

Filed On Behalf Of:
Atea Pharmaceuticals, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ATEA PHARMACEUTICALS, INC.

Petitioner,

v.

GILEAD SCIENCES, INC.

Patent Owner

PGR No.: To Be Assigned

U.S. Patent No. 11,642,361

DECLARATION OF ALEXANDER M. KLIBANOV, Ph.D.

UNDER 37 C.F.R. §1.68 and §42.53(a)

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LIST OF EXHIBITS

Exhibit No.	Document
1001	U.S. Patent No. 11,642,361
1002	Excerpted File History of U.S. Patent No. 11,642,361
1003	U.S.S.N. 60/909,315 (filed March 30, 2007)
1004	U.S.S.N. 60/982,309 (filed October 24, 2007)
1005	U.S. Patent No. 7,964,580 , filed as U.S.S.N. 12/053,015 on March 21, 2008
1006	U.S. Patent No. 8,334,270, filed as U.S.S.N. 13/099,671 on May 3, 2011
1007	U.S. Patent No. 8,580,765, filed as U.S.S.N. 13/609,614 on September 11, 2012
1008	U.S. Patent No. 9,085,573, filed as U.S.S.N. 14/013,237 on August 29, 2013
1009	U.S. Patent No. 9,585,906, filed as U.S.S.N. 14/656,546 on March 12, 2015
1010	U.S. Patent No. 10,183,037, filed as U.S.S.N. 15/411,506 on January 20, 2017
1011	U.S.S.N. 16/169,878 (filed October 24, 2018) (abandoned)
1012	U.S.S.N. 16/516,192 (filed July 18, 2019) (abandoned)
1013	U.S.S.N. 16/817,318 (filed March 12, 2020) (abandoned)
1014	U.S.S.N. 17/077,267 (filed October 22, 2020)
1016	U.S.S.N. 62/129,319 (filed March 6, 2015)
1017	U.S.S.N. 62/253,958 (filed November 11, 2015)
1018	U.S.S.N. 62/276,597 (filed January 8, 2016)
1019	U.S.S.N. 15/063,461 (filed March 7, 2016)
1020	U.S. Publication 2016/0257706 (published September 8, 2016)
1021	U.S. Patent No. 9,828,410 (issued November 28, 2017)
1022	IPR2017-01712 - <i>Gilead Sciences, Inc. v. Regents of the University of Minnesota</i> , Paper 1 (Gilead's Petition for <i>Inter Partes</i> Review of U.S. Patent No. 8,815,830) (June 30, 2017)
1023	IPR2017-01712 - <i>Gilead Sciences, Inc. v. Regents of the University of Minnesota</i> , Paper 57 (Petitioner's (Gilead's) Reply) (October 30, 2020)

1024	IPR2017-01712 - <i>Gilead Sciences, Inc. v. Regents of the University of Minnesota</i> , Paper 67 (Final Written Decision) (May 21, 2021)
1025	IPR2017-01712 - <i>Gilead Sciences, Inc. v. Regents of the University of Minnesota</i> , Ex.1011 (Declaration of Victor E. Marquez, Ph.D., in Support of Petition for <i>Inter Partes</i> Review of U.S. Patent No. 8,815,830)
1026	<i>Regents of the Univ. of Minn. v. Gilead Scis., Inc.</i> , 61 F.4th 1350 (Fed. Cir. 2023)
1027	Crowther, T.W., et al., “Mapping Tree Density at a Global Scale.” <i>Nature</i> , 525: 201-205 (2015)
1028	U.S. Patent No. 7,429,572 (issued September 30, 2008)
1029	EP 2955190B1, titled “Chemical Compounds,” and issued to NuCana plc on March 28, 2018
1030	Opposition Division of The European Patent Office, Revocation (Opposition) Proceedings of EP2955190B1, Gilead Sciences, Inc.’s Request to Institute Revocation (Opposition) Proceedings of EP2955190B1 (filed December 17, 2018)
1031	<i>Gilead Sciences, Inc. and Gilead Sciences Limited v. NuCana plc</i> , Claim No: 2021-00007, High Court of Justice, Business and Property Courts of England and Wales (UK), Intellectual Property List, Patent Courts, Particulars of Claim to Invalidate European Patent (UK) No. 2955190B1 (filed February 15, 2021, on behalf of the Claimants Gilead Sciences, Inc. and Gilead Sciences Limited)
1032	<i>Gilead Sciences, Inc. and Gilead Sciences Limited v. NuCana plc</i> , Claim No: 2021-00007, High Court of Justice, Business and Property Courts of England and Wales (UK), Intellectual Property List, Patent Courts, Expert Report of Jason Micklefield, Ph.D., 02 November 2022, Filed on Behalf of the Claimants (Gilead Sciences, Inc. and Gilead Sciences Limited)
1033	Seppelt, K., “Trifluoromethanol, CF ₃ OH.” <i>Angew. Chem. Int. Ed. Engl.</i> , 16: 322-323 (1977)
1034	Willis, C. J., “Fluorinated Alcohols and their Metal Complexes.” <i>Coord. Chem. Rev.</i> , 88: 133-202 (1988)
1035	Cheburov, Y., et al., “Perfluoroalcohols” <i>J. Fluorine Chem.</i> , 118: 123-126 (2002)
1036	<i>Idenix Pharmaceuticals, Inc. v. Gilead Sciences, Inc., Gilead Sciences Limited, Center National De La Recherche Scientifique, Universita Degli Studi Di Cagliari, and L’Universite Motpellier II</i> ;

	<i>Gilead Sciences, Inc. and Gilead Sciences Limited (Part 20 Claimants) v. Idenix Pharmaceuticals, Inc., Centre National De La Recherche Scientifique, Universita Degli Studi Di Cagliari, L'Universite Montpellier II,</i> Claim No. HP 14D 010169, In The High Court of Justice, Chancery Division, Patents Court, Expert Report of Geert-Jan Boons, 31 July 2014, Filed on Behalf of First and Second Defendants and Part 20 Claimants (Gilead Sciences, Inc. and Gilead Sciences Limited)
1037	Opposition Division of The European Patent Office, Revocation (Opposition) Proceedings of EP2955190B1, Second Declaration of Geert-Jan Boons, Filed on Behalf of (Opponent) Gilead Sciences, Inc. (filed December 8, 2020)
1038	Board of Appeal of The European Patent Office, Case No. T 0795/21, Statement of Grounds of Appeal on Behalf of Gilead Sciences, Inc. (filed August 17, 2021)
1039	<i>Gilead Sciences, Inc. and Gilead Sciences Limited v. NuCana plc,</i> Claim No: 2021-00007, High Court of Justice, Business and Property Courts of England and Wales (UK), Intellectual Property List, Patent Courts, Second Expert Report of Jason Micklefield, Ph.D., 09 December 2022, Filed on Behalf of the Claimants (Gilead Sciences, Inc. and Gilead Sciences Limited)
1040	<i>Gilead Sciences, Inc. and Gilead Sciences Limited v. NuCana plc,</i> Claim No: 2021-00007, High Court of Justice, Business and Property Courts of England and Wales (UK), Intellectual Property List, Patent Courts, Expert Report of Professor Mathias Götte, Ph.D., 1 November 2022, Filed on Behalf of the Claimants (Gilead Sciences, Inc. and Gilead Sciences Limited)
1041	<i>Gilead Sciences, Inc. and Gilead Sciences Limited v. NuCana plc,</i> Claim No: 2021-00007, High Court of Justice, Business and Property Courts of England and Wales (UK), Intellectual Property List, Patent Courts, Second Expert Report of Professor Mathias Götte, Ph.D., 6 December 2022, Filed on Behalf of the Claimants (Gilead Sciences, Inc. and Gilead Sciences Limited)
1042	Perkins, E. S., et al., “Anti-viral Activities of Several Iodinated Pyrimidine Deoxyribonucleosides.” <i>Nature</i> , 194: 985-986 (1962)
1043	U.S. Publication 2005/0009737 (published January 13, 2005)
1044	U.S. Publication 2006/0199783 (published September 7, 2006)
1045	U.S. Publication 2006/0122146 (published June 8, 2006)
1046	U.S. Publication 2007/0197463 (published August 23, 2007)

I. INTRODUCTION

I, Alexander M. Klibanov, Ph.D., hereby declare as follows:

1. My name is Alexander M. Klibanov. I am the Novartis Endowed Chair Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology (“M.I.T.”), where I taught both undergraduate and graduate courses in many areas of chemistry, including general, organic, and biological, and conducted research for over 40 years. My Curriculum Vitae is attached as Attachment A to this Declaration.

2. I have been retained by Knowles Intellectual Property Strategies, LLC (counsel) on behalf of Atea Pharmaceuticals, Inc. (“Atea” or “Petitioner”) as an independent expert to provide my opinions on claim 1 of U.S. Patent No. 11,642,361 (the “’361 patent”; Ex.1001) to Jinfa Du et al., titled “Nucleoside Phosphoramidate Prodrugs”, owned by Gilead Sciences, Inc. (“Gilead,” also “Patent Owner” or “PO”).

3. I have earned numerous prestigious professional awards and honors for my research work. For example, I have been elected to the U.S. National Academy of Sciences (considered among the highest honors that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer). I am also a Founding Fellow of the American Institute for Medical and Biological

Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society, as well as the International Enzyme Engineering Prize.

4. I obtained an M.S. degree in Chemistry in 1971 and a Ph.D. in Chemical Enzymology (a branch of pharmaceutical chemistry) in 1974, both from Moscow University in Russia. Thereafter, I worked as a Research Chemist at Moscow University's Department of Chemistry for three years. After immigrating to the United States, I was a Post-Doctoral Associate in the Department of Chemistry at the University of California in San Diego from 1977 to 1979. I am a naturalized U.S. citizen.

5. From 1979 to 1988, I was an Assistant Professor, then an Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences at M.I.T. From 1988 to 2007, I was a Professor of Chemistry in the Department of Chemistry and from 2000 also a Professor of Bioengineering in the Department of Biological Engineering at M.I.T. From 2012 to 2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry at M.I.T.

6. From 2007 to 2012 and then again from 2014 to 2019, I was the Novartis Endowed Chair Professor of Chemistry and Bioengineering at M.I.T. I retired from full-time teaching and research responsibilities at M.I.T. in 2019, and am now the Novartis Endowed Chair Professor Emeritus of Chemistry and Bioengineering at M.I.T. I am also now an independent consultant in the pharmaceutical area.

7. Over the past approximately 50 years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of organic, medicinal, and biological chemistry.

8. I currently serve on the Editorial Boards of over a dozen scientific journals, including "Journal of Antivirals and Antiretrovirals", "Biocatalysis and Biotransformation", "Applied Biochemistry and Biotechnology", "Open Chemistry Journal", "Biotechnology Progress", "Biotechnology & Bioengineering", "Microbial Biotechnology", "Open Journal of Pharmacology", "Nanocarriers", "Open Access Academic Books in Chemistry", "Journal of Biological Chemistry and Molecular Pharmacology", "Archives of Natural Products and Medicinal Chemistry", "Recent Patents in Biotechnology", "Current Pharmaceutical Biotechnology", "Archives of Medical Biotechnology", and "International Journal of Drug Design, Delivery and Safety".

9. I have published over 315 scientific papers in various chemical disciplines, including medicinal, organic, and biological chemistry. I am also a named inventor on 32 issued United States patents and on a number of pending patent applications (both domestic and foreign).

10. I have given over 370 invited lectures, including many distinguished named lectureships, at professional conferences, universities, and corporations all over the world, many of them dealing with assessment and characterization of biologically active compounds. According to a recent Stanford University paper, the overall impact of my published work places me in the top 0.01% of scientists in the world.

11. In addition to my research and teaching activities at M.I.T., I have consulted widely for pharmaceutical and biotechnology companies.

12. I also have founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies, as well as of many others. A number of these entrepreneurial, consulting, advisory, and directorship activities have dealt with medicinal chemistry, discovery, development, administration, and pharmacological evaluation of therapeutic agents, as well as enzyme-substrate interactions.

13. I have substantial experience with nucleoside chemistry. For example, I consulted and acted as an expert for Emory University (Atlanta,

Georgia, U.S.A.) for a number of years in connection with Emory University's patent portfolio on the nucleoside emtricitabine ("FTC"), a leading global drug for the treatment of HIV, which was acquired by Gilead (PO in this proceeding), and is now sold in nine Gilead HIV franchise drugs: Biktarvy, Complera, Descovy, Emtriva, Genvoya, Odefsey, Stribild, Truvada, and Atripla. I understand from counsel that emtricitabine has been an enormous financial success for Gilead. I also consulted for Emory University in connection with its interests in the nucleoside lamivudine ("3TC"), now sold for the treatment of HIV by Viiv Healthcare (a joint venture of GSK and Pfizer).

14. I understand from counsel that Atea is challenging claim 1 of the '361 patent as Petitioner in a Post-Grant Review ("PGR") proceeding at the Patent Trial and Appeal Board ("PTAB" or "Board") and that it is asking the PTAB to cancel claim 1 of the '361 patent on the grounds of violation of 35 U.S.C. §112(a) and 35 U.S.C. §102. These patent laws have been explained to me by counsel, as discussed in Section IX below.

15. I provide this Declaration based on my personal knowledge, as well as my expert academic and industrial experience in the area of pharmaceutical drug discovery and development, including with nucleosides and nucleotides in particular.

16. I am being compensated for my time spent working on this matter at my customary consulting rate of \$1100 per hour. My compensation does not depend on my opinions, conclusions, or the outcome of this proceeding. I am over 21 years old and believe to be competent to provide this Declaration.

II. SCOPE OF WORK

17. I have been asked by counsel in my capacity as an independent expert to provide a technology tutorial for the Board in the field of pharmaceutical nucleotides and their use to treat viral diseases, in particular of hepatitis C, which I do in Section V below.

18. I have also been asked to form and provide my opinions on certain topics related to the '361 patent (Ex.1001), including:

(i) How a person of ordinary skill in the art ("POSA") should be defined in regard to claim 1 of the '361 patent;

(ii) How a POSA would interpret claim 1 of the '361 patent;

(iii) Whether the written description in the specification of the '361 patent indicates to a POSA that PO had possession of the full scope of the subject matter in claim 1 as of its filing date or its asserted priority dates;

(iv) Whether claim 1 of the '361 patent is technically inconsistent with litigation positions previously taken by PO in its submissions in IPR 2017-01712 (Gilead Sciences v. Regents of the Univ. of Minn.; Exs.1022 and

1023), which positions were agreed with by the PTAB in a Final Written Decision (Ex.1024) and subsequently affirmed by the U.S. Court of Appeals for the Federal Circuit (“Federal Circuit;” Ex.1026);

(v) Whether claim 1 of the ’361 patent is enabled across its full scope and, in particular, whether a POSA would be able to synthesize the compounds within the full scope of the claim;

(vi) Whether statements made by PO during a previous opposition proceeding against another party addressing similar subject matter at the European Patent Office (“EPO”) and concurrent litigation in the United Kingdom (Exs.1030, 1031, 1032, and 1037-1041) are technically inconsistent with a representation by PO that a POSA can synthesize the range of compounds within the full scope of claim 1 of the ’361 patent;

(vii) Whether PO provided sufficient confirmatory pharmaceutical efficacy and/or toxicity data for the compounds of claim 1 of the ’361 patent, as of the relevant filing date and priority dates;

(viii) Whether certain statements made by PO during the previous Opposition proceeding at the EPO and concurrent litigation in the United Kingdom (Exs.1030, 1031, 1032, and 1037-1041) are technically inconsistent with a representation that the range of compounds that fall within the scope of claim 1 of

the '361 patent would be therapeutically active against hepatitis C virus ("HCV") in a host;

(ix) What, if any, teachings and data provided by U.S. Publication 2016/0257706 (the Atea "'706 U.S. Publication") (Ex.1020) are relevant to claim 1 of the '361 patent; and

(x) Whether the '706 U.S. Publication would be considered an anticipatory disclosure of species that fall within the scope of claim 1 of the '361 patent if the latter patent is not entitled to its asserted priority filing dates.

III. SUMMARY OF MY EXPERT OPINIONS

19. Based on my extensive pharmaceutical chemistry experience, including in pharmaceutical drug discovery and nucleosides, my decades-long interactions with POSAs during my professional career, and my review of the '361 patent and other documents referenced throughout this Declaration, below I summarize my opinions as follows:

- (i) My definition of a POSA is provided in Section IV below.
- (ii) A POSA would interpret claim 1 of the '361 patent based on the plain and ordinary meanings of the chemical terms and structures used in the claim and the definitions provided by PO in the patent specification.
- (iii) My review of the '361 patent indicates that the written description provided in the '361 patent specification of claim 1 is insufficient in that PO

failed to show possession of the full scope of the subject matter of the claim as of its filing date or its asserted priority dates, as described in detail in Section VI below, at least because of the following:

- (a) While the '361 patent presented an enormous “Supergen” of different compounds, it never presented either the subgenus of claim 1 or any subgenus of compounds with a N⁶(H)(C₁₋₆ alkyl),N²-aminopurine nucleotide phosphoramidate within the patent specification, until the amendment of March 19, 2021, as further amended November 15, 2022.
- (b) The subgenus referred to by PO during prosecution that has the closest resemblance to the '361 patent claim 1's scope (the “fourteenth aspect of the third embodiment;” col. 37, lines 46-47, of the '361 patent) includes a “proviso[.]” (see (e), col. 37, lines 61-62) that is defective and renders the specification subgenus indefinite and confusing, as described in Section VI.B below. In fact, the proviso in the fourteenth aspect of the third embodiment was altered/corrected by PO during patent prosecution, which suggests that PO knew there was a problem with the proviso and tried to fix it. However, the supposed “fix” led to a written description problem for claim 1 because the patent specification disclosure does not match the issued claim language. The presence of the defective proviso in the relevant aspects and embodiments results in the situation that none of

them adequately describes the subgenus in claim 1 of the '361 patent (see Table 1 below).

(c) Even if the defective proviso of the fourteenth aspect of the third embodiment is ignored and one assumes (incorrectly in my opinion) that the fourteenth aspect of the third embodiment provides adequate support for claim 1, a different problem arises. The combination of variables recited in claim 1 of the '361 patent would have to be selected from as many as over 10^{27} possible combinations described in the fourteenth aspect of the third embodiment of Formula I-6 (ignoring the technical defect), as described below in Section VI.C below. The selected claimed combination is thus much narrower than the closest subgenus in the '361 patent with no guidance in the patent specification on how to get there (in fact, there are many “don’t go in this direction” signs). Despite its more limited scope, claim 1 still covers over 15 billion different compounds, of which only one compound was reported as actually synthesized by PO and none was reported as tested for either biological activity or toxicity.

(d) The subgenus of claim 1 appears to be a cobbled-together selection from multiple separate lists for which there is no motivation for a POSA to combine; in fact, the patent specification “teaches away”

because the guidance in the '361 patent pointed away from the claimed subgenus.

(e) The '361 patent includes as many as 524 columns of tables with 12,400 specific compounds listed therein (cols. 54-579) provided as teaching embodiments by PO; but none of them is drawn to the subgenus of claim 1 or even includes a single compound that falls within the scope of the claim.

(f) The expansive definition of “purine” base in the '361 patent specification (Ex.1001, col. 11, lines 55-end, and col. 12, lines 1-14) fails to mention, and thus points a POSA away from, a N⁶-alkyl,N²-aminopurine in a nucleotide.

(g) The '361 patent specification only includes the synthesis of a single compound within the entire subgenus of claim 1, which is hardly enough to describe the totality of claim 1, or to point the POSA to the metes and bounds of the subgenus.

(h) The '361 patent specification includes no efficacy or toxicity data for any of the compounds falling within the scope of claim 1 (even though the specification includes efficacy data for other compounds), which indicates a lack of guidance pointing a POSA to the issued claim 1 subgenus and, in fact, points a POSA away from claim 1.

- (i) Claim 1 of the '361 patent is technically inconsistent with, and indeed contradictory to, litigation positions taken by PO in its prior IPR 2017-01712 (Gilead Sciences v. Regents of the Univ. of Minn.; Exs.1022 and 1023) submissions, which positions were agreed with by the PTAB in a Final Written Decision (Ex.1024) and subsequently affirmed by the Federal Circuit (Ex.1026).
- (iv) Claim 1 of the '361 patent is not enabled across its full scope for at least the following reasons, as described in more detail in Section VI.E below:
 - (a) PO provided no efficacy and/or toxicity data for any of the compounds of claim 1 of the '361 patent.
 - (b) Certain 2'-combinations within the scope of the subgenus of claim 1 are unstable and cannot be made as pharmaceutical agents according to statements made by PO during a very similar Opposition proceeding at the Opposition Division and to the Technical Boards of Appeal at the EPO (see Section VI.F below).
 - (c) Statements made by PO during the Opposition proceeding at the EPO contradict PO's representation that the range of compounds falling within the scope of claim 1 of the '361 patent would be therapeutically active against HCV in a host (see Section VI.G below).

(v) Further, as described in detail herein, because the '361 patent claim 1 is not entitled to any priority date earlier than the date it presented claim 1 (November 15, 2022, amending its March 19, 2021, amendment), the claims are also invalid as anticipated under 35 U.S.C. §102 over intervening U.S. Publication 2016/0257706 (Ex.1020); published September 8, 2016; issued as U.S. Patent No. 9,828,410 (Ex.1021)); which claims priority to U.S.S.N. 62/129,319 (Ex.1016); filed March 6, 2015), U.S.S.N. 62/253,958 (Ex.1017), filed November 11, 2015) and U.S.S.N. 62/276,597 (Ex.1018, filed January 8, 2016)). In fact, U.S. Publication 2016/0257706 (Ex.1020) does something that the '361 patent fails to do—it actually draws, makes, and tests species encompassed by the '361 patent claim 1, including Petitioner's bemnifosbuvir currently in Phase 3 human clinical trials.

IV. A PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

20. Since I am neither a lawyer nor a patent expert, the legal principles used in this opinion have been explained to me by counsel (see Section IX below). I have considered the definition of a person of ordinary skill in the art (“POSA”) provided in paragraph 21 below and provide my opinion on the level of skill a POSA in paragraph 22 below. For the remaining relevant legal standards, a summary of information explained to me by counsel is provided in Section IX at the end of this Declaration.

21. Patent validity issues addressed in this Declaration should be evaluated from the perspective of a “POSA”. The ’361 patent is in the field of drug discovery generally and specifically antiviral nucleotide phosphoramidates. A POSA is a hypothetical person presumed to use conventional wisdom in the art and to have knowledge of all related publicly available material references to the claimed invention as of its priority date. A POSA shows ordinary creativity in the application of the relevant scientific principles in the field as of the time of the invention, but (s)he is not expected to be an innovator.

22. As claim 1 of the ’361 patent is a composition-of-matter claim covering a subgenus of antiviral pharmaceutical compounds (selected purine nucleotide phosphoramidates), in my opinion, a POSA would be a person with (a) a Ph.D. in organic chemistry, medicinal chemistry, or a closely related discipline in the pharmaceutical area that includes drug discovery experience, or (b) an M.S. degree in organic chemistry, medicinal chemistry, or a closely related discipline in the pharmaceutical area with three or more years of drug discovery experience (some of which could be during his/her postgraduate work). Since the subject matter

of the '361 patent is directed to compounds for the treatment of viral diseases, a POSA would normally be able to interpret relevant biological testing and its results.¹

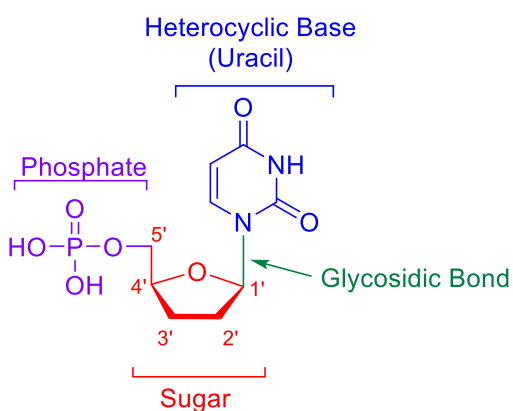
V. TECHNOLOGY TUTORIAL

23. The following technology tutorial on nucleosides, nucleotides, and derivatized nucleotide phosphoramidates is provided for the convenience and ready reference of the Board.

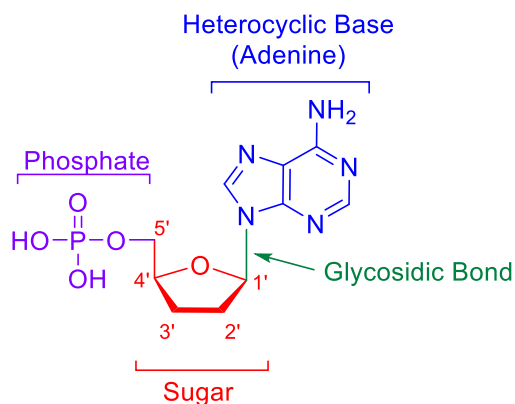
24. A nucleoside has a nitrogenous pyrimidine (monocyclic) or purine (bicyclic) base covalently bound to a five-carbon sugar (pentose) through a

¹ In its IPR 2017-01712 Petition (Ex.1022, 26-27), PO defined a POSA as follows: “A POSA 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 or master’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.” I have considered this POSA definition, and none of my conclusions contained in this declaration changes when I use it instead of that in paragraph 22 above.

glycosidic linkage. A nucleoside becomes a nucleotide if the 5'-hydroxyl group on the sugar has a substituent other than hydrogen (such as a phosphate). Nucleotides found in the body typically have a 5'-mono-, di-, or tri- phosphate. The activated form of a nucleotide is the triphosphate, which is used to make DNA and RNA *in vivo*. Below are annotated examples of a pyrimidine nucleotide and a purine nucleotide:



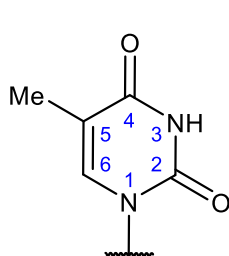
Pyrimidine Nucleotide



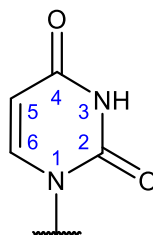
Purine Nucleotide

25. Nucleotides are building blocks for DNA and RNA and also have other important functions in the body. DNA features a 2'-deoxyribose sugar, and RNA has a ribose sugar.

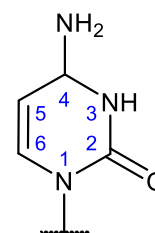
26. Pyrimidine bases in naturally occurring² nucleosides and nucleotides include the following:



Thymine

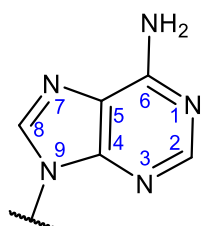


Uracil

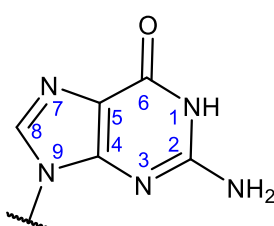


Cytosine

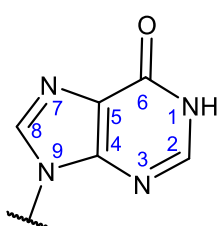
27. Naturally occurring purines include the following:



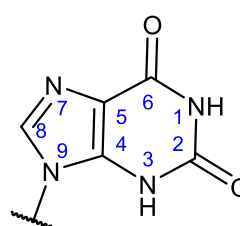
Adenine



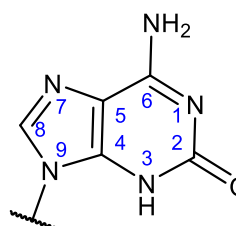
Guanine



Hypoxanthine

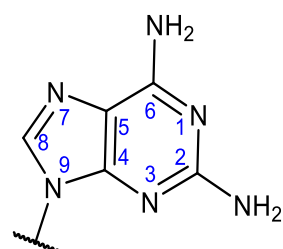


Xanthine

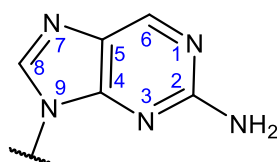


Isoguanine

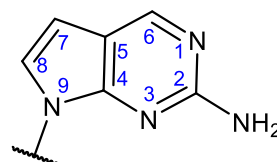
28. Non-naturally occurring purines include the following:



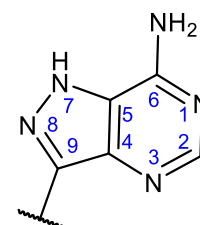
2,6-diaminopurine



2-aminopurine



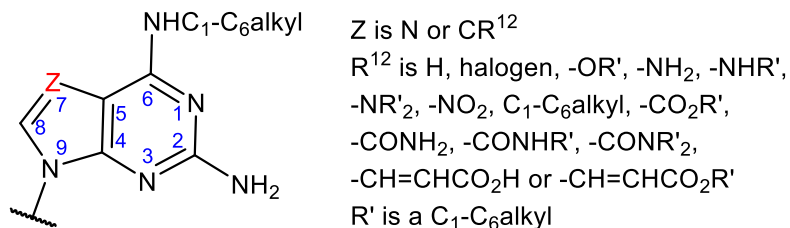
2-amino-7-deazapurine



Formycin

² The term “naturally occurring”, as used herein, refers to occurring in humans.

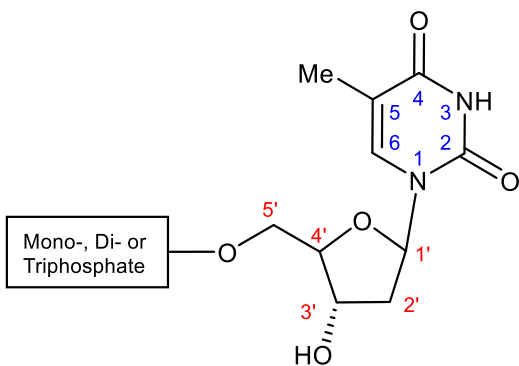
29. The purine base in the nucleotide phosphoramidate of claim 1 of the '361 patent is:



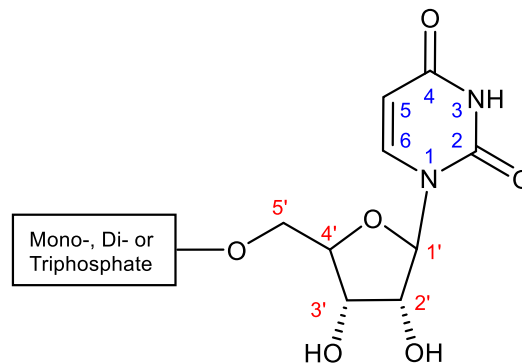
Purine of Claim 1

The '361 purine base is non-naturally occurring because it has amino substituents in both the 6-position and the 2-position of the nitrogenous base. In certain embodiments, the purine can also be a “deazapurine,” which is missing a nitrogen in the 7-position of the base and instead has a CR¹², wherein the R¹² itself can be selected from over 4,800 distinct chemical moieties.

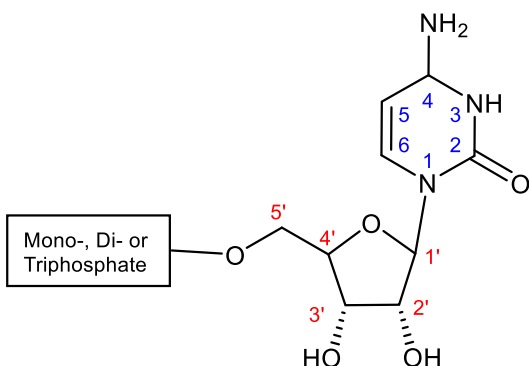
30. The numbering system for nucleo(s/t)ides assigns atoms in the nitrogenous base with integers (e.g., 1, 2, 3) and in the sugar with integers prime (e.g., 1', 2', 3'). Examples of naturally-occurring nucleotides include the following structures:



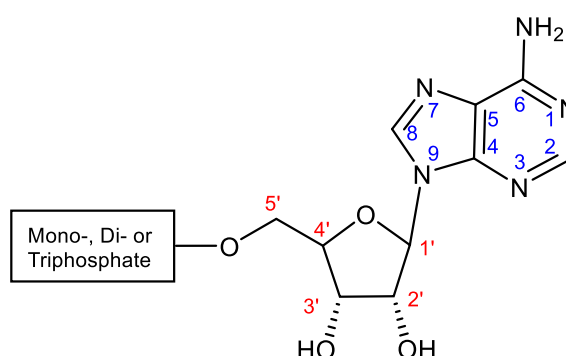
**Thymidine
(DNA Only)**



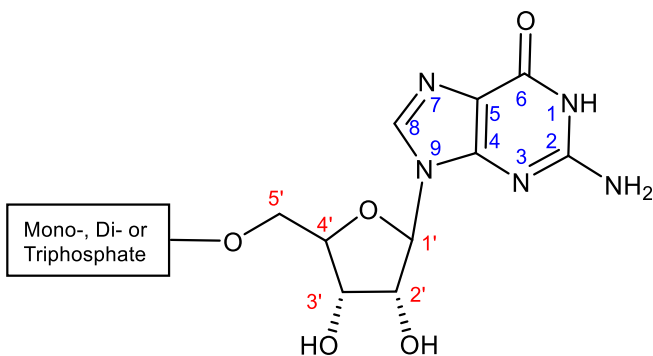
**Uridine
(RNA Only)**



**Cytidine
(RNA Only)**



**Adenosine
(RNA Only)**



**Guanosine
(RNA Only)**

These nucleotides are “DNA only” when missing a 2’-hydroxyl group and “RNA only” when having a 2’-hydroxyl group.

