Synthesis Of New Nucleoside Analogue (6-Uracil-L-Ascorbic Acid)

تحضير مماثل النيوكليوسيد الجديد (6-يوراسيل- لـ - حامض الاسكوربيك)

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Abstract

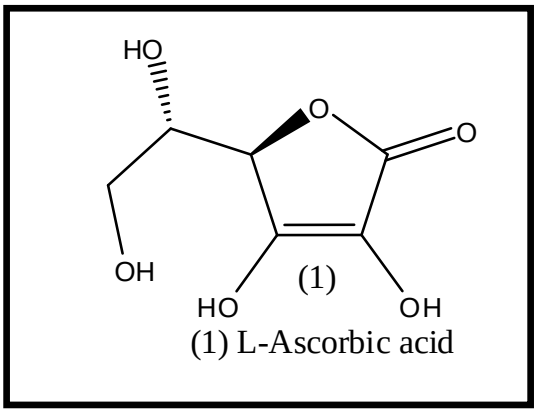
In this research new nucleoside analogues of L-ascorbic acid was synthesized *via* protection of diol group of 5,6 positions of L-ascorbic acid by cyclic acetal formation, then protection of OH groups of 2,3 positions by benzoyl, after that deprptection of diol group to link tosyl group in 6 position of L-ascorbic acid by selective method then formation of nucleoside by the reaction with mercury salt of uracil that was synthesized previously by reaction of uracil with mercuric chloride in presence of ethanol as solvent.

الخلاصة:

في هذا البحث حضر مماثل نيوكليوسيدي جديد لحامض (لـ - حامض الاسكوربيك) وذلك من خلال حماية مجموعة ثنائي الكحول للموقعين 5,6 لحامض الاسكوربيك بواسطة تكوين الاسيتال الحلقي , بعد ذلك حماية مجاميع الهيدروكسيل للموقعين 3,2 بواسطة البنزويل يعقبها إزالة الحماية عن مجموعة ثنائي الكحول لربط مجموعة التوسايل عند الموقع 6 لحامض الاسكوربيك باستخدام طريقة انتقائية ومن ثم تكوين النيوكليوسيد بتفاعله مع ملح الزئبق لليوراسيل المحضر مسبقا من تفاعل اليوراسيل مع كلوريد ألزئبقيك بوجود الايثانول كمذيب.

Introduction

L-Ascorbic acid or (vitamin C) (1) is a white, odorless, crystalline powder. It is freely soluble in water and relatively insoluble in organic solvents. In a dry state, away from light, it is stable for a considerable length of time(7). Structurally, L-AA is one of the simplest vitamins. It is related to the C6 sugars, being the aldono-1, 4-lactone of a hexonic acid (3) It is a sugar acid, biosynthesized in plants, and also found in the livers of most vertebrates, except human beings Therefore, human beings need an external supply of this vitamin, mainly from fresh vegetables and fruits. The name *ascorbic* means antiscurvy and denotes the ability of ascorbic to combat this disease. its deficiency in humans results in the body's inability to synthesize collagen, which is the most abundant protein in vertebrates.(17)In addition to that it serves as antioxidant agent. the important of ascorbic acid in the forming of collagen, a protein that gives structure to bones, cartilages, muscles, and blood vessels. also aids in the absorption of iron, and helps maintain capillaries, bones, and teeth. It is the most common electroactive biological compound and one of the most ubiquitous vitamins ever discovered. Rich sources include blackcurrant, citrus fruit, leafy vegetables, tomatoes, green and red peppers. Ascorbic acid is known for its reductive properties. Hence, it is used on a large scale as antioxidant in food and drinks.(11) .



