.

New Drugs for Old

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***University of Plymouth, ^ University of Hull**

2002

Appendix A: Student Handouts

New Drugs for Old

You are screening natural herbal remedies for their active ingredients.

Dr. Overdone has offered you some dried leaves that he claims cured his high fever.

New Drugs for Old

SCIENTIFIC SKILLS

- pharmaceutical analysis
- interpretation of MS, FT-IR & NMR spectra
- separation and purification techniques
- economics: costing synthetic routes

TRANSFERABLE SKILLS

- working with others
- communication
- decision making
- analytical/critical thinking
- independent learning
- time management

What you need to do

Part 1

- Decide short term and long term plans

Part 2

- Interpret spectra
- Identify active ingredient

Part 3

- Cost suitable reaction schemes
- Recommend any further action

The University of Midshire

Department of Anthropology
Darwin Building, Beauport, Midshire.

Green Chem Inc.,
University Science Park,
Midshire.

Dear Dr. Somersby, Director of Research

Further to my communication of the 1st January, I have returned from Malaysia and I would like to bring your attention to some remarkable observations that may interest your company who I know from my colleague, Dr. Allan Childus, are investigating natural herbal remedies.

Deep in the interior, having lost most of my belongings including my medicine kit, I was taken ill with a high fever. The local 'midwife,' a native of the Matillie Tribe gave me an infusion of a bitter tasting tea. The 'midwife' explained that it is used to assuage the evil spirits that make the soul boil. She did warn that if the fight was prolonged, there could be stomach cramps and bleeding.

On recovering I was able to discover that the tea was made from the dried leaves of a particular indigenous tree that I am reliably informed is not known outside this region and takes 50 years to reach maturity.

I am willing to supply you with a suitable sample (about 250 g) of the dried leaves if you are still interested in investigating this remarkable remedy. I would like to see an outline of how you propose to proceed with the project.

Yours sincerely

Dr. S. Overdone

The Company

Your company is a subsidiary of the large international chemical / pharmaceutical company of Green-Chem Inc. which is based in the Science Park next to the University of Midshire, Beauport.

Your parent company have tasked you to screen natural herbal remedies for their active ingredients.

Initial Assignment

In response to Dr. Overdone you must decide upon: -

1. The immediate short term experiments that need to be carried out in order to isolate and characterise the active ingredients.

2. The longer term plans after the active ingredient has been identified.

Produce a one-page summary assuming that the compound is of further interest. This plan should be submitted in a sealed envelope with your company's name and those of the team members on the outside.

Card Game

Use the cards to construct a logical sequence consistent with short and long-term plans

- Place the cards in a logical order
- The blank cards may be used

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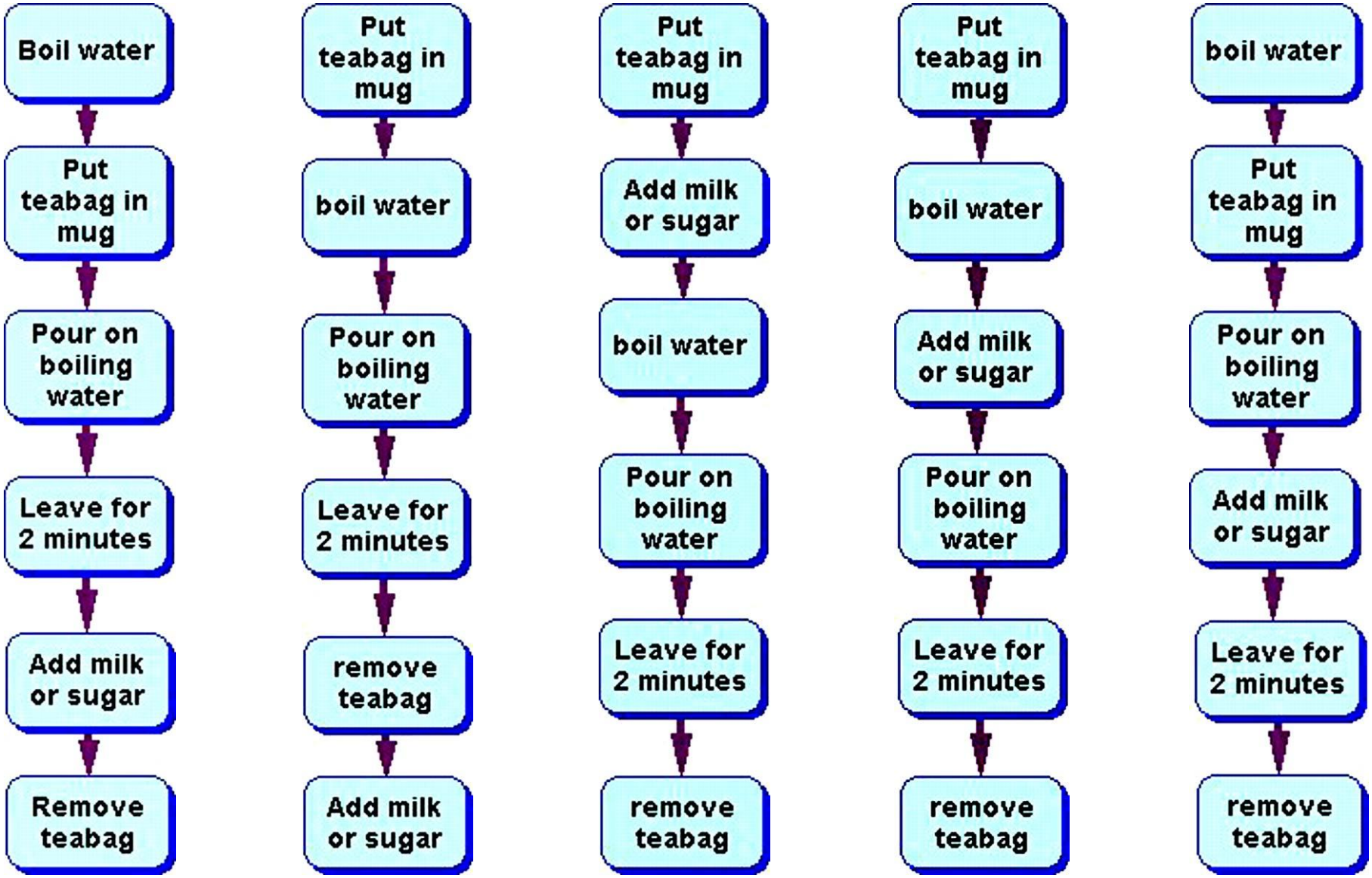
Your parent company have tasked you to screen natural herbal remedies for their active ingredients.

Initial Task

1. Discuss what initial experiments you would carry out after receiving the sample of leaves in order to isolate the active ingredients.

2. Place the cards in what you would consider a logical order to indicate how a new pharmaceutical is developed from the discovery of biological activity to the new product going on sale.

3. The extra blank cards may be used to add any further steps that you consider important.



Making a mug of tea

Biological activity observed

Clinical trials

Isolation of the active ingredient

Approval

Structure determination

Marketing

Synthesis

Economics

Toxicity screening

Drug goes on sale

Formulation

Extraction and separation of components

Go to the Library

Ethics

Investigating analogs

Investigation and modelling of the active site

Stability trials

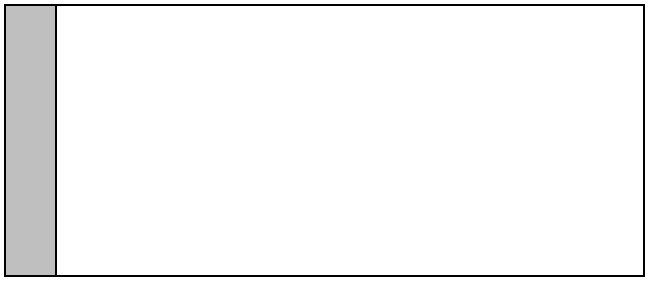
Submit new drug application

Packaging design

Comparison with competition

Mode of delivery

Post-marketing/ licensing surveillance



Identification of Components

Your technicians have carried out a Soxhlet extraction of the dried leaves that you supplied. Liquid-liquid extraction and chromatography have isolated the components A-D.

Before the components are sent away to pharmacology for identification of the active ingredient, the compounds need to be characterised and their structures determined using the information supplied by your spectroscopy technicians. The following information has been obtained:

- Physical appearance
- Melting point
- Solubility
- UV/Visible spectrum
- CHN analysis
- FT-IR spectrum
- Mass spectrum
- ^{1}H-NMR spectrum
- ^{13}C and DEPT NMR spectra

From this information, the structure of the components can be determined.

Notes

Compound A

Appearance	White crystalline powder that gradually discoloured in sunlight.
mp	157-159 °C
bp	Decomposes
solubility	Very soluble in ethanol, acetone & ether; soluble in chloroform; slightly soluble in water
λAbs	236 nm and 303 nm in aqueous acid; 298 nm in aqueous alkali.
CHN analysis	C 60.87%, H 4.38%

Compound B

Appearance	White plate crystals
mp	190-192 °C (some decomposition)
bp	Decomposes
solubility	Very soluble in water and propylene glycol; soluble in ethanol, glycerol; insoluble in ether, chloroform, benzene, oils, and fats.
λAbs	243 nm in 0.2 M ammonium sulfate solution; 299 nm in basic solution
CHN analysis	C 40.92%, H 4.58%

