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Synthesis, identification, and antibacterial activity screening of some 1*H*-tetrazol-5-amine derivatives

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Abstract

In this work, new compounds mj1-10 derived from 1*H*-tetrazol-5-amine and p-(dimethylamino) benzaldehyde moieties have been prepared through Schiff and Mannich reactions, which are well known for their medical importance. The chemical structures were confirmed spectrophotometrically using IR, ^{1}H NMR, and ^{13}C NMR spectra. The antibacterial activity of the newly synthesized compounds against *Streptococcus mutans* and *Staphylococcus epidermidis* was tested at different concentrations. It was found that the Mannich base 5mj achieved the highest inhibition efficacy compared to Tetracycline and Amikacin at 100 mg/ml. Accordingly, these candidates may serve as new scaffold to develop promising antibacterial agents in the future.

Introduction:

The tetrazole ring has an eclectic range of uses due to its medical and pharmaceutical importance, where many effective medicinal compounds possess the tetrazole moiety [1-4]. It has antiviral activity [5], anticancer [6], antibacterial [7,8], antifungal [9], antioxidant [10], anti-microbial [11], and anti-inflammatory [12]. On the other hand, modern medicinal chemistry research focusing on the tetrazole ring is still progressing, resulting in the emergence of new tetrazoles with broad biological activities and promising significance [13-16].

Schiff bases are nitrogenous compounds formed by the reaction of aldehydes or ketones with primary amines, in which the carbonyl group is condensed with amine to produce an azomethine group (CH = N-R). The Schiff base is usually prepared from a simple condensation reaction of an aldehyde or a ketone with an amine in an acidic medium [16,17], and is widely used for industrial purposes and biological activities, as it has shown efficacy as an antibacterial, and an antimicrobial agent [18-20], anti-inflammatory [21], anticancer [22,23], antidiabetic [24], and antioxidant agents [25].

Oxazepines are heterocyclic compounds that contain oxygen and a nitrogen atom in the heptagon ring. They were prepared from the reaction of Schiff bases with an anhydride acid [26]. Oxazepines are of great interest because they possess broad biological and pharmacological activities such as antioxidant [27,28], antifungal [29], antibacterial [30], antidepressant [31], anticonvulsant, and psychotropic activities [32].

Mannich base preparation is an example of a three-component reaction in which an amine is condensed with an aldehyde to yield an imine tracked via the addition of an acidic hydrogen-containing compound [33]. Mannich bases are of varied importance in therapeutic arenas [34,35], as they are used as antituberculosis [36], anticonvulsants [37], and antimicrobials [38]. Mannich base derived from urea and thiourea has antimicrobial activity [39], antifungal activity [40], and toxicity in contradiction of cancer cells [41,42].

In light of what was presented, the aim is to prepare Schiff bases that contain a tetrazole ring and then use them in the ring closure to prepare the oxazepines, as well as to prepare Mannich bases for urea and thiourea with some substituents for benzaldehyde.

Materials and Methods

Raw chemicals, agents and organic solvents provided by international companies were used without the need for any purification. Infrared spectra were measured using a device (FTIR-8400S) manufactured by Shimadzu Japan using the potassium bromide KBr method. ^{1}H NMR and ^{13}C NMR spectra were measured with an AVIII-HD800 BioSpin 400 MHZ in the Islamic Republic of Iran with DMSO-d6 solvent. The microbiological media was sterilized using an autoclave device from a Spanish company, while the dish was developed in an incubator device, and tests were carried out in laboratories (Microbiology Division - Quality Control Department - General Company for the Manufacture of Pharmaceuticals and Medical Supplies - Samarra).

The method for preparing Schiff bases:

(E)-4-(((*1H*-tetrazol-5-yl) imino) methyl)-N, N-dimethylaniline mj1:

Dissolve (0.04mol, 3.4 g) of 1H-tetrazol-5-amine with (0.04 mol, 5.96g) p-(Dimethylamino) benzaldehyde in 50 ml of absolute ethanol and after mixing add two drops of glacial acetic acid, then reflux the mixture for 6 hours. Cool the mixture and leave it overnight. The precipitate was collected, washed with cold ethanol and dried, recrystallized with ethanol. Yellow powder, M.P: 177-179^{0}C, M.Wt.: 216.25, $C_{10}H_{12}N_6$,83%yeild, I.R, KBr disc, υ=cm^{-1}, 3394 (NH tetrazole), 1662(C=N tetrazole),1600(C=N azomethine), 1H NMR (400 MHz, DMSO-d_6), δ 9.02 (s, He, C<u>H</u>=N azomethine), 7.85-7.66 (dd, 2Hd, phenyl), 6.80-6.75 (dd, 2Hc, phenyl), 6.49 (s, 1Hb, NH tetrazole),3.02 (s,6Ha, N(C<u>H</u>$_3$)$_2$), ^{13}C NMR (100 MHz, DMSO-d_6), m1: δ 168.16 (<u>C</u>=N, tetrazole), 162.09(<u>C</u>H=N, azomethine), (154.29 -111.49) phenyl, 56.52 N(<u>C</u>H$_3$)$_2$.

General method for Preparation Oxazepine compounds (mj2-4):

Dissolve (0.001 mol,0.21 g) of Schiff base **mj1** in 20 ml of dry dioxane with (0.001 mol) the anhydrides of acids (succinic, malic, and phthalic), after that the mixture was refluxed for (9-10) hours at a temperature of 70 ^{0}C, the mixture was cooled in an ice bath, and the precipitate was filtered and dried.

