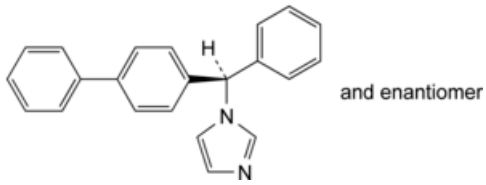
Edition: BP 2025 (Ph. Eur. 11.6 update)

Bifonazole

General Notices

(Ph. Eur. monograph 1395)



$C_{22}H_{18}N_2$ 310.4 *60628-96-8*

Action and use

Antifungal.

Ph Eur

DEFINITION

1-[(*RS*)-(Biphenyl-4-yl)phenylmethyl]-1*H*-imidazole.

Content

98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Practically insoluble in water, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison bifonazole CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of 2-propanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Buffer solution pH 3.2 Mix 2.0 mL of phosphoric acid R with 980 mL of water R, adjust to pH 3.2 (2.2.3) with triethylamine R and dilute to 1000.0 mL with water R.

Test solution Dissolve 50.0 mg of the substance to be examined in 25 mL of acetonitrile R and dilute to 50.0 mL with buffer solution pH 3.2.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with buffer solution pH 3.2. Dilute 1.0 mL of this solution to 10.0 mL with buffer solution pH 3.2.

Reference solution (b) Dissolve 2 mg of bifonazole for system suitability CRS (containing impurities A, B, C, D and E) in 2 mL of acetonitrile R and dilute to 10.0 mL with buffer solution pH 3.2.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: octadecylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, buffer solution pH 3.2 (20:80 *V/V*);

— *mobile phase B*: buffer solution pH 3.2, acetonitrile R1 (20:80 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	60	40
8 - 12	60 → 10	40 → 90
12 - 30	10	90

Flow rate 1 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL.

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

Relative retention With reference to bifonazole (retention time = about 4 min): impurity C = about 0.2; impurity B = about 0.7; impurity A = about 3.2; impurity D = about 3.6; impurity E = about 5.8.

System suitability Reference solution (b):

— resolution: minimum 2.5 between the peaks due to impurity B and bifonazole.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2;

— *impurities B, D*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurities A, C*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity E*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

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

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

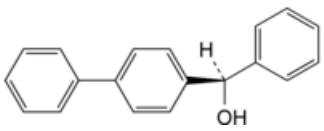
ASSAY

Dissolve 0.250 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 31.04 mg of $C_{22}H_{18}N_2$.

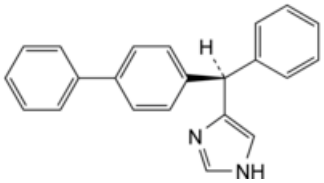
IMPURITIES

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



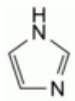
and enantiomer

A. (*RS*)-(biphenyl-4-yl)phenylmethanol,

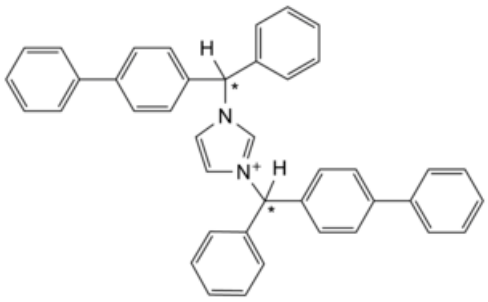


and enantiomer

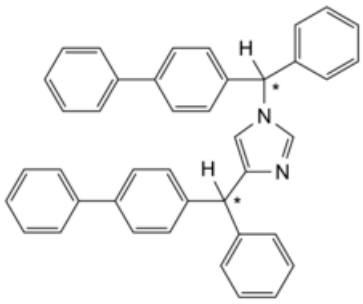
B. 4-[(*RS*)-(biphenyl-4-yl)phenylmethyl]-1*H*-imidazole,



C. 1*H*-imidazole,



D. 1,3-bis[(biphenyl-4-yl)phenylmethyl]-1*H*-imidazolium ion,



E. 1,4-bis[(biphenyl-4-yl)phenylmethyl]-1*H*-imidazole.

Ph Eur