(1)

(1) L-Ascorbic acid

nucleoside consists of a purine or pyrimidine base linked to a sugar(14) generally it is formed by covalently linking a base to the number 1 carbon of a sugar(4). Nucleosides can be classified in natural nucleosides such as those involved in the genetic storage of information, naturally modified nucleosides, and synthetic nucleosides(15). Structurally modified nucleosides represent an important class of medicinal compounds which have been found to behave as therapeutic agents and are currently used in pharmaceuticals as anti tumor, antiviral, and antibiotic agents(6,8,12,16). As a consequence, nucleoside analogs have been used in the treatment of anti-immunodeficiency syndrome (AIDS), and other viral infections, such as those caused by herpes viruses, and influenza A and B viruses (13)

Aim of research:

Synthesis of new nucleoside analogue of L-ascorbic acid by using new selective method .

Experimental :

*general notes:

-All chemicals and solvents used were supplied from Merck, Fluka and BDH chemicals .

-Melting points were recorded using GallenKamp electro-thermal melting point apparatus and were uncorrected.

-Infrared spectra were recorded as KBr discs using Fourier Transform Infrared Spectrophotometer FTIR-8400s SHIMADZU, Kufa University (Iraq)

^{1}H-NMR spectra were recorded by Brukur ,Ultra Shield 300 MHz, Switzerland with TMS as internal standard in D_2O, Al-albayt University(Jordan) .

1-Synthesis of 5,6-*O*-isopropylidene-L-ascorbic acid:[2] (15)

2-Synthesis of 2,3-*O*-dibenzoyl-5,6-*O*-isopropylidine-L-ascorbic acid:[3] (16)

3-Synthesis of 2,3-*O*-dibenzoyl-L-ascorbic acid:[4] (17)

4- Synthesis of 2,3-*O*-dibenzoyl-5-hydroxy-6-tosyloxy-L-ascorbic acid :[5]

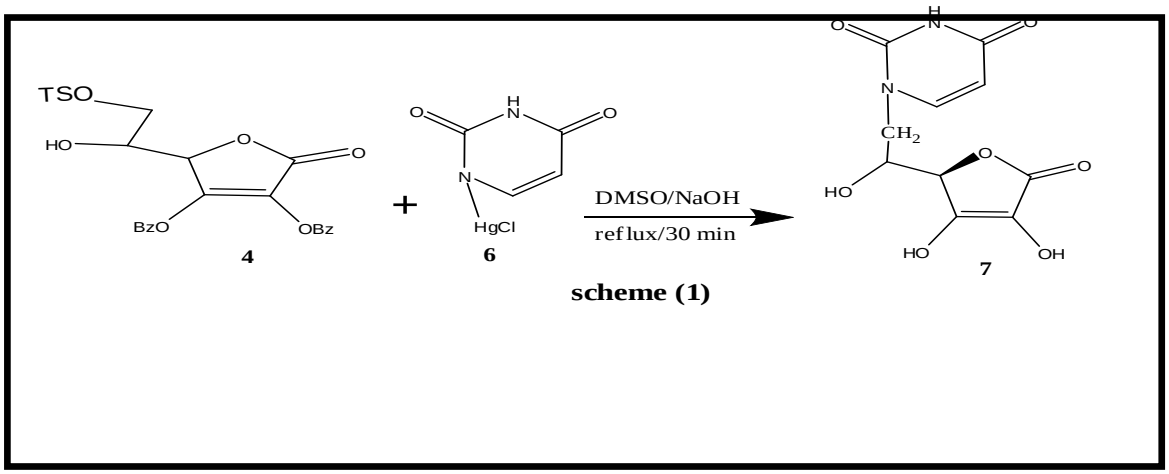
A solution of compound (4)(1mmol)in(15ml) pyridine was cooled to (-20°C).A solution of tosyl chloride (1.2mmol) in pyridine (15ml)was added drop wise to the first solution .The mixture was kept at (-15°C) for (1 h) then allowed to warm to(r.t.),with stirring for(24 hrs).The mixture was poured on(ice distilled water)(100ml)and extracted with Dichloromethane (3x50 ml). The combined organic layer washed with 10% of HCl (3x50 ml) saturated solution $NaHCO_3$ (3x50 ml) and with distilled water (100ml) dried with $MgSO_4$ then evaporated with toluene (3x50ml). TLC show R_f (0.875)

(methanol :benzene) 2:5.