2-(4-(Dimethylamino) phenyl)-3-(1*H*-tetrazol-5-yl)-1,3-oxazepane-4,7-dione mj2:

Yellow powder, M.P: 139 – 140 ^{0}C, M.Wt.: 316.32g.mol^{-1}, $C_{14}H_{16}N_6O_3$, 75%yield, I.R, KBr disc, υ=cm^{-1}, 3390 (NH tetrazole), 1730 (C=O lactone), 1644 (C=O lactam), 1589 C=N tetrazole),1242,1211(C-O), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, H, N-C<u>H</u>-O, Oxazepane), 7.39-7.37 (dd, 2H, phenyl), 6.72-6.71 (dd, 2H, phenyl), 6.29 (s, 1H, NH tetrazole),3.00 (s, N(C<u>H</u>$_3$)$_2$), 2.84-2.81 (t,2H,CO-C<u>H</u>2-O ,Oxazepane), 2.73-2.70 (t,2H,CO-C<u>H</u>2-N ,Oxazepane),^{13}C NMR (100 MHz, DMSO-*d6*): δ 171.22 (O-<u>C</u>=O, Oxazepane), 168.73 (N-<u>C</u>=O, Oxazepane), 161.07 (<u>C</u>=N tetrazole), (151.62-114.03) phenyl ring, 80.03 (N-<u>C</u>H-O, Oxazepane), 40.27 (N(CH$_3$)$_2$), 33.30 (CO-<u>C</u>H$_2$-O ,Oxazepane), 30.30 (CO-<u>C</u>H$_2$-N ,Oxazepane) .

2-(4-(Dimethylamino) phenyl)-3-(1*H*-tetrazol-5-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione mj3: Brown powder, M.P: 153-155^{0}C, M.Wt.: 314.31g.mol^{-1}, $C_{14}H_{14}N_6O_3$, 68%yield, I.R, KBr disc, υ=cm^{-1}, 3274 (NH tetrazole), 1720 (C=O lactone), 1660 (C=O lactam), 1550 C=N tetrazole), 1352, 1232(C-O).

3-(4-(Dimethylamino) phenyl)-4-(1*H*-tetrazol-5-yl)-3,4dihydrobenzo[e][1,3]oxazepine-1,5-dione mj4:

Yellow powder, M.P: 228- 230^{0}C, M.Wt.: 364.37g.mol^{-1}, $C_{18}H_{16}N_6O$, 68%yield, I.R, KBr disc, υ=cm^{-1}, 3274 (NH tetrazole), 1703 (C=O lactone), 1674 (C=O lactam), 1587 C=N tetrazole),1282,1070(C-O), ^{1}H NMR (400 MHz, DMSO-d_6), m1: δ 8.18 (s, 1Hi, N-C<u>H</u>-O, Oxazepine), 7.78-7.55 (m, 6Hd-h,fused phenyl, phenyl), 6.78-6.75 (dd, 2Hc, phenyl), 6.47 (s, 1Hb, NH tetrazole),3.89(s,6H (N(C<u>H</u>$_3$)$_2$), ^{13}C NMR (100 MHz, DMSO-d_6): 169.19(-O-<u>C</u>=O , Oxazepine), 164.29(-N-<u>C</u>=O, Oxazepine), 160.66 (<u>C</u>=N tetrazole), 150.66-115.27 (fused phenyl, phenyl), 79.73 (N-<u>C</u>H-O, Oxazepine), 53.41 (N(<u>C</u>H$_3$)$_2$).

General method for preparing Mannich bases mj5-10:

Urea or thiourea (0.001 mol) is mixed with various aldehydes (0.001 mol) in absolute ethanol (25 ml) and stirred in an ice bath for one hour. Then add (0.001 mol, 0.21 g) of mj1 dissolved in (10 ml) of absolute ethanol and add to the mixture while stirring. Heat the mixture for (5-6) hours. Leave to cool overnight. The precipitate is collected, washed with a cold 1:1 solution (water/ethanol), dried, and purified by recrystallization with ethanol.

(E)-1-((2,4-Dichlorophenyl) (5-((4-(dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) methyl) urea mj5:

Yellow powder, M.P: 140-143^{0}C, M.Wt.: 433.30 g.mol^{-1}, $C_{18}H_{18}Cl_2N_8O$, 85%yield, I.R, KBr disc, υ=cm^{-1}, 3436, 3394,3344 (NH$_2$, NH), 1660 (C=O), 1596 (C=N tetrazole), ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1Hj, CH=N azomethine), 7.78-7.76 (dd, 2Hi, phenyl), 7.72(s, 1Hh, N-C<u>H</u>-NH), 7.51 (s, 1Hg, phenyl), 7.36-7.35 (d, 2Hf, phenyl), 7.31-6.29 (d, He, phenyl), 6.72-6.71 (d, 2Hd, phenyl), 6.14 (s, 1Hc, CON<u>H</u>), 5.85 (s, 2Hb, CON<u>H</u>$_2$), 3.01 (s,6Ha, N(C<u>H</u>$_3$)$_2$).

(E)-1-((5-((4-(Dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) (4 (dimethylamino) phenyl) methyl) urea mj6:

Yellow powder, M.P: 112-115^{0}C, M.Wt.: 407.48g.mol^{-1}, $C_{20}H_{25}N_9O$, 82%yield, I.R, KBr disc, υ=cm^{-1}, 3446, 3348,3179 (NH$_2$, NH), 1666 (C=O), 1593 (C=N tetrazole), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s, 1Hg, CH=N azomethine), 7.68-7.66 (d, 4Hf, phenyl),7.13(s, 1He, N-C<u>H</u>-NH), 6.76-6.74 (d, 4Hd, phenyl), 6.49 (s, Hc, CON<u>H</u>), 5.53 (s, 2Hb, CONH$_2$), 3.01 (s,12Ha, N(CH$_3$)$_2$).

