ISSN: 0974 - 7516 Volume 12 Issue 2

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 12(1), 2016 [016-028]

Synthesis of new nucleoside analogues via mannich base and studding their biological activities

Thanaa M.Al-Mouamin[1], Dehyaa J.Mehdi[2]*

[1]Department of chemistry, college of science, Baghdad University, Baghdad, (IRAQ)

[2]Ministry of Education – Baghdad, (IRAQ)

E-mail: sarahf.hameed@yahoo.com

ABSTRACT

Our goal in this research, was synthesized of some new nucleoside anologues. Starting from α-D glucose and α-D mannose which were converted to per acetylated β-D-gluco pyronoside and β-D-mannose furannose, then converted to active 1-Bromo sugar (2,5) as a sugar moiety. The base 2-substituted imidazoline was prepared from condensation of ethylene diamine with different aromatic aldehydes, which were subjected to amino alkylation via Mannich reaction forming new nucleoside derivatives. Condensation of nucleo base with bromo sugar in presence of *o*-xylene through nucleophilic substitution of anomeric carbon with nitrogen of Mannich base forming a new protected nucleoside analogues. To obtain our target the free nucleoside analogues, the protected nucleoside analogues were hydrolyzed with methoxide in methanol. All prepared compounds were identify by FT-IR spectroscopy and some of them with ^{1}H-NMR and ^{13}C-NMR spectroscopy, screened for their anti-bacterial activity in vitro against four types of bacteria including Bacillus, staphylococcus (gram positive). E. coli and pseudomonas as (gram negative). And also were screened against four types of fungi.

KEYWORDS

Nucleoside analogues; Mannich reaction and imadazoline.

INTRODUCTION

Nucleoside are the building blocks required in constructing nucleic acid. Billions of combination are possible using four type of nucleoside as RNA or DNA which is represent the repository of genetic information in living system[1,2]. Nucleosides analogues have been the focus of attention, because of their vital role played by carbohydrates in a variety of biological processes[3-6]. Mainly as antitumor or antiviral drugs[7,8]. Also to improve the pharmacologic activity[9,10]. A variety of functionalities have been introduced into either the sugar moiety[11,12] or the heterocyclic moiety[13]. Nucleosides are implicated in all aspects of cellular life, catalysis, metabolic regulation, energy supply, and storage of gentic information through the nucleic acid[14].

Mannich reaction is amino methylene of carbonyl compounds and other acidic of active methylene groups with formaldehyde and ammonia also primary or secondary amines after elimination of water

molecule[15]. Based on widely applications of Mannich bases. Such as antibacterial, anti-cancer[16] antimicrobial and algesic drugs, which is proved toxic and more effective than parent nucles. Some of Mannich bases are found in the backbone or as additives of some industrially important polymers[17].

The 2-substituted imidazoline have attracted considerable attention for the development of compounds with useful pharmacological properties. Such as anti-viral, anti-becterial, anti-tumer and breast concer[18].

Imidazoline derivatives have extensive application in surfacent in small properties for improving detergent qualities for virous purpose (hair, fabric, softeners and industrial product of imidazoles carried out by dehydrogenation of imidazoles[19].

Based on these observation inspire us to synthesis new nucleoside analogues containing imidazoline derivatives with Mannich base as a nucleo base and sugar moiety (glucose and mannose) and study some of their biological activity.

EXPERIMENTAL PART

Materials

The quality of all these chemicals supplied from BDH England, Fluga merch, and sigma-alderich chemicals. All chemicals in this study were of a highest purity and used without purifications.

Experimental instruments

Melting points were recorded by Gallen-Kamp, England. Melting points apparatus and were uncorrected. Infrared spectra were recorded using SHMADZU, FT-IR 8400 spectrophotometer (Japan) as a thin film or KBr disk. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with help of ultra – high field 400 MHz Auance 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 C^{13}-NMR spectrum. TLC plates were used with an aluminum backing (0.2 mm 60 F_{254}). Biological activity using incubator memmert.

Synthesis of *α-D*-glucose penta acetate (1)[20]

α-D-glucose (1g, 0.0055 mole) and (0.8g, 0.00975 mole) of anhydrous sodium acetate was dissolved in (6ml) acetic anhydride then refluxed on water bath with stirring for (2h). then pour the reaction mixture on to (50mL) of ice-cold water filtered and recrystallized from ethanol to afford a white crystal (1) m.p (131-132 C°)

Preparation of 2,3:5,6-di-*o*-isopropylidene-*α-D*-manno furanose(2)[21]

α-D-mannose (5g, 27 mmole) was stirred together with a (15) fold amount of anhydrous acetone (75mL) containing (3.5mL) of concentrated sulfuric acid. After (3-4h) all the *α-D*-mannose sugar were dissolved and the yellow solution was neutralized with anhydrous sodium carbonate. Filtered, then the filtrate was evaporated under reduced pressure and dissolved in a little ether and petroleum ether yielded as syrup.

Preparation of 2,3,5,6-tatra-*o*-acetyl *α*-D-manno furanose (3)[20]

The solution of protect sugar (2) in acetic acid (10ml) and acetic anhydride, (8ml). concentration sulfuric acid (0.6mL) was added. The reaction mixture was stirred for (24h) at room temperature. Then detection by TLC (ethyl acetate : benzene (1:10)). Then the mixture was poured into (35mL) of water and was extracted with chloroform (3×15 mL). The combined chloroform extracts were dried over anhydrous ($MgSO_4$). And the solvent was evaporated to give (3) as syrup (0.64g, 64%).

General procedure for synthesis of 1-bromo acetylated sugar (4,5)[22]

The acetylated sugar (1,) (0.38g, 1.08 mmole) was dissolved in (3ml) of (50%) hydrogen bromide in glacial acetic acid which was added at (0C°), and kept for one hour at (0C°). finally kept at room temperature for (15). after washed with ice-water (2x15mL) and then with saturated aqueous solutions of sodium bicarbonate to remove the trace of acid. After a final wash with ice-water (20mL), then dried over anhydrous $MgSO_4$ and solvent was removed to give compound (4 or 5) as syrup, respectively. Then the isolated sugar bromide (4,5) used directly for synthesis of the nucleoside analogues.

Full Paper

General procedure for synthesis 2-substitut phenyl imidazoline

The mixture of substituted benzaldehyde (0.01 mole) and (0.01mole) of ethylene diamine was refluxed for (4h). Using (4mL) DMF and (0.312g, 0.01mole) $NaHSO_3$ as a ring closing agent. The precipitate obtained after cooling and recrystallized from DMF (6,7)[21].

General procedure for synthesis of mannich base (8-12)[22]

The solution of imidazoline derivatives (6,7) (0.0045 mole) in methanol (10mL) and (1mL) of 10% dilute HCl. The primary amine (0.0054 mole) and (0.0054mole) formaldehyde was added. Then refluxed on water bath for (3h), the product formed after cooling, was filtered, and dried over anhydrous sodium sulphate and the solvent was removed to give the Mannich base (8-12).

