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A Novel Dihydropyridines C-Glycosylated Compound by Hantzsch Cyclo-Condensation

Soheila Sedaghat, Shabnam Madjdpour

Chemistry Department, Islamic Azad University, Tehran North Branch, Tehran, Iran
Email: s_sedaghat@iau-tnb.ac.ir

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Abstract

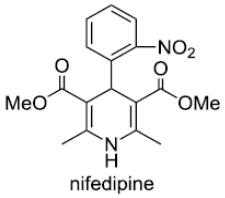
The Hantzsch synthesis has been used for the preparation of the 1,4-Dihydropyridines compounds with different pharmacophore groups. The use of a designed glycosylated compound in Hantzsch synthesis would lead to a novel Dihydropyridines C-Glycosylated compound. We used the 6-methoxy-2, 2-dimethyltetrahydrofuro [3, 4-d] [1, 3] dioxole-4-carbaldehyde as a glycosylated-based aldehydes. The 4-(3,4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester was synthesized. The structure of compounds was determined by NMR spectroscopy, FTIR and mass spectroscopy methods. We synthesized this 1,4-Dihydropyridines compound by ionic liquid under ultrasound irradiation as a green chemistry synthesis.

Keywords

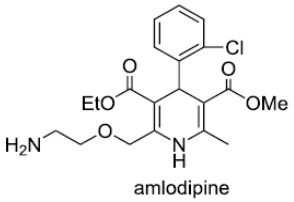
1,4-Dihydropyridines, c-Glycosylated, Multi Component Reaction, Hantzsch Reaction

1. Introduction

1,4-Dihydropyridines (1,4-DHPs) have attracted interest significantly because of their versatile pharmaceutical properties such as antibacterial and antitumor effects. The 1,4-DHPs have applied as a calcium channel blocker in cardiovascular disease. Some methods for the synthesis of 1,4-DHPs have been reported [1] [2] [3] [4] [5].



nifedipine



amlodipine

1,4-DHPs are synthesized by Hantzsch method which involves cyclo condensation of an aldehyde, β-diketone and ammonia in acetic acid which leads to derivatives of dihydropyridines. The synthesis of Dihydropyridines C-Glycosylated has importance because of their good pharmacokinetic and the role of compound in molecular recognition [6]. Dondoni has reported the synthesis and use of a designed glycosylated compound in some of the possible combinations in Hantzsch synthesis. He prepared them as a collection of C-nucleosides dihydropyridines compounds and some exhibiting significant biological activities have been reported [7] [8] [9] [10].

Ultrasound method improved some chemical reaction by a physical phenomenon named cavitation. Cavitation can contribute to the development of chemical reactions in the solution through a radical mechanism. There are the formation, growth, and collapse of bubbles in a medium. Compared to the traditional synthesis, this technique is more convenient by green chemistry concept [11] [12] [13] [14].

We synthesized substituted Dihydropyridines C-Glycosylated under mild condition. We prepared it by ultrasound irradiation method in an ionic liquid which leads to an efficient and eco-friendly method.

2. Experimental

2.1. Materials

All the reagents were purchased from Merck Chemical Company. IR spectra were recorded on a Perkin-Elmer 297 FT-IR spectroscopy. H-NMR, C-NMR and DEPT were recorded on Broker 300 and 500 MHz spectroscopy. The MS spectra were obtained on a JEOL JMS HX-110 mass spectroscopy. Column chromatography was conducted with silica gel 230 - 400 mesh (Merck). Reactions were monitored by thin layer chromatography (TLC).

2.2. Synthesis of Glycosylated Aldehyde

1-(6-Methoxy-2,2-dimethyl-tetrahydro-furo [3, 4-d] [1, 3] dioxol-4-yl)-ethane-1,2-diol

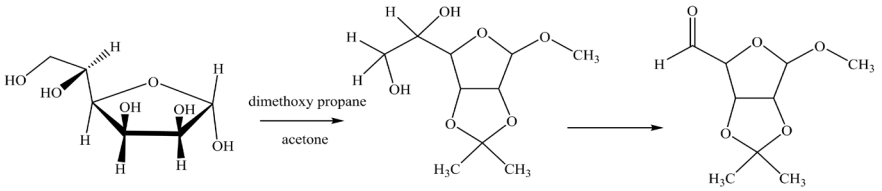
A mixture of D-mannose (5 g, 27.77 mmol), 2,2-dimethylpropane (17 ml), acetone (16.5 ml), methanol (16.5 ml) and concentrated HCl (0.5 ml) was refluxed for 2 h. The water was added and the solution concentrated under reduced pressure. Methanol (50 ml) and concentrated HCl (1.25 ml) was then added. The mixture was stirred at room temperature for 3 h, neutralized with a saturated sodium hydrogen carbonate solution. The residue was taken in hot chloroform and the solution was filtered. The product was methyl-2,3-O-isopropylidene-mannofuranoside as a oil colorless (5.43 g, 83%).

H-NMR (300 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.72 (d, 1H), 4.49 (d, 1H), 3.12 (brs, 1H), 4,30 (dd, 1H), 3,57 (dd, 1H), 3.61 (dd, 1H), 3.32 (s, OCH_3, 3H), 1.37 (s, CH_3, 3H), 1.22 (s, CH_3, 3H)as shown in **Figure A1**. **C-NMR** (500 MHz, $CDCl_3$): 113, 107 64.8, 80.4, 79.5, 70.7, 85.1, 54.9, 26.3, 25.1 as shown in **Figure A2**. **FTIR**: 3448, 1638, 1084 cm^{-1} as shown in **Figure A3**.

6-Methoxy-2,2-dimethyl-tetrahydro furo [3, 4-d] [1, 3] dioxole-4-carbaldehyde

A solution of sodium periodate (5.46 g 25.52 mmol) in water was added to methyl-2,3-O-isopropylidene-mannofuranoside (5.43 g) in methanol (150 ml). In room temperature the mixture was stirred and dried under reduced pressure. The residue was filtered and evaporated to give the aldehyde (4.1 g 75%).

