Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Synthesis of New *β*-Lactam, Tetrazole, Thiazolidinone, and Oxazepine Compounds from Schiff Bases and Study of Their Biological Activity

Raghad AbdalrazaqIbrahem*, Shetha F. N. Al.Zobadyi

Department of Chemistry, College of Science for Women University of Baghdad, Iraq

ARTICLE INFO

Article history

Receive: 2022-05-13
Received in revised: 2022-07-07
Accepted: 2022-09-08
Manuscript ID: JMCS-2208-1635
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Ali H. Jawad Al-Taie

DOI:10.26655/JMCHEMSCI.2023.3.4

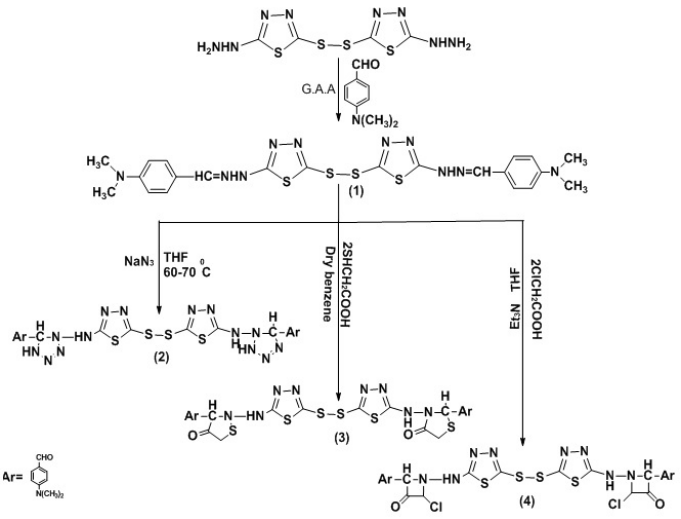
KEYWORDS

Schiff base
Tetrazole
β-lactam
thiazoleidinones
oxazepine

ABSTRACT

In this research, the first Schiff bases (**1**) were prepared from the reaction of 4-dimethyl amino benzaldehyde with hydrazine derivative in the presence of glacial acetic acid, and then, from reaction of Schiff bases (**1**) with sodium azide, mercaptoacetic acid, chloroacetyl chloride, and various anhydrides (maleic anhydride, succinic anhydride, and 3-nitro phathalic anhydride), tetrazole (**2**), thiazolidinone (**3**), β-lactam (**4**), and oxazepine compounds (**5-7**), respectively were synthesized and their physical characteristics were studied. ^{1}H-NMR and infrared spectra were used to identify the produced derivatives. Likewise, the antibacterial strains and fungi revealed the activity against Gram-positive bacteria (*Stapylococcus*), Gram-negative bacteria (*Escherichia coli*), and Gram-positive bacteria (*Candida albicans*).

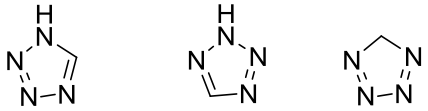
GRAPHICAL ABSTRACT



* Corresponding author: Raghad AbdalrazaqIbrahem
✉ E-mail: Email: raghd.abdulrazaq1205a@csw.uobaghdad.edu.iq

Introduction

The broadest family of organic compounds is made up of heterocyclic substances. Due to the extensive synthetic study and their utility in synthetic processes, there are currently a large number of heterocyclic compounds that are known. This number is permanently growing [1]. (-C=N) functional group exists in Schiff bases. Hugo Schiff first condensed the compound azomethine. Numerous fields, including biological chemistry, organic chemistry, and inorganic chemistry utilize azomethine extensively [2]. The initial stage in the nucleophilic addition process that creates Schiff bases is an attack by the amine nitrogen on the electrophilic carbonyl carbon of an aldehyde or ketone. This reaction results in the unstable chemical carbinolamine, which then loses its water molecule [3] due to the biological activities of Schiff bases, which are composed of four, five, and seven-membered rings, and their spectrum, which is used in many commercial and medical applications such pigments and dyes [4]. Tetrazole is a heterocyclic compound containing a carbon atom and four nitrogen atoms in a five-membered ring. Theoretically, tetrazole has 3 isomers: 1*H*-tetrazole (**1**), 2*H*-tetrazolium (**2**), and 5*H*-tetrazole (**3**) (Scheme 1) [5].