General procedure for synthesis of protected nuleoside analogues (13,17)[23]

Mannich base (0.0001 mole) (8-13) was finally grinded and suspended in (30 ml) of dried *o*-xylene. The solvent was practically distilled off until 137 C° to remove trace of water. Then the residual suspension was allowed to cool below (50 C°). The acetylated sugar bromide (0.0001 mole) was dissolved in dried *o*-xylene, then added to the Mannich base solution and refluxed with vigorous and stirring for (1h). The organic layer was washed (2x15 mL) with water then dried over anhydrous sodium sulphate. And the solvent was remove to give the acetylated nucleoside (13-17).

General procedure for hydrolysis of protected nucleoside analogues (18-22)[24]

A solution of (0.003 mole) of the blocked nucleoside analogues in (7mL) of (0.1M) methanolic sodium methoxide was refluxed and stirring (0.5h). A mixture was neutralized by acetic acid and evaporated to dryness, the residue was partitioned between water and chloroform. The aqueous phase was evaporated to dryness under vacuum, to obtain free nucleoside (18-22).

Biological activity[25]

This test was performed with disk of diffusion method. Nutrient agar was added to (1L) of distilled water in suitable conical flask with stirring and heating autoclave for 20 minutes at (121C°) under pressure at (15) pound/inch.

The medium was placed in peteridishes about (20mL) for each one and left to cool and solidified, the studied bacteria and fungi were placed on the nutrient agar surface using loop and by streaking processor then the disk saturated with tested compound solutions. The samples were incubated for (24h) at 37C° and (72h) for fungi. The inhibition zones which were caused by virus compounds on the microorganism were examined.

RESULTS AND DISCUSSION

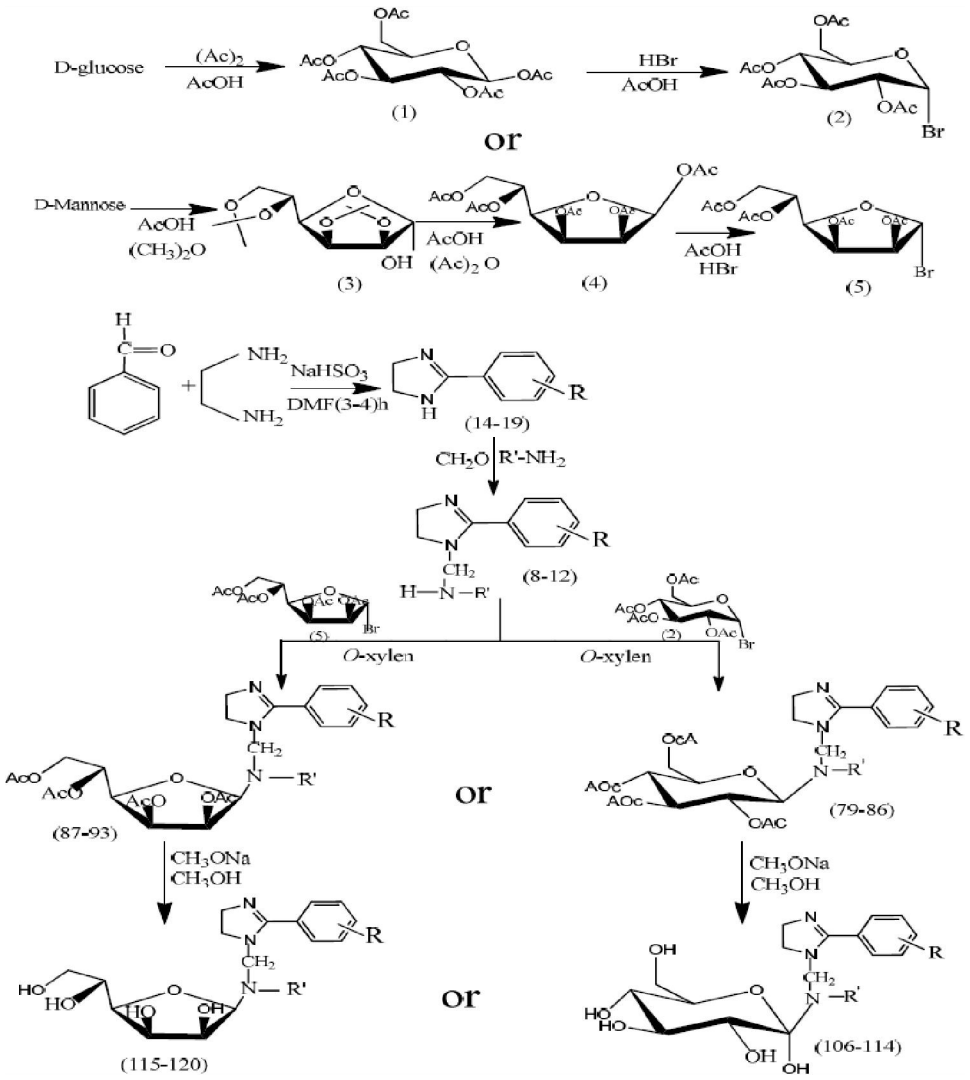
Our target is to synthesized a new modified nucleoside analogues. The most common modification of nucleoside analogues represent by important of medicinal compounds which have been found to behave agent and are currently used pharmaceuticals as antitumor, antiviral and anti-biotic agents. In view of these activities it was considered to synthesis new nucleoside analogues according to designed multi steps. Scheme (1)

The synthetic rout was started with sugar moiety (D-glucose and D-mannose), and imidazoline derivatives containing Mannich base as a base moiety,

D-glucose and D-mannose were protected with acetic anhydride in presence of sodium acetate afforded β-D-glucose penta acetate (1) and β-D-mannose penta acetate (3) which were brominated using hydrogen bromide in glacial acetic to give acetylated bromo sugar bromide (2and5). Compounds (1,2,3,4and5) were confirmed by their properties due to literature[26].

The FT-IR[27] spectrum of compounds (1) and (3) showed several characteristic bands mainly the stretching of carbonyl of acetyl group at 1744 cm^{-1} and 1753 cm^{-1} respectively while compounds (2) and (5) showed in addition to carbonyl band the appearance of (C-Br) band at 661 $cm^{-1}$and, 621 cm^{-1} respectively.

On the other hand imidazoline pharmaceutical



Scheme 1 : Synthetic route for synthesis of nucleoside analogues

importance due to the biological activities, therefore it was chosen as a nucleobase, which was synthesis by condensation of ethylene diamine with substituted benzaldehyde using sodium with hydrogen sulfite as a ring closing agent according to the suggest mechanism showed in Scheme (2).

