Ahmed Obaid Jasim et al /J. Pharm. Sci. & Res. Vol. 10(12), 2018, 3233-3240

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and biological activity of new esters derived from D-fructose-containing isoxazole moiety

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Abstract

Background: Isoxazoles are an important class of five-membered unsaturated heterocyclic compounds. They show several applications in diverse areas such as pharmaceuticals, agrochemistry and industry. Isoxazoles are also found in natural sources showing insecticidal, plant growth regulation and pigment functions. Current study was conducted for synthesis of twenty five new Isoxazole derivatives and to evaluate the *in vitro* antibacterial activities of these derivatives.

Methods: Benzaldoxime and their substituted $[I]_{a-e}$ were prepared via addition-elimination reactions between aromatic aldehyde and hydroxylamine hydrochloride. In a second step, para- or meta-substituted benzaldoximes $[I]_{a-e}$ were reacted with N-chlorosucceinimide in DMF to yield the para- or meta-substituted benzhydroxamic chlorides $[II]_{a-e}$ .On the other hand D-fructose was converted to 2,3:4,5-di-O-isopropylidene-D-fructopyranose[III] using dry acetone and sulfuric acid as a catalyst.

Results and Conclusions: The reaction of compound [III] with propargyl bromide in DMF yielded the terminal alkyne [IV]. The esterification reaction of hydroxyl groups of compounds $[VI]_{a-e}$ with different acid chloride in mixture THF and DMF using triethylamine as a catalyst give new compounds $[VII]_{a-e}$, $[VIII]_{a-e}$ and $[IX]_{a-e}$. All synthesized compounds were identified by FTIR and most of them were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Also the synthesized compounds showed variable antimicrobial activities *in vitro* against *Escherichia coli*, *Bacillus substilis*, *Staphylococcus aureus* and *Candida albicans.*

Key words: Fructose, Isoxazoles, antibacterial activity, Esterfication.

1. INTRODUCTION

Fructose is a sweet, white, odorless, crystalline solid and is the most water-soluble of all the sugars [1]. Fructose is also used by pharmaceutical and chemical industries. The use of fructose as an excipient is mostly to make medicines more palatable [2]. Also, it serves as a cry protectant [3,4], an aid for the solubility of hydrophobic active ingredients [5,6] and a component to alter the osmolality of injectable solutions [7].

Isoxazoles are an important class of five-membered unsaturated heterocyclic compounds. They show several applications in diverse areas such as pharmaceuticals, agrochemistry and industry ([8,9]. Isoxazoles are also found in natural sources showing insecticidal, plant growth regulation and pigment functions [10].

Moreover, 1,3- dipolar cyclo-addition is the complete conversion of terminal alkyne and oxime into corresponding 3,5-disubstituted Isoxazoles [11]. Himo and co-works [12] prepared new triazoles and isoxazoles via cyclo-additions of copper(I) acetylides to azides, and nitrile oxides provided ready access to 1,4-disubstituted 1,2,3-triazoles and 3,5-disubstituted isoxazoles, respectively. The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a non-concerted mechanism involving unprecedented metallacycle intermediates. During the drug discovery program of Watterson et al. [13], 1-(4-(5-(3-phenyl-4-(trifluoromethyl)isoxazol-5-yl)-1,2,4-oxadiazol-3-yl)benzyl)azetidine-3-carboxylic acid, was identified as a novel isoxazole-based S1P1 receptor agonist.

Current study was conducted for synthesis of twenty five new Isoxazole derivatives starting from D-fructose and to evaluate the *in vitro* antibacterial activities of these derivatives against three kinds of bacteria: *Escherichia coli* (Gram-negative), *Bacillus substilis* and *staphylaococcus aureus* (Gram-positive). In addition, antifungal activity of these derivatives against *Candida albicans* will be investigated, as well.

2. METHODS

2.1. General experimental information

The chemicals and solvents consumed for synthesizing target compounds were Sigma-Aldrich, Fisher and Merck brands. Uncorrected open capillary tube was used to distinguish the melting point by MEL-TEMP II instrumental. The reaction and purities of compounds were checked with a thin layer chromatography (Silica gel TLC) plate's Merck brand. The spot is located by iodine vapors. FTIR spectra were recorded by using potassium bromide discs on a SHIMADZU (IR Affinity-1) FTIR spectroscopy at Central Service Laboratory, College of Education for Pure Science (Ibn-Al-Haitham)/ University of Baghdad. ^{1}H and ^{13}C-NMR spectra were carried out by Ultra Shield 300 MHz, Bruker, Switzerland at Gazi University College of Science, Ankara, Turkey. Also some spectra were carried out Ultra Shield 400 MHz at Bruker Center Lab./ University of Tehran, Iran and were reported in ppm(δ). DMSO-d6 was used as a solvent with TMS as an internal standard. The mass spectra recorded by MS model: 5975c VL MSD with Tripe-Axis Detector Center Lab./ University of Tehran, Iran.

2.2. Synthetic procedures

2.2.1. Para or meta-substituted benzaldoximes $[I]_{a-e}$: was prepared as it was described in the literature [14] and its physical properties were corresponding to what is in the literature.

