Faculty of Pharmacy
Ain Shams University

Molecular Modeling and Synthesis of New 5, 7 Dihalo-8-Hydroxy Quinoline Derivatives Having Potential Antimicrobial Activity.

Thesis
Presented by

Noha Mohamed Mostafa Zain El Abedeen
Bsc. in Pharmaceutical Sciences, May 2005
Therapeutical Chemistry Department,
National Research Center

Submitted for the partial fulfillment of the
Master Degree
In Pharmaceutical Chemistry

Under the supervision of

Prof. Dr. Mohamed Abdel Hamid Ismail
Professor of Pharmaceutical Chemistry
Ain Shams University

Prof. Dr. Hoda Hanem Fahmy Said
Professor of Pharmaceutical Chemistry,
Therapeutical Chemistry Department, National Research Center

Prof. Dr. Dalal A. Abou El Ella
Professor & Head of Pharmaceutical Chemistry Department
Ain Shams University

Faculty of Pharmacy
Ain Shams University
2011

Acknowledgement

*I am deeply thankful to **ALLAH** who helps and supports me in all my steps and granted me the strength and patience to achieve this work.*

*I am sincerely indebted and profoundly grateful to **Professor Dr. Mohamed Abdel Hamid Ismail,** Professor of Pharmaceutical Chemistry, for his kind supervision, valuable advice, constant support and continuous guidance during all stages of this work.*

*I am extremely grateful and sincerely appreciated to **Dr. Hoda Hanem Fahmy Sayed Ahmed**, professor of Pharmaceutical Chemistry, Therapeutical Chemistry Department, Pharmaceutical and Drug industries Division, National Research Center, for her untiring help, valuable assistance, constant encouragement, priceless guidance, innovative ideas and fruitful opinions throughout the whole practical work and during writing the thesis.*

*It is also my pleasure to give my deepest gratitude to **Dr. Dalal A. Abou El Ela**, Professor of Pharmaceutical Chemistry, for her scientific supervision, for her kindness, sentimental support, constant encouragement, guidance and continuous advice throughout this work and during writing this thesis. I really thank her for her great efforts and tremendous support.*

It's also my pleasure to express my sincere appreciation and gratitude to ***Dr. Nagy Mahmoud Khalifa****, Assistant Professor of Organic Chemistry, Therapeutical Chemistry Department, Pharmaceutical and Drug Industries Division, National Research Center, for his innovative ideas and fruitful opinions, Kindness, continuous interest, encouragement, indispensable comments, and real support throughout the practical part in this work.*

Special thanks to ***Prof. Dr. Abdelhamid Ali Hamdy****, Professor of Microbiology, Natural and Microbial Products department, National Research Center, for carrying out the microbiological screening.*

I owe my deepest gratitude to ***Dr. Nasser Saad Mohamed****, my dearest friends* ***Eman Mousa El-labbad*** *and* ***Abeer Hussain*** *for their help in the molecular modeling part.*

I acknowledge with thankfulness all members of our Therapeutical Chemistry Department, Pharmaceutical and Drug industries Division, National Research Center, for their friendly cooperation, support, unconditional love and aid.

I am also indebted profoundly to my grandfather, my father, my mother and my brothers for their patience, understanding and encouragement during the whole work.

Contents

List of Figures and Graphs

List of Tables

List of Abbreviations

ATP: Adenosine triphosphate.

°C: Degree centigrade.

DMSO: Dimethyl sulphoxide.

DMF: Dimethyl formamide.

DCMQ: 2, 8-dicyclopentyl-4-methylquinoline.

5-FC: 5-Fluorocytosine.

g : Gram.

HCMV: Human cytomegalovirus.

HSV-2: Herpes simplex virus type 2.

IR: Infrared

M.tb.: Mycobacterium tuberculosis.

MPK: Mappicine ketone.

MIC: Minimum inhibitory concentration.

μ: Micro

mL: Milliliter

min: Minute.

nm: Nanometer.

PDGF-RTK: Platelet derived growth factor receptor tyrosine kinase.

%: Percentage.

PDF: Peptide deformylase.

SE: Squalene epoxidase.

SDR: Single drug-resistant strains.

SQLs: Styrylquinolines.

LpxC: UDP-3-O-acyl-N-acetylglucosamine deacetylase.

Abstract

Title of Thesis:

Molecular modeling and synthesis of New 5,7 Dihalo-8-hydroxy quinoline derivatives Having Potential Antimicrobial Activity.

This thesis contains the following sections:

1-Introduction:

It contains a survey covering different antibacterial and antifungal drugs, quinoline biological uses, chemistry of quinolines and a brief introduction about the ligand base pharmacophore modeling.

2-Research Objectives:

It includes the design of 5,7 diiodo-8-hydroxyquinoline quinoline dervatives as antibacterial and antifungal agents.

3-Theoritical Discussion of experimental work :

It includes different methods of preparation that are reported in literature which were used for the preparation of the intermediate and final compounds.

4- Microbiological evaluation:

22 newely synthesized compounds were evaluated as antibacterial and antifungal agents against two bacterial and two fungal strains.

