

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

INTAS PHARMACEUTICALS LTD.,  
Petitioner

v.

ATOSSA THERAPEUTICS, INC.,  
Patent Owner

---

Case PGR2023-00043

Patent No. 11,572,334

---

**EXPERT DECLARATION OF RON BIHOVSKY, Ph.D.**

## TABLE OF CONTENTS

I.	Introduction.....	1
II.	Education and Professional Background.....	1
III.	Compensation .....	3
IV.	Scope of engagement.....	3
V.	Ahmad.....	4
VI.	References teaching synthesis of 90% (Z)-Endoxifen .....	7
	A.    Liu.....	7
	B.    Fauq .....	10
VII.	Responses to Dr. Davies' Opinions.....	11
	A.    Response to Dr. Davies' Prior Art Analysis .....	11
	1.    Response to Dr. Davies' Opinions Regarding Ahmad .....	11
	2.    Response to Dr. Davies' Opinions Regarding Liu .....	19
	B.    Response to Dr. Davies' Opinions Regarding the Enablement of Ahmad .....	21
	C.    Laboratory Testing of Methods Taught by Liu.....	25
	1.    Synthesis of a mixture of (E)- and (Z)-Endoxifen as taught by Liu .....	26
	2.    Sequential recrystallizations of a mixture of (E)- and (Z)- Endoxifen to produce highly pure (Z)-Endoxifen as taught by Liu .....	28
	3.    Isomerization of (E)-Endoxifen followed by sequential recrystallizations to produce highly pure (Z)-Endoxifen as taught by Liu .....	30

I, Ron Bihovsky, Ph.D., do hereby declare:

## **I. Introduction**

1. I have been retained to provide my expert opinions on behalf of Intas Pharmaceuticals, Limited., in support of a petition for post grant review of claims 1-22 of U.S. Patent No. 11,572,334 (“the ‘334 patent”; Ex. 1001), which challenges the validity of the ‘334 patent.

2. The opinions set out by this declaration are based on my education, knowledge and experience. I have considered the materials and items identified by this declaration.

## **II. Education and Professional Background**

3. My qualifications and credentials to testify as an expert in this case are set forth in my curriculum vitae (attached as Appendix A).

4. I am an organic chemistry and medicinal chemistry expert. In my laboratory, I synthesize organic compounds for the pharmaceutical, biotechnology, and agrochemical industries. I have more than 35 years of academic and industrial chemistry experience. My research has resulted in more than 50 publications in refereed journals, 20 granted U.S. Patents, and numerous foreign patents.

5. I obtained a Bachelor of Science degree in chemistry, magna cum laude, from the State University of New York, Stony Brook in 1970. I earned a Ph.D. in organic chemistry from the University of California, Berkeley in 1977,

and was a National Institute of Health postdoctoral fellow at the University of Wisconsin, Madison from 1978 to 1980. My research included synthesis and structure elucidation of biologically-active molecules.

6. From 1980 to 1987, I was an assistant professor of organic chemistry at the State University of New York, Stony Brook, where I performed organic chemistry research, synthesized natural products, supervised undergraduates, graduate students, and postdoctoral fellows, and taught classes including graduate level synthetic organic chemistry and undergraduate organic chemistry courses.

7. From 1987, I worked in the pharmaceutical industry as a medicinal chemist in roles of increasing responsibility at Berlex Laboratories and Cephalon Inc., where I synthesized numerous classes of small molecules ranging from heterocycles to peptide mimetics as potential pharmaceuticals. I also supervised teams of Ph.D. chemists in my capacity as principal project chemist and coordinated multidisciplinary teams of biochemists, pharmacologists, cell biologists and medicinal chemists in my role as project team leader.

8. From 2001 to 2003, I was an adjunct professor of chemistry at Villanova University, where I created and taught a graduate medicinal chemistry course.

9. In 2001, I founded Key Synthesis LLC, an organic chemistry laboratory located in the Philadelphia, Pennsylvania metropolitan area. Key

Synthesis is fully equipped to conduct custom organic synthesis, contract medicinal chemistry research, and process research for the pharmaceutical and biotechnology industries. I have worked continuously at Key Synthesis since 2001.

10. I have served on the steering committee of Chemical Consultants Network, a topical group of the American Chemical Society, from 2007 to present, and served as its chairman from 2009 to 2012.

### **III. Compensation**

11. I am being compensated for the time I spend on this matter at my ordinary rate of \$375 per hour for expert consulting and \$450 per hour for laboratory work and expert testimony. I am reimbursed for my reasonable expenses incurred in connection with my work on this matter. My compensation does not depend on the opinions I offer or on the outcome of this proceeding or any other proceeding.

### **IV. Scope of engagement**

12. I was asked by counsel for Intas to respond to certain opinions by Patent Owner's expert Dr. Davies relating to whether Ahmad's teaching of using 90% (Z)-Endoxifen was an enabling disclosure. I understand that an enabling disclosure means that the disclosure allows one of ordinary skill in the art to make the claimed invention without undue experimentation, i.e., the subject matter was in the public's possession. I understand that a disclosure need not contain a

working example, if its teachings, combined with the knowledge of one of ordinary skill in the art, would allow one of ordinary skill to make the claimed invention. I further understand that other prior art references, even those that post-date the reference, may demonstrate enablement.

13. I understand that the claims are directed to formulations. I am not an expert in formulations, and I have not been asked to offer any opinions outside of my expertise or concerning the ultimate issues of validity of the claims. I have been asked to consider the enablement issues using Dr. Davies' definition of a POSA, which I understand is "an individual holding a graduate degree in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed inventions." While I far exceed this definition, I have considered the issues from the perspective of someone with such ordinary skill. I understand that the invention date is either September 11, 2017 or September 10, 2018. My opinions do not change based on which date is used.

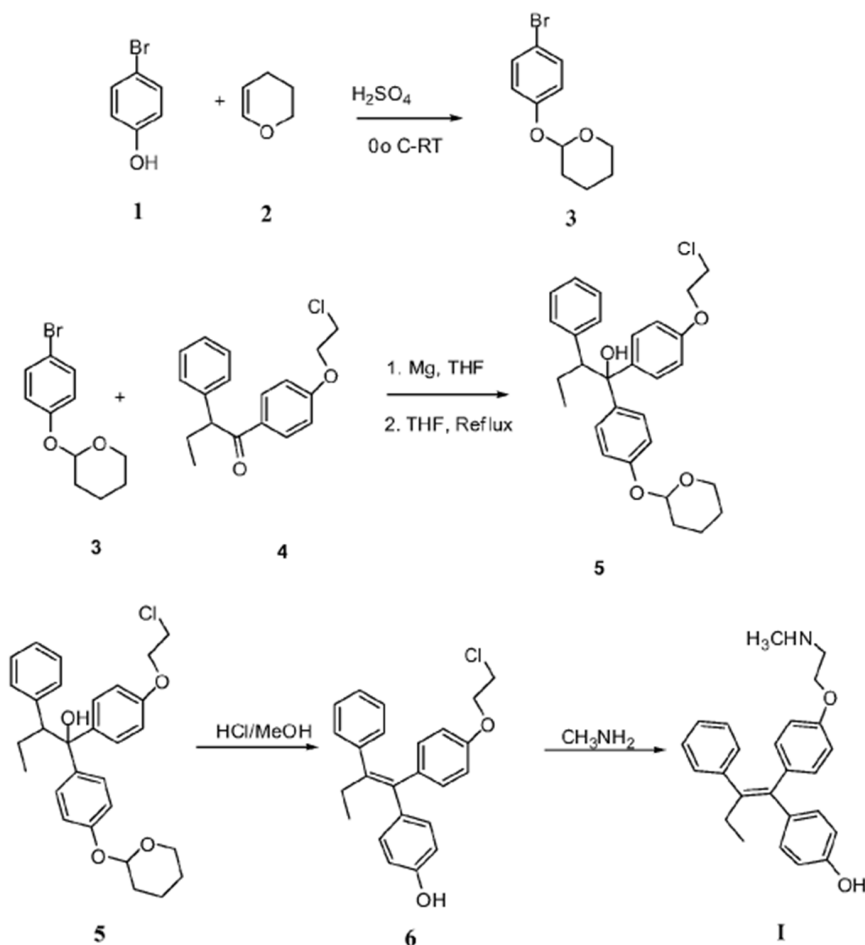
## **V. Ahmad**

14. I understand that Intas has asserted that the claims of the '334 patent are either anticipated by, or obvious over, U.S. Patent No. 9,333,190 ("Ahmad"). I understand that Ahmad issued on May 10, 2016, from a PCT application filed

November 21, 2007, and claims priority to provisional application No. 60/860,420, filed November 21, 2006 (Ex. 1003 at Cover). Therefore, I understand that Ahmad is prior art to the '334 patent.

15. Ahmad “provides compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other breast diseases and diseases susceptible to endoxifen.” Ex. 1003 at Abstract. Ahmad discloses Endoxifen formulations including the free base, salt forms, and complexes with lipids. Ex. 1003 at 2:14-40. In addition, Ahmad teaches a method for synthesizing Endoxifen starting from 4-Bromophenol and 3,4-dihydro-2H-pyran. *See, e.g., id.* at 11:1-16. Figure 2 of Ahmad depicts a reaction scheme for the synthesis of endoxifen:

Figure 2



Ex. 1003 at Figure 2. Ahmad further describes detailed experimental protocols for synthesizing Endoxifen according to the scheme of Figure 2. *Id.* at 22:35-25:67 (Examples 1-4).

