Global Academic Journal of Pharmacy and Drug Research

Available online at https://www.gajrc.com
DOI: 10.36348/gajpdr.2022.v04i01.004

OPEN ACCESS

ISSN (P): 2706-9044
ISSN (O): 2707-255X

Original Research Article

Synthesis and Identification of New Heterocyclic Compounds from Isatin by Schiff Base Reaction

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Article History
Received: 22.12.2021
Accepted: 05.02.2022
Published: 09.02.2022

Abstract: Heterocyclic compounds possess a cyclic structure with two or more different kinds of atoms in the ring. The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Since rings can be of any size, from three-membered upwards, and since the heteroatoms can be drawn in almost any combination from a large number of the elements (though nitrogen, oxygen, and sulfur are still by far the most common), the number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds are known and this number continues to increase very rapidly. This work is divided into two different parts: First part: Synthesis of imines by Schiff base reaction, this part involves synthesis three of imines by treatment isatin with a variety of cyclo primary amines. Second part: [3 + 2] Cycloaddition reaction, this part includes reacting each product of the first part with two types of amino acids. All steps of reactions followed by TLC– papers. All synthesized compounds were confirmed through the use of different spectroscopic techniques (IR and NMR), melting points.

Keywords: Heterocyclic, Schiff Base, Isatin.

INTRODUCTION

A heterocyclic compound, also known as a heterocycle, is a type of organic chemical compound in which part or all of the atoms in its molecules are connected in rings containing at least one atom of a non-carbon element (C). Many biological materials required for life are heterocyclic molecules. Nucleic acids, for example, are long chains of heterocyclic units bound together by other types of molecules. They carry the genetic information that controls heredity. Most hallucinogens, as well as many naturally occurring colors, vitamins, and antibiotics, are heterocyclic compounds. Synthetic heterocycles are used in modern culture as medications, insecticides, colors, and polymers [1]. In this time being the synthesis of Schiff base derivatives play an important role in various sciences [2]. During recent years, estimated two thousand papers were published per year in accordance with Scopus document search [3]. Schiff bases derivatives are observed as a very important class of organic compounds that's because of their capability to form complexes with transition metal ions by nitrogen of the azomethine group and have been studied widely [4]. These complexes had a diversity of applications inclusive of analytical, biological, industrial, and clinical, in addition to their important roles in organic synthesis and catalysis [5]. Isatins are compounds of great synthetic versatility and can be used to obtain several heterocyclic compounds, such as quinolones and indole derivatives, which makes them important raw materials in the synthesis of

drugs. Isatins have also been detected in mammalian tissues, which have aroused interest in their study as modulators in several biochemical processes [6]. Isatin is a stable, shining orange solid. Because it easily undergoes reactions of aromatic nucleophilic substitution, it is available in great quantities [7]. Isatin derivatives have important applications as they show biological properties such as anticonvulsant [8], antidepressant [9], anti inflammatory activities [10], anticancer [11], antifungal [12] and anti-HIV [13].

EXPERIMENTAL AND APPARATUSES

Chemicals and instrumentation

All materials were purchased from Merck, Sigma, BDH, and GCC. The formation of compounds was confirmed using IR, and NMR spectrometry techniques. Silica gel precoated aluminum sheets (Merck), for thin-layer chromatography (TLC), were used for determining Rf and monitoring the reaction progress. The melting points were determined in the open capillary, using melting point apparatus, provided by Cole-Parmer Ltd, UK. Fourier Transform Infrared Spectrophotometer was recorded in Shimadzu, Japan. Bruker Avance400 MHz NMR spectrometer was used for ^{1}H and ^{13}C NMR using deuterated DMSO as solvent.

MATERIALS AND METHODS

General Procedure for Synthesis of Schiff Base Derivatives a-c

Equivalent moles (1:2 mole) of various aromatic amines with Isatin, at prepare the compounds a and c, and (1:1 mole), for the compound b, in (50ml) of absolute ethanol with three drops of glacial acetic acid. This mixture was refluxed for (7-15) hours at 75 ˚C. TLC was used to check the reaction's progress. Solid product obtained was crystallized from ethanol to form (a, b, and c) [14-16].

Preparation of (3Z)-3, 3'-(1,2-phenylenebis (azanylylidene)) bis(indolin-2-one) a

A mixture of Isatin (0.02mol, 2.94g) and o-phenelendiamine (0.01mol, 1.08g) was refluxed in absolute ethanol in presence of 3 drops GAA for 12 hr. at 75 °C. Solid product obtained was crystallized from ethanol.

Preparation of 3-((4-chlorophenyl)imino) indolin-2-one b

A mixture of Isatin (0.01mol, 1.47g) and 4-chloroaniline (0.01mol, 1.2757g) was refluxed in absolute ethanol in presence of 3 drops GAA for 6 hr. at 75 °C. Solid product obtained was crystallized from ethanol.

Preparation of 3, 3'-(naphthalene-1,4-diylbis(azanylylidene)) bis(indolin-2-one) c

A mixture of Isatin (0.02mol, 2.94g) and naphthalene-1,4-diamine (0.01mol, 1.58g) was refluxed in absolute ethanol in presence of 3 drops GAA for 15 hr. at 75 °C. Solid product obtained was crystallized from ethanol.

General Procedure for Synthesis of Imidazolidine Derivatives (I8-I21) [17, 18] (140, 141)

When the compounds were prepared (a1, a2, c1, and c2), (1:2 mole) equivalent of Schiff base derivatives with histidine once and with tryptophan one more times. While when the compounds were prepared (b1 and b2), (1:1 mole) equivalent of Schiff base derivatives with histidine once and with tryptophan one more times, in (50ml) of dry benzene. This mixture was reflexed for (30-45) hours at 65 °C. TLC was used to check the reaction's progress. The combination was cooled to ambient temperature after completion, and the solid was recrystallized from ethanol to form compounds (a1, a2, b1, b2, c1, and c2).

