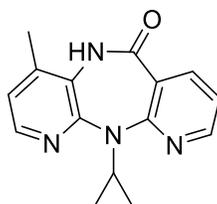


TECHNOLOGY TRANSFER REPORT

The Medicines for All Initiative Nevirapine Process Optimization

NEVIRAPINE



11-cyclopropyl-4-methyl-5,11-dihydro-6*H*-
dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one

May 2015

Executive Summary

An ultra-efficient synthetic method has been developed for nevirapine drug substance which requires a single unit operation to convert starting materials into product in high yield (87% overall). The new process employs inexpensive raw materials and limited unit operations to produce an API that meets or exceeds all USP specifications.

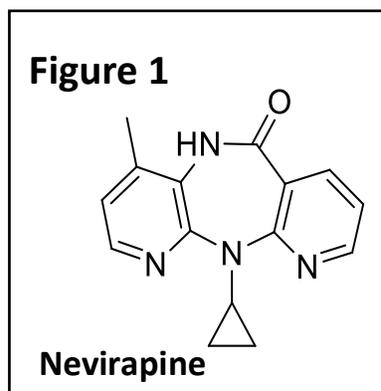
Table of Contents

1. Introduction.....	3
2. Prior Art.....	4
3. Process Chemistry.....	5
4. Experimental Procedures.....	7
5. Analytical Methods	12
6. Flow Diagram and Mass Balance.....	14
7. Economic Analysis.....	16
8. Conclusion and Recommendations.....	17

INTRODUCTION:

Nevirapine (Figure 1) is currently a major component of front-line treatment in HIV combination drug therapy. Furthermore, it is one of the most effective treatment options in perinatal HIV applications. Though its prominence as a frontline therapy may be supplanted by new drug alternatives, the World Health Organization forecasts that over 600 metric tons per year will be required to treat existing patients for the foreseeable future.

A new low cost process has been developed to produce nevirapine from two highly substituted pyridine precursors: methyl 2-cyclopropylamino nicotinate (Me-CAM) and 2-chloro-3-amino-4-picoline (CAPIC). The two pyridine starting materials are converted into nevirapine by two discrete chemical reactions that are carried out in under strongly basic conditions in high yield. By employing a common solvent system, these reactions have been consolidated into a single process step, which significantly reduces the number of manufacturing unit operations and lowers operating cost.



The overall yield for the new process is 87% and the total raw material cost for the new process is estimated to be \$58.39/kg based on Chemical Marketing Reporter/ISIS pricing information for commodity based raw materials as well as from individual suppliers. This new streamlined process represents a substantial improvement over the existing five step process that has an overall yield of 59%. Furthermore, the nevirapine API produced from this new process contains no detectable new impurities while the impurity profile and chromatographic purity meets or exceeds USP specifications.

The new Nevirapine process consists of the following two steps:

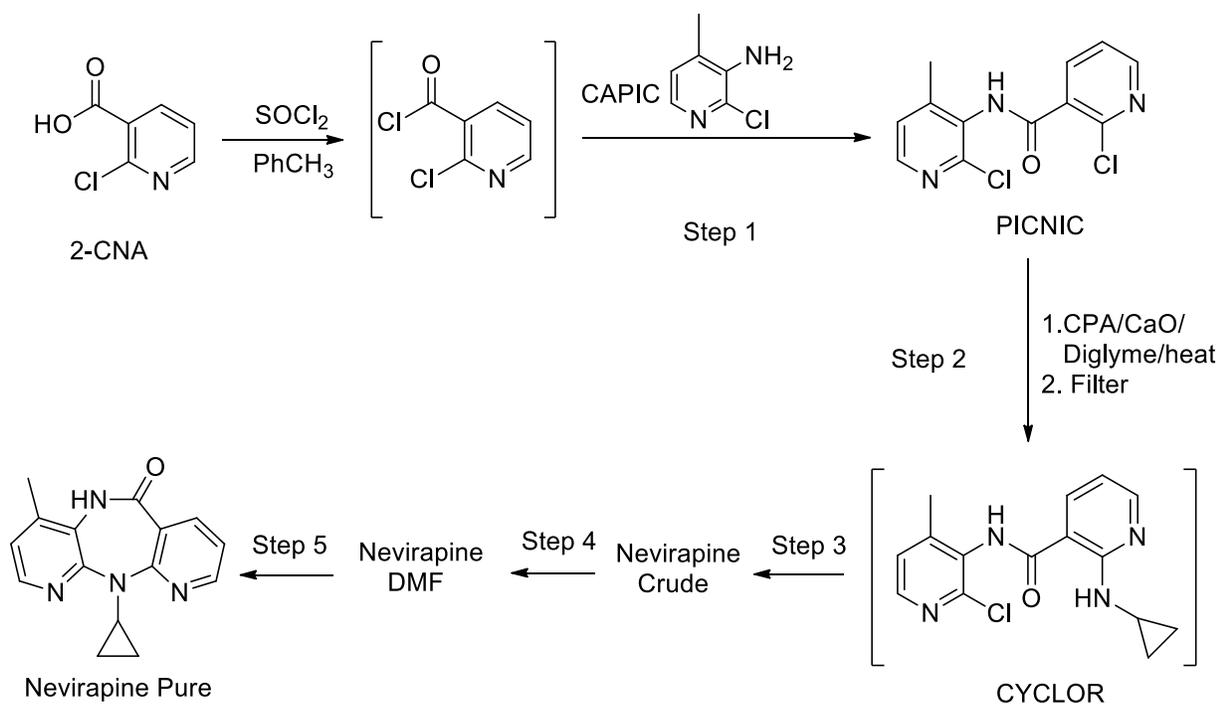
- Step. 1A: 2-(Cyclopropylamino) nicotinamido-3'-amino-2'-chloro-4'-methylpyridine (CYCLOR)
- Step. 1B: Nevirapine Crude
- Step. 2: Nevirapine Pure