16. Ahmad further teaches that “[o]ne object of the present invention is to provide E-Endoxifen or Z-Endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.” *Id.* at 12:14-17; *see also id.* at 2:24-40, 3:55-61. Ahmad teaches that “[t]he

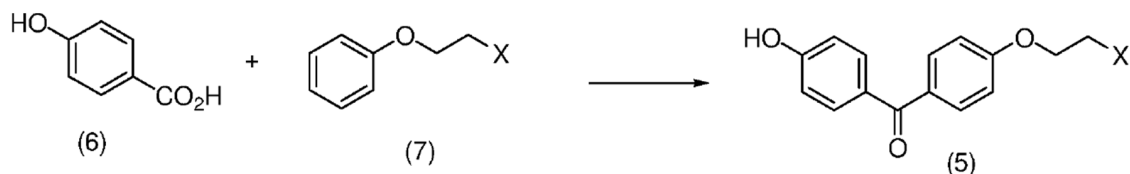


separation of E- and Z -isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).” *Id.* at 11:19-23; *see also* 11:24-42; 11:60-12:13; 3:55-61. With respect to recrystallization, Ahmad discloses various solvents and solvent mixtures “that can be employed in present invention for the separation of (E)- and (Z)- isomers.” *Id.* at 11:24-42.

## VI. References teaching synthesis of 90% (Z)-Endoxifen

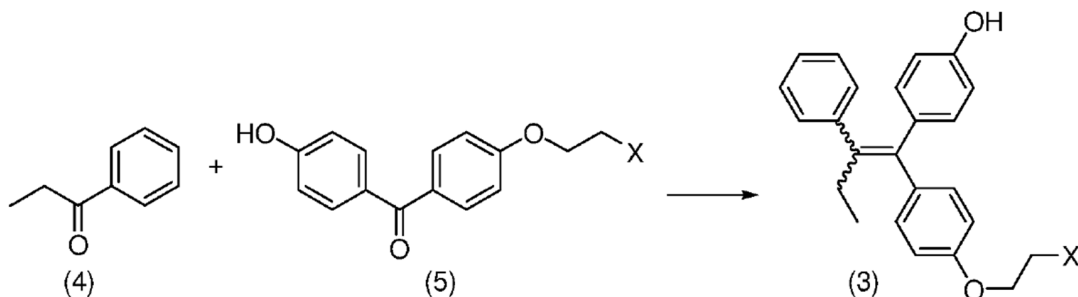
### A. Liu

17. WO 2017/070651 (“Liu”) teaches that “Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor.” Ex. 1004 at [0004]. Liu teaches a method for synthesizing and purifying (Z)-Endoxifen with a 99% isomeric purity. *See, e.g., id.* at [0076] (“The solid was dried in vacuo at 35 °C to a constant weight to give 1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis).”). Liu’s synthesis begins with a first step of “generating the (4-(2-haloethoxy)phenyl)(4-hydroxyphenyl)methanone (5) by reacting 4-hydroxybenzoic acid (6) with 1-(2-haloethoxy)benzene (7).” *Id.* [0035].

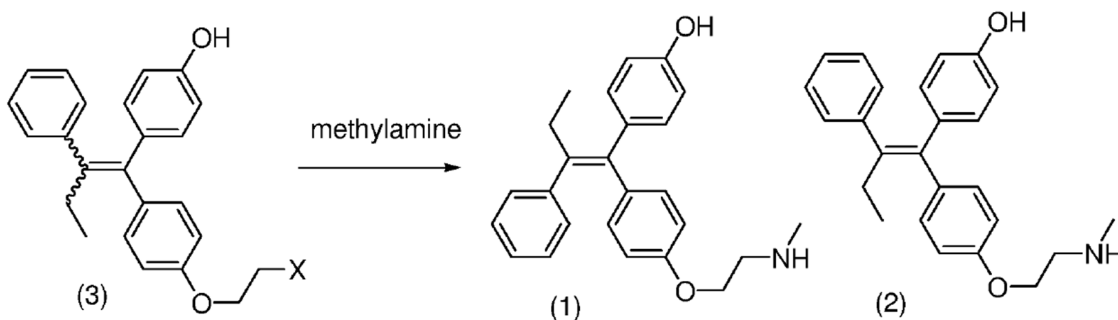


Following completion of the above reaction, Liu reports a second step of “generating the 4-(1-(4-(2-haloethoxy)phenyl)-2-phenylbut-1-enyl)phenol (3) by

reacting propiophenone (4) with (4-(2-haloethoxy)phenyl)(4-hydroxyphenyl)methanone (5) in the presence of a titanium halide reagent.” *Id.* at [0032].



Following the above transformation, Liu teaches “generating the input crystalline solid by reacting 4-(1-(4-(2-haloethoxy)phenyl)-2-phenylbut-1-en-1-yl)phenol (3) with methylamine to produce a mixture of (Z)-endoxifen (1) and (E)-endoxifen (2), wherein X is chloro, bromo, or iodo.” *Id.* at [0030].



18. The above process reported by Liu provides a mixture of (Z) and (E)-Endoxifen (*i.e.*, compounds (1) and (2) in the above scheme). Liu teaches processes for preparing highly pure (Z)-Endoxifen (*i.e.*, 99% isomeric purity) from this mixture. More specifically, Liu discloses:

a process for preparing (Z)-endoxifen, comprising (i) recrystallizing an input crystalline solid comprising a mixture of (Z)-endoxifen (1) and (E)-endoxifen (2) from a first solvent to provide a first crystalline solid and a first mother liquor, wherein the first mother liquor has a ratio of (1) to (2) at least 1.3 times greater than the ratio in the input crystalline solid (1) and (2); (ii) recrystallizing a solid produced by concentrating the first mother liquor, or by removal of the first solvent from the first mother liquor, from a second solvent to give a second crystalline solid and a second mother liquor; (iii) optionally recrystallizing the second crystalline solid from the second solvent one to five additional times to give a third crystalline solid; wherein the third crystalline solid has a ratio of (Z)-endoxifen (1) to (E)-endoxifen (2) greater than 20:1.

*Id.* at Abstract.

19. A by-product of Liu's process is the (E)-Endoxifen from the mixture that precipitated during the recrystallization process. Liu teaches that "[t]he conversion of the E-isomer by-product to additional Z-isomer is accomplished via an innovative recycling procedure, which uses thermal isomerization exclusively, and selective recrystallizations with two different solvents." *Id.* at [0005]. The "first solvent, which can be isopropyl acetate, serves the dual functions as the equilibration medium and solvent with the suitable differential solubility between the E- and Z-isomers." *Id.* "Recrystallization of the isomeric mixture in the first solvent results in the preferential removal of the E-isomer as a solid [precipitate] and enrichment of the Z-isomer in the supernatant. Recrystallization of similar mixtures in the second solvent, which can be acetone, allows the precipitation of Z-isomer with increasing isomeric purity." *Id.* Liu explains that this "combined methodology greatly enhances the efficiency and productivity." *Id.*

20. In addition to detailed disclosure of the synthesis and purification approach described above (*see id.* at [0017]-[0059]), Liu also teaches specific Examples, including experimental protocols, of the preparation of (Z)-Endoxifen having 99% isomeric purity. *See* Examples 2-7 ([0062]-[0077]). As I discuss in more detail below, I have reproduced in my laboratory methods taught by Liu, including synthesis of a mixture of (E)- and (Z)-Endoxifen (starting from 4-hydroxybenzoic acid and 2-phenoxyethyl bromide), selective recrystallizations of a mixture of (E)- and (Z)-Endoxifen, and isomerization of (E)-Endoxifen. My testing confirms that Liu's procedure provides (Z)-Endoxifen with greater than 90% isomeric purity.

**B. Fauq**

21. Fauq, A.H., et al., *A convenient synthesis of (Z)-4-hydroxy-N-desmethyldamoxifen (endoxifen)*, 20 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 3036-3038 (2010) ("Fauq") discloses that "[a] mixture of the (Z)- and (E)-isomers of 4-hydroxy-N-desmethyldamoxifen [Endoxifen] was conveniently prepared in four steps." *Id.* at Abstract. Further, "[t]hese geometrical isomers were then neatly separated by semi-preparative Reverse Phase High Performance Liquid Chromatography (RP-HPLC) using specified conditions." *Id.*; *see also id.* at 3036 ("we report synthesis and purification protocols that have resulted in production of pure endoxifen in excess of 200 mg quantities."). Fauq reports that the separation

of these isomers using HPLC was scalable due to the large retention time (RT) difference between the two isomers. *Id.* at 3038 (“The remarkably large RT difference between the two isomers achieved under specified buffer conditions was critical to their successful larger scale separation because semipreparative RP-HPLC column could be safely overloaded.”).

22. Fauq also teaches a method for isomerizing (E)-Endoxifen, produced as a by-product of its process, followed by further purification to provide (Z)-Endoxifen. For example, Fauq explains that “the isolated E-isomer could be equilibrated in aqueous strong acid in acetonitrile or trifluoroacetic acid/dichloromethane to give a clean 1:1 mixture of Z/E isomers that was re-subjected to HPLC separation.” *Id.* at abstract. Further, “[i]n this way, most of the undesired (E)-isomer could be readily converted to the desired (Z)-isomer providing quick access to over 200 mg quantities of pure endoxifen (Z)-isomer), a potent antiestrogenic metabolite of tamoxifen traditionally used in breast cancer treatment.” *Id.*

## **VII. Responses to Dr. Davies’ Opinions**

### **A. Response to Dr. Davies’ Prior Art Analysis**

#### **1. Response to Dr. Davies’ Opinions Regarding Ahmad**

23. In Paragraph 74 of his declaration (Ex. 2020), Dr. Davies states that Ahmad “wholly lacks enabling disclosures on how to obtain pure (Z)-endoxifen compositions, as discussed in detail below.” I disagree. Ahmad explicitly discloses

the use of greater than 90% (Z)-Endoxifen. *See* Ex. 1003 at 12:14-17 (“[o]ne object of the present invention is to provide E-endoxifen or ***Z-endoxifen*** with at least 80% purity, ***such as at least 90% pure*** or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.”); *see also id.* at 2:30-33, 3:55-61. (Italics added). Additionally, Ahmad discloses a detailed method for the synthesis of Endoxifen starting from commercially available starting materials. *Id.* at 22:35-25:67 (Examples 1-4).

