Efficient Synthesis and Biological Activities of New Pyridine and Pyrimidine Thioglycosides as Potential Antimicrobial and Anti-inflammatory Agents

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Abstract

Glycosylation of small molecules based heterocycles can improve the biological importance of the parent scaffold. In the current study, various new substituted pyridine and substituted pyrimidine thioglycosides were synthesized via the reaction of substituted pyridine and pyrimidine thiols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in presence of sodium acetate and ethanol .The chemical structures of the synthesized compounds were confirmed by elemental and spectral techniques including FT-IR, ^{1}H NMR In addition to ^{13}C NMR and mass spectroscopy for some of them. Alternatively, some of the synthesized compounds revealed significant antibacterial and antifungal activates. Also, most of these compounds exhibited highly promising anti-inflammatory activities compared with indomethacin.

Keywords: S-glycoside; Pyridine; Pyrimidine; Synthesis; Antimicrobial activity; Anti-inflammatory activity

Introduction

Pyridine and its annulated heterocyclic compounds are considered to be prominent scaffolds in medicinal chemistry due to their existence in many natural products having therapeutic importance. Consequently, pyridine- containing heterocycles exhibit broad spectrum of biological applications such as: anticancer[1-4], Antitumor[5], antioxidant[6], antiviral[7-9] , antidiabetic [10], antimicrobial [11,12] and anti-arrhythmic [13].

Furthermore, thioglycosides have received considerable attention because they are widely utilized as biological inhibitors [14],

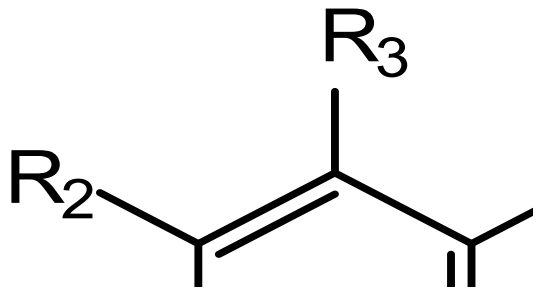
inducers[15], and ligands [16] for chromatographic separation of carbohydrate processing enzymes and proteins. A Series of novel synthesized pyridine *S*-Glycosides exhibited antagonistic activity against human carcinoma cells and HIV-Virus [17, 18]. Additionally, dihydropyridine glycosides as P-glycoprotein (pgp) are used as substrates or inhibitors in the protein glycosylation process[19].
Alternatively, pyrimidine nucleus is an essential part of DNA and RNA which plays an important role in several biological processes and have considerable chemical and pharmacological significance. The pyrimidine ring is found in antibiotics, antiviral nucleosides and exist in antibacterial, antitumor, cardiovascular as well as agrochemical, veterinary products and anti-mycobacterial agents.[20-25].Moreover, the pyrimidine thione nucleosides can interact with DNA synthesis, t-RNA transcription and protein synthesis which have antiviral, antibacterial, antitumor and cytotoxic activities [26-29].

In the light of the biological importance of pyridine and pyrimidine heterocycles and their thioglycosides and in continuation of synthesis of new heterocyclic compounds containing pyridine and pyrimidine moiety[30-35], we have synthesized a series of novel substituted pyridine, cyclopentapyridine, tetrahydroisoquinoline and substituted pyrimidine S-Glycosides. Therefore, as a result to the resistance of the pathogenic strains of bacterial and fungi to the current antimicrobial therapy, we are interested in synthesis of more effective agents. Additionally, non- steroidal anti-inflammatory drugs (NSAID's), that are widely employed for reducing pain and swelling associated with inflammatory display on attractive zone of containing progress. Hence, the promising biological activities of pyridine and pyrimidine *S*-Glycosides
encouraged us to study the *in-vitro* antimicrobial and *in-vivo* anti-inflammatory activities for the newly synthesized *S*-glycosides in comparison with the standard drugs. The obtained results from biological screening confirmed that most of these compounds revealed promising antibacterial, antifungal and anti-inflammatory importance.

Results and Discussion

The key intermediates for synthesis of cyclic S-glycoside are displayed in Schemes **1** and **2**. In the current study, we represented synthesis of some novel substituted pyridine, cyclopenta[*c*]pyridine, tetrahydroisoquinoline and pyrimidine thioglycoside. Thus, treatment of the cyclopenta[*c*]pyridine-3-thione or tetrahydroisoquinoline-3-thione **1a-c** or pyridine -2-thione **1d** and **1e** with sodium acetate in ethanol furnished the corresponding sodium salts of 3-thioxo tetrahydroisoquinoline, 3-thioxo cyclopentapyridine **2a-c** and 2-thioxo pyridines **2d** and **2e** which *in turn* were treated with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **3** to afford the S–glycosated compounds **4a-e** in moderate to good yields (Scheme 1). The chemical structures of the S-glycosides were assigned by micro analytical and spectral techniques (FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy). For example, FT-IR Spectrum of compound **4b** revealed absorption bands at 2210 cm^{-1} unique for CN group and at and at 1757 cm^{-1} for CO of acetoxy groups of glucopyranoside. ^{1}H NMR spectrum $CDCl_3$ exhibited the anomeric proton of the glucose moiety as a doublet signals at 5.80, 5.85 ppm with a coupling constant $J_{1,2}$= 8.20 Hz indicating the α configuration of the anomeric centre. The other proton of the glucopyranose ring resonated at 3.79-5.85 ppm, while the four acetoxy groups appears as two singlet signals at 2.05 and 2.06 ppm, in addition to multiplet signals at 1.75-3.33 ppm attributed to piperidinyl protons. ^{13}C NMR in $CDCl_3$ represented signal at 161.61 particular for N=C-S and four Signals at 169.14-170.54 ppm distinctive for four CO acetoxy groups. Mass Spectrum showed peak at *m/z* 603.22 as a molecular ion peak. Whereas, FT-IR Spectrum of compound **4e** displayed bands at 2214 cm^{-1} specific for CN group and at 1723 cm^{-1} characteristic for CO of acetoxy groups of glucopyranoside. ^{1}H NMR spectrum of **4e** exhibited the anomeric proton of the glucose moiety as a doublet signals at 5.96, 5.98 ppm with a coupling constant $J_{1,2}$= 7.20 Hz confirming the α configuration of the anomeric centre. the other glucopyranose protons resonated at 3.88-5.98 ppm, while the four acetoxy groups appears as single signal at 2.06 ppm, in addition to two singlet

signals at 2.47, 2.56 ppm attributed to the dimethyl pyridine protons. ^{13}C NMR in $CDCl_3$ represented signals at 161.52 ppm typical for N=C-S and four signals at 169.23-170.64 ppm distinctive for four CO of acetoxy groups.



