

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.
Petitioner

v.

REGENTS OF THE UNIVERSITY OF MINNESOTA
Patent Owner

U.S. Patent No. 8,815,830

“Nucleosides With Antiviral and Anticancer Activity”

Inter Partes Review No.: Unassigned

**DECLARATION OF VICTOR E. MARQUEZ, Ph.D. IN SUPPORT OF
PETITION FOR INTER PARTES REVIEW UNDER 35 U.S.C. §§ 311-319
AND 37 C.F.R. §§ 42.100 *et seq.***

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I. ENGAGEMENT

1. I have been engaged by counsel for Petitioner Gilead Sciences, Inc. (“Gilead”) and am submitting this declaration on Gilead’s behalf in the above-captioned proceeding. I have been asked to provide analysis and my opinion about the state of the art of the technology described in U.S. Patent No. 8,815,830 (“the ’830 patent,” Ex. 1001) and on the patentability of claims 1-9, 11-21, and 23-28 of the ’830 patent (“the Challenged Claims”).

II. BACKGROUD AND QUALIFICATIONS

2. I am a Scientist Emeritus at the Chemical Biology Laboratory of the Center for Cancer Research, National Cancer Institute, National Institutes of Health (“NIH”), in Frederick, MD, having retired from there in September 2009.

3. I received a B.S. in Pharmacy from the Central University of Venezuela in 1966, an M.S. in Medicinal Chemistry from the University of Michigan in 1968, and a Ph.D. in Medicinal Chemistry from the University of Michigan in 1970. See Exhibit 1012, which is a copy of my *curriculum vitae*, for this and the succeeding paragraphs.

4. After serving as a Visiting Fellow at the NIH from 1970 to 1971, I was the Director of Research at Laboratorios Cosmos, S.A., in Venezuela from 1972 to 1977. From 1977 to 1988, I was employed as an

NIH Visiting Scientist at the National Cancer Institute of the NIH (“NCI”).

In 1988 I became the Deputy Chief of the Laboratory of Medicinal Chemistry at NCI, a position that I held through 1998. In 1999 I became Acting Chief of that laboratory and from 2001 to 2009 I was Chief of the Laboratory.

5. I have received a number of honors and awards, including the following:

- U.S. Department of Commerce Inventor's award, 1979;
- NIH Merit Award, 1992;
- Gordon Conference on Purines, Pyrimidines and Related Compounds (Vice- Chair, 1993; Chair, 1995);
- National Cancer Institute, Division of Basic Sciences (DBS) Intramural Research Award, 1997;
- Pharmazie-Wissenschaftspreis 2001 (Pharmazeutische Chemie), sponsored by Phoenix Pharmahandel AG & Co KG, Mannheim, November 26, 2001;
- Member of the Medicinal Chemistry Division Long Range Planning Committee, American Chemical Society, Division of Medicinal Chemistry, 2003-2005;

- 2003 Bernard Belleau Memorial Lecturer, McGill Chemical Society, McGill University, Montreal, Canada, March 18, 2003;
- Intramural AIDS Targeted Antiviral Program (IATAP) award (co-investigator Dr. Stephen Hughes), 2005 and 2006;
- Federal Technology Transfer Act Cash Award, each year 1998-2008;
- Leopoldo García-Colín-Scherer Medal, Mexico City, Mexico, September 10-14, 2007;
- Symposium Honoring Victor Marquez for His Contributions to Conformational Analysis, Nucleosides, Nucleotides and Oligonucleotides, Division of Carbohydrate Chemistry, American Chemical Society, 236th National Meeting, Philadelphia, PA, August 18-19, 2008;
- Vice-President of the International Society for Nucleosides, Nucleotides and Nucleic Acids (IS3NA), 2008-2010;
- Maryland Chemist of the Year, 2008 (Citation: In acknowledgment and appreciation of his outstanding research accomplishments in medicinal chemistry and in recognition of his significant contributions to nucleoside chemistry and synthetic organic chemistry as tools for the rational design of

antitumor and antiviral agents, December 10, 2008, Towson, Maryland);

- 2008 Raymond U. Lemieux Lecture on Biotechnology, University of Alberta, Edmonton, Alberta, Canada, May 7, 2009;
- Inducted into the Medicinal Chemistry Hall of Fame, August 24, 2010;
- President of the International Society for Nucleosides, Nucleotides and Nucleic Acids (IS3NA), 2010-2012;
- University of Michigan, School of Graduate Studies, Centennial Lecturer, Interdepartmental Program in Medicinal Chemistry, October 4, 2012; and
- National Cancer Institute, Certificate of Appreciation. In grateful recognition of your outstanding contributions to research and innovation in FY 2013. Bethesda, MD, January 14, 2014.

6. I have authored and co-authored 418 publications including scientific papers, book chapters, and articles. Of these publications, more than 230 pertain to nucleosides, dinucleotides (compounds having two nucleosides), or oligonucleotides (compounds having several nucleosides),

with more than 25 relating to fluorinated nucleosides, in particular nucleosides fluorinated at the 2' and/or 3' position.

7. I have also lectured widely in the nucleoside area. More than 85 of my 125 lectures have been directed toward nucleoside chemistry or the biological activity of nucleosides. I am listed as an inventor on 29 U.S. patents, with 25 pertaining to nucleosides.

8. I am a member of several professional societies, including:

- American Chemical Society, Division of Medicinal Chemistry;
- American Chemical Society, Division of Organic Chemistry;
- American Chemical Society, Division of Carbohydrate Chemistry; and
- International Society for Nucleosides, Nucleotides and Nucleic Acids.

9. As can be seen from the foregoing, I have 40 years of experience spanning the period from 1977 to present day in the area of nucleoside chemistry, including specific experience with the chemistry of fluorinated nucleosides. In particular, my experience has involved designing and synthesizing novel nucleoside compounds intended to be useful for the treatment of viral infections. Additionally, my experience has involved working with colleagues in related fields such as virology and molecular

biology to assess and study the biological activity of such compounds.

Therefore I believe that I am well-qualified to provide my opinions regarding these subjects.

III. COMPENSATION AND PRIOR TESTIMONY

10. I am being compensated for my time consulting in this matter at my customary rate of \$750 per hour to provide analysis and testimony in this *inter partes* review proceeding.

11. I have no stake in the outcome of this matter, and my compensation in this matter is in no way contingent upon either the nature or substance of my opinions or the outcome of any aspect of this proceeding.

12. I have previously provided expert testimony in approximately seven patent-related matters.

IV. MATERIALS CONSIDERED

13. My opinions, as explained below, are based on my years of education, research, experience, and background in the fields discussed above, as well as my investigation and study of relevant materials. In forming my opinions, I have studied and considered the materials identified below. It is my understanding that each of the exhibits listed are true and accurate copies.

- U.S. Patent No. 8,815,830, *Nucleosides With Antiviral And Anticancer Activity* (“the ’830 patent”) (Ex. 1001).
- File History of U.S. Patent Application No. 14/229,292, filed Mar. 28, 2014 (“NP5”) (Ex. 1002).
- U.S. Patent Application Publication No. 2010/0016251, *Nucleoside Phosphoramidate Prodrugs* (“Sofia”) (Ex. 1004).
- U.S. Patent Application No. 13/753,252, *Nucleosides With Antiviral And Anticancer Activity* (“NP4”) (Ex. 1005).
- Preliminary Amendment, U.S. Patent Application No. 11/721,325 (Jun. 8, 2007) (“NP3”) (Ex. 1006).
- International Application No. PCT/US2005/044442, *Nucleosides With Antiviral And Anticancer Activity* (“NP2”) (Ex. 1007).
- U.S. Provisional Application No. 60/634,677, *Nucleosides With Antiviral And Anticancer Activity* (“P1”) (Ex. 1008).
- U.S. Patent No. 8,765,935, *Nucleosides With Antiviral And Anticancer Activity* (“the ’935 patent”) (Ex. 1009).
- U.S. Patent No. 8,399,428, *Nucleosides With Antiviral And Anticancer Activity* (“the ’428 patent”) (Ex. 1010).

- Anastasi et al., *Current Medicinal Chemistry* 2003, 10: 1825-1843 (Ex. 1013).
- Calogeropoulou et al., *Current Topics in Medicinal Chemistry* 2003, 3: 1467-1495 (Ex. 1014).
- Cahard et al., *Mini-Reviews in Medicinal Chemistry* 2004, 4: 371-381 (Ex. 1015).
- Highleyman, "Lodenosine trials stopped due to safety concerns," *BETA* 12(4): 4 (1999) (Ex. 1016).
- Sicardi et al., *European Journal of Pharmaceutical Sciences*, 22: 25-31 (2004) (Ex. 1017).
- Kim et al., *Molecular Pharmaceutics*, 1: 102-111 (2004) (Ex. 1018).
- 2005 FDA Approved Drugs, available at:
<https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2005> (Ex. 1019).
- Yoo et al., *J. Med. Chem.* 2008, 51: 7593-7601 (Ex. 1020).
- Pauling, *J. Amer. Chem. Soc.*, 54: 3570-3582 (1932) (Ex. 1021).

14. Additionally, I am aware of information generally available to, and relied upon by, persons of ordinary skill in the art (see below) at the

relevant times, including technical dictionaries and technical reference materials (including textbooks, manuals, technical papers, and articles). Some of my statements below are expressly based on such awareness.

V. OVERVIEW OF TOPICS DISCUSSED

15. By way of overview, among the main topics that I will address in this declaration are the following:

- The claims at issue in the '830 patent;
- The qualifications of a person having ordinary skill in the art (the “artisan”) throughout the time period spanning from December 9, 2004 through January 29, 2013;
- The state of the art between December 9, 2004 and January 29, 2013 as pertinent to the applications to which the '830 patent claims priority;
- How the applications to which the '830 patent claims priority fail to support the narrowed subgenus encompassed by the '830 patent claims; and
- How an intervening disclosure of sofosbuvir on January 21, 2010 anticipates every challenged claim of the '830 patent because the '830 patent is not entitled to an effective filing date earlier than March 28, 2014.

VI. TECHNOLOGY AT ISSUE

A. The '830 Patent

16. Speaking very generally, the '830 patent provides a disclosure of numerous genera encompassing an enormous number of potential antiviral or anticancer agents, specifically nucleotide phosphoramidate prodrugs that are averred to be substrates for human histidine triad nucleotide-binding protein 1 ("hHINT1"). Ex. 1001, col.2 ll.13-47.

17. The term "prodrug" is defined in the pharmaceutical field as a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

18. The '830 patent specification states that these compounds are useful against viral infections, including but not limited to: HIV, HSV-2, varicella zoster, vaccinia, CMV, ebola, hepatitis B virus, hepatitis C virus, "and the like"; metabolic liver disorders; and various cancers including but not limited to breast, lung, ovarian, and brain cancer. Ex. 1001, col.4 ll.15-67, col.6 ll.13-16, col.16 ll.19-24.

B. Prosecution History Of The '830 Patent

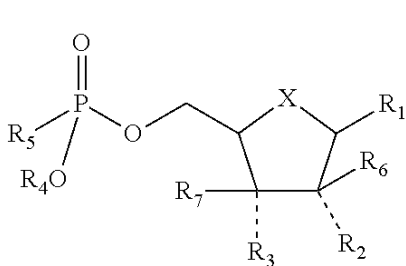
19. The '830 Patent issued on August 26, 2014 with 28 claims from U.S. Patent Application No. 14/229,292 filed five-months earlier on March

28. Ex. 1001, at 1. The prosecution history of the '830 patent is very brief; pertinent to this Petition, the Examiner did not expressly address whether or not the application that led to the '830 patent was entitled to the benefit of any of the earlier applications to which it claimed priority. See Ex. 1002.

C. The Challenged Claims Of The '830 Patent

20. Among the Challenged Claims, claim 1 is the only independent claim. Claim 1 is directed to a genus of nucleoside compounds:

1. A compound of formula I:



wherein:

R₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil, optionally substituted by 1, 2, or 3 U; wherein each U is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, hydroxy(C₁-C₆)alkyl, —(CH₂)₁₋₄P(=O)(OR_w)₂, aryl, aryl(C₁-C₆)alkyl, or NR_xR_y;

R₂ is halo;

R₆ and R₇ are independently H or (C₁-C₆)alkyl;

R₃ is hydroxy;

R₄ is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, aryl(C₁-C₆)alkyl, or 2-cyanoethyl;

R₅ is an amino acid;

X is oxy, thio, or methylene;

each R_w is independently hydrogen or (C₁-C₆)alkyl;

R_x and R_y are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl; or R_x and R_y together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

wherein any (C₁-C₆)alkyl of R₁, R₄-R₇, R_w, R_x, and R_y is optionally substituted with one or more halo, hydroxy, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, oxo (=O), (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, alkyl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl, or NR_{aj}R_{ak}; wherein each R_{aj} and R_{ak} is independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl;

and wherein any aryl or heteroaryl may optionally be substituted with one or more substituents selected from the group consisting of halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, and amino;

or a pharmaceutically acceptable salt thereof.