(E)-1-((4-Chlorophenyl) (5-((4-(dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) methyl) urea mj7:

Yellow powder, M.P: 98-100^{0}C, M.Wt.: 398.86g.mol^{-1}, $C_{18}H_{19}ClN_8O$, 73%yield, I.R, KBr disc, υ=cm^{-1}, 3404,3274,3210 (NH_2, NH), 1676 (C=O), 1616 (C=N tetrazole).

(E)-1-((2,4-Dichlorophenyl) (5-((4-(dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) methyl) thiourea mj8:

Yellow powder, M.P: 90-92^{0}C, M.Wt.: 449.36.mol^{-1}, $C_{18}H_{18}Cl_2N_8S$, 79%yield, I.R, KBr disc, υ=cm^{-1}, 3369,3272,3174 (NH_2, NH), 1620 (C=N tetrazole), 1163(C=S), ^{1}H NMR (400 MHz, DMSO-d_6): δ ,10.24 (s,1Hj, CSN<u>H</u>),9.64 (s, 1Hl, CH=N azomethine), 9.01 (s, 2Ha, CSN<u>H</u>$_2$), 7.67-7.65 (d, 2Hg,phenyl) 7.58-7.41 (d, , 2He,f phenyl),7.09 (s, 1Hd,phenyl), 6.76-6.73(d, 2Hc, phenyl), 6.46 (s, 2Hb, N-C<u>H</u>-NH), 3.01 (s,6Ha,N(CH_3)$_2$).

E)-1-((5-((4-(Dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) (4-(dimethylamino) phenyl) methyl) thiourea mj9:

Yellow powder, M.P: 104-106^{0}C, M.Wt.: 423.54g.mol^{-1}, $C_{20}H_{25}N_9S$, 65%yield, I.R, KBr disc, υ=cm^{-1}, 3377,3282,3174 (NH_2, NH), 1647 (C=N tetrazole), 1163(C=S).

(E)-1-((4-Chlorophenyl) (5-((4-(dimethylamino) benzylidene) amino)-1*H*-tetrazol-1-yl) methyl) thiourea mj10:

Yellow powder, M.P: 117-119^{0}C, M.Wt.: 414.92g.mol^{-1}, $C_{18}H_{19}ClN_8S$, 70%yield, I.R, KBr disc, υ=cm^{-1}, 3377, 3280, 3203 (NH_2, NH), 1635 (C=N tetrazole),1166 (C=S).

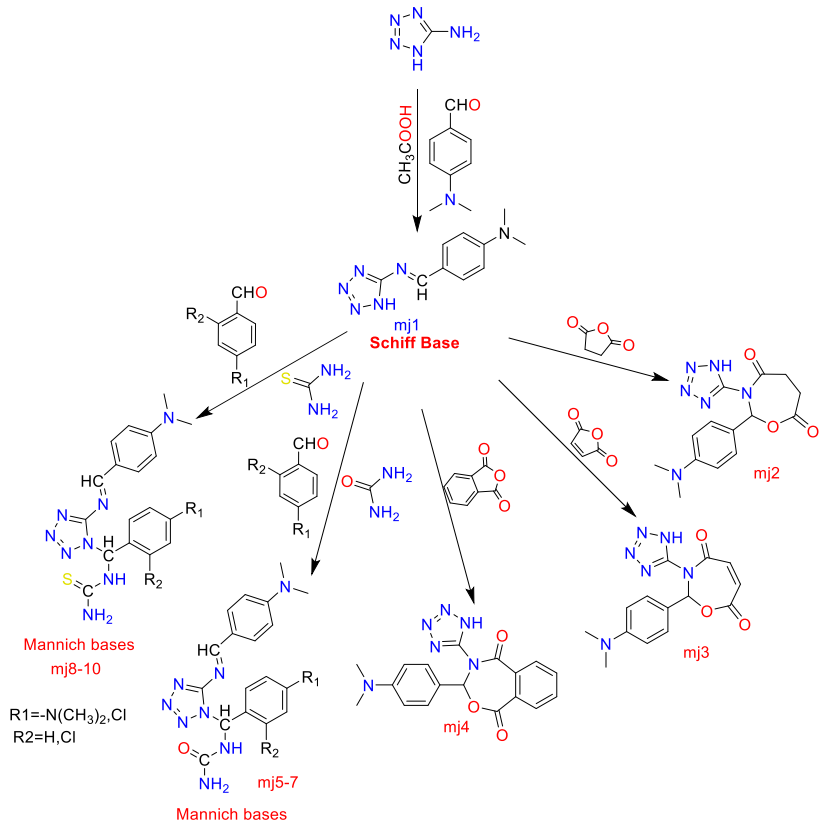
Testing the bacterial activity of the prepared compounds

The effect of some compounds prepared in this research has been studied on the growth of two kinds of bacteria, which are Gram-positive, *Staphylococcus epidermidis*, and *Streptococcus mutans*. The sensitivity of the compounds was studied using the method of diffusion in the agricultural medium, as the agricultural medium was prepared by Acker-Muller-Hinton Agar and sterilized by the autoclave. The dishes were inoculated with bacterial isolates by the diffusion method, and placed in the incubator for two hours, and the dishes were dug at a rate of five holes in the circumference of each plate and, were added to (5,10,25,50,100) mg/ml each hole of the solutions of the materials prepared using a solvent (DMSO) and then incubated at a temperature of 37 ^{0}C [43].

Results and Discussion

Chemistry

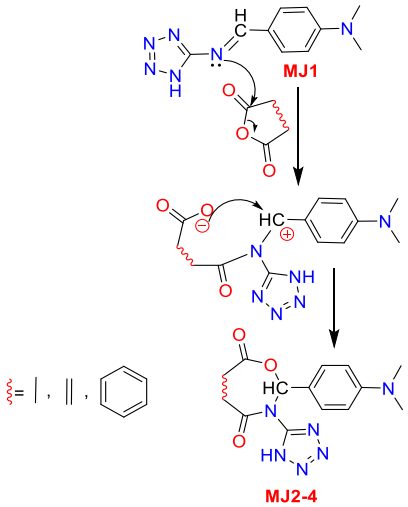
The target tetrazole derivatives were created following Scheme 1. The precursor for the synthesis of Oxazepanes, Oxazepines, and Mannich bases isthe Schiff base **mj1** compound which was created by mixing equal molar quantities of 1H-tetrazol-5-amine with p-(Dimethylamino)benzaldehyde in absolute ethanol with glacial acetic acid, then refluxing.