31. Because nucleotides are the building blocks of DNA and RNA used for cellular replication by all organisms, they have long served as the starting

point for drug discovery research. A particularly fertile ground in this regard has been anti-viral research. Derivatized nucleosides and nucleotides have been used, for example, to treat HIV and hepatitis B, and also were the subject of hepatitis C research in the 1980's and 1990's, leading to commercial anti-HCV products in the 2010's (e.g., sofosbuvir in 2013).

32. Antiviral therapeutic nucleotides work by interfering with viral enzymes. Viral polymerase enzymes synthesize long chains of nucleic acids (DNA or RNA, depending on the virus) from nucleotide building blocks. In the case of HCV, the relevant enzyme targeted by derivatized nucleotides is an RNA-dependent RNA polymerase (RdRp), which is also referred to as the HCV NS5B enzyme. In the case of HIV, the viral polymerase is a reverse transcriptase. In the case of HBV, the viral polymerase is a DNA polymerase (which has both RNA- and DNA-dependent functions). In the case of the SARS-CoV-2 virus (causing the human disease COVID-19), the relevant polymerase is also a RNA-dependent RNA polymerase, but it is different from the HCV enzyme and is referred to as the SARS-CoV-2 nsp12 enzyme.

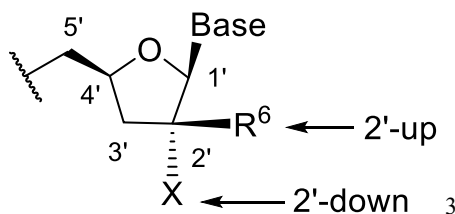
33. Drug discovery efforts to identify derivatized nucleosides/nucleotides for combating a virus, such as HCV, have focused on finding nucleosides or nucleotides that are recognized by the relevant polymerase enzyme and can lead to disruption or termination of viral replication. For

recognition by a polymerase, the nucleotide is typically presented to the enzyme in the activated triphosphate form. This fact implicates the importance of a first activating enzyme—a monophosphate kinase that adds one phosphate group to the 5'-hydroxy group of a nucleoside. Another enzyme adds the second phosphate to create the 5'-diphosphate nucleotide, and a third enzyme adds the third phosphate to complete the formation of the activated nucleotide triphosphate. It is only after these three steps have taken place that the derivatized nucleotide can typically be acted upon by the polymerase enzyme.

34. A critical requirement for drug discovery in the antiviral area, therefore, has been the phosphate pre-activation steps. The nucleoside must possess the correct chemical structure to be able to be activated to the triphosphate form by the relevant available kinase enzymes.

35. This requirement presented a particular challenge for potential anti-hepatitis C nucleosides. In the 1990's and early 2000's, pharmaceutical companies and academic laboratories embarked on extensive research programs to identify the correct nucleoside structure that would act as an inhibitor of the HCV RNA-dependent RNA polymerase. There were many false starts and failures along the way. In general, previously discovered and successfully commercialized nucleosides active against HIV and HBV were not active against HCV.

36. The HCV “code” was ultimately cracked by two researchers, Dr. Jean-Pierre Sommadossi, now the chief executive officer of Atea Pharmaceuticals, Inc. (Petitioner) and Dr. Paulo LaColla of the University of Cagliari (Italy), who discovered that the HCV RdRp enzyme is inhibited by a nucleoside that has a methyl (Me, i.e., CH₃) group in the 2'-up-position of the nucleoside (see graphic demonstrating “2'-up” vs. “2'-down” below). This was an important discovery because none of the derivatized nucleosides active to treat HIV or HBV had a methyl group in the 2'-up-position. In fact, researchers at the time were focusing neither specifically on this position of the nucleoside nor specifically on this methyl substituent. The breakthrough by Drs. Sommadossi and LaColla taught other scientists where to look and led to a flurry of subsequent research in that direction.

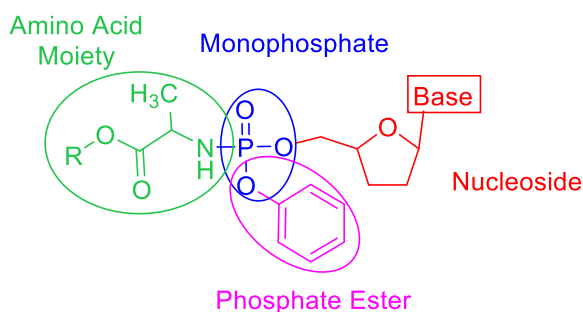


37. Once the subsequent drug discovery research was carried out on 2'-methyl nucleosides, however, another problem arose. While the synthetic 2'-

³ As defined in claim 1 of the '361 patent, the R⁶ substituent corresponds to 2'-up and the X substituent corresponds to 2'-down.

methyl nucleosides could inhibit the HCV RdRp enzyme, they were poor substrates for the preactivating kinase enzymes, in particular for the monophosphate kinase that adds the first phosphate group to the 5'-position of the nucleoside. Therefore, a solution was sought for that problem.

38. This research led to the groundbreaking work of Prof. Christopher McGuigan from the University of Cardiff in the U.K., who had pioneered and for years carried out drug discovery studies on prodrugs of nucleosides that are able to circumvent the monokinase activation step by metabolizing directly to a 5'-phosphate. In the late 1980s, Prof. McGuigan discovered a way of masking the nucleotide 5'-monophosphate using the 5'-phosphoramidate prodrug approach (see below):



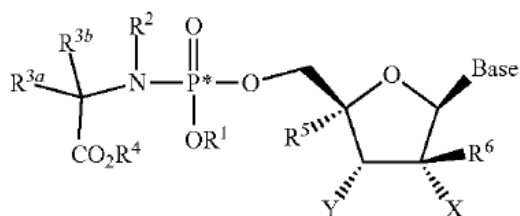
This advance allowed for administration of a membrane-soluble nucleotide prodrug that could be rapidly hydrolyzed in the human cell to the active nucleotide 5'-monophosphate. An additional benefit of this strategy is that, after hydrolysis to the 5'-monophosphate, the active nucleotide 5'-monophosphate formed, being electrostatically charged, is trapped within the cell.

39. The '361 patent, with its provisional applications reaching back to 2007, follows the groundbreaking work of Drs. Sommadossi and LaColla to discover the key 2'-up-methyl structure that inhibits the HCV RNA-dependent RNA polymerase, additional work by Jeremy Clark at Pharmasset focusing on the 2'-methyl,2'-fluoro motif (U.S. Patent No. 7,429,572; Ex.1028), and Prof. McGuigan's ProTide prodrug strategies.

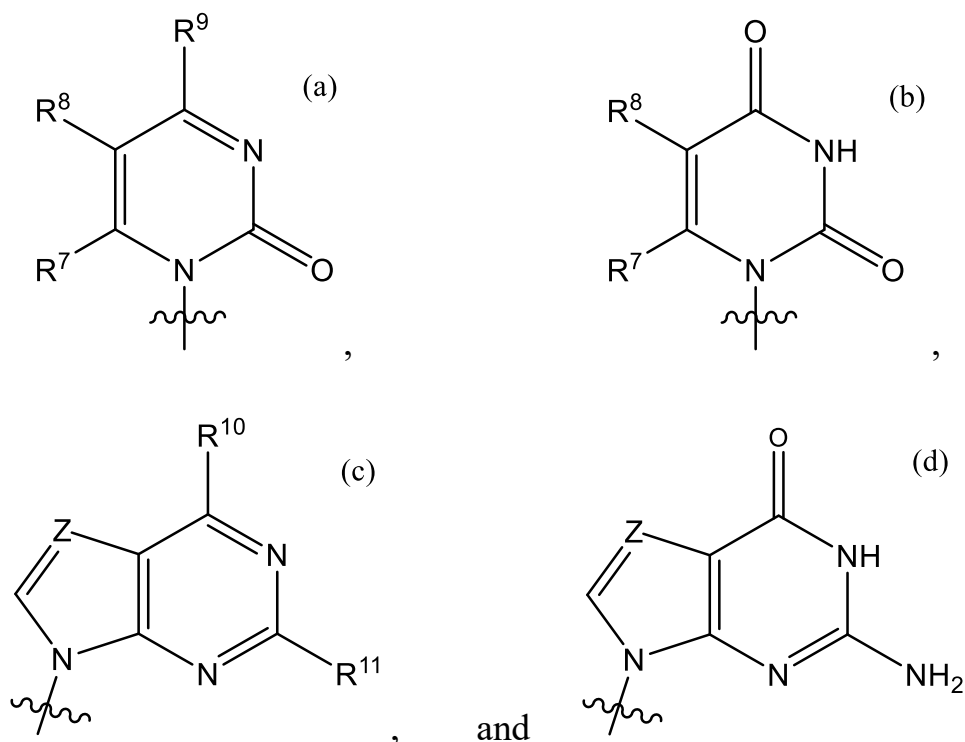
VI. SUMMARY OF THE '361 PATENT AND VIOLATION OF 35 U.S.C. § 112

40. The '361 patent "pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases" (Ex.1001, col. 1, lines 39-47). These compounds are inhibitors of RNA-dependent RNA viral replication and are purported to be useful as inhibitors of HCV.

41. The Summary of the Invention in the '361 patent presents an enormously broad chemical formula that seeks to cover an almost incalculable number of nucleotide phosphoramidates (*id.*, col. 5, lines 25-38), with variables at every possible position, and wherein each variable itself covers a huge scope of layered substituent possibilities (referred to below as the "'361 Supergenus"):



42. The term nitrogenous “base” in the ’361 patent is defined as “a naturally occurring or modified purine or pyrimidine base” represented by the following four structures (*id.*, col. 13, lines 66-end, and col. 14, lines 1-36):



Purine base (c) above is the only one that is relevant to claim 1 of the ’361 patent.

43. While the presented structure of purine (c) is very broad, it should be read in the context of the direction given to a POSA by the actual definition of purine in the ’361 patent specification, which is stated to “include[], but [] not [be] limited to,” a broad list of various purines (Ex.1001, col. 11, lines 55-end, and col. 12, lines 1-15). The purines listed are (removing the interspersed pyrimidines): adenine, N⁶-alkylpurines, N⁶-acylpurines, N⁶-benzylpurine, N⁶-halopurine, N⁶-vinylpurine, N⁶-acetylenic purine, N⁶-acyl purine, N⁶-

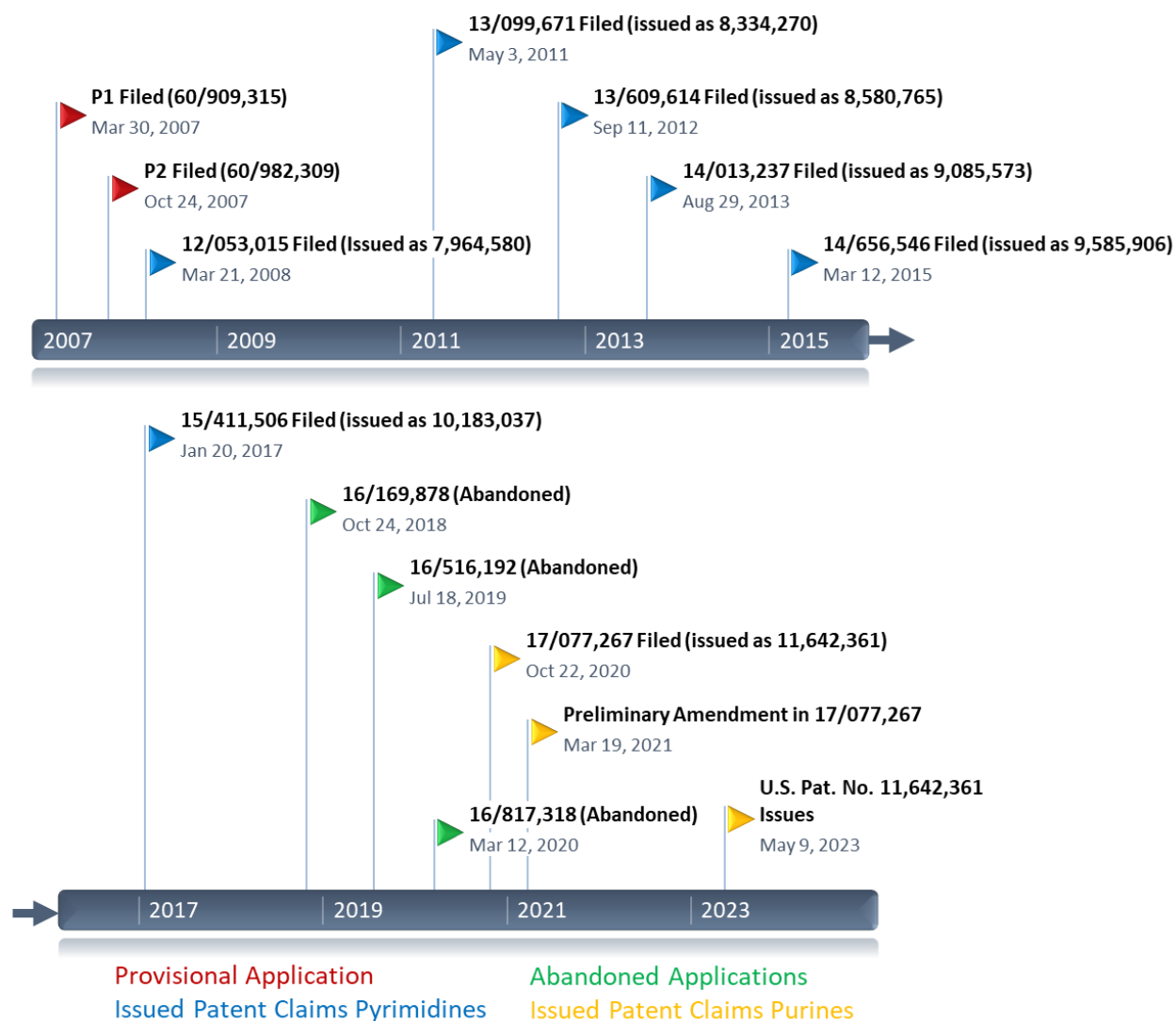
hydroxyalkylpurine, N⁶-allylaminopurine [*sic*], N⁶-thioallyl [*sic*] purine, N²-alkylpurines, N²-alkyl-6-thiopurines, C⁵-hydroxyalkylpurine, N²-alkylpurines, N²-alkyl-6-thiopurines, guanine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine.

44. Notably, the express definition of a “purine” in the ’361 patent specification (i) distinguishes between the N⁶ and N² purine substituents and (ii) *does not mention N⁶-alkyl, N²-aminopurines at all* (which is the formula of the purine base in claim 1 of the ’361 patent) (*id.*). It hence would be logical for a POSA to assume that if PO had specifically envisioned a class of N⁶-alkyl, N²-aminopurines, as presented in claim 1 of the ’361 patent as of the filing date, then PO would have expressly listed N⁶-alkyl, N²-aminopurines in the definition of “purine[s].” This is but one of many “blaze marks” (or “trail markers”) that point a POSA away from the subgenus of compounds presented by claim 1 of the ’361 patent.

A. File History of the ’361 Patent

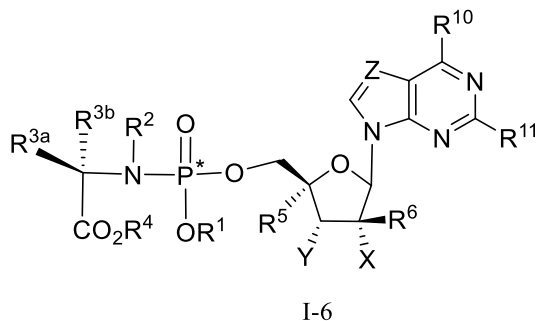
45. I have been advised by counsel of the following file history details of the ’361 patent. PO filed U.S. Pat. App. No. 17,077,267 (the “’267 app”, Ex.1014) on Oct. 22, 2020, as a continuation application of U.S. Pat. App. No. 16/817,318 (Ex.1013), with additional priority claims through seven previously filed applications (Exs.1006-1012) back to U.S. Pat. App. No. 12/053,015 (the

“’015 app”, Ex.1005) filed on Mar. 21, 2008, and provisional applications U.S. Prov. App. No. 60/909,315 (Ex.1003), filed on Mar. 30, 2007, and U.S. Prov. App. No. 60/982,309 (Ex.1004), filed on Oct. 24, 2007. The ’267 app was filed on behalf of Gilead Pharmasset LLC and named Jinfa Du, Dhanapalan Nagarathnam, Michael Joseph Sofia, and Peiyuan Wang as inventors (Ex.1002, 93). The ’267 app was filed with the same claim set as originally filed in the early ’015 app. Because all of the continuation priority documents (Exs.1005-1013) contain the same specification disclosure as the ’361 patent, I focus on the ’361 patent specification and provide a timeline for Board’s convenience below.

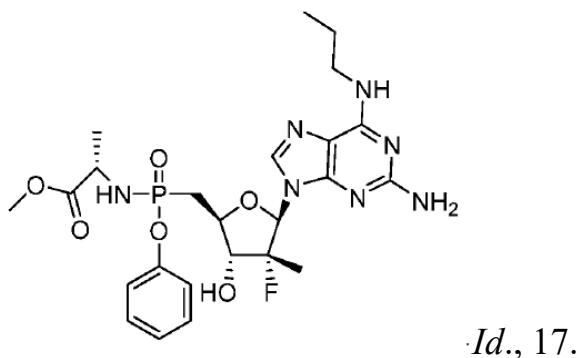


46. In response to a Notice to File Missing Parts, on March 19, 2021, PO filed a Preliminary Amendment amending the claims (Ex.1002, 84-92). The amended claims canceled previously filed claims 1-12, replacing them with new claims 13-19, specifically citing pp. 19, 51, 61, and 67-68 (which includes “the fourteenth aspect of the third embodiment” discussed further below) and Examples 67-80 (syntheses of certain 2'-methyl,2'-fluoro nucleotide phosphoramidates) for

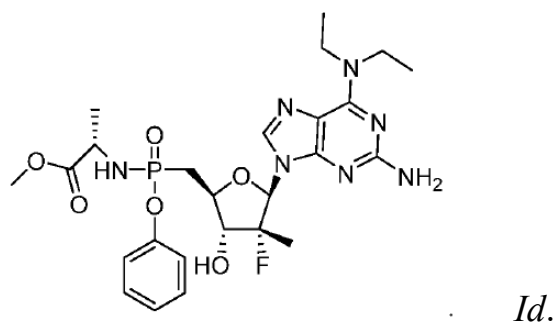
support (*id.*, 91). Claim 13 was a compound claim to a subgenus purportedly of formula I-6:



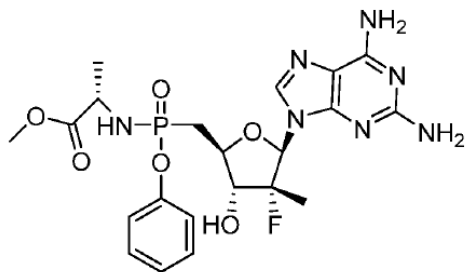
or a pharmaceutically acceptable salt thereof (*id.*, 87-88). Claims 14-16 further narrowed the broad subgenus (*id.*, 88-89). Claim 17 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



Claim 18 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



Claim 19 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



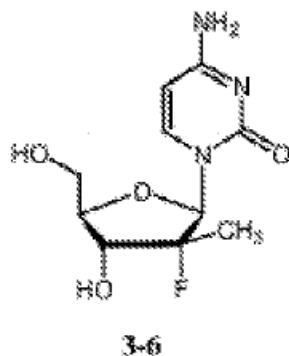
Id., 89-90.

47. On Apr. 19, 2021, PO filed an information disclosure statement (“IDS”) (*Id.*, 97-155). During prosecution of the ’361 patent, PO failed to provide the USPTO with Exs.1020-1028 and 1030-1042.

48. On Apr. 12, 2022, a Non-Final Office Action was mailed rejecting claims 13-19 under 35 U.S.C. §103 (*id.*, 156-166). Claims 13-16 were rejected as unpatentable over Gilead’s (formerly Pharmasset’s) Clark WO 2005/003147 (“Clark”) and Perrone et al., J. Med. Chem. (2007) Vol. 50, pp. 1840-1849 (“Perrone”) (from the McGuigan laboratory) in combination (*id.*, 160). The USPTO Examiner did not raise any rejections under 35 U.S.C. §112.

49. On July 12, 2022, PO filed a Response to the outstanding Non-Final Office Action (*id.*, 232-237). PO made no amendments to subgenus claims 13-16 and amended claims 17-19 to correct a technical defect. With respect to the obviousness rejection, PO urged the USPTO Examiner to follow the “lead

compound analysis,” whereby a *prima facie* case of obviousness could not be made (*id.*, 239). PO argued that if a POSA would choose a compound from Clark, it would be 2'-deoxy-2'-fluoro-2'-C-methylcytidine (shown below) as a lead compound for further modification based on the biological data provided in Tables 1-5 of Example 5 in Clark:



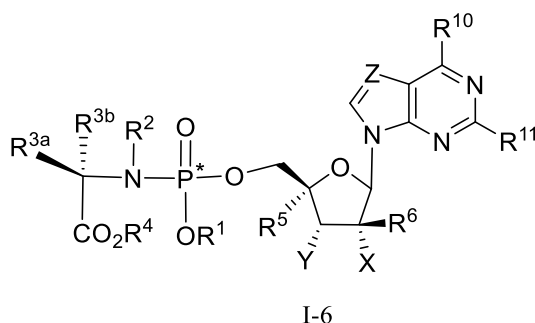
Id., 243-244.

Furthermore, PO argued that Perrone fails to cure the deficiencies of Clark because Perrone only teaches protide approaches for 4'-azido-uridine, which Perrone notes was inactive as an inhibitor of HCV replication (*id.*).

50. On September 22, 2022, the USPTO Examiner issued a Final Office Action, maintaining the previous rejection of subgenus claims 13-15 and species claim 19 as obvious in light of Clark and Perrone (*id.*, 248-256). The Examiner withdrew the rejection of claim 16 because “the combination of Clark and Perrone does not reasonably teach or suggest a compound wherein: (a) R⁴ is -CH₃, ethyl, n-propyl or i-propyl; (b) R¹⁰ is -NHR' and R¹¹ is -NH₂; and (c) R' is

C₁₋₆ alkyl” (*id.*, 250-251). The Examiner again did not raise any rejections under 35 U.S.C. §112.

51. On November 15, 2022, PO filed an Amendment After Final Action, amending subgenus claim 13 and canceling claims 14-16 (*id.*, 269-274). Claim 13 was amended to incorporate the previous limitations of claim 16, as shown below:



wherein:

- a) R¹ is H, -CH₃, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;
- b) R² is H;
- c) R^{3a} is H and R^{3b} is H, -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH₂Ph or lower cycloalkyl;
- d) R⁴ is ~~hydrogen~~, -CH₃, ethyl, *n*-propyl, *i*-propyl, ~~*n*-butyl, 2-butyl, *t*-butyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl or di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl~~;

- e) R^5 is H;
- f) R^6 is H, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$ or $-F$;
- g) X is H, $-OH$, $-OCH_3$, $-F$, $-NH_2$ or $-N_3$;

with the proviso that X cannot be OH when R^6 is $-CH_3$ or $-CH_2F$;

- h) Y is $-OH$, $-NH_2$, $-OCH_3$ or $-OC(O)CH_3$;
- i) R^{10} is $-NHR'$ and R^{11} is $-NH_2$; ~~R^{10} and R^{11} are independently H, F, Br, I, $-OH$, $-OR'$, $-NH_2$, $-NHR'$, $-NR'_2$, $-CO_2R'$, $-CONH_2$, $-CONHR'$, $-CONR'_2$, $-CH=CHCO_2H$ or $-CH=CHCO_2R'$,~~

~~with the proviso that when R^{10} is $-OH$, R^{11} is not $-NH_2$;~~

- j) Z is N or $-CR^{12}$;

wherein R^{12} is H, halogen, $-OR'$, $-NH_2$, $-NHR'$, $-NR'_2$, $-NO_2$, C_{1-6} alkyl, $-CO_2R'$, $-CONH_2$, $-CONHR'$, $-CONR'_2$, $-CH=CHCO_2H$ or $-CH=CHCO_2R'$;

- k) R' is C_{1-6} alkyl, ~~a lower cycloalkyl or $C(O)(C_{1-6}$ alkyl) or alternatively, in the instance of $-NR'_2$, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and~~

- l) P^* is a chiral phosphorus atom;

or a pharmaceutically acceptable salt thereof (*id.*, 270-271).

These amendments to claim 13 removed the '361 patent compounds 68-71 and 73-80 from the scope of the claim. PO also amended claim 17 to depend from claim 13

and amended claim 18 to make it independent, as the formula of amended claim 13 no longer encompassed the species of claim 18 (*id.*, 271-272).

52. On December 7, 2022, the USPTO issued a Notice of Allowance (*id.*, 283). On December 22, 2022, PO filed a Request to Change the Applicant from Gilead Pharmasset LLC to Gilead Sciences, Inc. (*id.*, 317).

53. On May 9, 2023, the '267 application issued as U.S. Pat. No. 11,642,361 (Ex.1001).

B. Analysis of Embodiments and Aspects of the Invention

54. The '361 patent specification attempts to provide guidance on genres and subgenres of the '361 Supergenous through a complex maze of “embodiments” and “aspects” using some 42 columns of text (Ex.1001, cols. 12-54). Tellingly, ***none*** of these embodiments or aspects directly, or even indirectly, leads a POSA to the claim 1 subgenous of the '361 patent. These embodiments and aspects are set out in Table 2 below.

55. Claim 1 of the '361 patent includes a negative limitation that states (Ex.1001, col. 619, lines 25-27; emphasis added):

“X is H, -OH, -OCH₃, -F, -NH₂ or -N₃; ***with the proviso that X cannot be OH when R⁶ is -CH₃ or -CH₂F;***”

56. PO first presented amended claims which included this proviso in a Second Preliminary Amendment dated March 19, 2021, wherein it indicated

that support for amended claim 1 generally is found on pp. 19, 51, 67-68, and Examples 67-80 of the submitted application (Ex.1002, 91). Pp. 67-68 of the application correspond to “the fourteenth aspect of the third embodiment” in the ’361 patent specification, which is also found in col. 37, lines 46-end, to col. 38, lines 1-10, of the issued patent (Ex.1001).⁴

57. However, a careful review of the fourteenth aspect of the third embodiment shows that this proviso added by claim amendment in March of 2021 is not found in the exact language in the referenced sections of (or anywhere else in) the application. Instead, the fourteenth aspect of the third embodiment states:⁵

⁴ In its Response to the first Office Action of April 12, 2022, PO indicated that support for the claims is also found on pages 671-672 of the submitted application (Ex.1002, 91), which include the only one compound made that falls within the claims.

⁵ The fourteenth aspect of the third embodiment of the ’361 patent also states: “ R^{10} and R^{11} are independently H, F, Br, I, OH, OR’, NH_2 , NHR' , NR'_2 , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$, with the proviso that ***when R^{10} is OH and R^{11} is not NH_2*** ,” (Ex.1001, col. 37, lines 66-67, and col. 38, lines 1-2; emphasis added), which is nonsensical because the proviso abruptly stops without completing the clause.

“R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H;” (Ex.1001, col. 37, lines 61-62).

58. The actual proviso in the fourteenth aspect of the third embodiment as set out in the specification and which focuses on R⁵ is indefinite, not to mention vague, because it is amenable to at least the following three distinct interpretations by a POSA:

1. **Interpretation 1**: “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” — must be interpreted exactly as written without modification. This statement says what R⁵ is not, but not what it is, under the set condition. What is R⁵ then when X is OH and R⁶ is CH₃ or CH₂F? A POSA might conclude that R⁵ then reverts to the full definition of substituents of R⁵ in the formula (minus H), which are “lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., (CH₂)_pOH, where p is 1-6, including hydroxyl methyl (CH₂OH), CH₂F, N₃, CH₂CN, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I” (the way R⁵ is defined in Formula I-6 (Ex.1001, col. 35, lines 32-36)) or even at a minimum “CN, CH₂F, F, Cl, Br, or I” (the way R⁵ is defined in the twelfth aspect of the third embodiment (Ex.1001, col. 36, lines 64-65)). Or a POSA might conclude that there is simply not enough information to complete the proviso and thus (s)he

would not know what R⁵ substituents were intended to be in this situation, making it hopelessly vague. I understand from counsel that legally it is not the POSA's responsibility to complete an incomplete clause on behalf of the inventors.

2. **Interpretation 2:** Alternatively, "R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H" can be interpreted to mean that "X cannot be OH, and R⁶ cannot be CH₃ or CH₂F" because R⁵ is defined as hydrogen. However, this is not how the proviso is actually worded in the '361 patent. Rather, it is worded as an exclusion of R⁵ substituents, not an exclusion of X and R⁶ substituents (...R⁵ cannot be H...). Again, the wording is indefinite because a POSA would be confused.
3. **Interpretation 3:** Alternatively, "R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H" can be interpreted to mean that "compounds where X is OH and R⁶ is CH₃ or CH₂F" are excluded from the claim because R⁵ is defined as hydrogen. However, again, this is not how the proviso is actually worded. Rather, it is worded as an exclusion of R⁵ substituents, not an exclusion of X and R⁶ substituents (...R⁵ cannot be H...). Again, the wording is indefinite because a POSA would be confused.

59. PO must have recognized the indefiniteness problem here because it took the affirmative step to re-word the proviso in amended claim 1 (Ex.1002, 86-87). In doing so, PO converted an R⁵ proviso to become an X proviso:

“X is H, -OH, -OCH₃, -F, -NH₂ or -N₃; ***with the proviso that X cannot be OH when R⁶ is -CH₃ or -CH₂F;***”

in other words, PO eliminated reference to R⁵ (Ex.1002, 87; emphasis added).

60. I see no plausible reason why PO would have taken this affirmative step if it did not realize that the patent specification was confusing and thus indefinite on this point. Otherwise, why convert an R⁵ proviso into an X proviso (and ignore the R⁵ altogether)? The likely answer is to remove ambiguity, which was, in fact, baked into the patent specification as originally drafted. Regardless of the PO's intent, however, the proviso in claim 1 of the '361 patent does not have support in the patent specification because of the conversion of a R⁵ proviso into a X proviso.

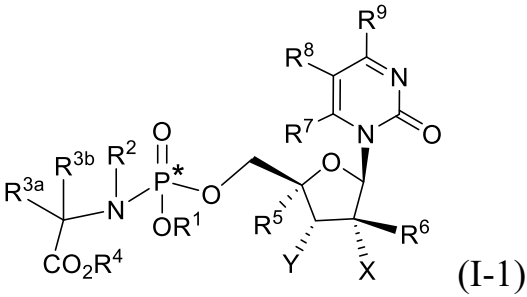
61. I am informed by counsel that the Federal Circuit recently addressed the issue of negative limitations in an issued claim. The Court confirmed that while a claimed negative limitation (or proviso using the '361 patent's language) does not have to be found in the patent specification verbatim, the specification must nevertheless reasonably convey to a POSA that the inventor had possession of the claimed subject matter as of the filing date.

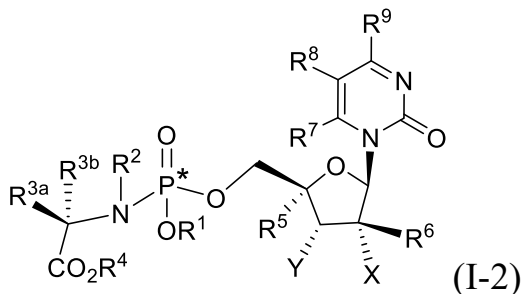
62. In the case of the '361 patent claim 1, a POSA could interpret the negative limitation in the definition of R⁵ of the fourteenth aspect of the third embodiment in at least the three aforementioned distinct ways, thus making the proviso indefinite. And PO's attempt to circumvent this indefiniteness by rewriting the proviso into an "X" proviso from an "R⁵" proviso leads to a written description problem by using language in claim 1 that is not unambiguously provided in the patent specification.

63. In Table 1 below, I list the embodiments and aspects presented in the '361 patent specification and indicate whether the subgenus of claim 1 is covered by them.

Table 1

Embodiment	Relevant to '361 patent claim 1?
An aspect of the invention is directed to a compound represented by Formula I (I) Ex.1001, col. 12, lines 37-end, through col. 15, line 18.	No, because R⁵ is a list of substituents, with the proviso that "when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H," and this proviso is not in claim 1.

