M.Sc. Project- 2022

Schiff Base Synthesis and its Biological Activity

Submitted by

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BIDHANNAGAR COLLEGE

Under the supervision of

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DECLARATION

The work described in this literature review entitled "*Schiff Base Synthesis and its Biological Activity*" as part requirement for the award of M. Sc. degree, has been carried out at the Department of Chemistry, Bidhannagar College, Kolkata. It is the result of my own work. Its contents have not been previously submitted elsewhere for any degree, diploma, or other qualification.

Sanjit Bera.

(Sanjit Bera)

CERTIFICATE

I recommend that this review be placed before the examiners for evaluation.

(Head)

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19.07.2022

(Supervisor)

SUSANTA KUMAR

Acknowledgement

I have immense pleasure in successful completion of this project work entitled *"Schiff Base synthesis and its Biological Activity"*. I wish to express my deep respect and sincere gratitude to my supervisor **Dr.Susanta Kumar Manna,** Depertment of Chemistry, Bidhannagar College, Salt Lake for his co-operation , judicious help and constant inspiration during the entire period of the review work. I am thankful to Prof.achintya Kumar Sarkar,Head of the Department, Bidhannagar College, for providing me the necessary facilities to carry out this project work. I am also grateful to all of the other teachers of the department. I would also like to express my thanks to my classmates for their help and co-operation during the entire period of the execution of this review work. I am thankful to my parents for their invaluable help and support during this work.

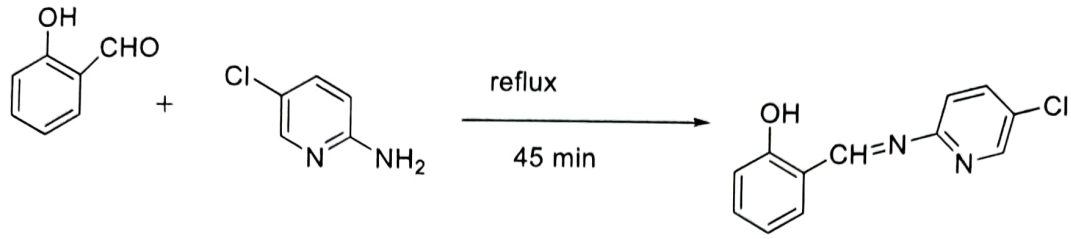
Date:

(Sanjit Bera)

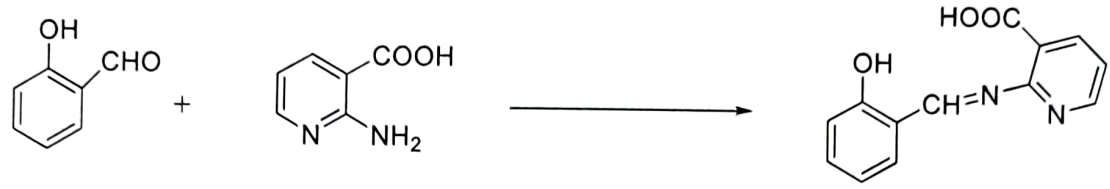
Introduction

Methodologies for the formation of azomethines are attractive to synthetic chemists due to occurrence of this structural unit in a variety of naturally and pharmacologically important molecules[1]. Diverse broad-spectrum biological activities like anti-proliferative[2], anti-inflammatory[3], analgesic[4], antimicrobial, antiviral, anticonvulsant, antifungal, antimalarial, antileishmanial, antitubercular[5], antibacterial, antioxidant, anthelmintic[6] etc. prevail in the properties of azomethines. Some important pharmacologically active molecules containing azomethine unit include a cistrocladidine, chitosan-derived Schiff base, N-(salicylidene)-2-hydroxyaniline[7]. Azomethines are also good Mannich electrophiles and excellent heterodienophiles for the construction of six-membered nitrogen heterocycles[8-9]. Conventional methods for the formation of azomethines involve condensation between a carbonyl compound and a primary amine in a suitable solvent usually at its boiling point. Addition of a small amount of acid is often necessary to enhance electrophilicity of the carbonyl carbon to hasten the reaction. Long reaction time, low yield of the product and cost to attain the appropriate temperature for the reaction and evaporation of the solvent during isolation of the product cripple this conventional procedure from economic and environmental point of view. In recent years mechanochemistry has emerged as an efficient tool for the performance of reactions under solvent-free conditions. Azomethines with pyridine framework frequently appear in agrochemicals and pharmaceuticals[10]. Employment of mechanochemistry and studies on the effects of substituents on the course of reaction, however, have not been found for the synthesis of azomethines from 2-aminopyridine and various aromatic aldehydes to the best of our knowledge. Our present study is, therefore, mainly focused on mechanochemical synthesis of azomethines from aromatic aldehydes and 2-amino pyridine and finding out the effects of substituents on the rate of the reaction and yield of the products. In addition to the synthetic aspects a detailed study of the radical scavenging and antimicrobial activity of the prepared azomethines is also presented.

