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Synthesis of Novel N- and C-acyclic Nucleosides Derived from 2-hydrazino-6-methyluracil

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THE reaction of 2-hydrazino-6-methyl uracil with different aldo- sugars yields the corresponding N-acyclic glycosides. However, some of them have cyclized successfully to form a new fused triazole ring. Apparently, such cyclization depends upon the Stereochemistry of the N-glycoside intermediates that produce the C-glycosides.

Keywords: Uracil, N-glycoside, C-glycoside, Acyclic nucleoside.

Introduction

Although, the therapeutic routs for treatment lethal diseases such as cancer and immune diseases, are so many ways; however the main role of treatment still on the active material on new drugs[1,2]. The designing and synthesis of such drugs which affect DNA biosynthesis have attracted much attention, among them is the synthesis of new glycoside analogues that remains the most important [3,4]. The modification of the nucleic acid was based on either modification of the nitrogen base or the carbohydrate part or both of the two components that compose the nucleic acid system [2].

The chemistry of N-nucleosides, the building constituents of DNA and RNA are the source of many biologically active complexes, has been extensively reviewed [5]. The importance of nucleoside derivatives have been investigated by many researchers [6]. The synthesis of naturally occurring compounds containing a uracil ring attracting much interest due to their extensive variety of biological properties such as antitumor [7,8], antimicrobial [9,10], antihypertensive [11], hepatoprotective [12], cardiotonic [13] and antialergic [14] activities.

Upon those facts, it was promoting us to combine the nitrogen base uracil though its hydrazino derivatives with aldo monosaccharide sugars to form new series of acyclic nucleotides. Throughout the previous works, [15, 16] it was reported the synthesis of 6-methyl 2-hydrazino derivatives which are used in the present study to build a synthesized route of acyclic nucleotides.

Results and Discussion

Heating under reflux compound 2-hydrazinyl-6-methylpyrimidin-4(3H)-one (**1**) with xylose or ribose (equal molecular ratio) for 5h. in absolute ethanol furnish compound **3a,b**. The ^{1}HNMR data is compatible with this structure, it shows clearly the compounds **3a,b** are in the open form without forming the triazole ring which is clear from the singlet signal at δ≈ 7.55ppm., corresponding to the azomethine proton of the sugar moiety (for the rest of other data please see the experimental).

Using the noble sugar fucose as hexose by the same reaction condition produces the open form glycoside **5**. All attempts used as above to produce ring closure are failed. The ^{1}HNMR displayed the azomethine proton at δ = 7.45ppm, is clearly visible.

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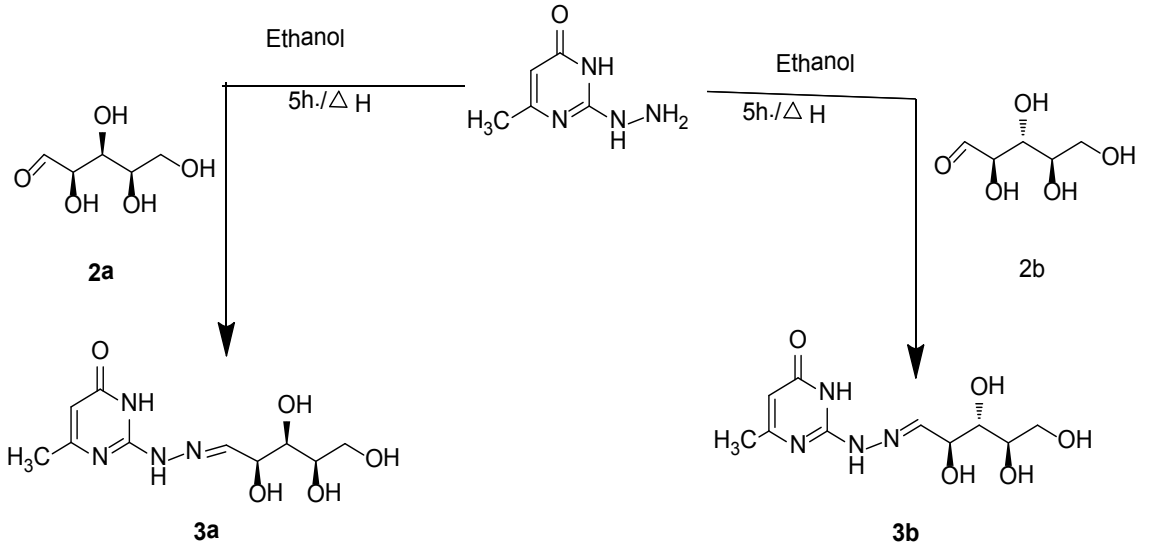
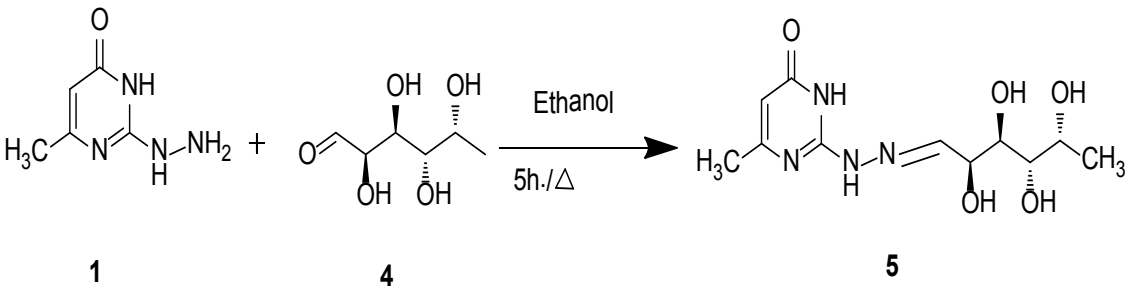