Scheme 1: Structures of the regioisomeric tetrazole rings

2-azetidine is an organic compound with a four-member ring containing different cyclic amide moieties, penicillins, and cephalosporins examples from β-lactam compounds [6].

Derivatives of 4-thiazolidinones demonstrated a broad range of biologically beneficial and pharmacological properties, including antibacterial, antioxidant, and hypoglycemic activity. Anti-fungal and anti-bacterial activity was present in the majority of 4-thiazolidinones that were produced [7]. The 1,3-oxazepine-4,7-diones ring, which has seven members, and two carbonyl groups make up the main structure. The extensive research and documentation have been done on the oxazepine synthesis over time. It is made by combining maleic, phthalic, and succinic anhydrides with Schiff base or hydrazone [8].

Materials and Methods

All ingredients and solvents were obtained from Fluka and Sigma-Aldrich. Gallen Kamp capillary melting point apparatus was used to measure the melting points. Shimadzu model FT-IR-8400S was used to take FT-IR measurements. ^{1}H-NMR spectra were collected in DMSO solution by using a Bruker spectrophotometer ultra-shield at 500 MHz by TMS as an internal standard.

*Synthesis of Schiff base compound (**1**) [9]*

4-Dimethyl amino benzaldehyde (1.77 g, 0.02 mole) with (3.5 g, 0.01 mole) of hydrazine derivative in a few drops of glacial acetic acid were mixed in absolute ethanol (40 mL). The reaction mixture was refluxed for 8 hours, and then the mixture was cooled at room temperature, filtered, recrystallized from absolute ethanol, and dried. $C_{22}H_{24}N_{10}S_4$, yellow solid, yield: 68%, mp 180-182 °C, FT-IR (KBr): 3378, 3143, 2908, 1705, 1600, 1512.

*Synthesis of tetrazole compound (**2**) [10]*

The Schiff base (**1**) (0.00149 mol, 0.8 g) was dissolved in (10 mL) of tetrahydrofuran, and then sodium azide (0. 093 g) was added. T.L.C. examined the combination after it had been heated at 60-70 °C for 9-11 hours. The reaction mixture was filtered and the formed solids were purified by using ethanol before being dried. $C_{22}H_{26}N_{16}S_4$, light green solid, yield: 47%, mp 170-172 °C, FT-IR (KBr): 3387, 3140, 2912, 1604, 1512.

*Synthesis of thiazolidinone compound (**3**) [11]*

The Schiff base (**1**) (0.00187 mol, 1 g) was dissolved in (10 mL) dried benzene, and then mercaptoacetic acid (0.053 mL) was added. T.L.C. examined the mixture after it had been refluxed for 12-14 hours. The reaction mixture was filtered, and the formed solids were recrystallized from acetone before being dried. $C_{26}H_{28}O_2N_{10}S_6$,

red solid, yield: 43%, mp 180-182 °C, FT-IR (KBr): 3387, 3132, 2900, 1720, 1519. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.2 (s, 6H, N(CH_3)$_2$), δ 3.7(s, 2H, S-CH), δ 4.1 (s, 1H, NH), δ 5.2 (s, 2H, N-$CH_{thiazolidinone}$), δ 6.5-8 (m, 8H, Ar-H).