H-NMR (300 MHz, $CDCl_3$): δ = 9.5 (s, 1H), 5.1 (s, 1H), 5.08(d, 1H), 4.63(d, 1H), 4.38 (d, 1H), 3.36(s, OCH_3, 3H), 1.44(s, CH_3, 3H), 1.30 (s, CH_3, 3H) as shown in Figure A4; **C-NMR** (500 MHz, $CDCl_3$): 200.7, 109.1, 89.4, 84.4, 80.7, 55.6, 25.8, 24.8 as shown in Figure A5; **FTIR**: 3448, 1638, 1088 cm^{-1}.



2.3. Synthesis of 1,4-Dihydropyridines Derivative

Hantzsch reaction:

A solution of glycosylated aldehyde compound (1.08 g, 2.5 mmol) and ethyl aceto acetate (0.65 g, 2.5 mmol) in the presence of 0.1 ml piperidine and 0.25 ml glacial acetic acid in 50 ml methanol was refluxed for 72 h. after removing the solvent, the reaction mixture was refluxed with ethyl acetoacetate (0.65 g, 2.5 mmol) ammonium acetate (1.2 g) for 12 h. The residue was purified and the product was crystallized to give 426 mg (40%) of 4-(3, 4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester.

H-NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, H), 4.53 (s, 1H), 4.19 (d, CH2), 4.13(d, 1H), 3.24 (d, CH_3), 1.71 (s, CH_3, 3H), 1.41 (s, CH_3, 3H), 1.30 (s, CH_3, 3H) as shown in Figure A6; **C-NMR** (500 MHz, $CDCl_3$): 165, 141.2, 108.5, 102.4, 101.9, 79.9, 73.3, 66.4, 59.9, 48.3, 28.6, 24.0 as shown in Figure A7, MW=425, $C_{21}H_{31}NO_8$ as shown in Figure A9.

2.4. Ultrasound Accelerated Synthesis

A mixture of ethyl acetoacetate (0.259 g, 2 mmol), glycosylated aldehyde (0.5 g 1.25 mmol), ammonium acetate (0.154 g, 2 mmol) and ionic liquid [bmim] BF_4 (0.120 g 0.5 mmol) was successively charged into a screw-capped vial. The mixture was irradiated in a water bath for two hours. The reaction mixture was washed with water. The crude product purified by silica gel column chromatography using dichloromethane: ethyl acetate (98:2). The crystallized product yield was 50%.

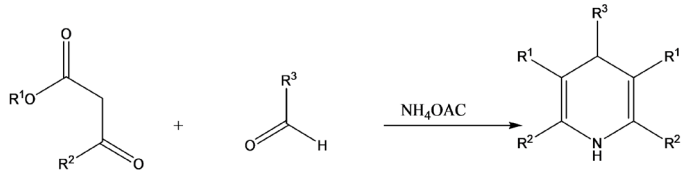
3. Results and Discussion

The original Hantzsch synthesis is usually completed via one-pot thermal cyclo-

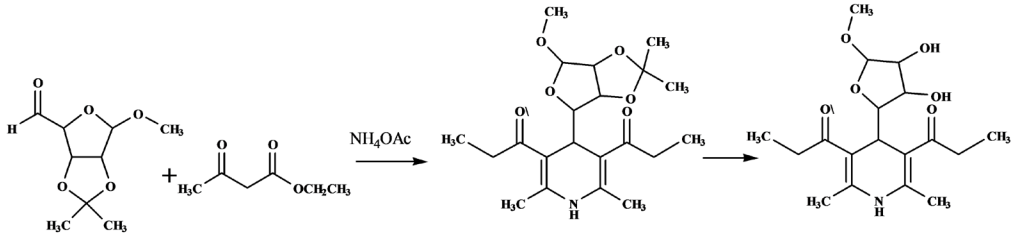
condensation of the reaction of a β-diketone with an aldehyde and ammonia in acetic acid which leads to dihyropyridine derivatives (Scheme 1). Compounds have different pharmacophores groups to prepare by Hantzsch cyclocondensation.

A Dihydropyridines C-Glycosylated has been prepared by a three-component reaction of β-keto ester, examines and glycosylated aldehyde (Scheme 2). Glycosylated aldehyde could undergo the Hantzsch cyclo condensation reaction effectively to afford the corresponding products in good yields.

The compounds were obtained as a solid, and its molecular formula, $C_{21}H_{31}NO_8$, was established by MS (*m/z* 252,196). The proposed mechanism of Dihydropyridines C-Glycosylated synthesis showed in Scheme 3. The structure of compound was assigned by NMR spectroscopy (Table 1).