Scheme1



Scheme 2

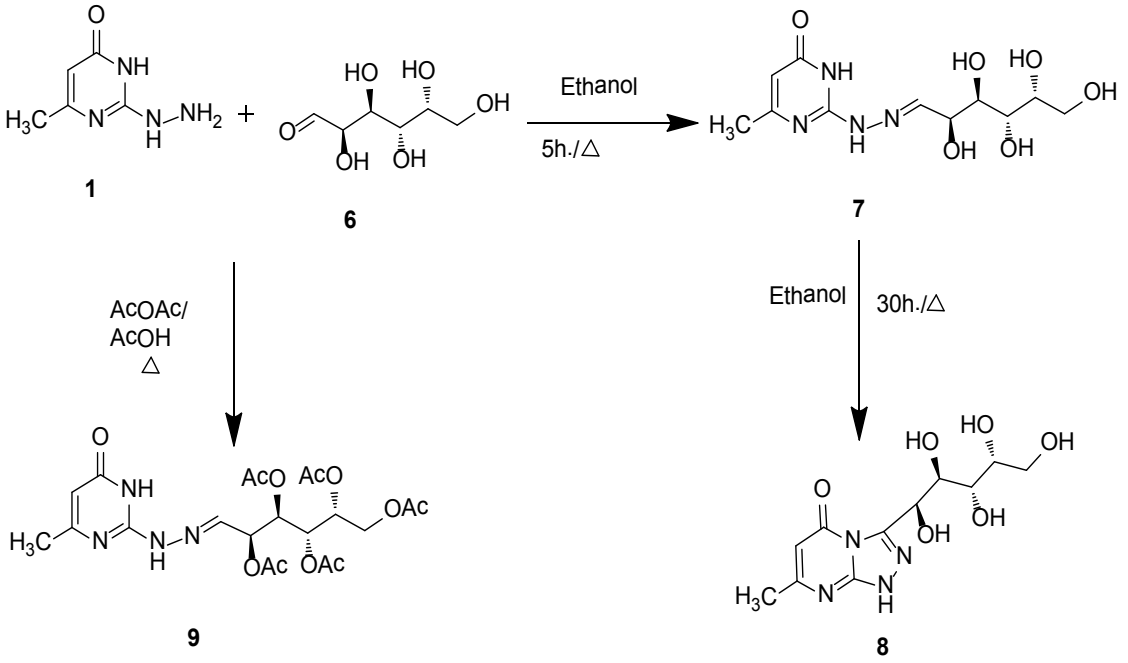
Applying the same reaction condition by using galactose as hexose short time (5h.) refluxes delivers the open form which prompts us to put the reaction product under Harsher reaction condition by acetylating with Acetic acid/ Acetic anhydride. Unfurtionatlly this condition does not give us the desired product and what we have obtained the open form without the ring closure and there is no triazole ring obtained moreover the azomethine proton of the sugar moiety is clearly visible at δ=7.48 ppm., the only different from the first attempt are the acetylation of the sugar moiety. The IR spectrum of compound **9** shows no absorption band at ν = 3500 cm^{-1}. More over the acetyl group are displayed at 1740-1750cm^{-1}.

