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Attorneys for Plaintiff
PLEXXIKON INC.

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

PLEXXIKON INC., Plaintiff, v. NOVARTIS PHARMACEUTICALS CORPORATION, Defendant.	Case No.: 3:17-cv-04405 **COMPLAINT FOR PATENT INFRINGEMENT** DEMAND FOR JURY TRIAL

Plaintiff Plexxikon Inc. ("Plexxikon"), for its Complaint against Defendant Novartis Pharmaceuticals Corporation ("Novartis"), alleges as follows:

NATURE OF THE ACTION

1. This is an action arising under the patent laws of the United States, codified at 35 U.S.C. §§ 1, *et seq*. for infringement of U.S. Patent No. 9,469,640 ("the '640 patent") through Novartis's importation, offer for sale, and sale of the drug dabrafenib. Novartis markets dabrafenib under the trademark Tafinlar®.

PARTIES

2. Plexxikon is a corporation organized and existing under the laws of the State of California, with its principal place of business at 91 Bolivar Drive, Berkeley, California 94710.

3. Novartis Pharmaceuticals Corporation is a corporation organized and existing under the laws of the State of Delaware and has a principal place of business at One Health Plaza, East Hanover, New Jersey 07936. Novartis Pharmaceuticals Corporation is a wholly owned subsidiary of Novartis AG, a corporation organized and existing under the laws of Switzerland with its principal place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

JURISDICTION AND VENUE

4. This civil action arises under the patent laws of the United States, 35 U.S.C. § 1, *et seq*. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

5. This Court has personal jurisdiction over Novartis pursuant to the laws of the State of California, including California's long-arm statute (California Code of Civil Procedure § 410.10) because Novartis regularly and continuously transacts business in this jurisdiction, including marketing and selling Tafinlar® throughout the State of California. Novartis derives substantial revenue from its sales in the State of California. Novartis maintains and operates facilities at 150 Industrial Road, San Carlos, CA 94070; 5300 Chiron Way, Emeryville, CA 94608; and 10675 John Jay Hopkins Drive, San Diego, CA 92121.

6. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400 because Novartis has a regular and established place of business within the district and has committed acts of infringement within the district. Novartis maintains and operates at least two facilities within this district, in San Carlos

and Emeryville. Novartis's acts of infringement within this district include, but are not limited to, selling and offering to sell the infringing product within the district to its distributor, San Francisco-based McKesson Corporation ("McKesson"). McKesson lists Tafinlar® in its catalog of available products through its distribution division, McKesson Specialty Health, which also has multiple locations within the district. Novartis also employs oncology sales representatives within the district whose customers include office-based physicians, consultant pharmacists, medical directors, and key medical and nursing personnel. The infringing product is also used by healthcare providers and patients within this district.

BACKGROUND

7. Plexxikon is a leader in the discovery and development of novel, small molecule pharmaceuticals. The company has utilized its proprietary discovery platform to successfully develop targeted medicines to treat cancer.

8. At least as early as 2005, Plexxikon's scientists discovered and started making compounds that reduce the growth of cancer cells that have a mutated form of the BRAF gene. The BRAF gene encodes information used by cells to produce enzymes (called "BRAF kinases") that increase cellular metabolism and growth. The mutated BRAF gene substantially increases BRAF kinase activity, driving the proliferation of cancer cells.

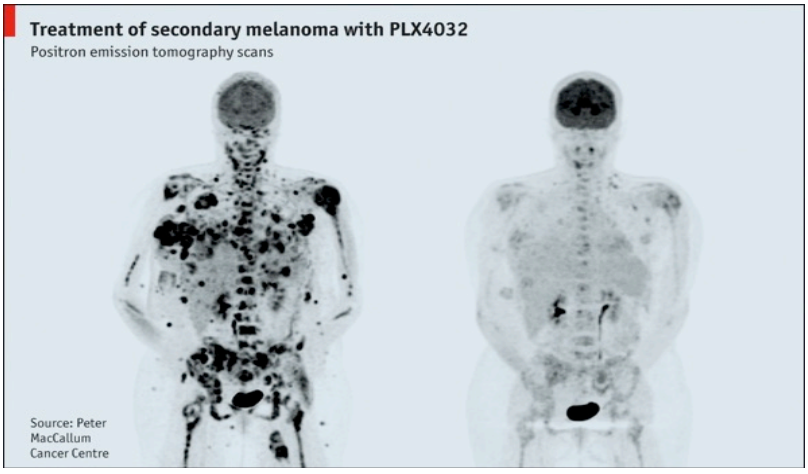
9. The compounds Plexxikon discovered target and bind with the BRAF kinase produced by the mutated BRAF gene in a manner that inhibits its activity, and thereby disrupts the cancer cells' ability to metabolize energy. For this reason, the compounds Plexxikon discovered are referred to as "selective BRAF kinase inhibitors."

