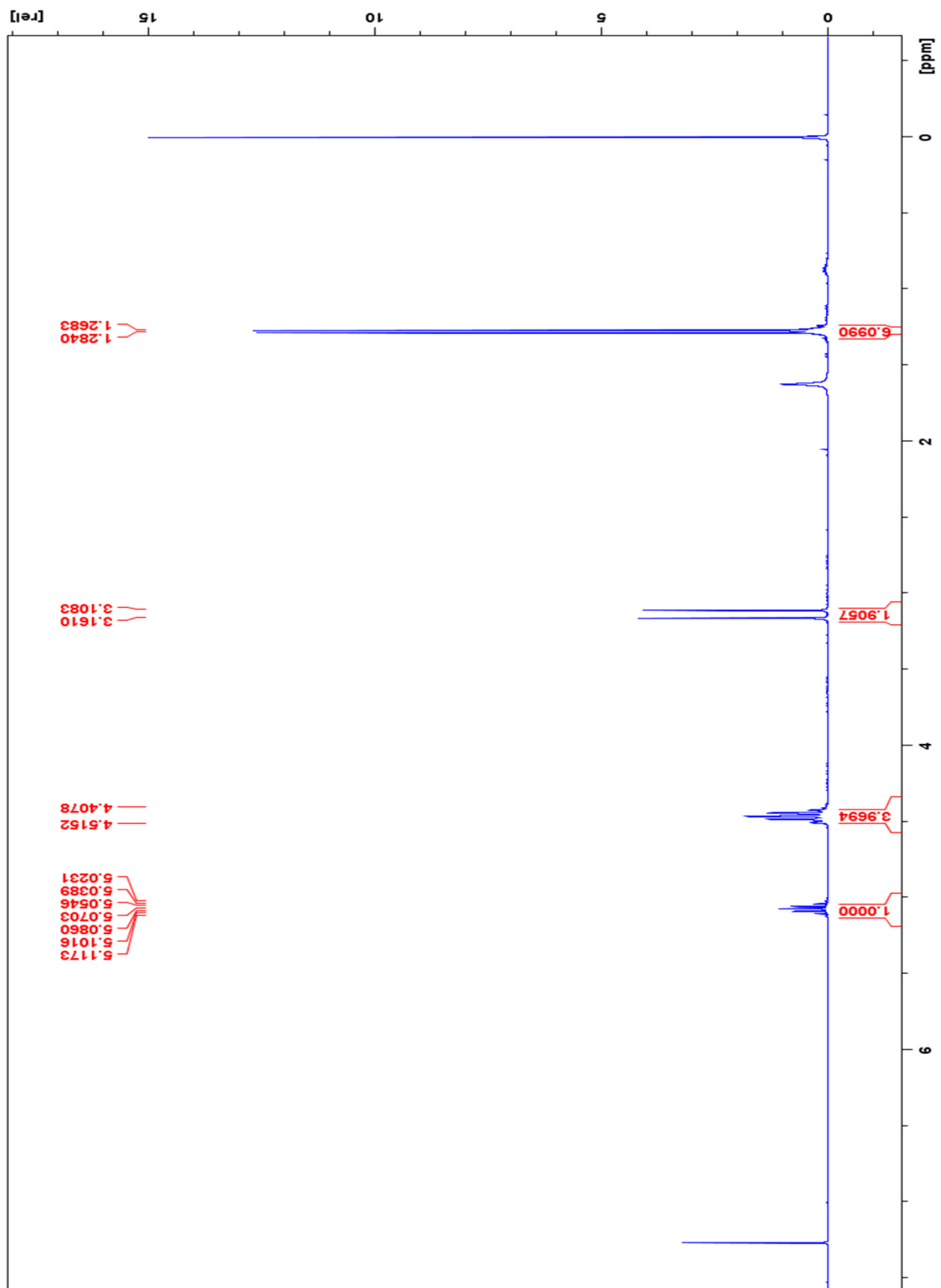
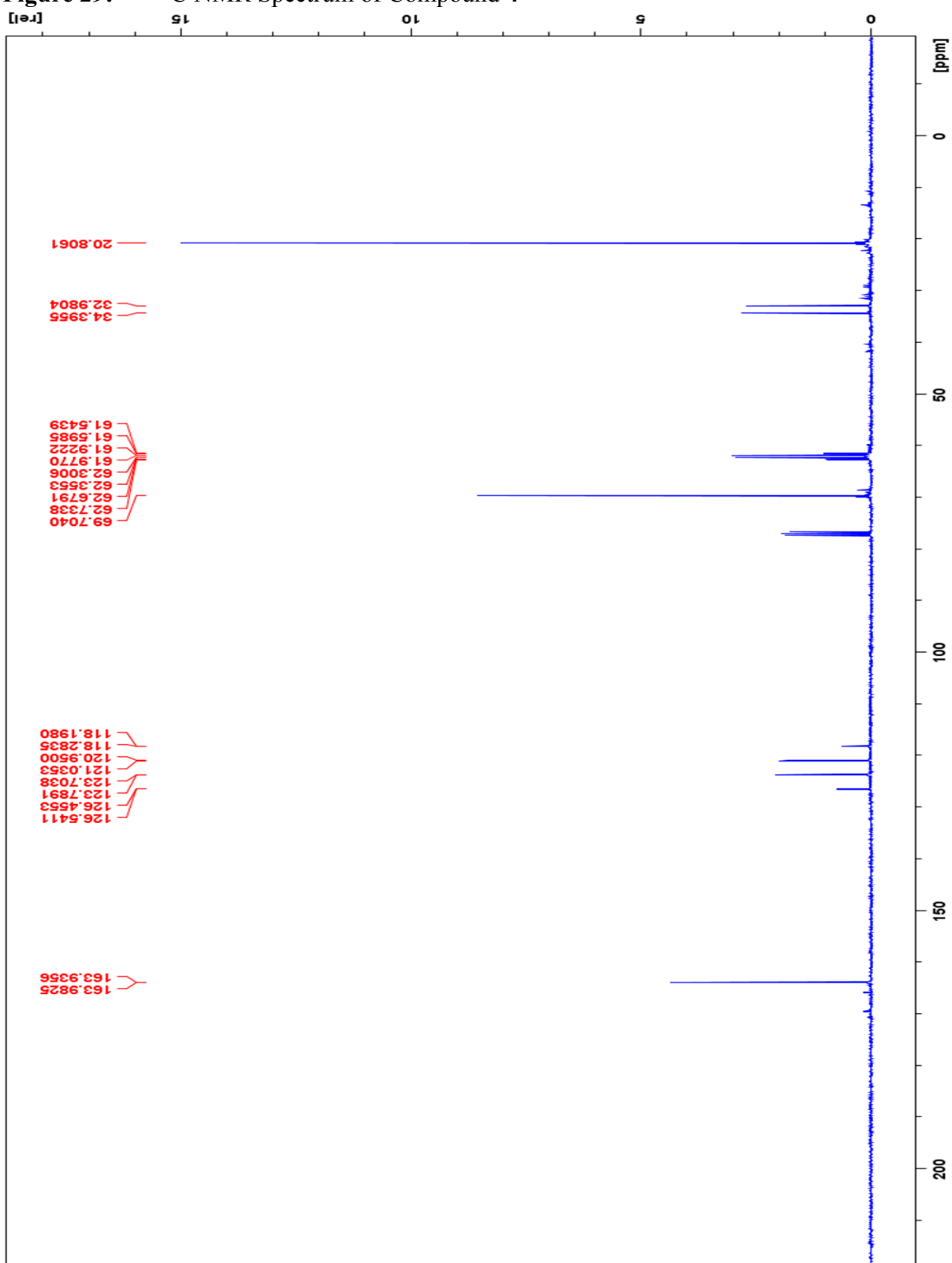


Figure 29:  $^{13}\text{C}$  NMR Spectrum of Compound 4



**Figure 30:**  $^{31}\text{P}$  NMR Spectrum of Compound 5

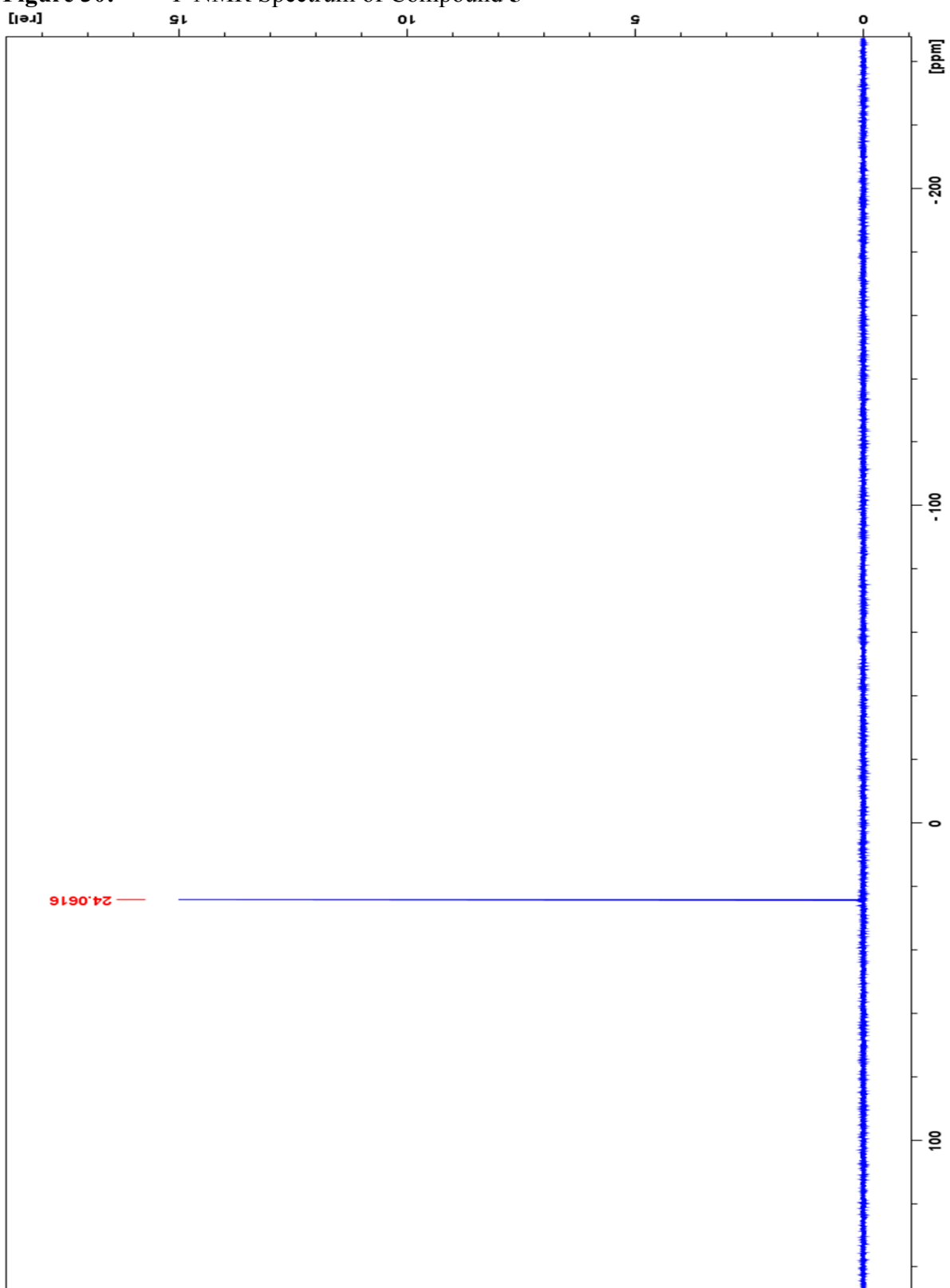


Figure 31:  $^1\text{H}$  NMR Spectrum of Compound 5

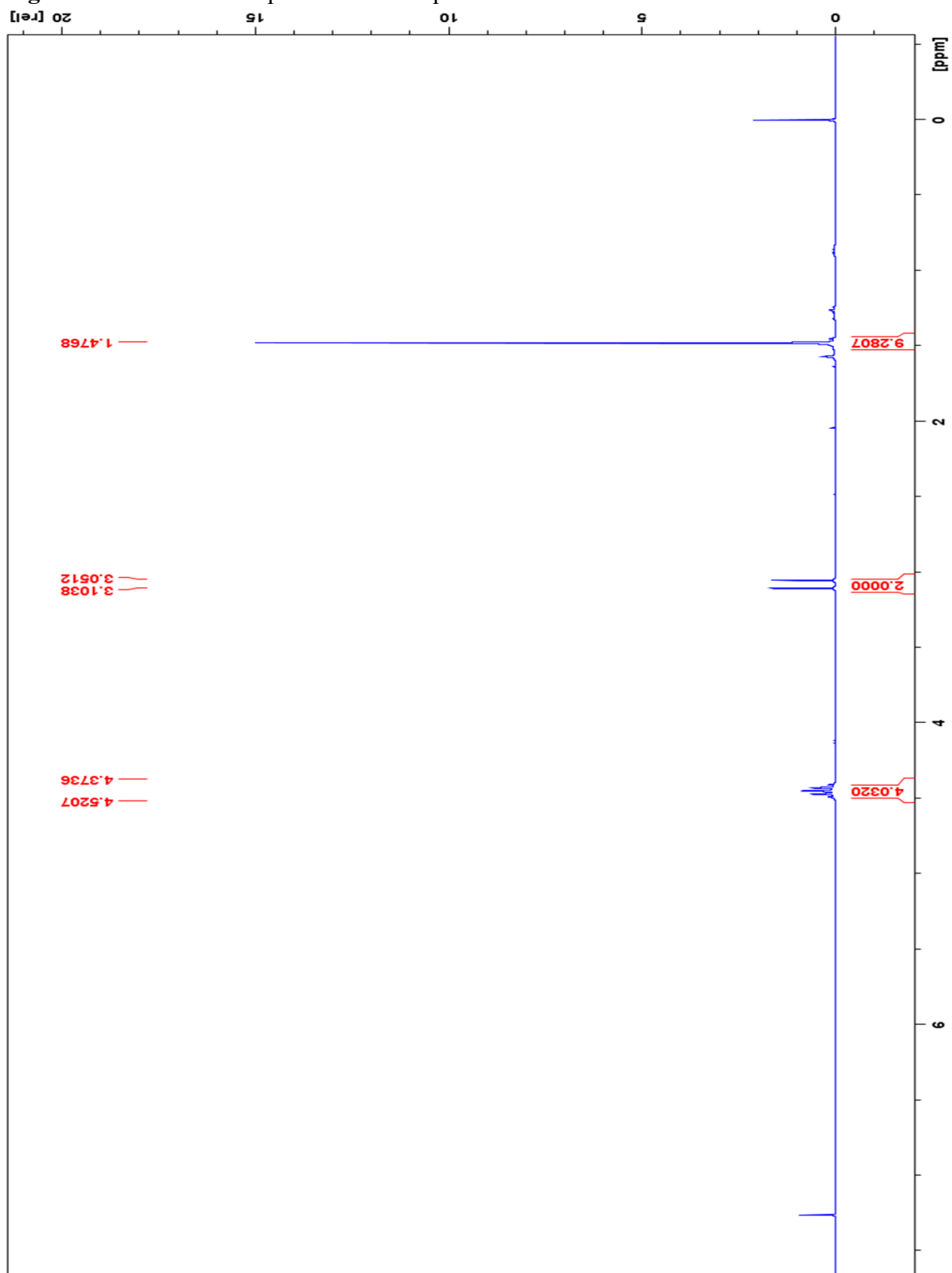
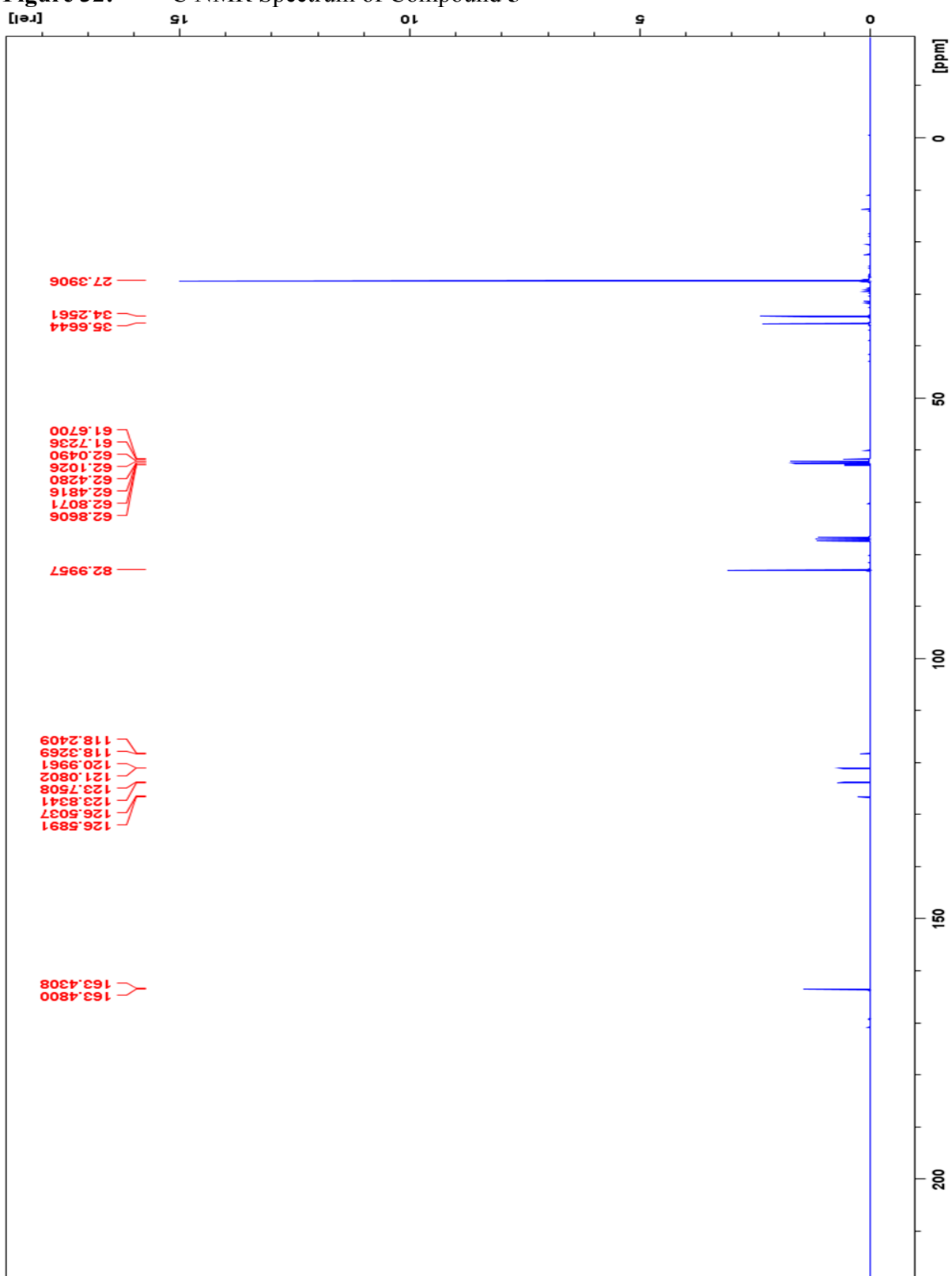


