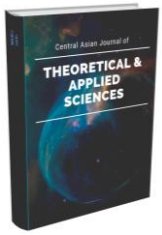

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Article

Creation of Novel Heterocyclic Compounds from (Triazole) Derivatives and Assessment of Their Biological Functions

Ali H. Alsadoon[1*]

1. Collage of Pharmacy, University of Babylon, Babylon, Iraq
* Correspondence: Alialsoud1987@gmail.com

Abstract: Heterocyclic compounds containing a 1,2,4-triazole moiety have attracted significant scientific and medical interest due to their unique structure and wide-ranging applications in drug development, organic synthesis, and chemical biology. Despite their absence in nature, triazole derivatives are integral to various disciplines, yet their potential in antibacterial and antifungal therapies remains underexplored. This study aims to synthesize novel 1,2,4-triazole derivatives by modifying the antibiotic triazole and evaluate their structural and biological properties. Characterization was performed using FTIR, H-NMR, and melting point analyses. The antibacterial activity against Staphylococcus aureus, Bacillus spp., Escherichia coli, Pseudomonas aeruginosa, and antifungal activity against Candida albicans were tested at concentrations of 250–500 mg/mL. A delayed hypersensitivity skin test confirmed their non-allergenic properties. Results demonstrated significant antimicrobial efficacy, highlighting the potential of 1,2,4-triazoles in developing novel therapeutic agents. Future research should explore their detailed mechanisms of action and broader pharmaceutical applications.

Keywords: Triazole, Heterocyclic rings, Schiff bases, Biological activity, Hypersensitivity, Imiadazoldine, β-Lactam, Oxazepine

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1. Introduction

Any substantial family of (organic chemical) compounds in which all or some of the atoms are organized in rings with at least one atom of an element other than carbon is known as a heterocyclic compound, or heterocyclic (C) compound [1]. Our survival depends on heterocyclic substances including hormones, hemoglobin, alkaloids, antibiotics, and a wide range of specifically made drugs and pigments. [2]. The majority of naturally occurring colors, vitamins, and medications, as well as the majority of hallucinogens, are heterocyclic compounds.

Schiff bases are well-known in the pharmaceutical and medical industries because they are commonly used in forensic and clinical contexts. Schiff bases have been shown to have a broad spectrum of biological effectiveness, making them effective as hypnotics, muscle relaxants, light tranquilizers, and relaxants [3]. Schiff bases are the condensation products of primary amines and energetic carbonyl groups. according to their chemical makeup, mode of operation, etc.

In recent years, a lot of attention and research has been focused on the biological properties of 1,2,4-triazole derivatives, including their diuretic, antiprotozoal, cardio tonic, fungicidal, sedative, anesthetic, antimalarial, central nervous system depressant,

hypoglycemic, anti-inflammatory, and antimicrobial activities. Given this, the current study sought to create new heterocyclic substituted 1,2,4-triazole compounds with antitubercular and antidiuretic qualities and a lower risk of side effects.[4]. The 1,2,4-triazole unit, a physiologically active molecule with a wide range of uses as an anti-cancer agent, helps the pharmaceutical and medical industries deal with the challenges of modern medicine in the aftermath of the global emergence of drug-resistant diseases. However, triazole is a well-known heterocyclic compound with five members and three nitrogen atoms. Triazole compounds are frequently used in agrochemicals like herbicides and in pharmaceuticals including antibacterial, anti-inflammatory, anticonvulsant, and anticancer drugs. [5].

Recently, medicinal chemistry has been more interested in the use of triazoles as a selective analgesic and anti-inflammatory drug. The majority of anticancer drugs work by blocking enzymes, interfering with the synthesis of proteins, RNA, or DNA, or interfering with the metabolism of other components of cells. Often, these drugs have little or no specific anticancer activity. It is frequently impossible for traditional anticancer drugs to distinguish between normal and nontumorous cells. [6], particularly with regard to the quickly proliferating cells that comprise malignancies.

Among the many cutting-edge technologies are anticancer drug prodrugs, antibody-drug conjugates, anticancer agents specific to certain (cancer) tissues, and micro-drug anticancer agents that target tumors through transporter-related mechanisms.. The antimicrobial medications were evaluated in relation to Gram-positive (G+) bacteria such as Staphylococcus aureus and Bacillus, Gram-negative (G-) bacteria such as Escherichia coli and Pseudomonas aeruginosa, and the fungus Candida albicans. Heteroatom-containing derivative inhibitors, like "N, O, and S," have been demonstrated to harm the cell walls and membranes of bacteria and fungi, changing their permeability. They can also cause growth and cell death, interfere with a cell's metabolic process, and stop cell proteins from doing their jobs. Both theory and practice have noted these consequences.. [7].

