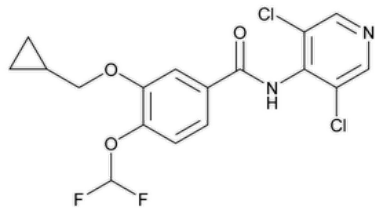


Roflumilast

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-notice-roflumilast-20241122.



$C_{17}H_{14}Cl_2F_2N_2O_3$ 403.21
Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-;
3-(Cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide. CAS RN®: 162401-32-3; UNII: 0P6C6ZOP5U.

DEFINITION
Roflumilast contains NLT 98.0% and NMT 102.0% of roflumilast ($C_{17}H_{14}Cl_2F_2N_2O_3$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. [SPECTROSCOPIC IDENTIFICATION TESTS \(197\)](#), [Infrared Spectroscopy](#):** 197A or 197K
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

- **PROCEDURE**

Protect all solutions containing roflumilast from light.

Solution A: 1.74 g/L of [potassium phosphate dibasic](#) and 1.02 g/L of [tetrabutylammonium hydrogen sulfate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 5.9.

Solution B: 1.02 g/L of [tetrabutylammonium hydrogen sulfate](#) in [methanol](#)

Mobile phase: See [Table 1](#). [NOTE—Equilibrate the instrument for NLT 1 h. If necessary, inject the solvent blank at least 3 times before the start of the analysis.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	20	80
26	20	80
26.1	75	25
36.1	75	25

System suitability solution: 0.2 mg/mL of [USP Roflumilast RS](#) and 0.001 mg/mL of [USP Roflumilast Related Compound D RS](#) in [methanol](#)

Standard solution: 0.2 mg/mL of [USP Roflumilast RS](#) in [methanol](#)

Sample solution: 0.2 mg/mL of Roflumilast in [methanol](#)

Chromatographic system(See [Chromatography \(621\), System Suitability](#).)**Mode:** LC**Detector:** UV 248 nm**Column:** 2.0-mm × 12.5-cm; 5-μm packing [L1](#). [NOTE—A guard column of 2.0-mm × 1.0-cm; 5-μm packing [L1](#) may be used.]**Column temperature:** 40°**Flow rate:** 0.4 mL/min**Injection volume:** 10 μL**System suitability****Samples:** *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for roflumilast related compound D and roflumilast are 0.9 and 1.0, respectively.]

Suitability requirements**Resolution:** NLT 2.0 between roflumilast related compound D and roflumilast, *System suitability solution***Tailing factor:** NMT 1.5, *Standard solution***Relative standard deviation:** NMT 0.85% from 6 replicate injections, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of roflumilast (C₁₇H₁₄Cl₂F₂N₂O₃) in the portion of Roflumilast taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response of roflumilast from the *Sample solution* r_S = peak response of roflumilast from the *Standard solution* C_S = concentration of [USP Roflumilast RS](#) in the *Standard solution* (mg/mL) C_U = concentration of Roflumilast in the *Sample solution* (mg/mL)**Acceptance criteria:** 98.0%–102.0% on the anhydrous basis**IMPURITIES**• [RESIDUE ON IGNITION \(281\)](#): NMT 0.2%• **ORGANIC IMPURITIES**

Protect all solutions containing roflumilast from light.

Buffer: 1.74 g/L of [potassium phosphate dibasic](#) and 1.02 g/L of [tetrabutylammonium hydrogen sulfate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 5.9.**Solution A:** [Tetrahydrofuran](#) and *Buffer* (5:95)**Solution B:** 1.02 g/L of [tetrabutylammonium hydrogen sulfate](#) in [acetonitrile](#)**Mobile phase:** See [Table 2](#). After each run, return to the original conditions and re-equilibrate the system. [NOTE—A re-equilibration time of 5 min may be suitable.]**Table 2**

Time (min)	Solution A (%)	Solution B (%)
0	75	25
5	70	30
60	70	30

Diluent: *Buffer* and *Solution B* (50:50)**Impurity stock solution 1:** 0.4 mg/mL each of [USP Roflumilast Related Compound A RS](#), [USP Roflumilast Related Compound B RS](#), [USP Roflumilast Related Compound C RS](#), [USP Roflumilast Related Compound D RS](#), and [USP Roflumilast Related Compound E RS](#), prepared as follows. Transfer a suitable quantity of each Reference Standard to an appropriate volumetric flask and dissolve in *Solution B* to volume.