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Synthesis of Some 1, 6- and 6-Derivatives of Methyl D-Fructofuranosides

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Abstract – Derivatives of methyl β-D-fructofursnsides modified at C_{-1} and C_{-6} have been prepared in which the hydroxyl group has been replaced by heterocyclic aromatic or non-aromatic ring linked by thio-bridge to the sugar. These derivatives were made by displacements on methyl 1, 6-di-*O*-*P*-toluenesulfonyl-β-D-fructofuranose with mercptans .

Introduction

D-Fructose - D-arabino-hex-2 ulose- is also known as levulose (or "laevulose"- an older common name) due to its levorotatory property . It is the most important and the most exploited of all ketoses. [1] In nature it can exist mainly in two forms, either as a free monosaccharide or bound to D-glucose as in sucrose (disaccharide). During the past thirty years , D-fructose (especially its β-D-fruranose form) has received increasing recognition for its role in biochemistry , and the use of new chemical and physical methods has permitted the study of certain characteristic properties of the 2-keto grouping[2] .The furanose form is found to occur in most oligo- and poly-saccharides in the furanoid form probably because of the greater stability of this form of sugar as compared with its pyranoid form[3] .The substantial amounts of this ketohexose are mainly prepared by base -catalyzed isomerization of starch-derived glucose,[4]yet may also be generated by hydrolysis of inulin, a fructooligosaccharide.[5] In oligosaccharide syntheses, today thioglycosides are the most frequently used type of compounds[6].They are mostly crystalline and have long shelf lives[7], and stable under most protecting group transformations, highly functionalized derivatives are made relatively easily.[8]Also they have been shown to be attractive building blocks for the construction of oligosaccharides.[9] Importantly, as a result of the stability of the thioglycoside function, this class of compounds can serve not only as glycosyl donors but also as glycosyl acceptors.[10]

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In the formation of interglycosidic linkages, the anomeric thiogroup may not only function as a protecting group but also as a leaving group in the formation[11] .The anomeric sulphur atom has varying nucleophilicity and can turn the glycosylation properties of thioglycosides[12].Thioglycoside can be stored for a long time without possible degradation[13], and also because their synthesis is shorter than that of trichloroacetimidates.[14] Synthesis of thioglycoside is highly dependent on the carbohydrate structure and on the reactivity of the different hydroxyl groups[15]. The formation of S-glycosidically linked oligosaccharides by coupling of acceptors bearing a suitably positioned nucleophilic thiol group with donors having a good leaving group.[16,17]

2-Experimental Part

Instrumentation and materials

H^1 NMR spectra were recorded in DMSO-d_6 on a Varian Mercury Plus spectrometer operating at 500MHz. Infrared spectra (IR) were recorded using a SHIMADZU 8400S FT-IR (film), in the laboratories of Kufa University, college of pharmacy. Analytical TLC was conducted on Silica Gel F254 (Merck), and the detecting was through coloring with iodine vapor. All the materials were pure and supplier by BDH company and Merck company.

Preparation of Methyl D-fructofuranosides from D-fructose [1][18]

A solution of (0.5%) hydrochloric acid was prepared by dissolving acetyl chloride (1ml) in dry methanol (106 ml) and dried D-fructose (5.7g) was added. The reaction mixture was left for three hours at room temperature. The solution then neutralized by drop wise addition of sodium hydroxide in methanol . The solvent was then removed under vacuum at 30C° and a syrup product (4.5g) was obtained by treatment with ethyl acetate/pet-ether yield (79%). *Rf* : 0.39, TLC. (CH_2Cl_2: MeOH) (8:2/V: V) IR (film) 3500 cm^{-1} (OH), 1000-1100 cm^{-1} (C-O-C) Fig. (1)

Preparation of Methyl 1, 6-Di-*O*- Toluenesulphonyl-D-fructofuranoside [2][19]

In a conical flask with a stopper methyl D-fructofuranoside (3g, 15.4mmol) was dissolved in pyridine (20 ml) and cooled to 0C°. P-Toluene sulfonyl chloride (2.948g, 15.46 mmol) was dissolved in 10 ml cold pyridine added at room temperature to above solution drop by drop and left for 24h. , with stirring . TLC (benzene : methanol) (8:2) (v:v) showed the completion of the reaction .The mixture was poured on crushed ice , then extracted by chloroform (5x15 ml),the chloroform layer was dried byMgSO4 ,filtered and evaporated under vacuum to give a syrup (2.18g) in 72% yield. *Rf*: 0.59 ,TLC. (CH2CL2: MeOH) (8:2 /V: V) IR (film) 3200 cm^{-1} (OH), 1150 and1370 cm^{-1} (SO_2) , 1030 cm^{-1} (C-O-C) Fig. (2)

Synthesis of Methyl 1,6-di-thio-2-benzothiazolyl-1,6-di-deoxy-β-D-fructofuranoside [3]

A solution of methyl 1, 6-di-*O*-P-toluensulfonyl-β-D-fructofuranoside (0.5g, 1 mmol) and 2-mercaptobenzothiazol (0.835g,5mmol) in dimethylformamide DMF (5 ml) was stirred for 38 h at 140C° .The mixture was evaporated to a syrup which was purified by column chromatography (ethyl acetate / hexane, 1:2) to give (1.53g) as a syrup (81 %) . *Rf:* (0.65) (ethyl acetate:hexan)(1:2/V:V)
IR (film),1310cm^{-1}(C-N),760cm^{-1}(C-S),1629cm^{-1}(C=N), Fig.(4).

Synthesis of Methyl-1,6-di-thio-2-benzimidazolyl-1,6-di-deoxy-β-D- fructofuranoside [4]

A solution of methyl1,6-di-*O-P*-toluenesulfonyl-β-D–fructofuranoside (0.5g, 1mmol) and 2-mercaptobemzimidazol (0.75g,5mmol) in dimethylformamide DMF (5ml) was stirred for 38 h at 140C°.The mixture was evaporated to a syrup which was purified by column chromatography (ethyl acetate / hexane)(1:2) to give (1.62) as a syrup (77 %). *Rf* (0.47)
IR(film),1625cm^{-1}(C=N),1270cm^{-1}(C-N), 750cm^{-1} (C-S), Fig.(5).