The imidazoline derivatives (6) and (7) were characterized with FT-IR spectrum. Compound (6 and 7) showed the υ (N-H) stretching bands at (3330) cm^{-1} and (3396) cm^{-1} for amine respectively. In additional to above groups, the asymmetrical stretching band and symmetrical stretching band appeared at(1282) and(1062) respectively for (O-CH_3) in compounds (6)

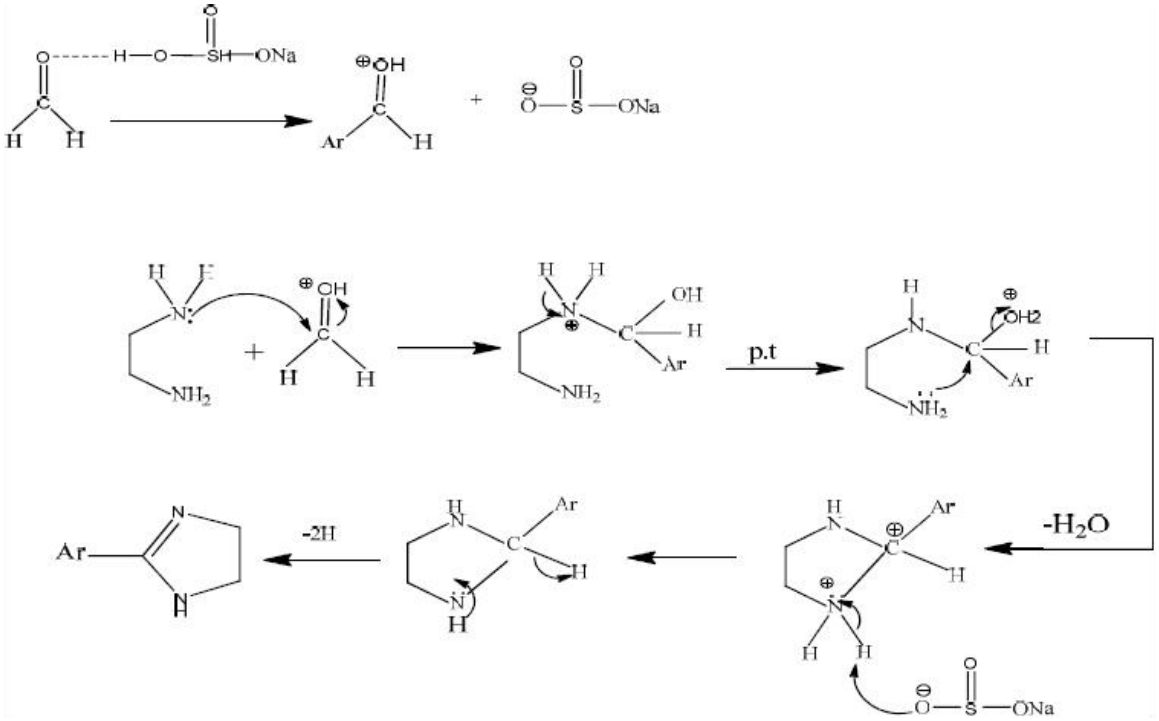
Mannich bases(8-12) were synthesised by condensation of 2-subsituted phenyl 1H-imidazoline with primary amine using CH_2O in methanol through mannich reaction. Scheme (3)

The FT-IR spectrum for Mannich base compounds (8-12), showed stretching bands between (3330-3477) cm^{-1} for amine group. Stretching bands between (3043-3066) cm^{-1} belong to υ(C-H) aromatic. All these data are listed in TABLE (1).

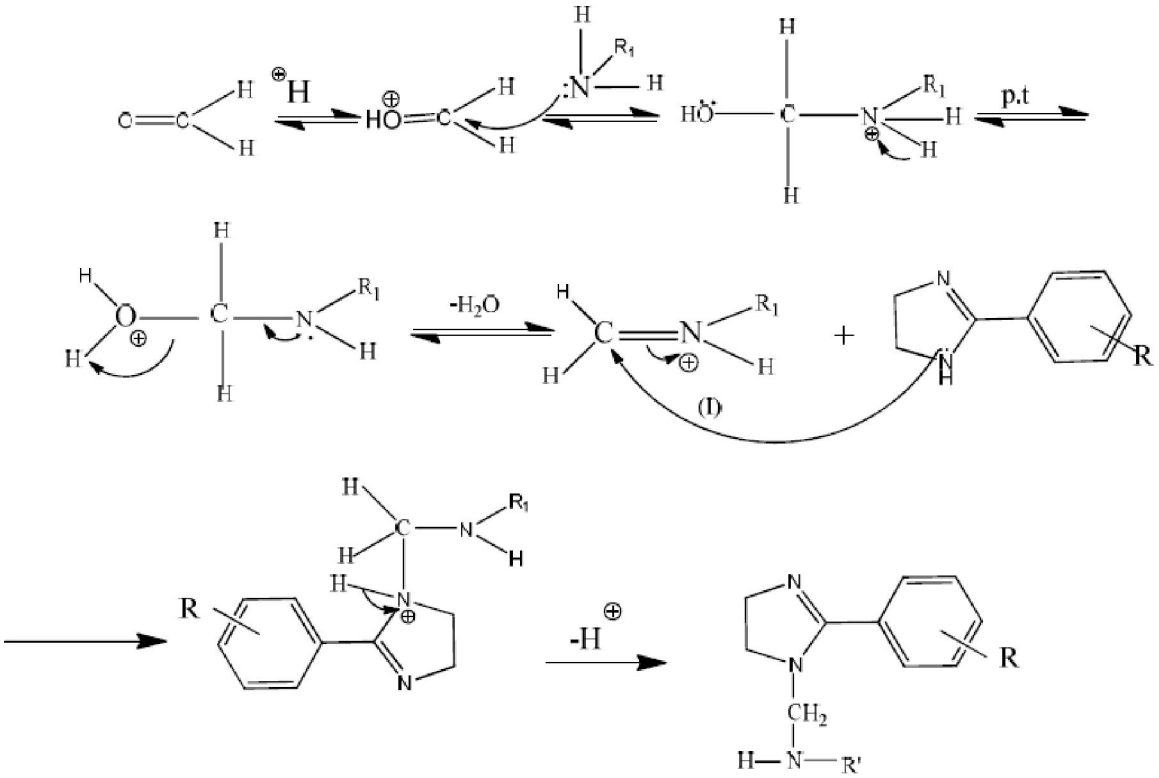
To achieve our synthetic protected nucleoside analogues. The modified nucleobase compounds (8-12) were coupled with 1-bromo sugar (2,5) afforded the new blocked nucleoside (13-17).

The FT-IR of compound (13-17) showed the disappearance of (N-H) band at(3330-3419)cm^{-1} and appearance of carbonyl for acetyl group between(1691-1747)which gives a good evidence for coupling reaction. All data were listed in TABLE (2).

Full Paper



Scheme 2



Scheme 3

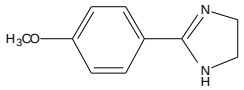
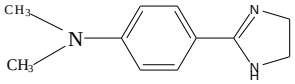
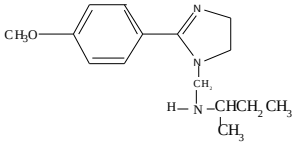
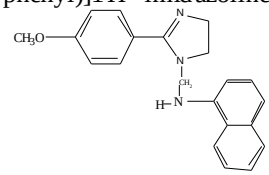
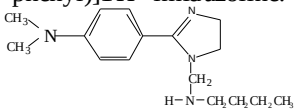
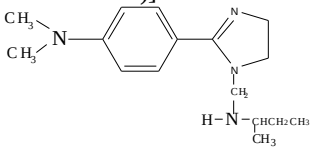
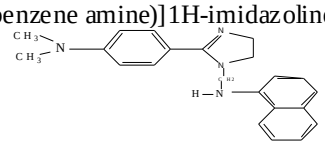
To achive our synthetic target the free nucleoside analogues (18-22), the protected nucleoside (13-17) were de blocked with methanolic sodium methoxide to afford our synthetic goal the free nucleoside analogues.

