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SYNTHESIS AND *IN VITRO* ANTIBACTERIAL ACTIVITY STUDY OF SOME NEW TETRAZOLE DERIVATIVES

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ABSTRACT

With the appearance of the antibacterial resistance, new antibacterial agents are needed to be synthesized. In this work, new 2,5-disubstituted tetrazole derivatives (**6-10)** were synthesized by the reaction of synthesized Schiff bases (**1-5)** with sodium azide according to1,3-dipolar cycloaddition reaction. The final structures of the obtained compounds were confirmed by ^{1}H NMR, FT-IR and mass spectral data. Antibacterial activity of the synthesized compounds (**6-10)** was tested against Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli by using the broth microdilution method. The *in vitro* anti-bacterial evaluation of the synthesized compounds (**6-10)** was showed that all these compounds have a relatively higher antibacterial activity than the control drug against both Gram negative and Gram positive bacteria.

Keywords: Heterocyclic compounds; Tetrazole; Schiff base; Amino acids; Microdilution method.

Introduction

The growth of bacterial infections constitutes a worldwide health problem and the increase in the number of human diseases caused by pathogenic bacteria is observed (Zha et al., 2017). These infections are difficult to treat and significantly dangerous for elderly people and patients with an impaired immune system(Łukowska-Chojnacka, 2016), Moreover, bacterial drug-resistance has become a global health concern(Pazik & Skwierawska, 2014). Therefore, developing new methods for inhibition or slowing down the growth of bacteria seems to be necessary(Kenawy et al., 2019). A potent approach to overcome this problem is to design new and innovative agents with a completely different mode of action, (Rakesh et al., 2019) tetrazole derivatives have a potent and effective influence on the antibacterial activity(Zhu et al., 2018). Tetrazoles are heterocyclic compounds(Pawar & Chikate, 2021) containing a one carbon atom and four nitrogen atoms in a five-membered ring(Wei et al., 2015). These compounds have received much attention in medicinal chemistry (Molaei et al., 2018) and drug design(Kocabey et al., 2004) due to its diverse applicability, low toxicity(Figueiredo et al., 2012), metabolic stability(Salimi et al.,2020), high lipophilicity (Lee et al.,2018), and other beneficial physicochemical properties(Dofe et al., 2020). among various bioactive heterocyclic rings, tetrazole rings have possessed biological activity against various diseases(Allab et al., 2020). such as cancer(X. Zhang et al., 2020), HIV, hypertension, Alzheimer (Kushwaha et al., 2019), ulcer(Xiong et al., 2019), tuberculosis and diabetes(Sribalan et al., 2019) (Aziz et al., 2018; Mitra et al., 2018). There are several drugs containing tetrazole moiety such as losartan, TAK-456 and Ceforanide which are used as antihypertensive, antifungal and anti-bacterial drugs, respectively (Xiong et al., 2019). Depending on the above facts, there is a considerable need for discovery of new scaffolds and new chemical moieties to act as antibacterial agents(Wang et al., 2019). However, tetrazole derivatives do not exist in nature (Neochoritis et al., 2019), therefor there are several conventional methods to synthesize 5-substituted 1H-tetrazoles (Tisseh et al., 2012), the most convent methods are based on reaction of cyano or imine group with hydrazoic acid (HN_3) (Kritchenkov et al., 2019), trimethylsilyl azide ($TMSN_3$)(Zhang et al., 2020), or sodium azide (NaN_3) (Nemati, et al., 2019). In view of the previously mentioned methods, we were inspired to synthesize a series of new tetrazole derivatives via reaction of some Schiff bases

with sodium azide and investigate their anti-bacterial activity.

Experimental

Chemicals and Instruments

All solvents and chemical that used in this work were purchased from commercially sources and they were directly utilized without further purification. FT-IR spectra were recorded on an FT-IR Shimazdzo 8400S spectrometer operating from 4000–500 cm^{-1} as KBr disc. ^{1}H-NMR spectra were recorded at 500 MHz on a Bruker AC400 spectrometer, chemical shifts (σ) were reported in ppm. Mass data were measured on Agilent Technology (HP).

