ZANAMIVIR

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June 2016

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ABSTRACT

INFLUENZA IS AN INFECTION DISEASE CAUSED BY THE INFLUENZA VIRUS A, B OR C. THE COMMON SYMPTOMS ARE HIGH FEVER, RUNNY NOSE, MUSCLE PAINS AND HEADACHE. INFLUENZA SPREADS AROUND THE WORLD IN A YEARLY OUTBREAK. APPRAISALS FROM THE WORLD HEALTH ORGANISATION (WHO) SHOWS THAT 10–20% OF THE WORLD POPULATION ARE INVOLVED. THE LARGE OUTBREAKS IN THE LAST CENTURY IN SPANISH (1918), ASIAN (1958) AND HONG KONG (1968) ARE AN CAUTIONARY TALE FOR THE WORLD. THE WHO DECLARED AN OUTBREAK OF A NEW TYPE OF INFLUENZA IN JUNE 2009, CALLED A/H1N1 SO THE DEVELOPMENT OF DRUGS IS AN IMPORTANT STEP TO FIGHT AGAINST THIS VIRUS. ZANAMIVIR IS A NEURAMINIDASE INHIBITOR AND THE FIRST INHIBITOR WHO WAS COMMERCIALLY DEVELOPED. THE ACTUAL TRADE NAME FOR THIS ORAL INHALATION POWDER IS RELENZA®. IT IS USED FOR TREATMENT AND PROPHYLAXIS OF UNCOMPROMICATED ACUTE ILLNESS OF INFLUENZA A AND B. THE STRUCTURE IS BASED ON A 3,4-DIHYDRO-2H-PYRAN. THE IUPAC-NAME IS (2R,3R,4S)-4-GUANIDINO-3-((PROP-1-EN-2-YLAMINO)-2-((1R,2R)-1,2,3-TRIHYDROXYPROPYL)-3,4-DIHYDRO-2H-PYRAN-6-CARBOXYLIC ACID.
1 INTRODUCTION

This Article will give you an short overview about the neuraminidase inhibitor Zanamivir, called Relenza®. First of all we will give you an short introduction into the history of this substancens, where and when was it discovered and about the chemical and physical properties. After that we will show you two common ways to synthesise Zanamivir, the first is a general route. The other way is shorter, include a better yield and is used in the pharmaceutical industry. In addition to the synthesises strategie we will introduce the way of impact in the human body and where are the advantages and disadvantages by using Zanamivir.

2 HISTORY

The Development of Zanamivir was based on the synthesis of the natural Substrate of Neuraminidase, the Sialic Acid. The C₄-hydroxylogroup was changed into a guanidino group. The new substituent causes the increased interaction with the active center of Neuraminidase. First successful medical results were achieved during a study in the USA in winter of 1997. 1588 patients took part in this study, whereof 455 patients were symptom-free, 1.5 days earlier than the average. First accreditation was given in Switzerland in 1999. The Australian company Biota Holdings developed Zanamivir as Relenza®, an inhalable powder. Because of the inconvenient method of consuming, the competitive product Oseltamivir (which is based on a very similar substance) replaced Relenza on the market. Since 1999 the British pharma company GlaxoSmithKline commercialized Zanamivir. In Germany Zanamivir was declared as dispensable by the federal committee.

3 PHYSICAL PROPERTIES

The following table will give you an short overview about the physical properties:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass</td>
<td>332.31 g/mol</td>
</tr>
<tr>
<td>CAS Number</td>
<td>139110-80-8</td>
</tr>
<tr>
<td>State</td>
<td>solid</td>
</tr>
<tr>
<td>Melting point</td>
<td>(253-255)°C (760 Torr)</td>
</tr>
<tr>
<td>pKa Value</td>
<td>3.82</td>
</tr>
<tr>
<td>Density</td>
<td>1.75 g/cm³</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>2 % (oral)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Biological half-life</td>
<td>2.5–5.1 h</td>
</tr>
<tr>
<td>Routes of administration</td>
<td>Inhalation</td>
</tr>
</tbody>
</table>

3.1 Structure

Zanamivir is based on a 3,4-Dihydro-2H-pyran, substituted on various positions. The chemical formula is C₁₂H₂₀N₄O₇. On the molecules position
two (starting from the oxygen going clockwise) is a Glycerol respectively a 1,2,3-Propanetriol rest. At position three an Acetamide or Ethanamide rest bound via the nitrogen atom, on position four a guanidine or iminomethanediamine rest and on position six a carboxylic acid rest. Except from position 4, which has a S, each stereogenic center in this molecule has a R as descriptor. Combining these informations, the IUPAC-Name can be build together: (2R,3R,4S)-4-Guanidino-3-(prop-1-en-2-ylamino)-2-((1R,2R)-1,2,3-trihydroxypropyl)-3,4-dihydro-2H-pyran-6-carboxylic acid. Zanamivir has a molar mass of 332.31 g/mol and melts between 253°C and 255°C. All other thermal properties are only predicted and not confirmed by experiments. The pKa value is 3.82, mainly caused by the carboxylic acid group. Zanamivirs density is at 1.75 g/cm³, induced by the nitrogen atoms in the molecule since regular organic molecules have densities smaller than 1 g/cm³. It is slightly soluble (4 g/L) in normal water but becomes more soluble the more acidic the solvent gets (947 g/L at pH 1).