Preparation of 1,1''-(1,2-phenylene)bis(4-((1H-imidazol-4-yl)methyl)spiroImidazolidine-2,3'-indoline]-2',5-dione) a1:

3-((2-oxoindolin-3-ylidene) amino)-4-((2-oxoindolin-3-ylidene)amino) benzene-1-ylium **a,** (0.001 mol, 0.366g) and histidine (0.002 mol, 0.31g) was dissolved in THF with constant stirring, and heated at 65 °C under reflux for 38 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

Preparation of 1,1''-(1,2-phenylene)bis(4-((1H-indol-3-yl)methyl)spiroImidazolidine-2,3'-indoline]-2',5-dione a2:

3-((2-oxoindolin-3-ylidene) amino)-4-((2-oxoindolin-3-ylidene) amino) benzene-1-ylium **a,** (0.001 mol, 0.366g) and tryptophan (0.002 mol, 0.408g) was dissolved in THF with constant stirring and heated at 65 °C under reflux for 36 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

Preparation of 4-((1H-imidazol-4-yl) methyl)-1-(4-chlorophenyl) spiroImidazolidine-2,3'-indoline]-2',5-dione b1:

3-((4-chlorophenyl)imino)indolin-2-one **b,** (0.001 mol, 0.257g) and histidine (0.001 mol, 0.155g) was dissolved in THF with constant stirring. and heated at 65 °C under reflux for 32 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

Preparation of 4-((1H-indol-3-yl) methyl)-1-(4-chlorophenyl) spiroImidazolidine-2,3'-indoline]-2',5-dione b2:

3-((4-chlorophenyl)imino)indolin-2-one **b,** (0.001 mol, 0.257g) and tryptophan (0.001 mol, 0.204g) was dissolved in THF with constant stirring and heated at 65 °C under reflux for 30 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

Preparation of 1,1''-(naphthalene-1,4-diyl)bis(4-((1H-imidazol-4-yl)methyl)spiroImidazolidine-2,3'-indoline]-2',5-dione) c1:

3, 3'-(naphthalene-1, 4-diylbis(azanylylidene)) bis (indolin -2-one) **c,** (0.001 mol, 0.416g) and histidine (0.002 mol, 0.31g) was dissolved in THF with constant stirring and heated at 65 °C under reflux for 45 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

Preparation of 1,1''-(naphthalene-1,4-diyl)bis(4-((1H-indol-3-yl)methyl)spiroImidazolidine-2,3'-indoline]-2',5-dione) c2:

3, 3'- (naphthalene-1, 4-diylbis (azanylylidene)) bis(indolin-2-one) **c,** (0.001 mol, 0.416g) and tryptophan (0.002 mol, 0.408g) was dissolved in THF with constant stirring and heated at 65 °C under reflux for 45 hr. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice-cold water, dried, and recrystallized from ethanol.

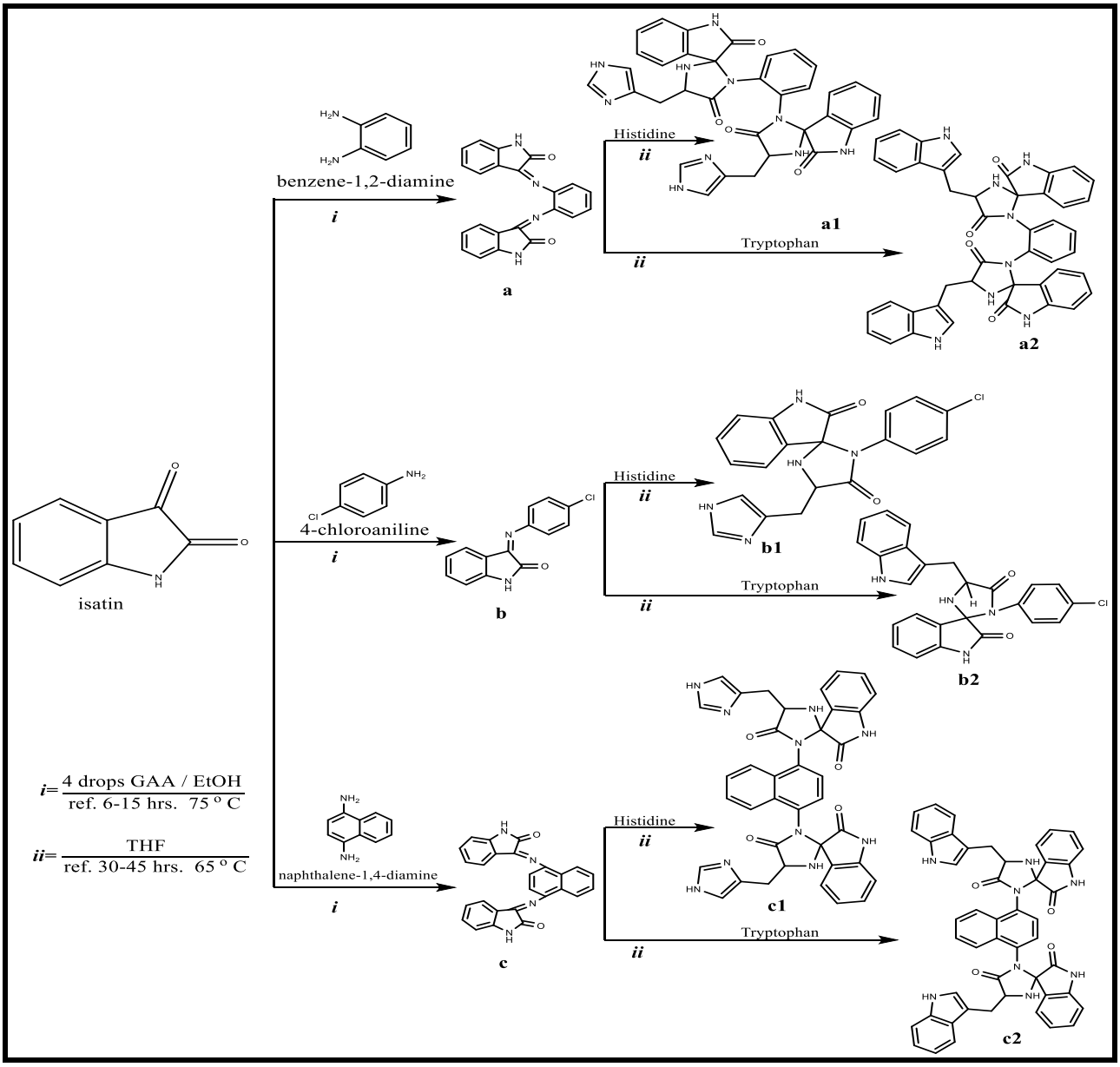
RESULTS AND DISCUSSION

All synthesized compounds [**a (1, 2), b (1,2), c(1,2)**] were characterized by [FT.IR-spectra, melting points, ^{1}H.NMR-spectra and some of them by ^{13}C.NMR-spectra].

