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Synthesis of New Gemcitabine Derivatives Linked Tetrazole Ring as Antibacterial Activity

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Abstract--- *A series of novel tetrazole derivatives contain nucleoside analog were synthesized by reaction between azido gemcitabine with nitrile compounds in presence ammonium chloride as catalyst. The structures of all prepared compounds were analyzed by NMR and FTIR spectroscopic methods. The antibacterial activity of tetrazole derivatives were determined by using Streptococcus Pneumonia and Escherichia Coli, Staphylococcus aureus.*

Keywords--- *Antibacterial Activity, Gemcitabine, Tetrazole, Heterocyclic*.

I. INTRODUCTION

Gemcitabine is organic compounds contains a pyrimidine fluorinated nucleoside analog, also systematic named [1-(2'Deoxy-2',2'-difluoro-D-ribofuranosyl)-4-aminopyrimidin-2-one] [1,2]. It's one of many type of chemotherapy to treat cancer diseases including ovarian cancer pancreatic cancer, breast cancer and lung cancer [3,4,5]. Tetrazole derivatives are organic heterocyclic compounds having a five membered ring containing four nitrogen and one carbon atoms [6]. Tetrazole compounds have a wide range of applications in various field one of them pharmaceutical chemistry [7,8]. Biphenyl tetrazole derivatives are used for the synthesis of sartan family drugs [9], and also used as ligands in the synthesis of imidoylazides [10,11]. Tetrazole compounds are widely used as explosives and propellants [12,13]. In crop protection they are used as plant growth regulators [14], fungicides and herbicides [15]. In addition to this they have anti-allergic [16], antibiotic [17], antiviral activities [18], antihypertensive [19] and antagonists [20]. Recently tetrazole compounds were used for binding aryl thiotetrazolyl acetanilides with HIV-1 reverse transcriptase [21]. To the best of our knowledge, compounds possessing both the gemcitabine and tetrazoles in the core structure are not reported till now. General synthesis method of novel tetrazole/nucleoside analog gemcitabine based on sulfonamide derivatives, substituted phenyl and biphenyl is shown in scheme 1. Conceptually, the work will lead to compounds with interesting properties for pharmaceutics due to an increase of water solubility.

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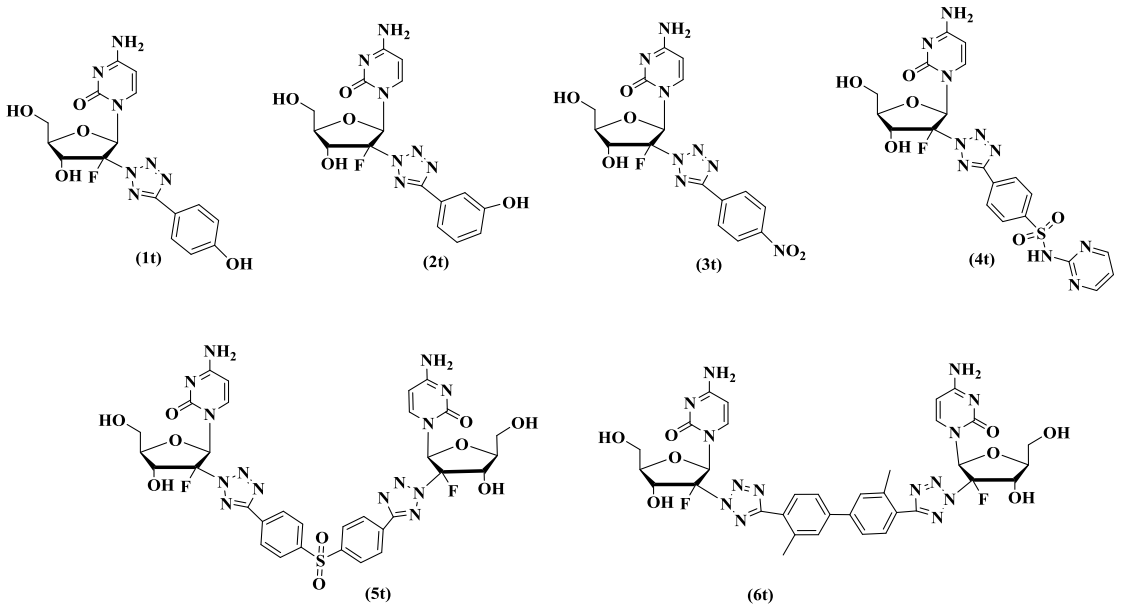