10. Although BRAF kinase inhibitors existed prior to Plexxikon's discoveries, those BRAF kinase inhibitors were not selective and therefore inhibited many different RAF kinases. As a result, those BRAF kinase inhibitors caused severe side effects that prevented them from being used in doses that were high enough to effectively fight the cancer cells.

11. In contrast, the selective BRAF kinase inhibitors developed by Plexxikon have a core molecular structure – in particular, a sulfonamide with its nitrogen attached to a halogenated phenyl – that allows them to bind *selectively* to the kinase created by the $BRAF^{V600E}$ (or V600E BRAF) mutation. The $BRAF^{V600E}$ mutation is frequently found in metastatic melanoma and found to a lesser degree in other

forms of non-resectable or metastatic cancers. This $BRAF^{V600E}$ selectivity of Plexxikon's kinase inhibitors allows them to be given in much higher doses, resulting in a far more pharmacologically effective treatment than non-selective BRAF kinase inhibitors.

12. Plexxikon's invention of kinase inhibitors that bind only to the kinase produced by cells with the V600E mutation in the BRAF gene was a true scientific breakthrough that gave hope to patients facing a disease (metastatic melanoma) for which hope had previously been in desperately short supply. For example, USA Today quoted Dr. Lynn Schuchter (the Chief of the Division of Hematology Oncology and the C. Willard Robinson Professor of Hematology-Oncology at the University of Pennsylvania) as saying that Plexxikon's discovery "is the most important breakthrough in melanoma, ever." Liz Szabo, 'Breakthrough' Melanoma Drug Shrinks Tumors, USA TODAY (Aug. 26, 2010, 1:08 AM), http://usatoday30.usatoday.com/news/health/2010-08-26-1Amelanoma26_ST_N.htm. The following before-and-after picture illustrates the dramatic tumor-shrinking in a patient with metastatic melanoma who was treated with vemurafenib, a selective BRAF kinase inhibitor developed by Plexxikon and having the same core molecular structure described above (published by the Economist (Marathon Man Genomics Has Not Yet Delivered the Drugs, but it Will, THE ECONOMIST (Jun. 17, 2010), http://www.economist.com/node/16349422#print) as part of its coverage of the breakthrough):



13. The results of treatment with Plexxikon's selective BRAF kinase inhibitors were not merely visually compelling. The New England Journal of Medicine published a study showing that vemurafenib "induced complete or partial tumor regression in 81% of patients who had melanoma with the V600E BRAF mutation" and noted that the "efficacy data [is] particularly encouraging in light of the

high disease burden in most of [the study's] patients." (Keith T. Flaherty et al., *Inhibition of Mutated, Activated BRAF in Metastatic Melanoma*, 363 NEW ENG. J. MED. 809, 816 (2010)). Similarly, Plexxikon's vemurafenib was described as a "First-in-Class BRAF-Mutated Inhibitor for the Treatment of Unresectable or Metastatic Melanoma" by the Journal of the Advanced Practitioner in Oncology. (Lindsay Shelledy et al., *Vemurafenib: First-in-Class BRAF-Mutated Inhibitor for the Treatment of Unresectable or Metastatic Melanoma*, J. ADV. PRACT. ONCOL., Jul.-Aug. 2015, at 361-65).

14. Plexxikon licensed vemurafenib to its development partner and began clinical trials in 2006. On August 17, 2011, the Federal Drug Administration ("FDA") granted approval for the drug for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test. Vemurafenib was the first targeted therapy approved for melanoma.

15. Shortly after vemurafenib won FDA approval, Plexxikon's development partner began selling it under the trademark Zelboraf®. Zelboraf® was a medical and commercial success, offering life extending treatment to terminally ill cancer patients with metastatic melanoma and achieving worldwide sales of over $1,500,000,000 to date. Today Zelboraf® is approved in 99 countries and has extended the lives of many thousands of terminally ill cancer patients.