Scheme 1. Synthesis of substituted pyridine S-glycosides 4a-f

In similar manner, reaction of the substituted pyrimidine-2-thione **5a, b** with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside bromide **3** in presence of ethanol and fused sodium acetate afforded the corresponding pyrimidine thioglycoside derivatives **6a, b.** The chemical structure and homogeneity of compound **6a** and **b** were confirmed by their elemental micro analysis. FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. FT-IR Spectrum of compound **6a** revealed absorption bands at 2222 cm^{-1} unique for CN group and at 1747 cm^{-1} characteristic for CO of acetoxy groups of glucopyranoside and at 1682 cm^{-1} unique for (CONH). ^{1}H NMR spectrum in $CDCl_3$ exhibited the anomeric proton of the glucose moiety as a doublet signals at 6.03, 6.06 ppm with a coupling constant $J_{1,2}$=8.80 Hz demonstrating the α configuration of the anomeric carbon. The other protons of the glucopyranose ring resonated at 3.89-6.06 ppm, while the four acetoxy groups appears as four single signals at 1.97,2.0,2.02.2.03 ppm, in

addition to multiplet signals at 7.56-8.12 ppm attributed to the aromatic protons and singlet signal at 13.19 ppm characteristic for pyrimidine NH proton. ^{13}CNMR in $CDCl_3$ represented at 161.42 particular for N=C-S and four CO signals at 167.52-170.38 for four CO acetoxy groups and Signals at 128.94-135.36 specific for the phenyl carbon atoms. Mass Spectrum showed peak at *m/z* 535 as a molecular ion peak.

Scheme 2. Synthesis of substituted pyrimidine S-glycosides 6a and 6b

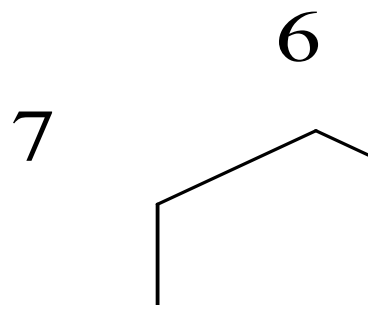


Figure 1. Carbon numbering of compounds 4b, 4e, 6a

Biological activity

1. Antimicrobial activity:

One of the main targets in our work is the synthesis of new heterocyclic thioglycosides which may be of special importance in biological and medicinal chemistry. So, all the synthesized thioglycosides were screened in vitro for their antimicrobial activity against four strains of bacteria (Bacillus Cereus, staphylococcus aureus, pseudomonas aurginose, Escherichia coli). The inhibition zones (mm) and minimum inhibitory concentrations (MIC) (mg/µL) of the screened compounds were compared with ciprofloxacin and clotrimazole as standard anti-bacterial and antifungal reference drugs respectively.

2. Antibacterial activity

Table (1). Antibacterial activity, (inhibition zone, mm) and MIC (mg µL-1) of compounds (4a-f) and 6a, 6b

Compound bacterial strain	4a	4b	4c	4d	4e	4f	6a	6b	Ciprofl oxacin
Bacillus cereus (Gram +ve)	15 (12)	14 (8)	21 (9)	17 (7)	18 (10)	11 (7)	12 (9)	11 (10)	25 (3)
Staphylococcus aureus (Gram +ve)	15 (18)	13 (8)	16 (9)	11 (9)	22 (9)	18 (9)	14 (9)	16 (8)	23 (3)
Pseudomonas aruginose (Gram -ve)	15 (9)	18 (9)	18 (9)	15 (9)	16 (8)	14 (8)	13 (8)	11 (10)	25 (3)
Escherichia coli (Gram -ve)	12 (9)	14 (8)	14 (9)	13 (8)	11 (8)	15 (9)	13 (7)	12 (8)	20 (3)

The amount added in each pore is 50 µg/ ml

The results of antibacterial assessment confirmed that the tested compounds revealed promising activity and were summarized in **Table 1**. Compounds **4b-d, 4f** and **6a** displayed the best activity against *Bacillus cereus* with MIC (7-9 mg/µL) parallel to Ciprofloxacin (MIC 3 mg/µL) while compounds **4a, 4e** and **6b** showed good moderate effects. In case of *Staphylococcus aureus*, all the synthesized thioglycosides as exhibited significant antibacterial activities against all genera of bacteria (MIC 8-9 mg/µL). Compounds **4e** and **4f** offered the highest efficacy with very close inhibition zones (18-22 mm) compound to the reference

drug (23mm). Alternatively, compounds **4a –f** and **6b** were found to be the most active derivatives versus *Pseudomonas aurginose* with MIC values (8-9 mg/µL), Whereas compound **6b** represented moderate activity (MIC 10 mg/µL) Moreover, compound **6a** displayed the highest effectiveness against *E-coli* (MIC 7.00 mg/µL) relative to Ciprofloxacin (MIC 3.00 mg/µL), While compound **4a-f** and **6b** revealed excellent activity (MIC 8-9 mg/µL) against *E.coli*. It's known that the bacterial effect of ciprofloxacin works through interfering with replication and transcription of bacterial DNA, which leads to increased oxidative stress, and death of bacterial cells. Accordingly, the power of antibacterial effects of the newly synthesized thioglycosides be returned to release of the free radicals which causes bacterial death[36].

3. Antifungal Activity:

Table (2). Antifubgal activity, (inhibition zone, mm) and MIC (mg µL-1) of compounds (4a-f) and 6a, 6b

Compounds Fungal Strain	4a	4b	4c	4d	4e	4f	6a	6b	Clotrim azole
Geotrichum candidium	**16 (7)**	**14 (8)**	**12 (9)**	**15 (18)**	**17 (9)**	**15 (9)**	**18 (10)**	**15 (10)**	**24 (5)**
Candida albicans	**20 (8)**	**20 (6)**	**18 (8)**	**19 (9)**	**23 (8)**	**18 (7)**	**17 (7)**	**19 (7)**	**25 (3)**
Trichophyton rubrum	**17 (9)**	**19 (10)**	**21 (9)**	**19 (10)**	**18 (18)**	**16 (9)**	**13 (9)**	**0.0**	**21 (6)**
Aspergillus flavus	**13 (11)**	**15 (9)**	**17 (10)**	**0.0**	**18 (9)**	**14 (9)**	**16 (9)**	**17 (10)**	**24 (4)**

The amount added in each pore is 50 µg/ ml .

