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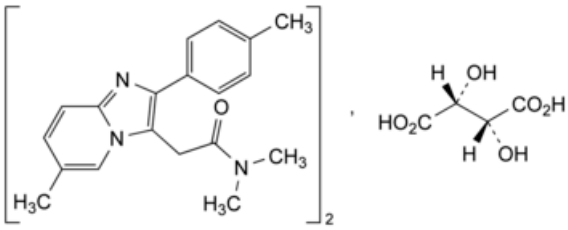
Edition: BP 2025 (Ph. Eur. 11.6 update)

Zolpidem Tartrate

General Notices

(Ph. Eur. monograph 1280)



$C_{42}H_{48}N_6O_8$ 765 *99294-93-6*

Action and use

Non-benzodiazepine hypnotic.

Preparation

Zolpidem Tablets

Ph Eur

DEFINITION

Bis[*N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide] (2*R*,3*R*)-2,3-dihydroxybutanedioate.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, hygroscopic, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

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First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Preparation Dissolve 0.10 g in 10 mL of a 10.3 g/L solution of *hydrochloric acid R*. Add 10 mL of *water R*. Add dropwise with stirring 1 mL of *dilute ammonia R2*. Filter and collect the resulting precipitate. Wash the precipitate with *water R* and then dry at 105 °C for 2 h. Examine the precipitate as a disc.

Comparison Repeat the operations using 0.10 g of *zolpidem tartrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 50 mg of the substance to be examined in 5 mL of *methanol R*, add 0.1 mL of *diethylamine R* and dilute to 10 mL with *methanol R*.

Reference solution (a) Dissolve 50 mg of *zolpidem tartrate CRS* in 5 mL of *methanol R*, add 0.1 mL of *diethylamine R* and dilute to 10 mL with *methanol R*.

Reference solution (b) Dissolve 50 mg of *flunitrazepam CRS* in 5 mL of *methylene chloride R* and dilute to 10 mL with the same solvent. Mix 1 mL of this solution and 1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *diethylamine R*, *cyclohexane R*, *ethyl acetate R* (10:45:45 *V/V/V*).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Zolpidem = about 0.3; flunitrazepam = about 0.5.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve about 0.1 g in 1 mL of *methanol R*, heating gently. 0.1 mL of this solution gives reaction (b) of tartrates (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 or BY_6 (2.2.2, *Method II*). *Prepare the solutions protected from light and carry out the test as rapidly as possible.*

Triturate 0.25 g with 0.125 g of *tartaric acid R*. Dissolve the mixture in 20 mL of *water R* and dilute to 25 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

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Reference solution (b) Dissolve 2.5 mg of *zolpidem for system suitability CRS* (containing impurities A and B) in the mobile phase and dilute to 5 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, *Ø* = 3.9 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase Mix 18 volumes of *acetonitrile R*, 23 volumes of *methanol R* and 59 volumes of a 5.6 g/L solution of *phosphoric acid R* previously adjusted to pH 5.5 with *triethylamine R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL.

Run time 4 times the retention time of zolpidem.

Identification of impurities Use the chromatogram supplied with *zolpidem for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and B.

Relative retention With reference to zolpidem (retention time = about 7 min): tartaric acid = about 0.1; impurity A = about 0.8; impurity B = about 3.6.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity A and zolpidem.

Calculation of percentage contents:

— for each impurity, use the concentration of zolpidem tartrate in reference solution (a).

Limits:

— *impurity B*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to tartaric acid.

Water (*2.5.12*)

Maximum 3.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in a mixture of 20 mL of *anhydrous acetic acid R* and 20 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 38.24 mg of $C_{42}H_{48}N_6O_8$.

STORAGE

In an airtight container, protected from light.

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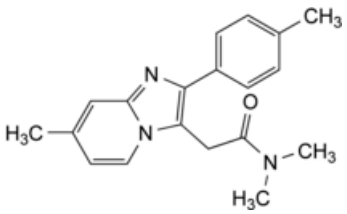
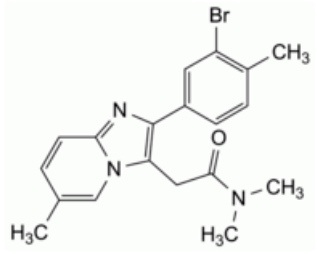
IMPURITIES

Specified impurities B.

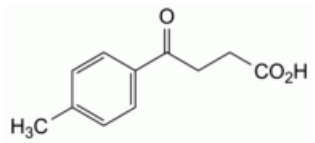
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, D, E, F.



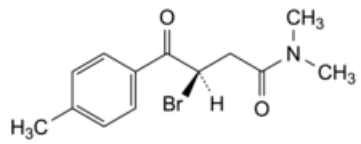
A. *N*,*N*-dimethyl-2-[7-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]acetamide,



B. 2-[2-(3-bromo-4-methylphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl]-*N*,*N*-dimethylacetamide,

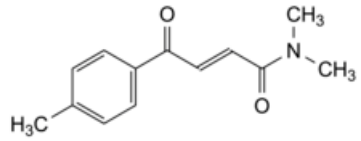


C. 4-(4-methylphenyl)-4-oxobutanoic acid,



and enantiomer

D. (3*RS*)-3-bromo-*N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobutanamide,



E. (2*E*)-*N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobut-2-enamide,

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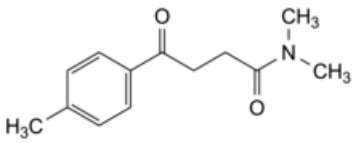

F. *N*,*N*-dimethyl-4-(4-methylphenyl)-4-oxobutanamide.

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