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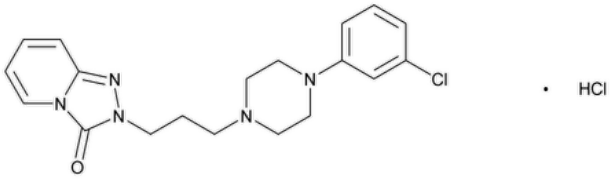
# Trazodone Hydrochloride



$C_{19}H_{22}ClN_5O \cdot HCl$ 408.32

1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-, monohydrochloride;

2-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-*s*-triazolo[4,3-*a*]-pyridin-3(2*H*)-one monohydrochloride CAS RN®: 25332-39-2; UNII: 6E8ZO8LRNM.

## DEFINITION

Trazodone Hydrochloride contains NLT 98.0% and NMT 102.0% of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$), calculated on the dried basis.

## IDENTIFICATION

***Change to read:***

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (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*.

## ASSAY

• **Procedure**

**Solution A:** 0.01% (v/v) of triethylamine in water

**Solution B:** 0.01% (v/v) of triethylamine in acetonitrile

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 80 | 20 |
| 12 | 32 | 68 |
| 12.01 | 80 | 20 |
| 15 | 80 | 20 |

**Diluent:** *Solution A* and *Solution B* (80:20)

**System suitability solution:** 1 µg/mL each of USP Trazodone Related Compound C RS and USP Trazodone Related Compound D RS, and 0.1 mg/mL of USP Trazodone Hydrochloride RS in *Diluent*

**Standard solution:** 1 mg/mL of USP Trazodone Hydrochloride RS in *Diluent*

**Sample solution:** 1 mg/mL of Trazodone Hydrochloride in *Diluent*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 7.5-cm; 3.5-µm packing L1

**Flow rate:** 2 mL/min

**Injection volume:** 10 µL

[NOTE—A mixture of acetonitrile, 2-propanol, acetone, and formic acid (400:300:300:2) is recommended for injector wash to minimize the sample carry-over.]

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 1.5 between trazodone related compound C and trazodone; NLT 2.8 between trazodone and trazodone related compound D, *System suitability solution*

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

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) in the portion of Trazodone Hydrochloride taken:

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

$r_U$ = peak response of trazodone from the *Sample solution*

$r_S$ = peak response of trazodone from the *Standard solution*

$C_S$ = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (mg/mL)

$C_U$ = concentration of Trazodone Hydrochloride in the *Sample solution* (mg/mL)

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

## IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%
- **ORGANIC IMPURITIES**

**Solution A, Solution B, Mobile phase, Diluent,** and **Chromatographic system:** Proceed as directed in the *Assay*.

**System suitability solution:** 1 µg/mL each of USP Trazodone Related Compound C RS and USP Trazodone Related Compound D RS in the *Standard solution*

**Standard solution:** 1 µg/mL of USP Trazodone Hydrochloride RS in *Diluent*

**Sample solution:** 1 mg/mL of Trazodone Hydrochloride in *Diluent*

**System suitability**

**Sample:** *System suitability solution*

[NOTE—Refer to *Table 2* for the relative retention times.]

**Suitability requirements**

**Relative standard deviation:** NMT 5.0% for the trazodone peak

**Resolution:** NLT 1.5 between trazodone related compound C and trazodone; NLT 2.8 between trazodone and trazodone related compound D

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Trazodone Hydrochloride taken:

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

$r_U$ = peak response of each individual impurity from the *Sample solution*

$r_S$ = peak response of trazodone from the *Standard solution*

$C_S$ = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (mg/mL)

$C_U$ = concentration of Trazodone Hydrochloride in the *Sample solution* (mg/mL)

$F$ = relative response factor (see *Table 2*)

**Acceptance criteria:** See *Table 2*.

**Table 2**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Triazolopyridinone[a] | 0.1 | 0.48 | 0.10 |
| Trazodone *N*-oxide[b] | 0.40 | 1.0 | 0.1 |
| Deschloro trazodone[c] | 0.65 | 0.71 | 0.1 |
| Trazodone related compound C | 0.96 | 1.0 | 0.1 |
| Trazodone | 1.0 | — | — |
| Trazodone related compound D | 1.1 | 1.0 | 0.1 |
| 4-Ethyl trazodone[d] | 1.4 | 1.0 | 0.1 |
| Trazodone isobutyl ether analog[e] | 2.0 | 1.0 | 0.1 |
| Bispiperazine analog[f] | 2.1 | 1.3 | 0.1 |
| Any individual unspecified impurity | — | 1.0 | 0.10 |
| Total impurities | — | — | 1.0 |

[a] [1,2,4]Triazolo[4,3-*a*]pyridin-3(2*H*)-one.