FT.IR-spectra

The FT-IR spectrum showed peak at 3336 cm^{-1} to stretching vibration of secondary amine (NH) groups [19-22]. And peak at 3088 cm^{-1} belonging to stretched C-H aromatic ring [23], the peak 1707 cm^{-1} to stretching vibration of (C=O) cyclic amide [24-27], while the peak at 1637 cm^{-1} can be attributed to the stretching vibration of imine (C=N) group [28]. Showed shifting at 1602 cm^{-1} to stretching vibration of (Ar. C=C) [29]. In compound a. The FT-IR spectrum showed peak at 3349 cm^{-1} to stretching vibration of secondary amine (NH) groups. And peak at 3097 cm^{-1} belonging to stretched C-H aromatic ring, the peak 1704 cm^{-1} to stretching vibration of (C=O) cyclic amide, while the peak at 1642 cm^{-1} can be attributed to the stretching vibration of imine (C=N) group. Showed shifting at 1594 cm^{-1} to stretching vibration of (Ar. C=C), finally, we note the presence of the peak at 747 cm^{-1} belongs to stretching vibration of (C-Cl). In compound b. The FT-IR spectrum showed peak at 3347 cm^{-1} to stretching vibration of secondary amine (NH) groups. And peak at 3090 cm^{-1} belonging to stretched C-H aromatic ring, the peak 1702 cm^{-1} to stretching vibration of (C=O) cyclic amide, while the peak at 1618 cm^{-1} can be attributed to the stretching vibration of imine (C=N) group. Showed shifting at 1576 cm^{-1} to stretching vibration of (Ar. C=C). In compound c. The FT-IR spectrum of compound a1 showed peak at 3208 cm^{-1} to stretching vibration of secondary amine (NH) groups. The peak 2992 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 2902 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1703 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1555 cm^{-1} to stretching vibration of (Ar. C=C). The FT-IR spectrum of compound a2 showed peak at 3243 cm^{-1} to stretching vibration of secondary amine (NH) groups. The peak 3051 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 2983 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1703 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1585 cm^{-1} to stretching vibration of (Ar. C=C). The FT-IR spectrum of compound b1 showed peak at 3216 cm^{-1} to stretching vibration of secondary amine (NH) groups. The peak 3115 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 2973 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1677 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1548 cm^{-1} to stretching vibration of (Ar. C=C). The FT-IR spectrum of compound b2 showed peak at 3196 cm^{-1} to stretching vibration of secondary amine (NH) groups. The peak 3137 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 3061 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1690 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1576 cm^{-1} to stretching vibration of (Ar. C=C). The FT-IR spectrum of compound c1 showed peak at 3281 cm^{-1} to stretching vibration of secondary amine (NH) groups. The peak 3003 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 2913 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1674 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1552 cm^{-1} to stretching vibration of (Ar. C=C). The FT-IR spectrum of compound c2 showed peak at 3211 cm^{-1} to stretching vibration of secondary

amine (NH) groups. The peak 3136 cm^{-1} belonging to stretched C-H aromatic ring, while the peak at 3057 cm^{-1} can be attributed to the stretching vibration of (C-H) aliphatic. The peak 1705 cm^{-1} to stretching vibration of (C=O) cyclic amide. Finally, at 1537 cm^{-1} to stretching vibration of (Ar. C=C).



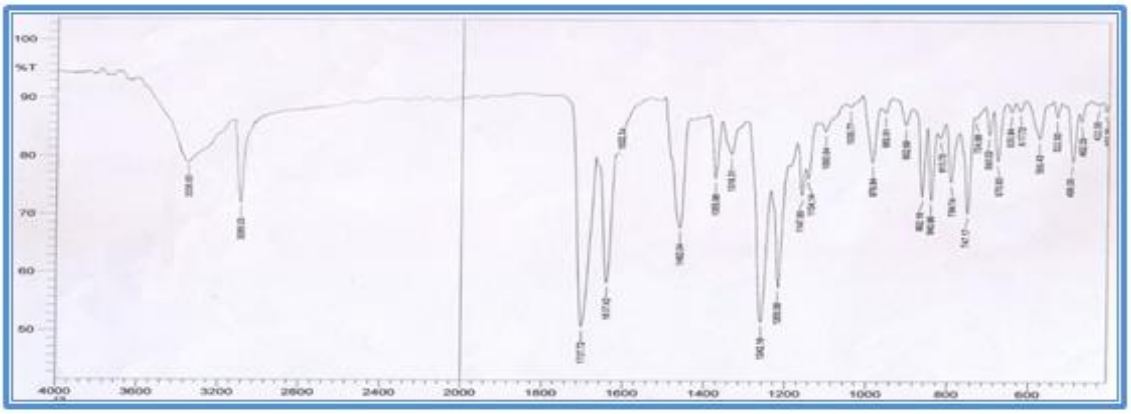


Fig-1: FT-IR Spectrum of Comp. (a)

