سامية محمد مصطفى

شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

سامية محمد مصطفى

شبكة المعلومات الجامعية

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

سامية محمد مصطفى

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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

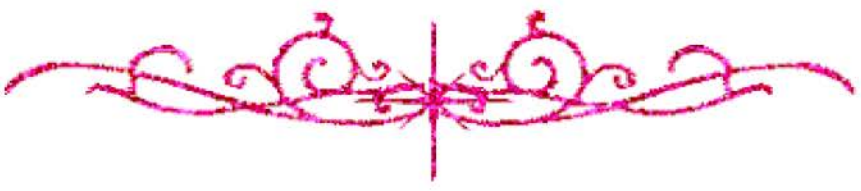
يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

سامية محمد مصطفى

شبكة المعلومات الجامعية

بعض الوثائق الأصلية تالفة



سامية محمد مصطفى

شبكة المعلومات الجامعية

بالرسالة صفحات لم ترد بالأصل

Synthesis and Biological Investigation of Some Phthalazine Derivatives

THESIS

Presented by

Heba Attia Hamed Abd El Razik

B. Pharm. Sci., 1998

M. Pharm. Sci (Pharmaceutical Chemistry), 2002

for the

Degree of Doctor of Philosophy in Pharmaceutical Sciences

(Pharmaceutical Chemistry)

Department of Pharmaceutical Chemistry
Faculty of Pharmacy
University of Alexandria
Egypt

2005

B
١٥٢٧٣

Supervisory committee

Dr. Ahmed M. Farghaly

Professor of Pharmaceutical Chemistry

Dr. Nargues S. Habib

Professor of Pharmaceutical Chemistry

Dr. Fawzia A. Ashour

Professor of Pharmaceutical Chemistry

Dr. Adnan A. Bekhit

Assistant Professor of Pharmaceutical Chemistry

Faculty of Pharmacy
Alexandria University

ACKNOWLEDGEMENT

Deepest appreciation and my everlasting thanks with sincere gratitude to *Dr. Ahmed M. Farghaly*, Professor of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, for his active supervision, continual encouragement, sincere cooperation, creative insights, parental patience, efficient guidance, valuable advice and great effort which enabled this work to be completed.

Cordial thanks and sincere gratitude are conveyed to *Dr. Nargues S. Habib*, Professor of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, for her wise and active supervision, continuous help, valuable advice, profound cooperation, efficient assistance and great effort throughout the processing stages of my work.

Profound appreciation and thankfulness to *Dr. Fawzia A. Ashour*, Professor of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, for her kindness, active supervision, valuable advice, continuous encouragement, efficient assistance and great effort along the course of this investigation.

I wish to express my sincere gratitude and deepest appreciation to *Dr. Adnan A. Bekhit*, Assistant Professor of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, for his continuous encouragement, great effort and efficient guidance during this research and for performing the preliminary antimicrobial screening.

Sincere thanks are also expressed to *Dr. Tarek Abdel-Aziem*, Department of Pharmacology, Faculty of Medicine, University of Alexandria, for performing the anti-inflammatory screening.

Extendable appreciation and thanks are expressed to *Dr. Azza M. Baraka*, Department of Pharmacology, Faculty of Medicine, University of Alexandria, for carrying out the antihypertensive evaluation.

I wish to acknowledge with appreciation the interest offered by *Dr. Saeid Belal*, Professor Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, University of Alexandria.

I would like to acknowledge Muhammed Kunhi, Manogaran S. Pulicat, Khalid Al-Hussain, Fahad Al-Khodairy, Jamal Arif Biological and Medical Research Department, and Prof. Dr. Hassan Y. Aboul-Enein, Center for Clinical Research, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia for performing the anticancer screening.

Above all, thanks GOD for giving me the potential to achieve this work.

CONTENTS

ABSTRACT

It is well-documented that phthalazines and more precisely triazolophthalazines possess broad spectrum of biological interest especially antihypertensive, anticancer, antimicrobial and anti-inflammatory activities.

Based on the above-mentioned information, different series of compounds were synthesized in this thesis containing various heterocyclic moieties joined or fused to phthalazine or triazolophthalazine ring systems to be screened for their antihypertensive, anticancer, anti-inflammatory and /or antimicrobial activities. The present thesis comprises the following chapters.

Introduction:

It constitutes a concised survey on the recent researches on biologically active phthalazines as antihypertensive, anticancer, antimicrobial, antiviral, anti-inflammatory, analgesic, antidiabetic, antihistaminic, anticonvulsant agents and many others.

Research objectives:

It deals with the rationale upon which the synthesized compounds have been designed.

Results and Discussion:

This chapter includes a discussion of the theoretical basic concepts for the already reported acceptable methods for the synthesis of the designed compounds, referring to the available knowledge in the literature. This necessitated a survey of the reported methods utilized for the preparation of compounds of comparable structures. This chapter is subdivided into five parts:

Part I: It describes preparation of the key intermediate 3-methyl-1,2,4-triazolo[3,4-a]phthalazin-6(5H)-one and its reaction with 1,3-diaryl-pyrazole-4-carbaldehydes, 4-substituted benzaldehydes and arylglyoxal

yielding the corresponding 3-[2-(1,3-diaryl-1H-pyrazol-4-yl)ethenyl]-, 3-(4-substituted styryl)- and 3-(3-aryl-3-oxopropenyl)-1,2,4-triazolo[3,4-a]-phthalazin-6(5H)-ones, respectively. The latter compounds were subjected to cyclization using hydrazine hydrate, substituted hydrazines, malononitrile/ammonium acetate, hydroxylamine and substituted thiosemicarbazides into the corresponding pyrazolinyl-, pyrazolyl-, cyanopyridyl-, oxazolyltriazolophthalazinones and substituted pyrazoloimidazotriazolophthalazinones, respectively. However, the prepared chalcones were allowed to react with thioglycolic acid to give 2-(4-substituted aroyl)-1-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)ethylthioacetic acids.

Part II: It discusses reaction of 4-hydrazino-1(2H)-phthalazinone with N-benzoyl α- and β-amino acids to yield the corresponding N-[1-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)alkyl or aralkyl]benzamides or N-[1-aryl-2-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)ethyl]benzamides, respectively. The former compounds were deprotected with concentrated hydrochloric acid to yield the corresponding 3-aminoalkyl-1,2,4-triazolophthalazinones. These were reacted again with N-benzoyl α- and β-amino acids affording N-{1-[1-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)alkylcarbamoyl]alkyl or aralkyl}benzamides and N-{2-[1-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)alkylcarbamoyl]-1-phenethyl}benzamides.

Part III: It describes synthesis of 2-(6-oxo-5,6-dihydro-1,2,4-triazolo[3,4-a]phthalazin-3-yl)acetonitrile and its reaction with aromatic aldehydes, aryl diazonium acetates, ethyl acetoacetate and thioglycolic acid affording 2-arylidene-, 2-(arylhydrazono)-2-(6-oxo-5,6-dihydrotriazolophthalazin-3-yl)acetonitriles, 4,11-dioxo-2-methyl-11,12-dihydropyridotriazolophthalazine-1-carbonitrile and 3-(4-oxothiazolidin-2-ylidene)methyltriazolophthalazinone, respectively. The latter was reacted with aromatic