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A Facile Synthesis, Spectroscopic Identification, and Antimicrobial Activities of Some New Heterocyclic Derivatives from D-erythro-2,3-hexodiuloso-1,4-lactone-2-(*o*-chlorophenyl hydrazone)-3-oxime

Nagwa M. M. Hamada[1], Sohila H. Mancy[1], Mohamed A. El Sekily[2]

[1]Department of Physics and Chemistry, Faculty of Education, University of Alexandria, 21526 Alexandria, Egypt

[2]Department of Chemistry, Faculty of Science, University of Alexandria, 21321 Alexandria, Egypt

Correspondence: Nagwa M. M. Hamada, Department of Physics and Chemistry, Faculty of Education, University of Alexandria, 21526 Alexandria, Egypt.

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Abstract

A new series of different heterocyclic derivatives was prepared via a facile unimolecular condensation of D-iso ascorbic acid with *o*-chlorophenyl hydrazine to give D-**erythro**-2,3-hexodiulosono-1,4-lactone 2-(*o*-chlorophenyl hydrazine (**2**)**.** Reactions of (**2**) with hydroxylamine gave the 2-(*o*-chlorophenyl hydrazone)-3-oxime (**3**). On boiling with boiling acetyl chloride, (**3**) gave 2-*o*-chlorophenyl-4-(2,3-di-O-acetyl-D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (**4**). In the treatment of (**3**) with benzoyl chloride in pyridine the same dehydrative cyclization occurred giving, 2-*o*-chlorophenyl-4-(2,3-di-o-benzoyloxy-D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (**5**)**.** On the treatment of compound (**4**) with liquid ammonia in methanol, deacetylation occurred concurrently with the opening of the lactone ring, to afford the 2-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxamide **(6).** Similarly, treatment of compound (**4**) with hydrazine hydrate in methanol, afforded 2-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid hydrazide (**7**)**.** The controlled reaction of (**3**) with sodium hydroxide, followed by neutralization, gave 3-(D-erythro-glycerol-1-yl)-4,5-isoxazoline-5-(4H)-one-4-*o*-chlorophenyl hydrazone **(8).** Reaction of (**3**) with HBr-AcOH gave 5-O-acetyl-6-bromo-6-deoxy-D-erythro-2,3-hexodiulosono-1,4-lactone-2-(o-chlorophenyl hydrazone)-3-oxime (**9**); these were converted into 4-(2-**O**-acetyl-3-bromo-3-deoxy-L-**threo**-glycerol-l-yl)-2-aryl-1,2,3-triazole-5-carboxylic acid 5,4[1]-lactones on treatment with acetic anhydride-pyridine. Compound (3) treatment with bromine-water caused its cyclization and bromination of the phenyl group to give carboxylic acid 5,1′-lactone (**10**)**.** Acetylation of **(10)** gave the diacetate **(11),** which upon treatment with hydrazine hydrate in methanol, afforded compound **(12),** mild acetylation of compound (**12**) gave the triacetate **(13)** boiling of (**13**) with acetic anhydride afforded hexa acetyl derivative (**14**). on the treatment of compound (**11**) with liquid ammonia in methanol deacetylation occurred to afford 1,2,3-triazole-5-carboxamide derivative (**15**)**.** On the other hand, treatment of compound (**3**) with bromine-water for a short time yielded 3-oxime (**16**)**.** Subsequent acetylation with boiling acetic anhydride afforded compound **(11).** In addition, acetylation of compound **3** afforded a diacetyl derivative assigned as 5,6-di-O-acetyl-D-erythro-2,3-hexodilusono-1,4-lactone-(2-*o*-chlorophenyl hydrazone)-3-acetoxime (**17**), which on boiling with acetic anhydride cyclization occurred giving compound **(4).** On the treatment of Dehydro-L-ascorbic acid-2-phenyl hydrazone (L-threo-2,3-hexodiulosono- 1,4-lactone 2-phenylhydrazone **(19)** with acetic anhydride/pyridine, afforded 5,6-di-O-acetyl-3-acetoxime **(20)** that upon treatment with boiling acetic anhydride, afforded the triazole derivative **(21).** Furthermore, treatment of the monophenyl hydrazone **(18)** with S-benzyl hydrazine carbodithiolate in the presence of acetic acid, afforded the bis-hydrazone, L-threo-2,3-hexodilusono-1,4-lactone-3-(S-benzylhydrazinocarbodithiolate)-2-phenylhydrazone **(22)**. Acetylation of compound **(22)** with acetic anhydride and pyridine did not give the di-O-acetyl derivative expected but instead, elimination of a molecule of acetic acid and partial hydrolysis of a hydrazone residue took place to give compound **(23).** The structures of all the synthesized compounds were confirmed using elemental analysis and different spectral tools. Eight samples from the synthesized compounds, **2,3, 4,10.16,11,12,17** were tested for their antimicrobial activity and they showed no activities.

Keywords: *o*-chlorophenyl hydrazine, isoxazoline, triazole, acetoxime, antibacterial, antifungal

