

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and UNIVERSITY OF SOUTH FLORIDA,
Patent Owners.

IPR2023-01346
U.S. Patent No. 10,633,344

PETITIONER'S DEMONSTRATIVE EXHIBITS FOR ORAL HEARING

January 8, 2025

Exhibit 1084
Novartis v. Regents
IPR2023-01346

Disputed Issue: Priority Date of '344 Patent Claims 10, 11, and 18

Disputed:

- Whether '956 application (filed March 2003) describes challenged claims
- Whether '956 application (filed March 2003) enables challenged claims

Not in Dispute:

- '768 application (filed March 2002) does not describe or enable challenged claims
- Challenged claims anticipated and obvious if not described or enabled in '956 application (Petitioner's Grounds 1 and 2)

Overview: Claims Lack Written Description and Enablement in '956 Application

- Patent Owners claimed too broadly
- Co-crystal formation not predictable in advance of making co-crystal
- **No written description:**
 - '956 application is at best a research plan for co-crystals beyond those in examples
 - No representative species (undisputed)
 - No common structural features; no correlation between structure and function of forming synthons and co-crystals
 - Knowledge of hydrogen bonding/Etter's "rules" did not make co-crystal formation predictable
- **No enablement:**
 - '956 application is at best a research plan for co-crystals beyond those in examples
 - Knowledge of hydrogen bonding/Etter's "rules" did not make co-crystal formation predictable
 - Undue experimentation even with ability to do certain pre-formulation work and knowledge of *polymorph* high throughput screening
- USPTO previously rejected similar claims in related patent applications for lack of written description and enablement support in the same '956 specification (undisputed)

Claim 10

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a **co-crystal** comprising **supramolecular synthons**, each supramolecular synthon formed from stoichiometric amounts of at least one **active pharmaceutical ingredient (API)** and at least one **co-former**,

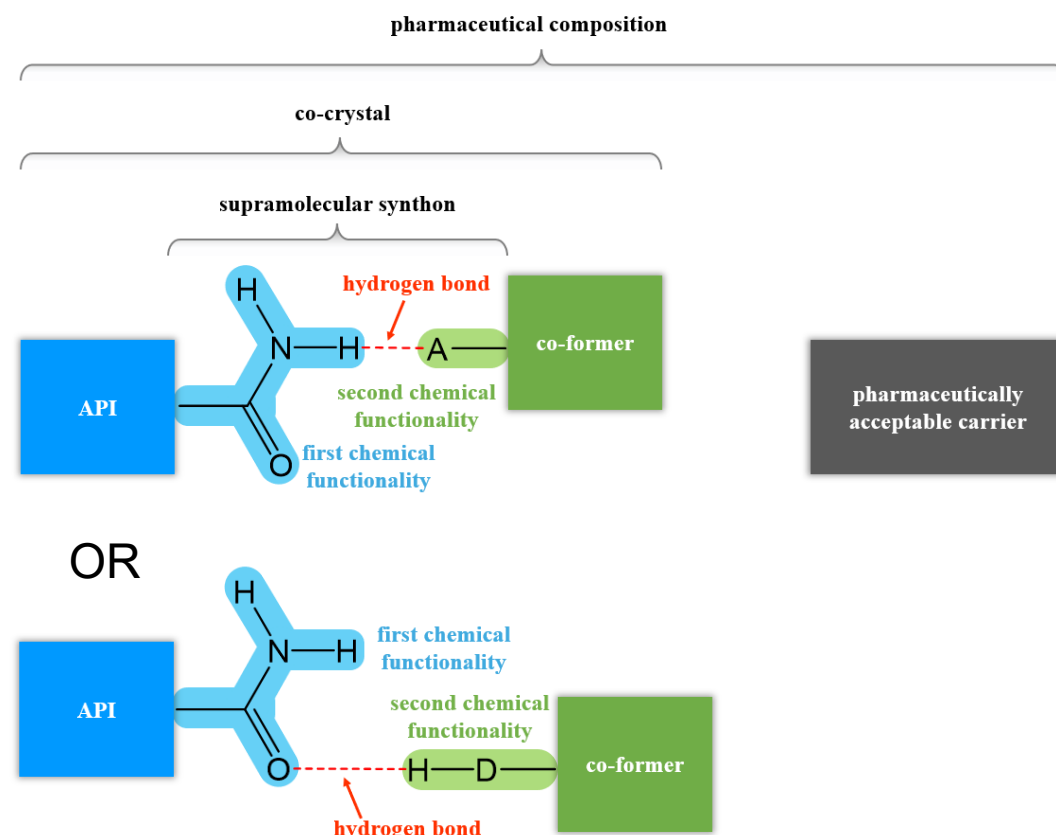
wherein **the API** has a **first chemical functionality** that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein **the co-former** has a **second chemical functionality** complementary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

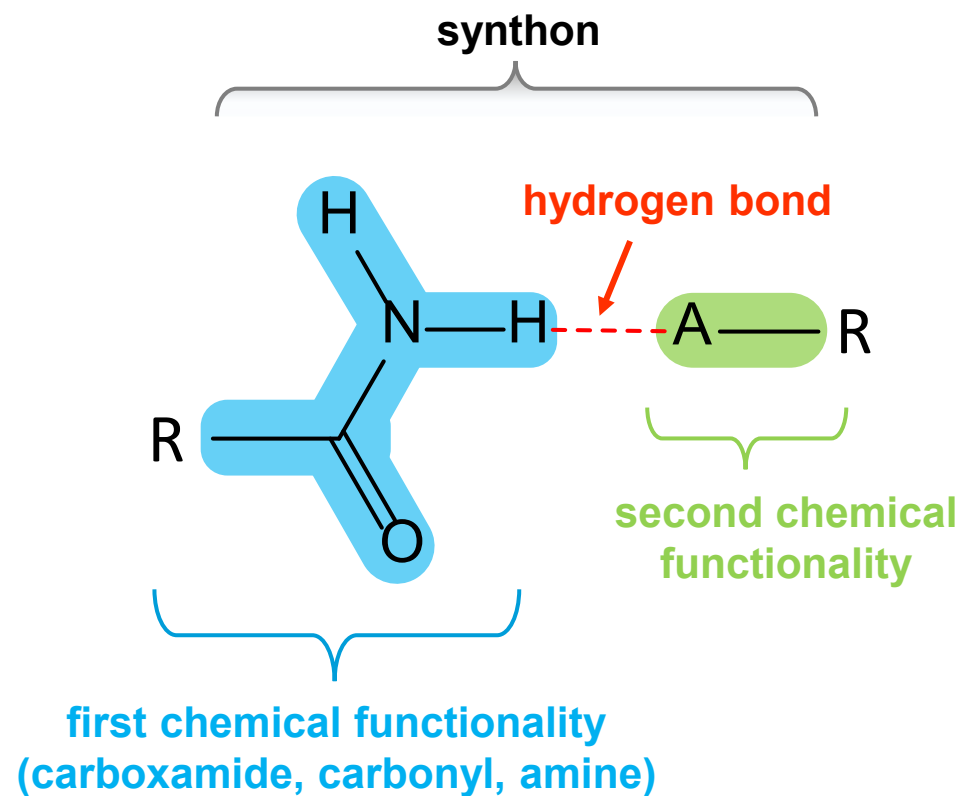
wherein **supramolecular synthons** are formed via **non-covalent hydrogen bonding** between the **first chemical functionality of the API** and the **second chemical functionality of the co-former**, and

wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.



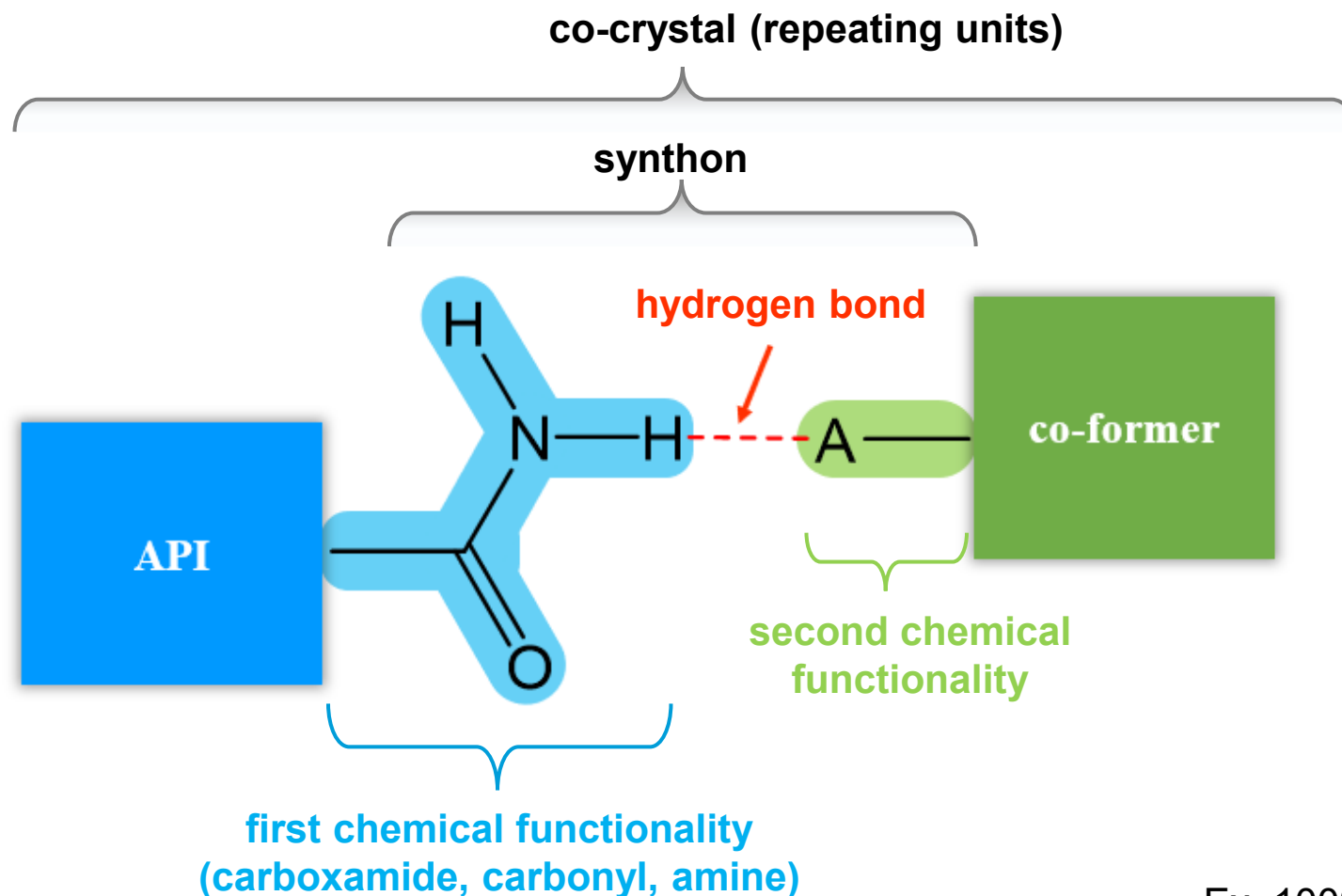
Ex. 1002 Rogers Declaration ¶ 30

Hydrogen Bond Between Two Functional Groups/Synthon



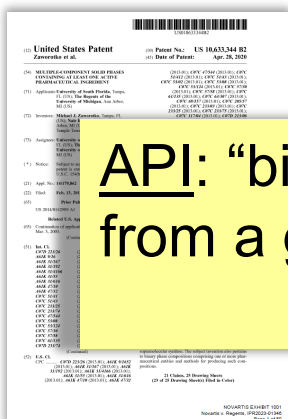
Ex. 1002 Rogers Declaration ¶ 30

Hydrogen Bond/Synthon vs. Co-Crystal



Ex. 1002 Rogers Declaration ¶ 30

Scope of Potential APIs



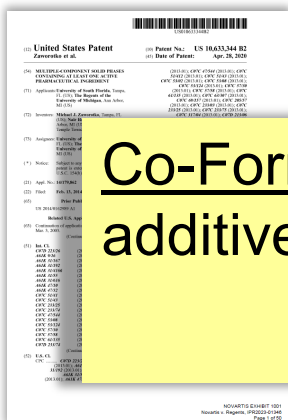
API: “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration”

Ex. 1001 ('344 Patent) at col. 9, ll. 27–34

Undisputed:

- Patent's definition covers APIs of all shapes, sizes, and complexity (provided they have one of the claimed first chemical functionalities)
- As of 2003, there were **50+** carboxamide-containing APIs in the Merck Index alone

Scope of Potential Co-Formers



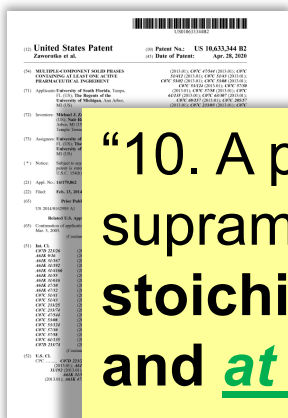
Co-Former: Includes “other drug molecules, GRAS compounds, or approved food additives.”

