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Design and Facile Synthesis of New Bioactive C-glycosidic Semi-Natural Compounds

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THE presented work aims to synthesize new bioactive molecules of wide spectrum biological activity. In this study, a new series of α,β unsaturated ketones having acylic sugar residue was synthesized along with their hydrazone analogues.
Those new compounds were obtained via mild condensation reactions to avoid side products and were investigated by spectral analysis including IR, ^{1}HNMR (Proton Nuclear Magnetic Resonance),^{13}CNMR (C-13 Nuclear Magnetic Resonance) and mass spectrometer. In addition, they were tested and evaluated as antimicrobial and antioxidant agents.

Results revealed that compound **2d** is the most promising antimicrobial agent among the tested compounds and it even exceeds the activity of the used standard antibacterial drug Ampicillin as well as it competes with the standard antifungal drug Amphotericin B. On the other hand, compound **3b** shows potent antioxidant activity in comparison with the used standard drug Trolox. Structure-activity relationship is also discussed.

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Keywords: Bioactive molecules, C-glycosides, Antioxidant, Antimicrobial, Acetylfuran.

Introduction

Natural products, including sugars and coumarins, resemble main precursors for many naturally occurring antibiotic systems and compounds of

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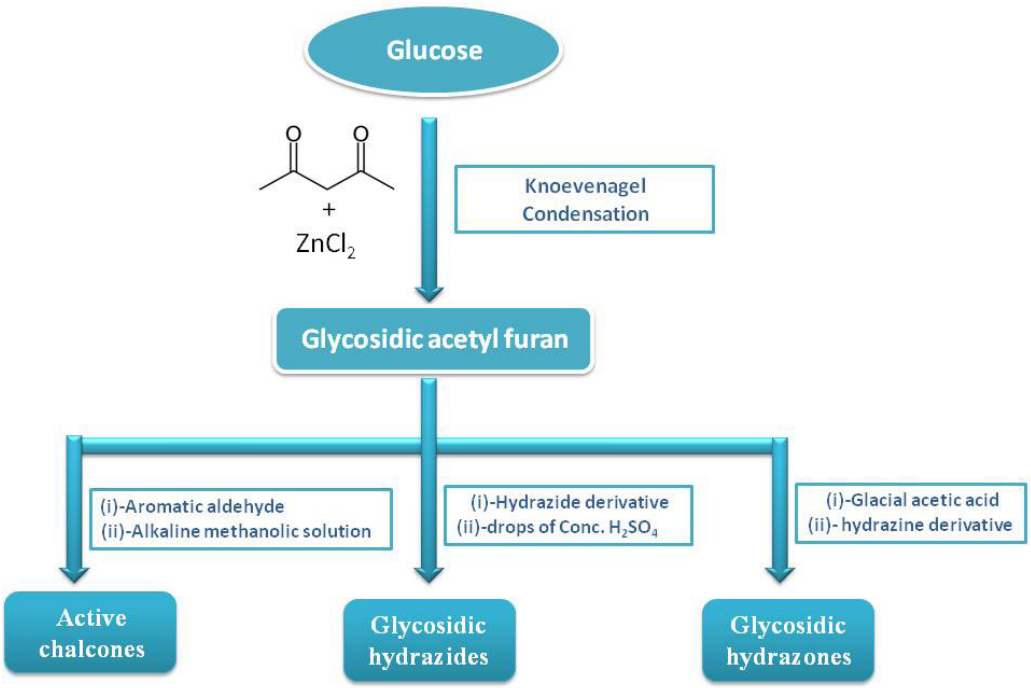
various biological activities [1,2], a reason directed our attention to utilize natural sugars for the synthesis of new anticipated bioactive molecules. Glycosides represent an interesting class in carbohydrate chemistry as they comprise a large group of secondary metabolites that play numerous important roles in living organisms. Many glycosides occur in plants, often as flower and fruit pigments; for example, anthocyanins which have antioxidant effects, may offer anti-inflammatory, anti-cancer and anti-viral benefits and appear to improve the cholestrol level and blood sugar metabolism [3]. In addition, various medicines, condiments and dyes from plants occur as glycosides; of great value are the heart-stimulating glycosides of *Digitalis* and *Strophanthus,* members of a group known as cardiac glycosides [4]. Several antibiotics are also glycosides such as streptomycin [5]. Saponins, widely distributed in plants, are glycosides which lower the surface tension of water and their solutions have been used as cleansing agents [6].

