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Synthesis of N-glycosides Analogues Containing Thiouracil Unite and Evaluated as Antibacterial, Antifungal and Antioxidant Active

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Abstract

New N-glycosides contain thiouracil derivatives were produced, and their antioxidant actions were determined. The N- glycosides were obtained by the reaction of azido sugar with croton or cinam aldehyde get in 1,3cycloaddition reaction to give the triazoline derivatives. Triazoline derivatives condensation with thiourea or phenyl thiourea and ethylcyano acetate in present potassium carbonate.

Keyword: N-glycosides, Thiouracil, Crotonaldehyde, Cinamaldehyde, Triazoline

Introduction

A number of N – glycoside derivatives appealed to posses stimulating bioactivity such as antibacteriale, antifungal(El Malah, Nour, Satti, Hemdan, & El-Sayed, 2020), anticonvulsant(Zhu et al., 2014), antiinflammatory(Cheng et al., 2020), anti-malarial(Murakami et al., 2001), analgesic(Khan et al., 2020), antioxidant, antiplatelets(Ansari, Arif, Hussain, Siddiqui, & Dixit, 2016), antituberculosis (Sharipova et al., 2011) and anticancer (Khan, Saeedi, Nabavi, Mubarak, & Bishayee, 2019) activities. N-glycoside containing hetero ring such as 1,2,3-triazole and pyrimidine ring have attracted special consideration. Oxazole and thiazole heterocycles of medicinal and biological attention are found naturally, which display antimycobacterial(Ashok et al., 2018; Goud et al., 2017; Pogaku et al., 2019), anticancer(Huang et al., 2019; Khan et al., 2020),antitubercular (Ruddarraju et al., 2017), antidiabetic(Avula et al., 2018; Ferreira et al., 2010), antiviral (Głowacka, Andrei, Schols, Snoeck, & Piotrowska, 2015; Khalil et al., 2017; Saeedi et al., 2019), antifungal (Kaushik et al., 2019), anti-inflammatory (Naaz et al., 2018), anti-HIV (Raj et al., 2013), anti- oxidant (Singh, Gangrade, Jana, Mandal, & Das, 2019), antimalarial, anti-proliferative (Sommer et al., 2019) properties. The intriguing biological activity of oxazoles and thiazole, together with their favorable pharmacokinetic profiles, has led to their use in a variety of therapeutic agents, including antibacterial, sulfonamide, and sulfamoxol (Zhou et al., 2019). As a result, incorporating these heterocycles into conformationally restrained bicyclic nucleosides is of interest.

Instruments and Chemicals:

Instruments:

- Melting points were noted by using hot stage Gallen Kamp melting point device and were un corrected, England.
- FTIR spectra were noted using (FTIR) spectrometer, Japan, KBr disc in the 4000-600 cm-1 spectral range was performed by Baghdad University.
- 1H-NMR,13C-NMR noted on magnetic resonance in the vicinity Bruker, Ultrasheild 300 MHz in mashahd, using tetramethyl saline as standard and DMSO as a solvent.
- Thin layer chromatography was approved available using Fertig follen recoated pieces type polygramSilg, and the plates were advanced with iodine vapor.

Experimental

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Preparation of 2,3,4-Tri -O-acetyl - β-L arabino and β-D-xylo pyranosyl bromides [1 or 2].

D-Xylose or L- Arabinose (2g, 0.013mol) and (1.6g, 0.019mol) of anhydrase sodium acetate were refluxed with (12ml) acetic anhydride in (60-65C^{o}) for(3h). TLC [$CHCl_3$: ethyl acetate; 8:2] indicated that the reaction was finished. The mixture was poured on ice water, then extracted with $CHCl_3$ and evaporated to dryness under vacuo to give a brown syrup (tetra acetyl xylo or arabinopyranose) as inetmidete compound. (tri acetyl xylo or arabinopyranose) dissolve in (5 ml) of glacial acetic acid, Hydrogen bromide (3 ml) (45%) was added in ice bath, the mixture was stirred for (6 h) at 25C^{o}, then the mixture left-hand 24h at 5˚C, after that mixture was neutralized with (2g $NaHCO_3$) in 20ml distal water. Extracted with dichloromethane, dried with anhydrous sodium sulphate to give a brown syrup compound **(1,** 65% yield, Rf = 0.62), (**2**, 67 % yield, Rf= 0.6).

Preparation of 2,3,4-Tri -O-acetyl -1-azido-1- deoxy- β-D-xylo-and β-L arabinopyranose [3 or 4].

