Synthesis and Characterization of New Oxo-Aztedine ,Imidazoldine and Thiazolidine Rings on Creatinine and Evaluation of their Biological Activity

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Abstract

This work included preparation of new imine from the reaction of creatinine with aldehydes (4-nitro benzaldehyde, 4- amino benzaldehyde, cinnamaldehyde) and ketone (acetophenone) in ethanol and the presence of few drops glacial CH_3COOH to obtain Schiff bases (1a,1b,1c,1d) Schiff bases were treated with monochloroacetyl chloride to produced (2a,2b,2c,2d), with glycine to synthesis (3a,3b,3c,3d) and with 2-mercaptoacetic acid to prepare (4a,4b,4c,4d). The Prepared compounds had beenmeasured by (FT-IR,and^{1}HNMR) spectroscopic techniques. Some of the derivatives were studied activity against antibacterial, antifungal and antioxidant.

Keyword : *Schiff bases,β-lactam, Oxo imidazolidine, thiazolidine derivatives .*

Introduction

Schiff bases are the compounds containing (–C=N–) asa functional group.They are a condensation products of ^{0}1 amines with C=O compounds, these compounds were first reported by Hugo Schiff [1-3]. Schiff bases have also been reported to have a broad range of biological activities, like antifungal, antibacterial, antimalarial, anti-inflammatory, antiviral, and antipyretic properties [4]. Heterocyclic compounds containing four and five-member rings have given industrial and medical reasons. Azetidinone derivatives are one of these compounds, they represent an important commonly known as b- lactam, due to their antibacterial, antifungal,anti-tubercular,antianthelminic, and enzymatic activity[5]. Furthermore they found to inhibit cholesterol absorption[6]. The imidazoles are an important class of heterocyclic and many naturally occurring imidazoles are known to possess biological activity, anti-fungal, anti-bacterial, anti anthelmintic, anti-neoplastic, antipyreticand anti-spasmolytic activities[7]. On the other hand thiadiazole, fused heterocyclic ring compounds have many biological activities as antimicrobial activity [8],anti-inflammatory[9].

Materials and Methods

All initial chemicals necessary for Schiff bases preparation were obtained from Fluka, Sigma- Aldrich, Alfa Aesar, Japan and BDH used without further purification. The stuart melting point apparater was used to measure melting points. IR Affinity-1 Shimadzu as KBr disc, results are given in cm^{-1}, ^{1}HNMR BrukerSpectro spin ultrashield magnets 300 MHz instruments, using DMSO-d_6 solvent.

Schiff bases[10] (1a, 1b, 1c, and 1d) preparation procedure

Schiff bases were prepared by the reaction of creatinine (0.113g, 0.001 mol) with variable aldehydes and ketone (0.001 mol), in30 ml EtOH and few drops of glacial acetic acid. This mixture was refluxed for (10-12hrs). The excess solvent was evaporated and the formed product was recrystallized from absolute C_2H_5OH. Physical properties are listed in Table1.

Synthesis of azitidine-2-oxo derivatives [11] (2a, 2b, 2c and 2d)

Schiff base (1a,1b,1c, and 1d) solution (0.003mol) in (25 ml) THF was quantify poured into the mixture of $ClCH_2COCl$ (0.34 g, 0.004 mol) and TEA (0.56 g,0.004 mol).Solutions was well mixed at (0-5ºC), then the reaction was conducted for (6-8) hrsat room temperature. The mixturethen kept for additional 2 days in the sealed containers at RT., after that the mixture was poured in a container with ice to obtain the compound in a solid form. The products were filtered and washed by distilled water then dried and recrystallized. Table 1show the physical properties of the newly generated compound.

Synthesis of 4-oxo- imidazoldine derivatives[12] (3a,3b,3c and 3d)

A mixture of Schiff base (1a,1b,1c and 1d) (0.001 mol),glycine (a-amino acetic acid),(0.07g, 0.001mol) in (25ml)ethanol and few drops DMF was refluxed for (20h.),the excess solvent was evaporated. The solid product was collected and recrystallized from absolute CH_3CH_2OH. Physical properties are listed in Table 1.

Synthesis of4- oxo-thiazolidine derivatives [13] (4a, 4b, 4c and 4d)

To a mixture of Schiff bases (1a,1b,1c and 1d) (0.002 mol) and 2-mercaptoacetic acid (0.92g, 0.01 mol) dissolved in DMF (25 ml), anhydrous $ZnCl_2$ (0.21g, 0.0016 mol) was added and refluxed for (18-20 hrs). The reaction mixture was then poured into crushed ice, filtered and washed with water, dried, and recrystallized from absoluteethanol. Physical properties are listed in Table l.

