

BDG SYNTHESIS

Certificate of Analysis

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

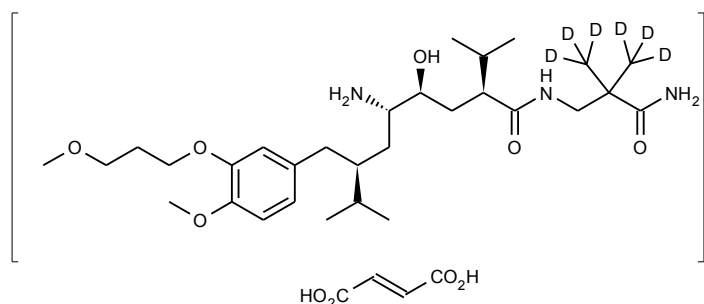
Barry Dent

Barry R. Dent, PhD, Director
2 October 2010

Name: Aliskiren-d₆ Hemifumarate

CAS Number: 173334-58-2 (unlabelled)

Structure:



Molecular Weight: $2C_{30}H_{47}D_6N_3O_6 \cdot C_4H_4O_4 = 1231.66$

Lot Number: BDG 5957.1

Appearance: White, crystalline powder

Corrected Purity: 99.4 % (HPLC) - 0.3 % (diethyl ether) - 3.8 % (water) = 95.3 %

Isotopic Purity: Under 0.5 % d₀

Re-test Date: 2 October 2015

Storage and Handling:

Temperature: refrigerate for prolonged storage; may be handled and shipped at ambient temperature.

Humidity: hygroscopic; open under dry conditions; store desiccated; recommended to flush container with dry nitrogen before re-sealing; determine water content periodically.

Light: protect from strong sunlight.

Caution: only experienced laboratory personnel should handle the material. The material is susceptible to static electricity.

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: a small amount of diethyl ether (0.3 % w/w) is observed.

Impurities: no significant impurities are evident in the spectrum.

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 558.4395. $C_{30}H_{48}D_6N_3O_6$ $[M+H]^+$ (free base) requires m/z 558.4384. The deviation of 2.0 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 (99.4 %). The signal at 2.6 minutes is fumaric acid as confirmed by a cross-reference experiment with an authentic sample. 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 60.03, H 8.23, D 1.98, N 6.52 %
$2C_{30}H_{47}D_6N_3O_6 \cdot C_4H_4O_4 \cdot 2.5H_2O$	Requires:	C 60.21, H 8.13, D 1.89, N 6.58 %
$2C_{30}H_{47}D_6N_3O_6 \cdot C_4H_4O_4$	Requires:	C 62.41, H 8.02, D 1.96, N 6.82 %

The elemental analyses fall somewhat outside those expected for anhydrous material; the presence of water is reasonably expected from the method of purification and/or the type of material, and the "best-fit" hydrated molecular formula is given.

Karl-Fischer Analysis

	Found:	H ₂ O 3.8 %
$2C_{30}H_{47}D_6N_3O_6 \cdot C_4H_4O_4 \cdot 2.5H_2O$	Requires:	H ₂ O 3.5 %

Of necessity, only a small sample could be used and only a single or duplicate analysis performed. We are unable to state what the errors in the reported water content are, but recommend that the result be used, as the best available, when determining corrected purity.