16. To protect its pioneering discovery, Plexxikon filed patent applications as early as June 22, 2005, disclosing novel compounds having the core molecular structure that Plexxikon had invented. Several of those applications matured into patents which cover selective BRAF kinase inhibitors, including some directed to the molecular structure of vemurafenib and one (filed on July 17, 2007) that matured into the '640 patent at issue in this case.

17. The '640 patent covers a class of selective BRAF kinase inhibitors which selectively bind to the BRAF kinase that results from the V600E mutation. One of the molecules within this class (dabrafenib) was brought to market by Novartis's predecessor in interest, GlaxoSmithKline plc ("GSK"). In 2013, GSK received FDA approval to sell dabrafenib for treatment of melanoma and began selling it under the trademark Tafinlar®. Tafinlar® directly competes with Plexxikon's Zelboraf®.

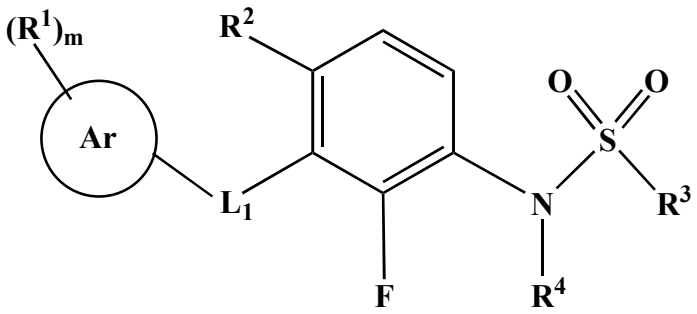
18. GSK transferred a portfolio of oncology drugs, including Tafinlar®, to Novartis in 2015 in exchange for approximately $16 billion. In June of 2017, Novartis received FDA approval to sell dabrafenib under the trademark Tafinlar® for treatment of non-small cell lung cancer. Novartis has

continued (and is continuing) to sell, import and offer dabrafenib for sale under the trademark Tafinlar® and those sales continue to erode sales of Zelboraf®.

NOVARTIS'S INFRINGEMENT OF THE '640 PATENT

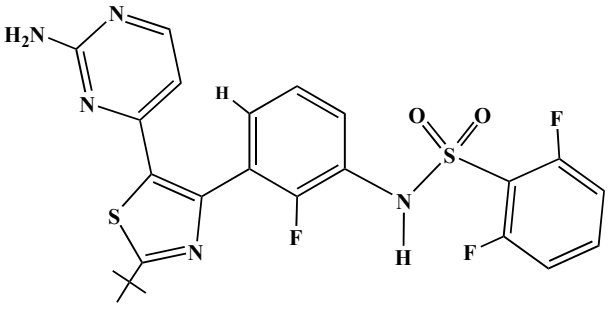
19. The '640 patent was duly and legally issued on October 18, 2016, by the United Patent and Trademark Office ("PTO"). A true and correct copy of the '640 patent is attached as **Exhibit A** to this Complaint. By assignment, Plexxikon owns all right, title, and interest in and to the '640 patent. The application leading to the '640 patent was published on June 16, 2016.

20. The '640 patent has 12 claims, including independent claim 1. Independent claim 1 recites a compound of formula Ia:



or a pharmaceutically acceptable salt thereof, wherein: L_1 is a bond or —N(H)C(O)—; each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl; R^2 is hydrogen or halogen; R^4 is hydrogen; R^3 is optionally substituted lower alkyl or optionally substituted aryl; m is 0, 1, 2, 3, 4, or 5; and Ar is a monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen.

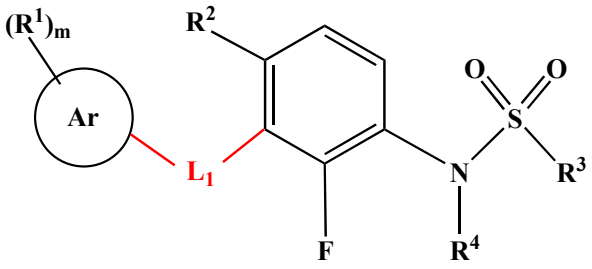
21. Dabrafenib (Tafinlar®) as sold by Novartis has the following formula, which infringes at least claim 1 of the '640 patent:

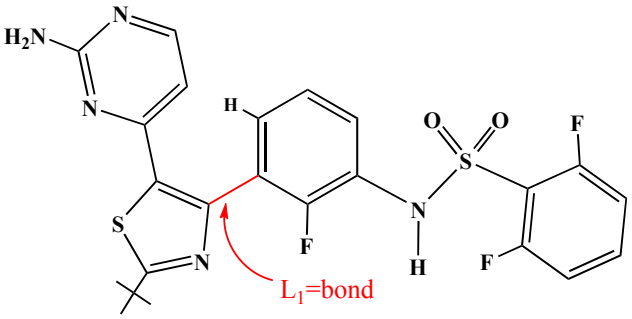


wherein: L_1 is a bond; each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl; R^2 is hydrogen; R^4 is hydrogen; R^3 is optionally substituted aryl; m is 2; and Ar is a monocyclic heteroaryl

containing 5 to 6 atoms wherein at least one atom is nitrogen. The following is a direct comparison (in red) between the claimed Formula Ia and the formula of dabrafenib.

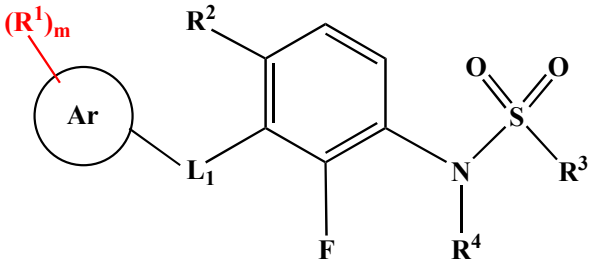
a. L_1 is a bond:

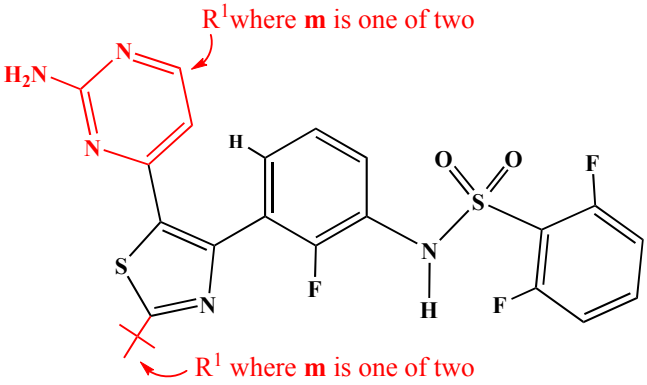




'640 patent Dabrafenib

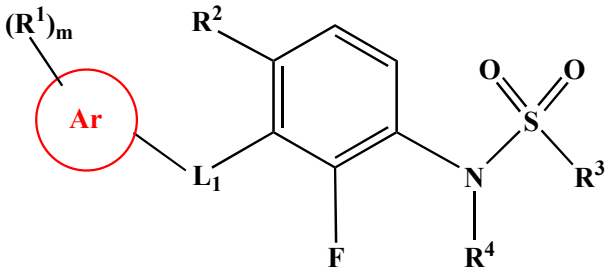
b. Each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl and m=2:

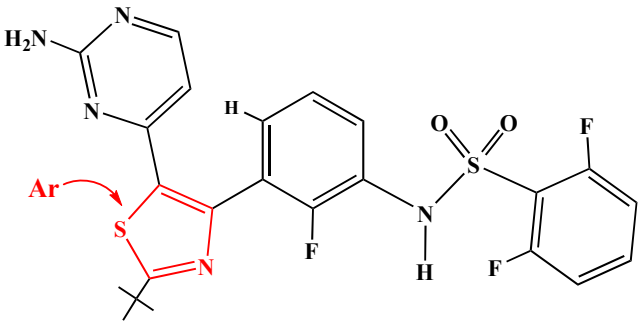




'640 patent Dabrafenib

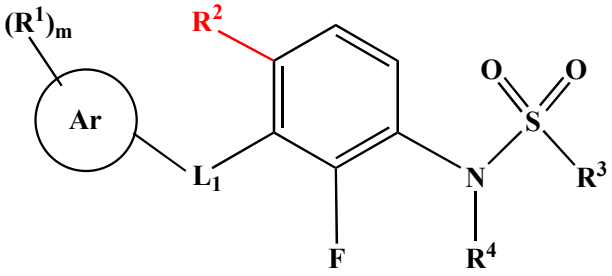
c. Ar is a monocyclic heteroaryl containing 5 to 6 atoms wherein at least one atom is nitrogen:

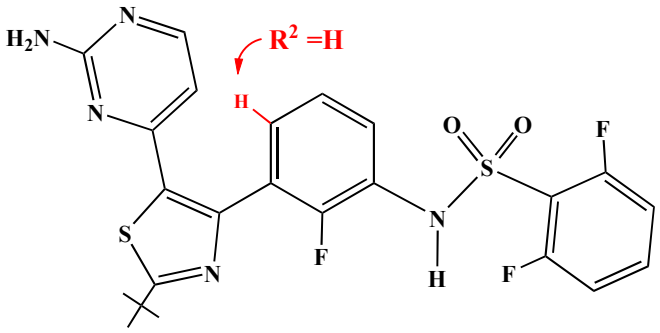




'640 patent Dabrafenib

d. R^2 is hydrogen:

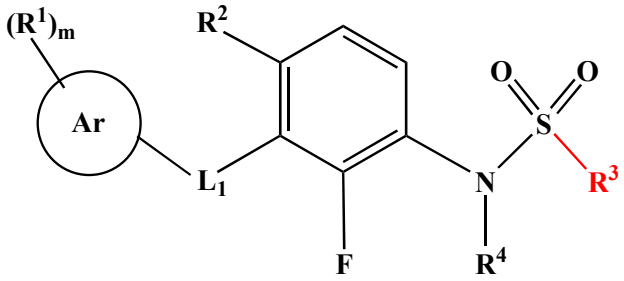


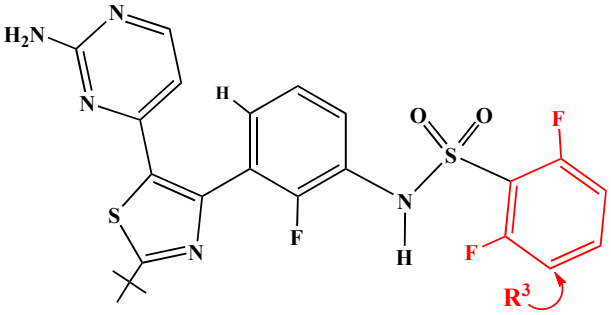


’640 patent

Dabrafenib

e. R^3 is optionally substituted aryl:

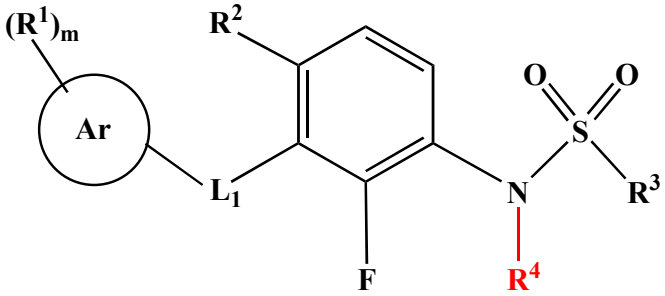


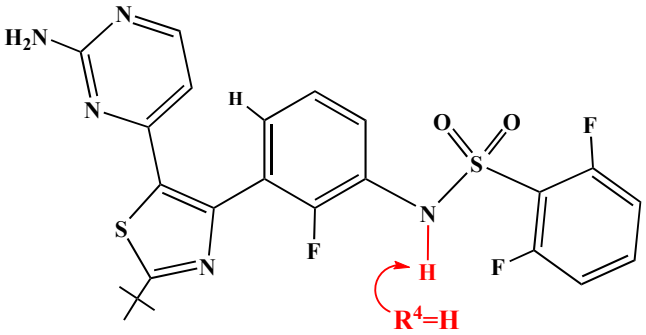


’640 patent

Dabrafenib

f. R^4 is hydrogen:





’640 patent

Dabrafenib

EVIDENCE OF GSK’S COPYING

22. GSK (or SmithKline Beecham Corporation, which merged with Glaxo Wellcome to form GSK in 2000) began filing patent applications on non-selective wild-type BRAF kinase inhibitors as early as November 20, 2000. Over the next seven years, GSK filed at least ten patent applications directed to wild-type BRAF kinase inhibitors. None of these applications disclosed a core molecular structure comprising a sulfonamide with its nitrogen attached to a halogenated phenyl.

23. In September of 2005, Plexxikon's CEO, Peter Hirth, approached GSK, disclosed the genetic target of Plexxikon's selective kinase inhibitors, and offered to engage in a dialogue about possible collaboration. Plexxikon needed a partner to conduct large clinical trials and introduce a drug to the market. GSK was enthusiastic about the possible collaboration and, as a result, Plexxikon and GSK entered into a Confidential Disclosure Agreement ("CDA") on October 14, 2005.

