

Synthesis, Characterization and Evaluation of Antimicrobial Activity of Few New Heterocyclic Compounds Derived from Nicotinic Acid

Abbas H. Sakhil*, Rasmia M. Rumez

Department of Chemistry, College of Education for Pure Science, Ibn-Al-Haitham, University of Baghdad, Baghdad, Iraq

Received: 12th June, 2022; Revised: 09th August, 2022; Accepted: 20th August, 2022; Available Online: 25th September, 2022

ABSTRACT

New schiff bases series (VIII) a-e and 1,3-thiazolidin-4-one derivatives (IX) a-e containing the 1,2,4-triazole and 1,3,4-thiazazole rings were synthesized and screening their biological activities. These compounds were identified *via* Fourier transform infrared (FT-IR) spectra, some *via* Proton nuclear magnetic resonance (¹H-NMR) and mass spectra. The biological results indicated that all of these compounds did not reveal antibacterial effectiveness against (*Escherichia coli* and *Klebsiella* species) (G-). Some of these compounds showed moderate antibacterial activity against (*Staphylococcus aureus*, and *Staphylococcus epidermidis*) (G+), and all compounds exhibited moderate activity against *Candida albicans*.

Keywords: 1,3-Thiazolidin-4-one, Nicotinic acid, Schiff base, Triazole, Thiadiazole.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.08

How to cite this article: Sakhil, AH, Rumez, RM, Synthesis. Characterization and Evaluation of Antimicrobial Activity of Few New Heterocyclic Compounds Derived from Nicotinic Acid. Journal of Drug Delivery Technology. 2022;12(3):970-976.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Triazole is a heterocyclic aromatic compound that has recently received considerable attention due to its biological activities.¹ Bladin in 1855 was first use the name “triazole” for describing the carbon-nitrogen ring system C₂H₃N₃.² Two isomeric forms like 1,2,3-triazole and 1,2,4-triazole for triazole ring.³ The researchers attention of 1,2,4-triazole due to its wide spectrum of biological effectiveness like antiviral,⁴ antiparasitic,⁴ antimicrobial,^{5,6} antimigrain,^{7,8} anti-inflammatory,^{6,9} anticancer,^{10,11} antioxidant,¹² anticonvulsant¹³ and anti-urease.¹⁴

Thiadiazoles are kind of azole compounds and five-membered heterocyclic compounds containing two nitrogen atoms with sulfur atom. Aromatic ring due to the presence of two double bonds; the Hantzsch-Widman nomenclature using for the name thiadiazole.¹⁵ Derivatives of thiadiazole are four isomeric forms: 1,2,3-thiadiazole; 1,2,4-thiadiazole; 1,2,5-thiadiazole; and 1,3,4-thiadiazole. Derivatives of 1,3,4-thiadiazole show the most important therapeutic ability.¹⁶ These derivatives exhibited a broad range of therapeutic effectiveness such as antimycobacterial,¹⁷ antifungal,¹⁸ antimicrobial,¹⁹ antipsychotic,²⁰ analgesic,²¹ anti-inflammatory,²¹ anti-leishmanial,²² antidepressant,²³ anticonvulsant.^{24,25} In many published studies, derivatives of 1,3,4-thiadiazole revealed the antitumor activity.

Schiff bases named after Hugo Schiff (1864), a German Scientist, are formed when primary amine reacts with ketones or aldehydes under specified mole ratio and conditions. The functional group for these compounds are imine or azomethine

(-C=N-), referred to as products of condensation of primary amines with carbonyl compounds.²⁶

Schiff bases are significant kind of the most widely used organic compounds and possess many applications such as biological, inorganic chemistry, analytical, medicinal and as fine chemicals.²⁷ The important and interesting roles of schiff bases are as intermediates in the biologically important transmutation reactions. In schiff bases, the C=N bond is main for molecular interactions, as some schiff bases have been reported to possess anticancer, antimalarial, antibacterial, and antifungal activity.^{28,29}

Thiazolidinones are derivatives of ketone and they called thiazolidin due to containing saturated form of thiazol. They described as a heterogeneous pentagonal ring containing of five members including one sulfur atom and one nitrogen.³⁰ Thiazolidinones showed a wide range of biological effectiveness³¹ like antimicrobial,³² antitumor,³³ antidiabetic,³⁴ anti-inflammatory,³⁵ and analgesic.³⁵