5-Molecular Modeling:

This part discusses the ligand base pharmacophore modeling to obtain a qualitative common feature hypothesis for antifungal agents and the fit values of the newly synthesized compounds.

6-Experimental:

It contains methods used in preparation of compounds and the different conditions of each reaction. The structures of these compounds were confirmed by microanalytical and spectral data.

This thesis comprises the synthesis of the following reported intermediates:

1- 1-(5,7-diiodoquinolin-8-yloxy)propan-2-one **(IX)**.

2- Ethyl 2-(5,7-diiodoquinolin-8-yloxy)acetate **(XV)**.

3- 2-(5,7-diiodoquinolin-8-yloxy)acetohydrazide **(XVIII)**.

Furthermore, the study involves the synthesis of the following new targeted compounds:

1- Ethyl 2-(5,7-diiodoquinolin-8-yloxy) propanoate **(IIa)**.

2- Ethyl 3-(5,7-diiodoquinolin-8-yloxy) propanoate **(IIb)**.

3- 2-(5,7-diiodoquinolin-8-yloxy) propanoic acid **(IIIa)**.

4- 3-(5,7-diiodoquinolin-8-yloxy) propanoic acid **(IIIb)**.

5- 2-(5,7-diiodoquinolin-8-yloxy) propanehydrazide **(IV)**.

6-2-(5,7-diiodoquinolin-8-yloxy)-1-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-one **(V)**.

7- 1-(2-(5,7-diiodoquinolin-8-yloxy)propanoyl)-3-methyl-1H-pyrazol-5(4H)-one **(VI)**.

8- 2-(5,7-diiodoquinolin-8-yloxy)-N-(1,3-dioxoisoindolin-2-yl)propanamide **(VII)**.

9- 2-(5,7-diiodoquinolin-8-yloxy)-N-(2,5-dioxopyrrolidin-1-yl)propanamide **(VIII)**.

10- 6-((5,7-diiodoquinolin-8-yloxy)methyl)-4-(4-fluorophenyl) -1,2-dihydro-2-oxopyridine-3-carbonitrile **(Xa)**.

11- 6-((5,7-diiodoquinolin-8-yloxy)methyl)-4-(4-methoxy pheny)-1,2-dihydro-2-oxopyridine-3-carbonitrile **(Xb)**.

12- 6-((5,7-diiodoquinolin-8-yloxy)methyl)-1,2-dihydro-2-imino-4-(3,4,5-trimethoxyphenyl)pyridine-3-carbonitrile **(XI)**.

13- 1-(5,7-diiodoquinolin-8-yloxy)-4-phenylbut-3-en-2-one **(XIIa)**.

14- 1-(5,7-diiodoquinolin-8-yloxy)-4-(4-fluorophenyl)but-3-en-2-one **(XIIb).**

15-1-(5,7-diiodoquinolin-8-yloxy)-4-p-tolylbut-3-en-2-one **(XIIc).**

16- 8-((4,5-dihydro-5-phenyl-1H-pyrazol-3-yl)methoxy)-5,7-diiodoquinoline **(XIV).**

17- 8-((4,5-dihydro-1,5-diphenyl-1H-pyrazol-3-yl)methoxy)-5,7-diiodoquinoline **(XIII)**.

18-1- (2- (5,7- diiodoquinolin -8- yloxy) acetyl) thiosemicarbazide

19-2-(5,7-diiodoquinolin-8-yloxy) -N- (2-hydroxyethyl)acetamide

20- 2- (5,7- diiodoquinolin -8- yloxy)-N,N-bis(2-hydroxyethyl)acetamide.

21- 2-(5,7-diiodoquinolin-8-yloxy) -N'-(D-glucose) acetohydrazide **(XIXa)**.

22- 2-(5,7-diiodoquinolin-8-yloxy) -N'- (D-xylose) acetohydrazide **(XIXb)**.

23- 2-(5,7-diiodoquinolin-8-yloxy) -N'- (D-arabinose) acetohydrazide **(XIXc)**.

24-2-(5,7-diiodoquinolin-8-yloxy) -N'- (D-mannose) acetohydrazide **(XIXd)**.

25-2-(5,7-diiodoquinolin-8-yloxy)-N'- (D-galactose) acetohydrazide **(XIXe)**.

26- (1,2,3,4,5-penta-O-acetyl-D-gluco) -(5,7-diiodoquinolin-8-yl)]acetohydrazide **(XXa)**.

27- (1,2,3,4-tetra-O-acetyl-D-xylo) -(5,7-diiodoquinolin-8-yl)]acetohydrazide **(XXb)**.

28- (1,2,3,4-tetra-O-acetyl-D-arbino) -(5,7-diiodoquinolin-8-yl)]acetohydrazide **(XXc)**.

29- N'-(1-((diethylamino)methyl)-2-oxoindolin-3-ylidene)-2-(5,7-diiodoquinolin-8-yloxy)acetohydrazide

30- N'-(1- (morpholino methyl)-2-oxoindolin-3-ylidene)acetohydrazide

7-Final Conclusion.

8-References:

This thesis includes 178 reference covering the time period from 1851 till 2011.

