BDR# 258948
Hansen, K.

70316-001

to

70316 -

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Jan 16, 2002	0104441	70130-313	C-224715	

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD		

COMPLETE STRUCTURE

CHEMICAL NAME: Boc-amino amide MLS

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR	
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR	
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS	

DO NOT WRITE BELOW THIS LINE

RESULTS

RT	RRT	Area %
7.31		11.97%
8.09		0.20
11.51		0.13
11.95		0.77
14.00		0.09
14.87		28.07
16.84		28.68
19.06		7.39
19.45		22.68

PP LAB PROC. #	ANALYST	DATE
	J.GD.	Feb 21, 2002

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
JAN 30, 2002				

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD		

COMPLETE STRUCTURE

CHEMICAL NAME
L-224,715-000T001

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS

DO NOT WRITE BELOW THIS LINE

RESULTS

RRT	Area %
0.83	0.06
0.93	0.11
0.94	0.08
0.96	0.09
1.50	99.65

Total imp = 0.34

PP LAB PROC. #	ANALYST	DATE
	J.G.D.	Feb 21, 2002

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Jan16. 2002	0104440	70130-313	C-224.715	

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD			

COMPLETE STRUCTURE

CHEMICAL NAME: Boc-amino amide

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR	
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR	
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS	

DO NOT WRITE BELOW THIS LINE

RESULTS

Time	RRT	Area %
1.72	0.12	0.05%
3.87	028	1.16%
4.00	0.29	3.06%
8.24	059	0.24%
12.74	091	0.21%
13.18	094	0.08%
13.99	1.00	95.07%
18.63	1.33	0.05%

Total, imp = 4.85%

PP LAB PROC. #	ANALYST	DATE
	J.G.D.	Feb 21.2002

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Jan 16.2002	0104442	70130-347	C-224715	

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD			

COMPLETE STRUCTURE

CHEMICAL NAME: Besylate salt From IPAC

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS

DO NOT WRITE BELOW THIS LINE

RESULTS

Time	RRT	Area%	
2.91	0.24	0.36%	
11.49	0.94	0.25%	(group of peaks)
12.23	1.00	98.72%	
28.73	2.35	0.65%	

PP LAB PROC #	ANALYST	DATE
	J-6D	Feb 21. 2002

MERCK

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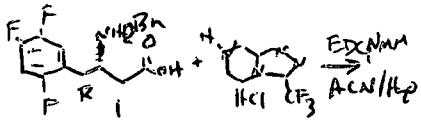
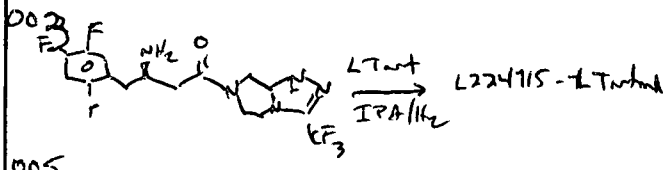
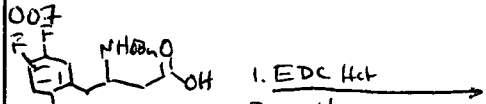
70316 Page 1

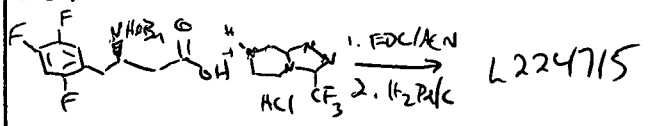
(Please list keywords or subject information for each page or series of pages)

001  L224715-NoBn

002  L224715-L Tartrate

005 L224715 Freebase $\xrightarrow[IPAc]{PhSO_2H}$ L224715 Besylate.

007  1. EDC HCl 2. Pd/C 3. → L224715 +/-

009  1. EDC/ACN 2. H_2 Pd/C → L224715

011 L224715 $\xrightarrow[THF/H_2O]{H_3PO_4}$ L224715 Phosphate

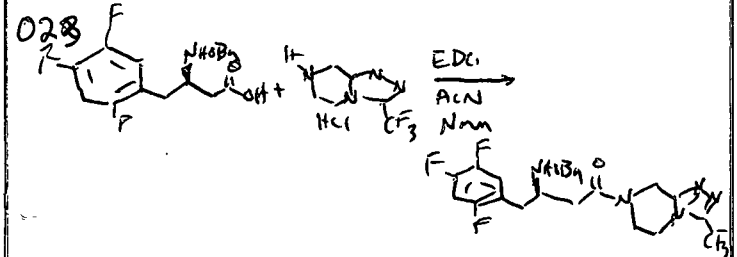
013 L224715 $\xrightarrow[ACN/H_2O]{H_3PO_4}$ L224715 Phosphate

015 L224715 $\xrightarrow[IPA/H_2O]{H_3PO_4}$ L224715 Phosphate

017 L224715 $\xrightarrow[EtOH/H_2O]{H_3PO_4}$ L224715 Phosphate

019 L224715 $\xrightarrow[EtOH/H_2O \text{ slow cooldown}]{H_3PO_4}$ L224715 Phosphate

021 L224715 $\xrightarrow[MeOH]{H_3PO_4}$ L224715 Phosphate salt.

023 

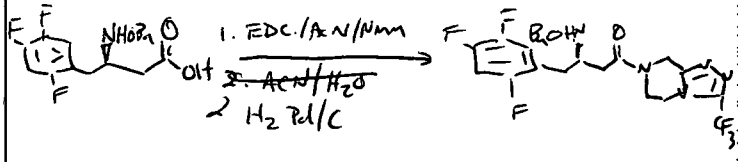
025 L224715 Freebase $\xrightarrow[EtOH/H_2O]{H_3PO_4}$ L224715 H_3PO_4

027 L224715-$PhSO_3H$ $\xrightarrow[2. \text{ Tartaric acid}]{1. \text{ EtOAc/NaOH}}$ L224715-Tartrate

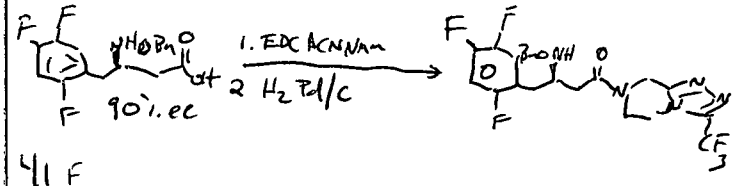
029 L224715-$PhSO_3H$ $\xrightarrow{wet\ N_2}$ L224715 Besylate hydrate

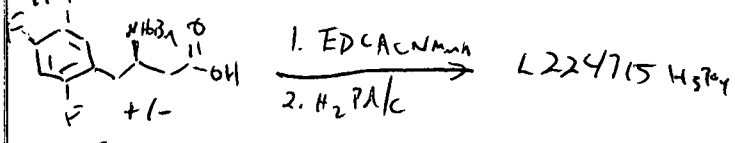
031 L224715 $PhSO_3H$ $\xrightarrow[2. H_3PO_4]{1. \text{ EtOAc/NaOH}}$ L224715 Phosphate

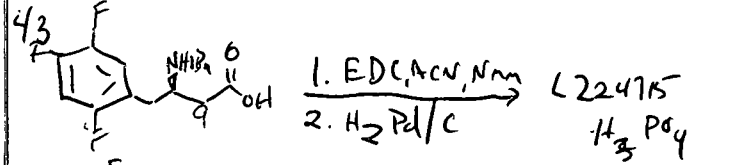
033 L224715 $PhSO_3H$ $\xrightarrow[2 \text{ IPAc}, \Delta]{1 \text{ ACN}}$ L2

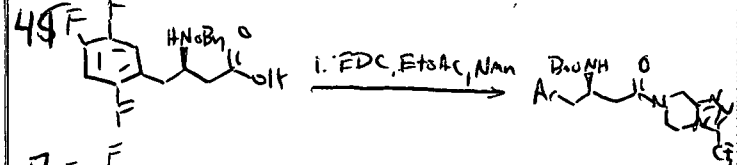
035  1. EDC/ACN/NMM 2. H_2 Pd/C

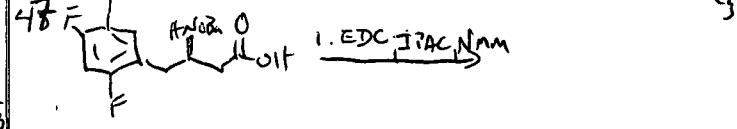
037 L224715-Tartrate $\xrightarrow[2\ H_3PO_4]{1 \text{ EtOAc/NaOH}}$ L224715-Phosphate

039  1. EDC ACN NMM 2 H_2 Pd/C

041  1. EDC ACN NMM 2. H_2 Pd/C → L224715 H_3PO_4

043  1. EDC, ACN, NMM 2. H_2 Pd/C → L224715 H_3PO_4

045  1. EDC, EtOAc, NMM

047  1. EDC, IPAc, NMM

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(Please list keywords or subject information for each page or series of pages)

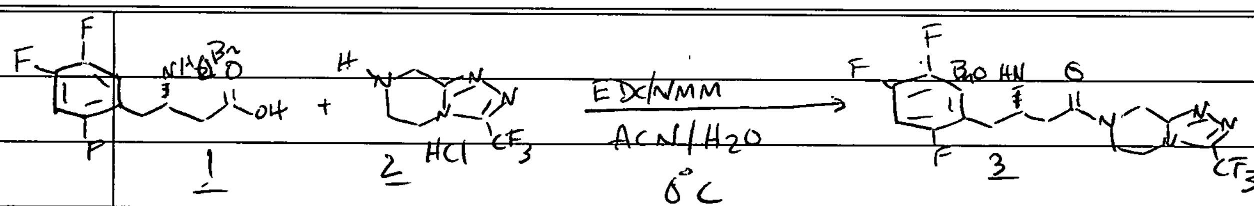
Book 70316 Page 1 Project No. 224715 Project Page

Investigator Date 25 Jan 2002

Subject Coupling of N-Bno Aminoacid w/ EDC/NMM

Restricted Confidential limited access

Filed in Book Number/Title



Reagents:

		FW	Amt	mmol	eq
Bno-Amino Acid	72324-047 1	~~407~~ 339	500 mg	~~1.23~~ 1.47	1.0
Triazole HCl salt	72176-058 2	228	~~420 mg~~ 504 mg	~~1.84~~ 2.21	1.5
EDC	Aldrich	191.71	~~354 mg~~ 424 mg	~~1.84~~ 2.21	1.5
N-methyl morpholine (~~NMM~~)	Aldrich 0.920 g/ml	101.15	~~0.124 g / 135 ml~~ 149 mg, 162 ml	~~1.23~~ 1.47	1.0
ACN			5 ml		
H_2O			0.5 ml		

Procedure: 1. Added 500 ml of H_2O to soln of 1 in ACN. Then Added 2, EDC & N-methyl morpholine sequentially @ 0°C. After ~2 hr no starting material by LC. Added 3 ml H_2O @ 0°C then added 5 ml EtOAc. Cut layers washed organics w/ 2.5 ml sat NaCl. Collected into 100 ml RBF, concentrated to Thick oil stored in freezer over weekend. [signature] 25 Jan 2002

28 Jan 2002

3 —10% Pd/C, H_2→ L224715

Reagents:

	FW	Amt	mmol	eq
3	513	~750 mg	1.5	1.0
10% Pd/C		150 mg		
MeOH		10 ml		

gave to hydrog lab as methanol soln.

Countersigned by

Date

MERCK & CO., INC./MRL

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

29Jan2002 Hydrogenated O/N @ 40PSI RT. Rxn ~30% complete
filtered concentrated & Resubmit.
30Jan2002 Hydrogenated w/ 150mg 10% Pd/C. 40PSI 50°C
O/N. Rxn complete by LC filtered & washed solids
HPLC assay shows 422mg of 715 along w/ Benzyl alcohol
& a byproduct @ 12.9 min which has UV max 268nm.
71% assay yield.
Dissolved oil in IPAC & concentrated Then dissolved
in 15ml IPAC - white solids present. ~~At~~ filtered
& then washed w/ 5ml IPAC. Charged 167mg ~~Ph~~ $SO_3H \cdot H_2O$
in 2ml IPAC, heated to 60°C & seeded batch cloudiness
ensued & then white xtals formed. Kept @ 50°C for 1hr. Cooled
to RT & Filtered. Washed w/ IPAC dried in vac oven @ 40°C
w/ N_2 sweep O/N
31Jan2002 isolated 520mg of white solids (63% yield over 4 steps)
LC shows 69.1 wt% L224715 Freebase ~~theoretical: 72% Free~~
96 wt% pure. Gave sample to Phys. Meas. & Analytical
[signature] 31Jan2002
2002Feb01. 1H-NMR of material looks good in D_3-ACN. Peaks
are well resolved. Some IPAC present [signature] 1Feb2002
5Feb2002 - Crystals had formed in NMR tube. collected &
gave to Phys. Meas. Analytical Report indicating material is
SF 99.9% ee & 99.27% pure by HPLC.
↑ desired enantiomer
6Feb2002 C. Lindemann indicates ACN xtals are another form.

Countersigned by

Date

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Jan 31, 2002	0104445	70316-001	0726	

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD			

COMPLETE STRUCTURE

CHEMICAL NAME
C-224.715 Besylate Salt

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS

DO NOT WRITE BELOW THIS LINE

RESULTS

RRT	Area%
0.65	~~0.07~~ 0.06
0.93	0.16
0.95	0.20
1.00	99.27
1.04	0.09
1.37	0.13

Total imp = 0.64%

Chiral

major enantiomer = 99.92%

minor enantiomer = 0.08%

NB# 25878-108/109

PP LAB PROC #	ANALYST	DATE
	J.GD	Feb 21, 2002

Hansen, Karl

From: Dorwart, Jason G.
Sent: Tuesday, February 05, 2002 11:13 AM
To: Hansen, Karl

Karl,

Here are the results of the L-224715 Besylate salt NB# 70316-001.

LCAP

RRT	Area %
0.65	0.06%
0.93	0.16%
0.95	0.20%
1.00	99.27%
1.04	0.09%
1.37	0.13%

Chiral
Major Enantiomer = 99.92%
Minor Enantiomer = 0.08%

Jason

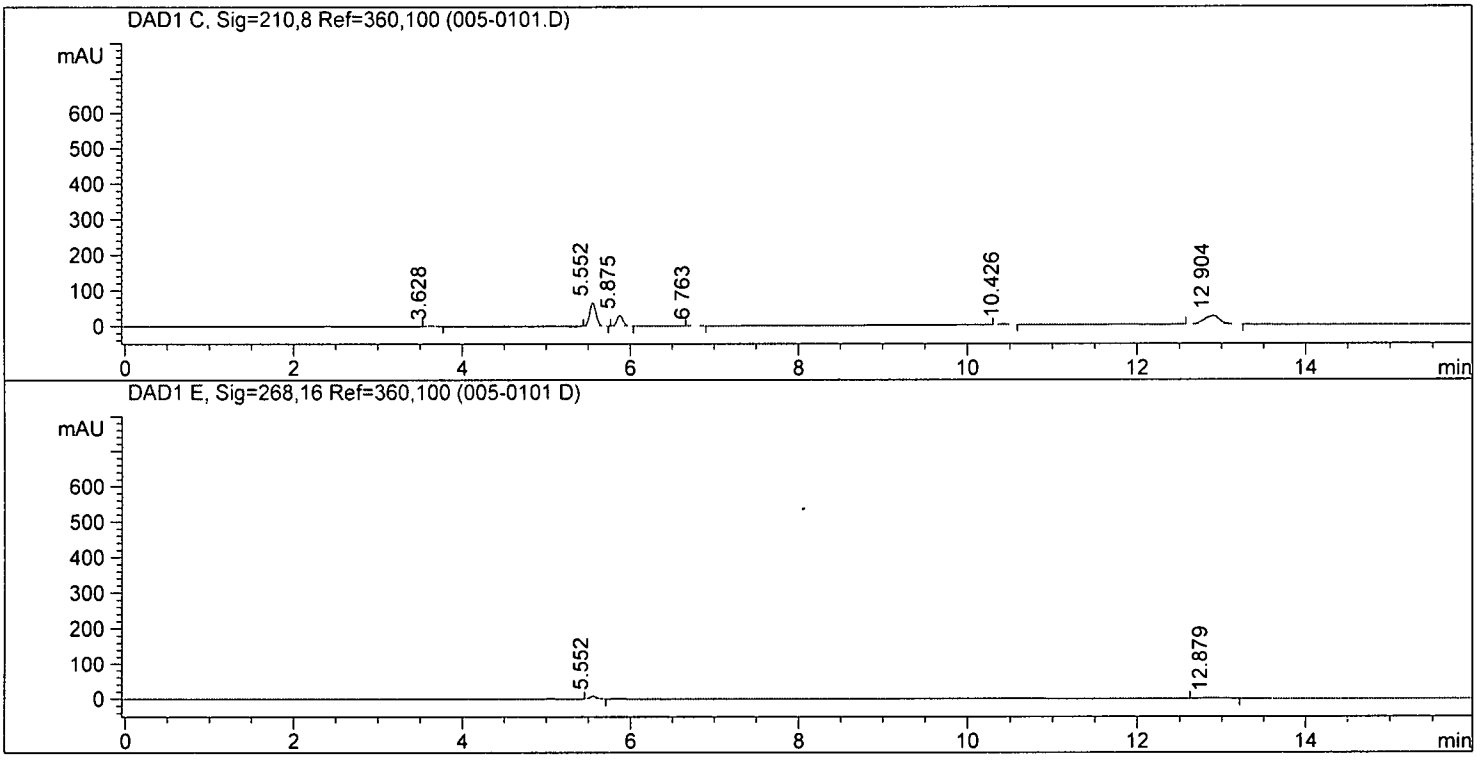
Data file :C:\HPCHEM\HPLC0157\DATA\005-0101.D Sample Name: 70316-001

0.1900g/50ml of hydrog soln 17.85 g ->

==========

Injection Date : 01/30/2002 12:29:35 PM Seq Line : 1
Sample Name : 70316-001 Vial No : 5
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm

4/22 ~, of 715



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	3.63	BB	0.084	1.52	8.311	0.99	0.00000C	
2	5.55	BB	0.082	65.94	350.924	41.82	0.08999C	L-224,715
3	5.88	BB	0.078	30.31	149.939	17.87	0.00000C	Benzyalcohol
4	6.76	BB	0.083	1.06	5.689	0.68	0.00000C	
5	10.43	BB	0.091	2.62	15.583	1.86	0.00000C	
6	12.90	BB	0.201	24.14	308.655	36.78	0.00000C	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.082	7.55	40.148	61.99	0.08999C	L-224,715
2	12.88	PB	0.204	1.86	24.616	38.01	0.00000C	

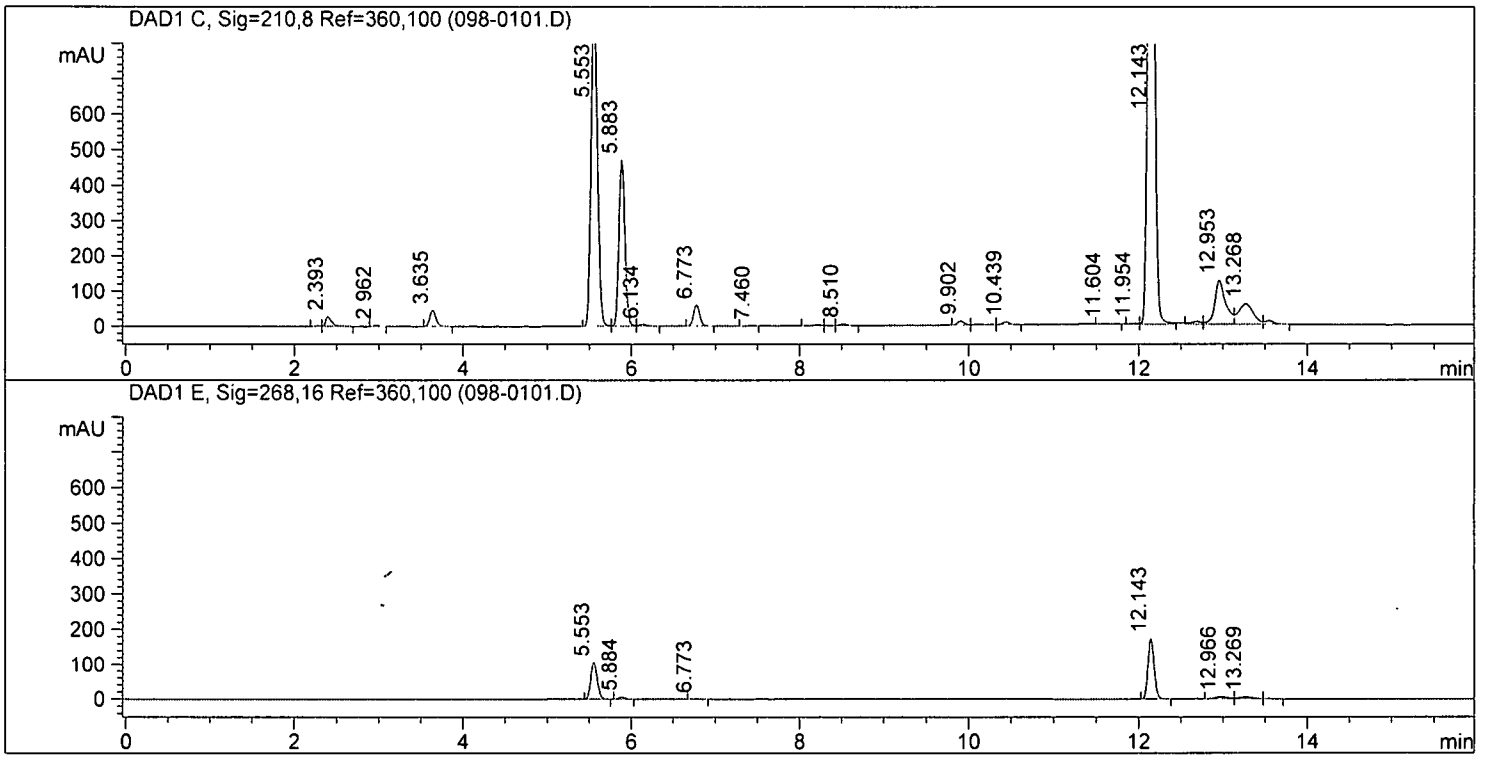
Data file :C:\HPCHEM\HPLC0157\DATA\098-0101.D Sample Name: 70316-001

methanol soln of hydrog after ->

==========

Injection Date : 01/29/2002 8:26:05 AM Seq Line : 1
Sample Name : 70316-001 Vial No : 98
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.28	BV	0.064	2.04	8.408	0.04	0.000000	
2	2.39	VB	0.074	28.29	145.682	0.73	0.000000	
3	2.96	BB	0.071	2.66	12.500	0.06	0.000000	
4	3.63	PB	0.080	45.98	236.239	1.18	0.000000	
5	5.55	BV	0.085	896.79	4819.326	23.99	1.276818	L-224,715
6	5.88	VV	0.078	470.40	2342.150	11.66	0.000000	
7	6.13	VB	0.103	5.08	35.195	0.18	0.000000	
8	6.77	BB	0.080	60.29	309.151	1.54	0.000000	
9	7.46	PV	0.098	1.10	7.578	0.04	0.000000	
10	8.21	BV	0.099	2.42	17.173	0.09	0.000000	
11	8.35	VV	0.084	1.11	6.073	0.03	0.000000	
12	8.51	VP	0.085	4.92	27.312	0.14	0.000000	
13	9.90	BV	0.086	11.38	62.772	0.31	0.000000	
14	10.11	VB	0.116	3.01	24.672	0.12	0.000000	
15	10.44	BB	0.085	8.08	44.743	0.22	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\098-0101.D Sample Name: 70316-001

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	11.60	BB	0.194	2.25	33.466	0.17	0.000000	
17	11.95	BV	0.105	3.70	27.092	0.13	0.000000	
18	12.14	VB	0.087	1.83e3	9921.391	49.40	0.000000	
19	12.69	BV	0.123	8.67	76.832	0.38	0.000000	
20	12.95	VV	0.129	125.53	1132.982	5.64	0.000000	
21	13.27	VV	0.185	58.48	715.638	3.56	0.000000	
22	13.55	VB	0.108	10.69	79.096	0.39	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.082	106.70	566.822	34.94	1.276818	L-224,715
2	5.88	BB	0.081	5.96	31.159	1.92	0.000000	
3	6.77	BB	0.082	1.27	6.741	0.42	0.000000	
4	12.14	BB	0.079	173.36	881.732	54.35	0.000000	
5	12.97	VV	0.175	5.89	66.176	4.08	0.000000	
6	13.27	VV	0.182	5.19	62.412	3.85	0.000000	
7	13.55	VB	0.104	1.05	7.419	0.46	0.000000	

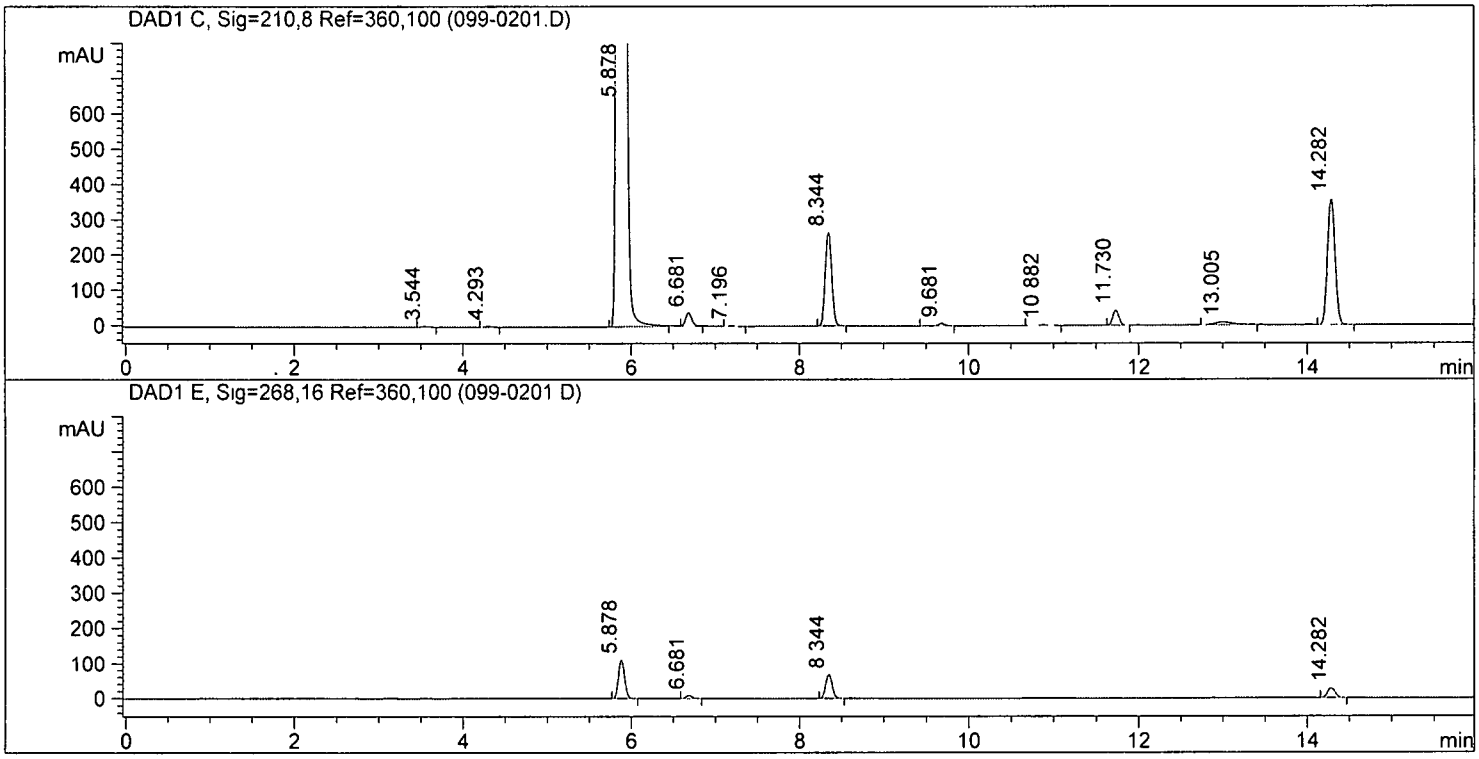
==========

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\099-0201.D Sample Name: 70316-001

benzyl alcohol ->

```
==========================================================================
Injection Date : 01/29/2002  8:44:40 AM        Seq Line  : 2
Sample Name    : 70316-001                     Vial No   : 99
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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                    Customized Report:karlo
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Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	3.54	BB	0.081	2.15	11.170	0.05	0.000000	
2	4.29	PB	0.080	3.05	15.769	0.07	0.000000	
3	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
4	5.88	PB	0.132	2.23e3	1.786e4	80.64	0.000000	
5	6.68	BB	0.081	37.91	198.693	0.90	0.000000	
6	7.20	PP	0.072	1.39	6.156	0.03	0.000000	
7	8.34	BB	0.085	264.54	1423.633	6.43	0.000000	
8	9.68	BP	0.084	6.80	36.172	0.16	0.000000	
9	10.88	BB	0.115	2.13	16.999	0.08	0.000000	
10	11.73	BP	0.078	42.61	213.630	0.96	0.000000	
11	13.00	BB	0.239	7.86	127.571	0.58	0.000000	
12	14.28	VB	0.099	356.95	2238.477	10.11	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\099-0201.D Sample Name: 70316-001
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

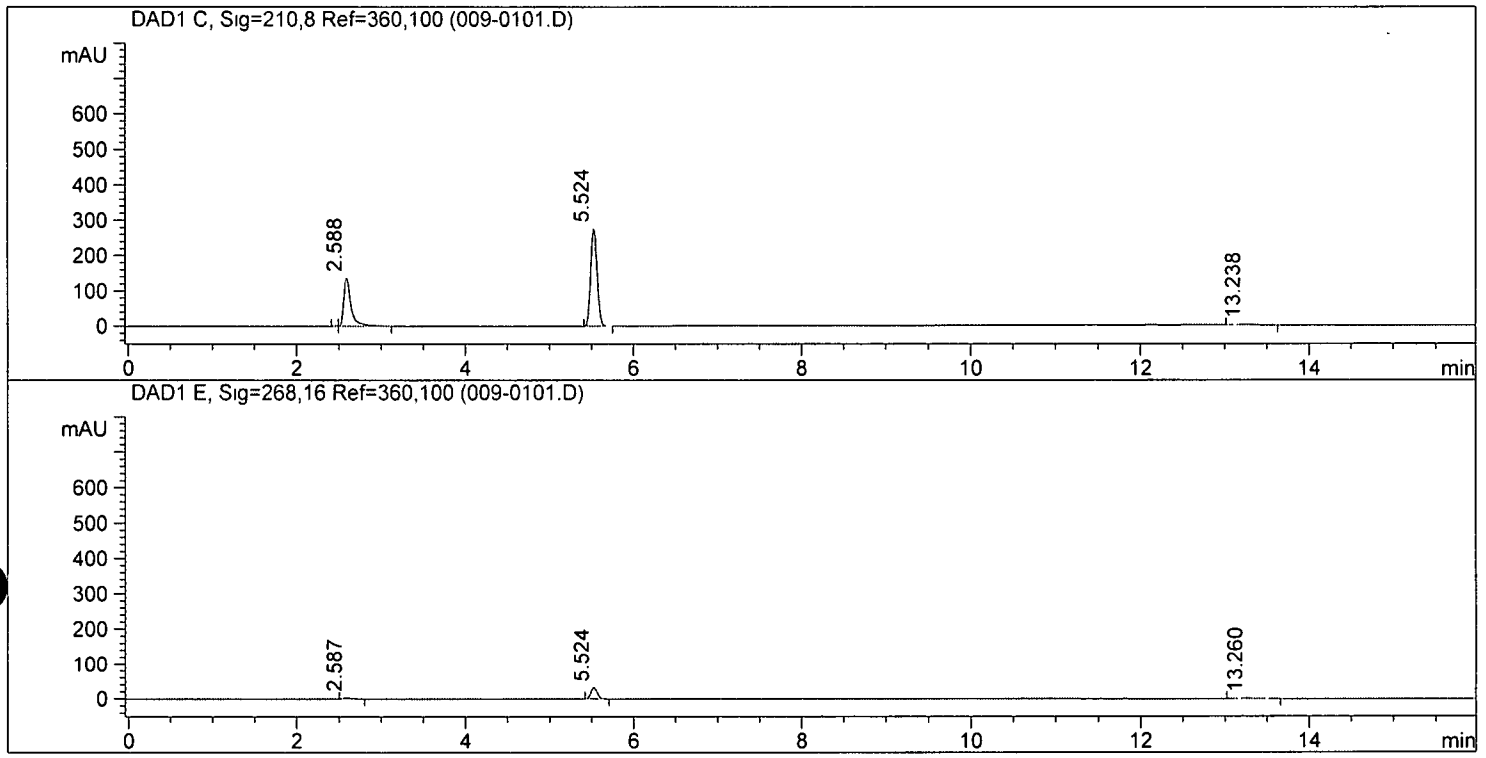
Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	5.88	BB	0.078	111.34	555.977	49.31	0.000000	
3	6.68	BB	0.079	8.36	42.036	3.73	0.000000	
4	8.34	BB	0.085	67.02	359.367	31.88	0.000000	
5	14.28	BB	0.099	27.21	170.028	15.08	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\009-0101.D Sample Name: 70316-001

14.0mg/25ml of isolated besylate salt ->

```
==========================================================================
Injection Date : 01/31/2002  6:59:40 AM        Seq Line  : 1
Sample Name    : 70316-001                     Vial No   : 9
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==========================================================================
                Customized Report:karlo
==========================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000
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Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.48	VV	0.047	1.70	5.400	0.23	0.000000	
2	2.59	VB	0.089	137.80	837.035	35.89	0.000000	
3	5.52	BB	0.082	276.52	1469.249	63.00	0.387022	L-224,715
4	13.24	BP	0.195	1.74	20.490	0.88	0.000000	

9,67

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.59	BB	0.088	4.11	24.614	11.80	0.000000	
2	5.52	BB	0.082	31.93	169.240	81.15	0.387022	L-224,715
3	13.26	PP	0.215	1.10	14.711	7.05	0.000000	

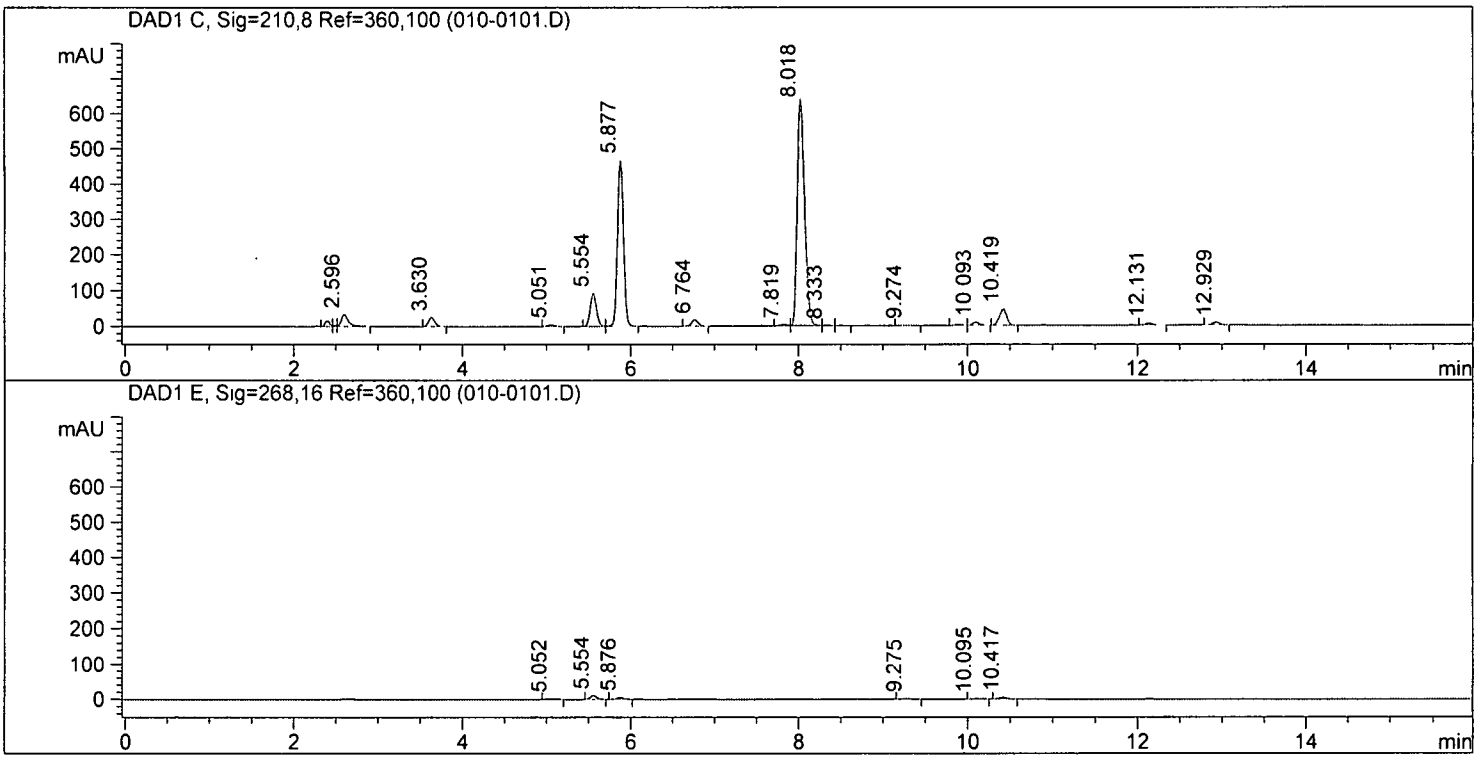
Data file :C:\HPCHEM\HPLC0157\DATA\010-0101.D Sample Name: 70316-001

3.108g/50ml of 16.8g ML's ->

==========

Injection Date : 01/31/2002 9:16:19 AM Seq Line : 1
Sample Name : 70316-001 Vial No : 10
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.39	VV	0.058	16.56	62.327	0.82	0.000000	
2	2.49	VV	0.042	2.87	8.389	0.11	0.000000	
3	2.60	VB	0.089	33.48	196.788	2.57	0.000000	
4	3.63	BB	0.082	25.57	135.755	1.78	0.000000	
5	5.05	PB	0.086	5.27	29.600	0.39	0.000000	
6	5.55	PV	0.083	92.12	482.583	6.31	0.124960	L-224,715
7	5.88	VB	0.078	468.64	2325.245	30.42	0.000000	
8	6.76	BB	0.084	18.33	100.029	1.31	0.000000	
9	7.82	BV	0.085	4.16	23.759	0.31	0.000000	
10	8.02	VV	0.092	641.83	3852.972	50.40	0.000000	
11	8.33	VV	0.107	1.27	9.215	0.12	0.000000	
12	8.50	VB	0.082	1.11	6.116	0.08	0.000000	
13	9.27	VP	0.100	1.21	7.634	0.10	0.000000	
14	9.89	BV	0.087	2.56	14.137	0.18	0.000000	
15	10.09	VB	0.084	8.60	47.343	0.62	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	10.42	BB	0.091	45.48	269.598	3.53	0.000000	
17	12.13	VB	0.092	4.99	30.715	0.40	0.000000	
18	12.93	VB	0.089	7.43	42.450	0.56	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

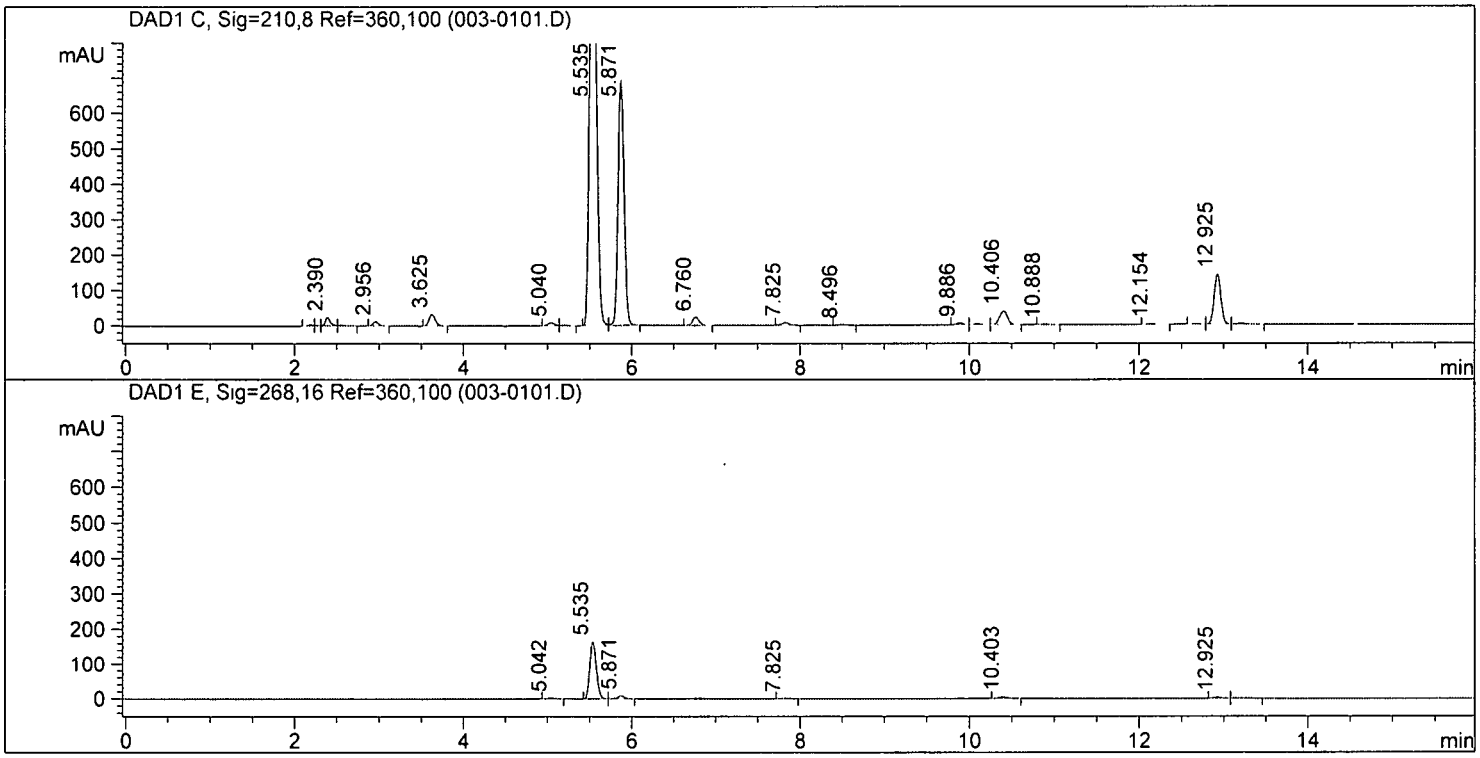
Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.05	BB	0.087	1.62	9.085	6.68	0.000000	
2	5.55	BB	0.081	10.55	55.201	40.57	0.124960	L-224,715
3	5.88	BP	0.083	5.50	29.482	21.67	0.000000	
4	9.27	PP	0.098	1.45	8.968	6.59	0.000000	
5	10.09	PP	0.088	1.00	5.712	4.20	0.000000	
6	10.42	BP	0.093	4.53	27.611	20.29	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\003-0101.D Sample Name: 70316-001

