Norwegian University of Life Sciences

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The Hammick reaction – A comparison of traditional and microwave oven heating

Hammick-reaksjonen – Sammenligning av tradisjonell og mikrobølgeoppvarming

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Organic chemistry

Foreword

All of the chemical experiments were performed in the chemistry wing at the faculty of chemistry, biotechnology and food science at the Norwegian University of Life Sciences.

Firstly, a huge thanks to professor Yngve H. Stenstrøm for the excellence as my supervisor for this master thesis. You have undoubtedly made it a lot easier to keep my spirits high through the difficult times of both Covid-19 and my spinal surgery. Also, a huge thanks to co-supervisor doctor Jens M. J. Nolsøe for enchanting me into this project. Your passion for synthetical chemistry has definitely rubbed off on me.

Thank you doctor Simen Antonsen for always having the solutions to my problems, however small they would be. Thank you, senior engineer Anne Gravdahl, for the ordering of chemicals needed to complete the lab work.

The doctors and nurses that helped me through my surgery also deserve a huge thanks.

Lastly, I want to thank my family and partner for making sure I didn't procrastinate too much.

Abstract

2-picolinic acid is a simple alkaloid that is produced in the human body. The compound has sparked interest in the medical field due to its relatively cheap production and the possibility of it being a precursor to new drugs. 2-picolinic acid react readily with carbonyl groups if heated through the Hammick reaction. The Hammick reaction include a simple decarboxylation and does not require any catalyst.

The goal of this thesis was to investigate the many carbonyl containing compounds that could be reacted with 2-picolinic acid through the Hammick reaction and optimize the possibility for cascade cyclization reactions. The work-up was done as easy as possible so that as many carbonyl compounds as possible could be tested. This would also make it easy to scale up the reaction if the need should arise.

This study proved that the Hammick reaction can be done in the microwave oven, reducing the reaction time from 24 hours to around 2 hours. This is significant due to the rearrangement of the intermediate azomethine ylid to pyridine. This rearrangement is irreversible.

To be able to get cascade cyclizations the carbonyl compounds that were reacted with 2-picolinic acid had to be prepared with allyl bromide from their 2-hydroxide counterparts. This step was hampered by Covid-19. The main focus of the investigation was limited to find the optimal conditions for the addition of the carbonyl compounds targeting starting materials for total syntheses of alkaloids.

Sammendrag

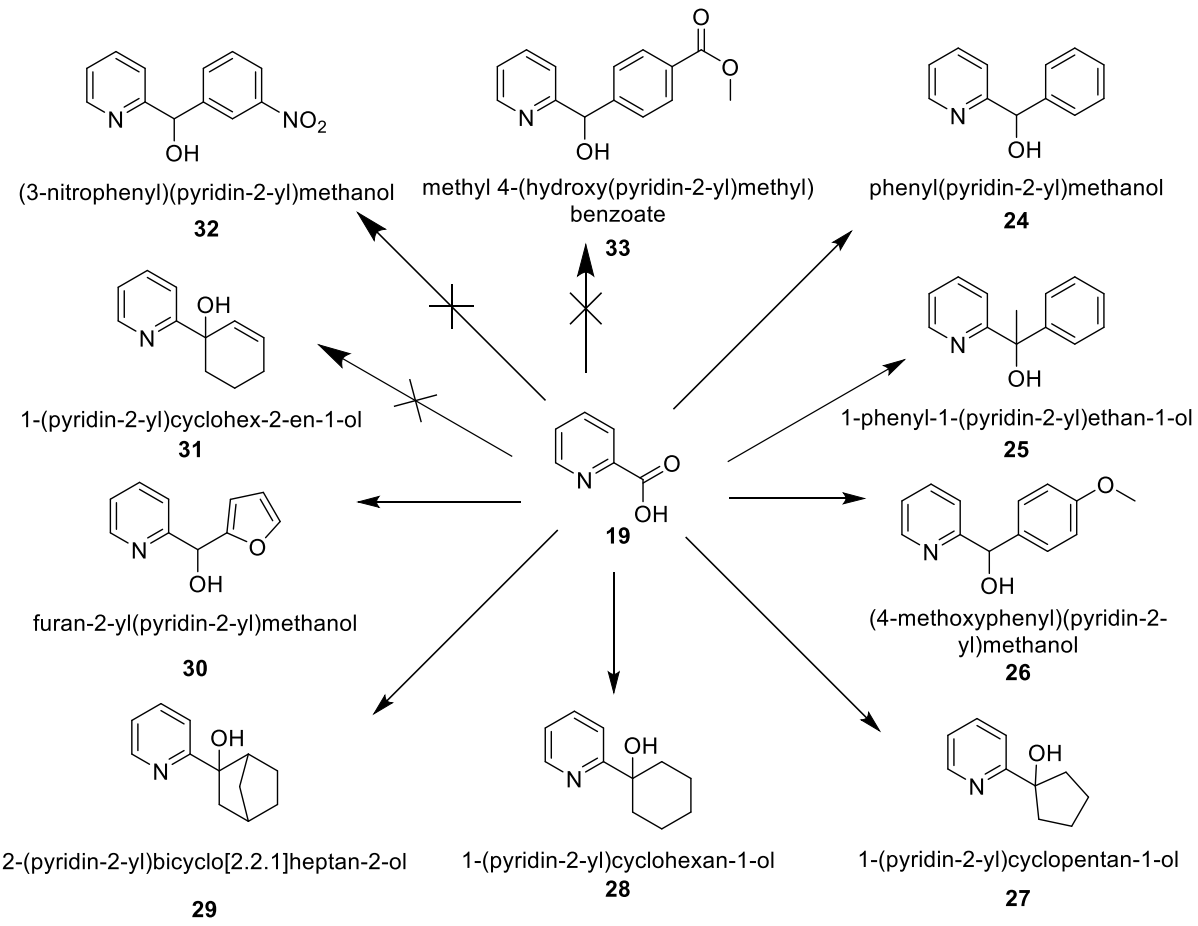
2-pikolinsyre er et enkelt alkaloid som blir produsert i menneskekroppen. Forbindelsen har vekket interesse innen medisin fordi det er relativt billig å produsere og forbindelsen er lovende som et utgangspunkt for nye medisiner. 2-pikolinsyre reagerer med karbonylgrupper ved oppvarming gjennom Hammick reaksjonen. Hammick reaksjonen inkluderer en dekarboksylering og krever ingen katalysator.

Målet med denne oppgaven var å se på flere karbonyler-forbindelser som kunne reagere med 2-pikolinsyre gjennom Hammick-reaksjonen og optimalisere muligheten for kaskadesyklisering under reaksjonen. Opparbeidelsen ble gjort så enkel som mulig slik at så mange karbonyl-forbindelser kunne bli testet som mulig. En enkel opparbeidelse gjorde det også enkelt å skalere opp reaksjonen om det skulle bli nødvendig.

Det ble bevist at Hammick reaksjonen fungerer i mikrobølgeovn, reaksjonstiden ble redusert fra 24 timer til rundt 2 timer. Dette har betydning fordi azomethinylidet omleirer til pyridin. Denne omleiringen er irreversibel.

For å få kaskadesykliseringen til å skje måtte karbonylforbindelsene som skulle reageres med 2-pikolinsyre forberedes med allylbromid fra 2-hydroxid motpartene deres. Dette ble ikke gjennomført på grunn av Covid-19. Fokuset ble derfor skiftet til å finne de best egnet karbonylforbindelsene til å gå videre med.

Graphical representation



Abbreviations

DCM	Dichloromethane
TLC	Thin Layer Chromatography

Remarks

This master thesis has been severely diminished due to Covid-19, a lab fire during covid and the author had a major spinal surgery with minor implications post-surgery.

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1. Introduction

1.1 Natural Products

Natural products are referred to as compounds that are produced by living organisms through the primary or secondary metabolism. In organic chemistry, natural products are isolated compounds from the primary or secondary metabolism and does not include carbon dioxide or water.

The primary metabolites can be found amongst a large variety of living species and do not differ much between the species, the primary metabolites are responsible for the basic functions of an organism such as growth and reproduction. They include nucleic acids, amino acids, proteins, peptides, carbohydrates, lipids and more. These compounds have the same biosynthetic pathways in organisms that are otherwise different species.[1]

Secondary metabolites are compounds found in a few or a family of organisms that have evolved to produce more specific compounds. These compounds are not involved in the functionality of the organism. However, they do play a part in how an organism interact with its surroundings. Metabolites from both primary and secondary metabolism is thought to play important roles for an organism's survival.[1] Figure 1 shows three widely known natural products and how much natural products can differ from one another.

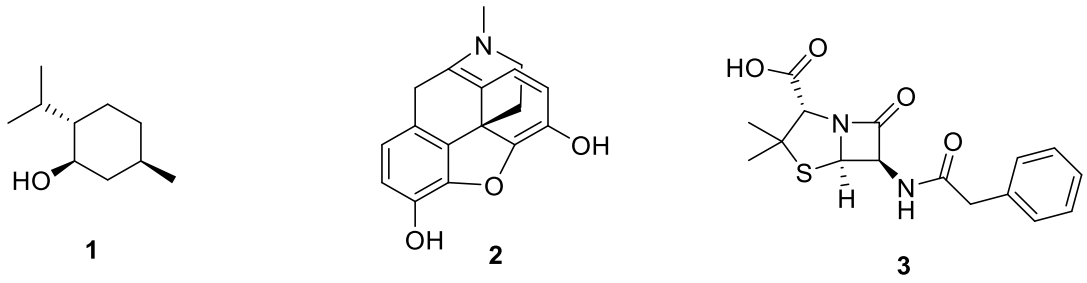


Figure 1: Menthol **(1)**, morphine **(2)**, penicillin G **(3)**

Natural products have been used as medicine for centuries, herbs and plants even longer. The earliest recorded use of exploiting plants as medicine come from the Sumerian empire 5000 years ago.[2] Half of the drugs used in modern medicine are natural products directly extracted from organisms or derivatives of them.[3] Menthol **(1)** which is a food additive that also gives a chilling effect when used in soaps, morphine **(2)** which is a painkiller drug, and penicillin G **(3)** which was the first antibiotic discovered, are all examples of natural products produced

commercially from plants mushrooms or other biological sources, menthol from *Mentha arvensis*,[4] morphine from *Papaver somniferous*,[5] and penicillin G from *Penicillium* fungi.[6]

Extracting natural products from organisms may not always be the ideal way of supplying this to the market. Direct extraction may produce small amounts, purification may be difficult or the organism in question is a protected species.[7] In these cases, the only viable solution is to synthesise them. Producing natural products synthetically makes it possible to tweak the end product to increase its impact and efficacy. An example being penicillin. Over time bacteria evolved resistances to penicillin G **(3)**. Tweaks had to be made to keep the antibacterial properties of penicillin G. Amoxicillin **(4)** and dicloxacillin **(5)** are examples of such changes.[6, 8]

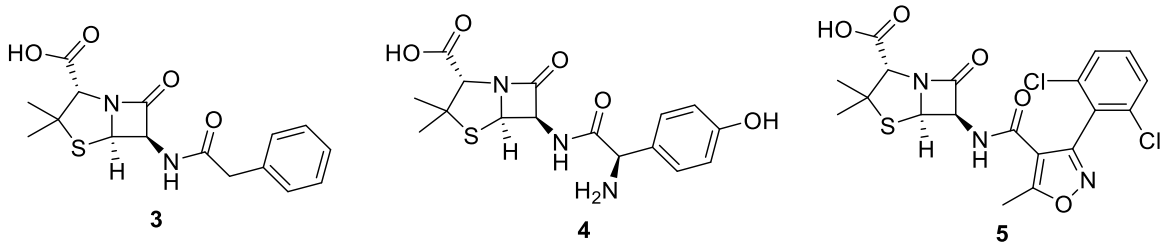


Figure 2: Penicillin G **(3)**, amoxicillin **(4)** and dicloxacillin **(5)**

1.2 Alkaloids

Alkaloids are a sub-class of natural products with large structural variations. Both **(2)** and **(3)** belong to the alkaloid subgroup. Alkaloids are organic compounds usually produced and found in plants. Alkaloids contain at least one, often multiple, nitrogen atoms and often have a physiological effect on humans. These nitrogen atoms are usually found as primary, secondary, or tertiary amines, or they are part of aromatic moiety. The polarity, and to some extent the alkalinity, of amines makes them largely water soluble, but this also depends on the size of the lipophilic part of the amine. The alkalinity also makes amines very well suited for acid base extraction. The degree of alkalinity depends on the skeletal structure around the nitrogen atom as well as the presence of other functional groups.[9] One of the most common alkaloid group encountered from plants is the aromatic alkaloids.

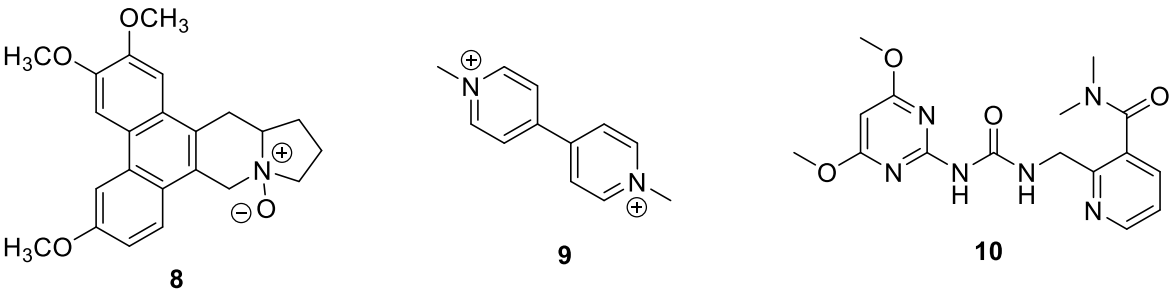
1.2.1 Aromatic heterorings and dipoles

Heterorings are special in the sense that their chemical properties are enhanced compared to their normal ring counterparts. A basic example is benzene *vs.* pyridine. Benzene is completely non-polar and a perfect hexagonal shape allowing for a shared π-orbital between all 6 π-electrons. This increases benzenes stability compared to normal conjugated systems. Introducing a heteroatom to this system skews both the ring structure and the electron density due to the different electronegativity caused by the heteroatom.

6 **7**

Figure 3: Benzene **(6)** and pyridine **(7)** with charges being partial charges

In figure 3 benzene **(6)** and pyridine **(7)** are shown with the charges on pyridine being partial charges to show how the nitrogen affect the electron distribution in the ring.[10] Pyridine derivatives are widely used in several fields of chemistry. Medicine and pest control are two common ones, due to many of its derivatives are compounds that are biologically active.[11] Figure 4 shows some of the most common pesticides based on pyridine, Antofine N-oxide **(8)** a widely used insecticide , paraquat **(9)** is a general herbicide, and nicosulfuron **(10)** which is mostly used to control weeds in corn fields due to its selectivity, but still wide range effectiveness.



8 **9** **10**

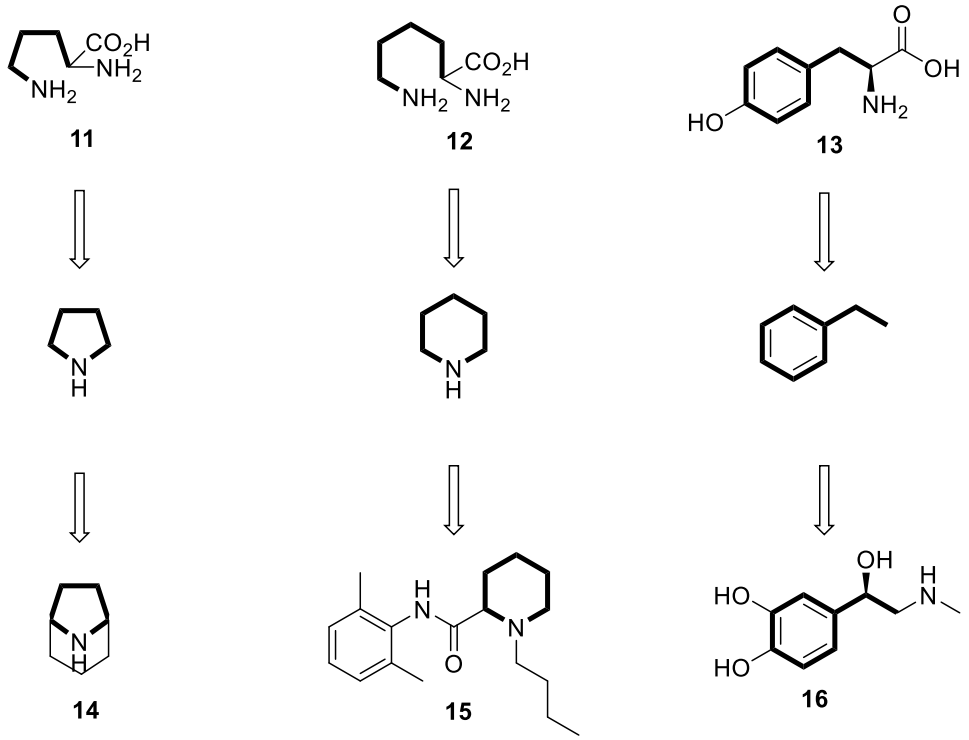
Figure 4: Antofine N-oxide **(8)**, paraquat **(9)**, and nicosulfuron **(10)**

These pesticides also have a benzene counterpart that can also be used as pesticides, but they have a higher toxicity and a lower bioactivity which then results in a much lower selectivity

than their pyridine counterparts. The hydrophilicity of the pesticides also contributes a large amount to their bioactivity.[12]

Nicosulfuron **(10)** also contains a pyrimidine ring which has very similar chemical properties to pyridine. Pyrimidine rings have the same electron structure as pyridine, but with two nitrogen atoms in the ring each contributing an electron pair to the π- system. The added electron pair in the plane will make pyrimidine more basic than pyridine, which could influence the work up of pyrimidine products.[10]

Biosynthetically most of these alkaloids have their origin from an amino acid.[13] The classification of alkaloids was first based on the structure that contained the nitrogen atom. However, over time, the structural complexity of some alkaloids made it increasingly difficult to classify alkaloids this way. The nitrogen atom in alkaloids usually come from amino acids. It was found that the carbon structure of the precursor amino acid was mostly passed on to its alkaloid. This made an easy method of alkaloid classification using the precursor amino acid as basis.[9]



Scheme 1: Core structures of different alkaloid classifications. L-Ornithine **(11)**, L-lysine **(12)**, L-tyrosine **(13)**.

The first alkaloid to be isolated was morphine **(2)**. Morphine has strong analgesic properties.[5] Other alkaloids such as epinephrine **(16)** is a human hormone.

Alkaloids also show great potential as building blocks for new antibacterials. The quinolone alkaloid ciprofloxacin **(17)** is antibacterial. Squalamine **(18)** is a polyamine that increases effectiveness of **17**.[14] These are just a few examples of the pharmacological properties of alkaloids.

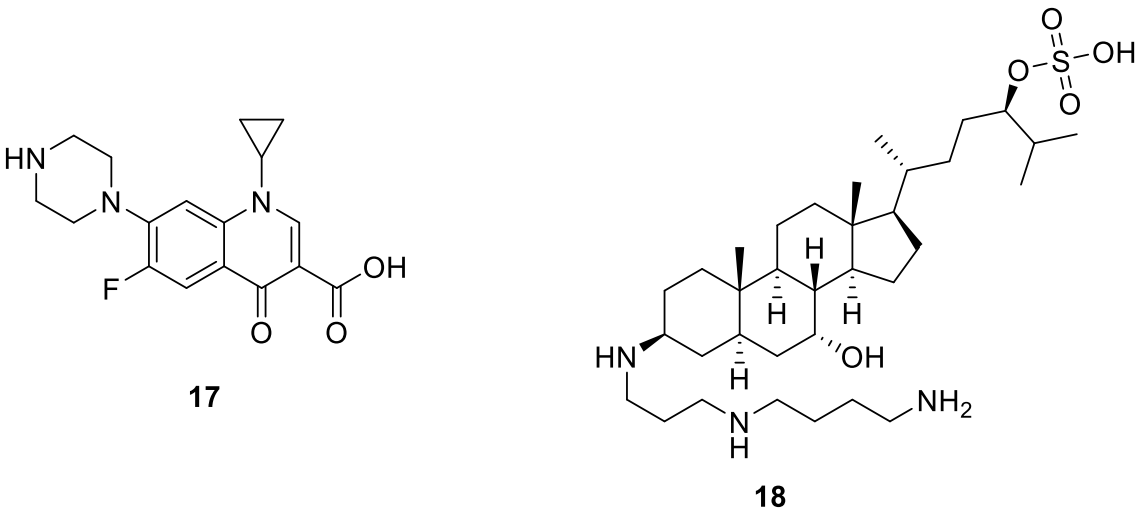


Figure 5: Chemical structure of ciprofloxacin **(17)** and squalamine **(18)**.

1.2.2 Picolinic Acid

Picolinic acid **(19)** is a small aromatic alkaloid built up of a pyridine ring with a carboxylic acid in the 2-position. It is an isomer of nicotinic acid **(20)**, and both are biochemically produced in mammals from L-tryptophan.

