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FULL PAPER

Synthesis of new heterocyclic containing azo group from 2-N-chloro acetamido creatinine and studying their biological activity

Raed Muslim Mhaibes* | **Entesar O. Al-Tamimi**

[a]*Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq*

[b]*Department of Biochemistry, College of Medicine, University of Missan, Missan, Iraq*

The present work include synthesized new 2-amino-4-subs. thiozole(1) from reaction of 2-N-chloro acetamido Creatinine with thiourea. Compound (1) was treated with sodium nitrate and hydrochloric acid in (0-5°C) to form diazonium salt (2), then diazonium salt reacted with acetylacetone and hydrazine, phenyl hydrazine and 2,4-dinitrophenyl hydrazine to give pyrazole ring (4-6). On the other hand, diazonium salt was react with pyrrole in the presence of glacial acetic acid to form compound (7) and with different Schiff bases to produce compounds (8-9). Prepared compounds were measured by IR and melting point and some of them by ^{1}HNMR and their biological activity was studied.

***Corresponding Author:**
Raed Muslim Mhaibes
Email: Raadmuslim7@gmail.com
Tel.: +9647721014811

KEYWORDS

Thiozole; diazonium salt; azo compounds; biological activity.

Introduction

Heterocyclic compounds constitute a key component in a lot of natural products, to name a few; vitamins, hormones, alkaloids, a wide range of antibiotics, pharmaceutical products, herbicides, anti-aging medicines, and plenty other industrial products of high importance (different types of dyes, corrosion inhibitors, stabilizing agents, sensitizers, etc.) [1]. Aryl diazonium salts are easily prepared, common, and highly applicable intermediates in synthetic organic chemistry because of their high reactivity and varied reactions. They are synthesized starting from primary aromatic amines by diazotization and coupling with aromatics like phenols (or primary aromatic amines). Azo dyes are industrially very important for technical purposes. Azo compounds have many applications such as their use as antioxidants, polymeric biodegradable pro-drugs, and many of them are used in the food, cosmetics, and drug industry as synthetic colorants [2]. Pyrazoles heterocyclic compound has a five-membered ring containing two nitrogen atoms prepared by many methods, one of these methods is the condensation of hydrazine or substituted hydrazine with α, β-unsaturated carbonyl compounds [3]. Azo compounds are well known for their medicinal importance and are recognized for their applications as antifungal, antidiabetics, antineoplastics, anti-inflammatory, antiseptic [4]–[6], and other useful chemotherapeutic agents. They are involved in many biological reactions such as inhibition of DNA, RNA, carcinogenesis, protein synthesis, and nitrogen fixation [7]. Azo compounds are valuable in the medicinal and pharmaceutical fields [8].

Material and methods

In this research, all starting material and solvents that used obtained from (Sigma-

Aldrich, and Fluke Company, Germany). FT-IR spectra (KBr disc) were recorded with Affinity-1 Shimadzu as an FT-IR spectrometer using KBr pellets. ^{1}HNMR spectra scanned on Bruker Spectro spin ultrashield magnets 400 MHz instruments.

Synthesis of 1-methyl-2-(2-amino-thiazole-4-yl) amino-4-oxo-4,5-dihydro imidazoline[9](1).

A mixture of thiourea (0.01 mol, 0.76 g) and (0.005 mol, 0.94 g) of 2-N-chloro acetamido Creatinine dissolved in 100 mL of CH_3OH in the flask and refluxed for 3–4 hr. The initial product cooled then poured into cold H_2O. The solid separation was collected by filtration. The residue obtained was dried and purified by using C_2H_5OH.

Synthesis of 1-methyl-2-(2-diazenyl-2,4-dioxo-3-pentane--thiazol-3-yl)amino-4-oxo-4,5-dihydro imidazoline[10](2).

Compound [1] (0.21 g, 0.001 mmol) was dissolved in 2 mL conc. HCl. Cooled at 0 °C, then $NaNO_2$ (0.07 g, 0.001 mol) in (5 mL) of H_2O was added dropwise with stirring for 30 min. in an ice bath at 0-5 °C, then acetylacetone (0.1 g,0.001 mol), CH_3COONa(0.16 g, 0.002 mmol) in CH_3CH_2OH (5 mL) was added drop by drop. The mixture was then stirred for (30 min.). The product was purified by methanol.

Synthesis of 1-methyl-2-[(2-(3,5-dimethyl-pyrazol-4-yl)diazinyl] amino-4-oxo-4,5-dihydro imidazoline derivatives[11](4-6).

NH_2-NH_2 derivatives (0.006 mol) were added to compound [3] (0.19 g, 0.006 mol) in (10 mL) EtOH. The mixture was stirred and refluxed for (10-12 hour), then the solvent was evaporated and the product was washed with H_2O then $(C_2H_5)_2O$.

