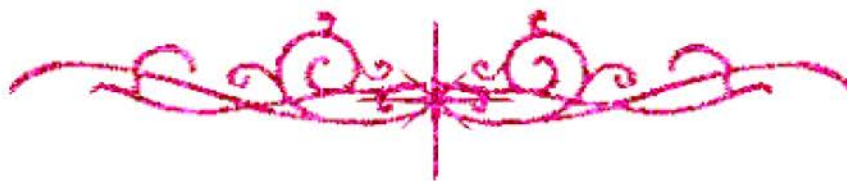


بسم الله الرحمن الرحيم





شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

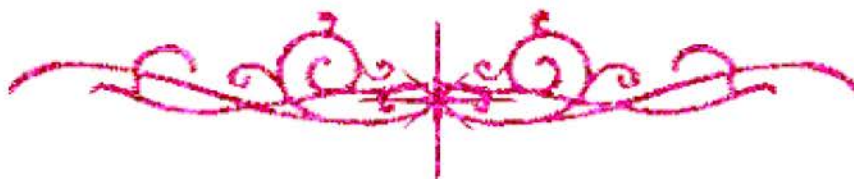
قسم

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



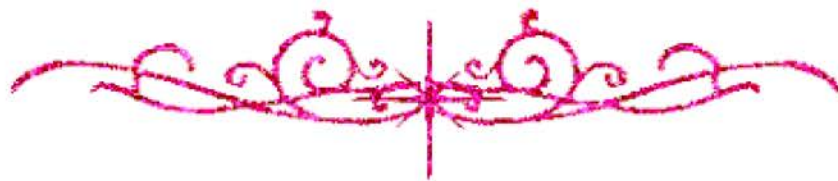
يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



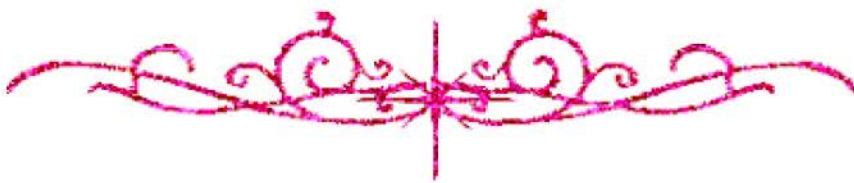


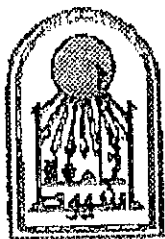
بالرسالة صفحات
لم ترد بالأصل





بعض الوثائق الأصلية تالفة





B11E.4

PREPARATION OF SOME NALIDIXIC ACID HYDRAZIDES OF POTENTIAL ANTIDEPRESSANT ACTIVITY

Thesis

Presented by

Gamal El -Din Ali Ahmed Abuo-Rahma

B. Pharm. Sci., 1990, Assiut University

For the partial fulfilment of
Master Degree of Pharmaceutical Science
(Pharmaceutical Medicinal Chemistry)

Under

Supervision of

Prof. Dr. Adel Fawzy Youssef

Prof. of Pharm. Med. Chem.,
Faculty of Pharmacy,
Assiut University

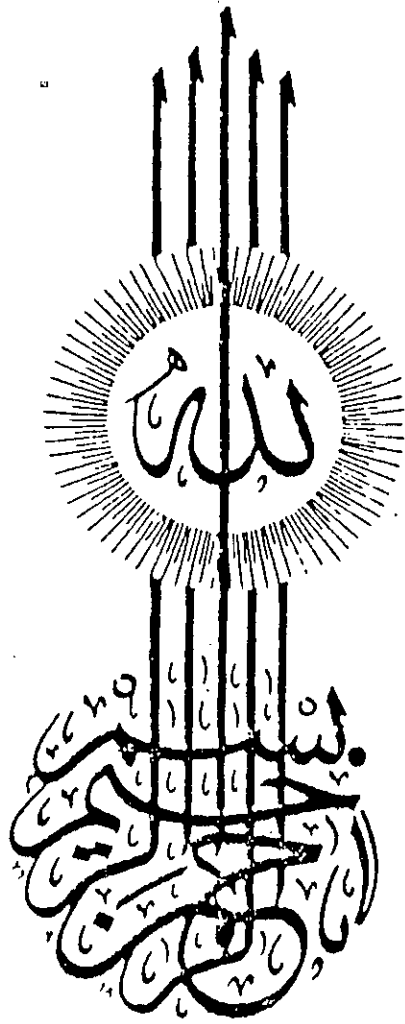
Dr. Farghaly A. Omar

Associate Prof. of Pharm. Med. Chem.,
Faculty of Pharmacy,
Assiut University

Dr. Hosney A. Elsherief

Lecturer of Pharm. Chem.,
Faculty of Pharmacy,
Al-Azhar University at Assiut

Assiut University
(1998)



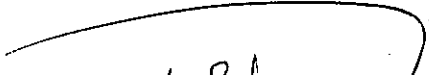
عَلَّمَ الْاِنْسَانَ مَا لَمْ يَعْلَمْ

وَالْحَمْدُ لِلّٰهِ الْعَلِيِّ الْكَبِيْرِ

Approval sheet

Committee in charge

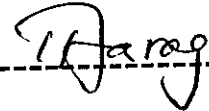
Prof. Dr. Mouhamed Y. Ebeid


M. Ebeid

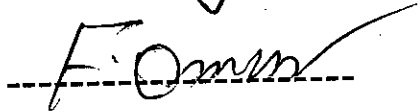
Prof. Dr. Adel F. Youssef


A. F. Youssef

Prof. Dr. Hassan H. Farag


H. H. Farag

Dr. Farghaly A. Omar


F. A. Omar

Date 24 / 8 / 1998

***To the memory of my
father, the memory of my
brothers Moustafa and
Abou-Osman, my mother
and my teachers***

ACKNOWLEDGEMENT

Praise be to Allah, the Benevolent, the Bounteous of His Guidance to perform this work.

