World Health Organization

DARUNAVIR

(DARUNAVIRUM)

Draft proposal for inclusion for *The International Pharmacopoeia*

(13 August 2024)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Bezawit Kibret (kibretb@who.int)
Comments should be submitted through the online platform by **20 October 2024**. Please note that only comments received by this deadline will be considered for the preparation of this document.
Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under "Working documents in public consultation".
If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/affiliation and email address to jonessi@who.int, nsp@who.int and your name will be added to our electronic mailing list and review platform.

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Please send any request for permission to: Ms Sinead Jones, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications, Department of Health Products Policy and Standards, World Health Organization, CH-1211 Geneva 27, Switzerland, email: jonessi@who.int, nsp@who.int.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.829:

DARUNAVIR

(DARUNAVIRUM)

Description	**Date**
Monograph drafted based on information received from manufacturers and on laboratory investigations.	February 2020
Discussion at the consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	May 2020
Discussion at the consultation on Quality Control and Pharmacopoeial Specifications for Medicines.	April 2023
Discussion at the consultation on Quality Control and Pharmacopoeial Specifications for Medicines.	May 2024
Draft monograph sent out for public consultation.	August – October 2024
Presentation at the 58th Meeting of the Expert Committee on Specifications for Pharmaceutical Preparations	October 2024
Further follow-up action as required.	

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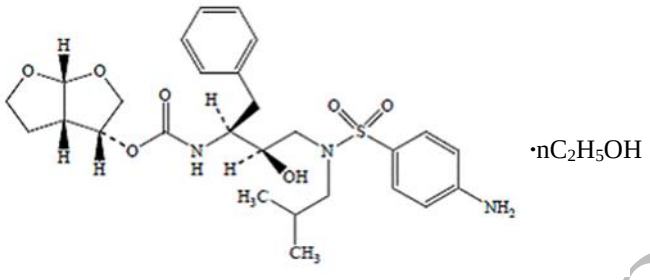
DARUNAVIR (DARUNAVIRUM)

Molecular formula. $C_{27}H_{37}N_3O_7S$ (darunavir); $C_{29}H_{43}N_3O_8S$ (darunavir ethanolate).

Relative molecular mass. 547.66 (darunavir); 593.73 (darunavir ethanolate).

Graphic formula.



·nC_2H_5OH

Darunavir: n = 0

Darunavir ethanolate n = 1

Chemical name. [(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester; Carbamic acid, [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester (darunavir); [(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester, ethanol solvate; Carbamic acid, [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester, ethanol solvate (darunavir ethanolate).

CAS Registry Number. 206361-99-1 (darunavir); 635728-49-3 (darunavir ethanolate).

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Description. A white to off-white powder.

Solubility. Freely soluble in tetrahydrofuran R and acetonitrile R; sparingly soluble in methanol R; slightly soluble in toluene R; very slightly soluble in water R.

Category. Antiretroviral. Protease inhibitor.

Storage. Darunavir should be stored between 2-8 °C under nitrogen, protected from moisture and light.

Additional information. Darunavir may exhibit polymorphism. Where Darunavir is in the ethanol solvate form, the label so indicates.

Requirements

Manufacture. The production method is validated to ensure the enantiomeric and diastereomeric purity of the substance.

Definition. Darunavir contains not less than 97.0% and not more than 102.0% of $C_{27}H_{37}N_3O_7S$, calculated with reference to the anhydrous and ethanol-free substance.

Identity tests

- Either test A or tests B and C or tests C and D may be applied. If the test substance is labelled as darunavir ethanolate, apply also test E.

A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from darunavir RS or with the reference spectrum of darunavir.

If the spectra thus obtained are not concordant, heat the test substance in a preheated oven for 1 hour at about 100 °C and repeat the test. The infrared absorption spectrum is concordant with the reference spectrum of darunavir.

[Note from the Secretariat. The reference spectrum will be recorded using

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anhydrous darunavir.]

B. Carry out the test as described under *1.14.1 Chromatography,* High-performance liquid chromatography, using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to darunavir in the chromatogram obtained with solution (2).

C. The absorption spectrum (*1.6 Spectrophotometry in the visible and ultraviolet regions*) of a 10 µg/mL solution of the test substance in equal volumes of acetonitrile R and water R, when observed between 200 nm and 400 nm, exhibits a maximum at about 266 nm.