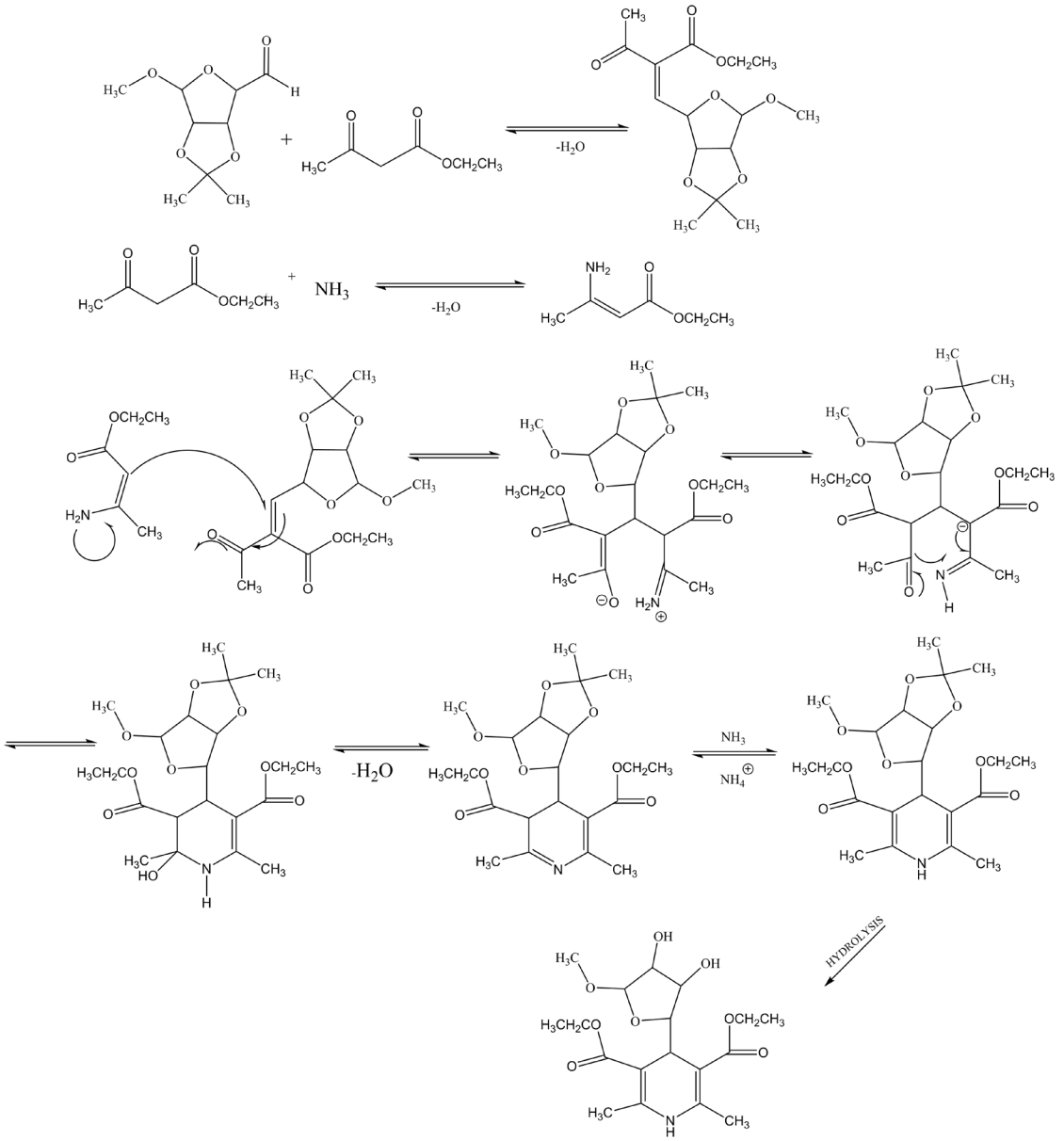
Scheme 1. Hantzsch cyclocondensation reaction.



Scheme 2. Synthesis of C-Glycosylated 1, 4-Dihydropyridine.

Table 1. 1H NMR and 13C NMR Data for compound (CDCl3, 500 MHz , ppm, J/Hz).

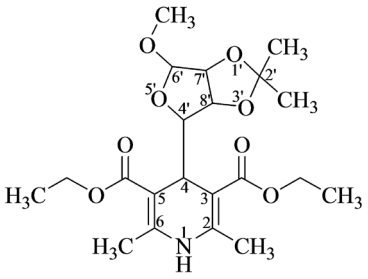
C atom	□δ_H	δ_C	C atom	δ_H	δ_C
C2-CH3	2.25 s (3H)	19.1	C2	-	144.1
C6-CH3	2.32 s (3H)	18.5	C6	-	144.3
H-4'	3.60 dd (1H) (J = 8.15 - 2.45)	79.7	C2	-	112.4
H-6'	4.7 s (1H)	106.6	C3	-	100.9
H-7'	4.41 d (1H) (J = 5.8)	85.3	C5	-	99.98
H-8'	4.49 dd (1H) (J = 5.8, 2.7)	81.8	CO	-	168.1
C2'-CH3	1.259 s (3H)	26.3	CO	-	168.4
C2'-CH3	1.440 s (3H)	25.8	CH3(side group)	1.309 t(3H)	14.29
C6'-OCH3	3.17 s (3H)	53.9	CH3 (side group)	1.284 t(3H)	14.22
H-4	4.64 d (1H) (J = 8.15)	33.6	CH2(side group)	4.1 m (2H)	59.7
			CH2 (side group)	4.1 m (2H)	59.4



Scheme 3. Proposed mechanism of Dihydropyridines C-Glycosylated.

The H-NMR spectrum showed characteristic resonances for two methyl groups as singlets at 2.25 and 2.32, one allylic resonance at 4.64 (1H, q, J = 7.2 Hz), and four CH resonances at 3.60 (1H, dd, J = 8.15, 2.45 Hz), 4.7 (1H, s), 4.41 (1H, d, J = 5.8 Hz) and 4.49 (1H, dd, J = 5.8, 2.7 Hz).

The C-NMR resonances showed 21 carbon signals, which could be resolved by DEPT experiments into seven CH3 groups at 19.1 (C-2), 18.5 (C-6), 26.3 (C-2'), 25.8 (C-2'), 53.9 (C-OCH_3) 14.29 and 14.22 (CH_3 side group), two CH_2 groups at 59.7 and 59.4 (CH_2 side group), five CH groups at 33.6 (C-4), 79.9 (C-4'), 81.8 (C-8'), 85.3 (C-7') 106.6 (C-6'), and seven quaternary carbons at 99.8 (C-5), 100.9 (C-3), 112.4 (C-2), 144.1 (C-2), 144.3 (C-6),168.1 (CO),168.4 (CO) as two carbonyl functional groups as shown in Figure A8.



Using ultrasound method with an ionic liquid [brim]BF_4 or 1-butyl-3-methyl imidazolium tetrafluoroborate as promoter for the synthesis of Hantzsch 1,4-dihydropyridines does not present improvement at room temperature, but the reaction times are considerably shorter (2.30 h) compared to classical synthesis. After the reaction was complete, the reaction mixture is simply washed with water and the ionic liquid is isolated from the product. The ionic liquid is recyclable as reaction medium.

