ABSTRACT

The Synthesis of New Pyrylium and Pyridinium Salts

Holland T. Korbitz

Director: Charles Garner, Ph.D.

The synthesis, properties, and applications of symmetrical and unsymmetrical pyrylium and pyridinium salts is investigated. Our group has found particular interest in chiral pyrylium salts due to the fact that they are almost unknown in the literature. We have applied the reaction of acyl chlorides with *tert*-butanol to the preparation of new pyrylium tetrafluoroborate salts. Some of these pyrylium salt derivatives form diastereomers when prepared. Moreover, they are favorable to study epimerization at the alpha centers. The ease of epimerization at pyrylium chiral centers has not been studied previously. We also applied the reaction of acyl chlorides with dypnone to form asymmetrical pyrylium salts. Our group has also found interest in positively charged pyridinium salts, which provide a route for the possible improvement on the bioavailability of hydrophobic compounds and also an interesting interaction with different substrates. We optimized reaction conditions for reacting substituted pyrylium salts with primary amines to obtain pyridinium salts. Future work will be directed towards obtaining pyridinium salts from primary amines with known biological activity. The objective of this study is to synthesize new pyrylium and pyridinium salts.

APPROVED BY DIRECTOR OF HONORS THESIS:

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Dr. Charles Garner, Department of Chemistry

APPROVED BY THE HONORS PROGRAM:

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Dr. Andrew Wisely, Director.

DATE: _____

THE SYNTHESIS OF NEW PYRYLIUM AND PYRIDINIUM SALTS

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

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By

Holland T. Korbitz

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ACKNOWLEDGEMENTS

I would first like to give all the glory to God, who has gifted me with many talents. He has opened up doors for me that I could have never imagined, and led me down paths that have challenged me. I am anxious to see what the future has in store.

I would like to thank my research advisor, Dr. Garner, for supporting and encouraging me throughout this entire process. I have gained much knowledge about chemistry and research while working in the Garner group for the past two years. Working in the Garner group has been one of my most memorable and enjoyable experiences as an undergraduate student.

I would also like to thank the members of the Garner group for their constant guidance and support. I want to give a big thank you to Nelson van der Velde for teaching me everything I know. Not only has he taught me everything I know about chemistry, he has also taught me many important life lessons. You are an exceptional teacher and I hope that I have made you proud.

I want to give thanks to my family, for constantly encouraging and spurring me on. My mother has taught me to work hard and to be the best at everything I do. Her love has shaped me into the person I am today, and I hope that I can be half of the woman she is.

I want to thank my friends for their encouragement and companionship. Thank you for constantly supporting me in my decisions. I appreciate your patience and understanding. Thank you for always cheering me on and always being there when I truly needed you.

CHAPTER ONE

Introduction

Aromaticity

Aromaticity is a property that describes a ring with continuous conjugation of π-electrons. Benzene, as shown in Figure 1.1, demonstrates aromaticity.

Figure 1.1: Aromatic compound – benzene

The resonance and delocalization of electrons on an aromatic compound is of great importance. There are no single and double bonds, and electrons are free to circulate around the ring due to the conjugation. Amongst all the aromatic compounds, heterocyclic compounds, which are cyclic compounds with at least two different elements in the ring system, provide the most diverse properties and uses of aromatics. The pyridine in Figure 1.2 represents a heterocyclic compound.

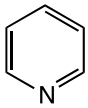


Figure 1.2: Heterocyclic compound – pyridine

Aromatic rings with one heteroatom from groups 15 (nitrogen family) and 16 (oxygen family) in the periodic table prove to be the most stable towards air and humidity

under normal conditions.[1] These have been extensively researched. Only heterocycles containing oxygen or nitrogen occur naturally.

Pyrylium Salts

Pyrylium salts are heterocyclic compounds, similar to the pyridine previously shown. A pyrylium salt is a six-membered carbon ring system with one carbon replaced by a positively charged oxygen, making the compound a cation.

The knowledge of pyrylium salts has greatly increased over the years. Figure 1.3 displays the number of papers published on pyrylium salts between the years 1950 and 2010. Due to the work done by Katritzky and Balaban in the 1970s, the synthesis of pyrylium salts increased rapidly until its decline in the mid 1980s. This decline is due to the difficulties in synthesizing these types of compounds. However, there is still much to explore and understand of these interesting compounds.

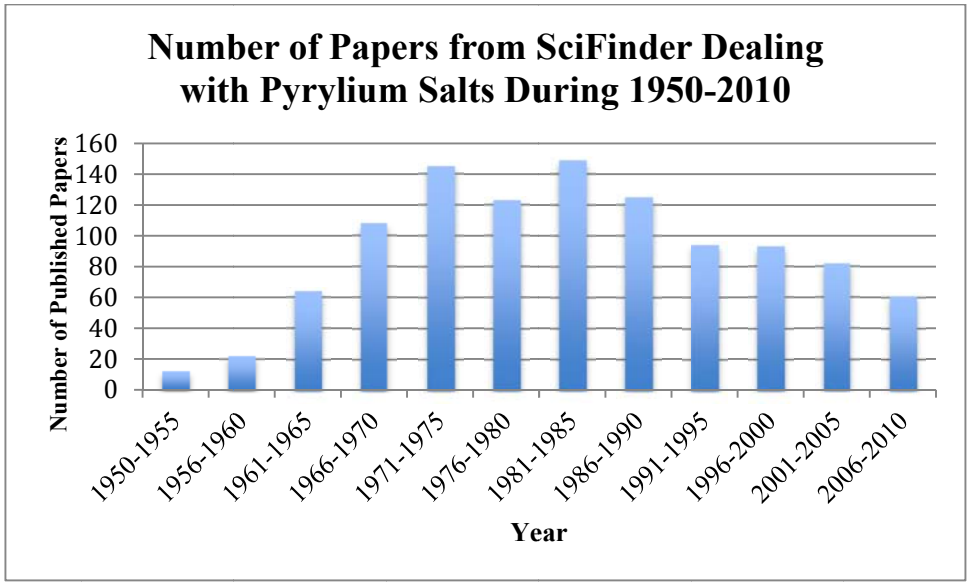
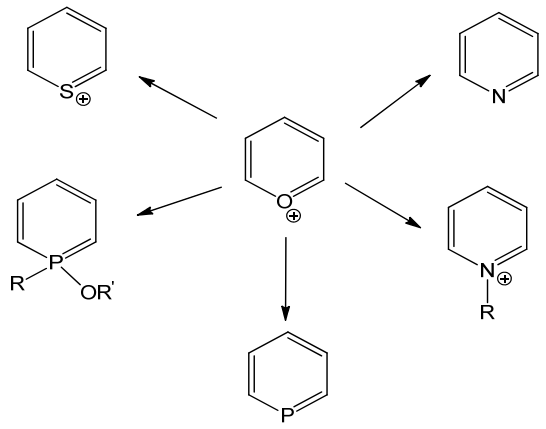


Figure 1.3: Number of papers from SciFinder dealing with pyrylium salts during 1950-2010

The pyrylium salts ionic character allows the salt to be easily separated from the non-polar starting materials.[1] Due to its aromaticity, pyrylium salts have a high reactivity towards nucleophiles, leading to many other products. Aromaticity also explains why pyrylium salts are used to obtain other compounds with stronger aromatic character. In general, pyrylium salts represent a nodal point for many different synthetic routes (Scheme 1.1).[2]



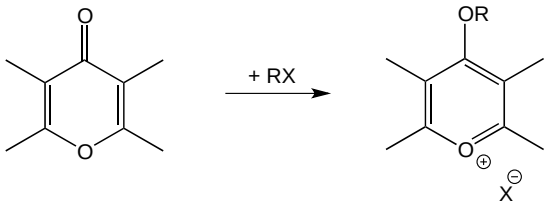
Scheme 1.1: Pyrylium salts as a precursor for many synthetic routes[2]

In regards to the synthesis of pyrylium salts, it is without doubt that from simple building blocks, pyrylium salts can be synthesized from a substitution pattern, for the majority of syntheses, at least one carbonyl derivative (ketone, aldehyde, or carboxylic acid) must be present and that alternative synthetically equivalent reagents may be employed due to convenience, cost, and availability.[3]

Synthesis of Pyrylium Salts

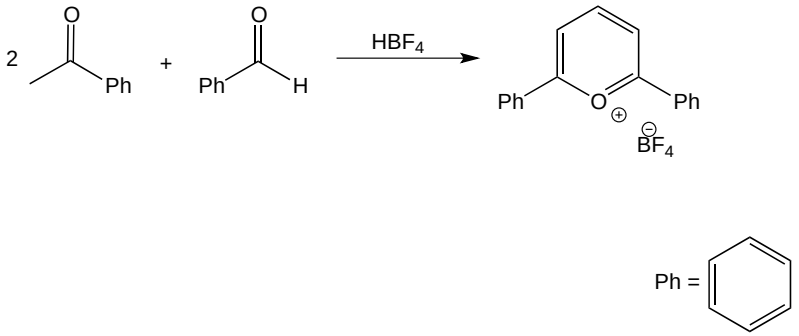
There are many different ways to synthesize a pyrylium salt. In general, there are one-component syntheses, two-component syntheses, and three-component syntheses. A

one-component synthesis includes the protonation, alkylation and acylation of 4-pyrones leading to 4-hydroxy-, 4-alkoxy-, and 4-acyloxypyrylium salts (Scheme 1.2).[3] Due to pyrylium salts' low solubility, the compound easily precipitates and crystallizes, making it an easy task to purify and analyze.



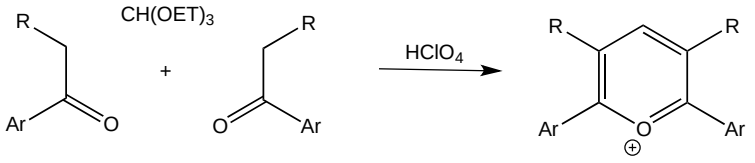
Scheme 1.2: One-component syntheses – alkylation, protonation, and acylation of pyrones[3]

A two-component synthesis is a little more difficult task, however, it works well in some cases. Scheme 1.3 shows an example of a two-component synthesis.[3]



Scheme 1.3: Two-component syntheses – acylation of unsaturated ketones[3]

Moreover, many three-component syntheses give high yields (Scheme 1.4). This route is convenient and there are many different possible pyrylium derivatives.



Scheme 1.4: Three-component syntheses – from orthoesters and methyl(ene) ketones[3]

Reactions of Pyrylium Salts

Oxonium ions are generally not stable, isolable species. Pyrylium salts owe their formation to the aromatic stability. These are stable in both acidic and neutral solutions, though they react easily with a variety of nucleophiles.[1] As indicated in Figure 1.4 below, nucleophilic attack may occur at three different positions, the 2 (α-position), the 4 (γ-positions), or the 6 (α-position).

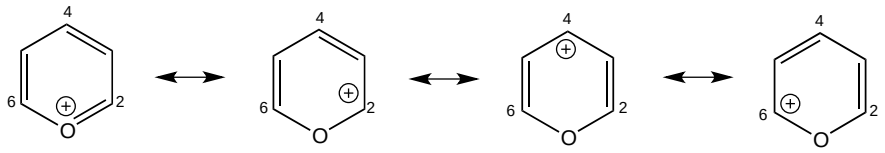


Figure 1.4: Nucleophilic attack at positions 2,4 and 6

Nucleophilic attack is preferentially at the α-position because of the large electron deficit at these positions. However, nucleophilic attack may occur at the γ-position, leading to isolable γ-pyrans. The structure of pyran is shown below in Figure 1.5.

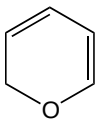
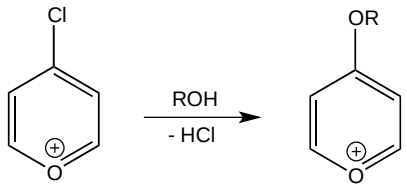


Figure 1.5: Structure of pyran

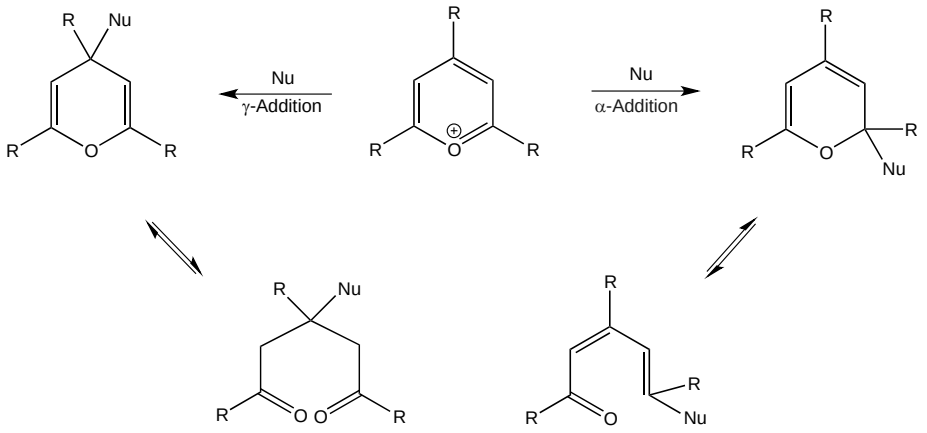
Due to the positive charge on the oxygen, electrophilic substitution reactions do not normally occur,[3] unless the pyrylium has strong electrophilic donating substituents. For example, Scheme 1.5 is an example of a reaction of chloropyrylium salt that leads to a stable ring.[3]



Scheme 1.5: Reaction that conserves the ring[3]

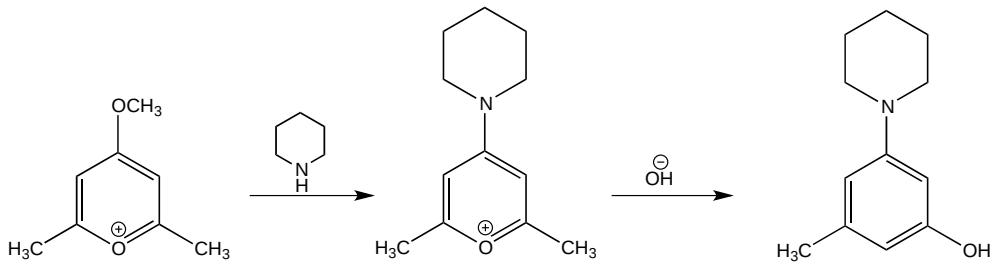
The three main reactions are (a) reactions that conserve the pyran ring, (b) reactions involving ring opening to stable end products, and (c) ring transformation reactions. Reactions that conserve the pyran ring, the six-membered heterocyclic ring consisting of five carbons and one oxygen, give a stable end product.

The ring opening reactions leading to stable end products are another reaction of pyrylium salts. A pyrylium ring is attacked by a nucleophile at either the α or γ position. The α-position is preferred in regards to pyrylium salts because the electron deficiency is more significant. Both positions, however, may undergo consecutive reactions converting them to acyclic products, which will then recyclize to another ring system. However, the present discussion will only address stable, open ring conformations (Scheme 1.6).[3]



Scheme 1.6: Reaction involving ring opening to a stable end product[3]

The third type of reaction, ring transformation reactions, involves the modification of the ring skeleton. The primary step of such reaction is the addition of a nucleophile to one of the two α-positions. In order to regain aromaticity, these reactions generally recyclize spontaneously. The aromatic end products usually have a more even charge distribution amongst the ring and a higher delocalization energy.[3] Ring transformation (Scheme 1.7) reactions lead to a wide variety of possibilities for recyclization.[3]



Scheme 1.7: Ring transformation reaction – formation of six-membered rings[3]

Properties of Pyrylium Salts

Pyrylium salts have many unique characteristics. For example, 2,4,6-triphenyl pyrylium has the ability to emit a strong green fluorescence (Figure 1.5). If the phenyl group positions are fixed with respect to the pyrylium ring by CH_2 chains, an increase in planarity of the π-system, a decrease of the Stokes shift, and an increase of the fluorescence quantum yields will be observed.[3] The Stokes shift is the difference in the positions of the maxima absorption and emission spectra.

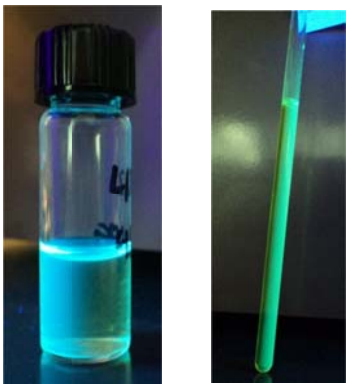


Figure 1.6: Pyrylium salt fluorescence

Another spectral property is the infared (IR) spectra, which gives information about the ground state of the molecules.[3] It is easy to distinguish a pyrylium salt based on its vibrations at around 3100 $cm^{-1}$and 1610-1640 cm^{-1} which correspond to the CH stretching and the aromatic region, respectively.

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra are also useful when analyzing pyrylium salts. For ^1H NMR, the general trend for a methyl substituted pyrylium salts is that the methyl groups appear in the same order of increasing magnetic fields, namely, they increase as such: $\alpha > \gamma > \beta$ where α corresponds to

positions 2 and 6, β corresponds to positions 3 and 5, and γ corresponds to position 4. If there are no methyl substituents present, the general trend is that the protons on the aromatic ring will appear in the order α > β > γ. The closer the proton is to the positively charged oxygen atom in the ring, the more downfield it will appear. For ^{13}C NMR, the introduction of a heteroatom into the ring deteremines the carbon NMR shifts. Since oxygen is the most electronegative heteroatom, the desheilding of the carbons is the strongest, thus, the desheilding trend is such: β < γ < α. The normal chemical shift in pyrylium salts is that the carbon atoms closest to the positively charged oxygen atom in the ring (the aromatic carbons), the more downfield they will appear. As substituent groups are added to the pyrylium salt, the carbons will appear in order of nearest proximity to the posibively charge oxygen atom.

Applications of Pyrylium Salts

There are many applications of pyrylium salts. The field that benefits from these compounds the most is in the photographic industry, specifically color photography. Pyrylium salts are used as photosensitive layers in film and paper.[3] There are a variety of uses in this industry, but paralleling its fluorescence characteristic, pyrylium salts are used as internal labeling agents for photographic films. These films are easily identified by the fluorescence of the specific pyrylium salt and their respective color when exposed to ultraviolet light.[3]

In addition, pyrylium salts are used as fluorescent dyes and dye lasers.[4] The lasers have the advantage of pyrylium salts' wavelengths, dissipation of thermal energy, and

long lasting effects. The fluorescence of pyrylium salts can be used in luminophors in tracing water courses, luminescent plants, or incorporated into various plastics.[3]

On biological level, some pyrylium salts function as plant growth stimulants, have genetic activity, pharmacological properties, sedative effects, neurotropic activity, and antitumor activity. Pyrylium salts are also used as anticorrosion agents.[1]

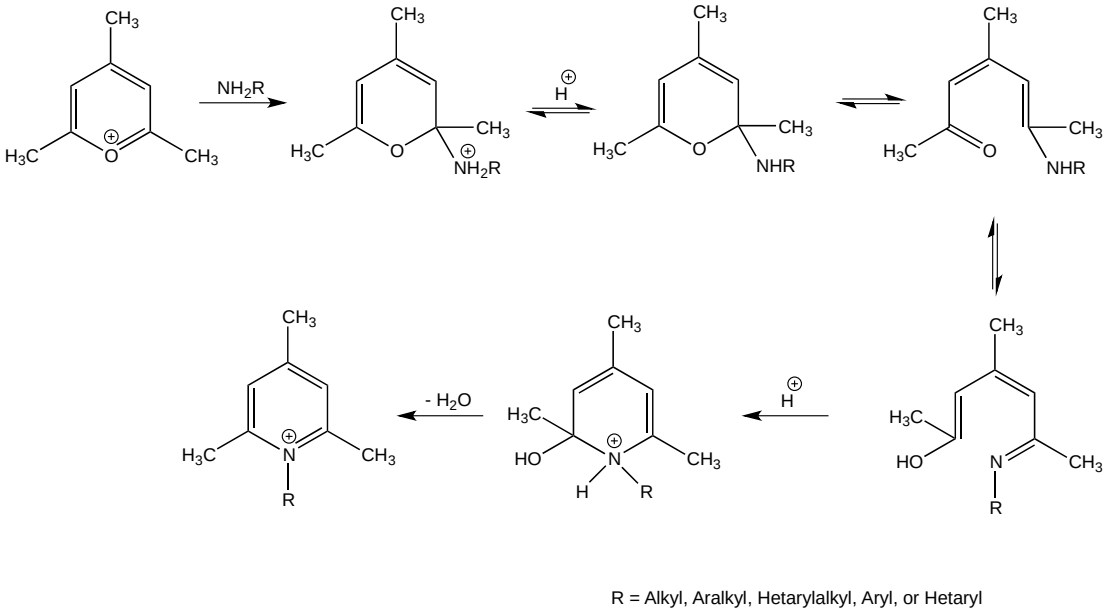
Pyridinium Salts

Pyridinium salts are heterocyclic compounds that closely resemble pyrylium salts. Although pyridinium salts are six-membered carbon ring systems, a positively charged nitrogen instead of a positively charged oxygen replaces one carbon. Pyridinium salts are useful building blocks for a variety of compounds.

Synthesis of Pyridinium Salts

The reactivity of pyridinium salts differs from pyrylium salts in that the α-positions require a strong nucleophile for the attack because oxygen is more electronegative than nitrogen. This is due to the effects of the "R" group on the nitrogen. The "R" group attached to the nitrogen in the pyridinium salt is tilted out of the plane, caused by the steric hindrance, and causes the shielding of the protons bonded to the α-carbons.

Pyridinium salts are synthesized from the ring transformation reaction of pyrylium salts with primary amines, or from pyridines. The reaction of pyrylium salts with primary amines is the simplest and most efficient way to obtain pyridinium salts (Scheme 1.8).[3]

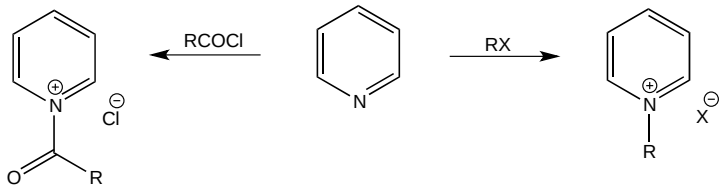


R = Alkyl, Aralkyl, Hetarylalkyl, Aryl, or Hetaryl

Scheme 1.8: Mechanism of the synthesis pyridinium salts from pyrylium salts and primary amines[3]

These reaction types are also interesting because instead of primary amines, an amino acid may be incorporated. These reactions lay the foundation for the study of the biological activity of pyrylium salts derived from the chemical modification for terminal amino grounds in proteins.[3]

Moreover, pyridinium salts may also be synthesized from pyridines (Scheme 1.9) by reaction with strong electrophiles.



Scheme 1.9: Pyridinium salts from pyridine

As the pyridine is converted into the pyridinium, the nucleophilic attack patterns change. For the pyridine, the nucleophile prefers to attack at the α-positions, however, in the pyridinium the nucleophile prefers to attack at the γ-position. Also on the conversion of a pyridine to a pyridinium, the higher electronegativity of the heteroatom and the electron withdrawing group on the heteroatom allow ring opening reactions to occur.[1]

Properties of Pyridinium Salts

The general trend for pyridinium its simliar to that of pyrylium salts. In regards to proton NMR, the protons appear in the same order of increasing magnetic fields, namely, they increase as such: $\alpha > \gamma > \beta$ where α corresponds to positions 2 and 6, and β corresponds to positions 3 and 5. However, it is important to keep in mind that sheilding may occur at the α-position, allowing the protons in the γ-position to experience a greater chemical shift. For ^{13}C NMR, it is the same case for pyridinium salts as it is for pyrylium salts. The desheilding trend is such that $\beta < \gamma < \alpha$.

Characteristics of Pyridinium Salts Studied

There are many notable characteristics of pyridinium salts and their derivatives, specifically the ones we focused on. These characteristics lead to a promising future for these compounds. Some pyridinium salts are known for being ionic liquids (Figure 3.7).[5] Ionic liquids have high thermal capacities and they have many applications, such as powerful solvents and electrically conducting fluids. This is important when considering the field of green chemistry. Many ionic liquids are safe electrolyte solutions that can be used in indoor energy devices.

