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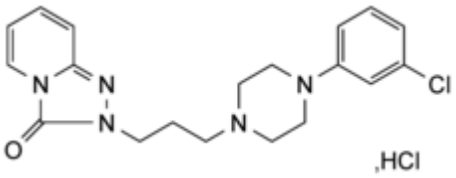
Trazodone Hydrochloride



$C_{19}H_{22}ClN_5O,HCl$ 408.3 *25332-39-2*

Action and use

Monoamine reuptake inhibitor; antidepressant.

Preparations

Trazodone Capsules

Trazodone Tablets

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 1
Contact Details	helen.corns@mhra.gov.uk laxsaan.elanganathan@mhra.gov.uk amelia.thomson@mhra.gov.uk
Deadline for Comment	30 June 2021
Target Publication Date (subject to change)	BP 2023
Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Production** limit of 2.5 ppm for impurity F removed

DEFINITION

Trazodone Hydrochloride is 2,3-[4-(3-chloro)phenylpiperazin-1-yl]propyl-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride. It contains not less than 99.0% and not more than 101.0% of $C_{19}H_{22}ClN_5O,HCl$, calculated with reference to the dried substance.

CHARACTERISTICS

A white or almost white, crystalline powder.

Soluble in *water*; sparingly soluble in *ethanol (96%)*; practically insoluble in *ether*.

IDENTIFICATION

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of trazodone hydrochloride *(RS 346)*. In the preparation of the disc, avoid excessive grinding when triturating the substance being examined with *potassium chloride*.

B. Yields the reactions characteristic of *chlorides*, Appendix VI.

TESTS

Acidity

pH of a 1% w/v solution, 3.9 to 4.5, Appendix V L.

3-Chloroaniline

To 10 mL of a 1% w/v solution of the substance being examined in a mixture of equal volumes of *water* and *ethanol* add 2 mL of a freshly prepared 5% w/v solution of *4-dimethylaminobenzaldehyde* in *ethanol* and 0.1 mL of *hydrochloric acid*. Shake well and allow to stand for 5 minutes. Any yellow colour produced at 5 minutes from the preparation of the solution is not more intense than that produced by treating at the same time and in the same manner 10 mL of a 1 µg per mL solution of *3-chloroaniline* in a mixture of equal volumes of *water* and *ethanol* beginning at the words 'add 2 mL…' (100 ppm).

Related substances

Carry out the procedures protected from light. The combined nominal total content of impurities determined in tests A and B below is not more than 1.0% and no single unknown impurity is more than 0.1%.

A. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) 0.1% w/v of the substance being examined.

(2) 0.0001% w/v of the substance being examined.

(3) 0.00005% w/v of the substance being examined.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2.0 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 3 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 350 volumes of *acetonitrile* and 650 volumes of *water*. If necessary, adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 10 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to impurity C and trazodone is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D, identified from reference chromatogram A supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* with a retention time of less than or equal to impurity E, identified from reference chromatogram A supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

B. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) 0.1% w/v of the substance being examined.

(2) 0.0001% w/v of the substance being examined.

(3) 0.00005% w/v of the substance being examined.

(4) 0.1% w/v of *trazodone hydrochloride impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Waters XTerra RP18 or Phenomenex Prodigy are suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.7 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for at least 5 times the retention time of the principal peak.

MOBILE PHASE

0.4 volumes of *diethylamine*, 320 volumes of *water* and 680 volumes of *acetonitrile*. If necessary, adjust the proportions of *acetonitrile* and *water* in the mobile phase to obtain a retention time of about 2.5 minutes for the principal peak.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to trazodone and impurity E is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* with a retention time longer than that of impurity E identified from reference chromatogram B, supplied with *trazodone hydrochloride impurity standard BPCRS*, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Disregard any peak with an area less than that of the principal peak in the chromatogram obtained with solution (3) (0.05%).