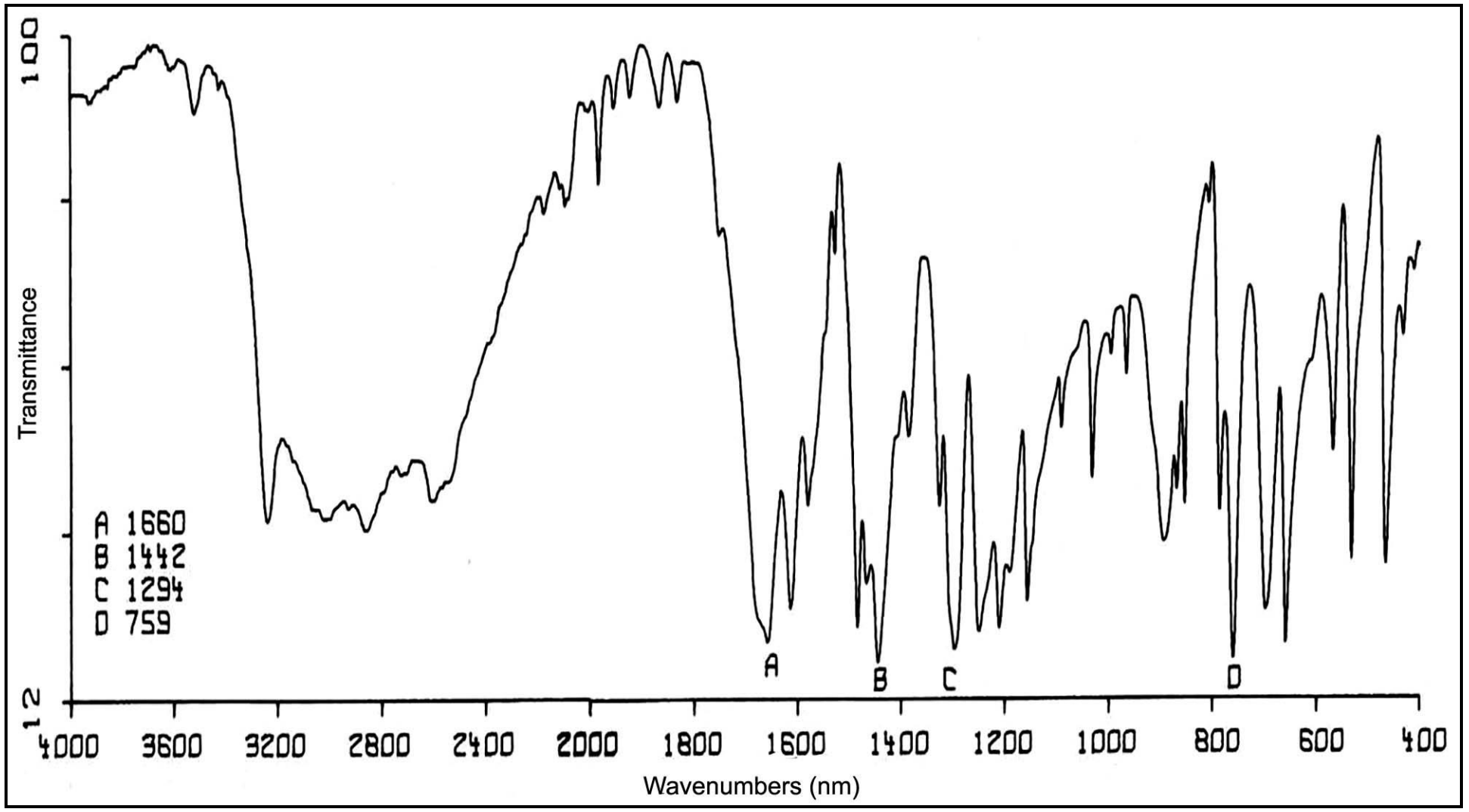
Compound C

Appearance	Yellowish oily liquid with a sweet odour.
mp	-8,6 °C
bp	220-224 °C
Solubility	Soluble in chloroform & ether; miscible in ethanol & glacial acetic acid; very slightly soluble in water
λAbs	243 nm in aqueous acid.
CHN analysis	C 63.15%, H 5.30%

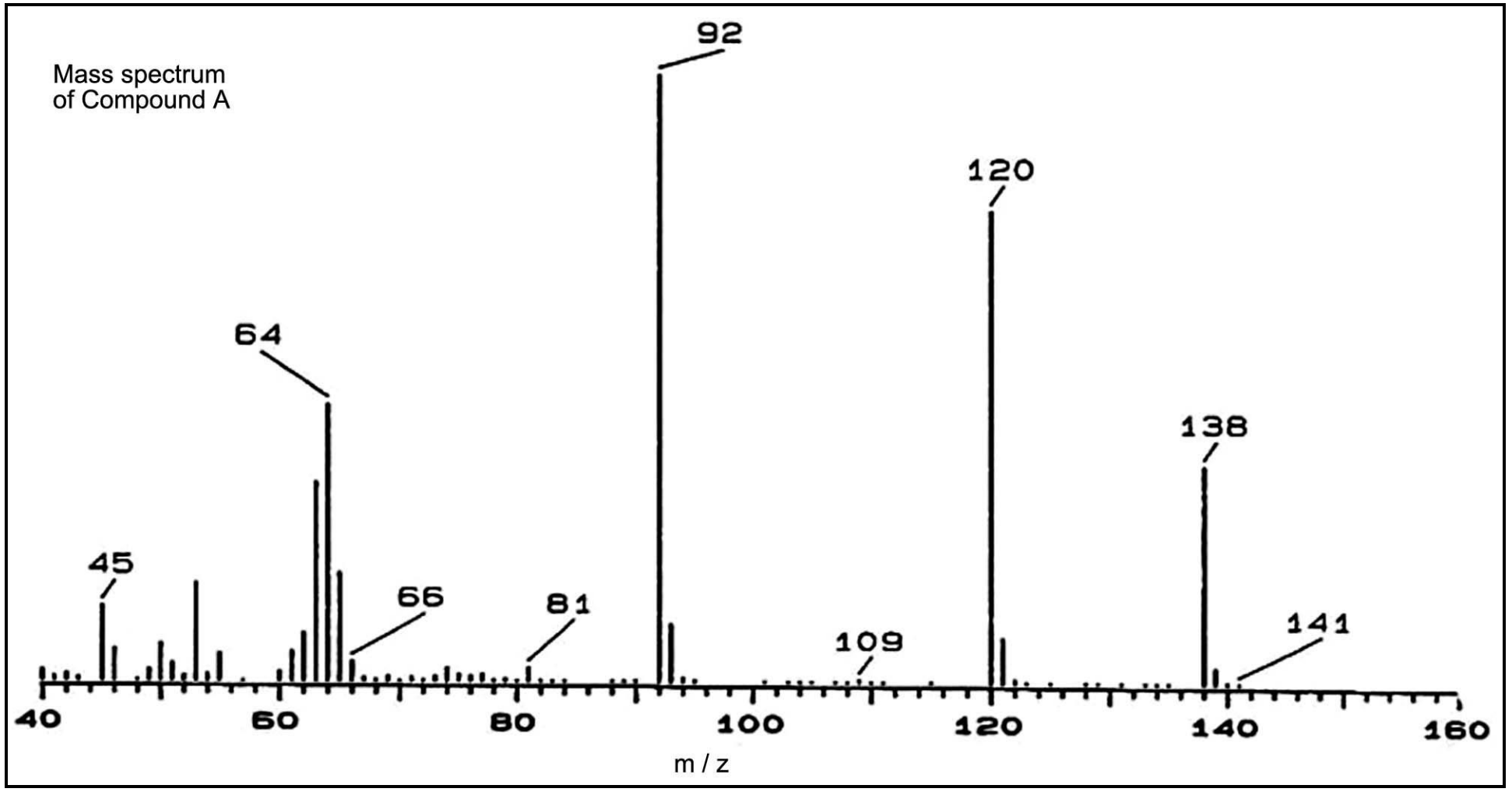
Compound D

Appearance	Monoclinic crystals.
mp	122 °C
bp	249 °C
solubility	Very soluble in ethanol, chloroform, ether, acetone and alkaline solution; soluble in oils: slightly soluble in pet. ether and water.
λAbs	230 nm and 273 in aqueous acid; 269 nm in basic solution
CHN analysis	C 68.85%, H 4.95%

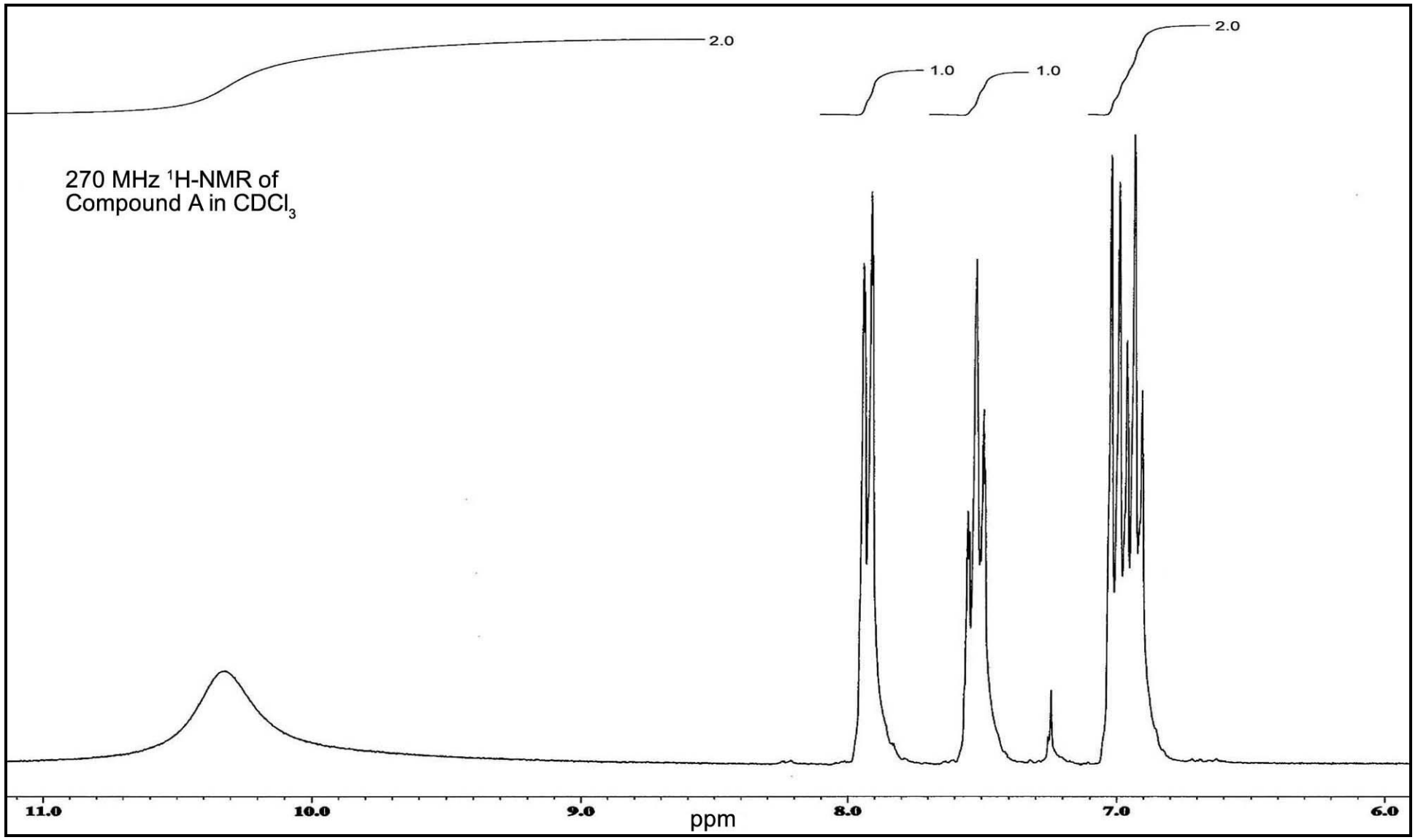
FT-IR spectrum of Compound A (KBr disc)