hydrog after resubmission more concentrated ->

```
==================================================================
Injection Date : 01/30/2002  8:54:32 AM        Seq Line  : 1
Sample Name    : 70316-001                     Vial No   : 3
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==================================================================================================
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==================================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.19	BV	0.061	3.34	14.120	0.11	0.000000	
2	2.26	VV	0.052	1.57	5.355	0.04	0.000000	
3	2.39	VV	0.062	24.77	101.057	0.81	0.000000	
4	2.56	VB	0.091	2.20	13.440	0.11	0.000000	
5	2.96	BB	0.069	12.52	56.805	0.45	0.000000	
6	3.63	PB	0.081	32.89	171.121	1.37	0.000000	
7	5.04	BV	0.089	8.27	47.409	0.38	0.000000	
8	5.20	VP	0.082	2.24	12.356	0.10	0.000000	
9	5.54	BV	0.089	1.32e3	7313.577	58.41	1.939303	L-224,715
10	5.87	VB	0.078	691.48	3458.091	27.62	0.000000	
11	6.76	BB	0.085	24.08	129.711	1.04	0.000000	
12	7.82	BB	0.090	7.97	49.417	0.39	0.000000	
13	8.50	BB	0.082	1.51	8.044	0.06	0.000000	
14	9.89	BV	0.087	5.33	29.603	0.24	0.000000	
15	10.09	VV	0.105	2.88	20.953	0.17	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\003-0101.D Sample Name: 70316-001

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	10.41	VB	0.107	38.65	254.861	2.04	0.000000	
17	10.89	BP	0.104	1.29	9.002	0.07	0.000000	
18	12.15	PP	0.116	1.85	14.832	0.12	0.000000	
19	12.66	BV	0.109	1.31	10.214	0.08	0.000000	
20	12.92	VV	0.086	140.72	777.889	6.21	0.000000	
21	13.21	VB	0.164	2.18	23.185	0.19	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.04	BB	0.090	2.20	12.764	1.27	0.000000	
2	5.54	BV	0.083	164.74	888.075	88.11	1.939303	L-224,715
3	5.87	VB	0.085	8.23	45.889	4.55	0.000000	
4	7.82	BP	0.085	1.15	6.638	0.66	0.000000	
5	10.40	BB	0.109	4.06	27.613	2.74	0.000000	
6	12.92	BB	0.089	2.99	17.188	1.71	0.000000	
7	13.21	BB	0.148	1.04	9.788	0.97	0.000000	

*** End of Report ***

2002012956.001
DO NOT WRITE IN THIS SPACE

HYDROGENATION OR HIGH PRESSURE REACTION

QUESTED BY [illegible] BLDG/RM 800B269 EXT. 0552 DATE [illegible]

PROJECT NO. [illegible] PROJECT [illegible] 2218 NOTEBOOK - PAGE NO. [illegible]

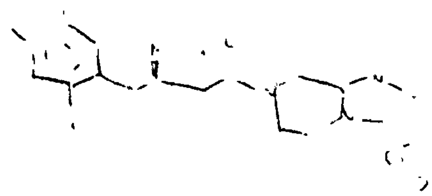
CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

NO. 1 ______ NO. 2 ______

M.W. ______ AMOUNT ______ G. MOLES ______ M.W. ______ AMOUNT ______ G. MOLES ______

STRUCTURAL FORMULA: [illegible]



EMPIRICAL FORMULA: [illegible]

CATALYST ______ G. OF [illegible]

SOLVENT ______ ML. OF [illegible]

MOLES OF HYDROGEN REQUIRED [illegible]

OTHER MATERIALS [illegible]

REACTION CONDITIONS, ETC. [illegible]

PRECAUTIONS: ______

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: 750 G. MOLES 0.0015 NO.2: ______ G. MOLES ______

CATALYST 0.15 G. OF 10% [illegible] Lot # EC 95286

SOLVENT [illegible] ML. OF MeOH

OTHER MATERIALS ______

CELL NO. ____ HEATER NO. ____ REC. POINT INTERNAL ____ EXTERNAL ____ BOMB NO. ____ VESSEL SIZE 80 ML.

SHAKER NO. 56 LINER ____ SHAKER TANK ____ AUX. TANK ____ SYSTEM VOLUME 72 ML.

LC'D H_2 PRESSURE DROP = [illegible] LBS./MOLE 0.0015 MOLES = 7.41 LBS.

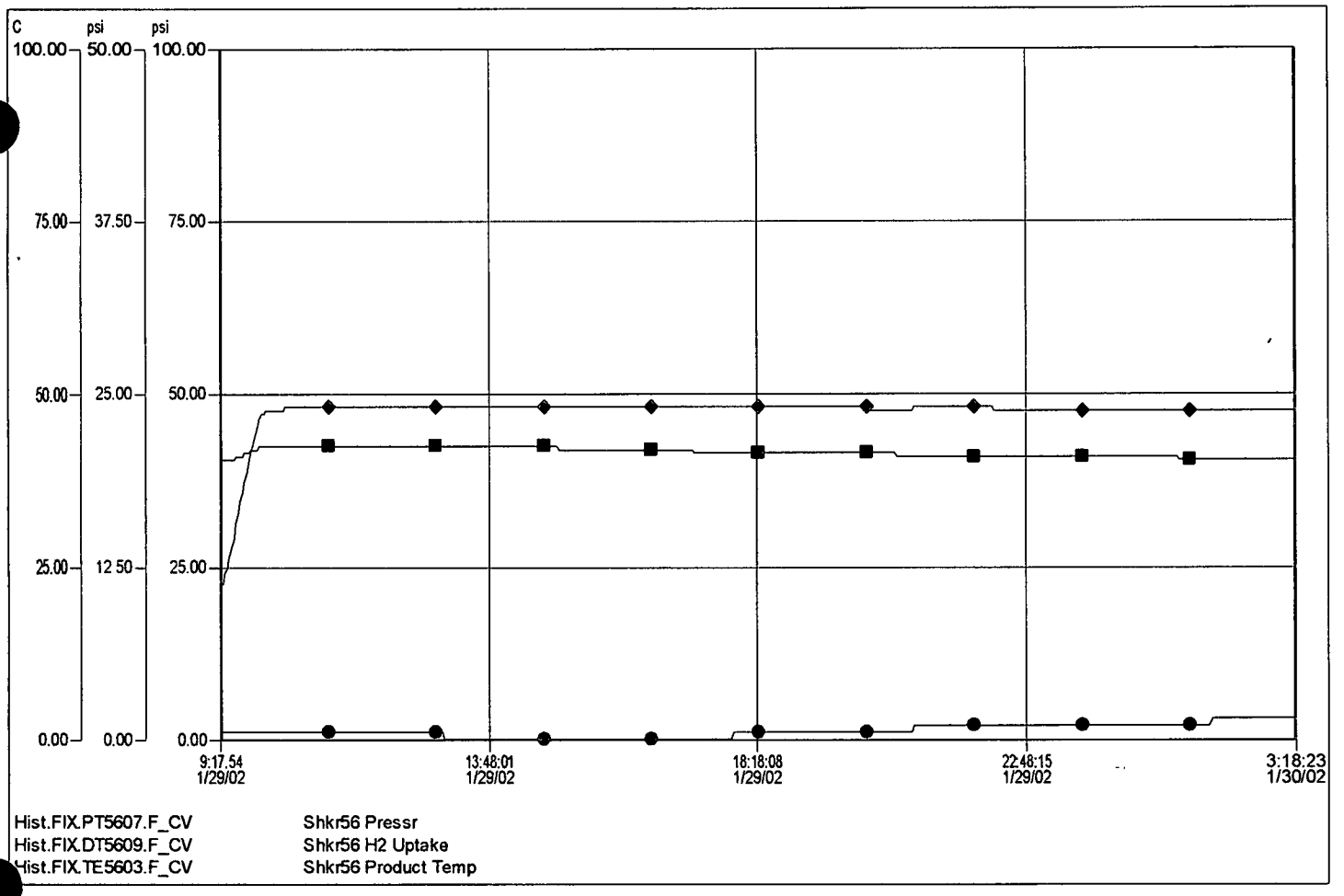
NDITIONS ______ HRS. AT 50 C. MISC. DATA: [illegible]

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
09:18	19.6	40	0	17:18	48.2	41	0	01:18	47.7	41	1
09:33	31.5	41	1	17:33	48.2	41	0	01:33	47.7	40	1
09:48	41.7	42	1	17:48	48.2	41	0	01:48	47.7	40	1
10:03	47.7	42	1	18:03	48.2	41	1	02:03	47.7	40	2
10:18	47.7	42	1	18:18	48.2	41	1	02:18	47.7	40	2
10:33	48.2	42	1	18:33	48.2	41	1	02:33	47.7	40	2
10:48	48.2	42	1	18:48	48.2	41	1	02:48	47.7	40	2
11:03	48.2	42	1	19:03	48.2	41	1	03:03	47.7	40	2
11:18	48.2	42	1	19:18	48.2	41	1				
11:33	48.2	42	1	19:33	48.2	41	1				
11:48	48.2	42	1	19:48	48.2	41	1				
12:03	48.2	42	1	20:03	48.2	41	1				
12:18	48.2	42	1	20:18	47.7	41	1				
12:33	48.2	42	1	20:33	47.7	41	1				
12:48	48.2	42	1	20:48	47.7	41	1				
13:03	48.2	42	0	21:03	48.2	41	1				
13:18	48.2	42	0	21:18	48.2	41	1				
13:33	48.2	42	0	21:33	48.2	41	1				
13:48	48.2	42	0	21:48	48.2	41	1				
14:03	48.2	42	0	22:03	48.2	41	1				
14:18	48.2	42	0	22:18	47.7	41	1				
14:33	48.2	42	0	22:33	47.7	41	1				
14:48	48.2	42	0	22:48	47.7	41	1				
15:03	48.2	42	0	23:03	47.7	41	1				
15:18	48.2	42	0	23:18	47.7	41	1				
15:33	48.2	42	0	23:33	47.7	41	1				
15:48	48.2	42	0	23:48	47.7	41	1				
16:03	48.2	42	0	00:03	47.7	41	1				
16:18	48.2	42	0	00:18	47.7	41	1				
16:33	48.2	42	0	00:33	47.7	41	1				
6:48	48.2	42	0	00:48	47.7	41	1				
7:03	48.2	42	0	01:03	47.7	41	1				

RUN BY I. Nurrell DATE Jan 29 2002

RUN BY ______ DATE ______

MERCK & CO., INC.
R-654-O REV. 6/88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Shkr56 Pressr
Hist.FIX.DT5609.F_CV
Shkr56 H2 Uptake
Hist.FIX.TE5603.F_CV
Shkr56 Product Temp

2002012856.001 1/28/02 - 1/29/02

HYDROGENATION OR HIGH PRESSURE REACTION

2002012856.001
DO NOT WRITE IN THIS SPACE

REQUESTED BY H[illegible] BLDG/RM [illegible]B269 EXT. [illegible] DATE 2

PROJECT NO. [illegible] PROJECT ~~[illegible]~~ Mano 2218 NOTEBOOK - PAGE NO. 10316-[illegible]

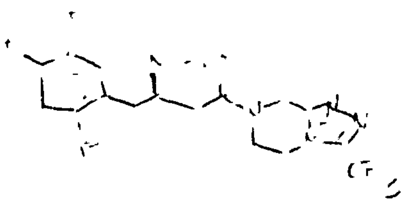
CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

NO. 1 ______ NO. 2 ______

M.W. [illegible] AMOUNT [illegible] G. MOLES [illegible] M.W. ______ AMOUNT ______ G. MOLES ______

STRUCTURAL FORMULA:



EMPIRICAL FORMULA: [illegible]

CATALYST [illegible] G. OF ______
SOLVENT [illegible] ML. OF MeOH
MOLES OF HYDROGEN REQUIRED ______
OTHER MATERIALS [illegible]
REACTION CONDITIONS, ETC. [illegible] RT
PRECAUTIONS: ______

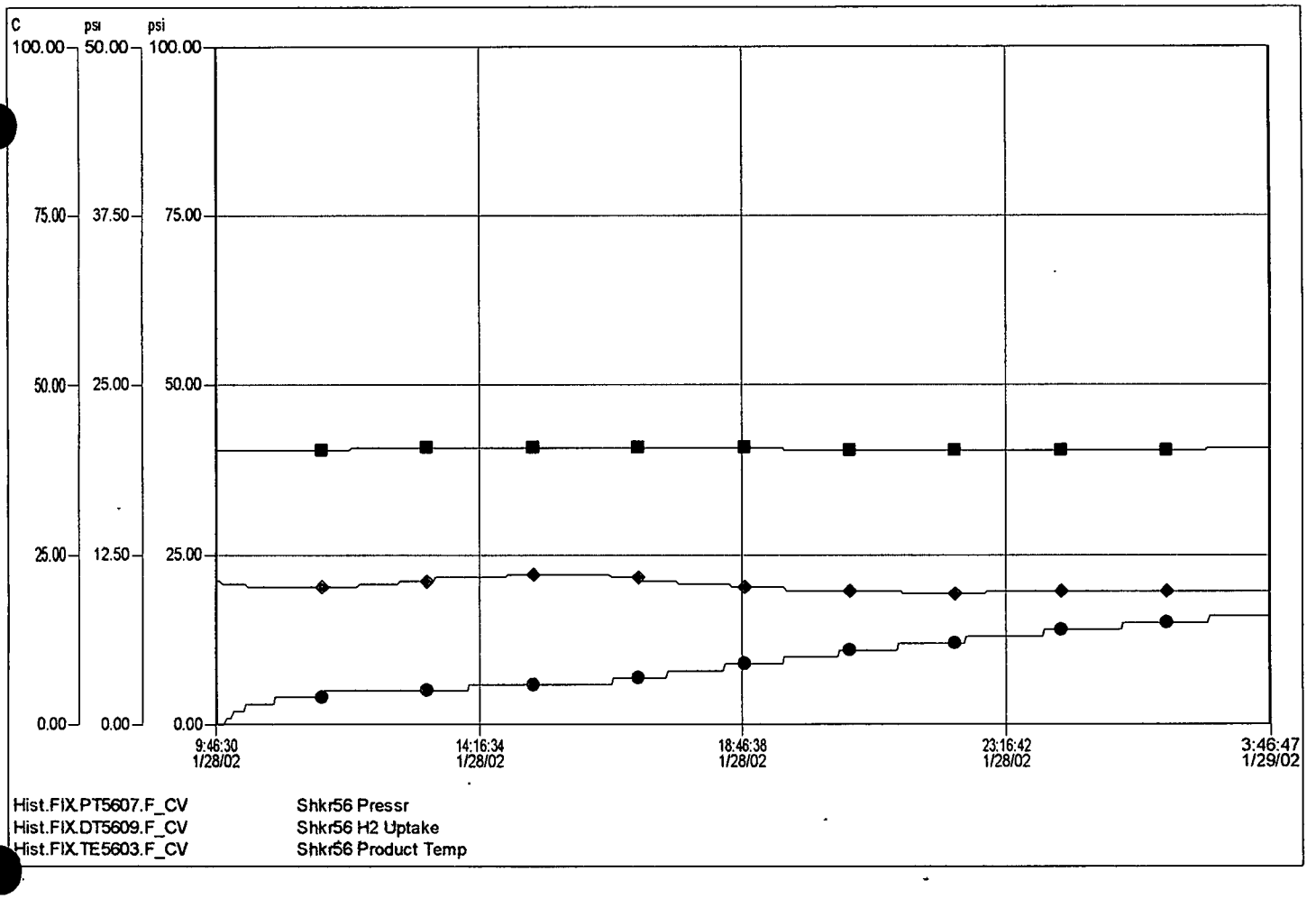
TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: .750 G. MOLES 0.0015 NO.2: ______ G. MOLES ______
CATALYST .150 G. OF [illegible] 1# FC95286
SOLVENT 1 ML. OF MeOH
OTHER MATERIALS ______
CELL NO. ____ HEATER NO. ____ REC. POINT INTERNAL ____ EXTERNAL ____ BOMB NO. ____ VESSEL SIZE 80 ML.
SHAKER NO. 56 LINER ____ SHAKER TANK ____ AUX. TANK ____ SYSTEM VOLUME 72 ML.
CALC'D H_2 PRESSURE DROP = 4962.9 LBS./MOLE 0.0015 MOLES = 7.4 LBS.
CONDITIONS ______ HRS. AT rt C. MISC. DATA: [illegible] H_2

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
09:47	21.7	40	0	17:15	21.2	41	4
10:01	20.7	40	0	17:29	21.2	41	4
10:15	20.7	40	1	17:43	20.7	41	4
10:29	20.2	40	2	17:57	20.7	41	4
10:43	20.2	40	2	18:11	20.7	41	4
10:57	20.2	40	2	18:25	20.7	41	4
11:11	20.2	40	2	18:39	20.2	41	4
11:25	20.2	40	2	18:53	20.2	41	4
11:39	20.2	40	2	19:07	20.2	41	4
11:53	20.2	40	2	19:21	20.2	41	4
12:07	20.2	41	2	19:35	19.7	40	5
12:21	20.7	41	2	19:49	19.7	40	5
12:35	20.7	41	2	20:03	19.7	40	5
12:49	20.7	41	2	20:17	19.7	40	5
13:03	21.2	41	2	20:31	19.7	40	6
13:17	21.2	41	2	20:45	19.7	40	6
13:31	21.7	41	2	20:59	19.7	40	6
13:45	21.7	41	2	21:13	19.7	40	6
13:59	21.7	41	2	21:27	19.7	40	6
14:13	21.7	41	3	21:41	19.2	40	6
14:27	21.7	41	3	21:55	19.2	40	6
14:41	21.7	41	3	22:09	19.2	40	6
14:55	22.2	41	3	22:23	19.2	40	6
15:09	22.2	41	3	22:37	19.2	40	6
15:23	22.2	41	3	22:51	19.2	40	6
15:37	22.2	41	3	23:05	19.7	40	6
15:51	22.2	41	3	23:19	19.7	40	6
16:05	22.2	41	3	23:33	19.7	40	6
16:19	22.2	41	3	23:47	19.7	40	6
16:33	21.7	41	4	00:01	19.7	40	7
16:47	21.7	41	4	00:15	19.7	40	7
17:01	21.7	41	4	00:29	19.7	40	7

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
00:43	19.7	40	7
00:57	19.7	40	7
01:11	19.7	40	7
01:25	19.7	40	8
01:39	19.7	40	8
01:53	19.7	40	8
02:07	19.7	40	8
02:21	19.7	40	8
02:35	19.7	40	8
02:49	19.7	41	8
03:03	19.7	41	8
03:17	19.7	41	8
03:31	19.7	41	8
03:45	19.7	41	8

RUN BY [illegible] DATE Jan 28 [illegible]
RUN BY ______ DATE ______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0.00
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14:16:34
1/28/02
18:46:38
1/28/02
23:16:42
1/28/02
3:46:47
1/29/02
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Shkr56 Pressr
Hist.FIX.DT5609.F_CV
Shkr56 H2 Uptake
Hist.FIX.TE5603.F_CV
Shkr56 Product Temp

HYDROGENATION OR HIGH PRESSURE REACTION

2002013056-001
DO NOT WRITE IN THIS SPACE

REQUESTED BY Hansen BLDG/RM 800-B269 EXT. 0552 DATE 30 Jan 2002

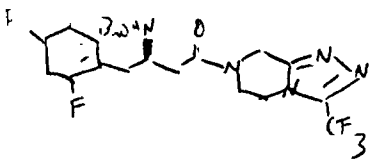
PROJECT NO. 224715 PROJECT MU002218 NOTEBOOK - PAGE NO. 10311-057

CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

NO. 1		NO. 2	
M.W. 515	AMOUNT 150 mg G. MOLES 1.5	M.W.	AMOUNT G. MOLES

STRUCTURAL FORMULA:



EMPIRICAL FORMULA: $C_{22}H_{21}N_4O_2F_6$

CATALYST 0.15 G. OF 10% Pd/C

SOLVENT 10 ML. OF THF

MOLES OF HYDROGEN REQUIRED

OTHER MATERIALS Rinse w/ 1 ml THF

REACTION CONDITIONS, ETC. 40 PSI, 50°C

PRECAUTIONS:

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: .750 G. MOLES .0015 NO.2: G. MOLES

CATALYST 0.15 G. OF 10% Pd/C

SOLVENT 10 ML. OF THF

OTHER MATERIALS

CELL NO. HEATER NO. REC. POINT INTERNAL EXTERNAL BOMB NO. VESSEL SIZE 80 ML.

SHAKER NO. 56 LINER SHAKER TANK AUX. TANK SYSTEM VOLUME 72 ML.

CALC'D H_2 PRESSURE DROP = 49.2 LBS./MOLE 0.0015 MOLES = 7.2 LBS.

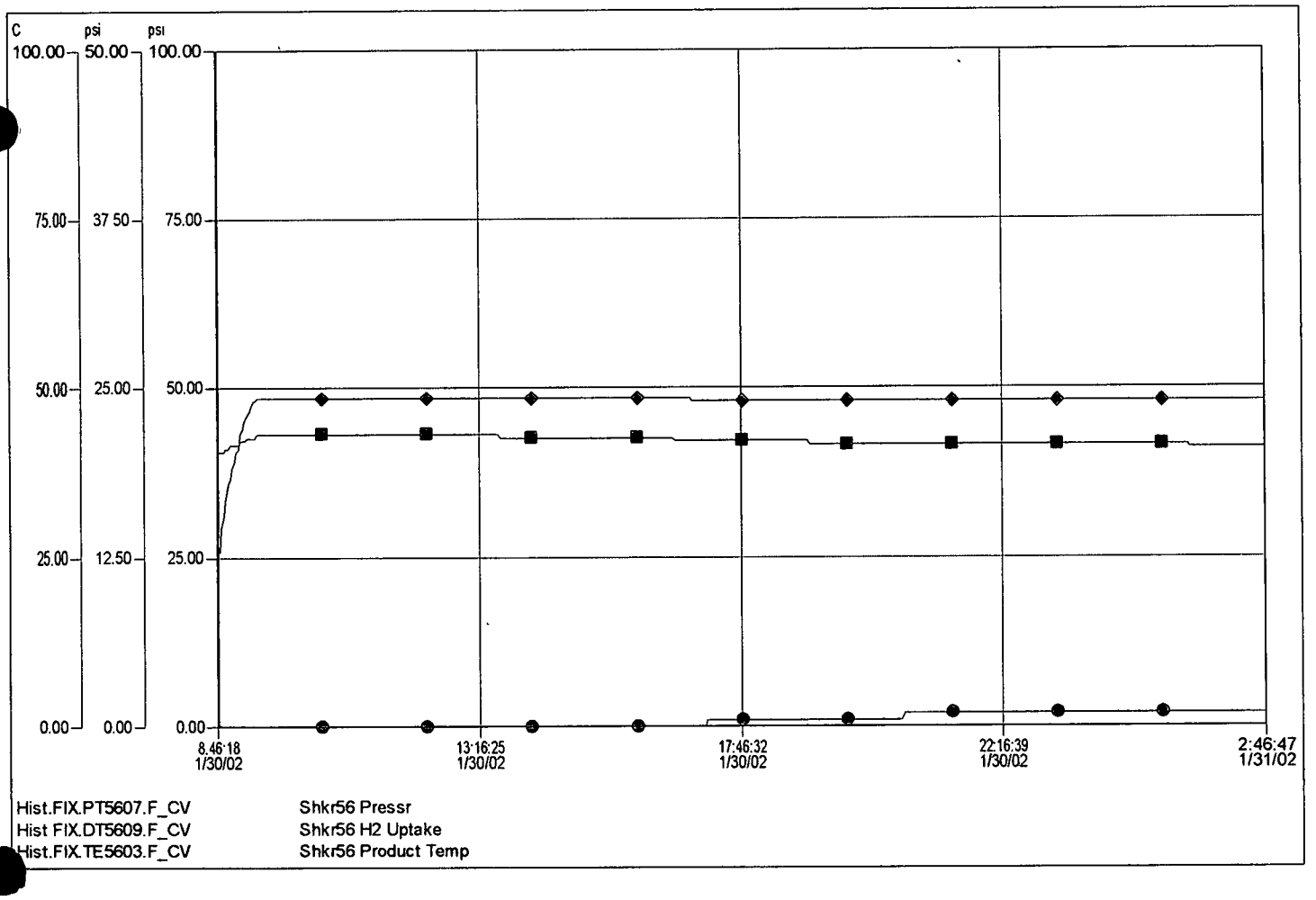
CONDITIONS 14 HRS. AT 50 C. MISC. DATA: 40 psig H_2

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
08:47	22.0	40	0	16:47	48.5	42	0	00:47	48.0	42	1
09:02	38.8	42	0	17:02	48.0	42	0	01:02	48.0	42	1
09:17	46.4	43	0	17:17	48.0	42	0	01:17	48.0	42	1
09:32	48.5	43	0	17:32	48.0	42	0	01:32	48.0	41	1
09:47	48.5	43	0	17:47	48.0	42	0	01:47	48.0	41	1
10:02	48.5	43	0	18:02	48.0	42	0	02:02	48.0	41	1
10:17	48.5	43	0	18:17	48.0	42	0	02:17	48.0	41	1
10:32	48.5	43	0	18:32	48.0	42	0	02:32	48.0	41	1
10:47	48.5	43	0	18:47	48.0	42	0				
11:02	48.5	43	0	19:02	48.0	42	0				
11:17	48.5	43	0	19:17	48.0	42	0				
11:32	48.5	43	0	19:32	48.0	42	0				
11:47	48.5	43	0	19:47	48.0	42	0				
12:02	48.5	43	0	20:02	48.0	42	0				
12:17	48.5	43	0	20:17	48.0	42	0				
12:32	48.5	43	0	20:32	48.0	42	0				
12:47	48.5	43	0	20:47	48.0	42	1				
13:02	48.5	43	0	21:02	48.0	42	1				
13:17	48.5	43	0	21:17	48.0	42	1				
13:32	48.5	43	0	21:32	48.0	42	1				
13:47	48.5	43	0	21:47	48.0	42	1				
14:02	48.5	43	0	22:02	48.0	42	1				
14:17	48.5	43	0	22:17	48.0	42	1				
14:32	48.5	43	0	22:32	48.0	42	1				
14:47	48.5	43	0	22:47	48.0	42	1				
15:02	48.5	43	0	23:02	48.0	42	1				
15:17	48.5	43	0	23:17	48.0	42	1				
15:32	48.5	43	0	23:32	48.0	42	1				
15:47	48.5	43	0	23:47	48.0	42	1				
16:02	48.5	43	0	00:02	48.0	42	1				
16:17	48.5	43	0	00:17	48.0	42	1				
16:32	48.5	43	0	00:32	48.0	42	1				

RUN BY J. Nelson DATE Jan 30, 2002

RUN BY DATE

MERCK & CO., INC.
R-654-O REV. 6/88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0.00
8:46:18
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13:16:25
1/30/02
17:46:32
1/30/02
22:16:39
1/30/02
2:46:47
1/31/02
Hist.FIX.PT5607.F_CV
Shkr56 Pressr
Hist FIX.DT5609.F_CV
Shkr56 H2 Uptake
Hist.FIX.TE5603.F_CV
Shkr56 Product Temp

HYDROGENATION OR HIGH PRESSURE REACTION

2002013055.001
DO NOT WRITE IN THIS SPACE

REQUESTED BY Hansen BLDG/RM 800 B269 EXT. 0552 DATE 30 Jan 2002

PROJECT NO. L 224715 PROJECT M000 2218 NOTEBOOK - PAGE NO. 70315-001

CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

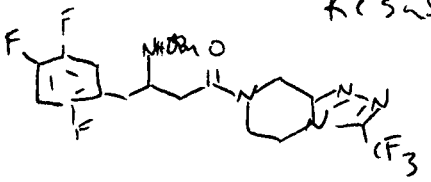
NO. 1 _____

M.W. 513 AMOUNT 750 G. MOLES 1.5

NO. 2 _____

M.W. _____ AMOUNT _____ G. MOLES _____

STRUCTURAL FORMULA: Resubmit



EMPIRICAL FORMULA: $C_{22}H_{21}N_4O_2F_6$

CATALYST 150 mg G. OF 15% Pd/C

SOLVENT 10 ML. OF MeOH

MOLES OF HYDROGEN REQUIRED 1.5 mmol

OTHER MATERIALS _____

REACTION CONDITIONS, ETC. 50°C 40 PSI

PRECAUTIONS: _____

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: .750 G. MOLES 0.0015 NO.2: _____ G. MOLES _____

CATALYST .150 G. OF 10% Pd/C

SOLVENT 10 ML. OF MeOH

OTHER MATERIALS _____

CELL NO. _____ HEATER NO. _____ REC. POINT INTERNAL _____ EXTERNAL _____ BOMB NO. _____ VESSEL SIZE 80 ML.

SHAKER NO. 55 LINER _____ SHAKER TANK _____ AUX. TANK _____ SYSTEM VOLUME 57 ML.

CALC'D H_2 PRESSURE DROP = 10283 LBS./MOLE 0.0015 MOLES = 9.4 LBS.

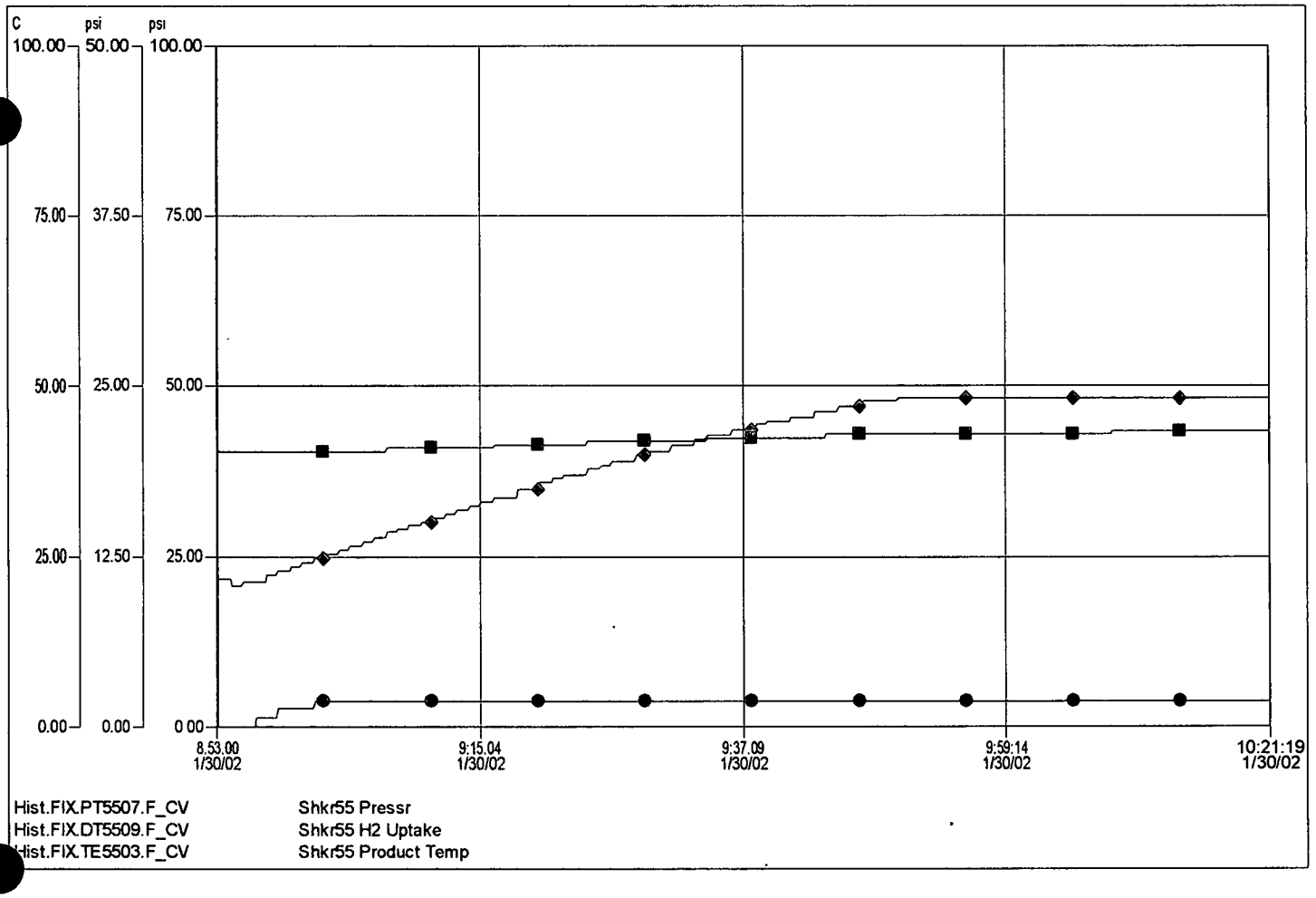
CONDITIONS _____ HRS. AT 50 C. MISC. DATA: 40 psig H_2

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
08:54	21.8	40	0	09:26	38.4	42	2	09:58	48.3	43	2
08:55	20.7	40	0	09:27	39.0	42	2	09:59	48.3	43	2
08:56	21.3	40	0	09:28	39.0	42	2	10:00	48.3	43	2
08:57	21.3	40	1	09:29	39.9	42	2	10:01	48.3	43	2
08:58	22.3	40	1	09:30	40.4	42	2	10:02	48.3	43	2
08:59	22.9	40	1	09:31	40.4	42	2	10:03	48.3	43	2
09:00	23.5	40	1	09:32	41.4	42	2	10:04	48.3	43	2
09:01	24.2	40	1	09:33	41.4	42	2	10:05	48.3	43	2
09:02	24.7	40	2	09:34	42.2	42	2	10:06	48.3	43	2
09:03	25.4	40	2	09:35	42.8	42	2	10:07	48.3	43	2
09:04	25.9	40	2	09:36	42.8	42	2	10:08	48.3	43	2
09:05	26.6	40	2	09:37	43.5	42	2	10:09	48.3	43	2
09:06	27.1	40	2	09:38	43.5	42	2	10:10	48.3	43	2
09:07	27.7	40	2	09:39	44.3	42	2	10:11	48.3	43	2
09:08	28.5	41	2	09:40	44.9	42	2	10:12	48.3	43	2
09:09	29.0	41	2	09:41	44.9	42	2	10:13	48.3	43	2
09:10	29.6	41	2	09:42	45.5	42	2	10:14	48.3	43	2
09:11	30.1	41	2	09:43	45.5	42	2	10:15	48.3	43	2
09:12	30.7	41	2	09:44	46.3	42	2	10:16	48.3	43	2
09:13	31.3	41	2	09:45	46.3	43	2	10:17	48.3	43	2
09:14	31.9	41	2	09:46	47.1	43	2	10:18	48.3	43	2
09:15	32.5	41	2	09:47	47.1	43	2	10:19	48.3	43	2
09:16	33.0	41	2	09:48	47.8	43	2	10:20	48.3	43	2
09:17	33.6	41	2	09:49	47.8	43	2				
09:18	33.6	41	2	09:50	47.8	43	2				
09:19	34.9	41	2	09:51	48.3	43	2				
09:20	34.9	41	2	09:52	48.3	43	2				
09:21	35.8	41	2	09:53	48.3	43	2				
09:22	36.5	41	2	09:54	48.3	43	2				
09:23	37.0	41	2	09:55	48.3	43	2				
09:24	37.0	41	2	09:56	48.3	43	2				
09:25	37.9	42	2	09:57	48.3	43	2				

RUN BY Q. Newell DATE Jan 30, 2002

RUN BY _____ DATE _____

MERCK & CO., INC.
R-654-O REV. 6/88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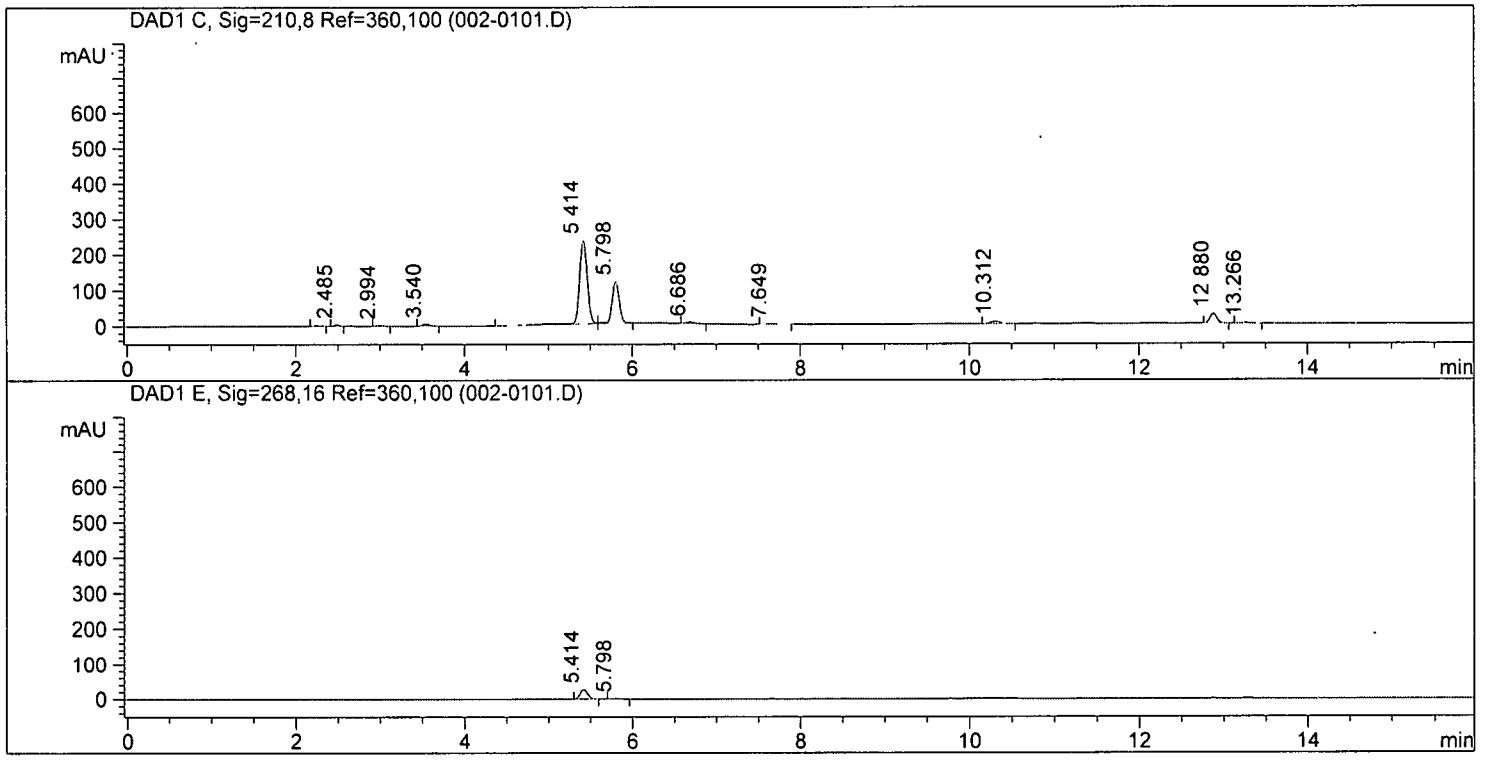
25.00
0.00
0.00
0 00
8.53.00
1/30/02
9:15.04
1/30/02
9:37.09
1/30/02
9:59:14
1/30/02
10:21:19
1/30/02
Hist.FIX.PT5507.F_CV
Shkr55 Pressr
Hist.FIX.DT5509.F_CV
Shkr55 H2 Uptake
Hist.FIX.TE5503.F_CV
Shkr55 Product Temp

Data file :C:\HPCHEM\HPLC0157\DATA\002-0101.D Sample Name: 70316-001

hydrog after resubmission ->

==========

Injection Date : 01/30/2002 8:25:41 AM Seq Line : 1
Sample Name : 70316-001 Vial No : 2
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.24	BB	0.070	2.02	9.424	0.37	0.000000	
2	2.48	BV	0.065	4.22	17.655	0.69	0.000000	
3	2.99	BB	0.075	2.32	11.327	0.44	0.000000	
4	3.54	BB	0.089	5.67	32.437	1.26	0.000000	
5	5.41	PV	0.103	234.39	1553.550	60.30	0.000000	
6	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
7	5.80	VB	0.094	116.77	699.888	27.17	0.000000	
8	6.69	BP	0.096	4.00	24.515	0.95	0.000000	
9	7.65	BB	0.113	1.50	12.218	0.47	0.000000	
10	10.31	PB	0.119	6.59	47.711	1.85	0.000000	
11	12.88	BB	0.089	27.20	155.375	6.03	0.000000	
12	13.27	BB	0.132	1.35	12.066	0.47	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\002-0101.D Sample Name: 70316-001
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.41	BB	0.098	26.83	165.704	95.41	0.000000	
2	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
3	5.80	BB	0.094	1.34	7.981	4.59	0.000000	

*** End of Report ***

L224715 besylate
c-13 nmr400c

Current Data Parameters
NAME 70316-001
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020201
Time 7.20
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 210
DS 0
SWH 26246.719 Hz
FIDRES 0.400493 Hz
AQ 1.2485108 sec
RG 8192
DW 19.050 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec

========== CHANNEL f1 ==========
NUC1 13C
P1 2.50 usec
PL1 0.00 dB
SFO1 100.6237964 MHz

========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 120.00 dB
PL12 18.00 dB
SFO2 400.1322007 MHz

F2 - Processing parameters
SI 32768
SF 100.6127796 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 40.00 cm
F1P 240.000 ppm
F1 24147.07 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6.25000 ppm/cm
HZCM 628.82983 Hz/cm

169.9
169.8
150.6
145.7
129.7
128.1
125.4
119.5
117.2
49.1
43.2
42.9
41.8
41.0
38.7
37.6
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0.6
0.4
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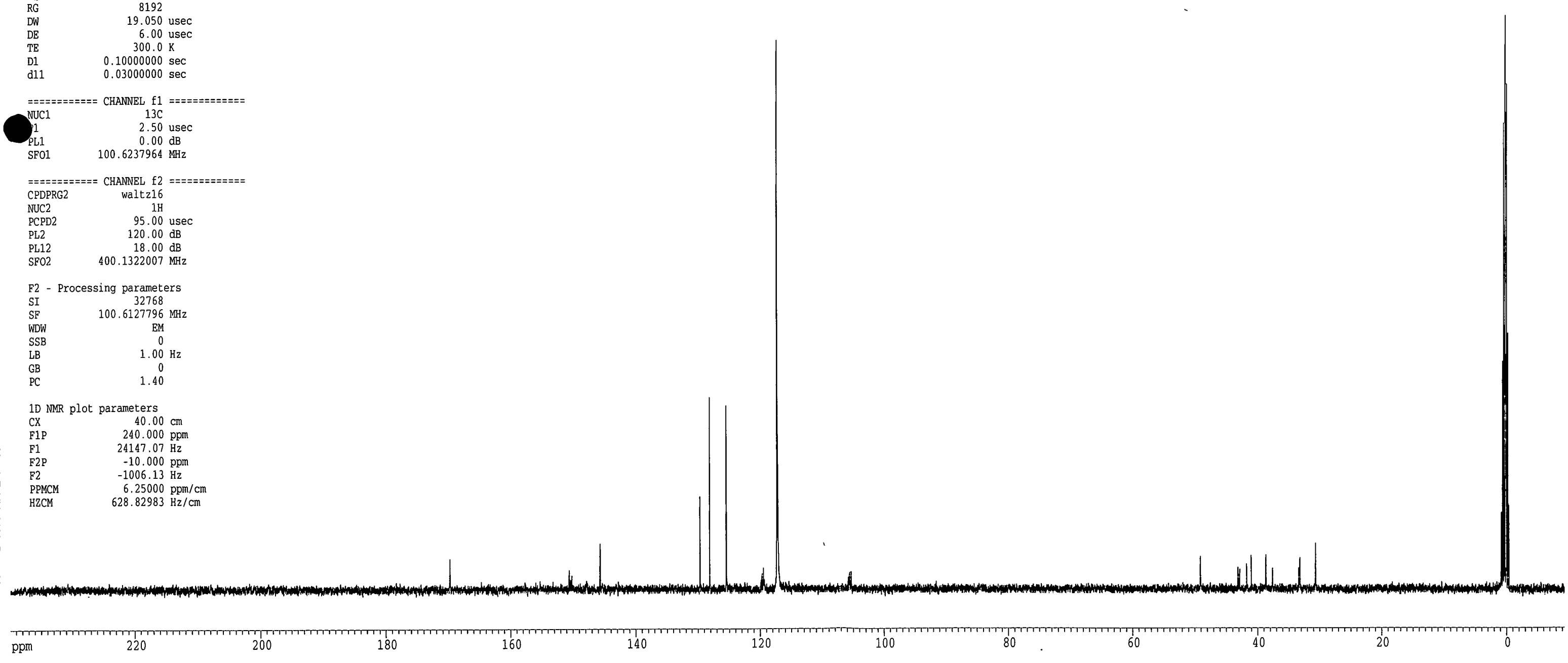
-0.4



isolated besylate salt
nmr400c h1

```
Current Data Parameters
NAME          70316-001
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20020201
Time               7.16
INSTRUM           spect
PROBHD    5 mm QNP 1H/1
PULPROG            zg30
TD                32768
SOLVENT           CD3CN
NS                   32
DS                    2
SWH            6561.680 Hz
FIDRES         0.200247 Hz
AQ            2.4969716 sec
RG                322.5
DW                76.200 usec
DE                 6.00 usec
TE                300.0 K
D1           0.10000000 sec

============ CHANNEL f1 =============
NUC1                 1H
P1                10.00 usec
 L1               -5.00 dB
SFO1        400.1322007 MHz

F2 - Processing parameters
SI                16384
SF          400.1300056 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                40.00 cm
F1P                9.750 ppm
F1              3901.27 Hz
F2P               -0.250 ppm
F2              -100.03 Hz
PPMCM          0.25000 ppm/cm
HZCM         100.03250 Hz/cm
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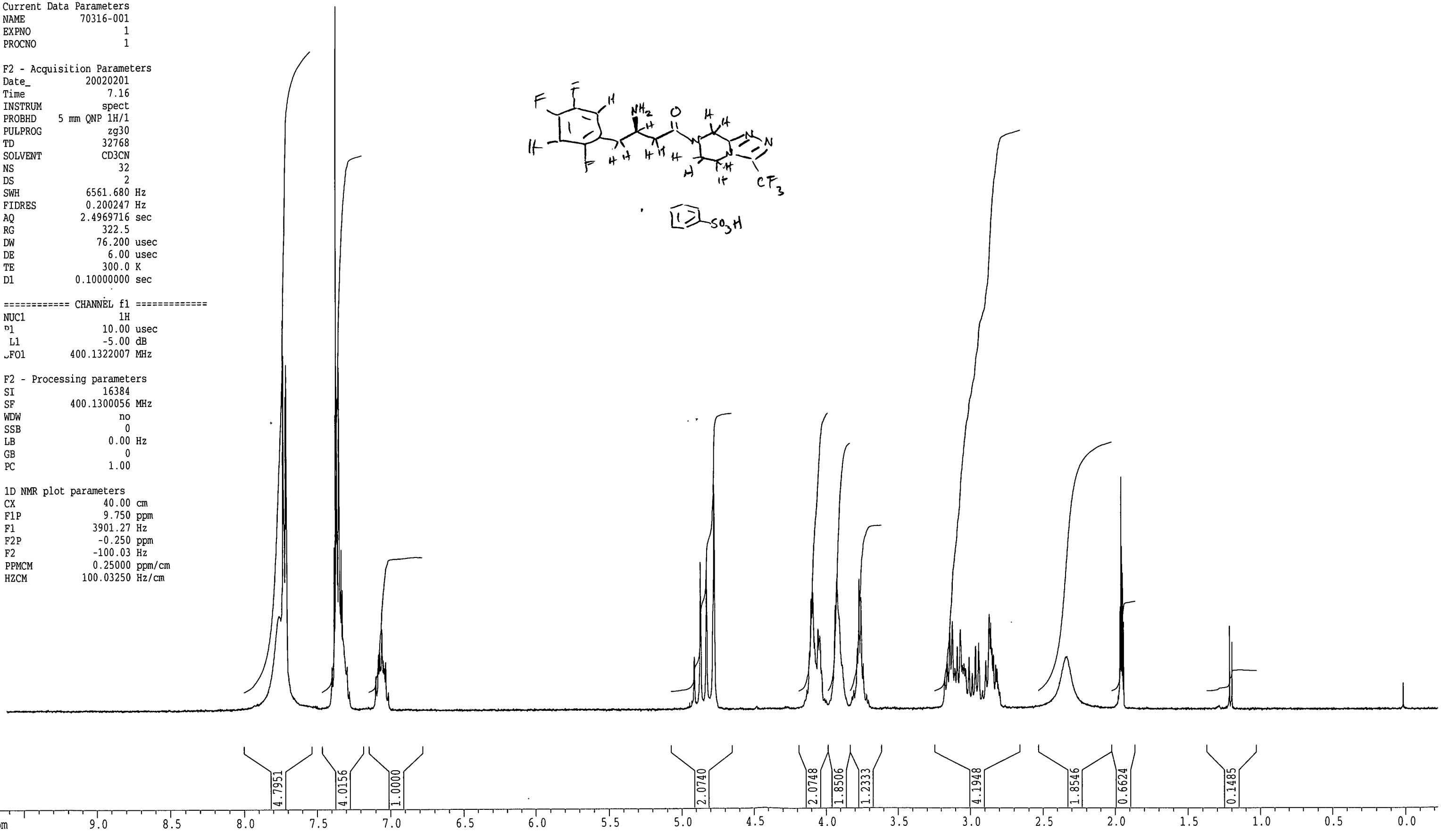
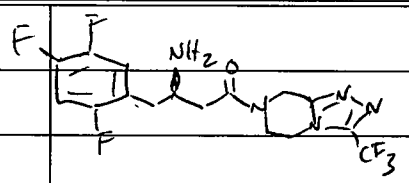




L-Tartaric acid, IPA-H_2O → L224715-L Tartrate salt

Reagents:	FW	Amt	mmol	eq
L224715	407	150 mg	0.369	1.0
L-Tartaric acid ~~@ 75 mg/ml sln with H_2O~~	150	553 mg	0.740	0.367	1.0
IPA		7.5 ml		

Procedure: Added L Tartaric acid soln to soln of 715 @ RT solids quickly formed. heated to 60°C for O/N ~~28 Jan 2002~~ 29 Jan 2002. solids now stirred easily cooled to RT. Filtered - washed w/ IPA. dried in oven @ 40°C w/ N_2 sweep/vac. 30 Jan 2002 isolated 177 mg of white solids 86% yield. gave sample to PR&D & Phys. Meas.

30 Jan 2002

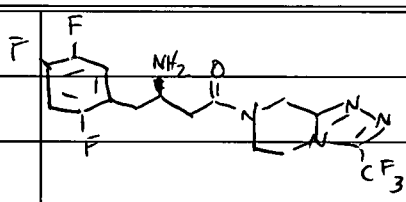
Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

Date



$PhSO_3H$ / IPAC, 60°C → L224715 - Besylate

Reagents:		FW	Amt	mmol	eq
L224715		407	150 g	0.369	1.0
$PhSO_3H$	~~75~~ 79 mg/mL soln in IPAC	158	582 g, 0.74 mL	0.369	1.0
IPAC			7.5 mL		

Procedure: followed earlier procedure. Added IPAC soln of $PhSO_3H$ to soln of 715 in IPAC. heated to 60°C O/N. ~~RBL~~ 28 Jan 2002

29 Jan 2002. cooled to RT filtered washed w/ IPAC. dried in vac oven @ 40°C O/N. ~~RBL~~ 29 Jan 2002

30 Jan 2002 isolated. 185 g of white solids. 89% yield

samples given to Phys. Mers & PR&D ~~RBL~~ 30 Jan 2002

Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

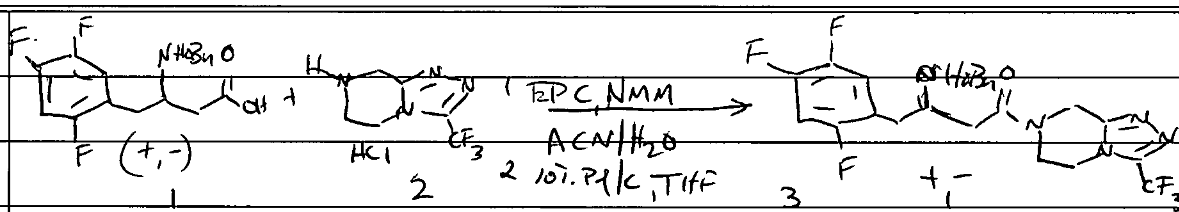
Date

Book 70316 Page 7 Project No. ______ Project Page ______

Investigator ______ Date 28 Jan 2002

Subject ______ Restricted Confidential limited access

Filed in Book Number/Title ______



Reagents:		Fw	Amt	mmol	eq
BnO Aminoacid (+,-)	1 72324-648	339	~530mg	1.56	1.0
Heterocycle-HCl	72176-058 2	228	535mg	2.35	1.5
EDC		191.71	450mg	2.34	1.5
N-methylmorpholine	0.920g/ml	101.15	158mg 172ul	1.56	1.0
ACN			5ml		
H_2O			0.5ml		

Procedure: Dissolved Aminoacid in ACN/H_2O Added Heterocycle EDC, NMM @ 0°C. After 1hr layers had separated slowly ~10% conv was observed added 2.5ml of ACN to get layers to mix better. Stirred O/N. ~~[illegible]~~ 28 Jan 2002

29 Jan 2002 Rxn >95% complete by LC! Added 10ml EtOAc & 5ml H_2O - layers cut slowly! Washed with 5% $NaHCO_3$. Concentrated EtOAc to yellow oil. Added IPAc & reconcentrated. Then Added 2x5ml ACN & reconcentrated. ^{1}H-NMR is consistent with the desired product only major impurity seems to be ACN. Reconcentrated to yellow oil. ~700mg of yellow viscous oil. Re-dissolved in 9ml THF & submitted to Hydrog lab. 40 PSI H_2 150mg 10% Pd/C.