	See Ex.1001 col. 13, lines 33-40.
1st embodiment: a compound of Formula I-1  (I-1) Ex.1001, col. 15, lines 19-end, to col. 16, lines 1-59.	No, because the Base is a pyrimidine.
1st aspect of the 1st embodiment: a compound of Formula I-1 Ex.1001, col. 16, lines 60-end, to col. 17, lines 1-53.	No, because the Base is a pyrimidine.
2nd aspect of the 1st embodiment: a compound of Formula I-1 Ex.1001, col. 17, lines 54-end, to col. 18, lines 1-43.	No, because the Base is a pyrimidine.
3rd aspect of the 1st embodiment: a compound of Formula I-1 Ex.1001, col. 18, lines 44-end, to col. 19, lines 1-27.	No, because the Base is a pyrimidine.
4th aspect of the 1st embodiment: a compound of Formula I-2	No, because the Base is a pyrimidine.



Ex.1001, col. 19, lines 28-end, to col. 20, lines 1-26.

5th aspect of the 1st embodiment: a compound of Formula I-2

Ex.1001, col. 20, lines 27-65.

No, because the Base is a pyrimidine.

6th aspect of the 1st embodiment: a compound of Formula I-2

Ex.1001, col. 20, lines 66-end, to col. 21, lines 1-29.

No, because the Base is a pyrimidine.

7th aspect of the 1st embodiment: a compound of Formula I-2

Ex.1001, col. 21, lines 30-59.

No, because the Base is a pyrimidine.

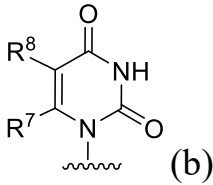
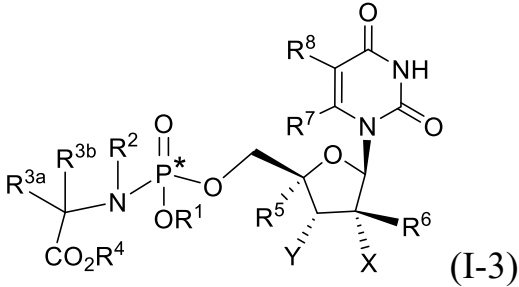
8th aspect of the 1st embodiment: a compound of Formula I-2

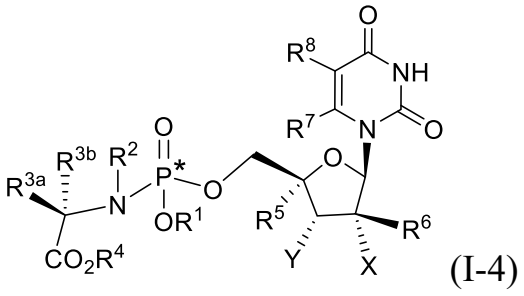
Ex.1001, col. 21, lines 60-end, to col. 22, lines 1-22.

No, because the Base is a pyrimidine.

2nd embodiment: a compound of Formula I, in which the Base is of Formula (b)

No, because the Base is a pyrimidine.

 (b) Ex.1001, col. 22, lines 23-27.	
1st aspect of the 2nd embodiment: a compound of Formula I-3  (I-3) Ex.1001, col. 22, lines 28-end, to col. 23, lines 1-62.	No, because the Base is a pyrimidine.
2nd aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001, col. 23, lines 63-end, to col 24, lines 1-56.	No, because the Base is a pyrimidine.
3rd aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001, col. 24, lines 57-end, to col. 25, lines 1-40.	No, because the Base is a pyrimidine.
4th aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001, col. 25, lines 41-end, to col. 26, lines 1-14.	No, because the Base is a pyrimidine.

5th aspect of the 2nd embodiment: a compound of Formula I-4  (I-4) Ex.1001, col. 26, lines 15-end, to col. 27, lines 1-2.	No, because the Base is a pyrimidine.
6th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001, col. 27, lines 3-31.	No, because the Base is a pyrimidine.
7th aspect of the 2nd embodiment: a compound of formula I-4 Ex.1001, col. 27, lines 32-55.	No, because the Base is a pyrimidine.
8th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001, col. 27, lines 56-end, to col. 28, lines 1-11.	No, because the Base is a pyrimidine.
9th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001, col. 28, lines 12-33.	No, because the Base is a pyrimidine.

3rd embodiment: a compound of Formula I, in which the Base is of Formula (c) (c) Ex.1001, col. 28, lines 35-40.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 13, lines 33-40.
1st aspect of the 3rd embodiment: a compound of Formula I-5 (I-5) Ex.1001, col. 28, lines 41-end, to col. 30, lines 1-34.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, and B is a purine base, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 29, lines 38-45.
2nd aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 30, lines 35-end, to col. 31, lines 1-8.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be

	H” and this proviso is not in claim 1. See <i>Id.</i>, col. 30, lines 56-58.
3rd aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 31, lines 9-41.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 31, lines 24-25.
4th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 31, lines 42-end, to col. 32 lines 1-7.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 31, lines 57-58.
5th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 32, lines 8-36.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵

	cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 32, lines 21-22.
6th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 32, lines 37-end, to col. 33, lines 1-6.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 32, lines 56-58. Also, not relevant because R¹⁰ must be NH₂. See <i>id.</i>, col. 32, line 63.
7th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 33, lines 7-40.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1.

	See <i>id.</i>, col. 33, lines 23-24. Also not relevant because R¹⁰ must be NH₂. See <i>id.</i>, col. 33, line 30.
8th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 33, lines 41-end, to col. 34, lines 1-6.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 33, lines 57-58. Also not relevant because R¹⁰ must be NH₂. See <i>id.</i>, col. 33, line 62.
9th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001, col. 34, lines 7-33.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be

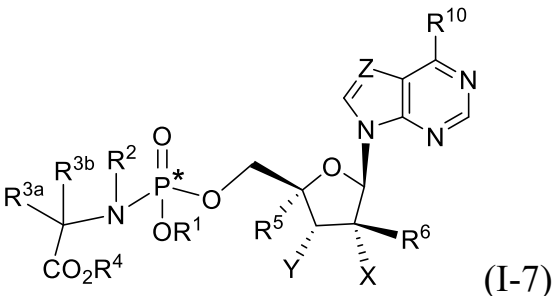
	H” and this proviso is not in claim 1. See <i>id.</i>, col. 34, lines 19-20. Also not relevant because R¹⁰ must be NH₂. See <i>id.</i>, col. 34, line 24.
10th aspect of the 3rd embodiment: a compound of Formula I-6 (I-6) Ex.1001, col. 34, lines 34-end, to col. 36, lines 1-8.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 35, lines 32-39.
11th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 36, lines 9-47.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be

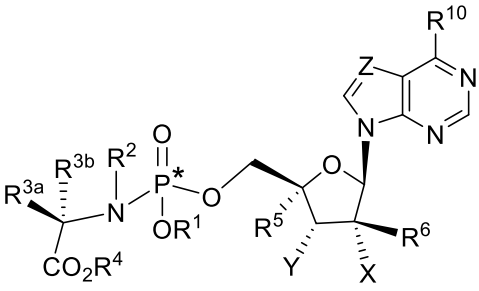
	H” and this proviso is not in claim 1. See <i>id.</i>, col. 36, lines 29-31.
12th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 36, lines 48-end, to col. 37, lines 1-13.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 36, lines 64-65.
13th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 37, lines 14-45.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 37, lines 29-30.
14th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 37, lines 46-end, to col. 38, lines 1-10.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be

	H” and this proviso is not in claim 1. See <i>id.</i>, col. 37, lines 61-62.
15th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 38, lines 11-end, to col. 39, lines 1-37.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F and B is a purine base, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 38, lines 62-end, to col. 39, lines 1-2. Also, not relevant because R¹⁰ is NH₂. See <i>id.</i>, col. 39, line 27.
16th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 39, lines 38-end, to col. 40, lines 1-8.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be

	H” and this proviso is not in claim 1. See <i>id.</i>, col. 39, lines 58-60.
17th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 40, lines 9-41.	No, because R⁵ is a list of substituents, with the proviso that “when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 40, lines 25-26.
18th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 40, lines 42-end, to col. 41, lines 1-6.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵ cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 40, lines 58-59.
19th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001, col. 41, lines 7-39.	No, because “R⁵ is H, with the provisos that when X is OH, R⁶ is CH₃ or CH₂F, R⁵

	cannot be H” and this proviso is not in claim 1. See <i>id.</i>, col. 41, lines 23-24. Also, not relevant because R¹⁰ is NH₂. See <i>id.</i>, col. 41, line 28.
4th embodiment: a compound of Formula I, in which the Base is of Formula (c), where R¹¹ is H (c) Ex.1001, col. 41, lines 40-44.	No, because the purine Base does not have a N²-amino.

1st aspect of the 4th embodiment: a compound of formula I-7  (I-7) Ex.1001, col. 41, lines 45-end, to col. 43, lines 1-37.	No, because the purine Base does not have a N²-amino.
2nd aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001, col. 43, lines 38-end, to col. 44, lines 1-10.	No, because the purine Base does not have a N²-amino.
3rd aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001, col. 44, lines 11-43.	No, because the purine Base does not have a N²-amino.
4th aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001, col. 44, lines 44-end, to col. 45, lines 1-10.	No, because the purine Base does not have a N²-amino.
5th aspect of the 4th embodiment: a compound of Formula I-7	No, because the purine Base does not have a N²-amino.

Ex.1001, col. 45, lines 11-40.	
6th aspect of the 4th embodiment: a compound of Formula I-8  (I-8)	No, because the purine Base does not have a N ² -amino.
Ex.1001, col. 45, lines 41-end, to col. 47, lines 1-17.	
7th aspect of the 4th embodiment Ex.1001, col 47, lines 18-57.	No, because the purine Base does not have a N ² -amino.
8th aspect of the 4th embodiment Ex.1001, col. 47, lines 58-end, to col. 48, lines 1-24.	No, because the purine Base does not have a N ² -amino.
9th aspect of the 4th embodiment Ex.1001, col. 48, lines 25-58.	No, because the purine Base does not have a N ² -amino.
10th aspect of the 4th embodiment Ex.1001, col. 48, lines 59-end, to col. 49, lines 1-25.	No, because the purine Base does not have a N ² -amino.

5th embodiment: a compound of Formula I, in which the Base is of Formula (d) (d) Ex.1001, col. 49, lines 26-30.	No, because the purine Base is a guanine.
1st aspect of the 5th embodiment: a compound of Formula I-9 (I-9) Ex.1001, col. 49, lines 31-end, to col. 50, lines 1-58.	No, because the purine Base is a guanine.
2nd aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001, col. 50, lines 59-end, to col. 51, lines 1-17.	No, because the purine Base is a guanine.
3rd aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001, col. 51, lines 18-38.	No, because the purine Base is a guanine.

4th aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001, col. 51, lines 39-58.	No, because the purine Base is a guanine.
5th aspect of the 5th embodiment a Compound of formula I-9 Ex.1001, col. 51, lines 59-end, to col. 52, lines 1-11.	No, because the purine Base is a guanine.
6th aspect of the 5th embodiment: a compound of Formula I-10 (I-10) Ex.1001, col. 52, lines 12-61.	No, because the purine Base is a guanine.
7th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001, col. 52, lines 62-end, to col. 53, lines 1-20.	No, because the purine Base is a guanine.
8th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001, col. 53, lines 21-41.	No, because the purine Base is a guanine.

9th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001, col. 53, lines 42-62.	No, because the purine Base is a guanine.
10th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001, col. 53, lines 63-end to col. 54, lines 1-16.	No, because the purine Base is a guanine.

**C. Numerical Comparison of '361 Patent Claim 1 and the
“Fourteenth Aspect of the Third Embodiment”**

64. If the technical defect in the proviso described above is ignored (which it should not be in my view), let us analyze claim 1 of the '361 patent by comparing its scope to what PO refers to as the patent specification support for its amended claim 1, which is the “fourteenth aspect of the third embodiment.” In its second preliminary amendment, PO cites pages “19, 51, 61, and 67-68, and Examples 67-80” for support for the newly added claims (Ex.1002, 91). The fourteenth aspect of the third embodiment is described on pp. 67-68 (Ex.1014, 71-72).

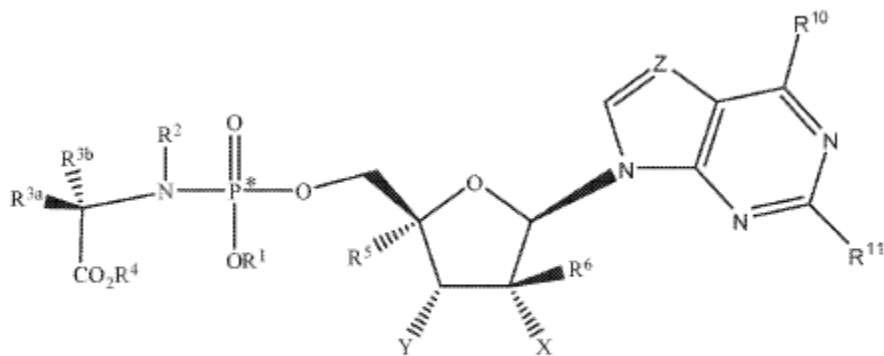
65. The fourteenth aspect of the third embodiment includes an incredible over 10^{27} different possible combinations of variables (see below) from which PO selected just a single specific combination. I have reviewed PO's petition in IPR2017-01712 and understand that it emphasized that the University of

Minnesota's patent at issue lacked written description because, metaphorically, it selected "seven trees from a forest of 7,441,875 trees, with no guidance pointing the POSA to those seven particular trees." (Ex.1022, 52).

66. Here the "forest," using the same PO's tree analogy, is far greater because PO has selected a "tree" from an astronomically large "forest" of over 10^{27} "trees" with no guidance whatsoever in the '361 patent specification pointing a POSA to the specific "tree" of claim 1. In fact, the '361 patent specification points away from the claimed invention because Formula I-6 of the specification requires that " R^5 is H, with the provisos that when X is OH, R^6 is CH_3 or CH_2F , R^5 cannot be H," while the proviso of claim 1 instead recites that "X cannot be OH when R^6 is $-CH_3$ or $-CH_2F$ " (Ex.1001, 30 and 321). Here PO selects a "tree" from an enormous "forest" that PO fails to describe.

(i) The '361 patent lacks "blaze marks" leading a POSA to claim 1

67. PO took the position during prosecution that claim 1 of the '361 patent is based on the genus of Formula I-6 (Ex.1002, 87 and 91). Although the '361 patent specification describes Formula I-6, the scope of Formula I-6, as disclosed in the '361 patent (Ex.1001, 28-30) is much broader than that in claim 1, even if the defective proviso is somehow ignored by a POSA.



I-6

There are no “blaze marks” in the patent specification to direct a POSA to the specific combination of variables and substituents recited in claim 1 of the ’361 patent.

68. PO may argue that the fourteenth aspect of the third embodiment of the ’361 patent is merely the starting point that a POSA would consider for purposes of determining written description support for claim 1 instead of Formula I-6 itself. But, having reviewed the application, I find no indication that the fourteenth aspect of the third embodiment would be a more likely starting point for a POSA than any other embodiment of the patent application other than through use of impermissible hindsight (i.e., looking at the claim first and then finding the “closest” embodiment).⁶ However, even starting from the fourteenth aspect of the

⁶ I have not been able to identify any subgenus in the patent application that is more similar to the claimed subgenus than the fourteenth aspect of the third embodiment.

third embodiment, claim 1 is still very different from the subgenus disclosed in the patent specification. Differences between the described and claimed subgenus are provided in Table 2 below.

Table 2

Substituent Class	'361 Patent Closest Subgenus (Ex.1001, 30)	'361 Patent Claim 1 (Ex.1001, 321)
R⁴	hydrogen, CH ₃ , Et, <i>i</i> Pr, <i>n</i> Pr, <i>n</i> Bu, 2-butyl, <i>t</i> Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl	CH ₃ , ethyl, n-propyl, or <i>i</i> -propyl
R¹⁰	H, F, Br, I, OH, OR', NH ₂ , NHR', NR' ₂ , CO ₂ R', CONH ₂ , CONHR', CONR' ₂ , CH=CHCO ₂ H, or	NHR'

	CH=CHCO ₂ R', with the proviso that when R ¹⁰ is OH and R ¹¹ is not NH ₂ (incomplete clause)	
R¹¹	H, F, Br, I, OH, OR', NH ₂ , NHR', NR' ₂ , CO ₂ R', CONH ₂ , CONHR', CONR' ₂ , CH=CHCO ₂ H, or CH=CHCO ₂ R', with the proviso that when R ¹⁰ is OH and R ¹¹ is not NH ₂ (incomplete clause)	NH ₂
R'	lower alkyl, a lower cycloalkyl, or C(O)(lower alkyl) or, alternatively, in the instance of NR' ₂ , each R' comprise [<i>sic</i>] at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms	C ₁₋₆ alkyl
Proviso	R ⁵ is H, with the provisos that when X is OH, R ⁶ is CH ₃ or CH ₂ F, then R ⁵ cannot be H	with the proviso that X cannot be OH when R ⁶ is CH ₃ or CH ₂ F

69. I see no “blaze marks” in the ’361 patent specification to direct a POSA to the specific variables which have been chosen for narrowed R groups R⁴, R¹⁰, R¹¹, and R’, or for the new proviso recited in the granted claim.

70. As shown in Table 3 below, there are 20 possible substituent classes or elements (referred to as Markush Elements) for R⁴, 15 Markush Elements for R¹⁰, 15 Markush Elements for R¹¹, and 4 Markush Elements for R’.

Table 3

	R⁴	R¹⁰	R¹¹	R’
hydrogen	1	1	1	
CH ₃ (Me)	1			
Et	1			
ⁱ Pr	1			
ⁿ Pr	1			
ⁿ Bu	1			
2-butyl	1			
^t Bu	1			
benzyl	1			
cyclopropyl	1			
cyclobutyl	1			

	R⁴	R¹⁰	R¹¹	R'
cyclopentyl	1			
cyclohexyl	1			
N-methyl-aziridin-2-yl	1			
N-methyl-azetidin-3-yl	1			
N-methyl-pyrrolidin-3-yl	1			
N-methyl-pyrrolidin-4-yl	1			
N-methyl-piperidin-4-yl	1			
lower haloalkyl	1			
di(lower alkyl)amino-lower-alkyl	1			
F		1	1	
Br		1	1	
I		1	1	
OH		1	1	
OR'		1	1	
NH ₂		1	1	
NHR'		1	1	
NR' ₂		1	1	
CO ₂ R'		1	1	

	R⁴	R¹⁰	R¹¹	R'
CONH ₂		1	1	
CONHR'		1	1	
CONR' ₂		1	1	
CH=CHCO ₂ H		1	1	
CH=CHCO ₂ R'		1	1	
lower alkyl				1
lower cycloalkyl				1
C(O)(lower alkyl)				1
two R' form a heterocycle				1
Total	20	15	15	4
Selected by PO	4	1	1	1

71. I see no “blaze marks” for the specific combination of Markush Elements which PO selected from narrowed substituents R⁴, R¹⁰, R¹¹, and R'. Additionally, PO chose to modify only variables R⁴, R¹⁰, R¹¹, and R' but did not modify variables R¹, R², R^{3a}, R^{3b}, R⁵, R⁶, X, Y, Z, R¹², or P*. This represents just one combination of selections out of over 10²⁷ possible combinations.

72. For example, there are 20 Markush Elements to choose from for R⁴, and PO chose four specific elements. However, there is no teaching in the

specification that discusses a preference for only choosing four specific elements out of a list of twenty, as compared to instead choosing one, two, three, five, six, etc., elements. For example, instead of selecting CH₃, ethyl, n-propyl, and *i*-propyl, PO could have instead selected cyclobutyl, or the combination of cyclobutyl and N-methyl-azetidin-3-yl, or even all 20 Markush Elements.

73. To quantify possible combinations of variables for the fourteenth aspect of the third embodiment of the '361 patent, I reviewed and accepted Petitioner's combinatorial analysis provided below. The equation to determine the number of possible combinations is mathematically represented as:

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

where n is the number of total elements in the set and m is the number of selections made from the set.⁷

74. This equation is a standard mathematical method for determining the number of possible combinations of selections that can be made from a set that has distinct members. For example, if given a green marble, a yellow marble, and a

⁷ I note that PO also used this equation in its IPR petition against U.S. Patent No. 8,815,830 (Ex.1025, ¶56). This calculation can also be carried out using Microsoft Excel using the command =COMBIN(n,m), wherein n is the number of elements and m is the number of selections.

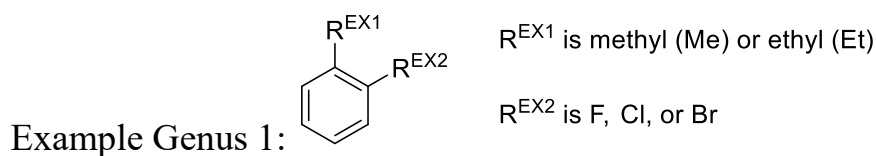
red marble, a POSA would have three possible combinations of choosing one marble (green, or yellow, or red); three possible combinations of choosing two marbles (green and red, or green and yellow, or yellow and red); and one possible combination of choosing all three marbles (green, yellow, and red). Thus, there are seven total possible combinations ($3 + 3 + 1 = 7$):

$$1 \text{ of } 3 \text{ marbles} = 3! / [(3-1)! \times 1!] = 3$$

$$2 \text{ of } 3 \text{ marbles} = 3! / [(3-2)! \times 2!] = 3$$

$$3 \text{ of } 3 \text{ marbles} = 3! / [(3-3)! \times 3!] = 1$$

75. This same formula can be readily applied to determine the number of different combinations of variables in a genus of chemical compounds because each variable is a set that has distinct members. For example, Example Genus 1 includes 21 different possible combinations, which can be demonstrated by the formula or by manually writing out the combinations.



76. Using the formula, the number of combinations is found by determining how many combinations R^{EX1} can have and then multiplying that number by the number of combinations R^{EX2} can have. As demonstrated by the aforementioned marble analogy, there are 7 possible combinations for R^{EX2} because

the set has three Markush Elements. For R^{EX1} , there are 3 possible combinations ($2 + 1 = 3$):

$$1 \text{ of } 2 \text{ Markush Elements} = 2! / [(2-1)! \times 1!] = 2$$

$$2 \text{ of } 2 \text{ Markush Elements} = 2! / [(2-2)! \times 2!] = 1$$

These combinations are (1) R^{EX1} is Me; (2) R^{EX1} is Et; and (3) R^{EX1} is Me or Et.

77. By multiplying the 3 possible combinations for R^{EX1} by the 7 possible combinations for R^{EX2} , a POSA would arrive at 21 possible combinations. For this relatively modest genus size, these 21 combinations can be readily listed out:

Possible combinations: (1) R^{EX1} is Me and R^{EX2} is F; (2) R^{EX1} is Me and R^{EX2} is Cl; (3) R^{EX1} is Me and R^{EX2} is Br; (4) R^{EX1} is Et and R^{EX2} is F; (5) R^{EX1} is Et and R^{EX2} is Cl; (6) R^{EX1} is Et and R^{EX2} is Br; (7) R^{EX1} is Me or Et and R^{EX2} is F; (8) R^{EX1} is Me or Et and R^{EX2} is Cl; (9) R^{EX1} is Me or Et and R^{EX2} is Br; (10) R^{EX1} is Me and R^{EX2} is F or Cl; (11) R^{EX1} is Me and R^{EX2} is F or Br; (12) R^{EX1} is Me and R^{EX2} is Cl or Br; (13) R^{EX1} is Et and R^{EX2} is F or Cl; (14) R^{EX1} is Et and R^{EX2} is F or Br; (15) R^{EX1} is Et and R^{EX2} is Cl or Br; (16) R^{EX1} is Me or Et and R^{EX2} is F or Cl; (17) R^{EX1} is Me or Et and R^{EX2} is F or Br; (18) R^{EX1} is Me or Et and R^{EX2} is Cl or Br; (19) R^{EX1} is Me and R^{EX2} is F, Cl, or Br; (20) R^{EX1} is Et and R^{EX2} is F, Cl, or Br; (21) R^{EX1} is Me or Et and R^{EX2} is F, Cl, or Br.

78. For the fourteenth aspect of the third embodiment, every possible combination cannot be feasibly listed; however, using the combinatorial formula, a POSA can calculate the number of possible combinations.

79. For R^4 , the possible number of combinations is provided in Table 4 below:

Table 4

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
20	20	1
20	19	20
20	18	190
20	17	1140
20	16	4845
20	15	15504
20	14	38760
20	13	77520
20	12	125970
20	11	167960
20	10	184756

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
20	9	167960
20	8	125970
20	7	77520
20	6	38760
20	5	15504
20	4	4845
20	3	1140
20	2	190
20	1	20
TOTAL NUMBER OF POSSIBLE COMBINATIONS		1,048,575

80. Thus, even without considering any variables other than R^4 , there are already well *over a million* possible combinations of variables from which PO somehow selected just one combination to present in claim 1 of the '361 patent. R^{10}

and R¹¹ add a further 32,767 possible combinations of variables each (see Table 5 below).⁸

Table 5

Total Number of Markush Elements (n)	Selected Number of Markush Elements (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

⁸ I note that PO also applied this equation to a variable with 15 elements in its IPR petition against U.S. Patent No. 8,815,830 and came to the same result (i.e., 32,767 possible combinations in a 15-element R variable). Ex.1025, ¶57.

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
15	5	3003
15	4	1365
15	3	455
15	2	105
15	1	15
TOTAL NUMBER OF POSSIBLE COMBINATIONS		32,767

81. R' adds a still further 15 possible combinations of variables:

Table 6

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
4	4	1
4	3	4
4	2	6
4	1	4
TOTAL NUMBER OF POSSIBLE COMBINATIONS		15

82. Looking at the narrowed variables alone, therefore, there are over 16 quadrillion (16×10^{15} , i.e., sixteen million billion) possible combinations from which PO somehow selected just one combination ($1,048,575 \times 32,767 \times 32,767 \times 15 = 16,887,451,721,072,600$ possible combinations). Further, the >16 quadrillion figure is actually conservative because it does not consider the variables recited in the fourteenth aspect of the third embodiment that PO did not limit. PO also selected:

14 of 14 Markush Elements for R^{12} (1 of 16,383 possible selections)

7 of 7 Markush Elements for R^{3b} (1 of 127 possible selections)

6 of 6 Markush Elements for R^1 (1 of 63 possible selections)

6 of 6 Markush Elements for R^6 (1 of 63 possible selections)

6 of 6 Markush Elements for X (1 of 63 possible selections)

4 of 4 Markush Elements for Y (1 of 15 possible selections)

2 of 2 Markush Elements for Z (1 of 3 possible selections)

83. With all the variables of the fourteenth aspect of the third embodiment considered, PO selected a specific combination of elements from an enormous list of more than three hundred octillion (10^{27}) combinations ($1,048,575 \times 32,767 \times 32,767 \times 15 \times 16,383 \times 127 \times 63 \times 63 \times 63 \times 15 \times 3 = 395,362,464,081,506,000,000,000,000,000$ possible combinations).

84. If, to continue with PO's own proposed "forest/tree" analogy, each possible combination is represented as a tree and, since there are about 3 trillion trees on our planet, then it would take over 130 quadrillion (10^{15}) Earths to hold all the "trees" in the "forest" from where PO somehow chose the single tree of claim 1 of the '361 patent.⁹

85. PO may argue that claim 1 of the '361 patent only selects 4 elements of 20 for R^4 , 1 element of 15 for R^{10} , 1 element of 15 for R^{11} , and 1 element of 4 for R' . However, even if this argument is accepted (thus ignoring the mind-boggling quantity of other selections), the number of possible combinations of R group substituents is still overwhelming. As shown in the tables above, the number of possibilities for 4 elements of 20 is 4,845 (Table 4), 1 element of 15 is 15 (Table 5), and 1 element of 4 is 4 (Table 6). This results in well over four million possible combinations of R group substituents for R^4 , R^{10} , R^{11} , and R' even when all other

⁹ A recent *Nature* article estimates that there are 3.04 trillion trees on Earth. See Ex.1027. 395 octillion trees divided by 3.04 trillion trees per Earth equals to over 1.3×10^{17} (130 quadrillion) Earths. I certify that Exhibit 1027 is a true and correct copy of Crowther, T.W., et al., "Mapping Tree Density at a Global Scale." *Nature*, 525: 201-205 (2015).

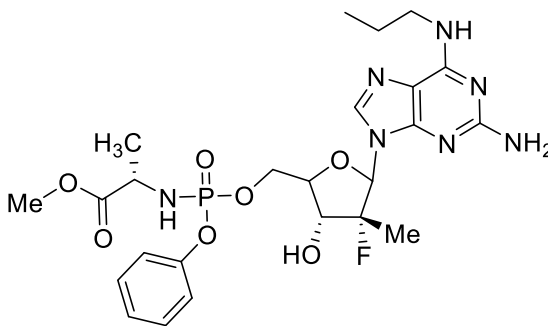
numbers of selections and other variables are ignored ($4,845 \times 15 \times 15 \times 4 = 4,360,500$).

86. There is no disclosure in the '361 patent that provides any guidance for a POSA on how to select just one out of over 10^{27} possible combinations. Nor is there any guidance for the individual selections of: (1) CH₃, ethyl, n-propyl, and *i*-propyl for R⁴ out of 20 possibilities; (2) NHR' for R¹⁰ out of 15 possibilities; (3) NH₂ for R¹¹ out of 15 possibilities; and (4) C₁-C₆ alkyl for R' out of 4 possibilities.

87. Therefore, the disclosure of the '361 patent specification provides utterly insufficient “blaze marks” to point a POSA to the subgenus recited in claim 1.

(ii) The '361 patent has insufficient syntheses to create “blaze marks” to visualize the claim 1 subgenus

88. The '361 patent only provides the synthesis for one compound that falls within the scope of claim 1, whose chemical structure is:

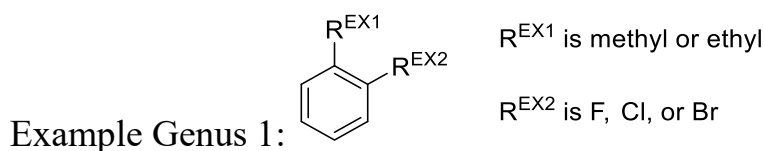


'361 Compound 72

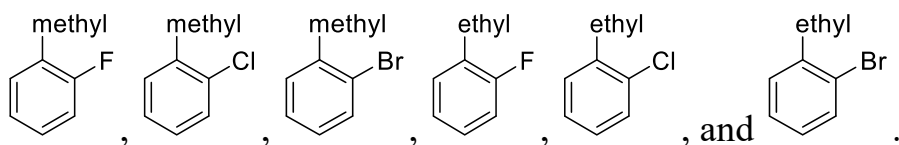
Ex.1001, col. 607

89. In my opinion, the synthesis of merely this single compound cannot create sufficient “blaze marks” for a POSA to visualize the entire huge subgenus of claim 1 that includes multiple variations at each position of the claimed “compound of formula I-6.”

90. The number of compounds covered by a patent claim can be calculated by multiplying the number of different substituents that each R variable covers. For example, in a simple hypothetical claim like the one below, the genus covers 6 compounds (two values for R^{EX1} and 3 values for R^{EX2}, where 2 x 3 = 6).