24. While Ahmad does not state the isomeric purity of the Endoxifen synthesized according to its Examples, Ahmad teaches several approaches that can be employed to obtain 90% pure (Z)-Endoxifen from a mixture of (E)- and (Z)-Endoxifen. To that end, Ahmad teaches that “[t]he separation of E- and Z-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).” *Id.* at 11:19-23; *see also* 11:24-42; 11:60-12:13; 3:55-61. Thus, Ahmad teaches that the well-known techniques of crystallization or chromatography could be utilized to purify (Z)-Endoxifen. Employment of crystallization and/or chromatography to separate (E)- and (Z)-Endoxifen and produce highly pure (Z)-Endoxifen as taught by Ahmad would have been well within the skill of a POSA and would not have required undue experimentation. Indeed, methods of using both crystallization and chromatography to produce pure

(Z)-Endoxifen were well known in the prior art as disclosed by several references.

I understand from counsel that enablement of a prior art reference may be demonstrated by another reference. Thus, I outline below several prior art disclosures of methods of synthesizing and purifying (Z)-Endoxifen.

25. As already discussed above, Liu teaches a method of synthesizing a mixture of (E)- and (Z)-Endoxifen and subsequent purification of the mixture to produce (Z)-Endoxifen with a 99% isomeric purity. Ex. 1004 at [0076] (“1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis).”) Liu also teaches a process whereby (E)-Endoxifen is converted to (Z)-Endoxifen, followed by subsequent recrystallizations to provide pure (Z)-Endoxifen. *Id.* at [0005] (“The conversion of the E-isomer by-product to additional Z-isomer is accomplished via an innovative recycling procedure, which uses thermal isomerization exclusively, and selective recrystallizations with two different solvents.”); *see also* Example 6 (“Isomerization<sup>1</sup> of an Endoxifen Mixture Enriched in E Isomer and Recrystallization to Produce Endoxifen Mixture Enriched in Z Isomer”). A POSA would find Liu’s teachings sufficiently detailed to allow a POSA to make 90% pure (Z)-Endoxifen for a capsule as taught in

---

<sup>1</sup> The conversion of one isomer to another isomer (*e.g.*, (E)-Endoxifen to (Z)-Endoxifen) is referred to as an isomerization reaction.

Ahmad without undue experimentation. Indeed, one would need only follow the detailed teachings in Liu, which as described below, I did with little difficulty.

Other references, such as Ali, S. et al., *Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder*, 20 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 2665-2667 (2010) (“Ali”) (Ex. 2011) also teach formation of pure (Z)-Endoxifen by fractional recrystallization from benzene. Ex. 2011 at 2666.

While I agree with Dr. Davies (paragraph 93) that Ali’s recrystallization from benzene would not be suitable for pharmaceutical use, it demonstrates that pure (Z)-Endoxifen could be obtained by fractional recrystallization, and a POSA would understand other solvents could be employed. In fact, Ahmad discloses various solvents and solvent mixtures “that can be employed in present invention for the separation of E- and Z- isomers.” *Id.* at 11:24-42. In addition, Milroy, L.-G., et al., *A multi-gram-scale stereoselective synthesis of Z-endoxifen*, 28 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1352-1356 (2018) (“Milroy”) (Ex. 1019) have reported a stereoselective multi-gram-scale synthesis of (Z)-Endoxifen with an isomeric purity of >99%. Ex. 1019 at 1354 (“[A]ny trace amounts of the E-isomer were removed by trituration of the crude material.”); *see also* Milroy Supplementary Material (Ex. 1025) at 16 (describing method for synthesizing pure (Z)-Endoxifen and associated NMR data); 7 (Figure S4).



26. Other references also teach the synthesis and purification of (Z)-Endoxifen by chromatography (as Ahmad taught could be used). For example, Fauq utilized reverse phase high performance liquid chromatography (RP-HPLC) to separate the mixture. Ex. 1022. Similar to Liu, Fauq teaches that a mixture of (E)- and (Z)-Endoxifen produced according to its synthesis could be enriched in (Z)-Endoxifen via an isomerization process. *Id.* at 3038 (“Fortunately, this unfavorable ratio was readily and cleanly enhanced to 1:1 by heating the isomeric mixture in 6 N-HCl in aqueous acetonitrile for 6 h or by, more simply, stirring the mixture with 1:1 DCM/TFA for 1 h. The (Z)-and (E)-isomers were then separated using the RP-HPLC conditions as outlined above.”); *see also id.* (“Additionally, the undesired (E)-isomer (**8b**)-containing fractions obtained from the HPLC runs were combined and re-equilibrated cleanly to 1:1 mixture of endoxifen and **8b** either by heating with equal volume of 6 N-HCl at 60 °C for 4-6 h, or, by evaporating to dryness and stirring with 1:1 DCM/TFA at rt [room temperature]. In both cases, the equilibrated mixture was directly subjected to HPLC purification resulting in enhanced overall yield of the endoxifen.”). Additionally, Milroy achieved an even higher Z/E ratio by conducting chromatography on alumina compared to the silica employed by Fauq.

27. Further demonstrating the routine nature of synthesizing and purifying (Z)-Endoxifen having greater than 90% isomeric purity, I reproduced methods of

synthesis and purification disclosed by Liu. More specifically, I synthesized and purified (Z)-Endoxifen using both approaches taught by Liu: (i) synthesis of a mixture of (Z)- and (E)-Endoxifen followed by sequential recrystallizations as well as (ii) synthesis followed by isomerization and sequential recrystallizations. Each of these approaches, consistent with Liu's teachings, afforded compositions with an isomeric purity of 100% and 93%, respectively. I describe in detail in Section VII.C. below the experimental protocols I followed as well as the results of those experiments.

28. In Paragraph 76, Dr. Davies states that "the use of ethyl acetate in Ahmad's crystallization steps necessarily teaches away from producing the purified (Z)-endoxifen compositions described in the '334 patent because it would predominantly result in an isomerically enriched (E)-endoxifen solid." But teaching the use of ethyl acetate does not necessarily lead to enriched (E)-Endoxifen. Dr. Davies bases this opinion on the statement in the '334 patent that "(Z)-endoxifen is more soluble in ethyl acetate than (E)-endoxifen." Even if, as the '334 patent reports, (Z)-Endoxifen is more soluble in ethyl acetate than (E)-Endoxifen, that does not mean that Ahmad teaches away. First, Dr. Davies fails to point out that Ahmad does not use pure ethyl acetate for its crystallization step. Rather, as Dr. Davies recognizes in Paragraph 75, Ahmad reports the use of a 1:1 mixture of ethyl acetate and hexane. Ex. 1003 at 25:62-66 ("Ethyl acetate (50 mL)

was added and heated to dissolve the residue completely. The solution was cooled to RT and hexane (50 mL) was added and stirred for 12 h. The solid was filtered and washed with cold ethyl acetate-hexane (1:1, 10 mL) mixture.”). The solubility of a material in a single solvent cannot be equated to the solubility of that same material in a solvent mixture. A POSA would understand that Ahmad used ethyl acetate as the solvent and hexane as an anti-solvent. Furthermore, a POSA would know that even if the precipitate from recrystallization contains mainly (E)-Endoxifen, the filtrate would obviously be enriched in (Z)-Endoxifen. The experiments disclosed in the '334 patent confirm this is true. For example, a 1:1.8 (36:64) mixture of (E)- and (Z)-Endoxifen which was recrystallized from ethyl acetate (EtOAc) by heating to 50 °C, followed by cooling to 20 °C produced a filtrate with an (E)- to (Z)- ratio of 12.6:84.3. *See* Ex. 1001 at Table 2 (Sample 5). After observing this result, a POSA would understand that this filtrate could be further enriched in (Z)-Endoxifen by repeated recrystallization optionally from other solvents (such as acetone), such as taught by Liu. Indeed, Ali found that “Z-Endoxifen was isolated in pure form by fractional crystallization in benzene.” Ex. 2011 at 2666. Additionally, Dr. Davies seems to imply that the examples from Ahmad are the only relevant disclosure. As discussed above, Ahmad (naming the authors of Ali as inventors) discloses that other purification methods, such as additional crystallization and chromatography, can be used following the synthesis

of the (E)- and (Z)-Endoxifen mixture to purify the composition and provide pure (Z)-Endoxifen. Ex. 1003 at 11:19-42 (“The separation of E- and Z-isomers of Endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).”); *see also* 11:60-12:13; 3:55-61.

29. In Paragraph 77, Dr. Davies states that “Ahmad further teaches away from the ’334 patent because it lacks an initial step for (Z)-Endoxifen purification: first crystallizing out (E)-Endoxifen to obtain an enriched solution of (Z)-Endoxifen.” Further, in Paragraphs 78-79, Dr. Davies states “[b]y contrast, to the teachings of Ahmad, the ’334 patent uses ethyl acetate during a crystallization step in order to crystallize out and remove (E)-endoxifen and obtain a (Z)-endoxifen-enriched filtrate...Accordingly, Ahmad teaches away from the ’334 patent claims by: (i) describing only methods of purifying endoxifen with ethyl acetate, which favors (E)-endoxifen solid collection, and (ii) failing to describe any method for producing and further purifying a (Z)-endoxifen-enriched filtrate.” I understand from counsel that if a POSA reading the reference would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path that was taken in the patent claim at issue, then the reference teaches away. As discussed above, multiple prior art references taught the synthesis of pure (Z)-Endoxifen through different synthetic pathways and using different

purification approaches. Even to the extent Ahmad, and other references, teach a different “initial step” than the ’334 patent, this would not teach away from the compositions claimed in the ’334 patent. Indeed, I note that the ’334 patent claims only a formulation comprising (Z)-Endoxifen, and does not include any claims directed to a method of manufacturing (Z)-Endoxifen.