2.2.2. General preparation of para or meta-substituted benzhydroxamic chlorides $[II]_{a-e}$

The para or meta-substituted benzaldoximes $[I]_{a-e}$ (30mmol) was dissolved in DMF (50 mL) with stirring and N-chlorosucceinimide (30mmol) was added in two portions at room temperature. Initiation of the reaction was accelerated by use of a slight increase in the temperature to $40^{0}C$ for 20min. The reaction was monitored by TLC (cyclohexane/ ethyl acetate 8:2). After about 12h the reaction was complete, an ice/ water mixture was added and extracted twice with diethyl ether. The organic phase was washed twice with ice/ water, dried over Na_2SO_4, and concentrated to give compounds $[II]_{a-e}$. The physical properties were corresponding to those described in the literature [15].

2.2.3. Preparation of 2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose [III]

D-Fructose (20mmol) was dissolved in acetone (70mL) and concentrated H_2SO_4 (3.5mL) was added. The reaction was stirred for (90 min) and then cooled in ice-salt bath to($0^{0}C$), NaOH (11g in 50mL H_2O) was then gradually added with stirring. The solution was then concentrated and extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were then washed with distilled water (2 x 10mL). The organic phases was dried over Na_2SO_4 and concentrated. The resulting crude product was dissolved in hot Et_2O (5 mL) and n-pentane was added to precipitate the desired bis – acetal as a crystalline solid

recrystallization from Et_2O: n-hexane 1:1 (25 mL) to give compound [III] as a white crystals (55%), m.p.116 -118^{0}C (reference value reported in the literature was 118-120^{0}C [16].

2.2.4. Preparation of 1-*O*-propargyl- 2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose [IV]

Compound [III] (4mmol) was dissolved in DMF (15mL) and NaOH pellets (15mmol) were added. The mixture was cooled in ice-salt bath to (-15^{0}C) and the contents was stirred for (10 min) and then propargyl bromide (0.4mL, 4.3mmol) was added drop-wise. The heterogenous reaction mixture was stirred for (2 h) slowly, warming to room temperature. The mixture was filtered and H_2O (50mL) was added and the product was extracted with Et_2O (3 x 50mL). The organic phases were combined and washed sequentially with 5% HCl (2 x 50mL) and distilled water (50mL). The organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to dryness under reduced pressure to yield Compound [IV] (75%) as pale yellow oil.

2.2.5. Synthesis of 3-(para or meta-substituted phenyl)-5-{(2,3,4,5-di-*O*-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole [V]$_{a-e}$

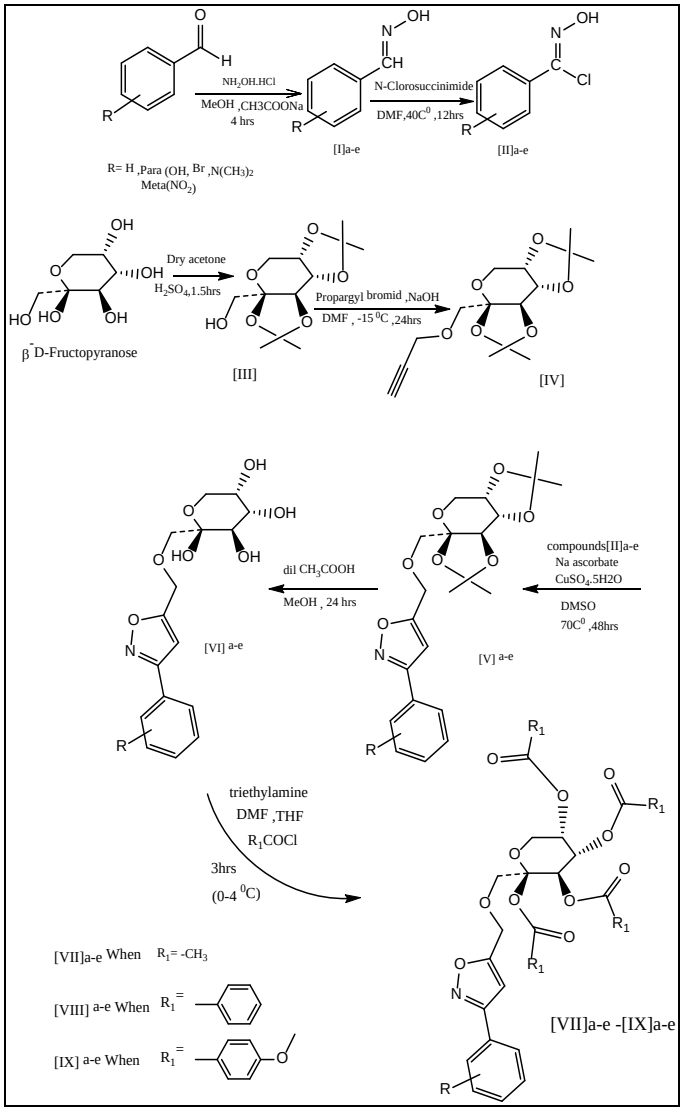
Alkynyl sugar compound [IV] (1mmol) and para- or meta-substituted benzhydroxamic chlorides [II]$_{a-e}$ (1mmol) were added to a suspension of sodium ascorbate (0.018g; 0.09mmol) and $CuSO_4.5H_2O$ (0.011g; 0.045mmol) in DMSO (5mL) . The mixture was heated to (70^{0}C) and stirred for (48 h). The reaction mixture was diluted with water (30mL). Extracted with EtOAc (3 x 30 mL). Dried over Na_2SO_4 and evaporated to dryness under reduced pressure to yield oily Compounds [V]$_{a-e}$. The nomenclature, structural formula, molecular formula, yields and physical properties are listed in Table (1).