In the array of our attempts to close compound **7** we heat it under reflux in absolute alcohol for long time (30h.).

Furtionatilly, we obtained the desired compound **8** which is had the closed triazole ring forming the C- acyclic nucleosides.

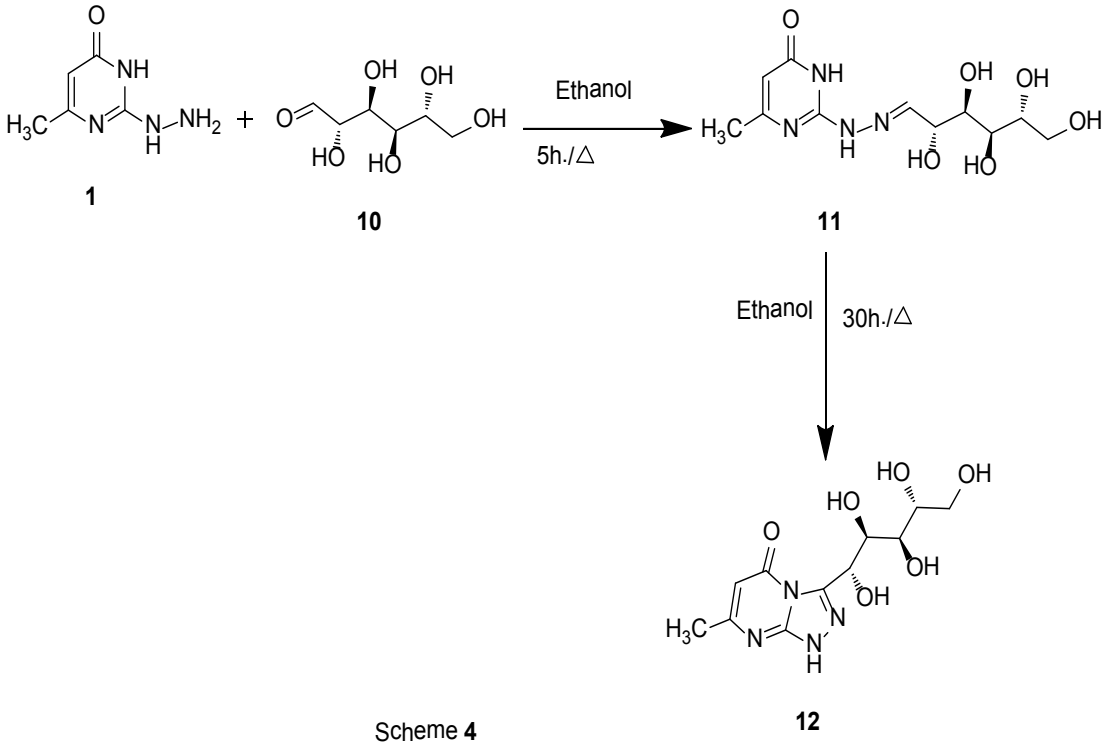
Like the above reaction **(scheme 3**) reacting compound **1** with different hexose namely mannose for short time (5h.) yields compound **11** which upon spectral data is the open glycoside as the azo methine proton displayed at δ = 7.71ppm(^{1}HNMR) which is clearly visible indicating the existence the open form are not the closed form.

Applying the same reaction condition for ring closure as compound **8** (scheme 3) delivers the closed triazole ring as galactose. In ^{1}HNMR of compound **12** the azomethine proton displayed ≈7.11 ppm, is not showed at all this indicating the presence of the closed formula.



