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

PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 11,642,361

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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
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1034	Willis, C. J., "Fluorinated Alcohols and their Metal Complexes." *Coord. Chem. Rev.*, 88: 133-202 (1988)
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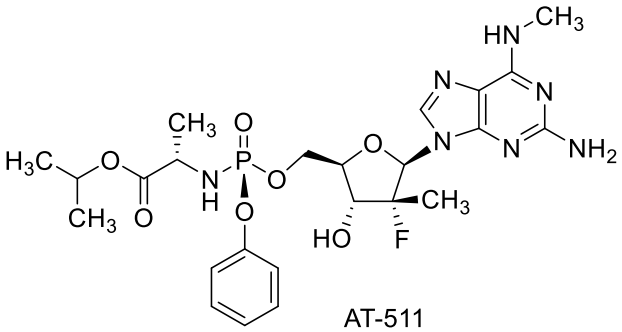
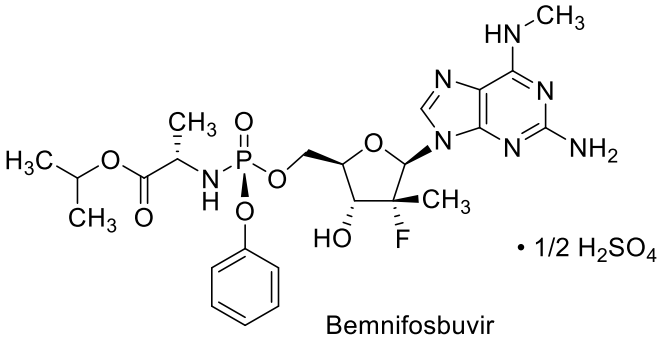
I. INTRODUCTION

Atea Pharmaceuticals, Inc. ("Petitioner") requests Post Grant Review ("PGR") of claim 1 of United States Patent No. 11,642,361 to Du et al., titled "Nucleoside Phosphoramidate Prodrugs" ("'361 patent") (Ex.1001), owned by Gilead Sciences, Inc. ("Patent Owner" or "PO"). This Petition establishes that it is more likely than not that claim 1 of U.S. Patent No. 11,642,361 is invalid. Petitioner supports this Petition with a Declaration from Prof. Alexander M. Klibanov, Ph.D. (Ex.1015).

Petitioner is a clinical stage public company in Boston, MA developing pharmaceutical compounds for treatment of viral diseases such as hepatitis C ("HCV") and SARS-CoV-2 ("COVID19") with a pharmaceutically acceptable salt of AT-511 (shown below), which when used as a hemisulfate salt, is referred to as AT-527, or bemnifosbuvir.



AT-511



Bemnifosbuvir
(AT-527)

PO is a public pharmaceutical company based in Foster City, CA, that sells pharmaceutical products, including Sovaldi (sofosbuvir) and combination products thereof to treat HCV, Veklury (remdesivir) to treat COVID19, and FTC (emtricitabine) and combinations thereof to treat HIV.

Claim 1 of the ’361 patent is drawn to a cobbled-together patchwork-like subgenus of compounds that was not presented in that form and lacks written description in the ’361 specification and priority documents (Ex.1015,¶¶19,99). PO did not invent this subgenus nor did it place it in the possession of the public (*id*.). In fact, among all of the billions of compounds described in the ’361 specification, PO only provided a synthesis for one of the compounds and biological data for none of the compounds in claim 1 (Ex.1015,¶¶19,102,137).

This after-the-fact manufactured genus was filed by PO as a competitive play against Petitioner, which is in advanced clinical trials with bemnifosbuvir to treat HCV and COVID19 and will compete with Gilead’s Sovaldi and Veklury products.

PO was apparently so eager to obtain a patent on Petitioner's late-stage clinical drug that it presented and prosecuted a claim to issuance that directly contradicted PO's own arguments on written description it urged in *Regents of the Univ. of Minnesota v. Gilead* (Exs.1022,1023)(Ex.1015,¶¶19,65,95) which were accepted by PTAB in its Final Written Decision in IPR2017-01712 (Ex.1024) and confirmed by the Federal Circuit on appeal (Ex.1026). These contradictory positions taken by PO were shockingly even overlapping in time, as discussed further below (Section VIII.C(ii)), and were not provided to the USPTO during '361 patent prosecution despite a clear obligation to do so (*see* 37 C.F.R. §1.56; 87 FR 45764 (July 29, 2022); *see also Spectrum, Solutions LLC v. Longhorn Vaccine and Diagnostics*, IPR2021-00860, Paper 107, 7 (May 3, 2023)).

In addition, PO's eagerness to obtain a patent on Petitioner's late-stage clinical drug caused it to prosecute a claim at the USPTO that is directly inconsistent with arguments PO made on the record to the European Opposition Division and the European Technical Boards of Appeal, with parallel litigation in the United Kingdom, with supporting expert testimony regarding the difficulty of synthesizing compounds with various groups in the sugar portion of the nucleotide that fall within issued '361 patent claim 1 (Exs.1030;1037;1038;1015,¶109-136). These inconsistencies were also not provided to the USPTO during prosecution (Ex.1015,¶47) and constitute additional violations of the Duty of Candor.

Claim 1 of the ’361 patent violates 35 USC §112(a) for at least the following reasons, as described below and in the Declaration of Prof. Alexander M. Klibanov, Ph.D. (Ex.1015).

(i) While the ’361 patent presented an enormous “Supergenus” of different compounds, it never presented either the subgenus of claim 1 or any subgenus of compounds with a N^6(H)($C_{1\text{-}6}$ alkyl),N^2-aminopurine nucleotide phosphoramidate within the patent specification, until the amendment of March 19, 2021, as further amended for allowance November 15, 2022 (Ex.1015,¶19, 51).

(ii) The subgenus referred to by PO during prosecution that has the closest resemblance to the ’361 patent claim 1 the “fourteenth aspect of the third embodiment” (Ex.1001,30:col.37,l.46-47), includes a “proviso[]” (see (e), col.37,l.61-62) that is defective and renders the specification subgenus indefinite and confusing (Ex.1015,¶19,58-62). In fact, the proviso in the fourteenth aspect of the third embodiment was altered/corrected during patent prosecution by PO, which suggests that PO knew there was a problem with the proviso and tried to fix it (*id*.,¶60) However, the “fix” led to a written description problem for claim 1 because the patent specification disclosure does not match the issued claim

language (*id*.). The presence of the defective proviso in the relevant aspects and embodiments results in none of them adequately describing the subgenus in claim 1 of the '361 patent (*id*.¶63, and see Table 1 below).

(iii) Even if the defective proviso of the fourteenth aspect of the third embodiment is ignored and one incorrectly assumes that it provides adequate support for claim 1, a different problem arises (Ex.1015,¶¶19,64-66). The combination of variables recited in claim 1 of the '361 patent would have to be selected from over 10^{27} possible combinations described in the fourteenth aspect of the third embodiment of Formula I-6 (ignoring the technical defect) (*id*). The selected claimed combination is thus much narrower than the closest subgenus in the '361 patent, without any guidance in the patent specification how to get there (in fact, there were many "don't go in this direction" signs) (*id.*,¶¶19,97,139). 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 none were tested for biological activity or toxicity (*id.,*¶¶19,143).

(iv) The ’361 patent includes 524 columns of tables with 12,400 specific compounds listed (Ex.1001,38-301:cols.54-579) as teaching embodiments by PO, none of which are drawn to the subgenus of claim 1 or even includes a single compound that falls within the scope of the claim (Ex.1015,¶19,97).

(v) The expansive definition of “purine” base in the ’361 patent specification (Ex.1001,17:col.11,l.55-col.12,l.14) does not mention, and thus points a POSA away from, a N^6-alkyl,N^2-aminopurine nucleotides (Ex.1015,¶19,44).

(vi) The ’361 patent specification only includes the synthesis of a single compound within the entire subgenus of claim 1, which is not enough to describe the totality of claim 1, or point the POSA to the metes and bounds of the subgenus (*id.*,¶19,88-89).

(vii) The ’361 patent specification includes no efficacy or toxicity data for any of the compounds falling within the scope of claim 1 (even though it included efficacy data for other compounds), which indicates a lack of guidance pointing a POSA to the issued claim 1 subgenus, and in fact points the POSA away from claim 1 (*id.*,¶19,137).

(viii) Certain 2'-combinations within the scope of the subgenus of the '361 claim 1 are unstable and cannot be made 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 (*id.*,¶19,112-121).

(ix) 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 (*id.*,¶19,137-153).

In summary, there are no blaze marks in the dense forest of the '361 patent that lead a POSA to the subgenus of claim 1, and in fact, there are a multitude of "don't go there" signs (Ex.1015,¶¶19,99).

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 Petitioner's 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 (COVID19) and Phase 2 (HCV) human clinical trials (Ex.1015,¶19).

II. MANDATORY NOTICES (37 C.F.R. §42.8)

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

The real party-in-interest is Atea Pharmaceuticals, Inc.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is not aware of any presently pending judicial matters that would affect, or be affected by, a decision in the proceedings.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

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D. Service Information (37 C.F.R. §42.8(b)(4))

Please address all correspondence to the lead and back-up counsel at the above addresses. Petitioner consents to electronic service to the email addresses above.

III. TIME FOR FILING PETITION (37 C.F.R. §42.202)

The '361 patent issued May 9, 2023 (Ex.1001). This Petition is timely filed on or before the date that is nine months after the date of the grant of the patent.

Consistent with 35 U.S.C. §325(d), the arguments presented in this Petition are not the same or substantially the same as any arguments presented or addressed by the USPTO during prosecution. In fact, no rejections were made by the USPTO under 35 U.S.C. §112(a) or §102 during prosecution of the '361 patent.

A. Payment of Fees (37 C.F.R. §§42.203(a) and 42.15(b))

Pursuant to 37 C.F.R. §42.203(a) and §42.15(b), the required fees are submitted with this Petition. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 50-5834.

B. Grounds for Standing (37 C.F.R. §42.204(a))

Petitioner certifies under 37 C.F.R. §42.204(a) that the '361 patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR to challenge the claims on the grounds identified in this Petition. Petitioner further certifies that the prohibitions of 35 U.S.C. §325(a) are inapplicable.

The '361 patent is available for PGR, because claim 1 has an effective filing date on or after March 16, 2013, as it is not entitled to any priority date earlier than November 15, 2022, the date PO amended its March 19, 2021 claim amendment to facilitate allowance (and not that date either), as discussed further below. Claim 1 as issued lacks written description support and is not enabled by the specification as required by §112(a).

The Board has consistently determined eligibility for post-grant review based on written description and enablement analyses. *See, e.g., Eli Lilly & Co. v. Genentech, Inc.*, PGR2019-00043, Paper 11, 11–12 (Oct. 7, 2019); *Daiichi Sankyo, Inc. v. Seagen, Inc.*, PGR2021-00030, Paper 17, 8−10 (Apr. 7, 2022).