[b] 4-(3-Chlorophenyl)-1-[3-(3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)propyl]piperazine 1-oxide.

[c] 2-[3-(4-Phenylpiperazin-1-yl)propyl]-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one.

[d] 2-{3-[4-(3-Chloro-4-ethylphenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one.

[e] 1-(3-Chlorophenyl)-4-(3-isobutoxypropyl)piperazine.

[f] 1,3-Bis(4-(3-chlorophenyl)piperazin-1-yl)propane.

• **Limit of Trazodone Related Compound F and Cyclophosphamide Related Compound A**

[Note—Perform this test only if trazodone related compound F and cyclophosphamide related compound A are known process impurities.]

**Solution A:** 5 mM ammonium bicarbonate solution

**Solution B:** Acetonitrile

**Diluent:** Acetonitrile, water, and formic acid (100:900:1)

**Standard solution:** 0.025 µg/mL each of USP Trazodone Related Compound F RS and USP Cyclophosphamide Related Compound A RS, in *Diluent*

**Sample solution:** 0.01 g/mL of Trazodone Hydrochloride in *Diluent*

**Mobile phase:** See *Table 3*.

**Table 3**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 90 | 10 |
| 6.5 | 20 | 80 |
| 6.51 | 90 | 10 |

**Chromatographic system**

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

**Mode:** LC

**Detector:** MS/MS (tandem mass spectrometer)

**MS conditions**

**Ionization:** Triple quadrupole ionization in positive ion mode

**Acquisition mode:** Multiple reaction monitoring (MRM) of the following mass transitions:

Cyclophosphamide related compound A 142 → 63

Trazodone related compound F 273 → 120

**Column:** 4.6-mm × 7.5-cm; 3.5-µm packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Flow rate to ion source:** 0.5 mL/min

**Injection volume:** Adjust to between 5 and 50 µL, depending on the mass spectrometer. [NOTE—A mixture of 2-propanol, water, and formic acid (800:200:1) is recommended for the injector wash to minimize the sample carry-over.]

**System suitability**

**Sample:** *Standard solution*

[NOTE—The relative retention times of cyclophosphamide related compound A and trazodone related compound F are 0.4 and 1.0, respectively.]

**Suitability requirements**

**Signal-to-noise ratio:** NLT 100 for the trazodone related compound F peak and NLT 50 for the cyclophosphamide related compound A peak

**Relative standard deviation:** NMT 15.0% each for trazodone related compound F and cyclophosphamide related compound A

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

[NOTE—Under the chromatographic conditions, the elution order is cyclophosphamide related compound A, trazodone, and trazodone related compound F. Use of an appropriate switching valve program in order to completely divert the trazodone peak to waste between the elution times of the two impurities is recommended.]

Calculate, in µg/g, the amount of trazodone related compound F and cyclophosphamide related compound A in the portion of Trazodone Hydrochloride taken:

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

$r_U$ = peak response of trazodone related compound F or cyclophosphamide related compound A from the *Sample solution*

$r_S$ = peak response of trazodone related compound F or cyclophosphamide related compound A from the *Standard solution*

$C_S$ = concentration of USP Trazodone Related Compound F RS or USP Cyclophosphamide Related Compound A RS in the *Standard solution* (µg/mL)

$C_U$ = concentration of Trazodone Hydrochloride in the *Sample solution* (g/mL)

**Acceptance criteria:** NMT 2.5 µg/g each of trazodone related compound F and cyclophosphamide related compound A

**SPECIFIC TESTS**

- **Loss on Drying ⟨731⟩**

**Analysis:** Dry at a pressure of 50 mm of mercury at 105° for 3 h.

**Acceptance criteria:** NMT 0.5%

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **USP Reference Standards** ⟨11⟩

USP Cyclophosphamide Related Compound A RS
Bis(2-chloroethyl)amine hydrochloride.
$C_4H_{10}Cl_3N$ 178.48

USP Trazodone Hydrochloride RS

USP Trazodone Related Compound C RS
2-{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.
$C_{19}H_{22}ClN_5O \cdot HCl$ 408.32

USP Trazodone Related Compound D RS
2-{3-[4-(3-Bromophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.
$C_{19}H_{22}BrN_5O \cdot HCl$ 452.78

USP Trazodone Related Compound F RS
1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride.
$C_{13}H_{18}Cl_2N_2 \cdot HCl$ 309.66

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| TRAZODONE HYDROCHLORIDE | Documentary Standards Support | SM42020 Small Molecules 4 |
| REFERENCE STANDARD SUPPORT | RS Technical Services<br>RSTECH@usp.org | SM42020 Small Molecules 4 |

**Chromatographic Database Information:** Chromatographic Database

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