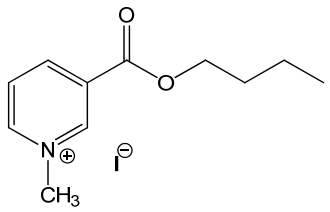


Figure 1.7: Ionic liquid[5, 6]

Pyridinium salts are also known for being cationic surface agents or intermediates in various syntheses (Figure 1.7). This means that they can lower the surface tension of the medium in which they are dissolved and can be absorbed at the interfaces.[7]

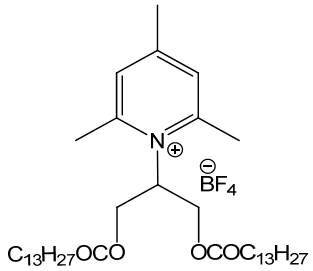


Figure 1.8: Cationic surface active agent[7]

Additionally, pyridinium derivatives are also known for acting as membrane-impermeable inhibitors and activators of carbonic anhydrase. Carbonic anhydrase is a metalloenzyme present in living systems that speed up with equilibrium between CO_2 and HCO_3^- in water.[10] These pyridinium derivatives can incorporate metals, which is a necessary part of enzyme catalysis. These pyridinium derivatives can also possess tumor cell growth inhibitory properties, and they have also been used to treat hypertension, obesity, epilepsy, and other illnesses.[11]An example of a carbonic anhydrase inhibitor is shown below in Figure 1.8:

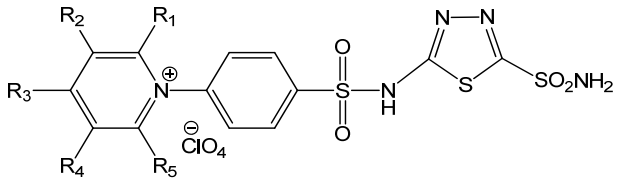


Figure 1.9: Carbonic anhydrase inhibitor[11]

Moreover, pyridinium salts are known to be interesting targets for the design of pharmacological agents, which are used to treat and prevent a variety of disorders. A pharmacological agent is a biologically active substance applied to the body for therapeutic effects on one or more tissues or organs.[12]

Applications of Pyridinium Salts

There are many interesting and beneficial applications of pyridinium salts. For example, pyridinium salts are beneficial in green chemistry. This is credited to the pyridinium salts characteristic of being an ionic liquid. One characteristic of cationic liquids its their ability to serve as gene transfer agents.[13]

In addition, pyridinium salts are the precursors for a variety of medicinal compounds. For example, pyridiniums are used to synthesize Nexium (Esomeprazole)[14] (Figure 1.9) and Aciphex (Rabeprazole)[15] (Figure 1.10), both pyridine derivatives, to treat gastroesophageal reflux disease. Gastroesophageal reflux disease is a disease that causes the acid from the stomach to flow backwards, causing heartburn and other symptoms.

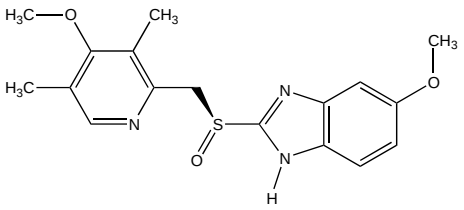


Figure 1.10: Structure of nexium[14]

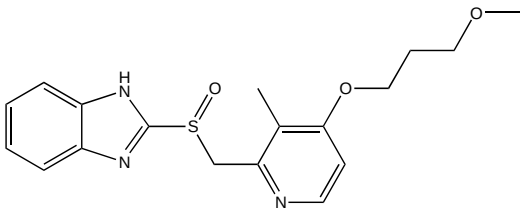


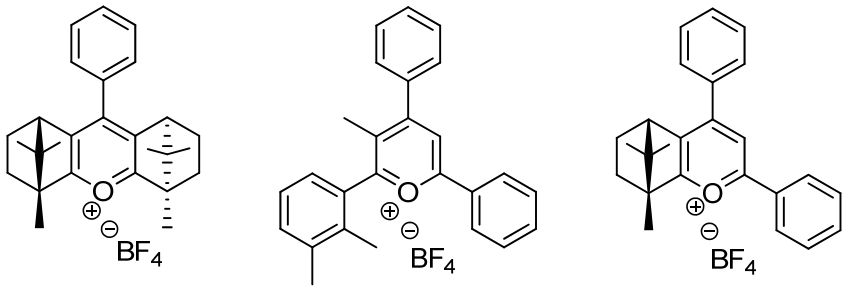
Figure 1.11: Structure of aciphex[15]

CHAPTER TWO

Pyrylium Salts

Chiral Pyrylium Salts

Our group has found particular interest in chiral pyrylium salts due to the fact that they are almost unknown in the literature. In addition, one could obtain chiral heteroaromatic compounds, for example pyridines and phosphinines. Chiral phosphinines are not well known, and they could be used for catalysis. We have found that to date, only three chiral pyryliums have been reported (Figure 2.0): the symmetrical chiral pyrylium salt that has recently been synthesized in our group (**1**),[16] a racemic atropisomer (**2**),[17] and an unsymmetrical chiral camphor derivative (**3**).[18]

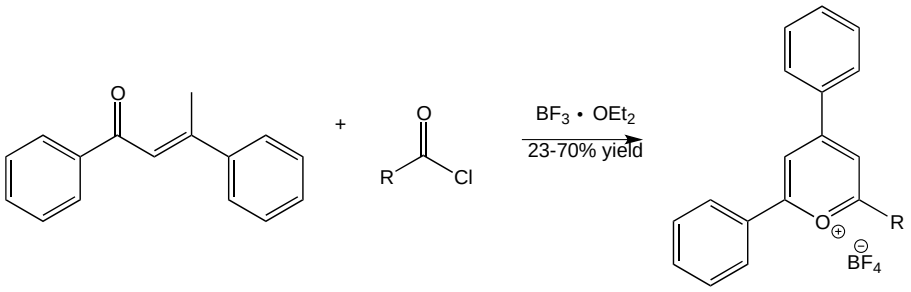


1 **2** **3**

Figure 2.0: Existing chiral pyrylium salts[19]

Synthesis of Unsymmetrical Pyrylium Salts

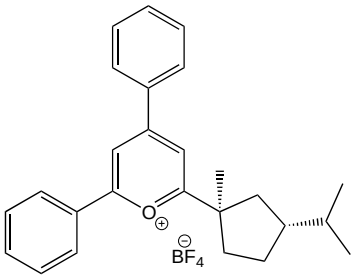
We employed the reaction developed by Katritzky to synthesize chiral pyryliums.[11]



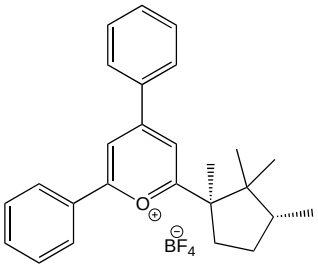
Dypnone **4a-f**

Scheme 2.0: Preparation of pyrylium salts from dypnone

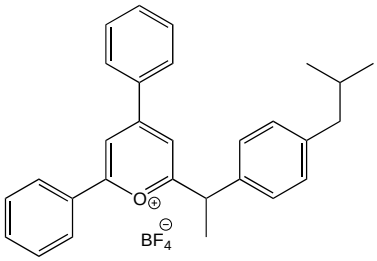
We synthesized and characterized compounds **4a-f.** Compounds **4a-d** are chiral pyrylium salts, and **4e,f** are non-chiral compounds. The yields were modest, in the range of 23-70%. The pyrylium products were isolated by simple dilution with ether because pyrylium salts are almost universally insoluble in that solvent.[20]



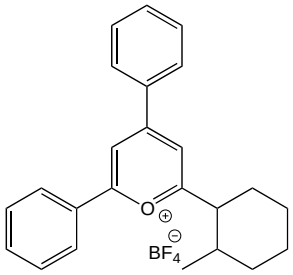
4a (23% yield)



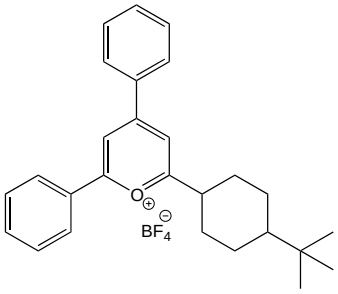
4b (25% yield)



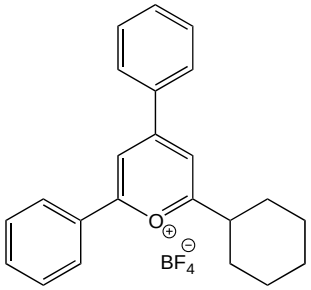
4c (23% yield)



4d (25% yield)



4e (70% yield)



4f (49% yield)

Whiteside's method was used for obtaining campholic and fencholic acid.[21] Pyrylium **4a** was then prepared from campholic acid and derived from (+)-camphor.[21] Pyrylium **4b** was also prepared by the same method from fencholic acid and derived from (-)-fenchone.[21] Both (+)-camphor and fenchone are regarded as enantionmerically pure materials.[19, 22, 23] Pyrylium **4c** was prepared from ibuprofen. Pyrylium **4d** was prepared from an 86:14 racemic mixture of cis:trans 2-methylcyclohexanecarboxylic acid. Pyrylium **4e** was prepared from 4-*tert*-butylcyclohexane carboxylic acid.

Characteristics of Pyrylium Salts 4a-f

From NMR analysis, we found that the cis isomer of pyrylium **4d** had a larger coupling constant than the trans isomer for the methyl doublet. With this information, specific stereochemistry was assigned to the compounds. Another important characteristic was that the methyl doublet for the cis isomer was always downfield of the trans isomer. Also, the cis:trans ratio (39:61 cis:trans) differs greatly from the cis:trans ratio of the carboxylic acid starting material (86:14 cis:trans).[19,24] This could be attributed to many factors such as the differential reactivity in pyrylium formation, isolation efficiency, or equilibration during acid chloride formation.[19]

Pyrylium **4e** exhibited a single diastereomer, even though the carboxylic acid was

made from is a mixture of cis:trans isomers.

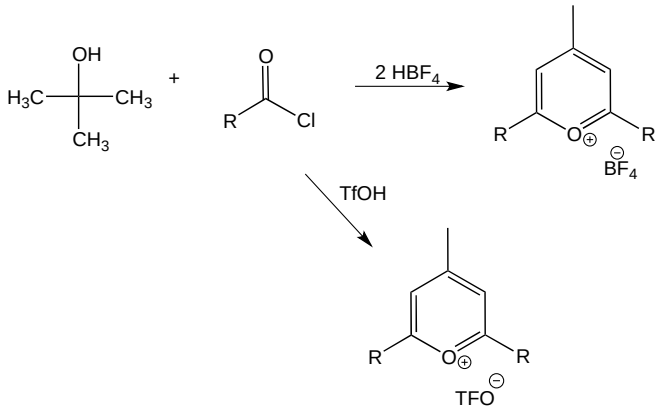
As stated before, many pyrylium salts are known for their fluorescence. Below in Figure 2.1 are some examples of the fluorescence of the compounds synthesized. Moreover, the reactions form yellow end products, as shown in Figure 2.2

Figure 2.1: Fluorescence of pyrylium salts **4a-f**

Figure 2.2: Color of pyrylium salts **4a-f**

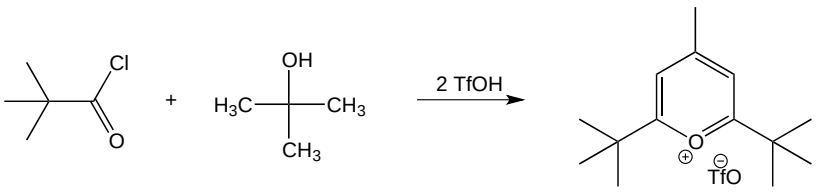
Synthesis of Symmetrical Pyrylium Salts

We employed the reaction of tert-butanol and acyl chloride to synthesize the symmetrical pyrylium salts shown below in Scheme 2.1.[25]



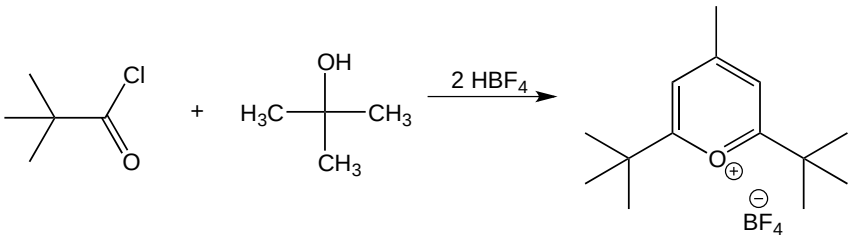
Scheme 2.1: Basic reaction to synthesize symmetrical pyrylium salts[25]

To optimize the conditions, we first reacted pivaloyl chloride with tert-butanol and trifluoromethanesulfonic acid to obtain **5a** in a 41% yield (Scheme 2.2). We then treated pivaloyl chloride (Scheme 2.3), 2-methylcyclohexanecarbonyl chloride (Scheme 2.4) and 4-(*tert*-butyl)cyclohexanecarbonyl chloride (Scheme 2.5) with tert-butanol and hyrdofluoroboric acid, as shown below.[26] The percent yields were between 37-42%, which is typical of pyrylium salts.



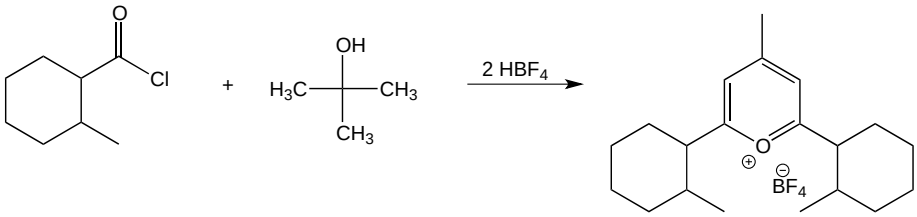
5a (41% yield)

Scheme 2.2: Derivative from pivaloyl chloride (5a)



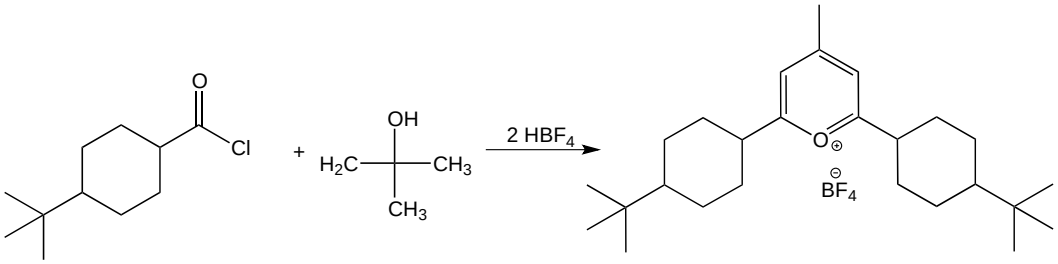
5b (56% yield)

Scheme 2.3: Derivative from pivaloyl chloride (5b)



5c (37% yield)

Scheme 2.4: Derivative from 2-methylcyclohexanecarbonyl chloride



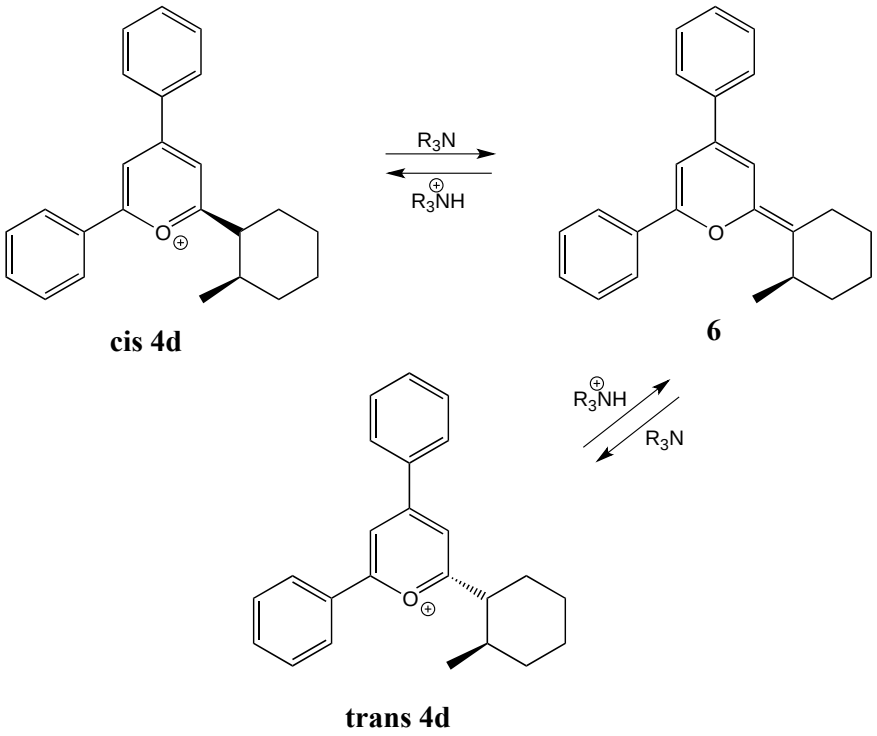
5d (43% yield)

Scheme 2.5: Derivative from 4-(*tert*-butyl)cyclohexanecarbonyl chloride

Epimerization of Unsymmetrical and Symmetrical Pyrylium Salts

Epimerization is a process where one diastereomer is transformed into another. Due to the fact that there are only three examples of chiral pyrylium salts known in literature, it has not been shown that pyrylium salts undergo epimerization. However, there is an indication that epimerizability would be possible from deuterium exchange experiements.[19, 27, 28] Most importantly, it has been observed that **4d** can be epimerized by

catalytic amounts of *N*-methylmorphline, which yields a 9:91 cis:trans ratio.[19] This reaction proceeds through an intermediate **(6),**[29] which can be isolated when any of the pyrylium salts **4c** or **4d-f** are treated with stoichiometric triethylamine. This is shown below in Scheme 2.5[19]



Scheme 2.6: Mechanism of amine-catalyzed epimerization[19]

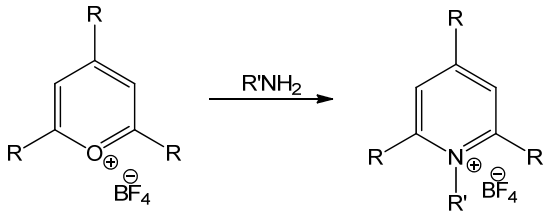
In regards to pyryliums **5b** and **5c**, these pyrylium salts form diastereomers when prepared and are thus are useful when studying epimerization at the α centers. As previously stated with unsymmetrical pyrylium salts, mild amine bases affect efficient epimerization.

CHAPTER THREE

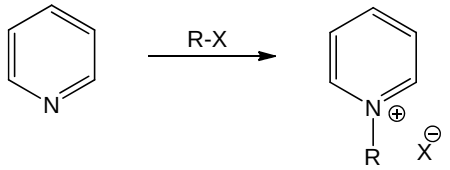
Pyridinium Salts

Synthesis of Pyridinium Salts

Positively charged pyridinium salts provide a route for the possible improvement on the bioavailability of hydrophobic compounds and also little-used pharmaceuticals motif. We are optimizing reaction conditions for reacting substituted pyrylium salts with primary amines to obtain pyridinium salts (Scheme 3.1). This is a more versatile approach compared to simple alkylation (Scheme 3.2). Simple alkylation is limited to primary alkyl halides. The reaction of pyrylium salts with primary amines is versatile because many different amines can attach to the ring.



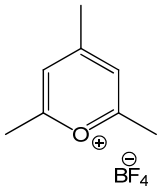
Scheme 3.1: Synthesis of pyridinium salt from pyrylium salt and primary amine



Scheme 3.2: Alkylation of the pyridine

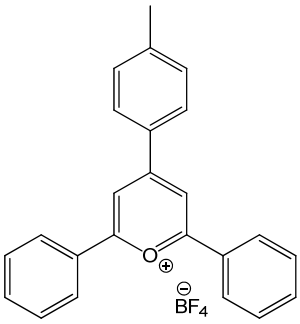
The ease of the reaction depends on the basicity of the primary amine and the

steric nature of the pyrylium ring. In this experiment, the pyrylium salts we used. (Figure 3.1 and Figure 3.2)[25, 30] were previously prepared in our lab.



7

Figure 3.1: 2,4,6-trimethylpyrylium tetrafluoroborate[30]

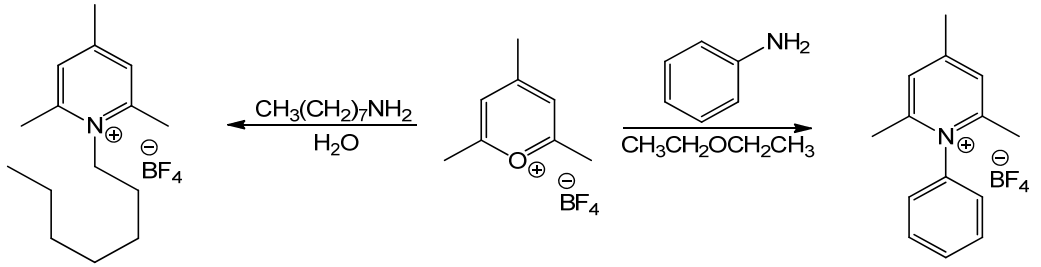


8

Figure 3.2: 2,6-diphenyl-4-*p*-toluylpyrylium tetrafluoroborate[25]

Model Reactions

To begin the study, we optimized reaction conditions for making substituted pyrylium salts with primary amines to obtain pyridinium salts (Scheme 3.3)[10, 31]



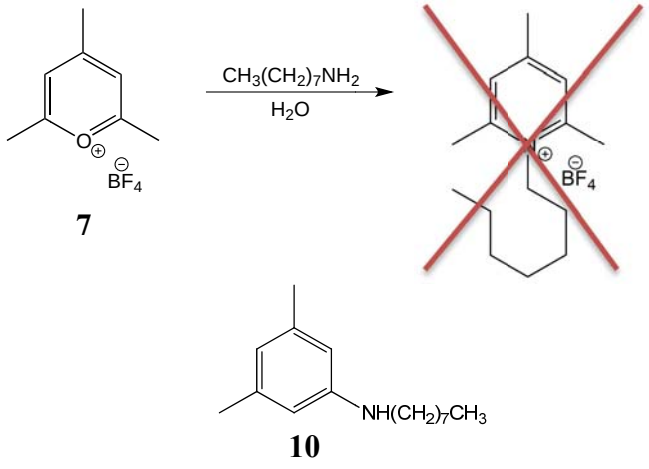
9b (7%yield) **7** **9a (96% yield)**

Scheme 3.3: Pyridinium salt model reactions[10, 31]

Amine was added over a suspension of pyrylium **7** in methanol. The solution turned red, and an even deeper red as more amine was added. The reaction mixture was refluxed for four and a half hours and monitored with TLC in 20:80 ethyl acetate:hexane solution. Aqueous ammonium hydroxide was added to the reaction mixture to convert any unreacted pyrylium salt into the corresponding pyridine. Compound **9a** was crystallized from methanol. Unfortunately, the starting material was still present.

Moreover, we performed the experiment a second time. This time, we decreased the amount of the aniline by half and used 2,4,6-trimethylpyrylium perchlorate instead of pyrylium **7**. 2,4,6-trimethylpyrylium perchlorate was refluxed with aniline in ether for one hour. The resulting oil crystallized when put in the freezer overnight. To recrystallize, the reaction mixture was dissolved in ethyl acetate. As the product precipitated with ether it turned an orange-yellow color. The reaction was successful with a 96% yield.

In the course of the investigation with octylamine ($C_8H_{19}N$), we did not get the product the first time, as shown in the side reaction in Scheme 3.4.[31]

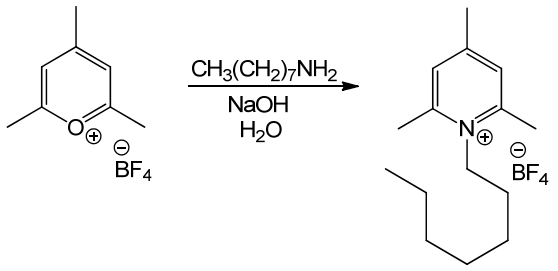


7 **10**

Scheme 3.4: Side reaction of pyrylium salt with octylamine[31]

First, octylamine was added to pyrylium **7**. It was refluxed in water for two hours. After cooling, diethyl ether was added and the reaction mixture was put in the freezer. The reaction mixture was extracted with ether for higher amines. The ether extract was evaporated. The amines were prepared in and recrystallized form aqueous ethanol. We checked NMR and did not get the desired product. The reason we did not get the desired pyridinium **9b** was because NaOH was not added to the reaction like the procedure had suggested.

However, upon repeating the experiment, NaOH was added. Pyrylium **7** and octylamine were refluxed for four hours in water. After cooling, the solution with the oily reaction products was made alkaline with NaOH and extracted with ether for the higher amines. NaOH was added until the pH of the reaction mixture was 14. The pyridinium was prepared in and recrystallized from aqueous ethanol. With the addition of the NaOH, pyridinium **9b** (Scheme 3.5) was produced in a 7% yield. This low yield could have been from not adding enough base, or not refluxing long enough.

