BDG SYNTHESIS

Certificate of Analysis

BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

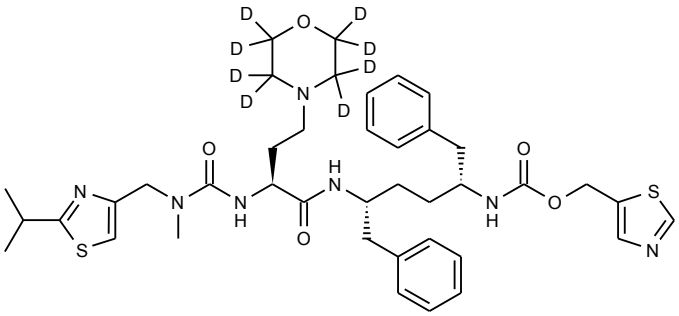
Barry Dent

Barry R. Dent, PhD, Director
15 February 2013

Name: **Cobicistat-d_8**

CAS Number: 1004316-88-4 (unlabeled)

Structure:



Molecular Weight: $C_{40}H_{45}D_8N_7O_5S_2$ = 784.07

Lot Number: BDG 12687.2

Appearance: White, amorphous solid

Corrected Purity: 97.7 % (HPLC) - 3.9 % (chloroform) - 1.0 % (hexanes) = 92.8 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 15 February 2018

Storage and Handling:

Temperature:	refrigerate for prolonged storage; may be handled and shipped at ambient temperature.
Humidity:	not believed to be hygroscopic; may be handled in normal laboratory atmosphere.
Light:	protect from strong sunlight.
Caution:	only experienced laboratory personnel should handle the material.

Mailing:
BDG Synthesis Limited
PO Box 38627, Wellington Mail Centre,
Wellington 5045, New Zealand.

Shipping:
BDG Synthesis Limited
Gracefield Research Centre, Building F,
69 Gracefield Rd, Lower Hutt 5010, New Zealand.

Phone: + 64 4 569 0520
Fax: + 64 4 569 0521

info@bdg.co.nz
www.bdg.co.nz

Identity and Purity

Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration are absent, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: small amounts of hexanes (1 % *w/w*) and chloroform (3.9 % *w/w*) are observed.
Impurities: traces of unidentified impurities are seen in the baseline.

Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration have collapsed to small multiplets compared with the spectrum of unlabelled material, indicating clean deuteration.

High-resolution Mass Spectrum (ESI+)

Found *m/z* 784.4130. $C_{40}H_{46}D_8N_7O_5S_2$ $[M+H]^+$ requires *m/z* 784.4130. The deviation of 0.0 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for d_0 material was seen (detection limit about 0.5 %).

HPLC

A sharp, symmetrical peak is observed (97.7 %). Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

Elemental Analysis

	Found:	C 59.25, H 5.74, D 2.04, N 11.73 %
$C_{40}H_{45}D_8N_7O_5S_2.0.26CHCl_3$	Requires:	C 59.33, H 5.60, D 1.96, N 12.03, $CHCl_3$ 3.9%
$C_{40}H_{45}D_8N_7O_5S_2$	Requires:	C 61.27, H 5.78, D 2.06, N 12.50 %

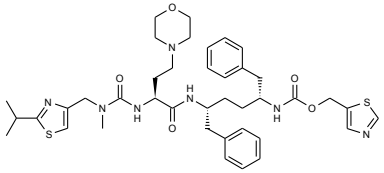
The elemental analyses fall within generally accepted limits for establishing the molecular formula given. The results may also be taken to imply the absence of significant quantities of water or inorganic salts (which have not been elsewhere tested for because of sample size limitations).

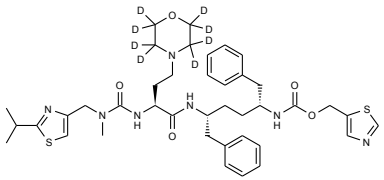
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration. Structures are shown with relative stereochemistry unless otherwise specified.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

BDG SYNTHESIS

Proton NMR Spectrum of Cobicistat (top) and Cobicistat-d_8 (bottom) in DMSO-d_6

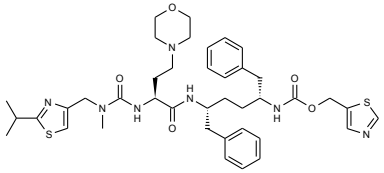


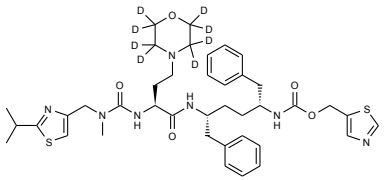


Lot Number: BDG 12687.2

BDG SYNTHESIS

Carbon-13 NMR Spectrum of Cobicistat (top) and Cobicistat-d_8 (bottom) in DMSO-d_6