31 Jan 2002. only ~10% conversion of hydrog. Filtered washed w/ meat Reconcentrated.

[signature] 31 Jan 2002

Countersigned by ______

Date ______

MERCK & CO., INC./MRL 6497654 (01/00)

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

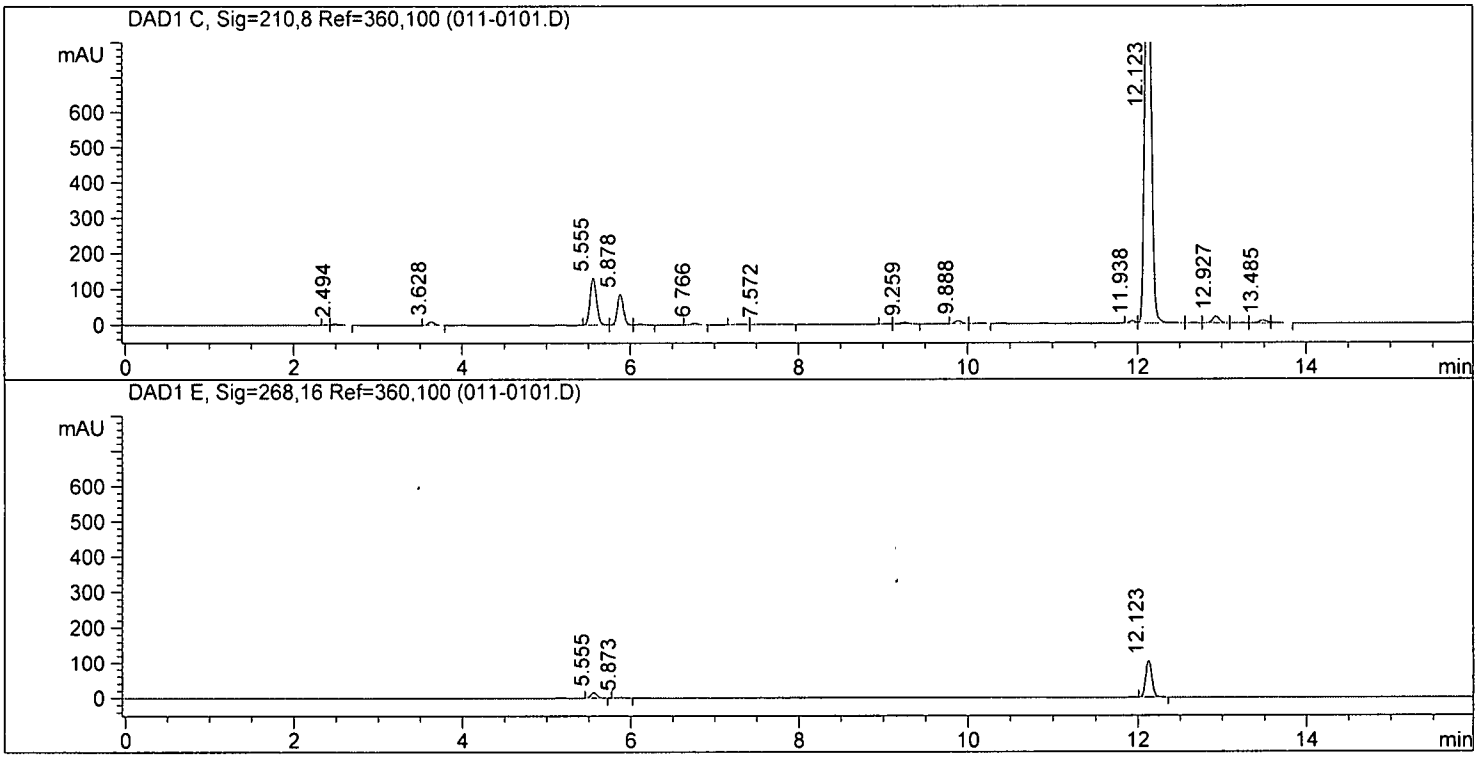
Date

Data file :C:\HPCHEM\HPLC0157\DATA\011-0101.D Sample Name: 70316-007

hydrog in THF o/n ->

==========

Injection Date : 01/31/2002 11:59:11 AM Seq Line : 1
Sample Name : 70316-007 Vial No : 11
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.39	VV	0.055	1.47	5.148	0.06	0.000000	
2	2.49	VB	0.087	4.29	26.119	0.32	0.000000	
3	3.63	BB	0.086	9.96	54.936	0.68	0.000000	
4	5.56	BV	0.085	132.18	714.237	8.82	0.186488	L-224,715
5	5.88	VV	0.078	86.40	430.913	5.32	0.000000	
6	6.12	VB	0.088	2.56	14.993	0.19	0.000000	
7	6.77	BB	0.087	5.01	28.932	0.36	0.000000	
8	7.29	PV	0.115	1.41	12.269	0.15	0.000000	
9	7.57	VB	0.187	1.67	22.570	0.28	0.000000	
10	9.05	BV	0.080	1.04	5.567	0.07	0.000000	
11	9.26	VP	0.099	4.70	32.631	0.40	0.000000	
12	9.89	VV	0.084	8.78	46.677	0.58	0.000000	
13	10.16	VV	0.099	2.61	18.107	0.22	0.000000	
14	11.94	VV	0.078	7.22	36.003	0.44	0.000000	
15	12.12	VB	0.080	1.24e3	6415.681	79.21	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	12.66	BV	0.113	2.10	16.639	0.21	0.000000	
17	12.93	VV	0.095	19.38	121.148	1.50	0.000000	
18	13.25	VV	0.143	1.45	15.458	0.19	0.000000	
19	13.49	VV	0.112	8.09	59.698	0.74	0.000000	
20	13.63	VB	0.087	3.78	21.794	0.27	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.56	BB	0.085	15.15	81.270	13.04	0.186488	L-224,715
2	5.87	BP	0.083	1.40	7.551	1.21	0.000000	
3	12.12	VB	0.079	104.85	534.267	85.75	0.000000	

==========

*** End of Report ***

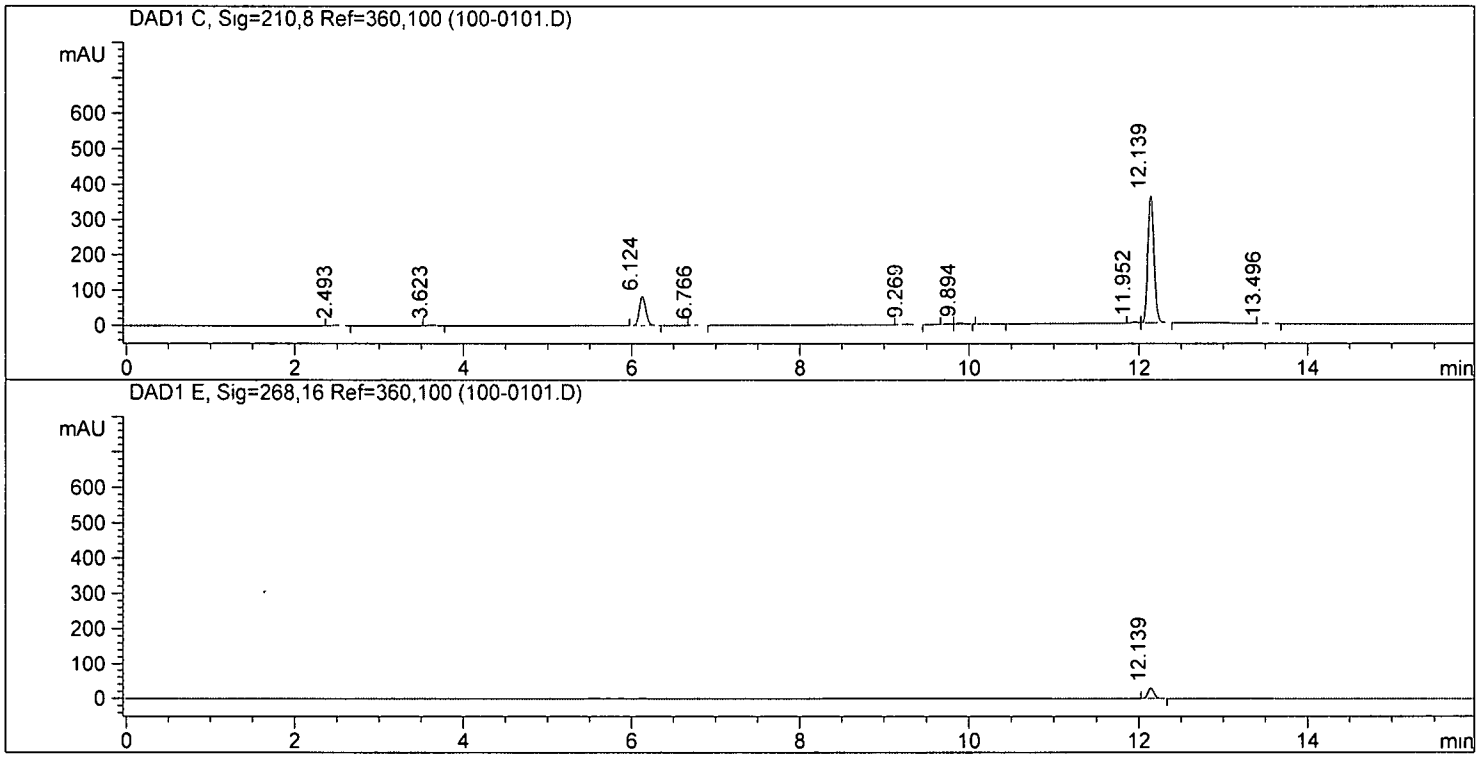
Data file :C:\HPCHEM\HPLC0157\DATA\100-0101.D Sample Name: 70316-007

EtOac after bicarb wash ->

==========

Injection Date : 01/29/2002 11:16:54 AM Seq Line : 1
Sample Name : 70316-007 Vial No : 100
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.49	BP	0.089	1.98	12.403	0.52	0.000000	
2	3.62	BB	0.086	2.33	12.728	0.53	0.000000	
3	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
4	6.12	VB	0.083	82.85	447.725	18.62	0.000000	
5	6.77	PB	0.081	1.12	5.860	0.24	0.000000	
6	9.27	BP	0.092	2.15	13.601	0.57	0.000000	
7	9.76	BV	0.086	1.59	9.015	0.37	0.000000	
8	9.89	VB	0.094	3.32	20.423	0.85	0.000000	
9	10.18	BB	0.112	1.00	7.719	0.32	0.000000	
10	11.95	PV	0.076	3.46	16.780	0.70	0.000000	
11	12.14	VB	0.080	361.39	1850.438	76.95	0.000000	
12	13.50	PP	0.087	1.40	7.989	0.33	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	12.14	VB	0.080	29.41	150.539	100.00	0.000000	

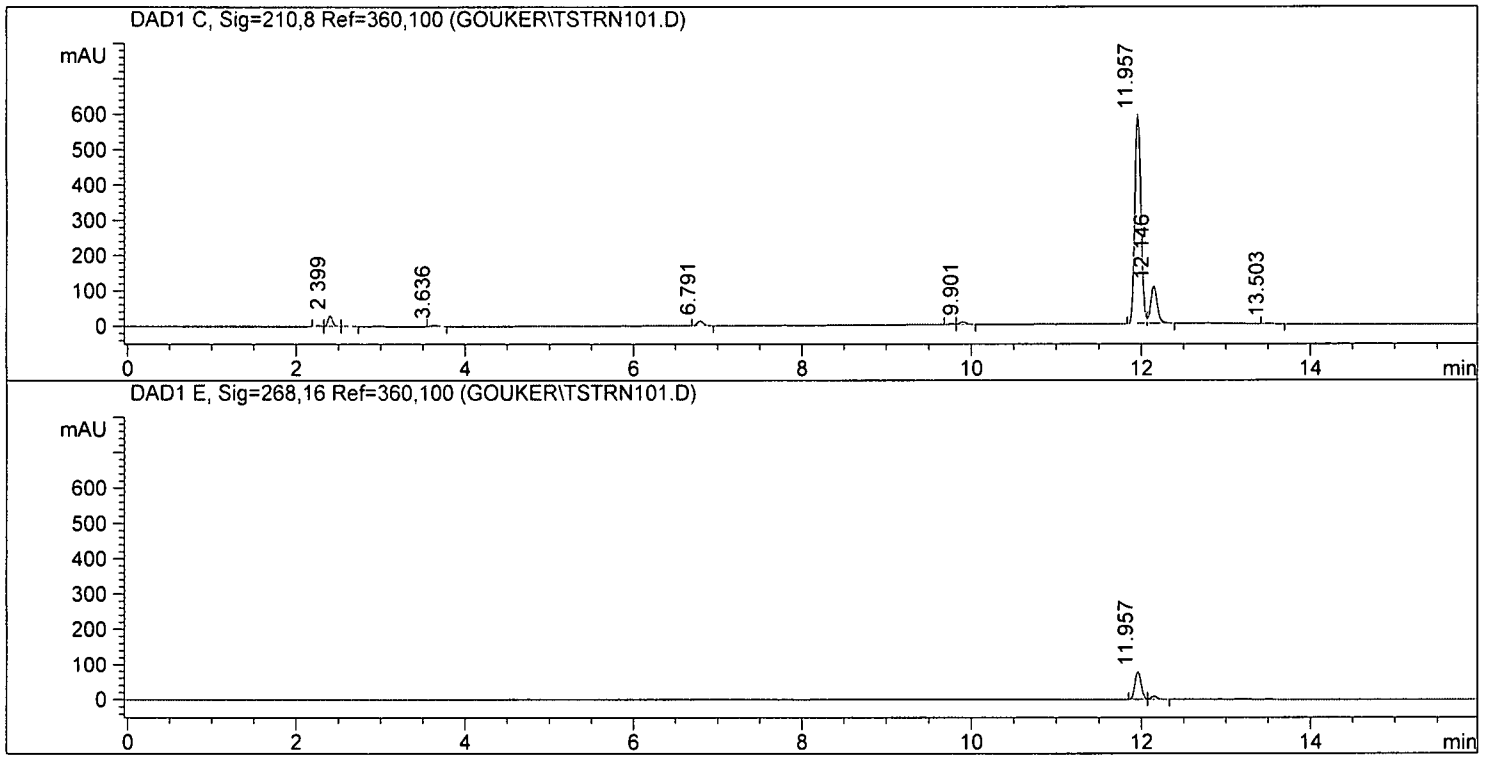
*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\GOUKER\TSTRN101.D Sample Name: 70316-007

Racemic edc coupling after 0.75 h ->

==========

Injection Date : 01/28/2002 3:23:34 PM Seq Line : 1
Sample Name : 70316-007 Vial No : 95
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.26	BV	0.060	2.51	9.850	0.26	0.000000	
2	2.40	VV	0.057	29.45	108.979	2.84	0.000000	
3	2.59	VB	0.084	1.21	6.453	0.17	0.000000	
4	3.64	BB	0.077	3.72	18.923	0.49	0.000000	
5	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
6	6.79	BB	0.080	13.41	69.059	1.80	0.000000	
7	9.77	BV	0.075	2.94	13.922	0.36	0.000000	
8	9.90	VP	0.085	7.51	40.813	1.06	0.000000	
9	11.96	PV	0.079	590.22	2989.865	77.92	0.000000	
10	12.15	VB	0.082	106.45	565.568	14.74	0.000000	
11	13.50	PP	0.084	2.57	13.683	0.36	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\GOUKER\TSTRN101.D Sample Name: 70316-007
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

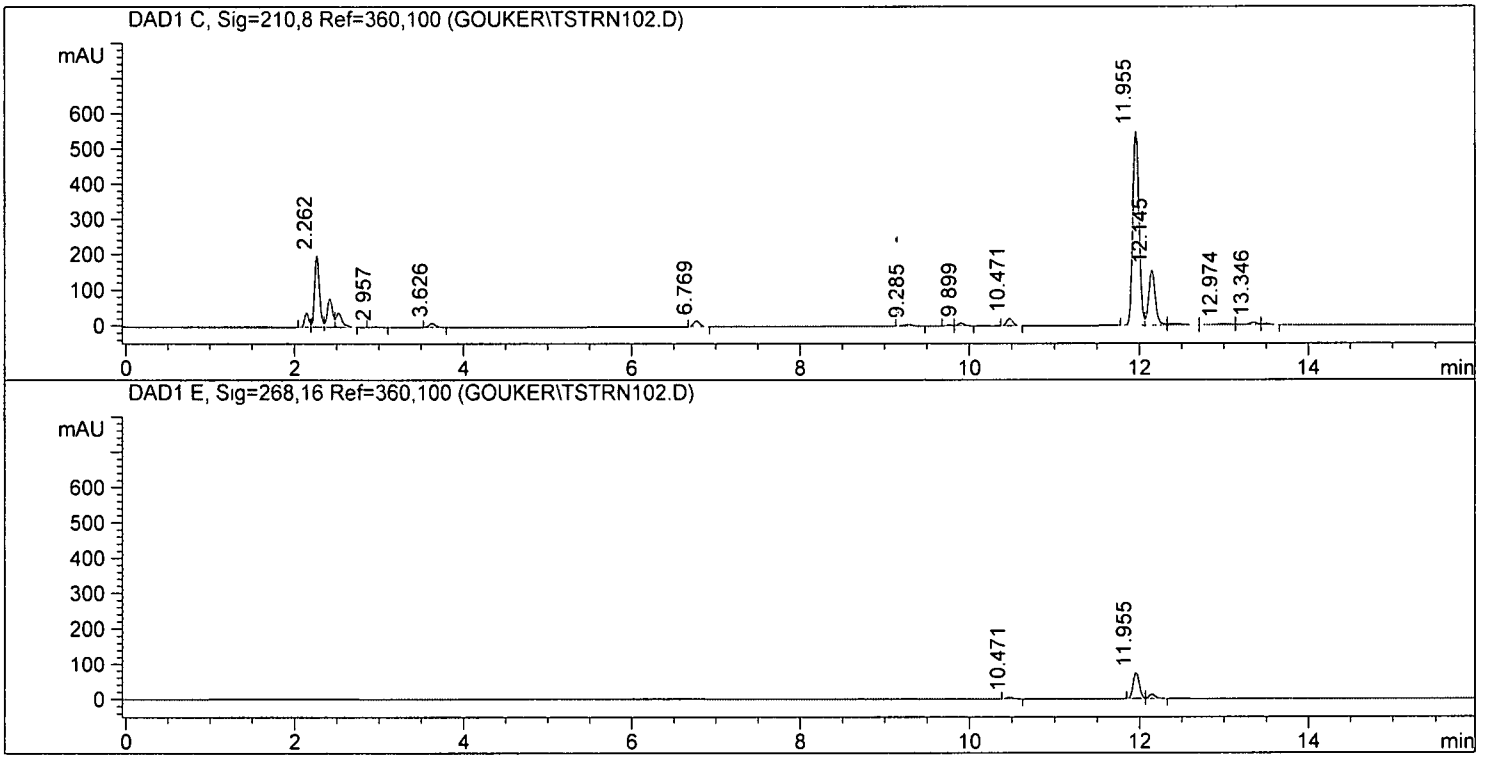
Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	11.96	BV	0.079	78.64	397.585	89.38	0.000000	
3	12.15	VB	0.083	8.70	47.250	10.62	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\GOUKER\TSTRN102.D Sample Name: 70316-007

Racemic edc coupling after 1h both layers ->

```
==========================================================================
Injection Date : 01/28/2002  3:42:04 PM        Seq Line  : 2
Sample Name    : 70316-007                     Vial No   : 96
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==========================================================================
                Customized Report:karlo
==========================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.14	BV	0.054	41.03	140.499	2.48	0.000000	
2	2.26	VV	0.062	201.33	799.254	14.13	0.000000	
3	2.42	VV	0.066	80.49	344.952	6.10	0.000000	
4	2.52	VB	0.074	40.22	206.023	3.64	0.000000	
5	2.96	BB	0.080	1.15	6.088	0.11	0.000000	
6	3.63	BB	0.084	11.03	60.920	1.08	0.000000	
7	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
8	6.77	BB	0.080	16.60	84.964	1.50	0.000000	
9	9.28	BB	0.098	4.79	33.547	0.59	0.000000	
10	9.76	BV	0.073	3.10	14.652	0.26	0.000000	
11	9.90	VP	0.082	7.72	41.214	0.73	0.000000	
12	10.47	PB	0.081	20.29	102.279	1.81	0.000000	
13	11.95	BV	0.080	549.16	2805.776	49.60	0.000000	
14	12.14	VV	0.083	154.34	830.613	14.68	0.000000	
15	12.42	VV	0.205	3.96	53.222	0.94	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	12.97	VV	0.237	3.06	49.058	0.87	0.000000	
17	13.35	VV	0.117	7.03	58.780	1.04	0.000000	
18	13.50	VB	0.098	3.78	24.545	0.43	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	10.47	BP	0.080	4.58	22.887	4.99	0.000000	
3	11.95	BV	0.079	72.89	370.146	80.76	0.000000	
4	12.14	VB	0.081	12.39	65.304	14.25	0.000000	

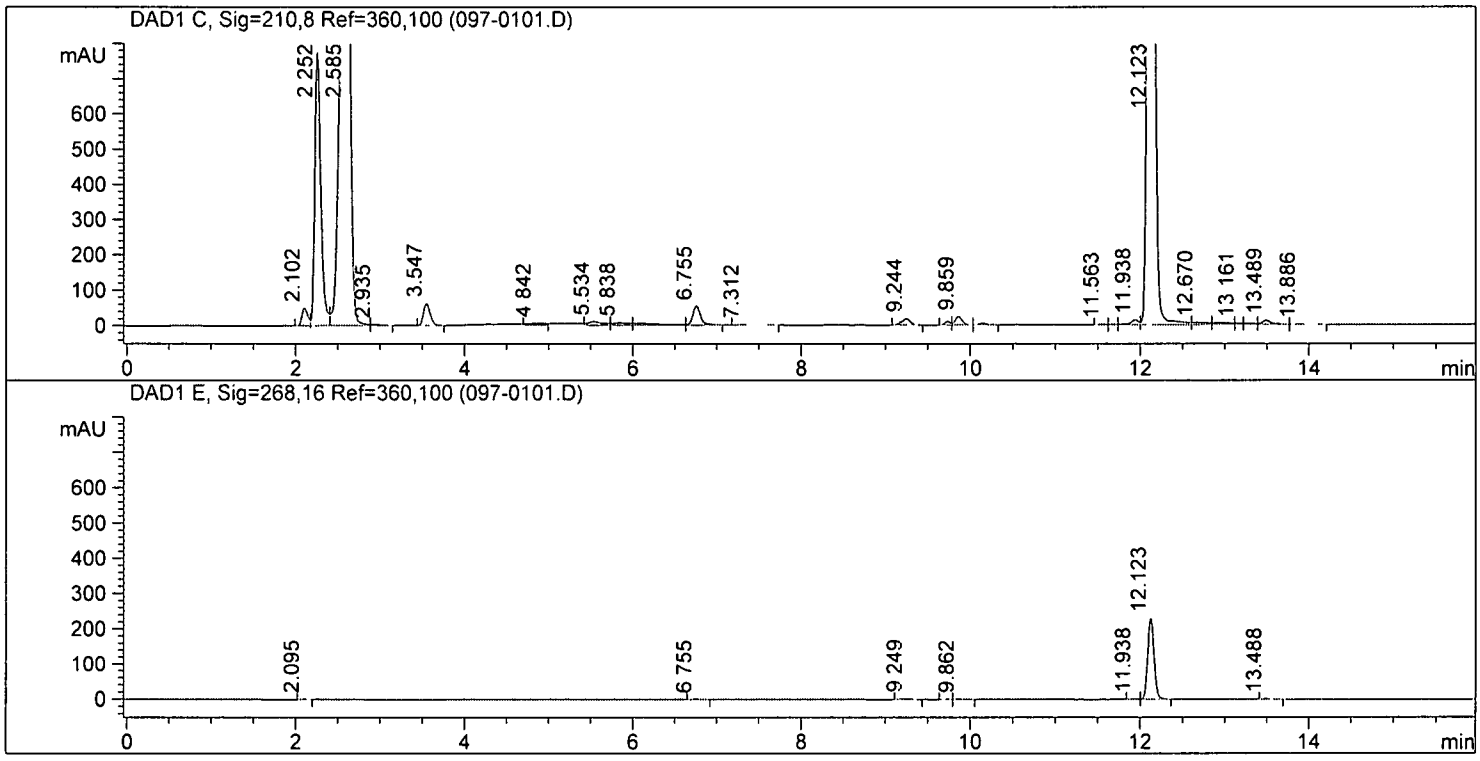
*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\097-0101.D Sample Name: 70316-007

Racemic edc coupling after o/n at rt ->

==========

Injection Date : 01/29/2002 7:10:03 AM Seq Line : 1
Sample Name : 70316-007 Vial No : 97
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.10	BV	0.075	49.73	241.802	0.76	0.000000	
2	2.25	VV	0.073	775.68	3808.313	11.95	0.000000	
3	2.58	VV	0.114	1.83e3	1.346e4	42.21	0.000000	
4	2.93	VB	0.102	3.61	25.874	0.08	0.000000	
5	3.55	PB	0.087	62.21	348.626	1.09	0.000000	
6	4.84	BV	0.210	5.43	86.628	0.27	0.000000	
7	5.53	BV	0.173	10.55	131.221	0.41	0.031636	L-224,715
8	5.84	VV	0.170	7.22	88.821	0.28	0.000000	
9	6.09	VV	0.313	5.50	134.085	0.42	0.000000	
10	6.75	VB	0.100	54.01	354.083	1.11	0.000000	
11	7.31	BB	0.157	1.64	19.241	0.06	0.000000	
12	9.24	BB	0.100	18.44	130.072	0.41	0.000000	
13	9.73	PV	0.076	9.47	45.632	0.14	0.000000	
14	9.86	VB	0.089	23.65	136.060	0.43	0.000000	
15	10.14	BB	0.095	4.94	30.889	0.10	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\097-0101.D Sample Name: 70316-007

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	11.56	VV	0.106	1.36	9.287	0.03	0.000000	
17	11.68	VV	0.087	1.40	8.302	0.03	0.000000	
18	11.94	VV	0.099	13.88	93.935	0.29	0.000000	
19	12.12	VV	0.095	2.09e3	1.241e4	38.92	0.000000	
20	12.67	VV	0.164	6.09	77.148	0.24	0.000000	
21	12.92	VV	0.185	5.36	76.840	0.24	0.000000	
22	13.16	VV	0.084	3.50	20.303	0.06	0.000000	
23	13.30	VV	0.130	3.77	34.156	0.11	0.000000	
24	13.49	VB	0.115	12.24	97.746	0.31	0.000000	
25	13.89	BB	0.154	1.51	17.080	0.05	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.10	PV	0.072	1.16	5.753	0.46	0.000000	
2	0.00		0.000	0.00	0.000	0.00	0.031636	L-224,715
3	6.76	PB	0.099	1.07	6.874	0.54	0.000000	
4	9.25	BB	0.103	2.59	17.949	1.42	0.000000	
5	9.73	PV	0.078	1.01	5.015	0.40	0.000000	
6	9.86	VB	0.100	1.08	7.345	0.58	0.000000	
7	11.94	BV	0.080	1.43	7.407	0.59	0.000000	
8	12.12	VB	0.081	230.62	1202.830	95.36	0.000000	
9	13.49	VB	0.104	1.13	8.155	0.65	0.000000	

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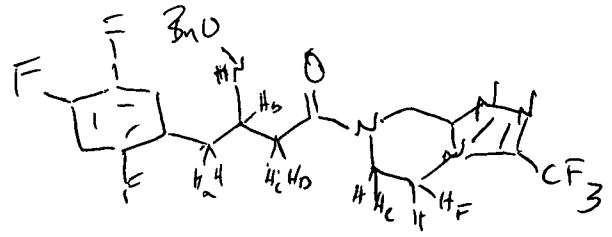
*** End of Report ***

crude coupling product
nmr400b h-1



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Current Data Parameters
NAME          70316-007
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
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Time              14.07
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG           zg30
TD               32768
SOLVENT          CD3CN
NS                  32
DS                   2
SWH            6578.947 Hz
FIDRES         0.200774 Hz
AQ             2.4904180 sec
RG                  57
DW                76.000 usec
DE                 6.00 usec
TE                300.0 K
D1           0.10000000 sec

============ CHANNEL f1 =============
NUC1                1H
P1                10.50 usec
PL1                6.00 dB
SFO1        399.8724592 MHz

F2 - Processing parameters
SI                 16384
SF          399.8700208 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 40.00 cm
F1P                9.750 ppm
F1              3898.73 Hz
F2P                -0.250 ppm
F2                 -99.97 Hz
PPMCM           0.25000 ppm/cm
HZCM           99.96751 Hz/cm
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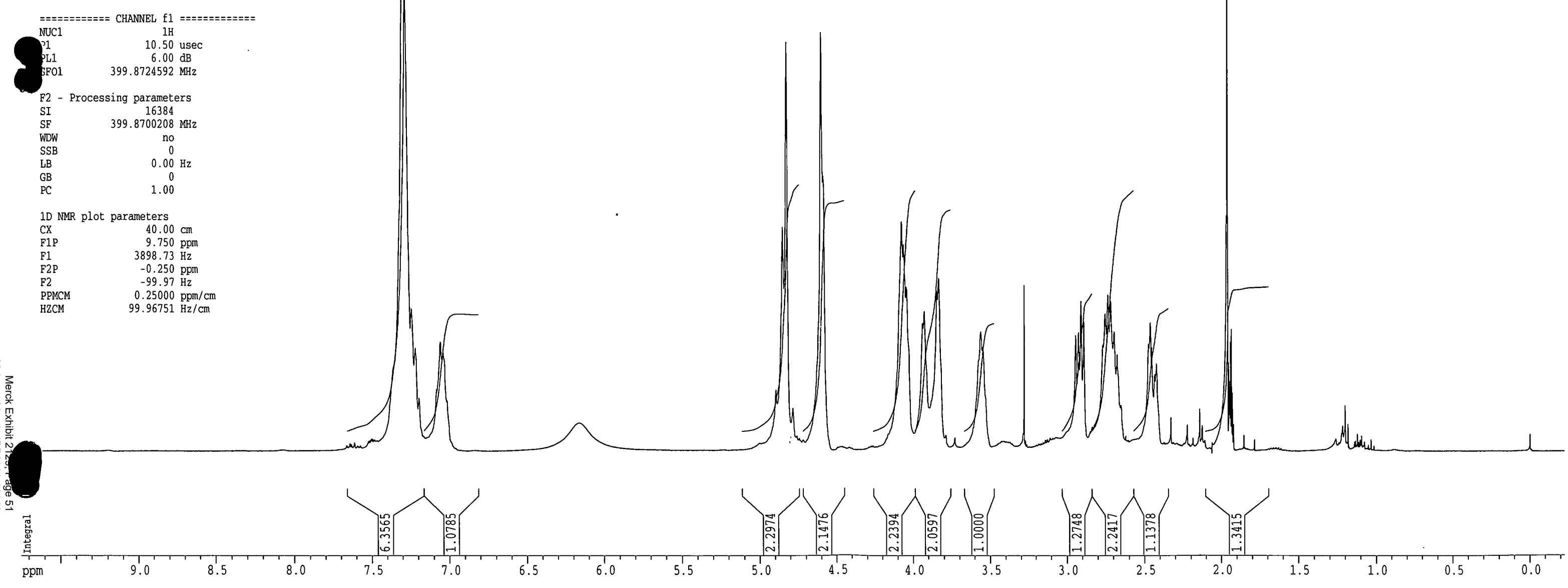


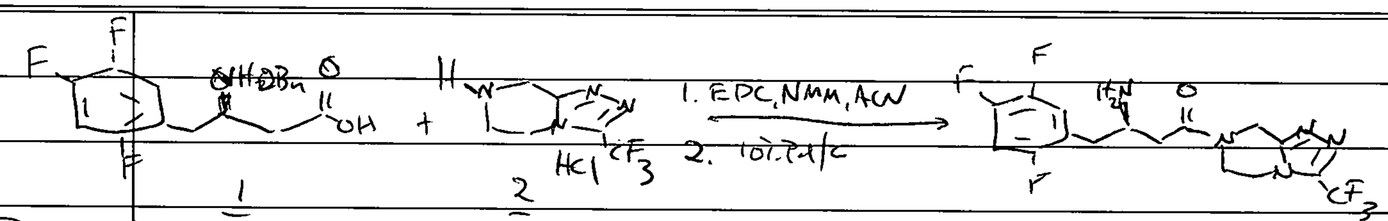
Book 70316 Page 9 Project No. Project Page

Investigator Date 30 Jan 2002

Subject Coupling w/ 1 & 2

Restricted Confidential limited access

Filed in Book Number/Title



Reagents		FW	Amt	mmol	eq
BuOAmino Acid	72324-52	339	10.0 g	29.5	1.0
Triazole HCl salt	72176-100	228	10.08 g	44.2	1.5
EDC		191.71	8.50 g	44.2	1.5
NMM ← N-methylmorpholine	Aldrich 07946JF 0.920	101.15	2.98 g (3.24 ml)	29.5	1.0
ACN			100 ml		

Dissolved acid in 100 ml ACN. Added Triazole HCl salt. Cooled to 0°C. Added EDC & then N-methyl morpholine immediately. After 4 hrs Rxn is @ >98% conv. Added 60 ml H₂O then 100 ml EtOAc. Cut layers, ~~washed w/~~ pH of Aq was ~4-5 by Paper. Washed w/ ~~sat~~ 5% NaHCO₃ ~~100~~ 60 ml ~~then~~ had to add ~5 ml sat NaCl. Washed 1 x 60 ml 20% NaCl. Concentrated IPAc to Thick oil. HPLC of Aq 1st layer shows No product. ~~[initials]~~ 30 J-2002

31 Jan 2002 - Redissolved in 100 ml MeOH. Submitted For Hydrog 40 PSI, 50°C ~~20 wt%,~~ ~~3.00~~ 0.3 g 10% Pd/C.

1 Feb 2002 - Rxn not complete (10% conv) by LC. Resubmitted to Hydrog w/ 2.7 g additional 10% Pd/C

4 Feb 2002. Assayed soln - no sm by LC. 1 major impurity @ 13 min. Filtered through celite & then assayed organics to contain 10.4 g of product. -over- ~~[initials]~~ 4 Feb 2002

Countersigned by

Date

MERCK & CO., INC./MRL

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

xferred soln to RBF w/ IPAC & concentrated to clear oil. Rediluted to ~~520 ml~~ w/ IPAC. 420 KF = 320 ppm. Filtered into 3 neck RBF to remove fine solids. washed flask w/ 100 ml IPAC. ~~Char~~ Dissolved 4.10g $PhSO_3H$ in ~~45~~ 50 ml IPAC. Heated soln of freebase to 50°C then added $PhSO_3H$ soln dropwise. Temp rose slightly during addn. After 20% of Acid addn seeded w/ 17mg of 70130-379 seed did not dissolve. As addn continued white solids began to form. Addn took 1hr. Aged ~~1hr~~ 10 min then cooled to RT. Filtered & washed w/ 25 ml IPAC & 50 ml Hexanes. Dried w N_2 sweep on frit. isolate 13.26g white solids

Assayed MLs, solids

406g ML's	1.14 mg/g	→	0.461 g 715
13.26g solids	70.9% 715 actual		
	72.0% 715 theoretical for besylate salt		
	98.4 wt% pure.		

n expanded chromatogram shows a few impurities eluting close to 715 including BuOH. ^{1}H-NMR shows more of Rotamer & some IPAC or Hexanes

95% Mass balance on rxn

78% overall yield of 715.

Conclusion: need to lower wt loss in crystallization. yield is pretty good for 4 step process.

[signature] 5Feb2002

sent 3g material MK-Up2 to Des lab 15Feb2002 Bdu L224715-005D001

~~20Feb2002 3.5g sent to Kari Lynn WP L224715-006 For 2 [illegible]~~ 20Feb2002 KB 20Feb2002

Countersigned by

Date

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Feb 6, 2002	021302	70316-009		

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
Karl Hawsen	[ ]RETAIN [ ]RETURN [ ]DISCARD		Karl Hawsen	

COMPLETE STRUCTURE

CHEMICAL NAME

L-224,715
Besylate Salt

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS

DO NOT WRITE BELOW THIS LINE

RESULTS

Ru / Pd

Ru = < 3 ppm

Pd = 6 ppm

Time	RRT	Area%
11.56	0.93	0.15%
11.86	0.95	0.20%
12.23	0.98	0.17%
12.47	1.00	99.06%
17.06	1.37	0.18%
17.83	1.43	0.17%

Total imp = 0.87%

CC Chiral Assay

major enantamer = 99.98%

minor " = 0.02%

PP LAB PROC. #	ANALYST	DATE
	J.O.D.	Feb 21, 2002

new form of base. N

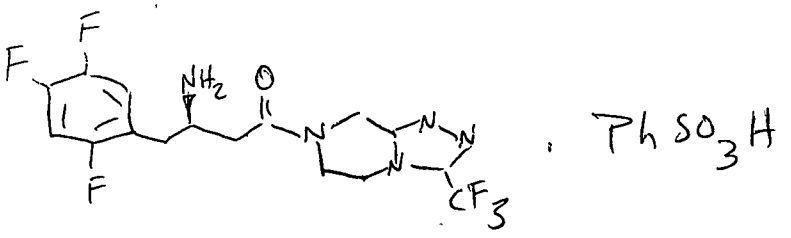
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L-224715-005 D001

MOLECULAR FORMULA:	MOLECULAR WT.:	DATE.	ASSIGNED BY:
$C_{22}H_{21}F_6N_5O_4S$	~~505~~ 565.50	15 Feb 2002	Hansen 2/20/02

CHEMICAL/TRIVIAL NAME: MK-U-2

STRUCTURE:



L224715 Benzensulfonte salt

LABELING INSTRUCTIONS (FOR OUTSIDE DELIVERIES)
- ☐ L NUMBER
- ☒ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER: L224715

Prepared by/Commercial Source:	Notebook Ref./Lot No:
	70316-009

Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC
☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*:
☒ data generated by Analytical Research

99.13 LCAP

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT
☐ YES ☒ NO

LIT. REF./CAS REG. NO

REMARKS

PB ECL-

Storage Conditions: (check one)
- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ –70°C freezer.
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited.

☐ For safety information and special handling precautions, access CHIS.

SEND TO: (NAME, LOCATION, QUANTITY, TEST NO. OR ACRONYM AND INDICATE IF DELIVERED)
Richard Hazell Dev lab

Material is (select one) ___ GMP, X non-GMP and will be used in (select one): ___ GMP/GLP study; ___ non-GMP study.

CC: NAMES AND LOCATIONS: Armstrong, Joe RY800-D371; Hurter Patricia WP78-304; Paluck RY800-B363

Transfer Requested By	Delivery Sheet By:	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By:
Name: Location:	Name Location	Dept. Approval	Quality Approval	

Data file :C:\HPCHEM\HPLC0157\DATA\020-0101.D Sample Name: 70316-009

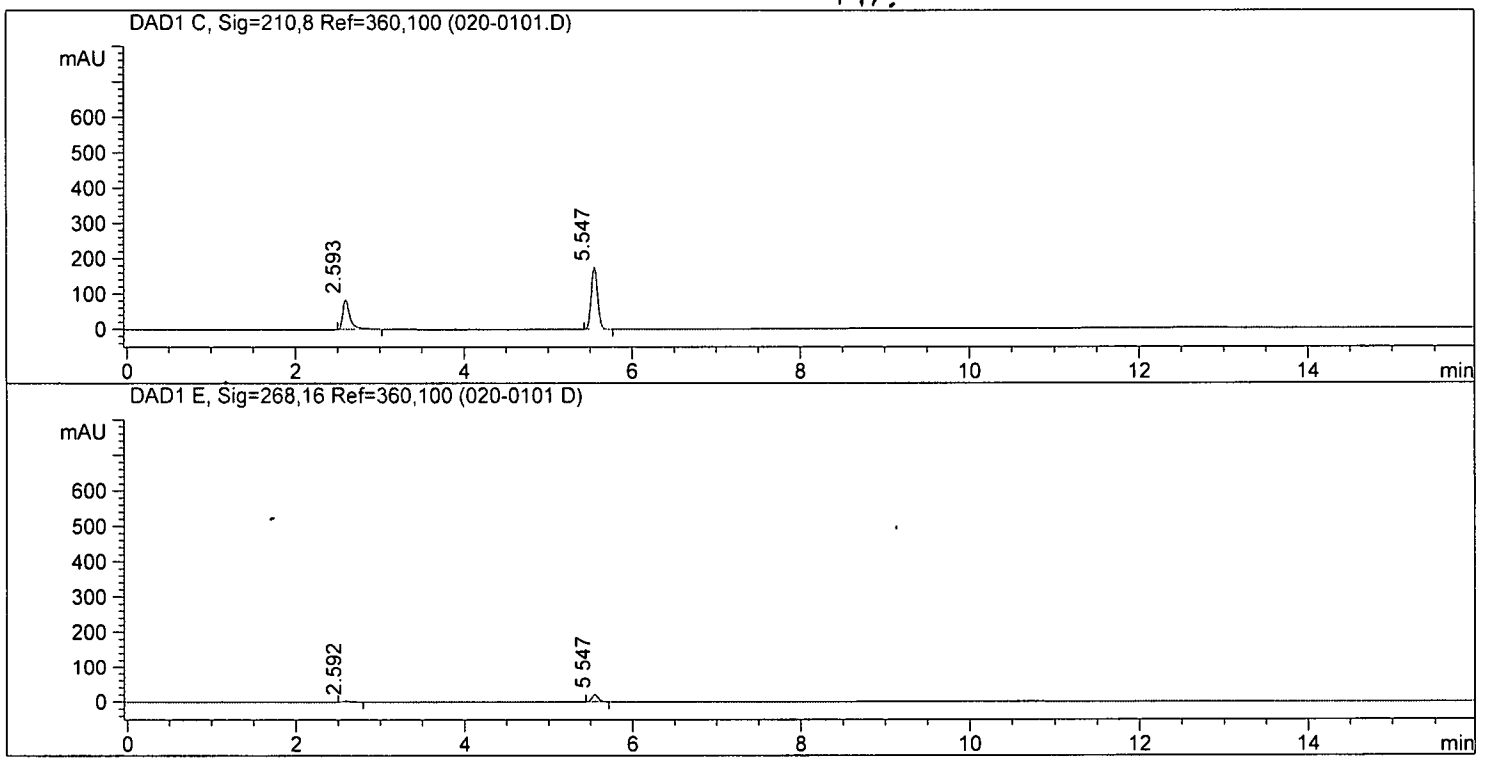
17.2mg/50ml of isolated solids ->

==========

Injection Date : 02/04/2002 2:34:34 PM Seq Line : 1
Sample Name : 70316-009 Vial No : 20
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm

Actual 70.9wt%
Theo 71.6
99%



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.59	PB	0.090	84.41	506.647	35.26	0.000000	
2	5.55	BB	0.084	175.39	930.297	64.74	0.243874	L-224,715

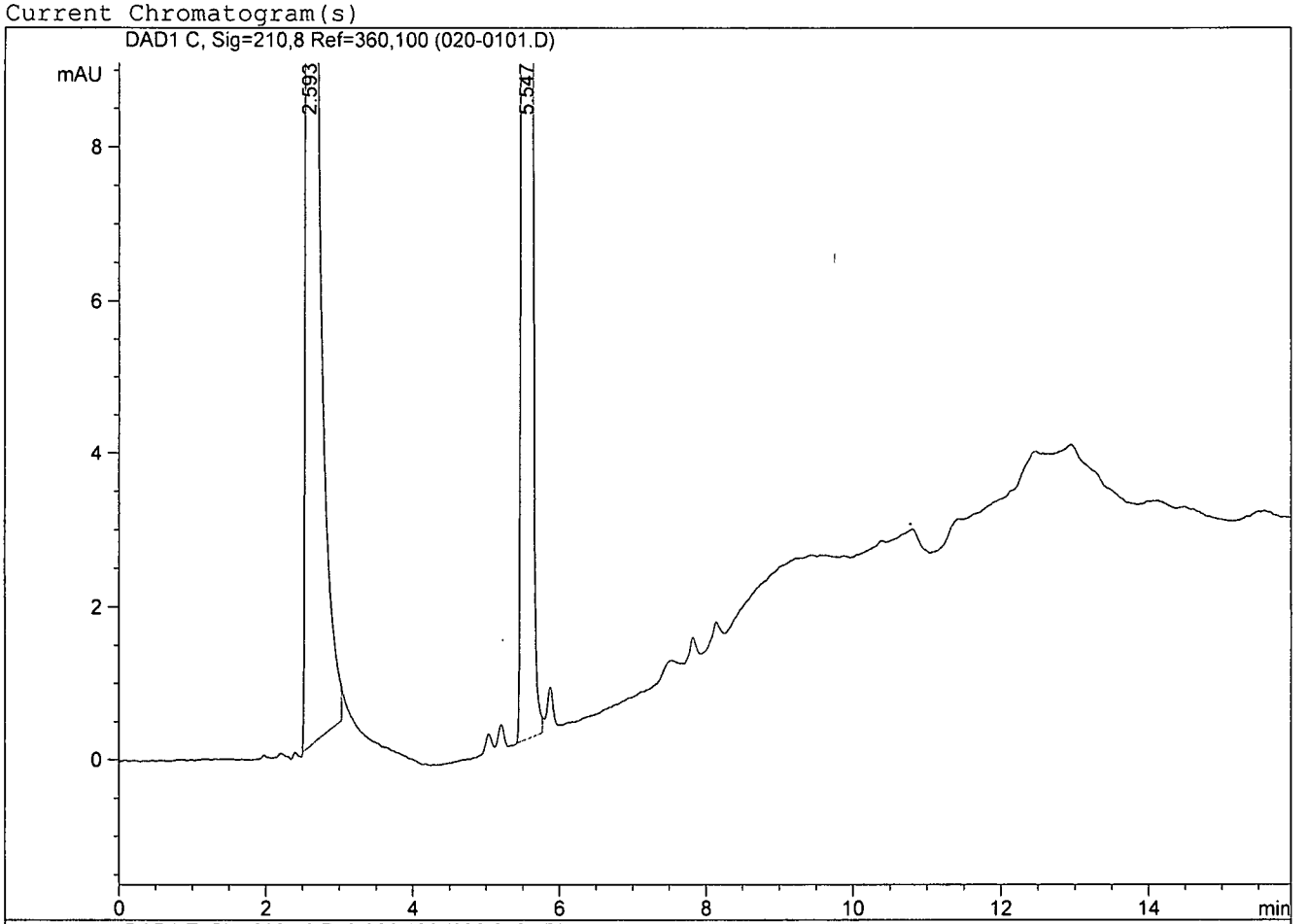
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

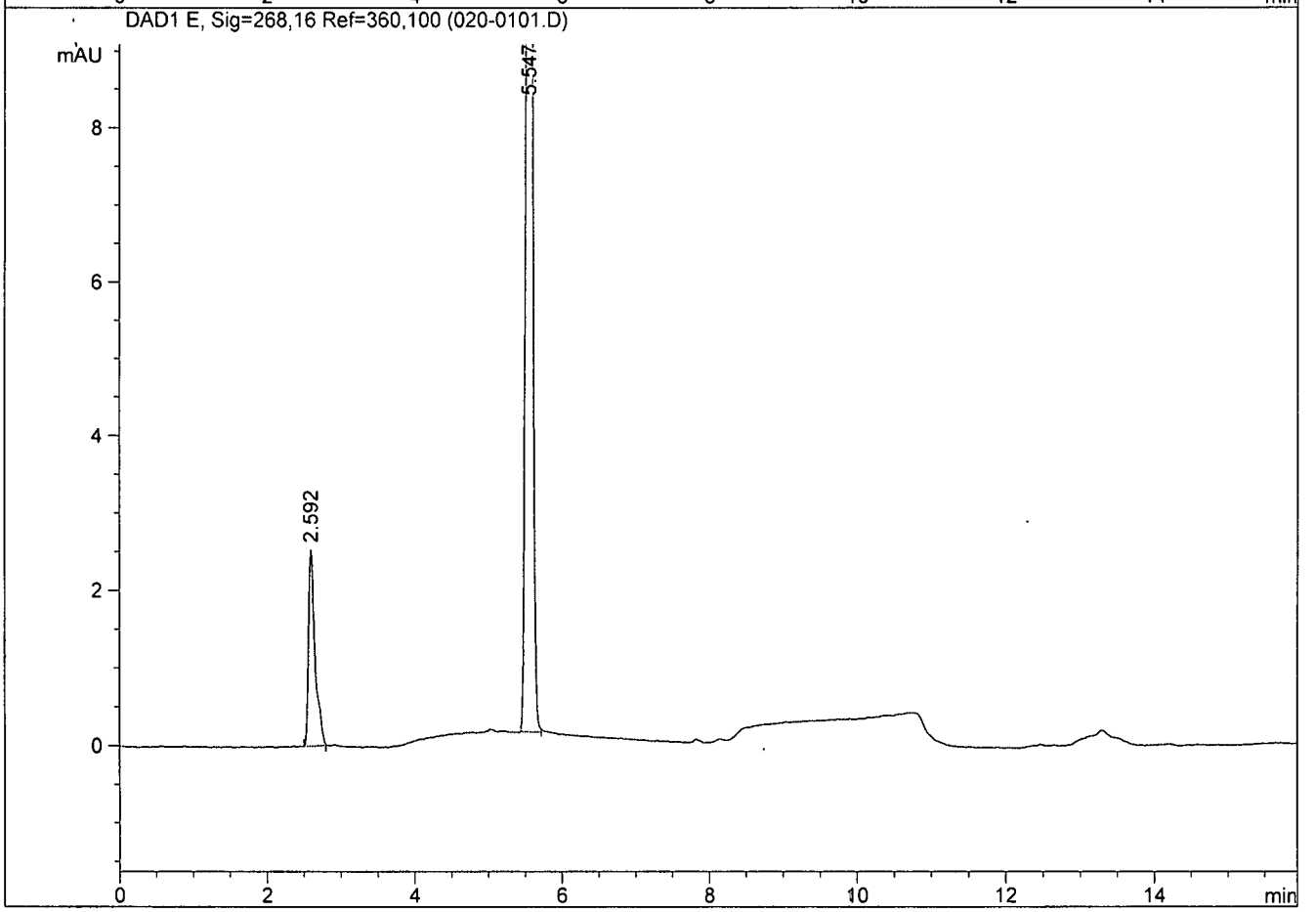
Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.59	PB	0.089	2.54	15.478	12.68	0.000000	
2	5.55	BB	0.084	20.15	106.553	87.32	0.243874	L-224,715

==========

*** End of Report ***

Current Chromatogram(s)





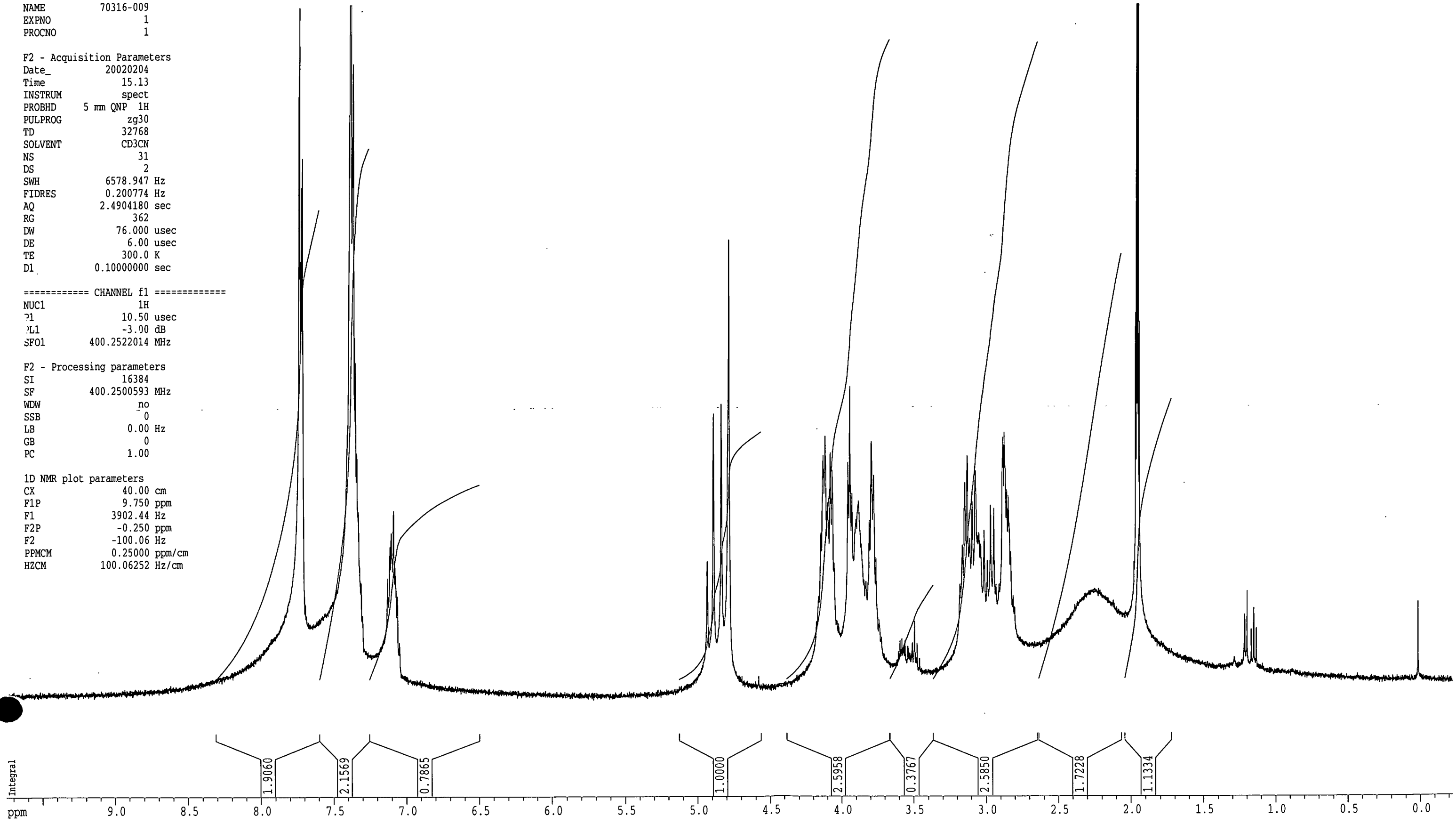
Current Data Parameters
NAME 70316-009
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020204
Time 15.13
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CD3CN
NS 31
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 362
DW 76.000 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.50 usec
PL1 -3.00 dB
SFO1 400.2522014 MHz

F2 - Processing parameters
SI 16384
SF 400.2500593 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3902.44 Hz
F2P -0.250 ppm
F2 -100.06 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.06252 Hz/cm



Data file :C:\HPCHEM\HPLC0157\DATA\006-0201.D Sample Name: 70316-009

coupling 2 h ->

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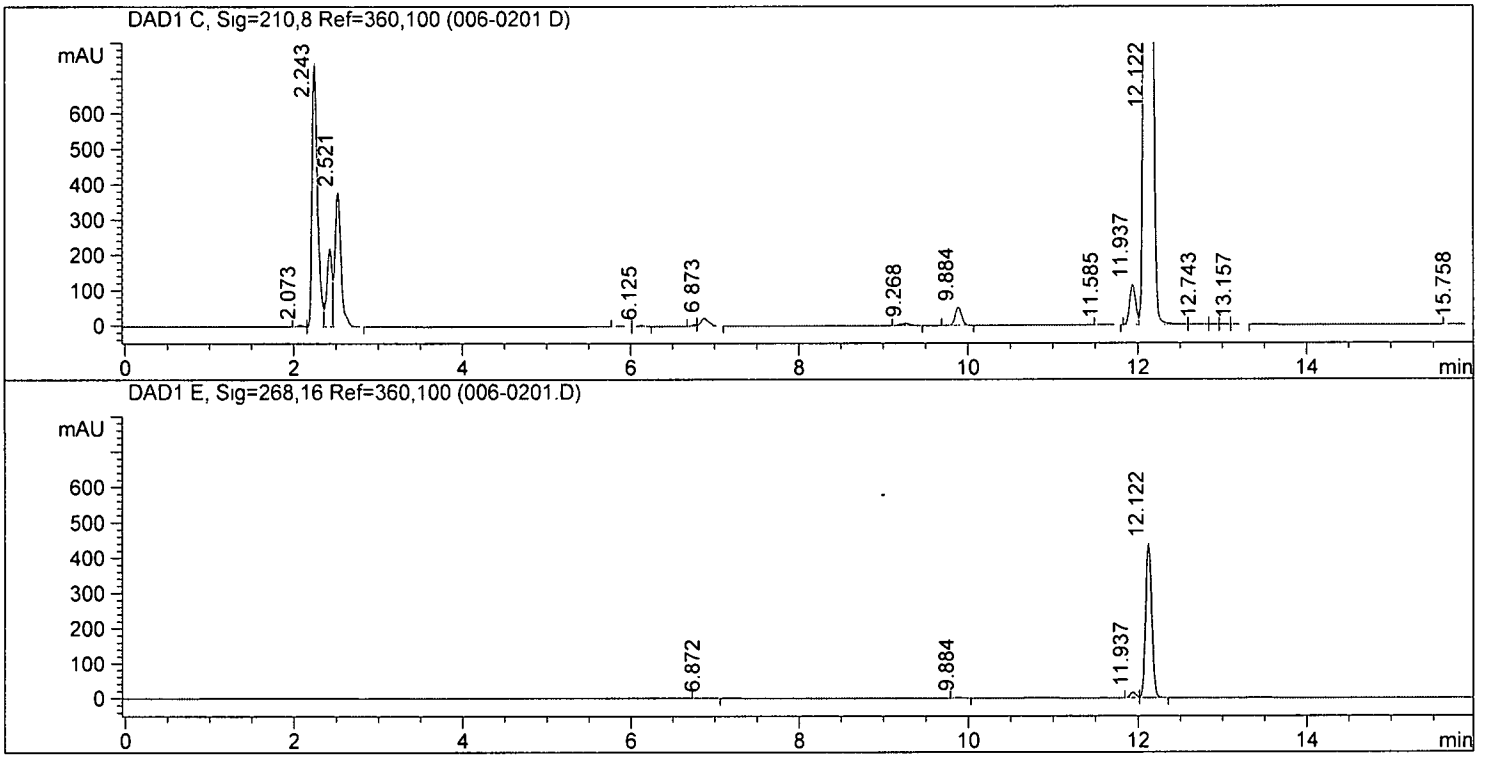
Injection Date : 01/30/2002 12:48:05 PM Seq Line : 2
Sample Name : 70316-009 Vial No : 6
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.07	BV	0.074	4.02	19.822	0.09	0.000000	
2	2.24	VV	0.069	744.07	3375.116	14.55	0.000000	
3	2.42	VV	0.062	223.33	928.086	4.00	0.000000	
4	2.52	VB	0.076	380.22	1897.303	8.18	0.000000	
5	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
6	5.87	PB	0.078	2.53	12.598	0.05	0.000000	
7	6.12	BV	0.086	2.79	15.356	0.07	0.000000	
8	6.77	BV	0.056	4.48	15.980	0.07	0.000000	
9	6.87	VB	0.098	22.52	150.357	0.65	0.000000	
10	9.27	BB	0.101	6.32	45.917	0.20	0.000000	
11	9.88	VP	0.085	51.19	274.379	1.18	0.000000	
12	11.58	BP	0.107	2.31	17.536	0.08	0.000000	
13	11.94	BV	0.078	114.15	564.836	2.43	0.000000	
14	12.12	VB	0.112	2.31e3	1.581e4	68.17	0.000000	
15	12.74	BV	0.148	2.23	25.296	0.11	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	12.90	VV	0.092	1.59	10.111	0.04	0.000000	
17	13.02	VV	0.092	1.52	9.366	0.04	0.000000	
18	13.16	VB	0.104	1.00	7.397	0.03	0.000000	
19	15.76	BBA	0.121	2.03	15.795	0.07	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	6.87	BB	0.105	1.27	9.232	0.40	0.000000	
3	9.88	BP	0.082	2.26	11.950	0.52	0.000000	
4	11.94	PV	0.077	14.89	73.299	3.17	0.000000	
5	12.12	VB	0.081	438.32	2219.411	95.92	0.000000	

*** End of Report ***

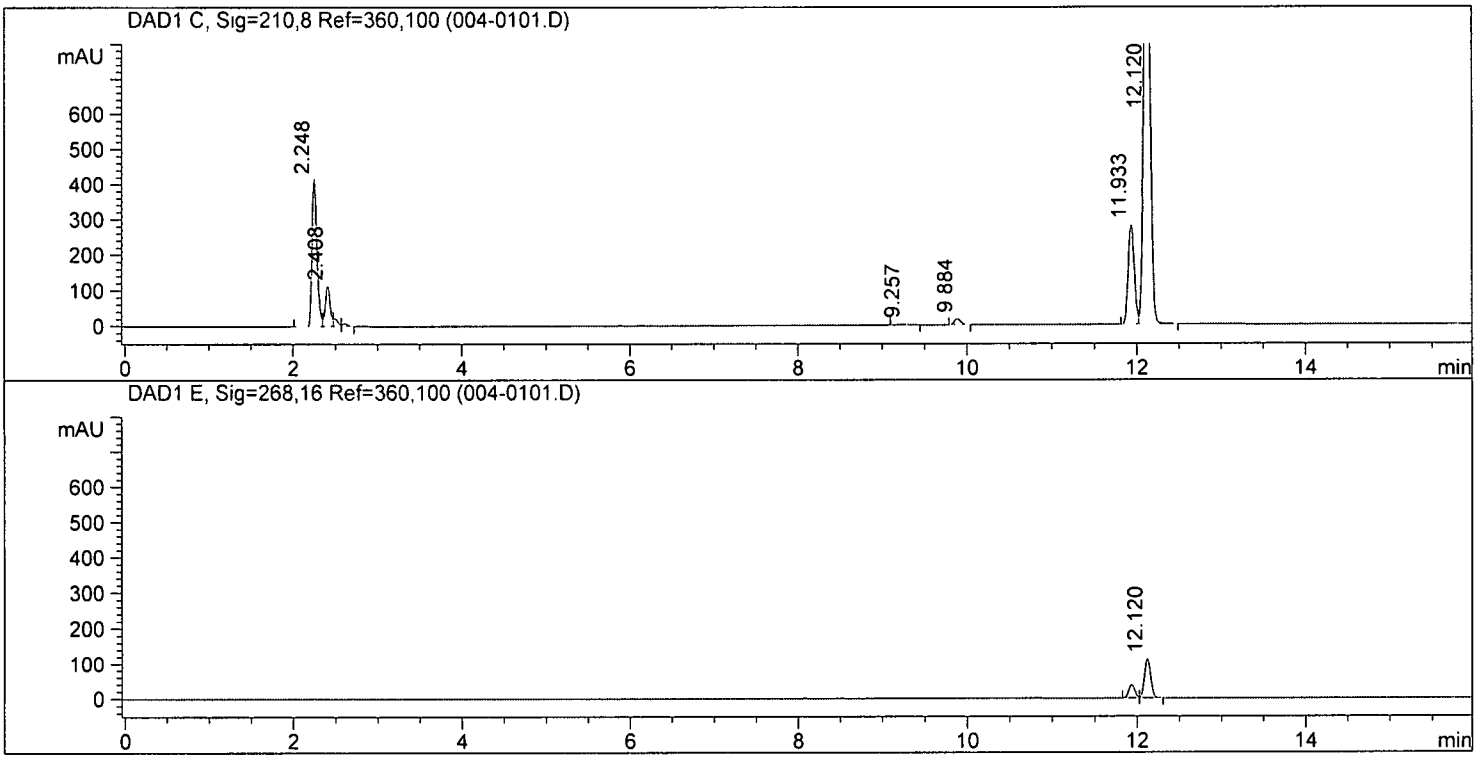
Data file :C:\HPCHEM\HPLC0157\DATA\004-0101.D Sample Name: 70316-009

coupling 15 min at 0C ->

==========

Injection Date : 01/30/2002 10:36:53 AM Seq Line : 1
Sample Name : 70316-009 Vial No : 4
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.25	BV	0.064	413.87	1693.212	16.01	0.000000	
2	2.41	VV	0.060	112.77	447.862	4.24	0.000000	
3	2.49	VV	0.056	21.58	81.628	0.77	0.000000	
4	2.61	VB	0.065	7.43	30.922	0.29	0.000000	
5	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
6	9.26	BP	0.099	2.03	14.543	0.14	0.000000	
7	9.88	BB	0.082	16.50	87.039	0.82	0.000000	
8	11.93	PV	0.079	279.88	1404.360	13.28	0.000000	
9	12.12	VB	0.080	1.32e3	6813.733	64.44	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

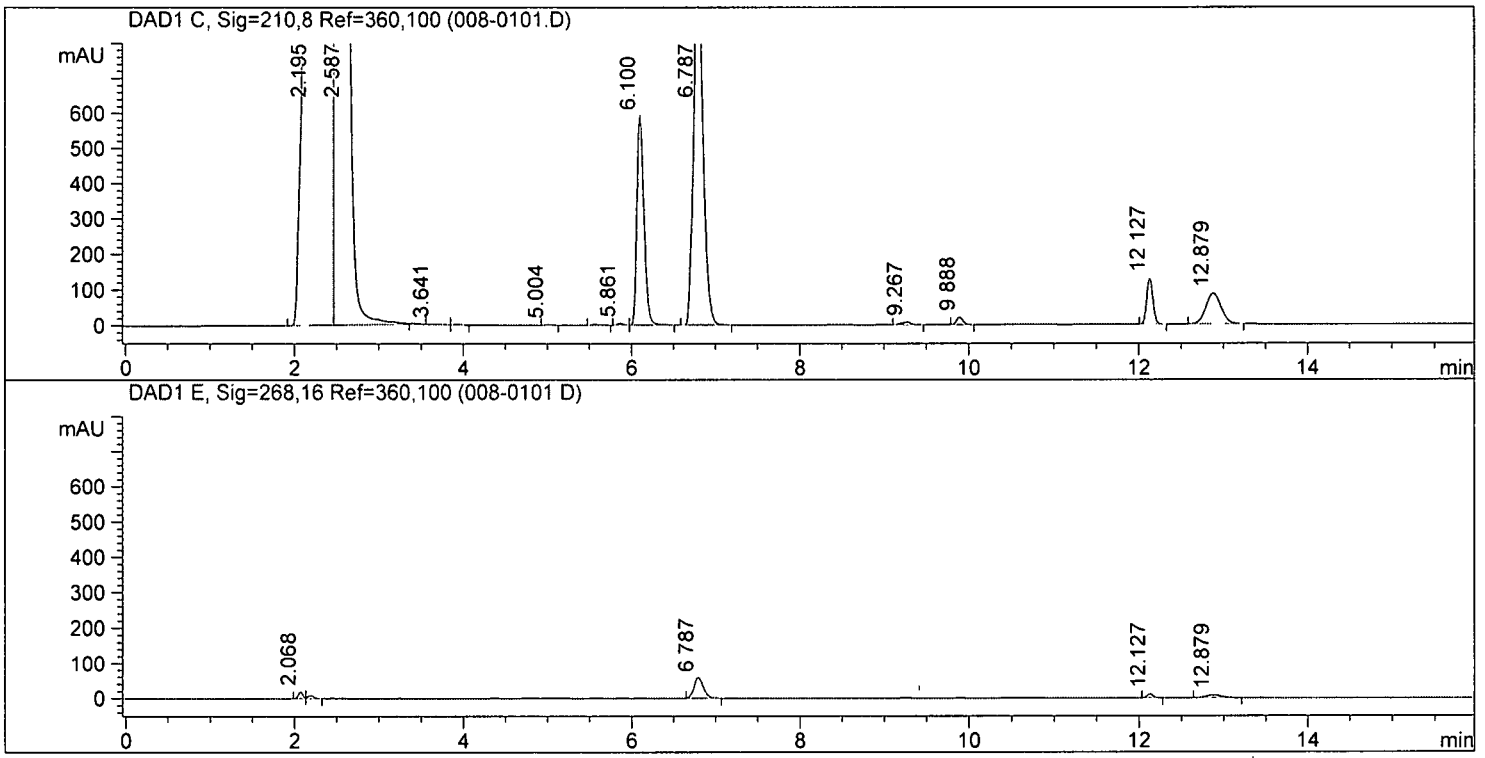
Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	11.93	BV	0.079	36.97	185.434	24.51	0.000000	
3	12.12	VB	0.079	112.87	571.223	75.49	0.000000	

*** End of Report ***

1st aq ->

==========

Injection Date : 01/30/2002 3:49:50 PM Seq Line : 1
Sample Name : 70316-009 Vial No : 8
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.19	PV	0.233	2.67e3	4.513e4	57.21	0.000000	
2	2.59	VB	0.135	2.17e3	2.039e4	25.85	0.000000	
3	3.64	PV	0.122	1.16	10.463	0.01	0.000000	
4	3.94	VP	0.088	1.43	8.153	0.01	0.000000	
5	5.00	BB	0.078	1.71	9.099	0.01	0.000000	
6	5.56	PB	0.090	3.30	20.277	0.03	0.002169	L-224,715
7	5.86	BV	0.084	5.36	29.394	0.04	0.000000	
8	6.10	VB	0.090	592.39	3463.487	4.39	0.000000	
9	6.79	BB	0.120	1.00e3	7894.454	10.01	0.000000	
10	9.27	BB	0.104	8.09	61.239	0.08	0.000000	
11	9.89	BP	0.084	21.32	113.154	0.14	0.000000	
12	12.13	VB	0.081	129.60	658.824	0.84	0.000000	
13	12.88	BB	0.198	86.34	1091.649	1.38	0.000000	

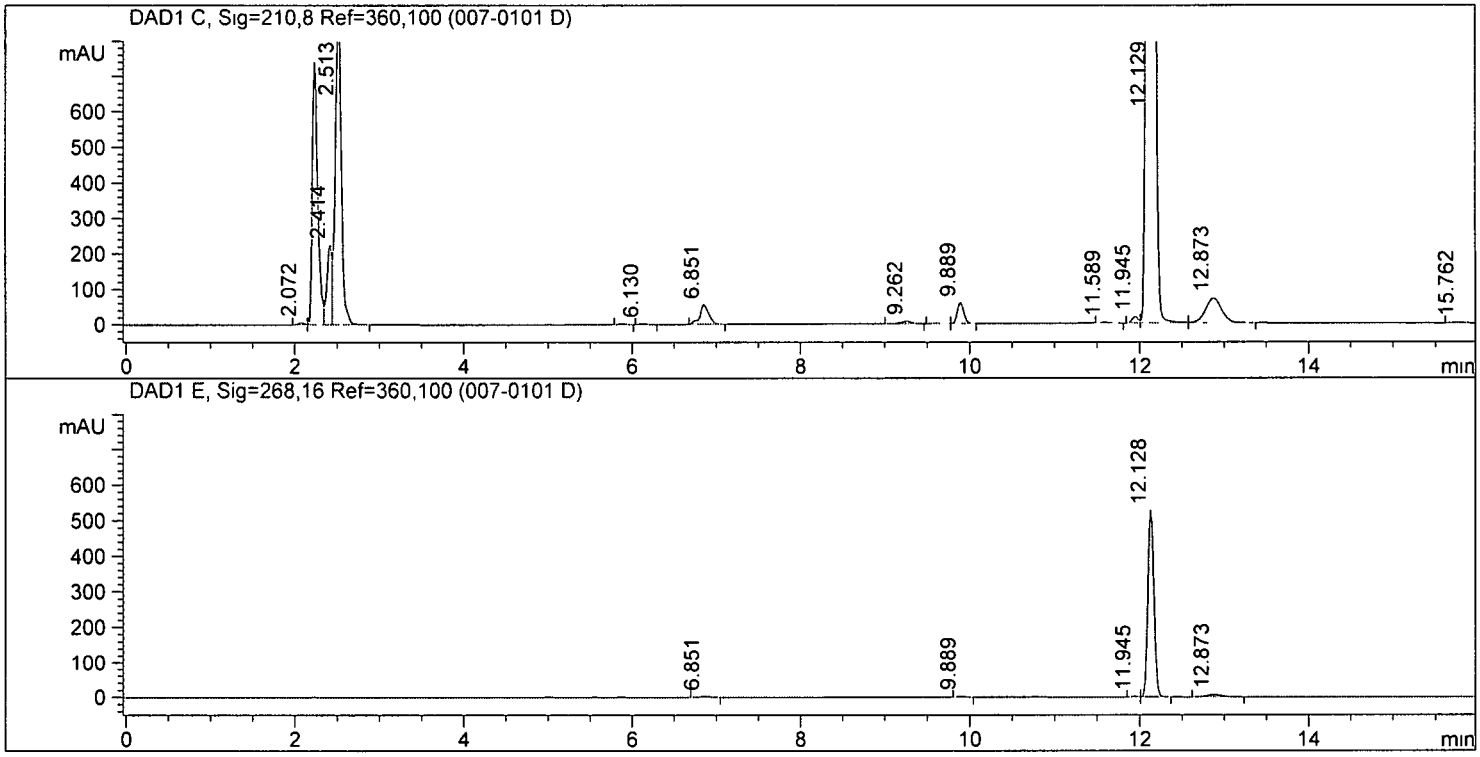
Data file :C:\HPCHEM\HPLC0157\DATA\008-0101.D Sample Name: 70316-009
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.07	BV	0.058	19.29	72.039	10.06	0.000000	
2	2.19	VB	0.080	8.30	42.441	5.93	0.000000	
3	0.00		0.000	0.00	0.000	0.00	0.002169	L-224,715
4	6.79	BB	0.119	58.18	453.822	63.40	0.000000	
5	12.13	BB	0.079	10.48	53.127	7.42	0.000000	
6	12.88	BB	0.193	7.60	94.374	13.18	0.000000	

*** End of Report ***

coupling 4 h ->