Loss on drying

When dried to constant weight at 105° at a pressure of 3.5 to 6.5 kPa, loses not more than 0.5% of its weight. Use 1 g.

Sulfated ash

Not more than 0.2%, Appendix IX A.

ASSAY

Carry out the procedure protected from light.

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) 0.01% w/v of the substance being examined.

(2) 0.01% w/v of *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Spherisorb C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 254 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of a 0.115% w/v solution of *diammonium hydrogen orthophosphate*, previously adjusted to pH 6.0 with 10% v/v *orthophosphoric acid* or 1M *sodium hydroxide*, and 60 volumes of *methanol*.

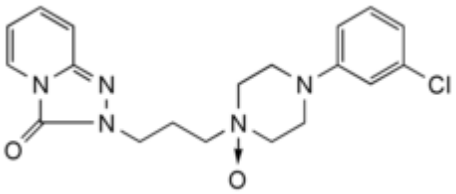
DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{22}ClN_5O,HCl$ in the substance being examined using the declared content of $C_{19}H_{22}ClN_5O,HCl$ in *trazodone hydrochloride BPCRS*.

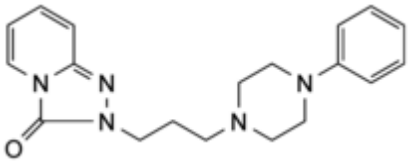
STORAGE

Trazodone Hydrochloride should be kept in an airtight container and protected from light.

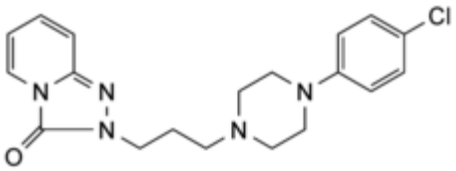
IMPURITIES



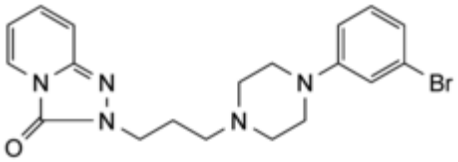
A. 4-(3-chlorophenyl)-1-[3-(3-oxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyridin-2-yl)propyl]piperazine N^1-oxide



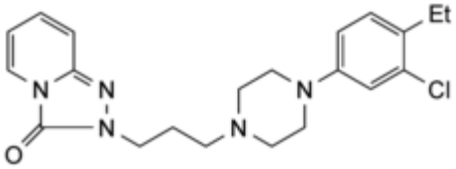
B. 2-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one



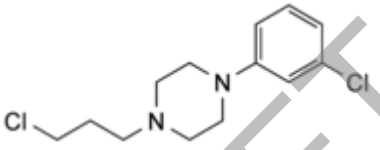
C. 2-3-[4-(4-chlorophenyl)piperazin-1-yl]propyl-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one



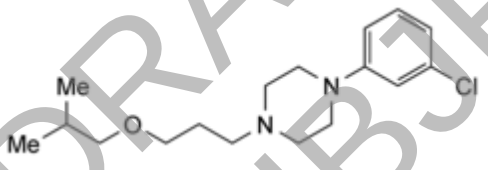
D. 2-3-[4-(3-bromophenyl)piperazin-1-yl]propyl-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one



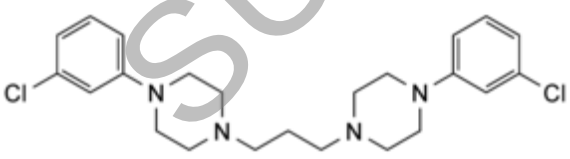
E. 2-3-[4-(3-chloro-4-ethylphenyl)piperazin-1-yl]propyl-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one



F. 1-(3-chloropropyl)-3chlorophenylpiperazine



G. 3-[4-(3-chlorophenyl)piperazin-1-yl]propyl isobutyl ether



H. 1,3-bis-[4-(3-chlorophenyl)piperazin-1-yl]propane