Herein we report the new CAPIC process chemistry, process flow diagrams, mass balance, procedures, use tests, and raw material cost information.

Prior Art

Nevirapine has been made commercially by at least two alternative reaction pathways. The first generation method that was used for the nevirapine launch in 1996 (US 5620974) employed 2-chloro-nicotinic acid (2-CNA) and 2-chloro-3-amino-4-picoline (CAPIC) as a starting materials and is provided in Scheme 1.

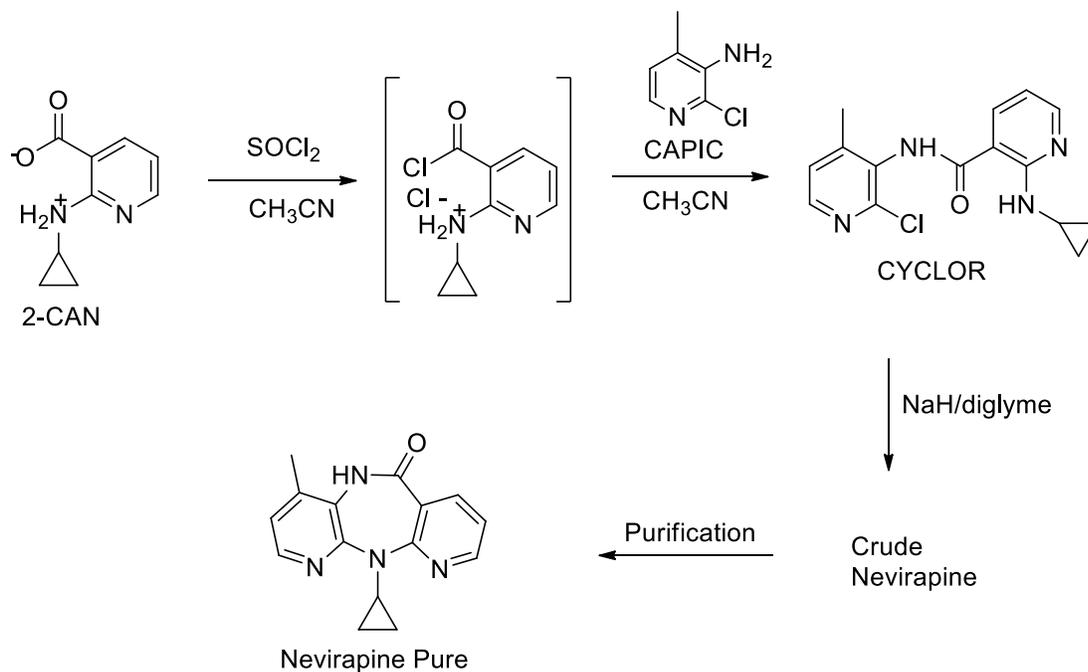
Scheme 1: First Generation Nevirapine Process



Overall Yield 59%

A second generation method was developed that uses 2-cyclopropylamino-nicotinic acid as an alternative starting material (US 6680383) and is provided in Scheme 2. The innovator drug company, Boehringer Ingelheim Pharmaceuticals currently practices the second generation process at a cost in excess of \$800/kg. However, the original process is currently being used in other countries to supply the majority of the current nevirapine market. For these suppliers, the selling price ranges from \$175/kg to less than \$100/kg.