Synthesis of Methyl-1, 6-di-thio-benzoxazolyl-1, 6-di-deoxy-β-D-fructofuranoside [5]

A solution of methyl 1,6-di-O-P-toluenesulfonyl-β-D-fructofuranoside (0.5g,1mmol) and 2-mercaptobenzoxazol (0.8g,5mmol) in dimethylformamide DMF (5 ml) was stirred for 38 h at 140C°.The mixture was evaporated to a syrup which was purified by column chromatography (ethyl acetate / hexane, 1:2) to give (0.95g) as a syrup (77 %) . *Rf*: (0.33).
IR (film), 1630cm^{-1}(C=N), 1370cm^{-1}9(C-N), 760cm^{-1}(C-S), 1140cm^{-1}(C-O), Fig.(3-7)

Synthesis of Methyl 6-thio-2-benzothiazolyl-6-deoxy-1-*O-P*-toluenesulfonyl-β-D-fructofuranoside [6]

Methyl 1,6-di-*O-P*-toluenesulfonyl-β-D-fructofuranoside (0.5g,1mmol) was treated with 2-mercaptobenzothiazol (0.167g,3mmol) in dry dimethylformamide DMF (5ml) overnight at 100C°.The mixture was evaporated to a syrup which was chromatographed (ethyl acetate / hexane, 1:1) to give (1.34g) as a syrup (83%). *Rf* : (0.4) .IR (film), 1620cm^{-1}(C=N), 1320cm^{-1}(C-N), 760cm^{-1}(C-S)

Synthesis of Methy 6-thio-2-benzimidazolyl-6-deoxy-1-*O-P*-toluenesulfonyl-β-D-fructofuranoside [7]

Methyl 1,6-di-*O-P*-toluenesulfonyl-β-D-fructofuranoside (0.5g,1mmol) was treated with 2-mercaptobenzimidazol (0.451g,3mmol) in dry dimethylformamide DMF (5 ml) overnight at 100C°.The mixture was evaporated to a syrup which was chromatographed (ethyl acetate / hexane , 1:1) to give (1.09g) as a syrup (83 %). *Rf* : (0.4)IR(film),1620cm^{-1}(C=N),1320cm^{-1}(C-N),760cm^{-1}(C-S),1690cm^{-1}(=N-H), Fig.(3-10)

Synthesis of Methyl -6-thio-2-benzoxazolyl-6-deoxy-1-*O-P*-toluenesulfonyl-β-D-fructofuranoside [8]

Methyl 1,6-di-*O-P*-toluenesulfonyl-β-D-fructofuranoside (0.5g,1mmol) was treated with 2-mercaptobenzoxazol (0.454g,3mmol) in dry dimethylformamide DMF (5 ml) overnight at 100C°. The mixture was evaporated to a syrup which was chromatographed (ethyl acetate / hexane , 1:1) to give (1.62g) as a syrup (83 %) . *Rf* : (0.8)IR(film), 1620cm^{-1}(C=N),1320cm^{-1}(C-N),760cm^{-1}(C-S),1140cm^{-1}(C-O),F.

Synthesis of Methyl -6-thio-2-thiazolyl-6-deoxy-1-*O-P*-toluenesulfonyl-β-D-fructofuranoside [9]

Methyl 1,6-di-*O-P*-toluenesulfonyl-β-D-fructofuranoside (0.5g,1mmol) was treated with 2-mercaptothiazol (0.35g ,33mmol) in dry dimethylformamide DMF (5 ml) overnight at 100C°.The mixture was evaporated to a syrup which was chromatographed (ethyl acetate / hexane , 1:1) to give (1.9g) as a syrup .(83 %) ,*Rf* : (0.35) .IR (film), 1620cm^{-1}(C=N), 1320cm^{-1}(C-N), 760cm^{-1}(C-S), 760cm^{-1}(C-S).

3-Results and Discussion

The research aims at preparing new derivatives of D-fructose in form of furanose , contain a heterocyclic ring linked by thio-bridge with sugar molecule ,which is obtained by replacing primary hydroxyl group in carbon atom at position 1,carbon atom at postion 6 for D-fructofuranose, with mercaptocompounds(2-mercaptobenzothiazol,2-mercaptobenzoimidazol,2-mercaptobenzoxazol, 2-mercaptothiazol). The thiofructofuranoside accumulated efficiently after synthesis, indicating it was very stable against the hydrolytic action of the β-fructofuranosidase[125].

Preparation of Derivative Methyl D-fructofuranosides [1]

Simple fructofuranoside can be prepared by glycosidation of D-fructose in the presence of an acid catalyst. IR spectrum show apparent absorption band for two primary hydroxyl groups at 3500 cm^{-1} and the bands was broad because there four hydroxyl groups and may be the hydrogen bonds are effecting in these cases and stretching band at 1000-1100cm^{-1} for (C-O-C) as in figure (1).

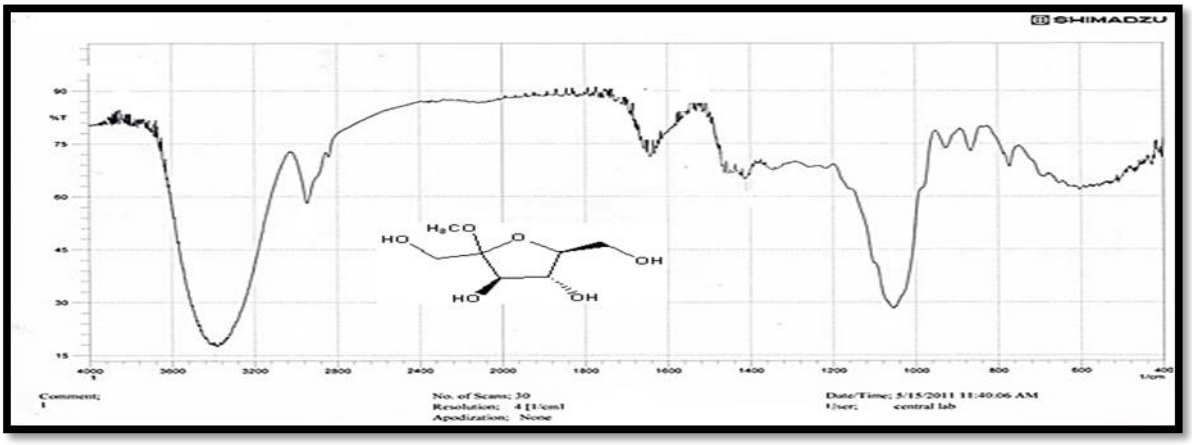


Figure (1) IR Spectrum of compound [1]

