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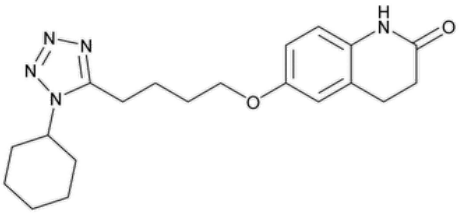
Cilostazol



$C_{20}H_{27}N_5O_2$ 369.46

2(1*H*)-Quinolinone, 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-.

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril CAS RN®: 73963-72-1; UNII: N7Z035406B.

» Cilostazol contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{27}N_5O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩—

USP Cilostazol RS

USP Cilostazol Related Compound A RS

6-Hydroxy-3,4-dihydro-1*H*-quinolin-2-one.

$C_9H_9NO_2$ 163.17

USP Cilostazol Related Compound B RS

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one.

$C_{20}H_{25}N_5O_2$ 367.45

USP Cilostazol Related Compound C RS

1-(4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butyl)-6-(4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one.

$C_{31}H_{45}N_9O_2$ 575.75

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩, *Infrared Spectroscopy: 197K*▲ (CN 1-May-2020) ·

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Loss on drying ⟨731⟩—Dry it at 110° for 3 hours: it loses not more than 0.3% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chloride ⟨221⟩—

Test solution—Dissolve 0.5 g of Cilostazol in 40 mL of dimethylformamide, add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Control solution—To 0.25 mL of 0.01 M hydrochloric acid add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Procedure—Add 1 mL of silver nitrate TS to the *Test solution* and to the *Control solution,* mix well, and allow to stand for 5 minutes, protecting from direct sunlight. Compare the opalescence developed in both solutions against a black background by viewing downward or transversely. The opalescence developed in the *Test solution* is not more than that of the *Control solution* (0.018%).

Related compounds—

Diluent, Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay*.

Standard solution—Dissolve accurately weighed quantities of USP Cilostazol RS and USP Cilostazol Related Compound C RS in acetonitrile, with sonication if necessary, to obtain a solution having known concentrations of about 0.5 mg per mL of each component. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water to volume. Further dilute this solution, stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 0.4 µg per mL of each component.

Test solution—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL of acetonitrile, with sonication if necessary. Dilute with water to volume, and mix.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of cilostazol related compound C by the formula:

$$0.1(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in µg per mL, of cilostazol related compound C in the *Standard solution;* C_T is the concentration, in mg per mL, of Cilostazol in the *Test solution;* r_U is the peak response for cilostazol related compound C obtained from the *Test solution;* and r_S is the peak response for cilostazol related compound C obtained from the *Standard solution*. Calculate the percentage of other impurities by the formula:

$$0.1(1/F)(C_S/C_T)(r_U/r_S)$$

in which F is the relative response factor from *Table 1;* C_S is the concentration, in µg per mL, of cilostazol in the *Standard solution;* C_T is the concentration, in mg per mL, of cilostazol in the *Test solution;* r_U is the peak response for any other impurity obtained from the *Test solution;* and r_S is the peak response for cilostazol obtained from the *Standard solution*.

Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Cilostazol related compound A[1]	0.2	1.7	0.1
Cilostazol related compound B[2]	0.9	0.58	0.1
Cilostazol	1.0	1.0	—
Cilostazol related compound C[3]	1.9	—	0.1
Any other individual impurity	—	1.0	0.1

[1] 6-Hydroxy-3,4-dihydro-1*H*-quinolin-2-one

[2] 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one

[3] 1-(4-(5-Cyclohexyl-1*H*-tetrazol-1-yl)butyl)-6-(4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one

In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.4% of total impurities is found.

Assay—

Diluent—Use a mixture of water and acetonitrile (60:40).

Solution A—Use a mixture of water and acetonitrile (70:30).

Solution B—Use a mixture of water and acetonitrile (50:50).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

System suitability solution—Prepare a solution in *Diluent* having known concentrations of about 0.05 mg per mL each of USP Cilostazol RS, USP Cilostazol Related Compound A RS, and USP Cilostazol Related Compound B RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Cilostazol RS in acetonitrile, with sonication if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water to volume. Further dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL of acetonitrile, sonicate if necessary, dilute with water to volume, and mix. Transfer 1 mL of this solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm column that contains 3.5-µm packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 40°. The

chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6.5	100→50	0→50	linear gradient
6.5–10	50→0	50→100	linear gradient
10–20	0	100	isocratic
20–20.1	0→100	100→0	linear gradient
20.1–28	100	0	re-equilibration

Chromatograph the *System suitability solution,* identify the components using *Table 1,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cilostazol related compound B and cilostazol is not less than 3.0; the tailing factor for the cilostazol peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{20}H_{27}N_5O_2$ in the portion of Cilostazol taken by the formula:

$$500C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of cilostazol in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

Topic/Question	Contact	Expert Committee
CILOSTAZOL	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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