Synthesis and antimicrobial evaluation of Histidine Cinnamaldehyde Schiff base containing structural feature of 1, 3, 4-thiadiazole heterocyclic moiety

Doaa Mahmood Ibrahim*, Karima Fadhil Ali*, Mayada Hadi Abd_alwahab*
Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad-Iraq

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Corresponding Author email:
pharm.kar@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0002-4200-4371

Abstract:

Reaction of aqueous solution of amino acid Histidine with ethanolic solution Cinnamaldehyde to synthesize the desired Schiff base. Then, the derivative of 1, 3, 4-thiadiazole ring have been synthesized by reaction of the imine derivative with Thiosemicarbazide in presence of $POCL_3$.

The entire intermediate and final compound characterized and identified by elemental microanalysis as melting point, FT-IR spectra, 1H-NMR spectroscopy. Agar Well Diffusion method evaluated the antimicrobial activity on gram positive bacteria such as Staphylococcus aureus and Streptococcus pneumonia and gram-negative bacteria such as E coli & Acinetobacter species and also antifungal activity had been studied on one type of fungi (candida albicans).

Key words: Histidine, Schiff bases, 1, 3, 4-thiadiazole, Antimicrobial activity.

تحضير وتقييم الفعالية المضادة للميكروبات لقاعدة شيف هيستدين سينامليديهايد تحتوي على حلقة غير متجانسة 1و3و4- ثيادايازول

دعاء محمود ابراهيم*،كريمة فاضل علي*،ميادة هادي عبد الوهاب*
****الجامعة المستنصرية/كلية الصيدلة/ فرع الكيمياء الصيدلانية***

الخلاصة:

تفاعل المحلول المائي للحمض الأميني الهستيدين مع المحلول الايثانولي لسينامالديهايد لتوليف قاعدة شيف أو إيمين ، تم مشتق حلقة 1 ، 3 ، 4-ثيايازول بواسطة تفاعل مشتق الإيمين مع ثيوسيماربيسايد في وجود POCL3. كامل المركب الوسيط والنهائي يتميز ويحدد بواسطة التحليل الدقيق الأولي مثل نقطة الانصهار ، أطياف FT-IR ، التحليل الطيفي H-NMR1. قامت طريقة اكار المنتشر جيدا بتقييم النشاط المضاد للميكروبات على البكتريا الموجبة للجرام مثل المكورات العنقودية الذهبية والبكتريا العقدية الرئوية والبكتيريا سلبية الغرام مثل أنواع القولون والبكتريا Acinetobacter baumanii وأيضًا تم دراسة النشاط المضاد للفطريات على نوع واحد من الفطريات (المبيضات البيضاء).

الكلمات المفتاحية: الهستيدين ، قواعد شيف ، 1 ، 3 ، 4 - ثيايازول ، نشاط مضادات الميكروبات.

Introduction

Condensation of primary amines and aldehyde or ketones yields an imine which called Schiff base.

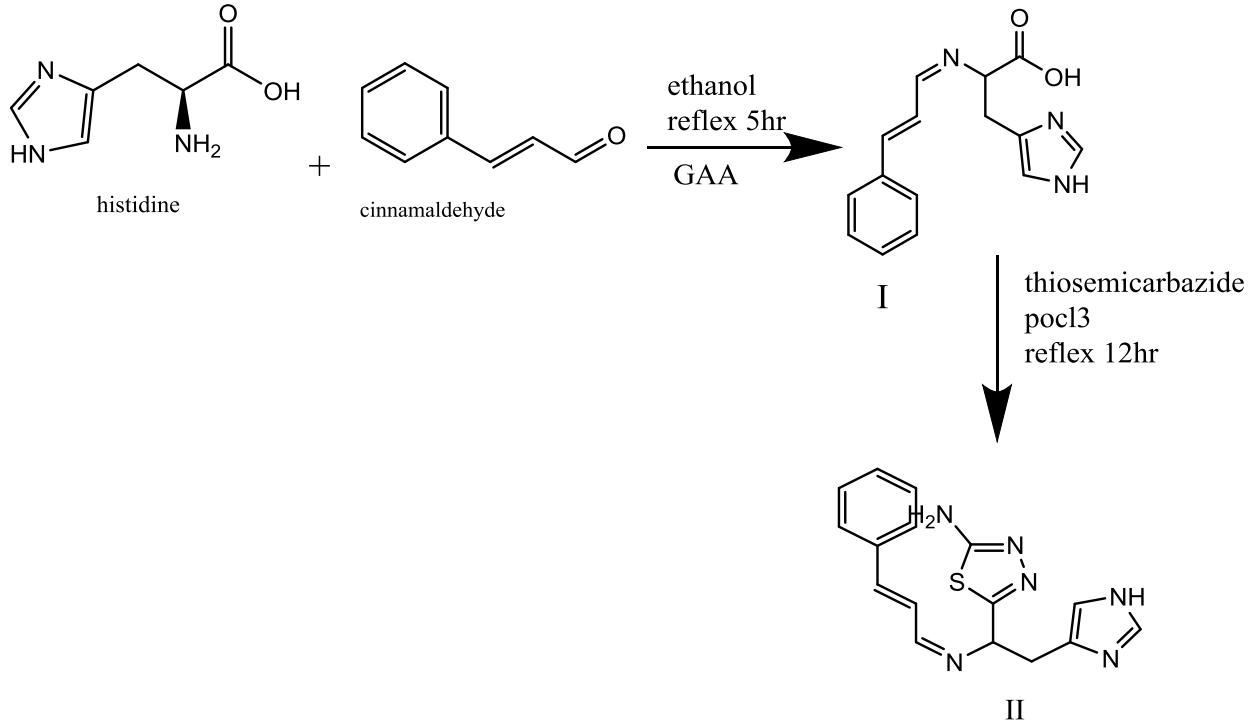
$$RNH_2 + R\text{-}COH \longrightarrow R\text{-}N{=}CH\text{-}R + H_2O$$