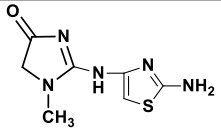
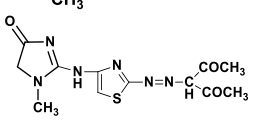
Synthesis of 1-methyl-2-(2-amino-thiazole-4-yl)amino-4-oxo4,5-dihydro imidazoline[12](7).

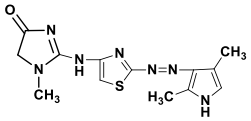
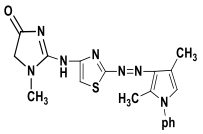
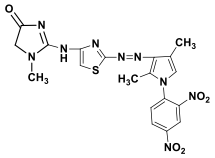
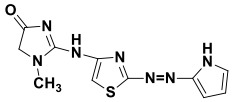
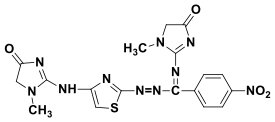
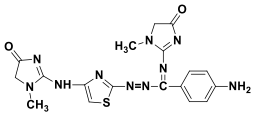
A (0.01 mole) of pyrrole was dissolved in ethanol (10 mL) and CH_3COONa (0.3 g) was added and the mixture cooled and stirred. Cold solution of ArN_2Cl salt of compound (1) was then added dropwise for 1 hr at (0-5 °C) and the mixture kept in a cold place for 3 hr and then poured into ice H_2O.

Synthesis of 1-methyl-2-[(2-(4-subs.)benzylidene] amino-1-methyl-4-oxo-4,5-dihydro imidazoline [13](8-9).

A (0.01 mol) solution of compound 1 was dissolved in 2 mL eq. HCl. It was cooled and 0.7 g of sodium nitrate was slowly added, 2-N-arylidene amino creatinine (0.01 mol) was dissolved in 10mL C_5H_5N and 0.3 g of sodium acetate was added to the mixture and then the mixture was stirred and cooled in the cold place. cold solution of ArN_2Cl salt of compound (1) was added dropwise for 1hr at (0-5 °C). The reaction mixture was kept in ice-bath for 3hr. The resulting dark-color mass was filtered, washed with H_2O until C_5H_5N removed. The product was purified from absolute CH_3CH_2OH.

TABLE 1 Some of physical properties and FT-IR spectral data $cm^{-1}$of synthesized compounds (1-9)

No.	Structure	m.p. °C	Color	Yield%	Major FT-IR Absorption Cm^{-1}								Other Bands
					ν (C=N) ν-C-N	ν (C=O) amide	ν (C-H) Aliph	ν (C-H) Arom.	ν (C=C) Arom	ν (N-H)	ν (N=N)	ν (C-S)	
1		170-172	yellow	70	1610 1384	1697	2941 2802	3050	1589 1521	3265	--	1244	ν NH_2 3346
3		210-212	yellowish	80	1631 1350	1701	2914 2810	3000	1587	3271	1546	1226	ν C=O ketone 1740

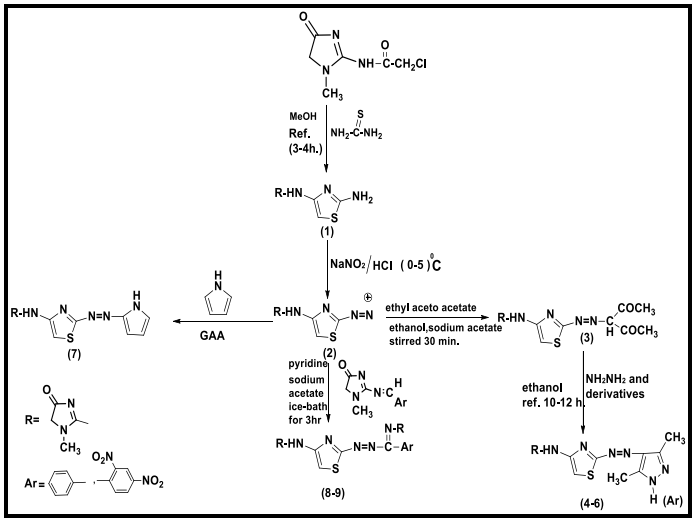
4		220-222	White	50	1669 1360	1699	2898 2799	3026	1556 1546	3230	1545	1240	--
5		256-258	Red	60	1600 1373	1658	2924 2854	3053	1560 1520	3240	1498	1251	--
6		270-272	crimson	75	1647 1384	1707	2978 2850	3060	1577 1500	3246	1487	1257	v NO_2 1490 1334
7		200-202	Red	80	1640 1350	1700	2945 2862	3050	1543 1498	3228	1440	1260	--
8		260-262	Whit	70	1658 1350	1705	2939 2850	3042	1505 1475	3200	1540	1250	v NO_2 1500 1330
9		253-255	Yellowish	65	1618 1365	1680	2976 2879	3050	1550 1470	3207	1550	1240	v NH_2 3394

Biological activity [14]

By using the agar plate diffusion method, the prepared compounds screened in vitro for two types of bacteria staphylococcus (gram-positive) and E-coli (gram-negative). Inhibition zone of bacterial growth show in Table 3.

