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Synthesis of novel Nucleoside Analogues from Imidizoline and Evaluation their Anti microbial Activity

Thanaa M. Al-Mouamin[1], Dehyaa J. Mehdi[2]*
[1]Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq
[2]Ministry of Education, Baghdad, Iraq

Abstract

In this research some new nucleoside analogues were synthesized. Starting from α-*D*- glucose which was protected to glucose penta acetat α-*D*- glucose pyronside (1). Which was converted to active form 1-bromo protected sugar (2) as a sugar moiety. The base moiety 2-substituted imidazoline (3,4) was prepared from condensation of ethylene diamine with two kind of aromatic aldehydes, which were subjected to amino alkylation via Mannich reaction forming new nucleaobase derivatives (5-10). Condensation of nucleobase with bromo sugar through nucleophilic substitution of anomeric carbon with nitrogen forming new protected nucleoside analogues (11-16). De blocking of these nucleoside analogues with sodium methoxide in methanol afforded our target the free nucleoside analogues (17-22).All prepared compounds were identified by FT-IR and some of them with ^{1}H-NMR and ^{13}C-NMR spectroscopy. Some of synthesized nucleoside analogues were screened for their antibacterial activity against four types of bacteria, also against four types of fungi.

Keywords: Nucleoside Analogues, Imidazoline, Mannich base.

تحضير مماثلات نيكلوسيدات جديدة وتقييم فعاليتها ضد الميكروبات

ثناء مهدي المؤمن[1]، ضياء جبار مهدي[2]*
[1]قسم الكيمياء ، كلية العلوم جامعة بغداد ، بغداد، العراق
[2]وزارة التربية ، مديرية تربية الرصافة الثانية ، بغداد ، العراق

الخلاصة

يتضمن البحث تحضير بعض مماثلات النيكلوسيدات جديدة. بتحويل α –*D*– كلكوز بايرونوز (1) الى الصيغة الفعالة 1– برومو السكر المحمي (2). اما جزء القاعدة 2– اميدازولين المعوض والذي تم تحضيره من خلال تكاثف ثنائي اثيل امين مع نوعين من الالديهايدات الاروماتية (3 ، 4) والتي تم مفاعلتها مع امينات احادية مختلفة بوجود الفورمالديهايد من خلال تفاعل مانخ . تم الحصول على قواعد نايتروجينية جديدة (5–10) والتي تم تكثيفها مع بروميد السكر تفاعل تعويض نيكلوفيلي للحصول على نيكلوسيدات محمية جديدة (11–16) والتي تم تحللها باستعمال ميثوكسيد الصوديوم في الميثانول للحصول على النيكلوسيدات الحرة الجديدة (17–22).تم تشخيص جميع المركبات المحضرة من خلال طيف الاشعة تحت الحمراء والبعض منها خلال طيف الرنين النووي المغناطيسي للهيدروجين والكاربون 13.تم دراسة الفعالية البايولوجية لبعض النيوكليوسيدات مع اربعة انواع من البكتريا وكذلك اربع انواع من الفطريات .

*Email:Dhyaa1959@yahoo.com

Introduction

Nucleoside analogues have found to be important moiety in creation of novel medical compounds [1, 2].Nucleosides are fundamental building blocks of biological systems that are widely used as therapeutic agents to treat cancer, fungal, bacterial, and viral infections [2-4].

Compounds not only in the laboratory but also in industrial production [5-7] consequently, extensive modifications have been made to both the hetrocyclic base, and the sugar moiety to avoid the drawbacks by nucleosides or analogues in certain applications. In recent years 2-substituted Imidizoline have attracted considerable attention for development of compounds with pharmacological useful properties [8-11]. The importance of imidozoline units arises, because they are found in adiverse range of biological revelent compounds [12-14]. Imidazoline containing natural product egspongontine, topsentim and nortopentine are sought after for their antiviral, and antitumor properties [14, 15]. In organic synthesis, imidazoline unit areused as a synthetic intermediate in medicinal chemistry [16, 17] , Mannich compounds, nucleosides, antibiotics, peptides and Mannich compounds have several like agro chemicals, paint, catalysts and polymer chemistry. The Mannich reaction is also employed in the synthesis of medicinal compounds [18]. These observations inspire us to synthesize new nucleoside analogues containing imidazoline derivatives with Mannich base as a nucleobase and glucose as a sugar moiety and investigated their biological activities.

Materials

The quality of all these chemicals supplied from BDH England, and Fluga Merk, pure materials used without purification.

Experimental instruments:

1- Melting points were recorded by Gallen Kamp, England, melting point apparatus and were uncorrected.
2- Infrared spectra were recorded using SHMADZU, FT-IR 8400 Spectrophotometer (Japan) as a thin film or KBr disk.
3- ^{1}H-NMR and ^{13}C-NMR Spectra were recorded with help of ultra – high field 400 MHZ Avance III 400 Bruker, Germany, using Me_4Si as the internal standard and DMSO-d_6 as a solvent, which was appeared at 2.5 ppm in ^{1}H-NMR and 40.45 in ^{13}C-NMR Spectrum.
4- TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}).
5- Biological activity using incubator memmert.

Preparation of $\propto -D-$ glucose penta acetate (1)[19]

α-D-glucose (1 g, 0.0055 mole) and (0.8 g , 0.00975 mole) of anhydrouse sodium acetate was dissolved in (6 ml) acetic anhydride then refluxed on water bath with stirring for (2h). then pour the reaction mixture on to (50 ml) of ice-cold water. The product was filtered and recrystalized from ethanol to afford compound (1) as a white crystal.

Synthesis of 1-bromo acetylated sugar (2)[20].

