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Synthesis and study biological activity of some 1,8- Naphthyriane Derivatives

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Abstract

The compound 4-carboxy -2-phenyl-1,8- naphthyridine was synthesized from pyruvic acid, 2-Aminopyridine and Benzaldchyde (I).4-Hydrocynoamine-2-phenyl-1,8- Naphthyridine synthhesized from 4-Carboxy-2-phenyl-1.8-naphthyridine and phosphor penta chloride anhydrous in carbon tetra chloride, the resultant derivative was then separated by crushed ice and filtrated, the solid acid chloride thus obtained was used for further reaction. to the solid which was form was added hydrazine hydrate (II).4(p-phenyl dimethyl aminc) -hydrazine)-1,8-Naphthyridine (III) was synthesized from refluxed equimolar quantities of (II) with p.Dimethylamino-Benzaldephyde in ethanol. The purity of the synthesized compounds were established through R spectroscopy. and the purity were confirmed by TLC. the physical properties such as melting point and percentage were determined. The antibacterial activity of synthesized compounds (I, II, III) were tested by using agar diffusion method against some bacterial species, the compounds exhibit highest antibacterial activity specially compound III, also the Minimal inhibitory concentration (MIC) of tested compounds (I, II, III) were determined, the results showed that MIC values ranged (5-20) µg/ml for all bacterial species in this study, *Pseudomsonas aerogenosa*, *Escherichia coli*,*Proteus* sp, *Staphylococcus aureus, Klebsiella sp., Sallmonella sp.* ,*Streptococcu*s sp.

Keyword : *1,8- Naphthyriane, multi- resistant, hydrazine hydrate, agar diffusion*

Introduction

The increment in antibiotic resistant strains of clinically important pathogens, which have led to the emergence of new bacterial strains that are multi- resistant (1). Therefore, there is a need to look for new substances from other sources with proven antimicrobial activity. Consequently. this has led to the search for more effective antimicrobial agents such as the hetrocyclic compounds (2, 3). The Importance of hetrocyclic compounds has long recognized in the field of synthetic organic chemistry. That is well known that heterocyclic compounds containing nitrogen, which exhibit a wide variety of biological activity. A series of pyridine derivative were evaluated for antitumor activities, so nicotinic acid schizophrenia (4). On the other hand Hydrazide derivatives are one of the interesting class of compounds in pharmaceutical chemistry, it has proven to play significant role in the synthesis of novel drugs (5, 6). recently a series of hydrazide compounds were screened for their wide range of biological activities, such as antimycobacterium activity against mycobacterium-tuberculosis, antimicrobial activities against various bacteria, fungi, and yeast species were determined (7, 8, 9). The increasing interest in derivatives result from the wide possibilities and their application for obtaining biologically active agents(10, 11), the introduction of nicotinic acid hydrazide an important anti

tubercular drug paved new interesting heteroaryl hydrazides and hydrazones. Therefore a series of virtual Schiff base of nicotinic acid hydrazones were synthesized (3).In view of this it was interesting to synthesize several new compounds to evaluate the effect of amino acids on the bioactivity of nicotinic acid hydrizide based on these studies were synthesis this type of compounds and evaluated for antibacterial activities very interesting (2) The aim of the present study is to synthesis of some Naphthyridine derivatives and investigate potentially useful active ingredients that can serve as source and template for new antimicrobial drugs.

Material and Methods

Experimental

1. Synthesis 2-phenyl-4- carboxy – Naphthyridine (I):

The mixture of pyruvic acid(22ml,0.25molar) and benazldehyde (24ml, 0.25mol) in 200 ml ethanol was heated to the boiling point on the water bath with slowly and frequent shacking (scheme l), a solution of pure 2- Aminopyridine (0.25mol) in 100 ml ethanol was added , the addition was done for one hour. The mixture was refluxed for about three hour and allowed to stand overnight. The crud derivative was concentrated and allowed to cool, the solid product obtained was filtered, and recrystallized using hot ethanol (6), as in table 1.

Synthesis 4-Hydrocynoamine-2-phenyl-1,8-Naphthyridine: 2.