EXPERIMENT

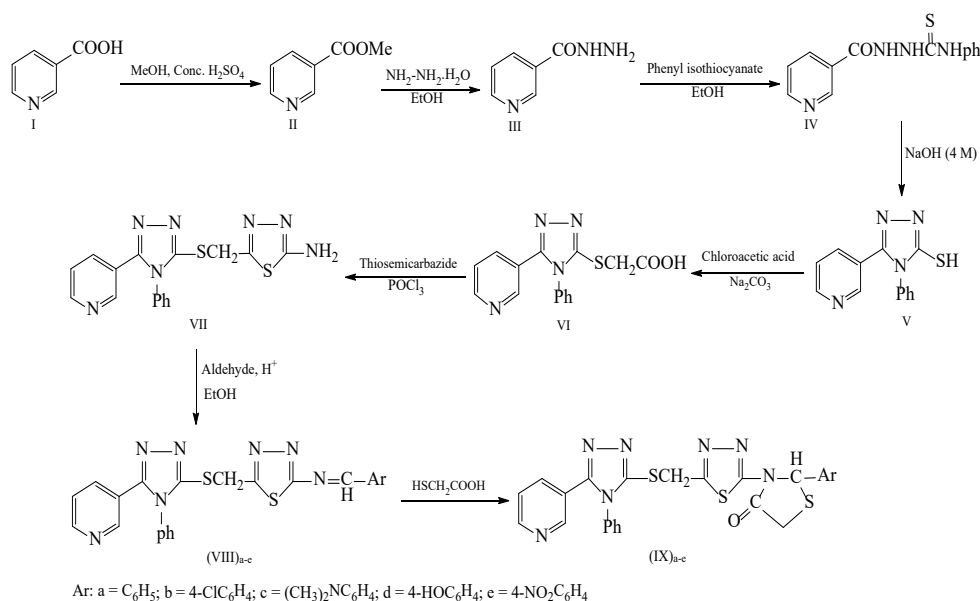
Materials

All chemicals were supplied by Sigma-aldrich, Merck, Fluka, and BDH companies.

Instruments

Melting points were recorded by Digimelt MPA 161 (MSRS) electronic. Fourier transform infrared (FT-IR) spectra were

*Author for Correspondence: Abbas.hasan1205a@ihcoedu.uobaghdad.edu.iq



Scheme 1: Scheme for prepared compounds

recorded at Ibn-Sina company *via* using Shimadzu FT-IR-8400S spectrophotometer. Mass spectroscopy were carried out *via* Agilent mass spectrometer model 5975C VL MSD at the University of Tehran, Iran. ¹H-NMR (500 MHz) spectra were recorded in DMSO-*d*₆ on Bruker BioSpin GmbH, University of Kashan, Iran. Biological activity for synthesized compounds estimated for antibacterial activity against (*Escherichia coli* and *Klebsiella species*) and (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and antifungal activity against (*Candida albicans*) in Department of Biology, College of Science, Al-Mustansiriyah University.

Synthesis of Methyl Nicotinate (II)³⁶

Add conc. H₂SO₄ (1 mL) to a solution of nicotinic acid (I) (1.23 g, 10 mmol) in absolute methanol (30 mL), and the mixture was heated for 24 hours. Concentrated, the reaction mixture after cooling under reduced pressure, Add (NaHCO₃) solution (20 mL, 10%, w/v), then extracted the ester with (CHCl₃) (2×15 mL). Dried the combined extract *via* (MgSO₄), filtered, concentrated under reduced pressure to give methyl nicotinate (II), (64%) as a white crystalline, m.p. (38–42°C), lit. (38–43°C).

Synthesis of Pyridine-3-carbohydrazide (III)³⁶

A mixture of the ester (II) (1.37 g, 10 mmol) & hydrazine hydrate (N₂H₄·H₂O) (80%) (50 mmol) in (C₂H₅OH) abs. ethanol (30 mL), was reflux a period 24 hours. The product of reaction was concentrated under reduced pressure and left over night. Filtered and washed with ethyl alcohol the white needle crystalline to yield nicotinic acid hydrazide (III), (68%), m.p. (162–164°C), lit. (159–161°C).

Synthesis of 2-nicotinoyl-*N*-phenylhydrazine-1-carbothioamide (IV)³⁷

A mixture of nicotinic acid hydrazide (III) (1.37 g, 10 mmol) and phenyl isothiocyanate (1.2 mL, 10 mmol) was heated in

abs. Ethyl alcohol (30 mL) for 12 hours cooled the solution and a white solid appeared. Filtered the obtained precipitate and recrystallized from abs. ethyl alcohol to give the thiosemicarbazide (IV), 60%; m.p. (188–190°C).

Synthesis of 4-phenyl-5-(pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol (V)³⁷

A solution of thiosemicarbazide (IV) (2.72 g, 10 mmol) in 100 mL of NaOH (4 mol L⁻¹) was heated for 12 hours cooled the resulting solution to (r. t.) and acidified with dilute HCl (1:1) to (pH=3). Filtered the precipitate formed, washed with (d. w.) and recrystallized from abs. ethyl alcohol to afford the white solid of triazole (V), 60%; m.p. (222–224°C).