4. Conclusion

We present a novel Dihydropyridines C-Glycosylated by Hantzsch cyclocondensation in which the glycosylated aldehyde was designed. We carried out an ultrasound-accelerated synthesis of compound in an ionic liquid. The significant improvements offered by this procedure are: fast reaction, simple operation and mild reaction conditions (room temperature) and green aspects avoiding organic solvents and toxic catalyst.

Acknowledgements

This research was supported by research department of Islamic Azad University—north Tehran branch.

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Supporting Information

Spectral and analytical data of compounds:

1-(6-*Methoxy*-2,2-*dimethyl-tetrahydro-furo* [3,4-*d*] [1,3] *dioxol*-4-*yl*)-*ethane*-1, 2-*diol* (1)

Yield: 5.60 g (85%). IR: 3448, 1638, 1084 cm^{-1}. ^{1}H-NMR(300 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.72 (d, 1H), 4.49 (d, 1H), 3.12 (brs, 1H), 4,30 (dd, 1H), 3,57 (dd, 1H), 3.61 (dd, 1H), 3.32 (s, OCH_3, 3H), 1.37 (s, CH_3, 3H), 1.22 (s, CH_3, 3H). ^{13}C-NMR (500 MHz, $CDCl_3$): 113, 107 64.8, 80.4, 79.5, 70.7, 85.1, 54.9, 26.3, 25.1.

6-*Methoxy*-2,2-*dimethyl-tetrahydro-furo* [3,4-*d*] [1,3] *dioxole-4-carbaldehyde* **(2)**

Yield: 4.0 g (75%).IR: 3448, 1638, 1088 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.5 (s, 1H), 5.1 (s, 1H), 5.08(d, 1H), 4.63(d, 1H), 4.38 (d, 1H), 3.36(s, OCH_3, 3H), 1.44(s, CH_3, 3H), 1.30 (s, CH_3, 3H) ^{13}C-NMR (500 MHz, $CDCl_3$): 200.7, 109.1, 89.4, 84.4, 80.7, 55.6, 25.8, 24.8

4-(3,4-*Dihydroxy*-5-*methoxy-tetrahydro-furan*-2-*yl*)-2,6-*dimethyl*-1,4-*dihydr o-pyridine*-3,5-*dicarboxylic acid* 3-*ethyl ester* 5-*methyl ester.* **(3)**

Yield: (40%),mp.185-190 C ^{1}H-NMR (300 MHz, CDCl3): δ = 5.42 (s, H), 4.53 (s, 1H), 4.19 (d, CH_2), 4.13(d, 1H), 3.24 (d, CH_3), 1.71 (s, CH_3, 3H), 1.41 (s, CH_3, 3H), 1.30 (s, CH_3, 3H) ^{13}C-NMR (500 MHz, CDCl3): 165, 141.2, 108.5, 102.4, 101.9, 79.9, 73.3, 66.4, 59.9, 48.3, 28.6, 24.0., MW = 425, $C_{21}H_{31}NO_8$.

Appendix

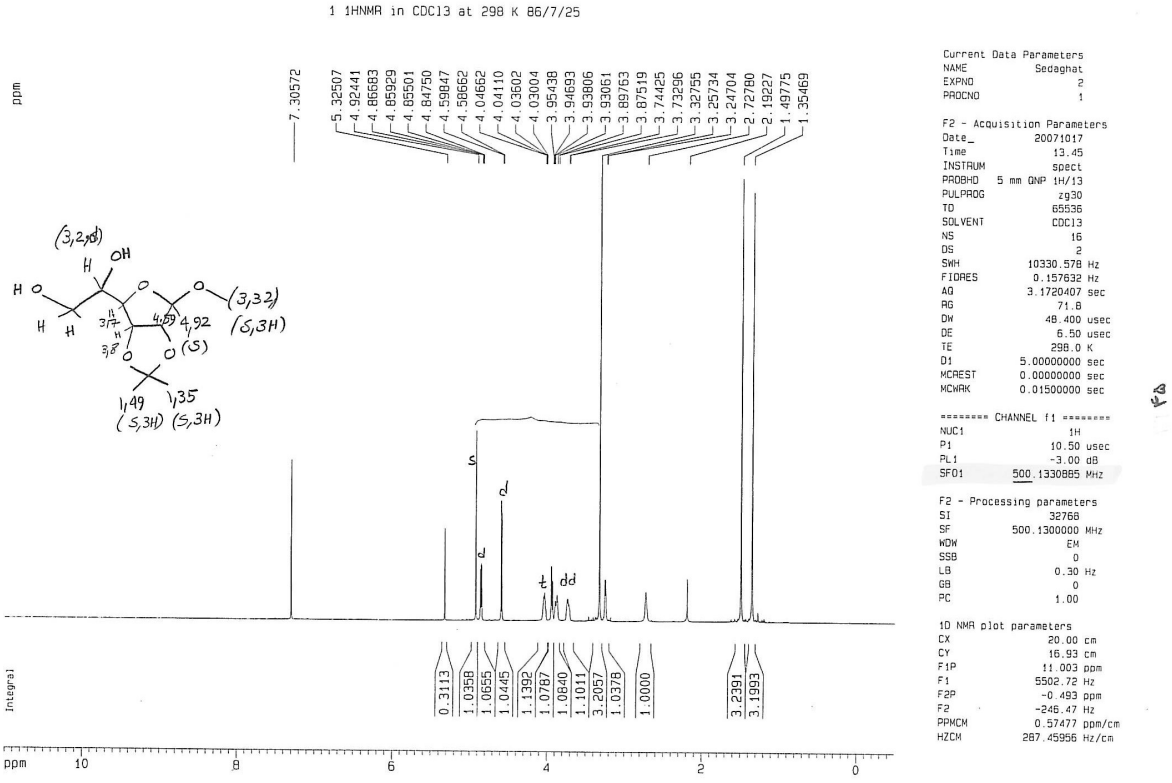

Figure A1. HNMR "methyl-2,3-O-isopropylidene-mannofuranoside".