Preparation of*O*-Methyl 1,6-di-*O*-Toluenesulphonyl-D-fructofuranoside[2]

Methyl 1,6-di-*O*-*P*-toluensulfonyl –β-D-fructofuranose**[2]** is a key intermediate for the synthesis of 1- and /or 6- substituted methyl-β-D-fructoruranosides. IR spectrum showed stretching band of two SO_2 groups at 1150cm^{-1} and 1370 cm^{-1}stretching bands of two secondary hydroxyl group 3340cm^{-1} and disappearance of stretching band to two primary hydroxyl groups at 3500cm^{-1}as in figure (2).

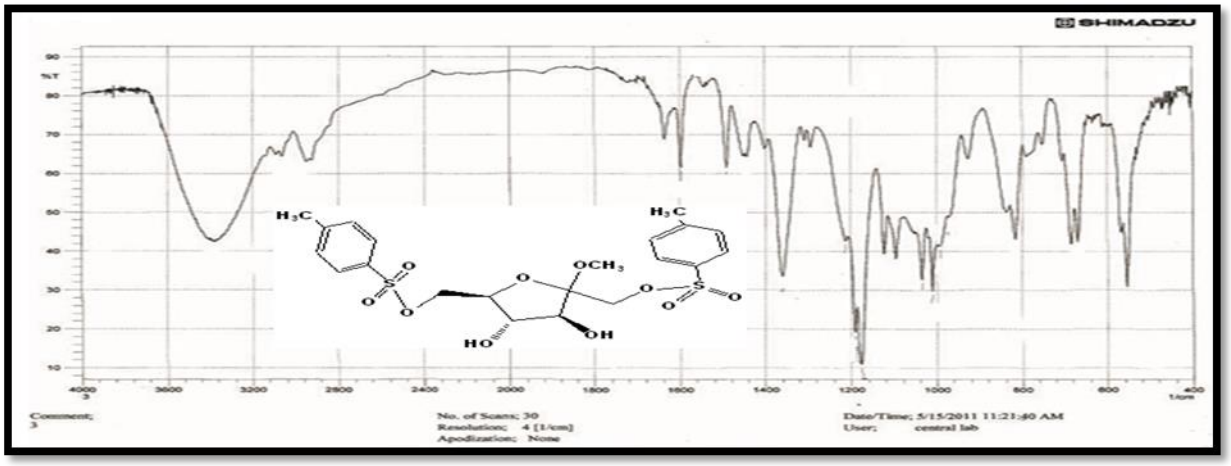


Figure (2) IR Spectrum of compound [2]

Synthesis of Derivative Methyl 1,6-di-thio-2-benzothiazolyl-1,6-di-deoxy-β-D-fructofuranoside [3]

The derivative **[3]** has been synthesized with reaction of 1mmol of compound **[2]** and (5 mmol) of 2-mercaptobenzothiazol in DMF for 38h at 140C°. The 1-sulfonyl group is of the neopentyl type, and is much less readily displaced.[20]

IR spectrum shows disappearance of stretching band of two SO_2 groups at 1150cm^{-1} and 1370cm^{-1}, and apparent absorption at 1310cm^{-1}for (C-N) ,760cm^{-1} for (C-S) ,1629cm^{-1} for (C=N) as in figure (4). Further support for the derivative **[3]** was provided from its H^1- NMR spectrum which was dissolved in DMSO, aromatic protons in benzene ring (4H) had resonance signals in multiple lines in region (δ=7.2-8.3) ppm . Multiple lines in region (δ=2.4-2.8) ppm to two methyl groups protons (2H) at

1, 6 and multiple single in (ƍ= 3-3.5) for (-OCH_3) protons and this result is because of the deference in an electronic environment figure (3).

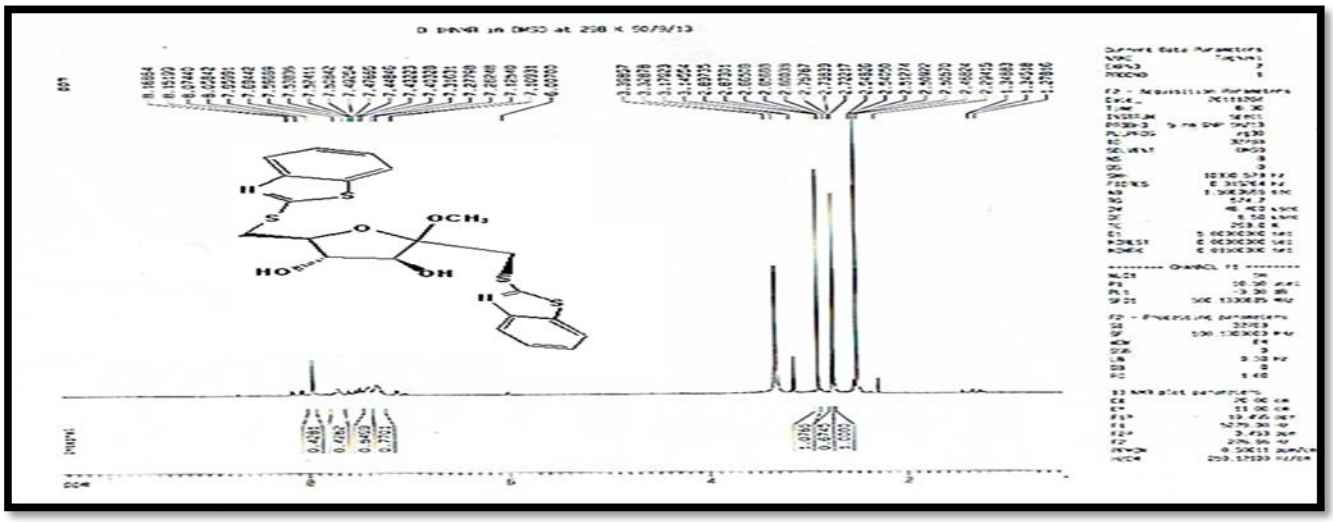


Figure (3) H^1 -NMR of Derivative [3]

