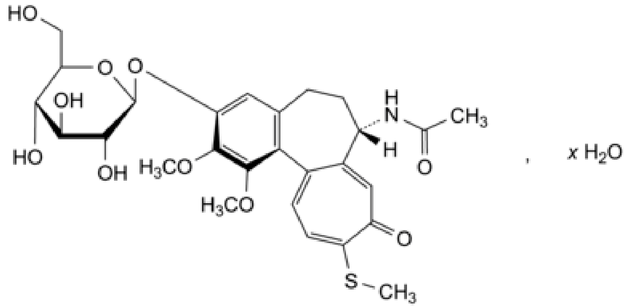
British Pharmacopoeia | Quality standards

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

Thiocolchicoside Hydrate

General Notices

(Ph. Eur. monograph 2814)



$C_{27}H_{33}NO_{10}S,xH_2O$ 563.6 (anhydrous substance) *1622135-03-8*

Action and use

Muscle relaxant.

Ph Eur

DEFINITION

N-[(7*S*,12a*R*$_a$)-3-(β-D-Glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide.

Content

96.0 per cent to 102.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

Yellow crystalline powder, slightly hygroscopic.

Solubility

Sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

mp

About 272 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison thiocolchicoside hydrate CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1).

Dissolve 0.100 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (2.2.7)

-600 to -570 (anhydrous substance).

Dissolve 0.500 g in *water R* and dilute to 100.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Test solution (a) Dissolve 20.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with *methanol R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 2.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 5 mg of *thiocolchicoside for system suitability CRS* (containing impurities D, E, G, H, K and L) in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (c) Dissolve 20.0 mg of *thiocolchicoside hydrate CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *methanol R*.

Column:

— *size*: *l* = 0.10 m, Ø = 2.1 mm;

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

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 0.22 g of *ammonium formate R* in 350 mL of *water for chromatography R* and mix with 25 mL of *tetrahydrofuran R*;

— *mobile phase B*: dilute 45 µL of *anhydrous formic acid R* in 900 mL of *acetonitrile R* and mix with 100 mL of *tetrahydrofuran R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	99	1
2 - 6	99 → 92	1 → 8
6 - 7.5	92 → 70	8 → 30
7.5 - 8.8	70 → 50	30 → 50
8.8 - 9.2	50 → 2	50 → 98
9.2 - 10	2	98

Flow rate 0.4 mL/min.

Detection Spectrophotometer at 370 nm.

Injection 1.0 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram supplied with *thiocolchicoside for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities D, E, G, H, K and L.

Relative retention With reference to thiocolchicoside (retention time = about 6 min): impurity D = about 0.2; impurity H = about 0.4; impurity G = about 0.7; impurity K = about 0.8; impurity E = about 1.05; impurity L = about 1.11.

System suitability:

— *signal-to-noise ratio*: minimum 50 for the principal peak in the chromatogram obtained with reference solution (a);

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to thiocolchicoside in the chromatogram obtained with reference solution (b).

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity H = 2.8;

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

Limits:

— *impurity E*: maximum 1.0 per cent;

— *impurity H*: maximum 0.7 per cent;

— *impurity K*: maximum 0.3 per cent;

— *impurities D, G*: for each impurity, maximum 0.2 per cent;

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

— *total*: maximum 2.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to impurity L.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{27}H_{33}NO_{10}S$ taking into account the assigned content of *thiocolchicoside hydrate CRS*.

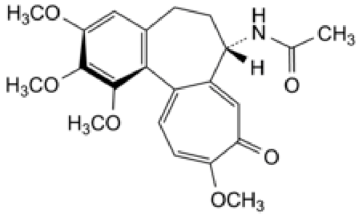
STORAGE

In an airtight container, protected from light.

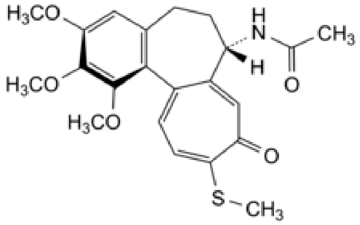
IMPURITIES

Specified impurities *D, E, G, H, K*.

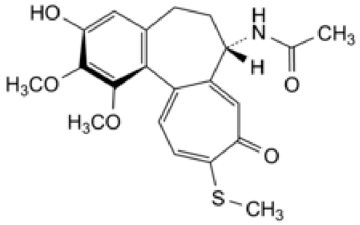
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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, J, L*.