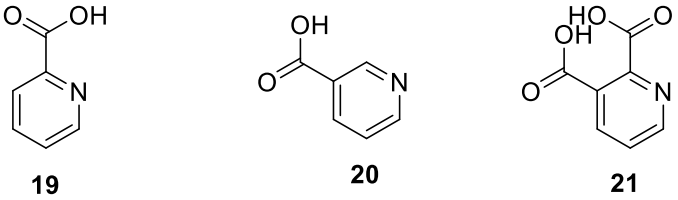
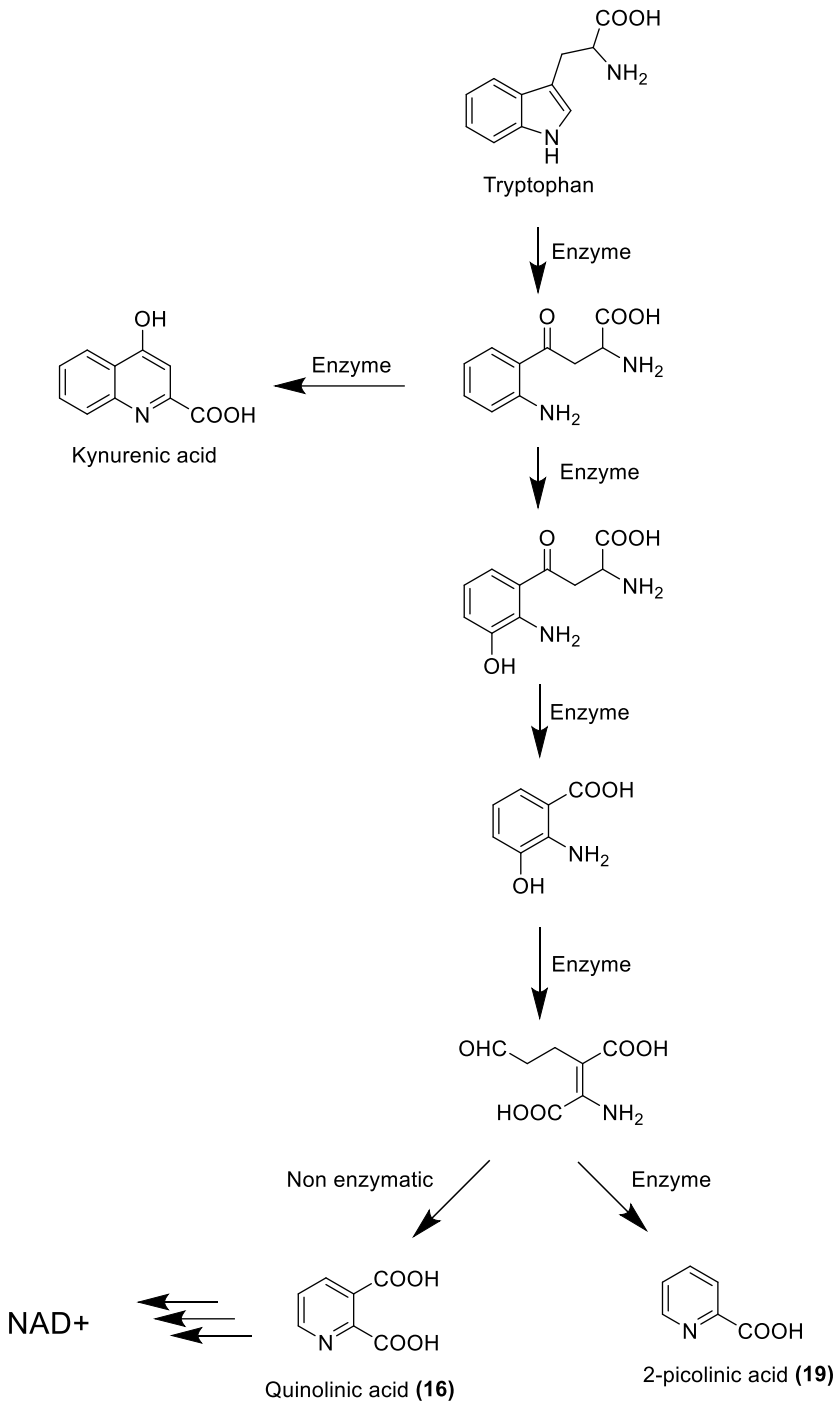


Figure 6: Picolinic acid **(19)**, nicotinic acid **(20)** and quinolinic acid **(21)**.

Picolinic acid **(19)** is a metabolite from the Kynurenine pathway (KP) in mammals (Scheme 2). The KP has been shown to be important in the development of neurogenic diseases like Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS).[15] Picolinic acid is produced from the KP and has shown anti-toxic effects towards the neurotoxicity of Quinolinic acid **(21)**, another metabolite of the KP, but this is in small doses.[16]



Scheme 2: The Kynurenine pathway

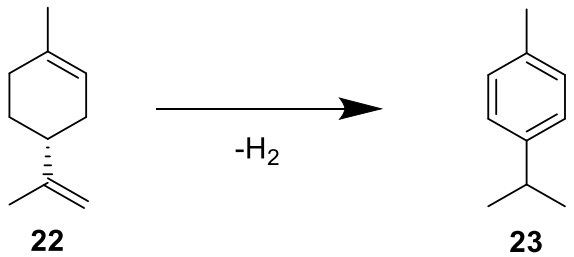
Picolinic acid seems to be very specific in its anti-toxic reactions.[16, 17] Modifications to picolinic acid might lead to other compounds with pharmacological importance.

1.3 Background

The study of pharmacological important compounds is largely a study on active natural products. The decarboxylation at the 2-position in picolinic acid was shown possible by P. Dyson and D. Ll. Hammick in 1937.[18] Using quinolinic acid **(21)** boiled together with a compound containing a carbonyl group, (benzaldehyde, acetophenone, etc.) carbon dioxide formed, and the carbonyl containing compound would then capture the decarboxylated quinoline-2-ide **(19a)**. This reaction has later been known as the Hammick reaction (Scheme 4).

Later studies have shown how the decarboxylation of 2-picolinic acid forms its pyridine ylid, the azomethine ylid (Scheme 3).[19, 20] Azomethine ylides favour 1,3-dipole cycloaddition reaction. However, in pyridine, the azomethine ylid is imbedded in the aromatic ring. The extra stability of 2-picolinic acids azomethine ylide comes from the aromatic ring. This stability makes it possible for them to undergo condensation reactions with molecules containing a carbonyl group.[21] 2-picolinic acid being the molecule of interest in this thesis.

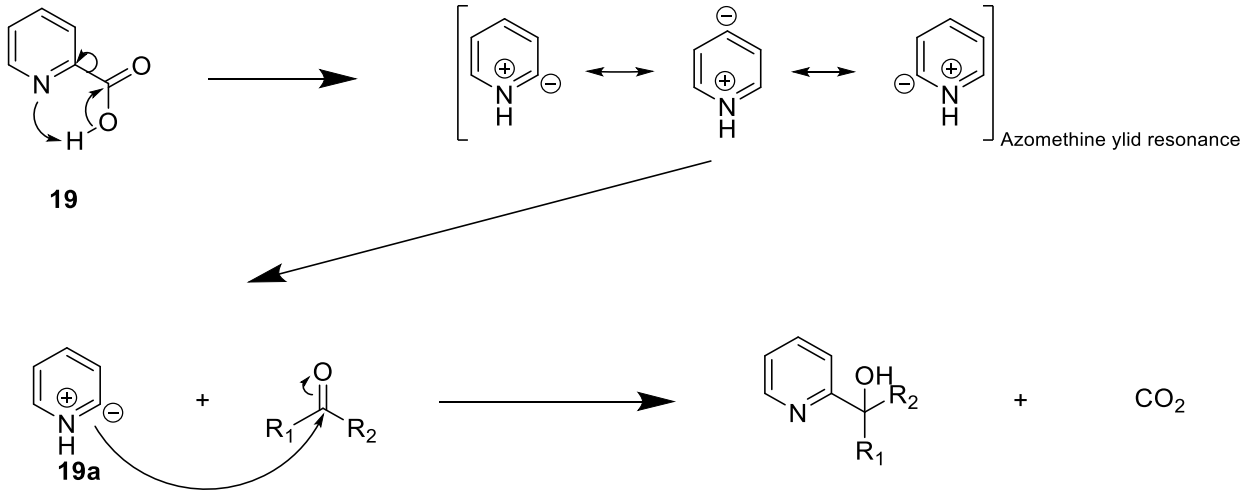
Investigations into improvements of the Hammick reaction has later shown that different solvents, primarily p-cymene, give increased yields.[22] p-Cymene **(23)** is a green sustainable solvent made from the monoterpene limonene, which is derived from orange peel. Limonene **(22)** is used in various degreasing products to absorb lipids, already being a good solvent. Turned into p-cymene **(23)** by dehydrogenation makes it an even more effective solvent due its low hydrogen bond acceptance, slightly higher polarity than that of limonene **(22)**, and there is no longer a terminal double bond that can interfere with the reagents.[23]



Scheme 3: Limonene **(22)** and p-cymene **(23)**

1.4 The Hammick Reaction

In general, the Hammick reaction is a decarboxylation reaction using carbonyl compounds shown in scheme 4.



Scheme 4: Complete Hammick reaction with a carbonyl

This decarboxylation works due to the azomethinylid intermediate, scheme 4, where the lone pair on the nitrogen atom stabilizes the charge by taking up a hydrogen atom. Carboxylic acids do not readily release carbon dioxide in the presence of other carbonyls. The nitrogen atom in picolinic acid stabilizes the azomethinylid by holding the positive charge so that further reaction becomes possible. This is due to the electronegativity of nitrogen. Further stability is being caused by the aromaticity of the azomethinylid. As illustrated in scheme 4. Electron donating substituents on the carbon atoms also have an effect on the stability of the azomethinylid. Positions 3, 4, and 5 give the best stability, but electron donating groups substituted on any of the carbon atoms seem to increase the stability of the azomethine ylid by some degree.[20, 24]

The stability of the azomethine intermediate seem to be the limiting factor. With yields reported of up to around 70% if the carboxylic acid is silylated, however, with considerably extended reaction times.[25] The problem with long reaction times is that the azomethine ylid rearranges to pyridine very quickly, reducing yields considerably.[26] Reducing the reaction time is the best and easiest way to increase yields by not allowing for much hydrogen rearrangement in the azomethine ylid.

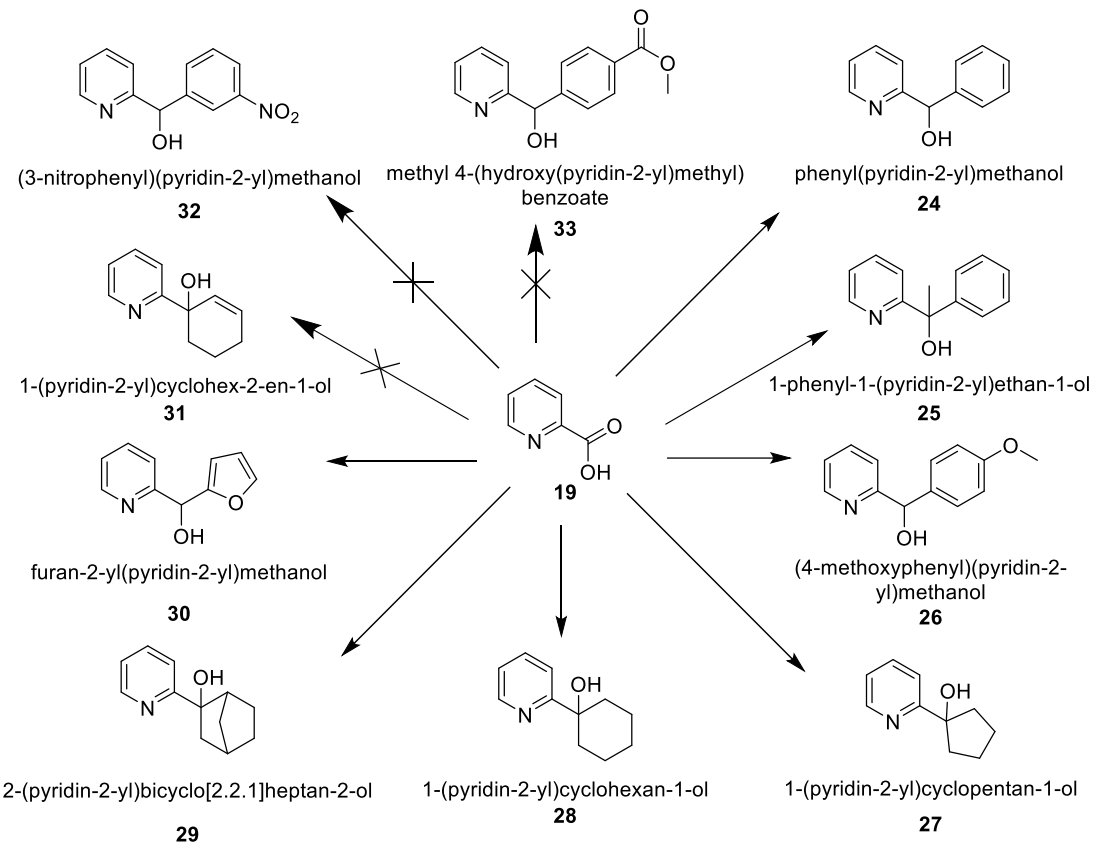
1.5 Microwave Reactions

The application of microwave irradiation for use in organic chemistry started in the early 1980s. In 1986 it was discovered that the rate of reactions could be notably increased by the use of microwave ovens. This increase in reaction rate has been credited to the different temperature regime cause by electromagnetic waves.[27] Heating by microwave irradiation is much faster, and much cheaper than conventional heating methods like oil baths. It provides uniform heating since the heat originates from the friction created by the solvent molecules. Neither the container walls nor the apparatus is heated by the microwaves. This drives the energy consumption down and thus costs as well.[28]

Microwave irradiation directly heats the reactants given that they are polar to a degree, meaning that the amount of solvent needed for a successful reaction is decreased or even removed. Microwave reactions reach the desired temperature much faster than for example an oil bath reducing reaction time.[28, 29] The rapid increase in temperature, and thus decreased reaction time, is due to the incredibly fast electromagnetic periods produced by the microwave. The microwave will transfer energy to the reaction mixture once every 10^{-9} second. The molecules cannot adapt to the change in energy fast enough causing friction. Thus, the molecules reach the required collision energy needed for a reaction to take place much faster.[30] The faster reaction time would decrease the amount of azomethine ylide that degrades to pyridine which would probably increase the yields since the azomethine ylide would be present for longer. The energy transfer is much more intense and direct than conventional heating from an oil bath, where the heat is first transferred to the container, then to the solvent, then to the reactants. In the microwave the heat is immediately applied to the reactants and there is no gradual build up for the reactants to "adapt" to. This can cause an increase of biproducts from the reactions performed in the microwave due to cleavage of bonds that would otherwise not have been broken from conventional heating methods.

1.5 Aim of study

The aim of this thesis was to make a library of pyridine derivatives by exploiting the Hammick reaction. The goal was to improve the Hammick reactions and optimize the possibility of cascade cyclisation reactions on the pyridine derivatives made from **19** while keeping the work-up as simple as possible. These more complex products may be utilized for the synthesis of compounds of pharmacological importance.

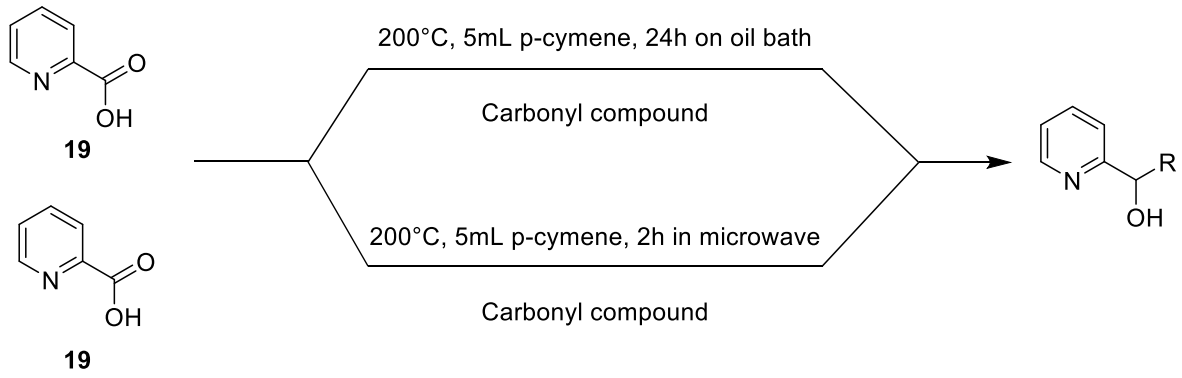


Scheme 5: Final library of pyridine derivatives

2. Results and Discussion

2.1 The procedures

Two procedures were utilized in this study. For all reactions completed during this investigation the set-up were exactly the same as exemplified in scheme 6:

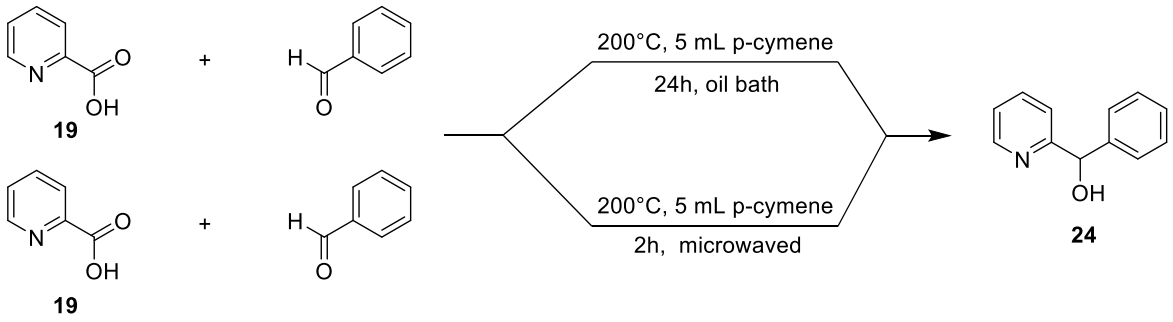


Scheme 6: The two procedures used during the investigation

The library of pyridine derivatives was made utilizing one of the two procedures in scheme 11. This was mainly done for simplicity's sake but also for consistency. Most of the reactions was done in a microwave oven. Since the reactants used in this investigation was both polar, especially 2-picolinic acid **19**, the reaction time could be significantly reduced.[28, 29] First 1 hour was tested, but it was found that 2 hours was optimal. The plan was to put all reaction in the microwave oven, but it kept exploding the reaction vials. This was most likely due to the focusing laser being knocked out of place by a previous explosion.

2.1.1 Synthesis of phenyl(pyridin-2-yl)methanol **24**

For comparison synthesis of **24** was done using both procedures. The same amount of 2-picolinic acid and benzaldehyde was used for both the oil bath reaction and the microwave reaction.

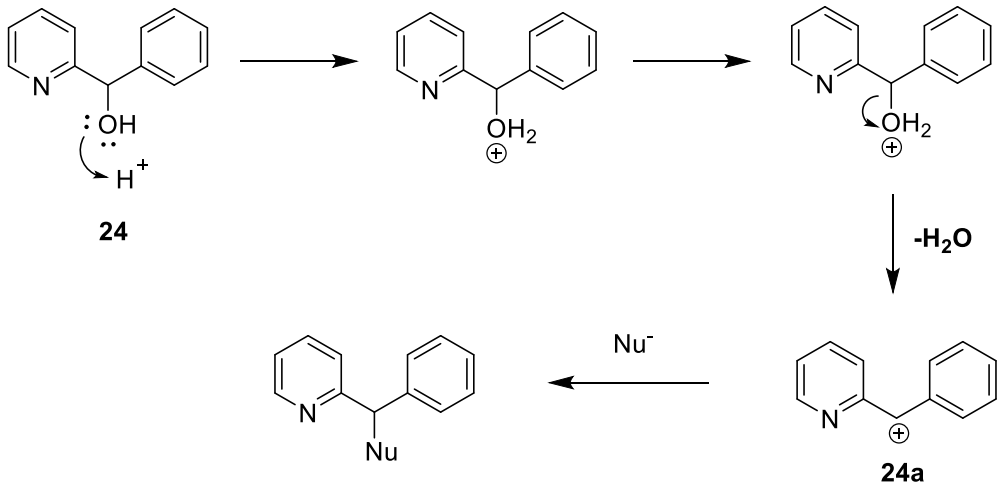


Scheme 7: Reaction of 2-picolinic acid and benzaldehyde

The oil bath reaction gave a poor yield of only 13%. This is most likely due to not adding sufficient base in the work-up and thus not moving as much as possible of the product into the organic phase.

The microwave reaction went better than the oil bath reaction. However, after the complete work-up there was some impurity present. The yield ended up at 75% but this might be an inflated number. Looking at the NMR data it is clear that **24** has been successfully made using both the oil bath reaction and the microwave reaction. The hydroxyl peak at 5.3 ppm, the carbinol hydrogen at 5.7 ppm, the double triplet at 7.6 ppm and the carbinol peak at 75.0 ppm are all peaks that confirm product **24**. In the mass spectrum of both products the higher m/z is 184. This is consistent with the molecular ion at 185 losing the mass of one *i.e.* a

hydrogen. Moreover, a loss of 17 *i.e.* an OH group is giving an m/z at 168, also consistent with the depicted structure **24**. The oil bath reaction seems to be the purest one of the two albeit with a very low yield. It is possible that the hydroxyl group got protonated during the reaction and thus led to unwanted products (scheme 8). However, none of these products was identified. If a reaction took place, it is likely that the possible product got washed out during the workup.

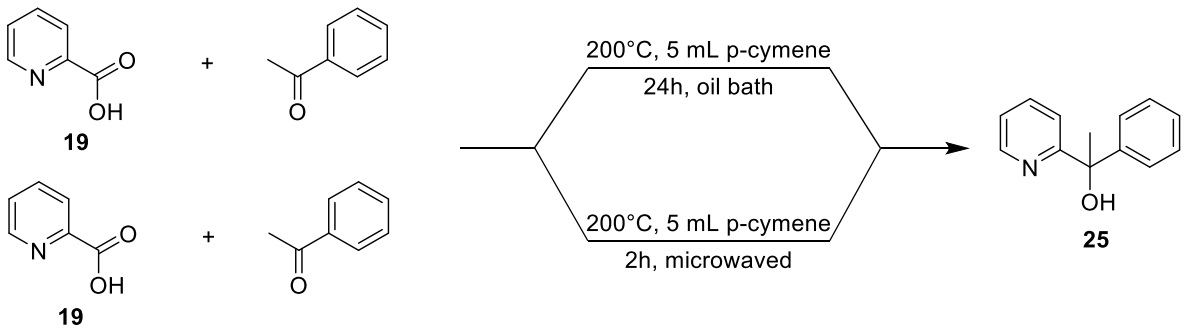


Scheme 8: Possible cleavage of the hydroxyl group

Intermediate **24a** would easily react with other potential products formed during the reaction and moved over to the final organic phase with the product **24**. It would also increase the intensity of all the peaks in the ^{1}H NMR spectra except for the hydroxyl one that would be diminished relatively to the others. Other reactions might also have occurred with **24a** that would otherwise not occur without protonation of the hydroxyl group.

2.1.2 Synthesis of 1-phenyl-1-(pyridin-2-yl)ethan-1-ol **25**

Synthesis of **25** was done using both procedures. The same amount of 2-picolinic acid and acetophenone was used in both the oil bath reaction and the microwave reaction.