C. Identification of Challenged Claims and Relief (37 CFR §42.204(b))

Petitioner requests institution of PGR and cancellation of claim 1 of the '361 patent as unpatentable under 35 U.S.C. §112(a) and §102(a)(1). It is more likely than not that claim 1 is unpatentable on the following grounds.

Ground	Claims	Statutory Basis	Prior Art References
1	1	35 U.S.C. §112(a) – Lack of Written Description	
2	1	35 U.S.C. §112(a) – Lack of Enablement	
3	1	35 U.S.C. §102(a)(1)	U.S. Pub. 2016/0257706 (Ex.1020)

IV. EXPERT TESTIMONY OF ALEXANDER M. KLIBANOV, PH.D.

Petitioner supports this Petition with a Declaration from Prof. Alexander M. Klibanov, Ph.D. (Ex.1015), the Novartis Endowed Chair Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology ("M.I.T."), where he taught both undergraduate and graduate courses in many areas of chemistry, including general, organic, and biological, and conducted research for over 40 years (*id*.,¶1). Prof. Klibanov's CV is attached to his Declaration.

Prof. Klibanov has substantial experience with nucleoside chemistry. For example, he consulted and acted as an expert for Emory University (Atlanta, Georgia) for a number of years in connection with Emory's patent portfolio on the nucleoside emtricitabine ("FTC", the leading drug in the world for the treatment of

HIV sold by Gilead Sciences, Inc., the PO, in nine of its franchise drugs: Biktarvy, Complera, Descovy, Emtriva, Genvoya, Odefsey, Stribild, Truvada and Atripla), as well as Emory's interests in the nucleoside lamivudine ("3TC"), sold for the treatment of HIV by Viiv Healthcare (a joint venture of GSK and Pfizer) (*id*.,¶13).

Prof. Klibanov has earned numerous prestigious professional awards and honors for his work in the biopharmaceutical area. He was 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). He is 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, he 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 (*id*.,¶3).

Prof. Klibanov obtained an M.S. degree in Chemistry in 1971 and a Ph.D. in Chemical Enzymology in 1974, both from Moscow University in Russia. Thereafter, he worked as a Research Chemist at Moscow University's Department of Chemistry for three years. After immigrating to the U.S., he was a Post-Doctoral Associate in

the Department of Chemistry at the University of California San Diego from 1977 to 1979. He is a naturalized U.S. citizen (*id*.,¶4).

From 1979 to 1988, Prof. Klibanov 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, he was a Professor of Chemistry in the Department of Chemistry and thereafter a Professor of Bioengineering in the Department of Biological Engineering at M.I.T. From 2012 to 2014, he held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry at M.I.T. (*id*.,¶5).

From 2007 to 2012 and then again from 2014 to 2019, he was the Novartis Endowed Chair Professor of Chemistry and Bioengineering at M.I.T. Prof. Klibanov retired from full-time teaching and research responsibilities at M.I.T. in 2019 and is now an independent consultant in the pharmaceutical area (*id.*,¶6).

Over the past some 50 years as a practicing chemist, Prof. Klibanov has extensively researched, published, taught, and lectured in many areas of medicinal and biological chemistry (*id.*,¶7).

Prof. Klibanov currently serves 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", and "Archives of Medical Biotechnology" and "International Journal of Drug Design, Delivery and Safety" (*id.*,¶8).

Prof. Klibanov has published over 315 scientific papers in various chemical disciplines, including medicinal, organic, and biological chemistry. He is also a named inventor on 32 issued United States patents and on a number of pending patent applications (both foreign and domestic) (*id.*,¶9).

Prof. Klibanov has 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 his published work, places him in the top 0.01% of scientists in the world (*id.*,¶10).

Prof. Klibanov has founded six pharmaceutical companies and has been on the scientific advisory boards and/or boards of directors of those companies, as well as many others. A number of these entrepreneurial, consulting, advisory, and directorship activities have dealt with medicinal chemistry and enzyme-substrate

interactions, as well as discovery, development, administration, and pharmacological evaluation of therapeutic agents (*id.*,¶12).

Prof. Klibanov's Declaration includes Section IX, which is a summary of the legal standards explained to him to address the issues he has been asked to opine on.

V. PERSON OF ORDINARY SKILL AND CLAIM CONSTRUCTION

Claim 1 of the '361 patent is a composition-of-matter claim covering a subgenus of antiviral pharmaceutical compounds (certain purine nucleotide phosphoramidates). According to Prof. Klibanov, 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) (Ex.1015,¶22). Because 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 (*id.*).[1]

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[1] In its IPR 2017-01712 Petition, PO defined a POSA as follows: "A POSA would have included someone with a doctoral degree with a background in organic,

According to Prof. Klibanov, 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 (*id.*,¶19,171). Petitioner does not seek Board construction of any terms.

VI. TECHNOLOGY TUTORIAL

Prof. Klibanov has provided a technology tutorial on nucleosides, nucleotides, and derivatized nucleotide phosphoramidates for the convenience of the Board (*id.*,¶¶23-39).

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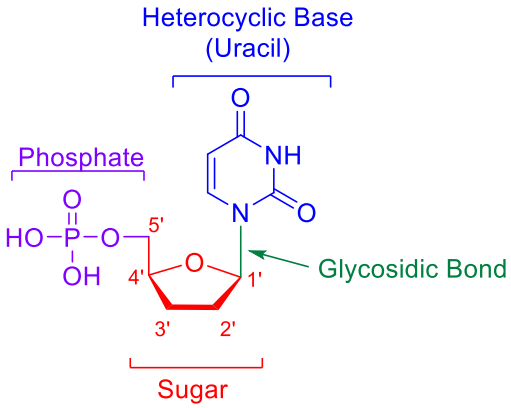
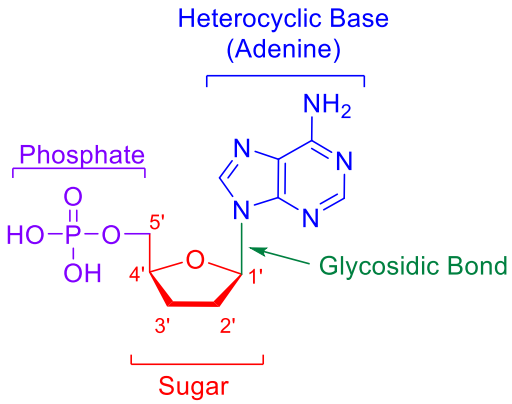
synthetic, or medicinal chemistry, or possibly a related discipline such as pharmacology, and who also had some practical experience (e.g., at least two years) in drug discovery. This person could also have been someone with a bachelor's or master's degree in one of these disciplines but with greater 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" (Ex.1022,15). According to Dr. Klibanov, he considered this POSA definition and determined that none of his conclusions contained in his Declaration would change when using it instead of his proposed POSA (Ex.1015,¶22,fn.1).

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



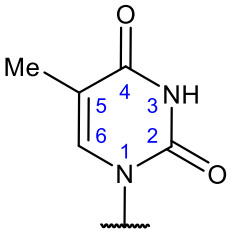
Pyrimidine Nucleotide



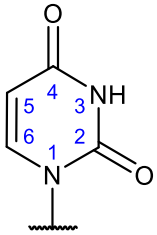
Purine Nucleotide

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

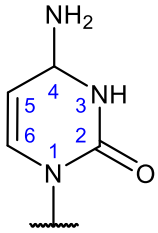
Pyrimidine bases in naturally occurring[2] nucleosides include (*id.*,¶26):



Thymine

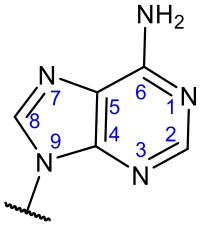


Uracil

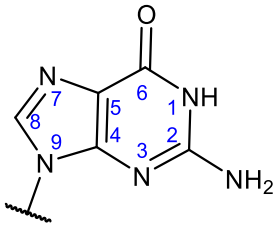


Cytosine

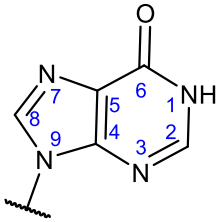
Naturally occurring purines include the following (*id.*,¶27):



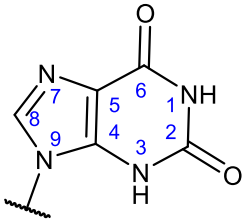
Adenine



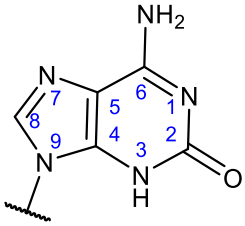
Guanine



Hypoxanthine

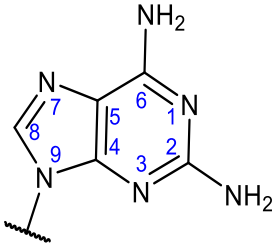


Xanthine

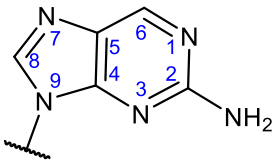


Isoguanine

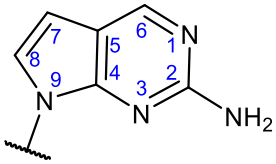
Non-naturally occurring purines include the following (*id.*,¶28):



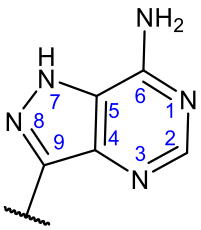
2,6-diaminopurine



2-aminopurine



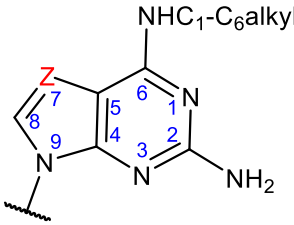
2-amino-7-deazapurine



Formycin

[2] The term "naturally occurring", as used herein, refers to in humans.

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

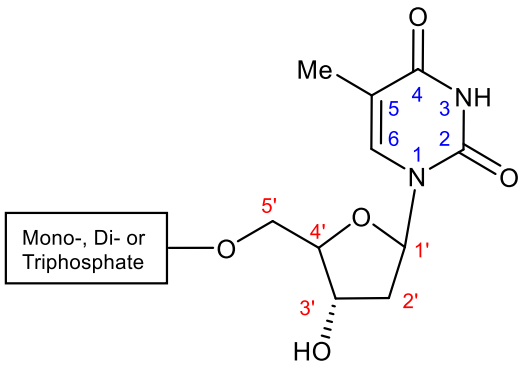


Z is N or CR^{12}
R^{12} is H, halogen, -OR', $-NH_2$, -NHR', $-NR'_2$, $-NO_2$, C_1-C_6alkyl, $-CO_2R'$, $-CONH_2$, -CONHR', $-CONR'_2$, $-CH=CHCO_2H$ or $-CH=CHCO_2R'$
R' is a C_1-C_6alkyl

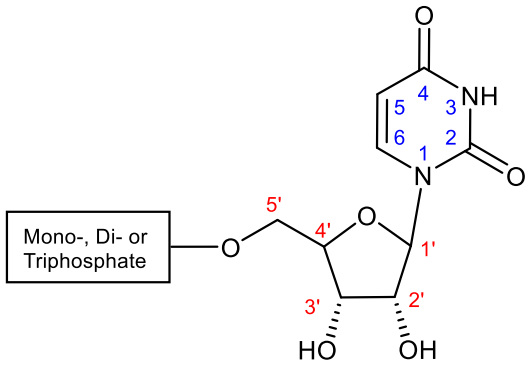
Purine of Claim 1

The claim 1 purine is non-naturally occurring because it has amino substituents in both the 6-position and the 2-position. In certain embodiments, the purine can also be a "deazapurine," which is missing a nitrogen in the 7-position and instead has a CR^{12}, wherein the R^{12} can itself be selected from over 4,800 chemical moieties (*id.*,¶29).

