

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.

Petitioner,

v.

EXELIXIS, INC.

Patent Owner.

Case No. Unassigned

Patent 12,128,039

**DECLARATION OF WILLIAM DICHTTEL, PH.D., IN SUPPORT OF
PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT 12,128,039**

TABLE OF CONTENTS

	Page No.
I. BACKGROUND AND QUALIFICATIONS	1
II. MATERIALS CONSIDERED	5
III. LEGAL STANDARDS	5
A. Prior Art Date	5
B. Obviousness	6
IV. THE PERSON OF ORDINARY SKILL IN THE ART	7
V. CLAIM CONSTRUCTION.....	9
VI. INTRODUCTION TO THE '039 PATENT	10
VII. GROUND 1: OBVIOUSNESS (BROWN AND KUBO)	16
A. Introduction to Brown	17
B. Introduction to Kubo	18
C. The synthesis of cabozantinib (<i>L</i>)-malate in Brown and the '039 patent contain very similar steps.....	23
D. Kubo teaches that the difference between Brown's synthesis and the '039 patent's synthesis is a choice between "alternatives"	28
E. A POSA would have been motivated to apply Kubo's one- step alternative to Brown's synthesis of cabozantinib (<i>L</i>)- malate	33
F. A POSA would have had a reasonable expectation of successfully obtaining cabozantinib (<i>L</i>)-malate upon applying Kubo's one-step alternative to Brown's synthesis	40

TABLE OF CONTENTS
(cont'd)

	Page No.
G. A POSA would have had a reasonable expectation of reducing the amount of any 6,7-dimethoxy-quinoline-4-ol impurity in cabozantinib (<i>L</i>)-malate by applying Kubo's one-step alternative to Brown's synthesis.....	41
VIII. GROUND 2: OBVIOUSNESS (BROWN AND ROBINSON)	47
A. Background Regarding Impurities	47
B. Introduction to Brown	51
C. Introduction to Robinson.....	51
D. Cabozantinib (<i>L</i>)-malate API containing the concentrations of 6,7-dimethoxy-quinoline-4-ol recited in claims 1-10 (and referred back to by claims 11-22) would have been obvious.....	55
1. A POSA would have been motivated to reduce the concentration of any 6,7-dimethoxy-quinoline-4-ol impurity in Brown's cabozantinib (<i>L</i>)-malate API to the concentrations recited in claims 1-10 (and referred back to by claims 11-22)	56
2. A POSA would have had a reasonable expectation that chromatographic purification of Brown's cabozantinib (<i>L</i>)-malate API could reduce the concentration of 6,7-dimethoxy-quinoline-4-ol to the concentrations recited in claims 1-10 (and referred back to by claims 11-22).....	64
IX. NO SECONDARY CONSIDERATIONS	72
X. CONCLUSION.....	72

LIST OF DOCUMENTS CITED

Exhibit No.	Description
1001	U.S. Patent 12,128,039 (“the ’039 patent”)
1003	WO 2010/083414 (“Brown”)
1008	U.S. Patent 7,579,473 (“the ’473 patent”)
1009	Mark Gibson, “Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form,” Informa Healthcare USA, Inc. (2009) (“Gibson”)
1019	<i>Exelixis v. MSN</i> , 22-cv-00228-RGA, D.I. 163 (D.Del.) (“Trial Volume III”)
1028	U.S. Patent 7,169,789 (“Kubo”)
1029	Hoffmann, “Elements of Synthesis Planning,” (2009), 133-144
1030	Newhouse <i>et al.</i> , “The economies of synthesis,” <i>Chem. Soc. Rev.</i> , 38 (2009), 3010-3021 (“Newhouse”)
1031	Burns <i>et al.</i> , “Redox Economy in Organic Synthesis,” <i>Angew. Chem. Int. Ed.</i> , 48 (2009), 2854-2867
1032	Pross <i>et al.</i> , “Theoretical Approach to Substituent Effects. Phenols and Phenoxide Ions,” <i>J. Org. Chem.</i> , 45 (1980), 818-826
1033	Furuta <i>et al.</i> , “Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation,” <i>J. Med. Chem.</i> , 49 (2006), 2186-2192.
1035	Felpin <i>et al.</i> , “A Useful, Reliable and Safer Protocol for Hydrogenation and the Hydrogenolysis of O-Benzyl Groups: The In Situ Preparation of an Active Pd0/C Catalyst with Well-Defined Properties,” <i>Chem. Eur. J.</i> , 16 (2010), 12440-12445.
1036	Toxicological Review of Quinoline (2001) by the U.S. Environmental Protection Agency (“EPA Tox. Review”)

Exhibit No.	Description
1037	Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008)
1038	European Medicines Agency, Guideline on the Limits of Genotoxic Impurities (2006)
1039	Robinson, “Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective,” <i>Organic Process Research & Development</i> (2010), vol. 14, 946-59 (“Robinson”)
1041	Guidance for Industry, Q3A Impurities in New Drug Substances (June 2008) (“FDA Q3A”)
1046	U.S. Patent 11,298,349 (“the ’349 patent”)
1049	Maddula <i>et al.</i> , “Preparative Chromatography Technique in the Removal of Isostructural Genotoxic Impurity in Rizatriptan: Use of Physicochemical Descriptors of Solute and Adsorbent,” <i>Organic Process Research & Development</i> (2009), vol. 13, 683-89 (“Maddula”)
1056	Guiochon, “Preparative liquid chromatography,” <i>Journal of Chromatography A</i> , 965 (2002), 129-161 (“Guiochon”)
1065	Brandt, A. and Kueppers, S., “Practical Aspects of Preparative HPLC in Pharmaceutical Development and Production,” <i>LCGC Asia Pacific</i> Volume 5, No. 2 (June 2002), 8-11 (“Brandt”).

1. I, William Dichtel, Ph.D., have been retained by Windels Marx Lane & Mittendorf, LLP, counsel for Azurity Pharmaceuticals, Inc. (“Azurity”). I understand from counsel that Azurity is petitioning for *inter partes* review (“IPR”) of U.S. Patent No. 12,128,039 (“the ’039 patent,” Ex. 1001) and requests that the United States Patent and Trademark Office (“PTO”) cancel claims 1-22 of the ’039 patent as unpatentable. The following discussion and analysis set forth my opinions in support of Azurity’s petition.

I. BACKGROUND AND QUALIFICATIONS¹

2. I am currently the Robert L. Letsinger Professor of Chemistry at Northwestern University where I have been teaching and conducting research since 2016. Before joining the faculty at Northwestern, I was a professor at Cornell University. I moved from Cornell to Northwestern after Northwestern created an endowed professorship and a state-of-the art research laboratory to support my research.

¹ Section headings and sub-headings are included in this declaration for the reader’s convenience. Information discussed in one section may be of interest to the reader in another section. I have attempted to include cross-citations when applicable. Any omission of a cross-citation is inadvertent.

3. I currently teach Organic Chemistry to 100 – 300 undergraduates per year. In addition to my undergraduate teaching responsibilities, I also mentor and advise approximately 15 graduate students pursuing doctorates and several post-docs in numerous chemistry disciplines, including organic chemistry.

4. I received a B.S. in Chemistry from the Massachusetts Institute of Technology in 2000. I received a Ph.D. in Chemistry from University of California, Berkeley in June 2005 where I studied under the mentorship of Professor Jean M. J. Fréchet. After my Ph.D., I worked as a research associate in the Chemistry Departments at UCLA and Caltech, under the mentorship of Professor J. Fraser Stoddart, who was awarded the 2016 Nobel Prize for contributions to the field of organic chemistry.

5. In 2008, I was hired as an Assistant Professor in the Department of Chemistry and Chemical Biology at Cornell University. In 2014, I was promoted to the rank of Associate Professor with Indefinite Tenure at Cornell. In 2016, I moved to Northwestern University to assume my current position.

6. I have received numerous honors and awards for my research including the MacArthur “Genius” Grant, which has been awarded to only 19 chemists in the 35-year history of this program. In 2021, 2022, and 2023, I was named as a Clarivate Highly Cited Researcher, which recognizes the top 0.1% of scientists based on citations to their publications over the previous 10 years. In 2018, I was awarded a

Guggenheim Fellowship, which typically recognizes 1-3 mid-career academic chemists in the United States each year. In 2017, I was recognized with the Leo Hendrik Baekeland Award from the American Chemical Society, which is given once every two years to the top American chemist younger than forty years old. In 2020, I was named the National Chemistry Laureate of the Blavatnik National Awards for Young Scientists, which is given annually to the top American chemist younger than 42 years old. In 2014, I was recognized with the Arthur C. Cope Scholar Early Career Award from the American Chemical Society, which is given to two notable organic chemistry researchers within the first ten years of earning their Ph.D.

7. I am a Fellow of the American Association for the Advancement of Science. I was a Founding Associate Editor for the American Chemical Society (“ACS”) journal, *ACS Materials Letters*, and I currently sit on the Editorial Advisory boards of the publications *ACS Central Science*, *Polymer International*, and *Chemical Society Reviews*. In July 2024, I completed a two-year term of service on the Defense Science Study Group (DSSG), which is a national panel of 14 highly regarded academic scientists and engineers who obtain security clearances, learn about national security capabilities and challenges, and provide the Department of Defense with scientific advice.

8. I have published over 200 peer-reviewed papers, most of which are related to organic and polymer chemistry. My work has appeared in top scientific journals such as *Science*, *Nature*, *Journal of the American Chemical Society*, *Proceedings of the National Academy of Sciences*, and many others.

9. Over the course of my career, I have received over \$20 million in grants for research projects where I am the principal investigator or co-principal investigator. I am also a reviewer of grant proposals for many government agencies and private foundations. I am a named inventor on five patents.

10. I am routinely invited to speak about my research in chemistry. To date, I have given 189 invited lectures and conference talks at many prestigious institutions, including recently as the Opening Keynote Speaker for the Fall 2022 ACS National Meeting. Typically, an ACS National Meeting attracts between 11,000 to 16,000 attendees.

11. A summary of my education, experience, publications, awards and honors, patents, publications, and presentations is provided in my CV, a copy of which is attached as Exhibit A to this Declaration.

12. I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$800 per hour. My compensation is not dependent in any way upon the outcome of this matter.

II. MATERIALS CONSIDERED

13. At the front of this document is a list of materials that I considered and reviewed in connection with providing this declaration.

III. LEGAL STANDARDS

14. I am not a patent attorney nor have I independently researched the law on patentability.

A. Prior Art Date

15. I understand from counsel that the relevant date for determining whether a reference is prior art may not be the actual filing date of a patent application. I also understand from counsel that a patent may be entitled to an earlier effective filing date if the claimed invention was previously described in an earlier patent application. I further understand from counsel this is sometimes called a “priority” date of the claimed invention.

16. I understand from counsel that the “prior art” includes patents and printed publications that existed before the earliest filing date (the “effective filing date”) of the claim in the patent.

17. I also understand from counsel that a prior art reference can disclose a claim feature because the feature is expressly described, or because the feature is inherent in the disclosure. I understand from counsel that something is inherent in a prior art reference if the missing description matter must necessarily be present, and

it would be so recognized by a person of ordinary skill in the art. I also understand from counsel that inherency cannot be established by probabilities or possibilities, and that the mere fact that something may result from a given set of circumstances is not sufficient to show inherency.

18. I also understand from counsel that it is acceptable to consider evidence other than the information in a particular prior art document to determine if a feature is necessarily present or inherently described by that reference.

B. Obviousness

19. I understand from counsel that 35 U.S.C. § 103 governs the determination of obviousness. I understand from counsel that 35 U.S.C. § 103 states:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

20. I further understand from counsel that the four factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the

pertinent art; and (4) secondary considerations including long-felt need, commercial success, and unexpected results.

21. I further understand from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the anticipated success, it is likely the result is a product of ordinary skill and common sense, not innovation.

22. I also understand from counsel that when a patent simply arranges old elements with each element performing the same function it had been known to perform and the combination yields no more than one would expect from such an arrangement, the claim to the combination is obvious.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

23. I understand from counsel that the legal standards of claim construction and obviousness are analyzed from the perspective of a hypothetical person of ordinary skill in the art.

24. I understand from counsel that Exelixis has proposed that a person of ordinary skill in the art (“POSA”) related to U.S. Patent 11,298,349 (the “’349 patent,” Ex. 1046) would have had at least a bachelor’s degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with

several years of experience working in pharmaceutical development and/or solid-state chemistry and would also have been part of a team which would have included synthetic organic chemists and process chemists, formulation scientists, analytical scientists and clinicians. I understand from counsel that the '039 patent (Ex. 1001) claims priority from the '349 patent. I have been asked to apply this definition of a POSA. Accordingly, my opinions, as set forth herein, are from the perspective of a POSA (and the team being consulted), as set forth above.

25. I understand from counsel that the earliest alleged priority application listed on the '039 patent is dated February 10, 2011. Ex. 1001 ('039 patent) at (60) ("Provisional application No. 61/441,520, filed on Feb. 10, 2011, provisional application No. 61/441,527, filed on Feb. 10, 2011."). I understand from counsel that, as a result, any publications from February 9, 2011 or earlier are available as prior art. Thus, I have carried out my analysis of obviousness from the perspective of a POSA using February 9, 2011 as the relevant time frame. However, my opinions discussed herein would not change if a later priority date were assigned.

26. Given my educational and professional background, and my collaborations with other scientists and clinicians in my career, I would have been a member of the team that a POSA would have consulted due to my expertise as a synthetic organic chemist.

V. CLAIM CONSTRUCTION

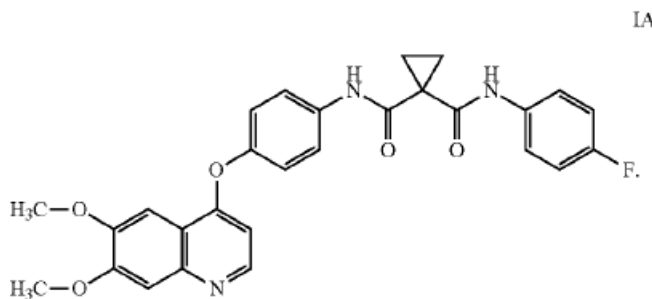
27. I understand from counsel that “claim construction” is the interpretation of the meaning of patent claims. I also understand from counsel that, in an IPR, words of a claim are generally given their plain and ordinary meaning, which is the meaning the term or phrase would have to a POSA at the time of the invention. I understand from counsel that both intrinsic and extrinsic evidence can be used to assist in understanding the meaning of a claim. Intrinsic evidence includes the claim language, language in other claims of the patent, the specification, and the prosecution history. I further understand from counsel that, unless required by the claim language or specification, claims should generally not be limited to embodiments in the specification, including preferred embodiments. I also understand from counsel that extrinsic evidence, which consists of all evidence external to the patent and prosecution history including expert and inventor testimony, dictionaries, and technical publications, including those known and authoritative in a particular technical field, may also be relevant to claim construction. I further understand from counsel that a patent applicant may act as his or her own lexicographer and set forth a special definition of a claim term in the specification.

28. Unless otherwise indicated, I have utilized the plain and ordinary meaning of any claim term in my analysis.

VI. INTRODUCTION TO THE '039 PATENT

29. The '039 patent is entitled “Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds.” Ex. 1001 ('039 patent) at (54).

30. In the section entitled “Background of the Invention,” the '039 patent identifies “compound IA” as being a “[s]mall-molecule compound[] that specifically inhibit[s], regulate[s], and/or modulate[s] the signal transduction of kinases.” Ex. 1001 ('039 patent) at col. 2, line 66 to col. 3, line 19. The structure of compound IA is set forth below:

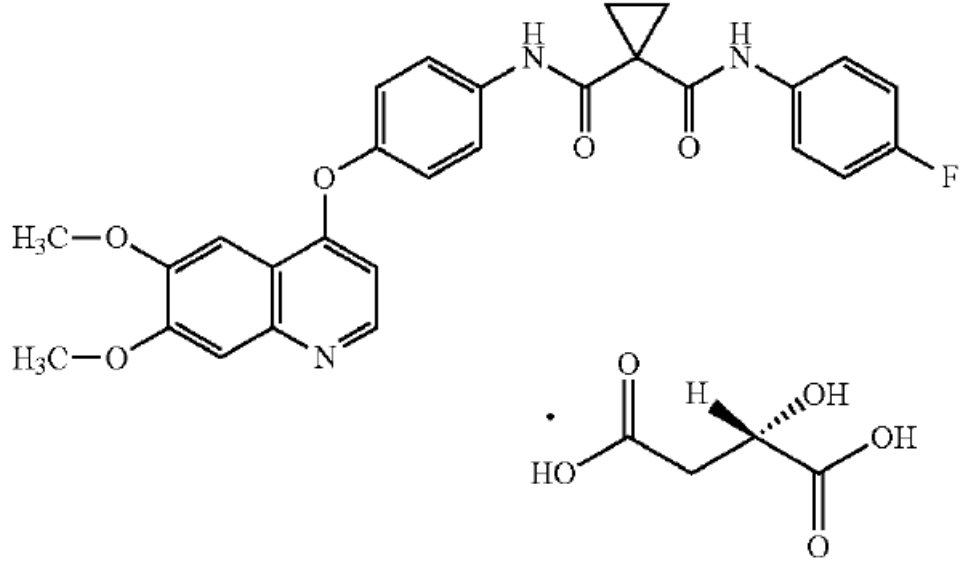


Ex. 1001 ('039 patent) at col. 3, lines 6-19.

31. After setting forth the structure of “compound IA,” the '039 patent states: “WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by

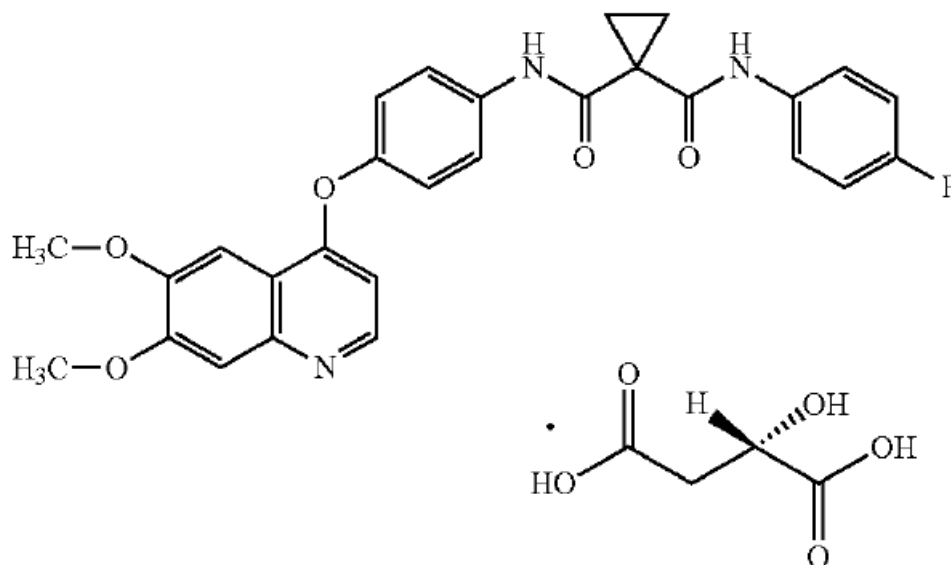
reference.” Ex. 1001 (’039 patent) at col. 3, lines 20-25. Thus, a POSA would understand from these statements that “compound IA” was a known compound in the prior art. I will refer to “compound IA” as cabozantinib.

32. I understand from counsel that Azurity is challenging the patentability of claims 1-22 of the ’039 patent (hereinafter, the “Challenged Claims”). These claims are recited in the table below:

Claim 1
1. A pharmaceutical composition for oral administration comprising Compound IB: IB  and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a tablet or a capsule, and wherein the pharmaceutical composition contains 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 2
2. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition contains 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 3
3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition contains 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 4
4. The pharmaceutical composition of claim 3, wherein the pharmaceutical composition contains 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 5
5. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition contains 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 6
6. A method of treating cancer, comprising administering to a subject in need thereof a pharmaceutical composition comprising Compound IB:

IB



and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a tablet or a capsule, and wherein the pharmaceutical composition contains 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 7

7. The method of claim 6, wherein the pharmaceutical composition contains 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 8

8. The method of claim 7, wherein the pharmaceutical composition contains 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 9

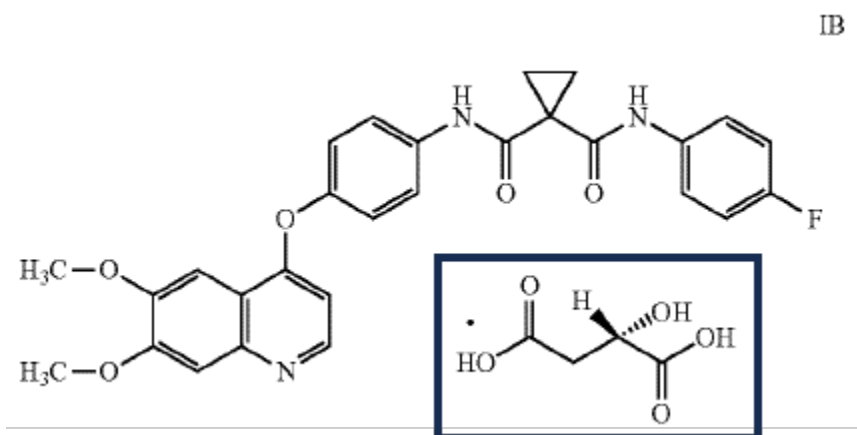
9. The method of claim 8, wherein the pharmaceutical composition contains 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Claim 10

10. The method of claim 9, wherein the pharmaceutical composition contains 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.
Claim 11
11. The method of claim 6, wherein the cancer is renal cancer.
Claim 12
12. The method of claim 6, wherein the cancer is prostate cancer.
Claim 13
13. The method of claim 6, wherein the cancer is hepatocellular carcinoma.
Claim 14
14. The method of claim 7, wherein the cancer is renal cancer.
Claim 15
15. The method of claim 7, wherein the cancer is prostate cancer.
Claim 16
16. The method of claim 7, wherein the cancer is hepatocellular carcinoma.
Claim 17
17. The method of claim 8, wherein the cancer is renal cancer.
Claim 18
18. The method of claim 8, wherein the cancer is prostate cancer.
Claim 19
19. The method of claim 8, wherein the cancer is hepatocellular carcinoma.

Claim 20
20. The method of claim 9, wherein the cancer is renal cancer.
Claim 21
21. The method of claim 9, wherein the cancer is prostate cancer.
Claim 22
22. The method of claim 9, wherein the cancer is hepatocellular carcinoma.

33. Claims 1 and 6 identity “Compound IB” by name and by structure, which is set forth below:



The relationship between cabozantinib and “Compound IB” is that Compound IB is a protonated salt form of cabozantinib. Because Compound IB is a salt, it also contains a counterion, the neutral form of which I have indicated with a blue box in the above structure. The salt counterion that I have identified is (*L*)-malate (shown as (*L*)-malic acid in the structure). *See, e.g.*, Ex. 1001 (’039 patent) at col. 28, line

61 to col. 29, line 16 (identifying “*L*-malic acid” in the preparation of “Compound IB”). Thus, I will refer to “Compound IB” as cabozantinib (*L*)-malate to indicate that it is the salt formed from cabozantinib and (*L*)-malic acid.

34. Later in the ’039 patent, the document states: “Processes for preparing the N-1 and N-2 forms of compound IB are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.” Ex. 1001 (’039 patent) at col. 19, lines 28-31. I will refer to “WO 2010/083414” as Brown (Ex. 1003). From this statement in the ’039 patent, and which I will explain in further detail herein, a POSA would understand that cabozantinib (*L*)-malate was a known compound in the prior art.

VII. GROUND 1: OBVIOUSNESS (BROWN AND KUBO)

35. I understand from counsel that another expert for Azurity will explain why the pharmaceutical composition and the methods of treatment recited in claims 1-22 would have been obvious having assumed that cabozantinib (*L*)-malate having equal to or less than the recited concentration range of 6,7-dimethoxy-quinoline-4-ol would have been obvious. *See, e.g.*, Ex. 1001 (’039 patent) at claims 1 and 6 (reciting “100 ppm or less”), claims 2 and 7 (reciting “50 ppm or less”), claims 3 and 8 (reciting “25 ppm or less”), claims 4 and 9 (reciting “10 ppm or less”), claims 5 and 10 (reciting “5 ppm or less”), and claims 11-22 (referring back to one of claims 6-9).

36. Accordingly, in this section, I explain why, in fact, it would have been obvious to a POSA (and the team being consulted) to prepare cabozantinib (*L*)-malate containing an amount of 6,7-dimethoxy-quinoline-4-ol that is equivalent to that produced by the '039 patent in view of Brown (Ex. 1003) and Kubo (Ex. 1028).

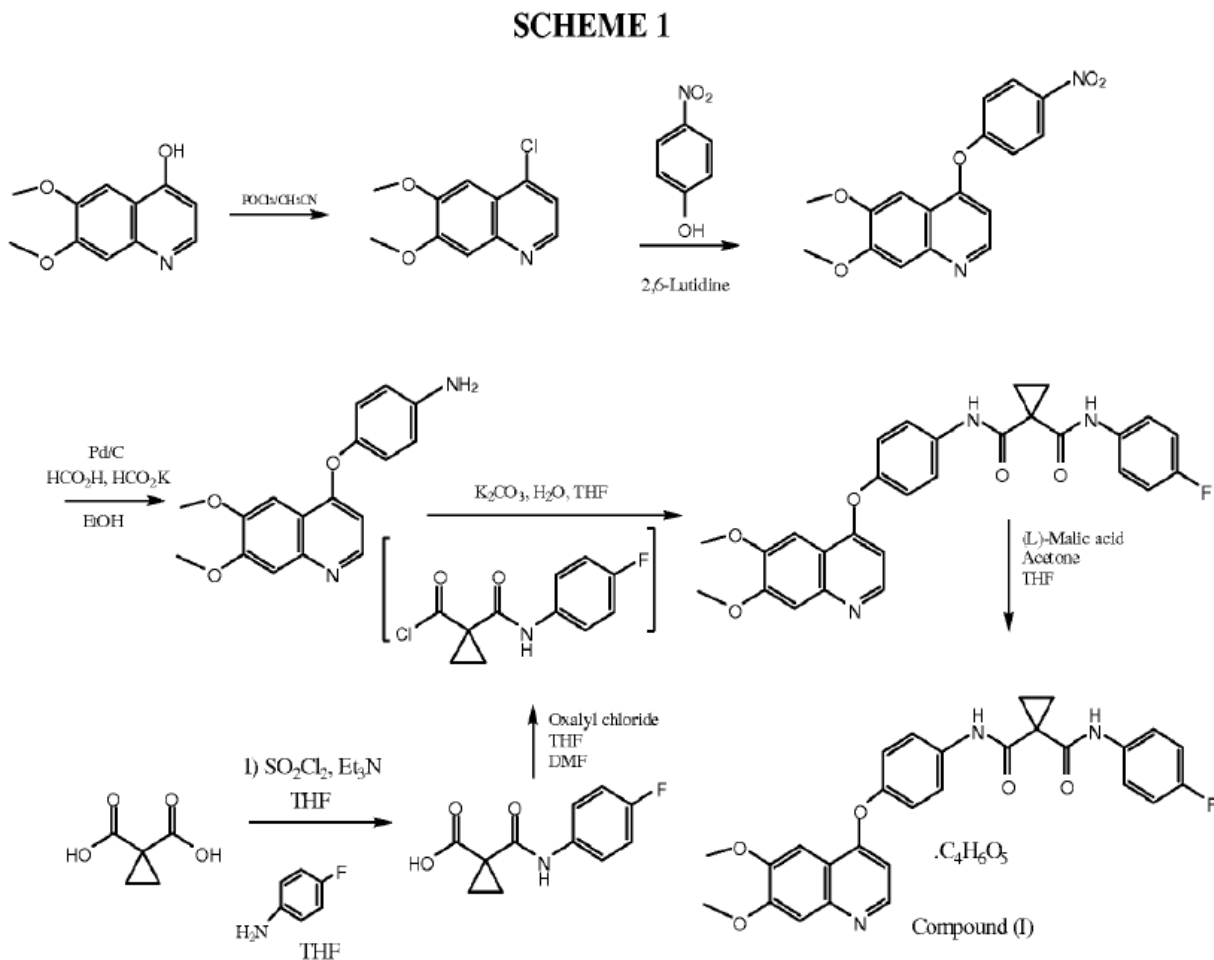
A. Introduction to Brown

37. Brown is entitled “Malate Salt of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1-dicarboxamide, and Crystalline Forms Thereof for the Treatment of Cancer.” I note that the International Publication Number for Brown is “WO 2010/083414.” This is the same publication number identified in the '039 patent as describing processes for preparing Compound IB and crystalline forms N-1 and N-2. Ex. 1001 ('039 patent) at col. 19, lines 28-31 (“Processes for preparing the N-1 and N-2 forms of compound IB are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.”).