A mixture of Compound (1 or 2) (1 g, 1.48 mmol) and sodium azide (1.5m mole) in DMF (20 mL). The mixture was reflux for 24 h. The reaction was checked by TLC [Benzene: MeOH; 8:2]. Mixture was poured onto ice cold water and extracted with chloroform (3&15 mL), thendried with Na_2SO_4, and evaporated solvent to give a syrup compound **(3,** 82 % yield, brown syrup), (**4**, 78 % yield, brown syrup).

Preparation of 1-(2,3,4-tri-O-acetyl – β-D-xylo-and β-L arabinopyranose)-1H-1,2,3-triazoles derivatives [5-8].

P Zinc chloride was applied to a mixture of azido sugar [3 or 4] (0,022mol.) and croton or cinam aldehyde (0,022mol.) in dioxin (20ml). For 20 hours, the mixture was stirred. TLC [Benzene:MeOH; 8:2] was used to regulate the reaction. The reaction mixture was poured into ice cold water, chloroform (3&15 mL) removed, and anhydrous sodium sulphate dried. To make a syrup, the solvent was evaporated. Physical properties for compounds [5-8] are listed in Table (1).

Table (1): physical properties for compounds [5-8]

No.	***Formula***	***M.Wt (g/mol.)***	***Yield (%)***	***Color***	***Rf***
5	$C_{15}H_{21}N_3O_8$	371	65	Brown	0.38
6	$C_{20}H_{23}N_3O_8$	433	72	Brown	0.32
7	$C_{15}H_{21}N_3O_8$	371	60	Pall orange	-
8	$C_{20}H_{23}N_3O_8$	433	66	Brown	-

1-(2,3,4-tri-O-acetyl – β-D-xylo-and β-L arabinopyranose)-1H-1,2,3-triazole 4- thiouracil derivatives [9-16].

In absolute ethanol (30 mL), a mixture of the proper compounds [5-8] (0.01 mol), ethyl, cyanoacetate (0.01,mol), thiourea. or phenyl thiourea, (0.01 mol), and potassium carbonate (0.01 mol) was refluxed for 30 minutes (18 h). The obtained substance was applied to 20 mL of water, which was then acidified with acetic acid. The precipitate was filtered and washed in cold water. Physical properties for compounds [9-16] are listed in Table (2).

Table (2): physical properties for compounds [9-17]

No.	**Formula**	**M.Wt (g/mol.)**	**m.p (C^{o})**	**Color**	**Yield (%)**	**Rf**
9	$C_{19}H_{22}N_6O_8S$	494	Oil	Brown	53	0.34
10	$C_{25}H_{26}N_6O_8S$	570	Oil	Brown	42	-
11	$C_{24}H_{24}N_6O_8S$	556	Oil	brown	52	-
12	$C_{30}H_{28}N_6O_8S$	632	Oil	Brown	48	-
13	$C_{19}H_{22}N_6O_8S$	494	Oil	Yellow	51	-
14	$C_{25}H_{26}N_6O_8S$	570	Oil	Red	46	-
15	$C_{24}H_{24}N_6O_8S$	556	Oil	Brown	53	-
16	$C_{30}H_{28}N_6O_8S$	632	Oil	Brown	48	-

Hydrolysis of glycoside analogues [17-24].

A solution of (0.001 mole) of the blocked glycoside [9-16] was refluxed with stirring in (7 ml) of (0.1 M) methanolic sodium methoxide. The mixture was neutralized with acetic acid after 0.5 hours refluxed. The reaction mixture was poured into ice water, extracted with chloroform (3 *15 ml), dried with anhydrous sodium sulphate, filtered, and

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evaporated in vacuum. The residue was recrystallized from ether to afford the free glycoside. physical properties for compounds [17-24] are listed in Table (3).

Table (3): physical properties for compounds [17-24]

No.	Formula	Structure	M.Wt (g/mol.)	m.p (C^o)	Color	Yield (%)	Rf
17	C13H16N6O5S		368	187-188	Off white	61	-
18	C19H20N6O5S		444	Oil	Brown	56	-
19	C18H18N6O5S		430	Oil	Brown	49	-
20	C24H22N6O5S		506	Oil	Brown	61	-
21	$C_{13}H_{16}N_6O_5S$		368	164-165	Pall yellow	58	-
22	$C_{19}H_{20}N_6O_5S$		444	190-191	Brown	61	-
23	$C_{18}H_{18}N_6O_5S$		430	182-184	Brown	63	-
24	$C_{24}H_{22}N_6O_5S$		506	Oil	Brown	62	-

DPPH Based, Free, Radical, Scavenging. Activity

Since then. DPPH is a stable free radical with an unusual electron in its structure that is commonly used to detect radical scavenging. Aliquots of the test sample at various concentrations (25,50, and 100 g/mL) are applied to a 100 mL DPPH (4 mg/100 mL methanol) solution. After 30 minutes, the absorbance at 517 nm is calculated.