2. Materials and Methods

Chemical study: [8-9]

{S1}: produced by dissolving (0.03) moles of 2-chloro benzaldehyde in 25 milliliters of pure ethanol, adding (0.03) moles of 3-mercapto-4-amino-5 methyl-1,2,4-triazole, and aggressively stirring the mixture for 20 minutes on a magnetic stirrer at (65–70) ȣC over the course of eight hours. To create the solution for recrystallization from pure ethanol, the mixture was dried and evaporated..

{S2 } : produced by shaking continuously while dissolving (0.03) moles of {S1} in 25 milliliters of dry benzene to complete the solution. To complete the reaction in 10 hours at 65 °C, we then added 0.03 mol of phathalic anhydride gradually. The solution was dry in order for 100% ethanol to recrystallize it.

{S3} prepared by giving a solution containing 0.03 mole of {S1} dissolved in 25 milliliters of THF (tetra hydrofuran) a good shake. The "imiazoldine" derivative was then created by gradually adding 0.03 moles of glycine over the course of 15 hours at "50 C0." To use pure ethanol for recrystallization, the solution must be dry.

{S4} Dioxin was used as a solvent for eight hours at 10 °C after (0.03) mol of {S1} was dissolved in 25 ml of triethylamine and chloroacetyl chloride to create the β-Lactam derivative. To prepare the solution for recrystallization from pure ethanol, the mixture was dried and evaporated. Table 1 (Scheme 1) displays the physical properties of each target molecule [S1–S4].

NOTE : All of the resulting products were subjected to thin layer chromatography, or TLC.

Table 1. Physical properties [S1–S4] of compounds

Compounds	Color	m.p. (C^0)	Rf	Yield (%)	(TLC)
S1	**Orange**	**133-142**	**0.9**	**85%,**	Ethanol:Hexane
S2	**Brown**	**143-148**	**0.8**	**87%,**	Ethanol:Hexane
S3	**Deep Yellow**	**188-190**	**0.7**	**79%,**	Ethanol:Hexane
S4	Pale yellow	**196- 186**	**0.8**	**73%**	Ethanol:Hexane

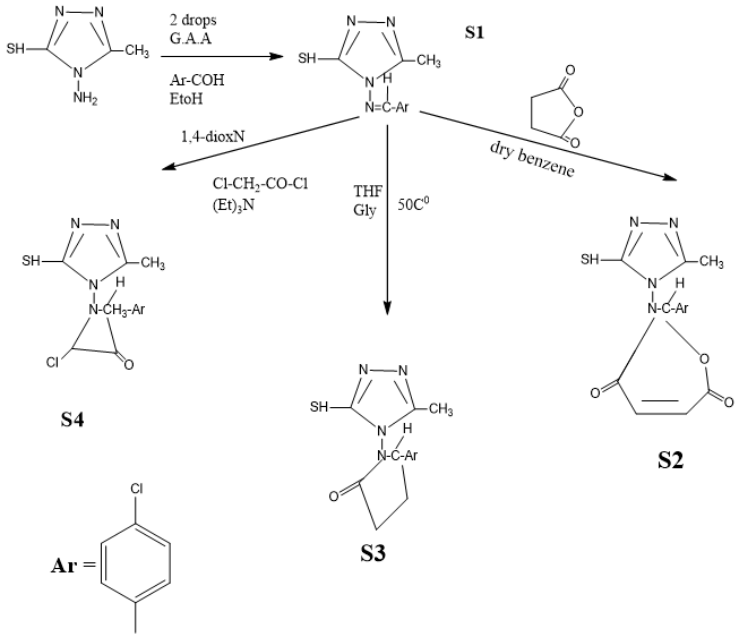

Figure 1. Pathways of chemical synthesis [S1–S4]

Microbiological study :

The antibacterial potential of the compounds (S2, S3, S4) was assessed in vitro. The pathogen panel consisted of the fungus Candida albicans, the Gram-positive bacteria Staphylococcus aureus and Bacillus, the Gram-negative bacteria Escherichia coli and Pseudomonas aeruginosa, and the agar diffusion method. Tetracycline, an antibiotic, was used to calibrate and compare the antibacterial materials. At 250, 350, and 500 mg/mL, tetracycline and the medications under study were dissolved in DMSO. Using a sterile cotton swab, 0.3 mL of bacterial inoculums were evenly distributed on a sterile Mueller Hinton Agar Petri plate for each component.

Agar, fungal, and potato dextrose agar were also utilized.. Tetracycline and tested substances at doses of 250–500 mg/mL were applied to each well (agar gel was perforated with holes 20 mm apart and with a diameter of 7 mm). The plates were incubated at "36" C0 for 24' hours in an aerobic atmosphere. After incubation, confluent bacterial growth was observed. The millimeter scale was used to express the suppression of bacterial growth. Additionally, Skin test for Delayed Hypersensitivity [10–11].