Ex. 1001, col.19 ll.1-47.

21. Claims 2-9, 11-21, and 23-28 are dependent upon claim 1 and recite specific R group substituents (claims 2-9 and 11-12), provide a method of treating a viral infection in an animal with compounds of claim 1 (claims 13-21 and 23-27), and provide a pharmaceutical composition comprising compounds of claim 1 and a pharmaceutically acceptable vehicle or carrier (claim 28). The '830 patent dependent claims are listed below:

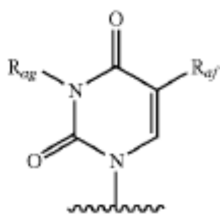
2. The compound or salt of claim 1 wherein R₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil.

3. The compound or salt of claim 1 wherein R₁ is cytosine, thymine, 3-deazaadenine, or uracil.

4. The compound or salt of claim 1 wherein R₁ is cytosine, thymine, or uracil.

5. The compound or salt of claim 1 wherein R₁ is a nitrogen linked radical of formula VI:

VI

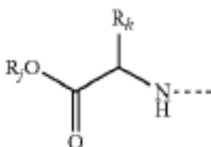


wherein R_{af} is hydrogen, halo, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, trifluoromethyl, hydroxyl (C_1-C_6) alkyl, or $-(CH_2)_{1-4}P(=O)(OR_w)_2$.

6. The compound or salt of claim 1 wherein R_2 is fluoro.

7. The compound or salt of claim 1 wherein R_5 is a nitrogen linked radical of formula III:

III



wherein R_h is hydrogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_1-C_6) alkyl-S— (C_1-C_6) alkyl-, aryl, heteroaryl, aryl (C_1-C_6) alkyl, or heteroaryl (C_1-C_6) alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C_1-C_6) alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkyloxy, (C_1-C_6) alkanoyl, (C_1-C_6) alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino.

8. The compound or salt of claim 7 wherein R_h is hydrogen, (C_1-C_6) alkyl, phenylmethyl, or 3-indolylmethyl.

9. The compound or salt of claim 8 wherein R_j is hydrogen or (C_1-C_6) alkyl.

11. The compound or salt of claim 1 wherein R_5 is a (C_1-C_6) alkyl ester of L-alanine.

12. The compound or salt of claim 11 wherein R_7 is hydrogen.

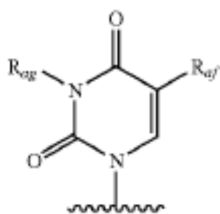
13. A method for treating a viral infection in an animal comprising administering to an animal in need of such treatment an effective amount of a compound or salt of formula I according to claim 1.

14. The method of claim 13 wherein R_1 is guanine, cytosine, thymine, 3-deazaadenine, or uracil.

15. The method of claim 13 wherein R_1 is cytosine, thymine, 3-deazaadenine, or uracil.

16. The method of claim 13 wherein R_1 is cytosine, thymine, or uracil.

17. The method of claim 13 wherein R_1 is a nitrogen linked radical of formula VI:

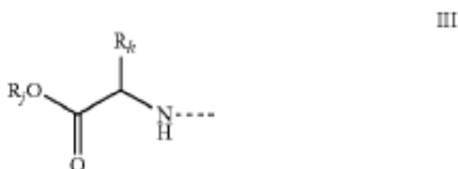


VI

wherein R_{af} is hydrogen, halo, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, trifluoromethyl, hydroxyl(C₁-C₆)alkyl, or –(CH₂)₁₋₄P(=O)(OR_w)₂.

18. The method of claim 13 wherein R₂ is fluoro.

19. The method of claim 13 wherein R₅ is a nitrogen linked radical of formula III:



wherein R_h is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C₁-C₆)alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino.

20. The method of claim 19 wherein R_h is hydrogen, (C₁-C₆)alkyl, phenylmethyl, or 3-indolylmethyl.

21. The method of claim 20 wherein R_j is hydrogen or (C₁-C₆)alkyl.

23. The method of claim 13 wherein R₅ is a (C₁-C₆)alkyl ester of L-alanine.

24. The method of claim 23 wherein R₇ is hydrogen.

25. The method of claim 13 wherein the viral infection is caused by HCV.

26. The method of claim 13 wherein the animal is a human.

27. The method of claim 26 wherein the compound or salt of formula I is orally administered.

28. A pharmaceutical composition comprising a compound or salt of formula I as described in claim 1 and a pharmaceutically acceptable vehicle or carrier.

Ex. 1001, col.19 l.49 – col.22 l.19.

D. Claim Construction

22. I understand that the claim terms in the '830 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable construction in light of the specification of the patent in which it appears.

23. The '830 patent specification offers numerous specific definitions, some of which are more broad than conventional terminology. For example, the specification defines “amino acid” as including “residues of the natural amino acids . . . as well as unnatural amino acids,” including

those “protected at the carboxy terminus” and “linked to the remainder of a compound of the invention through the carboxy terminus, the amino terminus, or through any other convenient point of attachment.” Ex. 1001, col.5, ll.39-63.

24. Other definitions offered in the specification of the ’830 patent are conventional. For example, the specification defines “halo” as “fluoro, chloro, bromo, or iodo” and “peptide” as “a sequence of 2 to 25 amino acids or peptidyl residues.” Ex. 1001, col.5, ll.15 (“halo”); col.5, ll.63-65 (“peptide”) (internal parenthetical omitted). Undefined claim terms are ordinary and conventional terminology.

VII. RELEVANT LEGAL STANDARDS

25. In addressing these topics, I have been advised and understand that the following principles and definitions apply:

A. Written Description

26. For a patent to claim priority from an earlier application, each application to which priority is claimed must provide written description support for the later claimed invention.

27. An earlier patent application contains support for a claim if one having ordinary skill in the art would have thought that the applicant(s) was/were in “possession” of the claimed subject matter as of the

application's filing date based upon the disclosure. A patent applicant is deemed to have "possession" of an invention if he describes the subject matter claimed as his invention using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth that subject matter. A mere wish or plan for obtaining the subject matter does not constitute possession. Further, one must make an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art to determine written description support.

28. A description of a group of chemical compounds does not constitute possession of a particular compound within that group unless one having ordinary skill in the art would immediately think of the particular compound based on the description of the group. Nor does a description of a group of chemical compounds constitute possession of a subset of compounds within it unless the application guides one having ordinary skill in the art to understand that the subset of compounds is preferred. In determining whether a patent application contains support for a claim, the entire application must be reviewed and one cannot pick and choose disparate portions in order to piece together the elements of a claim using hindsight. Further, an adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries.

B. Anticipation

29. A claim is anticipated if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. Anticipation by inherency may be found when the disclosure is appreciated by one having ordinary skill in the art to encompass the missing descriptive matter.

30. A later genus claim limitation is anticipated by an earlier species disclosed in the prior art.

VIII. THE PERSON OF ORDINARY SKILL IN THE ART

31. I understand that patents and relevant literature must be read and evaluated from the perspective of a hypothetical “person having ordinary skill” in the field of the invention at the time the invention was made. I understand this to be a hypothetical person of ordinary creativity, imparted with knowledge of all the relevant publicly available art (“prior art”), and the education and skills ordinarily associated with carrying out research in that particular field.

32. I further understand that the relevant dates for assessing the perspective of the hypothetical person having ordinary skill for the issues I address below are the filing dates of the patent applications at issue,

December 9, 2004, December 8, 2005, and January 29, 2013 (see page 27 below).

33. The art to which the '830 patent pertains is the field of drug discovery. Drug discovery is a multi-stage, multidisciplinary process that involves numerous people over a period of several years and draws upon a broad variety of expertise, including chemical and biological expertise. It is unlikely that any one individual could ever possess all of the relevant knowledge in the art or all of the necessary training in each of the relevant disciplines, including designing target compounds, synthesizing them and assessing their biological activity.

34. To accurately reflect the process of drug discovery, the hypothetical "person having ordinary skill in the art" (hereinafter referred to as the "artisan") would encompass a team of individuals each having the knowledge, education and skills ordinarily associated with the various disciplines involved in the process of drug discovery.

35. When I refer to an "artisan," I mean that term to encompass the range of dates between and including the December 9, 2004 filing date of the provisional patent application referenced in the priority chain of the '830 patent through the January 29, 2013 filing date of U.S. Application No.

13/753,252 (see patent family tree at page 28), unless specified otherwise by modifying the term with a particular date.

36. It is my opinion that the artisan would have included someone with a doctoral degree with a background in organic, synthetic or medicinal chemistry, or possibly a related discipline such as pharmacology, and who also had some practical experience (e.g., at least two years) in drug discovery. This person could also have been someone with a bachelor's (B.S.) or master's (M.S.) degree in one of these disciplines but with greater practical experience (e.g., at least four years) in drug discovery. This person would possess certain skills and experience relevant to conducting the chemical aspects of drug discovery. For example, the artisan would have had experience with standard laboratory techniques used to synthesize organic molecules. The artisan would also have had experience with standard purification and analytical techniques known in the art, such as basic chromatography and nuclear magnetic resonance ("NMR") spectroscopy, respectively. The artisan would have had experience planning and executing syntheses of organic compounds based on methods well known in the art. The artisan would further have had experience performing basic interpretations of biological testing data, for example interpreting

whether biological assay results indicated that a compound had biological activity.

37. Likewise, the artisan would have included someone with a doctoral degree (M.D. or Ph.D.) with a background in virology, microbiology or molecular biology who also had post-doctoral experience (e.g., at least two years). This person could also have been someone with a bachelor's (B.S.) or master's (M.S.) degree in one of these disciplines but with at least four years of practical experience. This person would possess certain skills and experience relevant to conducting the biological aspects of drug discovery. For example, this person would have had experience testing compounds for biological activity using methods well known in the art. The artisan would have had experience working with cell culture systems, including both conducting and interpreting the results of *in vitro* assays known in the art for screening compounds for biological activity and toxicity.

38. My understanding of the artisan's qualifications is based on my education and 40 years of work experience in this field, and my review of the '830 patent and the materials mentioned above.

39. Unless otherwise stated, any statements that I make about a document, a claim, or the subject matter at hand should be read as the

observations of the artisan, and specifically the facet of the hypothetical artisan involved in the chemical aspects of drug discovery. Thus, for example, when I say “it was known that . . .” without further qualification, I mean that the artisan, and in particular the artisan involved in the chemical aspects of drug discovery, would have known. Or, for example, if I say that the ’830 patent claim recites a certain limitation, without further qualification, I mean that the artisan, and in particular the artisan involved in the chemical aspects of drug discovery, would have understood the ’830 patent claim to recite that limitation.

IX. THE STATE OF THE ART

40. The existing knowledge as of December 9, 2004 in the field of antiviral or anticancer nucleosides was progressing, although the state of the art progressed at different rates for different indications. For example, HIV drug discovery was progressing at a faster rate than HCV drug discovery at this time. Researchers were investigating nucleosides and nucleotides in the fields of antiviral and anticancer therapeutics, and there was a general awareness of the desirability of using nucleotides to bypass the first kinase phosphorylation step to decrease drug resistance (Ex. 1013, Anastasi et al., *Current Medicinal Chemistry* 2003, 10: 1825-1843; Ex. 1014, Calogeropoulou et al., *Current Topics in Medicinal Chemistry* 2003, 3:

1467-1495), and the use of nucleotide prodrugs to mask the negative charges associated with nucleotides and permit cellular delivery of the antiviral agent (Ex. 1015, Cahard et al., *Mini-Reviews in Medicinal Chemistry* 2004, 4: 371-381).

41. As of December 9, 2004 there were no FDA-approved phosphoramidate nucleoside prodrugs. Drug failures are very common and typically occur early when drugs are in preclinical development. However, drug failures also occur during clinical development, after years of testing the drug in cell assays and preclinical animal studies, showing the unpredictability of this area of chemistry and biology. One example of a clinical failure of an anti-HIV drug pre-December 9, 2004 was for the drug lodenosine, which I was working on at the NCI. Phase 2 trials of the drug were suspended after a patient died and other patients showed signs of liver or kidney damage while on treatment. Ex. 1016, Highleyman, "Lodenosine trials stopped due to safety concerns," *BETA* 12(4): 4 (1999).

42. An artisan understood the large and unpredictable differences in the stereoselective metabolic rate of the pronucleotide series that could profoundly affect activity and toxicity, particularly for phosphoramidates. Ex. 1017, Sicardi et al., *European Journal of Pharmaceutical Sciences*, 22: 25-31 (2004).

43. The Applicant's (Wagner) lab also studied AZT phosphoramidates to deliver AZT-monophosphate and found that different levels of expression of 5'-nucleotidase were cell dependent which affected the efficiency and delivery of the phosphoramidate prodrug. Ex. 1018, Kim et al., *Molecular Pharmaceutics*, 1: 102-111 (2004).