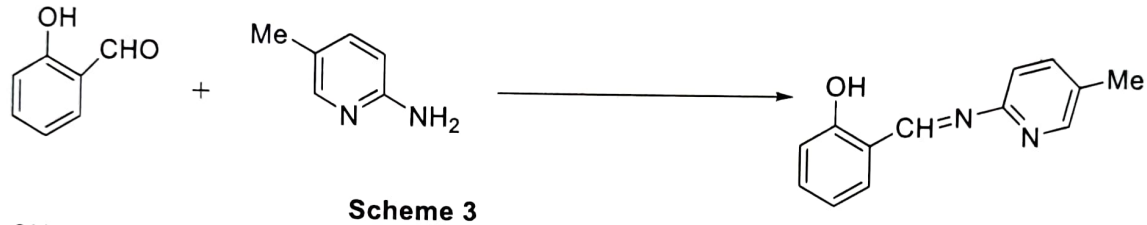
Some example of Schiff bases are:



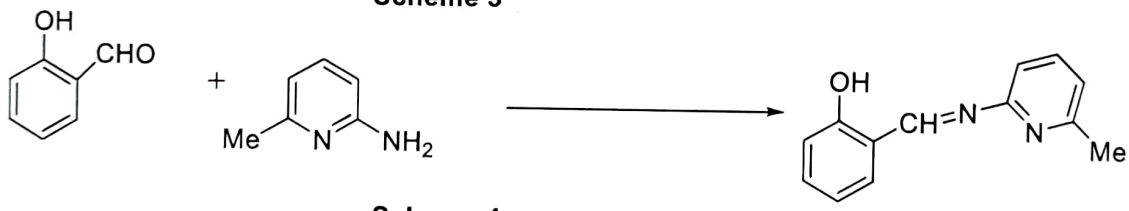
Scheme 1



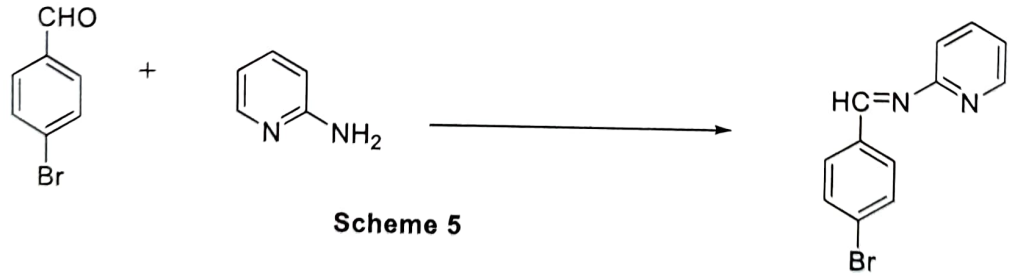
Scheme 2



Scheme 3



Scheme 4



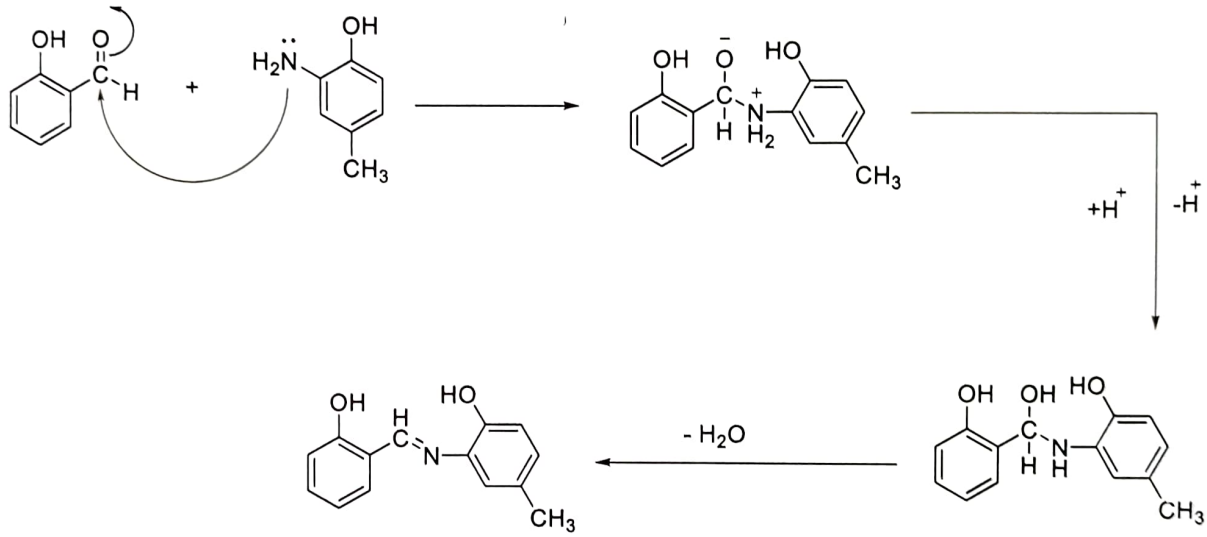
Scheme 5

Scheme 6

Results and discussion

Success of the reaction between a primary amine and an aldehyde classically depends on the electrophilicity and nucleophilicity of the carbonyl and amine counterparts respectively and the steric crowding around the electrophilic and nucleophilic sites. To examine the influence of the polar effects of the substituents on the rate of the reaction we have used aromatic aldehydes with electron attracting as well as electron releasing groups in the nucleus . For the study of steric effects aromatic aldehydes with ortho substituents with respect to the formyl group were used. Yields for all the reactions were excellent but surprisingly time needed for completion of the reactions were found to be almost insensitive to the electronic nature of the ring substituents. In the present case also yields for the reactions with aromatic aldehydes containing ortho hydroxy groups were nearly quantitative. In the neat phase, motion of reactant molecules is restricted and so further decrease in entropy during the formation of the transition state is much lower than that for solution phase reactions.

Mechanism

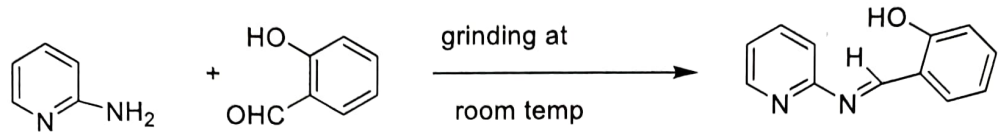


Plausible mechanistic pathway for reaction between 2-amino-4-methylephenol and salicylaldehyde

Biological activity:

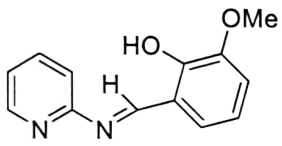
Biological properties of azomethines are often attributed to the presence of unshared pair of electrons on imino nitrogen. Capacity of the azomethines to undergo facile chelation plays a vital role in their antioxidant activities. The ability of the prepared azomethine derivatives to scavenge DPPH radical was evaluated and expressed in terms of IC50 values . Compound 3 displayed very poor activity when compared to the standard antioxidant L-ascorbic acid and the compound 4 was found to be inactive in this series. It could not scavenge 50% of the DPPH radicals even at the highest tested concentration (100 μM). Significantly, the compounds having phenolic -OH group exhibited relatively higher activities compared to the other analogues, suggesting that the substituents present in the respective aromatic

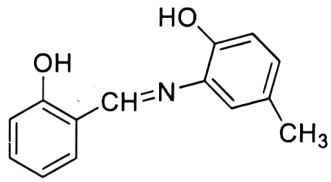
ring have a profound influence on the antioxidant activity by enhancing their ability of hydrogen donation. Generally phenolic compounds act as potent antioxidants due to the formation of stable phenoxyl radical through the abstraction of hydrogen atom by DPPH radical.



Scheme 7 : This Schiff base exhibited relatively higher biological activities due to presence of phenolic -OH group