5-Synthesis of mercury salt of uracil :[6] (18)

6-Synthesis of nucleoside (6-uracil-L-ascorbic acid):[7]

This compound was synthesized by adding (1.1mmole) of (6) in DMSO (15ml) to (1.0mmole) of (5) in DMSO (15ml),with reflux for (30 min) at (70 °C). Then extracted with distilled water and evaporated. TLC shows the completion of reaction R_f (0.879) using methanol : benzene 1:5.



scheme (1)

Results &discussion

The compound [5] was synthesized by treatment of compound [4] with tosyl chloride in presence of pyridine as solvent at -20 °C for 1hr with stirring for 24 hrs to yield brown syrup of compound [5]. Completion of the reaction was noted by TLC and show R_f (0.875)
(methanol :benzene) 2:5.

This compound was identified by using FTIR technique and shows the following data:

S=O of tosyl chloride at (1176-1200)cm-1,(1300-1371) cm-1 that of C-H aromatic of tosyl chloride at (3090)cm-1 that obtain from the original chart of tosyl chloride. Hydroxyl group of C5 at (3378)cm-1 (9).

The compound [7] (1-(2-((R)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl)pyrimidine-2,4(1H,3H)-dione) was synthesized from the reaction between the compound [5] with the compound 6 in the presence of DMSO as solvent and trace of NaOH from synthesis of compound 6.TLC show Rf (0.897) by using methanol : benzene5:1 ,the compound [7] is a glass crystalline has no m.p but sublimed at 298° C.

The compound [7] was identified by FTIR &^{1}HNMR.FTIR spectrum shows the following peaks.

Three peaks of hydroxy groups of (2,3,5)positions at (3508,3450,3350) cm^{-1} respectively ,one peak of N-H group of an amide (uracil) at (3620) cm^{-1} that obtained from the original chart of uracil,(10)(5). reduce of carbonyl group of L-AA to 1660 cm^{-1} and carbonyl group of an amide at 1615 cm^{-1} that's values comes identical to those in the reference .(5) ,.broad zone in the range of C-N bond (1100 -1225) cm^{-1} compared with the chart of compound (5),and remained of distinguishing peak of C-O of ascorbic acid in (5),(6) at (1014,1012) cm^{-1} respectively ,in reference at 1015 cm^{-1}(5)(10), and distinguishing peak of uracil ring stretching at (995.27) cm^{-1} in reference 996 cm^{-1}(5) , return to the chart of compound (5) , disappearance of following peaks was noted .

Methyl group at (2870-2929) cm^{-1} of Tosyl chloride , C-H aromatic of benzoyl ring and tosyl chloride at 3070 cm^{-1}(9)(20) that improved two reactions was occurs ,the first that of nucleoside formation and the second was de protection of 2,3 positions of L-AA by the residue of NaOH from 6 synthesis.

^{1}HNMR spectrum gives results that approved the previous explanation and shows the following signals:

multi signal of C-H of C5 of L-AA at (3.639,-,3.699) ppm,(11) multi signal of C=C-H of uracil at (5.599,5.618) ppm(20) ,multi signal of N-C=C-H of uracil at (10.875,10.900) ppm ,singlet signal of O-H group of C5 at (10.952)ppm , two singlet signals of O-H groups of C2,3 at (11.028,11.062) ppm respectively.(10). at last singlet signal of N-H group of uracil O=C-NH-C=O at (11.103) ppm that results from two carbonyl groups.(10)

