Atenolol (IUPAC: (R S)-2-[4-(2-Hydroxy-3-isopropylaminopropoxy)-phenyl]-acetamid) is a chiral drug from the group of the selective β1-adrenoreceptorblockersand is usually prescribed to cure arterialhypertension (high blood pressure).

Structural characterization

Narrowing it down to its rudimental structural element Atenolol simply is a para-substituted aromatic ring with two different substituents. The substituent at the ipso carbon atom is an acetamide function while the other substituent in para-position is a so called 2-Hydroxy-3-isopropylaminopropoxy group which comprises several individual functional groups.

Illustration 1: Atenolol in Lewisprojection.

Both enantiomers show a positive effect concerning the treatment of hypertension, angina and the elimination of cardiac dysrhythmia. That is the reason why the presently being marketed atenolol is a racemic mixture. Nevertheless, the (S)-isomer has recently been found to avoid the occasional side effect of a lowered heart rate sometimes encountered with the racemate. This also makes the production of atenolol in its optically pure form interesting.

Pure atenolol is a colourless, crystalline substance which is completely odourless. It dissolves perfectly in dimethylsulfoxide, moderately in ethanol, badly in water and is as good as not soluble in ether.
**Physical properties**

![Illustration 3: Picture of atenolol with Avogadro.](image)

**Molecular formula:** $C_{14}H_{22}N_2O_3$

**CAS-Number:** 29122-68-7

**Molar mass:** 266.3 g/mol

**State:** solid

**Melting point:** 155°C

**pKₐ-value:** 9.6

**Appearance:** White powder

**Half-life in plasma:** 4-6 h

**Absorption:** 50%

**Origin and development**

Atenolol is a derivative of one of the first discovered betablockers named Propranolol (1962). Propranolol is an unselective betablocker, what means it inhibits β₁ as well as β₂-receptors. Sir James Whyte Black received the Nobel Prize in medicine in 1988 for the achievement of discovering that drug. To improve the selectivity and to find more effective betablockers with less side-effects the research has been continued since the late 60’s. Atenolol was discovered as first β₁-selective-blocking drug in 1976 by Imperial Chemical Industries (ICI). It is prescribed for the treatment of high blood pressure and accounts positively for the therapy of angina pectoris.

Because of less frequent side effects Atenolol has received a big commercial success. An important contribution for that success is that Atenolol does not cause ISA (intrinsic sympathomimetic activity). Worldwide atenolol is the third most prescribed betablocker.

**Synthesis of Atenolol**

Atenolol is prepared from the easily obtained butyl-p-hydroxyphenylacetate which is formed by an esterification of p-hydroxyphenylacetic acid and 1-butanol. The following condensation of butyl-p-hydroxyphenylacetate with chloroepoxide and catalytic pyridine leads to a mixture of the desired intermediate 1-[p-[(butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol in 70% yield and to the byproduct 1-[p-[(butoxycarbonyl)methyl]phenoxy]-2,3-epoxypropane in 30% yield. By the addition of hydrochloric acid to the reacting mixture even almost all byproduct can be converted to the desired intermediate. The chiral intermediate 1-[p-[(butoxycarbonyl)methyl]phenoxy]-3-chloropropan-2-ol at this point forms a racemic mixture [1]. Through further reaction with 2-methyl-ethanamine (RS)-[p-(butoxycarbonyl)methyl]-phenoxy]-3-(isopropylamino)propan-2-ol is gained. To obtain atenolol with a yield of 95 percent, the butyl ester derivate is treated with ammoniumhydroxide in methanol. This is followed by a recrystallization in ethyl acetate. The atenolol prepared by the described process then is a racemate[2].
Selective biotransformation

To get the optically pure enantiomers of atenolol, it is necessary to subject 1-[p-[butoxy-carbonyl)methyl]phenoxy]-3-chloropropan-2-ol to a biocatalyzed acylation.

Therefore the lipase of Pseudomonas Cepacia, a gram-negative bacterium, can be used as the catalyzed acylation with this lipase shows high selectivity towards the (S)-1-[p-[butoxycarbonyl)methyl]-phenoxy]-2-acetoxy-3-chloropropane. For the reaction there are to different possible acylating agents: vinyl acetate (VA) or acetic anhydride. The solvent in this reaction is diisopropyl ether (DIPE). The conversion stops at 50%.

If starting the biotransformation process with racemic 1-[p-[butoxy-carbonyl)methyl]phenoxy]-2-acetoxy-3-chloropropane a deacylation using 1-butanol in DIPE gives (S)-1-[p-[butoxy-carbonyl)methyl]phenoxy]-3-chloropropan-2-ol.

The R-isomer of 1-[p-[butoxy-carbonyl)methyl]phenoxy]-2-oxy-3-chloropropanoanes prepared with the help of the lipase of Candida Cylindracea[3].

Physiological significance

Atenolol operates as a \( \beta_1 \)-adrenergic receptor blocker. As soon as it reaches a certain concentration in the human blood it competes with the natural agonists such as the catecholamine norepinephrine and epinephrine for the binding site of the protein.

The binding of one of the quoted agonists to the \( \beta_1 \)-adrenergic receptor triggers a complicated signal transduction pathway leading up to the contraction of the heart muscle. Thus higher heart rates and a higher blood pressure are achieved. This is normally a very useful method of our organism to respond to an external danger or stress situation.