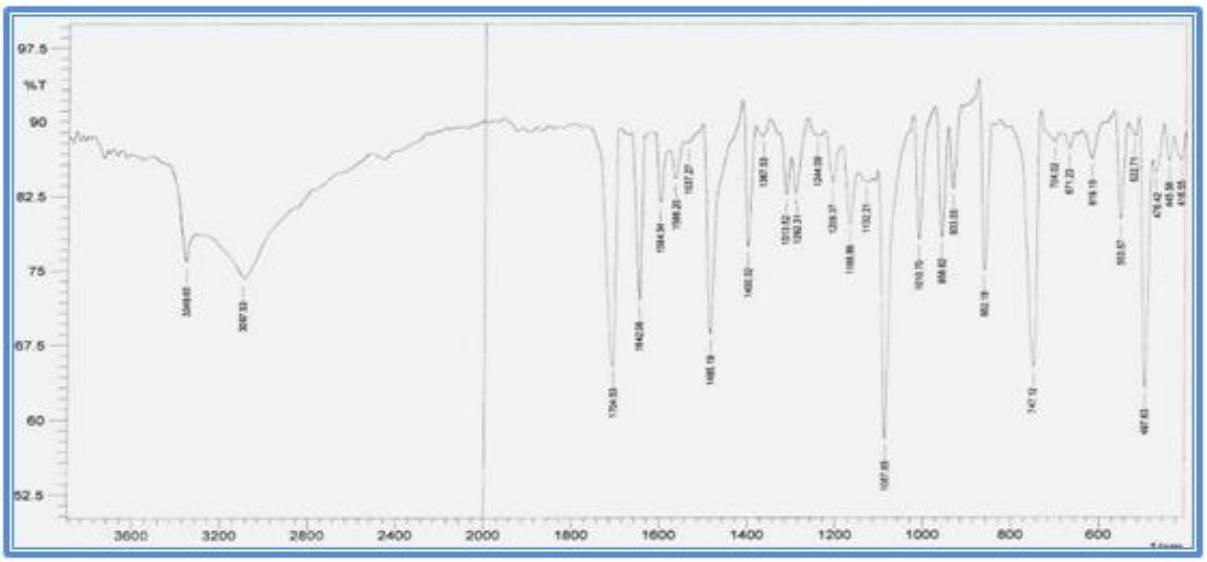


Fig-2: FT-IR Spectrum of Comp. (b)

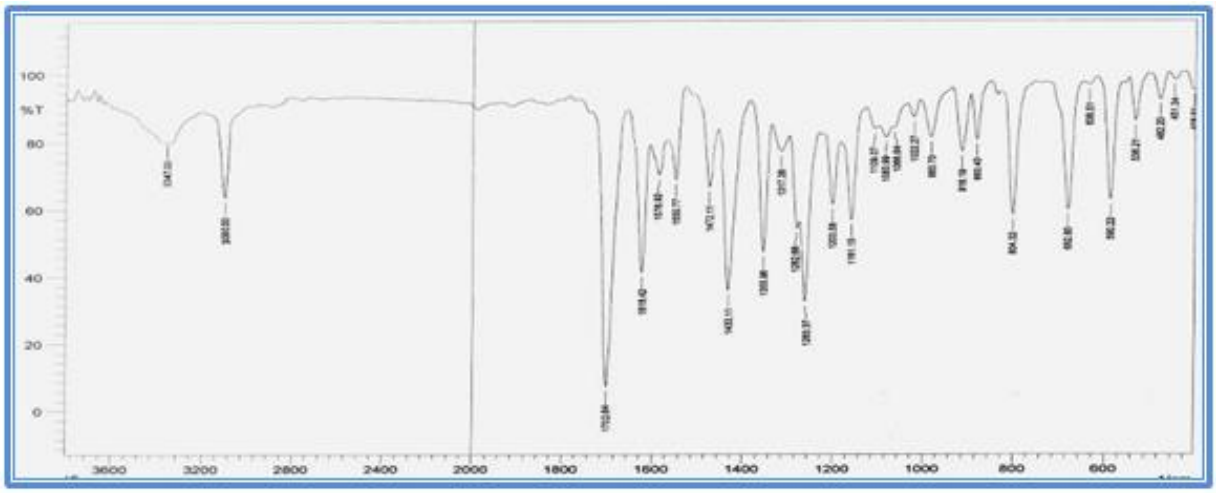


Fig-3: FT-IR Spectrum of Comp. (c)

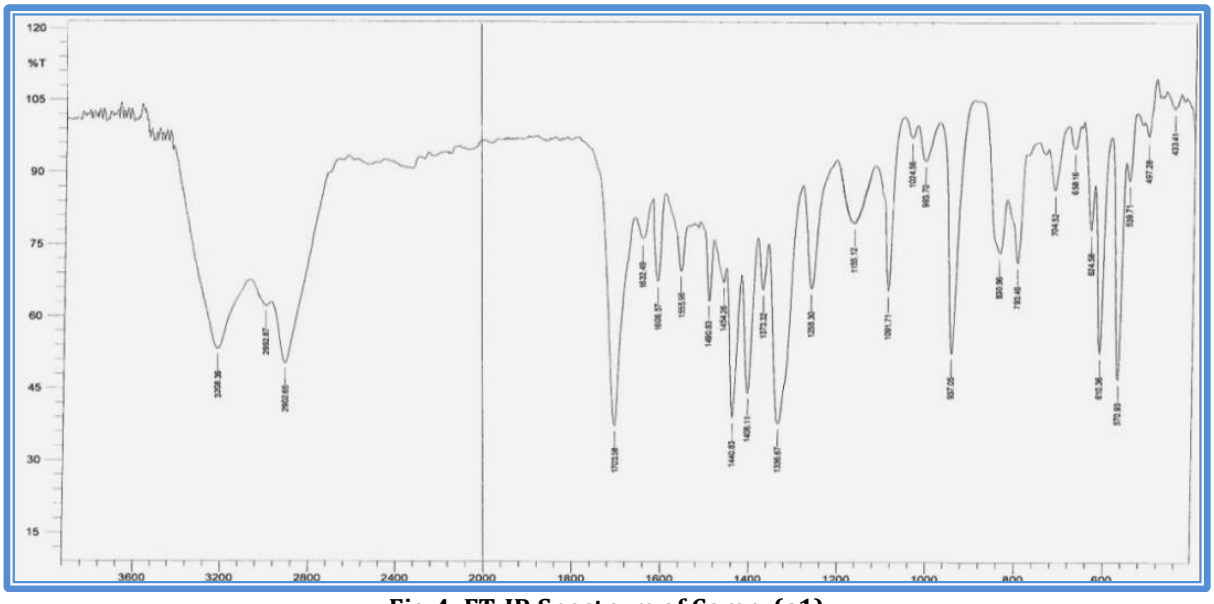


Fig-4: FT-IR Spectrum of Comp. (a1)