The acetylated sugar (0.380 g, 1.08 m mole) was dissolved in 3 (ml) of (50%) hydrogen bromide in glacial acetic acid which was added at (0^{o}C). The solution was kept at (0^{o}C) for one hour, and finally at room temperature for (15 min). Washed with ice water (2×15 m) and then with saturated equeous solutions of sodium bicarbonate to remove the remaining acid. After a final wash with ice – water (20 mL), the organic phase was dried over anhydrous $MgSO_4$ and solvent was removed to give compound (2) as asyrup. The Isolated sugar bromide (2) was used directly for the nucleoside synthesis.

General procedure for Synthesis of imidazoline derivatives (3,4)[21].

A mixture of substituted benzaldehyde (1.22g , 0.01 mole) and (0.6g , 0.01 mole) of ethylene diamine was refluxed for (4 h) using (4 mL) DMF and (0.312 g 0.01 mole) $NaHSO_3$ as a ring closing agent. The precptite obtained after cooling recrystallized from DMF.

General procedure for synthesis compounds (5-10) [22]

To a solution of imidazoline derivatives (0.0054 mole) in methanol (10 mL), and (1 ml) of 10% diluted HCL, the primary amine (0.0054 mole) and (0.3186 g , 0.0054 mole) formaldehyde were added, and refluxed on water bath (3 h.). The product formed after cooling, was filtered, dried over anhydrous sodium sulphate and the solvent was removed to give the Mannich products(5-10).

General procedure for synthesis of protected nucleoside analogues (11-16) [23].

Mannich base (0.00098 mole) (5-10) was finally grinded and suspended in (25 mL) dried *O*-xylene, and the solvent was practically distilled off until 137 ^{o}C to remove trace of water. The residual suspension was allowed to cool below (50^{o}C), then acetylated sugar bromide (0.00098 mole)

was dissolved in dried *O*-xylene, then added to the Mannich base solution and refluxed with vigorous stirring for (1 h.). The organic layer was washed (2×5 mL)with water , dried over anhydrous sodium sulphate and the solvent was removed to give the acetylated nucleoside as a syrup (11-16).

General procedure for hydrolysis of nucleoside analogues (17-22)[24]

A solution of (0.0026 mole) of the blocked nucleoside analogues in (7 mL) of (0.1 M.) methanolic sodium methoxide was refluxed with stirring for (0.5 h.). The mixture was neutralized with acetic acid and evaporated to dryness. The residue was partitioned between water and chloroform. The equeous phase was evaporated to dryness under vacuum, to obtain free nucleoside (17-22) which were recrystallized from diethyl ether.

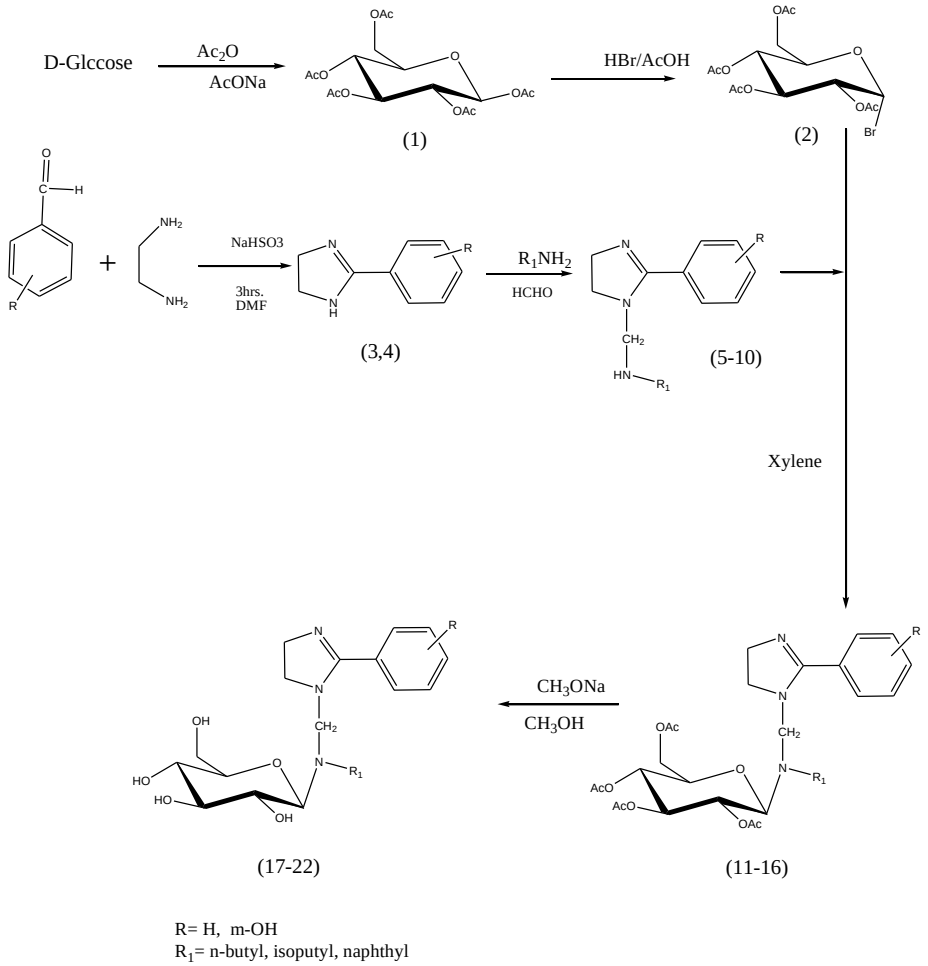
Biological activity [25]

Nutrient agar was added to (1L) of distilled water in suitable conical flask with stirring and heating unit complete dissolving then the flask was stoppred by cotton and the medium was sterilized in an autoclave for 20 minutes at (121^{o}) under pressure at (15) poundlinch. The medium was placed in petridishes about (20 ml) for each one and was left to cool and solidified. The studied bacteria and Fungi were placed on the nutrient agar surface using the loop and by streaking processor then the disc saturated with tested compound solutions. The samples were incubated for (24) h at 37^{o}C [25].

