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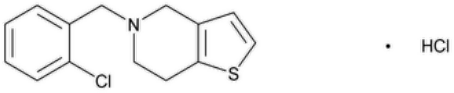
Ticlopidine Hydrochloride



$C_{14}H_{14}ClNS \cdot HCl$ 300.25

Thieno[3,2-*c*]pyridine, 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro-, hydrochloride;

5-(*o*-Chlorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine hydrochloride CAS RN®: 53885-35-1; UNII: A1L4914FMF.

DEFINITION

Ticlopidine Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{14}H_{14}ClNS \cdot HCl$, calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197M**▲ (CN 1-May-2020)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*
- **C.** **Identification Tests—General**, *Chloride*⟨191⟩**:** Meets the requirements

ASSAY

- **Procedure**

Buffer: 1.1 g of monobasic sodium phosphate and 0.28 g of dibasic sodium phosphate in 1000 mL of water. The pH of solution is between 6.1 and 6.6. If necessary, adjust to the required pH using phosphoric acid or sodium hydroxide.

Mobile phase: Acetonitrile, methanol, and *Buffer* (6:7:7)

System suitability solution: 0.2 mg/mL of USP Ticlopidine Hydrochloride RS and 0.2 mg/mL of USP Sulconazole Nitrate RS in *Mobile phase.* [Note—Sonication may be necessary for complete dissolution.]

Standard solution: 0.4 mg/mL of USP Ticlopidine Hydrochloride RS in *Mobile phase*

Sample solution: 0.4 mg/mL of Ticlopidine Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 10-µm packing L7

Flow rate: 2 mL/min

Column temperature: 40°

Run time: 1.5 times the retention time of the ticlopidine peak

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.6 between ticlopidine hydrochloride and sulcanazole nitrate, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{14}H_{14}ClNS \cdot HCl$ in the portion of Ticlopidine Hydrochloride taken:

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

r_U = peak response of ticlopidine from the *Sample solution*

r_S = peak response of ticlopidine from the *Standard solution*

C_S = concentration of ticlopidine in the *Standard solution*

C_U = concentration of ticlopidine in the *Sample solution*

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.1% on a 1-g sample

Organic Impurities

- **Procedure 1**

Adsorbent: 0.25-mm thickness of silica

Developing solvent: Butanol, water, and glacial acetic acid (4:5:1). Shake well in a separatory funnel, allow it to settle, discard the lower aqueous layer, and use the upper organic layer.

Diluent: Methylene chloride and methanol (1:2)

Iodine–methanol reagent: Iodine TS and methanol (1:1)

Standard solution A: 15 mg/mL of USP Ticlopidine Hydrochloride RS in *Diluent*

Standard solution B: 2.5 mg/mL of each of USP Ticlopidine Related Compound A RS and USP Ticlopidine Related Compound B RS in *Diluent*

Sample solution: 15 mg/mL of Ticlopidine Hydrochloride in *Diluent*

Combined standard solution: Transfer 1.5 mL of *Standard solution B* and 250 µL of the *Sample solution* to a 25-mL volumetric flask and dilute to volume with *Diluent*.

Application size: 2, 5, and 10 µL of the *Combined standard solution* and 20 µL of the *Sample solution*

Analysis

Samples: *Sample solution* and *Combined standard solution*

Develop the plate to a distance of at least 15 cm from the origin, and remove the plate and air dry for at least 1 h. Analyze visually under UV light. Estimate the amounts of ticlopidine related compound A and ticlopidine related compound B. Spray the plate with the *Iodine–methanol reagent*, and estimate any other impurities by comparing to the ticlopidine hydrochloride spots in the *Combined standard solution*.

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Impurity Table 1

Name	Retardation Factor (R_f)	Acceptance Criteria, NMT (%)
Ticlopidine hydrochloride	1.00	—
Ticlopidine hydrochloride related compound A[a]	1.26	0.5
Ticlopidine hydrochloride related compound B[b]	1.41	0.5

[a] (4-Oxo-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine.

[b] (5-(2-Chlorobenzyl)-4-oxo-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine).

- **Procedure 2**

Buffer, Mobile phase, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of *N*-methyl ticlopidine in the portion of Ticlopidine Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of *N*-methyl ticlopidine in the *Sample solution*

r_T = sum of all the peak responses from in the *Sample solution*

Calculate the percentage of any individual impurity in the portion of the Ticlopidine Hydrochloride taken:

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

r_U = peak response of any impurity in the *Sample solution*

r_S = peak response of ticlopidine in the *Standard solution*

Acceptance criteria

Individual impurities: See *Impurity Table 2.*

Total impurities: See *Impurity Table 2.*

Impurity Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ticlopidine hydrochloride	1	—
N-Methyl ticlopidine[a]	1.18	0.5
Any other individual impurity	—	0.10
Total impurities[b]	—	1.0

[a] 2-[*N*-Methyl-*N*-(2-chlorobenzyl)aminoethyl] thiophene hydrochloride.

[b] Total of *N*-methyl ticlopidine and sum of % individual impurities from *Procedure 1*.

SPECIFIC TESTS

- **Loss on Drying ⟨731⟩:** Dry a 1.0-g sample at 80° for 5 h: it loses NMT 1.0% of its weight.
- **Limit of Formaldehyde**

Mobile phase: Acetonitrile, water, and hydrochloric acid (3:2:0.004)

2,4 Dintirophenyl hydrazine solution: 1.65 mg/mL of 2,4-dinitrophenylhydrazine in acetonitrile

Standard stock solution: Transfer a known amount of formaldehyde solution, equivalent to 37 mg of formaldehyde, into a 100-mL volumetric flask. Dilute with methanol to volume.

Standard solution: Dilute the *Standard stock solution* with methanol to prepare a 1.85-µg/mL solution.

Sample solution: 0.50 g of Ticlopidine Hydrochloride in 10 mL methanol (sonication may be necessary for complete dissolution)

Derivatized standard and **sample solutions:** Transfer 2.0 mL of *2,4-Dinitrophenyl hydrazine solution* to five different 10-mL volumetric flasks: 50 µL of 2 N hydrochloric acid and 150, 250, and 500 µL of the *Standard solution* to the first three flasks; 500 µL of the *Sample solution* to the fourth; and 500 µL of methanol to the fifth flask. Mix each solution well and allow the solutions to react for at least 30 min at ambient temperature. Dilute each flask with *Mobile phase* to volume and mix well. The solutions should be analyzed within 4 h.

Chromatographic system

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

Mode: LC

Detector: UV 365 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Derivatized standard solution* prepared from 500 µL

Suitability requirements

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Derivatized standard solutions* and *Derivatized sample solution*

[NOTE—The approximate retention time for 2,4 dinitrophenylhydrazine is about 3.5 min and for the formaldehyde and 2,4 dinitrophenylhydrazine derivative is about 3.8 min.]

Calculate the formaldehyde concentration in ppm in the *Derivatized sample solution* as the concentration in the Ticlopidine Hydrochloride taken:

$$\text{Result} = (C \times D)/W$$

C = concentration of formaldehyde from the calibration curve generated from the peak areas of the derivatized methanol and the three *Derivatized standard solutions* (µg/mL)

D = dilution factor, 200

W = sample weight (g)

Acceptance criteria

Formaldehyde: NMT 20 ppm

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at a temperature below 30°.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Sulconazole Nitrate RS

USP Ticlopidine Hydrochloride RS

USP Ticlopidine Hydrochloride Related Compound A RS

4-Oxo-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

USP Ticlopidine Hydrochloride Related Compound B RS

5-(2-Chlorobenzyl)-4-oxo-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
TICLOPIDINE HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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