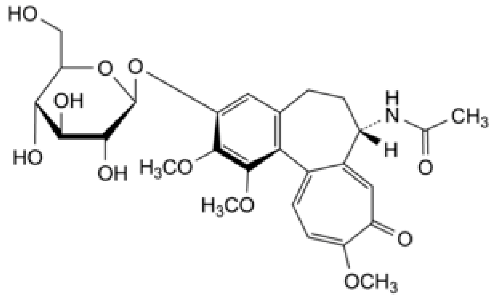
A. *N*-[(7*S*,12a*R*$_a$)-1,2,3,10-tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicine),



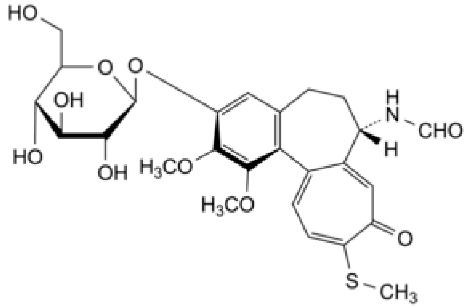
B. *N*-[(7*S*,12a*R*$_a$)-1,2,3-trimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicine),



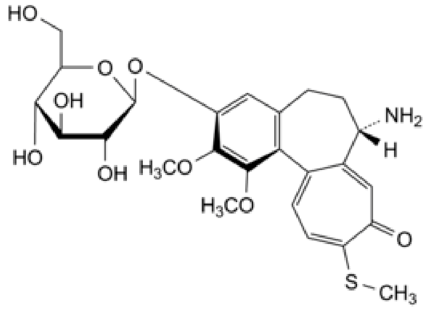
C. *N*-[(7*S*,12a*R*$_a$)-3-hydroxy-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (3-*O*-demethylthiocolchicine),



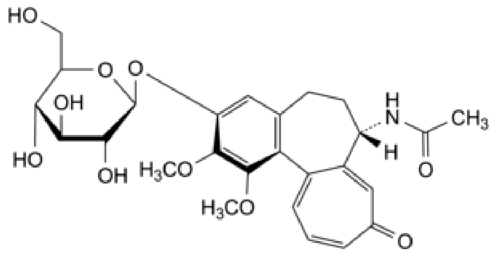
D. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2,10-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (colchicoside),



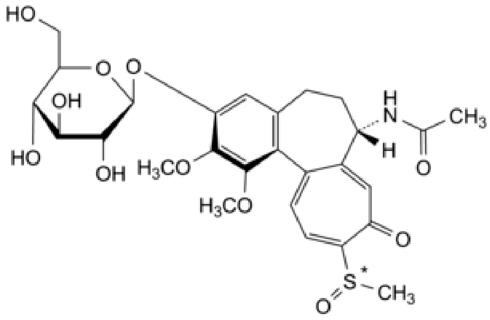
E. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]formamide (*N*-deacetyl-*N*-formylthiocolchicoside),



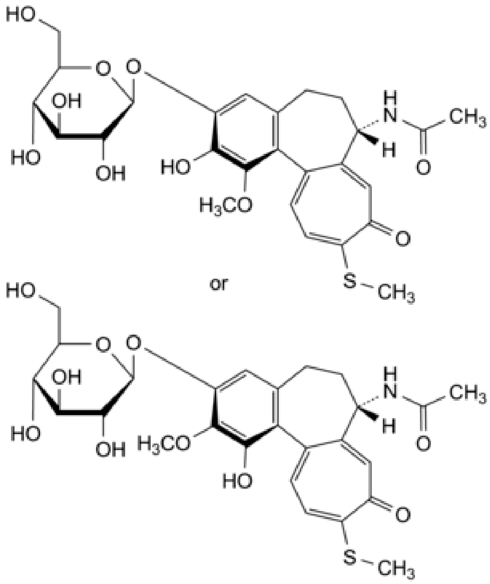
G. (7*S*,12aR_a)-7-amino-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-6,7-dihydrobenzo[*a*]heptalen-9(5*H*)-one (*N*-deacetylthiocolchicoside),



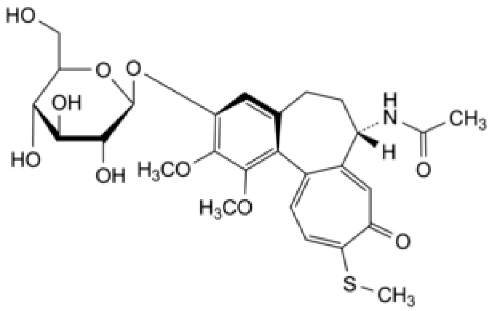
H. *N*-[(7*S*,12aR_a)-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (10-demethoxycolchicoside),



J. *N*-[(7*S*,12aR_{a})-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfinyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (thiocolchicoside *S*-oxide),



K. *N*-[(7*S*,12aR_{a})-3-(β-D-glucopyranosyloxy)-2-hydroxy-1-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide or *N*-[(7*S*,12aR_{a})-3-(β-D-glucopyranosyloxy)-1-hydroxy-2-methoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide,



L. *N*-[(7*S*,12aS_{a})-3-(β-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide (12aS_{a}-thiocolchicoside).

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