Result and Discussion

The most common modification of nucleosides represent an important of medicinal compounds which have been found to behave as a therpeutic agent and are currently used pharmaceuticals as antitumor, antirival, and antibiotics agents. Thus our target is to synthesized an a new modified nucleoside analogues.

The synthetic route was started with D-glucose as a sugar moiety and a new imidazoline containing Mannich base as a base moiety, in a series of reaction steps. Scheme-1:



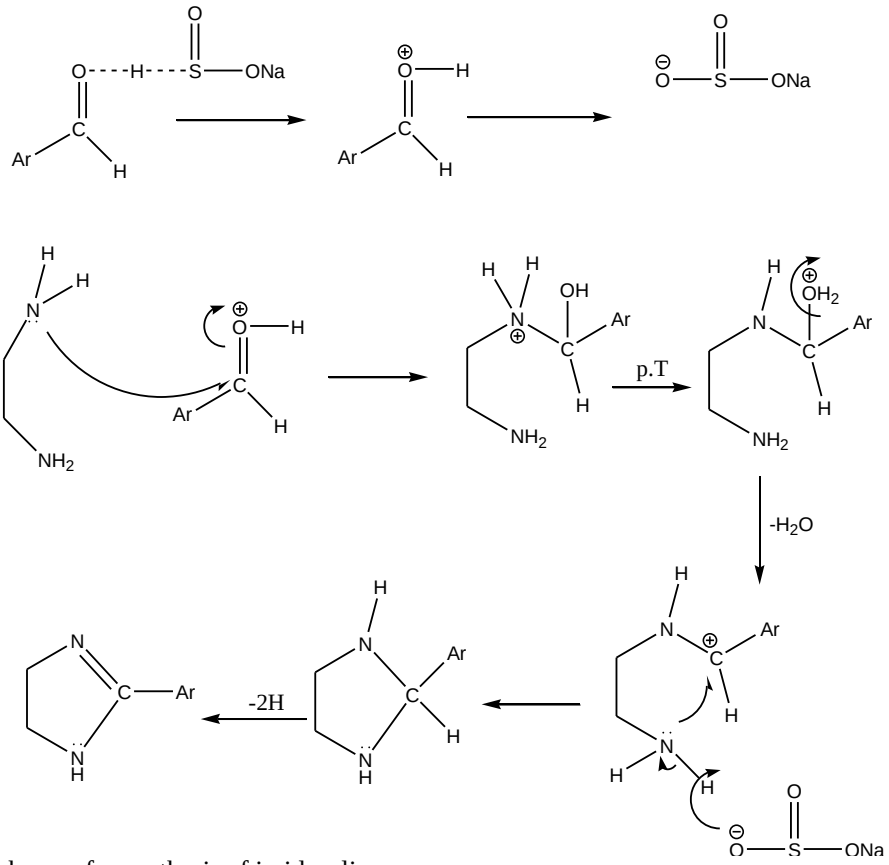
Scheme 1- Synthetic route for synthesis of nucleoside analogues

D-glucose was protected with acetic anhydride in presence of sodium acetate afforded *β-D*-glucose penta acetate (1), Which was brominated using hydrogen bromide in glacial acetic acid to give acetylated sugar bromide (2).

Compounds (1 and 2) were confirmed by their physical properties that give in literature [22]. The FT-IR spectrum of compound (1) showed several characteristic bands mainly the stretching band of carbonyl of acetyl groups at 1744 cm^{-1} while compound (2) showed in addition to the carbonyl band, the appearance of C-Br band at 761 cm^{-1}.

On the other hand imidazoline is important pharmacophore due to their biological; activities [15-18], therefore it was chosen as a nucleobase, which was synthesized by condensation of ethylene diamine with benzaldehyde and 3-hydroxy benzaldehyde using sodium hydrogen sulfate as a ring closer according to mechanism showed in scheme-2.

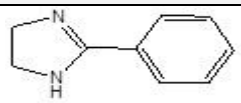
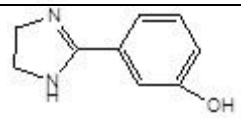
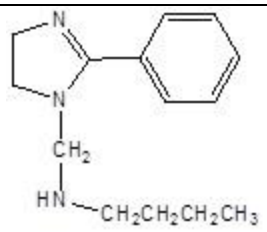
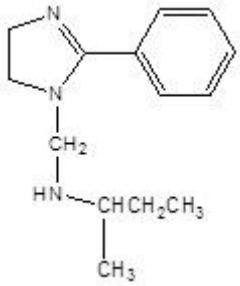
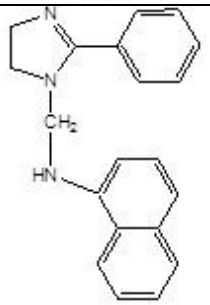
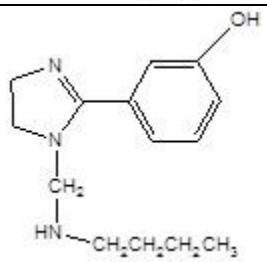
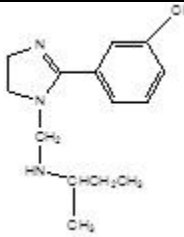
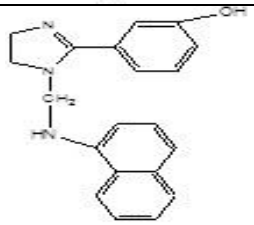
Mechanism:



Scheme 2- Mechansm for synthesis of imidazoline

The imidazoline derivatives (3) and (4) were characterized with FT-IR spectrum. Compound (3) showed the (N-H) stretching band at 3477 cm^{-1} , while compound (4) showed in addition of (N-H) band at(3329 cm^{-1}), the O-H stretching band at (3379 cm^{-1}). The imidazoline derivatives (3 and 4) were subjected to Mannich reaction, by reaction with different primary amine including (n-butyl amines, isobutyl amine, and α- naphthyl amine) and formaldehyde as amino alkylating agent, affording a new Mannich bases (5-10) Physical properties of the prepared compounds (3-10) and other data are listed in Table-1.