Figure 1: Structure of Zanamivir – Drawn by Accelrys Draw.

Figure 2: 3D-Structure of Zanamivir – Drawn by Chemsketch.
4 SYNTHESIS

In the following there are two typical ways presented for the synthesis of Zanamivir. The first is an generally route about many steps starting by N-Acetylneuramic Acid. The second way is shorter and give an better yield.

4.1 General synthesis

The first industrial synthesis was realized by an Australian Biotech Holdings, but since the 1990s it is licensed to GlaxoSmithKline. The actual trade name for this product is Relenza®. Zanamivir can be synthesized in many ways. Most of these ways build the same intermediate, Methyl-5-acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-D-glycero-D-galacto-non-2-enonante. It can be synthesized from N-Acetylneuramic Acid (NANA) in several steps including esterfication (a), acetylation (b), substitution (c) and elimination (d).

Figure 3: Sequence for the general synthesis of Zanamivir – Drawn by Chemsketch.

The first time Zanamivir was synthesized, the intermediate was used as a starting compound. Adding BF₃ * EtOH an intramolecular ring was built (e), so the next step, adding N₃(Me₃SiN₃) (f) would be stereo selective.

In the next step, N₃ was deoxidized to NH₂ using H₂/Pd/C (g). The protecting groups (Me, Ac) were removed using Amberlite-IRA 400, aqueous Sodium hydroxide and DOWEX-50W x 8 (H⁺) (h).

The last step of the synthesis is adding Aminooiminomethylsulfonicacid to get the product (i).
4.2 Industrial synthesis

Since this way of synthesizing Zanamivir has a very low yield, needs an expensive starting material, uses unsafe reagents and for example chromatography for isolating the intermediates, this synthesis cannot be used in industry to produce large quantities of Zanamivir. A less expensive synthesis with a higher yield can be done with an organocatalytic Michael addition (j) to (Z)-tert-butyl-(2-nitrovinyl)-carbamate and an anti-selective Henry reaction (k). This synthesis has 13 linear steps and an overall yield over 18%.

Figure 4: Sequence for the industrial synthesis of Zanamivir – Drawn by Chemsketch.

5 WAY OF IMPACT

Zanamivir bind to the actice center of the influenza virus neuraminidase protein, rendering the virus unable to escape from his host cell to infect others. A process that prevents infection of new host cells and thereby the spread of infection.

The replication of the influenza virus reaches its peak between 24 and 72 hours after the onset of the illness. Zanamivir and other neuraminidase inhibitors who act at the stage of viral replication must be administered as early as possible. Inhibitors closely mimic the natural substrate, fitting into the active site pocket. This is called the lock-and-key-model. All in-
Flu patterns viruses have two surface glycoproteins: hemagglutinin and neuraminidase, which define the type of influenza virus. The variation of these glycoproteins over time permits a human response. So the development of new formulations/inhibitors is necessary each year. The neuraminidase, the target of neuraminidase inhibitor compounds, cleaves the cellular receptor sialic acid residues to which newly formed particles are attached. This事实 releases viruses, which can now invade new cells. Without neuraminidase, the infection would be limited to one round of replication. Neuraminidase inhibitors are very effective against all neuraminidase subtypes and therefore against influenza. This fact is a key point in large outbreaks of influenza (epidemic) as preparedness and an important advantage over adamantanes, which are only effective against influenza A.

5.1 Pharmacokinetics

The oral bioavailability from Zanamivir is approx. 2%. Through this low availability Zanamivir is an inhalation powder, by using a diskhaler. The concentration in lungs where up to 15% of the dose. Five to Fifteen Percent are absorbed and excreted in the urine. The inhibitory effect starts within 10 seconds. The recommend dose for Zanamivir is 10 mg once a day for 10 days (adults and pediatric patients aged 7 years and older). It can reduced the time to symptom resolution by 1.5 days if therapy was started 48 h of the onset of symptoms.

In fact of the low bioavailability, the inconvenient method of inhalation and the fact that Zanamivir is only useful if you still ill (you cannot use Zanamivir in advanced like an flu jab), it is replaced by many other substances like Relenza on the market. The actual important advantages is, that Zanamivir is a dry powder. So it can be stored in a large scale for a long period of time in preparedness for the next outbreak of an epidemic influenza, such as the outbreak in 2009.
REFERENCES


[6] SciFinder - CAS Registry Number 139110-80-8; https://scifinder.cas.org/scifinder/view/link-v1/substance.html?l=t7c60yhXV6vtSu9mamnWnq97tNAOgd1zWGAoZwlmR3zZgzeRVr-dILjbNYEhCsN2 [22.06.16, 17:04]