

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,

Petitioner

v.

ATOSSA THERAPEUTICS, INC.,

Patent Owner

Case IPR2025-00799

Patent No. 11,261,151

EXPERT DECLARATION OF RON BIHOVSKY, Ph.D.

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Declaration of Ron Bihovsky, Ph.D.

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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 *inter partes* review of claims 1-21 of U.S. Patent No. 11,261,151 (“the 151 Patent”; Ex. 1001), which challenges the validity of the 151 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 in 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 40 years of academic and industrial chemistry experience. My research has resulted in more than 50 publications in refereed journals, 19 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 until 2001, 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. Background

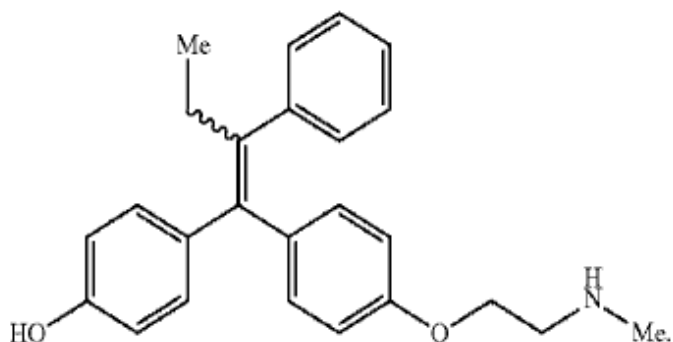
12. The claims of the 151 patent are directed to compositions comprising a crystalline form of endoxifen that is at least 90% by weight (Z)-endoxifen having a crystalline Form I, characterized by an x-ray powder diffraction pattern comprising certain peaks.

13. Endoxifen (4-hydroxy-N-desmethyltamoxifen) is a nonsteroidal selective estrogen receptor modulator. I understand that Intas sells endoxifen in India

under the brand name Zonalta for the treatment of manic depressive disorder. *See* Ex. 1015.

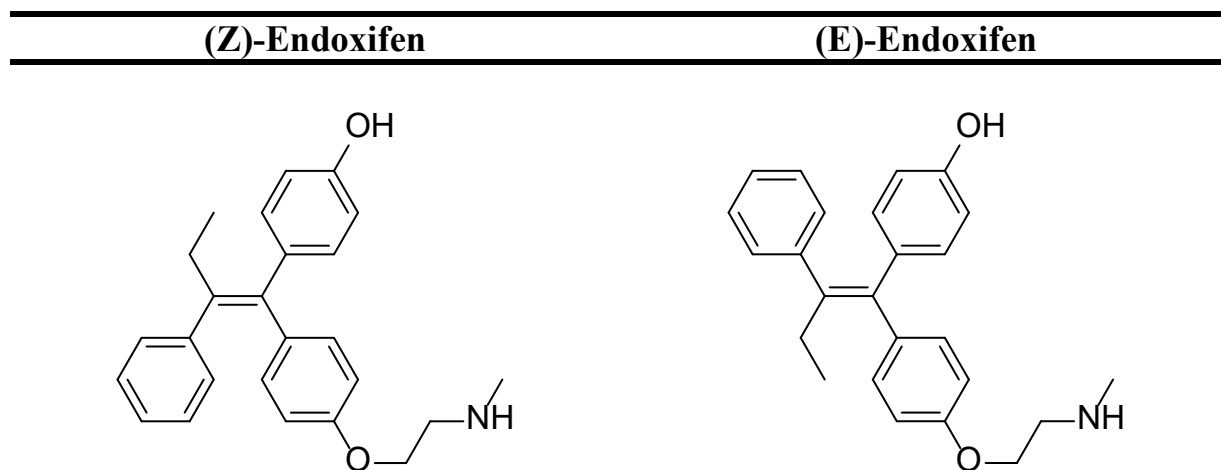
14. Endoxifen can be depicted as the below chemical structure, which is referred to as Formula (III) in the 151 patent:

Formula (III)



See, e.g., Ex. 1001 at 3:1-15.

15. The wavy line in the above structure is used to depict a chemical bond that can exhibit different possible stereochemical orientations. As such, the attached functional group, which in this example is an ethyl group (*i.e.*, Me, which can alternatively be expressed as  or CH₂-CH₃) can be oriented in space in two different ways. Molecules that have the same molecular formula but different orientations in space of certain bonds are called isomers. It was well-known in the art that “[e]ndoxifen exists as two forms, E and Z.” Ex. 1003 at [0004]. The structures (E)-endoxifen and (Z)-endoxifen are depicted below:



16. It was known in the art that (Z)-endoxifen is more active than (E)-endoxifen at the estrogen receptor. *Id.*

17. Methods of synthesizing highly pure (Z)-endoxifen were also well-known in the prior art. *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).”)

V. The 151 Patent

18. The 151 patent is entitled “Methods for Making and Using Endoxifen.” Ex. 1001 at Cover. I understand that the 151 patent is a U.S. National Phase Application of International Application No. PCT/US2018/050272, filed September 10, 2018 and claims priority to Provisional Application No. 62/556,799, dated September 11, 2017. *Id.* Thus, I have been instructed to use September 11, 2017 as the time of invention, and to consider my opinions from the perspective of a person of skill at that time.

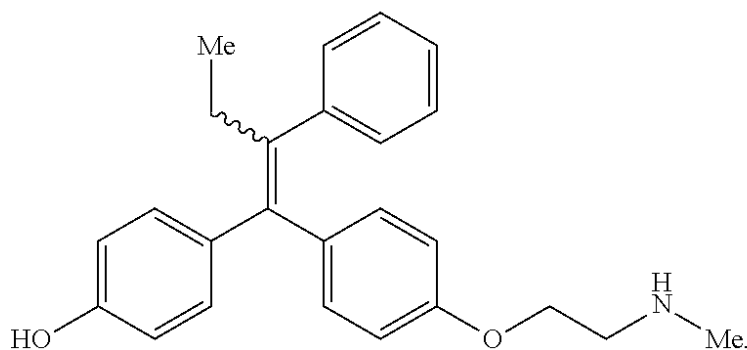
19. The 151 patent is directed to compositions of endoxifen that are at least 90% by weight of (Z)-endoxifen in a particular crystalline form (*i.e.*, Form I) and methods of administering such formulations.

20. I understand that the 151 patent contains the following 21 claims:

Independent Claim 1 and Dependent Claims 2-15 and 21

1. A composition comprising a crystalline form of a compound of Formula (III):

Formula (III)



wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

2. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $16.0 \pm 0.3^\circ$, $18.8 \pm 0.3^\circ$ and $26.5 \pm 0.3^\circ$ two theta.

3. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $12.3 \pm 0.3^\circ$, $28.0 \pm 0.3^\circ$ and $29.0 \pm 0.3^\circ$ two theta.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at $12.3 \pm 0.3^\circ$, $16.0 \pm 0.3^\circ$, $18.8 \pm 0.3^\circ$, $26.5 \pm 0.3^\circ$, $28.0 \pm 0.3^\circ$ and $29.0 \pm 0.3^\circ$ two theta.

5. The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10.
6. The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I.
7. The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent.
8. The composition of claim 7, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.
9. The composition of claim 7, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.
10. The composition of claim 7, wherein a mean half-life of the compound of Formula (III) in a subject treated with the composition is between 30 hours to 60 hours.
11. The composition of claim 1, formulated as an oral dosage form comprising 1 mg to 200 mg per unit dose of the composition, and wherein daily administration of the oral dosage form achieves in a subject treated with the composition one or more of:
 - a steady state plasma level of the compound of Formula (III) within 7 to 21 days;
 - a steady state plasma level of the compound of Formula (III) ranging from 25 nM to 300 nM;
 - a steady state plasma level of the compound of Formula (III) greater than 30 nM; or
 - maximal plasma levels of the compound of Formula (III) within 2 to 10 hours after administering.
12. The composition of claim 11, wherein a mean half-life of the compound of Formula (III) in the subject is between 40 hours to 55 hours.
13. The composition of claim 11, wherein the oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a

delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

14. The composition of claim 11, wherein at least 80% of the compound of Formula (III) in the oral dosage form is released in the intestines of the subject.

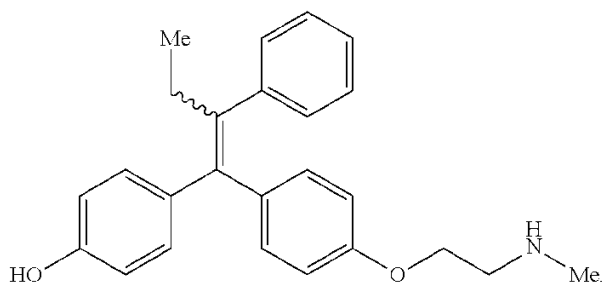
15. The composition of claim 11, having a mean area under the curve extrapolated to time infinity ($AUC_{0-\infty}$) of the compound of Formula (III) of 200 hr*ng/mL to 10000 hr*ng/mL.

21. The composition of claim 1, wherein the composition is stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity.

Independent Claim 16 and Dependent Claims 17-20

16. A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):

Formula (III)



wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

17. The method of claim 16, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

18. The method of claim 16, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

19. The method of claim 16, wherein the composition comprises 0.01 mg to 200 mg of the (Z)-isomer.

20. The method of claim 16, wherein a steady state plasma level of the compound of Formula (III) is achieved within 7 to 21 days of the first administration of the composition to the subject, and wherein the steady state plasma level of the compound of Formula (III) in the subject is greater than 30 nM.

VI. Person of Ordinary Skill in the Art

21. I understand that the content of a patent (including its claims) and prior art should be interpreted the way a person of ordinary skill in the art (or “POSA”) would have interpreted the material at the time of the alleged invention. In my opinion, a POSA for purposes of the 151 patent is a person with a graduate degree in organic chemistry, material science, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, analysis, design, and/or formulation of pharmaceutical compounds and derivatives.

22. I base my opinion on my review of the 151 patent, the problems the 151 patent was attempting to solve, the prior art discussed below, and my general experience with pharmaceutical synthesis and the people working in the field. I meet and/or exceed the definition of a POSA. I also note that my opinions would not change if the level of skill in the art were found to be lower.

VII. Claim Construction

23. I understand that terms should be given their plain and ordinary meaning to a person of skill at the time of invention. I have applied this principle to all terms in the 151 patent unless otherwise noted.

VIII. Summary of the Prior Art

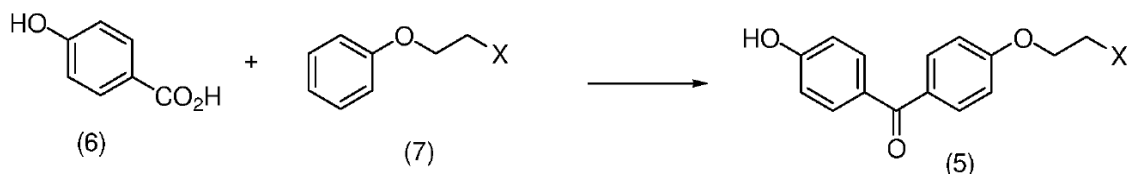
A. WO 2017/070651 (“Liu”)

24. I understand that International Application No. WO 2017/070651 (“Liu”) was filed on October 24, 2016, and published on April 27, 2017 and is therefore prior art to the 151 patent. Ex. 1003 at Cover.

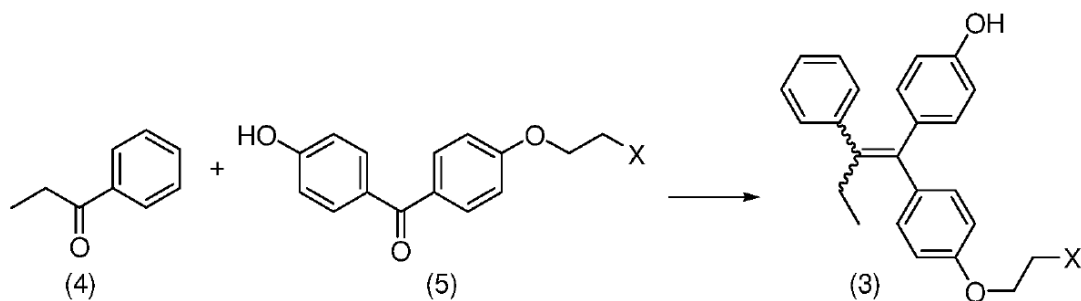
25. Liu teaches that “[e]ndoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor.” *Id.* at [0004]. Liu goes on to explain that “[e]ndoxifen is frequently synthesized as a mixture of E and Z, with a difficult separation of isomers required to obtain pure Z isomer” and that “[s]ome procedures in the art separate the E and Z isomers via methods which are expensive and difficult to perform on larger scale, such as preparative HPLC.” *Id.* “Thus there is a need in the art for a practical, scalable synthesis that gives access to highly pure (Z)-endoxifen.” *Id.*

26. Liu teaches a method for synthesizing and purifying (Z)-endoxifen with a 99% isomeric purity. *See, e.g., id.* at [0076]. Liu discloses a method for synthesizing what Liu refers to as the “input crystalline solid comprising a mixture of (Z)-endoxifen (1) and (E)-endoxifen (2).” *Id.* Liu’s synthesis begins with a first

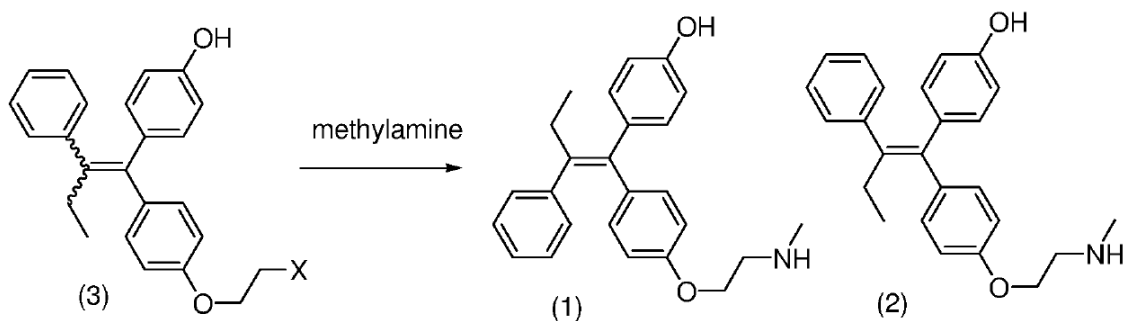
step of “generating the (4-(2-haloethoxy)phenyl)(4-hydroxyphenyl)methanone (5) by reacting 4-hydroxybenzoic acid (6) with 1-(2-haloethoxy)benzene (7).” *Id.* at [0035].



27. 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].



28. Following the above transformation, Liu teaches “generating the input crystalline solid by reacting 4-(1-(4-(2-haloethoxy)phenyl)-2-phenylbut-1-enyl)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].



29. The above process reported by Liu provides a mixture of (E) and (Z)-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.

30. Liu teaches that its “procedure provides a very attractive approach for obtaining the compound as it proceeds efficiently from commercially available starting materials and without the need of protection and de-protection steps.” *Id.* at [0005]. Liu’s procedure “avoids the use of chromatography in the separation of the Z- and E-isomers and enables facile scale-up operations in multi-kilogram quantities.” *Id.*

31. As described above, Liu’s process relies on sequential recrystallizations of a mixture of (E)- and (Z)-endoxifen to selectively crystallize (Z)-endoxifen and thus produce a final product that is highly enriched in (Z)-endoxifen (*i.e.*, up to 99% isomeric purity). A by-product of this process is (E)-endoxifen from the mixture that precipitates during the crystallization process. Liu further teaches a process for preparing highly pure (Z)-endoxifen from that by-product through an isomerization reaction followed by selective recrystallization. Liu explains 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.* 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 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.*

32. In addition to detailed disclosure of the synthesis and purification approach described above, *see id.* at [0017]-[0059], Liu also provides specific examples, including experimental protocols, of the preparation of (Z)-endoxifen having 99% isomeric purity. *See id.* at [0062]-[0077].

33. Liu does not report any X-ray powder diffraction (“XRPD”) data of the compounds Liu synthesized. Thus, Liu does not report whether its compounds exhibited the XRPD pattern recited in the claims of the 151 patent (*i.e.*, Form I). However, as I discuss in more detail below, I have conducted the synthesis of highly pure (Z)-endoxifen taught by Liu, including synthesis (starting from 4-hydroxybenzoic acid and 2-phenoxyethyl bromide), isomerization of (E)-endoxifen, and selective crystallization of a mixture of (E)- and (Z)-endoxifen. My testing confirms that Liu’s procedure provides (Z)-endoxifen with extremely high isomeric purity and that it exhibits an XRPD pattern consistent with Form I as claimed in the 151 patent.

B. Fauq, A.H., et al., *A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)*, 20 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 3036-3038 (2010) (“Fauq”)

34. Fauq discloses that “[a] mixture of the (Z)- and (E)-isomers of 4-hydroxy-N-desmethyltamoxifen [endoxifen] was conveniently prepared in four steps.” Ex. 1005 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 (“[W]e 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.”).