Alternatively, in combination with identity test B, where a diode array detector is available, record the UV spectra of the principal peaks in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time and the UV spectrum of the peak due to darunavir in the chromatogram obtained with solution (2).

D. Carry out the test as described under *1.14.1 Thin-layer chromatography*, using silica gel R2 as the coating substance and a mixture of 48 volumes of dichloromethane R, 25 volumes of methanol R, 22 volumes of ethyl acetate R and 5 volumes of ammonia (~260 g/L) TS as the mobile phase.

Apply separately to the plate 10 µL of each of the following solutions in methanol R. For solution (A), use a solution containing 5 mg of the test substance per mL. For solution (B), use a solution containing 5 mg of darunavir RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to the spot due to darunavir in the chromatogram obtained with solution (B).

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E. The test substance complies with the test for "Ethanol content".

Sulfated ash *(2.3)*. Not more than 1.0 mg/g, determined on 1.0 g.

Water. Determine as described under *2.8 Determination of water by the Karl Fischer method*, Method A. The water content is not more than 20 mg/g.

Ethanol content. Perform the test if the test substance is labelled as darunavir ethanolate. Carry out the test as described under *1.14.1 Chromatography*. Gas chromatography, using a fused-silica capillary column 30 m long and 0.53 mm in internal diameter, coated with 6% cyanopropylphenyl and 94% dimethylpolysiloxane (film thickness: 3.0 µm)[1]. As a detector, use a flame ionization detector.

Use helium for chromatography R as the carrier gas at an appropriate pressure and a split ratio 1:4 with a linear velocity of about 30 cm/s or a flow rate of 4 mL/min. Maintain the temperature of the injection port at 180 °C and that of the flame ionization detector at 250 °C. Raise the temperature of the column as described below.

Time (minutes)	Temperature (°C)
0–5	65
5–6	65 to 100
6–8	100
8–10	100 to 160
10–12.5	160

Prepare the following solutions. For the internal standard solution, dissolve 20 µL 2-butanol R in dimethylformamide R and dilute to 100.0 mL with the same solvent. For solution (1), dissolve 80.0 mg of the test substance in internal standard solution and dilute to 20.0 mL with the same solvent. For solution (2), dilute 40 µL anhydrous ethanol R with internal standard solution and dilute to 100.0 mL with the same solvent.

Inject 1 µL each of solutions (1) and (2).

[1] An Agilent J&W DB-624 column was found suitable.

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The test is not valid unless the relative standard deviation of the peak response ratios of ethanol to the internal standard in the chromatograms obtained with solution (2) is not more than 3.0% after 5 injections.

Measure the peak responses corresponding to ethanol and the internal standard in the chromatograms obtained with solutions (1) and (2). Calculate the content (m/m) of ethanol using the peak response ratios of ethanol to the internal standard and taking the *weight per millilitre (1.3.1)* at 20 °C to be 0.790 g/mL; the ethanol content is not less than 55 mg/g and not more than 85 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3; determine the heavy metals content according to Method A; not more than 20 µg/g.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).[2]

Use the following conditions for gradient elution:

Mobile phase A: a mixture of 90 volumes of 0.01 M potassium dihydrogen phosphate (~1.361 g/L) TS and 10 volumes of acetonitrile R.

Mobile phase B: a mixture of 30 volumes of 0.01 M potassium dihydrogen phosphate (~1.361 g/L) TS and 70 volumes of acetonitrile R.

Time (minutes)	Mobile phase A (% *V*/*V*)	Mobile phase B (% *V*/*V*)	Comments
0-2	100	0	Isocratic
2–55	100 to 0	0 to 100	Linear gradient

[2]A Zorbax-SB-C18 column has been found suitable.

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55–55.1	0 to 100	100 to 0	Return to initial composition
55.1–60	100	0	Re-equilibration

Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 264 nm. Maintain the column at a temperature of 35 °C.

Prepare the following solutions using a mixture of 50 volumes of water R and 50 volumes of acetonitrile R as a diluent.

For solution (1), transfer 50.0 mg of the test substance to a 100 mL volumetric flask, dilute to volume and mix. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL For solution (4), dissolve and dilute darunavir for peak identification RS (containing darunavir and the impurities A, C, E, F and D) as described in the leaflet of the reference substance.

Inject 75 µL each of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (4) and the chromatogram supplied with darunavir for peak identification RS to identify the peaks due to impurities A, C, E, F and D.

