BDG SYNTHESIS

Certificate of Analysis

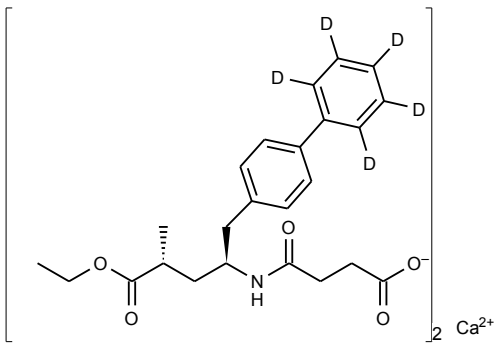
BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

Neil Beare, PhD, Director
5 May 2015

Name: **Sacubitril-d_5 Calcium Salt**

CAS Number: 1369773-39-6 (unlabelled)

Structure:



Molecular Weight: $2C_{24}H_{23}D_5NO_5 \cdot Ca = 871.11$

Lot Number: BDG 15226

Appearance: White, crystalline solid

Corrected Purity: 99.1 % (HPLC) - 4.5 % (water) = 94.6 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 5 May 2020

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.

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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: no residual solvents are 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* 871.4263. $C_{48}H_{47}CaD_{10}N_2O_{10}$ $[M+H]^+$ requires *m/z* 871.4267. The deviation of 0.5 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 somewhat broadened, symmetrical peak is observed (99.1 %). 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 63.16, H 5.56, D 2.20, N 3.15 %
$2C_{24}H_{23}D_5NO_5{\cdot}Ca{\cdot}2.3H_2O$	Requires:	C 63.18, H 5.59, D 2.21, N 3.07 %, H_2O 4.54 %
$2C_{24}H_{23}D_5NO_5{\cdot}Ca$	Requires:	C 66.18, H 5.32, D 2.31, N 3.22 %

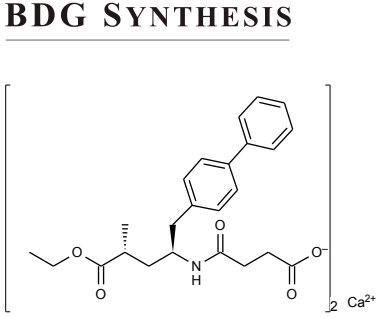
The elemental analyses fall substantially outside those expected for anhydrous material; the presence of water is reasonably expected from the method of purification and/or the type of material, and the “best-fit” hydrated molecular formula is given. In the absence of a Karl-Fischer water analysis, we recommend that the “best-fit” water content be used when determining corrected purity.

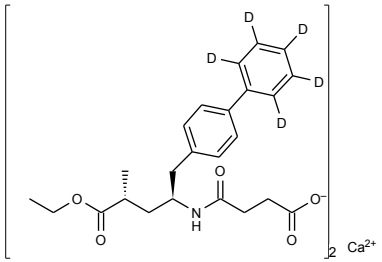
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials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

BDG SYNTHESIS

Proton NMR Spectrum of Sacubitril Calcium Salt (top) and Sacubitril-d_5 Calcium Salt (bottom) in DMSO-d_6

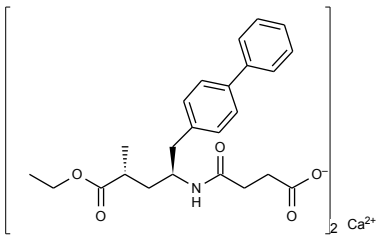


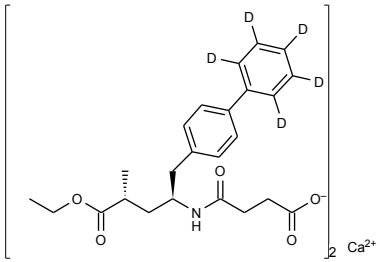


Lot Number: BDG 15226

BDG SYNTHESIS

Carbon-13 NMR Spectrum of Sacubitril Calcium Salt (top) and Sacubitril-d_5 Calcium Salt (bottom) in DMSO-d_6