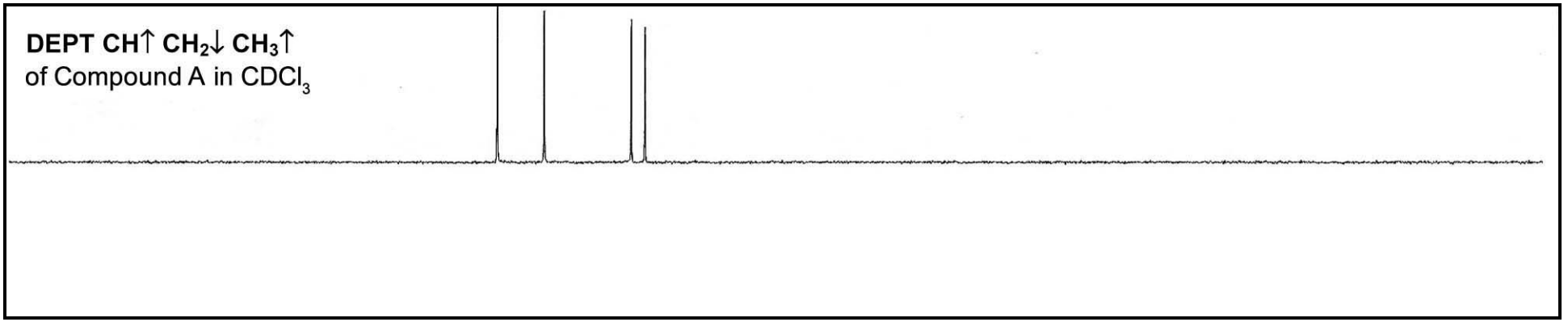
Mass Spectrum of Compound A

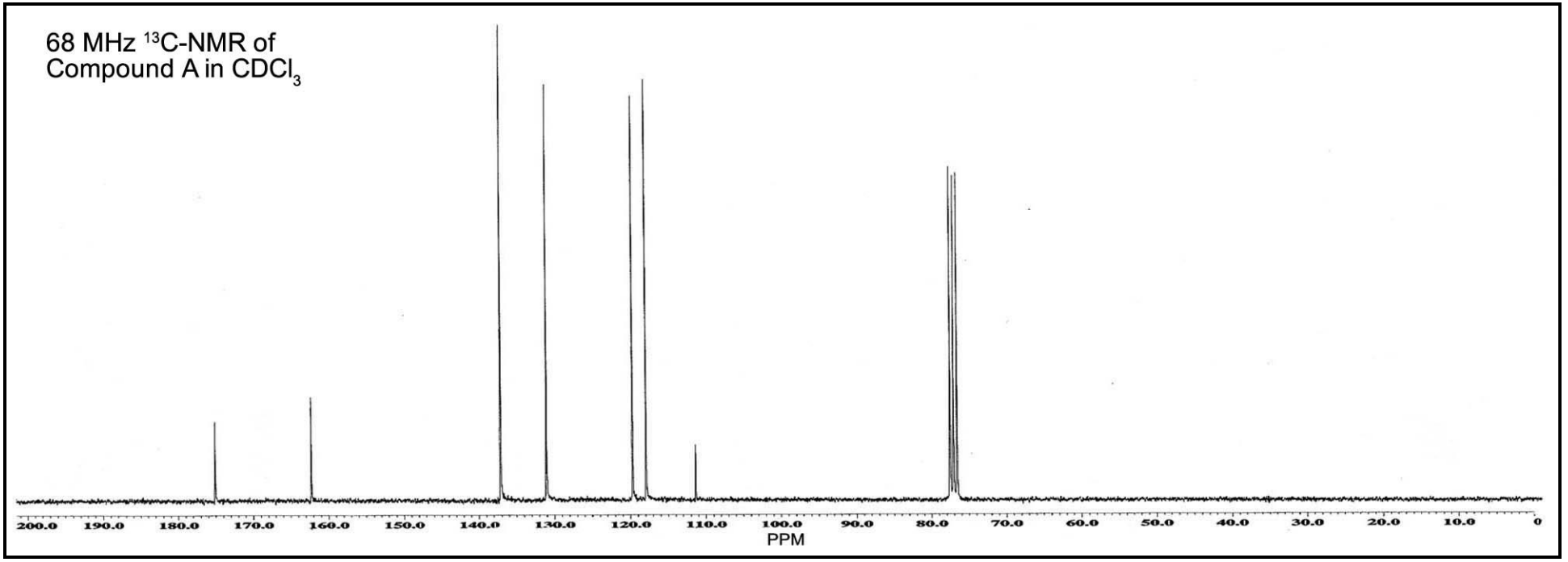


^{1}H-NMR spectrum of Compound A

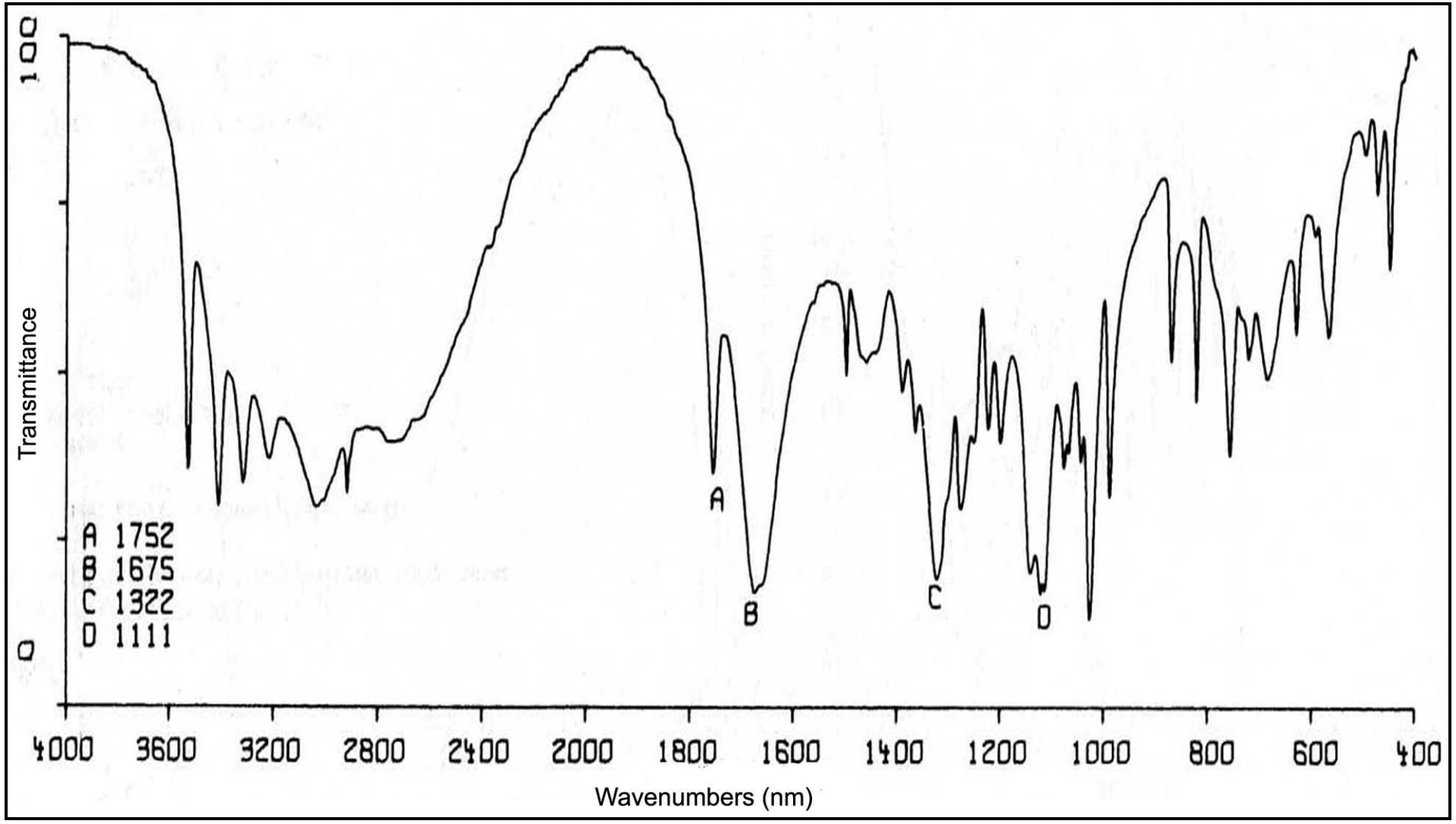


