Designing an Industrially Scalable, Flow-Based Synthesis for the Production of Nilotinib: Chemical Process Modeling and Economic Analysis

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Abstract — **Nilotinib (Tasigna) is a drug used to treat chronic myelogenous leukemia (CML), a disease which currently affects over 100,000 people in the U.S. The drug is manufactured by Novartis and has been one of its most profitable, bringing in a total revenue of well over $2 billion USD in 2016. Novartis's patent on Tasigna is set to expire in 2023 and cheaper, generic versions of the drug will soon be in great demand. An assessment of Novartis's existing patent on the synthesis of Tasigna indicates many drawbacks in the current process. Namely, the Novartis synthesis requires multiple days of reaction, nearly a dozen steps, multiple solvent switching processes, and gives very low yields. On the other hand, work published by Buchwald and coworkers has shown an efficient method of synthesizing nilotinib in fewer than four steps, in less than 24 hours, and at >85% yields. Unfortunately, the Buchwald reaction has only ever been applied in a laboratory setting and has never been scaled to an industrial level. Thus, it was the goal of this investigation to develop an industrially scaled, flow-based synthesis of the Buchwald synthesis of nilotinib. For this investigation, our team assumed the role of a generic pharmaceutical company with a hypothetical goal of producing 15% of the U.S. market share of nilotinib (1150 kg of nilotinib/year). Utilizing chemical reaction modeling software, ChemCAD, a chemical process for the large scale Buchwald synthesis of nilotinib was successfully designed at the 1150 kg production capacity of the active pharmaceutical ingredient of nilotinib per year. Economic analysis demonstrated the fiscal viability of this process with estimated gross revenue of >$250 million USD/year even with a predicted 60% drop in generic drug price factored in. This, we envision, would serve as an important improvement in the efficiency of industrial level synthesis of a life-saving cancer drug.**

I. INTRODUCTION

The use of tyrosine kinase inhibitors (TKIs) to treat chronic myeloid leukemia (CML) has been one of the greatest breakthroughs in modern oncology. The advent and introduction of TKIs into the clinic has extended 8-year survival rates of patients with CML from <15% in the 1980s to nearly 90% in 2012 (Kantarjian et al., 2012). Even today, over 10,000 people each year are newly diagnosed with CML and the vast majority, if not all, of these patients will rely on TKIs (National Cancer Institute, 2014).

The patent for Novartis's original first-generation TKI, known as Gleevec (imatinib), expired in 2016. To mitigate its loss of profit and market share, Novartis developed a second-generation TKI known as Tasigna (nilotinib), shown in Fig. 1. Tasigna is designed to be more potent in treating CML than its first-generation counterpart and also addresses many of the challenges of chemotherapy resistance that were faced by Gleevec (Huang et al., 2007). Tasigna received its final FDA approval to treat CML in 2010. However, Novartis's patent on Tasigna is set to expire in 2023. This makes it a particularly opportune time to plan the development of generic versions of Tasigna so that once Novartis's patent on the production of Tasigna expires, generic production can begin immediately.

In 2015 Tasigna represented 12.8% of the current market share of all TKI drugs for CML (Bloudek et al., 2015). Additionally, it is currently predicted that the incidence of CML will increase with an estimated prevalence of 112,000 patients in the US by 2020 (Cortes et al., 2012). By the year that Novartis's patent on Tasigna expires, it would be expected that there will be at least 140,000 patients with CML in the US in need of treatment. The cost on the patient to take Tasigna for one year is approximately $100,000, highlighting the importance of quickly bringing generic versions of the drug to market once the Novartis patent expires in order to reduce patient financial burdens. The large reliance of CML patients on TKI drugs in addition to the prohibitively expensive price of current Tasigna treatments highlights the great market potential and demand for developing a generic, cheaper version of Tasigna and thus, will be the focus of our investigation.

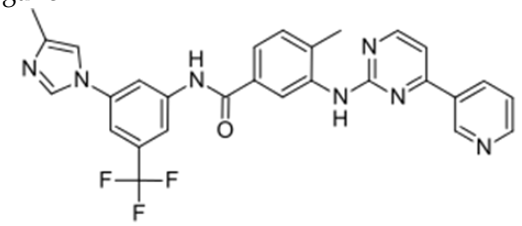


Figure 1. *Structure of nilotinib.*

Here, we outline our unique process design for an industrially scaled, flow-based process for the production of generic Tasigna (nilotinib). The ultimate goal of this investigation will be to computationally develop a scalable synthesis which could potentially be used to produce large quantities of nilotinib with a greater degree of efficiency than the existing Novartis method. Thus, once the Novartis patent over nilotinib production expires, efficient methods of producing generic Tasigna can be implemented to rapidly capture the large and profitable market which Tasigna currently holds. This will allow for the increased availability and lower price of a much needed drug to tens of thousands of CML patients.