1. Introduction

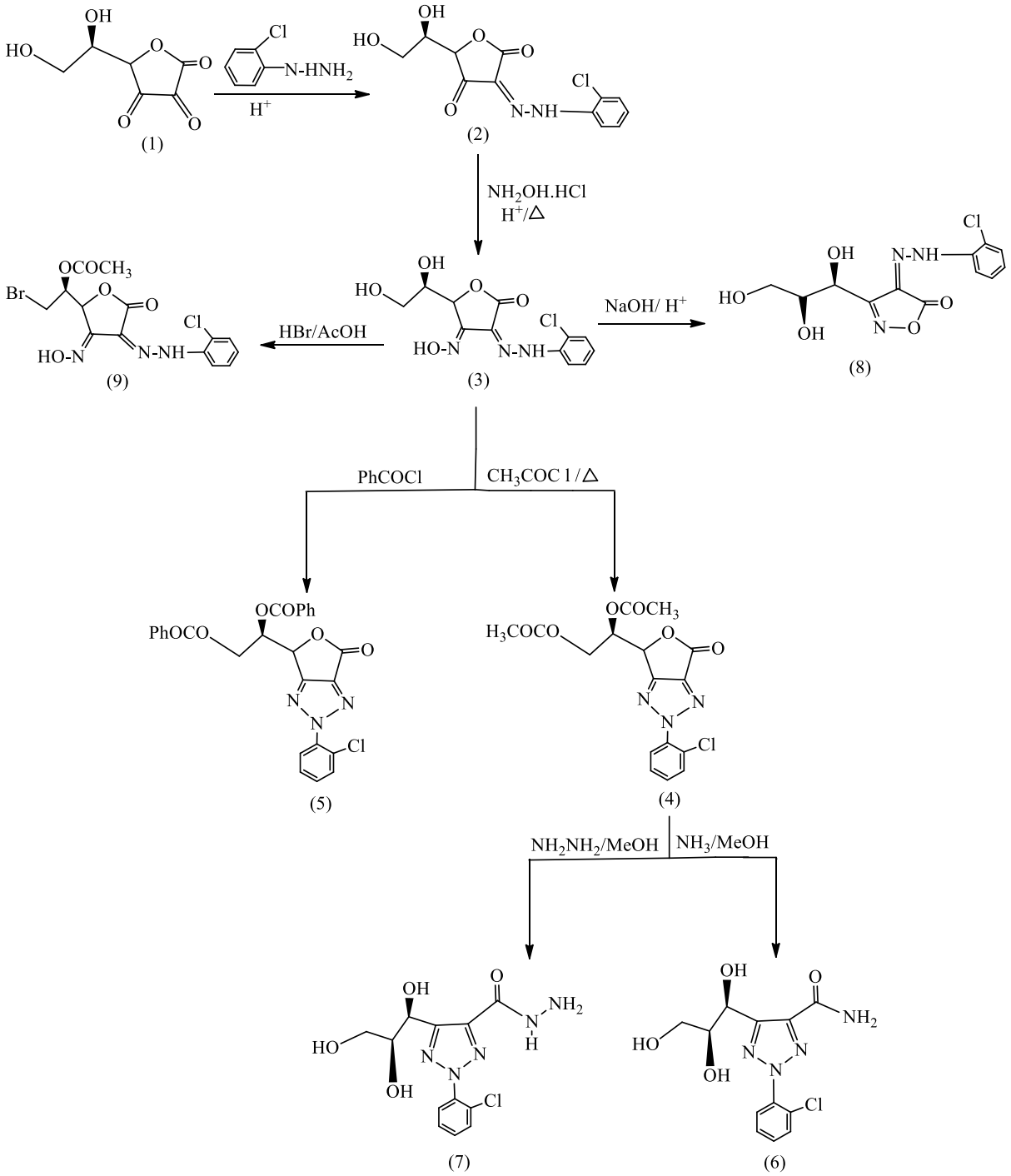
Biologically active compounds play a significant role in our daily life. Heterocycles are a significant component in drug development programs, as one of the prominent medical motifs, the oxime ester moiety is featured in many bioactive compounds by a wide range of activities, including antibacterial, antifungal, anti-inflammatory, antioxidant, anti-diabetes, and cytotoxic activities (Liu, X.H, et al., 2008; Gao, Y., et. al., 2012; Attia, M.I, et al., 2013; Wang, D, et al., 2014; Krishnan, G.K, et al., 2015). They also showed interesting insecticidal activities (Tsukamoto, Y, et al., 1991; Sun, R, et al., 2010; Song, H, et al., 2013; Yu, X, et al., 2015). Furthermore, these compounds are important starting materials in the preparation of photosensitive compositions (Xu, J, et al., 2012; Turro, N.J., et al., 2012). Nitrogen-containing heterocyclic rings are the main framework of various biologically active compounds showing a variety of applications in pharmacological and agrochemical industries. Because of their widespread potential for pharmacological activities, such as anti-inflammatory (A. Tewari, 2001), antitumor (A. Tewari, et al., 2007), anticonvulsant (V. Michon, et al., 1995), and antimicrobial (R. Sridhar, et al., 2004). Our continuous studies have demonstrated the utilization of heterocyclic compounds including triazoles, pyrazoles, imidazoles, and isoxazoles which possess different pharmaceutical activities. (Goverdhan, L., et al., 2001; Ren, R.X., et al., 2001; Ballini, R, et al., 1997; Kundu, S.K. et al., 2012). Oxime esters are most often prepared by a simple reaction of easily available oximes (Kumar, S.C.S, et al., 2014) with an acyl halide or anhydride (Bindu, P., et, al., 2012). It is known that the oxidation of dehydro-L-ascorbic bis hydrazone yields bicyclic azo compounds (El Khadem H, et al., 1968). The triazole derivatives of dehydro-L-ascorbic acid and its 5-epimer have been prepared (El Sekily MA, et al., 1982; El Sekily MA, et al., 2017; El Sekily MA, et al., 2018), through dehydrative cyclization of its 3-oxime-2-phenyl hydrazone. Similarly, the p-bromo phenyl analogs were prepared by bromine's action in water (El Sekily MA, et al., 1982). The insecticidal properties of 2-(*p*-chlorophenyl) and 2-(*m*- chlorophenyl)-1,2,3-triazoles have been discussed (El Sekily MA, et al., 2018). and as a continuation of our work (El Sekily MA, et al., 2019; Hamada, N.M.M., et al., 2019). we herein describe the synthesis and some reactions of the *o*-chloro- and *o*-chloro-*p*-bromo phenyl triazoles prepared from dehydro-D-iso ascorbic acid (D-erythro-2,3-hexodiulosono-1,4-lactone) and 2-*o*-chlorophenyl hydrazone-3-oxime.

2. Results and Discussion

2.1 Chemistry

Unimolecular condensation of dehydro-D-iso-ascorbic (D-Erythro-2,3-Hexodihlosono-1,4-lactone) **(1)** with *o*-chlorophenyl hydrazine at room temperature, afforded dehydro- isoascorbic acid hydrazone D-Erythro-2,3-Hexodiulosono-1,4-lactone-2-(*o*-chlorophenyl hydrazone) **(2),** and on treatment with hydroxylamine, it afforded D-Erythro-2,3-Hexodiulosono-1,4-lactone-2-(*o*-chlorophenylhydrazone)-3-oxime **(3)**. Dehydrative cyclization and concomitant acetylation of (**3)** with boiling acetyl chloride, gave 2-*o*-chlorophenyl-4-(2,3-di-O-acetyl-D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone **(4)** according to the mechanism described it was established, that when an oxime reacts with acetyl chloride (AcCl), an interesting transformation occurs to form an acetoxime, the acetoxime can undergo a rearrangement known as the Beckmann rearrangement (Corma A, 1991). In this rearrangement, the hydroxylamine group (-NH_2OH) migrates from the nitrogen atom to the adjacent carbon atom. the result is the formation of a new compound **(4).** The structural formula of compound **(4)** was confirmed using elemental analysis and several spectroscopic techniques such as IR, and ^{1}H-NMR spectroscopy. The IR data showed two vibrational bands at 1780 cm^{-1}, and 1710 cm^{-1} for the lactone carbonyl group and the ester one respectively. In addition, a vibrational band appeared at 1600 cm^{-1} belonging to the imine group C=N. The absence of the stretching band of the hydroxyl group initially indicates the synthesis of the expected compound. The ^{1}H-NMR spectra of (**4)** were obtained in which all the expected chemical shifts were observed. However, the spectrum showed two acetyl protons at δ 2.04 and 2.17 ppm in addition to the other proton signals of the compound**.**

