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Synthesis and Characterization of Heterocyclic Schiff Base, Thiazolidinone and Chalcone as Antibacterial Agents.

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ABSTRACT

New heterocyclic Schiff base were synthesized from o-phenylenediamine with pyridine-2- aldehyde, this Schiff base was converted into thiazolidinone by the action of mercaptoacetic acid. The chalcone compound carry out by converted heterocyclic thiazolidinone with treated benzaldehyde according to the Claisen-Schmidt condensation . The synthesis compounds have been characterized by CHN, UV, FT-IR, ¹HNMR and ¹³CNMR. The biological screening data of the synthesized compounds were also presented.

Keywords: Schiff base , 2-Thiazolidinone, Chalcone, Antibacterial

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INTRODUCTION

Heterocyclic systems containing mainly nitrogen, sulfur and oxygen atom constitute a large class of compounds of biological and medicinal interest [1]. A huge number of heterocyclic systems which include mainly five and six membered compounds represent a diverse group of molecules scaffolds. Several such heterocyclic scaffolds have been successfully incorporated into novel drug leads and therapeutic agents [2-4]. Example that illustrate the biological [5] importance and therapeutic utility of some heterocyclic derivatives include metronidazole (2-methyl-5-nitroimidazole 1-ethanol), a nitromidazole derivative used as antimoebic; thaibendazole [2-(4-thaizolyl)benzimidazole], a thaibendazole derivative used as anthelmintic. The study of chemistry and biological importance of heterocyclic compounds has been an interesting area of research for a long time. Recent literature has explored the biological importance of a various structural derivatives of heterocyclic compounds. On the other hand, Schiff bases, the condensed product of the aromatic imine and aromatic aldehydes, have been known to possess a wide variety of biological applications like antibacterial, antifungal, antitumor, analgesic, and anti-inflammatory [6]. Moreover, Schiff's bases obtained from various heterocyclic scaffolds covers a wide range of pharmacological potential such as antimicrobial, anthelmintic, anti-inflammatory, analgesic, antipyretic, diuretics, antitubercular, hypoglycemic, anti-HIV, cytotoxic, anticonvulsant, anticancer including other biological activities^(7,9). It is strongly believe that the specific grouping azomethane (-N=C-) is an important structural requirement for the bioactivity of Schiff bases.

The wide range of biological activities exhibited by thiazolidinones [10, 11] derivatives, the aim of this study is to prepare thiazolidinones containing pyridine ring in the molecule and to explore the pharmacological activity of this combination product. Thiazolidinone is a heterocyclic compound of five-membered unsaturated ring structure composed of three carbon atoms, nitrogen and sulfur atoms at nonadjacent positions. The chemistry of thiazolidinones compounds have been of much interest due to the presence of such heterocycles in a large variety of biologically important molecules [12].

Chalcones were prepared by condensation of aromatic ketones with aromatic aldehydes in presence of suitable condensing agent [13,14]. They undergo a variety of chemical reactions that leads to many heterocyclic compounds [15-17]. Chalcones have been used as intermediates for the preparation of compounds having therapeutic value [18-19] Many reviews reveal that chalcone derivatives exhibit diverse pharmacological activities, such as potential cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetic, etc. [20,21]. In the view of the varied biological and pharmacological applications, we have planned to synthesize some heterocyclic derivatives of chalcone and test their antibacterial activity.

Chalcones having α and β unsaturated carbonyl group are one of important biocides and versatile synthons for various chemical transformation. Chalcones are also key precursors in the synthesis of many biological important heterocyclic.

EXPERIMENTAL

Melting point were determined in Buchi thermal point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in EA300 Euro-Vector in University of Al-albyat in Jordon. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk in the range 40-4000 cm^{-1} . Ultraviolet spectra were recorded in spectro scan 80 in the wave length 200-800 nm. ¹HNMR and ¹³CNMR spectra were recorded on Bruker spectrosin ultra shield magnets 400MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d₆ as a solvent in university of Tabriz-Iran. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck company.