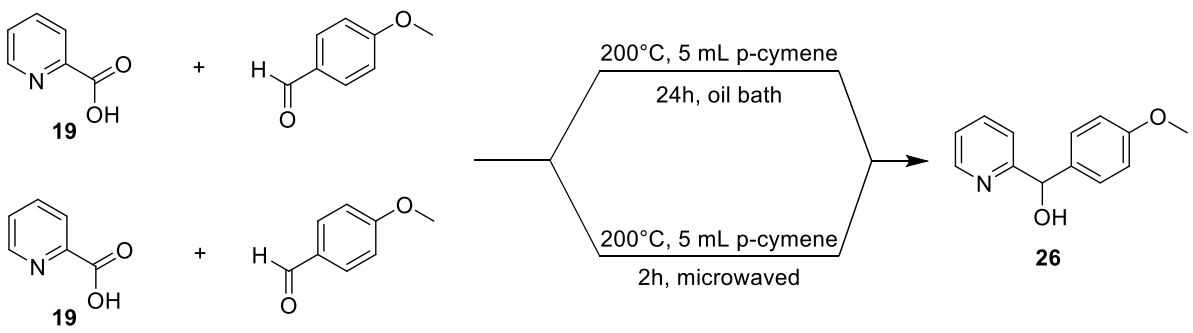


Scheme 9: Reaction of 2-picolinic acid and acetophenone

The same mistake occurred with the oil bath reaction for **25** as for **24**. Not enough base was added to move the product over in the organic phase. The reactions were done simultaneously which is why the same mistake was done for both the reactions. The yield was only 6%. The microwave reaction went much better, with a yield of 52% and close to no impurities. The hydroxide peak at 5.9 ppm, the double triplet at 7.6 ppm and the carbinol at 75.1 ppm confirms that the product was formed in both reactions. The molecular ion is present in the mass spectrum for both reactions at m/z 199 further confirming **25**. Furthermore, a loss of m/z 15 gives the 100% peak at m/z

2.1.3 Synthesis of (4-methoxyphenyl)(pyridin-2-yl)methanol 26

Synthesis of **26** was done using both procedures. The same amount of 2-picolinic acid and p-anisaldehyde was used in both the oil bath reaction and the microwave reaction.

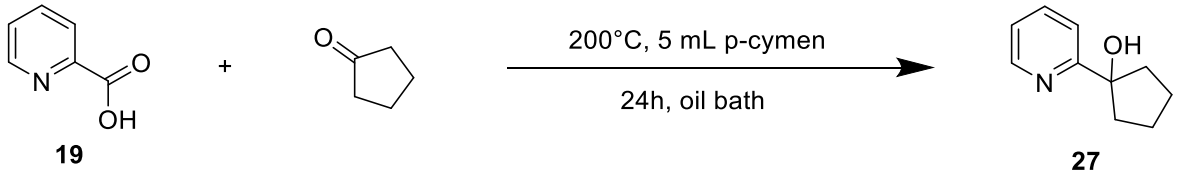


Scheme 10: Reaction of 2-picolinic acid and p-anisaldehyde

For the synthesis of **26** the oil bath reaction gave the best results with the least impurities and a yield of 37%. It seems the microwave reaction had similar problems as the microwave reaction of **24**. The microwave reaction of **26** was done twice and both reactions gave very large yields of 120% and 119% respectively, which of course is impossible. This could be due to other products forming during the reaction. It is unclear whether the unwanted products are being formed during the reaction or the work-up but given the high yields its most likely from the work-up. However, it could also be due to improper removal of the solvent. There is no data that proves or disproves any of these statements. Product **26** was formed in both reactions as the hydroxyl peak at 5.2 ppm, the double triplet at 7.6 ppm is both present, as well as the carbinol hydrogen at 5.7 ppm. The ^{13}C NMR carbinol peak at 74.5 is also present. The molecular ion at 215 m/z is present in both mass spectra and confirms that the reactions was successful.

2.1.4 Synthesis of 1-(pyridin-2-yl)cyclopentan-1-ol **27**

Synthesis of **27** was only done using an oil bath.

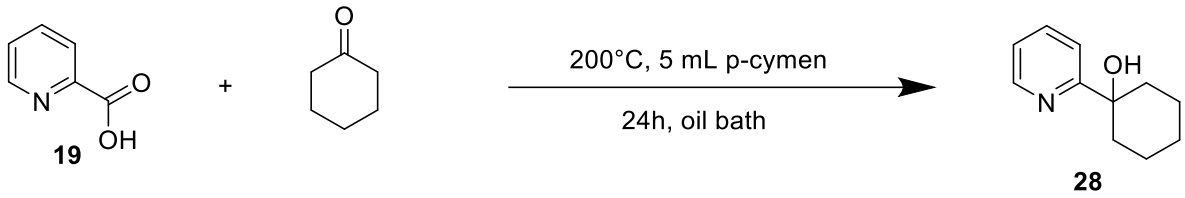


Scheme 11: Reaction of 2-picolinic acid and cyclopentanone

The synthesis of **27** gave good results with a yield of 31% and close to no impurities. This reaction should be done in a microwave. The yield would probably be increased up to that of the microwave reaction of **25**. Both the hydroxyl hydrogen at 5.0 ppm and the double triplet at 7.7 ppm are present, the carbinol carbon at 82.6 ppm is also present, indicating that the product has been formed. The mass spectrum show a peak at m/z 162 which is the molecular ion minus m/z 1 i.e. the loss of one hydrogen, confirming **27**.

2.1.5 Synthesis of 1-(pyridin-2-yl)cyclohexan-1-ol **28**.

Synthesis of **28** was only done using an oil bath.

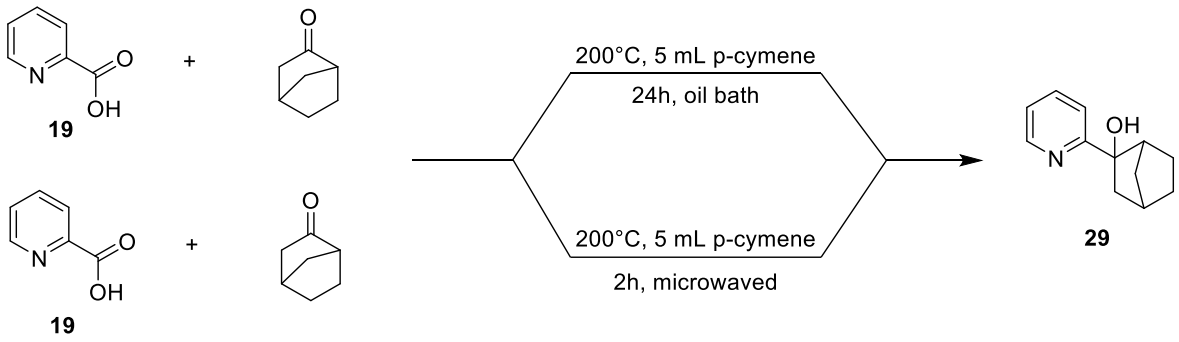


Scheme 12: Reaction of 2-picolinic acid and cyclohexanone

The synthesis of **28** gave a yield of 35% which is similar to that of **27**. Doing this reaction in a microwave would likely increase the yield as well. There was a bit more impurities than that of **27** but looking at the NMR data they seem miniscule compared to the product. The hydroxyl peak and the double triplet are both present in the ^{1}H NMR spectrum at 4.9 and 7.7 ppm respectively, as well as the carbinol carbon at 72.7 ppm, confirming the product. The peak at m/z 177 is the molecular ion and a peak at 160 revealing a loss of m/z 17 (*i.e.* an OH group), confirms a successful reaction.

2.1.6 Synthesis of 2-(pyridin-2-yl)bicyclo[2.2.1]heptan-2-ol **29**

Synthesis of **29** was done using both procedures. The same amount of 2-picolinic acid and norcamphor was used in both the oil bath reaction and the microwave reaction.

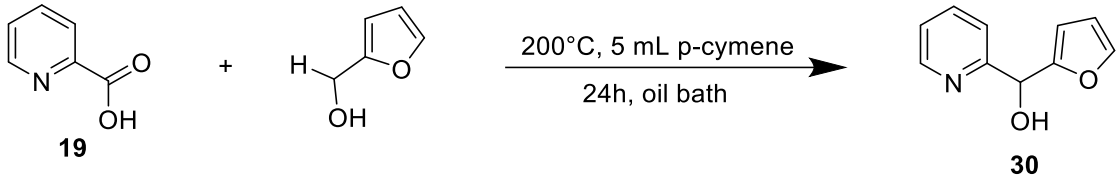


Scheme 13: Reaction of 2-picolinic acid and norcamphor

Both these reactions gave very poor results. The yield of the oil bath reaction was as low as 4%. The microwave reaction gave no results at all. The latter is probably due to the microwave breaking down right after this reaction was finished. The hydroxyl hydrogen at 4.6 ppm and the double triplet hydrogen at 7.7 ppm are both present as well as the carbinol carbon at 80.4 ppm. The intensities are quite low as expected from the low yields.

2.1.7 Synthesis of furan-2-yl(pyridin-2-yl)methanol 30

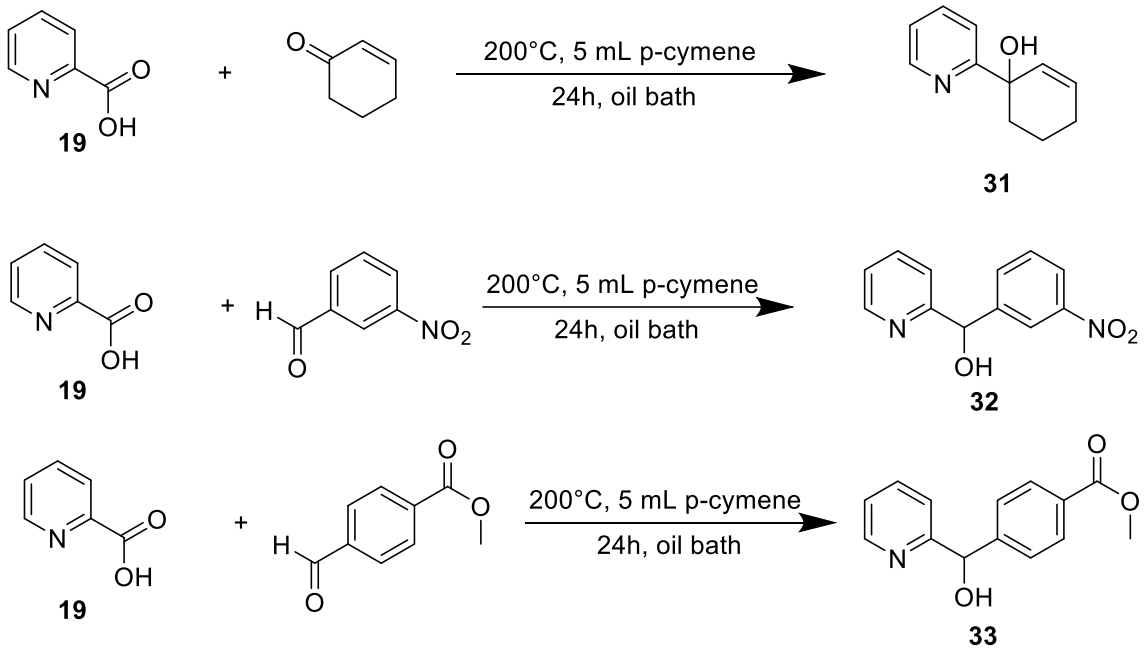
Synthesis of **30** was only done in oil bath before the possibility of microwave reaction took place. The reaction would be done in a microwave oven if it did not break.



Scheme 14: Reaction of 2-picolinic acid and furfural

The synthesis of **30** went well in the sense that the NMR data revealed it as successful. However, it also shows a lot of pyridine and possibly some 1,2-dihydropyridine. The yield after work-up was 43% but some of this is definitely from one or both of the pyridine products mentioned above. The hydroxyl hydrogen and the carbinol hydrogen at 5.1 and 5.7 ppm respectively are both present. The carbinol carbon, however, is not present and should be around 80 ppm.

2.1.8 Reactions that gave no products



Scheme 15: Reactions of 2-picolinic acid and cyclohexen-1-one, 3-nitrobenzaldehyde, and Methyl 4-formylbenzoate respectively.

The azomethine ylide is a hard nucleophile and reacts best with a hard electrophile. All of the reactants shown in scheme 20 have their electrophilic tendencies reduced by other functional groups in the molecule. This makes them softer electrophiles, and this is expected to decrease their usefulness in the reaction with the azomethine ylide. If electron withdrawing substituents is placed on 2-picolinic acid to reduce the nucleophilic tendencies of the azomethine ylid, these reactions might give better results.

2.2 Overall discussion

Generally, all of these reactions are time sensitive due to the degradation of the azomethine ylid to pyridine. Decreasing the reaction time by utilizing another form of heating yielded good results. The reactions in the microwave gave higher yields but some reactions seem to be sensitive to the irradiation effect from the microwave. Electromagnetic waves are the source of the heating, and they affect both the electronic and magnetic properties of the molecules. The irradiation effect should increase with increased polarization of the reactants so why the reactions of 2-picolinic acid and norcamphor gave such poor results is unclear (scheme 18). The reaction of 2-picolinic acid and p-anisaldehyde did also decompose much easier in the microwave than in the oil bath (scheme 15). Wherever necessary the final products should have been cleaned using column chromatography, but for medical reasons it was not possible to perform the column chromatography in its entirety. Cleaning up products **24** and **26** would most likely show a yield similar to that of product **25**.

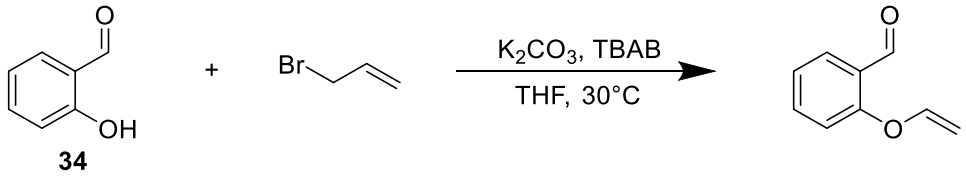
Due to time restrictions the reaction time and temperature for all reactions was set using only the reaction of 2-picolinic acid and acetophenone. This should of course be done individually for each reaction to obtain optimal results and would most likely increase the purity and yields of the other reactions as well.

When comparing reactions done in an oil bath to those done in the microwave oven, it is clear that the reactions done in the microwave oven yield significantly better results. The decreased reaction time alone is a significant improvement. Given that all yields improved to some extent as well suggests that the future of this investigation should be done solely by microwave reactions. The reaction parameters should be more thoroughly investigated for each reaction to find the optimal temperature and reaction time.

3. Further Research

One of the goals in this investigation was to find ways to increase the possibility of cascade cyclization's during the Hammick reaction. To do this it was necessary to first establish which carbonyls would perform the best in the Hammick reaction. The products **24**, **25**, **27**, and **28** gave by far the best results based on yield and purity. There is no reason to believe that products **27** and **28** would not also give increased yields in a microwave reaction. The NMR data for **26** shows that the desired product is formed. With better reaction conditions and a cleanup with column chromatography, **26** would probably also be a good choice for further investigation.

The next step would be to create an allyl group on the reacting carbonyl group. J. Pandet *et al.*[31] tested an efficient route for allylation using phenols and allyl bromide. Other reactants worked as well, producing very good yields of up to 90%. The reaction is shown modified to fit this investigation in scheme 21.



Scheme 16: Allylation of salicylaldehyde

Salicylaldehyde **(34)**, 2-hydroxyacetophenone **(35)**, and 2-hydroxy-4-methoxybenzaldehyde **(34)** are all available at Sigma-Aldrich at reasonable prices. Hydroxy versions of **27** and **28** would have to be made. The reaction would be the same with reactant **35** or **36**

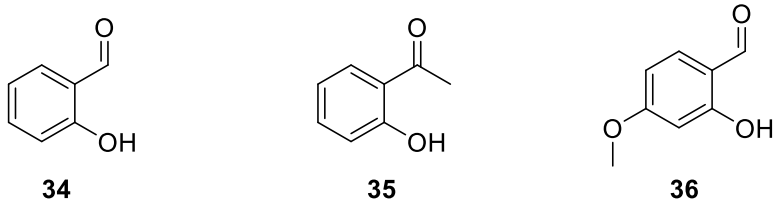
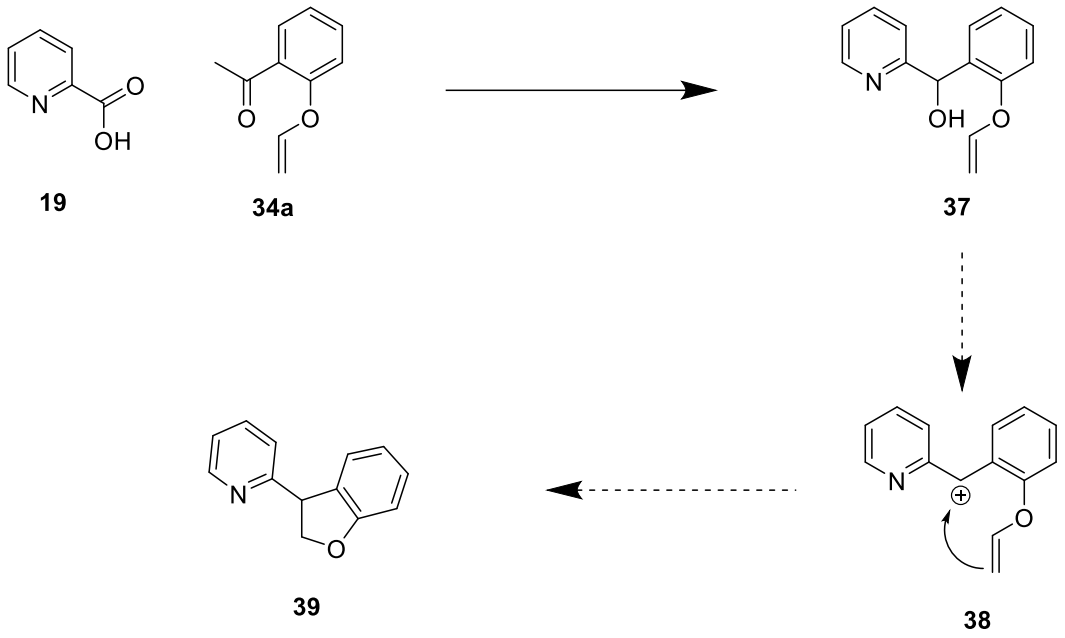


Figure 7: Salicylaldehyde **34**, 2-hydroxyacetophenone **35**, and 2-hydroxy-4-methoxybenzaldehyde **36**

By adding the allyl on the hydroxy group its possibly for the double bond to react in on the secondary or tertiary hydroxyl group in the Hammick product. The carbocation is substantially stabilized by its adjacent groups further increasing the possibility of a cascade

cyclisation. The complete reaction route is shown in scheme 23 using the allyl version of **34 (34a)** as an example but would be completed with as many allyl versions as possible.



Scheme 17: Complete reaction pathway

It is possible that a weak acidic buffer would speed up the reaction by facilitating the cleavage of the hydroxyl group. If the buffer is needed it should not be added until the last minute to make sure all reactants have formed intermediate **38**.

This cyclisation might be more challenging to produce with **27** and **28** due to the steric hindrance of the rings. However, the allylation reaction can be tested directly on the hydroxyl group from the Hammick derivative. This can then facilitate further reactions.

My colleague master student, Daniel Lundebrekke, tried to make a fluorenone from his Hammick reactions without luck, using the method described by H. Li *et al.*[32] They only used benzophenone derivatives in their investigation. Most of the Hammick derivatives are similar to benzophenone derivatives. Especially if the hydroxyl group is oxidized to a ketone. The method described by H. Li *et al.* might work on **24**, **25**, **26**, and possibly **30**, however the oxygen in the furfural ring might affect the reaction.

4. Experimental

4.1 General method

All the reactions were carried using the same procedure, no modifications were made between them. The same equipment was used for all reactions.

General reaction:

A mixture of 0.1 mmol of 2-picolinic acid and 0.2 mmol (or 2 mL if the reactant was a liquid) of a carbonyl compound was weighed out in a Biotage microwave glass vial. To this 5 mL p-cymene and a magnetic stirrer was added, and the vial was sealed with septa caps from Biotage.

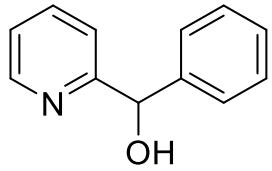
4.1.1 The oil bath reactions

The oil bath was preheated to 200°C and the vial was submerged until all of the reaction mixture was covered by the oil bath. All the oil bath reactions were left for 24 hours. The only problem that would arise with the oil bath reactions was that some of the reactants would evaporate and solidify in the top of the vial. The only way to work around this was to have a deeper oil bath to have the vials submerged further into the oil bath. The oil bath and the reaction vial could also have been covered with aluminium foil to retain the heat better, but this was done during this investigation.

4.1.2 The microwave reactions

A Biotage Initiator+ microwave was used for all microwave reactions. The temperature was set to 200°C and was heated with 400W. The time was set to 2h. The timer would not start until the reaction mixture reached the desired temperature. The focusing laser that delivers the microwaves into the reaction vial got knocked out of place during this investigation. This could not be fixed in time for this investigation which is why only some of the reactions was completed in the microwave oven.

4.2 Procedure for product 24



Oil bath:

0.123g of 2-picolinic acid was reacted with 2mL of benzaldehyde in 5mL p-cymene for 24h at 200°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, 1H, *J = 4.28 Hz*), 7.55 (dt, 1H, *J = 1.64, 7.72 Hz*), 7.42 – 7.17 (m, 7H), 5.78 (s, 1H), 5.33 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.87 (1C), 147.83 (1C), 143.23 (1C), 136.85 (1C), 128.59 (2C), 127.85 (1C), 127.08 (2C), 122.44 (1C), 121.38 (1C), 74.99 (1C).

GC-MS: 184 ($M^{+\cdot}$ – 1), 167, 156, 139, 128, 108, 96, 83, 79, 77 (m/z)

Microwave oven:

0.125g of 2-picolinic acid was reacted with 2mL of benzaldehyde in 5mL p-cymene for 2h at 200°C.