91. Across such small genuses, every compound within it can be readily identified and drawn. For example, Example Genus 1 covers the following six compounds:



92. Claim 1 of the '361 patent covers far more compounds than can practicably be drawn by hand; however, the number of compounds covered by the claim is nevertheless readily calculated as follows:

Table 7

Variable	Number of values	List of possible chemical moieties
R ¹	6	H, CH ₃ , phenyl, <i>p</i> -bromophenyl, <i>p</i> -chlorophenyl, and <i>p</i> -fluorophenyl
R ²	1	H
R ^{3a}	1	H
R ^{3b}	10	H, CH ₃ , CH(CH ₃) ₂ , CH ₂ CH(CH ₃) ₂ , CH(CH ₃)CH ₂ CH ₃ , CH ₂ Ph, and lower cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl)
R ⁴	4	CH ₃ , ethyl, n-propyl, and i-propyl
R ⁵	1	H
R ⁶	6	H, CH ₃ , CH ₂ F, CHF ₂ , CF ₃ , and F
X	6	H, OH, OCH ₃ , F, NH ₂ , and N ₃
Y	4	OH, NH ₂ , OCH ₃ , and OC(O)CH ₃
R ¹⁰	48	NR' (R' is C ₁ -C ₆ alkyl. There are 48 isomers of C ₁ -C ₆ alkyl, including: methyl, ethyl, n-propyl, i-propyl, n-butyl, R-sec-butyl, S-sec-butyl, i-butyl, t-butyl, n-

		pentyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, R-2-methylbutyl, S-2-methylbutyl, R-1-methylbutyl, S-1-methylbutyl, 1-ethylpropyl, R-1,2-dimethylpropyl, S-1,2-dimethylpropyl, n-hexyl, R-1-methylpentyl, S-1-methylpentyl, R-2-methylpentyl, S-2-methylpentyl, R-3-methylpentyl, S-3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, R,R-1,2-dimethylbutyl, R,S-1,2-dimethylbutyl, S,R-1,2-dimethylbutyl, S,S-1,2-dimethylbutyl, R-1,3-dimethylbutyl, S-1,3-dimethylbutyl, R-2,3-dimethylbutyl, S-2,3-dimethylbutyl, R-1-ethylbutyl, S-1-ethylbutyl, 2-ethylbutyl, R-1-ethyl-2-methylpropyl, S-1-ethyl-2-methylpropyl, 1,1,2-methylpropyl, R-1,2,2-trimethylpropyl, S-1,2,2-trimethylpropyl, and 1,1-ethylmethylpropyl)
R ¹¹	1	NH ₂
Z	4810	N, CH, C-halogen (F, Cl, Br, and I) C-OC₁₋₆ alkyl (there are 48 isomers of C₁-C₆ alkyl), C-NH₂, C-NH-C₁₋₆ alkyl, C-N(C₁₋₆ alkyl)₂ (there are 48 x 48

		– 48 = 2,256 isomers of (C₁₋₆ alkyl)₂), NO₂, C₁₋₆ alkyl, CO₂C₁₋₆ alkyl, CONH₂, CONHC₁₋₆ alkyl, CON(C₁₋₆ alkyl)₂, CH=CHCO₂H, and CH=CHCO₂C₁₋₆ alkyl (1+1+4+48+1+48+2256+1+48+48+1+48+2256+1+48 = 4810)
P*	2	R and S enantiomers
Number of compounds w/o proviso	15,958,425,600	
Proviso = minus 886,579,200 compounds	X cannot be OH when R⁶ is -CH₃ or CH₂F. Excludes 6 (R¹) x 1 (R²) x 1 (R^{3a}) x 10 (R^{3b}) x 4 (R⁴) x 1 (R⁵) x 2 (R⁶ is CH₂F or CH₃) x 1 (X is OH) x 4 (Y) x 48 (R¹⁰) x 4810 (R¹²) x 2 (P*) compounds = 886,579,200 compounds	
Total Number of Compounds	15,071,846,400	

93. As shown in Table 7 above, claim 1 of the '361 patent covers 15,071,846,400 (i.e., over 15 billion) compounds.¹⁰ The patent specification, on the other hand, only provides the synthesis of just one of them (Ex.1002, col. 607, line 72).

94. The single compound actually synthesized and described in the '361 patent cannot possibly support the written description of a genus that includes well over 15 billion compounds that are neither described nor synthesized in the patent specification.

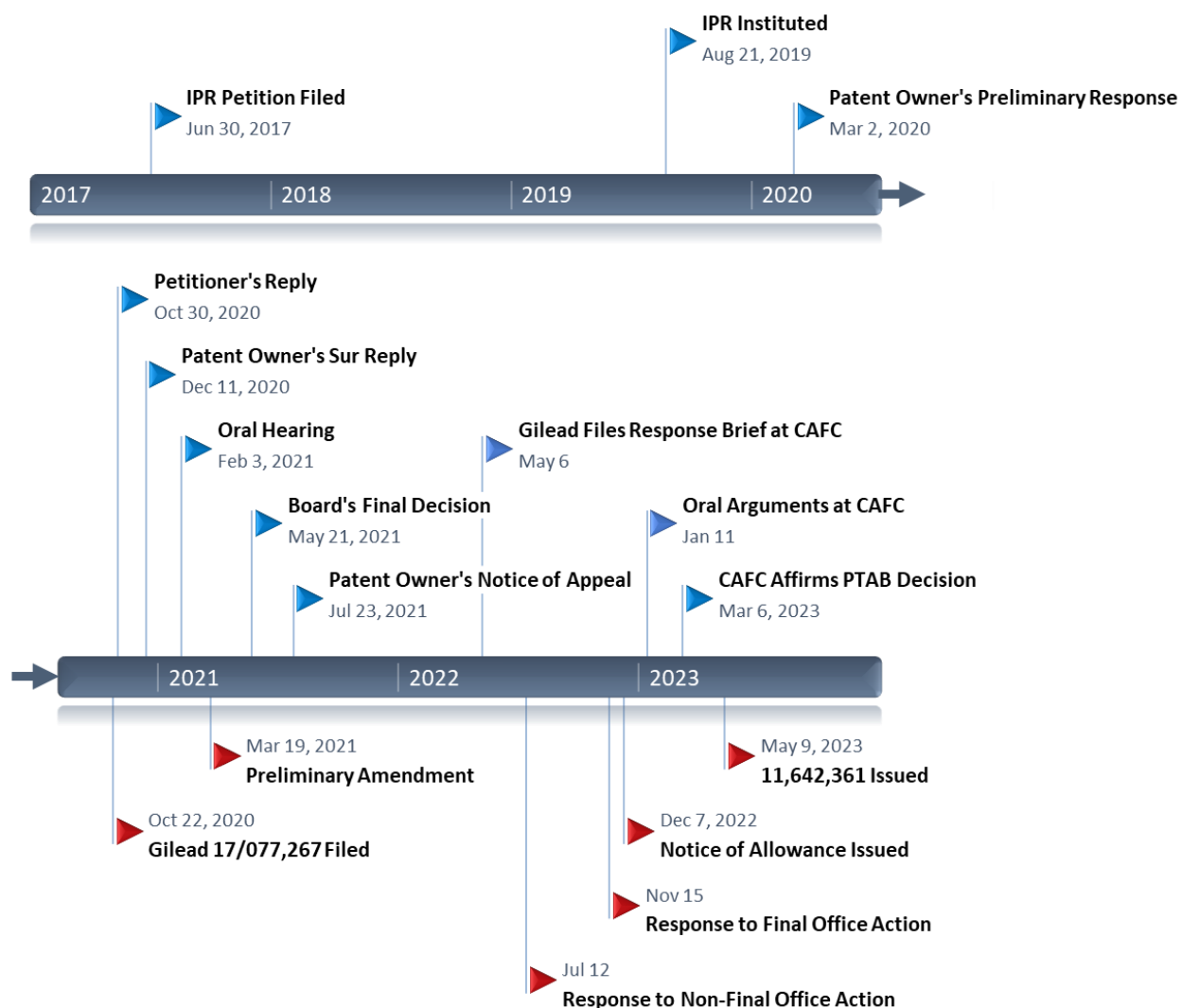
95. As stated by PO in its successful challenge of the issued '830 patent, "there is no reasonable justification for interpreting the examples as teaching the selections made at some positions ... but not at others." Ex.1023, 22 (Quoted by the PTAB in its final written decision. Ex.1024, 34-35). Applying the very same

¹⁰ Even if every R' substituent is treated as having to be the same (i.e., excluding compounds with N(R')₂ substituents like N(Me)(Et) because the two alkyl groups are different), claim 1 of the '361 patent would still cover a staggering 203,673,600 (i.e., over 200 million) distinct compounds. Similarly, even if chirality is ignored (i.e., only considering 33 isomers of hexyl and considering (R)-phosphate and (S)-phosphate to be the same compound), the claim would still cover 2,498,918,400 (i.e., over 2 billion) distinct compounds.

logic to the case at hand, the over 12,000 recited examples¹¹ which are not covered by the claims teach away from claim 1 of the '361 patent and show that PO lacked possession of the claimed invention. The substituents taught by the recited examples in the patent are limited to teaching the specific combination of substituents that each example provides. PO cannot point to specific examples to support its selections of R⁴, R¹⁰, R¹¹, and R', while ignoring the remaining selections made, in order to arrive at the specific example.

96. Notably, PO made and repeated the foregoing arguments while actively prosecuting the '361 patent, thus trying to have it both ways, as seen in the timeline below.

¹¹ The '361 patent has 524 columns of tables of compounds which disclose over 12,000 species (Ex.1001, 39-301).



D. Tables II-1 Through XXXII-50 of the '361 Patent Include No Compounds Within Claim 1

97. The '361 patent has 524 columns of tables of compounds that purportedly fall under the '361 Supergenous (Ex.1001, 39-301). There are 31 subgenous structures included, each of which has 50 sub-tables with 8 compounds in each. This amounts to well over 12,000 disclosed species in these tables. Nonetheless, not a single species in these tables falls within issued claim 1 of the '361 patent.

98. The only purine nucleotide phosphoramidates in the enormous list of species are N²-aminopurine (i.e., **not** N²,N⁶-diaminopurine) nucleotide phosphoramidates (Tables XXI-XXVIII) and guanine nucleotide phosphoramidates (Tables XXIX-XXXII), neither of which subgenus is covered by claim 1 of the '361 patent (Ex.1001, 230-301). This is consistent with the definition of a “purine” in col. 11, lines 55-end, to col. 12, lines 1-15, which does not name N⁶-alkyl,N²-aminopurines (Ex.1001).

Table 8

Table Nos.	Columns (Ex.1001)	General Structure	Covers '361 Patent Claim 1?
II 1-50	Cols. 54-77	Pyrimidine nucleotide phosphoramidate	No
III 1-50	Cols. 77-99	Pyrimidine nucleotide phosphoramidate	No
IV 1-50	Cols. 99-121	Pyrimidine nucleotide phosphoramidate	No
V 1-50	Cols. 121-143	Pyrimidine nucleotide phosphoramidate	No

VI 1-50	Cols. 143-159	Pyrimidine nucleotide phosphoramidate	No
VII 1-50	Cols. 159-183	Pyrimidine nucleotide phosphoramidate	No
VIII 1-50	Cols. 183-205	Pyrimidine nucleotide phosphoramidate	No
IX 1-50	Cols. 205-225	Pyrimidine nucleotide phosphoramidate	No
X 1-50	Cols. 225-241	Pyrimidine nucleotide phosphoramidate	No
XI 1-50	Cols. 241-257	Pyrimidine nucleotide phosphoramidate	No
XII 1-50	Cols. 257-275	Pyrimidine nucleotide phosphoramidate	No
XIII 1-50	Cols. 275-294	Pyrimidine nucleotide phosphoramidate	No
XIV 1-50	Cols. 295-313	Pyrimidine nucleotide phosphoramidate	No

XV 1-50	Cols. 313-333	Pyrimidine nucleotide phosphoramidate	No
XVI 1-50	Cols. 333-351	Pyrimidine nucleotide phosphoramidate	No
XVII 1-50	Cols. 351-369	Pyrimidine nucleotide phosphoramidate	No
XVIII 1-50	Cols. 369-392	Pyrimidine nucleotide phosphoramidate	No
XIX 1-50	Cols. 393-415	Pyrimidine nucleotide phosphoramidate	No
XX 1-50	Cols. 415-437	Pyrimidine nucleotide phosphoramidate	No
XXI 1-50	Cols. 437-451	N ² -Aminopurine nucleotide phosphoramidate	No
XXII 1-50	Cols. 451-461	N ² -Aminopurine nucleotide phosphoramidate	No
XXIII 1-50	Cols. 461-473	N ² -Aminopurine	No

		nucleotide phosphoramidate	
XXIV 1-50	Cols. 473-485	N ² -Aminopurine nucleotide phosphoramidate	No
XXV 1-50	Cols. 485-498	N ² -Aminopurine nucleotide phosphoramidate	No
XXVI 1-50	Cols. 498-509	N ² -Aminopurine nucleotide phosphoramidate	No
XXVII 1-50	Cols. 509-521	N ² -Aminopurine nucleotide phosphoramidate	No
XXVIII 1-50	Cols. 521-532	N ² -Aminopurine nucleotide phosphoramidate	No
XXIX 1-50	Cols. 532-546	Guanine nucleotide phosphoramidate	No

XXX 1-50	Cols. 546-556	Guanine nucleotide phosphoramidate	No
XXXI 1-50	Cols. 556-567	Guanine nucleotide phosphoramidate	No
XXXII 1-50	Cols. 567-579	Guanine nucleotide phosphoramidate	No

99. Based on the foregoing, in summary, there are multiple signs in the '361 patent that would convincingly point a POSA away from the claim 1 subgenus. In fact, the claim is drawn to a cobbled-together subgenus of moieties that was not presented in that form in the patent specification, as discussed herein.

(i) With regard to the aspects and embodiments, the 42 columns of genres and subgenres of the '361 Supergen discussed above misdirect the POSA with the following:

(a) The R⁵ proviso in the specification either excludes the subgenus of claim 1 or is vague and ambiguous, and when claim 1 was amended during prosecution the proviso was revised creating a written description problem (see Section VI.B).

(b) When the purine structure (c) subgenres are narrowed at R¹⁰ and R¹¹, in the forty-two columns of genres and subgenres, PO narrows

them to $R^{10} = \text{NH}_2$ (instead of NHR'). In fact, nine of the nineteen subgenres of I-5 and I-6 (i.e., almost half) narrow to $R^{10} = \text{NH}_2$ (the sixth, seventh, eighth, ninth, fifteenth, sixteenth, seventeenth, eighteenth, and nineteenth embodiments of I-5 and I-6), which is directly away from issued claim 1.

(c) There are **no** purine structure (c) subgenres in the embodiments and aspects in the 42 columns that narrow to R^{10} of NHR' , wherein R' is C_{1-6} alkyl and R^{11} is NH_2 , as required by claim 1 of the '361 patent. This is consistent with the purine definition in col. 11, lines 55-end, to col. 12, lines 1-15, which does not name N^6 -alkyl, N^2 -aminopurines.

(ii) The 524 columns of tables do not include a single compound that falls within issued claim 1 of the '361 patent.

(iii) The combination of variables recited in claim 1 of the '361 patent is selected from over 10^{27} possible combinations described in the fourteenth aspect of the third embodiment of Formula I-6. The selected claimed combination is much narrower than the closest subgenus in the '361 patent, with no guidance to a POSA in the patent specification on how to get there (in fact, there are many “don't go in this direction signs”). Despite its more limited nature, claim 1 still covers over 15 billion different compounds, of which only one compound was

actually synthesized by PO and of which none was tested for biological activity or toxicity

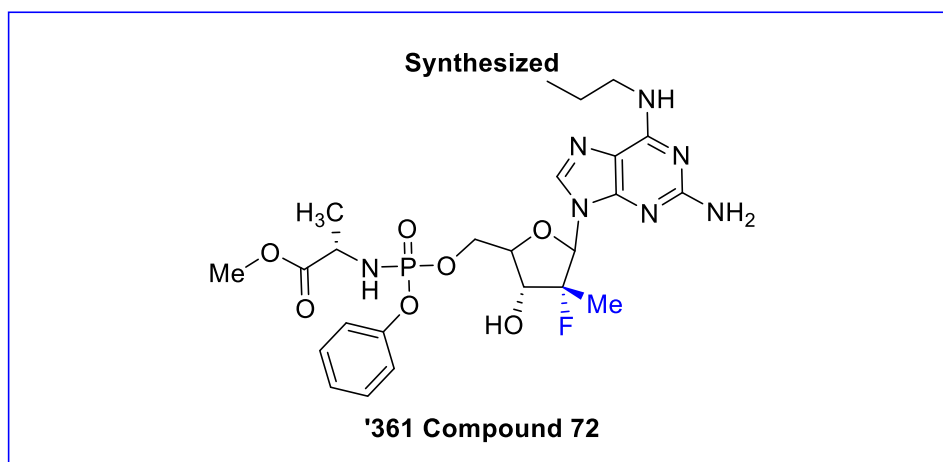
100. Based on the foregoing alone, I conclude that PO neither invented the subgenus of claim 1 nor placed it in the possession of the public by means of the '267 patent application specification (Ex.1014).

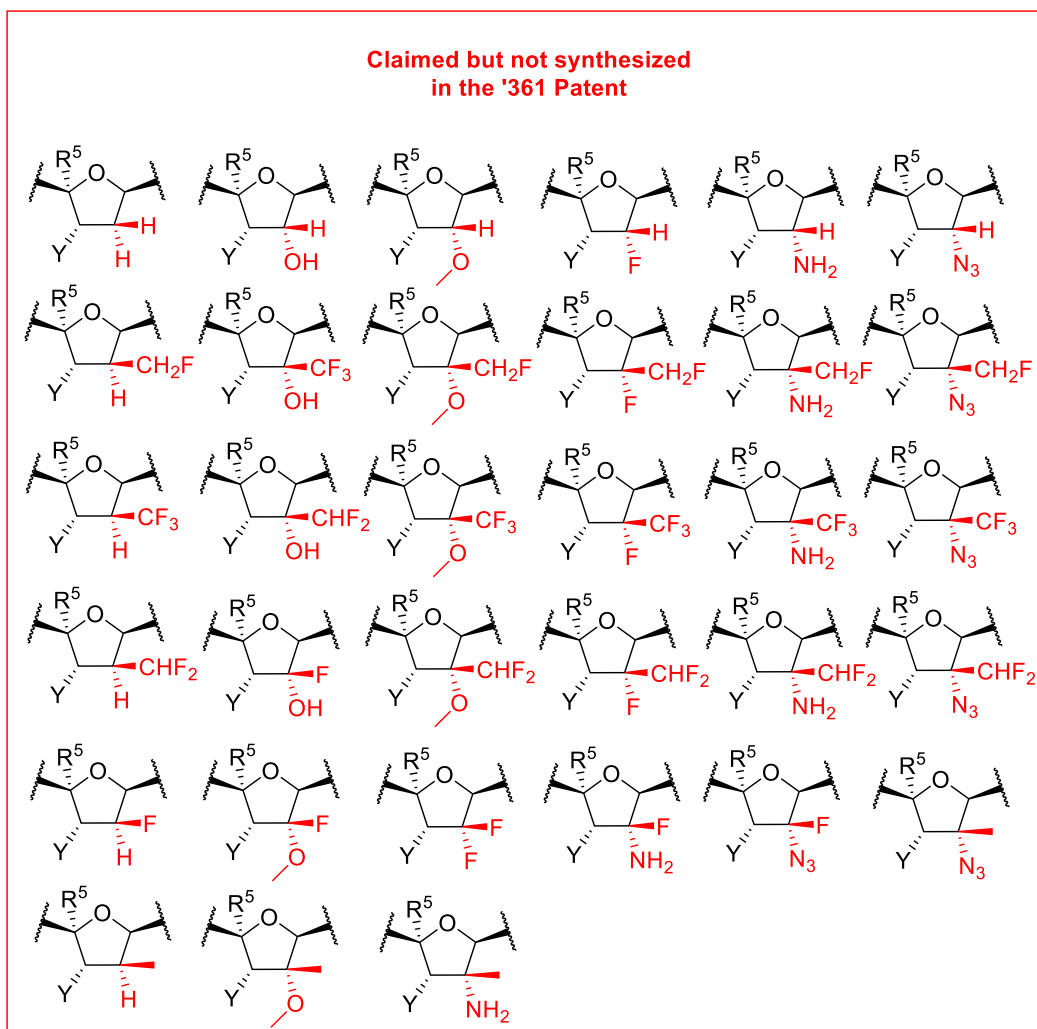
101. And despite all of the multitude of compounds covered by claim 1 and the billions of compounds described in the '361 patent specification, PO only provided a synthesis of just a *single* compound and biological data for *none* of the compounds in claim 1, as discussed in detail below. It is simply impossible that this meager disclosure provides sufficient “blaze marks” to describe the full scope of claim 1.

E. Synthesis

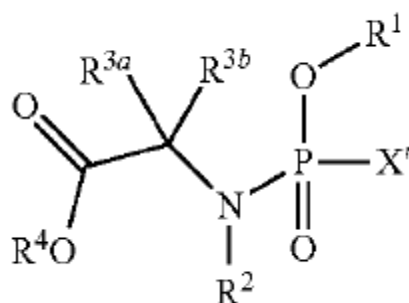
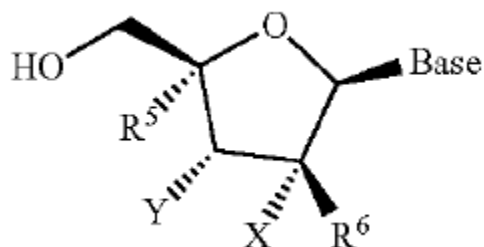
102. The '361 patent fails to disclose how to make the full scope of breadth of nucleotides within the claim 1 phosphoramidates (Ex.1001). In fact, only a single compound of the claimed subgenus was made. This is further evidence of the lack of written description for claim 1 due to the absence of “blaze marks” around the full scope of the claim. And regardless of whether a POSA could make compounds falling within the scope of claim 1, the fact that only one compound was made is woefully insufficient to lead a POSA in that direction.

103. Critically, all of the compounds synthesized in the '361 patent have a specific motif in the 2'-position—namely, 2'-methyl-up, 2'-fluoro-down (Ex.1001, 306-315). In contrast, the 2'-R⁶ (“up”) and 2'-X (“down”) positions in the nucleotide of claim 1 have thirty-four possibilities, and none of them other than 2'-methyl-up, 2'-fluoro-down was actually prepared in the '361 patent.





104. The sole example of supposedly how to make the enormous scope of compounds encompassed by the subgenus of claim 1 is found in cols. 584-609 of the '361 patent (Ex.1001). It provides an Example 3 “General Procedures for Nucleoside Phosphoramidate Derivatives” (Ex.1001, col. 588, lines 35-end) that simply instructs a POSA to react a preformed substituted nucleoside with an appropriate phosphorochloridate to obtain the nucleotide phosphoramidate:



105. In col. 586, lines 21-25, the '361 patent specification teaches that (Ex.1001, emphasis added): “*The nucleoside analog is made by conventional procedures* disclosed in any one of U.S. Published Application Nos. 2005/0009737, 2006/0199783, 2006/0122146, and 2007/0197463, each of which is incorporated by reference in its entirety.”¹² But none of these four references teaches how to make compounds within the full scope of claim 1 of the '361 patent; in fact, all of these references are limited to the same 2'-alkyl-up,2'-F-down structural motif.

¹² This statement in the '361 patent is misleading as applied to the full scope of claim 1.

(1) U.S. Published Application No. 2005/0009737 is limited to teaching how to make nucleosides wherein R^6 is CH_3 and X is F (see Ex.1043, Section VIII (¶¶293-333)).

(2) U.S. Published Application No. 2006/0199783 provides examples of how to make nucleosides wherein R^6 is alkyl and X is F (Ex.1044, ¶¶008 and 011). The specification states that the process invention includes syntheses of nucleosides wherein X is halogen (F, Cl, Br) and $R^{2'}$ (R^6) is C_{1-3} alkyl, vinyl, or ethynyl, but the application does not exemplify anything other than how to make nucleosides wherein R^6 is alkyl and X is F.

(3) U.S. Published Application No. 2006/0122146 (Ex.1045) provides processes to prepare nucleosides wherein R^6 is alkyl and X is F (as with the '783 application). In ¶¶0010 and 0013, the specification states that the process invention includes syntheses for nucleosides wherein X is halogen (F, Cl, Br) and $R^{2'}$ (R^6) is C_{1-3} alkyl, vinyl, or ethynyl, but the application does not exemplify anything other than how to make nucleosides wherein R^6 is alkyl and X is F (Ex.1045).

(4) U.S. Publication Application No. 2007/0197463 is limited to teaching how to make 3',5'-prodrugs of nucleosides wherein R^6 is CH_3 and X is F (see Ex.1046, Examples 1-4, pp. 12-14).

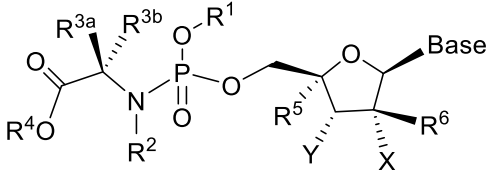
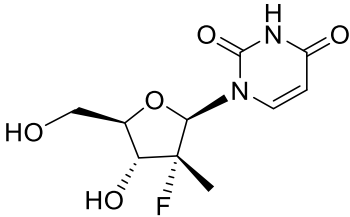
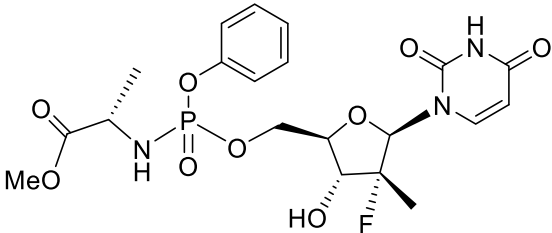
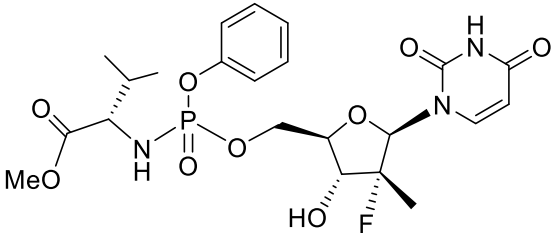
106. Thus, the entire scope of synthetic examples in the '361 patent is drawn to merely one embodiment—nucleotides with 2'-methyl- (or alkyl)-up and

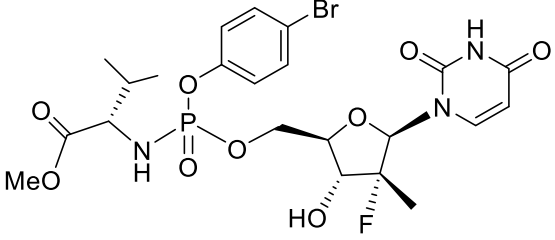
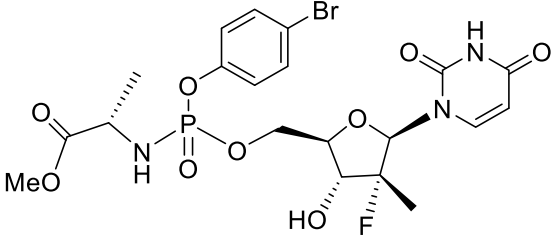
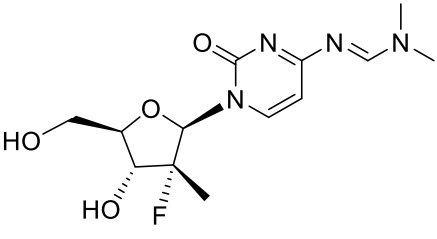
2'-fluoro-down. This is hardly sufficient to teach a POSA how to make compounds across the full claimed scope of compounds with varied 2'-substituents, or even to point a POSA in that direction.

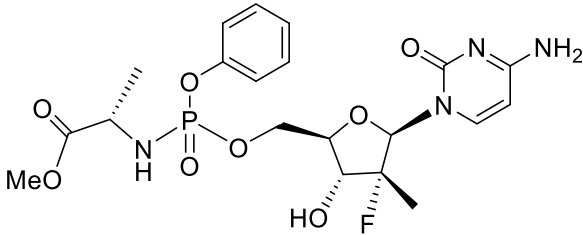
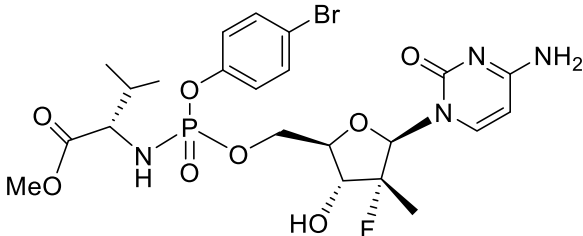
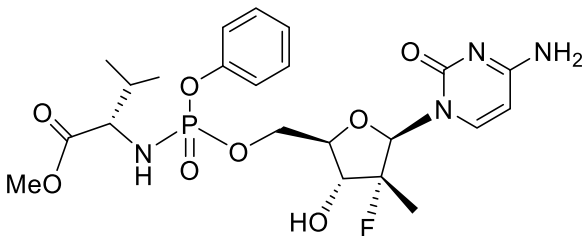
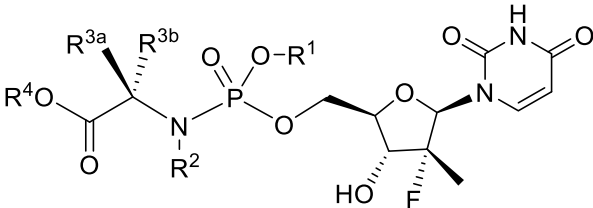
107. Table 9 below summarizes the synthetic Examples provided in the '361 patent (Ex.1001, 304-316) and indicates whether they include compounds that fall within claim 1. It is notable that *all* of the exemplified compounds include the same structural motif in the 2'-position and omit all others.