Wild ranges of biological activities have been achieved by Schiff bases. Heterocyclic compounds represent an important branch in pharmaceutical chemistry.

Schiff bases are used as substrates in the preparation of a numerous commercial and biologically active compounds via

condensation of carbonyl compounds with amines. The common basic feature of such compounds is the azomethine group with the general formula RHC = N-R1, where R and R1 are alkyl, alicyclic, aryl, or heterocyclic groups. Moreover, Schiff's bases display a wide range of biological activities such as antimicrobial, antifungal, antitumor, and as herbicides [1] Heterocyclic compounds consider one of the most active categories of compounds possessing a good spectrum of biological activities, as well as antibacterial drug, antifungal and different biological activities. Further, curing of infectious diseases still remains a vital and difficult downside as a result of a several factors such as rising infectious diseases and also the increasing range of multi-drug resistant microbic pathogens [2].

Cinnamaldehyde is an aromatic aldehyde and main part of bark extract of cinnamon. It's a natural antimicrobial substance for use in medicine [3]. In spite of a huge range of antibiotics and chemotherapeutics obtainable for medical use, at a similar time the emergence of previous and new antibiotic resistance created within the last decades created a considerable medical necessity for new categories of antimicrobial agents. There is a real observed need for the detection of new compounds awarded with antimicrobial activity [4]. Moreover, heterocyclic compounds having 1, 3, 4-thiadiazole ring system show antifungal, anthelmintic bacteriostatic, effect as well as depressant effect for nervous system [5].



Scheme (1): Synthesis of intermediate and final compounds

Materials and Methods

Chemicals used in this work, namely, L-Histidine, Cinnamaldehyde, Thiosemicarbazide were of analytical grade. Solvents used were dried and purified by typical methods. The melting points of the compounds were checked on a capillary melting point apparatus and were not corrected.

General procedure for Preparation of the Schiff base (I):

The Schiff base was prepared by the condensation of ethanolic solution of

Cinnamaldehyde (3.5mmole) with aqueous solution of the amino acid L-Histidine in 1:1 molar ratio using methanol\water as the reaction medium, and then it was refluxed for 6 hr. After this it was put on cooling at room temperature and the solid products were obtained. The excess solvent was removed on a rotary evaporator. It was further dried and then purified by recrystallization from methanol/water solvents [6].

3-(1H-imidazol-4-yl)-2-(((1Z,2E)-3-phenylallylidene)amino)propanoic acid was prepared by reacting Cinnamaldehyde with Histidine: color, light brown powder; yield, 70%; mp,99-101^{0}C; molecular weight found 269.12; ^{1}H NMR (DMSO-d6, δ ppm, 400MHz): 10.94 (s, 1H, COOH), 3.05 (t, 1H, N–CH–), 2.23 (d, 2H, –CH2), 7.33-8.15 (m, 6H, aromatic); Infrared (KBr, cm−1): ν(C=N), 1620, ν(COOH), 2742-3000, ν(C=O), 1690; ν(NH), 3315-3433.

General procedure for Preparation of 1, 3, 4-thiadiazole derivatives:

A mixture of compound 1 (0.0035mol, 1g) and an equivalent amount of Thiosemicarbazide (0.0035mol, 0.26g) in $POCl_3$ (25ml) was refluxed in a water bath for 10-12 h, and then filtered to get rid from unreacted materials. After evaporating under reduced pressure, a solid product was obtained. This was recrystallized from chloroform to obtain the desired product [7].

5-(2-(1H-imidazol-4-yl)-1-(((1Z,2E)-3-phenylallylidene)amino)ethyl)-1,3,4-thiadiazol-2-amine was prepared as mentioned above, color, brown, yield 60%, mp 120-122^{0}C, molecular weight 340.45; ^{1}H NMR (DMSO-d6, δ ppm, 400MHz): 6.70 (s, 2H, NH2), 10.60 (s, 1H, NH of diazole ring), 7.72-8.15 (m, 6H, aromatic protons), 2.75 (d, 2H, CH2 protons), 3.05 (t, 1H, N-CH proton);); Infrared (KBr, cm−1): ν(C=N), 1620.70, ν(NH2), 3450-3475; (C-S), 1165; (C-H Aliphatic), 2819-2916; (C-H aromatic), 3047.53.