Table 1-Physical properties of compounds (3-10)

Comp. No.	Compound Structure	Molecular formula	M.w g/mole	M.P °C	Colour	Yield%
3		$C_9N_2H_{10}$	146	50-53	Off – white	71%
4		$C_9N_2H_{10}O$	162	syrup	Deep Brown	68%
5		$C_{14}H_2N_3$	231	(210-212)	Yellow	72%
6		$C_{14}H_2N_3$	231	Dec. 210	Pale – yellow	58%
7		$C_{20}H_{19}N_3$	301	Dec. 230	Purple	91%
8		$C_{14}H_{21}N_3O$	247	Syrup	Deep – orange	65.65%
9		$C_{14}H_{21}N_3O$	247	Syrup	Deep orange	68%
10		$C_{20}H_{19}N_3O$	317	Dec. (248)	Orange	63%

The FT-IR of Mannich base compounds (5-10) showed a stretching band at (3404-3245 cm^{-1}) for amine group, while compounds (8-10) showed, in additional to amino group, the stretching band at (3425-3392 cm^{-1}) for phenolic hydroxyl group. The spectrum of compound (7) showed in Figure-1 and other characteristic bands are listed in Table-2[27].

Table 2-FT – IR data cm^{-1} for compounds (1-10)

Comp. No.	ν (O-H) Phenolic or alcoholic	ν (N-H)	ν (C-H) arom.	ν (C-H) aliph.	ν (C=N)	ν (C=C) arom.	ν (C=O)
1	3444	-	-	2890	-		1749
2	-	-	-	2960	-		1751
3	-	3477	3028 3059	2927	1641	1577	-
4	3379 Broad		3010	2948	1656	1566	
5	-	3404	3008	2956	1677	1596	
6	-	3421	3060	2968	1652	1458	
7	-	3421	3060	2925	1667	1664	
8	3404	3356	3008	2962	1697	1614	
9	3425	3363	3050	2974	1643	1614	
10	3392	3245	3040	2962	1664	1629	

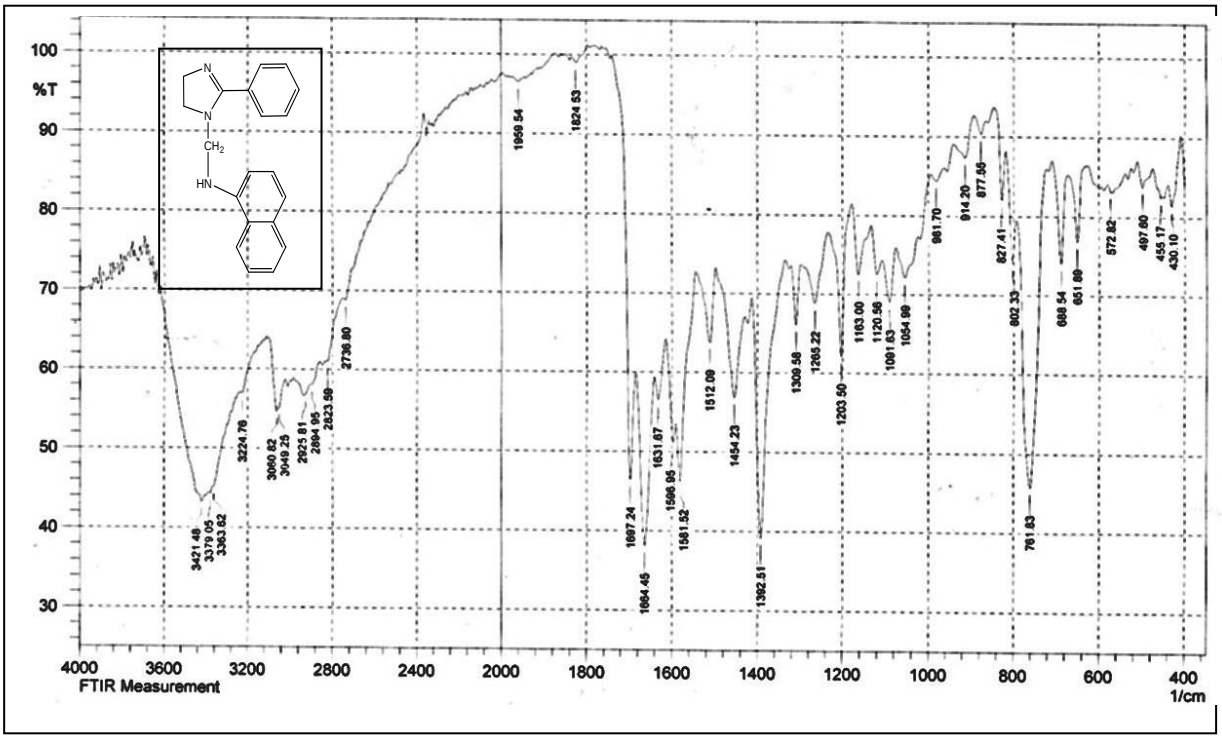


Figure 1- FT-IR Spectrum for compound (7)

To achieve our synthesis target nucleoside analogues, the 1-bromo sugar (2) was coupled with modified nucleobase (5-10) afforded the new blocked nucleoside (11-16). Physical properties of the prepared blocked nucleoside (11-16) and other data are listed in Table-3.