Although glycosides could be linked via *O*-, *N*-, *S*-, or *C*-glycosidic bonds, we are focusing in this work on the synthesis of new *C*-glycosides as they have received increasing interest recently due to their significant role as building blocks in the synthesis of many antibiotics and biologically active products [7,8]. They are considered as stable pharmacophores and are used in the synthesis of enzyme inhibitors [9] and drug molecules for certain viral diseases such as Hepatitis virus B, Human immunodeficiency virus (HIV), and Herpes viruses [10,11]. Besides, their substitution to *O*- or *N*- glycosidic linkages of the native carbohydrates structure increases the stability of such analogues against acidic or enzymatic hydrolysis with keeping similar flexibility and pharmacological characteristics [11,12].

Meantime, among various classes of heterocycles, naturally derived furans exhibit broad spectrum of biological activity such as antibacterial [13] and antifungal [14]. Therefore and in continuation to our program for synthesizing bioactive small molecules [15-17], it is interesting to synthesize new compounds linking both sugars and furyl moiety. The obtained *C*-furyl glycosides were synthesized *via* condensation of glucose with acetylacetone, followed by subsequent condensation with the corresponding aldehyde or hydrazino derivative under mild reaction condition. The newly synthesized derivatives were tested to evaluate their antimicrobial and antioxidant activities and the obtained results revealed that some of them showed high activity when compared with the used standard drugs.



Flow Chart

Result and Discussion

Chemistry:

When the reported acetylfuran **1** [18] was condensed with different aromatic aldehydes at room temperature, its ylidine chalcone derivatives **2a-d** were obtained in good yield (scheme 1). Their ^{1}HNMR spectra revealed involving of one CH_3 group of the parent acetylfuran **1** in condensation reaction, while the other methyl group remained in the newly synthesized chalcones and its signal appeared at δ 2.44 ppm. Furthermore, appearance of the characteristic olefinic ylidine protons at δ ~6.92 and 7.84 ppm supports the given propenone structure. ^{13}CNMR spectra as well showed new peaks attributed to the added aldehydic aromatic carbons.

Acetylfuran **1** was also condensed with cyanoacetohydrazide or thiocarbohydrazide in the presence of catalytic amount of H_2SO_4 to get the corresponding imino derivatives **3a,b**, respectively. IR spectrum of compound **3a** revealed the appearance of a new absorption band at υ 2265 cm^{-1} attributed to cyano group (CN) and a forked band at υ 3362-3247 cm^{-1} referring to the hydrazone NH. In addition, the parent carbonyl group band at υ 1677cm^{-1} disappeared and a forked one appeared at υ1681-1666cm^{-1} instead, which is characteristic to the hydrazone amide carbonyl group. The suggested structure of **3a** was also confirmed by^{1}HNMR spectrum which showed a new singlet signal at δ 4.00 ppm attributed to the cyano methylene group, along with a D_2O exchangeable signal for hydrazone NH at δ 10.82 ppm.

Moreover, spectral data obtained for **3b** was found to be compatible with the given structure. Its IR spectrum revealed the presence of (OH, NH and NH_2) absorption bands in the region of υ 3357-3101 cm^{-1}, as well as the presence of (C=S) band at υ 1215 cm^{-1}. ^{1}HNMR of **3b** showed D_2O exchangeable singlet signals at δ 6.85 and δ 10.90 ppm attributed to NH_2 and NH, respectively. Also, its ^{13}CNMR spectrum showed new peaks at 152.13 ppm for (C=N) and at 177.48 ppm for (C=S).

The given structure **3b** was also confirmed through its Mass spectrometer fragmentation pattern which showed molecular ion peak at m/z 332 for molecular formula $C_{12}H_{20}N_4O_5S$.