24. Pursuant to that CDA, Plexxikon met with scientists from GSK's biology team on November 18, 2005. GSK was represented at the meeting by, among others, Pearl Huang (GSK's Vice President of Oncology Biology) and Jerry Adams (GSK's Director of Medicinal Chemistry and, later, a developer of Novartis's infringing dabrafenib product).

25. On January 17, 2006, Plexxikon hosted the biology team from GSK at its laboratory in Berkeley, California. At that meeting, Plexxikon gave GSK detailed information about how the mutated BRAF kinase was involved in oncology and the efficacy of Plexxikon's inventions in cellular and animal models. After that meeting, Pearl Huang (one of the two GSK vice presidents who attended) sent a follow up email noting that Plexxikon's "outstanding science makes the prospect of working together very attractive" and that she was "very excited about the possibility of developing multiple compounds for BRAFV600E [sic]."

26. Following that meeting, on January 27, 2006, GSK wrote to ask "whether Plexxikon would be amenable to executing a Material Transfer Agreement with GSK so that we could evaluate some of the Plexxikon compounds in-house?" Plexxikon agreed, and the parties then negotiated and ultimately signed a Material Transfer Agreement ("MTA") dated June 1, 2006. Among other things, the MTA prohibited GSK from making derivatives of or attempting to determine the molecular structure of the transferred compounds and provided that Plexxikon would own any derivatives which GSK did make.

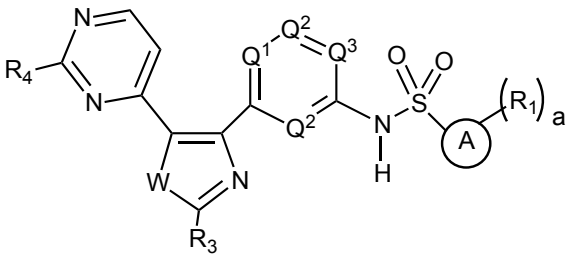
27. After GSK signed the MTA, and relying on its protections, Plexxikon shipped 10 mg of each of vemurafenib, then known as PLX4032, and another Plexxikon-discovered selective BRAF kinase inhibitor, known as PLX6098, to GSK's laboratory in Collegeville, PA. From that point up until August 2, 2006, GSK conducted due diligence (including *in vitro* studies) to confirm the activity of Plexxikon's molecules. That diligence culminated in a GSK report, dated August 2, 2006, confirming the activity of Plexxikon's molecules.

28. On the same day that GSK issued its diligence report, Plexxikon and GSK entered into a Confidential Disclosure Agreement with the law firm of Woodcock Washburn. Pursuant to this agreement, Plexxikon disclosed the structure of PLX4032 to Woodcock Washburn so that it could perform a prior art search. Woodcock Washburn was prohibited from disclosing the structure of PLX4032 to GSK. Woodcock Washburn delivered its (favorable) report on the prior art to both Plexxikon and GSK on September 20, 2006.

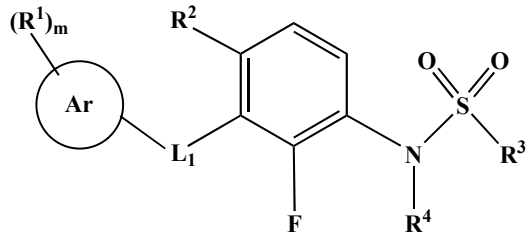
29. Plexxikon and GSK continued to discuss GSK's desire to license Plexxikon's technology. Between March 2006 and September 2006, the parties exchanged numerous term sheets. However, the parties could not reach a business arrangement, and Plexxikon ultimately entered into a development and licensing agreement with a different party.

30. The first publication of Plexxikon's core molecular structure occurred on January 4, 2007, in Plexxikon's international patent application publication WO2007/002433. This was followed with an article in Proceedings of the National Academy of Sciences (PNAS) on February 26, 2008, disclosing Plexxikon's core molecular structure and discussing the importance of this structure in selectively binding with the BRAF kinase produced due to the V600E mutation. The article explained that "[t]he critical binding determinant for oncogenic selectivity derives from the interaction between the sulfonamide and the beginning of the DFG region that subsequently directs the attendant alkyl chain into a small pocket unique to the Raf family." (James Tsai et al., *Discovery of a Selective Inhibitor of Oncogenic B-Raf Kinase with Potent Antimelanoma Activity*, 105 PROCEEDINGS NAT'L ACAD. SCI. 3041, 42 (2008), www.pnas.org/content/105/8/3041).