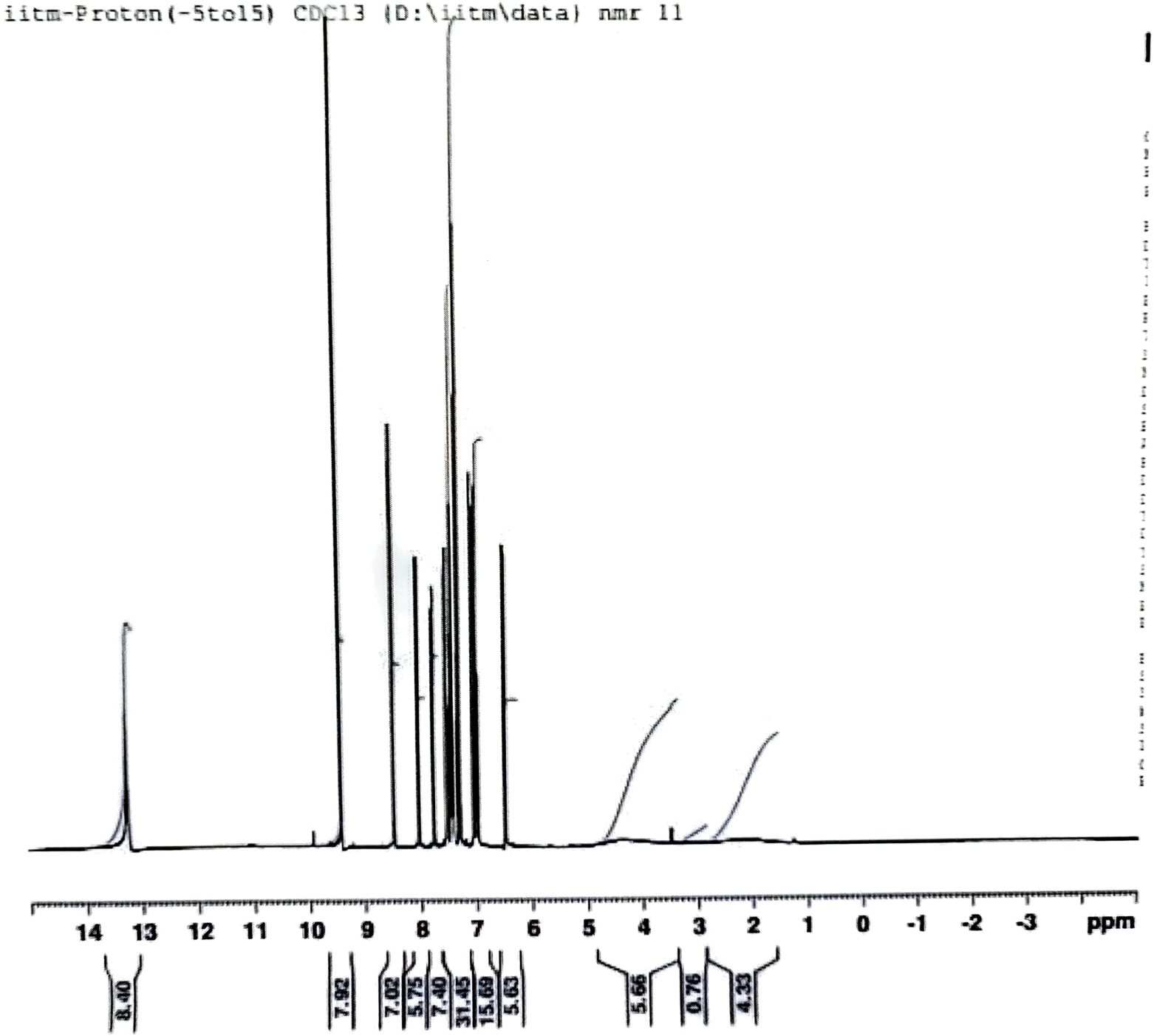
Other biological active Schiff bases are:





Antibacterial activity:

In the present study, antibacterial activity of all the synthesised azomethines were evaluated against one Gram positive and one Gram-negative strains over a range of concentrations (0.05–0.5 mg/mL) by agar well diffusion method. The solvent vehicle DMSO, was found to be inactive against all the tested bacteria. At 0.1 mg/mL concentration, the positive control ampicillin responded to a significant level of bacterial inhibition against both of these Gram-positive and Gram-negative organisms. The prepared azomethine derivatives displayed a broad spectrum of antibacterial activity against both the microorganisms in a concentration dependent manner. It is noteworthy that all the tested bacteria were highly susceptible to inhibition by the compounds derived