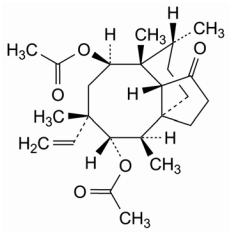
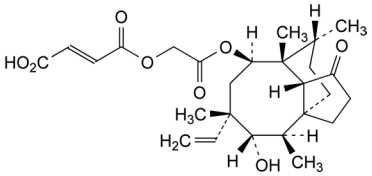
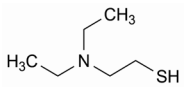


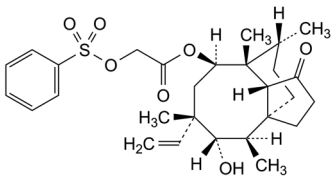
M. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-5,8-diyl diacetate (mutilin 11,14-diacetate),



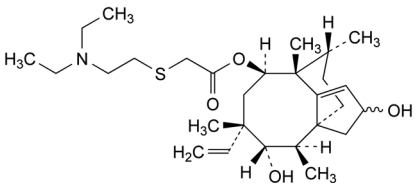
N. (2*E*)-4-[2-[[(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl]oxy]-2-oxoethoxy]-4-oxobut-2-enoic acid (pleuromutilin 22-fumarate),



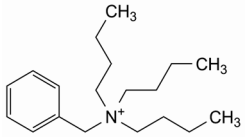
O. 2-(diethylamino)ethanethiol,



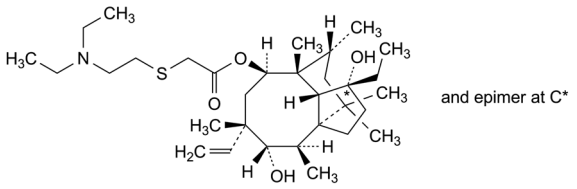
P. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [(phenylsulfonyl)oxy]acetate,



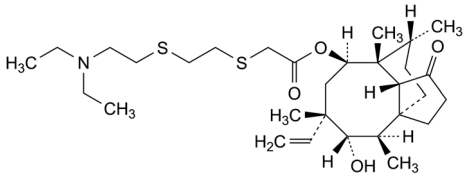
Q. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,10*R*)-6-ethenyl-2,5-dihydroxy-4,6,9,10-tetramethyl-2,3,4,5,6,7,8,9-octahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulfanyl]acetate (3,4-didehydro-2-hydroxytiamulin),



R. *N*-benzyl-*N*,*N*-dibutylbutan-1-aminium,



S. (1*RS*,3a*R*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-1-ethyl-1,5-dihydroxy-4,6,9,10,12,12-hexamethyldecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [[2-(diethylamino)ethyl]sulfanyl]acetate,

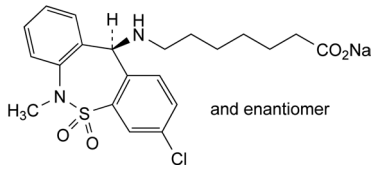


T. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl [[2-[[2-(diethylamino)-ethyl]sulfanyl]ethyl]sulfanyl]acetate.

01/2008:2022

TIANEPTINE SODIUM

Tianeptinum natricum



$C_{21}H_{24}ClN_2NaO_4S$ M_r 458.9
[30123-17-2]

DEFINITION

Sodium 7-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo-[*c*,*f*][1,2]thiazepin-11-yl]amino]heptanoate *S*,*S*-dioxide.
Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or yellowish powder, very hygroscopic.
Solubility: freely soluble in water, in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of tianeptine sodium*.

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Impurity A. Gas chromatography (*2.2.28*).
Internal standard solution. Dilute 1 mL of *ethyl 5-bromovalerate R* in *ethanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 250.0 mL with *ethanol R*.
Test solution. Dissolve 0.1000 g of the substance to be examined in the internal standard solution and dilute to 2.0 mL with the same solution.
Reference solution. Dissolve 10.0 mg of *tianeptine impurity A CRS* in the internal standard solution and dilute to 200.0 mL with the same solution.