It's interested to be mentioned that the results of antifungal screening for the S-glycosides revealed excellent impacts against all fungal strains especially *Candida albicans* as indicated in table 2. From the antifungal data, we can conclude that compounds **4a-f** and **6b** exhibited intense activates against *Geotrichum candidium* (MIC 70-90 mg/ µL) relative to the Clotrimazole reference drug (5.0 mg/ µL), while compound **6a** showed moderate to good activity. Subsequently, all the synthesized thioglycosides demonstrated the best activities versus *Candida albicans* (MIC 6-9

mg/µL) with very close inhibition zones (17-23mm) comparable to the reference drug (MIC 3.0 mg/µL, 25mm). In case of *Trichophyton rubrum* , compounds **4a,4c ,4f** and **6a** represented strong fungal inhibitory activities (MIC 8-9 mg/ µL) while compound **4b-d** displayed good to excellent efficacy (MIC 9-10 mg/ µL) with inhibitors zones (19-21 mm) which is almost the same as Clotrimazole (MIC 6 mg/ µL, 21mm).However, *Trichophyton rubrum* was resistant to compound **6b**. Furthermore, compounds **4b, 4e, 4f** and **6a** exhibited significant activity versus *Aspergillus flavus* (MIC 9 mg/ µL), whereas compounds **4a, 4c** and **6b** represented moderate effect (MIC 10 mg/ µL) compared to Clotrimazole (4 mg/ µL). At the same time, *Aspergillus flavus* was resistance to compound **4d**. Clotrimazole works by inhibition the growth of individual Candida or fungal cells by altering the permeability of the fungal cell wall. [37] it binds to phospholipids in the cell membrane and inhibits the biosynthesis of ergosterol and other sterols required for cell membrane production [37, 38]. Clotrimazole may slow fungal growth or result in fungal cell death [39]

Structure Activity Relationship:

Thioglycosides occupy a distinctive position in medicinal chemistry. Consequently, we tried to study the effect of different classes of heterocyclic containing pyridine and pyrimidine moieties on the microbial inhibitory activities. From the data that are listed in table 1. We can conclude that all substituted thioglycosides including pyridine and pyrimidine nucleus revealed promising antibacterial and antifungal activities. Replacement of the morpholinyl ring **4a** with the piperidinyl **4b** in the tetrahydroisoquinoline thioglycoside strongly enhanced the antibacterial effect by about 1.50 times against *Bacillus cereus* since it reduces the MIC values from 12 to 8 mg/ µL and increases the activities against *E. coli*, Otherwise, activity against *Staphylococcus aureus* and pseudomonas aurginose is still unchanged in MIC values. In comparing The activities of cyclopenta[*c*]pyridine thioglycosides derivatives **4c** and **4d**, we found that that displacement of the cyano group in **4c** by the ethyl carboxylate in **4d** highly improve the activity towards *Bacillus*

cereus, *Staphylococcus aureus* and *E-coli*, whereas, the activity towards *Pseudomonas aurginose* remains unchanged. Furthermore, condensation of the dimethyl pyridine **4d** with benzaldehyde to afford the corresponding chalcone **4e** strongly promotes the bacterial inhibitory activity against *Bacillus cereus* and slightly reduces the activity verses *E. coli* with remaining the effect against *Staphylococcus aureus* and *Pseudomonas aurginose* almost unchanged. Moreover, replacement of the phenyl rings **6a** by the indolyl nucleus. The pyrimidine thioglycoside moiety only promotes activity against *Staphylococcus aureus* with slightly suppressing the antibacterial efficacy to the other tested strains of bacteria. Alternatively, the newly synthesized thioglycoside compounds exhibit excellent fungal inhibitory activity. (Table2). The morpholinyl tetrahydroisoquinoline thioglycoside exhibited excellent anti-fungal activity against *Geotrichum candidium*, *Candida albicans* and *Trichophyton rubrum* and moderate activity against *Aspergillus flavus*. Replacement the morpholinyl in **4a** with the piperidinyl ring in **4b** slightly reduces the activity versus *Geotrichum candidium*, *Candida albicans* and *Trichophyton rubrum* and moderate activity against *Aspergillus flavus*. Replacement the morpholinyl in **4a** with the piperidinyl ring in **4b** slightly reduces the activity versus Geotrichum *candidium*, *Candida albicans* and *Trichophyton rubrum* and strongly enhanced the effect against *Aspergillus flavus*. In case of cyclopenta[*c*]pyridine, substituted the cyano group in **4c** by the carboxylate ester in **4d** improves the fungal inhibitory activity against Geotrichum candidium diminished the activity that the *Aspergillus flavus* is resistant to **4d** with slightly lowering the efficacy towards *Candida albicans* and *Trichophyton rubrum*. Furthermore, we found that conversion of the dimethyl pyridine **4e** to the dibenzyl dine derivatives **4f** the activity protons against *Candida albicans* and slightly lowers the effect against *Trichophyton rubrum* and the activity against *Geotrichum candidium* and *Aspergillus flavus* remains unchanged. Additionally, replacement of the phenyl **6a** with indolyl ring **6b** in the pyrimidine thioglycosides enhanced the activity towards *Geotrichum candidium* with slightly decrease in the activity versus

Aspergillus flavus, while the effect against Candida albicans remains unchanged. At the same time the indolyl pyrimidine **6b** revealed inferior activity against *Trichophyton rubrum*.

