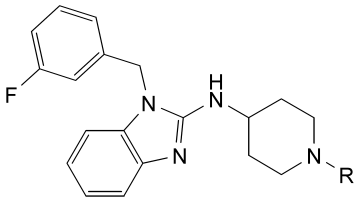
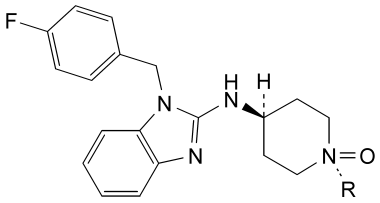
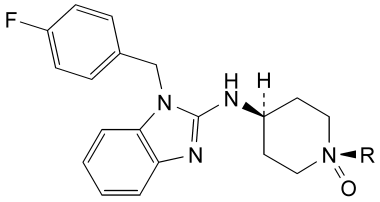


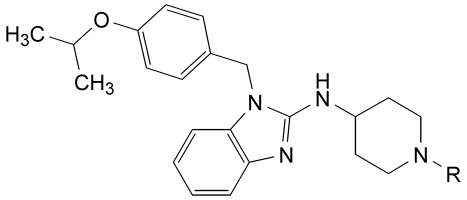
D. 1-(3-fluorobenzyl)-*N*-[1-[2-(4-methoxyphenyl)ethyl]-piperidin-4-yl]-1*H*-benzimidazol-2-amine,



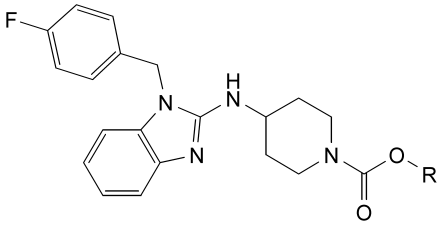
E. 1-(4-fluorobenzyl)-*N*-[*cis*-1-[2-(4-methoxyphenyl)ethyl]-piperidin-4-yl 1-oxide]-1*H*-benzimidazol-2-amine,



F. 1-(4-fluorobenzyl)-*N*-[*trans*-1-[2-(4-methoxyphenyl)ethyl]-piperidin-4-yl 1-oxide]-1*H*-benzimidazol-2-amine,



G. *N*-[1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl]-1-[4-(1-methylethoxy)benzyl]-1*H*-benzimidazol-2-amine,

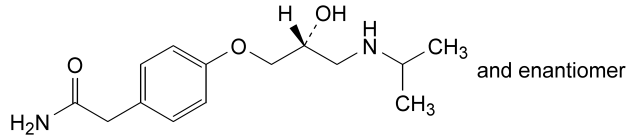


H. 2-(4-methoxyphenyl)ethyl 4-[[1-(4-fluorobenzyl)-1*H*-benzimidazol-2-yl]amino]piperidin-1-carboxylate.

01/2008:0703
corrected 6.0

ATENOLOL

Atenololum



and enantiomer

$C_{14}H_{22}N_2O_3$ M_r 266.3
[29122-68-7]

DEFINITION

Atenolol contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 2-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetamide, calculated with reference to the dried substance.

CHARACTERS

A white or almost white powder, sparingly soluble in water, soluble in ethanol, slightly soluble in methylene chloride.

IDENTIFICATION

First identification: C.

Second identification: A, B, D.

A. Melting point (*2.2.14*): 152 °C to 155 °C.

B. Dissolve 0.100 g in *methanol R* and dilute to 100 ml with the same solvent. Dilute 10.0 ml of this solution to 100 ml with *methanol R*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows two absorption maxima, at 275 nm and 282 nm. The ratio of the absorbance measured at the maximum at 275 nm to that measured at the maximum at 282 nm is 1.15 to 1.20.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *atenolol CRS*.

D. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 10 mg of the substance to be examined in 1 ml of *methanol R*.

Reference solution. Dissolve 10 mg of *atenolol CRS* in 1 ml of *methanol R*.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R1* and 99 volumes of *methanol R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Solution S. Dissolve 0.10 g in *water R* and dilute to 10 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than degree 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Optical rotation (*2.2.7*). Determined on solution S, the angle of optical rotation is + 0.10° to – 0.10°.

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in 20 ml of the mobile phase and dilute to 25.0 ml with the mobile phase.