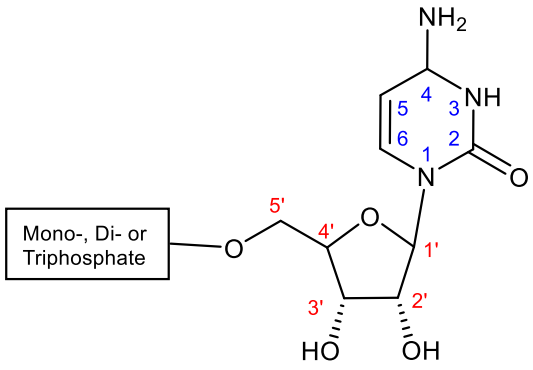
The numbering system for nucleo(s/t)ides assigns atoms in the nitrogenous base with integers (e.g., 1, 2, 3) and in the sugar with integers prime (e.g., 1', 2', 3'). Examples of naturally-occurring nucleotides include the following structures:



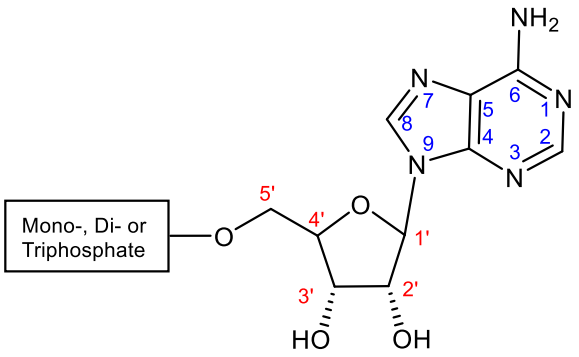
Thymidine (DNA Only)



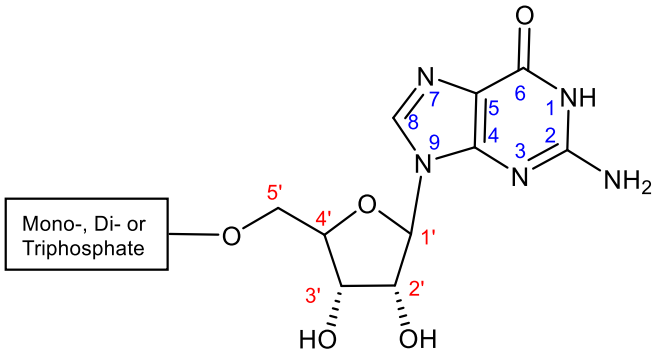
Uridine (RNA Only)



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.

Because nucleotides are the building blocks of DNA and RNA used for cellular replication, they have long served as the starting point for drug discovery research. A particularly fertile ground has been anti-viral research. Derivatized nucleosides and nucleotides have been used, for example, to treat HIV, hepatitis B ("HBV"), and also were the subject of HCV research in the 1980's and 1990's, leading to commercial anti-HCV products in the 2010's (e.g., sofosbuvir in 2013) (*id.*,¶31).

Therapeutic nucleotides work by interfering with viral enzymes. Anti-viral nucleotides primarily exhibit their effect by interfering with a viral polymerase enzyme, which is an enzyme that synthesizes 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). It 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 SARS-CoV-2 (causing the human disease COVID19), the relevant polymerase is also a RdRp, but it is different from the HCV enzyme and is referred to as the SARS-CoV-2 nsp12 enzyme (*id.*,¶32).

Drug discovery efforts to identify derivatized nucleosides/nucleotides for treatment of 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 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

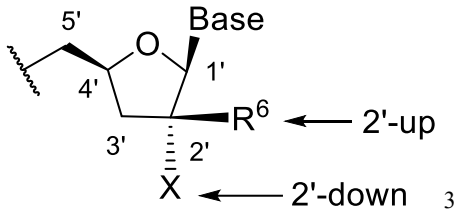
activated nucleotide triphosphate. It is only after these three steps have taken place that the derivatized nucleotide can typically be acted upon by the polymerase enzyme (*id.*,¶33).

A critical requirement for drug discovery in the antiviral area, therefore, has been the phosphate pre-activation steps for nucleosides. The nucleoside must be able to be activated to the triphosphate form by the relevant kinase enzymes (*id.*,¶34).

This presented a particular issue for potential anti-HCV 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 RdRp. There were many false starts and failures along the way. In general, commercialized nucleosides against HIV and HBV were not active against HCV (*id.*,¶35).

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., CH_3) 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 that were active to treat HIV or HBV

had a methyl group in the 2'-up-position. Researchers at the time were not focusing on this position of the nucleoside, nor on this methyl substituent. The breakthrough by Drs. Sommadossi and LaColla taught other researchers where to look and led to a flurry of subsequent research in that direction (*id.*,¶36).



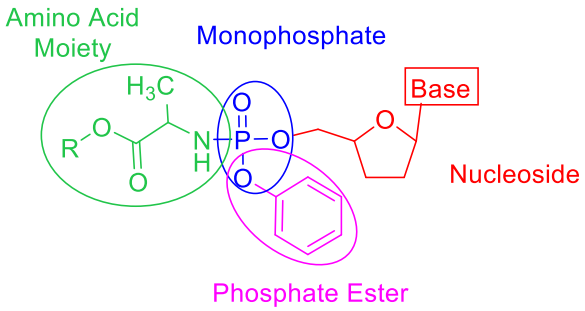
Once subsequent drug discovery research was carried out on 2'-methyl nucleosides, another problem arose. While the synthetic 2'-methyl nucleosides could inhibit the HCV RdRp enzyme, they were poor substrates for the preactivating kinase enzymes, and in particular for the monophosphate kinase that adds the first phosphate to the 5'-position of the nucleoside. Therefore, a solution was sought for that problem (*id.*,¶37).

This research led to the groundbreaking work of Prof. Christopher McGuigan from the University of Cardiff in the U.K., who had identified and for years been carrying out drug discovery studies on prodrugs of nucleosides that are able to

---

[3] As defined in claim 1, the R^6 position corresponds to 2'-up and the X position corresponds to 2'-down.

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 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 (*id.*,¶38).

The '361 patent, with its asserted 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 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 (Ex.1015,¶39).

VII. THE ’361 PATENT PRIORITY CLAIMS

The ’361 patent asserts priority to applications described in the following table.

Exhibit No.	Application/Patent No.
1003	U.S.S.N. 60/909,315
1004	U.S.S.N. 60/982,309
1005	U.S.S.N. 12/053,015; now U.S. Patent No. 7,964,580
1006	U.S.S.N. 13/099,671; now U.S. Patent No. 8,334,270
1007	U.S.S.N. 13/609,614; now U.S. Patent No. 8,580,765
1008	U.S.S.N. 14/013,237; now U.S. Patent No. 9,085,573
1009	U.S.S.N. 14/656,546; now U.S. Patent No. 9,585,906
1010	U.S.S.N. 15/411,506; now U.S. Patent No. 10,183,037
1011	U.S.S.N. 16/169,878; now abandoned[4]
1012	U.S.S.N. 16/516,192; now abandoned
1013	U.S.S.N. 16/817,318; now abandoned
1014	U.S.S.N. 17/077,267

This Petition focuses on the content of the ’361 patent specification. Petitioner accepts that the applications starting with Ex.1005 through Ex.1014 contain the

[4] The action of PO to file three consecutive patent applications without any meaningful attempt to progress prosecution implies prosecution laches.

same specification as they are designated as continuation applications (not continuations-in-part).

VIII. SUMMARY OF '361 PATENT AND VIOLATION OF 35 U.S.C. 112

The '361 patent "pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases" (Ex.1001,12:col.1,l.39-47). These compounds are inhibitors of RNA-dependent RNA viral replication and purported to be useful as inhibitors of HCV.

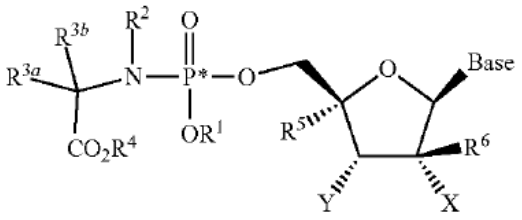
It is bedrock law that the purpose of the written description requirement of 35 U.S.C. §112(a) is to establish that the inventor(s) had possession of the claimed subject matter as of the filing date. *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997) (internal citations omitted). Where *ipsis verbis* disclosure does not exist, written description support for a claimed subgenus, in description of a broader genus, must be established through "blaze marks that single out particular trees in a forest." *In re Ruschig*, 379 F.2d 990, 994–95 (CCPA 1967); *see also Regents of the Univ. of Minn. v. Gilead Scis.*, 61 4th 1350, 1357 (Fed. Cir. 2023) (Ex.1026,10). These blaze marks must be clear because "it is easy to bypass a tree in the forest, even one that lies close to the trail." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("[J]ust because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support

for every species or sub-genus that chooses that moiety. Were this the case, a "laundry list" disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not "reasonably lead" those skilled in the art to any particular species. *Gilead*, 61 4th at 1357 (citing *Fujikawa*, 3 F.3d at 1571) (Ex.1026,9).[5]

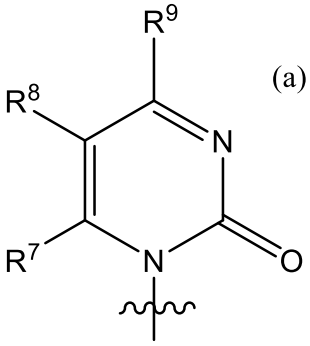
The Summary of the Invention presents an enormously broad chemical formula that seeks to cover an almost incalculable number of nucleotide phosphoramidates (*id*.,14;col.5,l.25-38), with variables at every possible position, and wherein each of the variables covers a huge scope of layered substituent

[5] Consistent with the Patent Trial and Appeal Board Consolidated Trial Practice Guide November 2019 at 39, Petitioner does not include extended discussions of the law in this Petition and instead focuses on the facts at hand, unless a discussion of case law is particularly pertinent. "Another factor to keep in mind is that judges of the Board are familiar with the general legal principles involved in issues which come before the Board. Accordingly, unless there is a dispute over the applicable law, extended discussions of the general patent law principles may not be necessary" (*id.*).