*Synthesis of β–Lactam compound (**4**) [12]*

In 10 mL of dimethyl formamide, a Schiff base (**1**) (0.00149 mol, 0.8 g) was mixed with triethyl amine (0.5 mL), and then, at room temperature for 6-7 hours, add -chloroacetyl chloride (0.18 mL) dropwise while stirring. After being maintained at room temperature for 48 hours, the reaction mixture was put into crushed-ice water. The solid precipitate was filtered out, rinsed with water, and purified with ethanol/H_2O (1:1) before being used. $C_{26}H_{26}O_2Cl_2N_{10}S_4$, orange solid, yield: 34%, mp 200-202 °C, FT-IR (KBr): 3309, 3182, 2908, 1651, 1600, 1523.

*Synthesis of oxazepine compounds (**5, 6, 7**) [13]*

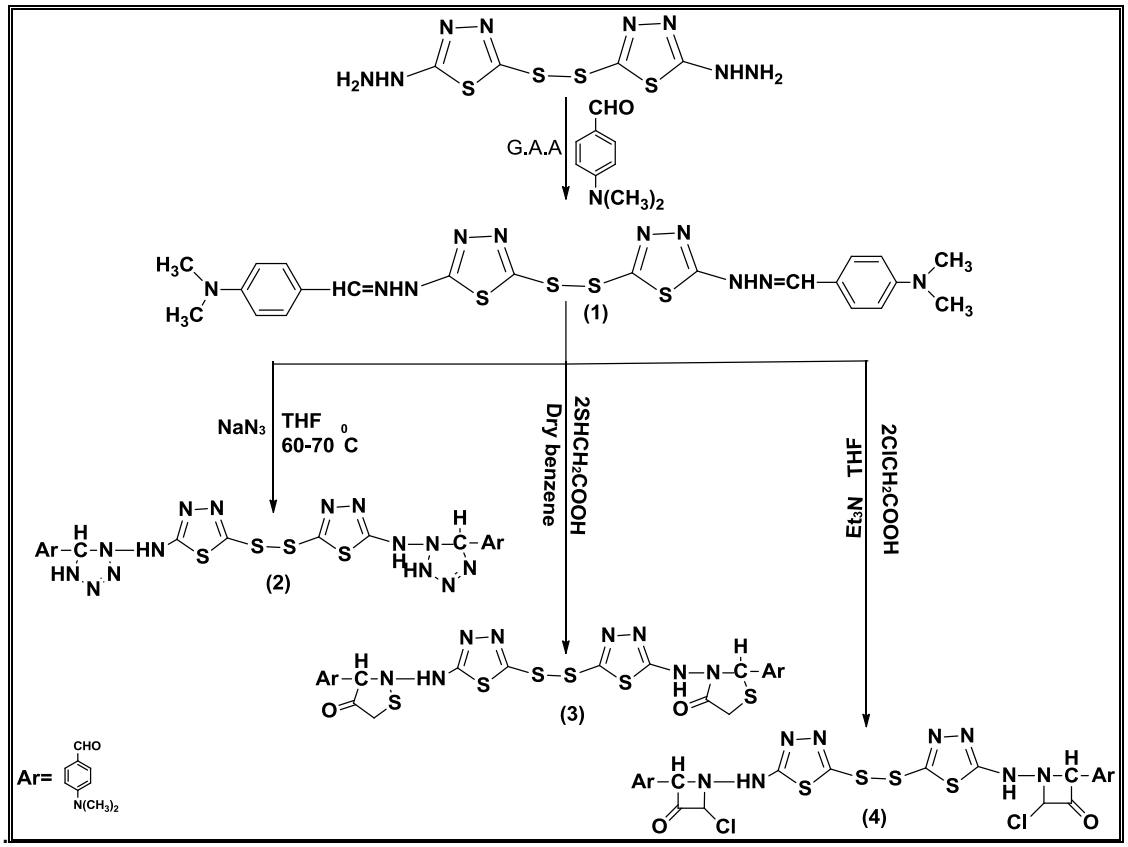
In 10 mL of dry benzene, a mixture of Schiff base (**1**) (0.00187 mol, 1 g) and 0.00187 g from various anhydrides (0.37 g) of 3-nitrophathalic anhydride, (0.2 g) of maleic anhydride, (0.2 g of succinic anhydride) was dissolved. For 5–6 hours, the mixture was refluxed. T.L.C. checked it once the reaction was finished. The reaction mixture was filtered, and the solids that resulted were recrystallization from acetone, and then took a ride. Compound **5**: $C_{39}H_{33}O_{10}N_{12}S_4$, dark red solid, yield: 39%, mp 160-162 °C, FT-IR (KBr): 3294, 3136, 2908, 1720, 1693, 1604, 1523; Compound **6**: $C_{30}H_{32}O_6N_{10}S_4$, yellow solid, yield: 42%, mp 159-161 °C, FT-IR (KBr): 3387, 3136, 2908, 1760, 1697, 1597, 1516; Compound **7:** $C_{30}H_{28}O_6N_{10}S_4$, red solid, yield: 37%, mp 152-154 °C, FT-IR (KBr): 3452, 3050, 2924, 1705, 1600, 1581, 1527. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.50 (s, 6H, N(CH_3)$_2$), δ 7.4 (s, 2H, N-CH), δ 2.99 (s, 1H, CH-N), 4.5 (s, 1H, N-NH), δ 6.7-8 (m, 14H, Ar-H).