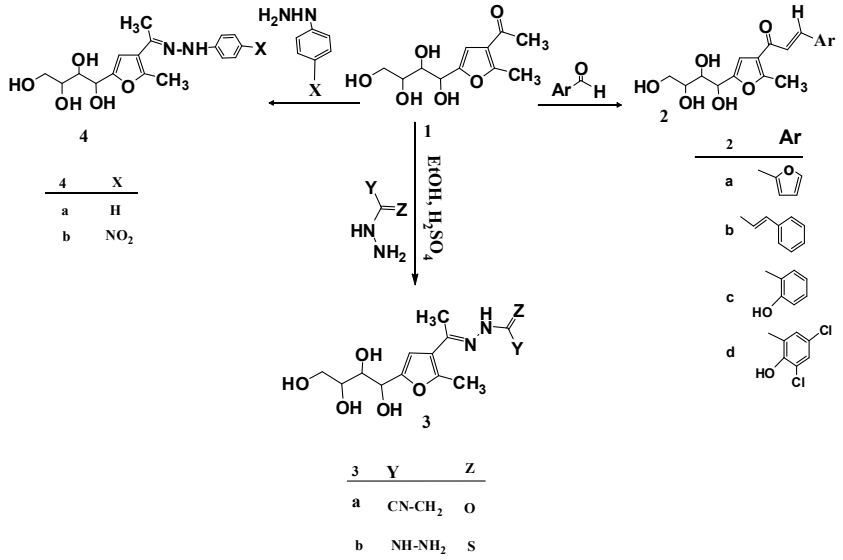
Continuing our investigation, acetylfuran **1** was stirred with phenyl hydrazine or it *p*-nitro derivative in glacial acetic acid at room temperature and the hydrazone derivatives **4a,b** were obtained. Structure of both products was evidenced by spectral data. IR spectra revealed the presence of new bands at υ 3463-3244 cm^{-1} for (NH), at υ 1600cm^{-1} for (C=N), and at υ1578-1561cm^{-1} for aromatic (C=C). ^{1}HNMR exemplified by **4a** showed a new multiplet signal at δ 6.97-7.82 ppm attributed to the phenyl protons as well as a new exchangeable singlet signal at δ 10.66 ppm attributing to (NH) proton.

Mass spectral fragmentation pattern of product **4b** confirmed its structure, and its IR spectrum showed the appearance of the two NO_2 characteristic bands at υ 1531-1469 cm^{-1}. In addition, its ^{13}CNMR spectrum revealed the presence of a new peak at 154.87 attributed to (C=N).

Some of the newly synthesized compounds were tested to evaluate their antimicrobial and antioxidant activities. Compound **2d** showed the highest antibacterial and antifungal activity, not only among the tested compounds, but also in comparison with the reference *Ampicillin* and *Amphotericin B*, respectively. The other tested compounds showed moderate antibacterial activity. On the other hand with regarding antioxidant activity, compound **3b** was more effective than the standard *trolox* while compounds **3a** and **4b** showed promising antioxidant activity.

In-vitro antimicrobial activity:

Measuring the diameters of inhibition zones to the nearest millimeter was performed and listed in Table 1. The results revealed that Compound **2d** is the most effective agent for both antibacterial and antifungal activities, even more than the standard ones (Ampicillin and Amphotericin B, respectively). Although the other tested compounds **1**,**2b**,**2c**,**3a**,**3b** and **4b** exhibited moderate anti-bacterial activity against all the test bacteria, only Compound **2b** showed high antifungal activity against ***Saccharomyces cerevisiae*** while the other compounds had no effect against any fungal species of the test except compound **1** with moderate antifungal activity on ***Saccharomyces cerevisiae***. It seems that the potency of **2d** was attributed to the presence of two electron-withdrawing chlorine atoms which enhanced the predominance of the bioactive quinonoid structure **5** [17] rather than the *O*-hydroxy configuration **2d**. In accordance with this view, the activity decreased in the absence of chlorine atoms as electron-withdrawing groups in derivatives **2a-c**.



Scheme 1

Scheme (1): Representative chart indicating the Methodology of the new compounds' synthesis

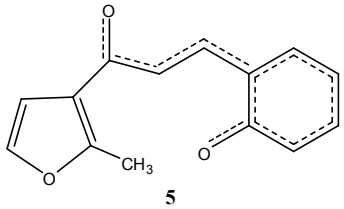


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TABLE 1: Screening for antimicrobial activities of the prepared compounds via measuring inhibition zones (mm):

	Inhibition zone diameter (mm/mg Sample)					
	Bacterial Species			Fungal Species		
	G^+	G-				
Sample	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Aspergillusflavus***	***Candida albicans***	***Saccharomyces cerevisiae***
Control: DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Ampicillin	21	25	26	--	--	--
Amphotericin	--	--	--	16	19	21
1	10	10	10	0.0	0.0	9
2a	0.0	0.0	0.0	0.0	0.0	0.0
2b	11	16	12	0.0	0.0	18
2c	11	12	12	0.0	0.0	0.0
2d	54	34	30	14	29	31
3a	10	10		0.0	0.0	
3b	13	13	11	0.0	0.0	0.0
4b	10	12	11	0.0	0.0	0.0

[1](*Ampicillin*), standard antibacterial drug.
[2](*Amphotericin B*), standard antifungal drug.