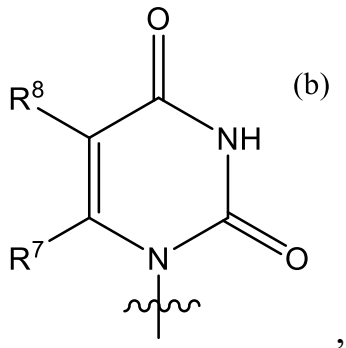
possibilities (referred to below as the "'361 Supergenus"). To place in context, the number of compounds in subgenus claim 1 reaches the billions (Ex.1015,¶¶19,93).



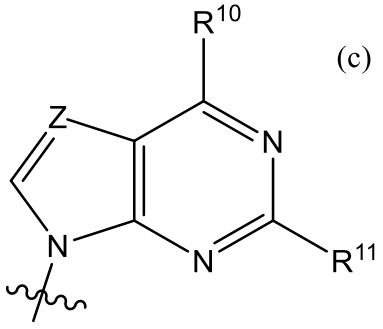
The term nitrogenous "base" is defined as "a naturally occurring or modified purine or pyrimidine base" represented by the following structures (Ex.1001,18:col.13,l.66-col.14,l.36):


(a)

,

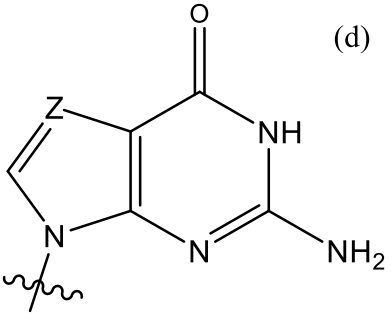

(b)

,


(c)

,

and


(d)

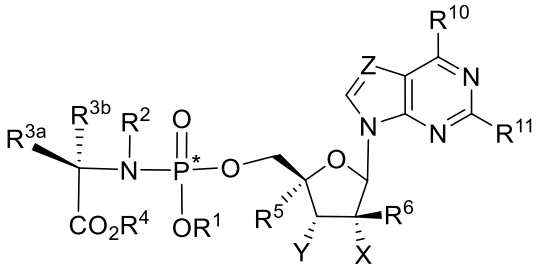
Purine base (c) above is the only one that is relevant to claim 1 of the '361 patent (Ex.1015,¶42).

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 patent specification, which is stated to include, but not be limited to, a broad list of various purines (Ex.1001,17:col.11,l.55-col.12,l.15). The purines listed are (removing the interspersed pyrimidines): adenine, N^6-alkylpurines, N^6-acylpurines, N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkylpurine, N^6-allcylaminopurine [*sic*], N^6-thioallcyl [*sic*] purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, C^5-hydroxyalkylpurine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, guanine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine (Ex.1015,¶43).

Notably, the definition of a "purine" in the '361 patent specification (i) distinguishes between the N^6 and N^2 purine substituents and (ii) ***does not mention N^6-alkyl,N^2-aminopurines at all*** (which is the formula of the purine base in claim 1 of the '361 patent) (*id*.,¶44). It would be logical for a POSA to assume that if PO had specifically envisioned a class of N^6-alkyl,N^2-aminopurines as presented in claim 1 of the '361 patent as of the filing date, then PO would have expressly listed N^6-alkyl,N^2-aminopurines in the definition of purines (*id*.). This is but one of many "blaze marks" that point a POSA away from the subgenus presented by claim 1 of the '361 patent (*id*.).

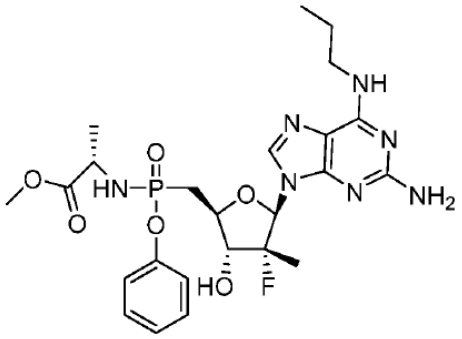
A. File History of the '361 Patent

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:

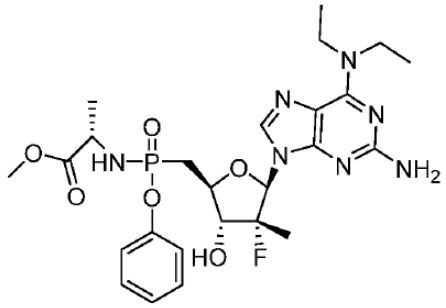


I-6

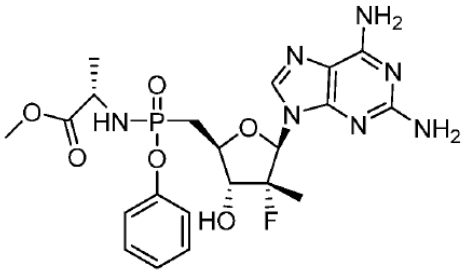
or a pharmaceutically acceptable salt thereof (*id*.,87-88). Claims 14-16 further narrowed the broad subgenus (*id*.,88-89). Claim 17 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



(*id*.,17). Claim 18 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



(*id.*). Claim 19 claimed the species, or a pharmaceutically acceptable salt thereof, of formula:



(*id*.,89-90).

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 Exhibits 1020-1028 and 1030-1042.

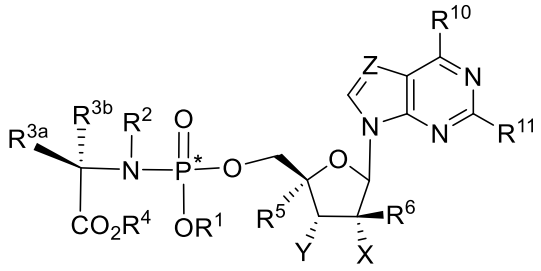
On Apr. 12, 2022, a Non-Final Office Action was mailed rejecting claims 13-19 under 35 U.S.C. §103 (*id*.,156-166). Claims 13-16 were rejected as unpatentable over Gilead's (formerly Pharmasset's) Clark WO 2005/003147 ("Clark") and Perrone et al., J. Med. Chem. (2007) Vol. 50, pp. 1840-1849 ("Perrone") (from the

McGuigan laboratory) in combination (*id*.,160). The Examiner did not raise any rejections under 35 U.S.C. §112.

On July 12, 2022, PO filed a Response to the outstanding NFOA (*id*.,232-237). PO made no amendments to subgenus claims 13-16 and amended claims 17-19 to correct a technical defect.

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, noting that "the combination of Clark and Perrone does not reasonably teach or suggest a compound wherein: (a) R^4 is -CH_3, ethyl, n-propyl or i-propyl; (b) R^{10} is -NHR' and R^{11} is -NH_2; and (c) R' is C_{1-6} alkyl" (*id*.,250-251). The Examiner again did not raise any rejections under 35 U.S.C. §112.

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:



I-6

wherein:

a) R^1 is H, $-CH_3$, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;

b) R^2 is H;

c) R^{3a} is H and R^{3b} is H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2Ph$ or lower cycloalkyl;

d) R^4 is ~~hydrogen,~~ $-CH_3$, ethyl, *n*-propyl, or *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(C_{1-6}-alkyl)amino-C_{1-6}-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).

On December 7, 2022, the Office 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).

On May 9, 2023, the '267 application issued as U.S. Patent 11,642,361.

B. Analysis Of Embodiments And Aspects Of Invention

The '361 patent specification attempts to provide guidance on genuses and subgenuses of the '361 Supergenus through a complex maze of "embodiments" and "aspects" using some 42 columns of text (Ex.1001,17-38:cols.12-54). Tellingly, ***none*** of these embodiments or aspects directly, or even indirectly, leads a POSA to

the claim 1 subgenus of the ’361 patent (Ex.1015,¶54). These embodiments and aspects are set out in Table 2 below.

Claim 1 of the ’361 patent includes a negative limitation that states:

“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***;”

(Ex.1001,321:col.619,l.25-27; emphasis added).

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 specification, which is also found in col. 37, lines 46-end, to col. 38, lines 1-10 of the issued patent (Ex.1001,30). [6]

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 with that exact language in the referenced sections of (or anywhere else in) the

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[6] 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 application (Ex.1002,238), which includes the only compound made that falls within the claims.

application (Ex.1015,¶57). Instead, the fourteenth aspect of the third embodiment states:[7]

> "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;" (Ex.1001,30:col.37,l.61-62).

The actual proviso in the fourteenth aspect of the third embodiment as set out in the specification and which focuses on R^5 is indefinite, not to mention vague, because it is amenable to at least three distinct interpretations (Ex.1015,¶58):

> **<u>Interpretation 1</u>**: "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" — must be interpreted exactly as written without modification. This statement says what R^5 is not, but not what it is, under the set condition. What is R^5 then when X is OH and R^6 is CH_3 or CH_2F? A POSA might conclude that R^5 then reverts to the full definition of substituents of R^5 in the formula (minus H), which are "lower alkyl, CN,

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[7] The fourteenth aspect of the third embodiment 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.1001,30;col.37,l.66-col.38,l.2; emphasis added), which is nonsensical because the proviso abruptly stops without completing the clause (Ex.1015,¶57,fn.5).

vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1-6, including hydroxyl methyl (CH_2OH), CH_2F, N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I" (the way R^5 is defined in Formula I-6 (Ex.1001,29:col.35,l.32-36)) or even at a minimum "CN, CH_2F, F, Cl, Br, or I" (the way R^5 is defined in the twelfth aspect of the third embodiment (*id*.:col.36,l.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 R^5 substituents were intended to be in this situation, making it hopelessly vague. It is not the POSA's responsibility to complete an incomplete clause on behalf of the inventors. Ex.1015,¶58.

Interpretation 2: Alternatively, "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" can be interpreted to mean that "X cannot be OH, and R^6 cannot be CH_3 or CH_2F" because R^5 is defined as hydrogen. However, this is not how the proviso is actually worded. Rather, the proviso is worded as an exclusion of R^5 substituents, not an exclusion of X and R^6 substituents (…R^5 cannot be H…). Again, the wording is indefinite because a POSA would be confused. *Id*.

Interpretation 3: Alternatively, "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" can be interpreted to mean that

"compounds where X is OH and R^6 is CH_3 or CH_2F" are excluded from the claim because R^5 is defined as hydrogen. However, again, this is not how the proviso is actually worded. Rather, the proviso is worded as an exclusion of R^5 substituents, not an exclusion of X and R^6 substituents (…R^5 cannot be H…). Again, the wording is indefinite because a POSA would be confused. *Id*.

PO must have recognized the indefiniteness problem here because it took the affirmative step to reword the proviso in amended claim 1. In doing so, it converted an R^5 proviso to become an X proviso:

"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***;"

in other words, PO eliminated reference to R^5 (Ex.1002,86-87, emphasis added).