For this investigation, our team has taken the hypothetical role of a generic pharmaceutical company in planning the development and production of generic Tasigna. As such, this investigation consists of four

distinct sections: (1) an assessment of the commercial efficacy of Novartis's existing production methods of nilotinib, (2) literature review assessing the efficiency and scalability of existing, laboratory level (small scale) synthesis methods of nilotinib, (3) selection of an existing small scale nilotinib production process and modeling its scaling to an industrial level using ChemCAD software, and (4) an economic analysis of the scaled process to assess its fiscal viability and profitability. The results of this investigation have the potential to provide a robust framework for the large-scale development of nilotinib upon the expiration of the Novartis patent on Tasigna.

II. METHODS

A three-stage literature search was initially conducted to address the following goals:

Firstly, market data on nilotinib drug pricing was collected in order to develop robust predictions of feasible generic pricing patterns as well as market share targets for our given scenario. This included a comprehensive search of articles pertaining to the prevalence of specific TKI usage in CML patients, marketing of each of these drugs, and pricing before and after generic introduction. The literature search mainly utilized the NCI (National Cancer Institute) database as well as pharmaceutical pricing literature.

Secondly, due to the lack of an existing published process flow diagram, all of Novartis's U.S. pa- tents for the production of Tasigna were collected and a predicted process flow chart of Novartis's current synthesis method was constructed based on the claims outlined in their filed patents.

Thirdly, all the currently published methods of synthesizing nilotinib at any scale were collected via literature search and analyzed for their efficiency across seven distinct criteria: (1) number of steps, (2) reaction temperatures, (3) reaction pressures, (4) reaction yields, (5) catalysts required, (6) solvents required, and (7) reaction time.

Once the most efficient of these methods was selected, process design modeling of the industrially scaled nilotinib synthesis was conducted using ChemCAD (Computer-aided design) 7 software (Chemstations). This allowed for the quantitative assessment and control of large flow rates of material, heat transfers, and separation efficiencies, allowing us to judge the success of the industrial scaling process.

During the process of envisioning the design through ChemCAD, special considerations were made to ensure that the process remained "flow-based" - eliminating the need for any manual handling of reaction intermediates and relying on a single series of reaction chambers. This was achieved using packed bed reactors (PBRs) in the model which allow for connections between parallel reactions and the use of solid catalysts without the need for interruption of the flow process.

The ChemCAD software was also utilized to verify that the proposed reaction schema remained thermodynamically viable throughout and that the output products were high in purity. Calculations of heat and material balances done via ChemCAD across each chemical reaction stage ensured that the reactions were well controlled, in the predicted state of matter, and exited each stage at the appropriate temperature and purity.

Lastly, economic analysis incorporated an assessment of the estimated costs of running the chemical production facility and raw material costs balanced against the predicted profits of the drug. Reactor, piping, and distillation tower cost estimates were made through two American Society of Mechanical Engineers (ASME) certified reactor manufacturers: Dominion Tank & Vessel Co., Inc. based in Richmond, Virginia and Procedyne Inc., based in New Brunswick, NJ.

III. RESULTS AND DISCUSSION

A. Chemical Process Model

Design Rationale & Market Scale Assessment

A recent study on patient CML drug preferences indicated that approximately 20% of all CML patients take Tasigna (nilotinib) as opposed to other TKI drugs (Sanford et al., 2014). Assuming that this trend continues, we can predict that the total CML patient pool taking nilotinib by the year 2023 is approximately 28,000 individuals. Based on historical precedent, as an emerging generic pharmaceutical company, our goal would be to capture approximately 15% of the nilotinib market share in the US, translating to about 4200 patients. The Food and Drug Administration (FDA) approved regimen for treatment of CML with nilotinib requires a dose of 0.3 mg twice daily (or approximately 230 g of nilotinib per patient per year) (National Cancer Institute, 2013). Thus, if we wish to pursue 15% of the nilotinib market share, production of at least 1150 kg nilotinib/year is the ultimate goal.

