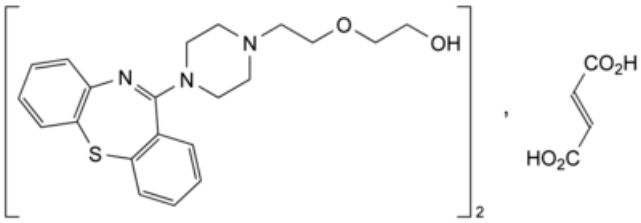
Edition: BP 2025 (Ph. Eur. 11.6 update)

Quetiapine Fumarate

General Notices

(Ph. Eur. monograph 2541)



$C_{46}H_{54}N_6O_8S_2$ 883 *111974-72-2*

Action and use

Dopamine receptor antagonist; neuroleptic.

Preparations

Quetiapine Prolonged-release Tablets

Quetiapine Tablets

Ph Eur

DEFINITION

Bis[2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethanol] (2*E*)-but-2-enedioate.

Content

— *quetiapine fumarate* ($C_{46}H_{54}N_6O_8S_2$; M_r 883): 99.0 per cent to 101.0 per cent (dried substance);

— *fumaric acid* ($C_4H_4O_4$; M_r 116.1): 12.5 per cent to 13.8 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Slightly soluble in water, in anhydrous ethanol and in methanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison quetiapine fumarate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 50 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of quetiapine for system suitability CRS (containing impurities G and N) in 1.0 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

— *stationary phase*: end-capped, charged surface, ethylene-bridged phenylhexylsilyl silica gel for chromatography (hybrid material) R (1.7 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 10 volumes of methanol R1 and 90 volumes of a 3.85 g/L solution of ammonium acetate R, previously adjusted to pH 9.0 with ammonia R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	80	20
8 - 14.50	80 → 60	20 → 40
14.50 - 22.60	60 → 50	40 → 50
22.60 - 26	50 → 30	50 → 70
26 - 29	30 → 10	70 → 90
29 - 30	10	90

Flow rate 0.5 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 3.0 µL.

Identification of impurities Use the chromatogram supplied with *quetiapine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities G and N.

Relative retention With reference to quetiapine (retention time = about 13 min): fumaric acid = about 0.05; impurity G = about 0.5; impurity N = about 1.04.

System suitability:

— *signal-to-noise ratio*: minimum 40 for the principal peak in the chromatogram obtained with reference solution (b);

— *peak-to-valley ratio*: minimum 5.0, where H_p = height above the baseline of the peak due to impurity N and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to quetiapine in the chromatogram obtained with reference solution (a).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity G = 0.5; impurity N = 2.0;

— for each impurity, use the concentration of quetiapine fumarate in reference solution (b).

Limits:

— *impurities G, N*: for each impurity, maximum 0.15 per cent;

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

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard any peak due to fumaric acid.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Quetiapine fumarate

Dissolve 0.170 g in 40 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 22.08 mg of $C_{46}H_{54}N_6O_8S_2$.

Fumaric acid

Dissolve 0.350 g in 70 mL of a mixture of equal volumes of *methanol R* and *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 5.804 mg of $C_4H_4O_4$.

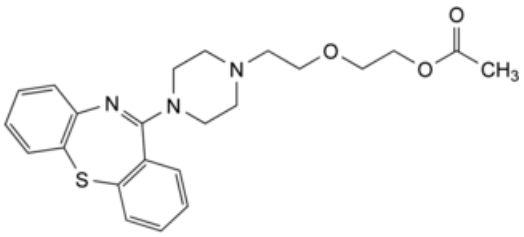
STORAGE

Protected from light.

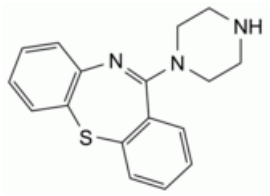
IMPURITIES

Specified impurities G, N.

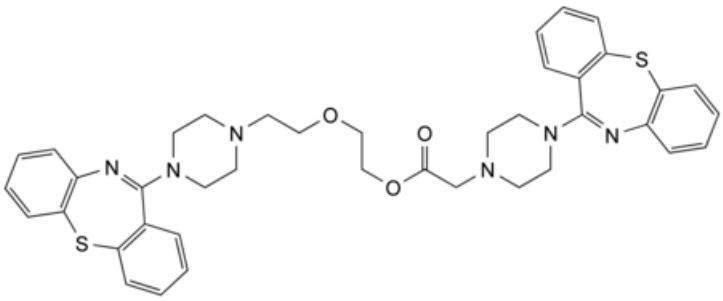
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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, B, C, D, E, F, H, I, J, K, L, O, P, Q, S, T, U, V, W.