Figure 32:  $^{13}\text{C}$  NMR Spectrum of Compound 5





**Figure 33:**  $^{31}\text{P}$  NMR Spectrum of Compound 6

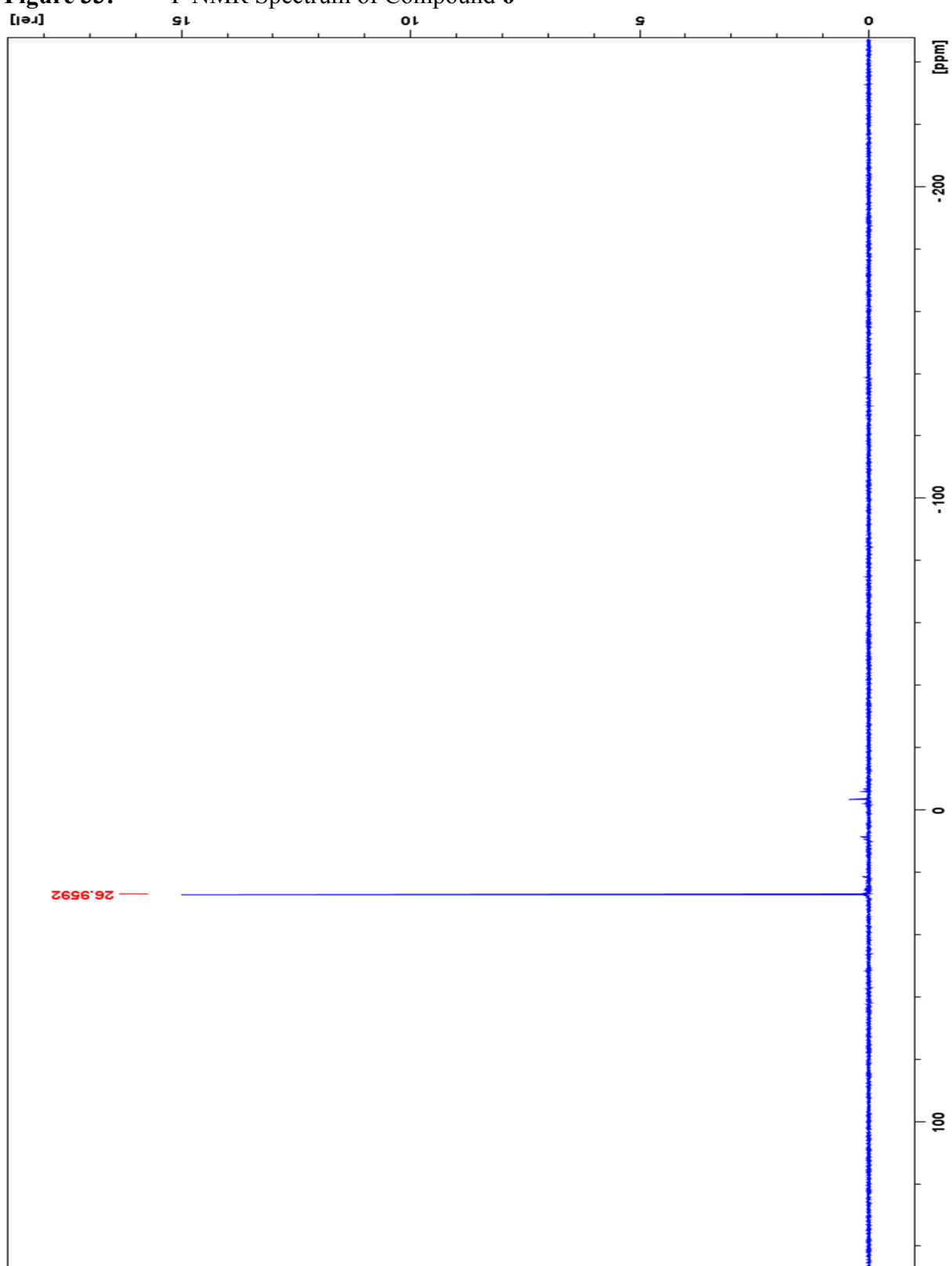


Figure 34:  $^1\text{H}$  NMR Spectrum of Compound 6

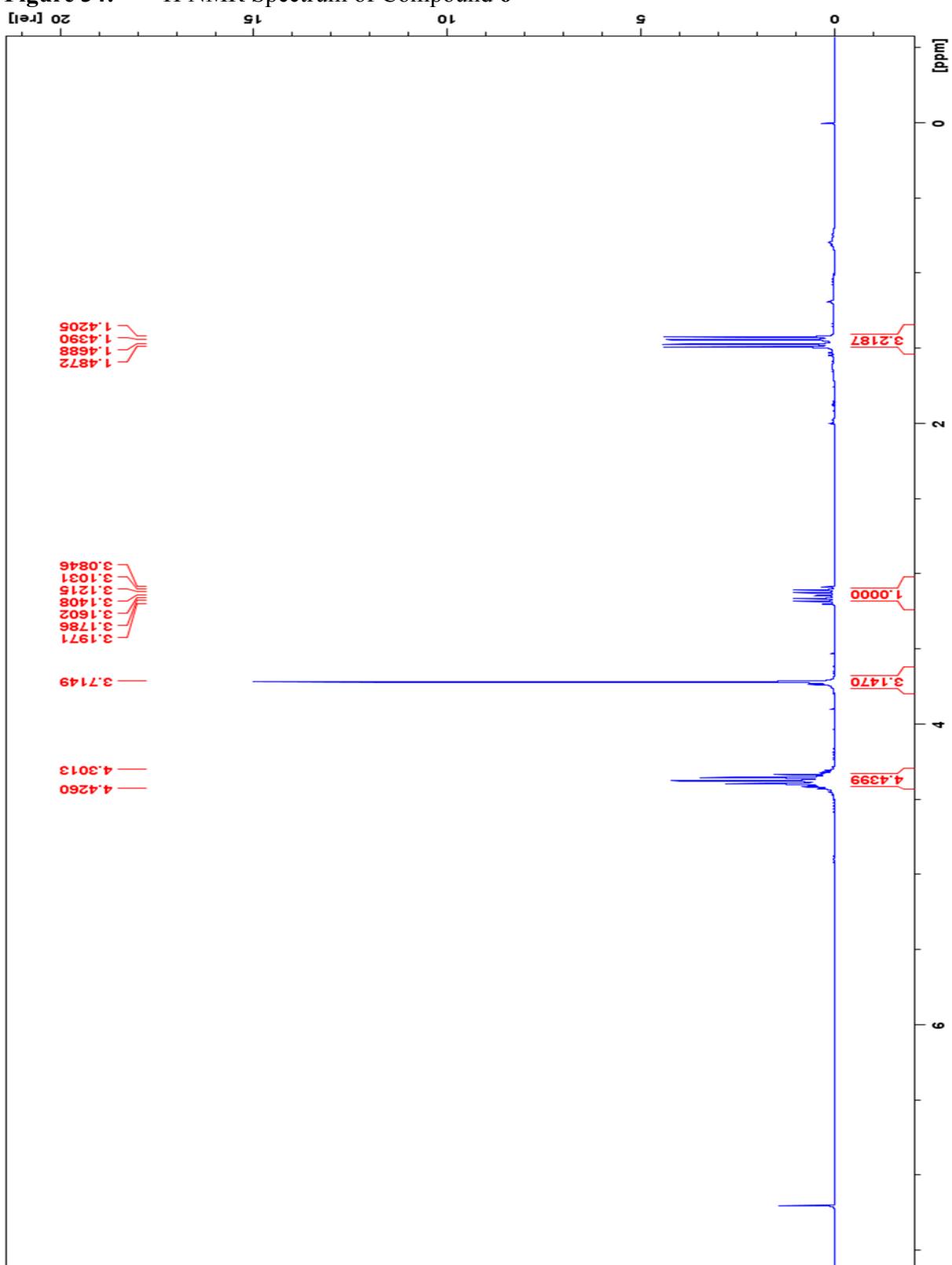


Figure 35:  $^{13}\text{C}$  NMR Spectrum of Compound 6

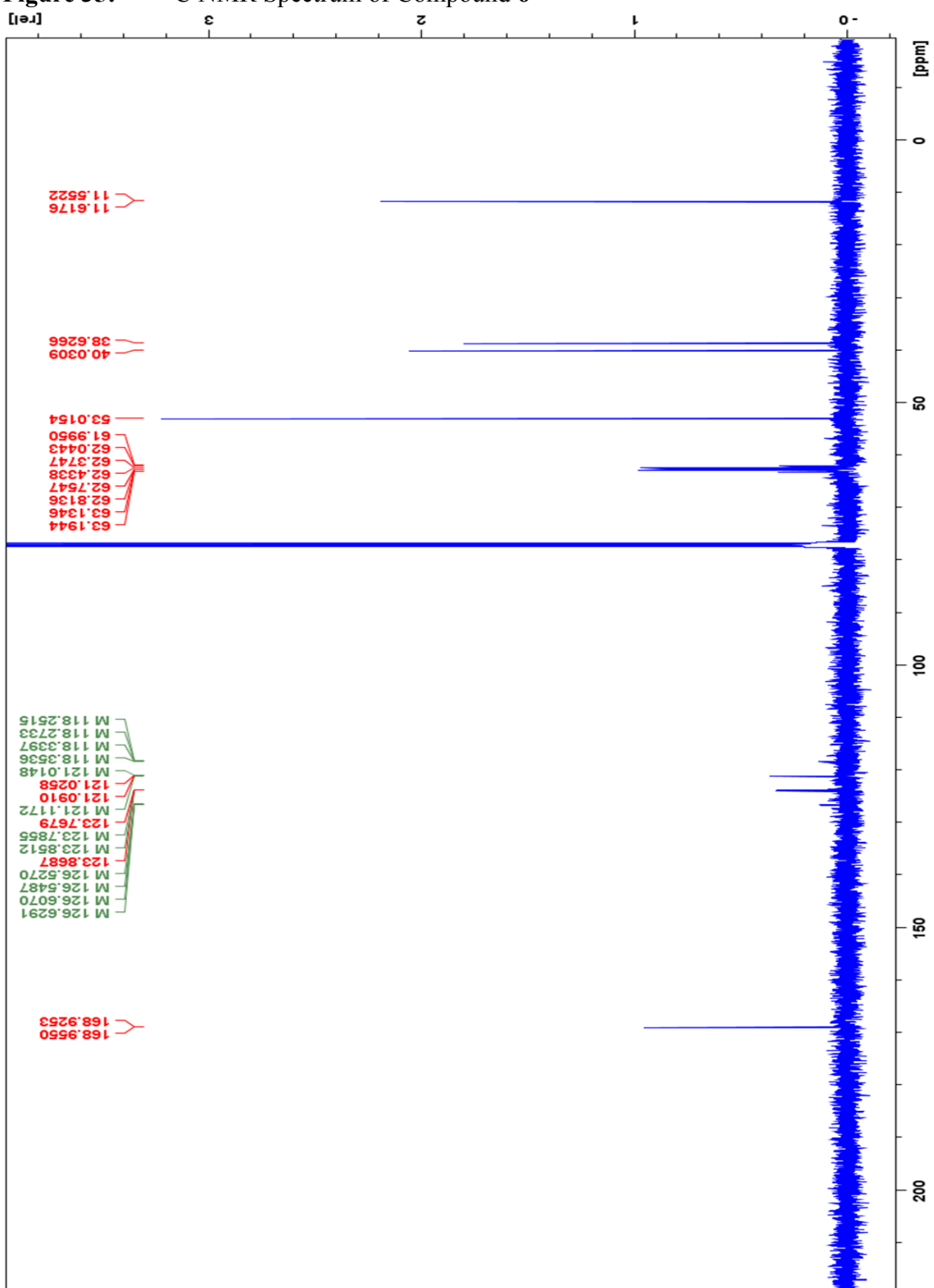


Figure 36: HSQC NMR Spectrum of Compound 6

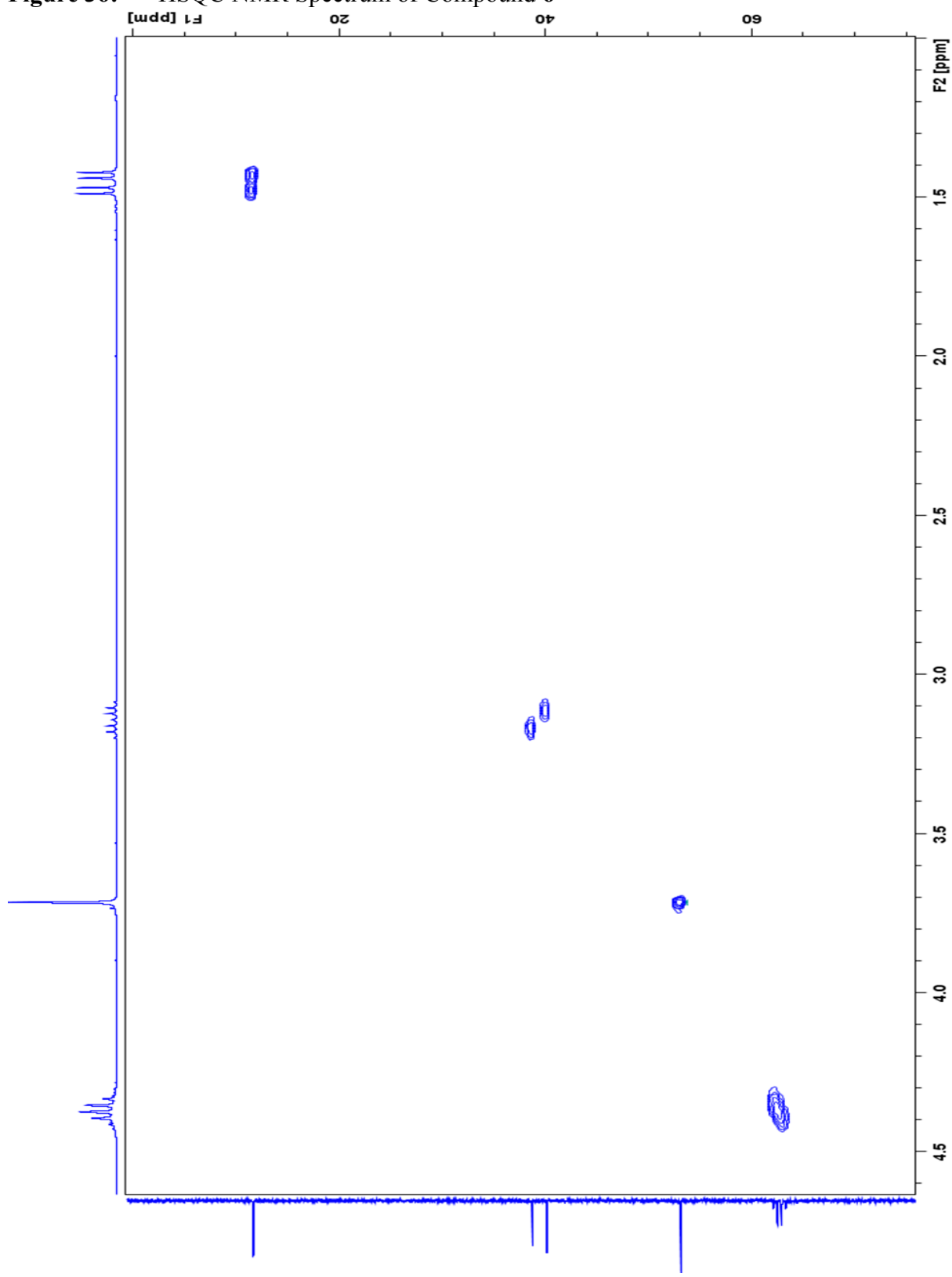


Figure 37:  $^{31}\text{P}$  NMR Spectrum of Compound 7

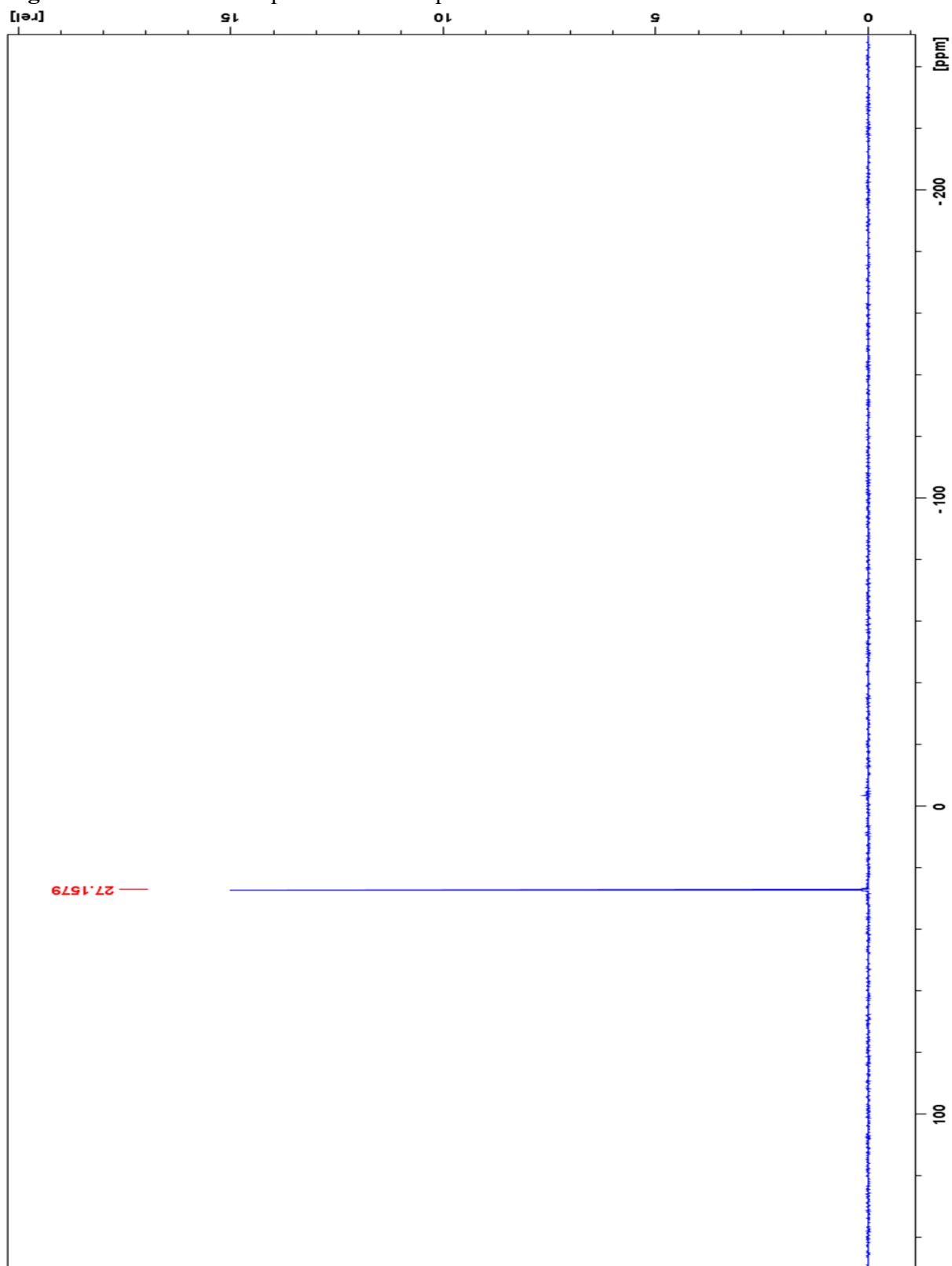


