

Saquinavir

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Abstract

Human immunodeficiency virus (HIV) is a subgroup of a retrovirus which causes HIV infection. It transforms over time into acquired immunodeficiency syndrome (AIDS). The human population had to fight against that virus for a long time now, so the development of drugs is an important step. The first approved drug is called "Saquinavir" (IUPAC: (2S)-N-[(2S,3R)-4-[(3S)-3-(tert-butylcarbamoyl)-decahydro isoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinolin-2-ylformamido)butanediamide). It is a HIV - protease inhibitor. Its structure is based on a polypeptide.

I. INTRODUCTION

Saquinavir is a medicament which is used for the treatment of HIV disease. The chemical structure of Saquinavir is based on a polypeptide including the amino acids Phenylalanine and Proline. The molecule can be synthesised in the laboratory as well as in a scaled up process. Considering the way of impact, it is noticeable that Saquinavir intervenes at the end of a HIV cycle.

II. HISTORY

The name "Saquinavir" was and is until today connected with hope and great expectations. Since 1900, when HIV was probably transmitted for the first time to a human, the infection has grown in an extraordinary amount and reached all around the planet. In 1999, AIDS became the fourth biggest reason for death worldwide. All around the world, scientists are working on a way to treat people who have been infected, but none of the developed medicine could meet what was needed, so far. In 1995, the situation seemed to change: Scientists had discovered that a combination of some medicine in addition with another substance had a greater effect

than just one of them. Additionally, there was another progress: Protease inhibitors were discovered. They allowed to interfere a new section of the HIV-Viruses life cycle that could not be influenced before : the most promising was Saquinavir.¹ Produced by Roche, it became approved as the medicament "Invirase" in 1995, sold in combination with other medicaments against HIV e.g. Ritonavir etc. But the contained Saquinavir was low dosed. Only 4% of effective component could be absorbed by the human body. Scientists feared that people who were taking Saquinavir in such low doses could develop a resistance against it and other Protease inhibitors. Roche reacted to those concerns with developing the medicament Fortovase being approved in 1997. Again, Saquinavir was the active component but it was higher dosed and dispensed within a soft gel formula that should help the body to absorb it better. A treatment with Fortovase, however, requires the taking of 18 pills a day. Additionally, Fortovase caused several side effects as irritation of the gastrointestinal tract, headaches and seldom liver enzymes.² In May 2005, Roche announced that they were planning to stop selling Fortovase until 2006. It shall be replaced by a more effective drug. The new medicament is considered to be

*A thank you or further information

more agreeable for the gastrointestinal tract. Furthermore, the pill's size was reduced and they do no longer have to be cooled while stored. Saquinavir is still included, combined with a small amount of Ritonavir or other medicaments against HIV. Together with Ritonavir the treatment could be reduced to 4 pills a day, taken in pairs of two times a day.³ So, Saquinavir is still a great hope in the fight against AIDS, its story has not reach its end, yet.

III. PHYSICAL PROPERTIES

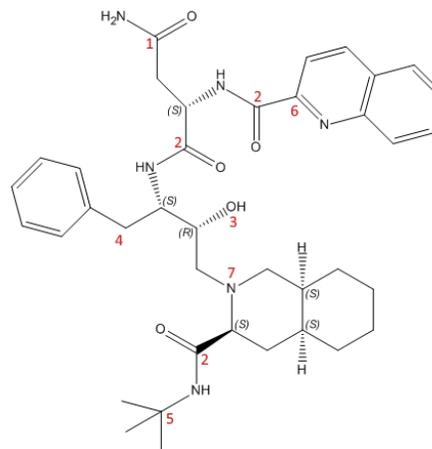
The table downsides describes the physical properties of Saquinavir.

Table 1: List of physical properties⁴⁻⁶

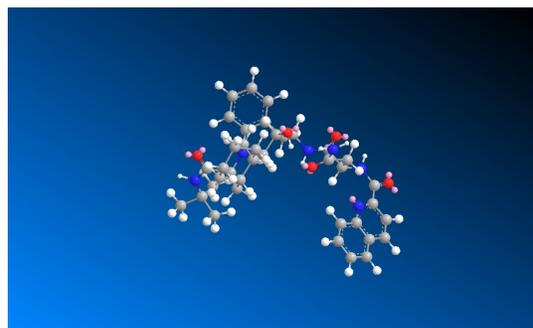
Property	Value
CAS - Number	127779-20-8
State	solid
Molecular mass	670.841 g/mol
Lethal dosis	> 5000 mg/kg (Rat, oral)
Protein binding	98%
Biological half-life	9-15 hours
Bioavailability	ca. 4%
Water solubility	Insoluble
Melting point	349.84 °C
pK _a (acid)	13.61
pK _a (base)	8.47

IV. STRUCTURE AND SYNTHESIS

I. Structure



Saquinavir is a complex molecule with many functional groups and six stereogen centres. It is noticeable that Saquinavir contains several carbonyl C-atoms. The stereogen centres are important for the impact, the CIP configuration is written in the figure. The change of only one could be harmful or dangerous. In the molecule, an amino- and three amide groups are present (1 & 2). No. 3 tags an alcohol function. There are two aromatic cycles, a benzyl (4) and quinoline (6) derivate. The tert-butyl (5) group ensures a steric obstruction in the molecule. The last noticable function is a decahydroisoquinoline group (7). Groups No. 7 and 4 are amino acid derivates. They look like Proline and Phenylalanine. So the structure is inspired by the HIV-Protease.