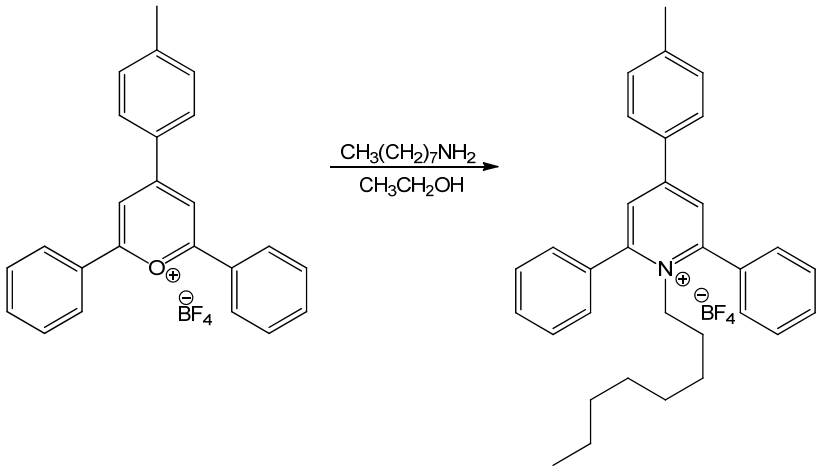


7 **9b (7% yield)**

Scheme 3.5: Reaction of trimethylpyrylium salt with octylamine

Another model reaction performed was the reaction of pyrylium **8** with octylamine (Scheme 3.6)[10, 31] 1 equivalent of pyrylium **8** and 2 equivalents amine were

stirred and refluxed for two hours. Precipitation occurred by pouring the reaction in cold acetone and diethyl ether. The pyridinium **9c** was obtained in an 85% yield.



8 **9c (85% yield)**

Scheme 3.6: Reaction of triphenylpyrylium salt with octylamine[10, 31]

Amines Chosen for Study

The first amine chosen for this study was thiosemicarbazide as shown in Figure 3.3 below. These types of compounds are interesting because some thiosemicarbazone derivatives (Figure 3.4 below) are Cathepsin L inhibitors. Cathepsin L is an enzyme involved in antigen processing, bone resorption, and tumor invasion and metastasis.[32] By catalyzing the degradation of the interstitial matrix and basement membranes, Cathepsin L can promote tumor cell invasion and metastasis.[32] This allows the cancer cells to metastasize at distant sites by local invasion.[32] The product in red represents the similarity to thiosemicarbazide.

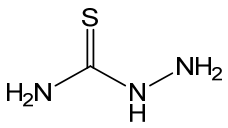


Figure 3.3: Thiosemicarbazide

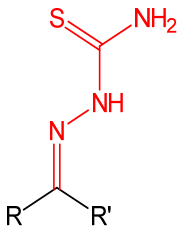
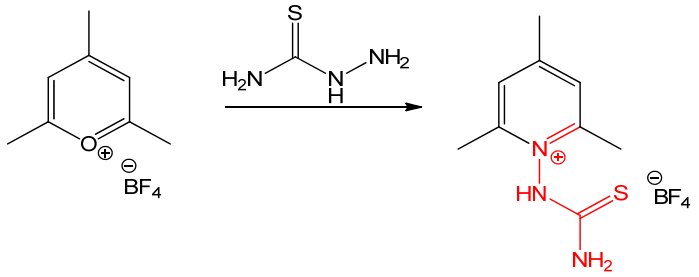


Figure 3.4: Thiosemicarbazone

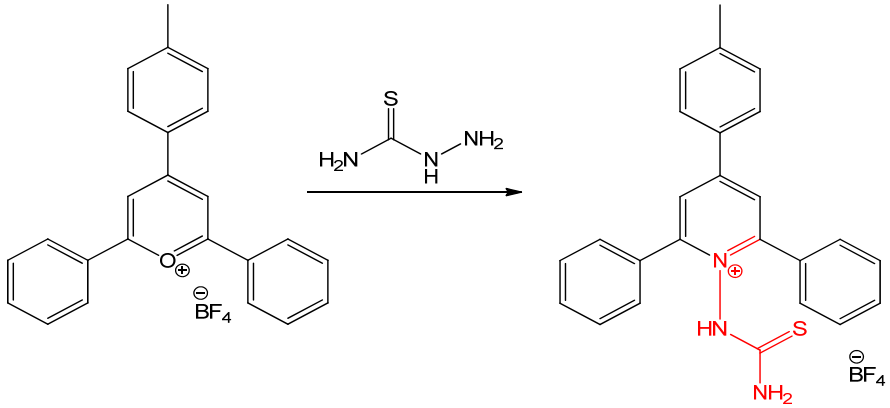
Specifically, we are interested in the effects of the positively charged environment provided by the pyridinium salt. It is important to remember that the positive charge on the nitrogen atom is distributed along the ortho and para positions due to resonance. These pyridinium derivatives are known in the literature; however, they have never been tested as Cathepsin L inhibitors, and this was the basis of this study. We synthesized the pyridinium salt from the reaction of pyrylium **7** with thiosemicarbazide in ethanol (Scheme 3.7).[33] The reaction mixture was refluxed for one hour at 78 ^{o}C and then cooled to room temperature, put in the freezer, and the precipitate was removed by filtration. The percent yield for pyridinium **11a** is 77%.



7 **11a (77% yield)**

Scheme 3.7: Synthesis of thiosemicarbazide from trimethylpyrylium salt and semicarbazide[33]

We also synthesized the pyridinium salt from the reaction of pyrylium **8** with thiosemicarbazide (Scheme 3.8)[33] The triphenyl pyrylium salt wad added to the thiosemicarbazide in ethanol and the reaction mixture was refluxed for one hour at 78 ^{o}C. It was then cooled to room temperature and put in the freezer. When the reaction mixture was in the freezer it was a solid, but melted to a gum-like material on warming. The gum-like solid was filtered off with ethanol, and this was placed in a separate round bottom flask with ether to precipitate. Sonication was used to break up the gum-like material. The percent yield for pyridinium **11b** is 37%.



8 **11b (37% yield)**

Scheme 3.8: Synthesis of thiosemicarbazide from triphenylpyrylium salt and semicarbazide[33]

The other amine chosen for study was 5-aminohexanoic hydroxamate, as shown below in Figure 3.5.

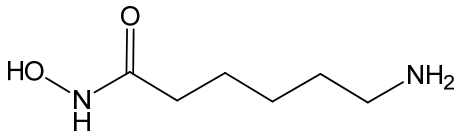


Figure 3.5: 5-aminohexanoic hydroxamate

Hydroxamates in general are known metal chelators that are widely used in metalloenzyme interactions. They are also known to be histone deacetylase inhibitors with anti-cancer properties. The hydroxamate above is known to induce the differentiation of mouse neuroblastoma cells.[34] Neuroblastoma is a childhood tumor that demonstrates the spontaneous regression from an undifferentiated stated to a completely benign appearance.[34] Undifferentiated or poorly differentiated cells grow and spread very fast, unlike the differentiated cells, which grow and spread at a slow rate and resemble normal cells. The importance of the hydroxamates is that they cause cell arrest and potentially apoptosis, or cell death.[34]

Another interesting characteristic about hydroxamates is that they are analogs of the drug Vorinostat, commonly known as the SAHA (suberoylanilide hydroxamic) drug, shown in Figure 3.6 below. This drug is also a histone deacetylase inhibitor that is used for chemotherapeutic drug treatment. It works by stopping or killing the growth of cancer cells.[35]

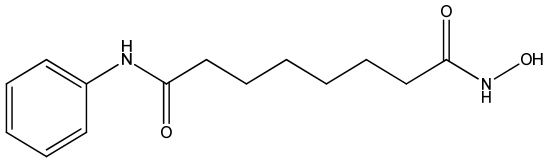
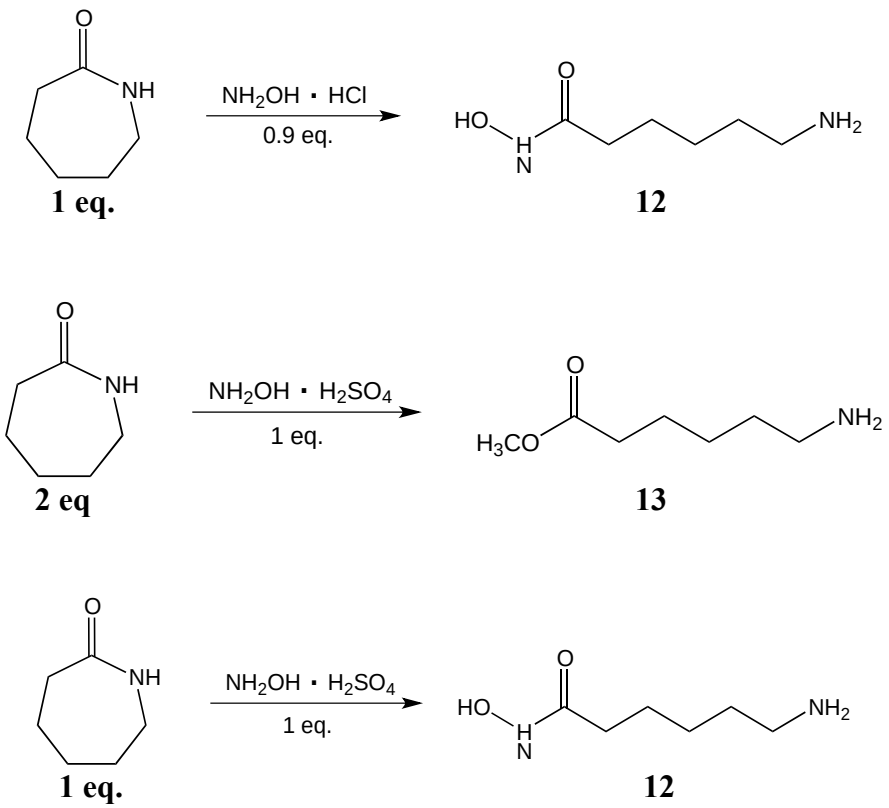


Figure 3.6: SAHA Drug (suberoylanilide hydroxamic)[35]

The synthesis of 5-aminohexanoic hydroxamate was not an easy task. We attempted three times, with different solvents and equivalents, as shown below in Scheme 3.9.[34]



Scheme 3.9: Synthesis of 5-aminohexanoic hydroxamate[34]

In the first reaction, 1 equivalent caprolactam was reacted with 0.9 equivalent hydroxylamine hydrochloride, but was incomplete. Hydroxylamine hydrochloride was added to molten caprolactam. The mixture was heated at the 85 ^{o}C overnight. After cooling to room temperature, a white, thick solid formed. The reaction mixture was rinsed and sonicated with $CHCl_3$, and infused with diethyl ether overnight. An oil was produced. The reaction was incomplete because it was hard to purify due to its polarity.

The second reaction, 2 equivalents caprolactam with 1 equivalent hydroxylamine sulfate, was also incomplete. This reaction followed the same procedure as in reaction one, the only difference being the equivalence values and hydroxylamine sulfate instead of hydroxylamine hydrochloride. Instead of the hydroxamate, a methyl ester was obtained. We obtained a methyl ester because after the reaction, we added methanol. The proton from the salt $NH_2OH \bullet H_2SO_4$ catalyzed the reaction and gave the methyl ester in product **13.**

In the third reaction, 1 equivalent caprolactam reacted with 1 equivalent hydroxylamine sulfate. The hydroxylamine sulfate was added to the molten caprolactam. The mixture was heated at the 85 ^{o}C overnight. This was a complete reaction, producing the desired product **14.**

*Biological Activity Evaluation of Pyridiniums **3d** and **3e***

Pyridiniums **3d** and **3e** were tested for their biological activity by the Trawick group from the department of Chemistry and Biochemistry at Baylor University.[37] The Trawick group tested cytotoxicity for human prostate cancer cells (DU-145) and the inhibition of cruzain (a Cathepsin L like, cysteine protease).

For the cytotoxic experiments, doxorubicin was used as the positive control. Pyridinium **11a** and **11b** had an IC_{50} value of greater than 177 μM and 24.4 ± 4.0 μM, respectively, for DU-145 cells, indicating that it was not cytotoxic for these cells (Table 3.1).

Table 3.1: Cytotoxicity results for DU-145 cells for pyridiniums **3d** and **3e**

Doxorubicin		**3d**		**3e**	
μg/mL	μM	μg/mL	μM	μg/mL	μM
0.0295	0.0544	> 50	> 177	11.1	23.0
0.0276	0.0508	> 50	> 177	14.4	29.8
0.0289	0.0531	> 50	> 177	9.80	20.3
$\bar{x}$ = 0.0287	**$\bar{x}$ = 0.0528**	**$\bar{x}$ > 50**	**$\bar{x}$ > 177**	**$\bar{x}$ = 11.77**	**$\bar{x}$ = 24.4**
St. Dev. = 0.00089	**St. Dev. = 0.0015**	**-**	**-**	**St. Dev. = 1.94**	**St. Dev. = 4**

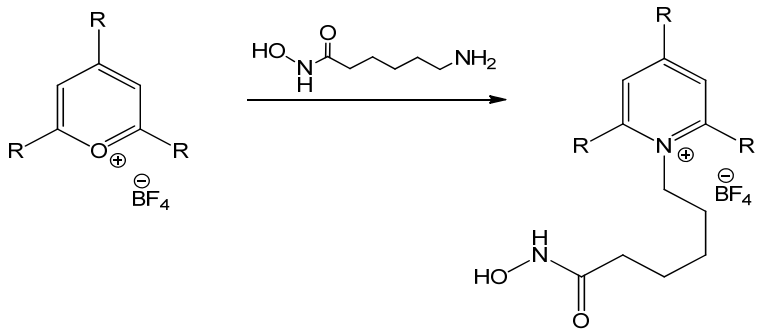
Moreover, pyridinium **11a** and **11b** inhibited the activity of cruzain by 15.6% and 5.2%, respectively, at a concentration of 10 μM (Table 3.2). Inhibition of greater than 50% at this concentration is required to determine the IC_{50} value.

Table 3.2: Inhibition of cruzain results for pyridiniums **11a** and **11b**

	11a	**11b**
Mean	15.58%	5.18%
Std. Deviation	3.91	2.06
Std. Error	2.25	1.19

Future Work

Future work will be directed towards obtaining pyridinium salts from primary amines with known biological activity. Moreover, work will be done in trying to obtain the pyridinium salt from the reaction between a pyrylium salt and the 5-aminohexanoic hydroxamate (Scheme 3.10).[35]



Scheme 3.10: Pyridinium from pyrylium salt and 5-aminohexanoic hydroxamate[35]

This reaction was attempted once in our lab. The appropriate amounts of pyrylium salt and amine were refluxed overnight. The reactants were not dissolving completely, so a few mL of methanol were added, and the reaction was heated at 40°C. Unfortunately, the reaction was incomplete. We will continue to investigate this reaction between pyrylium salts and the hydroxamate due to its potential biological activity.

In addition, the equilibration/epimerization of symmetric pyrylium salts is being investigated further.

CHAPTER FOUR

Experimental

Pyrylium Salts

Reagents and solvents were generally purchased from Aldrich Chemical Company or from Alfa Aesar, and were used as received unless otherwise noted. Dypnone was purchased from Frinton Laboratories. Fenchoic and campholic acid were previously synthesized following Whiteside's procedure.[21] 2,4,6-trimethyl-pyrylium tetrafluoroborate (**7**) and 2,6-diphenyl-4-tolouyl-pyrylium tetrafluoroborate (**8**) were previously synthesized following Balaban's procedures.[1,13] 2-methylcyclohexane carboxylic acid (Aldrich) was an 86:14 mixture of cis and trans isomers, respectively. This is based on NMR analysis and literature precedent.[24] Hexanes, ethyl acetate, and methylene chloride were distilled prior to use. TLC was used to identify the compounds according to its R_f value, which was compared to the R_f of a known compound. Mass spectrometry was used to measure the mass-to-charge-ratio of charged particles, determine the masses of particles, and determine the composition of a molecule. NMR spectra were obtained using a Varian 500 MHz NMR operating at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR. Spectra obtained in $CDCl_3$ were referenced to TMS (0 ppm) for ^{1}H and $CDCl_3$ (77.16 ppm) for ^{13}C. Spectra in acetone-d_6 were referenced to 2.05 ppm for ^{1}H and to 206.26 ppm for ^{13}C and CD_3CN solutions were referenced to 1.94 ppm for ^{1}H and to 118.26 ppm for ^{1}H.

General Procedure for the Preparation of the Acyl Chlorides

1 equivalent of the carboxylic acid and 1.5 equivalent of oxalyl chloride were treated with a catalytic amount (3 μL) of DMF and stirred for 1 hour under nitrogen. Excess oxalyl chloride was then removed by rotary evaporation and the product formation was confirmed by GC-MS. The compound was used without further purification.

General Procedure for the Preparation of the Unsymmetrical Pyrylium Salts 4a-f[11, 19]

1 equivalent of dypnone, 2 equivalents of acyl chloride and 2.1 equivalents of boron trifluoride diethyl etherate (47% BF_3, 8.0 M) were heated at 100 ^oC for 2 hours. The solution turned deep green. After cooling to room temperature, the reaction mixture was poured into diethyl ether and the pyrylium salt precipitated from the reaction mixture. Recrystallization from methanol gave yellow needles.

(4a). 2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.35 mL (1.6 mmol) of dypnone, 0.60 g (3.2 mmol) of (1R,3R)-1-methyl-3-isopropylcyclopentanoyl chloride and 0.46 mL (3.7 mmol) of boron trifluoride diethyl etherate, 0.163 g were obtained (23% yield). Mp 145-147 ^oC; $[\alpha]_D^{20}$ -20.9 (c = 1, CH_3CN); ^1H NMR (500 MHz, acetone-d6): δ 9.05 (s, 1H, ArH), 8.57 (s, 1H, ArH), 8.52 (d, *J* = 7.7 Hz, 2H, ArH), 8.46 (d, *J* = 7.7 Hz, 2H, ArH), 7.90-7.83 (m, 2H, ArH), 7.78 (t, *J* = 7.7 Hz, 2H, ArH), 7.76 (t, *J* = 7.7 Hz, 2H, ArH), 2.67-2.56 (m, 1H), 2.35 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.21-2.08 (m, 4H), 1.75 (s, 3H), 1.73-1.66 (m, 1H), 1.56 (dd, *J* = 13.7, 6.8 Hz, 1H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, acetone-d_6): δ 187.2 (C), 172.8 (C), 167.8 (C), 136.1 (CH), 135.9 (C), 134.0 (C), 130.9

(CH), 130.8 (two coincident CH), 130.3 (CH), 129.5 (CH), 116.8 (CH), 116.2 (CH), 50.7 (C), 47.1 (CH), 45.0 (CH), 38.8 (CH_2), 34.4 (CH_2), 30.4 (CH_2), 26.9 (CH_3), 21.8 (CH_3), 21.7 (CH_3). HRMS (ESI): calculated for $C_{26}H_{29}O$ [M+] 357.2213, found 357.2214.

(4b). 2-(1R,3R-1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.35 mL (1.6 mmol) of dypnone, 0.60 g (3.2 mmol) of (1R,3R)-1,2,2,3-tetramethylcyclopentanoyl chloride and 0.46 mL (3.7 mmol) of boron trifluoride diethyl etherate, 0.177 g were obtained (25% yield). Mp 187-189 ^{o}C; $[\alpha]_D^{20}$ +80 (c = 1, CH_3CN); ^{1}H NMR (500 MHz, acetone-d_6): δ 9.17 (s, 1H, ArH), 8.59 (d, *J* = 0.8 Hz, 1H, ArH), 8.56-8.52 (m, 2H, ArH), 8.49-8.46 (m, 2H, ArH), 7.92-7.83 (m, 2H, ArH), 7.81 (t, *J* = 7.8 Hz, 2H, ArH), 7.76 (t, *J* = 7.9 Hz, 2H, ArH), 3.08 (td, *J* = 12.5, 6.3 Hz, 1H), 2.37-2.26 (m, 1H), 2.25-2.14 (m, 1H), 1.98 (ddd, *J* = 9.6, 7.8, 4.2 Hz, 1H), 1.74 (s, 3H), 1.63 (dddd, *J* = 13.4, 11.8, 9.5, 4.2 Hz, 1H), 1.25 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.75 (s, 3H). ^{13}C NMR (126 MHz, acetone-d_6): δ 185.0 (C), 173.1 (C), 167.4 (C), 136.2 (CH), 136.0 (C), 133.9 (C), 131.0 (CH), 130.9 (two coincident CH), 130.3 (CH), 129.6 (CH), 118.3 (CH), 116.6 (CH), 57.0 (C), 49.8 (C), 42.8(CH), 33.9 (CH_2), 29.5 (CH_2), 22.9 (CH_3), 22.1 (CH_3), 19.8 (CH_3), 14.9 (CH_3). HRMS (ESI): calculated for $C_{26}H_{29}O$ [M+] 357.2213, found 357.2215.

(4c). 2-(1-(4-isobutylphenyl)-ethyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.28 mL (1.3 mmol) of dypnone, 0.58 g (2.6 mmol) of ibuprofen acid chloride and 0.35 mL (2.8 mmol) of boron trifluoride diethyl etherate, 0.144 g were obtained (23% yield). Mp 174-176 ^{o}C; ^{1}H NMR (500 MHz, acetone-d_6): δ 9.11 (s, 1H, ArH), 8.67 (s,

1H, ArH), 8.43 (d, *J* = 8.1 Hz, 4H, ArH), 7.85 (t, *J* = 7.4 Hz, 2H, ArH), 7.74 (t, *J* = 7.6 Hz, 4H, ArH), 7.58 (d, *J* = 8.1 Hz, 2H, ArH), 7.26 (d, *J* = 8.0 Hz, 2H, ArH), 5.03 (q, *J* = 7.2 Hz, 1H), 2.5 (d, 2H), 2.07-2.03 (m, 3H), 1.87 (tt, *J* = 13.5, 6.8 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, acetone-d_6): δ 182.3 (C), 173.2 (C), 168.1 (C), 142.5 (C), 138.2 (C), 136.3 (C), 136.3 (CH), 133.8 (CH), 131.1 (CH), 131.0 (CH), 130.9 (CH), 130.9 (CH), 130.16 (C), 129.7 (CH), 129.0 (CH), 118.3 (CH), 116.5 (CH), 45.8 (CH), 45.6 (CH_2), 31.0 (CH), 22.7 (CH_3), 19.1 (CH_3). HRMS (ESI): calculated for $C_{27}H_{29}O$ [M+] 393.2213, found 393.2213.

(4d). 2-(2-methyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.35 mL (1.6 mmol) of dypnone, 0.51 g (3.2 mmol) of 2-methyl-cyclohexanoyl chloride and 0.46 mL (3.7 mmol) of boron trifluoride diethyl etherate, 0.166 g were obtained (25% yield). Mp 155-156 ^{o}C; ^{1}H NMR (500 MHz, CD_3CN): δ 8.68 (d, *J* = 1.8 Hz, 1H, ArH), 8.35-8.31 (m, 2H, ArH), 8.22 (m, 2H, ArH), 8.18 (d, *J* = 1.8 Hz, 1H, ArH), 7.87-7.81 (m, 2H, ArH), 7.77-7.72 (m, 4H, ArH), 2.93 (ddd, *J* = 12.1, 11.0, 3.4 Hz, 1H), 2.15 (dd, *J* = 3.2, 1.5 Hz, 1H), 2.11-2.01 (m, 1H), 1.89-1.79 (m, 3H), 1.58-1.40 (m, 3H), 1.24 (qd, *J* = 13.1, 3.6 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $_{CD3CN}$): δ 183.7 (C), 173.2 (C), 167.5 (C), 136.4 (CH), 136.3 (CH), 133.6 (C), 131.1 (CH), 131.0 (CH), 130.6 (CH), 130.0 (C), 129.4 (CH), 119.0 (CH), 116.7 (CH), 52.5 (CH), 37.0 (CH), 35.5 (CH_2), 32.9 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 20.8 (CH_3). HRMS (ESI): calculated for C24H25O [M+] 329.1900, found 329.1907.