Ex. 1001 ('344 Patent) at col. 3, ll. 35–37,
see *also* col. 8, ll. 35–38

Undisputed:

- No restrictions on the number or types of functional groups (provided co-former has claimed second chemical functionality and is a solid)
- As of 2003, there were “**thousands**” of possible co-formers

Claims Encompass Co-Crystals With Multiple APIs and/or Multiple Co-Formers



“10. A pharmaceutical composition comprising ... a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from **stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former** ...”

Ex. 1001 ('344 Patent) at Claim 10

Undisputed:

- “at least one” = one or more
- Claims recite co-crystals with multiple APIs and/or co-formers

Paper 19 (PO Response) at 5; Ex. 1072 (Rogers Reply) at ¶ 15

Patent Owners Admit Co-Crystal Formation Was Not Predictable in 2003

“... prior to the present invention, it was not understood even by leading scientists which chemical factors would predetermine the formation of a drug co-crystal. The aspects of different kinds of charges, functional groups, size and shape in molecules and the relationships between them were heretofore not understood in a manner that one could predictably- to almost a certainty- predesign a co-crystal. In short, **prior to this invention, co-crystals were like polymorphs, solvates and hydrates in that random trial-and-error was used to isolate them.**”

Ex. 1017 ('956 App. Pros. History) at 4071–72

“Q: Could you predict whether any particular hydrogen bonds would form between two components of a cocrystal in advance of making it? ...

THE WITNESS: That was part of the process, was designing materials by evaluating different hydrogen bond potential. But **you couldn't predict what would actually occur.**”

Ex. 1020 (Childs Tr.) at 18:9–17

Co-Crystal Formation Was Not Predictable in 2003

Chemistry beyond

Supramolecular chemistry has grown in importance in recent years, particularly in the interface with biological and materials science. A key challenge in this field is the prediction of the structures that will form from a given set of components. The weakness of the interactions involved makes it difficult to predict the structures that will form.

"In any supramolecular assembly, a large number of intermolecular interactions is possible — but only a few are actually observed. The weakness of these interactions makes it **difficult to predict supramolecular structures ..."**

Ex. 1024 (Desiraju) at 398

"Predicting supramolecular structures is hard, not only because of the sheer numbers of possible interactions involved, but also because in energetic terms there is not much to choose between these various interactions."

Ex. 1024 (Desiraju) at 399

USPTO: "The skilled artisan would view the formation of different crystalline forms as being **unpredictable due to the numerous different crystallization factors needing to be controlled to provide different crystal states, as well as the **unpredictability in predicting the different types of crystals that may exist.**"**

Ex. 1023 (Almarsson Pros. History) at 747–51

Knowledge of H-Bonding and Synthons Did Not Make Co-Crystal Formation Predictable

Chemistry beyond the

news and views feature

Supramolecular chemistry has grown in importance

the molecule — the focus of chemical discovery is a

interface with biological and materials science.

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“Even after identifying an important intermolecular interaction, failure to predict a crystal structure can arise because the same interaction can be used to make many different synthons ... [T]he synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong.”

Ex. 1024 (Desiraju) at 399

Are crystal structures predictable?

Jack Dunitz

Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee

The one-word answer to the title question is “often” or “sometimes” or “maybe” or even a conditional “yes, if you’re lucky”.

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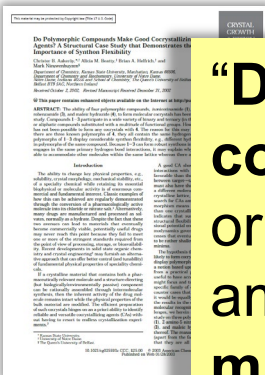
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“One can *describe* almost any observed crystal structure in terms of [hydrogen bond] interactions. The trouble with this approach is that its physical basis is shaky and **its predictive capacity is poor. Of course, inspired guessing may occasionally lead to a correct prediction with any approach.”**

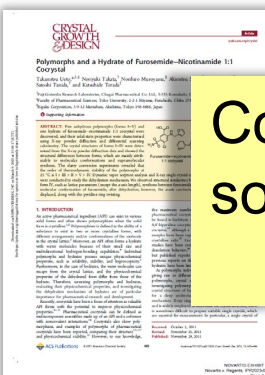
Ex. 1026 (Dunitz) at 546

Failures to Prepare Co-Crystals



“Despite numerous attempts (about 25 different compounds) at forming cocrystals with [maleic hydrazide] and a variety of aromatic (including heterocyclic) or aliphatic compounds with different functional groups, e.g., carboxylic acids, amides, oximes, etc. we were only ever able to isolate unreacted starting materials.”

Ex. 1025 (Aakeröy) at 160



Co-crystal screening of furosemide and nicotinamide in N,N-dimethyl formamide solvent did not result in any co-crystal, hydrate or solvate.

Ex. 1007 (Ueto) at 487

'956 Application Did Not Make Co-Crystals Predictable

'344 Patent Passages Relied on by Patent Owners Fail to Support Broad Claims

1. Definition of API (col. 9, ll. 27–40)
2. Categories of possible co-formers (col. 3, ll. 35–37)
3. List of six potential APIs and description of possible properties of co-crystals (col. 3, ll. 12–26)
4. Examples 1–19: limited number of co-crystals
5. Figure 24 “exemplified scheme” – research plan

'344 Patent Passages Cited by Patent Owners Fail to Support Broad Claims (cont'd)

3. List of six potential APIs and description of possible properties of co-crystals (col. 3, ll. 12–26)

“The subject invention concerns multiple-component solids having at least one active pharmaceutical ingredient. **Examples of** pharmaceutical molecules that may be utilized as **active pharmaceutical ingredients** in the multiple-component solids of the subject invention **include, but are not limited to, aspirin, one or more members of the profen series (e.g., ibuprofen and flurbiprofen), carbamazepine, phenyloin, and acetaminophen.** Multiple-component solids, such as multiple-component crystals, containing these pharmaceutical ingredients and complementary molecules (hereafter referred to as “co-crystal formers”) have been characterized by various techniques and can exhibit physical and/or chemical properties that are the same or different from the parent pharmaceutical ingredient as a direct result of alternative molecular recognition patterns.”

'344 Patent Passages Cited by Patent Owners Fail to Support Broad Claims (cont'd)

4. Examples 1–19

- Not representative of full scope of claims (undisputed)
- Patent Owners admit only 9 examples fall within claims 10, 18*
 - Only 3 of these 9 fall within scope of claim 11*
- Only three APIs represented in 9 examples (undisputed)
 - Dr. Ward admits no examples with “carbonyl” or “amine”*
- No examples with multiple APIs (undisputed)
- No examples with multiple co-formers (undisputed)

*Ex. 2014 (Ward Decl.) App'x C

*Claims cover: **50+** potential APIs, **thousands** of potential co-formers, **27+** potential solvents, **any** stoichiometric ratio of API(s):co-former(s)*

'344 Patent Passages Cited by Patent Owners Fail to Support Broad Claims (cont'd)

4. Examples 1–19

Ex. 2014 (Ward Decl.) Appendix C

Condition	Example																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Supramolecular synthons formed from stoichiometric amounts of at least one API and at least one co-former	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	N	Y
Supramolecular synthons formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
First chemical functionality is a carboxamide	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
First chemical functionality is an amine	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Supramolecular synthon is a heterosynthon dimer formed by non-covalent hydrogen bonding of the API and co-former	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	N	Y	N	N	Y	Y

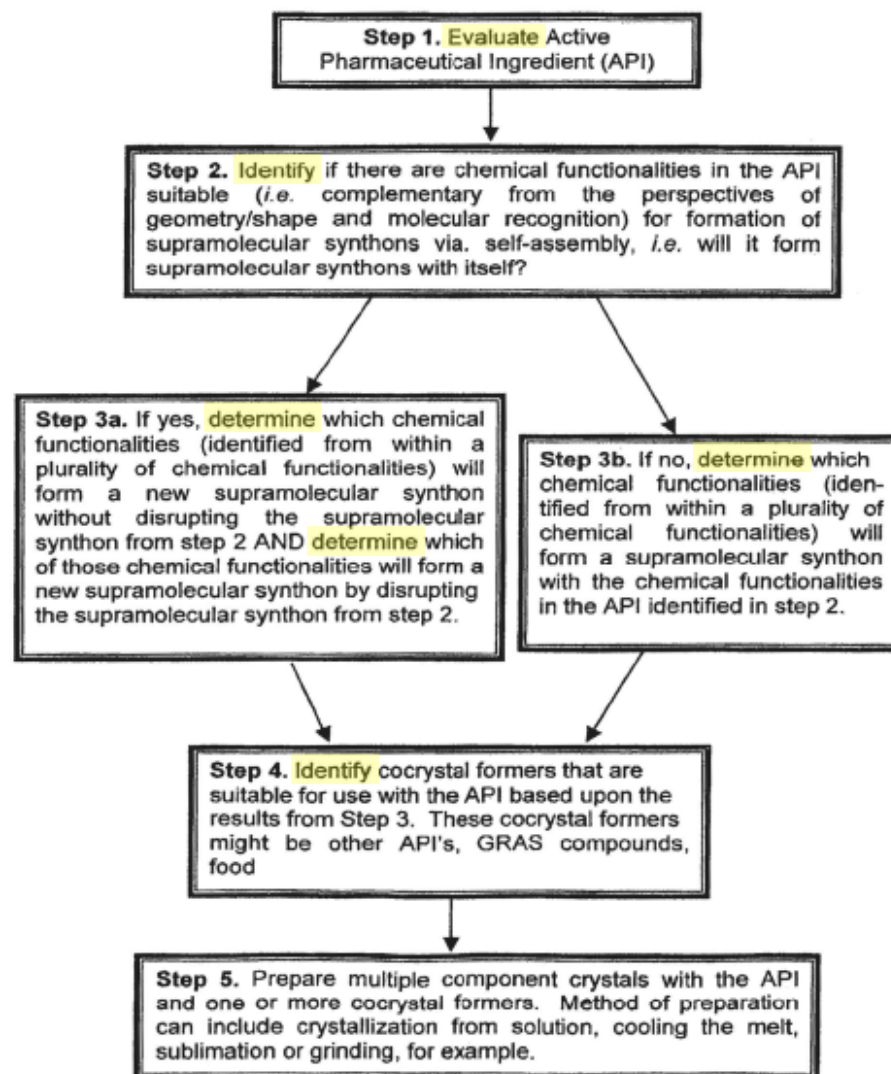
Claims 10 & 18

Claim 11

No "amine" or "carbonyl" first chemical functionality

'344 Patent Passages Cited by Patent Owners Fail to Support Broad Claims (cont'd)

5. Figure 24

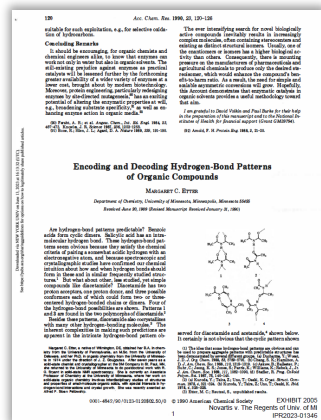


Ex. 1001 ('344 Patent) at Figure 24

Etter's Rules (Ex. 2005)

1. All good proton donors and acceptors are used in hydrogen bonding
2. Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds
3. The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another

Ex. 2005 (Etter 1990) at 124



Patent Owners' Examples Do Not Show Prospective Application of Etter's Rules

“Five cocrystals of diacid•IN with 1:2 stoichiometry are **isolated and characterized by XRD.**”

“These five acids afford the **expected 1:2 complex** of diacid and IN stabilized by acid–pyridine VI and amide–amide II hydrogen bonds (Scheme 2a).”

Ex. 1082 (Vishweshwar June 2003) at 784, 789

“**Inspection** of the carboxy dimer motif in these ten structures shows that while complexes 2–10 contain the ‘expected’ heterodimer, the crystal structure of 1 contains dinitrobenzoic and dimethylaminobenzoic homodimers (Fig. 2).”

Ex. 1081 (Sharma) at 2211

“A similar **classification of the three polymorphs of 2** reveals that the **expected intramolecular amine⋯nitro hydrogen bond** is present in all three forms.”