SYNTHESIS OF COMPOUNDS

Synthesis of bis (2-pyridyl benzidine) Schiff base (a)

A mixture of pyridine-2-aldehyde (2mmole, 2.14gm) and o-phenylenediamine (1mmole, 1.08gm) were dissolved in ethyl alcohol (40ml). drops of acetic acid was added and was refluxed for 4hrs, This reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered ,crystallized from ethyl alcohol to give crystalline pale yellow, yield 67%, Melting point 187-189°C, CHN

analysis that formula $C_{18}H_{14}N_4$ calculated C, 75.503 H, 4.935 N, 19.572 ; Found C, 75.334 H, 4.725 N, 19.455. Ultraviolet spectra λ_{max} 242, 266 and 320nm. FT-IR spectra ν_{max} 2964, 1612, 1620, 1454, 1217, 752 cm^{-1} . 1H NMR spectra δ ppm, (7.3,5H), and (8.1,1H)s. ^{13}C NMR spectra δ ppm, 107, 110, 113, 113, 114, 115,125, 127, 142, 145, 151, 164.

Synthesis of bis (2-pyridyl benzidine) 4-yaizoliinone (b)

A mixture of (1mmole, 4.34gm) Schiff base (a) and mercaptoacetic acid (15ml) in 40ml dry benzene, 2g of zinc chloride was added and refluxed for 5hrs, This reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethyl alcohol to give crystalline yellow. yield 77%, Melting point 202-204 $^{\circ}C$, CHN analysis that formula $C_{22}H_{18}N_4O_2S$ calculated C, 60.812 H, 4.181 N, 12.897; Found C, 60.765 H, 4.062 N, 12.814. Ultraviolet spectra λ_{max} 240, 255, 284 and 330 nm. FT-IR spectra ν_{max} 3113, 1730, 1533, 1290, 768 cm^{-1} . 1H NMR spectra δ ppm, (2,3H)d, (3,3H)s and (6.8,5H). ^{13}C NMR spectra δ ppm, 52, 55, 92, 114, 118, 120, 121, 123, 129, 130, 158, 158, 163, 163, 170.

Synthesis of bis (2-pyridyl benzidine) 4-thaizoliinone chalcone (c)

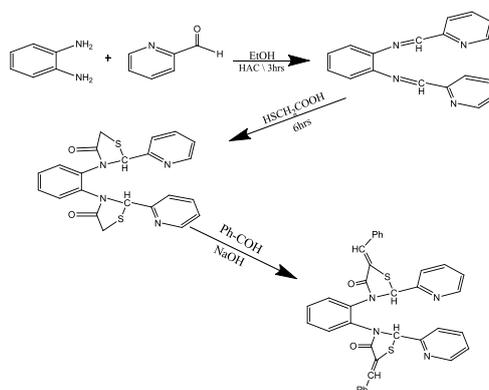
A mixture of (1mmole, 1.57gm) from compound (b) and 10ml of benzaldehyde in 40ml ethanol and (25ml) of 10% potassium hydroxide, added and refluxed in hotplate in 80 $^{\circ}C$ for 3hrs. This reaction was monitored by TLC. The mixture was cooled in ice to participate the solid white crystal, the participate solid was filtered and recrystallized from abs. ethanol, yield 76%. Melting point 240-242 $^{\circ}C$, CHN analysis that formula $C_{36}H_{30}N_4S_2$ calculated C, 74.193 H, 5.194 N, 9.615; Found C, 74.005 H, 4.994 N, 9.498. Ultraviolet spectra λ_{max} 232,245, 290, and 310nm. FT-IR spectra ν_{max} 3013,1440.1255,960 cm^{-1} . 1H NMR spectra δ ppm, (3,3H)s, (3,5H)s, (4,0H)d and (7.0,5H). ^{13}C NMR spectra δ ppm, 49, 53, 91, 103, 104, 111, 115, 120, 121, 133, 144, 158, 159, 160, 161, 163, 170.

RESULT AND DISCUSSION

The chemical synthesis started with the conversion of commercially available o-phenylenediamine to Schiff base by the reaction of 1mole diamines group with 2moles suitable aromatic aldehyde,(pyridine-2-aldehyde). Schiff bases [22] upon reaction with mercaptoacetic acid gave thiazolidinone derivative of o-phenylenediamine. Purity of the synthesized compounds was confirmed by TLC and structures were confirmed by NMR, infrared and nuclear magnetic spectroscopic techniques. The structures of Schiff bases and thiazolidinone derivatives were supported by elemental analyses.