Scheme 2: Second Generation Nevirapine Process



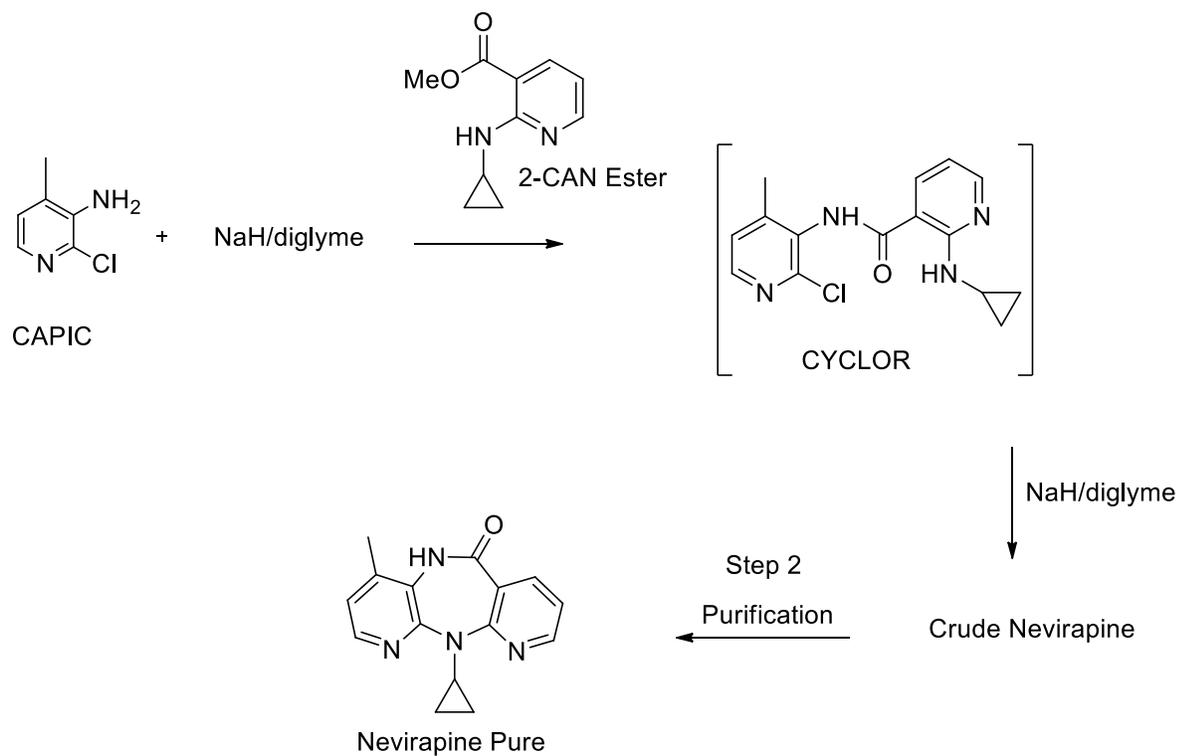
Overall Yield 68%

PROCESS CHEMISTRY

The new nevirapine process entails two reaction steps that can be carried out in a single unit operation (Scheme 3). This alternative approach requires the use of methyl 2-cyclopropylaminonicotinate (Me-CAN) and 2-chloro-3-amino-4-picoline as starting materials in a single solvent system with a common strong base, sodium hydride. A final purification step is used that is identical to the ones practiced in the current commercial processes in order to ensure that we are able to reproduce all of the solid state properties of the API including crystal morphology, particle size distribution and bioavailability.

The overall yield for the new process is 86% with an average yield per step of 93%, which represents a major improvement over the current commercial processes. By using a common solvent for both reaction steps, we were able to avoid costly solvent exchanges that add significant process complexity requiring waste treatment, remediation or recycling. Approximately 80% of the diglyme solvent is recovered and recycled as part of the process. The nevirapine API produced from this process was tested for chromatographic purity as well as impurity profile. There were no measurable new impurities by LC/MS and the API meets or exceeds all US Pharmacopeia standards.

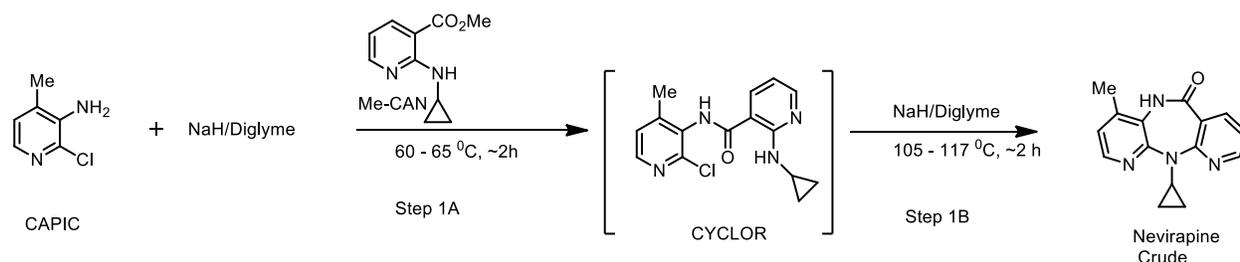
Scheme 3: Medicines for All Nevirapine Process



Overall Yield 87%

EXPERIMENTAL PROCEDURE:

Step 1: ONE POT PREPARATION OF NEVIRAPINE



SYNTHESIS OF NEVIRAPINE CRUDE

Materials	Amount g/ml	Mwt./Density	Mmole	Equiv.
CAPIC	15 g	142.6	105	1.0
NaH	7.56 g	24.0	189	1.8
	7.14 g	60% in Oil	178.5	1.7
2-CAN-OMe	21.19 g	192.2	110.25	1.05
Diglyme	75 ml			
	27.5 ml		-	
	27.5 ml			
Acetic Acid	19.5 g	60/1.04	325	3.09
Cyclohexane	51 ml	84/0.77	-	
Ethanol	23 ml	46/0.79	-	
Water		18		