II. Synthesis

In the following, a possible route for the synthesis of Saquinavir is presented. Since Diazomethane is used, the synthesis is not suitable for a scaled up process. Roche has solved this problem with another reaction mechanism. The mechanism for laboratories starts with a ring opening substitution of an epoxid derivative of Phenylalanine with decaisohydroquinoline in dry iso-propanol with nitrogen atmosphere. The intermediate is purified by flash chromatography. In the second step of synthesis, the protection group is removed with gaseous hydrogen and a carbon/palladium catalyst. Furthermore, the new product reacts with N-Benzyloxycarbonyl-L-asparagine(Cbz AsnOH) in the solvents Cbz Asparagine L(Cbz Asn L) and 1-Hydroxybenzotriazolehydrat(HBOT). Afterwards, the protecting group of the former Asparagine is removed with another mixture of gaseous hydrogen and carbon/palladium catalyst. The final intermediate gets stirred in the last step of synthesis together with the solvents Tetrahydrofuran, HBOT and DCC. The mechanism formulated in detail can be found in the Appendix (VIII).⁷

V. WAY OF IMPACT

Firstly, the general mechanism of HIV disease in the human body is described. For reproduction HIV needs a host cell which has a CD4-receptor on its surface.⁸⁻⁹ The next step is the combination of surface proteins gp120 with the cell membrane of the host cell. So the proteins bind to the CD4-receptors.¹⁰ Next, the binding causes a conformation changing in the transmembrane protein gp41. HIV incorporates its genetic material in form of a RNA genome into the host cell (reverse transcription). The enzyme reverse transcriptase now changes the viral RNA into a proviral DNA in the cytoplasm, an important step in the cycle of reproduction for retroviruses.¹¹ After transporting into the cell nucleus, the

integration of the virus genome into the human genotype closes through the integrase.¹² Now, the following step is the morphogenesis where RNA genomes and HIV proteins come together.¹³ Here, Saquinavir becomes important. The HIV-Protease normally cuts the protein between proline and histidine. So it is functional.¹⁴ Saquinavir is based on the protease structure but it contains a -CH₂-COOH group where the protein is cut normally. Finally, the protease binds irreversible onto Saquinavir. It is deactivated.¹⁵ The figure also can be found in VII. - Appendix.

VI. OUTLOOK

The research of HIV medicaments has not found its end, yet. Lots of scientists work on new HIV protease inhibitors to stop the distribution of HIV. The best way would be a molecule destroying HIV viruses completely and therefore actually cure infected patients.