A mixture of 4-carboxy-2-phenyl-1,8-Naphthyridine (l) (0.03mol) and phosphorus penta chloride (0.05mol) in carbon tetra chloride were refluxed for 2 hour at 100 °C, The resultant product was then separated by crushed ice and filtered, the solid acid thus obtained used without further purification o the solid acid chloride hydrazine was added hydrate(0.1 mol) drop wise below 5°C,and the resultant mixture was stirred for 5 hour at room temperature, allow to cool (scheme2). solid that separated out was washed with aqueous sodium bicarbonate (10%) and dried. It was recrystallized from methanol (8, 9), table 1.

3. Synthesis4-((p-(phenyldimetylamino)hydrazine)-2-phenyl-1, 8 Naphthyridine (III):

The (0.01mol) of (I I) and p.Dimethyl amino benzaldehyde (0.01 mol) in Tetrahydroluran was refluxed for 3 hour at 60 °C (scheme3) .The reaction mixture was then separated by ice cold water and it was filtered. The resultant solid was recrystallized from hot methanol (12), Table 1.

Antibacterial activity assay

For the purpose of antimicrobial activity seven microorganisms were used, *Psendomonas aerogenosa, Escherichia coli, Proteus sp., Staphylococcus aureus, Klehsieltla sp., Salmonella sp., Streptococcus sp.,* Microorganisms species were employed in this study obtained from stock cultures of Microbiology laboratory, Department of Microbiology , college of Medicine, university of Kufa. The bacterial species were identified according to (13), and maintain on nutrient agar slants and recovered for testing by sub-culturing in nutrient broth for 24hrs. The antimicrobial activity tests were then carried out by agar diffusion assay(14). for screening ,sterile 6mm diameter filter paper discs were impregnated with (25)µg of synthesized Compounds (I, I1, II). the paper discs were placed on to Mueller Hinton agar was cultured with test organisms(for each species)and then incubated at 37°C. The results

were recorded by measuring inhibition zones diameter surrounding the discs after 24hrs of incubation. Refampin (30)mg per disc Ciprofloxacin (30)mg per disc were used as reference standard antibiotics bioanalyse company) .Each assay in the experiment was repeated triple times. the analysis of variance ANOVA were used for the statistical analysis of the results using spss program.

Determination of Minimal inhibitory concentration(MIC)

The Minimal inhibitory concentration (MIC) were determined by using agar dilution method (15). The compounds (I, II, III) was tested by dissolved in sterilized distilled water, then transferred to the nutrient agar solution to yield the final concentrations (3,5,1,15,20,25) µ /ml. Seven strains of microorganisms cultured in nutrient broth at 37°C for 24hrs, were diluted with 0.9% normal saline solution to prepare the bacterial inoculum (for each species).the organisms were inoculated onto each plate by using micropipette about (0.1)ml, and incubated at 37°C the presented results were determined after 24hrs. The MIC were determined as the lowest concentration of compound inhibiting visible growth of each organism on agar(16). Experiments were carried out in two replicate