Procedure

*General Procedure for Synthesis of Schiff bases (**1-5**)*

All Schiff bases (**1-5**) that were used in the present work were previously synthesized as reported in the literatures. (Fan, & Li, 2003)**.** The compounds (**1-5**) were obtained by following the same procedure.

*General Procedure for Synthesis of Tetrazole Derivatives (**6-10**)*

The tetrazole derivatives (**6-10**) were synthesized according to a literature-reported method but with minor modifications (Kadem & Munahi, 2018). In 50 ml round-bottom flask, aqueous solution (25 ml) of KOH (1.0 mmol) and Schiff base **1-5** (1.0 mmol) was stirred, then sodium azide (1.0 mol) was added. The reaction mixture was heated to reflux for 24 h. After completion the reaction, the solution was cooled to room temperature, then the pH was adjusted to 6.8 with HCl solution (20%), and the stirring was continued for 30 min to break up the solid precipitate. The new precipitate was filtered and washed with ethanol.

*1-(5-Furan-2-yl-4,5-dihydro-tetrazol-1-yl)-acetic acid (**6**)*

It was prepared by using compound **1** (1.53 gm, 10 mmol), sodium azide (0.97 gm, 15 mmol) to give a yield (1.25 g, 63%), as a dark brown solid, M.wt:196, m.p: >380. **FT-IR** (KBr disc, cm^{-1}), 3500-2360 (OH, COOH), 3308 (NH), 3124 (Ar-H), 2848 (C-H aliphatic), 1722 (C=O), 1639 (Ar, C=C), 1400 (-N=N-). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ= 7.62(d, 1H, CH of Tetrazole ring), 7.46-6.20(m, 3H of furfural ring), 3.51(s, 2H, CH_2), 2.28(br, 1H, NH of Tetrazole ring). **HPMS-EI$^+$ (m/z):** calc. for $C_7H_8N_4O_3$ = 196.06, found = 197.

*2-(5-Furan-2-yl-4,5-dihydro-tetrazol-1-yl)-propionic acid (**7**)*

It was prepared by using compound **2** (1.67 gm, 10 mmol), sodium azide (0.97 gm, 15 mmol) to give a yield (1.54 g, 73%), as a dark brown solid, M.wt:210, m.p: >380. **FT-IR** (KBr disc, cm^{-1}), 3600-2365 (OH, COOH), 3390 (NH), 3122 (Ar-H), 2891 (C-H aliphatic), 1732 (C=O), 1653 (Ar, C=C), 1388 (-N=N-). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ= 7.60(d, 1H, C**H** of Tetrazole ring), 7.41-6.00(m, 3H of furfural ring), 3.58(q, 1H, C**H**-COO), 2.08(br, 1H, N**H** of Tetrazole ring), 1.05(d, 3H, CH_3). **HPMS-EI$^+$ (m/z):** calc. for $C_8H_{10}N_4O_3$ = 210.19, found = 211.

*2-(5-Furan-2-yl-4,5-dihydro-tetrazol-1-yl)-3-methyl-butyric acid (**8**)*

It was prepared by using compound **1** (1.95 gm, 10 mmol), sodium azide (0.97 gm, 15 mmol) to give a yield (1.7 g, 71%), as a dark brown solid, M.wt: 238, m.p: >380. **FT-IR** (KBr disc, cm^{-1}), 3480-2400 (OH, COOH), 3394 (NH), 3130 (Ar-H), 2964 (C-H aliphatic), 1734 (C=O), 1637 (Ar, C=C), 1465 (-N=N-). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ= 7.8(d, 1H, C**H** of Tetrazole ring), 7.51-6.43(m, 3H of furfural ring), 3.37(d, 1H, C**H**-COO), 2.36(m, 1H, C**H**$(CH_3)_2$), 2.08(br, 1H, N**H** of Tetrazole ring), 1.05(d, 6H, C**H**$_3$). **HPMS-EI$^+$ (m/z):** calc. for $C_{10}H_{14}N_4O_3$ = 238, found =239.

