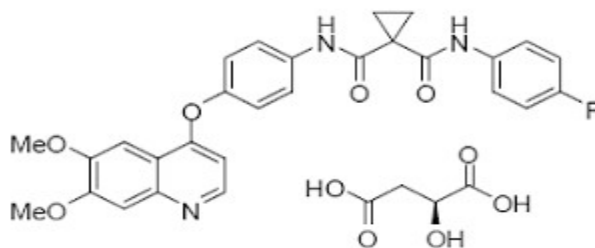


Cabozantinib-S-Malate



$C_{32}H_{30}FN_3O_{10}$

Mol. Wt. 635.6

Cabozantinib-S-Malate is N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

Cabozantinib-S-Malate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{32}H_{30}FN_3O_{10}$, calculated on anhydrous basis.

CAUTION - Cabozantinib is cytotoxic; extra care required to prevent inhaling particles and exposing the skin to it.

Category. Anticancer.

Description. A off white to pale yellow powder, slightly hygroscopic.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *Cabozantinib-S-Malate* IPRS or with the reference spectrum of Cabozantinib-S-Malate.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of acetonitrile, 50 volumes of water and 0.1 volume of trifluoroacetic acid.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with solvent mixture.

Reference solution (a). A 0.0025 per cent w/v solution of *Cabozantinib-S-Malate* IPRS in the Solvent mixture. Dilute 3.0 ml of the solution to 100.0 ml with solvent mixture.

Reference solution (b). A solution containing 0.5 per cent w/v solution of *Cabozantinib-S-Malate* IPRS and 0.00075 per cent of *Cabozantinib impurity A* IPRS in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture.

Reference solution (c). Dilute 3.0 ml of reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous (1.8 μ m) (Such as Acquity HSS C18),
- sample temperature: 10°,

- mobile phase: A. 0.1 per cent v/v solution of *orthophosphoric acid* in water,
B. *acetonitrile*,
- flow rate: 0.5 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 250 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	90	10
5.0	65	35
7.0	65	35
8.5	50	50
11.5	30	70
13.0	30	70
13.1	90	10
17.0	90	10

Name	Relative retention time	Correction factor
Cabozantinib Impurity A ¹	0.66	0.72
Cabozantinib	1.0	-

¹1-({4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl} carbamoyl)cyclopropanecarboxylic acid

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to Cabozantinib Impurity A and Cabozantinib is not less than 1.1 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 10 for the principal peak in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to Cabozantinib impurity A is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent). The area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and the sum of areas of all the secondary peaks is not more than 6.7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.33 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (2.3.13). 2.0 g complies with the limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent, using platinum crucible.

Water (2.3.43). Not more than 5.0 per cent, determined on 0.25 g.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *trifluoroacetic acid*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 5 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution. A 0.005 per cent w/v solution of *Cabozantinib-S-Malate IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous (1.8 µm) (Such as Acquity HSS C18),
- sample temperature: 10°,

- mobile phase: a mixture of 62 volumes of a mixture 0.2 per cent v/v solution of *orthophosphoric acid* and 0.2 per cent v/v of *triethylamine* in *water*, and 38 volumes of *acetonitrile*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 1 µl.

Inject the reference solution. The test is not valid unless, the tailing factor is not more than 1.8 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{32}H_{30}FN_3O_{10}$.

Storage. Store at a temperature between 2° to 8°.

Solubility (2.4.26). Freely soluble in *dimethyl sulphoxide*, very slightly soluble in *methanol* and practically insoluble in *water*.

DRAFT FOR COMMENTS