1 **6** **7** **9** **8**

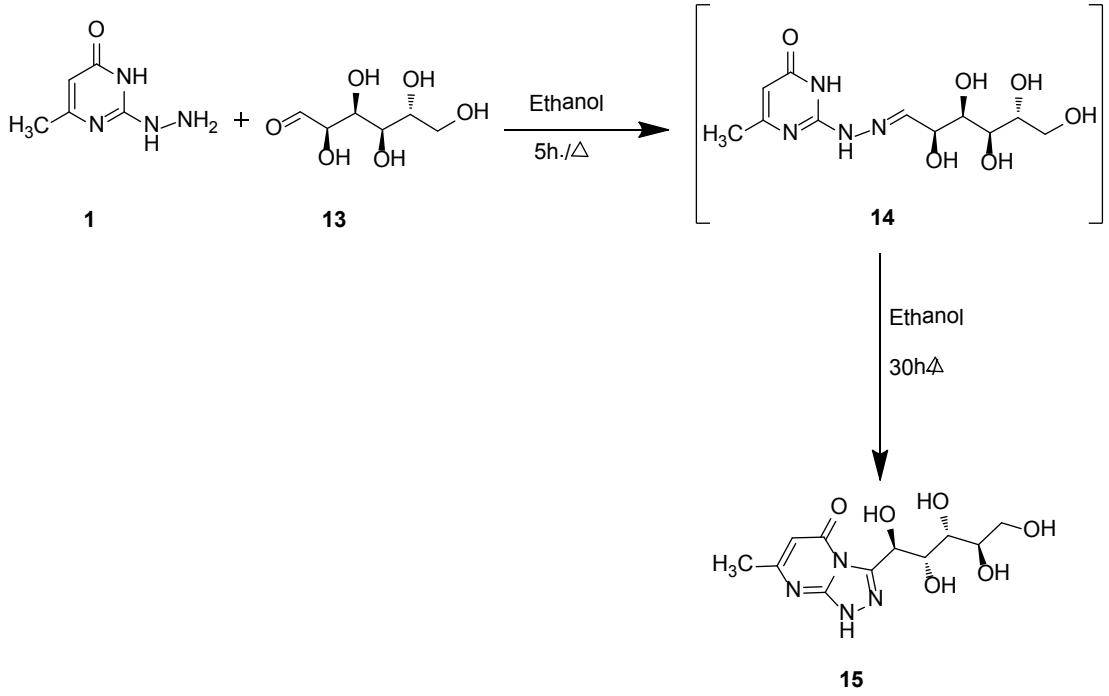
Scheme 3



1 **10** **11** **12**

Scheme **4**

Repeating the same reaction conditions above using the hexose glucose **13** produce the closed triazole ring compound **15** all attempts to obtain the open chain had been failed to separate the open form (intermediate **14**) which might be because the stereochemistry of glucose as in other reports of our research group the same phenomena occurred for glucose [17] with different heterocyclic systems.



1 13 14 15

Scheme 5

Conclusion

Reacting hydrazino compound **1** with different aldo sugars produces the corresponding open acyclic sugar. Trials made to close those acyclic sugars on the pyrimidine ring of uracil furnish the C-glycosides does not always succeeded which means the stereochemistry of the open sugar in glycoside controls the ring closure reaction.

Experimental

Solid compounds were re-crystallized to constant melting points and dried in vacuum in drying pistol containing sodium hydroxide. All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus.

Micro analyses were carried out at the Micro Analytical Unite, National Research Centre and Faculty of Science, Cairo University. IR spectra were carried out on FT/IR 300 E Jasco using KBr discs. ^{1}H-NMR spectra were measured in DMSO-d6, using Joel Ex. 270 and 500 NMR spectrometer. Signals were measured with reference to TMS as an internal standard. All reactions were followed up by TLC using $CHCl_3$/MeOH (9:1, v/v) and detected under UV Lamp. Yields are not optimized. All TLC was observed after burning with 10%ethanolic solution of H_2SO_4 to detect the reaction with sugar moiety as free sugar has no observation under UV.