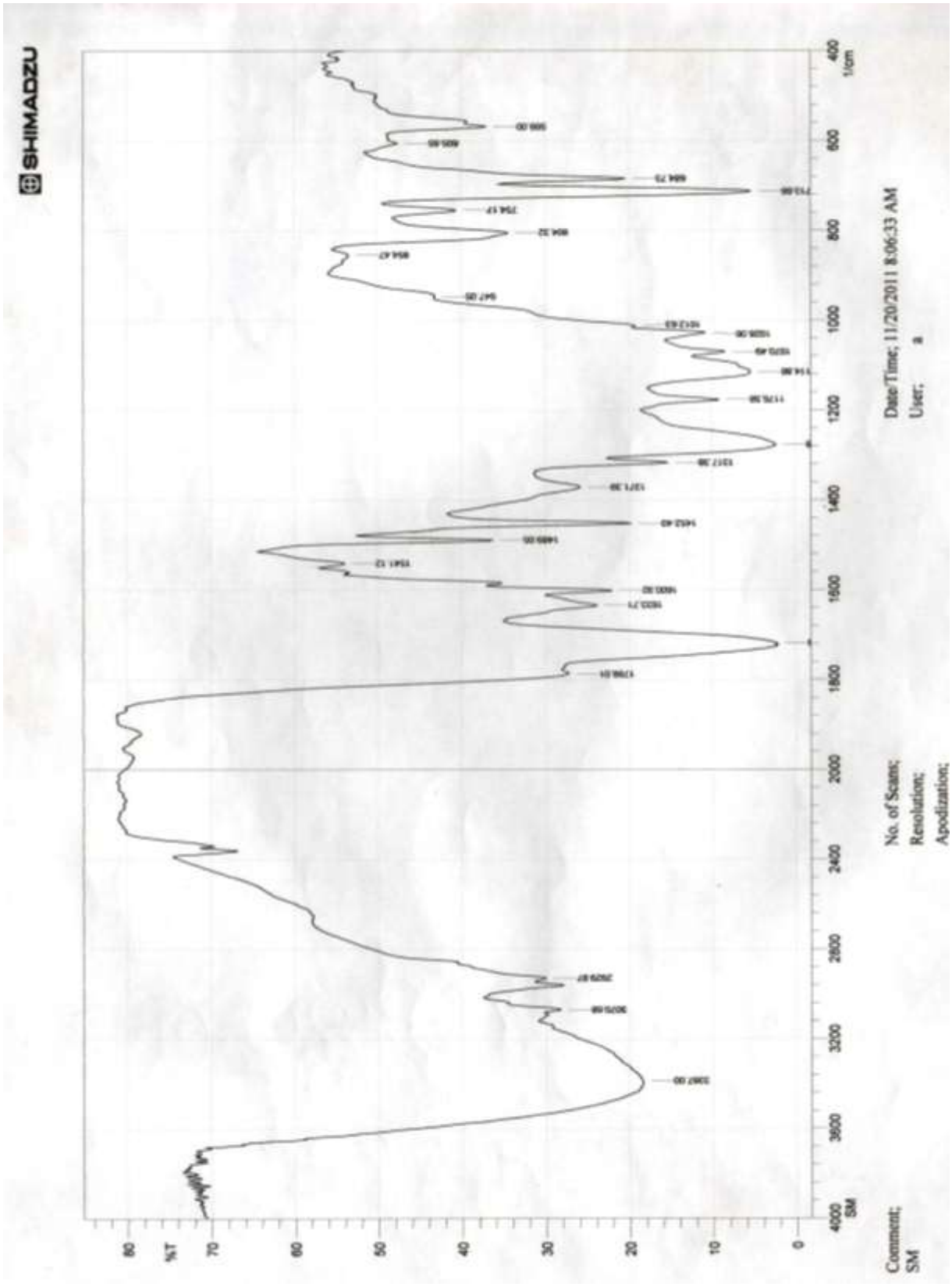


Figure 1: FTIR spectrum of (4)