Synthesis of 2-((4-phenyl-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid (VI)³⁸

Triazole (V), (2.54 g, 10 mmol) with (2.12 g, 20 mmol) anhydrous sodium carbonate in (30 mL) of distilled water as a solvent were heated, then (0.95 g, 10 mmol) of chloroacetic acid was added. The solution was refluxed for 3 hours. After cooling, acidified the solution used conc. Hydrochloric acid to (pH=2). Filtered the product and washed with distilled (H₂O) and recrystallized from absolute ethanol to give (VI), a white powder, (95%), m.p. (238–240°C).

Synthesis of 5-(((4-phenyl-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-amine (VII)³⁹

Added phosphorus oxychloride (15 mL) to a mixture of (NH₂CSNHNH₂) thiosemicarbazide (0.91 g, 10 mmol) and compound (VI) (3.12 g, 10 mmol). Heated the mixture at (90–100°C) a period 6 hours. Added the ice-cold water to the reaction medium and neutralized the mixture to pH 7 by adding the dropwise of NaOH solution (50%) with stirring. Filtered the precipitate, washed with distilled (H₂O) and recrystallization by using absolute ethanol to yield the amine (VII) as a brown solid, (40%), (m.p.190–194°C).

Antimicrobial Activity of New Heterocyclic Compounds Derived from Nicotinic Acid

Table 1: Nomenclature and physical properties for Schiff bases (VIII)_{a-e}

Compound no.	Nomenclature	Molecular formula	M. wt. (g/mole)	M. P. (°C)	Weight (g)	Yield%	Color
(VIII) _a	1-phenyl-N-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)methanimine	C ₂₃ H ₁₇ N ₇ S ₂	455	110–113	0.3	62	Deep brown
(VIII) _b	1-(4-chlorophenyl)-N-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)methanimine	C ₂₃ H ₁₆ ClN ₇ S ₂	490	114–116	0.4	82	Light brown
(VIII) _c	<i>N,N</i> -dimethyl-4-(((5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)imino)methyl)aniline	C ₂₅ H ₂₂ N ₈ S ₂	498	133–137	0.3	60	brown
(VIII) _d	4-(((5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol	C ₂₃ H ₁₇ N ₇ OS ₂	471	75–80	0.4	85	brown
(VIII) _e	1-(4-nitrophenyl)-N-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)methanimine	C ₂₃ H ₁₆ N ₈ O ₂ S ₂	500	85–90	0.3	60	Light brown

Table 2: Nomenclature and physical properties for 1,3-thiazolidin-4-one (IX)_{a-e}

Compound no.	Nomenclature	Molecular formula	M. wt. (g/mole)	M. P. (°C)	Weight (g)	Yield%	Color
(IX) _a	2-phenyl-3-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one	C ₂₅ H ₁₉ N ₇ OS ₃	529	240–242	0.12	46	Brown
(IX) _b	2-(4-chlorophenyl)-3-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one	C ₂₅ H ₁₈ ClN ₇ OS ₃	564	Oil	0.14	50	Brown
(IX) _c	2-(4-(dimethylamino)phenyl)-3-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one	C ₂₇ H ₂₄ N ₈ OS ₃	572	250–255	0.12	41	Deep brown
(IX) _d	2-(4-hydroxyphenyl)-3-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one	C ₂₅ H ₁₉ N ₇ O ₂ S ₃	545	246–248	0.14	52	Light brown
(IX) _e	2-(4-nitrophenyl)-3-(5-(((4-phenyl-5-(pyridin-3-yl)-4 <i>H</i> -1,2,4-triazol-3-yl)thio)methyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one	C ₂₅ H ₁₈ N ₈ O ₃ S ₃	574	210–215	0.2	70	brown

Table 3: FTIR spectra data (wave number $\hat{\nu}$) cm⁻¹ of the compounds (II-V)

Compound no.	$\nu(N-H)$, $\nu(N-H_2)$	$\nu(C-H)$ Aro.	$\nu(S-H)$ Triazole ring	$\nu(C=O)$ Est.	$\nu(C=O)$ Amide	$\nu(C=C)$ Aro.	$\nu(C=S)$	Others
II	-	3055, 3008	-	1728	-	1585	-	$\nu(C-H)$ = 2954, 2850 Ali.
III	3321, 3205, 3155	3012	-	-	1674	1597	-	-
IV	3163	3105	-	-	1681	1593	1130	-
V	3101	3070, 3024	2561	-	-	1577	1195	$\nu(C=N)$ = 1627, 1593 Triazole ring

Table 4: FTIR spectra data (wave number ν) cm^{-1} of the Schiff bases (VIII)_{a-e}

Compound No.	$\nu(\text{C-H})$ Aro.	$\nu(\text{C-H})$ Ali.	$\nu(\text{C=N})$	$\nu(\text{C=N})$ Triazole ring	$\nu(\text{C=N})$ Thiadiazole ring	$\nu(\text{C=C})$ Aro.	Others
(VIII) _a	3101	2927, 2785	1701	1593	1577	1543	-
(VIII) _b	3055	2978, 2846	1685	1593	1573	1554	$\nu(\text{C-Cl})$ Aro. = 1091
(VIII) _c	3055	2931	1697	1597	1546	1496	-
(VIII) _d	3101, 3070, 3024	2927, 2819	1681	1597	1581	1543	$\nu(\text{O-H})$ = 3383
(VIII) _e	3105, 3078, 3032	2912, 2769	1705	1597	1577	1546	$\nu(\text{NO}_2)$ Asy. = 1519 $\nu(\text{NO}_2)$ Sy. = 1342