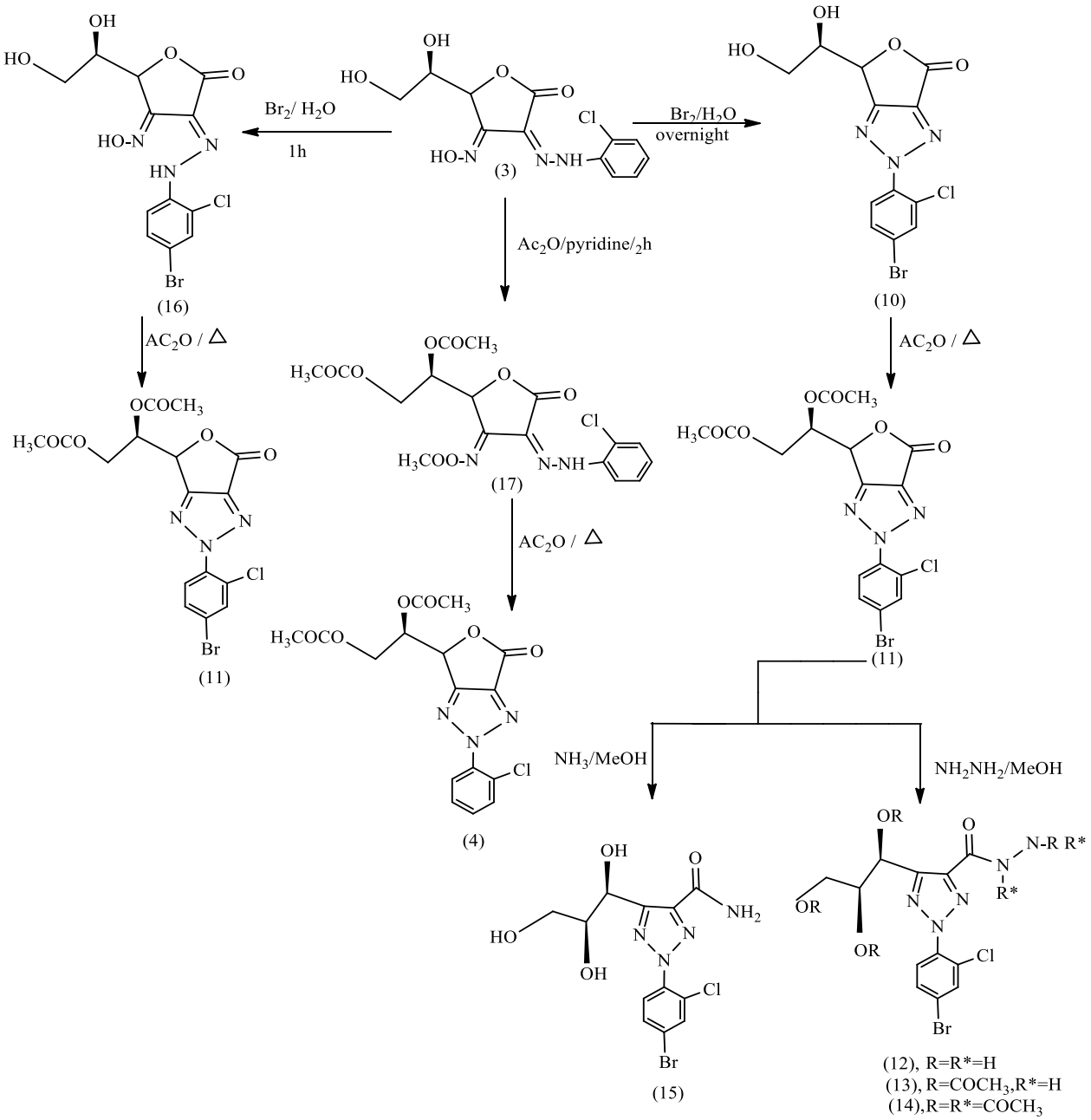
Similarly, treatment of (**3)** with benzoyl chloride in pyridine the same dehydrative cyclization occurred giving, 2-*o*-chlorophenyl-4-(2,3-di-o-benzoyloxy-D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (**5).** On the treatment of compound (**4)** with liquid ammonia in methanol, deacetylation occurred concurrently with the opening of the lactone ring, to afford the 2-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxamide **(6).** Similarly, treatment of compound (**4)** with hydrazine hydrate in methanol, afforded 2-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid hydrazide **(7).** On the controlled treatment of compound **(3)** with sodium hydroxide followed by acidification, the opening of the lactone ring occurred followed by the elimination of a molecule of water, affording 3-(D-erythro-glycerol-1-yl)-4,5-isoxazoline-5-(4H)-one-4-*o*-chlorophenyl hydrazone **(8).** Treatment of compound **(3)** with hydrogen bromide in acetic acid, gave 5-O-acetyl-6bromo-6-deoxy-D-erythro-2,3-hexodiulosono-1,4-lactone-2-(*o*-chlorophenyl hydrazone)-3-oxime (**9) (Scheme 1).**



Scheme (1). Preparation of new compounds (3-9)

The infrared spectrum of **(9)** showed a band at 1750 cm^{-1} due to the lactone and ester groups, in addition to the hydroxyl absorption at 3300 cm^{-1}. Treatment of compound (**3)** with bromine-water for 24 hours at room temperature, caused its cyclization and bromination of the phenyl group to give 2-(p-bromo-*o*-chlorophenyl)-4-(D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid 5,1′-lactone (**10).** Acetylation of **(10)** with boiling acetic anhydride, afforded the diacetate **(11),** which upon treatment with hydrazine hydrate in methanol, afforded 2-(p-Bromo-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid hydrazide (**12).** The infrared spectrum of (**12)** showed the amide band at 1678 cm^{-1} and the hydroxyl absorption at 3218 cm^{-1}, mild acetylation of compound (**12)** with acetic anhydride pyridine, afforded a triacetate designated as 2-p-Bromo-o-chlorophenyl-4-(1′,2′,3′-tri-O-acetyl- D-erythro-glycerol-1-yl) -1,2,3-triazole-5-carboxylic acid hydrazide (**13).** On the other hand, boiling of (**13)** with acetic anhydride afforded hexa acetyl

derivative 2-p-Bromo-*o*-chlorophenyl-4-(1′,2′,3′-tri-O-acetyl-D-erythro-glycerol-1-yl)-1,2,3-triazole- 5-carboxylic acid-tri-N-acetyl- hydrazide (**14**). The ^{1}H-NMR spectrum of compound (**14**) showed three O-acetyl singlets of three protons at δ 2.38, 2.45, and 2.74 ppm. Furthermore, on the treatment of compound (**11**) with liquid ammonia in methanol deacetylation occurred with the opening of the lactone ring to afford 2-(p-Bromo-*o*-chlorophenyl)-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxamide (**15**)**.** On the other hand, treatment of compound (**3**) with bromine-water for a short time yielded D-erythro-2,3-hexodiuloso-1,4-lactone-2-(p-bromo-o-chlorophenyl hydrazone)-3-oxime (**16**)**.** Subsequent acetylation with boiling acetic anhydride afforded compound **(11).** In addition, acetylation of compound **3** with acetic anhydride in pyridine for a short time, afforded a diacetyl derivative assigned as 5,6-di-O-acetyl-D-erythro-2,3-hexodilusono-1,4-lactone-(2-*o*-chlorophenyl hydrazone)-3-acetoxime (**17**), which on boiling with acetic anhydride cyclization occurred giving 4- (2-*o*-chlorophenyl-4-(2,3-di-O-acetyl-D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone **(4). (Scheme 2).**