Scheme 1: Structures of Tetrazole Derivatives

II. EXPERIMENTAL

Material and Methods

All reagents, solvents and starting materials were obtained from several supply chemicals companies like Sigma Aldrich chemicals, Thomas baker, Merck, Fluke, and commercial source. TLC plates were used for mentioned the progress of all reactions, supplied on a silica gel SG-40 by Merck company. Fourier transformation infrared was used to record FTIR spectra on Bruker ALPHA, University of Kufa, Faculty of Science. NMR spectrum were confirmed on Bruker apparatus, 300MHz for ^{1}HNMR and 75MHz for ^{13}CNMR, Mashhed University. Elemental analysis was analyzed using a Perkin- Elmer 204E Instrument.

General Procedure

Synthesis 2-Azido Gemcitabine(g)

The procedure method described for the preparation of 2-azido gemcitabine were used gemcitabine 0.001mol, sodium azide 0.001mol, in in 30 mL of THF.

2-Azido gemcitabine (1): It was prepared as a white solid powder , Chemical formula: $C_9H_{11}FN_6O_4$; reaction yield (67%); (m p: 240-242ºC); FTIR, 3441 cm^{-1}, 3408 cm^{-1} assigned to OH stretching, 2965 cm^{-1}, 2874 cm^{-1} assigned to CH stretching**,** 2112 cm^{-1} assigned to azide group stretching, 1678 cm^{-1} assigned to carbonyl group stretching, 1585 cm^{-1} assigned to C=N stretching**.**

General Procedure for Synthesis Nitrile Derivatives (n1-n6)

To a mixture of water (10 mL) and concentrated HCl (37%, 3 mL) cooled to 0 °C, primary aromatic amine (0.01 mol of *P*-hydroxy aniline, *m*-hydroxy aniline and *P*-nitro aniline, sulfadiazine and 0.005 mol of dapsone and *O*-toludine) was added slowly in portions over 20 min while keeping a temperature between -2 and 0 °C. To the

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solution which formed, equivalent number of moles of $NaNO_2$ solution was dissolved in water 7 Ml, added at same temperature. The resulting colored solution which formed and then stirred at 0 °C for 30 min, before it was added dropwise over 15 min to a solution of NaCN (equivalent number of moles) was dissolved in water 10 mL then stirred at 0 °C for 50 min. The separated nitrile derivatives product is filtered, washed with water many times and crystallized with ethanol.

4-hydroxybenzonitrile (n1): It was prepared as a light yellow powder, Chemical formula: C_7H_5ON,reaction yield(86%);(m p:112-114 ºC); FTIR, 3387 cm^{-1} due to OH stretching, 3078 cm^{-1} assigned to C-H aromatic stretching , 2241 cm^{-1} due to C≡N nitrile group stretching,1587cm^{-1} assigned to benzene ring stretching.

3-hydroxybenzonitrile (n2): It was prepared as a white to yellow powder, Chemical formula: C_7H_5ON, reaction yield (89%);(m p: 91-93 ºC); FTIR, 3412 cm^{-1} due to OH stretching 3085 cm^{-1} assigned to C-H aromatic stretching, 2219 cm^{-1} assigned to C≡N nitrile group stretching,1598 cm^{-1} assigned to benzene ring stretching.

4-nitrobenzonitrile (n3): It was prepared as a white to yellow powder, Chemical formula: $C_7H_4O_2N_2$, reaction yield (82%);(m p: 91-93 ºC); FTIR, 3065 cm^{-1} assigned to C-H aromatic stretching, 2212 cm^{-1} assigned to C≡N nitrile group stretching,1592 cm^{-1} assigned to benzene ring stretching.