Biological activity

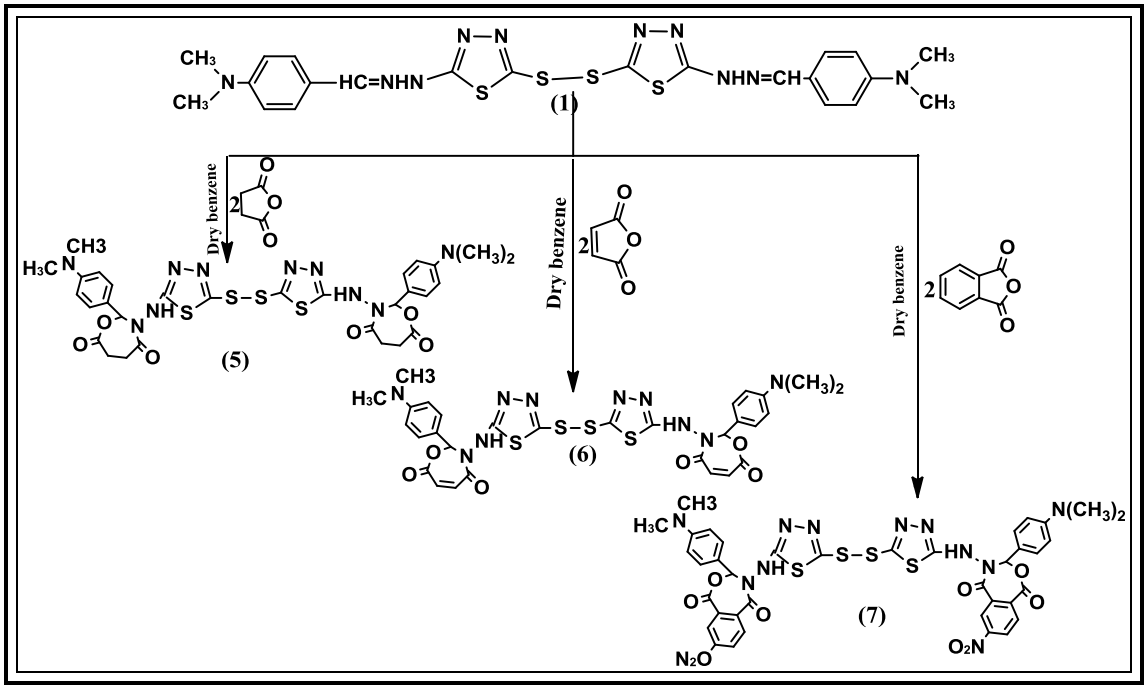
This study employed the ager well diffusion method with two different bacterial species *(St.ococcus aureus and E. coli)* and yeast species *(Candida albicans)*. By using a cork borer, five mm-diameter holes are made, with identical spaces between them for each type of pathogen. The center was then uniformly covered with (0.2 mL) of the pathogen suspension by using a cotton swap. Via a micropipette, the concentration was applied to the holes (0.2 mL) with the control hole remaining filled with DMSO and water. Thereafter, the plates were incubated in the incubator for 24 hours at 37 °C. A ruler was used to measure the diameter of the one inhibition surrounding each hole [14, 15]. Table 1 and Figure 1 display the biological activates and inhibitions of some prepared compounds.

