the outer epidermis with orange-yellow contents and a thick cuticle, the inner epidermis composed of thin-walled cells containing cluster crystals and occasional prisms of calcium oxalate; scattered lignified cells, isodiametric, with thickened and pitted walls forming the trichome bases; abundant long, unicellar trichomes, up to 2 mm long and 30-45 µm thick, tapering towards each end, walls heavily thickened and with a waxy cuticle which may show fissures in a spiral arrangement; numerous oily orange-yellow globules.

C. Thin-layer chromatography (*2.2.27*).

Test solution. To 5 g of the powdered drug (355) (*2.9.12*) add 25 ml of *ethanol (96 per cent) R*. Shake for 30 min and filter.

Reference solution. Dissolve 10 mg of *ascorbic acid R* in 5.0 ml of *ethanol (60 per cent V/V) R*.

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

Mobile phase: *acetic acid R, acetone R, methanol R, toluene R* (5:5:20:70 *V/V/V/V*).

Application: 20 µl of the test solution and 2 µl of the reference solution.

Development: over a path of 15 cm.

Drying: in air.

Detection A: examine in ultraviolet light at 254 nm.

Results A: the chromatogram obtained with the test solution shows a quenching zone similar in position to the principal zone in the chromatogram obtained with the reference solution.

Detection B: spray with a 0.2 g/l solution of *dichlorophenolindophenol, sodium salt R* in *ethanol (96 per cent) R*. Examine in daylight.

Results B: the chromatogram obtained with the test solution shows a white zone on a pink background similar in position and colour to the principal zone in the chromatogram obtained with the reference solution. The chromatogram also shows an intense orange-yellow zone near the solvent front and a yellow zone in the upper third (carotenoids).

TESTS

Foreign matter (*2.8.2*): maximum 1 per cent.

Loss on drying (*2.2.32*): maximum 10.0 per cent, determined on 1.000 g of the powdered drug (355) (*2.9.12*) by drying in an oven at 105 °C.

Total ash (*2.4.16*): maximum 7.0 per cent.

ASSAY

Test solution. In a round-bottomed flask, weigh 0.500 g of the freshly powdered drug (710) (*2.9.12*). Add a solution of 1.0 g of *oxalic acid R* in 50.0 ml of *methanol R*. Boil under a reflux condenser for 10 min, and cool in iced water until the temperature reaches 15-20 °C. Filter. Transfer 2.0 ml of the filtrate to a 50 ml conical flask. Add successively, with gentle shaking after each addition, 2.0 ml of *dichlorophenolindophenol standard solution R* and then, exactly 60 s later, 0.5 ml of a 100 g/l solution of *thiourea R* in *ethanol (50 per cent V/V) R* and 0.7 ml of *dinitrophenylhydrazine-sulphuric acid solution R*. Heat under a reflux condenser at 50 °C for 75 min, and place immediately in iced water for 5 min. Add dropwise 5.0 ml of a mixture of 12 ml of *water R* and 50 ml of *sulphuric acid R*, taking care to carry out the addition over a period of minimum 90 s and maximum 120 s while maintaining vigorous stirring in iced water. Allow to stand for 30 min at room temperature and measure the absorbance (*2.2.25*) at 520 nm using solution A as compensation liquid.

Solution A. Treat 2.0 ml of the filtrate obtained during the preparation of the test solution as described but adding the *dinitrophenylhydrazine-sulphuric acid solution R* just before the absorbance is measured.

Reference solution. Dissolve 40.0 mg of *ascorbic acid R* in a freshly prepared 20 g/l solution of *oxalic acid R* in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 5.0 ml of this solution to 100.0 ml with a freshly prepared 20 g/l solution of *oxalic acid R* in *methanol R*. Treat 2.0 ml of the solution as described above for the filtrate obtained during the preparation of the test solution. Measure the absorbance (*2.2.25*) at 520 nm using solution B as the compensation liquid.

Solution B. Treat 2.0 ml of the reference solution as described above for solution A.

Calculate the percentage content of ascorbic acid from the following expression:

$$\frac{2.5 \times A_1 \times m_2}{A_2 \times m_1}$$

A_1 = absorbance of the test solution;

A_2 = absorbance of the reference solution;

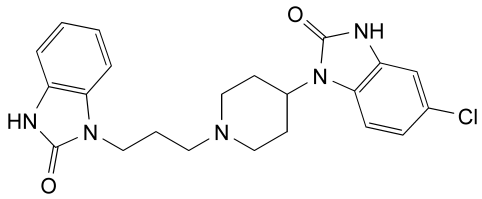
m_1 = mass of the substance to be examined, in grams;

m_2 = mass of ascorbic acid used, in grams.

01/2008:1009
corrected 6.0

DOMPERIDONE

Domperidonum



$C_{22}H_{24}ClN_5O_2$ M_r 425.9
[57808-66-9]

DEFINITION

5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, soluble in dimethylformamide, slightly soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 244 °C to 248 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *domperidone CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 20 mg of *domperidone CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 20 mg of *domperidone CRS* and 20 mg of *droperidol CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Plate: *TLC octadecylsilyl silica gel plate R.*

Mobile phase: *ammonium acetate solution R, dioxan R, methanol R* (20:40:40 *V/V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in a current of warm air for 15 min.

Detection: expose to iodine vapour until the spots appear. Examine in daylight.

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).