In-vitro antioxidant activity:

The Oxygen Radical Absorbance Capacity (ORAC) assay has been regarded as the golden standard assessment of antioxidant capacity. It can be used to assay the antioxidant activity of naturally occurring or synthetic compounds for use as dietary supplements, topical protection, and therapeutics. It depends on the free radical damage to a fluorescent probe through the change in its fluorescence intensity. The change of fluorescence intensity is an index of the degree of free radical damage. In the presence of an antioxidant, the inhibition of free radical damage by an antioxidant, which is reflected in the protection against the change of probe fluorescence in the ORAC assay, is a measure of its antioxidant capacity against the free radical (Figure 1 and Table 2).

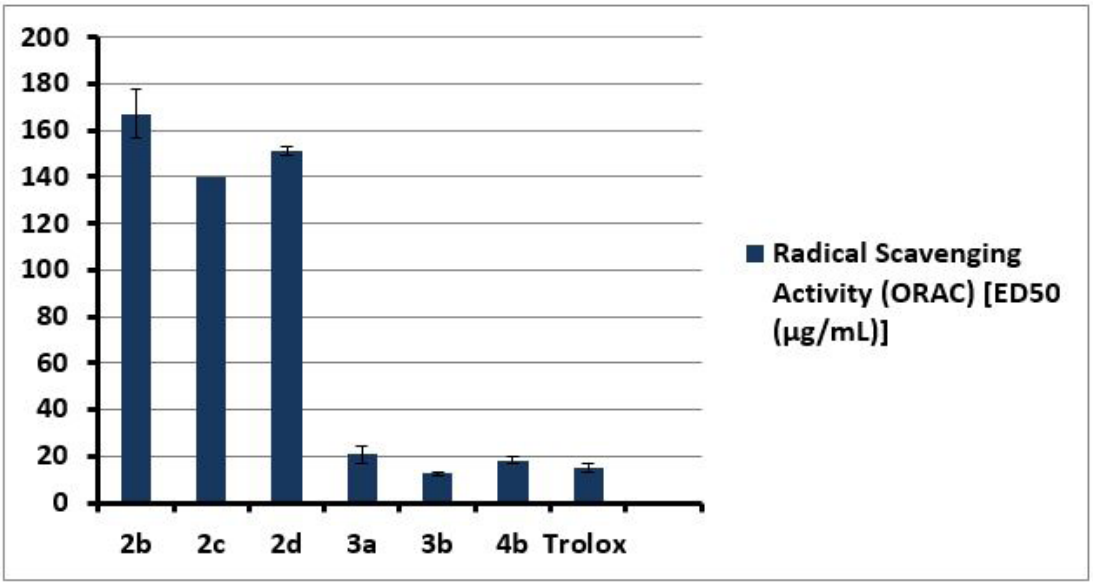


Figure (1): Radical Scavenging Activity (ORAC) of the newly synthesized compounds

TABLE 2: Radical scavenging activity (ORAC) of the prepared compounds:

	Radical Scavenging Activity (ORAC)
	ED_{50} (µg/mL)
2b	166.98±3.55
2c	140.31±1.88
2d	150.93±10.45
3a	20.67±1.45
3b	12.54±0.77
4b	18.35±1.93
Trolox	15±3.45

It could be noticed that the presence of an electron-withdrawing group such as cyano acetyl in **3a**, and *P*-nitro phenyl in **4b** decreased the availability of the hydrazino *N*-lone pair of electrons, while the thio hydrazino residue in **3b** enhanced the availability of this lone pair and added further available electron pairs which seem to enhance the ability for oxygen scavenging, rendering **3b** as potent antioxidant [19].