Table 5: FTIR spectra data (wave number ν) cm^{-1} of the thiazolidinone derivatives (IX)_{a-e}

Compound no.	$\nu(\text{C-H})$ Aro.	$\nu(\text{C-H})$ Ali.	$\nu(\text{C=O})$ Lactam ring	$\nu(\text{C=N})$ Triazole ring	$\nu(\text{C=N})$ Thiadiazole ring	$\nu(\text{C=C})$ Aro.	Others
(IX) _a	3062	2927	1720	1593	1570	1539	-
(IX) _b	3066	2920, 2870	1697	1597	1554	1496	$\nu(\text{C-Cl})$ Aro. = 1045
(IX) _c	3062	2927	1716	1597	1573	1543	-
(IX) _d	3062	2927	1716	1597	1543	1496	$\nu(\text{O-H})$ = 3410
(IX) _e	3105, 3043	2927, 2850	1708	1600	overlap	1436	$\nu(\text{NO}_2)$ Asy. = 1527 $\nu(\text{NO}_2)$ Sy. = 1340

Synthesis of Schiff bases (VIII)_{a-e}⁴⁰

A mixture of compound (VII) (1 mmol) with an aldehyde (1 mmol) in abs. EtOH (10 mL) and 3 drops of glacial acetic acid was heated for (24) hours. Evaporated the solvent, collected the solid and recrystallized by using absolute ethanol to afford the Schiff bases (VIII)_{a-e}. The physical properties and nomenclature for synthesized Schiff bases are given in Table 1.

Synthesis of 1,3-thiazolidin-4-one derivatives (IX)_{a-e}⁴¹

To a Schiff bases (VIII)_{a-e} (0.5 mmol) in benzene (20 mL) was added slowly mercaptoacetic acid (0.1 mL, 1 mmol). Then left the mixture reaction refluxing with continuous stirring for 24 hours in the water bath. The solid was filtered, washed with distilled (H_2O) and recrystallized with abs ethanol. The nomenclature and physical properties for synthesized 1,3-thiazolidin-4-one derivatives are given in Table 2.

Biological Evaluation

Synthesized compounds have been screened for antibacterial activities using agar well diffusion method.⁴² The compounds were screened for antibacterial activity against (*E. coli* and *Klebsiella* species) and (*S. aureus* and *S. epidermidis*) and antifungal activity against (*C. albicans*) in Muller Hinton agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 6 mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (0.01 M) were placed serially in the cavities with the help of a micropipette and allowed to diffuse for 1-hour. DMSO was used as a solvent for all the compounds and as a control. These plates were incubated at 37°C for 24 hours for antibacterial activities and at 25°C for 5 days for antifungal activities. The zone of inhibition observed around the cups after respective incubation was measured in mm.

RESULTS AND DISCUSSION

The aim of the present study is a synthesis of new heterocyclic compounds starting from nicotinic acid, Scheme (I), which is converted to ester (methyl nicotinate) by reaction of nicotinic acid (I) with absolute methanol in the presence of concentrated H_2SO_4 . The ester was characterized by FT-IR spectrum and melting point which exhibited the absorption band at (1728 cm^{-1}) due to the carbonyl group (C=O) of ester. Methyl nicotinate (II) reacted with an excess of hydrazine hydrate (80%) in abs. ethanol to give acid hydrazide (III). Acid hydrazide (III) was characterized by melting point and FT-IR spectrum, which exhibited the absorption peaks at (3321 cm^{-1}) belong to (N-H), ($3205, 3155 \text{ cm}^{-1}$) for (NH_2) and (1674 cm^{-1}) due to (C=O) of amide. Acid hydrazide (III) treatment with phenyl isothiocyanate in abs. ethanol to give thiosemicarbazide (IV). Thiosemicarbazide (IV) was identified by melting point and FT-IR spectrum. The FTIR spectrum revealed absorption bands at (3163 cm^{-1}) for (N-H) groups, (1681 cm^{-1}) for (C=O) amide and (1130 cm^{-1}) for (C=S).

Triazole (V) was prepared from cyclization of compound (IV) by using NaOH (4M). The structure of triazole (V) was confirmed by melting point, FT-IR, $^1\text{H-NMR}$ and mass spectra. The FT-IR spectrum exhibited the absorption bands at (3101 cm^{-1}) for (NH) tautomer, (2561 cm^{-1}) for (S-H), (1627 and 1593 cm^{-1}) for (2C=N) of triazole ring and (1095 cm^{-1}) for (C=S) tautomer. The $^1\text{H-NMR}$ spectrum for compound (V) showed the following signals: singlet signal at (4.52) ppm for proton of (S-H) group, multiplet signals at (7.30–8.60) ppm for aromatic proton and singlet signal at (11.1) ppm for proton of (N-H) tautomer. The mass spectrum of compound (5) revealed molecular ion [M^+], $m/z = 254$. The characteristic FT-IR spectra data for the compounds (II-V) were shown in Table 3.