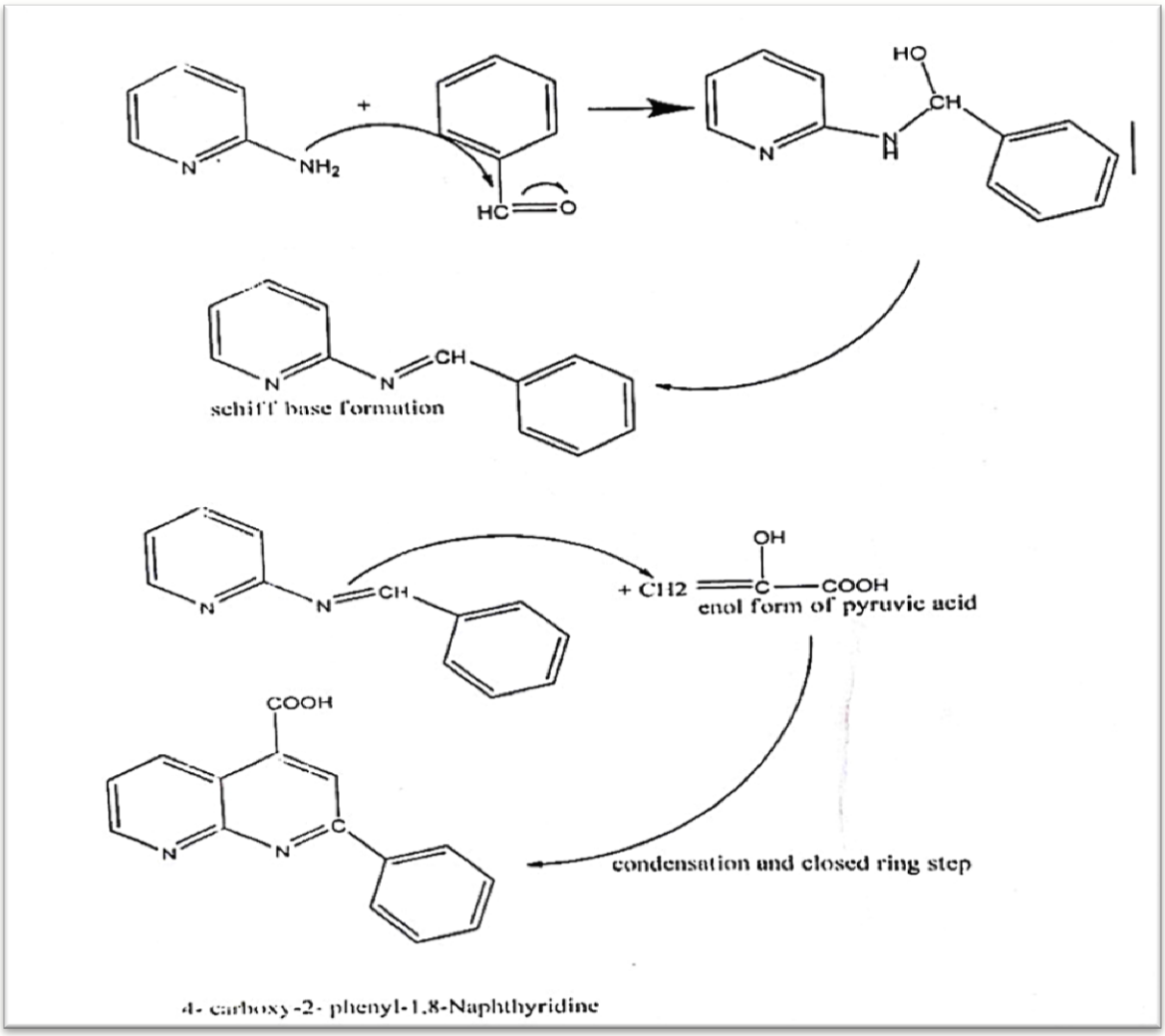
Results and discussion

For the synthesis of desired compounds, the sequence of reactions show in schemes 1,2 and 3. The reaction of pyruvic acid, Benzaldehyde and 2-Amino pyridine in the presence of ethanol by refluxed equimolar quantities of each compound for about three hour and stand overnight (scheme l), the structure of synthesized compound I was established by means IR. The infrared spectra for these compound showed stretching band of carbonyl group (C=O,of COOH) at 1704cm', C=C aromatic stretching band at stretching at 1590cm, and hydroxyl stretching band at 3360 cm^{-1}, C-H aromatic stretching at 3034 cm The acid chloride was then prepared by react I with phosphorus penta chloride and the resultant was then treated with hydrazine hydrate (scheme2). The structure of synthesized compound was confirmed by IR spectroscopy which appear the following stretching bands, HC=N band at 1636cm ,C=C aromatic stretching at 1610cm N-H strong band at 3230cm"C-H aromatic stretching al 3030and 2850cm'.The Schiff base II1 was prepared by refluxed Il with p.Dimethylaminobenzaldehyde in Tetra hydrofuran. The IR spectroscopy for these compound show strong stretching band of C=H at 1615 cm^{-1} ,C=C aromatic stretching at 1590 cm^{-1} and C-H aromatic stretching at 3077cm^{-1} (12,17).