4. Anti-inflammatory:

The anti-inflammatory activity of the newly synthesized thioglycosides was measured at 1,2,3 and 4 hrs after carrageenan injection. Indomethacin was utilized as a reference drug. The anti-inflammatory activity data (Tables 3-5 and Figures 2 and 3) indicated that most of the tested compounds exhibited the highest anti-inflammatory efficacy after 3 and 4 hrs of carrageenan injection. It's worth nothing that compound **4e** revealed the best anti-inflammatory activity with the same or higher potencies to indomethacin during the period of experiment. As shown in **Fig (2)** at 30 min, all the tested compounds showed significant differences from the reference drug ($p<0.05$) which means that the examined compounds didn't display similar effects as indomethacin. after 1 hr of carrageenan injection, only compound **4e** offered strong activity, while the other compounds showed moderate effects compared to indomethacin. in contrast, compounds **4c,4e,4f** and **6a** represented the best effects and the same potencies as indomethacin after 2 hrs. however, compounds **4d** and **4e** revealed the highest anti-inflammatory activity with higher potencies then indomethacin after 3 hrs of treatment. Whereas, the other examined compounds exhibited good to excellent activities with potencies 0.89-0.92 comparable to indomethacin. Alternatively, compounds **4a-c, 4e** and **6a, b** revealed the highest anti-inflammatory efficiency with very close potencies (0.90-0.95) to the indomethacin reference drug, while compounds **4d** and **4f** displayed moderate to good activities after 4 hrs of treatment.

Table 3. Anti-inflammatory activity of compounds 4a-f, 6a and 6b using acute carrageenan-induced Paw edema in rats (Statistical analysis)

Paw Edema inhibition (mean ± SEM) [a, b, c] /mm					
Compound Time	**30 min**	**1h**	**2h**	**3h**	**4h**
4a	0.70 ± 0.00	0.63 ± 0.06	0.57 ± 0.03	0.45 ± 0.05	0.40 ± 0.00
4b	0.67 ± 0.08	0.67 ± 0.03	0.48 ± 0.03	0.43 ± 0.08	0.43 ± 0.03
4c	0.68 ± 0.03	0.38 ± 0.03	0.43 ± 0.06	0.43 ± 0.03	0.43 ± 0.03
4d	0.70 ± 0.00	0.67 ± 0.03	0.52 ± 0.08	0.37 ± 0.03	0.47 ± 0.03
4e	0.68 ± 0.03	0.46 ± 0.06	0.43 ± 0.03	0.38 ± 0.03	0.40 ± 0.00
4f	0.68 ± 0.03	0.55 ± 0.05	0.42 ± 0.03	0.45 ± 0.05	0.49 ± 0.03
6a	0.68 ± 0.03	0.63 ± 0.03	0.42 ± 0.03	0.43 ± 0.03	0.43 ± 0.00
6b	0.72 ± 0.03	0.67 ± 0.03	0.55 ± 0.05	0.45 ± 0.05	0.43 ± 0.03
Indomethacin	0.62 ± 0.10	0.43 ± 0.06	0.42 ± 0.03	00.38 ± 0.03	0.37 ± 0.03
Control	0.75 ± 0.00	0.75 ± 0.00	0.75 ± 0.00	0.75 ± 0.05	0.76 ± 0.03

[a]Dose 20µmol/kg^{-1}, [b]n=3; [c]statistically significant for the indomethacin at $p<0.05$, SE: Standard

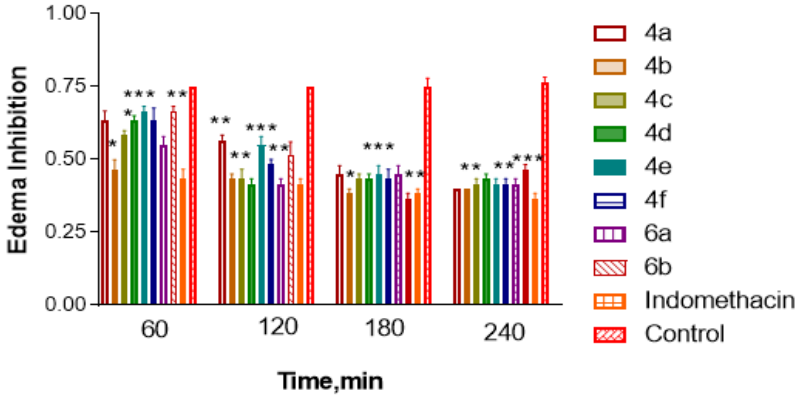


Figure 2. The relationship of Paw edema inhibition (mm) with time (min).

Table 4. Paw edema inhibition (%) for compounds 4a-f, 6a and 6b

Anti-inflammatory activity (inhibition)%					
Compound Time	30min	60min	120min	180min	240min
4a	40.00	49.33	57.33	73.33	78.94
4b	44.00	44.00	69.33	76.00	75.00
4c	42.66	56.00	76.00	76.00	76.32
4d	40.00	44.00	64.00	84.00	69.74
4e	42.66	72.00	76.00	82.67	78.74
4f	42.66	60.00	77.33	73.33	67.11
6a	42.66	49.33	77.33	76.00	75.00
6b	37.33	44.00	60.00	73.33	75.00
Indomethacin	50.66	76.00	77.33	82.6	82.89

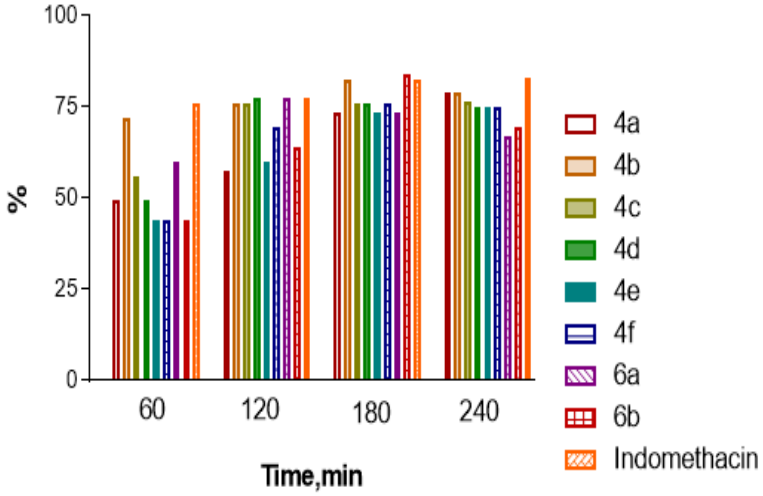


Fig. 3. The relationship of Paw edema inhibition (mm) with time (min).

Table5. Potency was expressed as % edema inhibition of the tested compounds relative to % edema inhibition of indomethacin (reference drug).