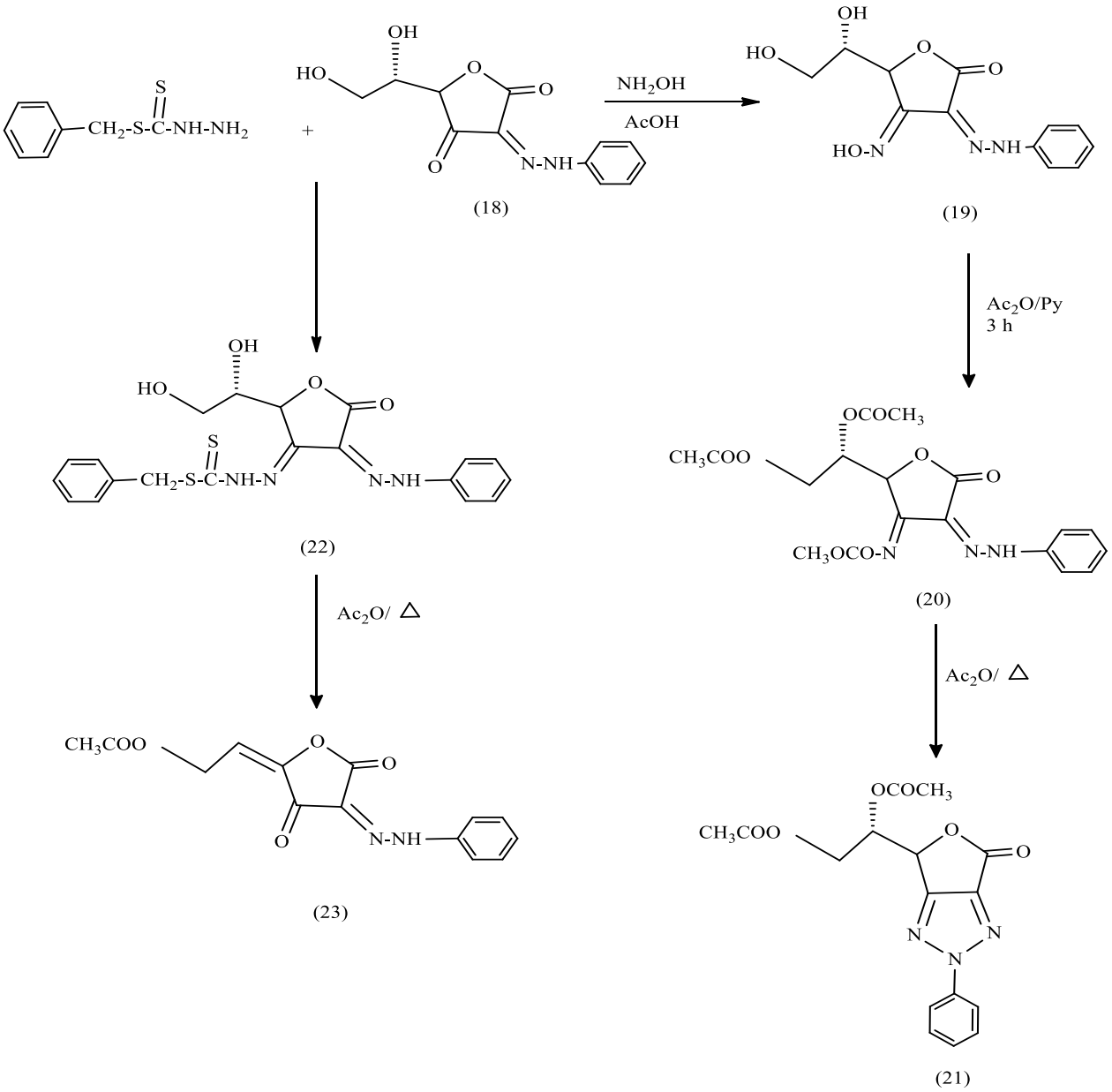


Scheme (2). Preparation of new compounds (10-17)

On the treatment of Dehydro-L-ascorbic acid-2-phenyl hydrazone (L-threo-2,3-hexodiulosono- 1,4-lactone 2-phenylhydrazone **(19)** with acetic anhydride/pyridine for short time (El Sekily, et al.,1994,1977) afforded 5,6-di-O-

acetyl-L-threo-2,3-hexodilosono-1,4-lactone-2-phenylhydrazone-3-acetoxime **(20)** that upon treatment with boiling acetic anhydride, afforded the triazole derivative **(21), (**Mancy, S.H., et al., 1994). **(Scheme 3).**

The H^1-NMR spectrum of **(21)** revealed two O-acetyl group signals at δ 2.04 and 2.06 ppm. Furthermore, treatment of the monophenyl hydrazone **(18)** with S-benzyl hydrazine carbodithiolate in the presence of acetic acid, afforded the bis-hydrazone, L-threo-2,3-hexodilusono-1,4-lactone-3-(S-benzylhydrazinocarbodithiolate)-2-phenylhydrazone **(22)**, Acetylation of compound **(22)** with acetic anhydride and pyridine did not give the di-O-acetyl derivative expected but instead elimination of a molecule of acetic acid and partial hydrolysis of a hydrazone residue took place to give 4-(2-acetoxyethylidene)-4-hydroxy-2,3-hexodiulosono-1,4-lactone-2-phenyl hydrazone **(23)**. (El Sekily MA., et al., 1979; El Khadem H., 1970).



Scheme (3). Preparation of new compounds (19-23)

2.2 Antimicrobial Activity

The antimicrobial activity of eight samples from the synthesized compounds, **2, 3, 4, 10, 11, 12, 16, 17** were tested against Gram-negative and Gram-positive bacterial strains Staphylococcus aureus (MRSA) (ATCC25923), Escherichia

coli (ATCC 8739), and a pathogenic yeast Candida albicans (ATCC 10231). The agar well-diffusion method (Ansari, F.L.,2005) was used for the qualitative evaluation of the antimicrobial activity and they showed no activities. **Table (1).**

Table (1). Antimicrobial activity of the tested synthesized compounds

References strains	Tested materials									
	+ve control	-ve control	2	3	4	10	11	12	16	17
Staphylococcus aureus (*MRSA)* (ATCC25923)	25 mm	-	-	-	-	-	-	-	-	-
E. coli (ATCC 8739)	20 mm	-	-	-	-	-	-	-	-	-
Candida albicans (ATCC) 10231)	28 mm	-	-	-	-	-	-	-	-	-

(-): no inhibition zone.