2.2.6. Synthesis of 3-(para or meta-substituted phenyl)-5-{(beta-D-fructopyranose-O-yl)methyl}1H-isoxazole [VI]$_{a-e}$

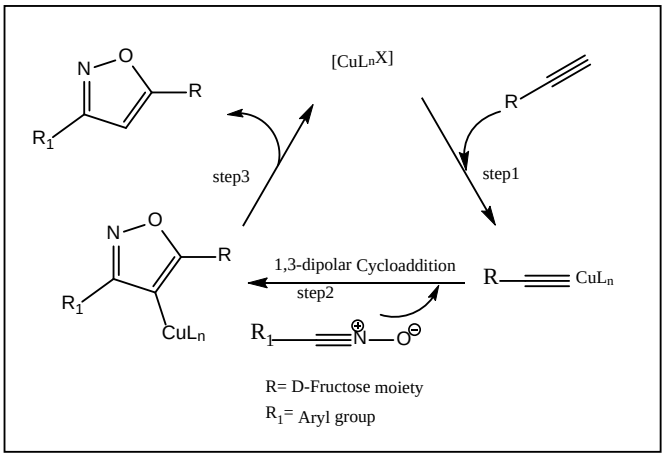
The compounds [VI]$_{a-e}$ were synthesized by dissolving compounds [V]$_{a-e}$ (2.36mmol) in a mixture of dilute acetic acid (3mL) and absolute methanol (1mL) and stirred for (48h) at room temperature. The TLC showed that the reaction was complete (benzene: methanol 6:4). To the resulting solution, a benzene (4mL), was added and evaporated (repeat this process four times). The residue recrystallized from chloroform. The nomenclature, structural formula, molecular formula, yields and physical properties are listed in Table (2).

2.2.7. Synthesis of ester compounds [VII]$_{a-e}$, [VIII]$_{a-e}$ and [IX]$_{a-e}$

To a stirred solution of compounds [VI a-e] (1mmol) in triethylamine (8mmol) and dried mixture of (5mL DMF: 10mL THF), carboxylic acid chloride (4 mmol) at (0-4^{0}C) was added drop-wise. After the addition had been completed, the resulting suspension was stirred at the same temperature for 3h. The triethylaminhydrochloride salt was precipitated. It was filtered and the filtrate was poured with stirring onto (100mL) ice- water then the mixture was extracted with Et_2O (3 x 50mL). The ether solvent was evaporated to give a residue which was recrystallized from ethanol / water. The nomenclature, structural formula, molecular formula, yields and physical properties are listed in Table (3). All compounds in paragraph (2.2.7) were prepared in the same way except for the three compounds [VII$_b$, VIII$_b$ and IX$_b$], because they contain another hydroxyl group, so we will need another mole of the base and the acid chloride.



Scheme 1 Outline for synthesis of esters derived from D-fructose-based isoxazole



Scheme 2 The mechanism of isoxazoles formation

3. RESULTS AND DISCUSSION

3.1. Synthesis and characterization

Benzaldoxime and their substituted $[I]_{a-e}$ were prepared via addition-elimination reactions between aromatic aldehyde and hydroxylamine hydrochloride. Chlorination of compounds $[I]_{a-e}$ by N-chlorosuccinimide in DMF to get the para- or meta-substituted benzhydroxamic chlorides $[II]_{a-e}$ The structures of compounds $[I]_{a-e}$ and $[II]_{a-e}$ were identified by their melting points and FT-IR spectroscopy. The physical properties and FT-IR spectroscopy were corresponding to those described in the literature. The overall synthetic route of ester derived from beta-D-fructopyranose based isoxazoles is shown in Scheme 1.

The acetal of beta -D-fructopyranose compound[III] was prepared from the reaction of acetone with beta-D-fructose in the presence of H_2SO_4 as a catalyst. FT-IR spectrum of compound [III] showed a stretching bonds at 3271$cm^{-1}$for OH, 2935 and 2897$cm^{-1}$for CH aliphatic and 1242$cm^{-1}$for C-O. The reaction of propargyl bromide with compound [III] was occurred under basic conditions to produce compound [IV]. The FT-IR spectral data at 3273cm^{-1} for (≡C-H) and 2119cm^{-1} for (C≡C) gave a very good proof for the formation of compound [IV]. By using $CuSO_4.5H_2O$ catalyzed 1,3-dipolar cyclo-addition reaction of compound [IV] with benzhydroxamic chlorides [II] a-e yielded the beta-D-fructose based isoxazoles $[V]_{a-e}$. The mechanism [17] of this reaction was outlined in Scheme 2.

The FT-IR spectrum of compound $[V_b]$ showed the following bands: 3292cm^{-1}(υ,-OH), 3066cm^{-1}(υ, C-H aromatic),2991,2937cm^{-1}(υ, C-H aliphatic),1647cm^{-1}(υ, C = N),1556cm^{-1}(υ, C = C)**.** All spectral data for other compounds are listed in Table (4).