Scheme 1: Course of the preparation of the targeted compounds mj1-10

Oxazepines/anes derivatives

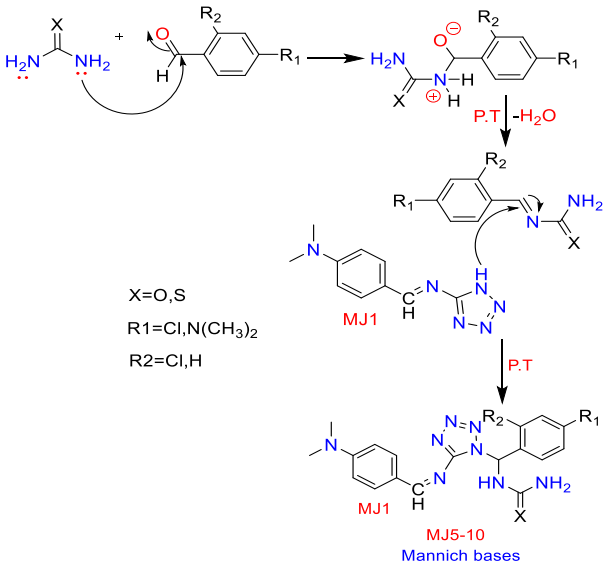
The reaction occurs through the mechanism of cycle addition, through nucleophilic attack of the electron pair of the nitrogen atom in Schiff base on the carbonyl group of anhydrides to give the intermediate dipole compound, which in turn converts to the Oxazepane ring, as shown in **Scheme 2**:



Scheme 2: Mechanism of preparation of Oxazepines mj2-4

Mannich bases:

The Mannich reaction tracked the one-pot process by condensation of three composites. The mechanism befalls over the nucleophilic addition at the carbonyl of aldehydes thru the pair urea or thiourea. Then the elimination of water particles to get an azomethine bond. followed by nucleophilic addition occurs via nitrogen pair in tetrazole ring on imine group and at that time proton transfer occurs to yield the Mannich base **mj5-10** as elucidated in the following scheme 3



Scheme 3: Mechanism of preparation of Mannich bases mj5-10

Spectral Identifications for mj1-10 compounds

All compounds were identified using the infrared spectrum, and the appearance of the expected absorption bands confirmed the validity of the obtained results, as the mj1 base showed the disappearance of stretching bands of the amine group of the tetrazole ring, and the appearance of a band of medium intensity due to stretching of azomethine at 1564 cm^{-1}, in addition to the presence of stretching band of NH for the tetrazole ring of compounds mj1-4 at (3274-3394) cm^{-1}, with the presence of carbonyl lactone bands and lactams of the rings of Oxazepane, Oxazepines at (1776-1641) cm^{-1}, while the spectra of the Mannich bases of the compounds mj5-1 showed strong stretching bands of NH_2 and NH groups for the urea or thiourea fraction at (3272-3409) cm^{-1}, and Figures 1-4 indicate the spectra of the compounds mj1, mj4, mj6, mj9, and mj10, respectively.

