شبكة المعلومات الجامعية

بسم اللّه الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم باللّه العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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لم ترد بالأصل

شبكة المعلومات الجامعية

بعض الوثائق الأصلية تالفة

SYNTHESIS OF SELECTED ANTIMICROBIAL AGENTS

THESIS

PRESENTED BY

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To My Family

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The Candidate

CONTENTS

ABSTRACT

In this investigation, the synthesis of thirteen final semisynthetic cephalosporins via substitution of 7-amino-3-desacetoxycephalosporanic acid with different coumarin residues at its 7-position, designed to possess antimicrobial activity, has been achieved.

Among these final compounds, eleven of them are new, and the other two are abstracted in the chemical abstracts with no details on its chemical structure and microbiological activity.

The rationale behined the synthetic schemes applied is discussed. The basis, on which these molecules were designed is given. The structures of the prepared compounds were confirmed using various chemical and spectroscopic tools.

In this study, synthesis, structural verification and quantitative antimicrobial activities of the following final compouds is reported.

Known Finals :

1. 7-(3-Coumarinoyl) amino-3-desacetoxycephalosporanic acid. (I)

2. 7-(3-Coumarinyl acetyl) amino-3-desacetoxycephalosporanic acid.(IV)

Novel Finals :

1. 7-(7-Methoxy-4-Coumainoyl) amino-3-desacetoxycephalosporanic acid.(II)

2. 7-(7-Hydroxy-4-coumarinyl acetyl) amino-3-desacetoxycephalosporanic acid.(III)

3. 7-(4-Methyl-6-coumarinyloxy acetyl) amino-3-desacetoxycephalo-sporanic acid.(V)

4. 7-(4,7-Dimethyl-6-coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(VI)
5. 7-(4-Methyl-7-coumarinyloxy acetyl) amino-3 desacetoxycephalosporanic acid.(VII)
6. 7-(4,8-Dimethyl-7-coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(VIII)
7. 7-(8-Acetyl-4-methyl-7-coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(IX)
8. 7-(8-Benzoyl-4-methyl-7-coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(X)
9. 7-(8-o-Toluoyl-4-methyl-7-coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(XI)
10. 7-(7-Coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(XII)
11. 7-(4-Coumarinyloxy acetyl) amino-3-desacetoxycephalosporanic acid.(XIII)

The antimicrobial activity of the final compounds has been tested, in reference to cephradine, a clinically useful semisynthetic cephalosporin. The results obtained were discussed and a conclusion was drawn. All of the compounds are found to have antimicrobial activity against most of the examined microorganisms, especially the highly resistant Pseudomonas aeroginosa.

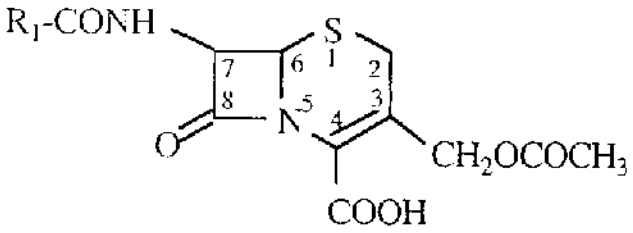
LIST OF ABBREVIATIONS

7-ACA	:	7-Aminocephalossporanic acid.
7-ADCA	:	7-Amino-3-desacetoxycephalosporanic acid.
PBP	:	Penicillin binding protein.
Staph.	:	Staphylococcus
Sar.	:	Sarcina
B.	:	Bacillus
M.	:	Myobacterium
Ps.	:	Pseudomonas
P.	:	Proteus
E.	:	Escherichia
Sh.	:	Shigella
K.	:	Klebsiella
S.	:	Salmonella
m	:	mass
amu	:	atomic mass unit
ppm	:	part per million
MIC	:	Minimum Inhibitory Concentration
AR	:	Activity Ratio
hrs	:	hours
^{1}H-NMR	:	Proton magnetic resonance spectroscopy
IR	:	Infrared spectroscopy
UV	:	Ultraviolet spectroscopy
m/z	:	mass to charge ratio

INTRODUCTION

I.1- Preview :

The historical development in the field of ß- lactam antibiotics started in 1929, when Sir Alexander Fleming accidently observed lysis of staphylococcus micro-organisms by an agent produced from a contaminating mold. Fleming discovered in the filterate a powerful, non-toxic antibacterial substance that he called Penicillin, in reference to the fungus that produced the antimicrobial substance, Penicillium notatum[1,2]. ß-Lactam antibiotics are now the most diverse and widely used of all antimicrobial agents[3]. The ß-lactam term refers to the 4 membered cyclic amide ring system[4].



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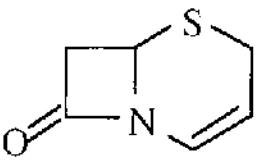

(2)

Interestingly, similar cyclic amide rings were also produced by a related family of cephalosporium fungi that came to be collectively termed, cephalosporins (1). Remarkably, cephalosporins currently constitute an important group of chemotherapeutic agents in clinical use because of their bactericidal activity and excellent stability[4,5]. Chemically, cephalosporins are acylated 7-aminocephalosporanic acids, in which the ß-lactam dihydrothiazine fused system is designated by chemical abstracts as 5-thia-1-azabicyclo [4.2.0] oct-2-ene. However, for reasons of simplicity, the bicyclic system is denoted as cepham ring. Hence, cephalosporins are essentially Δ^3-cephem derivatives (2)[6].

Historically speaking; the first cephalosporin isolated from cultures of