Step 1A: PROCEDURE FOR CYCLOR FORMATION:

1. To a 500 ml 3-neck round-bottom flask fitted with overhead stirrer, thermocouple and addition funnel under N₂ was charged CAPIC (15 g, 105 mmole, 1.0 equiv) and NaH (7.56g, 189 mmole, 1.8 equiv). *(Note 1)*
2. To the above mixture was charged diglyme (75 ml, 5ml/g of CAPIC) and the suspension was stirred. *(Note 1)*
3. The temperature was ramped to 30 °C and held between 30 – 35 °C for 30 minutes, upon which gradual evolution of H₂ gas was observed. *(Note 2)*
4. The temperature of the mixture was increased in 10 °C increments and held for about 1 hour for each increment until the temperature of the reaction mixture reaches 60 °C and the evolution of H₂ gas subsided. *(Note 2)*
5. In another 150 ml, 3 necked flask, purged with N₂, Me-CAN (21.19 g, 192.2 mmol, 1.05 equiv) and diglyme (22.5 ml, 1ml/g) was heated to ~55 °C. *(Note 3)*
6. The solution of Me-CAN in diglyme was charged slowly, drop-wise, in over 1 hour to the suspension of CAPIC and NaH in diglyme while maintaining the temperature of the reaction mixture at 60 – 65 °C. *(Note 4)*
7. The charge line of Me-CAN was rinsed with 5 ml of diglyme.
8. After the transfer of Me-CAN to NaH/diglyme/CAPIC solution, the reaction mixture was held at 60 – 65 °C for about 2 hours and was monitored by HPLC to ensure complete consumption of CAPIC and completion of reaction to form CYCLOR. *(Note 5, 6)*
9. After reaction was complete, the temperature of the reaction mixture was ramped to 80 °C and held at 80 – 85 °C.

Step 1B: PROCEDURE FOR NEVIRAPINE CRUDE:

10. In another 250 ml, 3 neck flask, fitted with overhead stirrer, thermocouple and addition funnel purged with N₂ was charged NaH (7.14 g, 178.5 mmol, and 1.7 equiv) and diglyme (22.5 ml) and the suspension was heated to 105 °C. *(Note 7)*
11. The reaction mixture of CYCLOR was added slowly drop-wise into the suspension of NaH in diglyme over a period of 30 minutes while keeping the temperature of the mixture at 105 – 110 °C. *(Note 7)*
12. The charge line of CYCLOR was rinsed with 5 ml diglyme.
13. After addition of CYCLOR was complete, the reaction mixture was kept at 112 – 117 °C for about 2 hours and monitored by HPLC to ensure complete ring closure or cyclisation of CYCLOR to Nevirapine. *(Note 8, 9)*
14. The mixture was cooled down to 0-5°C and the excess sodium hydride was quenched slowly by addition of 30 ml of water while keeping the temperature below 50 °C. *(Note 10)*

15. After quench was complete, distilled 60 – 70 ml of diglyme/water from the reaction mixture and charged 125 ml of water and stirred to ensure all salt becomes soluble. *(Note 11)*
16. To the above reaction mixture was charged 51 ml of cyclohexane and 15 ml of ethanol while stirring. *(Note 12, 13)*
17. The pH of the mixture was adjusted to 6 – 8 using glacial acetic acid (19.5 g, 3.09 mmol) upon which Nevirapine precipitated out as a solid. *(Note 14)*
18. The suspension was cooled to 0 –10°C and stirred for around one hour on which the precipitate of nevirapine increases.
19. The precipitate was filtered and washed successively with water (3x30ml) and 20% ethanol: water (2x20ml) mixture. *(Note 15)*
20. The wet cake was dried between 90-110°C under vacuum to a constant weight.
21. The dried weight of crude Nevirapine was 25.4 g (91%)

Process Notes:

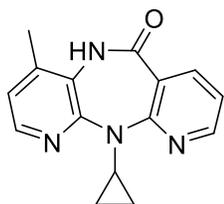
Step 1A:

1. This is not a commercial process. There is no reactivity of NaH, CAPIC and diglyme at room temperature. Therefore, charge sequence can be adjusted as it fits with production. NaH can be charged after charging CAPIC and diglyme.
2. There is significant foaming of the mixture seen with reaction of NaH with CAPIC. The NaH is allowed to react with CAPIC for 4 hours with multiple temperature ramps as described. Multiple temperature ramps are required to control the foaming and exotherm of the reaction.
3. Me-CAN can be stock solution produced in toluene/diglyme. Around 10% toluene should be acceptable. Heating is not necessary for dissolution. Me-CAN solution can be charged into CAPIC solution keeping reaction temperature between 60-65°C for fast reaction.
4. The reaction is only slightly exothermic. Slow addition is required to ensure that Me-CAN is not hydrolyzed. Faster addition increases hydrolysis of Me-CAN.
5. The reaction proceeds faster at higher temperature but more impurities are observed at higher temperature. Therefore, keeping it between 60-65°C ensures complete formation of first intermediate CYCLOR.
6. In process control (IPC)-We observed around 85A% of CYCLOR formed and complete consumption of CAPIC during completion of reaction. Excess Me-CAN has been used for this reaction.