The current market price of Tasigna is ~$600 per gram (or $600,000 per kg). At current pricing, the estimated profit for 1150 kg/year of is $690 mil- lion/year. However, once nilotinib comes off pa- tent and is generically produced, we can expect a sharp price drop. We developed our estimates of this change based on the price drop that Gleevec (the 1st generation version of Tasigna) underwent when it came off patent. In 2016, Gleevec cost ~$146,000/year. Since coming off patent, the cheapest generic Gleevec option is ~$57,000/year (Kantarjian, 2016). This is a 60% decrease in price from original to generic form of the first generation TKI drug. We will assume that this pattern (60% drop in price) will also hold for Tasigna/nilotinib, therefore, we can assume that Tasigna's generic will be priced at $240 per gram and that the estimated revenue for 1150 kg/year nilotinib production is $276 million/year.

In summary, our generic pharmaceutical company will aim to take 15% of the nilotinib market share when the drug comes off patent in 2023, equating to about 4200 patients. To meet this demand, our goal is to design a chemical process for nilotinib production with a minimum capacity of 1150 kg per year. Given, an expected 60% lower price of generic, the cost of our generic nilotinib will be ~$240/gram and our total yearly revenue is predicted to be $276 million.

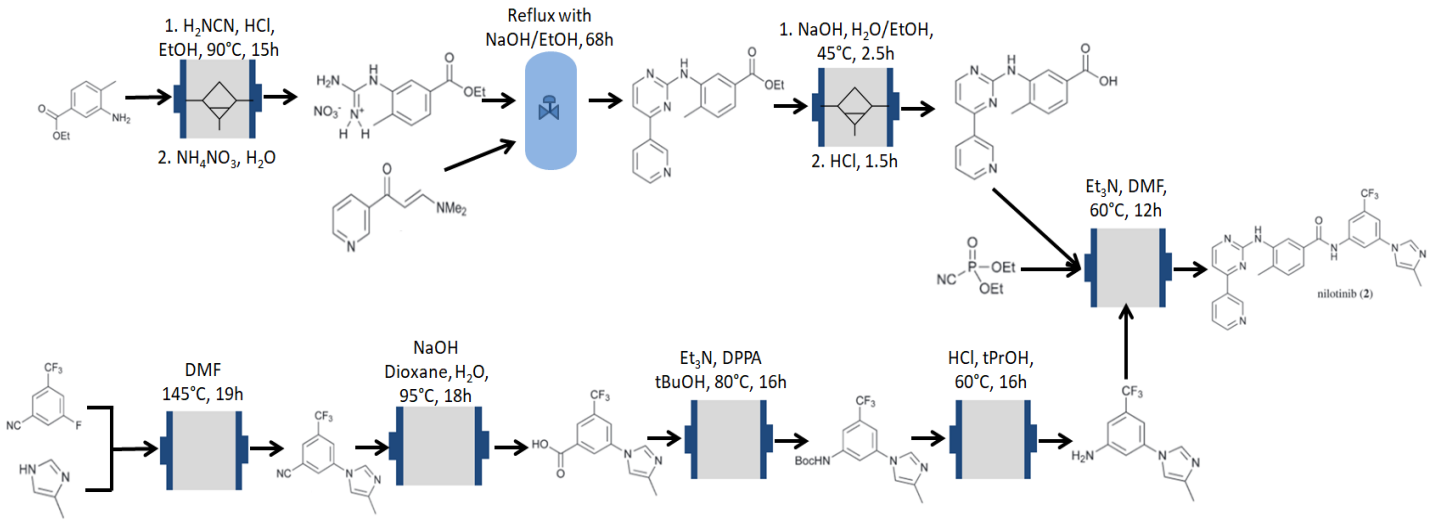


Figure 2. *Process flow diagram of Novartis's synthesis pathway of nilotinib.*

Critical assessment of the Novartis synthesis for nilotinib

Novartis has not made a process flow sheet for its synthesis of nilotinib publicly available. To circumvent this, our team has utilized the steps out- lined in Novartis's patent to create our own process flow sheet of the Novartis synthesis shown in Fig. 2 (Breitenstein et al., 2004).

Fig. 2 overviews Novartis's patented process chemistry for the synthesis of nilotinib which is currently used for the industrial production of Tasigna (Deadman et al., 2013). From the process flow diagram, it can be seen that the production of nilotinib consists of three main parts. The first part (the top portion of the reaction scheme) is required to produce the carbon-nitrogen bond (Fig. 2). The second part is the nucleophilic substitution which occurs concurrently to produce the required inter- mediate in the bottom portion of the reaction scheme (Fig. 2). With both parts completed, the third and final amide formation occurs during the last synthesis step to nilotinib formation (Fig. 2).

Although this process chemistry for nilotinib synthesis is currently in use for its commercial production, there are four distinct drawbacks of Novartis's currently patented method.

