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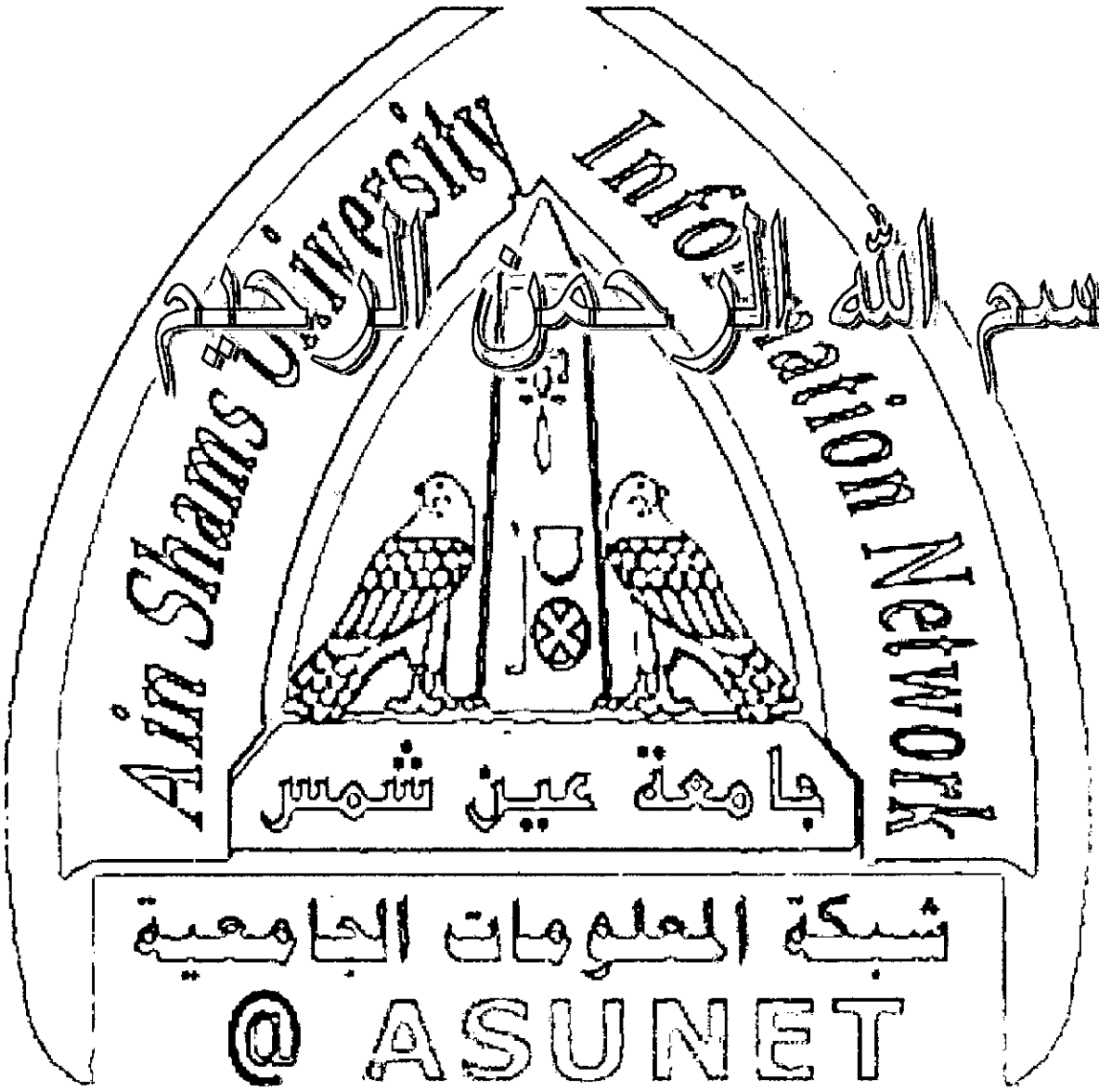