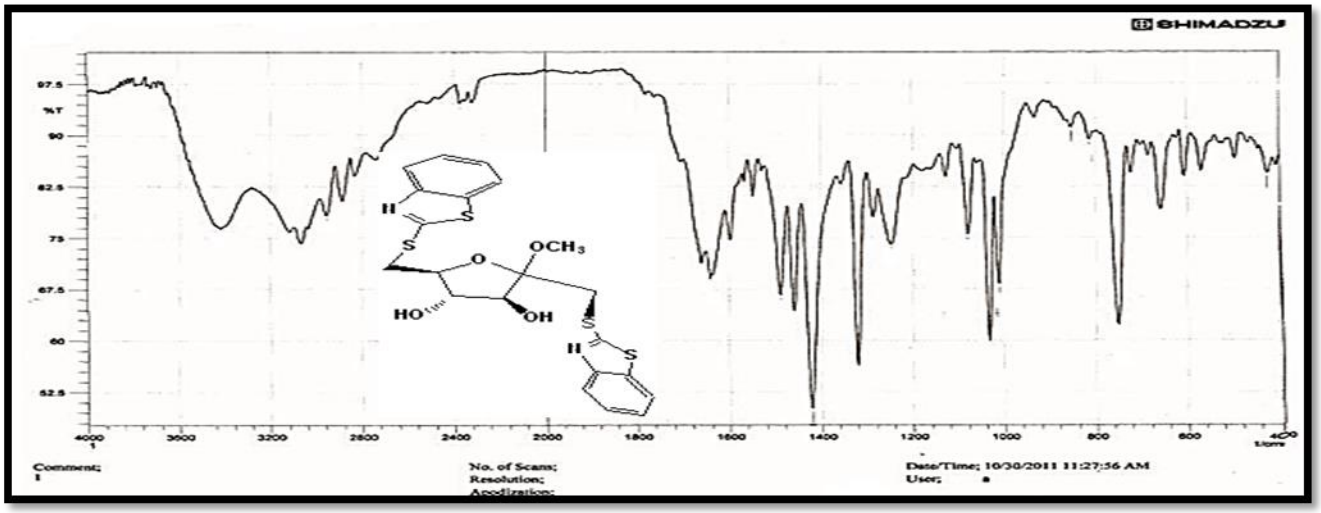


Figure (4) IR Spectrum of derivative [3]

Synthesis of Derivative Methyl-1,6-di-thio-2-benzimidazolyl-1,6-di-deoxy-β-D- fructofuranoside [4]

The derivative **[4]** has been synthesized by treating 1mmol of compound **[2]** with 5 mmol of 2-mercaptobenzimidazol in DMF for 38h at 140C°.

IR spectrum showed disappearance of stretching bands of two SO_2 groups at 1150cm^{-1} and 1370cm^{-1}, and apparent absorption at 1625cm^{-1} for (C=N) , 1270cm^{-1} for (C-N) ,750cm^{-1} for (C-S) , 1690cm^{-1} for (=N-H) as in figure (5) .

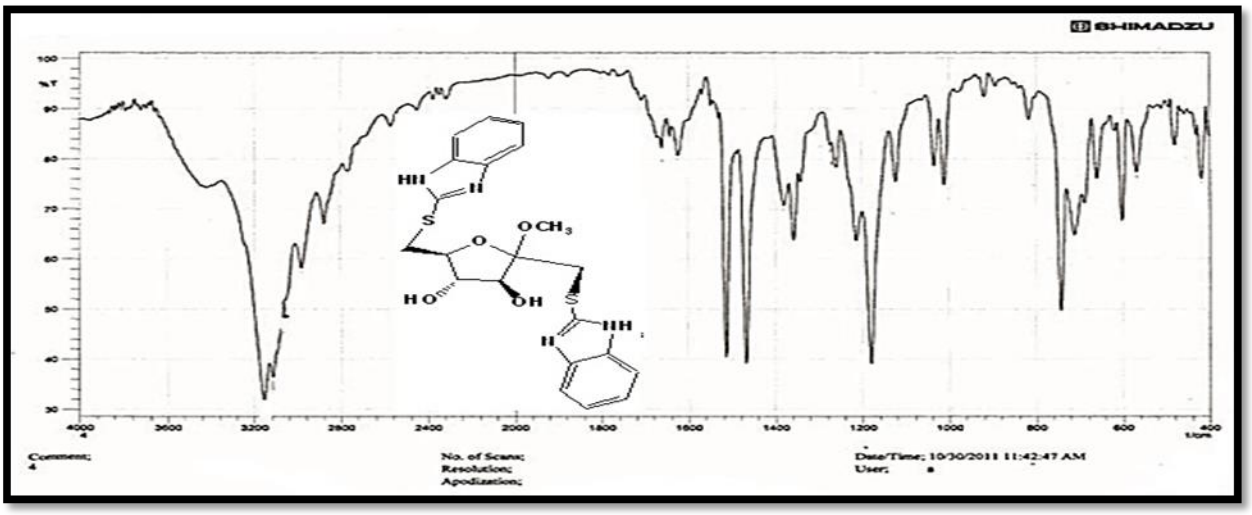


Figure (5) IR Spectrum of derivative [4]

Synthesis of Derivative Methyl-1,6-di-thio-benzoxazolyl-1,6-di-deoxy-β-D-fructofuranoside [5]