Ex. 1025 (Aakeröy) at 164

Etter's Rules Had Limitations Relevant Here

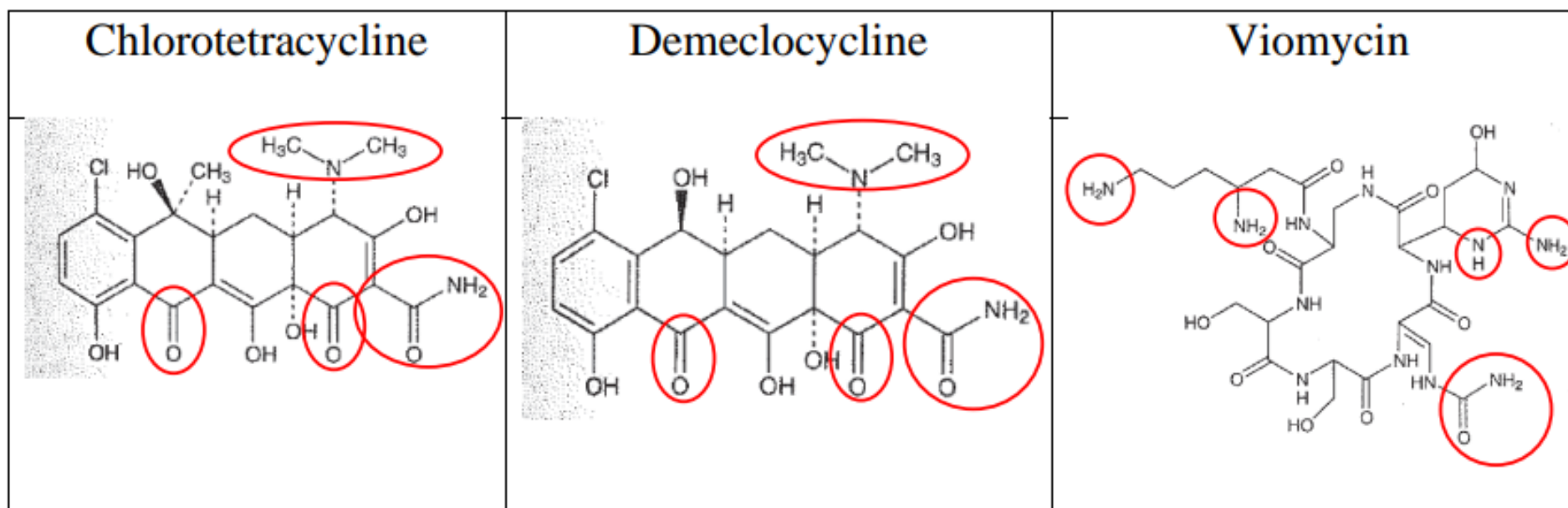
- Patent Owners admit:
 - Etter's rules are most useful for “systems with a limited number of functional groups” and “in the absence of other competing forces.”

Ex. 2014 (Ward Decl.) ¶ 40, quoting Ex. 2005 (Etter 1990) at 121
 - “[O]ther factors could steer synthon formation toward combinations that do not follow the ranking suggested by ... Dr. Etter's ‘rules’.”

Ex. 2014 (Ward Decl.) ¶ 55; POR at 17-18
- These “other competing forces” and “other factors” include:
 - Intermolecular interactions
 - Sterics
 - Geometry

Challenged claims not limited to components that lack “other competing forces” and “other factors”

Etter's Rules Had Limitations Relevant Here (cont'd)



Ex. 1072 (Rogers Reply) at ¶ 64

Etter's Rules Had Limitations Relevant Here (cont'd)

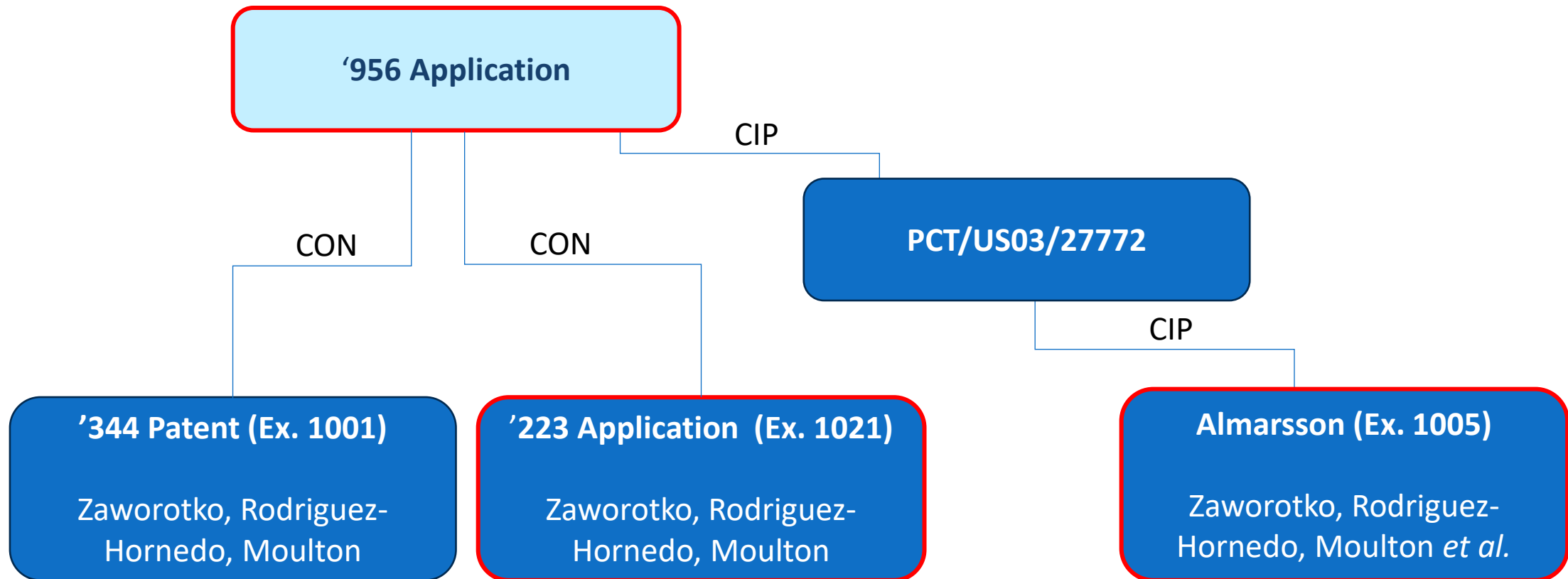
- Undisputed Etter's rules do not address:
 - Co-crystals with more than one API or more than one co-former
 - Co-crystals that also include solvent (e.g., water) in the co-crystal structure
- '344 named inventor Zaworotko:
 - “[T]he promiscuity of water molecules in terms of supramolecular synthons mean[s] that their composition, structure, and thermal stability remain **largely unpredictable**...”

Ex. 1078 (Clarke 2010) at 2166–67,
see also 2152

Challenged Claims Lack Written Description in '956 Application - Overview

- Per *Ariad*, written description of a genus claim requires (1) representative species or (2) common structural features (*Ariad v. Eli Lilly*, 598 F.3d 1336, 1350 (Fed. Cir. 2010))
- No representative species (undisputed)
- No common structural features
 - Claims require **forming** synthons and **forming** co-crystals between API and co-former
 - Patent Owner failed to demonstrate correlation between common structural features and claimed function (forming synthons and co-crystals)
 - No common structural features disclosed (beyond API's first chemical functionality)
 - Nothing teaching which possible APIs and co-formers will form claimed co-crystals
 - At best a research plan; need for extensive trial and error experimentation supports no written description (*PureCircle v. Sweegen*, 2024 U.S. App. LEXIS *2, *8 (Fed. Cir. 2024))

'344 Patent, '223 Application, and Almarsson All Claim Priority to '956 Application



Ex. 1022 ('223 App. Pros. History) at 217

'223 Application Claim 37 Has Similar Scope to Claim 10 of the '344 Patent

'344 Patent Claim 10	'223 Application Claim 37
a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,	a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-crystal former, and each supramolecular synthon comprising a heterosynthon formed via non-covalent hydrogen bonding,
wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,	wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, and wherein the first chemical functionality is selected from carboxylic acid, amide, N-heterocycle, and alcohol;
wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,	
wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.	wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former, and wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.

Ex. 1001 ('344 Patent) at Claim 10

Ex. 1022 ('223 App. Pros. History) at 368

'223 Application Claim 37 Was Rejected as “[B]road and [G]eneric”

“It is unquestionable that [application] claim(s) 37-41, 43-47, 49, and 50 is/are **broad and generic**, with respect to all possible compounds encompassed by the claims. The **possible structural variations are limitless to any [] pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding**. Although the claims may recite some functional characteristics, the claims lack written description because there is **no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification.**”

Ex. 1022 ('223 App. Pros. History) at 394–95

'223 Application Only Provided Sufficient Support for the Disclosed Examples

“Moreover, the **specification lacks sufficient variety of species** to reflect this variance in the genus. While having written description of examples 1-18 [sic, 19] and compounds identified in the specification tables and/or examples, the **specification does not provide sufficient descriptive support** for the myriad of compounds embraced by the claims.”

Ex. 1022 ('223 App. Pros. History) at 394–95

“Although [the 19] examples show the relationship of different groups for H-bonding ... they do not limit the scope of the claims.”

Ex. 1022 ('223 App. Pros. History) at 398

Almarsson Application Claim 1 (Amended)

1. A pharmaceutical **co-crystal** composition, comprising: an **API** and a **co-crystal former**, wherein:
 - a) the **API is selected from celecoxib, carbamazepine, 5-fluorouracil, acetaminophen, aspirin, flurbiprofen, phenytoin or ibuprofen**;
 - b) the **API** and **co-crystal former** are **hydrogen bonded** to each other; and
 - c) specifically excluding a co-crystal selected from the group consisting of: 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohydrate, acetaminophen:piperazine and acetaminophen:theophylline.

Ex. 1023 (Almarsson Pros. History) at 779–782

Almarsson Application Claims Lacked Written Description for Non-Disclosed Co-Crystals

Please type a plus sign (+) inside this box: ☐ PTO/SB/05 (03-01)
Approved for use through 10/31/2002. OMB 0601-0032
 U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
 Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL
(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. TPI-350C1
 First Inventor Om Almarsson
 Title
 Express Mail

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

1. ☒ Fee Transmittal Form (e.g. PTO/SB/117)
(Indicate on original and a duplicate to be processed)

2. ☒ Applicant claims small entity status.
See 37 CFR 1.27

3. ☒ Specification (Total Pages 437)
(Indicate sequence of items listed)
 - Descriptive title of the invention
 - Cross Reference to Related Applications
 - Statement Regarding Fed Sponsored R & D
 - Reference to sequence listing, a table, or a computer program listing appendix
 - Background of the invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description (Claims)
 - Abstract of the Disclosure

4. ☒ Drawings (35 U.S.C. 113) (Total Sheets 66)
(Total Pages 2)

5. Oath or Declaration (Total Pages 2)
 a. ☒ Newly executed (original or copy) (unsigned)
 b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)
 i. ☐ DELETION OF INVENTOR(S)
Significant statement attached detailing circumstances named in the prior application, 37 CFR 1.63(d)(2) and 1.53(b).

6. ☒ Application Data Sheet. See 37 CFR 1.76

18. If a CONTINUING APPLICATION, check appropriate box, and supply the requester info or in an Application Data Sheet under 37 CFR 1.76:
☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP)

Prior application information: Examiner:
 For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application is considered a part of the disclosure of the accompanying continuation or divisional. The incorporation can only be relied upon when a portion has been inadvertently omitted from

19. CORRESPONDENCE ADDRESS
☒ Customer Number or Bar Code Label 23557

Name
 Address
 City State Zip Code
 Country Telephone Fax

Name (Print/Type) Frank C. Eisenchenik, Ph.D. Registration No. (Attorney/Agent) 45,332
 Signature *Frank C. Eisenchenik* Date September 11, 2003

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Mail Stop Patent Application, P.O. Box 1450, Alexandria, VA 22313.

“Applicants have only shown the formation of the particular co-crystals listed in [application] claim 11 [i.e., those co-crystals in the Examples] but do not exemplify the formation of all co-crystals with the API’s listed in amended [application] claim 1. It is not described or shown how the numerous and diverse different co-crystals [encompassed within application claim 1] could be obtained.”

Ex. 1023 (Almarsson Pros. History) at 803,
see also at 747

Patent Owners' Written Description Arguments Lack Merit

Patent Owners' Arguments:

1. Claimed co-crystals have a hydrogen bond between the API and co-former, which is a common structural feature

Paper 19 (PO Response) at 2

➤ Response: Specification has to show possession

2. Knowledge of hydrogen bonding/Etter's rules allows for prediction of co-crystals and this is common information that need not be disclosed in the '956 application

Paper 19 (PO Response) at 16–20

➤ Response:

- Etter's rules subject to many limitations and not applicable across full claim scope
- Knowledge of hydrogen bonding ≠ ability to predict co-crystals (prior art, '223 Application Prosecution History)
- No evidence of co-crystal prediction let alone that it was “conventional” or “well-known”

Patent Owners Ignore the Structure of the Entire API and Co-Former

PTO/AA/15 (03-13)

Under the Paperwork Reduction Act of 1995 no person is required to furnish information on this form unless it is indicated by an instruction.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53)

See MPEP chapter 600 concerning utility patent applications.

APPLICATION ELEMENTS

1. ☐ Fee Transmittal Form (PTO/BB/17 or equivalent)

2. ☒ Applicant asserts small entity status. See 37 CFR 1.27

3. ☐ Applicant certifies micro entity status. See 37 CFR 1.27

4. ☒ Specification [Total Pages:] Both the claims and abstract must start on a new page. (See MPEP § 600.01(a) for information on the preferred and required format.)

5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets:]

6. ☐ Inventor's Oath or Declaration [Total Pages:] (Including substitute statements under 37 CFR 1.64 and interrogatories serving as an oath or declaration under 37 CFR 1.63(e))

7. ☒ Application Data Sheet * See note below. (See 37 CFR 1.76 (PTO/AA/14 or equivalent))

8. ☐ CD-ROM or CD-R (In duplicate, large table, or Computer Program (Appendix))

9. ☐ Nucleotide and/or Amino Acid Sequence Submissions (If applicable, items a - c are required)

10. ☐ Computer Readable Form (CRF)

11. ☐ Specification Sequence Listing on: i. CD-ROM or CD-R (2 copies); or ii. Paper

12. ☐ English Translation Document (If applicable)

13. ☐ Information Disclosure Statement (PTO/SD/26 or PTO/1449) ☐ Copies of citations attached

14. ☒ Preliminary Amendment

*Note: (1) Benefit claims under 37 CFR 1.78 and (2) For applications filed under 35 U.S.C. 111, by assignee, person to whom the inventor is and interest in the matter. See 37 CFR 1.48(b).