35. 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.

C. US 9,333,190 (“Ahmad”)

36. I understand that U.S. Patent No. 9,333,190 (“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 and is therefore prior art to the 151 patent. Ex. 1004 at Cover.

37. 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. 1004 at Abstract. 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.

38. As discussed above (*e.g.*, with respect to Liu), achieving such levels of purity was well known in the art. *See, e.g.*, Ex. 1003.

39. Ahmad further teaches that “[i]n some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.” Ex. 1004 at 4:41-44. Ahmad describes that “[w]hen desired, [the] composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach” and that the “term ‘enteric’ refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine.” *Id.* at 18:19-26. Ahmad discloses that “[m]ost enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.” *Id.*

40. Ahmad explains that the “compositions of the present invention can be employed to treat breast cancer and breast related diseases.” *Id.* at 18:47-66.

41. In sum, Ahmad teaches the use of enteric coated capsules of highly pure (Z)-endoxifen to treat breast cancer and other diseases, including hormone-dependent breast carcinoma. *See, e.g., id.* at 5:33-36.

42. I have been informed that a claim is not novel or non-obvious if the elements of the claim were known in one or more prior art references and a POSA

would have had a motivation to combine these references and a reasonable expectation of success at arriving at the claimed invention. I have also been informed that the motivation to combine can be found in the knowledge of a POSA and the state of the art. At least for the reasons set forth below, it is my opinion that a POSA would have been motivated to independently arrive at the claimed invention. Further, a POSA would have had a reasonable expectation of success at least because (i) the therapeutic advantages of Z-endoxifen over tamoxifen were well-known; and (ii) known synthesis methods at the time of the invention resulted in the claimed, inherent properties of “Form I” of Z-endoxifen. The claims do nothing to improve upon the then state of the art.

43. Although neither Liu nor Ahmad specifically disclose that their Z-endoxifen is the claimed “Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta,” at least Liu inherently discloses highly pure Z-endoxifen that exhibits such properties (*e.g.*, is in the claimed “Form I”). Indeed, as discussed in more detail below, I synthesized two samples of highly pure Z-endoxifen according to Liu’s disclosure and had the resulting Z-endoxifen analyzed by XRPD. As shown below, the XRPD results of my samples prepared by Liu’s recrystallization procedure (15-35-2P) and by Liu’s isomerization/recrystallization procedure (15-36-1P) confirmed that these procedures produce highly pure Z-endoxifen in the Form I claimed by the 151 patent.

The highlighted rows correspond to the XRPD peaks of Claim 1 of the 151 patent. Also below is a figure illustrating the XRPD patterns of my samples arranged for comparison with a stick pattern of the XRPD pattern data reported at Table 8 of the 151 patent (shown in blue), which corresponds to the XRPD patterns shown in Figures 9 and 10.

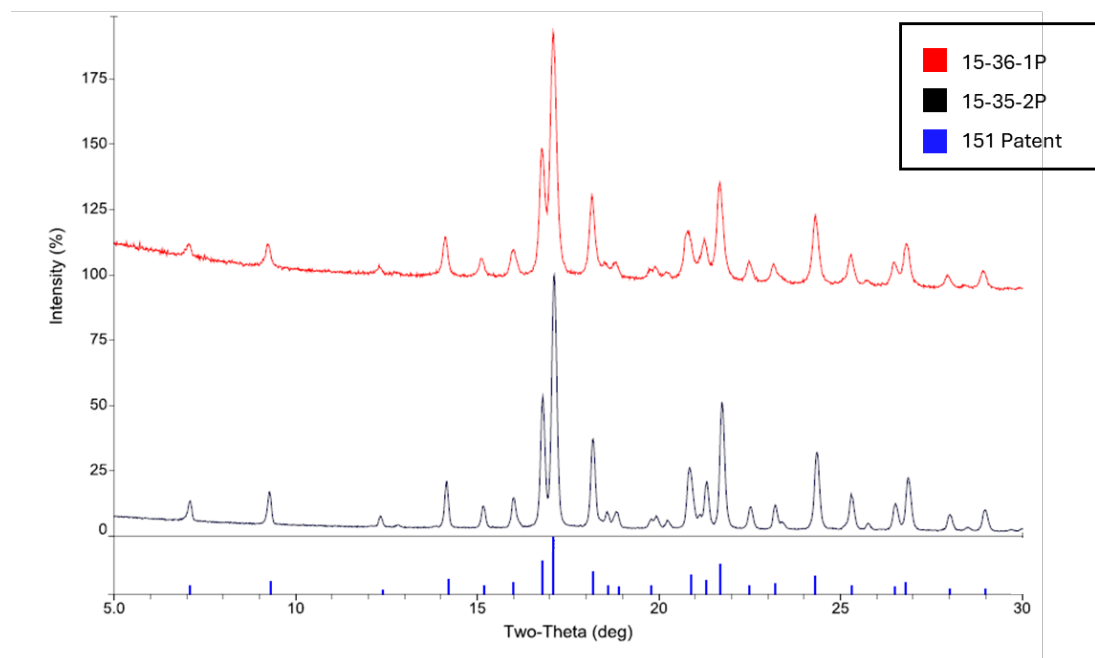
XRPD Results of My Sample 15-35-2P

2-Theta	d(Å)	Intensity (%)
7.092	12.454	7.80%
9.282	9.520	12.90%
12.329	7.173	4.30%
14.160	6.250	18.30%
15.167	5.837	8.50%
16.002	5.534	11.60%
16.803	5.272	51.70%
17.120	5.175	100.00%
18.189	4.873	34.60%
18.576	4.773	3.60%
18.827	4.710	6.60%
19.795	4.481	3.20%
19.929	4.452	4.40%
20.236	4.385	2.60%
20.848	4.258	23.90%
21.133	4.201	5.60%
21.315	4.165	15.40%
21.735	4.086	49.90%
22.532	3.943	8.60%
23.204	3.830	9.60%
23.386	3.801	2.80%
24.355	3.652	30.50%
25.296	3.518	13.70%
25.762	3.455	2.30%
26.513	3.359	10.30%
26.864	3.316	20.80%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

XRPD Results of My Sample 15-36-1P

2-Theta	d(Å)	Intensity (%)
7.0596	12.5113	5.3%
9.2221	9.5818	9.6%
12.2968	7.1921	3.3%
14.1140	6.2699	16.1%
15.1034	5.8613	7.4%
15.9991	5.5351	10.5%
16.7726	5.2815	52.0%
17.0879	5.1848	100.0%
18.1572	4.8818	32.8%
18.4964	4.7930	2.6%
18.8126	4.7132	2.4%
19.7344	4.4951	3.9%
19.8949	4.4592	4.8%
20.1986	4.3928	2.3%
20.7968	4.2678	19.3%
21.2492	4.1779	10.2%
21.6815	4.0956	39.9%
22.4860	3.9508	7.7%
23.1546	3.8382	7.5%
24.3068	3.6588	28.3%
25.2900	3.5188	12.1%
25.7163	3.4614	1.7%
26.4785	3.3635	9.3%
26.8135	3.3222	18.1%
27.9493	3.1897	5.2%
28.9206	3.0848	7.1%
30.7185	2.9082	1.3%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

XRPD Results of Liu's Procedures
Compared to the 151 Patent

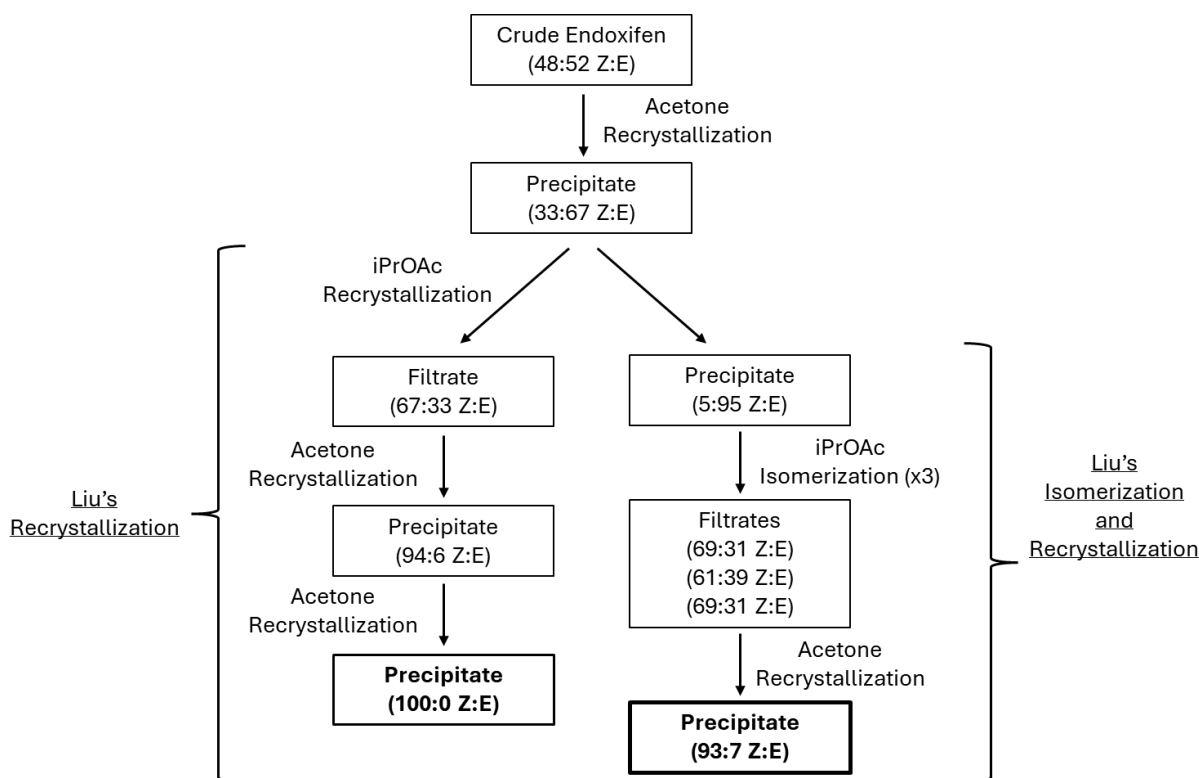


IX. Laboratory Testing of Methods Taught by Liu

44. 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 defined above (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 or undue experimentation to carry out Liu's teachings.

45. I reproduced methods of synthesis and purification disclosed by Liu. Liu reports synthesis of a 51:47 mixture of (Z)- and (E)-endoxifen and several methods for purification of (Z)-endoxifen. Ex. 1003 at [0060]-[0077]. As illustrated below, I reproduced the following methods as taught by Liu: (i) synthesis followed

by sequential recrystallizations, *id.* at [0018]-[0072] and [0076], and (ii) synthesis followed by isomerization and recrystallization. *Id.* at [0046]-[0055] and [0073]-[0076]. These approaches, consistent with Liu's teachings, afforded (Z)-endoxifen with isomeric purities of 100% and 93%, respectively. I describe in detail below the experimental protocols I followed as well as the results of those experiments.



46. Throughout the course of these experiments, I employed various analytical tools. For example, thin layer chromatography ("TLC") was employed to monitor reaction progress throughout the synthesis using silica gel plates. Endoxifen was eluted with a DCM:MeOH:NH₄OH (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_6 (“DMSO- d_6 ”) or $CDCl_3$. NMR spectra of (E)- and (Z)-endoxifen were consistent with data reported by Liu (Ex. 1003 at [0076]) as well as other literature. *See, e.g.*, Ex. 1023 (supplement to Ex. 1022), Figure S2, S4; Ex. 1024 at note 10, Ex. 1025 (supplement to Ex. 1005) at S8; Elkins, *Characterization of the isomeric configuration and impurities of (Z)-endoxifen by 2D NMR, high resolution LC MS, and quantitative HPLC*, 88 J. PHARMACEUTICAL AND BIOMEDICAL ANALYSIS 174-179 (2014) (Ex. 1026). I also utilized NMR to determine the ratios of the (E)- to (Z)-endoxifen through integration of NMR signals at δ 3.85 and 4.01 ppm, respectively, as is common in the art. My NMR spectra are attached as Appendix B. I note that Dr. Davies, Patent Owner’s expert in a prior proceeding, agreed that “[u]sing the teachings of Elkins, it is possible to ascertain the presence and relative concentrations of (E)-endoxifen and (Z)-endoxifen as taught by others where ^1H NMR data is reported.” PGR2023-00043 at Ex. 2020, ¶¶84-85; *see also* ¶91.

47. I made some minor adjustments compared to Liu’s Examples. Each of these adjustments were routine adjustments a POSA following Liu would have likely made. In my opinion, none of the modifications had any impact on the resulting crystalline solids. Importantly, the polymorphic form that a crystal adopts is driven

by the final crystallization of the material. With respect to Liu's crystallization of a mixture of (E)- and (Z)-endoxifen to produce greater than 90% (Z)-endoxifen, I followed Liu extremely closely. Thus, to the extent that I made any adjustments compared to the large-scale synthetic protocols described in Liu's Examples, these adjustments did not impact the final crystalline form of (Z)-endoxifen (e.g., "Form I").

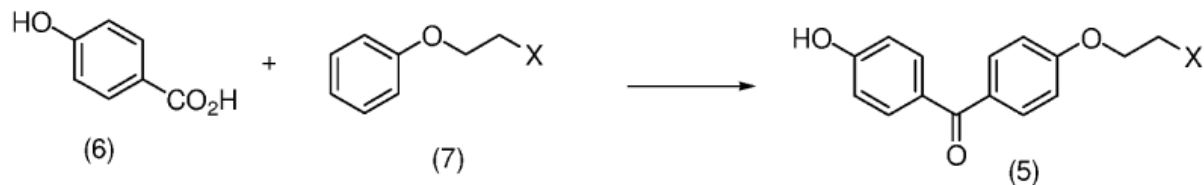
48. For example, I performed Liu's method on a smaller scale than disclosed in Liu's Examples (which is on a large, commercial manufacturing scale). However, there is no indication that performing Liu's method on a smaller scale would result in a different compound than the claimed Form I of Formula (III), *i.e.*, (Z)-endoxifen. While Liu's Examples are performed on a particular scale, Liu does not state anywhere that its method can **only** be run at a particular scale. Indeed, Liu merely suggests that its procedure is "a practical, **scalable** synthesis"—not that the synthesis has to be performed at a certain scale. *See* Ex. 1003 at [0004]; *see also id.* at [0005] ("This disclosure is directed to a new process for the preparation of the active metabolite of tamoxifen, (Z)-endoxifen."). Other minor adjustments that I made compared to Liu's Examples are described below.

A. Synthesis of a Mixture of (E)- and (Z)-Endoxifen as Taught by Liu

49. 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 Liu, including Examples 2-4 of Liu. Ex. 1003 at [0062]-[0070].

50. First, I synthesized 4-(2-bromoethoxy)phenyl(4-hydroxyphenyl)-methanone (5) from the reaction between 4-hydroxybenzoic acid (6) and 2-phenoxyethyl bromide (7). This reaction, shown below, is described by Liu in [0035]-[0038], and a detailed experimental protocol is described by Liu in Example 2. *Id.* at [0062]-[0064].



Id. at [0035].

51. I synthesized compound (5) by a modification of the procedure described by Liu at [0062]-[0063]. Initially when I performed this reaction on a small scale at 45 to 50 °C for 1 hour, I observed that the reaction was incomplete by TLC. After two more preliminary experiments, I performed the reaction at 70 °C as follows: I added zinc bromide¹ (27.1 g) to polyphosphoric acid (149 g). I added 4-

¹ Prior to using, I dried the zinc bromide at 230 °C. While Liu does not specify how the zinc bromide was dried, Liu does state that “[t]he reagents and solvents used

hydroxybenzoic acid (8.77 g) and 2-phenoxyethyl bromide (14.1 g) and stirred and heated the mixture to 55 °C (internal temperature). I then added phosphorus tribromide (24.51 g) while stirring mechanically under a nitrogen atmosphere. No increase in temperature occurred. The mixture was slowly heated to 68 to 70 °C over 1 hour, then stirred at 70 °C (internal temperature) for 5 more hours, at which time TLC² showed that the reaction was mostly complete.

52. I poured the reaction mixture onto ice water (360 mL) and allowed the mixture to sit at 5 °C overnight. I stirred and shook the aqueous mixture with ethyl acetate and vacuum filtered it through Celite to break up the emulsion.³ I rinsed the

were commercial anhydrous grade.” Thus, a POSA would understand that zinc bromide, a hygroscopic reagent, should be dried prior to use in this synthesis.

² I performed TLC by treating very small aliquots of the reaction mixture with water and extracting the resulting mixture with ethyl acetate.