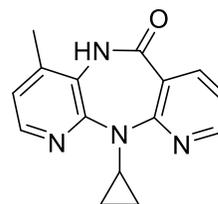
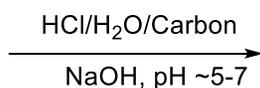
Step 1B:

7. During commercial process CYCLOR is always charged into NaH/diglyme mixture. Reverse addition is a safety risk and more impurities are generated.
8. During reaction foaming is observed due to gas evolution but can be controlled on production scale.
9. In process control (IPC) – Reaction is considered complete when there is ~1A% of CYCLOR is left to react.
10. Cool the reaction mixture to ~ 0-5°C before quenching with water. Quite exothermic and foaming observed. Control by slow charge of water or charging in portions.
11. This is azeotropic distillation which initially remove any free water and then diglyme. If diglyme is not concentrated, we will lose around 20-30% of product. Distillation is carried under vacuo below 80°C.
12. Reagent grade ethanol is used. Cyclohexane is needed to remove oil from NaH. The moisture will be triphasic two solvent plus solid. It does remove all the oil and color from the product.
13. If there is any residual oil left that will be removed in the next step crude to pure.
14. Precipitate will appear at around ~pH 3
15. This is not a commercial process. Washes need to be optimized during scale-up.

Step 2: Crude Nevirapine to Pure Nevirapine



Nevirapine Crude



Nevirapine Pure

Materials	Amount g/ml	Mwt./Density	Mmole	Equiv.
Nevirapine Crude	10g	266.3	37.55	1
H ₂ O	43 ml	18		
HCl (37%)	11.6 ml	36.5/1.189g/ml	138.8	0.313
Activated Carbon (Norit)	0.3g			
NaOH (50%)	4.64 ml	40/1.515g/ml	176.2	0.469
Celite	1gm	-	-	-

Procedure:

1. Nevirapine crude (10g, 37.55mmole) and purified water 43 ml were charged to a 250 ml 3-neck round-bottom flask fitted with magnetic stirrer, thermocouple and addition funnel.
2. This was stirred at room temperature and then the temperature was lowered to 0-5°C using ice/water bath.
3. HCl (11.6 ml, 138.8 mmole) was charged drop wise to the above slurry while keeping temperature below 5°C. (*Note 1*)
4. After the HCl charge was completed, the reaction mixture was stirred for around 30 minutes at 0-5°C to ensure that all nevirapine dissolved. (*Note 2*)
5. After nevirapine was in solution, activated carbon (0.3g) was charged and stirred for at least another 30 minutes with the temperature maintained between 0-5°C. (*Note 3*)
6. The solution was filtered using celite pad to capture all the carbon.
7. The celite pad was rinsed with 2x5ml water.
8. The clear filtrate was filtered using 4 µ filter to remove any insoluble material/fibers etc. before moving to next step to precipitate the final product. (*Note 4*)
9. The clear filtrate was transferred into a 250 ml 3-neck flask fitted with magnetic stirrer, thermocouple and addition funnel while keeping the solution between 0-5°C.
10. NaOH (50% solution) was charged drop-wise to pH 4-7, while keeping temperature below 5°C. A white precipitate appeared. When desired pH was reached the mixture was stirred for about 30 minutes. (*Note 5*)
11. The product was filtered under vacuo using filter paper. The solid was washed with water 3x10ml. (*Note 6*)
12. The cake was cut and dried between 90 -110°C under vacuo to a constant weight.
13. The isolated yield was 9.6g; (96%) Purity 100A% by HPLC. See attached chromatogram.

Process Notes:

1. We have seen some impurity if temperature is kept above 10 °C for an extended period of time.
2. The solution may not be completely clear. It may be hazy due to residual oil.
3. Carbon grade should be consistent with FDA requirements for API processes.
4. Since this is final API, filtering with 4 µ filter is needed to capture fibers etc.
5. Since this is final API, use of filtered NaOH is recommended. Less than 50% NaOH solution can be used as suitable for filtration.
6. Wash conditions need to be optimized during scale-up based on residual salt content of final product and specification. Nevirapine is not soluble in water therefore, more washes have no impact on the yield.

ANALYTICAL METHODS

The UPLC and HPLC methods used to determine chromatographic purity are as follows:

UPLC chromatograms were acquired on a Waters Acuity UPLC H-Class system using a Waters BEH C18 column (1.7 μm , 2.1 mm x 50 mm). A gradient of 5% ACN in H₂O to 90% ACN in H₂O was applied from 0.5 min to 9.0 min at a flow rate of 0.6 mL/min, followed by a hold at 90% ACN from 9.0 min to 10.0 min.