3. Results and Discussion

Spectral Investigation : [12-13]

Melting points (m.p.) and FT-IR spectroscopy were typically employed to investigate [Schiff base] (S1). A new stretching vibration, attributed to the CH=N azomethine group, appeared at 1660 cm-1, followed by a peak at 2470 cm-1, another band at 760 cm-1, attributed to the (C – Cl) group, and a peak at 3064 (C-H) aromatic, according to the FT-IR spectra. The absorption peaks of the NH2 and C=O groups also disappeared. New bands formed at 1651 cm-1 during the addition reaction (2+5) of azomethine C=N with maleic anhydrides in dry benzene, which resulted in 1,3-oxazepine (X1), due to the cyclic amid group (CO-N) in lactam. A band at 1720 cm-1 was caused by lactones, while a band at 3044 cm-1 was caused by alkenes (CH=CH). Due to the (C = O) Amide, the most characteristic FT-IR absorption band evidence for the chemical (S3) showed another band at (1612) cm-1. bands due to the (N–H) aliphatic group at 3142 cm-1 and the (C–H) aliphatic group at (2965). As per (S4), the band at (1292) was attributed to (C-N) β-Lactam, while the band at (1775) was attributed to (N-C=O).

1H-NMR spectral identification :

The 1H-NMR spectra of Compound (S1) (DMSO-d6) showed that a single proton of (CH=N) generated a strong signal at δ 8.2 ppm, whereas many signals at δ 7.82-7.76 ppm are attributed to aromatic protons. The substances (S2) displayed a singlet signal at δ 7.04 ppm for one proton of (CH-N) and a doublet signal at Ï 6.04-6.05 ppm for (2H, CH=CH) in the "1H-NMR" spectra (DMSO-d6).

Compound (S3)'s 1H-NMR spectra (DMSO-d6) revealed a singlet signal at (6.5) ppm for one proton of the (CH-N) imiadazoldine ring and twelve aromatic protons at δ 7.83-7.54 ppm. In its 1H-NMR spectra (DMSO-d6), compound (S4) showed a singlet signal for one proton of the (CH-N) β-Lactam ring at (6.4) ppm. A singlet proton signal of (S-H) was also found at 11.36 ppm.

Test for antibacterial activity and delayed hypersensitivity on the skin:

The disproportionate increase in bacterial resistance to the most widely used antibiotics in recent years has drawn attention from the public and medical organizations. Scientists and experts have therefore been looking for safer and more efficient antibiotic substitutes. as shown in Table 2. Figure 1 shows that the bacterial and fungal strains being studied in this study were inhibited by persistent compounds [S2-S4].. Gram-positive bacteria showed a greater susceptibility to all of the study's examined derivatives than Gram-negative bacteria, while compound [S4] indicated stronger antibacterial efficacy against fungal and Gram-positive/negative organisms when compared to other compounds [S2, S3].

The antibacterial activity varied according to the type of derivative chemical. [14–16]. This activity might be caused by triazole isons, which have been demonstrated to block the bacterial efflux pump. The structure of the compound [S4] includes (N, Cl, and O) atoms and a (β-Lactam) ring. The antibacterial activity of derivative compounds may originate from their ability to alter and disrupt the permeability of bacterial cell walls and membranes. or disrupt a cell's protein production, interfere with its metabolic process, and lower its activity—all of which can prevent a cell from proliferating and dying. The chemical properties of these compounds that give them their antimicrobial action dictate their antibacterial activity.

Amoxicillin and fluconazole were used as references for the antibacterial and antifungal properties, respectively. The compounds [S2-S4] seem to have strong antibacterial and weak antifungal properties [17]. Against the examined bacteria and fungi, all derivatives [S2-S4] shown antibacterial and fungal activity, which rises with compound concentration.These compounds are identified by the molecular properties that give them their antibacterial properties. Moreover, a delayed hypersensitivity skin test A

delayed type hypersensitivity test was used to ascertain how triazole compounds affected the experimental rabbit's skin (Table 2). The emergence of cellular sensitivity indicators that trigger hypersensitivity of redness, thickness, and necrosis 24 hours after injection of these substances served as a representation of the immune response.

Because these compounds are easy to use, reasonably priced, and yield vivid colors, they are frequently used to dye cotton, silk, and wool. due to the fact that they function as antigens that may be T-dependent kinds by activating Th1 and Th2. T-cells generate TNF, which acts on endothelial cells in dermal blood arteries to promote the successive production of adhesion molecules during the skin test. These chemicals activate the cell mediate immune response in animals in vivo. Erythema and indurations develop and peak 24–72 hours after these molecules infiltrate the leukocytes, mostly lymphocytes and macrophages, at the reaction site after 4 hours. The hypersensitive reactions could be difficult because the applied triazole derivatives don't go very deep into the test animals' skin. Intradermal testing may be more sensitive and accurate if different substances are used (Table 3).