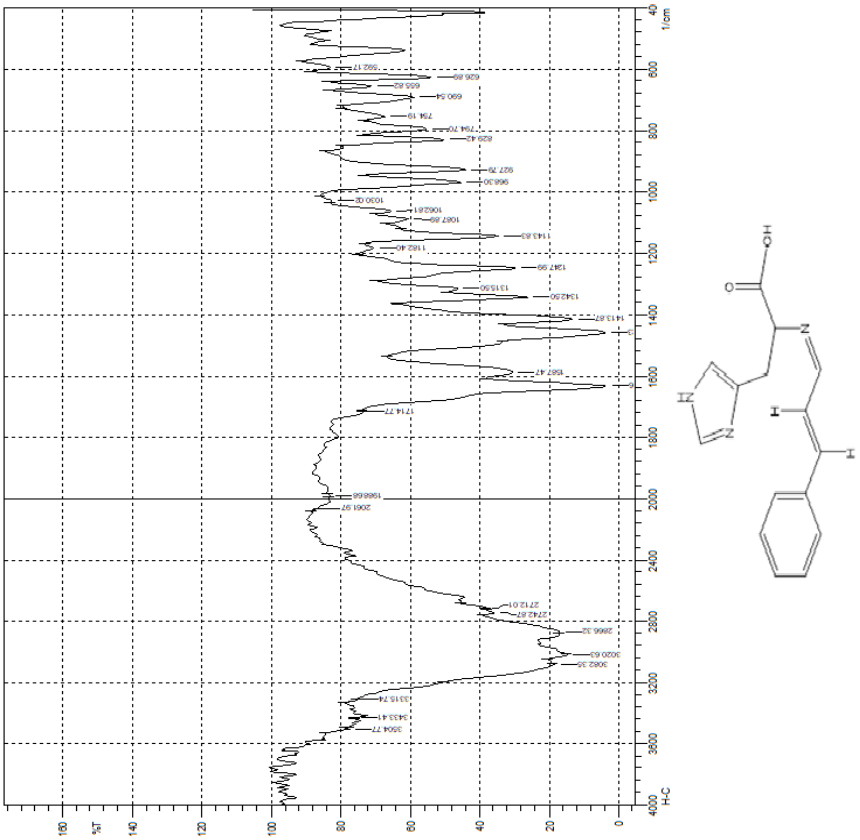


Figure (1): FT-IR spectrum of compound (III) using KBr disc

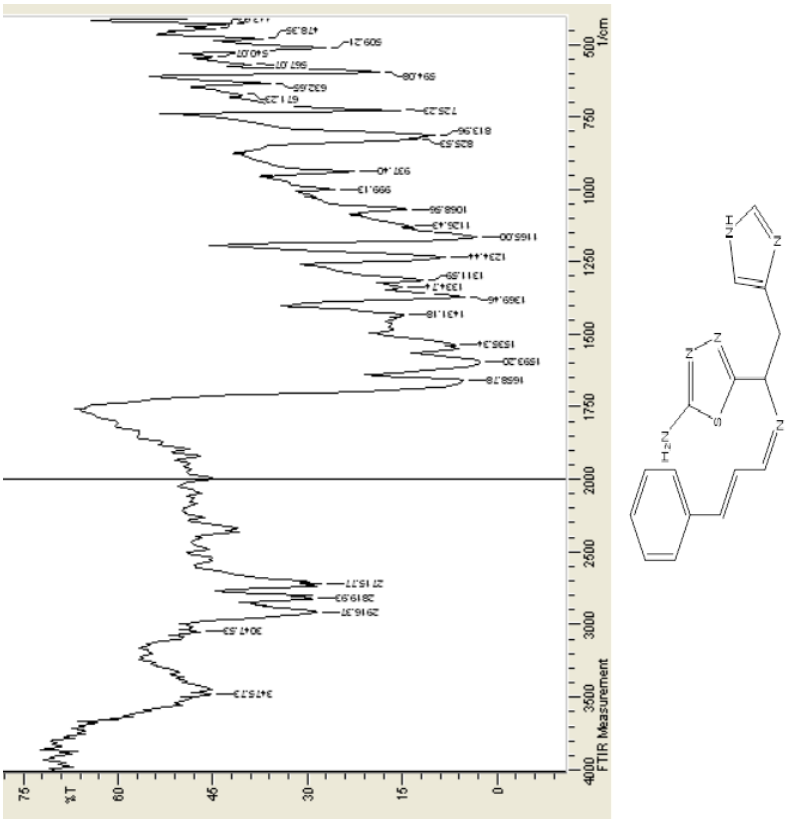


