An Efficient Procedure of Synthesis Acyclic C-Glycosides of Thiazolo [4, 5-b]Pyrazine and Imidazo[4,5-d]Thiazole with Expected Anti-Cancer Activities

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\textbf{ABSTRACT}

In this research, we aimed to synthesize a new series of C-glycosides that have thiazole-4, 5-diamine base. C-glycosides \textsuperscript{8} was prepared by coupling compound \textsuperscript{7} with D-glucose in the presence of iodine used as an oxidant/promoter dissolved in acetic acid and stirring at room temperature. Compound \textsuperscript{8} was protected by reaction with acetic anhydride in the presence of pyridine gave compound \textsuperscript{9}. Furthermore, cyclization compound \textsuperscript{7} with hydrazine hydrate and D-glucose gave the cyclic glycosides analogs \textsuperscript{10}. The compound \textsuperscript{7} was condensed with phenyl hydrazine hydrochloride and D-xylose gave C-glycoside \textsuperscript{11}. The anticancer activity of the newly synthesized compounds was tested in vitro for their anticancer activities against human colorectal carcinoma (HCT-116), human prostate adenocarcinoma (PC-3), and human liver hepatocellular carcinoma (HepG-2) cell lines.

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C-glycoside; D-glucose; oxidant; phenyl hydrazine; thiazole-4,5-diamine and anti-cancer activity

\textbf{Introduction}

The chemistry of thiazole derivatives has a wide range of medicinal and biological properties such as anti-HIV activities\textsuperscript{1}, antiviral\textsuperscript{2}, antimalarial\textsuperscript{3}, neuropeptides\textsuperscript{4}, Y5 adenosine receptors\textsuperscript{5} and used as a new bacterial DNA gyrase B inhibitors\textsuperscript{6} and for this reason it has been given an attention. Imidazole is one of the heterocyclic compounds as it has great importance in pharmaceutical chemistry and plays an important role in many diseases spread around the world\textsuperscript{7,8}. C-glycosides considered as a branch of glycosides heterocyclic compounds where, the anomeric carbon linkage to the heterocyclic by a carbon–carbon bond, which C-glycosides have powerful tools for biochemical or antifungal investigations\textsuperscript{9,10} and showed activity against HCV replication\textsuperscript{11,12} Al-Masoudi et al.\textsuperscript{13} synthesized a model of acyclic C-glycosides such as (A and B). A series of C-glycosides synthesized from different heterocyclic compounds used as pharmacological activities\textsuperscript{14} such as (C and D) in \textbf{Figure 1}. In this communication, the research relates to the synthesis of several C-linked different sugars. We explored a route to the synthesis of a new glycoside system including an imidazo[4,5-d]thiazole glycoside, and thiazolo[4,5-b]pyrazine glycoside using thiazole-4, 5-diamine derivatives \textsuperscript{7} as the starting material. The anticancer activities of new synthetics compounds were evaluated with determining IC\textsubscript{50} of them against the human liver hepatocellular
carcinoma (HepG-2), human prostate adenocarcinoma (PC-3), and human colorectal carcinoma (HCT-116) cancer cell lines.

Results and dissection

Reactions step to thiazole-4, 5-diamine derivatives 7 was reported in the literature\textsuperscript{16–18} and employed 2, 3-diaminomaleonitrile instead of tricyanovinylamine as start material following the Scheme 1. Compound 3 was reacted with thionyl chloride afforded imidoyl chloride derivative 4. Imidoyl chloride 4 was reacted with potassium isothiocyanate yielded intermediate 5 which was reacted with aniline to give thiourea derivatives 6. Compound 6 was cyclized with 2, 3-diaminomaleonitrile to obtain the corresponding thiazole derivatives 7 as in Scheme 1. Compound 7 was determined by IR spectrum which showed two absorption peaks at 3235–3124 cm\textsuperscript{-1} represented 2NH\textsubscript{2} group and disappearance absorption peak at 1373 cm\textsuperscript{-1} for (C\textsubscript{¼} S) of compound 6 which, considered as starting material. \textsuperscript{1}H-NMR spectra of thiazole-4, 5-diamine derivatives 7 showed a signal represents as a broad singlet due to 2NH\textsubscript{2} at 8.79 and 8.59 ppm. The reaction mechanism of 2,3-dihydro-2-phenylimino-3-(1-(phenylimino)propyl]thiazole-4,5-diamine 7 is proposed in Figure 2.