```
==========================================================================
Injection Date : 01/30/2002  3:25:37 PM        Seq Line  : 1
Sample Name    : 70316-009                     Vial No   : 7
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```




```
==========================================================================================
                    Customized Report:karlo
==========================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.07	BV	0.068	6.36	29.471	0.11	0.000000	
2	2.23	VV	0.066	741.62	3331.148	12.21	0.000000	
3	2.41	VV	0.060	225.89	899.545	3.30	0.000000	
4	2.51	VB	0.077	869.63	4367.185	16.01	0.000000	
5	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
6	5.88	PB	0.075	3.09	15.093	0.06	0.000000	
7	6.13	BB	0.085	3.11	16.935	0.06	0.000000	
8	6.85	BB	0.109	56.46	423.260	1.55	0.000000	
9	9.26	BB	0.104	7.72	58.157	0.21	0.000000	
10	9.61	BV	0.118	1.27	10.686	0.04	0.000000	
11	9.89	VP	0.084	59.12	313.669	1.15	0.000000	
12	11.59	BP	0.109	2.88	21.971	0.08	0.000000	
13	11.94	BV	0.077	18.52	91.036	0.33	0.000000	
14	12.13	VV	0.119	2.34e3	1.673e4	61.32	0.000000	
15	12.87	VB	0.205	70.90	956.743	3.51	0.000000	

nmr400c h1


```
Current Data Parameters
NAME          72324-47
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_         20020124
Time              8 26
INSTRUM          spect
PROBHD    5 mm QNP 1H/1
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  17
DS                   2
SWH           6561.680 Hz
FIDRES        0 200247 Hz
AQ           2.4969716 sec
RG                 128
DW              76.200 usec
DE               6 00 usec
TE              300.0 K
D1          0.10000000 sec

============ CHANNEL f1 =============
NUC1                1H
P1              10.00 usec
PL1             -5.00 dB
SFO1       400.1322007 MHz

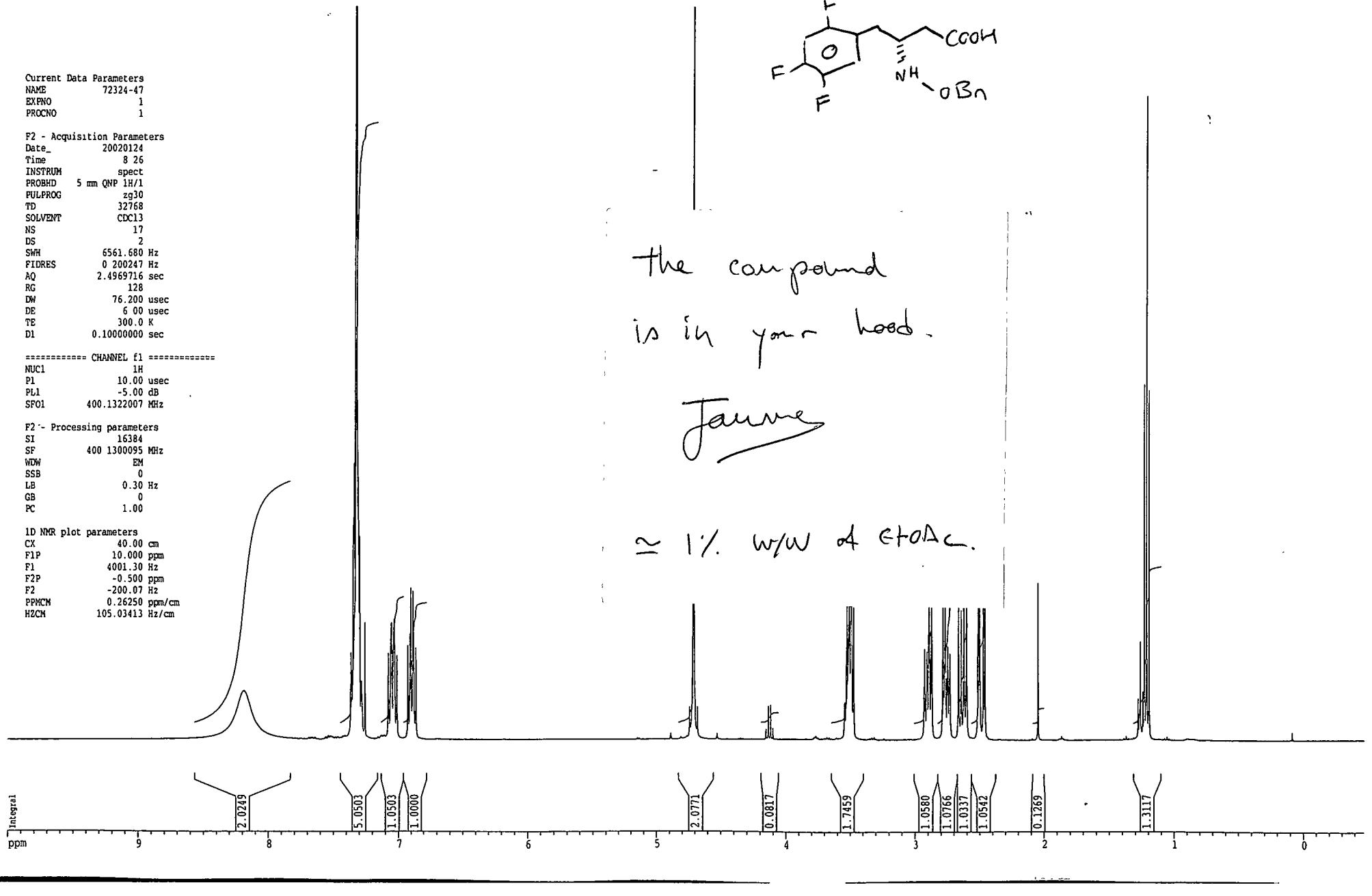
F2 - Processing parameters
SI                16384
SF         400 1300095 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                40.00 cm
F1P               10.000 ppm
F1              4001.30 Hz
F2P               -0.500 ppm
F2              -200.07 Hz
PPMCM          0.26250 ppm/cm
HZCM         105.03413 Hz/cm
```

the compound is in your hood.

Jaume

≃ 1% w/w of EtOAc.



nmr400c h1

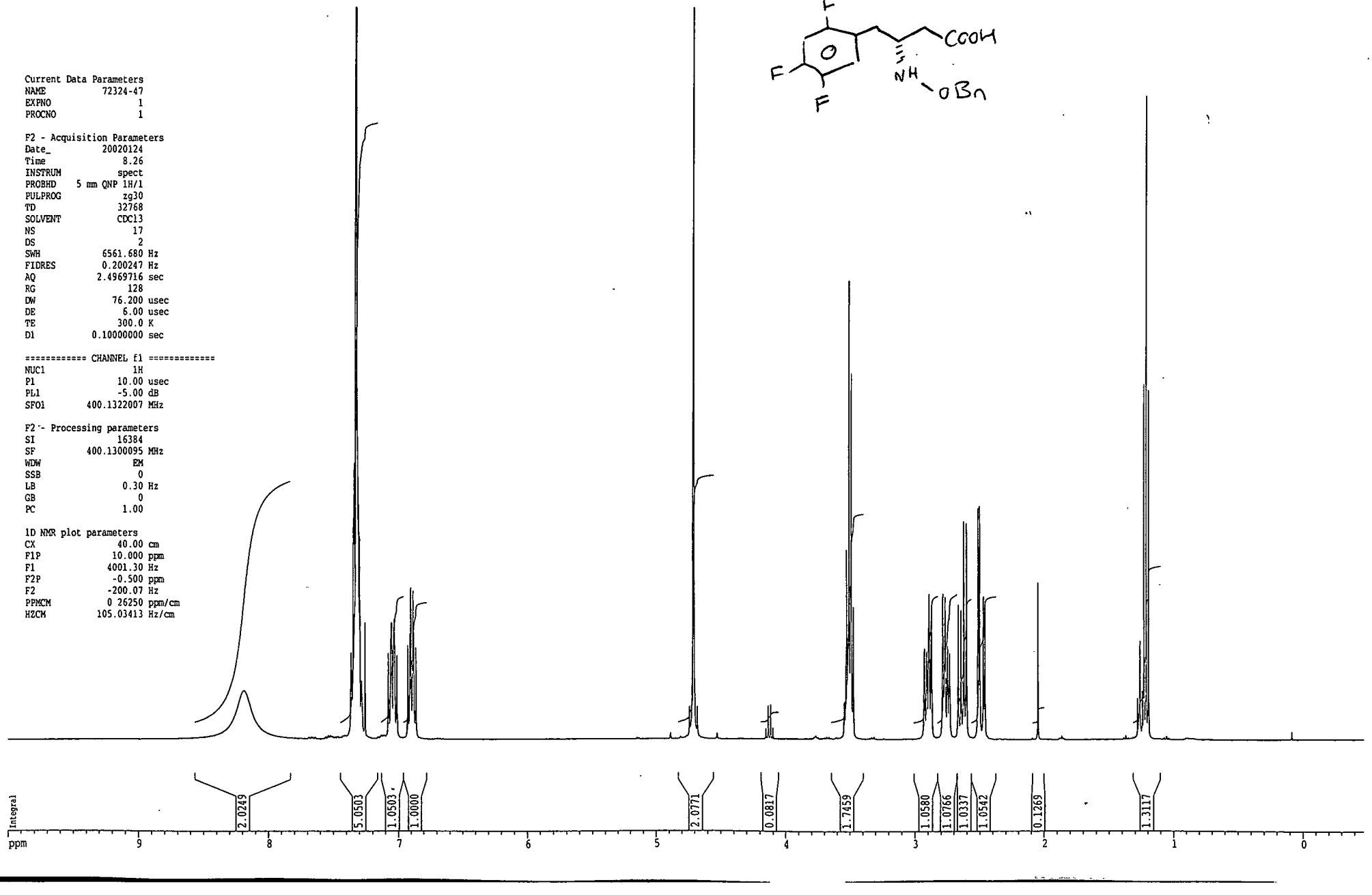

```
Current Data Parameters
NAME          72324-47
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_         20020124
Time              8.26
INSTRUM          spect
PROBHD    5 mm QNP 1H/1
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  17
DS                   2
SWH           6561.680 Hz
FIDRES        0.200247 Hz
AQ           2.4969716 sec
RG                 128
DW              76.200 usec
DE               6.00 usec
TE              300.0 K
D1          0.10000000 sec

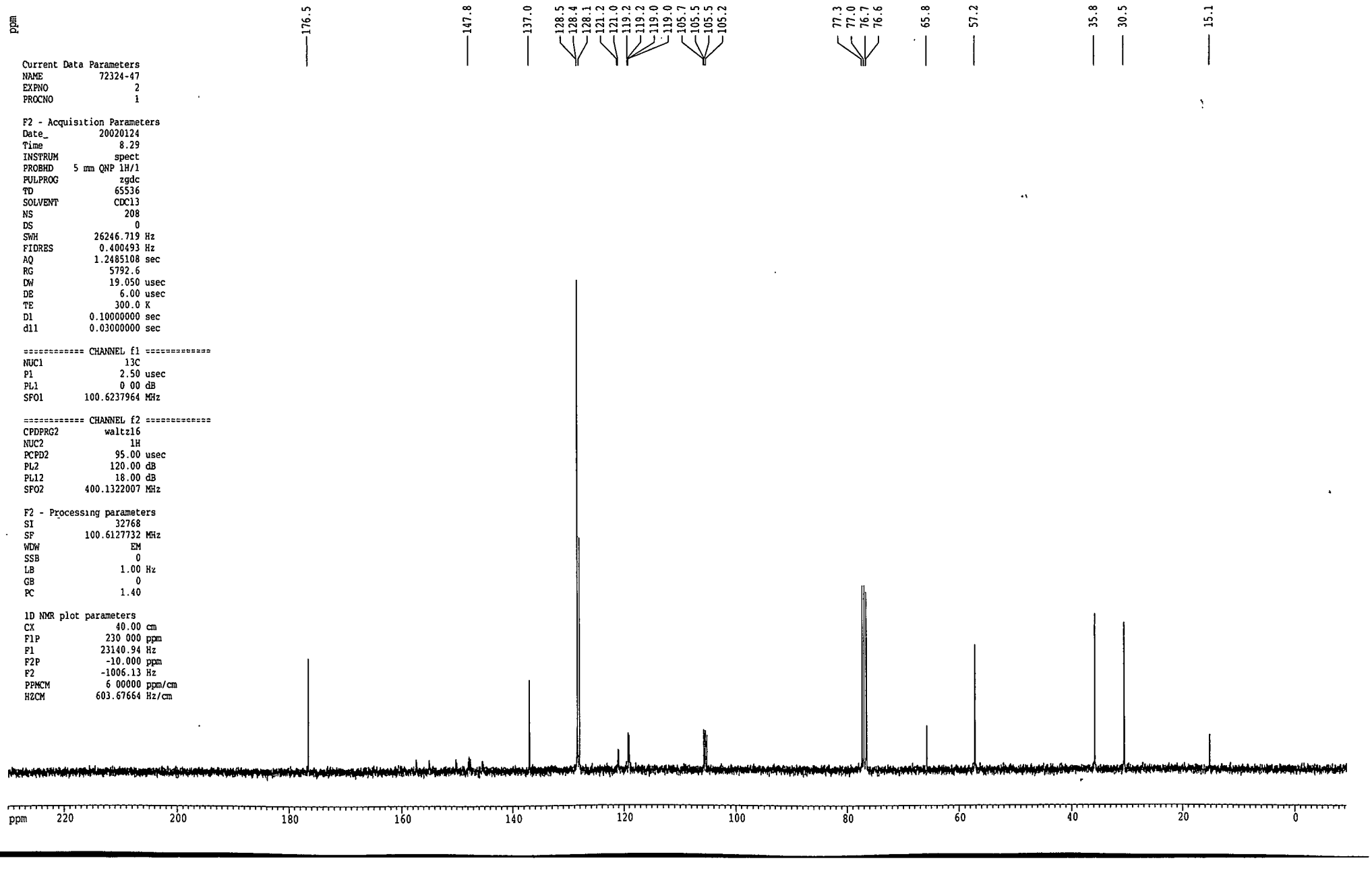
============ CHANNEL f1 =============
NUC1                1H
P1              10.00 usec
PL1             -5.00 dB
SFO1       400.1322007 MHz

F2 - Processing parameters
SI              16384
SF         400.1300095 MHz
WDW                EM
SSB                 0
LB               0.30 Hz
GB                  0
PC               1.00

