International Journal of Applied and Natural Sciences
ISSN: 3005-3471
DOI: https://doi.org/10.61424/ijans.v4i4.1148
Date Published Online: November 19, 2026
Journal Homepage: https://bluemarkpublishers.com/index.php/IJANS

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| RESEARCH ARTICLE

Synthesis of New β-aminocarbonyl Compounds via Mannich Reaction using Calcium Chloride as a Catalyst

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| ABSTRACT
Two sets of β-aminoketones **4a-c** and **5a-c** were synthesized in a three components one-pot Mannich reaction of different ketones, aldehydes, and amines in the presence of calcium chloride as catalyst in absolute ethanol with high yields. The advantages of this new method are a short reaction time (2 h), high yields, easy workup, convenience, low cost, and eco-friendly protocol**.** The titled compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, CHN elemental analysis.

| KEYWORDS
β-aminocarbonyl; Mannich Reaction; Mannich transformations; Heterocyclic amines; Three-component reaction

| ARTICLE INFORMATION
ACCEPTED: October 10, 2026 **PUBLISHED:** November 19, 2026 **DOI:** https://doi.org/10.61424/ijans.v4i4.1148

1. Introduction

The β-aminoketones play an important role in heterocyclic synthesis and act an intermediate molecule for many bioactive compounds [Ravn et al., 2019; Nguyen et al., 2014; Altmeyer et al., 2014; Jiang et al., 2018]. Drugs derived from the β-aminoketone moiety are known to exhibit remarkable biological potency [Hofer et al., 2006; Kaski et al., 1991; Deacon, 2020; Dai et al., 2020]. However, many derivatives of β-aminoketone have applications in different fields, including; medicine, pharmaceutical activities, other biological activity, anticancer, antibacterial, and antiviral properties [Bala et al., 2014]. Based on the literature survey, various synthetic procedures have been reported for the preparation of many β-aminoketones. For example, a series of a highly stereoselective three-component direct Mannich reaction between aromatic aldehydes, *p*-toluenesulfonamide, and unfunctionalized ketones in the presence of a bifunctional quinidine thiourea catalyst gives the corresponding *N*-tosylated β-aminoketones in high yields and excellent diastereo- and enantioselectivities [Guang & Zhao, 2013]. Also, A one-pot, three-component reaction between an aromatic aldehyde, an enolizable ketone or a β-keto ester, and a nitrile in the presence of acetyl chloride is accomplished efficiently using cyanuric chloride in an aqueous medium to give the corresponding β-acetamido ketone or ester in high yield [Das et al., 2010]. Moreover, A practical strategy that provides a modular and programmable synthesis of a wide range of α-amino carbonyls is made possible by an extremely mild method to generate carbamoyl radicals, proceeding via a Lewis acid-visible-light-mediated Norrish type-I fragmentation of a tailored carboxamide reagent and intercepted through addition to in situ generated unbiased imines [Liu et al., 2024]. So, it was considered worthwhile to develop and synthesize some new derivatives of β-aminoketones derived from available different aromatic amines, aldehydes and ketones via Mannich reaction with high expectation of revealing biological properties.

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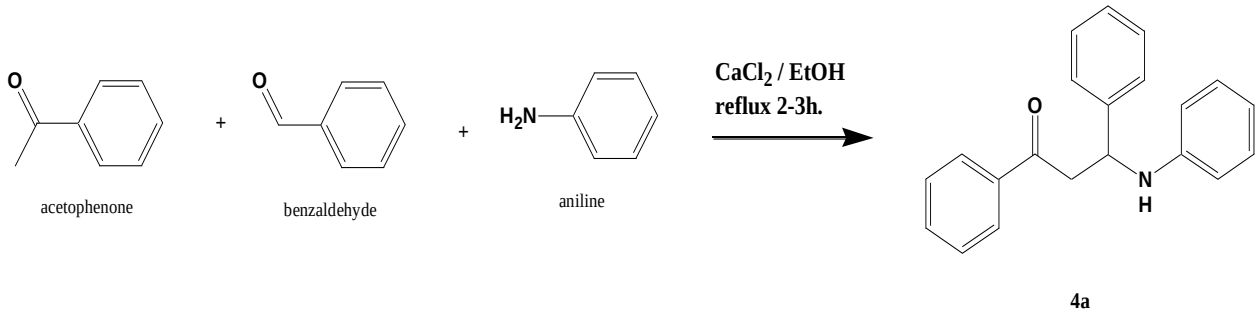
2. Experimental

2.1 Instruments

All reagents and solvents were used as it received from their commercial sources. Thin layer chromatography (TLC) technique was utilized to monitor reactions using aluminum plates coated with silica gel. Melting points (uncorrected) were recorded on Electro thermal SMP30 apparatus. CHN elements calculated with Carlo Erba 1108 (CHN) Elemental Analyzer. IR spectra were recorded on 8400s FTIR-Shimadzu using KBr disc spectrophotometer. The spectra of ^{1}H NMR and ^{13}C NMR have been outlined with Bruker spectrometer in DMSO-d_6 solvent, (400 and 100 MHz), respectively. CS Chem Draw Ultra (6.0) software was utilized to draw all the chemical structures.