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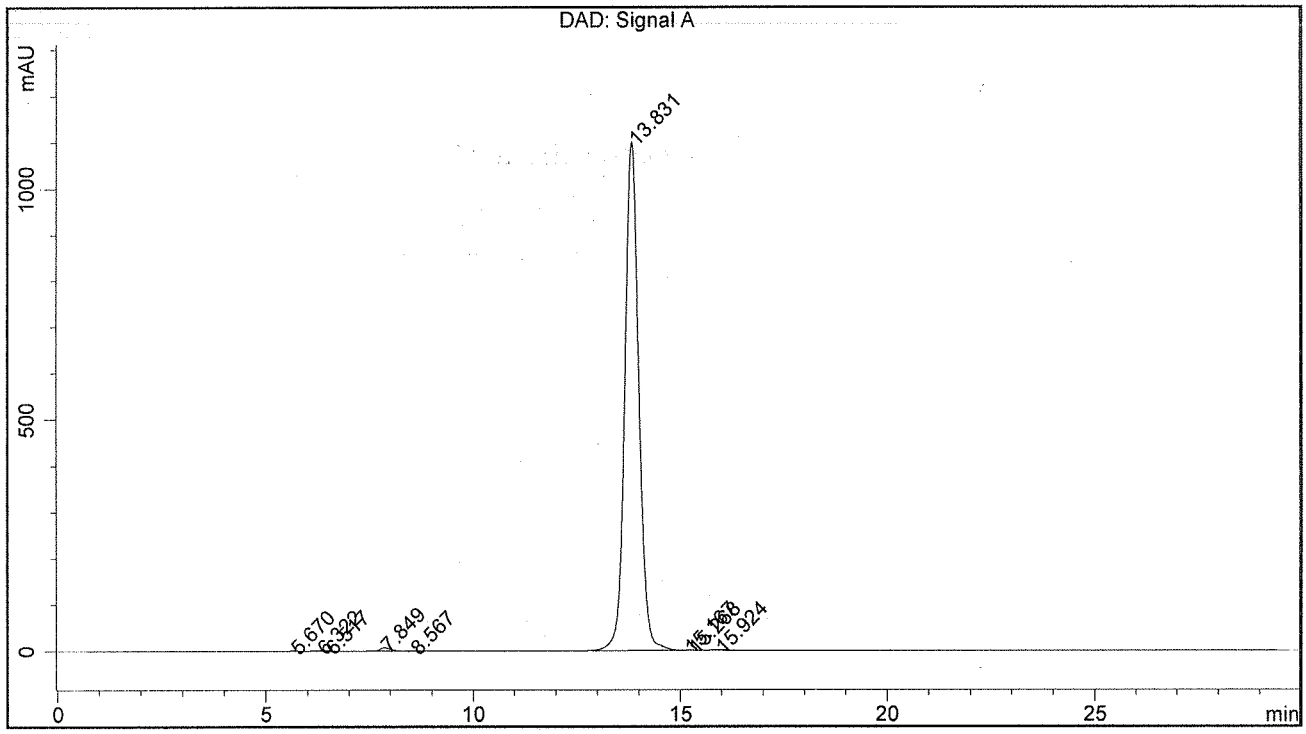
BDG - Analysis of Sacubitril Calcium Salt

Column : Phenomenex Luna C18(2) 5 um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 4 x 3 mm
Mobile Phase : 30:70:0.05 Water : Methanol : Trifluoroacetic Acid
Flow Rate : 1.0 mL/min . . . . . Column Temperature : 20 C
Sample Solvent : 30:70 Water : Methanol . . . . . Injection Volume : 10 uL
Detection : UV 254 nm

Sample Name	BDG 15226	**Instrument**	AnalyticalLC01
Acquisition	05/05/2015, 10:58:56	**Method (rev.)**	LC10649e (9)
Sequence	BDG_05May2015a - Reprocessed	**Vial Position**	51
Operator	solvation010\cerityadmin	**Injection**	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.67 min	1.2397	15.2015	0.1851 min	0.058 %
2	6.32 min	1.7631	28.5459	0.2069 min	0.109 %
3	6.52 min	1.2901	13.4617	0.1537 min	0.051 %
4	7.85 min	7.2243	125.0820	0.2580 min	0.478 %
5	8.57 min	0.6764	8.5393	0.1613 min	0.033 %
6	13.83 min	1100.3591	25910.7984	0.3607 min	99.078 %
7	15.17 min	0.5051	5.3888	0.1365 min	0.021 %
8	15.27 min	0.4979	5.1112	0.1358 min	0.020 %
9	15.92 min	1.6596	39.7755	0.2996 min	0.152 %