38. Brown refers to the (*L*)-malate salt of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as “Compound (I).” Ex. 1003 (Brown) at [0051]. Brown identifies “Compound (I)” as having “a preferred combination of pharmaceutical properties for development.” *Id.* at [0052]. To avoid confusion with the shorthand nomenclature in the various

references I discuss, I will endeavor to refer to Brown's "Compound (I)" and the '039 patent's "Compound IB" as cabozantinib (*L*)-malate.

39. Brown provides a synthetic route for the preparation of cabozantinib (*L*)-malate ("Scheme 1"), which is reproduced below:



Ex. 1003 (Brown) at [0099].

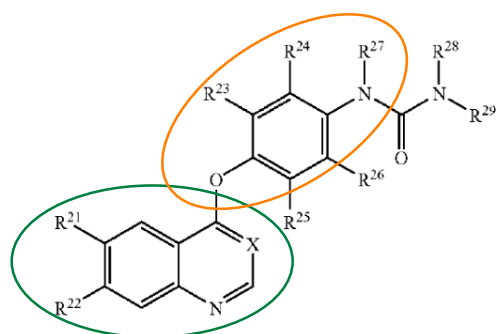
B. Introduction to Kubo

40. Kubo is entitled "Quinoline Derivatives and Quinazoline Derivatives."

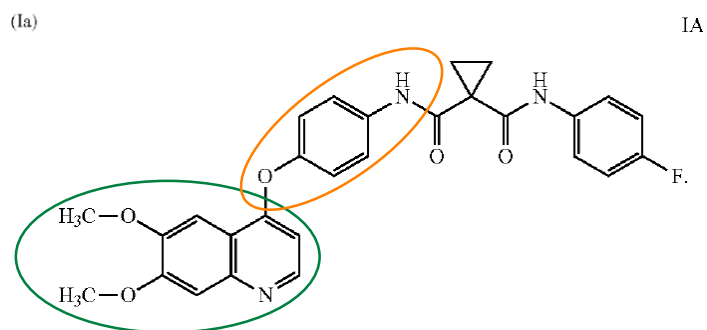
Kubo states that "the present invention relates to quinoline derivatives and

quinazoline derivatives that are useful for the treatment of diseases such as tumor” Ex. 1028 (Kubo) at col. 1, lines 7-13. Accordingly, Kubo’s compounds are similar in their stated function to those provided in Brown as well as the ’039 patent, Ex. 1003 (Brown) at [0010], [0012] (identifying cabozantinib and its malate salts for treating “cancer”); Ex. 1001 (’039 patent) at col. 1, lines 34-39 (“More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death”).

41. Kubo’s compounds are also similar in their skeletal structure to cabozantinib. An annotated comparison that highlights skeletal similarities is provided below:



Kubo at col. 4, line 34 to col. 5, line 23

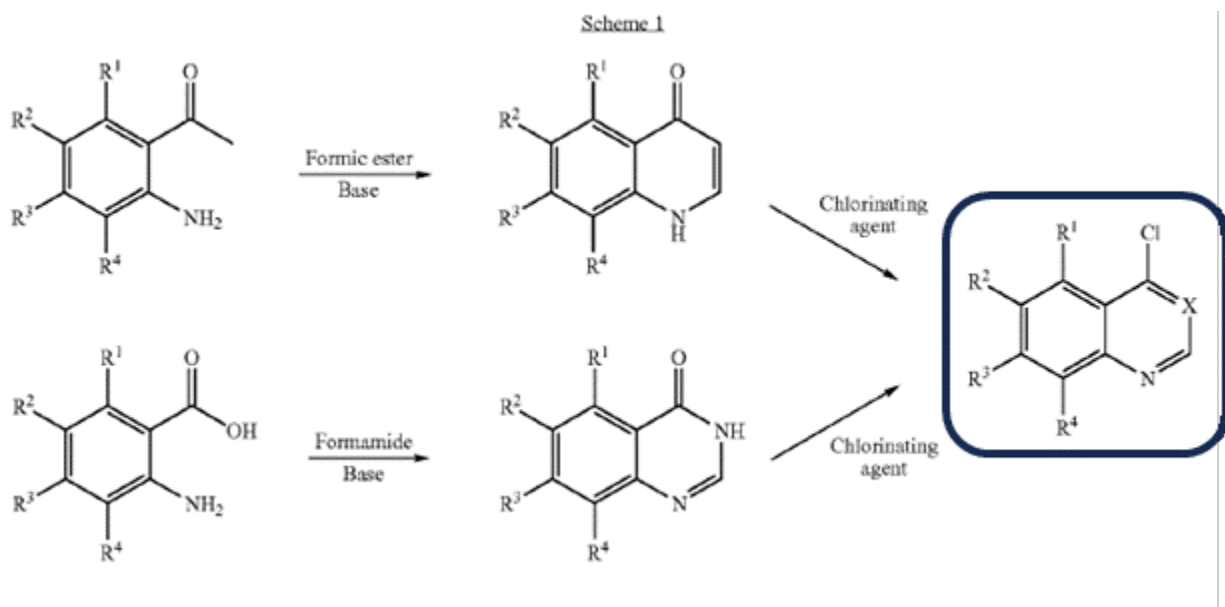


'039 patent at col. 3, lines 6 to 19

In the annotation above, I have used green circles to illustrate the common 6,7-disubstituted quinoline ring system that is present in Kubo and cabozantinib, and I

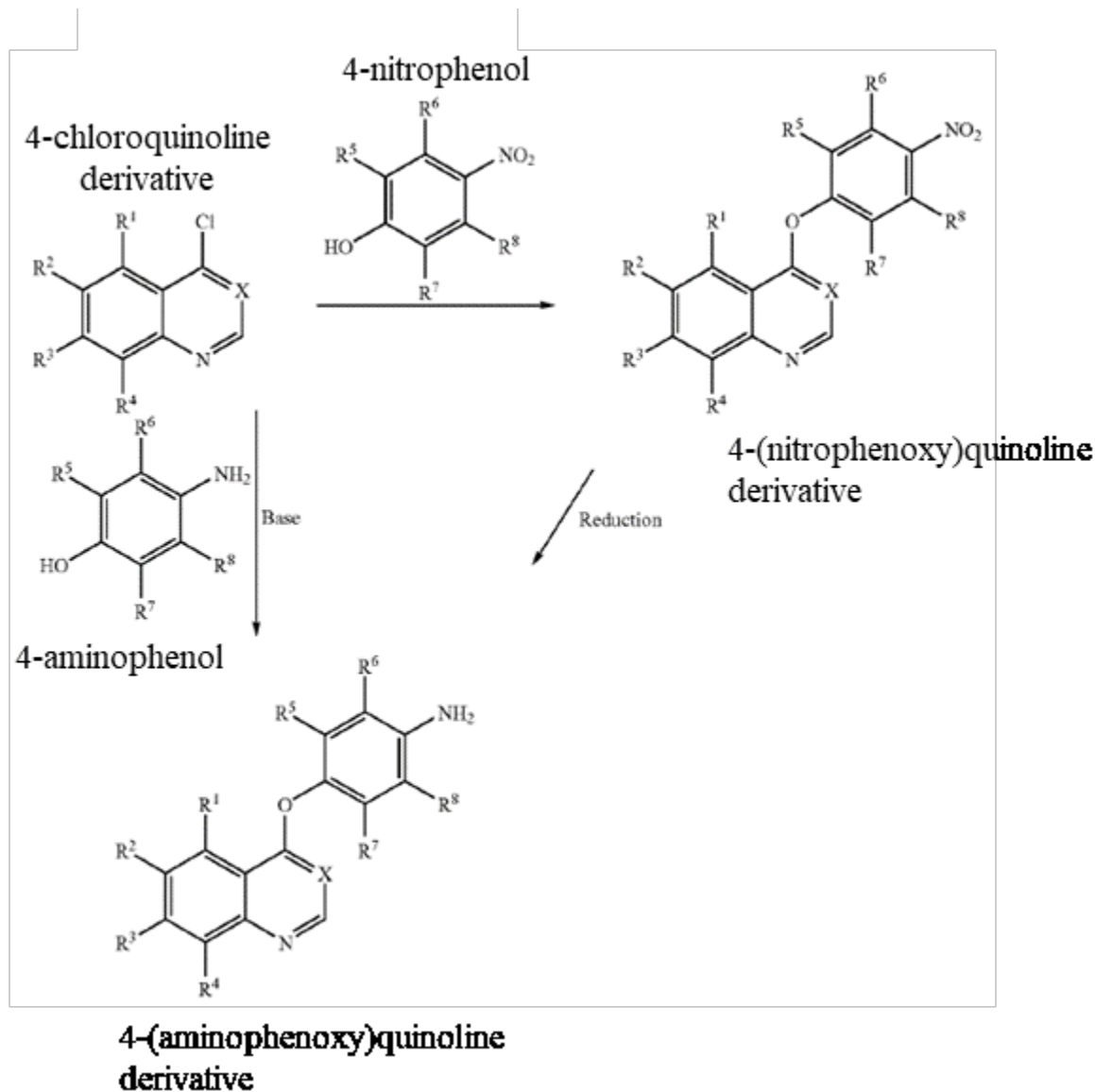
have used orange circles to highlight the 4-aminophenoxy motif that is appended to the 4-position of the quinoline ring system in both Kubo and cabozantinib.

42. Kubo provides a synthetic route that describes the approach to preparing the compounds identified therein. Ex. 1028 (Kubo) at cols. 9-12 (Scheme 1). Scheme 1 of Kubo begins with the preparation of a 4-chloroquinoline derivative:



Ex. 1028 (Kubo) at cols. 9-10 (annotated). I have indicated the 4-chloroquinoline derivative using a blue box. It is prepared by following the pathway across the top of the Scheme, in which the “X” in the obtained derivative is a carbon-hydrogen group (C–H), such that a quinoline ring is obtained. The lower pathway of the Scheme affords a 4-chloroquinazoline derivative, in which case the “X” is a nitrogen atom (N).

43. Kubo's Scheme 1 then proceeds to detail two alternative pathways that utilize the 4-chloroquinoline derivative to ultimately obtain the same 4-aminophenoxy-quinoline compound. Ex. 1028 (Kubo) at cols. 11-12. I have provided an annotated scheme below:



44. Kubo describes the two pathways of Scheme 1 as follows:

Next, 4-chloroquinoline derivative or a corresponding quinazoline derivative is allowed to act on nitrophenol in the presence of a suitable solvent or in the absence of a solvent to synthesize a 4-(nitrophenoxy)quinoline derivative or a corresponding quinazoline derivative which is then stirred in a suitable solvent, for example, *N,N*-dimethylformamide, in the presence of a catalyst, for example, palladium hydroxide-carbon or palladium-carbon, in a hydrogen atmosphere to give a 4-(aminophenoxy)quinoline derivative or a corresponding quinazoline derivative. Alternatively, a 4-chloroquinoline derivative or a corresponding quinazoline derivative may be allowed to act on aminophenol in the presence of a base, for example, sodium hydride, to give a 4-(aminophenoxy)quinoline derivative or a corresponding quinazoline derivative.

Ex. 1028 (Kubo) at col. 12, lines 46-59.

45. Thus, in Kubo's first alternative pathway, the 4-chloroquinoline derivative reacts with 4-nitrophenol to provide a 4-(nitrophenoxy)quinoline derivative. The 4-(nitrophenoxy)quinoline derivative is then subjected to reducing conditions to convert the nitro group to an amino group and afford the 4-(aminophenoxy)quinoline derivative. This first alternative is the synthetic approach described in Brown, in which 6,7-dimethoxy-4-chloroquinoline is reacted with 4-nitrophenol to afford 6,7-dimethoxy-4-(4-nitrophenoxy)quinoline that was

subsequently reduced to afford 6,7-dimethoxy-4-(4-aminophenoxy)quinoline. Ex. 1003 (Brown) at Scheme 1, [00103]-[00106].

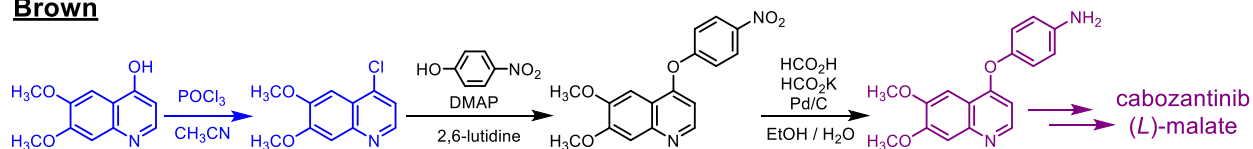
46. Moreover, in Kubo's second alternative pathway, the "4-chloroquinoline" derivative reacts with 4-aminophenol to provide the "4-(aminophenoxy)quinoline derivative" in a single synthetic step. This second alternative is the approach described in the '039 patent, in which the same 4-chloroquinoline starting material of Brown is reacted with 4-aminophenol to directly afford the "4-(aminophenoxy)quinoline derivative." Ex. 1001 ('039 patent) at col. 11, line 1 to col. 12, line 46; *id.* at col. 14, line 56 to col. 17, line 2; *id.* at col. 17, line 34 to col. 18, line 21.

C. The synthesis of cabozantinib (L)-malate in Brown and the '039 patent contain very similar steps

47. Brown provides a synthetic route for the preparation of cabozantinib (L)-malate (which is labeled as "Compound (I)" in Scheme 1). Ex. 1003 at [0099]. In Figure 1 below, I have drawn the synthetic approaches used in Brown and the '039 patent to highlight the only substantive difference between the two approaches. Brown uses a two-step reaction sequence to convert 4-chloro-6,7-dimethoxyquinoline to the 4-(aminophenoxy)quinoline derivative (shown in black), whereas the '039 patent accomplishes the same overall transformation in a single step (shown in red). Brown and the '039 patent use the same transformations to

prepare 4-hydroxy-6,7-dimethoxyquinoline and transform it into 4-chloro-6,7-dimethoxyquinoline (both shown in blue).

Brown



'039 Patent

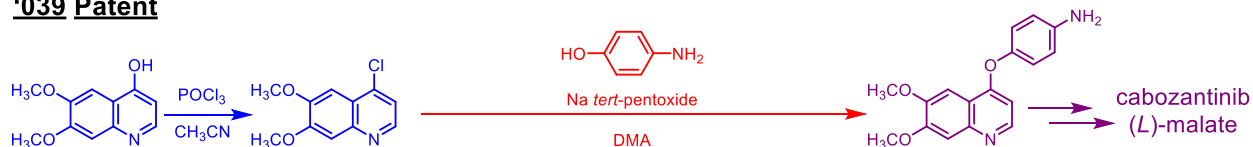


Figure 1. Comparison of synthetic routes in Brown and the '039 Patent

48. Furthermore, once both approaches converge on the 4-(aminophenoxy)quinoline derivative, Brown and the '039 patent use the same transformations to prepare cabozantinib (*L*)-malate from the 4-(aminophenoxy)quinoline derivative (shown in purple in the above Figure). To illustrate the similarities between Brown and the '039 patent downstream from the 4-(aminophenoxy)quinoline derivative, I have drawn the conserved transformations in detail below. These syntheses are identical except for the solvent used in the final crystallization step (shown in red), which a POSA would consider only a minor difference achieved through routine optimization. *See, e.g.*, Ex. 1001 ('039 patent) at col. 9, lines 51-56 ("The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can

be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.”).

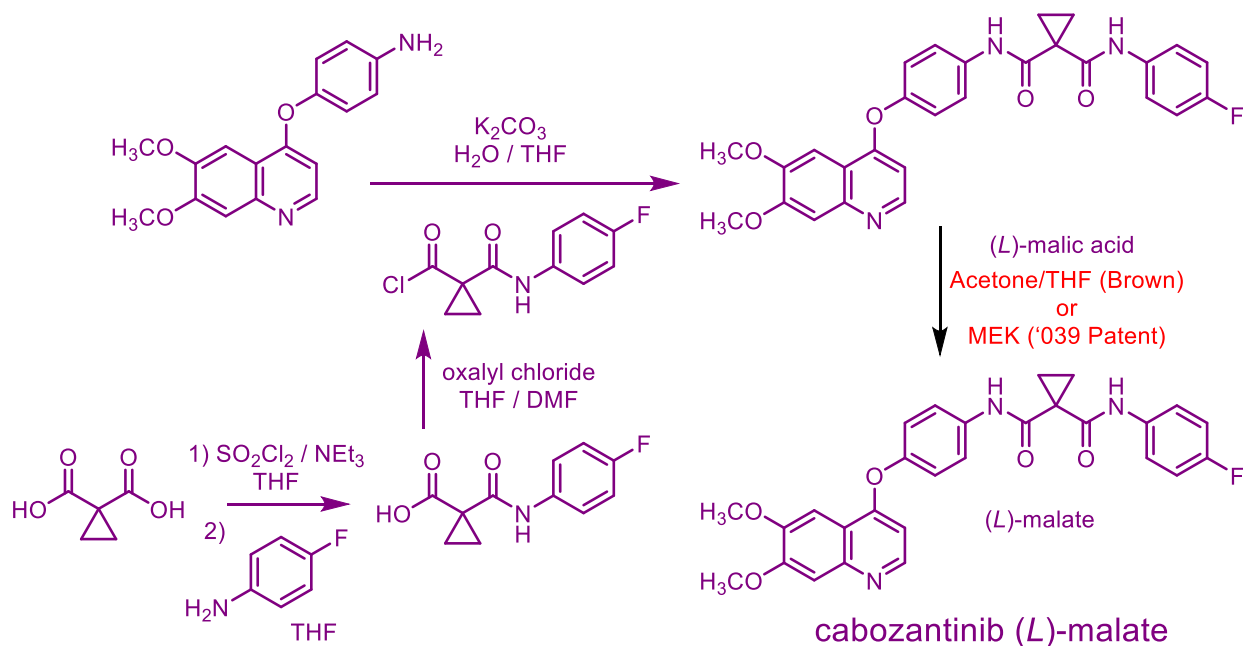


Figure 2. Transformation of the 4-(aminophenoxy)quinoline derivative to cabozantinib (L)-malate as described in Brown and the '039 patent.

49. Furthermore, with regard to forming certain crystalline forms of cabozantinib (L)-malate, Brown shares more than a great deal of similarity with the processes described in the '039 patent. When Brown describes the preparation of crystalline Forms N-1 and N-2 of cabozantinib (L)-malate, the processes that Brown provides are verbatim to the processes provided in the '039 patent for obtaining cabozantinib (L)-malate as the crystalline N-1 or N-2 form. *Compare* Ex. 1003

(Brown) at [00115]-[00127] *with* Ex. 1001 ('039 patent) at col. 29, line 54 to col. 31, line 3.

50. The conversion of 6,7-dimethoxy-quinoline-4-ol to the corresponding 4-chloro-6,7-dimethoxyquinoline, which is identical between Brown and the '039 patent, deserves further discussion in view of the impurity limitations recited in claims 1-10 of the '039 patent. Both Brown's process and the '039 patent's process utilize 6,7-dimethoxy-quinoline-4-ol as a starting material, which I have colored in blue in Figure 1, above. This is the same material identified by name in claims 1-10 of the '039 patent.

51. Additionally, in Brown's synthetic process, the reaction used to prepare 4-chloro-6,7-dimethoxy-quinoline from 6,7-dimethoxy-quinoline-4-ol is "deemed complete" at the time "when <2% of the starting material" (i.e. 6,7-dimethoxy-quinoline-4-ol) remains. Ex. 1003 (Brown) at [00102]. Thus, a POSA would understand from Brown that the 6,7-dimethoxy-quinoline-4-ol starting material may not be fully consumed by the reaction. Rather, it may remain in some unknown amount as a contaminant of the desired reaction product. Given the above benchmark for reaction completion, it is likely that the amount of residual 6,7-dimethoxy-quinoline-4-ol in the product will be <2%, with the exact amount present dependent on both the actual extent of the reaction and the effectiveness of the isolation of the desired product.

52. Because the product of the reaction (i.e., 4-chloro-6,7-dimethoxy-quinoline) is used as a starting material in the next step of Brown's process, if present, 6,7-dimethoxy-quinoline-4-ol may be carried through Brown's synthesis as an impurity. Brown acknowledges that such impurities may be present in the cabozantinib (*L*)-malate provided by the synthesis. Ex. 1003 (Brown) at [0097] ("The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or *reaction impurities*² and/or *processing impurities* that arise, for example, when the crystalline form is prepared."). However, Brown indicates that their presence "may be determined by analytical techniques known in the art." Ex. 1003 (Brown) at [0097]. Thus, a POSA would have understood from Brown's synthesis that 6,7-dimethoxy-quinoline-4-ol may exist as a reaction impurity in Brown's cabozantinib (*L*)-malate and may be readily detected.

53. However, even if small amounts of the 6,7-dimethoxy-quinoline-4-ol were present in crude reaction product, a POSA would not necessarily expect the 6,7-dimethoxy-quinoline-4-ol to be present in detectable amounts in the cabozantinib (*L*)-malate obtained by Brown's process. This is because each of the steps after the formation of the 4-chloro-6,7-dimethoxyquinoline include conditions and processes that would reasonably be expected to reduce the amount of any

² Unless otherwise indicated, all emphases are added.

“reaction impurity” or “process impurity” resulting from Brown’s synthesis. *See* Ex. 1003 (Brown) at [00102] (crystallizing the 4-chloro-6,7-dimethoxy-quinoline product), [00104] (precipitating the 6,7-dimethyl-4-(4-nitro-phenoxy)-quinoline [sic] product), [00106] (precipitating the 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine product), [00108] (precipitating the 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid product), [00112] (precipitating the N-(4-{[6,7-bis(methyloxy)quinoline-4-yl]oxy}phenyl)-N’-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide [i.e., “cabozantinib”] product), [00115]-[00127] (crystallizing the cabozantinib (*L*)-malate).

54. I understand from counsel that experts for Exelixis have admitted, and that the district court in a litigation over the ’349 patent (Ex. 1046), found Brown’s cabozantinib (*L*)-malate to contain “at most, de minimis” 6,7-dimethoxy-quinoline-4-ol. To avoid any confusion, I will adopt the same “de minimis” terminology for the product of Brown’s synthesis.

D. Kubo teaches that the difference between Brown’s synthesis and the ’039 patent’s synthesis is a choice between “alternatives”

55. In Figure 1, I compared the syntheses used in Brown and the ’039 patent. To aid in my discussion of these syntheses and Kubo, I have incorporated Kubo’s one-step transformation (shown in red) of 4-chloro-6,7-dimethoxyquinoline to the 4-(aminophenoxy)quinoline derivative as Figure 3.

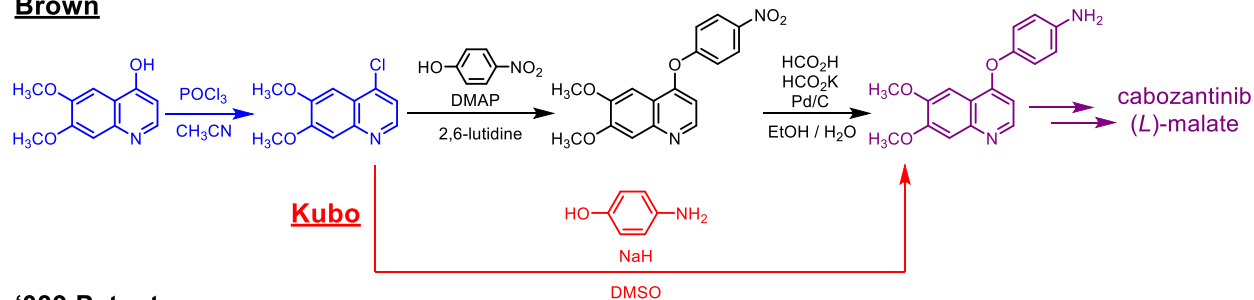
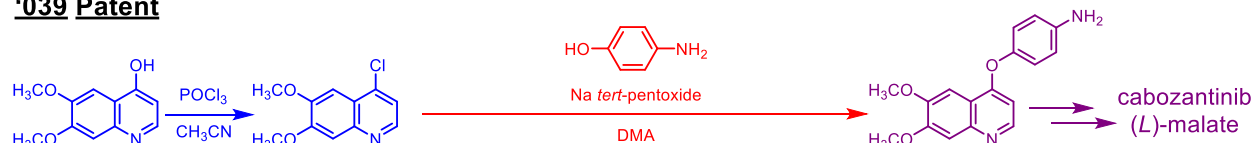
Brown**'039 Patent**

Figure 3. Schematic illustration of how a POSA would combine the teachings of Kubo and Brown to arrive at the claimed synthesis of the '039 patent.