Thus, thiazole-4, 5-diamine derivatives 7 was treated with D-glucose (1:1 equiv.) in stoichiometric amounts of iodine used as the oxidizing agent\textsuperscript{19,20} in the presence of acetic acid at room temperature for 9 h, to give C-glycoside imidazo[4,5-d]thiazole derivative 8 in 89% yield (Scheme 2). The reaction determined by TLC and analysis spectrum, IR spectra of compound 8 appearance absorption peak represents a free hydroxyl group of sugar at 3419. \textsuperscript{1}H NMR spectra demonstrated the signal as a singlet due to NH at δ 10.32 ppm and appearance of the signal characteristic sugar chain to hydroxyl group and other protons of the sugar moiety. Acetylating of C-glycoside 8 by reaction with acetic anhydride in the presence of pyridine under refluxing for 3 h, yielded protected glycosides 9. The IR spectrum of compound 9 showed absorption bands at 1733 cm\textsuperscript{-1} corresponding to (C\textsubscript{¼} O) group. The glycosyl moiety of compound 9 was confirmed also by \textsuperscript{1}H NMR spectrum which showed a single as the singlet at δ 2.02 ppm attributed to CH\textsubscript{3} of acetyl group.
Scheme 1. Synthesis of compound 7.

Figure 2. Plausible mechanism of compound 7.
The reaction mechanism of compound 8 was shown in Figure 3.

On the other hand, the reaction of thiazole derivatives 7 with hydrazine hydrate and D-glucose in the presence of acetic acid in water at 100°C the reaction takes place through the formation of glucose hydrazone intermediate to produce the corresponding acyclic analogs C-glycoside derivatives 10 (Scheme 3). The IR spectrum of compound 10 revealed the presence of absorption bands at 3436 cm⁻¹ characteristic (OH) group. Also, ¹H NMR spectrum showed a signal as the singlet at 8.74 ppm represented C–H of pyrazine ring. The reaction mechanism of 10 is proposed in Figure 4.

Compound 11 was synthesized by one-pot step where D-xylose condensation with compound 7 in the presence of excess from phenylhydrazine hydrochloride in acidic medium heating at 100°C the reaction takes place through the formation of glucose phenylhydrazone intermediate gave the corresponding acyclic analogs C-glycoside derivatives 11. IR spectrum of compound 11 showed disappearance absorption peak at at 3235–3124 cm⁻¹ of 2NH₂ and found absorption peak at 3428 cm⁻¹ due to (OH) group. ¹H NMR and ¹³C NMR spectra confirmed the structure of 11 (c.f. Scheme 4 and experimental part).

**Anti-cancer activity**

The new synthesized compounds were tested *in vitro* for their anticancer activities against human colorectal carcinoma (HCT-116), human prostate adenocarcinoma (PC-3), and human liver hepatocellular carcinoma (HepG-2) cell lines using 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) cytotoxicity assay. Then the anticancer activity of the compounds was monitored by percent (%) of inhibition of cell viability as well as calculating IC₅₀ of these compounds. The IC₅₀ values of examined compounds appear in Table 1. The percent of inhibition of cancer cells viability by the studied synthetic compounds at highest concentration (50 µg) were compared to well-known anticancer (doxorubicin) (Figure 5).
The IC50 values are the concentration that inhibit cell viability to 50% of the control cells. IC50 values of examined compounds appear in Table 1. The IC50 values after 48 h of incubation with HCT-116 were 119, 94, 91, and 106 nM for the compounds 8th, 9th, 10th, and 11th, respectively. These values were lower than the IC50 obtained for the well-established anticancer drug doxorubicin (126 nM). Therefore, these compounds have better IC50 than doxorubicin against HCT-116 cell line.