Potency relative to indomethacin					
Compound Time	**30min**	**60min**	**120min**	**180min**	**240min**
4a	**0.78**	**0.64**	**0.74**	**0.88**	**0.95**
4b	**0.86**	**0.57**	**0.89**	**0.92**	**0.90**
4c	**0.84**	**0.73**	**0.98**	**0.92**	**0.92**
4d	**0.78**	**0.57**	**0.82**	**1.01**	**0.84**
4e	**0.84**	**0.94**	**0.98**	**1.00**	**0.94**
4f	**0.84**	**0.78**	**1.00**	**0.88**	**0.80**
6a	**0.84**	**0.64**	**1.00**	**0.92**	**0.90**
6b	**0.73**	**0.57**	**0.77**	**0.88**	**0.90**

Experimental

All melting points are uncorrected and measured on a fisher-john apparatus. Elemental analyses were carried out at the Micro Analytical Centre of Chemistry Department, Assiut University-their results were found to be in an excellent agreement (±0.20%) with the calculated values. FT-IR Spectral analyses (ע, cm^{-1}) were recorded using potassium bromide disks on a FT-IR 820/pc (Shimadzu). ^{1}H NMR and ^{13}C NMR Spectra were obtained on a Bruker (^{1}H NMR: 400 MHz, ^{13}C NMR: 100MHz) Spectrometer in $CDCl_3$ and DMSO-d_6 Using (TMS) tetramethyl silane as an internal standard (chemical shifts are expressed in ppm). All the reactions were monitored by TLC technique on silica gel coated on aluminium sheets (Silica gel 60 F 254-Merck) using UV light. Mass Spectra were obtained on an ISO 7000(70ev) apparatus at chemistry Department Lab, Faculty of science.

1-((Substituted hetero aryl) thio)-1H-2, 3, 4, 6-tetra–O-acetyl-α-D-glucopyranoside

General Procedure

A mixture of equimolar amounts of the hetero aryl thiol compound **1a-f** (2mmol) and ***1***-bromo-2, 3, 4, 6-tetra–O-acetyl-α-D-

glucopyranose (2mmol) in ethanol (20 ml) in presence of fused sodium acetate (0.40 g, 5.00 mmol) was refluxed for 2 hrs. The solid precipitate which formed on cooling was filtered, washed with water several times, dried and recrystallized from the proper solvent.

1-((4-Cyano-1-morpholin-4-yl-5,6,7,8-tetrahydroisoquinoline-3-yl)Sulfanyl)-1H-2,3,4,6-tetra-O-acetyl-α-D-glucpyranoside :

White powder (EtOH); 44.00% (0.20g) yield, m.p. 200-202°C, FT-IR((ע,cm^{-1}): 2977, 2938, 2849(CH aliphatic) :2208 (CN), 1746(CO ester, 1562(C=N), 1229 (C-O); 1H NMR (CDCl3): 1.72, 1.84 (m, 4H, 2CH2 cyclohexeno), 1.84, 1.85 (m, 4H, 2CH2: C5,C8 cyclohexeno) 2.05, 2.06(s, 12H, 4CH3 acetoxy), 2.85-2.88 (m, 4H, (CH2)2N morpholinyl), 3.77, 3.78 (d, 1H, J = 5.20 H6a), 3.80-3.88 (m, 4H, $(CH_2)_2O$ morpholinyl), 4.06, 4.09 (d, 1H, H_5), 4.23-4.27 (dd, 1H, *J*= 4.02 Hz and *J* = 7.00 Hz, H_2), 5.15-5.19 (t,1H, *J*= 9.55 Hz, H_4), 5.28-5.37 (m, 2H, H_5+H_{6b}), 5.79, 5.81 (d, 1H, *J*= 4.85 Hz, H_1). Anal. Cald. for: $C_{28}H_{35}N_3O_{10}S$ (605.66): C, 55.53; H, 5.83; N; 6.94; S,5.29 %. Found: C, 55.40; H, 5.92; N, 6.81; S, 5.40 %.

1-((4-Cyano-1-piperidinyl-5,6,7,8-tetrahyroisoquinoline-3-yl)sulfanyl)-1H-2,3,4,6-tatra-O-acetyl-α-D-glucopyranoside (4b)

White crystals (ETOH), 48.50% (0.22g) yield, m.p. 92-94ºC, FT-IR (ν, cm^{-1}): 2936 (CH aliphatic), 2210(CN), 1747 (CO ester, 1560 (C=N), 1246(CO). ^{1}H NMR ($CDCl_3$): 1.75 (m, 6H, $3CH_2$: C3-C5 piperidinyl) 1.83 (m, 4H, $2CH_2$: C6, C7 cyclohexeno), 2.05, 2.06 (s, 12H, $4CH_3$ acetoxy), 2.56 (m, 2H, CH_2:C5 cyclohexeno), 2.83-2.86 (m, 2H, CH_2: C8 cyclohexeno) 3.26-3.33 (m, 4H, $2CH_2$:C2, C6 piperidinyl), 3.79, 3.81(d, 1H, *J*= 8.00Hz, H_{6a}), 4.07, 4.10 (d, 1H, *J*= 12.00 Hz, H_5), 4.24, 4.28 (dd, 1H, *J*=4.00 and *J*= 8.00Hz, H_2), 5.15-5.20 (t, 1H, *J*= 9.60 Hz, H_4), 5.29, 5.37 (m, 2H, H_3+H_{6b}), 5.83, 5.85(d, 1H, *J*= 8.00 Hz, H1). ^{13}C NMR ($CDCl_3$) : 20.62 (2CH3 : C15, C18 acetoxy), 20.70 (CH_3 : C12 acetoxy), 21,65 (CH_3 : C9 acetoxy), 22.46 (C6, C7 : cyclohexane), 26.54 (C8 : Cyclohexeno), 28.31 (C3-C5: piperidinyl), 29.68 (C5: cyclohexane), 49.49 (C2, C6 :piperidinyl), 62.20 (CH_2:C6 glucose), 66.78 (CH: C5 glucose), 68.20 (CH: C3 glucose), 74.14 (CH :C4 glucose), 76.06(CH: C2 glucose), 81.06 (CH: C1 glucose), 101.19(C4), 115.11(C8a), 120.77(C9, CN), 151.81 (C4a), 154.41(C1), 161.61(C3), 169.14

(CO:C14), 169.29 (CO:C17), 170.33 (CO: C11), 170.54(CO:C8). EI -MS(m/z):603.22, 502.03, 401.06, 273.16, 205.09, 97.1, 84.12, 44.06. Anal. Cald. For $C_{29}H_{37}N_3O_9S$ (603.68): C, 57.70; H, 6.18; N, 6.96; S, 5.31 %. Found: C, 57.55; H, 6.11; N, 7.15; S, 5.22%.