1D NMR plot parameters
CX              40.00 cm
F1P             10.000 ppm
F1            4001.30 Hz
F2P             -0.500 ppm
F2            -200.07 Hz
PPMCM          0 26250 ppm/cm
HZCM         105.03413 Hz/cm
```



c-13 nmr400c



Current Data Parameters
NAME 72324-47
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020124
Time 8.29
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 208
DS 0
SWH 26246.719 Hz
FIDRES 0.400493 Hz
AQ 1.2485108 sec
RG 5792.6
DW 19.050 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec

========== CHANNEL f1 ==========
NUC1 13C
P1 2.50 usec
PL1 0 00 dB
SFO1 100.6237964 MHz

========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 120.00 dB
PL12 18.00 dB
SFO2 400.1322007 MHz

F2 - Processing parameters
SI 32768
SF 100.6127732 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 40.00 cm
F1P 230 000 ppm
F1 23140.94 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 6 00000 ppm/cm
HZCM 603.67664 Hz/cm

besy;ate in water
nmr400c h1

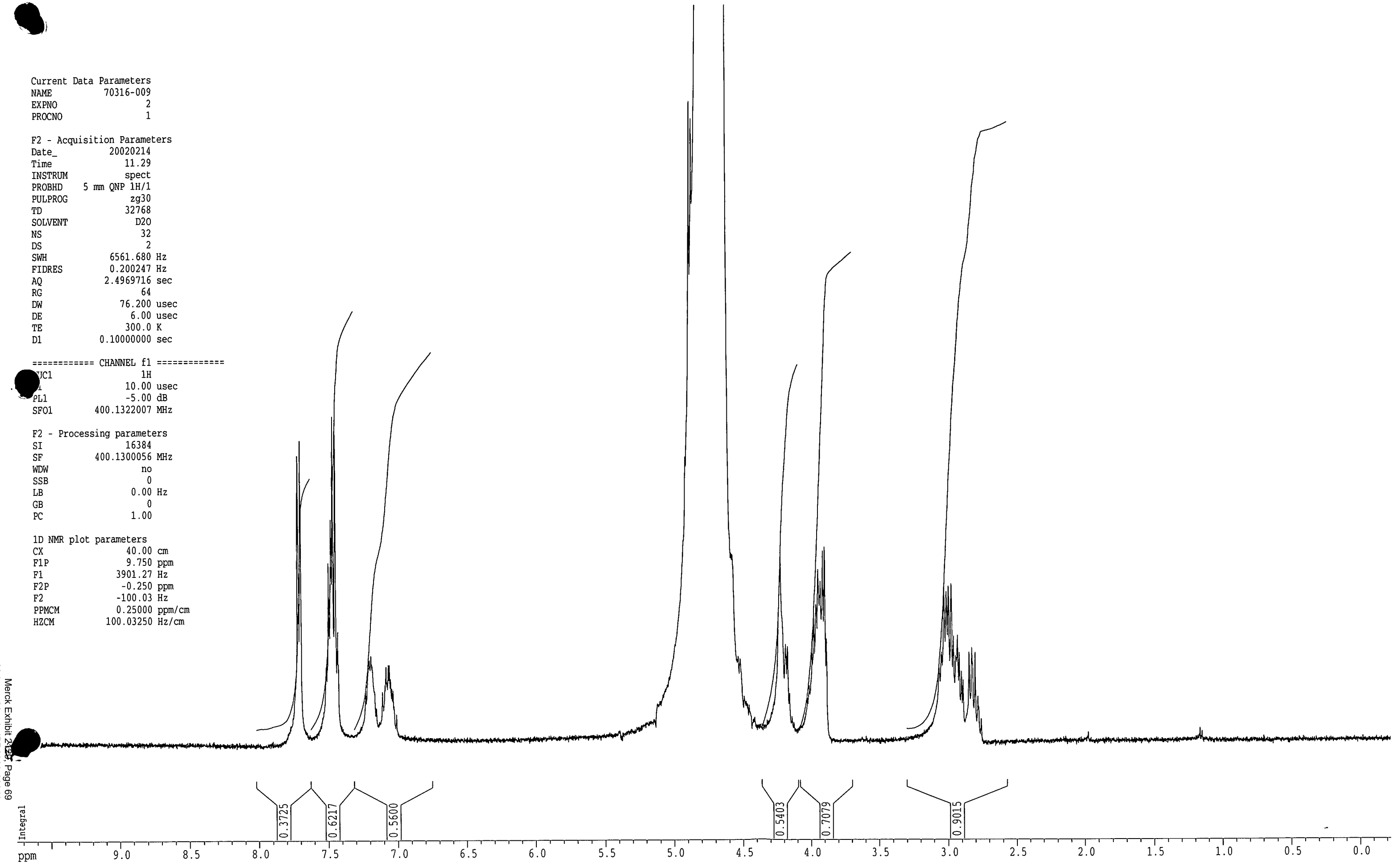
Current Data Parameters
NAME 70316-009
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020214
Time 11.29
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT D2O
NS 32
DS 2
SWH 6561.680 Hz
FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 64
DW 76.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

========== CHANNEL f1 ==========
[redacted]C1 1H
[redacted] 10.00 usec
PL1 -5.00 dB
SFO1 400.1322007 MHz

F2 - Processing parameters
SI 16384
SF 400.1300056 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3901.27 Hz
F2P -0.250 ppm
F2 -100.03 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.03250 Hz/cm



Data file :C:\HPCHEM\HPLC0157\DATA\019-0101.D Sample Name: 70316-009

5.97g/50ml of 406 g ML's ->

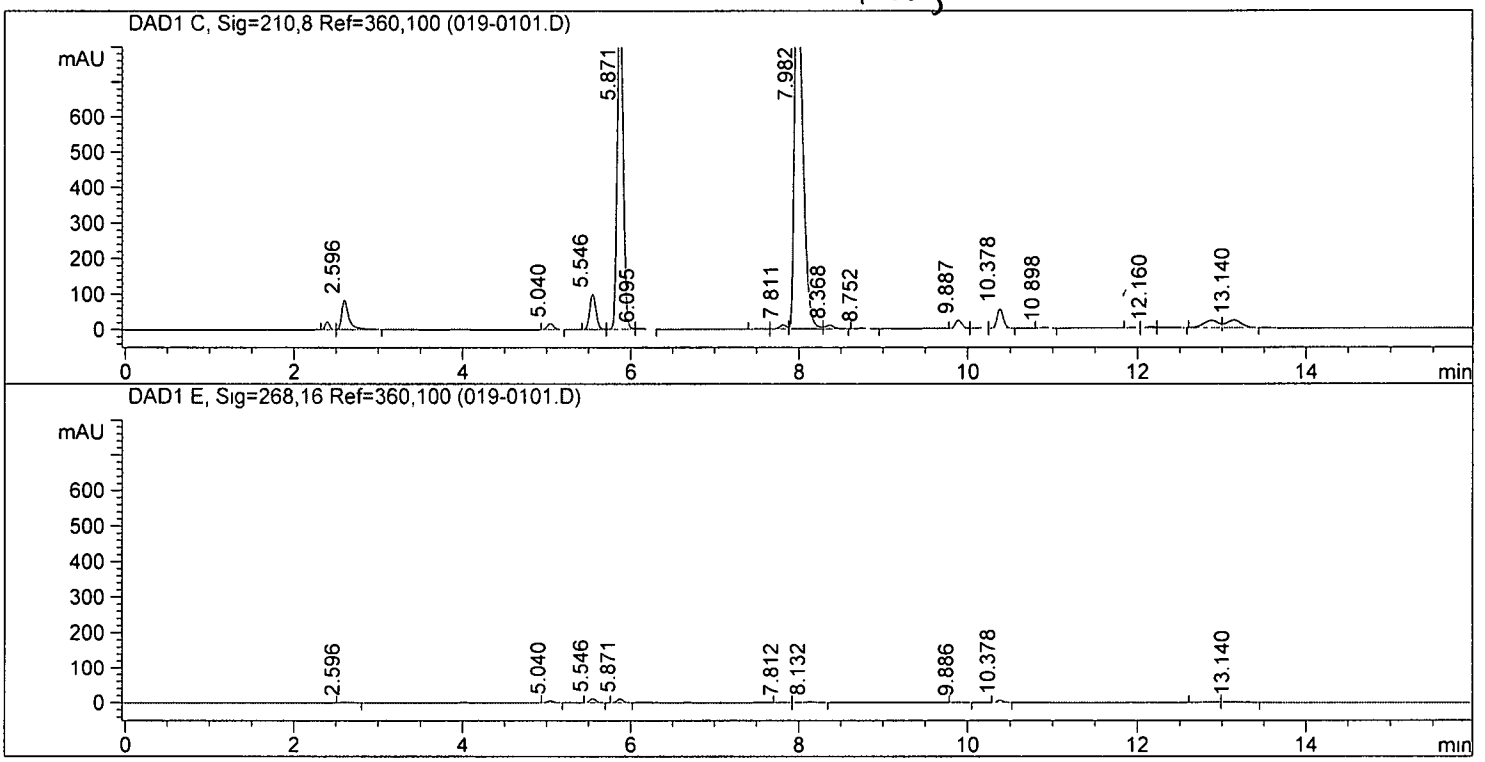
==========

Injection Date : 02/04/2002 1:46:13 PM Seq Line : 1
Sample Name : 70316-009 Vial No : 19
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm

1.14 mg/ml

0.462 g



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.39	VV	0.056	22.47	81.305	0.57	0.000000	
2	2.60	VB	0.090	83.77	499.567	3.49	0.000000	
3	5.04	BB	0.086	17.00	93.422	0.65	0.000000	
4	5.55	PV	0.081	100.47	523.467	3.66	0.135818	L-224,715
5	5.87	VV	0.078	915.81	4534.144	31.72	0.000000	
6	6.10	VB	0.097	2.88	20.026	0.14	0.000000	
7	7.52	BV	0.102	1.13	7.703	0.05	0.000000	
8	7.81	VV	0.081	11.97	66.629	0.47	0.000000	
9	7.98	VV	0.103	1.09e3	7316.946	51.18	0.000000	
10	8.37	VB	0.104	10.78	76.061	0.53	0.000000	
11	8.75	BV	0.114	1.88	15.798	0.11	0.000000	
12	9.89	BV	0.086	23.27	127.228	0.89	0.000000	
13	10.13	VV	0.127	1.74	13.822	0.10	0.000000	
14	10.38	VB	0.078	55.33	277.195	1.94	0.000000	
15	10.90	BP	0.088	2.32	13.150	0.09	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	11.93	BV	0.092	1.78	10.951	0.08	0.000000	
17	12.16	VV	0.098	3.70	24.692	0.17	0.000000	
18	12.28	VB	0.208	2.61	37.253	0.26	0.000000	
19	12.88	BV	0.200	20.98	272.840	1.91	0.000000	
20	13.14	VV	0.192	22.43	284.199	1.99	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.60	PB	0.089	2.53	15.319	5.48	0.000000	
2	5.04	BB	0.086	5.24	28.766	10.28	0.000000	
3	5.55	BB	0.080	11.48	59.321	21.21	0.135818	L-224,715
4	5.87	BP	0.078	10.84	54.255	19.40	0.000000	
5	7.81	BV	0.082	1.70	9.562	3.42	0.000000	
6	8.13	VB	0.111	3.00	24.411	8.73	0.000000	
7	9.89	PP	0.085	1.03	5.565	1.99	0.000000	
8	10.38	PB	0.078	6.51	32.222	11.52	0.000000	
9	12.87	PV	0.190	1.79	22.075	7.89	0.000000	
10	13.14	VB	0.201	2.12	28.196	10.08	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\017-0101.D Sample Name: 70316-009

0.2886 g/50ml of 116g meoh filtrate ->

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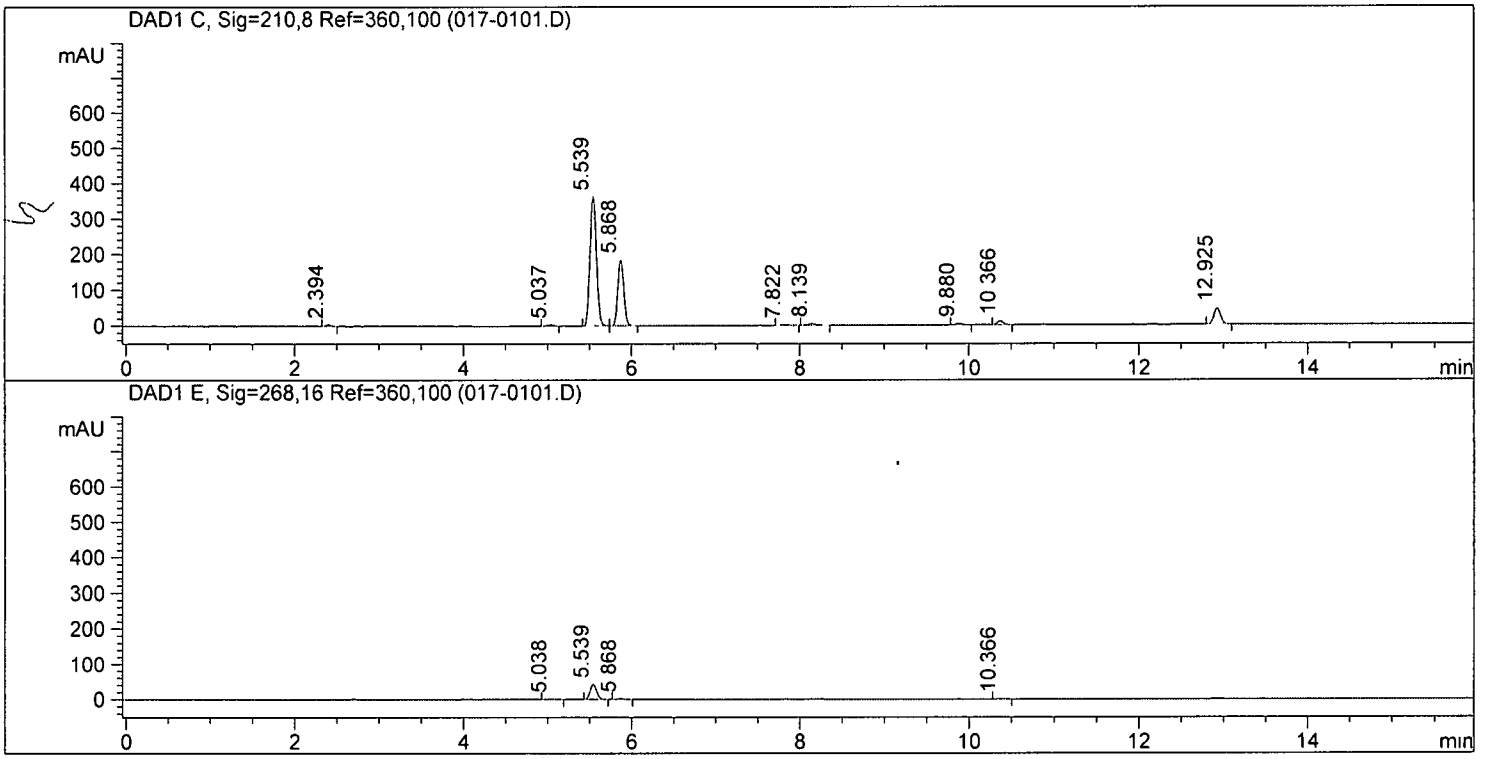
Injection Date : 02/04/2002 9:17:29 AM Seq Line : 1
Sample Name : 70316-009 Vial No : 17
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm

10.40 s 715



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.39	PB	0.059	4.59	16.850	0.51	0.000000	
2	5.04	BV	0.090	3.72	21.633	0.66	0.000000	
3	5.54	BV	0.083	363.93	1961.058	59.56	0.517649	L-224,715
4	5.87	VB	0.078	185.36	921.427	27.98	0.000000	
5	7.82	PP	0.083	2.81	16.112	0.49	0.000000	
6	8.14	BB	0.100	5.03	35.227	1.07	0.000000	
7	9.88	PP	0.081	4.54	23.739	0.72	0.000000	
8	10.37	BP	0.077	10.79	52.946	1.61	0.000000	
9	12.92	BB	0.086	44.42	243.855	7.41	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\017-0101.D Sample Name: 70316-009
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.04	BB	0.091	1.08	6.322	2.53	0.000000	
2	5.54	BB	0.083	42.11	226.111	90.60	0.517649	L-224,715
3	5.87	BP	0.079	2.17	11.026	4.42	0.000000	
4	10.37	PP	0.077	1.25	6.106	2.45	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\015-0101.D Sample Name: 70316-009

hydrog after 3g catalyst meoh ->

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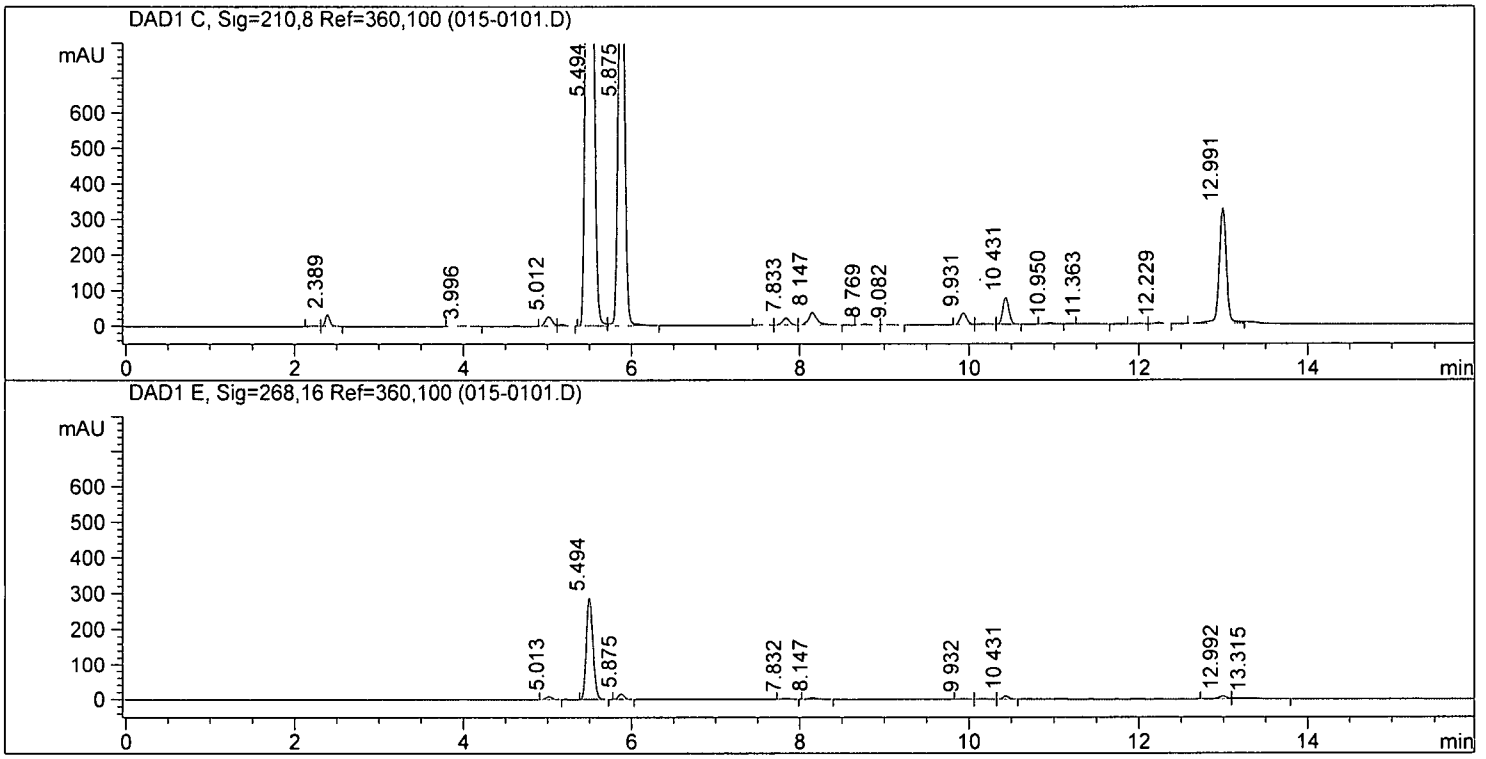
Injection Date : 02/04/2002 8:30:48 AM Seq Line : 1
Sample Name : 70316-009 Vial No : 15
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.23	BV	0.096	1.62	9.737	0.05	0.000000	
2	2.39	VB	0.058	32.93	125.358	0.59	0.000000	
3	4.00	BB	0.115	2.01	16.347	0.08	0.000000	
4	5.01	BV	0.089	26.67	152.368	0.72	0.000000	
5	5.17	VP	0.082	4.84	25.607	0.12	0.000000	
6	5.49	BV	0.099	1.89e3	1.151e4	54.08	3.054555	L-224,715
7	5.88	VB	0.079	1.26e3	6401.168	30.07	0.000000	
8	7.55	BV	0.099	1.39	9.609	0.05	0.000000	
9	7.83	VV	0.087	20.62	122.109	0.57	0.000000	
10	8.15	VB	0.101	36.62	267.188	1.26	0.000000	
11	8.77	PB	0.096	2.28	15.258	0.07	0.000000	
12	9.08	BB	0.089	1.52	8.905	0.04	0.000000	
13	9.93	PV	0.085	32.93	178.142	0.84	0.000000	
14	10.16	VV	0.142	2.41	23.087	0.11	0.000000	
15	10.43	VP	0.078	75.70	379.409	1.78	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	10.95	BB	0.114	3.99	30.761	0.14	0.000000	
17	11.36	BP	0.180	1.88	25.770	0.12	0.000000	
18	12.00	VV	0.081	2.24	11.755	0.06	0.000000	
19	12.23	VB	0.092	3.97	23.989	0.11	0.000000	
20	12.99	VB	0.094	325.19	1947.183	9.15	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.01	BB	0.089	7.63	43.739	2.28	0.000000	
2	5.49	BB	0.086	288.50	1578.905	82.16	3.054555	L-224,715
3	5.87	BB	0.079	15.07	76.170	3.96	0.000000	
4	7.83	BP	0.085	2.97	16.988	0.88	0.000000	
5	8.15	BB	0.101	4.74	34.518	1.80	0.000000	
6	9.93	BV	0.091	1.56	9.202	0.48	0.000000	
7	10.17	VP	0.118	1.02	7.549	0.39	0.000000	
8	10.43	VB	0.078	8.92	44.157	2.30	0.000000	
9	12.99	BV	0.109	7.92	57.986	3.02	0.000000	
10	13.31	VB	0.265	2.76	52.622	2.74	0.000000	

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*** End of Report ***

HYDROGENATION OR HIGH PRESSURE REACTION

2002020154.001
DO NOT WRITE IN THIS SPACE

REQUESTED BY Hansen B.DG/RM 800B26-1 EXT. 0552 DATE 1 Feb 2002

PROJECT NO. L224715 PROJECT ~~A 000 2237~~ M0002218 NOTEBOOK - PAGE NO. 70311-057

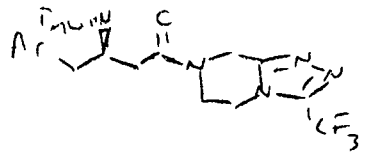
CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

NO. 1 _____ NO. 2 _____

M.W. 513 AMOUNT _____ G. MOLES 0.0295 M.W. _____ AMOUNT _____ G. MOLES _____

STRUCTURAL FORMULA: Reuse



EMPIRICAL FORMULA:

CATALYST 2.70 G. OF 10% Pd/C

SOLVENT 100 ML. OF MeOH

MOLES OF HYDROGEN REQUIRED 2.95

OTHER MATERIALS _____

REACTION CONDITIONS ETC. 40 PSI 50°C

PRECAUTIONS: _____

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: _____ G. MOLES 0.0295 NO.2: _____ G. MOLES _____

CATALYST 2.70 G. OF 10% Pd/C Lot # FC95286

SOLVENT 100 ML. OF MeOH

OTHER MATERIALS _____

CELL NO. _____ HEATER NO. _____ REC. POINT INTERNAL _____ EXTERNAL _____ BOMB NO. _____ VESSEL SIZE 250 ML.

SHAKER NO. 54 LINER _____ SHAKER TANK 1062.2 AUX. TANK _____ SYSTEM VOLUME 79 ML.

CALC'D H_2 PRESSURE DROP = 314 LBS./MOLE 0.0295 MOLES = 9.2 LBS.

CONDITIONS _____ HRS. AT 50 C. MISC. DATA: 40 psig H_2

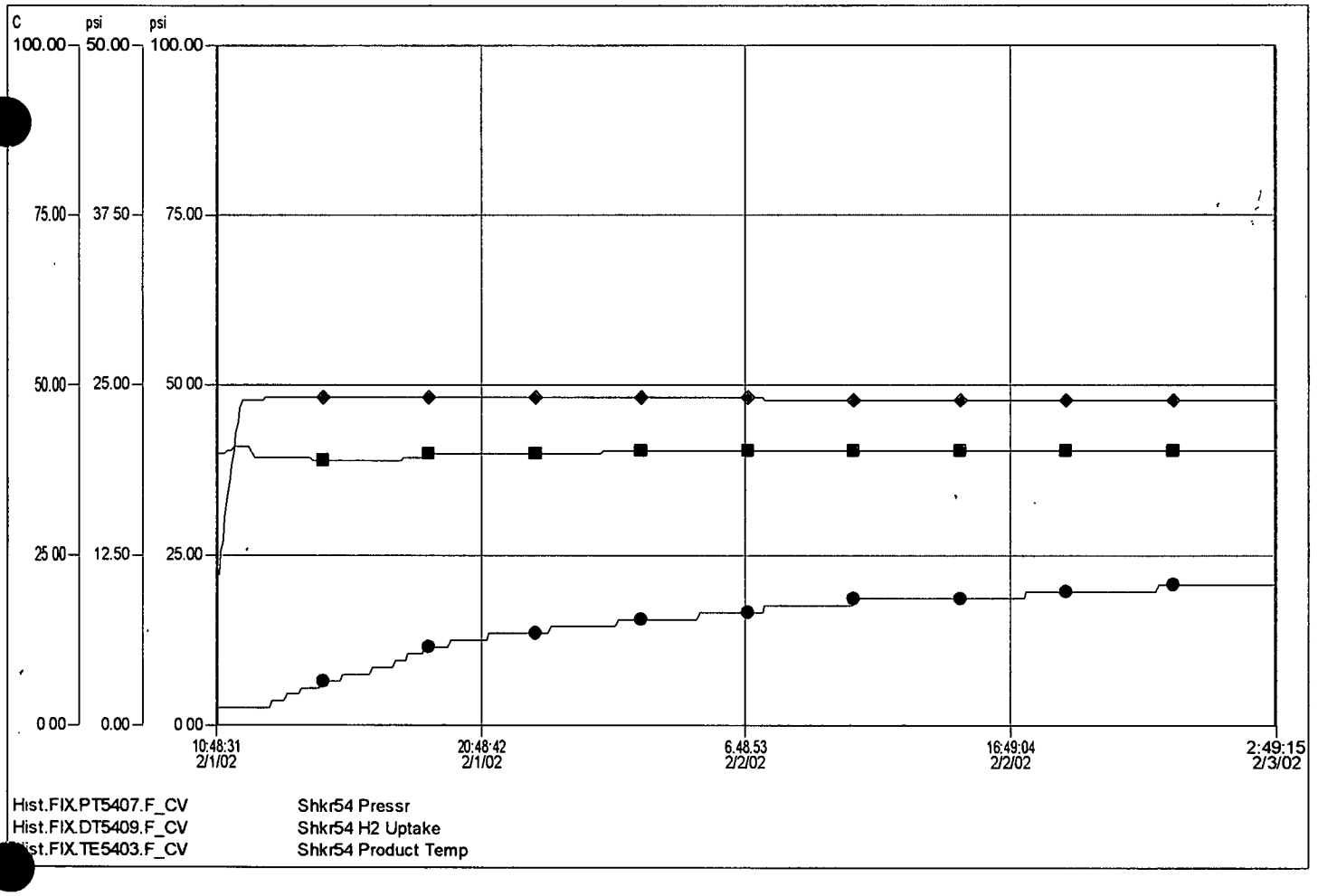
TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
10:49	19.4	39	0	02:49	48.3	40	8	18:49	47.8	40	10
11:19	36.8	40	1	03:19	48.3	40	8	19:19	47.8	40	10
11:49	47.8	41	1	03:49	48.3	40	8	19:49	47.8	40	10
12:19	47.8	39	1	04:19	48.3	40	8	20:19	47.8	40	10
12:49	48.3	39	1	04:49	48.3	40	8	20:49	47.8	40	10
13:19	48.3	39	2	05:19	48.3	40	8	21:19	47.8	40	10
13:49	48.3	39	2	05:49	48.3	40	8	21:49	47.8	40	10
14:19	48.3	39	3	06:19	48.3	40	8	22:19	47.8	40	10
14:49	48.3	39	3	06:49	48.3	40	8	22:49	47.8	40	10
15:19	48.3	39	3	07:19	48.3	40	8	23:19	47.8	40	10
15:49	48.3	39	4	07:49	47.8	40	9	23:49	47.8	40	10
16:19	48.3	39	4	08:19	47.8	40	9	00:19	47.8	40	10
16:49	48.3	39	4	08:49	47.8	40	9	00:49	47.8	40	10
17:19	48.3	39	4	09:19	47.8	40	9	01:19	47.8	40	10
17:49	48.3	39	5	09:49	47.8	40	9	01:49	47.8	40	10
18:19	48.3	39	5	10:19	47.8	40	9	02:19	47.8	40	10
18:49	48.3	40	6	10:49	47.8	40	9				
19:19	48.3	40	6	11:19	47.8	40	9				
19:49	48.3	40	6	11:49	47.8	40	9				
20:19	48.3	40	6	12:19	47.8	40	9				
20:49	48.3	40	6	12:49	47.8	40	9				
21:19	48.3	40	7	13:19	47.8	40	9				
21:49	48.3	40	7	13:49	47.8	40	9				
22:19	48.3	40	7	14:19	47.8	40	9				
22:49	48.3	40	7	14:49	47.8	40	9				
23:19	48.3	40	7	15:19	47.8	40	9				
23:49	48.3	40	7	15:49	47.8	40	9				
00:19	48.3	40	7	16:19	47.8	40	9				
00:49	48.3	40	7	16:49	47.8	40	9				
01:19	48.3	40	7	17:19	47.8	40	9				
01:49	48.3	40	7	17:49	47.8	40	10				
02:19	48.3	40	8	18:19	47.8	40	10				

RUN BY D. Jewell DATE Feb 1, 2002

RUN BY _____ DATE _____

MERCK & CO., INC.
R-654-O REV. 6/88

2002020154.001



HYDROGENATION OR HIGH PRESSURE REACTION

2002013156.001
DO NOT WRITE IN THIS SPACE

REQUESTED BY K. Hansen BLDG/RM 900-B249 EXT. 0552 DATE 31 Jan 2002

PROJECT NO. 224715 PROJECT MO002237 NOTEBOOK - PAGE NO. 70316-009

CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

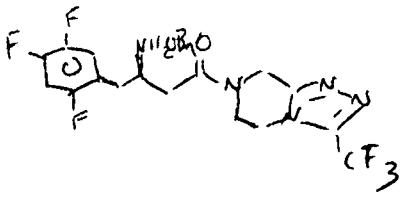
NO. 1 _____

M.W. 513 AMOUNT _____ G. MOLES 0.0295

NO. 2 _____

M.W. _____ AMOUNT _____ G. MOLES _____

STRUCTURAL FORMULA:



EMPIRICAL FORMULA:

CATALYST 0.30 G. OF 10% Pd/C

SOLVENT 100 ML. OF MeOH

MOLES OF HYDROGEN REQUIRED 0.0295

OTHER MATERIALS Rinse bottle w/ 10 ml MeOH

REACTION CONDITIONS, ETC. ~~50 PSI~~ → 40 PSI 50°C

PRECAUTIONS: _____

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: _____ G. MOLES _____ NO.2: _____ G. MOLES _____

CATALYST .30 G. OF 10% Pd/C Lot # FC95286

SOLVENT 100 ML. OF MeOH

OTHER MATERIALS _____

CELL NO. _____ HEATER NO. _____ REC. POINT INTERNAL _____ EXTERNAL _____ BOMB NO. _____ VESSEL SIZE 250 ML.

SHAKER NO. 56 LINER _____ SHAKER TANK _____ AUX. TANK _____ SYSTEM VOLUME _____ ML.

CALC'D H_2 PRESSURE DROP = 310.4 LBS./MOLE 0.0295 MOLES = 9.1 LBS.

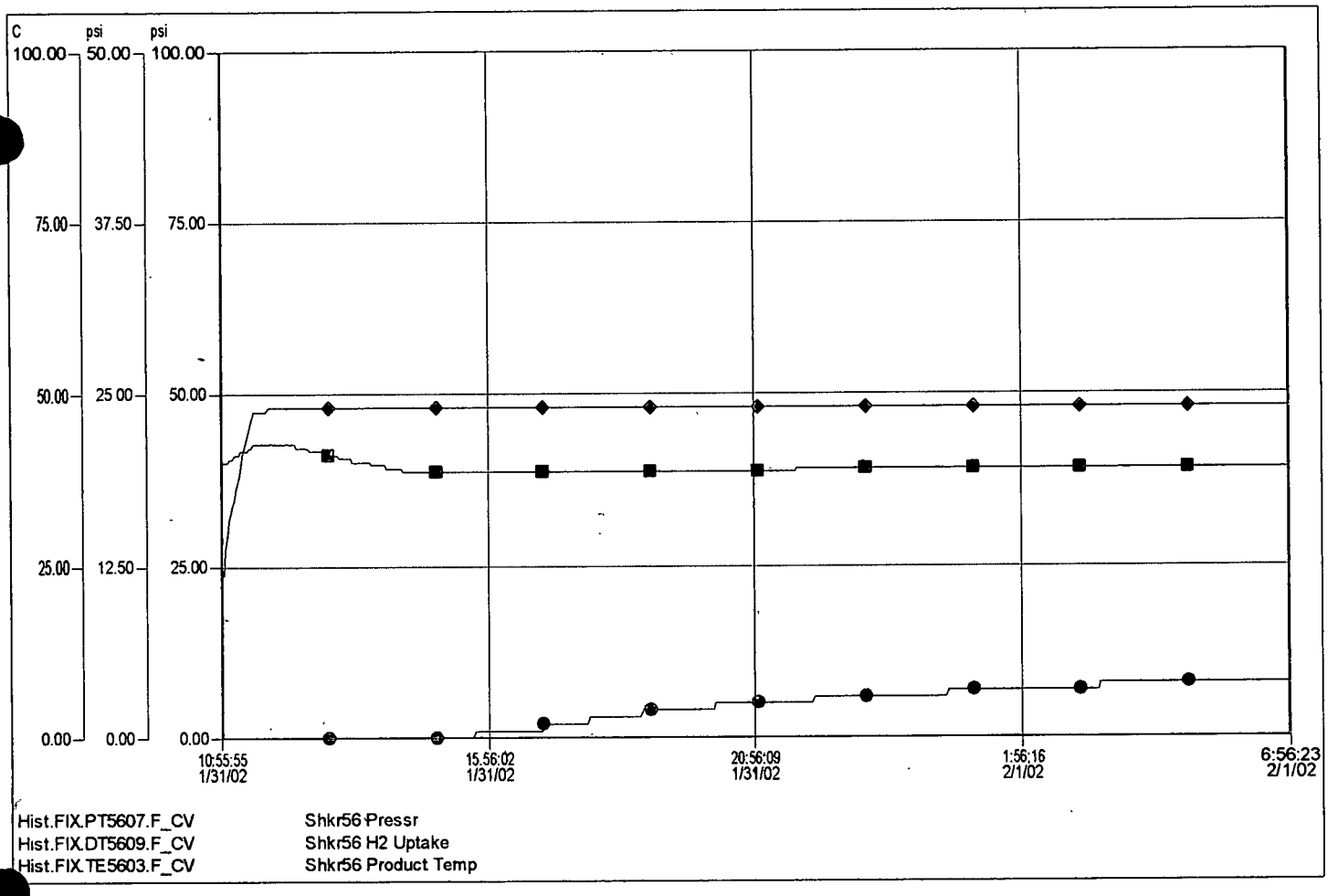
CONDITIONS _____ HRS. AT 50 C. MISC. DATA: 40 psig H_2

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
10:56	20.7	41	0	20:00	48.1	39	2	05:04	48.1	39	4
11:13	36.8	41	0	20:17	48.1	39	2	05:21	48.1	39	4
11:30	46.8	42	0	20:34	48.1	39	2	05:38	48.1	39	4
11:47	47.5	43	0	20:51	48.1	39	2	05:55	48.1	39	4
12:04	48.1	43	0	21:08	48.1	39	2	06:12	48.1	39	4
12:21	48.1	42	0	21:25	48.1	39	2	06:29	48.1	39	4
12:38	48.1	42	0	21:42	48.1	39	2	06:46	48.1	39	4
12:55	48.1	41	0	21:59	48.1	39	2				
13:12	48.1	41	0	22:16	48.1	39	3				
13:29	48.1	40	0	22:33	48.1	39	3				
13:46	48.1	40	0	22:50	48.1	39	3				
14:03	48.1	39	0	23:07	48.1	39	3				
14:20	48.1	39	0	23:24	48.1	39	3				
14:37	48.1	39	0	23:41	48.1	39	3				
14:54	48.1	39	0	23:58	48.1	39	3				
15:11	48.1	39	0	00:15	48.1	39	3				
15:28	48.1	39	0	00:32	48.1	39	4				
15:45	48.1	39	0	00:49	48.1	39	4				
16:02	48.1	39	0	01:06	48.1	39	4				
16:19	48.1	39	0	01:23	48.1	39	4				
16:36	48.1	39	0	01:40	48.1	39	4				
16:53	48.1	39	0	01:57	48.1	39	4				
17:10	48.1	39	1	02:14	48.1	39	4				
17:27	48.1	39	1	02:31	48.1	39	4				
17:44	48.1	39	1	02:48	48.1	39	4				
18:01	48.1	39	2	03:05	48.1	39	4				
18:18	48.1	39	2	03:22	48.1	39	4				
18:35	48.1	39	2	03:39	48.1	39	4				
18:52	48.1	39	2	03:56	48.1	39	4				
19:09	48.1	39	2	04:13	48.1	39	4				
19:26	48.1	39	2	04:30	48.1	39	4				
19:43	48.1	39	2	04:47	48.1	39	4				

RUN BY Q. Wilson DATE Jan 31, 2002

RUN BY _____ DATE _____

MERCK & CO., INC.
R-654-O REV. 6/88


C
psi
psi
100.00
50.00
100.00
75.00
37.50
75.00
50.00
25.00
50.00
25.00
12.50
25.00
0.00
0.00
0.00
10:55:55
1/31/02
15:56:02
1/31/02
20:56:09
1/31/02
1:56:16
2/1/02
6:56:23
2/1/02
Hist.FIX.PT5607.F_CV
Shkr56 Pressr
Hist.FIX.DT5609.F_CV
Shkr56 H2 Uptake
Hist.FIX.TE5603.F_CV
Shkr56 Product Temp

Hansen, Karl

From: Dorwart, Jason G.
Sent: Friday, February 08, 2002 9.55 AM
To: Hansen, Karl

Here are the results for the L-224,715 Besylate salt NB# 70316-009.

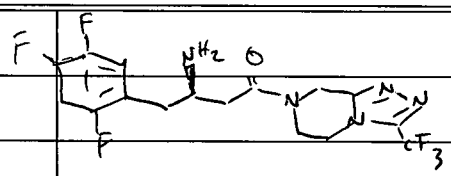
RRT	Area%
0.93	0.15%
0.95	0.20%
0.98	0.17%
1.00	99.06%
1.37	0.18%
1.43	0.17%

Total imp = 0.87%

LC Chiral

Major = 99.98%
Minor = 0.02%

Jason



H_3PO_4 / H_2O / THF → L224715 - H_3PO_4

Reagents:		FW	Amt	mol	eq
L224715-0005T001		407	20.4	0.050	1.0
H_3PO_4	98 g/mol soln	98	~~40~~ 0.05 ml	0.50	1.0
THF			0.50 ml		

Added 0.050 ml of Phosphoric acid soln to THF. Initially clear. Stirred after ~ 30 min added 0.5 ml THF

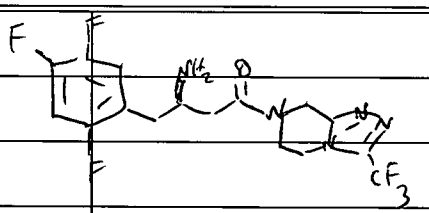
Countersigned by _____

Date _____

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

Date



$\xrightarrow[ACN/H_2O]{H_3PO_4}$ L224715-H_3PO_4

Reagents:		FW	Amt	mmol	eq
L224715.0001001		407	20.4 g	0.050	1.0
H_3PO_4	98 g/mol sol. in H_2O	98	0.050	0.050	1.0
ACN			0.5–1		

Mixed Reagents - clear sol after 1h added 0.5 ml MTBE white solids formed but these were amorphous. Heated to 60°C.

Countersigned by

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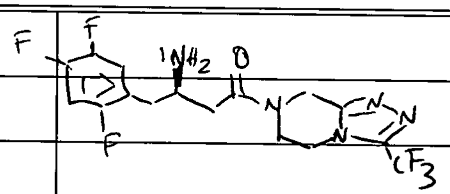
Date

Investigator ____ Date 30 Jan 2002

Subject ____

Filed in Book Number/Title ____



IPA, H_3PO_4 / H_2O → L224715 Phosphate

Reagents:

	Fw	Amt	mmol	eq
L224715-000T001	407	20.4 mg	0.05	1.0
H_3PO_4 98 mg/ml soln	98	0.05	0.05	1.0

Procedure: Added H_3PO_4 soln to ~~white amo~~ soln of 715 in IPA. white ppt formed amorphous. heated to 72°C - no ppt. Added 25 ml H_2O & some of solids dissolved added 25 ml H_2O - clear soln. Cooled to 5°C & oils formed - soln is saturated. Reheated to 60°C - soln became homogeneous. Cooled slowly to RT. Solids look like some small xtals might be present. Need to slow crystallization process down. H_2O/N@RT solids are amorphous

Conclusion - This sample was treated similarly to 70316-17 yet is far less crystalline - Ethanol is probably better crystallizing solvent for this stuff.

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Project No. _____ Project Page _____

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Countersigned by

Date

Investigator _____ Date 30 Jan 2002

Subject _____

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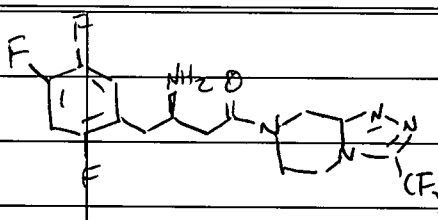
Filed in Book Number/Title _____



H_3PO_4, EtOH, ~12% H_2O → L224715 Phosplate.

Reagents:	Fw	Amt	mmol	eq
L224715-000T001	407	~20.35 g	0.05	1.0
H_3PO_4 in EtOH 98 mg/ml	98	50 ml	0.05	1.0
EtOH		0.50 ml		
		~30 ml/g total volume.		

Dissolved 230 mg of 85% H_3PO_4 in 2 ml EtOH

Added 50 ml of H_3PO_4 soln to EtOH soln of 715. heated to 50°C. white amorphous solids formed. Added 75 ml H_2O & solids dissolved when heated to reflux. put on 50°C oil bath & solids formed. These were definitely more crystalline than previous samples. but still a lot of amorphous material present.

31 Jan 2002 - placed sample in Thermolyne oven. heated to 70°C & then ~~cooled to 10°C~~ heated @ 70°C for 1 hr. some solids still present cooled slowly to 10°C over 16 hrs. 31 Jan 2002

1 Feb 2002 Solids present have plate morphology and appear to be crystalline. Isolated on frit & washed w/ EtOH dried in oven @ 40/50°C w/ N_2 sweep. Isolated 12 g white solids gave 1 Phys mass.

2 Feb 2002

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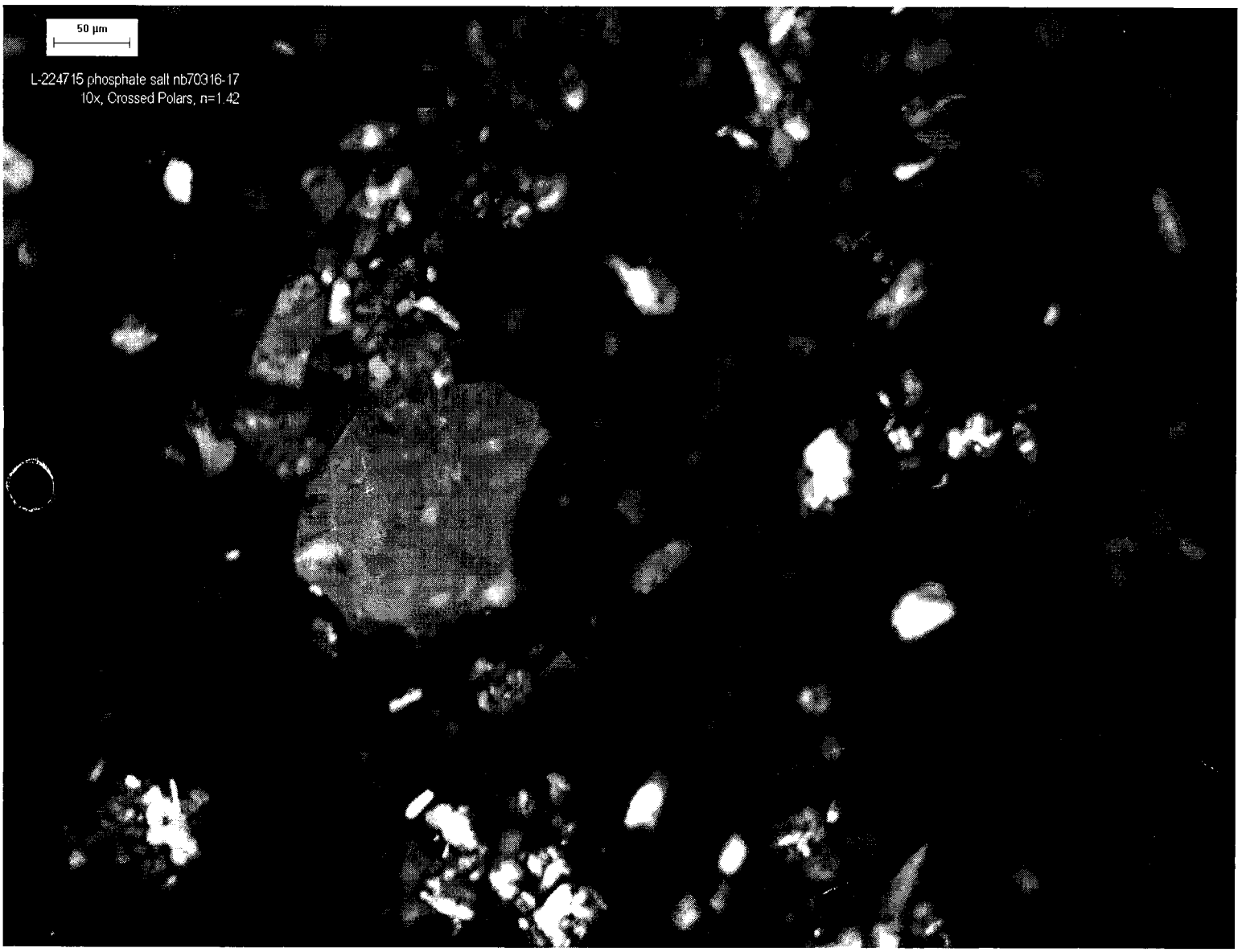
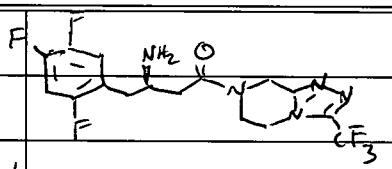

50 µm
L-224715 phosphate salt nb70316-17
10x, Crossed Polars, n=1.42



→ L224715 Phosphate.

Reagents:		Fw	Amt	mmol	eq
L224715-000T001		487	20.35 mg	0.05	1.0
H_3PO_4	98 wt/wt soln	98	0.05 mol	0.05	1.0

1- 122.1 mg of L224715 dissolved in 1.2 ml Ethanol

2- Dispensed 0.2 ml (20.35 mg, 0.05 moles). into 5 vials. then diluted with water, Ethanol & then added H_3PO_4 soln ~~0.50~~ 0.05 ml 98 wt/wt soln in EtOH.

vial	added Ethanol	water	% water
A	0.2	0.05	10
B	0.15	0.10	20
C	0.10	0.15	30
D	0.05	0.20	40
E	0.00	0.25	50.

RT observations:

A - white solid < 5 mins
B white solid ~2 hrs
C white solid 4 hrs
D small amt of solids after 6 hrs
E Nucleate

Placed in oven @ 70°C then performed control cool-down to 10°C after 1 hr @ 70°C. Cool down took 16 hrs Nucleation.

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1 Feb 2002 — 10°C next day

A	70°C - still not clear	amorphous
B	70°C still not clear	amorphous
C	clear @ 70°C	clear
D	clear @ 70°C	clear
E	clear @ 70°C	clear

stirring C,D resulted in solids forming within 1hr. solids were largely amorphous.

~~ABC~~ A B & C were placed in hot bath @ 80°C & cooled to RT over @ ~~5°C/hr~~ 2°C/hour.

4 Feb 2002. A B & C ~~are~~ contain solids. These are plates under microscope identical to previous synthesized phosphate salt. Did not isolate.

Phosphate salt seems to crystallized as plates when cooled slowly!

~~K~~ BK 4 Feb 2002.

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Project No. ______ Project Page ______

Investigator ______ Date 1 Feb 2002

Subject Phosphate salt from MeOH

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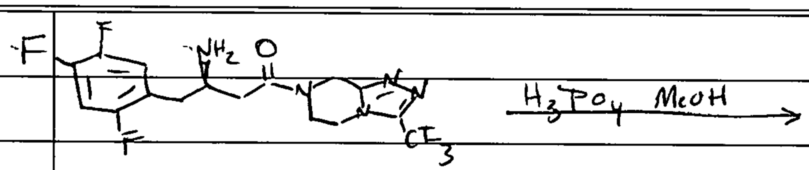

L224715 Phosphate salt

Reagents:

		FW	Amt	mmol	eq
L224715-000T001		407	20.35 mg	0.05	1.0
H_3PO_4	98 mg/ml	98	4.9 mg (50 µl)	0.05	1.0
MeOH					

Procedure: Dissolved 230 mg of 85% H_3PO_4 in 2 ml MeOH. Dissolved 20.4 mg of L224715 in 0.5 ml of MeOH. Added 50 µl of H_3PO_4 soln. heated to 70°C solids present. look small but xtalline. Reheated to 80°C in oil bath then cooled @ 5°C over weekend

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Date ______

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Date

Book 70316 Page 23

Project No. ______ Project Page ______

Investigator ______ Date 1 Feb 2002

Subject Prep of N-Boc L224715

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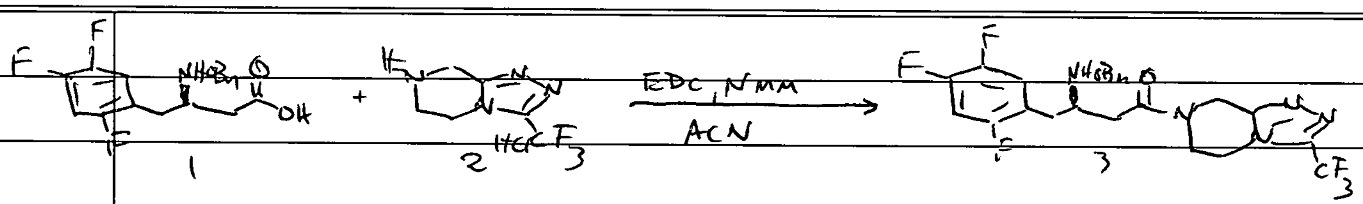
Filed in Book Number/Title ______



Reagents:

	FW	Amt	mmol	eq
Carboxylic acid 1 72324-74	339	3.16 g	9.33	1.0
Heterocycle 2 72176-100	228	3.19 g	14.0	1.5
EDC	191.71	2.68 g	14.0	1.5
N-methylmorpholine 0.920	101.15	0.943 g 1.02 ml	9.33	1.0
ACN		30 ml		

Added 30 ml ACN to 1 @ RT cooled to 0°C.
Added Heterocycle - slurry. Added EDC then NMM.
After 3 hrs no starting Acid by HPLC only 3 LCAP
of 13 min peak on 268 Nm trace. Added 15 ml H_2O &
30 ml EtOAc mixed & then cut layers washed w/ 15 ml 5%
$NaHCO_3$. Then 15 ml 20% NaCl - cut took a while
Concentrated to oil & put on Rotovap
4 Feb 2002. Diluted & Reconcentrated in IPAC Tol to remove
water. Took up in ~50 ml Toluene - ~~ & filtered off
insoluble material Reconcentrated Then redissolved in 20 ml
Toluene. Added 20 ml Hexanes product began to oil-out.
aged O/N
5 Feb 2002 No solids concentrated to oil.
19 Feb 2002 Flashed 12 g SiO_2 1:1 EtOAc/Hexanes concentrated to foam
20 Feb 2002 ^{1}H-NMR shows hexanes present in solids.
[signature] 20 Feb 2002

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20 Feb 2002 Re-concentrated in CH_2Cl_2. ^1H-NMR in D_3 ACN looked pretty good used as standard.

Calibrated HPLC 0157 by preparing stock soln of 58.0 mg of solids in 50 ml ACN. Then prepared two dilution (10 ml/25 ml & 3 ml/25 ml).

[Benzyloxyaminoamide]	Response
1.16 mg/ml	~~2224.55~~ 5396.9
0.464 mg/ml	2224.55
0.1392	671.9

Correlation was > 0.9999

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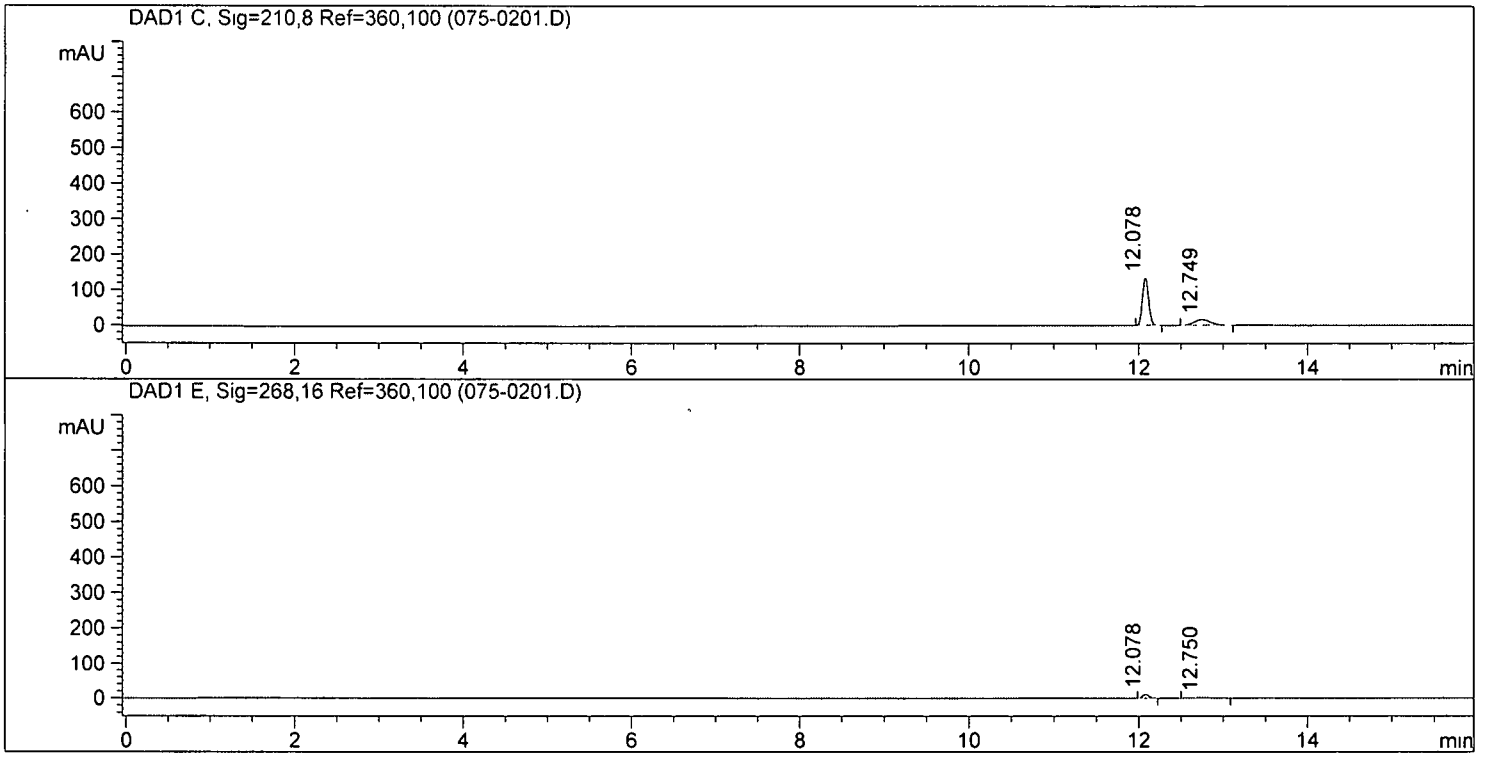
Data file :C:\HPCHEM\HPLC0157\DATA\075-0201.D Sample Name: 70316-023

58.0mg/50ml of flashed benzyloxy amide 3ml to 25ml dilute ->

==========

Injection Date : 02/20/2002 2:58:22 PM Seq Line : 2
Sample Name : 70316-023 Vial No : 75
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 02/20/2002 2:57:26 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 02/20/2002 2:57:24 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	12.08	BB	0.081	133.46	671.909	76.31	0.144418	
3	12.75	BB	0.205	15.72	208.582	23.69	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	12.08	BB	0.079	10.82	54.465	74.97	0.144418	
3	12.75	PP	0.202	1.40	18.185	25.03	0.000000	

==========

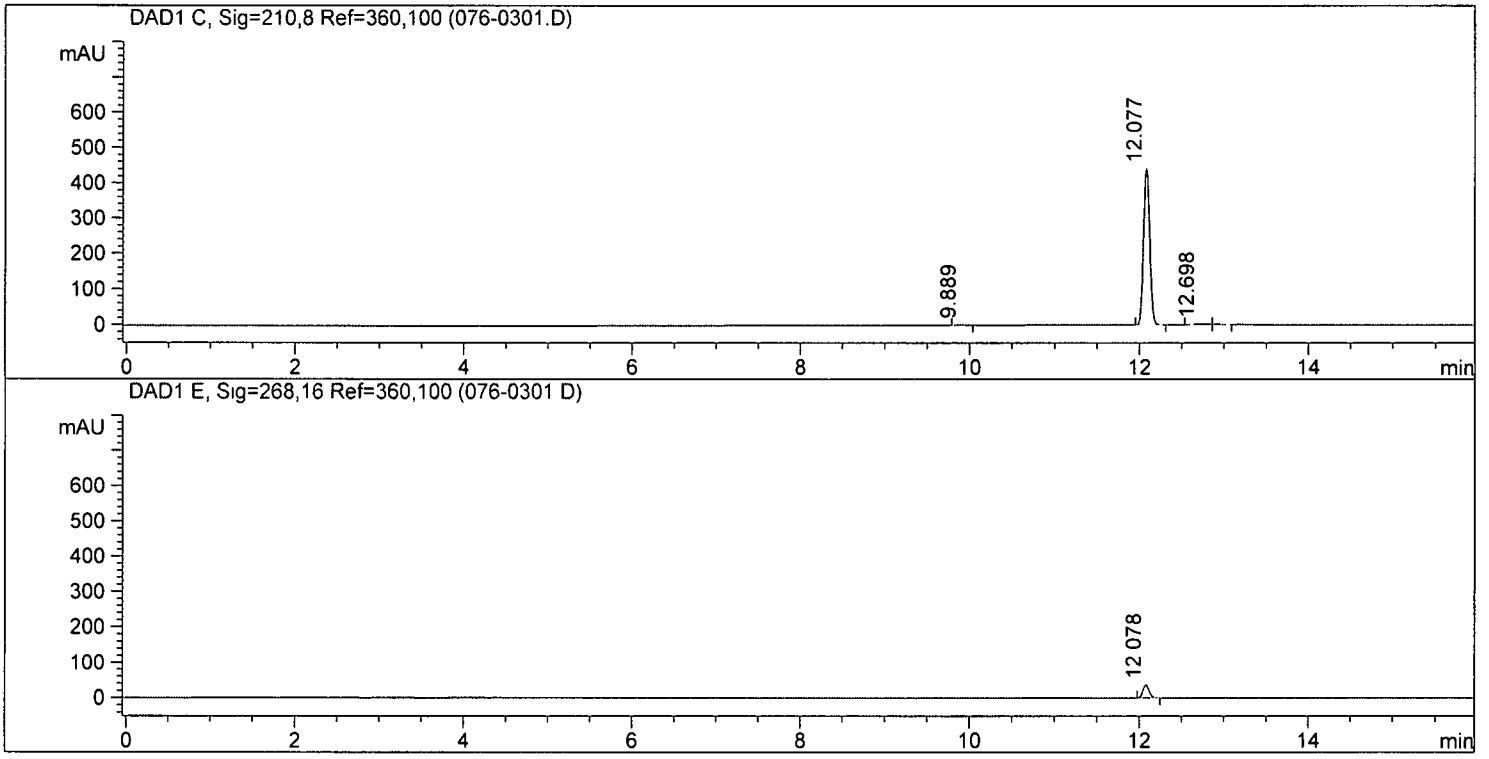
*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\076-0301.D 5.325 Sample Name: 70316-023

58.0mg/50ml of flashed benzyloxy amide 10ml to 25-1 dilution ->

Injection Date : 02/20/2002 3:16:57 PM
Sample Name : 70316-023
Acq Operator : hansen
Seq Line : 3
Vial No : 76
Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 02/20/2002 3:13:45 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



Customized Report:karlo

Sorted By : Signal
Calib. Data Modified : 02/20/2002 3:13:40 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	9.89	PP	0.083	1.25	6.562	0.29	0.000000	
3	12.08	VB	0.081	440.71	2224.550	98.09	0.476483	
4	12.70	PV	0.160	2.36	27.593	1.22	0.000000	
5	12.90	VB	0.098	1.37	9.148	0.40	0.000000	

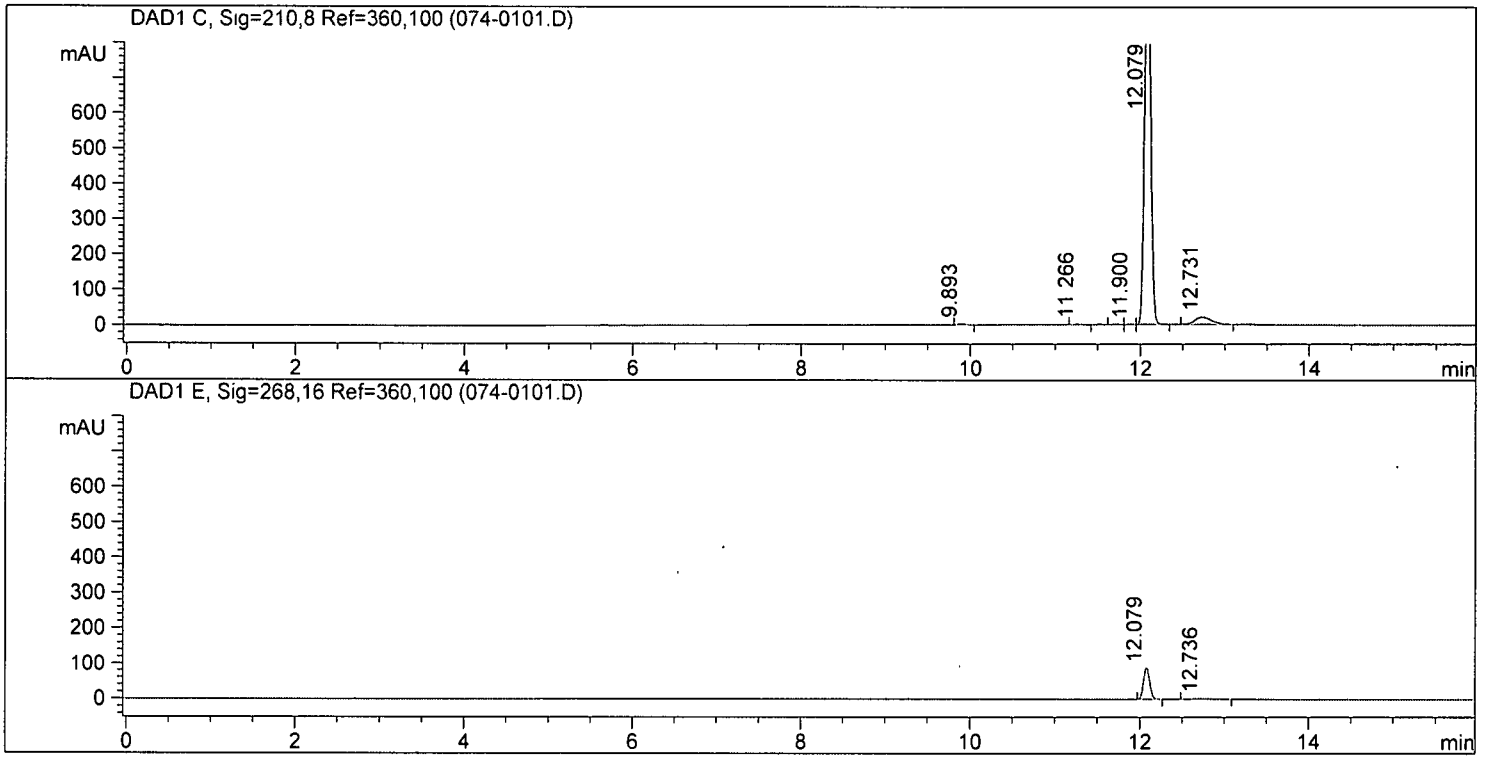
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	12.08	BB	0.081	35.91	180.772	100.00	0.476483	

Data file :C:\HPCHEM\HPLC0157\DATA\074-0101.D Sample Name: 70316-023

58.0mg/50ml of flashed benzyloxy amide ->