☒ The address associated with Customer Number:

Name: []

Address: []

City: []

Country: []

Signature: /Edward R. Gates/

Name (Print Type): Edward R. Gates

“Although [the 19] examples [in the specification] show the relationship of different groups for H-bonding ... they do not limit the scope of the claims.”

Ex. 1022 ('223 App. Pros. History) at 398

“The broad[est] reasonable interpretation (BRI) of claim 37 encompasses more than the functional groups participating in H-bonding in examples 1-19. The whole structure of each component of the co-crystal has to be taken into consideration. The functional groups only represent [] one part of the API and one or more co-crystal former(s).”

Ex. 1022 ('223 App. Pros. History) at 398

NOVARTIS EXHIBIT 1022
Novartis v. Regents, IPR2023-01346
Page 1 of 415

Patent Owners' Case Law Regarding Conventional Information Is Irrelevant

Non-disclosed information indisputably known in the art	• <i>Koito Mfg. Co.</i> (Fed. Cir. 2004) (parameters and gate size were “standard in the industry”) • <i>Falkner</i> (Fed. Cir. 2006) (poxvirus DNA sequence and its essential regions disclosed in the art) • <i>Hybritech Inc.</i> (Fed. Cir. 1986) (process to make monoclonal antibodies well-known and reference discussing process cited in specification) • <i>Capon</i> (Fed. Cir. 2005) (nucleotide sequences of chimeric genes known in the art) • <i>Zoltek Corp.</i> (Fed. Cir. 2016) (starting material commercially available) • <i>Immunex Corp.</i> (Fed. Cir. 2020) (amino acid sequence disclosed in art cited in specification) • <i>Forest Lab’ys, LLC</i> (Fed. Cir. 2019) (asenapine free base known in the art)
No reliance on conventional information	• <i>Streck</i> (Fed. Cir. 2012) • <i>Space Sys.</i> (Fed. Cir. 2005)
Other	• <i>Bos. Sci. Corp.</i> (Fed. Cir. 2011) (specification refuted that structural elements and mechanism of action of rapamycin were well known) • <i>Biogen Int’l GmbH</i> (Fed. Cir. 2022) (dissent (cited by Patent Owners) recommended en banc review <i>because</i> panel improperly relied on extrinsic material)

Challenged Claims Lack Enablement: *Wands* Analysis

Factor	Analysis	Outcome
Breadth of the Claims	Claims are extremely broad (undisputed)	Not enabled

Undisputed:

- “[P]ossible structural variations are limitless”
- Claims cover multiple APIs and/or co-formers
- Claims cover any stoichiometric ratio of API(s):co-former(s)
- Claimed co-crystals can also include solvent(s)
- As of 2003:
 - 50+ carboxamide-containing APIs
 - “[T]housands” of potential co-formers
 - 27+ pharmaceutically acceptable solvents

Challenged Claims Lack Enablement: *Wands* Analysis (cont'd)

Factor	Analysis	Outcome
Breadth of the Claims	- Claims are extremely broad (undisputed) - Formation of co-crystals was <u>not</u> predictable	Not Enabled
Nature of the Invention		Not Enabled
State of the Art		Not Enabled
Predictability of the Art		Not Enabled

Nature of the Invention; State of the Art; Predictability of the Art

“In any supramolecular assembly, a large number of intermolecular interactions is possible — but only a few are actually observed. The weakness of these interactions makes it **difficult to predict supramolecular structures ...**”

Ex. 1024 (Desiraju) at 398

“**Predicting supramolecular structures is hard....**”

Ex. 1024 (Desiraju) at 399

“The trouble with [using hydrogen bond interactions for crystal engineering] is that its physical basis is shaky and **its predictive capacity is poor.**”

Ex. 1026 (Dunitz) at 546

“**... prior to the present invention, it was not understood even by leading scientists which chemical factors would predetermine the formation of a drug co-crystal. ... [R]andom trial-and-error was used to isolate them.**”

Ex. 1017 ('956 App. Pros. History) at 4071–72

Nature of the Invention; State of the Art; Predictability of the Art

news and views feature

Chemistry beyond the molecule

Gautam R. Desiraju

Supramolecular chemistry has grown in importance because it goes beyond the molecule — the focus of classical chemistry. It also offers a fresh interface with biological and materials science.

For a long time chemists stand nature at a level molecular — they o structures and functions i covalent bonds. But some of tant biological phenomena making and breaking covalen linkages that connect atoms ules. Instead, biological stru ly made from loose aggregat together by weak, non-coval Because of their dynamic nat actions are responsible fo processes occurring in l Chemists have been slow enormous variety — in terms of structure, properties and functions — offered by this more relaxed approach to making chemical compounds.

The slow shift towards the began in 1894, when Emil F that an enzyme interacts w a key does with its lock'. This nism contains the two main would become a new i molecular chemistry?'. These are molecular recognition in lar function. Molecular recognition is lock-and-key model — pro geometry and the non-coval are compatible between the i mers, you get recognition. Suc interactions also lead to usef lar functions. For example, that an enzyme works only c

A classic example of a donor-acceptor complex is formed by silver ions (Ag^+) and ethene ($\text{CH}_2=\text{CH}_2$), in which the ethene donates some electrons from its double bond with another.

A classic example of a donor-acceptor complex is formed by silver ions (Ag^+) and ethene ($\text{CH}_2=\text{CH}_2$), in which the ethene donates some electrons from its double bond with another.

Chemists could not understand these inclusion compounds in terms of normal

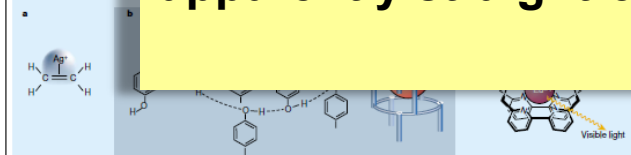


Figure 1 Supramolecular structures formed by intermolecular interactions. a, A donor-acceptor complex involving silver and ethene. b, Hydroquinone molecules assemble into a clathrate using hydrogen bonds. This means they can form solid-state host-guest complexes in which the hydroquinone network is the host and the guest is a small molecule, such as the xenon atom shown. c, A cryptand contains a spherical internal cavity studded with donor sites, suitable for enclosing a metal ion. Ultraviolet light absorbed by the cryptand shown here excites the metal ion, $\text{Eu}(\text{III})$, which then emits radiation at longer (visible) wavelengths.

NATURE | VOL 412 | 26 JULY 2001 | www.nature.com

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NOVARTIS EXHIBIT 1024
Novartis v. Regents, IPR2023-01346
Page 1 of 4

Patent Owners' cite: "Although at a simple level molecular recognition can be said to hinge on isotopic interactions, at a higher level it is an anisotropic interaction that is the master key: the hydrogen bond."

Ex. 1024 (Desiraju) at 399

"Even after identifying an important intermolecular interaction, failure to predict a crystal structure can arise because the same interaction can be used to make many different synthons ... [T]he synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong."

Ex. 1024 (Desiraju) at 399

Challenged Claims Lack Enablement: *Wands* Analysis (cont'd)

Factor	Analysis	Outcome
Breadth of the Claims	• Claims are extremely broad (undisputed)	Not enabled (undisputed)
Nature of the Invention	• Formation of co-crystals was <i>not</i> predictable	Not enabled
State of the Art		Not enabled
Predictability of the Art		Not enabled
Relative Skill of Those in the Art	• Relatively high (undisputed)	Neutral

Challenged Claims Lack Enablement: *Wands* Analysis (cont'd)

Factor	Analysis	Outcome
Breadth of the Claims	Claims are extremely broad (undisputed)	Not enabled
Nature of the Invention	Formation of co-crystals was <u>not</u> predictable	Not enabled
State of the Art		Not enabled
Predictability of the Art		Not enabled
Relative Skill of Those in the Art	Relatively high (undisputed)	Neutral
Working Examples	- At most 9 examples within scope of claims 10 and 18, and only 3 of these within scope of claim 11 (undisputed) - Examples not representative of full claim scope (undisputed) - No additional guidance in specification to predict co-crystal formation - Undue experimentation to test full scope of broad claims	Not enabled
Amount of Direction or Guidance		Not enabled
Quantity of Experimentation		Not enabled

High-Throughput Screening Does Not Provide Enablement Support

- High-throughput screening not reported for co-crystals prior to March 2003
 - Polymorph screening $\neq$ co-crystal screening
- '956 application: No guidance on how to apply polymorph high-throughput screening to co-crystals

High-Throughput Screening Requires Extensive Planning, Experimentation, and Analysis

Dr. Ward's Steps:

1. Preparing samples and compound libraries
2. Automating benchtop testing procedures
3. Configuring robotic workstation
4. Acquiring and processing testing data

Additional Considerations (undisputed):

- Amounts and stoichiometric ratios of API and co-former
- Solvent, including solvent combinations, concentration
- Timing, including time to dissolve API or co-former in solvent, evaporation time and incubation time
- Temperature and/or temperature range for each step (dissolution, incubation)
- Heating/cooling rates, mixing/stirring rates, evaporation rates
- Carrier gas, or combinations and ratios thereof
- Degree of supersaturation
- Additives, including concentrations thereof
- pH
- Co-crystallization vessel

High-Throughput Screening Does Not Provide Enablement Support

- High-throughput screening equipment could not have been used to analyze whether any product falls within the scope of the claims
 - Requires single crystal x-ray diffraction to examine location of hydrogen bonds
 - Must prepare sample of sufficient size and quality

Wands Factors

Factor	Analysis	Outcome
Breadth of the Claims	• Claims are extremely broad (undisputed)	Not enabled
Nature of the Invention	• Formation of co-crystals was <u>not</u> predictable	Not enabled
State of the Art		Not enabled
Predictability of the Art		Not enabled
Relative Skill of Those in the Art	• Relatively high (undisputed)	Neutral
Working Examples	• At most 9 examples within scope of claims 10 and 18, and only 3 of these within scope of claim 11 (undisputed) • Examples not representative of full claim scope (undisputed) • No additional guidance in specification to predict co-crystal formation • Undue experimentation to test full scope of broad claims	Not enabled
Amount of Direction or Guidance		Not enabled
Quantity of Experimentation		Not enabled

Almarsson's Broad Application Claims Rejected for Non-Enablement

Please type a plus sign (+) inside this box: ☐ PTO/SAS (03-01)
Approved for use through 10/31/2002. OMB 0551-0032
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UTILITY PATENT APPLICATION TRANSMITTAL
(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	TPI-350C1
First Inventor	Om Almarsson
Title	Pharmaceutical Co-Crystal Compositions
Express Mail Label No.	EU082848285US

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility applications.

- ☒ Fee Transmittal Form (e.g. PTO/SAS 03-01) (Indicate on original and a duplicate for the receiving office.)
- ☒ Applicant claims small entity status. See 37 CFR 1.27.
- ☒ Specification (Total Pages: 10) (Indicate on original and a duplicate for the receiving office.)
 - Descriptive title of the invention
 - Cross Reference to Related Applications
 - Statement Regarding Federal Sponsorship
 - Reference to sequence listing, a table or a computer program listing app.
 - Background of the invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings
 - Detailed Description (Claims)
 - Abstract of the Disclosure
- ☒ Drawing(s) (35 U.S.C. 113)
- ☒ Oath or Declaration
 a. ☒ Newly executed (original)
 b. ☐ Copy from a prior application (for continuations/divisions)
 i. ☐ DELETION OF INFORMATION
Signal statement attached dated 11/03/03 and 11/03/03.
- ☒ Application Data Sheet. See 37 CFR 1.53(b).