Figure (2): FT-IR spectrum of compound (IIIa) using KBr disc

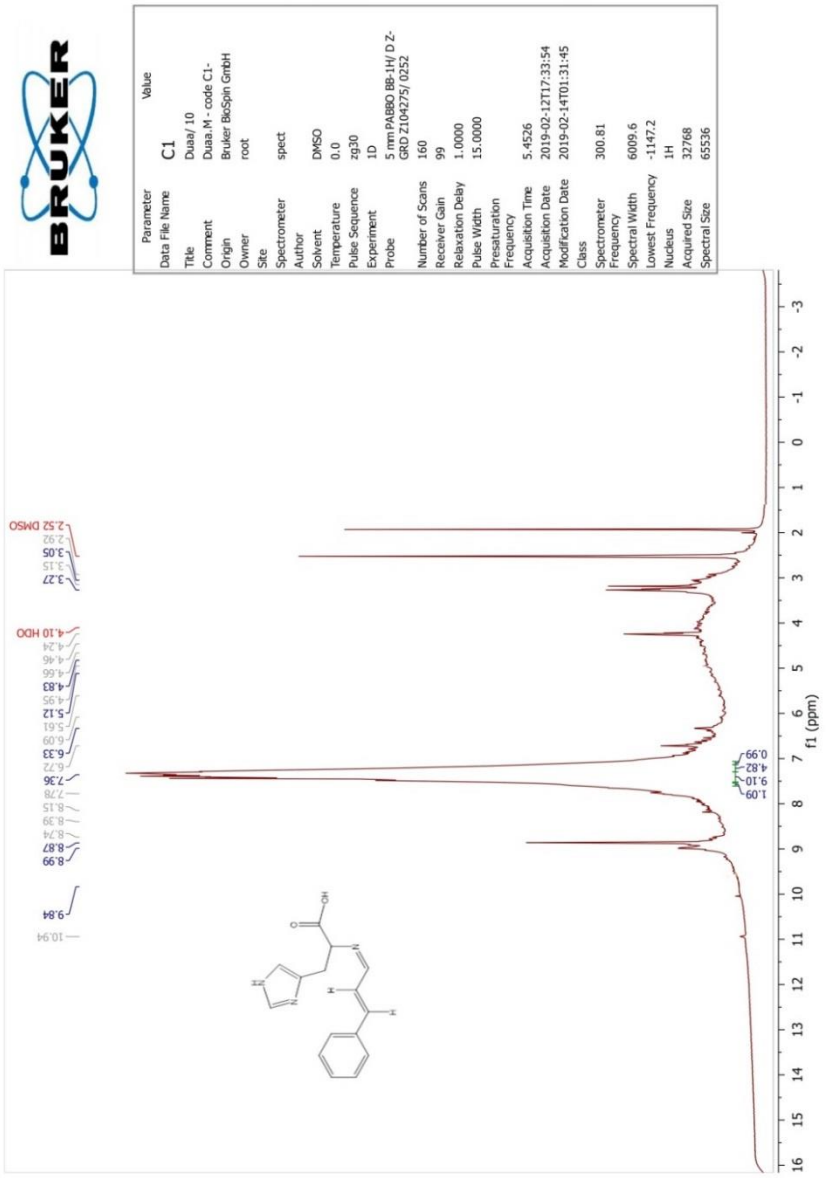


Figure (3): 1H-NMR spectrum of compound (III)