(4e). 2-(4-t-butyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.35 mL (1.6 mmol) of dypnone, 0.65 g (3.2 mmol) of 4-t-butyl-cyclohexanoyl chloride and 0.46 mL (3.7 mmol) of boron trifluoride diethyl etherate, 0.511 g were obtained (70% yield). Mp 180-182 ^{o}C; ^{1}H NMR (500 MHz, acetone-d_6): δ 9.10 (d, *J* = 1.5 Hz, 1H, ArH), 8.58 (d, *J* = 1.5 Hz, 1H, ArH), 8.57-8.53 (m, 2H, ArH), 8.45 (dd, *J* = 8.4, 1.0 Hz, 2H, ArH), 7.86 (q, *J* = 7.7 Hz, 2H, ArH), 7.79 (t, *J* = 17.9 Hz, 2H, ArH), 7.73 (t, *J* = 17.9 Hz, 2H, ArH), 3.45 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.46 (dd, *J* = 14.5, 2.0 Hz, 2H), 2.08 (d, *J* = 2.6 Hz, 1H), 2.01-1.89 (m, 2H), 1.44-1.21 (m, 4H), 0.93 (s, 9H). ^{13}C NMR (126 MHz, acetone-d_6) δ 184.4 (C), 173.0 (1), 167.7 (C), 136.1 (CH), 133.8 (C), 131.0 (CH), 130.9 (CH), 130.8 (CH), 130.3 (C), 129.6 (CH), 118.0 (CH), 116.3 (CH), 48.0 (CH), 45.0 (CH), 33.1 (C), 32.0 (CH_2), 27.9 (CH_3), 27.6 (CH_2). HRMS (ESI): calculated for $C_{27}H_{31}O$ [M+] 371.2369, found 371.2370.

(4f). 2-(cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

From 0.35 mL (1.6 mmol) of dypnone, 0.47 g (3.2 mmol) of cyclohexanoyl chloride and 0.46 mL (3.7 mmol) of boron trifluoride diethyl etherate, 0.309 g were obtained (48% yield). Mp 145-146 ^{o}C; ^{1}H NMR (500 MHz, acetone-d_6): δ 9.10 (d, *J* = 1.4 Hz, 1H, ArH), 8.58 (d, *J* = 1.5 Hz, 1H, ArH), 8.54 (d, *J* = 7.6 Hz, 2H, ArH), 8.45 (d, *J* = 7.5 Hz, 2H, ArH), 7.88 (d, *J* = 7.6 Hz, 1H, ArH), 7.84 (d, *J* = 7.6 Hz, 1H, ArH), 7.76 (dt, *J* = 15.5, 7.8 Hz, 4H, ArH), 3.51 (td, *J* = 11.8, 3.2 Hz, 1H), 2.37 (d, *J* = 11.9 Hz, 2H), 2.02-1.87 (m, 4H), 1.82 (d, *J* = 13.0 Hz, 1H), 1.65-1.50 (m, 2H), 1.50-1.36 (m, 1H). ^{13}C NMR (126 MHz, acetone-d_6): δ 184.2 (C), 173.0 (C), 167.7 (C), 136.1 (two coincident CH), 133.8 (C), 131.0 (CH), 130.9 (CH), 130.8 (CH), 130.3 (C), 129.6 (CH), 118.0 (CH), 116.3

(CH), 44.9 (CH), 31.5 (CH_2), 26.5 (CH_2), 26.2 (CH_2). HRMS (ESI): calculated for $C_{23}H_{23}O$ [M+] 315.1743, found 315.1744.

General Procedure for the Preparation of the Symmetrical Pyrylium Salts 5b-d[19, 26]

1 equivalent of *tert*-butanol, 4 equivalents of acyl chloride and 3 equivalents of tetrafluoroboric acid diethyl etherate (51-57% HBF_4 in diethyl ether, 7.3 M) were heated at 85 ^oC for 2 hours. After cooling to room temperature the reaction mixture was poured into diethyl ether and the pyrylium salt precipitated from the reaction mixture. Recrystallization from methanol gave white needles

(5b). 2,6-di-tert-butyl-4-methylpyrylium tetrafluoroborate

0.18 mL (2.07 mmol) of *tert*-butanol, 1.0 mL (8.29 mmol) of pivaloyl chloride and 0.6 mL (4.15 mmol) of tetrafluoroboric acid diethyl etherate (51-57% HBF_4 in diethyl ether, 7.3 M), 0.3061 g were obtained (56% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 2H), 2.84 (s, 3H), 1.53 (d, J = 11.4 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.70, 176.99, 120.49, 28.18, 24.58.

(5c). 2,6-bis(2-methyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

0.17 mL (1.9 mmol) of *tert*-butanol, 1.27 g (8 mmol) of 2-methyl-cyclohexanoyl chloride and 0.8 mL (5.8 mmol) of tetrafluoroboric acid diethyl etherate (51-57% HBF_4 in diethyl ether, 7.3 M). 0.272 g were obtained (37% yield). Mp 127-129 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, minor stereoisomer 7% of total), 7.79 (s, second stereoisomer 24% of total), 7.77 (s, major stereoisomer 26% of total), 7.74 (s, major stereoisomer), 7.73 (s,

second stereoisomer), 7.70 (s, fifth stereoisomer 21% of total), 7.68 (s, fourth stereoisomer 22% of total). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5 (*ortho*-pyrylium), 183.3 (*ortho*-pyrylium), 183.3 (*ortho*-pyrylium), 183.2 (*ortho*-pyrylium), 175.3 (*para*-pyrylium), 174.7 (*para*-pyrylium), 123.0 (*meta*-pyrylium), 122.9 (*meta*-pyrylium), 122.7 (*meta*-pyrylium), 122.4 (*meta*-pyrylium), 51.6, 46.5, 46.4, 46.3, 36.6, 36.2, 34.7, 34.6, 33.5, 33.5, 33.3, 32.6, 32.5, 32.5, 32.2, 31.7, 25.7, 25.5, 25.5, 25.1, 25.1, 25.0, 25.0, 24.2, 24.1, 22.5, 22.3, 22.2, 20.6, 20.1, 19.9, 19.9, 14.0 (CH_3), 13.8 (CH_3), 13.7 (CH_3). HRMS (ESI): calculated for $C_{20}H_{31}O$ [M^+] 287.2369, found 287.2371.

(5d). 2,6-bis(4-t-butyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

0.11 mL (1.25 mmol) of *tert*-butanol, 1 g (4.9 mmol) of 4-*t*-butyl-cyclohexanoyl chloride and 0.5 mL (3.65 mmol) of tetrafluoroboric acid diethyl etherate (51-57% HBF_4 in diethyl ether, 7.3 M), 0.241 g were obtained (43% yield). Mp 212-214 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, minor stereoisomer 15% of total), 7.80 (s, major stereoisomer 57% of total), 7.77 (s, major stereoisomer), 7.73 (s, third stereoisomer 28% of total), 2.82 (s, CH_3-Ar minor stereoisomer), 2.79 (s, major stereoisomer), 2.77 (s, third stereoisomer), 0.87 (s, *t*-butyl major stereoisomer), 0.82 (s, third stereoisomer), 0.79 (s, minor stereoisomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7 (*ortho*-pyrylium), 183.6 (*ortho*-pyrylium), 183.5 (*ortho*-pyrylium), 183.2 (*ortho*-pyrylium), 175.7 (*para*-pyrylium), 175.1 (*para*-pyrylium), 174.2 (*para*-pyrylium), 123.1 (*meta*-pyrylium), 122.8 (*meta*-pyrylium), 121.9 (*meta*-pyrylium), 121.7 (*meta*-pyrylium), 47.8, 47.8, 47.1, 47.1, 43.8, 43.7, 39.1, 39.0, 32.7, 32.6, 32.6, 31.1, 31.0, 28.5, 28.3, 27.5 (*t*-butyl), 27.5 (*t*-butyl), 27.4 (*t*-butyl), 26.6, 26.6, 24.2, 24.1, 24.1, 23.7, 23.7. HRMS (ESI): calculated for $C_{26}H_{43}O$ [M^+]

371.3308, found 371.3310.

Pyridinium Salts

Reagents and solvents were generally purchased from Aldrich Chemical Company or from Alfa Aesar, and were used as received unless otherwise noted. 2,4,6-trimethylpyrylium salt and 2 2,6-diphenyl-4-(*p*-tolyl)pyrylium salt were previously synthesized following Balaban's and Dimroth's procedure, respectively.[25, 30]

General Procedure for the Preparation of the Pyridinium Salts 9a, 11a,b[17]

1 equivalent of pyrylium tetrafluoroborate salt and 1.5 equivalents of amine were heated at 85^{o}C for 2 hours. After cooling to room temperature, the reaction mixture was left in the freezer overnight. To recrystallize, the reaction mixture was dissolved in ethyl acetate and it precipitated with ether.

(9a). 2,4,6-trimethyl-1-phenylpyridinium tetrafluoroborate

From 0.91 mL (10.0 mmol) of aniline, 1.05 g (5.0 mmol) of 2,4,6-trimethylpyrylium salt and 10.0 mL of ether, 0.318 g were obtained (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 3H), 7.62 (s, 2H), 7.44 – 7.39 (m, 2H), 2.61 (s, 3H), 2.35 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 154.9, 146.5, 138.5, 131.4, 131.3, 129.4, 128.0, 125.7, 118.6, 115.2, 22.2, 22.1, 22.1. HRMS (ESI): calculated for $C_{14}H_{16}N$ [M^+] 198.1277, found 198.1282.

(11a). 2,4,6-trimethyl-1-thioureidopyridinium tetrafluoroborate

From 0.68 g (7.5 mmol) of thiosemicarbazide, 1 g of (5.0 mmol) 2,4,6-trimethylpyrylium

tetrafluoroborate and 5 mL ethanol, 1.094 g were obtained (77% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.98 (s, 1H, NH), 8.10 (s, 2H, NH_2), 7.89 (s, 2H), 2.77 (s, 6H), 2.67 (s, 3H). ^{13}C NMR (126 MHz, acetone-d_6) δ 183.6 (C), 162.0 (C), 159.2 (CH), 128.7 (C), 22.0 (CH_3), 19.4 (CH_3). HRMS (ESI): calculated for $C_9H_{14}N_3S$ [M^+] 196.0903, found 196.0903.

(11b). 2,6-diphenyl-1-thioureido-4-(p-tolyl)pyridinium tetrafluoroborate

From 0.17 g (1.8 mmol) of thiosemicarbazide, 0.5 g (1.2 mmol) of 2,6-diphenyl-4-(*p*-toluoyl)pyrylium salt and 5 mL ethanol, 0.179 g were obtained (30% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 11.06 (s, 1H, NH), 8.56 (s, 2H), 8.24 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 7.3 Hz, 4H), 7.63 (dt, J = 24.6, 7.2 Hz, 8H), 7.51 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, acetone-d_6) δ 160.4 (C), 158.6 (C), 145.0 (C), 132.2 (C), 131.9 (CH), 131.7 (C), 131.4 (CH), 130.9 (CH), 129.8 (CH), 129.4 (CH), 126.1 (CH), 21.5 (CH_3). HRMS (ESI): calculated for $C_{25}H_{22}N_3S$ [M^+] 396.1529, found 396.1509.

General Procedure for the Preparation of the Pyridinium Salts 9b[31]

1 equivalent of pyrylium salt and 2 equivalents of amine were heated at 75^{o}C for 4 hours. After cooling to room temperature, the solution with the oily reaction mixture was made alkaline with NaOH, and extracted with ether for the higher amines. The amines recrystallized from aqueous ethanol.

(9b). 2,4,6-trimethyl-1-octylpyridinium tetrafluoroborate tetrafluoroborate

From 1.65 mL (10.0 mmol) of octylamine, 1.05 g (5.0 mmol) of 2,4,6-trimethylpyrylium

salt and 10.0 mL water, 0.103 g were obtained (7% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 2H), 4.33 (dd, *J* = 21.9, 13.4 Hz, 2H), 2.73 (s, 6H), 2.44 (s, 3H), 1.75 – 1.62 (m, 2H), 1.48 – 1.37 (m, 2H), 1.35 – 1.16 (m, 8H), 0.82 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 153.8, 128.9, 52.3, 31.6, 29.0, 28.9, 28.7, 26.5, 22.5, 21.3, 20.7, 14.0.

General Procedure for the Preparation of the Pyridinium Salt 9c[36]

1 equivalent of pyrylium salt and 2 equivalents of amine were heated at 75^{o}C for 4 hours. After cooling to room temperature, the crystalline solid was filtered off. The filtrate was treated with ether to give more product. The reaction product precipitated after the addition of acetone and diethyl ether. Recrystallization occurred by dissolving the reaction mixture in cold acetone and diethyl ether.

(9c). 1-octyl-2,6-diphenyl-4-(p-tolyl)pyridinium tetrafluoroborate

From 0.40 g (2.44 mmol) octylamine, 0.50 g (1.22 mmol) 2,6-diphenyl-4-(*p*-tolyl)pyrylium salt and 5 mL ethanol, 0.541 g were obtained (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.79 (dd, *J* = 6.5, 2.9 Hz, 4H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.58 (m, 6H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.42 – 4.36 (m, 2H), 2.41 (s, 3H), 1.46 – 1.33 (m, 2H), 1.19 – 1.08 (m, 2H), 1.00 (ddd, *J* = 14.1, 8.8, 6.9 Hz, 2H), 0.94 – 0.86 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.73 (dd, *J* = 6.7, 3.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 155.5, 143.3, 133.0, 131.1, 131.1, 130.6, 129.4, 129.2, 128.1, 126.2, 54.7, 31.5, 29.8, 28.6, 28.0, 26.1, 22.6, 21.6, 14.1.

APPENDIX

Selected NMR Spectra

4a). ^{1}H NMR 2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

4a). ^{13}C NMR 2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

4b). ^{1}H NMR 2-(1R,3R-1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

4b). ^{13}C NMR 2-(1R,3R-1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate

4c). ^{1}H NMR 2-(1-(4-isobutylphenyl)-ethyl)-4,6-diphenylpyrylium tetrafluoroborate

4c). ^{13}C NMR 2-(1-(4-isobutylphenyl)-ethyl)-4,6-diphenylpyrylium tetrafluoroborate

4d). ^{1}H NMR 2-(2-methyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

4d). ^{13}C NMR 2-(2-methyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

4e). ^{1}H NMR 2-(4-t-butyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

4e). ^{13}C NMR 2-(4-t-butyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

4f). ^{1}H NMR 2-(cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

4f). ^{13}C NMR 2-(cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate

5b). ^{1}H NMR 2,6-di-tert-butyl-4-methylpyrylium tetrafluoroborate

5b). ^{13}C NMR 2,6-di-tert-butyl-4-methylpyrylium tetrafluoroborate

5c). ^{1}H NMR 2,6-bis(2-methyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

5c). ^{13}C NMR 2,6-bis(2-methyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

5d). ^{1}H NMR 2,6-bis(4-t-butyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

5d). ^{13}C NMR 2,6-bis(4-t-butyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate

9a). ^{1}H NMR 2,4,6-trimethyl-1-phenylpyridinium tetrafluoroborate

9a). ^{13}C NMR 2,4,6-trimethyl-1-phenylpyridinium tetrafluoroborate

9b). ^{1}H NMR 2,4,6-trimethyl-1-octylpyridinium tetrafluoroborate

9b). ^{13}C NMR 2,4,6-trimethyl-1-octylpyridinium tetrafluoroborate

9c). ^{1}H NMR 1-octyl-2,6-diphenyl-4-(p-tolyl)pyridinium tetrafluoroborate

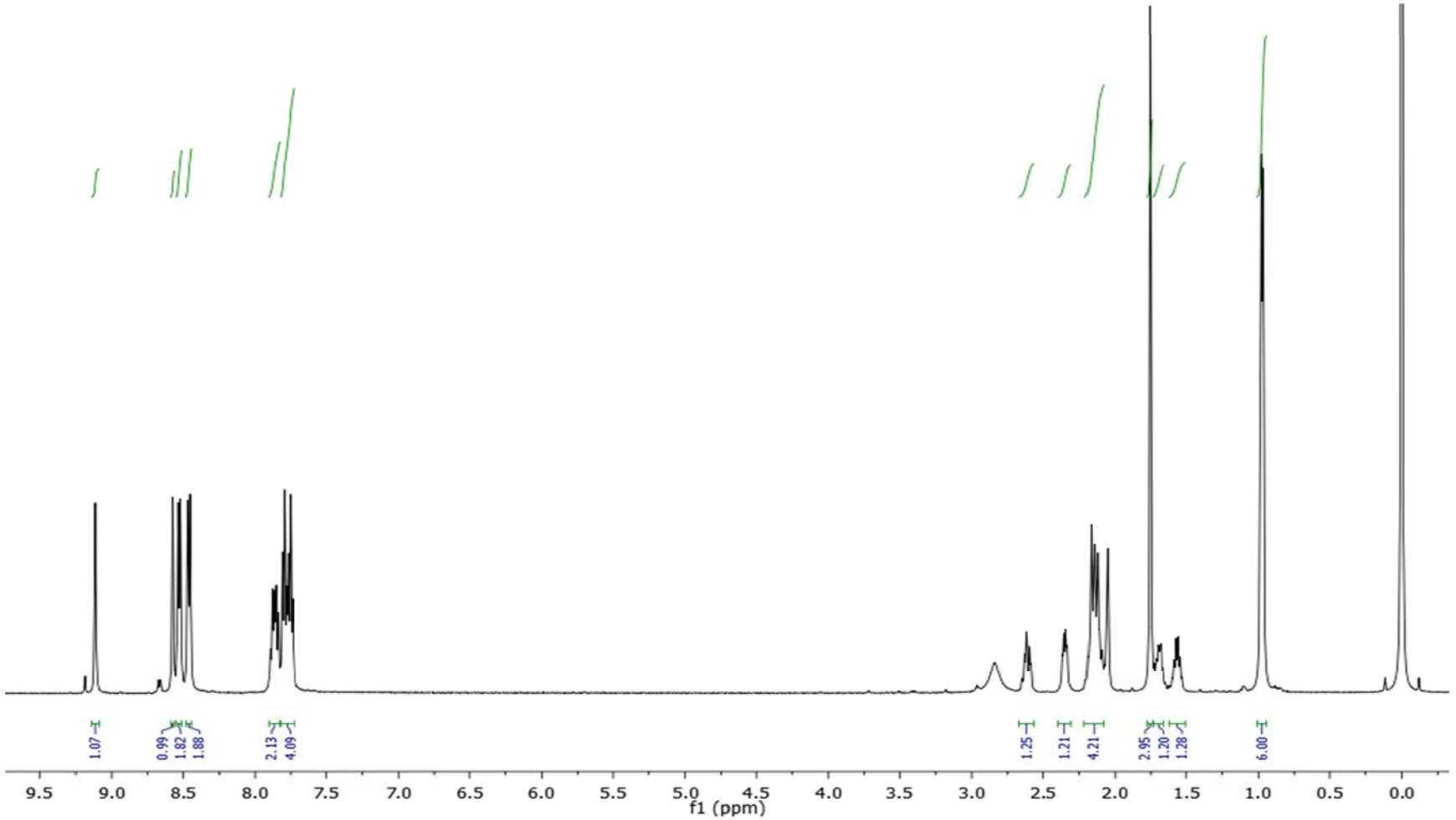
9c). ^{13}C NMR 1-octyl-2,6-diphenyl-4-(p-tolyl)pyridinium tetrafluoroborate

11s). ^{1}H NMR 2,4,6-trimethyl-1-thioureidopyridinium tetrafluoroborate

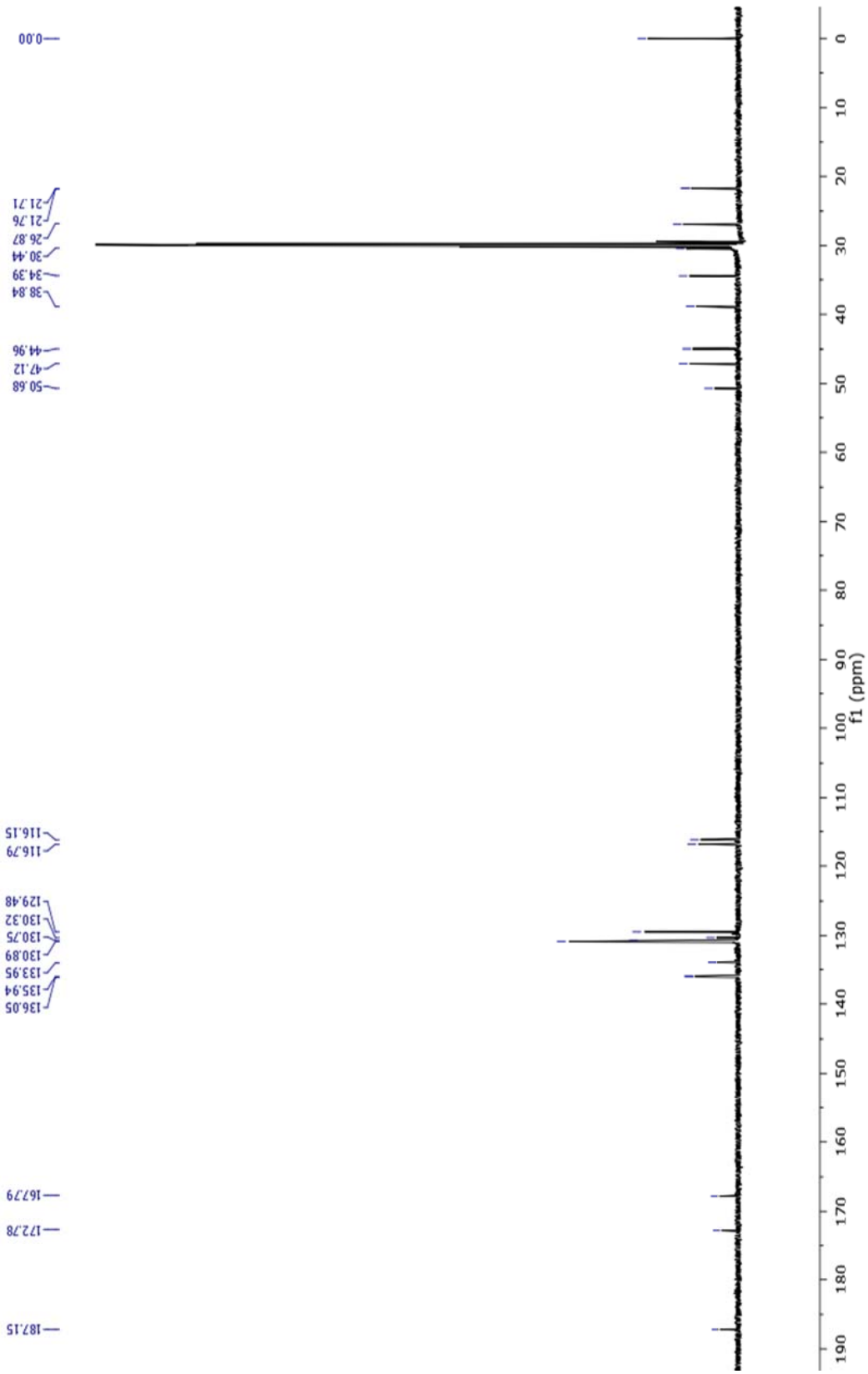
11s). ^{13}C NMR 2,4,6-trimethyl-1-thioureidopyridinium tetrafluoroborate

11b). ^{1}H NMR 2,6-diphenyl-1-thioureido-4-(p-tolyl)pyridinium tetrafluoroborate

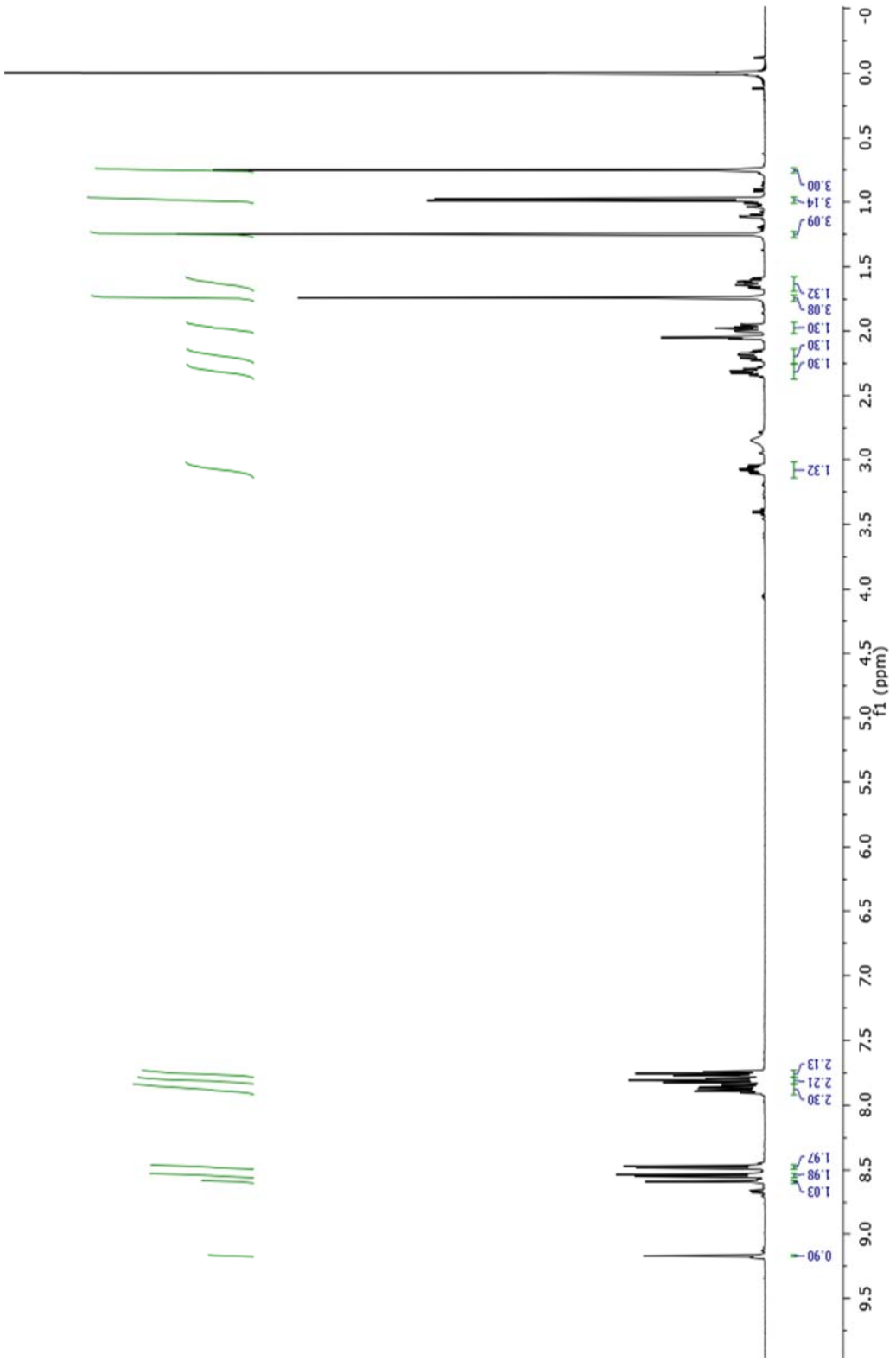
11b). ^{13}C NMR 2,6-diphenyl-1-thioureido-4-(p-tolyl)pyridinium tetrafluoroborate



