Diclofenac

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History and progress

The nonsteroidal anti-inflammatory drug (compounds that repress biological pain release processes) diclofenac sodium was developed in the years of 1973/1974 by the company Ciba-Geigy, which combined 1996 with the Sandoz AG to Novartis Consumer Health GmbH. The first OTC medicinal product was introduced 1979 in the United Kingdom under the trade name "Voltaren".

The development of this drug was based on three main factors: "the drug transport through biological membranes; the atomic and spatial structure of the molecule [...] and the electronic structure, which controls the specific interaction between the drug and the receptor."

By analysing the structures of anti-inflammatory drugs that were already introduced to the market, it was found, that there were some aspects in common: all had an acidity constant between 4 and 5, two aromatic rings twisted in relation to each other and a similar degree of lipophilicity, which is important for the biological transport. By considering these factors and the knowledge of cyclooxygenase receptors, the compound diclofenac sodium was designed, which fit to all these aspects.

Figure 1: Diclofenac Sodium

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The two chlorine atoms in ortho position are responsible for the twisting of the phenyl ring with an angle of torsion about 69°. It was found that the bigger the angle of torsion and the degree of lipophilicity is, the better is the biological activity of the drug and a smaller dose is needed to increase the required effects.

Figure 2 shows the different median effective dose (kaolin-edema test) in dependence of the factors torsion an lipophilicity.

Diclofenac sodium has a half-life of about 1.8 hours.

<table>
<thead>
<tr>
<th></th>
<th>Torsion</th>
<th>Partition coefficient n-octanol squ. buffer pH 7.4</th>
<th>Kaolin-edema ED₅₀ p.o. rat mg/kg</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>++ +</td>
<td>13.4</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>++</td>
<td>12.3</td>
<td>7</td>
</tr>
<tr>
<td>3.</td>
<td>+</td>
<td>6.3</td>
<td>17</td>
</tr>
<tr>
<td>4.</td>
<td>++</td>
<td>10.8</td>
<td>24</td>
</tr>
<tr>
<td>5.</td>
<td>+++</td>
<td>5.0</td>
<td>26</td>
</tr>
<tr>
<td>6.</td>
<td>+</td>
<td>1.5</td>
<td>160</td>
</tr>
</tbody>
</table>

Figure 2. Modifications of diclofenac structure at the N-phenyl ring

**Synthesis:**

Schotten-Baumann Reaction

Intramolekular Friedels Craft- Alkylation
How does it work?

Diclofenac retard tablets contain diclofenac sodium, which is a type of medicine called a non-steroidal anti-inflammatory drug (NSAID). NSAIDs are used to relieve pain and inflammation.

Diclofenac works by blocking the action of a substance in the body called cyclo-oxygenase (COX). Cyclo-oxygenase is involved in the production of various chemicals in the body, for example prostaglandin. Prostaglandins are produced by the body in response to injury and certain diseases and conditions, and cause pain, swelling and inflammation. Diclofenac blocks the production of these prostaglandins and is therefore effective at reducing inflammation and pain.

Diclofenac is used to relieve pain and inflammation in a wide range of musculoskeletal conditions, including various forms of arthritis, sprains, fractures, back pain. It is also used to relieve pain and inflammation following dental, orthopaedic and other minor surgery.
What is it used for?

**Applied as tablets:**

In adults, Diclofenac tablets are used to relieve pain and inflammation in a wide range of conditions, including those listed below (dose rate >25mg)

- Rheumatoid arthritis.
- Osteoarthritis.
- Lower back pain.
- Pain and inflammation following dental, orthopaedic and other minor surgery.

In children, Diclofenac 25 mg tablets are used for: Chronic juvenile arthritis.

**Applied as Gel:**

Diclofenac Gel is an osteoarthritis joint pain reliever that is applied topically. Diclofenac Gel is proven to work when applied directly to joints like the knees and hands.

*Figure 3: Voltaren Gel Application*
Interest

- The consumption of Diclofenac in Germany is approximately 86 tons a year. The exact amount is unknown. (2002)

- About 70% of the consumed Diclofenac leave the body unmodified, through excretion or (when gel is amplified) through shower. On this two ways Diclofenac reaches the waste water and ground-water.

- This water pollution leads to a concentration of Diclofenac in waste water of 2100 ng/L and in 1200 ng/L in surface water.

Reference

Pictures:

- Figure 1: Created with Chemsketch
- Figure 2: Sallmann A: "The history of diclofenac". *Am. J. Med.* **80** (4B): 29–33
- Figure 3: http://www.voltarengel.com/consumer/about_voltaren.aspx
- All Pictures of the Reaction was created with Chemsketch

Information

- Synthesis: omicron-online.de/cyberchem/cheminfo/diclolex.html
- Christoph Kullmer; Humanpharmaka- Rückstände in Böden: Labortests zum Abbau und Verlagerung; Cuvillier Verlag; 2005 Göttingen; Seite 2ff
- http://www.gesundheit.de/medizin/medikamente/wirkstoffe/diclofenac