



## Original Research Article

# Synthesis of derivatives of tetrazoline on Creatinine and study their biological activity

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### ARTICLE INFORMATION

Received: 13 October 2021

Received in revised: 19 November 2021

Accepted: 7 December 2021

Available online: 14 December 2021

DOI: 10.22034/ajgc.2021.315002.1321

### KEYWORDS

Schiff Bases

Tetrazoline Derivatives

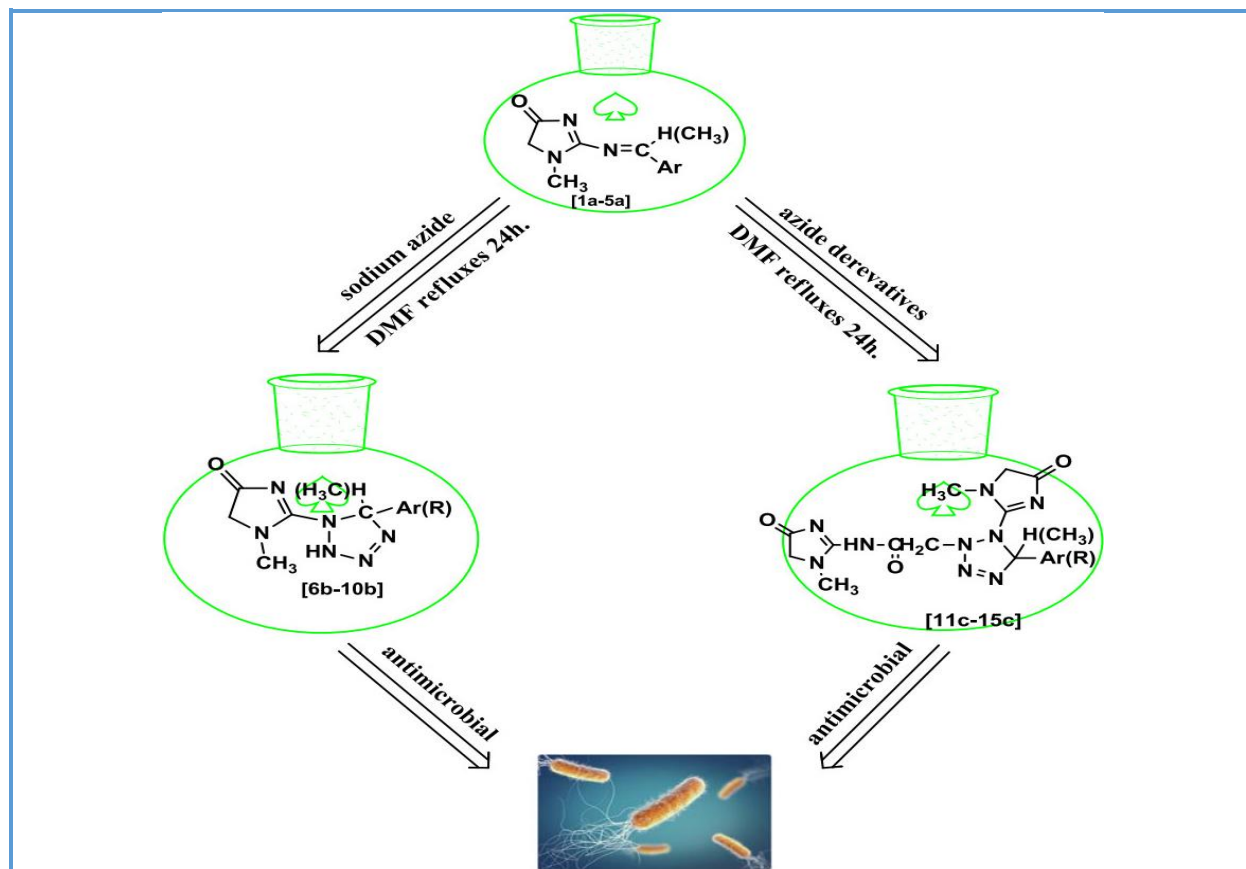
Biological Activity

### ABSTRACT

In this research study we synthesized new tetrazoline from a reaction of 2-*N*-arylidene amino creatinine with sodium azide and 2-*N*-azido acetamido creatinine. The prepared compound was characterized using the FT-IR, and <sup>1</sup>H NMR. All the physical properties and studied biological activity of synthesized compounds. The compounds **8b** and **13c** were given more active against gram positive, gram negative bacteria and fungi.