from the aldehydes having ortho hydroxy group. The azomethine analogue prepared from 3-ethoxy salicylaldehyde exhibited remarkable activity against both the bacteria. It was observed that the growth of Gram-negative bacteria viz. E. coli was strongly inhibited at the higher doses . In fact, at these concentrations this compound was found to show a greater potency in comparison to the standard drug ampicillin . The efficacy of azomethine , derived from 4-methoxy salicylaldehyde, was nearly equivalent to that exhibited by 0.1 mg/mL of ampicillin.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14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm
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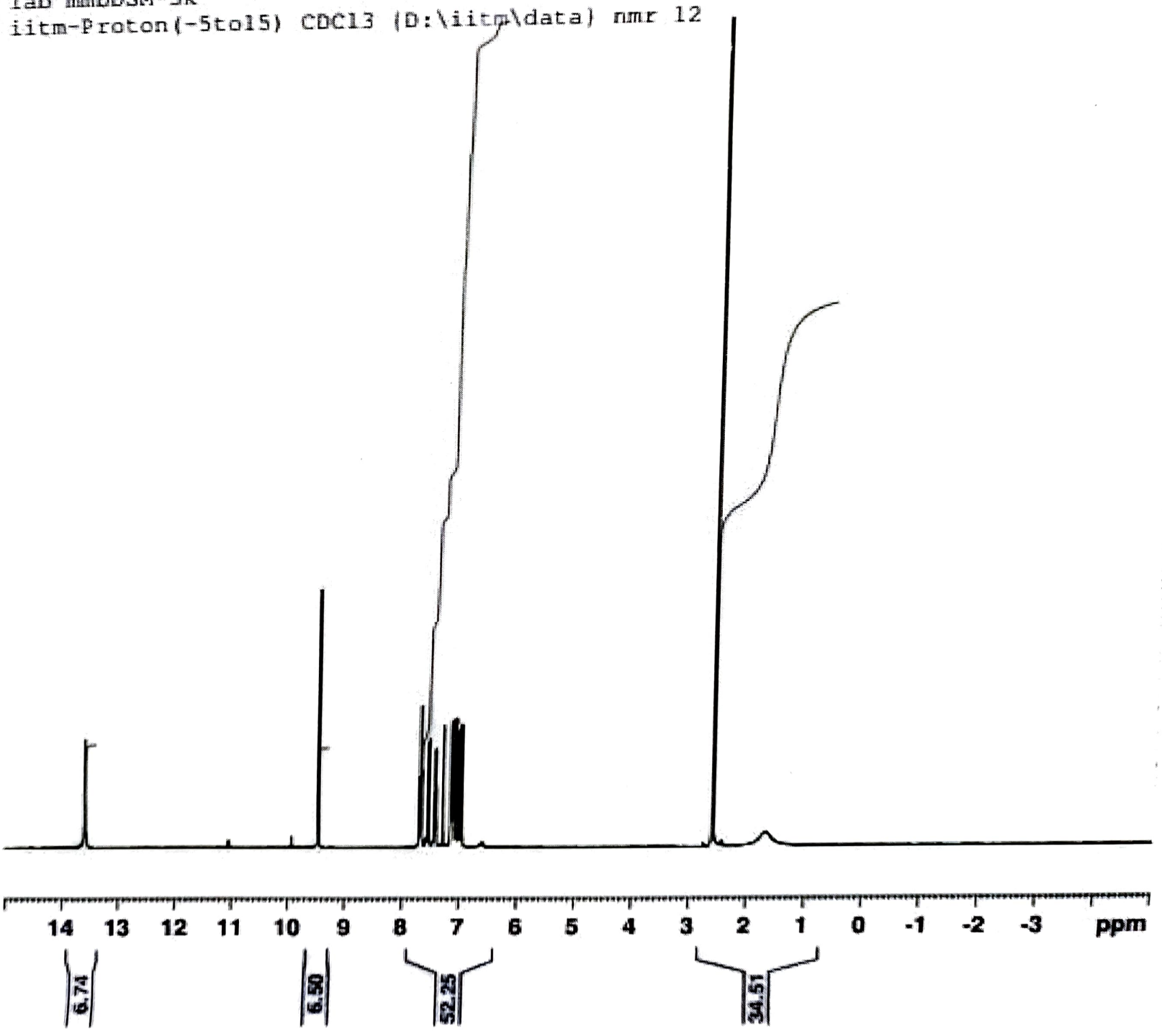
7.92
7.02
5.75
7.40
31.45
15.69
5.63
5.66
0.76
4.33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6.50
52.25
34.51

