Asian Journal of Green Chemistry 5 (2021) 404-411

Asian Journal of Green Chemistry

Journal homepage: www.ajgreenchem.com

Original Resarch Article

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

Raad Muslim Muhiebes*, Entesar O. Al-Tamimi

Department of chemistry, College of Science, University of Baghdad, Jadiriya, Baghdad, Iraq

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

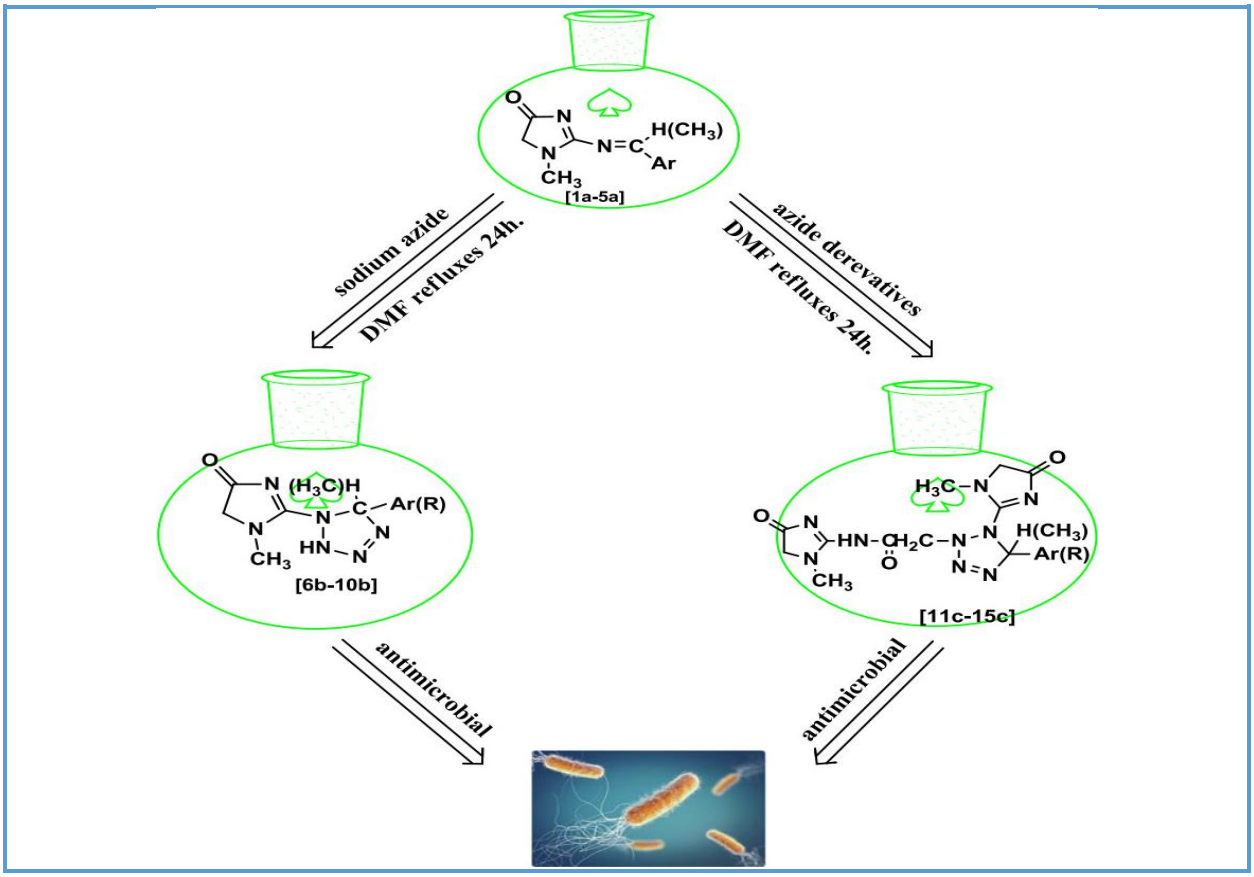
Schiff Bases
Tetrazoline Derivatives
Biological Activity

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 ^{1}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.

Corresponding authors, email: Raadmuslim7@gmail.com (R.M. Muhiebes).
Tel.: +9647721014811.

