جامعة عين شمس
Ain Shams University
كلية الصيدلة

Computer Aided Design and Synthesis of Certain Heterocyclic Compounds with potential Biological Activity

Thesis presented by

Madonna Michael Adeeb Mitry

BSc. In pharmaceutical science (May 2013)
Instructor of Pharmaceutical Chemistry
Faculty of pharmacy-Ain Shams University

Submitted for partial fulfillment of the
Master Degree
In Pharmaceutical Sciences
(Pharmaceutical Chemistry)

Under the supervision of

Dr. Rabah Ahmed Taha Serya

Associate Professor of Pharmaceutical Chemistry
Acting Head of Pharmaceutical Chemistry Department
Faculty of pharmacy-Ain Shams University

Dr. Nermine Samir Abdou

Lecturer of Pharmaceutical Chemistry
Faculty of pharmacy-Ain Shams University

Faculty of pharmacy

Ain Shams University
2018

Acknowledgments

*I am profoundly indebted to the late **Professor Mohammed Abdelhamid Ismail**, Professor of Pharmaceutical Chemistry, for his supervision, continuous encouragement and spiritual support. I truly thank him for his great efforts and support throughout the whole work.*

*I would like to express my deep appreciation and truthful gratitude to **Professor Khaled Abouzid Mohamed,** Professor of Pharmaceutical Chemistry & Dean of faculty of pharmacy-Sadat City University, for his guidance, precious suggestions and endless support.*

*I would like also to express my sincere thanks to **Dr. Rabah A. T. Serya,** Associate Professor of Pharmaceutical Chemistry & Head of Pharmaceutical Chemistry Department, for her scientific supervision, valuable guidance and constant support throughout all stages of this work, I am really thankful for her great efforts which allowed this thesis to appear in its final form.*

*It is my genuine pleasure to express my sincere thanks to **Dr. Nermine S. Abdou,** lecturer of Pharmaceutical Chemistry, for her fruitful opinion, valuable assistance and constant encouragement during writing this thesis.*

Great appreciation to all my colleagues in Pharmaceutical Chemistry department, for their kind support, cooperation and unconditional aid.

Also I would like to express my appreciation to the virology lab, Ku Leuven University, Belgium for performing the in-vitro antiviral assay of the synthesized compounds.

Finally, I am profoundly thankful to my parents and my family for their unconditional love and aid, patience, encouragement, understanding and full support throughout the whole long way.

Besides the work presented in this thesis, the candidate successfully passed general and special postgraduate courses in Pharmaceutical Chemistry for one year during academic year 2013/2014 with the following grades

1) Statistics	Excellent
2) Instrumental Analysis	Excellent
3) Computer Science	Excellent
4) Physical Chemistry	Excellent
5) Pharmaceutical Chemistry	Excellent
6) Drug Spectroscopy	Very Good
7)Selected Topics in Pharmaceutical Chemistry	Very Good
8) Drug Stereochemistry	Excellent

Table of contents

List of Figures

List of Tables

List of Abbreviations

A°: angstrom

CAN: ceric ammonium nitrate

DCC: Dicyclohexylcarbodiimide

DCM: dichloro methane

DMAP:4-(Dimethylamino)pyridine

DMF: dimethyl formamide

DMSO: dimethyl sulphoxide

DPAT: diphenylammonium triflate

EC_{50}: Effective concentration 50

EDC.HCl : N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

EtOAc: ethyl acetate

EtOH : ethanol

FT-IR: fourier transform infrared spectroscopy

HBA: hydrogen bond acceptor

HMPA: hexamethylphosphoramide

HOBT: hydroxybenzotriazole

hrs: hours

HTS: high-throughput screening

IC_{50}: Inhibitory concentration 50

MeOH: methanol

MS: Mass spectroscopy

NMR: Nuclear magnetic resonance

NNIs: Non-nucleoside inhibitors

NS: Non structural

pd: palladium

PIs: protease inhibitors

PMHS: polymethylhydrosiloxane

PPA: polyphosphoric acid

RdRp: RNA dependant RNA polymerase

rt: room temperature

SAM: S-adenosyl methionine

TBTU: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluranium tetrafluoroborate