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$$\% \text{ inhibition of DPPH radical} = \frac{\text{Abs. of control} - \text{Abs. of sample}}{\text{Abs. of control}} \times 100$$

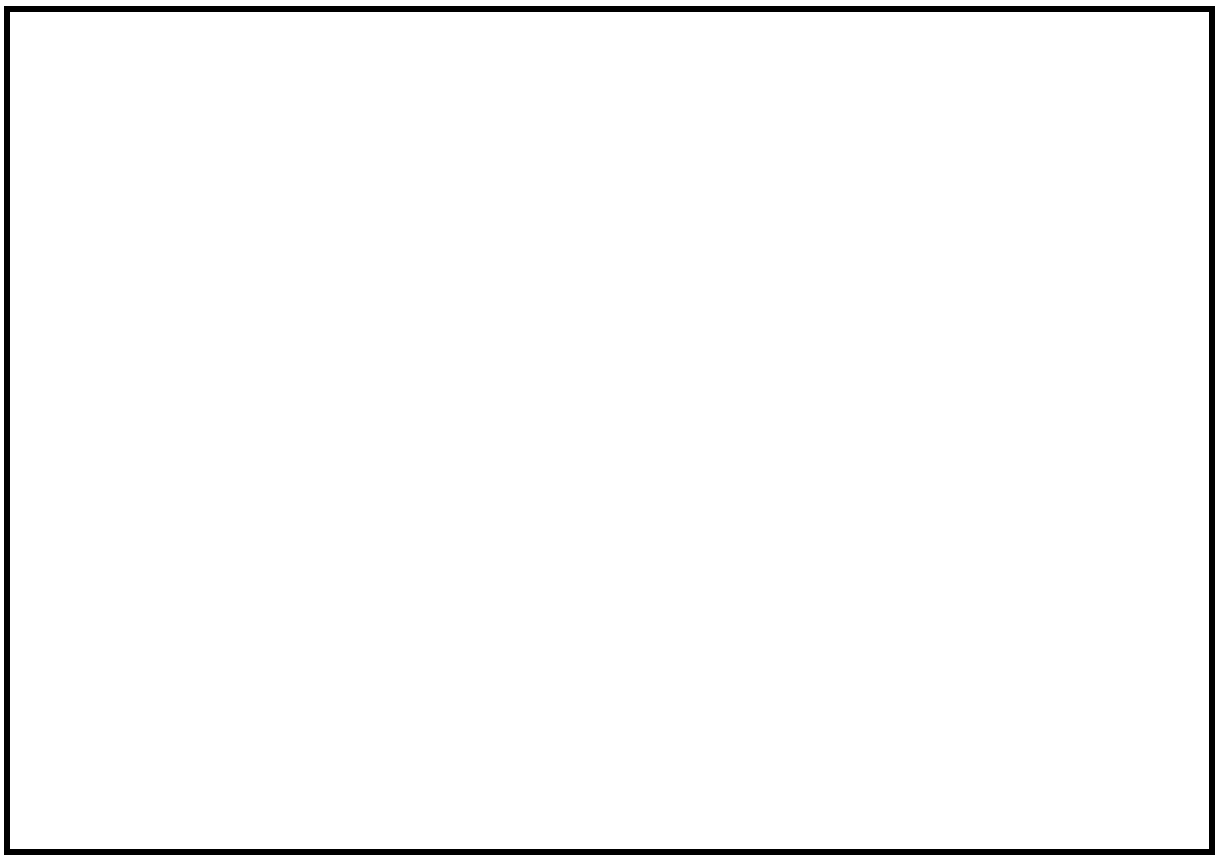
bacteriostatic and antifungal properties:

Some prepared compounds were examined for their in vitro growth inhibitory activity against Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Klebsiella pneumoniae bacteria and macrosporium fungi using the cup plate system with nutrient agar medium and dimethyl sulfoxide (DMSO) as the solvent. The research species were cultured in nutrient broth and incubated at 37°C for 24 hours before being spread onto "Nutrient Agar," while fungal spores were spread onto Potato Dextrose, Agar in a laminal, flow cabinet. The compounds were prepared by dissolving them in dimethyl sulfoxide and then adding (0.1 mL) of each compound at a known concentration was applied to the cups, and the Petri dishes were then incubated for 24 and/or 48 hours at 37°C. Every compound's inhibition zone was measured in (mm).