^{13}C and DEPT NMR spectra of Compound A

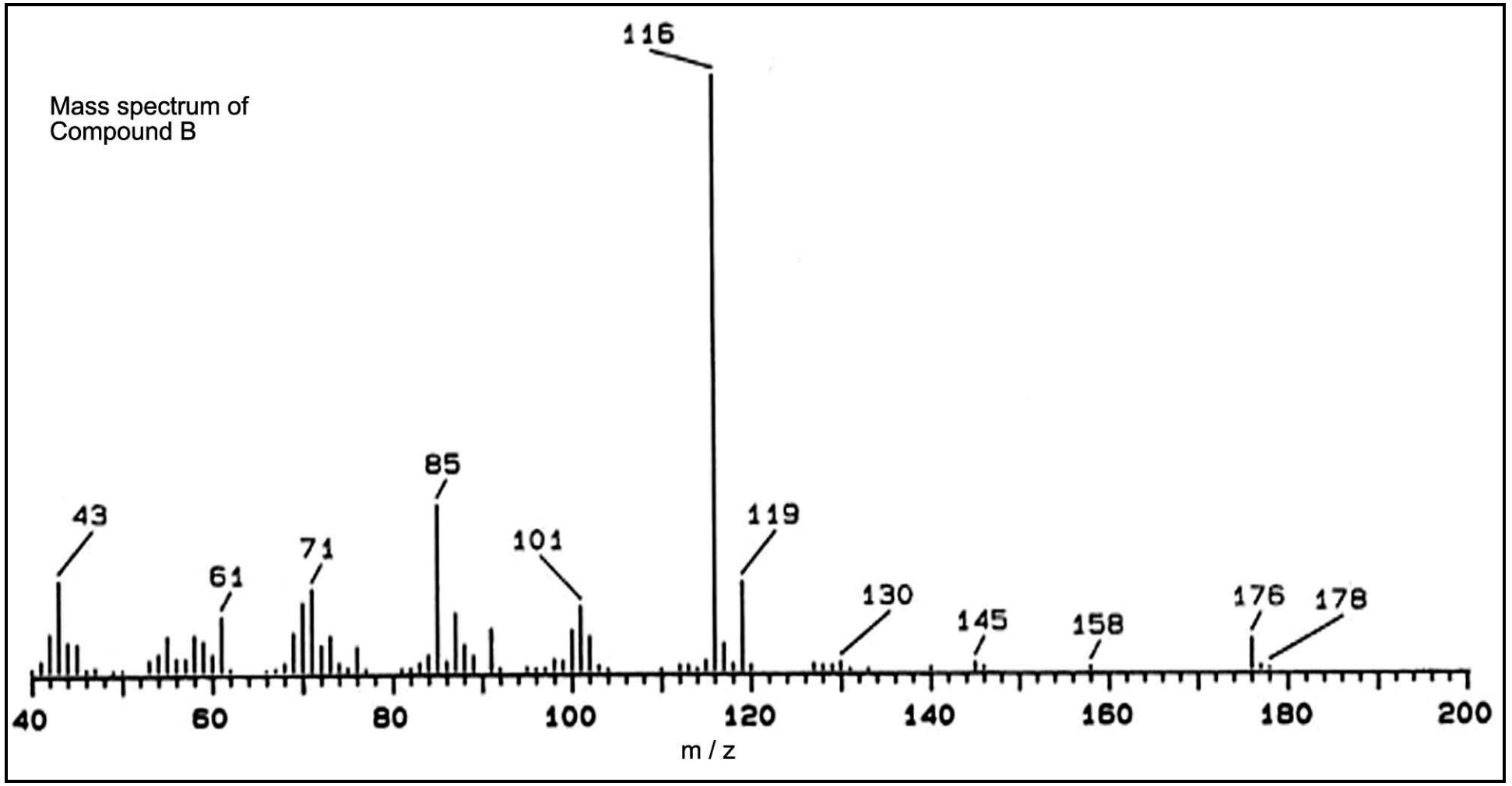




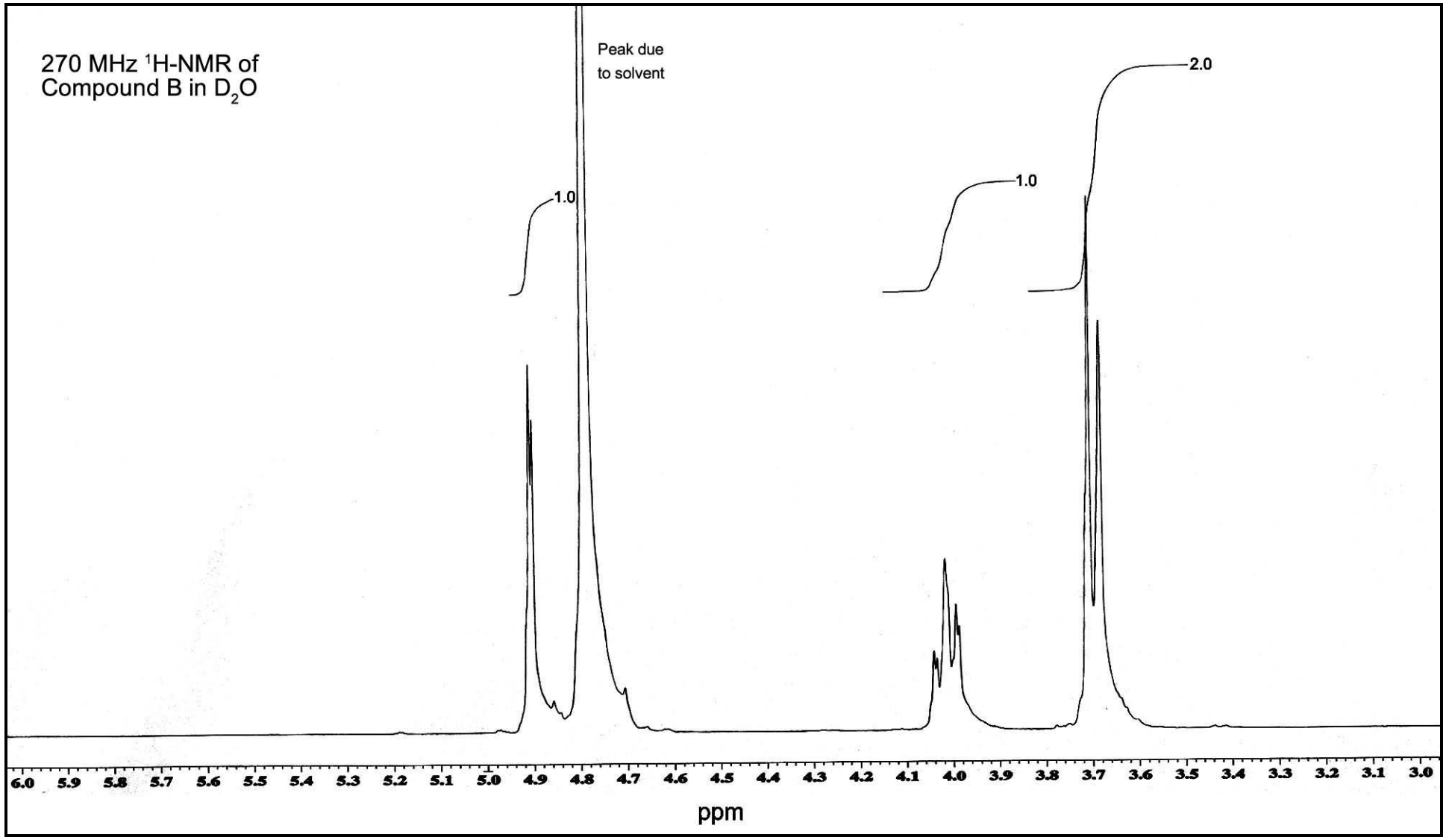
FT-IR spectrum of Compound B (KBr disc)



