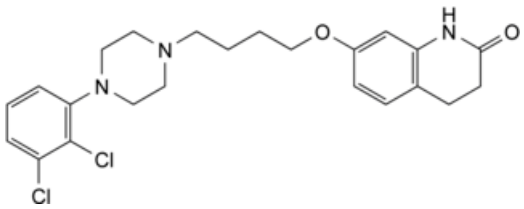
Edition: BP 2025 (Ph. Eur. 11.6 update)

Aripiprazole

General Notices

(Ph. Eur. monograph 2617)



$C_{23}H_{27}Cl_2N_3O_2$ 448.4 *129722-12-9*

Action and use

Dopamine D_2 receptor antagonist; neuroleptic.

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DEFINITION

7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one.

Content

98.0 per cent to 102.0 per cent (dried substance).

PRODUCTION

It is considered that impurities 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1*H*)-one, 7-(4-chlorobutoxy)-3,4-dihydroquinolin-2(1*H*)-one and 7-(4-iodobutoxy)-3,4-dihydroquinolin-2(1*H*)-one are genotoxic and are potential impurities in aripiprazole. These impurities are controlled by a suitable validated method.

CHARACTERS

Appearance

White or almost white crystals or crystalline powder.

Solubility

Practically insoluble in water, soluble in methylene chloride, very slightly soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison aripiprazole CRS.

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

TESTS

Appearance of solution

If intended for use in the manufacture of parenteral preparations, the solution is clear (2.2.1) and not more intensely coloured than reference solution GY_5 (2.2.2, Method II).

Dissolve 0.5 g in a mixture of 10 volumes of acetic acid R and 90 volumes of anhydrous ethanol R and dilute to 20 mL with the same mixture of solvents. Sonicate for about 15 min, shaking occasionally, until dissolution is complete.

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light.*

Solvent mixture acetic acid R, methanol R, acetonitrile R, water R (1:10:30:60 *V/V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of the substance to be examined and 5 mg of aripiprazole impurity F CRS in the solvent mixture and dilute to 100 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of aripiprazole CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

— *mobile phase A*: acetonitrile R, 0.05 per cent *V/V* solution of trifluoroacetic acid R (10:90 *V/V*);

— *mobile phase B*: 0.05 per cent *V/V* solution of trifluoroacetic acid R, acetonitrile R (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 10	80 → 65	20 → 35
10 - 20	65 → 10	35 → 90
20 - 25	10	90

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Relative retention With reference to aripiprazole (retention time = about 11 min): impurity F = about 1.1.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to aripiprazole and impurity F.

Calculation of percentage contents:

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

Limits:

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

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 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 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Dissolve 1.0 mg of the substance to be examined in 20 mL of a 5.17 g/L solution of *hydrochloric acid R*.

ASSAY

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

Injection Test solution and reference solution (c).

System suitability Reference solution (c):

— *symmetry factor*: maximum 2.0.

Calculate the percentage content of $C_{23}H_{27}Cl_2N_3O_2$ taking into account the assigned content of *aripiprazole CRS*.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

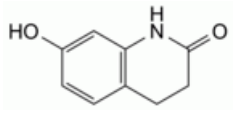
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

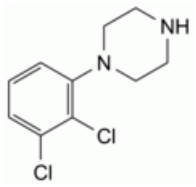
IMPURITIES

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

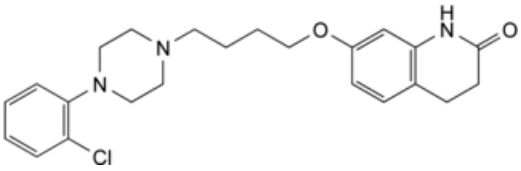
for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, D, E, F, G.



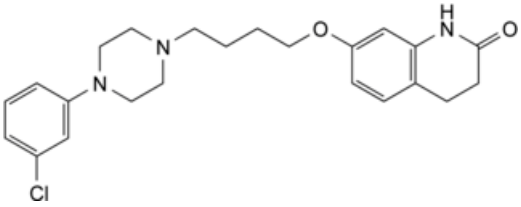
A. 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one,



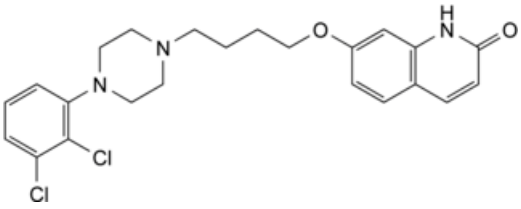
B. 1-(2,3-dichlorophenyl)piperazine,



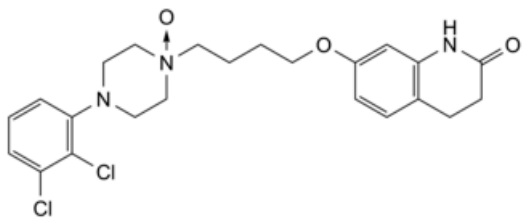
C. 7-[4-[4-(2-chlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one,



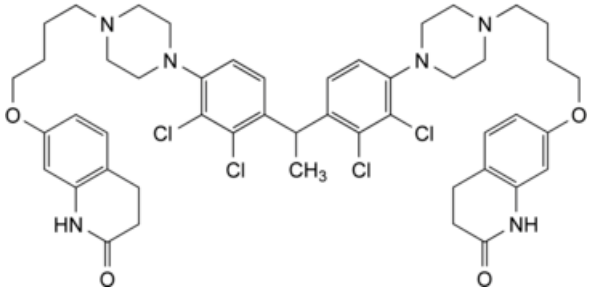
D. 7-[4-[4-(3-chlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one,



E. 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]quinolin-2(1*H*)-one,



F. 4-(2,3-dichlorophenyl)-1-[4-[(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy]butyl]piperazine 1-oxide,



G. 7,7′-[ethane-1,1-diylbis[(2,3-dichloro-4,1-phenylene)piperazine-4,1-diylbutane-4,1-diyloxy]]di(3,4-dihydroquinolin-2(1*H*)-one).

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