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# **Computer Based Ligand Design and Synthesis of Phenolic Compounds with Potential Anti HCV Activity**

***Thesis  
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## List of Abbreviations

**2D:** 2-Dimensional  
**3D:** 3-Dimensional.  
**Å:** Angstroms.  
**Abu:** 2-Aminobutyric acid  
**AcOH:** Acetic acid  
**Ala:** Alanine  
**Arg:** Arginine  
**Asp:** Aspartic acid  
**ATPase:** Adenosine triphosphatase  
**C:** Core protein  
**Cys:** Cysteine  
**DMF:** Dimethyl formamide  
**E1 :** Envelope glycoprotein 1  
**ELEMS:** Glu – Leu – Glu – Met - Ser  
**ER :** Endoplasmic reticulum  
**Glu:** Glutamic acid  
**Gly:** Glycine  
**HBA:** Hydrogen bond Acceptor  
**HBD:** Hydrogen bond Donor  
**HCl:** Hydrochloric acid  
**His:** Histidine  
**hr:** hour  
**IMPDH:** Inosine monophosphate dehydrogenase  
**IRBM:** Istituto di Ricerche di Biologia Molecolare  
**IRES:** Internal ribosome entry site  
**Lys:** Lysine  
**MaxOmitFeat:** Maximum omit features  
**Met:** Methionine  
**Min:** Minute  
**NANBH:** Non-A non-B hepatitis  
**NMR:** Nuclear magnetic resonance.  
**NS:** Non structural  
**PCR :** Polymerase Chain reaction  
**PDB:** Protein data bank  
**Phe:** Phenylalanine  
**Ppm:** Part per million  
**r.t.:** Room temperature  
**RdRp:** RNA-dependent RNA polymerase  
**SAR:** Structure activity relationship  
**Ser:** Serine

**SVR:** sustained virological response  
**TBAH:** Tertiary butyl ammonium hydroxide  
**TEA:** Triethylamine  
**THF:** Tetrahydrofuran  
**THNB:** 2,4,6-trihydroxy-3-nitrobenzamides  
**Thr:** Threonine  
**TLC:** Thin Layer Chromatography  
**UTR:** Untranslated region  
**UV:** Ultraviolet  
**Val:** Valine

## **Abstract**

**Title of Thesis:**

**Computer Based Ligand Design and Synthesis of  
Phenolic Compounds with Potential Anti HCV  
Activity**

**Name of candidate:**

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## **Abstract:**

This study involves a survey covering the design and synthesis of some Phenolic derivatives.

A number of new Phenolic derivatives were designed and synthesized as anti HCV agents. The design of these agents was based on the molecular modeling simulation, by direct molecular modeling method comprising docking study on NS3/4A HCV protease enzyme using Discovery Studio software.

This thesis comprises the synthesis of the following unavailable reported starting materials and intermediates:

- 1) 3, 5-Dibromo-4-hydroxyacetophenone (**I**).
- 2) 4-(3, 5-Dibromo-4-hydroxyphenyl)-4-oxobut-2-enoic acid (**II**).
- 3) 4-(4-Acetamidophenyl)-4-oxo-butyric acid (**III**).
- 4) 4-(4-Aminophenyl)-4-oxobutyric acid (**IV**).
- 5) 3-Acetamidoacetophenone (**VIa**) and 4-Acetamidoacetophenone (**VI-b**).
- 6) 3-(Substitutedcinnamoyl)acetanilide (**VIIa, d**) and 4-(Substitutedcinnamoyl)acetanilide (**VIIb, c, e**).
- 7) 4-(3-Aryl-3-cyanopropionyl)acetanilide (**VIIIb**).
- 8) 4-(4-Aminophenyl)- 2-aryl-4-oxo-butyric acid (**IXb**).
- 9) 2-Alkyl-2-(N-phthalimidyl) acetic acid (**XIa-e**).
- 10) 2-Alkyl-2-(N-phthalimidyl)acetyl chloride (**XIIa-e**).
- 11) Ethyl 4-(2-alkyl-2-(N-phthalimidyl)acetamido) benzoate (**XIIIa-b**).
- 12) Ethyl 4-(2-alkyl-2-aminoacetamido)benzoate (**XIVa-e**).

In addition, the study comprises the synthesis of the following new intermediates:

- 1) 3-(3-Aryl-3-cyanopropionyl)acetanilide (**VIIIa, d**) and 4-(3-Aryl-3-cyanopropionyl)acetanilide (**VIIIc,e**).
- 2) 4-(3-Aminophenyl)-2-aryl-4-oxo-butyric acid (**IXa, d**) and 4-(4-Aminophenyl)-2-aryl-4-oxo-butyric acid (**IXc, e**).
- 3) Ethyl-4-(2-alkyl-2-(N-phthalimidyl)acetamido)benzoate (**XIIIc-e**).

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

- 1) 4-[4-[N-[1-Carboxy-3-(3,5 dibromo-4-hydroxyphenyl)- 3-oxo-propyl]amino]phenyl]-4-oxo-butyric acid (**V**).
- 2) 4-[3-[N-[1-carboxy-3-(3,5 dibromo-4-hydroxyphenyl)- 3-oxo-propyl]amino]phenyl]-2-aryl-4-oxo-butyric acid (**Xa, d**) and 4-[4-[N-[1-carboxy-3-(3,5 dibromo-4-hydroxyphenyl)- 3-oxo-propyl]amino]phenyl]-2-aryl-4-oxo-butyric acid (**Xb, c, e**).
- 3) Ethyl-4-[2-alkyl-2-[N-[3-(3,5 dibromo-4-hydroxyphenyl)-1-carboxy-3-oxo-propyl]amino]acetamido]benzoate (**XVa-e**).

The structures of these compounds were confirmed by microanalytical and spectral data.

Detailed descriptions of the synthesis and molecular modeling were emphasized in this thesis.

# Introduction

## **History of HCV:**

By the middle of the seventies of the 20th century it was already known that hepatitis A and B viruses were not the only causative agents of viral hepatitis in humans. A number of patients with mild hepatitis did not fit into the clinical picture of hepatitis A or B infections and their blood serum was negative for immunological markers of the two known hepatitis viruses; this disease was called: non-A non-B hepatitis (NANBH).<sup>(1, 2)</sup> By the end of the seventies, the clinical picture of the disease was well established, but the etiological factor was still unknown and laboratory tests for identification of the disease were not available. No specific antibody was found in the blood of diseased individuals and infectivity was only shown with chimpanzees (this was the first direct proof of existence of NANBH), which, of course, was not suitable for broad screening. However, it was possible to observe virus-like particles in liver tissue from both infected humans and chimpanzees.<sup>(3)</sup> A long awaited discovery was made by Choo *et al* <sup>(4)</sup> in 1989 using an extensive set of random primers; where they were able to pick up a polynucleotide sequence from the plasma of HCV- infected chimpanzees that did not belong to humans or chimpanzees. Peptides encoded by this sequence did bind antibodies from the plasma of individuals infected with NANBH, but not of healthy individuals. Hepatitis C virus was thus discovered. The procedure used in the latter experiment was immediately recognized as a ready-to-use diagnostic tool by Kuo *et al* <sup>(5)</sup>. As blood screenings began, the extent of the hepatitis C problem was soon unveiled.