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Preparation of Triazole Mannose Derivatives from Galactaric Acid and Study their Antibacterial Activity

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ABSTRACT

In order to investigate new triazoles further, mannose derivatives were created. D-mannaric acid was first produced by oxidizing mannose with diluted nitric acid. 2,3,4,5-tetra-O-acetyl- mannaric acid was produced by acetylating d-mannaric acid with acetic anhydride, yielding the completely protected derivative having acetyl groups at positions (2,3,4,5). The acid chloride derivative produced by treating 2,3,4,5-tetra-O-acetyl- mannaric acid with thionyl chloride was then transformed into the semicarbazide and phenyl semicarbazide derivatives. The production of the bis-triazolyl derivatives was successfully achieved by intramolecular cyclization in the presence of potassium hydroxide. Additionally, we investigated the antibacterial activity of the produced compounds against two other strains of bacteria: Streptococcus pneumonia and Staphylococcus aureus. Some of these strains had the best antibacterial activity, matching that of the common antibiotic amoxicillin. Infrared spectra (IR) and nuclear magnetic resonance (NMR) for proton 1HNMR spectroscopy were used to confirm all derivatives.

Introduction

Triazole compounds' biological properties drew a lot of interest and made them attractive candidates for synthesis in organic chemistry.[1] Triazoles are heterocyclic substances with three nitrogen atoms and two carbon atoms arranged in a five-membered ring. Novel compounds having anticonvulsant, antidepressant, antioxidant, anti-inflammatory, analgesic, antinociceptive, antibacterial, antimycobacterial, antifungal, antiviral, anticancer, anti-parasitic, and other actions have been developed keeping these structures in mind. As a result, several scientists have created these compounds as target structures and assessed how biologically active they are.[2–5] Additionally, triazole-containing carbohydrates have been studied as potential inhibitors of fucosyl transferases and glycosidases, as well as a model for the substrate selectivity of β-1,2-mannosyltransferases.[6] Triazoles are extremely important because they are practically difficult to undergo oxidation or reduction and are stable hydrolytically.[7] Recent studies suggest that the 1,2,3-triazole moiety may be able to form dipole interactions and hydrogen bonds, which may facilitate the attachment to biomolecular targets and boost their solubility.[8] Pharmaceutical businesses are now concentrating on developing and researching new, safe medications for the market. As a result, scientists are inspired to create innovative structures in an effort to resolve these problems. In this sector, the chemistry of heterocycles and carbohydrates is difficult. In particular, heterocycles containing nitrogen have gained popularity in recent years and are thus found in many therapeutic compounds.[10,9] This paper discusses the biological activity of mannose-triazoles derivatives and their production.

Experimental.

Chemical and Apparatus

The following substances were purchased from their sources and utilized without additional purification: mannose, acetic acid, nitric acid, sulfuric acid, semicarbazide, and thionyl chloride. Standard procedures were followed in the laboratory to purify and dry the solvents. The remaining reagents were all analytical grade and were acquired from commercial sources. Using KBr disc, an IR spectrum was acquired in the 4000–500 cm-1 area using a Shimadzu spectrophotometer (FT-IR 8400S). The Bruker Am300 13MHz was used to collect all of the ^{1}H and ^{13}C NMR data.

Melting points of the synthesized compounds were determined using electro-thermal Stuart melting Point apparatus. The TLC plates (MERCK, 60F) was used to follow the development of the reaction and purity of the formed compounds, compounds were visualized by using KMNO4 solution.

Procedures

D-Mannaric acid (1)

A 500 mL container containing 30 g of dry mannose (0.142 mol) was filled with 150 mL of diluted nitric acid (HNO_3). The mixture was heated in a water bath until the volume reached 50 mL. At this point, we observed the formation of white crystals of D-Mannaric acid with a 50% yield. The R_F equaled 0.54 [benzene: methyl alcohol (8: 2)].

2,3,4,5- Tetra – O- acetyl – Mannaric acid (2)

After adding 25 mL of acidic acid to 10 g (47.58 mmol) of mannaric acid (1), drop by drop of concentrated H_2SO_4 was added. The mixture was then heated while being stirred to produce a transparent solution. Pour the solution over cold water when it has cooled. White crystals formed of 2,3,4,5-Tetra-O-acetyl- mannaric acid (2) will start to formed. After filtering and crystallizing the precipitate from ethanol, 72% of the precipitate was recovered, with a R_F of 0.72 [benzene: ethanol (9:1)].