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## Graphical Abstract



## Introduction

The Azomethine group (-C=N-) usually known as Schiff bases, this group is formed by condensation of a carbonyl compounds with a primary amine [1]. The Azomethine group are an important compound because it uses in industrial application and has good antibacterial activity [2]. 1,2,3,4-tetrazole are a class of synthetic organic hetero cyclic compounds consisting of five-member ring of four nitrogens and one carbon atom [3]. The most direct method to form tetrazoles is via the formal (2+3) cycloaddition of azides and nitriles [4]. Tetrazoles and its derivatives possess a broad spectrum of biological activities in both medicinal and pharmaceutical such as antimicrobial [5] anti-fungal [6] inhibitor of

HCV [7] potent hypoglycemic agent [8] cholinesterase inhibitors [9].

## Experimental

*Material and methods*

In this research, chemicals had been used provided from (Merck group, BDH and Fluke Company). FT-IR spectra (KBr disc) were recorded Affinity-1 Shimadzu as FT-IR spectrometer using KBr pellets. <sup>1</sup>H NMR spectra were scanned on Bruker spectro spin ultrashield magnets 300 MHz instrument.

*Synthesis of schiff bases from creatinine (1a-5a)*

A (1.13 g, 0.01 mol) of Creatinine and 0.01 mol of different aldehydes (4-nitro

benzaldehyde, 4-amino benzaldehyde, and cinnamaldehyde) and different ketones (acetophenone and cyclohexanone) in 20 mL absolute ethanol and 3-4 drops of glacial acetic acid had been refluxed for 10-12 hrs. The solvent was evaporated, and all the formed products were recrystallized from ethanol [10].

#### *Synthesis of [2-sub.3,5-dihydro-tetrazolin-1-yl]-4-oxoimidazole (6b-10b)*

A mixture of 0.01 mol of Schiff bases (**1a-5a**) in 30 mL DMF and sodium azide (0.025 g, 0.02 mol) were refluxed 24 h. The disappearance of the starting material had been tested by (TLC). The excess solvent was evaporated. The precipitate was dried and purified from ethanol [11].

#### *Synthesis of (1,5-substetrazole)methyl-4-oxo-4,5-dihydro-imidazolin-2-yl)tetrazolidin-3-yl acetamido creatinine derivatives (11c-15c)*

A solution of Schiff base (**1a-5a**) (0.01 mol) in 25 mL of DMF was mixed with (1.96 g, 0.01 mol) of 2-azidoacetamido-1-methyl-4-oxoimidazole and refluxed for 24 hrs. The end of the reaction was checked by (TLC). Evaporated of excess solvent. The precipitate was dried and purified from butanol [12].

#### *Biological activity*

Applying the agar plate diffusion technique, the prepared compounds were screened in vitro for anti-bacterial and anti-fungal activity against two types of bacteria *Staphylococcus aureus* (G+) and, *Escherichia coli* (G-) and *Aspergillus flavus* a fungus. The inhibition zone of bacterial growth around the disc was observed [13].

## Results and Discussion

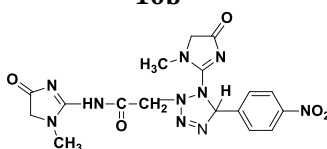
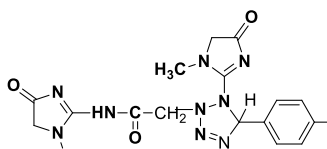
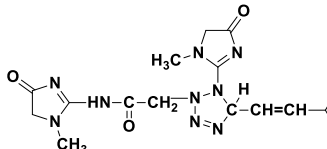
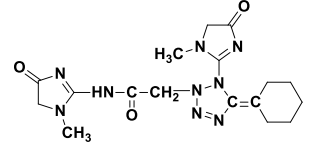
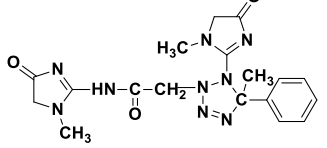
**Scheme 1** represented the reaction of imine with  $\text{NaN}_3$  and 2-*N*-azido acetamido creatinine to produce deferent tetrazoline. All the derivatives characterization by FT-IR and some derivatives by  $^1\text{H}$  NMR.