```
==========================================================================
Injection Date : 02/20/2002  2:39:46 PM        Seq Line  : 1
Sample Name    : 70316-023                     Vial No   : 74
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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                  Customized Report:karlo
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Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000
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Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	9.89	PP	0.082	3.03	15.689	0.27	0.000000	
3	11.27	BB	0.097	1.25	8.224	0.14	0.000000	
4	11.71	VV	0.076	1.05	5.247	0.09	0.000000	
5	11.90	VV	0.078	1.04	5.215	0.09	0.000000	
6	12.08	VB	0.081	1.06e3	5396.913	94.24	0.000000	
7	12.73	BB	0.219	20.60	295.583	5.16	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	12.08	BB	0.081	88.48	445.343	95.16	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
3	12.74	PB	0.206	1.72	22.634	4.84	0.000000	

*** End of Report ***

Current Data Parameters
NAME 70316-023
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 9.20
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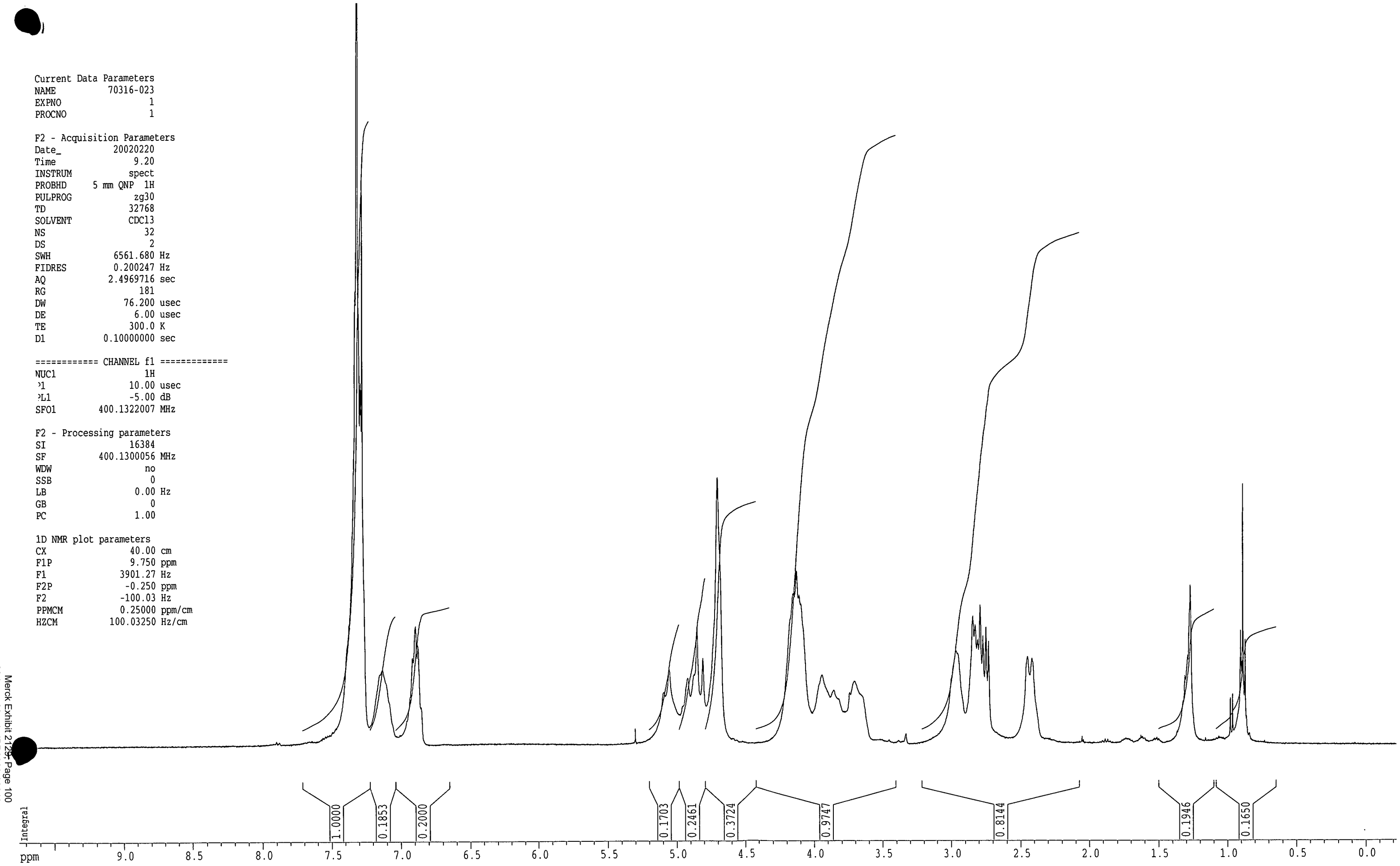
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6561.680 Hz
FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 181
DW 76.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

============ CHANNEL f1 =============
NUC1 1H
P1 10.00 usec
PL1 -5.00 dB
SFO1 400.1322007 MHz

F2 - Processing parameters
SI 16384
SF 400.1300056 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3901.27 Hz
F2P -0.250 ppm
F2 -100.03 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.03250 Hz/cm



bno amino amide vapped in dcm
nmr400c h1


```
Current Data Parameters
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EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
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Time              14.21
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG             zg30
TD                 32768
SOLVENT            CD3CN
NS                    32
DS                     2
SWH            6561.680 Hz
FIDRES         0.200247 Hz
AQ            2.4969716 sec
RG                  256
DW                76.200 usec
DE                 6.00 usec
TE                300.0 K
D1           0.10000000 sec

============ CHANNEL f1 =============
NUC1                  1H
P1                10.00 usec
PL1               -5.00 dB
SFO1        400.1322007 MHz

F2 - Processing parameters
SI                 16384
SF          400.1300056 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                 1.00

1D NMR plot parameters
CX                40.00 cm
F1P                9.750 ppm
F1              3901.27 Hz
F2P               -0.250 ppm
F2              -100.03 Hz
PPMCM          0.25000 ppm/cm
HZCM         100.03250 Hz/cm
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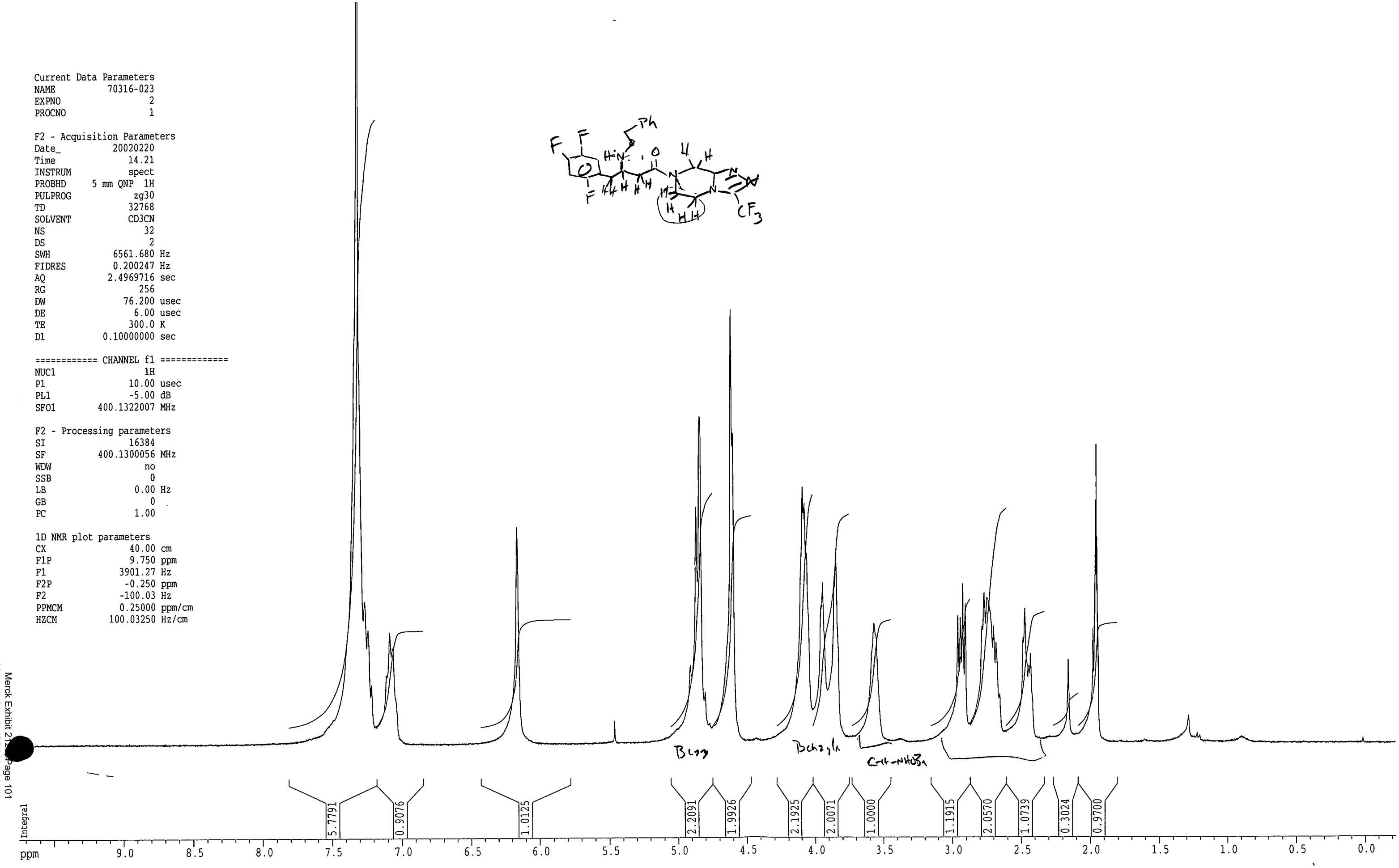

Data file :C:\HPCHEM\HPLC0157\DATA\022-0101.D Sample Name: 70316-023

isolated oil ->

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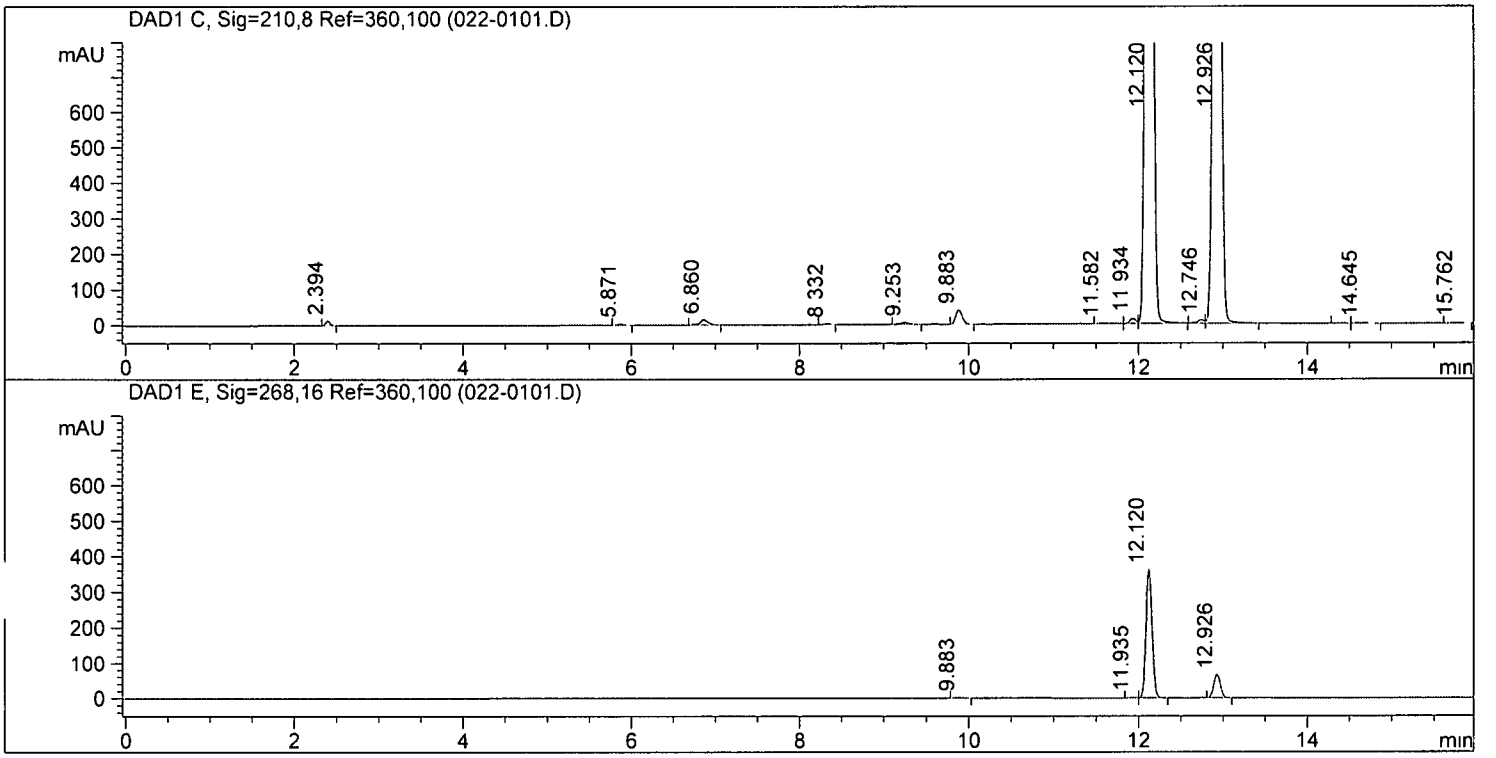
Injection Date : 02/05/2002 9:09:27 AM Seq Line : 1
Sample Name : 70316-023 Vial No : 22
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

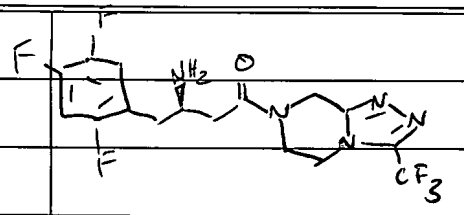
Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.39	PB	0.057	13.00	47.607	0.16	0.000000	
2	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
3	5.87	BP	0.077	2.98	14.639	0.05	0.000000	
4	6.86	BB	0.100	15.04	106.213	0.37	0.000000	
5	8.33	BV	0.086	2.51	13.833	0.05	0.000000	
6	9.25	BB	0.100	5.53	39.912	0.14	0.000000	
7	9.88	BP	0.084	39.89	211.828	0.73	0.000000	
8	11.58	BV	0.129	2.05	19.231	0.07	0.000000	
9	11.93	VV	0.077	14.72	72.445	0.25	0.000000	
10	12.12	VB	0.108	2.27e3	1.473e4	50.94	0.000000	
11	12.75	BV	0.087	10.33	60.854	0.21	0.000000	
12	12.93	VB	0.106	2.09e3	1.357e4	46.92	0.000000	
13	14.41	BV	0.098	1.22	7.467	0.03	0.000000	
14	14.64	VP	0.128	1.53	12.332	0.04	0.000000	
15	15.76	BBA	0.118	1.50	11.559	0.04	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	9.88	BP	0.084	1.76	9.407	0.43	0.000000	
3	11.93	PV	0.076	1.83	8.794	0.40	0.000000	
4	12.12	VB	0.079	361.88	1829.885	82.89	0.000000	
5	12.93	VP	0.086	65.49	359.639	16.29	0.000000	

*** End of Report ***



Reagents:		FW	Amt	mmol	eqs
L224715-000T001		407	200.0	0.491	1.0
H_3PO_4	98 g/mol 4EtOH	98	48.1 g (0.5 ml).	0.491	1.0
EtOH			4.5 ml		
WATER			0.875 ml		

Dissolved 715 in ~~0.5~~ 4.5 ml of EtOH. heated to 75°C Added 0.50 ml of H_3PO_4 soln @ 63°C white solids formed. Added 0.125 ml H_2O @ 67°C. Temp rose to 72°C - soln quite thick added 0.125 ml H_2O At 75°C, still slurry added 0.125 ml H_2O. 75°C for 5 min still slurry added 0.125 ml H_2O

20 minutes ~~for~~ @ 76°C still solids added 0.25 ml water most of solids dissolved Added 0.125 ml H_2O - soln not completely clear. Cooled from 77°C to 25°C over @ 5°C/hr ~~Sat~~ 4 Feb 2002

5 Feb 2002 - Crystals were present in batch large plate under microscope. Added 5 ml EtOH as anti solvent drop wise to slurry. Aged 1 hr then Filtered washed w/ EtOH. Dried in oven for 1 hr isolated 199 g of white solids ML's had [715] = 1.82 mg/g Solids were clean by ^{1}H-NMR (No EtOH). LC should

Countersigned by _____

Date _____

5 Feb 2002

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

83.6 wt%. theoretical is 80.5 wt%

50 mg given to Phys Mats.

100 mg given to PR&D

5 Feb 2002

Countersigned by

Date

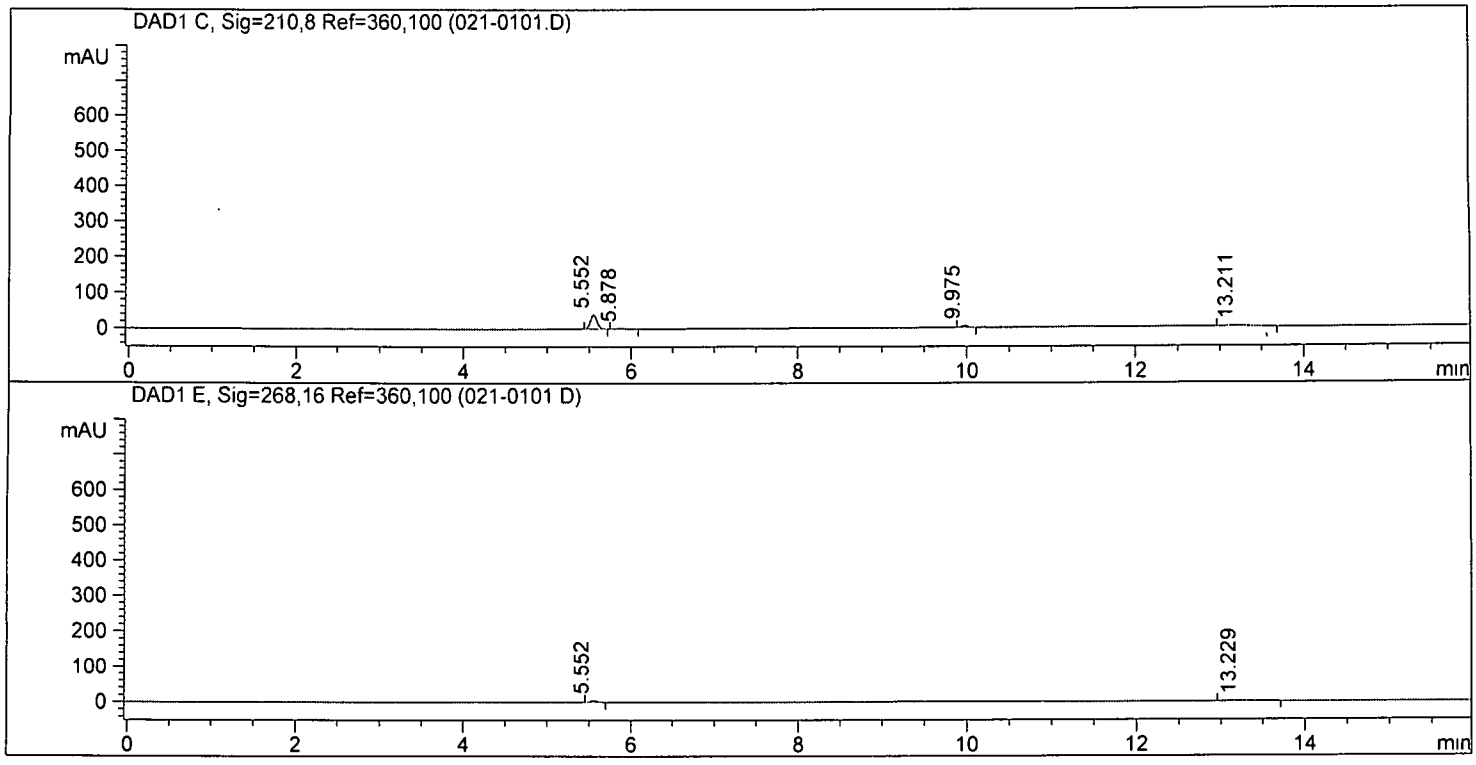
Data file :C:\HPCHEM\HPLC0157\DATA\021-0101.D Sample Name: 70316-025

0.2893g/10ml of super after 5ml extrat EtOH ->

==========

Injection Date : 02/05/2002 8:00:03 AM Seq Line : 1
Sample Name : 70316-025 Vial No : 21
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.082	39.74	210.740	77.85	0.052757	L-224,715
2	5.88	BP	0.084	1.12	6.145	2.27	0.000000	
3	9.97	BB	0.076	5.12	24.697	9.12	0.000000	
4	13.21	BP	0.236	2.05	29.119	10.76	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.082	4.54	24.120	54.70	0.052757	L-224,715
2	13.23	BP	0.253	1.29	19.979	45.30	0.000000	

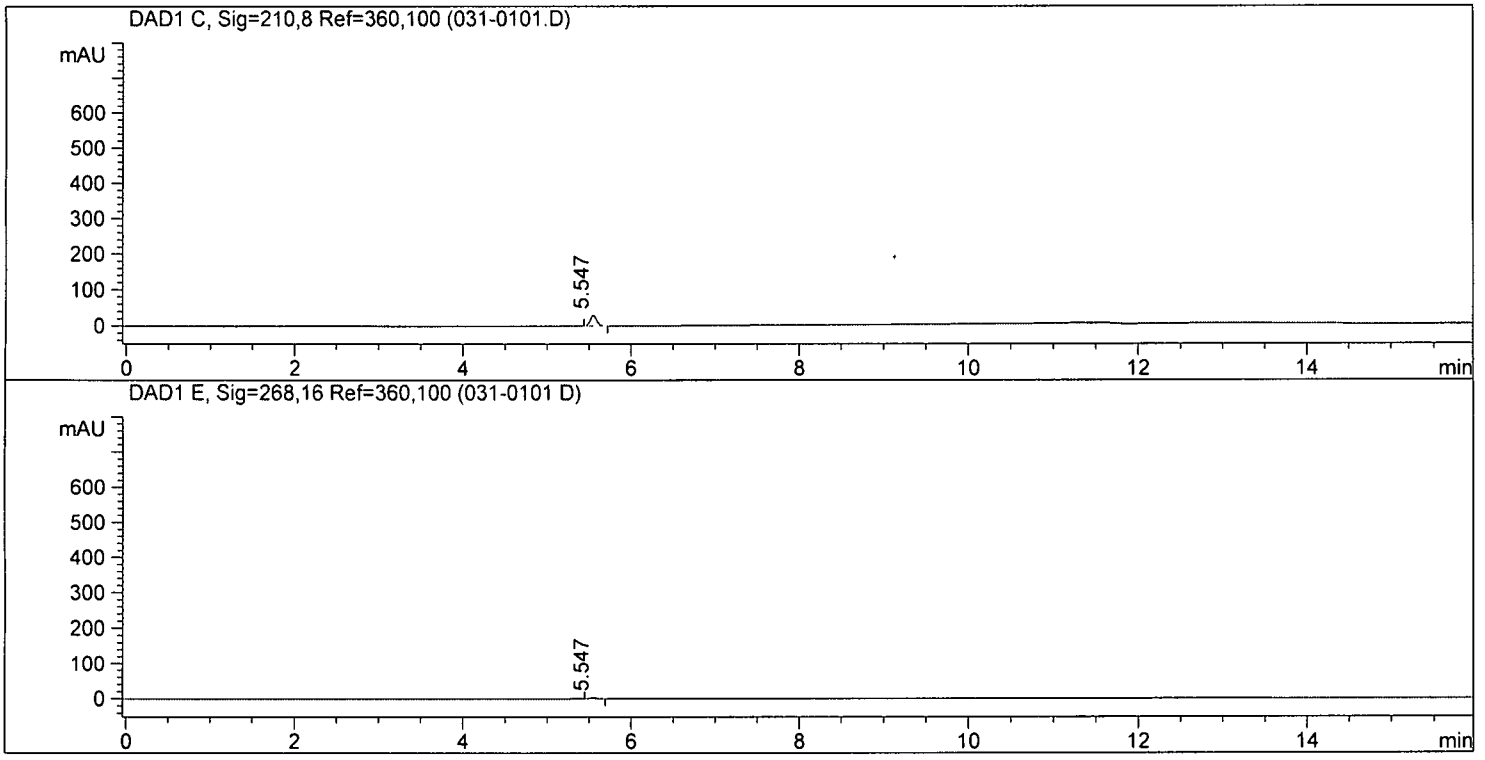
==========

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\031-0101.D Sample Name: 70316-025

0.0404mg/ml 715 ->

```
==========================================================================
Injection Date : 02/05/2002  12:06:46 PM       Seq Line  : 1
Sample Name    : 70316-025                     Vial No   : 31
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==========================================================================================
                Customized Report:karlo
==========================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100

 Peak  RT    Type Width Height   Area     Area     Amount          Name
  #   [min]      [min]         [mAU*s]     %      mg/ml
 ---- ----- ---- ----- ------ -------- ------ ---------- ------------------
    1  5.55 BB   0.082  29.23  155.833 100.00   0.038173          L-224,715


Signal:  2 DAD1 E, Sig=268,16 Ref=360,100

 Peak  RT    Type Width Height   Area     Area     Amount          Name
  #   [min]      [min]         [mAU*s]     %      mg/ml
 ---- ----- ---- ----- ------ -------- ------ ---------- ------------------
    1  5.55 BB   0.082   3.34   17.748 100.00   0.038173          L-224,715


==========================================================================================
                              *** End of Report ***
```

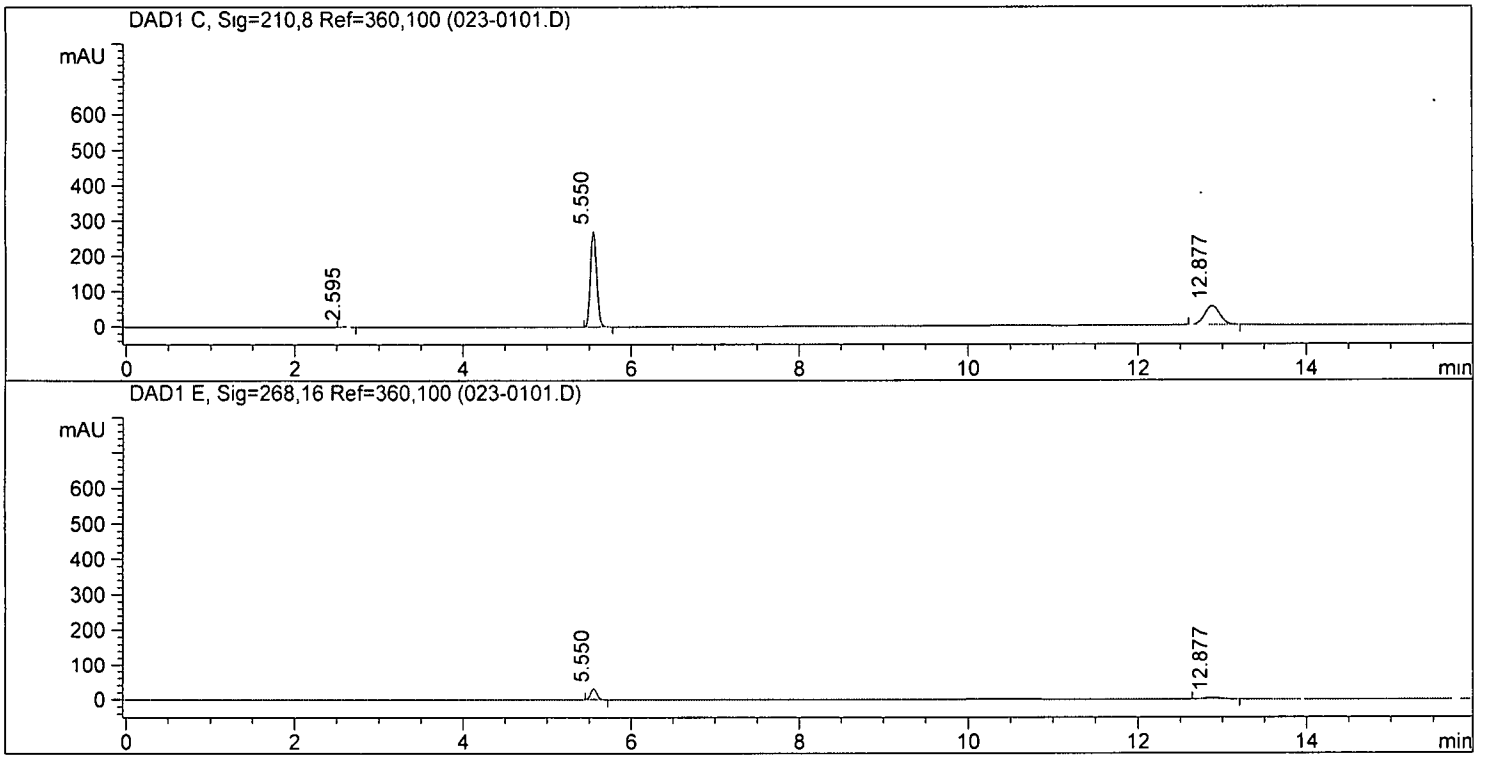
Data file :C:\HPCHEM\HPLC0157\DATA\023-0101.D Sample Name: 70316-025

11.1 mg/25ml og phosphate ->

==========

Injection Date : 02/05/2002 9:41:03 AM Seq Line : 1
Sample Name : 70316-025 Vial No : 23
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.60	PB	0.076	1.46	7.264	0.35	0.000000	
2	5.55	PB	0.080	272.03	1408.902	67.44	0.370994	L-224,715
3	12.88	BB	0.195	53.51	672.897	32.21	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.080	31.36	161.870	73.55	0.370994	L-224,715
2	12.88	BB	0.192	4.70	58.202	26.45	0.000000	

==========

*** End of Report ***

L224,715
H3PO4 salt
from EtOH/water

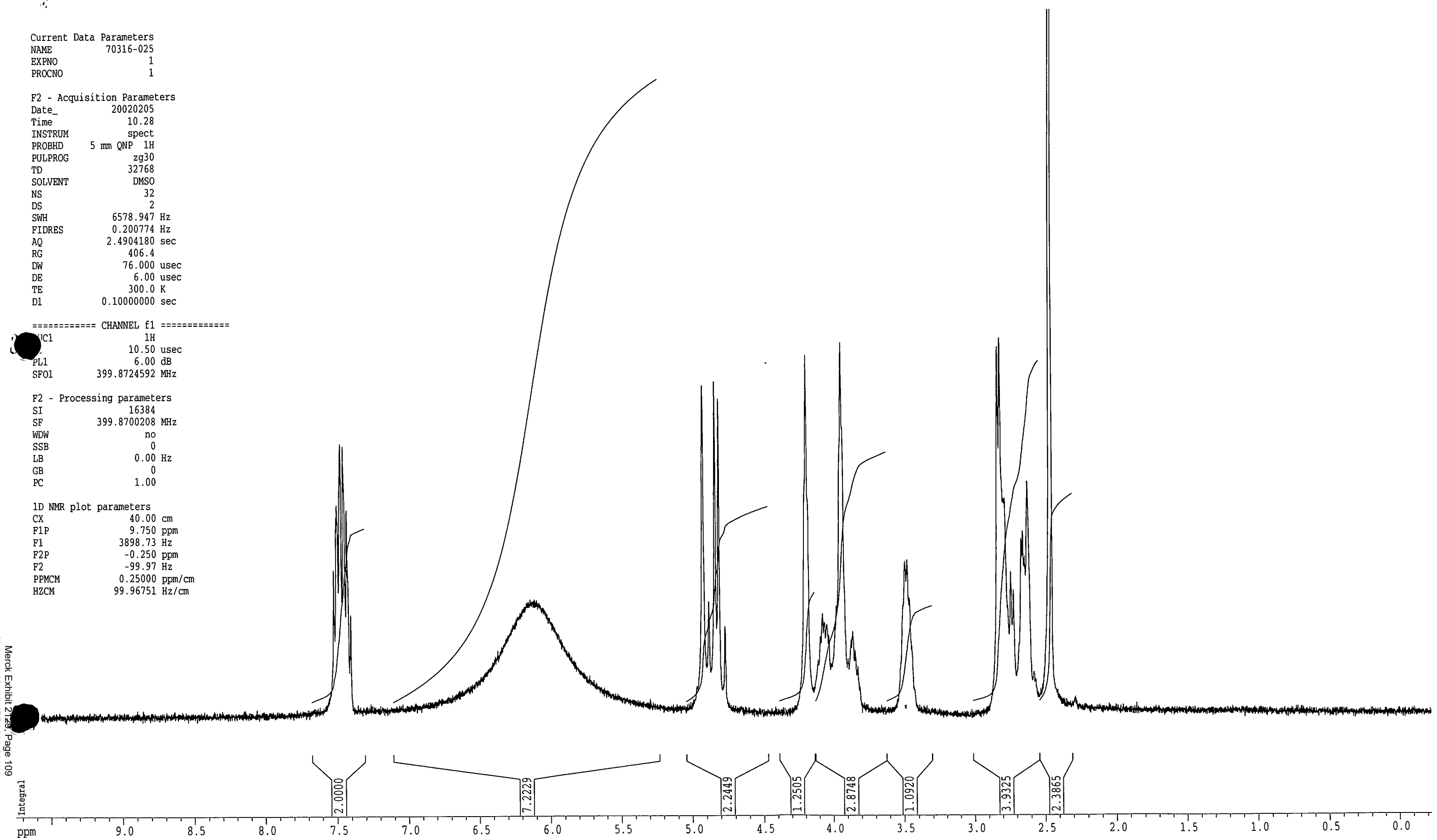
Current Data Parameters
NAME 70316-025
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020205
Time 10.28
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 6578.947 Hz
FIDRES 0.200774 Hz
AQ 2.4904180 sec
RG 406.4
DW 76.000 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

============ CHANNEL f1 =============
NUC1 1H
P1 10.50 usec
PL1 6.00 dB
SFO1 399.8724592 MHz

F2 - Processing parameters
SI 16384
SF 399.8700208 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3898.73 Hz
F2P -0.250 ppm
F2 -99.97 Hz
PPMCM 0.25000 ppm/cm
HZCM 99.96751 Hz/cm

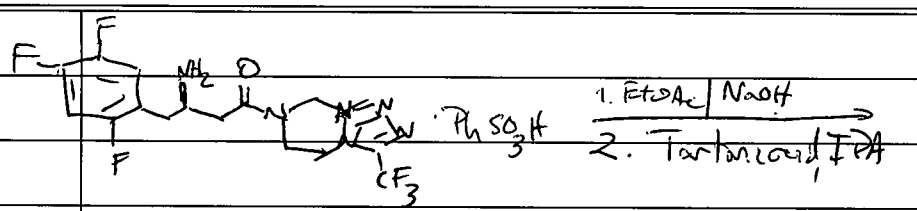


Investigator _____ Date 6 Feb 2002

Subject Formation of L224715 Tartrate

Restricted Confidential limited access

Filed in Book Number/Title _____



Reagents:		FW	Amt	mmol	eq
L224715. $PhSO_3H$	70316-009	565	2.50 g	4.42	1.0
EtOAc			25 ml		
NaOH		1M	10 ml	10.00	
L-tartaric acid	Aldrich BN8058 425 Au	150	0.675	4.50	1.02
IPA			90 ml		

Procedure: Suspended 2.5 g of $PhSO_3H$ salt in 25 ml EtOAc. Added NaOH soln - solids dissolved. Org layer did not contain $PhSO_3H$. assayed N 1.83 g (theoretical 1.80 g). washed w/ 10 ml 20% NaCl. Concentrated - redissolved w/ 20 ml IPA & Reconcentrated. Dissolved oil in 50 ml IPA. Filtered into 250 ml RBF. Added 40 ml additional IPA (50 ml/g volume). Heated to 50°C. Dissolved 0.675 g of tartaric acid in 9 ml H_2O. charged to addn Funnel. Added Tartaric acid soln after addn soln got hazy as crystals formed. heated to 60°C & aged o/N

7 Feb 2002 - cooled slurry to RT. solids are fine needles under microscope. Filtered @ RT washed w/ IPA. Dried in oven

8 Feb 2002 2.1 g, 85% yield

Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

Date

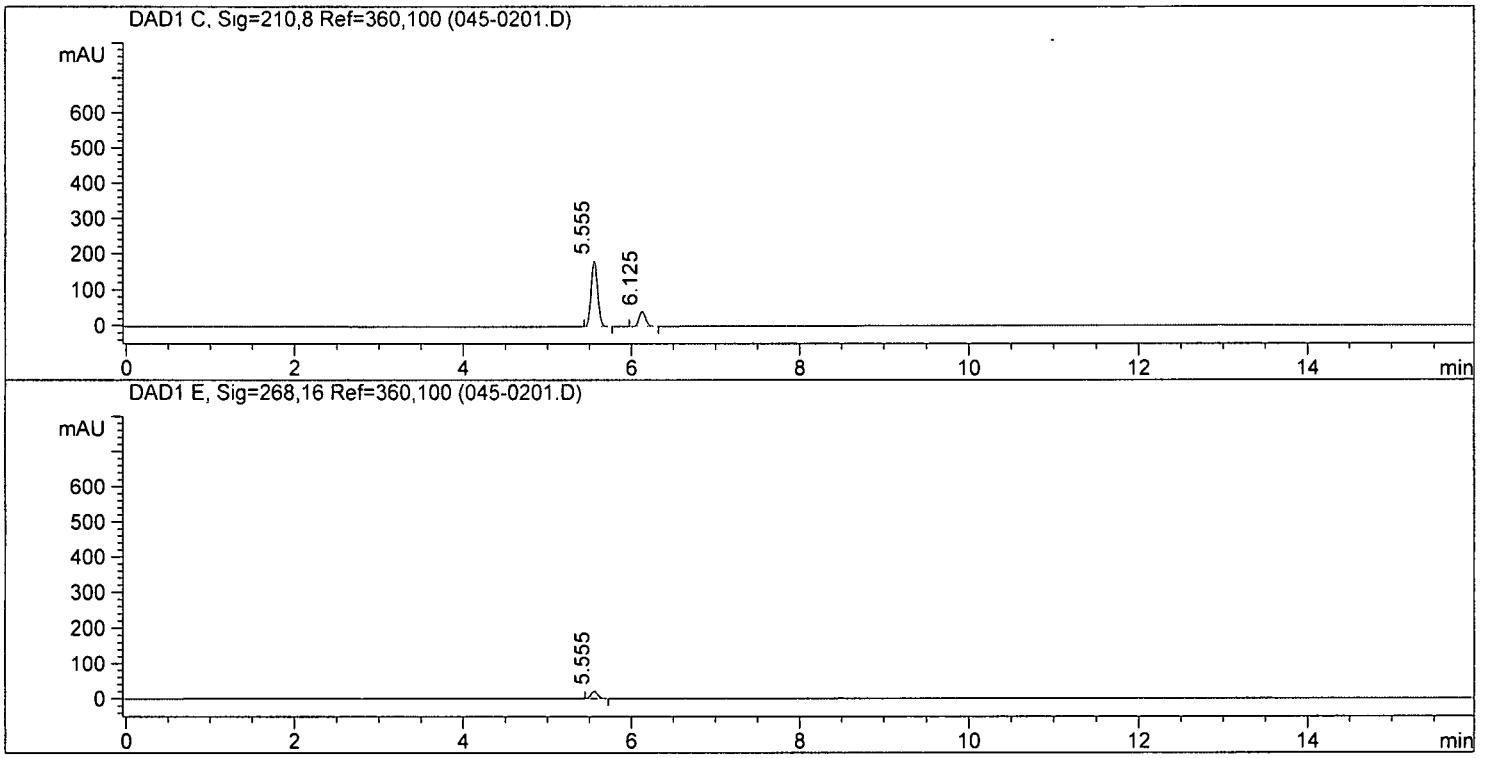
Data file :C:\HPCHEM\HPLC0157\DATA\045-0201.D Sample Name: 70316-027

0.1815mg/50ml of 25.55g etoac post brine ->

==========

Injection Date : 02/06/2002 8:01:41 AM Seq Line : 2
Sample Name : 70316-027 Vial No : 45
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

1.83g 715

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	PB	0.085	183.02	989.311	81.34	0.259549	L-224,715
2	6.12	VB	0.083	42.10	226.917	18.66	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.55	BB	0.085	21.06	113.644	100.00	0.259549	L-224,715

==========

*** End of Report ***

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.54	BB	0.082	85.12	455.852	100.00	1.034739	L-224,715

*** End of Report ***

Investigator _____ Date 6 Feb 2002

Subject Formation of $PhSO_3H$ - 715 H_2 link

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Filed in Book Number/Title _____

$L224715\text{-}PhSO_3H \xrightarrow{H_2O/N_2} L224715\text{-}PhSO_3H \cdot H_2O$

~~600~~ 750 mg of Besylate (76316-009) were placed in xtallizing dish. A bubbler of H_2O was attached to N_2 inlet & vacuum applied to oven. 48°C. ~~Took off~~ 7 Feb 2002. Removed material and gave to C. Linden He indicated that only a small amt of hemihydrate was present.

7 Feb 2002

Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

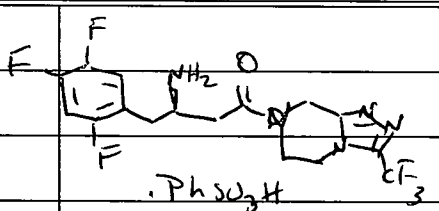
Date

Investigator _____ Date 6 Feb 2002

Subject Formation of L224715 Phosphate

Restricted Confidential limited access

Filed in Book Number/Title _____



1. EtOAc / NaOH
2. H_3PO_4, EtOH/H_2O

L224715 - H_3PO_4

Reagents:		FW	Amt	mmol	eq
L224715 $PhSO_3H$ salt 70316-009		565	4.00 g	7.08	1.0
~~H_3PO_4~~ EtOAc			40 ml		1.
1N NaOH			16 ml		
H_3PO_4	0.85%	98	0.820 mg	7.10	1.0
EtOH			28-1 +7		
H_2O					

Procedure: suspended 7.15 $PhSO_3H$ salt in 40 ml EtOAc. Added 1M NaOH, soln became clear. No exotherm. Cut layers, washed EtOAc w/ 20% NaCl (15 ml). Concentrated & then Re dissolved in 20 ml EtOH & reconcentrated twice. Dissolved in 28 ml EtOH w/ some heat & filtered into 250 ml RBF w/ mech stirrer. Heated to 70°C & added 2 ml H_2O. Added a soln of H_3PO_4 in 7 ml EtOH. After first couple of drops white ppt formed (0.2 ml of addn). Seeded w/ 6 mg of 70316-025. Resumed addn @ 75°C over. Crystals are small and some amorphous material may be present. After addn was complete a small slurry sample was taken. 3.2 ml of additional H_2O was added (5 ml total). Solids seemed to be dissolving. Added 2 more ml H_2O (7 ml total) still small amts of solids. Added 0.9 ml H_2O - soln went clear. Total volume ~~38.6~~ 42.9 ml 7.9 ml H_2O (~~0.215~~ 18.4% H_2O). Cooled over

RBA 6 Feb 2002

Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

@ 5°C / hr to RT O/N

TFA 2001 added dropwise, 57.1 ml of Ethanol to slurry

[715] @ 42.9 ml total vol

@ 100 ml total vol

Filtered washed w/ 80 ml Ethanol. Dried w/ N_2 on frit. Isolated 3.03 g 85% Recovery

Countersigned by

Date

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Feb 6, 2002	0213013	70316-031		

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
Karl Hanson	[ ]RETAIN [ ]RETURN [ ]DISCARD		Hanson	

COMPLETE STRUCTURE

CHEMICAL NAME

L-224,715 Phosphate Salt

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[X] IR	
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC	[ ] NMR	
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS	

DO NOT WRITE BELOW THIS LINE

RESULTS

Time	RRT	Area%
11.56	0.93	0.16%
11.85	0.95	0.13%
12.41	1.00	99.67%
~~14.57~~	~~1.58~~	not real

Total imp = 0.29%

Chiral

minor enantiomer – none detected

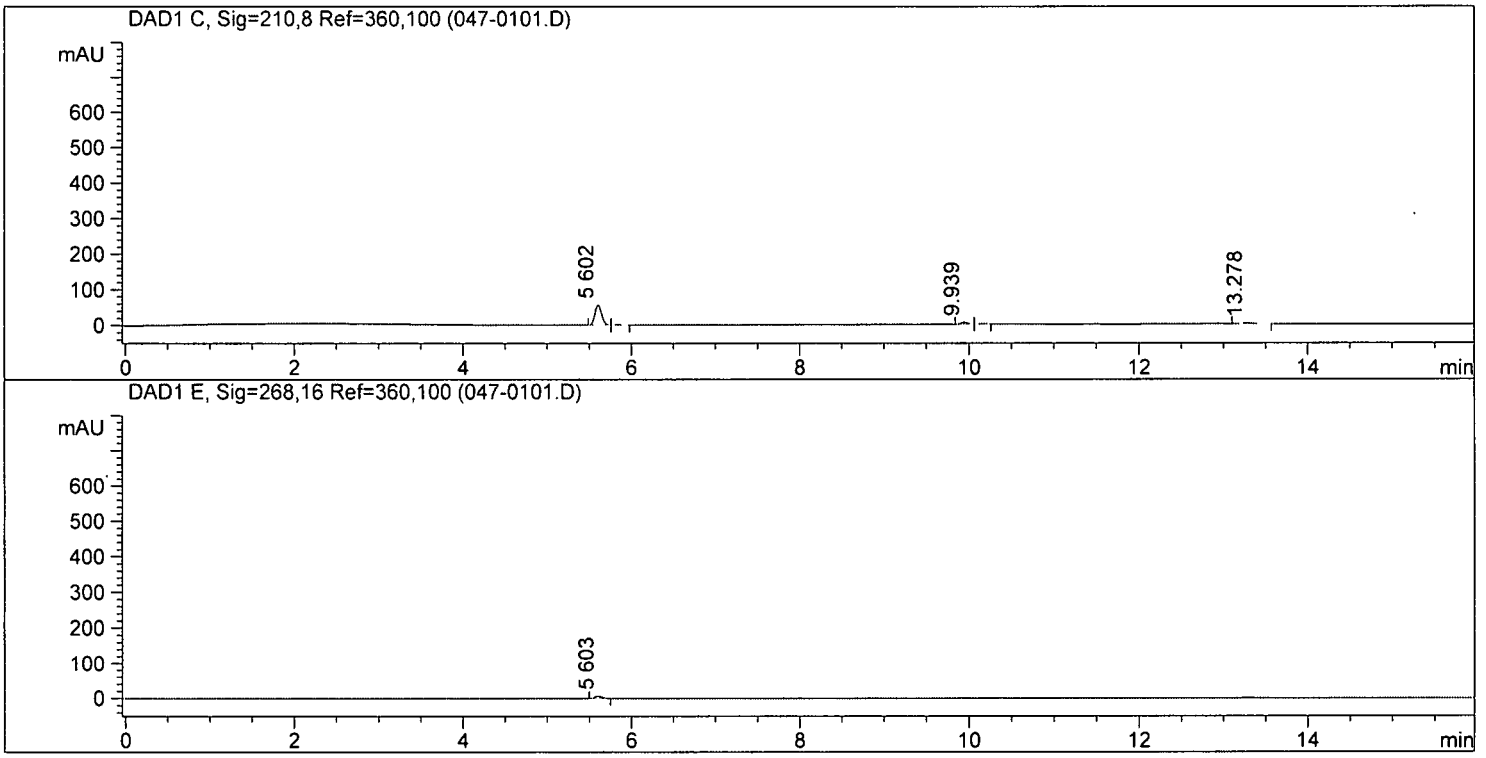
NB# 25878-111

PP LAB PROC. #	ANALYST	DATE
	J.G.D.	Feb 21, 2002

Data file :C:\HPCHEM\HPLC0157\DATA\047-0101.D Sample Name: 70316-031

0.3925g/50ml of super after cool down ->