D. It gives the reaction of non-nitrogen substituted barbiturates (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 0.20 g in *dimethylformamide R* and dilute to 20.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.10 g of the substance to be examined in *dimethylformamide R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 10.0 mg of *domperidone CRS* and 15.0 mg of *droperidol CRS* in *dimethylformamide R* and dilute to 100.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with *dimethylformamide R*. Dilute 5.0 ml of this solution to 20.0 ml with *dimethylformamide R*.

Column:

– *size*: *l* = 0.1 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: 5 g/l solution of *ammonium acetate R*;

– *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	70 → 0	30 → 100
10 - 12	0	100

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 280 nm.

Equilibration: with *methanol R* for at least 30 min and then with the mobile phase at the initial composition for at least 5 min.

Injection: 10 µl; inject *dimethylformamide R* as a blank.

Retention time: domperidone = about 6.5 min; droperidol = about 7 min.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to domperidone and droperidol; if necessary, adjust the concentration of methanol in the mobile phase or adjust the time programme for the linear gradient.

Limits:

– *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the blank.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test D. Prepare the reference solution using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.300 g in 50 ml of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R*. Titrate with *0.1 M perchloric acid* until the colour changes from orange-yellow to green using 0.2 ml of *naphtholbenzein solution R* as indicator.

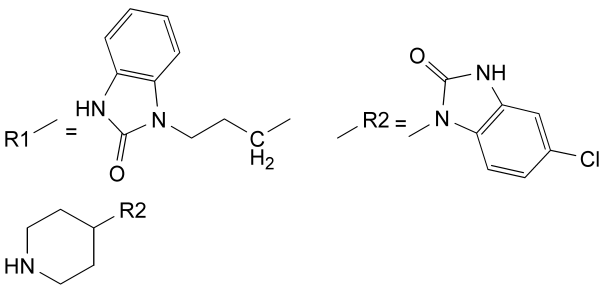
1 ml of *0.1 M perchloric acid* is equivalent to 42.59 mg of $C_{22}H_{24}ClN_5O_2$.

STORAGE

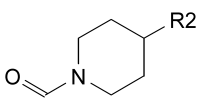
Protected from light.

IMPURITIES

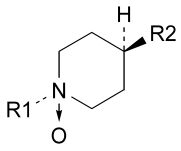
Specified impurities: A, B, C, D, E, F.



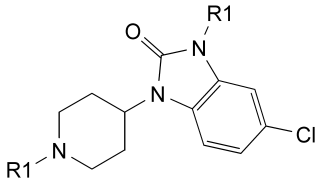
A. 5-chloro-1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one,



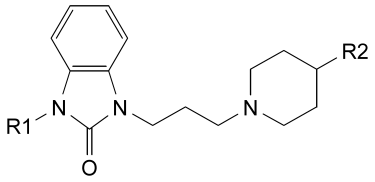
B. 4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-formylpiperidine,



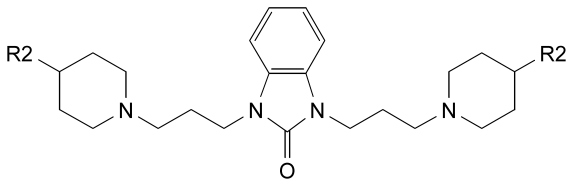
C. *cis*-4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine 1-oxide,



D. 5-chloro-3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one,



E. 1-[3-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]-1,3-dihydro-2*H*-benzimidazol-2-one,

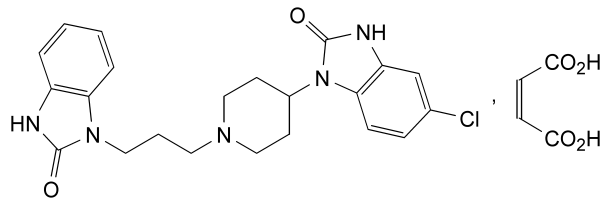


F. 1,3-bis[3-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-1,3-dihydro-2*H*-benzimidazol-2-one.

01/2008:1008
corrected 6.0

DOMPERIDONE MALEATE

Domperidoni maleas



$C_{26}H_{28}ClN_5O_6$ M_r 542.0
[83898-65-1]

DEFINITION

5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrogen (*Z*)-butenedioate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: very slightly soluble in water, sparingly soluble in dimethylformamide, slightly soluble in methanol, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *domperidone maleate CRS.*

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *2-propanol R*, evaporate to dryness on a water-bath and record new spectra using the residues.

B. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 20 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 20 mg of *domperidone maleate CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 20 mg of *domperidone maleate CRS* and 20 mg of *droperidol CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Plate: *TLC octadecylsilyl silica gel plate R.*

Mobile phase: *ammonium acetate solution R, dioxan R, methanol R* (20:40:40 *V/V/V*).

Application: 5 µl.

Development: over a path of 15 cm.

Drying: in a current of warm air for 15 min.

Detection: expose to iodine vapour until the spots appear. Examine in daylight.

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. Triturate 0.1 g with a mixture of 1 ml of *strong sodium hydroxide solution R* and 3 ml of *water R*. Shake with 3 quantities, each of 5 ml, of *ether R*. To 0.1 ml of the aqueous layer add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min. No colour develops. To the remainder of the aqueous layer add 2 ml of *bromine solution R*. Heat on a water-bath for 15 min and then heat to boiling. Cool. To 0.1 ml of this solution add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min. A violet colour develops.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 0.20 g in *dimethylformamide R* and dilute to 20.0 ml with the same solvent.