Results and discussion

In this research, synthesis of azo-compounds from 2-N-chloro acetamido creatinine was done, as shown in the Scheme 1. The azo-derivatives of creatinine measured by IR and some derivatives by ^{1}HNMR.



SCHEME 1 Syntheses new azo-derivatives from creatinine

Synthesized compounds (1-9) were detected by spectral (FTIR & ^{1}H-NMR). In the compound (1) 1697 cm^{-1} due to amide group [15]. The ^{1}HNMR of compound (1) δppm in DMSO-d_6 solvent showed singlet signal at δ(1.15) ppm due to (-C<u>H</u>$_3$) protons, singlet

signal at δ(2.48) ppm due to (C=O-C<u>H</u>$_2$-N-CH_3) proton, singlet signal at δ(3.05) ppm due to (C<u>H</u>-S-thiazole ring) singlet signal at δ(7.13) ppm due to (creatinine ring-N<u>H</u>-thiazole ring), and a single signal at δ(4.13) ppm due to NH_2 protons of thiazole ring. The presence of the band in compound (3) at 1546 cm^{-1} indicates the formation N=N and 1740 cm^{-1} that refer to C=O of diketone. In pyrazole compounds (3-5) the absorption band in compound (5), and ^{1}HNMR for compounds 5,6, and 7 are show in Table 2.

TABLE 2 ^{1}HNMR spectral data for some synthesized derivatives

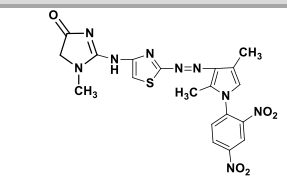
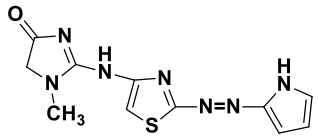
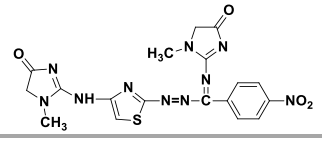
Structure	^{1}HNMR signals data,™ (ppm)
	δ 1.24 ppm (s,3H,C<u>H</u>$_3$); δ 2.27-2.52 ppm (s, 6H, C<u>H</u>$_3$ of pyrrole ring), δ 3.03 ppm (s,2H,C<u>H</u>$_2$-of creatinine ring.)), δ 4.08 ppm (s,1H,C<u>H</u>-thiazole ring)δ 7.00 ppm (s,1H, N<u>H</u> between creatinine and thiazole rings) and 7.37-8.8 ppm (m,3H,Ar-H).
	δ 1.25 ppm (s,3H,C<u>H</u>$_3$); δ 1.90 ppm (s, 2H, C<u>H</u>$_2$-CO), δ 3.71 ppm (s,1H,C<u>H</u>-thiazole ring), δ 4.80 ppm (s,1H, N<u>H</u> between creatinine and thiazole rings), δ 7.2 ppm (s, 1H, N<u>H</u> of pyrrole), and 7.31-7.64 ppm (t,3H,Ar-H of pyrrole).
	δ 1.70 ppm (s,6H,2C<u>H</u>$_3$); δ 2.30 ppm (s, 4H, 2C<u>H</u>$_2$-CO), δ 3.40 ppm (s,1H,C<u>H</u>-thiazole ring), δ 7.26 ppm (s,1H, N<u>H</u> between creatinine and thiazole rings), and 7.40-8.00 ppm (m,4H,Ar-H).

TABLE 3 Biological activity of compounds (5-9) against selected bacteria

Comp. Code	E.Coli	Staphylococcus
5	+	+
6	+++	++
7	++	+
8	++	+
9	+++	++
DMSO	--	--

Key to symbols inhibition Zone
Inactive = (-)<6 mm
Slightly active = (+) = 6-9 mm
Moderately active = (++) 9-12 mm
Highly active = (+++) 13-17 mm
Conc. = 10^{-3}

Conclusion

The prepared compounds were measured by using (FT-IR and ^{1}HNMR). The biological studies of the new azo compounds showed inhibitory effects on two types of bacteria, Staphylococcus aureus and Escherichia coli. Regarding Staphylococcus aureus, compounds No. 6 and 9 showed moderate inhibition, while compounds No. 5,7 and 8 exhibited slight inhibitory effect. On the other hand, the growth of E Coli was highly inhibited by the compounds No. 6 and 9 and moderately inhibited by compounds No. 7 and 8 and only slightly inhibited by the compound No. 5. In conclusion, the results of the current study demonstrated that these prepared compounds have good efficacy against the tested bacteria.

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Orcid:

Raad M. Muhiebes:

https://www.orcid.org/0000-0002-4835-0873

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