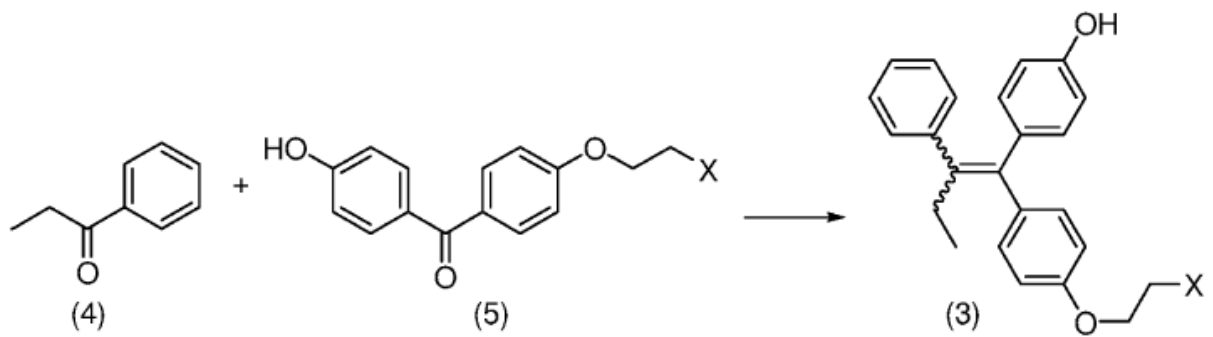
³ While Liu states that the mixture is filtered, Liu does not explicitly state to use Celite at this step. A POSA would have understood that Celite is a commonly employed filtration medium to break up an emulsion and/or remove fine particles from a solution. Indeed, Liu reports using Celite in the following step to remove Zinc power. *See* Ex. 1003 at [0065].

precipitate with ethyl acetate and extracted the aqueous layer three times with ethyl acetate. I rinsed the combined ethyl acetate layers twice with water and once with brine, and dried it over MgSO₄. The supernatant was evaporated in vacuo to provide the crude product. The resulting solid was then dissolved in ethyl acetate, absorbed onto silica gel (40 g), and the ethyl acetate was removed in vacuo. The product was purified by column chromatography⁴ on silica gel (7 X 30 cm) and eluted with petroleum ether – ethyl acetate (60:40) to afford 4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone (9.37 g, 15-23-1a) as a red wax as confirmed by NMR

⁴ While Liu does not specifically describe using chromatography in [0062], Liu teaches that chromatography should be employed after the following reaction in Example 3, described below. *Id.* at [0066]. Therefore, I decided to employ chromatography at this step as well to further purify the material. A POSA would understand that chromatography would have been a commonly used purification strategy that could be employed at this stage. While it is often desirable to minimize the number of chromatography steps in a commercial scale synthesis, such as that taught in Liu's examples, this was not a concern at the smaller scale I was using. A POSA would understand this would have no effect on the final crystal form of the (Z)-endoxifen.

and mass spectroscopy of a sample from a preliminary experiment: ^1H NMR (500 MHz, CD_3OD) δ 3.75 (t, 2H), 4.42 (t, 2H), 6.88 (d, 2H), 7.06 (d, 2H), 7.68 (d, 2H), 7.74 (d, 2H). Mass spec 321, 323 ($\text{M}+\text{H}$) $^+$, 343, 345 ($\text{M}+\text{Na}$) $^+$.

53. With compound (5) in hand, I synthesized 4-(1-4-(2-bromoethoxy)phenyl)-2-phenylbut-1-enyl)phenol (3) from the reaction between compound (5) and propiophenone (4). This reaction, shown below, is described by Liu at [0032]-[0034], and a detailed experimental protocol is described by Liu in Example 3. *Id.* at [0065]-[0067].



Id. at [0032].

54. I synthesized compound (3) according to the procedure described by Liu at [0065]-[0067]. First, I suspended zinc dust (32.23 g) in anhydrous

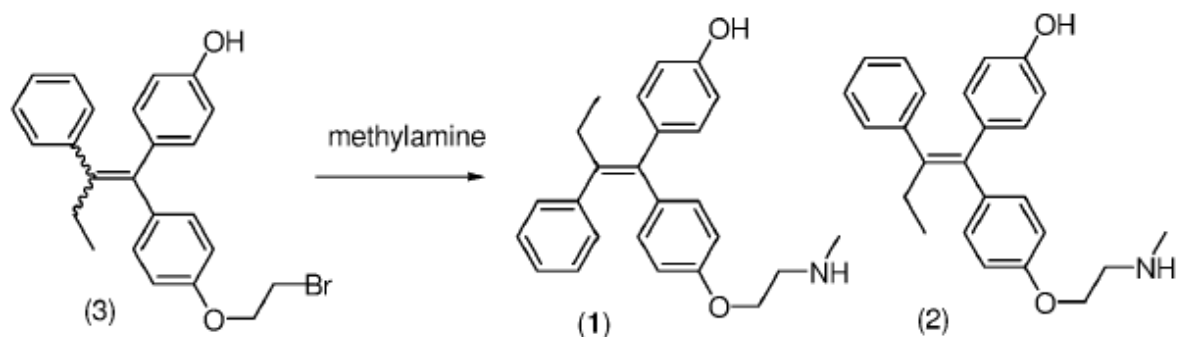
dimethoxyethane (190 mL). I then placed the mixture under nitrogen⁵ and cooled the mixture in an ice bath under a nitrogen atmosphere. I added titanium tetrachloride (26.4 mL) over the course of about one-half hour. I refluxed the mixture at 100 °C (bath temperature) for 1 hour and then cooled it in an ice bath. I added a mixture of propiophenone (4.09 g) and compound (5) (9.99 g) dissolved in dimethoxyethane (75 mL) and refluxed the mixture at 100 °C (bath temperature) for 6 hours. Stirring became impossible after 5 minutes. I maintained the mixture at ambient temperature overnight then cooled it in an ice bath. Methyl *t*-butyl ether (220 mL) and 5% aqueous HCl solution (98 mL) were slowly added and the mixture was stirred for 2 hours at room temperature. The organic layer was separated and the aqueous layer was vacuum filtered through Celite to remove any remaining zinc powder as described by Liu. *Id.* at [0065]. The organic phase and the precipitate were extracted three times with methyl *t*-butyl ether. The combined organic extracts were washed

⁵ Liu states that the suspension was placed under an argon atmosphere. Ex. 1003 at [0065]. Instead of an argon atmosphere, I placed the reaction under a nitrogen atmosphere. A POSA would understand that nitrogen could be used in place of argon to achieve an inert atmosphere.

three times with brine and then dried over MgSO₄. The MgSO₄ was separated and the solvent was removed in vacuo to provide 13.89 g of a brown oil.

55. The resulting oil was purified by column chromatography on silica gel (7.5 X 26 cm) using methylene chloride as an eluent as described by Liu. *Id.* at [0066]. The solvent was removed in vacuo. The resulting slight amber oil (9.43 g) was suspended in *n*-heptane (22 mL) at 45°C and then stirred at ambient temperature for 16 hours. The precipitate was collected by vacuum filtration and dried in air, then in vacuo for 72 hours at ambient temperature to afford a mixture of (E)- and (Z)-4-(1-(4-(2-bromoethoxy)phenyl)-2-phenylbut-1-enyl)phenol (3) (7.72 g, 15-25-1as) as a pale orange semisolid, mp ~65 – 75. NMR. (500 MHz, CDCl₃): δ 0.92 (2 X 3H, t), 2.47 (2 X 2H, m), 3.55 (2H, t), 3.66 (2H, t), 4.15 (2H, t), 4.31 (2H, t), 4.46 (1H, s), 4.68 (1H, s), 6.46 (2H, d), 6.54 (2H, d), 6.72 (2H, d), 6.78 (2H, d), 6.80 (2H, d), 6.89 (2H, d), 7.1-7.2 (14H, m).

56. Next, I used compound (3) to synthesize a mixture of (E)- and (Z)-endoxifen through the reaction between compound (3) and methylamine. This reaction, shown below, is described by Liu at [0057], and an example of a detailed experimental protocol is described by Liu in Example 4. *Id.* at [0068]-[0071]. In the reaction scheme from Liu below, compound (1) is (Z)-endoxifen and compound (2) is (E)-endoxifen.



Id. at [0057].

57. I synthesized a mixture of (E)- and (Z)-endoxifen as described by Liu at [0068]-[0071]. First, I mixed compound (3) (7.72 g) with a 33% methylamine solution in absolute ethanol (232 mL). I heated the reaction mixture to 33-35 °C for 21 hours in a sealed flask and then evaporated the solvent in vacuo to give a lilac foam (9.00 g). I then dissolved this solid in dichloromethane (90 mL) and washed it with a mixture of NaHCO₃ (7.23 g) and Na₂CO₃ (3.895 g) in water (90 mL). I re-extracted the aqueous phases with dichloromethane (45 mL) and dried the combined organic extracts over Na₂SO₄. I evaporated the solvent to obtain a solid material. I then added acetone and evaporated the acetone in vacuo twice (20 mL and 10 mL, respectively) to obtain the mixture of (E)- and (Z)-endoxifen (7.18 g, 15-27-1) as a pink foam which became an amorphous solid after drying in vacuo for several days at ambient temperature. *See id.* at [0070]. TLC indicated an inseparable mixture of (E)- and (Z)-endoxifen and several minor impurities. NMR indicated a 52:48 ratio

of (E)- to (Z)-endoxifen. *See id.* The NMR spectrum for this product was consistent with the NMR data reported by Liu. *See id.* at [0071].

58. The NMR spectra for the compounds I synthesized according to Liu's procedures are attached to this declaration as Appendix B. The lab notebook reflecting this work is attached to this declaration as Appendix C.

59. Liu's synthesis of the mixture of (E)- and (Z)-endoxifen included a recrystallization step. Thus, I performed a recrystallization of the 52:48 ratio of (E)- to (Z)-endoxifen mixture using acetone as taught by Liu. *Id.* at [0070] ("Acetone was added to the solid then removed in vacuo twice...to give a solid...."). To that end, I dissolved the crude 52:48 mixture of (E)- and (Z)-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. *Id.* ("[T]he resulting clear solution was slowly cooled to 20 °C for 19 hours and then kept in refrigerator at -10 °C for 4 days."). The cold mixture was quickly centrifuged to isolate the solid precipitate.⁶ *Id.* ("The resulting crystalline material was collected by filtration....").

⁶ 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. Additionally, Liu

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). *Id.* (“The resulting crystalline material (100 g) was collected by filtration and dried in vacuo....”). NMR of the precipitate indicated a 67:33 ratio of (E)- to (Z)-endoxifen. *Id.* at [0070]-[0071] (51/47 ratio of E/Z disclosed by Liu).

B. Sequential Recrystallizations of a Mixture of (E)- and (Z)-Endoxifen to Produce Highly Pure (Z)-Endoxifen as Taught by Liu

60. I then dissolved this precipitate⁷ (761 mg, 15-33-1P) of 67:33 mixture of (E)- and (Z)-endoxifen in refluxing isopropyl acetate (“iPrOAc”) (7.61 mL) while

teaches that the solid from the crystallization can be separated from the mother liquor by “filtration, decanting, aspiration, or any suitable method.” Ex. 1003 at [0021]. Filtration and centrifugation are both well-known techniques for isolating solids, and have been well-known long before September 11, 2017, and a POSA would have understood centrifugation to be a “suitable method” as described by Liu. Further, a POSA would understand this has no effect on the final crystal form of (Z)-endoxifen.

⁷ As discussed herein, I synthesized crude endoxifen following the procedure outlined in Liu. I then used this crude endoxifen as the starting material in following Liu’s Example 5. Liu, however, obtained a crude endoxifen mixture with a slightly different ratio of E:Z endoxifen (Liu: 51/47 ratio of E/Z; my synthesis: 67:33 ratio

stirring, then cooled slowly and stored it at 23 °C for 6 hours. *Id.* at [0072] (“[E]ndoxifen...was dissolved in 55L of hot isopropyl acetate at 88 °C. The clear solution was slowly cooled to 23 °C and kept for 6 hours.”). 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.* (“The crystalline material was collected in a filter funnel, washed with isopropyl acetate and dried in vacuo to a constant

of E/Z). *See* Ex. 1003 at [0072]. This is a distinction without a difference. In fact, my use of a started material with a **lower** (Z)-endoxifen content than Liu started with, indicates the robustness of Liu’s teachings in synthesizing highly pure (Z)-endoxifen.

Moreover, Liu’s method does not **require** a 1:1 ratio of (E):(Z)-endoxifen for the method to work. Indeed, despite Liu’s specific example using a starting mixture of approximately 1:1 (E):(Z)-endoxifen, Liu expressly contemplates crystallizing a mixture containing less than a 1:1 ratio. *Id.* at [0018] (“It has been unexpectedly discovered that isopropyl acetate (iPrOAc) can equilibrate a mixture of (Z)-endoxifen (1) and (E)-endoxifen (2) containing **less than 50%** (Z)-endoxifen....” (emphasis added)).

weight....”). NMR indicated this precipitate consisted of a 95:5 ratio of (E)- to (Z)-endoxifen. *Id.* (68/30 ratio of E/Z disclosed by Liu). Evaporation of the filtrate in vacuo afforded a pink solid (418 mg, 15-34-1S), which according to NMR had a 33:67 ratio of (E)- to (Z)-endoxifen. *Id.* (“The filtrate was concentrated to give a solid which was dried in vacuo to a constant weight to produce 2666 g (48%) of material enriched with the Z-isomer (E/Z-ratio:19/77)”).

61. This dried filtrate was then subjected to recrystallization as taught by Liu’s Example 7. *Id.* at [0076]-[0077]. I dissolved the dried filtrate (416 mg, 15-34-1S) in refluxing acetone (4.1 mL), then cooled and stirred for 40 hours at 4 °C. *Id.* at [0076] (“Endoxifen (5013 g, E/Z ratio ~30/7) was dissolved in 50 L of acetone which was heated to reflux in a 100-L reactor. The resulting solution was cooled and stirred for 40 hours at 1 to 5 °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. *See id.* at [0026] (“[T]hen the resulting solution is cooled to -10 to 20 °C or 0 to 10 °C, and held at the second temperature for 0.5 hours to 10 days or 2 to 72 hours. In some cases longer holding times at the second temperature may be required.”). 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.

62. This precipitate (147 mg, 15-35-1P) was then dissolved in refluxing acetone (2.2 mL), filtered while hot to remove a slight precipitate, then cooled and stirred for 50 hours at 4 °C. *Id.* at [0076] (“The remaining crystalline material was re-dissolved in boiling acetone (52 L). The resultant solution was stirred for 50 hours at 1 to 5 °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). *Id.* at [0076] (“The crystalline material which precipitated was collected by filtration and washed with ice-cooled acetone. The solid was dried in vacuo at 35 °C to a constant weight to give 1698 g (34%) of (Z)-endoxifen....”). NMR of this precipitate indicated a 100:0 ratio of (Z)- to (E)-endoxifen.⁸ *Id.* (99:1 (Z)- to (E)-endoxifen). (Z)-endoxifen: ¹H NMR (500 MHz, DMSO-d₆): δ 0.84 (t, 3H), 2.27 (s, 3H), 2.40 (q, 2

⁸ I did not perform the third recrystallization as discussed in Liu’s Example 7, *see* Ex. 1003 at [0076] (“The remaining crystalline material was again dissolved in boiling acetone (48 L). The hot solution was filtered and kept for 22 hours at 1 to 5 °C.”), because I had already obtained a ratio of 100:0 of (Z)- to (E)-endoxifen. Thus, there was no need to perform an additional recrystallization procedure on already pure (Z)-endoxifen.

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).

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

C. Isomerization of (E)-Endoxifen Followed by Sequential Recrystallizations to Produce Highly Pure (Z)-Endoxifen as Taught by Liu

64. As discussed 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.

65. As described above, I prepared a 52:48 ratio of (E)- to (Z)-endoxifen according to the method taught by Liu. *See id.* at [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. *See id.* at [0072]. As discussed above, 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). *See id.* at [0076]-[0077]. The crystalline precipitate enriched in (E)-endoxifen provided from Liu's process was then

subjected to the isomerization procedure taught by Liu's Example 6. *Id.* at [0073]-[0075].

66. 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. *Id.* at [0073] ("Endoxifen (2721 g, E/Z ratio ~70/30,) was suspended in isopropyl acetate (27 L) in a 100-L reactor. The suspension was heated at 85 °C for 2 hours."); *see also id.* at [0046] ("[H]eating at a temperature from 60 to 100°C for 0.5 to 4 hours, to produce an isomerized solution..."). The mixture was cooled slowly and kept at 15 °C for 2 days. *Id.* at [0073] ("The mixture was cooled slowly to 15°C, resulting in the preferential crystallization of the E-isomer."). The precipitate was collected by vacuum filtration, rinsed with iPrOAc (0.2 mL) at 15 °C, and dried in vacuo at 35 °C in vacuo to afford white crystals (182 mg, 15-34-2P). *Id.* ("The mother liquor (containing 71% Z-isomer) was removed from the reactor, evaporated to provide a solid and dried at 35°C to constant weight: 1314 g (48%, Z-isomer content: 73%)."). NMR of the crystalline precipitate indicated a 5:95 ratio of (Z)- to (E)-endoxifen. (E)-Endoxifen ¹H NMR (500 MHz, DMSO-d₆): 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).