^{1}H-NMR spectrum of compound $[V_b]$ (400 MHz, DMSO-d_6) δ ppm: 1.10, 1.17 (s, 12H, -*CH*$_3$,isopropylidene), 3.49 (d,1H, -*CH*-O), 3.53 (s, 2H, -*CH*$_2$-O), 3.74 (q,1H, -*CH*-O) 3.82 (d, 2H, -*CH*$_2$-O), 4.26 (t,1H, -*CH*-O) 4.61 (s, 2H, -*CH*$_2$-O), 6.79 (s, 1H, Ar-H isoxazole), 7.53-7.63 (m, 4H, Ar-H), 9.70 (s, 1H, OH phenolic), ^{13}C-NMR (75 MHz, DMSO-d6) δ, ppm; 29.0, 26.5 (4C, *CH*$_3$ isopropylidene), 62.4, 70.7,73.0 (3C, -*CH*$_2$-O), 70.7,75.7,77.5 (3C, -*CH*-O),115.3(1C, *O-C-O*) 100.2,140.4,156.5 (3C, C-isoxazole), 127.1 (2C, *C(CH*$_3$*)*$_2$ isopropylidene), 116.4,128.5, 129.0,140.4 (6C, C-Ar); EIMs, m/z= 433.6 [M+] 100%, (Calc. for $C_{22}H_{27}N_1O_8$, 433.4).

Isopropylidene group of compound $[V]_{a-e}$ were deprotected by using dil CH_3COOH. The broad band around (3200-3400) cm^{-1} which was attributed to the O-H stretching is a very good evidence of the deprotection and formation of compounds $[VI]_{a-e}$. FT-IR spectrum of compound $[VI]_a$ 3- phenyl-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole showed the following bands: 3292cm^{-1}(υ,-OH), 3066cm^{-1}(υ, C-H aromatic), 2991, 2937cm^{-1}(υ, C-H aliphatic),1647cm^{-1}(υ, C = N), 1556cm^{-1}(υ, C = C). All spectral data for other compounds are listed in Table (5). ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) δ ppm showed: 4.36, 4.54, 4.84, 4.90 (s, 4H, -*OH* D-fructose), 3.13 (d, 2H, -*CH*$_2$-O), 3.28 (d,1H, -*CH*-O), 3.60 (s, 2H, -*CH*$_2$-O), 3.72 (q,1H, -*CH*-O), 3.86 (t,1H, -*CH*-O), 4.60 (s, 2H, -*CH*$_2$-O), 6.74 (s, 1H, Ar-H isoxazole), 7.36-7.74 (m, 5H, Ar-H).

^{1}H-NMR spectrum of compound $[VI]_d$ 3-(4-N,N-dimethylamino phenyl)-5-{(beta-D-fructopyranose-O-yl)methyl}1H-isoxazole showed the following characteristic: chemical shifts (DMSO-d_6, ppm): 3.10 (s, 6H, -*N(CH*$_3$*)*$_2$), 4.32, 4.51, 4.74, 4.77 (s, 4H, -*OH* D-fructose), 3.62 (d,1H, -*CH*-O), 3.65 (s, 2H, -*CH*$_2$-O), 3.70 (q,1H, -*CH*-O) 3.82 (d, 2H, -*CH*$_2$-O), 3.89 (t,1H, -*CH*-O) 4.63 (s, 2H, -*CH*$_2$-O), 6.69 (s, 1H, Ar-H isoxazole), 7.10-7.68 (m, 4H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d6) δ ppm; 42.6, (2C, -*N(CH*$_3$*)*$_2$), 65.1, 68.2, 70.2 (3C, -*CH*$_2$-O), 70.2, 71.4, 73.5 (3C, -*CH*-OH), 115.3(1C, *O-C*-OH) 102.2, 150.3, 160.4 (3C, C- isoxazole), 115.2, 118.1, 128.2, 145.2 (6C, C-Ar); EIMs, m/z= 380.6 [M+] 100%, (Calc. for $C_{18}H_{24}N_2O_7$, 380.3).

The esterification reaction of hydroxyl groups of compounds $[VI]_{a-e}$ with different acid chloride in a mixture of THF and DMF using triethylamine as a catalyst at (0-4)^{0}C gave new esters compounds. The FT-IR spectrum of compounds $[VII]_{a-e}$, $[VIII]_{a-e}$ and $[IX]_{a-e}$ showed disappearance of the stretching vibration band of OH group in the region (3100-3450)cm^{-1},so that, the appearance of strong absorption stretching band at (1712-1738)cm^{-1} due to C=O beside to C-O around(1060-1270)cm^{-1} of ester group, is a very good evidence of the formation of esters compounds.

FT-IR spectrum of compound $[VII]_a$ 3-phenyl-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole showed the following bands: 1738cm^{-1}(υ,- C=O),3093cm^{-1}(υ, C-H aromatic), 2997, 2945cm^{-1}(υ, C-H aliphatic), 1614cm^{-1}(υ, C = N), 1585cm^{-1}(υ, C = C) All the spectral data for other compounds are listed in Table (6).^{1}H-NMR spectrum (400 MHz, DMSO-d_6) δ ppm: 2.24 (s, 12H, -*CH*$_3$,ester), 3.01(d,1H, -*CH*-O), 3.79 (s, 2H, -*CH*$_2$-O), 4.55 (d, 2H, -*CH*$_2$-O), 4.68 (s, 2H, -*CH*$_2$-O), 5.30 (t,1H, -*CH*-O) 5.53 (q,1H, -*CH*-O) 6.73 (s, 1H, Ar-H isoxazole), 7.42-7.79 (m, 5H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d6) δ, ppm; 22.6, (4C, *CH*$_3$ acetyl), 169.3(4C, C=O) 60.1, 67.2, 70.3 (3C, -*CH*$_2$-O), 69.2, 71.4, 72.6 (4C, -*CH*-OH), 112.4(1C, *O-C*-OH) 98.2, 150.3, 160.4 (3C, C- isoxazole), 120.2, 126.1,128.5,129.2, (6C, C-Ar); EIMs, m/z= 505.9 [M+] 100%, (Calc. for $C_{24}H_{27}N_1O_{11}$, 505.4).