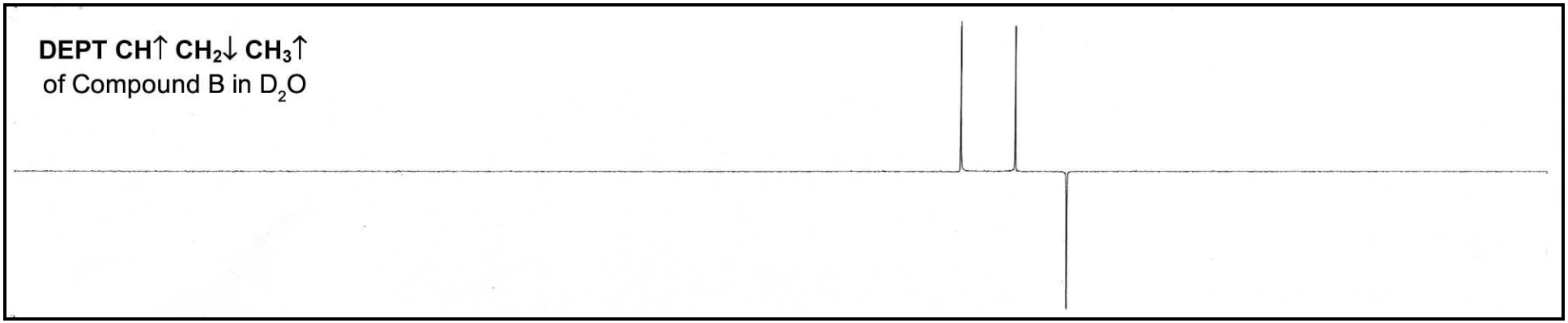
Mass Spectrum of Compound B

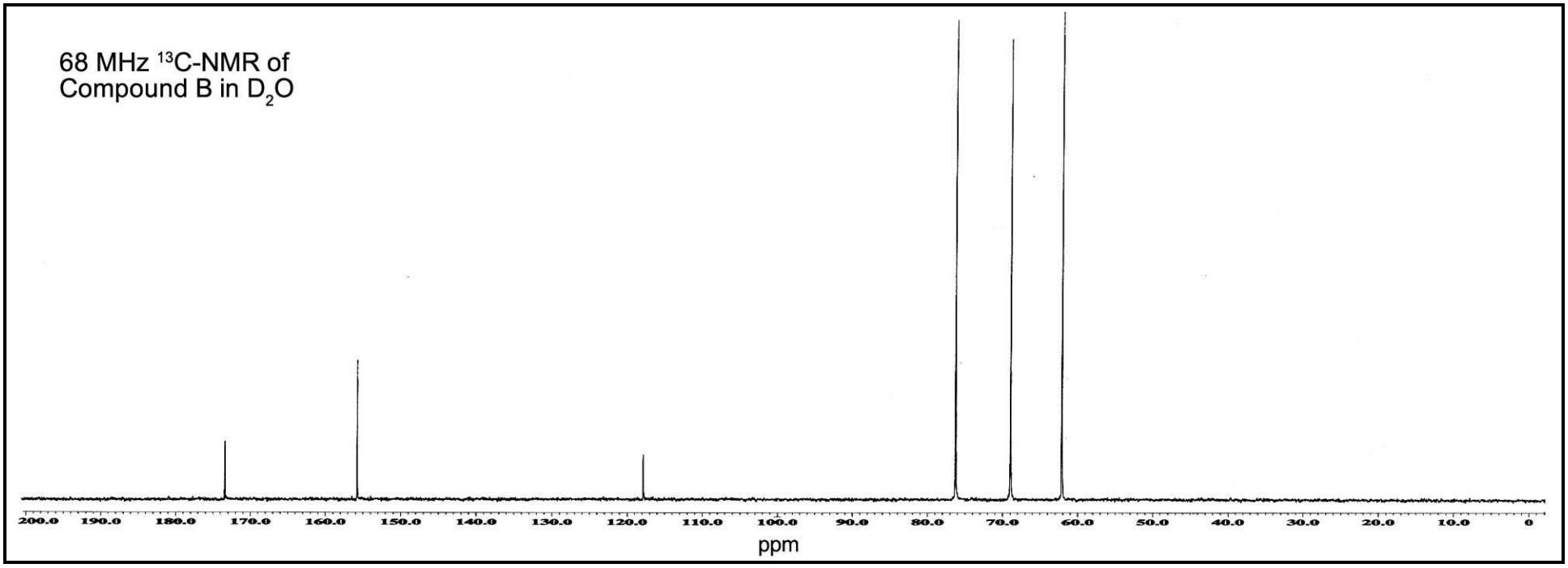


^{1}H-NMR spectrum of Compound B

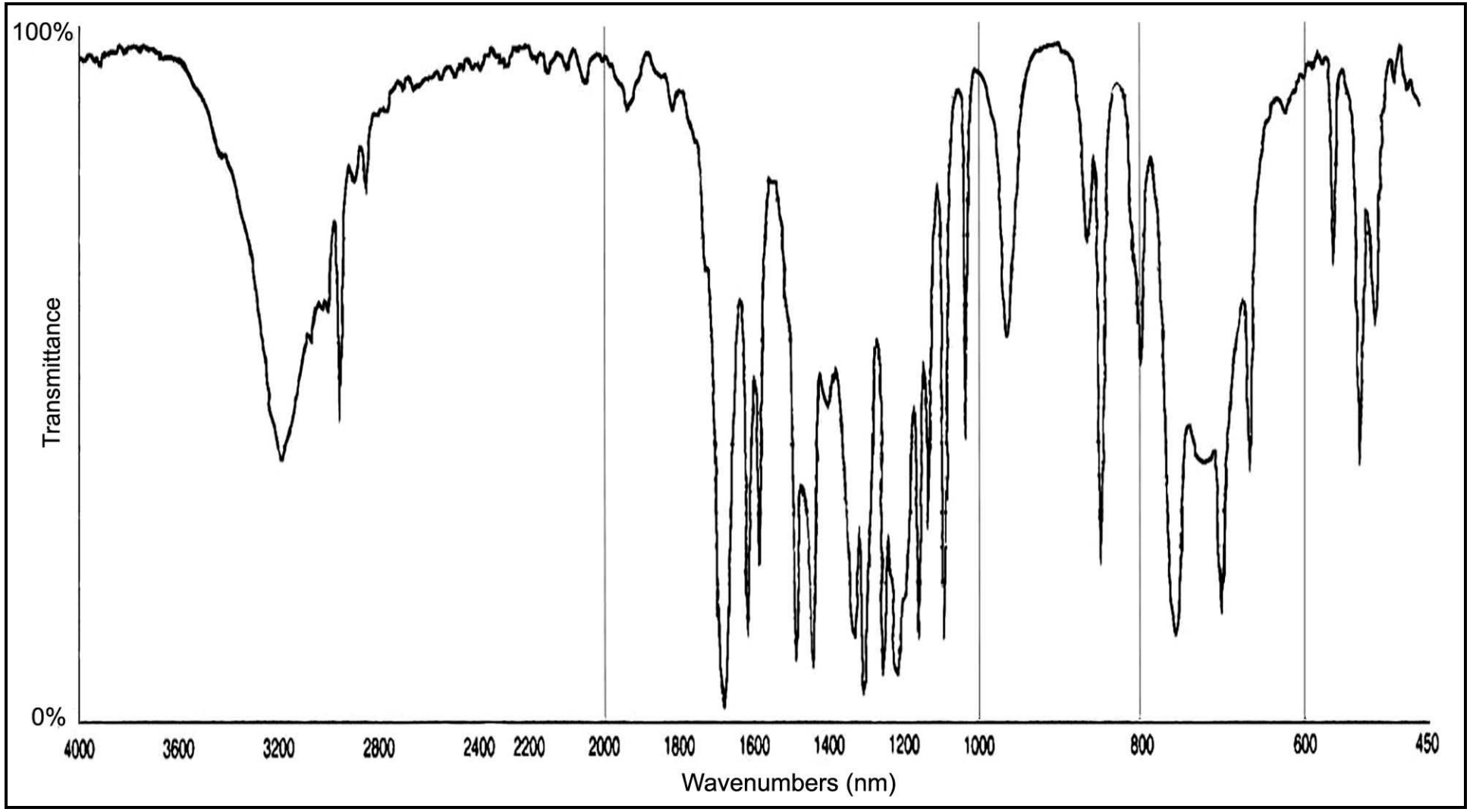


^{13}C and DEPT NMR spectra of Compound B

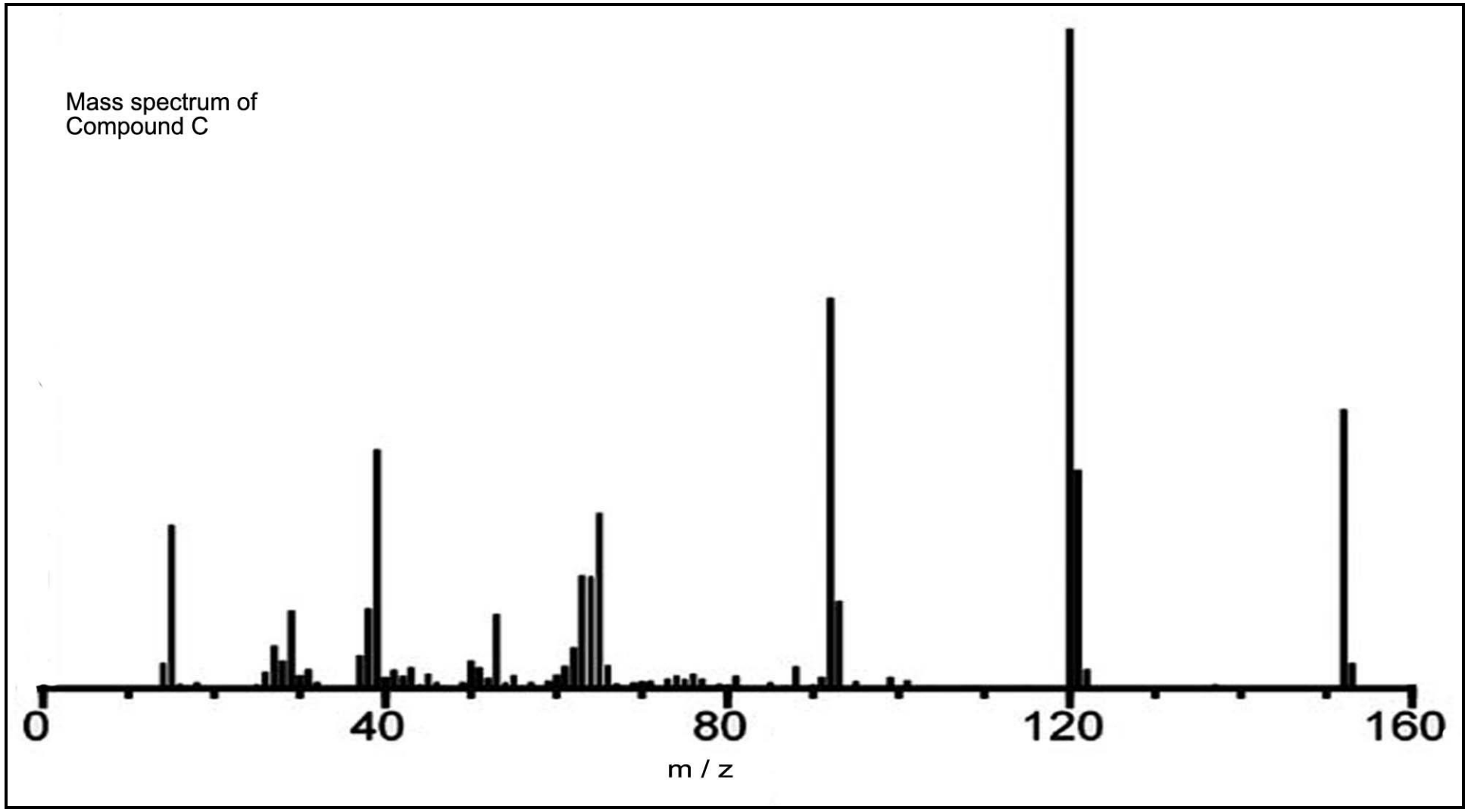




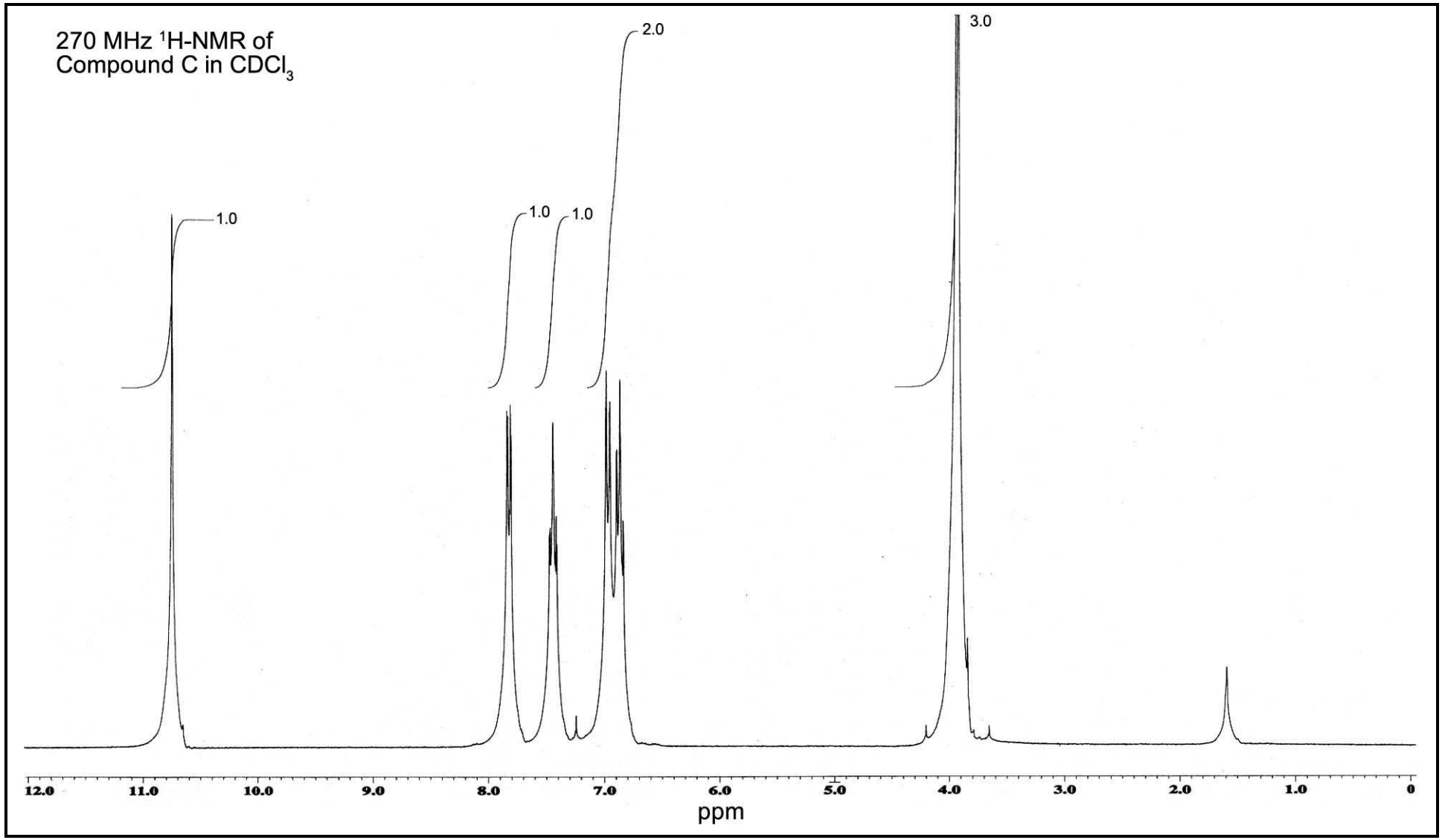
FT-IR spectrum of Compound C (KBr disc)