44. By December 8, 2005, only one new nucleoside antiviral agent, entecavir (a carbocyclic nucleotide) received FDA approval. Ex. 1019, <https://www.centerwatch.com/drug-information/fda-approved-drugs/year/2005>.

45. The existing knowledge as of January 29, 2013 in the field of antiviral and anticancer nucleosides and prodrugs thereof had progressed but there were still no phosphoramidate nucleoside antiviral or anticancer agents that were FDA-approved at that time. Indeed, even as of January 29, 2013 there was still no generally understood structure-activity relationships for phosphoramidate nucleoside prodrugs that would allow an artisan to predict, without specific data, and with any reasonable certainty, antiviral or anticancer activities for this large class of compounds. Ex. 1020, Yoo et al., *J. Med. Chem.* 2008, 51: 7593-7601. This is largely due to the continued lack of any detailed understanding of the mechanisms by which

phosphoramidate prodrugs were transported and metabolized and whether the metabolic products would be cytotoxic.

X. EFFECTIVE FILING DATE OF THE CHALLENGED CLAIMS

46. I have been informed by counsel for Petitioner that the '830 patent, which issued from an application filed on March 28, 2014, claims the benefit of priority to earlier applications. The related U.S. Application Data identified on the face of the '830 patent is:

Continuation of application No. 13/753,252 [Ex. 1005, "NP4"], filed on Jan. 29, 2013, which is a continuation of application No. 11/721,325 [Ex. 1006, "NP3"], filed as application No. PCT/US2005/044442 [Ex. 1007, "NP2"] on Dec. 8, 2005, now Pat. No. 8,399,428.

Provisional application No. 60/634,677 [Ex. 1008, "P1"].

Ex. 1001 cover sheet, *see also* col.1 ll.7-16.

47. NP3 contains the same disclosure as NP2 and the combined disclosure will hereinafter be referred to as "NP3/NP2."

48. NP4, NP3/NP2, and P1 are hereinafter collectively referred to as the "Alleged Priority Applications." For ease of reference, Figure 1 provides a graphical depiction of the Applicant's claims of priority in the chain leading to the '830 patent.

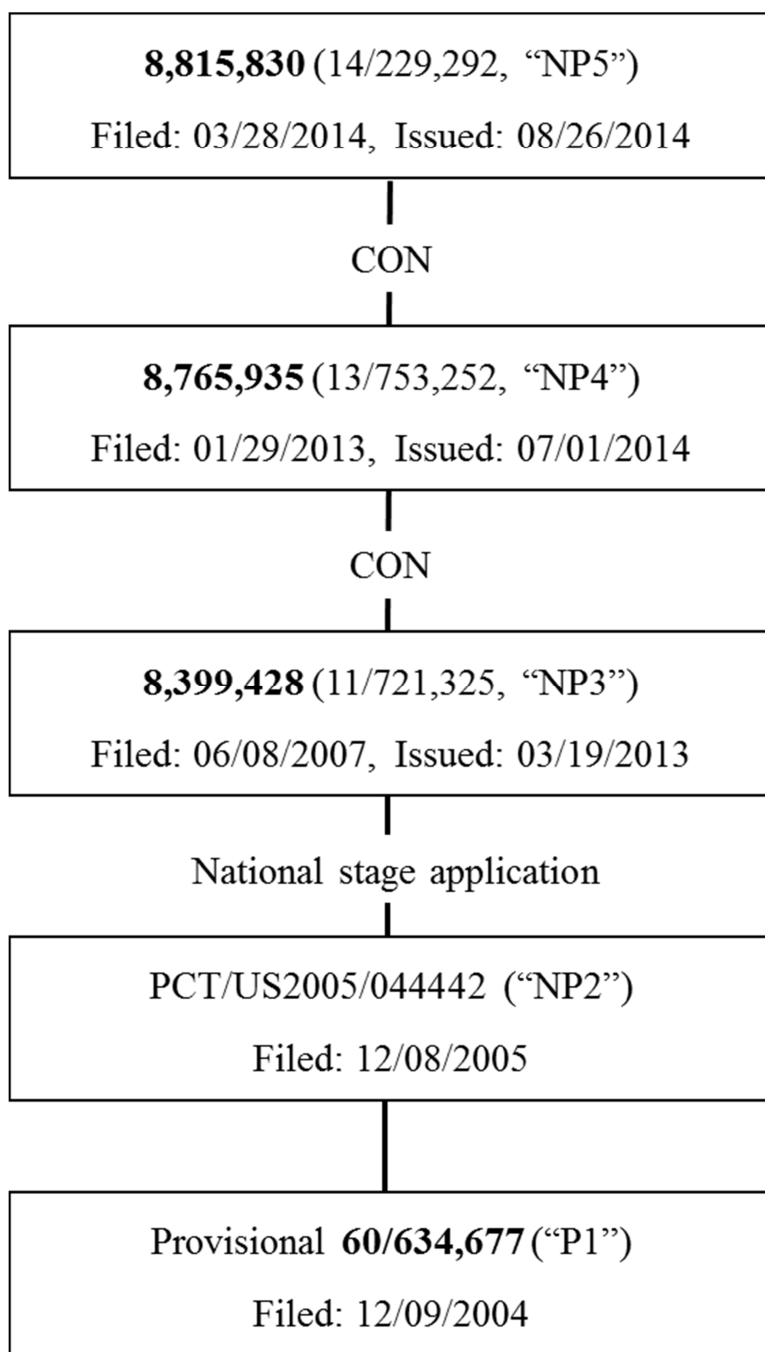


Figure 1: Priority Chain of the '830 Patent

49. In my opinion, the Challenged Claims of the '830 patent are not entitled to the benefit of any of the Alleged Priority Applications due to

Applicant not being in possession of the subject matter for the claimed '830 patent subgenus in the Alleged Priority Applications.

A. The Alleged Priority Applications Do Not Demonstrate That Applicant Was In Possession Of The Subject Matter Claimed In The '830 Patent

50. For the reasons discussed below, none of the Alleged Priority Applications demonstrate that Applicant was in possession of the subject matter claimed in the Challenged Claims. Accordingly, the Challenged Claims are not entitled to a priority date earlier than March 28, 2014, the filing date of NP5.

1. P1 Does Not Demonstrate That Applicant Was In Possession Of The Subject Matter Claimed In The '830 Patent

51. As stated above, the claims of the '830 patent are directed to a subgenus of the extremely large genera of compounds recited in P1. In my opinion, an artisan would understand P1 as evidencing that the Applicant was not in possession of the subgenus claimed in the '830 patent, which requires R_2 to be halo; R_3 to be hydroxy; R_5 to be an amino acid; and R_6 and R_7 to be independently H or $(C_1-C_6)alkyl$. While the disclosures of P1 include R groups encompassing the substituents claimed in the combination of narrowed R groups in the '830 patent claims, there are no guideposts directing an artisan to those later claimed combinations of narrowed

substituents (hereinafter referred to as “blaze marks”), leaving the artisan with the insurmountable task to mosaic together R groups from the broad genera in P1 with no guidance directing the artisan to those selections to arrive at the narrowed subgenus of the ’830 patent claims. In my opinion, and for the reasons discussed in detail below, an artisan in that situation would have understood P1 as demonstrating that Applicant was not in possession of the claimed subject matter.

a. P1 Is Devoid Of Blaze Marks To Direct An Artisan To Compounds Falling Within The ’830 Patent Claim 1 Subgenus

52. P1 discloses structural formula I reciting a large number of different R groups (see Ex. 1008, at 2:15-3:13). Differences between the disclosure in P1 and the later claimed subgenus in ’830 patent claim 1 is shown in Table 1.

TABLE 1.

	P1	’830 patent claim 1
R₂	H, <i>halo</i> , hydroxy, (C ₁ -C ₆)alkyl, (C ₃ -C ₆)cycloalkyl, (C ₁ -C ₆)alkoxy, (C ₃ -C ₆)cycloalkyloxy, (C ₁ -C ₆)alkanoyl, (C ₁ -C ₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R _z)C(=O)N(R _{aa})(R _{ab}), -N(R _z)C(=O)OR _{ac} , or NR _{ad} R _{ae} , provided that one of R ₂ and R ₆ is hydroxy halo, (C ₁ -C ₆)alkoxy, (C ₃ -	halo

	P1	'830 patent claim 1
	C₆)cycloalkyloxy, trifluoromethyl, cyano, or NR_{ad}R_{ae}; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	
R₃	H, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, - N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae} [Ex. 1008, at 4: 3-6]; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached	hydroxy

	P1	'830 patent claim 1
	are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	
R₅	<i>amino acid</i>, peptide, or NR_aR_b [Ex. 1008, at 3: 9]; The term “peptide” describes a sequence of 2 to 25 amino acids or peptidyl residues. The sequence may be linear or cyclic. A peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus, or through any other convenient point of attachment. Preferably, a peptide comprises 2 to 25, or 5-25 amino acids. [Ex. 1008, at 8: 18-22]; Each R_a and R_b is independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, or aryl(C₁-C₆)alkyl; or R_a and R_b together with the nitrogen to which they are attached form a pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 15-17].	amino acid
R₆	<i>H</i>, halo, hydroxy, <i>(C₁-C₆)alkyl</i>, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-	H or (C ₁ -C ₆)alkyl

	P1	'830 patent claim 1
	C₆)alkanoyloxy, trifluoromethyl, azido, cyano, - N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae}, provided that one of R₂ and R₆ is hydroxy halo, (C₁-C₆)alkoxy, (C₃- C₆)cycloalkyloxy, trifluoromethyl, cyano, or NR_{ad}R_{ae} [Ex. 1008, at 3:23-4:2]; R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃- C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	
R₇	H, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁- C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁- C₆)alkanoyloxy, trifluoromethyl, azido, cyano, - N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae};	H or (C ₁ - C ₆)alkyl

	P1	'830 patent claim 1
	R_z is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 3:23-4:2]; R_{aa} and R_{ab} are each independently H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino [Ex. 1008, at 4: 24-26]; R_{ac} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 27-28]; R_{ad} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 4: 29-30]; R_{ae} is H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl [Ex. 1008, at 5: 1-2].	

53. While '830 patent claim 1 narrows the scope of the R₂, R₃, R₅, R₆, and R₇ group substituents disclosed in P1, there are no blaze marks in P1 to guide an artisan to select those specific substituents from the myriad possibilities of substituents in the broad genera disclosed in P1.

54. As shown in Table 2 below, there are 15 possible classes of R group substituents in P1 formula I for R₂, 15 possible classes of R group substituents in P1 formula I for R₃, three possible classes of R group substituents in P1 formula I for R₅, 15 possible classes of R group

substituents in P1 formula I for R₆, and 15 possible classes of R group

substituents in P1 formula I for R₇.

TABLE 2.

Group	R ₂	R ₃	R ₅	R ₆	R ₇
H	1	1		1	1
Halo	1	1		1	1
Hydroxy	1	1		1	1
(C ₁ -C ₆)alkyl	1	1		1	1
(C ₃ -C ₆)cycloalkyl	1	1		1	1
(C ₁ -C ₆)alkoxy	1	1		1	1
(C ₃ -C ₆)cycloalkyloxy	1	1		1	1
(C ₁ -C ₆)alkanoyl	1	1		1	1
(C ₁ -C ₆)alkanoyloxy	1	1		1	1
Trifluoromethyl	1	1		1	1
Azido	1	1		1	1
Cyano	1	1		1	1
-N(R _z)C(=O)N(R _{aa})(R _{ab})	1	1		1	1
-N(R _z)C(=O)OR _{ac}	1	1		1	1
NR _{ad} R _{ae}	1	1		1	1
Amino acid			1		
Peptide			1		
NR _a R _b			1		
TOTAL NO. OF CLASSES	15	15	3	15	15

55. The absence of blaze marks is critical in determining whether P1 demonstrates that Applicant was in possession of the subject matter claimed in '830 patent claim 1 because the number of Markush elements (“classes of R group substituents”) encompassed by R₂, R₃, R₅, R₆, and R₇ in P1 formula I (the R groups narrowed in '830 patent claim 1) results in over eight quintillion possible combinations of classes of R group substituents from which the later claimed '830 patent subgenus is derived.

56. As shown in Table 2 above, there are 15 possible classes of R group substituents to choose from for R₂. However, there is no teaching in P1 that discusses any preference for only choosing one of these classes, as opposed to choosing a combination of two classes, or three classes, etc. For example, one could select hydroxy, azido, and cyano together; or one could select azido and cyano only; or one could select 14 out of the 15 classes and combine them into a later claim. Thus, this requires a combinatorial analysis to calculate the number of ways to select “m” classes out of a total of “n” total classes, as represented by the formula below:

$$\text{Number of possible combinations} = n! / [(n-m)! * m!]$$

The possible combinations of classes based on this calculation is shown in Table 3 below.