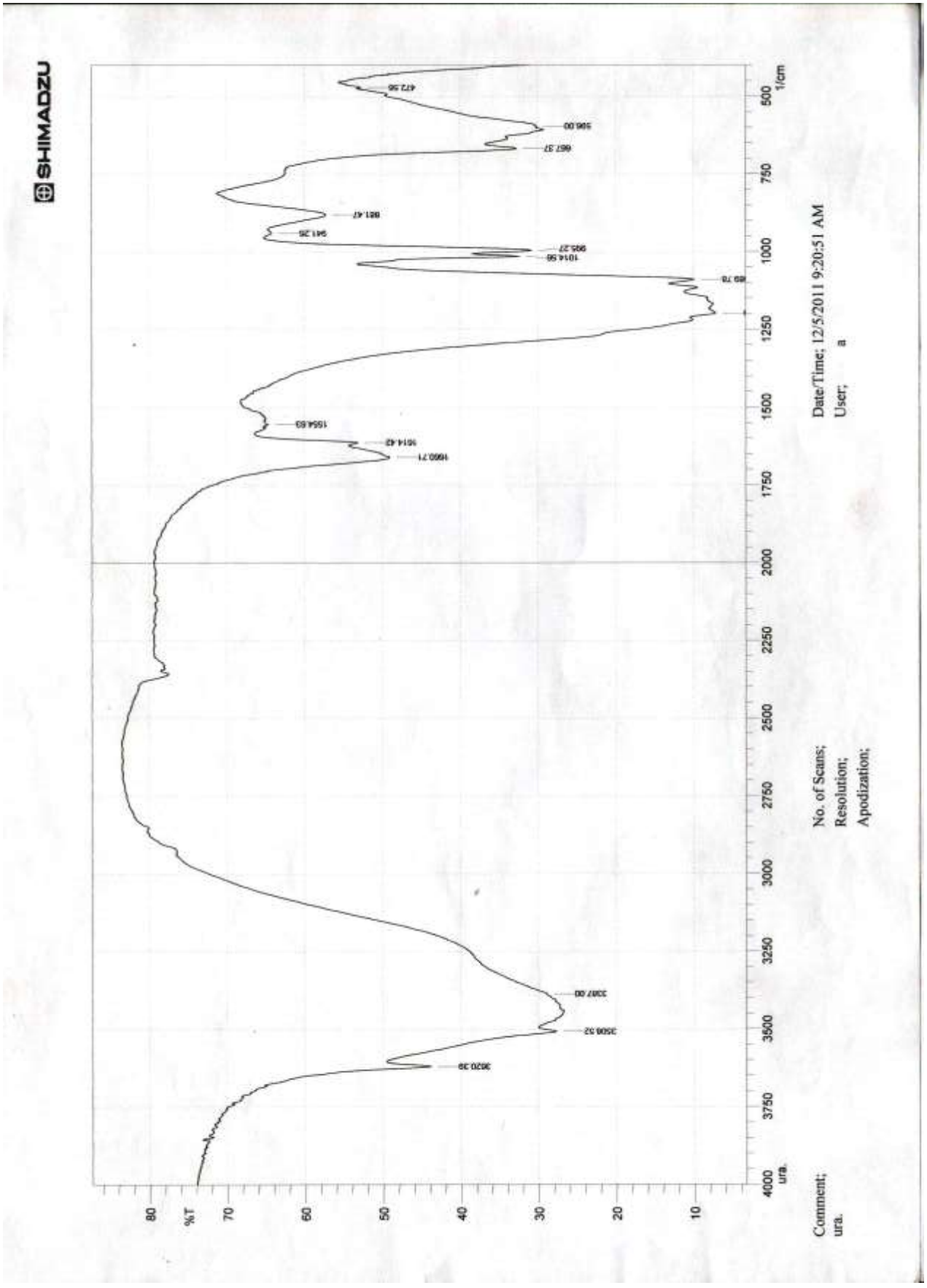


Figure 2:FTIR spectrum of (6)