4-cyano-N-(pyrimidin-2-yl)benzenesulfonamide(n4): It was prepared as a light orange solid powder, Chemical Formula: $C_{11}H_8N_4O_2S$, reaction yield: 86%; m p: 266-268 ºC; FTIR, 3081 cm^{-1} due to aromatic CH, 2204 cm^{-1} due to nitrile group, 1584 cm^{-1} due to C=C, and 1341,1169 cm^{-1} return to sy. and asy. of SO_2 group, ^{1}H NMR (300 MHz, DMSO-*d6*)δ 12.12 (s, N-H Sulfonamide, 1H), 8.49(d, *J* = 3.5 Hz, N=C-H pyrimidine ring, 2H), 7.96-7.78 (m, Ar-H, 4H),7.21 (t, *J* = 3.4 Hz, C5-H pyrimidine ring, 1H).

4,4'-sulfonyldibenzonitrile(n5): It was prepared as orange solid powder, Chemical Formula: $C_{14}H_8N_2O_2S$, reaction yield: 87%; m p:139-141ºC; FTIR , 3093 cm^{-1} due to aromatic CH, 2189 cm^{-1} due to nitrile group, 1589 cm^{-1} due to C=C, and 1341,1163 cm^{-1} return to sy. and asy. of SO_2 group, ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.11-7.99 (m, Ar-H, 4H), 7.85-7.78 (m, Ar-H, 4H).

3,3'-dimethyl-[1,1'-biphenyl]-4,4'-dicarbonitrile(n6): It was prepared as a light yellow solid e solid powder, Chemical Formula: $C_{16}H_{12}N_2$, reaction yield: 84%; m p: 193-195 ºC; FTIR , 3087 cm^{-1} due to aromatic CH, 2217 cm^{-1} due to nitrile group, 1602 cm^{-1} due to C=C, ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.49 (s, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 2.61 (s, 6H).

Synthesis Tetrazole Derivatives (1t-6t)

A mixture 0.003 mol of nitrile derivatives (n1-n5) and equivalent moles of azides and ammonium chloride were dissolved in 25 mL of DMF and refluxed at 90 ^{o}C for completed the reaction. The reactions were followed by TLC. The end products were extracted with water petroleum ether. The organic layer was washed many times salt water and then with water only, and dried it over anhydrous $MgSO_4$.The solvent was evaporated to yield end compounds(**1t-6t**).

3-(5-(4-nitro)-2H-tetrazol-2-yl)gemcitabine(1t): It was synthesized as semi solid product, Chemical formula: $C_{16}H_{15}FN_8O_6$, reaction yield (81%); FTIR, 3427 cm^{-1}, 3383 cm^{-1} assigned to OH stretching, 3056 cm^{-1} assigned to

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aromatic C-H stretching, 2974 cm^{-1}, 2864 cm^{-1} assigned to C-H stretching, 1604 cm^{-1}, 1574 cm^{-1} assigned to C=N and C =C stretching. ^{1}H NMR (300 MHz, DMSO-d*6*) δ 8.32 – 8.21 (m, Ar-H), 7.55 ppm (d, *J* = 7.9 Hz, 1H, H-6,HC=N proton of pyrimidine ring), 6.92 ppm (s, 1H-1),6.06 ppm (m, 1H-3), 5.81 ppm (d, *J* = 7.7 Hz, 1H-5,HC=N proton of pyrimidine ring), 4.41 ppm (dt, *J* = 4.7, 5.7 Hz, 1H-4), 3.77-3.68 ppm (m, 1H-5a,1H-5b).^{13}C NMR (75 MHz, DMSO-d*6*) δ 164.24 ppm, 163.18 ppm, 157.18 ppm,148.88 ppm, 143.32 ppm, 130.74 ppm, 127.59 ppm, 124.19 ppm, 114.82 ppm, 94.68 ppm, 92.79 ppm, 82.78 ppm, 71.85 ppm, 62.82 ppm.