TEA: triethyl amine

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

TLC: Thin layer chromatography

WHO: world health organization

YFV: yellow fever virus

ZIKV: Zika virus

Abstract

Title of thesis

"Computer Aided Design and Synthesis of Certain Heterocyclic Compounds with potential Biological Activity"

Name of candidate

Madonna Michael Adeeb

Instructor of Pharmaceutical Chemistry

Ain Shams University

Thesis supervised by:

Dr. Rabah Ahmed Taha Serya (PHD)
Associate Professor of Pharmaceutical Chemistry
Acting Head of Pharmaceutical Chemistry Department
Faculty of pharmacy-Ain Shams University

Dr. Nermine Samir Abdou (PHD)
Lecturer of Pharmaceutical Chemistry
Faculty of pharmacy-Ain Shams University

The presented thesis comprises the following chapters:

1-Introduction:

Flaviviridae family comprises the flavivirus genotype which represent a significant world health problem as it includes the Yellow fever virus and Zika virus for which novel therapies are in urgent demand. The benzoimidazole scaffold has been widely reported for its antiviral activity. In this thesis a novel class of anti-Flavivirus agents containing benzimidazole scaffold were designed, synthesized and biologically evaluated for their antiviral activity.

It contains a survey covering Flaviviridae family, epidemiology, prevalence, virus genome, life cycle, viral proteins, possible antiviral targets and current treatment with emphasis on flavivirus and literature review on the reported ZIKV and YFV inhibitors.

2-Rationale and design:

The objective of our research was to design new benzimidazole derivatives as anti-flaviviral agents. The design of these compounds was based on bioisosteric modification strategy of previously reported benzimidazole-based anti-flavivirus agents supported by molecular modeling study using Discovery Studio 2.5 software. This lead to design 35 new target molecules **VIIa-zi.** Synthesis of target compounds was carried out adopting the chemical pathway outlined in schemes **(1, 2).**

3-Theoritical discussion of experimental work:

This chapter involves the discussion of chemistry, biological evaluation and molecular modeling study of target compounds.

I-Chemistry

It includes different methods for preparation which are reported in literature to be used for the preparation of intermediates and final compounds.

II-Biological evaluation

Biological activity tests of the synthesized compounds against YFV and ZIKV were carried out using cell-based replicon assay on Huh-7 and VeroE6 cell lines, respectively. This chapter includes the interpretation of the results obtained.

III-Molecular modeling

The design of anti-flavivirus agents was based on the molecular modeling by Ligand-based Pharmacophore study using Discovery Studio software.

4-Experimental

It contains the materials and methods used in preparation of the target compounds and different conditions of each reactant. The structures of the prepared compounds were confirmed by microanalytical and spectral data.

This study involved the synthesis of the following reported intermediates:

1) 4-Chloro-3-nitrobenzoic acid **(I)**
2) Ethyl 4-chloro-3-nitrobenzoate **(II)**
3) Ethyl 4-(cyclohexylamino)-3-nitrobenzoate **(III)**
4) Ethyl 3-amino-4-(cyclohexylamino)benzoate **(IV)**
5) Ethyl 1-cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxylate **(Va)**
6) Ethyl 1-cyclohexyl-2-(4hydroxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylate **(Vd)**
7) Ethyl 1-cyclohexyl-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxylate **(Ve)**
8) 1-Cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxylic acid **(VIa)**
9) 1-Cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylic acid **(VIb)**
10) 1-Cyclohexyl-2-(4hydroxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylic acid **(VId)**

Also, it comprised the following new intermediates:

1) Ethyl 1-cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylate **(Vb)**
2) Ethyl 1-cyclohexyl-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylate **(Vc)**
3) 1-Cyclohexyl-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxylic acid **(VIc)**
4) 1-Cyclohexyl-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxylic acid **(VIe)**