Experimental

Chemistry:

General:

Melting points were determined using electrothermal 9100 digital melting point apparatus (closed capillary tube method and are uncor-

rected). FT-IR spectra were obtained by JASCO FT/IR-4100 LE, power 170VA. NMR spectra were determined using Jeol JMS-AX 400 MHz, FT-NMR spectrophotometer, DMSO-d_6, TMS as internal standard chemical shift in δ(ppm), while Mass spectra were recorded on Varian MAT 311A at 70 eV. Pre-coated silica gel 60 F254 plates with a layer thickness 0.25 from Merck were used for thin layer chromatography. The yield was not optimized. Compound **1** was synthesized according to the published method [18].

General procedure for the synthesis of 3-aryl-1-(2-methyl-5-1,2,3,4-tetrahydroxybutyl)furan-3-yl)alkene-1-one (2a,b):

0.01Mole of acetylfuran **1** was dissolved in methanol with the addition of 0.01 mole of the desired aldehyde (furfural or cinnamaldehyde, respectively) and drops of alkaline solution (NaOH) till PH =9 while stirring for 2 days. The yellow precipitate formed was filtered, recrystallized and dried.

3-(furan-2-yl)-1-(2-methyl-5-1,2,3,4-tetrahydroxybutyl)furan-3-yl)prop-2-en-1-one (2a):

Yellow crystals (ethanol);yield 90%; m.p.198^{o}C.

IR(KBr,cm^{-1})υ:3268(OH),2941(aliphatic C-H),2912(ylidinic CH),1660(C=O),1618(furan C=C).

^{1}H NMR (400 MHz, δ ppm, DMSO-d_6):2.44(s,3H,CH_3),3.35-4.41(butyl,5H),4.34-5.08(4H,butyl 4OH),6.64(s,1H,furan H-4),6.76-7.84 (m,5H, ylidinic 2H, furfural 3H).

^{13}C NMR: 14.67 (CH_3), 63.79-72.96(butyl,4C),106.83-157.55(10C,2furyl,CH=CH),184.79(C=O).

m/z:322(M^+,2%),231(53%),153(100%).

Anal.Calcd. for $C_{16}H_{18}O_7$(322.31):C,59.62;H,5.63 ;Found: C,59.40;H,5.42%.

(4E)-1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl) furan-3-yl)-5-phenylpenta-2,4-dien-1-one (2b):

Yellow crystals (ethanol); yield 85%; m.p.172^{o}C.

IR(KBr,cm^{-1})υ:3255(OH),2962(aliphatic C-H), 2919(ylidinic CH),1664(C=O),1612(aromatic C=C).

^{1}H NMR (400 MHz, δ ppm, DMSO-d_6):2.57(s,3H,CH_3),3.45-4.78(butyl,5H),4.38-5.17(4H,butyl 4OH),6.72(s,1H,furan H-4),7.01-7.60(m,9H, ylidinic 4H, C_6H_5).

^{13}C NMR: 14.66 (CH_3), 63.81-73.07(butyl,4C),106.85(furan C-3),122.46(furan C-4),127.67-143.06(10C,C_6H_5,2CH=CH),155.72 (furan C-2),157.34(furan C-5),185.44(C=O).

m/z:157(10%),153(100%),128(21%),77(85%).

Anal.Calcd. for $C_{20}H_{22}O_6$(358.39):C,67.03; H,6.19; Found:C,66.83; H,5.99.

Synthesis of 3-(2-hydroxyphenyl)-1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl)furan-3-yl)prop-2-en-1-one (2c):

0.01 Mole of acetylfuran **1** and 0.01mole of salicylaldehyde were dissolved in methanolic KOH solution (0.015mole of KOH) while stirring at 50^{o}c for 2hrs. After the end of the reaction noticed by TLC, the reaction mixture was allowed to cool, concentrated, followed by addition of drops of HCl till pH=5. After getting rid of inorganic salt, the remaining filtrate was evaporated on evaporator rotatory device to dryness followed by addition of water. The formed precipitate was filtered, collected and recrystallized to give **2c**.

Brownish Yellow crystals(ethanol);yield 70%; m.p.214-216^{o}C.

IR(KBr,cm^{-1})υ:3366-3304(OH),2924(aliphatic C-H),2852(ylidinic CH),1657(C=O),1617(aromatic C=C).

^{1}H NMR (400 MHz, δ ppm, DMSO-d_6):2.50(s,3H,CH_3),3.52-4.80(butyl,5H),4.38-5.14(4H,butyl 4 OH),6.88 (s,1H,furan H-4), 6.85-7.93(m,6H,ylidinic 2H,C_6H_4),10.25(s,1H, salicylaldehyde OH).