Compound (VI) was prepared from triazole (V) reaction with chloroacetic acid in distilled water as a solvent in basic

Table 6: $^1\text{H-NMR}$ data for the Schiff bases (VIII)_b, (VIII)_c, (VIII)_e and thiazolidinone derivatives (IX)_a, (IX)_b measured in DMSO- d_6 and chemical shift in ppm (δ)

Compound no.	Functional group	δ (ppm)
(VIII) _b	DMSO	2.39–2.50
	H ₂ O	3.19–3.37
	s, 2H, S-CH ₂	4.40
	m, 9H, aromatic	7.23–7.58
	s, 1H, HC=N	7.72
	d-d, 4H, aromatic	8.52–8.59
(VIII) _c	DMSO	2.38–2.65
	H ₂ O	3.35
	s, 6H, 2CH ₃	3.06
	s, 2H, S-CH ₂	4.31
	m, 9H, aromatic	6.51–7.70
	d-d, 4H, aromatic	8.59
(VIII) _e	DMSO	2.51
	H ₂ O	3.20–3.35
	s, 2H, S-CH ₂	4.89
	m, 9H, aromatic	6.59–8.17
	d-d, 4H, aromatic	8.27–8.59
	s, 1H, HC=N	8.87
(IX) _a	DMSO	2.51
	H ₂ O	3.36
	s, 2H, S-CH ₂	3.63
	s, 2H, CH ₂ CO	4.81
	s, 1H, HC-S	4.90
	m, 9H, aromatic	7.21–7.96
(IX) _b	DMSO	2.51
	H ₂ O	3.36
	s, 2H, S-CH ₂	3.64
	s, 2H, CH ₂ CO	4.39
	s, 1H, HC-S	4.62
	m, 9H, aromatic	7.44–7.76
d-d, 4H, aromatic	8.57–8.60	

medium. Compound (VI) was characterized by melting point, FT-IR and $^1\text{H-NMR}$ spectra. The FT-IR spectrum for compound (VI) showed the following stretching vibration bands: (3100-2542) cm^{-1} due to (OH) group, (3043 cm^{-1}) belong to (C-H) aromatic, (2951, 2810) for (C-H) aliphatic and (1716 cm^{-1}) belong to carbonyl group (C=O) of carboxylic acid and disappearance the peak at (2561) cm^{-1} for (S-H). The $^1\text{H-NMR}$ spectrum in DMSO- d_6 for compound (VI) revealed the following signals: singlet signal at (4.09) ppm for two proton of CH₂, multiplet signals at (7.40–8.66) ppm for aromatic protons and singlet signal at (12.99) ppm for proton of carboxylic acid.

Table 7: The inhibition zone of antibacterial activity for some synthesized compounds

Compound no.	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>E. coli</i>	<i>K. species</i>
DMSO	-	-	-	-
(IX) _e	13	-	-	-
(VIII) _d	14	12	-	-
(IX) _d	12	14	-	-
(VIII) _e	-	18	-	-
VII	-	13	-	-
V	-	-	-	-

Note: Slight activity = (5–10) mm, Moderate activity = (11–15) mm, High activity = (15 and more than 15) mm

Table 8: The inhibition zone (mm) of anti-fungal activity for some synthesized compounds

Compound no.	<i>C. albicans</i>
DMSO	-
(IX) _e	12
(VIII) _d	12
(IX) _d	12
(VIII) _e	13
VII	12
V	11

Compound (VI) reacted with (NH₂CSNHNH₂) thiosemicarbazide in the entity of POCl₃ under reflux for 6 hours led to the formation of amine (VII). Amine (VII) was identified by melting point, FT-IR, $^1\text{H-NMR}$ and mass spectra. The FT-IR spectrum of amine (VII) showed the following absorption bands: at (3417, 3275) cm^{-1} due to (NH₂) group, (3055) cm^{-1} for (C-H) aromatic, (2920, 2850) cm^{-1} for aliphatic (C-H), (1597) cm^{-1} for (C=N) and (1573) cm^{-1} for (C=C) aromatic. The $^1\text{H-NMR}$ spectrum in DMSO- d_6 for amine (VII) exhibited the following signals: singlet signal at δ (4.38) ppm belong to two proton of CH₂, singlet signal at δ (7.17) ppm due to two proton of NH₂, multiplet signal at δ (7.41–8.60) ppm for the aromatic protons. The mass spectrum of amine (VII) showed molecular ion [M⁺-4], m/z = 372.

