BDG SYNTHESIS

Certificate of Analysis

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

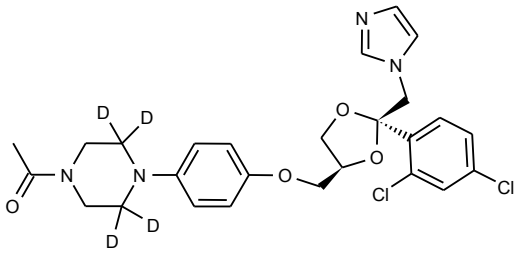
Barry Dent

Barry R. Dent, PhD, Director
18 January 2007

Name: **Ketoconazole-d_4**

CAS Number: 65277-42-1 (unlabelled)

Structure:



Molecular Weight: $C_{26}H_{24}D_4Cl_2N_4O_4$ = 535.46

Lot Number: BDG 6630.1

Appearance: Tan, crystalline solid

Corrected Purity: 98.3 % (HPLC) - 1.0 % (acetone) = 97.3 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 18 January 2012

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 what would be expected for unlabelled material, indicating clean deuteration. The acetyl group integrates for 2.4 H (instead of 3 H) as this moiety was initially trideuterated, but underwent subsequent H/D exchange.
Residual Solvents: a small amount of acetone (1 % *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 what would be expected for unlabelled material, indicating clean deuteration.

High-resolution Mass Spectrum (EI+)

Found *m/z* 535.1793. $C_{26}H_{25}D_4{}^{35}Cl_2N_4O_4$ $[M+H]^+$ requires *m/z* 535.1817. The deviation of 4.4 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, slightly tailing peak is observed (98.3 %). 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 58.48, H 4.73, D 1.58, N 10.23 %
$C_{26}H_{24}D_4Cl_2N_4O_4$	Requires:	C 58.32, H 4.52, D 1.50, N 10.46 %

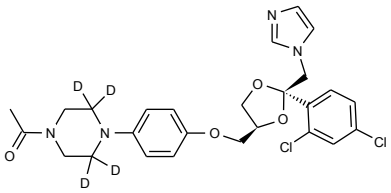
The elemental analyses fall within generally accepted limits for establishing the molecular formula given. The results may also be taken to imply the absence of significant quantities of water or inorganic salts (which have not been elsewhere tested for because of sample size limitations).

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

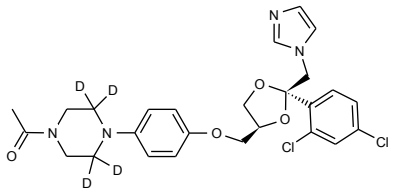
Proton NMR Spectrum of Ketoconazole-d_4 in Methanol-d_4



Lot Number: BDG 6630.1

BDG SYNTHESIS

Carbon-13 NMR Spectrum of Ketoconazole-d_4 in Methanol-d_4



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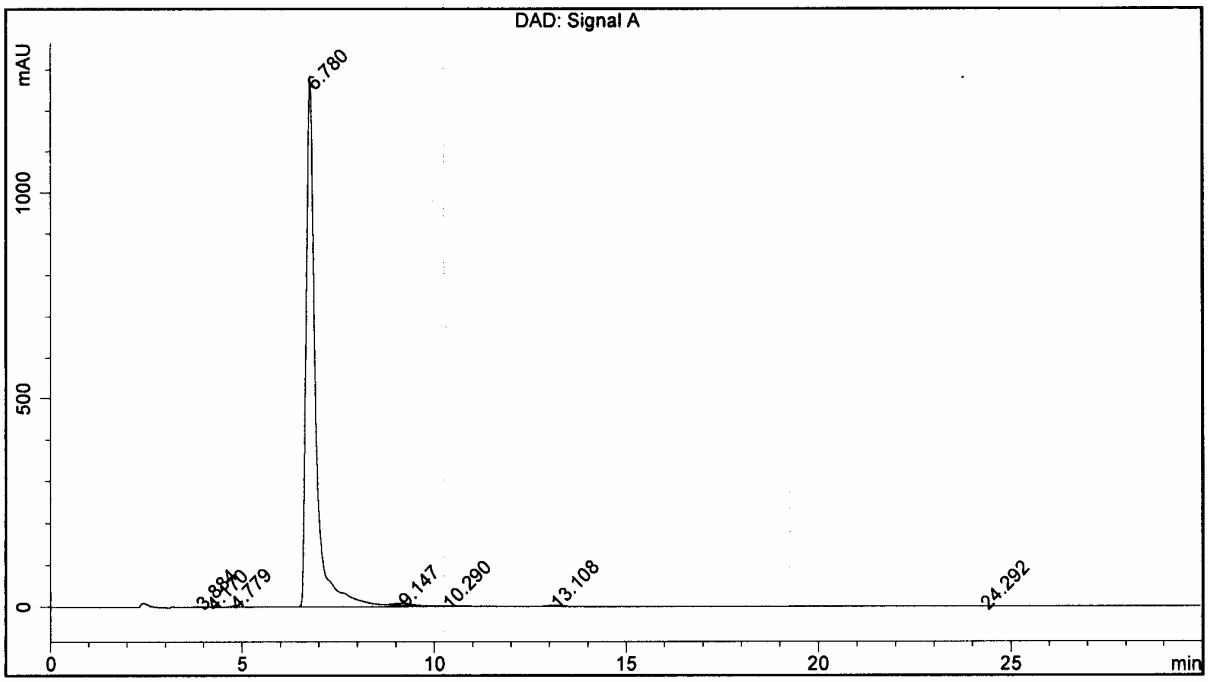
BDG - Analysis of Ketoconazole-(piperazinyl-3,3,5,5-d4)

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase : 75:25 0.01M Tetrabutylammonium hydrogen sulfate : Acetonitrile
Flow Rate : 1.0 mL/min
Sample Solvent : 1:1 Water:Methanol
Column Temperature : 30C
Injection Volume : 10 uL
Detection : UV at 223 nm
Run Time: 30 mins

Sample Name	BDG 6630.1	Instrument	AnalyticalLC01
Acquisition	19/12/2006, 13:19:08	Method (rev.)	LC10126a (8)
Sequence	BDG_19Dec2006a - Reprocessed	Vial Position	1
Operator	solvation010\cerityadmin	Injection	2 of 2



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	3.88 min	1.2403	14.6771	0.1741 min	0.066 %
2	4.17 min	0.8045	11.5657	0.2117 min	0.052 %
3	4.78 min	2.9438	32.5260	0.1689 min	0.146 %
4	6.78 min	1281.0852	21922.7464	0.2436 min	98.311 %
5	9.15 min	4.8736	152.2973	0.4886 min	0.683 %
6	10.29 min	0.6845	53.2638	0.9318 min	0.239 %
7	13.11 min	2.6629	78.8657	0.4495 min	0.354 %
8	24.29 min	0.5624	33.3625	0.7281 min	0.150 %