Nevertheless, people who suffer from a high blood pressure in rest risk their healthiness. This can lead to arteriosclerosis resulting in a myocardial infarction or a stroke.

The biological process

The target protein of atenolol, the \( \beta_1 \)-adrenoreceptor, is an integral protein of the heart muscle cells and comprises of 7 transmembrane domains. Its cytosolic side is coupled to a guanine nucleotide binding protein.

As soon as an agonistic ligand binds to the receptor its conformation changes dramatically which activates the coupled G-protein. The linked GDP is substituted by GTP and so one subunit of the G-protein is enabled to bind to the Adenylatcyclase. The Adenylatcyclase then catalyzes the production of cyclic AMP and contributes to a higher cAMP concentration in the cell. This in return induces the phosphorylation of Phospholamban, a protein which controls the membrane ionchannels for \( \text{Ca}^{2+} \).arteries.
The Adenylatcyclase then catalyzes the production of cyclic AMP and contributes to a higher cAMP concentration in the cell. This in return induces the phosphorylation of Phospholamban, a protein which controls the membrane ion channels for Ca\(^{2+}\). The regulation of the calcium stream now is the missing link between the mechanical contraction of the heart muscle caused by the movement of the actine and myosine filaments and the action potential. After the phosphorylation intracellular Ca\(^{2+}\) concentration can be increased faster which results in a shorter relaxation times and the possibility of pressing more blood through the arteries. The whole sympathomimetic stimulation is oppressed by Atenolol, as it blocks the binding sites for the activating agonists.

The affinity

The high affinity and selectivity of atenolol for the \(\beta_1\)-adrenoreceptors is due to the diverse interactions of the aryloxypropanolamine-group with different amino acids rests of the protein. The ionic interaction of the protonated form of the aminefunction with the negatively charged aspartic acid 113 is one of the stabilizing effects which make the binding of atenolol to the receptor energetically advantageous. Another interaction can be found between the hydroxyl group and the asparagine 293 in terms of a hydrogen bond. Last but not least it was proved that there is a sandwichlike-\(\pi\)-interaction between the aryrest of atenolol and phenylalanine 290 and tryptophan 286.
All of the three considered betablockers are β1-selective and do not cause ISA. An advantage of Atenolol is the rare appearance of side-effects. Most of them are a consequence of a lack of oxygen caused by low blood pressure in the muscles or the brain, for example tiredness and feeling of weakness.

One major cause for the lack of serious side effects of Atenolol is its low lipid solubility. High lipid solubilities generally facilitate the passing of drugs through the blood-brain-barrier where they can possibly result in symptoms of a damaged central nerve system like dizziness, hallucinations, mood swings and confusion. One betablocker which shows this high lipid solubility is Bisoprolol (515 mio DDD in 2007).

Consumers of Metoprolol (800 Mio DDD 2007) lament other side-effects such as the sometimes observed cardiac arrhythmia. Furthermore it can cause fetal growth-disorders, too. Complications in the phase of pregnancy in connection with the consumption of betablockers are generally not unusual. This sort of drug endangers the health of expectant mothers and their unborn children because the drugs can pass from the mother’s blood to the child’s.

One specific side effect of Atenolol is the stimulation of histamine-pouring mast cells which causes allergic reactions. If comparing the biological resorption of the three drugs the remarkable high resorption in the gastrointestinal tract of Metoprolol (95%) und Bisoprolol (90%) strikes out. But the effective biological availability of all three drugs account after 1-2 h for about 50 %, what can be lead back to the differences in hydro- or lipophilic properties. The biological half-life of Atenolol in blood plasma accounts 4-6h (Bisoprolol: 10-11h, Metoprolol: 3-5h). Thus Atenolol operates more slowly and evenly than Metoprolol and is more quickly available than Bisoprolol.

In contrast to the two other betablockers Atenolol does not undergo a first-pass metabolism in the liver because of its hydrophilie but is excreted by the kidney. Another advantage of Atenolol is the positive pharmacological effect of both enantiomers on blood pressure and heart frequency, where the S-enantiomer takes a much stronger effect. Betablocker are applied as a racemic mixture in which normally only one enantiomer shows the desired effect.

A study about Atenolol indicates that it actually lowers the blood pressure and avoids heart attacks but that it has no effect on the frequency of apoplectic strokes and on the mortality rate. Metoprolol and Bisoprolol improve the prognosis of cardiac insufficiency patients up to 35%. Positively there are no observed negative long term consequences after taking Atenolol regularly. But there were references for Atenolol being less effective on high blood pressure than other drugs.
[1] 

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \\
\text{O} & \quad \text{Cl}
\end{align*}
\]

\[\text{Pyridin}\]

\[S=70\%\]

[2] 

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[+\text{HCl}\]

\[Y=90\%\]

[3] 

Selective synthesis of S-Enantiomers

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\text{LAPS(Pseudomonas Cepacia), Acetanhydrid in Diisopropylether}\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\text{NH}_2, \text{NH}_2\text{OH, MeOH}\]

\[\text{And Enantiomer}\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[\text{And Enantiomer}\]
Selective Synthesis of R-Enantiomers

Sources:

[7] Griffin, Perry P.; Schubert-Zsilavecz, Manfred; Stark, Holger; Gemeinsamkeiten und Unterschiede: Hemmstoffe von Beta-Adrenozeptoren; Pharmazie unserer Zeit; Volume 33; Number 6; Weinheim 2004