Figure 38:  $^1\text{H}$  NMR Spectrum of Compound 7

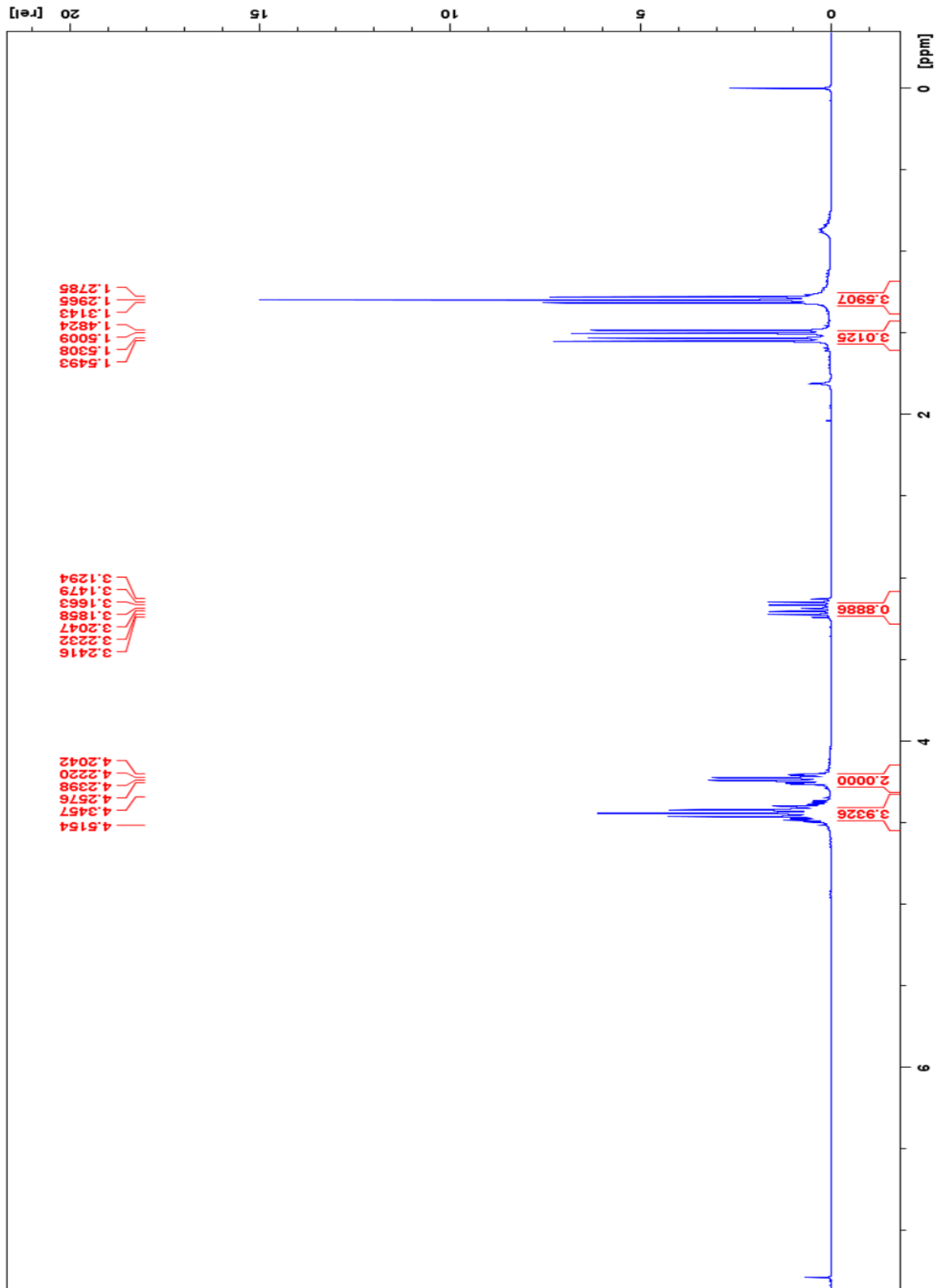


Figure 39:  $^{13}\text{C}$  NMR Spectrum of Compound 7

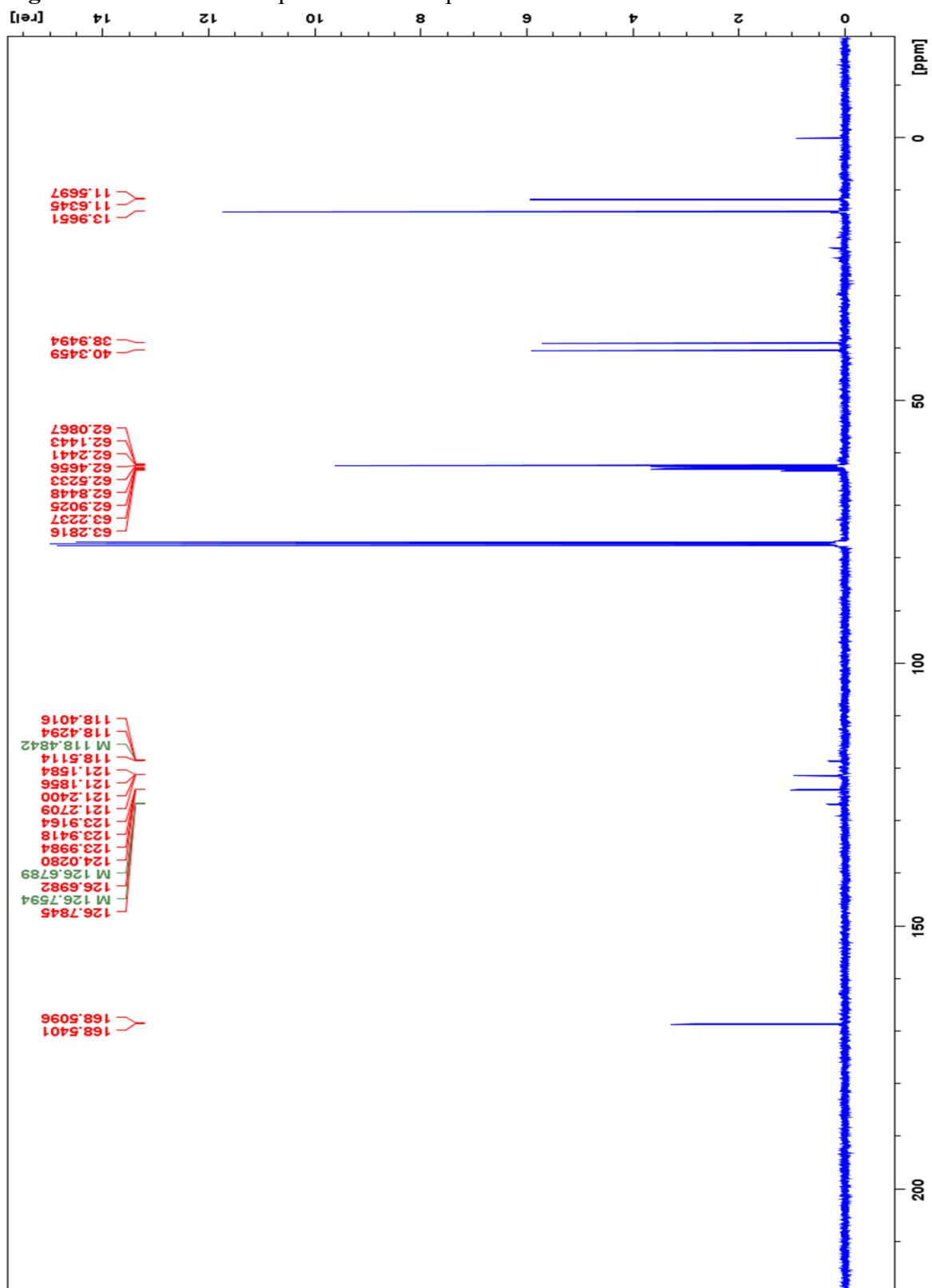


Figure 40: HSQC NMR Spectrum of Compound 7

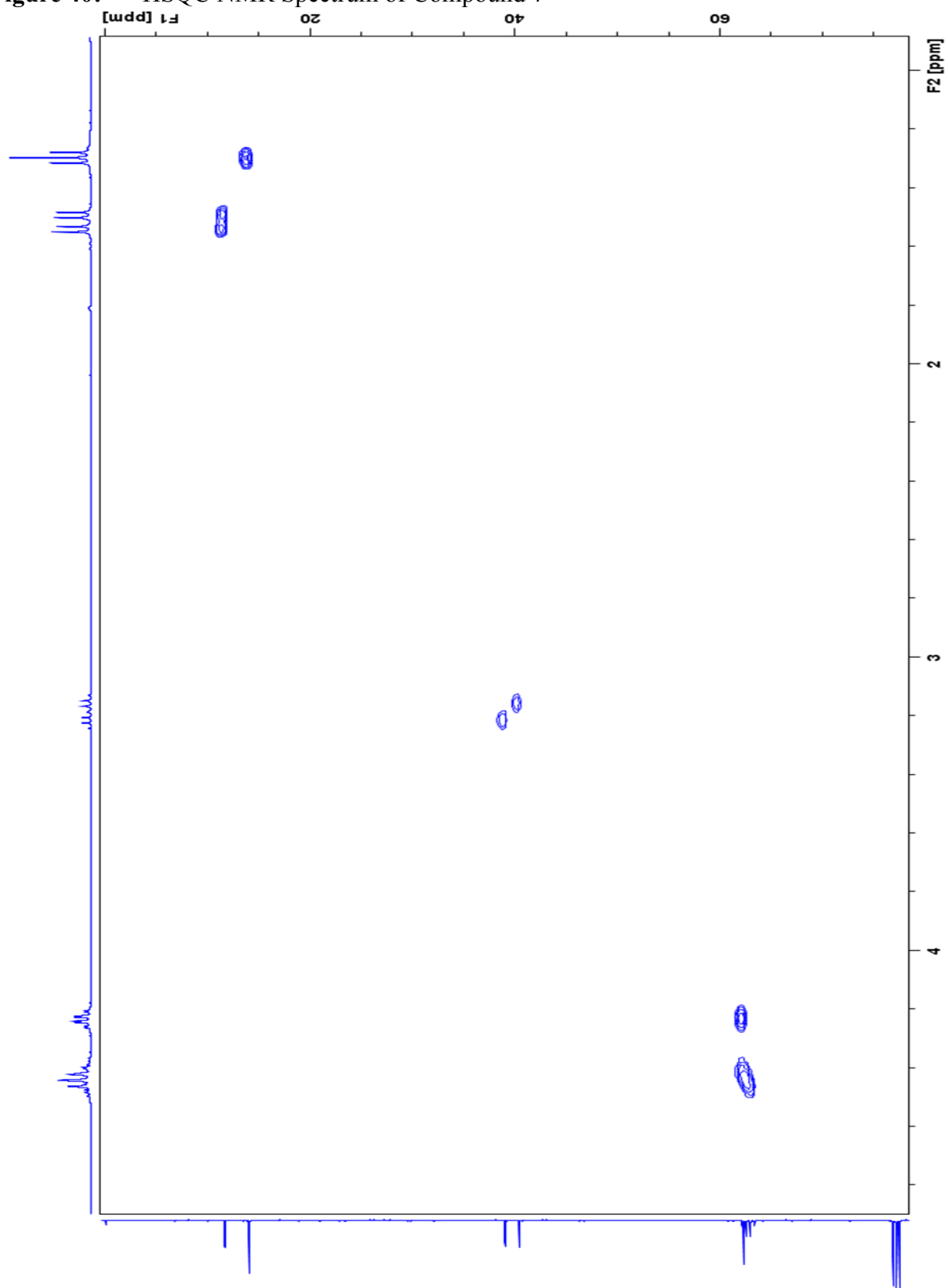




Figure 41: COSY NMR Spectrum of Compound 7

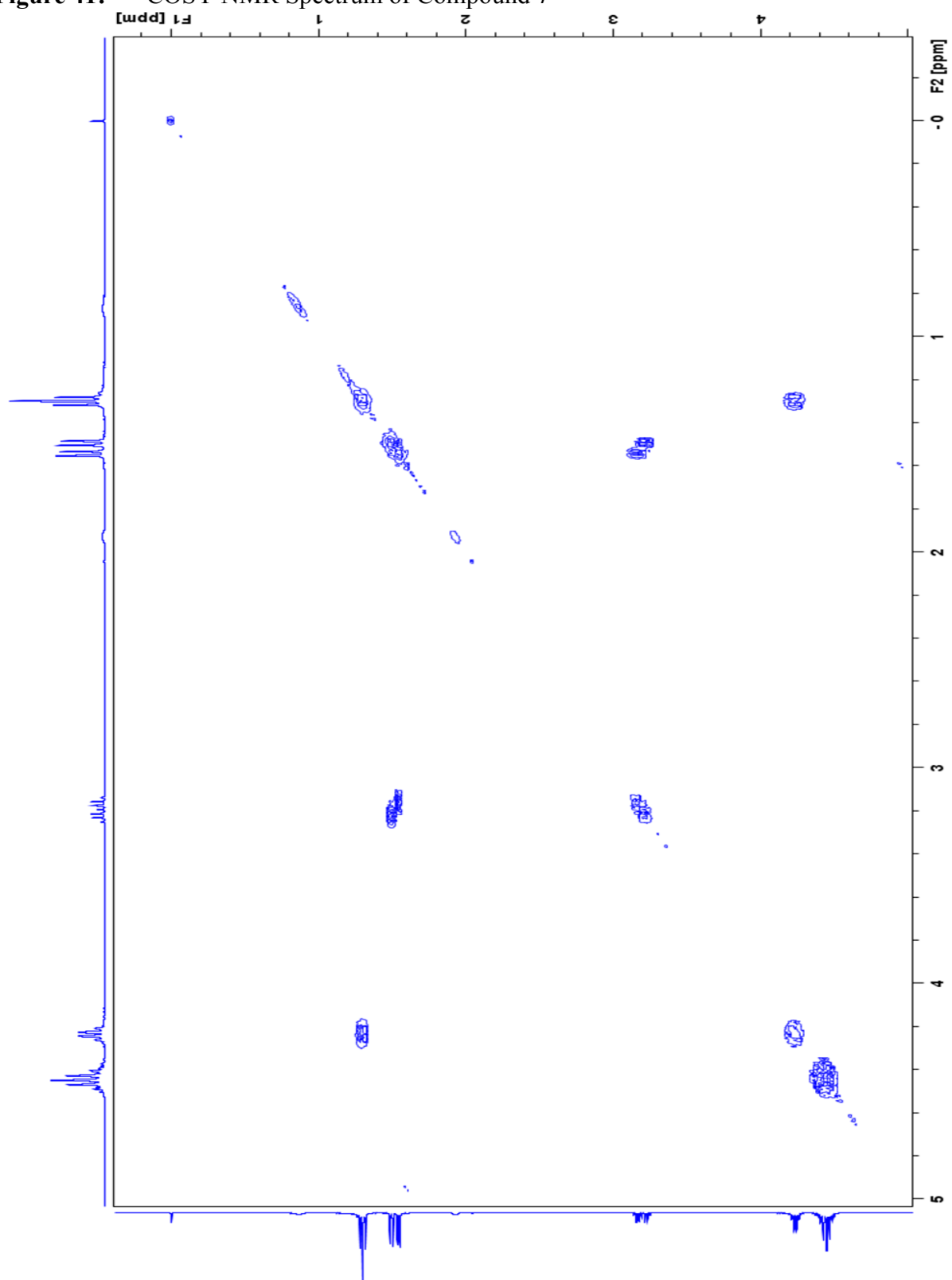


Figure 42:  $^{31}\text{P}$  NMR Spectrum of Compound 8

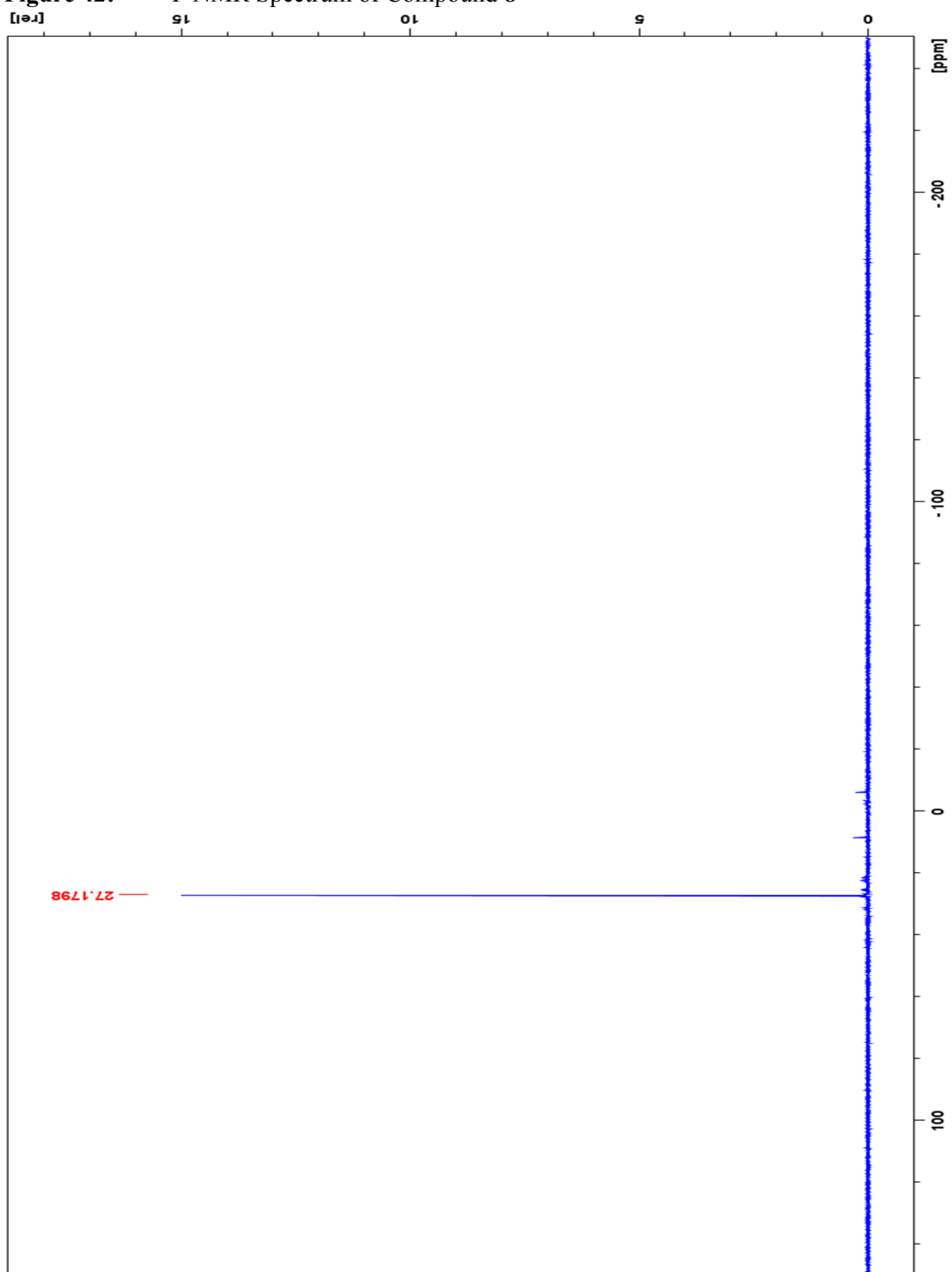


Figure 43:  $^1\text{H}$  NMR Spectrum of Compound 8