Table 2. At different concentrations (250, 350, and 500 mg/ml-1), the compounds S2-S4 show inhibitory zone diameters (mm) against the growth of bacteria and fungi.

Compounds	**Concentrations (mg/ml-1)**	**Gram positive (G^{+})**		**Gram negative (G^{-})**		**Fungi**
		S. aureus	***Bacillus***	***E.coli***	***P. aeruginosa***	***Candida lbican***
X2	**250**	**23**	**12**	**20**	**15**	**14**
	350	**22**	**16**	**22**	**17**	**16**
	500	**26**	**20**	**25**	**20**	**20**
X3	**250**	**23**	**20**	**22**	**18**	**20**
	350	**26**	**22**	**23**	**20**	**22**
	500	**28**	**26**	**26**	**23**	**26**
X4	**250**	**28**	**16**	**27**	**20**	**16**
	350	**30**	**20**	**30**	**24**	**20**
	500	**35**	**22**	**32**	**30**	**23**
Amoxicillin		**21**	**20**	**18**	**12**	**----------**
Fluconazole	**----**	**-----**	**-----**	**-----**	**-----**	**23**

Table 3. Testing for chemical compound hypersensitivity in vaccinated rabbits using skin delayed type

Type of Compound	Con. (mg/ml)	Skin test \ Hours		
		24	48	72
S2	10	-	-	-
	20	E (4mm)	-	-
	30	E (9mm)	-	-
S3	10	E (8mm)	EI (8mm)	-
	20	E (10mm)	EI (10mm)	-
	30	EI (11mm)	EI (11mm)	EIN (11 mm)
S4	10	-	-	-
	20	E (7mm)	EI (7mm)	EIN (7 mm)
	30	EI (12mm)	EIN* (12mm)	EIN (12 mm)
*Reaction area (mm) with negative results for all control groups: E = erythema, I = inflammation, and N = necrosis .				

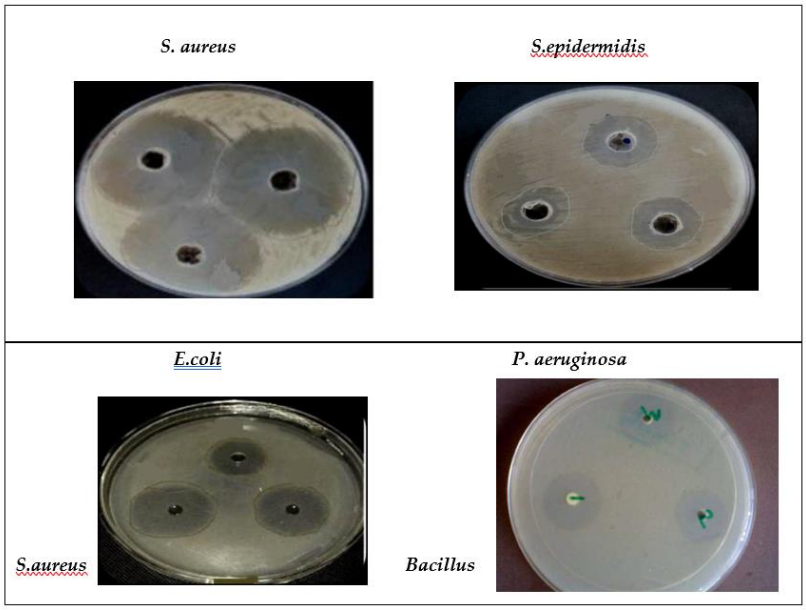

Figure 2. Antibacterial activity was measured in this study using the agar well diffusion method

Figure 3. Candida albican is susceptible to the antifungal effects of compounds S2, S3, and S4.

4. Conclusion

In conclusion, the synthesis and evaluation of novel 1,2,4-triazole derivatives in this study revealed promising antibacterial and antifungal activities, with compounds [S2-S4] showing significant efficacy against a range of bacterial strains, particularly Gram-positive bacteria, and moderate antifungal effects. The findings underscore the potential of these derivatives as alternative therapeutic agents in the face of increasing antibiotic resistance. The observed antimicrobial activity may be attributed to the structural characteristics of the compounds, such as their ability to disrupt bacterial cell membranes and interfere with cellular metabolic processes. Additionally, the compounds' non-allergenic properties, confirmed through a delayed hypersensitivity skin test, suggest their safety profile for further development. However, the antifungal activity was less pronounced compared to their antibacterial efficacy, indicating the need for further optimization of these derivatives for broader therapeutic use. Future research should focus on elucidating the precise mechanisms of action, exploring the pharmacokinetics and toxicity profiles of these compounds, and investigating their potential in combination therapies for enhanced efficacy against resistant pathogens.

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