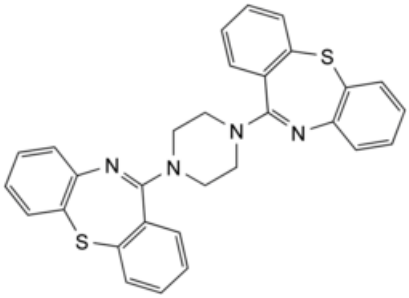
A. 2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethyl acetate,



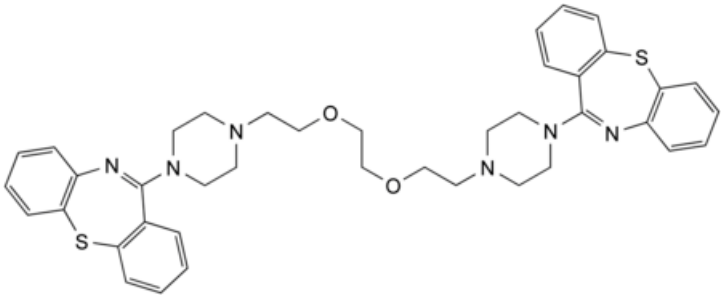
B. 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine,



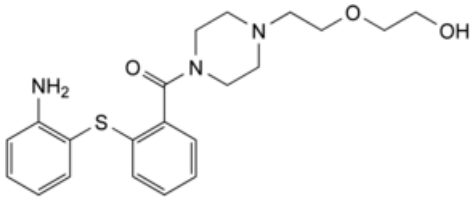
C. 2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethyl 2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]acetate,



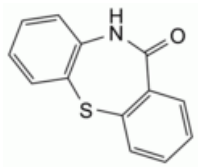
D. 11,11′-(piperazine-1,4-diyl)bis(dibenzo[*b*,*f*][1,4]thiazepine),



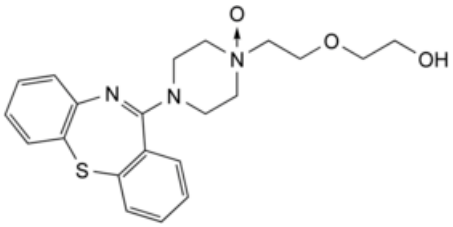
E. 11,11′-[ethylenebis(oxyethylenepiperazine-4,1-diyl)]bis(dibenzo[*b*,*f*][1,4]thiazepine),



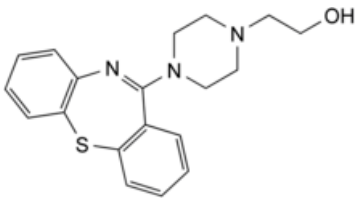
F. [2-[(2-aminophenyl)sulfanyl]phenyl][4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]methanone,



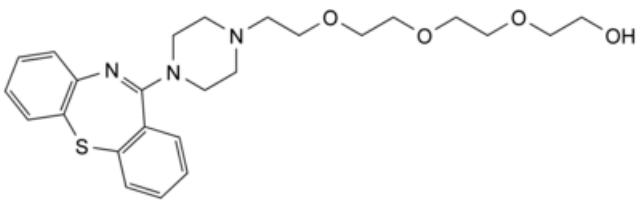
G. dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one,



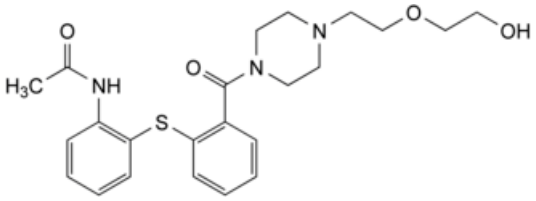
H. 2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1-oxidopiperazin-1-yl]ethoxy]ethanol,



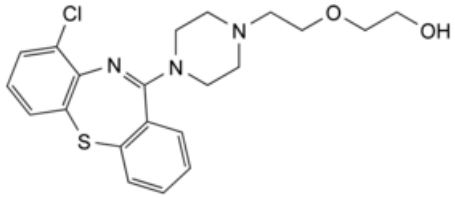
I. 2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol,



