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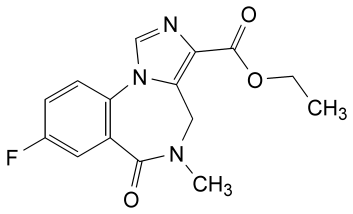
FLUMAZENIL

Flumazenilum



$C_{15}H_{14}FN_3O_3$ M_r 303.3
[78755-81-4]

DEFINITION

Ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in methanol.

mp: 198 °C to 202 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and is not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 0.10 g in *methanol R* and dilute to 10 ml with the same solvent.

Impurity C: maximum 1 per cent.

Dissolve 0.10 g in 0.5 ml of *methylene chloride R* and dilute to 10 ml with *butanol R*. To 5.0 ml of this solution add 2.0 ml of *ninhydrin solution R* and heat in a water-bath at 95 °C for 15 min. Any blue-purple colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 5.0 ml of a 0.1 g/l solution of *dimethylformamide diethylacetal R* in *butanol R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in 5 ml of *methanol R* and dilute to 25.0 ml with the mobile phase.

Reference solution (a). Dissolve 2.0 mg of *flumazenil impurity B CRS* and 2.0 mg of the substance to be examined in the mobile phase and dilute to 25.0 ml with the mobile phase. Dilute 2.0 ml of this solution to 25.0 ml with the mobile phase.

Reference solution (b). Dilute 10.0 ml of the test solution to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

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

Mobile phase: to 800 ml of *water R* adjusted to pH 2.0 with *phosphoric acid R*, add 130 ml of *methanol R* and 70 ml of *tetrahydrofuran R* and mix.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µl.

Run time: 3 times the retention time of flumazenil.

Relative retention with reference to flumazenil (retention time = about 14 min): impurity A = about 0.4; impurity D = about 0.5; impurity E = about 0.6; impurity B = about 0.7; impurity F = about 2.4.

System suitability: reference solution (a):

– *resolution*: minimum 3.0 between the peaks due to impurity B and flumazenil.

Limits:

– *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

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

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *disregard limit*: 0.5 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 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

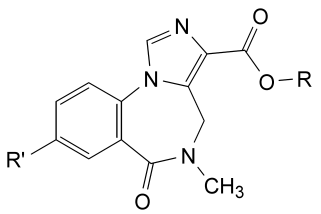
Dissolve 0.250 g in 50 ml of a mixture of 2 volumes of *acetic anhydride R* and 3 volumes of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 30.33 mg of $C_{15}H_{14}FN_3O_3$.

IMPURITIES

Specified impurities: *B, C.*

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, D, E, F.*

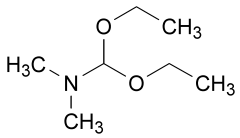


A. R = H, R′ = F: 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid,

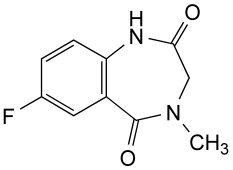
B. R = C_2-H_5, R′ = OH: ethyl 8-hydroxy-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,

E. R = C_2H_5, R′ = H: ethyl 5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,

F. R = C_2H_5, R′ = Cl: ethyl 8-chloro-5-methyl-6-oxo-5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate,



C. diethoxy-*N*,*N*-dimethylmethanamine,



D. 7-fluoro-4-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione.

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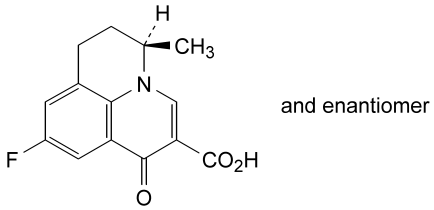
FLUMEQUINE

Flumequinum



$C_{14}H_{12}FNO_3$ M_r 261.3
[42835-25-6]

DEFINITION

(*RS*)-9-Fluoro-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]-quinolizine-2-carboxylic acid.

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

CHARACTERS

Appearance: white or almost white, microcrystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methylene chloride, very slightly soluble in methanol. It is freely soluble in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: A, B.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *flumequine CRS.*

B. Optical rotation (see Tests).

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 5 mg of the substance to be examined in 10 ml of *methylene chloride R.*

Reference solution. Dissolve 5 mg of *flumequine CRS* in 10 ml of *methylene chloride R.*

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

Mobile phase: *ammonia R, water R, ethanol (96 per cent) R* (10:10:90 *V/V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: 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. 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 2 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 changes from red to yellow and the blank remains red.

TESTS

Solution S. Dissolve 5.00 g in *0.5 M sodium hydroxide* and dilute to 50.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_5 (*2.2.2, Method II*).

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 35.0 mg of the substance to be examined in *dimethylformamide R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve the contents of a vial of *flumequine impurity B CRS* in 2.0 ml of a 50 µg/ml solution of *flumequine CRS* in *dimethylformamide R.*

Reference solution (b). Dilute 1.0 ml of the test solution to 200.0 ml with *dimethylformamide R.*

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

Mobile phase: *methanol R*, 1.36 g/l solution of *potassium dihydrogen phosphate R* (49:51 *V/V*).

Flow rate: 0.8 ml/min.

Detection: spectrophotometer at 313 nm.

Injection: 10 µl; inject *dimethylformamide R* as a blank.

Run time: 3 times the retention time of flumequine.

Relative retention with reference to flumequine (retention time = about 13 min): impurity A = about 0.67; impurity B = about 0.85.