2,3,4,5-Tetra – O-acetyl –Mannaroyl Dichloride (3)

Combine the 4, g, 0.019 mol compound of 2,3,4,5-Tetra-O-acetyl-mannaric acid (2) with the 18 mL of thionyl chloride. Allow the mixture to reflux in a water bath for two hours to produce a clear, slowly dissolving solution. After cooling the mixture at 0 °C, mixture until a suspension forms. The cooled water was filled with this suspension. After crystallizing the resultant product in chloroform, white crystals of 2,3,4,5-Tetra-O-acetyl-mannaroyl dichloride (3) 80% yield, Rf 0.62 [benzene –ethanol (6:4)] were obtained.

2,3,4,5 – Tetra – O –acetyl - semicarbazide Mannaric acid (4)

In 20 mL of ethanol, dissolve the derivative (3) (3 g, 0.012 mol). After 30 minutes, let the mixture sit, and then add 20 milliliters of the semicarbazide solution salt (it takes 5 percent sodium bicarbonate solution to dissolve 2.5 grams, 0.012 mol) to it. If the mixture turns basic, reflux it for a full day, filter it and let the filtrate settle to remove the ethanol. Next, add 50 mL of distilled water, and use chloroform to extract the aqueous solution. This will give derivative 4, which has a 48% yield and an Rf of 0.35 [benzene: ethanol 0.2:9.8].

Bis – 1,4(5 – Hydroxy – 4[H] – 1,2,4 – triazol – 3 – yl)- 1,2,3,4 –tetra-O– acetyl

– Mannaretol (5)

Semicarbazide salt (3.5 g, 24.0 mol) in 20 mL ethanol was added to potassium hydroxide solution (10%). Then, was refluxed for 24 hours, filtered and acetic acid (10%) was added to the

obtained solution. Where it is formation a gray precipitate for the derivative 5, recrystallized from ethanol gave 53% yield, Rf 0.33 [benzene –ethanol (9.5:0.5)].

Result and Discussion.

The aim of our study is to synthesize an compound 5 that contains two triazol rings derived from mannose. To do this, oxidation of the D- mannose by dilution nitric acid to obtained D- mannaric acid (1), then protection of the four hydroxyl groups at positions 2, 3, 4 and 5 of compound 1 was carried out using two equivalents of acetic anhydride. This was characterized by FTIR as the peak 1728 cm^{-1} belong to carbonyl group and peak at 1665 cm^{-1} which is indicate the existence of aromatic (C=C). Then, the remaining hydroxyl groups in compound 2 at positions 1 and 6 were treated with thionyl chloride under reflux to form chloride derivative compound 3 (scheme 1) The yield was very good, the FTIR and ^1H NMR spectrums show that the peak which belong to OH was disappeared, and the C=O stretching peak observed at 1743 cm^{-1}, and peak at 666 cm^{-1} indicate the existing of C–Cl, and shows that the hydroxyl peak was disappeared in the spectrum.

Figure 1 show FT-IR spectrum of compound (1) , which gave *vmax* (film)/cm^{-1} 3271–3332 (O–H), 2997(C−H), 1728 (C=O). ^1H NMR (400 MHz, DMSO) δ = 11.8 (2H, d, OH), 6.4 (1H, s, CH), 3.2 (1H, d, CH) and at 2.1(1H, m, CH).