3-(5-(4-hydroxyphenyl)-2H-tetrazol-2-yl)gemcitabine(2t): It was synthesized as semi solid product, Chemical formula: $C_{16}H_{16}FN_7O_5$, reaction yield (82%); FTIR, 3435 cm^{-1}, 3415 cm^{-1} assigned to OH stretching, 3065 cm^{-1} assigned to aromatic C-H stretching, 2985 cm^{-1}, 2877 cm^{-1} assigned to C-H stretching, 1598 cm^{-1}, 1565 cm^{-1} assigned to C=N and C =C stretching. ^{1}H NMR (300 MHz, DMSO-d*6*) δ 7.89 (s, 1H, Ar-OH),7.56 ppm (d, *J* = 7.7 Hz, 1H,1H-6,HC=N proton of pyrimidine ring), 7.51–6.94 (m, Ar-H), 6.91 ppm (s, 1H-1), 5.97 ppm (m, 1H-3), 5.78 ppm (d, *J* = 7.6 Hz,1H-5, HC=N proton of pyrimidine ring), 4.38 ppm (dt, *J* = 4.6, 5.8 Hz, 1H-4), 3.77-3.68 ppm (m, 1H-5a,1H-5b).^{13}C NMR (75 MHz, DMSO-d*6*) δ 165.17 ppm,158.60 ppm,156.98 ppm, 154.38 ppm, 142.87 ppm, 129.11 ppm, 122.87 ppm, 120.41 ppm, 113.89 ppm, 93.99 ppm, 91.98 ppm, 83.75 ppm, 71.68 ppm, 62.08ppm.

3-(5-(3-hydroxyphenyl)-2H-tetrazol-2-yl)gemcitabine(3t): It was synthesized as semi solid product, Chemical formula: $C_{16}H_{16}FN_7O_5$, reaction yield (85%); FTIR, 3450 cm^{-1}, 3425 cm^{-1} assigned to OH stretching, 3047 cm^{-1} assigned to aromatic C-H stretching, 2987 cm^{-1}, 2847 cm^{-1} assigned to C-H stretching, 1589 cm^{-1}, 1559 cm^{-1} assigned to C=N and C =C stretching. ^{1}H NMR (300 MHz, DMSO-d*6*) δ 7.71–6.73 (m, Ar-H), 7.57 ppm (d, *J* = 7.7 Hz, 1H,1H-6,HC=N proton of pyrimidine ring), 7.12 (s, 1H, Ar-OH), 6.93 ppm (s, 1H-1), 6.04 ppm (m, 1H-3), 5.79 ppm (d, *J* = 7.6 Hz,1H-5, HC=N proton of pyrimidine ring), 4.35 ppm (dt, *J* = 4.6, 5.8 Hz, 1H-4), 3.75-3.64 ppm (m, 1H-5a,1H-5b).^{13}C NMR (75 MHz, DMSO-d*6*) δ 164.69 ppm,157.96 ppm,155.12 ppm, 154.15 ppm, 143.45 ppm, 130.19 ppm, 127.92 ppm, 121.08 ppm, 120.77 ppm, 118.39 ppm,114.25 ppm, 94.58 ppm, 92.78 ppm, 82.88 ppm, 70.84 ppm, 61.26ppm.

3-(5-*N*-(pyrimidin-2-yl)benzenesulfonamide-2H-tetrazol-2-yl)gemcitabine (4t): It was synthesized as a solid product, Chemical formula: $C_{20}H_{19}F_2N_{10}O_6$**S**, reaction yield (86%); (m p: 199-201 ºC), FTIR, 3428 cm^{-1}, 3408confirmed to OH Str., 3071 cm^{-1} confirmed to aromatic CH stretching, 2969 cm^{-1}, 2848 cm^{-1} assigned to C-H stretching, 1590 cm^{-1} confirmed to C=N stretching, 1581 cm^{-1} confirmed to C=C stretching 1348 cm^{-1} confirmed to sy. stretching of SO_2 and 1156 cm^{-1} confirmed to asy. stretching of SO_2. ^{1}H NMR (300 MHz, DMSO-d*6*) δ12.12 ppm (s, 1H, NH sulfonamide), 8.55–7.23 (m, Ar-H), 6.91 ppm (s, 1H-1),6.02 ppm (m, 1H-3), 5.79 ppm (d, *J* = 7.6 Hz,1H-5, HC=N proton of pyrimidine ring), 4.36 ppm (dt, *J* = 5.4, 4.7 Hz, 1H-4), 3.79-3.68 ppm (m, 1H-5a,1H-5b). ^{13}C NMR (75 MHz, DMSO-d*6*) δ 164.87 ppm, 157.81 ppm,156.87 ppm, 156.13 ppm, 155.35 ppm, 142.14 ppm, 136.55 ppm, 129.88 ppm, 128.15 ppm,125.99 ppm, 118.24 ppm, 115.78 ppm, 94.31 ppm, 92.84 ppm, 82.78 ppm, 71.89 ppm, 61.97 ppm.