^{13}C NMR: 14.70 (CH_3), 63.80-73.06(butyl,4C),107.02(furan C-3),116.67-157.60(11C,C_6H_4,CH=CH,furan C-2,C-4,C-5),185.75 (C=O).

m/z:153(100%),121(53%),93(26%).

Anal.Calcd. for $C_{18}H_{20}O_7$(348.35):C,62.06; H,5.79; Found: C,61.84; H,5.58.

Synthesis of 3-(3,5-dichloro-2-hydroxyphenyl)-1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl)furan-3-yl)prop-2-en-1-one(2d):

0.01 Mole of acetylfuran **1** was dissolved in ethanolic solution of KOH (0.04mole), along with the addition of 0.01 mole of 3,5dichlorosalicylaldehyde. Stirring was kept for few days while testing by TLC. The reaction mixture was then evaporated to dryness and the residue was neutralized by 50% aqueous acetic acid and left overnight. The solid formed was then filtered, recrystallized and dried.

Buff crystals (ethanol);yield 90 %; m.p.156^{o}C.

IR(KBr,cm^{-1})υ:3395(OH),2927(aliphatic C-H),2900(ylidinic CH),1658(C=O),1598(aromatic C=C).

^{1}HNMR(400MHz,δppm,DMSO-d_6):2.50(s,3H,CH_3),3.44-4.76(butyl,5H),4.38-5.14(4H,butyl 4OH),6.97(s,1H,furan H-4),7.55-7.97(m,4H,ylidinic 2H,C_6H_2),10.11 (s,1H,OH).

^{13}CNMR:14.74(CH_3),63.79-73.13(butyl,4C),107.12(furan C-3),122.45-158.02(10C,C_6H_2,CH=CH,furan C-2,C-4),185.37(furan C-5),192.62 (C=O).

m/z:188(100%),161(9%).

Anal.Calcd. for $C_{18}H_{18}Cl_2O_7$(417.24):C,51.82; H,4.35; Cl,16.99; Found: C,51.60; H,4.12; Cl,16.76.

Synthesis of 2-(1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl)furan-3-yl)ethylidene)hydrazide derivatives (3a,b):

0.01 Mole of acetylfuran **1** was dissolved in ethanol along with 0.01mole of the desired hydrazide (cyanoacetohydrazide or thiocarbohydrazide, respectively), with the addition of catalytic amount of Conc.H_2SO_4. Stirring was kept overnight. The formed precipitate was then filtered, washed by ethanol and dried.

2-cyano-N'-(1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl)furan-3-yl)ethylidene)acetohydrazide (3a):

White crystals (ethanol);yield 80%; m.p.188-189^{o}C.

IR(KBr,cm^{-1})υ:3531(OH),3362-3247(NH),2964-2915(aliphatic C-H),2265(CN),1681-1666(C=O),1567 (furan C=C).

^{1}HNMR(400MHz,δppm,DMSO-d_6):2.06(s,3H,CH_3),2.37(s,3H,CH_3),3.36-4.65(butyl,5H),4.21-5.01(4H,butyl 4OH),6.43(s,1H, furan H-4), 10.82(s,1H,NH).

^{13}CNMR:14.95-16.31(2C,2CH_3),27.39(CH_2),70.74-76.52(butyl,4C),109.44(furan C-3),119.93(furan C-4),120.39(furan C-5), 151.08(furan C-2),134.12(C≡N),148.44(C=N),173.32(C=O).

Anal.Calcd. for $C_{14}H_{19}N_3O_6$(325.32):C,51.69; H,5.89; N,12.92; Found: C,51.47; H,5.68; N,12.74%.

2-(1-(2-methyl-5-(1,2,3,4-tetrahydroxybutyl)furan-3-yl)ethylidene)thiocarbohydrazide (3b):

Buff crystals (ethanol);yield 70%; m.p. >300 ^{o}C.

IR(KBr,cm^{-1})υ:3357-3101(OH,NH,NH_2),2946 (aliphatic C-H),1566(furan C=C),1215(C=S).

^{1}HNMR(400MHz,δppm,DMSO-d_6):2.20(s,3H,CH_3),2.49(s,3H,CH_3),3.59-4.44(butyl,5H),4.02-4.49(4H,butyl 4OH),6.70(s,1H, furan H-4),6.85(s, 2H,NH_2),9.20(s,1H,NH),10.90(s,1H,NH).