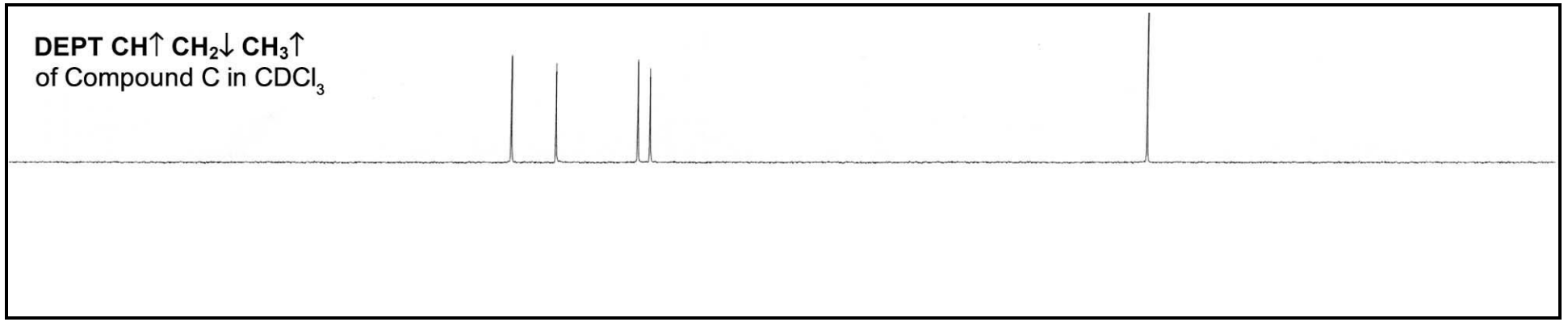
Mass Spectrum of Compound C

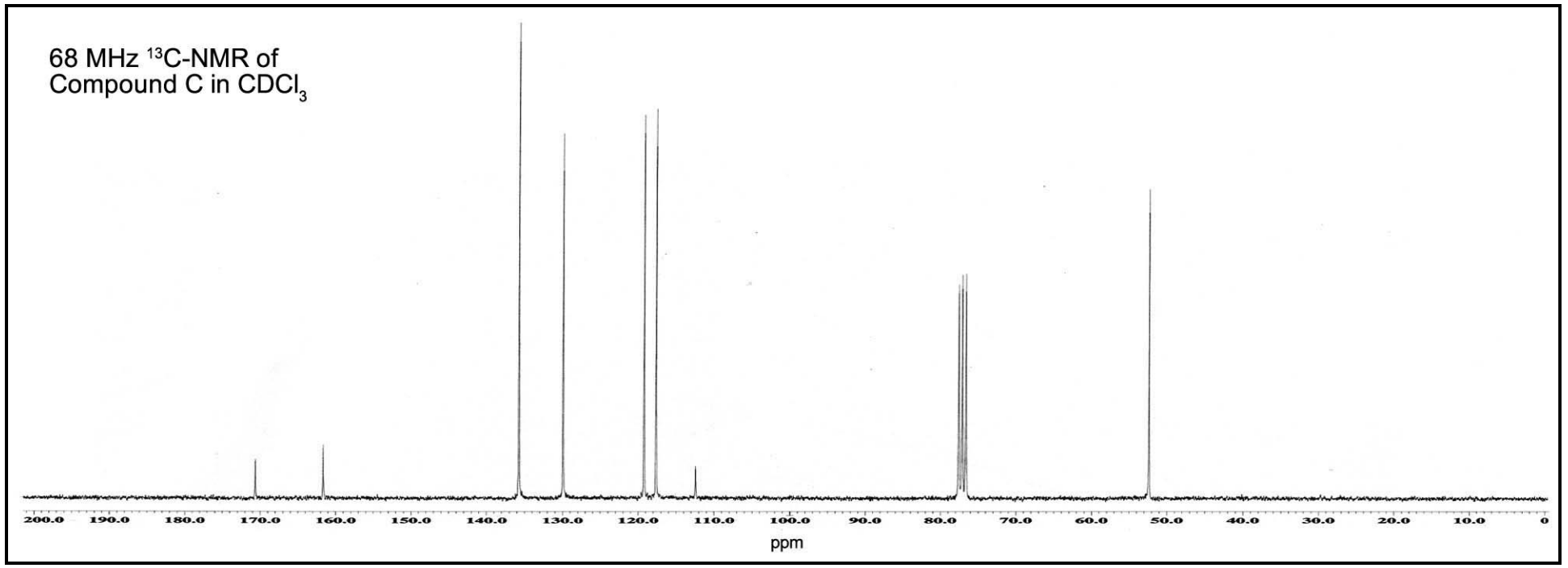


^{1}H-NMR spectrum of Compound C

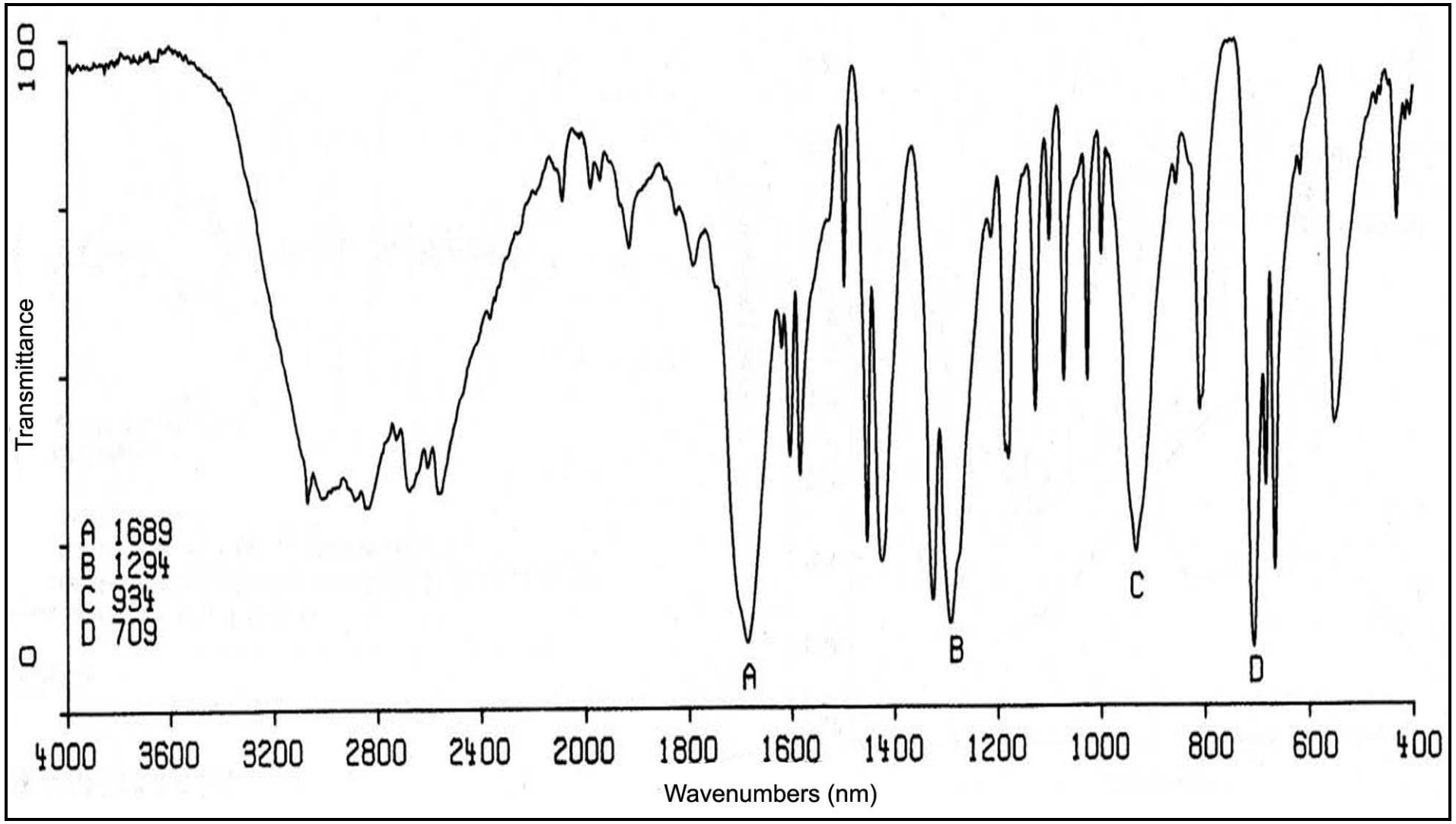


^{13}C and DEPT NMR spectra of Compound C

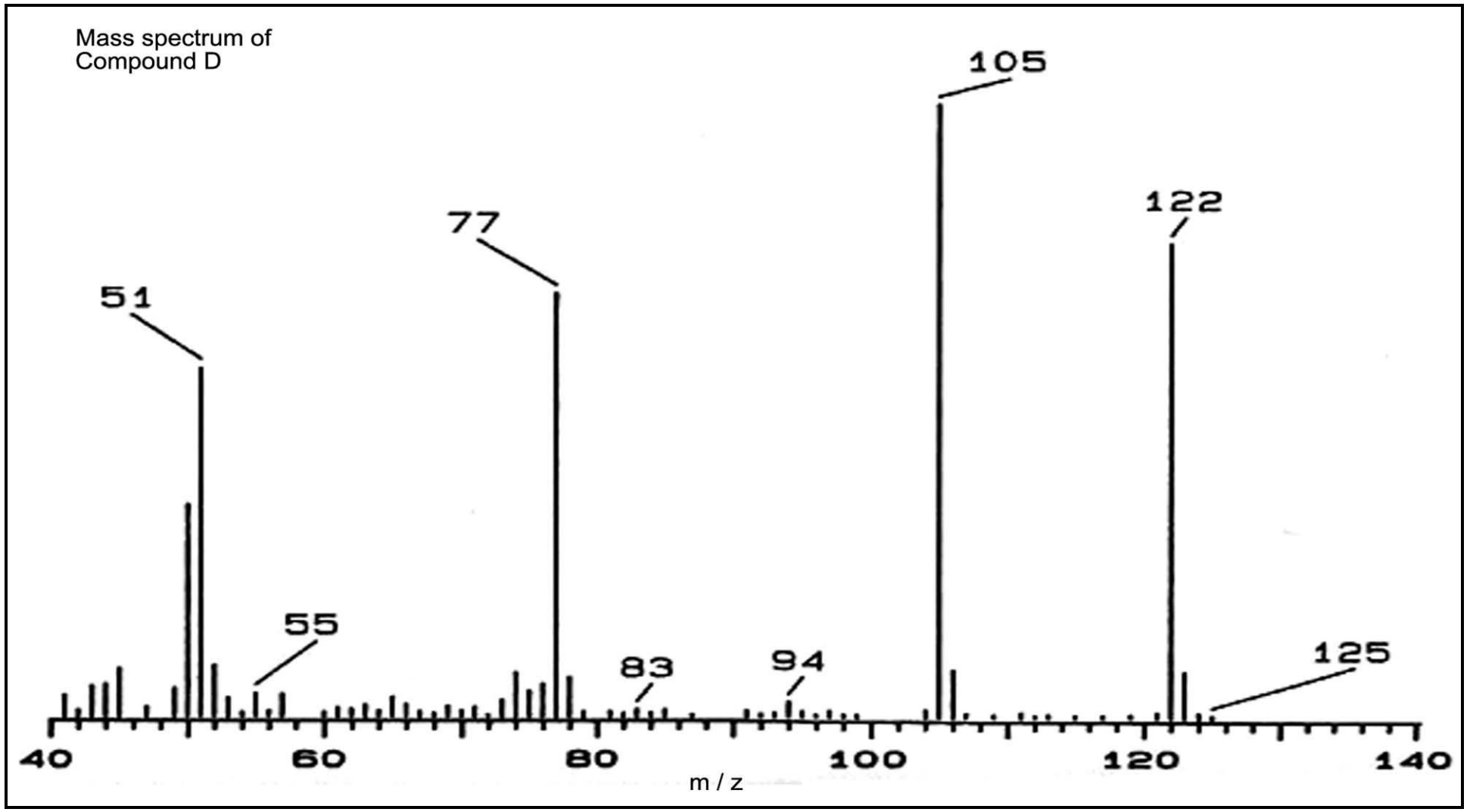




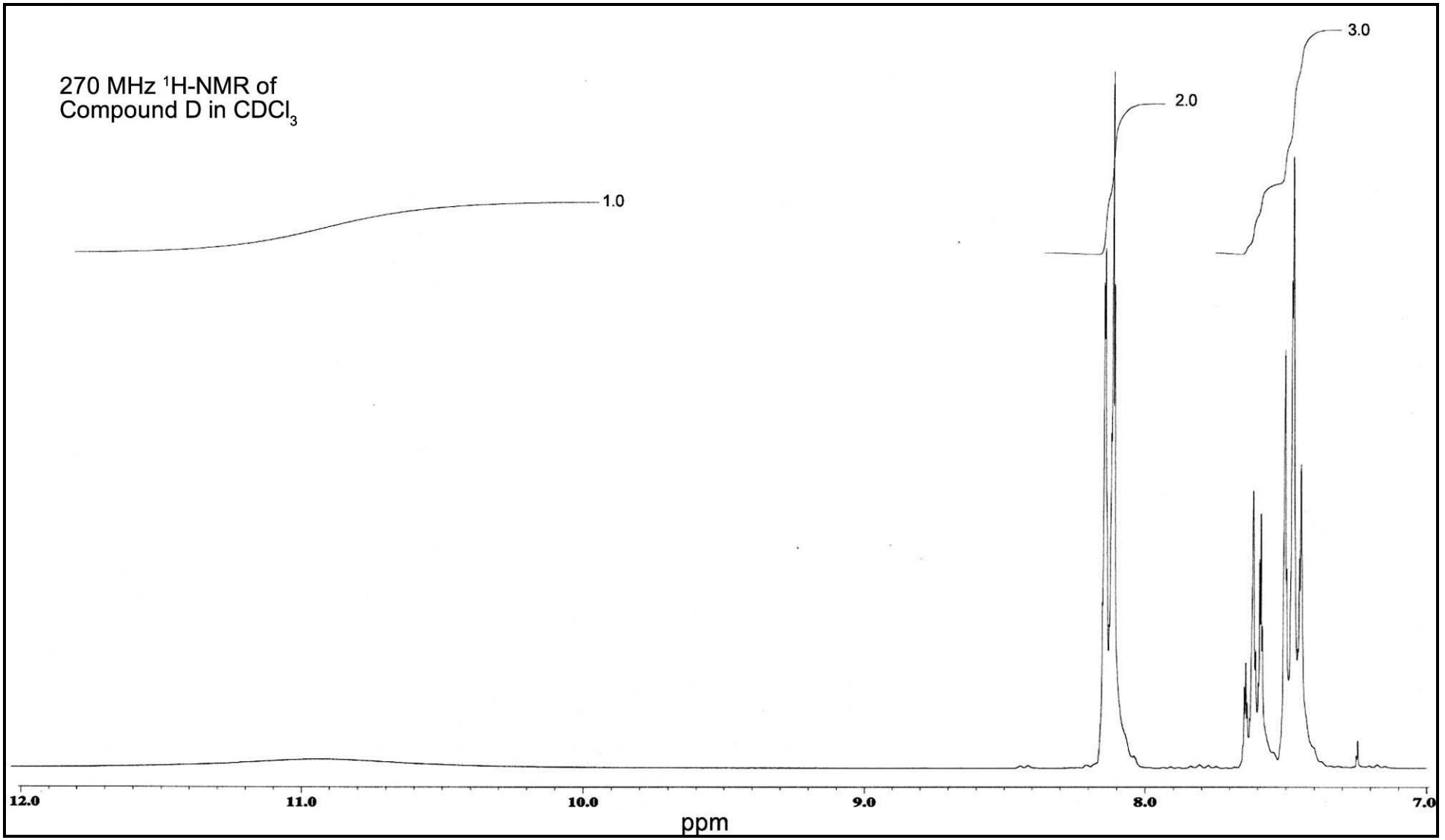
FT-IR spectrum of Compound D (KBr disc)