The new schiff bases were synthesized by refluxing equimolar of aldehyde with amine (VII) in abs. EtOH with few drops of (G.A.A.) glacial acetic acid. These new compounds were confirmed by measurement melting points, FT-IR spectra and $^1\text{H-NMR}$ spectra for some schiff bases and the mass spectrum for schiff base (VIII)_e. The FT-IR spectra for schiff bases (VIII)_{a-e} revealed the stretching vibration bands at (1701, 1685, 1697, 1681, 1705) cm^{-1} belong to (C=N) azomethine group and the disappearance of absorption bands at (3417, 3275) cm^{-1} due to (NH₂) group. The characteristic FT-IR spectra data of schiff bases (VIII)_{a-e} were illustrated in Table 4 and the $^1\text{H-NMR}$ data for compounds [(VIII)_b, (VIII)_c and (VIII)_e] were given in Table 4. The mass spectrum of schiff base (VIII)_e showed the molecular ion [M⁺-26], m/z = 474.

Thiazolidinone derivatives (IX)_{a-e} were synthesized by refluxing of schiff bases (VIII)_{a-e} with mercaptoacetic acid in

the presence of benzene as a solvent. The thiazolidinone derivatives were recognized by FT-IR, ¹H-NMR spectra and melting points for derivatives [(IX)_a and (IX)_b] and the mass spectrum for compound (IX)_c. The FT-IR spectra for thiazolidinone derivatives (IX)_{a-c} showed the following stretching vibration bands at (1720, 1697, 1716, 1708) cm⁻¹ for belong to (C=O) of lactam ring and disappearance of the absorption bands at (1701, 1685, 1697, 1681, 1705) cm⁻¹ belong to (C=N) azomethine group for schiff bases (VIII)_{a-c}. The characteristic FT-IR spectra data of thiazolidinone derivatives (IX)_{a-c} were listed in Table 5 and the ¹H-NMR data for compounds [(IX)_a and (IX)_b] were shown in Table 6. The mass spectrum of thiazolidinone (IX)_c revealed the molecular ion [M⁺-100], m/z = 474.

Antibacterial Activity

The results of antibacterial activities of some synthesized compounds for four microorganisms (*S. aureus*, *S. epidermidis* and *E. coli*, *Klebsiella* species) were shown in Table 7 where the inhibition zone measured in (mm) millimeters. The DMSO was used as control. All tested compounds didn't show any antibacterial activity against (*E. coli* and *Klebsiella* species) (G-). For *S. aureus*, compounds (VIII)_d, (IX)_d, (IX)_e showed moderate antibacterial activity against *S. aureus*, while compounds (V, VII, VIII)_c didn't show any activity towards this bacteria. Finally the tested compounds (V, VII, VIII)_d, (IX)_d, (IX)_e exhibited moderate activity towards *S. epidermidis* except for compound (VIII)_c revealed high activity.

Antifungal Activity

The prepared compounds were tested for their antifungal efficiency versus *C. albicans*. The cultured results against the growth of the fungi was listed in Table 8. All tested compounds exhibited moderate activity against *C. albicans*.

CONCLUSION

The biological results indicated that all of these compounds did not reveal antibacterial effectiveness against (*Escherichia coli* and *Klebsiella* species) (G-). Some of these compounds showed moderate antibacterial activity against (*Staphylococcus aureus*, and *Staphylococcus epidermidis*) (G+), and all compounds exhibited moderate activity against *Candida albicans*.

ACKNOWLEDGMENT

The authors extend their thanks and appreciation to the Baghdad University - [College of Education for Pure Science, Ibn Al-Haitham] - Department of Chemistry for supporting and assisting us in completing this research.