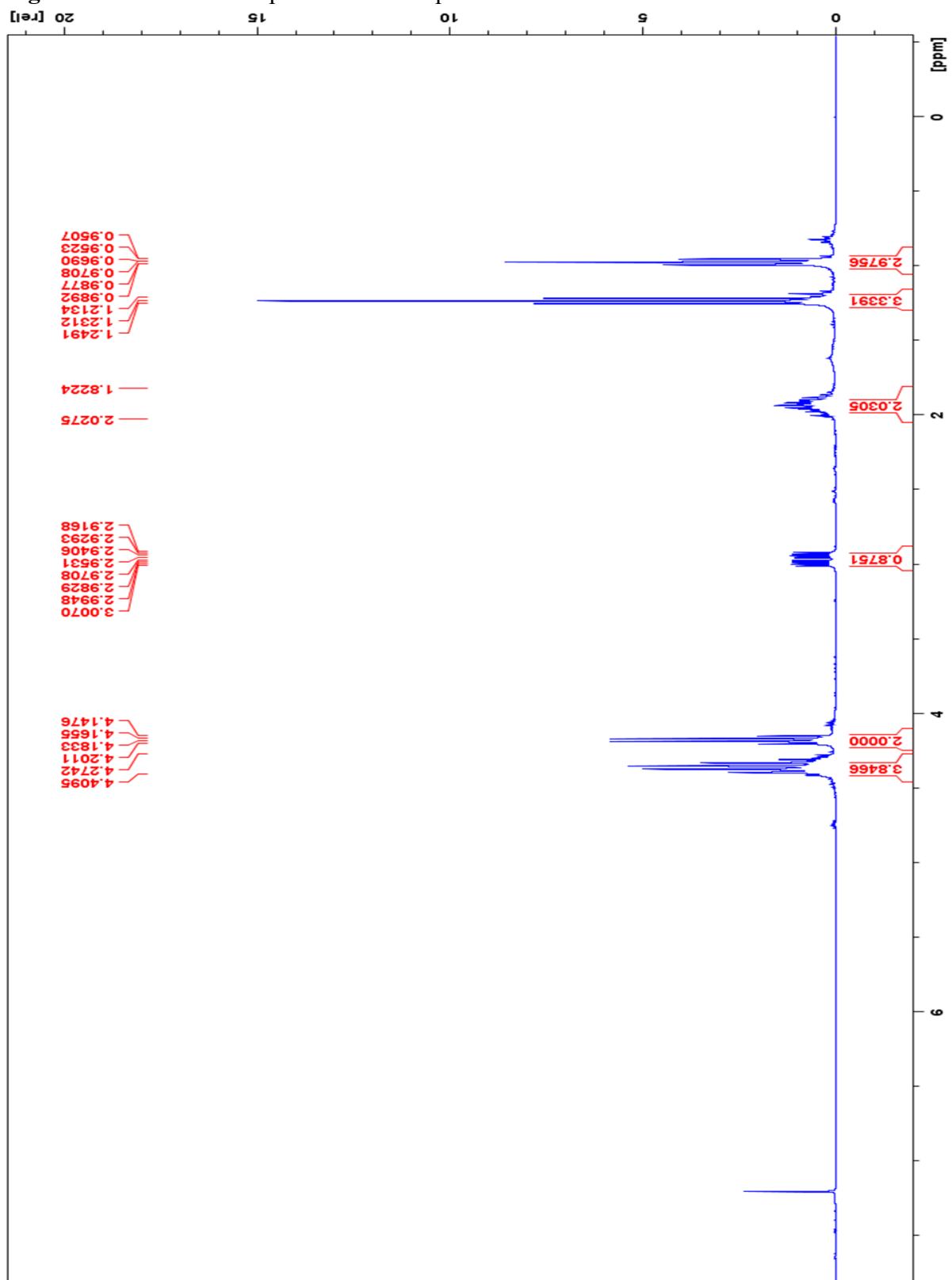


Figure 44:  $^{13}\text{C}$  NMR Spectrum of Compound 8

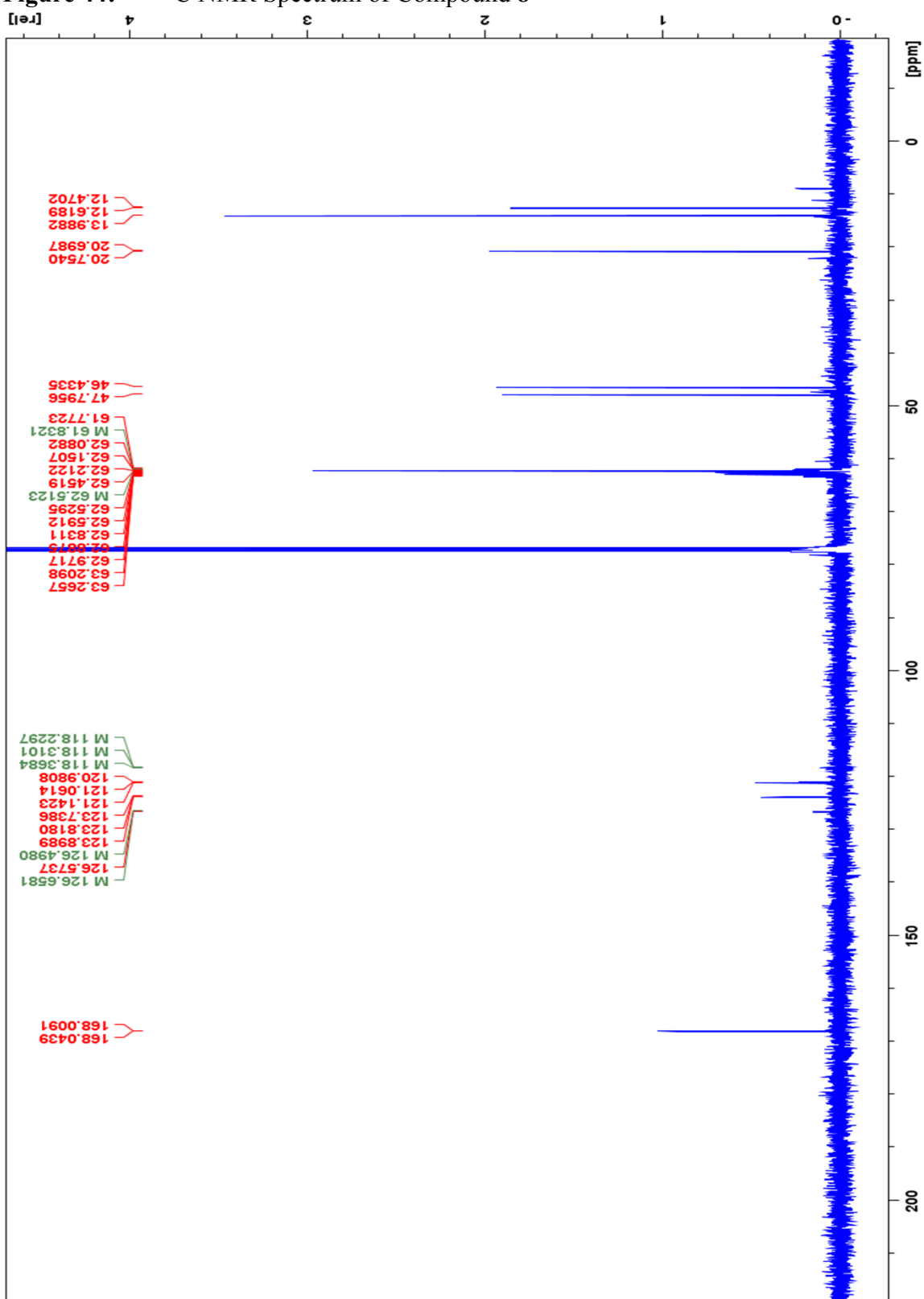


Figure 45: HSQC NMR Spectrum of Compound 8

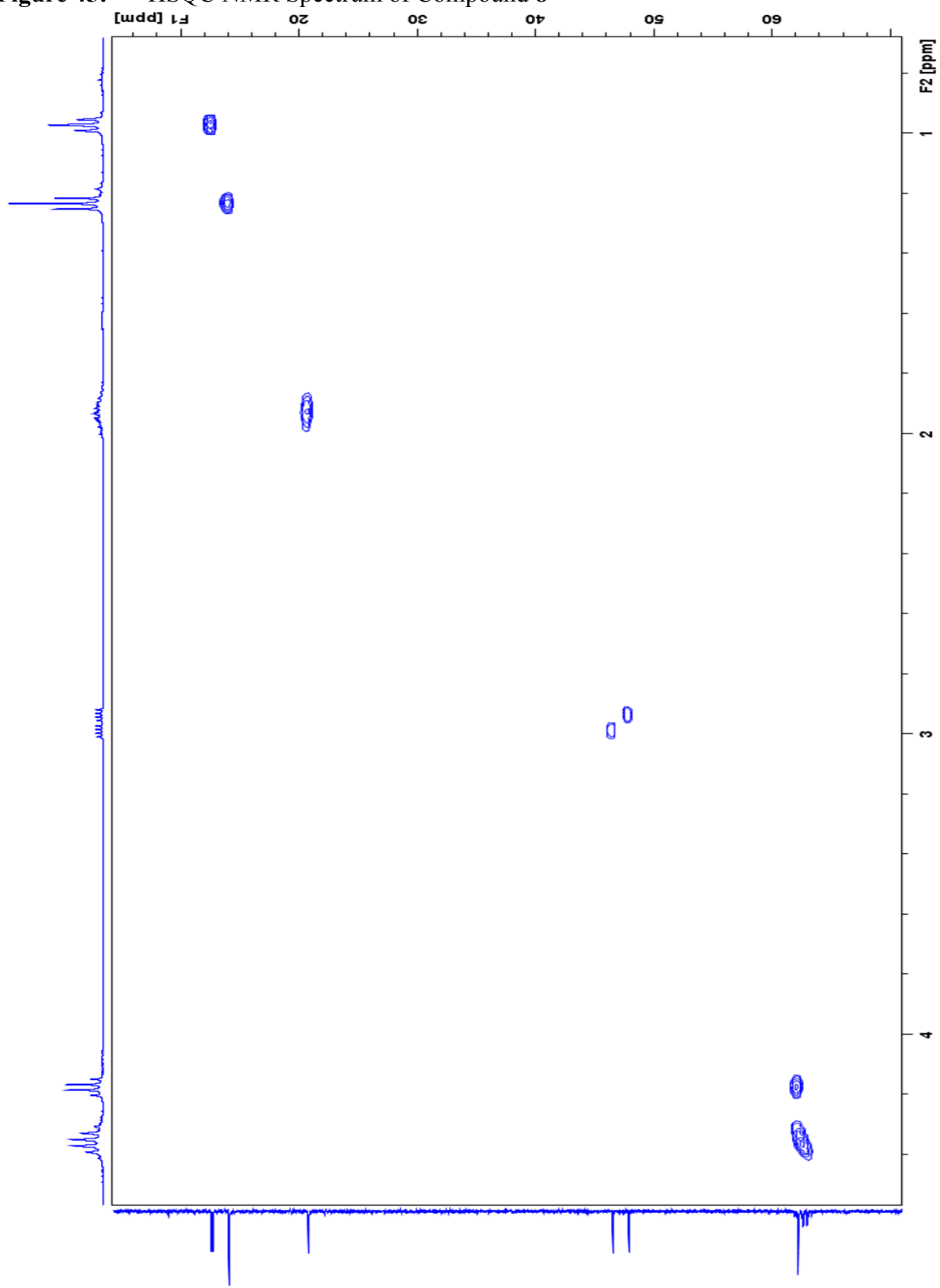


Figure 46:  $^{31}\text{P}$  NMR Spectrum of Compound 9

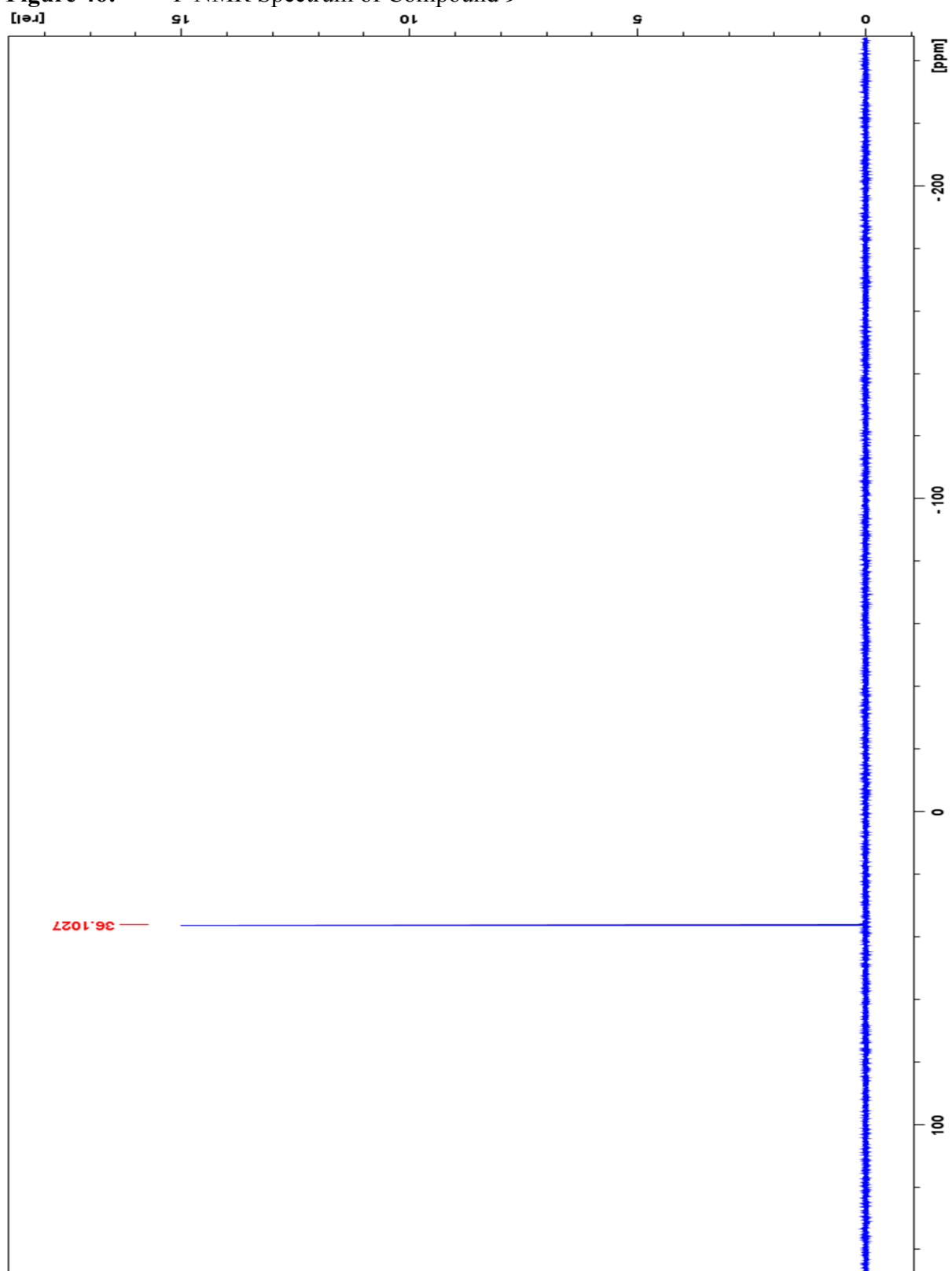


Figure 47:  $^1\text{H}$  NMR Spectrum of Compound 9

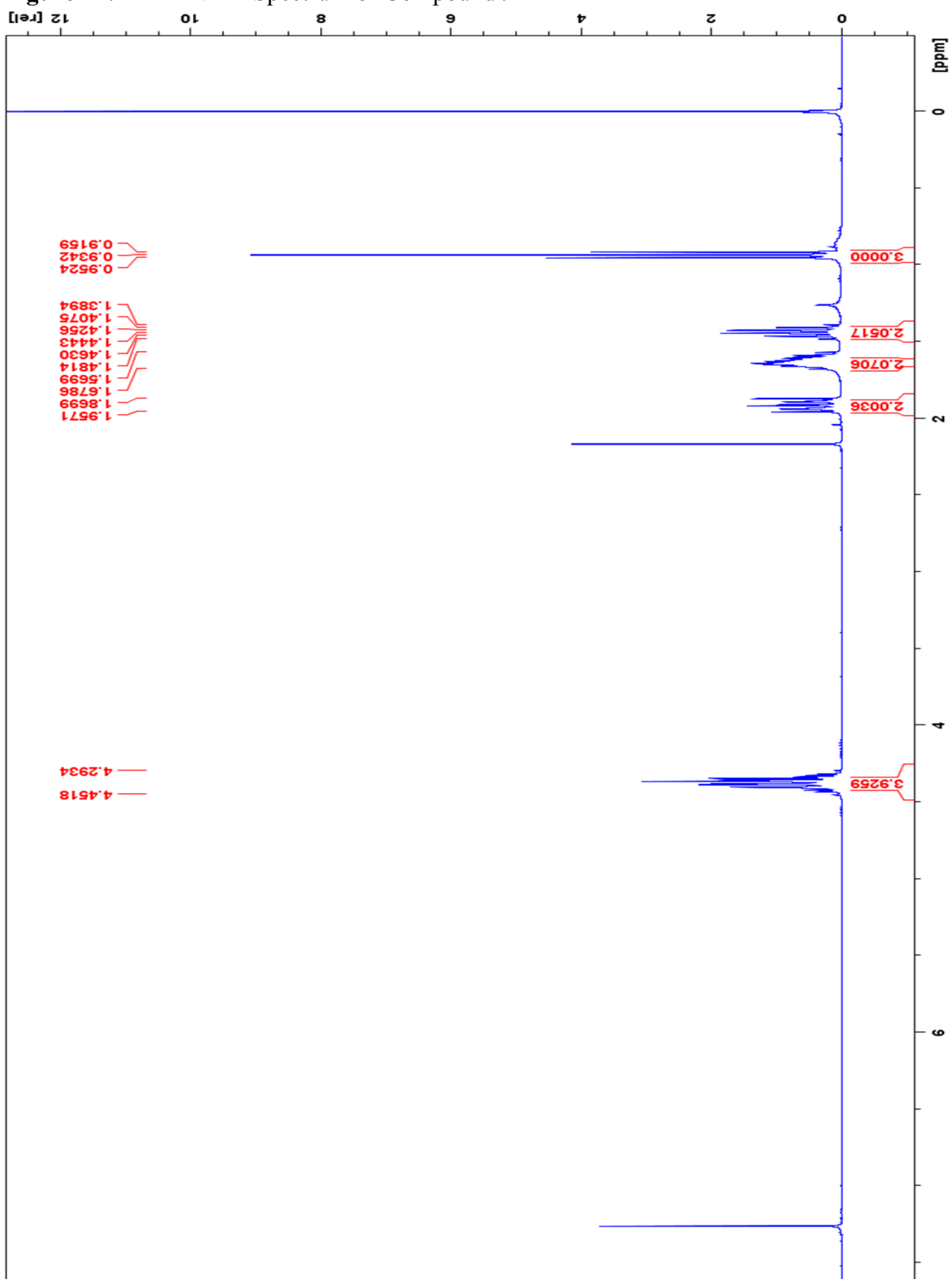


Figure 48:  $^{13}\text{C}$  NMR Spectrum of Compound 9

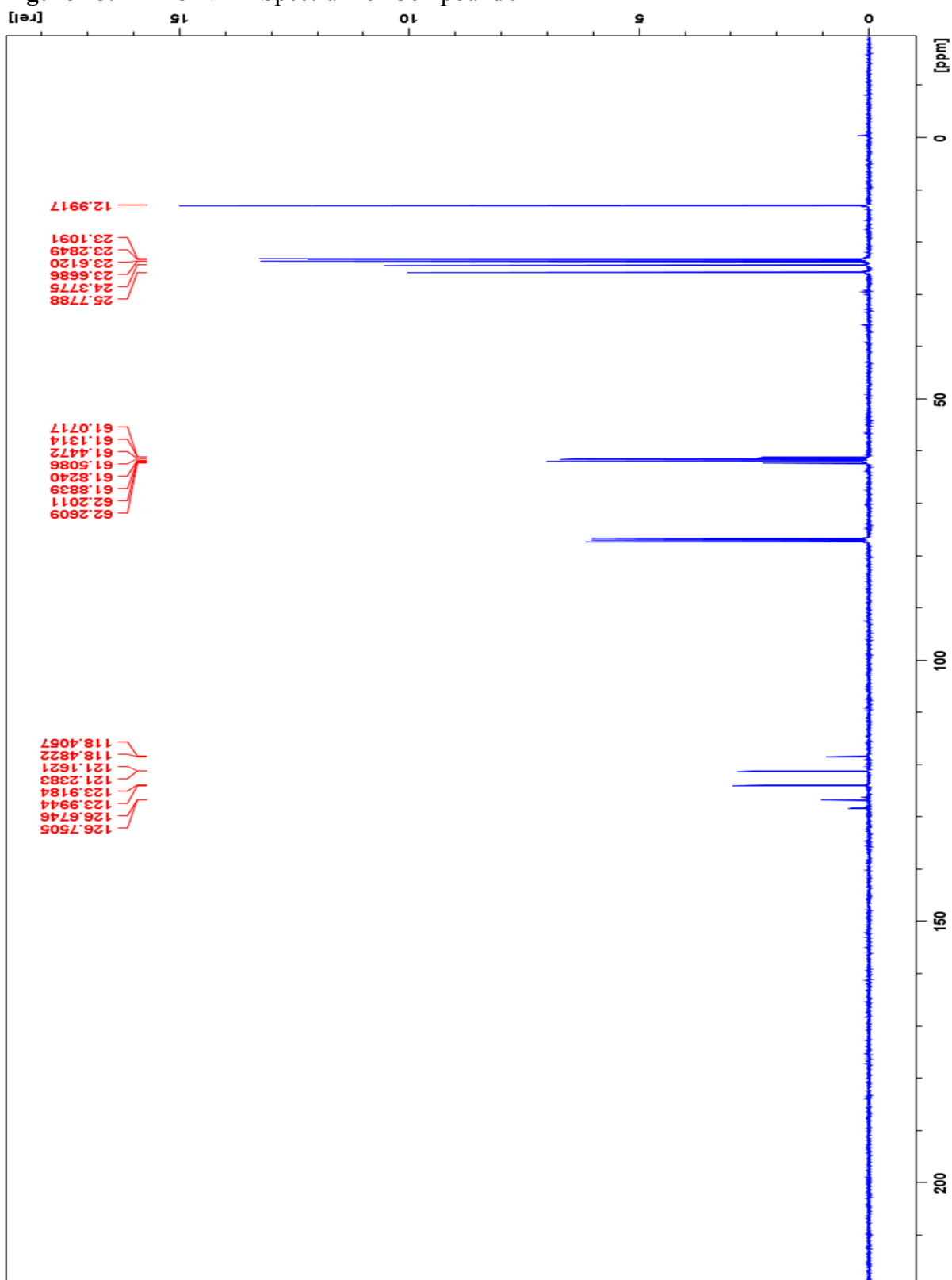