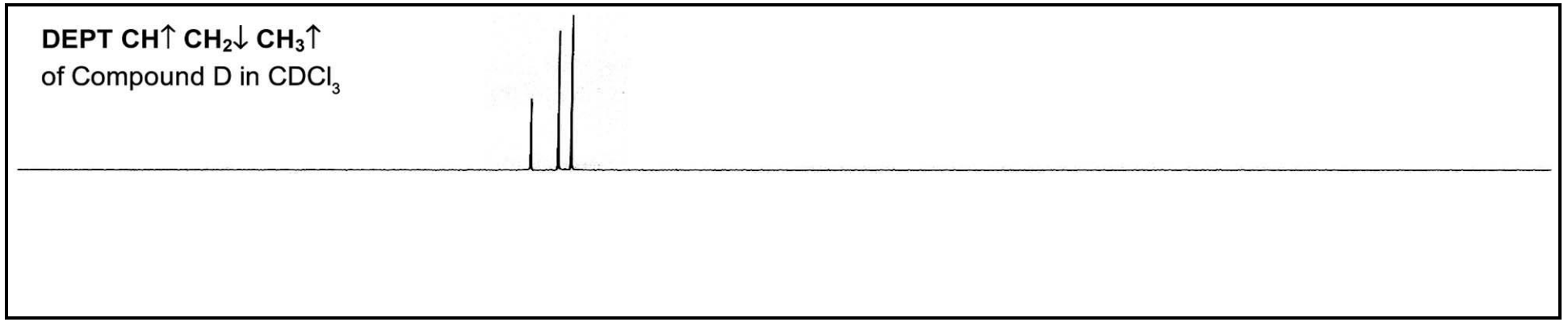
Mass Spectrum of Compound D

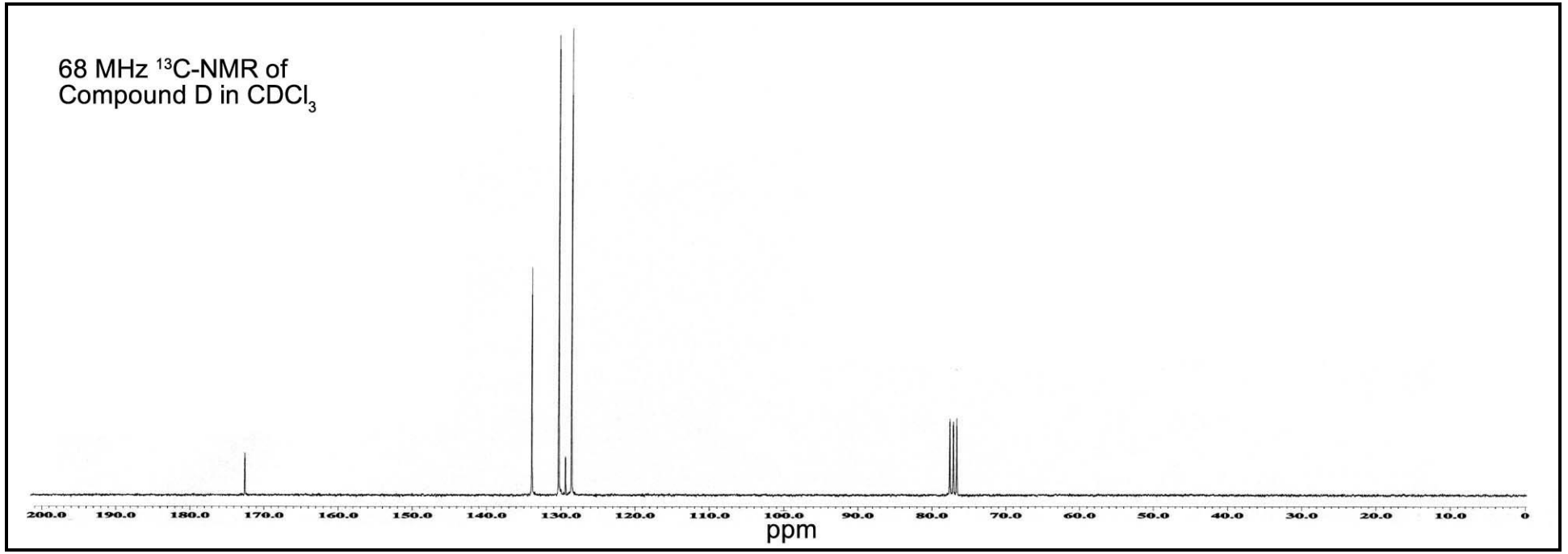


^{1}H-NMR spectrum of Compound D



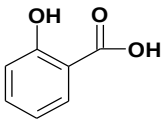
^{13}C and DEPT NMR spectra of Compound D



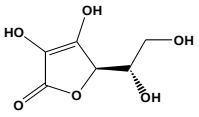


Synthesis of Active Component

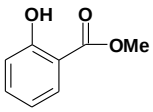
You have successfully identified Compounds A-C.