REFERENCES

1. Antunes MM, Amarante TR, Valente AA, Almeida Paz FA, Gonçalves IS, Pillinger M. A Linear Trinuclear Oxidodiperiodomolybdenum (VI) Complex with Single Triazole Bridges: Catalytic Activity in Epoxidation, Alcoholysis, and Acetalization Reactions. *ChemCatChem*. 2018 Jul 9;10(13):2782-91.
2. Jacob JH, Irshaid FI, Al-Soud YA, Al-Balushi AM, Al-Arqan HR. Synthesis, characterization and evaluation of antibacterial activity of six novel 1, 2, 4-triazole derivatives against standard and medical bacteria. *Adv Stud Biol*. 2013;5(6):303-18.
3. Potts KT. The Chemistry of 1, 2, 4-Triazoles. *Chemical reviews*. 1961 Apr 1;61(2):87-127.
4. Asif M. Antiviral and antiparasitic activities of various substituted triazole derivatives: A mini review. *Chemistry International*. 2015;1(2):71-80.
5. Gupta AK, Prachand S, Patel A, Jain S. Synthesis of some 4-amino-5-(substituted-phenyl)-4H-[1, 2, 4] triazole-3-thiol derivatives and antifungal activity. *Int. J. Pharm. Life Sci*. 2012 Jul;3(7):1848-57.
6. Al-Omar, MA, Al-Abdullah, ES, Shehata, IA Habib, EE, Ibrahim, TM and El-Emam, AA, (2010). Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles and related derivatives. *Molecules*, 15, 2526-2550.
7. Zhou, HC and Wang, Y (2012). Recent researches in triazole compounds as medicinal drugs. *Curr. Med. Chem.*, 19(2), 239-280.
8. Millson, D and Tepper, S, (2000). Migraine pharmacotherapy with oral triptans: a rational approach to clinical management. *Expert. Opin. Pharmacother*. 1(3), 391-404.
9. El-Serwy, WS, Mohamed, NA, Abbas, E M and Abdel-Rahman, RF, (2013). Synthesis and anti-inflammatory properties of novel 1,2,4-triazole derivatives. *Res. Chem. Inter. Med.*, 39(6), 2543-2554.
10. Goss, PE, (1998). Pre-clinical and clinical review of vorozole, a new third generation aromatase inhibitor. *Breast. Cancer Res. Treat.*, 49(1), S59-65.
11. Park, BK, Kitteringham, NR, Maggs, JL, Pirmohamed, M and Williams, DP, (2005). The role of metabolic activation in drug-induced hepatotoxicity. *Annu. Rev. Pharmacol. Toxicol.*, 45, 177-202.
12. Sancak, K, Unver, Y, Unluer, D, Dugdu, E, Kor, G, Celic, F and Birinci, E, (2012). Synthesis, characterization, and antioxidant activities of new tri-substituted triazoles. *Turk J. Chem.*, 36, 457-466.
13. Bektas, H, Ceylan, S, Demirba, N, Alpay-Karaoglu, S and Sokmen, B B, (2013). Antimicrobial and antiurease activities of newly synthesized morpholine derivatives containing an azole nucleus. *Med. Chem. Res.*, 22(8), 3629-3639.
14. Plech, T, Kapron, B, Luszczki, JJ, Wujec, M, Paneth, A, Siwek, A, and Nowak, G, (2014). Studies on the anticonvulsant activity and influence on GABA-ergic neurotransmission of 1,2,4-triazole-3-thione-based compounds. *Molecules*, 19(8), 11279-11299.
15. Sahu, S, Sahu, T, Kalyani, G and Gidwani, B, (2021). Synthesis and evaluation of antimicrobial activity of 1,3,4-thiadiazole analogues for potential scaffold. *J. Pharmacopuncture*, 24, 32-40.
16. Kalidhar, U and Kau, A, (2011). 1,3,4-Thiadiazole derivatives and their biological activities: A Review. *Res. J. Pharm. Biol. Chem. Sci.*, 2, 1091-1106.
17. Kolavi, G, Hegde, V, Khazi, IA, Gadad, P, (2005). Synthesis and evaluation of antitubercular activity of imidazo [2,1-b] [1,3,4] thiadiazole derivatives. *Bioorg. Med. Chem.*, 14, 3069-3080.
18. Chen, CJ, Song, BA, Yang, S, Xu, GF, Bhadury, PS, Jin, LH, Hu, DY, Li, ZQ, Liu, F, Xue, W, Lu, P and Chen, Z, (2007). Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3, 4-oxadiazole derivatives. *Bioorg. Med. Chem.*, 15(12), 3981-3989.
19. Foroumadi, A, Solani, F, Moshafi, MH, Ashraf-Askari, R, (2003). Synthesis and in vitro antibacterial activity of some N-(5-