67. 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.

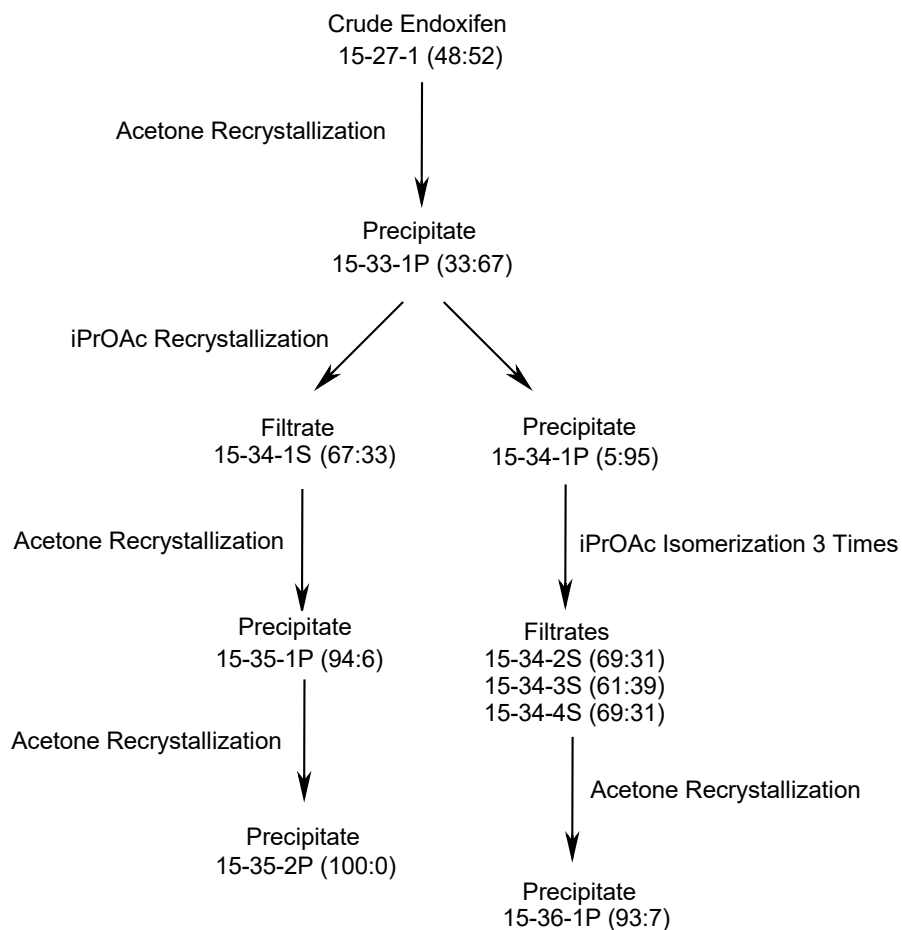
68. The above isomerization procedure was repeated two times as taught by Liu. *Id.* at [0074] (“The above operations were repeated twice with the residual E-isomer crystals in the reactor to provide two additional crops of Z-enriched material.”) Thus, I isomerized the above endoxifen precipitate from 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.

69. The filtrate was evaporated in vacuo to afford 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 cooled the solution 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. *Id.* at [0075] (96% (E)-endoxifen). The filtrate afforded a colorless glass (50 mg, 15-34-4S). NMR indicated a 69:31 ratio of (Z)- to (E)-endoxifen. *Id.* at [0074] (86% (Z)-endoxifen).

70. Then, 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. *Id.* 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 88 hours at 4 °C. *Id.*; *see also id.* at [0026] (“[T]hen the resulting solution is cooled to -10 to 20 °C or 0 to 10 °C, and held at the second temperature for 0.5 hours to 10 days or 2 to 72 hours. In some cases longer holding times at the second temperature may be required.”). Precipitation appeared to be complete after 64 hours. After a total of 88 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). *Id.* at [0076]. NMR indicated a 93:7 ratio of (Z)- to (E)-endoxifen. (Z)-endoxifen: ¹H NMR (500 MHz, DMSO-d₆): 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).

71. 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.



72. 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.

73. In sum, my experiments confirm that Liu’s methods work as Liu teaches—to produce highly pure (Z)-endoxifen. As such, the methods taught by Liu would have enabled a POSA to achieve highly pure (Z)-endoxifen at the time of the invention of the 151 patent. Indeed, my experiments following Liu’s procedures

provided (Z)-endoxifen with isomeric purities of 100% (recrystallization) and 93% (isomerization followed by recrystallization).

D. X-Ray Powder Diffraction of the Highly Pure (Z)-Endoxifen Obtained Following the Procedures Liu

74. As described above, I followed the procedures outlined in Liu to obtain highly pure (Z)-endoxifen. I sent the resulting crystalline solids of the (Z)-endoxifen to Dr. Steve Miller at H & M Analytical Services for XRPD testing. As discussed in Dr. Miller's declaration, the XRPD testing confirmed that the (Z)-endoxifen I obtained following Liu's procedures were the claimed "Form I."

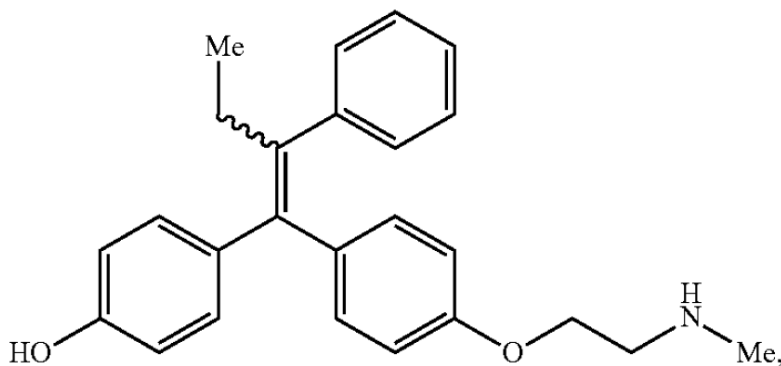
X. Claims 1-6, 16, 18, and 21 in View of Liu

75. I incorporate by reference Drs. McConville's and Miller's discussions of the claims in view of Liu.

A. Independent Claim 1

1. A composition comprising a crystalline form of a compound of Formula (III):

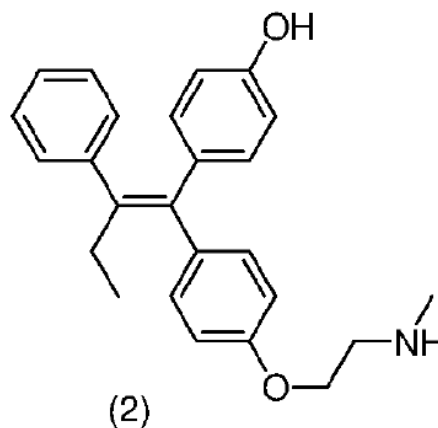
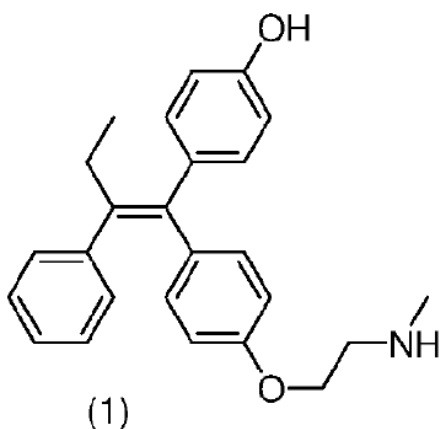
Formula (III)



wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer

76. Formula (III) recited in the claims is endoxifen (including E- and/or (Z)-endoxifen). *See* Ex. 1001 at 8:15-16. As described in the 151 patent, Formula (III) can include the polymorphic salt, free base, co-crystal, and/or solvate forms of (Z)-endoxifen. *See id.* at 12:48-52.

77. Liu teaches “a process for preparing (Z)-endoxifen” with “a ratio of (Z)-endoxifen (1) to (E)-endoxifen (2) greater than 20:1.” Ex. 1003 at Abstract.



Specifically, Liu teaches the use of crystallization procedures to purify (Z)-endoxifen from a mixture of (E)- and (Z)-endoxifen. *Id.* Liu further teaches that the (E)-isomer can be converted to the (Z)-isomer by isomerization, which increases the yield of (Z)-endoxifen. *Id.* at [0073]-[0076]. Liu teaches that his method results in a (Z)-endoxifen crystalline material with “an isomeric purity of 99% (HPLC analysis).” *Id.* at [0076]. Liu’s synthesis forms the free base of (Z)-endoxifen.

78. Thus, Liu teaches a composition comprising a crystalline form of a compound of Formula (III) wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer. Further, as evidenced by my reproduction of Liu’s teachings, Liu provides an enabling disclosure to a POSA.

[...] wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

79. I incorporate by reference Dr. Miller’s discussion of claim 1. As shown by Dr. Miller, Liu inherently discloses that the (Z)-endoxifen formed by following

its procedures is the claimed “Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8\pm 0.3^\circ$, $17.1\pm 0.3^\circ$ and $21.8\pm 0.3^\circ$ two theta.”

See Miller at ¶¶30-31.

B. Dependent Claims 2-5

2. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $16.0\pm 0.3^\circ$, $18.8\pm 0.3^\circ$ and 26.5 ± 0.3 two theta.

3. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $12.3\pm 0.3^\circ$, $28.0\pm 0.3^\circ$ and $29.0\pm 0.3^\circ$ two theta.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at $12.3\pm 0.3^\circ$, $16.0\pm 0.3^\circ$, $18.8\pm 0.3^\circ$, $26.5\pm 0.3^\circ$, $28.0\pm 0.3^\circ$ and $29.0\pm 0.3^\circ$ two theta.

5. The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10.

80. I incorporate by reference Dr. Miller’s discussion of claims 2-5. As shown by Dr. Miller, Liu inherently discloses that the (Z)-endoxifen formed by following its procedures is the claimed “Form I,” characterized by the claimed XRPD peaks.

C. Dependent Claim 6

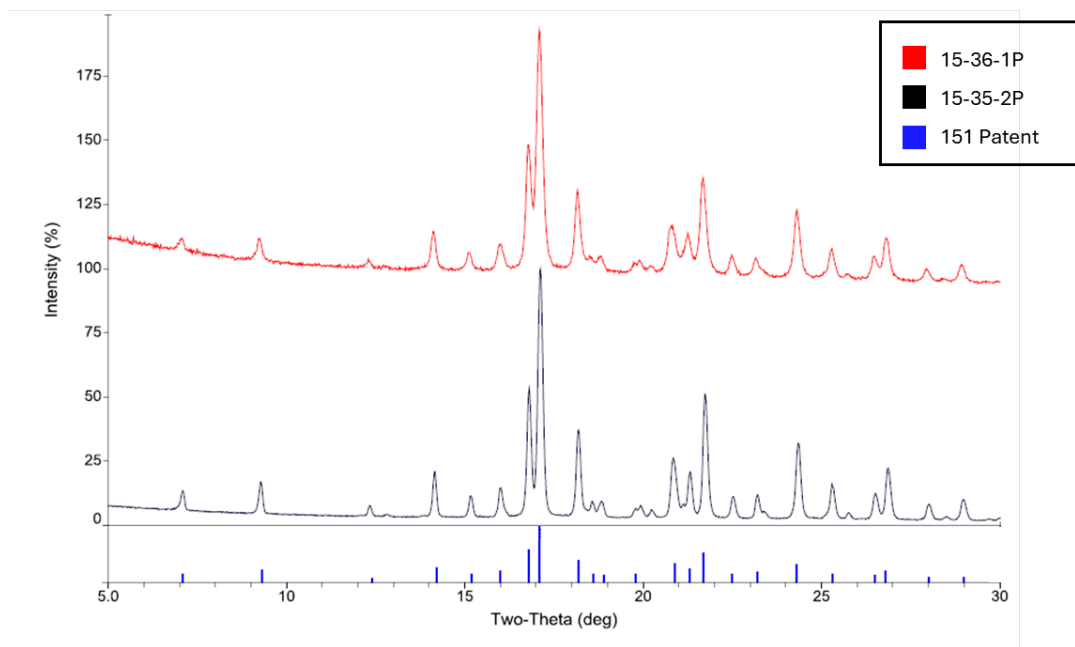
6. The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I.

81. As described above, Liu teaches a method a preparing (Z)-endoxifen that results in a (Z)-endoxifen crystalline material with “an isomeric purity of

99%....” Ex. 1003 at [0076]. My experiment following Liu’s procedure confirms this. *See supra* (obtaining 93% and 100% of (Z)-endoxifen).

82. The 151 patent defines Form I as exhibiting an XRPD pattern substantially as shown in Figure 9 or 10. Ex. 1001, 30:48-51. As discussed above, the (Z)-endoxifen that I prepared by the methods taught by Liu exhibit the claimed XRPD pattern (as shown below). *See Miller* at ¶¶30-31. The samples I synthesized following Liu consisted of greater than 90% (Z)-endoxifen and exhibited XRPD patterns completely consistent with Form I. My samples exhibited no XRPD peaks attributed to forms other than Form I. Thus, at least 90% of the (Z)-endoxifen of Liu would be in the claimed Form I.

XRPD Results of Liu’s Procedures
Compared to the 151 Patent

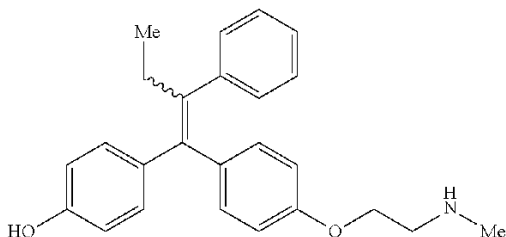


83. Therefore, Liu inherently teaches (Z)-endoxifen in the claimed Form I, and “wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I” as recited in claim 6.

D. Independent Claim 16

16. A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):

Formula (III)



wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8\pm0.3^\circ$, $17.1\pm0.3^\circ$ and $21.8\pm0.3^\circ$ two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

84. Liu teaches that (Z)-endoxifen may be used to treat hormone-dependent breast disorders. For example, Liu explains that (Z)-endoxifen is more active at the estrogen receptor, and therefore may be used to treat breast cancer. Ex. 1003 at [0002]-[0004]. Therefore, Liu discloses a method of using highly pure (Z)-endoxifen to “treat[] a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject” as recited in claim 16 of the 151 patent.

85. And as discussed above with respect to claim 1 (and as discussed in more detail in Dr. Miller’s declaration, which is incorporated herein by reference),

Liu inherently teaches that its (Z)-endoxifen is in the claimed “Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8\pm0.3^\circ$, $17.1\pm0.3^\circ$ and $21.8\pm0.3^\circ$ two theta.”

E. Dependent Claim 18

18. The method of claim 16, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

86. Tamoxifen has long been used to treat breast cancer. Ex. 1001 at Fig. 1, 1:61-2:4; Ex. 1003 at [0003]; Ex. 1004 at Fig. 3, 1:35-56. It was well-known in the art that (Z)-endoxifen is a metabolite of tamoxifen, and thus could be used on patients who could not metabolize or had difficulty metabolizing tamoxifen, leading them to be tamoxifen-refractory or tamoxifen-resistant. *See, e.g.*, Ex. 1003 at [0003]. For example, Liu describes that “[t]amoxifen’s efficacy relies on metabolism in the liver by cytochrome P450 isoforms CYP2D6 and CYP3A4 to transform tamoxifen into the active metabolites, 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen).” *Id.* Liu further teaches that the Z-isomer of endoxifen is “more active at the estrogen receptor.” *Id. at* [0004]. Liu also 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....” *Id.* Therefore, Liu teaches a method of using (Z)-endoxifen to treat

tamoxifen-refractory or resistant conditions, such as a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject with tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

XI. Claims 1-21 in View of Liu, Ahmad, and the Knowledge of a POSA

87. I incorporate by reference my discussion of the claims in Ground 1 above. I also incorporate by reference Dr. McConville's discussion of the claims in in view of Liu, Ahmad, and the knowledge of a POSA.

A. Claims 1-6, 16, and 18

88. The knowledge within the art at the time of the 151 patent's claimed priority date reinforces that Liu anticipates the 151 patent or, alternatively, renders the 151 patent obvious in view of Liu and the knowledge of a POSA that existed at the time. For example, although Liu discloses every element of claims 1-6, 16, and 18 of the 151 patent (as discussed above), each of the elements of these claims were also separately known and obvious in view of the knowledge of a POSA.