The impurities are eluted, if present, at the following relative retention with reference to darunavir (retention time about 36 minutes): impurity M about 0.67; impurity A about 0.84; impurity P about 0.98; impurity O about 1.03; impurity C about 1.11; impurity E about 1.13; impurity D about 1.15; impurity F about 1.16; impurity T about 1.39; impurity G about 1.40; impurity H about 1.43.

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution factor between the peaks due to impurity D and due to impurity F is at least 1.0. Also, the test is not valid unless, in the chromatogram obtained with solution (3),

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the peak due to darunavir is obtained with a signal-to-noise ratio of at least 20.In the chromatogram obtained with solution (1)

- the area of any peak corresponding to impurity E is not greater than 0.4 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.40 %);
- the area of any peak corresponding to impurity C is not greater than 0.3 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.30 %);
- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.27, is not greater than 0.25 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.25 %);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.64, is not greater than 0.25 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.25 %);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.35, is not greater than 0.15 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.15 %);
- the area of any other impurity peak is not greater than 0.1 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.10 %).
- The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to impurities A, F and D, is not greater than 1.2 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (1.2 %). Disregard any peak with an area or, in the case of impurities A, F and D a corrected area, of less than the area of the peak due to darunavir in the chromatogram obtained with solution (3) (0.05%).

Assay. Carry out the test as described under *1.14.4 High-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with particles

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of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).[3]

As the mobile phase use a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B described under "Related substances".

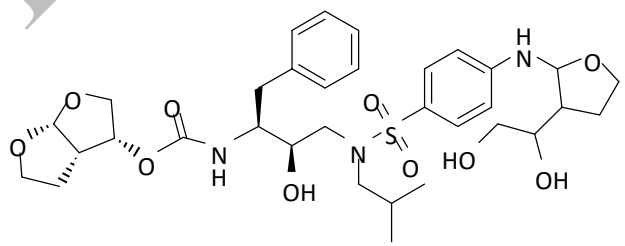
Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 264 nm. Maintain the column at a temperature of 35 °C.

Prepare the following solutions using a mixture of 50 volumes of water R and 50 volumes of acetonitrile R as a diluent. For solution (1), transfer 50.0 mg of the test substance to a 100 mL volumetric flask, dilute to volume and mix. Dilute 10.0 mL of this solution to 100.0 mL. For solution (2), transfer 50.0 mg of darunavir RS to a 100 mL volumetric flask, dilute to volume and mix. Dilute 10.0 mL of this solution to 100.0 mL.

Inject 10 µL each of solution (1) and (2) and record the chromatograms for 22 minutes. The retention time of darunavir is about 6 minutes.

Measure the areas of the peaks corresponding to darunavir obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of darunavir ($C_{27}H_{37}N_3O_7S$), using the declared content of darunavir ($C_{27}H_{37}N_3O_7S$) in darunavir RS.

Impurities



[3]A Zorbax-SB-C18 column has been found suitable.

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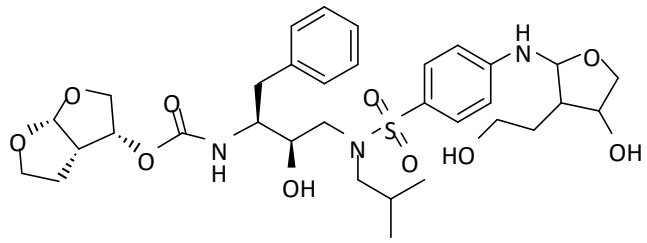
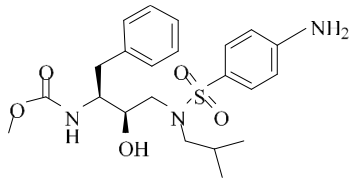
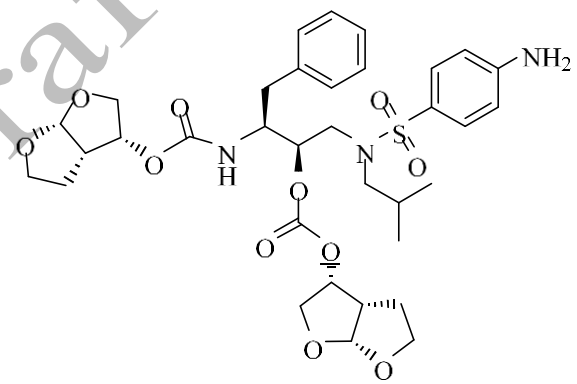
A. (3*R*,3a*S*,6a*R*]-Hexahydrofuro[2,3-b]furan-3-yl *N*-[[(1*S*,2*R*)-3-(4-[3-(1,2-dihydroxyethyl)-furan-2-yl]-aminobenzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl] carbamate (synthesis related impurity),