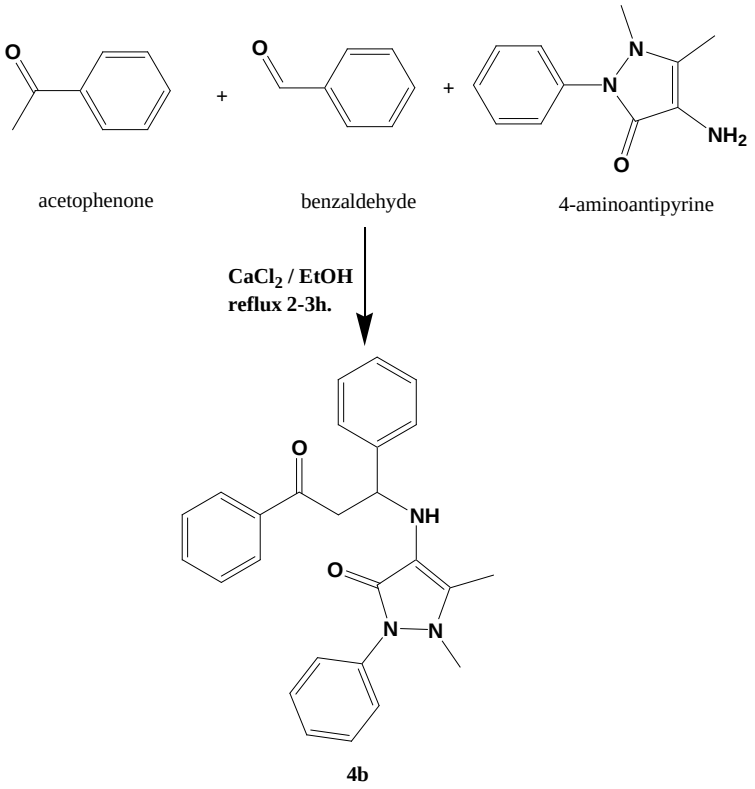
2.2 General Procedures

Preparation of 1,3-diphenyl-3-(phenylamino)propan-1-one, 4a: One equivalent of $CaCl_2$ was added to a mixture of acetophenone (5 mmol), benzaldehyde (5 mmol), and aniline (5 mmol) in ethanol 15 mL. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60-80°C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH. [Kulkarni, 2012].



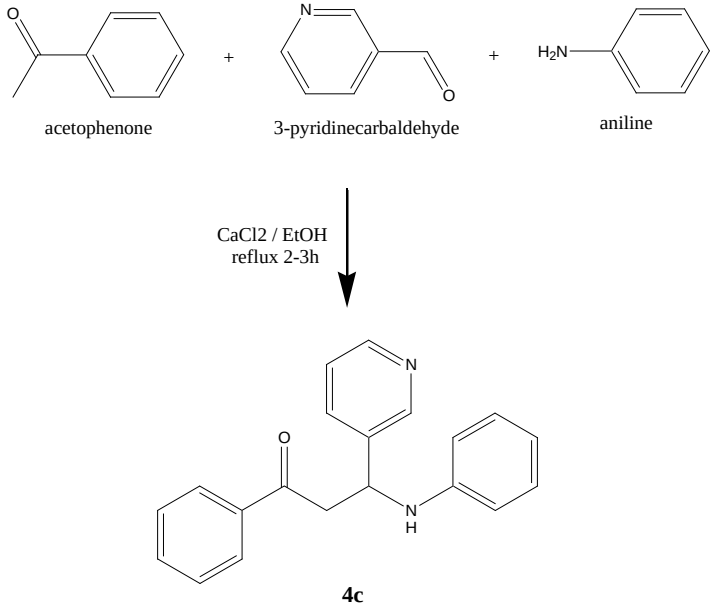
Scheme 1.

Preparation of 1,5-dimethyl-4-((3-oxo-1,3-diphenylpropyl)amino)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one, 4b: One equivalent of $CaCl_2$ was added to a mixture of acetophenone (5 mmol), benzaldehyde (5 mmol), and 4-aminoantipyrine (5 mmol) in ethanol 15 mL. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60-80°C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



Scheme 2.

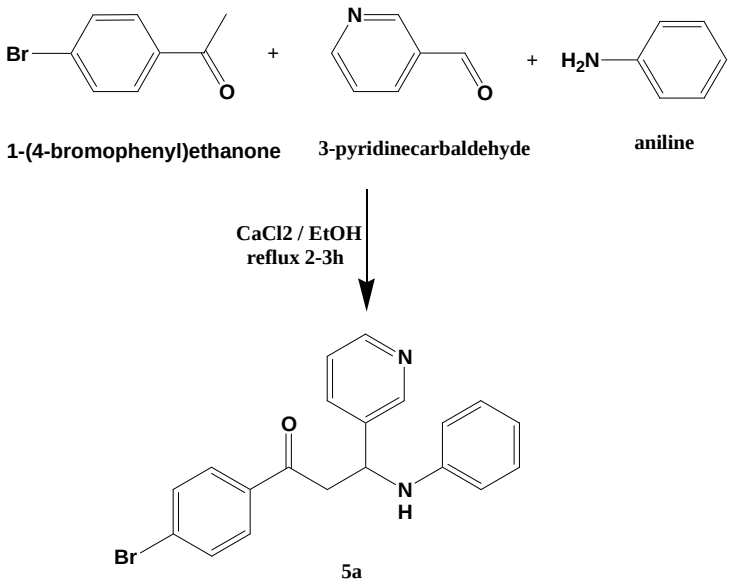
Preparation of 1-phenyl-3-(phenylamino)-3-(pyridin-3-yl)propan-1-one, 4c: One equivalent of $CaCl_2$ was added to a mixture of acetophenone (5 mmol), 3-pyridinecarbaldehyde (5 mmol), and aniline (5 mmol) in ethanol 15 mL. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60-80°C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



Scheme 3.

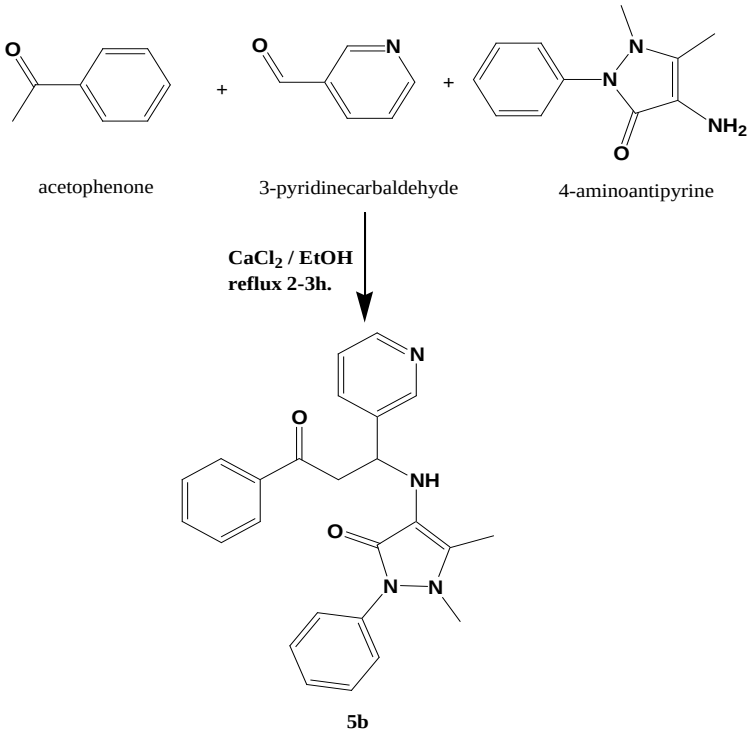
Preparation of 1-(4-bromophenyl)-3-(phenylamino)-3-(pyridin-3-yl)propan-1-one, 5a: One equivalent of $CaCl_2$ was added to a mixture of 4-bromoacetophenone (5 mmol), 3-pyridinecarbaldehyde (5 mmol), and aniline (5

mmol) in 15 mL ethanol. One drop of HCl was added when 4-bromoacetophenone was the starting material. The resulting mixture was stirred at 60- 80 °C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