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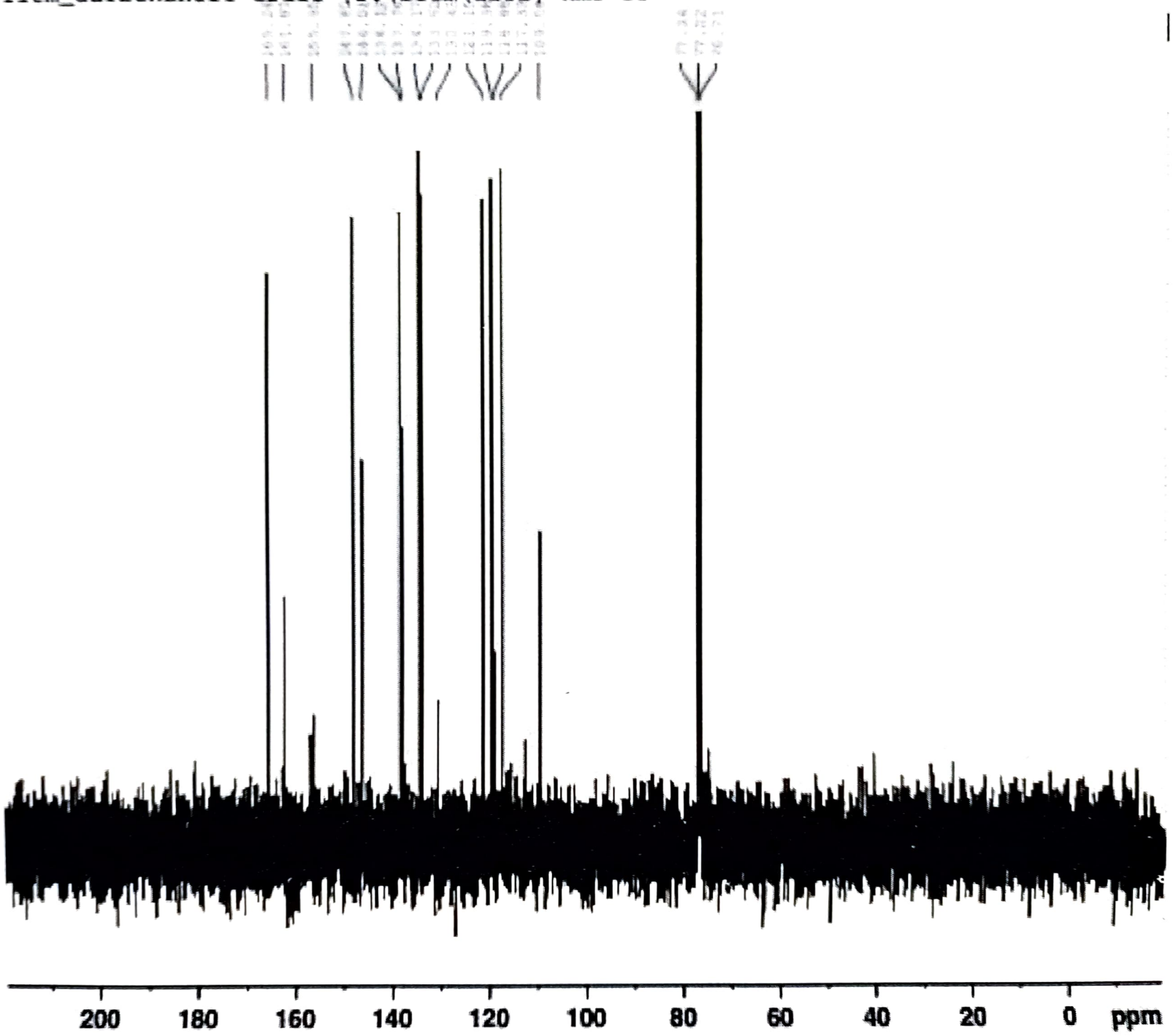