16. If a CONTINUING APPLICATION, check ☐ Continuation ☐ Divisional

For CONTINUATION OR DIVISIONAL APPS only: Box 3b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

☒ Customer Number or Bar Code Label 23557 or ☐ Correspondence address below

Name _____
 Address _____
 City _____ State _____ Zip Code _____
 Country _____ Telephone _____ Fax _____

Name (Print/Type) Frank C. Eisenreich, Ph.D. Registration No. (Attorney/Agent) 45,332
 Signature *Frank C. Eisenreich* Date September 11, 2003

“[T]he specification is not enabled for the preparation of all co-crystals having any API that is solid, as broadly recited in claim 1. As discussed in the rejection, **the state of the art regarding the formation of different crystalline forms is unpredictable due to the numerous different crystallization factors needed to be controlled to provide different crystal states.** Further, the formation of crystals is usually arrived at via **experimentation.**”

Ex. 1023 (Almarsson Pros. History) at 745, 747-751

NPC-UNIV-000004379
 NOVARTIS EXHIBIT 1023
 Novartis v. Regents, IPR2023-01346
 Page 1 of 1101

Several '956 Application Examples Use Toxic or Carcinogenic Co-Formers/Solvents

Solvents in Class 2 (Table 2) should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Table 2. – Class 2 Solvents in Pharmaceutical Products

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Dichloromethane	6.0	600
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
Tetrahydrofuran	7.2	720

Ex. 2012 (HHS Guidance 2003) at 8

Ex. 1001 ('344 Patent)

Example 3: Hexane

Example 7: Methanol

Example 8: Methanol

Example 11: Methanol

Example 13: Methanol

Example 14: Methanol or THF

Example 17: Methanol or THF

Example 19: Methanol and
dichloromethane (mixture)

Example 17: formamide co-former

Agreed-Upon Constructions

- **active pharmaceutical ingredient (API)**
 - biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration
- **API homonym**
 - synthons formed between identical complementary chemical functionalities of the API
- **carbonyl**
 - -C(=O)-
- **carboxamide**
 - encompasses -C(=O)NH_2
 - carbamazepine has a carboxamide group

Agreed-Upon Constructions

- **co-former**
 - component of a co-crystal
- **heterosynthon dimer**
 - synthon formed by two different, yet complementary chemical functionalities
- **supramolecular synthon**
 - The sum of the components of a multiple-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality

Construction of “co-crystal”

- Parties agree on construction of “co-crystal” for the purposes of IPR
 - a multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds

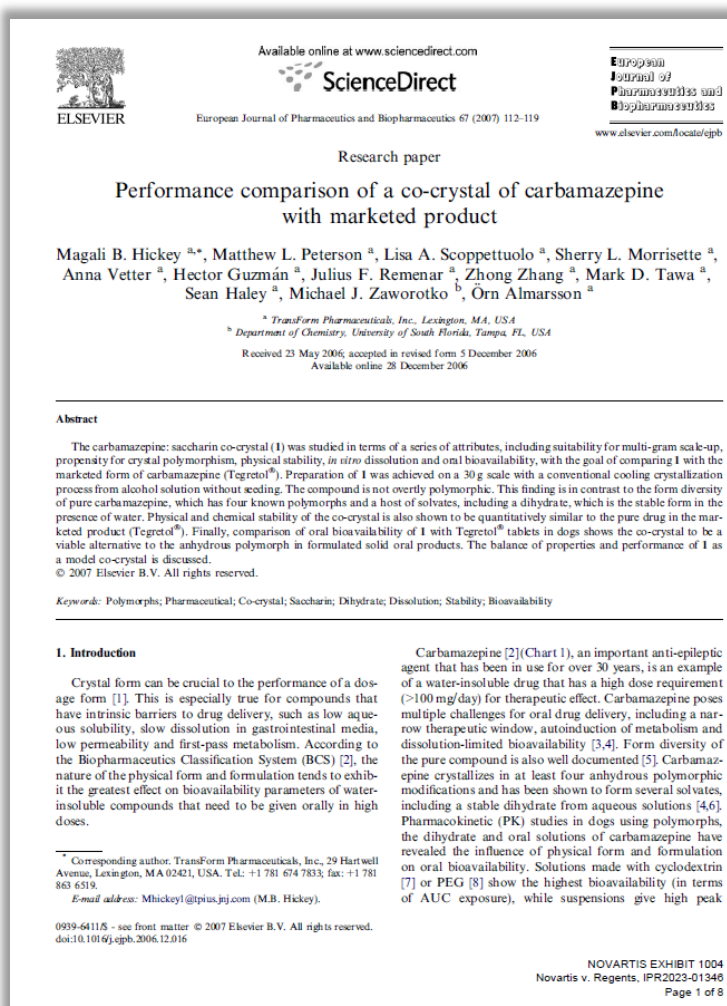
Construction of “permits formation”

- Parties disagree on the construction of “permits formation”
 - Petitioner: Requires actual formation of API homosynthons, not mere possibility
 - Patent Owners: Allows for formation, does not require it
- Specification supports Petitioner
 - Instructs selection of API “capable of forming supramolecular synthons”
 - Further instructs that “capable of forming” means API homosynthons can, and in fact are, formed

Ex. 1001 ('344 Patent) at col. 3, ll. 65-67, col. 7, ll. 47-49,
see also col. 3, ll. 41-44, 51-56, col. 9, ll. 57-62

Ex. 1001 ('344 Patent) at col. 4, ll. 13-33,
see also col. 3, l. 60 – col. 4, l. 12, col. 4, ll. 50-55, col. 7, l. 42 – col. 8, l. 15

Ground 1 – Anticipation by Hickey (Ex. 1004)



Ex. 1004 (Hickey)

- Authored by ‘344 patent named inventor Dr. Zaworotko
- Discloses 1:1 carbamazepine:saccharin co-crystal and pharmaceutical composition thereof
- Compares carbamazepine:saccharin co-crystal to carbamazepine pharmaceutical product using *in vitro* dissolution study and oral bioavailability study
- Every element of the challenged claims is disclosed in Hickey

Claim 10 Elements

[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

[10b] a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

[10c] wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

[10d] wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding,

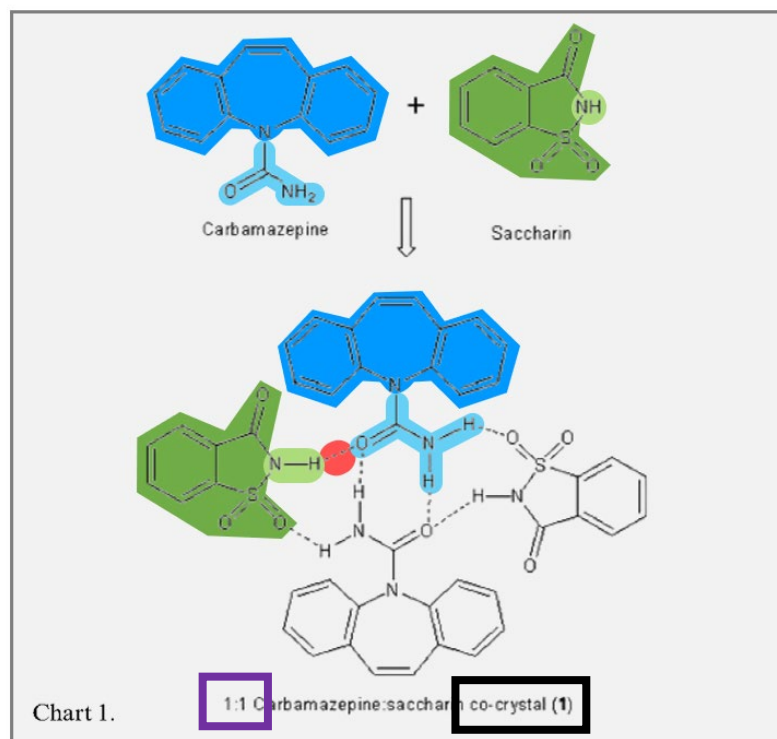
[10e] wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

[10f] wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

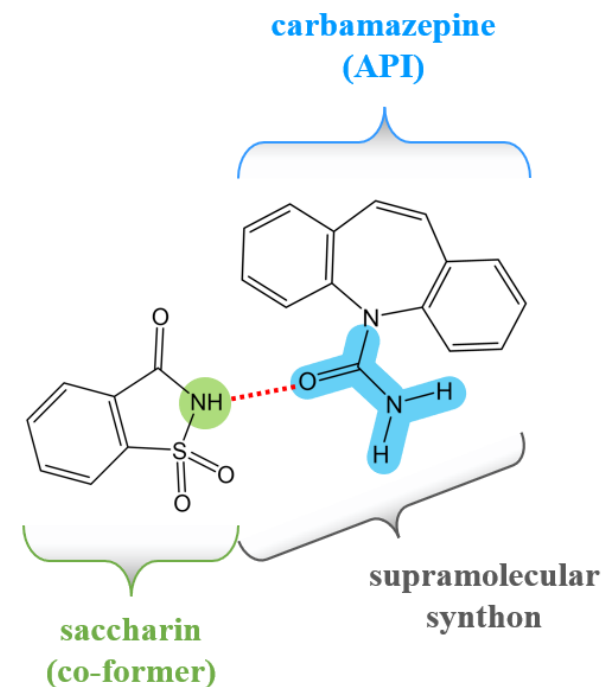
[10g] wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

Hickey Discloses Element 10b

[10b] a **co-crystal** comprising **supramolecular synthons**, each supramolecular synthon formed from **stoichiometric amounts** of at least one **active pharmaceutical ingredient (API)** and at least one **co-former**,



Ex. 1004 (Hickey) at 113 (Chart 1)



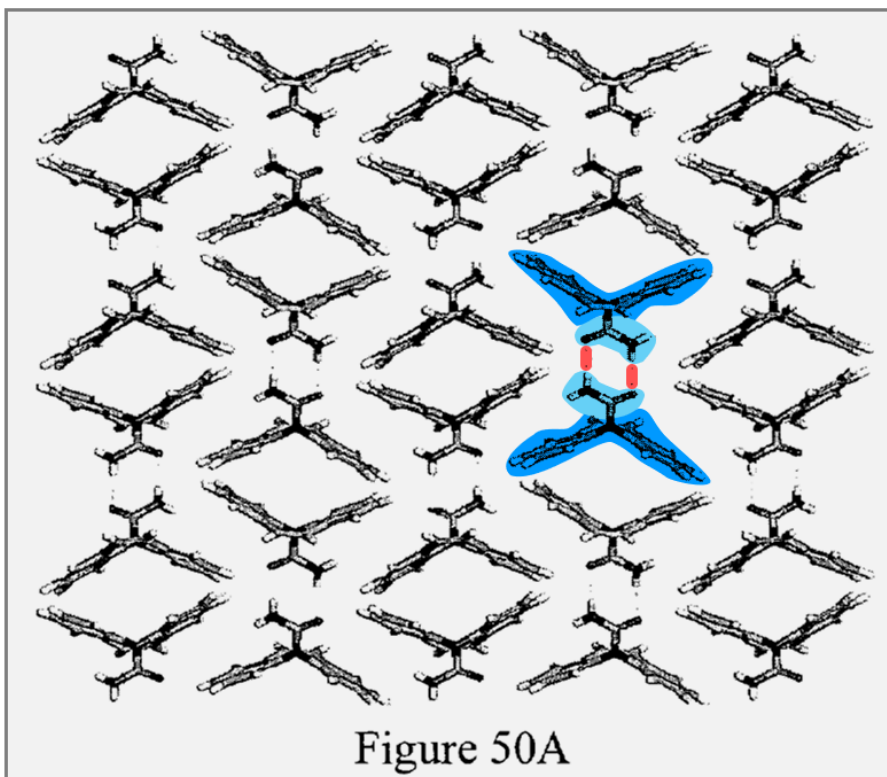
second chemical functionality

non-covalent hydrogen bond

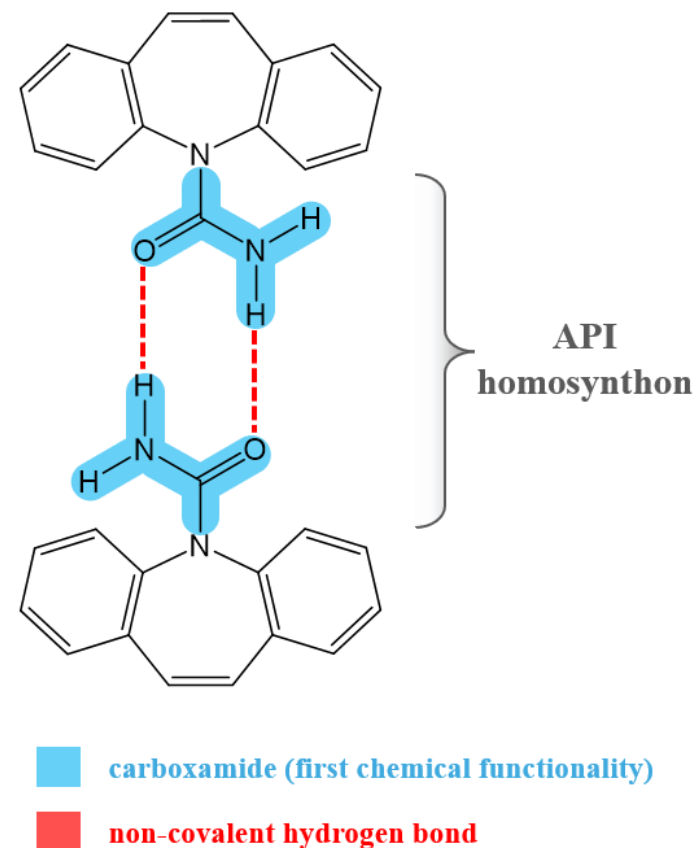
carboxamide (first chemical functionality)

Hickey Inherently Discloses Element 10c

[10c] wherein the **API** has a **first chemical functionality** that permits formation of **API homosynthons** through **non-covalent hydrogen bonding** when the API is in its pure form,