^{1}H-NMR spectrum of compound $[VIII]_c$ 3-(4-bromo phenyl)-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methl}1H-isoxazole showed the following characteristic chemical shifts (DMSO-d_6, ppm): 3.75 (d, 2H, -*CH*$_2$-O), 3.85 (s, 2H, -*CH*$_2$-O), 4.05 (d,1H, -*CH*-O), 4.63 (s, 2H, -*CH*$_2$-O),5.40 (q,1H, -*CH*-O), 5.83(t,1H, -*CH*-O) 6.43 (s, 1H, Ar-H isoxazole), 6.50 -7.83 (m,24H, Ar-H).

^{1}H-NMR spectrum of compound $[IX]_d$ 3-(4-N,N-dimethylamino phenyl)-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole showed the following characteristic chemical shifts (DMSO-d_6, ppm): 3.03 (s, 6H, -*N(CH*$_3$*)*$_2$),3.72 (s, 12H, -*OCH*$_3$), 4.05 (d,1H, -*CH*-O), 4.15 (s, 2H, -*CH*$_2$-O), 4.66 (s, 2H, -*CH*$_2$-O), 5.46 (q,1H, -*CH*-O), 5.72 (t,1H, -*CH*-O), 5.88 (d, 2H, -*CH*$_2$-O), 6.72 (s, 1H, Ar-H isoxazole), 7.17-7.82 (m, 20H, Ar-H).

3.2. Biological activity

Heterocyclic rings and carbohydrate considered an important class of compounds having a wide spectrum of biological activity. The heterocyclic compounds are well known for their antimicrobial activity [18]. Since the synthesized isoxazoles derivatives in this study were built from known biologically active compounds, they were expected to possess biological activity. Therefore, preliminary evaluation of anti-bacterial and antifungal activities for many synthesized compounds was performed.the latter was performed using agar diffusion method [19] on three types of pathological bacteria: the Gram-negative *Escherichia coli* and the Gram-positive *Staphylococcus aureus* and *Bacillus substilis* as well as one type of pathological fungus; *Candida albicans.* These compounds were dissolved in DMSO to give concentration 1ppm. The three types of bacteria were activated in a nutrient growth medium at 37^{0}C for 24h, then examined after 24h and 48h for antifungal activities. The zones of inhibition formed were measured in millimeter and recorded in Table (7).

The results, in general, showed that most of the tested compounds possess biological activities against the four microorganisms studied in current study. All the compounds exhibited high, moderate or low biological activity. This could be related to the types of heterocyclic and chirality of sugar moiety units and active groups in these molecules.

Table 1 Nomenclature, structural formula, molecular formula and physical properties of compounds $[V]_{a-e}$

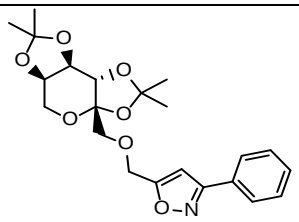
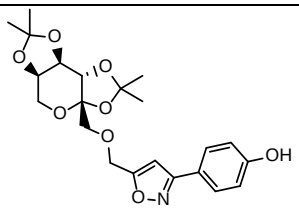
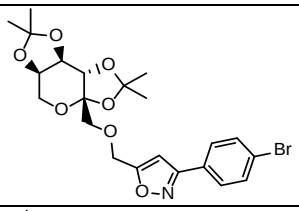
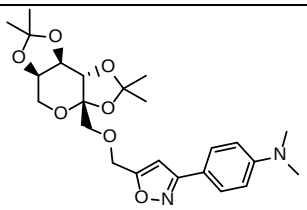
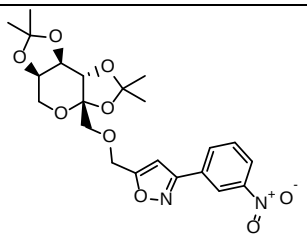
Comp No.	Nomenclature	Structural formula	Molecular formula	M. P ºC	Yield %	color
$[V]_a$	3-phenyl-5-{(2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{22}H_{27}N_1O_7$	Oily	67	Deep yellow oil
$[V]_b$	3-(4-Hydroxyl phenyl)-5-{(2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{22}H_{27}N_1O_8$	Oily	70	Red
$[V]_c$	3-(4-bromo phenyl)-5-{(2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{22}H_{26}N_1O_7Br$	Oily	75	Brown
$[V]_d$	3-(4-N,N-dimethylamino phenyl)-5-{(2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{24}H_{32}N_2O_7$	Oily	63	White
$[V]_e$	3-(3-nitro phenyl)-5-{(2,3,4,5-di-O-isopropylidene-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{22}H_{26}N_2O_9$	Oily	60	Deep Brown

Table 2 Nomenclature, structural formula, molecular formula and physical properties of compounds $[VI]_{a-e}$