B. (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl [(1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[(4-{[4-hydroxy-3-(2-hydroxyethyl)tetrahydrofuran-2-yl]amino}phenyl)sulfonyl](isobutyl)amino}propyl]carbamate (synthesis related impurity),



C. *N*-[[(1*S*,2*R*)-3-(4-amino-benzenesulphonyl)-isobutyl-amino]-1-benzyI-2-hydroxypropyl] methylcarbamate (synthesis related impurity, degradation product),



D. [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-[(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl]-oxy-1(phenylmethyl)

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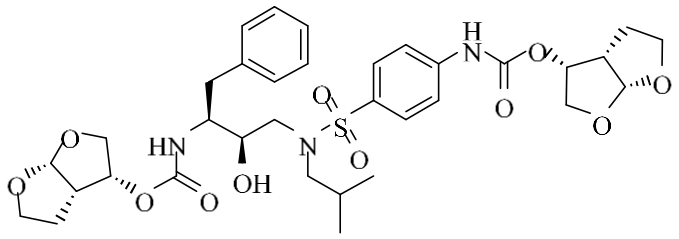
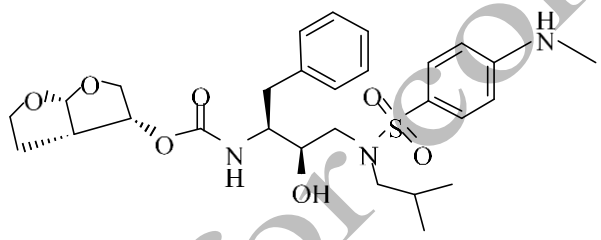
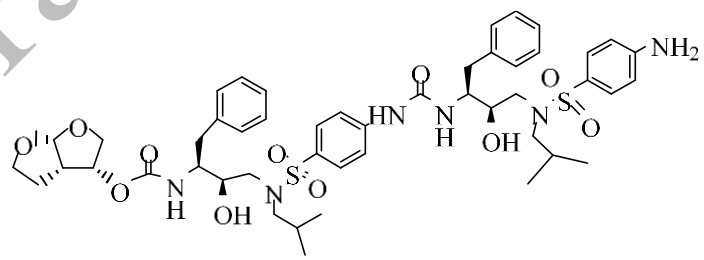
propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b] furan-3-yl ester (bisfuranyl O-protected impurity) (synthesis related impurity),



E. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl *N*-[[(1*S*,2*R*)-3-(4-[(3*R*,3a'*S*,6a'*R*)-Hexahydrofuro[2,3-b]furan-3-oxy]carbonylaminobenzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl]carbamate (bisfuranyl *N*-protected impurity (synthesis related impurity),



F. (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl *N*-[[(1*S*,2*R*)-3-(4-methylamino-benzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl]carbamate (synthesis related impurity),



G. 4-Sulfonamido-[*N*'-[1-(Hexahydrofuro[2,3-b]furan-3-oxycarbonylamino), 1-benzyl, 2-hydroxyprop-2-yl] *N'*-isobutyl)-phenyl *N*-[[3-(4-

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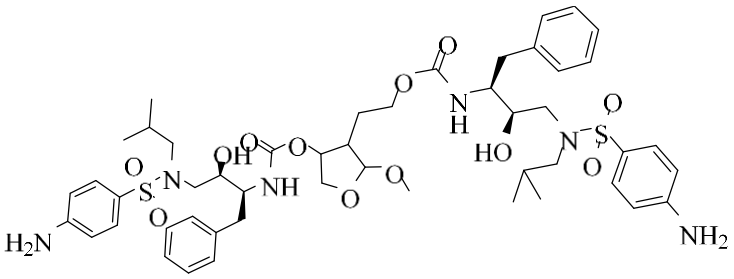
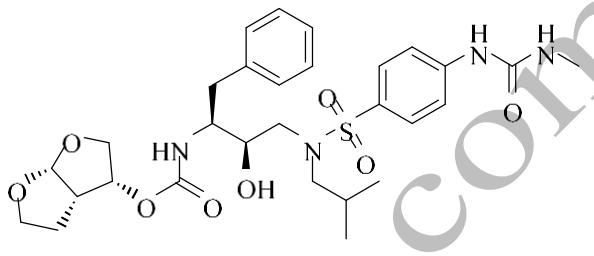
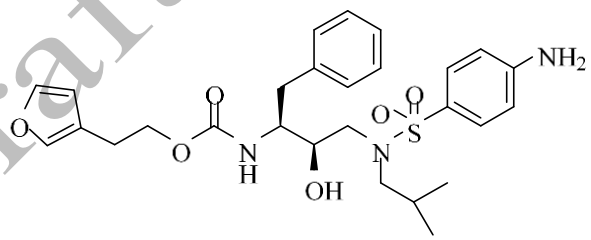
aminobenzenesulphonyI)-isobutyl-amino]-1-benzyl-2-hydroxypropyl] urea (synthesis related impurity),