The FT-IR of free nucleoside analogues (18-22) showed, the disappearance of carbonyl bands between (1691 -1747) cm^{-1}, and the appearance of

(O-H) group between (3396 -3463)cm^{-1} which indicate that the reaction was successful. Scheme(3)

The H^1-NMR[28] spectrum of compound (9) in ppm, TABLE (4) showed multiple signals at (2.75-3.21) belong to imidazoline protons, a singlet signal at (3.37) attributed to (N-H), while singlet signal at(3.86) refers to (OCH_3) protons, a singlet signal at 4.59 refers to (N-CH_2-N), and multiple signals at

TABLE 1 : Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (6-12)

Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}					
	Structures	M.P °C	Yield%	Color	ν(N-H)	ν(C-H) arom	ν(C-H) aliph.	ν(C=N)	ν(C=C)	Others
6	 2-(4-methoxy phenyl) 1H-imidazoline.	106-108	64	white	3330	3058	2920	1604	1510	υ(O-CH_3) asy (1282) sy (1062)
7	 2-(4-N,N dimethyl phenyl) 1H-imidazoline	192-194	31	Off - white	3396	3008	2910	1604	1558	
8	 1-[(Methylene – N- 2 – butyl amine) -2- (4 methoxy phenyl)]1H –imidazoline.	Gum	67	Deep orange	3380	3064	2962	1606	1512	υ(O-CH_3) asy1249 sy1031
9	 [(Methylene – N- 1 – naphthyl amine) -2- (4 methoxy phenyl)]1H –imidazoline.	105-108	70	Deep purple	3375	3047	2900	1586	1458	υ(O-CH_3) asy1250, sy1024
10	 1- [(Methylene – N- 1 –butyl amine) -2- (4-N,N, dimethyl benzene amine)]1H-imidazoline.	66-68	68	Pale yellow	3447	3047	2906	1596	1533-1550	
11	 1- [(Methylene – N- 2 – butyl amine) -2- (4- N,N, dimethyl benzene amine)]1H-imidazoline.	70-72	37	Transparent white	3385	3049	2908	1595	1533-1584	
12	 1- [(Methylene – N- 1 – naphthyl amine) -2- (4 N,N, dimethyl benzene amine)] 1H imidazoline.	Dec 66	61	Brown	3419	3066	2924	1593	1544	

Full Paper

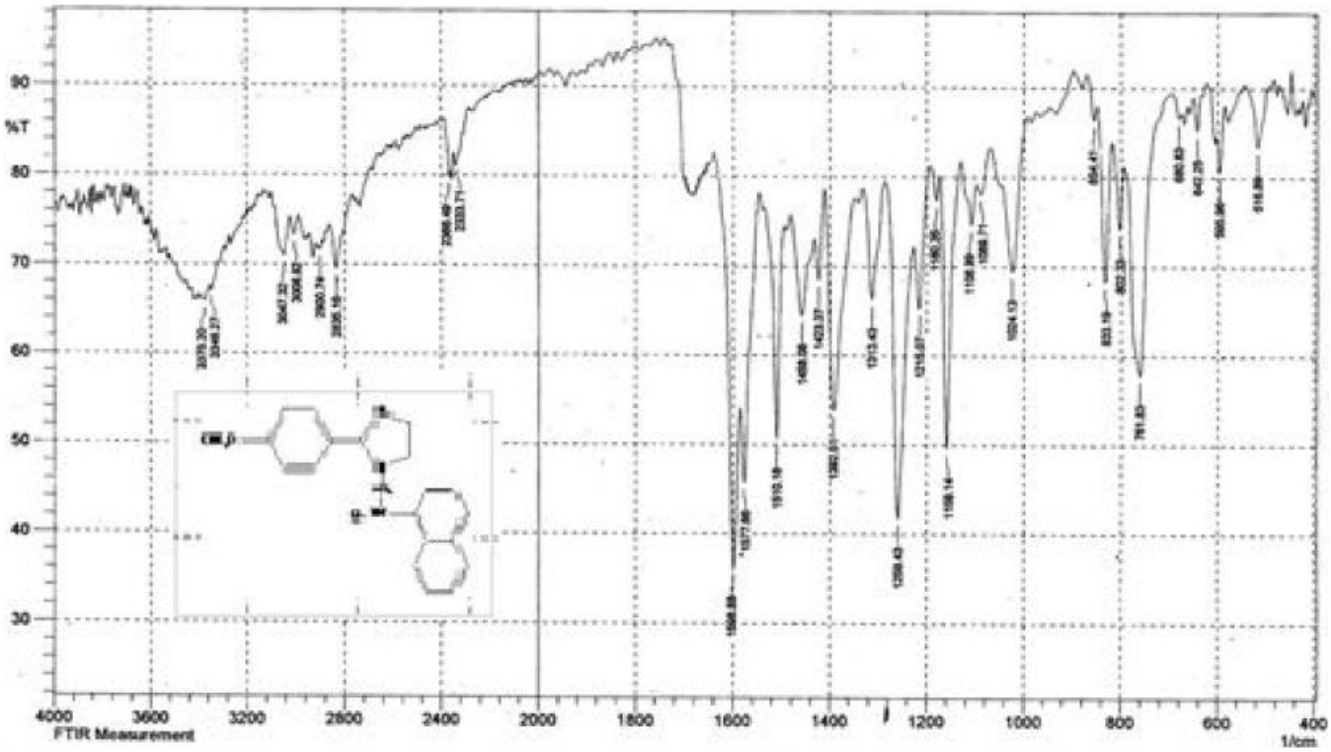


Figure 1 : FT-IR Spectrum for compound[9]

(6.81-8.06) for aromatic protons.

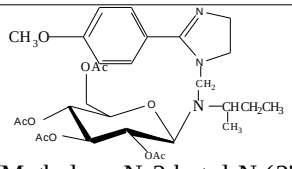
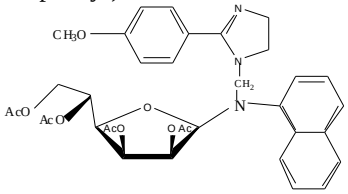
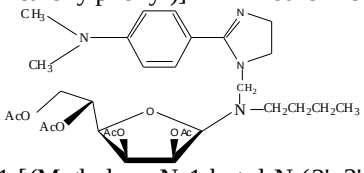
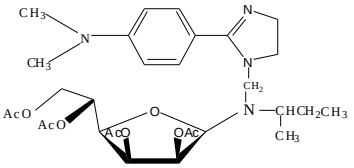
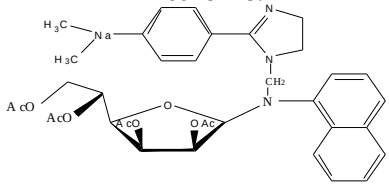
The ^{1}H-NMR spectrum of compound (15) in ppm TABLE (4) showed triplet signals between (0.83-0.87) due to methyl butyl (CH_3) butyl proton, multiplet signals at (1.19-2.28) referred to (three CH_2) butyl, while multiplet signals between (2.67-2.9) belong to two ($2CH_2$) imidazoline, singlet signal at (3.0) attributed to ($2CH_3$-N) protons. Also a signal at (3.04) refer to (four CH_3) acetyl protons, multiplet signals between (3.09-3.36) refer to (H'_6,H''_6,H'_5,H'_4,H'_3,H'_2) sugar protons respectively, a singlet single at (6.57)assigned to methylene protons (2H,N-CH_2-N). A doublet signals between (6.62-6.64) for ($H_{,1}$), and multiplet signals between (6.71-7.94) belong to aromatic protons.