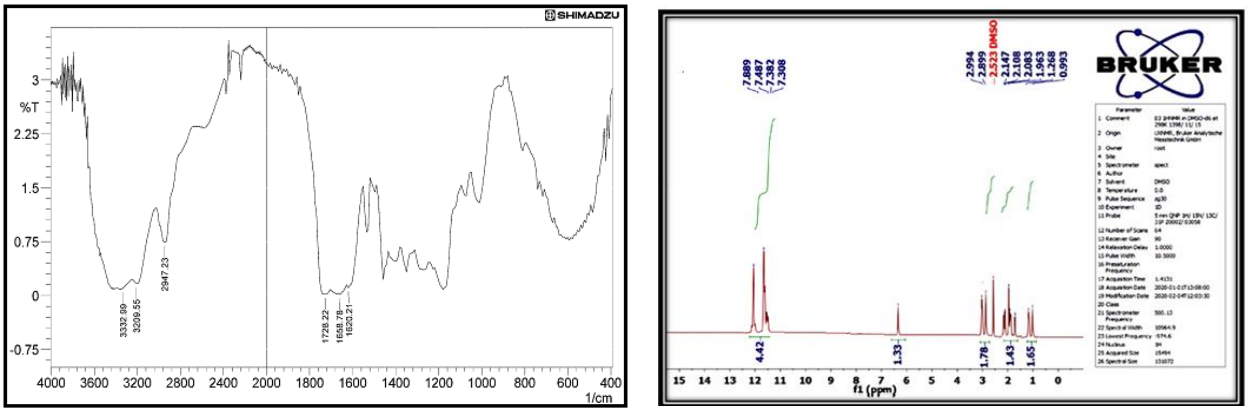


Fig.1. FTIR and 1HNMR spectrum of D- Mannaric acid (1)

Protection of four hydroxyl groups at positions 2,3,4 and 5 in compound (1) was carried out using acetic ahhydride to give compound 2 in very good yield about 72%; this will allow convert the both hydroxyl groups in positions 1 and 6 to chloride derivative. The product was confirmed by FTIR spectrum and ^{1}HNMR in figure 2, which explain by FT-IR spectrum of compound (2) , which gave *vmax* (film)/cm^{-1} 3363–3410 (O–H), 2939 (C−H), 1728 (C=O). ^1H NMR (400 MHz, DMSO) δ = 12.2 (2H, d, OH), 6.4 (1H, s, CH), 4.2 (1H, d, CH), 3.4(1H, m, CH) and at 2.2 (1H, d, CH).

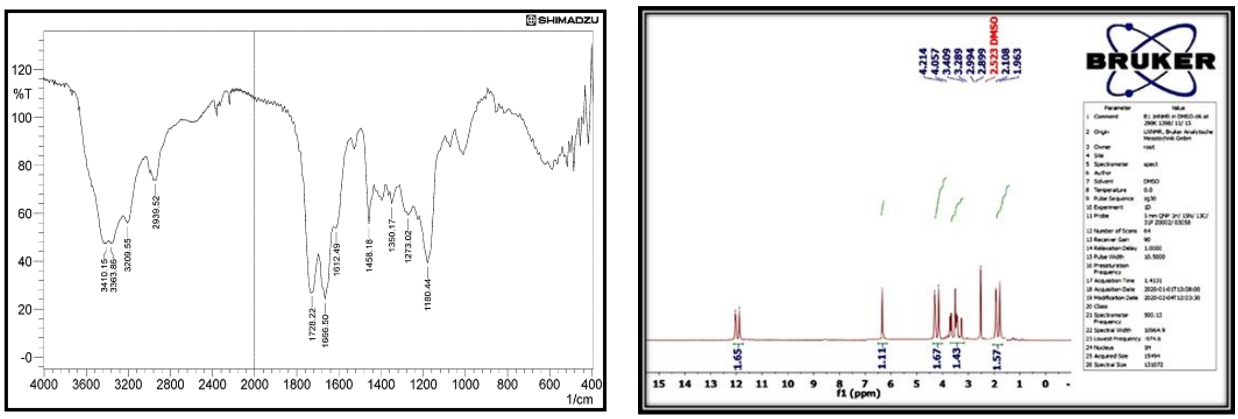


Fig.2. FTIR and ^{1}HNMR spectrum of 2,3,4,5- Tetra – O- acetyl – Mannaric acid (2)

Compound 2 was treated with thionyl chloride under reflux to form compound 3, the progress completion of the reaction was followed by TLC plate. The yield was very good , the FTIR and 1H NMR spectrums show that the peak which belong to OH was disappeared, and the C=O stretching peak observed at 1743 cm-1, and peak at 666 cm^{-1} indicate the existing of C–Cl, see figure 3.