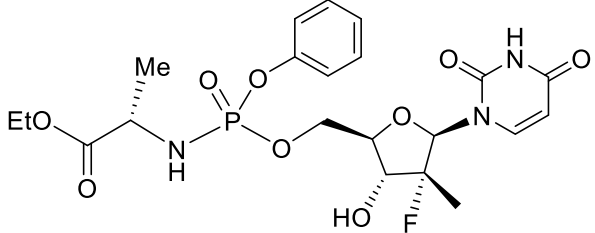
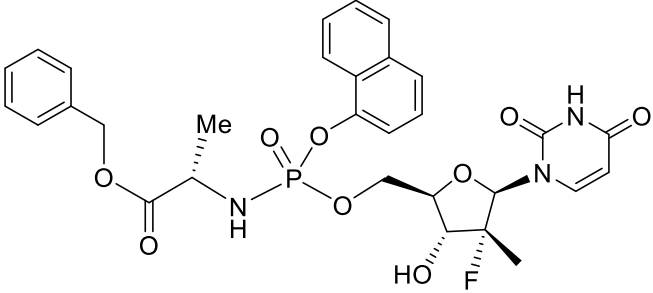
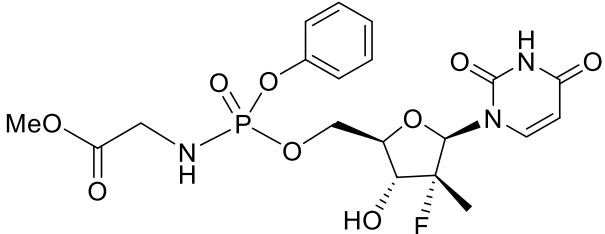
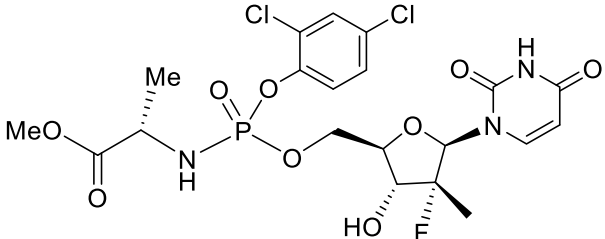
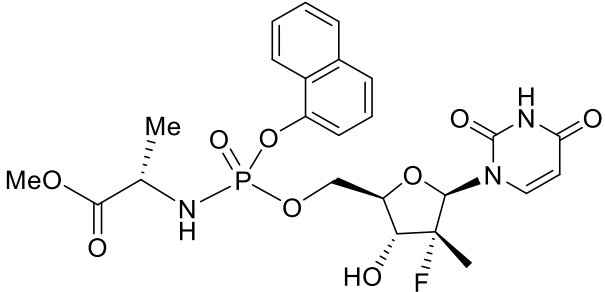
Table 9

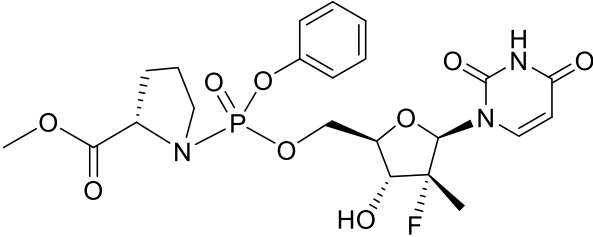
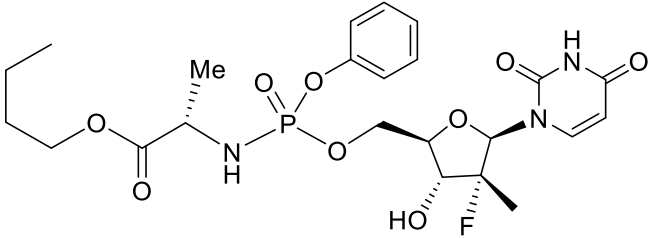
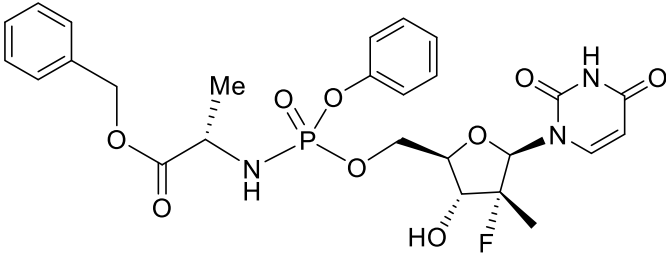
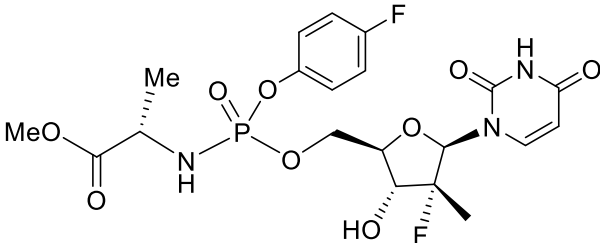
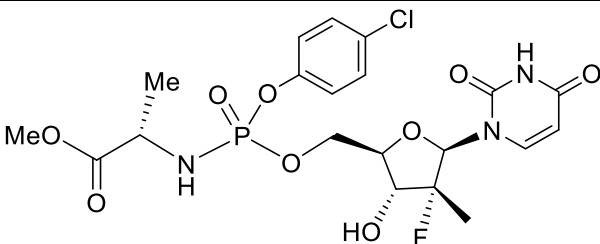
Example	Synthesis	Covered by claim 1 of the '361 patent?
1	General procedure for preparation of phosphorodichloridates $\begin{array}{c} \text{O}-\text{R}^1 \\ \\ \text{Cl}-\text{P}-\text{Cl} \\ \\ \text{O} \end{array}$	No
2	General procedure for preparation of phosphorochloridates $\begin{array}{c} \text{R}^{3a} \quad \text{R}^{3b} \quad \text{O}-\text{R}^1 \\ \diagup \quad \diagdown \quad \\ \text{O} \quad \text{C} \quad \text{N}-\text{P}-\text{Cl} \\ \quad \quad \\ \text{R}^4\text{O} \quad \text{R}^2 \quad \text{O} \end{array}$	No

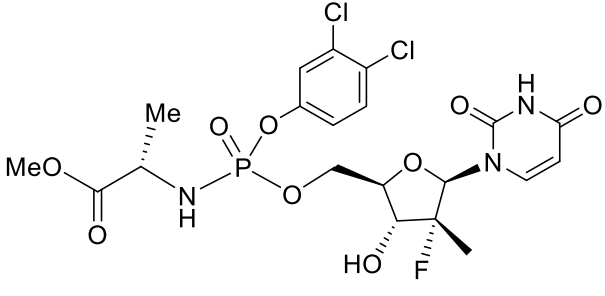
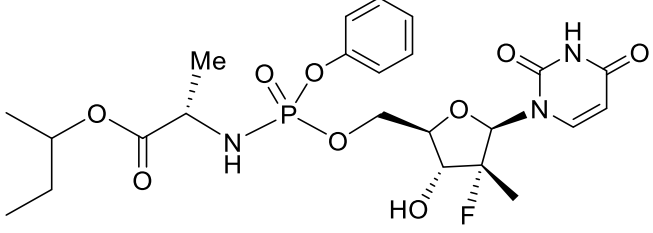
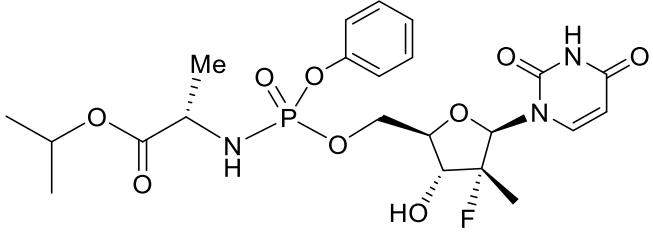
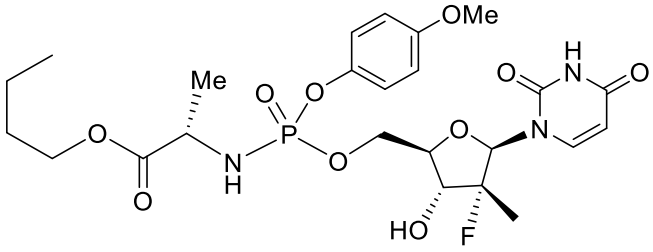
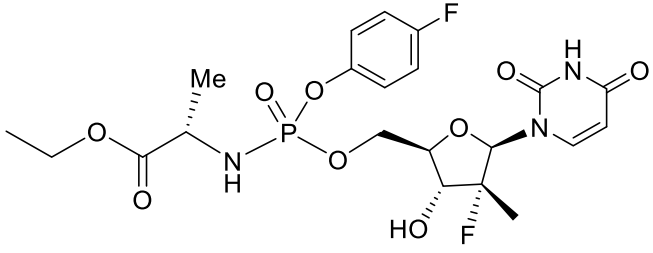
3	General procedures for nucleoside phosphoramidate derivatives 	No
4	2'-Deoxy-2'-fluoro-2'-C-methyluridine 	No
5	2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'- (phenyl methoxy-alanyl phosphate) 	No
6	2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'- (phenyl methoxy-valyl phosphate) 	No

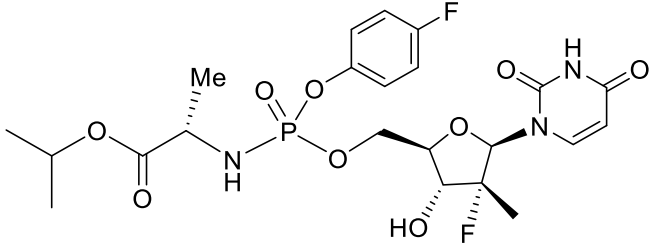
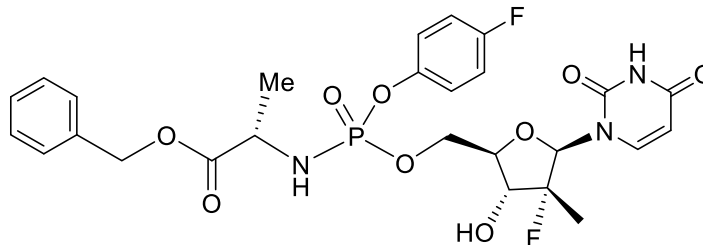
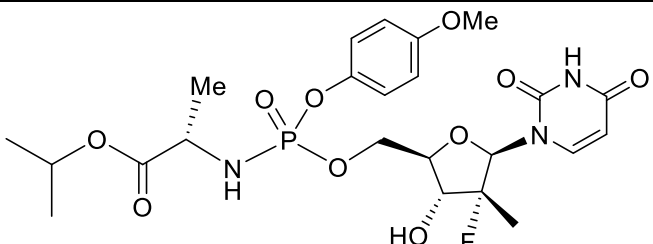
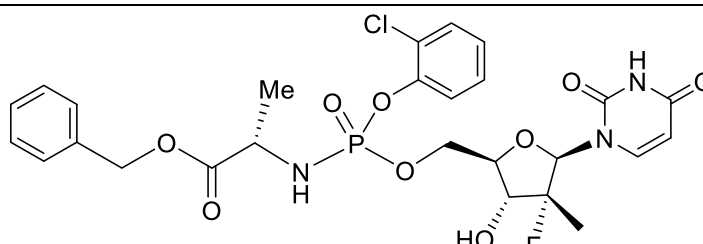
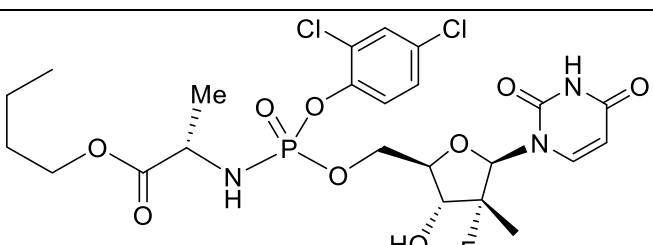
7	2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-valyl phosphate) 	No
8	2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-(4-bromophenyl methoxy-alanyl phosphate) 	No
9	N⁴-(N,N-Dimethylformamidinyl)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 	No
10	2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-alanyl phosphate)	No

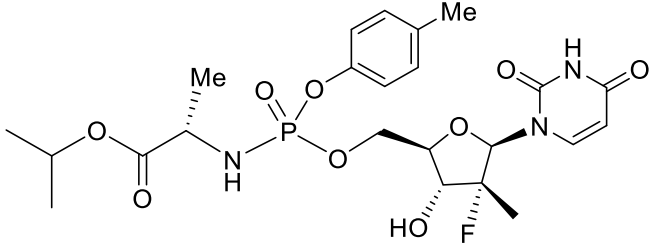
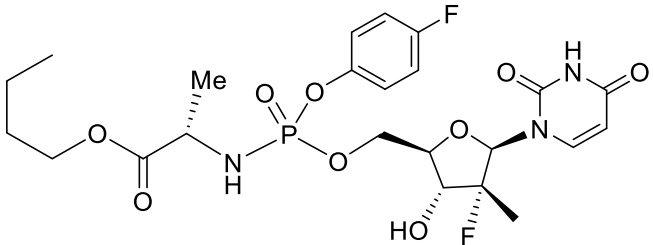
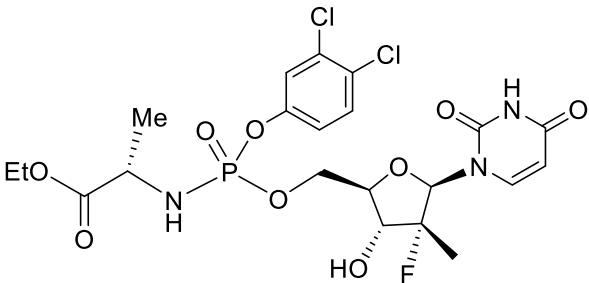
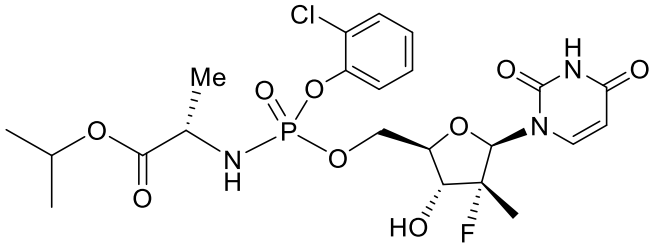
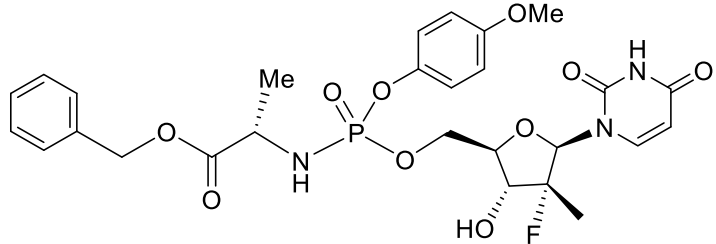
		
11	2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(4-bromophenyl methoxy-valyl phosphate) 	No
12	2'-Deoxy-2'-fluoro-2'-C-methylcytidine 5'-(phenyl methoxy-valyl phosphate) 	No
13-65	Uridine phosphoramidates 	No

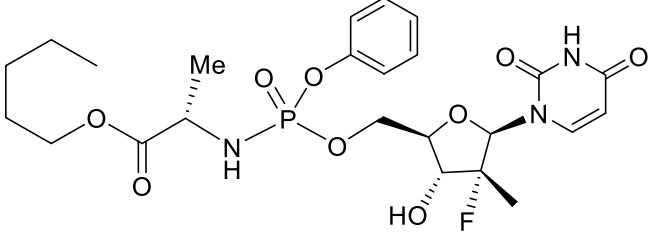
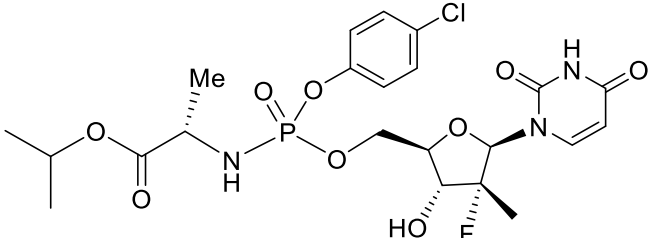
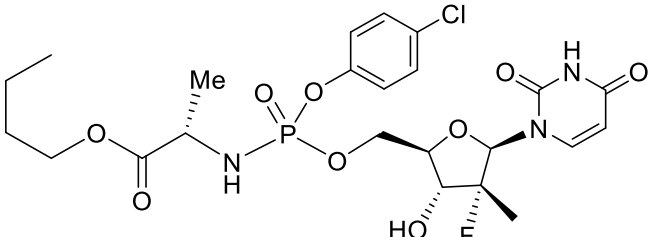
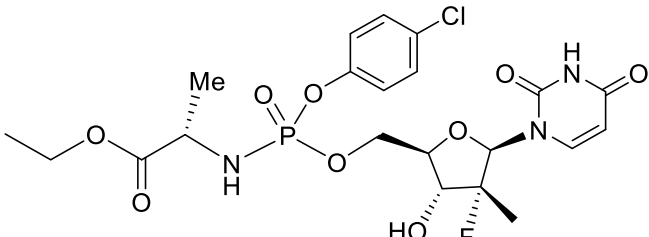
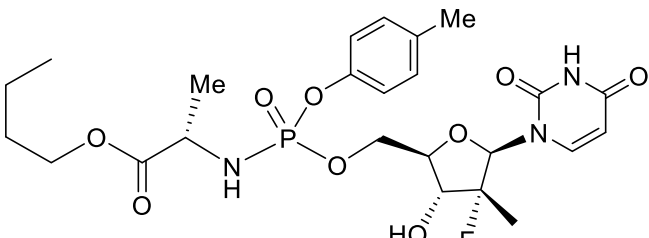
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14		No
15		No
16		No
17		No

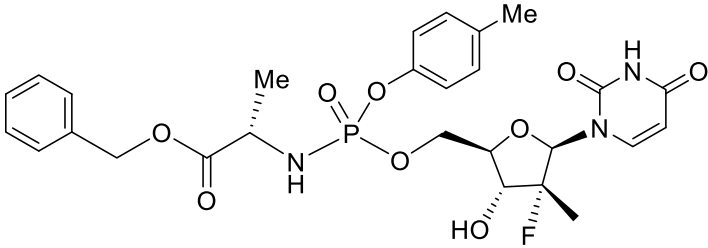
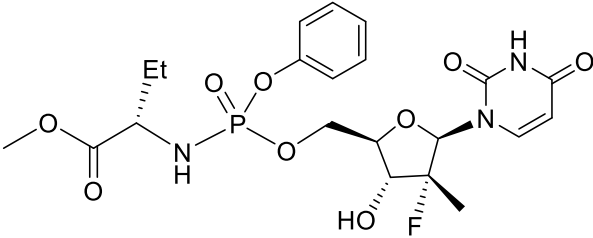
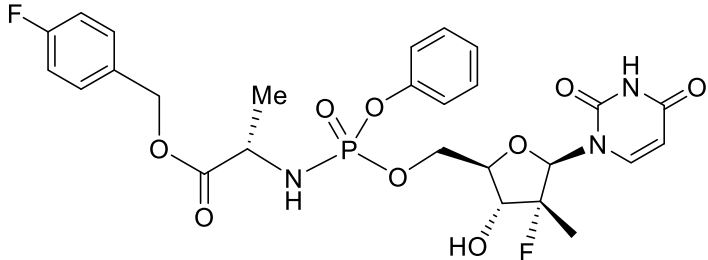
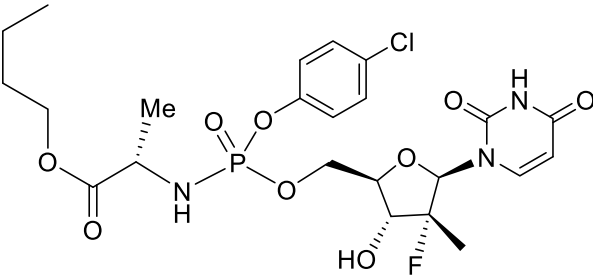
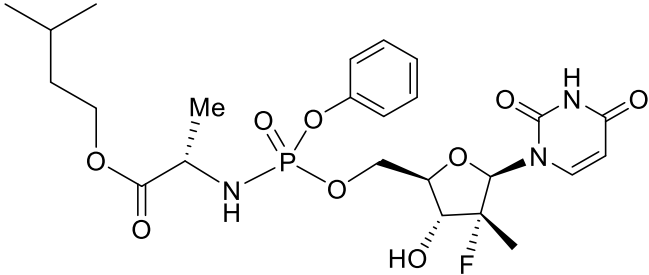
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20		No
21		No
22		No

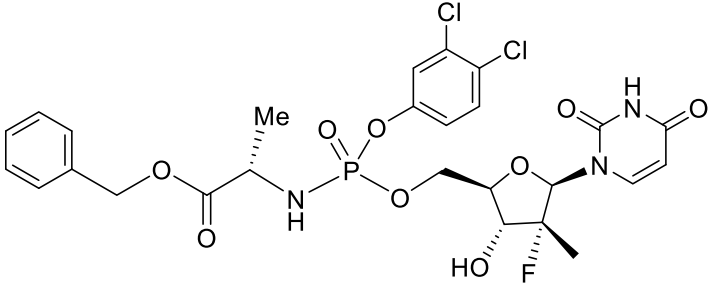
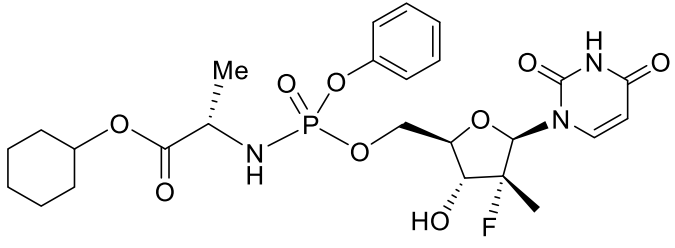
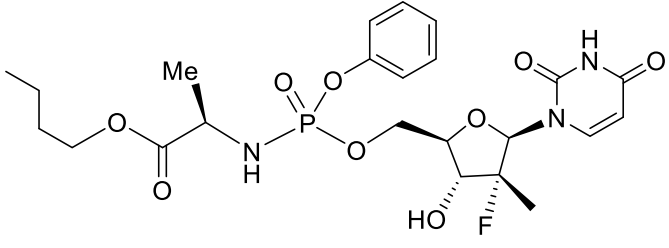
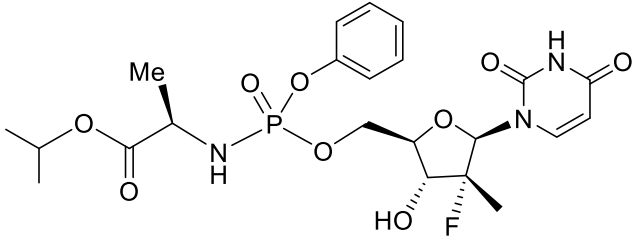
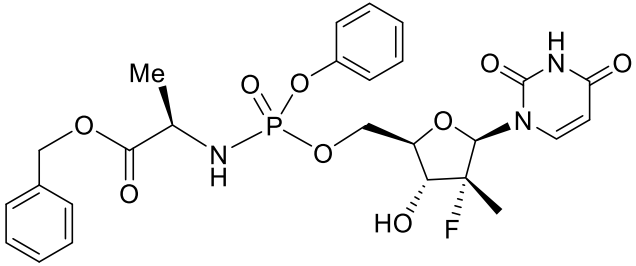
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27		No

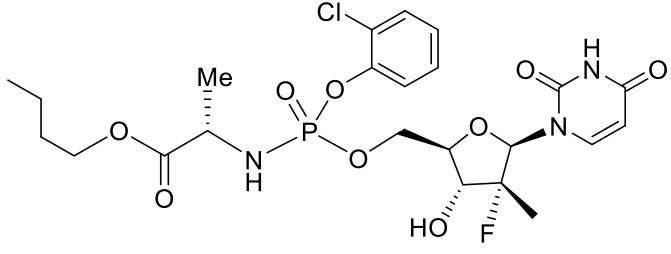
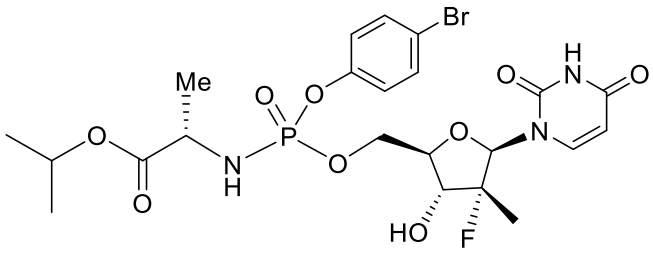
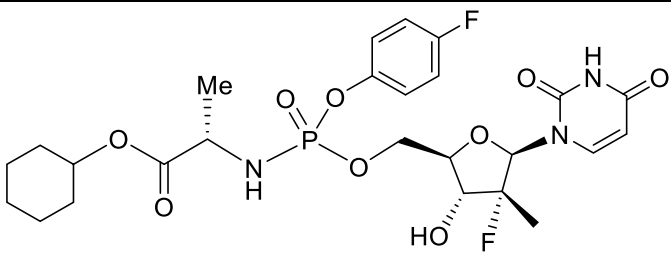
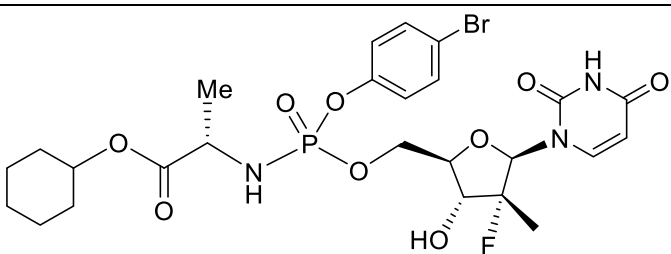
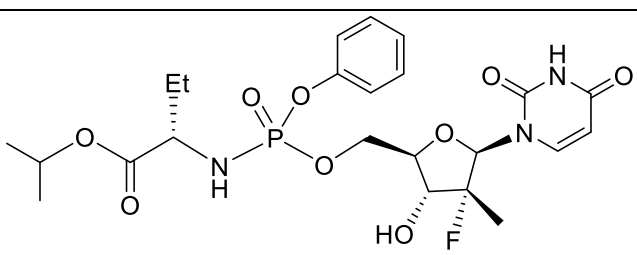
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32		No

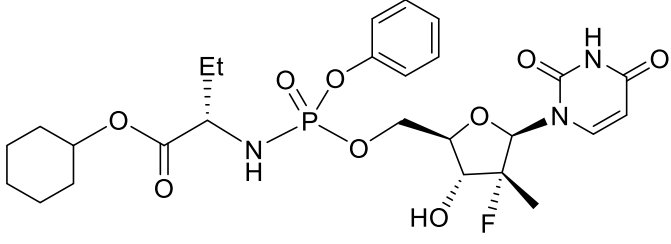
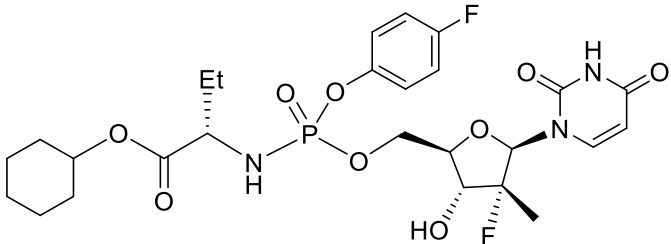
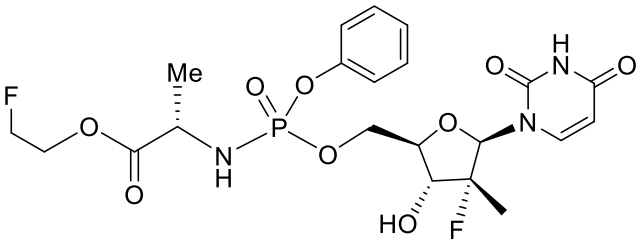
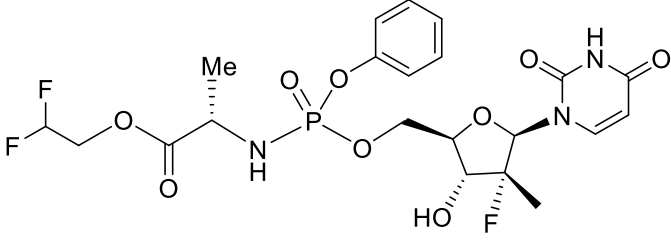
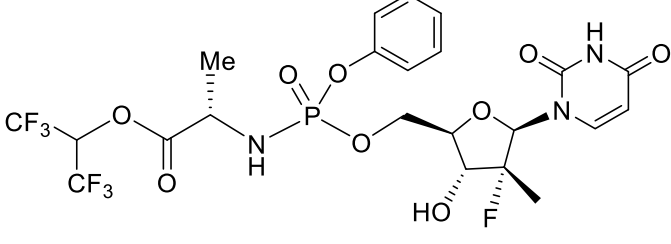
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37		No

38		No
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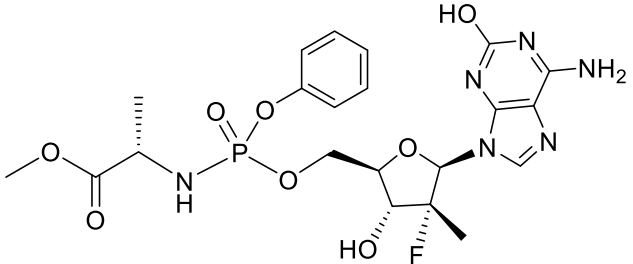
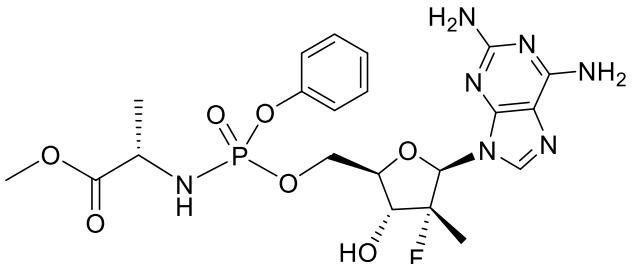
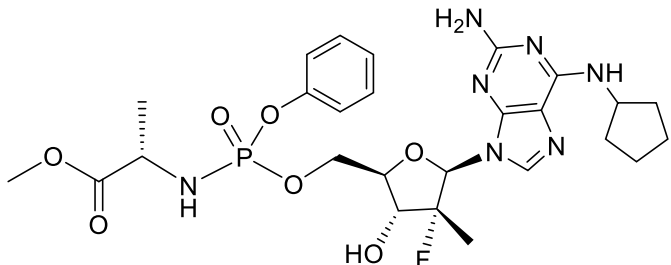
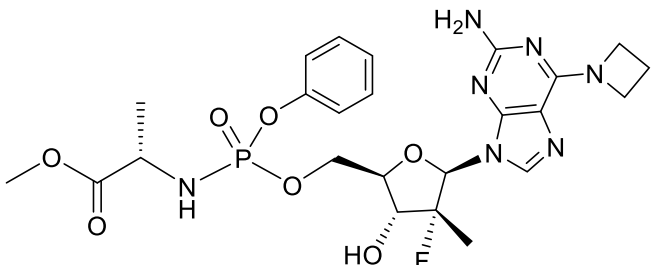
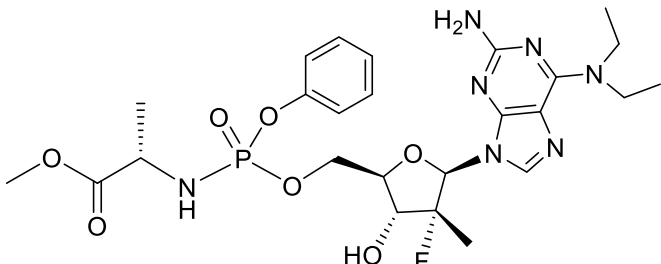
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45		No
46		No
47		No

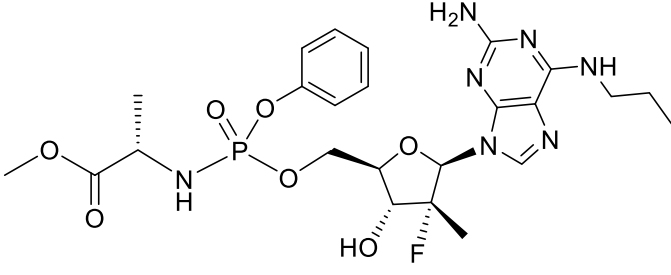
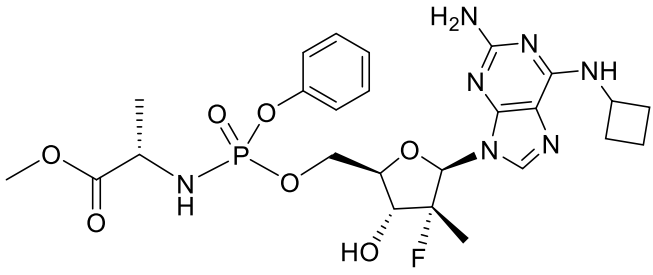
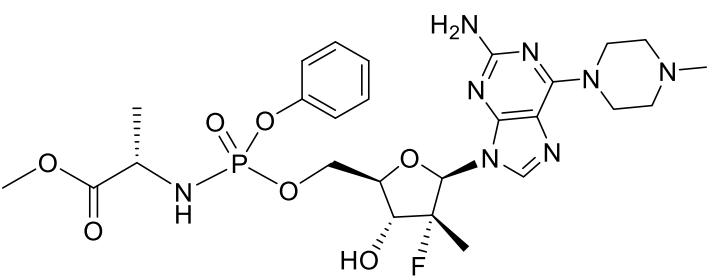
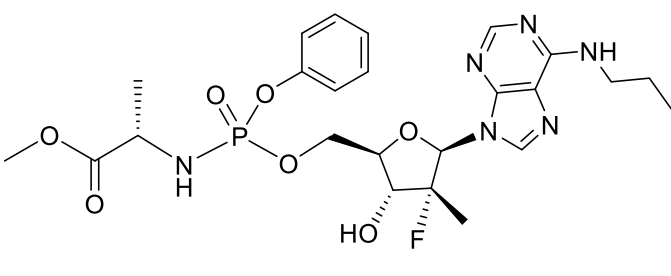
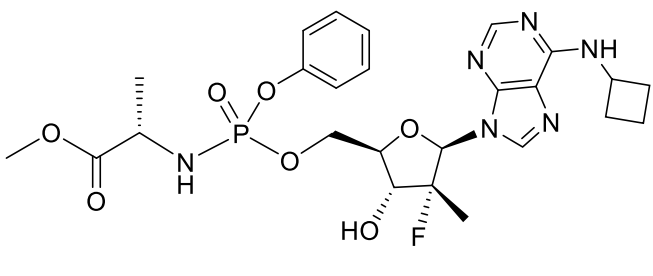
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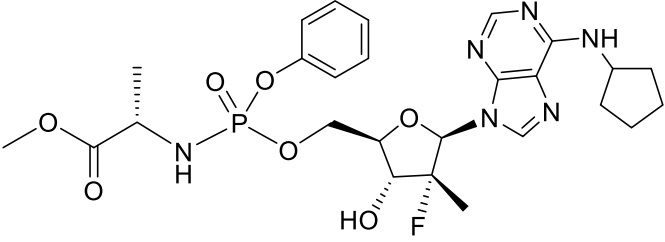
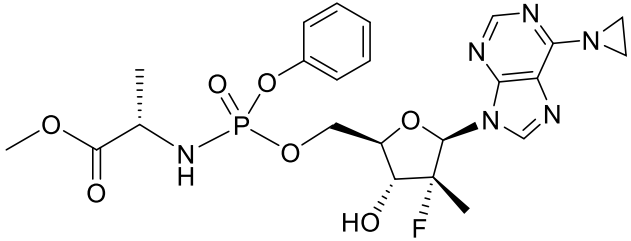
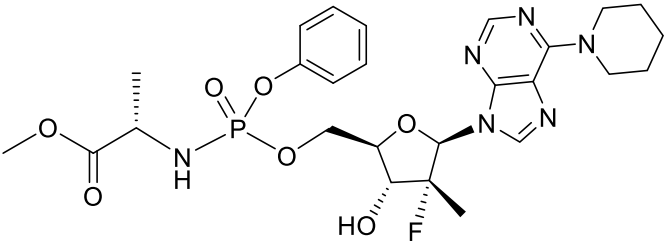
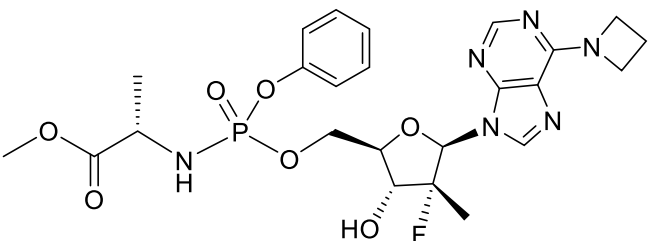
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54		No
55		No
56		No
57		No

58		No
59		No
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61		No
62		No

63		No
64		No
65		No
66	adenine	Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R¹⁰ and R¹¹
67-80		

67		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R ¹⁰ and R ¹¹
68		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R ¹⁰
69		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R'
70		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R ¹⁰
71		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R ¹⁰

72		Yes
73		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R'
74		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R ¹⁰
75		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitation of R ¹¹
76		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R ¹⁰ and R ¹¹

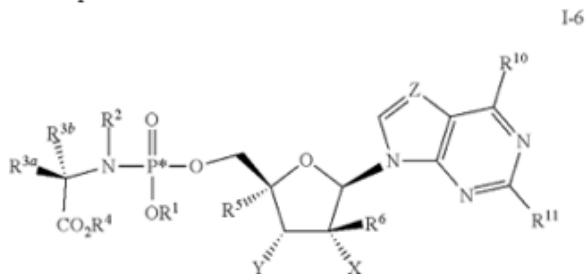
77		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R¹⁰ and R¹¹
78		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R¹⁰ and R¹¹
79		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R¹⁰ and R¹¹
80		Not covered by claim 1; amended out of the claim on Nov. 15, 2022, via limitations of R¹⁰ and R¹¹

F. Inconsistent Statements by PO Regarding Synthesis at the European Patent Office Opposition Division and Technical Boards of Appeal

108. I have been advised by counsel that, during time periods overlapping with PO's U.S. prosecution of the '361 patent, PO was concurrently opposing the grant of EP 2955190 ("EP'190;" Ex.1029) at the EPO Opposition Division and the Technical Boards of Appeal (Ex.1030), with a parallel proceeding at the U.K. Patents Court (92021-000007; EWHC 611 (Pat), Ex.1031). PO was doing so, with expert-backed arguments, on the basis that claims drawn to a nucleotide phosphoramidate (see below) that was very similar to the subgenus of claim 1 of the '361 patent were not valid (Exs.1030 and 1031) because it would be difficult or even impossible to make them.