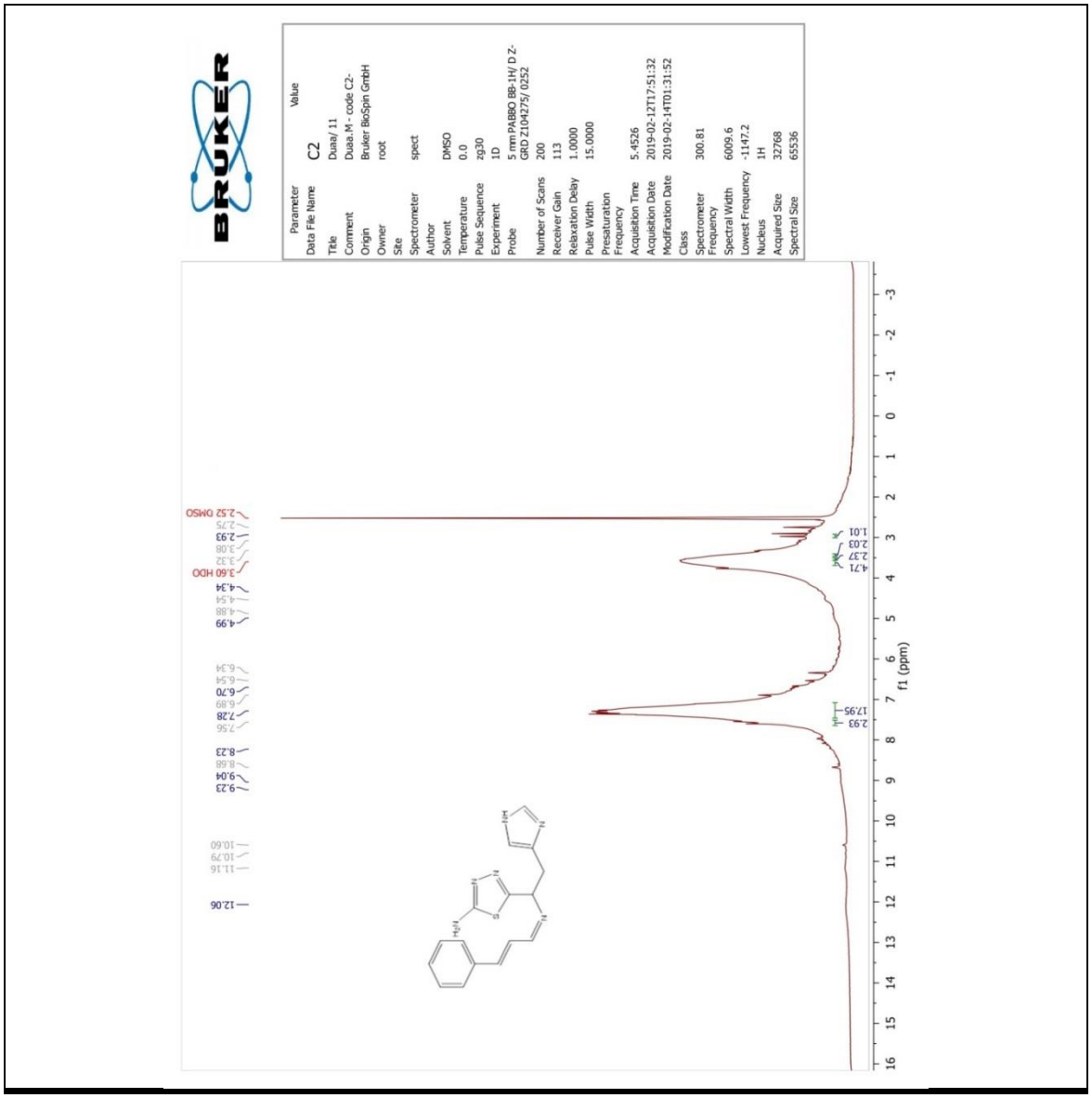
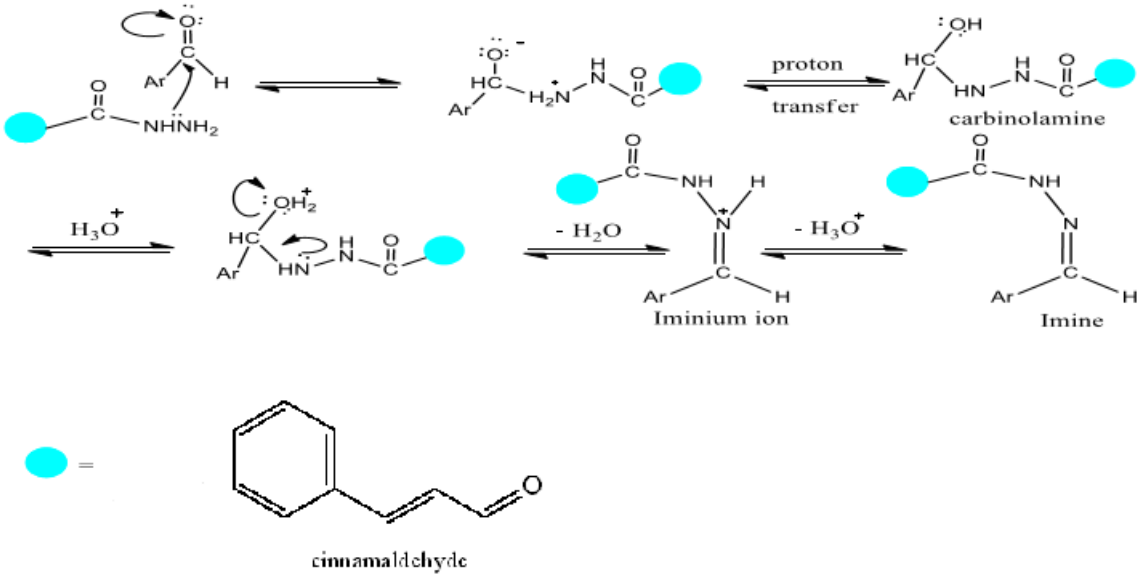


Figure (4): ^{1}H-NMR spectrum of compound (IIIa)

Result and discussion

Discussion the synthesis of compound (I):