The ^{1}H-NMR spectrum of compound (20) in ppm TABLE (4) showed triplet signals at (0.83-0.86) belong to (CH_3) butyl, multiplet signals at (1.0-1.24) assigned to three methylene of butyl ($3CH_2$), singlet signal at (1.70) belong to (2N-CH_3). Multiplet signals between (1.86-2.34) assigned to sugar protons (H'6,H''6,H'5), while multiplet signals between (2.26-2.77) referred to (H'_4,H'_3,H'_2) sugar protons. The multiplet signals between (2.88-3.0) belong to methylene of imidazoline, singlet signal at (3.05) for four hydroxyl sugar protons,singlet signal at (3.58) belong to (N-CH_2N) methylene protons, and multiplet signals at (6.74-7.75) referred to aromatic protons.

The ^{13}C-NMR spectrum (δ-ppm) for compound (9) TABLE (5) showed a signal at (28.98) belong to (CH_2) imidazoline, a signal at (34.1) referred to (CH_2) imidazoline, a signal at (52.74) assigned to (O-CH3), a signal at (55.64)attributed to methylene (N-CH_2-N),also a signal at (63.9) refer to (N-C=N) imidazoline and a signals at (114.27-164.18)refers to aromatic carbons.

The ^{13}C-NMR spectrum of compound (15), TABLE (5) showed the characteristic signals. The signal at (21.19) belong to methyl butane (CH_3), a signal at (28.55) refereed to ($2CH_3$-N), while a signal at (28.95) refer to (N-CH_2butan). A signals between (31.12-33.35) belong to four methyl of acetyl group (4CH3 acetyl), a signal between (61.2-62.3) attributed to methylene carbon (N=CH_2-N imidazoline). A signal at 64.71 (1C,C'6 sugar), while a signals between (72.41-77.5) refereed to other sugar carbons (C'_5,C'_4,C'_3,C'_2), while a signal at (110.71) (C'_1 sugar carbon). A signal at (110.93) belong to methylene carbon (N-CH_2-N), a signals at (120.12-131.70) refer to aromatic carbons

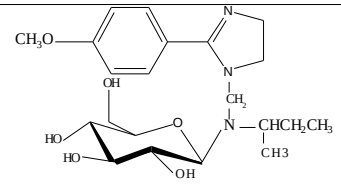
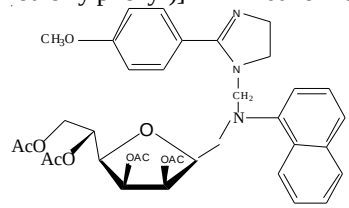
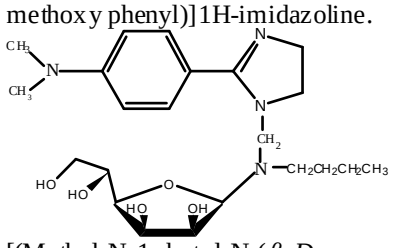
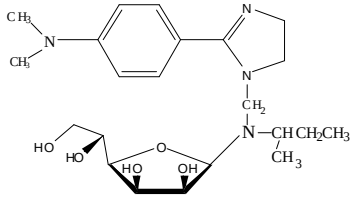
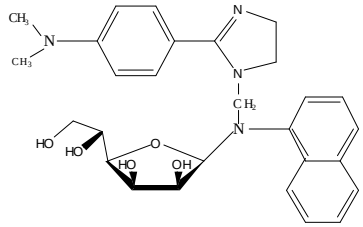
TABLE 2 : Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (13-17)

Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}					
	Structures	M.P °C	Yield%	Color	ν(C-H) arom	ν(C-H) aliph.	ν(C=N)	ν(C=C)	ν(C=O)	Others
13	 1-[(Methylene-N-2-butyl-N-(2', 3', 4', 6'-tetra –*O*- acetyl -*β*-*D*- gluco pyranosyl) amine)-2-(3-methoxy phenyl)] 1H-imidazoline.	Syrup	62	Off-white	3020	2966	1600	1512	1747	υ(O-CH_3) asy.1039 sy.1222
14	 1-[(Methylene-N-1-naphthyl-N-(2', 3', 5', 6'-tetra -*O*- acetyl- *β* -*D*- Manno furanosyl) amine)-2-(4-methoxy phenyl)] 1H-imidazoline.	syrup	52	Gray	3045	2921	1604	1514	1697	υ(O-CH_3) asy.1045 sy.1284
15	 1-[(Methylene-N-1-butyl-N-(2', 3', 5', 6'-tetra -*O*- acetyl-*β*-*D*-Manno furanosyl) amine)-2-(4- N,N dimethyl benzene amine)] 1H-imidazoline.	Dec. 98	58	white	3045	2999	1600	1515	1691	
16	 1-[(Methylene-N-2- butyl -N-(2', 3', 5', 6'-tetra -*O*- acetyl-*β*-*D*-manno furanosyl) amine)-2-(4-N,N,dimethyl benzene amine)] 1H-imidazoline.	Dec. 162	43	white	3014	2920	1614	1490	1731	
17	 1- [(Methylene-N-1- naphthyl -N-(2', 3', 5', 6'-tetra -*O*- acetyl-*β*-*D*-manno furanosyl) amine)-2-(4-methoxy phenyl)] 1H-imidazoline.	105-108	48	Deep purple	3014	2920	1612	1458	1704	υ(O-CH_3) asy.1020 sy.1190

(aromatic), a signal at (154.17) refereed to (N-C-N imidazaline), a signals between (189.5-191.78) refer

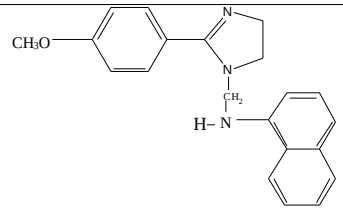
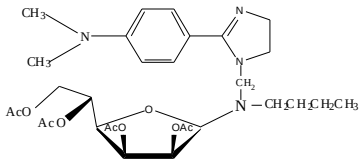
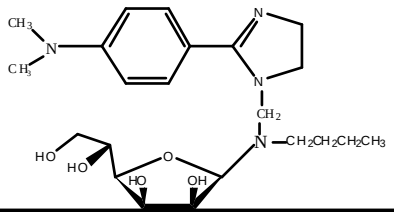
Full Paper

TABLE 3 : Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (18-22)