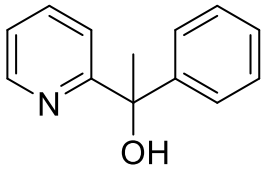
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, 1H, *J = 3.32 Hz*), 7.63 (dt, 1H, *J = 1.64, 7.76 Hz*), 7.40 – 7.36 (m, 5H), 7.20 (m, 2H), 5.79 (s, 1H), 5.29 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.96 (1C), 147.84 (1C), 143.22 (1C), 136.89 (1C), 128.58 (2C), 127.83 (1C), 127.04 (2C), 122.45 (1C), 121.38 (1C), 75.04 (1C)

GC-MS: 184 ($M^{+\cdot}$ – 1), 167, 156, 139, 128, 108, 96, 83, 79, 77 (m/z)

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.3 Procedure for product 25



Oil bath:

0.123g of 2-picolinic acid was reacted with 2mL of acetophenone in 5mL p-cymene for 24h at 200°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, 1H, *J = 4.56 Hz*), 7.62 (dt, 1H, *J = 1.72, 7.8 Hz*), 7.52 – 7.50 (m, 2H), 7.36 – 7.18 (m, 5H), 5.88 (bs, 1H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.78 (1C), 147.42 (1C), 147.16 (1C), 137.00 (1C), 128.22 (2C), 126.99 (1C), 125.91 (2C), 122.05 (1C), 120.31 (1C), 75.01 (1C), 29.25 (1C).

GC-MS: 199 ($M^{+\cdot}$), 184, 167, 156, 122, 106, 78 (m/z)

Microwave oven:

0.123g of 2-picolinic acid was reacted with 2mL of acetophenone in 5mL p-cymene for 2h at 200°C.

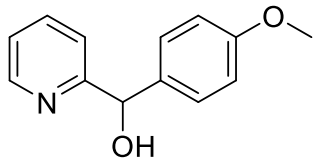
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, 1H *J = 4.72 Hz*), 7.63 (dt, 1H, *J = 1.81, 7.9 Hz*), 7.53 – 7.50 (m, 2H), 7.36 – 7.18 (m, 5H), 5.89 (bs, 1H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.78 (1C), 147.42 (1C), 147.16 (1C), 137.00 (1C), 128.22 (2C), 126.99 (1C), 125.91 (2C), 122.05 (1C), 120.31 (1C), 75.09 (1C), 29.25 (1C).

GC-MS: 199 ($M^{+\cdot}$), 184, 167, 156, 122, 106, 78 (m/z)

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.4 Procedure for product 26



Oil bath:

0.124g of 2-picolinic acid was reacted with 2mL of p-anisaldehyde in 5mL p-cymene for 24h at 200°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, 1H, *J = 4.28 Hz*), 7.64 (dt, 1H, *J = 1.6, 7.68 Hz*), 7.29 – 7.14 (m, 4H), 6.90 – 6.88 (m, 2H), 5.73 (s, 1H), 5.21 (bs, 1H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.16 (1C), 159.28 (1C), 147.76 (1C), 136.78 (1C), 135.51 (1C), 128.39 (2C), 122.32 (1C), 121.33 (1C), 113.98 (2C), 74.51 (1C), 55.28 (1C).

GC-MS: 215 ($M^{+\cdot}$), 186, 167, 154, 137,121, 109, 94, 79, 66 (m/z)

Microwave oven:

0.123g of 2-picolinic acid was reacted with 2mL p-anisaldehyde in 5mL p-cymene for 2h at 200°C.

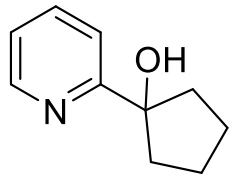
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, 1H, *J = 3.88 Hz*), 7.65 – 7.61 (dt, 1H, *J = 1.44, 7.72 Hz*), 7.31 – 7.15 (m, 4H), 7.01 – 6.88 (m, 2H), 5.73 (s, 1H), 5.23 (bs, 1H), 3.80 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.20 (1C), 159.27 (1C), 147.77 (1C), 136.80 (1C), 135.50 (1C), 128.38 (2C), 122.34 (1C), 121.32 (1C), 113.97 (2C), 74.55 (1C), 55.27 (1C).

GC-MS: 215 ($M^{+\cdot}$), 186, 167, 154, 137,121, 109, 94, 79, 66 (m/z)

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.5 Procedure for product 27



Oil bath:

0.128g of 2-picolinic acid was reacted with 2mL of cyclopentanone in 5mL p-cymene for 24h at 200°C.

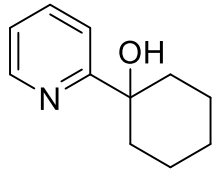
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, *J = 4.48 Hz*), 7.73 – 7.69 (dt, 1H, *J = 1.72, 15.44 Hz*), 7.41 (d, 1H), 7.19 (d, 1H), 5.01 (bs, 1H), 2.09 – 1.87 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.94 (1C), 147.31 (1C), 136.81 (1C), 121.69 (1C), 119.06 (1C), 82.67 (1C), 42.80 (2C), 24.88 (2C).

GC-MS: 162 ($M^{+\cdot}$ – 1), 144, 134, 122, 106, 93, 79, 65 (m/z)

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.6 Procedure for product 28



Oil bath:

0.126g 2-picolinic acid was reacted with 2mL of cyclohexanone in 5mL p-cymene for 24h at 200°C.

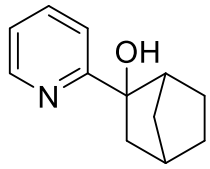
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, 1H, *J = 4.84 Hz*), 7.74 – 7.69 (dt, 1H, *J = 1.72, 7.88 Hz*), 7.40 (d, 1H), 7.20 (t, 1H), 4.91 (bs,1H), 1.90 – 1.67 (m,10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.09 (1C), 147.46 (1C), 136.87 (1C), 121.80 (1C), 118.95 (1C), 72.75 (1C), 38.57 (2C), 25.60 (1C), 22.14 (2C).

GC-MS: 177 ($M^{+\cdot}$), 158, 149, 134, 120, 106, 93, 79, 65 (m/z)

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.7 Procedure for product 29



Oil bath:

0.126g 2-picolinic acid was reacted with 0.216g of norcamphor in 5mL p-cymene for 24h at 200°C.

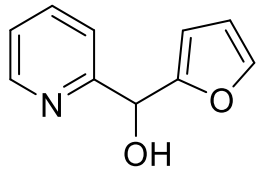
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, 1H, *J = 4.28 Hz*), 7.81 – 7.77 (dt, 1H, *J = 1.68, 7.88 Hz*), 7.51 (d, 1H) 7.27 (t, 1H), 4.66 (bs, 1H), 2.40 – 2.29 (m, 3H), 1.70 – 1.22 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.80 (1C), 146.79 (1C), 136.76 (1C), 122.12 (1C), 120.20 (1C), 80.40 (1C), 48.64 (1C), 45.28 (1C), 38.51 (1C), 37.28 (1C), 28.69 (1C), 22.68 (1C).

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M

NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.8 Procedure for product 30



Oil bath:

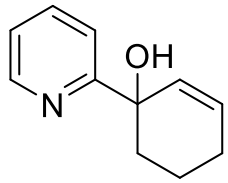
0.124g 2-picolinic acid was reacted with 2mL of furfural in 5mL p-cymene for 24h at 200°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, 1H, *J = 4.72 Hz*), 7.60 – 7.56 (dt, 1H, *J = 1.72, 7.68 Hz*), 7.25 (s, 1H), 7.20 – 7.12 (m, 2H), 6.20 (d, 2H), 5.71 (s, 1H), 5.12 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.14 (1C), 155.18 (1C), 148.04 (1C), 142.67 (1C), 136.94 (1C), 122.92 (1C), 121.33 (1C), 110.27 (1C), 107.61 (1C). 68.73 (1C).

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.9 Procedure for product 31

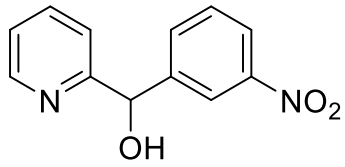


Oil bath:

0.123g 2-picolinic acid was reacted with 2mL of cyclohexen-1-one in 5mL p-cymene for 24h at 200°C.

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.10 Procedure for product 32

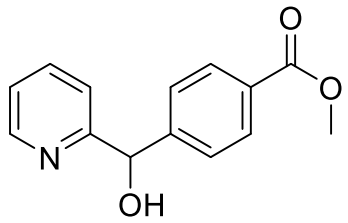


Oil bath:

0.122g 2-picolinic acid was reacted with 0.303g of 3-nitrobenzaldehyde in 5mL p-cymene for 24h at 200°C.

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

4.11 Procedure for product 33



Oil bath:

0.123g of 2-picolinic acid was reacted with 0.327g of methyl 4-formylbenzoate in 5mL p-cymene for 24h at 200°C.

After the reaction had cooled to room temperature it was acidified with 2M HCl and transferred to a separation funnel. The acidified solution was then washed with DCM until no more product showed under UV light with TLC. Then the solution was made basic with 2M NaOH and washed with ethyl acetate 5 times or until no more product showed in the organic phase. The ethyl acetate was then evaporated off.

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Attachments

^{1}H NMR, ^{13}C NMR and MS spectra of product **24**

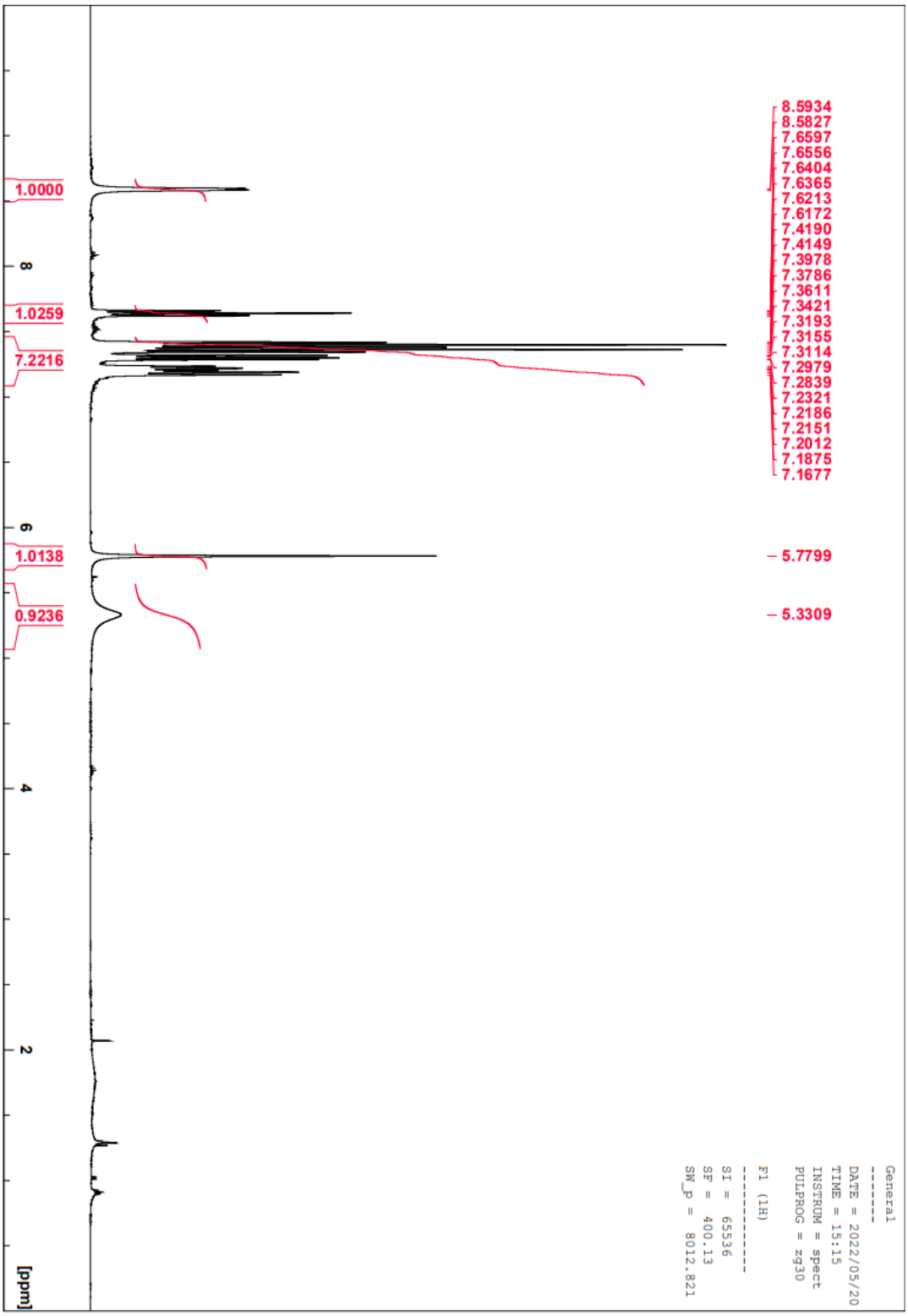

Figure 8: ^{1}H NMR of product **24** when reacted in oil bath.

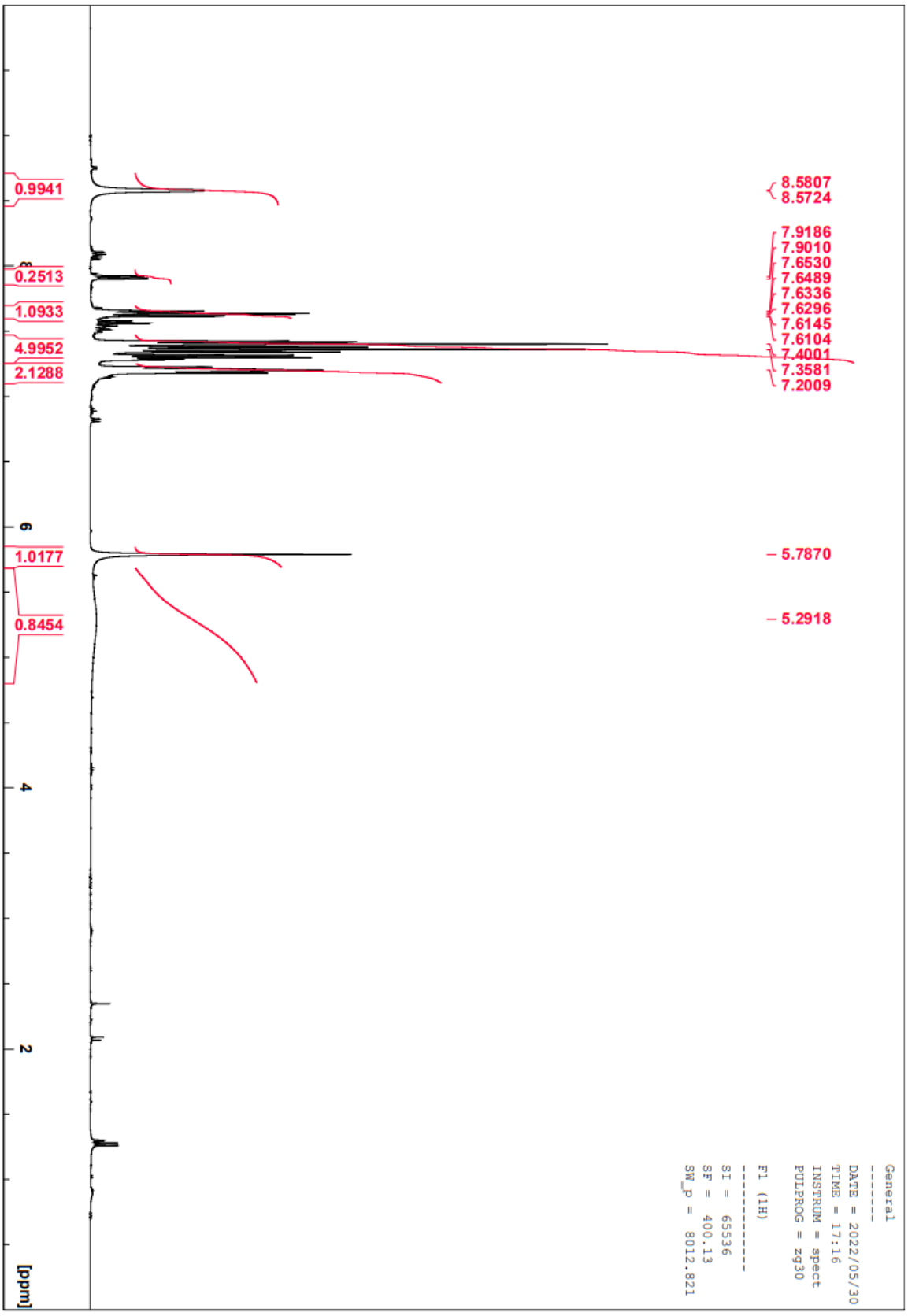

Figure 9: ^{1}H NMR of product **24** when reacted in microwave oven.

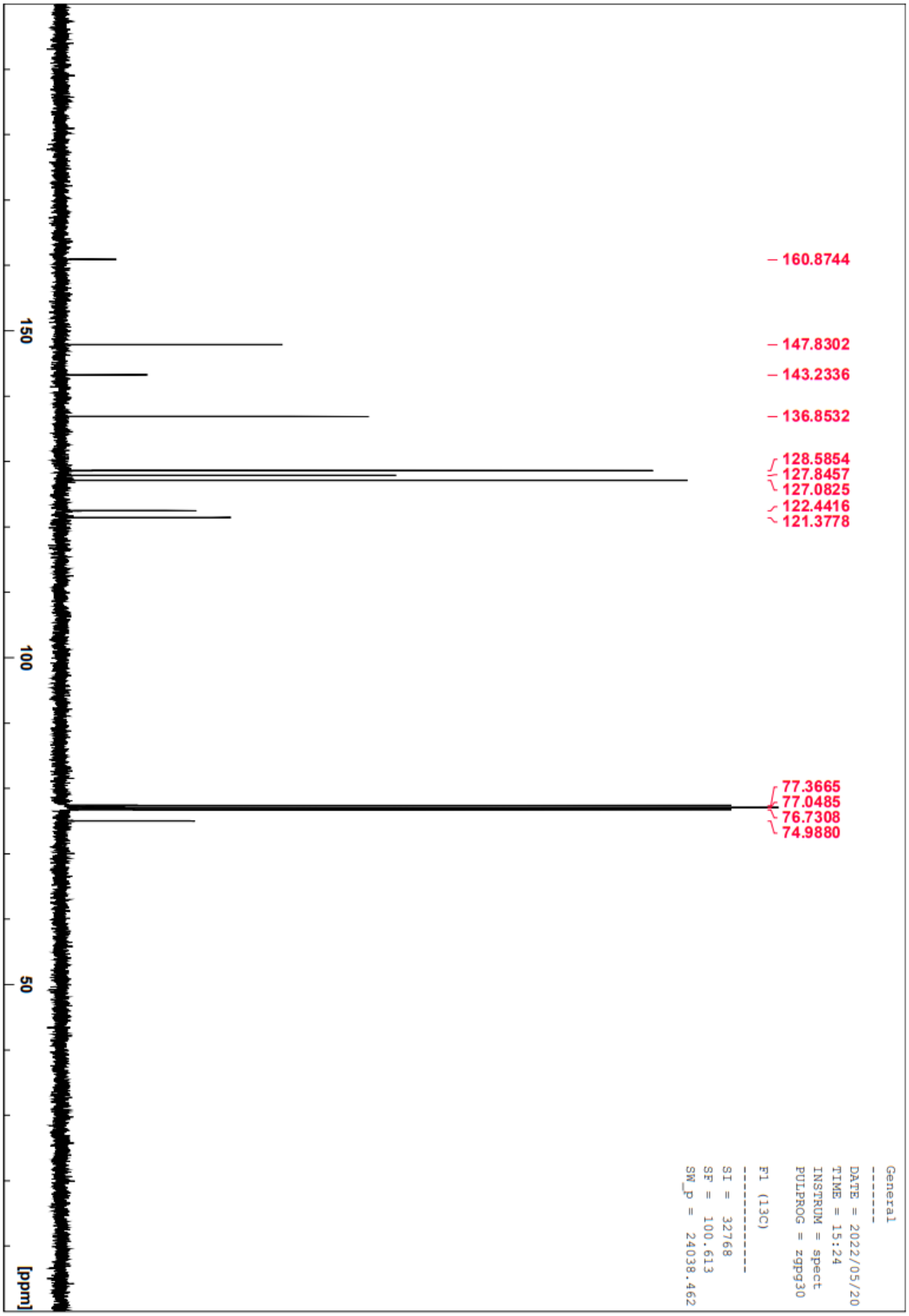

Figure 10: ^{13}C NMR of product **24** when reacted in oil bath.