Claim 1 of U.S. 11,642,361

A compound of formula I-6:

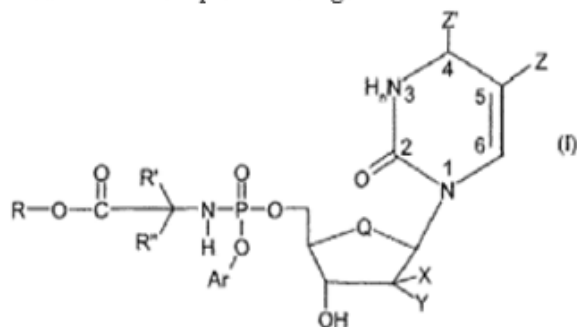


wherein:

- (a) R¹ is H, —CH₃, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;
- (b) R² is H;
- (c) R^{3a} is H and R^{3b} is H, —CH₃, —CH(CH₃)₂, —CH₂CH(CH₃)₂, —CH(CH₃)CH₂CH₃, —CH₂Ph or lower cycloalkyl;
- (d) R⁴ is CH₃, ethyl, n-propyl, or i-propyl;
- (e) R⁵ is H;
- (f) R⁶ is H, —CH₃, —CH₂F, —CHF₂, —CF₃ or —F;
- (g) X is H, —OH, —OCH₃, —F, —NH₂ or —N₃;
- with the proviso that X cannot be OH when R⁶ is —CH₃ or —CH₂F;
- (h) Y is —OH, —NH₂, —OCH₃ or —OC(O)CH₃;
- (i) R¹⁰ is —NHR' and R¹¹ is —NH₂;
- (j) Z is N or —CR¹²;
- wherein R¹² is H, halogen, —OR', —NH₂, —NHR', —NR'₂, —NO₂, C₁₋₆ alkyl, —CO₂R', —CONH₂, —CONHR', —CONR'₂, —CH=CHCO₂H or —CH=CHCO₂R';
- (k) R' is C₁₋₆ alkyl; and
- (l) P* is a chiral phosphorus atom; or a pharmaceutically acceptable salt thereof.

Claim 1 of EP 2,955,190

1. A chemical compound having formula I:



wherein:

- R is selected from the group alkyl, aryl and alkylaryl;
- R' and R'' are independently selected from the group H, alkyl and alkylaryl, or R' and R'' together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;
- Q is selected from the group —O— and —CH₂—;
- X is independently selected from the group H, F, Cl, Br, I, OH and methyl (—CH₃);
- Y is F;
- Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted;
- Z is selected from the group H, alkyl and halogen; and n is 0 or 1,
- wherein when n is 0, Z' is —NH₂ and a double bond exists between position 3 and position 4, and
- when n is 1, Z' is =O;
- or a pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula I.

While the base in the EP'190 patent was a pyrimidine and in the '361 patent claim 1 structure a purine, the sugar moiety and the phosphoramidate components of the two sets of structures overlap and bear a marked chemical resemblance.

109. Specifically, I have reviewed documents (Exs.1030-1032 and 1037-1039) indicating that, while prosecuting the '361 patent claims, PO also

presented arguments and expert testimony that it was difficult to impossible to make nucleotides with substituents in the 2'-position of the nucleotide that are included within the scope of X and R⁶ of the '361 patent claim 1. PO's litigation submissions to the Opposition Division and the Technical Boards of Appeal of the EPO appear to me, based on an analysis of the chemistry, to be technically inconsistent with an implied representation by PO that claim 1 of the '361 patent it presented for patenting is enabled by the patent specification. And I am informed by counsel that *none* of the EPO documents (Exs.1030-1042) submitted by PO was provided or described to the USPTO during prosecution of the '361 patent.

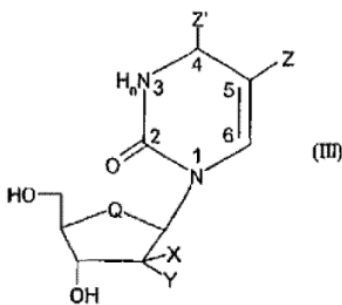
110. I conclude that PO's own positions on non-enablement taken in Europe, which I agree with, establish that, compounds within issued claim 1 of the '361 patent cannot be made without at least significant difficulty.

111. In the following paragraphs, I summarize some of the key arguments Gilead (PO) and its experts made to the EPO concerning the difficulty of making nucleosides having certain substitution patterns at the 2'-position. Specifically, PO's attack on EP'190 included an argument that its claims covered nucleotides with various 2'-substituents, such as 2'-F/OH, but included no specific synthetic routes to achieve these substitution patterns and, moreover, that these compounds, even if somehow made, would be unstable (Ex.1032, ¶134).

(i) PO's arguments on 2'-F/OH nucleosides

112. PO argued that nucleosides having 2'-F/OH would not be feasible to make due to HF elimination. For this argument, PO relied on expert testimony provided by Prof. Jason Micklefield (Ex.1032).

113. Specifically, Prof. Micklefield's report supporting PO as its expert on nucleotide phosphoramidate synthesis in a parallel U.K. proceeding ([2023] EWHC 611 (Pat)) concerning EP'190 was submitted to the EPO. As can be taken from its ¶1, Prof. Micklefield has "over 30 years of research experience in bioorganic chemistry, including the design and synthesis of nucleoside and nucleotide analogs." *Id.* In ¶131, he responded to PO's attorneys Bird & Bird to comment on whether a POSA could synthesize compounds of formula III shown below as of the priority date (July 21, 2003) in view of the common general knowledge and EP'190.

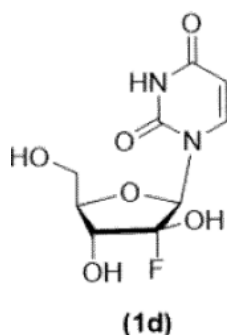


114. Concerning the 2' position, formula III was defined in EP'190 as "X is independently selected from the group H, F, Cl, Br, I, OH, and methyl (CH₃);

and Y is F.” Before commenting on any other substitution patterns, Prof. Micklefield made the following assertion at ¶134 (emphases added):

As a preliminary point, the Skilled Chemist [i.e., a POSA] would see that *some of the compounds of Formula III are not feasible to make. If X is OH and Y is F, that compound would be unstable and eliminate HF. I am not aware of any stable compounds which have an alcohol and a fluorine attached to the same carbon.* The Skilled Chemist would rule that out as a structure. *Inclusion of compounds where X is OH [and Y = F] would make the Skilled Chemist question how rigorously the authors have looked at the different substituents in the definition of Formula III.*

115. This view is reinforced at his ¶141, where Prof. Micklefield stated (emphasis added) that “*it would be apparent that 1d is not feasible to synthesise and isolate*”.



116. Prof. Micklefield returns to this point at ¶¶168 and 169 of his expert report and cites to the Seppelt (Ex.1033),¹³ Willis (Ex.1034),¹⁴ and Cheburkov (Ex.1035)¹⁵ articles to conclude (Ex.1032, emphases added):

As explained at paragraph 134 *compound 1d would not be a viable molecule to make*. That is clear from the search results, which include lots of patents but *no evidence that anybody has ever made any molecule similar to 1d with an OH group and F attached to the same carbon*.

The Skilled Chemist would find there were very few reports of the synthesis, isolation and characterisation of α -fluoroalcohols of any sort (i.e. alcohols with a fluorine bound to the same carbon). *The literature in 2003 indicates such functionality is unstable*. A Skilled Chemist would recognise that even if α -fluoroalcohols could be prepared it [sic] *would undergo facile elimination of HF and would therefore be too unstable for the pharmaceutical applications in mind*.

¹³ I certify that Exhibit 1033 is a true and correct copy of Seppelt, K., “Trifluoromethanol, CF₃OH.” *Angew. Chem. Int. Ed. Engl.*, 16: 322-323 (1977).

¹⁴ I certify that Exhibit 1034 is a true and correct copy of Willis, C. J., “Fluorinated Alcohols and Their Metal Complexes.” *Coord. Chem. Rev.*, 88: 133-202 (1988).

¹⁵ I certify that Exhibit 1035 is a true and correct copy of Cheburkov, Y., et al., “Perfluoroalcohols” *J. Fluorine Chem.*, 118: 123-126 (2002).

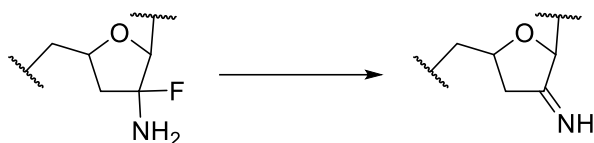
117. Clearly, Prof. Micklefield and PO were of the view that 2'-F/OH nucleosides are “unstable”, and “not feasible to synthesise and isolate” (Ex.1032, ¶¶141, 168, and 169). These comments were not limited to pyrimidine phosphoramidates and instead extended to any compound with an “an alcohol and a fluorine attached to the same carbon” (*id.*, ¶134). The fundamental chemical mechanism underlying this view is that the oxygen can form a double bond with the C2' position's carbon, eliminating fluoride and losing a proton in the process, to form HF and a carbonyl group.

118. Compounds of claim 1 of the '361 patent wherein X is OH and R⁶ is F would thus likely be unstable and eliminate HF. And, separately, I am not aware of any stable drug-like compounds which have an alcohol and a fluorine attached to the same carbon.

119. PO's stated position on the instability of 2'-F,2'-OH substituted nucleosides was never communicated to the USPTO during prosecution of the '361 patent, resulting in the issuance of a U.S. patent that includes this motif as one of the allowed combinations (Ex.1002).

(ii)Applying PO's arguments to 2'-F,2'-NH₂ nucleosides

120. I am not aware that PO expressly commented on the 2'-F,2'-NH₂ nucleoside substitution pattern.¹⁶ However, in my opinion, the same fundamental chemical reasoning should apply, as seen below. Just like O, NH can form a double bond with the C2' position's carbon, eliminating fluoride and losing a proton in the process, to give HF and a 2'-imine group.



121. Compounds of claim 1 of the '361 patent wherein X is NH₂ and R⁶ is F, following PO's logic, would likely be unstable and eliminate HF. And I am not aware of any stable drug-like compounds that have both an amino group and a fluorine atom attached to the same carbon atom.

(iii)Applying PO's arguments to other 2'-position substituents

122. As discussed in Section VI.E, claim 1 of the '361 patent includes thirty-four different combinations of 2' position substituents of which the synthesis of just one of the combinations is provided. According to PO and its experts, synthesizing claimed compounds across this entire scope of 2' position substituents would require at least a substantial research project. I agree with this position.

¹⁶ The claims of EP'190 did not include 2'-F,2'-NH₂ nucleosides.

123. Prof. Micklefield emphasized at ¶180 of his expert report (Ex.1032) that a POSA faced a “new territory” to make nucleosides having new substitution patterns at the 2’-position in nucleosides (emphases added):

The Skilled Chemist *is very much going into new territory with molecules that have not been synthesised before and more so where there are few examples of that kind of functionality in related molecules*. So, *this is a research project* for the Skilled Chemist.

124. I understand from counsel that PO also engaged Prof. Geert-Jan Boons as an expert witness concerning EP’190. According to Prof. Boons, he has a detailed knowledge of carbohydrate chemistry and has worked on projects involving the modification of carbohydrates and nucleosides, including fluorination (Ex.1036, ¶¶3.1-3.10). His second declaration at ¶17 (Ex.1037) highlights the difficulties associated with base coupling to a novel substrate (emphases added):

The *stereoselective formation of a glycosidic linkage is one of the most challenging aspects of synthesis of a nucleoside* or oligosaccharide...

There are many choices to be made regarding parameters such as the leaving group, protecting groups, reagents and reaction conditions. Furanoses can adopt multiple envelope configurations which will affect the stereochemistry of the glycosylation differently. It is not possible to generalise such a reaction. *Conditions that have been found to be adequate to install one particular base on one particular sugar cannot confidently be predicted to apply to a different combination of base/sugar.*

125. PO's Grounds of Appeal (Ex.1038) filed with the EPO concerning EP'190 emphasize at ¶6.144 (emphases and underlining added) that "an undue burden" arises where several unprecedented steps are required to arrive at a compound covered by the claims:

It must be the case that the number of entirely new reactions that a skilled medicinal chemist needs to carry out, and the time those entirely new reactions take to complete, are factors in the burden the skilled person faces. Thus, while a single reaction that takes a few hours or a day to complete might in some cases not represent undue burden, an entirely new synthesis involving eight to ten steps and taking at least "several weeks"... must necessarily impose a higher burden on the skilled person. The number of undisclosed steps and the duration of the synthesis must therefore be relevant factors in assessing whether there is undue burden. When carrying out an entirely new synthesis (as is the case here), a skilled person does not know in advance whether it will work, and so each additional step inevitably imposes an increasing burden.

126. Despite making these statements in Europe detailing the difficulties in preparing nucleoside compounds with new substitution patterns, PO presented claim 1 of the '361 patent to the USPTO which only provides the synthesis of one out of the thirty-four possible combinations of 2' substituents.

(iv) Fluorination chemistry is particularly complicated

127. According to my technical review, PO took a position at the EPO that was directly inconsistent with the patentability of claim 1 of the '361 patent because non-routine and challenging fluorination chemistry would be needed to access the full scope of the thirty-four claimed combinations of 2' substituents. I agree with this position. At ¶139 of his expert report on behalf of PO, for example, Prof. Micklefield stated (Ex.1032, emphasis added):

Generally, *introducing fluorine is quite difficult compared to other substituents because of fluorine's unusual reactivity*. It is still difficult to put fluorine into molecules now [i.e., in 2022] and that would have been more the case in 2003.

And at ¶153 Prof. Micklefield added (*id.*, emphasis added):

The Skilled Chemist would see exploratory fluorination chemistry on simple model compounds, with only a few examples of the chemistry being applied to more complex structures. The Skilled Chemist would also appreciate that *this is challenging chemistry and many of the reagents described were difficult to handle, toxic, corrosive, unstable or potentially explosive*.

(v) Delivering a tetra-substituted stereocenter at the 2'-position is challenging

128. Prof. Micklefield also pointed to “significant challenge[s]” to fluorination of tertiary alkyl groups in ¶139 of his expert report (*id.*):

there were very few examples of chemistry which allowed the introduction of fluorine at a position where there are tertiary alkyl groups. So, the Skilled Chemist would have appreciated that this tertiary fluoride would have presented a significant challenge to make.

129. I agree that it is challenging to fluorinate a tertiary alkyl site in a sugar ring.

(vi) Controlling the stereochemistry at the 2'-position contributes to the POSA's "undue burden"

130. At ¶185, Prof. Micklefield emphasized the difficulty of obtaining the correct stereochemistry in nucleoside syntheses, which generally introduce stereocenters at several positions (*id.*, emphasis added):

Unless the Skilled Chemist can find methods of controlling the stereochemistry at these centres, two new diastereomers will be formed in each step, one of which will need to be separated, one discarded and the correct diastereomer progressed to the next step. In each case it is not clear in advance how much (if any) of the desired diastereomer would be generated in the reactions, *so the amount of the desired product may be very low or none.*

131. I agree that it is difficult to isolate a specific stereoisomer for a compound with several stereocenters like those claimed in the '361 patent.

(vii) Nucleoside syntheses would be expected to be challenging and take a long time

132. Even conducting literature searches on nucleoside synthesis is a lengthy process according to Prof. Micklefield who made this point at ¶158 of his expert report (emphasis added):

Conducting a comprehensive literature review in relation to any of [2'-F-nucleoside] compounds 1a-1e¹⁷ *is a very substantial task*. In practice, in the context of a challenging synthetic project such as this, the Skilled Chemist would have taken at least two weeks (full time) and possibly much longer just to review March [an advanced organic chemistry textbook] as described above and conduct sub-structure searches and review the papers identified.

133. As for the actual synthesis, according to Prof. Micklefield, this realistically would be much longer, as noted at his ¶186 (emphasis added):

It is my initial view that if they [i.e., POSAs] were really fortunate (by which I mean they selected a research route that works first time and their syntheses worked as planned), they might be able to make compounds 1a-1c, or 1e in about six months per compound, but the

¹⁷ Compound 1d is the unstable 2'-F/OH nucleoside. Compound 1e is the 2'-F/CH₃ nucleoside. Compounds 1a, 1b, and 1c include 2' substitutions which are not covered by claim 1.

Skilled Chemist *would need to plan for up to three years to make each compound.*

134. The statements cited above by PO's experts would also apply to determining whether other substitution patterns in nucleosides could be accessed without "an undue burden," including, for example, combinations of CH₂F, CHF₂, and CF₃ with the X groups of claim 1 of the '361 patent. A POSA would need to apply this rigorous study to at least the thirty-three 2' substitution patterns that PO did not provide the synthesis for.

135. Table 10 below provides a timeline of positions taken by PO (Gilead) during prosecution of the '361 patent at the USPTO and PO's inconsistent (and indeed contradictory) statements at the EPO.

Table 10

Date of submission	Gilead's position in the U.S. for the '361 patent	Gilead's position in Europe (2'-F/OH statements in blue)
Dec. 8, 2020		Prof. Boons highlights the base coupling step in his second expert report as "one of the most challenging aspects of synthesis of a nucleoside," for which

		“success confidently cannot be predicted.” Ex.1037, ¶17.
Mar. 19, 2021	Gilead respectfully requested “[f]avorable consideration of the application.” The ‘361 patent application lacks synthetic routes to the scope of the compounds presented. (f) R⁶ is H, CH₃, CH₂F, CHF₂, CF₃, or F; (g) X is -H, OH, OCH₃, F, NH₂, or N₃ with the proviso that X cannot be OH when R⁶ is CH₃ or CH₂F Ex.1002, 91.	

Aug. 17, 2021		Gilead argues in its Grounds of Appeal that the “number of undisclosed steps and duration of the synthesis” are relevant factors in concluding that there is an undue burden. Ex.1038, ¶6.144.
July 12, 2022	Gilead asserts its belief that “the present application is now in condition for allowance,” while still claiming nucleotides having the 2’ substitution patterns highlighted above. Ex.1002, 242.	
Nov. 2, 2022		Gilead’s expert Prof. Micklefield states in his expert report in the U.K. that: • compounds with 2’-F/OH are “not feasible to make” and “too

		unstable for the pharmaceutical applications”; Ex.1032, ¶¶134 and 169. • a POSA would not be confident of success without literature routes to compounds with the desired 2’-substitution; Ex.1032, ¶178. • fluorine chemistry is relatively difficult; Ex.1032, ¶139. • making a nucleoside with a tetra-substituted stereocenter at the 2’-position would be a “significant challenge”; Ex.1032, ¶139.
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		- the stereochemical course of nucleoside synthesis reactions is unpredictable; Ex.1032, ¶184. - even carrying out a literature search on nucleoside synthesis is a “very substantial task”, and that the synthesis itself realistically may take “up to three years” Ex.1032, ¶¶158 and 186.
Nov. 15, 2022	Gilead asserts that claims covering nucleotides having the 2’ substitution patterns highlighted above are “patentable” and that “the present	

	application is now in condition for allowance.” Ex.1002, 247.	
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136. I am informed by counsel that PO’s litigation statements, as well as statements by experts presented on its behalf, regarding the state of the art in synthesis of nucleotides (and the predictability of antiviral activity) are admissible in this proceeding. As extensively detailed herein, PO has a long record of statements describing great challenges in deriving useful, active derivatized nucleosides, and thus their prodrugs as of the filing date of the ’361 patent. In my opinion, these statements qualify as highly relevant and probative admissions by PO against the patentability of claim 1 of the ’361 patent. In my opinion as an expert in pharmaceutical chemistry, PO directly contradicted itself with inconsistent technical statements to the U.S. and European Patent Offices.

**G. Inconsistent Statements by PO Regarding Anti-HCV Activity of
’361 Patent Claim 1 Compounds**

137. Just a handful of N⁶-derivatized N²-aminopurine phosphoramidate nucleotides were made and physically characterized in the ’361 patent (the seven compounds in Examples 68-74), and *only one* of them falls within the scope of claim 1 of the ’361 patent (compound 72) (Ex.1001, 315). In addition, no more than merely 19 compounds out of the entire huge ’361 Supergenous were

subjected to biological characterization *in vitro* (Ex.1001, cols. 610-617), only two of which are N⁶-derivatized N²-aminopurine phosphoramidates (Compounds 69 and 70), **none** of which falls within claim 1 of the '361 patent. One of the characterized diaminopurine compounds is a N⁶-cyclopentyl derivative and the other is a N⁶-azetidine derivative (Compounds 69 and 70, respectively, Ex.1001, 315), and both of these compounds were expressly excluded from the scope of claim 1 by the November 15, 2022, amendment after Final Office Action (Ex.1002, 269-272). No toxicity data are provided for any compound in the '361 patent (Ex.1001).

138. In my opinion, a POSA would find the '361 patent specification to be an unhelpful, if not impossible, document to use in order to arrive at the subgenus of claim 1 not only for the reasons explained above, but also because **no** biological data whatsoever were provided for any species within claim 1, even though PO did test a range of other compounds.

139. If a POSA somehow overlooked the '361 patent's strong emphasis on the pyrimidine (rather than purine) nucleotides and even without any "blaze marks" somehow decided to make a N⁶,N²-diaminopurine derivative instead, then (s)he would have just two structures with *in vitro* biological data to use as a starting point (the N⁶-cyclopentyl and N⁶-azetidine derivatives (Compounds 69 and 70, respectively)), both of which were eventually eliminated from claim 1 (Ex.1002, 269-272). In my opinion, selecting any other N⁶,N²-diaminopurine compound

would be illogical. There is no rational reason to select compounds with missing biological data over two compounds with reported biological activity data. And even for the two N⁶,N²-diaminopurine compounds with bioactivity characterized in the '361 patent there are no toxicity data.

140. As with the synthesis of nucleotide phosphoramidates, I have been directed by counsel to litigation documents that include arguments from PO or its expert on the unpredictability of biological activity of nucleotides with novel substitution patterns (Exs.1038-1041). I conclude that these litigation arguments are technically inconsistent with an inherent representation made by PO to the USPTO that the full scope of compounds in the '361 patent claim 1 would exhibit anti-HCV activity without any supporting data.

141. I am also told by counsel that PO failed to provide these real-time inconsistent statements to the USPTO during prosecution of the '361 patent.

142. I summarize below some of the key statements Gilead (PO) and its experts made in Europe concerning the unpredictability of the biological activity of nucleotides with new substitution patterns. Again, to place these in proper context, PO was attacking EP'190 which covered nucleotides with various substituents and reported biological activity for *three* of the claimed compounds in that case (as compared to *zero* compounds in the case of claim 1 of the '361 patent) (Ex.1029, 63-65, and Ex.1001). PO objected to EP'190 based on the fact that this

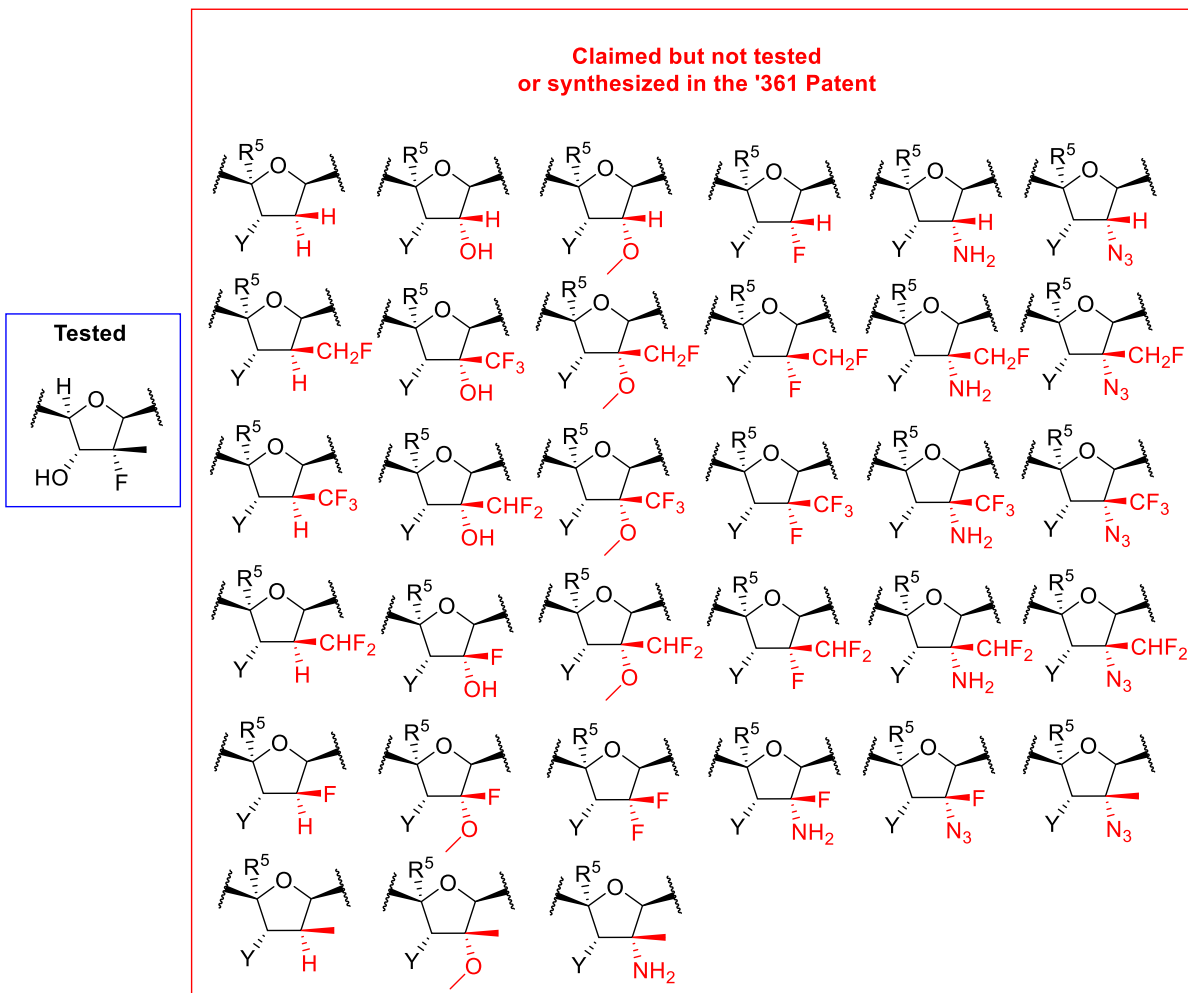
biological activity was not shown across the full scope of the claims, i.e., for claimed substitution patterns beyond the three for which such data were reported (Ex.1038, 4 and 82).¹⁸

143. In contrast, the '361 patent presented biological activities for *none* of the compounds falling within claim 1. The claim defines substituents at the 2'-position, the base, and the phosphoramidate that were absent in any of the (unclaimed) compounds for which biological activity data were presented in the '361 patent (Ex.1001, 316-321). PO's own statements below make clear that, in the view of PO and its experts, the biological activity data in the '361 patent for specific substitution patterns by no means indicates that the same activity will be achieved across the full scope of claim 1 in the '361 patent.

144. PO's European litigation arguments on the unpredictability of biological activity following changes at the 2'-position are strikingly inconsistent with its U.S. arguments with respect to claim 1 of the '361 patent. All of the

¹⁸ While EP'190 was primarily directed to anti-cancer nucleotides and the '361 patent is directed to antiviral nucleotides, the breadth of PO's comments regarding the lack of predictability of biological activity encompasses both. Further, PO presented an expert to directly bridge its comments to apply to both anti-cancer and anti-viral nucleotides (Prof. Götte's Exs.1040 and 1041).

(unclaimed) compounds for which biological activity data are presented in the '361 patent have 2'-up (Me) and 2'-down (F) substituents (Ex.1001, 316-321). Graphically, the data provided by PO can be compared to the scope claimed in the '361 patent as follows:



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¹⁹ I am informed by counsel that Petitioner has tested three compounds which fall within the scope of the '361 patent claim 1 which were active in an HCV inhibition assay. The three active compounds were (i) Petitioner's AT-511 (2'-CH₃-up, 2'-F-

145. Similar biological activity would only be expected to be achieved across the scope of the claims based on the arbitrary and improbable *assumption* that the following changes do not significantly impact the biological activity of nucleosides/nucleotides:

- 1) changing 2'-up (Me) to 2'-up (H, CH₂F, CHF₂, CF₃, or F); and, at the same time,
- 2) changing 2'-down (F) to 2'-down (H, OH, OCH₃, NH₂, or N₃).

Indeed, PO took the position in its European litigation submissions on EP'190 that this *assumption* is incorrect (Ex.1038 and 1039).

146. For example, at ¶7.52 of its Grounds of Appeal submitted to the EPO (Ex.1038) PO stated (and I generally agree):

down); and (ii) two N⁶(H),(CH₃),N²-diaminopurines, one with 2'-F-up, 2'-F-down and the other with 2'-CF₃-up, 2'-F-down. Petitioner also tested N⁶(H),(CH₃), N² diaminopurine with 2'-F-down and 2'-H-up which showed no activity even at >100 μM. In addition, Petitioner also tested an N⁶(CH₃)₂,N²aminopurine with 2'-F-down and 2'-H-up which showed no activity even at >100 μM. I am also informed by counsel that Petitioner is aware of no combination of substituents with a 2'-hydrogen in the up position active against HCV, nor 2'-hydrogen in the down position active against HCV.

It is also well established that in the field of drug design any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, a priori expected to disturb the pharmacological activity profile of the initial structure...

147. The '361 patent only provides biological data for 2'-up (Me) / 2'-down (F) compounds (Ex.1001, 316-320) and undeniably fails to establish a "correlation between structural features and activity" for the claimed 2'-up (H, CH₂F, CHF₂, CF₃, or F) and 2'-down (H, OH, OCH₃, NH₂, or N₃) compounds. According to PO's own reasoning, therefore, these substitutions are "expected to disturb the pharmacological activity profile" of compounds.

148. Specifically with respect to antiviral activity, PO relied on Prof. Matthias Götte as its expert witness in U.K. High Court proceedings (Exs.1040 and 1041). Prof. Götte's research included the development of novel strategies to inhibit viral RNA-dependent RNA polymerase, including the use of nucleotide analogs (Ex.1040, 2). At ¶61 of his first expert report (Ex.1040), Prof. Götte stated (emphasis added):

The general approach to the discovery of novel nucleoside analogues involved the synthesis and subsequent testing of multiple different compounds to uncover which compounds had activity. Nucleoside analogues can, in theory, be modified at most positions on the base or sugar ring of the molecule by adding a range of different substituents. However, the antiviral activity of the molecule is dependent on its

ability to be recognized by cellular enzymes in order for it to be phosphorylated to the active triphosphate form and be recognized by the target viral polymerase and thereby be incorporated into the viral nucleotide chain. The skilled virologist would have appreciated that ***even the slightest modification in the nucleoside analogue structure could lead to significant changes in activity, selectivity and therapeutic potential.***

149. Prof. Götte reiterated this view with respect to viruses in ¶¶11 and 43 of his second expert report (Ex.1041) before the U.K. High Court (emphases added):

As I will describe in more detail below, ***antiviral activity is highly dependent on the particular virus and the particular nucleoside analogue being studied.*** It is unrealistic to discuss SAR [i.e., structure-activity relationship] and rational drug design and seek to predict antiviral efficacy across the entire scope of viruses – both DNA and RNA viruses – and across a wide class of different nucleoside analogues. As I stated a number of times in my First [Expert] Report, this field was in 2003 largely empirical. ***Small changes to a molecule can have a significant impact on activity.***

As explained above, even well-studied obligate chain-terminators such as the aforementioned HIV drugs can show complex different kinetic properties that translate in differences in efficiency of inhibition. Given the relative lack of knowledge about mechanisms of action of the non-obligate chain terminators, ***seeking to predict any activity for an entire class of nucleoside analogues would not have made sense.*** In a class where antiviral activity is not a given and must be tested each time and

where even a known active antiviral compound could have an uncertain mechanism of action, I do not believe that the skilled team ***could have made legitimate predictions as to likely activity based on structural changes from a nucleoside analogue inhibitor with known activity.*** As I have stated previously, ***in the field of nucleoside analogue inhibitors even small structural changes can have significant effects.***

150. Prof. Götte also illustrated this point using the Perkins reference (Ex.1042)²⁰ at ¶¶12 and 13 of his second expert report (Ex.1041). Perkins showed that 2'-deoxy nucleosides kill DNA viruses, while the corresponding 2'-OH compounds do not, leading Prof. Götte to conclude at ¶14 that (Ex.1041, emphases added):

Even a change which on its face is small – swapping a 2'-H atom (deoxyuridine) in the sugar for a 2'-OH group (uridine) caused complete loss of antiviral activity. By 2003 it was known that compounds with a 2'-H atom would be accepted by DNA polymerases or reverse transcriptase whereas compounds with 2'-OH would be accepted by RNA polymerases. Therefore ***the 2' position in a nucleoside analogue is highly significant in an antiviral context*** as it

²⁰ I certify that Exhibit 1042 is a true and correct copy of Perkins, E. S., et al., “Anti-viral Activities of Several Iodinated Pyrimidine Deoxyribonucleosides.” *Nature*, 194: 985-986 (1962).

differentiates between DNA viruses or retroviruses and RNA viruses, respectively, as potential targets.