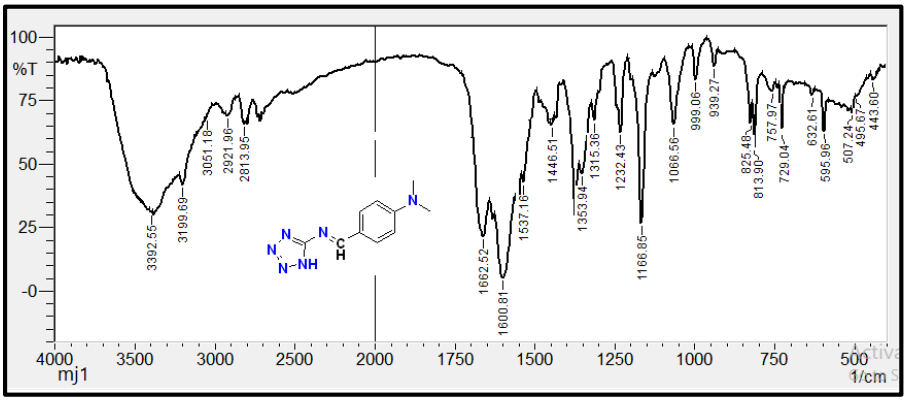


Fig.1: I.R. spectra for **mj1**

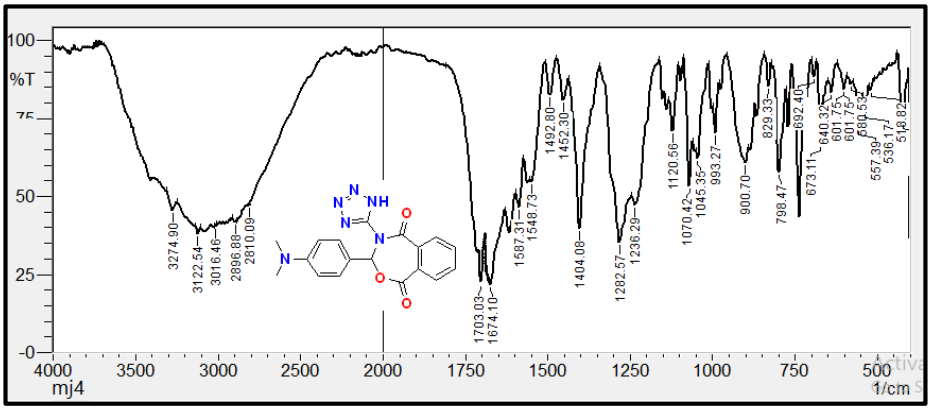


Fig.2: I.R. spectra for **mj4**

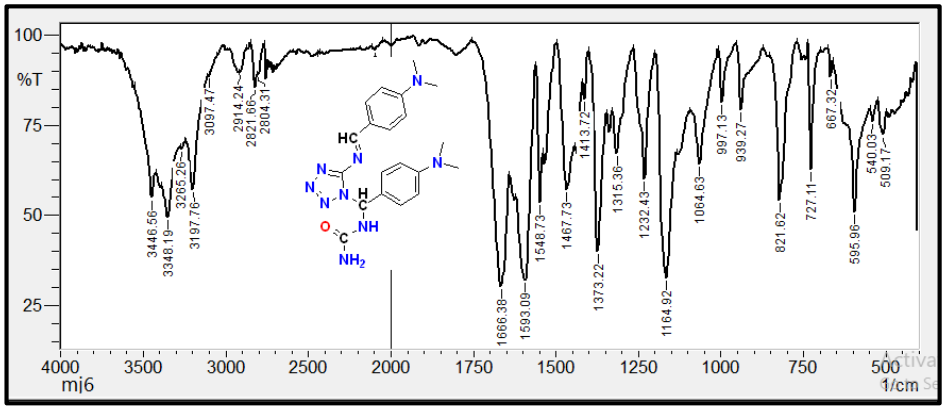


Fig.3: I.R. spectra for **mj6**

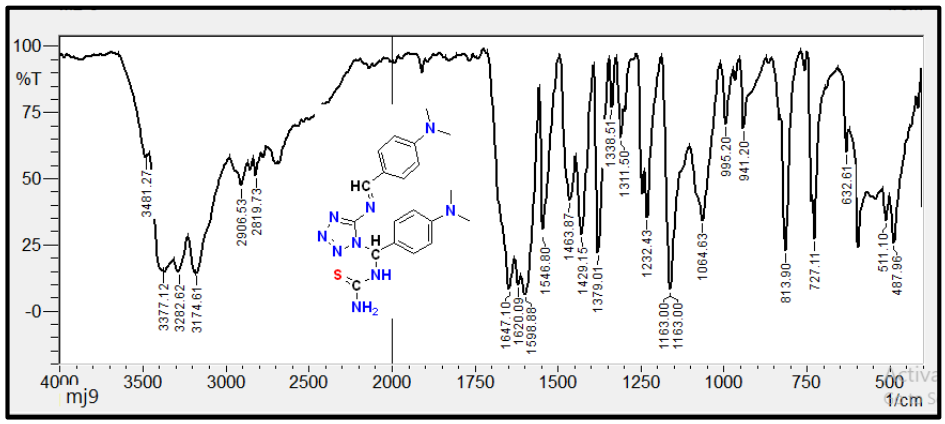


Fig.4: I.R. spectra for **mj9**

Some compounds were identified via proton nuclear magnetic resonance spectrum analysis, and the spectra confirmed the appearance of the expected signals, confirming the structures of the prepared compounds that were obtained, as the Schiff base mj1 showed the appearance of the azomethine signal CH=N at 9.02 ppm, as well as the appearance of the NH signal of the tetrazole ring of the mj1-4 compounds at (6.29-6.49) ppm, with the appearance of a signal at (8.12-8.35) ppm due to the proton of the rings of (Oxazepane, Oxazepines, N-C<u>H</u>-O) for compounds mj2-4, while the spectra of the bases of the compounds mj5-10 showed NH_2 signals, NH at (5.53-9.01) ppm, (6.14-10.24) respectively, and the appearance of the bridging proton N-CH-NH that links the amine condensation with aldehyde and urea or thiourea at an offset of (6.46-7.72) ppm .

Some compounds were identified using the ^{13}Carbon nuclear magnetic resonance spectra, where the **mj1** Schiff base spectrum showed a carbon azomethine signal, CH=N at 168.16 ppm,

as well as the appearance of a C=N signal for the tetrazole ring of mj1,2,4 compounds at (162.09-160.66) ppm. The structures were confirmed by the appearance of the carbon-lactone and lactam signal at (172.02-164.29) ppm (-O-C=O, N-C=O, Oxazepane), with a signal appearing at (86.03-79.73) ppm belonging to the same rings (Oxazepane, Oxazepines, N-CH-O and Figures 5-10 indicate the ^{1}H,^{13}CNMR spectra for compounds mj1, mj4, mj6, mj8 respectively.