For PC-3 cell line, compounds 10th (119 nM) and 11th (111 nM) have lower IC50 than doxorubicin (129 nM), indicating better IC50 comparing to doxorubicin. For HepG-2 cell line, all

Figure 3. Reaction mechanism of compound 8.

Scheme 3. Synthesis of compound 10.

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For PC-3 cell line, compounds 10th (119 nM) and 11th (111 nM) have lower IC50 than doxorubicin (129 nM), indicating better IC50 comparing to doxorubicin. For HepG-2 cell line, all
studied compounds show higher IC$_{50}$ comparing to doxorubicin, indicating that doxorubicin has more potent anticancer activity against liver cancer than studied compounds. However, for the 8th and 10th, values of IC$_{50}$ (133 and 175 nM, respectively) are near to that of doxorubicin (116.9 nM) indicating that they may give moderate anticancer activity against HepG-2 cells.

Figure 4. Reaction mechanism of compound 10.

Scheme 4. Synthesis of compound 11.
Finally, the results of bio-activity that were performed on the structural features of the compounds and sacrificed for us explained the highest activities, it was found that the heterocyclic linked to glucose moiety was found higher in activities than the five carbon xylose moiety. Thus, attachment of a pyrazine ring to the thiazolo ring (compounds 10–11) resulted in higher activities compared to their starting precursors.

The results showed that the new compounds have anticancer activities against the three cancers cell lines with variable potency. The results depend on the structures of compounds revealed the attachment of glycosyl moiety to the thiazole-4, 5-diamine derivatives.

### Conclusions

Acyclic C-glycosides were synthesized through the use of a synthetic convergent method as good yields. Firstly, Thiazole-4, 5-diamine derivatives 7 were synthesized by four steps. After then, acyclic C-glycosides derivatives 8, 10 and 11 were achieved. That, compound 7 was reacted with different sugars by different methods to produce C-glycosides derivatives. Anticancer activities of acyclic C-glycosides were tested against human colorectal carcinoma (HCT-116), human prostate adenocarcinoma (PC-3), and human liver hepatocellular carcinoma (HepG-2) cell. The results showed that the new compounds have anticancer activities against the three cancers cell lines with variable potency.
Experimental

Reagents purchased from Sigma Aldrich and used without further purification. Reaction progress monitored by thin-layer chromatography on silica gel pre-coated F254 Merck plates (Darmstadt, Germany). Spots visualized by ultraviolet irradiation. Melting points were determined on a Gallenkamp electro thermal melting point apparatus (Weiss-Gallenkamp, Loughborough, UK) and are uncorrected. IR spectra recorded as potassium bromide disks using Bruker-Vector 22 Fourier transform infrared spectrophotometer (Billerica, MA). 1H NMR and 13C NMR spectra were recorded on a Varian/Gemini 400 MHz and 100 MHz spectrometer, respectively, in DMSO-d6 as a solvent and TMS considered as an internal standard (chemical shifts in δ, ppm).

2-(Phenylimino)-3-[N-phenylpropanimidoyl]-2,3-dihydro-1,3-thiazole-4,5-diamine (7)

A solution of 6 (286 mg, 1 mmol) and 2,3-diaminomaleonitrile (108 mg, 1 mmol) dissolved in ethyl acetate (25 ml) and refluxed for 12 h, then the solid formed after addition a mixture of ethyl acetate and diethyl ether to yield compound 7, recrystallization from toluene. mp 263–265 °C. Yield: 78%; IR spectrum (KOH, cm⁻¹): 3235–3124 (NH₂), 1647 (C= N). 13C NMR (DMSO-d6): δ 113.3 (CH₂), 21.8 (CH₂CH₃), 124.5 (C₂), 129.3 (C₄), 131.2 (C₃), 149.4 (C₁’), 150.6 (C₄), 155.7 (C₅), 159.4 (C₂), 161.9 (N=C-CH₂CH₃). 1H NMR spectrum (DMSO-d6, δ, 400 MHz): δ 8.79 (s, 2H, NH₂, exchangeable with D₂O), 8.59 (s, 2H, NH₂, exchangeable with D₂O), 7.13–7.33 (m, 10H, 2C₆H₅), 2.65 (q, 2H, CH₂, J = 7.2 Hz), 1.14 (t, 3H, CH₃, J = 7.2 Hz). Anal. Calcd. For (C₁₈H₁₉N₅S; 337.44): C, 76.7%; H, 7.52%; N, 7.52%.