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

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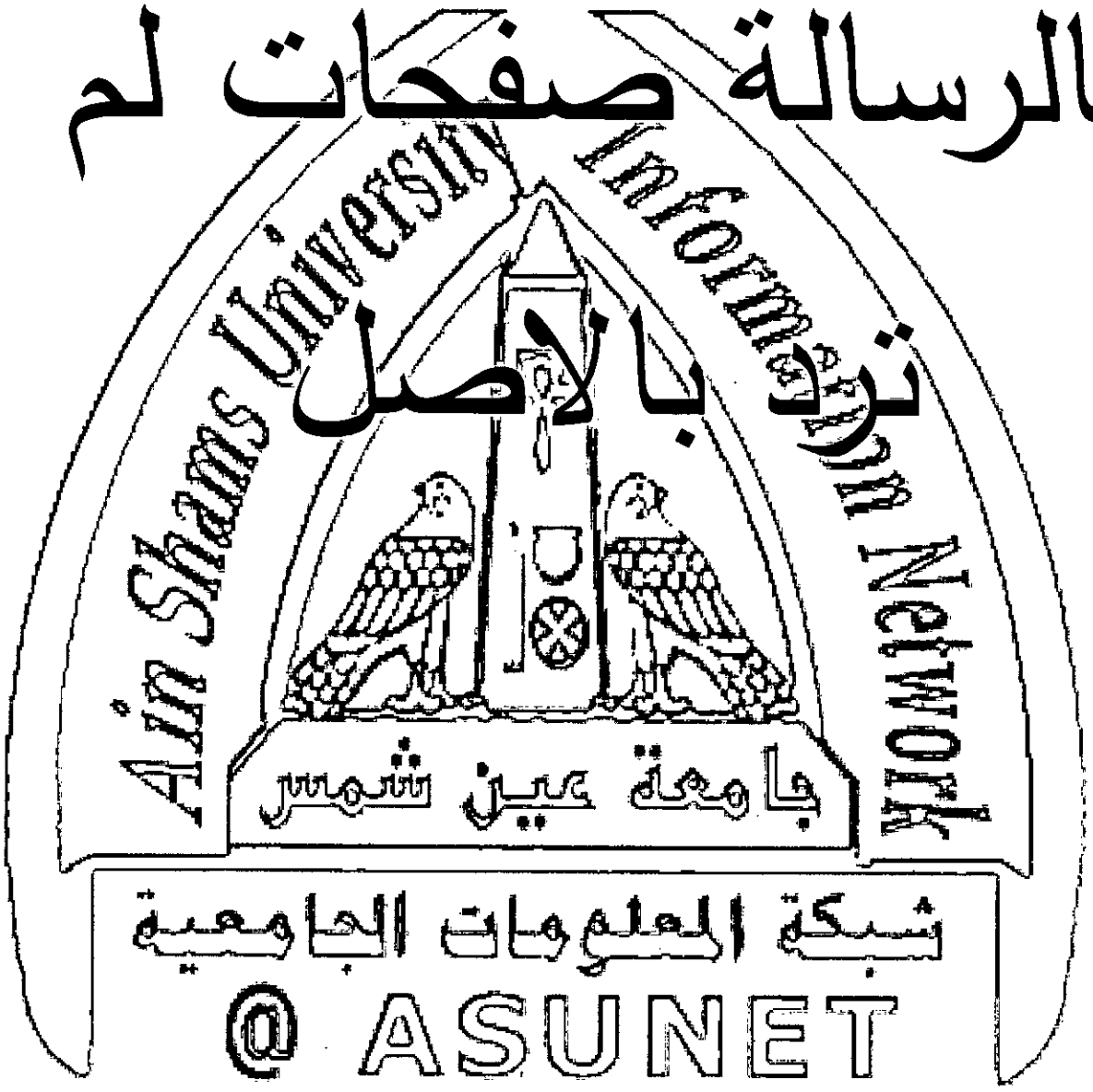