1-((4-Cyano-1-morpholin-4-yl6,7-dihydro-5h-cyclopenta[c]pyridin-3-yl) sulfanyl) -1H-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (4c)

White powder (EtOH), 52% (0.23g) yield, m.p. 200-202°C, FT-IR (ν, cm^{-1}): 2977, 2938, 2859 (CH aliphatic), 2204 (CN), 1759, 1731 (CO acetoxy ester), 1572(C=N), 1240,1218(C-O). ^{1}HNMR ($CDCl_3$): 2.05, 2.06 (s, 12H, $4CH_3$ acetoxy), 2.12-2.16 (m, 2H, CH_2:C6 Cyclopenteno), 2.90-2.97(m, 4H, $2CH_2$: C5 Cyclopenteno), 3.59-3.67(m, 4H, $(CH_2)_2$N-morpholinyl), 3.74, 3.76(d, 1H, *J*=8.00 Hz, H_{6a}), 3.84-3.86 (m, 4H, $(CH_2)_2$O morpholinyl), 4.0, 4.10 (d, 1H, *J*= 9.600 Hz, H_5), 4.24-4.29(dd, 1H, *J*= 6.400 Hz, H_2), 5.14-5.19(t, 1H, *J*= 9.70 Hz, H_4), 5.27-5.36(m, 2H, H_3+H_{6b}), 5.72-5.74 (d, 1H, *J*= 8.60 Hz, H_1). EI-MS (m/z) : 591.27, 532.28, 472.21, 412.17, 356.15, 331.18, 260.17, 216.17, 169.12, 127.12, 109.1, 97.09, 43.06. Anal. Cald. for: $C_{27}H_{33}N_3OH_{10}S$ (591.19): C, 54.81; H, 5.62; N; 7.10; S,5.42 %. Found: C, 54.75; H, 5.71; N, 7.05; S, 5.19 %.

1-((4-Ethoxycarbonyl-1-morpholin-4-yl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl) sulfanyl)-1H-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (4d)

Yellow powder (EtOH), 43% (0.21 g) yield, m.p. 95-97°C, FT-IR (ν, cm^{-1}): 2957, 2849 (CH aliphatic), 1706, 1757(CO acetoxy ester), 1251(C-O). ^{1}H NMR ($CDCl_3$): 1.29-1.33 (t, 3H, *J*= 7.20 Hz, CH_3 ethyl ester), 1.86-1.92 (m, 2H, CH_2: C6 cyclopenteno), 1.94, 1.96, 1.98, 2.02 (s, 12H, $4CH_3$ acetoxy), 3.04-3.18 (m, 4H, $2CH_2$:C5,C7 cyclopenteno), 3.67-3.69(d, J= 11.42 Hz, 1H, H_{6a}), 3.98-4.05 (q, 2H, *J*= 7.20 Hz, CH_2 ethyl ester) 4.19, 4.24(m, 2H, H2+H5), 4.28-4.58(m, 4H, $(CH_2)_2$N morpholinyl), 4.81-5.15(m, 4H, $(CH_2)_2$ O morpholinyl) 5.48, 5.52 (d, *J*= 8.00 Hz, 1H, H_2+H_4), 5.60-5.65(d, 1H, H_{6b}), 5.98-6.02 (m, 1H, H1+H_3). Anal. Cald. for: $C_{29}H_{38}N_2O_{12}S$ (638.21): C, 54.54; H, 6.00; N; 4.39; S, 5.02 %. Found: C, 54.61; H, 5.91; N, 4.51; S, 4.89 %.

1-((5-Cyano-4,6-dimethylpyridin-2-yl)sulfanyl)-1H-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (4e)

Yellow powder (EtOH), 52.00% (0.23 g) yield, m.p. 220-222ºC, FT-IR (ν, cm^{-1}): 2921 (CH aliphatic), 2214 (CN), 1756, 1723 (CO acetoxy ester), 1629(C=N), 1242, 1214 (C-O acetoxy), ^{1}H NMR ($CDCl_3$): 2.06 (s, 12H , $4CH_3$), 2.47, 2.56 (2s, 6H, $2CH_3$ pyridine), 3.88, 3.90 (d, 1H, *J*=8.00 Hz, H_{6a}), 4.10, 4.13 (d, 1H, *J*=7.20 Hz, H_5) , 4.24, 4.27, (dd, 1H, J= 9.90 Hz and J=7.00 Hz, H_2), 5.17-5.22 (t, 1H, J= 8.90 Hz, H_4), 5.29-5.42 (m, 2H, H_3+H_{6b}), 5.96, 5.98 (d, 1H , J= 7.20 Hz, H_1), 7.29 (s, 1H, CH pyridine). ^{13}C NMR ($CDCl_3$): 20.21(CH_3: C15, C18 glucose), 20.62(CH_3: C9, C12 glucose), 24.84(CH_3: C7 pyridine), 29.69(CH_3: C8 pyridine), 61.95(CH_2: C6 glucose), 68.24 (CH: C5 glucose), 68.94 (CH: C3 glucose) .74.24 (CH: C4 glucose), 76.13 (CH: C2 glucose) , 80.99(CH: C1 glucose), 106.1(C3: pyridine), 114.41(CN: C9), 121.09(C5: pyridine), 125.12 (C4: pyridine), 158.46(C6: pyridine), 161.52(C2: pyridine) 169.23(C14: CO), 169.35(C17: CO acetoxy), 170.29 (C11: CO acetoxy), 170.64(C8: CO acetoxy). Anal. Cald. for: $C_{22}H_{26}N_2O_9S$ (494.14): C, 53.43; H, 5.30; N; 5.66; S,6.48 %. Found: C, 53.50; H, 5.22; N, 5.52; S, 6.61 %.