151. Thus, according to PO's own expert, it is highly doubtful that antiviral activity will be achieved in the claimed compounds of the '361 patent, in which X is H.

152. In his second expert report, another PO expert, Prof. Micklefield, opined that the biological data for the three claimed 2'-up (F) / 2'-down (F) compounds in EP'190 did not allow conclusions to be drawn about the activity of the other claimed compounds with, for example, the 2'-Me substituent (Ex.1039, 21). At ¶41 of his expert report (*id.*, 15) Prof. Micklefield explained his view of the type of evidence which would be required to draw such conclusions about the biological activity following substitutions at the 2'-position:

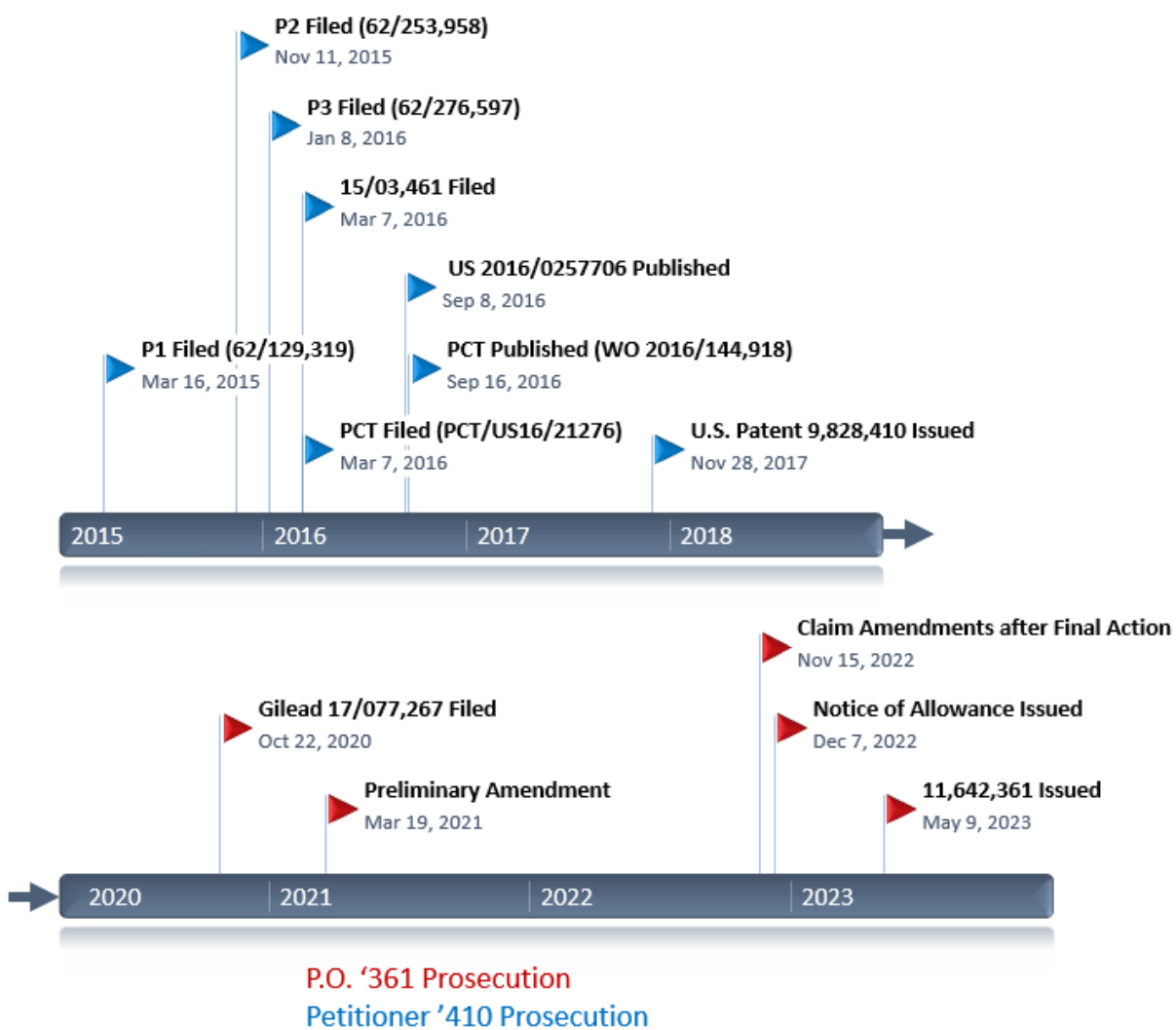
In order to be useful, any data for this study would need to be related to systematic variation of the parent gemcitabine nucleoside [i.e., 2'-up (F) / 2'-down (F)] or a prodrug of gemcitabine as opposed to a disparate series of other nucleoside analogues. For example, gemcitabine derivatives with substituents on the 5-position of the base and/or where the furanose ring oxygen atom was replaced with a methylene group. Likewise, gemcitabine derivatives where either one of the two 2'-fluoro substituents had been replaced by another halogen or methyl, for example.

153. Clearly, the PO's position was that the biological activity for claimed compounds with 2'-up (F) in EP'190 did not allow conclusions to be drawn

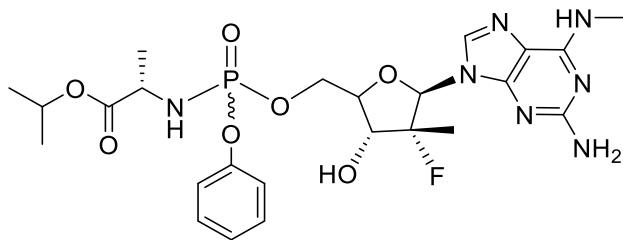
about the activity of claimed compounds with 2'-up (Me). It logically follows then that, according to PO, any biological activity for unclaimed (in claim 1) compounds with 2'-up (Me) in the '361 patent does not allow legitimate conclusions to be drawn about the activity of claimed compounds with any of the thirty-three untested 2'substiution patterns.

VII. PETITIONER'S INTERVENING U.S. 2016/0257706 PUBLICATION ANTICIPATES CLAIM 1 OF THE '361 PATENT

154. Petitioner's U.S. 2016/0257706 publication ("'706 U.S. Publication," Ex.1020), published on September 8, 2016, describes the synthesis and anti-HCV activity of a compound and its specific stereoisomers that anticipate the subgenus of claim 1 of the '361 patent. As shown in the timeline below, '706 U.S. Publication published more than six years prior to PO presenting claim 1 of the '361 patent on November 15, 2022. Claim 1 of the '361 patent is not entitled to any priority date earlier than that for the '706 U.S. Publication, and thus the publication anticipates claim 1.



155. Compound 5 (which structure is drawn in this paragraph) is synthesized in Example 1 of the '706 U.S. Publication (Ex.1020, 84).



156. It falls within the scope of claim 1 of the '361 patent because, using that claim's variable designations, in Compound 5:

R^1 is phenyl

R^2 is hydrogen

R^{3a} is hydrogen

R^{3b} is CH_3

R^4 is *i*-propyl

R^5 is H

R^6 is CH_3

X is F

Y is OH

R^{10} is NHR' , wherein R' is CH_3

R^{11} is NH_2

Z is N

P^* is a chiral phosphorus atom.

157. I am informed by counsel that neither the '706 U.S. Publication nor any of its family members were cited by PO to the USPTO during prosecution of the '361 patent.

158. The first synthetic scheme (Example 1) in the '706 U.S. Publication provides a POSA with the reagents and conditions to synthesize

Compound 5 (Ex.1020, ¶¶[0459]-[0466]). Example 1 provides detailed experimental procedures to synthesize Compound 5. Example 1 also includes the appropriate physicochemical characterization data so that a POSA can ensure that the correct compound was made. The characterization techniques used and described include ¹H nuclear magnetic resonance (NMR), ¹⁹F NMR, ³¹P NMR, and mass spectrometry. The details provided in the '706 U.S. Publication fully support the synthesis of Compound 5.

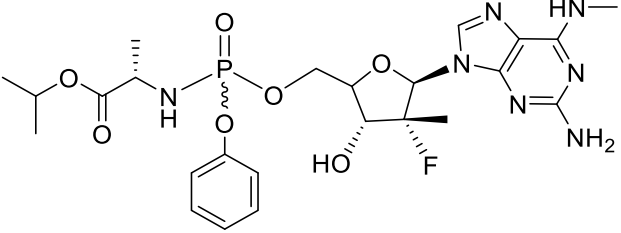
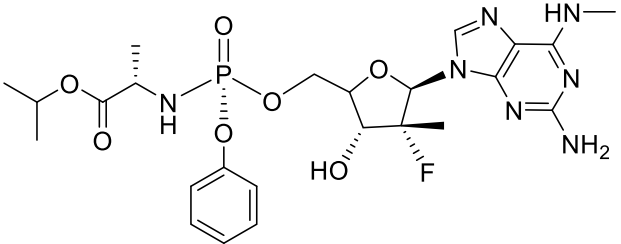
159. In addition to providing detailed synthetic procedures teaching how to make Compound 5 which anticipates the subgenus of claim 1 of the '361 patent, the '706 U.S. Publication also provides biological assays and data for the compound which confirms its' biological activity. In Examples 27-34, the '706 U.S. Publication describes the biological activity of Compound 5 and stereoisomers 5-1 and 5-2 in a diverse battery of tests (Ex.1020, ¶¶[0606]-[0637]).

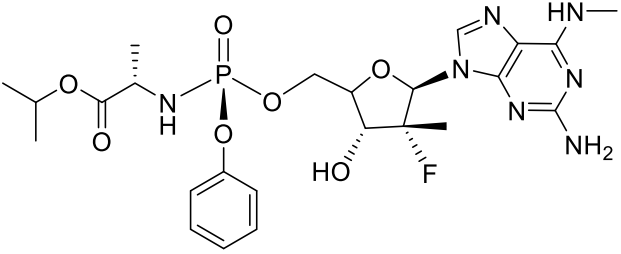
160. These numerous tests include antiviral activities against six different HCV genotypes, two mutant strains of HCV genotype 1a, one mutant strain of HCV genotype 1b, a transient infection assay, metabolic stability of the compound in human whole blood and liver S9 fraction, HCV genotype 1b NS5B polymerase assay, human DNA polymerase assay, cytotoxicity with iPS cardiomyocytes and human bone marrow progenitor cells, whole cell hepatocyte

toxicity, effects on ATP and on albumin secretion, metabolic studies, and a replicon assay (*id.*).

161. The replicon assay (data shown in Table 7, Ex.1020, ¶[0634]) provides half-maximal effective concentration (EC_{50}), 95%-maximal effective concentration (EC_{95}), and half-maximal cytotoxic concentration (CC_{50}) data. Assay data for Compounds 5, 5-1, and 5-2 (Ex.1020, 121) are reproduced below in Table 11 (the HCV replicon assay data are from Example 34; detailed procedures can be found in ¶[0606] of the '706 U.S. Publication).

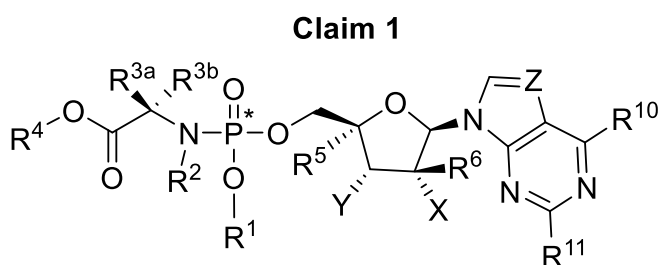
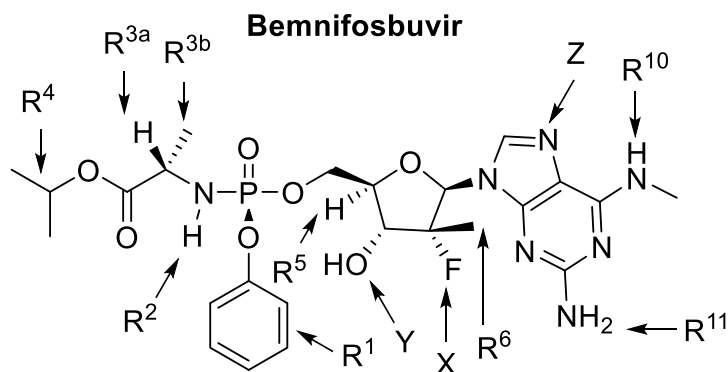
Table 11. Anti-HCV activity of compounds in the '706 U.S. Publication that anticipate claim 1 of the '361 patent.

Compound	Structure	EC_{50} μM	EC_{95} μM	CC_{50} μM
5		0.026	0.124	>100
5-1		0.0551	0.282	>100

5-2		0.004	0.028	>100
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162. I understand from counsel that 5-2 (which as the hemisulfate salt is referred to as bemnifosbuvir) is now in human clinical trials sponsored by Petitioner for the treatment of both HCV and COVID-19.

163. Because claim 1 of the '361 patent is not entitled to any priority date earlier than November 15, 2022, as explained above, the claim is invalid as anticipated over the intervening '706 U.S. Publication (Ex.1020, published on September 8, 2016, and issued as U.S. Patent No. 9,828,410 (Ex.1021)), which claims priority to U.S.S.N. 15/063,461 (Ex.1019, filed on March 7, 2016) U.S.S.N. 62/129,319 (Ex.1016; filed on March 6, 2015), U.S.S.N. 62/253,958 (Ex.1017, filed on November 11, 2015), and U.S.S.N. 62/276,597 (Ex.1018, filed on January 8, 2016)). In addition, the '706 U.S. Publication (Ex.1020) does something that the '361 patent fails to do — it actually draws the chemical structure, as well as makes, validates, and tests bemnifosbuvir and its isomers which are encompassed by claim 1 of the '361 patent:



VIII. CONCLUSIONS

164. For the reasons explained in detail above, I conclude that claim 1 of the '361 patent is invalid for violation of the written description and enablement requirements. Because claim 1 is not supported by the specification of the '361 patent, it is also not entitled to its asserted either filing date or priority dates. Specifically, claim 1 of the '361 patent was first presented on November 15, 2022, as a later-filed claim which, in my opinion, constituted new matter as of that date; therefore, it is at most entitled to that priority date.

165. Because claim 1 of the '361 patent is at most entitled only to a priority date of no earlier than November 15, 2022, the claim is also anticipated by Petitioner's '706 U.S. Publication (the publication date of September 8, 2016),

which presented Compound 5 (bemnifosbuvir) along with its syntheses and ample biological data confirming its activity as an anti-HCV agent.

IX. LEGAL STANDARDS

166. I have been informed by counsel of the following pertinent legal standards which I have endeavored to implement in my analyses in this Declaration.

A. Burden of Proof

167. A post-grant review (“PGR”) may be instituted by the PTAB if Petitioner shows that it is more likely than not that at least one claim of the challenged patent (here claim 1 of the ’361 patent) is unpatentable. Petitioner bears the ultimate burden of proving that the challenged claim is unpatentable by a preponderance of the evidence.

B. Preponderance of the Evidence

168. Preponderance of the evidence here means that the evidence must establish that it is more likely than not that a challenged claim is unpatentable for lack of written description or enablement, or that the claim is anticipated. In other words, preponderance of the evidence means that there is a greater than a 50% chance that the challenged claim is invalid.

C. Claim Construction

169. Patent claim terms are given their ordinary and customary meaning, which is the meaning that they would have to a POSA at the filing date.

Moreover, a POSA reads the claim terms not only in the context of the particular claim in which the terms appear but in the context of the entire patent, including the definitions, structures, examples, data, and figures.

170. The '361 patent specification provides several specific definitions for chemical terms used in the claims (see, e.g., col. 7, line 62, through col. 12, line 29). In such instances, I read a claim term as defined in the patent specification.

171. Claim 1 of the '361 patent primarily uses chemical terms, nomenclature, and Markush chemical structures which include variables at the referenced positions. In construing claim 1, I have given undefined terms and structures their plain and ordinary meanings to a POSA.

D. The Written Description Requirement

172. The patent law in 35 U.S.C. §112(a) says:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

173. The purpose of the written description requirement is to establish that the inventors had possession of the claimed subject matter as of the filing date.

174. The written description requirement, when applied to the '361 patent, specifically concerns the subgenus of claim 1 presented by PO for the first time in March of 2021, which was amended for allowance in November 2022, well after all of its priority dates. When a subgenus is presented for the first time well after all of the asserted priority filing dates, the scenario raises concern because it may violate the written description requirement as new matter.

175. The written description requirement for a claimed genus is satisfied through a sufficient description of a representative number of species by actual reduction to practice established in the specification or by a disclosure of relevant identifying characteristics, i.e., structures or other physical and chemical properties, sufficient to show possession of the later claimed subject matter. A representative number of species means that the species that are adequately described are representative of the entire genus.

176. As noted above, Gilead recently litigated the issue of written description support for a subgenus in the case against Regents of the University of Minnesota. The Federal Circuit has affirmed Gilead's request to invalidate patent claims that were very similar to claim 1 in the '361 patent. The Federal Circuit has ruled that the written description requirement, as applied to chemical genus claims, requires a description of both the outer limits of the genus and either a representative number of members of the genus or structural features common to the members of

the genus, in either case with enough precision that a POSA can visualize or recognize the members of the genus. A broad outline of a genus's perimeter is deemed insufficient.

177. The Federal Circuit has also confirmed that picking and choosing from a “laundry list” disclosure does not constitute a disclosure of every subgenus. Rather, written description support for a claimed subgenus, in the description of a broader genus, must be established through clear “blaze marks” that single out a particular “tree” in a “forest.” To provide adequate written description support for a single subgenus, a reasonably specific supporting disclosure is required (in other words, simply disclosing all of the individual limitations is not sufficient to establish “blaze marks” to a claimed subgenus). What is required is a guide for a POSA indicating or directing that this particular subgenus selection should be made rather than the many others which could also be made.

178. When the claimed invention is a subgenus, in order to show possession of the invention, the patent specification must set forth either a representative number of species falling within the scope of the subgenus or structural features common to members of the subgenus so that a POSA can visualize or recognize the subgenus. The representative species in the specification must reflect the full scope of the subgenus.

179. In order to claim the benefit of the filing date of an earlier application, each application in the chain leading back to the earlier application must comply with the written description requirement. Where priority applications do not satisfy this requirement, intervening references can novelty-destroy (i.e., anticipate) the granted claims.

180. The patent applicant has one year from its first provisional priority application filing to file a “non-provisional” U.S. application (or a PCT international application that designates the U.S.). The term “patent specification” refers to the full application and the claims, as originally filed in a provisional, or a U.S. non-provisional, or a PCT international application. The patent specification does not necessarily include patent claims that were filed in a later-continuing application after a priority date unless it is shown that the specification complies with the written description requirement for those later-added claims. A later-filed patent claim is only supported by the written description of a patent specification if the specification reasonably conveys to a POSA that the inventor had possession of the full scope of the claimed subject matter as of the filing date.

181. New matter cannot be introduced into a patent application after its asserted priority filing dates. This serves to prevent a patent applicant from adding information that goes beyond the subject matter originally filed. Therefore,

if new claims are added that do not find clear support in the priority specification, then new matter is deemed to have been added to the application.

182. A patent may still lack written description even when each element is individually described in the specification. Therefore, in reviewing the '361 patent, I looked for both the individual elements and whether they were combined in the specification (not including the claim) in the manner depicted in the claims later added.

E. The Enablement Requirement

183. Enablement under §112(a) requires the specification to teach a POSA how to make and use the invention without undue experimentation.

184. Whether experimentation is undue is a conclusion reached by weighing many factual considerations, including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. These factors are illustrative and not mandatory and some of them may be more important than others depending on the circumstances.

185. A patent claim is not enabled when, at the effective filing date of the patent, a POSA could not practice its full scope without undue experimentation.

186. A patent specification that requires a POSA to engage in an iterative, trial-and-error process to practice the claimed invention does not provide an enabling disclosure. In cases involving claims that require structural features and also require performance of some function (e.g., efficacy for a certain purpose), undue experimentation can include that in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement.

F. Anticipation

187. A U.S. patent may only be granted for a new process or composition of matter or for a new improvement thereof. The law provides categories of information that constitute prior art that may be used to anticipate (i.e., novelty-destroy) patent claims. To be prior art, a reference must have been made, known, used, published, patented, or described in a patent application by another, before the priority date of the patent at issue. A POSA is presumed to have knowledge of all publicly available relevant prior art as of the priority date.

188. For a prior art reference to anticipate a patent claim, all of the limitations of the claim must be disclosed in such a single prior art reference. Documents and materials that qualify as prior art can be used to render a claim unpatentable as novelty-destroyed (i.e., anticipated).

189. To qualify as prior art, a reference must predate the priority date of the challenged claim. In forming my opinions and conclusions herein, I have been instructed that to claim the benefit of an earlier-filed priority application, the earlier-filed application must meet the written description and enablement requirements for the claimed subject matter.

190. The “effective filing date” of a patent claim is the actual filing date of the patent, unless the patent properly claims the benefit of an earlier filing date from a parent application that discloses the claimed invention in actual compliance with the written description and enablement requirements.

191. A prior art reference “anticipates” a patent claim, and thus renders the claim unpatentable, if each element of a challenged claim is disclosed in that prior art reference, either explicitly or inherently (i.e., is necessarily present in the latter case).

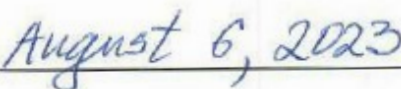
192. I further understand that the disclosure of a species in the prior art may anticipate a later-claimed genus if the species meets all of the limitations of (i.e., falls within) the genus. In order to anticipate, the prior art disclosure must be enabling for what it teaches.

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

Respectfully submitted by

A handwritten signature in blue ink, appearing to read "A. Klibanov", written over a horizontal line.

Alexander M. Klibanov, Ph.D.

A handwritten date "August 6, 2023" in blue ink, written over a horizontal line.

Date

ATTACHMENT A

Curriculum vitae

ALEXANDER M. KLIBANOV

Date and Place of Birth: July 15, 1949, in Moscow (Russia)

Nationality: Naturalized U.S. Citizen (1983)

Education:
1974 Ph.D. in Chemical Enzymology, Moscow University
1971 M.S. in Chemistry, Moscow University

Honors:

2015	Tau Beta Pi's Leonardo Da Vinci Lecturer, MIT
2007-11 and 2014	Novartis Chair Endowed Professorship, MIT
2012-13	Roger and Georges Firmenich Endowed Professorship, MIT
2011	MIT Biological Engineering Senior Class Faculty Award
2006	Distinguished GRUM Lecturer in Drug Discovery & Development, University of Montreal (Canada)
2004	UNAM Distinguished Lecturer, National University of Mexico (Mexico City)
2001	Walter Enz Lecturer in Pharmaceutical Chemistry, University of Kansas
2001	Elected a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters)
2000	Merck Distinguished Lecturer, Rutgers University
2000	Top 20 <i>Biotechnology & Bioengineering</i> Papers of the Last Forty Years
1998	Robert Lutz Lecturer, University of Virginia
1996	Perkin-Elmer Distinguished Lecturer, University of Pittsburgh
1995	Elected to the National Academy of Sciences of the U.S.A.
1995	Nathan O. Kaplan Memorial Lecturer in Biological Chemistry, University of California at San Diego
1994	R.W. Johnson PRI Lecturer, Pharmaceutical Research Institute
1994	Warren McCabe Lecturer, North Carolina State University
1993	Elected to the National Academy of Engineering of the U.S.A.
1993	Arthur C. Cope Scholar Award of the American Chemical Society
1993	Biotechnology Divisional Lectureship Award of the Institute of Food Technologists
1992	Charles Sabat Lecturer, Rutgers University
1992	Elected a Founding Fellow of the American Institute for Medical and Biological Engineering
1992	Louis C. Jordy Research Scholar Lecturer, Drew University
1991	International Enzyme Engineering Award
1991	Marvin J. Johnson Award of the American Chemical Society
1990	Monsanto Lecturer, Ohio State University
1990	NRC Distinguished Lecturer, Academia Sinica (Taiwan)
1989	Ipatieff Prize of the American Chemical Society
1989	Backer Lecturer, Groningen University (Holland)
1988	Dow Lecturer, University of Ottawa (Canada)
1987	Distinguished Scholar Lecturer, Hope College
1986	Leo Friend Award of the American Chemical Society
1984	Who's Who in Frontier Science and Technology

1984	Sohio Lecturer, Case Western Reserve University
1982	American Men and Women of Science
1981-1983	Henry L. Doherty Career Development Professorship, MIT
1975	U.S.S.R. Ministry of Higher Education Prize

Professional Experience:

2019-present	Novartis Chair Professor Emeritus of Chemistry and Bioengineering, MIT
2014-2019	Novartis Chair Professor of Chemistry and Bioengineering, MIT
2012-2013	Roger and Georges Firmenich Professor of Natural Products Chemistry Department of Chemistry, MIT
2007-2011	Novartis Chair Professor of Chemistry and Bioengineering, MIT
2000-2019	Professor of Bioengineering Department of Biological Engineering, MIT
1988-2019	Professor of Chemistry Department of Chemistry, MIT
1987-1988	Professor of Applied Biochemistry Department of Applied Biological Sciences, MIT
1983-1987	Associate Professor of Applied Biochemistry Department of Applied Biological Sciences (formerly Department of Nutrition and Food Science), MIT
1979-1983	Assistant Professor of Applied Biochemistry Department of Nutrition and Food Science, MIT
1977-1979	Postdoctoral Associate, Department of Chemistry University of California at San Diego
1974-1977	Research Chemist Department of Chemistry, Moscow University

Current Journal Editorial/Advisory Boards:

"Biocatalysis and Biotransformation", "Applied Biochemistry and Biotechnology", "Open Chemistry Journal", "Biotechnology Progress", "Biotechnology & Bioengineering", "Microbial Biotechnology", "Open Journal of Pharmacology", "Nanocarriers", "Journal of Antivirals and Antiretrovirals", "Open Access Academic Books in Chemistry", "Journal of Biological Chemistry and Molecular Pharmacology", "Archives of Natural Products and Medicinal Chemistry", "Recent Patents in Biotechnology", "Current Pharmaceutical Biotechnology", and "Archives of Medical Biotechnology", "International Journal of Drug Design, Delivery and Safety"

Professional Societies:

U.S. National Academy of Sciences, U.S. National Academy of Engineering, American Chemical Society, American Institute for Medical and Biological Engineering

Current Research Interests:

Drug synthesis and modification	Medicinal and formulation chemistry
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Protein and nucleic acid delivery Antimicrobial polymers
Enzymes as catalysts in organic syntheses
Stabilization and formulation of macromolecular pharmaceuticals

Publications:

1. Varfolomeyev, S.D., Klibanov, A.M., Berezin, I.V. 1971. Light-initiated enzymic activity caused by photostereoisomerization of *cis*-4-nitrocinnamoyl- α -chymotrypsin. FEBS Lett. **15**: 118 -120.
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5. Berezin, I.V., Klibanov, A.M., Martinek, K. 1974. The mechanochemistry of immobilized enzymes. How to steer a chemical process at the molecular level by a mechanical device. Biochim. Biophys. Acta **364**: 193-199.
6. Berezin, I.V., Klibanov, A.M., Goldmacher, V.S., Martinek, K. 1974. Mechanochemistry of catalytic systems. Regulation by a mechanical action of the enzymatic activity of trypsin entrapped in polyacrylamide gel. Dokl. Acad. Nauk SSSR **218**: 367-370.
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10. Martinek, K., Goldmacher, V.S., Klibanov, A.M., Berezin, I.V. 1975. Denaturing agents (urea, acrylamide) protect enzymes against irreversible thermoinactivation: a study with native and immobilized α -chymotrypsin and trypsin. FEBS Lett. **51**: 152-155.
11. Martinek, K., Klibanov, A.M., Tchernysheva, A.V., Berezin, I.V. 1975. The stabilization of α -chymotrypsin by entrapment in polymethacrylate gels. Dokl. Acad. Nauk SSSR **223**: 233-236.
12. Tchernysheva, A.V., Goldmacher, V.S., Klibanov, A.M., Martinek, K., Berezin, I.V. 1975. The catalytic activity and thermostability of α -chymotrypsin oligomers entrapped in cross-linked polymeric gels. Bull. Moscow Univ. **19**: 428-431.

13. Tchernysheva, A.V., Martinek, K., Klibanov, A.M., Mevkh, A.T., Berezin, I.V. 1975. The catalytic properties and thermostability of α -chymotrypsin in different polymethacrylate gels. Izvestia Acad. Nauk SSSR, Ser. Khim. No. 8: 1764-1768.
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Patents:

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2. Klibanov, A.M., Kirchner, G. Enzymatic production of optical isomers of 2-halopropionic acids. U.S. Patent No. 4,601,987; July 22, 1986.
3. Klibanov, A.M. Removal of combined organic substances from aqueous solutions. U.S. Patent No. 4,623,465; November 18, 1986.
4. Klibanov, A.M. Enzymatic resolution of racemic mixtures of hydroxy compounds. U.S. Patent No. 4,659,671; 1987.
5. Klibanov, A.M., Dordick, J.S. Enzymatic temperature change indicator. U.S. Patent No. 4,826,762; May 2, 1989.

6. Dorval, B.L., Denham, L., Klibanov, A.M. Radial flow assay, delivering membrane, test kit, and methods. U.S. Patent No. 5,547,833; August 20, 1996.
7. Dorval, B.L., Denham, L., Klibanov, A.M. Detection reagent, particle, and immunoassay method. U.S. Patent No. 5,561,045; October 1, 1996.
8. Dorval, B.L., Chow, M., Klibanov, A.M. Stabilized vaccine compositions. U.S. Patent No. 5,618,539; April 8, 1997. European Patent No. 0 487 632; March 4, 1998.
9. Klibanov, A.M., Lewis, K., Ferrante, A.A., Coyle, C.L., Zylstra, G., Logan, M.S.P., Grossman, M.J. Solvent-resistant microorganisms. U.S. Patent No. 5,807,735; September 15, 1998.
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11. Hekal, I.M., Langer, R.S., Klibanov, A.M., Mathiowitz, E. Monolithic polymer composition having a water absorption material. U.S. Patent No. 6,174,952; January 16, 2001.
12. Gresser, J.D., Trantolo, D.J., Langer, R., Lewandrowski, K.-U., Klibanov, A.M., Wise, D.L. Resorbable interbody spinal fusion devices. U.S. Patent No. 6,241,771; June 5, 2001.
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15. Klibanov, A.M. Nonaqueous solutions and suspensions of macromolecules for pulmonary delivery. U.S. Patent No. 6,660,715; December 9, 2003.
16. Tiller, J.C., Lewis, K., Liao, C.-J., Klibanov, A.M. Antimicrobial polymeric surfaces. U.S. Patent No. 7,151,139; December 19, 2006.
17. Hirsh, J.C., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent drug formulations. U.S. Patent No. 7,771,707; August 10, 2010.
18. Hirsh, J.C., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent drug formulations. U.S. Patent No. 8,449,909; May 28, 2013.
19. Rariy, R.V., Fleming, A.B., Hirsh, J.C., Klibanov, A.M. Abuse-deterrent pharmaceutical compositions of opioids and other drugs. U.S. Patent No. 8,557,291; October 15, 2013.
20. Hirsh, J., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent drug formulations. U.S. Patent No. 8,758,813; June 24, 2014.
21. Hirsh, J.C., Klibanov, A.M., Swager, T.M., Buchwald, S.L., Lo, W.Y., Fleming, A.B., Rariy, R.V. Abuse-deterrent pharmaceutical compositions of opioids and other drugs. U.S. Patent No. 9,044,398; June 2, 2015.
22. Schaer, T.P., Stewart, S., Klibanov, A.M. Antibacterial coatings that inhibit biofilm formation on implants. U.S. Patent No. 9,089,407; July 28, 2015.