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VII. APPENDIX

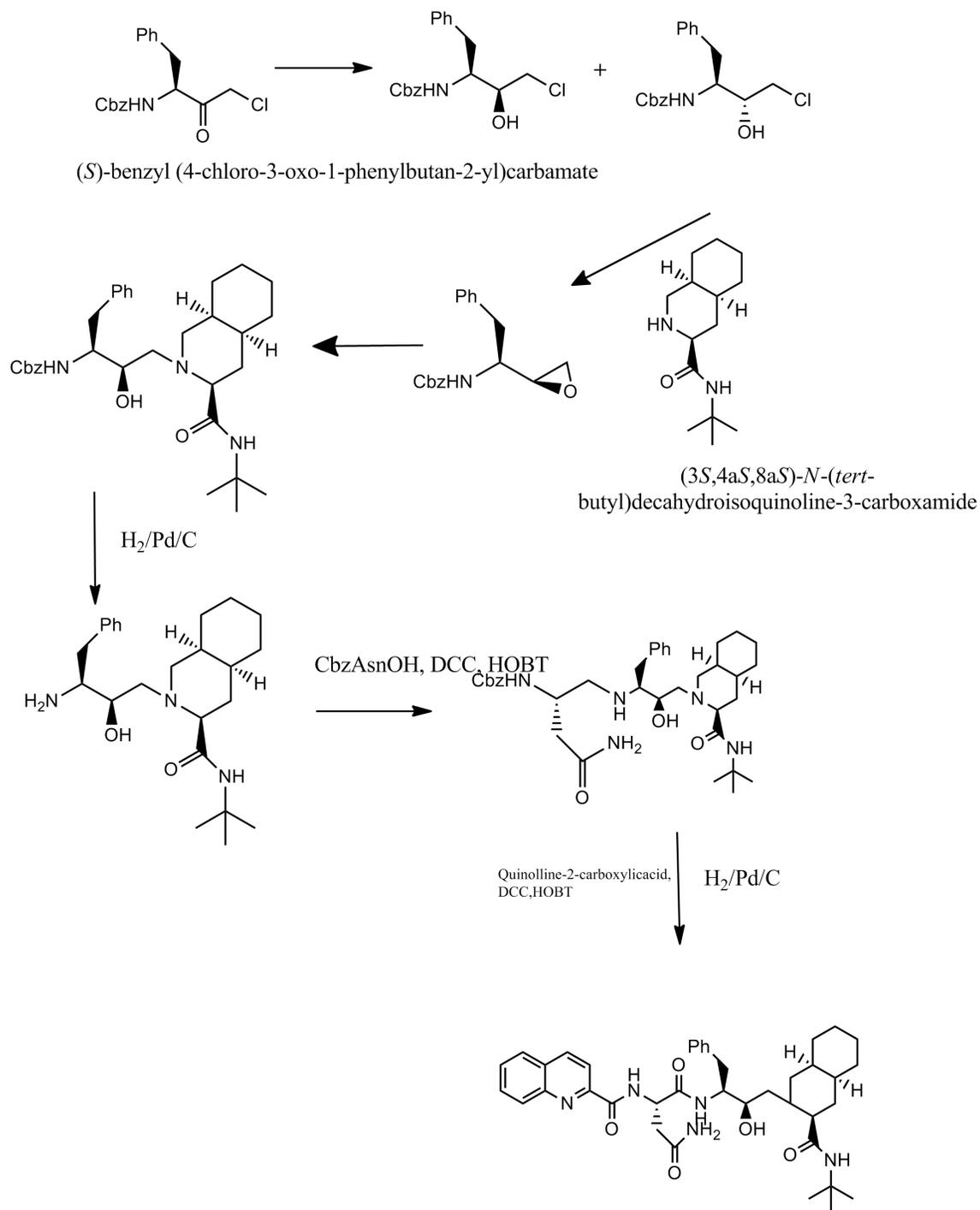


Figure 1: Laboratory synthesis of Saquinavir⁷

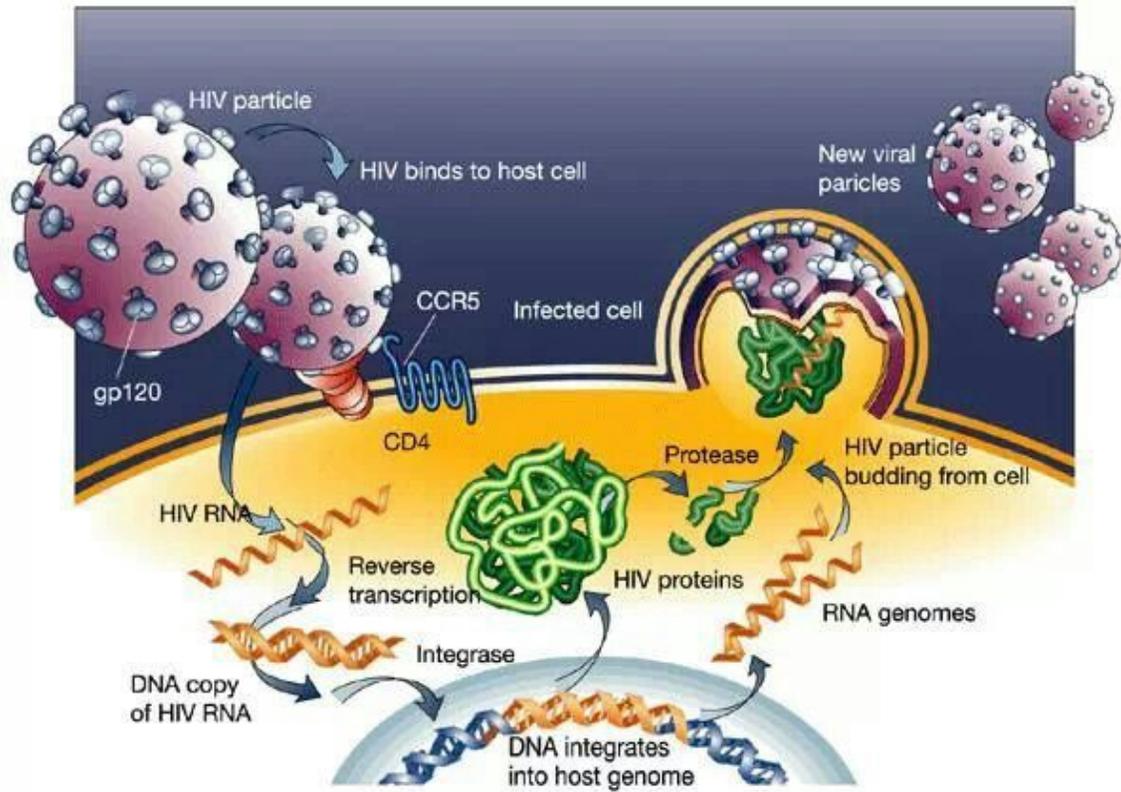


Figure 2: HIV replication cycle¹⁶