TABLE 3.

Total Number of Markush Elements (Classes) (“n”)	Selected Number of Classes (“m”)	Number of Possible Combinations
15	15	1
15	14	15
15	13	105
15	12	455
15	11	1365
15	10	3003
15	9	5005
15	8	6435
15	7	6435
15	6	5005
15	5	3003
15	4	1365
15	3	455
15	2	105
15	1	15
TOTAL NO. OF COMBINATIONS		32,767

57. Thus, for R₂ alone, there are 32,767 possible ways to combine the 15 classes of R group substituents into a later claim in multiple combinations. This number would be the same for R₃, R₆, and R₇ which also have 15 classes of R group substituents.

58. For R₅, which only has three classes of R group substituents, using the formula above would give seven potential combinations for those classes of R group substituents:

1. amino acid only
2. peptide only
3. NR_aR_b only
4. amino acid or peptide
5. amino acid or NR_aR_b
6. peptide or NR_aR_b
7. amino acid, peptide, or NR_aR_b

59. Using this methodology I calculated that there are 8×10^{18} (32,767 x 32,767 x 7 x 32,767 x 32,767) possible combinations of R group substituents for the combinations of R₂, R₃, R₅, R₆ and R₇.

60. Patent Owner may argue that the '830 patent only selects one class out of 15 classes for R₂, one class out of 15 classes for R₃, one class out of 3 classes for R₅, two classes out of 15 classes for R₆, and two classes out of 15 classes for R₇. However, even with such an argument the number of possible combinations of R group substituents is still enormous. The possibilities for R₂ and R₃ would be 15 each, three for R₅, and as shown in Table 3 above selecting two classes out of a combination of 15 possible

classes results in 105 possible combinations each for R₆ and R₇. This yields 7,441,875 possible combinations of R group substituents for R₂, R₃, R₅, R₆ and R₇ (15 x 15 x 3 x 105 x 105).

61. There are no disclosures in P1 that provide any guidance for an artisan to select: (1) R₂ as halogen from among the 15 classes of R group substituents in P1 formula I, (2) R₃ as hydroxy from among the 15 classes of R group substituents in P1 formula I, (3) R₅ as amino acid from among the three classes of R group substituents in P1 formula I, and (4) R₆ and R₇ as hydrogen or (C₁-C₆) alkyl from among the 15 classes of R group substituents in P1 formula I. And in addition, instead of guiding an artisan to those classes of R group substituents, P1 actually directs an artisan to select other classes of R group substituents by teaching that compounds “useful in the methods of the invention” (Ex. 1008, at 7) have **hydroxy at R₂** (Ex. 1008, Figure 3) and the only synthetic scheme taught in P1 for making the compounds of the invention is one that results in **hydroxy at R₂** (Ex. 1008, Figure 1).

62. Therefore, based on the disclosures in P1 an artisan would understand that Applicant was not in possession of the subgenus later claimed in '830 patent claim 1 as of the filing date of P1.

b. P1 Is Devoid of Compounds Or Examples That Fall Within The Scope Of The '830 Patent Claim 1 Subgenus

63. P1 does not disclose any compounds or a subgenus of compounds that fall within the scope of '830 patent claim 1. Nor does P1 contain any examples of compounds that fall within the scope of that subgenus.

64. Moreover, the compounds that are disclosed in P1 would not lead an artisan to select the R groups in the '830 patent claim 1 subgenus.

65. The only “illustrative” compounds defined as “useful in the methods of the invention,” or for which a synthetic scheme is provided are shown in Figures 1 and 3 of P1 (shown below), and all of these compounds include hydroxy in the 2'-down position of the nucleoside (R_2 in the nomenclature of the '830 patent), which is not within the scope of '830 patent claim 1. *See* Ex. 1008, fig.1, 3. Thus, P1's “illustrative” compounds teach a preference for something other than what is claimed in the '830 patent which limits R_2 to halo.

FIGURE 1

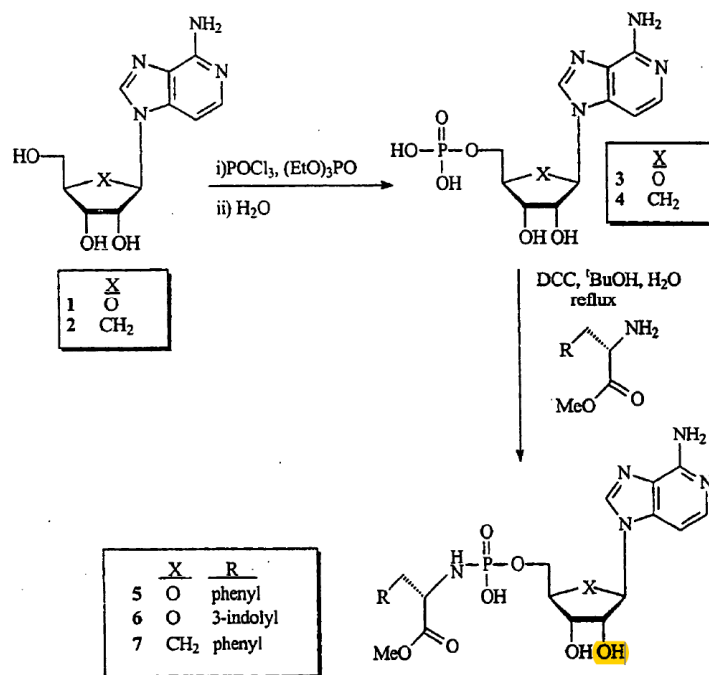
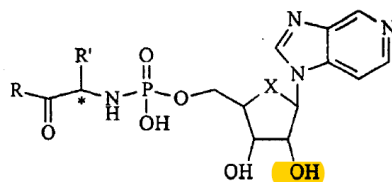


FIGURE 3



Compound	R	R'	X	*
5	methoxy	benzyl	O	(S)
6	methoxy	3-indolylmethyl	O	(S)
7	methoxy	benzyl	CH ₂	(S)
14	methylamino	benzyl	O	(S)
16	methylamino	3-indolylmethyl	O	(S)

66. Further, P1 also teaches that compounds containing an electropositive group at the 2' position are “especially good substrates for hHINT1”:

Inspection of the active site of hHINT1 has revealed that hydrogen bonding, ion pairing or polar interactions at the 2'- and 3'-positions preferentially interact with the active site residue Asp-43, which is consistent with the reduced ability of the 2'-deoxy nucleoside phosphoramidates to serve as substrates. In addition, phosphoramidates with a D-amino acid are hydrolyzed at least 20-fold more efficiently than phosphoramidates containing L-amino acids. Consequently, compounds containing 1) ***an electropositive group at the 2'-position***, and/or 2) a group having a stereochemistry that corresponds to that of an N-linked D-amino acid on the phosphorous are especially good substrates for hHINT1.

Ex. 1008, at 3: 3-11 (emphasis added). An artisan understood that the passage above refers to the 2'- and 3'-down positions (i.e., R₂ and R₃ in the '830 patent claims) because the P1 specification teaches that interactions between the hHINT1 enzyme(s) and the nucleotide phosphoramidate occur at “the 2'- and 3'-hydroxyl groups.” Ex. 1008, at 1: 23-25.

67. Electropositivity is a measure of the ability to release electrons and form positively charged ions, while electronegativity is a measure of an element's ability to attract electrons and form negatively charged ions.

Electropositivity and electronegativity are opposing concepts. An artisan understood P1 to favor electropositive groups at the 2'-down position because this would lead to more complete delivery of the nucleotide monophosphate to the cell interior. Halogens, and in particular fluorine, were understood to be electronegative, not electropositive. Indeed, ***fluorine is the most electronegative element in the periodic table.***¹

68. Because P1 teaches that the hHINT1 enzymes responsible for phosphoramidate hydrolysis favors electropositive groups at the 2'-position, an artisan would have been directed to substituents at R₂ that were not electronegative. Put another way, an artisan would not find in P1 any blaze marks to direct him or her to select halo, a term that encompasses some of the most electronegative atoms in the periodic table, at R₂. Therefore, an artisan understood that Applicant was not in possession of the '830 patent claim 1 subgenus which requires R₂ to be halo, as of the filing date of P1.

¹ The other R group substituent claimed at the 2' position in the '830 patent claims (i.e., R₆) is H or (C₁-C₆)alkyl, neither of which are electropositive. Ex. 1021, Pauling, *J. Amer. Chem. Soc.*, 54: 3570-3582 (1932).

c. **The Claims of P1 Do Not Demonstrate Preferences For The '830 Patent Claim 1 Subgenus**

69. Patent Owner may argue that the claims in P1 allegedly demonstrate that there were “preferences” for the classes of R group substituents claimed in the '830 patent subgenus. I disagree that the P1 claims provide any “preferences” for the '830 patent claimed R groups. Indeed, any suggestion otherwise can only be made using hindsight since there are no disclosures in P1 that point to the '830 patent claimed R group substituents, either as “preferred” embodiments of the invention or as demonstrating superior antiviral or anticancer activity.

70. And even if the claims of P1 could be viewed as providing some alleged “preference” for those later claimed R group substituents, there is nothing that would direct an artisan to specifically select the '830 patent claimed R groups from other R groups recited in the P1 claims.

71. To illustrate this point, claim 13 of P1 specifies R₂ as halo but other claims specify R₂ as hydroxy (claim 12); fluoro (claim 14); chloro (claim 15); (C₁-C₆)alkoxy (claim 16); methoxy (claim 17); trifluoromethyl (claim 18); cyano (claim 19); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 20), as shown below.

12. The compound of any one of claims 1-11 wherein R₂ is hydroxy.
13. The compound of any one of claims 1-11 wherein R₂ is halo.
14. The compound of any one of claims 1-11 wherein R₂ is fluoro.
15. The compound of any one of claims 1-11 wherein R₂ is chloro.
16. The compound of any one of claims 1-11 wherein R₂ is (C₁-C₆)alkoxy.
17. The compound of any one of claims 1-11 wherein R₂ is methoxy.
18. The compound of any one of claims 1-11 wherein R₂ is trifluoromethyl;
19. The compound of any one of claims 1-11 wherein R₂ is cyano.
20. The compound of any one of claims 1-11 wherein R₂ is amino, methylamino, dimethylamino, ethylamino, or dimethylamino.

Ex. 1008, at 23.

72. And while claim 21 specifies R₃ as hydroxy, other claims specify R₃ as hydrogen (claim 22); halo (claim 23); fluoro (claim 24); chloro (claim 25); trifluoromethyl (claim 26); azido (claim 27); cyano (claim 28); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 29), as shown below.

21. The compound of any one of claims 1-20 wherein R₃ is hydroxy.

- 22. The compound of any one of claims 1-20 wherein R_3 is hydrogen.
- 23. The compound of any one of claims 1-20 wherein R_3 is halo.
- 24. The compound of any one of claims 1-20 wherein R_3 is fluoro.
- 25. The compound of any one of claims 1-20 wherein R_3 is chloro.
- 26. The compound of any one of claims 1-20 wherein R_3 is trifluoromethyl.
- 27. The compound of any one of claims 1-20 wherein R_3 is azido
- 28. The compound of any one of claims 1-20 wherein R_3 is cyano.
- 29. The compound of any one of claims 1-20 wherein R_3 is amino, methylamino, dimethylamino, ethylamino, or dimethylamino.

Ex. 1008, at 23-24.

73. And while claim 33 specifies R_5 as an amino acid, other claims specify R_5 as a peptide (claim 34), as shown below.

- 33. The method of any one of claims 1-32 wherein R_5 is an amino acid.
- 34. The method of any one of claims 1-32 wherein R_5 is a peptide.

Ex. 1008, at 24. P1 defines peptide as “a sequence of 2 to 25 amino acids . . . or peptidyl residues.” Ex. 1008, at 8: 18-19.

74. As can be seen from the above, the P1 claims directed to individual classes of R group substituents or smaller genera are multiple dependent claims which themselves depend from large numbers of other multiple dependent claims. For example, claim 47 states: “The compound of any one of claims 1-46 wherein R₇ is hydrogen or (C₁-C₆)alkyl.” Ex. 1008, at 27. There are no blaze marks in this claim or any of the P1 claims specifically pointing to the narrowed substituents later claimed in '830 patent claim 1. The large number of multiple dependent claims which refer back to other multiple dependent claims results in an enormous number of possible combinations. For example, even if claim 47 were to be understood by an artisan as demonstrating a preference for R₇ as hydrogen or (C₁-C₆)alkyl, claim 47 still represents 70,875 classes of R group substituents for R₂, R₃, R₅, and R₆ with no blaze marks in P1 to direct the artisan to the classes of R group substituents later claimed in the '830 patent claim 1 subgenus (15 x 15 x 3 x 105, as shown in Tables 2 and 3 above, and giving Patent Owner the benefit of the lower number).