Figure 49: HSQC NMR Spectrum of Compound 9

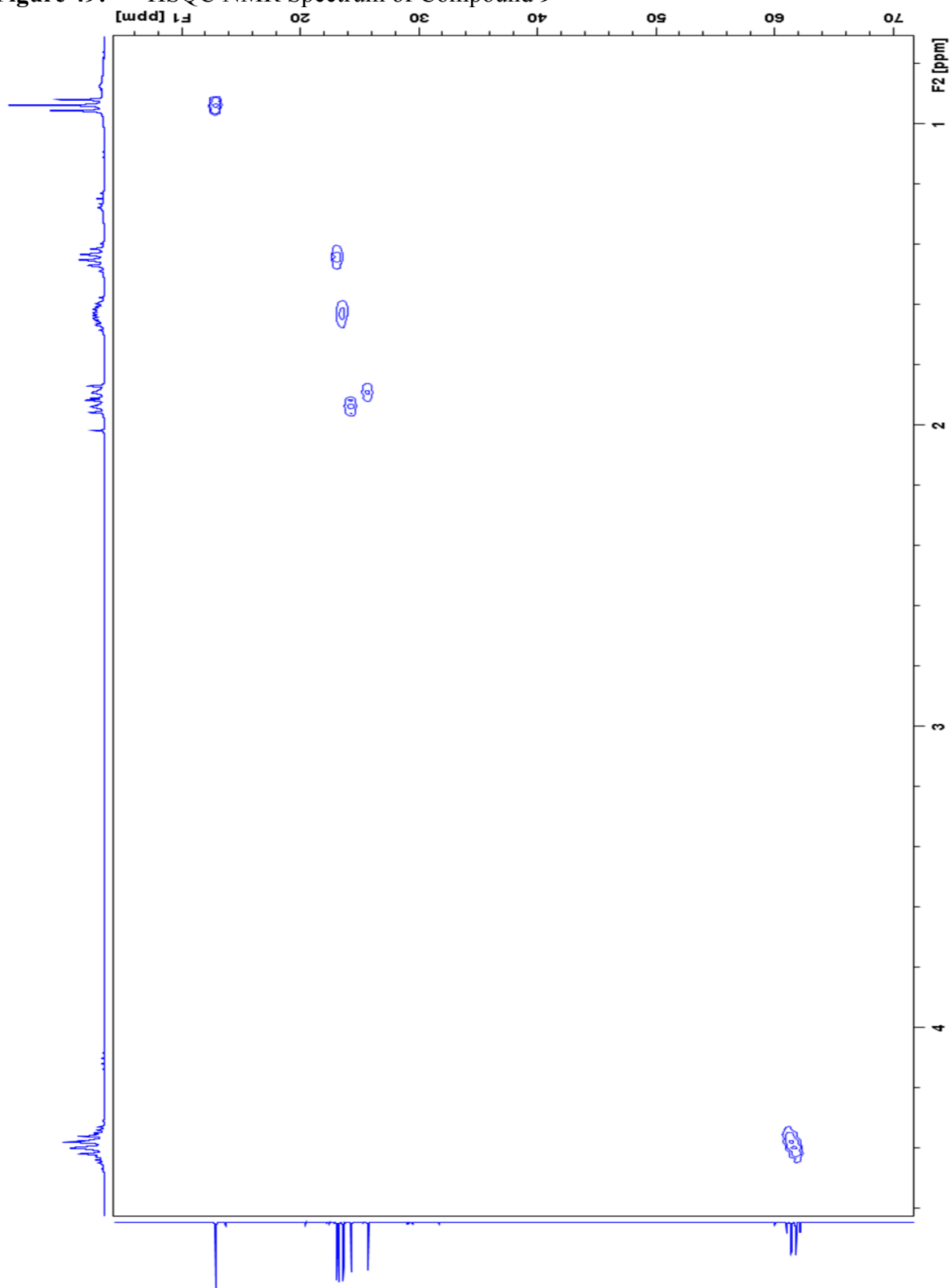
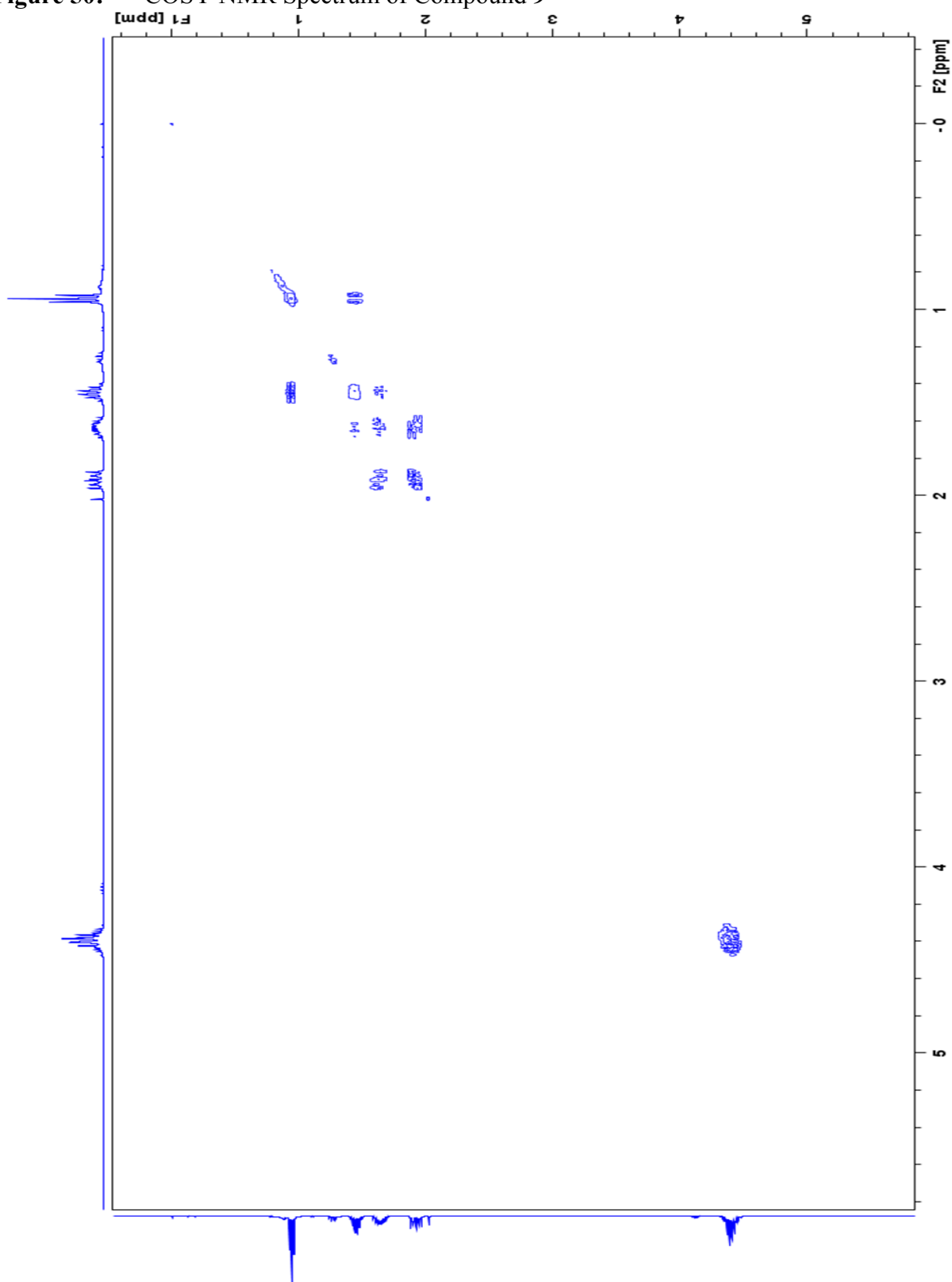


Figure 50: COSY NMR Spectrum of Compound 9



**Figure 51:**  $^{31}\text{P}$  NMR Spectrum of Compound **10**

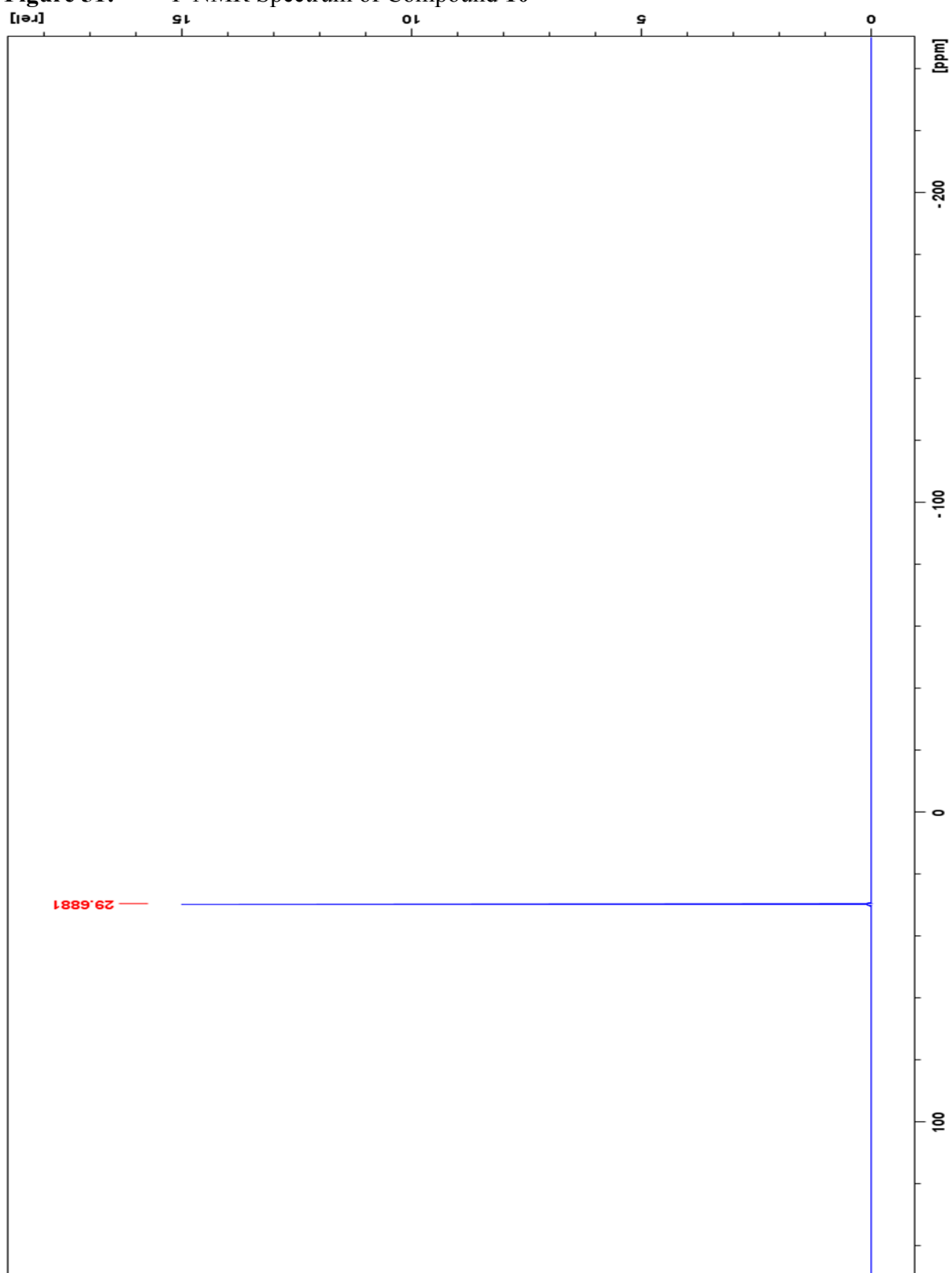


Figure 52:  $^1\text{H}$  NMR Spectrum of Compound 10

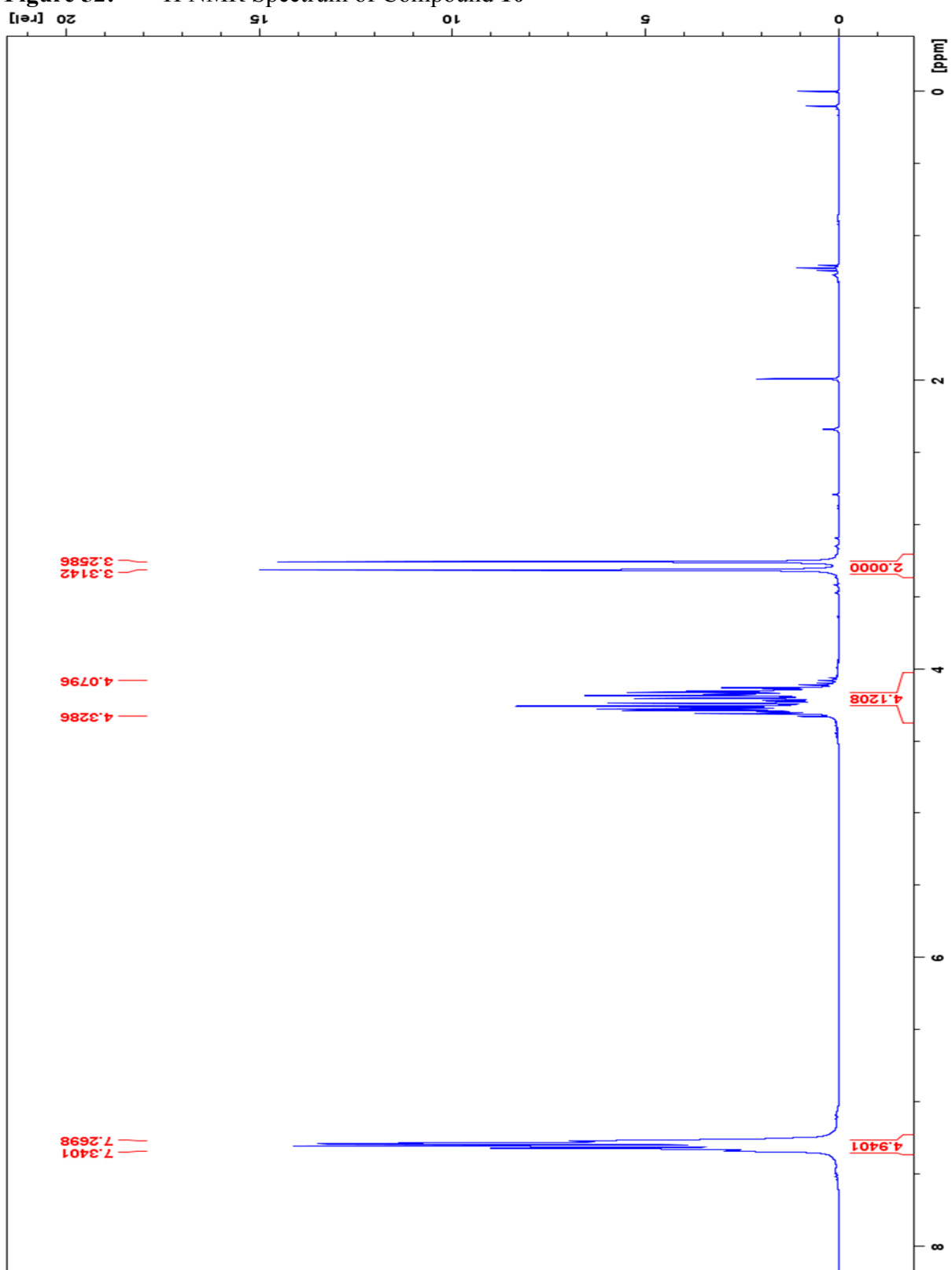


Figure 53:  $^{13}\text{C}$  NMR Spectrum of Compound 10

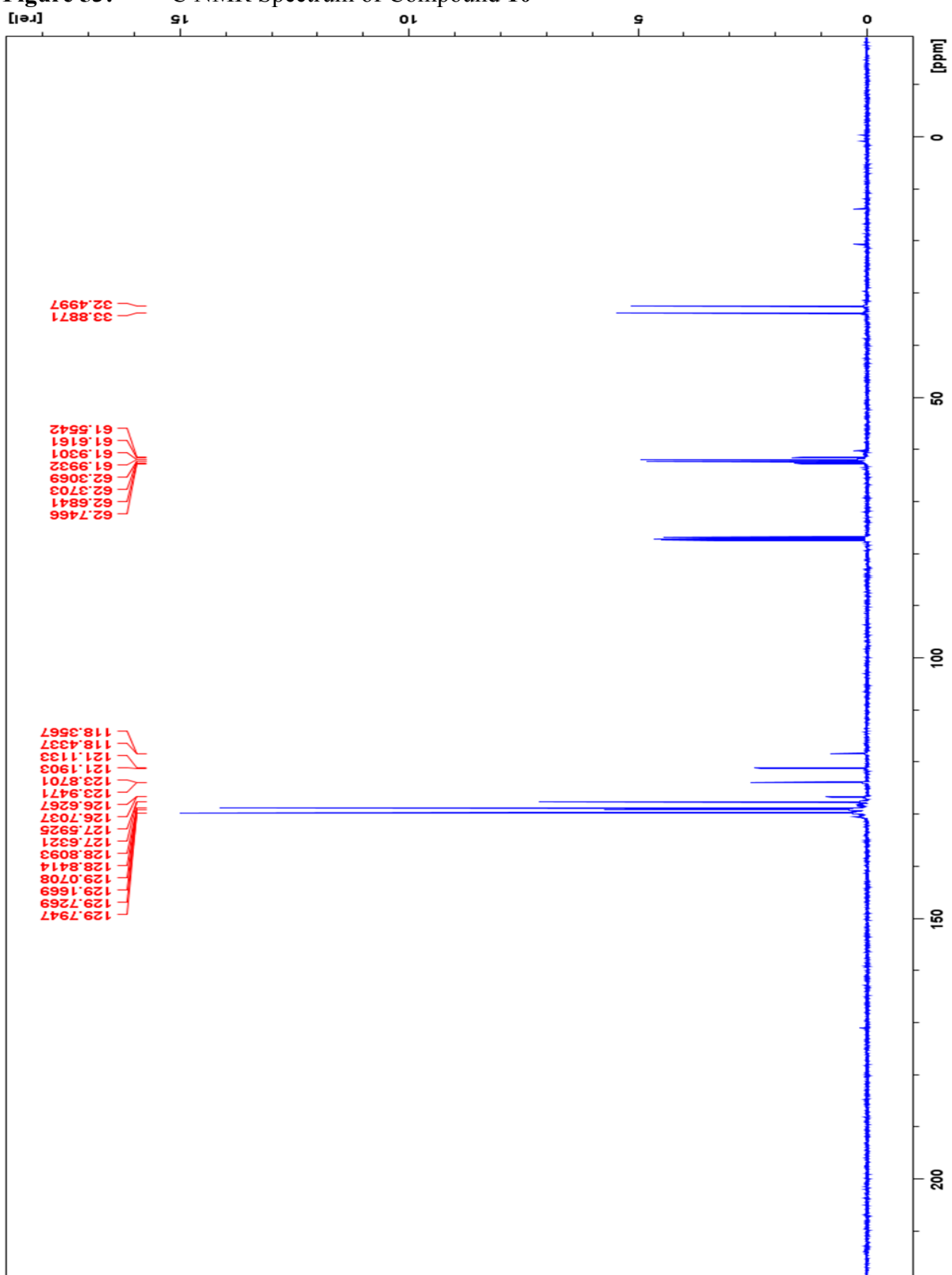
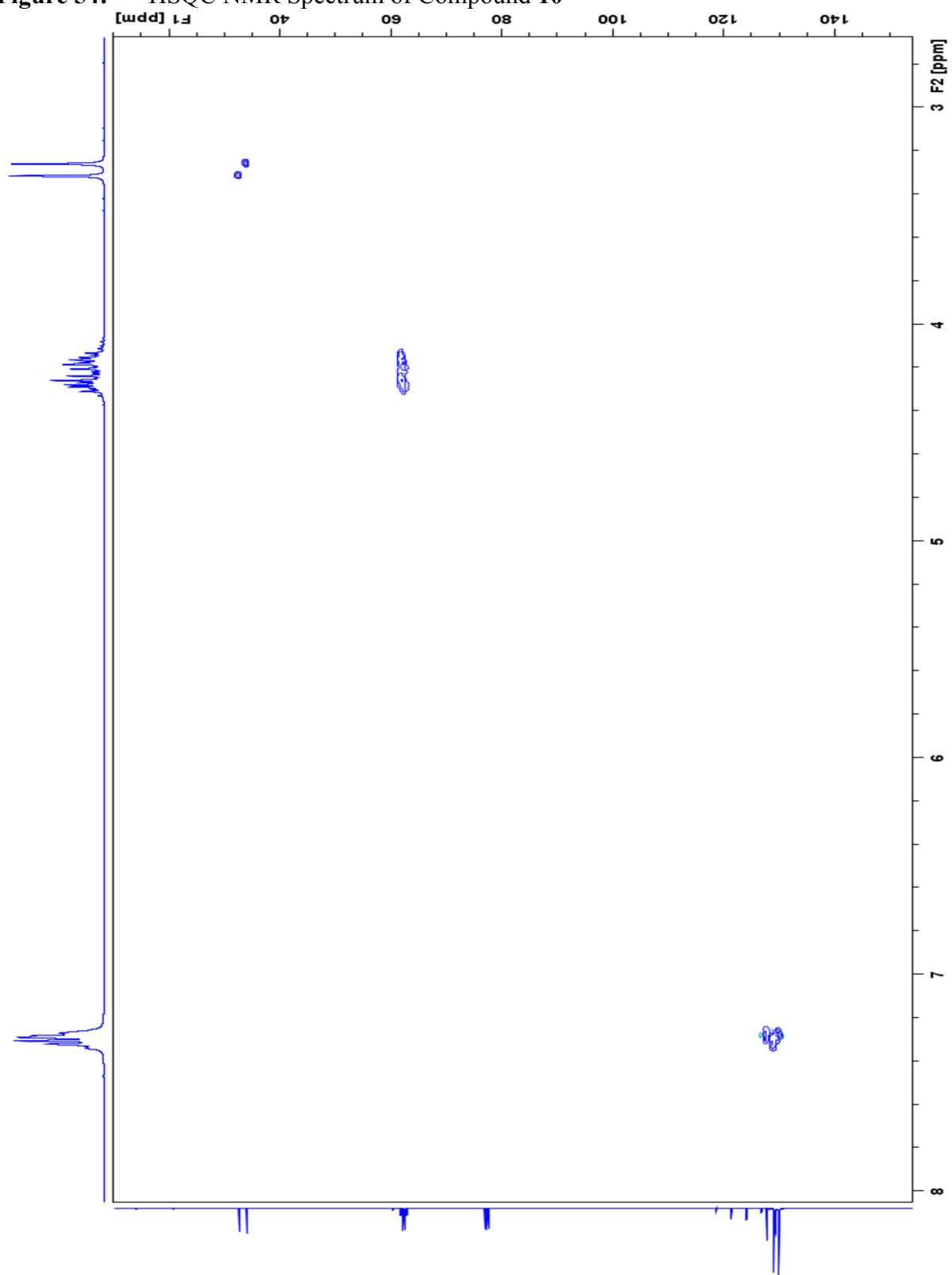