```
==========================================================================
Injection Date : 02/07/2002  7:34:01 AM        Seq Line  : 1
Sample Name    : 70316-031                     Vial No   : 47
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==========================================================================================
                  Customized Report:karlo
==========================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000
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Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.60	BV	0.084	56.36	310.212	83.01	0.079177	L-224,715
2	5.84	VB	0.091	1.10	6.687	1.79	0.000000	
3	9.94	BV	0.081	5.83	30.354	8.12	0.000000	
4	10.17	VV	0.092	1.71	10.590	2.83	0.000000	
5	13.28	PB	0.152	1.59	15.882	4.25	0.000000	

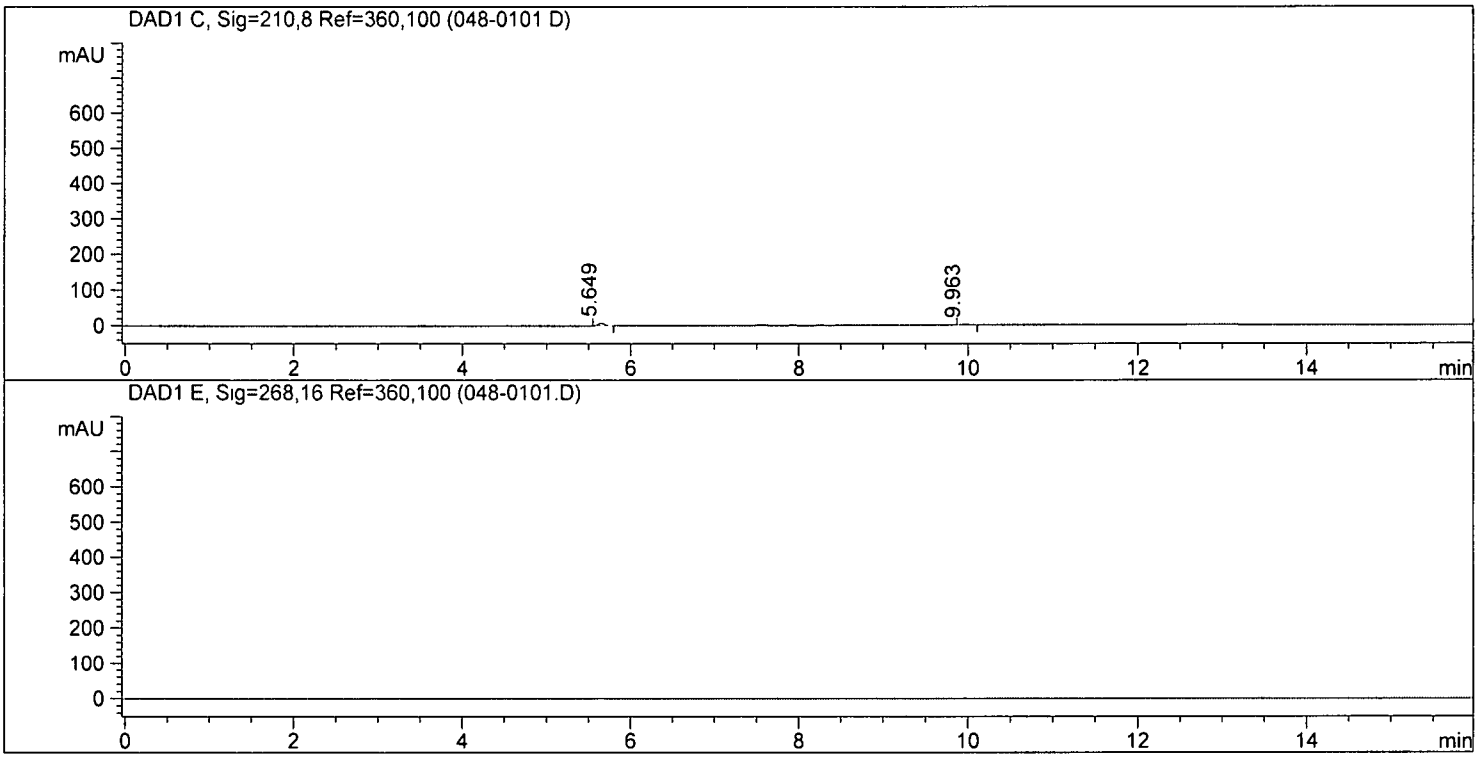
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.60	BB	0.087	6.51	36.136	100.00	0.079177	L-224,715

Data file :C:\HPCHEM\HPLC0157\DATA\048-0101.D Sample Name: 70316-031

0.2753g/50ml at 100ml total volume ->

```
==========================================================================
Injection Date : 02/07/2002  8:12:57 AM        Seq Line  : 1
Sample Name    : 70316-031                     Vial No   : 48
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```

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==========================================================================================
                Customized Report:karlo
==========================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	BB	0.083	7.50	39.065	80.15	0.007159	L-224,715
2	9.96	PB	0.081	1.80	9.677	19.85	0.000000	

```
Signal:  2 DAD1 E, Sig=268,16 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.007159	L-224,715

```
==========================================================================================
                              *** End of Report ***
```

L224715-$PhSO_3H$ Acetonitrile →

Reagnts		FW	A-t	mol eq
L224715-$PhSO_3H$	70316-009	565	50 mg	
ACN			0.5 ml	

dissolved salt in ACN w/ heat, cooled to RT slurry formed.

Countersigned by

Date

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

Countersigned by

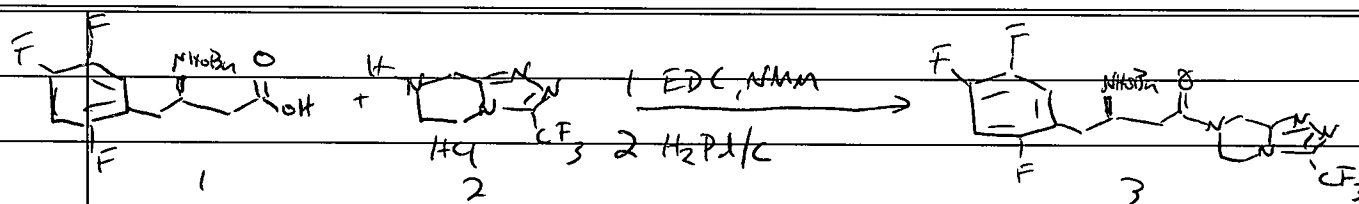
Date

Book 70316 Page 35 Project No. ______ Project Page ______

Investigator ______ Date 8Feb2002

Subject ______ Restricted Confidential limited access

Filed in Book Number/Title ______



Reagents:		FW	Amt		mmol	eq
BocAmino acid 72324-98		339	~~31~~ 10.54g		31.1	1.0
Triazole HCl salt 72176-100		228	10.64		46.65	1.5
EDC		191.71	8.95g		46.65	1.5
NMM (N-methylmorpholine)	0.920	101.15	3.16g	3.43ml	31.1	1.0
ACN			100ml			

Procedure: oil from 7232498 was dissolved in ACN & then Reconcentrated twice - slight smell of HOAC & oil was yellow. Redissolved in 100ml ACN in 250ml RBF. Added Heterocycle & assayed. soln has 1 impurity @ 9.95 min. Cooled to 3°C. Added EDC & then N-methyl morpholine. Temp rose to 5°C. After 1/2 hr 92% conversion of Aminoacid to Amide observed. After 15 hrs >99% conv of acid. Added 60ml H_2O, 100ml EtOAc, cut. Added 60ml 5% $NaHCO_3$, cut. Added 60ml sat NaCl, cut. Concentrated & then redissolved in ~~MeOH~~ MeOH (100ml). Submitted to H_2 lab - 3.00g 10% Pd/C, 40 PSI, 50°C 36h.

11Feb2002. Material took up theoretical H_2 after 8h. Assay showed all of N-Boc amide consumed. Filtered. Assayed filtrate to contain 10.30g (81% assay yield) of 7/5. Concentrated to oil.

[signature] 11Feb2002

Countersigned by ______

Date ______

MERCK & CO., INC./MRL 840(6/00)

DO NOT BEGIN NEW EXPERIMENTS ON THIS PAGE.

11Feb2002 - Redissolved & concentrated to oil in Ethanol. Dissolved in 20 ml EtOH & Filtered through Celite into 500 ml RBF ~~the~~ Washed Flask & Filter 3×5 ml silica floc.
Total 35 ml Ethanol (3.5 ml/g). Rinsed w/ 5 ml additional EtOH 40 ml total 4 ml/g. 2.91 g of H_3PO_4 dissolved in ~~10~~ 5 ml H_2O.
Seeded Ethanol soln w/ 50 mg of 70316-031. Added H_2O soln dropwise. Solids formed & these were very thick. under scope allamorphous material with a few xtals - (probably seed).
Heated to 75°C, After 1hr soln had loosened up but crystals small & slightly amorphous. Added 10 ml H_2O @ 72°C - Soln went homogeneous
12Feb2002 - Crystals had formed & they are huge by scope! Added 145 ml of EtOH dropwise to slurry

After 1/2 hr [715] = 2.22 mg/g
After 3 hr [715] = 2.34 mg/g

Filtered & washed w/ 50 ml Ethanol isolated 11.81 g white solids. ^1H-NMR in D_2O showed no Ethanol present
Assayed ML's & wash to contain 0.382 g of 715.
9.9 g total recovery (assuming 81 wt% solids) 96% mass balance
13Feb2002 - Assayed 25.7 mg of H_3PO_4 salt to contain 20.72 mg of L224715. 80.6 wt%. theoretical is 80.60 wt%.
15Feb2002 Sent 3 g marked MK-U-1 to Devlab
18Feb2001 - Analytical shows > 99.49% LCAP w/ 2 impurities @ <0.2 nonmeasurable
20Feb2002 3.50 g sent to Kari Lynn WP for dosing studies 3.00 g sent to R. Hazell Devlab for capsule studies L 224715-006 F001

[signature] 20Feb2002

Countersigned by

Date

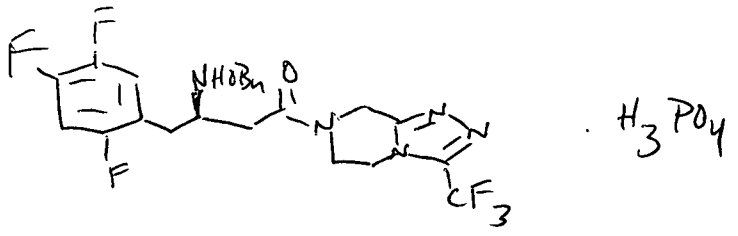
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L-224715-006 F001

MOLECULAR FORMULA:	MOLECULAR WT.:	DATE:	ASSIGNED BY:
$C_{16}H_{18}F_6N_5O_5P$	505	6 March 2002	Hansen

CHEMICAL/TRIVIAL NAME:

STRUCTURE.



. H_3PO_4

LABELING INSTRUCTIONS
(FOR OUTSIDE DELIVERIES)

- ☐ L NUMBER
- ☐ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER:

Prepared by/Commercial Source:	Notebook Ref /Lot No :
	70316-035

Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC

☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*:

☒ data generated by Analytical Research

99.69 LCAP

2 impurities

RRT	Area%
0.93	0.16
0.95	0.12

nominal enantiomer

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT

☐ YES ☒ NO

LIT. REF./CAS REG NO

REMARKS:

200 mg released to J. Robert Reed in vitro studies

PB ECL-

Storage Conditions: (check one)

- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ –70°C freezer
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited.

☐ For safety information and special handling precautions, access CHIS.

SEND TO: (NAME, LOCATION, QUANTITY, TEST NO OR ACRONYM AND INDICATE IF DELIVERED)

Material is (select one) ____ GMP ; ____ non-GMP and will be used in (select one). ____ GMP/GLP study, ___ non-GMP study.

CC: NAMES AND LOCATIONS:

Transfer Requested By	Delivery Sheet By:	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By
Name: Location:	Name Location:	Dept Approval	Quality Approval	

MERCK & CO., INC.
R827-L 4/75

REQUEST FOR ANALYSIS

DATE	PPCL #	NOTEBOOK OR BATCH #	PROJECT #	EXT
Feb 13, 2002	0213039 / 0213040	70316-035	L-224,715	

SUBMITTED BY	SAMPLE DISPOSITION	MOLECULAR WEIGHT	SEND REPORT TO	AREA
	[ ]RETAIN [ ]RETURN [ ]DISCARD			

COMPLETE STRUCTURE

CHEMICAL NAME
L-224715 Phosphate salt (13039)
Mother Liquors (13040)

OTHER TESTS AND COMMENTS

EMPIRICAL FORMULA

[X] TEST	[ ] KARL FISCHER	[ ] TOTAL SOLIDS	[ ] LOSS ON DRYING	[ ] UV	[ ] MELTING POINT	[ ] SPECIFIC ROTATION	[ ] RESIDUE ON IGNITION	[ ] IR
[ ] TITRATION	[ ] COLOR OF SOLUTION	[ ] HEAVY METALS	[ ] IRON	[ ] DISC	[ ] pH	[ ] VPC	[X] LC area % chiral	[ ] NMR
[ ] MICRO ANALYSIS CHN	[ ] PSA	[ ] DSC	[ ] TG	[ ] X-RAY	[ ] TLC	[ ] BULK	[ ] MESH ANALYSIS	[ ] ALL CONTROLS

DO NOT WRITE BELOW THIS LINE

RESULTS

0213039

RRT	Area%
0.93	0.16
0.95	0.12
1.00	99.69

Total imp = 0.28%

RRT	Area%
0.65	3.77
0.74	0.50
0.90	1.24
0.98	0.10
1.00	72.70
1.03	6.70
1.05	0.22
1.06	0.14
1.09	0.86
1.40	0.35
1.41	1.73
1.46	0.16
1.48	3.22
1.54	0.13
1.56	0.49
1.83	1.73
1.86	0.35
1.88	0.11
1.92	4.50
1.99	0.24
2.27	0.55

50ther imp

0.10 > Simp > 0.05

Chiral (0213039)

None detected for minor enantiomer

0213040

major = 98.4% (L-224,715)

minor = 1.6% (enantiomer/imp?)

PP LAB PROC #	ANALYST	DATE
	J.GD.	Feb 26, 2002

0

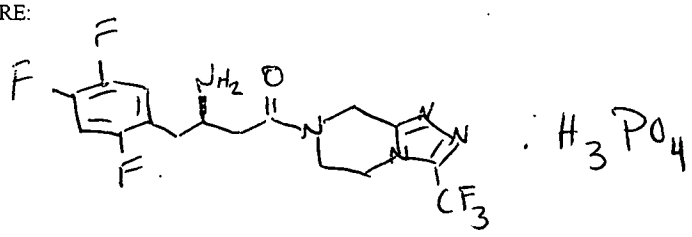
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L-224715-006F 001

MOLECULAR FORMULA:	MOLECULAR WT.:	DATE:	ASSIGNED BY
$C_{16}H_{18}F_6N_5O_5P$	505	15 Feb 2002	Hansen 2/20/02

CHEMICAL/TRIVIAL NAME: MK-4-1

STRUCTURE:



$\cdot H_3PO_4$

L224715 Phosphate salt

LABELING INSTRUCTIONS (FOR OUTSIDE DELIVERIES)

- ☐ L NUMBER
- ☒ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER: L224715

Prepared by/Commercial Source:	Notebook Ref./Lot No.:	Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC
	70316-035	☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*:

☒ data generated by Analytical Research

99.69 LCAP

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT ☐ YES ☒ NO

LIT. REF./CAS REG. NO.

REMARKS:

PB ECL-

Storage Conditions: (check one)

- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ –70°C freezer
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited.

☐ For safety information and special handling precautions, access CHIS.

SEND TO: (NAME, LOCATION, QUANTITY, TEST NO. OR ACRONYM AND INDICATE IF DELIVERED)

Richard Hazell Dculab

Material is (select one) ___ GMP, X non-GMP and will be used in (select one): ___ GMP/GLP study, ___ non-GMP study.

CC: NAMES AND LOCATIONS: Armstrong, Joesoph RY800-B371; Hunter Patricia WP78-304, Palucki RY800-B363

Transfer Requested By	Delivery Sheet By	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By:
Name: Location:	Name Location:	Dept. Approval	Quality Approval	

* new form of base N

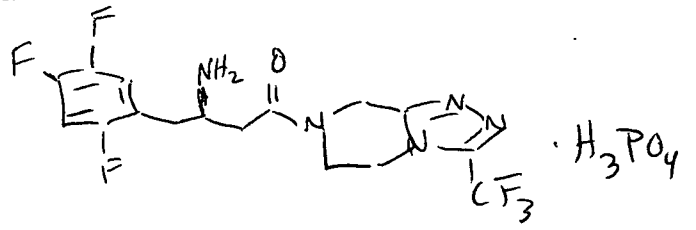
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L-224715-006F00

MOLECULAR FORMULA:	MOLECULAR WT.:	DATE:	ASSIGNED BY:
$C_{16}H_{18}F_6N_5O_5P$	505	20Feb2002	Hansen AP 2/20/02

CHEMICAL/TRIVIAL NAME: ~~L224715~~

STRUCTURE:



$\cdot H_3PO_4$

L224715 H_3PO_4 salt

LABELING INSTRUCTIONS
(FOR OUTSIDE DELIVERIES)
- ☐ L NUMBER
- ☐ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER:

Prepared by/Commercial Source:	Notebook Ref./Lot No.: 70316-035

Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC
☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*:
☒ data generated by Analytical Research

99.69LCAP

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT
☐ YES ☒ NO

LIT. REF./CAS REG. NO.

REMARKS:
3.50 S

PB ECL-

Storage Conditions: (check one)
- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ -70°C freezer.
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited.

☐ For safety information and special handling precautions, access CHIS

SEND TO: (NAME, LOCATION, QUANTITY, TEST NO. OR ACRONYM AND INDICATE IF DELIVERED)
Kari Lynn WP78-302

Material is (select one) ___ GMP ; X non-GMP and will be used in (select one): ___ GMP/GLP study; ___ non-GMP study.

CC: NAMES AND LOCATIONS: Armstrong RY800-D371, Hunter Patricia WP78-304 Palmer RY800-B363

Transfer Requested By	Delivery Sheet By:	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By:
Name: K. Hansen Location: RY800B269	Name Location:	Dept. Approval	Quality Approval	

* new form of base

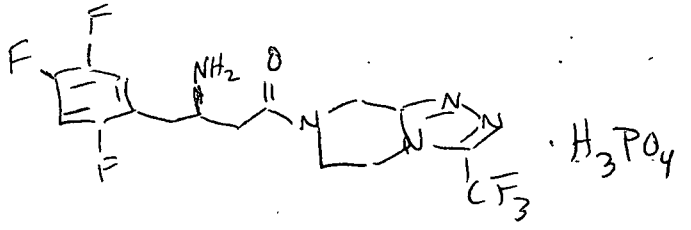
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L-224715-006F001

MOLECULAR FORMULA:	MOLECULAR WT.:	DATE:	ASSIGNED BY:
$C_{16}H_{18}F_6N_5O_5P$	505	20Feb2002	Hansen AB 2/20/02

CHEMICAL/TRIVIAL NAME: ~~L224715~~

STRUCTURE:



L224715 H_3PO_4 salt

LABELING INSTRUCTIONS (FOR OUTSIDE DELIVERIES)
- ☐ L NUMBER
- ☐ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER:

Prepared by/Commercial Source:	Notebook Ref./Lot No..	Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC
	70316-035	☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*

☒ data generated by Analytical Research

99.69LCAP

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT ☐ YES ☒ NO

LIT. REF./CAS REG. NO.

REMARKS:

3.50s

PB ECL-

Storage Conditions: (check one)
- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ –70°C freezer.
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited.

☐ For safety information and special handling precautions, access CHIS.

SEND TO: (NAME, LOCATION, QUANTITY, TEST NO. OR ACRONYM AND INDICATE IF DELIVERED)

Kari Lynn WP78-302

Material is (select one) ___ GMP ; X non-GMP and will be used in (select one): ___ GMP/GLP study; ___ non-GMP study.

CC. NAMES AND LOCATIONS: Armstrong RY800-D371, Hunter Patricia WP78-304 Palucki RY800-B363

Transfer Requested By	Delivery Sheet By:	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By:
Name: K. Hansen Location: RY800B269	Name Location:	Dept. Approval	Quality Approval	

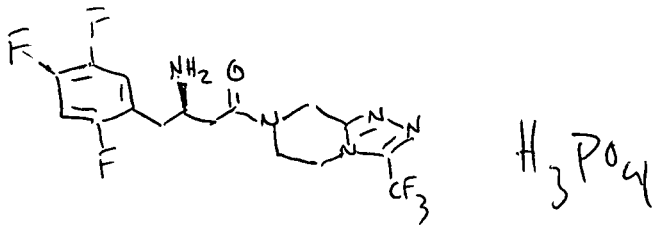
DELIVERY SHEET (A): CHEMICAL FOR NON-CLINICAL USE

L224715-006 F001

MOLECULAR FORMULA:	MOLECULAR WT ·	DATE:	ASSIGNED BY:
$C_{16}H_{18}F_6N_5O_5P$	505	7 Mar 2002	Hansch

CHEMICAL/TRIVIAL NAME:

STRUCTURE:



H_3PO_4

LABELING INSTRUCTIONS
(FOR OUTSIDE DELIVERIES)

- ☐ L NUMBER
- ☐ NAME AS SHOWN ABOVE
- ☐ QUANTITY
- ☐ OTHER (Specify Under "Remarks")
- ☐ HAZARDOUS
- ☐ NON-HAZARDOUS

PROJECT NUMBER:

Prepared by/Commercial Source:	Notebook Ref./Lot No.:	Criteria of Purity, Safety or Potency: ☐ TLC ☒ HPLC ☐ GC
	70316-035	☐ IR ☐ UV ☐ NMR ☐ MS

CHARACTERIZATION DATA

COMPOUND IS PUBLISHED ☐ YES ☒ NO ☐ UNDETERMINED

OTHER ASSAY RESULTS OR PHYSICAL CONSTANTS*:

☒ data generated by Analytical Research

99.69 LCAP

RRT	Area
0.93	0.16
0.95	0.12

no minor enantiomer

PERMISSION TO RELEASE TO CAS FOR NOMENCLATURE DEVELOPMENT
☐ YES ☒ NO

LIT REF /CAS REG NO

REMARKS

1g released to Leigh Shultz for Safety Assessment Formulation Development

PB ECL-

Storage Conditions: (check one)

- ☐ "controlled room temperature" (25°C)
- ☐ "refrigeration" (4°C)
- ☐ "freezer" (-20°C)
- ☐ –70°C freezer.
- ☐ other _____

*If GMP Compliance has not signed below, data has *not* been audited

☐ For safety information and special handling precautions, access CHIS.

SEND TO. (NAME, LOCATION, QUANTITY, TEST NO OR ACRONYM AND INDICATE IF DELIVERED)

Material is (select one) ____ GMP ; ____ non-GMP and will be used in (select one): ____ GMP/GLP study; ___ non-GMP study.

CC: NAMES AND LOCATIONS:

Transfer Requested By	Delivery Sheet By.	APPROVED FOR DELIVERY BY MRL GMP COMPLIANCE		Transfer Completed By:
Name: Location:	Name Location:	Dept. Approval	Quality Approval	

Hansen, Karl

From: Dorwart, Jason G.
Sent: Wednesday, February 13, 2002 4:36 PM
To: Hansen, Karl
Subject: RE:

Karl,

Got your voice mail. We can get together first thing tomorrow morning if you want to go over the process. What time will you be in tomorrow morning. I will be in before 8:00.

Here are the LCAP results for the Phosphate sample NB# 70316-035.

RRT	Area%
0.93	0.16%
0.95	0.12%
1.00	99.69%

Total imp = 0.28

Very clean. I will have the chiral results for you tomorrow.

Jason

-----Original Message-----
From: Hansen, Karl
Sent: Tuesday, February 12, 2002 3:59 PM
To: Dorwart, Jason G.
Subject: RE:

Jason,

I left a sample of phosphate salt and the ML's in your hood. Could you give me a read on purity/ee by thurs AM?

Thanks

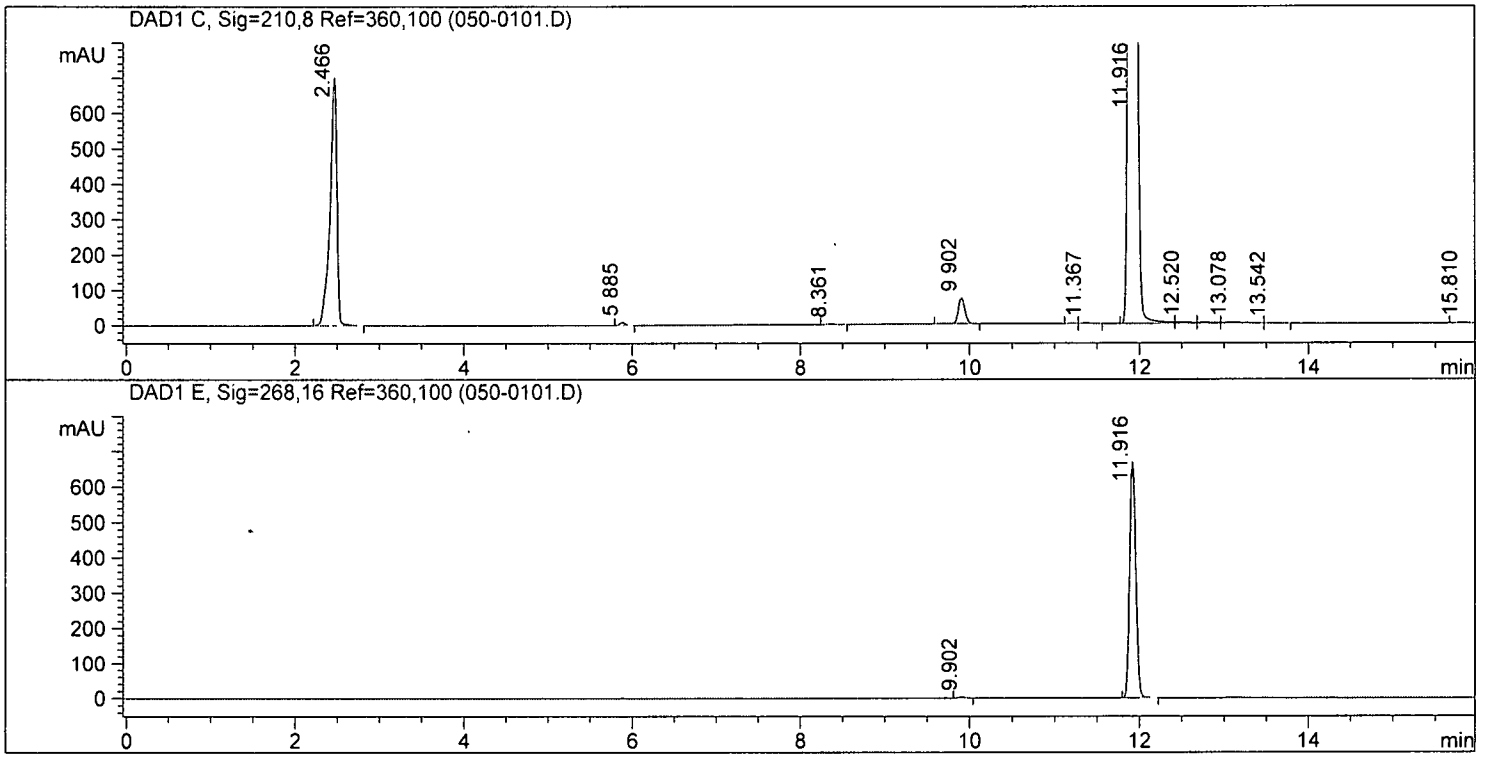
Karl

Data file :C:\HPCHEM\HPLC0157\DATA\050-0101.D Sample Name: 70316-035

triazole and amino acid in acn ->

==========

Injection Date : 02/08/2002 7:34:06 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 50
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.47	VB	0.084	702.86	3987.115	19.66	0.000000	
2	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
3	5.88	PB	0.077	8.36	40.533	0.20	0.000000	
4	8.36	BP	0.094	2.21	12.844	0.06	0.000000	
5	9.90	BB	0.083	73.63	399.917	1.97	0.000000	
6	11.21	PV	0.075	1.47	7.194	0.04	0.000000	
7	11.37	VB	0.099	2.65	17.412	0.09	0.000000	
8	11.92	VB	0.114	2.28e3	1.562e4	77.05	0.000000	
9	12.52	BV	0.168	3.93	49.850	0.25	0.000000	
10	12.77	VV	0.165	3.58	44.579	0.22	0.000000	
11	13.08	VV	0.273	3.06	64.734	0.32	0.000000	
12	13.54	VB	0.126	1.02	9.080	0.04	0.000000	
13	15.81	BBA	0.119	2.64	20.069	0.10	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

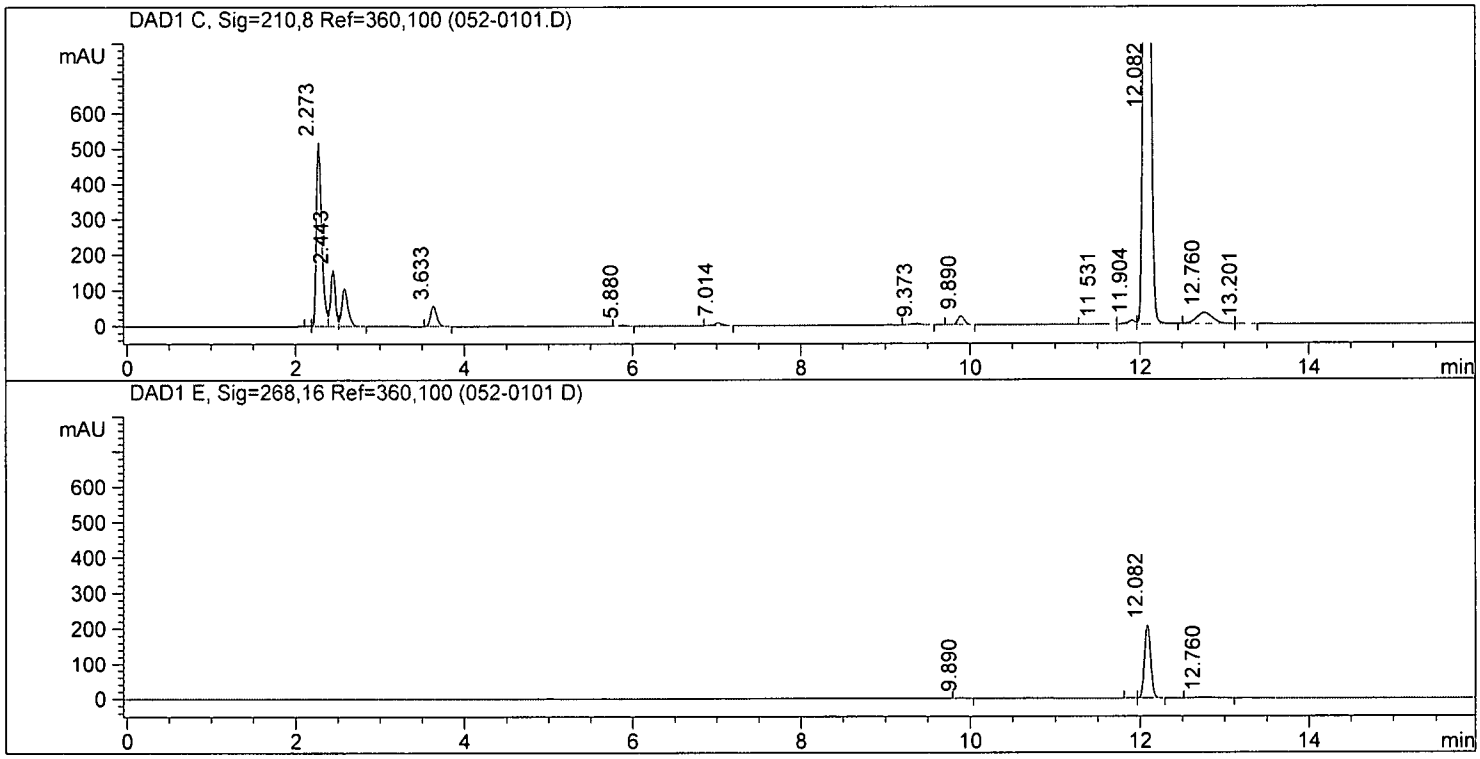
Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	9.90	PB	0.081	3.21	16.716	0.49	0.000000	
3	11.92	PB	0.080	670.87	3424.922	99.51	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\052-0101.D Sample Name: 70316-035

coupling after 1.5 h in acn ->

```
==========================================================================
Injection Date : 02/08/2002  9:15:27 AM        Seq Line  : 1
Sample Name    : 70316-035                     Vial No   : 52
Acq Operator   : hansen                        Inj. No.  : 1
                                               Inj. Vol. : 2 µl
Method         : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed   : 01/14/2002   1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm
```




```
==========================================================================================
                    Customized Report:karlo
==========================================================================================
Sorted By             : Signal
Calib. Data Modified  : 01/14/2002   1:00:30 PM
Multiplier            : 1.000000

Signal:  1 DAD1 C, Sig=210,8 Ref=360,100
```

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.16	VV	0.057	2.35	9.020	0.06	0.000000	
2	2.27	VV	0.065	520.13	2262.576	14.50	0.000000	
3	2.44	VV	0.059	157.84	609.726	3.91	0.000000	
4	2.58	VB	0.078	106.83	547.407	3.51	0.000000	
5	3.63	PB	0.080	56.56	292.918	1.88	0.000000	
6	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
7	5.88	VB	0.077	3.25	15.947	0.10	0.000000	
8	7.01	BB	0.096	7.90	52.874	0.34	0.000000	
9	9.37	BB	0.109	4.11	32.148	0.21	0.000000	
10	9.89	BP	0.085	24.57	131.621	0.84	0.000000	
11	11.53	BV	0.164	1.48	17.941	0.11	0.000000	
12	11.90	VV	0.094	11.46	72.284	0.46	0.000000	
13	12.08	VB	0.091	2.00e3	1.111e4	71.21	0.000000	
14	12.76	BB	0.211	31.89	439.530	2.82	0.000000	
15	13.20	BB	0.143	1.02	10.059	0.06	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	9.89	BP	0.084	1.09	5.794	0.53	0.000000	
3	11.91	BV	0.078	1.33	6.609	0.60	0.000000	
4	12.08	VB	0.079	207.53	1045.953	95.68	0.000000	
5	12.76	PP	0.199	2.73	34.853	3.19	0.000000	

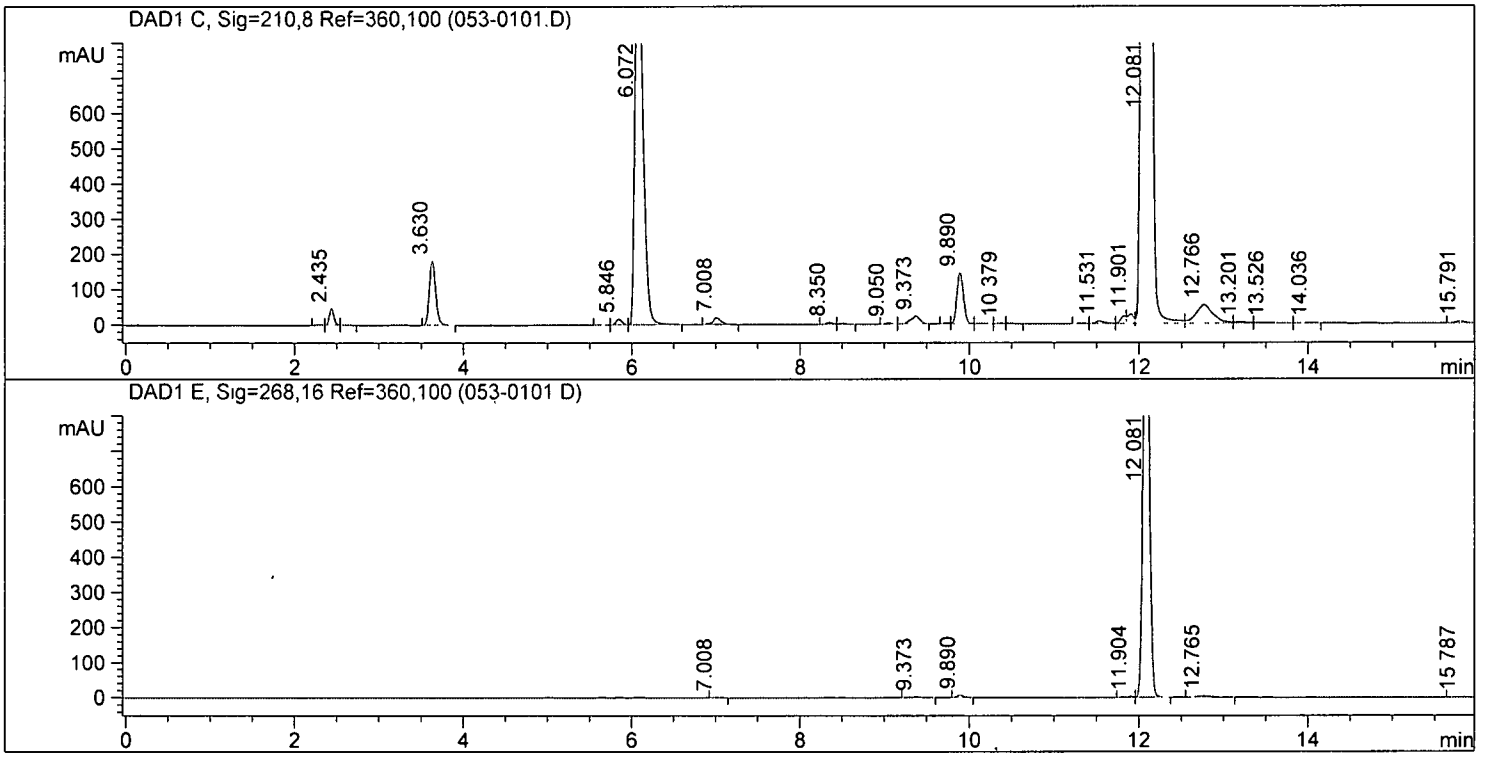
*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\053-0101.D Sample Name: 70316-035

ethyl acetate layer post brine ->

==========

Injection Date : 02/08/2002 9:57:47 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 53
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



==========

Customized Report:karlo

==========

Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.29	BV	0.067	1.90	8.004	0.02	0.000000	
2	2.44	VV	0.060	47.41	179.936	0.55	0.000000	
3	2.58	VB	0.085	1.04	6.326	0.02	0.000000	
4	3.63	PB	0.081	183.00	962.031	2.95	0.000000	
5	5.65	BP	0.082	1.40	7.240	0.02	0.000000	L-224,715
6	5.85	VV	0.077	16.14	78.637	0.24	0.000000	
7	6.07	VB	0.096	1.20e3	7548.808	23.18	0.000000	
8	7.01	BP	0.099	19.78	137.207	0.42	0.000000	
9	8.35	PV	0.093	4.82	28.376	0.09	0.000000	
10	8.50	VB	0.082	3.36	18.487	0.06	0.000000	
11	9.05	BV	0.082	3.57	18.934	0.06	0.000000	
12	9.37	VV	0.105	22.85	175.098	0.54	0.000000	
13	9.75	VV	0.076	3.49	17.369	0.05	0.000000	
14	9.89	VV	0.084	144.78	774.307	2.38	0.000000	
15	10.16	VV	0.134	1.25	10.713	0.03	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	10.38	VV	0.079	1.66	8.649	0.03	0.000000	
17	10.47	VB	0.080	1.19	6.092	0.02	0.000000	
18	11.32	PV	0.089	1.40	8.276	0.03	0.000000	
19	11.53	VV	0.114	6.93	55.649	0.17	0.000000	
20	11.82	VV	0.067	21.94	95.142	0.29	0.000000	
21	11.90	VV	0.076	26.87	132.692	0.41	0.000000	
22	12.08	VV	0.142	2.50e3	2.139e4	65.67	0.000000	
23	12.77	VV	0.201	53.08	759.701	2.33	0.000000	
24	13.20	VV	0.139	4.65	45.036	0.14	0.000000	
25	13.53	VV	0.188	2.50	35.276	0.11	0.000000	
26	14.04	VV	0.138	2.27	22.218	0.07	0.000000	
27	15.79	BBA	0.122	5.43	42.726	0.13	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	7.01	BB	0.089	1.09	6.657	0.10	0.000000	
3	9.37	BP	0.115	2.02	17.079	0.26	0.000000	
4	9.89	BP	0.084	6.46	34.387	0.53	0.000000	
5	11.90	PV	0.095	2.92	19.214	0.30	0.000000	
6	12.08	VB	0.080	1.23e3	6349.005	97.90	0.000000	
7	12.76	PP	0.169	4.27	50.165	0.77	0.000000	
8	15.79	BBA	0.123	1.12	8.963	0.14	0.000000	