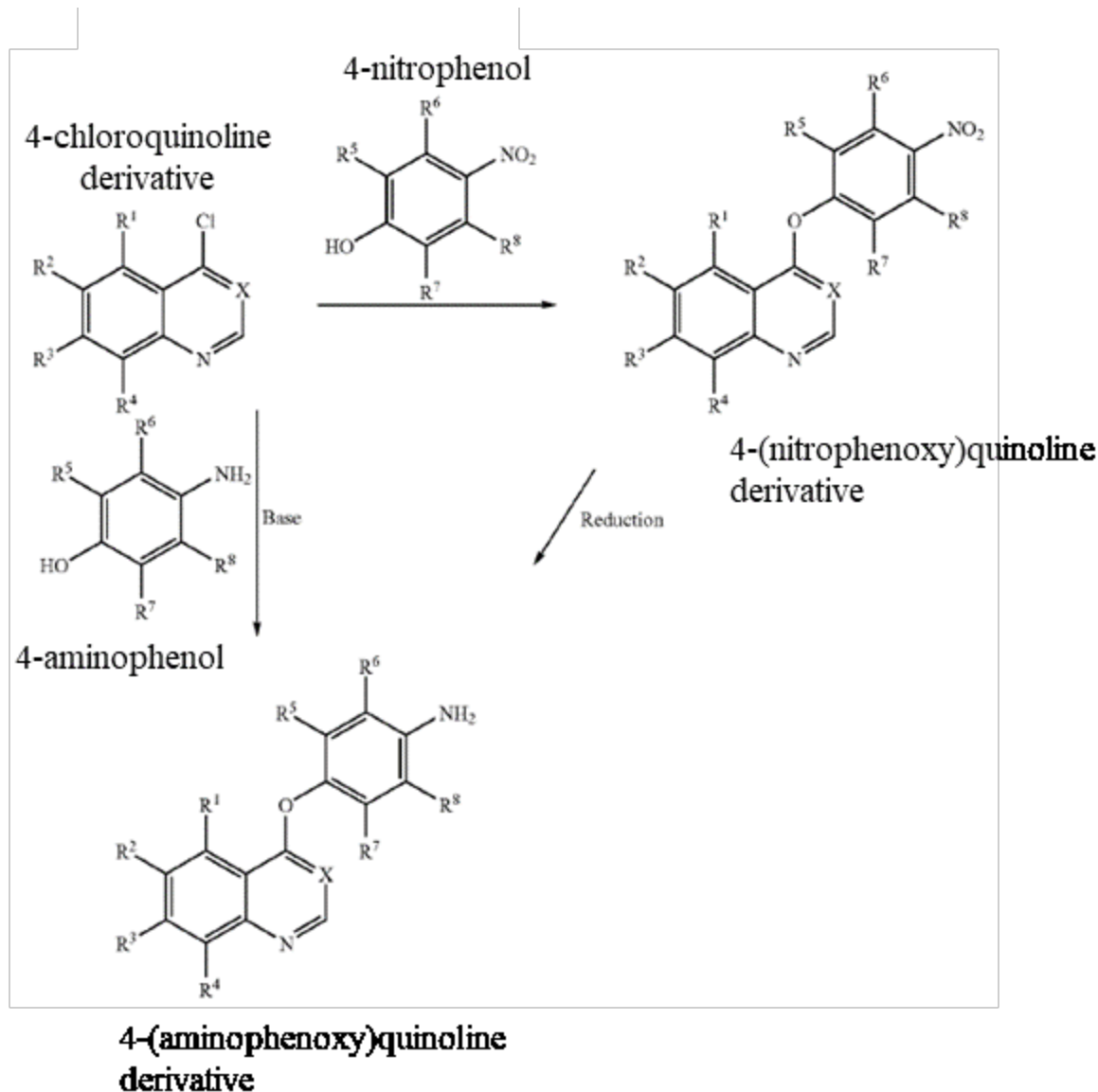
In Brown, the 4-chloro-6,7-dimethoxy-quinoline material is reacted with 4-nitrophenol to afford 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline. In the next step, the nitro group (-NO₂) of the 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline material is reduced using formic acid and a palladium on carbon catalyst (Pd/C), which transforms it into an amino group (-NH₂) to afford 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine.

56. In contrast, the '039 patent prepares the same product (i.e., 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine) by reacting the 4-chloro-6,7-dimethoxyquinoline with 4-aminophenol. In this way, the '039 patent replaces Brown's two-step sequence in favor of a single step process. This is illustrated in Figure 1 of the '039 patent. *See* Ex. 1001 ('039 patent) at cols. 23-24. The single-

step sequence of the '039 patent is also described at column 11, line 1 to column 12, line 46.

57. Accordingly, the only difference in the approach for preparing cabozantinib (*L*)-malate described in Brown and the '039 patent is the two-step pathway of Brown using 4-nitrophenol and the one-step pathway of the '039 patent using 4-aminophenol. However, the '039 patent was not the first to recognize that the transformation could be accomplished using 4-aminophenol rather than 4-nitrophenol.

58. Kubo (Ex. 1028) explains that the two-step sequence in Brown (which I indicated in black in Figures 1 and 3, above) can be accomplished in a single step using 4-aminophenol instead of 4-nitrophenol. Ex. 1028 (Kubo) at col. 12, line 46 to col. 14, line 4. Kubo's Scheme 1, which I have excerpted with annotations labeling compounds below, illustrates both the 2-step pathway of Brown (using 4-nitrophenol) and the 1-step pathway of the '039 patent (using 4-aminophenol):



Ex. 1028 (Kubo) at cols. 11-12 (Annotated).

59. Kubo describes the two pathways as “alternatives” that begin with a “4-chloroquinoline derivative”:

Next, *4-chloroquinoline derivative* or a corresponding quinazoline derivative *is allowed to act on nitrophenol* in the presence of a suitable solvent or in the absence of a solvent *to synthesize a 4-*

(nitrophenoxy)quinoline derivative or a corresponding quinazoline derivative *which is then stirred* in a suitable solvent, for example, N,N-dimethylformamide, *in the presence of a catalyst*, for example, palladium hydroxide-carbon or *palladium-carbon*, in a hydrogen atmosphere *to give a 4-(aminophenoxy)quinoline derivative* or a corresponding quinazoline derivative. *Alternatively, a 4-chloro-quinoline derivative* or a corresponding quinazoline derivative may be *allowed to act on aminophenol* in the presence of a base, for example, sodium hydride, *to give a 4-(aminophenoxy)quinoline derivative* or a corresponding quinazoline derivative.

Ex. 1028 (Kubo) at column 12, lines 46-59.

60. Kubo's "alternative" two-step pathway and Brown's two-step pathway are very similar. Both Kubo and Brown can be characterized as using a 4-chloroquinoline derivative as the starting material. Both Kubo and Brown can be characterized as teaching the use of a 4-nitrophenol to react with the 4-chloroquinoline derivative to afford a 4-(nitrophenoxy)quinoline derivative. And both Kubo and Brown teach the reduction of the nitro group on the 4-(nitrophenoxy)quinoline derivative using a palladium on carbon catalyst to afford a 4-(aminophenoxy)quinoline derivative.

61. Likewise, Kubo's "alternative" one-step pathway and the '039 patent's one-step pathway are very similar. Both Kubo and the '039 patent can be characterized as using a 4-chloroquinoline derivative as the starting material. Both

Kubo and the '039 patent can be characterized as teaching the use of 4-aminophenol to react with the 4-chloroquinoline derivative to afford a 4-(aminophenoxy)quinoline derivative.

62. In sum, Kubo's one-step alternative (which is followed by the '039 patent) to prepare the 4-(aminophenoxy)quinoline derivative merely avoids the two-step alternative (which is followed by Brown) of preparing a 4-(nitrophenoxy)quinoline derivative and reducing the nitro group using the same catalyst (palladium on carbon) to afford the "4-(aminophenoxy)quinoline derivative."

E. A POSA would have been motivated to apply Kubo's one-step alternative to Brown's synthesis of cabozantinib (L)-malate

63. A POSA would have been motivated to incorporate Kubo's alternative one-step pathway for preparing a "4-(aminophenoxy)quinoline derivative" into Brown's synthesis of cabozantinib (L)-malate because it would have been a more efficient approach.

64. First, it would have been obvious to a POSA that Kubo's single-step approach saves one step in the synthesis of cabozantinib (L)-malate as compared to Brown's (and Kubo's) alternative two-step approach. Saving even a single step in a multi-step synthesis is generally considered to be a more efficient approach when synthesizing a compound. *See, e.g.*, Ex. 1029 (Hoffmann) at 133 ("A synthesis that

reaches the target in fewer steps than another one is considered superior.”); Ex. 1030 (Newhouse) at 3012 (“[M]inimising the number of steps leads to an efficient multistep synthesis in terms of cost and time expended to obtain the desired product.”); Ex. 1031 (Burns) at 2855 (“Minimizing the total number of steps ... lays a foundation for achieving overall efficiency.”).

65. According to Hoffmann, “one could reach the nearly trivial conclusion that a synthesis is better, the shorter it is (the least number of bonds in the bond-set); the fewer the number of refunctionalization steps involved (oxidations, reductions); the fewer the number of protecting group steps; and the more it relies on reactions that form two or more skeletal bonds at a time.” Ex. 1029 (Hoffmann) at 136. Brown’s two-step approach to prepare a “4-(aminophenoxy)quinoline derivative” by first preparing a “4-(nitrophenoxy)quinoline derivative” to then reduce the “nitro” group to afford the “4-(aminophenoxy)quinoline derivative” is a quintessential example of Hoffmann’s reference to an unnecessary refunctionalization step—incorporating a “nitro” group only to reduce it to an “amino” group in the very next step. It is specifically inefficient when compared against Kubo’s alternative one-step preparation of the same 4-(aminophenoxy)quinoline derivative.

66. To further refine the inefficiency of Brown’s two-step approach in view of Kubo, I have revised Brown’s Scheme 1 below to illustrate how Kubo’s

[illegible]

35

metal-containing catalyst, palladium-on-carbon. It would further be expected to save a POSA from the expense of chemical waste disposal for this unnecessary functional group reduction. Similarly, it would be expected to save a POSA in terms of human effort and reactor space and time by not needing to perform the unnecessary reduction reaction. A POSA would also recognize that the one-step procedure would circumvent safety considerations of working with the Pd/C catalyst used in the unnecessary reduction step, as it is a flammable solid that can cause ignition of organic solvents if not handled correctly. *See, e.g.*, Ex. 1035 (Felpin) at 12440 (“For instance, from a safety perspective, Pd/C is highly pyrophoric and, thus, spontaneously flammable in the presence of oxygen and methanol vapours, causing serious handling issues.”). That is not to say that each of these expectations would necessarily come to fruition, but they are manifestly evident considerations motivating a POSA to incorporate Kubo’s alternative one-step approach.

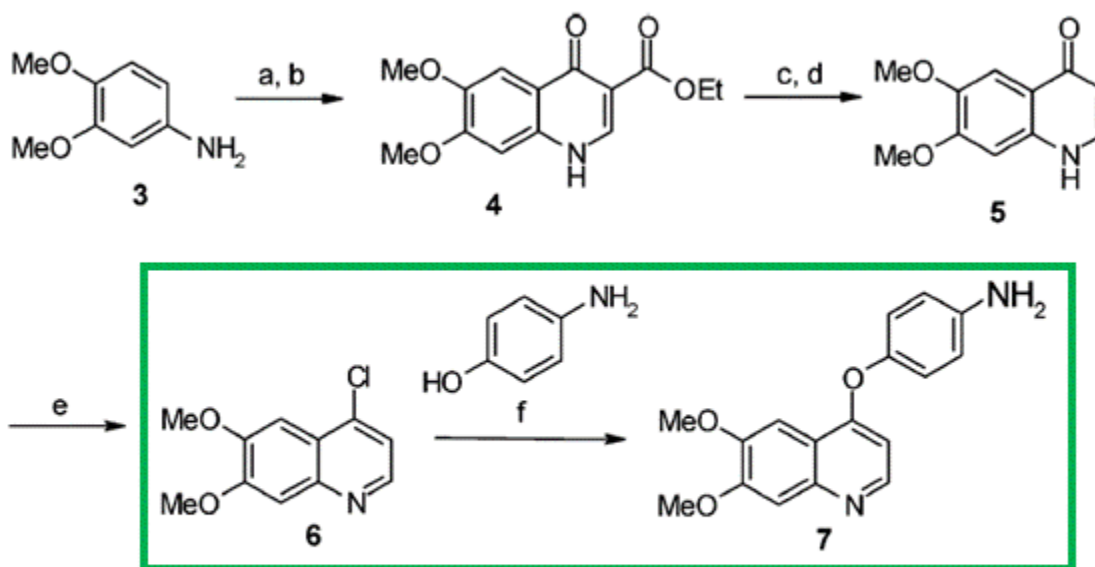
68. Third, it would have been obvious to a POSA that Kubo’s single-step approach could provide higher overall yield and product throughput. Brown does not directly report the yield of its two-step approach, but it is readily calculated from Brown’s description. Ex. 1003 (Brown) at [00103]-[00106]. In Brown’s synthesis of 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (Ex. 1003 at [00104]), there is sufficient information to determine the limiting reagent, theoretical yield, and isolated yield of the product of each reaction. For example, the 7.0 kg of 4-

nitrophenol (formula weight = 139.11 g/mol) that Brown uses in the reaction is 50.3 mol of this substance. Similarly, the 8.0 kg of 4-chloro-6,7-dimethoxy-quinoline (formula weight = 223.7 g/mol) is 35.8 mol of this reagent. These reactants combine in a 1:1 ratio to prepare 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (formula weight = 326.31 g/mol), such that 4-chloro-6,7-dimethoxy-quinoline is the limiting reagent. Therefore, the theoretical yield of the 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline product is 35.8 mol, or 11.7 kg. Brown reports that 4.0 kg of this product was obtained, corresponding to an isolated yield of 34.2%.

69. The same approach can be used to determine the yield for Brown's preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine by the reduction of 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (Ex. 1003 at [00106]). Here, 4.0 kg of 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline used in this procedure corresponds to 12.3 mol. Therefore, the theoretical yield of the product, 6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (formula weight = 296.3 g/mol), is also 12.3 mol, which corresponds to 3.64 kg. Brown reports that 3.0 kg of the 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was obtained, such that the isolated yield for this reaction is 82.4%. For Brown's two-step approach to preparing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine from 4-chloro-6,7-dimethoxy-quinoline, the overall isolated yield of the two steps is the product of the yields of the individual steps, in this case 28.1%.

70. However, a POSA would have known that the alternative one-step approach involving the reaction of 4-chloro-6,7-dimethoxy-quinoline with 4-aminophenol to provide 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine could be accomplished in greater yield:

Scheme 1^a



^a Reagents and conditions: (a) diethyl ethoxymethylenemalonate, 120 °C; (b) diphenyl ether, 280 °C (66% for 2 steps); (c) 10% aqueous NaOH/MeOH, reflux; (d) diphenyl ether, 280 °C (99% for 2 steps); (e) POCl₃, reflux (85%); (f) NaH, DMSO, 100 °C (92%).

Ex. 1033 (Furuta) at 2186 (Annotated Scheme 1); *id.* at 2190 (providing a description of the experiment performed on gram-sized quantities). I have indicated the reaction, conditions, and yield for this reaction in **green**, above. Based on the very high isolated yield (92%) in the one-step alternative performed in Furuta, a POSA would have known that the alternative one-step approach can afford the same compound as prepared in Brown and would have had a very reasonable expectation

to obtain a higher yield than Brown's two-step procedure (28%, as noted above). The potential for obtaining the key intermediate (noted as **7** above in Furuta) in higher yield would have provided yet another motivation to a POSA for adopting the one-step approach to this reaction for the synthesis of cabozantinib (*L*)-malate. Indeed, in order to achieve a 92% yield for a two-step sequence, one would need to average approximately 96% yield in each individual step. Thus, a POSA would have recognized the value of such a high-yielding, single-step procedure.

71. Additionally, Kubo's description of the one-step procedure would have motivated a POSA to incorporate this alternative approach. Kubo identifies the one-step approach utilizing biphasic reaction conditions as simplifying product isolation and improving purity. Ex. 1028 (Kubo) at col. 12, line 60 to col. 14, line 2. More specifically, Kubo states: "In this reaction, for example, phenol remaining unreacted and a decomposition product of 4-chloroquinazoline are left in the aqueous layer, while the target product is present in the organic layer. That is, the organic layer contains only the target product. Therefore, the post-treatment is advantageously simple." *Id.* at col. 13, line 1 to col. 14, line 2.

72. Kubo was clearly discussing benefits for the reaction of an aminophenol with either a 4-chloroquinoline or a 4-chloroquinazoline under biphasic conditions and chose to express the observed benefits using only "4-chloroquinazoline" as the "example." *Id.* However, a POSA would have understood

Kubo as teaching that the same benefits are obtained using either a 4-chloroquinoline or a 4-chloroquinazoline. Accordingly, the “phenol” that remains unreacted is the 4-aminophenol and the “decomposition product” is either a 4-hydroxyquinazoline or a 4-hydroxyquinoline which forms when water reacts with either a 4-chloroquinoline or a 4-chloroquinazoline. Thus, Kubo teaches that for the biphasic reaction, the 4-aminophenol and either the 4-hydroxyquinazoline or the 4-hydroxyquinoline that forms will remain in the aqueous layer while the organic layer only contains the desired product of the reaction. “Post-treatment is advantageously simple” because the desired product is separated from any unreacted 4-aminophenol and any 4-hydroxyquinazoline or 4-hydroxyquinoline that formed during the reaction. *Id.*

F. A POSA would have had a reasonable expectation of successfully obtaining cabozantinib (L)-malate upon applying Kubo’s one-step alternative to Brown’s synthesis

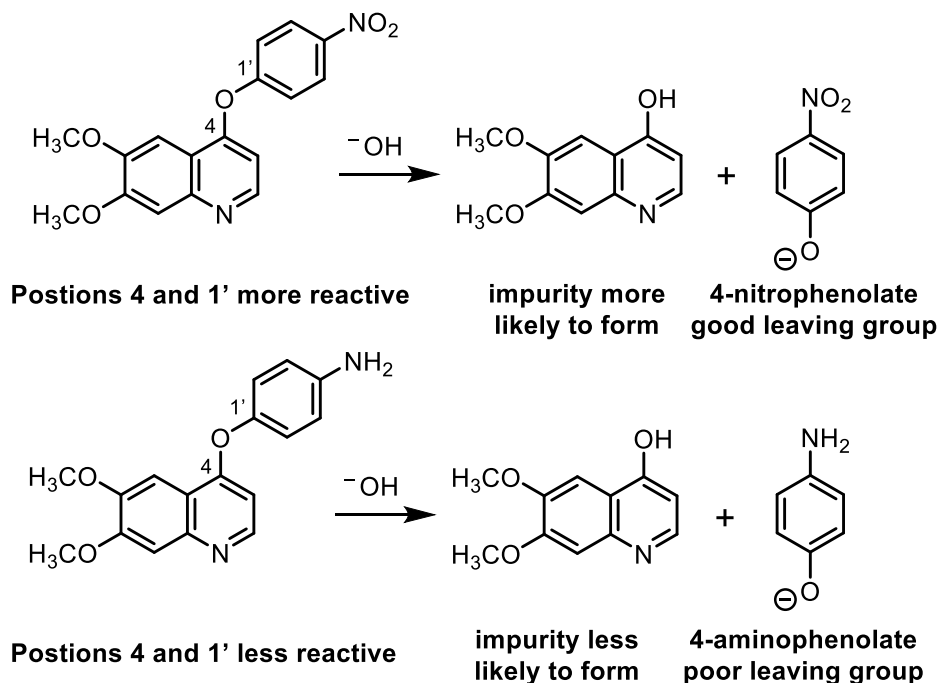
73. A POSA would have also had a reasonable expectation of successfully obtaining cabozantinib (L)-malate by applying Kubo’s one-step alternative in place of Brown’s two-step synthesis. As I have previously indicated in Figure 3 above, both approaches lead to the same intermediate, 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine, that Brown subsequently uses to prepare cabozantinib (L)-malate. Moreover, Furuta explicitly teaches that Kubo’s alternative one-step

approach will afford the desired intermediate. Ex. 1033 (Furuta) at 2186 (Scheme 1).

G. A POSA would have had a reasonable expectation of reducing the amount of any 6,7-dimethoxy-quinoline-4-ol impurity in cabozantinib (L)-malate by applying Kubo's one-step alternative to Brown's synthesis

74. I previously indicated that I understand that both Exelixis's expert and a district court have found that Brown's cabozantinib (*L*)-malate contained "at most, de minimis" 6,7-dimethoxy-quinoline-4-ol. A POSA would have had a reasonable expectation that, by applying Kubo's alternative one-step approach to Brown's synthesis of cabozantinib (*L*)-malate, the amount of 6,7-dimethoxy-quinoline-4-ol impurity would be decreased as a result of eliminating the 4-(nitrophenoxy)quinoline intermediate in Brown's synthesis.

75. A POSA would have recognized that in Brown's synthesis of cabozantinib (*L*)-malate, the 4-(nitrophenoxy)quinoline intermediate is slightly less stable than the corresponding 4-(aminophenoxy)quinoline intermediate. That is not to say that these compounds are unstable—clearly they are not because they are obtained in Brown's synthesis and the 4-(aminophenoxy)quinoline intermediate is obtained in the '039 patent's synthesis as well as in Furuta (Ex. 1033).



76. However, a POSA would expect the 4-(nitrophenoxy)quinoline compound to be less susceptible to degradation under basic conditions than the corresponding 4-(aminophenoxy)quinoline compound. There are two reasons that a POSA would have this expectation. First, when the 4-position (labeled in the above figure) of a quinoline contains a leaving group (such as the chloride atom used in the previous step of both synthetic routes), the quinoline undergoes nucleophilic substitution reactions at this position. However, the 4-position of the 4-(nitrophenoxy)quinoline will be much more activated for this type of reaction compared to the 4-(aminophenoxy)quinoline compound. Second, the liberation of a 4-aminophenolate ion is less likely to occur than the liberation of a 4-nitrophenolate ion, which is directly correlated with the relative acidities of their respective

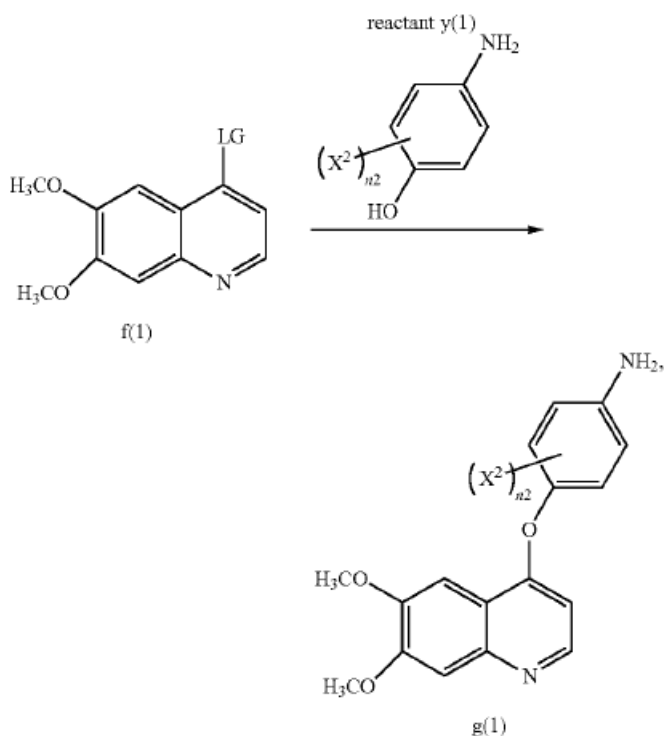
conjugate acids. Ex. 1032 (Pross) at 820 (Table II) (providing acidities of 4-aminophenol and 4-nitrophenol). Furthermore, the 1'-position of the 4-nitrophenylphenoxy group is also electrophilic, and a hydrolysis reaction at this position would also form 6,7-dimethoxy-quinoline-4-ol. Although these degradation reactions would not be expected to occur in high yield, a POSA would recognize that these processes might produce small amounts of the relevant impurity in the case of the 4-(nitrophenoxy)quinoline, and a POSA would further recognize that these reactions would be far less likely to occur in the case of the 4-(aminophenoxy)quinoline derivative. For either compound, hydrolytic degradation would form 6,7-dimethoxy-quinoline-4-ol, but this process is less likely to occur for the 4-(aminophenoxy)quinoline intermediate. And when a POSA is considering strategies to disfavor the formation of the 6,7-dimethoxy-quinoline-4-ol impurity at the 100 ppm level or lower as recited in claims 1-10 of the '039 patent, this potential difference in reactivity would further motivate the POSA to favor the direct 4-(aminophenoxy)quinoline synthesis. Thus, all things being equal, a POSA would have expected there to be a decrease in the amount of 6,7-dimethoxy-quinoline-4-ol at the end of cabozantinib (*L*)-malate's synthesis that was attributable to hydrolytic degradation of the 4-(nitrophenoxy)quinoline intermediate by avoiding its use in the synthesis.

77. Accordingly, a POSA would have had an expectation that the cabozantinib (*L*)-malate containing a “de minimis” amount of 6,7-dimethoxy-quinoline-4-ol as originally produced by Brown would contain even lower amounts of 6,7-dimethoxy-quinoline-4-ol as a result of the change in synthetic process to utilize Kubo’s one-step approach. Indeed, as I explained above in Paragraphs 73-74, Kubo teaches that when the reaction is performed using biphasic conditions, “only the target” 4-(aminophenoxy)quinoline derivative will be present in the organic layer while any 4-hydroxyquinoline “decomposition product” will be left in the aqueous layer. Thus, a POSA would be further motivated to use Kubo’s one-step approach. This is because Kubo teaches that the reaction can be run under biphasic conditions with facile purification of the 4-(aminophenoxy)quinoline derivative in the event that the reported single-solvent conditions resulted in products that were more difficult to purify.

78. Furthermore, as I previously explained, the only difference between Brown and the ’039 patent’s synthetic approaches is the two-step vs. one-step alternative as taught by Kubo. If the ’039 patent was able to synthesize cabozantinib (*L*)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (or even the lesser amounts recited in claims 2-5 and 7-10), then applying the one-step approach of Kubo would afford the same. After all, there is nothing in the ’039 patent that indicates what more must actually be done to obtain such material. The ’039 patent

certainly did not intend to require adherence to its examples. *See, e.g.*, Ex. 1001 ('039 patent) at col. 8, lines 35-42 (“The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.”); *id.* at col. 24, lines 15-30.