The derivative **[5]** has been synthesized by treating 1 mmol of compound **[2]** with 5 mmol of 2-mercaptobenzimidazol in DMF for 38h at 140C°.IR spectrum showed disappearance of stretching bands of two SO_2 groups at 1150cm^{-1} and 1370cm^{-1}, and apparent absorption at 1630cm^{-1} for(C=N) , 1370cm^{-1} for (C-N) ,760cm^{-1} for (C-S) , 1140cm^{-1} for (C-O-C) as in figure (7) . Further support for the derivative **[5]** was provided from its H NMR spectrum, aromatic protons in benzene ring (4H) had resonance signals in multiple lines in region (δ=7.2-8.3) ppm. Multiple lines in region (δ=2.4-2.8) ppm to two methyl groups protons (2H) at 1, 6and multiple single in (δ= 3-3.5) for (-OCH_3) protons and this result is because of the deference in an electronic environment figure (6).

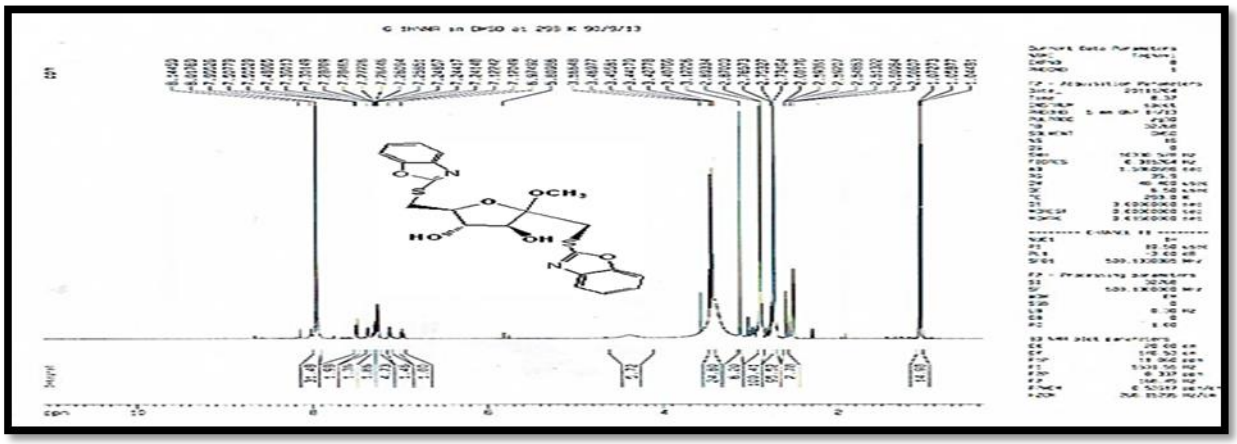


Figure (6) H^1 -NMR of Derivative [5]

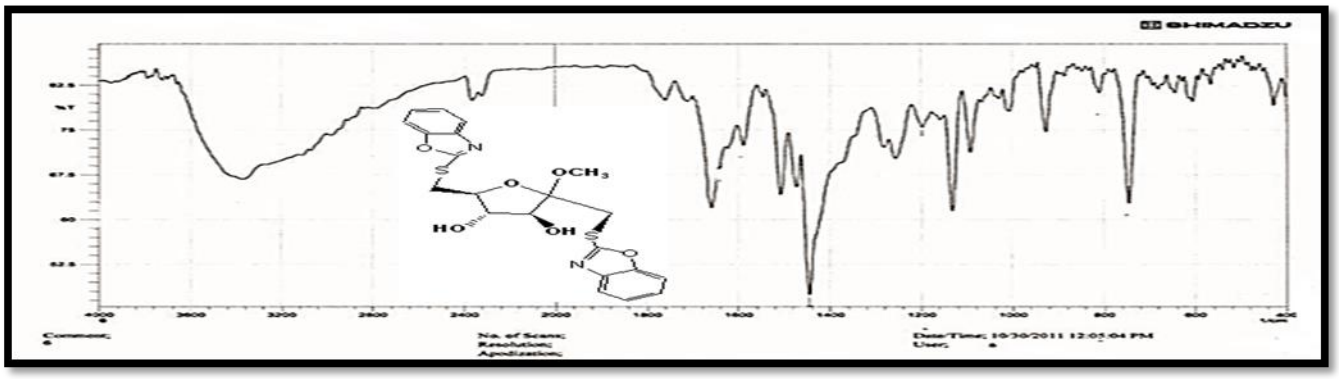


Figure (7) IR Spectrum of derivative [5]

Synthesis of Derivative Methyl-6-thio-2-benzothiazolyl-6-deoxy-1-*O*-*P*-toluenesulfonyl-β-D-fructo furanoside [6]

The derivative **[6]** has been synthesized by treating compound **[2]** 1mmol with 3 mmol of 2-mercaptobenzothiazol in DMF 5ml overnight at 100C°. IR spectrum showed still apparant of stretching bands of one SO_2 group at 1150$cm^{-1}$and 1370cm^{-1}, and appearance absorption at 1620cm^{-1} for (C=N) , 1320 cm^{-1} for (C-N) ,760cm^{-1} for (C-S) as in figure (8) .