1-(3,4-Dihydro-2-(phenylimino)-3-[(Z)-1-(phenylimino)propyl]-2H-imidazo[4,5-d]thiazol-5-yl]pentane-1,2,3,4,5-pentaol (8)

To a solution of D-glucose (180 mg, 1 mmol), thiazole diamine derivatives 7 (337 mg, 1 mmol) and iodine (6 mg, 0.1 mmol) in glacial acetic acid (15 ml) were stirred at room temperature. The reaction completed after 9 h appeared by TLC analysis. The mixture was triturated with Na₂S₂O₃ and iodine (6 mg, 0.1 mmol) in glacial acetic acid (15 ml) were stirred at room temperature. The reaction completed after 9 h and refluxed for 12 h, then the solid formed after addition a mixture of ethyl acetate and diethyl ether to yield compound 8, recrystallization from toluene. mp 217–219 °C. Yield: 67%; IR spectrum (KOH, cm⁻¹): OH (3419), NH (3178), C= N (1628) cm⁻¹; 13C NMR (DMSO-d6, 100 MHz): δ 10.9 (CH₃), 21.3 (CH₂CH₃), 67.7 (C₄), 74.1 (C₃), 74.9 (C₂), 75.3 (C₁’), 135.4 (C₃’), 153.1 (C₂), 151.5 (C₄), 161.3 (C₅), 165.2 (C₆), 160.3 (C= CH₂CH₃), 122.2 (C₂”), 127.3 (C₄”), 149.9 (C₁”). 1H NMR spectrum (DMSO-d6, δ, 400 MHz): 7.52–7.21 (m, 10H, arom.), 10.32 (s, 1H, NH, exchangeable with D₂O), 3.51 (dd, 2H, H-5’a, H-5’b, J = 5.4 Hz), 3.87–3.90 (t, 3H, H-2’, H-3’, H-4’, J = 4.36;5.40 Hz), 4.32–4.41 (m, 4H, OH-2’, OH-3’, OH-4’, OH-5’, exchangeable with D₂O), 5.41 (m, 1H, H-1’), 6.39 (d, 1H, J = 6.1 Hz, OH-1’, exchangeable with D₂O), 2.73 (q, 2H, CH₂, J = 7.2 Hz), 1.13 (t, 3H, CH₃, J = 7.2 Hz). Anal. Calcd. for (C₂₅H₂₇N₅O₅S; 497.57): C, 57.93%; H, 5.47%; N, 14.08%; S, 6.44%. Found: C, 57.90; H, 5.42; N, 14.21; S, 6.47.

1-(3,4-Dihydro-2-(phenylimino)-3-[(Z)-1-(phenylimino)propyl]-2H-imidazo[4,5-d]thiazol-5-yl]pentane-1’,2’,3’,4’,5’pentaacetoxypentayl (9)