4,4'-((sulfonylbis(4,1-phenylene))bis(2H-tetrazole-5,2-diyl))bisgemcitabine (5t): It was synthesized as a solid product, Chemical formula: $C_{32}H_{30}F_2N_{14}O_{10}$**S**, reaction yield (78%); (m p: 221-223 ºC), FTIR, 3432 cm^{-1}, 3389 cm^{-1}

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confirmed to OH Str., 3024 cm^{-1} confirmed to aromatic CH stretching, 2969 cm^{-1}, 2848 cm^{-1} assigned to C-H stretching,1608 cm^{-1} confirmed to C=N stretching, 1575 cm^{-1} confirmed to C=C stretching 1347 cm^{-1} confirmed to sy. stretching of SO_2 and 1168 cm^{-1} confirmed to asy. stretching of SO_2. ^{1}H NMR (300 MHz, DMSO-d*6*) δ 7.96–7.67 (m, Ar-H), 7.54 ppm (d, *J* = 7.7 Hz, 1H,1H-6,HC=N proton of pyrimidine ring), 6.91 ppm (s, 1H-1), 6.02 ppm (m, 1H-3), 5.77 ppm (d, *J* = 7.6 Hz,1H-5, HC=N proton of pyrimidine ring), 4.38 ppm (dt, *J* = 4.6, 5.8 Hz, 1H-4), 3.73-3.62 ppm (m, 1H-5a,1H-5b).^{13}C NMR (75 MHz, DMSO-d*6*) δ 164.47 ppm,157.31 PPM, 154.93 ppm, 143.14 ppm, 139.89 ppm, 129.87 ppm, 128.24 ppm,126.81 ppm, 115.16 ppm, 94.49 ppm, 91.93 ppm, 82.77 ppm, 71.82 ppm, 61.67ppm.

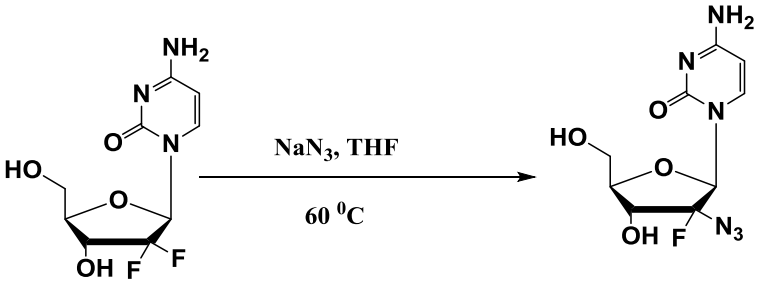
4,4'-((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(2H-tetrazole-2,5-diyl))bisgemcitabine (6t): It was synthesized as a solid product, Chemical formula: $C_{34}H_{34}F_2N_{14}O_8$, reaction yield (87%); (m p: 235-237 ºC); FTIR, 3447 cm^{-1}, 3421 cm^{-1} assigned to OH stretching, 3054 cm^{-1} assigned to aromatic C-H stretching, 2987 cm^{-1}, 2875 cm^{-1} assigned to C-H stretching, 1599 cm^{-1}, 1568 cm^{-1} assigned to C=N and C =C stretching. ^{1}H NMR (300 MHz, DMSO-d*6*) δ 7.69–7.49 (m, Ar-H), 7.56 ppm (d, *J* = 7.7 Hz, 1H,1H-6,HC=N proton of pyrimidine ring), 6.91 ppm (s, 1H-1), 5.99 ppm (m, 1H-3), 5.76 ppm (d, *J* = 7.6 Hz,1H-5, HC=N proton of pyrimidine ring), 4.37 ppm (dt, *J* = 4.6, 5.8 Hz, 1H-4), 3.74-3.62 ppm (m, 1H-5a,1H-5b), 2.43 ppm (s, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d*6*) δ 165.12 ppm, 159.87 ppm,155.28 ppm, 142.18 ppm,139.58 ppm, 135.17 ppm, 129.76 ppm, 128.22 ppm,126.58 ppm, 125.63 ppm, 114.54 ppm, 94.78 ppm, 92.87 ppm, 82.80 ppm, 71.98 ppm, 62.22ppm, 21.46 ppm.