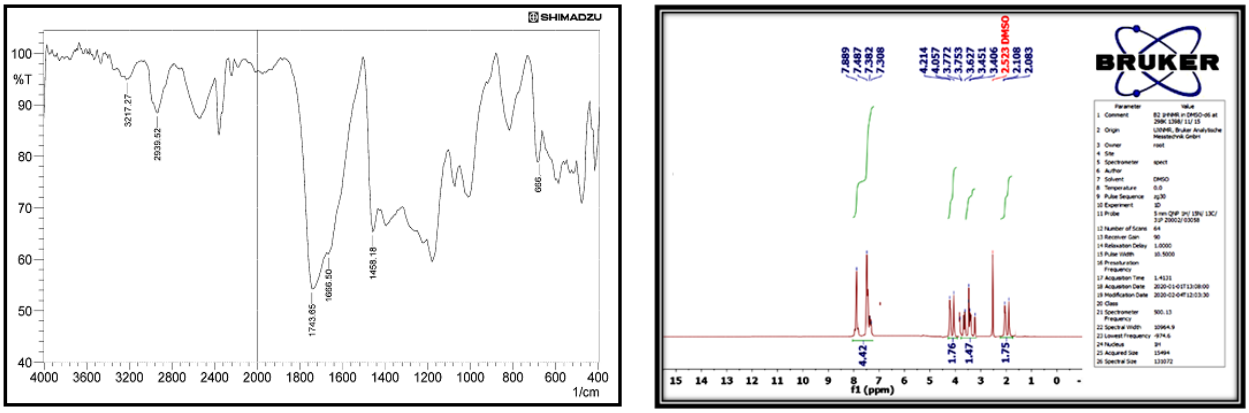


Fig.3. FTIR and ^{1}HNMR spectrum of 2,3,4,5-Tetra – O-acetyl –Mannaroyl Dichloride (3).

The acid chloride compound 3 was treated with semicarbazide in alkaline media, heated under reflux for 24 hour, to give compound 4 in moderate yield (scheme 1). The peak at 666 cm^{-1} was disappeared IR spectrum and the broad band at 3433 cm^{-1} for the amine group was appeared. The ^{1}HNMR spectrum shows that there are one peak at 10.4 ppm for NH proton. See figure 4.

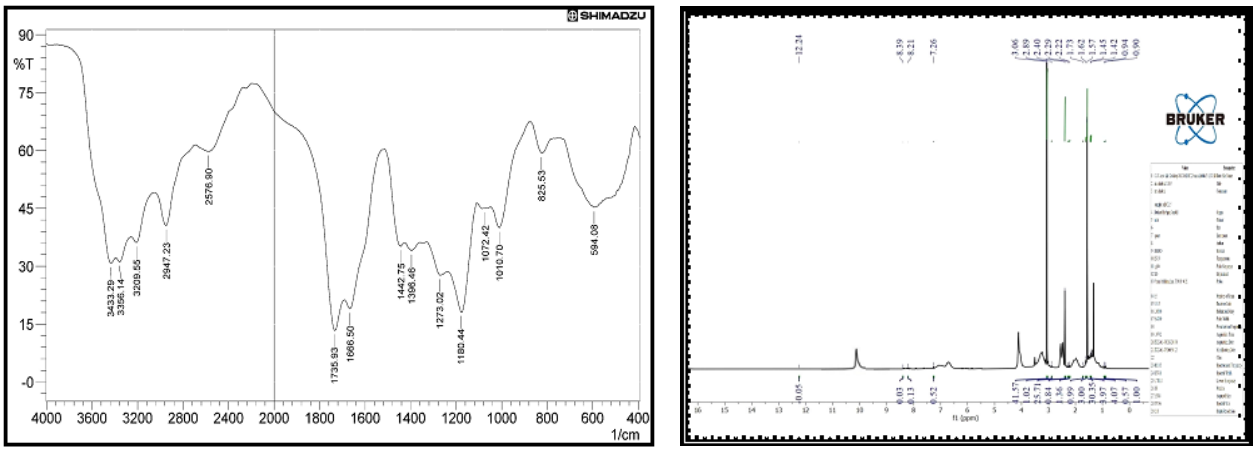


Fig.4. FTIR and ^{1}HNMR spectrum of 2,3,4,5 – Tetra – O –acetyl - semicarbazide Mannaric acid (4)

Having compound 4 in hand, become possible to test the cyclisation step to form compound 5 in the presence of base. To do this, compound 4 was treated with 10% KOH solution; heating under reflux gave compound 5 (scheme 1). Figure 5 show, FT-IR *vmax* (film)/cm^{-1} 3294−3132 (NH), 2947 (C−H), 1660 (C=O), 1573-1620 (C=N). ^{1}H NMR (400 MHz, DMSO) δ = 10.5 (1H, m, NH), 7.2−6.5 (4H, m, CH), 5.4 (1H, s, CH), 5.2 (1H, s, CH).