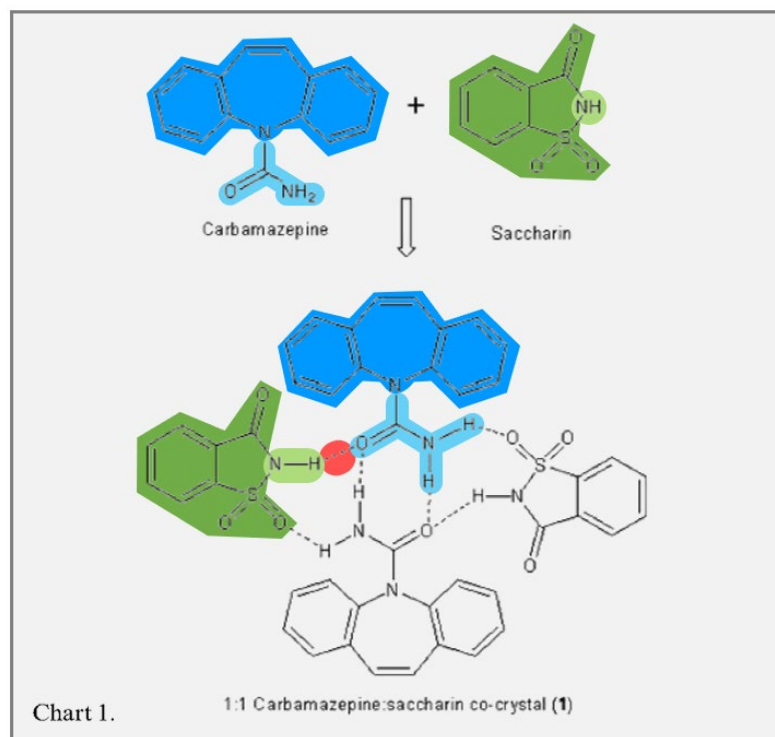


Ex. 1005 (Almarsson) at Figure 50A; col. 6, ll. 38–40

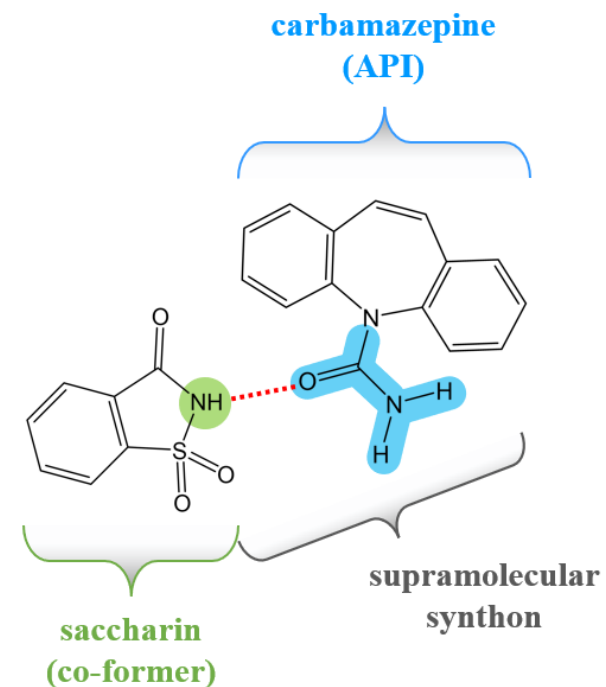


Hickey Discloses Element 10d

[10d] wherein the **co-former** has a **second chemical functionality** compl[e]mentary to the **first chemical functionality** via **non-covalent hydrogen bonding**,



Ex. 1004 (Hickey) at 113 (Chart 1)



■ second chemical functionality

■ non-covalent hydrogen bond

■ carboxamide (first chemical functionality)

Hickey Inherently Discloses Element 10e

[10e] wherein said **co-former** is a solid at room temperature and atmospheric pressure when the co-former is in its pure form

Co-former used in Hickey: Saccharin

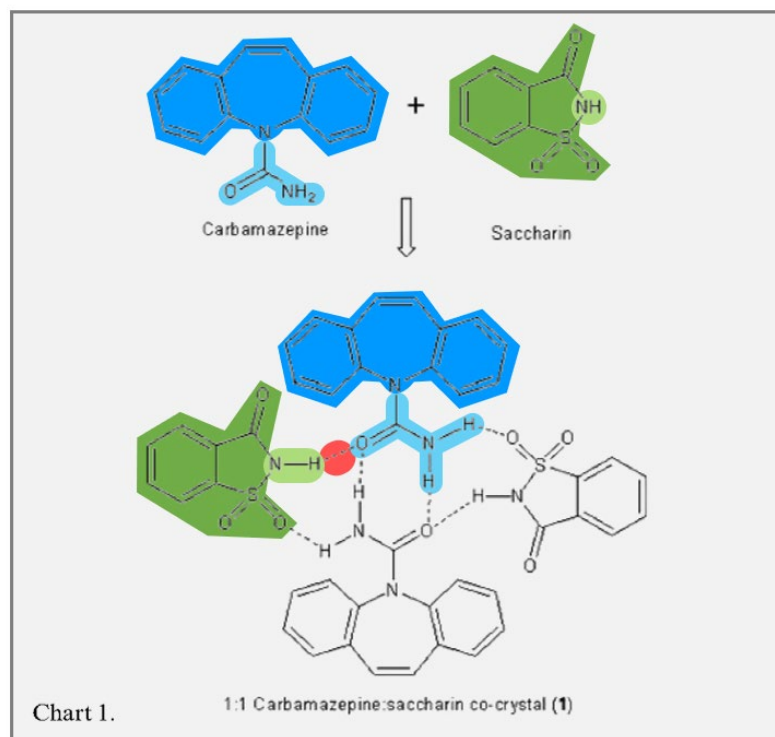
Saccharin melting point at room temperature and atmospheric pressure: 228.8 °C

Ex. 1005 (Almarsson) at col. 42, ll. 53–57

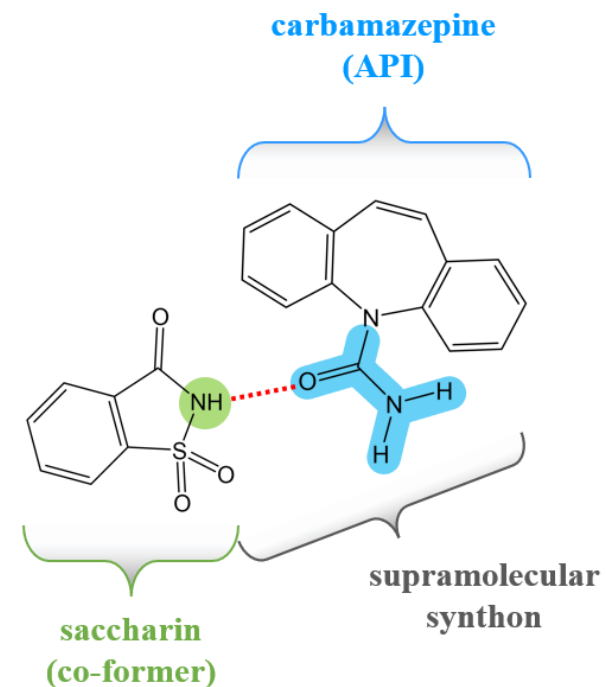
Saccharin melting point is *above* room temperature (about 20–25 °C), therefore, saccharin is solid at room temperature and atmospheric pressure when in its pure form

Hickey Discloses Element 10f

[10f] wherein **supramolecular synthons** are formed via **non-covalent hydrogen bonding** between the **first chemical functionality** of the **API** and the **second chemical functionality** of the **co-former**, and



Ex. 1004 (Hickey) at 113 (Chart 1)



■ second chemical functionality

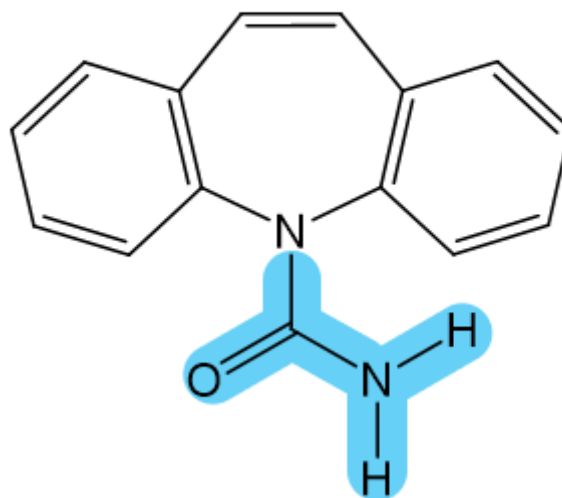
■ non-covalent hydrogen bond

■ carboxamide (first chemical functionality)

Hickey Discloses Element 10g

[10g] wherein the **first chemical functionality** is (i) a **carboxamide**, (ii) a carbonyl, or (iii) an amine.

carbamazepine (API)



Ex. 1004 (Hickey) at 113 (Chart 1)

Hickey Discloses Element 10a

[10a] A **pharmaceutical composition** comprising a **pharmaceutically acceptable carrier** and a **therapeutically effective amount** of [a **co-crystal**]

A prototype oral dosage form in an HPMC capsule (Shionogi Qualicaps) containing **1** was prepared by mixing **α -lactose monohydrate** (2.52 g, 0.0069 mol, Sigma, Lot 43254338) with **1** (3.654 g, 0.087 mol, particle size <53 μ m) and **blending the two solids** in a mortar and pestle. Capsules containing **600 mg of formulated co-crystal** (corresponding to **200 mg of carbamazepine**) were prepared.

1 = carbamazepine:saccharin co-crystal

Tegretol® includes 200 mg of carbamazepine (commercially available carbamazepine tablets)

Ex. 1004 (Hickey) at 115

Claim 11 Elements

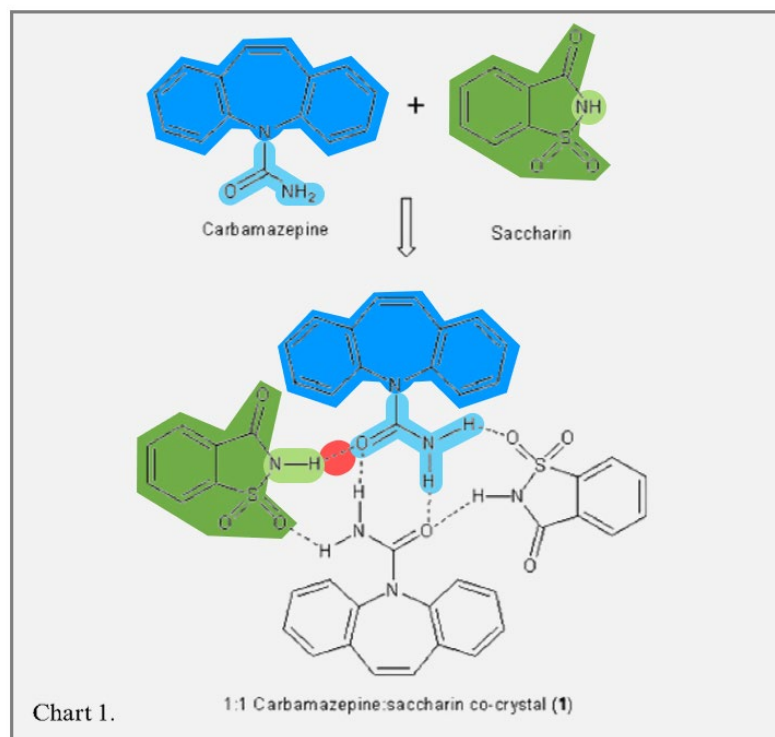
[11a] The pharmaceutical composition of claim 10

[11b] wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

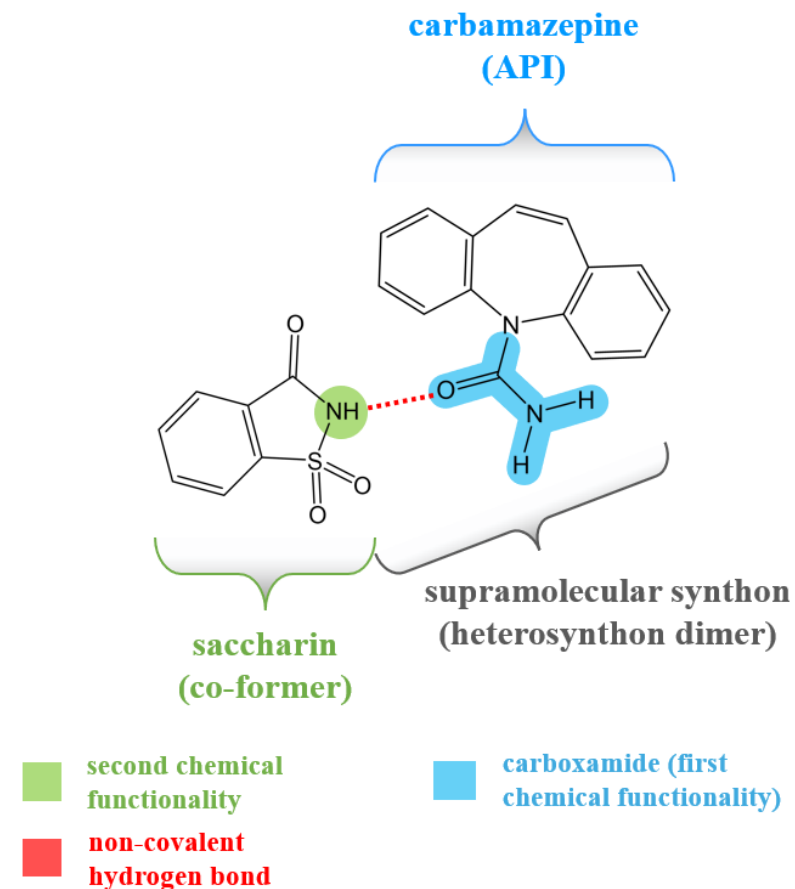
Hickey discloses Element 11a for the same reasons that it discloses all elements of claim 10

Hickey Discloses Element 11b

[11b] wherein the **supramolecular synthon** comprises a **heterosynthon dimer** formed by **non-covalent hydrogen bonding** of the **API** to the **co-former**.



