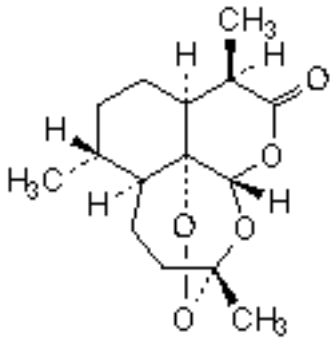
Artemisinin (Artemisininum)

2014-01



$C_{15}H_{22}O_5$

Relative molecular mass. 282.3

Chemical name. (3*R*,5a*S*,6*R*,8a*S*,9*R*,12*S*,12a*R*)-3,6,9-trimethyloctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one; CAS Reg. No. 63968-64-9.

Description. Colourless needles or white crystalline powder.

Solubility. Practically insoluble in water; very soluble in dichloromethane R; freely soluble in acetone R and ethyl acetate R; soluble in glacial acetic acid R, methanol R and ethanol (~750 g/L) TS.

Category. Antimalarial.

Storage. Artemisinin should be kept in a well-closed container and protected from light.

Requirements

Artemisinin contains not less than 97.0% and not more than 102.0% of $C_{15}H_{22}O_5$, calculated with reference to the dried substance.

Identity tests

-Either test A alone or tests B, C and D may be applied.

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from artemisinin RS or with the *reference spectrum* of artemisinin.

B. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography using silica gel R1 as the coating substance and a mixture of equal volumes of light petroleum R1 and ether R as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions in toluene R. For solution (A) use 0.1 mg of the test substance per mL. For solution (B) use 0.1 mg of artemisinin RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of cool air. Spray with anisaldehyde/sulfuric acid TS and heat the plate to 105 °C for about 7 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. Dissolve 5 mg in about 0.5 mL of dehydrated ethanol R, add about 0.5 mL of hydroxylamine hydrochloride TS2 and 0.25 mL of sodium hydroxide (~80 g/L) TS. Heat the mixture in a water-bath to boiling, cool, add 5 drops of hydrochloric acid (~70 g/L) TS and 2 drops of ferric chloride (50 g/L) TS; a deep violet colour is immediately produced.

D. Dissolve 5 mg in about 0.5 mL of dehydrated ethanol R, add 1.0 mL of potassium iodide (80 g/L) TS, 2.5 mL of sulfuric acid (~100 g/L) TS, allow to stand for one minute and add 4 drops of starch TS; a violet colour is immediately produced.

Specific optical rotation. Use a 10 mg/mL solution in dehydrated ethanol R and calculate with reference to the dried substance;

$[\alpha]_D^{20\,°C}$ = +75° to +78°

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant mass at 80 °C; it loses not more than 5.0 mg/g.

Related substances

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using the conditions given below under “Assay”.

Use solutions (1) and (2) as described below under “Assay”. For solution (3) dilute 1 mL of solution (1) to 100 mL with the mobile phase.

Inject separately 20 µL of solutions (1), (2) and (3). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) impurity A (artemisitene) is eluted at the relative retention of about 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution factor between the peaks due to impurity A and artemisinin is at least 4. The chromatogram obtained with solution (1) may show a peak due to impurity B (9-*epi*-artemisinin) eluting at a relative retention of about 0.85 with reference to artemisinin.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.027, is not greater than 0.15 times the area of the principal peak in the chromatogram obtained with solution (3) (0.15%);

- the area of any peak corresponding to impurity B is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

- the area of any other peak, other than the principal peak, is not greater than 0.15 times the area of the principal peak in the chromatogram obtained with solution (3) (0.15%);

- the sum of the corrected area of any peak corresponding to impurity A and the areas of all other peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (3) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (3) (0.05%).

Assay

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). As the mobile phase use a 50:50 mixture of acetonitrile R and water R.

Prepare the following solutions in the mobile phase. For solution (1) use 5.0 mg of the test substance per mL. For solution (2) use 5.0 mg of artemisinin RS (containing artemisinin and impurity A) per mL.

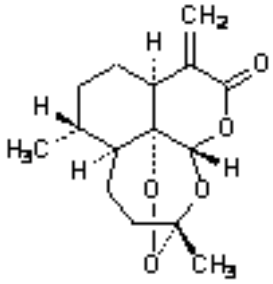
Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Inject separately 20 µL of solutions (1) and (2). Record the chromatograms for about 1.5 times the retention time of artemisinin. In the chromatogram obtained with solution (2) impurity A (artemisitene) is eluted at the relative retention of about 0.79 with reference to artemisinin (retention time about 10 minutes). The test is not valid unless the resolution factor between the peaks due to impurity A and artemisinin is at least 4.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of $C_{15}H_{22}O_5$, using the declared content of $C_{15}H_{22}O_5$ in artemisinin RS with reference to the dried substance.

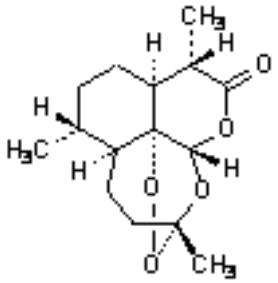
Impurities

A.



(3*R*,5a*S*,6*R*,8a*S*,12*S*,12a*R*)-3,6-dimethyl-9-methylideneoctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (artemisitene)

B.



(3*R*,5a*S*,6*R*,8a*S*,9*S*,12*S*,12a*R*)-3,6,9-trimethyloctahydro-3,12-epoxypyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (9-*epi*-artemisinin)