Figure 54: HSQC NMR Spectrum of Compound 10



**Figure 55:**  $^{31}\text{P}$  NMR Spectrum of Compound **11**

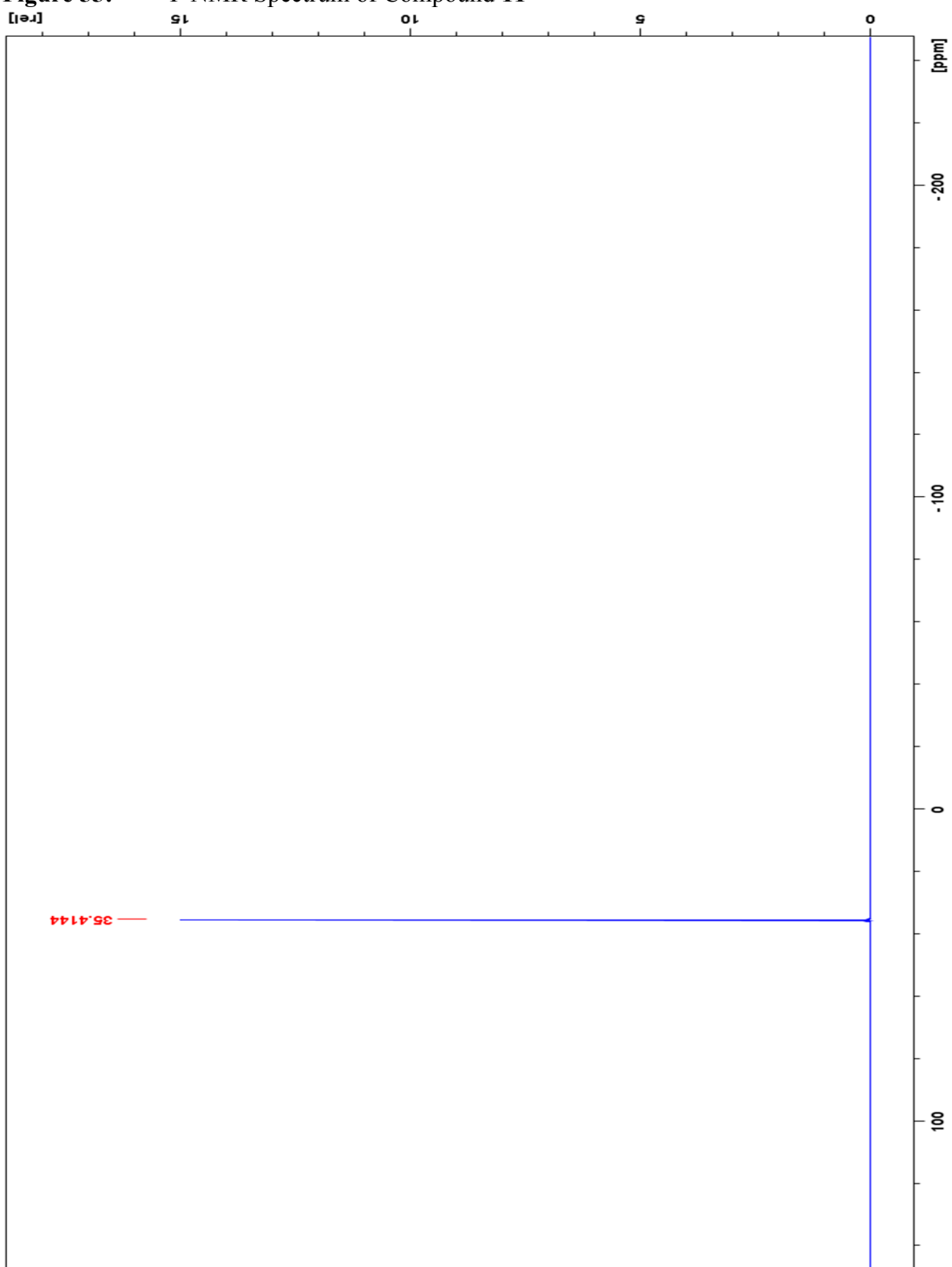


Figure 56:  $^1\text{H}$  NMR Spectrum of Compound 11

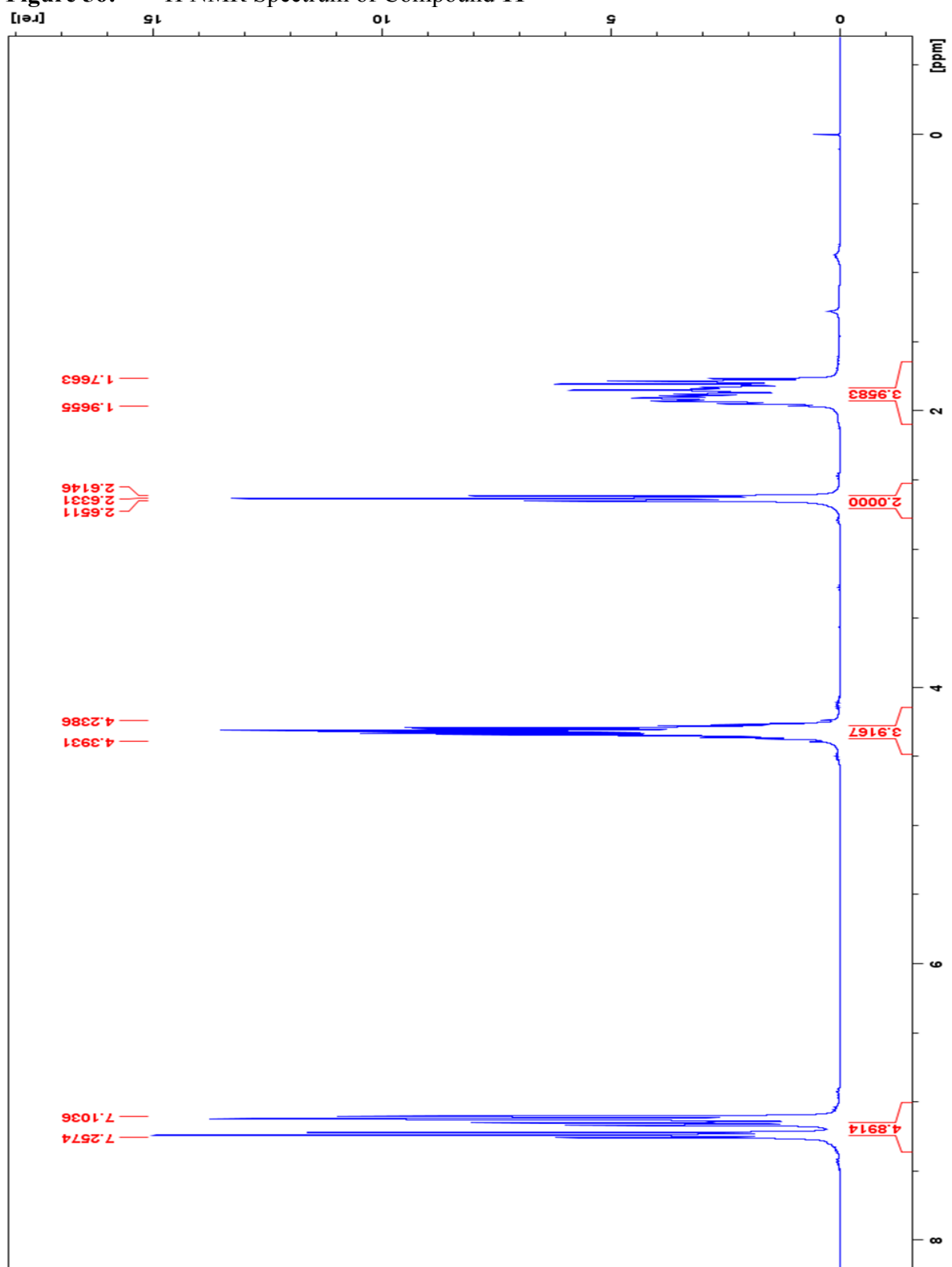




Figure 57:  $^{13}\text{C}$  NMR Spectrum of Compound 11

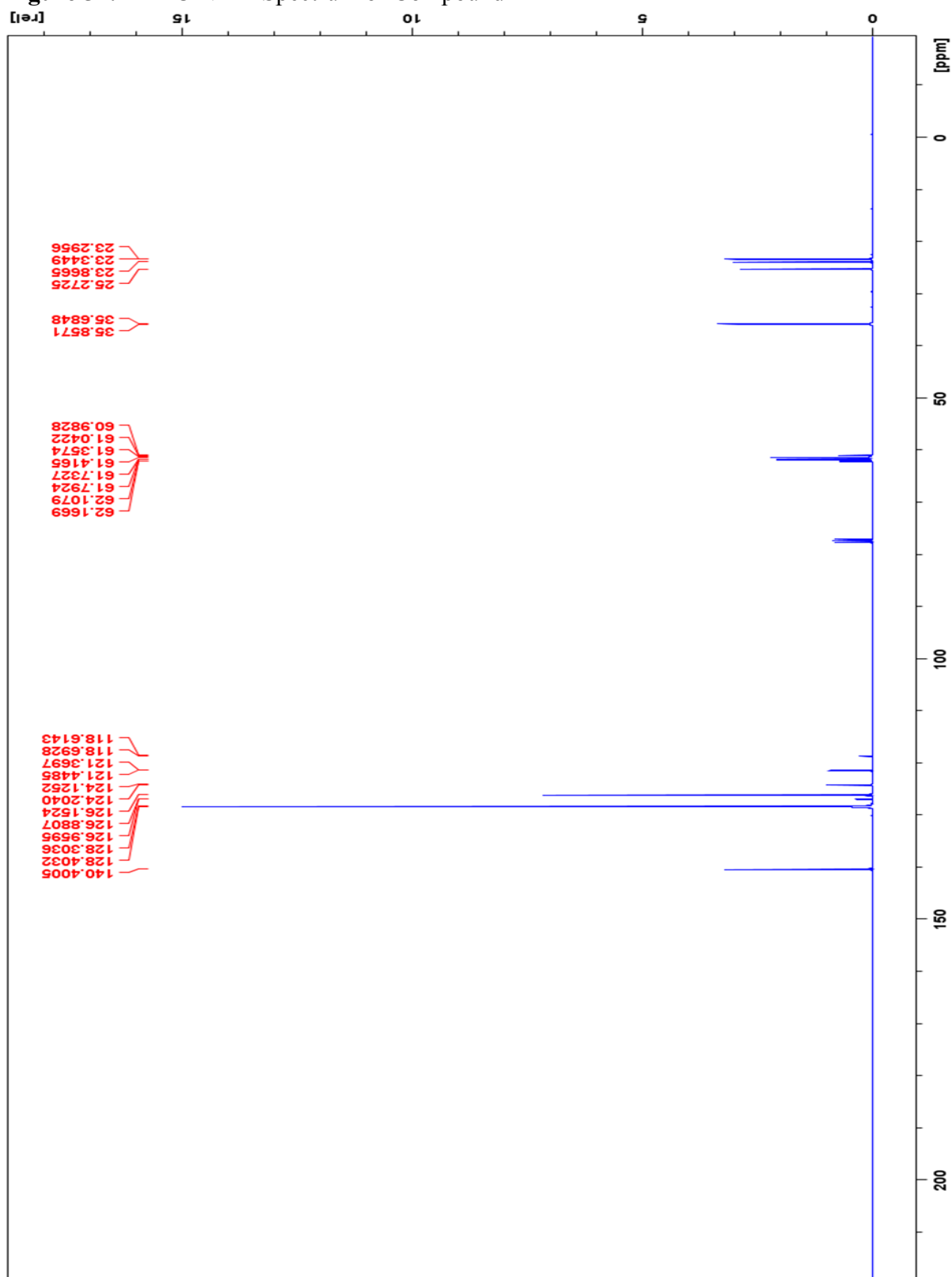


Figure 58: HSQC NMR Spectrum of Compound 11

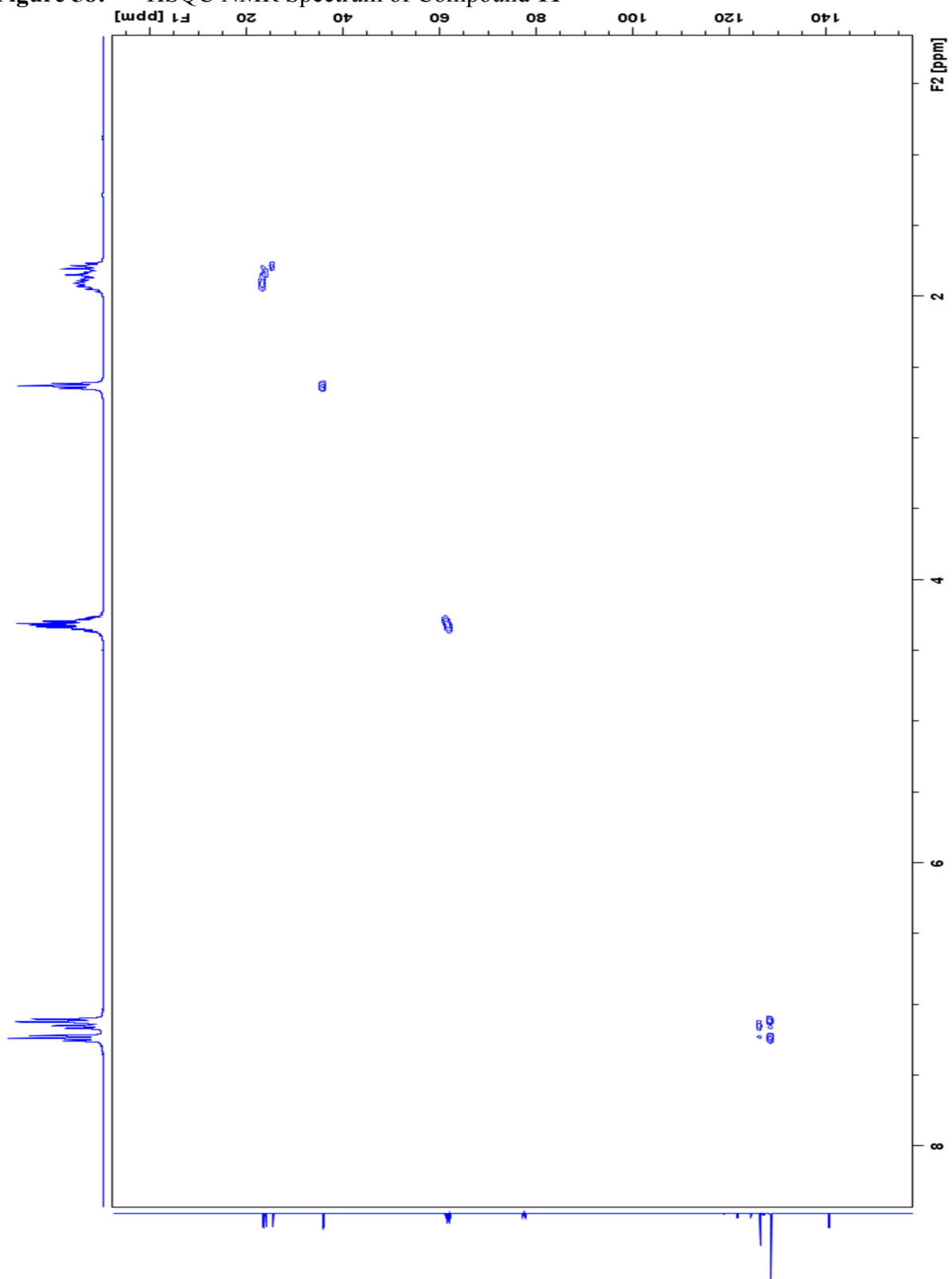
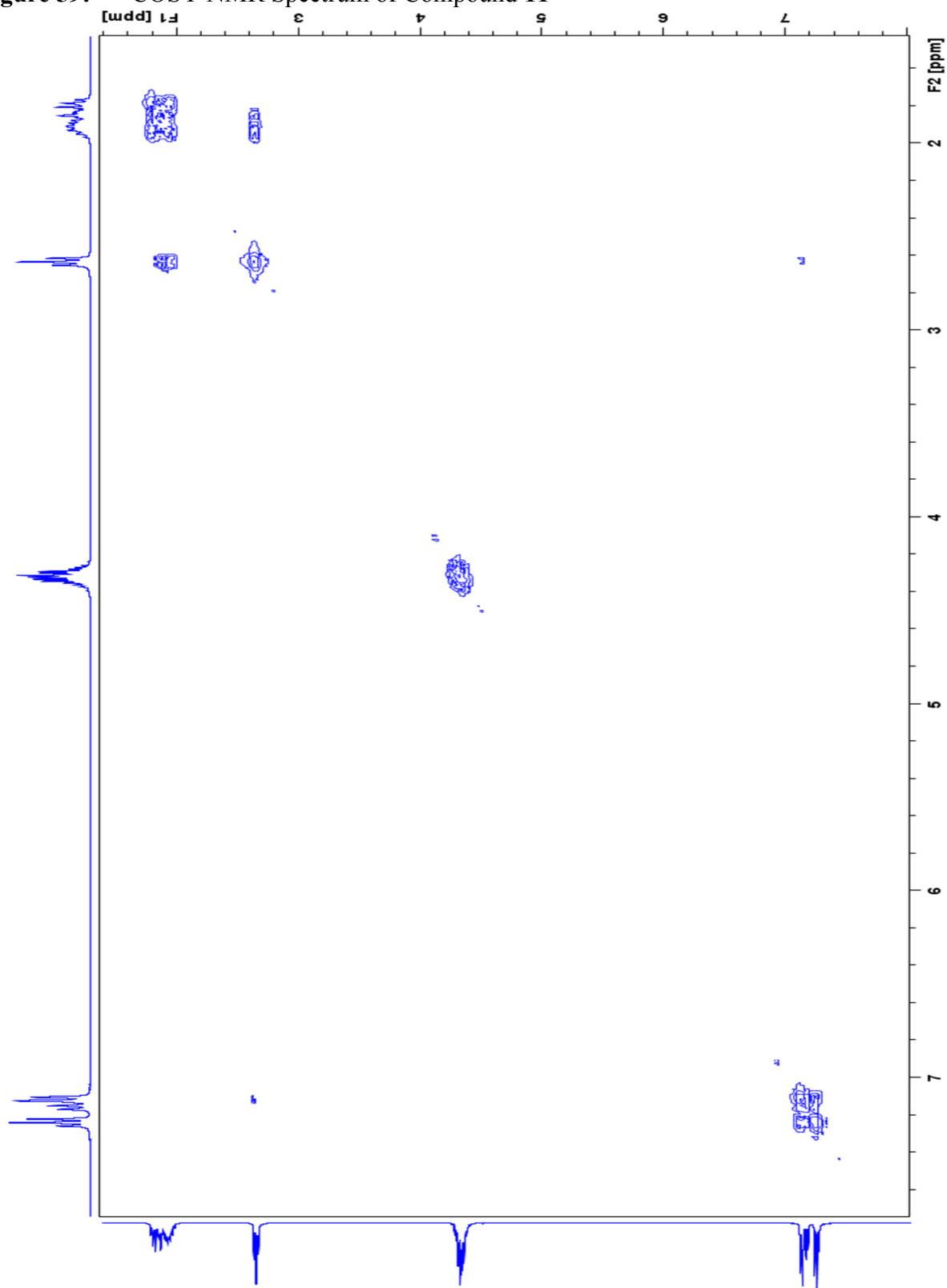