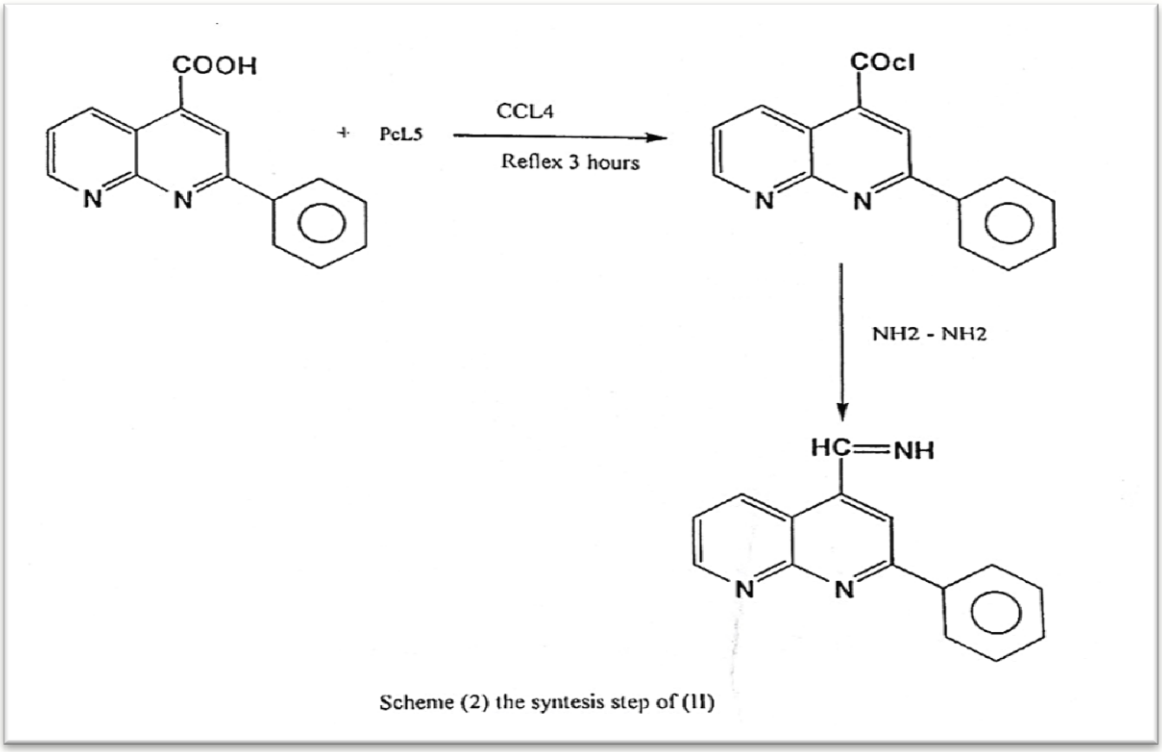
Table 1: The physical data of synthesized compounds

Compound	Molecular formula	Molecular weight	color	mp.	R_f.
I	$C_{15}N_2O_2H_{10}$	250	white	234	0.7
II	$C_{15}N_4H_9$	245	yellow	198	0.67
III	$C_{24}N_5H_{19}$	377	yellow	267	0.85