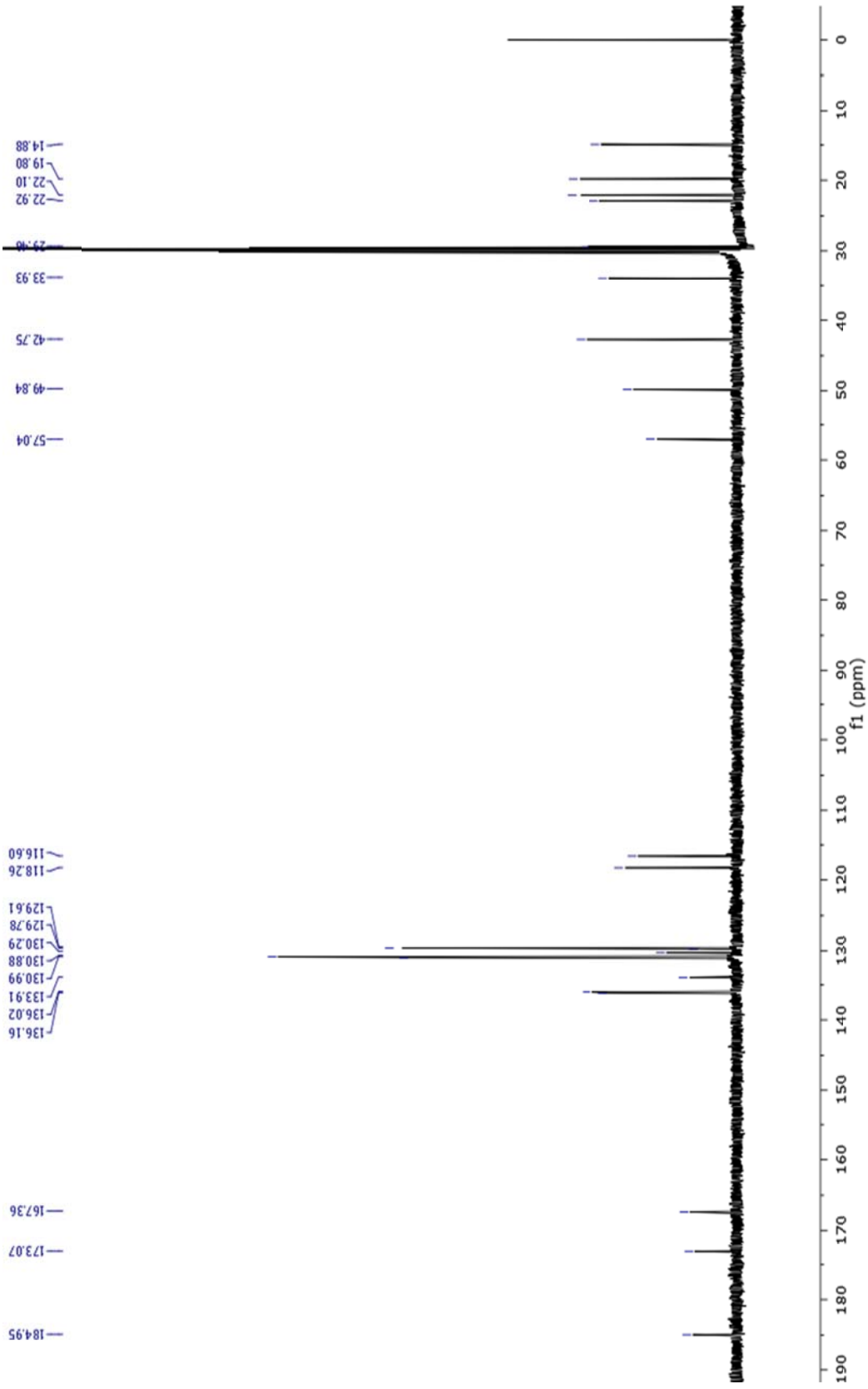
4a). ^{1}H NMR 2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate



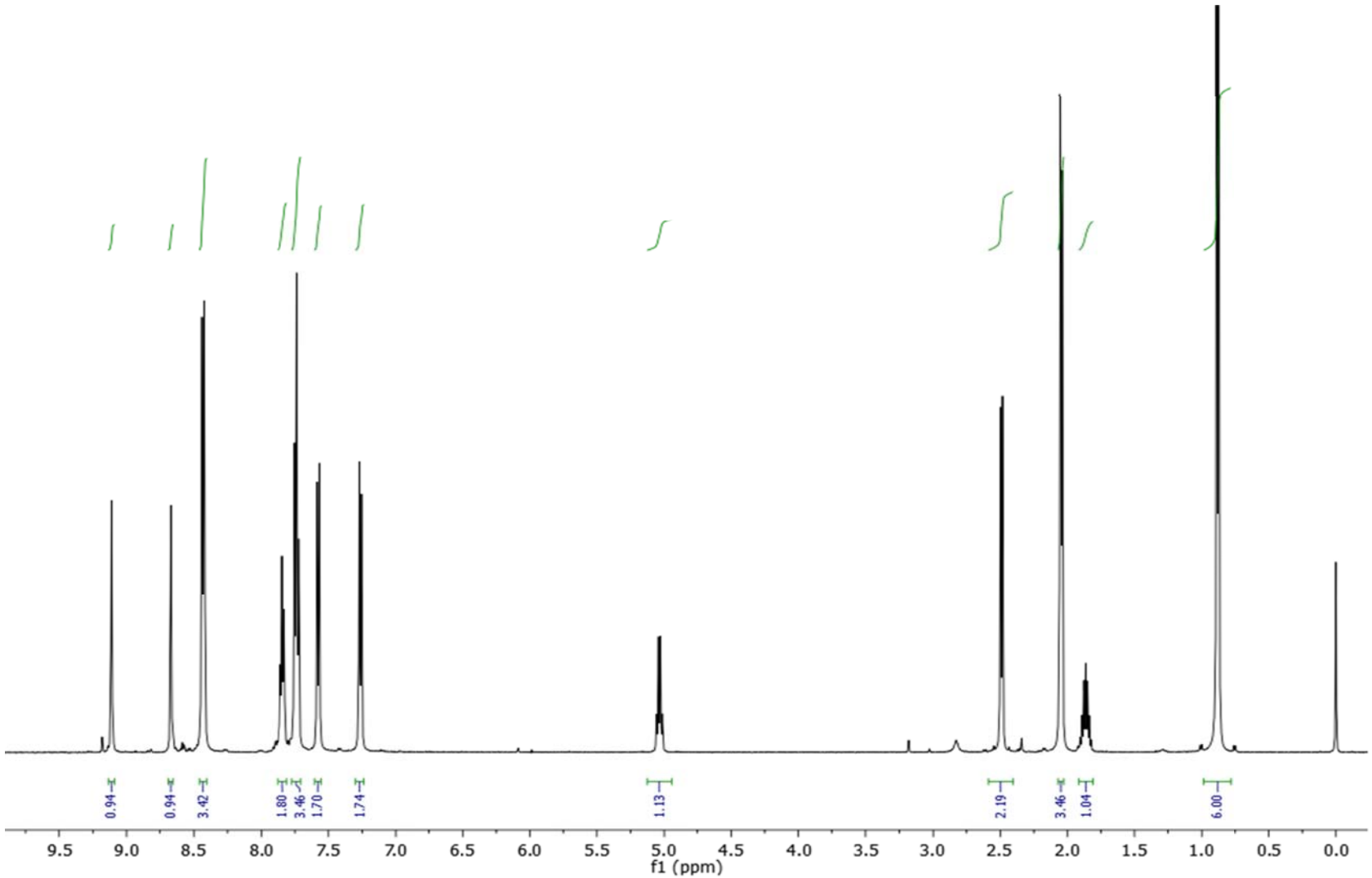
4a). ^{13}C NMR 2-(1R,3R-1-methyl-3-isopropyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate



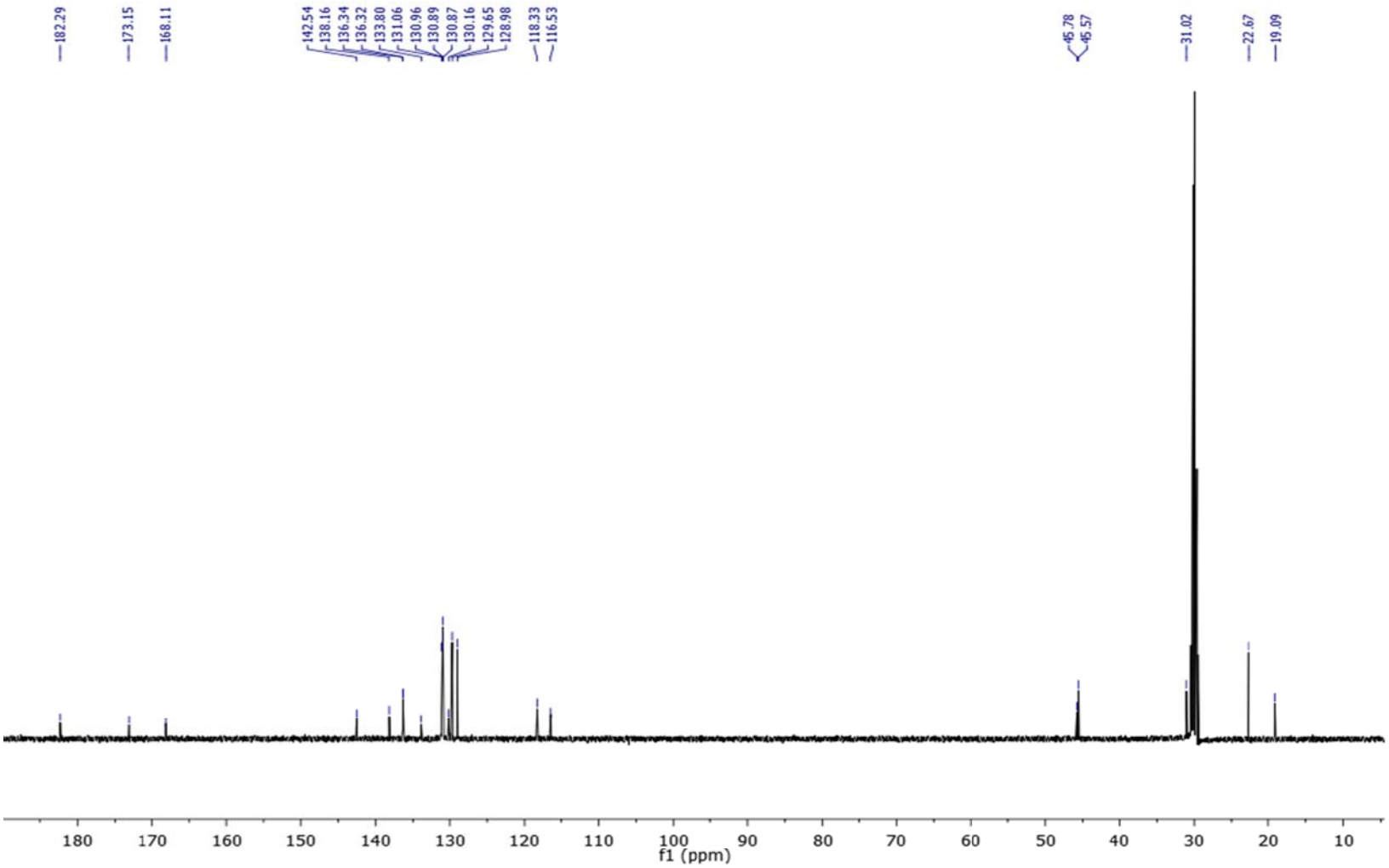
4b). ^{1}H NMR 2-(1R,3R-1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate



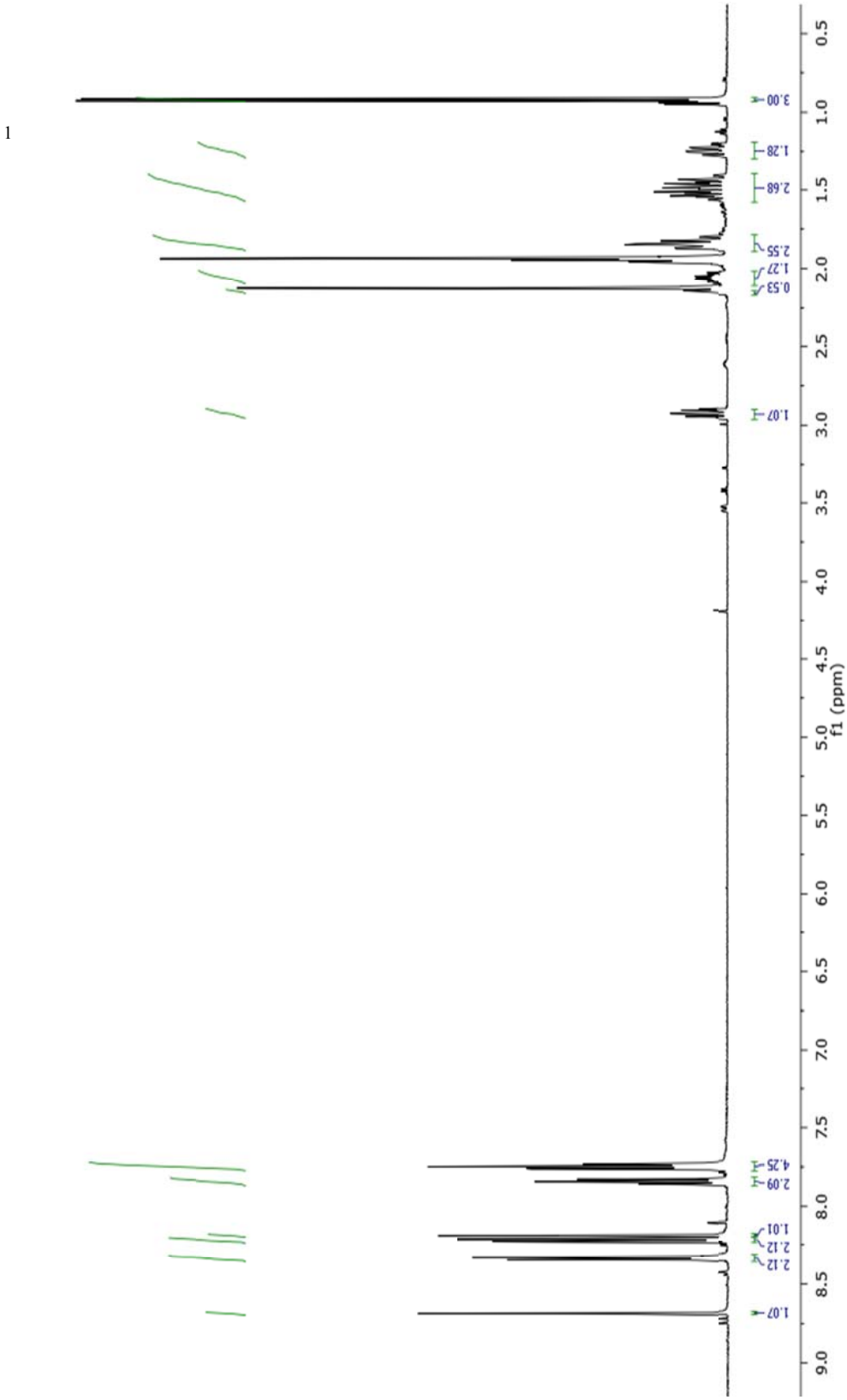
4b). ^{13}C NMR 2-(1R,3R-1,2,2,3-tetramethyl-cyclopentyl)-4,6-diphenylpyrylium tetrafluoroborate



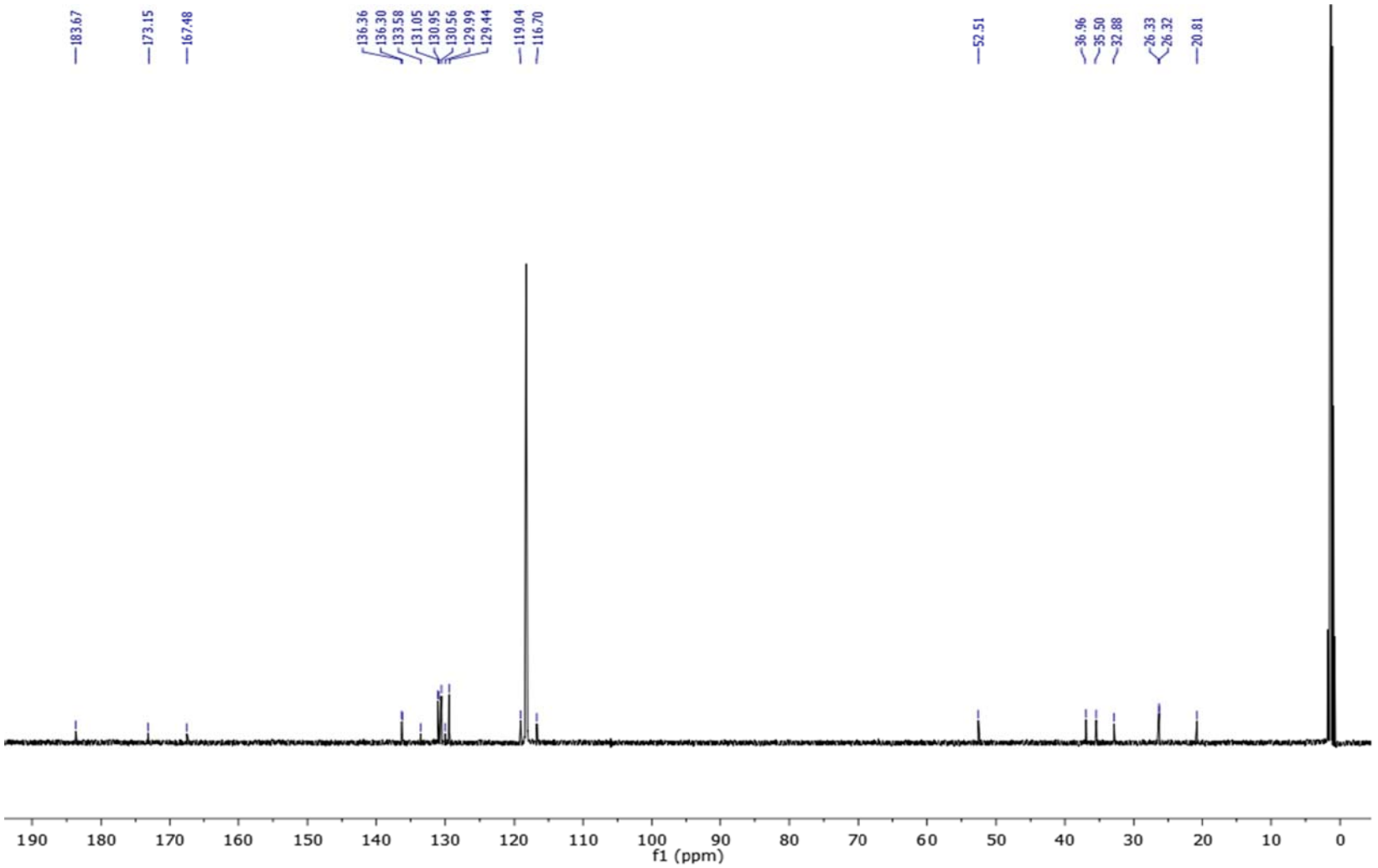
4c). ^{1}H NMR 2-(1-(4-isobutylphenyl)-ethyl)-4,6-diphenylpyrylium tetrafluoroborate



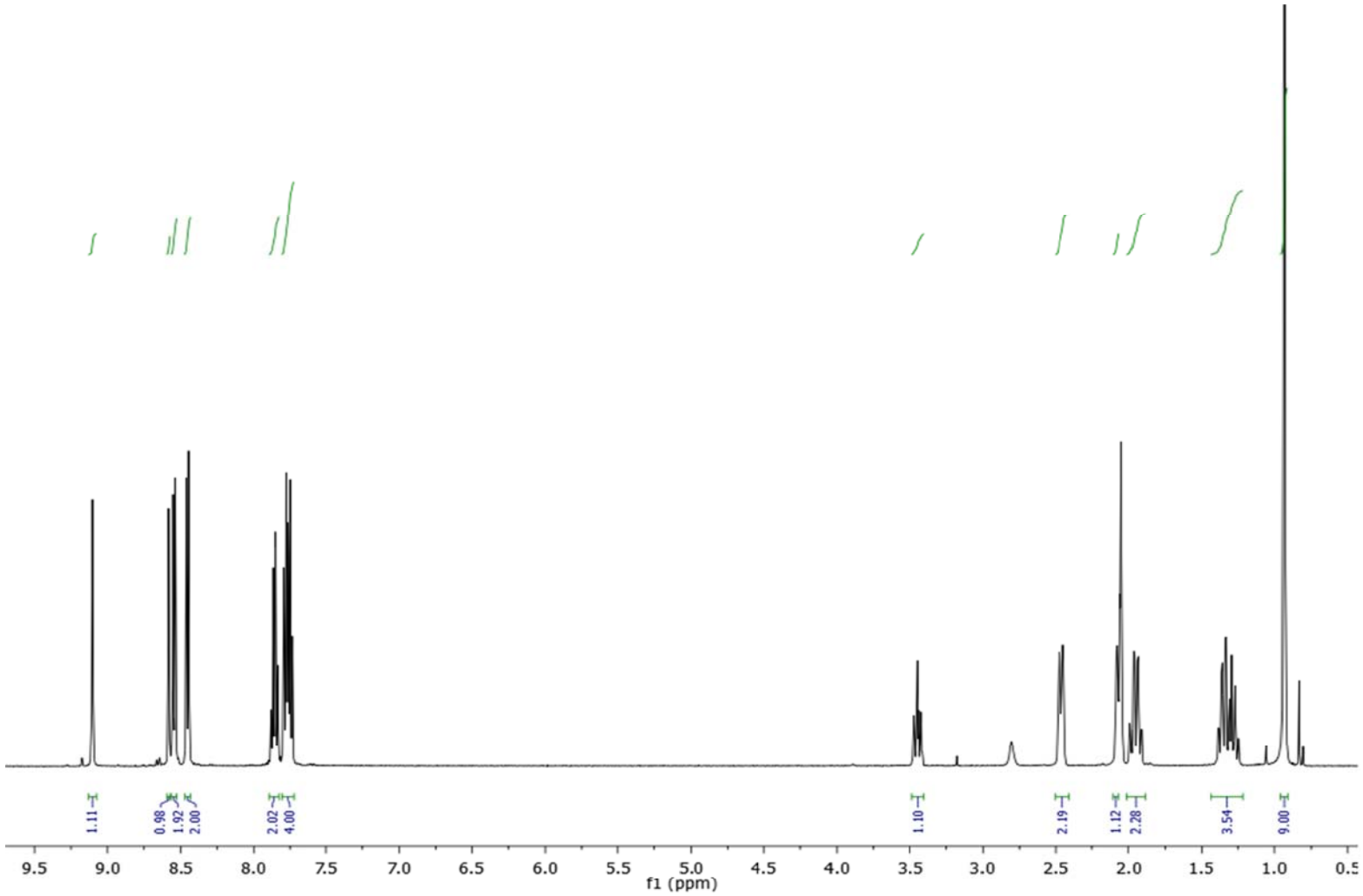
4c). ^{13}C NMR 2-(1-(4-isobutylphenyl)-ethyl)-4,6-diphenylpyrylium tetrafluoroborate