89. For example, it was well-known to a POSA that (Z)-endoxifen is an active metabolite of tamoxifen, which has been used in the treatment of breast cancer. Ex. 1001 at Fig 1, 1:61-2:4; Ex. 1003 at [1003]; Ex. 1004 at Fig. 3, 1:32-56. It was also well-known that the (Z)-form of endoxifen is more active at the estrogen receptor. Ex. 1003 at [0004]. Thus, it was known to use (Z)-endoxifen in the

treatment of breast cancer. Ex. 1004 at [0003]; Ex. 1004 at 1:64-2:4; Ex. 1004 at [0003]. And, as discussed above, the claimed XRPD patterns are inherently taught by Liu.

90. Therefore, arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so.

B. Dependent Claim 21

21. The composition of claim 1, wherein the composition is stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity.

91. A POSA would understand “stable” as used in claim 21 to mean “the continued presence of at least 90% (Z)-endoxifen in a composition...measurable by (Z)-endoxifen conversion to (E)-endoxifen starting from the date of synthesis.” Ex. 1001, 82:15-19. As discussed above, the (Z)-endoxifen disclosed by Liu is the same composition claimed in the 151 patent and therefore Liu inherently teaches the claimed stability.

92. As shown herein, the (Z)-endoxifen disclosed by Liu is the same composition claimed in the 151 patent. A POSA would understand that the stability of a composition is dependent on the chemical structure of the composition, its crystal structure, and its purity, but does not depend on the synthetic method used to

form it. The 151 patent itself explains that a drug's stability depends on its crystal structure. Ex. 1001, 30:16-22. And as discussed above, Liu teaches (Z)-endoxifen with the same crystalline structure (*e.g.*, Form I) as claimed. Therefore, because the chemical structure of the claimed composition and the composition taught by Liu are the same, Liu inherently discloses that its (Z)-endoxifen is "stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity" as recited in claim 21 of the 151 patent.

93. In addition, Elkins discusses the results of stability studies of (Z)-endoxifen. Ex. 1026 at 176. Elkins stored (Z)-endoxifen at 5° C and 25° C with a relative humidity of 60% for 12 months. *Id.* at 179. Elkins explains that the (Z)-endoxifen composition slowly degraded from 98% (Z)-endoxifen to 96% (Z)-endoxifen at 25° C with a relative humidity of 60% over 12 months, that (Z)-endoxifen was stable at 5° C, degrading only slightly from 98% to 97. *Id.* Thus, as provided by Elkins, (Z)-endoxifen is stable for "at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity," as claimed.

94. Even if not inherent in Liu, a POSA would understand that it is desirable for a pharmaceutical composition to be stable. Therefore, a POSA would have been motivated to obtain a composition of (Z)-endoxifen that was stable. Stability does not depend on the synthetic pathway used to generate a molecule. Indeed, compounds do not remember the way they were made. I tested the stability

of the (Z)-endoxifen I synthesized. The stability testing procedure I used was similar to the bulk stability testing procedure described in the 151 Patent. *See* Ex. 1001 at 83:29-47. I sealed samples of (Z)-endoxifen under nitrogen in capped vials inside ziplock plastic bags. I kept one sample of (Z)-endoxifen at 25° C and 60% relative humidity for ten (10) days and another sample of (Z)-endoxifen at 40° C and 75% relative humidity for ten (10) days. Neither sample indicated isomerization of (Z)-endoxifen to (E)-endoxifen after the ten (10) days. Therefore, the (Z)-endoxifen synthesized according to Liu does not readily convert to (E)-endoxifen and is stable. As such, and as shown by Elkins, a POSA would understand (Z)-endoxifen synthesized according to Liu would be stable.

95. However, to the extent any impurities arose during the course of synthesis that negatively impacted stability, a POSA would have been motivated to use well-known purification techniques to eliminate impurities to improve the stability of the compound. Evaluating impurity profiles and devising a purification strategy to remove impurities would have been something a POSA would do for any API synthesis. In the case of (Z)-endoxifen, it was well known in the prior art how to purify (Z)-endoxifen using crystallization (Liu) and chromatography (Fauq). Ex. 1003; Ex. 1013. Further, in addition to being known specifically for the purification of (Z)-endoxifen, crystallization would have been well-known to a POSA as an “extremely powerful tool to separate most unwanted byproducts.” Ex. 1029 at 599.

Indeed, “[m]ost API manufacturing processes consist of a series of chemical steps followed by a final crystallization that yields the API crystals.” *Id.*

96. If further purification or optimization were required, this would have been routine for a POSA. Crystallization and chromatography were both well-known techniques that a POSA would have understood how to conduct routine experiments to optimize. *Id.*; *see also* Ex. 1028. Further, in addition to crystallization and chromatography, a POSA would have understood how to employ other purification techniques should they be necessary to remove particular impurities. A POSA would have had numerous, well-known purification techniques at their disposal. For example, Richardson is a book detailing numerous purification techniques and strategies a POSA would have been motivated to employ. Ex. 1029. Richardson includes detailed chapters on crystallization (Chapter 15), chromatography (Chapter 19), filtration (Chapter 7), centrifugation (Chapter 9), extraction (Chapter 13), evaporation (Chapter 14), drying (Chapter 16), and adsorption (Chapter 17), among others. *Id.* Thus, if impurities from synthesis caused any issues with stability—and I have seen no evidence in Liu or in my experiments that this is the case—a POSA would have been familiar with various techniques for removing them. Such modifications would have been nothing more than utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of

success in doing so. Thus, purification of (Z)-endoxifen would have been well within the skill of a POSA.

97. My own experiments and NMR data confirm that (Z)-endoxifen synthesized and crystallized according to Liu's teachings provided highly-pure (Z)-endoxifen. Bihovsky, Appendix B. Indeed, the NMR of my sample 15-35-2P shows pure (Z)-endoxifen with the presence of 1 weight % of residual acetone. The NMR spectrum of my sample 15-36-1P shows a 93:7 mixture of (Z)- and (E)-endoxifen with the presence of 1 weight percent of residual acetone. the presence of 1 weight % of residual acetone would not change the stability of (Z)-endoxifen. And, even if the presence of a small amount of acetone did affect the stability of the (Z)-endoxifen, a POSA would know how to remove the acetone. For example, the last traces of acetone could be removed by drying the substance in a vacuum. I dried the (Z)-endoxifen I synthesized in vacuo at 35° C for 4 days and reduced the amount of residual acetone from 1 weight % to 0.6 weight %. If the amount of residual acetone needed to be reduced further, a POSA would know how to reduce it.

98. Therefore, a POSA would be motivated to achieve a stable (Z)-endoxifen formulation with a reasonable expectation of success.

99. 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.

A handwritten signature in cursive script, appearing to read "Ron Bihovsky", is written over a horizontal line.

Ron Bihovsky, Ph.D.

3/26/25

Date

APPENDIX A

Ron Bihovsky, Ph.D.

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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 most of the 20 US patents he was granted, 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 α -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)

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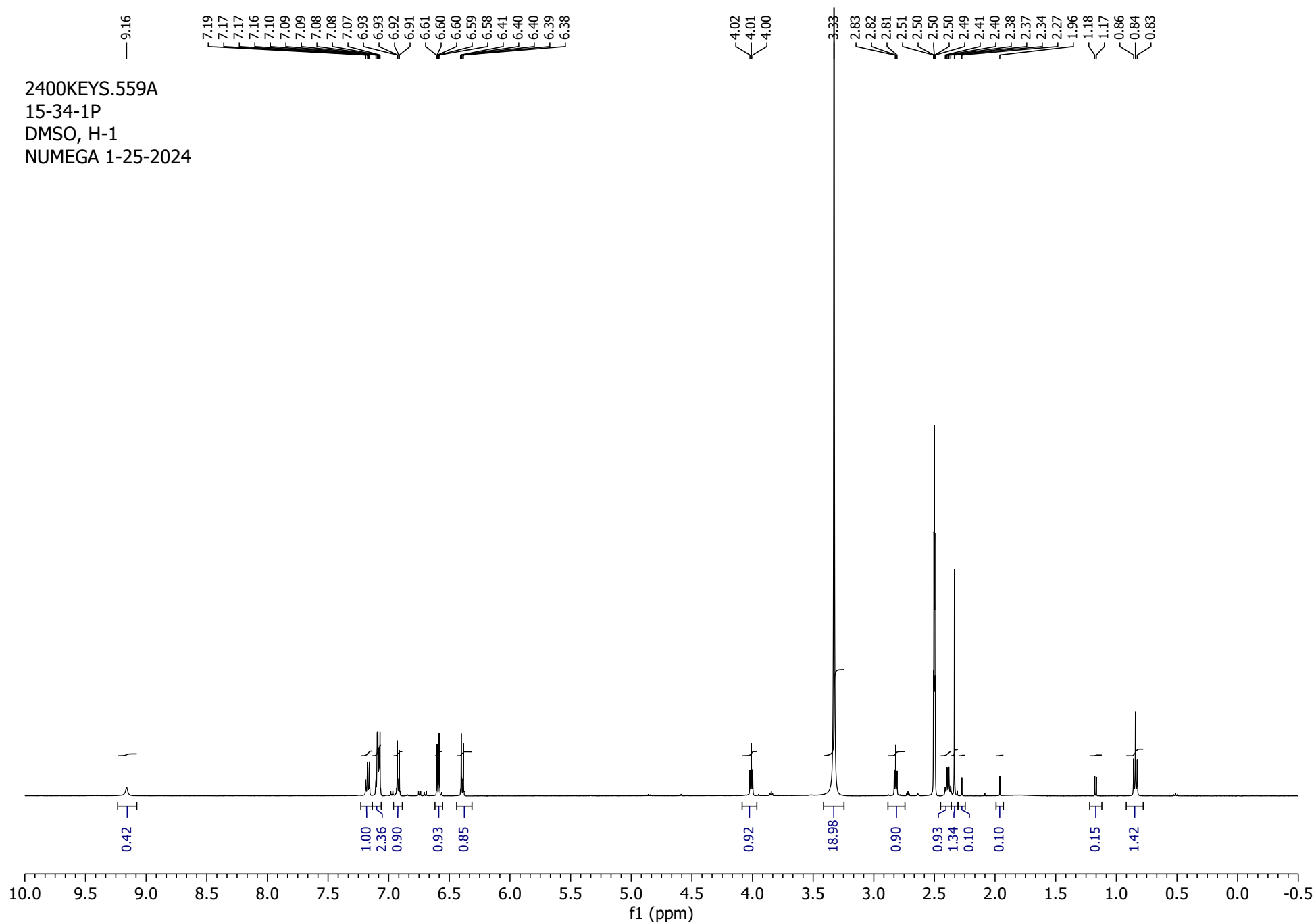
Patents:

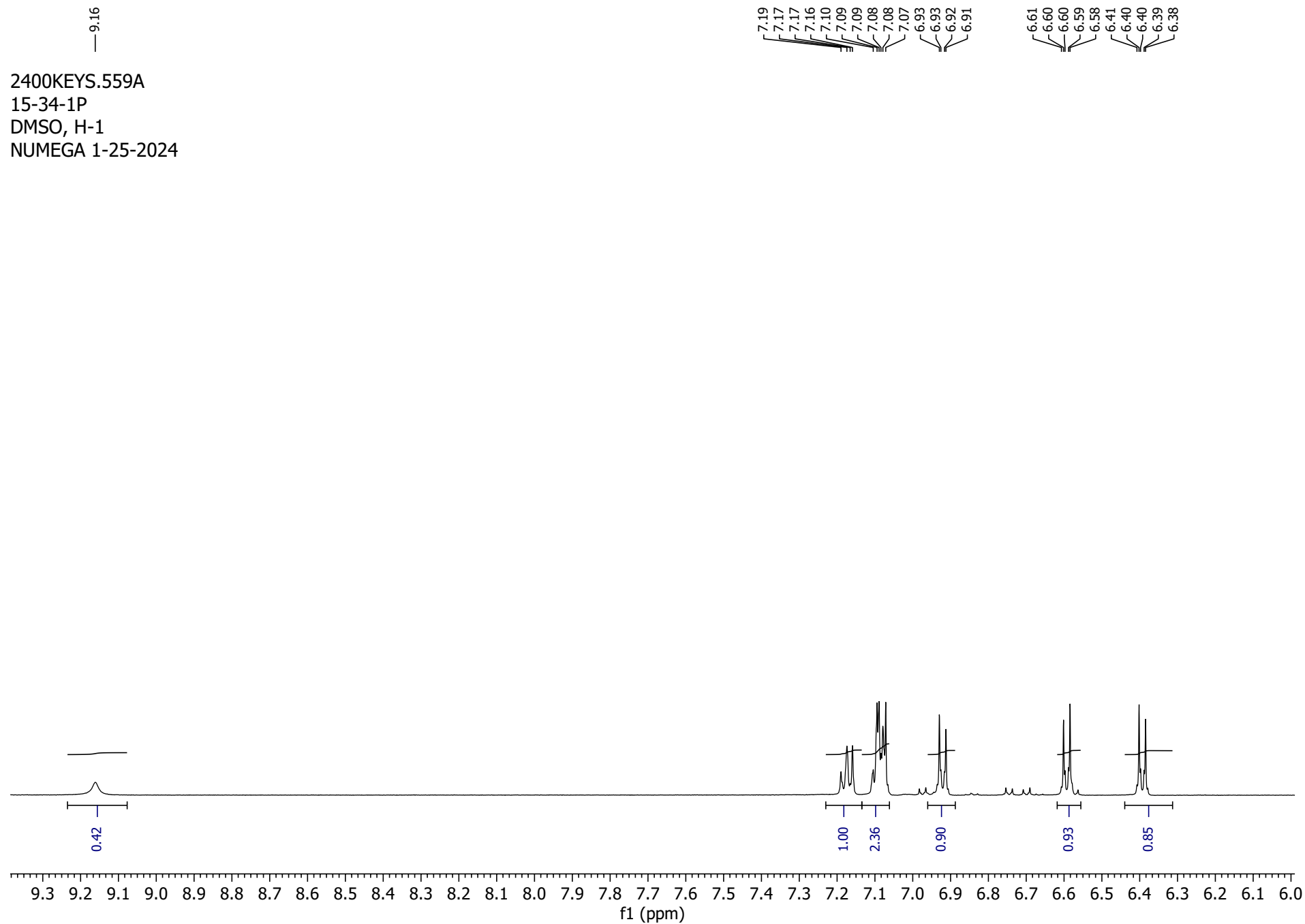
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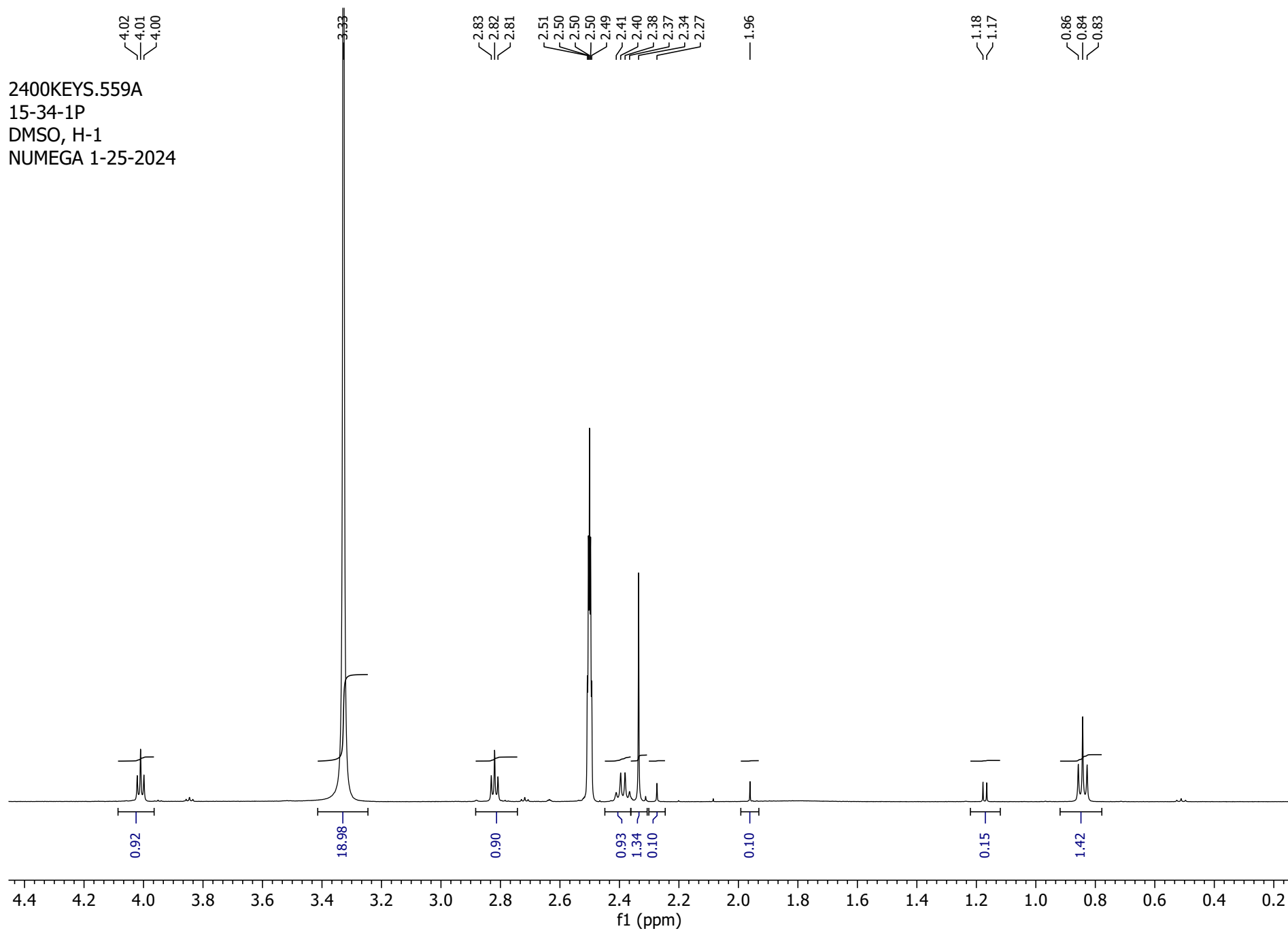
APPENDIX B