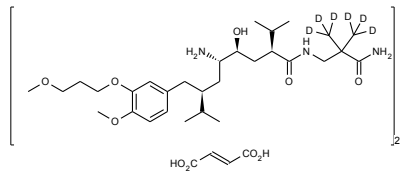
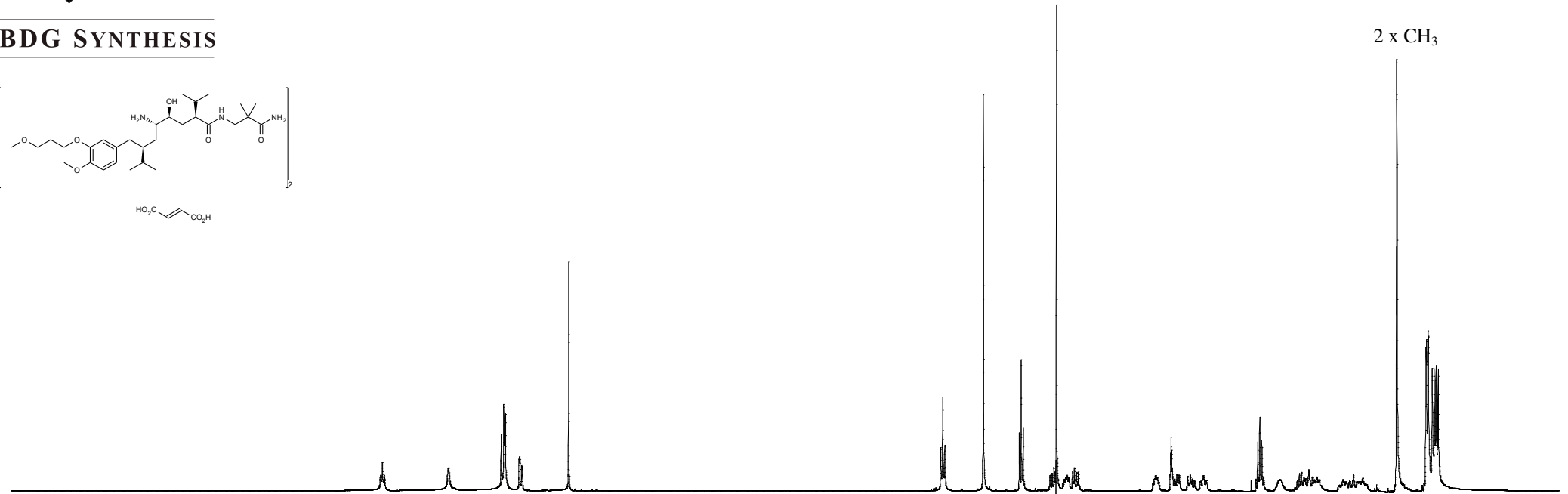
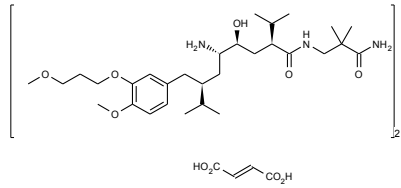
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials 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.

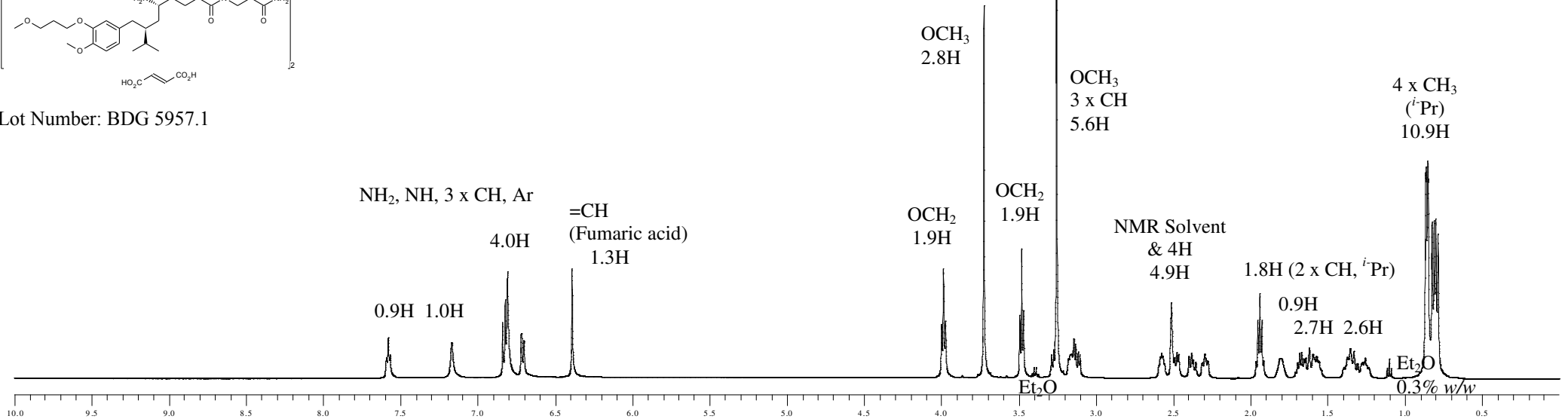


Proton NMR Spectrum of Aliskiren Hemifumarate (top) and Aliskiren-d₆ Hemifumarate (bottom) in DMSO-d₆