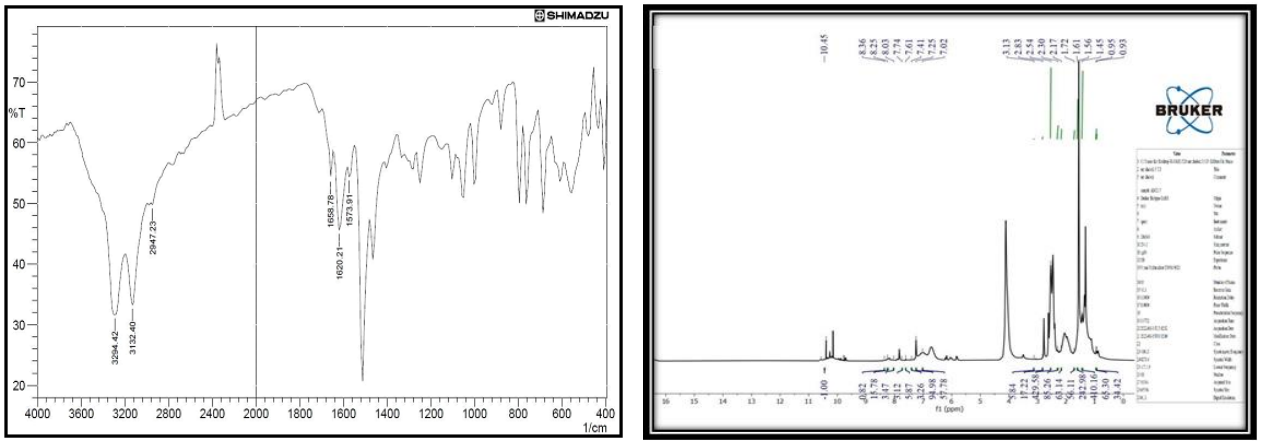
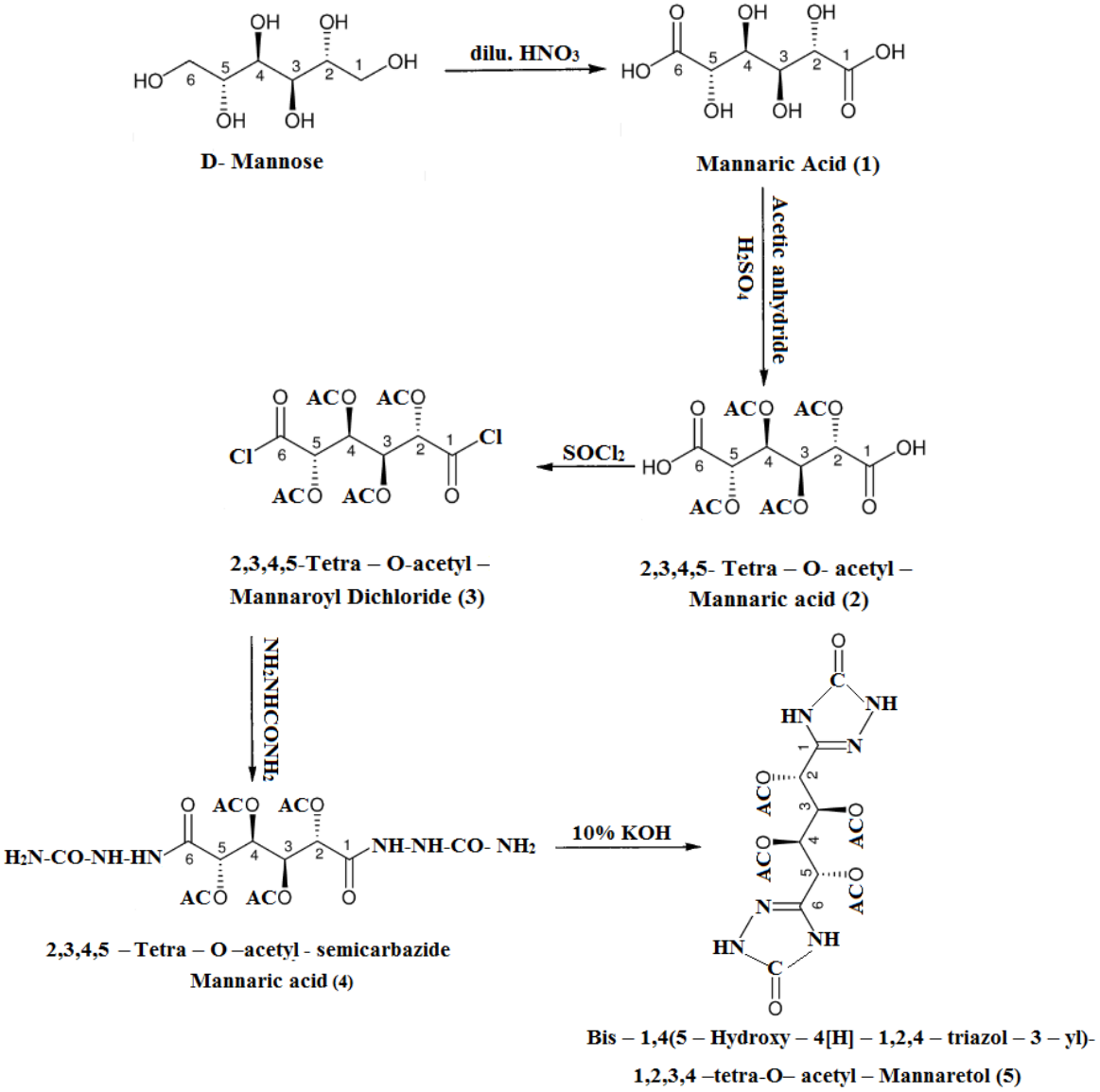


