BDG SYNTHESIS

Certificate of Analysis

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

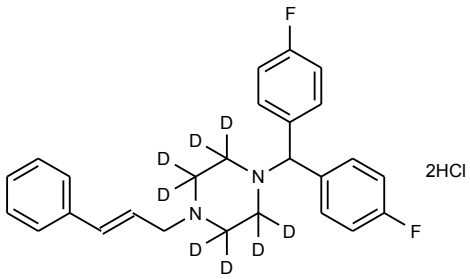
Barry Dent

Barry R. Dent, PhD, Director
13 February 2013

Name: **Flunarizine-d_8 Dihydrochloride**

CAS Number: 30484-77-6 (unlabelled)

Structure:



Molecular Weight: $C_{26}H_{18}D_8F_2N_2 \cdot 2HCl = 485.47$

Lot Number: BDG 6023.2

Appearance: White, crystalline solid

Corrected Purity: 99.3 % (HPLC) - 3.2 % (dioxane) - 3.4 % (water) = 92.7 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 13 February 2018

Storage and Handling:

Temperature:	ambient laboratory temperature; may be refrigerated.
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.

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 greatly diminished, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: a small amount of dioxane (3.2 % *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: both labelled and unlabelled N-alkyl carbons have collapsed into the baseline preventing an estimate of deuterium content.

High-resolution Mass Spectrum (ESI+)

Found *m/z* 413.2628. $C_{26}H_{19}D_8F_2N_2$ $[M+H]^+$ requires *m/z* 413.2636. 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 (99.3 %). 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 61.88, H 4.24, D 3.39, N 5.32 %
$C_{26}H_{18}D_8F_2N_2{\cdot}2HCl{\cdot}1.0H_2O$	Requires:	C 62.02, H 4.40, D 3.20, N 5.56 %
$C_{26}H_{18}D_8F_2N_2{\cdot}2HCl$	Requires:	C 64.33, H 4.15, D 3.32, N 5.77 %

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_2O 3.4 %
$C_{26}H_{18}D_8F_2N_2{\cdot}2HCl{\cdot}1.0H_2O$	Requires:	H_2O 3.6 %

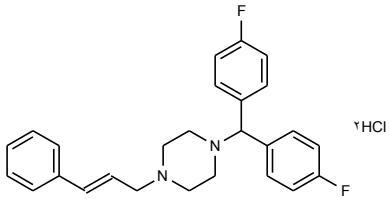
Of necessity, only a small sample could be used and only a single or duplicate analysis performed. We are unable to state what the errors in the reported water content are, but recommend that the result be used, as the best available, when determining corrected purity.

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.