Figure 59: COSY NMR Spectrum of Compound 11



**Figure 60:**  $^{31}\text{P}$  NMR Spectrum of Compound **12**

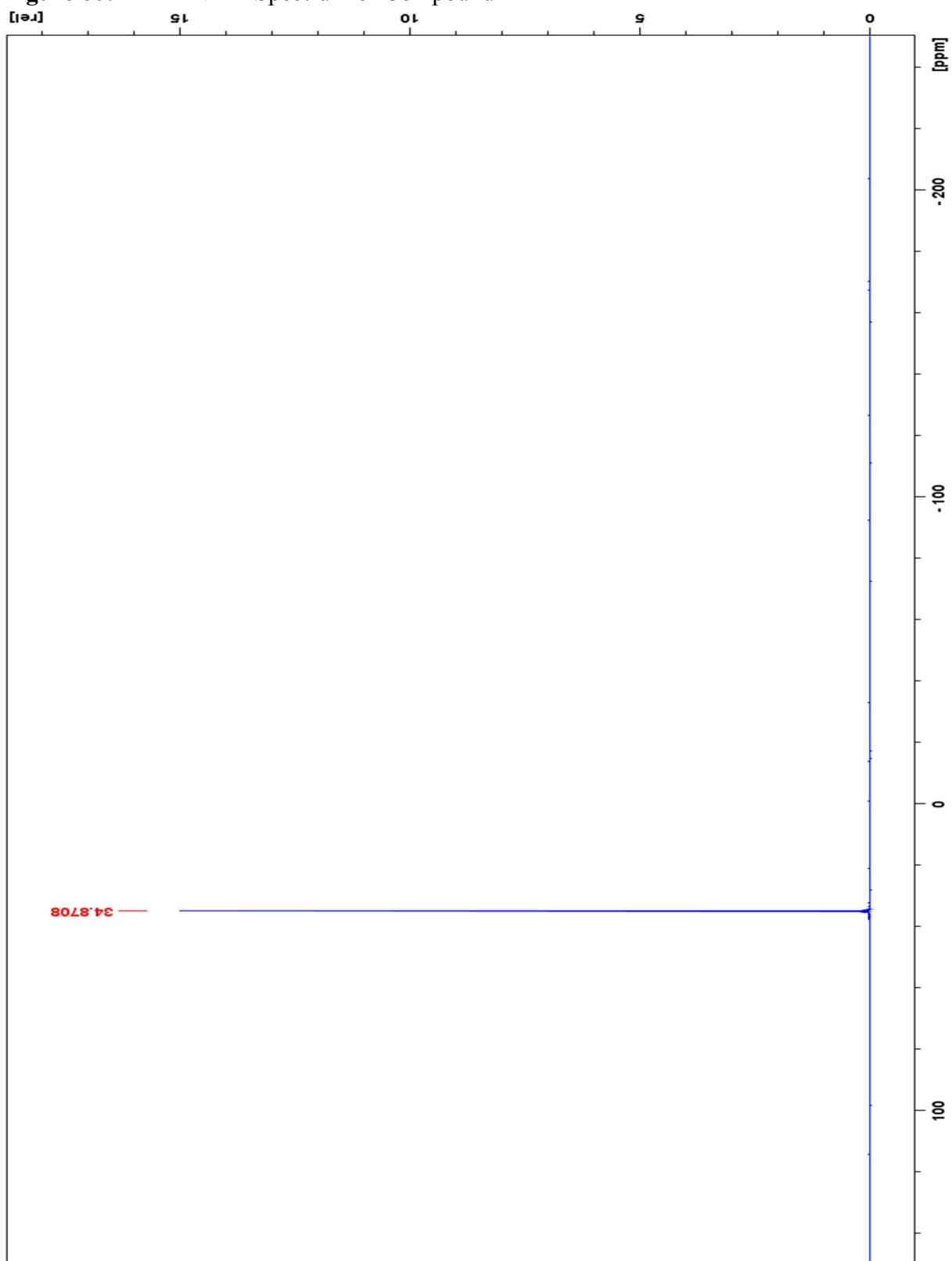


Figure 61:  $^1\text{H}$  NMR Spectrum of Compound 12

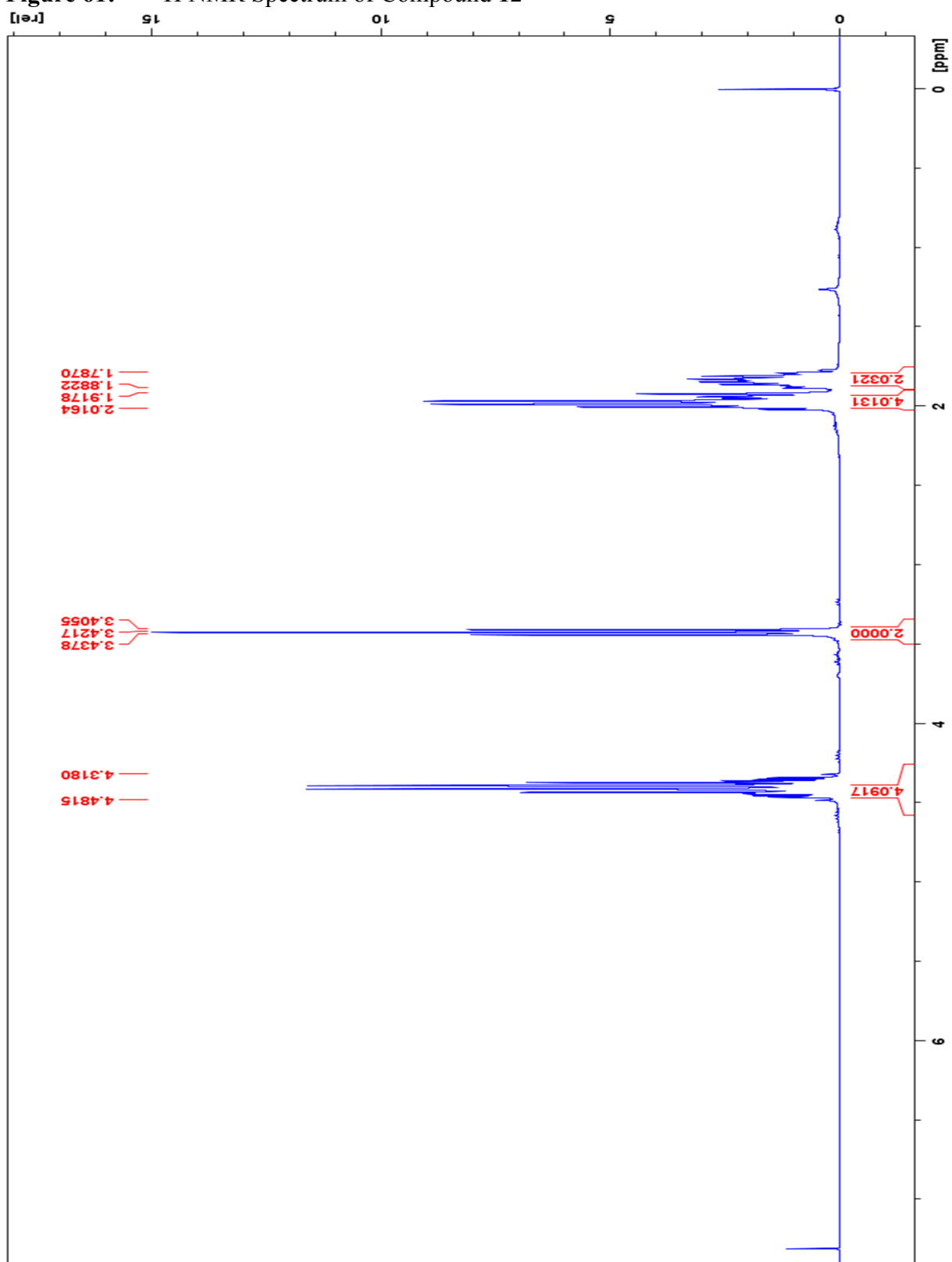


Figure 62:  $^{13}\text{C}$  NMR Spectrum of Compound 12

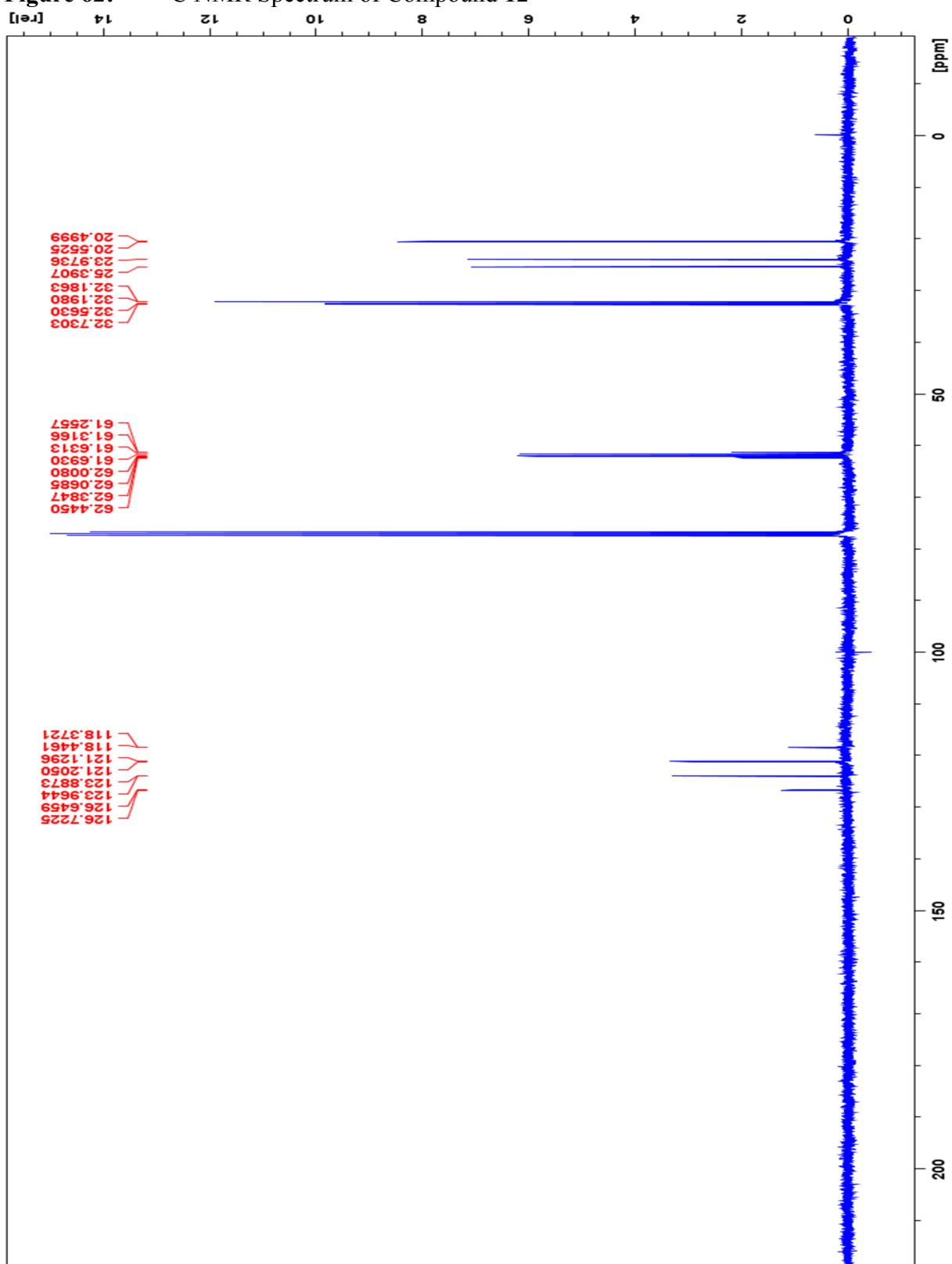


Figure 63: HSQC NMR Spectrum of Compound 12

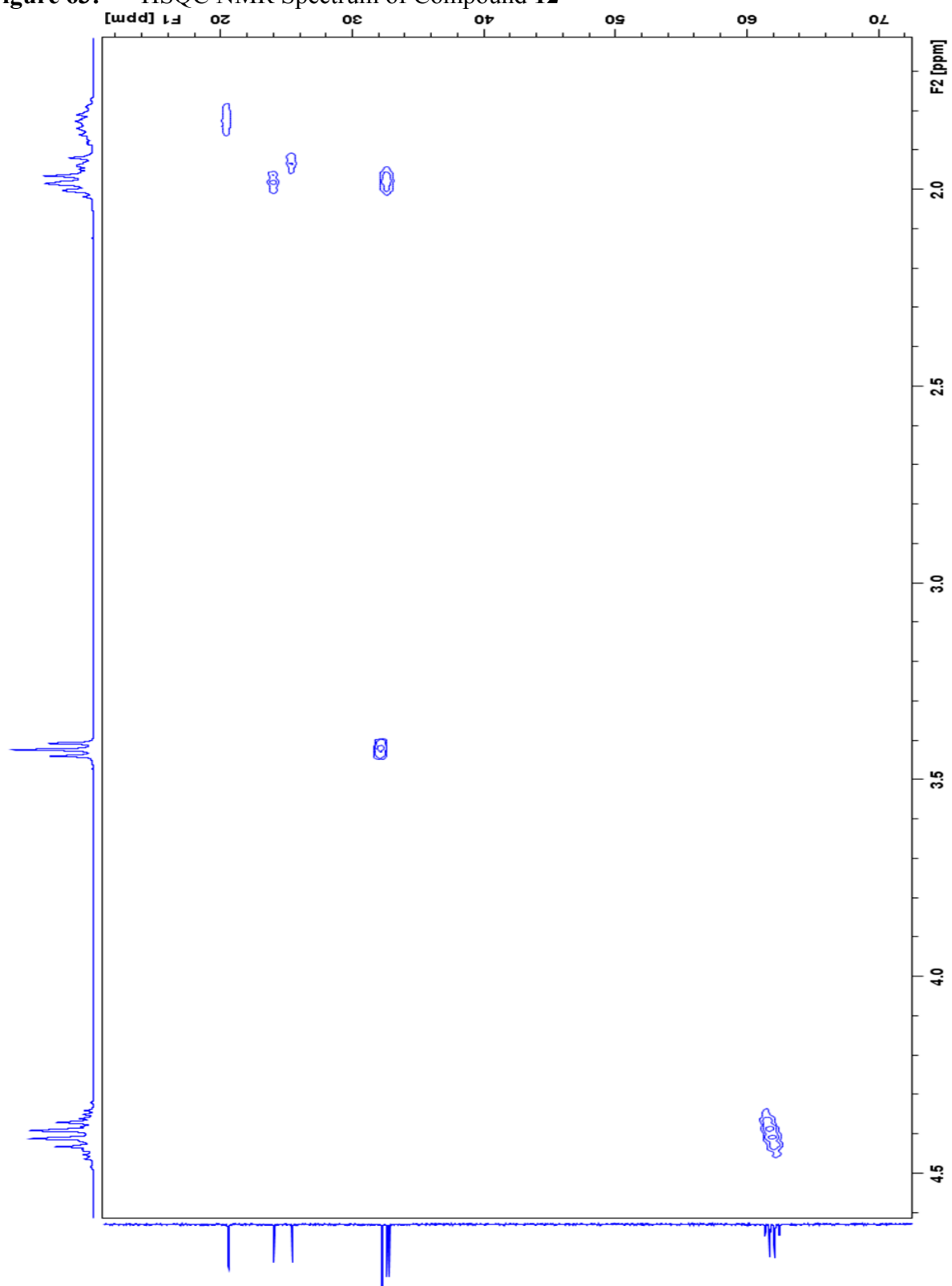
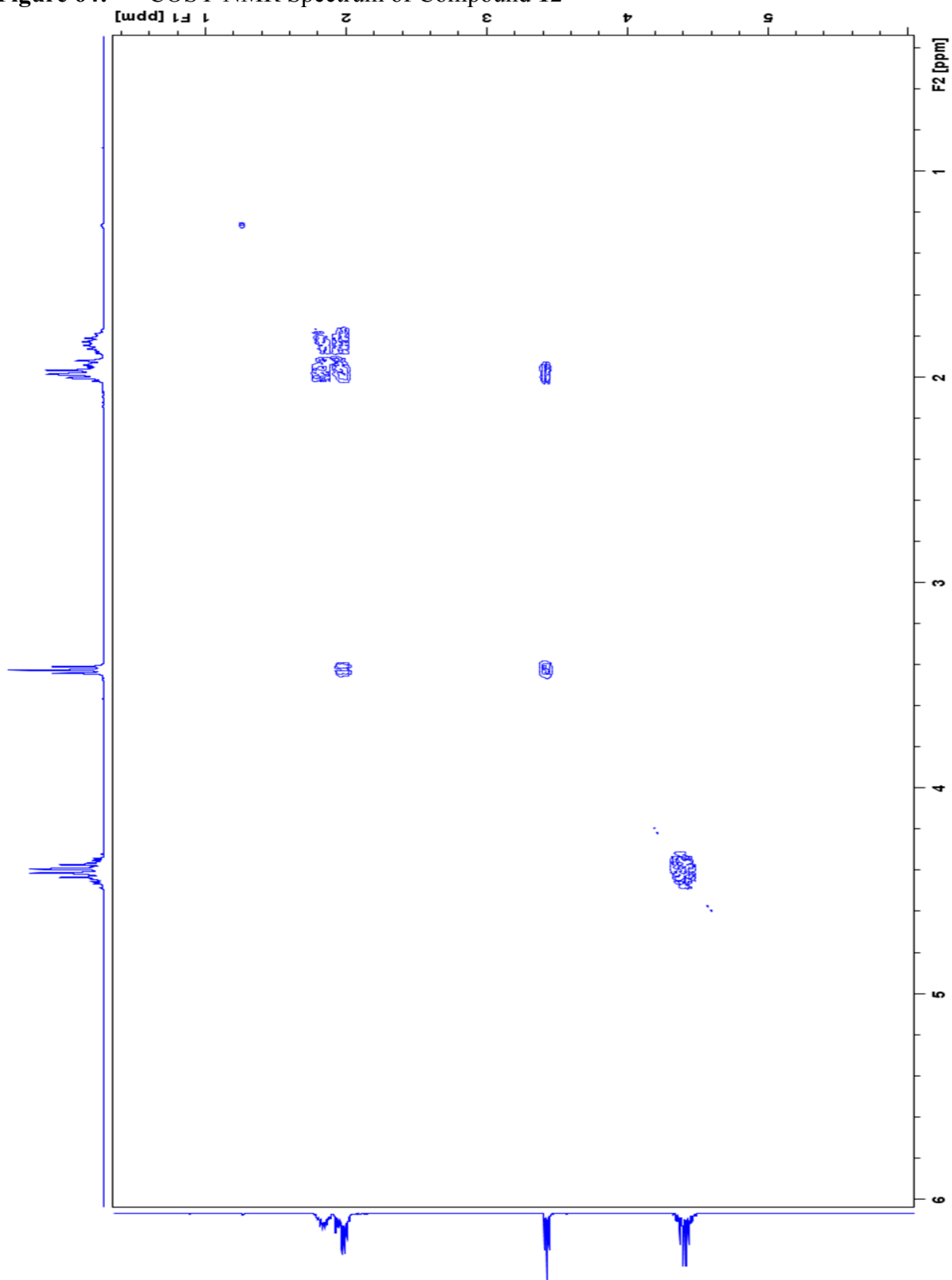