*2-(5-Furan-2-yl-4,5-dihydro-tetrazol-1-yl)-3-(4-hydroxy-phenyl)-propionic acid (**9**)*

It was prepared by using compound **1** (2.59 gm, 10 mmol), sodium azide (0.97 gm, 15 mmol) to give a yield (2 g, 66%), as a dark brown solid, M.wt:302, m.p: >380. **FT-IR** (KBr disc, cm^{-1}), 3524-2441 (OH, COOH), 3350 (NH), 3138 (Ar-H), 2983 (C-H aliphatic), 1716 (C=O), 1639 (Ar, C=C), 1442 (-N=N-). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ= 9.27(br, 1H, Ar-O**H**) ,7.65(d, 1H, C**H** of

Tetrazole ring), 7.24-6.63(m, 7H, Ar-**H**), 3.86(t, 1H, C**H**-COO), 2.26(d, 2H, C$\mathbf{H}_2$), 1.73(br, 1H, N**H** of Tetrazole ring). **HPMS-EI$^+$ (m/z):** calc. for $C_{14}H_{14}N_4O_3$ = 302, found = 303.

*2-(5-Furan-2-yl-4,5-dihydro-tetrazol-1-yl)-5-guanidino-pentanoic acid (**10**)*

It was prepared by using compound **1** (2.52 gm, 10 mmol), sodium azide (0.97 gm, 15 mmol) to give a yield (1.9 g, 64%), as a dark brown solid, M.wt:295, m.p: >380. **FT-IR** (KBr disc, cm^{-1}), 3500-2400 (OH, COOH), 3360 (NH), 3124 (Ar-H), 2945 (C-H aliphatic), 1722 (C=O), 1653(C=NH), 1630 (Ar, C=C), 1456 (-N=N-). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ= 9.11(br, 1H, C=N**H**), 7.62(d, 1H, C**H** of Tetrazole ring), 6.78-6.33(m, 3H of furfural ring), 5.97 (d, 2H, NH_2), 4.38(q, 1H,C-N**H**), 3.36(t, 1H, CH-COO), 2.91(q, 2H, αC$\mathbf{H}_2$), 2.51(q, 2H, γC$\mathbf{H}_2$), 1.77(br, 1H, N**H** of Tetrazole ring), 1.59(m, 2H, βCH_2). **HPMS-EI$^+$ (m/z):** calc. for $C_{11}H_{17}N_7O_3$ = 295, found =296.

Antibacterial activity

The microorganisms were obtained from Al Hussein teaching hospital, Al-Muthanna, Iraq. In this work two types of bacteria were used: Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. The synthesized compounds **(6-10)** and amoxicillin were dissolved by using 40% DMSO and diluted to a final concentration of 1000 µg/mL, amoxicillin was used as a control. Bacterial inoculum was obtained using bacterial strains which were previously cultured in the heart infusion agar (HIA), and then in a saline solution (0.9%), the concentration of microorganisms was optimized to 0.5 McFarland. The inoculum (150 µL) was added to tubes containing 1350 µL of brain heart infusion broth (10%). An amount of this solution (100 µL) was dropped into each well of the microtiter plate (96 well), followed by a serial dilution of the synthesized compounds solution (**6-10**), ranging between 500 and 0.1 µg/mL. Incubation of the microtiter plates were performed at 37 ºC for 24 h. After incubation time, the MIC was determined by measuring the optical density (OD) at 565 nm. MICs (Mounyr et al., 2016; Moura et al., 2018).