The present study reports the successful synthesis of Schiff bases and thiazolidinone derivatives of o-phenylenediamine with several structural variations. Pharmacological examination of synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism. Thiazolidinone derivative showed higher activity than Schiff base derivative. The heterocyclic derivatives of chalcone were subjected to antimicrobial screening using nutrient agar medium by well diffusion method⁽²³⁾. The antibacterial activity was tested against various types of bacteria and compared with standard drugs (Streptomycin).

The general reaction of this research indicate to scheme (1).

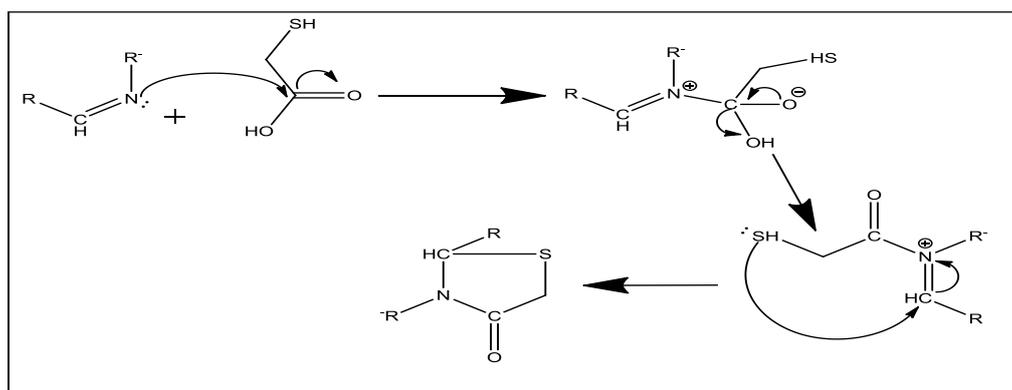


Scheme (1)

All the synthesized compounds (a-c) were purified by successive recrystallization using ethanol. The purity of the compounds synthesized was checked by performing TLC (benzene-methanol as the solvent system). Compound (a) characterized with UV spectrum⁽²²⁾ which showed the three band at (240-320)nm were due to transition (π - π^*) aromatic ring addition to heterocyclic ring. While the compound (b) and (c) which showing four band at (232-2310)nm were due to interferences transition (π - π^*) aromatic heterocyclic ring with aromatic benzene ring addition to (n - π^*) for carbonyl group come back to thiazolidinone compound (b) and transition (π - π^*) for double bond come back to chalcone compound (c) .

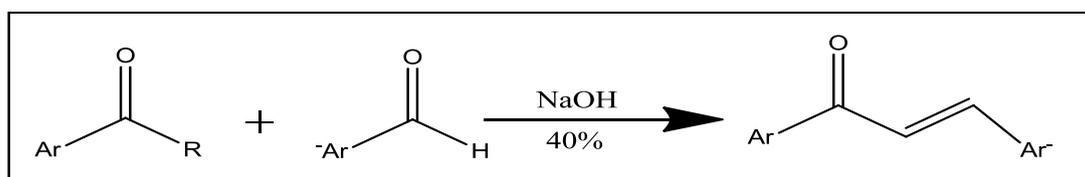
The structures of synthesized compounds were determined on the basis of their FTIR [24], The intense band at 1612 and 1620 cm^{-1} in compound (a) confirmed to the stretching vibrations for the C=N group. Cyclisation with mercaptoacetic acid gave compound (b). These were characterized as the carbonyl group and C-S-C linkage vibrations, hence confirming the process of cyclisation. This compound showed the appearance of new vibration mode at 1720 cm^{-1} which was characterized as the peak for carbonyl group and 1180 cm^{-1} for C-S. The formation of compound (c) was confirmed by appearance of new vibration modes at 1520 cm^{-1} and 1160 cm^{-1} which were characterized as the peaks for C=C and C-S. NMR data [25,26] as indicate in the figures (1-6), ¹H NMR signals for compound (a) showed at δ 7.3 ppm for the aromatic (benzene & pyridine) addition to signal of proton azomethane, ¹³C NMR signals appears 12 line according to 12 carbon atom. The CH₂ group of the thiazolidinone nucleus in (b) and ¹H NMR signal at δ 3.3 ppm, and signal for the CH at 2.3 ppm. In addition to signals at 6.5 ppm for aromatic systems, ¹³C NMR signals appears 14 line according to 14 carbon atom. The CH₂ group of the thiazolidinone nucleus in (c) and ¹H NMR signal at δ 3.5 ppm, signal for the CH at 3.0 ppm, and the signal in 7.0 ppm for the proton of double bond (alkene) In addition to signals at 6.5 ppm for aromatic systems, ¹³C NMR signals appears 19 line according to 19 carbon atom.