79. For example, there is no indication in the '039 patent that special conditions are needed to apply Kubo's alternative one-step approach. The single-step approach of the '039 patent is described at column 11, line 1 to column 12, line 46:



Ex. 1001 ('039 patent) at col. 11, lines 6-30. A POSA would find no evidence or discussion of necessary conditions for successfully applying the one-step approach. Indeed, the opposite is true. Reactions conditions need only be “suitable.” *Id.* at col. 11, lines 44-45. “Non-limiting examples of suitable reaction conditions” are indicated as including “polar solvents” such as “dimethylsulfoxide (DMSO), dimethylformamide (DMF)” and others. *Id.* at col. 11, lines 45-61. Nothing about temperature of the reaction is emphasized or discussed as being necessary, which ranges from room temperature to about 100 °C. *Id.* at col. 11, line 62 to col. 12, line 3. “Non-limiting” examples of bases are provided, which again say nothing as to necessity or importance of particular bases. *Id.* at col. 12, lines 4-20. Moreover, other sections of the '039 patent that describe the one-step approach provide additional examples of “basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent.” *Id.* at col. 17, line 32 to col. 18, line 21. Indeed, such examples of non-limiting conditions are the same as those described in Kubo and used in Brown.

80. Additionally, the '039 patent does not report or describe any measurement for levels of 6,7-dimethoxy-quinoline-4-ol in the cabozantinib (*L*)-malate active ingredient synthesized according to any description or even in any example. Moreover, there is no discussion in the '039 patent as to what reaction conditions are unsuitable for preparing such material. As I previously indicated, only “non-limiting” examples of conditions are provided with no indication of what

features are necessary or important for obtaining cabozantinib (*L*)-malate containing 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol (recited in claims 1 and 6 of the '039 patent) or even the lesser amounts recited in claims 2-5 and 7-10 of the '039 patent (and referred back to in claims 11-22).

81. Thus, in view of the disclosures of Brown and Kubo discussed above, a POSA would have obtained cabozantinib (*L*)-malate containing an amount of 6,7-dimethoxy-quinoline-4-ol that is equivalent to that afforded by the '039 patent. To the extent that the '039 patent afforded cabozantinib (*L*)-malate containing “100 ppm or less,” “50 ppm or less,” “25 ppm or less,” “10 ppm or less,” or “5 ppm or less” of 6,7-dimethoxy-quinoline-4-ol, then the combination of Brown and Kubo would have afforded the same.

VIII. GROUND 2: OBVIOUSNESS (BROWN AND ROBINSON)

A. Background Regarding Impurities

82. Active pharmaceutical ingredients (“APIs”) will inevitably contain impurities resulting from the route of synthesis and the work-up of the chemical reactions involved. Such impurities are unwanted because they “may have deleterious pharmacological and toxicological activities.” Ex. 1009 (Gibson) at 190; Ex. 1039 (Robinson) at 946 (“Impurities, however, are expected to bring no benefits – only risk. Manufacturers must therefore eliminate them (or at least mitigate the risk associated with them) to the greatest extent possible.”). Therefore, they “must

be removed from the final product” or at least be controlled to within consistent limits. Ex. 1009 (Gibson) at 190. Accordingly, the identification of impurities is “a crucial activity in drug substance” research and development. Ex. 1009 (Gibson) at 190. To facilitate research and development efforts, regulatory authorities publish guidelines for the treatment of impurities in APIs and final drug products “with the expectation that pharmaceutical companies will comply with them.” Ex. 1009 (Gibson) at 314. “Indeed, it is a regulatory requirement that the level of impurities in the drug substance be controlled.” Ex. 1009 (Gibson) at 190 (internal citations omitted).

83. There are three types of impurities routinely addressed in regulatory guidelines—organic (process- and drug-related), inorganic, and residual solvents. Ex. 1009 (Gibson) at 190; Ex. 1041 (FDA Q3A) at 2. “Organic impurities include, for example, starting materials, by-products, intermediates, degradation products as well as reagents, ligands, and catalysts.” Ex. 1009 (Gibson) at 190-91; Ex. 1041 (FDA Q3A) at 2 (“Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or nonvolatile, and include: [] starting materials[,] [] By-products[,] [] Intermediates[,] [] Degradation products[, and] [] Reagents, ligands, and catalysts”).

84. The identification and treatment of organic impurities are the ones that are relevant to the opinions expressed in this declaration. That is because the 6,7-

dimethoxy-quinoline-4-ol, which is the compound recited in claims 1-10, is an organic compound identified as a “byproduct” of synthesis in the ’039 patent. Ex. 1001 (’039 patent) at col. 22, lines 11-30. It would have been obvious that organic impurities would be present during the synthesis of an API. Ex. 1039 (Robinson) at 946 (“A drug substance will typically contain a range of low-level impurity compounds. . .”).

85. In a section entitled “Rationale for the Reporting and Control of Impurities,” the FDA’s guidance for new drug substances states:

The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH Q1A(R) on stability) used to identify potential impurities arising during storage.

The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences discussed.

Ex. 1041 (FDA Q3A) at 3. Such summaries, i.e., “the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance” and “the laboratory studies conducted to detect impurities in the new drug substance” would clearly need to address starting materials and degradation products (which were explicitly mentioned when discussing organic impurities).

86. Regulatory guidelines set limits for the amount of individual impurities that may be present in an API. The normal limit for any particular organic impurity is 0.15%, which corresponds to 1500 parts per million (ppm). Ex. 1039 (Robinson) at 946. However, “[g]enotoxic and potentially genotoxic impurities [PGIs] have been the subject of increasing regulatory and industry attention since the beginning of the 21st century.” Ex. 1039 (Robinson) at 959. “Recent guidelines from drug regulatory authorities in Europe and the United States of America (USA) require the control of genotoxic and potentially genotoxic impurities at parts per million levels in drug substances.” Ex. 1039 (Robinson) at Abstract. Accordingly, PGIs are subject to additional restrictions regarding their permissible concentration ranges. Ex. 1039 (Robinson) at 947-48, Table 1; Ex. 1037 (FDA Genotoxic Guidance) at 7, 11 (Table 1); Ex. 1038 (EMA Guidance) at 6-7.

87. Using either “existing genotoxicity data or the presence of structural alerts, potential genotoxic impurities should be identified.” Ex. 1038 (EMA Guidance) at 4; Ex. 1039 (Robinson) at 947 (“The EMA guideline recommends that any potentially genotoxic impurities (PGIs) in the drug substance should be identified, either from existing genotoxicity data or through the presence of ‘structural alerts.’”). If a PGI is present, guidance dictates that the developer should (1) “alter the route of synthesis so as to remove the PGI entirely;” (2) “reduce the PGI to below a level of concern;” (3) “demonstrate that the PGI will not be present at significant levels;” or (4) “demonstrate that the PGI is not actually harmful at its typical level in the API.” Ex. 1039 at 952.

B. Introduction to Brown

88. In Section VII, above, I discussed the teachings of Brown (Ex. 1003) in general and also how Brown’s teachings related to the ’039 patent (Ex. 1001). For the sake of being complete, and also to avoid being repetitive, I hereby incorporate by reference these prior explanations of Brown.

C. Introduction to Robinson

89. Robinson is entitled “Control of Genotoxic Impurities in Active Pharmaceutical Ingredients: A Review and Perspective.” Robinson’s Abstract explains:

Recent guidelines from drug regulatory authorities in Europe and the United States of America (USA) *require the control of* genotoxic and *potentially genotoxic impurities at parts per million levels* in drug substances. This review will discuss the background to the guidelines and the various strategies drug substance manufacturers have employed to comply with the very tight constraints.

Ex. 1039 (Robinson) at Abstract. Accordingly, to the extent that a POSA was developing a new drug substance and a PGI might be present, then Robinson's review of guidelines and strategies would be of interest. Indeed, Robinson states: "Ensuring the safety of pharmaceutical products is a primary responsibility of the chemists, engineers and formulators involved in their manufacture – regardless of whether the products are intended for commercial purposes or for clinical investigation." Ex. 1039 (Robinson) at 946.

90. Robinson teaches that "[a] drug substance will typically contain a range of low-level impurity compounds, for example arising as residues of starting materials ... or degradation reactions; these need to be understood and controlled within tight limits." Ex. 1039 (Robinson) at 946. "Manufacturers must therefore eliminate [impurities] (or at least mitigate the risk associated with them) to the greatest extent possible." *Id.* Thus, ignoring a PGI in a drug substance is not an option for the developer/manufacturer.

91. Robinson provides a summary of the Regulatory Viewpoint as it pertains to the European Medicines Agency (EMA). Ex. 1039 (Robinson) at 947-949. The EMA “recommends that any potentially genotoxic impurities (PGIs) in the drug substance should be identified” from existing data or the presence of “structural alerts.” Ex. 1039 (Robinson) at 947. A “structural alert” is simply an assessment of an impurity for a concerning functional group or feature. Figure 2 of Robinson provides “[s]ome examples of structurally alerting functional groups.” *Id.* at 951.

92. Once a PGI is identified, there are four courses of action:

(1) alter the route of synthesis so as to remove the PGI entirely; (2) alter relevant process parameters to reduce the PGI to below a level of concern; (3) deploy chemical and mechanistic arguments, ideally backed with experimental evidence, to demonstrate that the PGI will not be present at significant levels; (4) conduct testing to demonstrate that the PGI is not actually harmful at its typical level in the API.

Id. at 952.

93. With respect to the “level of concern” that Robinson references, Robinson provides a table that summarizes the recommendations of the pharmaceutical industry, the EMA, and the FDA:

Table 1. Proposed allowable daily intake (μg) for genotoxic impurities of unknown carcinogenic potential during clinical development

	duration of exposure	single dose	NMT 14 days	14 days to 1 month	1–3 months	3–6 months	6–12 months	>12 months
PhRMA recommendations	ref 15	120	120	120	40	20	10	1.5
EMA limits	ref 16	120	60	60	20	10	5	1.5
draft USFDA limits	ref 17	120	120	60	20	10	5	1.5

Ex. 1039 (Robinson) at 948. Each of the three stakeholders recommend concentration ranges for PGIs that range from 120 micrograms to as low as 1.5 micrograms, depending upon the duration of exposure, “for most known and all suspect carcinogens, unless experimental evidence can justify higher limits.” *Id.* (Robinson) at 969, 948 (Table 1). These limits apply to all “genotoxic impurities of unknown carcinogenic potential during clinical development.” *Id.* (Table 1’s caption). Accordingly, such limits (and Robinson’s discussion) would be relevant to the development of cabozantinib (*L*)-malate as a pharmaceutical product as indicated in Brown. *See* Ex. 1003 (Brown) at [0052] (“The malate salts of N-(4-{{6,7-bis(methoxy)quinolin-4-yl}oxy}phenyl)-N’-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I) [i.e., cabozantinib (*L*)-malate], have a preferred combination of pharmaceutical properties for development.”). For reasons that I explain further below, these limits (and Robinson’s discussion) would be applicable to the 6,7-dimethoxy-quinoline-4-ol impurity. *See* Paragraphs 103-107, below.

94. Robinson also discusses, with examples, of how the pharmaceutical industry have utilized each of the four-indicated options described above to satisfy

regulatory authorities’ concerns regarding genotoxic impurities and PGIs. *Id.* (Robinson) at 952-969. As discussed in further detail below, 6,7-dimethoxy-quinoline-4-ol is a potentially genotoxic impurity. Accordingly, with respect to Robinson’s option of “altering the synthesis to avoid PGIs,” one could consider that to be descriptive of altering Brown’s synthesis in view of Kubo as I explained in Sections VII, above. However, for purposes of the discussion of Brown in view of Robinson provided herein, this declaration will focus on Robinson’s second option—“Adjustment of Process Parameters” and the use of chromatography to purify an API such as cabozantinib (*L*)-malate.

D. Cabozantinib (*L*)-malate API containing the concentrations of 6,7-dimethoxy-quinoline-4-ol recited in claims 1-10 (and referred back to by claims 11-22) would have been obvious

95. Claim 1 of the ’039 patent is reproduced at Paragraph 32, above. As I have indicated, claims 1 and 6 require that the pharmaceutical composition contain “100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.” Additional claims (also reproduced at Paragraph 32, above) require that the pharmaceutical composition contain “50 ppm or less,” “25 ppm or less,” “10 ppm or less,” and “5 ppm or less” of 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition. *See, e.g.*, Ex. 1001 (’039 patent) at claims 1 and 6 (reciting 100 ppm or less), claims 2 and 7 (reciting 50 ppm or less), claims 3 and 8 (reciting 25 ppm or less), claims 4 and 9

(reciting 10 ppm or less), and claims 5 and 10 (reciting 5 ppm or less). These same claims are referred back to in claims 11-22.

96. Once again, I repeat my understanding from counsel that another expert for Azurity will explain why the pharmaceutical composition and treatment methods recited in claims 1-22 would have been obvious having assumed that cabozantinib (*L*)-malate having equal to or less than the recited concentration range of 6,7-dimethoxy-quinoline-4-ol would have been obvious.

97. Accordingly, in this section, I explain why, in fact, it would have been obvious to a POSA (and the team being consulted) to purify Brown's cabozantinib (*L*)-malate in view of Robinson to reduce the concentration of the 6,7-dimethoxy-quinoline-4-ol to an amount that renders the claimed concentrations obvious.

1. **A POSA would have been motivated to reduce the concentration of any 6,7-dimethoxy-quinoline-4-ol impurity in Brown's cabozantinib (*L*)-malate API to the concentrations recited in claims 1-10 (and referred back to by claims 11-22)**

98. In Section VII.C, above, I explained that Brown prepared cabozantinib (*L*)-malate using 6,7-dimethoxy-quinoline-4-ol as a starting material. *See, e.g.*, Ex. 1003 (Brown) at [0099] and [00102]; Paragraphs 47-54. I also explained in that Section why a POSA might have expected that some 6,7-dimethoxy-quinoline-4-ol could remain from the first synthetic step in Brown's synthesis and potentially be carried through to the cabozantinib (*L*)-malate that Brown prepared. *See id.*;

Paragraphs 51-53. I also explained in that Section how Brown acknowledged that “reaction impurities” and/or “processing impurities” (under which 6,7-dimethoxy-quinoline-4-ol would be included) may be present in the cabozantinib (*L*)-malate of Brown. *See id.*; Paragraphs 51-53. That Section concluded with my understanding from counsel that experts for Exelixis admitted, and that the district court in a litigation over the ’349 patent (Ex. 1046) found that Brown’s cabozantinib (*L*)-malate contained “at most, de minimis” 6,7-dimethoxy-quinoline-4-ol. *See id.*; Paragraph 54.

99. In Section VII.G, above, I explained that in Brown’s synthesis of cabozantinib (*L*)-malate, the 4-(nitrophenoxy)quinoline intermediate may be less stable than the corresponding 4-(aminophenoxy)quinoline intermediate that was used in the ’039 patent and rendered obvious by the combination of Brown and Kubo. *See* Paragraphs 75-76. I also explained in this Section why a POSA would have reasonably expected that small amounts of 6,7-dimethoxy-quinoline-4-ol could have been present in the cabozantinib (*L*)-malate that Brown prepared because of hydrolytic degradation of the 4-(nitrophenoxy)quinoline intermediate. *See id.*; Paragraphs 75-76.

100. My discussion of the expectations that a POSA would have regarding the presence of impurities in Brown’s cabozantinib (*L*)-malate is further supported by the general understanding in the pharmaceutical industry. For example, Robinson

explains: “A drug substance will typically contain a range of low-level impurity compounds, for example arising as residues of starting materials, reagents, intermediates, or as side-products generated by the synthetic processes or degradation reactions; these need to be understood and controlled within tight lights.” Ex. 1039 (Robinson) at 946.

101. Moreover, Brown identified cabozantinib (*L*)-malate for development. Ex. 1003 (Brown) at [0052]. “Ensuring the safety of pharmaceutical products is a primary responsibility of the chemists, engineers and formulators involved in their manufacture – regardless of whether the products are intended for commercial purposes or for clinical investigation.” Ex. 1039 (Robinson) at 946. Accordingly, a POSA would have had an obligation to evaluate Brown’s cabozantinib (*L*)-malate to understand and control the amount of impurities that were present.

102. In Brown’s synthesis of cabozantinib (*L*)-malate, 6,7-dimethoxy-quinoline-4-ol was the initial starting material. It was also a potential low-level degradant of the 4-(nitrophenoxy)quinoline intermediate in Brown’s synthesis. Accordingly, 6,7-dimethoxy-quinoline-4-ol falls within two of the categories (“residues of starting material” and “side-products generated by ... degradation reactions”) that Robinson indicates a drug substance “will typically contain” as “low-level impurity compounds.” A POSA would not have assumed, with no experimental evidence to confirm the assumption, that Brown’s cabozantinib (*L*)-

malate was devoid of 6,7-dimethoxy-quinoline-4-ol. That would be the opposite of the “typical” situation that Robinson explains. It would also be contrary to regulatory guidelines for APIs. *See, e.g.*, Ex. 1041 (FDA Q3A) at 3 (requiring summaries of “the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance” and “the laboratory studies conducted to detect impurities in the new drug substance”). A POSA (or the team being consulted) would have been motivated to ensure that the cabozantinib (*L*)-malate API of Brown would comply with regulatory guidelines—including those associated with impurities.

103. I understand from counsel that another expert for Azurity has identified the molecule “quinoline” as a known genotoxic compound. *See also* Ex. 1036 (EPA Tox. Review) at 23. As the name “6,7-dimethoxy-**quinoline**-4-ol” implies, the impurity recited in claims 1-10 of the ’039 patent shares the same structural “core” of the “**quinoline**” molecule. I also understand from counsel that one of Exelixis’s experts has previously testified that 6,7-dimethoxy-quinoline-4-ol has “a structure that has to be furtherly -- further evaluated. Because, of course, as we know, there are lots of quinolines that are actually drugs. And there are quinolines that are -- that are genotoxic. So you have to -- you have to say -- you have to study each particular quinoline to determine whether it’s useful, not harmful or harmful.” Ex. 1019 (Trial Volume III) at 769:5-770:4. Accordingly, it would be reasonable for a POSA to

suspect that 6,7-dimethoxy-quinoline-4-ol is a potentially genotoxic impurity (“PGI”) that may be present in Brown’s cabozantinib (L)-malate in view of the structure of this impurity. Thus, Robinson and the regulatory guidelines it reviews would have been of particular interest to a POSA developing cabozantinib (L)-malate as a pharmaceutical product.

104. Robinson explains that “any potentially genotoxic impurities (PGIs) in the drug substance should be identified, either from existing genotoxicity data or through the presence of ‘structural alerts.’” Ex. 1039 (Robinson) at 947. The FDA’s guidance is quite specific, particularly for starting material or an impurity that “may be expected based on the synthetic pathway.” Ex. 1037 (FDA Genotoxic Guidance) at 1 (“This Guidance is intended to inform pharmaceutical manufacturers of the Food and Drug Administration’s (FDA’s) current thinking regarding genotoxic and carcinogenic impurities in drug substances and drug products. . . . ***This guidance provides specific recommendations regarding*** the safety qualification of ***impurities with known or suspected genotoxic or carcinogenic potential.*** . . . This guidance also applies to ***known starting materials*** or anticipated reaction products.”); *id.* (FDA Genotoxic Guidance) at 6 (“However, in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified ***or where such an impurity may be expected based on the synthetic pathway,*** steps should be taken

during the clinical development stage to address safety concerns associated with these impurities.”).

105. The quinoline heterocycle found within “6,7-dimethoxy-*quinoline*-4-ol” would have provided a ‘structural alert’ for a POSA to evaluate Brown’s cabozantinib (L)-malate in accordance with the regulatory guidelines and descriptions discussed previously, identify the presence of 6,7-dimethoxy-quinoline-4-ol (even if “de minimis”), and follow the guidelines described in Robinson concerning the treatment of this impurity (if present)—such as removing it entirely or reducing it to a concentration below a level of concern. Ex. 1039 (Robinson) at 952 (listing “four courses of action open to the process development chemists”); Ex. 1037 (FDA Genotoxic Guidance) at 11 (“In cases where attempts to prevent the formation of an impurity of concern and/or to reduce the amount of the impurity to an acceptable level as per Table 1 [Acceptable Qualification Thresholds for Genotoxic and Carcinogenic Impurities] are not possible, further characterization of the genotoxic and carcinogenic potential should be conducted.”); *id.* 1037 (FDA Genotoxic Guidance) at 12 (Table 2) (providing “Recommended Approaches Based on Development Stage” such as: “[m]odify synthetic pathway to eliminate the impurity, if possible” or “[c]onduct genotoxicity assays to characterize the genotoxic potential if not already known” and/or “[s]et specification to that associated with a

potential daily impurity exposure supported by compound-specific risk assessment or relevant qualification threshold (see Table 1).”).

106. As I indicated in the paragraph above, regulatory guidelines for a PGI (which would include 6,7-dimethoxy-quinoline-4-ol) permit a manufacturer to limit its concentration to the point that it remains below a level of concern (the threshold of toxicological concern or “TTC”). Robinson provides a table that includes the recommended limits:

Table 1. Proposed allowable daily intake (µg) for genotoxic impurities of unknown carcinogenic potential during clinical development

	duration of exposure	single dose	NMT 14 days	14 days to 1 month	1–3 months	3–6 months	6–12 months	>12 months
PhRMA recommendations	ref 15	120	120	120	40	20	10	1.5
EMA limits	ref 16	120	60	60	20	10	5	1.5
draft USFDA limits	ref 17	120	120	60	20	10	5	1.5

Ex. 1039 (Robinson) at 948. The recommendations in Robinson’s Table 1 correspond to those in the FDA’s guidelines (Ex. 1037 (FDA Genotoxicity Guidance) at 11 (Table 1)). Such guidelines indicate that the permissible concentration ranges from less 120 µg/day to 1.5 µg/day depending upon the duration of treatment. Ex. 1039 (Robinson) at 948 (Table 1). These limits apply to all “genotoxic impurities of unknown carcinogenic potential during clinical development.” *Id.* (Table 1’s caption). Accordingly, such limits (and Robinson’s discussion) would be relevant to cabozantinib (*L*)-malate’s development as a pharmaceutical product as indicated in Brown. *See* Ex. 1003 (Brown) at [0052] (“The malate salts of N-(4-{[6,7-bis(methoxy)quinolin-4-yl]oxy}phenyl)-N’-(4-

fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I) [i.e., cabozantinib (*L*)-malate], have a preferred combination of pharmaceutical properties for development.”).

107. Although claims 1-10 recite concentration ranges for 6,7-dimethoxy-quinoline-4-ol in terms of parts-per-million (“ppm”), the European Medicines Agency (EMA) guidelines contain an equation that permits one to convert from micrograms/day to a ppm concentration limit if one knows the daily dose of the API. Ex. 1038 (EMA Guidelines) at 6. A patent document filed by Exelixis indicates that the amount of cabozantinib (*L*)-malate to be administered to a subject could be from “about 0.1 to about 1,000 mg per day.” Ex. 1008 (’473 patent) at col. 274, lines 52-57. Using this information, the permissible concentration for 6,7-dimethoxy-quinoline-4-ol in Brown’s cabozantinib (*L*)-malate API would have been 120 ppm or less to as low as 1.5 ppm or less. *See* Ex. 1038 (EMA Guidelines) at 6 (Eq. 1) (substituting 1000 mg or 1 g as the dose and either 120 µg/day or 1.5 µg/day as the Threshold of Toxicological Concern). Such permissible concentrations substantially overlap with, and in some instances fall completely within, the concentration ranges recited in claims 1-10 of the ’039 patent. Accordingly, a POSA would have been motivated by Robinson and the regulatory guidelines being described to limit the concentration of 6,7-dimethoxy-quinoline-4-ol in Brown’s

cabozantinib (*L*)-malate API to within permissible concentration ranges—which happen to be claimed by the '039 patent.

2. **A POSA would have had a reasonable expectation that chromatographic purification of Brown's cabozantinib (*L*)-malate API could reduce the concentration of 6,7-dimethoxy-quinoline-4-ol to the concentrations recited in claims 1-10 (and referred back to by claims 11-22)**

108. A POSA would have had a reasonable expectation of successfully reducing the “de minimis” concentration of 6,7-dimethoxy-quinoline-4-ol in Brown's cabozantinib (*L*)-malate to the threshold of 100 ppm or less (or even each of the “50 ppm or less,” “25 ppm or less,” “10 ppm or less,” and “5 ppm or less” ranges recited in claims 1-10 and referred back to by claims 11-22).

109. Robinson contains several pages outlining “Industry Approaches” for addressing PGIs. Ex. 1039 (Robinson) at 950-59. Robinson also concludes that the pharmaceutical industry was successfully complying with the regulatory guidelines: “it is clear that the control of PGIs at levels well below those of other impurities is here to stay. Indeed, industry has risen to the challenge of meeting the ppm levels with a variety of control strategies. . . .” *Id.* (Robinson) at 959. Although this statement is not specific as to any particular API and impurity, it does stand for the broader proposition that APIs can be purified such that they can reduce PGI concentrations to low ppm levels in accordance with the regulatory guidelines.

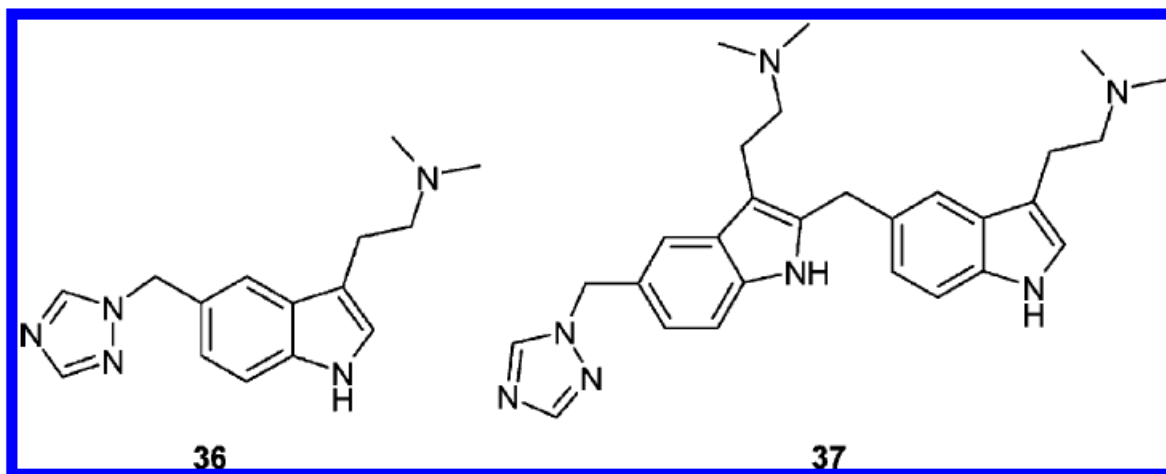
110. In particular, Robinson indicates that “[i]n many cases, PGIs have been successfully reduced below the TTC simply by altering appropriate conditions in either the reaction or workup stages.” Ex. 1039 (Robinson) at 954 (section entitled “Adjustment of Process Parameters”). Amongst Robinson’s examples in this section, one solution was to purify the final API using a chromatographic method:

In an extreme case, “end-of-pipe” solutions may have to be applied to the final API. Maddula et al. (Dr. Reddy’s Laboratories) have described the development of a negative hydrophobic interaction chromatographic process for removal of a genotoxic dimer impurity (37, Scheme 9) from the anti-migraine drug substance rizatriptan (36). Conventional processes such as fractional crystallization and recrystallization were unable to reduce the level below the acceptable limit of 0.01 wt %. By understanding the physicochemical properties of API, impurity, and adsorbent material, they were able to achieve a throughput of 33 g/L/h, reducing the impurity to below 0.008%, with 95% recovery of the API. However, it is not clear whether the company operates this process commercially.