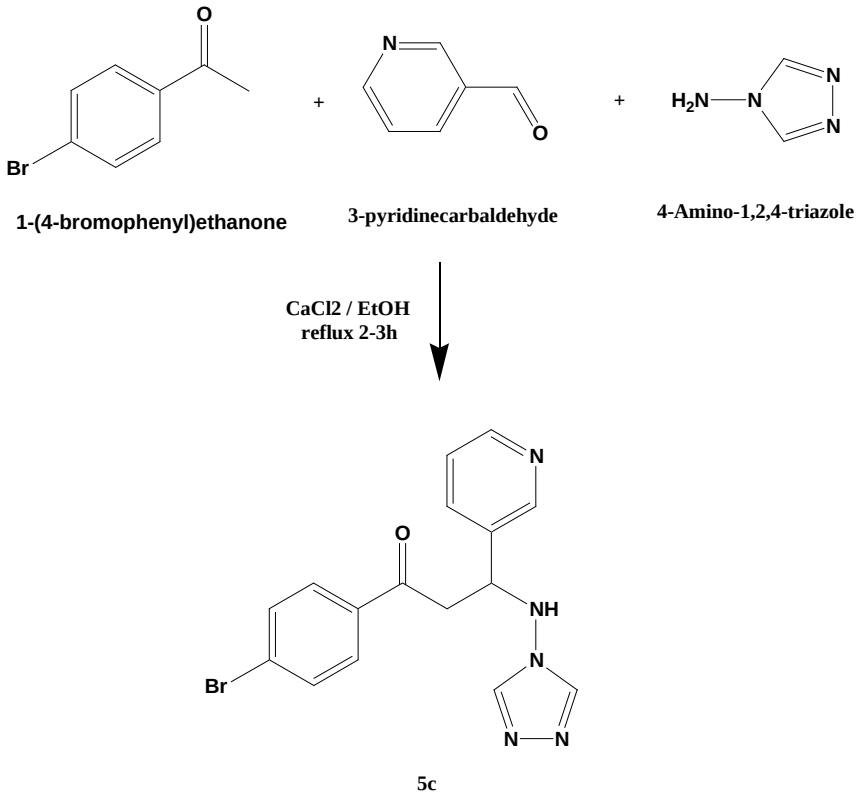
Scheme 4.

Preparation of 1,5-dimethyl-4-((3-oxo-1,3-diphenylpropyl)amino)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one, 5b: One equivalent of $CaCl_2$ was added to a mixture of acetophenone (5 mmol), 3 pyridinecarbaldehyde (5 mmol), and 4-aminoantipyrine (5 mmol) in ethanol 15 mL. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60- 80 °C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



Scheme 5.

Preparation of 1-(4-bromophenyl)-3-(pyridin-3-yl)-3-(4*H*-1,2,4-triazol-4-ylamino)propan-1-one, 5c: One equivalent of $CaCl_2$ was added to a mixture of 4-bromoacetophenone (5 mmol), 3-pyridinecarbaldehyde (5 mmol), and 4-amino-1,2,4-triazole (5 mmol) in ethanol 15 mL. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60-80 °C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



Scheme 6.

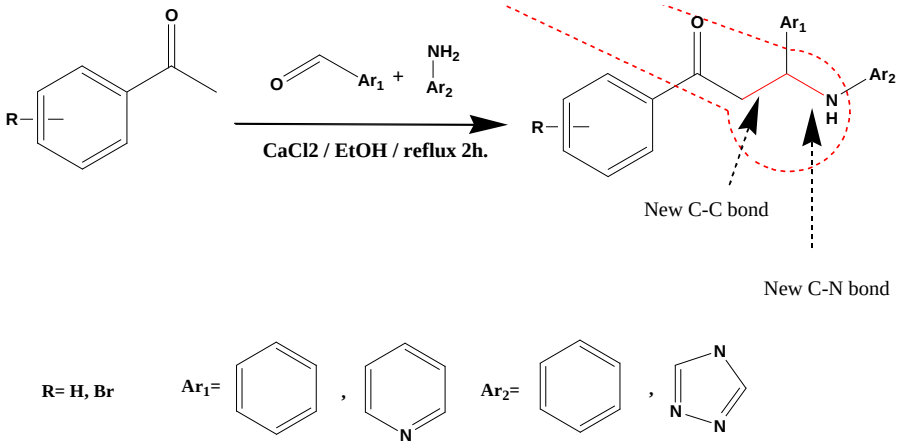
Table 1. Physical properties of the prepared compounds

Compd.	Molecular Formula	M. Wt. g/mole	M.p. C^0	Color
4a	$C_{21}H_{19}NO$	301.38	260	White
4b	$C_{26}H_{25}N_3O_2$	411.50	>300	Yellow
4c	$C_{20}H_{18}N_2O$	302.37	>250	Yellow
5a	$C_{20}H_{17}BrN_2O$	381.27	>250	White
5b	$C_{25}H_{24}N_4O_2$	412.48	>300	Pale-yellow
5c	$C_{16}H_{14}BrN_5O$	372.22	>300	White

3. Results & Discussion

In general, a series of β-aminoketones derived from available different aromatic amines, aldehydes and ketones in simple and cost effective procedures via the Mannich reaction was prepared, Scheme 7. The final product of a β-amino-carbonyl compounds, 4a-c and 5a-5c as shown in Figures (1 and 2) were prepared in a three-component organic reaction that involves the amino alkylation of an acidic proton next to a carbonyl (C=O) functional group by an aldehyde (H−CHO) and a primary or secondary amine (−NH_2). The structural assignments of the prepared β-aminoketones, 4a-c are based on their FTIR spectroscopy. FTIR spectra of compounds **4a-c and 5a-c** showed that new stretching bands appeared in the region (3298 - 3240 cm^{-1}) due to NH groups. Also, the stretching vibration band of C=O group was appeared in the region (1642-1678 cm^{-1}). On the

other hand, the spectrum showed the disappearance of amino groups NH_2 and CH-aldehydic bands of the starting materials. Figures (3-8). Besides the other proton signals which are observed in their H NMR spectra (Figures 9- 12).