1-((5-Cyano-4,6-distyrylpyridine-2yl)sulfanyl)-1h-2,3,4,6-tetra-O-acetyl-α-d-glucopyranoside (4f)

Yellow crystals, 37.40% (0.19g) yield, m.p. 230-232°C. FT-IR (ν, cm^{-1}): 3181 (CH=CH alkene), 2948, 2916, 2873, (CH aliphatic), 2218(CN), 1758, 1734(CO acetoxy ester), 1611(C=N), 1243, 1205(C-O). ^{1}H NMR (DMSO-d_6): 1.99, 2.00, 2.05, 2.6(s, 12H, $4CH_3$ acetoxy), 4.02-4.13 (m, 2H, H_5+H_{6a}), 4.38-4.42 (dd, J = 5.70 and J= 8.50 Hz , 1H, H_2), 4.99-5.04(t, J= 9.71 Hz, 1H, $1H_4$), 5.20-5.25(t, 1H, J= 6.80 Hz, H6b), 5.69-5.74(t, 1H, J= 9.71 Hz, H3), 6.28-6.30(d, 1H, J= 6.20 Hz, H1), 7.25-7.29 (2d, 2H, J = 13.30 Hz, CH=CH benzylidene, C7,C8 pyridine), 8.08, 8.12 (2d, 2H, J= 14.00 Hz, CH=CH benzylidene C9, C10), 7.91(s, 1H, CH pyridine), 7.32-7.86(m, 10H, 2ArH). EI-MS (m/z):644.30, 595.22, 502.16, 414.41, 288.13, 255.91, 219.17, 126.15, 71.14, 43.10. Anal. Cald. for: $C_{36}H_{34}N_2O_9S$ (670.73): C, 64.47; H, 5.11; N; 4.18; S,4.78 %. Found: C, 64.56; H, 4.98; N, 4.23; S, 4.69 %.

1-((5-Cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)sulfanyl)-1H-2,3,4,6-tetra-O-acetyl-α-d-glucopyranoside (6a)

Pale yellow crystals, 51.20% (0.21g) yield, m.p. 245-247°C, FT-IR (ν, cm^{-1}): 3428 (hump NH), 3088 (CH aromatic), 2923(CH aliphatic), 2222(CN), 1747(CO acetoxy ester), 1682(C-O). ^{1}H NMR (DMSO-d_6): 1.97 ,2.00, 2.02, 2.03(s, 12H, 4CH_3 acetoxy), 3.98-4.22 (m, 2H, H_5+H_6), 4.96-5.00 (t, *J*= 9.60 Hz, 1H, H_2), 5.12-5.18 (m, 2H, H_2+H_{6b}), 5.56-5.65(m, 2H, H_3+H_4), 6.03, 6.06(d, *J*= 8.00 Hz, 1H, H_1), 7.56, 8.12 (m, 5H, ArH) , 13.19(s, 1H, NH pyrimidine). ^{13}C NMR ($CDCl_3$) : 20.66, 20.77 (2CH_3 : C15, C18 acetoxy), 20.83, 20.87(2CH_3: C9, C12 acetoxy), 62.42(CH_2: C6 glucose), 68.54(CH: C5 glucose), 69.05 (CH: C3 glucose), 73.21 (CH : C4 glucose), 75.56 (CH: C2 glucose), 80.83 (CH: C1 glucose), 91.26 (C5, pyrimidine), 115.17(CN: C7), 128.94 (C4ˋ: phenyl), 129.09, 129.21(C2ˋ,C6ˋ phenyl), 132.45, 132.62(C3ˋ,C5ˋ: phenyl), 135.36 (C1ˋ: phenyl), 158.97(C4 pyrimidine), 161.42 (C2 pyrimidine), 167.52 (C14: CO), 169.85 (C17: CO) , 170.01 (C11: CO), 170.38(C8:CO). EI-MS(*m/z*): 543.63, 502.68, 430.92, 378.32, 331.03, 288.04, 186.10, 168.01 ,126.04,98.04. Anal. Cald. for: $C_{25}H_{25}N_3O_{10}S$ (559.55): C, 53.66; H, 4.50; N; 7.51; S,5.73 %. Found: C, 53.52; H, 4.36; N, 7.62; S, 5.80 %.

1-(4-(3-Chloro-1H-indol-2-yl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-yl)sulfanyl)-1H-2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (6b)

Yellow crystals, 41.00% (0.20 g) yield, m.p. 220-221^{o}C, FT-IR (ν, cm-1): 3270-3260 (broad 2NH), 2950 (CH aliphatic), 2221(CN),1757 (CO acetoxy ester), 1682(CONH), 1224(C-O). ^{1}H NMR (DMSO-d_6) :1.98, 2.00, 2.02 ,2.05(s, 12H, 4CH_3 acetoxy), 4.21, 4.22(d, 1H, J= 8.00 Hz, H6a), 4.24, 4.25 (dd, J=5.60 Hz, 1H, H_5), 4.24, 4.31(d, J= 3.20 Hz, 1H, H_2), 5.03-5.08(t, 1H, J= 9.60 Hz, H_4), 5.12-5.16 (t, J=8.00 Hz, 1H, H_{6b}), 5.45- 5.55 (t, 1H, J= 9.86 Hz , H_3), 6.15-.17(d, 1H, J= 5.10 Hz, H_1), 7.24-8.64 (m, 4H, ArH), 12.47 (s, 1H, NH indole), 13.22 (s, 1H, NH Pyrimidine). EI-MS (m/z): 606.41, 532.98, 499.03, 397.05, 337.05, 229.08, 201.09, 171.08, 129.11, 98.08, 77.07. Anal. Cald. for: $C_{27}H_{25}ClN_4O_{10}S$

(632.10): C, 51.23; H, 3.98; Cl, 5.60 N; 8.85; S,5.06 %. Found: C, 51.35; H, 4.09; Cl, 5.49 N, 9.01; S, 4.94 %.

Procedure of *in-vitro* antibacterial assay

All microorganisms utilized were attained from the culture combination of Microbiology Department, Faculty of Medicine, Assiut University. A variety of Gram-negative (*Escherichia coli* & *Pseudomonas aruginose*) and Gram-positive bacterial strains (*Staphylococcus aureus* & *Bacillus cereus*) was used to measure the efficacy of various synthesized compounds utilizing 5mL solution of the synthesized compounds in DMSO as a solvent. The examined compounds were primarily estimated by maximum concentration at 100 µg/ mL in DMSO and Amoxicillin as a reference. The sterile medium (Nutrient Agar Medium, 15 ml) in every Petri dish was uniformly smeared with cultures of Gram-positive and Gram-negative bacteria. The plates were incubated at 37± 2°C for 24 h.