Results and Discussion

Schiff base (**1**) was used to make new tetrazole (**2**), thiazolidinone (**3**), β-lactam (**4**), and oxazepines (**5**, **6**, **7**) from reaction of sodium azide, 2-mercpto acetic acid, chloroacetyl chloride and different anhydrides with Schiff base (**1**), as displayed in Schemes 2 and 3. Stretching vibrations band to the C=N group at 1554 cm^{-1} and absorption bands to the NH group at 3313 cm^{-1} were observed in the FT-IR spectra of compound (**1**). Stretching vibrations band to the C=O group at 1720 cm^{-1} and absorption bands to the C-H group at 2946 cm^{-1} were observed in the FT-IR spectra of compound (**3**), stretching vibrations band to the C-Cl group at 700 cm^{-1} and absorption bands to the C=O group at 1690 cm^{-1} were observed in the FT-IR spectra of compound (**4**), ^{1}H-NMR data of compound (**2**) in DMSO-d_6 as shown δ 3.00 (s, 6H, N(CH_3)$_2$), δ 3.5 (s, 1H, CH), δ 4.6 (s, 2H, N-CH), and δ 7-8 (m, 4H, Ar-H). The biological activity of compound number (**7**) will be better than all prepared compounds. The prepared compounds are depicted in Schemes 2 and 3.



Scheme 2: Synthesis of Schiff base, tetrazole, thiazolidinone, and β-lactam



Scheme 3: Synthesis of oxazepines (5,6,7)

Table 1: Biological activity for some synthesized compounds

Inhibition zone (mm)				
Gram-negative			Gram-positive	Fungi (yeast)
No. of inhibition zone	Compound No.1000 ppm	E.coli	St.coccus aureus	Candida albicans
1	3	13	10	13
2	4	19	16	16
3	5	18	20	18
Fluconazole		0	0	25
Ofoxacin		35	0	0

Figure 1: The effectiveness of compounds for inhibit bacteria (*E.coli*),(*Staphylococcus aureus*), and fungi (*Candida albicans*)

Conclusion

Various new synthesized compounds that were prepared from Schiff bases (**1**) has been characterized by FT-IR and ^{1}HNMR and some of synthesized compounds were studied for their antibacterial and antifungal activities. The results showed that had a good biological activity

Acknowledgments

Praise be to God, Lord of the worlds, and prayers and peace be upon the best of prophets and messengers. Many thanks and appreciation to prof. Shetha F. N. Al. Zobadyi for his ongoing monitoring and his precise observations during the study period.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

References

[1]. Salih A.R., Al-Messri Z.A.K., Synthesis of pyranopyrazole and pyranopyrimidine derivatives using magnesium oxide nanoparticles and evaluation as corrosion inhibitors for lubricants, *Eurasian Chemical Communications*, 2021, **3**:533 [Crossref], [Google Scholar], [Publisher]

[2]. Hameed L., Shaalan N., Synthesis, Characterization and Biological Activity Study of some New Metal Ions Complexes with Schiff's Bases Derived from Isatin With 2-Aminobenzohydrazide, *Chemical Methodologies*, 2022, **6**:137 [Crossref], [Google Scholar], [Publisher]

[3]. Wei C.X., Bian M., Gong G.H., Tetrazolium Compounds: Synthesis and Applications in

Medicine, *Molecules,* 2015, **20**:5528 [Crossref], [Google Scholar], [Publisher]