بالرسالة صفحات لم ترد بالأصل

PHARMACEUTICAL CHEMICAL STUDIES ON SOME NEW DERIVATIVES OF NALIDIXIC ACID AND NORFLOXACIN

Thesis

Presented by

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CONTENTS

ABSTRACT

Abstract

Nalidixic acid; 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **121a**, is a synthetic 4-quinolone analog antimicrobial agent, while norfloxacin; 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid **122a**, is considered a synthetic second generation 4-quinolone antibacterial agent. Both drugs suffer from some adverse reactions. They induce gastrointestinal disturbances which could be attributed to their strongly acidic character. Neurological side effects including visual disturbances, headache, dizziness and vertigo have been also reported. Other side effects include crystallurea encountered with large doses, which could be related to their poor aqueous solubility. Nalidixic acid provokes photosensitivity reactions, while norfloxacin shows a limited bioavailability, since only 35-40% of the dose is absorbed, which could be attributed to its zwitter-ionic character. Literature survey revealed that prodrug concept has been approached in order to improve their physicochemical and biological properties. However, there is much remaining to be done in this concern. The afore-mentioned facts motivated us to sysnthesize new bioreversible derivatives of nalidixic acid and norfloxacin. In this direction, the prodrug strategy involving the 3-carboxylic group has been proposed to synthesize some selected glycolamide esters as well as glycerides. Esterification of nalidixic acid and norfloxacin with metronidazole and secnidazole to obtain mutual bipartate ester prodrugs was also within the scope of our interest. These mutual prodrugs would be reverted *in vivo* delivering the two active parent drug molecules, thereby broadening the antibacterial spectra of both counterparts. Some of the synthesized prodrug derivatives were evaluated for their ability to release the parent drug *in vitro* using HPLC

technique. The tested compounds were found to release the parent drugs in simulated physiological buffer-plasma solution. It could be suggested that the tested derivatives could be considered as promising candidates as prodrugs for norfloxacin.

In addition, it was of interest to screen the synthesized derivatives, against some selected bacteria, for antibacterial evaluation *in vitro*.

The present thesis is subdevided into the following main parts:

Introduction :

It comprises a comprehensive review of the literature concerned with the advances in prodrug concept, classification of various types of prodrugs with illustrative examples with reference to their significance and application in prodrug design.

Research Objectives :

It deals with the rationale upon which the newly sysnthesized derivatives of nalidixic acid and norfloxacin has been proposed as prodrugs.

Results and Discussion :

It is concerned with the methods adopted for the synthesis of both intermediate and target compounds. Our corner-stone in this part was the available knowledge gained from literature. The structures assigned to the new compounds are substantiated by elemental analyses, I.R., as well as H^1-NMR and mass spectra for some compounds. The plausible fragmentation patterns of the selected compounds are also proposed, with possibility to find a common fragmentation pathway for related compounds with similar promoieties.

Experimental :

It describes the detailed experimental procedures that were adopted during the progress of the investigation. It includes the physical characters, microanalyses and spectral data that support the suggested chemical structures. The following new compounds were synthesized :

Carbamoylmethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **128a**, and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid **129a**

N-Cyclohexylcarbamoylmethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **128b**, and 1-ethyl-6-fluoro-1,4-dihdyro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid **129b**.

N-Benzylcarbamoylmethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **128c**, and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid **129c**.

Morpholinocarbonylmethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **128d**, and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic accid **129d**.

3-Ethoxycarbonyloxycarbonyl derivatives of :-

1-Ethyl-1,4-dihdyro-7-methyl-4-oxo-1,8-naphthyridine **131a**, and 1-ethyl-6-fluoro-1,4-dihydro-7-(piperazin-1-yl)quinoline **131b**.

2-(1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbonyl)glyceride **136a**, and 2-[1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carbonyl] glyceride **136b**.

2-(2-Methyl-5-nitroimidazol-1-yl)ethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **137a**, and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid **137b**.

1-Methyl-2-(2-methyl-5-nitroimidazol-1-yl)ethyl esters of :-

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid **138a**, and 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid **138b**.

Biological Study :

Comprises two parts :

1- Kinetic Study :

Three selected derivatives of norfloxacin were subjected to *in vitro* hydrolysis in plasma-buffer preparation at pH 7.4, in order to evaluate their ability to release the parent drug under physiological conditions. The three tested compounds showed promising results as potentially useful prodrug candidates for norfloxacin.