Com.No.	Physical Properties				Major FTIR Absorption cm^{-1}					
	Structures	M.P °C	Yield%	Color	ν(O-H)	ν(C-H) arom	ν(C-H) aliph.	ν(C=N)	ν(C=C)	Others
18	 1-[(Methylene-N-2-butyl -N-(β -*D*-gluco pyranosyl) amine)-2-(4-methoxy phenyl)]1H-imidazoline.	Syrup	53	Pale Brown	3406	3005	2948	1575	1413	υ(O-CH_3) Asy.1218 sy. 1014
19	 1-[(Methylene-N-1-naphthyl -N-(β -*D*-gluco pyranosyl) amine)-2-(4-methoxy phenyl)]1H-imidazoline.	Syrup	65	Off-white	3396	3008	2923	1560	1456	υ(O-CH_3) Asy.1274 sy. 1051
20	 1-[(Methyl-N-1- butyl-N-(β -*D*-manno furanosyl) amine)-2-(4-methoxy phenyl)]1H-imidazoline.	Dec. 230	72	Pale gray	3423	3010	2937	1639	1562	
21	 1-[(Methylene-N-2- butyl -N-(β -*D*-manno furanosyl) amine)-2-(4-N,N-dimethyl benzene amine)]1H-imidazoline	Dec. 210	51	Deep Brown	3463	3001	2935	1612	1550	
22	 1-[(Methylene-N-1- naphthyl -N-(β -*D*-manno furanosyl) amine) 2-(4-N,N-dimethyl benzene amine)]1H-imidazoline.	Syrup	53	Pale Brown	3423	3004	2923	1660	1598	

Full Paper

TABLE 4 : ^{1}H-NMR spectral data in (δ ppm) for compounds (9, 15 and 20)

Comp No	Structures	(δppm)
9		2.75-3.21 (m, 4H,2CH_2 imidazole; 3.37(s, 1H,NH); 3.86 (s,3H,OCH_3); 4.59 (s,2H,N-CH_2-N); 6.81-8.06 (m,11H, aromatic).
15		0.83-0.87 (t, 3H, CH_3 butyl); 1.19-2.28 (m, 6H, 3CH_2 aliphatic); 2.76-2.9 (m, 4H, 2CH_2 imidazoline); 3.0 (s, 6H, (N $(CH_3)_2$); 3.04 (s, 12H, 4CH_3 acetyl); 3.09-3.36 (m, 6H, H'$_6$, H''$_6$, H'$_5$, H'4, H'$_3$, H'$_2$); 6.57 (2H, N-CH_2-N), 6.62-6.64 (d, 1H, H'); 6.71-7.94 (m, 4H, aromatic
20		0.83-0.86 (t, 3H, CH_3); 1.0-1.24 (m, 6H, 3CH_2 butyl); 1.70 (s, 6H, 2CH_3N); 1.86-2.34(m, 4H, 2CH_2 imidazoline)); 2.67-2.68(t, 1H,H'$_5$); 2.76-2.77(d,2H, H'$_6$, H''$_6$); 2.88-2.96 (m,2H, H'$_4$, H'$_3$); 3.05(s,4OH); 3.22-3.35(d,1H, H'$_1$); 3.58 (s, 2H, N-CH_2N); 6.62-7.71 (m, 4H, aromatic).

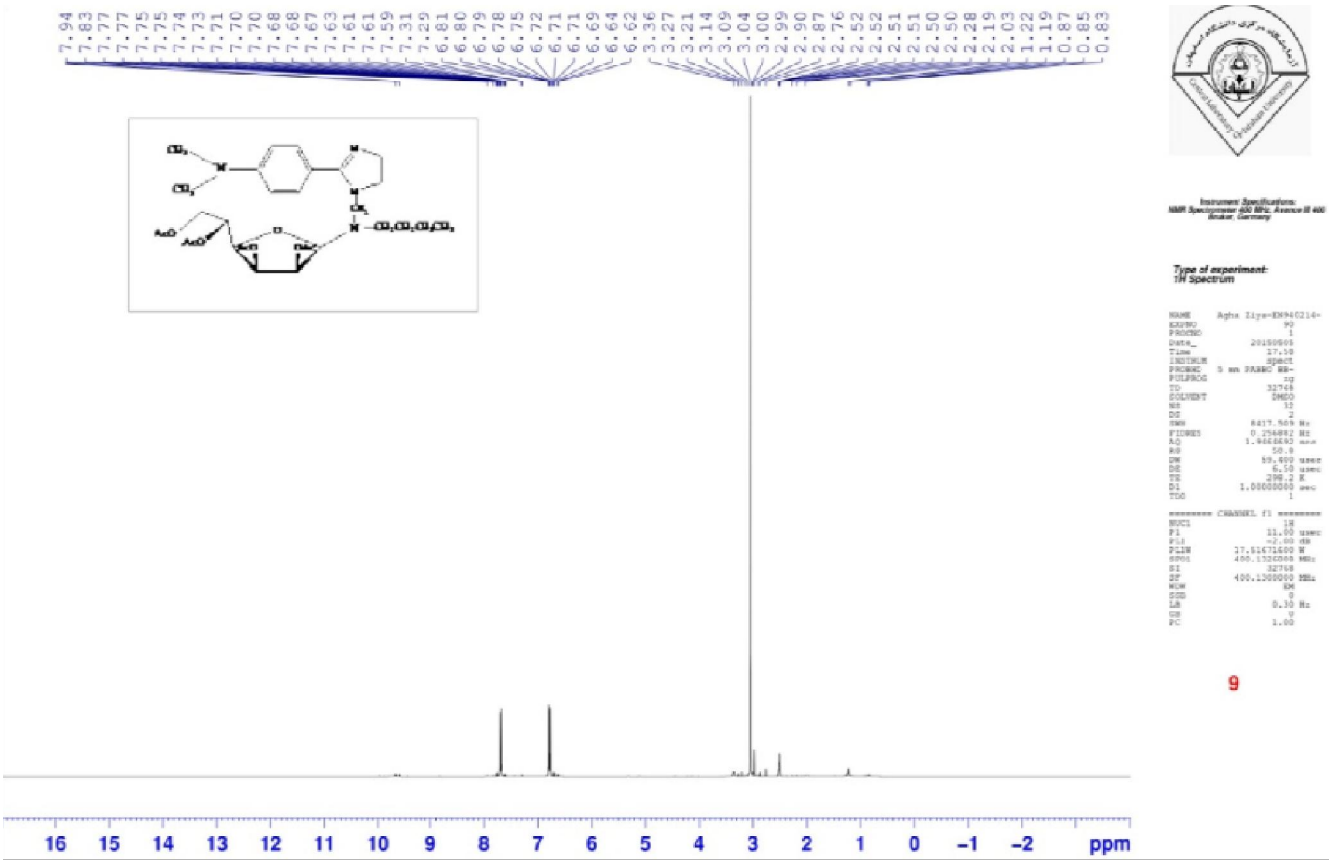


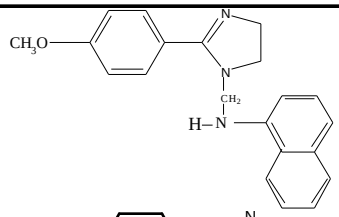
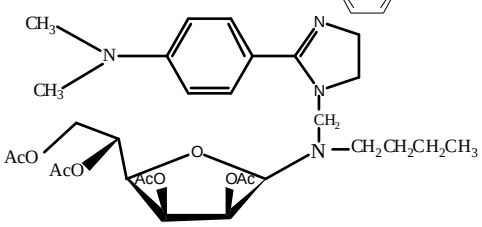
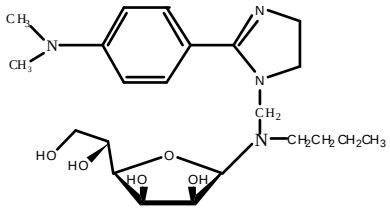
Figure 2 : ^{1}H-NMR Spectrum for compound[15]

to four carbonyl (C=O) groups.