General procedure for the synthesis of N-glycoside form (A)

A mixture of 6-methyl 2-hydrazinopyrimidine-3,5-diones **1** (01.40gm, 10 mmole) and an equimolar amount of the proper aldose (10 mmole) in (50 ml) of absolute ethanol was refluxed for 5h. The reaction mixture was poured onto ice water. The solid that formed was collected by filtration, dried and crystallized from the proper solvent.

General procedure for the synthesis of C-glycoside form (B)

The N- glycoside was allowed to heat under reflux for 30 h. The reaction mixture was poured onto ice water. The solid product that formed was collected by filtration, dried and crystallized from the proper solvent.

General procedure for the synthesis of N-acetylated form(C)

The N-glycoside was allowed to heat under reflux with a mixture of glacial acetic acid (20 ml) and acetic anhydride (20 ml) for 2h. The reaction mixture is poured onto ice water. The precipitate that formed in ice water was filtered off and washed with cold ethanol (10 ml) and dried to give the acetylated product.

6-Methyl-2-xylosylhydrazino-pyrimidin-4(3H)-one(3a)

The product was synthesized via the procedure (A) and re-crystallized from dioxane (30 ml) to yield the title compound as pale yellow powder (60%); mp= 215-218°C; Anal.calcd. for $C_{10}H_{16}N_4O_5$ (272.26);C, 44.12; H, 5.92; N, 20.58%; Found:,C,44.05; H, 5.87; N, 20.52%; IR (KBr) cm^{-1}: 3417 (OH), 3208 (H), 2908 (CH alkyl) and 1619 (CO), 1500(C=C). ^{1}H-NMR (DMSO-d6) ppm: 2.06 (m, 3H, CH_3), 3.32-3.3.49 (m, 4H, 4OH, D_2O exchangeable), 4.21(m, 1H, H-2`), 4.38-4.44 (m, 2H, H2-5`), 4.55 (m, 1H, H-3`), 4.21 (m, 1H, H-4`), 5.45 (s,1H,CH pyrimidine),7.44 (m, 1H, H-1`), 11.1 (br s, 1H, NH, D2O exchangeable) and 11.35 (br s, 1H, NH, D_2O exchangeable). 13C-NMR (DMSO-d6) ppm: 24.1(CH_3), 63.1, 67.5, 70.1, 72.2, 72.9 and 77.7 (CH of the sugar moiety), 101.1(C_5 of pyrimidine), 153.2(C_6 of pyrimidine), 157.2, 162.8(C=N) and 166.6 (CO)ppm.

6-Methyl-2-ribosylhydrazino-pyrimidin-4(3H)-one (3b)

The product was synthesized via the procedure (A) and re-crystallized from dioxane (30 ml) to yield the title compound as pale yellow powder (60%); mp=225-228°C. Anal.calcd. for [$C_{10}H_{16}N_4O_5$] (272.26);C, 44.12; H, 5.92; N, 20.58 %; Found:, C, 44.07; H,5.93; N, 20.49%. IR (KBr) cm^{-1}: 3410 (NH), 3250 (NH), 2929 (CH alkyl) and 1627 (CO). ^{1}H-NMR (DMSO-d6) ppm: 2.15 (m, 3H, CH_3), 3.15-3.65 (m, 4H, 2OH, D_2O exchangeable, OH-2`-OH-5`), 4.35(q, 1H, J = 6Hz, H-2`), 4.72 (m, 2H, H2-5`), 4.87 (d, 1H, J = 5Hz, H-3`), 5.35 (dd, 1H, J=7.5Hz, J=6.5Hz, H-4`), 5.55 (s,1H,CH pyrimidine),7.48 (d, 1H, J = 4Hz, H-1`), 11.1 (br s, 1H, NH, D_2O exchangeable) and 11.35 (br s, 1H, NH, D_2O exchangeable).

