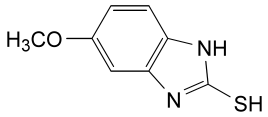
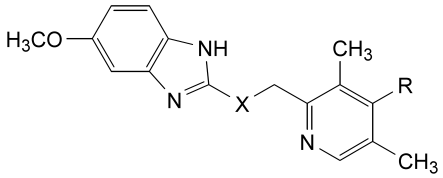


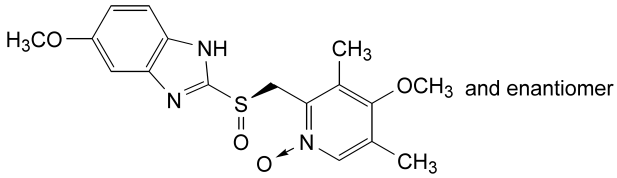
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



B. R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-5-methoxy-1*H*-benzimidazole,

C. R = OCH_3, X = S: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]thio]-1*H*-benzimidazole (ufiprazole),

D. R = OCH_3, X = SO_2: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulphone),



E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulphinyl]methyl]-3,5-dimethylpyridine 1-oxide,

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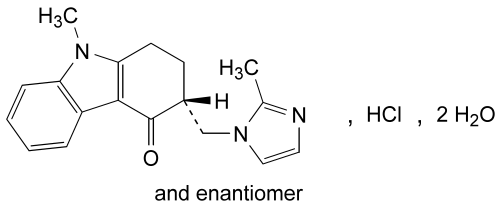
ONDANSETRON HYDROCHLORIDE DIHYDRATE

Ondansetroni hydrochloridum dihydricum



$C_{18}H_{20}ClN_3O,2H_2O$ M_r 365.9

DEFINITION

(3*RS*)-9-Methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one hydrochloride dihydrate.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: sparingly soluble in water and in alcohol, soluble in methanol, slightly soluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *ondansetron hydrochloride dihydrate CRS*.

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

TESTS

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

Test solution. Dissolve 0.125 g of the substance to be examined in a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*, and dilute to 10.0 ml with the same mixture of solvents.

Reference solution (a). Dissolve 12.5 mg of *ondansetron for TLC system suitability CRS* in a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*, and dilute to 1.0 ml with the same mixture of solvents.

Reference solution (b). Dilute 1 ml of the test solution to 100 ml with a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*. Dilute 4.0 ml to 10.0 ml with a mixture of 0.5 volumes of *concentrated ammonia R*, 100 volumes of *alcohol R* and 100 volumes of *methanol R*.

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

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R, methylene chloride R* (2:40:50:90 *V/V/V/V*).

Application: 20 µl.

Development: over 3/4 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Order of elution: ondansetron, impurity B, impurity A.

System suitability: the chromatogram obtained with reference solution (a) shows 3 clearly separated spots.

Limit:

– *impurity B*: any spot corresponding to impurity B in the chromatogram obtained with the test solution is not more intense than the principal spot in the chromatogram obtained with reference solution (b) (0.4 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Test solution (b). Dissolve 90.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 10.0 ml to 100.0 ml with the mobile phase.

Reference solution (a). Dilute 2.0 ml of test solution (a) to 100.0 ml with the mobile phase. Dilute 10.0 ml to 100.0 ml with the mobile phase.

Reference solution (b). Dissolve 10.0 mg of *imidazole R* and 10.0 mg of *2-methylimidazole R* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml to 100.0 ml with the mobile phase.

Reference solution (c). Dissolve 5.0 mg of *ondansetron for LC system suitability CRS* in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (d). Dissolve 5.0 mg of *ondansetron impurity D CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml to 100.0 ml with the mobile phase.

Reference solution (e). Dissolve 90.0 mg of *ondansetron hydrochloride dihydrate CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 10.0 ml to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: spherical *nitrile silica gel for chromatography R* (5 µm) with a specific surface area of 220 m^2/g and a pore size of 8 nm.

Mobile phase: mix 20 volumes of *acetonitrile R* and 80 volumes of a 2.8 g/l solution of *sodium dihydrogen phosphate monohydrate R* previously adjusted to pH 5.4 with a 40 g/l solution of *sodium hydroxide R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 216 nm.

Injection: 20 µl; inject test solution (a) and reference solutions (a), (b), (c) and (d).

Run time: 1.5 times the retention time of ondansetron.

Relative retentions with reference to ondansetron (retention time = about 18 min): impurity E = about 0.1; impurity F = about 0.2; impurity C = about 0.4; impurity D = about 0.5; impurity H = about 0.7; impurity A = about 0.8; impurity G = about 0.9.

System suitability:

– *resolution*: minimum of 1.3 between the peak due to impurity E (first peak) and the peak due to impurity F (second peak) in the chromatogram obtained with reference solution (b) and minimum of 2.5 between the peak due to impurity C (first peak) and the peak due to impurity D (second peak) in the chromatogram obtained with reference solution (c).

Limits:

– *correction factor*: for the calculation of contents, multiply the peak area of impurity C by 0.6,

– *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent),

– *impurity E*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *impurity F*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent),

– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent),

– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.04 per cent).

Water (*2.5.12*): 9.0 per cent to 10.5 per cent, determined on 0.200 g.

Sulphated 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.

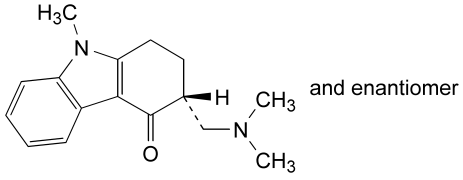
Injection: test solution (b) and reference solution (e).

Calculate the percentage content of $C_{18}H_{20}ClN_3O$.

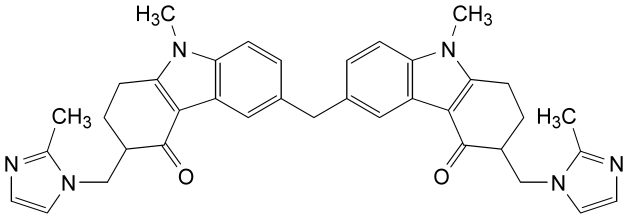
STORAGE

Protected from light.

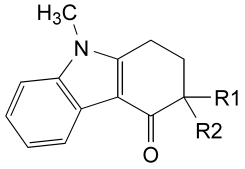
IMPURITIES



A. (3*RS*)-3-[(dimethylamino)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,

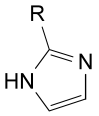


B. 6,6′-methylenebis[(3*RS*)-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one],



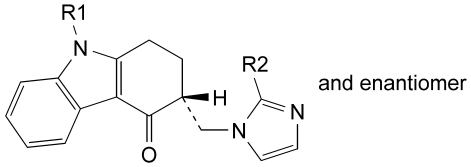
C. R1 = R2 = H: 9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,

D. R1 + R2 = CH_2: 9-methyl-3-methylene-1,2,3,9-tetrahydro-4*H*-carbazol-4-one,



E. R = H: 1*H*-imidazole,

F. R = CH_3: 2-methyl-1*H*-imidazole,



G. R1 = CH_3, R2 = H: (3*RS*)-3-[(1*H*-imidazol-1-yl)methyl]-9-methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*C*-demethylondansetron),

H. R1 = H, R2 = CH_3: (3*RS*)-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (*N*-demethylondansetron).