Test solution (b). Dissolve 50.0 mg of the substance to be examined in 0.1 ml of *dimethyl sulphoxide R*, if necessary applying gentle heat by placing the containing vessel in a water-bath for a few seconds, and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dilute 0.5 ml of test solution (a) to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 50.0 mg of *atenolol for column validation CRS* in 0.1 ml of *dimethyl sulphoxide R*, if necessary applying gentle heat by placing the containing vessel in a water-bath for a few seconds, and dilute to 25.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.15 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1.0 ml/min a mixture prepared as follows: dissolve 1.0 g of *sodium octanesulphonate R* and 0.4 g of *tetrabutylammonium hydrogen sulphate R* in 1 litre of a mixture of 20 volumes of *tetrahydrofuran R*, 180 volumes of *methanol R* and 800 volumes of a 3.4 g/l solution of *potassium dihydrogen phosphate R*; adjust to pH 3.0 with *phosphoric acid R*,

– as detector a spectrophotometer set at 226 nm.

Equilibrate the column with the mobile phase at a flow rate of 1.0 ml/min for about 30 min.

Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with 10 µl of reference solution (a) is at least 50 per cent of the full scale of the recorder.

Inject 10 µl of reference solution (b). The resulting chromatogram is similar to that of the specimen chromatogram provided with *atenolol for column validation CRS* in that the peak due to bis-ether precedes and is separated from that due to tertiary amine which normally appears as a doublet. If necessary, adjust the concentration of sodium octanesulphonate in the mobile phase. Increasing the concentration of sodium octanesulphonate increases the retention time of the tertiary amine.

Inject separately 10 µl of test solution (a) and reference solution (a). Continue the chromatography for four times the retention time of the principal peak. In the chromatogram obtained with test solution (a): the area of any peak apart from the principal peak is not greater than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent); the sum of the areas of all the peaks, apart from the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Disregard any peak with an area less than 0.1 times of that of the principal peak in the chromatogram obtained with reference solution (a).

If the substance to be examined is found to contain more than 0.15 per cent of bis-ether, its compliance is confirmed by repeating the chromatography using 10 µl of test solution (b).

Chlorides (*2.4.4*). Dissolve 50 mg in a mixture of 1 ml of *dilute nitric acid R* and 15 ml of *water R*. The solution, without further addition of *dilute nitric acid R*, complies with the limit test for chlorides (0.1 per cent).

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

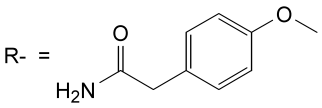
Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

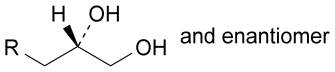
Dissolve 0.200 g in 80 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 26.63 mg of $C_{14}H_{22}N_2O_3$.

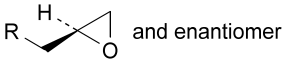
IMPURITIES



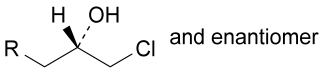
A. R-H: 2-(4-hydroxyphenyl)acetamide,



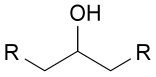
B. 2-[4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]acetamide,



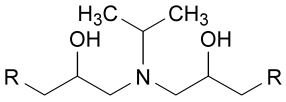
C. 2-[4-[[(2*RS*)-oxiran-2-yl]methoxy]phenyl]acetamide,



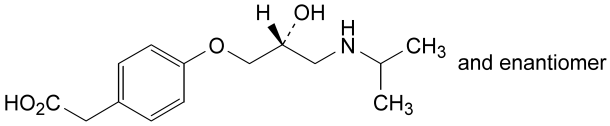
D. 2-[4-[(2*RS*)-3-chloro-2-hydroxypropoxy]phenyl]acetamide,



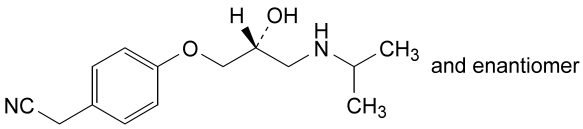
E. 2,2′-[2-hydroxypropan-1,3-diylbis(oxy-4,1-phenylene)]diacetamide,



F. 2,2′-[(1-methylethyl)iminobis(2-hydroxypropan-3,1-diyloxy-4,1-phenylene)]diacetamide,



G. 2-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetic acid,



H. 2-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetonitrile.