Specific optical rotation (*2.2.7*): + 69 to + 77 (dried substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (a). Dissolve 10 mg of *dexamethasone pivalate CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. To 5.0 mL of this solution, add 5.0 mL of the test solution, mix and dilute to 50.0 mL with the mobile phase.

Reference solution (b). Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *tetrahydrofuran R, acetonitrile R, water R, methanol R* (5:30:30:35 *V/V/V/V*).

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: 1.5 times the retention time of flumetasone pivalate.

Relative retention with reference to flumetasone pivalate: impurity C = about 1.1.

System suitability: reference solution (a):

– *resolution*: minimum 2.8 between the peaks due to flumetasone pivalate and impurity C; if necessary, adjust the concentration of tetrahydrofuran in the mobile phase.

Limits:

– *impurities A, B, C, D*: for each impurity, not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent);
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2 per cent);
– *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 4 h.

ASSAY

Dissolve 50.0 mg in *ethanol (96 per cent) R* and dilute to 100.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *ethanol (96 per cent) R*. Measure the absorbance (*2.2.25*) at the absorption maximum at 239 nm.

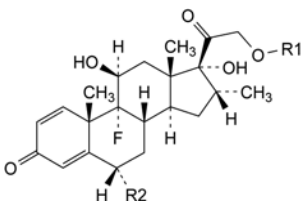
Calculate the content of $C_{27}H_{36}F_2O_6$ taking the specific absorbance to be 336.

STORAGE

Protected from light.

IMPURITIES

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



A. R1 = H, R2 = F: 6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (flumetasone),
B. R1 = CO-CH_3, R2 = F: 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl acetate (flumetasone acetate),
C. R1 = CO-$C(CH_3)_3$, R2 = H: 9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (dexamethasone pivalate),
D. R1 = CO-$C(CH_3)_3$, R2 = Cl: 6α-chloro-9-fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate (chlordexamethasone pivalate).

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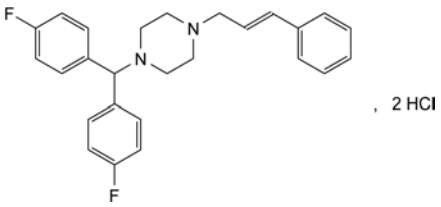
corrected 7.0

FLUNARIZINE DIHYDROCHLORIDE

Flunarizini dihydrochloridum



$C_{26}H_{28}Cl_2F_2N_2$ M_r 477.4
[30484-77-6]

DEFINITION

1-[Bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-enyl]piperazine dihydrochloride.

Content: 99.0 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder, hygroscopic.

Solubility: slightly soluble in water, sparingly soluble in methanol, slightly soluble in alcohol and in methylene chloride.

mp: about 208 °C, with decomposition.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of flunarizine dihydrochloride.*
B. Dissolve 25 mg in 2 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect from light.*

Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *flunarizine dihydrochloride for system suitability CRS* in *methanol R* and dilute to 1.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 20.0 mL with *methanol R*.

Column:

– *size*: *l* = 0.10 m, Ø = 4.6 mm,
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: solution containing 23.8 g/L of *tetrabutylammonium hydrogen sulfate R* and 7 g/L of *ammonium acetate R*,
– *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 12	80 → 40	20 → 60
12 - 15	40	60

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL.

System suitability: reference solution (a):

– *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to flunarizine,

– the chromatogram obtained is concordant with the chromatogram supplied with *flunarizine dihydrochloride for system suitability CRS*.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity A by 1.5,

– *impurities A, D*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

– *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent),

– *any other impurity*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),

– *total*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 5.0 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Dissolve 0.200 g in 70 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added at the second point of inflexion. Carry out a blank titration.

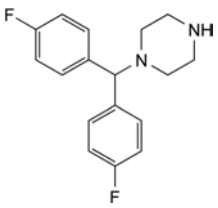
1 mL of *0.1 M sodium hydroxide* is equivalent to 23.87 mg of $C_{26}H_{28}Cl_2F_2N_2$.

STORAGE

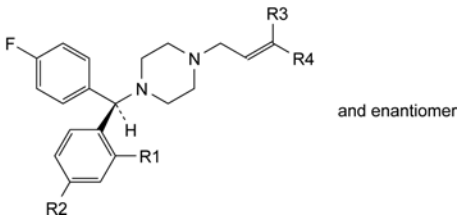
In an airtight container, protected from light.

IMPURITIES

Specified impurities: A, B, C, D.



A. 1-[bis(4-fluorophenyl)methyl]piperazine,



B. R1 = R2 = R3 = H, R4 = C_6H_5: 1-[(*RS*)-(4-fluorophenyl)phenylmethyl]-4-[(2*E*)-3-phenylprop-2-enyl]piperazine,

C. R1 = F, R2 = R3 = H, R4 = C_6H_5: 1-[(*RS*)-(2-fluorophenyl)(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-enyl]piperazine,

D. R1 = R4 = H, R2 = F, R3 = C_6H_5: 1-[bis(4-fluorophenyl)methyl]-4-[(2*Z*)-3-phenylprop-2-enyl]piperazine.

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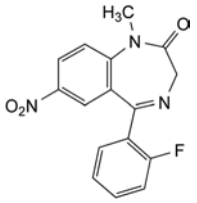
corrected 6.0

FLUNITRAZEPAM

Flunitrazepamum



$C_{16}H_{12}FN_3O_3$ M_r 313.3
[1622-62-4]

DEFINITION

5-(2-Fluorophenyl)-1-methyl-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

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

CHARACTERS

Appearance: white or yellowish, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone, slightly soluble in alcohol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of flunitrazepam*.

TESTS

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

Test solution. Dissolve 100.0 mg of the substance to be examined in 10 mL of *acetonitrile R* and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b). Dissolve 4 mg of the substance to be examined and 4 mg of *nitrazepam R* in 5 mL of *acetonitrile R* and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,

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

Mobile phase: *methanol R, acetonitrile R, water R* (50:305:645 *V/V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.