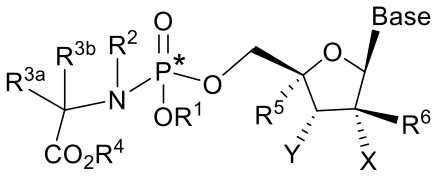
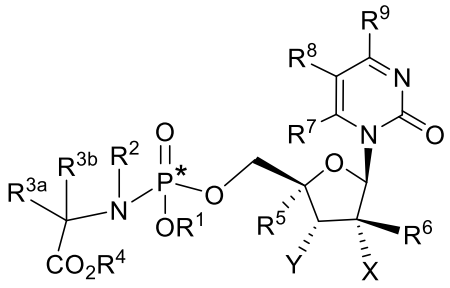
In Prof. Klibanov's opinion, PO would likely not have taken this affirmative step if it did not realize that the patent specification was confusing and thus indefinite on this point (Ex.1015,¶60). Otherwise, why convert an R^5 proviso into an X proviso (and ignore the R^5 altogether)? The likely answer is to remove ambiguity, which was, in fact, baked into the patent specification as originally drafted. Regardless of the intent, however, the proviso in claim 1 does not have support in the patent specification because of the conversion of a R^5 proviso into a X proviso (*id*.).

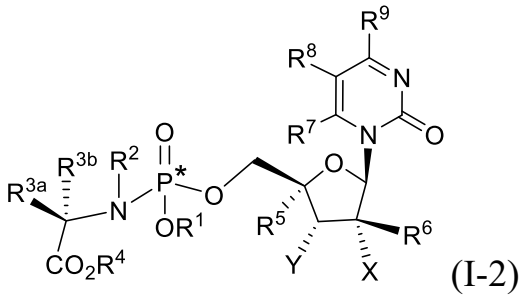
The Federal Circuit recently addressed the issue of negative limitations in an issued claim. While a negative limitation need not be recited in the specification *in haec verba*, there generally must be something in the specification that conveys to the skilled artisan that the inventor intended that exclusion such as a discussion of the disadvantages or alternatives. *Novartis Pharm. Corp. v. Accord Healthcare, Inc*., 38 F.4th 1013, 1016-1017 (Fed. Cir. 2022). When the specification is itself silent regarding a negative limitation, testimony from a skilled artisan as to possibilities or probabilities that the recited element would be excluded would not suffice, lest such testimony could effectively eliminate the written description requirement. *Id*.,1017. If silence were generally sufficient, all negative limitations would be supported by a silent specification. *Id*.,1017-18.

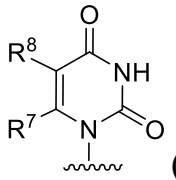
In the case of the ’361 patent claim 1, a reasonable POSA could interpret the negative limitation in the definition of R^5 of the fourteenth aspect of the third embodiment in at least the three distinct ways described above, thus making the proviso indefinite (Ex.1015,¶62). And PO’s attempt to circumvent this indefiniteness by rewriting the proviso into an “X” proviso from an “R^5” proviso leads to a written description problem by using language in claim 1 that is not unambiguously provided in the patent specification (*id*.).

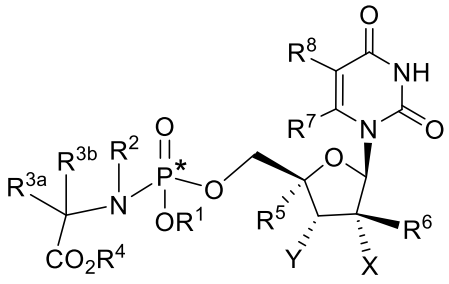
Table 1 below lists the embodiments and aspects presented in the ’361 patent specification and indicates whether the subgenus of claim 1 is covered (*id*.,¶63).

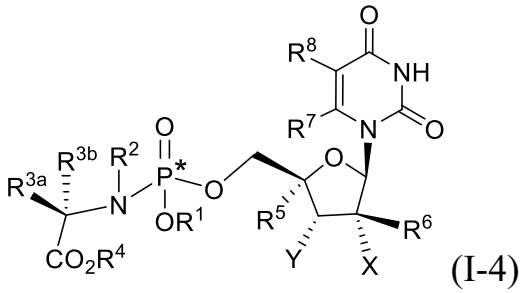
Table 1

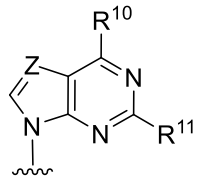
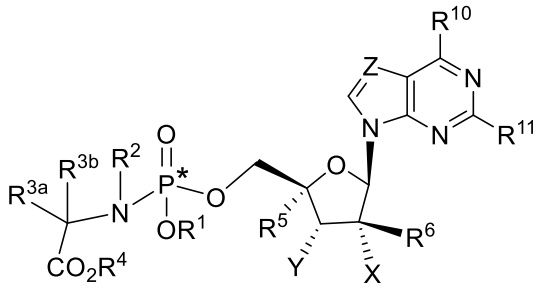
Embodiment	Relevant to '361 patent claim 1?
An aspect of the invention is directed to a compound represented by Formula I  (I) Ex.1001,17-19:col.12,l.37-col.15,l.18.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H," and this proviso is not in claim 1. See Ex.1001,17:col.13,l.33-40;Ex.1015,¶63.
1st embodiment: a compound of Formula I-1  (I-1) Ex.1001,19;col.15,l.19-col.16,l.59.	No, because the Base is a pyrimidine. Ex.1015,¶63.
1st aspect of the 1st embodiment: a compound of Formula I-1	No, because the Base is a pyrimidine.

Ex.1001,19-20:col.16,l.60- col.17,l.53.	Ex.1015,¶63.
2nd aspect of the 1st embodiment: a compound of Formula I-1 Ex.1001,20:col.17,l.54- col.18,l.43.	No, because the Base is a pyrimidine. Ex.1015,¶63.
3rd aspect of the 1st embodiment: a compound of Formula I-1 Ex.1001,20-21:col.18,l.44-col.19,l.27.	No, because the Base is a pyrimidine. Ex.1015,¶63.
4th aspect of the 1st embodiment: a compound of Formula I-2  (I-2) Ex.1001,21:col.19,l.28- col.20,l.26.	No, because the Base is a pyrimidine. Ex.1015,¶63.
5th aspect of the 1st embodiment: a compound of Formula I-2 Ex.1001,21:col.20,l.27-65.	No, because the Base is a pyrimidine. Ex.1015,¶63.
6th aspect of the 1st embodiment: a compound of Formula I-2	No, because the Base is a pyrimidine.

Ex.1001,21-22:col.20,l.66-col.21,l.29.	Ex.1015,¶63.
7th aspect of the 1st embodiment: a compound of Formula I-2 Ex.1001,22:col.21,l.30-59.	No, because the Base is a pyrimidine. Ex.1015,¶63.
8th aspect of the 1st embodiment: a compound of Formula I-2 Ex.1001,22:col.21,l.60-col.22,l.22.	No, because the Base is a pyrimidine. Ex.1015,¶63.
2nd embodiment: a compound of Formula I, in which the Base is of Formula (b)  (b) Ex.1001,22:col.22,l.23-27.	No, because the Base is a pyrimidine. Ex.1015,¶63.

1st aspect of the 2nd embodiment: a compound of Formula I-3  (I-3) Ex.1001,22-23:col.22,l.28-col.23,l.62.	No, because the Base is a pyrimidine. Ex.1015,¶63.
2nd aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001,23:col.23,l.63-col.24,l.56.	No, because the Base is a pyrimidine. Ex.1015,¶63.
3rd aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001,23-34:col.24,l.57-col.25,l.40.	No, because the Base is a pyrimidine. Ex.1015,¶63.
4th aspect of the 2nd embodiment: a compound of Formula I-3 Ex.1001,24:col.25,l.41-col.26,l.14.	No, because the Base is a pyrimidine. Ex.1015,¶63.

5th aspect of the 2nd embodiment: a compound of Formula I-4  (I-4) Ex.1001,24-25:col.26,l.15-col.27,l.2.	No, because the Base is a pyrimidine. Ex.1015,¶63.
6th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001,25:col.27,l.3-31.	No, because the Base is a pyrimidine. Ex.1015,¶63.
7th aspect of the 2nd embodiment: a compound of formula I-4 Ex.1001,25:col.27,l.32-55.	No, because the Base is a pyrimidine. Ex.1015,¶63.
8th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001,25:col.27,l.56-col.28,l.11.	No, because the Base is a pyrimidine. Ex.1015,¶63.
9th aspect of the 2nd embodiment: a compound of Formula I-4 Ex.1001,25:col.28,l.12-33.	No, because the Base is a pyrimidine. Ex.1015,¶63.

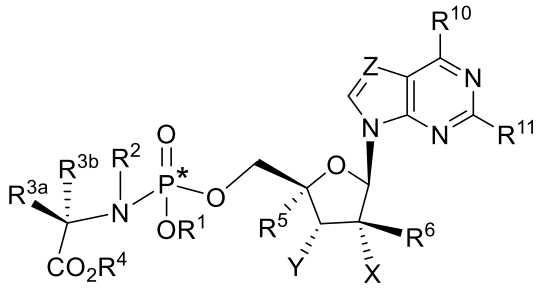
3rd embodiment: a compound of Formula I, in which the Base is of Formula (c)  (c) Ex.1001,25:col.28,l.35-40.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001;18:col.13,l.33-40;Ex.1015,¶63.
1st aspect of the 3rd embodiment: a compound of Formula I-5  (I-5) Ex.1001,25-26:col.28,l.41-col.30,l.34.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, and B is a purine base, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,26:col.29,l.38-45;Ex.1015,¶63.
2nd aspect of the 3rd embodiment: a compound of Formula I-5	No, because R^5 is a list of substituents, with the proviso

Ex.1001,26-27:col.30,l.35-col.31,l.8.	that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,26:col.30,l.56-58;Ex.1015,¶63.
3rd aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,27:col.31,l.9-41.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,27:col.31,l.24-25;Ex.1015,¶63.
4th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,27:col.31,l.42-col.32,l.7.	No, because "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" and this proviso is not in claim 1.

	See Ex.1001;27:col.31,l.57-58;Ex.1015,¶63.
5th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,27:col.32,l.8-36.	No, because "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" and this proviso is not in claim 1. *See* Ex.1001;27:col.32,l.21-22;Ex.1015,¶63.
6th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,27-28:col.32,l.37-col.33,l.6.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,27:col.32,l.56-58;Ex.1015,¶63. Also, not relevant because R^{10} must be NH_2.

	See Ex.1001,27:col.32,l.63; Ex.1015,¶63.
7th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,28:col.33,l.7-40.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. See Ex.1001,28:col.33,l.23-24;Ex.1015,¶63. Also not relevant because R^{10} must be NH_2. See Ex.1001,28:col.33,l.30; Ex.1015,¶63.
8th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,28:col.33,l.41-col.34,l.6.	No, because "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" and this proviso is not in claim 1.

