



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

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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 |

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## **List of Abbreviations**

**Å:** angstrom

**CAN:** ceric ammonium nitrate

**DCC:** Dicyclohexylcarbodiimide

**DCM:** dichloro methane

**DMAP:** 4-(Dimethylamino)pyridine

**DMF:** dimethyl formamide

**DMSO:** dimethyl sulphoxide

**DPAT:** diphenylammonium triflate

**EC<sub>50</sub>:** 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<sub>50</sub>:** 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”**

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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-Theoretical 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 (**VIId**)

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 (**VIIId**)
- 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 (**VIIIf**)
- 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 (**VIII**)
- 13) N-Benzyl-1-cyclohexyl-2-(4-methoxyphenyl)-1H-benzo[*d*]imidazole-5-carboxamide (**VIIIm**)
- 14) 1-Cyclohexyl-2-(4-methoxyphenyl)-N-(2-methyl-4-nitrophenyl)-1H-benzo[*d*]imidazole-5-carboxamide (**VIIIn**)
- 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 (**VIIIt**)
- 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**)
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- 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<sub>50</sub> ranging from 1.14-2.5 µm. One compound (**VIIId**) demonstrated good anti-ZIKV activity with ZIKV EC<sub>50</sub> = 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-References

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