Scheme 7. Overall reaction of the present work.

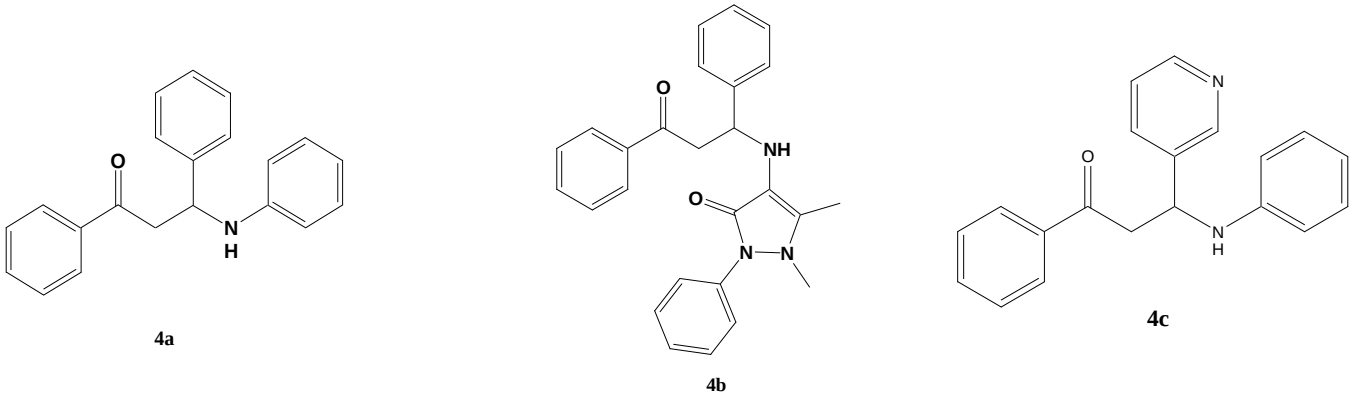


Figure 1. The prepared β-aminoketones, 4a-c.

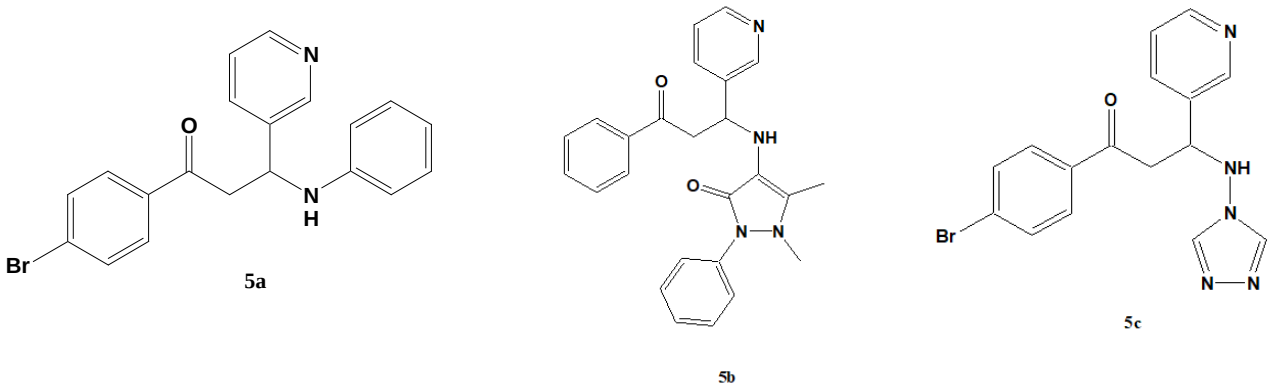


Figure 2. The prepared β-aminoketones, 5a-c.

4. Conclusion

In conclusion, a series of β-aminoketones has been prepared via the Mannich reaction derived from available different aromatic aldehydes, amines and ketones. The structural confirmation was deduced from their physical properties and FTIR, NMR spectra. These compounds are expected to exhibit acceptable antifungal activity and antibacterial properties.

Funding: This research received no external funding.
Conflicts of Interest: The authors declare no conflict of interest.
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Artificial Intelligence (AI) Use Disclosure: The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

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List of figures

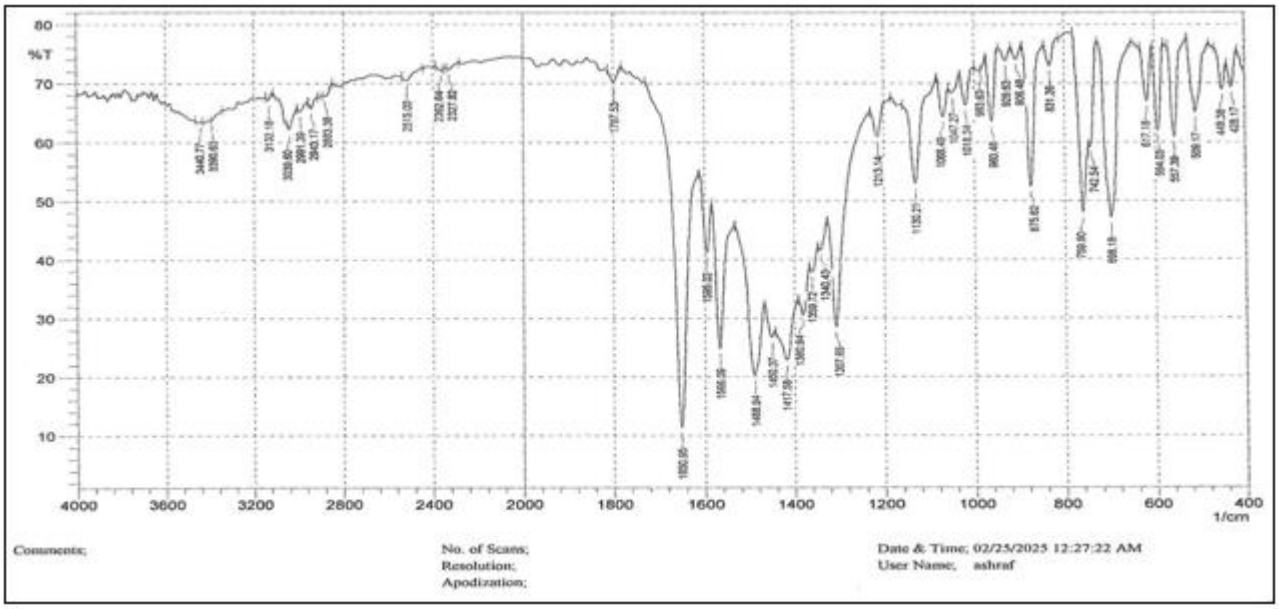


Figure 3. FT-IR spectrum of compound 4a.