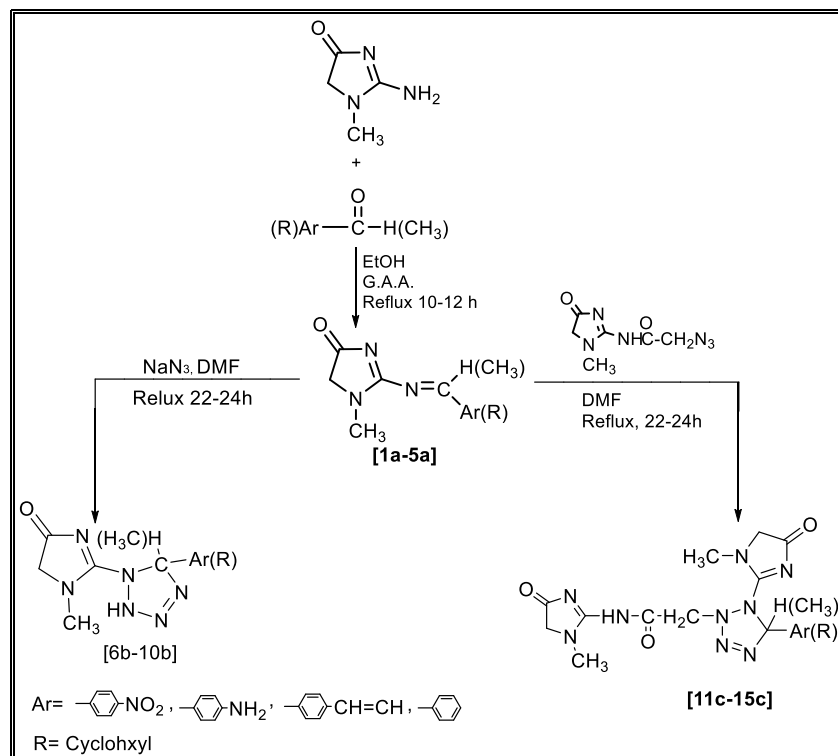
The FT-IR prepared Schiff bases **1a-5a** are illustrated in **Table 1**. Tetrazoline derivatives compounds **6b-10b** had been prepared by the [2+3] cycloaddition reaction implicit a reaction through sodium azide with Schiff base as shown in **Scheme 1**. And the compound 2-*N*-azido acetamido creatinine that characterized using FT-IR illustrated a band at  $2260\text{ cm}^{-1}$  which showed the presence of the  $-\text{N}_3$  and disappearance of absorbance band of C-Cl group of starting material (2-*N*-chloro acetamido creatinine) at  $644\text{ cm}^{-1}$  [14]. Also the band at  $1710\text{ cm}^{-1}$  due to C=O cyclic amide. All these absorption bands are good indicator to synthesis of 2-*N*-azido acetamido creatinine from the reaction of creatinine with chloroacetyl chloride.

From reaction of Schiff bases with 2-*N*-azido acetamido creatinine synthetized compounds (**11c-15c**) [15], the suggested mechanizes of prepared compounds as shown in **Scheme 2** [16]. The prepared compounds were characterized using FT-IR spectra as shown in **Table 1**. On the other hand,  $^1\text{H}$  NMR spectral data of compound **10b**  $\delta$  ppm in  $\text{DMSO-d}_6$  solvent showed singlet signal at  $\delta=2.26$  ppm due to  $-\text{CH}_3$  protons, singlet signal at  $\delta=2.93$  ppm due to  $-\text{CH}_2-$  proton, singlet signal at  $\delta=4.19$  ppm due to  $-\text{NH}-$  tetrazoline ring, signal at  $\delta=7.88-8.82$  ppm due to Ar-H.  $^1\text{H}$  NMR of compounds **7b**, **8b** and **13c** are listed in **Table 2**.

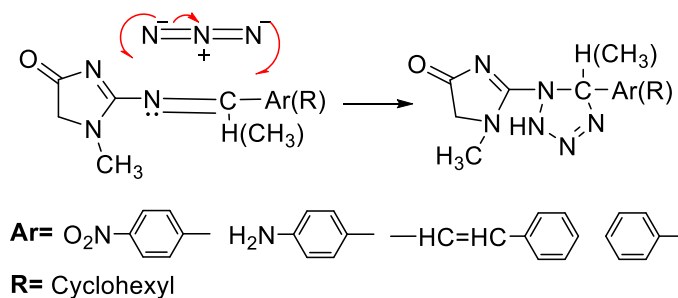
Compounds **8b** and **13c** gives a good inhibition zone against (G+), (G-) bacteria and fungi as shown in **Table 3**.