30. In Paragraph 97, Dr. Davies states that “Song erroneously assigned (E)-endoxifen NMR shifts as (Z)-endoxifen NMR shifts.” I have reviewed Song and it is my opinion that Song reports an NMR analysis that is inconsistent with the literature. The fact that one reference misreported its results would not prevent a POSA from forming pure (Z)-Endoxifen without undue experimentation. At most, a POSA might have followed Song, discovered that it didn’t work, and moved on to another reference. In fact, I initially tried to carry out the teachings of Song (recrystallization from EtOAc) and quickly discovered that it forms pure (E)-Endoxifen. As I discuss in detail in this declaration, numerous other references, including Liu, Fauq, Milroy, and Ali all report the synthesis and purification of (Z)-Endoxifen. The synthesis of pure (Z)-Endoxifen would have been well within the skill of a POSA.

## **2. Response to Dr. Davies’ Opinions Regarding Liu**

31. In Paragraph 87, Dr. Davies states that Liu does not provide “any teaching regarding use in a pharmaceutical composition.”; *see also* Paragraph 88

(“Liu (EX1004) does not provide any disclosure or description that would enable a POSA to be motivated to use these compositions and methods of obtaining isomerically pure (Z)-endoxifen for use in an oral formulation as claimed in the ’334 patent.”) I disagree. It is clear from Liu that the entire motivation for developing his synthesis of (Z)-Endoxifen was for pharmaceutical purposes. For example, in the background section, Liu explains that “[g]iving the active (Z)-endoxifen form directly to tamoxifen non-responsive patients has been shown to result in significantly higher endoxifen blood levels compared to giving a similar dose of tamoxifen, and shows evidence of tumor regressions as shown in a phase I study.” Ex. 1004 at [0003]. Further, Liu teaches that “there is a need in the art for a practical, scalable synthesis that gives access to highly pure (Z)-endoxifen.” *Id.* at [0004]. Thus, Liu teaches methods for obtaining pure (Z)-Endoxifen because (Z)-Endoxifen is an active pharmaceutical ingredient that could then be incorporated into a pharmaceutical formulation. Further, there is nothing in Liu suggesting that it would not be suitable for use as an oral formulation, nor does Dr. Davies appear to argue that it would not be. Tellingly, Dr. Davies points out that Ali’s use of benzene would make it unsuitable for pharmaceutical use, but does not make any such argument for Liu who does not use toxic recrystallization solvents. Fauq, who purified (Z)-Endoxifen by RP-HPLC, would similarly be usable in pharmaceutical formulations. Ex. 1022 at 3038.

**B. Response to Dr. Davies' Opinions Regarding the Enablement of Ahmad**

32. In Paragraph 127, Dr. Davies states that because “Ahmad does not enable a POSA to synthesize (Z)-endoxifen at high levels of purity, much less free base (Z)-endoxifen at levels of purity above 90%, as required by the ’334 invention, Ahmad cannot anticipate the claims of the ’334 patent.” I disagree. As I discuss in Section VI.A., Ahmad teaches that “[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.” *Id.* at 12:14-17; *see also id.* at 2:24-40, 3:55-61. Ahmad goes on to explain that “[t]he separation of E- and Z-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).” *Id.* at 11:19-23; *see also* 11:24-42; 11:60-12:13; 3:55-61. Crystallization and chromatography (including HPLC) are both well-known techniques that are commonly employed during the course of chemical synthesis. These techniques have been available and readily used since long before September 11, 2017. Indeed, as I discuss above, other prior art references in addition to Ahmad report using these same techniques for the separation of a mixture of (E)- and (Z)-Endoxifen to provide pure (Z)-Endoxifen. Ex. 1004 (Liu) (teaching recrystallizations); Ex. 1022 (Fauq) (teaching HPLC).

33. In Paragraph 135, Dr. Davies states that “Ahmad also teaches an entirely different synthetic pathway than what is described in the ’334 patent, and thus it likely starts with and produces different (E)/(Z) ratios, as discussed above.” Dr. Davies appears to imply that because Ahmad teaches a different synthetic pathway, Ahmad would produce a final product with different (E)/(Z) ratios. In chemical synthesis, there are generally many possible ways to synthesize and purify a particular compound of interest. In the case of Endoxifen, as I discuss throughout this report, there are a variety of references teaching different synthetic and purification approaches for preparing (Z)-Endoxifen. Ex. 1003; Ex. 1004; Ex. 1022. In fact, since Ahmad formed the double bond of endoxifen under strongly acidic conditions, known to cause isomerization, a POSA would expect Ahmad’s synthesis to produce an (E)/(Z) ratio similar to the 51:47 ratio obtained by Liu prior to purification. Further, something each of these prior art methodologies have in common is the employment of one or more purification steps following synthesis to separate a mixture of (E)- and (Z)-Endoxifen using crystallization or chromatography. These are the very same well-known techniques that Ahmad teaches can be used to separate these isomers and prepare pure (Z)-Endoxifen. Ex. 1003 at 11:19-23 (“[t]he separation of E- and Z-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).”);



*see also id.* at 11:24-42; 11:60-12:13; 3:55-61. A POSA would conclude that even if Ahmad produces a different E/Z ratio, purification by standard techniques would still be possible.

34. In Paragraph 135, Dr. Davies again argues that Ahmad “teaches away from the ’334 patent” due to its “ethyl acetate crystallization.” As I discuss above, this argument falls flat. First, Dr. Davies fails to point out that Ahmad does not use pure ethyl acetate for its recrystallization step. Rather, as Dr. Davies recognizes in Paragraph 75, Ahmad reports the use of a 1:1 mixture of ethyl acetate and hexane. Ex. 1003 at 25:62-66 (“Ethyl acetate (50 mL) was added and heated to dissolve the residue completely. The solution was cooled to RT and hexane (50 mL) was added and stirred for 12 h. The solid was filtered and washed with cold ethyl acetate-hexane (1:1,10 mL) mixture.”). Additionally, Ahmad does not teach that this crystallization from ethyl acetate/hexane is necessarily the final purification step. Rather, Ahmad explains that “[t]he separation of (E)- and (Z)-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).” Ex. 1003 at 11:19-23. Thus, Ahmad teaches that, to the extent a mixture of (E)- and (Z)-Endoxifen was formed following synthesis, that mixture could be separated using well-known techniques, such as crystallization or chromatography. Prior art references further confirm that it was known how to

employ these well-known techniques to isolate pure (Z)-Endoxifen from a mixture of (E)- and (Z)-Endoxifen. Ex. 1004; Ex. 1022.

35. In Paragraph 146, Dr. Davies states “even if Liu could be relied on to support enablement, it is unclear exactly what teachings of Liu would be relevant to enable a POSA to modify Ahmad to achieve a composition ‘wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen’ because so little can be taken from the sparse teachings of Ahmad.” First, I disagree with Dr. Davies’ assertion that “so little can be taken from the sparse teachings of Ahmad.” As I explain above, Ahmad teaches a method of synthesizing Endoxifen and explains how, to the extent an isomeric mixture is formed, such a mixture can be separated using well-known techniques (i.e., crystallization, chromatography). Second, I strongly disagree with Dr. Davies’ statement that “it is unclear exactly what teachings of Liu would be relevant.” Liu teaches a method of synthesizing a mixture of (E)- and (Z)-Endoxifen and also methods of purifying such a mixture using recrystallization to produce (Z)-Endoxifen having greater than 90% isomeric purity. Liu also teaches methods of isomerizing a mixture enriched in (E)-Endoxifen followed by recrystallization to produce (Z)-Endoxifen having greater than 90% isomeric purity. A POSA would understand either method could be used to make Ahmad’s 90% pure (Z)-Endoxifen capsules. Thus, Liu demonstrates the enablement of Ahmad’s teaching that separation of an isomeric mixture of (E)- and

(Z)-Endoxifen can be accomplished via recrystallization. Additionally, as discussed above, Ahmad's teaching that chromatography can be employed for this separation was also well within the skill of a POSA, as exemplified by Fauq. *See* Ex. 1022. In sum, the prior art, such as Liu and Fauq, demonstrate that achieving greater than 90% (Z)-Endoxifen as taught by Ahmad would have been well within the skill of a POSA. More specifically, it would have been routine for a POSA to purify the Endoxifen product synthesized according to Ahmad according to the procedures taught by Liu (crystallization) or Fauq (chromatography) to achieve greater than 90% (Z)-Endoxifen. Other approaches were also known to a POSA and also would have been routine. For example, it similarly would have been routine for a POSA to follow Liu's or Fauq's synthesis and purification process in its entirety to achieve greater than 90% (Z)-Endoxifen. My own experiments prove that this is true (Section VII.C.).

### **C. Laboratory Testing of Methods Taught by Liu**

36. The following describes my laboratory testing of methods taught by Liu. While I am a very experienced synthetic organic chemist, in my opinion, carrying out Liu's teachings would have been routine and well within the skill of a POSA as Dr. Davies has defined it (and even someone with much lower skill would have been able to follow Liu and synthesize 90% (Z)-Endoxifen). In other words, it took no extraordinary skill to carry out Liu's teachings.

**1. Synthesis of a mixture of (E)- and (Z)-Endoxifen as taught by Liu**

37. I reproduced methods of synthesis and purification disclosed by Liu.

As discussed above, Liu reports synthesis of a 51:47 mixture of (Z)- and (E)-Endoxifen and several methods for purification of (Z)-Endoxifen. I reproduced the following methods as taught by Liu: (i) synthesis followed by sequential recrystallizations as well as (ii) synthesis followed by isomerization and sequential recrystallizations. These approaches, consistent with Liu's teachings, afforded (Z)-Endoxifen with an isomeric purity of 100% and 93%, respectively. I describe in detail below the experimental protocols I followed as well as the results of those experiments.

38. Throughout the course of these experiments, I employed various analytical tools. Thin layer chromatography ("TLC") was employed to monitor reaction progress throughout the synthesis using silica gel plates. Endoxifen was eluted with a DCM:MeOH:NH<sub>4</sub>OH (90:9:1) solvent system. The plates were visualized by UV at 254 nm. No separation of (E)- and (Z)-Endoxifen was observed by TLC. Nuclear Magnetic Resonance ("NMR") spectroscopy (500 MHz) was used to confirm the structures of the chemical intermediates that I synthesized as well as (E)- and (Z)-Endoxifen. NMR spectra were obtained in dimethyl sulfoxide-d<sub>6</sub> ("DMSO-d<sub>6</sub>"). NMR spectra of (E)- and (Z)-Endoxifen were consistent with data reported by Liu (Ex. 1004 at [0076]) as well as other literature.