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. ^{1}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-oxoimidazoline (**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-subs.tetrazole)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-oxo-imidazoline 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

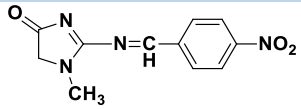
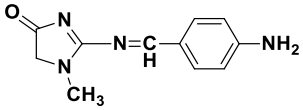
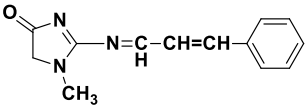
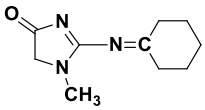
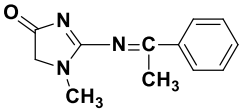
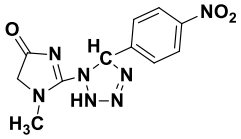
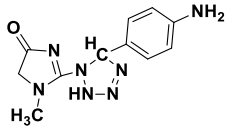
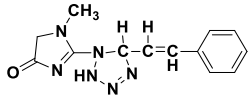
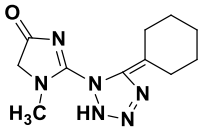
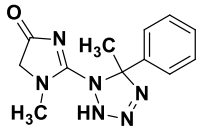
Scheme 1 represented the reaction of imine with NaN_3 and 2-*N*-azido acetamido creatinine to produce deferent tetrazoline. All the derivatives characterization by FT-IR and some derivatives by ^{1}H NMR.

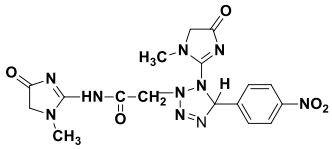
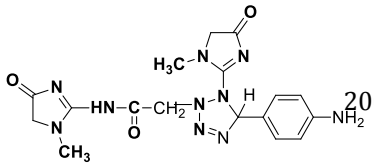
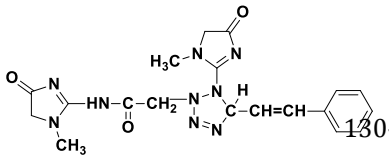
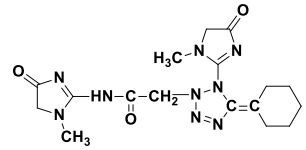
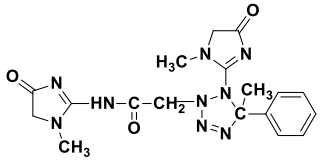
The FT-IR prepared Schiff bases **1a–5a** are illustrated in Table 1. Tetrazoline derivatives compounds **6b–10b** had been prepared by the [2+3] cycloaddition reaction implicit a reaction through sodium azide with Schiff base as shown in Scheme 1. And the compound 2-*N*-azido acetamido creatinine that characterized using FT-IR illustrated a band at 2260 cm^{-1} which showed the presence of the $-N_3$ and disappearance of absorbance band of C–Cl group of starting material (2-*N*-chloro acetamido creatinine) at 644 cm^{-1} [14]. Also the band at 1710 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.

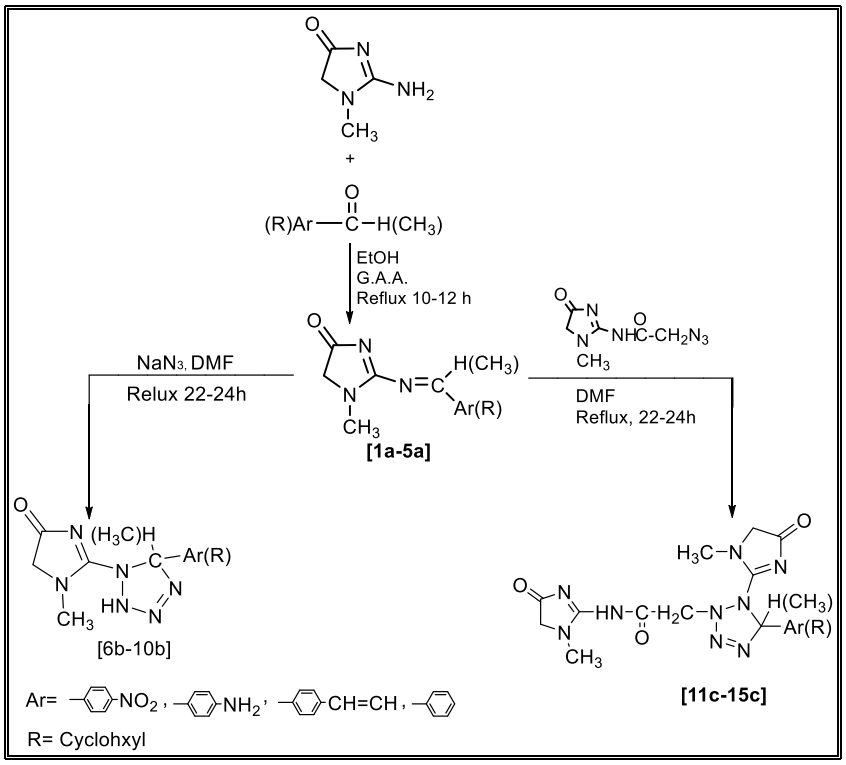
From reaction of Schiff bases with 2-*N*-azido acetamido creatinine synthetized compounds (**11c–15c**) [15], the suggested mechanizes of prepared compounds as shown in Scheme 2 [16]. The prepared compounds were characterized using FT-IR spectra as shown in Table 1. On the other hand, ^{1}H NMR spectral data of compound **10b** δ ppm in DMSO-d_6 solvent showed singlet signal at δ=2.26 ppm due to $-CH_3$ protons, singlet signal at δ=2.93 ppm due to $-CH_2-$ proton, singlet signal at δ=4.19 ppm due to -NH- tetrazoline ring, signal at δ=7.88-8.82 ppm due to Ar–H. ^{1}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.