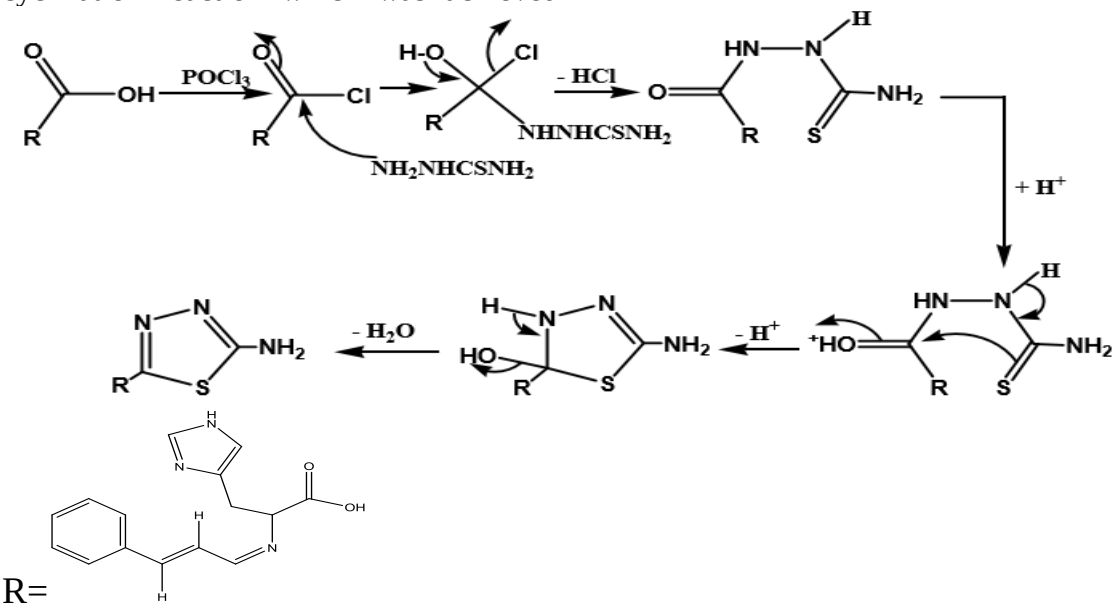
Imines are formed by acid catalyzed process that begins with the nucleophilic addition of the primary amine to the carbonyl group, followed by the transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol or carbinolamine. Protonation of the carbinolamine oxygen by an acid catalyst then converts the –OH into a better leaving group (H_2O), and loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst as shown in Scheme (2). [8].



Scheme (2) mechanism of Schiff base synthesis

Discussion the synthesis of 1, 3, 4-thiadiazole derivative (II)

Several procedures were reported for the synthesis of 2-amino-1,3,4-thiadiazoles, in many of these methods the Thiosemicarbazide was the starting material. Among the most important procedures was the one step acylation and cyclization reaction which was achieved by heating the carboxylic acid with Thiosemicarbazide in the presence of phosphorus halide. The required 2-amino-5-substituted -1,3,4-thiadiazoles was synthesized by refluxing the proper carboxylic acids with a Thiosemicarbazide in the presence of phosphorous oxychloride for one hour [9].



R=

(I)

Scheme (3) Synthesis of Amino-5-substituted-1,3,4–thiadiazole

Antibacterial assay:

Preliminary in vitro tests for antibacterial activity of synthesized compounds have been carried out by the agar Well Diffusion method. These compounds are dissolved in DMSO at concentrations of 500,250,125 and 62.5. The synthesized derivatives have a moderate activity against *E. coli*, high growth inhibition against *Acinetobacter baumanii* show that derivative (II) higher activity than (I), a weak growth inhibition against *staphylococcus aureus*, that show equal activity of the two derivatives except at conc. 500 its appear that derivative II more active than (I) and Nalidixic acid showed higher inhibition zone than both of them, and a moderate inhibition against *streptococcus pyougenes* except at conc. 500 and 250 that show larger inhibition zone than the other concentrations.