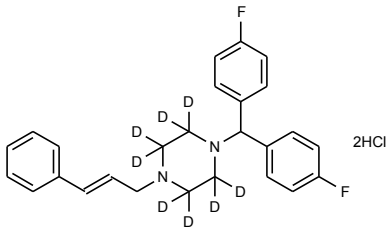
BDG SYNTHESIS

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



NMR
Solvent

2xCH
2.1 H



13xCH
13.4 H

dioxane
3.2 % *w/w*

2xCH
2.0 H

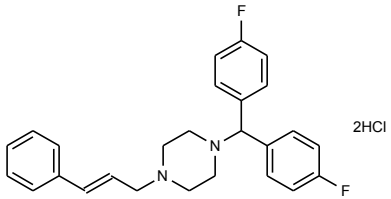
$NCH+NCH_2$
3.3 H

HOD

Lot Number: BDG 6023.2

BDG SYNTHESIS

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

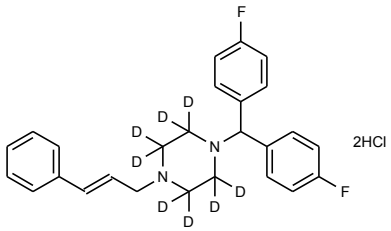


NMR Solvent

$5xNCH_2$

NCH

↑
2xC



Lot Number: BDG 6023.2

5xCH

dioxane

4xCH

4xCH

C

CH

CH

2xC-F

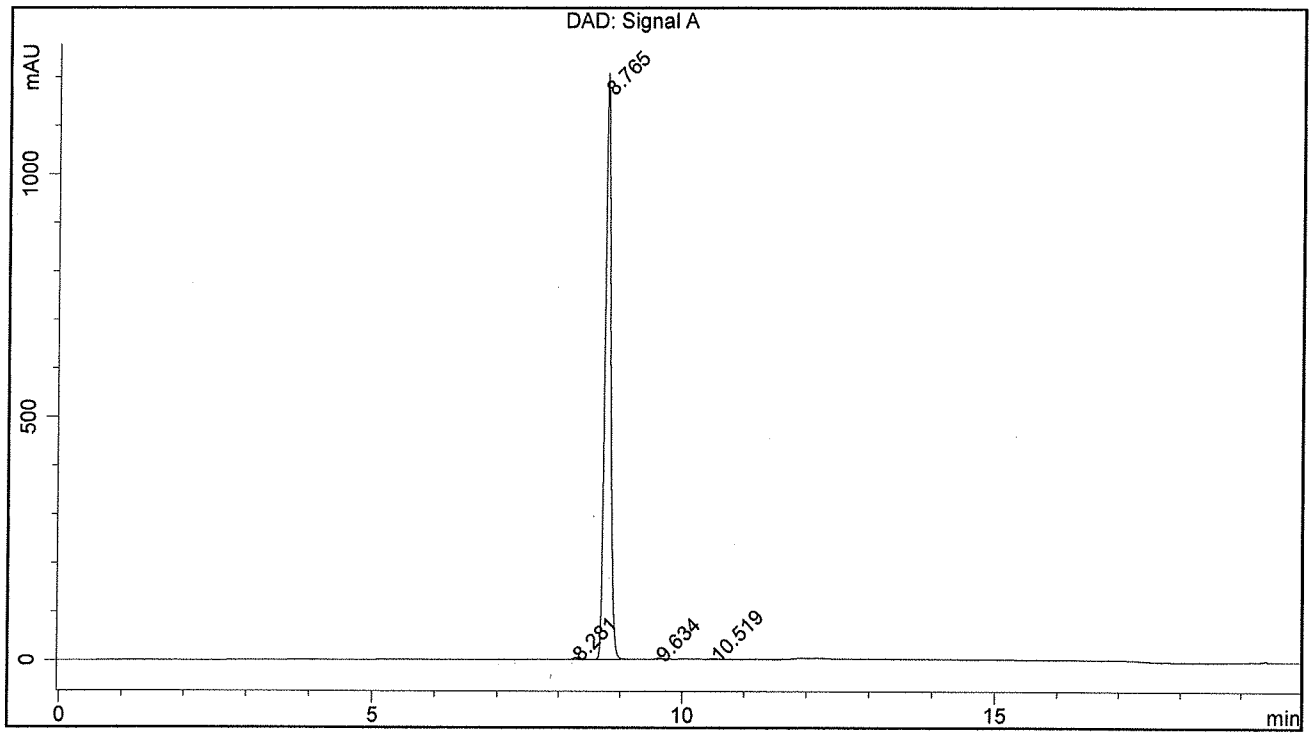
$4xNCD_2$
$+NCH_2$

200 175 150 125 100 75 50 25

BDG - Analysis of Flunarazine-d8 Dihydrochloride

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase A: 70:30 Ion Pair Reagent : Acetonitrile
Mobile Phase B: 30:70 Ion Pair Reagent:: Acetonitrile
Ion Pair Reagent = 23.8 g/L Tetrabutylammonium Hydrogen Sulphate + 7 g/L Ammonium Acetate
Gradient (A:B) : T0=100:0, T12=0:100, T15=0:100, T16=100:0, T20=100:0
Flow Rate : 1.5 mL/min
Sample Solvent : Initial Mobil Phase . . . . . Injection Volume : 10 uL
Column Temperature : 20C . . . . . Detection : UV at 230 nm

Sample Name	BDG 6023.2	**Instrument**	AnalyticalLC01
Acquisition	13/02/2013, 18:01:07	**Method (rev.)**	LC10557a (6)
Sequence	BDG_13Feb2013a - Reprocessed	**Vial Position**	1
Operator	solvation010\cerityadmin	**Injection**	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	8.28 min	3.7325	26.2886	0.1042 min	0.335 %
2	8.76 min	1208.5468	7796.9452	0.0973 min	99.284 %
3	9.63 min	2.3567	19.0960	0.1185 min	0.243 %
4	10.52 min	1.5026	10.8467	0.1122 min	0.138 %