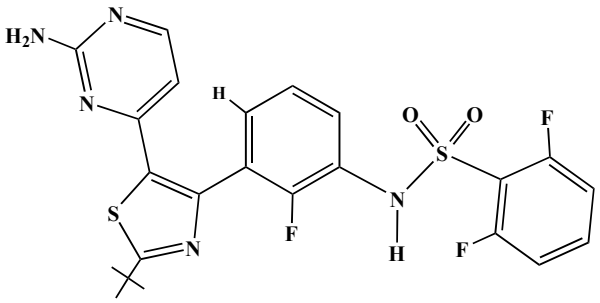
31. Mere months later, on May 6, 2008, GSK filed its first patent application—provisional patent application serial number 61/050,744—disclosing a sulfonamide with its nitrogen attached to an optionally halogenated phenyl. This same patent application was also the first in which GSK disclosed a selective kinase inhibitor targeting BRAF V600E. GSK filed this patent application more than a year after Plexxikon filed its first relevant patent application, and nearly one year after the priority date of the '640 patent, July 17, 2007. The compound formula I disclosed in GSK's application is shown below (reproduced from US 7,994,185 B2, column 3, lines 30-40), next to formula Ia of the '640 patent. GSK's infringing dabrafenib compound is also shown for comparison.



GSK's formula I

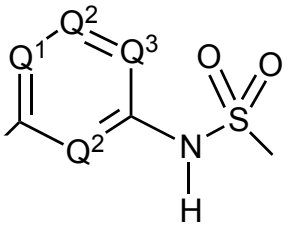


'640 patent formula Ia

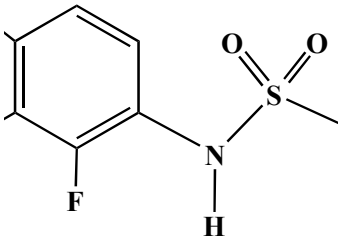


Dabrafenib

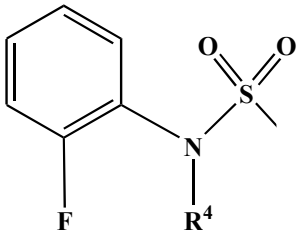
32. As these diagrams show, each of the GSK formula I, dabrafenib, and the '640 patent formula Ia have the same core molecular structure:



GSK's formula I

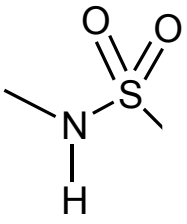


Dabrafenib

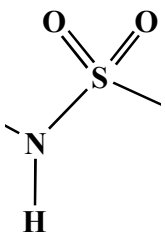


'640 patent formula Ia

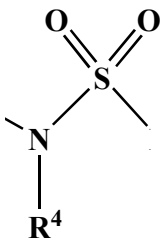
a. a structure that includes a sulfonamide, which binds to the kinase that results from $BRAF^{V600E}$ mutation; and



GSK's formula I

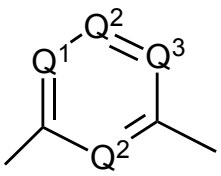


Dabrafenib

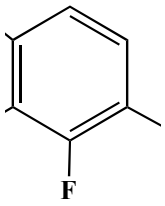


'640 patent formula Ia

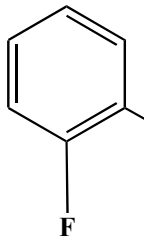
b. a halogenated phenyl (which stabilizes the binding of the sulfonamide to the mutated kinase) attached to the nitrogen of the sulfonamide.



GSK's formula I



Dabrafenib



'640 patent formula Ia

33. GSK was aware that this core structure was responsible for selective binding to the kinase produced by $BRAF^{V600E}$. For example, GSK published an article on June 16, 2011, stating that "[e]valuation of several different headgroup linkers . . . revealed that the sulfonamide-containing analog 11 showed a substantial improvement in cellular potency, particularly in the pERK mechanistic assay run in $B\text{-}Raf^{V600E}$ mutant SKMEL28 cells. . . . Thus, the sulfonamide N-H appeared to be a key pharmacophore for potent in vitro activity in this series." (John C. Stellwagen et al., *Development of Potent B-RafV600E Inhibitors Containing an Arylsulfonamide Headgroup*, 21 BIOORGANIC & MED. CHEMISTRY LETTERS 4436, 37-38 (2011)). In this same article, GSK referenced Plexxikon's earlier novel compounds, stating that "[t]his is similar to the binding modes observed for the sulfonamide groups in the B-Raf inhibitors PLX4720 and PLX4032." *Id*. at 4438.

