B. Dissolve 10 mg in *water R* and dilute to 1 ml with the same solvent. The solution gives reaction (b) of phosphates (*2.3.1*).

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 60.0 mg of the substance to be examined in *water R* and dilute to 20.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *water R* and dilute 10.0 ml of this solution to 50.0 ml with the same solvent.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 20.0 ml with *water R*.

Reference solution (c). Dissolve 15.0 mg of *rilmenidine for system suitability CRS* in *water R* and dilute to 5.0 ml with the same solvent.

Column:

– *size*: *l* = 0.15 m, Ø = 3 mm,
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 10 nm and a carbon loading of 25 per cent,
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: dissolve 3 g of *sodium heptanesulphonate R* in *water R* and dilute to 860 ml with the same solvent; add 130 ml of *methanol R2*, 10 ml of *tetrahydrofuran for chromatography R* and 1.0 ml of *phosphoric acid R*,
– *mobile phase B*: dissolve 3 g of *sodium heptanesulphonate R* in *water R* and dilute to 600 ml with the same solvent; add 350 ml of *acetonitrile for chromatography R*, 50 ml of *tetrahydrofuran for chromatography R* and 1.0 ml of *phosphoric acid R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 14	100 → 0	0 → 100
14 - 15	0 → 100	100 → 0
15 - 30	100	0

Flow rate: 1 ml/min.

Detection: spectrophotometer at 205 nm.

Injection: 20 µl.

Relative retention with reference to rilmenidine (retention time = about 13 min): impurity A = about 0.6; impurity B = about 0.9; impurity C = about 1.4.

With these conditions the inflexion of the baseline, corresponding to the beginning of the gradient, appears on the recorder after a minimum time *t* of 5 min. If this is not the case (*t* < 5 min) modify the chromatographic sequence by adding an isocratic elution with 100 per cent of mobile phase A for a time corresponding to (5-*t*) min before the linear gradient.

System suitability: reference solution (c):

– *peak-to-valley ratio*: minimum 3, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to rilmenidine.

Limits:

– *any impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),
– *disregard limit*: area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 50 °C over *diphosphorus pentoxide R* for 2 h.

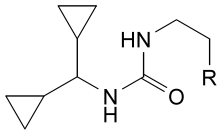
ASSAY

Dissolve 0.200 g in 50 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 27.82 mg of $C_{10}H_{19}N_2O_5P$.

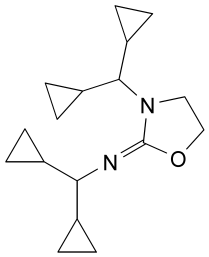
IMPURITIES

Specified impurities: A, B, C.



A. R = OH: 1-(dicyclopropylmethyl)-3-(2-hydroxyethyl)urea,

B. R = Cl: 1-(2-chloroethyl)-3-(dicyclopropylmethyl)urea,



C. *N*,3-bis(dicyclopropylmethyl)oxazolidin-2-imine.

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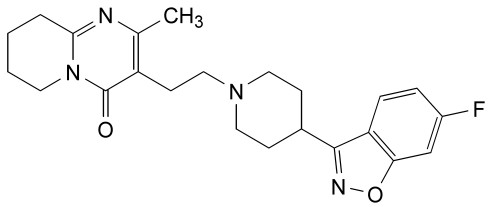
RISPERIDONE

Risperidonum



$C_{23}H_{27}FN_4O_2$ M_r 410.5

DEFINITION

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-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, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent). It dissolves in dilute acid solutions.

It shows polymorphism.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *risperidone CRS*.

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

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.1 g in a 7.5 g/l solution of *tartaric acid R* and dilute to 100 ml with the same acid solution.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 10 mg of *risperidone for system suitability CRS* (containing impurities A, B, C, D and E) in *methanol R* and dilute to 1.0 ml with the same solvent.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with *methanol R*. Dilute 5.0 ml of this solution to 25.0 ml with *methanol R*.

Column:

- *size*: *l* = 0.10 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 - 2	70	30
2 - 17	70 → 30	30 → 70
17 - 22	30	70
22 - 23	30 → 70	70 → 30
23 - 27	70	30

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 260 nm.

Injection: 10 µl.

Relative retention with reference to risperidone (retention time = about 12 min): impurity A = about 0.69; impurity B = about 0.75; impurity C = about 0.81; impurity D = about 0.94; impurity H = about 0.96; impurity G = about 1.04; impurity E = about 1.12; impurity F = about 1.32; impurity I = about 1.60.

System suitability: reference solution (a):

- *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to risperidone,
- the chromatogram obtained is similar to the chromatogram supplied with *risperidone for system suitability CRS*.

Limits:

- *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),
- *any other impurity*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 100-105 °C for 4 h.

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

ASSAY

Dissolve 0.160 g in 70 ml of a mixture of 1 volume of *anhydrous acetic acid R* and 7 volumes of *methyl ethyl ketone R* and titrate with *0.1 M perchloric acid*. Determine the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 20.53 mg of $C_{23}H_{27}FN_4O_2$.

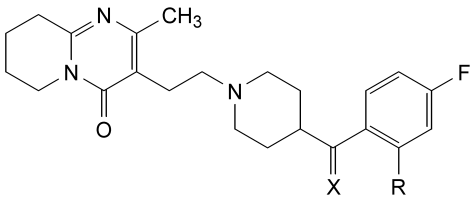
STORAGE

Protected from light.

