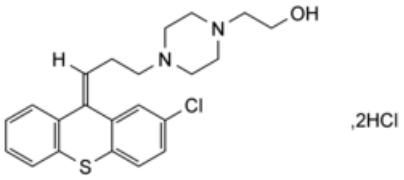
Edition: BP 2025 (Ph. Eur. 11.6 update)

Zuclopenthixol Hydrochloride

General Notices



$C_{22}H_{25}ClN_2OS,2HCl$ 473.9 *633-59-0*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Zuclopenthixol Tablets

DEFINITION

Zuclopenthixol Hydrochloride is (*Z*)-2-4-[3-(2-chlorothioxanthene-9-ylidene)propyl]piperazin-1-ylethanol dihydrochloride. It contains not less than 98.0% and not more than 101.0% of $C_{22}H_{25}ClN_2OS,2HCl$, calculated with reference to the anhydrous substance.

CHARACTERISTICS

An off-white, granular powder.

Very soluble in *water*; sparingly soluble in *ethanol (96%)*; very slightly soluble in *ether*.

IDENTIFICATION

A. The *light absorption* of a 0.0015% w/v solution in *ethanol (96%)*, Appendix II B, in the range 210 to 350 nm exhibits two maxima at 230 and 268 nm. The *absorbances* at the maxima are about 1.0 and 0.4, respectively.
B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of zuclopenthixol hydrochloride *(RS 365)*.
C. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 1.0% w/v solution, 2.0 to 3.0, Appendix V L.

Free amine

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions protected from light.

Solvent A Shake 0.6 mL of *diethylamine* with 150 mL of *ethanol (96%)* and add sufficient *ethanol (96%)* to produce 200 mL.

(1) 0.25% w/v solution of the substance being examined in solvent A.
(2) Dilute 1 volume of solution (1) to 400 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *TLC silica gel F_{254} plate* (Merck plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 4 µL of each solution.
(d) Develop the plate to 10 cm.
(e) After removal of the plate, allow it to dry in air, spray with a mixture of equal volumes of *sulfuric acid* and *absolute ethanol*, heat at 110° for 5 minutes and examine under *ultraviolet light (365 nm)* immediately.

MOBILE PHASE

2 volumes of *water*, 10 volumes of 13.5M *ammonia*, 20 volumes of *butan-1-ol* and 65 volumes of *acetone*.

LIMITS

In the chromatogram obtained with solution (1) any *secondary spot* of the same colour and at an Rf value lower than that of the principal spot is not more intense than the spot in the chromatogram obtained solution (2) (0.25%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions protected from light.

Solution A 18 volumes of *acetonitrile* and 82 volumes of *water*.

(1) Dissolve 20 mg of the substance being examined in 200 mL of solution A.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A and further dilute 1 volume of this solution to 10 volumes with solution A.
(3) Dilute 3 volumes of solution (1) to 100 volumes with solution A.
(4) 0.002% w/v each of *zuclopenthixol hydrochloride BPCRS* and *trans*-clopenthixol hydrochloride BPCRS (impurity B) in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 2.1 mm) packed with *octadecylsilyl silica gel for chromatography* (3.5 µm) (Symmetry Shield RP18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature 40°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 5 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *trifluoroacetic acid* and 2500 volumes of *water*.

Mobile phase B 1 volume of *trifluoroacetic acid* and 25 volumes of *acetonitrile*.

Mobile phase C *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-8	82	18	0	isocratic
8-17	82→5	18→10	0→85	linear gradient

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
17-19	5→82	10→18	85→0	linear gradient
19-30	82	18	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the retention times relative to zuclopenthixol (retention time about 6 minutes) are: impurity A, about 0.1; impurity B, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks corresponding to zuclopenthixol and impurity B is at least 2.0.

LIMITS

In the chromatogram obtained with solution (1):

The area of any peak due to *trans*-zuclopenthixol is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (3%);

The area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

The sum of the areas of any *secondary peak*, excluding *trans*-clopenthixol hydrochloride, is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Water

Not more than 2.5%, determined on 0.5 g, Appendix IX C.

Sulfated ash

Not more than 0.1%, Appendix IX A.

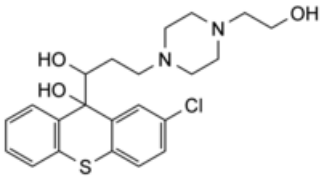
ASSAY

Dissolve 0.5 g in 50 mL of *anhydrous acetic acid* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using *crystal violet solution* as indicator. Each mL of *0.1M perchloric acid VS* is equivalent to 23.70 mg of $C_{22}H_{25}ClN_2OS,2HCl$.

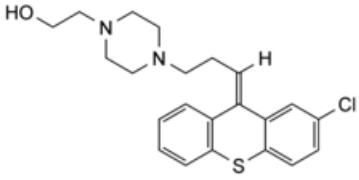
STORAGE

Zuclopenthixol Hydrochloride should be protected from light.

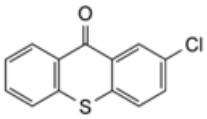
IMPURITIES



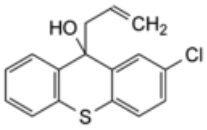
A. 2-chloro-9-(1-hydroxy-3-(4-(2-hydroxyethyl)]piperazin-1-ylpropyl)thioxanthen9-ol,



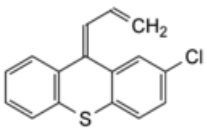
B. *trans*-clopenthixol,



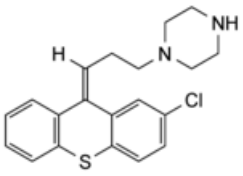
C. 2-chlorothioxanthone,



D. 9-allyl-2-chlorothioxanthen-9-ol,



E. 9-allylidene-2-chlorothioxanthene,



F. 2-chloro-9-(3-piperazin-1-ylpropylidene)thioxanthene.