HPLC chromatograms were acquired HPLC on an Agilent 1260 Infinity system using an Agilent Poroshell 120 EC-C18 column (2.7 μm , 4.6 mm x 50 mm). A gradient of 5% ACN in H₂O to 95% ACN in H₂O was applied from 0.5 min to 6.5 min at a flow rate of 1.5 mL/min.

Figure 1: Nevirapine Batch SA-1-27 HPLC

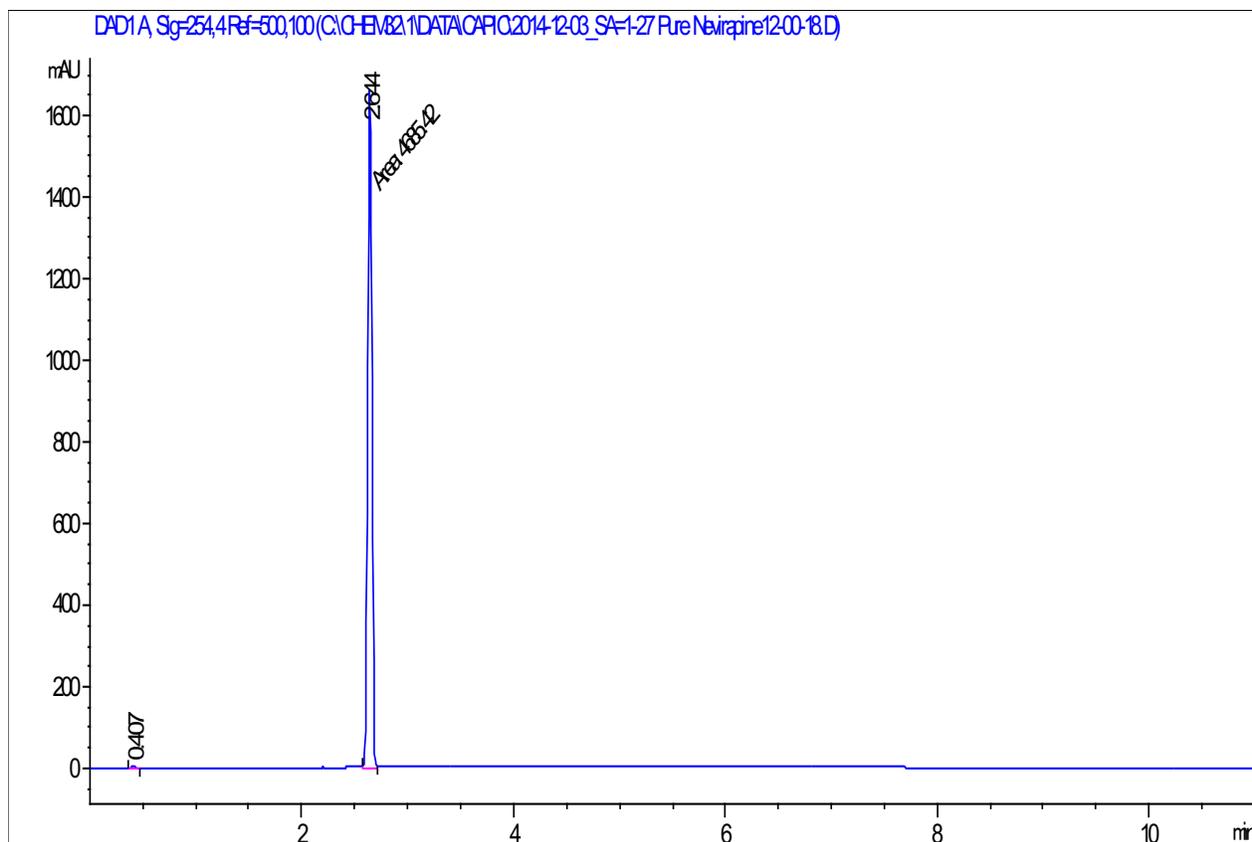
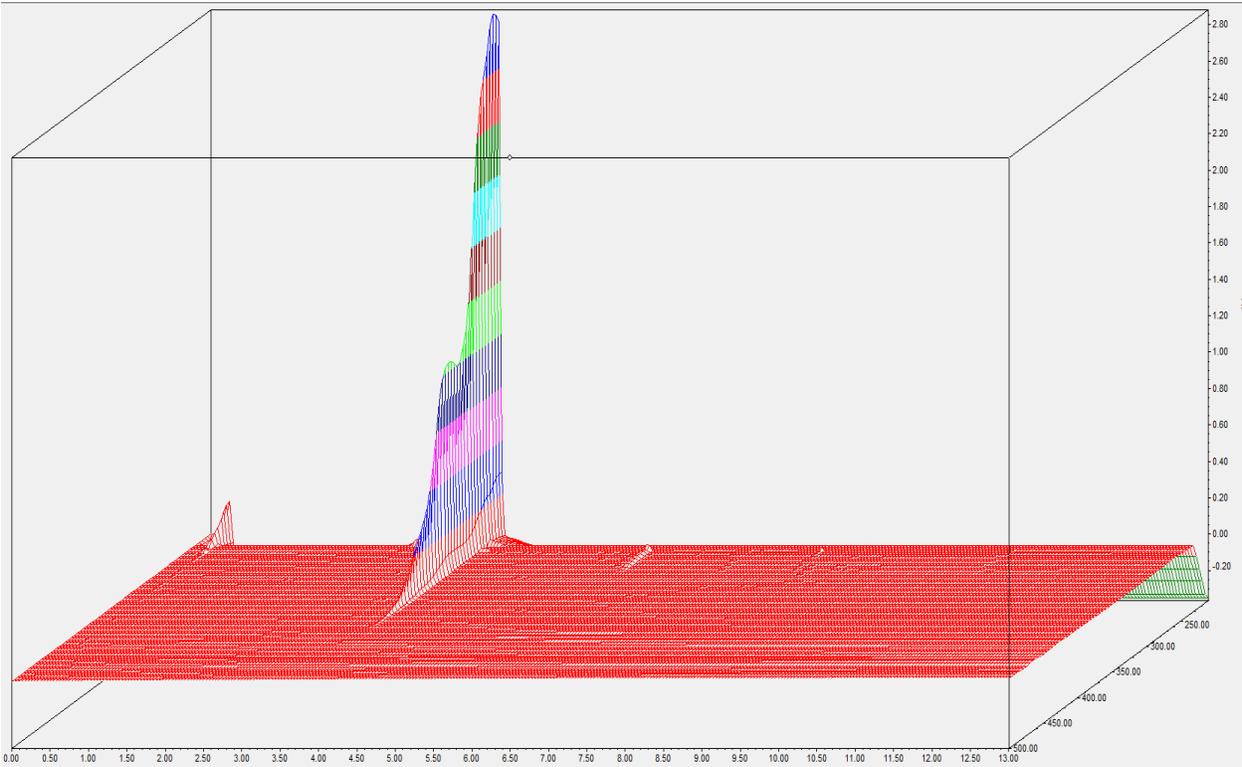