Table 3- Physical properties of compound (11-16)

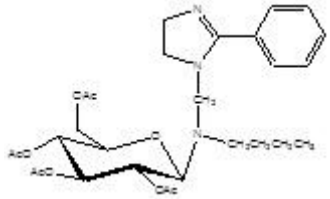
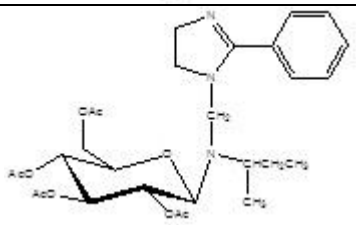
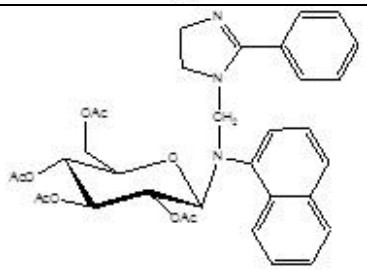
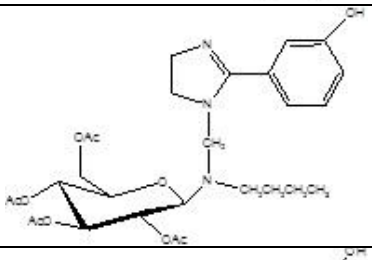
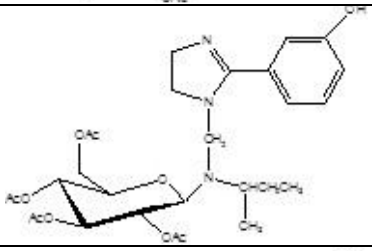
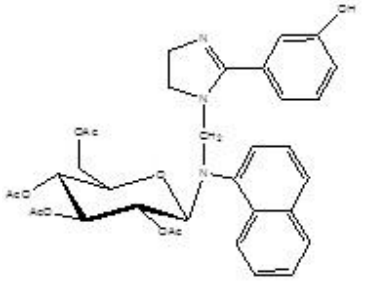
Comp. No.	Compound Structure	Molecular formula	M.w g/mole	M.P °C	Colour	Yield%
11		$C_{28}H_{39}N_3O_9$	561	116-118	Off – white	85%
12		$C_{28}H_{39}N_3O_9$	561	Dec. 158	Brown	56%
13		$C_{34}H_{37}N_3O_9$	631	Syrup	Purple	82%
14		$C_{28}H_{39}N_3O_9$	577	Syrup	Yellow	70%
15		$C_{28}H_{39}N_3O_{10}$	577	Dec. 198	Off – white	73%
16		$C_{28}H_{39}N_3O_{10}$	647	Syrup	White	82%

Table 4- FT – IR data cm^{-1} for compounds (11-16)

Comp. No.	ν(O-H) Phenolic or alcoholic	ν(N-H)	ν(C-H) arom.	ν(C-H) aliph.	ν(C=N)	ν(C=C) arom.	ν(C=O)
11	-	-	3040	2923 2958	1600	1530	1681
12	-	-	3010	2923	1635	1580	1735
13	-	-	3008	2954	1676	1596	1751
14	-	-	3064	2921	1681	1602	1697
15	3427	-	3018	2923	1600	1580	1693
16	3410	-	3030	2925	1681	1598	1720

The structures of the synthesized compounds (11-16) were confirmed by FT-IR.

The disappearance of the bands at (3200 cm^{-1}) of amino group gives a good evidence for formation of protected nucleoside analogues and appearance of stretching bands at (1751cm^{-1}) for carbonyl group gives other indication. The FT-IR spectrum of compound (11) showed in Figure-2, Table-4.