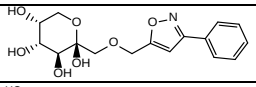
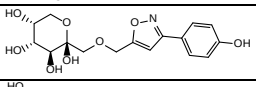
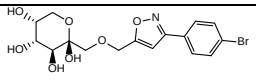
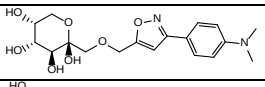
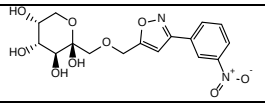
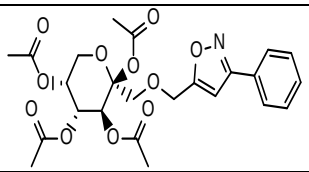
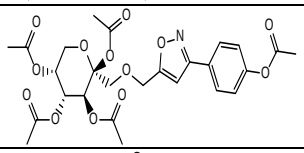
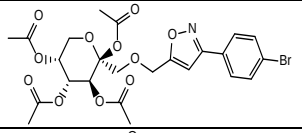
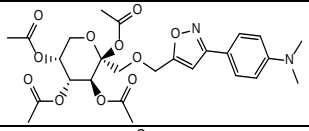
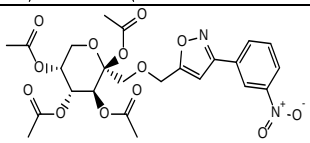
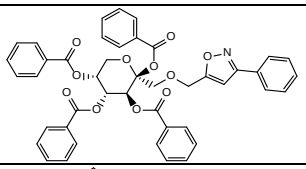
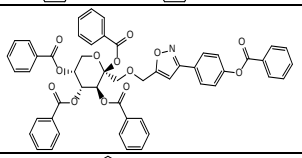
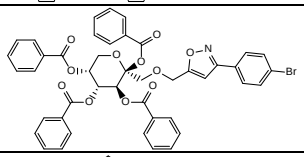
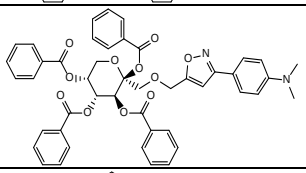
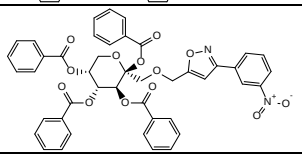
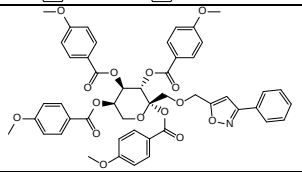
Comp No.	Nomenclature	Structural formula	Molecular formula	M. P ºC	Yield %	color
$[VI]_a$	3- phenyl-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole		$C_{16}H_{19}N_1O_7$	80-82	77	Pale yellow
$[VI]_b$	3-(4-Hydroxyl phenyl)-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole		$C_{16}H_{19}N_1O_8$	140-142	82	Red
$[VI]_c$	3-(4-bromo phenyl)-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole		$C_{16}H_{18}N_1O_7Br$	136-138	80	Brown
$[VI]_d$	3-(4-N,N-dimethylamino phenyl)-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole		$C_{18}H_{24}N_2O_7$	160-162	73	White
$[VI]_e$	3-(3-nitro phenyl)-5-{(beta-D-fructopyranose-O-yl) methyl}1H-isoxazole		$C_{16}H_{18}N_2O_9$	166-168	71	Brown

Table 3 Nomenclature , structural formula, molecular formula and physical properties of ester compounds [VII]a-e, [VIII]a-e and [IX]a-e

Comp No.	Nomenclature	Structural formula	Molecular formula	M. P ºC	Yield %	color
$[VII]_a$	3-phenyl-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{24}H_{27}N_1O_{11}$	158-160	60	Yellow
$[VII]_b$	3-(4-acetyloxy phenyl)-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{26}H_{29}N_1O_{13}$	190-192	65	Brown
$[VII]_c$	3-(4-bromo phenyl)-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{24}H_{26}N_1O_{11}Br$	170-172	67	Pale brown
$[VII]_d$	3-(4-N,N-dimethylamino phenyl)-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{26}H_{32}N_2O_{11}$	181-183	58	Yellow
$[VII]_e$	3-(3-nitro phenyl)-5-{(2,3,4,5-tetra-O-acetyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{24}H_{26}N_2O_{13}$	177-179	61	Deep yellow
$[VIII]_a$	3- phenyl-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{44}H_{35}N_1O_{11}$	161-163	62	Deep yellow
$[VIII]_b$	3-(4-benzoyloxy phenyl)-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{44}H_{27}N_1O_{11}$	197-199	66	Deep pink
$[VIII]_c$	3-(4-bromo phenyl)-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{44}H_{34}N_1O_{11}Br$	176-178	67	Brown
$[VIII]_d$	3-(4-N,N-dimethylamino phenyl)-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{46}H_{40}N_2O_{11}$	189-192	60	Yellow
$[VIII]_e$	3-(3-nitro phenyl)-5-{(2,3,4,5-tetra-O-benzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{44}H_{34}N_2O_{13}$	181-183	62	Yellow
$[IX]_a$	3-phenyl-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{48}H_{27}N_1O_{15}$	165-167	58	Pale yellow