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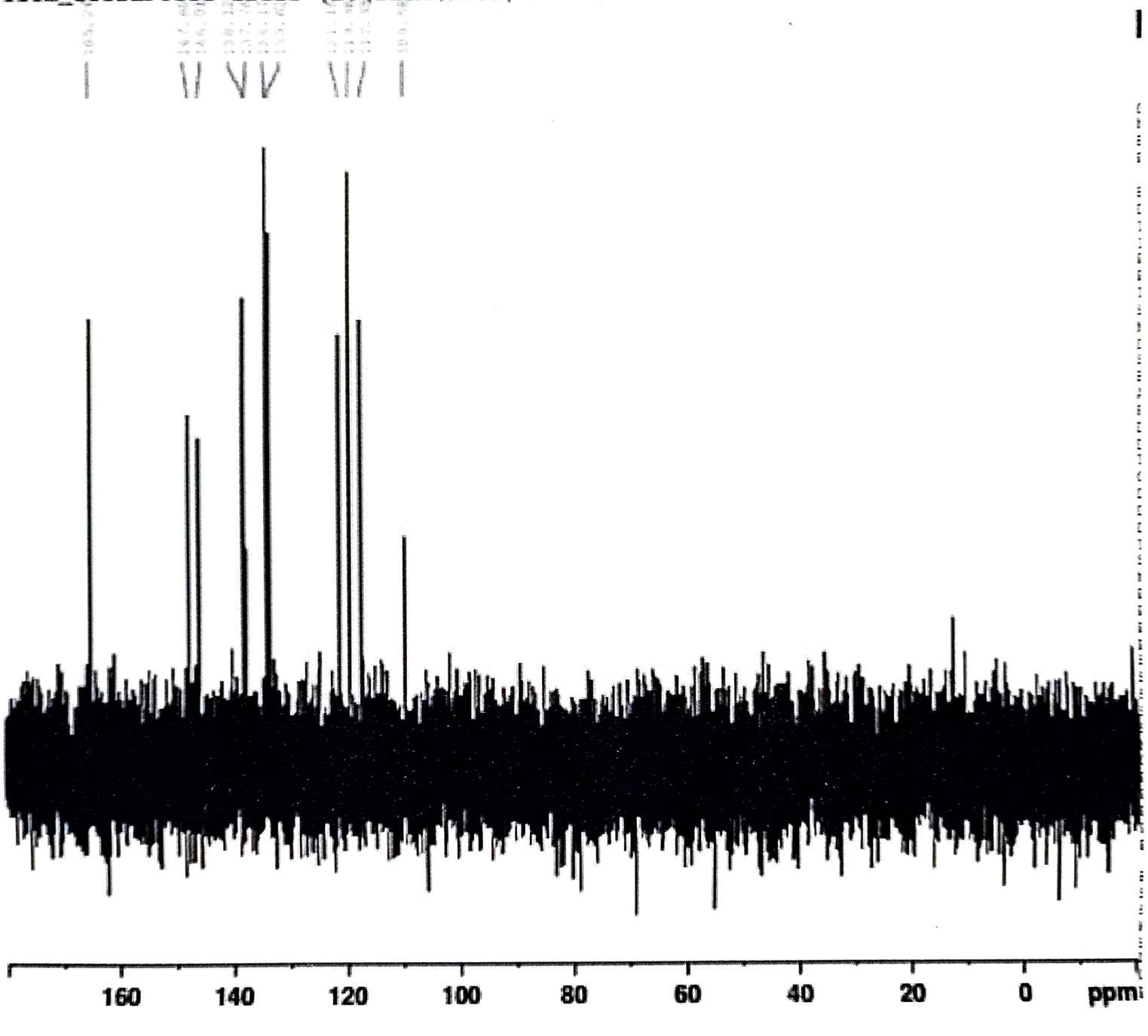