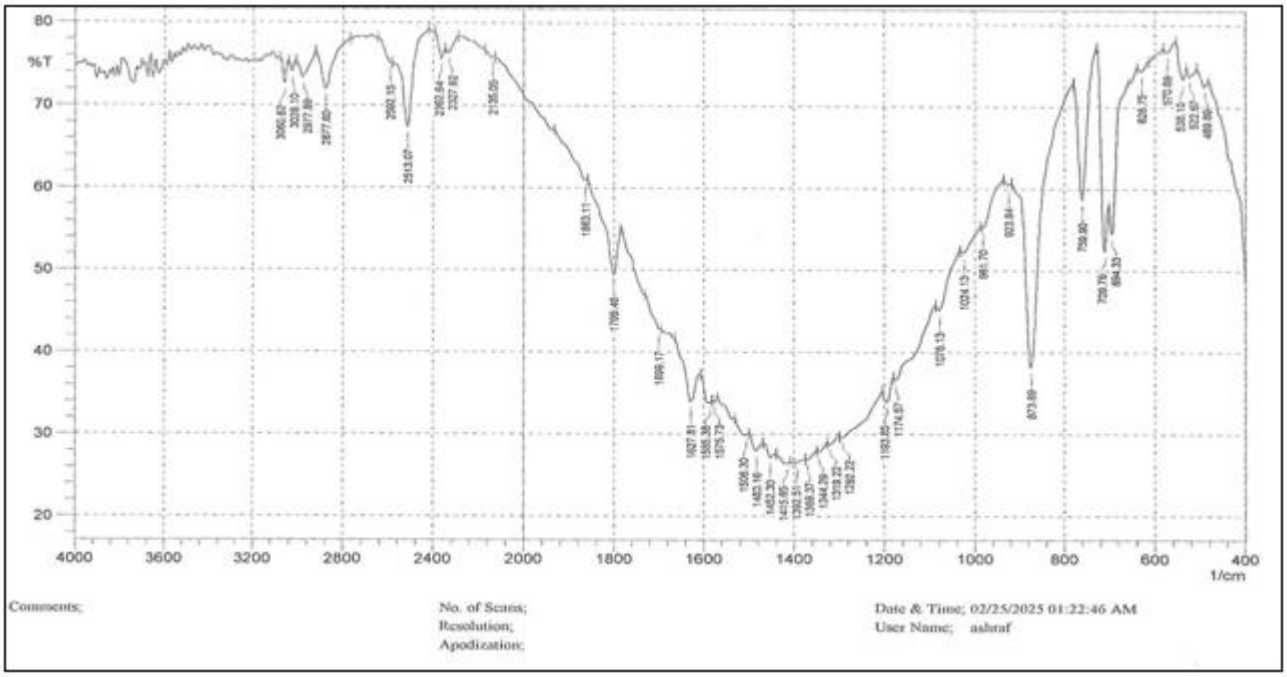


Figure 4. FT-IR spectrum of compound 4b.

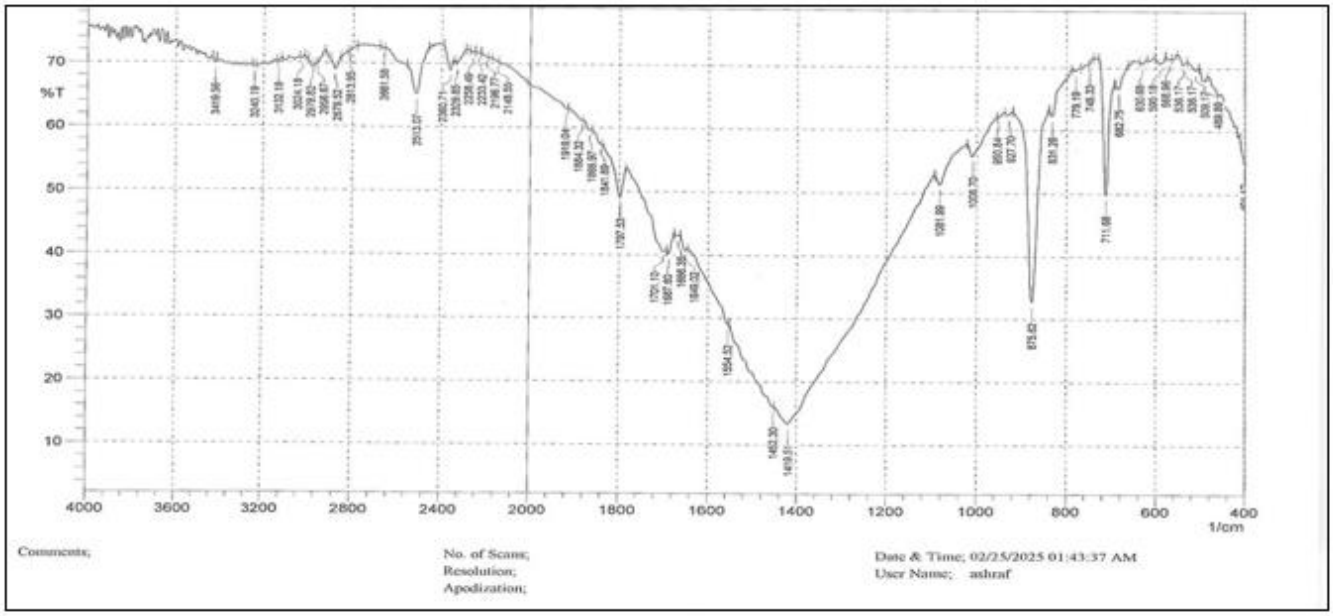


Figure 5. FT-IR spectrum of compound 4c.