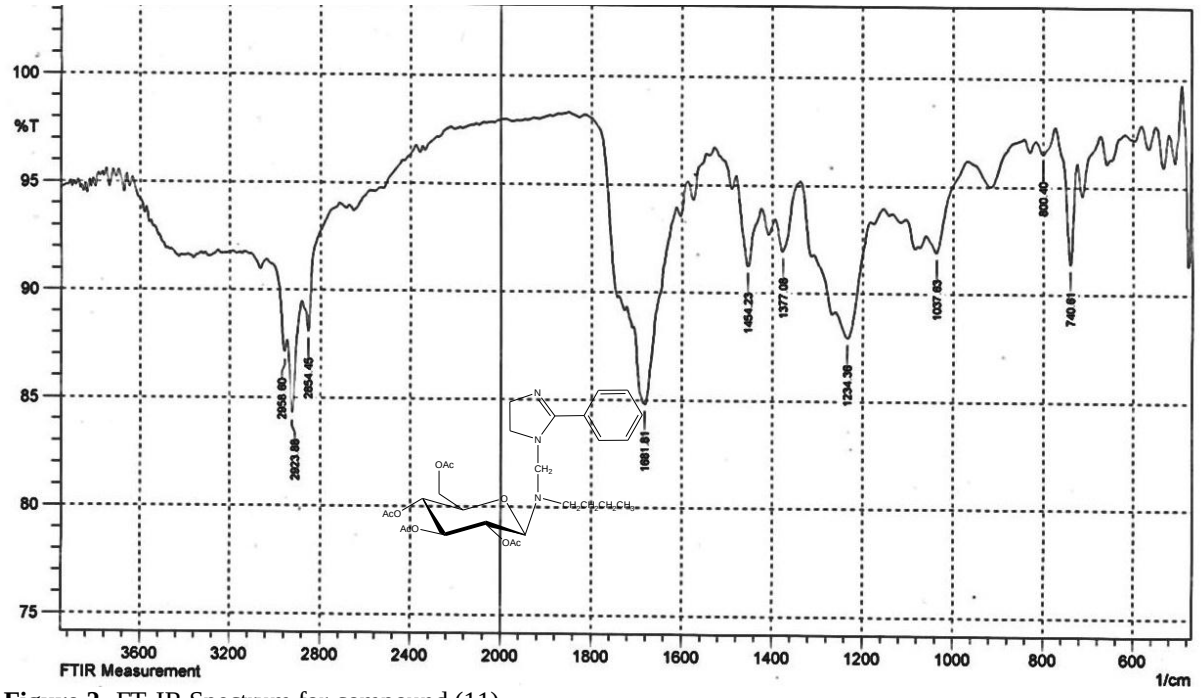


Figure 2- FT-IR Spectrum for compound (11)

Compounds (6, 7 and 14) were confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. ^{1}H-NMRspectrum of compound (6) showed two multiplet signals at (0.62-1.89) ppm for isobutyl and imidazoline respectively, while methylene protons and amine proton as a singlet at (3.54) and (4.22) respectively. Aromatic protons appeared as amultiplet at (6.1-8.5)ppm (Figure-4, Table-4) compound (7) showed imidazoline protons as amultiplet at 2.7-3.01) ppm other multiplet appeared at 7.39-8.27) ppm for aromatic protons. Methylene protons and amine proton appeared as asinglet at (3.18) and 3.58 ppm respectively compound (14) showed a signal at (0.87) ppm as triplet for terminal CH_3 of butyl group, other butyl protons appeared as amultiplet at (2.07)ppm.

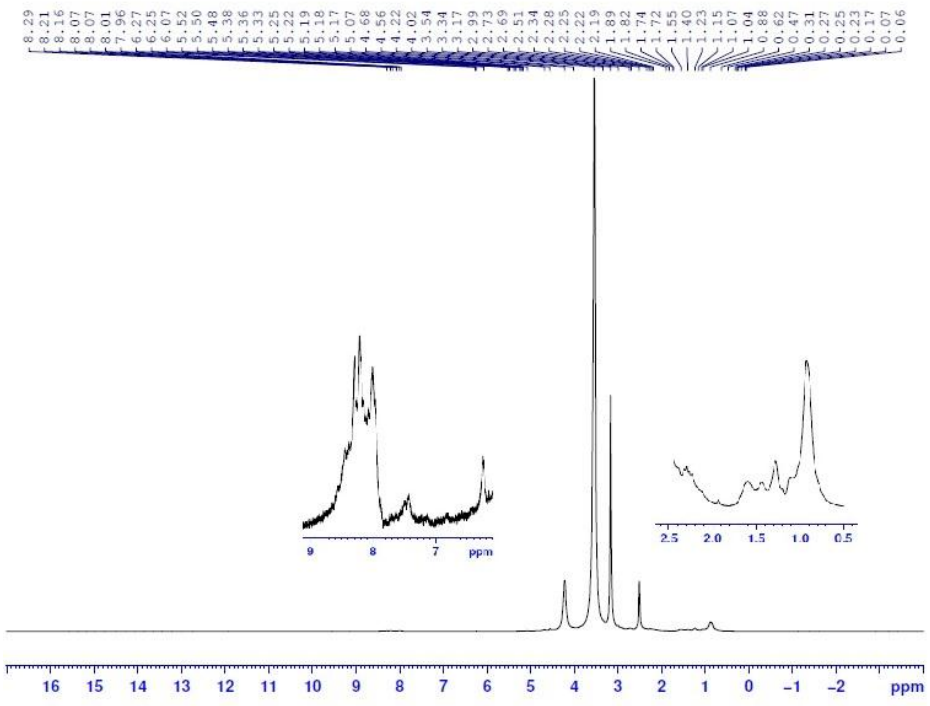


Figure 3- ^{1}H-NMR spectrum for compound (7)

Compound (7) showed two signals at (48.55) and (54.30)ppm for two (CH_2-N)imidazoline ring, while a signal at 164.49 ppm belong to (C2) imidazoline . methylene group appeared at (79.4) ppm, aromatic carbon showed signals between (121-136) ppm Figure-4.

The ^{13}C-NMR spectrum of compound (14), Figure-5 showed several signals between (18.15-31.2) ppm attributed to the butyl carbons. The methyl carbon of acetate groups appeared at the region between (38.8-39.4)ppm while signal at (60.9) and (67.2)ppm belong to two (CH_2-N) imidazoline ring, other imidazole carbon (C_2) appeared at 168.5ppm, signals appeared at (124.2-128.1)ppm, were attributed for six sugar carbon, while signals between (130-138)ppm belong to aromatic carbons. Carbonyl carbon appeared at downfield at 189ppm.

In ^{1}H-NMR spectrum of compound 14 four methyl groups of acetyl group appeared as a singlet at (1.25) ppm also methylene group appeared at a singlet at (4.5)ppm, imidazoline and aromatic protons appeared as a multiplet at (3.43-3.48)ppm and (7.12-8.16)ppm respectively. Sugar protons appeared as amultiplet at (4.6-5.46) ppm.

Table 5- ^{1}H-NMR – Spectral data for compounds (6,7 and 14 in Sppm).