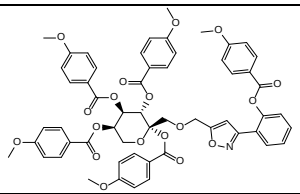
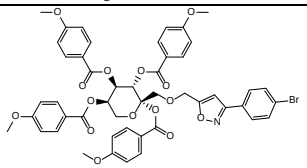
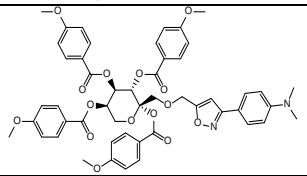
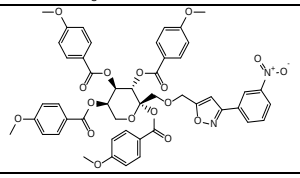
Comp No.	Nomenclature	Structural formula	Molecular formula	M. P °C	Yield %	color
$[IX]_b$	3-(4- methoxybenzoyloxy phenyl)-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose -O-yl)methyl}1H-isoxazole		$C_{56}H_{33}N_1O_{18}$	205-207	60	Red
$[IX]_c$	3-(4-bromo phenyl)-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose -O-yl)methyl}1H-isoxazole		$C_{48}H_{26}N_1O_{15}Br$	199-201	57	Brown
$[IX]_d$	3-(4-N,N-dimethylamino phenyl)-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{50}H_{32}N_2O_{15}$	211-213	59	Pale yellow
$[IX]_e$	3-(3-nitro phenyl)-5-{(2,3,4,5-tetra-O-para methoxybenzoyl-beta-D-fructopyranose-O-yl)methyl}1H-isoxazole		$C_{48}H_{26}N_2O_{17}$	200-202	55	Yellow

Table 4 Characteristic FTIR spectral data of compounds $[V]_{a-e}$

Comp. No.	υ(C-H) aromatic cm^{-1}	υ(C-H) Aliphatic cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	Others bands cm^{-1}
$[V]_a$	3034	2974,2933	1647	1606	υ(C-O) 1240,1068
$[V]_b$	3066	2991,2937	1647	1593	υ(OH) 3229 υ(C-O) 1248,1072
$[V]_c$	3042	2999,2962	1657	1585	υ(C-O) 1269,1072 υ(C-Br) 713
$[V]_d$	3038	2983,2893	1633	1577	υ $N(Me)_2$ 1301,1157 υ(C-O) 1240**,**1074
$[V]_e$	3037	2980,2927	1641	1560	υ(NO_2)1517, 1361 υ(C-O) 1256,1074

Table 5 Characteristic FTIR spectral data of compounds $[VI]_{a-e}$

Comp. No.	υ(OH) cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(C-H) Aliphatic cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	Others bands cm^{-1}
$[VI]_a$	3280	3061	2983,2893	1631	1577	υ(C-O) 1209,1074
$[VI]_b$	3259	3060	2987,2933	1624	1570	υ(C-O) 1211,1070
$[VI]_c$	3379	3061	2987,2935	1622	1555	υ(C-Br) 720 υ(C-O) 1212,1070
$[VI]_d$	3354	3062	2987,2931	1664	1577	υ $N(Me)_2$ 1331,1165 υ(C-O) 1214,1071
$[VI]_e$	3290	3068	2968,2905	1649	1580	υ(NO_2) 1531, 1348 υ(C-O) 1215,1076

Table 6 Characteristic FTIR spectral data of ester compounds $[VII]_{a-e}$, $[VIII]_{a-e}$ and [IX]a-e

Comp. No.	υ(C-H) aromatic cm^{-1}	υ(C-H) Aliphatic cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	Others bands cm^{-1}
$[VII]_a$	3093	2997, 2945	1738	1614	1585	υ(C-O) 1265 ,1070
$[VII]_b$	3057	2983, 2916	1735	1641	1539	υ(C-O) 1251,1066
$[VII]_c$	3095	2999, 2962	1734	1641	1585	υ(C-Br) 713 υ(C-O) 1267,1070
$[VII]_d$	3035	2971, 2845	1736	1661	1579	υ $N(Me)_2$ 1319,1157 υ(C-O) 1263,1045
$[VII]_e$	3003	2966, 2936	1735	1645	1579	υ(NO_2) 1533, 1348 υ(C-O) 1260,1076
$[VIII]_a$	3093	2960, 2861	1712	1660	1581	υ(C-O) 12651072
$[VIII]_b$	3091	2941, 2833	1712	1678	1587	υ(C-O) 1253,1067
$[VIII]_c$	3066	2987, 2936	1714	1674	1585	υ(C-Br) 717 υ(C-O) 1263,1068
$[VIII]_d$	3074	2983, 2895	1712	1649	1581	υ $N(Me)_2$ 1311,1153 υ(C-O) 1257,1068
$[VIII]_e$	3064	2983, 2872	1714	1679	1599	υ(NO_2) 1521, 1359 υ(C-O) 1257,1066
$[IX]_a$	3089	2981, 2933	1724	1678	1587	υ(C-O) 1263,1070
$[IX]_b$	3089	2983, 2935	1726	1676	1585	υ(C-O) 1249,1066
$[IX]_c$	3093	2960, 2837	1730	1678	1591	υ(C-Br) 713 υ(C-O) 1238,1069
$[IX]_d$	3091	2992, 2956	1721	1680	1557	υ $N(Me)_2$ 1319,1168 υ(C-O) 1265,1074
$[IX]_e$	3074	2983, 2881	1727	1686	1583	υ(NO_2) 1539, 1371 υ(C-O) 1259,1068

Table 7 Antimicrobial activities of compounds $[V]_{a-e}$, $[VI]_{a-e}$,$[VII]_{a-e}$, $[VIII]_{a-e}$ and $[IX]_{a-e}$