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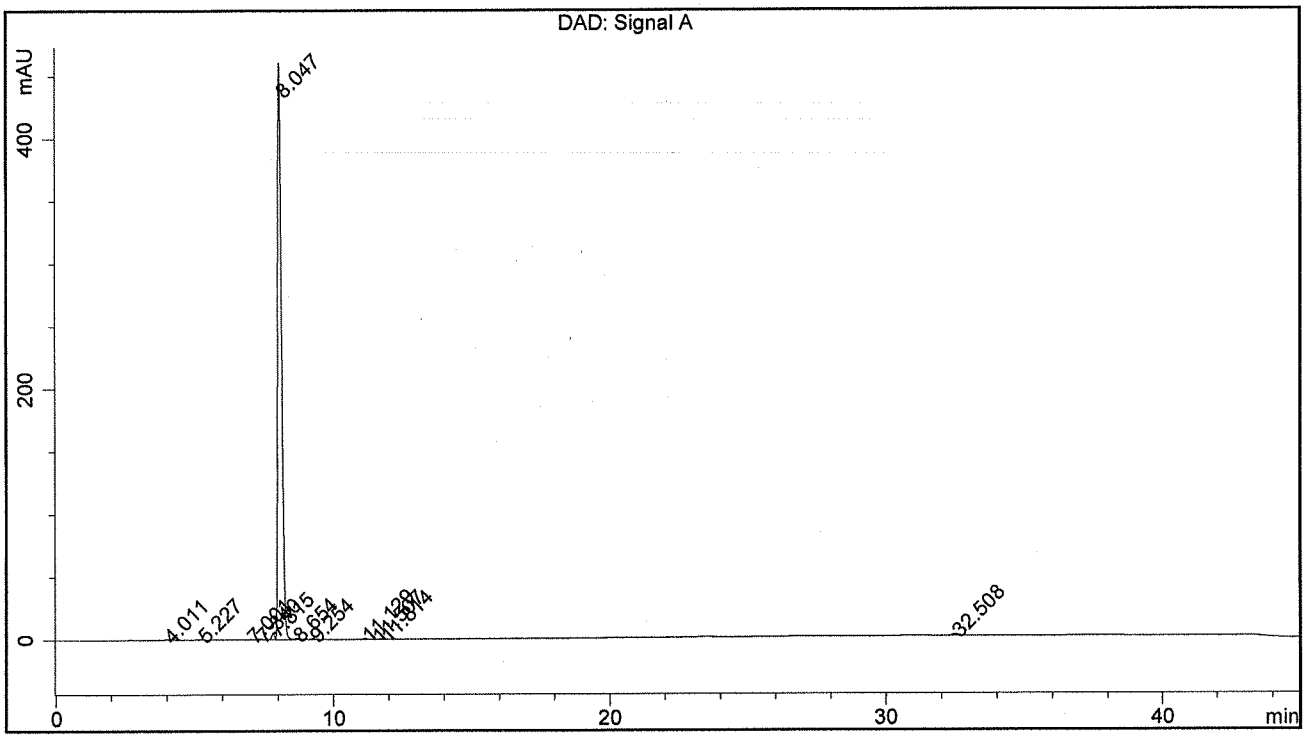
BDG - Analysis of Cobicistat-d8

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase A : 60:40 20mM Potassium DiHydrogen Phosphate pH 3.0 : Acetonitrile
Mobile Phase B : 20:80 20mM Potassium DiHydrogen Phosphate pH 3.0 : Acetonitrile
Gradient (A:B) : T0=100:0, T25=0:100, T40=0:100, T42=100:0, T45=100:0
Flow Rate : 1.0 mL/min . . . . . Column Temperature : 20C . . . . . Detection : UV 240 nm
Sample Solvent : 40:60 Water : Acetonitrile . . . . . Injection Volume : 10 ul

Sample Name	BDG 12687.2	**Instrument**	AnalyticalLC01
Acquisition	15/02/2013, 09:45:13	**Method (rev.)**	LC10558a (8)
Sequence	BDG_15Feb2013a - Reprocessed	**Vial Position**	2
Operator	solvation010\cerityadmin	**Injection**	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	4.01 min	0.3159	11.4021	0.4591 min	0.248 %
2	5.23 min	0.3841	2.6892	0.1077 min	0.059 %
3	7.00 min	0.2062	1.7462	0.1328 min	0.038 %
4	7.34 min	0.7285	5.2976	0.1108 min	0.115 %
5	7.82 min	5.1899	33.7267	0.0998 min	0.734 %
6	8.05 min	460.3725	4491.7097	0.1518 min	97.748 %
7	8.65 min	0.7191	6.7007	0.1347 min	0.146 %
8	9.25 min	0.7735	6.2888	0.1209 min	0.137 %
9	11.13 min	0.9256	7.1157	0.1177 min	0.155 %
10	11.51 min	0.2480	1.7056	0.1022 min	0.037 %
11	11.81 min	0.5139	6.5415	0.1745 min	0.142 %
12	32.51 min	1.3544	20.2710	0.2186 min	0.441 %