See Ex. 1025 (supplement to Ex. 1019), Figure S2, S4; Ex. 2011 at note 10, Ex. 1023 (supplement to Ex. 1022) at S8; Elkins, J. Pharmaceutical and Biomedical Analysis, “Characterization of the isomeric configuration and impurities of (Z)-endoxifen by 2D NMR, high resolution LC MS, and quantitative HPLC”, p. 174 – 179 (2014) (Ex. 2002). I also utilized NMR to determine the ratios of the (Z)- to (E)-Endoxifen through integration of NMR signals at  $\delta$  3.85 and 4.01 ppm respectively. (See above.) My NMR data are attached as Ex. 1024. First, I synthesized a mixture of (E)- and (Z)-Endoxifen according to the method taught by Liu. More specifically, this synthesis was conducted following the experimental protocols described in Examples 2-4 of Liu. Ex. 1004 at [0062]-[0072].

39. I obtained the product (7.82 g, Notebook number 15-27-1) in 82% yield as a pink foam which became solid after drying in vacuo followed by several days at ambient temperature. Thin layer chromatography (“TLC”) indicated an inseparable mixture of (Z)- and (E)-Endoxifen and several minor impurities. NMR indicated a 48:52 ratio of (Z)- to (E)-Endoxifen. The NMR spectrum for this product was consistent with the NMR data reported by Liu at paragraph [0071]. The NMR spectrum for the Endoxifen mixture I prepared was also consistent with NMR data reported in the literature. (See above.) The NMR spectra for the compounds I synthesized according to Liu’s procedures are attached to this declaration as Exhibit 1024.

**2. Sequential recrystallizations of a mixture of (E)- and (Z)-Endoxifen to produce highly pure (Z)-Endoxifen as taught by Liu**

40. Following synthesis of the mixture of (E)- and (Z)-Endoxifen as taught by Liu, I conducted a recrystallization of that mixture from acetone as taught by Liu. Ex. 1004 at [0070]. To that end, I dissolved the crude 48:52 mixture of (Z)- and (E)-Endoxifen (1.544 g, 15-27-1 and 15-27-2) in refluxing acetone (4.20 mL). *Id.* The crude mixture was then slowly cooled to 20 °C for 19 h, then kept for 4 days at -10 °C. The cold mixture was quickly centrifuged to isolate the solid precipitate.<sup>2</sup> *Id.* I evaporated the residual solvent in the precipitate with a stream of nitrogen, then dried in vacuo to afford a light pink solid (771 mg, 15-33-1P). NMR indicated a 33:67 ratio of (Z)- to (E)-Endoxifen. *Id.* at [0071].

41. I then dissolved this precipitate (761 mg, 15-33-1P) in refluxing isopropyl acetate (“iPrOAc”) (7.61 mL) with stirring for 1 hour, then cooled slowly and stored at 23 °C for 6 hours. *Id.* at [0072]. After vacuum filtration, the precipitate was rinsed with iPrOAc (0.2 mL) and dried in air to afford very light pink crystals (238 mg, 15-34-1P). *Id.* NMR indicated this precipitate consisted of a

---

<sup>2</sup> I note that centrifugation is a minor deviation from Liu’s procedure, which isolated the solid via filtration. Centrifugation was simply a more practical approach given the scale of the recrystallization I conducted in my laboratory. In any case, filtration and centrifugation are both well-known techniques for isolating solids, and have been well-known long before September 11, 2017.

5:95 ratio of (Z)- to (E)-Endoxifen. Evaporation of the filtrate in vacuo afforded a pink solid (418 mg, 15-34-1S), which according to NMR had a 67:33 ratio of (Z)- to (E)-Endoxifen.

42. This dried filtrate was then subjected to recrystallization as taught by Liu's Example 7. Ex. 1004 at [0076]-[0077]. I dissolved this dried filtrate (416 mg, 15-34-1S) in refluxing acetone (4.1 mL) with stirring, then cooled and stirred for 40 hours at 4 °C. At this stage, a small amount of precipitate was observed. The flask was scratched to increase crystallization and stirred at 4 °C for 24 more hours. The precipitate was collected by vacuum filtration, rinsed with cold acetone, and dried to afford a white solid (149 mg, 15-35-1P). NMR indicated a 94:6 ratio of (Z)- to (E)-Endoxifen. This precipitate (147 mg, 15-35-1P) was then dissolved in refluxing acetone (2.2 mL), filtered to remove a slight precipitate, then cooled and stirred for 50 hours at 4 °C. The precipitate was collected by vacuum filtration, rinsed with cold acetone, and dried to afford a light beige solid precipitate (91 mg, 15-35-2P). NMR of this precipitate indicated a 100:0 ratio of (Z)- to (E)-Endoxifen. (Z)-Endoxifen: <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 0.84 (t, 3H), 2.27 (s, 3H), 2.40 (q, 2 H), 2.72 (t, 2H), 3.85 (t, 2H), 6.58 (d, 2H), 6.70 (d, 2H), 6.75 (d, 2H), 6.98 (d, 2H), 7.09 (m, 3H), 7.17 (m, 2H), 9.42 (br s, 1H).

43. Thus, my experiments confirm Liu's teaching of the synthesis of a mixture of (E)- and (Z)-Endoxifen followed by sequential recrystallizations which afforded (Z)-Endoxifen with 100% isomeric purity.

**3. Isomerization of (E)-Endoxifen followed by sequential recrystallizations to produce highly pure (Z)-Endoxifen as taught by Liu**

44. As I discuss above, Liu also teaches a process whereby (Z)-Endoxifen can be prepared via isomerization of (E)-Endoxifen (or a mixture of (E)- and (Z)-Endoxifen) followed by recrystallizations. I have also reproduced that process, and I have confirmed that it provides greater than 90% (Z)-Endoxifen.

45. As described above, I prepared a 48:52 mixture of (Z)- and (E)-Endoxifen according to the method taught by Liu. *See* Ex. 1004 at Examples 2-4 ([0062]-[0071]). I recrystallized this crude mixture (15-27-1 and 15-27-2) from iPrOAc to provide a precipitate enriched in (E)-Endoxifen and a filtrate enriched in (Z)-Endoxifen. Ex. 1004 at [0072]. As discussed above in Paragraph 42, I subjected the filtrate to recrystallization as taught by Liu's Example 7 to produce a 100:0 ratio of (Z)- to (E)-Endoxifen (i.e., 100% (Z)-Endoxifen as confirmed by NMR). The crystalline precipitate enriched in (E)-Endoxifen provided from Liu's process taught in [0072] was subjected to the isomerization procedure taught by Liu's Example 6. Ex. 1004 at [0073]-[0075].



46. To that end, I dissolved the Endoxifen precipitate from iPrOAc enriched in (E)-Endoxifen (236 mg, Z:E ratio of 5:95, 15-34-1P) in refluxing iPrOAc (2.36 mL) for 4 hours.<sup>3</sup> The mixture was cooled slowly and kept at 15 °C for 2 days. The precipitate was collected by vacuum filtration, rinsed with iPrOAc (0.2 mL) at 15 °C, and dried in vacuo at 35 °C to afford white crystals (182 mg, 15-34-2P). NMR indicated a 5:95 ratio of (Z)- to (E)-Endoxifen. (E)-Endoxifen <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 0.84 (t, 3H), 2.34 (s, 3H), 2.39 (q, 2 H), 2.82 (t, 2H), 4.01 (t, 2H), 6.40 (d, 2H), 6.59 (d, 2H), 6.93 (d, 2H), 7.08 (m, 5H), 7.15 (m, 2H), 9.16 (br s, 1H). The filtrate was evaporated in vacuo to afford a colorless glass (58 mg, 15-34-2S). NMR indicated a 69:31 ratio of (Z) to (E)-Endoxifen.

47. The above isomerization procedure was repeated two times as taught by Liu. Ex. 1004 at [0074] (“The above operations were repeated twice with the residual E-isomer crystals in the reactor to provide two additional crops of Z-enriched material.”) Thus, I isomerized the above Endoxifen precipitate from iPrOAc enriched in the (E)-isomer (182 mg, (Z)- to (E)-ratio 5:95, 15-34-2P) by refluxing in iPrOAc as above. The precipitate afforded white crystals (148 mg, 15-34-3P). NMR indicated a 3:97 ratio of (Z)- to (E)-Endoxifen. The filtrate afforded