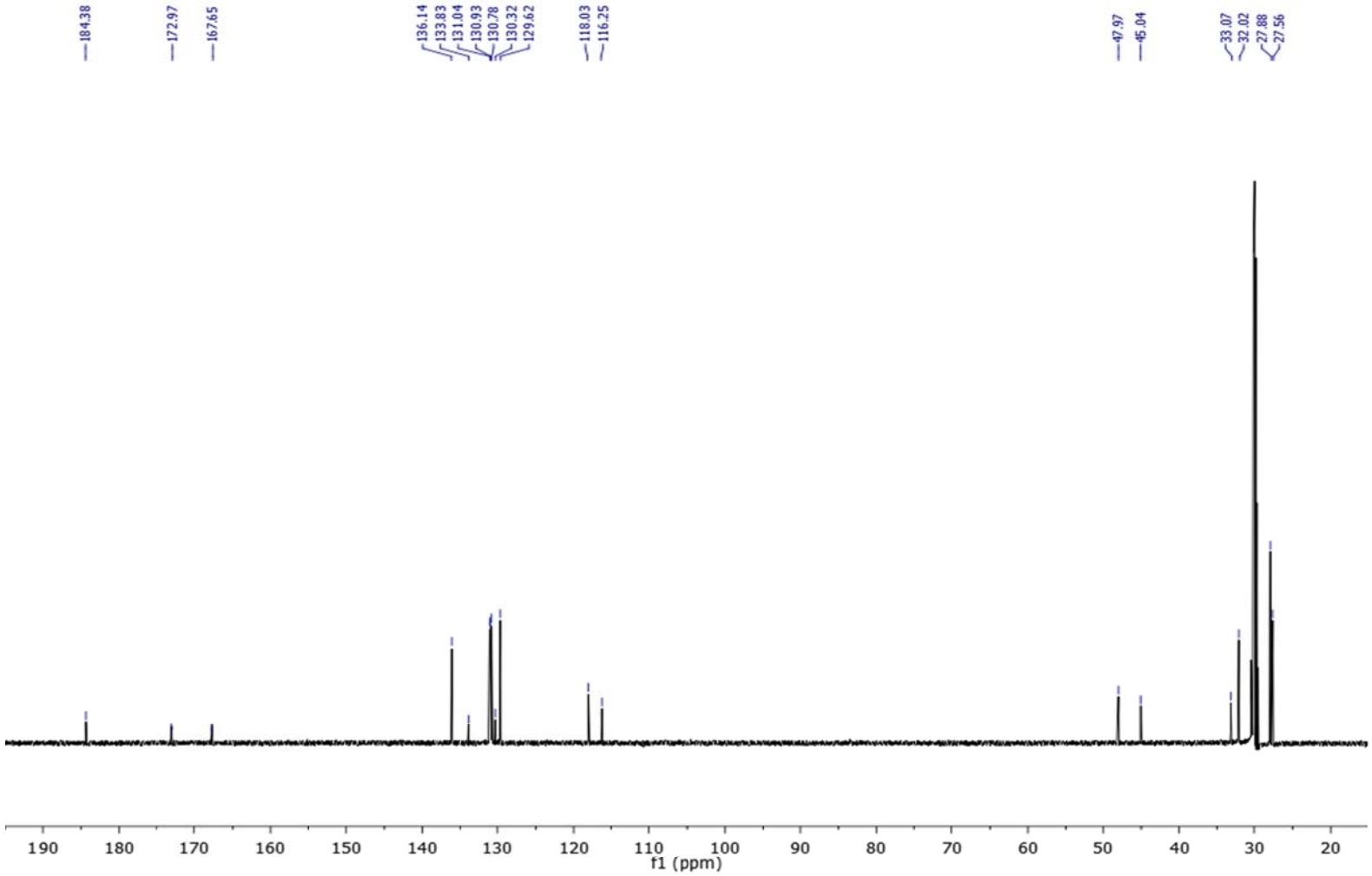
4d). ^{1}H NMR 2-(2-methyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



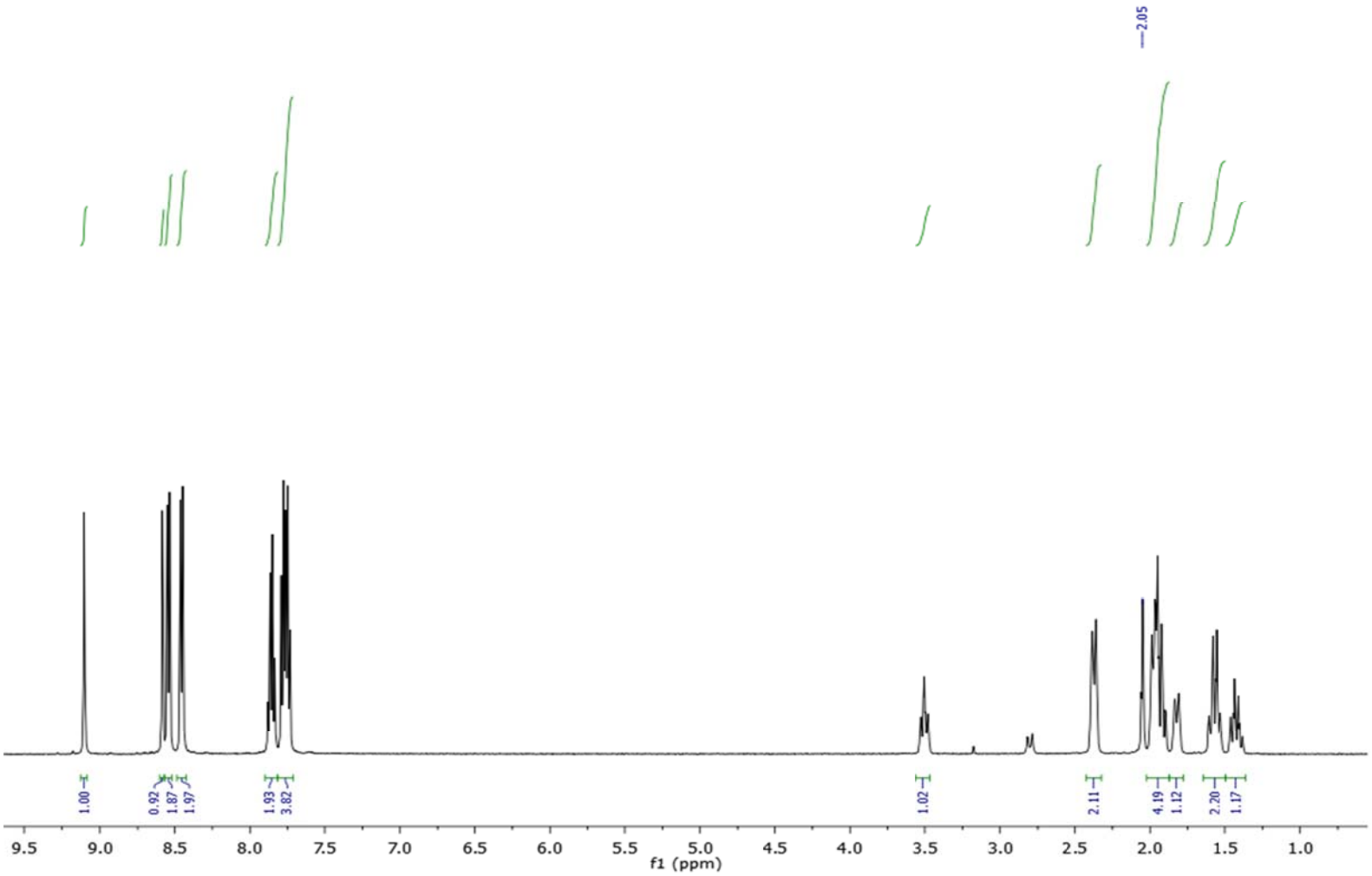
4d). ^{13}C NMR 2-(2-methyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



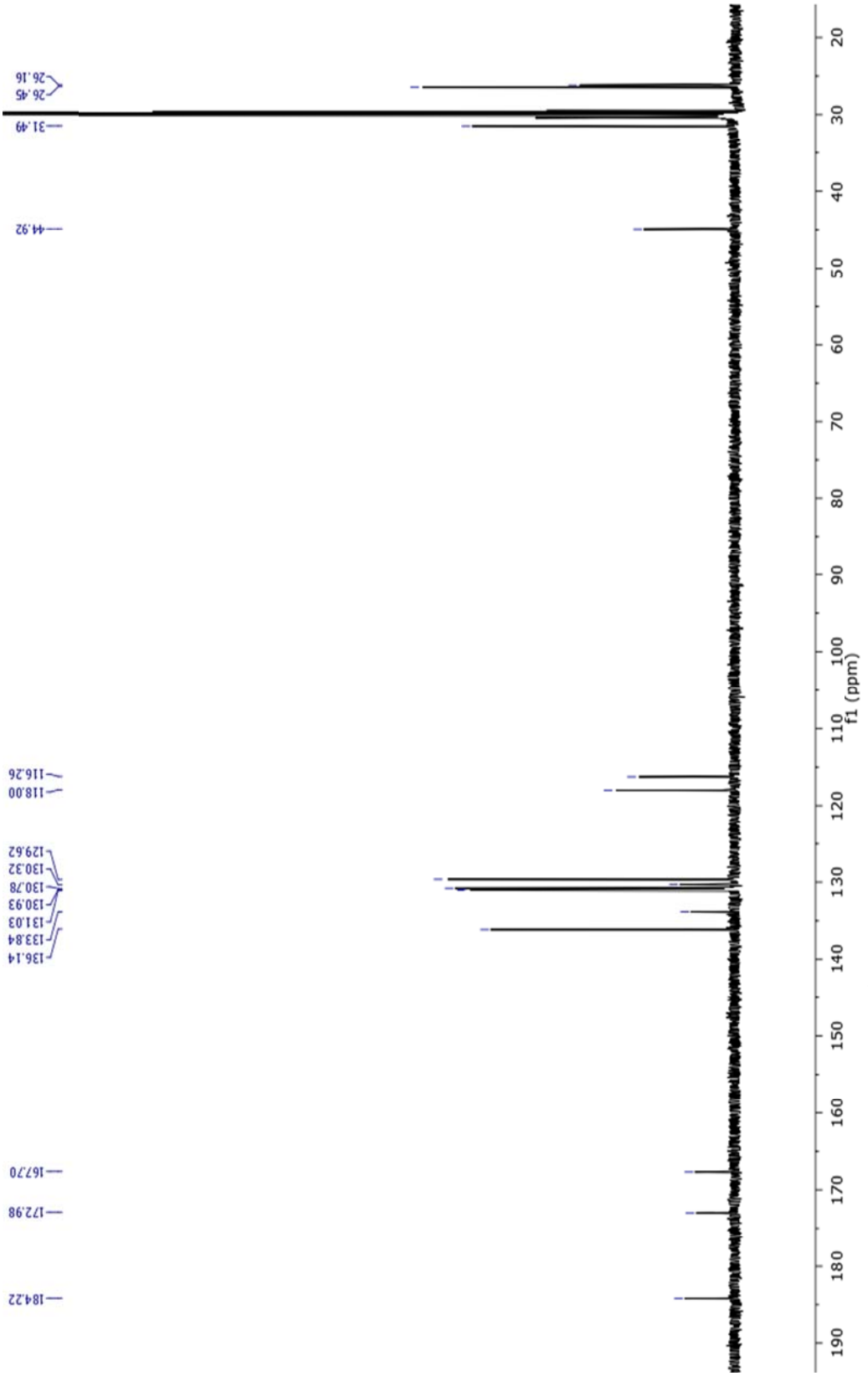
4e). ^{1}H NMR 2-(4-t-butyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



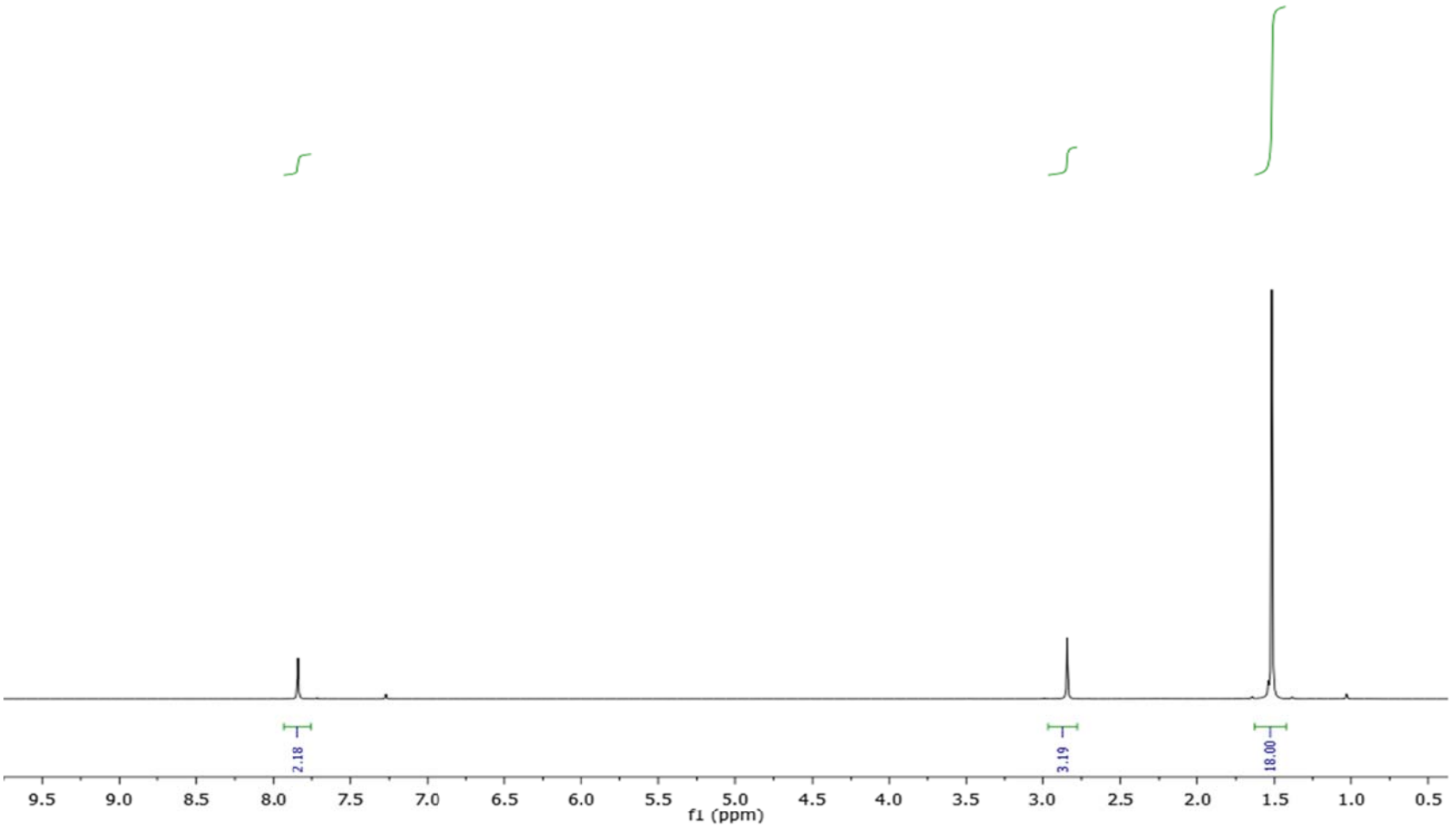
4e). ^{13}C NMR 2-(4-t-butyl-cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



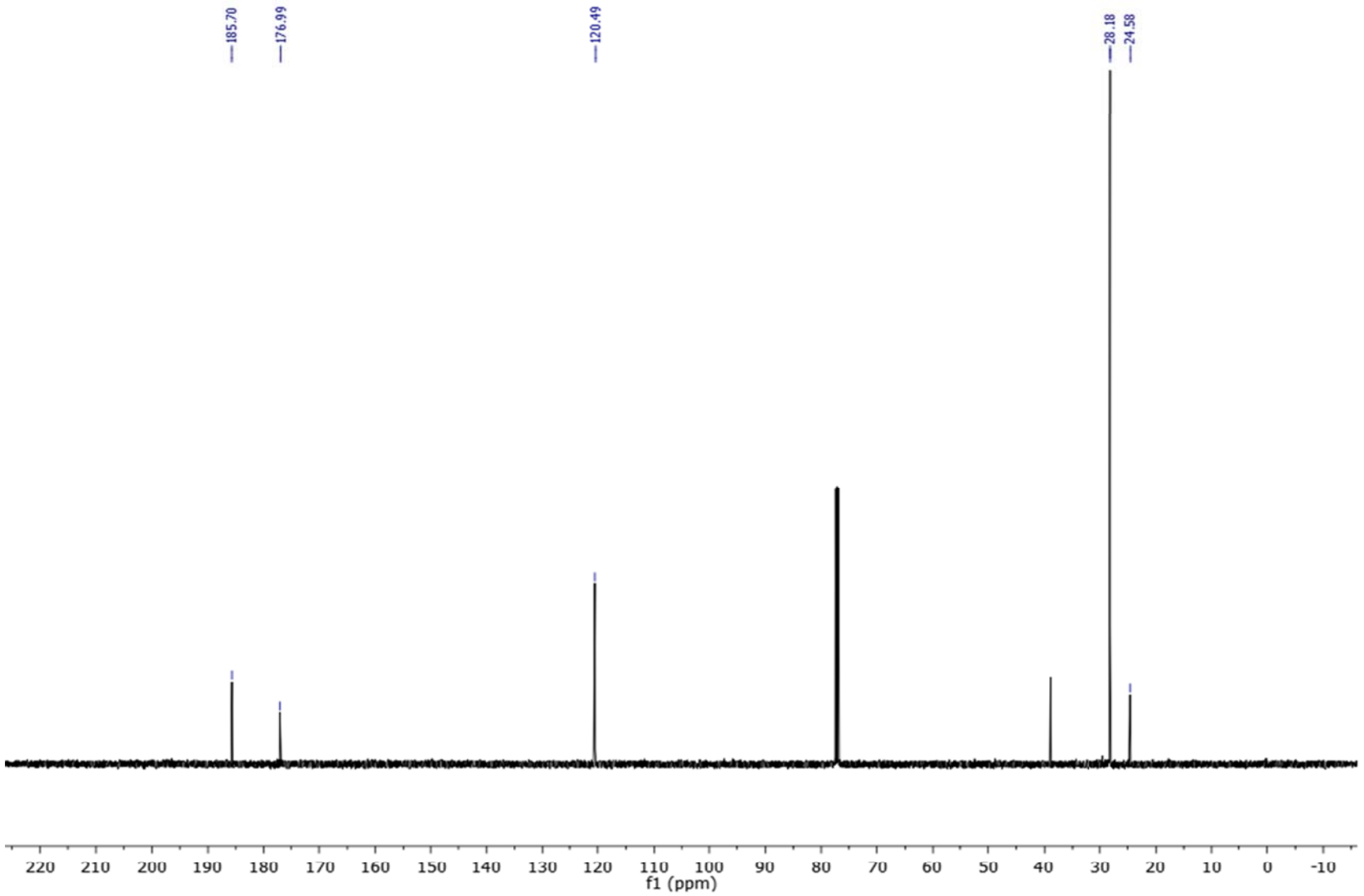
4f). ^{1}H NMR 2-(cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



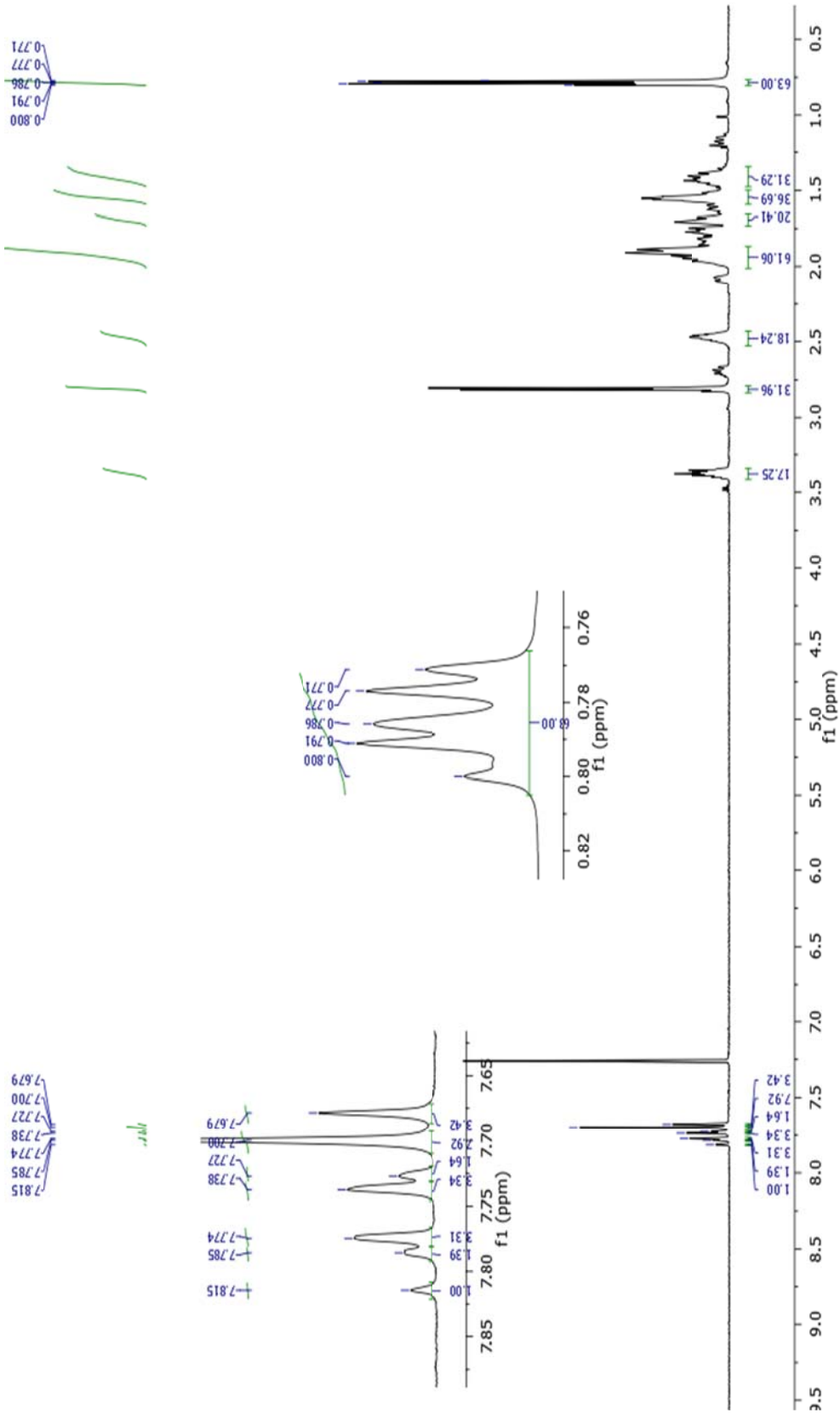
4f). ^{13}C NMR 2-(cyclohexyl)-4,6-diphenylpyrylium tetrafluoroborate