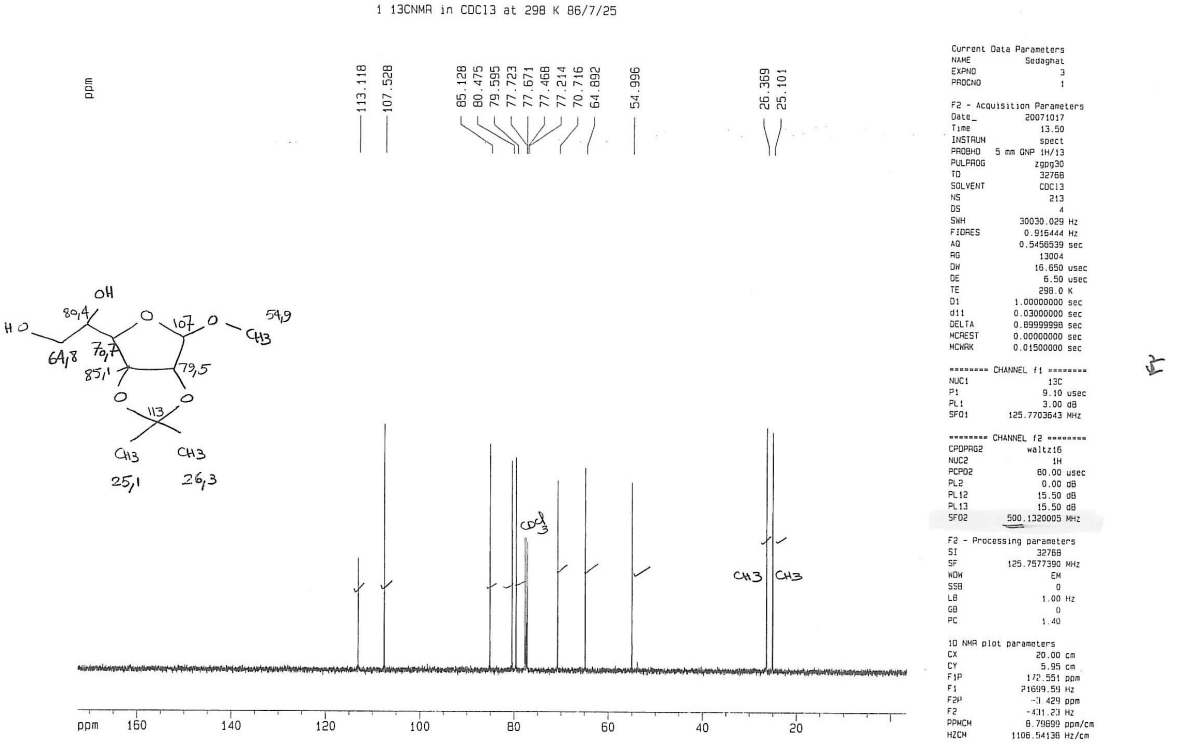

Figure A2. CNMR "methyl-2,3-O-isopropylidene-mannofuranoside".

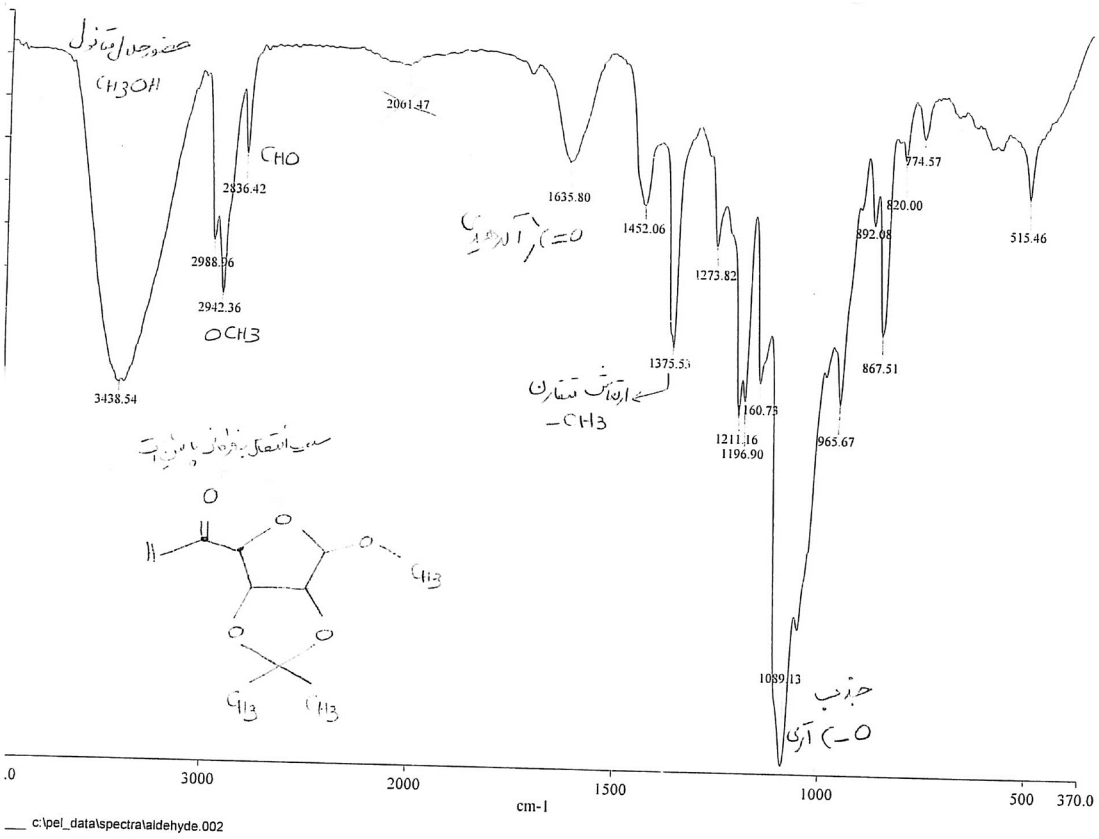

Figure A3. FTIR "6-Methoxy-2, 2-dimethyl-tetrahydro-furo [3, 4-d] [1, 3] dioxole-4-carbaldehyde".