Results and discussion

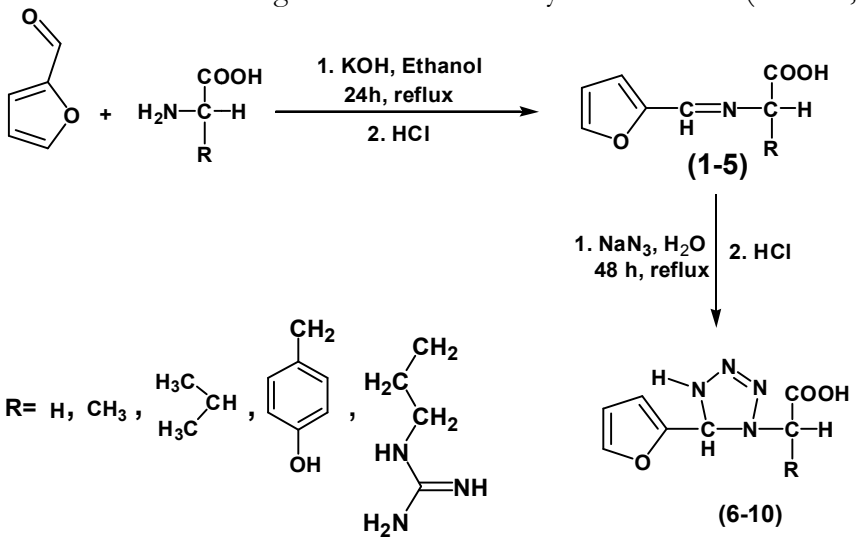
Chemistry

Tetrazoles and their derivatives are some of the most stable nitrogen-rich heterocyclic compounds that have gained bewildering range of applications in the field of medicinal chemistry (Herr et al., 2002)(Wang et al., 2019). Where, some of the tetrazole-containing derivatives are displaying a good antibacterial activity (Gao et al., 2019). There are different synthetic strategies have been employed to obtain heterocyclic compounds with tetrazole moiety, one convenient strategy is based on the cycloaddition reaction of sodium azide to Schiff bases, hence, we were motived to prepare a series of Schiff bases as a starting material to achieve new tetrazole derivatives. Synthesis of the key-intermediate Schiff bases was achieved with a good yield, through reaction of some amino acid with furfuraldehyde in KOH alcoholic solution. The biocompatibility of amino acids and furfuralaldehyde was encouraged us to use them as a starting material. By using a previously reported synthetic methodology(Kadem & Munahi, 2018), five new tetrazole derivatives (**6-10**) were successfully synthesized in a good yield as shown in Scheme 1.

Our initial attempt to the synthesis of tetrazole derivatives was involved dissolving of Schiff bases in water, after that sodium azide was added and stirred under reflux condition for 24 h, this attempt was successful to give the target product, however in a relatively low yield (10-20)%. Also our work up showed that the crud product containing an amount of unreacted Schiff bases. Our first investigation revealed that the solubility of Schiff base in water was insufficient, to overcome this problem potassium hydroxide was used to convert carboxyl(-COOH) of Schiff base derivatives into carboxylate ion (-COO^-), the letter is increasing the solubility of organic compound in water, furthermore, an excess amount of sodium azide was used to ensure complete reaction. By following this reaction conditions higher yield was obtained (60-70)%.

After completing the reaction, an acidification to pH=6 with an aqueous solution of hydrochloric

acid (10%) was performed, that led to precipitate the desired compounds (**6-10**), this step was carefully cared out in the fume hood to avoid the *in situ* generated hydrazoic acid HN_3, which is produced by reaction of the remaining sodium azide with hydrochloric acid(Firdous, 2012).



Scheme 1: Synthesis of some tetrazole derivatives (**6-10**).

Characterization of tetrazole derivatives

The structure of the synthesized tetrazoles **6-10** was characterized by FT-IR, ^{1}H-NMR and Mass spectra. Characteristic absorption bands of all the synthesized tetrazoles were found in the FT-IR spectra, where, in the range of 2400-3600 cm^{-1} a broad band was appeared which confirms the presence of hydroxyl group (–OH). Also, a strong peak correspondent to the stretching frequency of carbonyl (C=O) group was appeared in the range of 1734–1716 cm^{-1}. The FT-IR spectra of compounds **6-10** also showed two peaks at around 3390 cm^{-1} and 1400 cm^{-1} related to the presence of N-H and N=N, respectively. Moreover, ^{1}H-NMR spectra of compounds **6-10** were showed characteristic signal due to tetrazole ring proton (-CH) at 7.6-7.8 ppm. The signals of aromatic protons (furane) were found in the expected region of Ar-H and in the range 6.0-7.5 ppm, whereas the signal of tetrazole ring proton (-NH) was found in the range of 1.73-2.28 ppm.

MS spectra were showed expected peaks $[M]^+$ which are attributed to the proposed molecular fragments of the target compounds.