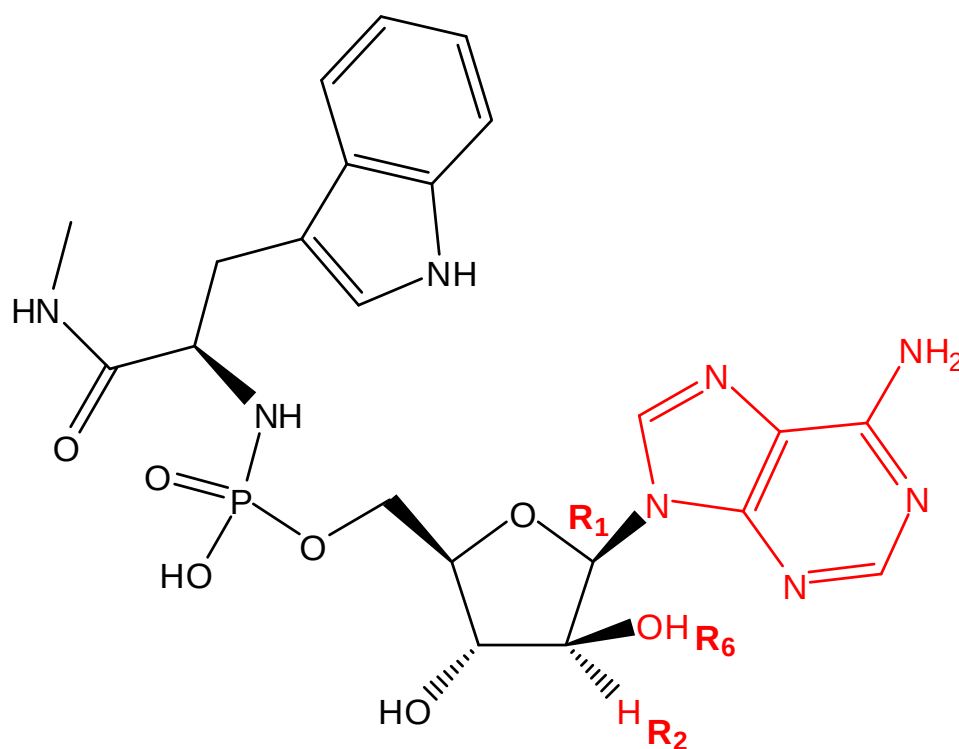
75. It would require hindsight to review claim 47 and pick (among 46 claim possibilities) claims 13, 21, 33, and 45 to combine with that claim. There is no disclosure in P1 specifically pointing an artisan in the direction of choosing any of those claims over any of the others. An artisan could just

as likely combine claim 17 (where R₂ is methoxy), claim 27 (where R₃ is azido), and claim 35 (where R₅ is a peptide), in combination with claim 47, or any other combination of claims.

76. An artisan would understand that Applicant was not in possession of the '830 patent claim 1 subgenus as of the filing date of P1 given that the P1 claims recite multiple classes of R group substituents for each of R₂, R₃ and R₅, and the lack of blaze marks in P1 to direct him or her to select R₂ as halo, R₃ as hydroxy, and R₅ as amino acid (as specifically claimed in the '830 patent claim 1 subgenus) from the 7,441,875 other possible combinations. Indeed, as discussed in subsection (b) above, P1 directs an artisan away from choosing any of the halogens at the 2'-down position because the disclosure in P1 ***focused on electropositive groups at R₂*** which would not lead an artisan to select R₂ as halogen because halogens were known to be strongly electronegative (see ¶ 64 above).

77. Moreover, P1 claim 46 recites a subgenus which ***excludes R₂ as being halogen and excludes R₆ as being hydrogen***, thus directing an artisan to select R groups at those locations that are not within the scope of the '830 patent claims which limit R₂ to halogen and R₆ to hydrogen and (C₁-C₆)alkyl. Ex. 1008, at 26.

78. And the only compound expressly disclosed by name in P1, (2-(3-indolyl)-1(R)-methylcarbamoyl ethyl)phosphoramidic acid mono (1-B-arabinofuranosyladenosine)ester (illustrated below), which is recited in claim 49 (Ex. 1008, at 27), **contains hydrogen at R_2** , which would direct an artisan to select compounds that fall outside the scope of the '830 patent claims, i.e., that do not have a halogen at R_2 .



79. In addition to the named compound not containing halogen at R_2 , it also contains adenine at R_1 (using the nomenclature of the '830 patent) whereas ***all of the '830 patent claims exclude adenine*** at that position, and contains hydroxy at R_6 whereas ***all of the '830 patent claims exclude hydroxy*** at that position.

80. Moreover, other disclosures in P1 would direct an artisan to select a substituent at R_3 that is not within the scope of the '830 patent claims. For example, claim 48 of P1 recites a subgenus where **R_3 is hydrogen or alkyl**. Ex. 1008, at 27. Just as claims 46 and 49 would direct an artisan to select something other than R_2 as halogen, claim 48 would direct an artisan to select something other than R_3 as hydroxy.

81. Taken together, the disclosures of P1 would direct an artisan to select substituents for the R_1 , R_2 and R_3 groups that are not in the scope of the '830 patent claims.

82. In summary, only through hindsight would an artisan be directed by P1 to make a subgenus with the classes of R group substituents later claimed in the '830 patent claim 1 subgenus.

* * *

83. For similar reasons that P1 does not demonstrate that Applicant was in possession of '830 patent claim 1, the disclosures of those applications do not demonstrate that Applicant was in possession of the '830 patent dependent claims.

84. While the dependent claims of the '830 patent narrow the broad scope of the classes of R group substituents in independent claim 1, there are no “preferences” or other teachings in P1 that would provide direction to an

artisan, with no foreknowledge of the later-claimed '830 patent subgenus, to select each narrowed R₂, R₃, R₅, R₆, and R₇ group to arrive at the subgenera claimed in the '830 patent dependent claims.

85. Dependent claims 2-5 of the '830 patent limit R₁ to specific bases. Ex. 1001, col.19 l.48 – col.20 l.4. While claims 8-11 of P1 also limit R₁ to the same specific bases (Ex. 1008, at 22-23), for the reasons discussed for claim 1 above, P1 provides no direction to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent claims 2-5. Just focusing on those narrowed R groups, claims 8-11 of P1 encompass 7,441,875 possible combinations of classes of R group substituents with no guidance as to which of each of those classes of R group substituents at various positions should be combined.²

² R₂ and R₃ each encompass 15 possible combinations of classes of R group substituents, R₆ and R₇ each encompass 105 possible combinations of classes of R group substituents, and R₅ encompasses three possible combinations of classes of R group substituents as shown in Tables 2 and 3 above. The total number of classes of R group substituents contained in a genus comprising R₂, R₃, R₅, R₆ and R₇ is 7,441,875 (15 x 15 x 3 x 105 x 105).

86. Dependent claim 6 of the '830 patent limits R₂ to fluoro. Ex. 1001, col.20 l.5. While claim 14 of P1 limits R₂ to fluoro (Ex. 1008, at 23), P1 provides no blaze marks to direct an artisan to select R₂ fluoro in combination with the other narrowed R₃, R₅, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent. Just focusing on those narrowed R groups, claim 14 of P1 encompasses 496,125 possible combinations of classes of R group substituents with no guidance as to which of each of those classes of R group substituents at various positions should be combined.³ And, as discussed above, the disclosure of P1 points an artisan away from choosing fluoro at R₂ because of its electronegativity which is taught away from for delivery of the nucleotide to the cell interior.

87. '830 patent claims 7-9 and 11 limit R₅ to amino acids. Ex. 1001, col.20 ll.6-36. While claims 33 and 40-44 of P1 limit R₅ to amino

³ R₃ encompasses 15 possible combinations of classes of R group substituents, R₆ and R₇ each encompass 105 possible combinations of classes of R group substituents, and R₅ encompasses three possible combinations of classes of R group substituents as shown in Tables 2 and 3 above. The total number of classes of R group substituents contained in a genus comprising R₃, R₅, R₆ and R₇ is 496,125 (15 x 3 x 105 x 105).

acids (Ex. 1008, at 24-26), P1 provides no blaze marks to direct an artisan to select R₅ amino acid in combination with the other narrowed R₂, R₃, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent. Just focusing on those narrowed R groups, claims 33 and 40-44 of P1 encompass 2,480,625 possible combinations of classes of R group substituents with no guidance as to which of each of those classes of R group substituents at various positions should be combined.⁴

88. '830 patent claim 12 limits R₇ to hydrogen. Ex. 1001, col.20 ll.37-38. There is no disclosure in P1 which limits R₇ to hydrogen. Ex. 1008, at 19-31. Thus, for the same reasons as discussed for claims 1-5, P1 provides no blaze marks to direct an artisan to select R₇ hydrogen in combination with the other narrowed R₂, R₃, R₅, and R₆ groups to arrive at the claimed subgenera of the '830 patent claim 12.

⁴ R₂ and R₃ each encompass 15 possible combinations of classes of R group substituents and R₆ and R₇ each encompass 105 possible combinations of classes of R group substituents. The total number of classes of R group substituents contained in a genus comprising R₂, R₃, R₆ and R₇ is 2,480,625 (15 x 15 x 105 x 105).

89. Dependent claims 13-21 and 23-27 of the '830 patent are directed to a method for treating a viral infection comprising administering various subgenera of claims 1-9 and 11-12 of the '830 patent. Ex. 1001, col.20 l.39 – col.22 l.16. For the same reasons as discussed for claims 1-9 and 11-12, P1 provides no blaze marks to direct an artisan to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent claims 13-21 and 23-27.

90. Dependent claim 28 of the '830 patent is directed to pharmaceutical compositions comprising the genus of claim 1 and a pharmaceutically acceptable vehicle or carrier. Ex. 1001, col.22 ll.17-19. For the same reasons as discussed for claim 1, P1 provides no blaze marks to direct an artisan to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ groups to arrive at the claimed subgenera of the '830 patent claim 28.

* * *

91. In summary, given the enormous size of the genus disclosed in P1, the lack of blaze marks that would direct an artisan to the '830 patent claims and the teachings in P1 that would direct an artisan towards something other than selecting the R groups later claimed in the '830 patent, an artisan understood that P1 did not demonstrate that Applicant was in possession of the subject matter of the Challenged Claims. In my opinion,

this is nothing less than a bold attempt by Applicant to capture an invention that Applicant did not invent, sofosbuvir, years after the filing of those applications.

2. NP3/NP2 Do Not Demonstrate That Applicant Was In Possession Of The Subject Matter Claimed In The '830 Patent

92. NP3/NP2 contain additional disclosure from what is in P1. In particular, NP3/NP2 contain 24 “representative compounds” which were added after the filing of P1 (see ¶ 101 below), and anticancer *in vitro* cell assay data was added on three of these “representative compounds.” No antiviral activity was provided for any of these “representative compounds.” None of these “representative compounds” fall within the scope of the '830 patent claims.

93. As stated above, the claims of the '830 patent are directed to a subgenus of the extremely large genera disclosed in NP3/NP2. In my opinion, an artisan would understand NP3/NP2 as demonstrating that Applicant was not in possession of the later claimed '830 patent claim 1 subgenus.

a. **NP3/NP2 Is Devoid Of Blaze Marks To Direct An Artisan To Compounds That Fall Within The Full Scope Of The '830 Patent Claim 1 Subgenus**

94. NP3/NP2 disclose the same structural formula I as in P1, reciting a large number of classes of R group substituents (see Ex. 1007, at 3:18-4:13). Differences between the disclosure in NP3/NP2 and the later claimed '830 patent claim 1 subgenus is the same as shown above in Table 1.

95. While '830 patent claim 1 narrows the scope of the classes of R group substituents disclosed in NP3/NP2, similar to the situation for P1, there are no blaze marks in NP3/NP2 to guide an artisan to select those specific classes of R group substituents from the myriad possibilities in the broad genera disclosed in NP3/NP2.

96. As stated above for P1, the absence of blaze marks is critical in determining whether NP3/NP2 demonstrate that Applicant was in possession of the subject matter claimed in '830 patent claim 1 because a calculation based on the number of Markush elements encompassed by R₂, R₃, R₅, R₆, and R₇ in NP3/NP2 formula I (the R groups narrowed in '830 patent claim 1) results in 7,441,875 possible combinations of classes of R group substituents from which the later claimed '830 patent claim 1 subgenus is derived, as shown in Tables 2 and 3 above.