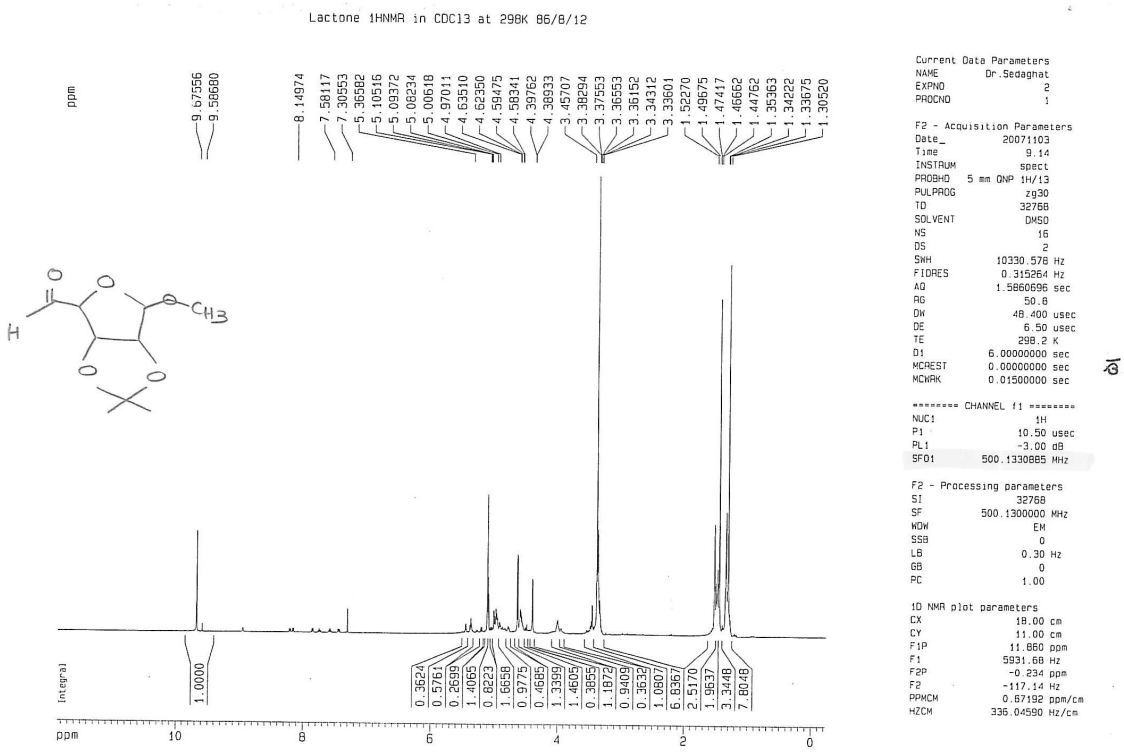

Figure A4. HNMR "6-Methoxy-2, 2-dimethyl-tetrahydro-furo [3, 4-d] [1, 3] dioxole-4-carbaldehyde".

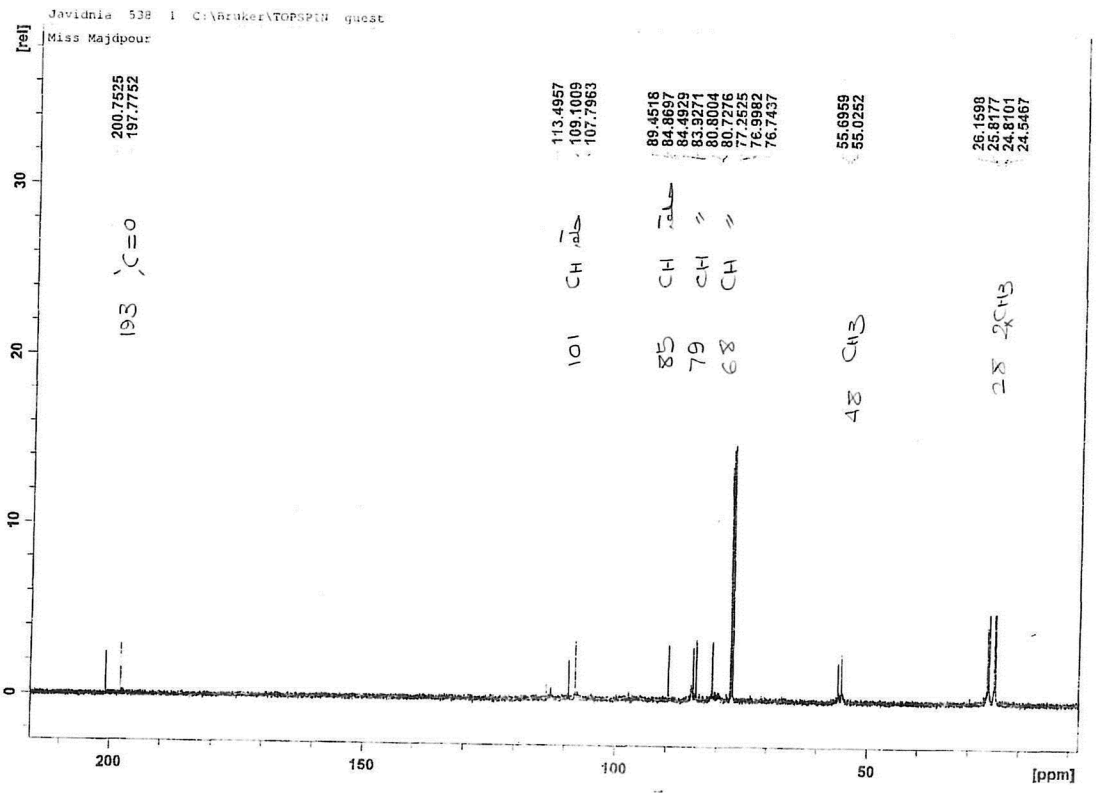

Figure A5. CNMR" 6-Methoxy-2, 2-dimethyl-tetrahydro-furo [3, 4-d] [1, 3] dioxole-4-carbaldehyde".