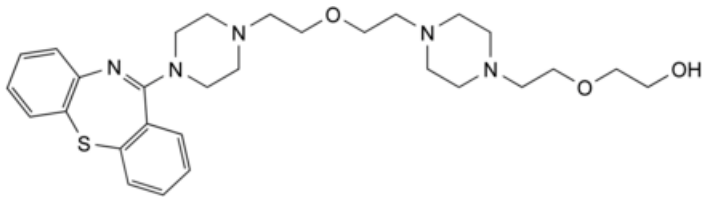
J. 2-[2-[2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethoxy]ethoxy]ethanol,



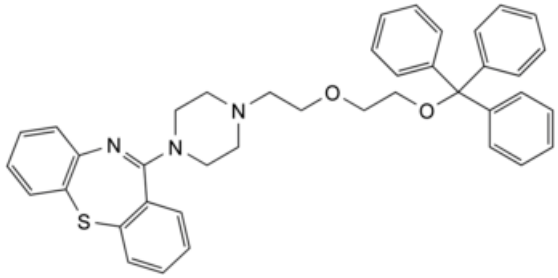
K. *N*-[2-[[2-[[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]carbonyl]phenyl]sulfanyl]phenyl]acetamide,



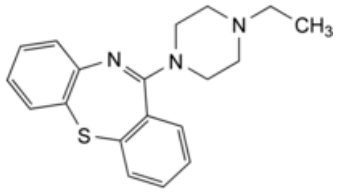
L. 2-[2-[4-(9-chlorodibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethanol,



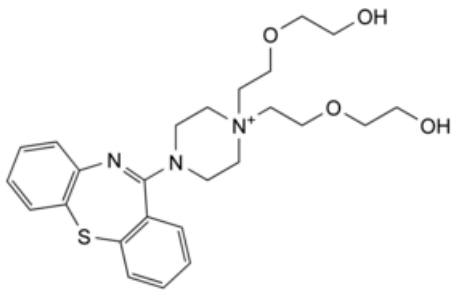
N. 2-[2-[4-[2-[2-[4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethyl]piperazin-1-yl]ethoxy]ethanol,



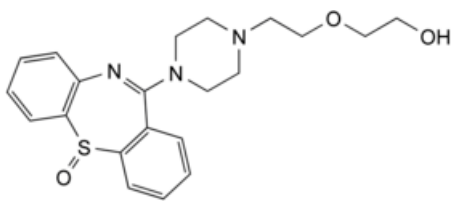
O. 11-[4-[2-[2-(triphenylmethoxy)ethoxy]ethyl]piperazin-1-yl]dibenzo[*b*,*f*][1,4]thiazepine,



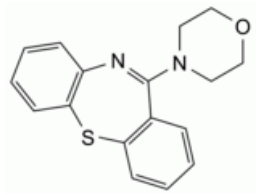
P. 11-(4-ethylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine,



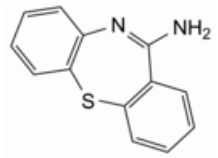
Q. 4-(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1,1-bis[2-(2-hydroxyethoxy)ethyl]piperazin-1-ium,



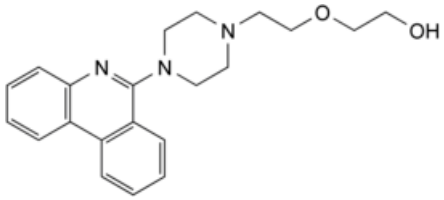
S. 2-[2-[4-(5-oxidodibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethanol,



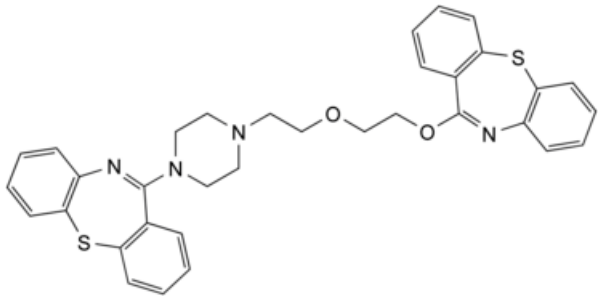
T. 11-(morpholin-4-yl)dibenzo[*b*,*f*][1,4]thiazepine,



U. dibenzo[*b*,*f*][1,4]thiazepin-11-amine,



V. 2-[2-[4-(phenanthridin-6-yl)piperazin-1-yl]ethoxy]ethanol,



W. 11-(4-[2-[2-(dibenzo[*b*,*f*][1,4]thiazepin-11-yloxy)ethoxy]ethyl]piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine.

Ph Eur