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DMSO, H-1
NUMEGA 1-25-2024

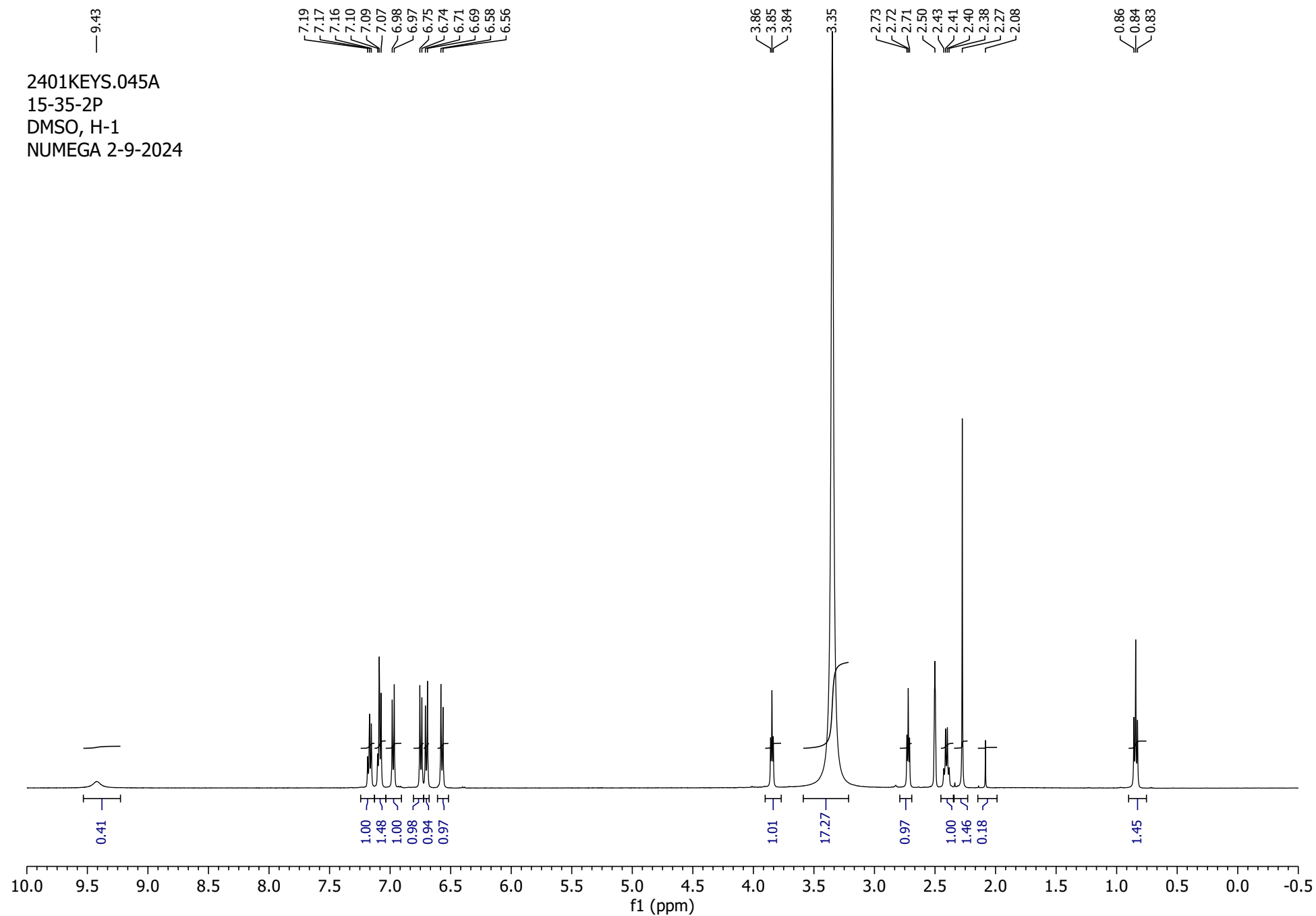




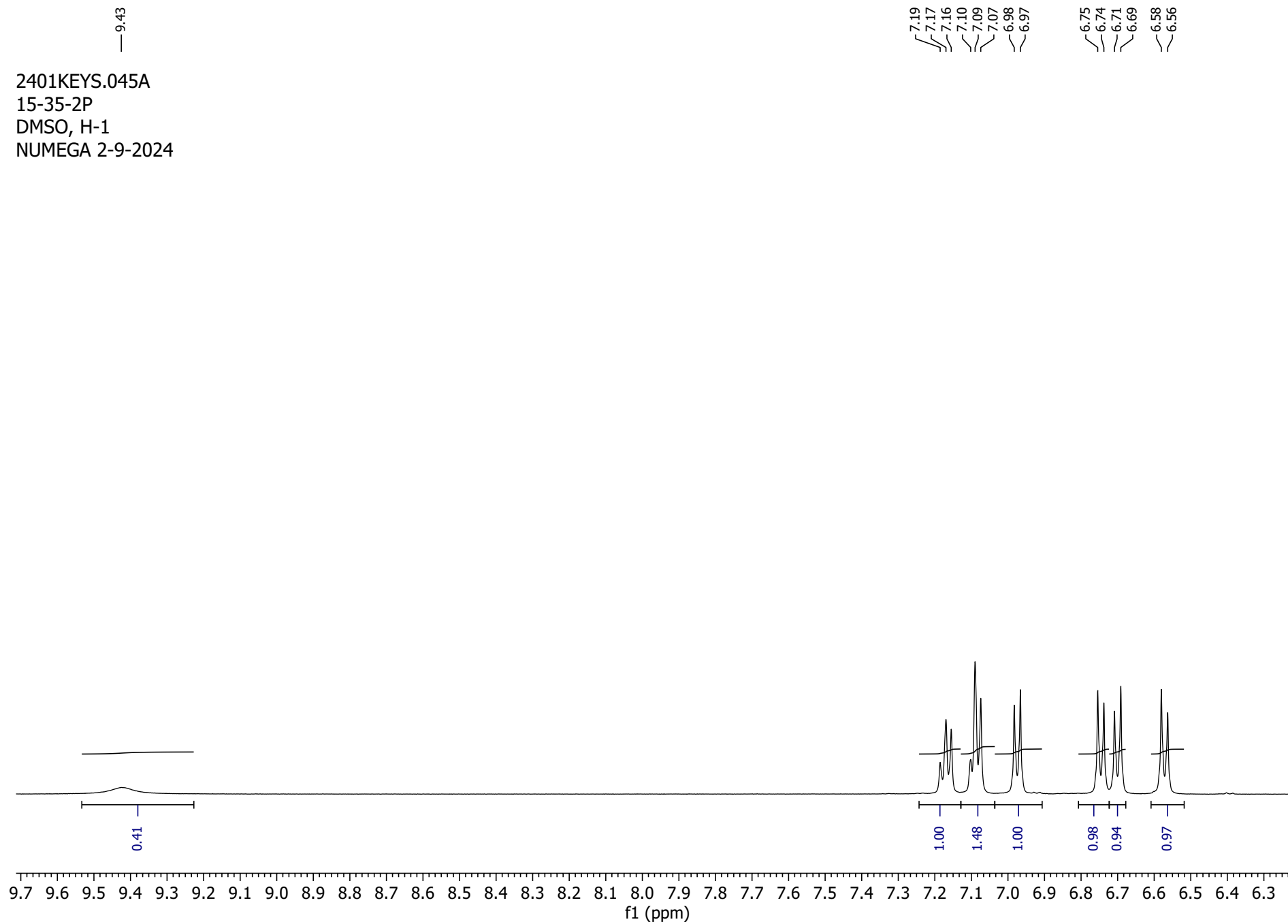
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DMSO, H-1
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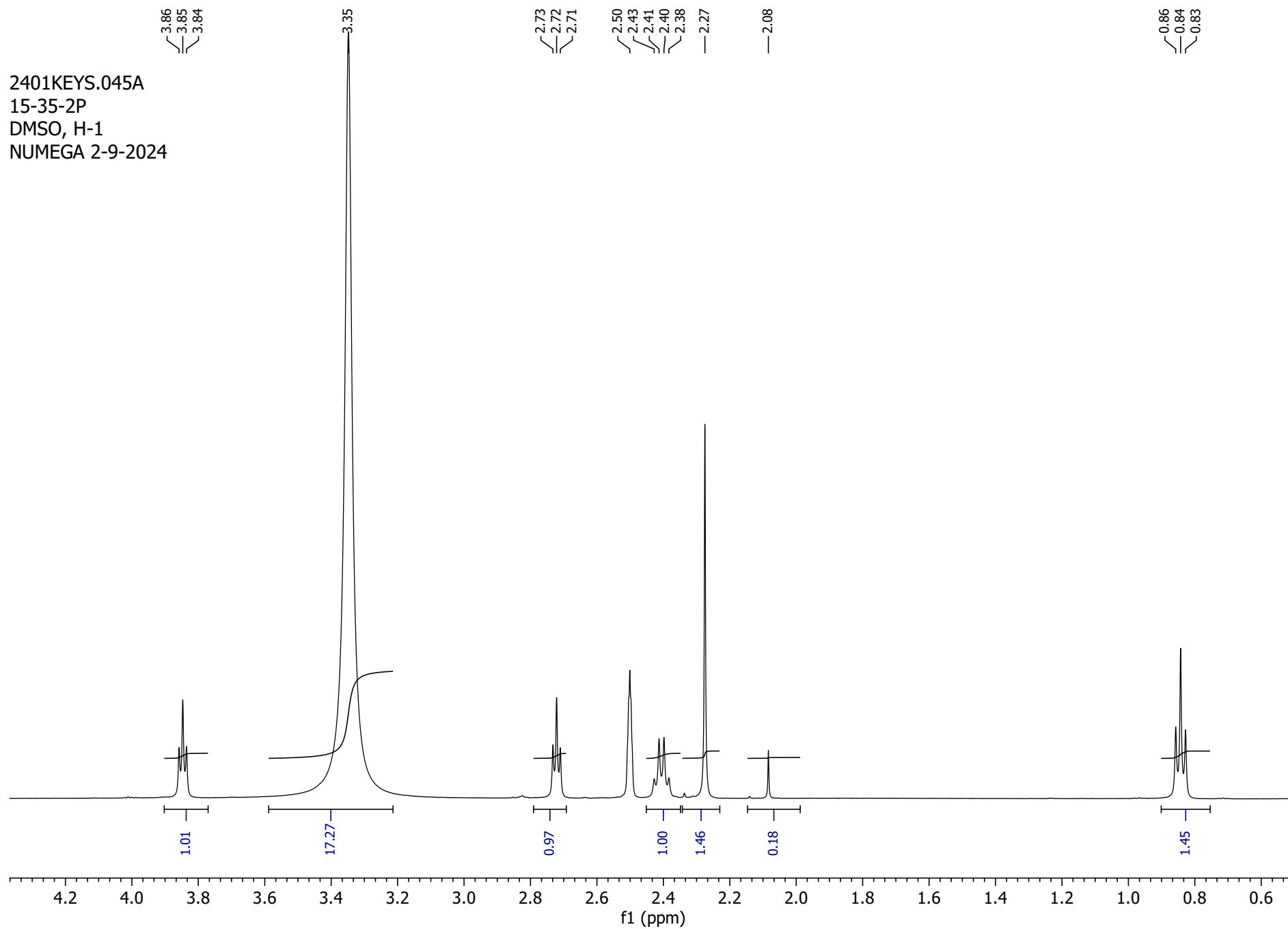


