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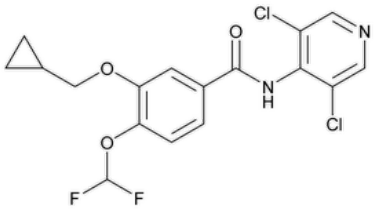
Roflumilast

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 ($C_{17}H_{14}Cl_2F_2N_2O_3$) 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.

Impurity stock solution 2: 0.04 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 from *Impurity stock solution 1*, in *Diluent*

Standard stock solution: 1.0 mg/mL of USP Roflumilast RS, prepared as follows. Transfer an appropriate quantity of USP Roflumilast RS to a suitable volumetric flask, dissolve in 50% of the flask volume of *Solution B*, and then dilute with *Buffer* to volume.

Standard solution: 0.001 mg/mL of USP Roflumilast RS from the *Standard stock solution*, in *Diluent*

System suitability solution: 1.0 mg/mL of USP Roflumilast RS and 1.5 µg/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. Pipet an appropriate volume of *Impurity stock solution 2* into a suitable volumetric flask and dilute with *Standard stock solution* to volume.

Sensitivity solution: 0.3 µg/mL of USP Roflumilast RS from the *Standard stock solution* in *Diluent*

Sample solution: 1.0 mg/mL of Roflumilast prepared as follows. Transfer an appropriate quantity of Roflumilast to a suitable volumetric flask and dissolve in 50% of the flask volume of *Solution B*. Dilute with *Buffer* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 252 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 30 µL

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between roflumilast related compound B and roflumilast related compound A; NLT 1.5 between roflumilast and roflumilast related compound E, *System suitability solution*

Tailing factor: NMT 1.5 for roflumilast and each related compound, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any specified and unspecified impurity in the portion of Roflumilast taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of specified or unspecified impurity 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)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Roflumilast related compound C	0.06	1.5	0.15

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Roflumilast related compound B	0.16	1.1	0.15
Roflumilast related compound A	0.18	0.87	0.15
Roflumilast related compound D	0.24	0.53	0.15
Roflumilast	1.0	—	—
Roflumilast related compound E[a]	1.06	—	—
Total specified impurities[b]	—	—	0.4
Any individual unspecified impurity	—	1.0	0.10
Total unspecified impurities	—	—	0.3
Total impurities[b]	—	—	0.60

[a] This impurity is listed for information only. It is controlled using the *Limit of Roflumilast Related Compound E* procedure and excluded from the total impurities calculation.

[b] Excluding roflumilast related compound E.

Change to read:

• Limit of Roflumilast Related Compound E

[Note—Perform this test in addition to the *Organic Impurities* test if roflumilast related compound E is present in the drug substance due to the manufacturing process.]

Protect all solutions containing roflumilast from light.

Mobile phase: ▲*n*-Hexane▲ (RB 1-Dec-2024) and dehydrated alcohol (90:10)

Impurity stock solution 1: 360 µg/mL of USP Roflumilast Related Compound E RS, prepared as follows. Transfer an appropriate quantity of USP Roflumilast Related Compound E RS to a suitable volumetric flask, dissolve in 10% of the flask volume of ▲dehydrated alcohol,▲ (RB 1-Dec-2024) and then dilute with ▲*n*-hexane▲ (RB 1-Dec-2024) to volume.

Impurity stock solution 2: 36 µg/mL of USP Roflumilast Related Compound E RS from *Impurity stock solution 1* in *Mobile phase*

Impurity sensitivity solution: 0.3 µg/mL of USP Roflumilast Related Compound E RS from *Impurity stock solution 1* in *Mobile phase*

Standard stock solution: 600 µg/mL of USP Roflumilast RS, prepared as follows. Transfer an appropriate quantity of USP Roflumilast RS to a suitable volumetric flask, dissolve in 10% of the flask volume of ▲dehydrated alcohol,▲ (RB 1-Dec-2024) and then dilute with ▲*n*-hexane▲ (RB 1-Dec-2024) to volume.

Standard solution: 0.6 µg/mL of USP Roflumilast RS from the *Standard stock solution* in *Mobile phase*

System suitability solution: 600 µg/mL of USP Roflumilast RS and 0.9 µg/mL of USP Roflumilast Related Compound E RS, prepared as follows. Pipet an appropriate volume of *Impurity stock solution 2* to a suitable volumetric flask and dilute with *Standard stock solution* to volume.

Sample solution: 600 µg/mL of Roflumilast, prepared as follows. Transfer an appropriate quantity of Roflumilast to a suitable volumetric flask, dissolve in 10% of the flask volume of ▲dehydrated alcohol,▲ (RB 1-Dec-2024) and then dilute with ▲*n*-hexane▲ (RB 1-Dec-2024) to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 212 nm

Column: 4.6-mm × 10-cm; 3.0-µm packing L8

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 8 µL

Run time: NLT 1.8 times the retention time of roflumilast

System suitability

Samples: *Impurity sensitivity solution*, *Standard solution*, and *System suitability solution*

[NOTE—The relative retention times for roflumilast and roflumilast related compound E are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2.5 between roflumilast and roflumilast related compound E, *System suitability solution*

Tailing factor: NMT 1.5 for roflumilast related compound E, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Impurity sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of roflumilast related compound E in the portion of Roflumilast taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of roflumilast related compound E 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* (µg/mL)

C_U = concentration of Roflumilast in the *Sample solution* (µg/mL)

F = relative response factor for roflumilast related compound E, 0.89

Acceptance criteria: NMT 0.15%

SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩, *Method I*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature. Protect from light.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Roflumilast RS

USP Roflumilast Related Compound A RS

3-(Cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-hydroxybenzamide.

$C_{16}H_{14}Cl_2N_2O_3$ 353.20

USP Roflumilast Related Compound B RS

N-(3,5-Dichloropyridin-4-yl)-4-(difluoromethoxy)-3-hydroxybenzamide.

$C_{13}H_8Cl_2F_2N_2O_3$ 349.11

USP Roflumilast Related Compound C RS

3,5-Dichloropyridin-4-amine.

$C_5H_4Cl_2N_2$ 163.00

USP Roflumilast Related Compound D RS

3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzoic acid.

$C_{12}H_{12}F_2O_4$ 258.22

USP Roflumilast Related Compound E RS

N-(3-Bromo-5-chloropyridin-4-yl)-3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamide.

$C_{17}H_{14}BrClF_2N_2O_3$ 447.66

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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