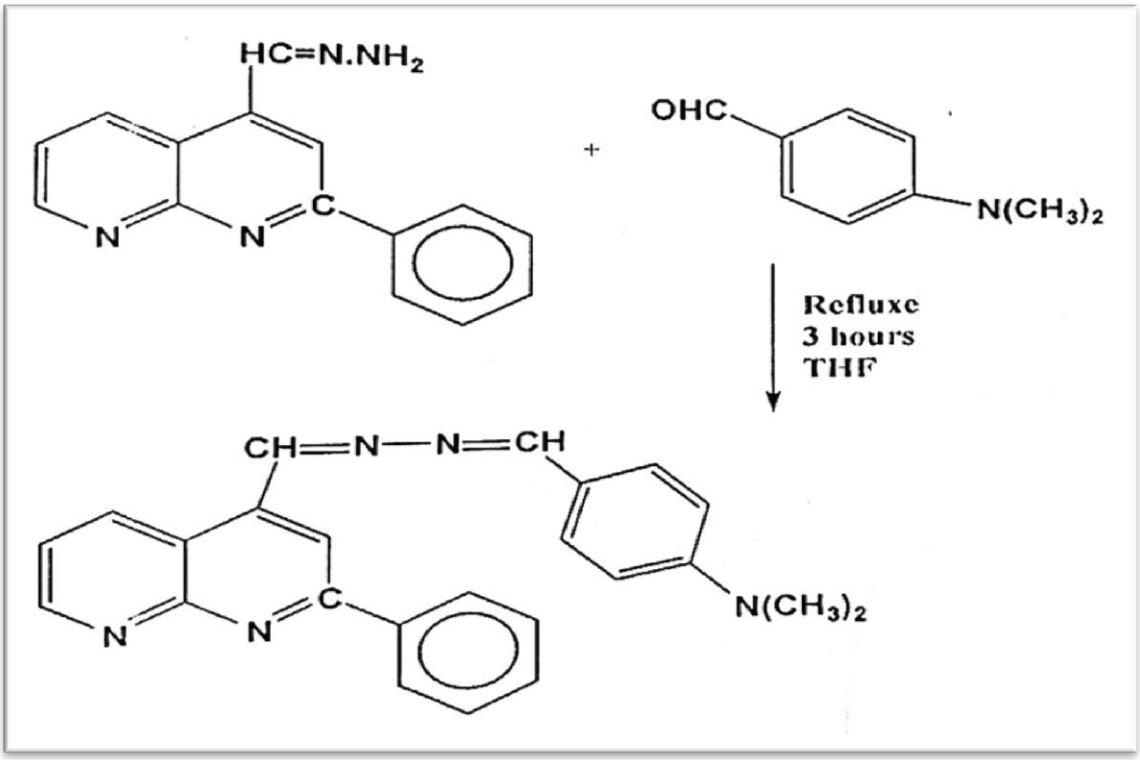
mp: melting point
R_f.: rate of flue



Scheme (1): The synthesis steps of 4- carboxy-2-phenyl-1,8- Naphthyridine



Scheme (2): The synthesis step of (II)



Scheme (3): The synthesis step of (III)

The result in figure (1) showed significant increasing P<0.05 in antibacterial activity of comp I against *P.aeruginosa*, *Salmonella* and *E.coli* compared with standard antibiotics also there is no significant differences between the comp I and standard

antibiotics specially against S.aureus, Kiebseilla, Proteus, while comp I showed no antibacterial activity against Streptococcus bacteria compared with standard antibiotics. The result in figure (2) showed significant increasing $P<0.05$ in antibacterial activity in compound II against most tested bacteria except in *Streptococcus* compared with standard antibiotics .The results also showed no significant differences between the compound and standard antibiotics against *Klebseilla*.The result in figure (3) showed there is significant increasing $P<0.05$ in antibacterial activity in compound II compared with standard antibiotics in most tested bacteria, while there is no antibacterial activity against *Streptococcus* bacteria. The comparison the antibacterial activity between the compound I, II, III was showed in figure (4) the results appear that compound III has a significant increasing $P<0.05$ in antibacterial activity against *S.aureus, Klebseilla, Proteus, Salmonella* species, compared with compound I and compound I while there is no significant differences against *P. aeruginosa* and *E.coli* specis. These results agree with (5), who suggest the uncomplexed and complexed compounds of hydrazide derivatives were higher antibacterial activity specially against *E.coli* and *S.aureus*. The results presented in table (2) revealed that the MIC of compound I active against all species of bacteria used in the study with value 10(µg/ml), while *Klehseilla* and Salmonella with value 15(µg/ml) the MIC of comp II with value 10(µ/ml) for most species of tested bacteria, except *Salmonela* sp. with value 15(µg/ml). On the other hand the comp showed higher active against most species of bacteria were used in this study with value 5(µ/ml),and *Salmonella* sp. with the MIC value 10(µg/ml).Also the results showed low inhibitory activity on Streptococcus bacteria with the MIC value ≥20(µ/ml) for all the tested compounds (I, II, III). These results were agreed with other studies (15) which concluded that tested nicotinic acid derivatives exhibited antibacterial activity against *Streptococcuus* with the MIC values 15-30 (µg/ml), while the results of present study disagree with (18), whom suggest the nicotinic acid derivatives display growth inhibition against Streptococcus at 15(µg/ml),also suggest the activity of these compounds may be due to the presence of pyridine ring in its constituents or may be due to the activity of the Schiff base and its complexes. Which can be explained on the basis of Overtone's concept and Tweedy's chelation theory (19, 20). According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble material which liposolubility is considered to be an important factor that controls the multiplicity of the microorganisms activity (21).The variation in the activity of different complexes against different organisms depend either on the in permeability of the cells of the microbes or difference in ribosomes of the microbial cells. The antibacterial activity may be also due to the hetero atom which bonding with trace elements present in microorganisms this may combine with the uncoordinated site and inhibit the growth of microorganisms (20). Another explanation of The antibacterial activity may be due to the Effect of azomethine (>C=N) group. which The mode of action of this compounds may involve formation of a hydrogen bond through the azomethine group (>C=N-) with the active centers of cell constituents resulting in interferences with the normal cell processes (22, 23).