I-Biological Part

At present, the role of heterocyclic compounds has become increasingly important in designing new class of structural entities of medicinal importance. Among pharmacologically important heterocyclic compounds, quinoline and its derivatives have been well known in pharmaceutical chemistry because of their wide spectrum of biological activities and their presence in naturally occurring compounds[1-3]. They have been shown to possess antimicrobial[4], anti-inflammatory[5], anticancer[6,7], antibiotic[8], antihypertensive[9], antiarrythmic[10], anti HIV[11,12], antifungal[13], antiparasitic[14], antimalarial[15], antileshmanial[16], anticonvalusant[17], cardiac stimulant[18] and DNA-intercalating carriers[19]. They also function as inhibitors of 5-lipooxygenase[20], gastric (H+/K+)-ATPase[21,22] and tyrokinase PDGF-RTK[23].

I.1-Antimicrobial agents:

Infectious diseases are the confrontation of two worlds, the microbial world and the world of human physiology. Although these two worlds are as a whole governed by the same laws of nature, they show substantial differences: the microbiological world is 1000 times older, and its biomass and diversity are immense[24]. In our modern world, infectious diseases still claim millions of lives every year. Globally, infectious disease represents the second leading cause of death, and the leading cause of death for children and adults under the age of 50[25].

I.1.1-Antibacterial agents:

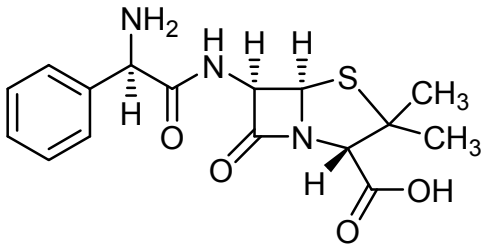
Back in the 1940s and 1950s, when the first antibiotics such as penicillin began making their way into clinical use, they were regarded as miracle drugs[26]. However, the widespread use and misuse of antibiotics since their introduction into the medical practice led to an undesired effect which is the selection for antibiotic resistant pathogens[27,28].

Resistance is reducing the effectiveness of antimicrobial therapies, increase morbidity, mortality and health care expenditure[29,30].

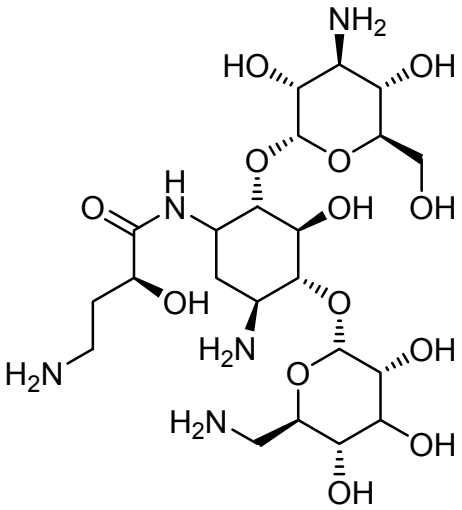
Different approaches have been taken to overcome the problem of bacterial resistance and to resolve the chemotherapeutic inefficiency. The first approach focuses on agents that combat the bacterial resistance mechanisms to revive the antibacterial potency of the parent compound. These include inhibitors of β-lactamases[31], efflux–pump inhibitors[32], etc. The second approach focuses on developing antibacterial agents with novel structures and mechanisms of action different from those of the currently utilized compounds[33,34].

Based on mechanism of action, the antibacterial agents are traditionally classified as: those that interfere with bacterial cell wall/membrane formation and function including β-lactam antibiotics (Ampicillin **1**)[35]; those that interfere with bacterial nucleic acid synthesis and replication, including rifamycins[36] and quinolones[37]; those that interfere with

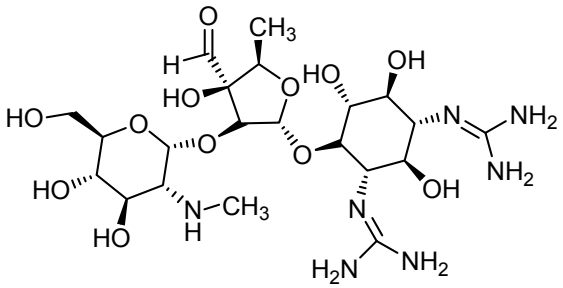
protein biosynthesis including natural products such as aminoglycosides (amikacin **2,** streptomycin **3**)[38], macrolides[39], tetracyclines[40], and synthetic products like oxazolidinones (linezolid **4**)[41]; and antimetabolites such as sulfonamides[42]. Recently, inhibitors of other bacterial targets, such as peptide deformylase (PDF)[43,44] and the enzyme required for bacterial fatty acid biosynthesis (LpxC)[45,46], have been explored as potential antibacterial agents.



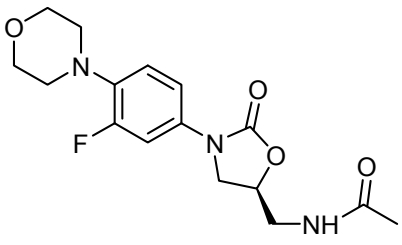
Ampicillin **1**



Amikacin **2**



Streptomycin **3**



Linezolid **4**