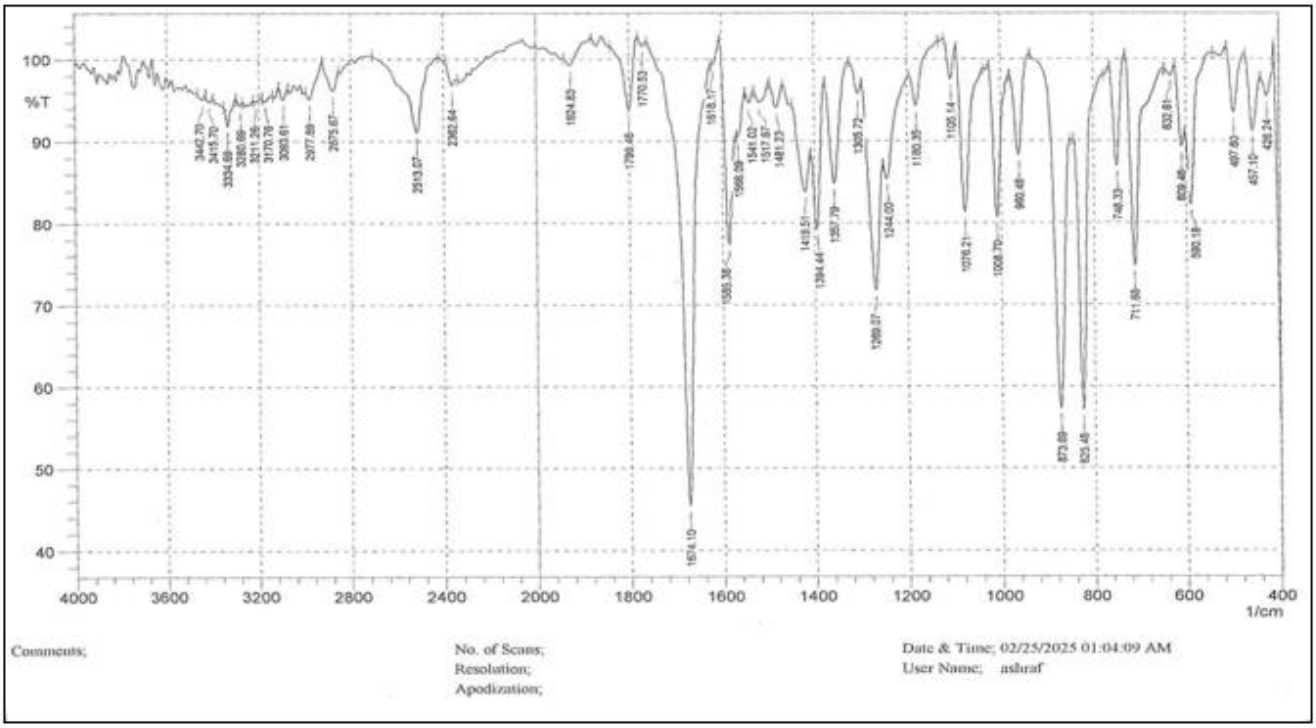


Figure 6. FT-IR spectrum of compound 5a.

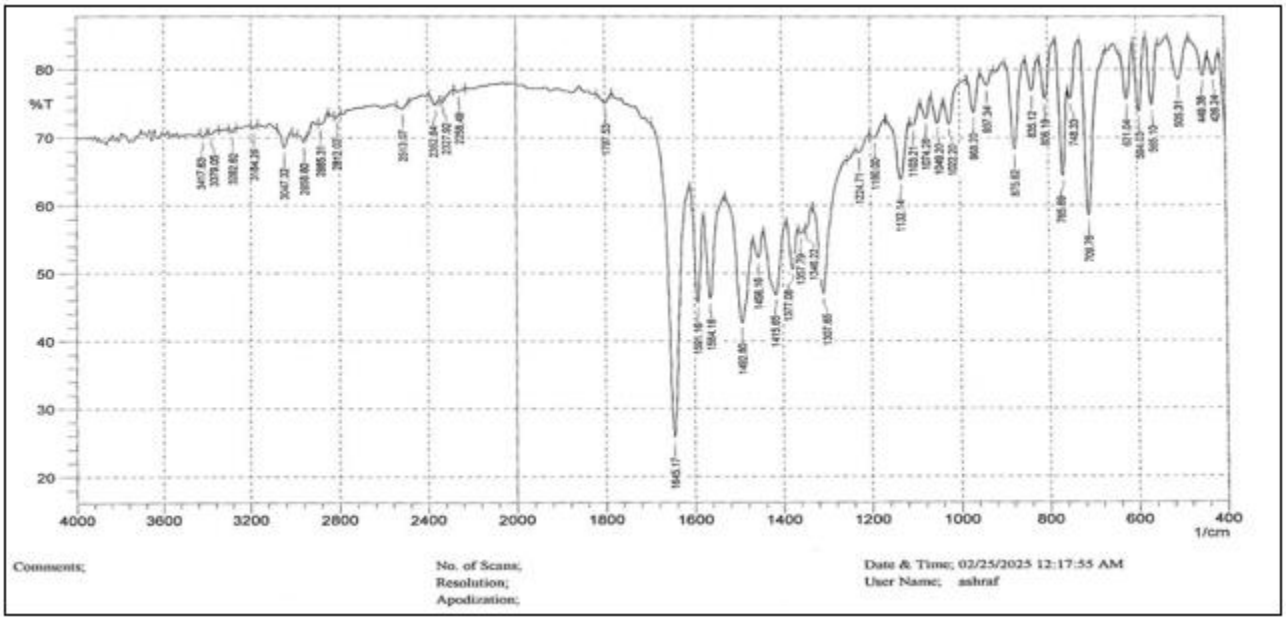


Figure 7. FT-IR spectrum of compound 5b.