(1) During the production of the intermediate at the top of the reaction scheme (Fig. 2), the use of nucleophilic substitution allows for the possible formation of two intermediate isomers. The formation of these two distinct isomers means that regioselectivity of the reaction becomes a great challenge since only one of thregioisomers is desired (Deadman et al., 2013). As such, this would mean that Novartis's non-regioselective method for the synthesis of this particular intermediate would re- quire a great deal of subsequent separation and purification to obtain only the desired regioisomer, steps that diminish efficiency and induce great time and monetary penalties on the production process.

(2) From Fig. 2 it is evident that the entirety of the Novartis synthesis is an extremely lengthy multi-stage process. For instance, the reflux stage of the reaction takes over 68 hours, alone.

(3) The process's use of multi-stage batch reactors is highly unfavorable due to the time-consuming transfer requirements that will inevitably also re- quire a great deal of manpower, further prolonging the total length of the reaction. In addition, separation procedures such as evaporation and filtration will likely have to be applied after each batch reaction since solvent switching will be required. These separation techniques will be clumsy and greatly reduce the degree of process control over the reaction.

(4) From a hazard and operability (HAZOP) stand- point, the overall Novartis synthesis is particularly dangerous as it requires many steps and solvents. This presents a concern for health and safety, particularly since the use of multi-stage batch reactor processes will create a large degree of exposure risk to chemical plant workers who will have to directly deal with carcinogenic solvents such as dioxane and toluene during mass transfer operations.

While Novartis does not publicly disclose their production processes, this entire synthesis would take over 100 hours in reaction time and an estimated 50 hours in cleaning and separation down- time. Therefore, Novartis's primary pathway method is an expensive and time-consuming process with undisclosed yields that are expected to require additional purification steps.

Review of the alternative nilotinib synthesis pathways

Although the Novartis synthesis for nilotinib is functional, there has been much effort in developing alternative syntheses which mitigate the drawbacks present in the Novartis synthesis pathway. The five known paths for nilotinib synthesis were compiled and are outlined in Table 1.

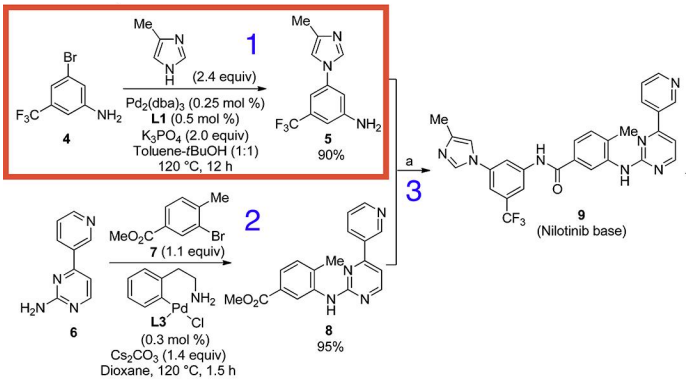
In addition to the aforementioned weaknesses to the Novartis synthesis, the other syntheses (Table 1) also feature several key weaknesses affecting their practicality and profitability. The Buchwald synthesis requires many solid catalysts. However, this is balanced by the minimal number of steps and the significantly shorter reaction time required (24h) in comparison to the Novartis method

(>100h) (Ueda et al., 2012). The Chen synthesis has been found to have long reaction times with certain steps taking 68 hours to complete, while the total reaction time for the process was over three days. Furthermore, the Chen synthesis features a very low overall yield, around 40%. Additionally, the copper catalyst used in step 1a of the Chen synthesis is particularly slow and non-regioselective, resulting in the need for additional separation in order to isolate the key aniline intermediate, further complicating an already unwieldy process (Chen et al., 2009). The Teva synthesis likewise was found to be exceptionally long, taking over five days total. Additionally, the many solvents used can complicate the unit operations involved due to the extensive solvent switching they necessitate (Yeori et al., 2010). Lastly, the Ariad synthesis, although brief at only four steps, was reported to have be unscalable, as its final step has been found to give inconsistent yields at scales above 250 milligrams, resulting in impracticality at an industrial scale (Deadman et al., 2013).