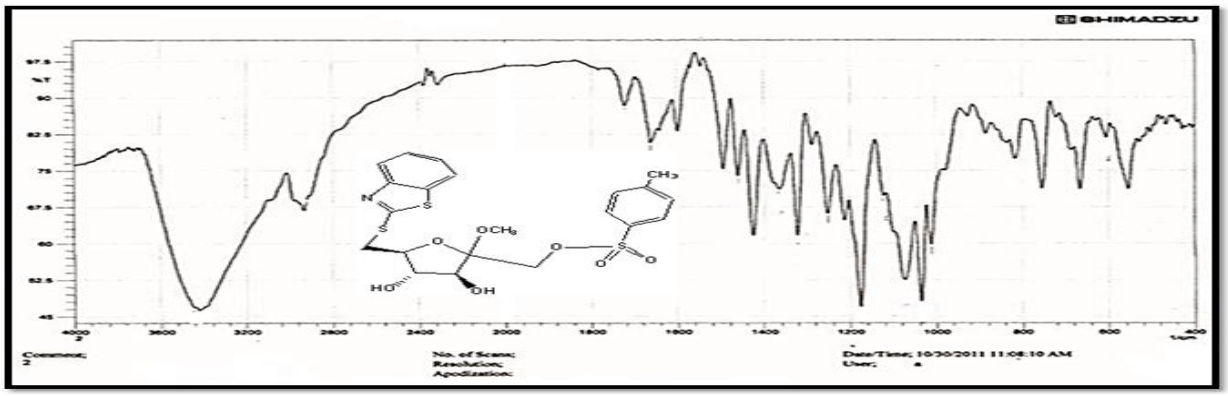


Figure (8) IR Spectrum of derivative [6]

Synthesis of Derivative Methyl 6-thio-2-benzimidazolyl-6-deoxy-1-*O*-*P*-toluenesulfonyl-β-D-fructofuranoside[7]

The derivative **[7]** has been synthesized by treating compound **[2]** mmol with 3 mmol of 2-mercaptobenzimidazol in DMF 5ml overnight at 100C°.IR spectrum shows still appearance of stretching bands of one SO_2 group at 1150cm^{-1} and 1370cm^{-1}, and apparant absorption at 1620cm^{-1} for (C=N) , 1320 cm^{-1} for (C-N) ,760cm^{-1} for (C-S) , 1690cm^{-1} for (=N-H) as in figure (9) .

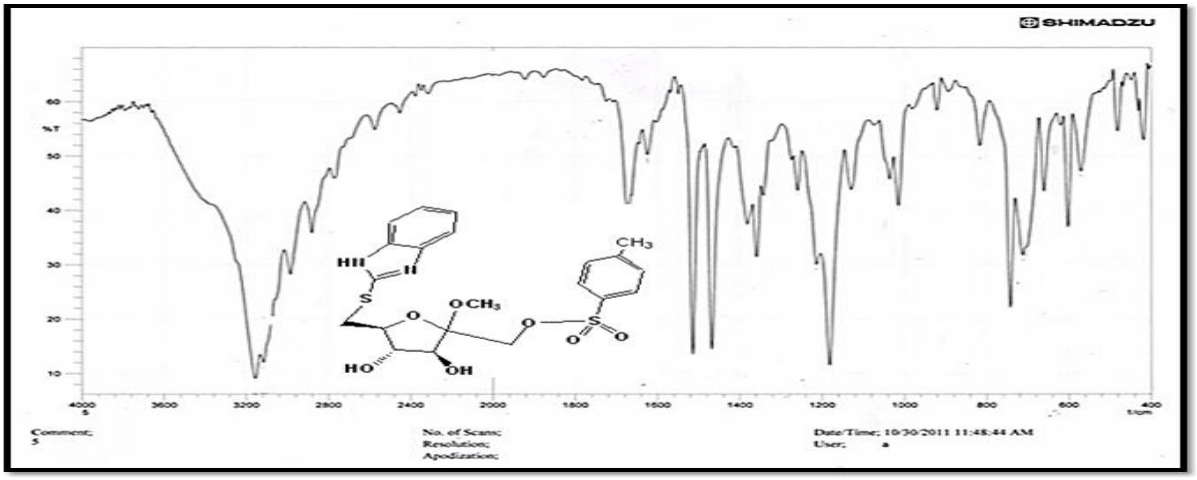


Figure (9) IR Spectrum of derivative [7]

Synthesis of Derivative Methyl -6-thio-2-benzoxazolyl-6-deoxy-1-*O*-*P*-toluenesulfonyl-β-D-fructofuranoside [8]

The derivative **[8]** has been synthesized by treating compound **[2]** 1 mmol with 3 mmol of 2-mercaptobenzoxazol in DMF 5ml overnight at 100C°. IR spectrum shows still appearance of stretching bands of one SO_2 group at 1150cm^{-1} and 1370cm^{-1}, and apparant absorption at 1620cm^{-1} for (C=N) , 1320cm^{-1}for (C-N) ,760cm^{-1} for (C-S) , 1140cm^{-1} for (C-O-C) as in figure (10) . Further support for the derivative **[8]** was provided from its H NMR spectrum, aromatic protons in benzene ring (4H) had resonance signals in multiple lines in region (δ=7.2-8.3) ppm . Multiple lines in region (2.4-2.8) ppm to two methyl groups protons (2H) at 1,6 and multiple single in (δ= 3-3.5) for (-OCH_3) protons and this result is because of the deference in an electronic environment. There is single signal in δ=2.4 for protons (-CH_3) which is connected to benzene ring in sulfonyl group and single signal in δ=3.25 for (-CH_2) protons which is connected to benzene ring in sulfonyl group figure (11) .

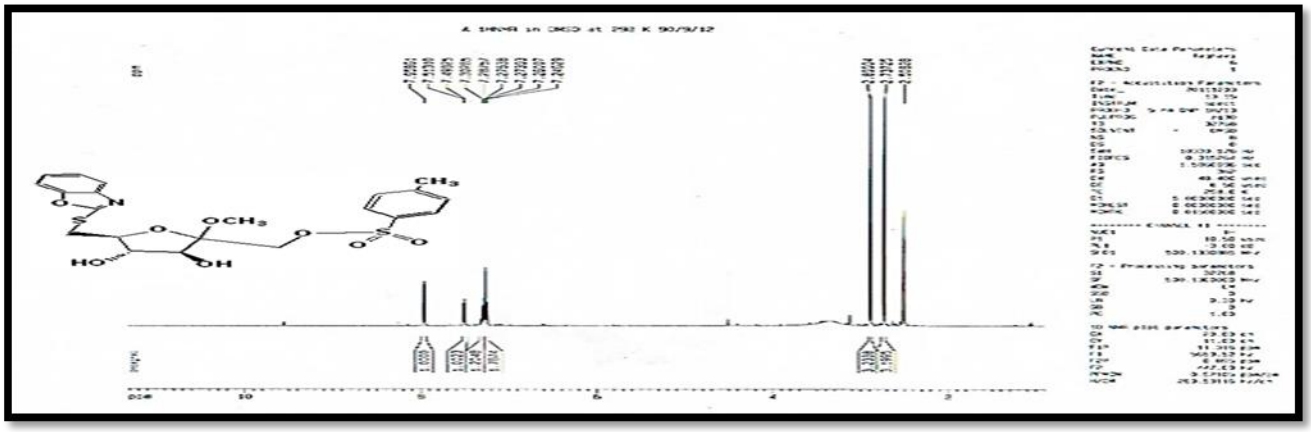


Figure (10) H^1 -NMR of Derivative [8]