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DMSO, H-1
NUMEGA 2-9-2024

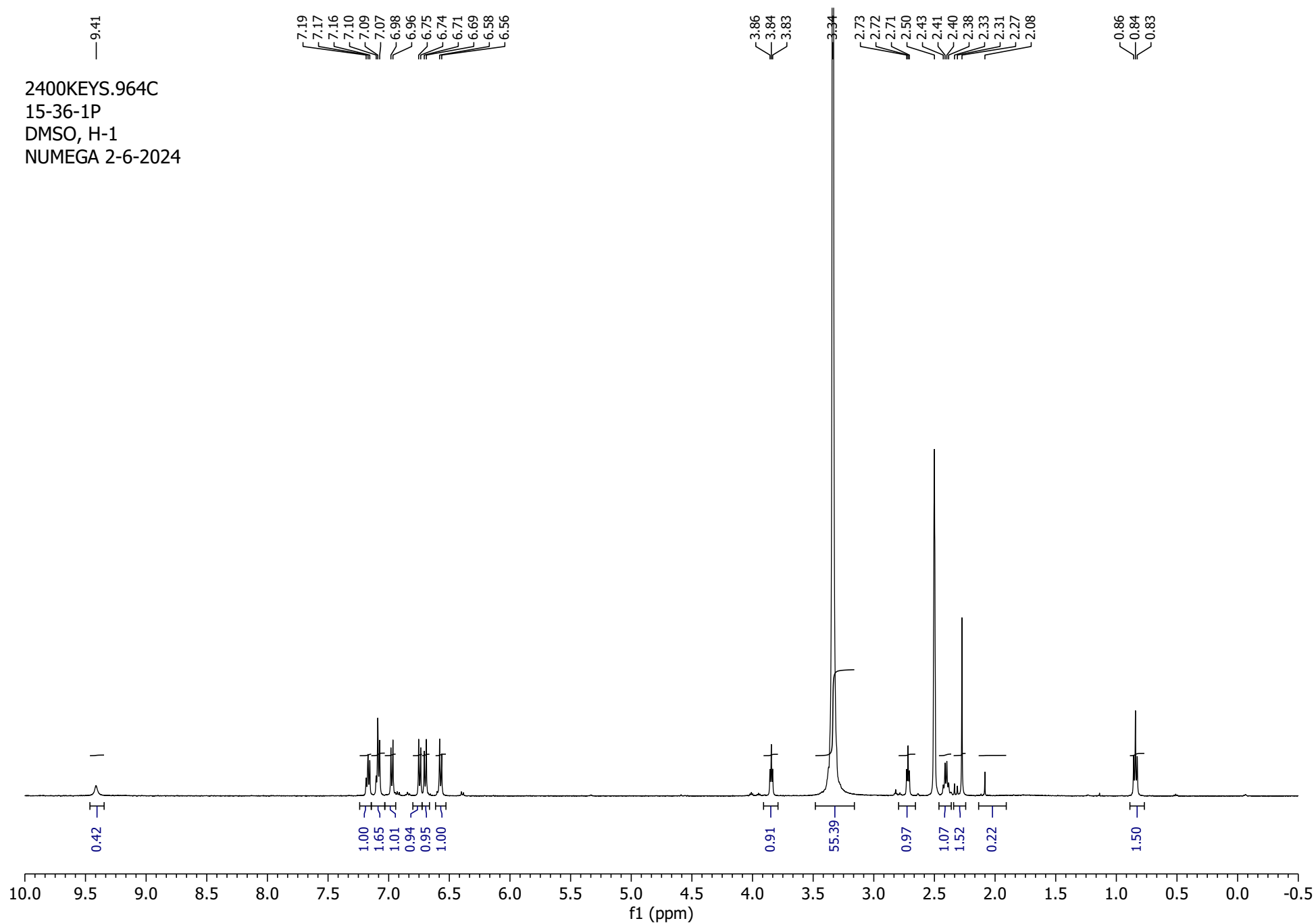


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DMSO, H-1
NUMEGA 2-9-2024

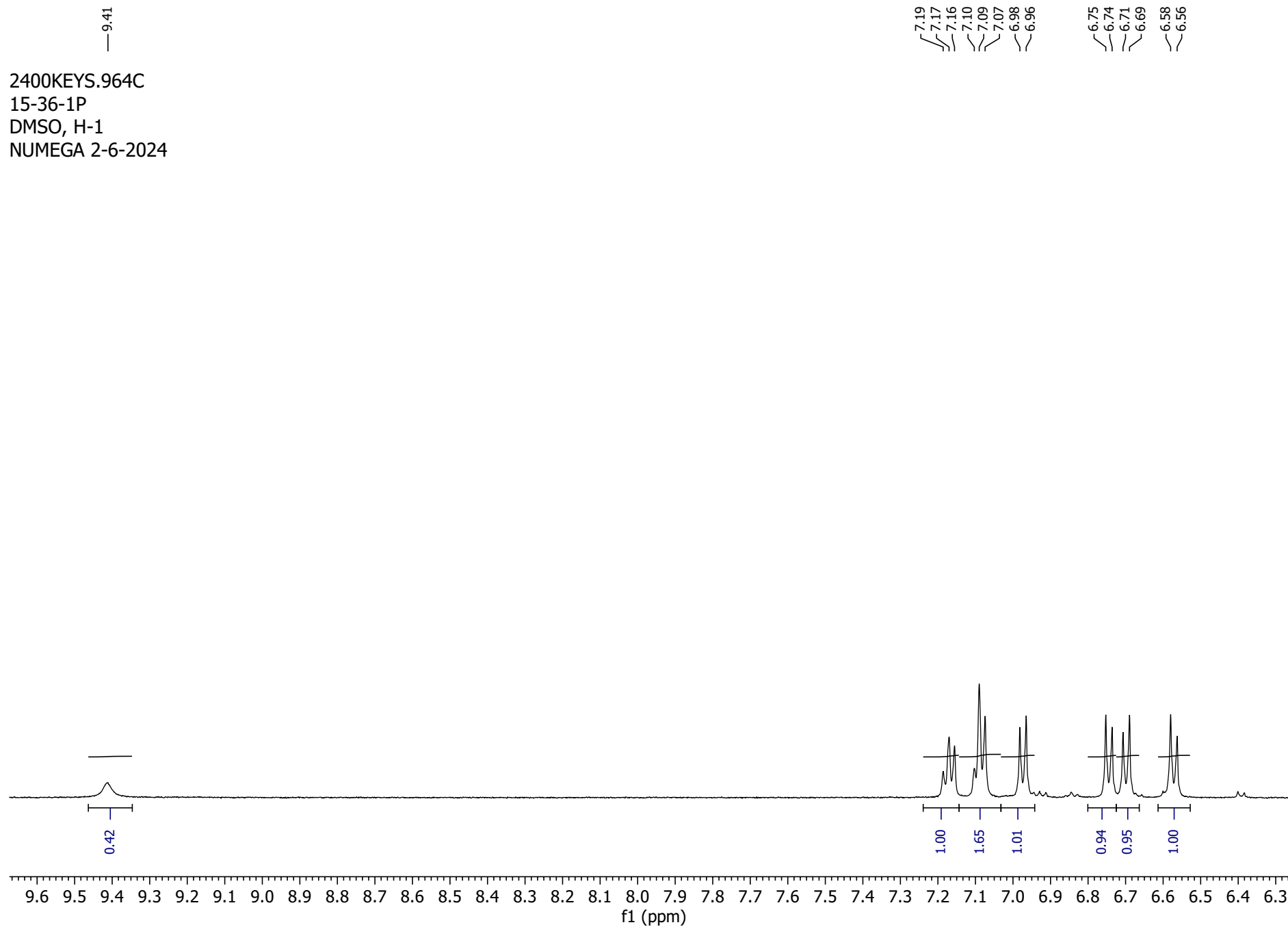




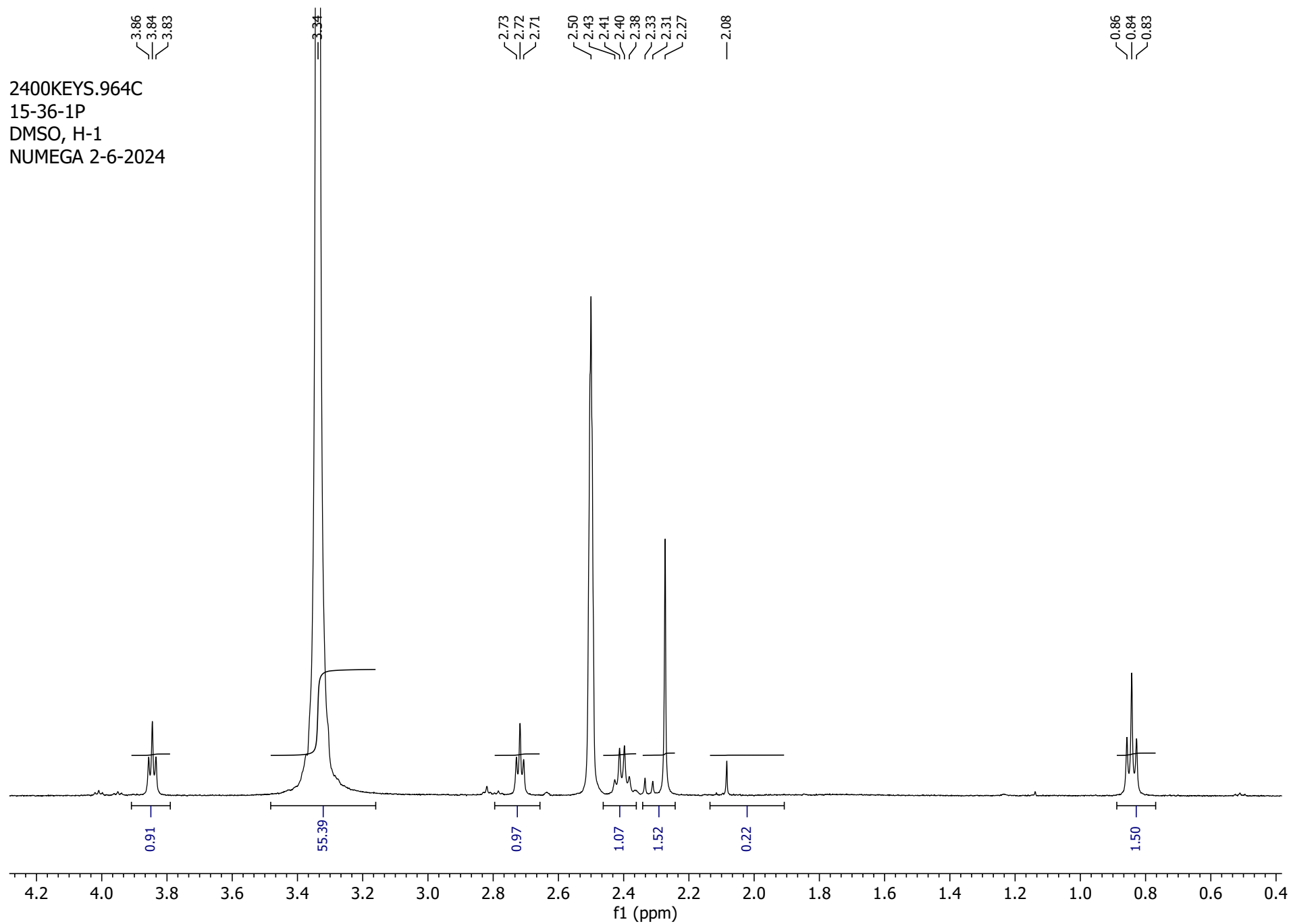
2400KEYS.964C
15-36-1P
DMSO, H-1
NUMEGA 2-6-2024



2400KEYS.964C
15-36-1P
DMSO, H-1
NUMEGA 2-6-2024



2400KEYS.964C
15-36-1P
DMSO, H-1
NUMEGA 2-6-2024



APPENDIX C

Repeat: 50-75° i

7/24/23 ZnBr₂ 3.011g, 13.9 mmol over dried at 230°C

PPA 16.5g

Heat 50° i Cinnamic⁵³ 4th b. 5th #1, Heat # 75

4-Hydroxybenzoic acid 27.0mg, 7.85 mmol

Br- ϕ 1.302g, 6.47 mmol

PBr₃ 0.25 ml, 2.71g, 10.0 mmol, dist @ -170°

5:50 over 10 min. Not methanol

KOS col vol

7/25/23 use drying tube. Heat 50° i 22h

2.358 (1.43)

3:30 use N₂ bubbler. Heat 55° i (58° b) Heat # 95 21h

3:30 7/26/23 Heat to 75° i (78° b) Heat # 140 ~1.5h - orange

clump separates from orange fluid (contains most product).

Pour into ice-water (38 ml). Stir 30 min.

(still clump in water). Extract clump + oil 4x EA

filter to remove interface ppt. 260 mg, 15-21-812. Rinse with 10% NaOH

Dry MgSO₄, Evap. (contains HCl). Dissolve.

7/27/23 in EtOAc, rinse w fresh 10% NaHCO₃ (10 ml), sat.

NaCl, dry MgSO₄, Evap. → 1.41g red oil.

Dissolve in EA, add 5% (39? mg) conc. chrom on

SG (4x16 cm) w. PE-EA (60:40, RF 0.4)

Yellow band 682 mg (6 mm pump) red wax 33% yield - 2A

* some prod in NaHCO₃ layer after + HCl, sat. w EA. - 9

PE-EA

50:50

(UV)

HFA 1 50° 55° 55° 60° 75° (10 ml) - 2-9
21h 3h 30h 2h 1.5h
H₂O-EA 10:1 10:1 10:1 10:1 10:1

Repeat 75 i

2M Br₂ 3.811 g, 13.4 mmol. Dried 23°C
1/11/23 PPA 16.5 g

4-Hydroxybenzoic acid 374 mg, 7.85 mmol
Bromoph 1.56 g, 7.76 mmol (110 mol %)
PBr₃ 0.95 ml, 2.71 g, 12.0 mmol (142 mol %) (Dist)
Heat 120° (b) = 75° (i). Heat concn #140
under N₂, stir 2-3, 20h (less prod)

Clump forms overnight
pour fluid into ice-H₂O (45ml) stir w. EA till
Add H₂O + ice to clump 500ml sol (~30 min)
shake in sep funnel, var filter to remove
interface ppt. → 275mg orange solid. 1.5ml. - 15
separate phases. Ext w 3x EtOAc. Reuse EA
with H₂O (2x). NO prod from fluid (TLC) -H
Little prod from clump (TLC) -15

7/28/83 Repeat 15-22-1 but stop after 4h. (Sit 5° in H₂O
7/31/83 over (about) work up as above. Infrared 334mg - 2I
only EA layer over MgSO₄, strip → 2.50g red oil - 2
Dissolve in EA, add 5K₂(H₂O) strip.
Chrom on 5G (4x15 cm) g. PE-EA (60:40)
It yld band 620mg (27%) red w/ 15-22-2A
after h₂ over (Germ)

[illegible]

8/1/23 Scale up 15-22-2 x 9

EtBr₂ (27.1 g, 120 mmol) Dried at 270°C

PPA 149 g

4-Hydroxybenzoic acid (8.77 g, 63.5 mmol)

Br₂ (114.1 g, 70.1 mmol, 110 mol %). Heat 35°C, add

1:30 PBr₃ (8.6 mL, 24.51 g, 90.5 mmol) NE H₂O then mix
while stirring mechanically. Slowly heat to
68 to 70° over 1 hr. Stir total 6 h.

Pour into ice-water (360 mL) stir 5 min. O.N.
Stir + shake w. EtOAc, Use filter (10 cm)

through Celite to break emulsion. Rinse
ppt w. EA (5 L). Extr. layers w. EA (3 x 2)
Residue combined org. w. H₂O (2 L), sat. NaCl.

Dry MgSO₄, Evap. → 2.35 g red oil 15-23-1

3/11/23 Dissolve in EA, add SG (40 g) strip.

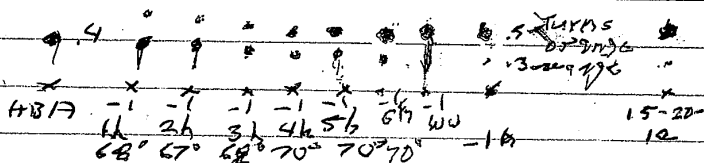
Chrom. on SG (7 x 30 cm) w. PE-EA (60:40).

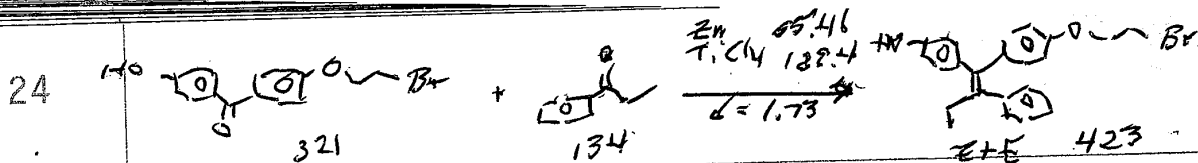
Yellow to orange band. Evap. H₂ vac (6 mm -
frames) → 9.37 g (46%) red wax 15-23-12

PE-EA

TO:50

(UV)





140 '651 EX. 3.

8/14/23 Zn (2.2g, 33.6 mmol, 1615 kcal/h) + DME (13 ml) (3.5 ml)
 cooled in ice bath under N₂ stir, add
 TiCl₄ (3.29g, 1.8 ml, 3.11g, 16.4 mmol, 788 mol/l)
 over ~5 mins (Exothermic), rx gently (95° C)
 for 1h. ^{Dark green} Cool in ice bath. add mixture
 of SM (15-21-2A, 682 mg, 2.125 mmol) +
 propiophenone (279 mg, 2.08 mmol, 98 mol/l)
 dissolved in DME (5 ml), rx gently (95° C)
 (→ dark brown) for 6h (stirring impossible
 after ~2h) (~Black after 6h). ✓ Set at RT
 8/15/23 O.N. cool in ice bath. add MTBE (15 ml),
 5% HCl (6.7 ml) slowly with stirring.
 Stir 2h at RT. separate organic layer.
 vac filter ag. through Celite, ^{slow} Extract ag (black
 + ppt 3x MTBE. Wash combined org. w/
 3x sat. NaCl. Dry MgSO₄. Evap in vacuo,
 hi vac (Gent) → 966 mg (108%) of brown oil. -
 Chrom on (2.5 x 17 cm) SLG with ^{most polar} CH₂Cl₂/hexane
 → 590 mg of yel. waxy. Foams badly when
 try hi vac (Gent). NMR (CDCl₃) Empirical 19
 8/16/23 Stir with Hexane (1.4 ml) at 45° 1h (→ ppt), then
 RT ON. Vac filt, dry ppt in ^{air} → 413 mg
 8/18/23 off-white solid, dry 313 mg in vacuo → 309 mg
 (48% yield). NMR (CDCl₃) OK. mp ~110-124° +5-24

Evap filtrate → 62 mg off-white solid

CH₂Cl₂

(CDCl₃)

5.12 15.24-1 1.0 1.97-1.95

3/17/23 Repeat x 14.65 scale
 Zn (32.23 g)
 DCE (190 mL)
 TiCl₄ (26.4 mL) over ~ 1/2 hour. Ice bath → 100 °C
 SM (15-22-2A + 15-23-1a) (9.99 g) (31.1 mmol)
 Propylphenone (4.09 g) (30.5 mmol)
 DME (75 mL) (stirring impossible after 5 min)

MTBE (220 mL)
 HCl 5% (98 mL)

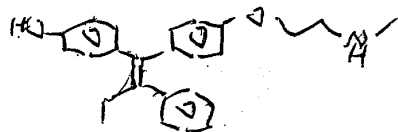
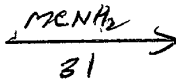
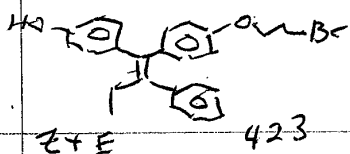
WU lab p 24 → 13.88 g (106%) brown oil -1

8/22/23 Chrom on SG (7.5 x 26 cm) with CH₂Cl₂
 → 9.43 g lt. amber oil -1a
 Suspend in Heptane (22 mL) at 45°, stir 16 h
 at RT. Vac filter, dry ppt in air → 7.09 g
 Show in vacuo 3 d. → 7.72 g (59%) pale orange solid, mp ~ 103-110° NMR (CDCl₃) - OK
 Evap filtrate → 622 mg white semi-solid (5%) - 1a5
 (Not dried in vacuo) mp ~ 65-75°

(14.25/14)
 (2V)