Biological Activity[14]

Using the culture media called Muller-Hinton for determination of the biological effectiveness of the following material (2a to 4d) on ranges of isolated microorganism(Bacteria and Fungi). After being dissolved, Muller-Hinton was sterilized by using autoclave (121^0C for 15 min.) and poured onto petri-dishes (plate-count).Once Muller-hinton and been left to solidify and to be ready for use, the specific microorganism were used in this study. Then 0.1 mm had been added to the material mentioned in the middle of the plates contaminated previously with bacteria or fungi to determine the biological effects of each material. After then the plates were incubated with a particular incubator (37^0C for 24hur.)the inhibition zones were seen clearly after 24hr, for bacterial and 48hr.for fungi incubation on each plate-count. However, these zones were differed according to material in addition to isolated microorganisms used on each Petri dish. The result of all tested compound is listed in table (3) .

Results & Discussion

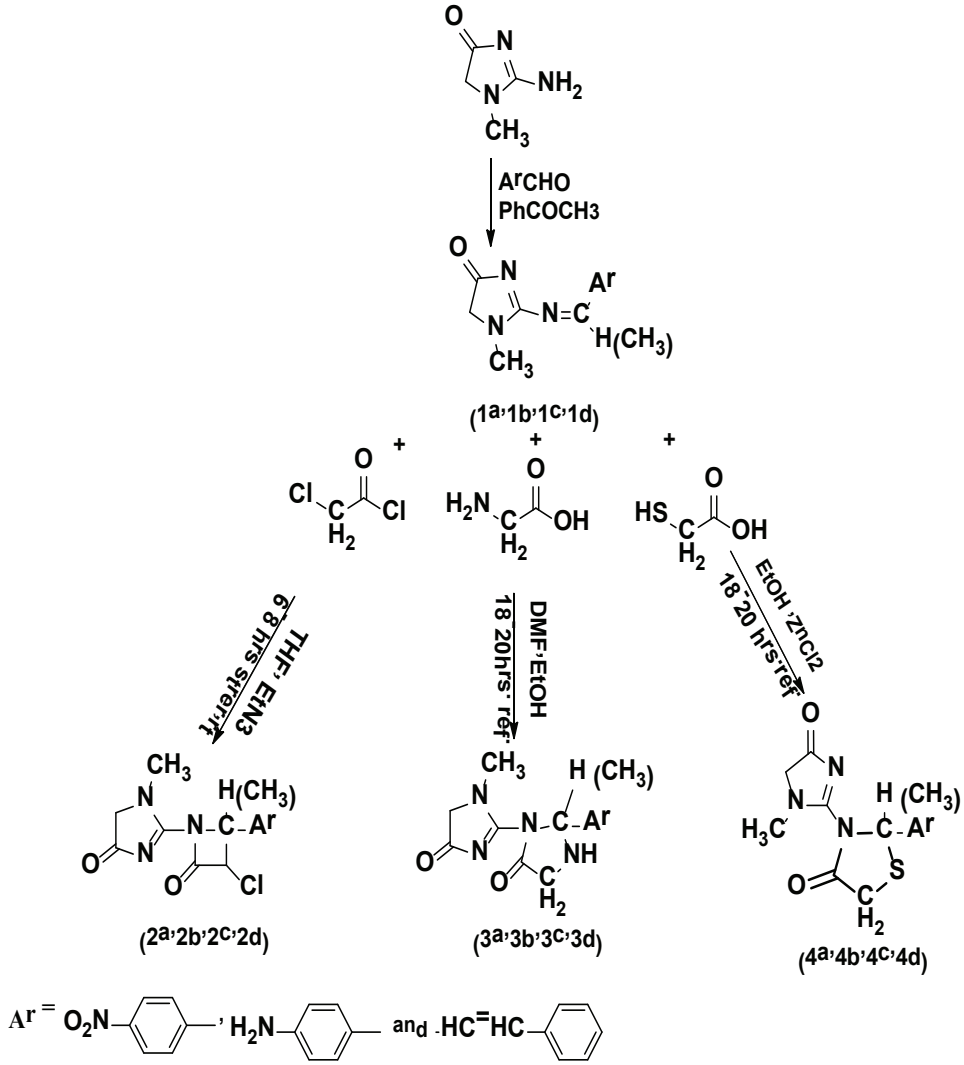
Table 1: Some physical properties and FT-IR spectral data $cm^{-1}$of synthesized creatinine derivatives (1a-4d)