Compound	*E. coli*	*S. aureus*	*substils B.*	*C. albicans*
DMSO	Nil	Nil	Nil	Nil
$[V]_a$	30	30	25	0
$[V]_b$	19	22	20	4
$[V]_c$	15	34	20	12
$[V]_d$	0	14	12	0
$[V]_e$	21	27	21	8
$[VI]_a$	20	25	18	0
$[VI]_b$	19	32	10	6
$[VI]_c$	24	30	22	12
$[VI]_d$	20	15	16	0
$[VI]_e$	22	30	20	14
$[VII]_a$	20	25	28	4
$[VII]_b$	28	22	25	8
$[VII]_c$	9	19	8	6
$[VII]_d$	16	15	12	4
$[VII]_e$	28	32	26	16
$[VIII]_a$	28	30	24	15
$[VIII]_b$	20	28	19	13
$[VIII]_c$	22	28	20	10
$[VIII]_d$	21	15	10	0
$[VIII]_e$	29	24	18	7
$[IX]_a$	30	26	22	15
$[IX]_b$	32	30	20	16
$[IX]_c$	26	22	20	12
$[IX]_d$	25	20	20	4
$[IX]_e$	28	22	25	20

Note: Data in the table represent zones of bacterial growth inhibition in millimeters.

Ethical Clearance: The study was approved by the Scientific Research Committee at College of Education for Pure Science (Ibn-Al-Haitham)/ University of Baghdad, Iraq.

Financial Disclosure: There is no financial disclosure.

Conflict of Interest: None to declare.

REFERENCES

1- Hyvonen L. and Koivistoinen P. *"Fructose in Food Systems". In Birch, G.G. & Parker, K.J. Nutritive Sweeteners.* London & New Jersey: Applied Science Publishers. 1982; 133–144.
2- Mulderrig K. Placebo evaluation of selected sugarbased excipients: in pharmaceutical and nutraceutical tableting. Pharm Technol. 2000; 24: 34-44.
3- Date PV, Samad A, Devarajan PV. Freeze thaw: A simple approach for prediction of optimal cryoprotectant for freeze drying. AAPS Pharmscitech. 2010; 11: 304-313.
4- Toegel S, Salar-Behzadi S, Horaczek-Clausen A, Viernstein H. Preservation of aerial conidia and biomasses from entomopathogenic fungi *Beauveria brongniartii* and *Metarhizium anisopliae* during lyophilization. J Invertebr Pathol. 2010; 05: 16-23.
5- Schmidt E, Dooley N, Ford SJ, Elliott M, Halbert GW. Physicochemical investigation of the influence of saccharide-based parenteral formulation excipients onL-*p*boronphenylalanine solubilisation for boron neutron capture therapy. J Pharm Sci. 2011; 101: 223-232.
6- Mallard C, Coudane J, Rault I, Vert M. In vitro delivery of a sparingly water soluble compound fromnPLA50 microparticles. J Microencapsul. 2000; 17: 13-28.
7- Evans R, Nawrocki D, Isopi L. Development of stable liquid formulations for adenovirus-based vaccines. J Pharm Sci. 2004; 93: 2458-2475.
8- Pinho e Melo, T. M. V. D,. Curr. Org. Chem. 2005; 9: 925.
9- Taylor RD, MacCoss M, Lawson ADG. J Med Chem. 2014; 57: 5845.
10- Comprehensive Heterocyclic Chemistry III; Giomi, D., Cordero FM, Machetti F, Eds; Elsevier: Oxford, 2008; p 365.
11- K. N. Tu, J. J. Hirner, S. A. Blum, Org,. Lett., 2016, 18, 480-483.
12- Himo F, Lovell T, Hilgraf R, Rostovtsev VV, Noodleman L, Sharpless KB, Fokin VV. J Am Chem Soc. 2005; 127: 210-216.
13- Watterson SH, Guo J, Spergel SH, Langevine CM, Moquin RV, Shen DR, Yarde M, Cvijic ME, Banas D, Liu R, Suchard SJ, Gillooly K, Taylor T, RexRabe S, Shuster DJ, McIntyre KW, Cornelius G, D'Arienzo C, Marino A, Balimane P, Saltercid L, McKinnon M, Barrish JC, Carter PH, Pitts WJ, Xie J. and Dyckman AJ, Potent, J. Med Chem. 2016; 59: 2820-2840.
14- Ravi Kumar P, Behera M, Sambaiah M, Kandula V, Payili N, Shree AJ. and Yennam S. ,Hindawi Publishing Corporation Journal of Amino Acids. 2014. Article ID 721291, 14 pages.
15- McIntosh ML, Naffziger MR, Ashburn BO, Zakharov LN. and Carter RG. ,Org Biomol Chem. 2012; 10: 9204.
16- A.I.Mohammed, N.H. Mansoor and J.H. Mohammed ,J.Kerbala of Pharmaceutical Sciences.2013, N.6
17- F.Heaney ,European. J Org Chem. 2012; 3043-3058.
18- V. kumar, P. Prasanthi, K. Muni, K. Kumar, R. Makesh, P. Nishanthi, M. Nagendramma and M. Nishanthi, Int J Med Chem Anal. 2013; 3(1): 10-21.
19- Macfaddin J. "Biochemical test for the identification of medical bacteria", 3rd Ed. William and Wilkins. Baltimor, USA, 2000; 175.