Result and discussion

Present work has been directed toward syntheses of N- glycosides analogues with modified of sugar moiety as azido protected sugar [3, 4].

azido sugar reacted with croton aldehyde or cinam aldehyde via 1,3-dipolar cycloaddition reaction [5-8]. condensation of compounds [5-8] via one-pot with thiourea or phenyl thiourea and ethyl cyanoacetate in basic condition to give compounds[9-16].which gives after hydrolysis in basic medium (MeOH/MeONa), our synthetic goal the free N-glycosides analogues. The reaction series are outlined in Schemes 1.



Scheme 1

D-Xylose and L- arabinose were first converted to 1,2,3, 4-tetra- O- acetyl- β- D- xylopyranose and 1,2,3,4-tetra- O-acetyl- β- L- arabinopyranose. then treated, with 45% HBr solution in glacial acetic acid it gave 2,3,4- tri-O-acetyl -β-D-xylopyranosyl bromide [1] and 2,3,4-tri - O- acetyl- β- L- arabinopyranosyl bromide [2]. The FTIR spectrum of [1,2] showed stretching band at 642, 684 cm−1 of the (C-Br). The acetylated bromide compounds [1,2] were treated with

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sodium azide to produce azidosugar [3,4]. The stretching band at 2102, 2289 cm-1 on the FTIR spectrum of [3,4] indicated the existence of an azido group with the absence of the (C-Br) stretching band at 642, 684 cm-1, indicating the presence of an azido group. The azidosugar [3,4] arrived 1,3- cycloaddition reaction with crotonalde was used to make the 1,2,3-triazoline derivatives [5-8] as indicated by showed stretching band at (1818-1843) cm-1 of (C=O al) and disappearance of (N3) vibration band. Condensation aldehyde with thiourea or phenylthiourea to give thiouracil derivatives [9-16]. The FTIR spectrum of compounds [9-16] showed a characteristic range band at (3103-3220) cm−1 of (NH), characteristic range band at (2189-2262) cm−1 of (CN) , characteristic range band at(1720-1743) cm−1 of (C=O amides) and disappearance of (C=O al) vibration band. Treatment of the compounds [9-16] with catalytic amount of sodium methoxide in methanol under reflux afforded the free N-glycoside derivatives [17-24]. The IR spectrum showed stretching range band at (3280- 3424) cm−1 for hydroxy groups. Compound [17]; ^{1}H NMR (DMSO-d6): 1.08 (d, 3H, C$\underline{H}_3$), 2.05,2.53 (d, 2H, C$\underline{H}$ triazoline ring), 3.46-3.76 (d,4H, C$\underline{H}$ sugar), 4.51-4.68(s,4H, O$\underline{H}$ sugar), 7.68, 13.14(s,2H, N$\underline{H}$). ^{13}C NMR: 62.74, 68.23 (C triazoline ring), 115.85 (CN), 162.64(C=O), 175.12 (C=S).

Compound [18]; ^{1}H NMR (DMSO-d6): 1.30 (d, 3H, C$\underline{H}_3$), 2.52,2.53 (d, 2H, C$\underline{H}$ triazoline ring), 3.75- 3.93 (d,4H, C$\underline{H}$ sugar), 4.43-47 (s,4H, O$\underline{H}$ sugar), 7.26-7.46 (m, 5H, Ar H) 8.45 (s,1H, N$\underline{H}$). ^{13}C NMR: 62.98, 65.14 (C triazoline ring), 115.43 (CN), 128.15-128.98(C Ar), 163.87 (C=O), 166.78, 176.40 (C=S).

Compound [23]; ^{1}H NMR (DMSO-d6): 2.05,2.53 (d, 2H, C$\underline{H}$ triazoline ring), 3.30-3.58 (d,4H, C$\underline{H}$ sugar), 4.45-4.78 (s,4H, O$\underline{H}$ sugar), 7.28-8.03 (m, 5H, Ar H), 10.25 (s,1H, N$\underline{H}$). ^{13}C NMR: 64.36, 64.67 (C triazoline ring), 115.82 (CN), 166.58 (C=O), 166.78, 178.39 (C=S).