6-Methyl-2-fucosylhydrazino-pyrimidin-4(3H)-one (5)

The product was synthesize via procedure (A) and re-crystallized from DMF/H_2O (30 ml) to give the product as yellow powder (73%); mp. 198-200 ^{O}C, Anal.calcd.for: $C_{11}H_{18}N_4O_5$ (286.28): C, 46.15; H, 6.34; N, 19.57; Anal. Found: C, 46.05; H, 6.27; N,19.46; IR (KBr) cm^{-1}: 3350 (OH, NH), 2905 (CH alkyl) and 1668 (CO); ^{1}H-NMR (DMSO-d6) ppm: 1.33(s, 3H, CH_3), 2.12(s, 3H, CH_3), 3.17-3.72 (m, 5H, 3OH, , OH-2`-OH-6`, D_2O exchangeable), 4.28-4.45 (m, 2H, H2-6`), 4.71 (m, 1H, H-3`), 5.42(s,1H,CH pyrimidine), 5.75 (m, 1H,-H-4`), 7.45 (s, 1H, H-1`), 8.55 (br. s, 1H, NH, D_2O exchangeable) and 10.35 (br. s, 1H, NH, D_2O exchangeable).

6-Methyl-2- Galactosylhydrazino-pyrimidin-4(3H)-one (7)

The product was prepared via the procedure (A) and re-crystallized from dioxaneto yield the title product as reddish brown crystals (65%)mp. 230-233 ^{O}C; Anal.calcd. for $C_{11}H_{18}N_4O_6$ (302.28) C, 43.71; H, 6.00; N, 18.53; Found: C, 43.64; H, 5.95; N, 18.46; IR (KBr) cm^{-1}: 3247 (OH), 2950 (CH alkyl) and 1678 (CO). ^{1}H-NMR (DMSO-d6) ppm: 2.19 (s, 3H, CH_3), 3.22-4.45 (m, 5H, 3OH, D_2O exchangeable OH-2`-OH-6`), 4.35-4.55 (m, 2H, H2-6`), 4.98 (m, 1H, H-3`), 5.25 (m, 1H,-H-5`), 5.6 (d, 1H, J = 7.5Hz, H-2`), 5.49 (s,1H,CH pyrimidine), 5.72 (m, 1H,-H-4`), 7.44 (s, 1H, H-1`), 8.88 (br. s, 1H, NH, D_2O exchangeable) and 10.51 (br. s, 1H, NH, D_2O exchangeable).

7-Methyl-3- galactosyl-[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one(8)

The product was synthesize via procedure (B) and re-crystallized from DMF (30 ml) to yield the product as white powder (64%); mp. 215-218 ^{O}C, Anal. calcd. for $C_{11}H_{16}N_4O_6$ (300.27) C, 44.00; H, 5.37; N, 18.66; %; Anal. Found: C, 44.08; H, 5.21; N, 18.62; IR (KBr) cm-1: 3420, 3400 (OH), 3250 (NH), 2930 (CH alkyl) and 1677 (CO). ^{1}H-NMR (DMSO-d6) ppm: 2.11 (s, 3H, CH_3), 3.09-3.99 (m, 5H, 5OH, D_2O exchangeable, OH-1`-OH-5`), 4.44 (m, 2H, CH_2, H2-5`), 4.66 (m, 1H, 1CH, H-2`), 4.82 (m, 1H, H-4`), 5.25(m, 1H, H-3`),5.55 (s, 1H, CHpyrimidine), 5.75 (m, 1H, CH, H-1`) and 8.81 (br. s, 1H, NH, D_2O exchangeable), 10.6(br. s, 1H, NH, D_2O exchangeable),

6-Methyl-2- (1`,2`,3`,4`,5`-O-pentacetylgalactosyl-pyrimidin-4(3H)-one(9)

The product was synthesize via procedure (C) and re-crystallized from dioxane (30 ml) to yield the product as yellow powder (62%); mp. 215-220 ^{O}C,Anal.calcd. for$C_{16}H_{13}N_4O_6$(512.47); C, 49.22; H, 5.51; N, 10.93; Found: C, 49.12; H5.42; N, 10.79, IR (KBr) $cm^{-1.}$ 2895(CH alkyl), 1745-1720, (ester carbonyls) and 1688 (CO). ^{1}H-NMR (DMSO-d6) ppm: 1.55-2.42(m, 18H, 6CH_3),2.75-2.83 (m, 2H, CH_2, H2-5`), 3.75-4.05 (m, 1H, 1CH, H-2`), 4.82-5.27 (m, 2H, H-4`,CHpyrimidine), 5.85-6.09 (m, 1H, H-3`),7.85(m, 1H, CH, H-1).