Fig.5. FTIR and ^{1}HNMR spectrum of Bis – 1,4(5 – Hydroxy – 4[H] – 1,2,4 – triazol – 3 – yl)- 1,2,3,4 –tetra-O– acetyl– Mannaretol (5)



Scheme 1. diagram for the synthesis reactions of compounds (1-5)

Antibacterial activity

Using the disk diffusion technique, the antibacterial activity of synthetic compound 5 was

evaluated, and the inhibition zone was quantified in millimeters.[11] For the test, amoxicillin at 50 and 100 mg/mL served as the reference medication. At doses of 100 and 150 mg/mL on Muller Hinton agar, the synthetic compound's antibacterial efficacy against *Streptococcus pneumonia* and *Staphylococcus aureus* was assessed. After the agar medium had been sterilized, it was added to petri dishes and left to harden. A loop was then used to distribute the microbial suspension throughout the surface. For the cultures, DMSO was the solvent of choice 48 hours were spent incubating the resulting plates at 37 ^{o}C. Table 1 contains the results. The test chemical (5) had good antibacterial activity, as Table 1 illustrates. The generated chemical (5) has action against *S. pneumonia* at 100 and 150 mg/mL doses that is almost identical to the reference. Given the medication's resistance to moderate activity against *S. aureus*, the activities against the drug at 100 and 150 mg/ml were outstanding.

Table 1: Anti-bacterial activity towards *Staphylococcus Aureus, Staphylococcus Pneumonia,* (100 and 150 mg/mL)

Sample	*S. Aureus*		*S. Pneumonia*	
con. mg/mL	100	150	100	150
Compound 5	45	51	20	27
Amoxicillin	19	26	23	25
DMSO	0	0	0	0

Conclusion

FT-IR and 1HNMR spectroscopy were used to establish that we had successfully synthesized a triazole containing mannose sugar in this study. Protection of hydroxyl groups and oxidation processes were well-produced. In the last step, the cyclization and condensation of the molecule hydrazinecarboxamide in an alkali medium allowed for the easy synthesis of the triazole rings. Due to the drug's resistance to moderate activity against *S. aureus*, compound 5 demonstrated exceptional activity against the pathogen at concentrations of 100 and 150 mg/ml.

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