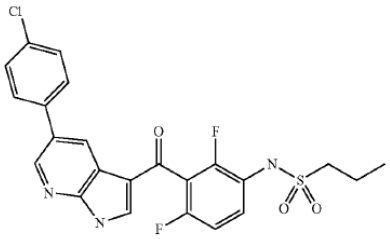
# Preparation And Clinical Usage of Vemurafenib

## 1. Introduction:



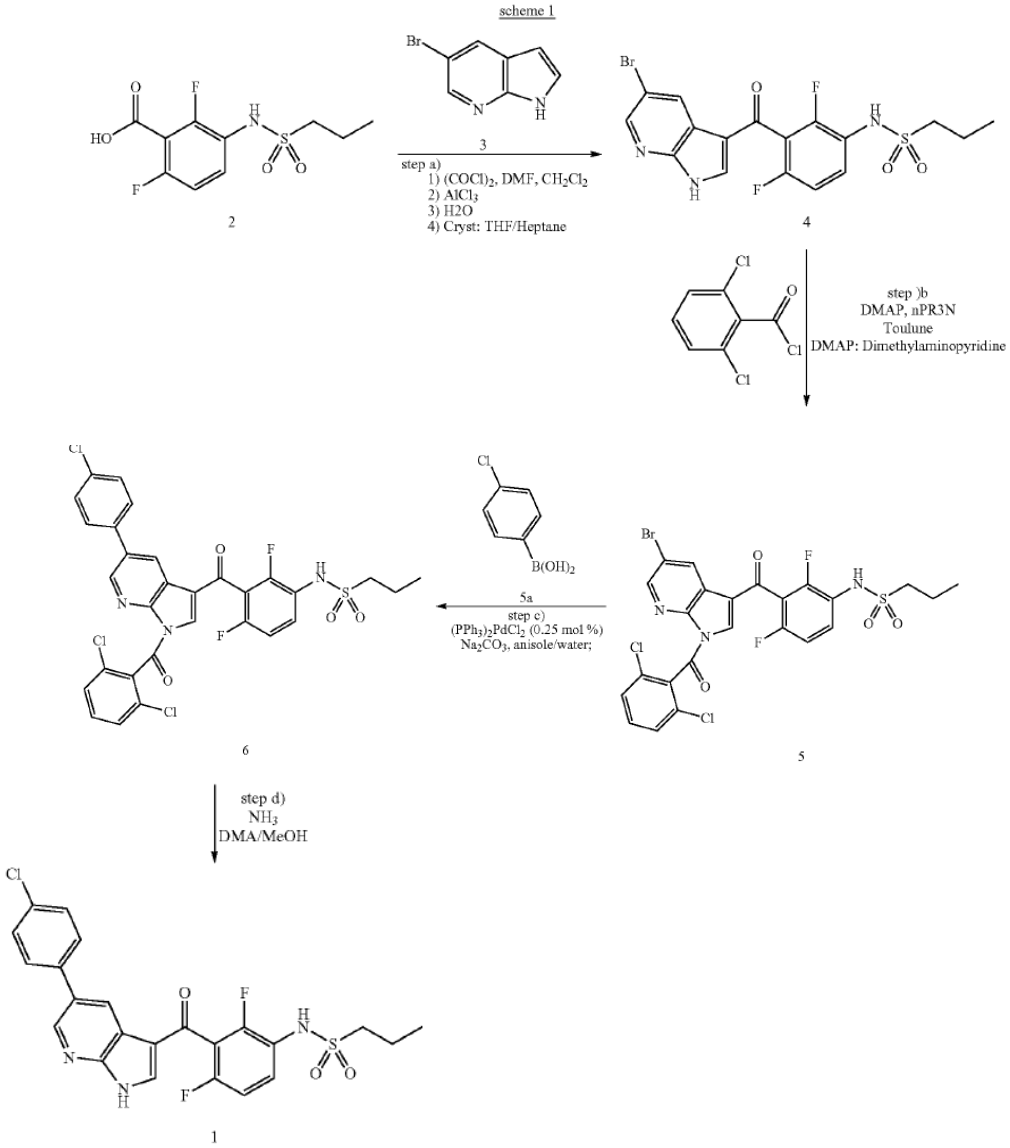
Vemurafenib

Vemurafenib (propane-1-sulfonic acid {3-[5-(4-chlro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide), also known as Zelboraf, PLX4032, and RG7204, is a highly selective inhibitor of B-RAF kinase inhibitor which is co-developed by Plexxikon and Hoffmann-La Roche/Genentech.[1] It was approved by the FDA on August 17, 2011, as a first-line single-agent therapy for the treatment of BRAF V600E–positive malignant melanoma[2,3].