Figure 2: 3-D UPLC Plot of Nevirapine Sample SA-1-28



PROCESS FLOW DIAGRAM AND MASS BALANCE

A process flow diagram of the new CAPIC process is provided in Scheme 4. Since all reaction steps up through the formation of nevirapine crude are carried out under strongly alkaline conditions, 316 stainless steel reactors should be the preferred materials of construction. Solvent recycle streams have been excluded from the scope of the flow diagram but a 20% solvent purge is included in the cost calculation in order to preclude any buildup of byproduct impurities in the process. A summary mass balance is also provided in Table 1.

Scheme 4: Medicines for All Nevirapine Process Flow Diagram

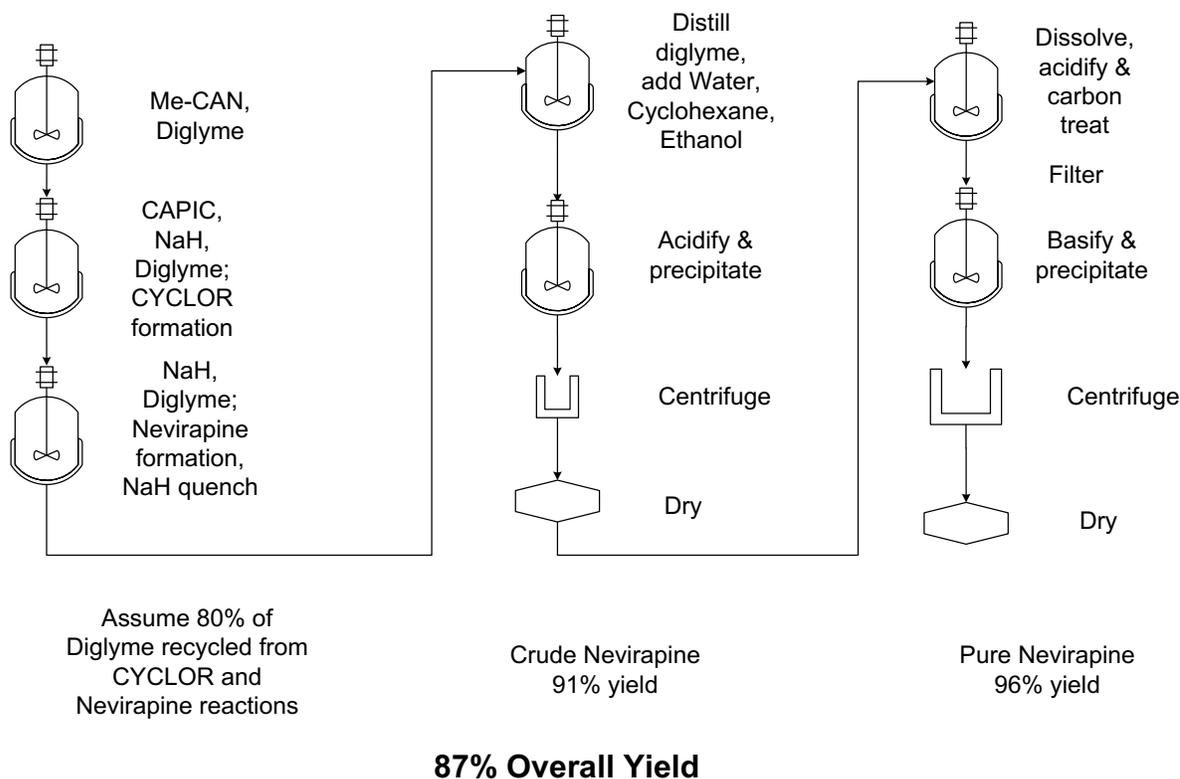


Table 1: Medicines for All Nevirapine Process Mass Balance

Reaction (molar yield %)	Chemical	Molecular Formula	Stoichiometry (equiv)	Molecular Weight / **	Solvent Density gm / ml	Reagent Charge (kg)	RM Cost (\$ / kg RM)	RM Cost (\$ / kg CAPIC)	Reaction Mass Balance Check by MW (0 = balanced reaction)	kg of each intermediate required	
<i>CYCLOP</i>	CAPIC	C5H2N-Cl-NH2-CH3	1.0	142.586		0.613	19.74	12.099	R1-NH2 + CH3COO-R2 ->		
<i>Nevirapine Crude</i>	Sodium Hydride	NaH	3.5	24.00		0.361	7.5000	4.513	-> R1-NH-CO-R2 + CH3OH		
91.0%	oil (with NaH)					0.241			Cl-R-NH -> R-N + HCl		
	Me-CAN	C10H12N2O2	1.05	192.216		0.868	34.703	30.106	'302.76 + 32.02		
Solvent	Diglyme		8.67 ml / gram	60.094	0.786	0.835	4.8000	4.010	Mat'l balance check		
	Acetic Acid		3.09	60.052		0.798	1.199	0.957	0.00		
	Cyclohexane		3.4 ml / gram	84.156	0.77	1.605	2.181	3.500	Cl-R-NH -> R-N + HCl		
	Ethanol		2.067 ml / gm	46.068	0.79	1.001	1.086	1.087	'302.76 -> 266.3 + 36.6		
	Water		18.467 ml / gm	18.016	1.00	11.318	0.000	0.000	Mat'l balance check		
									0.00		
Intermediate 1	Nevirapine	C9H9N3		266.302						1.042	
	Nevirapine	C9H9N3	1.0	266.302		1.042	---				
96.0%	Water	H2O	7.3 ml / gram	18.016	1.00	7.604		0.000			