- aryl-1,3,4-thiadiazole-2-yl) piperazinyl quinolone derivatives. *Farmaco.*, 58, 1023-1028.
20. Kaur, H, Kumar, S, Vishwakarma, P, Sharma, M, Saxena, KK. and Kumar, A, (2010). Synthesis and antipsychotic and anticonvulsant activity of some new substituted oxa/thiadiazolylazetidinyll/thiazolidinonylcarbazoles. *Eur. J. Med. Chem.*, 45, 2777-2783.
 21. Hafez, HN, Hegab, MI, Ahmed-Farag, IS, El-Gazzar, ABA, (2008). A facile regioselective synthesis of novel spiro-thioxanthene and spiro-xanthene-9', 2-[1,3,4] thiadiazole derivatives as potential analgesic and anti-inflammatory agents. *Bioorg. Med. Chem. Lett.*, 18, 4538-4543.
 22. Poorrajab, F, Ardestani, SK, Emami S, Behrouzi-Fardmoghadam, M, Shafiee, A and Foroumadi, A, (2009). Nitroimidazolyl-1,3,4-thiadiazole-based anti-leishmanial agents: Synthesis and in vitro biological evaluation. *Eur. J. Med. Chem.*, 44, 1758-1762.
 23. Yusuf, M, Khan, RA and Ahmed, B (2008). Syntheses and antidepressant activity of 5-amino-1, 3, 4-thiadiazole-2-thiol imines and thiobenzyl derivatives. *Bioorg. Med. Chem.*, 16, 8029-8034.
 24. Jatav, V., Mishra, P., Kashaw, S. and Stables, J. P., (2008). CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1, 3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. *Eur. J. Med. Chem.*, 43, 1945-1954.
 25. Yar, MS and Akhter MW, (2009). Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives. *Acta Polon. Pharm.*, 66, 393-397.
 26. Ndahi, NP and Nasiru, YP, (2012). Complexes of Cobalt (II), Nickel (II) and Zinc (II) with Schiff bases derived from 4-anisaldehyde. *Int. J. Pharm. Sci. Res.*, 3(12), 5116-5120.
 27. Gangani, BJ, Parsania, PH, (2014). Ultrasonic speed and related acoustical parameters of symmetric double Schiff bases solutions at 308.15K. *J. Chem. Pharm. Res.*, 6(11), 243-247.
 28. Sridha, SK, Saravan, M and Ramesh, A, (2001). Synthesis and antibacterial screening of hydrazones Schiff and Mannich bases of isatin derivatives. *Eur. J. Med. Chem.*, 36, 615-623.
 29. Raman, N, Kulandaisamy, A and Thangaraja, C, (2003). Redox and antimicrobial studies of transition metal (II) tetradentate Schiff base complexes. *J. Trans. Met. Chem.*, 28, 29-36.
 30. Magtoof, ZR and Magtoof, MS, (2019). Synthesis and characterization of some 4- substituted thiazolidinone derivatives. *Int. J. Pharm. Qua. Ass.*, 10(4), 631-636.
 31. Sharma, D, Bansal, KK, Sharma, A, Pathak, M and Sharma, PC, (2019). A Brief literature and review of patents on thiazole related derivatives. *Curr. Bioact. Compd.*, 15, 304-315.
 32. Pucci, MJ, Bronson, JJ, Barrett, JF, DenBleyker, KL, Discotto, LF, Fung-Tomc, JC and Ueda, Y, (2004). evaluation of nocardiacins, a thiazole peptide class of antibiotics. *Antimicrobial Agents Chemother.*, 48, 3697-3701.
 33. Morigi, R, Locatelli, A, Leoni, A and Rambaldi, M, (2015). Recent patents on thiazole derivatives endowed with antitumor activity. *Recent Pat. Anti-Cancer Drug Discovery*, 10, 280-297.
 34. Hosseinzadeh, N, Seraj, S, Bakhshi-Dezffoli, M E, Hasani, M, Khoshneviszadeh, M, Fallah-Bonekohal, S, Abdollahi, M, Foroumadi, A and Shafiee, A, (2013). Synthesis and Antidiabetic Evaluation of Benzenesulfonamide Derivatives. *Iran J. Pharm. Res.*, 12, 325-330.
 35. Muhammad, ZA, Masaret, GS, Amin, MM and Abdallah, MA, Farghaly, TA Anti-Inflammatory, Analgesic and Anti-Ulcerogenic (2017). Activities of Novel Bis-Thiadiazoles, Bis-Thiazoles and Bis-Formazanes. *Med. Chem.*, 13, 226-238.
 36. Khalil, N. A., Ahmed, E. M., Mohamed K. O. and Zaitone, S. A., (2013). Synthesis of new nicotinic acid derivatives and their evaluation as analgesic and anti-inflammatory agents. *Chem. Pharm. Bull.*, 61(9) 933-940.
 37. Aouad, MR, Messall, M, Rezak, N, Ali AA and Lesimple, A, (2015). Synthesis and characterization of some novel 1,2,4-triazoles, 1,3,4-thiadiazoles and Schiff bases incorporating imidazole moiety as potential antimicrobial agents. *Acta Pharm.*, 65, 117-132.
 38. Yousif, SA, (2013). Synthesis of substituted (oxazepine, diazepine, tetrazde) via Schiff bases for 2-aminobenzo thiazole derivatives. *Baghdad Sci. J.*, 10(3), 736-748.
 39. Noolvi, MN, Patel, HM, Kamboj S and Cameotra, SS, (2016). Synthesis and antimicrobial evaluation of novel 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid. *Arabian J. Chem.*, 9, S1283-S1289.
 40. Samir, AH, Rumez RM and Fadhil, HA, (2017). Synthesis and characterization of some new oxazepine compounds containing 1,3,4-thiadiazole ring derived from D-erythroascorbic acid. *Int. J. App. Chem.*, 13(3), 393-407.
 41. El-masry, AH, Fahmy, HH and Abdelwahed, SHA, (2000). Synthesis and antimicrobial activity of some new benzimidazole derivatives. *Molecules*, 5, 1429-1438.
 42. Barry, AL, *The Antimicrobial Susceptibility: Test Principle and Practices.* (Len and Febiger, Philadelphia, USA), 1976 (180), *Bio Abstr*, 64, 25183 (1977).