It is a pleasure to express my sincere appreciation and deep gratitude to Prof. Dr. **Adel Fawzy Youssef**, Professor of Pharmaceutical Medicinal Chemistry, Assiut University for proper choice, planning of the research project and for his kind continuous encouragement and unfailing advice throughout this investigation and finally for revising the text.

I am deeply indebted to Dr. **Farghaly A. Omar**, Associate Professor of Pharmaceutical Medicinal Chemistry, Assiut University for proper choice, generous help, direct kind supervision, continuous encouragement during the course of this work and for revising the text.

I am deeply indebted to Dr. **Hosney A. Elsherief**, Lecturer of pharmaceutical Chemistry, Al-Azhar University at Assiut for planning of the research project and for his direct kind continuous encouragement during the course of this work and for revising the text.

My cordial gratitude to all the members of the Pharmaceutical Medicinal Chemistry Department, Faculty of Pharmacy, Assiut University; for their kind hospitality and co-operation.

I am much indebted to all members of the Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Azhar University at Assiut for their generous help.

My sincere appreciation and everlasting thanks to all members of Pharmacology Department, Faculty of Medicine, Al-Azhar University at Assiut for their valuable help in performing the biological screening.

I wish to acknowledge with appreciation the interest shown by Prof. Dr. **Hassan El-Sherief**, professor of organic Chemistry, Faculty of science, Assiut University; for helping in performing microanalysis of the synthesised compounds.

Gamal El-Din A. A. Abuo- Rahma

Assiut - Egypt

1998

CONTENTS

	Contents	Page
		i
	List of figures	iii
	List of tables	v
	List of schemes	vi
Part 1:	Introduction	1
1.1	The antidepressants	3
1.1.1	Biogenic amines reuptake inhibitors.	3
1.1.2	Atypical antidepressants.	7
1.1.3	Monoamine oxidase inhibitors (MAOIs).	7
1.1.3.1	Mechanism of action of hydrazide MAOIs.	8
1.1.3.2	Classification of MAOIs.	10
1.1.3.3	Natural MAOIs.	13
1.2	Recent aspects in MAOIs.	18
1.3	Structure activity relationship of MAOIs.	21
Part: 2	Scope of investigation.	24
Part: 3	Results and discussion.	27
3.1	Chemistry.	28
3.1.1	Resonance properties of 1,8-naphthyridine	29
3.1.2	3-(N-Formylidene, N-Alkylidene or N-Arylidene)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazides 4-23 .	34
3.1.3	3-(N-Substitutedthiocarbamoylhydrazinocarbonyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 24 and 25 .	57
3.1.4	3-(5-Substitutedamino-1,3,4-oxadiazol-2-yl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridines 26-28 .	59
3.1.5	6-Bromonalidixic acid derivatives.	69
3.1.6	3-(N-(Alkylidene or Arylidene)- 6-bromo -1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazides 34-39 .	79
3.2	Antidepressant Activity	83
Part 4:	Experimental	92
4.1	Chemistry	93

4.1.1	Synthesis of, 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 3 .	95
4.1.2	Synthesis of, 3-N-(formylidenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 4 .	96
4.1.3	Synthesis of, 3-N-(alkylidenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazides 5-8 .	97
4.1.4	Synthesis of, 3-N-(Arylidenyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazides 9-23 .	98
4.1.5	Synthesis of, 3-(N-substitutedthiocarbamoylhydrazino-carbonyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 24 and 25 .	99
4.1.6	Synthesis of, 3-(5-amino-1,3,4-oxadiazol-2-yl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 26 .	100
4.1.7	Synthesis of, 3-(5-substitutedamino-1,3,4-oxadiazol-2-yl)-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 27 and 28 .	101
4.1.8	Synthesis of, 6-bromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid 31 .	102
4.1.9	Synthesis of, Methyl 6-bromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate 32 .	103
4.1.10	Synthesis of, 6-bromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 33 .	104
4.1.11	Synthesis of, 3-N-alkylidene and arylidene-6-bromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazides 34-39 .	105
4.1.12	Synthesis of, 3-bromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 29 .	106
4.1.13	Synthesis of, 3,6-dibromo-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine 30 .	107
4.2	Antidepressant screening.	108
Part 5:	References	110

Part 6:	Abstract	121
Part 7:	Arabic summary	127

LIST OF FIGURES

Fig: 1	Diagrammatic representation showing the potential sites of action of antidepressant drugs.	4
Fig: 2	¹ H-NMR spectrum of 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 3 .	35
Fig: 3	¹ H-NMR spectrum of 3-[N-(formylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 4 .	41
Fig: 4	¹ H-NMR spectrum of 3-[N-(2-propylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 7 .	42
Fig: 5	¹ H-NMR spectrum of 3-[N-(1-propylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 6 .	43
Fig: 6	¹ H-NMR spectrum of 3-[N-(benzylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 9 .	44
Fig: 7	¹ H-NMR spectrum of 3-[N-(p-methoxybenzylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 13 .	48
Fig: 8	¹ H-NMR spectrum of 3-[N-(p-N,N-dimethylaminobenzylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 12 .	49
Fig: 9	¹ H-NMR spectrum of 3-[N-(thienylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 23 .	50
Fig: 10	¹ H-NMR spectrum of 3-[N-(p-bromoacetophenylidenyl)]-1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrazide 16 .	51