The ^{13}C-NMR spectrum of compound (20), TABLE (5) showed the characteristics signal at (24.24) referred to methyl of butyl (CH_3) a signal

Full Paper

TABLE 5 : C[1]-NMR spectral data in (δ ppm) for compounds (9, 15 and 20)

Comp No	Structures	(δppm)
9		28.98 (1C, imidazoline); 34.1 (1C, imidazoline) 52.74 (1C, OCH_3); 55.64 (1C, NCH_2N); 63.9 (1C, N-C=N imidazoline); 11427-164.18 (16C, aromatic carbons).
15		21.19 CH_3 butyl ;28.55(2CH_3-N);28.67 (2C $CH_2CH_2CH_3$); 28.95 (1C N- CH_2 butan);31.12-33.35 (4C,4CH_3 acetyl) 61.2-62.3(1C N=CH_2-N) imidazoline, 64.71 (1C,C'$_6$); (72.41-77.5) (4C, C'$_5$, C'$_4$, C'$_3$, C'$_2$); 110.71 (1C, C'$_1$ sugar), 120.12 (N-CH_2-N) 124.4-131.70 (6C aromatic carbons); 154.17 (4C carbonyl)
20		24.24 (1C CH_3 butyl); 27.04-31.26(3C, 3CH2 butyl); 40.10 (2C, 2CH_2 imidazol); 44.31, 45.1 (2C, 2CH_3N); 61.31-69.84 (5C, C'$_6$, C'$_5$, C'$_4$, C'$_3$, C'$_2$); 111.04 (1C, C'$_1$),124.48 (1C, N-CH_2-N); 124.96--131.52 (6C aromatic); 154.18 (1C, imidaz.).

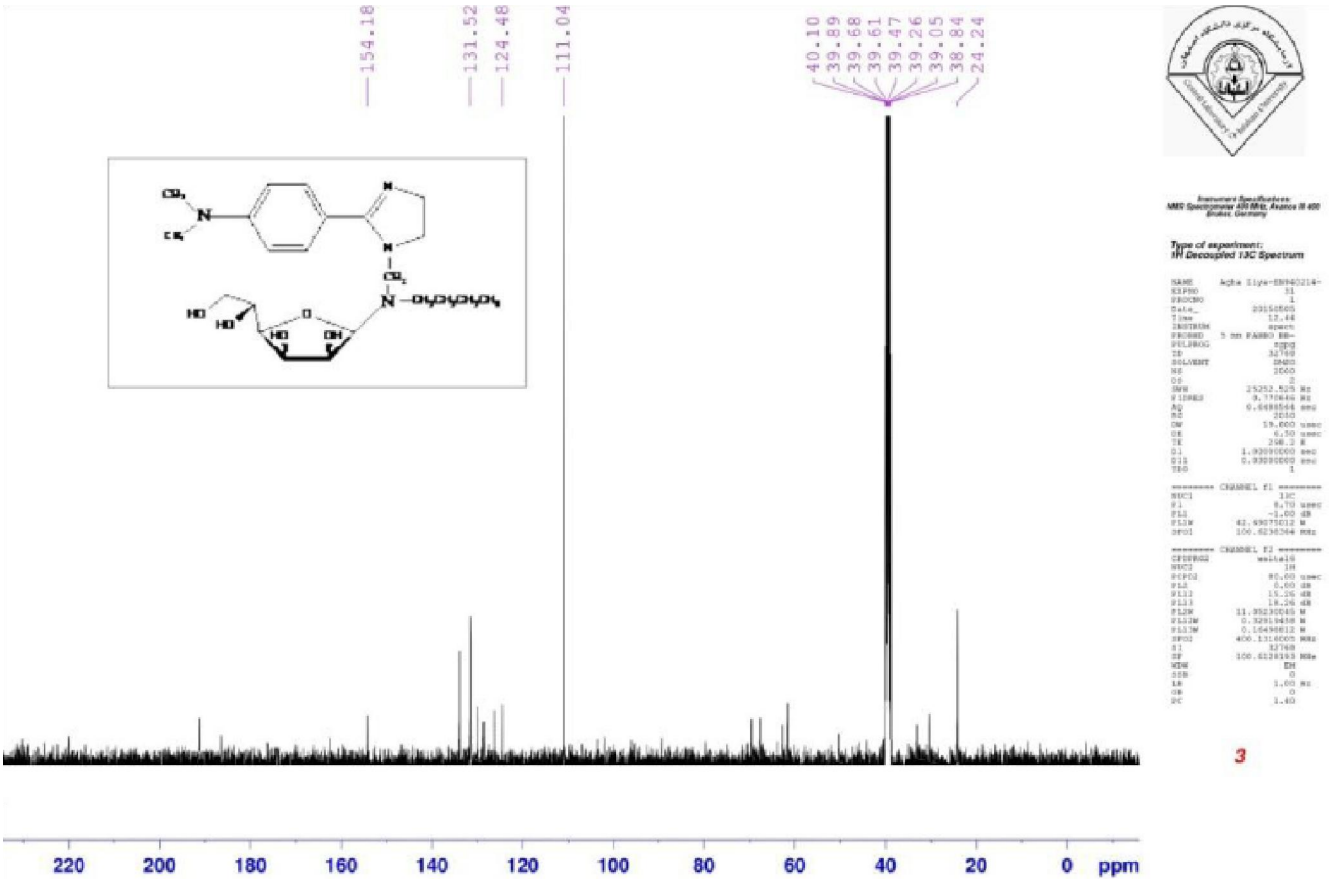


Figure 3 : [13]C-NMR Spectrum for compound[20]

TABLE 6 : inhibition zones for compounds (18-22)

control DMSO	Bacillus	staphlycoccus	E-coli	pseudomonas
18	11	11	13	9
19	10	-	13	-
20	9	-	13	-
21	11	16	14	10
22	9	-	12	-

between (27.04-31.26) belong to three methylene of butyl, a signal between (38.84-39.05) attributed to methyl ($2CH_3$-N),a signal at (40.10) belong to (N=C-N) imidazoline. A signal at (62.04) refereed to ($C_{'6}$ sugar), while a signals between (63.04-64.03) belong to (C'_5,C'_4,$C_{'3}$,C'_2 sugar carbons), signals at (111.04) assigned to (C'_1 sugar), a signal at (124.48) belong to (N-CH_2-N). The aromatic carbon appeared between signals (124.48-131.52), a signal at (154.18) refer to (N-C-N imidazoline).