C-glycoside 8 (149 mg, 0.3 mmol) added to acetic anhydride (307 mg, 3 mmol) in 3 ml of pyridine. The solution heating under reflux for 4 h, and then poured on to ice water the precipitated formed, filtrated and recrystallized from ethanol. mp 215–217 °C. Yield: 69%; IR spectrum (KOH, cm⁻¹): NH (3243), C= O (1733), (3075) amor, C= N (1578) cm⁻¹; 13C NMR (DMSO-d₆, 100 MHz): δ 19.8 (CH₃), 21.5 (CH₂CH₃), 23.3 (5 × COOCH₃). 68.3 (C₄”), 74.5 (C₃”), 75.4 (C₂”), 76.7 (C₁’), 134.9 (C₃”), 153.5 (C₂), 151.9 (C₄), 161.8 (C₅), 165.6 (C₈), 161.1 (C= CH₂CH₃),
122.1 (2\textsuperscript{''}), 128.2 (C\textsuperscript{4}), 148.7 (C\textsuperscript{1}), 171.3 (5 × CO). \textsuperscript{1}H NMR spectrum (DMSO-\textit{d}_6, \delta, 400 MHz): 7.52–7.21 (m, 10H, arom.), 10.25 (s, 1H, NH, exchangeable with D\textsubscript{2}O), 3.42 (t, 2H, CH\textsubscript{2}), 3.42–3.75 (m, 4H, H-3\textsuperscript{a}, H-4\textsuperscript{a}, H-5\textsuperscript{a}, H-5\textsuperscript{b}), 6.01 (d, 1H, J = 6.1 Hz, 1\textsuperscript{b}-H), 2.21 (s, 3H, CH\textsubscript{3}), 2.02 (s, 15H, 5COCH\textsubscript{3}). Anal. Calcd. for (C\textsubscript{36}H\textsubscript{39}N\textsubscript{5}O\textsubscript{11}S; 749.79): C, 57.67; H, 5.24; N, 9.34; S, 4.28. Found: C, 57.64; H, 5.20; N, 9.31; S, 4.24.

\textbf{1-[2-(Phenylimino)-2,3-dihydro[1,3]thiazolo[4,5-b]pyrazin-5-yl]butane-1,2,3,4-tetrol (10)}

A mixture of 7 (33.7 mg, 0.1 mmol), hydrazine hydrate (0.1 mmol) and glacial acetic acid (3 ml) added to glucose (18 mg, 0.1 mmol) dissolved in water (15 ml). The reaction mixture was heated at 100°C for 6 h, poured into cold water with stirring to give a precipitate. The solid was recrystallized from hot water. mp 196–198°C. Yield: 59%; IR spectrum (KOH, cm\textsuperscript{-1}): OH (3436), arom. (3098), C=\(\text{N}\) (1578) cm\textsuperscript{-1}; \textsuperscript{13}C NMR (DMSO-\textit{d}_6): \delta 8.9 (CH\textsubscript{3}), 19.3 (CH\textsubscript{2}CH\textsubscript{3}), 65.7 (C\textsubscript{4}), 73.1 (C\textsubscript{3}), 74.2 (C\textsubscript{2}), 75.6 (C\textsubscript{1}), 135.2 (C\textsubscript{2}), 151.5 (C\textsubscript{4}), 162.3 (C\textsubscript{5}), 164.2 (C\textsubscript{8}), 159.3(C=CH\textsubscript{2}CH\textsubscript{3}), 123.2(2\textsuperscript{''}), 129.3 (C\textsuperscript{4}),149.6 (C\textsuperscript{1}). \textsuperscript{1}H NMR spectrum (DMSO-\textit{d}_6, \delta, 400 MHz): 8.74 (s, 1H, pyrazin ring), 7.63–7.31 (m, 10H, arom.), 3.73 (t, 2H, CH\textsubscript{2}), 3.52–3.83 (m, 5H, H-2\textsuperscript{a}, H-3\textsuperscript{b}, H-4\textsuperscript{a}, H-4\textsuperscript{b}, OH-4\textsuperscript{a}, exchangeable with D\textsubscript{2}O), 4.32–4.41 (m, 3H, OH-1\textsuperscript{b}, OH-2\textsuperscript{b}, OH-3\textsuperscript{a}, exchangeable with D\textsubscript{2}O), 5.63 (d, 1H, J = 5.4 Hz, 1\textsuperscript{b}-H), 2.05 (t, 3H, CH\textsubscript{3}). Anal. Calcd. for (C\textsubscript{24}H\textsubscript{25}N\textsubscript{5}O\textsubscript{4}S; 479.55): C, 60.11; H, 5.25; N, 14.60; S, 6.69. Found: C, 60.14; H, 5.23; N, 14.58; S, 6.67.