Conclusions

The compounds (I, II, III) have significantly antibacterial activity with potential medicinal values which may be used in pharmaceutical applications.

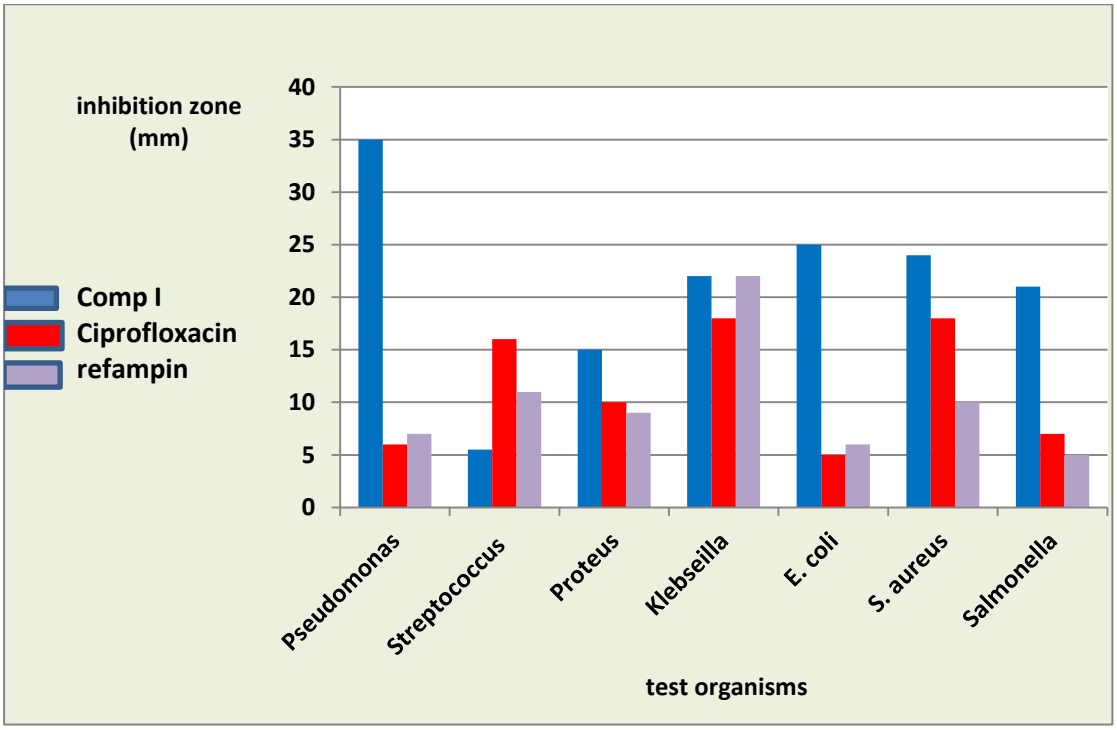


Figure (1): Antibacterial activity of compound I compared with standard antibiotics