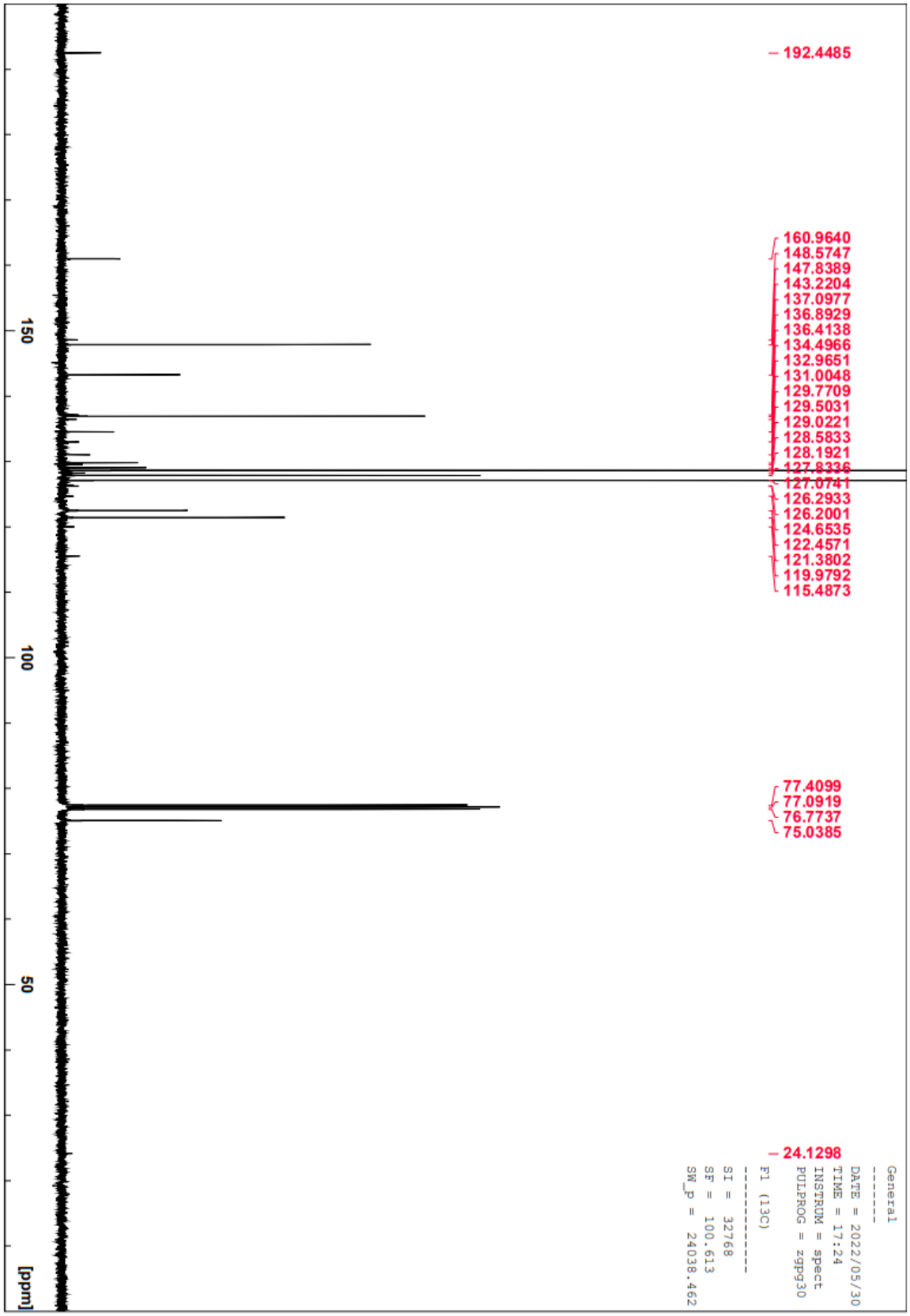

Figure 11: ^{13}C NMR of product **24** when reacted in microwave oven.

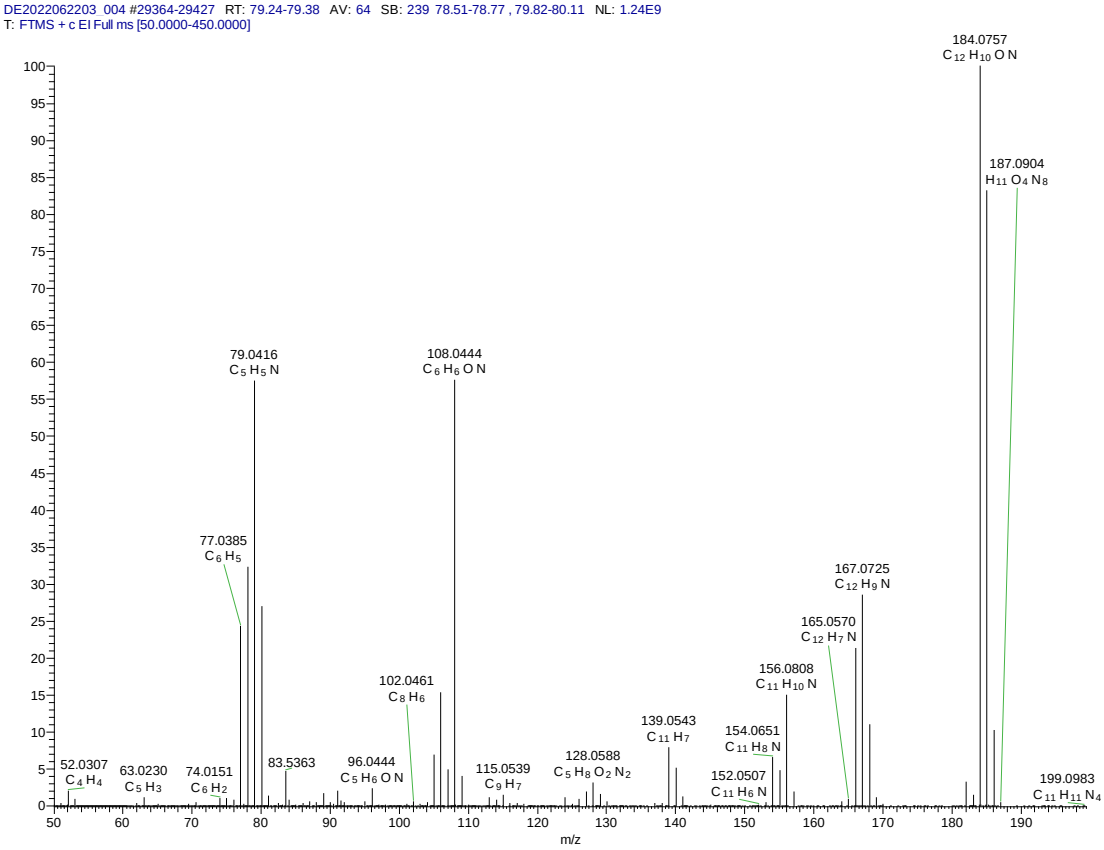

Figure 12: Mass Spectrum of product **24** in oil bath

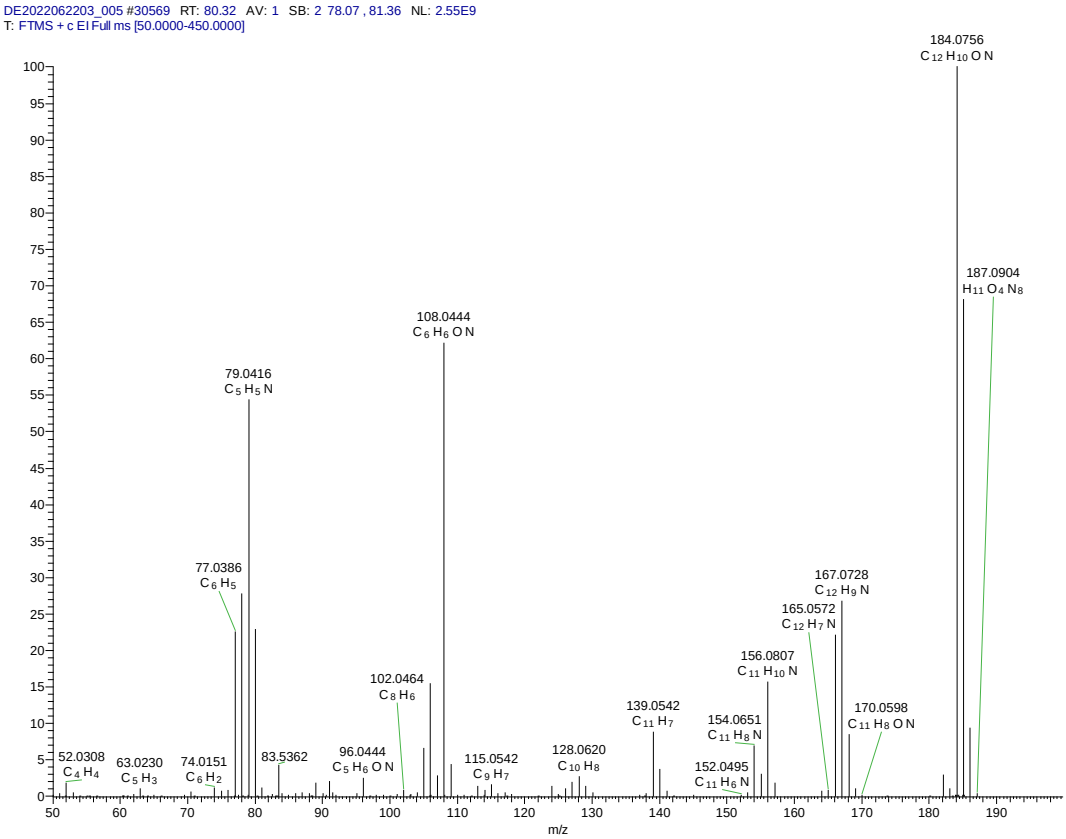

Figure 13: Mass spectrum of product **24** in microwave oven

^{1}H NMR and ^{13}C NMR spectra of product **25**

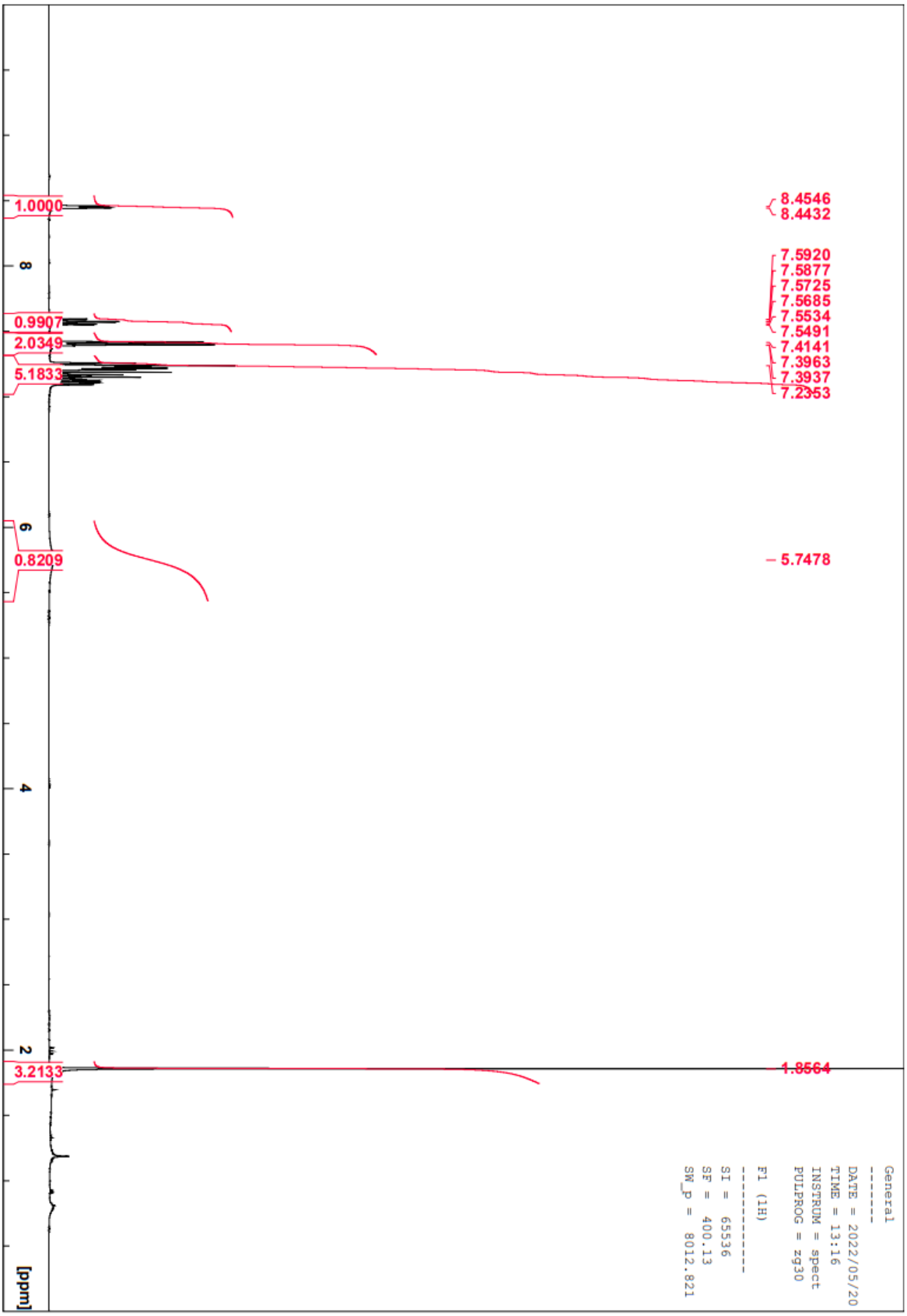

Figure 14: ^{1}H NMR of product **25** when reacted in oil bath.

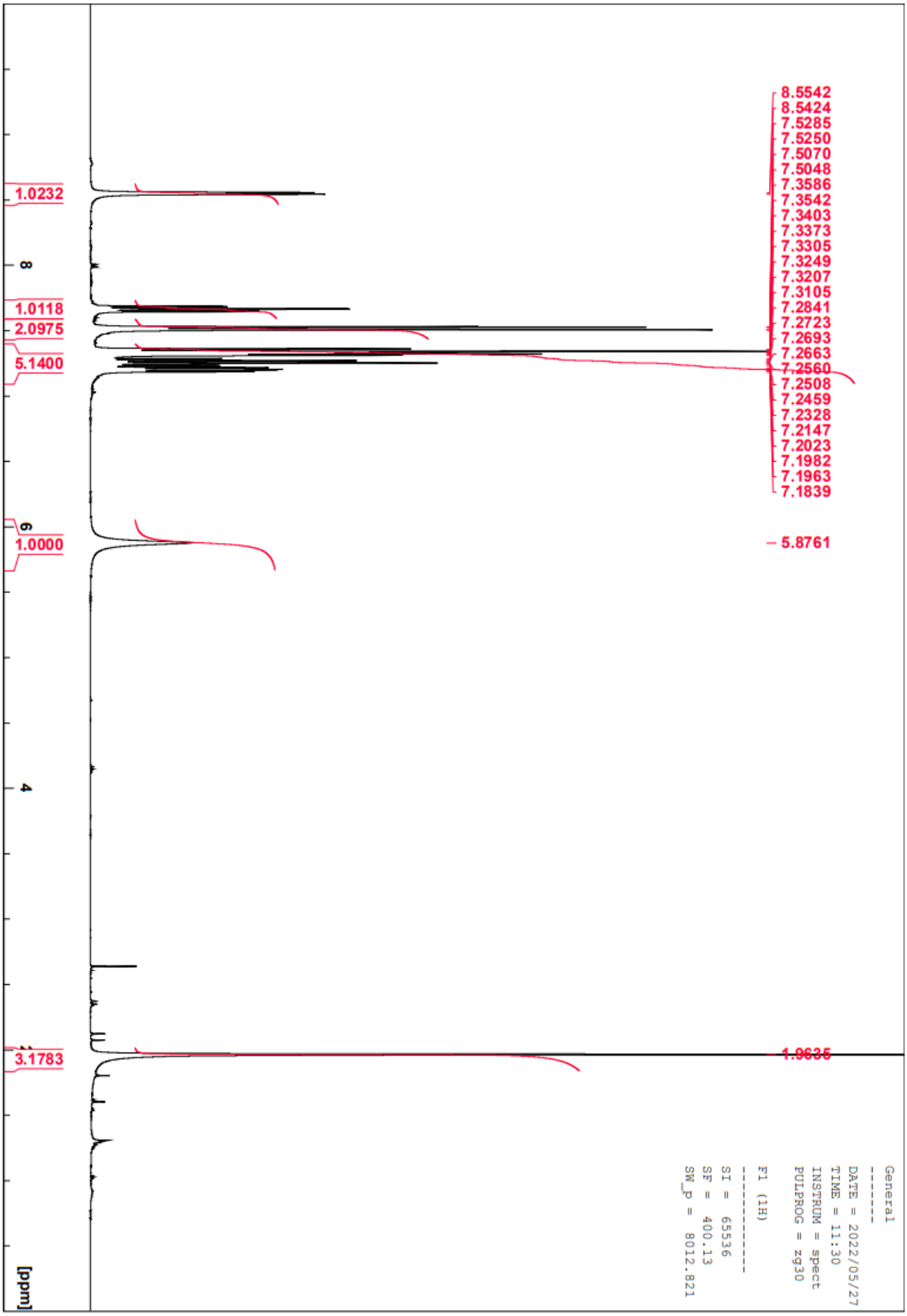

Figure 15: ^{1}H NMR of product **25** when reacted in microwave oven.

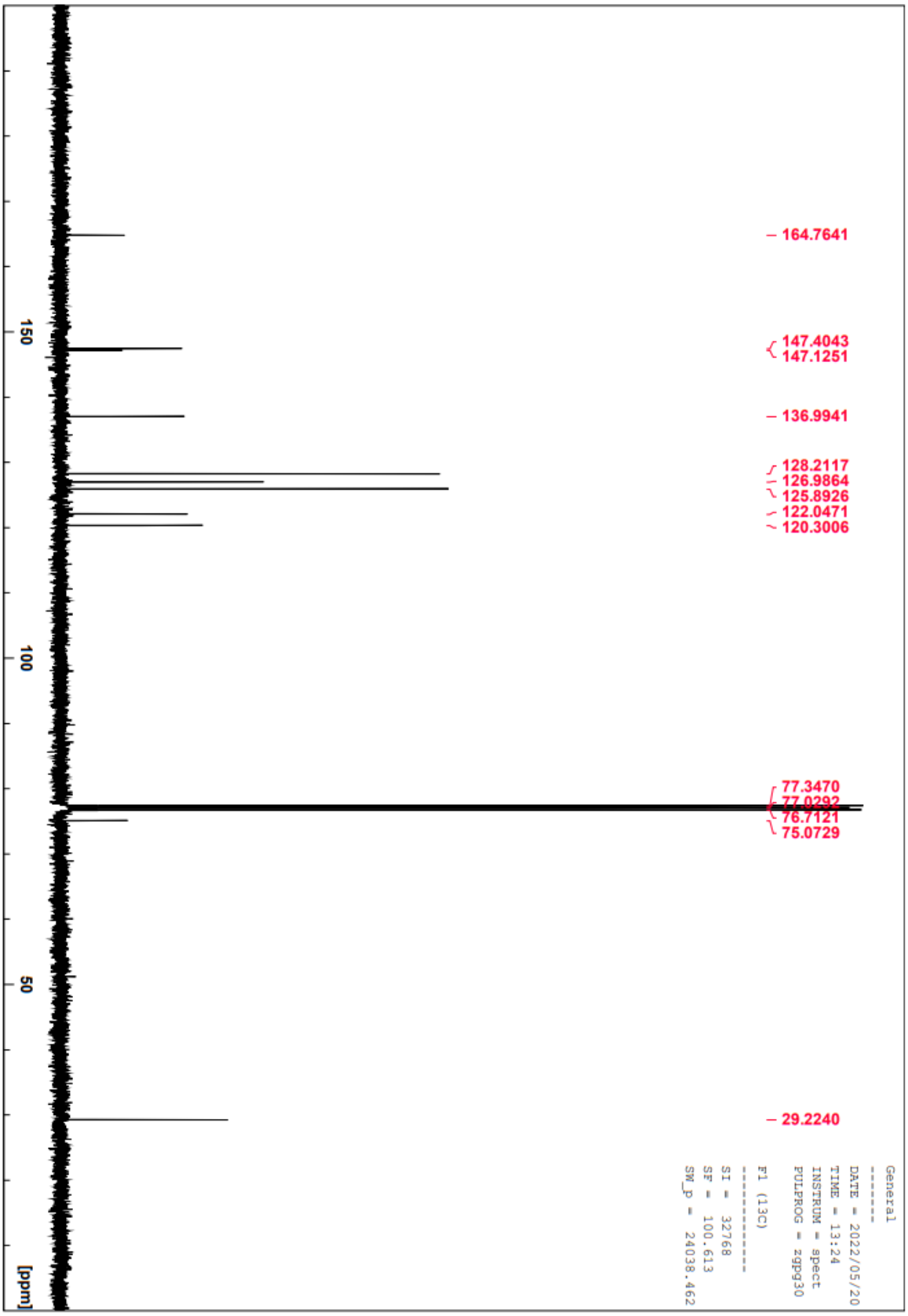

Figure 16: ^{13}C NMR of product **25** when reacted in oil bath.

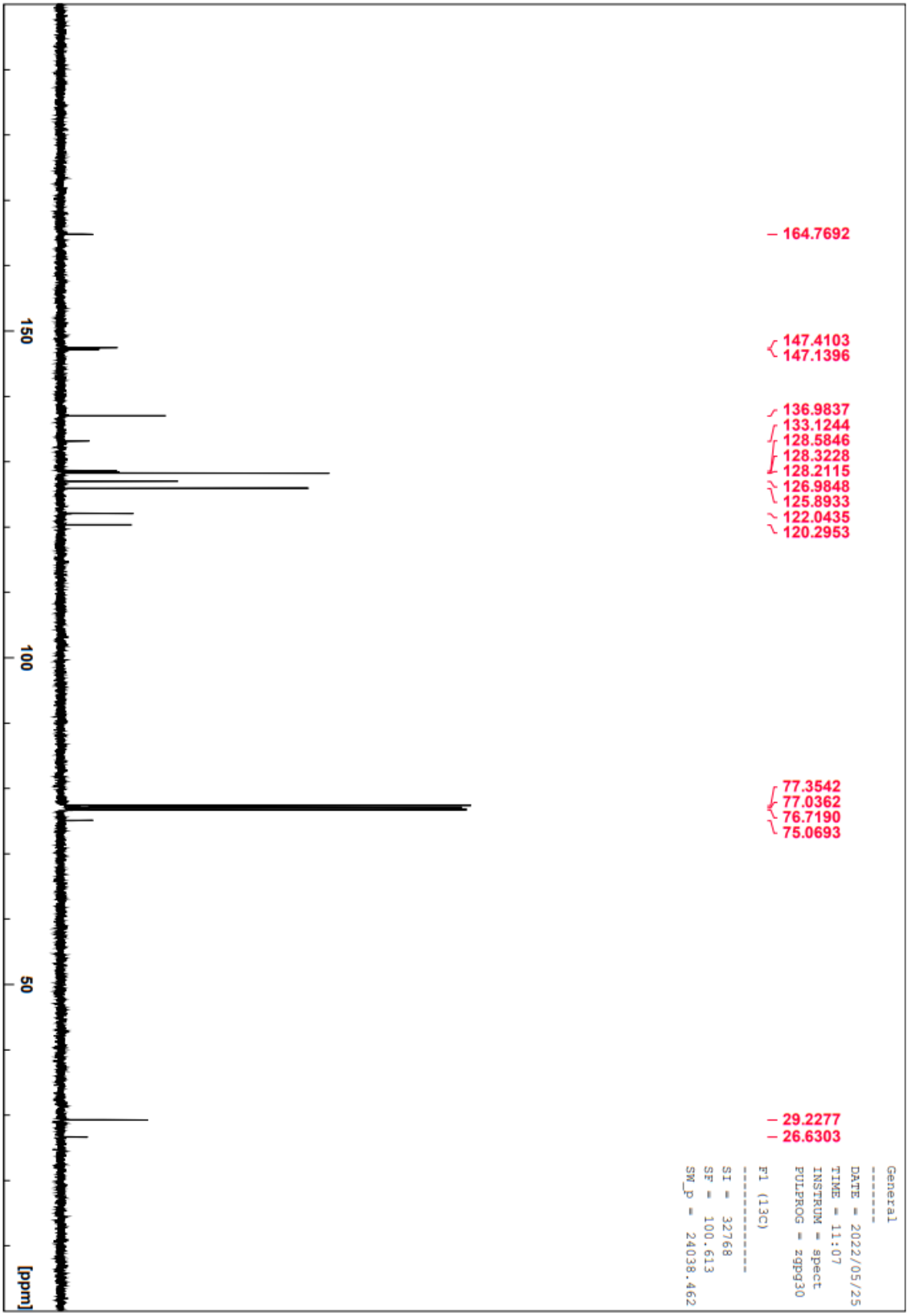

Figure 17: ^{13}C NMR of product **25** when reacted in microwave.