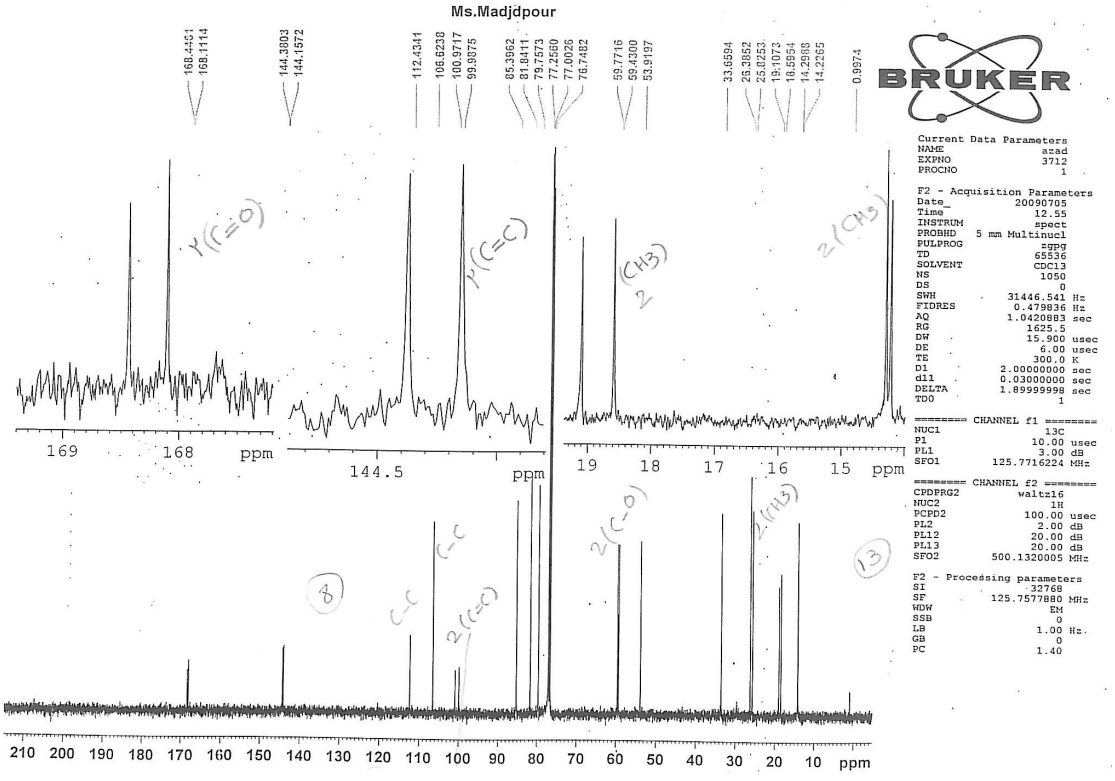

Figure A6. HNMR "4-(3,4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester".

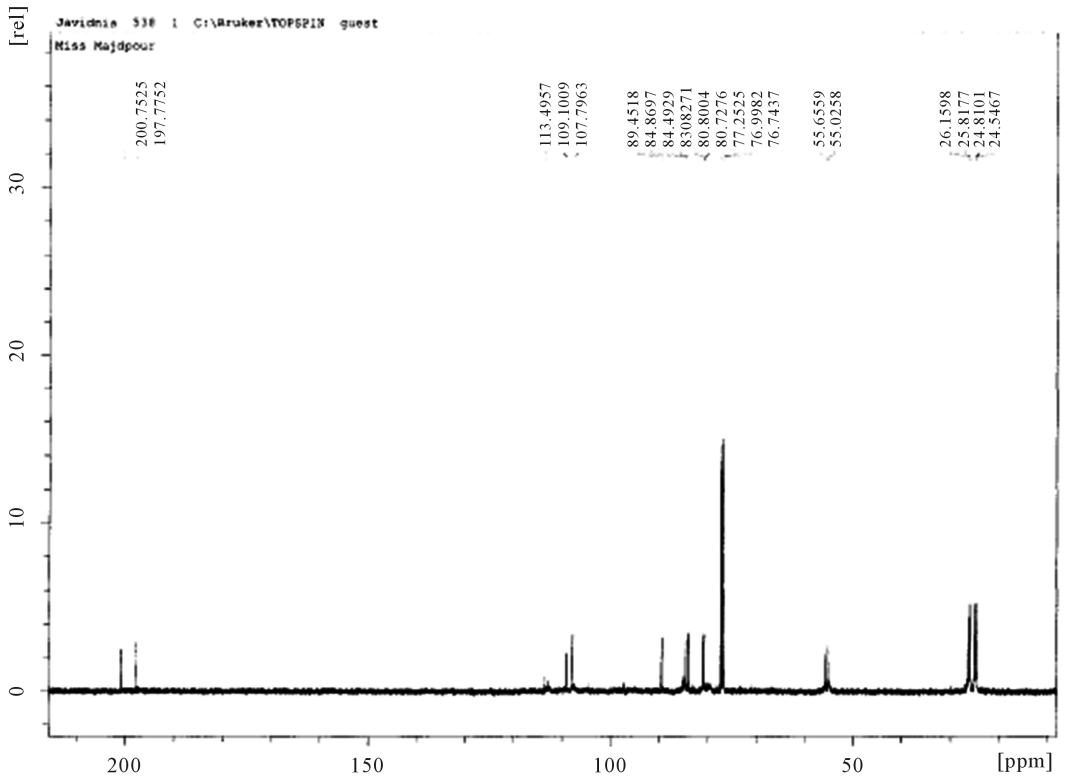

Figure A7. CNMR "4-(3, 4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester".