Mechanism of the pericyclic reaction between an imine group and mercaptoacetic acid for preparing thiazolidinone ring systematically investigated. The breaking and formation of bonds occur simultaneously and thus the reaction proceeds via a single cyclic as show in scheme (2) .



Scheme (2)

The synthesis of chalcone was accomplished according to the Claisen-Schmidt condensation [27] of ketones with aromatic aldehydes under heating reaction as indicate to scheme (3).



Scheme (3)

Several strategies for the synthesis of the system based on the formation of carbon-carbon bond have been reported. Among them the direct aldol condensation and Claisen-Schmidt condensation still occur prominent position. The main method for the synthesis of Chalcones is the classical Claisen-Schmidt condensation in presence of aqueous alkali⁽²⁸⁾, however of this methods suffered from harsh reaction conditions, toxic, reagents, strong acid or base condition, prolonged reaction time, poor yield and low

selectivity. Although, several modification have been made to counter these problems. There is a still a need for the development of selective and better strategies for the synthesis of α and β unsaturated carbonyl compounds.

BIOLOGICAL ACTIVITIES

The antibacterial [29, 30] activities of the series (a-c) have been carried out against some strain of bacteria. The result (table 1) showed that prepared compounds are toxic against the bacteria. the compounds(a), (b) and (c) were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with penicillin shows that these compounds have almost similar activity.

Table (1) The antibacterial activities of the compounds (a-c)

Antibacterial data in MIC(μ g/ml)		
Compound	Staphylococcus aureus(gram +ve)	E. Coli (gram -ve)
a	6	7
b	8	10
c	4	10
Streptomycin standard	9	12

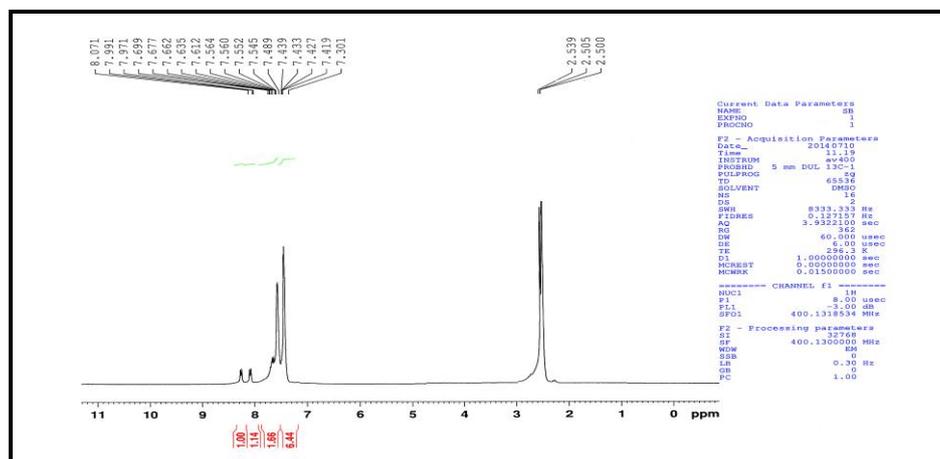


Figure (1): ¹H NMR for Compound (a)