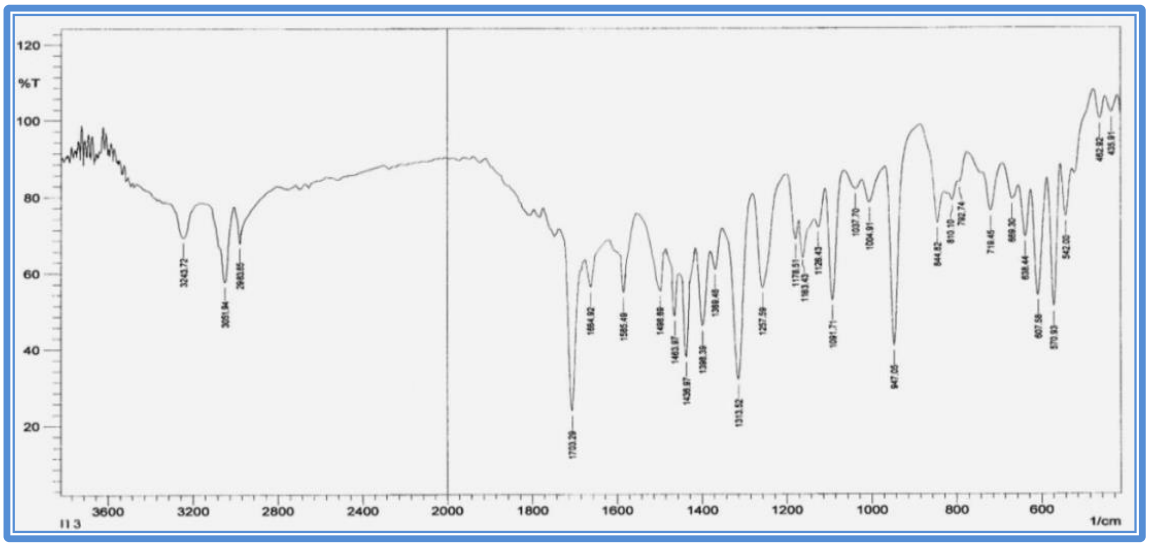


Fig-5: FT-IR Spectrum of Comp. (a2)

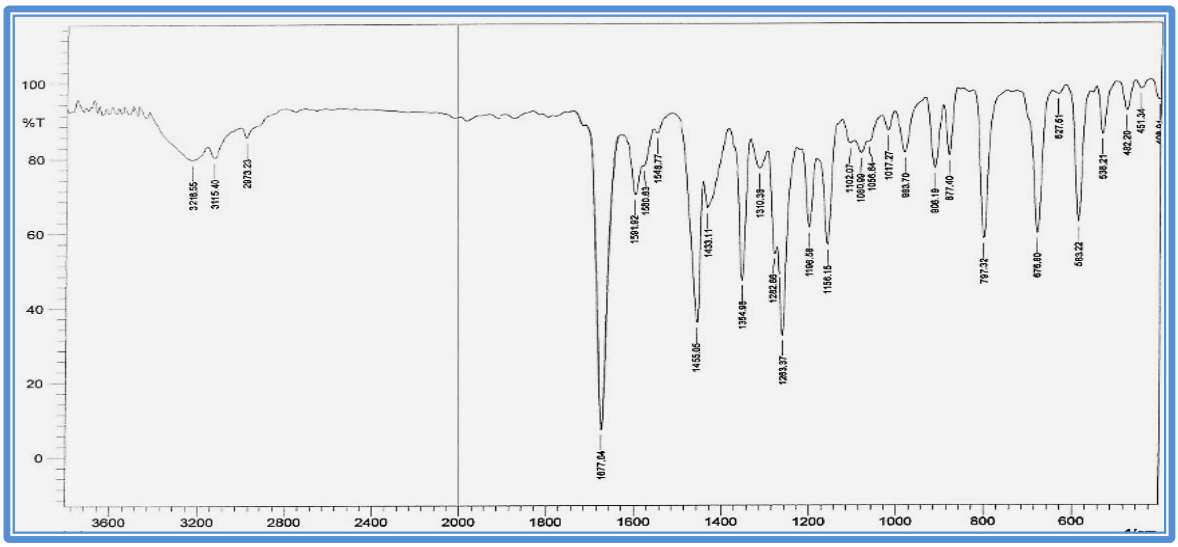


Fig-6: FT-IR Spectrum of Comp. (b1)

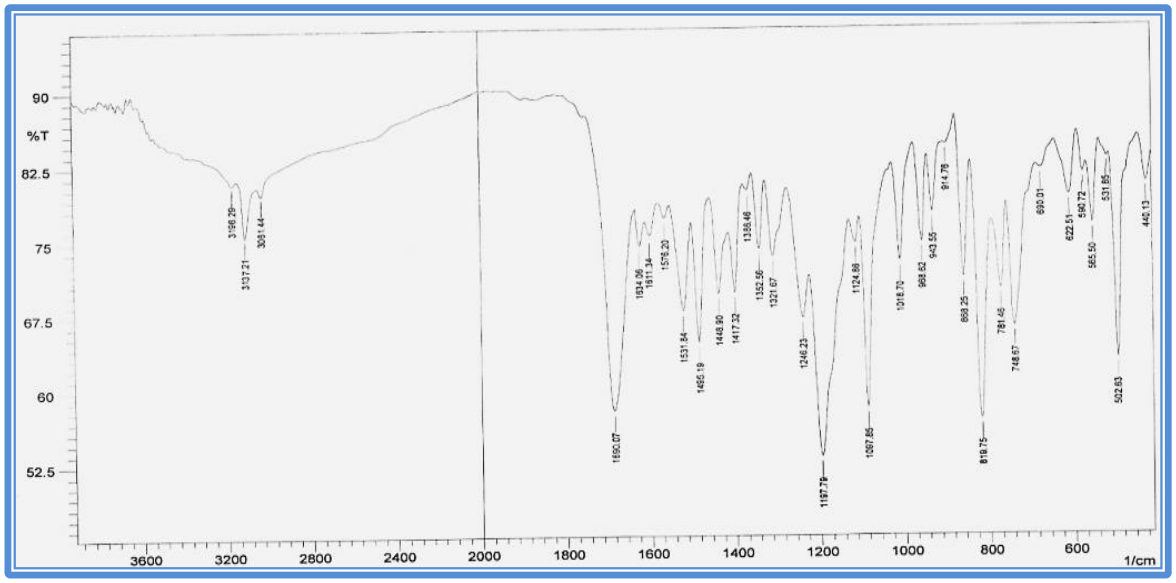


Fig-7: FT-IR Spectrum of Comp. (b2)