IMPURITIES

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

Other detectable impurities: F, G, H, I.

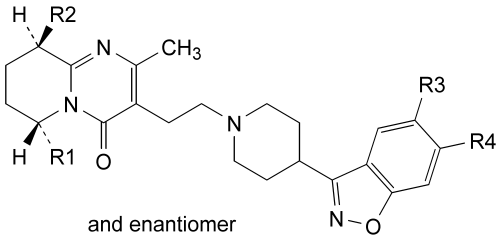


A. R = F, X = N-OH: 3-[2-[4-[(*E*)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

B. R = F, X = N-OH: 3-[2-[4-[(*Z*)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

G. R = OH, X = O: 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

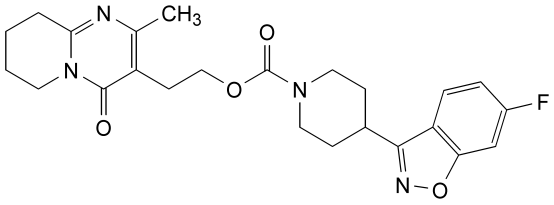
H. R = F, X = O: 3-[2-[4-(2,4-difluorobenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



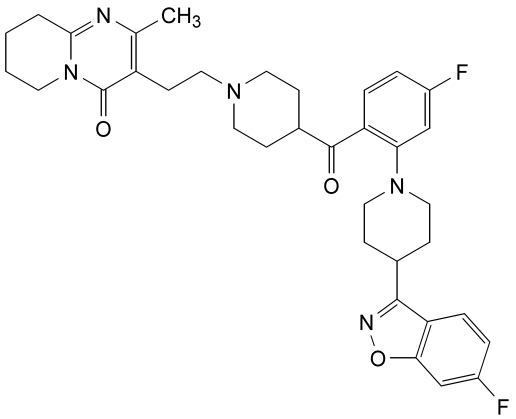
C. R1 = R3 = H, R2 = OH, R4 = F: (9*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

D. R1 = R2 = R4 = H, R3 = F: 3-[2-[4-(5-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,

E. R1 = CH_3, R2 = R3 = H, R4 = F: (6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one,



F. 2-[2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]ethyl 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-carboxylate,



I. 3-[2-[4-[4-fluoro-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]benzoyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.

01/2005:1623

ROSELLE

Hibisci sabdariffae flos

DEFINITION

Whole or cut dried calyces and epicalyces of *Hibiscus sabdariffa* L. collected during fruiting.

Content: minimum 13.5 per cent of acids, expressed as citric acid ($C_6H_8O_7$; M_r 192.1) (dried drug).

CHARACTERS

Acidic taste.

Macroscopic and microscopic characters described under identification tests A and B.

IDENTIFICATION

A. The calyx is joined in the lower half to form an urceolate structure, the upper half dividing to form 5 long acuminate recurved tips. The tips have a prominent, slightly protruding midrib and a large, thick nectary gland about 1 mm in diameter. The epicalyx consist of 8 to 12 small, obovate leaflets which are adnate to the base of the calyx. The calyx and epicalyx are fleshy, dry, easily fragmented and coloured bright-red to deep-purple, somewhat lighter at the base of the inner side.

B. Reduce to a powder (355). The powder is red to purplish-red. Examine under a microscope using *chloral hydrate solution R*. The powder shows predominantly red coloured fragments of the parenchyme containing numerous crystal clusters of calcium oxalate and, sporadically, mucilage filled cavities, sometimes associated with polygonal epidermal cells and anisocytic stomata (*2.8.3*); numerous fragments of vascular bundles with spiral and reticulate vessels; sclerenchymatous fibres with a wide lumen; rarely, rectangular, pitted parenchymatous cells; fragments of unicellular, smooth, bent covering trichomes and occasional glandular trichomes; rounded pollen grains with spiny exine.

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

Test solution. To 1.0 g of the powdered drug (355) add 10 ml of *alcohol (60 per cent) V/V R*. Shake for 15 min and filter.

Reference solution. Dissolve 2.5 mg of *quinaldine red R* in 10 ml of *alcohol R*.

Plate: *TLC silica gel plate R*.

Mobile phase: *acetic acid R, water R, butanol R* (15:30:60 *V/V/V*).

Application: 20 µl, as bands.

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in daylight.

Results: see below the sequence of the zones present in the chromatograms obtained with the reference and test solutions.

Top of the plate	
Quinaldine red: an orange red zone	
	A pale violet zone
	A violet-blue zone
	A violet-blue zone
	A violet-blue zone
Reference solution	**Test solution**

TESTS

Foreign matter (*2.8.2*): maximum 2 per cent of fragments of fruits: red funicles and parts of the 5 caverned capsule with yellowish-grey pericarp, whose thin walls consist of several layers of differently directed fibres; flattened, reniform seeds with a dotted surface.

Loss on drying (*2.2.32*): maximum 11.0 per cent, determined on 1.000 g of the powdered drug (355) by drying in an oven at 100-105 °C for 2 h.

Total ash (*2.4.16*): maximum 10.0 per cent.

Colouring power: reduce the drug to a coarse powder (1400) and mix 100 g of drug. Reduce about 10 g of this mixture to a powder (355). To 1.0 g of the powdered drug (355) add 25 ml of boiling *water R* in a 100 ml flask and heat for 15 min on a water-bath with frequent shaking. Filter the