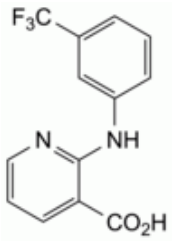
Edition: BP 2025 (Ph. Eur. 11.6 update)

Niflumic Acid

General Notices

(Ph. Eur. monograph 2115)



$C_{13}H_9F_3N_2O_2$ 282.2 *4394-00-7*

Ph Eur

DEFINITION

2-[[3-(Trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

Pale yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent) and in methanol.

Melting point (*2.2.15*)

About 204 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison niflumic acid CRS.

TESTS

Impurity C

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.50 g of the substance to be examined in 5 mL of methanol R and dilute to 10.0 mL with the same solvent.

Reference solution Dissolve 25 mg of 3-trifluoromethylaniline R (impurity C) in 20 mL of methanol R and dilute to 100 mL with the same solvent. Dilute 1.0 mL of the solution to 100 mL with methanol R.

Plate TLC silica gel F_{254} plate R.

Mobile phase acetic acid R, ethyl acetate R, toluene R (5:25:90 *V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air, until the solvents have evaporated.

Detection Spray with 4-dimethylaminocinnamaldehyde solution R and heat at 60 °C for 10 min.

Limit:

— *impurity C*: any spot due to impurity C is not more intense than the principal spot in the chromatogram obtained with the reference solution (50 ppm).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in 10 mL of acetonitrile R and dilute to 20.0 mL with water R.

Reference solution Dissolve 5.0 mg of niflumic acid impurity A CRS, 5.0 mg of niflumic acid impurity B CRS and 6.0 mg of niflumic acid impurity E CRS in 20 mL of acetonitrile R, add 5.0 mL of the test solution and dilute to 50.0 mL with water R. Dilute 1.0 mL of this solution to 100.0 mL with a mixture of equal volumes of acetonitrile R and water R.

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

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

— *temperature*: 25 °C.

Mobile phase *phosphoric acid R*, *acetonitrile R*, *water for chromatography R* (2.5:500:500 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 267 nm.

Injection 10 µL.

Run time 4 times the retention time of niflumic acid.

Relative retention With reference to niflumic acid (retention time = about 3.5 min): impurity A = about 0.4; impurity E = about 0.7; impurity B = about 0.8 (the peaks due to impurities E and B may be inverted).

System suitability Reference solution:

— *resolution*: minimum 1.5 between the peaks due to impurities E and B.

Limits:

— *impurity B*: not more than 4 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.4 per cent);

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.10 per cent);

— *sum of impurities other than B*: not more than twice the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.2 per cent);

— *disregard limit*: 0.5 times the area of the peak due to niflumic acid in the chromatogram obtained with the reference solution (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 200 ppm.

Dissolve 0.5 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *methanol R* and dilute to 20 mL with *water R*. To 10 mL of the solution add 5 mL of *water R*.

Phosphates (*2.4.11*)

Maximum 100 ppm.

Dilute 1.0 mL of the test solution prepared as described in general chapter *2.4.8* (method C) to 100 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.3 per cent, determined on 2.000 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

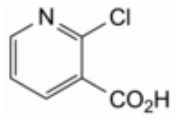
Dissolve 0.200 g in a mixture of 10 mL of *water R* and 40 mL of *ethanol (96 per cent) R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.22 mg of $C_{13}H_9F_3N_2O_2$.

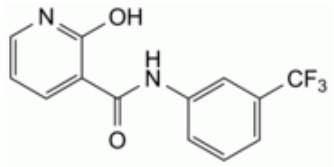
IMPURITIES

Specified impurities *A, B, C.*

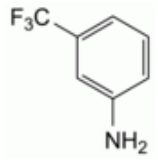
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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) *E, F.*



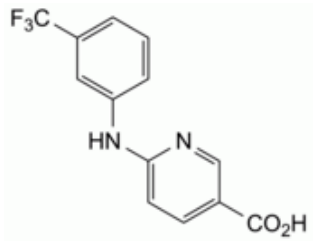
A. 2-chloropyridine-3-carboxylic acid,



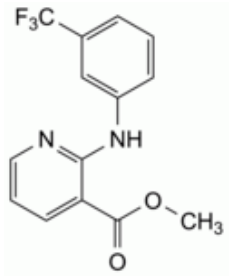
B. 2-hydroxy-*N*-[3-(trifluoromethyl)phenyl]pyridine-3-carboxamide,



C. 3-(trifluoromethyl)aniline,



E. 6-[[3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid,



F. methyl 2-[[3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylate.

Ph Eur