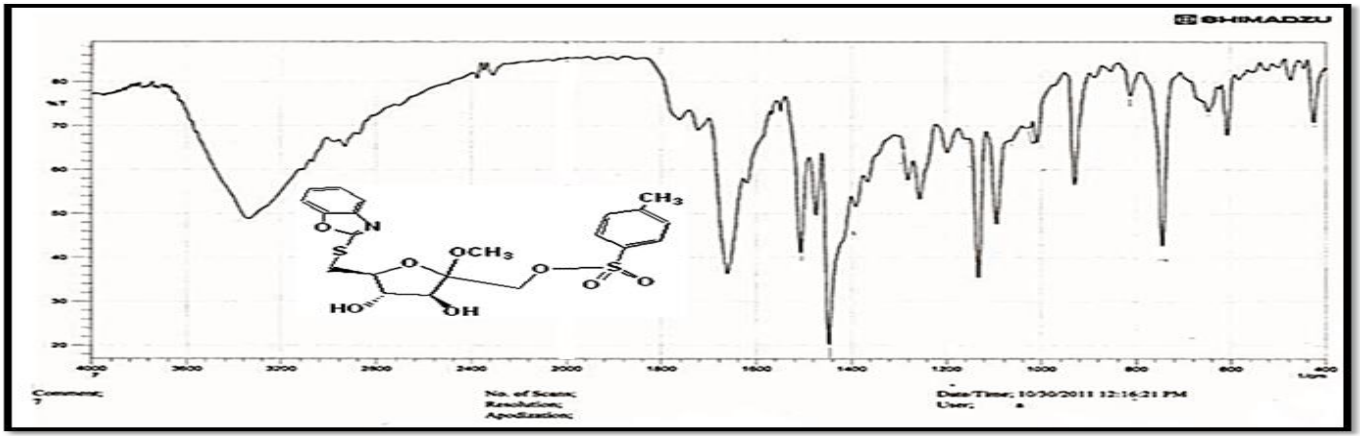


Figure (11) IR Spectrum of derivative [8]

Synthesis of Derivative Methyl -6-thio-2-thiazolyl-6-deoxy-1-*O*-*P*-toluenesulfonyl-β-D-fructofuranoside [9]

The derivative **[9]** has been synthesized by treating compound **[2]** 1 mmol with 3mmol of 2-mercaptothiazol in DMF 5ml overnight at 100C°. IR spectrum shows still appearance of stretching bands of one SO_2 group at 1150cm^{-1} and 1370cm^{-1}, and apparent absorption at 1620cm^{-1} for (C=N) , 1320 cm^{-1} for (C-N) ,760cm^{-1} for (C-S) as in figure (12).

