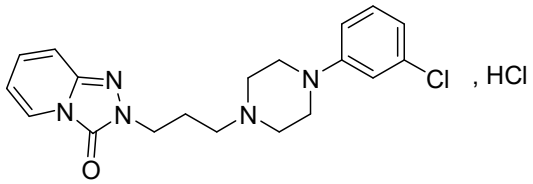
Trazodone Hydrochloride



$C_{19}H_{22}ClN_5O$, HCl Mol. Wt. 408.3

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

Trazodone Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{19}H_{22}ClN_5O$, HCl, calculated on the dried basis.

Category. Antidepressant.

Description. A white to off white, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *trazodone hydrochloride IPRS* or with the reference spectrum of trazodone hydrochloride.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 80 volumes of mobile phase A and 20 volumes of mobile phase B.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.0001 per cent w/v solution of *trazodone hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *trazodone related compound C IPRS* and *trazodone related compound D IPRS* in reference solution (a).

Chromatographic system
- a stainless steel column 7.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- mobile phase: A. a 0.01per cent v/v solution of *triethylamine* in *water,*
  B. a 0.01per cent v/v solution of *triethylamine* in *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
12	32	68
12.01	80	20
15	80	20

	retention time	factor
Triazolopyridinone[1]	0.1	2.08
Trazodone N-oxide[2]	0.40	—
Deschloro trazodone[3]	0.65	1.41
Trazodone related compound C	0.96	—
Trazodone	1.0	—
Trazodone related compound D	1.1	—
4-Ethyl trazodone[4]	1.4	—
Trazodone isobutyl ether analog[5]	2.0	—
Bispiperazine analog[6]	2.1	0.77

[1][1,2,4]Triazolo[4,3-a]pyridin-3(2H)-one.
[2]4-(3-Chlorophenyl)-1-[3-(3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)propyl]piperazine 1-oxide.
[3]2-[3-(4-Phenylpiperazin-1-yl)propyl]-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
[4]2-{3-[4-(3-Chloro-4-ethylphenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one.
[5]1-(3-Chlorophenyl)-4-(3-isobutoxypropyl)piperazine.
[6]1,3-Bis(4-(3-chlorophenyl)piperazin-1-yl)propane.

Note: A mixture of 40 volumes of acetonitrile, 30 volumes of 2-propanol, 30 volumes of acetone and 0.2 volume of formic acid may be used for injector wash to minimize sample carry-over.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks corresponding to trazodone related compound C and trazodone is not less than 1.5 and the peaks corresponding to trazodone and trazodone related compound D is not less than 2.8 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to triazolopyridinone, trazodone n-oxide, deschloro trazodone, trazodone related compound C, trazodone related compound D, 4-ethyl trazodone, trazodone isobutyl ether analog and bispiperazine analog, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Limit of Trazodone related compound F and Cyclophosphamide related compound A. Determine by liquid chromatography/mass spectrometry (2.4.39)

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

Solvent mixture. 10 volumes of *acetonitrile,* 90 volumes of *water* and 0.1 volume of *formic acid.*

Test solution. Dissolve 1g of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution . A solution containing 0.00025 per cent w/v, each of, *trazodone related compound F IPRS* and *cyclophosphamide related compound A IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 7.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- column temperature : 40°,
- mobile phase: A. a 0.005 M *ammonium carbonate* in *water,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- MS/MS (tandom mass spectrophotometer) set as,
  Ionization: Triple quadrupole ionization in positive ion mode.
  Aquisition mode: Multiple reaction monitoring (MRM) of the following mass transitions;
  cyclophosphamide related compound A 142→ 63
  trazodone related compound F 273→120
- flow rate: 1.5 ml per minute,
- flow rate to ion source: 0.5 ml per minute,
- injection volume: Adjust between 5 and 50 µl , depending on the mass spectrometer.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
6.5	20	80
6.51	90	10
10.0	90	10

Note: A mixture of 40 volumes of acetonitrile, 30 volumes of 2-propanol, 30 volumes of acetone and 0.2 volume of formic acid may be used for injector wash to minimize sample carry-over.

The relative retention time with reference to trazodone related compound F for cyclophosphamide related compound A is about 0.4.

Inject the reference solution. The test is not valid unless the signal-to-noise ratio is not less than100 for the trazodone related compound F peak, and not less than 50 for the cyclophosphamide related compound A peak and the relative standard deviation for replicate injections is not more than 15.0 per cent for each of trazodone related compound F and cyclophosphamide related compound A peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to trazodone related compound F and cyclophosphamide related compound A, each of, is not more than 0.01 times the area of the principal peak in the chromatogram obtained with the reference solution (0.00025 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.2 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, at a pressure of 50 mm of Hg for 3 hours.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Weigh accurately 0.1g of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution. A 0.1 per cent w/v solution of *trazodone hydrochloride IPRS* in the solvent mixture.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{22}ClN_5O.HCl$.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Solubility: Sparingly soluble in *chloroform* and in *water.*