Compound [24]; ^{1}H NMR (DMSO-d6): 3.50, 3.53 (d, 2H, C$\underline{H}$ triazoline ring), 3.55-3.75 (d,4H, C$\underline{H}$ sugar), 4.42-4.52 (s,4H, O$\underline{H}$ sugar), 7.43-7.68 (m, 10H, Ar H), 8.26 (s,1H, N$\underline{H}$). ^{13}C NMR: 60.16, 66.55 (C triazoline ring), 117.62 (CN), 164.11 (C=O), 166.78, 179.09 (C=S).

Antioxidant Activity

The (DPPH) method has been commonly used to assess the free radical scavenging ability of various antioxidants, including N-glycoside. The absorbance decreased when the color changed from purple to yellow as a result of the color change. An antioxidant scavenges DPPH by donating hydrogen, resulting in the formation of a stable. The DPPH molecule had an absorbance when it was in its radical form. at a wavelength of 517 nm, which vanished after an electron, or hydrogen, radical from an antioxidant compound was accepted, resulting in the reduced. DPPH-R is an abbreviation for diphenyl phosphate Some synthesized

compounds[17,20 and23] have antioxidant properties are reported in **figure 4,5 and 6**. Compound A12 shown scavenged 100% Equated with the ascorbic acid.

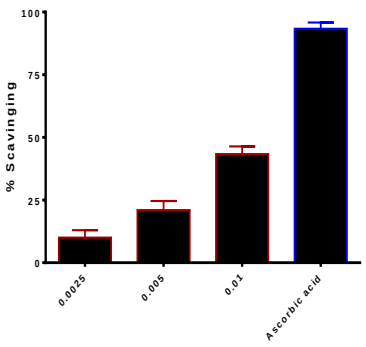

Figure 4: Antioxidant activity of compound 17 using DPPH

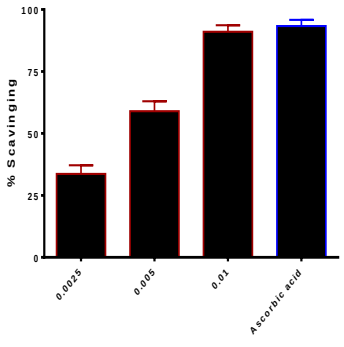

Figure 5: Antioxidant activity of compound 20 using DPPH

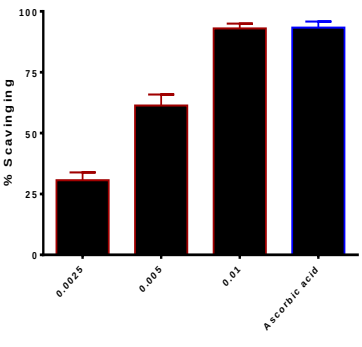

Figure 6: Antioxidant activity of compound 23 using DPPH

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Antibacterial and antifungal screening of synthetic compounds in vitro.

Antibacterial activity of some of our synthesized compounds N- glycoside was tested against four test organisms: Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Klebsiella pneumoniae bacteria and against macrosporium fungi, propylthiouracil using as standard drugs. The possible activities of these compounds were investigated using the agar well-diffusion process. Compound [17] shown inhibition zones (10- 15) mm when determined with Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia bacteria and against macrosporium fungi, while showed inhibition zones (17 ,18) mm when determined with Escherichia coli, Bacillus subtilis respectively. Compounds 19 showed inhibition zones > 15 mm when determined with Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumonia bacteria and against macrosporium fungi, inhibition zones zero when determined with Pseudomonas aeruginosa. Compounds 22 showed inhibition zones > 15 mm when determined with Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia bacteria, while showed inhibition zones (20 ,23) mm when determined with Bacillus subtilis bacteria and against macrosporium fungi respectively. All result listed in table 3.

Table 3. Antimicrobial activity of some synthesized compounds
Inhibition zone diameter (mm)

No.	inhibition zones of bacteria					inhibition zones of fungi
	Escherichia coli	**Pseudomonas aeruginosa**	**Staphylococcus aureu**	**Klebsiella pneumonia**	**Bacillus subtilis**	**macrosporium**
17	17	12	13	12	18	11
19	13	-ve	13	11	14	11
22	13	12	15	13	20	23
Propyl thiouracil	12	9	12	12	11	9

-ve = No inhibition.

DMSO shows no activity.

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