Table 1. *A comparison of the five existing nilotinib syntheses according to their number of steps. The associated reaction temperatures, reaction pressures, step yields, solvents, catalysts, and reaction times are also noted with respect to each reaction stage.*

Method Name	# of Steps	T (°C)	P (atm)	Yields for each step	Catalysts	Solvents	Time (h)
Novartis	8	**1a.** 90 **1b.** reflux **1c.** 45 **2a.** 145 **2b.** 95 **2c.** 80 **2d.** 60 **3.** 60	**1a.** 1 **1b.** 1 **1c.** 1 **2a.** 1 **2b.** 1 **2c.** 1 **2d.** 1 **3.** 1	**Unknown** **2d.** 74% with no regio-select ivity	**1a.** N/A **1b.** N/A **1c.** N/A **2a.** N/A **2b.** N/A **2c.** N/A **2d.** Copper(I) catalyst **3.** N/A	**1a.**, H2O/Ethanol **1b.** Ethanol **1c.** H2O/Ethanol **2a.** DMF **2b.**Dioxane/H2O **2c.** N/A **2d.** Isopropyl alcohol **3.** DMF	**1a.** 15 **1b.** 68 **1c.** 4 **2a.** 19 **2b.** 18 **2c.** 16 **2d.** 5 **3.** 12
Buchwald	3	**1a.** 120 **1b.** 120 **3.** 25	**1a.** 1 **1b.** 1 **3.** 1	**1a.** 90% **1b.** 95% **3.** 90%	**1a.** Pd2(dba)3 K3PO4 **1b.** CsCO3 **3.** Potassium tert-butoxide	**1a.** Toluene - BuOH **1b.** Dioxane **3.** THF	**1a.** 12 **1b.** 1.5 **3.** 12
Chen	6	**1a.** 120 **1b.** R.T **3.** R.T **4.** 30,50 **5.** R.T **6.** 45	**1a.** 1 **1b.** 1 **3.** 1 **4.** 1 **5.** 1 **6.** 1	**1a.** 77.4% **1b.** 73.2% **3.** 73.7% **4.** 90.4% **5.** 94% **6.** 86.8%	**1a.** CuI **1b.** N/A **3.** N/A **4.** N/A **5.** N/A **6.** N/A	**1a.** DMSO **1b.** Ethanol **3.** Ethanol **4.** N/A **5.** Acetonitrile **6.** Methanol	**1a.** 40 **1b.** 12 **3.** 68 **4.** 7 **5.** 12 **6.** 6
Teva	6	**1.** 90 **2.** R.T **3.** 45 **4.** 60 **5.** 90 **6.** 120	**1.** 1 **2.** 1 **3.** 1 **4.** 1 **5.** 1 **6.** 1	Yields were not mentioned	**1.** N/A **2.** N/A **3.** N/A **4.** N/A **5.** N/A **6.**CuI,NaI, DBU	**1.** Ethanol/H2O **2.** Ethanol **3.** Ethanol/H2O **4.** SOCl2, NMP **5.** SOCl2, NMP **6.** DMF	**1.** 15 **2.** 68 **3.** 4 **4.** 2.5 **5.** 3 **6.** 46.5
Ariad	4	**1a.** 120 **1b.** R.T. **2.** R.T. **3.** 100	**1a.** 1 **1b.** 1 **2.** 1 **3.** 1	**1a.** 75% **1b.** -- **2.** 95% **3.** 89%	**1a.** CuI **1b.** -- **2.** DIPEA **3.** $Pd_2(dba)_2$	**1a.** K_2CO_3, DMSO **1b.** -- **2.** THF; **3.** Cs_2CO_3,	**1a.** 15 **1b.** 8 **2.** 2 **3.** 7

Of the syntheses of nilotinib that were discussed in Table 1, the Buchwald synthesis seemed by far the most promising in terms of developing a scalable, flow-based synthesis process of nilotinib for the production of a generic brand.



[a]Reagents and conditions: (a) KO*t*Bu (5.5 equiv), THF, rt, 12 h; 90%.

Figure 3. *Reaction scheme for the Buchwald synthesis of nilotinib, modified from Ueda et al., 2012.*

The advantages of the Buchwald synthesis that make it the most promising are its three steps taking approximately 24 hours of reaction time, fast and efficient compared to the other existing methods of nilotinib synthesis. More importantly, the Buchwald synthesis is highly regioselective in the step where an important aniline compound is produced (highlighted in the red box in Fig. 3). This gives the Buchwald synthesis a distinct advantage over other methods of synthesizing nilotinib and more importantly, reduces the need for time-intensive regioselective purification at this initial step. Lastly, the Buchwald synthesis requires only four, readily purchasable starting reactants:

(1) 3-amino-5-bromobenzotrifluoride
(2) 4-methylimidazole
(3) 4-pyrimidin-3-yl-pyrimidine-2-amine
(4) Methyl 3-bromo-4-methylbenzoate

Thus, we chose the Buchwald synthesis to be the focus of our computational process scaling methodology.