Ex. 1004 (Hickey) at 113 (Chart 1)



Claim 18 Elements

[18a] The pharmaceutical composition of claim 10

[18b] wherein the first chemical functionality is a carboxamide.

Hickey discloses Element 18a for the same reasons that it discloses
all elements of claim 10

Hickey discloses Element 18b for the same reasons that it discloses
Element 10g of claim 10

Ground 2—Anticipation or Obviousness Over Almarsson (Ex. 1005) Optionally With Hickey (Ex. 1004) and Martindale (Ex. 1006)

Ex. 1005 (Almarsson)

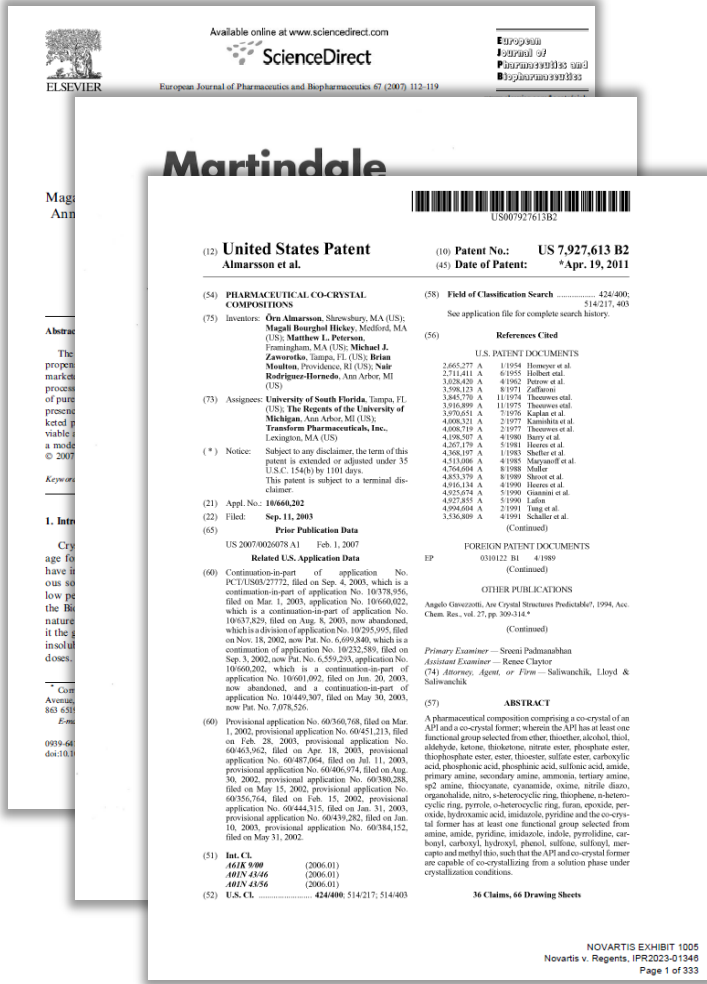
- Authored by '344 patent inventors
- Discloses 1:1 carbamazepine:saccharin co-crystal
- Discloses process for preparing pharmaceutical compositions
- Every element of the challenged claims is disclosed in Almarsson

Ex. 1006 (Martindale)

- Discloses therapeutically effective amount of carbamazepine

Ex. 1004 (Hickey)

- Discloses preparation of pharmaceutical composition of 1:1 carbamazepine:saccharin co-crystal



Claim 10 Elements

[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

[10b] a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

[10c] wherein the API has a first chemical functionality that permits formation of API homosynths through non-covalent hydrogen bonding when the API is in its pure form,

[10d] wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding,

[10e] wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

[10f] wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

[10g] wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

Almarsson Discloses Element 10b

[10b] a **co-crystal** comprising **supramolecular synthons**, each supramolecular synthon formed from **stoichiometric amounts** of at least one **active pharmaceutical ingredient (API)** and at least one **co-former**,

Example 32

Carbamazepine:saccharin (Form II) **(1:1 stoichiometry)**

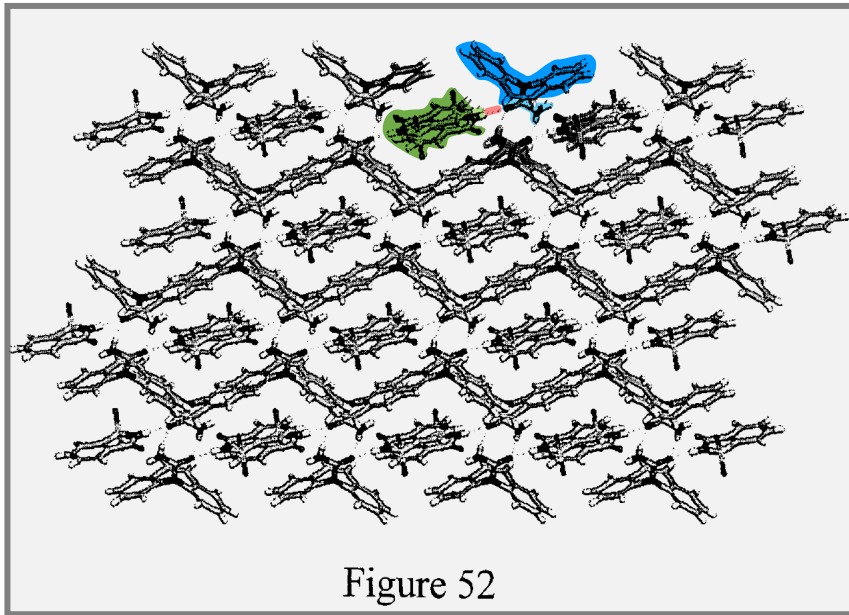
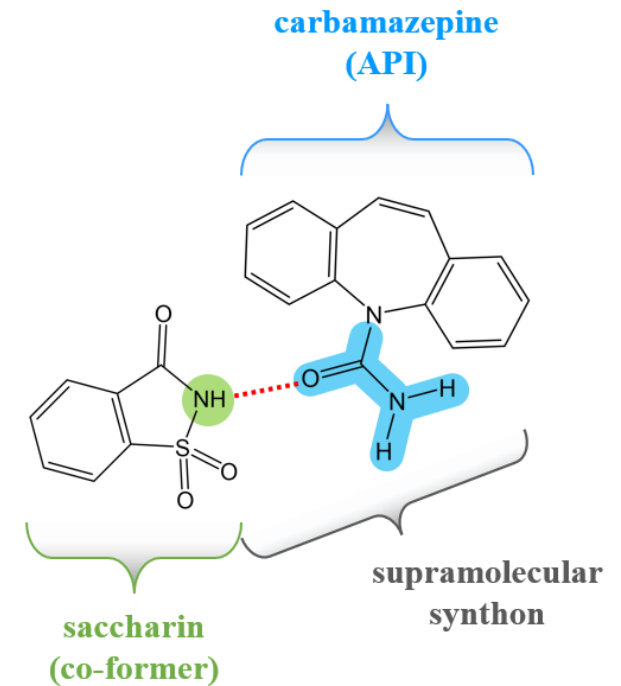


Figure 52



second chemical
functionality

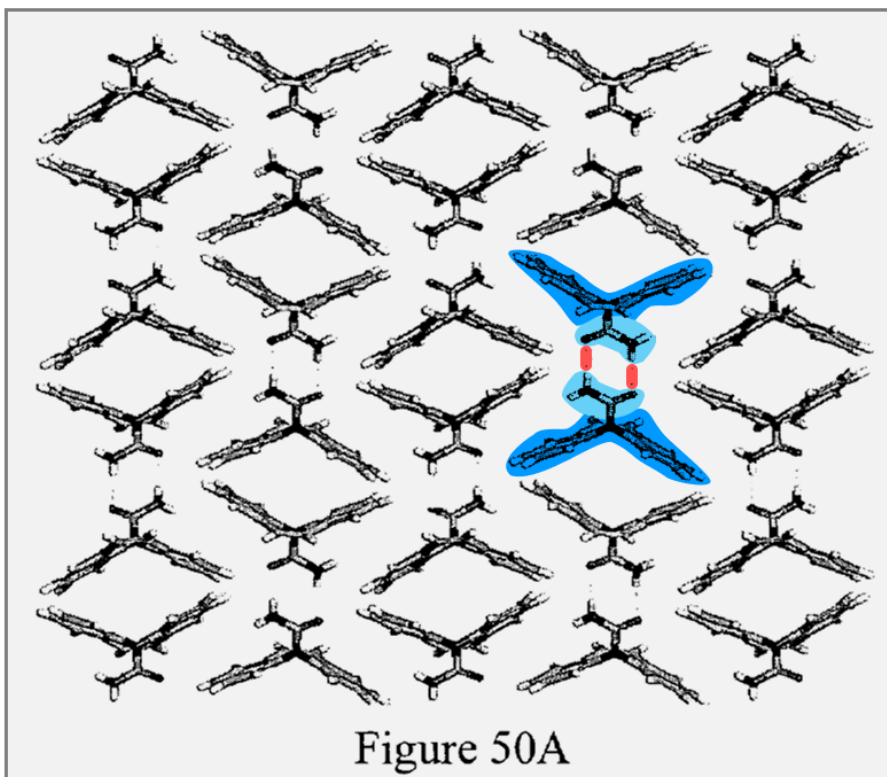
carboxamide (first
chemical functionality)

non-covalent
hydrogen bond

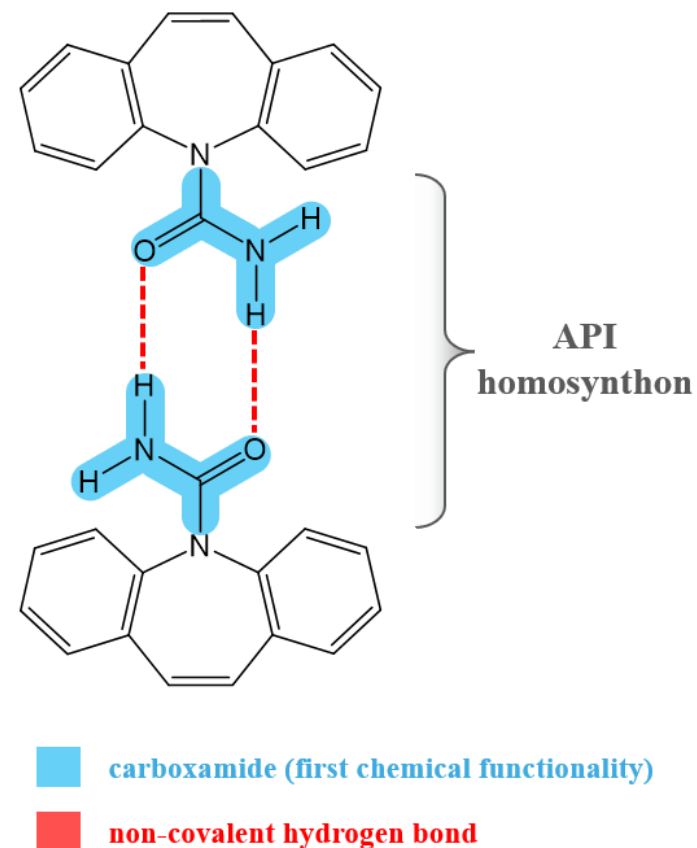
Ex. 1005 (Almarsson) at Figure 52; col. 6, ll. 43–44; col. 42, l. 20–col. 43, l. 3

Almarsson Discloses Element 10c

[10c] wherein the **API** has a **first chemical functionality** that permits formation of **API homosynthons** through **non-covalent hydrogen bonding** when the API is in its pure form,



Ex. 1005 (Almarsson) at Figure 50A; col. 6, ll. 38–40

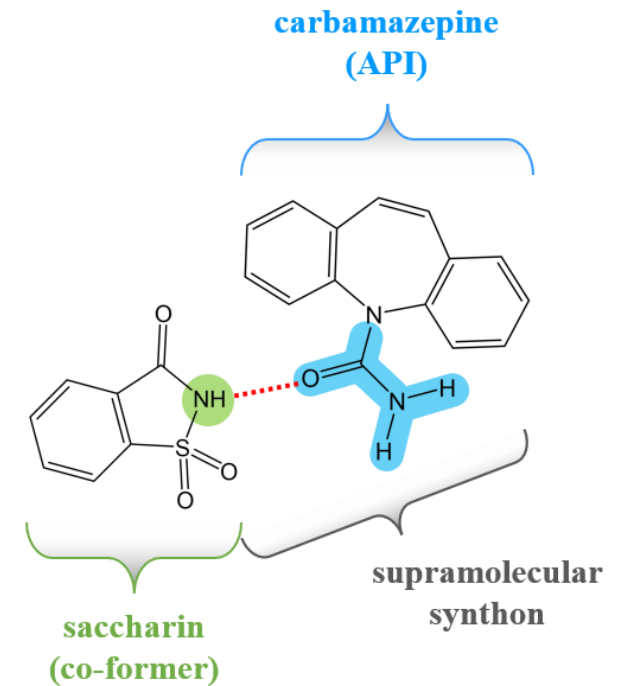
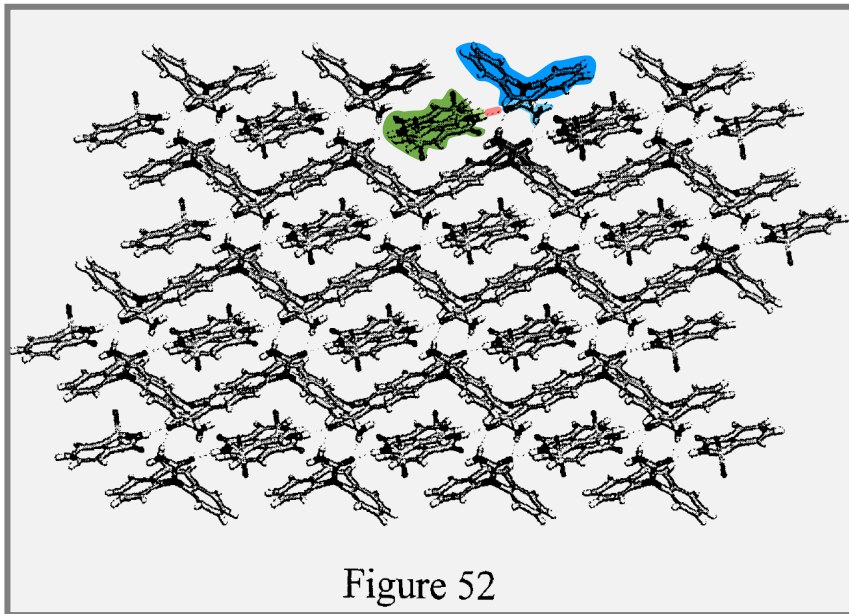