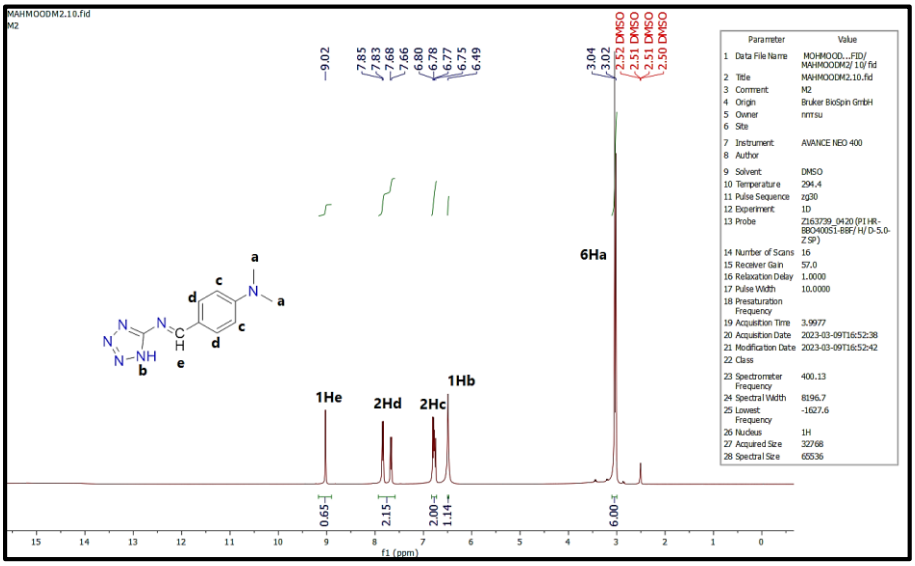


Fig.5: ^{1}H NMR spectra for **mj1**

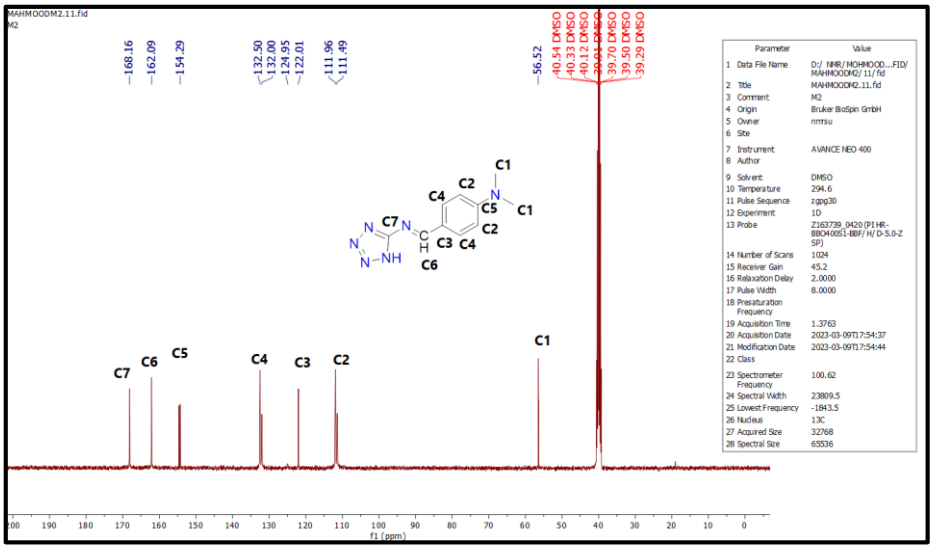


Fig.6: ^{13}C NMR spectra for **mj1**

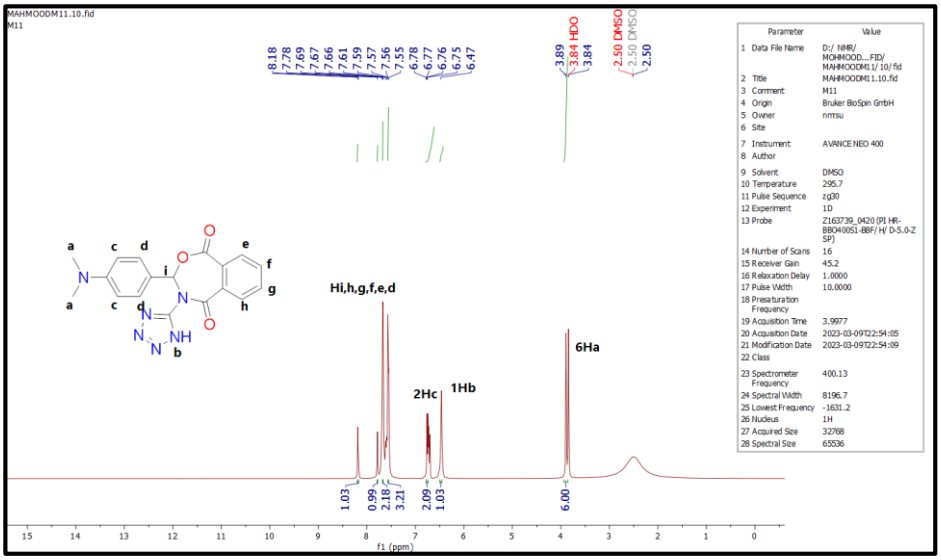


Fig.7: ^{1}H NMR spectra for **mj4**

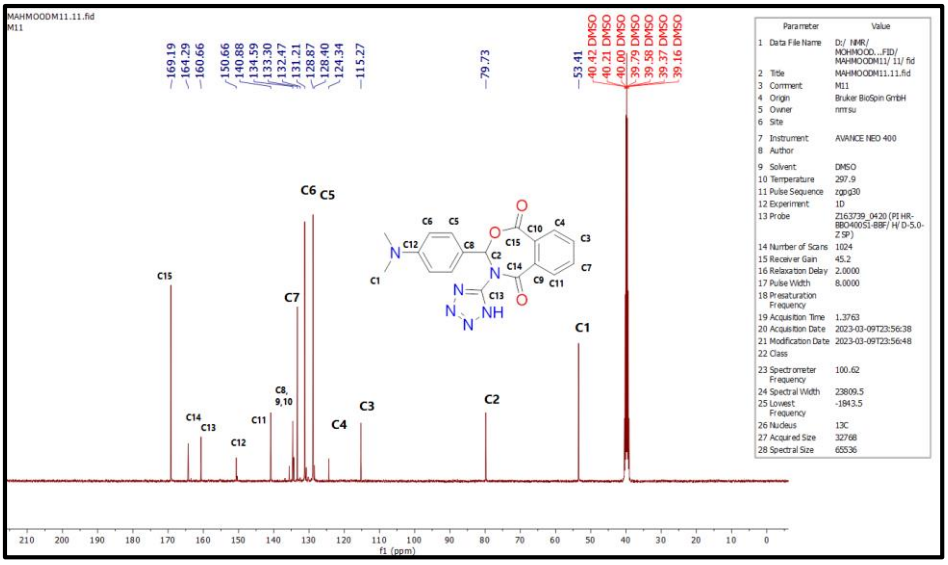


Fig.8: ^{13}C NMR spectra for **mj4**

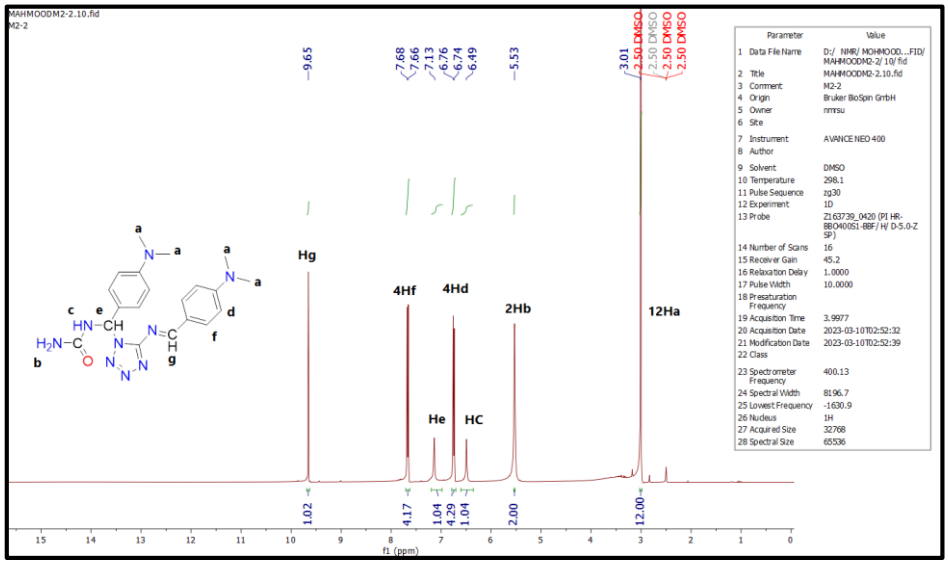


Fig.9: ^{1}H NMR spectra for **mj6**

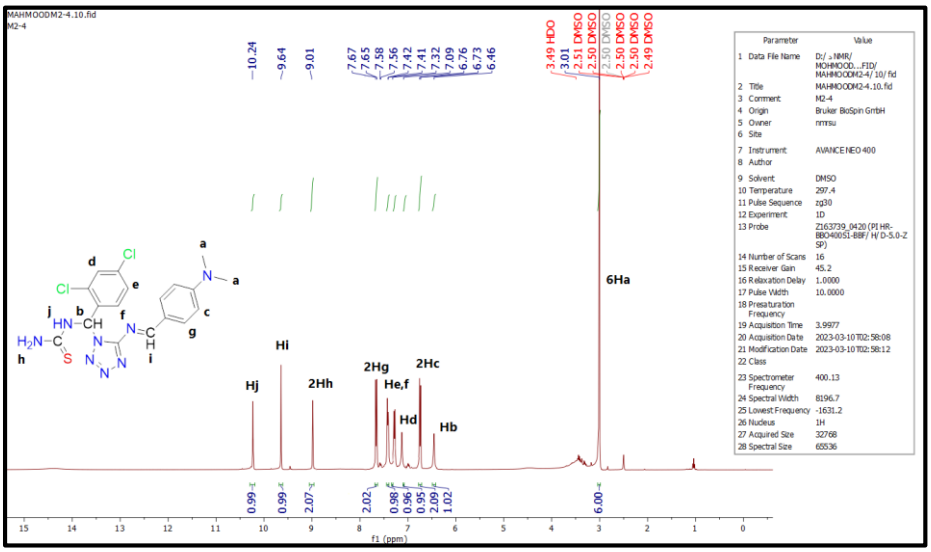


Fig.10: ^{1}H NMR spectra for **mj8**

Evaluation of biological activity

The test results showed that all compounds showed different antibacterial efficacies, according to the type of compound and the type of bacteria. The Oxazepane ring and Mannich bases derived from Schiff base showed moderate to good activity against *Streptococcus mutans* and *Staphylococcus epidermidis* compared to Amikacin and Tetracycline correspondingly, where compound mj5 showed the maximum inhibition at (100 mg/ml) against both bacteria. On the other hand, the same compounds did not show inhibitory activity at concentrations (5,10) mg/ml except compound mj5. The results are listed in Tables 1,2 and Figures 11,12 show the inhibitory efficacy of some compounds against tested bacteria.

Table 1: Bacterial inhibition against *Streptococcus mutans* compared to the antibiotic Amikacin.

Comp. No.	St.	5	10	25	50	100
mj1	33	……	……	6	10	19
mj2	32	……	……	7	10	20
mj5	31	……	……	10	21	26
mj6	32	……	……	8	12	20
mj7	31	……	……	6	10	19