97. Similar to my analysis of P1 above, there are no disclosures in NP3/NP2 that provide any direction to select any of those classes of R group substituents over others, i.e., there are no disclosures in NP3/NP2 that would direct an artisan to select: (1) R₂ as halogen from among the 15 classes of R group substituents in NP3/NP2, (2) R₃ as hydroxy from among the 15 classes of R group substituents in NP3/NP2, (3) R₅ as amino acid from among the three classes of R group substituents in NP3/NP2, and (4) R₆ and R₇ as hydrogen or (C₁-C₆) alkyl from among the 15 classes of R group substituents in NP3/NP2. Importantly, instead of guiding an artisan to those later claimed classes of R group substituents, NP3/NP2 would instead direct an artisan to select other classes of R group substituents because the only compounds “useful in the methods of the invention” in NP3/NP2 have hydroxy at R₂ (NP3/NP2 Figure 3) and the only synthetic scheme for making the compounds in NP3/NP2 is one that results in hydroxy at R₂ (NP3/NP2 Figure 1).

98. Therefore, based on the disclosures in NP3/NP2, an artisan would understand that Applicant was not in possession of the subgenus later claimed in '830 patent claim 1 as of the filing date of NP3/NP2.

b. NP3/NP2 Is Devoid Of Compounds Or Examples That Fall Within The Scope Of The '830 Patent Claim 1 Subgenus

99. Similar to P1, NP3/NP2 do not disclose any compounds or a subgenus of compounds that fall within the scope of '830 patent claim 1. Nor do NP3/NP2 contain any examples of compounds that fall within the scope of that subgenus.

100. Moreover, similar to P1, the compounds that are disclosed would not lead an artisan to select the R groups in the '830 patent claim 1 subgenus.

101. NP3/NP2 disclose 24 “representative” compounds, as shown below.

Example 2. Representative compounds of the invention can be prepared using a procedure similar to those described by T. Chou et al., *The Journal of Biological Chemistry*, **2005**, 280, 15356-15361. The following compounds were prepared using such a procedure.

Compound	Nucleotide	Amino Acid	Theoretical mass	[M-H] ⁻	Error (ppm)
100	AMP	L-TrpCOOMe	546.1508	546.1503	-0.9
101	AMP	L-TrpCONMe	547.1824	547.1851	4.9
102	AMP	L-TrpCONH ₂	533.1668	533.1669	0.3
103	AMP	D-TrpCOOMe	546.1508	546.1513	1.0

104	AMP	Tryptamine	488.1447	488.148	6.7
105	GMP	L-TrpCOOMe	562.1451	562.1468	3.0
106	GMP	L-TrpCONMe	563.1773	563.1813	7.1
107	GMP	L-TrpCONH ₂	547.146	547.1444	-3.0
108	GMP	D-TrpCOOMe	562.1451	562.1462	1.9
109	GMP	Tryptamine	504.1397	504.140	0.7
110	IMP	L-TrpCOOMe	547.1342	547.1351	1.6
111	IMP	D-TrpCOOMe	547.1342	547.1335	-1.4
112	IMP	Tryptamine	489.1288	489.1279	-1.8
113	Ara-AMP	L-TrpCOOMe	546.1508	546.1496	-2.1
114	Ara-AMP	D-TrpCOOMe	546.1508	546.1503	-0.9
115	Ara-AMP	Tryptamine	488.1447	488.1422	-5.2
116	TMP	L-TrpCONMe	520.1597	520.1592	-1.0
117	TMP	D-TrpCOOMe	521.1437	521.1426	-2.2
118	TMP	Tryptamine	463.1383	463.1396	2.9
119	CMP	D-TrpCOOMe	522.139	522.1399	1.7
120	CMP	L-TrpCONH ₂	507.1393	507.1399	1.1
121	CMP	Tryptamine	464.1335	464.1335	0.0
122	UMP	D-TrpCOOMe	523.123	523.124	1.9
123	UMP	Tryptamine	465.1175	465.1174	-0.3

A = Adenosine, G = Guanosine, I = inosine, T = thymidine, U = uridine, Ara-A = 9-beta-D-arabinofuranosyladenosine
Trp=tryptophan COOME=carbomethoxy ester, CONMe = methyl amide

*Most of compounds were analyzed in negative mode except compounds 101, 102, and 106.

Ex. 1007, at 26-27. Most of these compounds are phosphoramidate prodrugs of natural nucleosides that have a hydroxy at the 2'-down position of the sugar (R₂ using the nomenclature of the '830 patent) which make them outside the scope of the '830 patent claims which require a halo at that position. Only one compound, Ara-A, is an non-natural nucleoside, but that

compound contains a hydroxy in the 2'-up position ($R_6 = OH$) and a hydrogen in the 2'-down position ($R_2 = H$) of the sugar, consistent with the D-arabino sugar indicated by the name "Ara-A." This compound is also outside the scope of the '830 patent claims which require a hydrogen or (C_1 - C_6) alkyl at the 2'-up (R_6) position and a halo at the 2'-down (R_2) position.

102. In addition, NP3/NP2 contain the same Figures 1 and 3 as in P1 (see page 41 above) which teach compounds "useful in the methods of the invention" (Figure 3) and a synthetic scheme to make compounds (Figure 1), both of which include only those compounds having hydroxy in the 2'-down (R_2) position of the sugar. None of those compounds fall within the scope of the '830 patent claims which require halo at the 2'-down (R_2) position. Thus, not only is there a complete absence of any teaching that would direct an artisan to select a compound having halo at the 2'-down (R_2) position but there is actually a direction to select compounds that do not have halo at that position based on the NP3/NP2 disclosures.

103. Moreover, because NP3/NP2 teach that the hHINT1 enzyme responsible for phosphoramidate hydrolysis favors electropositive groups at the 2'-position (see ¶ 66 above), an artisan would have been directed to substituents at R_2 that were not electronegative, just as in P1. Because halogens are among the most electronegative groups in the periodic table

(see ¶ 67 above), an artisan would not be directed to choose halo at R₂ based on these statements in the NP3/NP2 specification.

104. The absence of any blaze marks that would direct an artisan to select halo at R₂ (required by the '830 patent claims) combined with the disclosures in Figures 1 and 3 that compounds useful in the methods of the invention and those for whom a synthetic scheme is provided do not have halo at R₂, in my opinion, would direct an artisan to select something other than halo at R₂. Taken together with the fact that halo is disfavored at R₂ because of its strongly electronegative property, this is clear evidence demonstrating that Applicant was not in possession of the '830 patent claim 1 subgenus at the time of the filing of NP3/NP2.

c. **The Claims Of NP3/NP2 Do Not Demonstrate Preferences For The '830 Patent Claim 1 Subgenus**

105. Similar to my analysis above of P1, Patent Owner may argue that the claims in NP3/NP2 allegedly demonstrate that there were “preferences” for the classes of R group substituents claimed in the '830 patent subgenus. I disagree that the NP3/NP2 claims provide any “preferences” for the '830 patent claimed R groups. Indeed, any suggestion otherwise can only be made using hindsight since there are no disclosures in NP3/NP2 that point to the '830 patent claim 1 R group substituents as

“preferred” embodiments of the invention. For example, while the ’830 patent claim 1 subgenus limits R_3 to hydroxy, no rationale other than hindsight would direct an artisan to avoid selecting other groups such as azido at R_3 , which is specifically claimed in NP3/NP2 claim 41. An artisan understood in the December 8, 2005 timeframe that FDA-approved antiviral agents exhibiting high potency had an azido group at R_3 , e.g. AZT.

106. And even if the claims of NP3/NP2 could be viewed as providing some alleged “preference” for those later claimed R group substituents, there is nothing that would direct an artisan to specifically select the ’830 patent claim 1 R groups from the other R groups recited in the NP3/NP2 claims.

107. To illustrate this point, claim 27 of NP3/NP2 specifies R_2 as halo, but other claims specify R_2 can be hydroxyl (claim 26); fluoro (claim 28); chloro (claim 29); (C_1 - C_6)alkoxy (claim 30); methoxy (claim 31); trifluoromethyl (claim 32); cyano (claim 33); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 34), as shown below.

26. The compound of any one of claims 1-13 or 16-25 wherein R₂ is hydroxy.
27. The compound of any one of claims 1-13 or 16-25 wherein R₂ is halo.
28. The compound of any one of claims 1-13 or 16-25 wherein R₂ is fluoro.
29. The compound of any one of claims 1-13 or 16-25 wherein R₂ is chloro.
30. The compound of any one of claims 1-13 or 16-25 wherein R₂ is (C₁-C₆)alkoxy.
31. The compound of any one of claims 1-13 or 16-25 wherein R₂ is methoxy.
32. The compound of any one of claims 1-13 or 16-25 wherein R₂ is trifluoromethyl.
33. The compound of any one of claims 1-13 or 16-25 wherein R₂ is cyano.
34. The compound of any one of claims 1-13 or 16-25 wherein R₂ is amino, methylamino, dimethylamino, ethylamino, or dimethylamino.

Ex. 1007, at 40.

108. And while claim 35 specifies R₃ as hydroxyl, other claims specify R₃ can be hydrogen (claim 36); halo (claim 37); fluoro (claim 38); chloro (claim 39); trifluoromethyl (claim 40); azido (claim 41); cyano (claim

42); or “amino, methylamino, dimethylamino, ethylamino, or dimethylamino” (claim 43), as shown below.

35. The compound of any one of claims 1-13 or 16-34 wherein R_3 is hydroxy.

36. The compound of any one of claims 1-13 or 16-34 wherein R_3 is hydrogen.

37. The compound of any one of claims 1-13 or 16-34 wherein R_3 is halo.

38. The compound of any one of claims 1-13 or 16-34 wherein R_3 is fluoro.

39. The compound of any one of claims 1-13 or 16-34 wherein R_3 is chloro.

40. The compound of any one of claims 1-13 or 16-34 wherein R_3 is trifluoromethyl.

41. The compound of any one of claims 1-13 or 16-34 wherein R_3 is azido

42. The compound of any one of claims 1-13 or 16-34 wherein R_3 is cyano.

43. The compound of any one of claims 1-13 or 16-34 wherein R_3 is amino, methylamino, dimethylamino, ethylamino, or dimethylamino.

Ex. 1007, at 40-41.

109. And while claim 47 specifies R_5 as an amino acid, other claims specify R_5 as a peptide (claim 48), as shown below.

47. The compound of any one of claims 1-2 and 16-46 wherein R₅ is an amino acid.

48. The method of any one of claims 1-2 and 16-46 wherein R₅ is a peptide.

Ex. 1007, at 41. NP3/NP2 define peptide as “a sequence of 2 to 25 amino acids . . . or peptidyl residues.” Ex. 1007, at 8: 22-23.

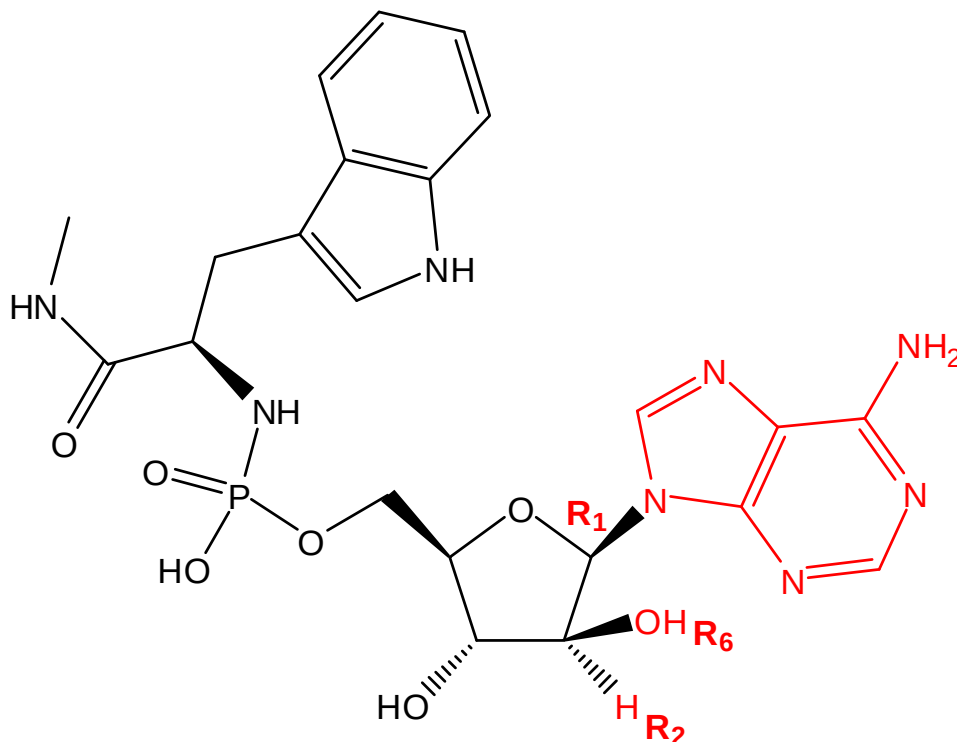
110. In my opinion, the NP3/NP2 claims would actually direct an artisan to select other classes of R group substituents claimed in the '830 patent claim 1 subgenus.