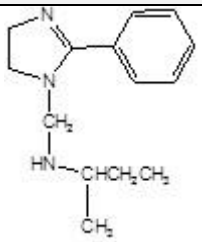
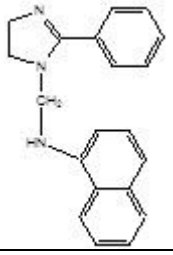
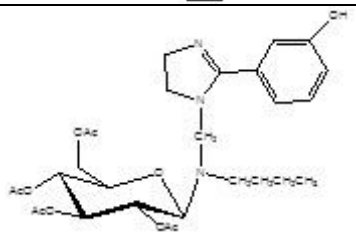
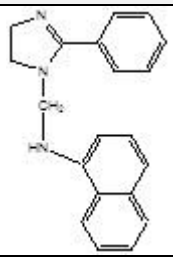
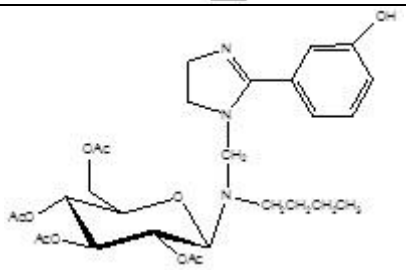
Comp. No	Structure	^{1}H-NMR Spectral data (δ ppm)
6		0.62-1.89 (m,9H,CH_3 isobutyl); 2.19-2.25 (m,4H,2CH_2imidazoline); 3.54 (S,2H, N-CH_2-N); 4.22 (S,1H,NM); 6.1-8.5 (m,5H,aromatic)
7		2.712-3.010 (m,4H,CH_2 imidazoline); 3.18 (S,2H,N-CH_2-N); 3.58 (S,1H,NH); 7.39-8.27 (m,12 H aromatic)
14		0.87 (t,3H,CH_3 aliph.); 1.25 (s 12H,4(—C(=O)—CH_3); 1.33-2.07 (m 6H, 3CH_2butan); 3.43-3.48 (m-4Himidazoline); 4.5 (s,2H CH_2-N); 3-3.8 (m, 3H, H`$_5$, 2H`$_6$); 4.6-5.46 (m,4H,H`$_4$, H`$_3$, H`$_2$, H`$_1$); 7.12-8.16 (m4H Aromatic); 10.12 (s1H,OH phenolic)

Table 6- ^{13}C-NMR – Spectral data for compound (7 and 14)

Comp. No	Structure	^{13}C-NMR Spectral data (δ ppm)
7		48.55 (CH_2-N imidazoline); 54.30 (CH_2-N) imidazoline); 79.4 (N-CH_2-N) ; 121-136 (16C-aromatic) 164.24-164.49 C2 imidazoline.
14		18.15-31.2 (4C, butyl); (60.9 - 67.23) (2CCH_2N, imidazoline); 97.1 (CH_2-N); 124-126 (6C,sugar). 130-138 (6C aromatic) 189 (4C, C=O), acetate (38.84-39.47)

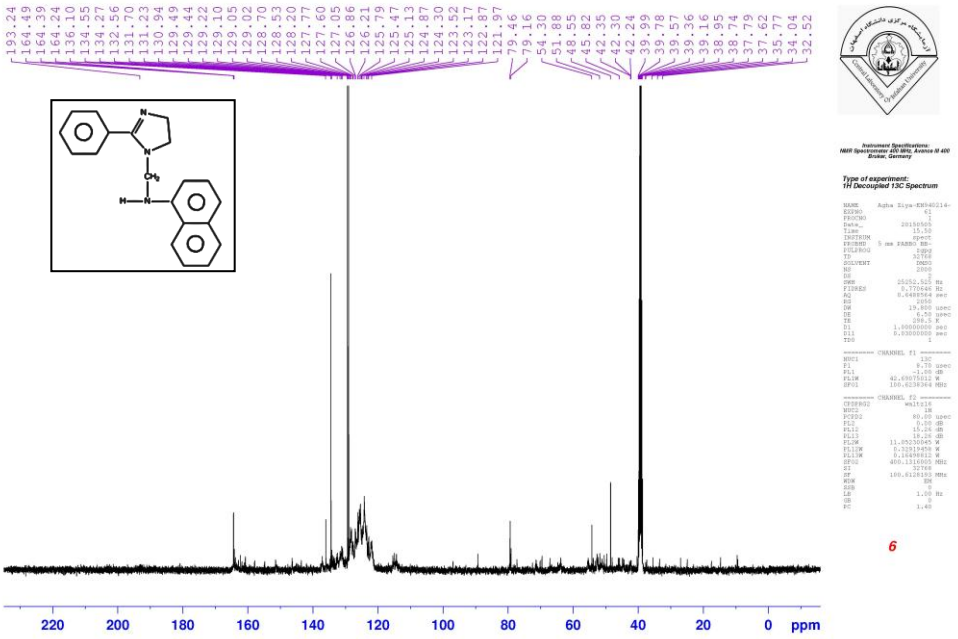


Figure 4- ^{13}C-NMR spectrum for compound (7)