6-Methyl-2-mannosylhydrazinypyrimidin-4(3H)-one(11)

The product was synthesize via procedure (A) and re-crystallized from DMF/H_2O(30 ml) to yield the product as yellow powder (70%); mp. 205-

208 ^{O}C,Anal.calcd. for:$C_{11}H_{18}N_4O_6$(302.28), C, 43.71; H, 6.00; N, 18.53; Anal. Found**:** C,43.64; H, 5.92; N,18.45., IR (KBr) cm^{-1}: 3247 (OH, NH), 2930(CH alkyl) and 1678 (CO). ^{1}H-NMR (DMSO-d6) ppm: 2.13 (s, 3H, CH_3), 3.25-4.75 (m, 5H, 3OH, D_2O exchangeable OH-2`-OH-6`), 4.18 (m, 2H, H2-5`), 4.45 (m, 2H, H-3`,-H-5`), 5.25 (m, 2H, H-2`,-H-4), 5.58 (s,1H,CH pyrimidine), 7.71(s, 1H, H-1`), 11.81 (br. s, 1H, NH, D_2O exchangeable).

7-methyl-3-mannosyl-[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one (12)

The product was synthesize via procedure (B) and re-crystallized from dioxin (30 ml) to give the product as white powder (62%); mp. 220-223 ^{O}C,Anal.calcd.for: $C_{11}H_{16}N_4O_6$ (300.27), C, 44.00; H, 5.37; N, 18.66;Anal. Found: C,43.89; H, 5.31; N, 18.59.,IR (KBr) cm^{-1}: 3320 (OH, NH), 2900 (CH alkyl) AND 1663 (CO); ^{1}H-NMR (DMSO-d6) ppm: 2.05 (s, 3H, CH_3), 3.1-3.61 (m, 5 H,5OH,D_2O exchangeable), 3.85-4.05 (m, 1H, H-4`), 4.59 (m, 2H, H2-5`), 4.79 (d, 1H, H-3`), 5.22 (m, 1H, H-2`,H-1`), 5.45 (s,1H,CH pyrimidine), 7.45 (br. s, 1H, NH, D_2O exchangeable), 10.15 (br. s, 1H, NH, D_2O exchangeable).

7-Methyl-3-glycosyl-[1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one (15)

The product was prepared via the procedure (A) and re-crystallized from DMF with drop of water to yield the title product as a white powder (80%); m.p. 243-245°C. Anal.calcd. for $C_{11}H_{16}N_4O_6$ (300.27): C, 44.00; H, 5.37; N, 18.66; Found: C, 43.93; H, 5.32; N, 18.58;IR (KBr) cm^{-1}: 3355, 3212 (5OH, NH), 2904 (CH alkyl), 1666 (CO). ^{1}H-NMR (DMSO-d6) ppm: 1.97 (s, 3H, CH_3), 2.75-3.72 (m, 5H, 3OH, D_2O exchangeable, OH-2`-OH-5`), 4.52 (m, 2H, H2-4`), 4.92 (m, 1H, H-3`), 5.27 (m, 1H, H-2`), 5.37 (s,1H,CH pyrimidine), 5.72 (d, 1H,J=9.6 Hz,H-1`), 8.9 (br s, 1H, NH, D_2O exchangeable), 10.62(br s, 1H, NH, D_2O exchangeable). 13C-NMR (DMSO-d6) ppm: 24.1(CH_3), 63.9, 71.7, 71.8, 77.4 and 78.2 (CH of the sugar moiety), 100.9(C_5 of pyrimidine), 156.7(C_6 of pyrimidine), 163.1(C=N) and 166.6 (CO)ppm.

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تحضير النيوكليوسيدات الحلقية N- و C المستمدة من -2هيدرازينو6--ميثيل يوراسيل

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تفاعل 2-هيدرازينو-6- ميثيل يوراسيل مع عدد من السكريات الالدهيديه المختلفه لتنتج ال ن جليكوزيدات المقابله وبعض من هذه المركبات تم غلقها بنجاح اعتمادا علي الهندسه الفراغيه لل-ن-جليكوزيدات لتنتج ال-س- جليكوزيداتـ.