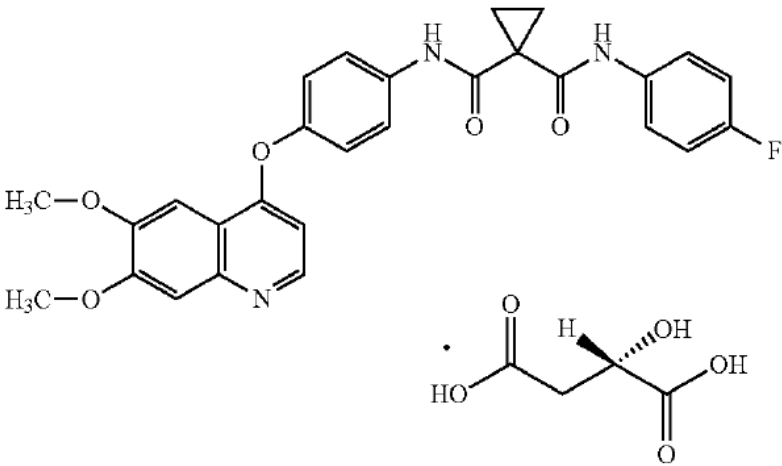
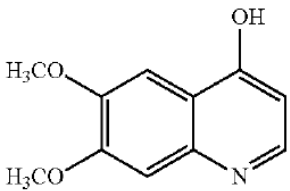
Ex. 1039 (Robinson) at 955 (citing Maddula (Ex. 1049). Robinson also provides another example of establishing a purification process to reduce an impurity from levels around 200 ppm to below 6 ppm, before subsequently changing the synthetic route to afford impurity levels of <2 ppm. *Id.* (Robinson) at 955 (discussing “Mathad”).

111. A chromatographic purification solution for reducing impurity concentrations may very well be “extreme” for a situation in which the impurity (compound 37) so closely resembles the API (compound 36) and crystallization efforts have been unsuccessful:

Scheme 9. Rizatriptan (36) and the dimeric impurity (37)
(from ref 48)



Ex. 1039 (Robinson) at 955. But here, 6,7-dimethoxy-quinoline-4-ol and cabozantinib (or cabozantinib (*L*)-malate) are not nearly as similar as Maddula’s situation, as illustrated in the comparison below:

IB 	
cabozantinib (<i>L</i>)-malate	6,7-dimethoxy-quinoline-4-ol

For example, cabozantinib contains a 4-aminophenoxy group in place of the 4-hydroxyl group of the 6,7-dimethoxy-quinoline-4-ol impurity. These groups alone are substantially different and would be expected to be separable by preparative chromatography. However, cabozantinib also has a large side chain added onto the 4-aminophenoxy group that contains an additional fluorinated aromatic ring, two amide groups capable of donating and accepting hydrogen bonds, and a cyclopropyl ring. The 6,7-dimethoxy-quinoline-4-ol impurity contains none of these groups. A POSA would recognize that these substantial structural differences will confer different molecular properties, which will in turn be reflected in different molecular descriptors (pK_a , $\log P$, $\log D$, etc.) that were used in Maddula to develop effective chromatographic separation parameters. A POSA would also recognize that the

considerable structural differences between cabozantinib (*L*)-malate and the 6,7-dimethoxy-quinoline-4-ol impurity would impact many other molecular descriptors commonly used in quantitative structure-activity relationship (QSAR) studies in the pharmaceutical industry, which also could be used to develop effective separation conditions as was done by Maddula.

112. A chromatographic approach to purifying cabozantinib (*L*)-malate API from 6,7-dimethoxy-quinoline-4-ol to the levels recited in claims 1-10 would have a reasonable expectation of success. “[P]reparative chromatography is becoming a well established separation and purification method in the pharmaceutical industry.” Ex. 1056 (Guiochon) at Abstract. It is considered “a powerful separation method” and a “ubiquitous analytical method.” *Id.* (Guiochon) at 130. Indeed, “[i]ts separation power kept attracting the attention of those interested in producing pure chemicals in large amounts for a variety of purposes.” *Id.* (Guiochon). Of relevance here, Brown identified “chromatography” for monitoring impurities and specifically used it to monitor 6,7-dimethoxy-quinoline-4-ol’s consumption in the first reaction for synthesizing cabozantinib (*L*)-malate. Ex. 1003 (Brown) at [0097], [00102]. While Brown’s reference to “chromatography” was likely in the analytical sense of reaction monitoring, the pharmaceutical industry has recognized that “[a]s a possible basis for preparative separations, analytical HPLC methods are tested first.” Ex. 1065 (Brandt) at 9 (“Preparative LC in Process Development”). Thus, it would be

reasonable for a POSA to have turned to preparative chromatography to further purify cabozantinib (*L*)-malate.

113. This is particularly so when “the engine behind the considerable development that has taken place in preparative chromatography during the last 10 years was the recognition by the pharmaceutical industry that chromatography is the only general separation method for the purification of the drug intermediates and the pharmaceuticals that it produces.” Ex. 1056 (Guiochon) at 131. As Guiochon explains:

The use of a separation method as expensive as chromatography is acceptable if it is required to achieve production of a marketable product. . . . [T]he pharmaceutical industry is not free to adjust the specification of its products to achieve maximum profit. These specifications must be accepted by the regulatory agency, the FDA. In many cases, preparative chromatography is the method needed to satisfy the purity specifications required on a routine basis.

Id. (Guiochon) at 131. Accordingly, purification costs associated with preparative chromatography can be readily justified for products as valuable as pharmaceuticals.

114. Robinson’s example of Maddula (Ex. 1049) is an industry reminder regarding the use of preparative chromatography to afford low (ppm) concentrations of a genotoxic impurity. Maddula relied upon structural descriptors, physicochemical descriptors, and distribution coefficients to develop a procedure for

the “removal of structurally related impurities from synthetic API using low-pressure preparative chromatography on commercially available adsorbants.” Ex. 1049 (Maddula) at Abstract; *id.* at 689. In one experiment, Maddula reduced the dimer impurity’s concentration to as little as 10 ppm (0.001%) while recovering 98% of the API. Ex. 1049 (Maddula) at 688. This was said to be a 4,120-fold reduction in the dimer impurity’s concentration. *Id.* If a POSA were to begin with Brown’s cabozantinib (*L*)-malate containing a “de minimis” amount of 6,7-dimethoxyquinoline-4-ol and subject it to preparative chromatography, it would not be unreasonable to expect to obtain API containing concentrations of 6,7-dimethoxyquinoline-4-ol within each of the ppm limits recited in claims 1-10 of the ’039 patent.

115. Furthermore, in a second experiment by Maddula, the dimer impurity was reduced to a non-detectable level (ND) when beginning at a level of 3.4% (corresponding to 34,000 ppm):

Table 3. Reuse of resin column after CIP

entry	% of a (before elution)	% of b (before elution)	% of a (after elution)	% of b (after elution)	% of a (after CIP)	% of b (after CIP)
1	79.9	3.7	86.2	0.007	ND	ND
2	81.6	3.5	91.1	0.008	ND	ND
3	84.0	3.4	93.7	ND	ND	ND
4	79.1	4.0	92.4	0.004	ND	ND

Ex. 1049 (Maddula) at 689 (Table 3, Annotated, wherein **a** is the API and **b** is the dimer impurity). For this entry, Maddula described the dimer content as being “less than 1 ppm or not detected.” *Id.* (Maddula) at 689. Once again, it would not be unreasonable for a POSA to expect to obtain cabozantinib (*L*)-malate containing

concentrations of 6,7-dimethoxy-quinoline-4-ol within each of the ppm limits recited in claims 1-10 of the '039 patent by subjecting Brown's API to preparative chromatography purification—Maddula was able to achieve such results for an isostructural genotoxic impurity in rizatriptan.

116. Admittedly, cabozantinib (*L*)-malate and 6,7-dimethoxyquinoline-4-ol are not the same API and structurally related impurity that Maddula successfully removed using preparative chromatography. However, I am not suggesting that Brown's cabozantinib (*L*)-malate be subjected to the exact procedure that Maddula developed. Instead, Maddula and the observed results merely serve to provide a reasonable expectation that preparative chromatography can be used to reduce the concentration of an impurity such as 6,7-dimethoxy-quinoline-4-ol to levels that comply with regulatory guidelines for the treatment of PGIs. Systematic methods to develop the parameters for preparative chromatography are generally known (*see, e.g.*, Ex. 1056 (Guiochon) at 151-152), and a POSA would have a reasonable expectation that a method could be developed and applied to purify Brown's cabozantinib (*L*)-malate and reduce the concentration of 6,7-dimethoxy-quinoline-4-ol (as evidenced by Maddula) to comply with regulatory guidelines described in Robinson for permissible concentrations of PGIs.

117. Thus, in view of the disclosures of Brown and Robinson discussed above, a POSA would have been motivated to obtain cabozantinib (*L*)-malate

containing “100 ppm or less,” “50 ppm or less,” “25 ppm or less,” “10 ppm or less,” or “5 ppm or less” of 6,7-dimethoxy-quinoline-4-ol. A POSA would have had a reasonable expectation of successfully obtaining this material in view of Robinson’s disclosures, and more specifically in view of using preparative chromatography as evidenced by Maddula. Accordingly, the cabozantinib (*L*)-malate API as recited in claims 1-10 (and referred back to by claims 11-22) would have been obvious.

IX. NO SECONDARY CONSIDERATIONS

118. I am not aware of any secondary considerations of non-obviousness that affect my opinions disclosed herein. Should Exelixis provide any in response, I reserve my right to address them.

X. CONCLUSION

119. For the reasons identified above, a POSA would have found it obvious to combine Brown with Kubo to afford the synthesis of cabozantinib (*L*)-malate in a more efficient manner. Such cabozantinib (*L*)-malate, to the extent it contained any 6,7-dimethoxy-quinoline-4-ol, would have been expected to be less than the “de minimis” amount attributed to Brown’s original synthesis and equivalent to that afforded by the processes described in the ’039 patent.

120. Additionally, and for the reasons I have provided, a POSA would have found it obvious in view of Robinson to identify the presence of 6,7-dimethoxy-quinoline-4-ol as a potential genotoxic impurity in Brown’s cabozantinib (*L*)-malate

and reduce the concentration of this impurity in the obtained API to 120 ppm or less to as low as 1.5 ppm or less to comply with regulatory guidelines. A POSA would have had a reasonable expectation of successfully doing so using preparative chromatography in view of Maddula. Accordingly, it would have been obvious for a POSA to purify Brown's cabozantinib (*L*)-malate and obtain API that contained "100 ppm or less," "50 ppm or less," "25 ppm or less," "10 ppm or less," or even "5 ppm or less" amounts of 6,7-dimethoxy-quinoline-4-ol as recited in claims 1-10 of the '039 patent.

121. I 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.

Dated: January 8, 2025

By: William Dichtel

William Dichtel, Ph.D.

Exhibit A

William R. Dichtel, Ph.D.
NORTHWESTERN UNIVERSITY
ROBERT L. LETSINGER PROFESSOR OF CHEMISTRY

EDUCATION AND TRAINING

Massachusetts Institute of Technology	Chemistry	B.S.	2000
University of California - Berkeley	Chemistry	Ph.D	2005
Advisor: Jean M. J. Fréchet			
UCLA and Caltech	Chemistry	Postdoc	2005–2008
Advisors: J. Fraser Stoddart and James R. Heath			

PROFESSIONAL APPOINTMENTS

Robert L. Letsinger Professor of Chemistry	Northwestern University	2016-Present
Associate Professor	Cornell University	2014-2016
Assistant Professor	Cornell University	2008-2014
Research Associate	UCLA & Caltech (jointly appointed)	2005-2008
Graduate Research Assistant	University of California, Berkeley	2000-2005

HONORS AND AWARDS

ACS/PMSE Global Outstanding Student & Mentor Awards in Polymer Science & Engineering (2021)
Fellow, American Association for the Advancement of Science (2021)
National Laureate, Blavatnik Award for Young Scientists in Chemistry (2020)
Finalist, Blavatnik Award for Young Scientists (2019)
Akron Local Section Award, American Chemical Society (2018)
Research Corporation Frontiers in Research Excellence and Discovery (FRED) Award (2018)
Guggenheim Fellowship (2018)
Crain's 40 under 40 in Chicago Business (2017)
Leo Hendrik Baekeland Award, North Jersey Section of the ACS (2017)
Finalist, Blavatnik Award for Young Scientists (2017)
Arthur K. Doolittle Award, ACS PMSE Division (2017)
Visiting Miller Professor, University of California, Berkeley (2016)
John D. and Catherine T. MacArthur Fellowship (2015)
Kavli Frontiers of Science Fellow (2015)
Kavli Emerging Leader in Chemistry Lecturer, 250th ACS National Meeting (2015)
Polymer International – IUPAC Award for Creativity in Applied Polymer Science (2014)
ACS National Fresenius Award (2013)
Camille Dreyfus Teacher Scholar Award (2013)
ACS Arthur C. Cope Scholar Award (2013)
Beckman Young Investigator Award (2012)
Sloan Research Fellowship (2012)
Research Corporation Cottrell Scholar Award (2012)
NSF CAREER Award (2011)
3M Nontenured Faculty Award (2010-2012)

PEER-REVIEWED PUBLICATIONS

207. Wang, JY; Lin, ZW; Dichtel, WR; Helbling, DE; "Perfluoroalkyl Acid Adsorption by Styrenic B-Cyclodextrin Polymers, Anion-Exchange Resins, and Activated Carbon is Inhibited by Matrix Constituents in Different Ways." *Water Research*. **2024**, 260, DOI: 10.1016/j.watres.2024.121897
206. Kim, S; Swartz, JL; Sala, O; Sun, M; Oanta, AK; Brutman, JP; Alsbaiee, A; Dichtel, WR; "Thermal Activation of Zirconium(IV) Acetylacetonate Catalysts to Enhance Polyurethane Synthesis and Reprocessing." *Macromolecules*. **2024**, DOI: 10.1021/acs.macromol.4c00625
205. Monsky, RJ; Li, YL; Houk, KN; Dichtel, WR; "Low-Temperature Mineralization of Fluorotelomers with Diverse Polar Head Groups." *J. Am. Chem. Soc.* **2024**, 146, 17150-17157, DOI: 10.1021/jacs.4c03117
204. Natraj, A; Landman, IR; Pelkowski, CE; Burke, DW; Kewalramani, S; Dichtel, WR; "Nonclassical Crystallization Processes of Single-Crystalline Two-Dimensional Covalent Organic Frameworks." *J. Am. Chem. Soc.* **2024**, 146, 16775-16786, DOI: 10.1021/jacs.4c04674
203. Lin, ZW; Wang, JY; Dyakiv, Y; Helbling, DE; Dichtel, WR; "Structural Features of Styrene-Functionalized Cyclodextrin Polymers That Promote the Adsorption of Perfluoroalkyl Acids in Water." *ACS Appl. Mater. Int.* **2024**, 16, 28409-28422, DOI: 10.1021/acsami.4c01969
202. Traxler, M; Dichtel, WR. "Continuous Flow Synthesis and Post-Synthetic Conversion of Single-Crystalline Covalent Organic Frameworks." *Chem Sci.* **2024**, 15, 7545-7551. DOI: 10.1039/d4sc01128g
201. Lin, ZW; Shapiro, EF; Barajas-Rodriguez, FJ; Gaisin, A; Ateia, M; Currie, J; Helbling, DE; Gwinn, R; Packman, AI; Dichtel, WR. "Trace Organic Contaminant Removal from Municipal Wastewater by Styrenic β -Cyclodextrin Polymers." *Env. Sci. Technol.* **2023**, 57, 19624-19636. DOI: 10.1021/acs.est.3c04233
200. Burke, DW; Jiang, ZW; Livingston, AG; Dichtel, WR. "2D Covalent Organic Framework Membranes for Liquid-Phase Molecular Separations: State of the Field, Common Pitfalls, and Future Opportunities." *Adv. Mater.* **2023**, 36, 2300525. DOI: 10.1002/adma.202300525
199. Pelkowski, CE; Natraj, A; Malliakas, CD; Burke, DW; Bardot, MI; Wang, ZX; Li, HY; Dichtel, WR. "Tuning Crystallinity and Stacking of Two-Dimensional Covalent Organic Frameworks through Side-Chain Interactions." *J. Am. Chem. Soc.* **2023**, 145, 21798-21806. DOI: 10.1021/jacs.3c03868
198. Sun, M; Sheppard, DT; Brutman, JP; Alsbaiee, A; Dichtel, WR. "Green Catalysts for Processing Thermoset Polyurethanes." *Macromolecules* **2023**, 56, 6978-6987. DOI: 10.1021/acs.macromol.3c01116
197. Kim, S; Li, K; Alsbaiee, A; Brutman, JP; Dichtel, WR "Circular Reprocessing of Thermoset Polyurethane Foams." *Adv. Mater.* **2023**, 35, 2305387. DOI: 10.1002/adma.202305387
196. Oanta, AK; Collins, KA; Evans, AM; Pratik, SM; Hall, LA; Strauss, MJ; Marder, SR; D'Alessandro, DM; Rajh, T; Freedman, DE; Li, H; Brédas, JL; Sun, L; Dichtel, WR. "Electronic Spin Qubit Candidates Arrayed within Layered Two-Dimensional Polymers." *J. Am. Chem. Soc.* **2023**, 145, 689-696. DOI: 10.1021/jacs.2c11784

195. Moisanu, CM; Jacobberger, RM; Skala, LP; Stern, CL; Wasielewski, MR; Dichtel, WR. "Crystalline Arrays of Copper Porphyrin Qubits Based on Ion-Paired Frameworks." *J. Am. Chem. Soc.* **2023**, *145*, 18447–18454. DOI:10.1021/jacs.3c04786
194. Yang, AN; Bukowski, BC; Anstine, DM; Colina, CM; Snurr, RQ; Dichtel, WR. "Defect engineering of porous aromatic frameworks via end capping improves dioxane removal from water." *Matter* **2023**, *6*, 2263-2273. DOI: 10.1016/j.matt.2023.06.013
193. Vasileiadou, ES; Tajuddin, IS; De Siena, MC; Klepov, VV; Kepenekian, M; Volonakis, G; Even, J; Wojtas, L; Spanopoulos, I; Zhou, XQ; Iyer, AK; Fenton, JL; Dichtel, WR; Kanatzidis, MG. "Novel 3D Cubic Topology in Hybrid Lead Halides with a Symmetric Aromatic Triammonium Exhibiting Water Stability." *Chem. Mater.* **2023**, *35*, 5267-5280. DOI: 10.1021/acs.chemmater.3c00164
192. Burke, DW; Dasari, RR; Sangwan, VK; Oanta, AK; Hirani, Z; Pelkowski, CE; Tang, YJ; Li, RF; Ralph, DC; Hersam, MC; Barlow, S; Marder, SR; Dichtel, WR. "Synthesis, Hole Doping, and Electrical Properties of a Semiconducting Azatriangulene-Based Covalent Organic Framework." *J. Am. Chem. Soc.* **2023**, *145*, 11969-11977. DOI: 10.1021/jacs.2c12371
191. Oanta, AK; Pelkowski, CE; Strauss, MJ; Dichtel, WR; "Competition between side-chain interactions dictates 2D polymer stacking order." *Chem. Commun.* **2023**, *59*, 6203-6206. DOI: 10.1039/d3cc01016c
190. Skala, LP; Stern; Bancroft, L; Moisanu, CM; Pelkowski, C; Aguilar-Enriquez, X; Swartz, JL; Wasielewski, MR; Dichtel, WR; "A modular platform for the precise assembly of molecular frameworks composed of ion pairs." *Chem.* **2023**, *9*, 1208-1220. DOI: 10.1016/j.chempr.2023.01.011
189. Skala, LP; Aguilar-Enriquez, X; Stern, CL; Dichtel, WR; "Dissipative crystallization of ion-pair receptors." *Chem.* **2023**, *9*, 709-720. DOI: 10.1016/j.chempr.2022.12.010
188. Bradshaw, NP; Hirani, Z; Kuo, LD; Li, SY; Williams, NX; Sangwan, VK; Chaney, LE; Evans, AM; Dichtel, WR; Hersam, MC; "Aerosol-Jet-Printable Covalent Organic Framework Colloidal Inks and Temperature-Sensitive Nanocomposite Films." *Adv. Mater.* **2023**, *35*, 2303673. DOI: 10.1002/adma.202303673
187. Ching, CS; Lin, ZW; Dichtel, WR; Helbling, DE; "Evaluating the Performance of Novel Cyclodextrin Polymer Granules to Remove Perfluoroalkyl Acids (PFAAs) from Water." *ACS ES&T Eng.* **2023**, *3*, 661-670. DOI: 10.1021/acsestengg.2c00379
186. Leonard, AA; Diroll, BT; Flanders, NC; Panuganti, S; Brumberg, A; Kirschner, MS; Cuthriell, SA; Harvey, SM; Watkins, Yu, J; Wasielewski, MR; Kanatzidis, MG; Dichtel, WR; Zhang, XY; Chen, LX; Schaller, RD; "Light-Induced Transient Lattice Dynamics and Metastable Phase Transition in CH₃NH₃PbI₃ Nanocrystals." *ACS Nano*. **2023**, *17*, 5306-5315. DOI: 10.1021/acsnano.2c06950
185. Yusuf, K; Natraj, A; Li, K; Ateia, M; AlOthman, ZA; Dichtel, WR; "Inverse Gas Chromatography Demonstrates the Crystallinity- Dependent Physicochemical Properties of Two-Dimensional Covalent Organic Framework Stationary Phases." *Chem. Mater.* **2023**, *35*, 1691-1701. DOI: 10.1021/acs.chemmater.2c03448
184. Vasileiadou, ES; Tajuddin, IS; De Siena, MC; Klepov, VV; Kepenekian, M; Volonakis, G; Even, J; Wojtas, L; Spanopoulos, I; Zhou, XQ; Iyer, AK; Fenton, JL; Dichtel, WR; Kanatzidis, MG; "Novel 3D Cubic

Topology in Hybrid Lead Halides with a Symmetric Aromatic Triammonium Exhibiting Water Stability.” *Chem. Mater.* **2023**, *35*, 5267-5280. DOI: 10.1021/acs.chemmater.3c00164

183. Yang, AN; Bukowski, BC; Anstine, DM; Colina, CM; Snurr, RQ; Dichtel, WR; “Defect engineering of porous aromatic frameworks via end capping improves dioxane removal from water.” *Matter*, **2023**, *6*, 2263-2273. DOI: 10.1016/j.matt.2023.06.013

182. Burke, DW; Dasari, RR; Sangwan, VK; Oanta, AK; Hirani, Z; Pelkowski, CE; Tang, YJ; Li, RF; Ralph, DC; Hersam, MC; Barlow, S; Marder, SR; Dichtel, WR; “Synthesis, Hole Doping, and Electrical Properties of a Semiconducting Azatriangulene-Based Covalent Organic Framework.” *J. Am. Chem. Soc.*, **2023**, *145*, 11969-11977. DOI: 10.1021/jacs.2c12371

181. Oanta, A.K.; Collens, K.A.; Evans, A.M.; Pratick, S.M.; Hall, L.A.; Strauss, M.J.; Marder, S.R.; D’Alessandro, D.M.; Rajh, T.; Freedman, D.E.; Li, H.; Bredas, J.L.; Sun, L.; and Dichtel, W.R.; “Electronic Spin Qubit Candidates Arrayed within Layered Two-Dimensional Polymers.” *J. Am. Chem. Soc.*, **2023**, *145*, 689-696. DOI: 10.1021/jacs.2c11784

180. Aguilar-Enriquez, X.; Skala, L.P.; and Dichtel, W.R.; " Divergent Synthesis of Alternant Bisanthenequinone and Nonalternant Heptalenodifluorenedione Ring Systems via a Concentration-Dependent Rearrangement.” *J. Org. Chem.* **2022**, *87*, 16307-16312. DOI: 10.1021/acs.joc.2c01877

179. Natraj, A.; Ji, W.; Xin, J.; Catano, I.; Burke, D.W.; Evans, A.M.; Strauss, M.J.; Ateia, M.; Hamachi, L.S.; Gianneschi, N.C.; Alothman, Z.A.; Sun, J.; Yusuf, K.; and Dichtel, W.R.; “Single Crystalline Imine-Linked Two -Dimensional Covalent Organic Frameworks Separate Benzene and Cyclohexane Efficiently.” *J. Am. Chem. Soc.* **2022**, *144*, 19813–19824. DOI: 10.1021/jacs.2c07166

178. Kramar, B.V.; Flanders, N.C.; Helweh, W.; Dichtel, W.R.; Hupp, J.T.; Chen, L.X.; “Light Harvesting Antenna Properties of Framework Solids.” *Acc. Mater. Res.*, **2022**, *3*, 1149-1159. DOI: 10.1021/accountsmr.2c00137

177. Swartz, J.L.; Elling, B.R.; Castano, I.; Thompson, M.P.; Sheppard, D.T.; Gianneschi, N.C.; and Dichtel, W.R.; “Copolymers Prepared by Exchange Reactions Enhance the Properties of Miscible Polymer Blends.” *Macromolecules* **2022**, *55*, 8548–8555. DOI: 10.1021/acs.macromol.2c01268

176. Strauss, M.J.; Evans, A.M.; Roesner, E.K.; Monsky, R.J.; Bardot, M.I. and Dichtel, W.R.; “Divergent Nanotube Synthesis through Reversible Macrocyclization.” *Acc. Mater. Res.* **2022**, *2*, 935-947. DOI: 10.1021/accountsmr.2c00062

175. Trang, B.; Li, Y.; Xue, X-S.; Ateia, M.; Houk, K.N.; and Dichtel, W.R.; “Low-temperature Mineralization of Perfluorocarboxylic Acids.” *Science*, **2022**, *377*, 839-845. DOI: 10.1126/science.abm8868

174. Jiang, Z.; Dong R.; Evans, A.M.; Ebrahim, M.; Li, S.; Dichtel, W.R.; Dario, A.; and Livingston, A.G. “Aligned Macrocyclized Pores in Ultrathin Films for Accurate Molecular Sieving.” *Nature*, **2022**, *609*, 58–64. DOI: 10.1038/s41586-022-05032-1