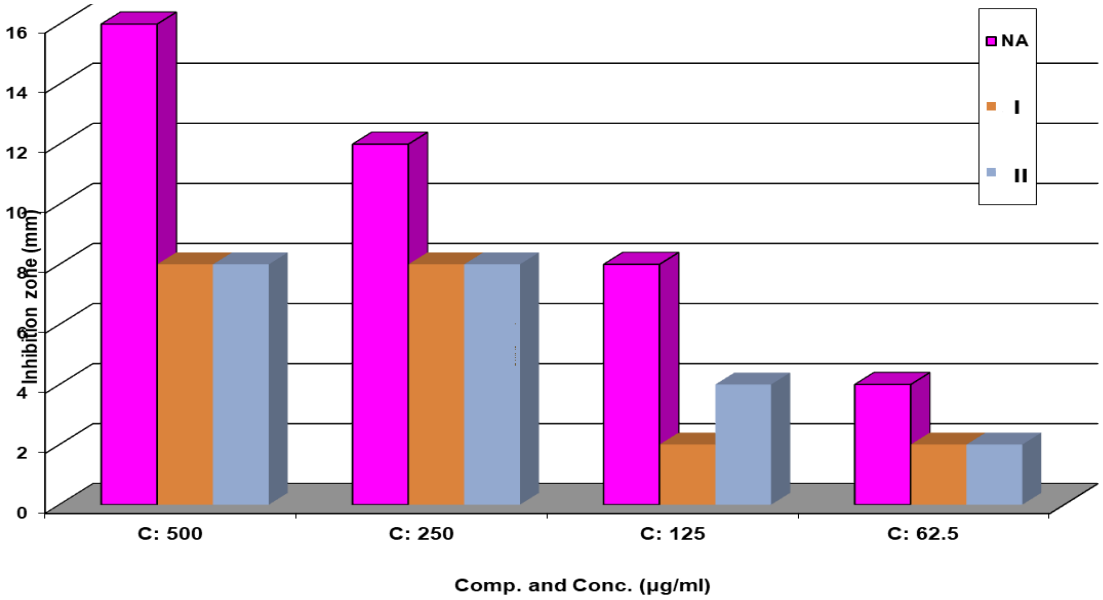


Figure 1. Effect of Comp. and Conc. in Inhibition zone(mm)//Escherichia coli

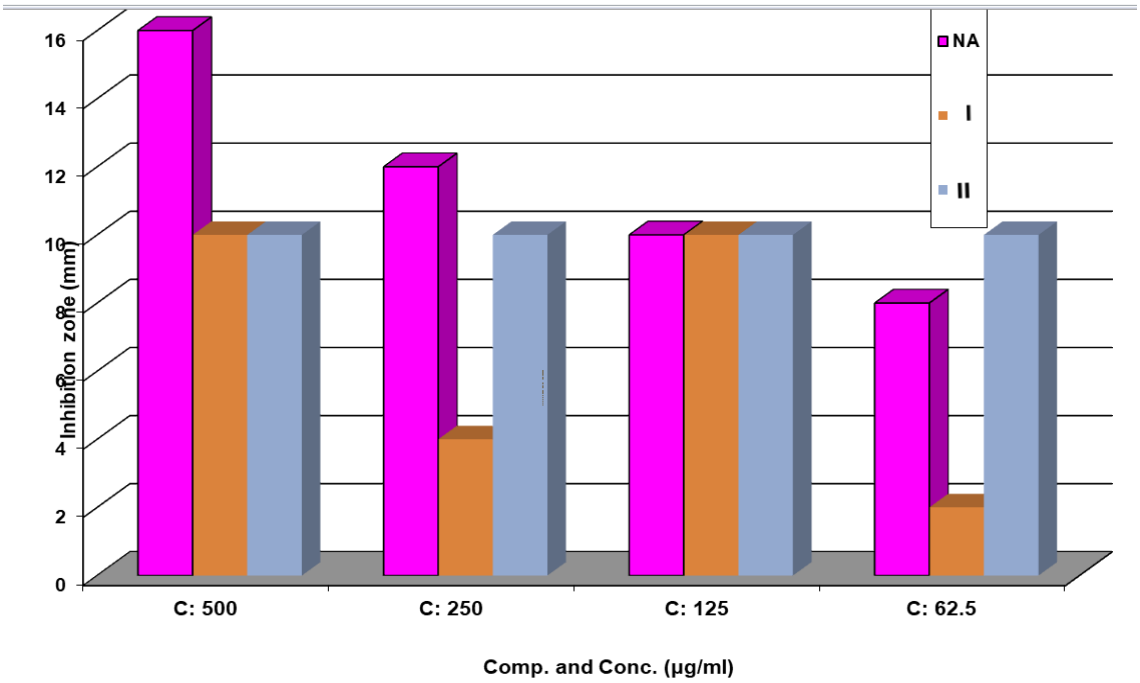


Figure 2. Effect of Comp. and Conc. in Inhibition zone(mm)//Acinetobacterbaumannii

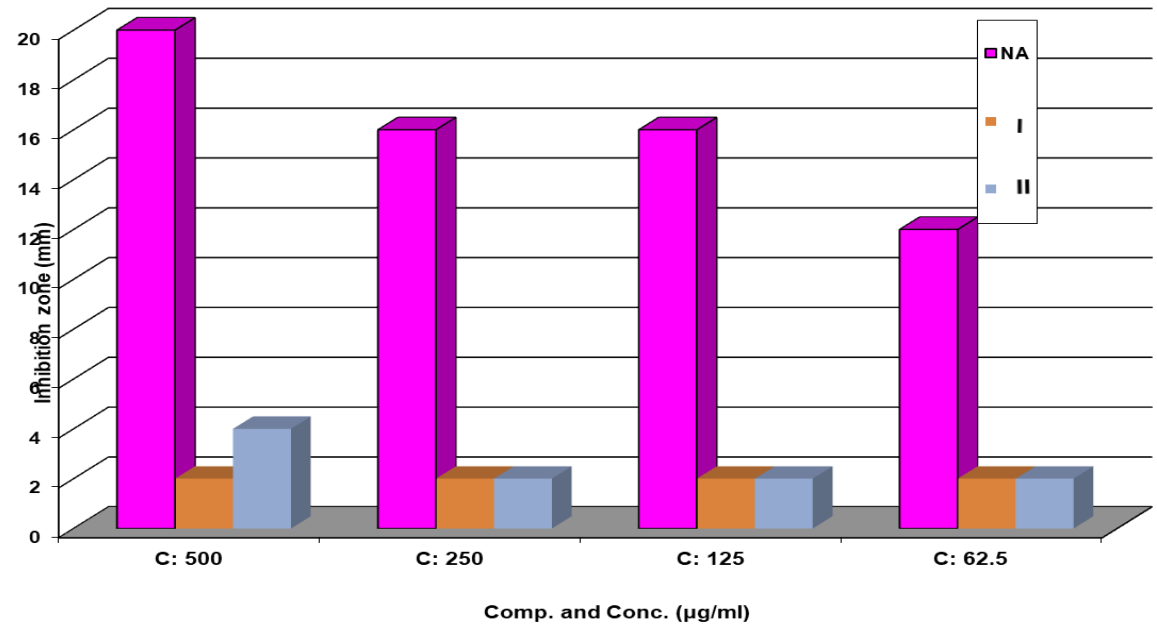


Figure 3. Effect of Comp. and Conc. in Inhibition zone(mm)//Staphylococcus aureus