^{13}CNMR:14.95-16.82(2C,2CH_3),70.81-76.63(butyl,4C),109.63(furan C-3),120.31(furan C-4),120.68(furan C-5),151.16(furan C-2),152.13(C=N),177.48(C=S).

m/z:332(M^+,1%),313(3%),239(4.5%),213(4%), 203(6%),129(15%),111(18%),110(15%).

Anal.Calcd. for $C_{12}H_{20}N_4O_5S$(332.38):C,43.36; H,6.07; N,16.86; S,9.65; Found: C,43.14; H,5.86; N,16.64; S,9.44.

Synthesis of 1-(5-methyl-4-(1-(2-hydrazono)ethyl)furan-2-yl)butane-1,2,3,4-tetraol derivatives (4a,b):

0.01 Mole of acetylfuran was dissolved in glacial acetic acid at 50^{o}C for 5 minutes, followed by addition of 0.01 mole of the desired hydrazine (phenyl hydrazine or 4-nitrophenylhydrazine, respectively) while stirring at room temperature. After the precipitate had been formed, it was filtered, washed and dried.

1-(5-methyl-4-(1-(2-phenylhydrazono)ethyl)furan-2-yl)butane-1,2,3,4-tetraol(4a):

Red crystals (ethanol); yield 70%; m.p.201-203^{o}C.

IR(KBr,cm^{-1})υ:3544-3244(OH,NH),3061-3030(aromatic CH),2967-2907(aliphatic CH),1600 (C=N),1578-1561(aromatic C=C).

^{1}HNMR(400MHz,δppm,DMSO-d_6):2.19(s,3H,CH_3),2.46(s,3H,CH_3),3.43-5.06 (butyl,5H), 4.33-4.55(4H,butyl 4OH), 6.80(s,1H, furan H-4), 6.97-7.82(m,5H, C_6H_5), 10.66(s,1H, NH).

^{13}CNMR:14.97-15.74(2C,2CH_3),62.95-73.09(butyl,4C),106.99(furan C-3),112.01(furan C-4),118.13-151.71(8C,C_6H_4,furan C-2,C-5),153.94(C=N).

Anal.Calcd. for $C_{17}H_{22}N_2O_5$(334.37):C,61.07; H,6.63; N,8.38; Found:C,60.80; H,6.42; N,8.16.

1-(5-methyl-4-(1-(2-(4-nitrophenyl)hydrazono) ethyl)furan-2-yl)butane-1,2,3,4-tetraol (4b):

Red crystals(ethanol);yield %; m.p.199-201°C.

IR(KBr,cm^{-1})υ:3559-3332 (OH,NH),2923(aliphatic C-H),1600(C=N),1531-1469(NO_2).

^{1}HNMR(400MHz,δppm,DMSO-d_6):2.22(s,3H,CH_3),2.51(s,3H,CH_3),3.39-4.72(butyl,5H),4.41-5.04(4H,butyl 4OH),6.53(s,1H, furan H-4),7.22-7.25(d,2H,$C_6H_4NO_2$,H-2 and H-6),8.11-8.13(d,2H, $C_6H_4NO_2$,H-3 and H-5),10.08(s,1H,NH).

^{13}CNMR:15.03-15.84(2C,2CH_3),63.79-73.22(butyl,4C),107.12(furan C-3),112.03(furan C-4),120.86-151.93(8C,C_6H_4,furan C-2,C-5),154.87(C=N).

m/z:230(50%),153(23%),138(20%),108(45%),92(50%).

Anal.Calcd. for $C_{17}H_{21}N_3O_7$(379.36):C,53.82; H,5.58; N,11.08; Found:C,53.60; H,5.37; N,10.86%.

Antimicrobial screening:

Antimicrobial activity of the tested Compounds was determined at Micro Analytical center of Cairo University, Egypt, using a modified Kirby-Bauer disc diffusion method [20].The activity of the tested samples was studied against ***Staphylococcus aureus***(as Gram positive bacteria), ***Escherichia coli*** as well as ***Pseudomonas aeruginosa***(as Gram negative bacteria), and three different pathogenic fungi ***Aspergillus flavus,*** ***Candida albicans*** and ***Saccharomyces cerevisiae***. Briefly, 100 µl of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/ml for fungi [21]. 100 µl of microbial suspension were spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method [22].