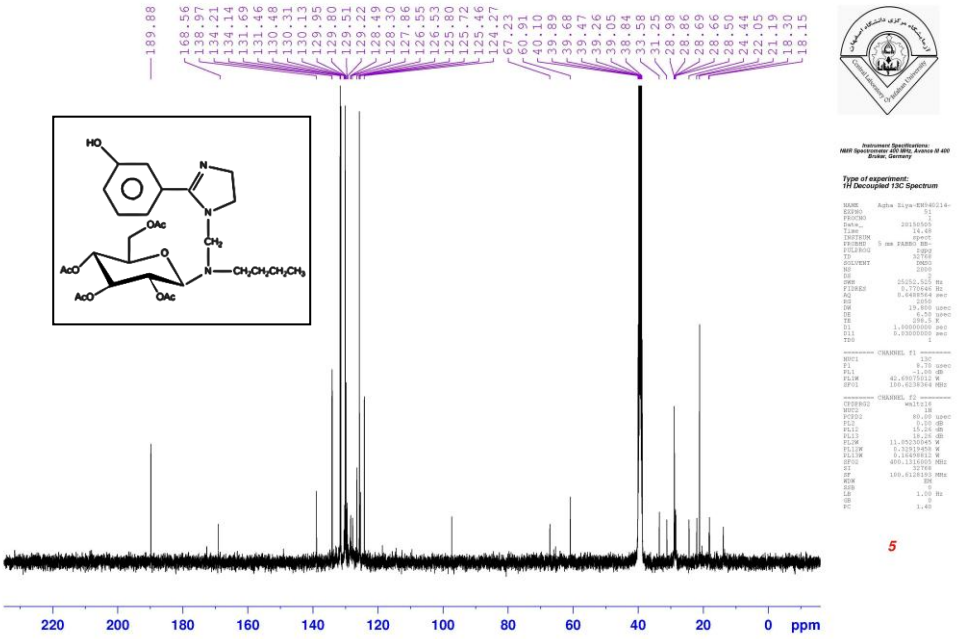


Figure 5- ^{13}C-NMR spectrum for compound (14)

To obtain our synthetic goal, the free nucleoside analogues, the acetyl group was hydrolyzed using methanolic sodium methoxide afforded the free nucleoside analogues (17-22). FT-IR spectra showed the appearance of O-H bands at (3500-3200 cm^{-1}) Table-2 gives a good indication for formation of free nucleoside analogues, Physical properties of the prepared compounds (17-22) and other data are listed in Table-7.

Table 7- Physical properties of compounds (17-22)

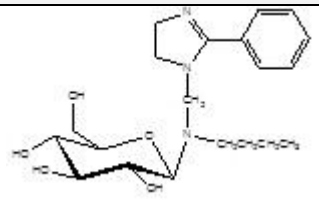
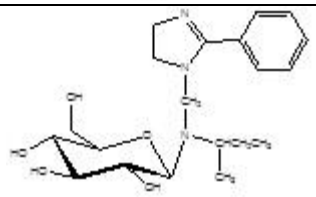
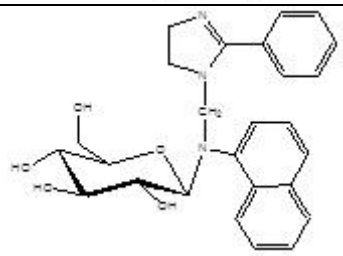
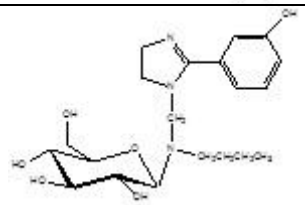
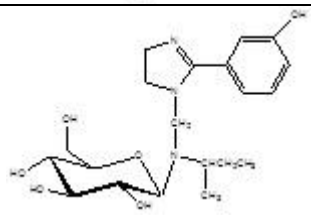
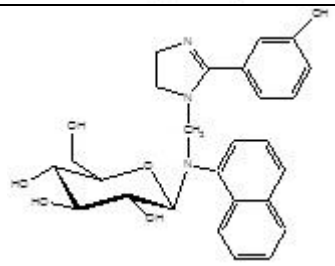
Comp. No.	Compound Structure	Molecular formula	M.w g/mole	M.P °C	Colour	Yield %
17		$C_{20}H_{32}N_3O_5$	394	Dec. 240	White	60%
18		$C_{20}H_{32}N_3O_6$	394	Dec. 208	White	68%
19		$C_{26}H_{29}N_3O_5$	463	Dec. 200	White	73%
20		$C_{20}H_{32}N_3O_6$	410	Dec. 215	Off – white	62%
21		$C_{20}H_{32}N_3O_6$	410	Dec. 202	Pale Brown	62%
22		$C_{26}H_{29}N_3O_6$	479	Dec.218	Redish Brown	68%

Table 8- FT – IR data cm^{-1} for compounds (17-22).

Comp. No.	ν (O-H) Phenolic or alcoholic	ν (N-H)	ν (C-H) arom.	ν (C-H) aliph.	ν (C=N)	ν (C=C) arom.	ν (C=O)
17	3400	-	3010	2933-2997	1673	1431	-
18	3419	-	3002	2935	1575	1575	-
19	3434-3471	-	3014	2933	1639	1639	-
20	3406	-	3000	2948	1690	1690	-
21	3431	-	3001	2910	1583	1583	-
22	3404	-	3015	2935	1577	1577	-

Biological activity:

Table 9- Inhibition Zones of compounds (17, 19, 20, 21)

Comp. No.	Gram positive		Gram negative	
	Bacillus subtilis	***Staphylococcus aureus***	***Esherichia. Coli***	***Pseudomonas aeruginosa***
Control DMSO	14	-	-	-
17	14	-	9	-
19	12	-	-	11
20	12	-	-	11
21	13	-	10	10

Compounds 17, 19, 20 and 21 showed good or moderated activites against *Bacillas subtilis,* while compounds 19, 20 and 21 showed good activity against *Pseudomonas Aeruginosa*. Compounds 17 and 21 showed moderate activity against *E.Coli.* All other compounds showed no inhibition against *Staphylococcus aureus.*

The difference of biological activity refers to different substituents in the compounds. On the other hand all these compounds were completely inactive against of types for fungi namely (*Aspergines flurs, Aspergillus fumgntns, Aspergillus niger and pencillum*). Which indicate the specify of the action of the nucleoside analogues as antibacterial but not against fungi, that is accordance to the literature [14-17].

Conclusions

Nucleoside analogues are important medical materials, therefor new nucleoside analogues were synthesized from imidazoline, derivatives containing Mannich base which also they have abroad spectrum of biological application. The nucleoside analogues are characterized on the basis of analytical and spectral data. Screening of these compounds against two types of Gram positive and two types of gram negative bacteria, showed good and moderate activity.

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