34. Further, GSK published another article on February 7, 2013, describing its development of dabrafenib and touting the importance of the core molecular structure that Plexxikon had developed: "Having established the sulfonamide as a key pharmacophore required for potent cellular inhibition of $B\text{-}Raf^{V600E}$," the authors explained, "we performed significant structural modifications elsewhere to lower the molecular weight and reduce the number of metabolic sites contained within the template." (Tara R. Rheault et al., *Discovery of Dabrafenib: A Selective Inhibitor of Raf Kinases with Antitumor Activity against B-Raf-Driven Tumors*, 4 ACS MED. CHEMISTRY LETTERS 358 (2011)).

35. The facts establish that GSK: had access to Plexxikon's revolutionary selective BRAF kinase inhibitors having a core molecular structure of a sulfonamide with its nitrogen attached to a halogenated phenyl; confirmed the activity of Plexxikon's selective BRAF kinase inhibitors; confirmed the novelty of Plexxikon's selective BRAF kinase inhibitors; wanted to license them; and failed to come

to commercial terms with Plexxikon. Thereafter, GSK developed a selective BRAF kinase inhibitor that incorporated Plexxikon's novel core molecular structure that is selective to BRAF V600E. This occurred well over one year after Plexxikon made its novel selective BRAF kinase inhibitors public in a published patent application. In short, there is substantial evidence to suggest that GSK built dabrafenib by copying Plexxikon's invention.

COUNT I

(DIRECT INFRINGEMENT OF U.S. PAT. NO. 9,469,640)

36. Plexxikon incorporates each of the preceding paragraphs as if fully set forth herein.

37. The commercial offer for sale, sale and/or importation of dabrafenib, sold under the trademark Tafinlar®, by Novartis does and will constitute an act of infringement of one or more claims of the '640 patent.

38. Novartis has committed and continues to commit these acts of infringement without license or authorization.

39. Unless Novartis is enjoined from infringing the '640 patent, Plexxikon will suffer irreparable injury for which damages are an inadequate remedy.

40. As a result of Novartis's infringement of the '640 patent, Plexxikon has suffered damages pursuant to 35 U.S.C. § 284.

41. At least as of the filing of this Complaint, if not earlier, Novartis knows or should know that its selling, offering to sell, and/or importing Tafinlar®, does and will constitute an unjustifiably high risk of infringement of the '640 patent.

42. Novartis had actual notice of the published patent application that led to the '640 patent. The invention claimed in the '640 patent is substantially identical to the invention claimed in that published patent application.

43. Novartis is selling, offering to sell, and/or importing Tafinlar® despite an objectively high likelihood that its actions do and will constitute infringement of a valid patent. Thus, Novartis's infringement is willful.

44. Novartis, as successor-in-interest to GSK, knew or should have known of any copying on GSK's part of Plexxikon's novel structure to develop Tafinlar®.

45. The history of improper development of Tafinlar® combined with Novartis's ongoing deliberate, willful, and wanton infringement of the '640 patent, makes this case exceptional pursuant to 35 U.S.C. § 285.

REQUEST FOR RELIEF

Wherefore, Plexxikon requests the following relief:

(a) Judgment that Novartis infringes one or more claims of the '640 patent due to its past and present commercial offer for sale, sale and/or importation of dabrafenib, trade name Tafinlar®;

(b) An injunction enjoining Novartis, and all persons acting in concert with Novartis, from selling, offering for sale, or importing Tafinlar®, or any other product the making, using, selling, offering for sale, or importing of which infringes one or more claims of the '640 patent;

(c) Judgment awarding Plexxikon damages adequate to compensate Plexxikon for Novartis's infringement of the '640 patent, with pre-judgment and post-judgment interest and costs pursuant to 35 U.S.C. § 284;

(d) Judgment that Novartis's infringement has been willful and that the damages awarded Plexxikon be trebled pursuant to 35 U.S.C. § 284;

(e) Judgment awarding Plexxikon reasonable royalties under 35 U.S.C. §154(d);

(d) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(e) An award of Plexxikon's costs and expenses in this action; and

(f) Such further and other relief as this Court may deem just and proper.

JURY DEMAND

Plaintiff demands trial by jury on all issues so triable.

DATED: August 3, 2017

Respectfully submitted,
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