Plates inoculated with filamentous fungi *as* ***Aspergillus flavus*** were incubated at 25°C for 48 hours; inoculated with Gram (+) bacteria as ***Staphylococcus aureus***, ***Bacillus subtilis***; Gram (-) bacteria as ***Escherichia coli***, ***Pseudomonas aeuroginosa,*** were incubated at 35-37°C for 24-48 hours and inoculated with yeast as ***Candida albicans*** were incubated at 30°C for 24-48 hours. Then diameters of the inhibition zones were measured in millimeters [20]. Standard discs of **Ampicillin** (Antibacterial agent), **Amphotericin B** (Antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control.

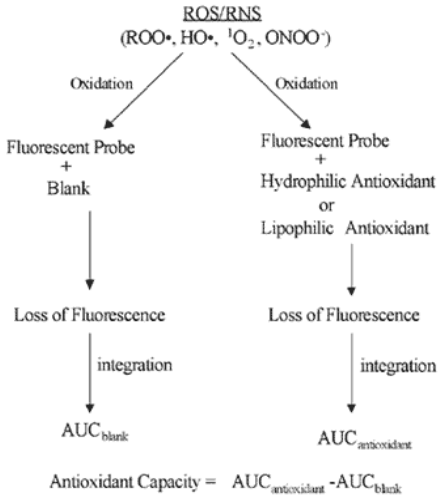
Blank paper disks (Schleicher&Schuell, Spain) with a diameter of 8.0 mm were impregnated 10µ of tested concentration of the stock solutions. When a filter paper disc impregnated with a tested chemical is placed on agar, the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc. If an organism is placed on the agar, it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as a "**Zone of inhibition**" or" **Clear zone**".

For the disc diffusion, the zone diameters were measured with slipping calipers of the National Committee for Clinical Laboratory Standards [23].Agar-based methods such as Etest and disk diffusion can be good alternatives because they are simpler and faster than broth-based methods[24,25].

Oxygen radical absorbance capacity (ORAC) assay:

Reactive oxygen species(ROS) are generated by the thermal degradation of 2,2"-azobis (2-amidinopropane) dihydrochloride (AAPH)

and quench the signal of the fluorescent probe fluorescein. The subsequent addition of antioxidants reduces the quenching by preventing the oxidation of the fluorochrome(Brand-Williams, et al. 1995). [26] A vitamin E derivate, 6-hydroxy-2,5,7,8-tetra-methylchroman-2- carboxylic acid (Trolox), was used as a positive control. Tested compounds were dissolved in phosphate buffered saline (10mM, pH 7.4) and investigated for their antioxidant capacity. Experiments were done in black 96well plates. In each well of a 96 well plate, 150µl fluorescein (final concentration: 2.5 nM), 25µl Trolox (final concentrations: 0.78–25 µM) or 25µl tested compound were pipetted in quadruplicate. Plate was allowed to equilibrate at 37°C for 30min. After this time, fluorescence measurements (Ex. 485 nm, Em. 520 nm) were taken every 90 sec; first to determine the background signal. After three cycles, 25 µl AAPH (final concentration: 60 mM) was added manually in each well with a multi-channel-pipette. This was done as quickly as possible since the ROS generator displays immediate activity after addition. Fluorescence measurements were continued for 90min [27]. Half life time of fluorescein was determined using MS Excel software.



Conclusion

This work aims to synthesize new semi-natural bioactive molecules utilizing available starting materials and using simple and productive methods as important industrial aspects to produce the potent candidates. The chemical structures of the newly synthesized compounds were evidenced by spectral analysis. Their antimicrobial and antioxidant activities were also evaluated. Results revealed that compound **2d** is the most promising antimicrobial agent when compared with the other tested compounds and the used standard antibacterial and antifungal drugs, while compound **3b** shows potent antioxidant activity in comparison with the used standard drug *Trolox*. It could be concluded that the presence of electron withdrawing groups such as chlorine atom in **2d** enhances the antimicrobial activity in the presented chalcones. On the other hand, it seems that the availability of *N*-electron lone pairs enhances the oxygen scavenging ability of the hydrazone group as in thiohydrazino derivative **3b** which increases the antioxidant activity.

Conflicts of interest

None.

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