Table (1): Antibacterial activity of Nalidixic acid and compounds (I-II) against tested bacteria:

Comp. No.	Conc. (µg/ml)	Inhibition zone(mm)			
		Gram negative		Gram positive	
		Escherichia coli	Acinetobacter baumanii	Staphylococcus aureus	Streptococcus pyougenes
Nalidixic acid	500	16	16	20	14
	250	12	12	16	10
	125	8	10	16	8
	62.5	2	8	12	6
DMSO	Pure	-	-	-	-
I	500	8	10	0	10
	250	8	8	0	10
	125	0	8	0	2
	62.5	0	0	0	0
II	500	8	10	2	10
	250	8	10	2	6
	125	2	10	0	2
	62.5	0	10	0	0

Antifungal assay:

Preliminary in vitro tests for antifungal activity of synthesized compounds have been carried out by the fungi growth inhibition method. These compounds are dissolved in DMSO at a concentration of 500,250,125 and 62.5. The data are summarized in Table (2), and show that both derivatives display a moderate antifungal effect but still fluconazole had higher inhibition zone than both of the two derivatives.

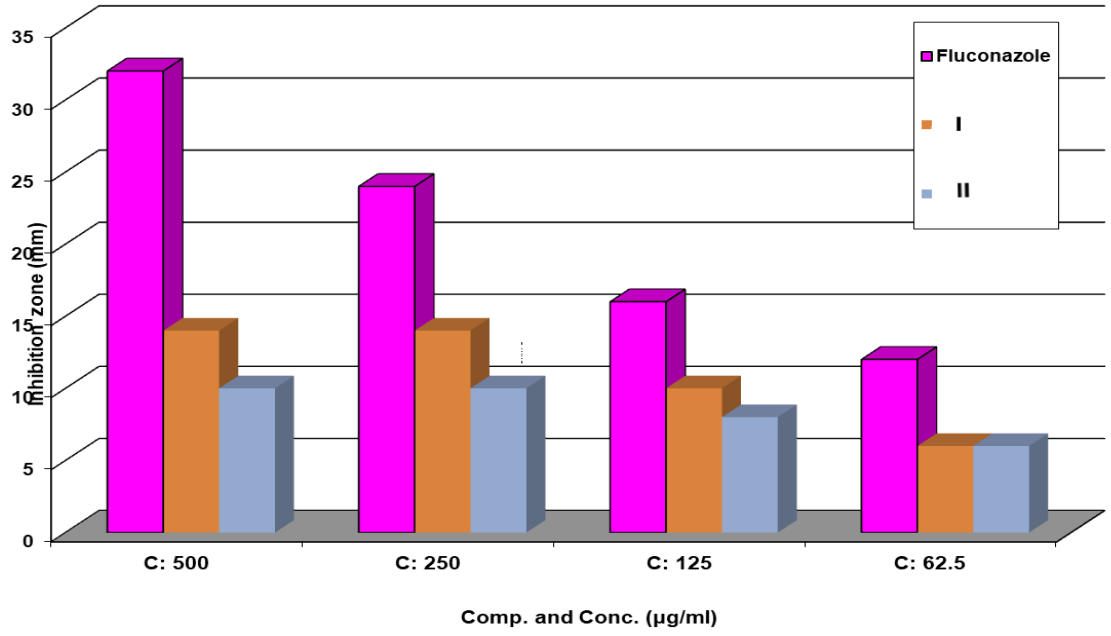


Figure 5. Effect of Comp. and Conc. in Inhibition zone(mm)//Candida albicans

Table (2): antimicrobial activity of the ligands (I-II) and their complexes against tested fungi.

Comp. No.	Conc. (µg/ml)	Inhibition zone(mm)
		Candida albicans
Fluconazole	500	32
	250	24
	125	16
	62.5	12
DMSO	Pure	-
I	500	14
	250	14
	125	10
	62.5	6
II	500	10
	250	10
	125	8
	62.5	6

Conclusion

1. The designed compounds have been successfully synthesized.
2. Identification and characterization of the prepared compounds were confirmed by determination of melting point, FT-IR spectroscopy and 1H-NMR spectra
3. The antimicrobial assessment of the final product indicate that the incorporation of 1, 3, 4-thiadiazole pharmacophore into Schiff base derivative of Histidine introduced a significant antibacterial and antifungal actions.

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