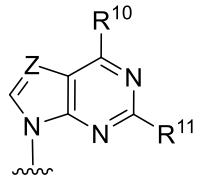
	See Ex.1001,28:col.33,l.57-58;Ex.1015,¶63. Also not relevant because R^{10} must be NH_2. *See* Ex.1001,28:col.33,l.62; Ex.1015,¶63.
9th aspect of the 3rd embodiment: a compound of Formula I-5 Ex.1001,28:col.34,l.7-33.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,28:col.34,l.19-20;Ex.1015,¶63. Also not relevant because R^{10} must be NH_2. *See* Ex.1001,28:col.34,l.24; Ex.1015,¶63.

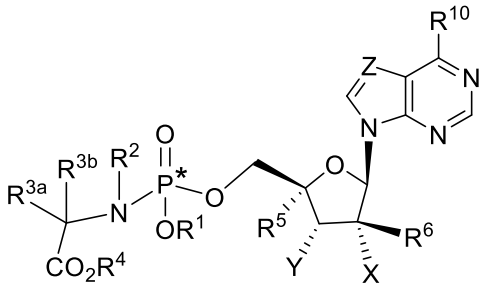
10th aspect of the 3rd embodiment: a compound of Formula I-6  (I-6) Ex.1001,28-29:col.34,l.34- col.36,l.8.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,29:col.35,l.32-39;Ex.1015,¶63.
11th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,29:col.36,l.9-47.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,29:col.36,l.29-31;Ex.1015,¶63.
12th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,29-30:col.36,l.48-col.37,l.13.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is

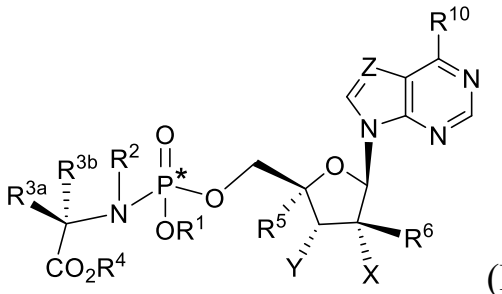
	CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,29:col.36,l.64-65;Ex.1015,¶63.
13th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,30:col.37,l.14-45.	No, because "R^5 is H, with the provisos that when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,30:col.37,l.29-30;Ex.1015,¶63.
14th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,30:col.37,l.46-col.38,l.10.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,20:col.37,l.61-62;Ex.1015,¶63.

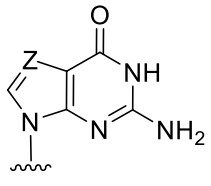
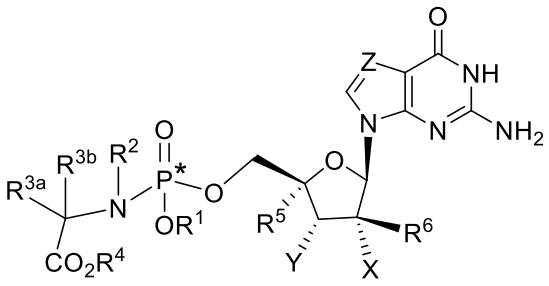
15th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,30-31:col.38,l.11-col.39,l.37.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F and B is a purine base, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,30:col.38,l.62-col.39,l.2;Ex.1015,¶63. Also, not relevant because R^{10} is NH_2. *See* Ex.1001,31:col.39,l.27; Ex.1015,¶63.
16th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,31:col.39,l.38 col.40,l.8.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1.

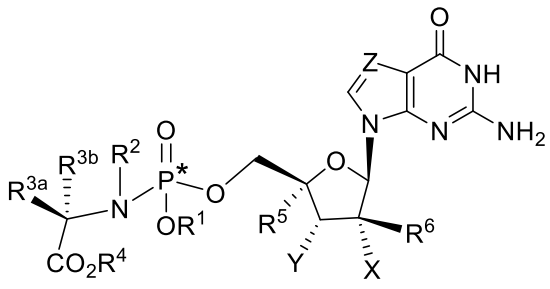
	See Ex.1001,31:col.39,l.58-60;Ex.1015,¶63.
17th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,31:col.40,l.9-41.	No, because R^5 is a list of substituents, with the proviso that "when X is OH, R^6 is CH_3 or CH_2F, R^5 cannot be H" and this proviso is not in claim 1. *See* Ex.1001,31:col.40,l.25-26;Ex.1015,¶63.
18th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,31-32:col.40,l.42-col. 41,l.6.	No, because "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" and this proviso is not in claim 1. *See* Ex.1001,31:col.40,l.58-59;Ex.1015,¶63.
19th aspect of the 3rd embodiment: a compound of Formula I-6 Ex.1001,32:col.41,l.7-39.	No, because "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" and this proviso is not in claim 1. *See* Ex.1001,32:col.41,l.23-24;Ex.1015,¶63. Also, not relevant because R^{10} is NH_2. *See* Ex.1001,32:col.41,l.28; Ex.1015,¶63.
4th embodiment: a compound of Formula I, in which the Base is of Formula (c)  (c) Ex.1001,32:col.41,l.40-44.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.

1st aspect of the 4th embodiment: a compound of formula I-7  (I-7) Ex.1001,32-33:col.41,l.45- col.43,l.37.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
2nd aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001,33:col.43,l.38-col.44,l.10.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
3rd aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001,33:col.44,l.11-43.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
4th aspect of the 4th embodiment: a compound of Formula I-7 Ex.1001,33-34:col.44,l.44-col.45,l.10.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
5th aspect of the 4th embodiment: a compound of Formula I-7	No, because the purine Base does not have a N^2-amino.

Ex.1001,24:col.45,l.11-40.	Ex.1015,¶63.
6th aspect of the 4th embodiment: a compound of Formula I-8  (I-8) Ex.1001,34-35:col.45,l.41-col.47,l.17.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
7th aspect of the 4th embodiment Ex.1001,35:col.47,l.18-57.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
8th aspect of the 4th embodiment Ex.1001,35:col.47,l.58- col.48,l.24.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
9th aspect of the 4th embodiment Ex.1001,35:col.48,l.25-58.	No, because the purine Base does not have a N^2-amino. Ex.1015,¶63.
10th aspect of the 4th embodiment Ex.1001,35-36:col.48,l.59-col.49,l.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.1001,36:col.49,l.26-30.	No, because the purine Base is a guanine. Ex.1015,¶63.
1st aspect of the 5th embodiment: a compound of Formula I-9  (I-9) Ex.1001,36:col.49,l.31-col.50,l.58.	No, because the purine Base is a guanine. Ex.1015,¶63.
2nd aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001,36-37:col.50,l.59-col.51,l.17.	No, because the purine Base is a guanine. Ex.1015,¶63.
3rd aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001,37:col.51,l.18-38.	No, because the purine Base is a guanine. Ex.1015,¶63.

4th aspect of the 5th embodiment: a compound of Formula I-9 Ex.1001,37:col.51,l.39-58.	No, because the purine Base is a guanine. Ex.1015,¶63.
5th aspect of the 5th embodiment a Compound of formula I-9 Ex.1001,37:col.51,l.59-col.52,l.11.	No, because the purine Base is a guanine. Ex.1015,¶63.
6th aspect of the 5th embodiment: a compound of Formula I-10  (I-10) Ex.1001,37:col.52,l.12-61.	No, because the purine Base is a guanine. Ex.1015,¶63.
7th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001,37-38:col.52,l.62-col.53,l.20.	No, because the purine Base is a guanine. Ex.1015,¶63.
8th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001,38:col.53,l.21-41.	No, because the purine Base is a guanine. Ex.1015,¶63.

9th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001,38:col.53,l.42-62.	No, because the purine Base is a guanine. Ex.1015,¶63.
10th aspect of the 5th embodiment: a compound of Formula I-10 Ex.1001,38:col.53,l.63-col.54,l.16.	No, because the purine Base is a guanine. Ex.1015,¶63.

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

Even if the written description defect in the proviso described above is ignored (which according to Prof. Klibanov it should not be (Ex1015,¶64)), claim 1 is still invalid because there is no written description support for the breadth of the claim (Ex1015,¶64-96). There is no literal support for claim 1 in the '361 description and the closest subgenus (the "fourteenth aspect of the third embodiment"[8]) does not provide sufficient support for claim 1 (*id*.).

The fourteenth aspect of the third embodiment includes over 10^{27} different possible combinations of variables from which PO selected just a single specific

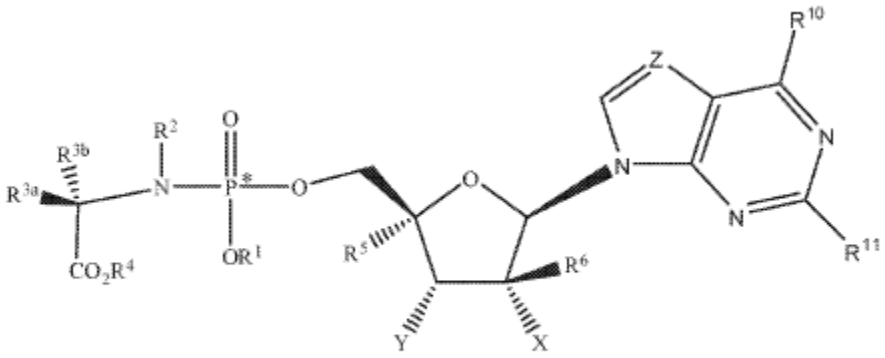
[8] Prof. Klibanov reviewed the '361 patent and determined that the "fourteenth aspect of the third embodiment" is the closest subgenus to issued claim 1 (Ex.1015,¶68).

combination (*id.*,¶65). PO's petition in IPR2017-01712 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).

Here, as Prof. Klibanov notes, the "forest," using 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 (Ex.1015,¶66). 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, then 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" (*Id.*;Ex.1001,30,321). Here PO selects a "tree" from an enormous "forest" that PO fails to describe (Ex.1015,¶66).

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

PO took the position during prosecution that claim 1 of the '361 patent is based on the genus of Formula I-6 (Ex.1002,87,91). 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 (Ex.1015,¶67)



I-6

Prof. Klibanov determined that 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 (*id*.,¶67).

PO may argue that the fourteenth aspect of the third embodiment of the '361 patent is 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, Prof. Klibanov found 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 hindsight (i.e., looking at the claim first and then finding the "closest" embodiment) (*id*.,¶68). However, even starting from the fourteenth aspect of the third embodiment, Dr. Klibanov determined that claim 1 is still very different from the subgenus disclosed in the patent specification (*id*.). 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)
R^4	hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}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*-propyl
R^{10}	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	NHR'

	that when R^{10} is OH and R^{11} is not NH_2; (incomplete clause)	
R^{11}	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 (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 [*sic*] 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_2F, then R^5 cannot be H	with the proviso that X cannot be OH when R^6 is CH_3 or CH_2F

Prof. Klibanov found no "blaze marks" in the '361 patent specification to direct a POSA to the specific variables which have been chosen for narrowed R groups R^4, R^{10}, R^{11}, and R', or for the new proviso recited in the granted claim (*id*.,¶69).