111. For example, claim 61 recites: “The compound of any one of claims 1-13 wherein R₇ is hydrogen or (C₁-C₆)alkyl.” Ex. 1007, at 43: 25-26. Claims 3-13 recite that R₅ is NR_aR_b, and provide preferences for the specific R_a and R_b groups which exclude amino acids, which is required at R₅ in the '830 patent claim 1 subgenus. Ex. 1007, at 34-38.

112. And claim 60 recites a subgenus which excludes R₂ as being halo and R₆ as being hydrogen, both of which are required by the '830 patent claims. Ex. 1007, at 43: 20-24.

113. And, as discussed for P1, a compound expressly disclosed by name in NP3/NP2, (2-(3-indolyl)-1(R)-methylcarbamoyl)ethyl)phosphoramidic acid mono (1-B-arabinofuranosyladenosine)ester (illustrated below), which is recited in

claim 63 (Ex. 1007, at 44: 1-3), contains hydrogen at R₂, which would direct an artisan to select compounds that fall outside the scope of the '830 patent claim 1 subgenus, i.e. that do not have halo at R₂.



114. In addition to the named compound not containing halogen at R₂, it also contains adenine at R₁ (using the nomenclature of the '830 patent) whereas ***all of the '830 patent claims exclude adenine*** at that position, and contains hydroxy at R₆ whereas ***all of the '830 patent claims exclude hydroxy*** at that position.

115. Moreover, other disclosures in NP3/NP2 would direct an artisan to select a substituent at R₃ that is not within the scope of the '830 patent claim 1 subgenus. For example, claim 62 of NP3/NP2 recites a subgenus

where ***R₃ is hydrogen or alkyl***. Ex. 1007, at 43: 28-31. Just as claims 60 and 63 would direct an artisan to select something other than R₂ as halogen, claim 62 would direct an artisan to select something other than R₃ as hydroxy.

116. Taken together, the disclosures of NP3/NP2 would direct an artisan to select classes of R group substituents for R₁, R₂, and R₃ that are not in the scope of the '830 patent claims.

117. Patent Owner may point to claim 59 as allegedly providing support for the '830 patent claim 1 subgenus. Claim 59 recites: “The compound of any one of claims 1-58 wherein R₆ is hydrogen or (C₁-C₆)alkyl.” Ex. 1007, at 43: 17-18. But while R₆ in claim 59 matches R₆ in the '830 patent claim 1 subgenus, there are no blaze marks in the NP3/NP2 specification or claims that would direct an artisan to ***combine*** R₆ from claim 59 with the other narrowed classes of R group substituents, i.e., R₂, R₃, R₅ and R₆, later claimed in the '830 patent claims. Even if claim 59 were to be understood by an artisan as demonstrating a “preference” for R₆ as hydrogen or (C₁-C₆)alkyl, claim 59 still represents 70,875 possible combinations of classes of R group substituents for R₂, R₃, R₅, and R₇ (15 x 15 x 3 x 105).

118. This is emblematic of any argument that Patent Owner could make with regard to the alleged R group “preferences” taught by the

NP3/NP2 claims: there is simply no disclosure in NP3/NP2 that would direct an artisan to combine a particular class of R group substituents recited in one claim with classes of R group substituents recited in other claims. There are no blaze marks in NP3/NP2 that would direct him or her to choose any particular R group substituent with any understanding that those R groups are preferred or in any way distinguished over those recited in other claims.

119. Further, unlike the case for P1, the organization of the claims of NP3/NP2 and their relationship to one another through their dependencies, precludes combinations that would result in the classes of R group substituents later claimed in the '830 patent. This means that even if an artisan were to view the disclosures in NP3/NP2 with the aid of foreknowledge regarding the later-claimed '830 patent claim 1 subgenus, which I understand is not allowed, an artisan would still not be able to piece together the classes of R group substituents in the '830 patent claim 1 subgenus using the dependencies of the dependent claims of NP3/NP2.

120. In summary, given the enormous size of the genera of compounds disclosed in NP3/NP2, the lack of blaze marks that would direct an artisan to the '830 patent claims combined with the teachings in NP3/NP2 that would direct an artisan to select something other than the R groups later claimed in the '830 patent, an artisan understood that NP3/NP2

demonstrated that Applicant was in not in possession of the subject matter of '830 patent claim 1.

* * *

121. For similar reasons that NP3/NP2 do not demonstrate that Applicant was in possession of '830 patent claim 1, the disclosures of those applications do not demonstrate that Applicant was in possession of the '830 patent dependent claims.

122. While the dependent claims of the '830 patent narrow the broad scope of the classes of R group substituents in independent claim 1, there are no “preferences” or other teachings in NP3/NP2 that would provide direction to an artisan, with no foreknowledge of the later-claimed '830 patent subgenus, to select the R₂, R₃, R₅, R₆, and R₇ classes of R group substituents claimed in the '830 patent dependent claims.

123. Dependent claims 2-5 of the '830 patent limit R₁ to specific bases. Ex. 1001, col.19 l.48 – col.20 l.4. While claims 22-25 of NP3/NP2 limit R₁ to the same bases (Ex. 1007, at 39-40), for the reasons discussed above, NP3/NP2 provide no blaze marks to direct an artisan to **combine** R₁ in claims 22-25 with the narrowed R₂, R₃, R₅, R₆, and R₇ classes claimed in '830 patent claims 2-5.

124. Just focusing on those R group classes, claims 22-25 of NP3/NP2 encompass 7,441,875 possible combinations of classes of R group substituents with no guidance as to which of those should be combined.

125. Similarly, dependent claim 6 of the '830 patent limits R₂ to fluoro. Ex. 1001, col.20 l.5. While claim 28 of NP3/NP2 limits R₂ to fluoro (Ex. 1007, at 40: 10), NP3/NP2 provide no blaze marks to direct an artisan to **combine** R₂ recited in claim 28 with the narrowed R₃, R₅, R₆, and R₇ classes claimed in '830 patent claim 6.

126. Just focusing on those narrowed R groups, claim 28 of NP3/NP2 encompasses 496,125 possible combinations of classes of R group substituents with no guidance as to which of those should be combined. And, as discussed above, the disclosure of NP3/NP2 points an artisan away from selecting fluoro at R₂ because of its strongly electronegative properties and the teaching in NP3/NP2 that electropositive groups are favored at the 2'-down position (see also ¶ 66 above).

127. Dependent claims 7-9 and 11 of the '830 patent limit R₅ to amino acids. Ex. 1001, col.20 ll.6-36. While claims 47 and 54-58 of NP3/NP2 limit R₅ to amino acids (Ex. 1007, at 41-43), NP3/NP2 provide no blaze marks to direct an artisan to **combine** R₅ recited in claims 47 and 54-

58 with the narrowed R₂, R₃, R₆, and R₇ classes of R group substituents claimed in '830 patent claims 7-9 and 11.

128. Just focusing on those narrowed R groups, claims 47 and 49-58 of NP3/NP2 encompass 2,480,625 possible combinations of classes of R group substituents with no guidance as to which of those should be combined.

129. Dependent claim 12 of the '830 patent limits R₇ to hydrogen. Ex. 1001, col.20 ll.37-38. There is no disclosure in NP3/NP2, including the claims, which limits R₇ to hydrogen. *See* Ex. 1007, at 30-48.

130. Dependent claims 13-21 and 23-27 of the '830 patent are directed to a method for treating a viral infection in an animal comprising administering various subgenera of claims 1-9 and 11-12 of the '830 patent. Ex. 1001, col.20 l.39 – col.22 l.16. For the same reasons as discussed above for '830 patent claims 1-9 and 11-12, NP3/NP2 provide no blaze marks to direct an artisan to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ classes of R group substituents claimed in '830 patent claims 13-21 and 23-27.

131. Dependent claim 28 of the '830 patent is directed to pharmaceutical compositions comprising the genera of claim 1 and a pharmaceutically acceptable vehicle or carrier. Ex. 1001, col.22 ll.17-19. For the same reasons as discussed above for '830 patent claim 1, NP3/NP2

provide no blaze marks to direct an artisan to select the specific narrowed R₂, R₃, R₅, R₆, and R₇ classes of R group substituents claimed in '830 patent claim 28.

132. In summary, given the enormous size of the genera of compounds disclosed in NP3/NP2, the lack of blaze marks that would direct an artisan to the '830 patent claims, combined with the teachings in NP3/NP2 that would direct an artisan to select something other than the R groups later claimed in the '830 patent, an artisan understood that NP3/NP2 did not demonstrate that Applicant was in possession of the subject matter of the '830 patent dependent claims. In my opinion, this is nothing less than a bold attempt by Applicant to capture an invention that Applicant did not invent, sofosbuvir, years after the filing of those applications.

3. NP4 Does Not Demonstrate That Applicant Was In Possession Of The Subject Matter Claimed In The '830 Patent

133. NP4, the fourth application in the alleged chain of priority, was filed on January 29, 2013.

134. Prior to NP3 issuing as a patent, Applicant filed NP4, labelling that application as a “continuation” of NP3. However, the disclosures in NP4 and NP3/NP2 differed – instead of including the NP3/NP2 claims in NP4, Applicant replaced them with 16 new claims. Ex. 1005, at 30-33.

135. In my opinion, an artisan would understand these claims as directing him or her to select something other than the subgenus claimed in the '830 patent.

136. None of the NP4 claims recite R_2 as halo, instead ***requiring R_2 to be hydroxy***. An artisan as of January 29, 2013 would have understood this to mean that Applicant was focused on nucleosides with hydroxy at R_2 , not halo. Thus, NP4 would direct an artisan to compounds that contain hydroxy at R_2 .

137. Further, none of the NP4 claims recite R_5 as amino acid, instead ***requiring R_5 to be NR_aR_b*** . An artisan as of January 29, 2013 would have understood this to mean that Applicant was focused on nucleosides with NR_aR_b at R_5 , not amino acid. Thus, NP4 would direct an artisan to compounds that contain NR_aR_b at R_5 .

138. Because the specification of NP4, absent the claims, is identical to that of NP3/NP2, there are no blaze marks in NP4 that would direct an artisan to the '830 patent claimed subgenus. Therefore, an artisan would understand from the disclosure in NP4 that Applicant was not in possession of the subject matter of the '830 patent claims as of the January 29, 2013 filing date of NP4.

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139. In conclusion, none of the Alleged Priority Applications demonstrate to an artisan that Applicant was in possession of the subject matter claimed in the '830 patent. In particular:

- There are no blaze marks in P1, NP3/NP2, or NP4 that would direct an artisan to compounds falling within the scope of the '830 patent claims, as demonstrated by the fact that:
 - o All of the compounds disclosed in P1, NP3/NP2, and NP4 have **hydroxy or hydrogen at R_2** whereas the '830 patent claims require **halogen at R_2** ;
 - o The only synthetic scheme disclosed in P1, NP3/NP2, and NP4 for making the claimed nucleotides results in compounds having **hydroxy at R_2** whereas the '830 patent claims require **halogen at R_2** ;
 - o P1, NP3/NP2, and NP4 teach that **electropositive** groups are favored at the 2'-down position to allow for phosphoramidate hydrolysis and delivery of the nucleotide monophosphate into the cell, whereas halogens, particularly fluorine, are strongly **electronegative**;

- o The only compound described by name in the claims of P1 and NP3/NP2 contains substituents at R₁, R₂ and R₆ that are ***not within the scope of the '830 patent claims***;
- o The claims of P1 and NP3/NP2 recite subgenera that ***do not contain hydroxy at R₃*** whereas the '830 patent claims ***require hydroxy at R₃***; and
- o The combinations encompassed by R₂, R₃, R₅, R₆, and R₇ in P1, NP3/NP2, and NP4 result in between ***70,000 and over 7,000,000 classes of R group substituents*** from which the later claimed '830 patent subgenus selects 7 specific classes with no blaze marks to direct an artisan to select those specifically narrowed classes of R groups claimed in the '830 patent.

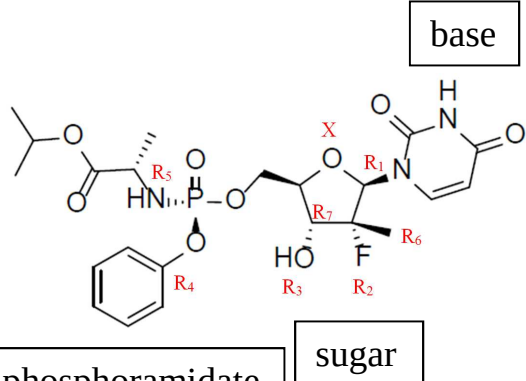
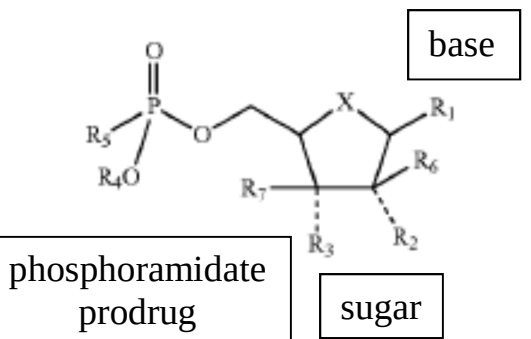
140. Thus, in my opinion, an artisan would understand that none of the Alleged Priority Applications demonstrate that Applicant was in possession of the subject matter claimed therein. Therefore, Applicant should not be able to claim the benefit of any of those Alleged Priority Applications for the later claimed subgenera in the '830 patent.