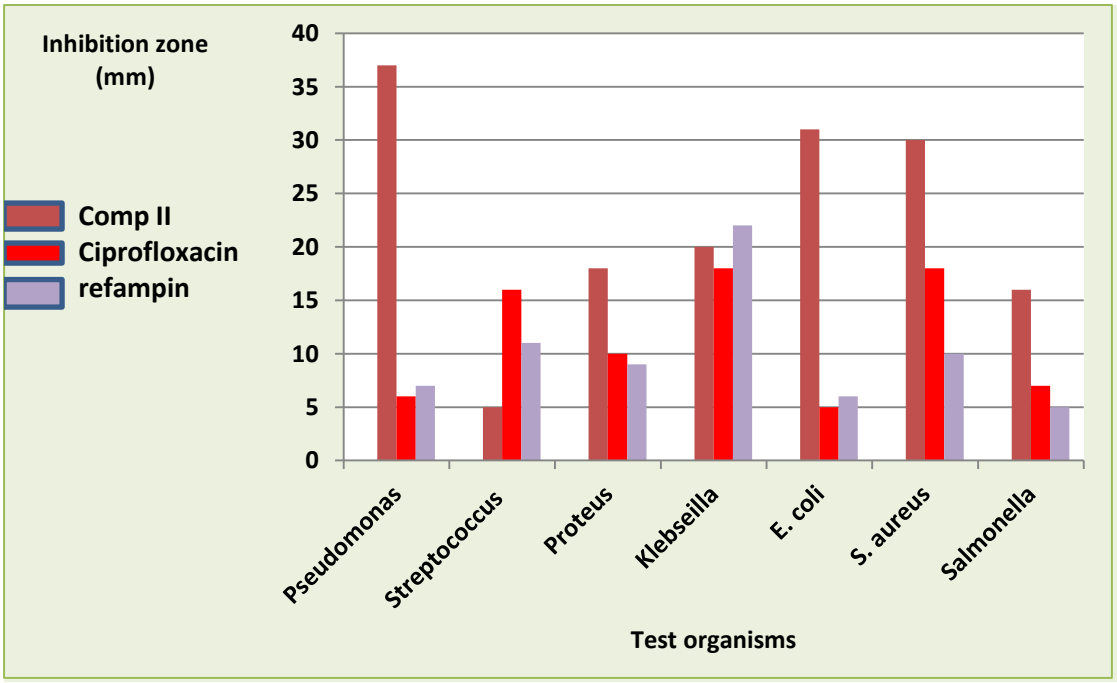


Figure (2): Antibacterial activity of compound II compared with standard antibiotics