Process design for an industrial scale Buchwald synthesis of nilotinib

Our goal was to develop a scalable, flow-based synthesis of nilotinib which has greater time efficiency, safety, and yield than the existing Novartis synthesis. We hoped to employ a flow-chemistry based synthesis of nilotinib. In contrast to batch production methods, a flow-based synthesis would involve the use of a single, continuous flowing stream wherein the reaction would take place in a series of controlled steps without the need for multiple batch reactors. As reported in previous literature, multi-step batch processes require process control and purification techniques which are highly complex in comparison to flow-based reactions (Hopkin et al., 2010).

As such, a general process flow diagram which illustrates the changes and modifications we wish to make to the existing Buchwald synthesis is shown in Fig. 4.

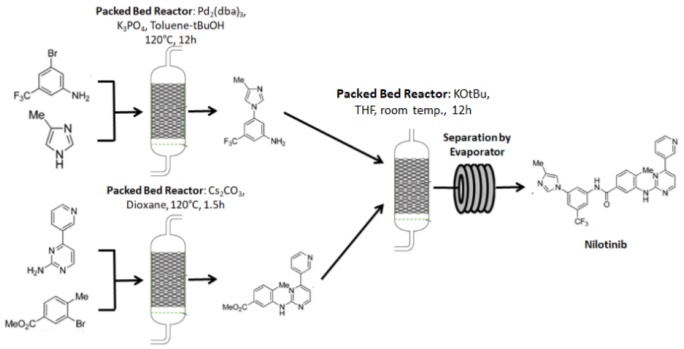


Figure 4. *Envisioned process flow diagram for the flow-based Buchwald synthesis of nilotinib using packed bed reactors.*

Firstly, we re-designed the reaction scheme of the Buchwald synthesis to take place under flow chemistry conditions (rather than a multi-stage batch series). This should allow for: (1) greater efficiency by reducing manual mass transfers be- tween batch reactors, (2) greater degree of process control over the synthesis wherein controlling re- action flow rates will be the key concern, (3) greater degree of safety by minimizing the need for reactor transfers and thus eliminating unnecessary exposure to dangerous solvents, (4) greater scalability of the reaction to an industrial scale.

The Buchwald synthesis requires palladium and cesium solid-state catalysts at several stages. To address this challenge within the scope of the flow-based model and make the use of such catalysts feasible on an industrial scale, we have designed for the implementation of packed bed reactors (PBRs) into our process. This will allow for the large-scale use of the solid-state catalysts in the reaction under flow chemistry conditions while also facilitating catalyst recovery and cleaning.

Fig. 5 illustrates the final process flow sheet that was constructed in ChemCAD. It illustrates the components entering the PBRs in each stage of the reaction and distillation towers for separation.

The model successfully converged with respect to the mass and energy balances and was able to produce nilotinib at a desired rate that would allow us to achieve the 1150 kg /year design basis goal. Furthermore, according to the ChemCAD model, the final distillation tower of nilotinib production achieved over 98% separation, indicating the robust final purity of our desired nilotinib product.

To produce our desired output of 1150 kg of Nilotinib per year, we approximate that our plant will need to run for at least 350 days of the year. Assuming constant production, a minimum output of 137 g/hour (0.263 moles) of Nilotinib is required. Due to the conversion rates of 90%, 95%, and 90% for each of the three stages of the Buchwald synthesis, respectively, that translates to a basis of approximately 0.325 mol/hr for the starting reactants of both initial reactions, with mole equivalencies accounted for appropriately. A table detailing the mass balance from our reactor system designed in ChemCAD is shown in Table 2.

Here, an output of 138 g/hr is shown, successfully achieving our design basis of 1150 kg per year. Additionally, very little accumulation is shown, as evidenced by the near identical input/output masses. The energy balance from the reactor process, including energy added by each distillation tower, is also shown in Table 3.

