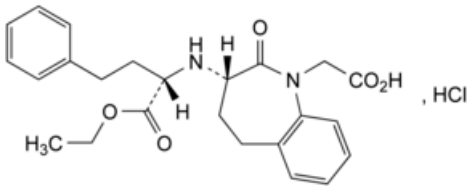
Edition: BP 2025 (Ph. Eur. 11.6 update)

Benazepril Hydrochloride

General Notices

(Ph. Eur. monograph 2388)



$C_{24}H_{29}ClN_2O_5$ 461.0 *86541-74-4*

Action and use

Angiotensin converting enzyme inhibitor.

Ph Eur

DEFINITION

[(3*S*)-3-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid hydrochloride.

Content

97.5 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Slightly soluble in water, freely soluble in anhydrous ethanol, very slightly soluble in ethyl acetate, practically insoluble in cyclohexane.

It shows polymorphism (*5.9*).

IDENTIFICATION

Carry out either tests A, B, D or tests B, C, D.

A. Specific optical rotation (2.2.7): -141 to -136 (dried substance).

Dissolve 1.000 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *benazepril hydrochloride CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness and record new spectra using the residues.

C. Enantiomeric purity (see Tests).
D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Test solution (b) Dilute 10.0 mL of test solution (a) to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *benazepril hydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 10.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dissolve the contents of a vial of *benazepril for system suitability CRS* (containing impurities B, C, D, E, F and G) in 1.0 mL of test solution (a).

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.30 m, Ø = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase Add 0.2 mL of *glacial acetic acid R* to 1000 mL of a mixture of 360 volumes of *water R* and 640 volumes of *methanol R2*; add 0.81 g of *tetrabutylammonium bromide R* and stir to dissolve.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 25 µL of test solution (a) and reference solutions (b) and (c).

Run time 3 times the retention time of benazepril.

Relative retention With reference to benazepril (retention time = about 6 min): impurity E = about 0.3; impurity F = about 0.4; impurity C = about 0.5; impurity B = about 1.8; impurity D = about 2.0; impurity G = about 2.5.

Identification of impurities Use the chromatogram supplied with *benazepril for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E, F and G.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to benazepril and impurity B and minimum 1.5 between the peaks due to impurities E and F.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.5; impurity F = 0.7;

— *impurity B*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *impurities D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29).

Buffer solution pH 6.0 Dissolve 3.58 g of disodium hydrogen phosphate dodecahydrate R and 9.66 g of potassium dihydrogen phosphate R in water R and dilute to 1000.0 mL with the same solvent.

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5.0 mg of benazepril impurity A CRS in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 100.0 mL with the mobile phase.

Reference solution (c) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: spherical silica gel AGP for chiral chromatography R (5 µm);

— *temperature*: 30 °C.

Mobile phase methanol R2, buffer solution pH 6.0 (20:80 *V/V*).

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 50 µL of the test solution and reference solutions (b) and (c).

Run time 3.5 times the retention time of benazepril.

Relative retention With reference to benazepril (retention time = about 6 min): impurity A = about 1.9.

System suitability Reference solution (c):

— peak-to-valley ratio: minimum 2.5, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to benazepril.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Loss on drying (2.2.32)

Maximum 1.5 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (a).

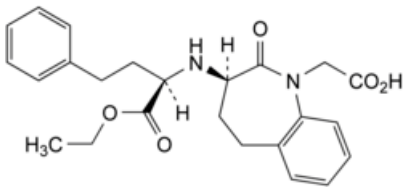
Calculate the percentage content of $C_{24}H_{29}ClN_2O_5$ from the declared content of *benazepril hydrochloride CRS*.

STORAGE

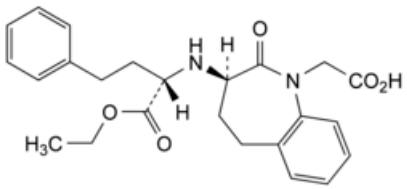
Protected from light, in an airtight container.

IMPURITIES

Specified impurities *A, B, C, D, E, F, G.*

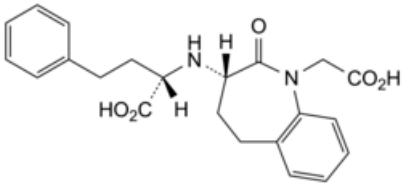


A. [(3*R*)-3-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,

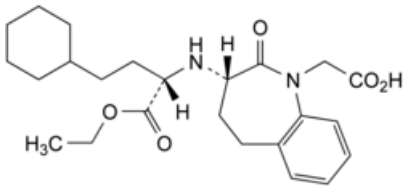


and enantiomer

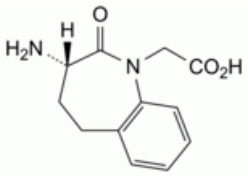
B. [(3*RS*)-3-[[(1*SR*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



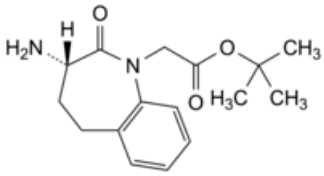
C. (2*S*)-2-[[(3*S*)-1-(carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoic acid,



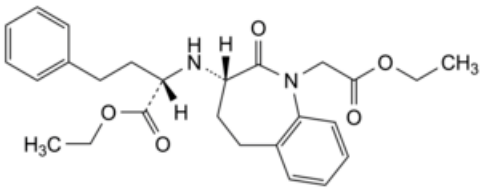
D. [(3*S*)-3-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



E. [(3*S*)-3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid,



F. 1,1-dimethylethyl [(3*S*)-3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetate,



G. ethyl (2*S*)-2-[[(3*S*)-1-(2-ethoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-3-yl]amino]-4-phenylbutanoate.

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