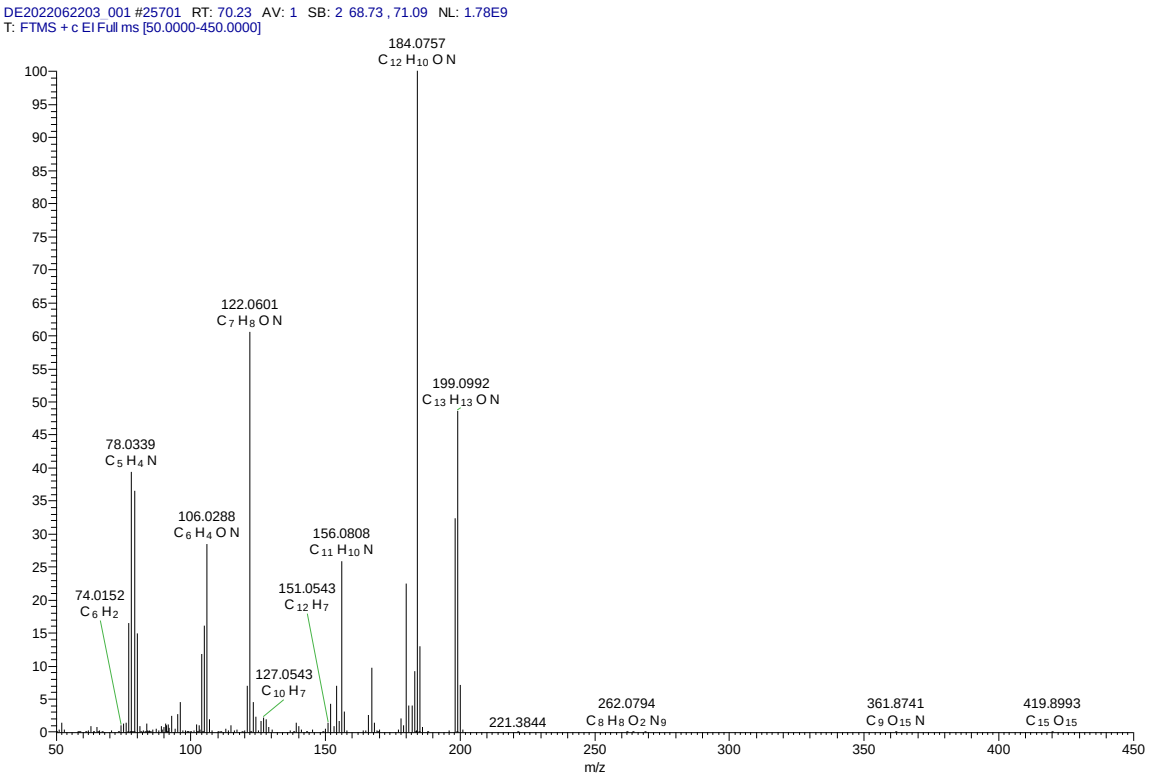

Figure 18: Mass spectrum of product **25** in oil bath

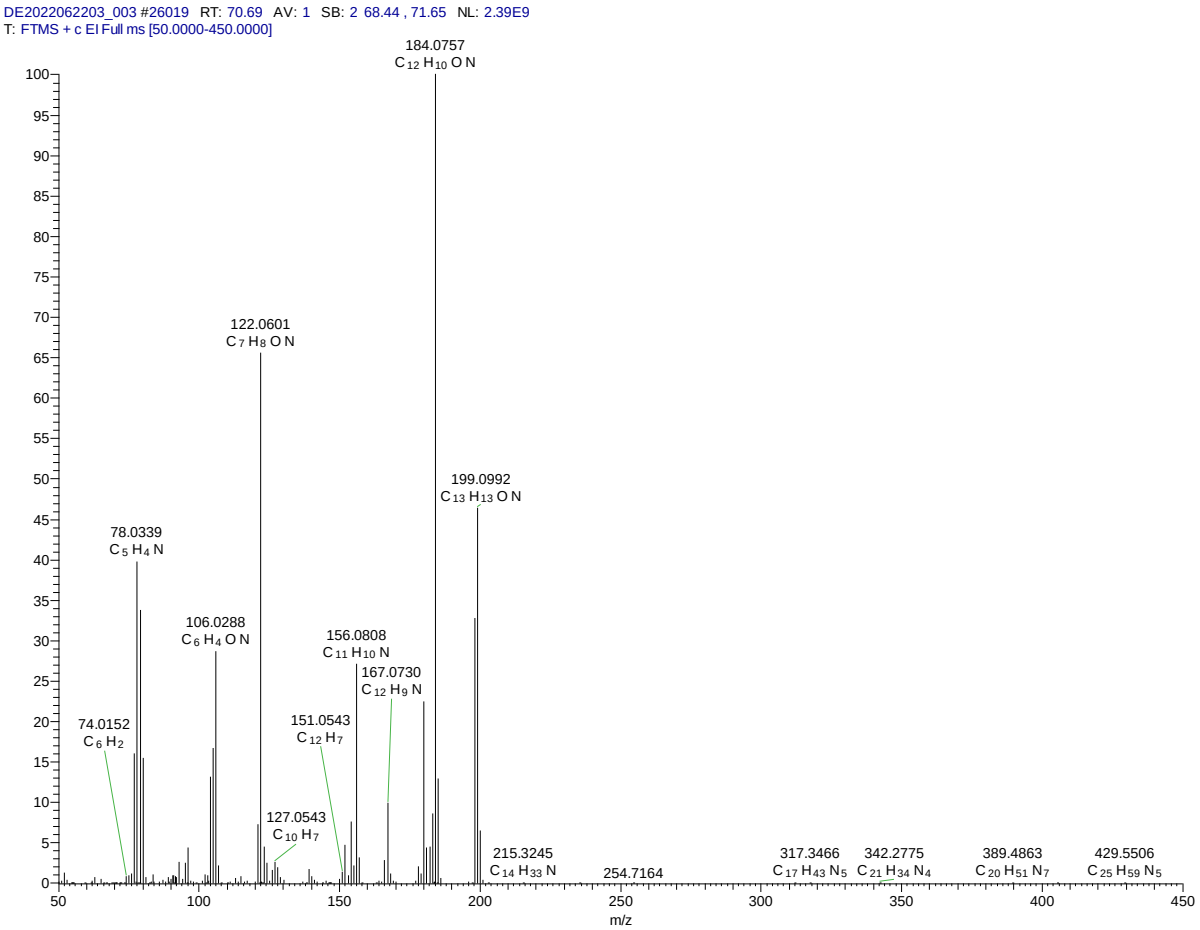

Figure 19: Mass Spectrum of product **25** in microwave oven

^{1}H NMR and ^{13}C NMR spectra of product **26**

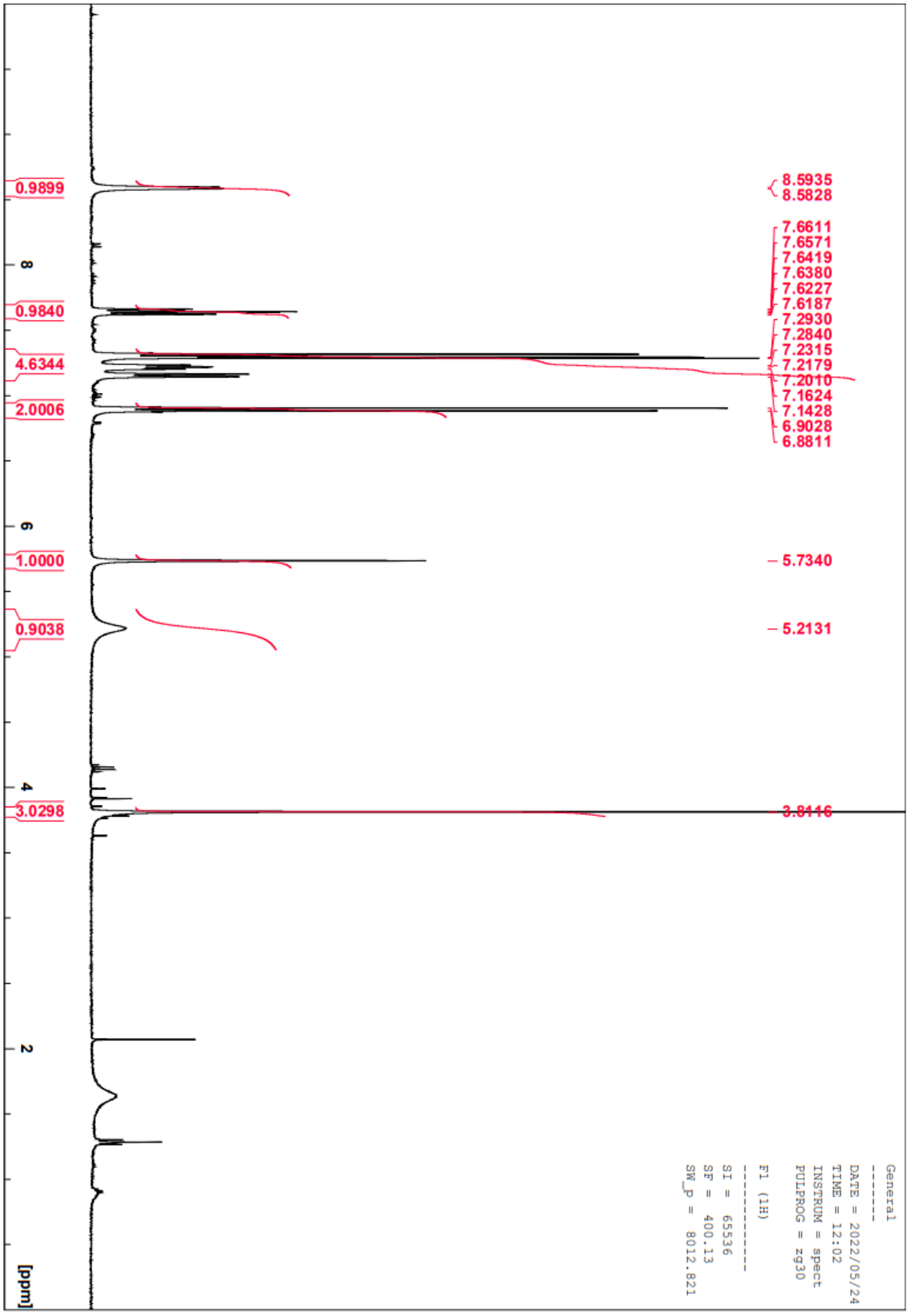

Figure 20: ^{1}H NMR of product **26** when reacted in oil bath.

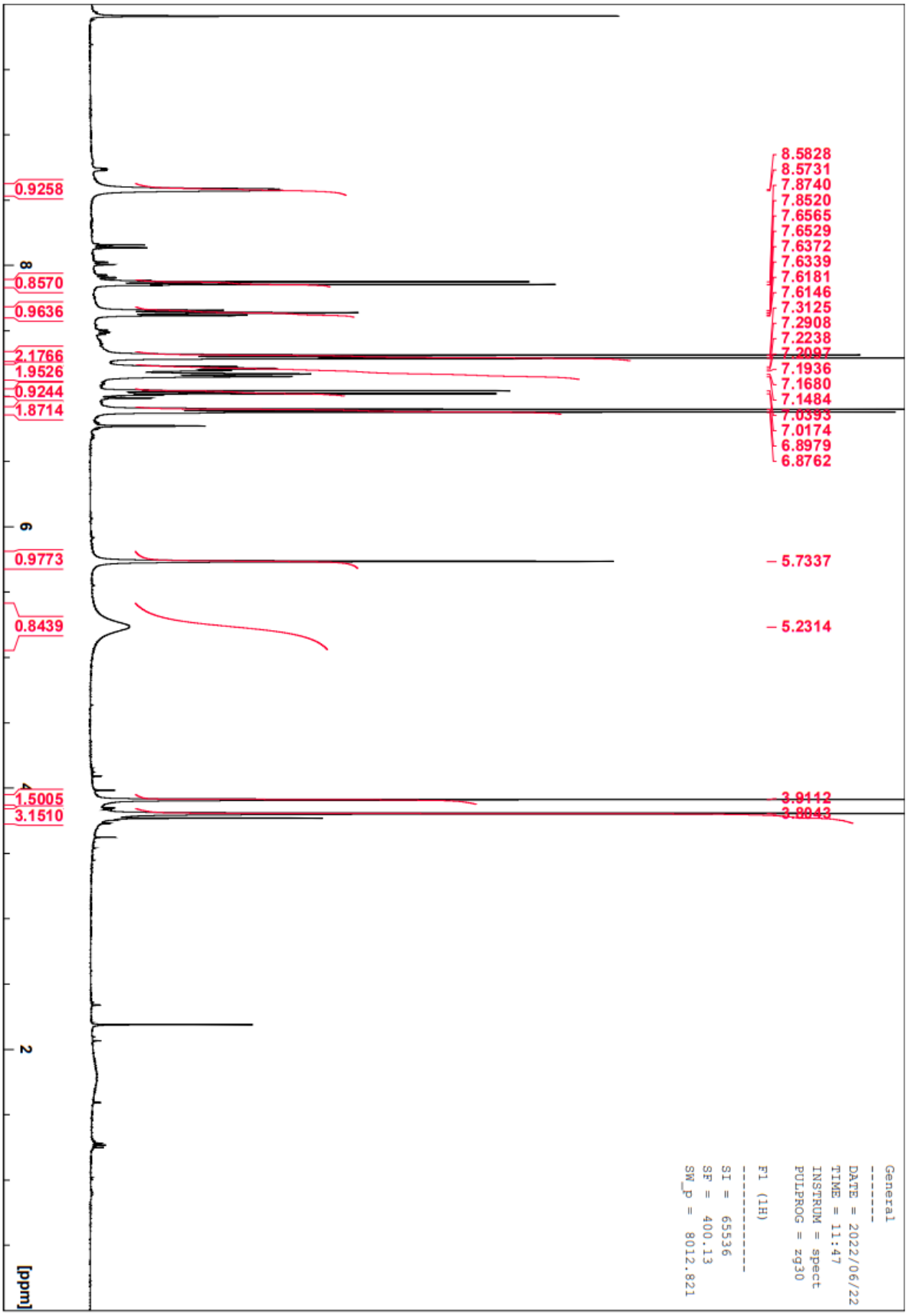

Figure 21: ^{1}H NMR of product **26** when reacted in microwave oven.

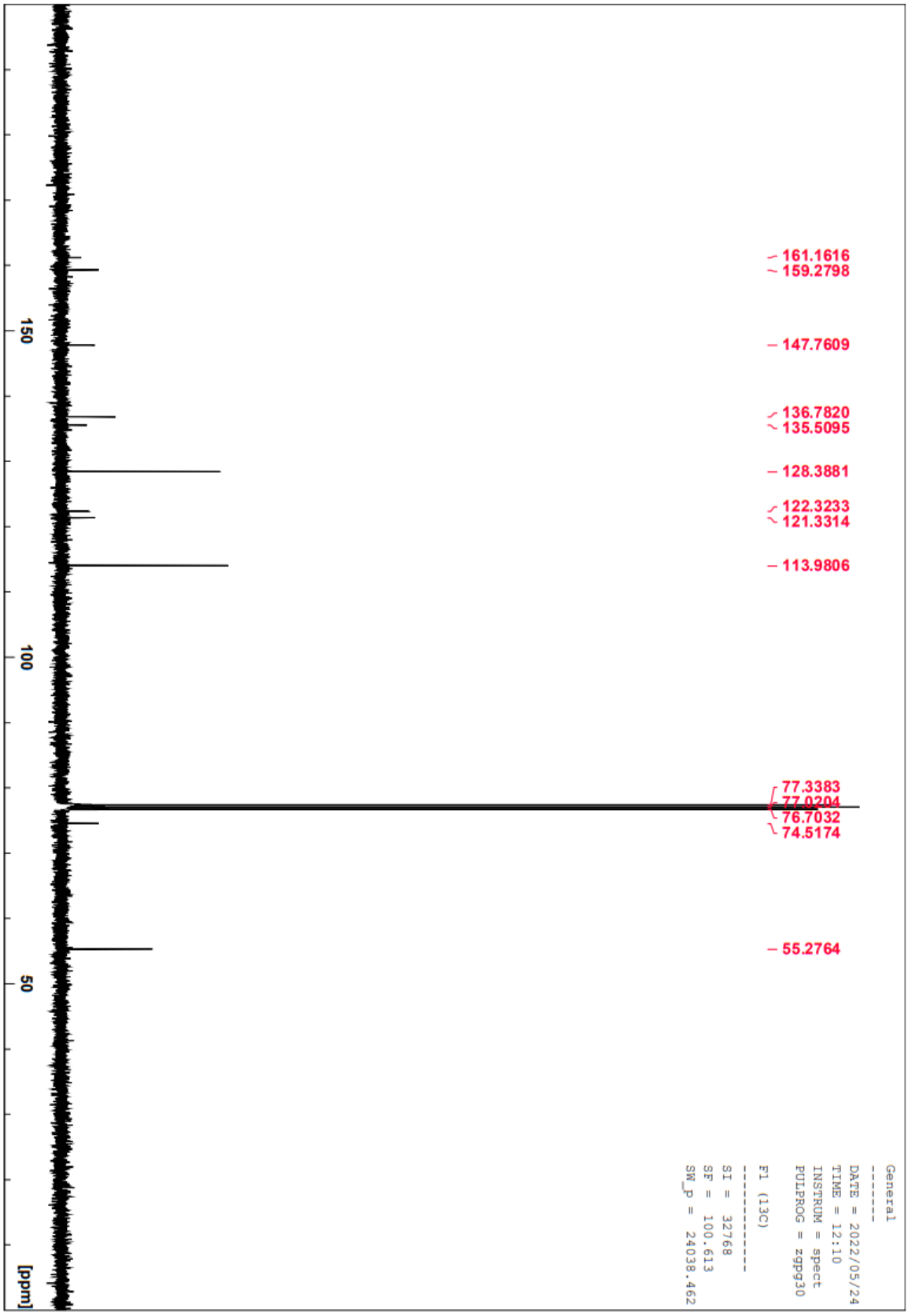

Figure 22: ^{13}C NMR of product **26** when reacted in oil bath.

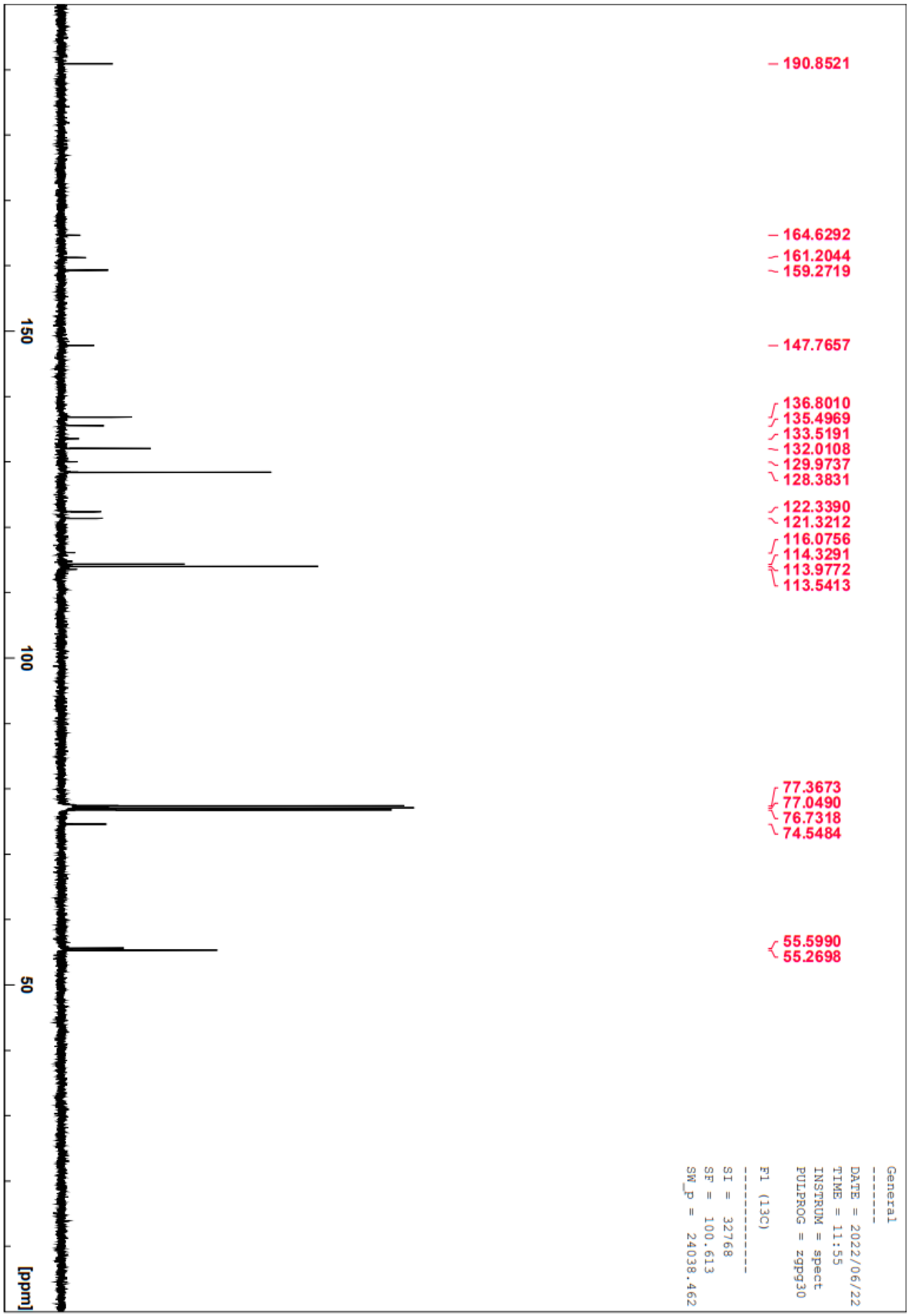

Figure 23: ^{13}C NMR of product **26** when reacted in microwave.