H. 2-Methoxyfuran-3-(1',2'-Ethyliden)-4-yl Bis *N*-[[(1*S*,2*R*)-3-(4-aminobenzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl]carbamate (synthesis related impurity),



I. [(1*S*[(2*R*)-3-[[(4-methylaminocarbonylaminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b] furan-3- yl ester (synthesis related impurity),



J. [(1*S*,2*R*)-3-[[(4-methylamino carbonylaminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3 -b]furan-3-yl ester (synthesis related impurity),

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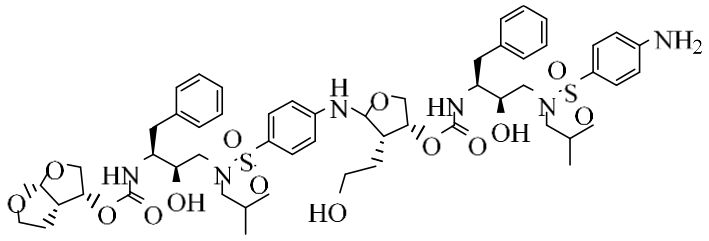
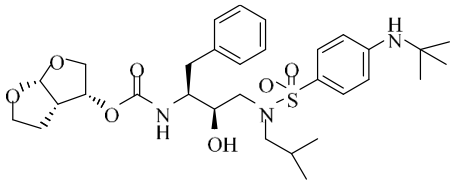
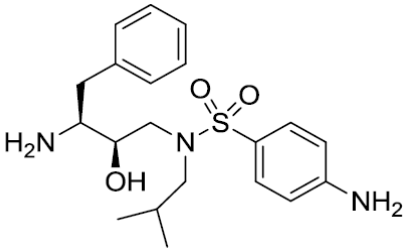


K. (3*R*,4*S*)-5-{[4-({[(2*R*,3*S*)-3-({[(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3yloxy]carbonyl}amino)-2-hydroxy-4-phenylbutyl](isobutyl)amino}sulfonyl)phenyl]amino}-4-(2-hydroxyethyl) tetrahydrofuran-3-yl [(1*S*,2*R*)-3-{[(4-aminophenyl)sulfonyl](isobutyl)amino}-1-benzyl-2-hydroxypropyl]carbamate (synthesis related impurity, degradation product),

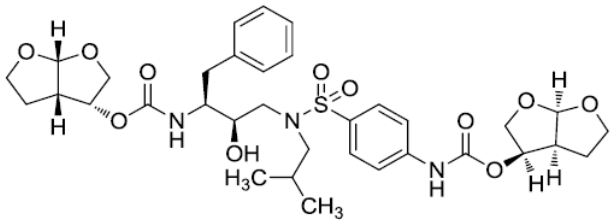


L. [1-Benzyl-3-[(4-tert-butylamino-benzenesulphonyl)-isobutyl-amino]-2-hydroxypropyl]-carbamic acid hexahydrofuro[2,3-b]furan-3-yl ester,

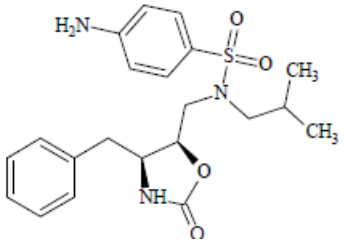


M. 4-Amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutylbenzene sulphonamide or *N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-isobutyl-4-aminobenzenesulfonamide (process related impurity, degradation product) (diamine impurity),