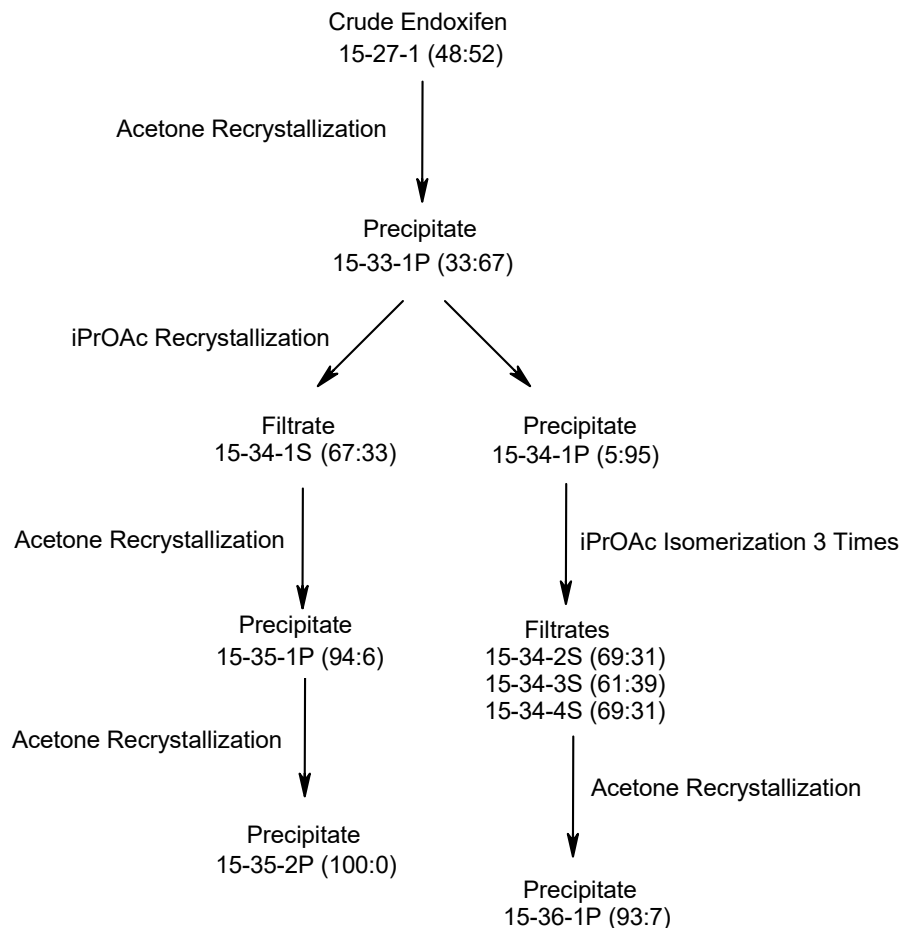
---

<sup>3</sup> Liu disclosed that (E)-Endoxifen can be isomerized by heating in solvents for 0.5 to 4 hours. Ex. 1004 at [0046].

a colorless glass (34 mg, 15-34-3S) that had a 61:39 ratio of (Z)- to (E)-Endoxifen as indicated by NMR. I again subjected the precipitate from iPrOAc (146 mg, 15-34-2P) to the isomerization procedure by refluxing in isopropyl acetate as above then cooling to 15 °C for 1 day. The precipitate afforded white crystals (95 mg, 15-34-4P). NMR indicated a 3:97 ratio of (Z)- to (E)-Endoxifen. The filtrate afforded a colorless glass (50 mg, 15-34-4S). NMR indicated a 69:31 ratio of (Z)- to (E)-Endoxifen.

48. I combined the material obtained from evaporation of the filtrates from two isomerization reactions, and subjected the mixture to recrystallization from acetone to produce a material further enriched in (Z)-Endoxifen as taught by Liu's Example 7. Ex. 1004 at [0076]-[0077]. As taught by Liu, I dissolved this material (108 mg, (Z)- to (E)- ratio 69:31, 15-34-2S and 15-34-4S) in refluxing acetone (1.1 mL), then cooled and stirred for 64 hours at 4 °C. No further precipitation occurred after an additional 24 hours. The precipitate was collected by vacuum filtration, rinsed with cold acetone (~0.1 mL) and dried to afford a white solid (17 mg, 15-36-1P). NMR indicated a 93:7 ratio of (Z)- to (E)-Endoxifen.

49. The purification scheme that I used, as taught by Liu, is depicted in the figure below. The notebook numbers of each sample are indicated followed by the (Z)- to (E)-Endoxifen ratio in parentheses.



50. Thus, my experiments confirm Liu's teaching of the isomerization of a mixture enriched in (E)-Endoxifen followed by sequential recrystallizations afforded (Z)-Endoxifen with 93% isomeric purity.

51. In sum, my experiments confirm that the Liu's methods work as Liu teaches and produce highly pure (Z)-Endoxifen. As such, the methods taught by Liu would enable a POSA to achieve highly pure (Z)-Endoxifen. Indeed, my experiments following Liu's procedures provided (Z)-Endoxifen with isomeric

purities of 93% (recrystallization) and 100% (isomerization followed by recrystallization).

52. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

*Ron Bihovsky* 7/16/2024

Ron Bihovsky, Ph.D.

# **APPENDIX A**

## Ron Bihovsky, Ph.D.

rbihovsky@keysynthesis.com

804 Primrose Lane  
Wynnewood, PA 19096

Phone (610) 357-3281

---

**Organic Chemistry and Medicinal Chemistry Expert with Laboratory.** Specialist in pharmaceutical patent cases requiring laboratory investigation. Testifying experience. Extensive drug discovery and lead optimization accomplishments in the pharmaceutical industry. Discovered novel, potent heterocyclic and peptide mimetic enzyme inhibitors and receptor antagonists. Good working knowledge of biochemistry and pharmacology. Good communication and interpersonal skills. Strong patent and publication record.

Expertise includes:

- |                       |                                    |
|-----------------------|------------------------------------|
| • Medicinal Chemistry | • Structure-Activity Relationships |
| • Organic Synthesis   | • Molecular Modeling               |
| • Drug Design         | • Intellectual Property            |
| • Lead Optimization   | • Hatch-Waxman Patent Litigation   |
- 

### EXPERT WITNESS EXPERIENCE:

**2001-Present KEY SYNTHESIS LLC, Wynnewood, PA.** President and Founder.

- Organic chemistry and medicinal chemistry expert witness or fact witness in over 50 Hatch-Waxman pharmaceutical patent litigation cases. Have been deposed and testified in eight high-profile cases with favorable outcomes. Consult for intellectual property firms and perform experiments to establish the validity of patent claims. Perform custom organic synthesis. Specialize in pharmaceutical patent cases requiring laboratory investigation. Patent and literature searching capability. Wrote the genus and examples for my 16 granted US patents, and worked closely with patent attorneys and patent agents to construct claims.
- Steering Committee (2007 – present), Treasurer (2007-2008) and Chairman (2009-2012) of Chemical Consultants Network, a topical group of the American Chemical Society.

### RESEARCH EXPERIENCE AND ACCOMPLISHMENTS:

**2001-Present KEY SYNTHESIS LLC, Wynnewood, PA.** President and Founder.

Custom Organic Synthesis, Medicinal Chemistry, Expert Witness, Consultant.

- Founded Key Synthesis LLC. Responsible for all aspects of the company: Located and equipped the laboratory, developed business strategy, attracted customers. Key Synthesis prepares compounds including enzyme inhibitors, receptor antagonists, enzyme substrates, and synthetic intermediates for the pharmaceutical and biotechnology industries. Pharmaceutical chemistry, biotechnology, and intellectual property consultant.

**1992-2001 CEPHALON, INC., West Chester, PA.** Principal Project Chemist and Senior Scientist, Medicinal Chemistry. Treatment of Cerebral Ischemia, Cancer.

- PARP Inhibitors - Principal Project Chemist: Designed novel, potent, selective heterocyclic inhibitors of poly(ADP-ribose) polymerase. Optimized potency and properties of screening hit to provide lead molecule. Lead compounds crossed blood-brain barrier, reduced infarct volume in cerebral ischemia, and inhibited tumor growth in vivo.

- Calpain Inhibitors - Team Leader and Principal Project Chemist: Designed and synthesized novel peptide-mimetic and non-peptide cell-permeable calpain inhibitors with new enzyme-reactive groups for neurodegenerative therapy. Coordinated multidisciplinary team of 20 biochemists, pharmacologists, cell biologists and medicinal chemists. Supervised team of 7-10 medicinal chemists in calpain inhibitor program. Collaborated with directors of chemistry, biochemistry and pharmacology to evaluate hypotheses and plan new directions. Recruited the chemistry staff. Designed the laboratories.

**1987-1992      BERLEX LABORATORIES, Cedar Knolls, NJ.** Scientist, Medicinal Chemistry. Cardiovascular Research.

- Project Leader - Directed group of medicinal chemists in synthesis of enzyme inhibitors and peptide mimetics. Represented medicinal chemistry on core team of biochemists and pharmacologists.
- Designed and synthesized highly potent endothelin converting enzyme inhibitors.
- Investigated mechanism of epoxysuccinate class of cysteine protease inhibitors.
- Identified novel peptide-mimetic construct which was incorporated into angiotensin II.
- Performed molecular modeling on peptides, peptide mimetics, and enzyme inhibitors.

**1980-1987      STATE UNIVERSITY OF NEW YORK, Stony Brook, NY.** Assistant Professor of Chemistry. Synthetic Organic and Bio-organic Chemistry.

- Synthesized biologically significant natural products: biotin, ouidenone, civet acid, C-glycoside antibiotics, lignans, tetrahydroisoquinolines.
- Generation and utilization of  $\alpha$ -halo ethers and oxonium ions in synthesis.
- Regioselectivity of Pictet-Spengler reaction.
- Determined structures of crown gall tumor metabolites.
- Wrote computer software programs for literature reference retrieval and elemental analysis.
- Supervised research of 2 Postdoctoral Fellows, 9 Graduate Students, and 20 Undergraduates.
- Taught Graduate Synthetic Organic Chemistry and Undergraduate Organic Chemistry courses.

**1978-1980      UNIVERSITY OF WISCONSIN, Madison, WI.** NIH Postdoctoral Fellow. Organic Synthesis and Structure Elucidation.

- Synthesized natural products; introduced chirality via microbial transformation. Isolated and elucidated structures of compounds with smooth muscle-contracting activity (Leukotriene and G-acid) from animal tissue; determined mechanism of action.
- Performed smooth-muscle contractility assays.

**1972-1978      UNIVERSITY OF CALIFORNIA, Berkeley, CA.** Graduate student, Organic Chemistry. Organic Synthesis and Structure Elucidation.

- Synthesized anatoxin-a via intramolecular cyclization of iminium ion.
- Isolated and determined structure of saxitoxin, potent marine neurotoxin.
- Developed sensitive oxidative fluorescence assay for saxitoxin.
- Cultured microscopic marine algae, isolated toxins, performed bioassay, and determined structures.

#### **Additional Academic Experience:**

**2001-2003      Villanova University, Villanova, PA.** Adjunct Professor of Chemistry.

- Created and taught graduate Medicinal Chemistry course.