173. Turetsky, D.; Alzate-Sanchez, D.M.; Wasson, M. C.; Yang A.; Noh, H.; Atilgan, A.; Islamoglu, T.; Farha, O.K.; and Dichtel, W.R. "Hot Press Synthesis of MOF/Textile Composites for Nerve Agent Detoxification." *ACS Mater. Lett.* **2022**, *4*, 1511-1515. DOI: 10.1021/acsmaterialslett.2c00258
172. Wang, R.; Lin, Z.W.; Klemes, M.J.; Ateia, M.; Trang, B.; Wang, J.; Ching, C.; Helbling, D.E., and Dichtel, W.R. "A Tunable Porous Beta-Cyclodextrin Polymer Platform to Understand and Improve Anionic Pfas Removal." *ACS Cent. Sci.* **2022**, *8*, 663-669. DOI: 10.1021/acscentsci.2c00478
171. Rashid, R.B.; Evans, A.M.; Hall, L.A.; Dasari, R.R.; Roesner, E.K.; Marder, S.R.; D'Allesandro, D.M.; Dichtel, W.R., and Rivnay, J. A. "Semiconducting Two-Dimensional Polymer as an Organic Electrochemical Transistor Active Layer." *Adv. Mater.* **2022**, *34*, 2110703. DOI: 10.1002/adma.202110703
170. Roy, I.; Evans, A.M.; Das, P.J.; Ateia, M.; Ryder, M.R.; Jones, L.O.; Kazem-Rostami, M.; Goswami, S.; Beldjoudi, Y.; Shen, D.K.; Schatz, G.C.; Hupp, J.T.; Dichtel, W.R., and Stoddart, J.F. "Cyclophane-Based Two-Dimensional Polymer Formed by an Interfacial Click Reaction." *Cell Rep. Phys. Sci.* **2022**, *3*, 100806. DOI: 10.1016/j.xcrp.2022.100806
169. Haque, F.M.; Ishibashi, J.S.A.; Lidston, C.A.L.; Shao, H.L.; Bates, F.S.; Chang, A.B.; Coates, G.W.; Cramer, C.J.; Dauenhauer, P.J.; Dichtel, W.R.; Ellison, C.J.; Gormong, E.A.; Hamachi, L.S.; Hoye, T.R.; Jin, M.Y.; Kalow, J.A.; Kim, H.J.; Kumar, G.; LaSalle, C.J.; Liffland, S.; Lipinski, B.M.; Pang, Y.T.; Parveen, R.; Peng, X.Y.; Popowski, Y.; Prebihalo, E.A.; Reddi, Y.; Reineke, T.M.; Sheppard, D.T.; Swartz, J.L.; Tolman, W.B.; Vlaisavljevich, B.; Wissinger, J.; Xu, S., and Hillmyer, M.A. "Defining the Macromolecules of Tomorrow through Synergistic Sustainable Polymer Research." *Chem. Rev.* **2022**, *122*, 6322-6373. DOI: 10.1021/acs.chemrev.1c00173
168. Evans, A.M.; Collins, K.A.; Xun, S.N.; Allen, T.G.; Jhulki, S.; Castano, I.; Smith, H.L.; Strauss, M.J.; Oanta, A.K.; Liu, L.J.; Sun, L.; Reid, O.G.; Sini, G.; Puggioni, D.; Rondinelli, J.M.; Rajh, T.; Gianneschi, N.C.; Kahn, A.; Freedman, D.E.; Li, H.; Barlow, S.; Rumbles, G.; Bredas, J.L.; Marder, S.R., and Dichtel, W.R. "Controlled *n*-Doping of Naphthalene-Diimide-Based 2D Polymers." *Adv. Mater.* **2022**, *34*, 2101932. DOI: 10.1002/adma.202101932
167. Roesner, E.K.; Asheghali, D.; Kirillova, A.; Strauss, M.J.; Evans, A.M.; Becker, M.L., and Dichtel, W.R. "Arene-Perfluoroarene Interactions Confer Enhanced Mechanical Properties to Synthetic Nanotubes." *Chem. Sci.* **2022**, *13*, 2475-2480. DOI: 10.1039/d1sc05932g
166. Ching, C.; Ling, Y.H.; Trang, B.; Klemes, M.; Xiao, L.L.; Yang, A.; Barin, G.; Dichtel, W.R., and Helbling, D.E. "Identifying the Physicochemical Properties of Beta-Cyclodextrin Polymers That Determine the Adsorption of Perfluoroalkyl Acids." *Water Res.* **2022**, *209*, 117938. DOI: 10.1016/j.watres.2021.117938
165. Helweh, W.; Flanders, N.C.; Wang, S.W.; Phelan, B.T.; Kim, P.; Strauss, M.J.; Li, R.L.; Kelley, M.S.; Kirschner, M.S.; Edwards, D.O.; Spencer, A.P.; Schatz, G.C.; Schaller, R.D.; Dichtel, W.R., and Chen, L.X. "Layered Structures of Assembled Imine-Linked Macrocycles and Two-Dimensional Covalent Organic Frameworks Give Rise to Prolonged Exciton Lifetimes." *J. Mater. Chem. C*, **2022**, *10*, 3015-3026. DOI: 10.1039/d1tc05840a
164. Hanna, S.L.; Chheda, S.; Anderson, R.; Ray, D.; Malliakas, C.D.; Knapp, J.G.; Otake, K.; Li, P.; Li, P.H.; Wang, X.J.; Wasson, M.C.; Zosel, K.; Evans, A.M.; Robison, L.; Islamoglu, T.; Zhang, X.; Dichtel, W.R.;

Stoddart, J.F.; Gomez-Gualdrón, D.A.; Gagliardi, L., and Farha, O.K. "Discovery of Spontaneous De-Interpenetration through Charged Point-Point Repulsions." *Chem* **2022**, *8*, 225-242. DOI: 10.1016/j.chempr.2021.10.027

163. Evans, A.M.; Strauss, M.J.; Corcos, A.R.; Hirani, Z.; Ji, W.; Hamachi, L.S.; Aguilar-Enriquez, X.; Chavez, A.D.; Smith, B.J., and Dichtel, W.R. "Two-Dimensional Polymers and Polymerizations." *Chem. Rev.* **2022**, *122*, 442-564. DOI: 10.1021/acs.chemrev.0c01184

162. Swartz, J.L.; Sheppard, D.T.; Haugstad, G., and Dichtel, W.R. Blending Polyurethane Thermosets Using Dynamic Urethane Exchange." *Macromolecules*, **2021**, *54*, 11126-11133. DOI: 10.1021/acs.macromol.1c01910

161. Ji, W.; Hamachi, L.S.; Natraj, A.; Flanders, N.C.; Li, R.L.; Chen, L.X., and Dichtel, W.R. "Solvothermal Depolymerization and Recrystallization of Imine-Linked Two-Dimensional Covalent Organic Frameworks;" *Chem. Sci.* **2021**, *12*, 16014-16022. DOI: 10.1039/d1sc03963f

160. Strauss, M.J.; Hwang, I.; Evans, A.M.; Natraj, A.; Aguilar-Enriquez, X.; Castano, I.; Roesner, E.K.; Choi, J.W., and Dichtel, W.R. "Lithium-Conducting Self-Assembled Organic Nanotubes." *Journal of the American Chemical Society*, **2021**, *143*, 17655-17665. DOI: 10.1021/jacs.1c08058

159. Ateia, M., Skala, L.P., Yang, A. and Dichtel, W.R. "Product Analysis and Insight into the Mechanochemical Destruction of Anionic PFAS with Potassium Hydroxide." *J. Hazard. Mater. Adv.* **2021**, 100014. DOI: 10.1016/j.hazadv.2021.100014

158. Hamachi, L.S., Rau, D.A., Arrington, C.B., Sheppard, D.T., Fortman, D.J., Long, T.E., Williams, C.B. and Dichtel, W.R. "Dissociative Carbamate Exchange Anneals 3D Printed Acrylates." *ACS Appl. Mater. Int.* **2021**, *13*, 38680-38687. DOI: 10.1021/acsami.1c09373

157. Li, R.L., Yang, A., Flanders, N.C., Yeung, M.T., Sheppard, D.T. and Dichtel, W.R. "Two-Dimensional Covalent Organic Framework Solid Solutions." *J. Am. Chem. Soc.*, **2021**, *143*, 7081-7087. DOI: 10.1021/jacs.1c01683

156. Evans, A.M., Giri, A., Sangwan, V.K., Xun, S., Bartnof, M., Torres-Castaneda, C.G., Balch, H.B., Rahn, M.S., Bradshaw, N.P., Vitaku, E. and Burke, D.W. "Thermally conductive ultra-low-k dielectric layers based on two-dimensional covalent organic frameworks." *Nature Mater.* **2021**, 1-7, DOI: 10.1038/s41563-021-00934-3

155. Strauss, M.J., Jia, M., Evans, A.M., Castano, I., Li, R.L., Aguilar-Enriquez, X., Roesner, E.K., Swartz, J.L., Chavez, A.D., Enciso, A.E. and Stoddart, J.F. "Diverse Proton-Conducting Nanotubes via a Tandem Macrocyclization and Assembly Strategy." *J. Am. Chem. Soc.* **2021**, *143*, 8145–8153, DOI: 10.1021/jacs.1c02789

154. Li, H., Evans, A.M., Dichtel, W.R. and Bredas, J.L. "Quantitative Description of the Lateral Growth of Two-Dimensional Covalent Organic Frameworks Reveals Self-Templation Effects." *ACS Mater. Lett.* **2021**, *3*, 398–405, DOI: 10.1021/acsmaterialslett.1c00002

153. Castano, I.; Evans, A. M.; dos Reis, R.; Dravid, V. P.; Gianneschi, N. C.; Dichtel, W. R. "Mapping Grains, Boundaries, and Defects in 2D Covalent Organic Framework Thin Films." *Chem. Mater.* **2021**, *33*, 1341-1352. DOI: 10.1021/acs.chemmater.0c04382

152. Brumberg, A.; Kirschner, M. S.; Diroll, B. T.; Williams, K. R.; Flanders, N. C.; Harvey, S. M.; Leonard, A. A.; Watkins, N. E.; Kinigstein, E. D.; Yu, J.; Evans, A. M.; Liu, Y.; Cuthriell, S. A.; Panuganti, S.; Dichtel, W. R.; Kanatzidis, M. G.; Wasielewski, M. R.; Zhang, X.; Chen, L.; Schaller, R. D. "Anisotropic Transient Disorder of Colloidal, Two-Dimensional CdSe Nanoplatelets upon Optical Excitation" *Nano Lett.* **2021**, *21*, 1288-1294. DOI: 10.1021/acs.nanolett.0c03958
151. Fenton, J. L.; Burke, D. W.; Qian, D.; de la Cruz, M. O.; Dichtel, W. R. "Polycrystalline Covalent Organic Framework Films Act as Adsorbents, Not Membranes" *J. Am. Chem. Soc.* **2021**, *143*, 1466-1473.
150. Robison, K.; Gong, X.; Evans, A. M.; Son, F. A.; Wang, X.; Redfern, L. R.; Wasson, M. C.; Syed, Z. H.; Chen, Z.; Idrees, K. B.; Islamoglu, T.; Delferro, M.; Dichtel, W. R.; Coudert, F.-X.; Gianneschi, N. C.; Farha, O. K. "Transient Catenation in a Zirconium-Based Metal-Organic Framework and Its Effect on Mechanical Stability and Sorption Properties" *J. Am. Chem. Soc.* **2021**, *143*, 1503-1512.
149. Li, K.; Wong, N. K.; Strauss, M. J.; Evans, A. M.; Matsumoto, M.; Dichtel, W. R.; Adronov, A. "Postsynthetic Modification of a Covalent Organic Framework Achieved via Strain-Promoted Cycloaddition" *J. Am. Chem. Soc.* **2021**, *143*, 649-656. DOI: 10.1021/jacs.0c11811
148. Zhang, D.; Wang, G.; Chen, C.; Joshi, T.; Chen, X.-K.; Evans, A. M.; Matsumoto, M.; Dichtel, W. R.; Li, H.; Crommie, M. F.; Bredas, J.-L. "Mechanism of Formation of Benzotrithiophene-Based Covalent Organic Framework Monolayers on Coinage-Metal Surfaces: C-C Coupling Selectivity and Monomer-Metal Interactions" *Chem. Mater.* **2020**, *32*, 10688-10696. DOI: 10.1021/acs.chemmater.0c03901
147. Balch, H. B.; Evans, A. M.; Dasari, R. R.; Li, H.; Li, R.; Thomas, S.; Wang, D.; Bisbey, R. P.; Slicker, K. Castano, I.; Xun, S. N.; Jiang, L. L.; Zhu, C. H.; Gianneschi, N. C.; Ralph, D. C.; Bredas, J.-L.; Marder, S. R.; Dichtel, W. R.; Wang, F. "Electronically Coupled 2D Polymer / MoS₂ Heterostructures" *J. Am. Chem. Soc.* **2020**, *142*, 21131-21139. DOI: 10.1021/jacs.0c10151
146. Yu, C.-J.; von Kugelgen, S.; Krzyaniak, M. D.; Ji, W.; Dichtel, W. R.; Wasielewski, M. R.; Freedman, D. E. "Spin and Phonon Design in Modular Arrays of Molecular Qubits" *Chem. Mater.* **2020**, *32*, 10200-10206. DOI: 10.1021/acs.chemmater.0c03718
145. Wang, R.; Ching, C.; Dichtel, W.R.; Helbling, D.E. "Evaluating the Removal of Per- and Polyfluoroalkyl Substances from Contaminated Groundwater with Different Adsorbents Using a Suspect Screening Approach" *Env. Sci. & Tech. Lett.* **2020**, *7*, 954-960. DOI: 10.1021/acs.estlett.0c00736
144. Ateia, M.; Helbling, D.E.; Dichtel, W.R. "Best Practices for Evaluating New Materials as Adsorbents for Water Treatment" *ACS Mater. Lett.* **2020**, *2*, 1532-1544, DOI: 10.1021/acsmaterialslett.0c00414
143. Feriante, C.; Evans, A.M.; Jhulki, S.; Castano, I.; Strauss, M.J.; Barlow, S.; Dichtel, W.R.; Marder, S.R. "New Mechanistic Insights into the Formation of Imine-Linked Two-Dimensional Covalent Organic Frameworks" *J. Am. Chem. Soc.* **2020**, *142*, 18637-18644. DOI: doi.org/10.1021/jacs.0c08390
142. Ching, C.; Klemes, M.J.; Trang, B.; Dichtel, W.R.; Helbling, D.E. "β-cyclodextrin polymers with different crosslinkers and ion exchange resins exhibit variable adsorption of anionic, zwitterionic, and non-ionic PFASs" *Environ. Sci. Technol.* **2020**, *54*, 12693-12702. DOI: 10.1021/acs.est.0c04028
141. Harvey, S.M.; Houck, D.W.; Kirschner, M.S.; Flanders, N.C.; Brumberg, A.; Leonard, A.A.; Watkins, N.; Chen, L.X.; Dichtel, W.R.; Zhang, X.; Korgel, B.A.; Wasielewski, M.R.; Schaller, R.D. "Transient Lattice

Response upon Photoexcitation in CuInSe₂ Nanocrystals with Organic or Inorganic Surface Passivation” *ACS Nano*, **2020**, *14*, 13548–13556. DOI: 10.1021/acsnano.0c05553

140. Elling, B.R.; Dichtel, W.R. “Reprocessable Cross-Linked Polymer Networks: Are Associative Exchange Mechanisms Desirable?” *ACS Cent. Sci.* **2020**, *6*, 1488-1496. DOI: 10.1021/acscentsci.0c00567

139. Evans, A.M.; Bradshaw, N.P.; Litchfield, B.; Strauss, M.J.; Seckman, B.; Ryder, M.R.; Castano, I.; Gilmore, C.; Gianneschi, N.C.; Mulzer, C.R.; Hersam, M.C.; Dichtel, W.R. “High-Sensitivity Acoustic Molecular Sensors Based on Large-Area, Spray-Coated 2D Covalent Organic Frameworks” *Adv. Mat.* **2020**, *32*, 42, 2004205. DOI: 10.1002/adma.202004205

138. Klemes, M.J.; Skala, L.P.; Ateia, M.; Trang, B.; Helbling, D.E.; Dichtel, W.R. “Polymerized Molecular Receptors as Adsorbents to Remove Micropollutants from Water” *Acc. Chem. Res.* **2020**, DOI: 10.1021/acs.accounts.0c00426

137. Swartz, J.L.; Li, R.L.; Dichtel, W.R. “Incorporating Functionalized Cellulose to Increase the Toughness of Covalent Adaptable Networks” *ACS App. Mat. & Inter.* **2020**, *12* (39), 44110-44116 DOI: 10.1021/acсами.0c09215

136. Yang, A.; Ching, C.; Easler, M.; Helbling, D.E.; Dichtel, W.R. “Cyclodextrin Polymers with Nitrogen-Containing Tripodal Crosslinkers for Efficient PFAS Adsorption” *ACS Mater. Lett.*, **2020**, DOI: 10.1021/acsmaterialslett.0c00240

135. Hoffman, J. M.; Strzalaka, J.; Flanders, N. C.; Hadar, I.; Cuthriel, S. A.; Zhang, Q.; Schaller, R. D; Dichtel, W. R.; Chen, L. X.; Kanatzidis, M. G.; “In Situ Grazing-Incidence Wide-Angle Scattering Reveals Mechanisms for Phase Distribution and Disorientation in 2D Halide Perovskite Films” *Adv. Mat.* **2020**, *32*, 2002812. DOI: 10.1002/adma.2020028122

134. Flanders, N.C.; Kirschner, M.S.; Kim, P.; Fauvell, T.; Evans, A.; Helweh, W.; Spencer, A.P.; Schaller, R.D.; Dichtel, W.R; Chen, L.X. “Large Exciton Diffusion Coefficients in Two Dimensional Covalent Organic Frameworks with Different Domain Sizes Revealed by Ultrafast Exciton Dynamics” *J. Am. Chem. Soc.* **2020**, *142*, 14957-14965. DOI: 10.1021/jacs.0c05404

133. Wu, C.; Klemes, M.J; Trang, B.; Dichtel, W.R; Helbling, D.E. “Exploring the factors that influence the adsorption of anionic PFAS on conventional and emerging adsorbents in aquatic matrices” *Water Res.*, **2020**, *182*, 115950. DOI: 10.1016/j.watres.2020.115950

132. Ling, Y.; Alzate-Sánchez, D.M.; Klemes, M.J.; Dichtel, W.R.; Helbling, D.E. “Evaluating the effects of water matrix constituents on micropollutant removal by activated carbon and β-cyclodextrin polymer adsorbents” *Water Res.* **2020**, *173*, 115551. DOI: 10.1016/j.watres.2020.115551

131. Sheppard, D.T.; Jin, K.; Hamachi, L.S; Dean, W.; Fortman, D.J.; Ellison, C.J.; Dichtel, W.R. “Reprocessing Postconsumer Polyurethane Foam Using Carbamate Exchange Catalysis and Twin-Screw Extrusion” *ACS Cent. Sci.* **2020**, *6*, 6, 921-927, DOI: 10.1021/acscentsci.0c00083

130. Burke, D.W.; Sun, C.; Castano, I.; Flanders, N.C.; Evans, A.M.; Vitaku, E.; McLeod, D.C.; Lambeth, R.H.; Chen, L.X.; Gianneschi, N.C.; Dichtel, W.R. "Acid Exfoliation of Imine-linked Covalent Organic Frameworks Enables Solution Processing into Crystalline Thin Films" *Angew. Chem. Int. Ed.* **2020**, *59*, 2–9 DOI: 10.1002/anie.201913975

129. Rizzo, D.J.; Dai, Q.; Bronner, C.; Veber, G.; Smith, B.J.; Matsumoto, M.; Thomas, S.; Nguyen, G.D.; Forrester, P.R.; Zhao, W.; Jørgensen, J.H.; Dichtel, W.R.; Fischer, F.R.; Li, H.; Brédas, J.-L.; Crommie, M.F. "Revealing the Local Electronic Structure of a Single-Layer Covalent Organic Framework through Electronic Decoupling" *Nano Lett.* **2020**, *20*, 2, 963 – 970. DOI: 10.1021/acs.nanolett.9b03998
128. Jhulki, S.; Evans, A.M.; Hao, X.-L.; Cooper, M.W.; Feriante, C.H.; Leisen, J.; Li, H.; Lam, D.; Hersam, M.C.; Barlow, S.; Brédas, J.-L.; Dichtel, W.R.; Marder, S.R. "Humidity Sensing through Reversible Isomerization of a Covalent Organic Framework" *J. Am. Chem. Soc.* **2020**, *142*, 2, 783–791. DOI: 10.1021/jacs.9b08628
127. Evans, A.M.; Ryder, M.R.; Ji, W.; Strauss, M.J.; Corcos, A.; Vitaku, E.; Flanders, N.C.; Bisbey, R.P.; Dichtel, W.R. "Trends in the Thermal Stability of Two-Dimensional Covalent Organic Frameworks" *Faraday Discussions*, **2021**, *225*, 226-240. DOI: 10.1039/D0FD00054J
126. Feriante, C. H.; Jhulki, S.; Evans, A. M.; Dasari, R. R.; Slicker, K.; Dichtel, W. R.; Marder, S. R. "Rapid Synthesis of High Surface Area Imine-Linked Two-Dimensional Covalent Organic Frameworks by Avoiding Pore Collapse During Isolation" *Adv. Mater.* **2020**, *32*, 1905776.
125. Strauss, M.J.; Evans, A.M.; Castano, I.; Li, R.L.; Dichtel, W.R. "Supramolecular polymerization provides non-equilibrium product distributions of imine-linked macrocycles" *Chem. Sci.*, **2020**, *11*, 1957–1963. DOI: 10.1039/C9SC05422G
124. Li, H.; Evans, A. M.; Castano, I.; Strauss, M. J.; Dichtel, W. R.; Bredas, J.-L. "Nucleation-Elongation Dynamics of Two-Dimensional Covalent Organic Frameworks" *J. Am. Chem. Soc.* **2019**, *3*, 1367-1374. DOI: 10.1021/jacs.9b10869
123. Vitaku, E.; Gannett, C. N.; Carpenter, K. L.; Shen, L.; Abruna, H. D.; Dichtel, W. R. "Phenazine-Based Covalent Organic Framework Cathode Materials with High Energy and Power Densities" *J. Am. Chem. Soc.* **2019**, *142*, 16-20. DOI: 10.1021/jacs.9b08147
122. Ateia, M.; Alsbaiee, A.; Karanfil, T.; Dichtel, W. R. "Efficient PFAS Removal by Amine-Functionalized Sorbents: Critical Review of the Current Literature." *Environ. Sci. Technol. Lett.* **2019**, *6*, 688-695.
121. Evans, A. M.; Castano, I.; Brumberg, A.; Parent, L. R.; Corcos, A. M.; Li, R. L.; Flanders, N. C.; Gosztola, D. J.; Gianneschi, N. C.; Schaller, R. D.; Dichtel, W. R. "Emissive single-crystalline boroxine-linked colloidal covalent organic frameworks." *J. Am. Chem. Soc.* **2019**, *141*, 19728-19735. DOI: 10.1021/jacs.9b08815
120. Castano, I.; Evans, A. M.; Li, H.; Vitaku, E.; Strauss, M. J.; Bredas, J.-L.; Gianneschi, N. C.; Dichtel, W. R. "Chemical Control Over Nucleation and Anisotropic Growth of Two-Dimensional Covalent Organic Frameworks." *ACS Cent. Sci.* **2019**, *5*, 1892-1899.
119. Strauss, M. J.; Asheghali, A.; Evans, A. M.; Li, R. L.; Chavez, A. D.; Sun, C.; Becker, M. L.; Dichtel, W. R. "Cooperative Self-Assembly of Pyridine-2,6-Diimine-Linked Macrocycles into Mechanically Robust Nanotubes." *Angew. Chem. Int. Ed.* **2019**, *58*, 14708-14714.
118. Corcos, A. R.; Levato, G. A.; Jiang, Z.; Evans, A. M.; Livingston, A. G.; Marinas, B. J.; Dichtel, W. R. "Reducing the Pore Size of Covalent Organic Frameworks in Thin-Film Composite Membranes Enhances Solute Rejection." *ACS Mater. Lett.* **2019**, *1*, 440-446. (Cover Article)

117. Fortman, D. J.; Sheppard, D. T.; Dichtel, W. R. "Reprocessing Cross-Linked Polyurethanes by Catalyzing Carbamate Exchange." *Macromolecules* **2019**, *52*, 6330-6335.
116. Skala, L. P.; Yang, A.; Klemes, M. J.; Xiao, L.; Dichtel, W. R. "Resorcinarene Cavitand Polymers for the Remediation of Halomethanes and 1,4-Dioxane." *J. Am. Chem. Soc.* **2019**, *141*, 13315-13319.
115. Wang, S.; Chavez, A. D.; Thomas, S.; Li, H.; Flanders, N. C.; Sun, C.; Strauss, M. J.; Chen, L. X. Markvoort, A. J.; Brédas, J.-L.; Dichtel, W. R. "Pathway Complexity in the Stacking of Imine-Linked Macrocycles Related to Two-Dimensional Covalent Organic Frameworks." *Chem Mater.* **2019**, *31*, 7104-7111. (Jean-Luc Brédas 65th Birthday Festschrift)
114. Klemes, M. J.; Ling, Y.; Ching, C.; Wu, V.; Helbling, D. E.; Dichtel, W. R. "Reduction of a Tetrafluoroterephthalonitrile- β -Cyclodextrin Polymer to Remove Anionic Micropollutants and Perfluorinated Alkyl Substances from Water." *Angew. Chem. Int. Ed.* **2019**, *58*, 12049-12053.
113. Xiao, L.; Ching, C.; Ling, Y.; Nasiri, M.; Klemes, M. J.; Reineke, T. M.; Helbling, D. E.; Dichtel, W. R. "Cross-linker Chemistry Determines the Uptake Potential of Perfluorinated Alkyl Substances by Beta-Cyclodextrin Polymers." *Macromolecules* **2019**, *52*, 3747-3752.
112. Evans, A. M.; Ryder, M. R.; Flanders, N. C.; Vitaku, E.; Chen, L. X.; Dichtel, W. R.; "Buckling of Two-Dimensional Covalent Organic Frameworks Under Thermal Stress." *Ind. Eng. Chem. Res.* **2019**, *58*, 9883-9887.
111. Thomas, S.; Li, Hong; Desari, R. R.; Evans, A. M.; Castano, I.; Allen, T. G.; Reid, O. G.; Rumbles, G.; Dichtel, W. R.; Gianneschi, N. C.; Marder, S. R.; Coropcaenu, V.; Brédas, J.-L.; "Design and Synthesis of Two-Dimensional Covalent Organic Frameworks with Four-Arm Cores: Prediction of Remarkable Ambipolar Charge-Transport Properties." *Mater. Horiz.* **2019** *6*, 1868-1876
110. Thomas, S.; Li, Hong; Zhong, C.; Matsumoto, M.; Dichtel, W. R.; Brédas, J.-L.; "Electronic Structure of Two-Dimensional π -Conjugated Covalent Organic Frameworks." *Chem. Mater.* **2019**, *31*, 3051-3065.
109. Ling, Y.; Klemes, M. J.; Steinschneider, S.; Dichtel, W. R.; Helbling, D. E.; "QSARs to Predict Adsorption Affinity of Organic Micropollutants for Activated Carbon and Beta-Cyclodextrin Polymer Adsorbents." *Water Res.* **2019**, *154*, 217-226.
108. Zhukhovitskiy, A. V.; Kobylanskiy, I. J.; Thomas, A. A.; Evans, A. M.; Delaney, C. P.; Flanders, N. C.; Denmark, S. E.; Dichtel, W. R.; Toste, F. D.; "A Dinuclear Mechanism Implicated in Controlled Carbene Polymerization." *J. Am. Chem. Soc.* **2019**, *141*, 6473-6478.
107. Li, R. L.; Flanders, N. C.; Evans, A. M.; Ji, W.; Castano, I.; Chen, L. X.; Gianneschi, N. C.; Dichtel, W. R.; "Controlled Growth of Imine-Linked Two-Dimensional Covalent Organic Frameworks." *Chem. Sci.* **2019**, *10*, 3796-3801.
106. Daugherty, M. C.; Vitaku, E.; Li, R. L.; Evans, A. M.; Chavez, A. D.; Dichtel, W. R.; "Improved Synthesis of Beta-Ketoenamine-Linked Covalent Organic Frameworks via Monomer Exchange Reactions." *Chem. Commun.* **2019**, *55*, 2680-2683.
105. Alzate-Sanchez, D. M.; Ling, Y.; Li, C.; Frank, B. P.; Blehar, R.; Fairbrother, D. H.; Helbling, D. E.; Dichtel, W. R.; "Beta-Cyclodextrin Polymers on Microcrystalline Cellulose as a Granular Media for Organic Micropollutant Removal from Water." *ACS Appl. Mater. Interfaces*, **2019**, *11*, 8089-8096.