23. Rariy, R.V., Fleming, A.B., Hirsh, J.C., Klibanov, A.M. Abuse-deterrent pharmaceutical compositions of opioids and other drugs. U.S. Patent No. 9,248,195; February 2, 2016.
24. Rariy, R.V., Fleming, A.B., Hirsh, J., Klibanov, A.M. Abuse-deterrent pharmaceutical compositions of opioids and other drugs. U.S. Patent No. 9,592,200; March 14, 2017.
25. Haldar, J., An, D., Álvarez de Cienfuegos, L., Chen, J., Klibanov, A.M. Polymeric coatings that inactivate viruses and bacteria. U.S. Patent Appl. Publ. No. 2010/0136072; June 3, 2010.
26. Pedersen, M., Stanley, M., Gouin, S., Klibanov, A.M., Hsu, B.B. Antimicrobial quat coating on fabrics. PCT Intl. Appl. WO 2012/06561, 2012.
27. Haldar, J., Alvarez de Cienfuegos, L., Klibanov, A.M., Chen, J. Bi-functional polymer-attached inhibitors of influenza virus. PCT Intl. Appl. WO 2009/032605, 2012.
28. Klibanov, A.M., Su, E. Neat liquid pharmaceutical formulations. U.S. Patent No. 9,731,026; August 15, 2017.
29. Hirsh, J.C., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent pharmaceutical compositions. U.S. Patent No. 9,763,883; September 19, 2017.
30. Larson, A.M., Weight, A.K., Love, K., Crane, A., Langer, R.S., Klibanov, A.M. Liquid pharmaceutical formulations for injection comprising thiamine pyrophosphate 1-(3-aminopropyl)-2-methyl-1H-imidazole and uses thereof. U.S. Patent No. 9,913,905; March 13, 2018.
31. Larson, A.M., Love, K., Weight, A.K., Crane, A., Langer, R.S., Klibanov, A.M. Liquid pharmaceutical formulations for injection comprising procaine and uses thereof. U.S. Patent No. 9,925,263; March 27, 2018.
32. Larson, A.M., Love, K., Weight, A.K., Crane, A., Langer, R.S., Klibanov, A.M. Liquid pharmaceutical formulations for injection comprising Yellow 5 Orange G and uses thereof. U.S. Patent No. 10,179,172; March 27, 2018.
33. Schaer, T.P., Stewart, S., Klibanov, A.M. Antibacterial coatings that inhibit biofilm formation on implants. U.S. Patent No. 10,500,317; December 10, 2019.
34. Hirsh, J.C., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent drug formulations. U.S. Patent No. 10,525,052; January 7, 2020.

Invited Lectures:

1. Gordon Conference on Immobilized Enzymes, Complexes, and Cells (Plymouth, NH). August 1978.
2. 5th International Conference on Enzyme Engineering (Henniker, NH). August 1978.
3. Miles Laboratories (Elkhart, IN). February 1980.
4. Gordon Conference on Immobilized Species (Henniker, NH). August 1980.
5. Novo Laboratories (Wilton, CT). October 1980.

6. Corning Glass Works Co. (Corning, NY). October 1980.
7. Stauffer Chemical Co. (Dobbs Ferry, NY). December 1980.
8. DuPont Experimental Station (Wilmington, DE). January 1981.
9. Dow Chemical Co. (Wayland, MA). April 1981.
10. Cetus Corp. (Berkeley, CA). April 1981.
11. Exxon Research & Engineering Co. (Linden, NJ). April 1981.
12. Meeting of the American Solar Energy Society (Philadelphia, PA). May 1981.
13. 6th International Conference on Enzyme Engineering (Kashikojima, Japan). September 1981.
14. Genex Corp. (Rockville, MD). October 1981.
15. ILP Symposium for Senior Executives (London, England). November 1981.
16. California Institute of Technology (Pasadena, CA). December 1981.
17. Symposium of the American Society for Microbiology (Atlanta, GA). March 1982.
18. Kodak Research Center (Rochester, NY). March 1982.
19. Repligen Corp. (Cambridge, MA). April 1982.
20. Symposium on the Biological Basis of New Developments in Biotechnology (Minneapolis, MN). May 1982.
21. Meeting of the Biochemical Society (Oxford, England). July 1982.
22. Meeting of the American Chemical Society (Kansas City, MO). September 1982.
23. Rotenburger Symposium on Enzyme Technology (Kassel, Germany). September 1982.
24. Genetics Institute (Boston, MA). September 1982.
25. Meeting of the American Institute of Chemical Engineers (Los Angeles, CA). November 1982.
26. G.D. Searle Co. (Chicago, IL). October 1982.
27. Halcon International Research Center (Montvale, NJ). October 1982.
28. International Workshop on Immobilized Enzymes and Cells (Bangkok, Thailand). December 1982.
29. Amoco Research Center (Naperville, IL). January 1983.

30. University College London (London, England). May 1983.
31. International Conference on Biotechnology Biotech '83 (London, England). May 1983.
32. Tufts University Workshop on Immobilized Enzymes and Proteins (Medford, MA). June 1983.
33. Gordon Conference on Organic Reactions and Processes (New Hampton, NH). July 1983.
34. Symposium "Biocatalysis: New Discoveries and Uses", Meeting of the American Society for Industrial Microbiology (Sarasota, FL). August 1983.
35. Monsanto Co. (St. Louis, MO). September 1983.
36. Pasteur Biosciences '83 Conference (Paris, France). September 1983.
37. 7th International Conference on Enzyme Engineering (White Haven, PA). September 1983.
38. University of Iowa (Iowa City, IA). October 1983.
39. CPC Moffett Technical Center (Summitt-Argo, IL). December 1983.
40. General Foods Co. (Dobbs Ferry, NY). December 1983.
41. U.S. National Bureau of Standards (Gaithersburg, MD). April 1984.
42. Millipore Corp. (Bedford, MA). April 1984.
43. Technical University of Munich (Munich, F.R.G.). May 1984.
44. Danish Academy of Technical Sciences (Copenhagen, Denmark). May 1984.
45. Novo International Biotechnology Symposium (Copenhagen, Denmark). May 1984.
46. CRA Scientific Conference (St. Charles, IL). June 1984.
47. Gordon Conference on Immobilized Species in Biotechnology (Plymouth, NH). August 1984.
48. Meeting of the American Chemical Society (Philadelphia, PA). August 1984.
49. International Biotechnology Conference Biotech '84 (Washington, DC). September 1984.
50. Staley Manufacturing Co. (Decatur, IL). October 1984.
51. Case Western Reserve University (Cleveland, OH). October 1984.
52. IMC Corp. (Terre Haute, IN). October 1984.
53. Syracuse University (Syracuse, NY). November 1984.
54. National University of Mexico (Mexico City, Mexico). November 1984.

55. National Starch & Chemical Corp. (Bridgewater, NJ). November 1984.
56. Mead Corp. (Chillicothe, OH). November 1984.
57. Hebrew University of Jerusalem (Jerusalem, Israel). November 1984.
58. U.S. Army Chemical R&D Center (Aberdeen Proving Ground, MD). December 1984.
59. Allied Corp. (Morristown, NJ). December 1984.
60. Bristol Laboratories (Syracuse, NY). January 1985.
61. University of Rochester (Rochester, NY). January 1985.
62. G.D. Searle Co. (Chicago, IL). February 1985.
63. Wellcome Research Laboratories (Research Triangle Park, NC). February 1985.
64. UCLA Symposium on Protein Structure, Folding and Design (Keystone, CO). April 1985.
65. International Conference on Application of Biocatalysts in Organic Synthesis (Noordwijkerhout, Holland). April 1985.
66. Guido Donegani Research Institute (Novara, Italy). April 1985.
67. Hoffmann-LaRoche Co. (Basel, Switzerland). April 1985.
68. Pittsburgh-Cleveland Catalysis Society Meeting (Pittsburgh, PA). May 1985.
69. Ethyl Corp. (Baton Rouge, LA). May 1985.
70. Stony Brook Symposium on Protein Engineering (Stony Brook, NY). May 1985.
71. Amgen Corp. (Thousand Oaks, CA). June 1985.
72. Gordon Conference on Applied Microbiology (New London, NH). August 1985.
73. International Congress of Biochemistry (Amsterdam, Holland). August 1985.
74. IUPAC Congress (Manchester, England). September 1985.
75. International Enzyme Engineering Conference (Helsingor, Denmark). September 1985.
76. Biotechnica '85 (Hannover, West Germany). October 1985.
77. Biotec 85 (Dusseldorf, West Germany). October 1985.
78. Smith Kline & French Co. (Philadelphia, PA). November 1985.
79. Exxon Corporate Research (Anandale, NJ). December 1985.

80. Pennsylvania State University (University Park, PA). December 1985.
81. Georgetown University (Washington, DC). February 1986.
82. Columbia University (New York, NY). February 1986.
83. Upjohn Co. (Kalamazoo, MI). February 1986.
84. UNIDO Workshop on Biotechnology (Trieste, Italy). March 1986.
85. Enircherche (Monterotondo, Italy). March 1986.
86. EEC Biomolecular Engineering Meeting (Compiègne, France). April 1986.
87. ACS Conference on Chemical Aspects of Biotechnology (Gaithersburg, MD). May 1986.
88. Biotech '86 Europe International Conference (London, England). May 1986.
89. IUPAC International Symposium on Organic Chemistry in Technological Perspective (Jerusalem, Israel). June 1986.
90. University of Tel-Aviv (Ramat-Aviv, Israel). June 1986.
91. Annual Meeting of the Canadian Biochemical Society (Guelph, Canada). June 1986.
92. International Symposium on Biologically Engineered Polymers (Cambridge, England). July 1986.
93. TNO Institute of Applied Chemistry (Zeist, The Netherlands). August 1986.
94. IUPAC International Symposium on the Chemistry of Natural Products (The Hague, The Netherlands). August 1986.
95. American Chemical Society National Meeting (Anaheim, CA). September 1986.
96. Catalytica Annual Science and Technology Symposium (San Jose, CA). September 1986.
97. International Conference on Enzyme Engineering (Cambridge, England). September 1986.
98. Ohio State University (Columbus, OH). October 1986.
99. Michigan State University (Lansing, MI). October 1986.
100. Biotechnology Process Engineering Symposium (Cambridge, MA). October 1986.
101. University of Delaware (Newark, DE). November 1986.
102. American Red Cross Blood Research Institute (Bethesda, MD). November 1986.
103. International Symposium on Biocatalysis in Non-Aqueous Solvents (Wageningen, The Netherlands). December 1986.
104. University of Trondheim (Trondheim, Norway). December 1986.

105. Colgate-Palmolive Research Center (Piscataway, NJ). January 1987.
106. International Paper Co. (Tuxedo Park, NY). January 1987.
107. University of Massachusetts (Amherst, MA). February 1987.
108. American Society for Microbiology Biocatalysis Symposium (Atlanta, GA). March 1987.
109. Hope College (Holland, MI). March 1987.
110. Pfizer Corporate Research Center (Groton, CT). April 1987.
111. OBBS Symposium on Protein Engineering (Ottawa, Canada). April 1987.
112. University of Texas (Austin, TX). April 1987.
113. Florida Catalysis Conference (Palm Coast, FL). May 1987.
114. PPG Industries (Barberton, OH). May 1987.
115. Abbott Laboratories (North Chicago, IL). May 1987.
116. American Oil Chemists Society Symposium on Lipases (New Orleans, LA). May 1987.
117. Argonne National Laboratory (Argonne, IL). June 1987.
118. Canadian Chemical Conference (Quebec City, Canada). June 1987.
119. Squibb Co. (New Brunswick, NJ). June 1987.
120. FEBS Annual Meeting (Ljubljana, Yugoslavia). July 1987.
121. L'Oreal Research Institute (Paris, France). July 1987.
122. International Symposium on Biointeractions (Cambridge, England). July 1987.
123. Eli Lilly Co. (Indianapolis, IN). August 1987.
124. Upjohn Co. (Kalamazoo, MI). September 1987.
125. International Enzyme Engineering Conference (Santa Barbara, CA). October 1987.
126. Shell Development Co. (Houston, TX). October 1987.
127. DuPont Experimental Station (Wilmington, DE). October 1987.
128. University of Helsinki (Helsinki, Finland). November 1987.
129. International Conference on Bioreactors and Biotransformations (Gleneagles, Scotland). November 1987.
130. Sandoz Co. (Basel, Switzerland). November 1987.

131. University of Waterloo (Waterloo, Canada). December 1987.
132. Norwegian Biochemical Society Annual Meeting (Bejito, Norway). January 1987.
133. Rutgers University (New Brunswick, NJ). February 1988.
134. University of Ottawa (Ottawa, Canada). February 1988.
135. Boston Biomedical Research Institute (Boston, MA). March 1988.
136. Princeton University (Princeton, NJ). March 1988.
137. Royal Society of Chemistry Meeting (Kent, England). April 1988.
138. Stanford University (Stanford, CA). May 1988.
139. University of Graz (Graz, Austria). May 1988.
140. Belgian Organic Chemistry Symposium (Ghent, Belgium). May 1988.
141. Dow Chemical Co. (Midland, MI). May 1988.
142. Michigan State University (Lansing, MI). May 1988.
143. American Chemical Society Meeting (Toronto, Canada). June 1988.
144. Proctor & Gamble Co. (Cincinnati, OH). June 1988.
145. International Congress of Biochemistry (Prague, Czechoslovakia). July 1988.
146. International Biotechnology Symposium (Paris, France). July 1988.
147. Gordon Conference on Catalysis (Newport, RI). August 1988.
148. Conference on Biocatalytic Synthesis of Organic Compounds (Saratoga, NY). August 1988.
149. International Symposium on Thermodynamics Applied to Biological Systems (Santa Margherita, Italy). September 1988.
150. Cornell University (Ithaca, NY). September 1988.
151. Eastman Kodak Co. (Kingsman, TN). September 1988.
152. Symposium on Biotechnology Challenges in the Food Industry (Williamsburg, VA). October 1988.
153. University of California at Irvine (Irvine, CA). October 1988.
154. UCSF Symposium on Protein and Drug Design (San Francisco, CA). October 1988.
155. Boston University (Boston, MA). October 1988.
156. Wayne State University (Detroit, MI). November 1988.

157. Kyoto Symposium on Frontiers in Biocatalysis (Kyoto, Japan). November 1988.
158. Rohm & Haas Co. (Spring House, PA). January 1989.
159. Block Drug Co. (Jersey City, NJ). January 1989.
160. State University of New York (Albany, NY). March 1989.
161. Scripps Clinic and Research Foundation (La Jolla, CA). April 1989.
162. Texas A&M University (College Station, TX). May 1989.
163. University of Texas (Austin, TX). May 1989.
164. International Congress of Food Engineering (Cologne, F.R.G.). May 1989.
165. University of Groningen (Groningen, The Netherlands). June 1989.
166. Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways (Meridan, NH). July 1989.
167. American Peptide Symposium (La Jolla, CA). July 1989.
168. International Symposium on Prospects in Protein Engineering (Haren, The Netherlands). August 1989.
169. Connaught Laboratories (Toronto, Canada). September 1989.
170. University of Georgia (Athens, GA). October 1989.
171. Spanish National Congress of Biochemistry (Alicante, Spain). October 1989.
172. Symposium on Receptor- and Enzyme- Based Drug Design (Chapel Hill, NC). October 1989.
173. Wesleyan University (Middletown, CT). November 1989.
174. University of Wisconsin (Madison, WI). February 1990.
175. Merck Sharp & Dohme Research Laboratories (Rahway, NJ). February 1990.
176. International Symposium on Biochemical Engineering (Stuttgart, F.R.G.). March 1990.
177. University of Geneva (Geneva, Switzerland). March 1990.
178. University of Lausanne (Lausanne, Switzerland). March 1990.
179. University of Bern (Bern, Switzerland). March 1990.
180. University of Fribourg (Fribourg, Switzerland). March 1990.
181. International Conference on Protein Stability (Cambridge, England). March 1990.

182. AFRC Institute of Food Research (Reading, England). March 1990.
183. Lehigh University (Bethlehem, PA). April 1990.
184. Biotechnology Research Institute (Montreal, Canada). April 1990.
185. Ohio State University (Columbus, OH). April 1990.
186. Pharmaceutical Manufacturers Association Annual Meeting (St. Louis, MO). April 1990.
187. International Conference on Industrial Use of Enzymes (Chicago, IL). May 1990.
188. Korea Advanced Institute of Science and Technology (Seoul, Korea). June 1990.
189. Academia Sinica and National Taiwan University (Taipei, Taiwan). June 1990.
190. Gordon Conference on Biocatalysis (Plymouth, NH). June 1990.
191. IUPAC Conference on Organic Synthesis (Helsinki, Finland). July 1990.
192. International Conference on Solution Chemistry (Ottawa, Canada). August 1990.
193. Gordon Conference on Biomolecular Recognition (Plymouth, NH). August 1990.
194. University of Naples (Naples, Italy). September 1990.
195. International Conference on Water and Life (Crans-sur-Sierre, Switzerland). September 1990.
196. International Symposium on Thermodynamic Basis of Protein Structure and Function (Kansas City, MO). October 1990.
197. Johns Hopkins University (Baltimore, MD). October 1990.
198. Institute of Medicine Workshop on Microheterogeneity of Biological Macromolecules (Arlington, VA). November 1990.
199. U.S.-Japan Biotechnology Conference (Honolulu, HI). January 1991.
200. Ciba-Geigy Corp. (Summit, NJ). February 1991.
201. City University of New York (New York, NY). March 1991.
202. Rensselaer Polytechnic Institute (Troy, NY). March 1991.
203. Bristol-Myers Squibb Co. (Wallingford, CT). April 1991.
204. British Biochemical Society Meeting (Reading, England). April 1991.
205. University of California at Berkeley (Berkeley, CA). April 1991.
206. California Institute of Technology (Pasadena, CA). April 1991.
207. Merck, Sharp & Dohme Research Laboratories (West Point, PA). May 1991.

208. Bristol-Myers Squibb Research Institute (Princeton, NJ). May 1991.
209. International Conference on Biocatalysis (Orlando, FL). June 1991.
210. U.S. Army Research, Development and Engineering Center (Natick, MA). July 1991.
211. Gordon Conference on Natural Products (Plymouth, NH). July 1991.
212. Lederle-Praxis Biologicals Co. (Sanford, NC). July 1991.
213. International Biochemistry Congress (Jerusalem, Israel). August 1991.
214. American Chemical Society Meeting (New York, NY). August 1991.
215. International Enzyme Engineering Conference (Kona, HI). September 1991.
216. University of Lowell (Lowell, MA). October 1991.
217. Rutgers University (Piscataway, NJ). November 1991.
218. International Symposium on Enzymes in Organic Synthesis (New Delhi, India). January 1992.
219. International BioSymposium Nagoya '92 (Nagoya, Japan). January 1992.
220. International Symposium on Biomolecules in Organic Solvents (Taxco, Mexico). February 1992.
221. Rockefeller University (New York, NY). March 1992.
222. Symposium on Molecular Chirality of the Pharmaceutical Society of Japan (Tokyo, Japan). April 1992.
223. Conference on Enzymes in Organic Chemistry of the Dutch Chemical Society (Wageningen, The Netherlands). April 1992.
224. International Symposium on Bioprocessing of Coal (Clearwater Beach, FL). May 1992.
225. Exxon Workshop on New Leads in Coal Depolymerization (Montgomery, TX). May 1992.
226. Italian Symposium on Biochemical Biotechnology (Capri, Italy). June 1992.
227. Gordon Conference on Biocatalysis (Meriden, NH). July 1992.
228. FEBS Meeting (Dublin, Ireland). August 1992.
229. International Biotechnology Symposium (Washington, DC). August 1992.
230. International Symposium Bio Japan '92 (Yokohama, Japan). August 1992.
231. Texas College of Osteopathic Medicine (Fort Worth, TX). October 1992.

- 232. Rutgers University (Newark, NJ). October 1992.
- 233. Schering-Plough Co. (Bloomfield, NJ). November 1992.
- 234. International Symposium ISOPOW-V: *Properties of Water in Foods* (Peniscola, Spain). November 1992.
- 235. Carlsberg Laboratory (Copenhagen, Denmark). November 1992.
- 236. International Food Technology Conference (The Hague, The Netherlands). November 1992.
- 237. Singapore Institute of Standards and Industrial Research (Singapore). November 1992.
- 238. Drew University (Madison, NJ). December 1992.
- 239. Northeastern University (Boston, MA). January 1993.
- 240. Ciba Corning Diagnostics Corp. (Irvine, CA). January 1993.
- 241. University of Kansas (Lawrence, KS). January 1993.
- 242. 6th International Symposium on Recent Advances in Drug Delivery Systems (Salt Lake City, UT). February 1993.
- 243. Pennsylvania State University (University Park, PA). March 1993.
- 244. Northwestern University (Evanston, IL). March 1993.
- 245. International Symposium on Technologies for the Production of Enantiomerically Pure Chemicals (Amelia Island, FL). March 1993.
- 246. Gordon Conference on Bioanalytical Sensors (Ventura, CA). March 1993.
- 247. Pharmaceutical Manufacturers Association Analytical R&D/Pharmaceutical Development Subsections Joint Annual Meeting (Lake Buena Vista, FL). April 1993.
- 248. University of Massachusetts Symposium on Breakthrough Technologies: *Paradigms for a New Century* (Amherst, MA). May 1993.
- 249. Parke-Davis Corp. (Ann Arbor, MI). May 1993.
- 250. NutraSweet Co. (Mt. Prospect, IL). June 1993.
- 251. IGT/GRI Workshop on Novel Concepts for the Production of Regio- and Stereospecific Compounds (Chicago, IL). June 1993.
- 252. Northeast Regional Meeting of the American Chemical Society (Boston, MA). June 1993.
- 253. Institute of Food Technologists' Biotechnology Meeting (Chicago, IL). July 1993.
- 254. Annual Meeting of Department of Energy's Biological and Chemical Technology Research Program Principal Investigators (Tiburon, CA). July 1993.

- 255. Allied-Signal Corp. (Des Plaines, IL). July 1993.
- 256. American Chemical Society Meeting (Chicago, IL). August 1993.
- 257. University of Illinois at Urbana-Champaign (Urbana, IL). September 1993.
- 258. International Enzyme Engineering Conference (Deauville, France). September 1993.
- 259. Queens College (Flushing, NY). November 1993.
- 260. Exxon Chemical Research Meeting (Galveston, TX). November 1993.
- 261. Hoffmann-LaRoche Co. (Nutley, NJ). December 1993.
- 262. U.S.-Japan Symposium on Drug Delivery (Maui, HI). December 1993.
- 263. North Dakota State University (Fargo, ND). February 1994.
- 264. Annual Meeting of the American Institute for Medical and Biological Engineering (Washington, DC). March 1994.
- 265. Rhone-Poulenc Rorer Symposium on Visions in Chemistry (Collegeville, PA). May 1994.
- 266. International Flavors & Fragrances R&D (Union Beach, NJ). May 1994.
- 267. Istituto degli Ormoni (Milan, Italy). June 1994.
- 268. Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways (Meriden, NH). July 1994.
- 269. Annual Meeting of Department of Energy's Biological and Chemical Technology Research Program Principal Investigators (Denver, CO). July 1994.
- 270. William S. Johnson Symposium in Organic Chemistry (Stanford, CA). October 1994.
- 271. R.W. Johnson Pharmaceutical Research Institute (Spring House, PA). October 1994.
- 272. International Congress of Biochemical Engineering (Mexico City, Mexico). October 1994.
- 273. National University of Mexico (Mexico City, Mexico). October 1994.
- 274. DuPont Merck Pharmaceutical Co. (Deepwater, NJ). December 1994.
- 275. Symposium on Therapeutic Protein Production and Processing (Cambridge, MA). January 1995.
- 276. International Symposium on Biocatalysts for Flavor Production, BioFlavour '95 (Dijon, France). February 1995.
- 277. Institut Pasteur (Paris, France). February 1995.
- 278. Florida State University (Tallahassee, FL). March 1995.
- 279. Abbott Laboratories (North Chicago, IL). March 1995.

- 280. University of Maryland, Baltimore County (Baltimore, MD). March 1995.
- 281. University of California at San Diego (La Jolla, CA). April 1995.
- 282. Great Lakes Regional Meeting of the American Chemical Society (LaCrosse, WI). June 1995.
- 283. Gordon Conference on Bioorganic Chemistry (Andover, NH). June 1995.
- 284. Annual Meeting of Department of Energy's Biochemical and Chemical Technology Research Principal Investigators (Albuquerque, NM). July 1995.
- 285. International Symposium "Biocatalysis-95" (Suzdal, Russia). August 1995.
- 286. International Enzyme Engineering Conference (San Diego, CA). October 1995.
- 287. Symposium on Biomacromolecules: *From 3-D Structure to Applications* (Pasco, WA). October 1995.
- 288. Enzymol International Inc. (Columbus, OH). December 1995.
- 289. International Symposium PacifiChem '95 (Honolulu, HI). December 1995.
- 290. 3rd U.S.-Japan Symposium on Drug Delivery (Maui, HI). December 1995.
- 291. New England Section of the Society for Industrial Microbiology (Cambridge, MA). February 1996.
- 292. Brown University (Providence, RI). February 1996.
- 293. University of Pittsburgh (Pittsburgh, PA). February 1996.
- 294. Food Research Institute (Reading, England). March 1996.
- 295. International Symposium Chiral USA '96 (Boston, MA). May 1996.
- 296. BP Catalyst Colloquium (Uxbridge, England). June 1996.
- 297. International Symposium on Homogeneous Catalysis (Princeton, NJ). August 1996.
- 298. Juan March Foundation's International Workshop on Novel Biocatalysts (Madrid, Spain). March 1997.
- 299. University of Kentucky (Lexington, KY). April 1997.
- 300. Gordon Conference on Organic Reactions and Processes (Henniker, NH). August 1997.
- 301. Novo Nordisk Symposium on Protein Stability (Klampenborg, Denmark). August 1997.
- 302. International Enzyme Engineering Conference (Beijing, China). October 1997.
- 303. Biogen Inc. (Cambridge, MA). December 1997.

304. INBIO Europe'98 Conference on Advances in Industrial Biocatalysis (Amsterdam, The Netherlands). February 1998.
305. International Symposium on Stability and Stabilization of Biocatalysts (Córdoba, Spain). April 1998.
306. International Symposium on Protein Structure, Stability and Folding: *Fundamental and Medical Aspects* (Moscow, Russia). June 1998.
307. International Conference on Protein Stabilization (Leeds, England). June 1998.
308. University of Virginia (Charlottesville, VA). September 1998.
309. Danish Biotechnology Conference (Vejle, Denmark). May 1999.
310. International Conference on Biocatalysis and Biotransformation Biotrans '99 (Giardini Naxos, Italy). September 1999.
311. Annual Meeting of the American Association of Pharmaceutical Scientists (New Orleans, LA). November 1999.
312. Brandeis University (Waltham, MA). November 1999.
313. Rutgers University (Piscataway, NJ). March 2000.
314. Chiral USA 2000 Conference (Boston, MA). May 2000.
315. Land O'Lakes Conference on Solid-State Reactivity in Pharmaceutical Systems (Merrimac, WI). June 2000.
316. Agouron Pharmaceuticals Inc. (San Diego, CA). July 2000.
317. U.S. Patent and Trademark Office Technology Fair (Arlington, VA). July 2000.
318. 23rd Gulf Coast Chemistry Conference (Pensacola, FL). September 2000.
319. Avon Products (Suffern, NY). November 2000.
320. Procter & Gamble Co. (Cincinnati, OH). November 2000.
321. Flamel Technologies (Venissieux, France). December 2000.
322. BioVision 2001 International Conference (Lyon, France). February 2001.
323. 9th Baxter Science and Technology Symposium (Hyland, IL). May 2001.
324. International Symposium on Applications of Enzymes in Chemical and Biological Defense (Orlando, FL). May 2001.
325. International Conference on Applied Biocatalysis (Trondheim, Norway). June 2001.
326. PPG Industries (Allison Park, PA). August 2001.

- 327. University of Kansas (Lawrence, KS). August 2001.
- 328. Alkermes Inc. (Cambridge, MA). October 2001.
- 329. 6th U.S.-Japan Symposium on Drug Delivery Systems (Maui, HI). December 2001.
- 330. Acambis Inc. (Cambridge, MA). January 2002.
- 331. Baxter BioScience Co. (Duarte, CA). January 2002.
- 332. International Symposium on Challenges in Drug Discovery and Development in the 21st Century (Kolkata, India). March 2002.
- 333. National Institute of Standards and Technology (Gaithersburg, MD). April 2002.
- 334. Albany Molecular Research, Inc. (Mt. Prospect, IL). April 2002.
- 335. Institute for International Research Conference on Protein and Peptide Formulation Strategies for Drug Development and Delivery (San Francisco, CA). August 2002.
- 336. R&D Management Council Meeting of the Technical Association of the Pulp and Paper Industry (Cambridge, MA). November 2002.
- 337. DuPont Central R&D Center (Wilmington, DE). December 2002.
- 338. ACTIVEPack 2003 Conference (Ponte Verde Beach, FL). February 2003.
- 339. International Symposium on Industrial Applications of Biocatalysis: *Chemical Development Issues* (Boston, MA). September 2003.
- 340. U.S. Army Workshop on Self-Decontaminating Materials and Multifunctional Coatings (Arlington, VA). October 2003.
- 341. British Royal Society Meeting on Biocatalysis in Alternative Media (London, England). December 2003.
- 342. National Autonomous University of Mexico (Mexico City, Mexico). March 2004.
- 343. Healthcare Research Initiative Workshop on the Effect of Radiofrequency Radiation on Pharmaceutical Product Quality (Cambridge, MA). June 2004.
- 344. Rensselaer Biotechnology Symposium on Biological Discoveries That Will Change the World (Troy, NY). September 2004.
- 345. Barnett International Conference: *The Consequences of Aggregation in Drug Development, Immunology, Quality Control, and Disease Genesis* (Philadelphia, PA). September 2004.
- 346. 4th Annual IBC Conference on Formulation Strategies for Protein Therapeutics (Boston, MA). October 2004.
- 347. U.S. Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD). August 2005.

- 348. World Congress on Synthetic Receptors (Salzburg, Austria). September 2005.
- 349. International Conference "Celebrating 30 Years of Robert Langer's Science" (Cambridge, MA). July 2006.
- 350. University of Montreal (Montréal, Québec, Canada). October 2006.
- 351. The Boeing Company Research Center (Everett, WA). December 2006.
- 352. Instrumentation Laboratory (Lexington, MA). December 2006.
- 353. Acambis Inc. (Cambridge, MA). January 2007.
- 354. 6th International Symposium on Industrial Microbiology and Biotechnology (Cambridge, MA). August 2007.
- 355. Scientific Conference on Chemical & Biological Defense Research (Timonium, MD). November 2007.
- 356. MIT Research and Development Conference (Cambridge, MA). November 2007.
- 357. Nanotech '2008 International Conference (Boston, MA). June 2008.
- 358. Materials Research Society Symposium (Boston, MA). December 2008.
- 359. Johnson & Johnson Research Briefing at MIT (Cambridge, MA). January 2009.
- 360. 3rd Annual Lyophilization Conference: *Ensuring Optimum Formulations for Pharmaceuticals and Biologics* (Boston, MA). February 2010.
- 361. DSM Corporate Research Center (Geleen, The Netherlands). June 2010.
- 362. Merck Serono Pharmaceutical Co. (Darmstadt, Germany). June 2010.
- 363. NanoFormulations '2010 International Conference (Stockholm, Sweden). June 2010.
- 364. Covidien Surgical Devices and Vascular Therapies Divisions (Cambridge, MA). October 2010.
- 365. World Lyophilization Summit (Cambridge, MA). May 2011.
- 366. Alvogen (Cambridge, MA). March 2012.
- 367. Colgate-Palmolive Co. (Cambridge, MA). April 2012.
- 368. FDA Parenteral Drug Association Glass Quality Conference (Washington, DC). June 2012.
- 369. University of Puerto Rico (Humacao, Puerto Rico). January 2013.
- 370. International Conference on Creating and Leveraging Intellectual Property in Developing Countries (Durban, South Africa – *via teleconference*). November 2013.

- 371. Northwestern University (Evanston, IL). April 2015.
- 372. FDA and Parenteral Drug Association Joint Regulatory Conference (Washington, DC). September 2016.
- 373. Annual Partnership Opportunities in Drug Delivery (PODD) Conference (Boston, MA). October 2017.