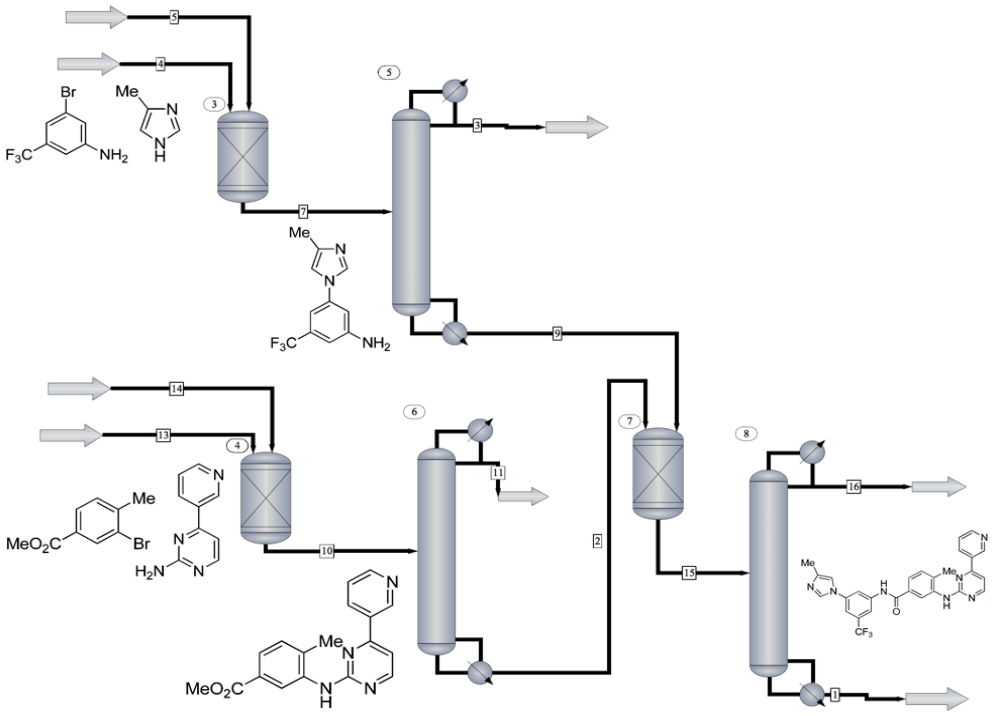


Figure 5. *Final process flow sheet for synthesis of nilotinib as constructed by ChemCAD.*

Table 2. *ChemCAD Report of Overall Mass Balance.*

Overall Mass Balance	gmol/h		g/h	
	Input	Output	Input	Output
3 Amino 5 bromob	0.325	0.033	78.000	7.816
4 methylimidazo	0.780	0.488	63.960	39.981
4 pyridin 3 yl	0.325	0.016	55.900	2.797
Methyl 3 bromo	0.370	0.061	84.730	14.030
53a	0.000	0.030	0.000	7.208
67	0.000	0.046	0.000	14.788
Nilotinib	0.000	0.263	0.000	138.876
Hydrogen Bromide	0.000	0.601	0.000	48.642
Methanol	0.000	0.263	0.000	8.412
Total	1.800	1.800	282.590	282.548

Table 3. *ChemCAD Report of Overall Energy Balance.*

Overall Energy Balance	kJ/h	
	Input	Output
Feed Streams	-395.382	
Product Streams		171.91
Total Heating	678.977	
Total Cooling	-111.697	
Power Added	0	
Power Generated	0	
Total	171.898	171.91

Similar to the mass balance, it is evident that an almost perfect energy balance is achieved, indicating the convergence success of our ChemCAD model. This mass and energy balance from the ChemCAD model serves to highlight that our industrial scaled synthesis of nilotinib using the Buchwald synthesis was successful and that, computationally, there is strong evidence to indicate that this process can be scaled to effectively pro- duce at least 1150 kg of nilotinib per year. Given our flow-based design and the nature of the Buchwald synthesis itself, this represents a great improvement with respect to the time, safety, and ease of nilotinib production as compared to the existing Novartis methodology.

B. Process Economics

Process economics of the scaled Buchwald synthesis

i. Capital and operating costs

To calculate profitability of the process, considered the capital cost of procuring and maintaining a manufacturing facility and the operating cost of the process based on our production design basis of 1150 kg of nilotinib. We estimated a small-scale manufacturing facility will cost ~ $2 million USD and an additional ~$2 million to have the facility cGMP certified for production.

Direct costs associated with production include employee cost, utility cost and waste management cost. We evaluated our employee needs based on existing industry data. Based on estimations for a small-scale production facility and accounting for employee benefits and human resources cost, our estimation for employee cost was $1,100,000- $1,400,000 USD per year.

We have also predicted a budget of $50,000 for the annual maintenance and servicing of the equipment. To implement a system to dispose of the organic waste in an environmentally friendly way in accordance with EPA and OSHA regulations, we estimate the cost of a waste management system for our design will be $200,000 on an annual basis. Based on our energy and water needs, we will require a budget of $500,000 for yearly utility cost.

ii. Reactor, piping, and distillation tower costs

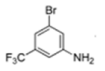
The design of the synthesis process for nilotinib will require properly sized industrial reactors and piping. The PBRs must be capable of resisting the organic solvents and the catalysts that will be re- acting inside the vessels. 316L grade steel is the pharmaceutical industry standard for contact with drug-based flow to avoid contamination.