Antibacterial Activity Assay [22]

The end tetrazoles derivatives (**1t-6t)** were tested for antibacterial activity against *Escherichia coli*, *Streptococcus pneumonia*, *Staphylococcus aureus* bacteria in Muller Hinton agar method and measuring the zone of inhibition in (mm). The tetrazole compounds dissolved in 1ml of DMSO, ($1x10^{-5}$M) and then take 0.5 ml of prepared solution to fill holes. The isolation bacteria was injected in to holes with the suspension of tested compounds by used a cotton swab and streaking over the agar plates surface. four holes with (6 mm) were made in the solidified medium. Finally plates were incubated at 37 ^{o}C for 24 hours and measured inhibition zone.

III. RESULTS AND DISCUSSION

General prepare method of new tetrazole/ nucleoside analog gemcitabine based on sulfonamide derivatives, substituted phenyl and biphenyl. The synthetic rout for the synthesis of starting compound is presented in Schemes 2. At beginning gemcitabine refluxed with sodium azide were dissolved in THF as solvent.



Scheme 2: Synthesis 2-Azido Gemcitabine

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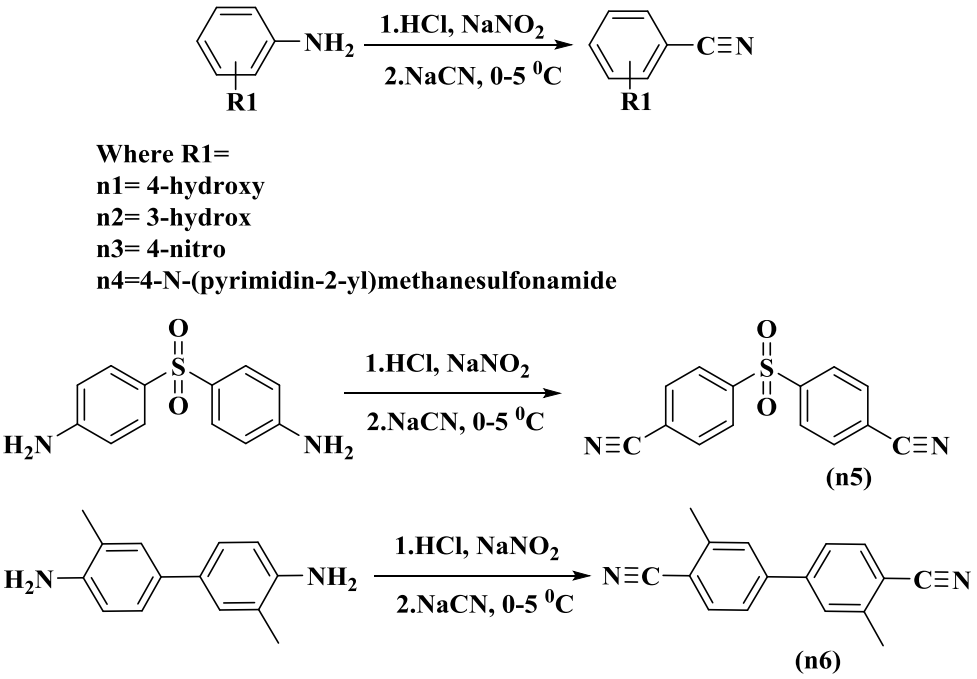
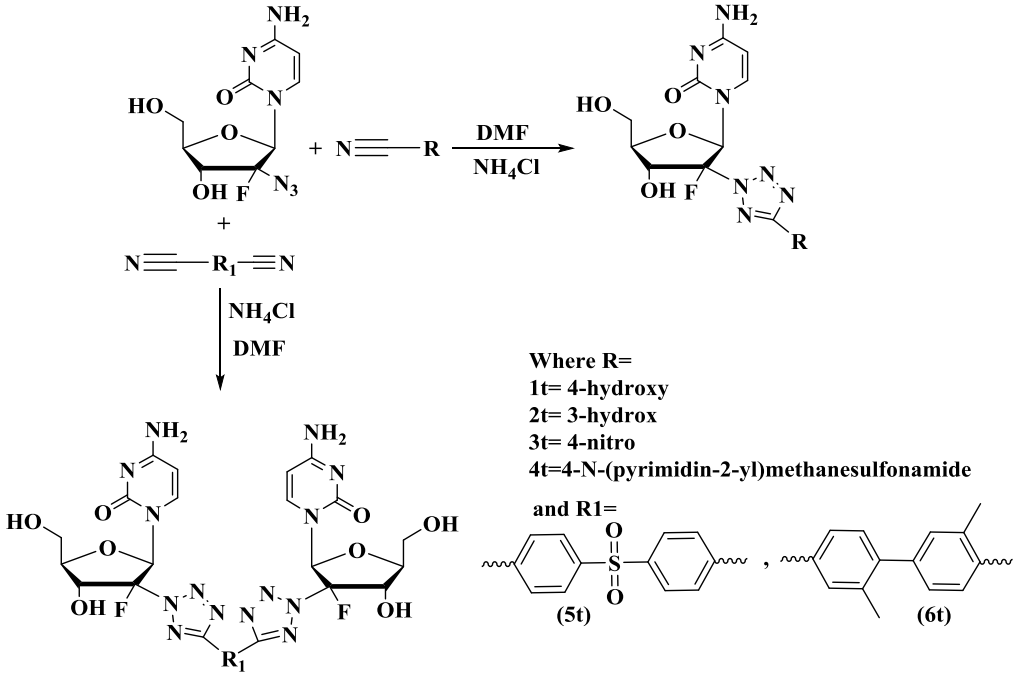
On the other hand nitrile derivatives were synthesized by nucleophilic substitution reaction of diazonium salt and sodium cyanide to produce(n1-n6) is presented in Schemes 3.