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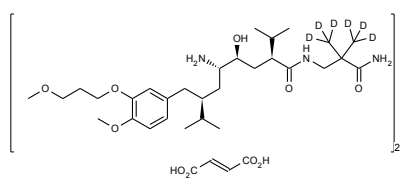
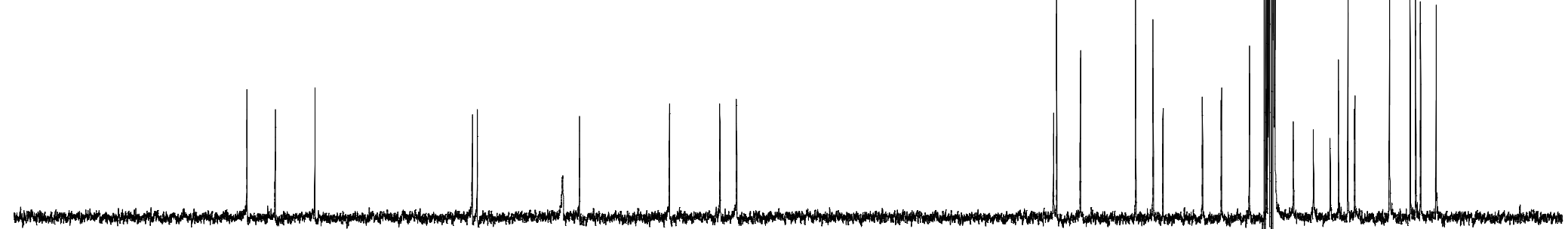
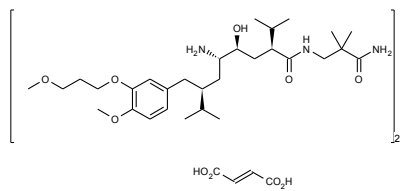
Lot Number: BDG 5957.1



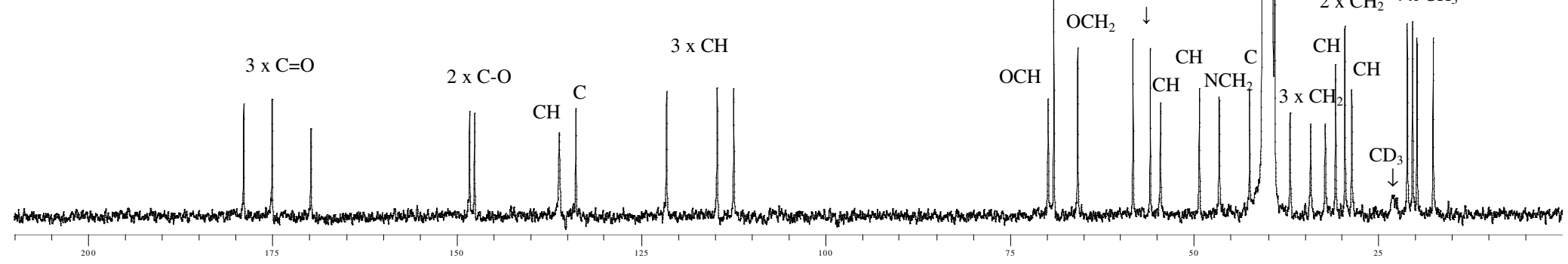


Carbon-13 NMR Spectrum of Aliskiren Hemifumarate (top) and Aliskiren-d₆ Hemifumarate (bottom) in DMSO-d₆