104. Brutman, J. P.; Fortman, D. J.; De Hoe, G. X.; Dichtel, W. R.; Hillmyer, M. A.; "Mechanistic Study of Stress-Relaxation in Urethane-Containing Polymer Networks." *J. Phys. Chem. B*, **2019**, *123*, 1432-1441.
103. Kirschner, M. S.; Diroll, B. T.; Guo, P.; Haryey, S. M.; Helweh, W.; Flanders, N. C.; Brunberg, A.; Watkins, N. E.; Leonard, A. A.; Evans, A. M.; Wasielewski, M. R.; Dichtel, W. R.; Zhang, X.; Chen, L. X.; Schaller, R. D. "Photoinduced, Reversible Phase Transitions in All-Inorganic Perovskite Nanocrystals." *Nature Commun.* **2019**, *10*, 504.
102. Klemes, M. J.; Ling, Y.; Chiapasco, M.; Alsbaiee, A.; Helbling, D. E.; Dichtel, W. R.; "Phenolation of Cyclodextrin Polymers Controls Their Lead and Organic Micropollutant Uptake." *Chem. Sci.* **2018**, *9*, 8883-8889.
101. Ji, W.; Xiao, L.; Ling, Y.; Ching, C.; Matsumoto, M.; Bisbey, R. P.; Helbling, D. E.; Dichtel, W. R. "Removal of GenX and Perfluorinated Alkyl Substances from Water by Amine-Functionalized Covalent Organic Frameworks." *J. Am. Chem. Soc.* **2018**, *140*, 12667-12681.
100. Fortman, D. J.; Snyder, R. L.; Sheppard, D. T.; Dichtel, W. R. "Rapidly Reprocessable Cross-Linked Polyhydroxyurethanes Based on Disulfide Exchange." *ACS Macro Lett.* **2018**, *7*, 1226-1231.
99. Fortman, D. J.; Brutman, J. P.; De Hoe, G. X.; Snyder, R. L.; Dichtel, W. R.; Hillmyer, M. A. "Approaches to Sustainable and Continually Recyclable Cross-Linked Polymers." *ACS Sustainable Chem. Eng.* **2018**, *6*, 11145-11159.
98. Sun, C.; Shen, M.; Chavez, A. D.; Evans, A. M.; Liu, X.; Harutyunyan, B.; Flanders, N. C.; Hersam, M. C.; Bedzyk, M. J.; de la Cruz, M. O.; Dichtel, W. R.; "High Aspect Ratio Nanotubes Assembled from Macrocyclic Iminium Salts." *Proc. Natl. Acad. U. S. A.* **2018**, *115*, 8883-8888.
97. Evans, A. M.; Parent, L. R.; Flanders, N. C.; Bisbey, R. P.; Vitaku, E.; Chen, L. X.; Gianneschi, N. C.; Dichtel, W. R.; "Seeded Growth of Single-Crystal Two-Dimensional Covalent Organic Frameworks." *Science*, **2018**, *361*, 52-57.
96. Li, C.; Klemes, M. J. Dichtel, W. R.; Helbling, D. E. "Tetrafluoroterephthalonitrile-crosslinked β -cyclodextrin polymers for efficient extraction and recovery of organic micropollutants from water." *J. Chrom. A*. **2018**, *1541*, 52-56.
95. Chavez, A. D.; Evans, A. M.; Flanders, N. C.; Bisbey, R. P.; Vitaku, E.; Chen, L. X.; Dichtel, W. R.; "Equilibration of Imine-Linked Polymers to Hexagonal Macrocycles Driven by Self-Assembly." *Chem. Eur. J.*, **2018**, *24*, 3989-3993.
94. Matsumoto, M.; Valentino, L.; Stiehl, G. M.; Balch, H. B.; Corcos, A. R.; Wang, F.; Ralph, D. C.; Marinas, B. J.; Dichtel, W. R.; "Lewis-Acid-Catalyzed Interfacial Polymerization of Covalent Organic Framework Films." *Chem*, **2018**, *4*, 308-317.
93. Snyder, R. L.; Fortman, D. J.; De Hoe, G. X.; Hillmyer, M. A.; Dichtel, W. R.; "Reprocessable Acid-Degradable Polycarbonate Vitrimers." *Macromolecules*, **2018**, *51*, 389-397.
92. Miskin, M. C.; Sun, C.; Cohen, I.; Dichtel, W. R.; McEuen, P. L.; "Measuring and Manipulating the Adhesion of Graphene." *Nano Lett.* **2018**, *18*, 449-454.

91. Chen, C.; Joshi, T.; Li, H.; Chavez, A. D.; Pedramrazi, Z.; Liu, P.; Li, H.; Dichtel, W. R.; Bredas, J.; Crommie, M. F.; "Local Electronic Structure of a Single-Layer Porphyrin-Containing Covalent Organic Framework." *ACS Nano*, **2018**, *12*, 385-391.
90. Valentino, L.; Matsumoto, M.; Dichtel, W. R.; Marinas, B. J.; "Development and Performance Characterization of a Polyimine Covalent Organic Framework Thin-Film Composite Nanofiltration Membrane." *Environ. Sci. Technol.* **2017**, *51*, 14532-14539.
89. Li, H.; Chavez, A. D.; Li, H.; Li, H.; Dichtel, W. R.; Bredas, J.-L.; "Nucleation and Growth of Covalent Organic Frameworks from Solution: The Example of COF-5." *J. Am. Chem. Soc.* **2017**, *139*, 16310-16318.
88. Hein, S. J.; Lehnherr, D.; Arslan, H.; Uribe-Romo, F. J.; Dichtel, W. R.; "Alkyne Benzannulation Reactions for the Synthesis of Novel Aromatic Architectures." *Acc. Chem. Res.* **2017**, *50*, 2776-2778.
87. Fortman, D.; Brutman, J. P.; Hillmyer, M. A.; Dichtel, W. R.; "Structural effects on the reprocessability and stress relaxation of crosslinked polyhydroxyurethanes." *J. Appl. Polym. Sci.* **2017**, *134*, 44984.
86. Vitaku, E.; Dichtel, W. R. "Synthesis of 2D Imine-Linked Covalent Organic Frameworks through Formal Transimination Reactions." *J. Am. Chem. Soc.* **2017**, *139*, 12911-12914.
85. Hein, S.; Lehnherr, D.; Dichtel, W. R. "Rapid access to substituted 2-naphthyne intermediates via the benzannulation of halogenated silylalkynes." *Chem. Sci.* **2017**, *8*, 5676-5681.
84. Xiao, L.; Ling, Y.; Alsbaiee, A.; Li, C.; Helbing, D. E.; Dichtel, W. R. "β-Cyclodextrin Polymer Network Sequesters Perfluorooctanoic Acid at Environmentally Relevant Concentrations." *J. Am. Chem. Soc.* **2017**, *139*, 7689-7692.
83. Ling, Y.; Klemes, M. J.; Xiao, L.; Alsbaiee, A.; Dichtel, W. R.; Helbling, D. E. "Benchmarking Micropollutant Removal by Activated Carbon and Porous β-cyclodextrin Polymers Under Environmentally Relevant Scenarios." *Environ. Sci. Technol.* **2017**, *139*, 7590-7598.
82. Benia, G.; Fortman, D. J.; Heath, W. H.; Dichtel, W. R.; Torkelson, J. M. "Non-Isocyanate Polyurethane Thermoplastic Elastomer: Amide-Based Chain Extender Yields Enhanced Nanophase Separation and Properties in Polyhydroxyurethane." *Macromolecules*, **2017**, *50*, 4425-4434.
81. Bisbey, R. P.; Dichtel, W. R. "Covalent Organic Frameworks as a Platform for Multidimensional Polymerization." *ACS Cent. Sci.* **2017**, *3*, 533-543.
80. Csernica, P. M.; McKone, J. R.; Mulzer, C. R.; Dichtel, W. R.; Abruna, H. D.; and DiSalvo, F. J. "Electrochemical Hydrogen Evolution at Ordered Mo₇Ni₇." *ACS Catalysis*, **2017**, *7*, 3375-3383.
79. Matsumoto, M.; Dsari, R. R.; Ji, W.; Feriante, C. H.; Parker, T. C.; Marder, S. R.; and Dichtel, W. R. "Rapid, Low Temperature Formation of Imine-Linked Covalent Organic Frameworks Catalyzed by Metal Triflates." *J. Am. Chem. Soc.* **2017**, *139*, 4999-5002.
78. Fortman, D. J.; Brutman, J. P.; Hillmyer, M. A.; Dichtel, W. R. "Structural effects on the reprocessability and stress relaxation of cross-linked polyhydroxyurethanes." *J. Appl. Polym. Sci.* **2017**, 44984.
77. Sun, C.; Holowka, D. A.; Baird, B. A.; Dichtel, W. R. "Beyond Media Composition: Cell Plasma Membrane Disruptions by Graphene Oxide." *Chem* **2017**, *2*, 324-325.

76. Lehnherr, D.; Alzola, J. M.; Mulzer, C. R.; Hein, S. J.; Dichtel, W. R. "Diazatetracenes Derived From the Benzannulation of Acetylenes: Electronic Tuning via Substituent Effects and External Stimuli." *J. Org. Chem.*, **2017**, *82*, 2004–2010.
75. Smith, B. J.; Parent, L. R.; Overholts, A. C.; Beaucage, P. A.; Bisbey, R. P.; Chavez, A. D.; Hwang, N.; Park, C.; Evans, A. M.; Gianneschi, N. C.; Dichtel, W. R. "Colloidal covalent organic frameworks." *ACS Cent. Sci.*, **2017**, *3*, 58–65.
74. Alzate-Sánchez, D. M.; Smith, B. J.; Alsbaiee, A.; Hinestroza, J. P.; Dichtel, W. R. "Cotton Fabric Functionalized with a β -Cyclodextrin Polymer Captures Organic Pollutants from Contaminated Air and Water." *Chem. Mater.* **2016**, *28*, 8340–8346.
73. Mulzer, C. R.; Shen, L.; Bisbey, R. P.; McKone, J. R.; Zhang, N.; Abruna, H. D.; Dichtel, W. R. "Superior Charge Storage and Power Density of Conducting Polymer Modified Covalent Organic Framework." *ACS Cent. Sci.* **2016**, *2*, 667–673.
72. Sun, C.; Wakefield, D. L.; Han, Y.; Muller, D. A.; Holowka, D. A.; Baird, B. A.; Dichtel, W. R. "Graphene Oxide Nanosheets Stimulate Ruffling and Shedding of Mammalian Cell Plasma Membranes." *Chem.*, **2016**, *1*, 273–286.
71. Bisbey, R. P.; DeBlase, C. R.; Smith, B. J.; Dichtel, W. R. "Two-dimensional covalent organic framework thin films grown in flow." *J. Am. Chem. Soc.* **2016**, *138*, 11433–11436.
70. DeBlase, C. R.; Dichtel, W. R. "Hybrid Supercapacitors from Framework Materials." *Chem* **2016**, *1*, 16–31. [Highlight]
69. Lehnherr, D.; Chen, C.; Pedramrazi, Z.; DeBlase, C. R.; Alzola, J. M.; Keresztes, I.; Lobkovsky, E. B.; Crommie, M. F.; Dichtel, W. R. "Sequence-defined oligo(*ortho*-arylene) foldamers derived from the benzannulation of *ortho*(arylene ethynylene)s." *Chem. Sci.* **2016**, *7*, 6357–6364.
68. Chavez, A. D.; Smith, B. J.; Smith, M. K.; Beaucage, P. A.; Northrop, B. H.; Dichtel, W. R. "Discrete, Hexagonal Boronate Ester-Linked Macrocycles Related to Two-Dimensional Covalent Organic Frameworks." *Chem. Mater.* **2016**, *28*, 4884–4888.
67. DeBlase, C. R.; Dichtel, W. R. "Moving Beyond Boron: The Emergence of New Linkage Chemistries in Covalent Organic Frameworks." *Macromolecules*, **2016**, *49*, 5297–5305. (Invited Perspective)
66. Gao, J.; Uribe-Romo, F. J.; Saathoff, J. D.; Arslan, H.; Crick, C. R.; Hein, S. J.; Itin, B.; Clancy, P.; Dichtel, W. R.; Loo, Y.-L. "Ambipolar Transport in Solution-Synthesized Graphene Nanoribbons" *ACS Nano*, **2016**, *10*, 4847–4856.
65. Smith, B. J.; Overholts, A. C.; Hwang, G.; Dichtel, W. R. "Insight into the crystallization of amorphous imine-linked polymer networks to 2D covalent organic frameworks." *Chem. Comm.* **2016**, *52*, 3690–3693.
64. Alsbaiee, A.; Smith, B. J.; Xiao, L.; Ling, Y.; Helbling, D. E.; Dichtel, W. R. "Rapid removal of organic micropollutants from water by a porous β -cyclodextrin polymer." *Nature*, **2016**, *529*, 190–194. *This work was highlighted on the cover of the January 14, 2016 issue of Nature.*

63. Fortman, D. J.; Brutman, J. A.; Cramer, C. J.; Hillmyer, M. A.; Dichtel, W. R. "Catalyst-free Polyhydroxyurethane Vitrimers." *J. Am. Chem. Soc.* **2015**, *137*, 14019–14022.
62. Lehnherr, D.; Alzola, J. M.; Lobkovsky, E. B.; Dichtel, W. R. "Regioselective Synthesis of Polyheterohalogenated Naphthalenes via the Benzannulation of Haloalkynes." *Chem. Eur. J.* **2015**, *21*, 18122–18127.
61. DeBlase, C. R.; Hernández-Burgos, K.; Rotter, J. M.; Fortman, D. J.; Timm, R. A.; dos S. Abreu, D.; Diógenes, I. C. N.; Kubota, L. T.; Abruña, H. D.; Dichtel, W. R. "Cation-dependent stabilization of electrogenerated naphthalene diimide dianions in porous polymer thin films." *Angew. Chem. Int. Ed.* **2015**, *54*, 13225–13229.
60. van Humbeck, J. F.; Aubrey, M. L.; Alsbaiee, A.; Ameloot, R.; Coates, G. W.; Dichtel, W. R.; Long, J. R. "Tetraarylborate polymer networks as single-ion conducting solid electrolytes." *Chem. Sci.* **2015**, *6*, 5499–5505.
59. Bradforth, S. E.; Miller, E. R.; Dichtel, W. R.; Leibovich, A. K.; Feig, A. L.; Martin, J. D.; Bjorkman, K. S.; Schultz, Z. D.; Smith, T. L. "Improve undergraduate science education." *Nature*, **2015**, *523*, 283–284.
58. Sun, C.; Wakefield, D.; Dichtel, W. R. "Retaining the activity of enzymes and fluorophores attached to graphene oxide." *Chem. Mater.* **2015**, *27*, 4499–4504.
57. Gopalakrishnan, D.; Dichtel, W. R. "Real-time detection of RDX vapors using thin films of a conjugated polymer network." *Chem. Mater.* **2015**, *27*, 3813–3816.
56. Smith, B. J.; Hwang, N.; Chavez, A.; Novotney, J. L.; Dichtel, W. R. "Growth rates and water stability of 2D boronate ester covalent organic frameworks." *Chem. Commun.* **2015**, *51*, 7532–7535.
55. DeBlase, C. R.; Hernández-Burgos, K.; Silberstein, K. E.; Rodríguez-Calero, G. G.; Bisbey, R. P.; Abruña, H. D.; Dichtel, W. R. "Rapid and efficient redox processes within 2D covalent organic framework thin films." *ACS Nano* **2015**, *9*, 3178–3183.
54. Arslan, H.; Walker, K. L.; Dichtel, W. R. "Regioselective Asao–Yamamoto benzannulations of diarylacetylenes." *Org. Lett.* **2014**, *16*, 5926–5929.
53. Colson, J. W.; Mann, J. A.; DeBlase, C. R.; Dichtel, W. R. "Patterned Growth of Oriented 2D Covalent Organic Framework Thin Films on Single-Layer Graphene." *J. Poly. Sci. A: Polym. Chem.* **2015**, *53*, 378–384. (Special issue dedicated to Jean M. J. Fréchet for his 70th birthday)
52. Hein, S. J.; Arslan, H.; Keresztes, I.; Dichtel, W. R. "Rapid synthesis of crowded aromatic architectures from silyl acetylenes." *Org. Lett.* **2014**, *16*, 4416–4419.
51. Smith, B. J.; Dichtel, W. R. "Mechanistic studies of two-dimensional covalent organic frameworks rapidly polymerized from initially homogenous conditions." *J. Am. Chem. Soc.* **2014**, *136*, 8783–8789.
50. Jung, B.; Satish, P.; Bunck, D. N.; Dichtel, W. R.; Ober, C. K.; Thompson, M. O. "Reaction pathways for ester cleavage of an acrylic polymer at high temperatures during laser-induced sub-millisecond heating." *ACS Nano*, **2014**, *8*, 5746–5756.

49. DeBlase, C. R.; Silberstein, K. E.; Truong, T.; Abruña, H. D.; Dichtel, W. R. " β -Ketoenamine-linked covalent organic frameworks capable of pseudocapacitive energy storage." *J. Am. Chem. Soc.* **2013**, *135*, 16821–16824.
48. Bunck, D. N.; Dichtel, W. R. "Bulk synthesis of exfoliated 2D polymers using hydrazone-linked covalent organic frameworks." *J. Am. Chem. Soc.* **2013**, *135*, 14952–14955.
47. Brucks, S. D.; Bunck, D. N.; Dichtel, W. R. "Functionalization of 3D covalent organic frameworks using monofunctional boronic acids." *Polymer* **2014**, *55*, 330–334. (*Special issue on porous polymers*)
46. Mann, J. A.; Dichtel, W. R. "Noncovalent functionalization of graphene by molecular and polymeric adsorbates" *J. Phys. Chem. Lett.* **2013**, *4*, 2649–2657.
45. Mann, J. A.; Dichtel, W. R. "Improving the binding characteristics of tripodal compounds on single layer graphene." *ACS Nano*, **2013**, *7*, 7193–7199.
44. Arslan, H.; Uribe-Romo, F. J.; Smith, B. J.; Dichtel, W. R. "Accessing extended and partially fused hexabenzocoronenes using a benzannulation / cyclodehydrogenation approach." *Chem. Sci.* **2013**, *4*, 3973–3978.
43. Colson, J. W.; Dichtel, W. R. "Rationally synthesized two-dimensional polymers." *Nature Chem.* **2013**, *5*, 453–465.
42. Gopalakrishnan, D.; Dichtel, W. R. "Direct detection of RDX vapor using a conjugated polymer network." *J. Am. Chem. Soc.* **2013**, *135*, 8357–8362. *This paper was highlighted in a video documentary produced by the American Chemical Society "Breakthrough Science" series.*
41. Novotney, J. L.; Dichtel, W. R. "Conjugated porous polymers for TNT vapor detection." *ACS Macro Lett.* **2013**, *2*, 423–426.
40. Bunck, D. N.; Dichtel, W. R. "Postsynthetic functionalization of 3D covalent organic frameworks." *Chem. Comm.* **2013**, *49*, 2457–2459.
39. Alava, T.; Mann, J. A.; Théodore, C.; Benitez, J. J.; Dichtel, W. R.; Parpia, J. M.; Craighead, H. G. "Control of the graphene-protein interface is required to preserve absorbed protein function." *Anal. Chem.* **2013**, *85*, 2754–2759.
38. Mann, J. A.; Alava, T.; Craighead, H.; Dichtel, W. R. "Preservation of antibody selectivity on graphene by conjugation to a tripod monolayer." *Angew. Chem. Int. Ed.* **2013**, *52*, 3177–3180.
37. Bunck, D. N.; Dichtel, W. R. "Mixed linker strategies for organic framework functionalization." *Chem. Eur. J.* **2013**, *19*, 818–827. (*Invited Review*)
36. Arslan, H.; Saathoff, J. Bunck, D. N.; Clancy, P.; Dichtel, W. R. "Highly efficient benzannulation of poly(phenylene ethynylene)s." *Angew. Chem. Int. Ed.* **2012**, *51*, 12051–12054.
35. Koo, B. T.; Dichtel, W. R.; Clancy, P. "A classification scheme for the stacking of two-dimensional covalent organic frameworks." *Chem. Mater.* **2012**, *22*, 17460–17469. (*Highlighted on Journal Cover*)
34. Uribe-Romo, F. J.; Dichtel, W. R. "Two-dimensional materials: Polymers stripped down." *Nature Chem.* **2012**, *4*, 244–245.

33. Rodríguez-López, J.; Ritzert, N. L.; Mann, J. A.; Tan, C.; Dichtel, W. R.; Abruña, H. D.; "Quantification of the surface diffusion of tripodal binding motifs on graphene using scanning electrochemical microscopy." *J. Am. Chem. Soc.* **2012**, *134*, 6224–6236.
32. Bunck, D. N.; Dichtel, W. R. "Internal functionalization of 3D covalent organic frameworks." *Angew. Chem. Int. Ed.*, **2012**, *51*, 1855–1859.
31. Spitler, E. L.; Colson, J. W.; Woll, A. R.; Giovino, M. R.; Saldivar, A.; Dichtel, W. R. "Pore expansion of highly oriented zinc phthalocyanine covalent organic framework films." *Angew. Chem. Int. Ed.*, **2012**, *51*, 2623–2627.
30. Spitler, E. L.; Koo, B.; Novotney, J. L.; Colson, J. W.; Uribe-Romo, F. J.; Gutierrez, G. D.; Clancy, P.; Dichtel, W. R. "Covalent organic frameworks with 4.7 pores and insight into their interlayer stacking." *J. Am. Chem. Soc.* **2011**, *133*, 19416–19421.
29. Mann, J. A.; Rodriguez-Lopez, J.; Abruña, H. D.; Dichtel, W. R. "Multivalent binding motifs for the noncovalent functionalization of graphene" *J. Am. Chem. Soc.*, **2011**, *133*, 17614–17617.
28. Spitler, E. L.; Giovino, M. R.; White, S.; Dichtel, W. R.; "Lewis acid-catalyzed formation of boronate ester-linked covalent organic frameworks." *Chem. Sci.*, **2011**, *2*, 1588–1593.
27. Colson, J. W.; Woll, A. R.; Mukherjee, A.; Levendoff, M. A.; Spitler, E. L.; Shields, V. S.; Spencer, M. A.; Park, J.; Dichtel, W. R.; "Oriented 2D covalent organic framework thin films on single layer graphene." *Science*, **2011**, *332*, 228–231.
26. Spitler, E. L.; Dichtel W. R.; "Lewis acid-catalysed formation of two-dimensional phthalocyanine covalent organic frameworks." *Nature Chem.* **2010**, *2*, 672–677. This paper was recognized as a "Highly Cited Paper" by ISI Web of Science in December 2014, which places it among the top 1% of papers in the field of chemistry for its publication year.

25 Publications as a graduate student and postdoctoral researcher available upon request

SELECTED PATENTS

1. Dichtel, W. R.; Alsbaiee, A.; Smith, B. J. Hinestroza, J.; Alzate-Sanchez, D.; Xiao, L.; Ling, Y.; Helbling, D. E. "Porous Cyclodextrin Polymeric Materials and Methods of Making and Using Same." US Patent Numbers 10086360 (10/2/2018), 9855545 (1/2/2018), 9624314 (4/18/17)
This patent family protects compositions of matter related to porous cyclodextrin polymers as novel adsorbents for sequestering organic pollutants from various fluids. Licensed to CycloPure, Inc.
2. Dichtel, W. R.; DeBlase, C. R.; Bisbey, R. P.; Shen, L.; Abruña, H. D. "Conducting-polymer modified Covalent Organic Frameworks and Methods of Making Same." PCT/US2016/047046 (8/15/2015)
This US and international patent application protects a combination of redox-active COF films and conducting polymers for use in electrical energy storage devices.
3. Dichtel, W. R.; Gopalakrishnan, D. "Cross-linked polymer networks and methods of making and using same." Publication Number 20160002421 (1/7/2016)
This US and International patent application protects a cross-linked polymer network capable of detecting trace amounts of nitramine-based explosives from the air.

4. Dichtel, W. R.; Arslan, H.; Uribe-Romo, F. J. "Graphene nanoribbons derived from poly(phenylene ethynylene) polymer, methods of making same, and uses thereof."
US Patent Number 9556085 (1/27/17), International patents pending
This patent protects a method based on benzannulation chemistry to transform conjugated polymers into graphene nanoribbons.
5. Dichtel, W. R.; Colson, J. W.; Spitler, E. L.; Mukherjee, A.; Levendorf, A.; Woll, A. R.; Park, J. "Covalent Organic Framework Films, and Methods of Making and Uses of Same"
PCT/US11/051350 filed September 15, 2011.
This pending US and international patent applications protect methods to grow covalent organic frameworks as thin films on graphene.