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*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\051-0101.D Sample Name: 70316-035

coupling after 0.5 h in acn ->

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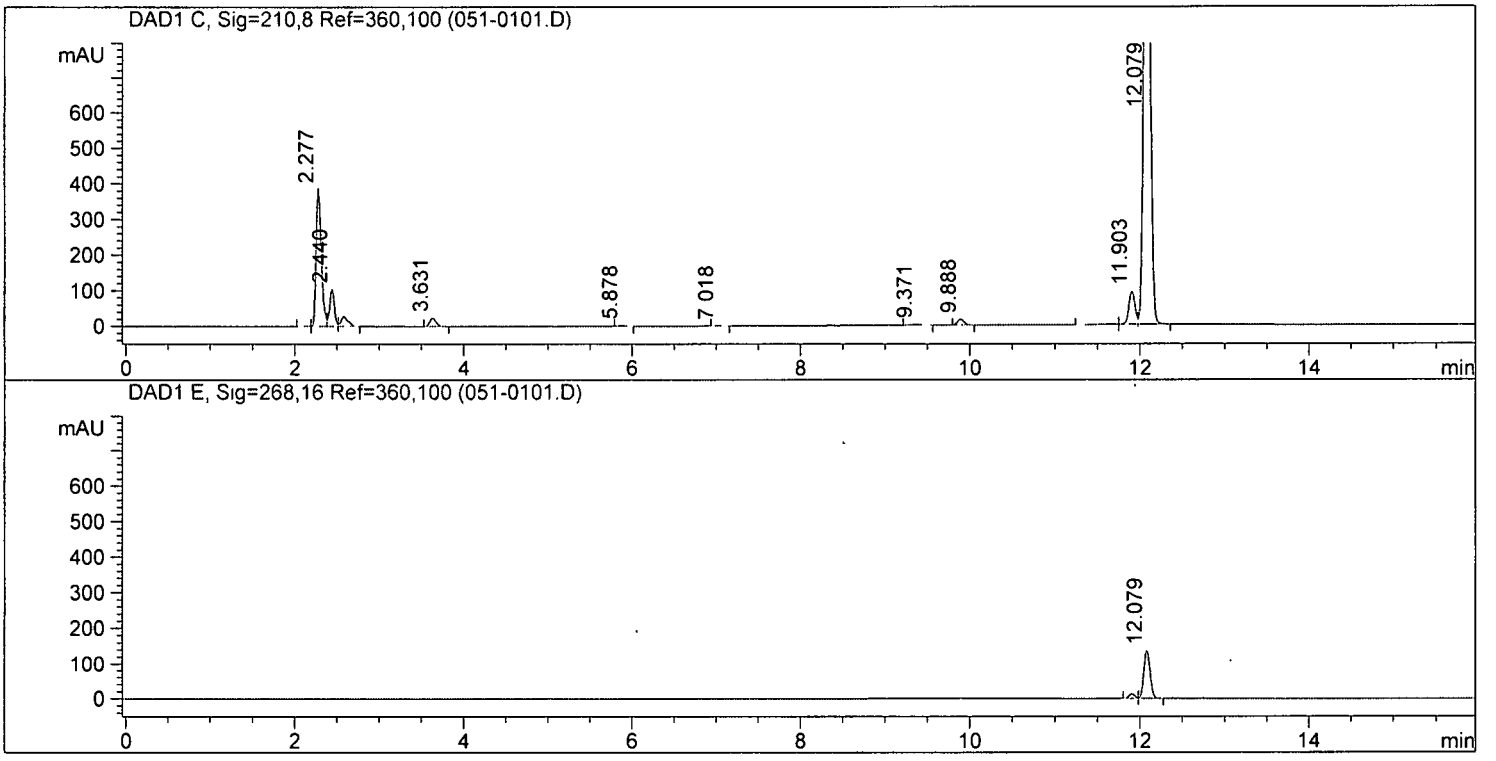
Injection Date : 02/08/2002 8:18:40 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 51
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.16	BV	0.073	1.69	8.808	0.08	0.000000	
2	2.28	VV	0.063	385.91	1635.640	14.87	0.000000	
3	2.44	VV	0.061	105.27	404.325	3.68	0.000000	
4	2.58	VB	0.084	28.16	164.020	1.49	0.000000	
5	3.63	BB	0.078	23.99	124.300	1.13	0.000000	
6	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
7	5.88	BB	0.077	2.05	10.026	0.09	0.000000	
8	7.02	BB	0.087	1.21	7.180	0.07	0.000000	
9	9.37	BB	0.108	2.75	21.603	0.20	0.000000	
10	9.89	BP	0.083	16.67	87.458	0.80	0.000000	
11	11.68	PV	0.182	1.69	22.653	0.21	0.000000	
12	11.90	VV	0.079	93.58	470.670	4.28	0.000000	
13	12.08	VB	0.083	1.55e3	8041.720	73.12	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\051-0101.D Sample Name: 70316-035
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	0.00		0.000	0.00	0.000	0.00	0.000000	L-224,715
2	11.90	BV	0.077	12.20	60.016	8.03	0.000000	
3	12.08	VB	0.079	136.69	687.794	91.97	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\056-0101.D Sample Name: 70316-035

hydrog 18 h ->

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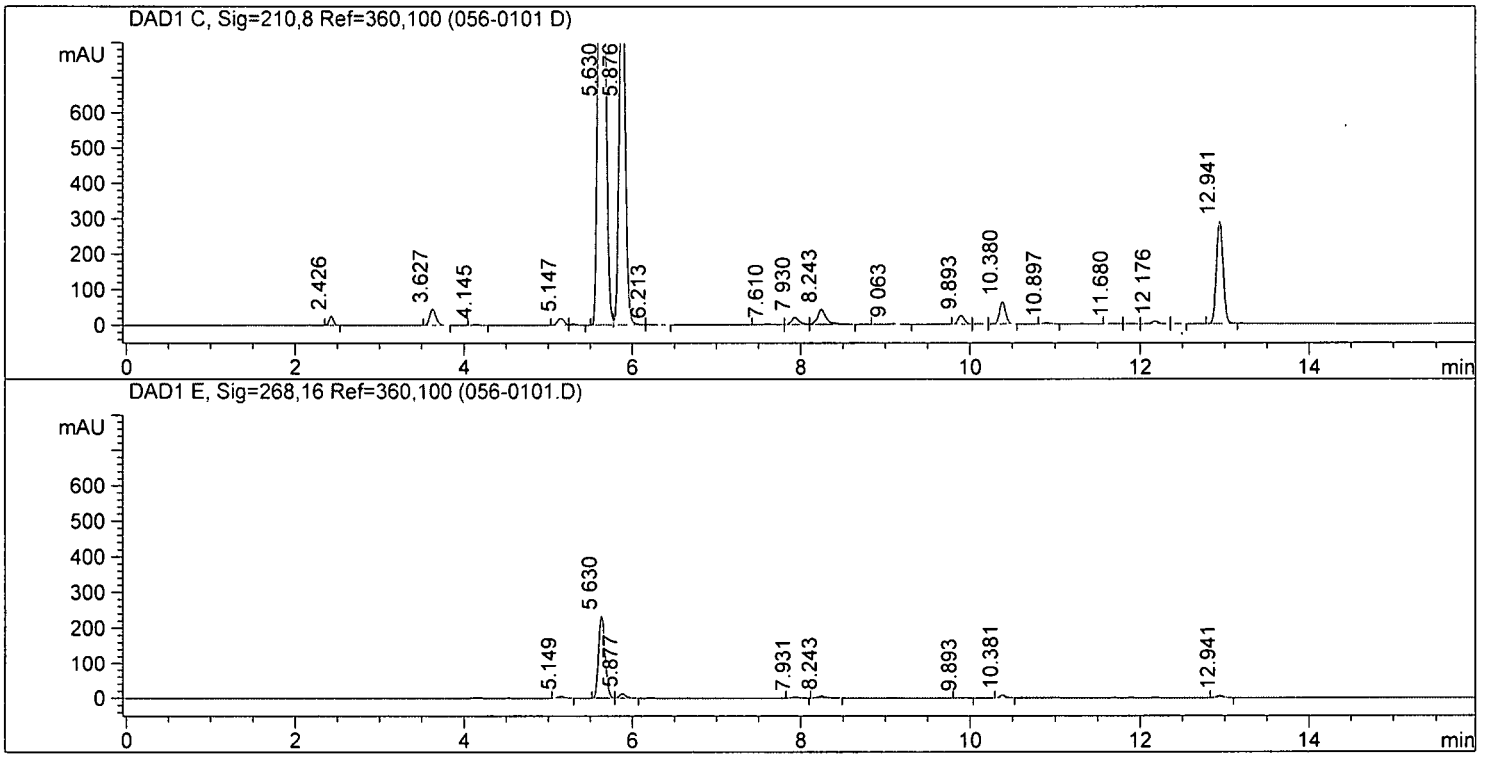
Injection Date : 02/11/2002 9:37:44 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 56
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.43	VB	0.055	26.02	91.523	0.50	0.000000	
2	3.63	BB	0.082	45.26	239.994	1.32	0.000000	
3	4.15	BP	0.086	1.93	10.983	0.06	0.000000	
4	5.15	BV	0.086	19.90	111.879	0.62	0.000000	
5	5.30	VP	0.080	3.66	18.818	0.10	0.000000	
6	5.63	BV	0.091	1.70e3	9840.690	54.22	2.610516	L-224,715
7	5.88	VV	0.079	1.03e3	5188.998	28.59	0.000000	
8	6.21	VB	0.113	1.64	13.083	0.07	0.000000	
9	7.61	PV	0.142	1.47	15.057	0.08	0.000000	
10	7.93	VV	0.091	21.16	132.813	0.73	0.000000	
11	8.24	VB	0.103	43.60	317.297	1.75	0.000000	
12	9.06	BP	0.130	1.83	15.385	0.08	0.000000	
13	9.89	VV	0.081	24.12	127.094	0.70	0.000000	
14	10.10	VV	0.088	1.41	8.391	0.05	0.000000	
15	10.38	VB	0.079	62.55	314.957	1.74	0.000000	

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	10.90	BB	0.093	3.26	19.857	0.11	0.000000	
17	11.68	BV	0.100	2.57	18.004	0.10	0.000000	
18	11.90	VP	0.094	2.24	14.290	0.08	0.000000	
19	12.18	VV	0.096	8.05	53.999	0.30	0.000000	
20	12.44	VP	0.080	1.39	7.433	0.04	0.000000	
21	12.94	VB	0.088	288.65	1590.085	8.76	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.15	BB	0.088	5.68	31.914	2.12	0.000000	
2	5.63	BV	0.085	233.61	1267.366	84.12	2.610516	L-224,715
3	5.88	VB	0.084	12.49	70.151	4.66	0.000000	
4	7.93	PB	0.088	3.08	18.367	1.22	0.000000	
5	8.24	BB	0.103	5.70	42.469	2.82	0.000000	
6	9.89	PP	0.082	1.08	5.744	0.38	0.000000	
7	10.38	PB	0.078	7.41	37.135	2.46	0.000000	
8	12.94	PB	0.089	6.02	33.488	2.22	0.000000	

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*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\054-0101.D Sample Name: 70316-035

0.1487g/50ml of 40.86gin etoac ->

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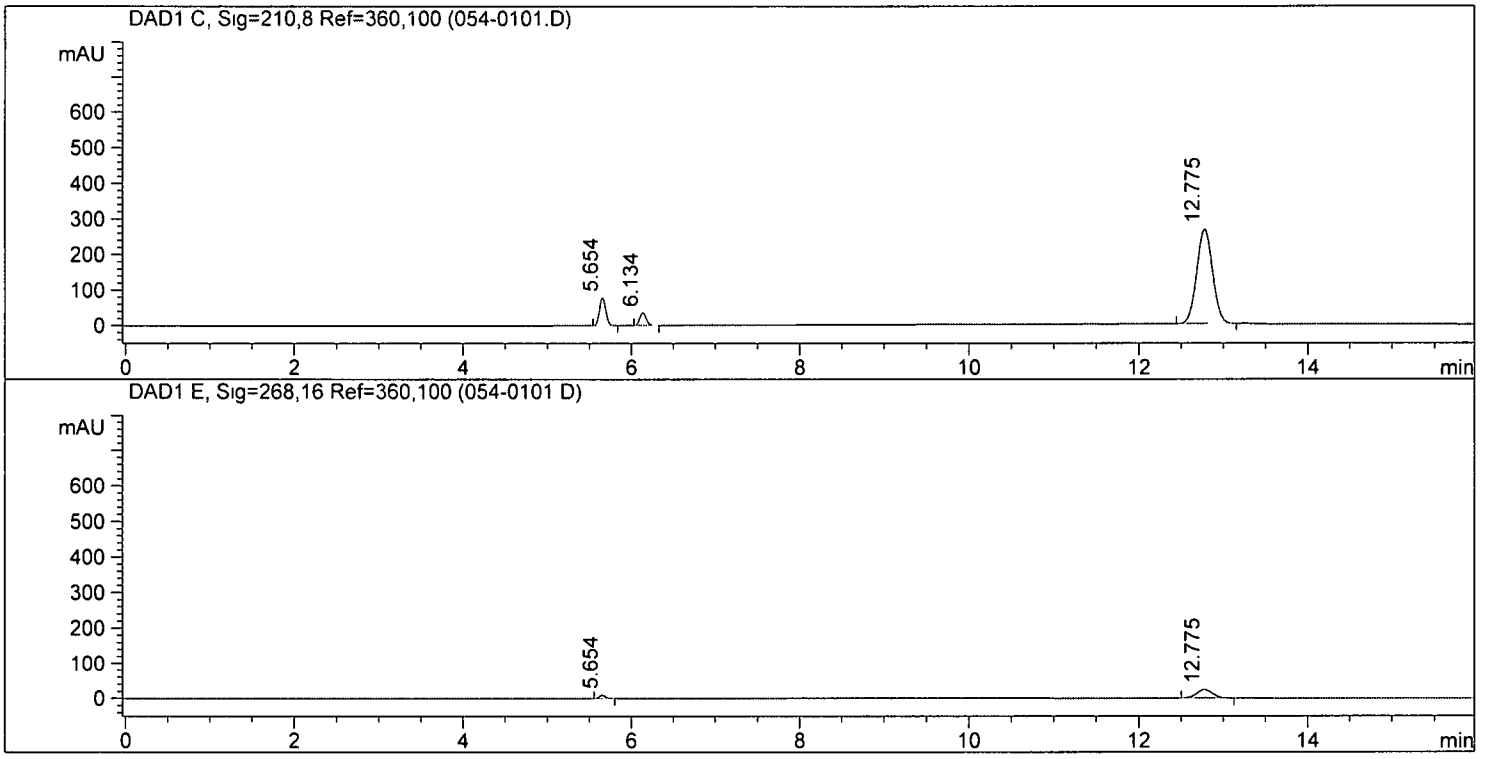
Injection Date : 02/08/2002 11:20:17 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 54
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method . : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm

1.45



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	BB	0.081	78.30	406.762	9.99	0.104821	L-224,715
2	6.13	BB	0.082	36.08	192.517	4.73	0.000000	
3	12.77	PP	0.204	265.73	3471.686	85.28	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	BB	0.081	8.97	46.638	13.08	0.104821	L-224,715
2	12.77	BP	0.204	23.75	309.841	86.92	0.000000	

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*** End of Report ***

7,75

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
16	9.05	VP	0.074	3.36	16.106	0.09	0.000000	
17	9.69	BV	0.123	2.94	26.522	0.15	0.000000	
18	9.89	VV	0.096	68.99	450.439	2.55	0.000000	
19	10.10	VV	0.124	7.35	68.174	0.39	0.000000	
20	10.38	VB	0.079	182.94	922.375	5.22	0.000000	
21	10.90	BB	0.118	10.80	86.724	0.49	0.000000	
22	11.20	BB	0.195	1.80	26.977	0.15	0.000000	
23	11.62	BV	0.148	2.30	24.012	0.14	0.000000	
24	11.75	VV	0.098	3.46	23.130	0.13	0.000000	
25	11.91	VV	0.103	5.19	37.096	0.21	0.000000	
26	12.17	VB	0.120	24.48	214.955	1.22	0.000000	
27	12.67	BV	0.142	4.13	43.069	0.24	0.000000	
28	12.92	VV	0.137	4.47	43.826	0.25	0.000000	
29	13.06	VV	0.256	3.16	64.284	0.36	0.000000	
30	13.67	VP	0.156	1.18	13.565	0.08	0.000000	

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	4.15	BP	0.085	2.95	16.485	2.19	0.000000	
2	5.16	BB	0.086	12.71	69.850	9.30	0.000000	
3	5.65	BV	0.081	27.61	144.223	19.20	0.331258	L-224,715
4	5.88	VP	0.085	33.53	192.903	25.68	0.000000	
5	7.65	BV	0.091	3.09	19.431	2.59	0.000000	
6	7.93	VV	0.087	8.70	51.563	6.86	0.000000	
7	8.24	VB	0.096	12.71	85.202	11.34	0.000000	
8	8.89	PB	0.096	3.06	20.879	2.78	0.000000	
9	9.90	BV	0.119	3.11	27.422	3.65	0.000000	
10	10.38	VP	0.077	21.57	106.282	14.15	0.000000	
11	12.17	VB	0.095	2.56	16.910	2.25	0.000000	

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*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\059-0101.D Sample Name: 70316-035

0.3512g/25ml of ml's at 20ml/g RT 3h ->

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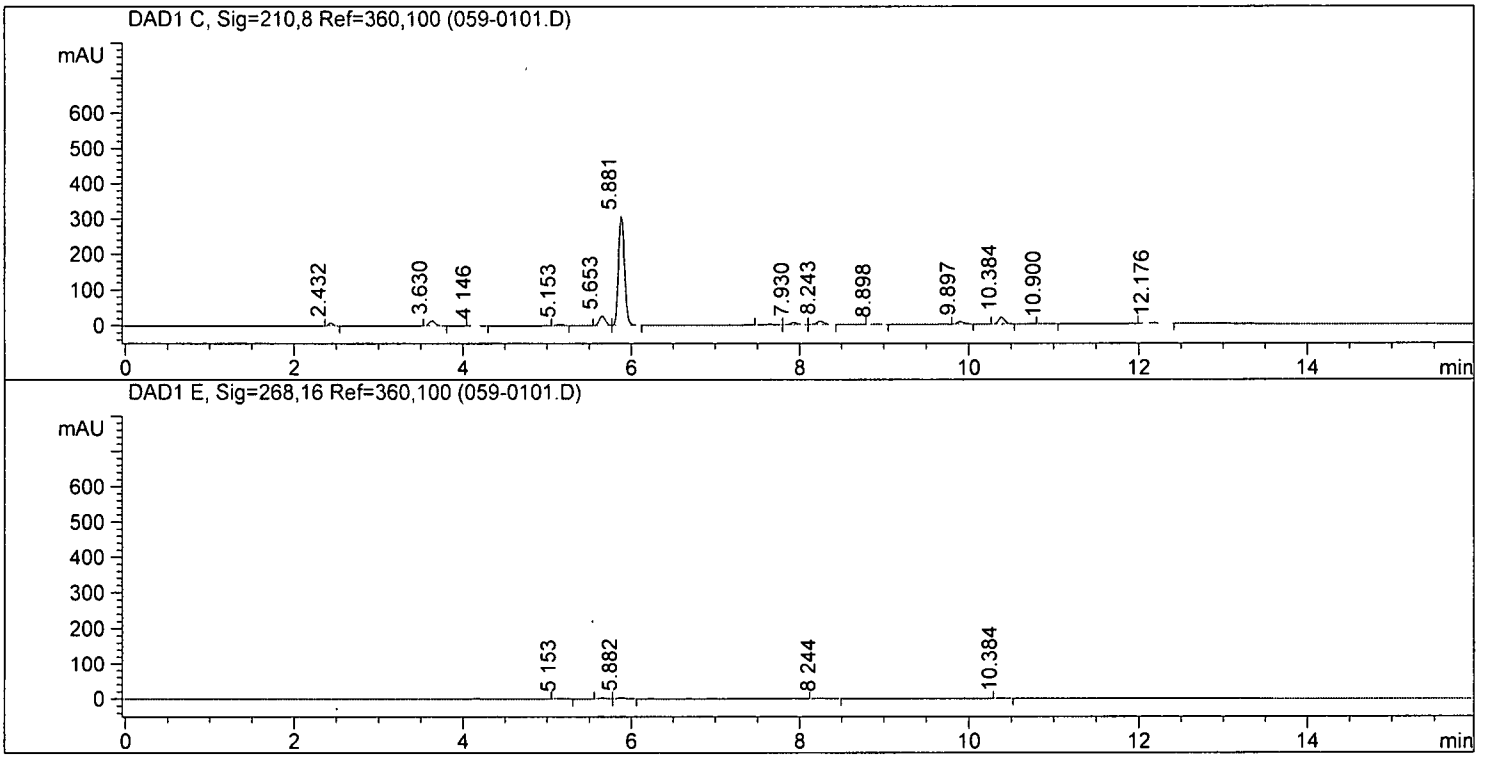
Injection Date : 02/12/2002 11:46:35 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 59
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.43	BB	0.058	8.00	30.308	1.45	0.000000	
2	3.63	BB	0.082	13.77	73.417	3.51	0.000000	
3	4.15	BP	0.087	1.22	6.818	0.33	0.000000	
4	5.15	BV	0.086	4.34	23.743	1.13	0.000000	
5	5.65	BV	0.083	26.16	136.047	6.50	0.032918	L-224,715
6	5.88	VB	0.078	306.93	1525.690	72.89	0.000000	
7	7.65	BV	0.111	1.81	14.501	0.69	0.000000	
8	7.93	VV	0.088	6.24	37.719	1.80	0.000000	
9	8.24	VB	0.091	10.28	66.441	3.17	0.000000	
10	8.90	BB	0.098	1.57	10.713	0.51	0.000000	
11	9.90	PV	0.093	7.17	45.116	2.16	0.000000	
12	10.38	VP	0.078	19.45	96.168	4.59	0.000000	
13	10.90	BP	0.097	1.11	7.169	0.34	0.000000	
14	12.18	VB	0.110	2.46	19.367	0.93	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\059-0101.D Sample Name: 70316-035
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.15	BB	0.087	1.36	7.515	11.78	0.000000	
2	5.65	BV	0.081	2.99	15.556	24.38	0.032918	L-224,715
3	5.88	VB	0.086	3.62	20.572	32.24	0.000000	
4	8.24	BB	0.093	1.35	8.985	14.08	0.000000	
5	10.38	PB	0.077	2.29	11.185	17.53	0.000000	

*** End of Report ***

Data file :C:\HPCHEM\HPLC0157\DATA\058-0101.D Sample Name: 70316-035

0.1678mg/25ml of super at 20ml/g 0.5 h ->

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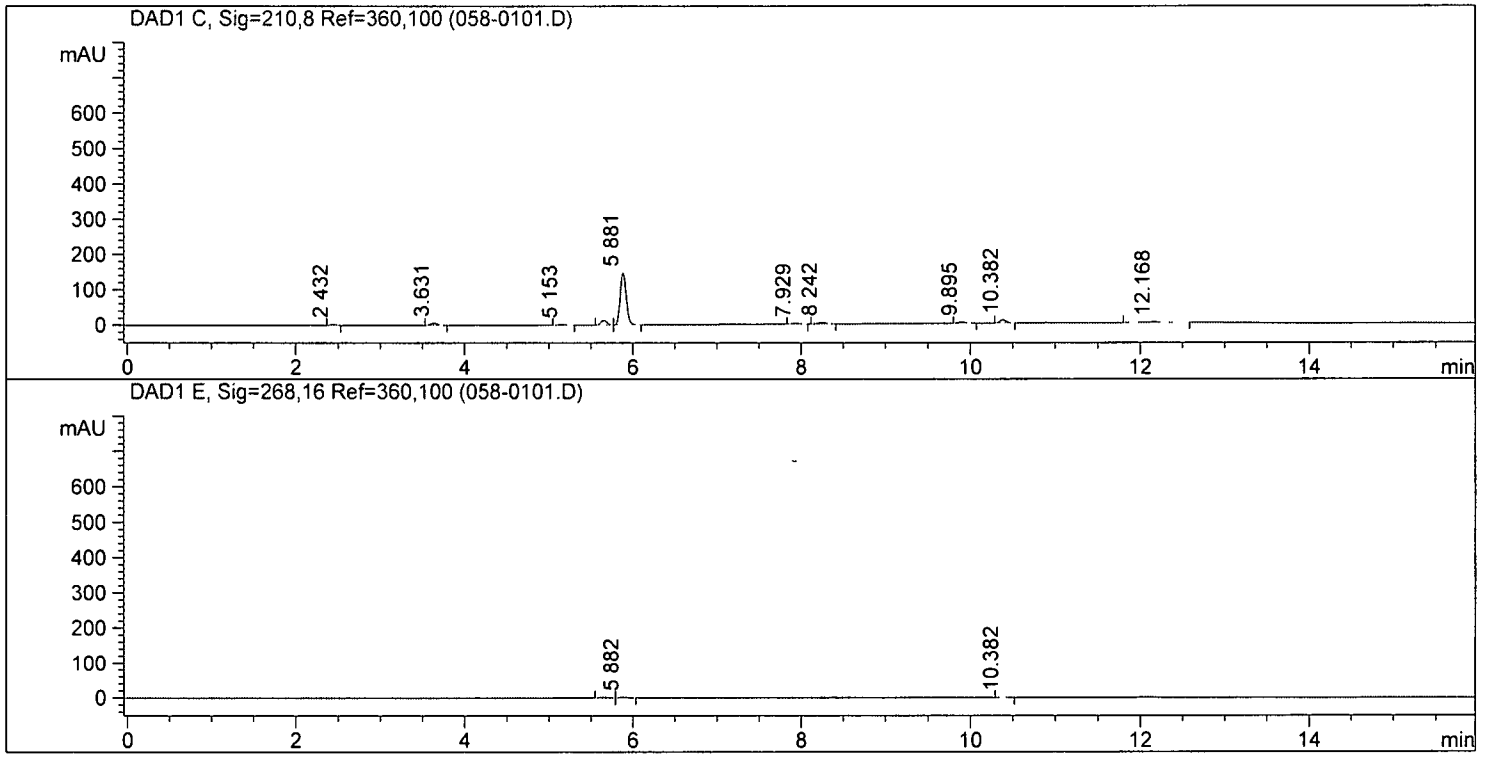
Injection Date : 02/12/2002 8:45:35 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 58
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl
Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	2.43	BB	0.059	3.87	14.990	1.46	0.000000	
2	3.63	BB	0.083	6.59	35.427	3.46	0.000000	
3	5.15	BB	0.088	2.08	11.778	1.15	0.000000	
4	5.65	BV	0.082	13.23	68.347	6.67	0.014936	L-224,715
5	5.88	VB	0.078	147.32	732.519	71.49	0.000000	
6	7.93	BB	0.085	2.92	16.821	1.64	0.000000	
7	8.24	BP	0.089	4.85	30.162	2.94	0.000000	
8	9.89	PB	0.092	3.40	20.918	2.04	0.000000	
9	10.38	PP	0.077	9.27	45.359	4.43	0.000000	
10	12.17	PB	0.256	2.37	48.362	4.72	0.000000	

Data file :C:\HPCHEM\HPLC0157\DATA\058-0101.D Sample Name: 70316-035
Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	BB	0.081	1.52	7.917	34.40	0.014936	L-224,715
2	5.88	BB	0.086	1.73	9.730	42.28	0.000000	
3	10.38	PP	0.077	1.09	5.367	23.32	0.000000	

*** End of Report ***

HYDROGENATION OR HIGH PRESSURE REACTION

2002020856.001
DO NOT WRITE IN THIS SPACE

REQUESTED BY [illegible] BLDG/RM [illegible] EXT. 0557 DATE 8 Feb 2002

PROJECT NO. 24715 PROJECT MK0431 2215 NOTEBOOK - PAGE NO. 70316-035

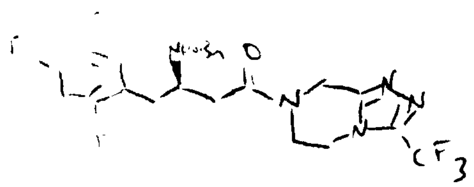
CHECK HERE IF REACTION IS GMP/GLP ☐

STARTING MATERIAL

NO. 1 ______ NO. 2 ______

M.W. [illegible] AMOUNT ______ G. MOLES 31.5 [illegible] M.W. ______ AMOUNT ______ G. MOLES ______

STRUCTURAL FORMULA:



EMPIRICAL FORMULA:

CATALYST 3.00 G. OF 10% Pd/C

SOLVENT 100 ML. OF MeOH

MOLES OF HYDROGEN REQUIRED 315

OTHER MATERIALS
Please rinse w/ 10ml MeOH

REACTION CONDITIONS, ETC.
40 PSI 50°C 36hrs

PRECAUTIONS:

TO BE FILLED IN BY HYDROGENATION LABORATORY

NO. 1: 11.1 G. MOLES 0.0315 NO.2: ______ G. MOLES ______

CATALYST 3.0 G. OF 10% Pd/C Lot# FC95286

SOLVENT 100 ML. OF MeOH

OTHER MATERIALS ......

CELL NO. ____ HEATER NO. ____ REC. POINT INTERNAL ____ EXTERNAL ____ BOMB NO. ____ VESSEL SIZE 250 ML.

SHAKER NO. 56 LINER ____ SHAKER TANK 1093 AUX. TANK ____ SYSTEM VOLUME 72 ML.

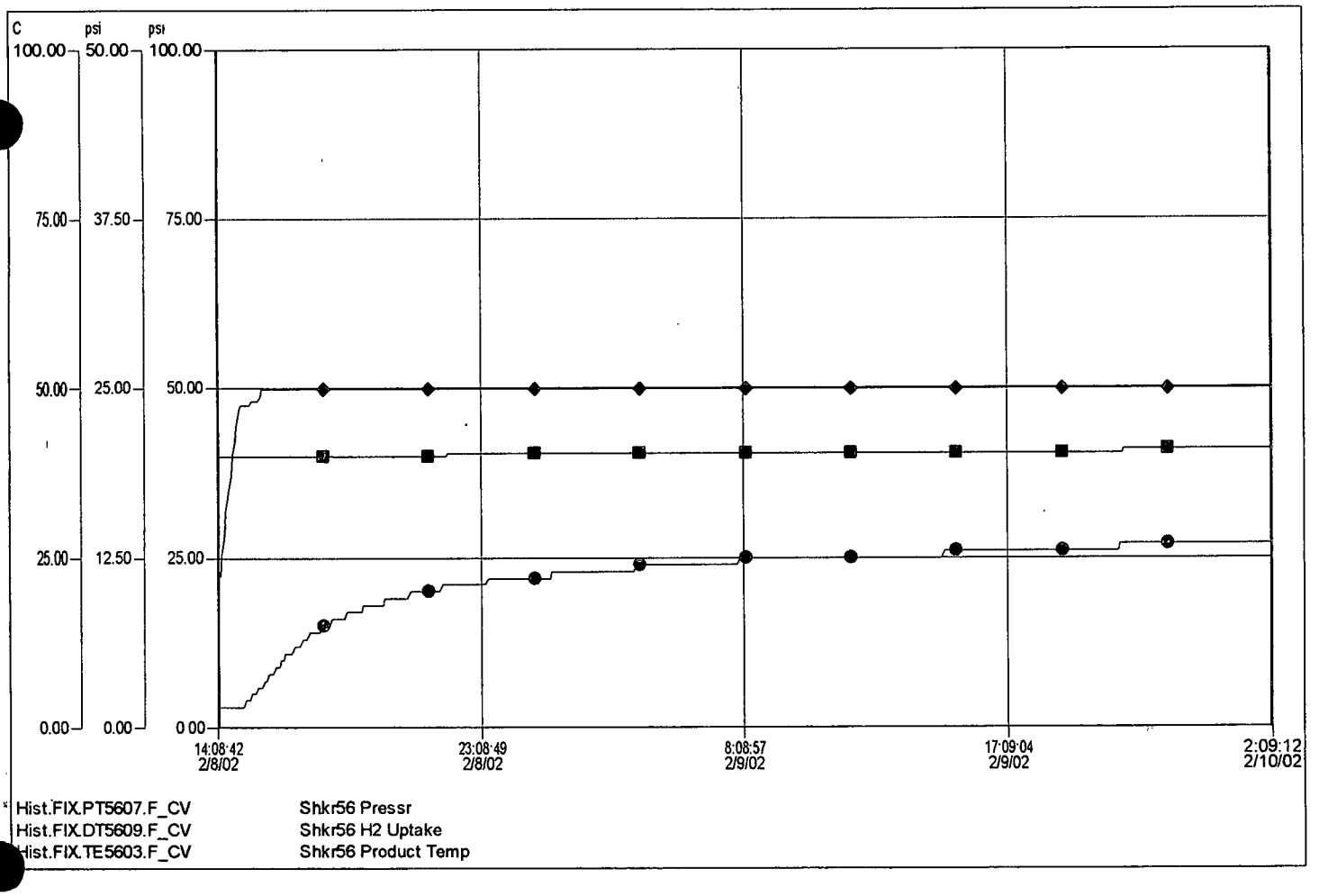
CALC'D H_2 PRESSURE DROP = 310.4 LBS./MOLE 0.0315 MOLES = 10 LBS.

CONDITIONS 36 HRS. AT 50 C. MISC. DATA: 40 psig H_2

TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP	TIME	TEMP.	PRESSURE OBS.	PRESSURE DROP
14:09	19.5	40	0	06:09	49.9	40	12	22:09	49.9	41	14
14:39	40.2	40	2	06:39	49.9	40	12	22:39	49.9	41	14
15:09	47.5	40	2	07:09	49.9	40	12	23:09	49.9	41	14
15:39	49.9	40	3	07:39	49.9	40	12	23:39	49.9	41	14
16:09	49.9	40	4	08:09	49.9	40	12	00:09	49.9	41	14
16:39	49.9	40	6	08:39	49.9	40	12	00:39	49.9	41	14
17:09	49.9	40	6	09:09	49.9	40	12	01:09	49.9	41	14
17:39	49.9	40	8	09:39	49.9	40	12	01:39	49.9	41	14
18:09	49.9	40	8	10:09	49.9	40	12				
18:39	49.9	40	8	10:39	49.9	40	12				
19:09	49.9	40	9	11:09	49.9	40	12				
19:39	49.9	40	9	11:39	49.9	40	12				
20:09	49.9	40	10	12:09	49.9	40	12				
20:39	49.9	40	10	12:39	49.9	40	12				
21:09	49.9	40	10	13:09	49.9	40	12				
21:39	49.9	40	10	13:39	49.9	40	12				
22:09	49.9	40	10	14:09	49.9	40	12				
22:39	49.9	40	10	14:39	49.9	40	12				
23:09	49.9	40	10	15:09	49.9	40	13				
23:39	49.9	40	11	15:39	49.9	40	13				
00:09	49.9	40	11	16:09	49.9	40	13				
00:39	49.9	40	11	16:39	49.9	40	13				
01:09	49.9	40	11	17:09	49.9	40	13				
01:39	49.9	40	12	17:39	49.9	40	13				
02:09	49.9	40	12	18:09	49.9	40	13				
02:39	49.9	40	12	18:39	49.9	40	13				
03:09	49.9	40	12	19:09	49.9	40	13				
03:39	49.9	40	12	19:39	49.9	40	13				
04:09	49.9	40	12	20:09	49.9	40	13				
04:39	49.9	40	12	20:39	49.9	40	13				
05:09	49.9	40	12	21:09	49.9	41	14				
05:39	49.9	40	12	21:39	49.9	41	14				

RUN BY R. Newman DATE Feb 8 2002

RUN BY ______ DATE ______


C
psi
psi
100.00
50.00
100.00
75.00
37.50
75.00
50.00
25.00
50.00
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12.50
25.00
0.00
0.00
0.00
14:08:42
2/8/02
23:08:49
2/8/02
8:08:57
2/9/02
17:09:04
2/9/02
2:09:12
2/10/02
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Shkr56 Pressr
Hist.FIX.DT5609.F_CV
Shkr56 H2 Uptake
Hist.FIX.TE5603.F_CV
Shkr56 Product Temp

Data file :C:\HPCHEM\HPLC0157\DATA\061-0101.D Sample Name: 70316-035

25.7mg/50ml of isolated salts ->

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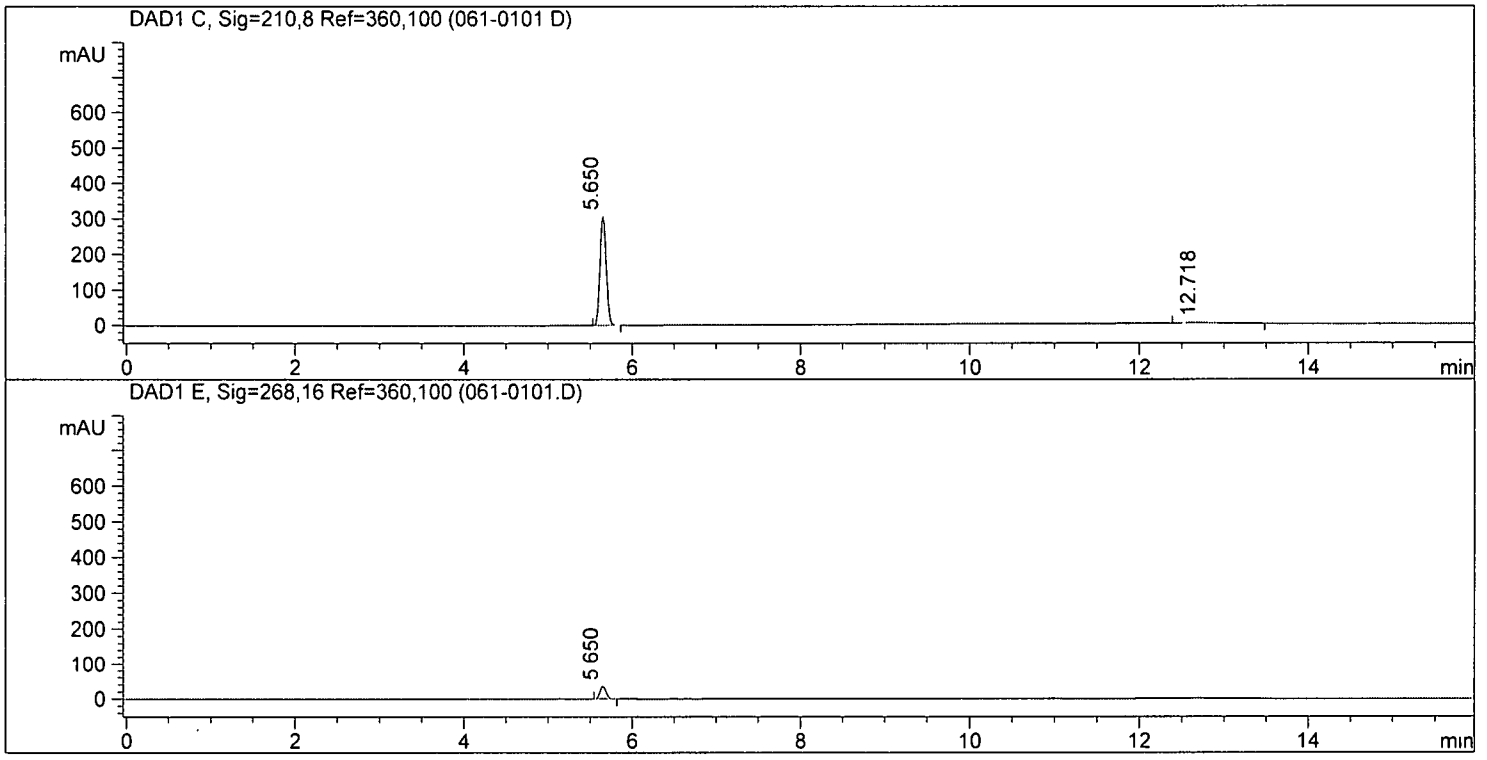
Injection Date : 02/13/2002 7:54:44 AM Seq Line : 1
Sample Name : 70316-035 Vial No : 61
Acq Operator : hansen Inj. No. : 1
Inj. Vol. : 2 µl

Method : C:\HPCHEM\HPLC0157\METHODS\715.M
Last Changed : 01/14/2002 1:00:57 PM
75/25 0.1% HClO4/Acetonitrile, 1ml/min
10min 25/75 water/acn; 75/25 from 10 to 14 min
waters c18 symmetry, 250 nm



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Customized Report:karlo

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Sorted By : Signal
Calib. Data Modified : 01/14/2002 1:00:30 PM
Multiplier : 1.000000

Signal: 1 DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	PB	0.080	306.34	1571.970	95.90	0.414306	L-224,715
2	12.72	BB	0.432	1.96	67.194	4.10	0.000000	

80

Signal: 2 DAD1 E, Sig=268,16 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Height [mAU*s]	Area [mAU*s]	Area %	Amount mg/ml	Name
1	5.65	BB	0.080	35.37	180.988	100.00	0.414306	L-224,715

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*** End of Report ***

isolated phosphate salt from
etoh/water
nmr400c h1

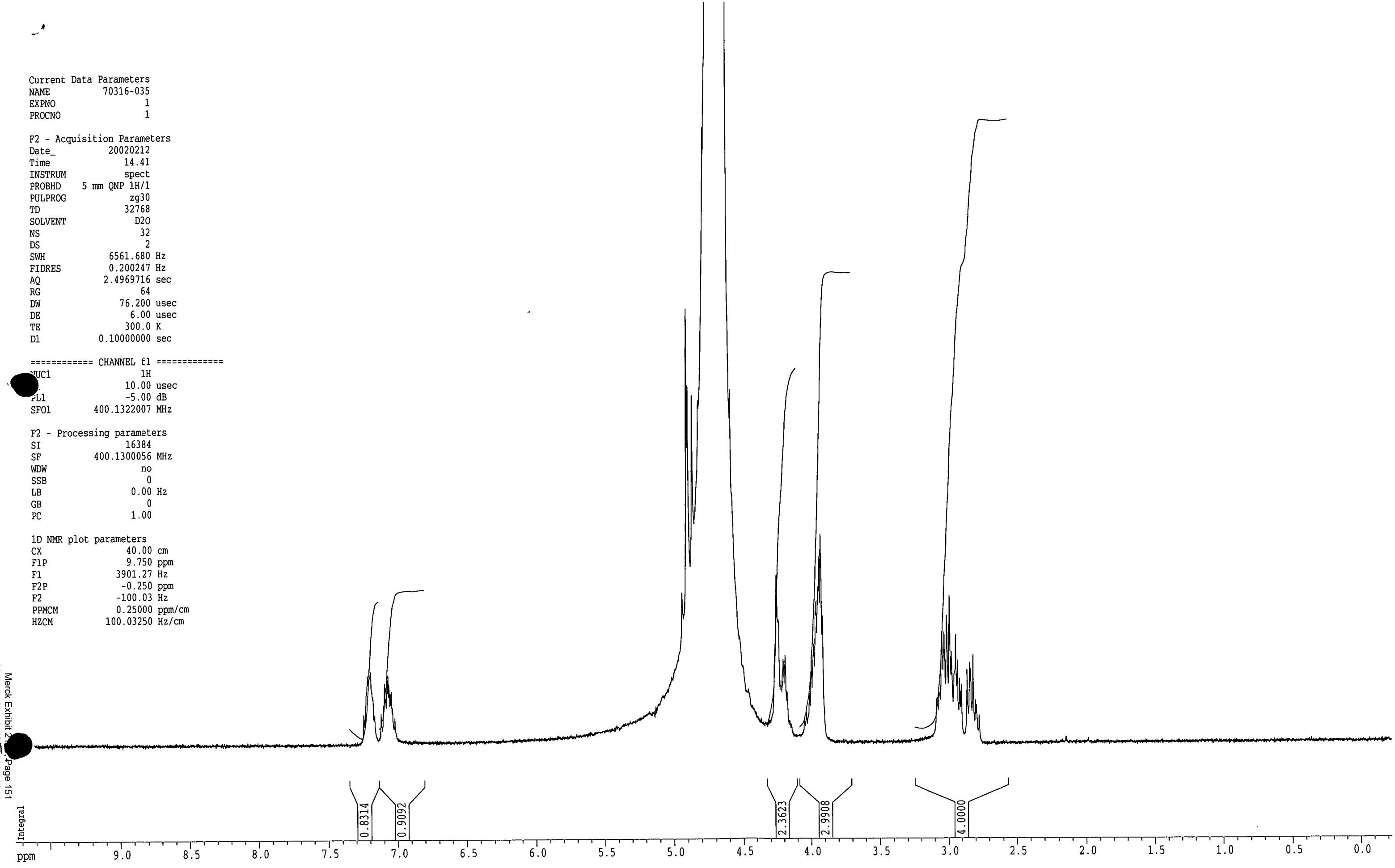
```
Current Data Parameters
NAME          70316-035
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20020212
Time              14.41
INSTRUM           spect
PROBHD    5 mm QNP 1H/1
PULPROG           zg30
TD               32768
SOLVENT            D2O
NS                  32
DS                   2
SWH           6561.680 Hz
FIDRES        0.200247 Hz
AQ           2.4969716 sec
RG                  64
DW              76.200 usec
DE               6.00 usec
TE               300.0 K
D1          0.10000000 sec

============ CHANNEL f1 =============
NUC1                1H
P1                10.00 usec
PL1               -5.00 dB
SFO1        400.1322007 MHz

F2 - Processing parameters
SI                16384
SF          400.1300056 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                40.00 cm
F1P                9.750 ppm
F1              3901.27 Hz
F2P               -0.250 ppm
F2              -100.03 Hz
PPMCM           0.25000 ppm/cm
HZCM          100.03250 Hz/cm
```



Book 70316 Page 37 Project No. ________ Project Page ________

Investigator ________ Date 8 Feb 2002

Subject ________ Restricted Confidential limited access

Filed in Book Number/Title ________

~~L224715-L-Tartrate~~ 1. EtOAc - NaOH → 2. H_3PO_4 EtOH/H_2O

Reagents:	FW	Amt	mmol	eq
L224715 Tartrate	557	2.00 g	3.60	1.0
EtOAc		~~20~~ 40 ml		1.
NaOH		~~10~~ 20 ml	10	

Procedure: Slurried material in EtOAc Added NaOH. Cut layers washed w/ 20 ml 20% NaCl. Assayed EtOAc layer to contain 1.45 g of 715 ~99%. Concentrated to oil

Redissolved in 6 ml Ethanol & filtered into 3 neck RBF Added 1.5 ml H_2O (20% water), Dissolved ~~415~~ 420 mg of Phosphoric acid in 1.5 ml EtOH Heat soln to 78°C, Added H_3PO_4 soln - it was clear - no xtals. Removed heat & cooled to 76°C slurry formed Reheated to 72°C but still solids added 0.75 ml H_2O & ~~most of~~ all of solids dissolved Cooled to RT @ 5°C/hr & then aged overnight

11 Feb 2002 - slurry present dark material in it from probe rubbing up against stir shaft. Added 48 ml Ethanol filter isolated 1.20 g white solids 67% Recovery

Dissolved in 1 ml until saturated w/ solid - material is 90 mg/g solubility in H_2O

12 Feb 2002 ^{1}H NMR of salt (10 mg/ml in D_2O) & a saturated soln of Freebase

Methine α to amine is clear shifted downfield in salt sample relative to Freebase. [signature] 12 Feb 2002

Countersigned by ________

Date ________

MERCK & CO., INC./MRL 0497 (10/00)