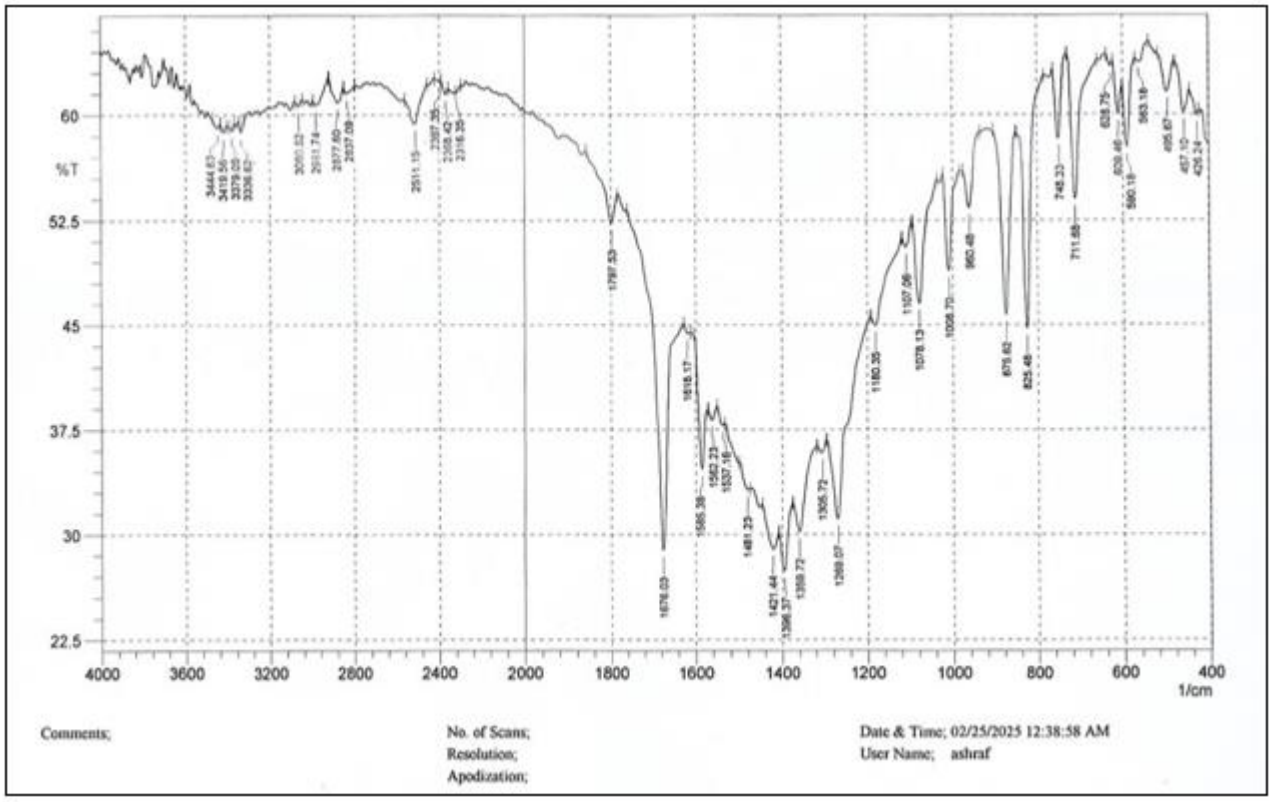


Figure 8. FT-IR spectrum of compound 5c.

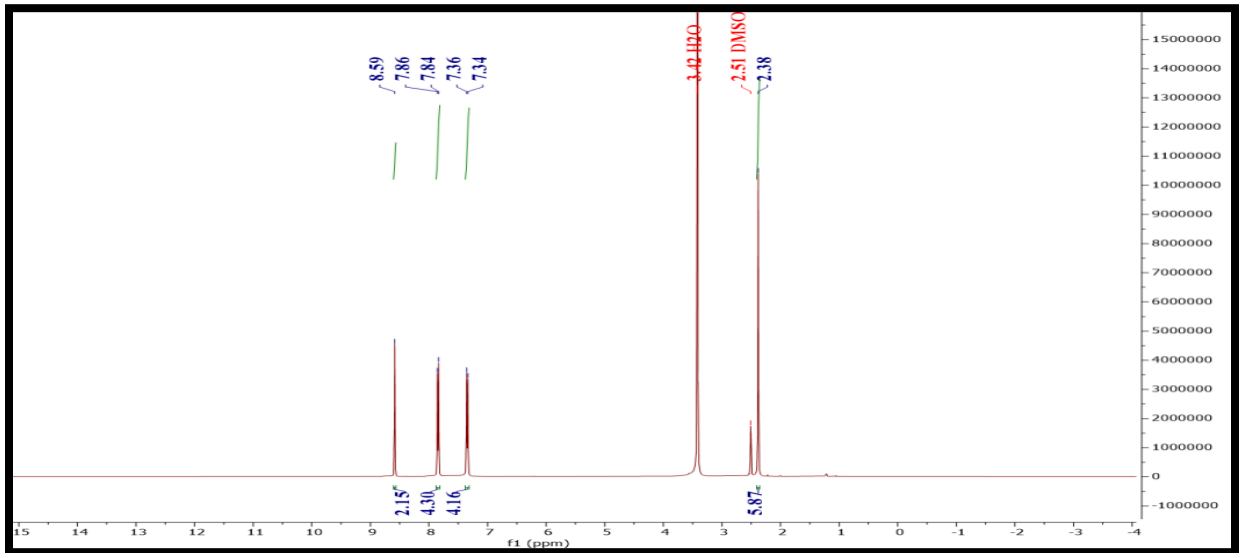


Figure 9. H NMR spectrum of compound 4a.