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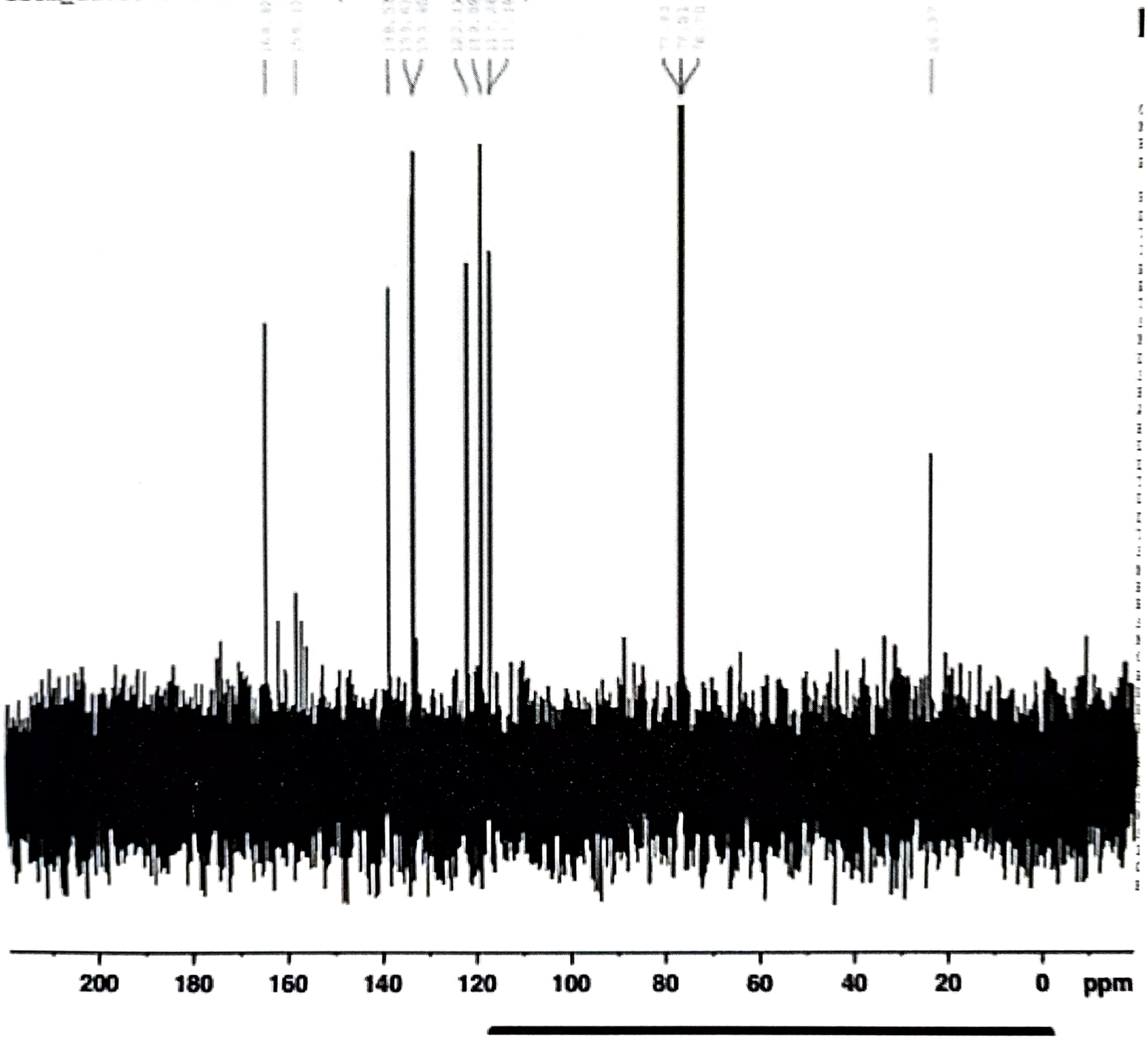