As summarized in Table 3 below, there are 20 possible substituent classes or elements (referred to as Markush Elements) for R^4, 15 Markush Elements for R^{10}, 15 Markush Elements for R^{11}, and 4 Markush Elements for R' (*id*.,¶70).

Table 3

	R^4	**R^{10}**	**R^{11}**	**R'**
Total Substituent Classes	**20**	**15**	**15**	**4**
Selected by PO	**4**	**1**	**1**	**1**

Prof. Klibanov found no "blaze marks" for the specific combination of Markush Elements which PO selected from narrowed substituents R^4, R^{10}, R^{11}, and R' (*id*.,¶71). Additionally, PO chose to modify only variables R^4, R^{10}, R^{11}, and R' but did not modify variables R^1, R^2, R^{3a}, R^{3b}, R^5, R^6, X, Y, Z, or R^{12} (*id*.). This represents just one combination of selections out of over 10^{27} possible combinations *id*.).

Of the 20 Markush Elements for R^4, PO chose four specific elements (*id*.,¶72). 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 (*id.*). For example, instead of selecting CH_3, 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 (*id.*).

Prof. Klibanov reviewed and accepted the following combinatorial analysis to quantify possible combinations of variables for the fourteenth aspect of the third embodiment of the '361 patent. The equation to determine the number of possible combinations is mathematically represented as:

number of possible combinations = n! / [(n-m)! x m!]

where n is the number of total elements in the set and m is the number of selections made from the set (*id*.,¶73).[9] A brief tutorial and illustrative examples of using combinatorial analysis is provided in Prof. Klibanov's declaration (*id*.,¶¶73-78).

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

[9] PO also used this equation in its IPR petition against U.S. Patent No. 8,815,830 (Ex.1025,¶56).

Table 4 (Ex.1015,¶79)

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
20	9	167960
20	8	125970
20	7	77520
20	6	38760
20	5	15504

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
20	4	4845
20	3	1140
20	2	190
20	1	20
TOTAL NUMBER OF POSSIBLE COMBINATIONS		**1,048,575**

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 (*id*.,¶80). R^{10} and R^{11} add a further 32,767 possible combinations of variables each (see Table 5 below).[10]

[10] 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).

Table 5 (Ex.1015,¶80)

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
15	5	3003
15	4	1365
15	3	455
15	2	105
15	1	15

Total Number of Markush Elements (n)	Selected Number of Markush Elements (m)	Number of Possible Combinations
TOTAL NUMBER OF POSSIBLE COMBINATIONS		**32,767**

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

Table 6 (Ex.1015,¶81)

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**

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 x 32,767 x 32,767 x 15 = 16,887,451,721,072,600 possible combinations) (*id*.,¶82). Prof. Klibanov notes that

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 (*Id*.). 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) (*Id*.)

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 x 32,767 x 32,767 x 15 x 16,383 x 127 x 63 x 63 x 63 x 15 x 3 = 395,362,464,081,506,000,000,000,000,000 possible combinations) (*id*.,¶83).

If each possible combination is represented as a tree, 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 (*id*.,¶84).

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 seven remaining variables), the number of possible combinations of R group substituents is still overwhelming (*id*.,¶85). 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 numbers of selections and other variables are ignored (4,845 x 15 x 15 x 4 = 4,360,500) (*id.*).

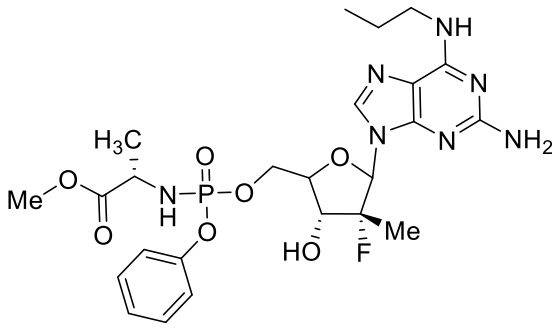
There is no disclosure in the '361 patent that provides any guidance for a POSA on how to select just one out of over 10^{27} possible combinations (*id*.,¶86). Nor is there any guidance for the individual selections of: (1) CH_3, ethyl, n-propyl, and *i*-propyl for R^4 out of 20 possibilities; (2) NHR' for R^{10} out of 15 possibilities; (3) NH_2 for R^{11} out of 15 possibilities; and (4) C_1-C_6 alkyl for R' out of 4 possibilities (*id.*).

Therefore, Prof. Klibanov concludes that "the disclosure of the '361 patent specification provides insufficient 'blaze marks' to point a POSA to the subgenus recited in claim 1" (*id*.,¶87).

(ii) <u>The '361 patent provides insufficient syntheses to create "blaze marks" to visualize the claim 1 subgenus</u>

The combinatorial analysis above calculates the number of different combinations (for example subgenuses) of variables that are covered by the

fourteenth aspect of the third embodiment from which PO selected one specific combination out of over 10^{27} possible combinations. It is also instructive to consider the number of compounds covered by the issued claim (over 15 billion). The ’361 patent only provides the synthesis for one of these over 15 billion compound that falls within the scope of claim 1, which chemical structure is:



'361 Compound 72

(Ex.1001,315:col.607).

In Prof. Klibanov’s opinion the synthesis of a single compound cannot create sufficient “blaze marks” for a POSA to visualize the entire huge subgenus of claim 1 (Ex.1015,¶88).

The number of compounds covered by a patent claim can be calculated by multiplying the number of different substituents that each R variable covers (*id*.,¶89). Prof. Klibanov provides a brief tutorial on calculating the number of compounds covered by a claim in his declaration (*id*.,¶¶90-91).

The number of compounds covered by the claim is calculated as follows:

Table 7 (Ex.1015,¶92)

Variable	Number of values	List of possible chemical moieties
R^1	6	H, CH_3, phenyl, *p*-bromophenyl, *p*-chlorophenyl, and *p*-fluorophenyl
R^2	1	H
R^{3a}	1	H
R^{3b}	10	H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, 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_2F, 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-OC_{1-6} alkyl (there are 48 isomers of C_1-C_6 alkyl), C-NH_2,

		C-NH-C_{1-6} alkyl, C-N(C_{1-6} alkyl)$_2$ (there are 48 x 48 – 48 = 2,256 isomers of (C_{1-6} alkyl)$_2$), NO_2, C_{1-6} alkyl, CO_2C_{1-6} alkyl, $CONH_2$, $CONHC_{1-6}$ alkyl, CON(C_{1-6} alkyl)$_2$, CH=$CHCO_2H$, and CH=$CHCO_2C_{1-6}$ 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 R^6 is -CH_3 or CH_2F. Excludes 6 (R^1) x 1 (R^2) x 1 (R^{3a}) x 10 (R^{3b}) x 4 (R^4) x 1 (R^5) x 2 (R^6 is CH_2F or CH_3) x 1 (X is OH) x 4 (Y) x 48 (R^{10}) x 4810 (R^{12}) x 2 (P*) compounds = 886,579,200 compounds
Total Number of Compounds	**15,071,846,400**	

As shown in Table 7 above, claim 1 of the ’361 patent covers 15,071,846,400 (i.e., over 15 billion) compounds.[11] The patent specification, on the other hand, only provides the synthesis of just one of them (Ex.1001,315:col.607,l.72;Ex.1015,¶93).

The single compound 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 (Ex.1015,¶94).

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.1023,31 (Quoted by the PTAB in its final written decision (Ex.1024,34-35)). Applying the very same logic to the case

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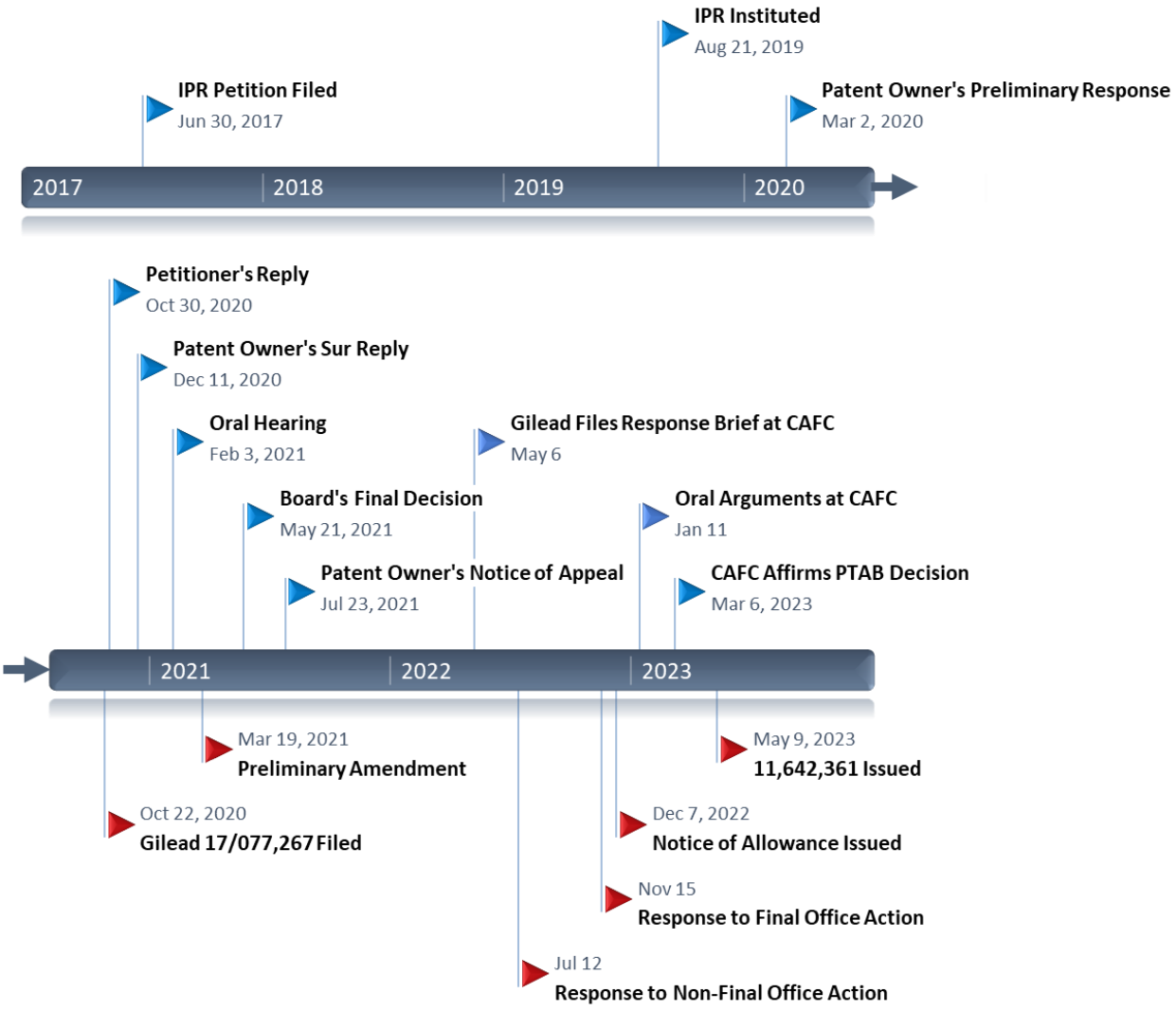
[11] Prof. Klibanov notes that “even if every R’ substituent is treated as having to be the same (i.e., excluding compounds with $N(R')_2$ substituents like N(Me)(Et) because the two alkyl groups are different), claim 1 of the ’361 patent would still cover a staggering 203,673,600 (i.e., over 200 million) 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” (Ex.1015,¶93).

at hand, the over 12,000 recited examples 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 (Ex.1015,¶94). The substituents taught by the recited examples in the patent are limited to teaching the specific combination of substituents that each example provides (Ex.1024,34-35). PO cannot point to specific examples to support its selections of R^4, R^{10}, R^{11}, and R’, while ignoring the remaining selections made, in order to arrive at the specific example (Ex.1015,¶95).