3. Materials and Methods

3.1 General Methods

Melting points were carried out on a Tottoli (Büchi) apparatus and were not corrected. IR (KBr) was recorded on Perkin-Elmer 580 VB spectrophotometer and ^{1} H- NMR spectra (CDCl3) and (DMSO-d6) on Camica 250 Hz spectrometer using TMS as an internal standard. Microanalyses were performed in microanalytical units in the Department of Chemistry, Faculty of Science, Cairo University, Cairo, Egypt. The antimicrobial activities were determined at the Pharmaceutical Science Park Unit (PSPU) Faculty of Pharmacy, Alexandria University. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60 f 254 plates.

3.2 Chemistry

D-erythro-2,3-hexodiuloso-1,4-lactone-2-(*o*-chlorophenyl hydrazone) (2). A solution of dehydro iso ascorbic acid (dehydro-D-arabino ascorbic acid) obtained by oxidizing iso ascorbic acid (20 g) in water (300 ml), was treated with o-chlorophenyl hydrazine (3g) and few drops of acetic acid, the reaction mixture was heated on a steam bath for about 1h and then kept at room temperature. Compound **2** was filtered off, washed successively with water, and ethanol, and dried (yield 1.2 g). It was recrystallized from ethanol to give yellow needles, m.p.155-156 °C. IR (KBr), ν_{max} = 3320 (OH), 3112 (NH), 1753 (lactone CO), 1672 (C=O) and 1600 cm^{-1} (C=N). Elemental Analysis:(%) Calcd for $C_{12}H_{11}ClN_2O_3$ (298.5): C,48.25; H,3.60; N,9.54. Found: C,48.25; H,3.72; N, 9.38.

D-erythro-2,3-hexodiuloso-1,4-lactone-2-(*o*-chlorophenyl hydrazone)-3-oxime (3). A solution of compound **2** (1g) in ethanol (30 ml) was treated with hydroxylamine hydrochloride (1g), sodium acetate (1g), and a few drops of acetic acid. The reaction mixture was boiled under reflux for 2h, concentrated, and cooled and the solid that separated was filtered off, successively washed with water, and ethanol, and dried (yield 0.5 g). It was recrystallized from ethanol in yellow needles, m.p.218-219°C. IR (KBr), ν_{max} = 3350 (OH), 1730 (lactone C=O), 1600 cm^{-1} (C=N). Elemental Analysis (%) Calcd for $C_{12}H_{12}ClN_3O_5$ (313): C,45.94; H, 3.85; N, 13.38. Found: C,46.38; H, 3.71; N, 13.73.

2-*o*-chlorophenyl-4-(2,3-di-O-acetyl-D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (4). A suspension of compound **3** (1g) in acetic anhydride (60 ml) was boiled under reflux for 1h. The reaction mixture was then cooled and poured onto crushed ice, the separated product was filtered off, successively washed with water, and ethanol, and dried (yield 0.4 g). Compound **4** crystallized from ethanol, to give colorless needles, m.p.99-100 °C. IR (KBr), ν_{max} = 1780 (lactone C=O), 1710 ($OCOCH_3$), and 1600 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 2.04, 2.10 (3H each, 2s, 2x $OCOCH_3$), 4.44 (2H, dd, H-3) ($J_{2,3'3.84}$,13. 20 Hz) 5.52 (1H, m, H-2′), 5.86 (1H, d, H-1) ($J_{1',2'}$ 5.23 Hz).7.42-8.10 (4H, m, Ar H). Elemental analysis: (%) Calcd for $C_{16}H_{14}ClN_3O_6$ (379.75): C, 50.60; H, 3.72; N, 11.07. Found: C, 50.72; H, 3.46; N, 11.19.

2-*o*-chlorophenyl-4-(2,3-di-o-benzoyloxy-D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (5). A solution of compound **3** (0.5 g) in dry pyridine (10 ml) was treated with benzoyl chloride (0.5 ml) and kept overnight at room temperature. The reaction mixture was poured onto crushed ice, and the separated product was filtered off washed with water, and ethanol, and dried (yield 0.6 g). It was recrystallized from ethanol to give colorless needles, m.p.103-104 °C. IR (KBr), ν_{max} = 1763 (lactone C=O and ester), and 1600 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 4.36 (2H, dd, C-3), ($J_{3',2'}$ 11.16 Hz), 5.80 (1H, m, H-2), 6.76 (1H, d, H-4) ($J_{4,5}$ 4.56 Hz).7.36-8.00 (14H, m, Ar H). Elemental

analysis (%) Calcd for $C_{26}H_{18}ClN_3O_6$ (503.89): C, 61.97; H, 3.60; N, 8.34. Found: C, 61.72; H, 3.46; N, 8.19.

2-*o*-chlorophenyl-(4-D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxamide (6). A solution of compound **4** (0.1g) in methanol (20 ml) was treated with concentrated ammonia (10 ml) and kept overnight at room temperature. The solution was concentrated under diminished pressure to a small volume, and the solid that separated was filtered off and dried (yield 0.6 g). It was recrystallized from ethanol in colorless needles, m.p.120-121°C. IR (KBr), ν_{max} = 3360 (OH), 3116 (NH), and 1600 cm^{-1} (C=N). Elemental analysis (%) Calcd for $C_{12}H_{13}ClN_4O_4$ (312.71**):** C, 46.09; H, 4.19; N, 17.92. Found: C, 45.88; H, 4.32; N, 17.31.

2-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid hydrazide (7). A solution of compound **4** (0.1g) in methanol (10 ml) was treated with hydrazine hydrate (0.5 ml) and was kept overnight at room temperature, water was added (10 ml), the product that separated was filtered off, washed with methanol, and dried (yield 0.4 g). It was recrystallized from ethanol to give colorless needles.m.p.186-187 °C; IR (KBr), ν_{max} = 3450 (OH), 3116 (NH), and 1600 cm^{-1} (C=N). Elemental analysis (%) Calcd for $C_{12}H_{14}ClN_5O_4$ (327.5**):** C, 43.97; H, 4.31; N, 21.40. Found: C, 44.02; H, 4.56; N, 21.32.

3-(D-erythro glycerol-1-yl)-4,5-isoxazoline-5-(4*H)*-one-4-(o-chlorophenyl hydrazone) (8). A solution of compound **3** (1g) in water (10 ml) was treated with a 10% solution of sodium hydroxide. The reaction mixture was heated for 10 minutes at 80 °C, then cooled and acidified with acetic acid, and kept overnight at room temperature. The separated product was filtered off, washed with water, and ethanol, and dried (yield 0.4 g). It was recrystallized from ethanol to give colorless needles, m.p.148-149 °C. IR (KBr), ν_{max} = 3380 (OH), 1730 (lactone C=O), and 1600 cm^{-1} (C=N). Elemental Analysis (%) Calcd for $C_{12}H_{12}ClN_3O_5$ (313.50): C,45.94; H,3.85; N, 11.48. Found: C, 45.62; H, 3;34; N, 11.12.