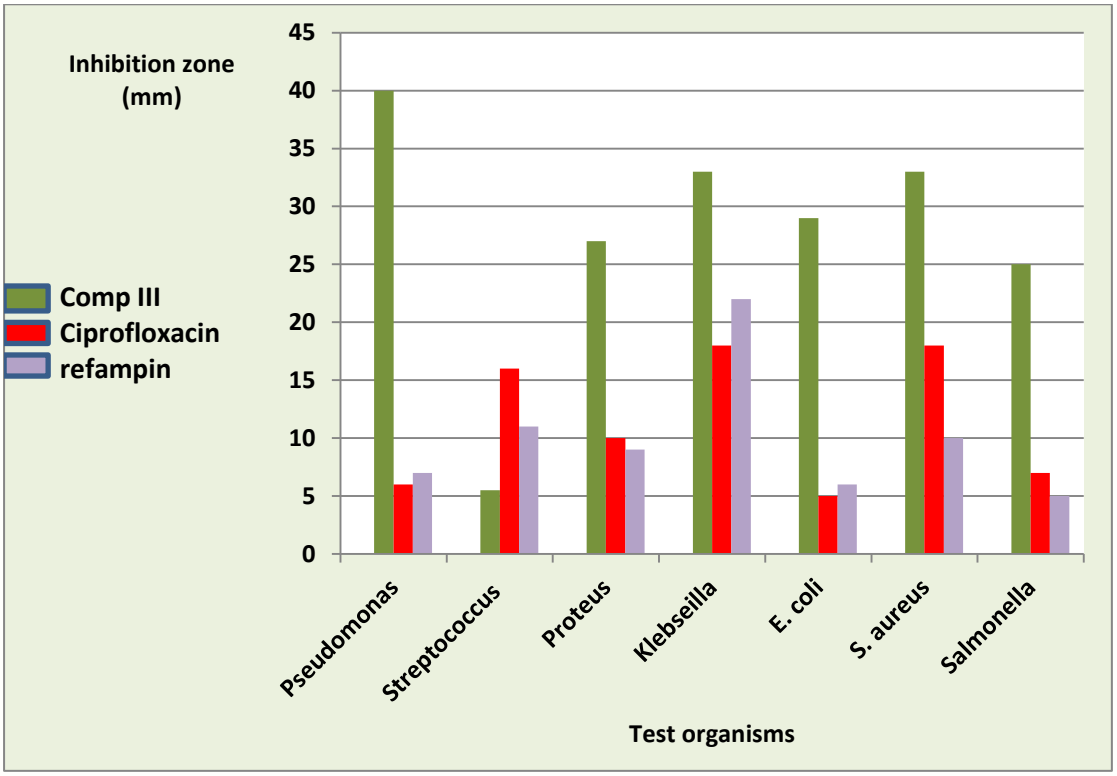


Figure (3): Antibacterial activity of compound III compared with standard antibiotics

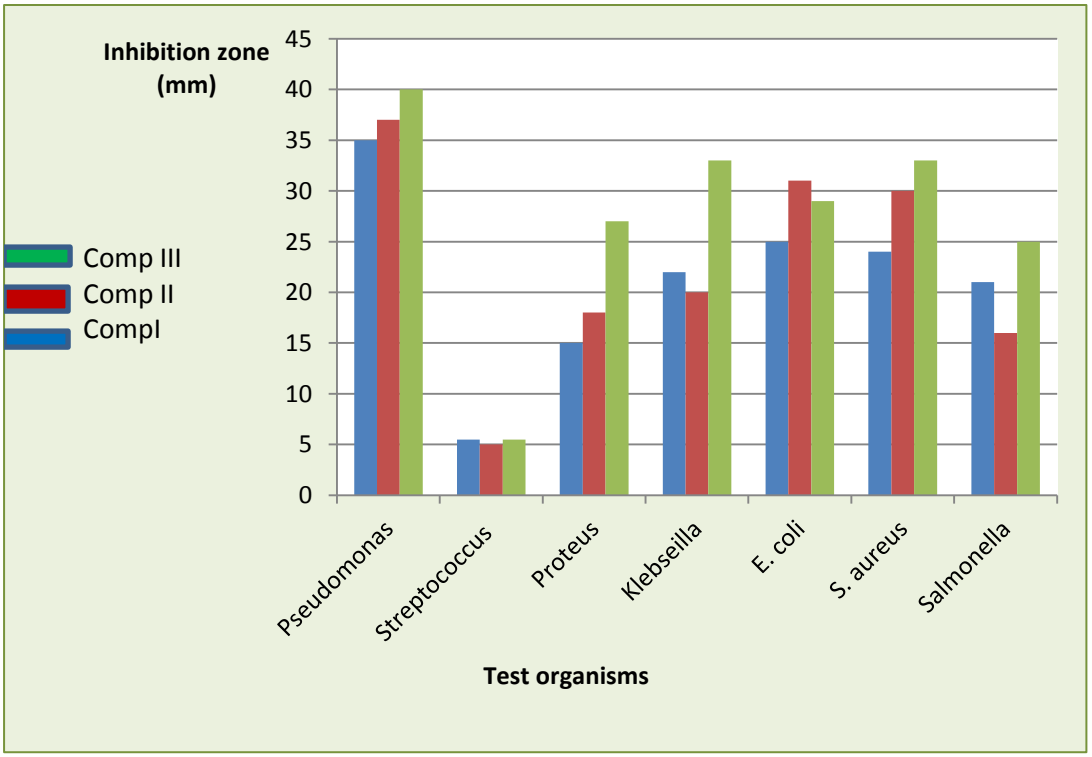


Figure (4): Comparison between the Antibacterial activity of synthesis compounds (I, II, III)

Table (2): Minimal inhibitory concentration (µg/ ml) of tested compounds (I, II, III) against different strains

Test organisms	MIC (µg/ ml)		
	I	II	III
Pseudomonas aerogenosa	10	10	5
Escherichia coli	10	10	5
Proteus sp.	10	10	5
Staphylococcus aureus	15	10	5
Klebsiella sp.	15	15	10
Sallmonella sp.	10	10	5
Streptococcus sp.	20≥	20≥	20≥

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