2- Preliminary Antimicrobial Screening :

Fourteen compounds were chosen for screening their activity against selected Gram-positive and Gram-negative bacteria. Results indicate that some of the tested compounds showed promising activity comparable to that of reference standards.

References :

Thesis is terminated with 109 references relevant to the present study. They are cited in accordance with their notation in the context.

INTRODUCTION

The term prodrug was first introduced by Albert in 1958 to describe compounds which undergo biotransformations prior to exhibiting their pharmacological effects[1]. The rationale for prodrug design is that a molecule, with optimal structural configuration and physicochemical properties for eliciting a desired pharmacological action and expected therapeutic effect, does not necessarily possess the best molecular form and properties for its delivery at the receptor sites. Attachment of a promoiety to an active moiety would produce a prodrug that could overcome the barriers that hinder the optimal use of the active drug[1]. A basic requirement for prodrug is its adequate reconversion to the active moiety *in vivo*, **Figure 1**[2].

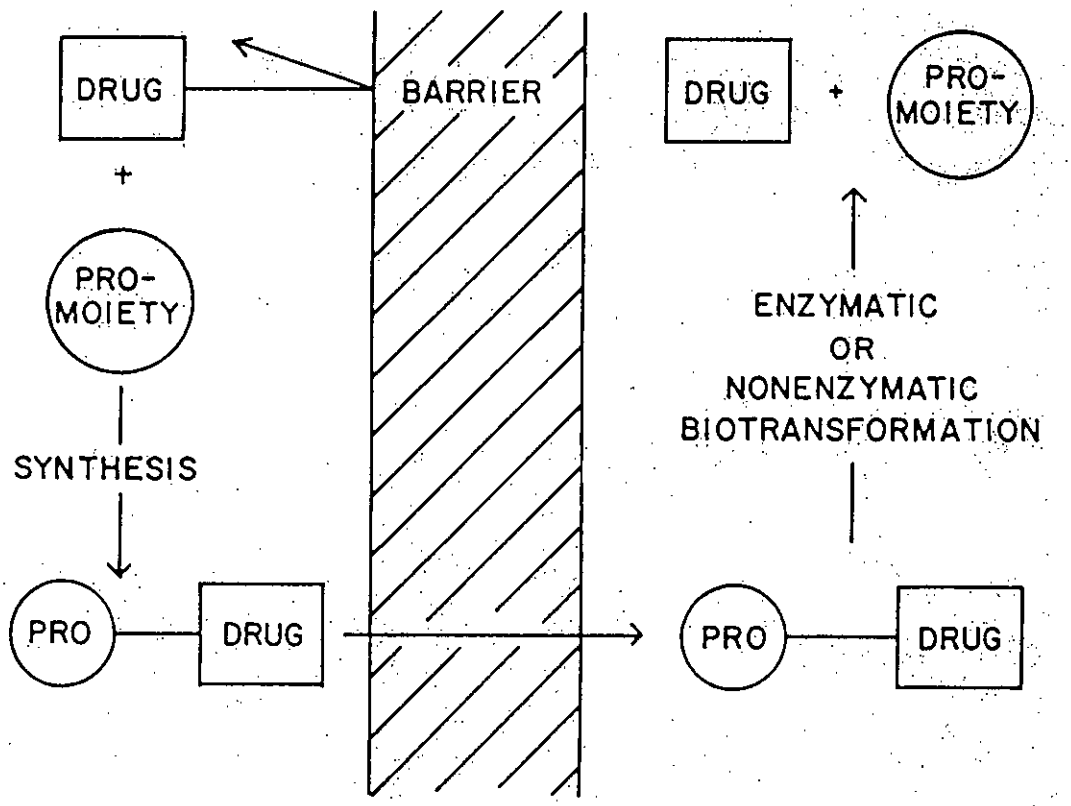

Figure 1 : The conversion of prodrug to its active form *in vivo*