 <p><b>10b</b></p>	148-150	Yellow	60	1/3050 2/2922 2816	1691	1/1666 2/1340	1589 - 1502	vN=N 1441 vN- H 3261
 <p><b>11c</b></p>	200-202	brown	65	1/3076 2/2941 2850	1770- 1699- 1627	1/1595 2/1398	1544 - 1489	vN=N 1420 vN- H 3257
 <p><b>13c</b></p>	130-132	yellow	60	1/3030 2/2926 2818	1720- 1668	1/1591 2/1334	1496 - 1450	vN=N 1417 vN- H 3259
 <p><b>14c</b></p>	136-138	White	65	- 2/2922 2814	1700- 1680	1/1589 2/1334	1504 - 1430	vN=N 1419 vN- H 3257
 <p><b>15c</b></p>	140-142	Off white	70	1/3045 2/29342 812	1705- 1656	1/1541 2/1362	1485 - 1440	vN=N 1417 vN- H 3235

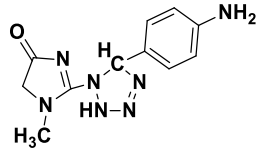
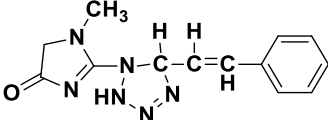


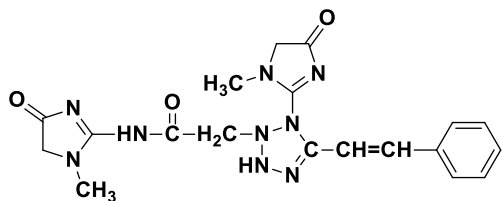
**Scheme 1.** Syntheses new tetrazoline from 2-*N*-Arylidene amino creatinine



**Scheme 2.** The suggest mechanism of the synthesis compound's

**Table 2.**  $^1\text{H}$  NMR spectral data for some prepared compounds

Structure	$^1\text{H}$ NMR signal $\delta$ (ppm)
	2.45 (s, 3H, N-CH <sub>3</sub> ), 2.65 (s, 2H, CH <sub>2</sub> ), 2.92 (s, 2H, NH <sub>2</sub> ), 3.39 (s, 1H, -CH- tetrazoline ring), 4.19 (s, 1H, -NH-triazoline ring), 7.22-7.46 (m, 4H, Ar-H).
	2.62 (s, 3H, N-CH <sub>3</sub> ), 2.79 (d, 1H, -CH-CH=CH-Ph), 2.92 (s, 2H, CH <sub>2</sub> ), 4.19 (s, 1H, -NH-triazoline ring), 5.33 (d, 1H, -CH-CH=CH-ph), 6.01 (t, 1H, -CH-CH=CH-ph), 7.70-8.04 (m, 5H, Ar-H).



2.52 (s-s, 6H, N-CH<sub>3</sub>), 2.63 (s-s, 4H, CH<sub>2</sub>), 2.74 (s, 2H, -tetrazole ring-CH<sub>2</sub>-CO-NH-), 3.03, -NH-Cereating ring, 4.19 (s, 1H, -NH-triazoline ring), 5.30 (d, 1H, -CH-CH=CH-ph), 6.03 (d, 1H, -CH-CH=CH-ph), 7.38-8.49 (m, 5H, Ar-H).

**Table 3.** Biological activity of compounds **8b**, **10b**, **13c** and **15c** against selected bacteria and fungi

Comp. Code	Staphylococcus aureus	E.Coli	Asp.flavous
8b	+++	+++	++
10b	+	++	+
13c	+++	+	++
15c	+	+	+
Amoxicillin	+++	+++	-
Flucanazole	-	-	++
DMSO	-	-	-

In active = (-) inhibition zone <6 mm

Low activity = (+) 6-9 mm

Moderate activity= (++) 9-12 mm

More active = (+++) 13-17 mm

Concentration 10<sup>-3</sup> μL/mL

## Conclusions

The synthesized compounds were confirmed using spectroscopic techniques (FT-IR and <sup>1</sup>HNMR). Some of the prepared compounds gave excellent efficiency. The biochemical studies revealed that the newly synthesized compounds caused activators effects on two types of bacteria (*Staphylococcus aureus*, *Escherichia coli*), and one type of fungal (*Aspergillus flavus*).

## Disclosure Statement

No potential conflict of interest was reported by the authors.

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**How to cite this manuscript:** Raad M. Muhibes\*, Entesar O. Al-Tamimi. Synthesis of derivatives of tetrazoline on Creatinine and study their biological activity. *Asian Journal of Green Chemistry*, 5(4) 2021, 404-411. DOI: 10.22034/ajgc.2021.315002.1321