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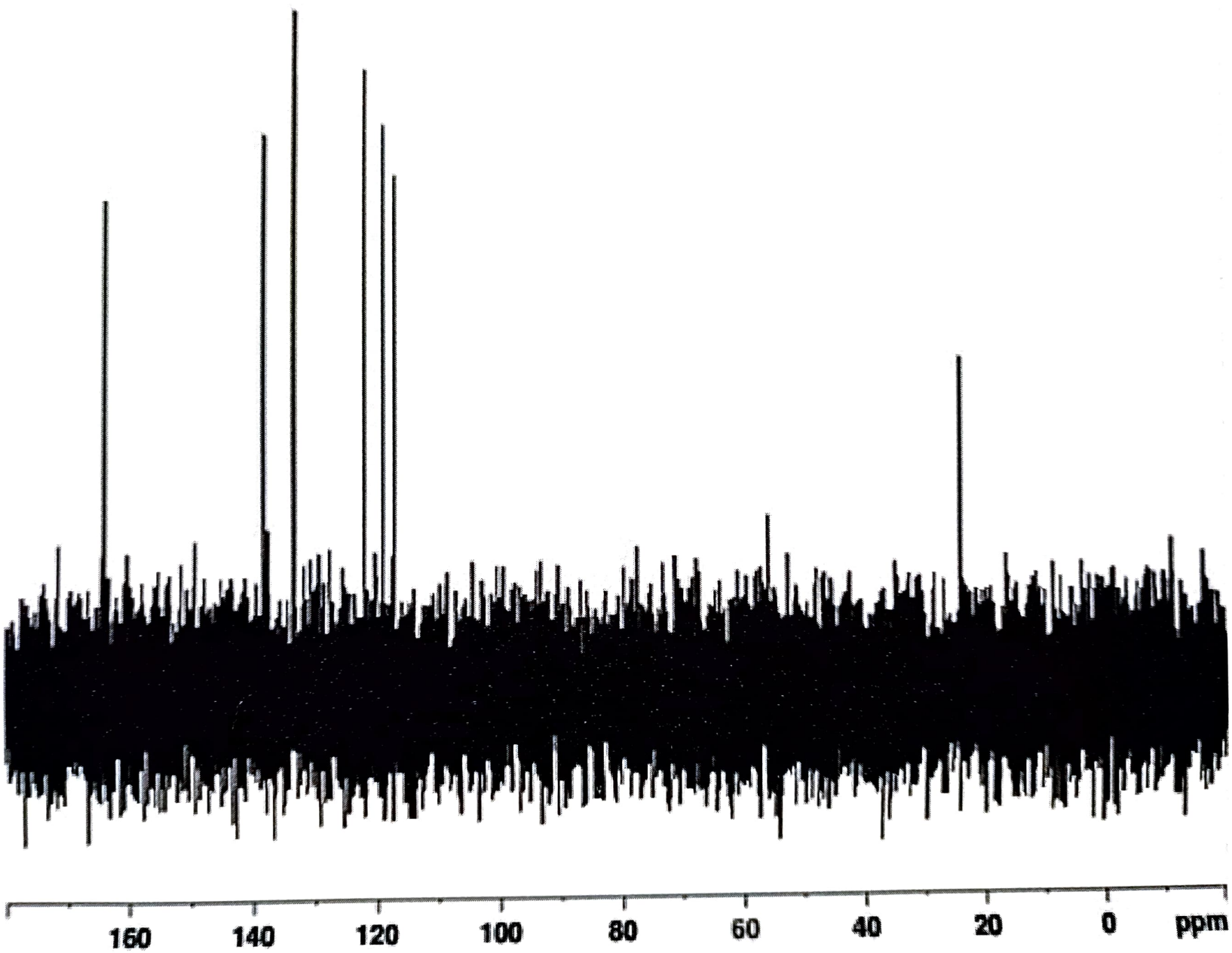

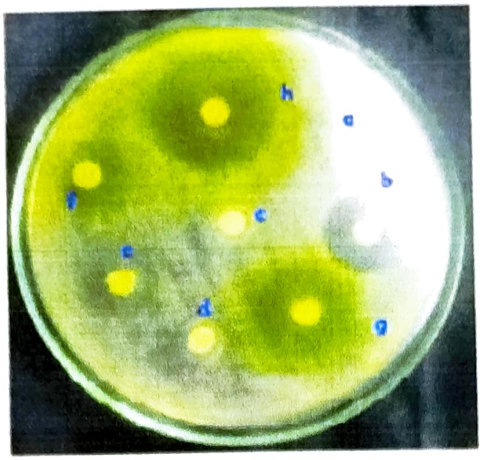

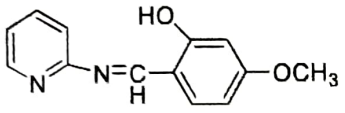

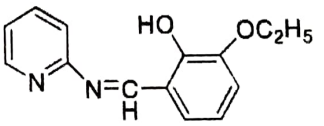

These Schiff bases are shows Antibacterial activities.

CONCLUSION

A number of azomethines were prepared in good to nearly quantitative yields from 2-aminopyridine and various aromatic aldehydes through mechanochemical protocol. The methodology was found to be much superior in comparison to the conventional procedure with respect to yield of the product, reaction time and operational simplicity. Scrutiny of the effect of ring substituents showed that the reaction was almost insensitive to the electronic nature of the substituents. In contrast presence of an ortho hydroxy functionality in the nucleus of aromatic aldehydes led to completion of the reactions in a flash. Some of the prepared azomethines were found to exhibit appreciable radical scavenging and antibacterial activity. Remarkable rate enhancement caused by ortho hydroxy function coupled with promising antimicrobial activity found in azomethines with hydroxylated aromatic nuclei prompt us to undertake such studies on similar systems in future.

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