No. Com	m.p.0C	Color	Yield%			Major FT-IR Absorption Cm-1				
				v (C=N) v-C-N	v (C=O) amide	v (C-H) Aliph	v (C-H) Arom.	v (C=C) Arom	v (C-H) olfin.	v (C=O) lactam
1a	220-222	Off-white	90	1666 1421	1707	2848 2941	3060	1589 1521	1600	-
1b	230-232	Brown	88	1622 1419	1689	2925 2866	3022	1570 1500	1622	-
1c	182-184	Bile yellow	75	1669 1417	1699	2898 2799	3026	1556 1546	1637 1622	-
1d	180-182	White	80	1670 1419	1700	2923 2810	3035	1591 1504	-	-

Cont... **Table 1: Some physical properties and FT-IR spectral data cm^{-1} of synthesized creatinine derivatives (1a-4d)**

2a	178-176	Green	70	- 1435	1651	2941 2802	3060	1577 1500	-	1718
2b	204-206	Brown	65	- 1433	1633	2976 2877	3062	1558 1475	-	1732
2c	152-154	Brown	60	- 1417	1700	2939 2802	3042	1505 1475	1558	1739
2d	222-224	Yellow	70	- 1400	1627	2978 2850	3064	1558 1475	-	1710
3a	160-162	Orange	90	1672 1415	1755 1714	2918 2850	3080	1598 1521	-	-
3b	122-124	Brown	65	1597 1411	1693 1662	2931 2883	3022	1597 1508	-	-
3c	88-90	Yellow	75	1639 1415	1668 1639	2902 2800	3028	1595 1550	1494	-
3d	196-198	White	80	1670 1419	1750 1689	2900 2806	3024	1593 1500	-	-
4a	170-172	White	60	- 1413	1708 1755	2931 2796	3050	1577 1490	-	-
4b	180-182	Yellow	55	- 1406	1700 1670	2983 2816	3080	1544 1490	-	-
4c	175-177	Yellow	50	- 1417	1745 1680	2924 2852	3045	1579 1492	1430 1417	-
4d	186-188	Off white	45	- 1415	1732 1701	2922 2852	3035	1575 1506	-	-

Characterization of all the derivatives was carried out by FTIR and some of others was done by ^{1}H-NMR Scheme (1) showed different organic compounds contained heterocyclic rings from imins derivatives.



Scheme1: Synthesis of substance heterocyclic on creatinine

The derivative compounds (1a,1b,1c, and 1d) prepared from the reaction of (4-nitrobenzaldehyde,4-amino benzaldehyde, and cinnamaldehyde) and acetophenone with Creatinine in the presence of glacial acetic acid, characterized first by the actionof them with 2,4-DNPH to give (-$_V$e) test, theactionshowed disappearance of the C=O group. Table (2) show IR spectral data of these derivatives, it reveals the disappearance of the absorption band υNH_2 and its appearance at (1670-1622) cm^{-1} due C=N group[15].

The heterocyclic compounds that contain azitidine-2-oxo ring (2a, 2b, 2c, and 2d) synthesized from the reaction between chloroacetylchloride and (1a,1b,1c, and 1d) derivatives in triethylamine, the IR showed demies absorption band of azomethane group and appearance bands to the C=O group, NMR for some derivatives show appear the chemical shift to (CH proton) in b-lactam ring and (CH proton) fused with chlorine[16], the ^{1}H-NMR spectrum for compound (2b) show appear signals δ 1.2 ppm (s,3H, CH_3);δ 3.0ppm (s, 2H, CH_2-NH) and δ 3.8 ppm (s,1H, -N-C=O-CH-CI), δ 4.25 ppm (s,2H, -NH_2-Ar), and δ 7.2-7.75 ppm (m, 4H, Arm.). ^{1}HNMR spectrum for (2c) shows signals listed in Table (2).

4-oxo- imidazoldine derivatives (3a,3b,3c, and 3d) prepared from the reaction of glycine with Schiff base(1a,1b,1c, and 1d) in absolute ethanol, FTIR spectral data of these derivatives list in Table (2).The

^{1}H-NMR spectrum for compound (3a) δ 2.9 ppm (s,3H,-CH_3); δ 3.04ppm (d, 2H, Ar-CH-NH-CH_2) ,δ 3.7 ppm (s,2H, CH_3-N-CH_2), δ 4.0 ppm (s, 1H,CH_2-NH-CH); δ 7.72-8.1 ppm (m, 4H, Arom.) and δ 8.25ppm (s, 1H, NH-CH_2). (^{1}HNMR spectrum for (3c and 3d) show signals listed in Table (2).