Scheme 3: Synthesis Nitrile Derivatives

The end step included preparation tetrazole derivatives by reaction nitrile compounds with 2-azido gemcitabine in presence ammonium chloride as shown in Scheme 4.



Scheme 4: Synthesis Tetrazole Derivatives

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The structures of all the prepared compounds were confirmed on the basis of their ^{1}H NMR, ^{13}C NMR and FTIR. The FTIR spectra of azide compound (1) a peak appeared in the 2112 cm^{-1} due to azide group. Whereas nitriles (n1-n5) new bands appeared in the region 2241,2184 cm^{-1} due to C≡N nitrile stretching, but the FTIR spectra of tetrazole derivatives (1t-6t) were showed disappearance a band of azide and nitrile groups which consider good evidence for synthesized these compounds. On the other hand ^{1}HNMR spectra of tetrazole derivatives (1t-6t) were gave multiple peaks in aromatic region due to phenyl protons. ^{13}C NMR spectra of the same compounds the additional peaks of tetrazole ring carbon in the region 155.35-148.88ppm

Antibacterial Activities

All prepared tetrazole compounds were evaluated for antibacterial activity against two types of bacteria are Gram-positive (*Staphylococcus aureus*), *Pseudomonas aeruginosa* and Gram negative (*Escherichia coli*). Whereas used Ampicillin drug as positive control. The results summarized in **Table**1. the results of antibacterial activity showed (4t) compound more active than other prepared compounds against *Escherichia coli* but (5t) compound have a higher activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared with other synthesized compounds.

Table 1: Antimicrobial Activity of Tetrazole Compounds

Polymers	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*
1t	**7**	**7**	**11**
2t	**8**	**11**	**11**
3t	**7**	**9**	**9**
4t	**10**	**9**	**13**
5t	**11**	**12**	**12**
6t	**9**	**9**	**11**
DMSO	**5**	**5**	**5**
Ampicillin	**9**	**7**	**16**

Inhibition zone was measured in diameter (mm):

(5 mm: no antimicrobial activity; > 5 mm: positive antimicrobial activity).

IV. CONCLUSIONS

In conclusion, the synthesis and identification of new tetrazole compounds. The prepared compounds exhibited good antibacterial activity against selected types of bacteria (*Staphylococcus aureus*), *Pseudomonas aeruginosa* and Gram negative (*Escherichia coli*).

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