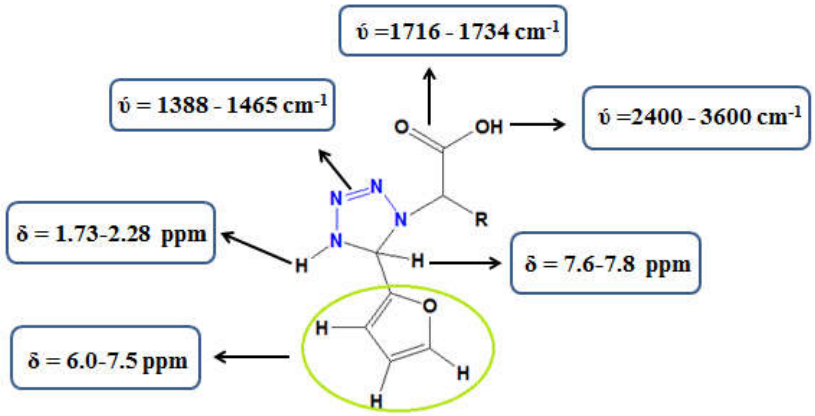


Figure 1: Illustration of spectral data (^{1}H-NMR and FT-IR) of 5-Furan-2-yl-4,5-dihydro-tetrazole derivatives.

Biological Activity

Among several bioactive heterocyclic scaffolds, the tetrazoles derivatives have gained much attention in drug synthesis(Sribalan et al., 2019). The study of the biological significance of the tetrazoles and their derivatives are an interesting area in the field of pharmaceutical chemistry(Khan et al., 2018). In the second part of our work, the antibacterial activity of the newly synthesized tetrazole derivatives **6-10** was screened against *Escherichia coli* as Gram-negative bacteria, and *Staphylococcus aureus* as Gram-positive bacteria, at concentrations ranging 0.1–1000 μg/mL**.** The minimal inhibitory concentration (MIC) values for compounds **6-10** defined as the lowest concentration of the compound preventing the growth, which was estimated by using the microdilution broth method(Abdelhalim et al., 2007).

The results of the antibacterial activity indicated that the tetrazoles derivatives **6-10** were exhibited excellent antibacterial activity against the tested bacteria and in comparison with the standard drug Amoxycillin as described in Table 1. In particular, compound **10** exhibited the greatest significant activity, with MIC value 0.24μg/mL against *Escherichia coli* and MIC value 0.78μg/mL against *Staphylococcus aureus,* while compound **6** was showed the lowest activity, with MIC value 0.97μg/mL against *Escherichia coli* and MIC value 2.92μg/mL against *Staphylococcus.* On the Other hand, compounds **7**, **8, 9** exhibited a good activity, with MIC values ranging from 1.95 to 0.73 μg/mL against both types of bacteria. However, all tested compounds **6-10** were significantly more potent than the reference drug Amoxicillin as shown in Table 1. This excellent activity makes these compounds potential antibacterial candidates. Studies to perform *in vivo* validation and toxicity are being planned for further development of these compounds.

Table 1: Antibacterial activities of the tested compounds (**6-10**) using the microdilution method expressed as MIC and IC_{50} (μg/mL).

Comp. NO	*Staphylococcus aureus*		*Escherichia coli*	
	MIC	**IC_{50}**	**MIC**	**IC_{50}**
6	2.92	1.42	0.97	0.61
7	1.46	0.82	0.73	0.47
8	1.95	0.95	0.78	0.48
9	1.56	0.87	0.48	0.39
10	0.78	0.51	0.24	0.21
Amoxycillin	3.16	1.81	6.32	3.41

Conclusions

The tetrazole derivatives are an interesting class of heterocycles, and have been used as drugs, in this work, all the tetrazole derivatives were synthesized using an efficient synthetic method and simple workup. The synthesized compounds **6-10** were characterized by FT-IR, ^{1}H-NMR and mass spectroscopies, also the antibacterial activity against two types of bacteria: Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* was investigated by using the broth microdilution method, Moreover, our finding indicates that all the newly synthesized tetrazole derivatives **6-10** have an excellent antibacterial efficacy. However, further biological assessments are needed to estimate the potential pharmacological activities of these compounds. We hope that in the future work more biological investigations of compounds **6-10** can be established and used in the field of medicinal sciences.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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