5-O-acetyl-6-bromo-6-deoxy-D-erythro-2,3-hexodiulosono-1,4-lactone-2-(*o*-chlorophenyl hydrazone)-3-oxime (9). Compound **3** (0.1 g) reacted with HBr/ HOAc (10 ml) by stirring for about 24 hours at room temperature. Water (20 ml) was added. The solid that separated was filtered off, washed successively with water, ethanol, and ether, and dried (yield 0.5 g). It was recrystallized from ethanol in yellow needles.m.p.210-211 °C, IR (KBr), ν_{max} = 3300 (OH), 1750 (lactone C=O and $OCOCH_3$), and 1600 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm)= 2.08, (3H, s, OAc), 4.36 (2H, d, H-3′), 5.22 (1H, m, H-2), 5.84 (1H, d, H-1′) ($J_{1',2'}$4.68 Hz). Elemental Analysis (%) Calcd for $C_{15}H_{15}BrClN_3O_5$ (432.65): C, 41.64; H, 3.49; N, 9.71; Found: C, 41.26; H, 3.36; N, 9.24.

2-(p-bromo-*o*-chlorophenyl)-4-(D-erythro-glyceryl-1-yl)-1,2,3-triazole-5-carboxylic acid 5,1′-lactone (10).

A suspension of compound **3** (1g) in water (30 ml) was treated portion-wise with bromine (1 ml) in water (10 ml) with stirring. Stirring was continued overnight at room temperature and then the excess of bromine was removed by passing a stream of air through the mixture. The solid that separated was filtered off, washed successively with water, and ethanol, and dried (yield 0.6 g). It was recrystallized from ethanol to give pale colorless needles, m.p.185-186°C. IR (KBr), ν_{max} = 3490 (OH), 1770 (lactone C=O) and 1600 cm^{-1} (C=N). Elemental analysis (%), calcd for $C_{12}H_9BrClN_3O_4$ (374.59): C, 38.47; H, 2.43; N,11.21. Found: C,38.58; H,2.46; 11.49.

2-(p-Bromo-*o*-chlorophenyl-4-(2′,3′-di-O-acetyl-D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (11). A suspension of compound **10** (0.1 g) in acetic anhydride (10 ml), was heated under reflux for 1 h and then cooled. The reaction mixture was poured onto crushed ice, and the solid that separated was filtered off, washed with water, and ethanol, and dried (yield 0.8 g). It was recrystallized from ethanol in colorless needles, m.p.110-111°C. IR (KBr), ν_{max} = 1780 (lactone C=O), 1710 ($OCOCH_3$), and 1600 cm^{-1} (C=N). ^{1}H- NMR ($CDCl_3$) δ (ppm) = 2.03, 2. 09 (3H each, 2s, 2x OAc), 4.32 (2H, dd, H-2′) ($J_{2',3'}$3.84, 3. 20 Hz) 4.52(1H, m, H-2), 5.52 (1H, d, H-1) ($J_{1',2'}$ 4.32 Hz).7.08-8.12 (3H, m, Ar H). Elemental Analysis, (%) Calcd for $C_{16}H_{13}BrClN_3O_6$ (458.65):C, 41.90; H, 2.86; N, 9.16. Found: C, 41.70; H, 2.26; N, 9.10.

2-(p-Bromo-*o*-chlorophenyl-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxylic acid hydrazide (12)

A solution of compound **11** (0.4 g) in methanol (20 ml) was treated with hydrazine hydrate (2 ml) and kept overnight at room temperature. Water (40 ml) was added and the solid that separated was filtered off, washed successively with water, and ethanol, and dried (yield 0.2 g). Compound **12** recrystallized from ethanol in colorless needles, m.p.130-131 °C. IR (KBr), ν_{max} = 2936 (NH), 1660 (OCN), and 1590 cm^{-1} (C=N). Elemental analysis (%) Calculated for $C_{12}H_{13}BrClN_5O_4$ (406.5): C, 35.42; H, 3.04; N, 17.22. Found: C,35.28; H, 3.21; N, 17.50.

2-p-Bromo-*o*-chlorophenyl-4-(1′,2′,3′-tri-O-acetyl- D-erythro-glycerol-1-yl) -1,2,3-triazole-5-carboxylic acid hydrazide (13).

A solution of compound **12** (0.1 g) in dry pyridine (10 ml) and acetic anhydride (5 ml) was kept overnight at room temperature. The reaction mixture was poured onto crushed ice, the separated solid was filtered off, washed with water, and ethanol, and dried (yield 0.4 g). It was recrystallized from ethanol in colorless needles, m.p.112-113 °C. IR (KBr),

ν_{max} = 3218 (NH), 1746 (ester), and 1678 cm^{-1} (OCN). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 2.01, 2.04, 2.10 (3H each, 3s, 3x OAc), 4.28 (2H, dd, H-2′) ($J_{2;3'}$ 3.38, 14.0 8 Hz). 5.36 (1H, m, H-2), 5.78 (1H, d, H-1) ($J_{1;2'}$,4.92 Hz), 7.32-8.02 (3H, m, Ar H). Elemental analysis (%) Calcd for $C_{18}H_{19}$ $ClBrN_5O_7$ (532.5): C, 40.56; H, 3.57; N, 13.14. Found: C,40.39; H, 3.32; N, 13.26.

2-p-Bromo-*o*-chlorophenyl-4-(1,2′,3′-tri-O-acetyl- D-erythro-glycerol-1-yl)-1,2,3-triazole- 5-carboxylic acid-tri-N-acetyl- hydrazide (14).

A suspension of compound 12 (0.1 g) in acetic anhydride (10 ml), was heated under reflux for 1 h and then cooled. The reaction mixture was poured onto crushed ice, and the solid that separated was filtered, washed with water, and ethanol, and dried (yield 0.8 g). It was recrystallized from ethanol in colorless needles, m.p.190-191 °C. IR(KBr), ν_{max} = 1748(ester), 1670 (OCN), and 1600 cm^{-1} (C=N). ^{1}H- NMR ($CDCl_3$) δ (ppm) = 2.05, 2.08, 2.14 (3H each, 3s, 3x O Ac), 2.38, 2.45, 2.74 (3H each, 3s, 3x N Ac), 4.38 (2H, dd, H-2) ($J_{2',3'}$ 5.12, 14.0 Hz). 5.82(1H, m, H-2), 6.47(1H, d, H-1($J_{1',2'}$ 6Hz), 7.26-7.94 (3H, m, Ar H). Elemental Analysis (%) Calculated for $C_{24}H_{25}BrClN_5O_{10}$ (658.85): C,43.75; H, 3.82; N, 10.86. Found: C,43.59; H, 3.66; N, 10.68.