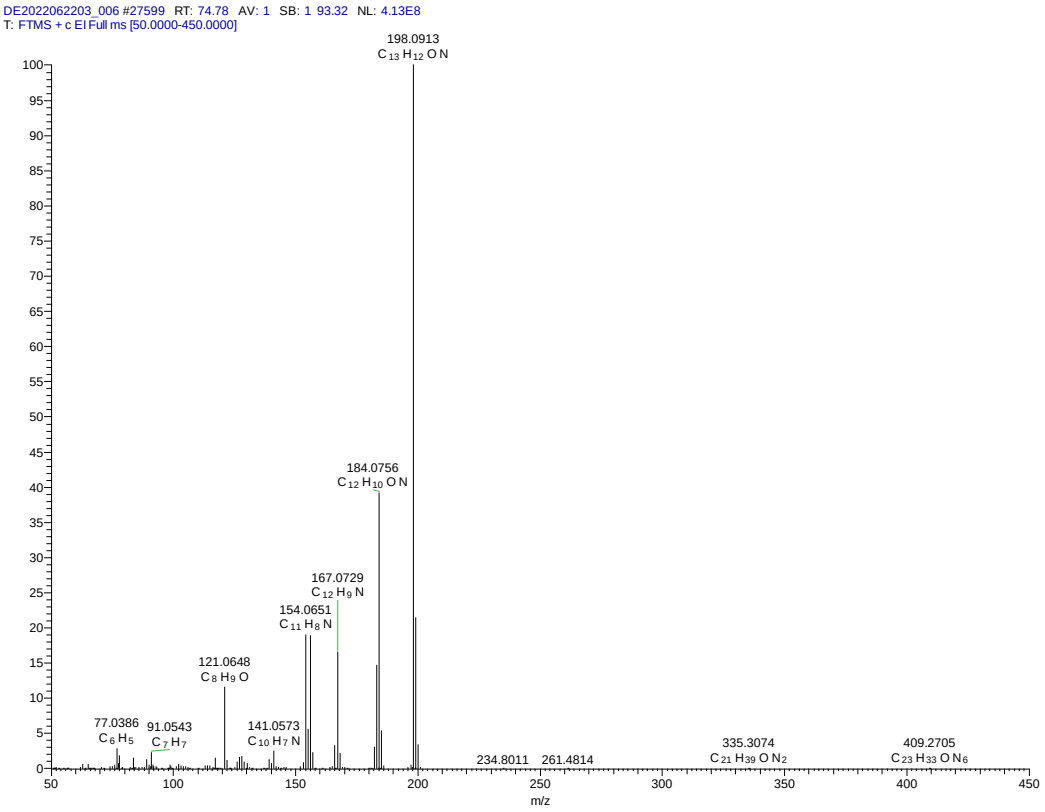

Figure 24: Mass spectrum of product **26** in oil bath

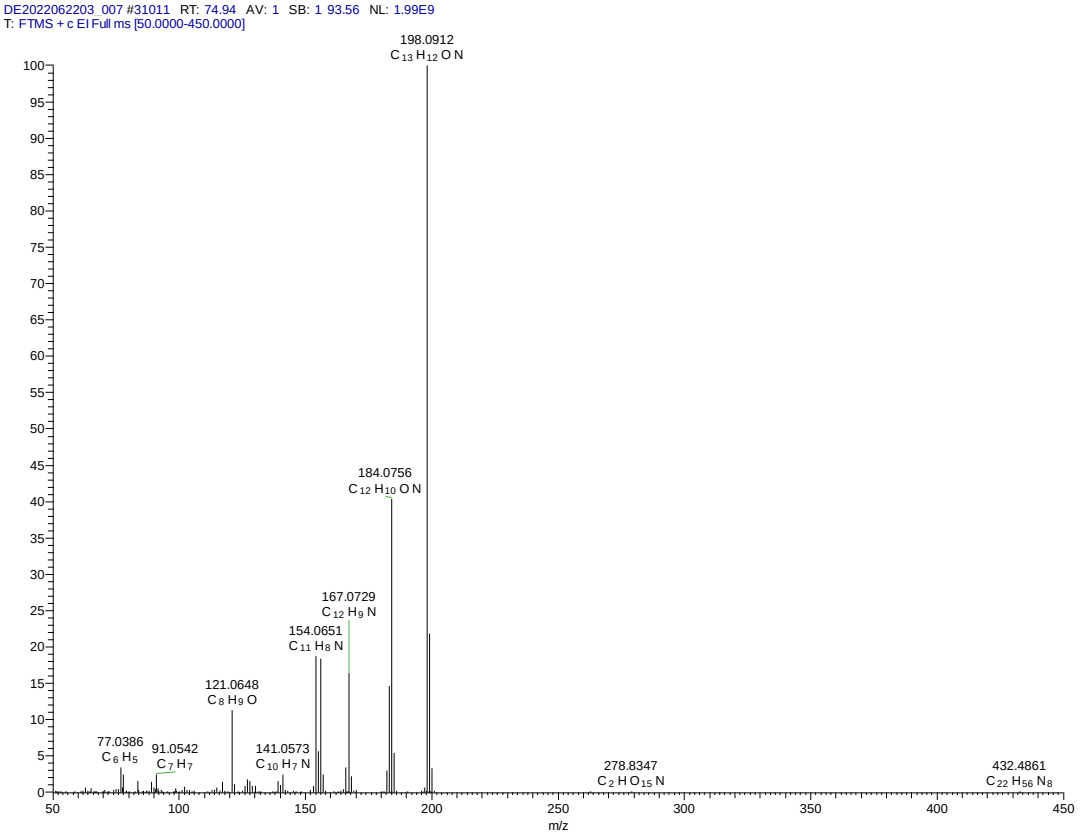

Figure 25: Mass spectrum of product **26** in microwave oven

^{1}H NMR and ^{13}C NMR spectra of product **27**

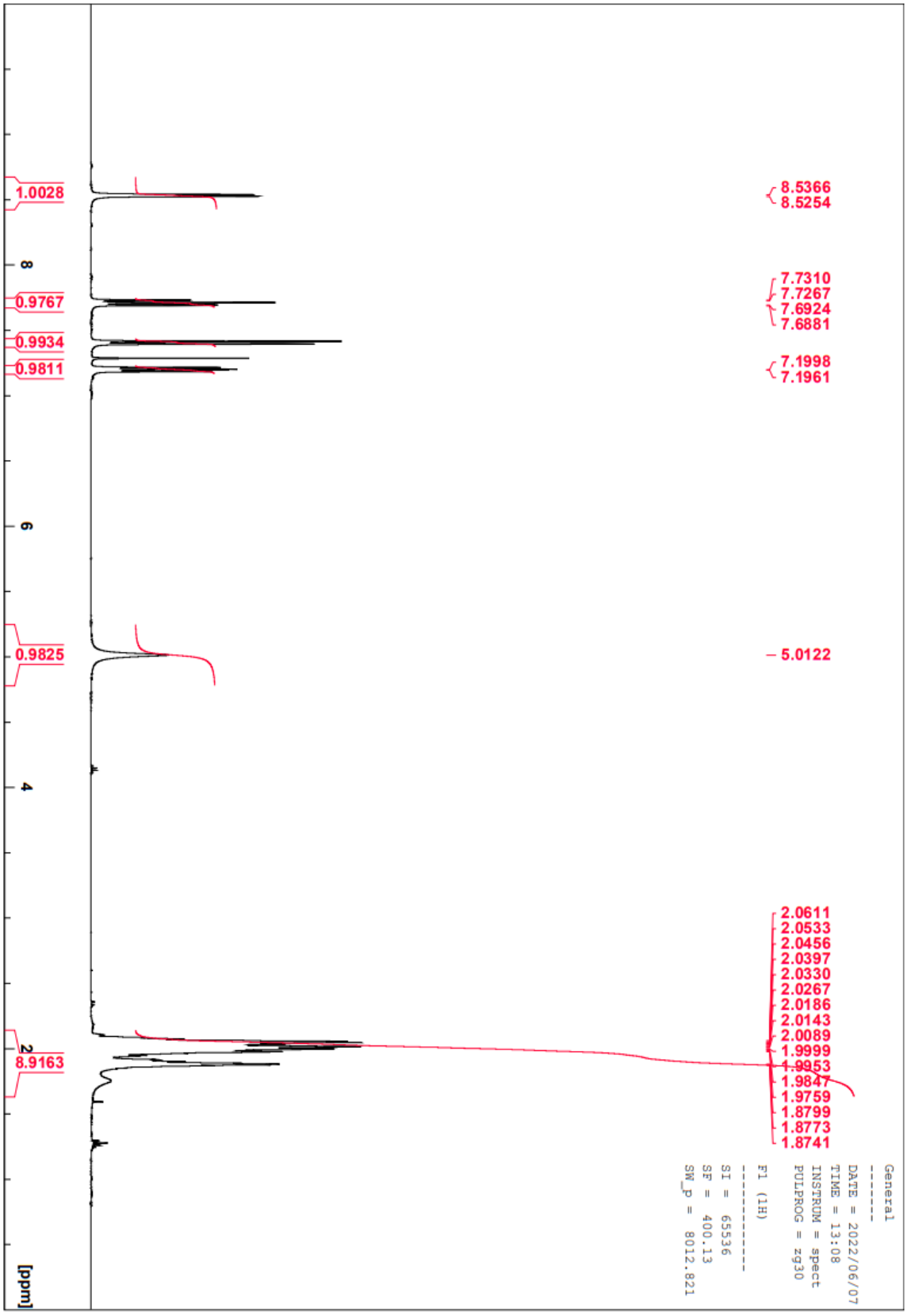

Figure 26: ^{1}H NMR of product **27** when reacted in oil bath.

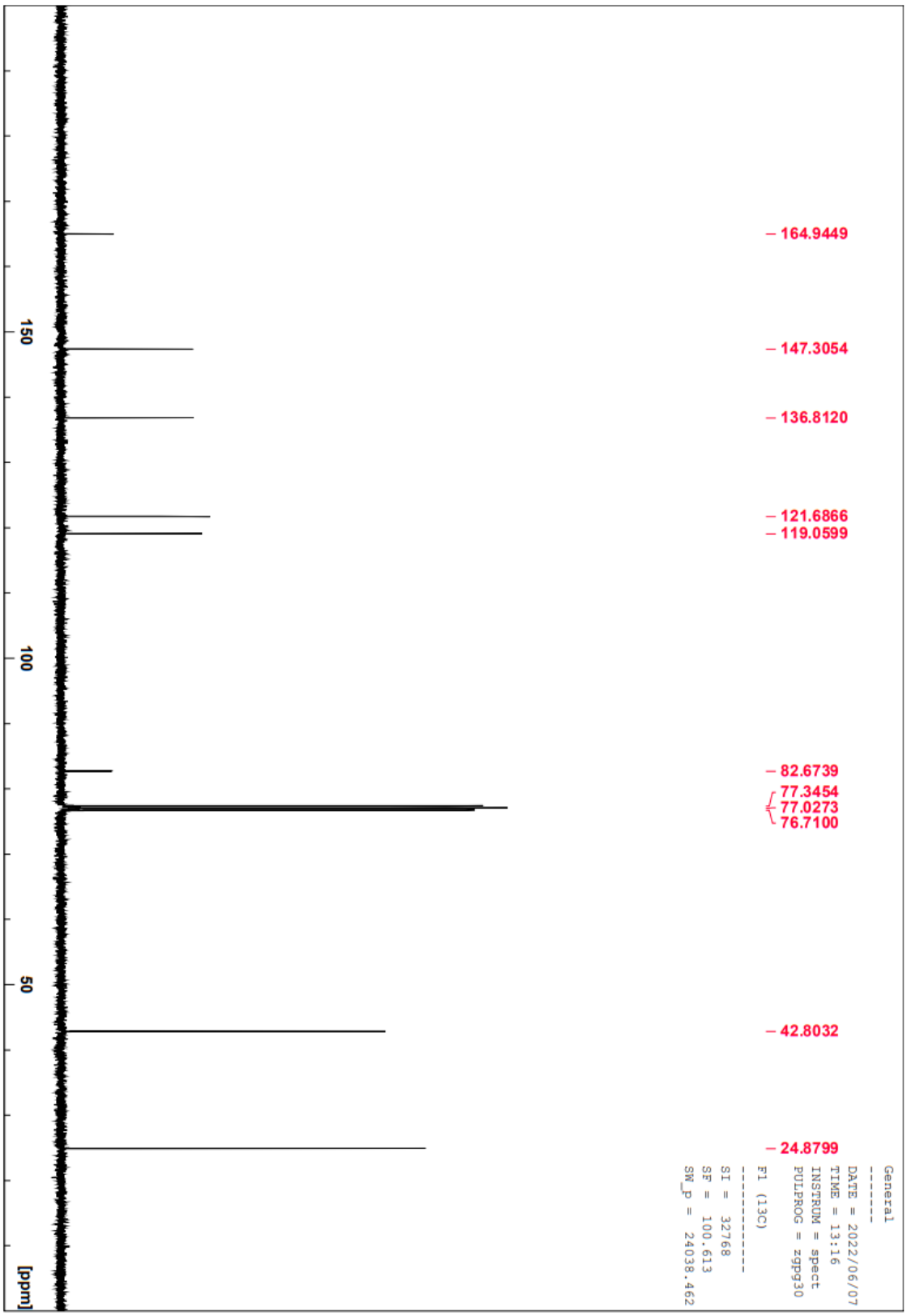

Figure 27: ^{13}C NMR of product **27** when reacted in oil bath.

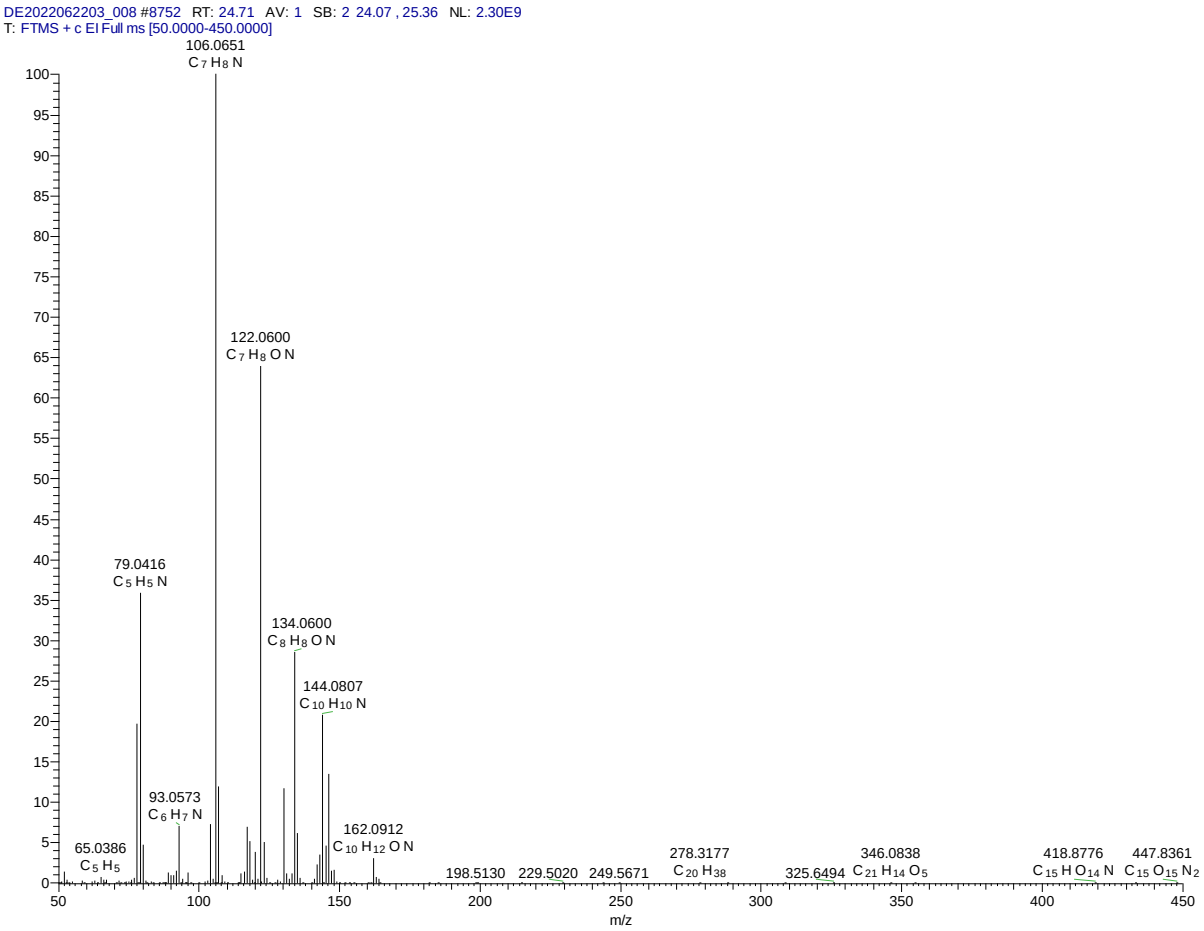

Figure 28: Mass spectrum of product **27** in oil bath

^{1}H NMR and ^{13}C NMR spectra of product **28**

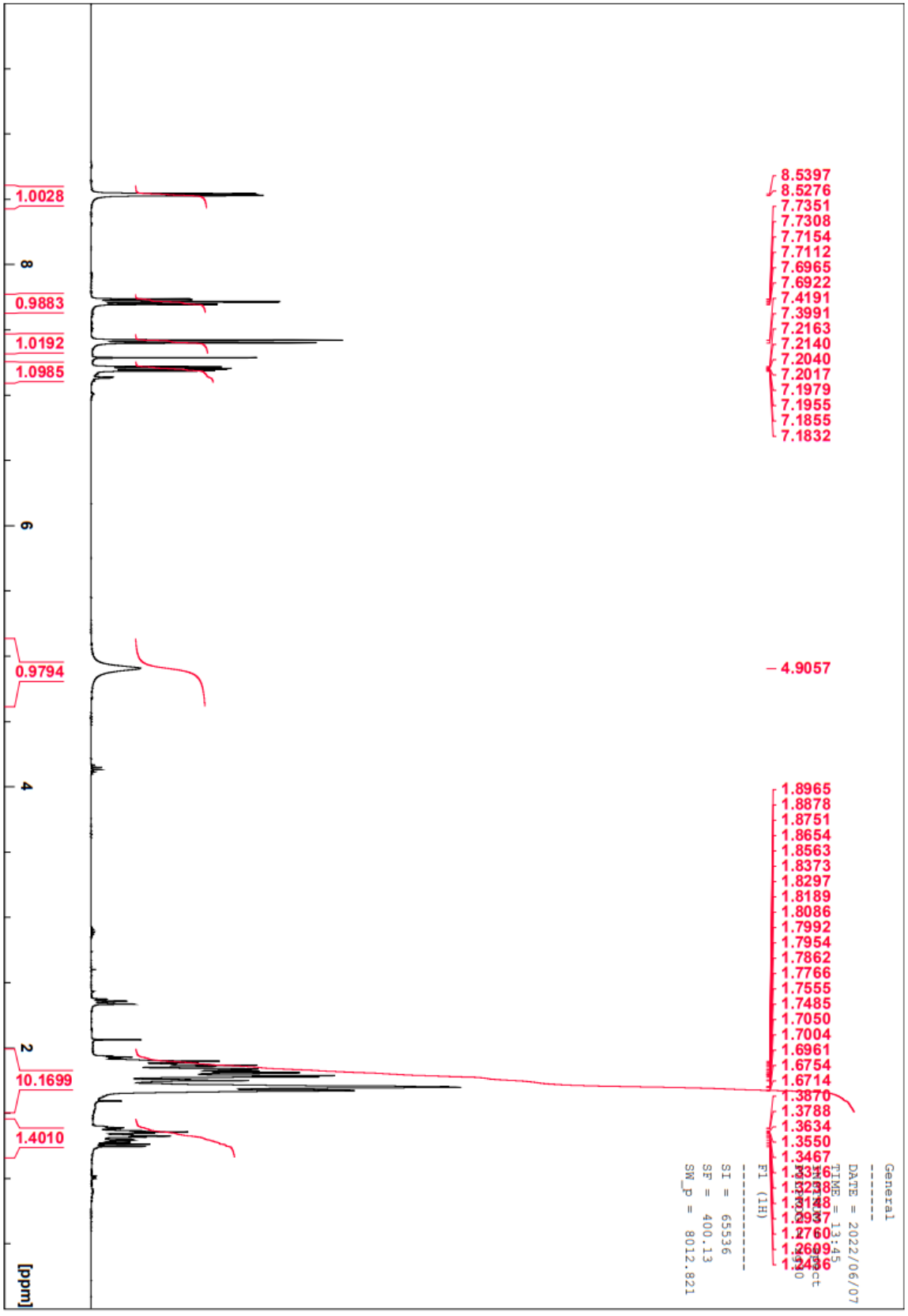

Figure 29: ^{1}H NMR of product **28** when reacted in oil bath.