15-25-1-24-1 12 108-25-
 105

26

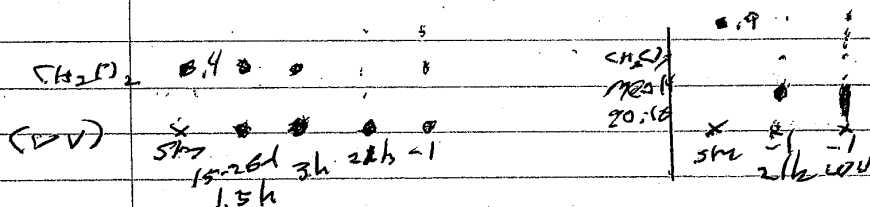


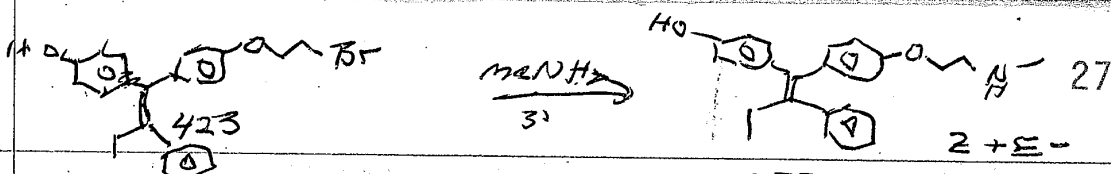
Endoxifog
112823-28-4
110025-28-0

WO '651 Ex. 4

8/17/23 5mL (15-24-18p, 100mg, 0.236 mmol, dried in air but not in vacuo) + 33% MeNH₂ in also EtOH, 3.0 mL, 990 mg, 31.9 mmol, stir at 33°-35° for 2 h. ^{Evaporate w. pressure} Evaporate in vacuo → 156 mg, ^{Gen 140} it leaves oil. Dissolve in CH₂Cl₂ (1.3 mL) Rinse w. NaHCO₃ (114 mg) + Na₂CO₃ (62 mg) in H₂O (1.4 mL). Re-extract w. CH₂Cl₂ (0.7 mL) x 2. Rotap. add 1 (0.25 mL) Rotap. add 1 (0.13 mL) Rotap. → (foam) → 106 mg (120%) pink glass. NMR (DMSO) ~ OK ^{52.48} ~~50.50~~ MeX E=E -1

8/21/23 Dissolve in 1 (153 mg, 0.193 mL) at 56°. Cool to RT, -10° (5 watch) -10° 4 days. Van filter (Small volume - difficult). Rinse w. acetone (-10° ~ 0.2 mL) ^{65.2d} 16 mg white ppt. mp ~ 127-134° (lit 127-129° chemical book) -1X (E mp 141° ^{WO 12/050263} NMR (DMSO) ~~52.48~~ 50.50) Evaporate → 82 mg pink glass ¹⁵⁻²⁶⁻¹⁵ E-isomer per '263, 95% E-isomer per '651 E-isomer per BML 20,2665 (2014) Not E per APX B10 E-isomer per J.H. Bixard (Aug) 88,174 (2014)



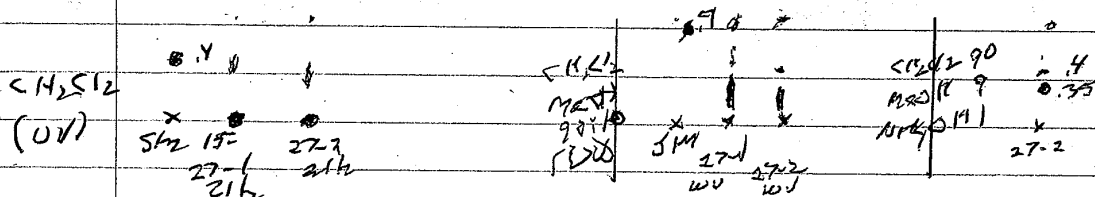


373
Endoxifen

8/25/23 SIM (7.72 g, 18.3 mmol, 15-25-197) + 35% MeNH₂ in
 4:25 also EtOH (232 ml, 30 volumes) 33-35°, 21h
 capped w. pressure. Evap in vacuo, then
 hi vac (GenK frame!) → 9.00 g lilac foam.
 Dissolve in CH₂Cl₂ (90 ml). Rinse w
 NaHCO₃ (7.23 g) + Na₂CO₃ (3.895 g) in H₂O (190 ml)
 (pH = 8.75). Re-extract w. CH₂Cl₂ (45 ml)
 Dry over Na₂SO₄. Rotovap (frame) add acetone
 (25 ml). Rotovap (frame), add acetone (10 ml)
 rotovap (frame) → 7.18 g (82%) pink foam
 → amorphous solid. NMR (DMSO-d₆) 5.2-4.8 E:Z 15-27-1

Repeat w SIM (lean pure, 15-24-195 + 15-25-195,
 6701 mg) + MeNH₂ & EtOH above. Evap → 696 mg
 lilac amorphous solid. Dissolve in CH₂Cl₂,
 rinse w NaHCO₃ + Na₂CO₃ as above. Dry, sig,
 add acetone + evap 24 as above → 642 mg (109%)
 pink crystalline solid mp 76-79° 15-27-2

9/19/23 HPLC of 15-27-1 & SEC '691
 Column Lichrosphere RP18, 5 μm, 150 x 4.6 mm UV 254 nm
 + 0.1% TFA 1 ml/min
 H₂O - MeCN 5-95% 12 min No separation
 18 mM NH₄⁺ HCO₃⁻ in H₂O - MeOH 40:60 to 0:100 8 min
 possible shoulder



- 1651 P 70, WD 2012/050263
- 9/8/23 15-27-1 (200 mg) was dissolved in acetone (10%
 0.545 ml w. 5% scratch
 43 mg 20°C to 20° slowly scratch then -10° 4
 days in 4 ml test tubes within 100° centrifuge
- 9/12/23 15-28-1P
 crushed. After 4d quickly centrifuge.
 ppt: 194 mg - pink solid.
 Strip supernatant → 21 mg pink glass -15
- 9/12/23 15-28-1 (200 mg) dissolved in MeOH (40°/43° b,
 P 93 1.584g, 2.00 ml) w stir flask cool to 30° then
 4:00 10° scratches. Some ppt after 1.5h. More after 2h.
 Store 20-22° 20h. (Same ppt). Vac. filter, rinse
 w MeOH (0.2 ml) dry in air → 32 mg white solid 95% E 2P
 Strip filtrate → 123 mg pink glass 15-28-25
- 9/12/23 15-27-1 (200 mg) dissolved in 95% EtOH (40°)
 P 98 43° b, 1.578g, 2.00 ml) w stir flask. Cool to
 4:05 30° then 20° scratches. S.p. ppt after 1.5h. More
 after 2h. Store 20-22° 20h (Same ppt). Vac. filter,
 rinse w EtOH (0.2 ml) dry in air → 12 mg white solid
 ~100% E (NMRX & MSOX) + CD(13). mp 161-3° -3P
 Strip filtrate → dark pink semi-cryst 202 mg glass -35.
- 9/13/23 Repeat like -3P, but EtOH 43°(b) to 20° 1h w stirring
 4:18 Ppt 43 mg off white solid 94% E -4P
 P 100 Filtrate → 135 mg pink semi-cryst sol. 86% E -45
- 9/14/23 Repeat like -4P but EtOH
 3:48 Ppt 71 mg white solid 94% E -5P
 P 96 Filtrate → 116 mg pink semi-cryst sol. 80% E -55
- MS 112 90
 MeOH 9
 NH4OH 1
 15-28 15-28
 15-28 15-28

8/15/23 15-27-1 (200 mg) dissolved in iPrOAc (2.0 ml) at 1:40 85° w. stirring. Cool to 40° over 1h (starts to crystallize). Cool slowly to 25°, then 15° over 1.5h. Vac. filter, rinse w iPrOAc (0.2 ml, 15°)
 ppt 54 mg white solid 94% E⁻ 15-29-1P
 Styr filtrate → 138 mg pink solid ^{reprecip} 70% E⁻ -15

9/25/23 Rg/1651 p14 entry 11 and Ex 5.
 15-27-1 (3.65 g) was dissolved in iPrOAc (31.6 ml) at 80°, then cooled slowly to 21°. Sit 21° 16h. Vac. filter, rinse w 2 ml cold iPrOAc → 912 mg lt. pink ppt (25%) crystals
 NMR 100% E⁻ (DMSO) mp 157-159° -2P
 Rotavap filtrate at 50-55° ^{rem} 2.83 g (78%) (form) ^{at 15°}
 pink form. NMR 68% E⁻ (DMSO) 15-29-2S

9/29/23 Dissolve 15-29-2S + 15 (2.97 g) in acetone (29.7 ml) at Δx briefly. Cool + stir at 4° 40h. Vac filter, dry ppt → 5437 mg white solid 8% E⁻ pink -3P
 ← TLC Cool filtrate to 4° 5h (ppt), rotavap → 2.55 g form -3S
 NMR (DMSO, combined w -4S) 76% E⁻ + impurities

10/2/23 Dissolve -3P (427 mg) in Δx (briefly) acetone (12 ml, ~ minimum amount). Cool 4° 5h w. stirring. (ppt starts after few mins).
 filter + dry ppt → 304 mg white solid -4P
 Styr filtrate in vac. → 126 mg pink glass -4S

10/4/23 Dissolve -4P (304 mg) in Δx acetone (9.5 ml) (~ minimum). Filter hot. Cool 4° (→ small xts after ~20 mins) 2h
 ← TLC Vac. Filter + dry ppt → 232 mg tiny white xts mp 159-61° -5P
 NMR (DMSO) 100% E⁻
 Rotavap filtrate → 53 mg white solid mp 154-157° NMR 88% E⁻ -5S

'651 P 73

10/12/23 combine E- parts 15-28- 2P, 3P, 4P, 5P +
15-29- 1P, 2P, 5P, 5S (1.336g)

2.40 Reflux (lit bp 88°) with iPrOAc (13.4 ml)
with stirring for 2h. Most dissolved over
2h → turbid soln. Cool slowly to 15°.
(20° O.N. then 15° 2h). Vac filter rapidly
Rotovap filtrate → 160 mg pink solid
NMR (DMSO) 44% Z- + impurity 15-30-15
Dry ppt → 1.13 mg white solid
NMR (DMSO) 100% E. XRPD - Not Form I 15-30-1P

10/16/23 Reflux 15-30-1P (1.13g) with iPrOAc (11.3 ml)
with stirring for 10h. Cool to 30° O.N.
then to 15° 3h. Vac filter rapidly.
Rotovap filtrate (50° b) (brown) → 20P mg
lt. pink solid 75% Z- + ^{slight} impurity 74 -25
Dry ppt → 860 mg v. lt. pink solid. 68% E -2P

10/19/23 15-30-25 (1971 mg) dissolved in OX acetone (1.97 ml)
4:30 stir while cooling to 4° 4 days (some ppt after 1d)
vac filter, rinse w. 0.3 ml cold acetone → 192 mg
fine v. lt. ^{pink} powder 78% Z- -3P

Rotovap filtrate (50° b) → 641 mg ^{severe cryst.} pink solid 68% Z- -35

10/19/23 Reflux 15-30-2P (850 mg) w. iPrOAc (8.5 ml) 2h. Cool to
4:00-6:35 20° over 2.5h then 15° 3d. Rotovap filtrate → 257 mg -4S
CH₂(C)₂ 90
MeOH 2
NH₄OH 1
(CO) 15-30-16 35 2P
It pink, xites. 78% Z
Dry ppt → 49.2 mg of white solid -4P
8% Z

651 P 70 (compare 15-28-1P @ -10°)
 (6/12/23) 15-27-1 (1.43 g) was dissolved in acetone
 (3.07 g, 3.89 ml) and refluxed (bp 56°)
 → soln then some ppt. Slowly cool to 20°.
 6:30 Sit 18h at 20°, then 4d at 4°. Van filter
 10/13/23 rapidly + rinsed w cold acetone (1 ml).
 Retain filtrate → 830 mg red glass 15-31-15
 80% E + impurities
 Dry ppt → 550 mg of pink solid 87% E. -1P
 10/18/23 15-31-15 (830 mg) dissolved in 2x acetone (8.3 ml).
 10/23/23 Cool 4° 4d - No ppt - 5 ml w 15-30-3P + stir
 10/31/23 Very little ppt after 7+ days 15-31-2
 1/2/24 Some needles.

S
 CH₂SH 90
 NCOH 19
 NH₂SH 1

(UV)

15-31-1P 15

10/24/23 Dissolve 15-30-45 (206 mg) in IPAC (2.06 ml)
 big ΔX. Cool slowly (~1h) to 20° then 15°
 Reg '651 for 2 days. Vac filter, rinse ppt ~0.1 ml cold
 0054 IPAC. Dry → 109 mg xrt. 97% Z. NOT FORM I 15-32-(P
 Rotap fillate → 98 mg from 36% Z -15

10/24/23 Dissolve 15-30-3P (98 mg) in Δx acetone (1.00 ml)
 cool to 20° → 4° (stirring) for 1 day.
 Vap filter + dry → 54 mg off white "cryst." 15-32-2P
 88% Z- XRPD = Form I
 Rotap fillate → 31 mg v. lt. pink from -25
 63% Z-

11/1/23 Combine 15-30-4P + 15-31-1P (980 mg)
 Reg '651 Δx 4H₁₆ with IPAC (9.8 ml) (all sol in 435 mm)
 0061 + Feb. Cool slowly to 30° over 3h, then 15° 3h
 Vac filter + dry ppt → 780 mg 43% Z white solid 15-32-3
 Rotap fillate ⁵⁰⁰ → 200 mg pink from 72% Z -35

WO 2017/070651 EX 4, P 70

11/24 Mix 15-27-1 + 2 (1.544 g), dissolve in Δ x
acetone (3.32 g, 4.20 ml). cool slowly to 20°
19h. Then -10° 4 days
-15 11/22/24 collect ppt by centrifugation, wash, solvent w
N₂ then hi vac → 771 mg light pink
powder, NMR (DMSO-d₆) 67:33 EIE 15-33-1P

32-2P
-25 11/22/24 cool filtrate to -10° for 3 weeks. collect
11/22/24 ppt by decantation → 68 mg lt pink powder
15-33-15P

Evap filtrate → 797 mg dark pink oil
15-33-155

CH₂Cl₂ 20

MESH 9

11/14 → 15-27-1+2 -1P -15P
(UV) 15-33-15 -155

WO 2017/070651, Ex 5, P 72

1/24/24 Dissolve 15-33-IP (761 mg) in 2x iPrOH
 12:05 (7.61 mL) w. stirring. Cool w.o. stirring
 to 23° over 1h. Set at 23° 6h. Vac
 filter ~~the~~ ^{res} rinsed w iPrOH (~0.2 mL)
 dry ppt in air → 238 mg v. lt pink xth.
 NMR 25:5 E:Z 15-34-IP

Evap filtrate in vac then rinse → pink
 oil, then add: 418 mg - NMR 33:67 E:Z
 15-34-1S

Ex. 6, P 73-74 Isomerization

1/26/24 Dissolve 15-39-IP (236 mg) in 2x iPrOH
 (2.36 mL) (~105°) for 4h. Cool slowly to
 15°. Set 15° 2d. ^{vac filter} ~~res~~ ^{res} rinsed w iPrOH (0.2 mL) at
 15°. Dry at 35° in vac. 182
 217 mg white xth
 NMR 5:95 Z:E -2P

Evap filtrate, dry 35° → 58 mg colorless glass
 NMR 69:31 Z:E -2S

1/28/24 Repeat isomerization on 15-34-2P → 148 mg ppt
 NMR 3:27 Z:E -3P

Evap filtrate, dry → 39 mg glass
 NMR 62:39 Z:E -3S

1/30/24 Repeat isomerization on 15-34-3P but -15° 1d → 95 mg -4P
 NMR 3:27 Z:E white xth x

Evap filtrate, dry → 50 mg glass
 NMR 67:31 Z:E -4S

EX. 7, IP 76

12/24 Dissolve 15-34-15 (416 mg) in 5x acetone
 (4.1 mL) cool + stir at 4° for 40h (40h → ppt)
 15/24 acetone, total 64h. Vac filter, dry → 147 mg
 white powder NMR 94:8 Z:E.

15-35-1P

Evap filtrate → 228 mg amber glass.
 NMR 60:40 Z:E

-15

2/6/24 Dissolve 15-35-1P (147 mg) in 5x acetone (2.2
 mL). Filter hot to remove sl. ppt. Cool +
 stir at 4° for 50h (ppt after 24h). Vac
 filter, dry → 91 mg off. beige powder.
 NMR 100:0 Z:E

-2P

Evap. filtrate → 43 mg amber glass
 NMR 77:23 Z:E

-25

36

Ex 7, TP 76

2/2/24 Combine 15-34-25 + 15-34-45 (108 mg), dissolve
 6.45 in 2x acetone (1.1 ml). Cool & stir 4° for
 (40h - same ppt) (64h - more) (88h - same)

2/6/24 88h. Filter, rinses ^{1st cold} w/ acetone (20.1 ml).

Dry → 17 mg white powder

NMR 93:7 Z:E XRPD: Form I 15-36-1P

Filtrate → 80 mg pink, floss

NMR 68:32 Z:E

15