2-(p-Bromo-*o*-chlorophenyl)-4-(D-erythro-glycerol-1-yl)-1,2,3-triazole-5-carboxamide (15). A solution of compound **11** (0.1g) in methanol (20 ml) was treated with concentrated ammonia (10 ml) and kept overnight at room temperature. The solution was concentrated under diminished pressure to a small volume. The solid that separated was filtered off, and dried (yield 0.2 mg), m.p. 162-163°C. IR (KBr), ν_{max} =3360 (OH), 1662 (OCN), and 1600 cm^{-1} (C=N). Elemental Analysis, (%) Calculated for $C_{12}H_{12}BrClN_4O_4$ (389.97): C,36.08; H,3.66; N, 14.29. Found: C, 36.72; H, 3;48; N, 14.36.

D-erythro-2,3-hexodiuloso-1,4-lactone-2-(p-bromo-*o*-chlorophenyl hydrazone)-3-oxime (16). A suspension of compound **3** (0.5 g) in water (30 ml) was treated with bromine. (2 ml) in water (10 ml), portion wise with stirring for 1h. Excess bromine was removed by passing a stream of air, the solid that separated was filtered off, washed with water, and ethanol, and dried (yield 0.3 g). It was recrystallized from ethanol to give pale yellow needles, m.p.254-255°C. IR (KBr), ν_{max} = 3335 (OH), 3135(NH), 1753 (lactone C=O), 1600 cm^{-1} (C=N). Elemental analysis (%) calcd for $C_{12}H_{11}BrClN_3O_5$ (392.60): C,36.71; H, 2.82; N, 10.70. Found: C,36.54; H, 2.61; N, 10.39. A suspension of compound **16** was treated with boiling acetic anhydride and proceeded as for compound **11,** it gave colorless needles, m.p.110-111°C, alone or mixed with compound **11** both products have the same IR and elemental analysis.

5,6-Di-O-acetyl-D-erythro-2,3-hexodilusono-1,4-lactone-2-(*o-chlorophenyl* hydrazone)-3-acetoxime (17). A solution of D-erythro-2,3-hexodiuloso-1,4-lactone-2-(*o*-chlorophenyl hydrazone)-3-oxime **3** (0.1g) in dry pyridine was treated with acetic anhydride (10 ml) and left for 2 hours at room temperature. The reaction mixture was poured onto crushed ice, and the product that separated was filtered off, washed with water, and ethanol, and dried (yield 80 mg). The product was recrystallized from ethanol to give red needles, m.p. 145-146 °C. IR (KBr), ν_{max} = 3252 (NH), 1746 (lactone C=O and ester), and 1600 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 2.04, 2.08, (3H each, 2s, 2 x OAc), 2.18 (3H, s, NOAc), 4.38 (2H, dd, C-2′) ($J_{2;3'}$ 4.53, 12.42 Hz). 5.80 (1H, m, H-5), 6.62 (1H, d, H-4) ($J_{4,5}$,6 Hz), 7.34-8.00 (4H, m, Ar H), 8.32 (1H, s, NH). Elemental Analysis (%) Calculated for $C_{17}H_{18}ClN_3O_8$ (427.79): C,47.69; H, 4.21; N, 9.82. Found: C,47.59; H, 4.44; N, 10.06. A suspension of compound **17** (0.1 g) in acetic anhydride (10 ml) was heated under reflux for one hour and proceeded as for compound **3.** It was crystallized from ethanol to give colorless needles m.p. 99-100 °C alone or mixed with compound **4.** Both products have identical IR and elemental analyses.

5,6-Di-O-acetyl-L-threo-2,3-hexodilosono-1,4-lactone-2-phenylhydrazone-3-acetoxime (20). A solution of L-threo-2,3-hexodilosono-1,4-lactone-2-phenylhydrazone-3-oxime **(19)** (El Sekily MA., et al., 1977); **(0.1g)** in dry pyridine (10 ml) was treated with acetic anhydride (10 ml) and kept for 4 hours at room temperature, (El Sekily, M.A, et al., 1977). The reaction mixture was poured onto crushed ice, the separated product was filtered off, washed with water, and ethanol, and dried (yield 70 mg). Compound **20** was recrystallized from ethanol to give yellow needles, m.p. 220-221 °C. IR(KBr), ν_{max} =3214 (NH), 1745 (lactone and ester), and 1600 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 2.05, 2.16, (3H each, 2s, 2 x OAc), 2.36 (3H, s, $NOCOCH_3$), 4.86 (2H, m, H-6), 5.22 (1H, m, H-5), 5.76 (1H, d, H-4) ($J_{4,5}$ 4.6 Hz), 7.54-8.30 (5H, m, Ar H), 9.32 (1H, s, NH). Elemental Analysis (%) Calculated for $C_{18}H_{19}N_3O_8$ (405.36): C,53.33; H,4.32; N, 10.37. Found: C, 53.32; H, 4.51; N, 10.12.

4-(L-threo-2,3-diacetoxy-1-hydroxy propyl)-2-phenyl-1,2,3-triazole-5-carboxylic acid-5,1′-lactone (21).

A compound **20** (0.1g) suspension in acetic anhydride (10 ml) was boiled under reflux for 1h. The mixture was cooled and poured onto crushed ice, and the product was filtered off, washed with water and ethanol, and dried (yield 70 mg). compound **21** was recrystallized from ethanol to give colorless needles, m.p. 99-100 °C (lit. m.p.100-101 °C), (El Sekily M.A, 1979).

L-threo-2,3-hexodilusono-1,4-lactone-3-(S-benzyl hydrazine carbodithiolate)-2-phenylhydrazone (22).

A solution of L-threo-2,3-hexodilusono-1,4-lactone-2-phenylhydrazone (El Sekily, M.A, et al., 1977). (0.1g) in ethanol

was treated with S-benzyl hydrazine carbodithiolate (0.2 g) and few drops of acetic acid and boiled under reflux for 3 hours, then concentrated and left to cool at room temperature. Compound **22** crystallized out, filtered off, and dried (yield 60 mg). It was recrystallized from ethanol in yellow needles, m.p.230-231 ˚C. IR (KBr), ν_{max} =3455 (OH), 1761 (lactone C=O), 1590 (C=N) and 1172 cm^{-1} (C=S). Elemental Analysis (%) Calculated for $C_{20}H_{20}S_2N_4O_2$ (444.39): C,54.04; H,4.53; N, 12.60. Found: C, 54.09; H, 4.32; N, 12.41.

4-(2-Acetoxyethylidene)-4-hydroxy-2,3-hexodiulosono-1,4-lactone-2-phenyl hydrazone (23).