BDG SYNTHESIS



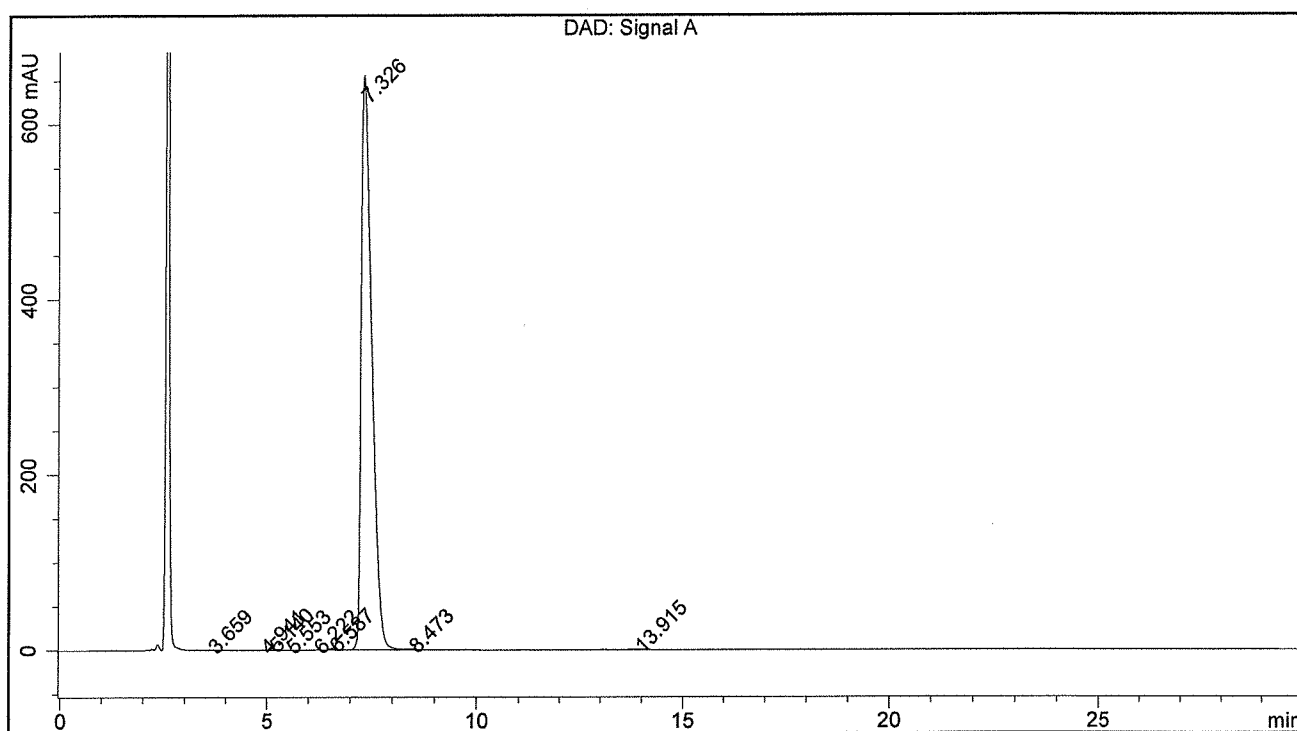
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BDG - Analysis of Aliskiren-d6 Hemifumarate

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
 Guard : Phenomenex Security Guard C18 4 x 3 mm
 Mobile Phase : 60:40 IP : Acetonitrile
 IP = 5 mM Sodium Heptanesulphonate, 20 mM Potassium diHydrogen Phosphate pH=3.0
 Flow Rate : 1.0 mL/min
 Sample Solvent : 70:30 Water : Acetonitrile
 Column Temperature : 20C
 Injection Volume : 10 uL
 Detection : UV at 224 nm

Sample Name	BDG 5957.1	Instrument	AnalyticalLC01
Acquisition	02/10/2010, 14:43:46	Method (rev.)	LC10401c (12)
Sequence	BDG_02Oct2010e	Vial Position	1
Operator	solvation010\cerityadmin	Injection	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	3.66 min	0.6362	5.5481	0.1217 min	0.048 %
2	4.94 min	0.2618	1.6663	0.0903 min	0.014 %
3	5.14 min	1.8878	16.0106	0.1269 min	0.138 %
4	5.55 min	0.1624	1.3043	0.1037 min	0.011 %
5	6.22 min	0.2289	2.3339	0.1310 min	0.020 %
6	6.59 min	1.8989	21.0429	0.1713 min	0.182 %
7	7.33 min	655.1923	11499.1980	0.2628 min	99.371 %
8	8.47 min	0.7759	9.2531	0.1771 min	0.080 %
9	13.91 min	0.8089	15.6714	0.2520 min	0.135 %