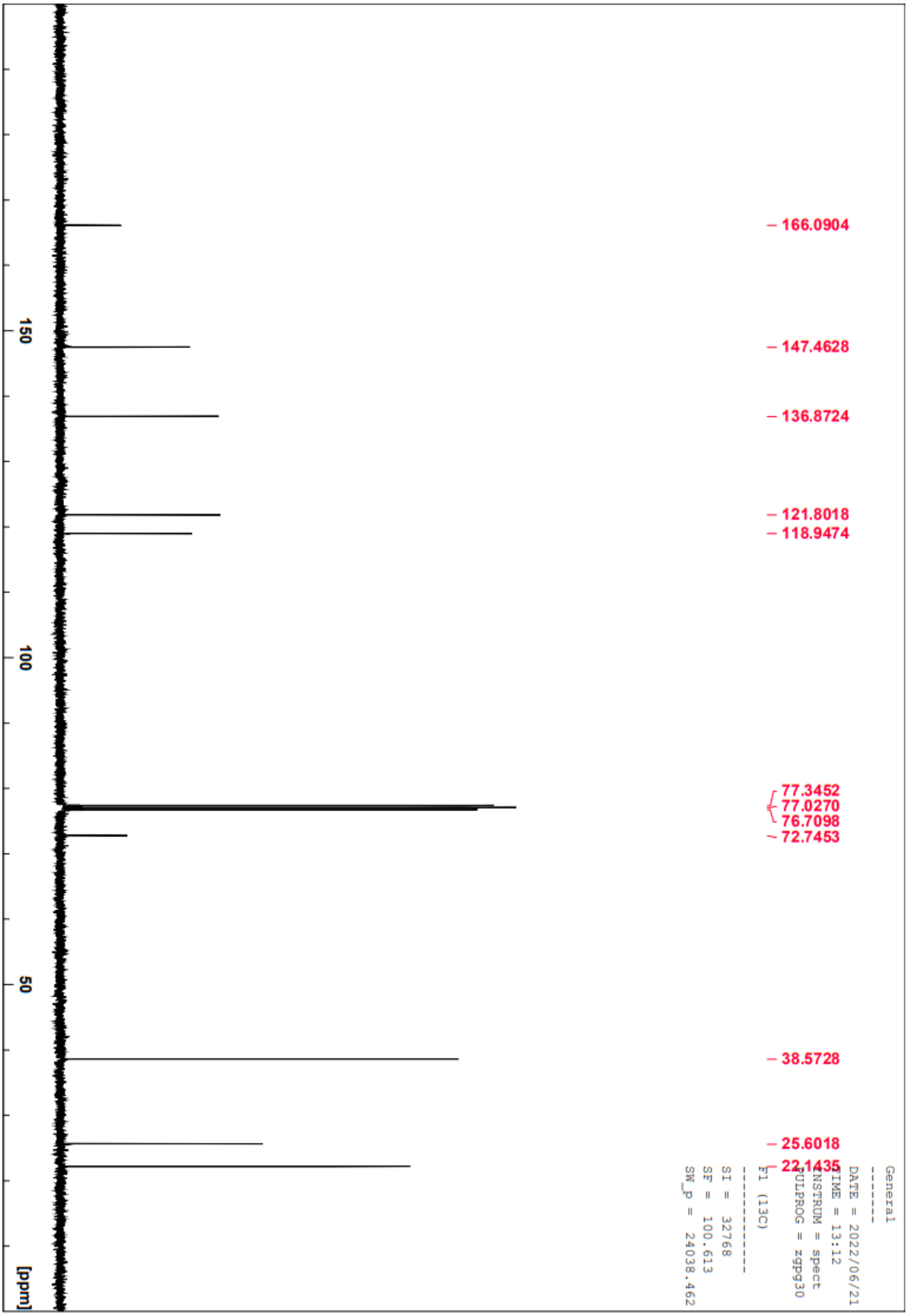

Figure 30: ^{13}C NMR of product **28** when reacted in oil bath.

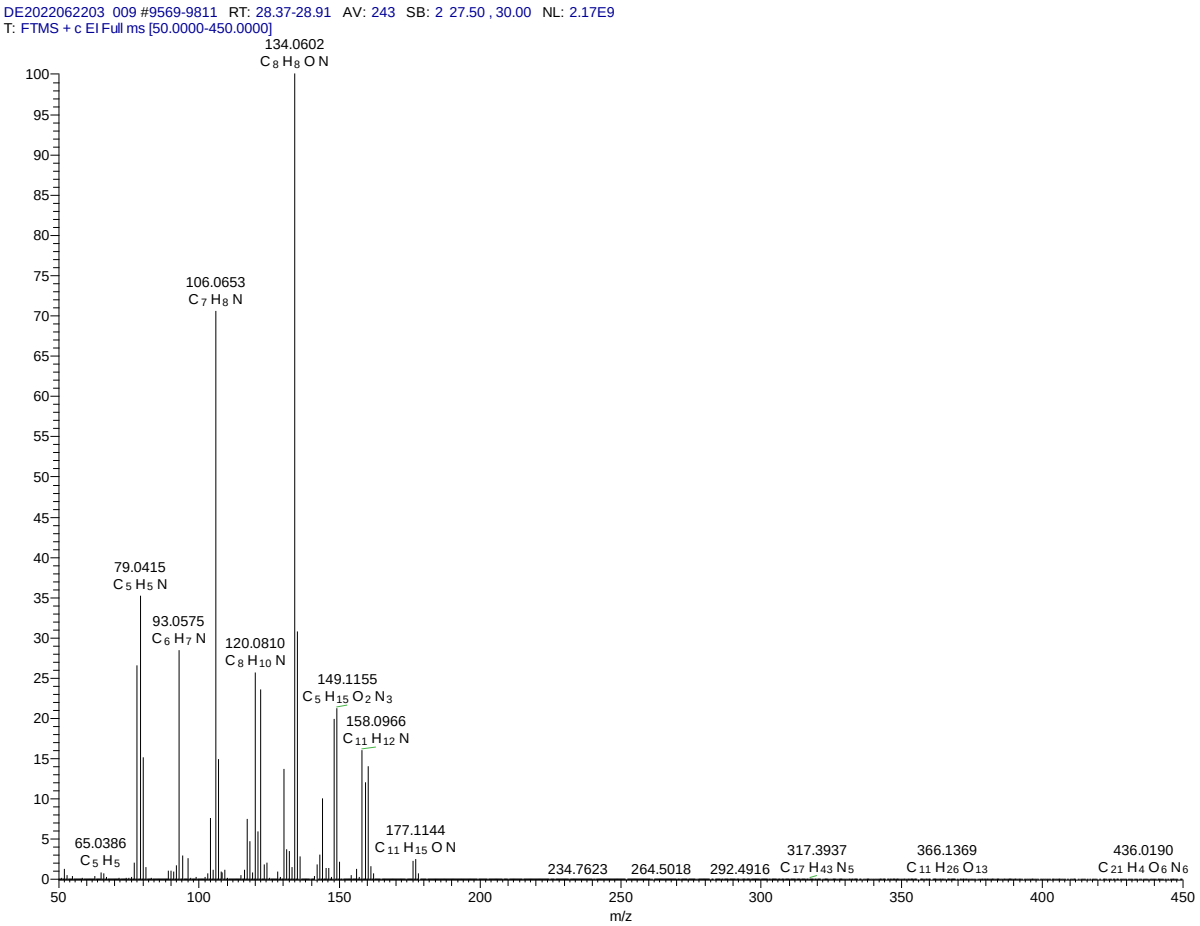

Figure 31: Mass spectrum of product **28** in oil bath

^{1}H NMR and ^{13}C NMR spectra of product **29**

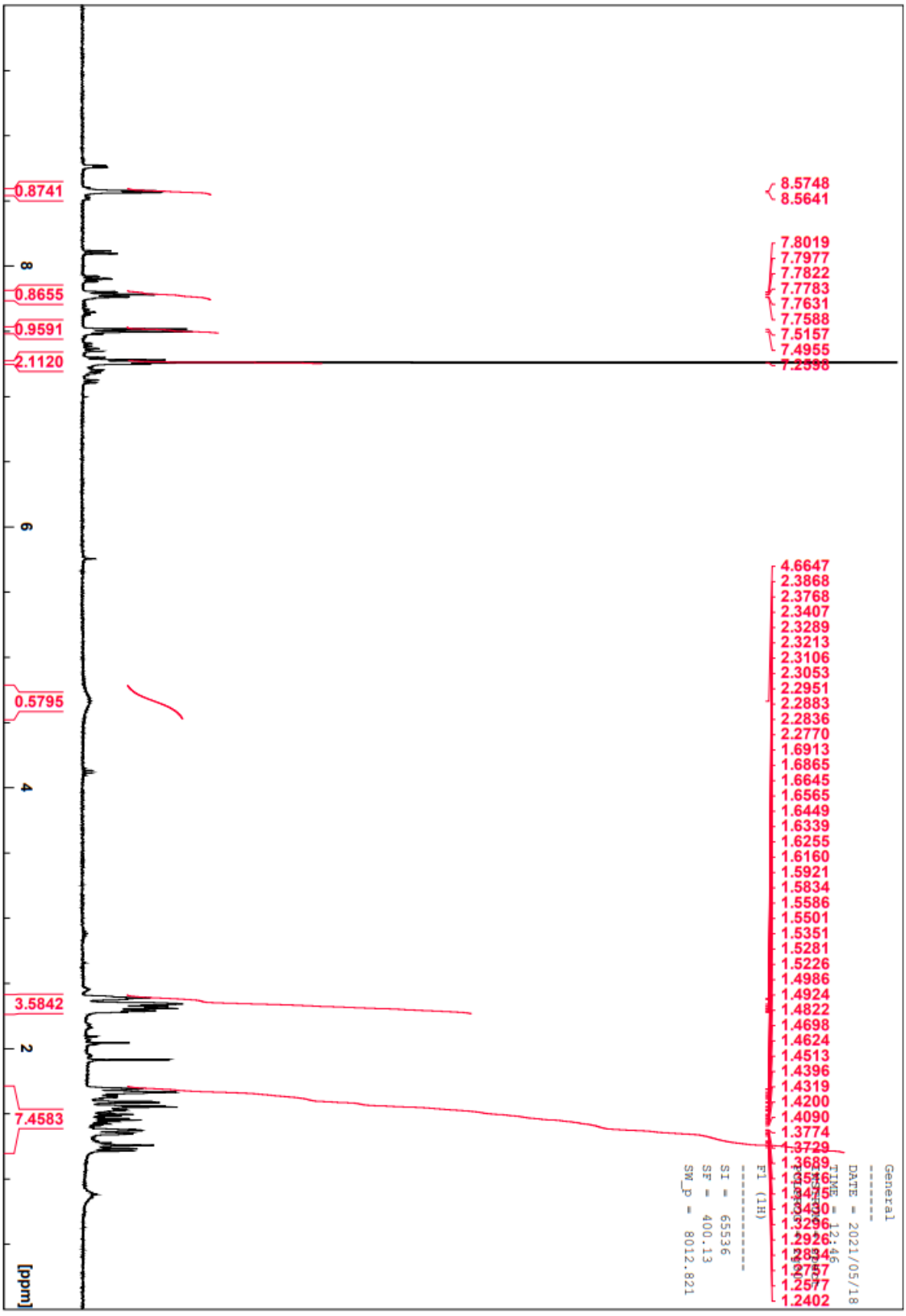

Figure 32: ^{1}H NMR of product **29** when reacted in oil bath.

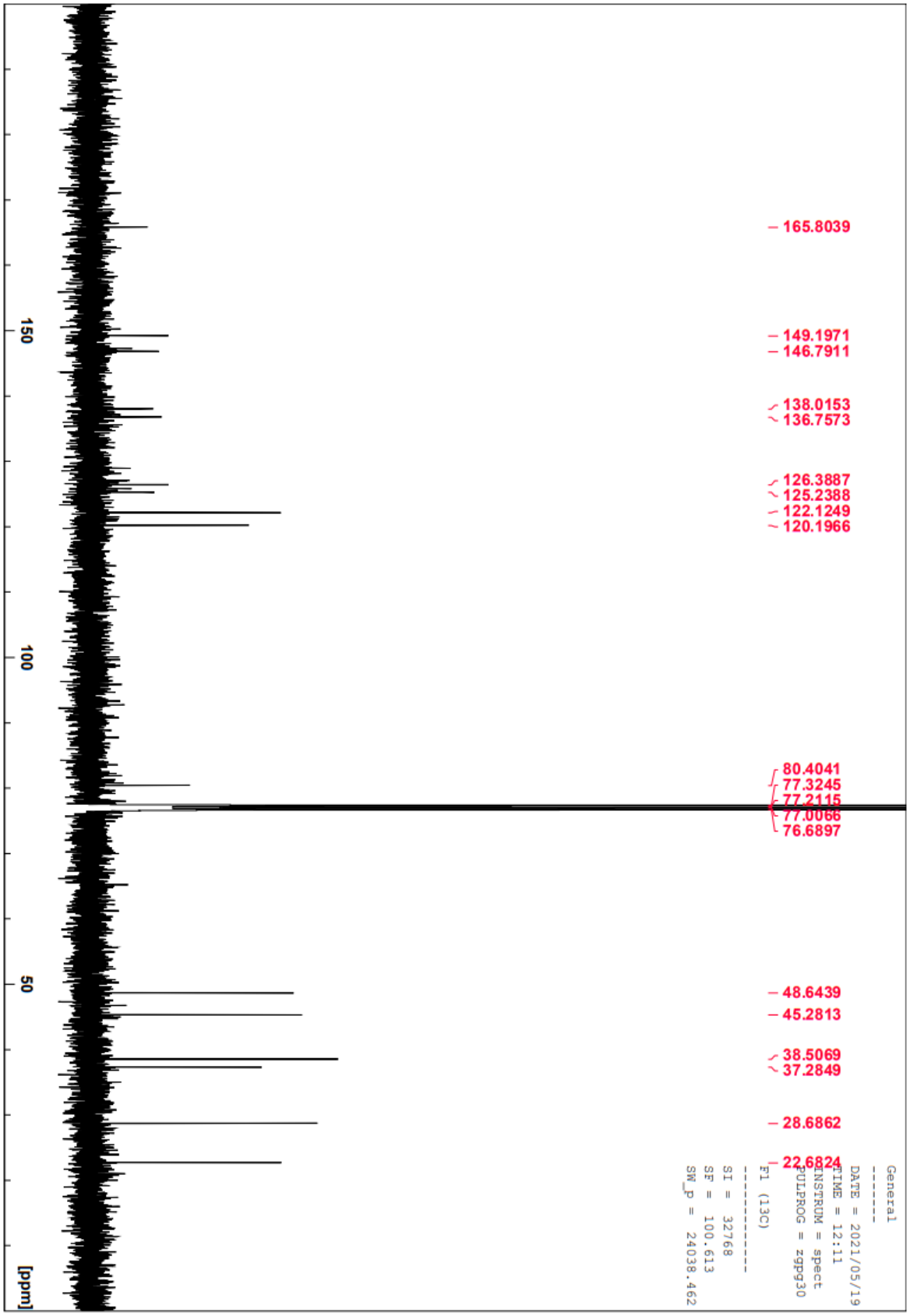

Figure 33: ^{13}C NMR of product **29** when reacted in oil bath.

^{1}H NMR and ^{13}C NMR spectra of product **30**

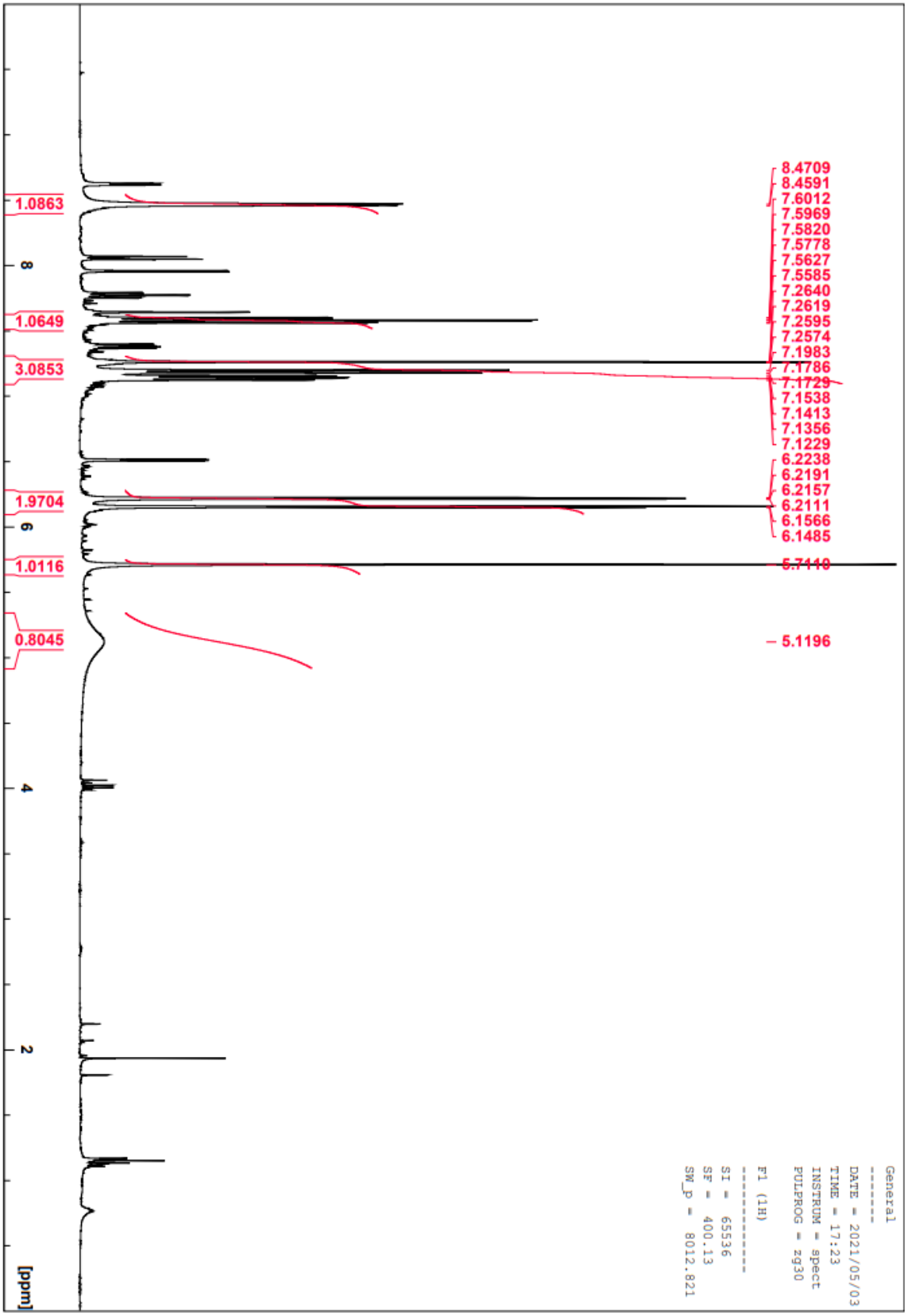

Figure 34: ^{1}H NMR of product **30** when reacted in oil bath.

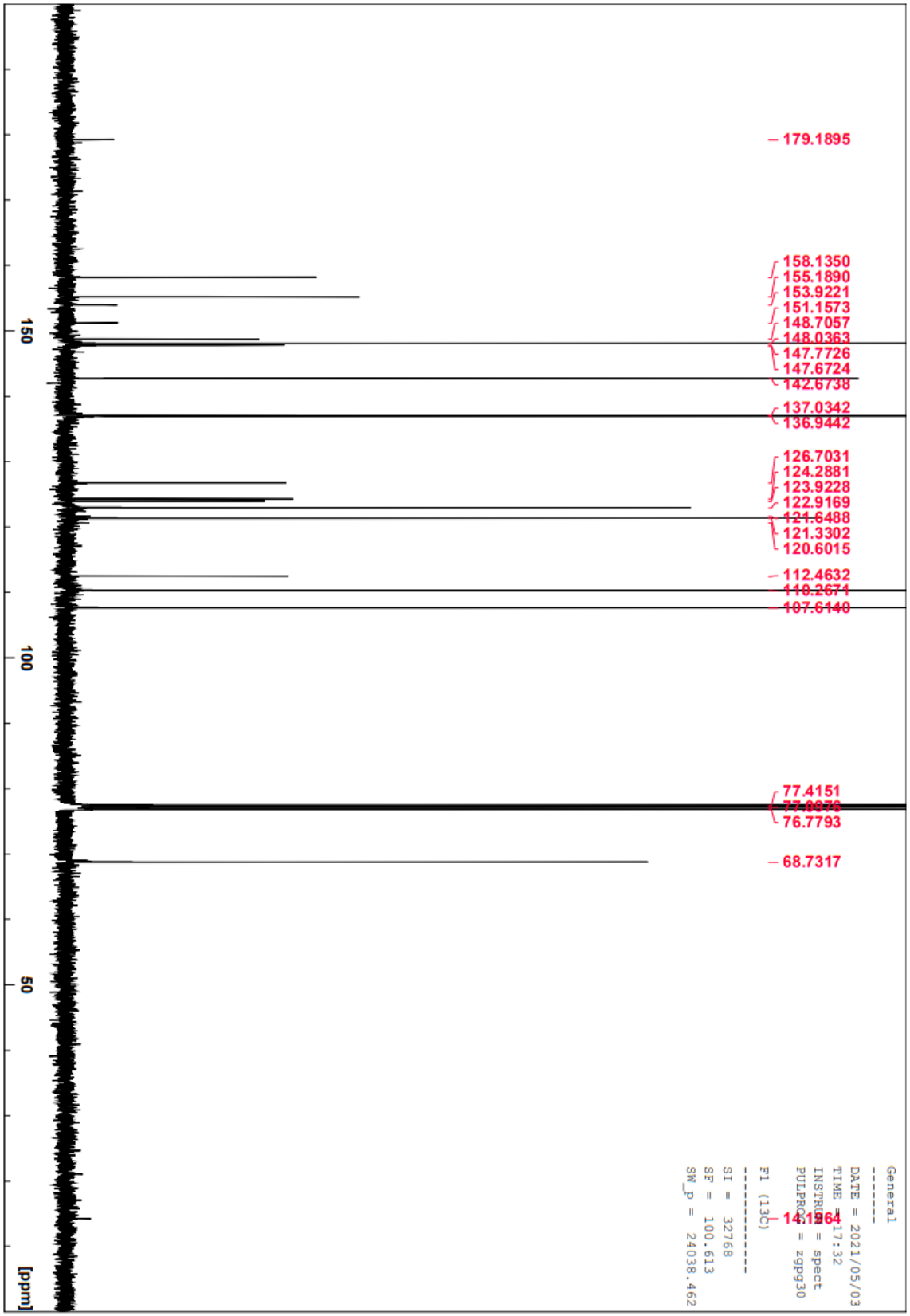

Figure 35: ^{13}C NMR of product **30** when reacted in oil bath.

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