A suspension of compound **22** (50 mg) in acetic anhydride (10 ml) was boiled under reflux for 1 hour, cooled, and poured onto crushed ice, the product was filtered off, washed with water and ethanol, and dried (yield 40 mg). Recrystallization from ethanol gave compound **23** as golden yellow plates, m.p.132-134 ˚C. (lit. m.p.132-134 ˚C), **(**Mancy, S.H. et al., 1994). Acetic anhydride and pyridine did not give the expected di-O-acetyl derivative, but instead, elimination of acetic acid and partial hydrolysis of a hydrazone residue took place to give 4-(2-Acetoxyethylidene)-4-hydroxy-2,3-hexodiulosono-1,4-lactone-2-phenyl hydrazone **23**. (El Sekily M.A, 1977; El Khadem, H, 1970)

3.3 Antimicrobial Activity

All compounds were tested against three different microorganisms Staphylococcus aureus, Escherichia coli, and Candida albicans. The agar well-diffusion method was applied for the determination of the inhibition zone.

3.3.1 Inoculum Preparation

- The stock culture of the reference strain (in glycerol broth) was sub-cultured onto soy broth.
- After overnight incubation, we cultivate the reference strains by swabbing on tryptic soy agar.
- After overnight incubation, the tops of each of 3-5 colonies of the organism pure culture to be tested were touched with a loop and suspended in a test tube containing 2 mL sterile saline.
- Turbidity of suspended colonies was compared to the 0.5 McFarland turbidity standard equivalent to 1-2x 10^8 CFU/Ml, and the density of organism suspension was adjusted by adding more bacteria or more sterile saline.

3.3.2 Preparation of Inoculated Agar

- Muller Hinton agar is weighed and dissolved in distilled water then sterilized by autoclaving after being divided into 25 Ml portions in 24 separate flasks.
- Flasks left to cool to 50˚C.
- Flasks were shaken and poured onto 28 sterile Petri dishes and left to solidify.
- Selected organisms were swabbed (each organism on 8 sterile Muller Hinton agar plates).
- With a sterile cork poorer, 4 wells (each 8 mm diameter) were made in each seeded agar plate.

3.3.3 Placing of Tested Material

- The eight compounds to be evaluated were dissolved in DMSO to give a final concentration of 1mg per ml.
- 70 µl for each of DMSO (negative control), selected antimicrobial agents (levofloxacin 80 µg/ml) for each of Staphylococcus aureus (ATCC 25923) and Escherichia coli (ATCC8739) and Natamycin 5% for candida albicans (ATCC 10231) (positive control) and tested compound were placed on the inoculated plates using a sterile automatic pipette directly onto its specific well (1 well for negative control, 1 well for positive control, 2 wells for the tested compound).

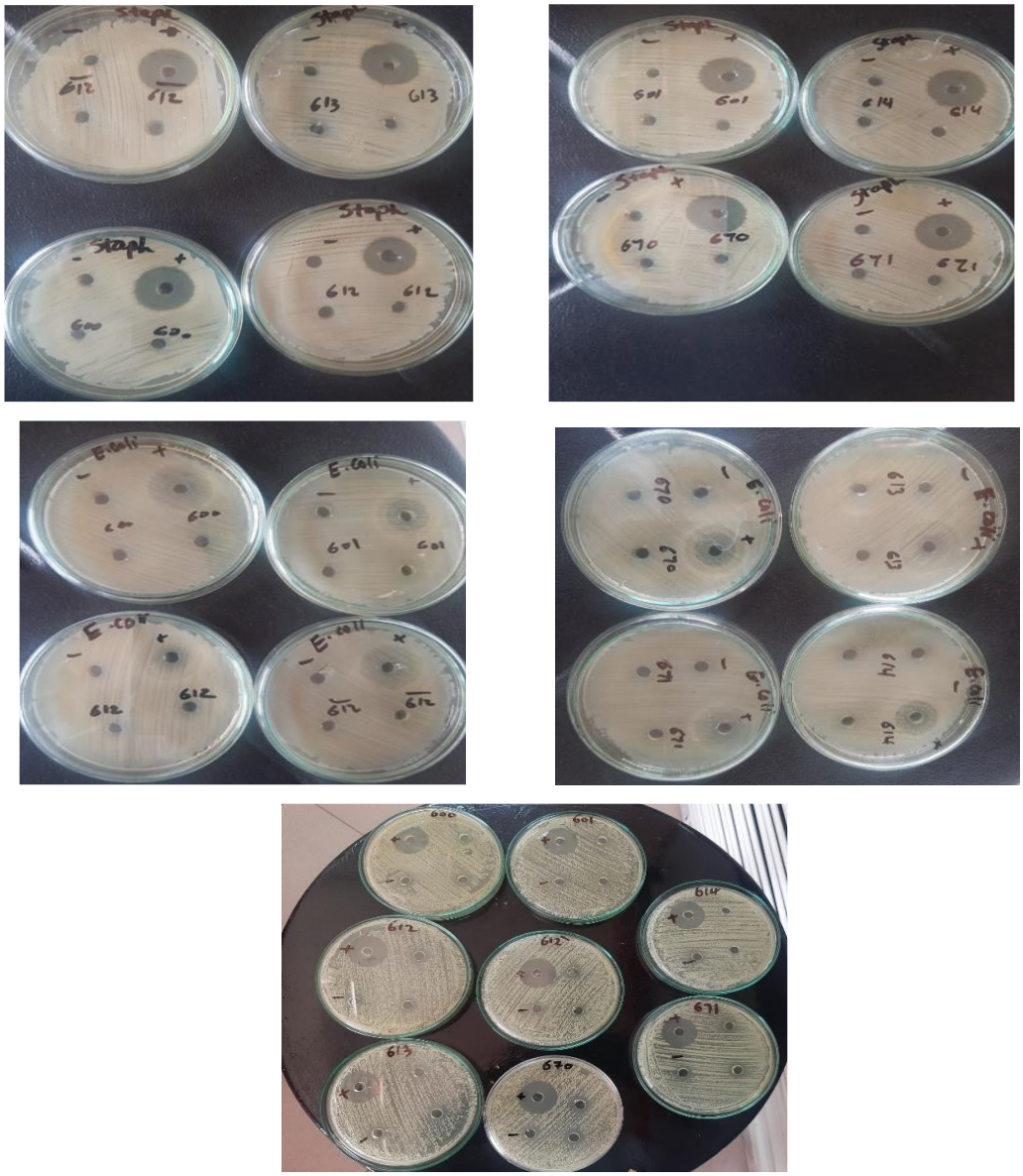


Figure 1. Inhibition zones of the tested compounds against Staphyllococus aureus, Escherichia coli and Candida albican

Key of compound numbers: 600=2; 601=3; 612=4;612=10 ;613=11 ;614= 12 ;670=16 ;671= 17.

3.3.4 Incubation

- Plates were incubated at 35 + 2° C for 24 hours.

3.3.5 Reading Results

- All measurements were made with the unaided eye while viewing the back of the Petri dish a few inches above a black, non-reflecting background and illuminated with reflected light.

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Authors contributions

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No additional data are available.

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