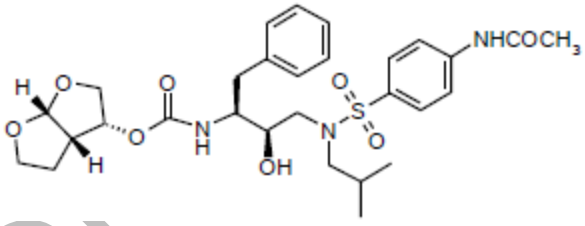
for comments



N. Carbamic acid, *N*-[4-[[[(2*R*,3*S*)-3-[[[[(3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-b]furan-3-yl]oxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](2-methylpropyl)amino]sulfonyl]phenyl]-,(3*R*,3a*S*,6a*S*)-hexahydrofuro[2,3-b]furan-3-yl ester,

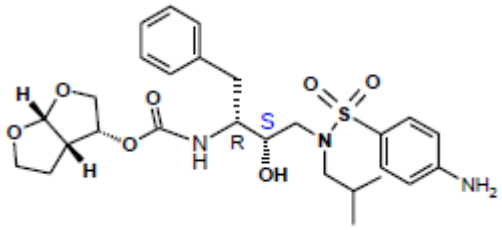


O. 4-Amino-*N*-(((4*S*,5*R*)-4-benzyl-2-oxooxazolidin-5yl)methyl)-*N*-isobutyl benzenesulfonamide (Oxazolidine impurity) (synthesis related impurity, degradation product)

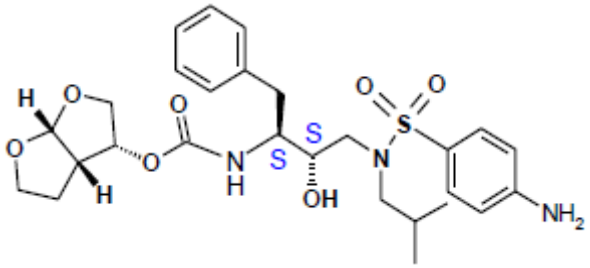


P. (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl(1*S*,2*R*)-3-[[(4-acetylaminophenyl) sulfonyl] (2-methyl propyl)amino]-1-benzyl-2-hydroxypropyl]carbamate (*N*-Acetyl darunavir) (synthesis related impurity)

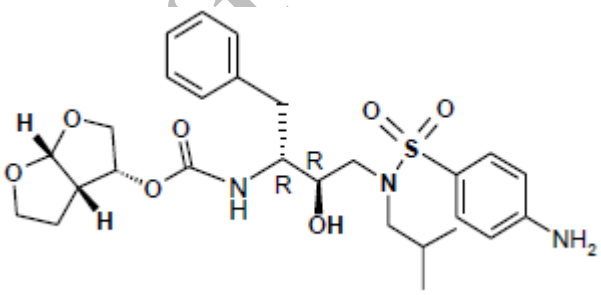
Draft for comments



Q. (3*R*, 3a*S*, 6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl- (1*R*,2*S*)-3-[[(4-aminophenyl)sulfonyl](2-methyl propyl) amino]-1-benzyl-2-hydroxypropyl] carbamate; (1*R*,2*S*) diastereomer (synthesis related impurity)



R. (3*R*, 3a*S*, 6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl- (1*S*,2*S*)-3-[[(4-aminophenyl)sulfonyl](2-methyl propyl) amino]-1-benzyl-2-hydroxypropyl] carbamate; (1*S*,2*S*) diastereomer (synthesis related impurity)



S. (3*R*, 3a*S*, 6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl- (1*R*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methyl propyl) amino]-1-benzyl-2-hydroxypropyl] carbamate; (1*R*,2*R*) diastereomer (synthesis related impurity)

Draft for comments

[The structure of the impurity T will be added at a later stage]

T. [(3a*S*,4*R*,6a*R*)-2,3,3a,4,5,6a-hexahydrofuro[2,3-b]furan-4-yl] *N*-[(1*S*,2*R*)-3-[4-[(5-[[(2*R*,3*S*)-3-[[(3a*S*,4*R*,6a*R*)-2,3,3a,4,5,6a-hexahydrofuro[2,3-b]furan-4-yl]oxycarbonylamino]-2-hydroxy-4-phenyl-butyl]-isobutyl-sulfamoyl]-2-amino-phenyl]methylamino]phenyl]sulfonyl-isobutyl-amino]-1-benzyl-2-hydroxy-propyl]carbamate

Draft for comments

Reference substances to be established

Darunavir for peak identification RS (containing darunavir and the impurities A, C, E, F and D)

- ICRS to be established.

Darunavir RS

- ICRS to be established.

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Draft for comments