Almarsson Discloses Element 10d

[10d] wherein the **co-former** has a **second chemical functionality** compl[e]mentary to the **first chemical functionality** via **non-covalent hydrogen bonding**,

Example 32

Carbamazepine:saccharin (Form II) (1:1 stoichiometry)



second chemical functionality

carboxamide (first chemical functionality)

non-covalent hydrogen bond

Ex. 1005 (Almarsson) at Figure 52; col. 6, ll. 43–44; col. 42, l. 20–col. 43, l. 3

Almarsson Discloses Element 10e

[10e] wherein said **co-former** is a solid at room temperature and atmospheric pressure when the co-former is in its pure form

Co-former used in Almarsson: Saccharin

Saccharin melting point at room temperature and atmospheric pressure: 228.8 °C

Ex. 1005 (Almarsson) at col. 42, ll. 53–57

Saccharin melting point is *above* room temperature (about 20–25 °C), therefore, saccharin is solid at room temperature and atmospheric pressure when in its pure form

Almarsson Discloses Element 10f

[10f] wherein **supramolecular synthons** are formed via **non-covalent hydrogen bonding** between the **first chemical functionality** of the **API** and the **second chemical functionality** of the **co-former**, and

Example 32

Carbamazepine:saccharin (Form II) (1:1 stoichiometry)

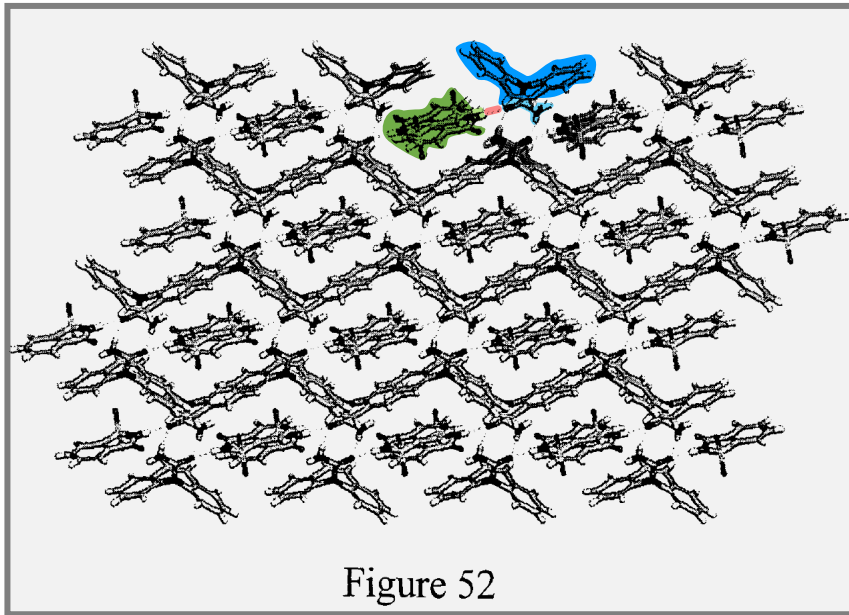
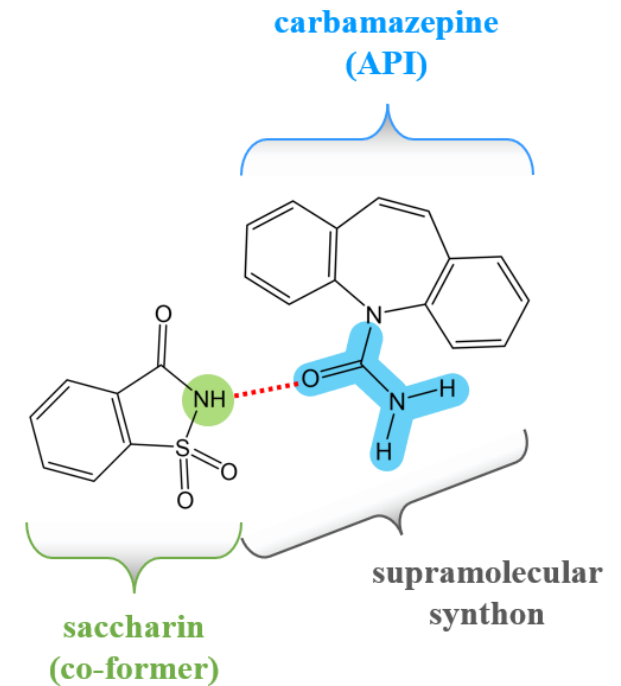


Figure 52



■ second chemical functionality

■ carboxamide (first chemical functionality)

■ non-covalent hydrogen bond

Ex. 1005 (Almarsson) at Figure 52; col. 6, ll. 43–44; col. 42, l. 20–col. 43, l. 3

Paper 4 (Petition) at 52–54; Ex. 1002 (Rogers Decl.) at ¶¶ 240–242

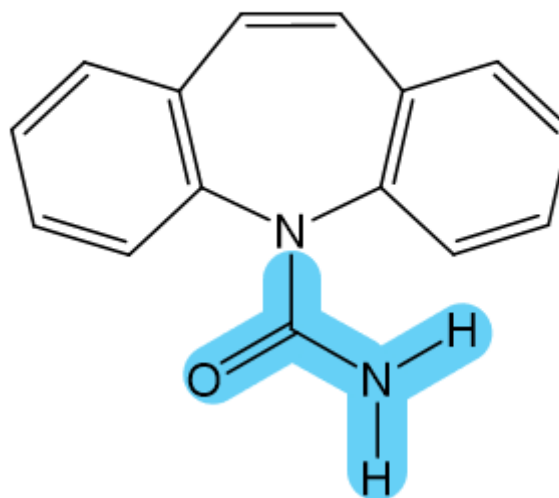
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

68

Almarsson Discloses Element 10g

[10g] wherein the **first chemical functionality** is (i) a **carboxamide**, (ii) a carbonyl, or (iii) an amine.

carbamazepine (API)



Ex. 1005 (Almarsson) at col. 42, ll. 22, 25–27

Almarsson Discloses Element 10a

[10a] A **pharmaceutical composition** comprising a **pharmaceutically acceptable carrier** and a **therapeutically effective amount** of [a **co-crystal**]

19. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, excipient, or carrier and a co-crystal comprising an API and a co-crystal former selected from:

(a) carbamazepine and saccharin;

20. The pharmaceutical composition according to claim 19, wherein said co-crystal comprises carbamazepine and saccharin.

Ex. 1005 (Almarsson) at Claims 19–20

A pharmaceutical composition of the invention contains a desired amount of API per dose unit

Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the API, such as tablets or capsules.

Ex. 1005 (Almarsson) at col. 21, ll. 39–52

Almarsson Renders Obvious Element 10a in View of Hickey

[10a] A **pharmaceutical composition** comprising a **pharmaceutically acceptable carrier** and a **therapeutically effective amount** of [a co-crystal]

A prototype oral dosage form in an HPMC capsule (Shionogi Qualicaps) containing **1** was prepared by mixing **α -lactose monohydrate** (2.52 g, 0.0069 mol, Sigma, Lot 43254338) with **1** (3.654 g, 0.087 mol, particle size <53 μ m) and **blending the two solids** in a mortar and pestle. Capsules containing **600 mg of formulated co-crystal** (corresponding to **200 mg of carbamazepine**) were prepared.

1 = carbamazepine:saccharin co-crystal

Tegretol® includes 200 mg of carbamazepine (commercially available carbamazepine tablets)

Ex. 1004 (Hickey) at 115

Almarsson Renders Obvious Element 10a in View of Martindale

[10a] A **pharmaceutical composition** comprising a **pharmaceutically acceptable carrier** and a **therapeutically effective amount** of [a **co-crystal**]

In the treatment of **epilepsy** (below), the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary.

Ex. 1006 (Martindale) at 518

Claim 11 Elements

[11a] The pharmaceutical composition of claim 10

[11b] wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

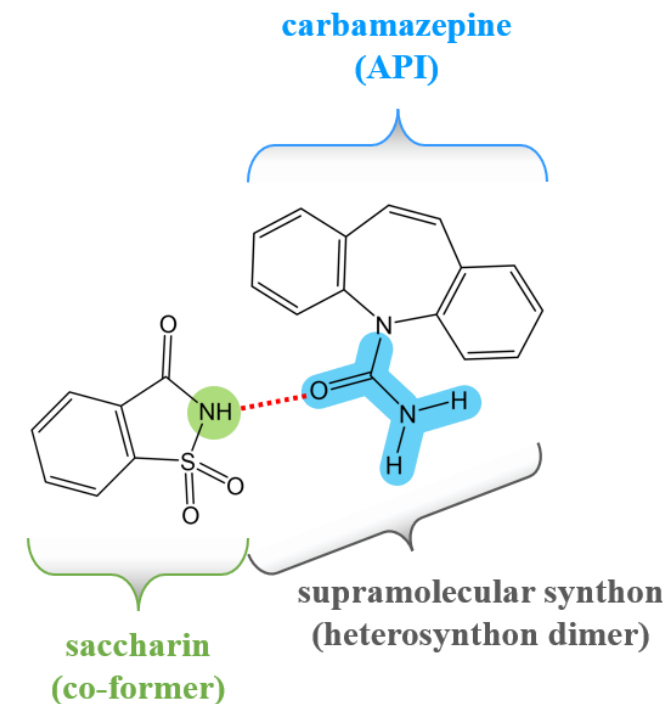
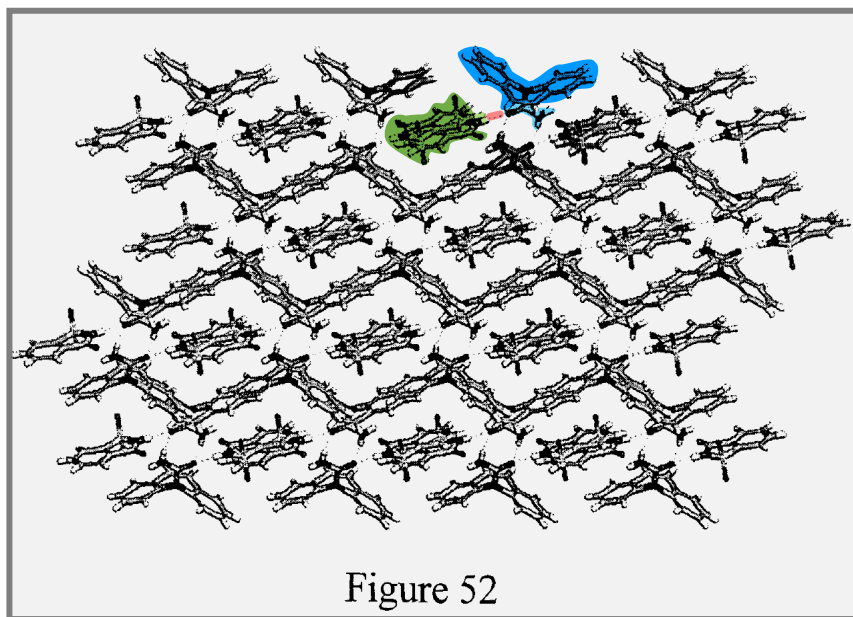
Almarsson anticipates or renders obvious Element 11a for the same reasons that it anticipates or renders obvious all elements of claim 10

Almarsson Discloses Element 11b

[11b] wherein the **supramolecular synthon** comprises a **heterosynthon dimer** formed by **non-covalent hydrogen bonding** of the **API** to the **co-former**.

Example 32

Carbamazepine:saccharin (Form II) (1:1 stoichiometry)



second chemical functionality

non-covalent hydrogen bond

carboxamide (first chemical functionality)

Ex. 1005 (Almarsson) at Figure 52; col. 6, ll. 43–44; col. 42, l. 20–col. 43, l. 3

Claim 18 Elements

[18a] The pharmaceutical composition of claim 10

[18b] wherein the first chemical functionality is a carboxamide.

Almarsson anticipates or renders obvious Element 18a for the same reasons that it anticipates or renders obvious all elements of claim 10

Almarsson discloses Element 18b for the same reasons that it discloses Element 10g of claim 10