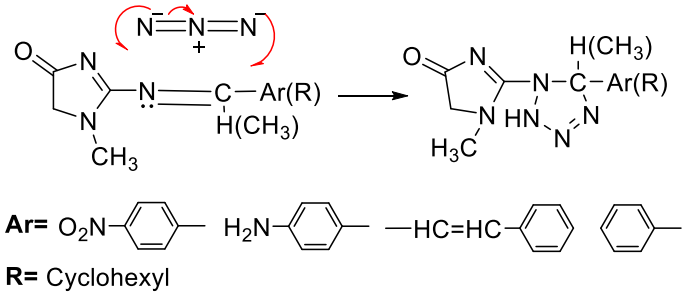
Table 1. Physical properties and IR spectral data $cm^{-1}$of compounds (**1a–15c**)

Structure	m.p (°C)	Color	Yield (%)	Major FT-IR Absorption cm^{-1}				
				1/ν(C-H) aromatic *2/ν*(C-H) aliphatic	*ν*(C=O) amide	*ν*(C=N) *ν*(C- N)	*ν*(C=C) arm.	Other bands
 **1a**	220-222	White	90	1/3060 2/2941 2848	1693	1/1660 2/1421	1589 1521	νNO_2 1500 1346–
 **2a**	230-232	Brown	88	1/3022 2/2925 2866	1689	1/1622 1419 2/	1570 1500	$\nu NH_2$3415
 **3a**	182-184	Yellow	75	1/3026 2/2898 2799	1699	1/1665 2/1417	1556 1546	*ν*C-H olefn. 1637
 **4a**	176-178	White	70	- 2/2943 2816	1670	1/1591 2/1419	-	-
 **5a**	180-182	Off white	80	1/3049 2/2923 2810	1680	1/1670 2/1419	1591 1504	-
 **6b**	194-196	Off white	75	1/3035 2/2924 2854	1695	1/1645 2/1417	1581 1517	νNO_2 1500 1346- *ν*N=N1517 *ν*N-H 3126
 **7b**	200-202	Brown	70	1/3043 2/29242 852	1700	1/1666 2/1419	1595 - 1560	νNH_2 3390 *ν*N=N1498 *ν*N-H 3100
 **8b**	158-160	Yellow	65	1/3040 2/2926 2854	1732	1/1649 2/1417	1562 - 1494	*ν*N=N 1450 *ν*N-H 3120
 **9b**	186-188	Orange	80	- 2/2923 2810	1699	1/1668 2/1419	-	*ν*N=N 1450 *ν*N-H 3143
	210-212	White	75	1/3035 2/2931 2802	1697	1/1668 2/1400	1593 - 1550	*ν*N=N 1440 *ν*N-H 3120