4- oxo-thiazolidine derivatives (4a, 4b, 4c, and 4d) was prepared from adding 2-mercbtoacitic acid to derivatives of Schiff base(1a,1b,1c, and 1d) with anhydrous $ZnCl_2$, table (1) showed the IR spectra data for these derivatives, the spectrum of IR show disappearance (–N=C-) group and appear the absorption bands at (1732-1708) cm^{-1} due to carbonyl group, ^{1}H-NMR used to characterization for some of the derivatives show appear signals due to CH_2 and C=O groups in thiazolidinone ring, the ^{1}H-NMR spectrum for derivative (4a) appear signals 3.08 ppm (s, 3H, CH_2NCH_3); δ 3.20 ppm(s,2H, CH_2NCH_3),δ 3.72 ppm (s,2H, C=O-CH_2-S); δ 4.2 ppm (s, 1H, N-CH-Ar) and δ .2-7.5 ppm (d,4H, Arom) while derivative (4b and 4d) are listed in the table (2)

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

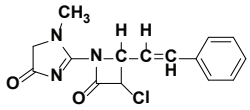
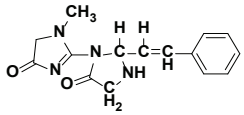
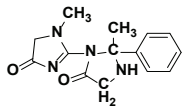
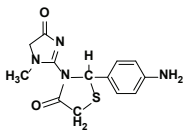
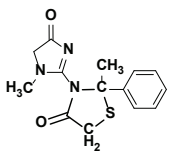
Structure	^{1}HNMR signals data,δ (ppm)
	δ 1.2 ppm (s,3H,C<u>H</u>$_3$); δ 3.35ppm (s, 2H, C<u>H</u>$_2$-NH) and δ 3.64 ppm (s,1H,-N-C=O-C<u>H</u>-Cl), δ 4.3-4.5 ppm (d,2H,Ar -CH=C<u>H</u>$_2$aliph.) and δ 7.2-7.6 ppm (m, 5H, Arom.)
	δ 2.94 ppm (s, 3H,CH_2-N-C<u>H</u>$_3$); δ 3.36ppm (s, 2H,-C=O- NH-C<u>H</u>$_2$) ,δ 3.64 ppm (s,2H, CH_3-N-C<u>H</u>$_2$), 6.9 ppm (d,2H,Ar -CH=C<u>H</u>$_2$aliph.) δ 7.16-8.0 ppm (m, 5H, Arom.) and δ 8.4ppm (s, 1H, N<u>H</u>-CH_2).
	δ 2.93ppm(s,3H,N-C(C<u>H</u>$_3$)-Ar;δ 3.69 ppm (s, 3H,CH_2-N-C<u>H</u>$_3$); δ 2.80ppm (s, 2H,-C=O- NH-C<u>H</u>$_2$) ,δ 3.44 ppm (s,2H, CH_3-N-C<u>H</u>$_2$), 7.46-7.60 ppm (m,5H,Arom.)and δ 8.0ppm (s, 1H, N<u>H</u>-CH_2).
	2.96 ppm (s, 3H,CH_2NC<u>H</u>$_3$); δ 3.45 ppm(s,2H, C<u>H</u>$_2$NCH$_3$), δ 3.63 ppm (s,2H, C=O-C<u>H</u>$_2$-S); δ 4.01 ppm (s, 1H, N-C<u>H</u>-Ar), δ 4.70 ppm (s, 2H, N<u>H</u>$_2$-Ar) and δ7.2-8.4 ppm (m,4H, Arom.).
	1.8 ppm (s, 3H,Ar-C-C<u>H</u>$_3$); 3.15 ppm (s, 3H,CH_2NC<u>H</u>$_3$); δ 3.61ppm (s, 2H,-C=O-C<u>H</u>$_2$- N-CH_3) ,δ 3.90 ppm (s,2H, C=O-C<u>H</u>$_2$-S); and δ7.0-8.45 ppm (m,4H, Arom.).

Table 3: Antibacterial and antifungal activity of some synthesized derivatives

Compound Code	Staphylococcus	E.Coli	Asp.flavous
2a	++	++	+
2b	+++	+++	++
2d	++++	---	---
3a	---	---	---
3c	++++	++++	+++
4a	+++	+++	+++
4b	++	++	---
4c	++++	++++	++++
DMSO	---	---	---

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

Conclusions

The prepared compounds were confirmed by using spectroscopic techniques(FT-IR and ^{1}HNMR). The biochemical studies revealed that the new aztedine , imidazoldine and thiazolidine caused activator effects on two types of bacteria Staphylococcus aureus and Escherichia coli.and one type of fungiAspergillusflavous. The organisms Staphylococcus aureus,Escherichia coli and Aspergillusflavousshow very high activity toward the compounds (2a, 2b, 2d,3c,and4c) .

Ethical Clearance : Taken from University of Baghdad ethical committee

Source of Funding : Self

Conflict of Interest : Nil

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