Monographs T

Column:
- *material*: fused silica,
- *size*: *l* = 25 m, Ø = 0.25 mm,
- *stationary phase*: *poly(cyanopropyl)siloxane R* (film thickness 0.2 µm).

Carrier gas: *helium for chromatography R*.

Linear velocity: 26 cm/s.

Split ratio: 1:100.

Temperature:
- *column*: 150 °C,
- *injection port and detector*: 210 °C.

Detection: flame ionisation.

Injection: 1 µL.

Run time: twice the retention time of ethyl 5-bromovalerate.

System suitability: reference solution:
- *elution order*: ethanol, ethyl 5-bromovalerate, impurity A,
- *resolution*: minimum 10 between the peaks due to ethyl 5-bromovalerate and impurity A,
- *signal-to-noise ratio*: minimum 20 for the peak due to impurity A.

Limit:
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture. Mix 50 volumes of *methanol R* and 50 volumes of *water for chromatography R*.

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (b). Dissolve 20.0 mg of *sodium tianeptine for system suitability CRS* in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

Column:
- *size*: *l* = 0.15 m, Ø = 4.6 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm) with a pore size of 0.01 µm,
- *temperature*: 30 °C.

Mobile phase:
- *mobile phase A*: mix 21 volumes of *methanol R1*, 31.5 volumes of *acetonitrile R1* and 47.5 volumes of a 2 g/L solution of *sodium laurilsulfate R*, adjusted to pH 2.5 with *phosphoric acid R*,
- *mobile phase B*: mix 20 volumes of *methanol R1*, 20 volumes of a 2 g/L solution of *sodium laurilsulfate R*, adjusted to pH 2.5 with *phosphoric acid R* and 60 volumes of *acetonitrile R1*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 35	100	0
35 - 45	100 → 40	0 → 60
45 - 60	40	60
60 - 70	40 → 100	60 → 0

Flow rate: 1 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Relative retention with reference to tianeptine (retention time = about 30 min): impurity C = about 0.4; impurity D1 = about 0.6; impurity D2 = about 0.8; impurity E = about 1.1; impurity B = about 1.7.

System suitability: reference solution (b):
- *resolution*: minimum 2.5 between the peaks due to tianeptine and impurity E.

Limits:
- *any impurity*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *total*: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),
- *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): maximum 5.0 per cent, determined on 0.100 g.

ASSAY

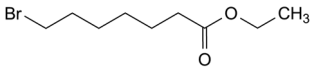
Dissolve 0.165 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 22.95 mg of $C_{21}H_{24}ClN_2NaO_4S$.

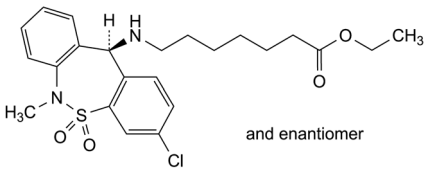
STORAGE

In an airtight container.

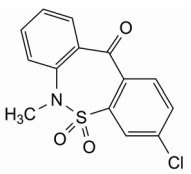
IMPURITIES



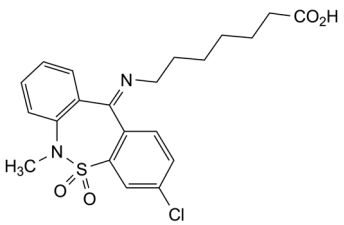
A. ethyl 7-bromoheptanoate,



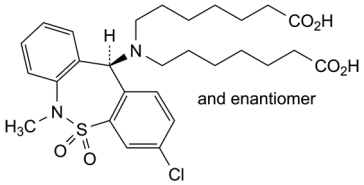
B. ethyl 7-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo-[*c*,*f*][1,2]thiazepin-11-yl]amino]heptanoate *S*,*S*-dioxide,



C. 3-chloro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-one *S*,*S*-dioxide,



D. 7-[[(11*RS*)-3-chloro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11(6*H*)-ylidene]amino]heptanoic acid *S*,*S*-dioxide,



E. 7,7′-[[(11*RS*)-3-chloro-6-methyl-6,11-dihydrodibenzo-[*c*,*f*][1,2]thiazepin-11-yl]imino]diheptanoic acid *S*,*S*-dioxide.