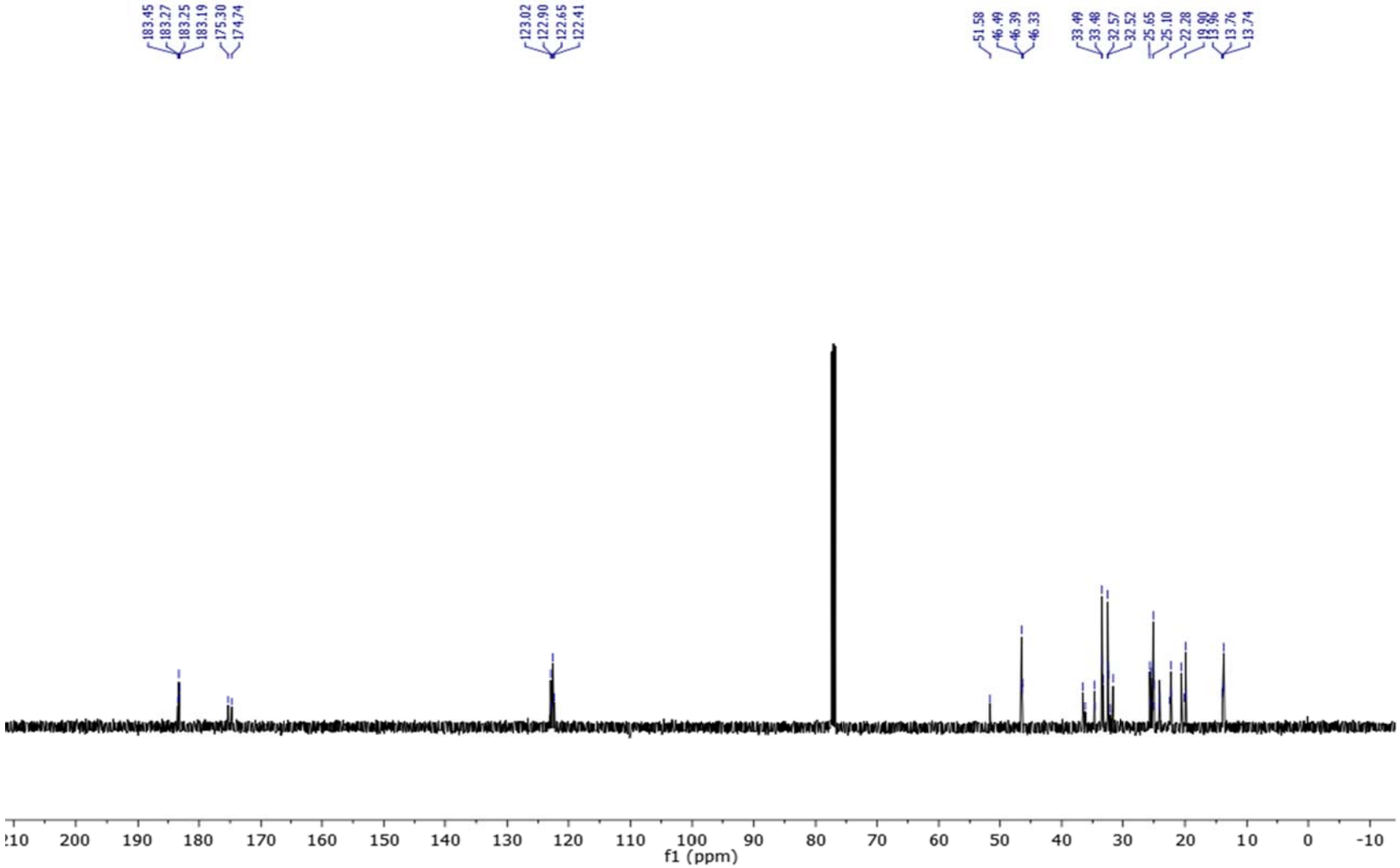
5b). ^{1}H NMR 2,6-di-tert-butyl-4-methylpyrylium tetrafluoroborate



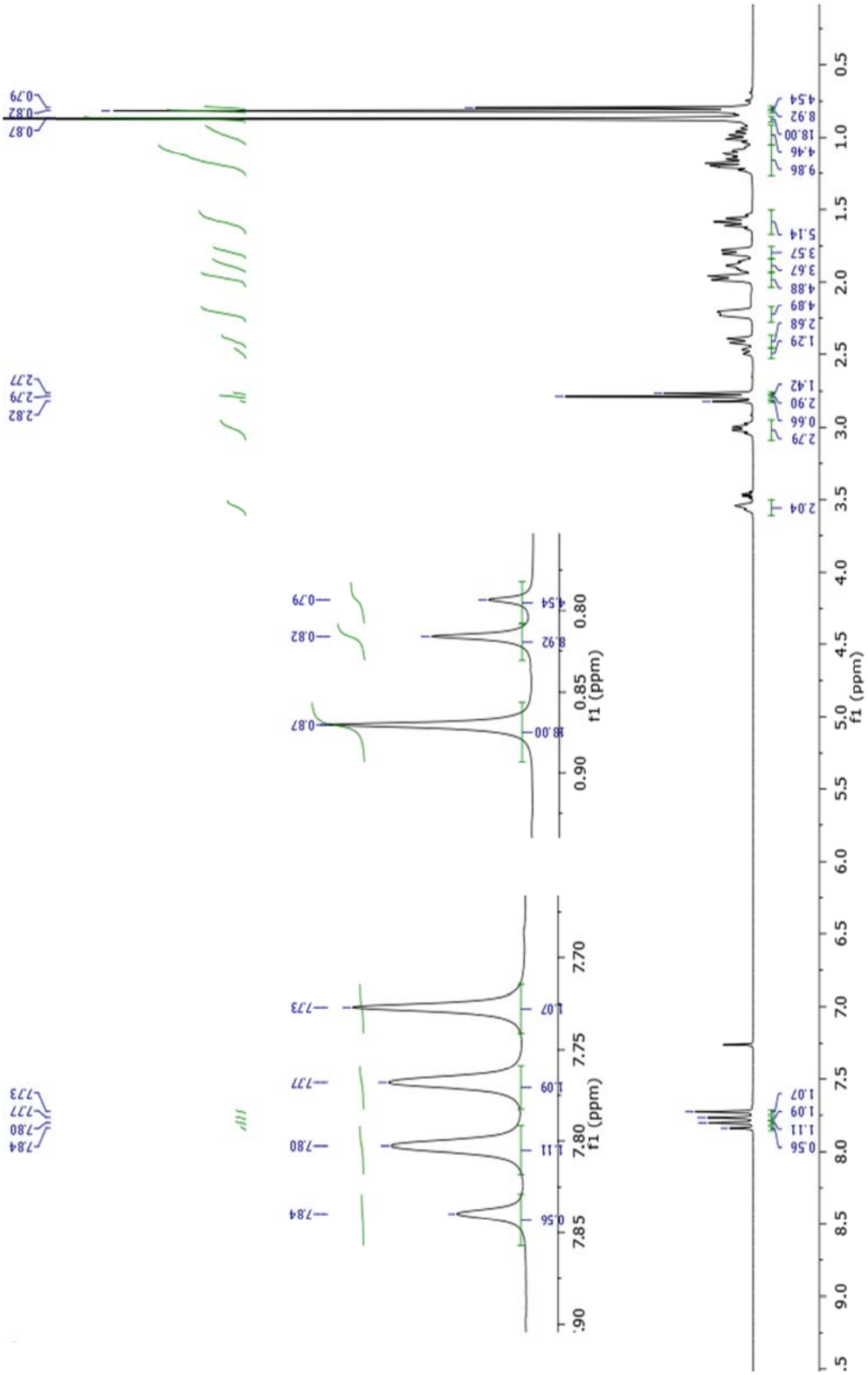
5b). ^{13}C NMR 2,6-di-tert-butyl-4-methylpyrylium tetrafluoroborate



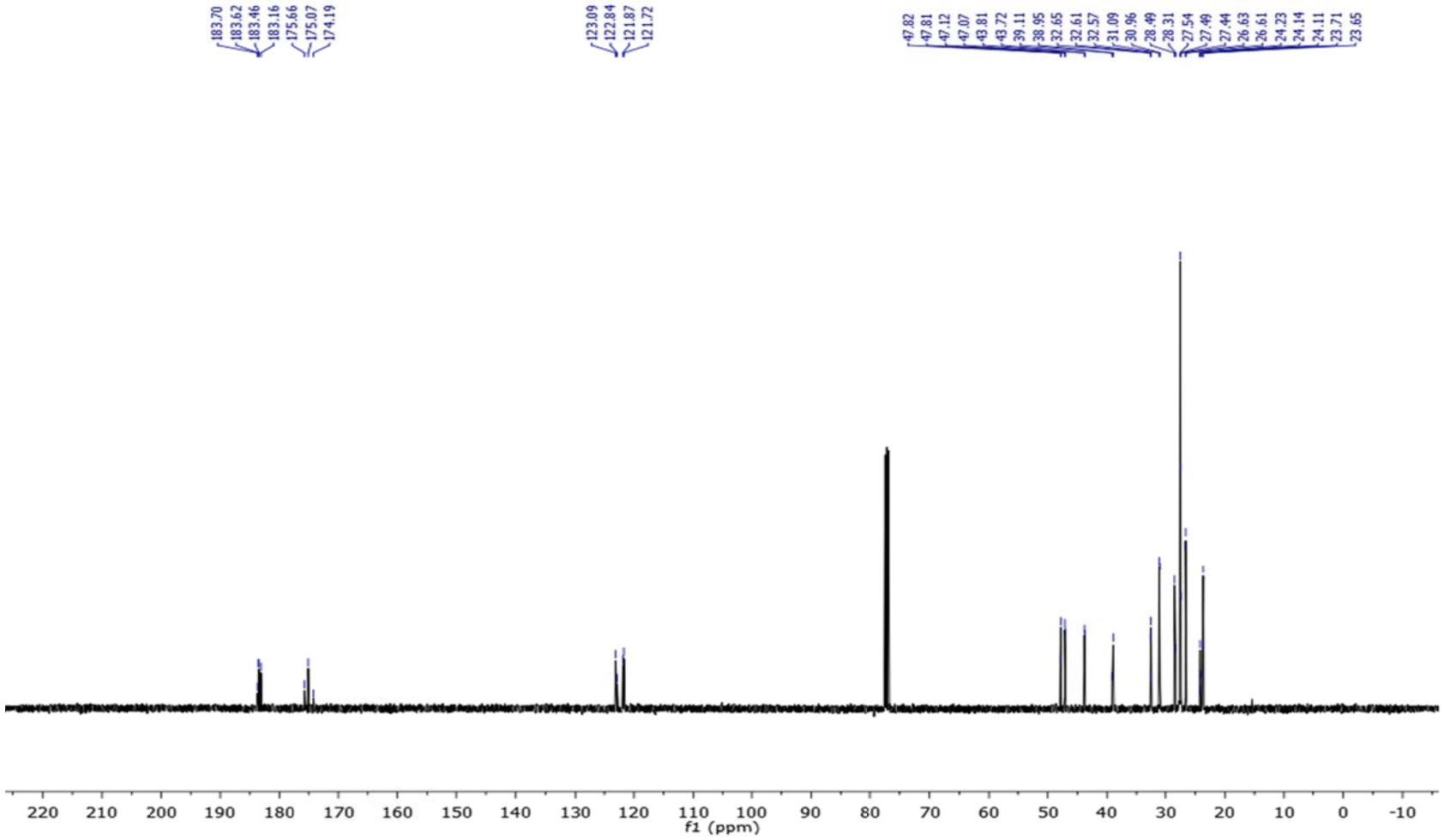
5c). ^{1}H NMR 2,6-bis(2-methyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate



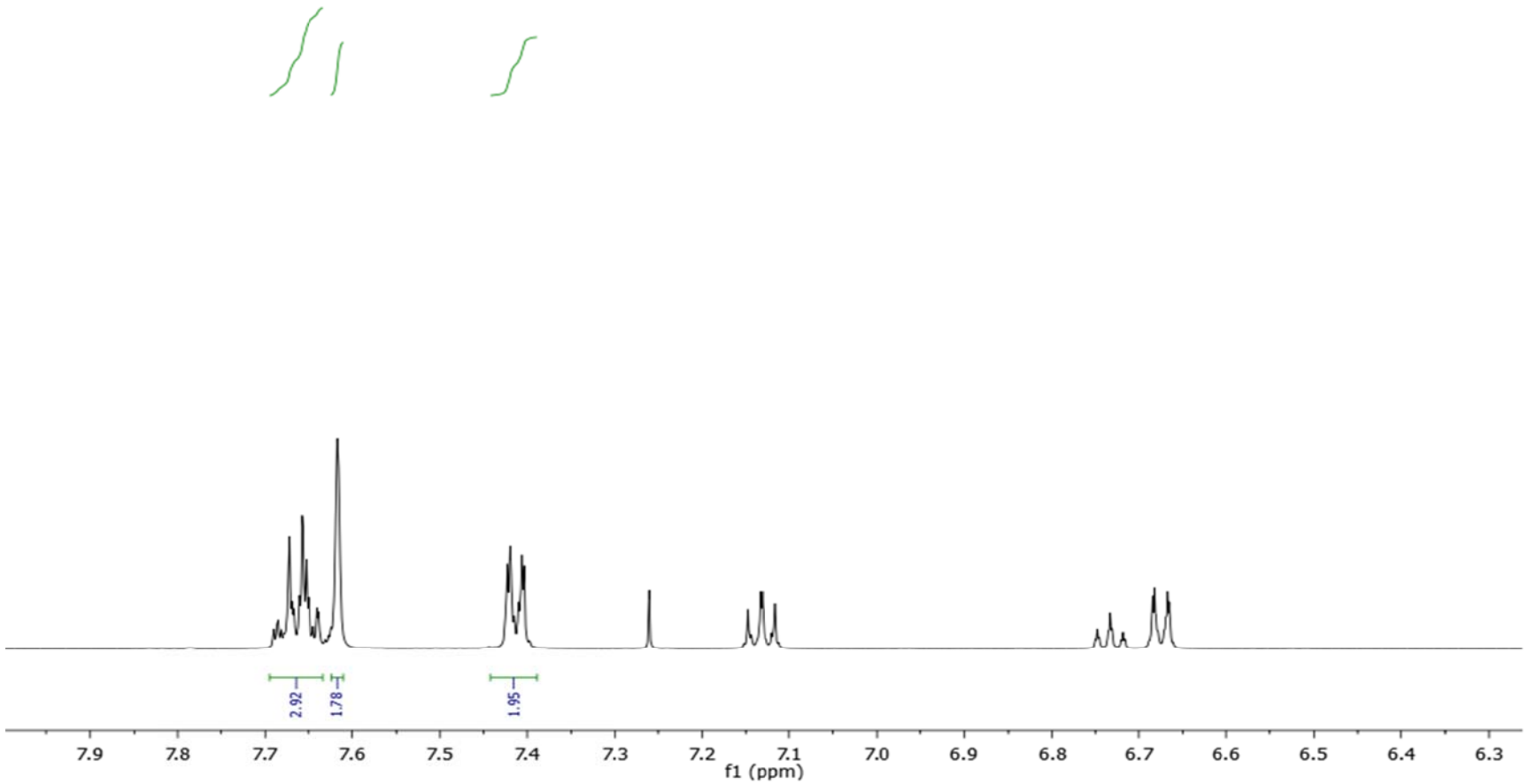
5c). ^{13}C NMR 2,6-bis(2-methyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate



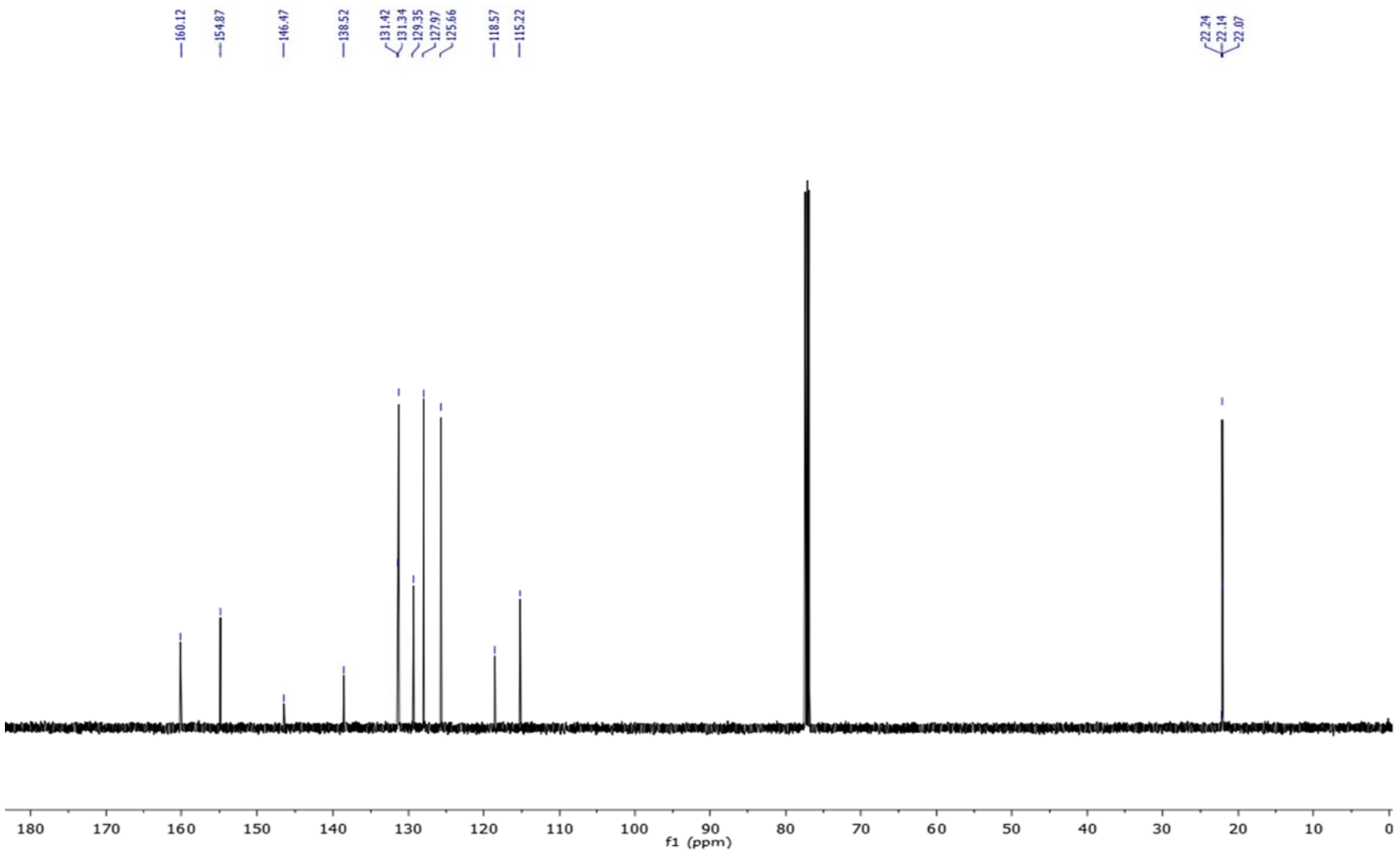
5d). ^{1}H NMR 2,6-bis(4-t-butyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate



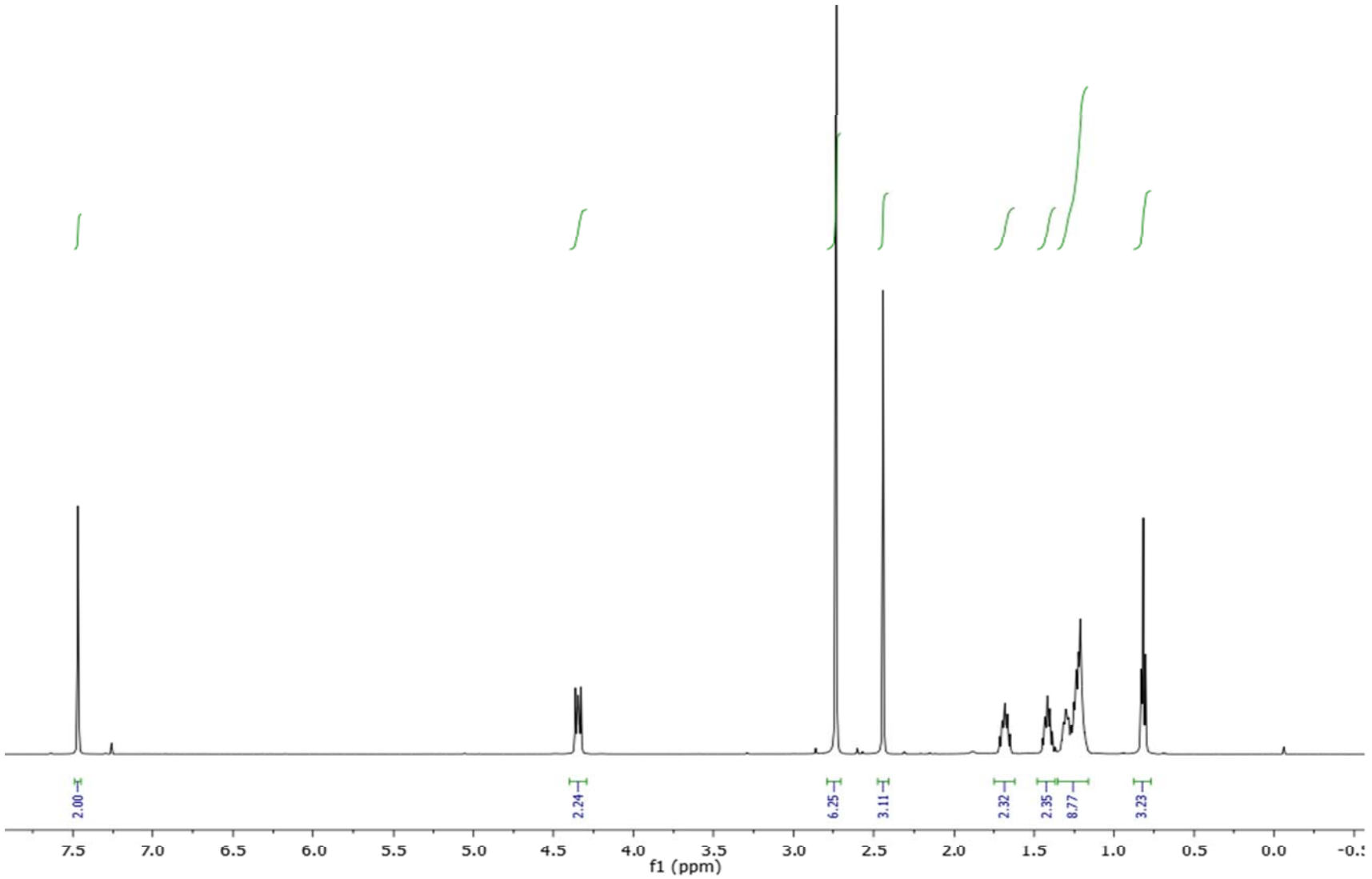
5d). ^{13}C NMR 2,6-bis(4-t-butyl-cyclohexyl)-4-methyl-pyrylium tetrafluoroborate



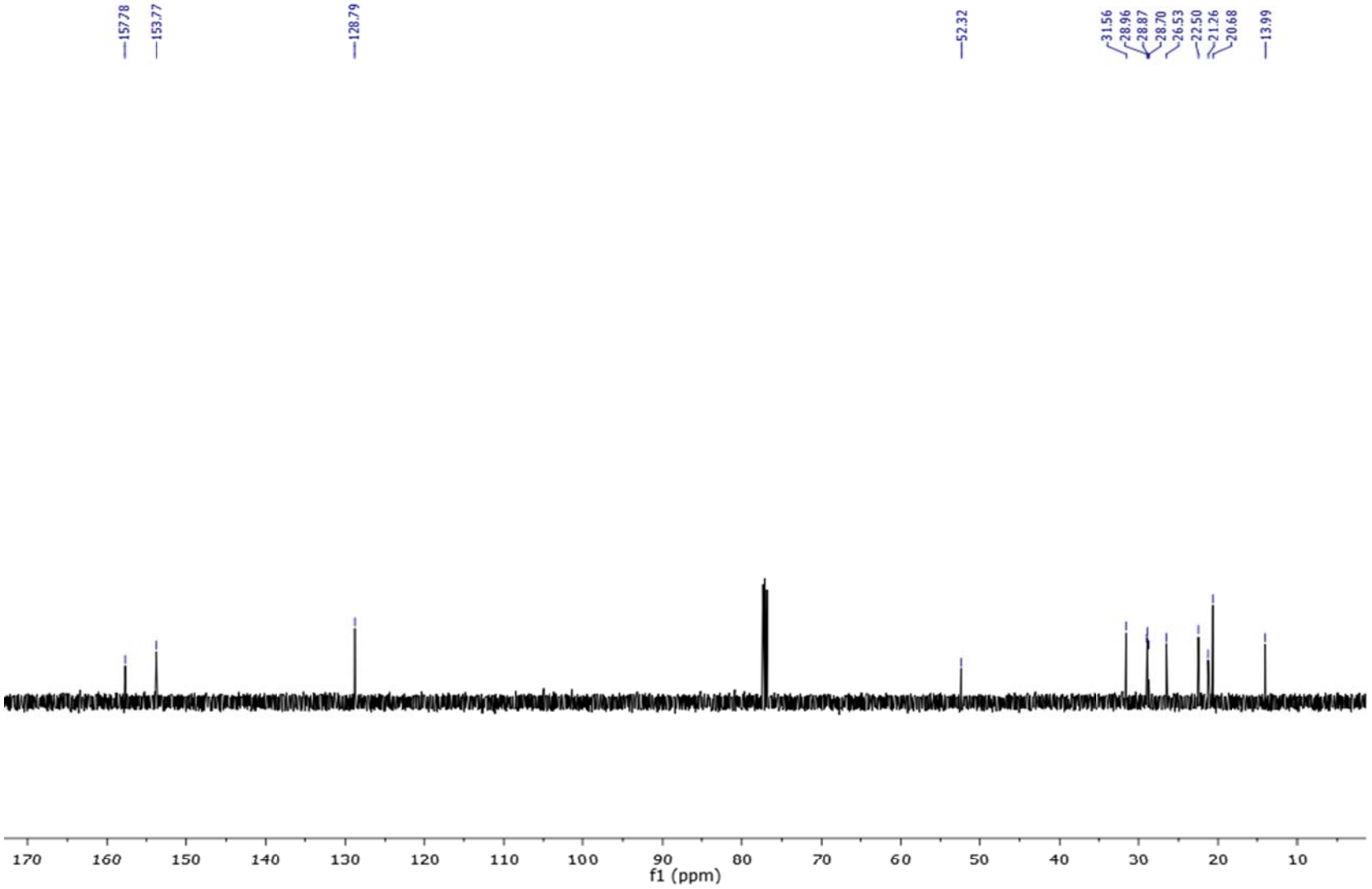
9a). ^{1}H NMR 2,4,6-trimethyl-1-phenylpyridinium tetrafluoroborate