Micro biological test

Compounds (18-22) showed strong activity against Bacillus subtilize and E. coli, while these compounds showed in active against staphylococcus aura accept compound (18-22) showed moderate active. And compounds (18-22) showed moderate activity against pseudomonas aeruginosa while compound (19, 20 and 22) showed in active.

The deference of biological activity indicate to deferent substituent in the compounds.

But all these compounds were inactive against four types of fungi namely (asparagines flurs, aspergillus fumqntnts. Aspergillus niger and penicillum) which indicat the specify of the action of the nucleoside analogues as anti-bacterial but not against fungi, that is accordance to the literature[29-30]

CONCLUSION

Nucleoside analogues are important which also have abroad spectrum of biological application in medical materials. Therefor new nucleoside analogues synthesis from imidazoline derivatives containing Mannich bases. All nucleoside analogues are characterized on the basis of analytical and spectra data. Screening these compound against two types of gram positive and two types of gram negative of bacteria showed good and moderate activity also inactive. While these compound showed in active against four types of fungi.

REFERENCES

[1] L.P.Jordim, D.D.zoulim, C.Dowmontent; "advances in the development of nucleotide for concur and viral disease" Review Drug Discovery", **12**, 447-464 **(2013)**.

[2] I.A.Mikhailopulo, A.Miroshnikov; "New trends in nucleoside biotechnology", Acl Not, **2**, 36-38 **(2010)**.

[3] M.K.Kukhanova; "Anti-HIV nucleoside drugs Aretosective view into the future", Mol.Biol., **46**, 768-779 **(2012)**.

[4] L.Christophe, E.Gerald; "synthesis of C-Aryl nucleoside analogues" Molecules, **20**, 4967-4997 **(2015)**.

[5] A.Luis, J.Antonio, Rafael Robles; "Convenient synthesis of nucleoside and iso nucleoside Analogues", ORGANIC Letters, **7(11)**, 2161-2164 **(2005)**.

[6] Al T.M.Muamin, A.K.kabhim; "Synthesis and characterization of some of new nucleoside analogues from substituted benzimidazole and evaluation of their biological activities", I.J.S., **56(1)**, 633-644 **(2015)**.

[7] W.Zhou, G.Gurmina, Changy J.Wong, R.Shinaz; "Synthesis, Structure – Activity relationships and drug resistance of β-D-3-unsaturated nucleosides as Anti- HIV Agents", J.Med.Chem., **47**, 3399-3408 **(2014)**.

[8] M.Maccoss, M.Robins; "Anticancer pyrimidine nucleoside and prodrugs, In the chemistry of antiumor Agents" Willman, D.E.V; Chapman and Hall : New York, 261-298 **(1990)**.

[9] C.Perigaud, G.Gosselin, J.Imbach; "Nucleosides analogues as chemotherapeutic agents" A Review Nucleosides Nucleotides, **11**, 903-945 **(1992)**.

[10] M.Soul, F.Suasan, S.Yogesh, C.Jyoti,

G.Muthupandian, G.Namakkal, V.Ramesh, F.Miguel; "Design and divergent synthesis of azo nucleosides from a chiral imino sugar ", The Journal of Organic Chemistry, **77**, 4671-4678 **(2012)**.

[11] C.Collins, M.Patricia; "Chemical synthesis of nucleoside analogues" Published by John wiely and sons onc, Hoboken New York 2nd Addition, **(2013)**.

[12] T.Al-Mouamin; "Synthesis of 2,3 dideoxy-3,3-gen-di-C-alkyl pyrano-nucleoside analogues ph.D.thesis department of chemistry, Clloge of science, University of baghdad, Iraq, **(2007)**.

[13] M.Thana, A.Suror, A.Omar, H.Yasmeen; "Synthesis of some new nucleoside analogues containing seven membered ring and studding their biological activity", **(2015)**.

[14] O.Jason, T.Kathleen, E.Craig; "Lethal mudified purine nucleoside analogues" Antimicrob Agent Chemother, **52**, 971-979 **(2008)**.

[15] K.Vastmans, M.Froeyen, L.Kerremans, Van A.Aershot, C.Hendrix, P.Marliere; "Enzymatic incorporation in DNA of 1,5 anhydrohexitol nucleosides" Nucleic Acids Res., **29**, 3154-3164 **(2001)**.

[16] R.K.Robins, G.D.KiNi; "Purines and purine Nucleoside analoguse as Anti-tumer agent.in the chemistry of Antitumer agent" Wilman, D.E.V.Ed.Chapman and Hall, New York, 299-321 **(1990)**.

[17] A.Michael, W.Brenhard, R.Nikolaus; "Modern variants of the mannich reaction" Angew.Chem.Int.Ed., **(37)**, 1044-1070 **(1998)**.

[18] R.D.Crouch; "Synthesis routs towards 2-substituted 2-imidazolines, Tetrahedran", **65**, 2387-2389 **(2009)**.

[19] W.Deana, A.Sadijah, Buchari, A.BambaNg; "Synthesis of imidazoline derivative compound as corrosion inhibitor towards carbon steel in 1% NaCl "the Solution"ITB.J.SCI., **40A(1)**, 33-48 **(2008)**.

[20] A.I.Vogel; "Atext book of paractjical organic chemistry" Longman Group Limited, **(1971)**.

[21] R.L.Whistler, M.L.Wolform; "Methods in carbohydrate chemistry" Acadmicpress, Newyork, London, **(1963)**.

[22] A.Mohamed, G.Mohamed, M.Rahim; "Synthesis and specral studies of mannich bases derived from 2-subsitituted benzimidazoles" IAAST, **1**, 84-86 **(2010)**.

[23] Al T.M.Mouman; "Synthesis of 2,3 dideoxy 3,3 gem-di-C- alkyl pyrono nucleouside analogues" Ph.D thesis department of chemistry college of science university of Bagdad, Iraq, **1**, **(2007)**.

[24] G.Zemplen, A.Gerecs, Hadacsy; I, Ber, **69**, 1827 **(1936)**.

[25] Swat.Ran, D.Kawade; "Synthesis and biological activity of some novel 2-phenyl benzimidazole 1-acetamide derivatives as potential anthelmintic agents", Acta pharm., **30**, 335-361 **(2011)**.

[26] R.L.Whistler, M.L.Wolform; "Methods in carbohydrate chemistry, academic press, New york and London, (a), **2**, 237(b), 247 **(1963)**.

[27] R.M.Silverstein, G.C.Bassler; "Spectrometric identification of organic compounds, 4th Edition, Jonwiley and Sons Inc, U.S.A., **(1981)**.

[28] P.Crews, J.Rodigez, M.Jaspars; "Organic Structure Analysis", Oxford University Press, **(1998)**.

[29] A.Bharti, S.Hishpandeya; "Synthesis of imidazole derivatives" / IJRAP, **2(4)**, 1124-1129 **(2011)**.

[30] K.Byju, C.R.Biju, V.B.Arunlal, K.R.Vimal; "Synthesis and biological evolution of imidazoline", International Journal Research in pharmacy and Science, **4(3)**, 12-17 **(2014)**.