**Education:** Ph.D. 1977, Organic Chemistry, University of California, Berkeley (Advisor: H. Rapoport)  
B.S. 1970, Chemistry, Magna cum laude, Honors in Chemistry,  
State University of New York, Stony Brook

**Languages:** Reading and Speaking – English, German  
Scientific Reading – English, German, French, Italian, Spanish

**Publications:** (Note: Ron Bihovsky previously published under the name H. Bates)

1. S. Patil,\* R. Bihovsky, S. Smith, W. Potter, V. Stella, Novel Prodrug PRX-P4-003, Selectively Activated by Gut Enzymes, May Reduce the Risk of Iatrogenic Addiction and Abuse." *Drug and Alcohol Dependence* 186, 159-166 (2018).
2. M. Tao,\* C. H. Park, R. Bihovsky, G. J. Wells, J. Husten, M. A. Ator, R. L. Hudkins, "Synthesis and Structure-Activity Relationships of Novel Poly(ADP-ribose) Polymerase-1 Inhibitors." *Bioorg. Med. Chem. Lett.* 16, 938-942 (2006).
3. G. W. Wells,\* R. Bihovsky, R. L. Hudkins, M. A. Ator, and J. Husten, "Synthesis and Structure-Activity Relationships of Novel Pyrrolocarbazole Lactam Analogs as Potent and Cell-Permeable Inhibitors of Poly(ADP-ribose)polymerase-1 (PARP-1)." *Bioorg. Med. Chem. Lett.* 16, 1151-1155 (2006).
4. R. Bihovsky, M. Tao, J. P. Mallamo, and G. Wells,\* "1,2-Benzothiazine 1,1-Dioxide  $\alpha$ -Ketoamide Analogues as Potent Calpain I Inhibitors." *Bioorg. Med. Chem. Lett.* 14, 1035-1038 (2004).
5. S. J. Miknyoczki,\* S. Jones-Bolin, S. Pritchard, K. Hunter, H. Zhao, W. Wan, M. Ator, R. Bihovsky, R. Hudkins, S. Chatterjee, A. Klein-Szanto, C. Dionne, and B. Ruggeri, "Chemopotential of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-ribose) polymerase inhibitor." *Mol. Cancer Ther.* 2, 371-382 (2003).
6. G. J. Wells, M. Tao, K. A. Josef, and R. Bihovsky,\* "1,2-Benzothiazine 1,1-dioxide P<sub>2</sub> - P<sub>3</sub> Peptide Mimetic Aldehyde Calpain I Inhibitors." *J. Med. Chem.* 44, 3488-3503 (2001).
7. K. A. Josef,\* F. W. Kauer, and R. Bihovsky, "Potent  $\alpha$ -Ketohydroxamate Inhibitors of Recombinant Human Calpain I." *Bioorg. Med. Chem. Lett.* 11, 2615-2617 (2001).
8. S. Chatterjee,\* D. Dunn, M. Tao, G. Wells, Z.-Q. Gu, R. Bihovsky, M. A. Ator, R. Siman, and J. P. Mallamo, "P<sub>2</sub>-Achiral, P'-Extended  $\alpha$ -Ketoamide Inhibitors of Calpain." *Bioorg. Med. Chem. Lett.* 9, 2371-2374 (1999).
9. G. J. Wells\* and R. Bihovsky, "Calpain Inhibitors as Potential Treatment for Stroke and Other Neurodegenerative Diseases. Recent Trends and Developments." *Expert Opin. Ther. Patents* 8, 1707-1727 (1998).
10. M. Tao,\* R. Bihovsky, G. J. Wells, and J. P. Mallamo, "Novel Peptidyl Phosphorous Derivatives as Inhibitors of Human Calpain I." *J. Med. Chem.* 41, 3912-3916 (1998).
11. S. Chatterjee,\* Z.-Q. Gu, D. Dunn, M. Tao, K. Josef, R. Tripathy, R. Bihovsky, S. E. Senadhi, T. M. O'Kane, B. A. McKenna, S. Mallya, M. A. Ator, D. Bozyczko-Coyne, R. Siman, and J. P. Mallamo, "D-Amino Acid Containing High Affinity Inhibitors of Recombinant Human Calpain I." *J. Med. Chem.* 41, 2663-2666 (1998).
12. S. Chatterjee,\* M. A. Ator, D. Bozyczko-Coyne, K. Josef, G. Wells, R. Tripathy, M. Iqbal, R. Bihovsky, S. Mallya, S. E. Senadhi, T. M. O'Kane, B. A. McKenna, R. Siman, and J. P. Mallamo, "Synthesis and Biological Activity of a Series of Potent Fluoromethyl Ketone Inhibitors of Recombinant Human Calpain I." *J. Med. Chem.* 40, 3820-3828 (1997).
13. R. Bihovsky\* and M. A. Ator, "Calpains: Their Role in Pathology, and New Therapeutic Opportunities." *Investigational Drugs Weekly Highlights*, 22-25, May, 1997.
14. M. Iqbal, P. Messina, B. Freed, M. Das, S. Chatterjee, R. Tripathy, M. Tao, K. A. Josef, B. Dembofsky, D. Dunn, E. Griffith, R. Siman, S. E. Senadhi, W. Biazzo, D. Bozyczko-Coyne, S. L. Meyer, M. A. Ator, and R. Bihovsky\*, "Subsite Requirements for Peptide Aldehyde Inhibitors of human Calpain I." *Bioorg. Med. Chem. Lett.*, 7, 539-544 (1997).



15. M. Tao\*, R. Bihovsky, and J. C. Kauer "Inhibition of Calpain by Peptidyl Heterocycles." *Bioorg. Med. Chem. Lett.*, 6, 3009-3012 (1996).
16. R. Bihovsky\*, and I. Pendrak, "Synthesis of Cystamidin A (Pyrrole-3-propanamide), a Reported Calpain Inhibitor." *Bioorg. Med. Chem. Lett.*, 6, 1541-1542 (1996).
17. S. Chatterjee\*, K. Josef, G. Wells, M. Iqbal, R. Bihovsky, J. P. Mallamo, M. Ator, D. Bozyczko-Coyne, S. Mallya, S. Senadhi, and R. Siman "Potent Fluoromethyl Ketone Inhibitors of Recombinant Human Calpain I." *Bioorg. Med. Chem. Lett.*, 6, 1237-1240 (1996).
18. S. L. Meyer\*, D. Bozyczko-Coyne, S. K. Mallya, C. M. Spais, R. Bihovsky, J. K. Kawooya, D. M. Lang, R. W. Scott, and R. Siman "Biologically Active Monomeric and Heterodimeric Recombinant Human Calpain I Produced Using the Baculovirus Expression System". *Biochem. J.* 314, 511-519 (1996).
19. R. Bihovsky\*, B. Levinson, R. Loewi, P. W. Erhardt, and M. Polokoff, "Hydroxamic Acids as Potent inhibitors of Endothelin Converting Enzyme," *J. Med. Chem.* 38, 2119-2129 (1995).
20. R. Bihovsky\*, J. C. Powers, C.-M. Kam, R. Walton, and R. Loewi, "Further Evidence for the Importance of Free Carboxylate in Epoxysuccinate Inhibitors of Thiol Proteases," *J. Enzyme Inhib.* 7, 15-25 (1993).
21. R. Bihovsky\*, "Reactions of  $\alpha,\beta$ -Epoxy Carbonyl Compounds with Methanethiolate: Regioselectivity and Rate," *J. Org. Chem.*, 57, 1029-1031 (1992).
22. R. Bihovsky\*, "Applications of Cyclic  $\alpha$ -Haloethers and Unsaturated Oxonium Ions to Natural Product Synthesis: Carbon-Carbon Bond Formation," *Trends in Organic Chemistry*, 3, 1-6 (1992).
23. R. Mohan\*, Y. L. Chou, R. Bihovsky, W. C. Lumma, Jr. P. Erhardt, and K. Shaw, "Synthesis and Biological Activity of Angiotensin II Analogs Containing a Val-His Replacement, Val $\Psi$ [CH(CONH<sub>2</sub>)NH]His," *J. Med. Chem.*, 34, 2402-2410, (1991).
24. S. Rosenblum and R. Bihovsky\*, "Synthesis of the Papulacandin C-Arylglucosylspiroketal Nucleus," *J. Amer. Chem. Soc.*, 112, 2746-2748 (1990).
25. R. Bihovsky\* and V. Bodepudi, "Synthesis of (+)-Biotin: Efficient Resolution of Key Intermediates," *Tetrahedron*, 46, 7667-7676, (1990).
26. R. Bihovsky\*, M. U. Kumar, S. Ding, and A. Goyal, "Oxonium Ions in Organic Synthesis: Condensation of 2,3-Dihydrofuran and 3,4-Dihydro-2H-pyran with 1,3-Dicarbonyl Compounds," *J. Org. Chem.*, 54, 4291-4293 (1989).
27. R. Bihovsky\*, C. Selick, and I. Giusti, "Synthesis of C-Glucosides by Reactions of Glucosyl Halides with Organocuprates," *J. Org. Chem.*, 53, 4026-4031 (1988).
28. H. Bates\*, K. Bagheri, and P. Vertino, "Effect of pH on the Regioselectivity of Pictet-Spengler Reactions of 3-Hydroxyphenethylamines with Formaldehyde and Acetaldehyde," *J. Org. Chem.* 51, 3061-3063 (1986).
29. H. Bates\*, J. Farina, and M. Tong, "An Approach to Pseudomonic Acids from Acetylenic Precursors: Synthesis of 2-(Hydroxymethyl)-3-butyne-1-ol," *J. Org. Chem.*, 51, 2637-2641 (1986).
30. H. Bates\* and S. Rosenblum, "Nucleophilic Displacements on an  $\alpha$ -Chlorothioether by Organocuprates: A Novel Synthesis of Desoxybiotin," *J. Org. Chem.*, 51, 3447-3451 (1986).