XI. PATENTABILITY ANALYSIS OF THE CHALLENGED CLAIMS

A. Overview of the Prior Art

141. U.S. Patent Application Publication No. 2010/0016251 to Michael Joseph Sofia et al. (“Sofia,” provided as Ex. 1004), published on January 21, 2010.

142. Sofia is directed to phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections, including hepatitis C viral infections, and specifically discloses sofosbuvir as example 25 (“Sofia 25”): “(S)-2-[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phosphorylamino}-propionic acid isopropyl ester” (*see, e.g.*, Ex. 1004, at 49, 58), represented by the chemical structure below:

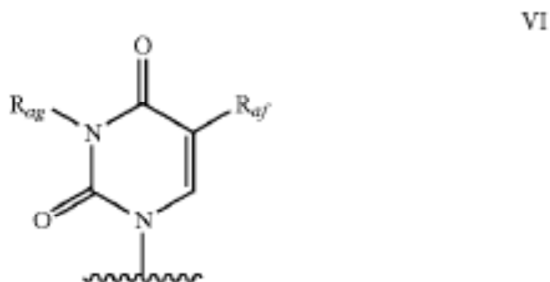
Sofia 25	'830 patent genus
	

B. Ground 1: Sofia Discloses Every Limitation Of The Challenged Claims

143. Sofia 25 meets every limitation of '830 patent claim 1 where R_1 is uracil, R_2 is fluoro, R_3 is hydroxy, R_4 is phenyl, R_5 is an amino acid (i.e., the isopropyl ester of L-alanine), R_6 is methyl, R_7 is hydrogen, and X is oxy. In Sofia 25, the base, represented by R_1 in the '830 patent, is uracil. Further, the sugar in Sofia 25 is a ribose derivative, represented by X being oxy in the '830 patent. The sugar portion also contains a fluoro in the 2'-down position, represented by R_2 in the '830 patent; a methyl group in the 2'-up position, represented by R_6 in the '830 patent; a hydroxy group in the 3'-down position, represented by R_3 in the '830 patent; and hydrogen in the 3'-up position, represented by R_7 in the '830 patent. In the phosphoramidate prodrug portion of Sofia 25, a phenyl group is attached to the oxygen, represented by R_4 in the '830 patent and an isopropyl ester of L-alanine is attached to the phosphorus, represented by R_5 in the '830 patent.

144. '830 patent claim 2 recites: "The compound or salt of claim 1 wherein R_1 is guanine, cytosine, thymine, 3-deazaadenine, or uracil." '830 patent claim 3 recites: "The compound or salt of claim 1 wherein R_1 is cytosine, thymine, 3-deazaadenine, or uracil." Claim 4 recites: "The compound or salt of claim 1 wherein R_1 is cytosine, thymine, or uracil." Ex. 1001, col.19 ll.48-53. Sofia 25 contains uracil at R_1 .

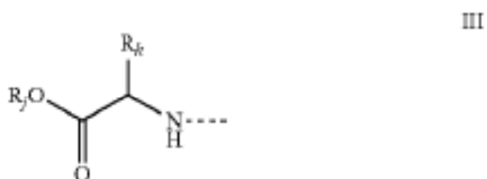
145. '830 patent claim 5 recites: "The compound or salt of claim 1 wherein R₁ is a nitrogen linked radical of formula VI:



wherein R_{af} is hydrogen, halo, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, trifluoromethyl, hydroxyl(C₁-C₆)alkyl, or -(CH₂)₁₋₄P(=O)(OR_w)₂." Ex. 1001, col.19 l.54 – col.20 l.4. R_{af} and R_{ag} can both be hydrogen in formula VI, which represents the base uracil. Sofia 25 contains uracil at R₁.

146. '830 patent claim 6 recites: "The compound or salt of claim 1 wherein R₂ is fluoro." Ex. 1001, col.20 l.5. Sofia 25 contains fluoro at R₂.

147. '830 patent claim 7 recites: "The compound or salt of claim 1 wherein R₅ is a nitrogen linked radical of formula III:



wherein R_h is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C₁-C₆)alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino.” Ex. 1001, col.20 ll.6-26. When R_h is methyl and R_j is isopropyl (both C₁-C₆ alkyls), R_5 is the isopropyl ester of L-alanine in Sofia 25.

148. '830 patent claim 8 recites: “The compound or salt of claim 7 wherein R_h is hydrogen, (C₁-C₆)alkyl, phenylmethyl, or 3-indolylmethyl.” Ex. 1001, col.20 ll.27-28. When R_h is methyl and R_j is isopropyl, R_5 is the isopropyl ester of L-alanine in Sofia 25.

149. '830 patent claim 9 recites: “The compound or salt of claim 8 wherein R_j is hydrogen or (C₁-C₆)alkyl.” Ex. 1001, col.20 ll.29-30. When R_h is methyl and R_j is isopropyl (both C₁-C₆ alkyls), R_5 is the isopropyl ester of L-alanine in Sofia 25.

150. '830 patent claim 11 recites: "The compound or salt of claim 1 wherein R₅ is a (C₁-C₆)alkyl ester of L-alanine," which includes the isopropyl ester of L-alanine in Sofia 25. Ex. 1001, col.20 ll.34-35.

151. '830 patent claim 12 recites: "The compound or salt of claim 11 wherein R₇ is hydrogen." Ex. 1001, col.20 ll.36-37. Sofia 25 contains hydrogen at R₇.

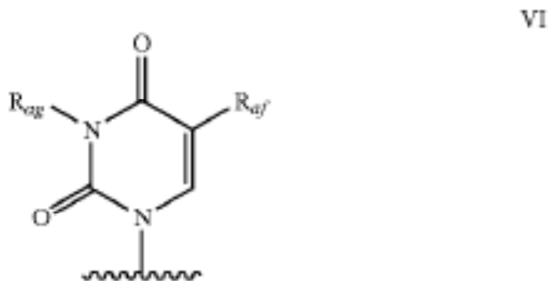
152. '830 patent claim 13 recites: "A method for treating a viral infection in an animal comprising administering to an animal in need of such treatment an effective amount of a compound or salt of formula I according to claim 1." Ex. 1001, col.20 ll.39-42. Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. Sofia further states that: "The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases." Ex. 1004, at 1 ¶ 0001. Thus, Sofia 25's use in a method for treating viral infections is disclosed in Sofia.

153. '830 patent claim 14 recites: "The method of claim 13 wherein R₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil." '830 patent claim 15 recites: "The method of claim 13 wherein R₁ is cytosine, thymine, 3-deazaadenine, or uracil." '830 patent claim 16 recites: "The method of

claim 13 wherein R₁ is cytosine, thymine, or uracil.” Ex. 1001, col.20 ll.43-

49. Sofia 25 contains uracil at R₁.

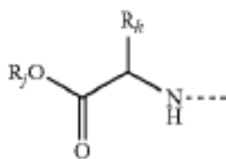
154. '830 patent claim 17 recites: “The method of claim 13 wherein R₁ is a nitrogen linked radical of formula VI:



wherein R_{af} is hydrogen, halo, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, or trifluoromethyl; and R_{ag} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, trifluoromethyl, hydroxy(C₁-C₆)alkyl, or —(CH₂)₁₋₄P(=O)(OR_w)₂.” Ex. 1001, col.20 ll.50-67. R_{af} and R_{ag} can both be hydrogen in formula VI, which represents the base uracil. Sofia 25 contains uracil at R₁.

155. '830 patent claim 18 recites: “The method of claim 13 wherein R₂ is fluoro.” Ex. 1001, col.21 l.1. Sofia 25 contains fluoro at R₂.

156. '830 patent claim 19 recites: “The method of claim 13 wherein R₅ is a nitrogen linked radical of formula III:



wherein R_h , is hydrogen, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_1-C_6) alkyl-S— (C_1-C_6) alkyl-, aryl, heteroaryl, aryl (C_1-C_6) alkyl, or heteroaryl (C_1-C_6) alkyl; wherein any aryl or heteroaryl may optionally be substituted with 1, 2, or 3 Z; R_j is hydrogen, (C_1-C_6) alkyl, phenyl, benzyl, or phenethyl; and wherein each Z is independently halo, hydroxy, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkyloxy, (C_1-C_6) alkanoyl, (C_1-C_6) alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino.” Ex. 1001, col.21 l.2 – col.22 l.3.

When R_h is methyl and R_j is isopropyl (both C_1-C_6 alkyls), R_5 is the isopropyl ester of L-alanine in Sofia 25.

157. ’830 patent claim 20 recites: “The method of claim 19 wherein R_h is hydrogen, (C_1-C_6) alkyl, phenylmethyl, or 3-indolylmethyl.” Ex. 1001, col.22 ll.4-5. When R_h is methyl and R_j is isopropyl, R_5 is the isopropyl ester of L-alanine in Sofia 25.

158. ’830 patent claim 21 recites: “The method of claim 20 wherein R_j is hydrogen or (C_1-C_6) alkyl.” Ex. 1001, col.22 ll.6-7. When R_h is methyl

and R_j is isopropyl (both C₁-C₆ alkyls), R₅ is the isopropyl ester of L-alanine in Sofia 25.

159. '830 patent claim 23 recites: "The method of claim 13 wherein R₅ is a (C₁-C₆)alkyl ester of L-alanine," which includes the isopropyl ester of L-alanine in Sofia 25. Ex. 1001, col.22 ll.9-10.

160. '830 patent claim 24 recites: "The method of claim 23 wherein R₇ is hydrogen." Ex. 1001, col.22 l.11. Sofia 25 contains hydrogen at R₇.

161. '830 patent claim 25 recites: "The method of claim 13 wherein the viral infection is caused by HCV [hepatitis C virus]." Ex. 1001, col.22 ll.12-13. Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. Sofia further states that:

The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals.

Ex. 1004, at 1 ¶ 0001. Thus, Sofia 25's use in a method for treating HCV is disclosed in Sofia.

162. '830 patent claim 26 recites: "The method of claim 13 wherein the animal is a human." Ex. 1001, col.22 l.14. Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. "Subject" is defined in Sofia as a mammal, preferably a human. See Ex. 1004, at 32 ¶ 0817. Thus, Sofia 25's use in a method for treating viral infections in humans is disclosed in Sofia.

163. '830 patent claim 27 recites: "The method of claim 26 wherein the compound or salt of formula I is orally administered." Ex. 1001, col.22 ll.15-16. Claim 8 of Sofia recites a method of treating a subject in need thereof by administering a therapeutically effective amount of Sofia 25. Ex. 1004, at 65-66. The specification of Sofia states: "The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers." See Ex. 1004, at 30 ¶ 0801. Thus, Sofia 25's use in an orally administered formulation for treating viral infections in humans is disclosed in Sofia.

164. '830 patent claim 28 recites: "A pharmaceutical composition comprising a compound or salt of formula I as described in claim 1 and a pharmaceutically acceptable vehicle or carrier." Ex. 1001, col.22 ll.17-19. Claim 4 of Sofia recites: "A composition for the treatment and/or

prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium” in combination with Sofia 25. *See* Ex. 1004, at 57-58. Thus, a pharmaceutical composition comprising Sofia 25 in a pharmaceutically acceptable carrier is disclosed in Sofia.

165. In summary, Sofia, published on January 21, 2010, expressly discloses each element of the Challenged Claims of the '830 patent.

XII. CONCLUSION

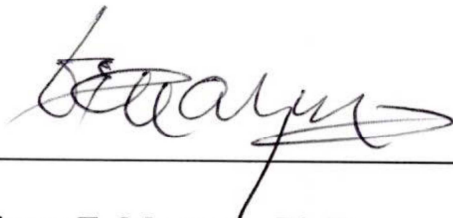
166. For the reasons stated above, the '830 patent is entitled to a priority date no earlier than the filing date of NP5 (March 28, 2014). Sofia was published January 21, 2010, over one year prior to March 28, 2014. As discussed above, Sofia expressly discloses each element of the Challenged Claims of the '830 patent. Therefore, those claims are anticipated by Sofia.

167. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information that comes to light throughout this proceeding.

168. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the

knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code.

DATED: June 30, 2017



Victor E. Marquez, Ph.D.