10b  **11c**	148-150	Yellow	60	1/3050 2/2922 2816	1691	1/1666 2/1340	1589 - 1502	*ν*N=N 1441 *ν*N-H 3261
12c 	200-202	brown	65	1/3076 2/2941 2850	1770-1699-1627	1/1595 2/1398	1544 - 1489	*ν*N=N 1420 *ν*N-H 3257
13c 	130-132	yellow	60	1/3030 2/2926 2818	1720-1668	1/1591 2/1334	1496 - 1450	*ν*N=N 1417 *ν*N-H 3259
14c 	136-138	White	65	- 2/2922 2814	1700-1680	1/1589 2/1334	1504 - 1430	*ν*N=N 1419 *ν*N-H 3257
15c 	140-142	Off white	70	1/3045 2/29342 812	1705-1656	1/1541 2/1362	1485 - 1440	*ν*N=N 1417 *ν*N-H 3235

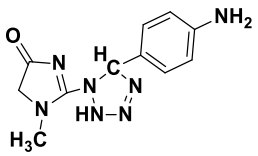
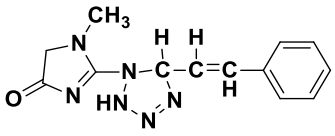


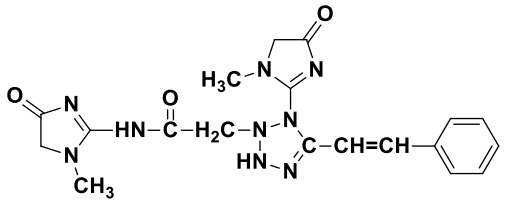
Scheme 1. Syntheses new tetrazoline from 2-*N*-Arylidene amino creatinine



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

Table 2. ^{1}H NMR spectral data for some prepared compounds

Structure	^{1} H NMR signal δ (ppm)
	2.45 (s, 3H, N-CH_3), 2.65 (s,2H,CH_2), 2.92 (s, 2H, NH_2), 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_3), 2.79 (d, 1H, -CH-CH=CH-Ph), 2.92 (s, 2H, CH_2), 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_3), 2.63 (s-s, 4H, CH_2), 2.74 (s, 2H, -tetrazole ring-CH_2-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^{-3} µL/mL

Conclusions

The synthesized compounds were confirmed using spectroscopic techniques (FT-IR and ^{1}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.

References

[1]. Anu K., Suman B., Sunil K., Neha Sh., Vipin S., *Journal of Catalysts*, 2013, **13**:1

[2]. Anita R., Manoj K., Rajshree K., Hardeep S.T. *Journal of Biological and Chemical Sciences*, 2015, **2**:62

[3]. Hussein I.A., Narren S.F., Hasan I.M.M., Saleh A.M. *J. Pharm. Sci. Res.* 2018, **10**:2461

[4]. Fahmi H., Zachary P.D., Louis N., Sharpless K.B. *J. American. Chem. Soc*., 2003, **125**:9983

[5]. Avaji P.G., Kumar C.H.V., Patil S.A. *Eur. J. Med. Chem*., 2009, **44**:3552

[6]. Zang Y., Zang L., Liu L. *Chim. Acta*., 2010, **363**:289

[7]. Lima L.M., Frattani F.S., Dos Santos J.L. *Eur. J. Med. Chem*., **43**:348

[8]. Bhaskar V.H., Mohite P.B., Pandhare R.B. *Acta Pharm. Sci*., 2010, **52**:504

[9]. Mamdouh A.S., Samy B.S., Said H.K. *Der Pharma Chemica*, 2012, **4**:1064

[10]. Shukla S., Srivastava R.S., Shrivastava S.K., Sodhi A.P.K. *Med Chem Res*., 2013, **22**:1604

[11]. AL-Rawi M.S., Hassan H.A., Hassan D.F., *Orient. J. Chem*., 2018, **34**:2826

[12]. Hutham M.Y., Al-Labban, *Research J. Pharm. and Tech*., 2017, **10**:3645

[13]. Muna S., Al-Rawi, Hussei A.F., Al-Taie M.M., Al-Halbosiy, Hameed B.A. *IOP Conf. Series: Journal of Physics:Conf. Series*., 2018, **1003**:012012

[14]. Sliverstien R.M., Websters X., *John Wiely and Sons. New York*., 1998
[15]. Suaad M.H., Lawand H.K. *Journal of Zankoi Sulaimani*, 2015, **17**:49
[16]. Basheer H.A., Ibrahim A.A., Ahmed M.S. *Swift J. Pure Appl. Chem.*, 2018, **2**:4

How to cite this manuscript: Raad M. Muhiebes*, 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