[4]. Al-Sultani K.T.A., 'Synthesis, Identification and Evaluation the Biological Activity for Some New Heterocyclic Compounds Derived from Schiff Bases', *IOSR Journal of Pharmacy and Biological Sciences*, 2017, **12**:39 [Crossref], [Publisher]

[5]. Fonkui T.Y., Ikhile M.I., Ndinteh D.T., Njobeh P.B., 'Microbial activity of some heterocyclic schiff bases and metal complexes: A review', *Tropical Journal of Pharmaceutical Research*, 2018, **17**:2507 [Crossref], [Google Scholar], [Publisher]

[6]. González-Bello C., Rodríguez D., Pernas M., Rodriguez A., Colchón E., β-Lactamase inhibitors to restore the efficacy of antibiotics against superbugs, *Journal of medicinal chemistry*, 2019, **63**:1859 [Crossref], [Google Scholar], [Publisher]

[7]. Tahlan S., Verma P.K.., Biological potential of thiazolidinedione derivatives of synthetic origin, *Chemistry Central Journal*, 2017, **11**:130 [Crossref], [Google Scholar], [Publisher]

[8]. Taha N.I., Synthesis of 1,3-Oxazepine Derivatives Derived from 2-(1H-Benzo[d][1,2,3]Triazol-1-yl) Acetohydrazide by Using Microwave Irradiation, *International Journal of Organic Chemistry*, 2017, **7**:219 [Crossref], [Publisher]

[9]. Patel N.B., Patel J.C., Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3H)-one, *Arabian Journal of Chemistry*, 2011, **4**:403 [Crossref], [Google Scholar], [Publisher]

[10]. Londhe B., Khillare S., Nalawade R., Nalawade A., 'Convenient synthesis of 2,3-diaryl-4-thiazolidinones in aqueous SDS micelles', *Journal of Applied Organometallic Chemistry*, 2021, **1**:86 [Crossref], [Publisher]

[11]. AL-Khazraji S.I.C., Ahmed L.M., Synthesis and Characterization of Some New Heterocyclic Compounds Derived from Thiosemicarbazide (A Response Surface Methodology Approach), *Chemical Methodologies*, 2022, **6**:157 [Crossref], [Google Scholar], [Publisher]

[12]. Alabady A.A., Al-Majidi S.M.H., Synthesis, characterization and evaluation molecular docking,and experimented antioxidant activity of some newchloroazetidine-2-one and diazetine-2-one derivatives from 2-phenyl-3-amino-quinazoline-4(3H)-one, *Eurasian Chemical Communication,* 2023, **5**:1 [Crossref], [Publisher].

[13]. Hamad B.K., Ahamed M.R., Synthesis of new compounds with seven rings (oxazepine) through the ring closure of Schiff bases with study of biological activity, *Eurasian Chemical Communication*, 2022, **4**:1306 [Crossref], [Google Scholar], [Publisher].

[14]. Pawar D.C., Gaikwad S.V., Kamble S.S., Gavhane, P.D., Gaikwad M.V., Dawane B.S., Design, Synthesis, Docking and Biological Study of Pyrazole-3,5-diamine Derivatives with Potent Antitubercular Activity, *Chemical Methodologies*, 2022, **6**:677 [Crossref], [Google Scholar], [Publisher]

[15]. Al Abdeen S.H.Z., Mustafa Y.F., Mutlag S.H., Synthesis and biomedical activities of novel multifunctional benzodipyrone-based derivatives, *Eurasian Chemical Communications*, 2022, **4**:938 [Crossref], [Google Scholar], [Publisher]

HOW TO CITE THIS ARTICLE

Raghad AbdalrazaqIbrahem, Shetha F. N. Al.Zobadyi. Synthesis of New β-Lactam, Tetrazole, Thiazolidinone, and Oxazepine Compounds from Schiff Bases and Study of Their Biological Activity. *J. Med. Chem. Sci*., 2023, 6(3) 480-485
http://dx.doi.org/10.26655/JMCHEMSCI.2023.3.4
URL: http://www.jmchemsci.com/article_157172.html