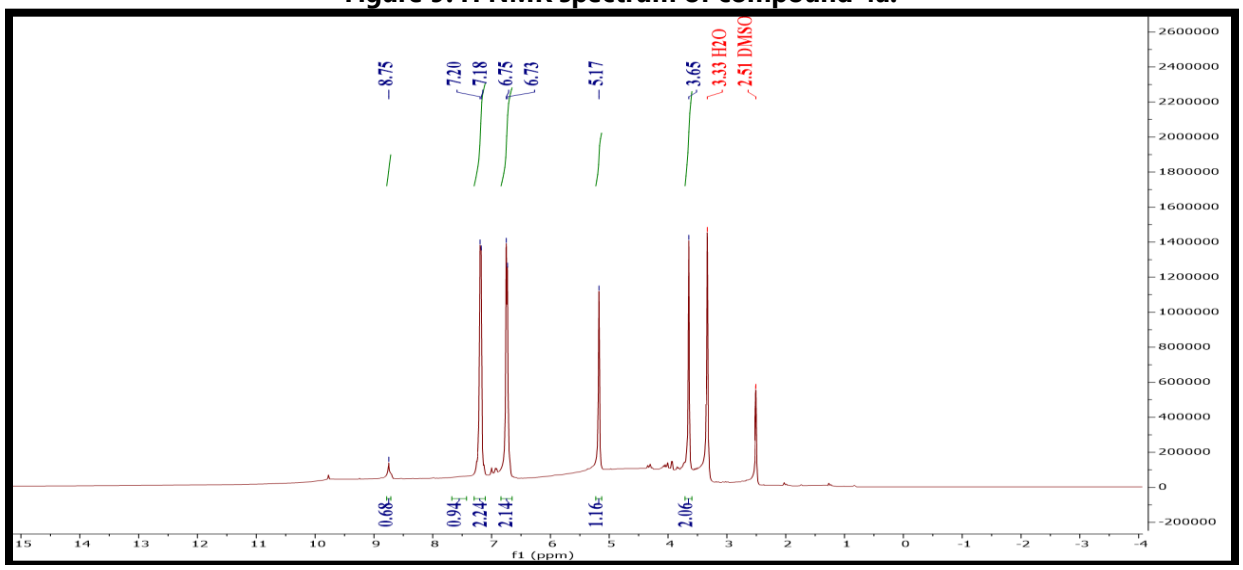


Figure 10. H NMR spectrum of compound 4c.

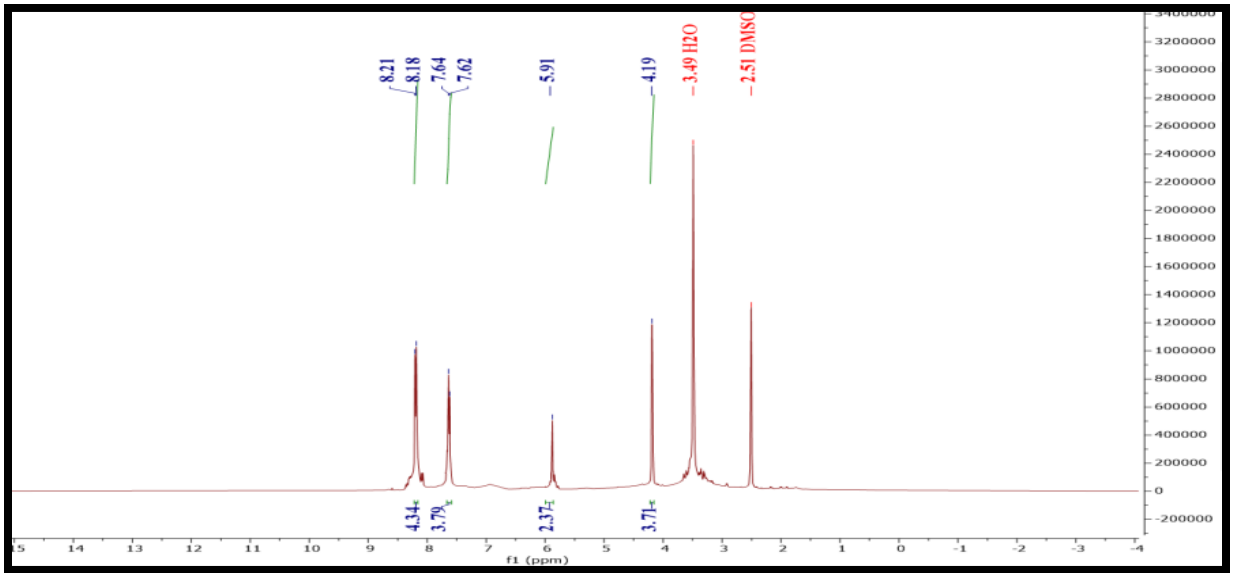


Figure 11. H NMR spectrum of compound 5a.

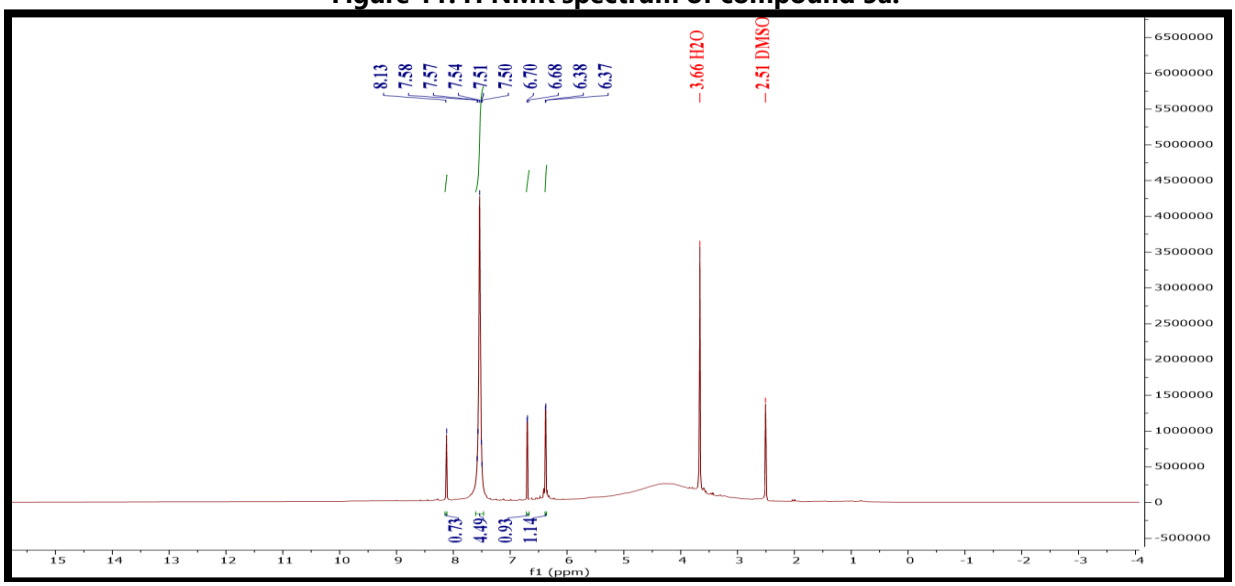


Figure 12. H NMR spectrum of compound 5a.