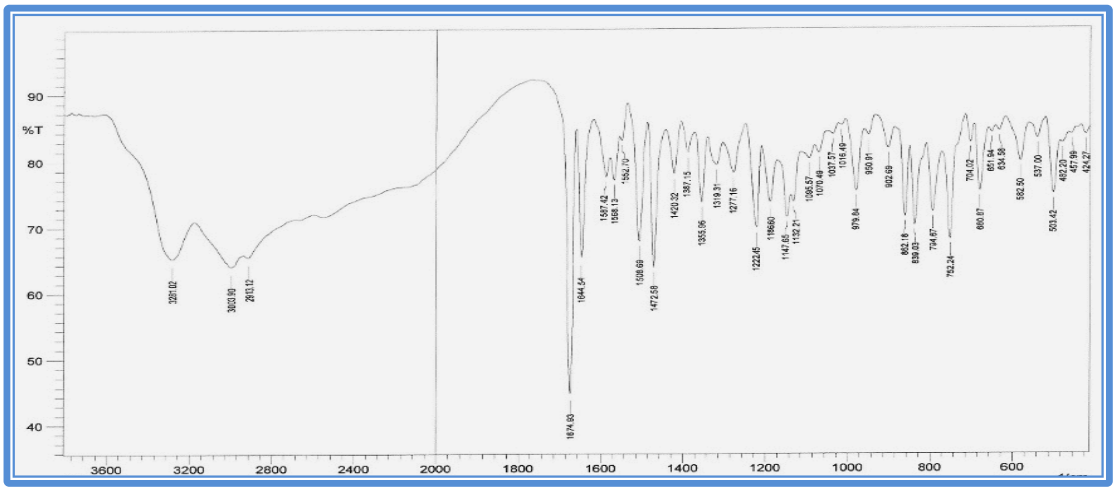


Fig-8: FT-IR Spectrum of Comp. (c1)

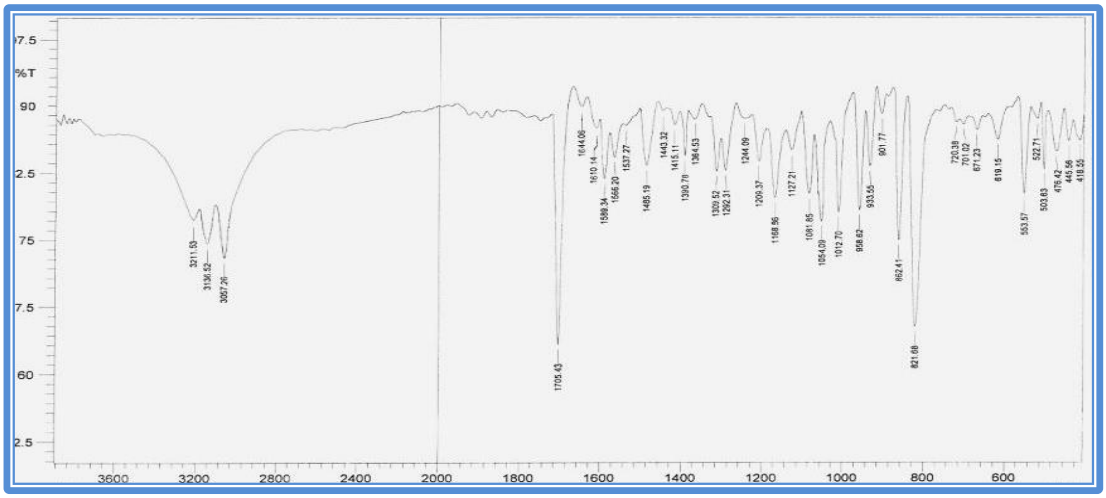


Fig-9: FT-IR Spectrum of Comp. (c2)

^{1}H.NMR spectra: The ^{1}H NMR spectrum of compound a showed that significant signal at 10.8 ppm for the proton of cyclo amide (N-H) [30, 31] group. While signals at the range of 6.6-8.2 ppm complex splitting of (C-H) of benzene. Showed that significant signal at 11.04 ppm for the proton of cyclo amide (N-H) group. While signals at the range of 6.65-7.8 ppm complex splitting of (C-H) of benzene to compound b. The ^{1}H NMR spectrum of compound c showed that significant signal at 10.98 ppm for the proton of cyclo amide (N-H) group. While signals at the range of 7.02-8.1 ppm complex splitting of (C-H) of benzene. The ^{1}H NMR spectrum of compound a2 showed that significant signal at 11.10 ppm for the proton of secondary amine (N-H) group. And signal at 10.89 ppm for the proton of cyclo amide (N-H) group. While signals at the range of 6.46 - 7.77 ppm complex splitting of (C-H) of benzene. Finally, significant signal at range 2.70 – 3.79 ppm of (C-H) aliphatic.

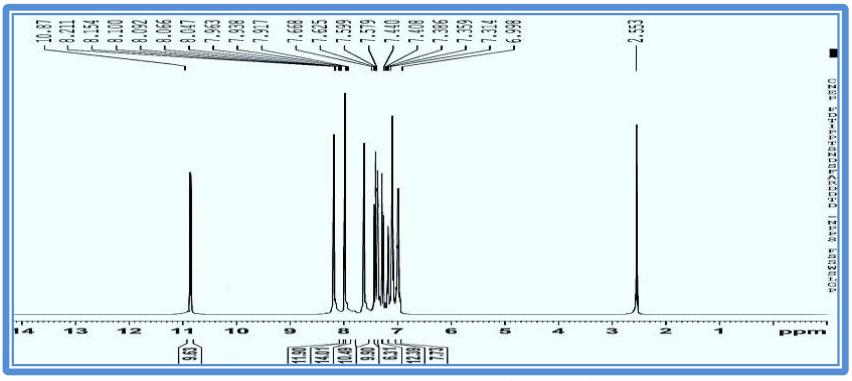


Fig-10: ^{1}H NMR Spectrum of Comp. (a)