RESEARCH SUPPORT

- Co-PI NSF Grant No. [CHE-0847926]: CCI-I: Center for Molecular Interfacing, Total Award: \$1,500,00, Individual Award: \$165,000, 2008-2011
- PI NSF CAREER Grant No. [CHE-1056657]: Synthesis of Covalent Organic Frameworks with Novel Optoelectronic Properties, \$650,000, 2011-2016
- PI NSF Grant No. [CHE-1124754]: Nanoelectronics in 2020 and Beyond Program Ultimate Electronic Device Scaling Using Structurally Precise Graphene Nanoribbons, \$1,400,000, 2011-2016
- PI ACS PRF Doctoral New Investigator Program Grant No. [52019-DNI7]: Synthesis of Structurally Precise Graphene Nanoribbons, \$100,00, 2012-2013
- PI Alfred P. Sloan Foundation: Sloan Research Fellowship, \$50,000, 2012-2014
- PI Research Corporation: Cottrell Scholar Award, \$75,000, 2012-2014
- PI Schlumberger Foundation: Faculty for the Future Fellowship, \$150,000, 2012-2015
- PI The Arnold and Mabel Beckman Foundation: Beckman Young Investigator Award, \$750,000 2012-2016
- PI Cornell Center for Materials Research SEED: Nanometer-scale patterning from templates of covalent organic frameworks, \$380,000, 2012-2014
- PI American Chemical Society: ACS Cope Scholar Award, \$40,000, 2013
- PI Camille and Henry Dreyfus Foundation: Camille-Dreyfus Teacher-Scholar Program, \$75,000 2013-2018
- Co-PI NSF Grant No. [CHE-1413862]: CCI Phase II: The Center for Sustainable Polymers, Total Award: \$20,000,000, Individual Award: \$1,307,105, 2014-2019
- PI Army Research Office MURI Grant No. [W911NF-15-1-0447]: Center for Advanced 2D Organic Networks, Total Award: \$6,749,996, Individual Award: \$1,334,505, 2015-2020
- PI Atkinson Center for a Sustainable Future: Academic Venture Fund, \$140,000, 2015-2016
- PI John D. and Catherine T. MacArthur Foundation Fellowship, \$625,000, 2015-2020 (to W.R.D.)
- Co-PI NSF MRI Grant No. [CHE-1531632]: Cryoprobe for Enhanced NMR Sensitivity at Cornell University, \$349,300, 2015-2017
- PI NSF EAGER: Grant No. [CHE-1541820]: Biomass-derived Porous Polymers to Remove Organic Pollutants, \$250,000, 2015-2017
- PI Camille and Henry Dreyfus Foundation, [EP-16-087]: Superior removal of organic pollutants from water by cyclodextrin polymers, \$120,000, 2018-2020
- PI Honeywell [DE-NA0002839]: Reprocessable Polyhydroxyurethane Vitrimers, \$130,0234, 2017-2019

- Co-PI CBET-EP SRC [CBET-1706219]: A Game-Changing Approach for Tunable Membrane Development: Novel Covalent Organic Framework Active Layers Supported by Solvent Resistant Materials, \$224,997, 2018-2020
- Co-PI DoD SERDP [W912HQ18C052]: Rational design and implementation of novel polymer adsorbents for selective uptake of per- and polyfluoroalkyl substances from groundwater, \$294,497, 2018-2021
- PI John Simon Guggenheim Memorial Foundation, Fellowship: \$50,000, 2018-2019 (to W.R.D.)
- PI SuperSEED addition to NSF MRSEC [DMR1720139]: Center for Multifunctional Materials, Total Award: \$15,842,003, Individual Award: \$41,000, 2017-2018
- Co-PI DOE [DE-SC0019356]: Creating and Interfacing Designer Chemical Qubits, Total Award: \$3,600,004, Individual Award: \$200,000, 2018-2021
- PI Research Corporation FRED Award, Robust Methods for Controlling Polymerization in Two Dimension, \$249,000, 2018-2021
- Co-PI NSF [CHE-1901635]: Center for Sustainable Polymers, Total Award, \$10,000,000, Individual Award: \$1,075,000 (estimated), 2019-2024
- Co-PI DOE/BIRD Foundation: Israel-US Collaborative Water-Energy Research Center (Israel-US CoWERC), Total Award, \$21,422,000, Individual Award TBD, 07/2020-06/2025 (estimated)
- PI DOE/REMADE Institute, Polyurethane Upcycling, Total Award \$900,000 (estimated), 2021-2024
- PI DARPA Grant No. [HR00112320041]: Efficient Synthesis and Emergent Properties of Catenated Molecular Networks, Total Award: \$886,998, Individual Award: \$553,665 2023-2024
- PI Army Research Office Grant No. [W911NF2310306]: Semiconducting Paramagnetic Covalent Organic Frameworks as a New Class of Organic Electronics and Spintronic Materials, \$780,000, 2023-2026
- Co-PI DoD SERDP Grant No. [W912HQ23C0020]: Next-generation-cyclodextrin-based adsorbents for PFAS remediation: \$374,090, 2023-2026
- PI Trienens Institute (Northwestern): Ultraviolet/Visible/Near Infrared Spectrophotometer to Develop PFAS Destruction Methods and Two-Dimensional Polymer Separation Membranes: \$95,000, 2023.

SCIENTIFIC LEADERSHIP

Associate Chair, Department of Chemistry, Northwestern University (2022-Present)

National Science Foundation, Chemistry Division Director Search Committee (2023)

American Chemical Society National Award Selection Committee Member (2020-2023)

Defense Science Study Group (original term: 2021-2022; extended through 2024 due to covid-19 pandemic)

Co-founder and Chief Science Officer (2016-2021), CycloPure, Inc.

Founding Associate Editor, *ACS Materials Letters* (2019-2023)

Executive Leadership Committee, NSF Center for Sustainable Polymers (2019-present)

Editorial Advisory Board, *ACS Central Science* (ACS)

Editorial Advisory Board, *Polymer International and ChemPlusChem* (Wiley)

Editorial Advisory Board, *Chemistry of Materials* (ACS)

Editorial Advisory Board, *Macromolecules* and *ACS Macro Letters* (ACS) (2013-2016)

Editorial Advisory Board, *iScience*, *Chem* (2015-2018)

Member-at-Large of the Executive Committee of the ACS PMSE Division (2013–2015)

Co-organizer of six porous polymer symposia (once every two years) at ACS National Meetings, most recently Fall 2022 in Chicago.

Co-organizer of a national workshop (2015) on evaluating teaching and learning in research universities, jointly supported by Research Corporation for Science Advancement and the Association of American Universities.

Our working group produced the following reports:

“Searching for Better Approaches: Effective Evaluation of Teaching and Learning in STEM” (2015) AAU and Research Corporation.

“Improve undergraduate science education” *Nature*, **2015**, *583*, 282–284.

“Aligning Practice to Policies: Changing the Culture to Recognize and Reward Teaching at Research Universities” (2017) AAU and Research Corporation

EXTERNAL LECTURES AND CONFERENCE TALKS

210. University of Texas at Dallas Richardson, TX (Invited Speaker)	02/2024
209. University of North Texas Denton, TX (Invited Speaker)	02/2024
208. University of South Florida Tampa, FL (Invited Speaker)	11/2023
207. MacArthur Fellows Forum Chicago, IL (Invited Speaker)	10/2023
206. Cornell University Ithaca, NY (Invited Speaker)	09/2023
205. Vanderbilt University Nashville, TN (Invited Speaker)	09/2023
204. Gordon Conference, Nanoporous Materials and their Applications Concord, NH (Invited Speaker)	08/2023
203. Western Washington University: Scholars’ Week Keynote Speaker Bellingham, WA (Keynote Speaker)	05/2023
202. Oregon State University Corvallis, OR (Invited Speaker)	05/2023
201. Science Philanthropy Association National Meeting: Future of Water Technologies Tucson, AZ (Invited Speaker and Panelist)	03/2023
200. United States Environmental Protection Agency: Environmental Science Symposium Public Webex Meeting (Invited Lecture)	02/2023
199. McGill University	01/2023

- Montreal, Canada (Invited Lecture)
198. University of North Carolina at Chapel Hill: PFAS Remediation and Removal Workshop 01/2023
Chapel Hill, NC (Keynote Lecture)
197. Royal Society of Chemistry: PFAS in the UK 11/2022
London, UK (Invited Lecture, given remotely)
196. Nankai University: Porous Materials Symposium 11/2022
Nankai, China (Keynote Lecture, given remotely)
195. WE-Heraeus Symposium on Molecular Structures on Surfaces 10/2022
Bad Honnef, Germany (Keynote Lecturer)
194. Texas A&M; The Covestro Lectures in Polymer Science 09/2022
College Station, TX (Distinguished Lecturer)
193. Fall 2022 ACS National Meeting: Emerging Water Treatment Symposium 08/2022
Chicago, IL (Invited Speaker)
192. Fall 2022 ACS National Meeting: PFAS Remediation Symposium 08/2022
Chicago, IL (Invited Speaker)
191. Fall 2022 ACS National Meeting: Porous Polymer Symposium 08/2022
Chicago, IL (Symposium organizer and speaker)
190. Fall 2022 ACS National Meeting: Opening Keynote Lecture and Panel on Sustainability 08/2022
Chicago, IL (Keynote)
189. 3M Corporation 08/2022
St. Paul, MN (Invited Speaker)
188. BASF Polyurethane Division 05/2022
Wyandotte, MI (Invited Speaker)
187. University of Colorado, Boulder 05/2022
Boulder, CO (Invited Speaker)
186. NSF Center for Sustainable Polymers Annual Meeting 04/2022
Minneapolis, MN (Invited Speaker)
185. ACS Spring National Meeting 03/2022
San Diego, CA (Invited Speaker)
185. Harvard – MIT Inorganic Seminar Series 03/2022
Cambridge, MA
184. Current: Chicago Water Week 10/2021
Chicago, IL (Keynote Speaker)
183. ACS Fall National Meeting: Henkel Award Symposium 08/2021
Atlanta, GA (Symposium in honor of Austin M. Evans)
182. ACS Fall National Meeting: CME and PMSE Global Mentor in Polymer Science Award 08/2021
Atlanta, GA (Symposium in honor of Austin M. Evans and WRD)

181.	POSTECH Pohang, South Korea (Lecture given virtually)	08/2021
180.	UMass-Lowell Lowell, MA (Lecture given virtually)	03/2021
179.	New York Academy of Sciences New York, NY (Webinar Speaker)	03/2021
178.	University of Maryland College Park, MD (Lecture given virtually)	03/2021
177.	Arizona State University Tempe, AZ (Lecture given virtually)	01/2021
176.	MacArthur Fellows Virtual Gathering Virtual Conference (Invited Speaker)	11/2020
175.	General Motors Sustainability Day Virtual Conference (Invited Speaker and Panelist)	10/2020
174.	Faraday Discussion on Dynamic Processes in Framework Materials Virtual Conference (Invited Speaker and Panelist)	10/2020
173.	King Abdullah University of Science and Technology (KAUST) Jeddah, Saudi Arabia (Lecture given virtually)	10/2020
172.	2020 Polyurethanes Technical Conferences Virtual Conference (Invited Speaker and Panelist)	09/2020
171.	ACS National Meeting (Colloid Division) Virtual Conference (Invited)	03/2020
170.	Emerging Contaminants Summit Denver, CO (Lecturer and Panelist)	03/2020
169.	ETH-Zurich Zurich, Switzerland (Invited)	03/2020
168.	Washington University St. Louis, MO (Invited)	02/2020
167.	University of Tennessee at Knoxville Knoxville, TN (invited)	01/2020
166.	ARO Advanced Membranes Workshop Philadelphia, PA (Keynote)	12/2019
165.	University of Pittsburgh Pittsburgh, PA (Invited)	11/2019
164.	University at Buffalo, The State University of New York Buffalo, NY (Invited)	11/2019
163.	University of Washington	10/2019

Seattle, WA (Invited)	
162. University of Virginia (Berger Lecture) Charlottesville, VA	10/2019
161. Porous Organic Polymers 2019 Heidelberg, Germany (Invited)	09/2019
160. Chem2DMat Conference Dresden, Germany (Keynote)	09/2019
159. ACS National Meeting: Materials Making a Splash – Emerging Trends in Nanoscience, Nanoscience, Materials Science, and Photonics San Diego, CA (Invited)	08/2019
158. ACS National Meeting: Polymers for Defense Applications San Diego, CA (Invited)	08/2019
157. University of Minnesota (Dept. of Environmental Engineering) Minneapolis, MN (Invited)	06/2019
156. International Symposium of Molecular Design for Optoelectronic Materials Beijing, China (Keynote)	05/2019
155. Miami University Oxford, OH (Invited)	04/2019
154. ACS National Meeting (Opening Session Keynote Address) Orlando, FL	03/2019
153. Columbia University (Grandpierre Lecture) New York, NY	02/2019
152. University of Chicago Supramolecular Symposium (Burns Day) Chicago, IL (Invited)	01/2019
151. Singapore International Chemistry Conference-10 (SICC-10) Singapore (Keynote)	12/2018
150. University of Arizona Tucson, AZ (Invited)	12/2018
149. MRS National Meeting Boston, MA (Invited)	11/2018
148. UC-Irvine Irvine, CA (Invited)	11/2018
147. California Institute of Technology Pasadena, CA (Invited)	11/2018
146. Akron Award Symposium Akron, OH (Award Address)	11/2018
145. University of Kentucky	10/2018

Lexington, KY (Invited)	
144. Marquette University, Raj Rathore Memorial Symposium Milwaukee, WI (Invited)	08/2018
143. ACS National Meeting: Porous Polymer Symposium Boston, MA (Invited and Co-organizer)	08/2018
142. ACS National Meeting: Henkel Award Symposium in Honor of Alex Zhukovitsky Boston, MA (Invited)	08/2018
141. Oak Ridge National Laboratory CNMS User Meeting Oak Ridge, TN (Keynote)	08/2018
140. 43 rd International Conference on Coordination Chemistry (ICCC 2018) Sendai, Japan (Keynote)	07/2018
139. Lanzhou University, State Key Laboratory for Organic Chemistry Lanzhou, China (Invited)	07/2018
138. Zhejiang University Hangzhou, China (Invited)	07/2018
137. Fudan University Shanghai, China (Invited)	07/2018
136. 2018 POLYMAT Spotlight Conference San Sebastian, Spain (Keynote)	06/2018
135. Universidad Autónoma de Madrid Madrid, Spain (Invited)	06/2018
134. The 3M Corporation Saint Paul, MN (Invited)	06/2018
133. Functional Polymeric Materials Fusion Conference Nassau, Bahamas (Invited)	06/2018
132. Princeton University (Semmelhack Lecture) Princeton, NJ	05/2018
131. University of Chicago Chicago, IL (Invited)	04/2018
130. Marquette University Milwaukee, WI (Invited)	04/2018
129. American Physical Society National Meeting Los Angeles, CA (Invited)	03/2018
128. Yale Chemical Engineering New Haven, CT (Invited)	02/2018
127. Exxon Houston, TX (Invited)	02/2018

126. UC-Davis Davis, CA (Invited)	01/2018
125. Simon Fraser University Vancouver, BC (Invited)	01/2018
124. University of British Columbia Vancouver, BC (Invited)	01/2018
123. ACS POLY Workshop on Polymers and Nanotechnology San Diego, CA (Invited)	12/2017
122. Leo Hendrik Baekeland Award Symposium Newark, NJ (Award Lecture)	12/2017
121. Arkema Chemical Company King of Prussia, PA (Invited)	12/2017
120. Dow Chemical Company (Electronic Materials Division) Marlborough, MA (Invited)	10/2017
119. Chicago Organic Symposium Chicago, IL (Invited)	09/2017
118. UT-San Antonio Department of Chemistry San Antonio, TX (Invited)	09/2017
117. Texas A&M Department of Chemistry College Station, TX (Student Invited Seminar)	09/2017
116. ACS National Meeting – PMSE Division (Mark Award to Garrett Miyake) Washington, DC (Invited)	08/2017
115. ACS National Meeting – PMSE Division (Stimuli Responsive Polymers Symposium) Washington, DC (Invited)	08/2017
114. ACS National Meeting – PMSE Division (JPS Award to Luis Campos) Washington, DC (Invited)	08/2017
113. ACS National Meeting – PMSE Division (Henkel Award to John Colson) Washington, DC (Invited)	08/2017
112. Blavatnik National Award Symposium New York, NY (Invited)	07/2017
111. International Symposium on Novel Aromatic Systems (ISNA) Stony Brook, NY (Keynote Presentation)	07/2017
110. Functional Pi Systems 13 (F-Pi-13) Hong Kong (Keynote Presentation)	06/2017
109. Supramolecular Gordon Conference Les Diablerets, Switzerland (invited)	05/2017
108. Eastman Chemical Company	05/2017

Kingsport, TN (invited)	
107. Johns Hopkins University Baltimore, MD (invited)	02/2017
106. 8 th International Conference on Advanced Materials and Nanotechnology (AMN8) Queenstown, New Zealand (Keynote Presentation)	02/2017
105. Purdue University West Lafayette, IN (Invited)	02/2017
104. University of Calgary Calgary, AB (Invited)	01/2017
103. University of Alberta Edmonton, AB (Invited)	01/2017
102. University of Florida Gainesville, FL (Invited)	01/2017
101. Linus Pauling Medal Symposium in honor of Timothy M. Swager Tacoma, WA (Invited)	11/2016
100. Southeastern Regional ACS Meeting (SERMACS) – Cope Award Symposium Columbia, SC (Invited)	10/2016
99. Southeastern Regional ACS Meeting (SERMACS) – MOF Symposium Columbia, SC (Invited)	10/2016
98. Virginia Tech Blacksburg, VA (Invited)	10/2016
97. Metal Organic Frameworks 2016 Long Beach, CA (Keynote)	9/2016
96. ACS National Meeting – PMSE Division (Henkel Award to Maxwell Robb) Philadelphia, PA (Invited)	8/2016
95. ACS National Meeting – ENFL Division Philadelphia, PA (Invited)	8/2016
94. ACS National Meeting – PMSE Division Philadelphia, PA (Invited)	8/2016
93. 2 nd International Symposium on Two-Dimensional Polymers Nara, Japan (Invited)	6/2016
92. 2015 MacArthur Fellows Conference Racine, WI (Invited)	5/2016
91. Dartmouth College Hanover, NH (Invited)	4/2016
90. Southern Illinois University – Distinguished Arnold Lecturer Carbondale, IL (Invited)	4/2016

- | | |
|---|--------|
| 89. California Environmental Protection Agency, Environmental Chemistry Laboratory
Berkeley, CA (Invited) | 3/2016 |
| 88. Stanford University
Stanford, CA (Invited) | 3/2016 |
| 87. University of California, Berkeley
Berkeley, CA (Invited) | 3/2016 |
| 86. Lawrence Berkeley National Laboratory Distinguished Lecturer Series
Berkeley, CA (Invited) | 3/2016 |
| 85. Miller Institute for Basic Science
Berkeley, CA (Invited) | 2/2016 |
| 84. University of Colorado at Boulder
Boulder, CO (Invited) | 9/2015 |
| 83. University of Pennsylvania
Philadelphia, PA (Invited) | 9/2015 |
| 82. Northwestern University
Evanston, IL (Invited) | 8/2015 |
| 81. ACS National Meeting – Analytical Chemistry Division
Boston, MA (Invited) | 8/2015 |
| 80. ACS National Meeting – Energy and Fuels Division
Boston, MA (Invited) | 8/2015 |
| 79. ACS National Meeting – Kavli Emerging Leader in Chemistry Lecture
Boston, MA (Keynote Speaker) | 8/2015 |
| 78. Physical Organic Chemistry Gordon Research Conference
Holderness, NH (Invited) | 6/2015 |
| 77. Polymers Gordon Research Conference
South Hadley, MA (Invited) | 6/2015 |
| 76. 2015 American Chemical Society Northeast Regional Meeting
Ithaca, NY (Keynote Speaker) | 6/2015 |
| 75. Cornell Center for Materials Research Symposium
Ithaca, NY (Co-organizer and Speaker) | 5/2015 |
| 74. ACS National Meeting: Design Principles of Functional Macromolecular Materials (PMSE)
Denver, CO (Invited) | 3/2015 |
| 73. ACS National Meeting – Graphene and Carbon Nanotubes (PMSE)
Denver, CO (Invited) | 3/2015 |
| 72. ACS National Meeting – Geoff Coates Applied Polymer Science Award (PMSE)
Denver, CO (Invited) | 3/2015 |
| 71. Smart Coatings 2015 | 2/2015 |

- Orlando, FL (Invited)
70. Ohio State University 2/2015
Columbus, OH (Invited)
69. University of Tokyo – Inaugural BASF Innovation Lecturer 12/2014
Tokyo, Japan (Invited)
68. Institute for Molecular Science 12/2014
Okazaki, Japan (Invited)
67. 10th SPSJ International Polymer Conference (IPC2014) 12/2014
Tsukuba, Japan (Invited)
66. Massachusetts Institute of Technology – Program in Polymer Science Lecture 10/2014
Cambridge, MA (Invited)
65. ACS National Meeting – Porous Polymers (PMSE Division) 8/2014
San Francisco, CA (Invited)
64. ACS National Meeting – National Fresenius Award Symposium and Lecture 8/2014
San Francisco, CA (Award Lecture)
63. 2014 IUPAC World Polymer Congress (MACRO 2014) 7/2014
Polymer International – IUPAC Polymer Award Symposium, Chiang Mai, Thailand (Award Lecture)
62. Telluride Meeting: Metal-Organic Frameworks 7/2014
Telluride, CO (Invited)
61. The 35th Reaction Mechanisms Conference (ACS Organic Division) 6/2014
Davis, CA (Invited)
60. International Symposium on Synthetic Two-Dimensional Polymers 6/2014
Zurich, Switzerland (Invited)
59. University of Texas at Dallas 3/2014
Dallas, TX (Invited)
58. University of North Carolina at Chapel Hill 2/2014
Chapel Hill, NC (Invited)
57. University of Iowa 12/2013
Iowa City, IA (Invited)
56. University of California, Berkeley 11/2013
Berkeley, CA (Invited)
55. University of Rochester 11/2013
Rochester, NY (Invited)
54. University of Southern California 10/2013
Los Angeles, CA (Invited)
53. UCLA 10/2013
Los Angeles, CA (Invited)

- | | |
|---|---------|
| 52. California Institute of Technology
Pasadena, CA (Invited) | 10/2013 |
| 51. University of Nevada, Reno
Reno, NV (Invited) | 10/2013 |
| 50. ACS National Meeting – Porous Materials for Energy Conversion and Storage
Indianapolis, IN (Invited) | 08/2013 |
| 49. ACS National Meeting – Cope Scholar Award Symposium
Indianapolis, IN (Award Address) | 08/2013 |
| 48. Canadian Society for Chemistry Annual Meeting
Quebec City, Quebec (Invited) | 05/2013 |
| 47. PPG Industries, Inc.
Pittsburgh, PA (Invited) | 04/2013 |
| 46. University of Minnesota – Center For Sustainable Polymers Symposium
St. Paul, MN (Invited) | 04/2013 |
| 45. ACS National Meeting - Carbon Nanotube and Graphene Symposium
New Orleans, LA (Invited) | 04/2013 |
| 44. ACS National Meeting – Porous Polymer Symposium
New Orleans, LA (Invited) | 04/2013 |
| 43. ACS National Meeting – Award Symposium for Craig Hawker
New Orleans, LA (Invited) | 04/2013 |
| 42. University of Houston
Houston, TX (Invited) | 04/2013 |
| 41. SUNY-Potsdam
Potsdam, NY (Invited) | 03/2013 |
| 40. Massachusetts Institute of Technology
Cambridge, MA (Invited) | 02/2013 |
| 39. Penn State University
State College, PA (Invited) | 02/2013 |
| 38. Tulane University
New Orleans, LA (Invited) | 01/2013 |
| 37. University of Texas
Austin, TX (Invited) | 01/2013 |
| 36. Princeton University
Princeton, NJ (Invited) | 12/2012 |
| 35. US-Japan Seminar on Polymer Synthesis
Santa Barbara, CA (Invited) | 12/2012 |
| 34. Zing Polymer Conference: From Biomedical Applications to Energy | 11/2012 |

- Cancun, Mexico (Invited)
33. University of Michigan
Ann Arbor, MI (Invited) 11/2012
 32. Pennsylvania State University
State College, PA (Invited) 10/2012
 31. Humboldt-Universität zu Berlin
Berlin, Germany (Invited) 10/2012
 30. Technische Universität Berlin
Berlin, Germany (Invited) 10/2012
 29. BASF
Ludwigshafen, Germany (Invited) 10/2012
 28. Ludwig Maximilians University Munich
Munich, Germany (Invited) 10/2012
 27. University of South Florida
Tampa, FL (Invited) 10/2012
 26. ACS National Meeting: Organic and Metal-Organic Frameworks
Philadelphia, PA (Symposium organizer and speaker) 09/2012
 25. Challenges in Inorganic and Materials Chemistry (ISACS8)
Toronto, Ontario, Canada (Invited) 07/2012
 24. IUPAC World Polymer Congress
Blacksburg, VA (Invited) 06/2012
 23. University of Notre Dame
South Bend, IN (Invited) 05/2012
 22. Northwestern University
Evanston, IL (Invited) 05/2012
 21. Materials Research Society National Meeting: Section Z
San Francisco, CA (Invited) 04/2012
 20. New York University
New York, NY (Invited) 02/2012
 19. Columbia University
New York, NY (Invited) 02/2012
 18. Bryn Mawr College
Bryn Mawr, PA (Invited) 02/2012
 17. Wesleyan College
Middletown, CT (Invited) 02/2012
 16. Exxon-Mobil
Annandale, NJ (Invited) 02/2012

- | | |
|--|---------|
| 15. Materials Research Society National Meeting: Section U
Boston, MA (Invited) | 12/2011 |
| 14. University of Chicago
Chicago, IL (Invited) | 11/2011 |
| 13. McGill University
Montreal, Canada (Invited) | 09/2011 |
| 12. Universite de Montreal
Montreal, Canada (Invited) | 09/2011 |
| 11. IUPAC International Chemistry Congress
San Juan, PR (Invited) | 08/2011 |
| 10. International Symposium on Novel Aromatic Compounds (ISNA)
Eugene, OR (Contributed) | 07/2011 |
| 9. UMass Amherst, Department of Polymer Science and Engineering
Amherst, MA (Invited) | 05/2011 |
| 8. The 3M Corporation
St. Paul, MN (Invited) | 11/2010 |
| 7. Xerox Research Centre
Mississauga, Ontario, Canada (Invited) | 09/2010 |
| 6. ACS National Meeting, Organic Division
Boston, MA (Contributed) | 08/2010 |
| 5. Gordon Conference, Electronic Processes in Organic Materials
Mount Holyoke College, South Hadley, MA (Invited) | 07/2010 |
| 4. University of California, Santa Barbara
Santa Barbara, CA (Invited) | 05/2010 |
| 3. Cornell University, Department of Materials Science and Engineering
Ithaca, NY (Invited) | 04/2010 |
| 2. University of South Carolina
Columbia, SC (Invited) | 04/2010 |
| 1. University of Scranton
Scranton, PA (Invited) | 03/2009 |