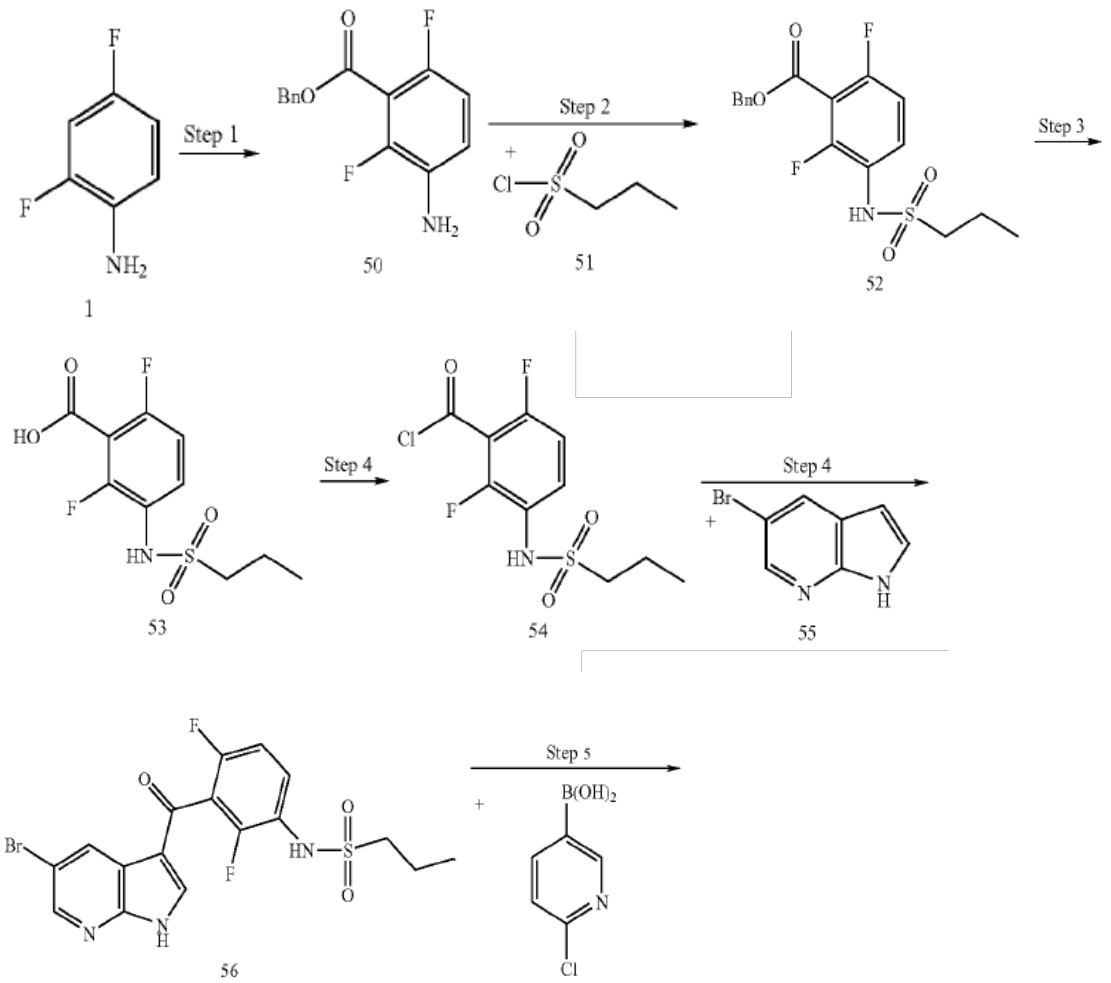
## 2. Preparation:

There are four patented chemical reactions to produce Vemurafenib.