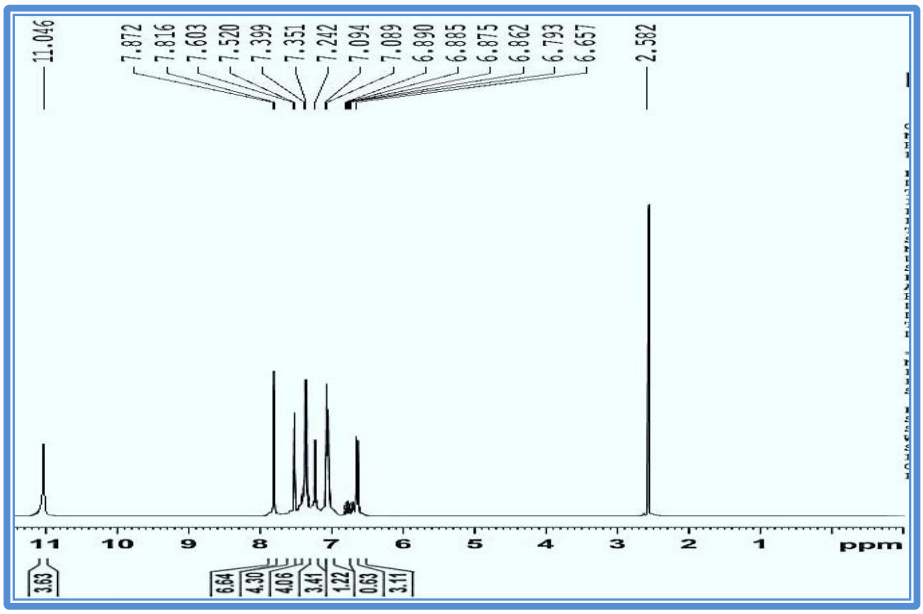


Fig. 11 ^{1}H NMR Spectrum of Comp. (b)

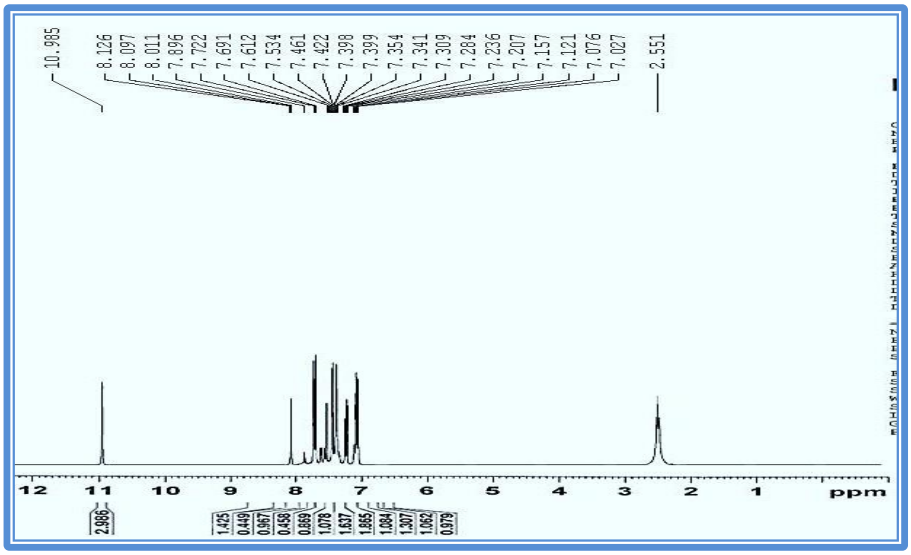


Fig-12: ^{1}H NMR Spectrum of Comp. (c)

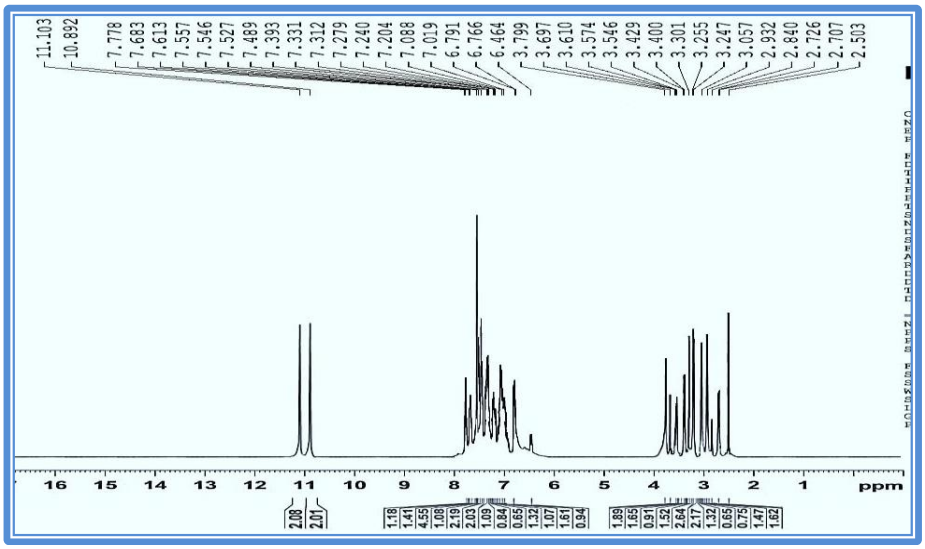


Fig-13: ^{1}H NMR Spectrum of Comp. (a2)

^{13}C NMR Spectra

The appearance of a signal at 160 ppm belonging to the carbon of imine (C=N) group [32, 33]. While a signal appeared at 157 and 158 ppm, referring to carbon of amide (C=O) group [34, 35]. The spectrum also showed signal at 142 ppm belonging to carbon (C-N). in addition to significant signals between (116-135) ppm belonging to the aromatic ring carbon (C=C) of different environment to compound a. The appearance of a signal at 161 ppm belonging to the carbon of imine (C=N) group. While a signal appeared at 153 ppm, referring to carbon of amide (C=O) group. The spectrum also showed signal at 149 ppm belonging to carbon (C-N). While a signal appeared at 142 ppm, referring to carbon of (C=C-Cl). In addition to significant signals between (105-133) ppm belonging to the aromatic ring carbon (C=C) of different environment to compound **b**. The appearance of a signal at 161 ppm belonging to the carbon of imine (C=N) group. While a signals appeared at 150 and 149 ppm, referring to carbon of amide (C=O) group. The spectrum also showed signal at 140 ppm belonging to carbon (C-N). In addition to significant signals between (114-130) ppm belonging to the aromatic ring carbon (C=C) of different environment to compound **c**.