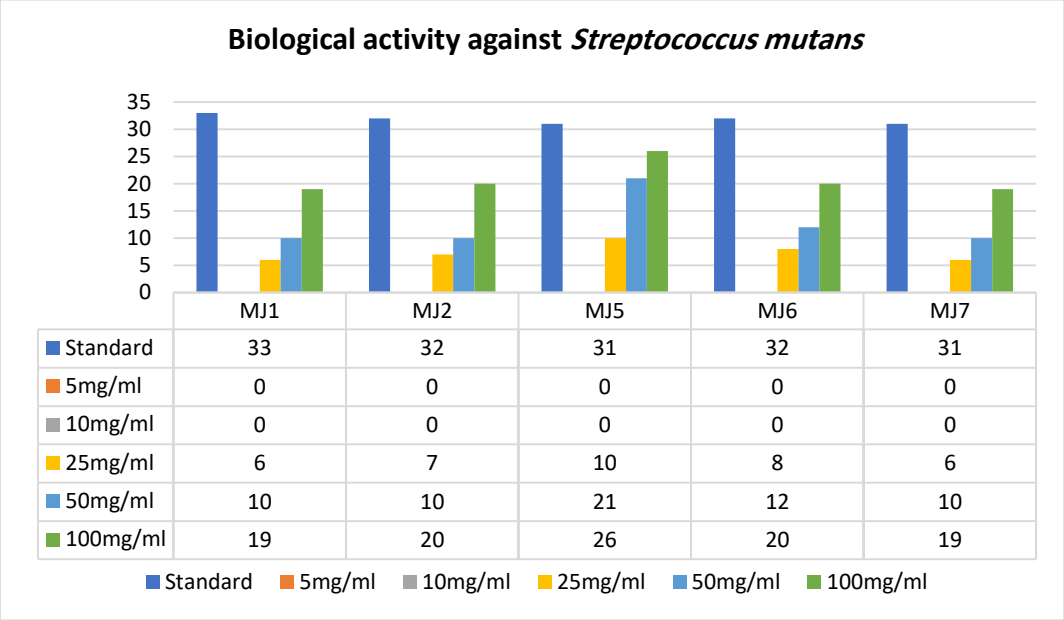


Fig. 11: The inhibitory efficacy of some compounds against *Streptococcus mutans*

Table 2: Bacterial inhibition against *Staphylococcus epidermidis* compared to the antibiotic Tetracycline.

Comp. No.	St.	5	10	25	50	100
mj1	10	.....	.....	6	10	12
mj2	10	.....	.....	6	9	10
mj5	10	.....	7	8	11	15
mj6	10	.....	.....	6	8	10
mj7	10	.....	.....	6	9	10

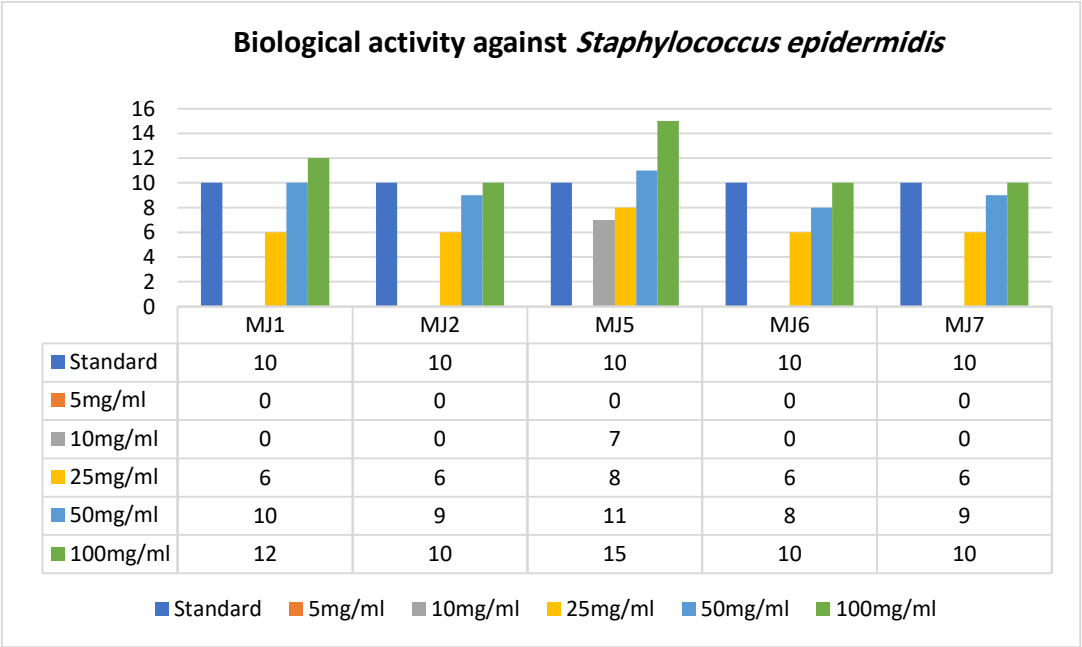


Fig. 12: The inhibitory efficacy of some compounds against Staphylococcus epidermidis.

Conclusions

In this study, ten tetrazole derivatives were designed and synthesized using the recommended antibacterial agents in good yields and under mild reaction conditions. Some synthetic compounds have been tested for the antibacterial activity against *Streptococcus mutans* and *Staphylococcus epidermidis*. Mannich Base **5mj** proved to be an excellent growth inhibitor against both bacterial strains. These findings hold promise for future development of new antibacterial candidates.

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تحضير وتشخيص وفحص النشاط المضاد للبكتيريا لبعض مشتقات H1-تترازول-5-أمين

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الخلاصة:

في هذا الدراسة، تم تحضير المركبات الجديدة mj1-10 المشتقة من 1H-tetrazol-5-amine وبارا-ثنائي مثيل امينو بنزالدهايد من خلال تفاعلات شف ومانيخ، والمعروفة بأهميتها الطبية. تم تأكيد التركيبات الكيميائية طيفيًا باستخدام أطياف IR، ^{1}H NMR، ^{13}C NMR 13). تم اختبار النشاط المضاد للبكتيريا للمركبات المصنعة حديثًا ضد *Streptococcus mutans* و*Staphylococcus epidermidis* بتركيزات مختلفة. وجد أن قاعدة مانيخ 5mj حقق أعلى فعالية في التثبيط مقارنة مع Tetracycline وAmikacin عند 100 مجم / مل. وفقًا لذلك، من المتأمل الحصول على تطوير عامل جديدة واعد لمضادات الجراثيم في المستقبل.