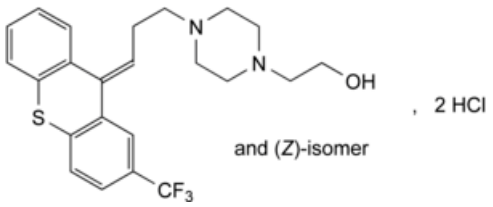
Edition: BP 2025 (Ph. Eur. 11.6 update)

Flupentixol Hydrochloride

General Notices

(Flupentixol Dihydrochloride, Ph. Eur. monograph 1693)



$C_{23}H_{27}Cl_2F_3N_2OS$ 507.4 *2413-38-9*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparation

Flupentixol Tablets

Ph Eur

DEFINITION

2-[4-[3-[(*EZ*)-2-(Trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethan-1-ol dihydrochloride.

Content

— *flupentixol dihydrochloride*: 99.0 per cent to 101.0 per cent (dried substance);

— *(Z)-isomer*: 42.0 per cent to 52.0 per cent.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very soluble in water, soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *flupentixol dihydrochloride CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution Dissolve 20 mg of *flupentixol dihydrochloride CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *water R*, *diethylamine R*, *methyl ethyl ketone R* (1:4:95 *V/V/V*).

Application 2 µL.

Development Twice over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

Results A 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. Doubling of the spot may be observed in both chromatograms.

Detection B Spray with *alcoholic solution of sulfuric acid R*; heat at 110 °C for 5 min and allow to cool; examine in ultraviolet light at 365 nm.

Results B 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. Doubling of the spot may be observed in both chromatograms.

C. Mix about 5 mg with 45 mg of *heavy magnesium oxide R* and ignite in a crucible until an almost white residue is obtained (usually less than 5 min). Allow to cool, add 1 mL of *water R*, 0.05 mL of *phenolphthalein solution R1* and about 1 mL of *dilute hydrochloric acid R* to render the solution colourless. Filter and add to the filtrate a freshly prepared mixture of 0.1 mL of *alizarin S solution R* and 0.1 mL of *zirconyl nitrate solution R*. Mix, allow to stand for 5 min and compare the colour of the solution with that of a blank prepared in the same manner. The test solution is yellow. The blank is red.
D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and its absorbance (2.2.25) at 410 nm is not greater than 0.125.

Dissolve 0.500 g in 5.0 mL of *water R*.

pH (2.2.3)

2.0 to 3.0.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Buffer solution Dissolve 6.3 g of *ammonium formate R* in about 900 mL of *water for chromatography R*, adjust to pH 8.2 with *concentrated ammonia R* and dilute to 1000 mL with *water for chromatography R*.

Test solution Dissolve 58.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 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 the contents of a vial of *flupentixol for system suitability CRS* (containing impurities A, C, H and I) in 1 mL of mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: buffer solution, *acetonitrile for chromatography R*, *water for chromatography R* (58:420:522 *V/V/V*);

— *mobile phase B*: buffer solution, *acetonitrile for chromatography R* (100:900 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	90 → 5	10 → 95

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL.

Identification of peaks Use the chromatogram supplied with *flupentixol for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to both isomers of flupentixol and impurities A, C + I, and H.

Relative retention With reference to flupentixol (*Z*)-isomer (retention time = about 11 min): impurity A = about 0.83; impurity H = about 0.90; impurities C and I = about 0.97; flupentixol (*E*)-isomer = about 1.04.

System suitability Reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurities A and H;

— *peak-to-valley ratio*: minimum 10.0, where H_p = height above the baseline of the peak due to impurities C+I and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to flupentixol (*Z*)-isomer.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurities C and I = 2.0; impurity H = 2.0;

— for each impurity, use the concentration of flupentixol dihydrochloride (both isomers) in reference solution (a).

Limits:

— *impurity H*: maximum 0.5 per cent;

— *sum of impurities C and I*: maximum 0.3 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 1.0 per cent;

— *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*)

Maximum 2.0 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 in a platinum crucible.

ASSAY

Flupentixol dihydrochloride

Dissolve 0.200 g in 30 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 50.74 mg of $C_{23}H_{27}Cl_2F_3N_2OS$.

(*Z*)-Isomer

Liquid chromatography (*2.2.29*).

Test solution Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution Dissolve 20.0 mg of *flupentixol dihydrochloride CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm;

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

Mobile phase *water for chromatography R*, *concentrated ammonia R*, *2-propanol R*, *heptane R* (2:4:150:850 *V/V/V/V*).

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 1.5 times the retention time of flupentixol (*Z*)-isomer.

Identification of peaks Use the chromatogram supplied with *flupentixol dihydrochloride CRS* and the chromatogram obtained with the reference solution to identify the peaks due to both isomers of flupentixol.

Relative retention With reference to flupentixol (*Z*)-isomer (retention time = about 6 min): flupentixol (*E*)-isomer = about 1.2.

System suitability Reference solution:

— *resolution*: minimum 3.0 between the peaks due to flupentixol (*Z*)-isomer and flupentixol (*E*)-isomer.

Calculate the percentage content of the (*Z*)-isomer of $C_{23}H_{27}Cl_2F_3N_2OS$ taking into account the assigned content of flupentixol (*Z*)-isomer in *flupentixol dihydrochloride CRS*.

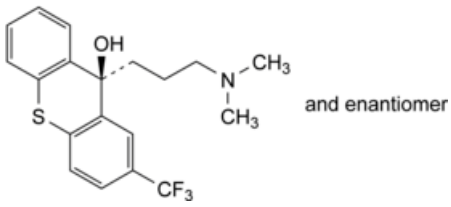
STORAGE

Protected from light.

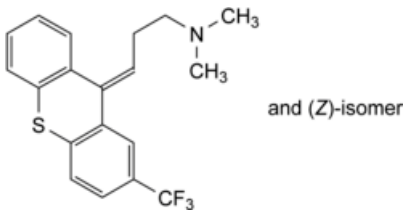
IMPURITIES

Specified impurities C, H, I.

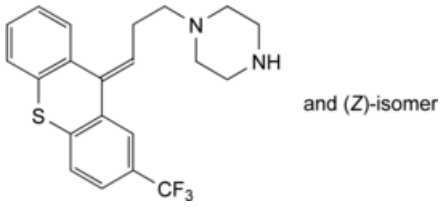
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, E, G.



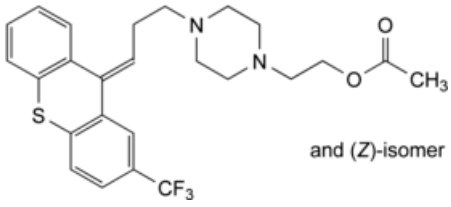
A. (9*RS*)-9-[3-(dimethylamino)propyl]-2-(trifluoromethyl)-9*H*-thioxanthen-9-ol,



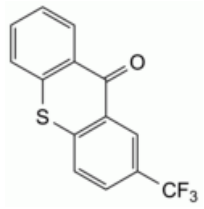
B. *N*,*N*-dimethyl-3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propan-1-amine,



C. 1-[3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazine,



E. 2-[4-[3-[(*EZ*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-ylidene]propyl]piperazin-1-yl]ethyl acetate,



G. 2-(trifluoromethyl)-9*H*-thioxanthen-9-one,

H. either 2-[4-[(*E*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol or 2-[4-[(*Z*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol,

I. either 2-[4-[(*E*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol or 2-[4-[(*Z*)-3-[(9*RS*)-2-(trifluoromethyl)-9*H*-thioxanthen-9-yl]prop-2-en-1-yl]piperazin-1-yl]ethan-1-ol.

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