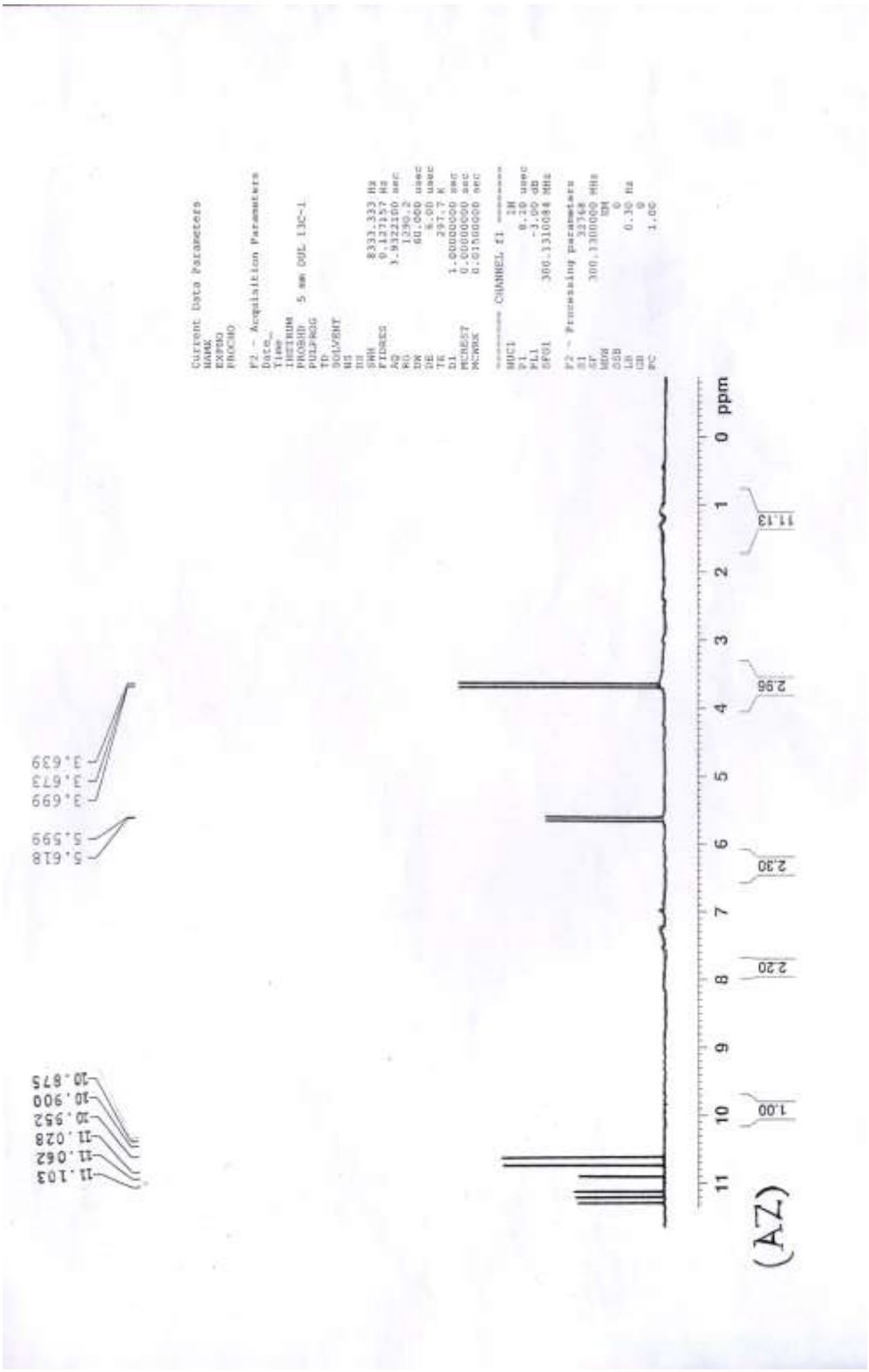


figure 3: ^{1}H-NMR spectrum of (6)

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