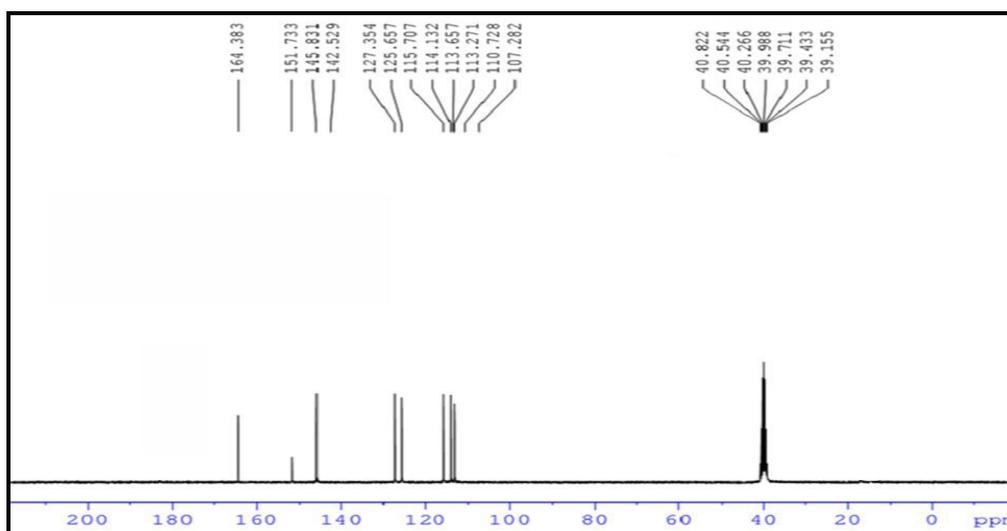


Figure (2): ¹³C NMR for Compound (a)

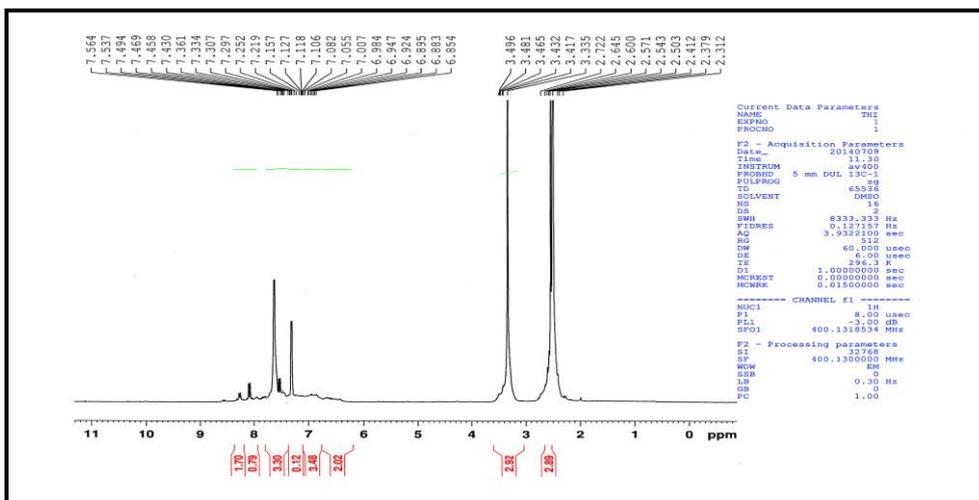


Figure (3): ¹H NMR for Compound (b)

