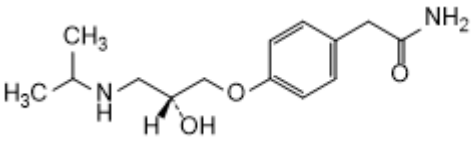
Atenolol (Atenololum)

2018-01



and enantiomer

$C_{14}H_{22}N_2O_3$

Relative molecular mass. 266.3

Chemical name. *rac*-2-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide (*IUPAC*), 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]benzeneacetamide (*CAS*), CAS Reg. No. 29122-68-7.

Description. A white or almost white powder.

Solubility. Sparingly soluble in water; soluble in ethanol (~750 g/L) TS; slightly soluble in dichloromethane R.

Category. Antihypertensive.

Storage. Atenolol should be kept in a tightly closed container.

Requirements

Atenolol contains not less than 99.0% and not more than 101.0% of $C_{14}H_{22}N_2O_3$, calculated with reference to the dried substance.

Identity tests

-Either test A or tests B and C may be applied.

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from atenolol RS or with the *reference spectrum* of atenolol.

B. The absorption spectrum of a 0.10 mg/mL solution in methanol R, when observed between 230 nm and 350 nm, exhibits 2 maxima at about 275 nm and 282 nm. The ratio of the absorbance at 275 nm to that at 282 nm is between 1.15 and 1.20.

C. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silanized silica gel R4 as the coating substance and a mixture of 99 volumes of methanol R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of 2 solutions in methanol R containing (A) 10 mg of the test substance per mL and (B) 10 mg of atenolol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

Solution S. Dissolve 0.10 g of the test substance in carbon-dioxide-free water R and dilute to 10.0 mL with the same solvent.

Optical rotation (*1.4*). Use solution S; α= +0.10° to -0.10°.

Clarity and colour of solution. Solution (S) is clear and not more intensely coloured than degree 6 of the range of reference solutions of the most appropriate colour, when compared as described under *1.11.2 Degree of coloration of liquids*, Method II.

Chlorides. Dissolve 0.25 g in a mixture of 2 mL of nitric acid (~130 g/L) TS and 20 mL of water R and proceed as described under *2.2.1 Limit test for chlorides*; the chloride content is not more than 1.0 mg/g.

Sulfated ash (*2.3*). Not more than 1.0 mg/g, determined using 1.0 g.

Loss on drying. Dry 1.0 g of the test substance to constant mass at 105 °C; it loses not more than 5.0 mg/g.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (12.5 cm × 4.0 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

Use the following mobile phase: dissolve 1.0 g of sodium octanesulfonate R and 0.4 g of tetrabutylammonium hydrogen sulfate R in 1000 mL of a mixture of 80 volumes of a 3.4 mg/mL solution of potassium dihydrogen phosphate R, the pH of which has been adjusted to 3.0 with phosphoric acid (~1440 g/L), 18 volumes of methanol R and 2 volumes of tetrahydrofuran R.

Prepare the following solutions in mobile phase. For solution (1) dissolve 50 mg of the test substance in 20 mL and dilute to 25.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 2

mg of atenolol for system suitability RS (containing atenolol and the impurities B, F, G, I and J) in 1.0 mL of the mobile phase.

Operate with a flow rate of 0.6 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 226 nm.

Inject 10 µL of solution (3). Record the chromatograms for 5 times the retention time of atenolol (retention time about 8 minutes). Use the chromatogram obtained with solution (3) and the chromatogram supplied with atenolol for system suitability RS to identify the peaks due to atenolol and the impurities B, F, G, I and J. The impurities are eluted at the following relative retention with reference to atenolol: impurity B about 0.3; impurity J about 0.7; impurity I about 0.8; impurity F about 2.0 (pair of peaks) and impurity G about 3.5.

The test is not valid unless the resolution between the peaks due to the impurities J and I is at least 1.4.

Inject alternately 10 µL each of solutions (1) and (2).

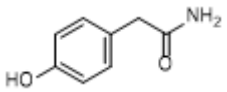
In the chromatogram obtained with solution (1):

- -the area of any peak corresponding to impurity B is not greater than 2 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.2%);
- -the area of any peak corresponding to either impurity F, G, I or J is not greater than 1.5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.15%);
- -the area of any other impurity peak is not greater than the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.10%);
- -the sum of the areas of all impurity peaks is not greater than 5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.05%).

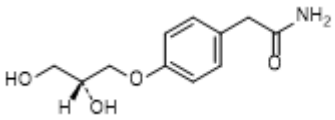
Assay. Dissolve 0.200 g in 80 mL of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/L) VS as described under *2.6 Non-aqueous titration*, Method A, determining the end-point potentiometrically.

Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.63 mg of $C_{14}H_{22}N_2O_3$.

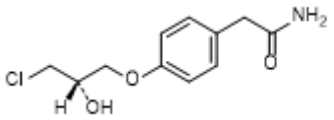
Impurities



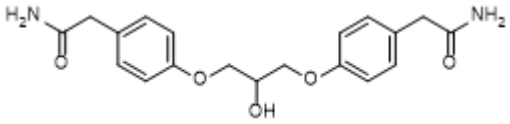
A. 2-(4-hydroxyphenyl)acetamide



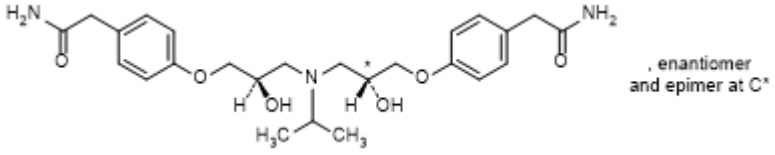
B. *rac*-2-[4-(2,3-dihydroxypropoxy)phenyl]acetamide



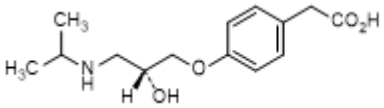
D. *rac*-2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetamide



E. 2,2'-[(2-hydroxypropane-1,3-diyl)bis(oxy-4,1-phenylene)]diacetamide

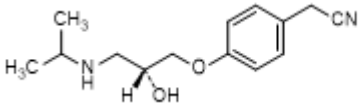


F. 2,2'{[(propane-2-yl)azanediyl]bis[(2-hydroxypropane-3,1-diyl)oxy-4,1-phenylene]}diacetamide (mixture of (2*R*,2'*R*), (2*S*,2'*S*) and (2*R*,2'*S*) isomers)



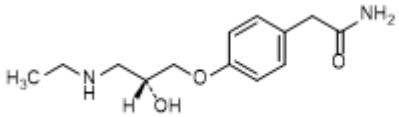
and enantiomer

G. *rac*-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetic acide



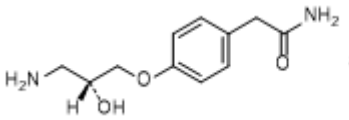
and enantiomer

H. *rac*-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetonitrile



and enantiomer

I. *rac*-2-{4-[3-(ethylamino)-2-hydroxypropoxy]phenyl}acetamide



and enantiomer

J. *rac*-2-[4-(3-amino-2-hydroxypropoxy)phenyl]acetamide.