And finally, the study involved the synthesis and characterization of the following new-targeted compounds:

1) N,1-dicyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIa)**
2) 1-Cyclohexyl-N,2-diphenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIb)**
3) N-Benzyl-1-cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIc)**
4) 1-Cyclohexyl-N-(2-methyl-4-nitrophenyl)-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIId)**
5) 1-Cyclohexyl-N-(3,4-dichlorophenyl)-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIe)**

6) 1-Cyclohexyl-N-phenethyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIf)**

7) 1-Cyclohexyl-N-isobutyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIg)**

8) 1-Cyclohexyl-N-(4-fluorophenyl)-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIh)**

9) N-(3-Chlorophenyl)-1-cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIi)**

10) N-Butyl-1-cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIj)**

11) N,1-Dicyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIk)**

12) 1-Cyclohexyl-2-(4-methoxyphenyl)-N-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIl)**

13) N-Benzyl-1-cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIm)**

14) 1-Cyclohexyl-2-(4-methoxyphenyl)-N-(2-methyl-4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIn)**

15) 1-Cyclohexyl-N-isobutyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIo)**

16) 1-Cyclohexyl-N-cyclopropyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIp)**

17) N,1-dicyclohexyl-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIq)**

18) 1-Cyclohexyl-2-(2-methoxyphenyl)-N-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIr)**

19) N-Benzyl-1-cyclohexyl-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIs)**

20) 1-Cyclohexyl-2-(2-methoxyphenyl)-N-(2-methyl-4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIt)**

21) 1-Cyclohexyl-N-(3,4-dichlorophenyl)-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIu)**

22) 1-Cyclohexyl-2-(2-methoxyphenyl)-N-phenethyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIv)**

23) N,1-Dicyclohexyl-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIw)**

24) 1-Cyclohexyl-2-(4-nitrophenyl)-N-phenyl-1H benzo[*d*] imidazole-5-carboxamide **(VIIx)**

25) N-benzyl-1-cyclohexyl-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIy)**

26) (S)-ethyl 2-(1-cyclohexyl-2-(2-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamido)-3-phenylpropanoate **(VIIz)**

27) (S)-ethyl 2-(1-cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamido)-3-phenylpropanoate **(VIIza)**

28) N-(6-Chlorobenzo[*d*]thiazol-2-yl)-1-cyclohexyl-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzb)**

29) 1-Cyclohexyl-N-(6-nitrobenzo[*d*]thiazol-2-yl)-2-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzc)**

30) N,1-Dicyclohexyl-2-(4-hydroxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzd)**

31) 1-Cyclohexyl-2-(4-hydroxyphenyl)-N-phenyl-1H-benzo[*d*]imidazole-5-carboxamide **(VIIze)**

32) N-Benzyl-1-cyclohexyl-2-(4-hydroxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzf)**

33) 1-Cyclohexyl-2-(4-hydroxyphenyl)-N-(2-methyl-4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzg)**

34) 1-Cyclohexyl-N-(2-methyl-4-nitrophenyl)-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzh)**

35) 1-Cyclohexyl-N-(3,4-dichlorophenyl)-2-(4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide **(VIIzi)**

The biological evaluation was accomplished through testing anti-YFV activity and anti-ZIKV activity. It was performed in the virology lab of Ku Leuven University, Belgium.

12 compounds demonstrated high anti-YFV activity with YFV EC_{50} ranging from 1.14-2.5 µm. One compound **(VIId)** demonstrated good anti-ZIKV activity with ZIKV EC_{50} = 3.04 µm.

Finally, Ligand pharmacophore mapping study using ligand pharmacophore mapping algorithm in Discovery Studio 2.5 software was performed to investigate the fitting of active molecules on the generated pharmacophore model.

5-Refrences

This thesis comprises 191 refrences supporting the information in the thesis.