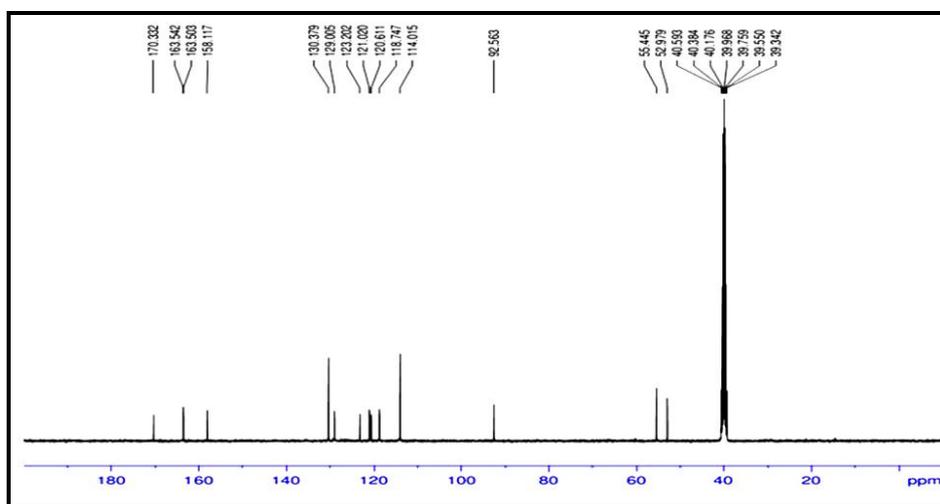


Figure (4): ¹³C NMR for Compound (b)

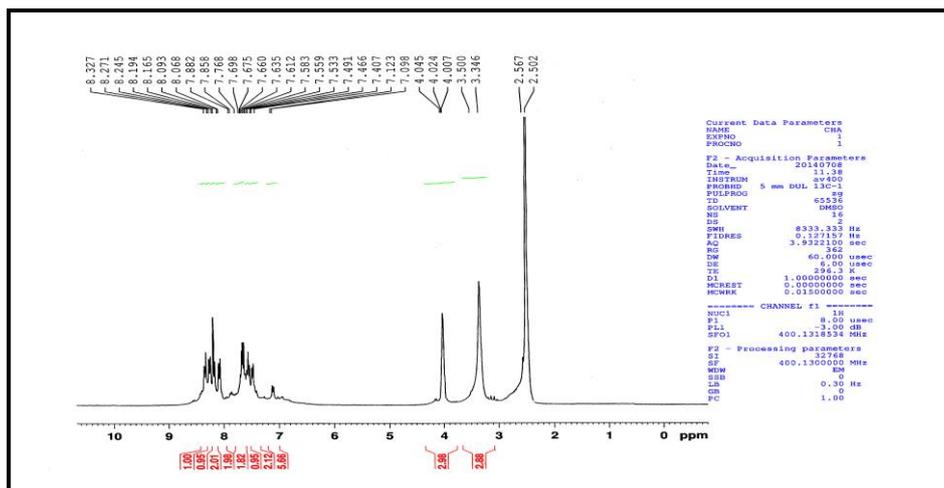


Figure (5): ¹H NMR for Compound (c)

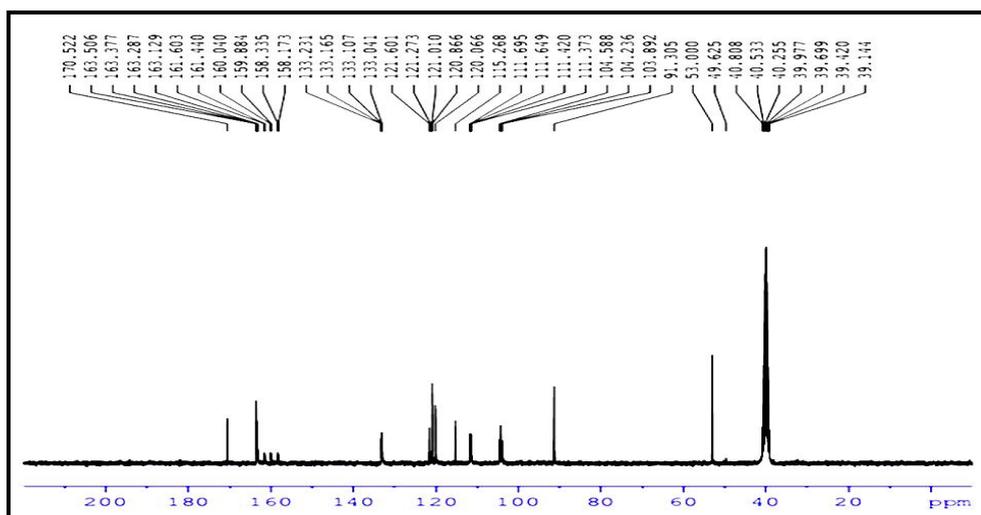


Figure (6): ^{13}C NMR for Compound (c)

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