3-[(1\text{z})-N-Phenylpropanimidoyl-1-[1-phenyl-6-(phenylimino)-5,6-dihydro-1H-pyrazolo[3,4-b][1,3]thiazolo[4,5-e]pyrazin-3-yl]ethane-1,2-diol (11)

A mixture of 7 (337 mg, 1 mmol), (5 ml) glacial acetic acid and phenylhydrazine hydrochloride (540 mg, 5 mmol) added to D-xylose (150 mg, 1 mmol) in (25 ml) water. The reaction mixture heating in a water bath for 12 h, at a temperature of 100°C. mp 228–230°C. The precipitated is filtration and washed with water then recrystallized from ethanol. Yield: 73%, IR spectrum (KOH, cm\textsuperscript{-1}): OH (3428), arom. (3069), C = N (1597) cm\textsuperscript{-1}; \textsuperscript{13}C NMR (DMSO-\textit{d}_6): \delta 19.2 (CH\textsubscript{3}), 21.9 (CH\textsubscript{2}CH\textsubscript{3}), 78.2(CH\textsubscript{2}OH), 66.6(CH\textsubscript{2}OH), 112.3(C2), 139.2 (C1), 153.2 (C5), 152(C4), 162.3 (C8), 159.3(N = C-CH\textsubscript{2}CH\textsubscript{3}), 154.6(C10), 123.5(C\textsuperscript{2}), 131.2(C\textsuperscript{3}), 129.5(C\textsuperscript{4}). \textsuperscript{1}H NMR spectrum (DMSO-\textit{d}_6, \delta, 400 MHz): 7.2167–7.35 (m, 15H, arom.), 3.82 (t, 2H, CH\textsubscript{2}), 3.52–3.83 (m, 2H, 2OH, exchangeable with D\textsubscript{2}O), 5.61 (d, 1H, J = 4.9 Hz, 1\textsuperscript{b}-H), 1.83 (t, 3H, CH\textsubscript{3}). Anal. Calcd. for (C\textsubscript{29}H\textsubscript{25}N\textsubscript{7}O\textsubscript{2}S; 535.62): C, 65.03; H, 4.70; N, 18.31; S, 5.99. Found C, 65.07; H, 4.73; N, 18.34; S, 5.96.

\textbf{Anticancer activity}

\textbf{Cell material}

Human colorectal carcinoma (HCT-116), human prostate adenocarcinoma (PC-3), and Human liver carcinoma (HepG-2) cell culture were purchased from the American Type Culture Collection (Rockville, MD, USA).

\textbf{Cell culture}

The cells were maintained in the medium of Roswell Park Memorial Institute (RPMI-1640) that was supplemented with 10% heat-inactivated FBS (fetal bovine serum), 100 U/mL penicillin, and 100 U/mL streptomycin. The cells were grown at 37°C in 95% moisture and 5% CO\textsubscript{2}.
**Cytotoxicity**

The cells were dispensed in a 96-well sterile micro plate (5 × 10^4 cells/well), and incubated with each of synthesized compound or Doxorubicin (positive control), prepared in a set of different concentrations (6.25, 12.5, 25, and 50 μg/ml) of dimethylsulfoxide, at 37°C for 48h in a serum-free medium. The media were cautiously isolated after incubation, and then MTT (2.5 mg/mL, 40 μL) was provided to each well and then incubated for a further4 hours. The crystals of purple formazan dye were solubilized by the addition of dimethylsulfoxide (200 μL). At 590 nm, the absorbance was measured. The mean percentage of viable cells with respect to the untreated control cells expresses the relative cell viability. Then the IC₅₀ was calculated for each compound in nM concentration.²¹,²² Compounds were studied, and some of these compounds showed potential antitumor activity.

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**Disclosure statement**

The authors declare no conflict of interest, financial or otherwise.

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