1. The present invention synthetic process comprises the reaction of formula (5) with palladium catalyst and 4-chlorophenylboronic acid to form formula (6), which then goes through cleavage of 2,6-dichlorobenzamide group to yield interested compound. [3]



2. The goal product is obtained after a series of reactions from reagent compound, 2,4-difluoro-phenylamine.[4]




**3. Clinical Usage:**

1. Vemurafenib has been proved to block the RAF/MEK/ERK pathway in *BRAF* mutant cells, caused regression of *BRAF* mutant xenografts.[1]
2. Dosage administration is suggested to take PO 960mg twice daily for adult patients.[6]
3. Adverse reaction has been reported, including hypersensitivity, cutaneous squamous cell carcinoma, dermatologic effects(rash, Stevens-Johnson syndrome), hepatic side effect, New primary malignant melanoma, uveitis, and QT prolongation.[6]
4. Precaution for patients:[6]
   1) It is warned to take Vemurafenib with drugs that is metabolized by CYP substrates such as Waffarin because there would be obvious drug interaction.
   2) Vemurafenib would increase the risk of such life-threatening cardiac arrhythmia as torsades de pointes and therefore should not be recommended for those potential patients.
   3) The dosage should be modified when the drug is use in elderly, pregnancy, or patention with renal impairment, hepatic impairment, hypersensitivity.

## 4. Conclusion:

This assignment gave me the opportunity to get familiar with various sources to reach medical information. Instead of using only SciFinder to search for materials, I used a diversity of such on-line databases as Drug.com, PubMed, and so on, to help me filter the large amount of information.

First, I used Drug.com to find the basic information of my interested drug, Vemurafenib, and then gained more specific therapeutic usage through MedlinePlus.

After getting the rough concept of this drug, SciFinder became my first choice to find its chemical preparation, and fortunately, I refined the answer set, which was gained through the special function "Explore Substance", to patented ones, and was allowed to reach their full text from SciFinder to their official patent approval websites, which cannot be found in Thomson Innovation(TI) because it hasn't uploaded the data yet.

Finally, as for therapeutic usage, I used SciFinder as well as PubMed to be my information sources in that it was relatively convenient to find closely related papers I was interested in. Additionally, it could refine the answer set to that with free-full-text links.

As a result, this assignment makes me organize the knowledge and Internet medical information I know to a more lucid report, which is exactly the ability a researcher should possess when doing essays. Therefore, I really appreciate that we have this chance to have SciFinder and TI classes this semester because the know-how I learn are seldom mentioned in other mandatory or selective courses. For instance, the speaker explicated the details of patent and trademarks in TI class. However, there are still rooms that I think can be improved:

1) Both SciFinder and TI are too strong databases to master in just a couple of hours, and the operations are also too complicated to remember. Hence, I suggest that either teacher can prolong the class or retrench the content, eliminating information which is minor or not accessible to students. In this way, we can therefore digest the content we learn better.
2) Next time I hope that the speaker of TI class can offer special one-day account, just like we did in SciFinder class, for us to practice the operations rather than just let us listen to a lecture. This way of delivering a lecture should be changed definitely because it neither draws our full attentions nor gives us practical experiences.

If speakers can alter their teaching styles to better those parts, the concepts we learn can be mastered more easily and completely.

## 5. Information Materials:

SciFinder, PubMed, MedlinePlus, Drug.com, Wikipedia

## 6. Reference:

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2. Bollag G; Hirth P, Tsai J, *et al.* Clinical efficacy of a RAF inhibitor needs broad target blockade in *BRAF*-mutant melanoma *Nature 467* (7315): 596–599.(**2010**)
3. FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer (press release, 2011 Aug 23) (**2011**)
4. Hildbrand, Stefan; Mair, Hans-Juergen; Radinov, Roumen Nikolaev; Ren, Yi; Wright, James Anderson. Process for The Manufacture of Pharmaceutically Active Compounds
   a) US20110028511 A1
   b) WO2011015522 (A2)
   c) WO2011015522 (A3)
5. Visor, Gary Conard; Ibrahim, Prabha N.; Spevak, Wayne; Cho, Hanna; Shi, Songyuan; Wu,

Guoxian. N-[3-(1H-Pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl]sulfonamide Derivatives as Protein Kinase Inhibitors And Their Preparation And Use for The Treatment of Diseases
a) WO2010129570 A1
b) US2010286142 (A1)
c) TW201041888 (A)
d) AR076749 (A1)
6. Vemurafenib. Wolters Kluwer Health. http://www.drugs.com/ppa/vemurafenib.html