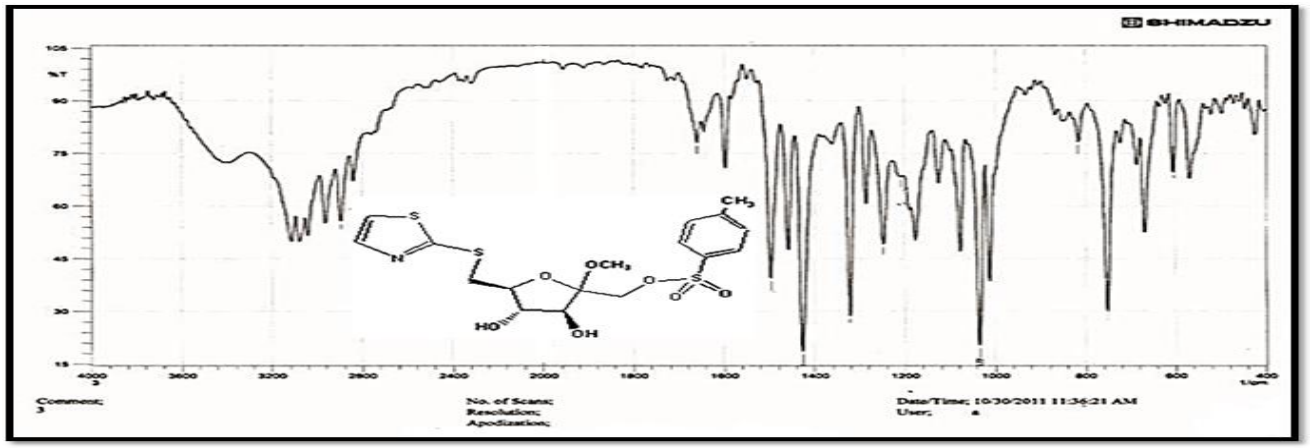
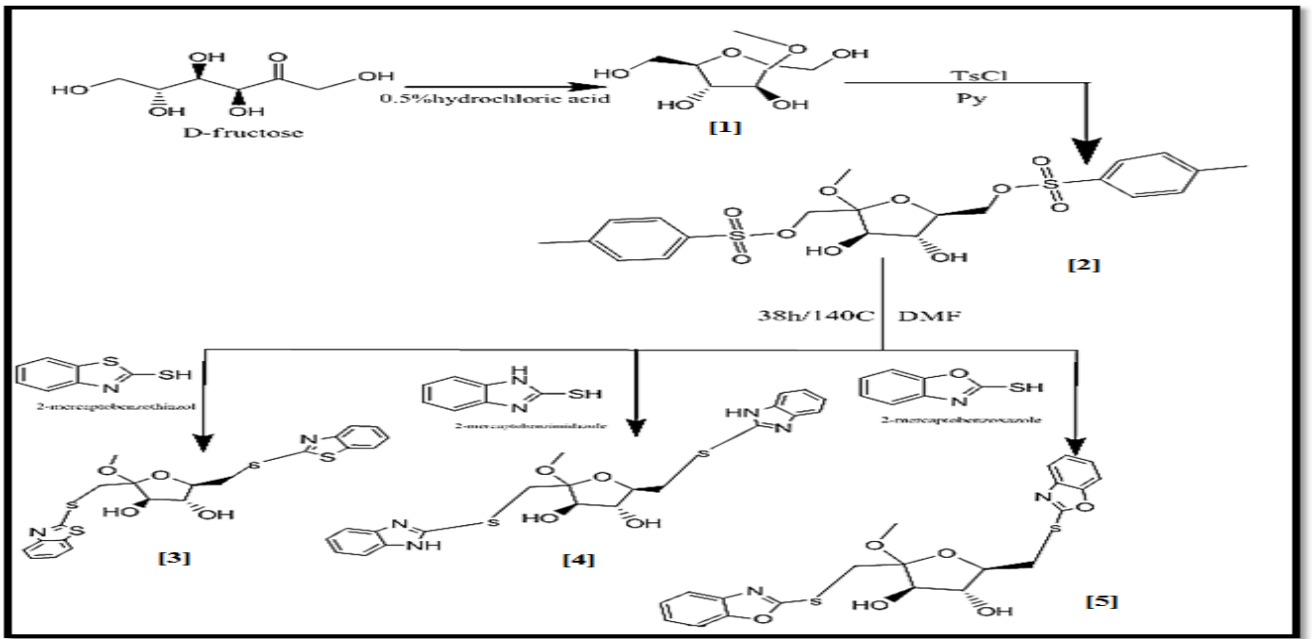
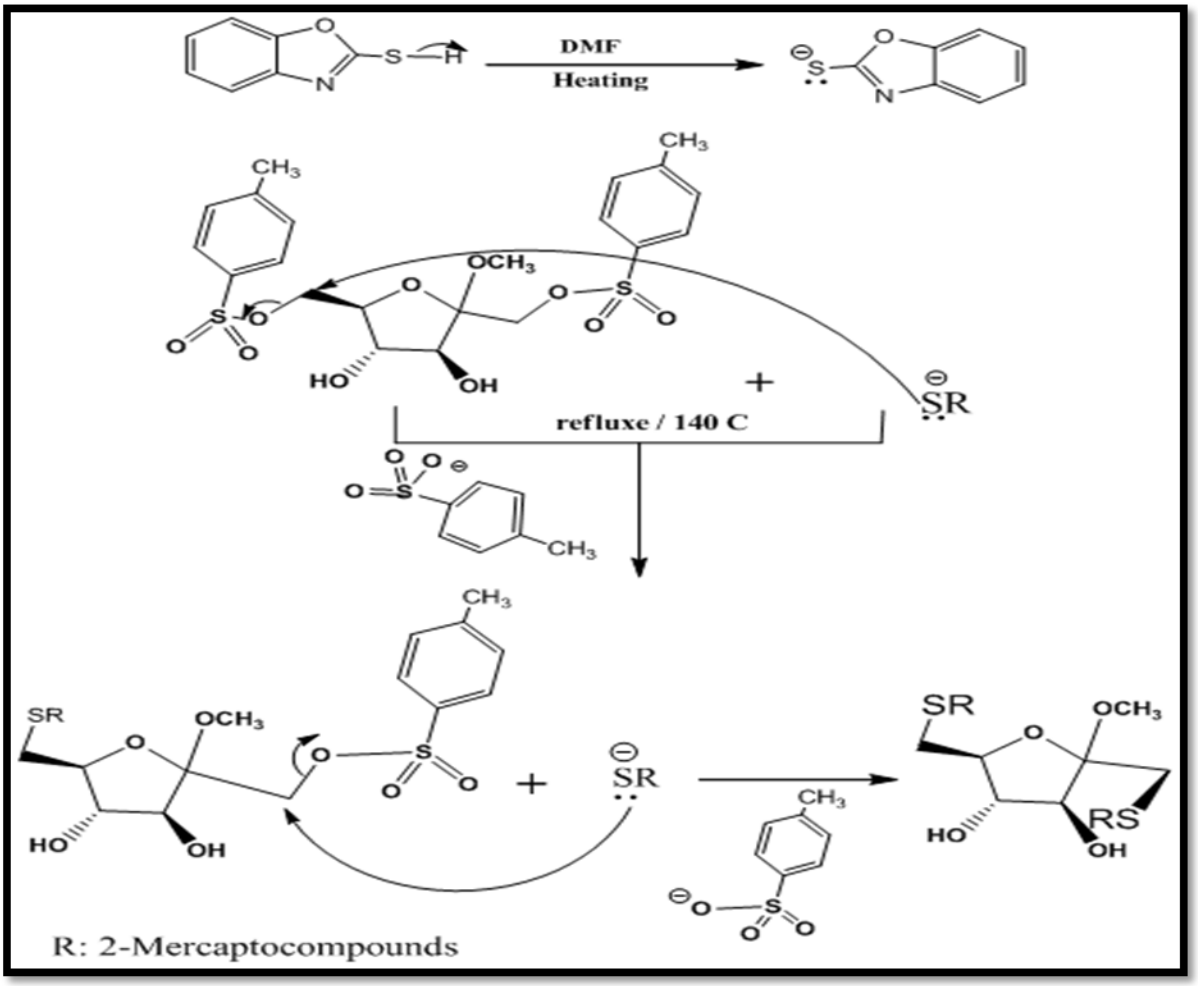


Figure (12) IR Spectrum of derivative [9]



Shceme of synthesis of 1,6-D-Fructofuranose derivatives



Mechanism of synthesis of 1,6-D-Fructofuranose derivatives

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