	Hydrochloric Acid (as 36% aq. Solution)	HCl	0.3	36.458		0.045	0.752	0.093			
	Water (from HCl solution)	H2O		18.016		0.079					
	Activated Carbon		0.03 gm / gm			0.031	10.7473	0.336			
	Sodium Hydroxide (as 50% aqueous)	NaOH	0.5	39.998		0.073	0.302	0.044			
	Water (from NaOH solution)	H2O		18.016		0.073					
	Celite		0.1 gm / gm			0.104	15.7499	1.641			
Product	Nevirapine	C10H12N2O2		266.302						1.000	
	Key Raw Material (KRM) and Intermediates in Bold							58.385	\$ / kg Nevirapine		
									Basis of calculation:	1.0	kg Nevirapine

ECONOMIC ANALYSIS

Our economic analysis of the new nevirapine process is restricted to raw material cost, as other manufacturing and operating costs are highly site dependent. A breakdown of raw material costs for the new nevirapine process is provided in Table 2. The two pyridine fragments (CAPIC and Me-CAN) represent approximately 72% of the total raw material cost for the new process and have been optimized in parallel process development programs within this initiative . All other raw materials are commodity items of low cost.

Table 2. Nevirapine Raw material Cost

Raw Material (RM)	RM kg /	RM \$ /	RM Cost	% of
	Nev kg	kg	(\$ / kg Nev)	total
CAPIC	0.613	19.74	12.099	20.72%
Sodium Hydride	0.602	7.5	4.513	7.73%
Me-CAN	0.868	34.70	30.106	51.56%
Diglyme	0.835	4.80	4.010	6.87%
Acetic Acid	0.798	1.20	0.957	1.64%
Cyclohexane	1.605	2.18	3.500	5.99%
Ethanol	1.001	1.09	1.087	1.86%
Hydrochloric Acid (as 36% aq. Solution)	0.124	0.752	0.093	0.16%
Activated Carbon	0.031	10.747	0.336	0.58%
Sodium Hydroxide (as 50% aqueous)	0.147	0.302	0.044	0.08%
Celite	0.104	15.750	1.641	2.81%
			58.385	100.00%

CONCLUSIONS AND RECOMMENDATIONS

An ultra-efficient synthetic method has been developed for nevirapine. The new process has the following attributes:

- High yielding reactions, averaging 93%
- Inexpensive raw materials
- A single unit operation to convert starting materials into product
- Minimal solvent requirements
- Limited unit operations
- High product purity