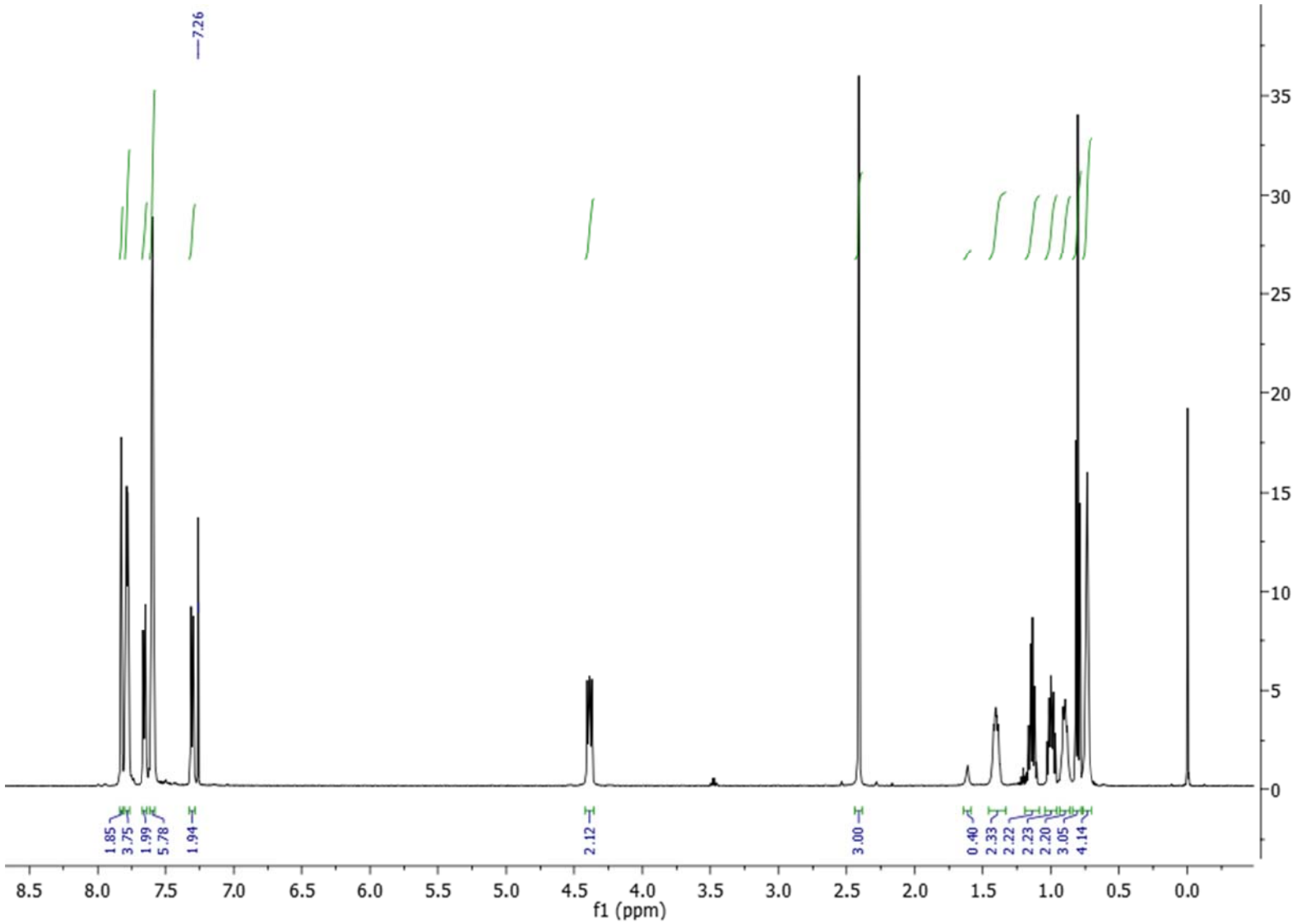
9a). ^{13}C NMR 2,4,6-trimethyl-1-phenylpyridinium tetrafluoroborate



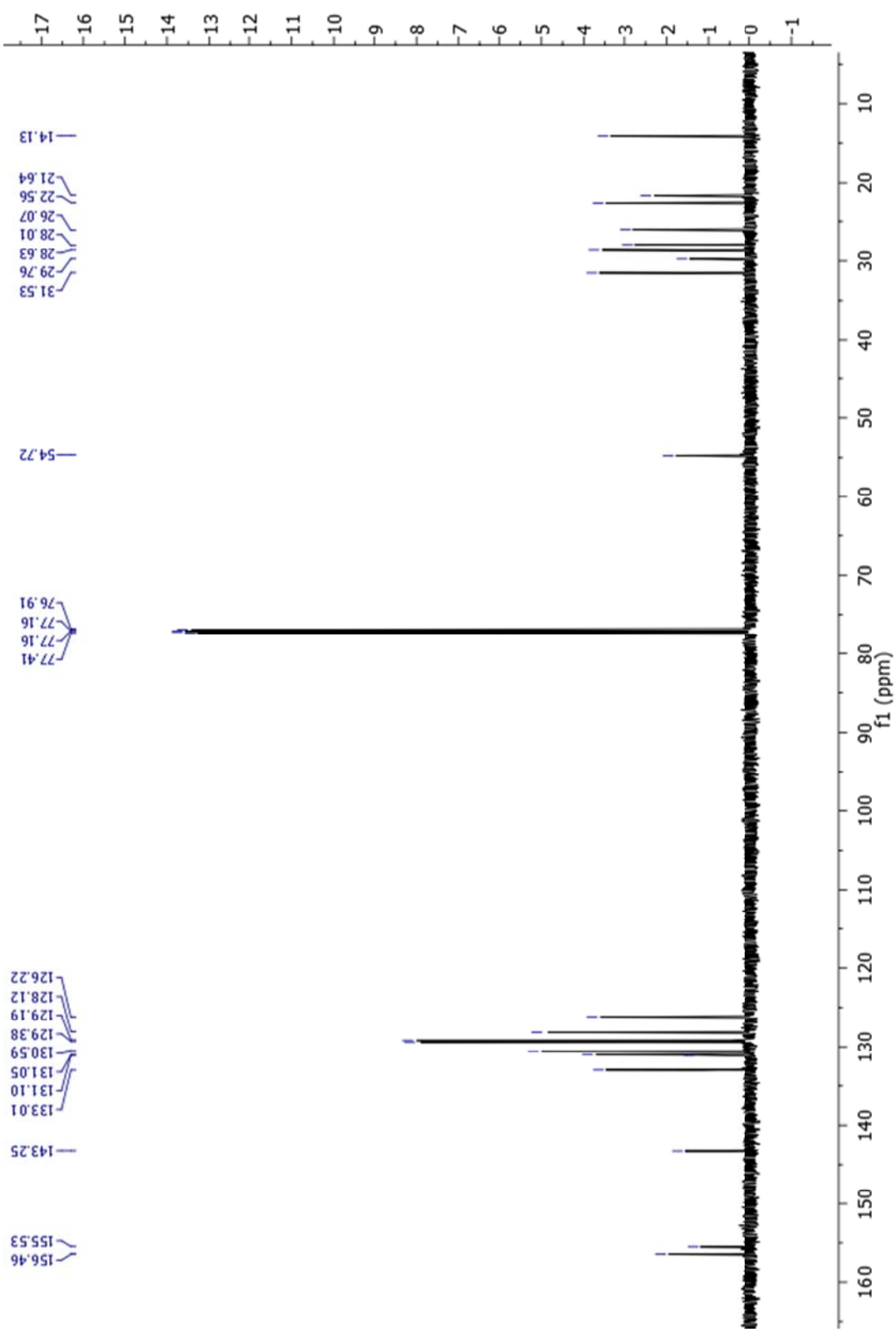
9b). ^{1}H NMR 2,4,6-trimethyl-1-octylpyridinium tetrafluoroborate



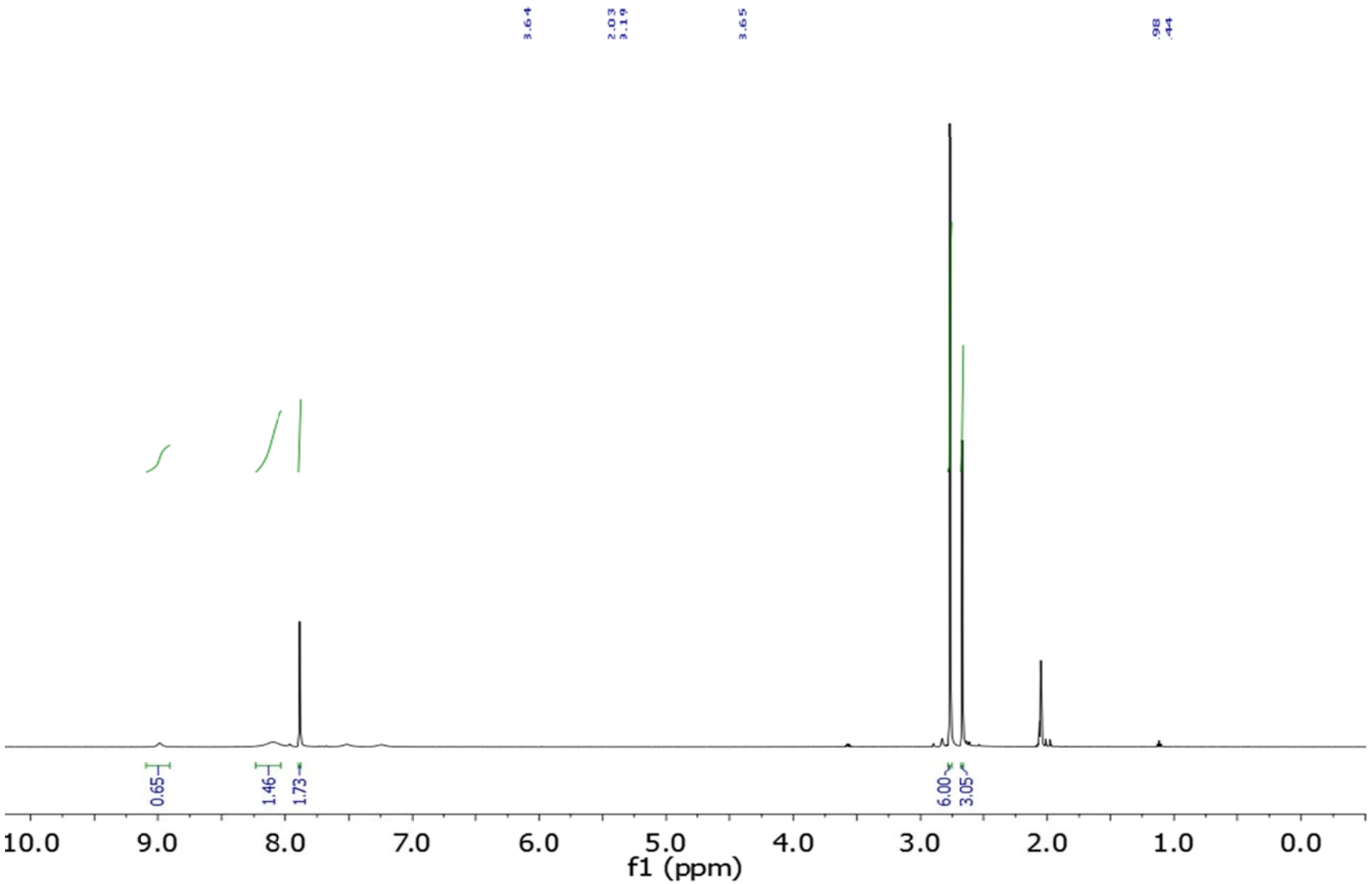
9b). ^{13}C NMR 2,4,6-trimethyl-1-octylpyridinium tetrafluoroborate



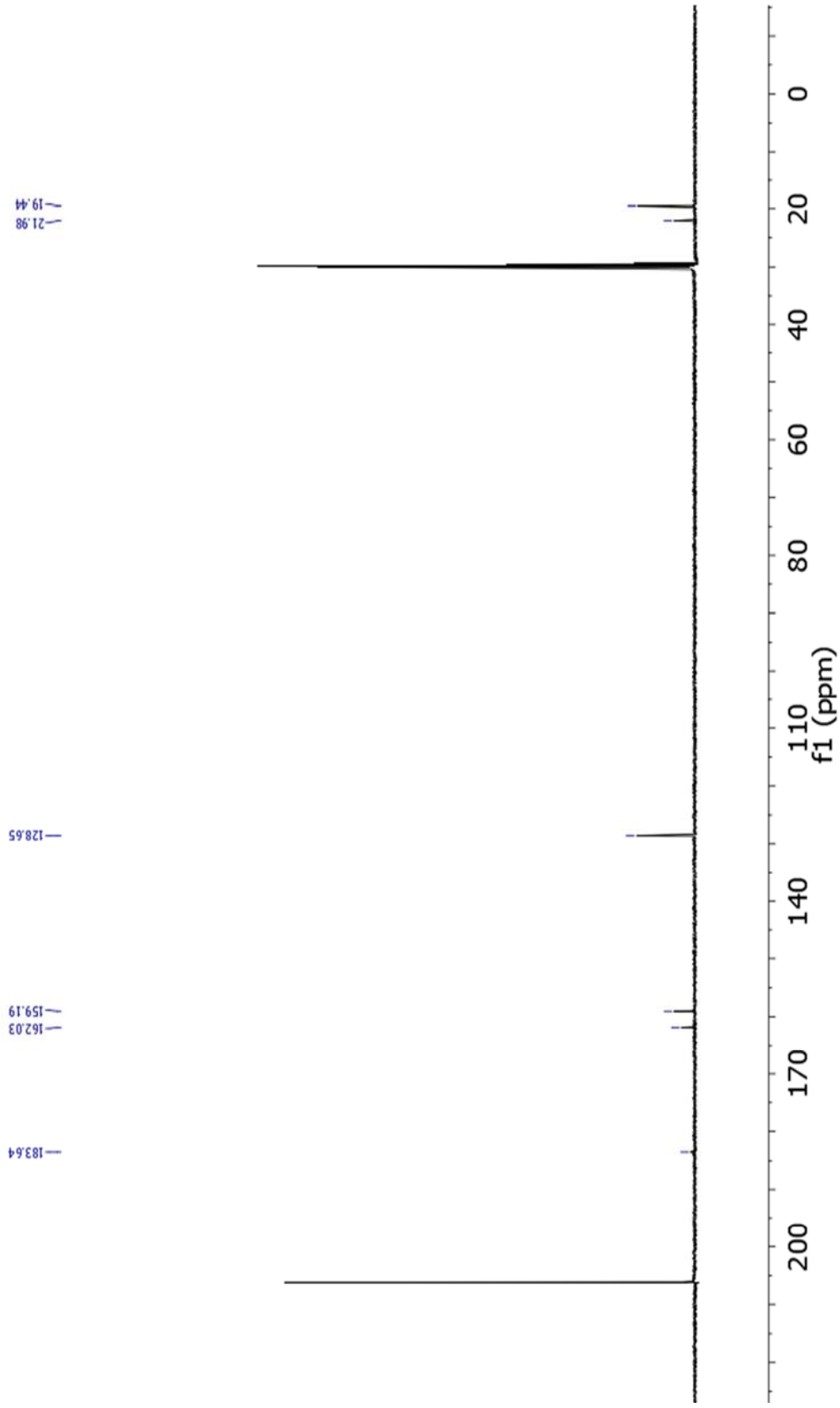
9c). ^{1}H NMR 1-octyl-2,6-diphenyl-4-(p-tolyl)pyridinium tetrafluoroborate



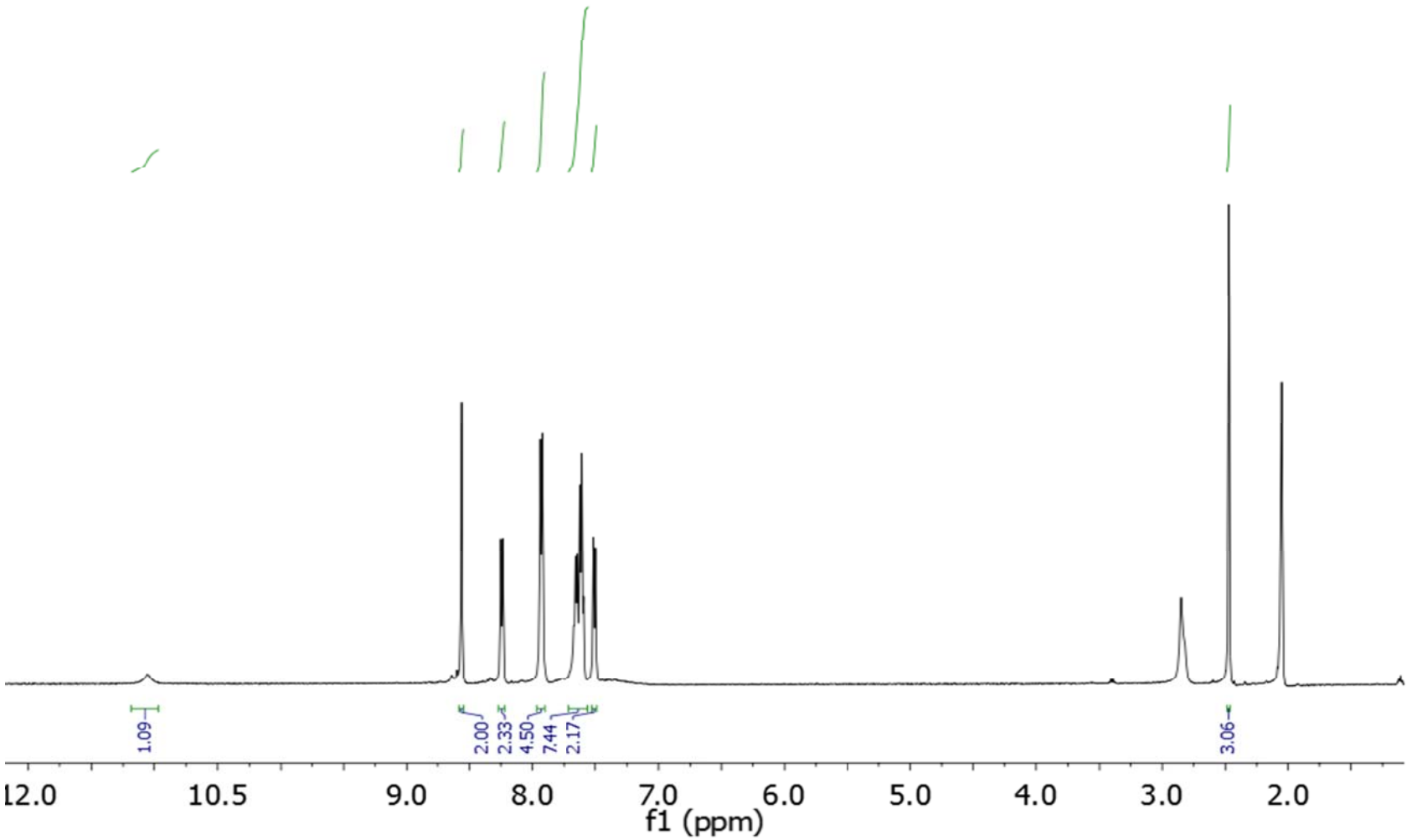
9c). ^{13}C NMR 1-octyl-2,6-diphenyl-4-(p-tolyl)pyridinium tetrafluoroborate



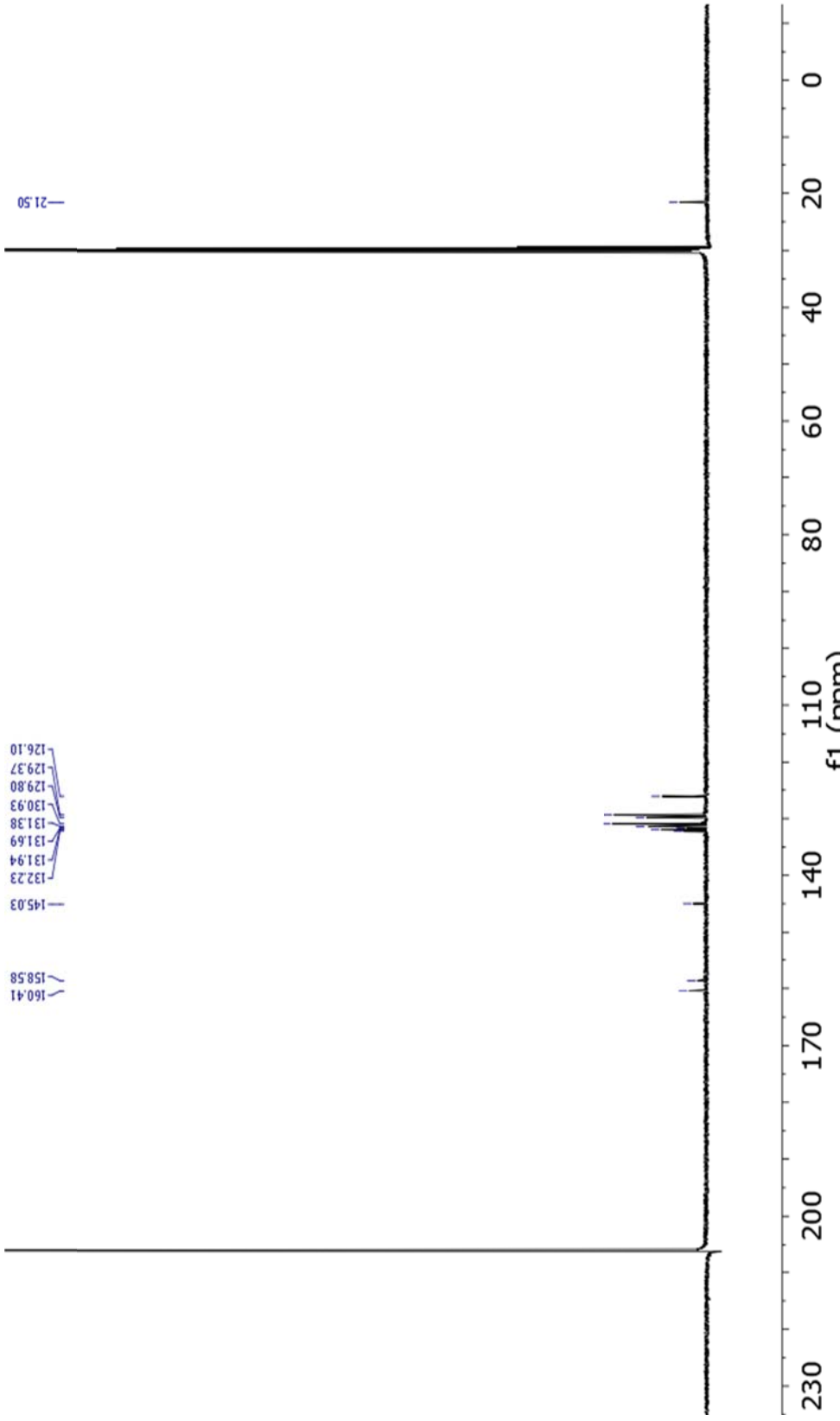
11a). ^{1}H NMR 2,4,6-trimethyl-1-thioureidopyridinium tetrafluoroborate



11a). ^{13}C NMR 2,4,6-trimethyl-1-thioureidopyridinium tetrafluoroborate



11b). ^{1}H NMR 2,6-diphenyl-1-thioureido-4-(p-tolyl)pyridinium tetrafluoroborate



11b). ^{13}C NMR 2,6-diphenyl-1-thioureido-4-(p-tolyl)pyridinium tetrafluoroborate

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