31. H. Bates, "Structure of Crown Gall Tumor Metabolites: Chemical Mediators of Parasitism," *Anal. New York Acad. Sci.*, **471**, 289-290 (1986).
32. H. Bates\*, N. Condulis, and N. Stein, "Reduction of Cyclic Ureas with Lithium Aluminum Hydride," *J. Org. Chem.*, **51**, 2228-2229 (1986).
33. H. Bates\*, J. Magrath, and A. Kaushal, "A Direct Method for Assignment of Absolute Configurations in Crown Gall Metabolites: The Structure of Nopaline," *J. Nat. Prod.*, **48**, 598-601 (1985).
34. H. Bates\* and J. Farina, "Oxonium Ion Electrophiles: Synthesis of the Hypotensive Oudenone," *J. Org. Chem.*, **50**, 3843-3845 (1985).
35. H. Bates\* and S. Rosenblum, "300 MHz  $^1\text{H}$  NMR Spectra and Conformations of Biotin and Related Hexahydrothienoimidazolone Derivatives," *Tetrahedron Lett.*, **41**, 2331-2336 (1985).
36. H. Bates\*, L. Smilowitz, and S. Rosenblum, "A Practical Stereospecific Synthesis of the Biotin Precursor (3 $\alpha$ ,6 $\alpha$ )-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one 1,1-Dioxide," *J. Chem. Soc., Chem. Commun.*, 353-354 (1985).
37. H. Bates\* and C. Selick, "Convenient Preparation of 2,3,4,6-Tetra-*O*-Methyl- $\alpha$ -D-Glucopyranosyl Bromide," *J. Carbohydr. Chem.*, **4**, 273-275 (1985).
38. H. Bates\*, L. Smilowitz, and J. Lin, "Preparation of (3 $\alpha$ ,6 $\alpha$ )-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one: A Key Biotin Intermediate," *J. Org. Chem.*, **50**, 899-901 (1985).
39. H. Bates\* and J. Garelick, "Synthesis of Tetrahydro-4,6,7-Isoquinolinetriols and Tetrahydro-4,7,8-isoquinolinetriols," *J. Org. Chem.*, **49**, 4552-4557 (1984).
40. H. Bates\*, A. Kaushal, P. Deng, and D. Sciaky, "Structure and Synthesis of Histopine, a Histidine Derivative Produced by Crown Gall Tumors," *Biochemistry*, **23**, 3287-3290 (1984).
41. H. Bates\* and P. Deng, "Synthesis of the Civet Constituent *cis*-(6-Methyltetrahydropyran-2-yl)acetic Acid," *J. Org. Chem.*, **48**, 4479-4481 (1983).
42. H. Bates, "Characterization of Tetrahydroisoquinolines Produced by Pictet-Spengler Reactions of Norepinephrine with Formaldehyde and Acetaldehyde," *J. Org. Chem.*, **48**, 1932-1934 (1983).
43. H. Bates, "Decarbonylation of Tetrahydrofuran-2-carboxylic Acids and Tetrahydropyran-2-carboxylic Acids in Concentrated Sulfuric Acid: Formation of Oxonium Ions," *J. Am. Chem. Soc.*, **104**, 2490-2493 (1982).
44. H. Bates\*, "Pictet-Spengler Reactions of Epinephrine with Formaldehyde," *J. Org. Chem.*, **46**, 4931-4935 (1981).
45. H. Bates and C. Sih\*, "Arachidonic Acid is Responsible for the Smooth Muscle-Contracting Activity of G-Acid," *Proc. Nat. Acad. Sci.*, **76**, 2712-2714 (1979).
46. H. Bates and H. Rapoport\*, "Synthesis of Anatoxin a via Intramolecular Cyclization of Iminium Salts," *J. Am. Chem. Soc.*, **101**, 1259-1265 (1979).
47. H. Bates, R. Kostriken, and H. Rapoport\*, "The Occurrence of Saxitoxin and Other Toxins in Various Dinoflagellates," *Toxicon*, **16**, 595-601 (1978).
48. H. Bates, R. Kostriken, and H. Rapoport\*, "A Chemical Assay for Saxitoxin: Improvements and Modifications," *J. Agr. Food Chem.*, **26**, 252-254 (1978).

49. J. Bordner, W. Thiessen, H. Bates, and H. Rapoport\*, "The Structure of a Crystalline Derivative of Saxitoxin. The Structure of Saxitoxin," *J. Am. Chem. Soc.*, 97, 6008-6012 (1975).
50. H. Bates and H. Rapoport\*, "A Chemical Assay for Saxitoxin, the Paralytic Shellfish Poison," *J. Agr. Food Chem.*, 23, 237-239 (1975).
51. H. Ruben, H. Bates, A. Zalkin\*, and D. Templeton, "2,4,4-Triphenyl-1,2-diazetidone-3-one-1-carboxylic Acid, Ethyl Ester," *Acta Cryst. B.*, 30, 1631-1633 (1974).

#### **Patents:**

1. S. Patil, R. Bihovsky, S. Smith, Y. Ji, V. Stella, D. Long, and D. Marquess, "Prodrugs of Fencamfamine" US Patent 11,919,836 (2024)
2. A. Fleischman, R. Bihovsky, et al., "Electrochemical Biosensor for Leukocyte Esterase" US 63/523,213 (2023).
3. S. Patil, R. Bihovsky, S. Smith, Y. Ji, V. Stella, D. Long, and D. Marquess, "Prodrugs of Fencamfamine" US Patent 11,731,935 (2023)
4. A. Fleischman, C. Geddes, C. McMurrin, E. Stamkou, E. Blair, R. Bihovsky, "Compositions and Methods for Determining the Presence of Active Leukocyte Cells Using an Electrochemical Assay" Application submitted (2023).
5. A. Fleischman, J. Parvizi, and R. Bihovsky, "Compositions and Methods for Determining the Presence of Active Leukocyte Cells Using an Electrochemical Assay" WO 2020069176; US 11,104,933 (2021).
6. S. Patil, R. Bihovsky, S. Smith, Y. Ji, V. Stella, D. Long, and D. Marquess, "Prodrugs of Fencamfamine" WO 2017048720 (2017); US Patent 10,662,146 (2020); US 2019/023650; US 2020/0399203.
7. K. A. Josef, J. P. Mallamo, and R. Bihovsky, "Hydroxamate-Containing Cysteine and Serine Protease Inhibitors" US Patent 7,060,683 (2006), WO 185686 (2001), EP 1754707 (2007).
8. M. Ator, R. Bihovsky, S. Chatterjee, D. Dunn, and R. Hudkins, "Multicyclic Compounds and the use thereof as Inhibitors of PARP, VEGFR2 and MLK3 Enzymes." WO 01/85686 (2001), EP 1294725. (2003), US Patent 7,122,679 (2006).
9. S. Chatterjee, J. P. Mallamo, R. Bihovsky, and G. Wells, "Peptide-Containing  $\alpha$ -Ketoamide Cysteine and Serine Protease Inhibitors" US Patent 7,001,907 (2006).
10. S. Chatterjee, J. P. Mallamo, R. Bihovsky, and G. Wells, "Peptide-Containing  $\alpha$ -Ketoamide Cysteine and Serine Protease Inhibitors" US Patent 6,703,368 (2004).
11. K. A. Josef, J. P. Mallamo, and R. Bihovsky, "Hydroxamate-Containing Cysteine and Serine Protease Inhibitors" WO 00/16767 (2001), EP 1115390 (2004), US Patent 6,686,335 (2004).
12. M. Tao and R. Bihovsky, "Peptidyl-2-Amino-1-hydroxyalkanesulfonic Acid Cysteine Protease Inhibitors" US Patent 6,500,802 (2002).
13. M. Tao and R. Bihovsky, "Peptidyl-2-Amino-1-hydroxyalkanesulfonic Acid Cysteine Protease Inhibitors" WO 98/47523 (1998); US Patent 6,348,448 (2002).

14. S. Chatterjee, J. P. Mallamo, R. Bihovsky, and G. Wells, "Peptide-Containing  $\alpha$ -Ketoamide Cysteine and Serine Protease Inhibitors" US Patent 6,288,231 (2001).
15. S. Chatterjee, J. P. Mallamo, R. Bihovsky, and G. Wells, "Peptide-Containing  $\alpha$ -Ketoamide Cysteine and Serine Protease Inhibitors" WO 99/17790 (1999); US Patent 6,150,378 (2000).
16. S. Chatterjee, J. P. Mallamo, D. Dunn, K. Josef, Z. Gu, R. Daines, W. Kingsbury, I. Pendrak, and K. Sham, "Quinoline-Containing C-Ketoamide Cysteine and Serine Protease Inhibitors" US 6,083,944 (2000)
17. R. Bihovsky, G. Wells, and M. Tao, "Benzothiazole and Related Heterocyclic Group-Containing Cysteine and Serine Protease Inhibitors," WO 98/21186 (1998); US Patent 5,952,328 (1999).
18. J. P. Mallamo, R. Bihovsky, M. Tao, and G. Wells, "Phosphorous-Containing Cysteine and Serine Protease Inhibitors," WO 97/03679 (1997); US Patent 5,639,732 (1997).
19. J. P. Mallamo, R. Bihovsky, S. Chatterjee, and R. Tripathy, "Cysteine Protease and Serine Protease Inhibitors," US Patent 5,658,906 (1997).
20. J. P. Mallamo, R. Bihovsky, S. Chatterjee, and R. Tripathy, "Cysteine Protease and Serine Protease Inhibitors," WO 96/14067 (1996); US Patent 5,498,616 (1996).
21. R. Bihovsky, P. Erhardt, J. Lampe, R. Mohan, and K. Shaw, "Inhibitors of the Conversion of Big Endothelin to Endothelin," WO 93/11154 (1993); US Patent 5,504,070 (1996).
22. H. Bates and S. Rosenblum, "Improved Synthesis of Biotin," US Patent 4,656,289 (1987).