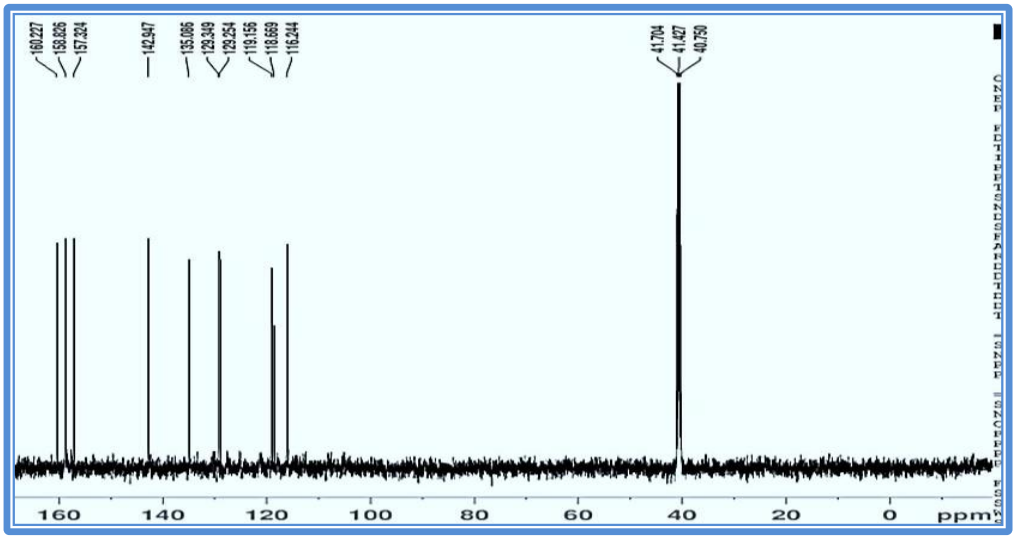


Fig-14: ^{13}C NMR Spectrum of Comp. (a)

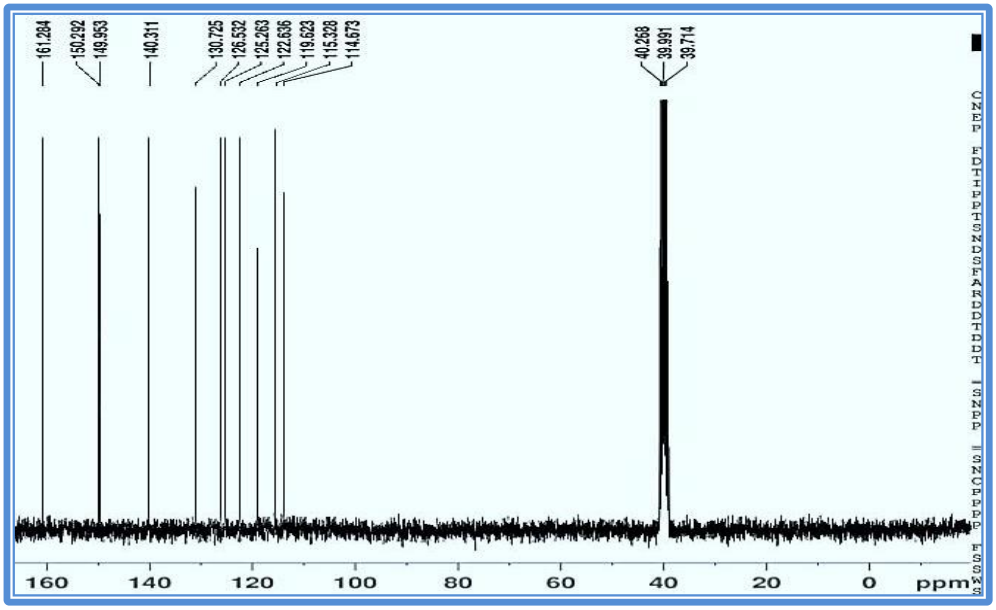


Fig-15: ^{13}C NMR Spectrum of Comp. (b)

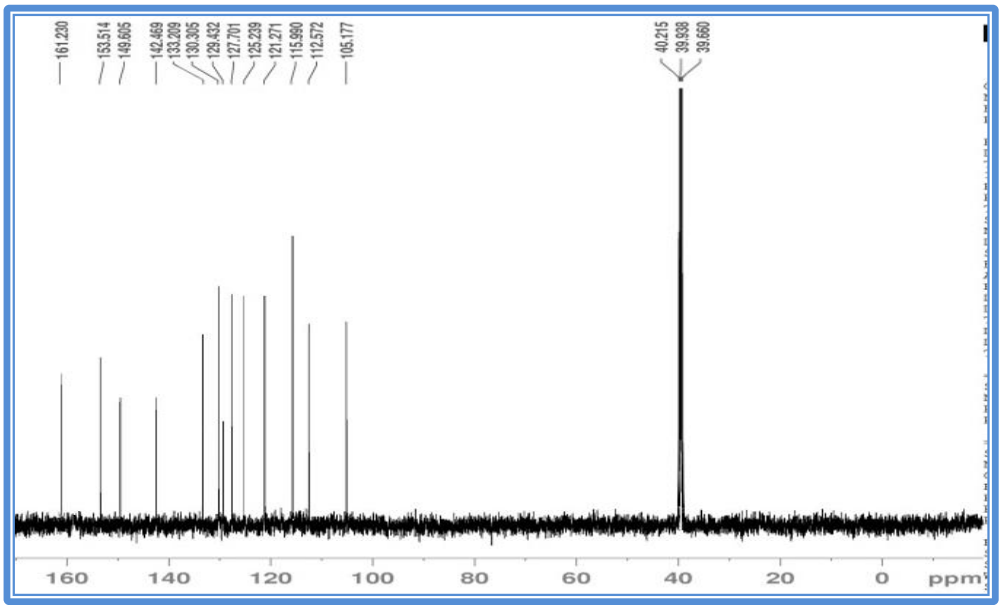


Fig-16: ^{13}C NMR Spectrum of Comp. (c)

Comp.	m.p. °C	Yield%	M.Wt	Color	Chemical Formula
a	225-227	82	366.38	Burnt Orang	$C_{22}H_{14}N_4O_2$
b	211-213	70	256.69	Chocolate	$C_{14}H_9ClN_2O$
c	232-234	66	416.44	Pumpkin	$C_{26}H_{16}N_4O_2$
a1	231-233	66	640.23	Burnt Orang	$C_{34}H_{28}N_{10}O_4$
a2	233-235	60	738.81	Burnt Orang	$C_{44}H_{34}N_8O_4$
b1	202-205	62	393.83	Chocolate	$C_{20}H_{16}ClN_5O_2$
b2	220-222	73	442.9	Chocolate	$C_{25}H_{19}ClN_4O_2$
c1	230-232	61	690.72	Pumpkin	$C_{38}H_{30}N_{10}O_4$
c2	235-237	66	788.87	Pumpkin	$C_{48}H_{36}N_8O_4$

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