Figure 64: COSY NMR Spectrum of Compound 12





**Figure 65:**  $^{31}\text{P}$  NMR Spectrum of Compound **13**

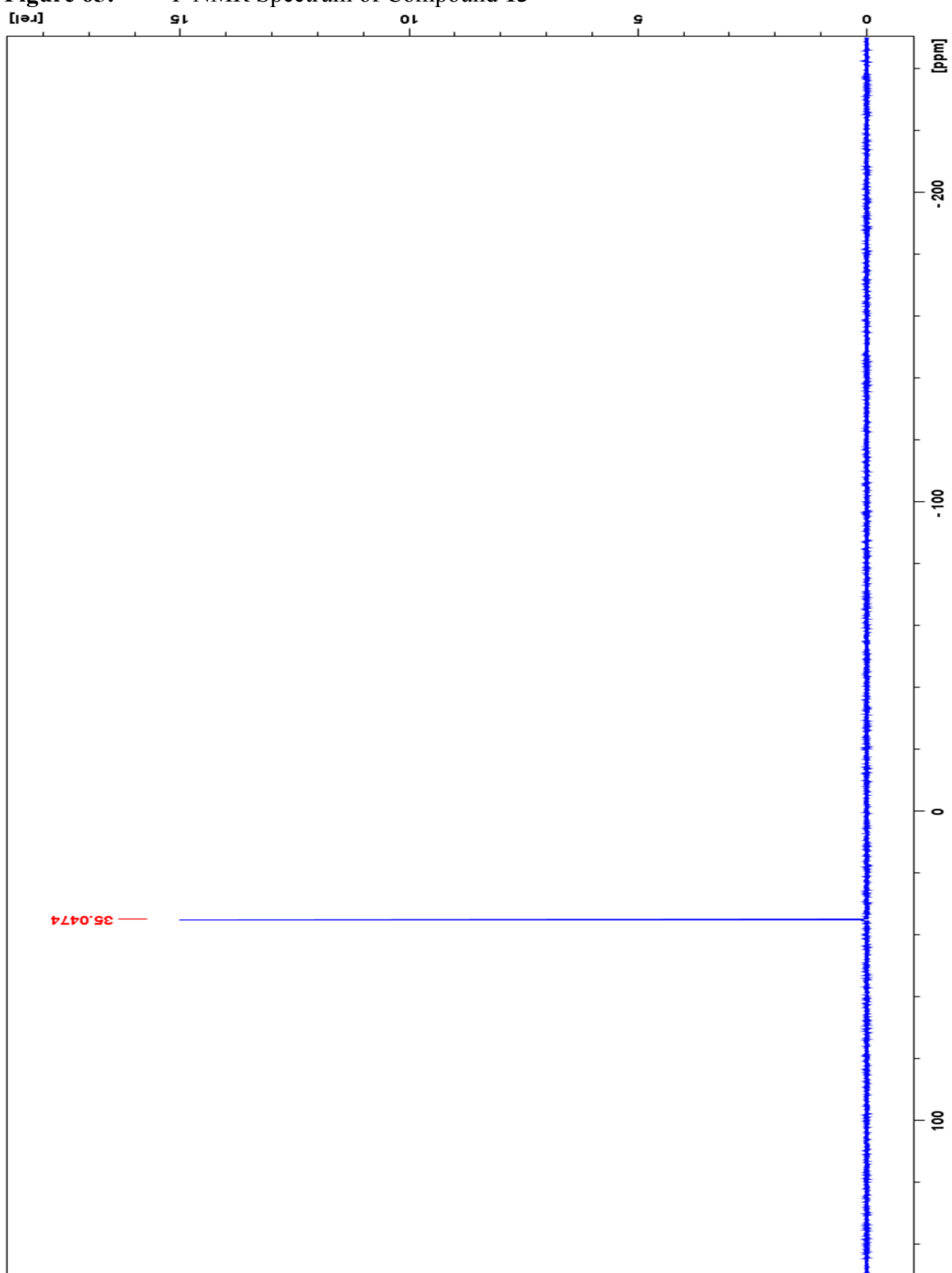


Figure 66:  $^1\text{H}$  NMR Spectrum of Compound 13

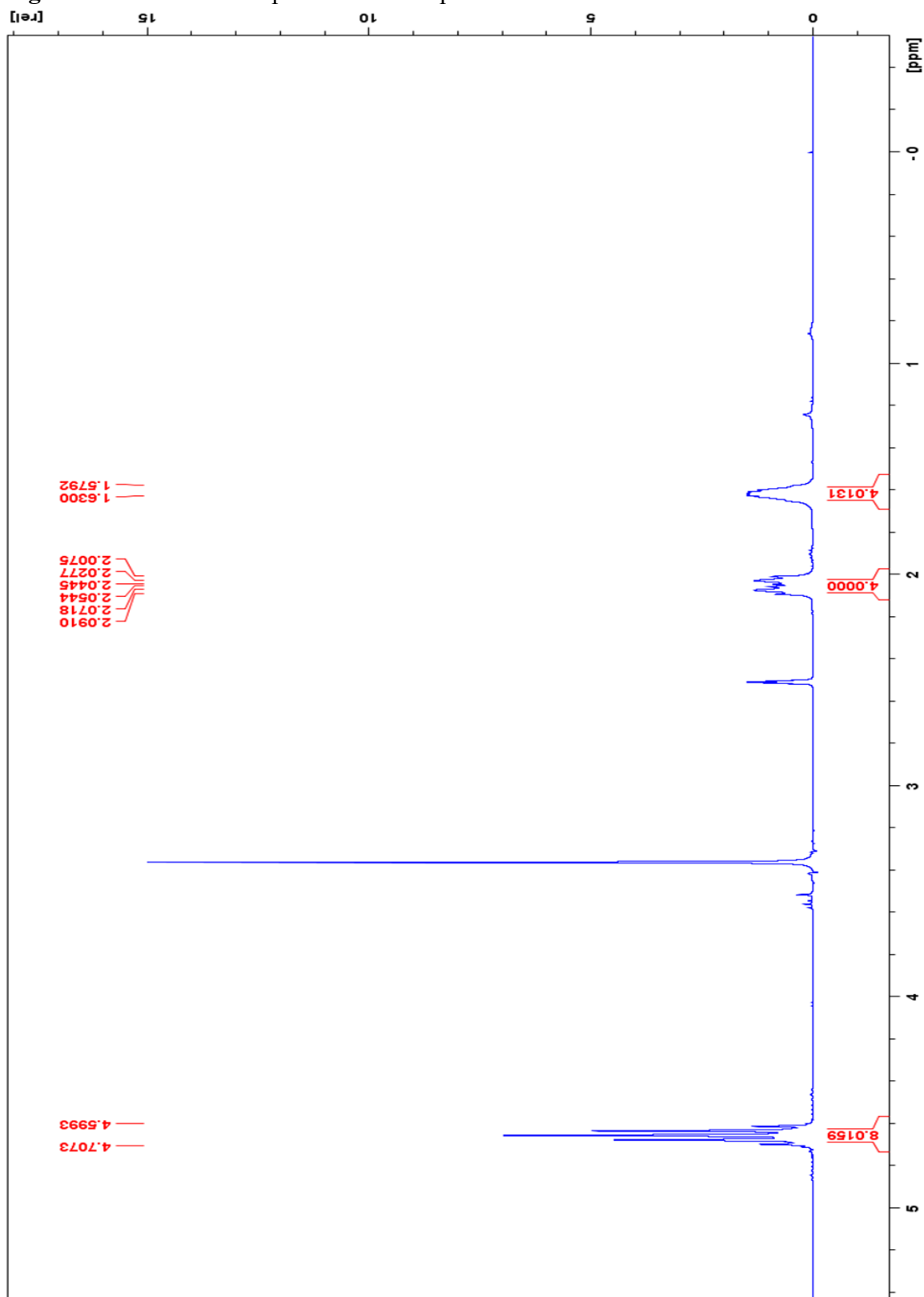
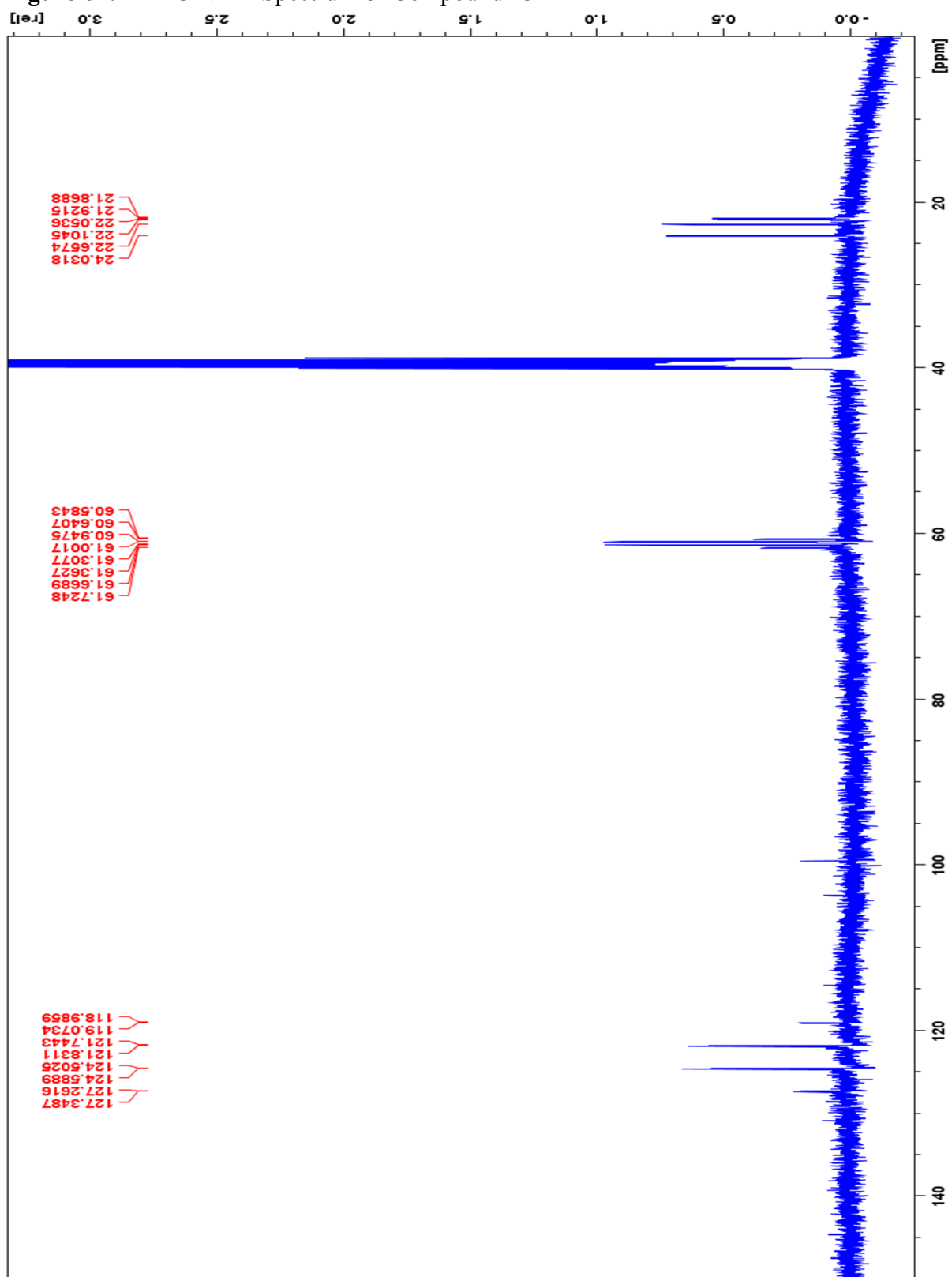


Figure 67:  $^{13}\text{C}$  NMR Spectrum of Compound 13



**Figure 68:**  $^{31}\text{P}$  NMR Spectrum of Compound **14**

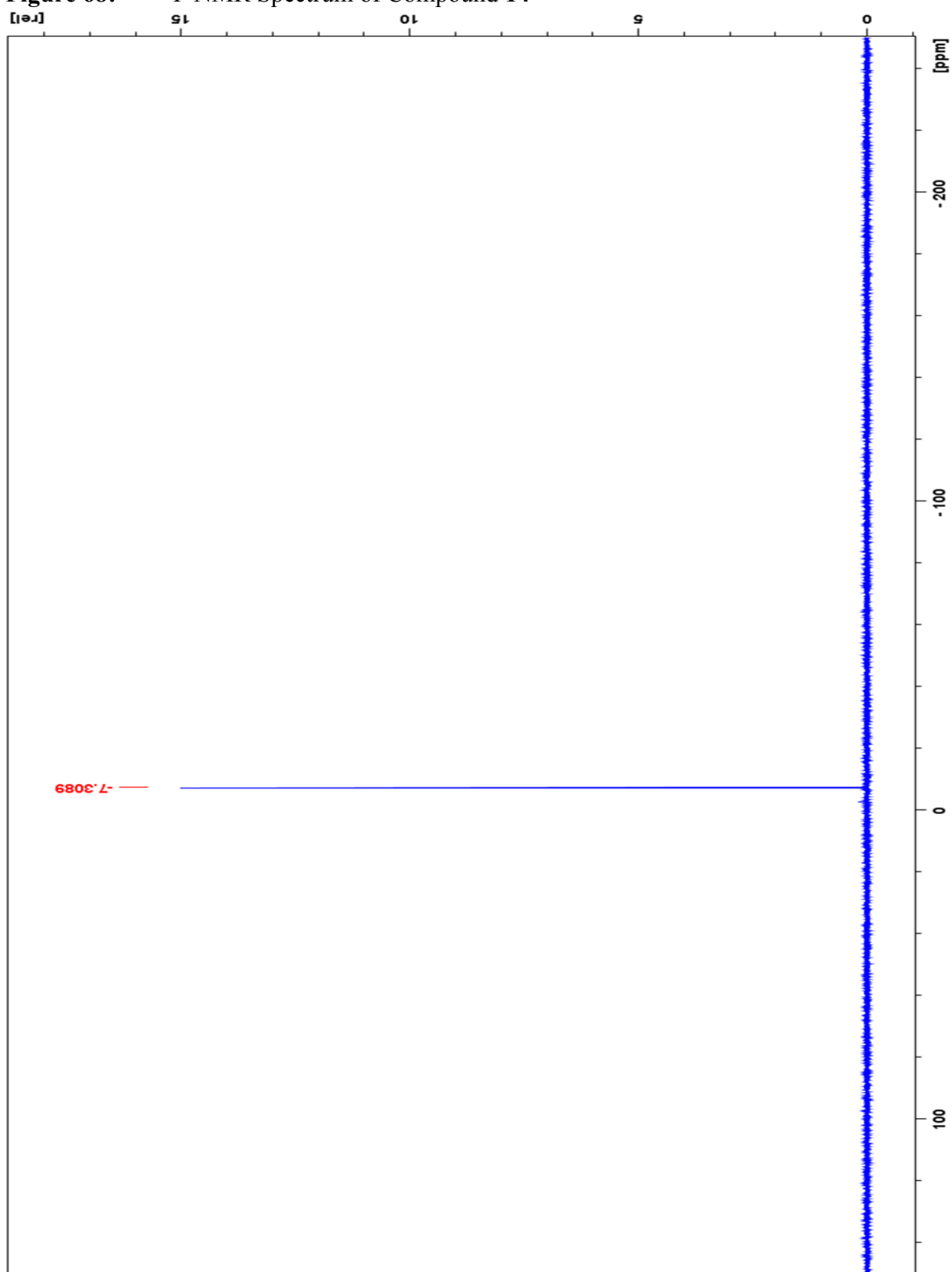


Figure 69:  $^1\text{H}$  NMR Spectrum of Compound 14

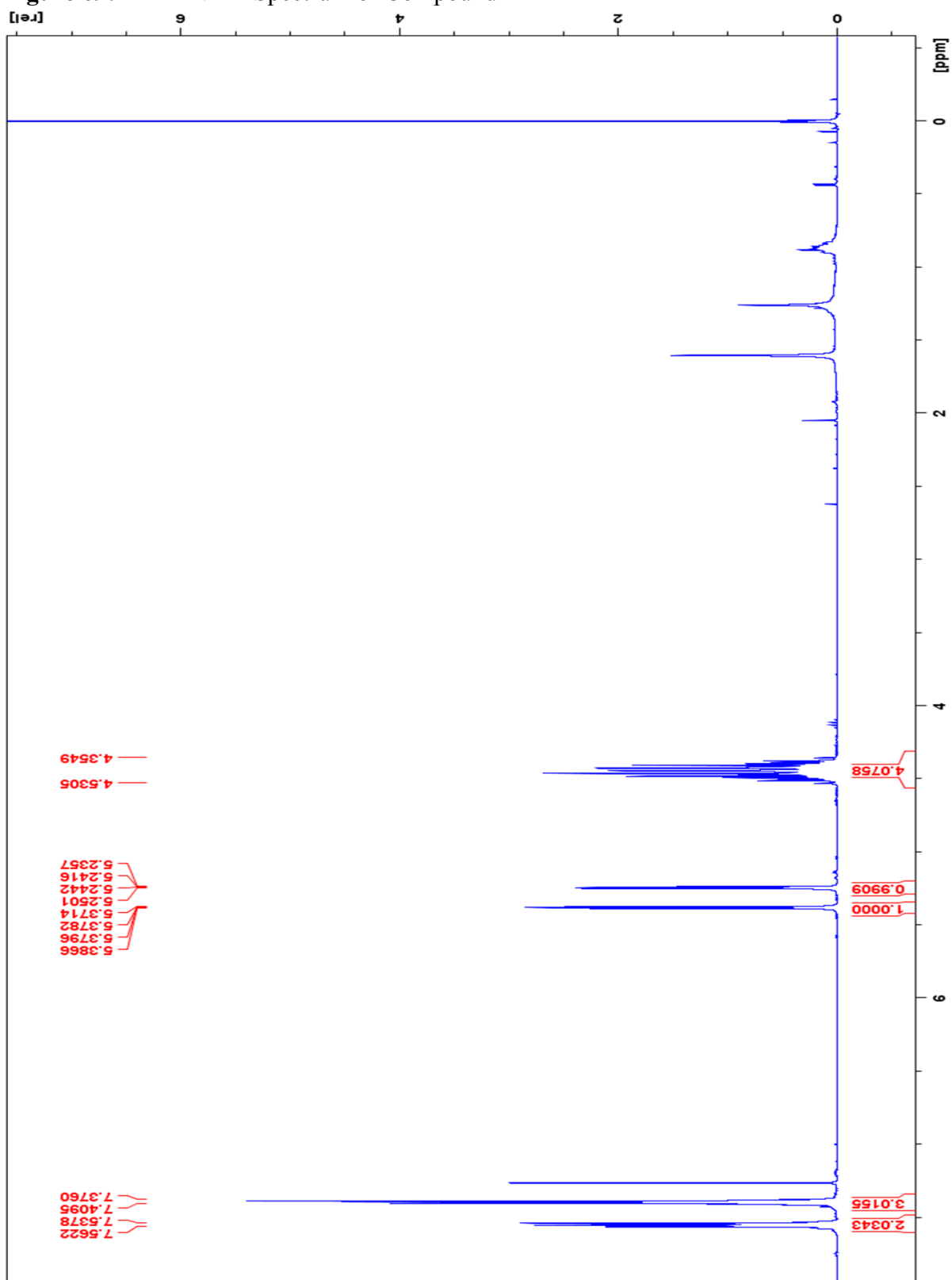


Figure 70:  $^{13}\text{C}$  NMR Spectrum of Compound 14

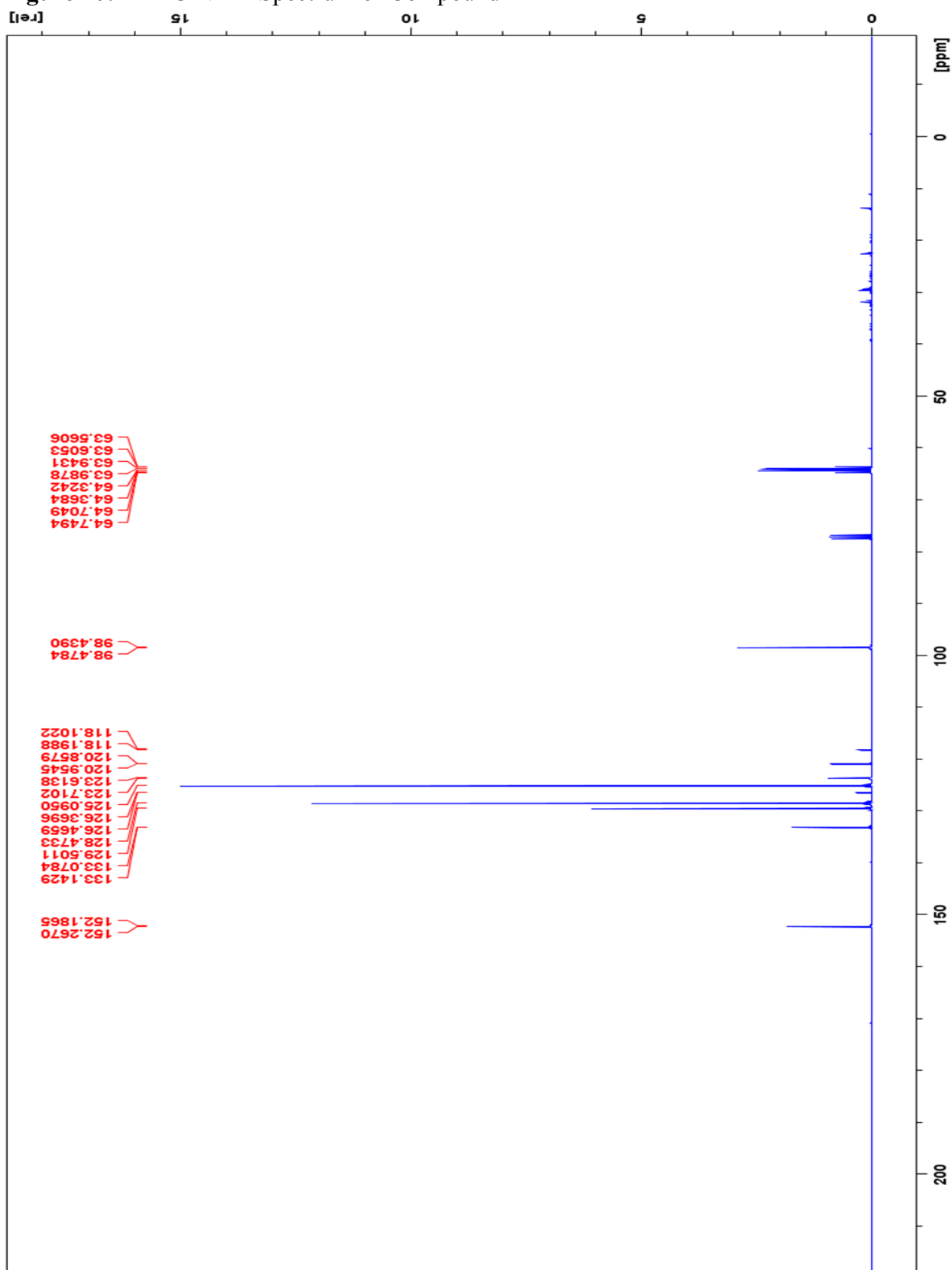


Figure 71: HSQC Spectrum of Compound 14