Procedure of *in-vitro* antifungal assay

The fungal strains (*Candida albican*s, Aspergillus flavas, Geotrichum candidium and Trihophyton rubrum) were gained from selected conditions of human dermatophytosis (Assiut University Mycological Center, AUMC). The fungal kinds were developed in sterilized 9-cm Petri dishes containing Sabouraud's dextrose agar (SDA) supplemented with 0.05 % of amoxicillin to inhibit contamination of bacteria.[40]. The agar disks (10 mm diameter) containing spores from these cultures were aseptically transferred to screw-topped vials containing 20 mL sterile distilled water. After shaking, samples of the spore suspension (1 mL) were pipetted into sterile Petri dishes, followed by the addition of 15 mL liquefied SDA medium which was then left to solidify. The screened compounds **4a-f and 6a, 6b** and the reference drug (Clotrimazole) were dissolved in DMSO to provide 2.0 % concentration. The inoculated plates were incubated at room temperature for 4 days.

Antibacterial and antifungal activities of the tested compounds were determined consistent with the strategy described by Kwon-Chung and Bennett[41] using 5-mm-diameter wells loaded with 50 µL of the solution under study. Furthermore, stock solutions of the standard drugs (Amoxicillin and Clotrimazole) were prepared in

DMSO and 100 µg/ml concentration utilized for antimicrobial and antifungal efficiency. The zones of inhibition were determined and listed in **Tables 3** and **4**, respectively.

Procedure of in-vitro inhibition zone and (MIC)

The examined compounds **4a-f** and **6a,b** to be screened, were dissolved in DMSO to afford a solution of 2% concentration. Filter paper discs (Whatman No. 3) with about 5 mm in diameter were saturated with 15 mL of the tested compound solutions and then sited on the surface of the previously prepared agar plates which seeded by the tested bacteria. To ensure complete contact with the agar surface, each disc was immersed down. Subsequently, the agar plates were incubated at 37oC for 16–18 h for bacteria then at room temperature. The zones' diameters of the compound inhibition were measured and recorded in previously table. A similar procedure[40, 41] was implemented for commercial antibiotics Amoxicillin which was utilized as positive control for bacteria. The minimum inhibitory concentration (*MIC*) of every compound was determined by micro dilution method. The biologically active compounds were successively diluted in DMSO and incubated with 10 mL broth tubes vaccinated with the examined culture for 24 h. MIC of each compound was measured as the lowest concentration (µg mL^{-1}) that did not display any visible bacteria.

In vivo anti-inflammatory activity

Anti-inflammatory activity for the newly synthesized compounds 4a-f and 6a,b were measured in vivo using carrageenan-induced rat paw edema assay in comparison with indomethacin as a reference drug.[42, 43] The test is based on the pedal inflammation in rat paw induced by sub plantar injection of 100 µL of 1% freshly prepared solution of carrageenan in distilled water into the right-hind paws of each rat for all the groups; the tested compounds were dissolved in distilled water with sonication. Male adult albino rats (150-200g) were divided into six groups; each group contains three animals. The thickness of the rat paw edema was measured by a Vernier Caliper (SMIEC, China). Animals of groups A/ B/ C, were treated with a single dose of the tested compound, group D was treated with Indomethacin drug, respectively. Paw thickness were measured just

before the carrageenan injection, that is, at "0 hour" and then at 30 minutes,1, 2, 3, and 4 hours after carrageenan injection. Increasing in paw thickness was measured as a difference in the paw thickness at "0 hour" and paw thickness respective hours. The edema was expressed as a mean reduction in paw volume (mL) after treatment with tested compounds. The percent edema inhibition was calculated from the mean effect in the control and treated animals according to the following equation:

$$\textbf{Percent edema inhibition} = (1 - V_t/V_c) \times 100 \quad \textbf{Equation} \quad (1)$$

Where: V_t, means an increase in paw volume of test; Vc, means an increase in paw volume of control group of rats.

Statistical analysis

The results were analyzed by one way analysis of variance (ANOVA) followed by Newman-Keuls multiple comparison test as a post-test. These analyses were carried out using a computer prism program for windows, version 3.0 (Graph pad software, Inc., San Diego, CA, US). The significant differences between groups were accepted at P <0.05*, 0.01** or 0.001***, and the data are expressed as a mean ± standard error (SE).

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الملخص العربي

تخليق مركبات جديدة لمشتقات البيريدين ثيوجلكوزيد والبيريمدين ثيوجليكوزيد واستخدامها كمضادات للبكتيريا والفطريات ومضادات للالتهابات

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نظرا للاهميه البيولوجيه لمركبات الغيرمتجانسه الحلقه والتي تحتوي علي رابطه ثيوجليكوزيد قمنا في هذه الدراسه بتحضير العديد من مشتقات البيريدين والبريميدين الثيوجليكوزيد والتي تنتج من تفاعل كلا من : المورفولينيل ورباعي هيدروايزوكينولين ثيول ،المورفولينيل سيكلوبنتا [c] بيريدين ثيول و 3 كلوروراندوليل بريميدين ثيول مع 1برومو- 2،3،4، -6 رباعي-O-اسيتيل الفا -D-جلوكوبيرانوز في وجود خلات الصوديوم والايثانول . وتم اثبات التراكيب الكيميائيه للمواد الجديده المخلقه عن طريق التحاليل الطيفيه (وتشمل تحاليل الاشعه تحت الحمراء ،الطيف الرنين المغناطيسي لكلا من الهيدروجين والكربون 13 والتحليل الكتلي للمركبات) وايضا تحليل العنصر. وتم اختبار مركبات الثيوجليكوزيد الجديده المخلقه علي سلالات متنوعه من البكتيريا والفطريات المسببه للامراض وقد اظهر التحليل البيولوجي نتائج واعده للمركبات كمضادات للبكتيريا والفطريات كما اظهرت نتائج مبهره كمضادات للالتهاب مقارنه بعقار الاندميثاسين .

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