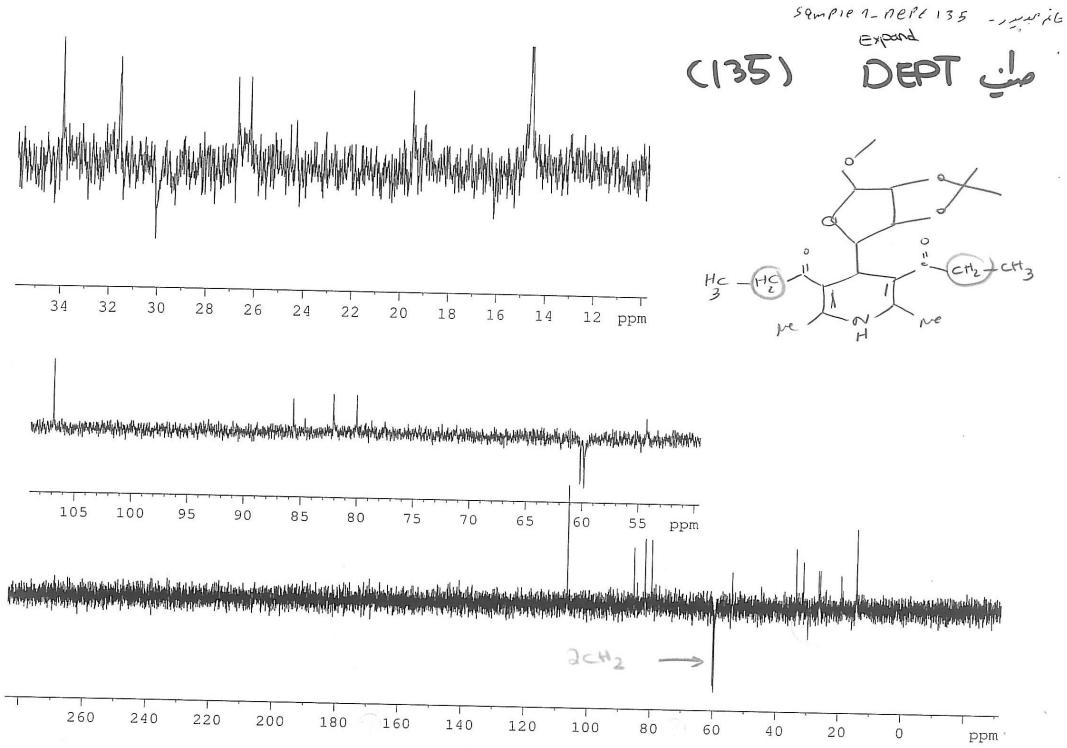

Figure A8. NMR-DEPT "4-(3,4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester".

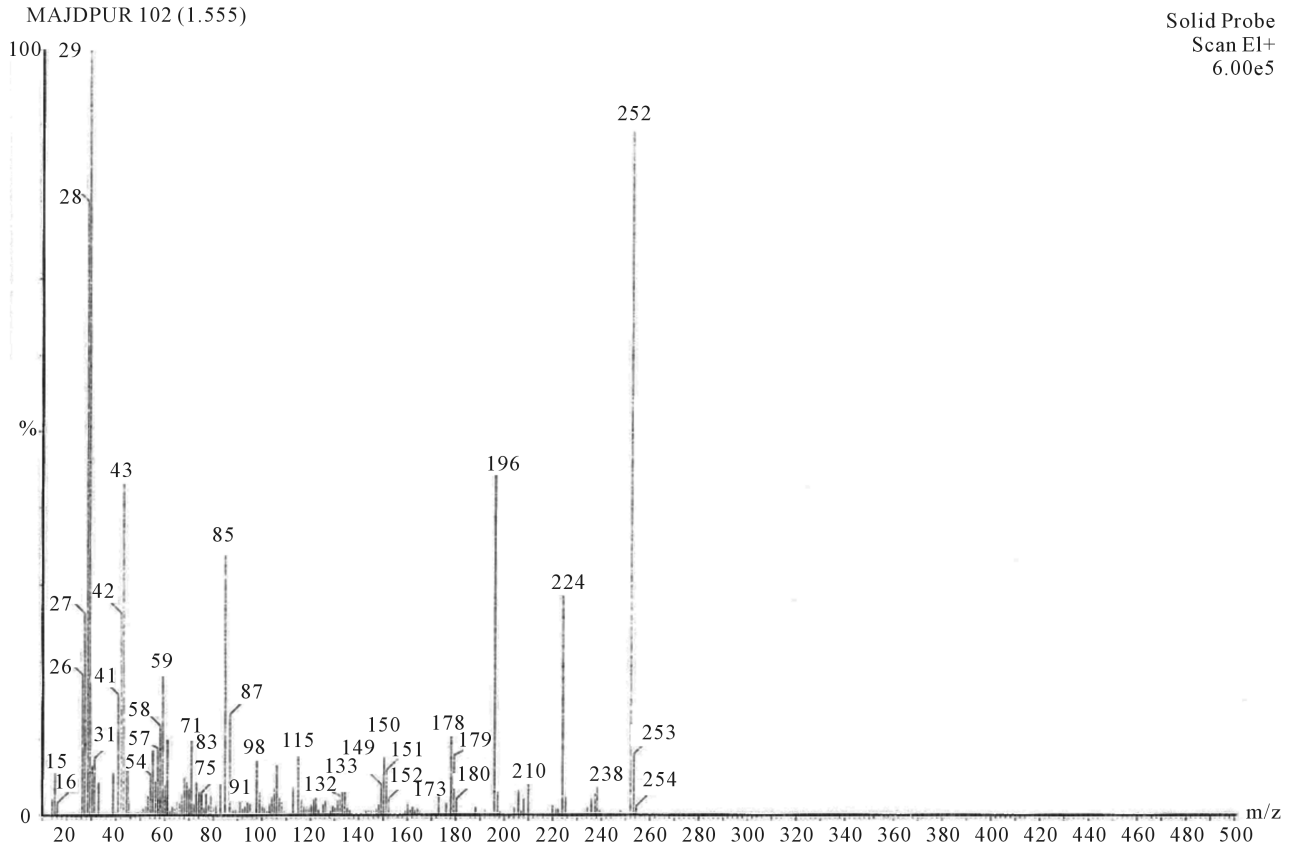

Figure A9. MS "4-(3,4-Dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester".