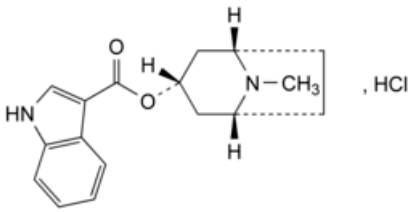
Edition: BP 2025 (Ph. Eur. 11.6 update)

Tropisetron Hydrochloride

General Notices

(Ph. Eur. monograph 2102)



$C_{17}H_{21}ClN_2O_2$ 320.8 *105826-92-4*

Action and use

Serotonin $5HT_3$ receptor antagonist; antiemetic.

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DEFINITION

Hydrochloride of (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1*H*-indole-3-carboxylate.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble or soluble in water, sparingly soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 50 mg in methanol R and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with methanol R.

Spectral range 220-360 nm.

Absorption maxima At 228 nm and 282 nm.

Absorbance ratio A_{228}/A_{282} = 1.3 to 1.4.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison tropisetron hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 5 mL with the same mixture of solvents.

Reference solution Dissolve 5 mg of tropisetron hydrochloride CRS in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 5 mL with the same mixture of solvents.

Plate TLC silica gel F_{254} plate R.

Mobile phase anhydrous formic acid R, water R, methanol R, methylene chloride R (2:2:30:70 *V/V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In cold air.

Detection A Examine in ultraviolet light at 254 nm.

Detection B Spray first with a solution prepared as follows: dissolve 0.85 g of bismuth subnitrate R in a mixture of 10 mL of acetic acid R and 40 mL of water R; to 5 mL of this solution add 5 mL of a 400 g/L solution of potassium iodide R and dilute to 100 mL with water R. Then spray with strong hydrogen peroxide solution R.

Results For both detection methods, 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.

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution B_7 (2.2.2, Method II).

Dissolve 1.00 g in water R and dilute to 20 mL with the same solvent.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.200 g of the substance to be examined in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 5.0 mL with the same mixture of solvents.

Reference solution (a) Dissolve 5.0 mg of tropine CRS (impurity A) in a mixture of equal volumes of methanol R and methylene chloride R and dilute to 25.0 mL with the same mixture of solvents.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with a mixture of equal volumes of methanol R and methylene chloride R. To 0.1 mL of this solution add 1.0 mL of reference solution (a).

Plate TLC silica gel F_{254} plate R.

Mobile phase *ammonia R*, *methanol R*, *methylene chloride R* (5:40:60 *V/V/V*).

Application 10 µL.

Development Over 2/3 of the plate.

Drying In a current of cold air.

Detection Dip the plate in *potassium iodobismuthate solution R1*.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 20.0 mL with mobile phase A.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b) Dissolve 5.0 mg of *tropisetron impurity B CRS* and 5 mg of *ethyl indole-3-carboxylate CRS* in mobile phase A and dilute to 20.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:35:400:565 *V/V/V/V*);

— *mobile phase B*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:100:100:800 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	100	0
14 - 32	100 → 0	0 → 100
32 - 36	0	100
36 - 37	0 → 100	100 → 0
37 - 52	100	0

Flow rate 2 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Relative retention With reference to tropisetron (retention time = about 22 min): impurity B = about 0.05; ethyl indole-3-carboxylate = about 0.2.

System suitability Reference solution (b):

— *resolution*: minimum 4 between the peaks due to impurity B and ethyl indole-3-carboxylate.

Limits:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

***N*,*N*-Dimethylaniline**

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Dissolve 250 mg of the substance to be examined in mobile phase A and dilute to 5.0 mL with mobile phase A.

Reference solution Dissolve 10.0 mg of *N,N-dimethylaniline R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *triethylamine R*, *acetonitrile R*, *water R*, *methanol R* (0.3:35:400:565 *V/V/V/V*);

— *mobile phase B*: *triethylamine R*, *acetonitrile R*, *water R*; *methanol R* (0.3:100:100:800 *V/V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 11	100 → 0	0 → 100
11 - 30	0	100
30 - 31	0 → 100	100 → 0
31 - 50	100	0

Flow rate 1 mL/min.

Detection Spectrophotometer at 248 nm.

Injection 20 µL.

Limit:

— *N,N-dimethylaniline*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (20 ppm).

Loss on drying (2.2.32)

Maximum 0.3 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.

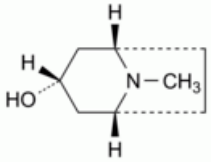
ASSAY

Dissolve 0.250 g in 10 mL of *anhydrous acetic acid R* and add 70 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

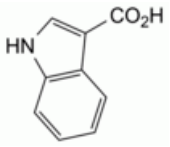
1 mL of *0.1 M perchloric acid* is equivalent to 32.08 mg of $C_{17}H_{21}ClN_2O_2$.

IMPURITIES

Specified impurities *A, B.*



A. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (tropine),



B. 1*H*-indole-3-carboxylic acid.

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