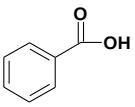
Compound A



Compound B



Compound C

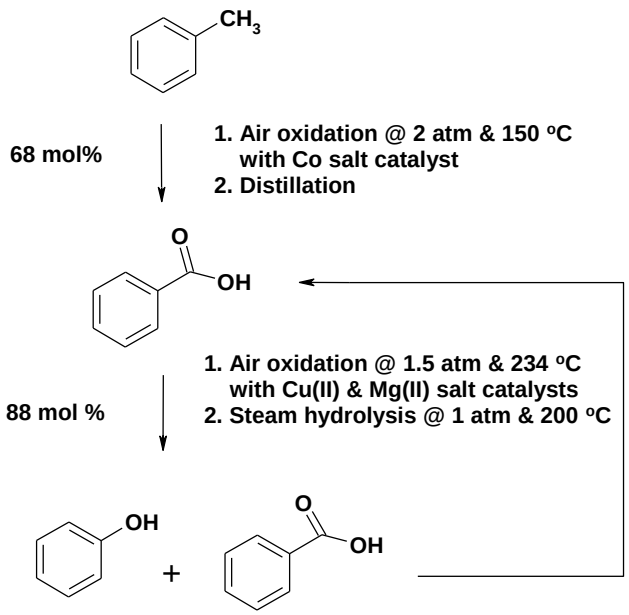


Compound D

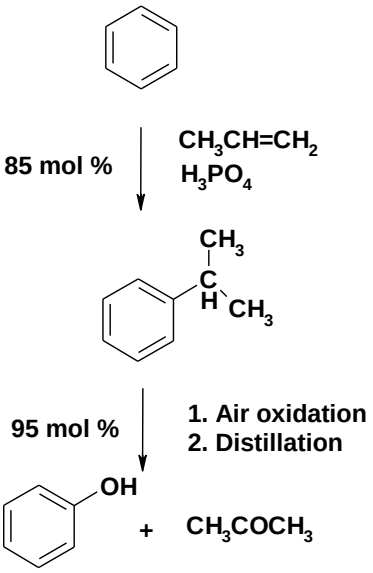
Pharmacology has determined that the most active ingredient for reducing fever is Compound A. Your organic chemist has suggested the following reaction pathways (routes I-IV) to Compound A.

- Consider how you would synthesise compound A.
- Estimate the cost per kg for the synthesis.

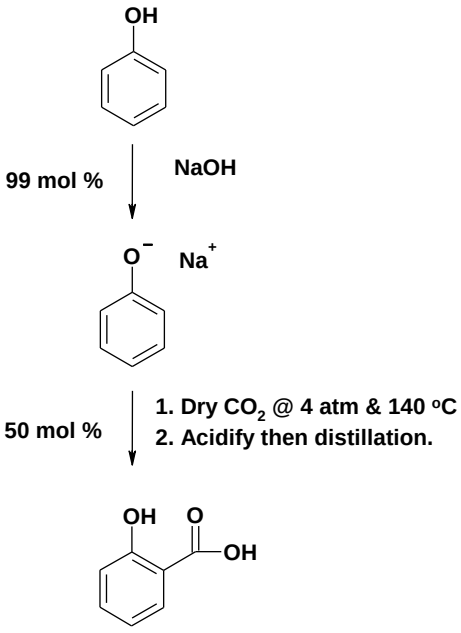
Route I



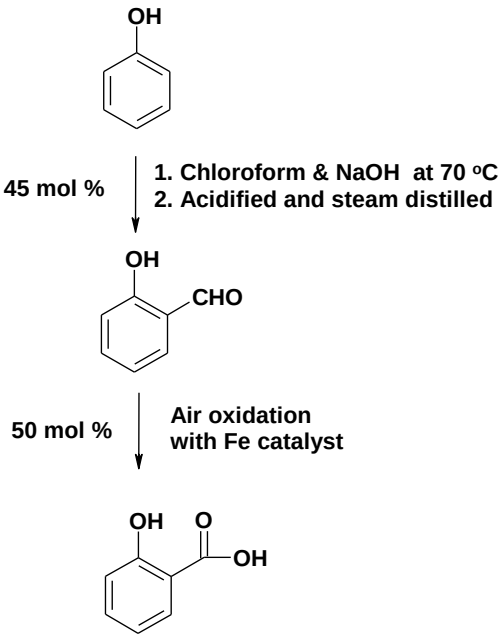
Route II



Route III



Route IV



Urgent message from

Green Chem Inc.

Since your e-mail informing us of the potential of this new compound, there has been a major review of our R&D commitments. Consequently, you are required to give a **five-minute** presentation to the Director of Research outlining the potential for the project.

You might consider including some of the following in your presentation:

- The methods that have been used to isolate and identify the active ingredient
- How the project will develop once the active ingredient has been identified.
- Your plan for future investment
- Your chosen method of synthesis and costings at the pilot plant scale (1 kg) if appropriate.
- Your plans for marketing the new product if appropriate (What are the approximate costs and activities of related pharmaceuticals?).

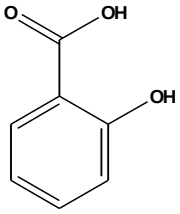
Submit an **executive summary** of the progress of the project so far to the Director of Research on the specified date.

Notes

The Aspirin Story

The early years

The use of infusions of willow bark (Salix alba) had been used for many centuries before Reverend Edmund Stone (an English parson living in the Cotswold village of Chipping-Norton, Oxfordshire) tasted willow bark in 1757. He noted that its very bitter taste was reminiscent of Peruvian bark (Cinchona), a rare and expensive remedy. On 25 April 1763, he wrote a letter to the Royal Society stating.



salicylic acid

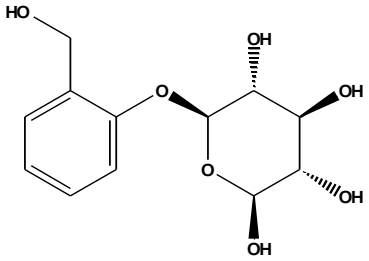
"There is a bark of an English tree, which I have found by experience to be a powerful astringent, and very efficacious in curing anguish and intermitting disorders."

Although he did not realise it, Reverend Stone discovered that salicylates (the general term for derivatives of salicylic acid) reduced fever and relieved aches. In the century that followed, this simple but effective treatment continued even though it had unpleasant side effects. Salicylic acid is a strong irritant, causing bleeding and ulcers in the mouth and stomach.

Synthesis of salicylic acid

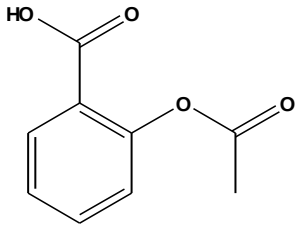
In 1828, Johann A. Buchner of the Pharmacologic Institute of Munich isolated the natural product salicin In 1837, salicylic acid was first synthesised in 1837 through the action of potassium hydroxide on salicin.

In 1859, Kolbe at Marburg University reported the synthetic route of treating phenol with carbon dioxide and metallic sodium. In 1874, Freidrich von Heyden, a former student of Kolbe established the first factory devoted to the production of salicylic acid. This proved to be a tenth of the cost of the salicin route.



salicin

Aspirin



aspirin

In 1898, Felix Hofmann worked for the German chemical company of Bayer. His father could not tolerate sodium salicylate for his arthritis because of chronic and acute stomach irritation so he searched the literature for a less acidic derivative. He came upon acetylsalicylic acid.

Bayer called it 'aspirin' from 'a' from acetyl and from the German Spirsaure for the French root that yields asalicylin. Aspirin works by blocking an enzyme that makes prostaglandins, the chemicals that signal that the body has been injured or invaded by a micro-organism. Prostaglandins are generated in excess, and the result is inflammation, pain and fever.

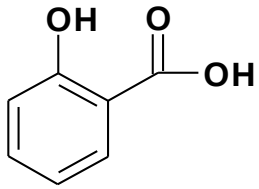
Over 20 billion tablets are taken each year in the USA alone despite the side effects. In the UK, 16 300 mg tablets can be purchased for less than a pound. Aspirin is also prescribed by doctors to patients who have suffered a heart attack since it inhibits the formation of those chemicals that cause blood platelets to aggregate together, which is what starts a blood clot.

Natural sources of salicylates.

Many people do not realise that they are also getting salicylate from many vegetables, herbs and fruits especially from warm climates. These include tomatoes, onions, tarragon, aubergine, courgettes, red peppers, pineapples, melons, currants, raisins, chichory leaves, gherkins, almonds, peanuts, coconut, honey, licorice, peppermint, broccoli, cucumbers, olives, sweetcorn and mangoes.

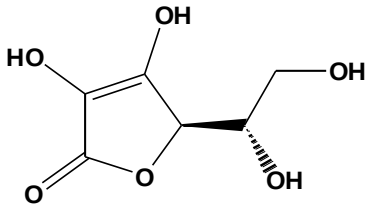
By far the easiest way to boost our salicylate intake is to drink tea. A cup, made with one tea bag, will provide 3 mg. Coffee drinkers, on the other hand, would need to take in 20 mugs of their brew to get this amount. Salicylates are also present in fruit juices, beer and wine.

“New drugs for old”



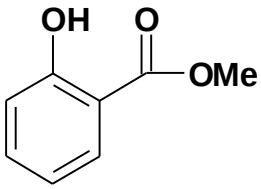
Compound A

salicylic acid



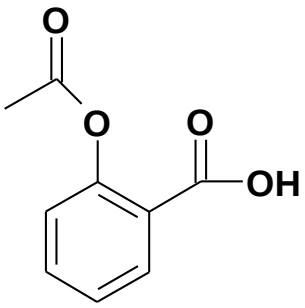
Compound B

ascorbic acid (Vitamin C)



Compound C

methyl salicylate



aspirin

- analgesic
- 20 billion tablets taken each year.
- Safer than salicylic acid.
- 16 x 300 mg tablets cost < £1

Author	Tina Overton, Simon Belt, Stephen Summerfield
Title	Problem-Based Learning Case Study
Classification	Case Study
Keywords	sfsoer, ukoer, chemistry, pharmaceutical, analytical, case study, problem-based learning
Description	Appendix A
Creative Commons Licence (url)	http://creativecommons.org/licenses/by-nc-nd/2.0/uk/
Language	English
File size	2000 kB
File format	pdf