The total cost of three 0.15 m3 316L steel PBRs is $75,600. It is estimated from our process flow diagram that at least 300 feet of 316L steel piping at 1″ piping size will cost $8,850. The thickness of the piping is appropriate for the expected flow rates and the pressure drops expected from the sys- tem and confirmed with ChemCAD. The distillation towers that our process will require for the separation and purification of products are expected to cost $55,100 in total. Thus, the overall equipment cost is estimated to be ~ $140,000. This relatively low cost is achieved through the low process flow rate as the active ingredient will be produced in small amounts throughout the year and does not require enormous vessel capacities.

iii. Starting reagent costs

We have also calculated the costs of purchasing the four starting material components of the Buchwald reaction as shown in Table 4. The total molar amount and subsequent mass of each reactant required was calculated based on the process production demands. The total estimated annual costs of purchasing the starting components of the Buchwald synthesis is estimated to be around $5,500,000.

Table 4. *Material economics of starting material for nilotinib production.*

Design Basis of Nilotinib (moles): ~2200 moles 529.5245 g/mol	 3-Amino-5-bromobenzotrifluoride	 4-methylimidazole	 4-pyridin-3-yl pyrimidin-2-amine	 Methyl 3-bromo-4-methylbenzoate
Molecular Weight	0.240 kg/mol	0.0821 kg/mol	0.172 kg/mol	0.229 kg/mol
Mole Ratio to Nilotinib	1.33:1	2.76:1	1.18:1	1.19:1
Yield from Reaction Process	81%	90%	95%	95%
Minimum Amount Required	700 kg	550 kg	450 kg	650 kg
Purchasing Cost	$50 / kg	$500 / kg	$11,000 / kg	$220 / kg
Total Annual Cost	$35,000	$275,000	$4,950,000	$143,000

Overall costs and final profit calculation

For the first year of production, the overall process cost will be near $12 million, after which the overall costs drop to around $8 million as shown in Table 5. Considering the annual projections of a profit of $276 million dollars, capital and operating expenditure only accounts for 4.2% and 2.8% of revenue in the first and

second year, respectively. Altogether, in balancing our predicted revenue with predicted capital/operating expenditures, yearly profits greater than $250 million are expected if the design basis criteria are met and 15% of the nilotinib market share can be captured.

Table 5. *Table of capital and operating costs.*

Category	Estimated operating cost
Facility purchase *	$4,000,000 *
Equipment *	$140,000 *
Starting material	$5,500,000
Employee cost	$1,400,000
Utility Cost	$500,000
Waste management	$200,000
Maintenance	$50,000
Total * = Only required for first year	$7,650,000 * = $11,790,000

IV. CONCLUSIONS

In this investigation, we have described a new method for the large scale production of nilotinib, an important chemotherapy drug. Current Novartis practices of nilotinib synthesis require upwards of 8 steps and 97 hours of reaction time. By contrast, a recently developed approach by Buchwald and coworkers allows for the synthesis of nilotinib in 3 steps and 24 hours. Until now, this approach had only been designed for small scale (< 1 g) synthesis of nilotinib in laboratory settings. This investigation provides a framework for which the Buchwald synthesis of nilotinib can be scaled up to produce 1150 kg per year much more efficiently than Novartis's current methods.

We adopted the role of a generic pharmaceutical company seeking to produce nilotinib upon Novartis's patent expiration in 2023. Our goal of capturing 15% of nilotinib's market share allowed us to calculate our needed production to be 1150 kg/year with projected revenue of $276 mil- lion/year (assuming 60% price drop in generic drugs).

Using ChemCAD software, a new process flow diagram was constructed for the scaled production of nilotinib using the Buchwald synthesis. Our approach focused on the use of plug flow reactors in order to achieve a flow-based synthesis and improve the overall efficiency and safety of nilotinib production, minimizing the need for solvent switching or complex unit operations for mass transfers. Our ChemCAD program successfully converged and mass and energy balances across the system were achieved. This serves to demonstrate that it is possible to industrial scale the Buchwald synthesis while maintaining profitability. This we hope serves to establish an initial framework by which the generic form of a life-saving medication can be produced safely and efficiently.

ACRONYMS

ASME – American Society of Mechanical Engineers
CAD – Computer-aided design
CML – Chronic myelogenous leukemia
cGMP – Current good manufacturing practices
EPA – Environmental protection agency
FDA – Food and Drug Administration
HAZOP – Hazards and operability
NCI – National Cancer Institute
OSHA – Occupational safety and health administration
PBR – Packed bed reactor
TKI – Tyrosine kinase inhibitor

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