Notably, PO repeatedly made and supported the above arguments while actively prosecuting the ’361 patent, thus trying to have it both ways, as seen in the timeline below (Exs.1022,46, 1023,31, and 1024,34-35).



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

The '361 patent has 524 columns of tables of compounds that purportedly fall under the '361 Supergenus (Ex.1001,39-301). There are 31 subgenus 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 (Ex.1015,¶97).

The only purine nucleotide phosphoramidates in the enormous list of species are N^2-aminopurine (i.e., ***not*** N^2,N^6-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 N^6-alkyl,N^2-aminopurines (*id*.,17;Ex.1015,¶98).

Table 8

Table Nos.	**Columns (Ex.1001)**	**General Structure**	**Covers '361 Patent Claim 1?**
II 1-50	Cols. 54-77	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
III 1-50	Cols. 77-99	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
IV 1-50	Cols. 99-121	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
V 1-50	Cols. 121-143	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)

VI 1-50	Cols. 143-159	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
VII 1-50	Cols. 159-183	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
VIII 1-50	Cols. 183-205	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
IX 1-50	Cols. 205-225	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
X 1-50	Cols. 225-241	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XI 1-50	Cols. 241-257	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XII 1-50	Cols. 257-275	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XIII 1-50	Cols. 275-294	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XIV 1-50	Cols. 295-313	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)

XV 1-50	Cols. 313-333	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XVI 1-50	Cols. 333-351	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XVII 1-50	Cols. 351-369	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XVIII 1-50	Cols. 369-392	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XIX 1-50	Cols. 393-415	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XX 1-50	Cols. 415-437	Pyrimidine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXI 1-50	Cols. 437-451	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXII 1-50	Cols. 451-461	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXIII 1-50	Cols. 461-473	N^2-Aminopurine	No (Ex.1015,¶98)

		nucleotide phosphoramidate	
XXIV 1-50	Cols. 473-485	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXV 1-50	Cols. 485-498	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXVI 1-50	Cols. 498-509	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXVII 1-50	Cols. 509-521	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXVIII 1-50	Cols. 521-532	N^2-Aminopurine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXIX 1-50	Cols. 532-546	Guanine nucleotide phosphoramidate	No (Ex.1015,¶98)

XXX 1-50	Cols. 546-556	Guanine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXXI 1-50	Cols. 556-567	Guanine nucleotide phosphoramidate	No (Ex.1015,¶98)
XXXII 1-50	Cols. 567-579	Guanine nucleotide phosphoramidate	No (Ex.1015,¶98)

Based on the foregoing, there are multiple flashing red signs in the '361 patent that would convincingly point a POSA away from the claim 1 subgenus (Ex.1015,¶99).

(i) With regard to the aspects and embodiments, the 42 columns of genuses and subgenuses of the '361 Supergenus discussed above misdirect the POSA with the following:

(a) The R^5 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 (*id*.).

(b) When the purine structure (c) subgenuses are narrowed at R^{10} and R^{11}, in the forty-two columns of genuses and subgenuses, PO narrows them to $R^{10} = NH_2$ (instead of NHR'). In fact, nine of the nineteen

subgenuses of I-5 and I-6 (i.e., almost half) narrow to $R^{10} = NH_2$ (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 (*id*.).

(c) There are ***no*** purine structure (c) subgenuses in the embodiments and aspects in the 42 columns that narrow to R^{10} is 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 (*id*.).

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

(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 (*id*.).

Based on the foregoing alone, Prof. Klibanov concludes 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 (*id*.).

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 provides sufficient blaze marks to describe the metes and bounds of claim 1 (*id*.).

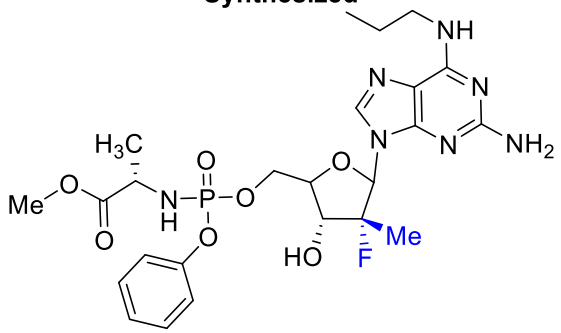
E. Synthesis

The '361 patent fails to disclose how to make the full scope of breadth of nucleotides within the claim 1 phosphoramidates (*id*.,¶102). In fact, only a single compound of the claimed subgenus was made (*id*.). 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, that fact that only one compound was made is strongly insufficient to lead a POSA in that direction (*id*.).

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. In contrast, the 2'-R^6 ("up") and 2'-X ("down") positions in the nucleotide of claim 1 have thirty-four

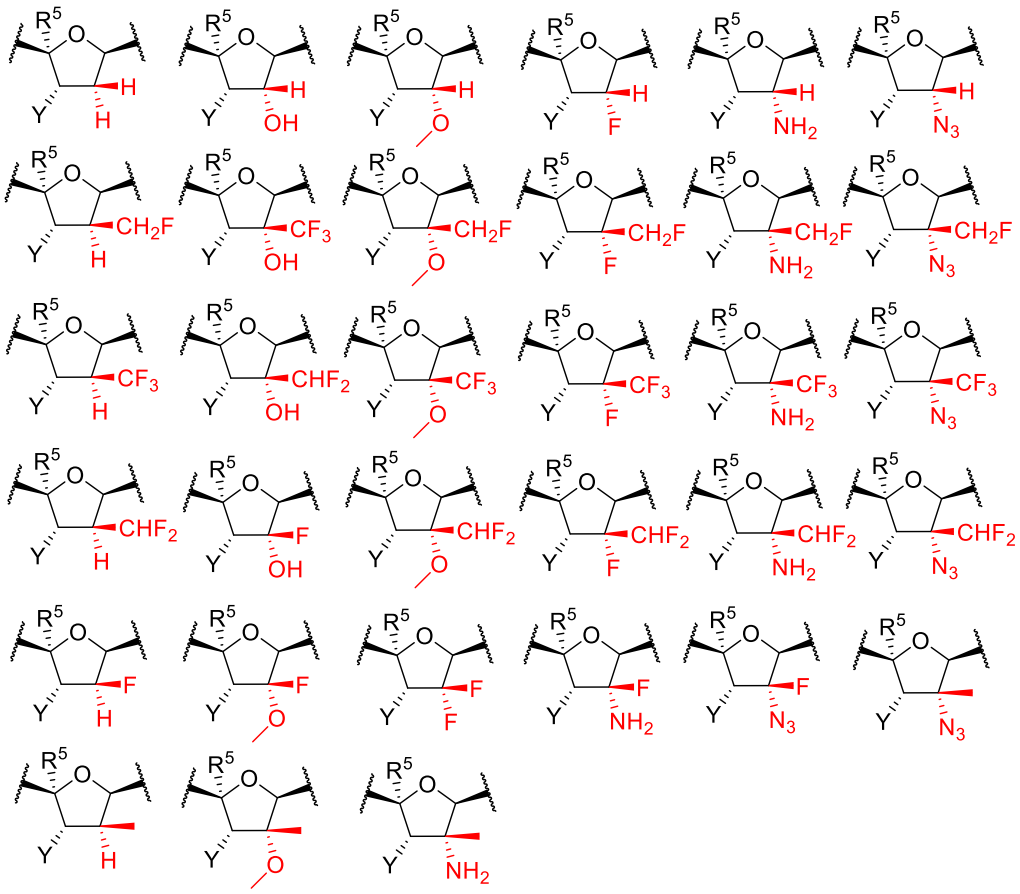
possibilities, and none of them other than 2'-methyl-up, 2'-fluoro-down was actually made in the '361 patent (*id.*,¶103).

Synthesized

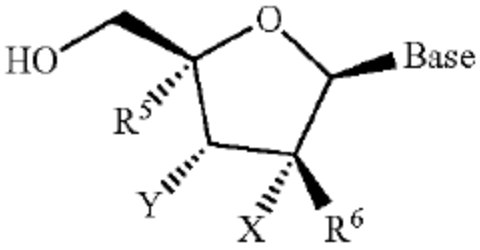


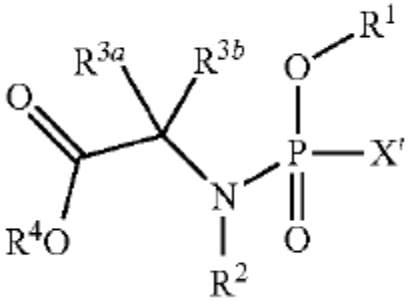
'361 Compound 72

Claimed but not synthesized in the '361 Patent



The sole example of 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.1001,303-316). It provides an Example 3 “General Procedures for Nucleoside Phosphoramidate Derivatives” (*id*.,305:col.588,l.35-67) that simply instructs a POSA to react a preformed substituted nucleoside with an appropriate phosphorochloridate to get the nucleotide phosphoramidate (Ex.1015,¶104).





In col. 586, lines 21-25, the ’361 patent specification teaches that (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 2007/019463, each of which is incorporated by reference in its entirety" (Ex.1001,304). 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 (Ex.1015,¶105).

(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 (Ex.1043:Section VIII (¶¶293-333)) (Ex.1015,¶105).

(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 0011). 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 (Ex.1015,¶105).

(3) U.S. Published Application No. 2006/0122146 provides processes to prepare nucleosides wherein R^6 is alkyl and X is F (as with the '783 application) (Ex.1045). In paras. 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.1015,¶105).

(4) U.S. Publication Application No. 2007/019463 is limited to teaching how to make 3',5'-prodrugs of nucleosides wherein R^6 is CH_3 and X is F (Ex.1046:see Examples 1-4,pp.12-14) (Ex.1015,¶105).

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 not sufficient to teach a POSA how to make compounds across the full claimed scope of compounds with varied 2'-substituents, or even to point them in that direction (Ex.1015,¶106-107; see specifically Table 9).

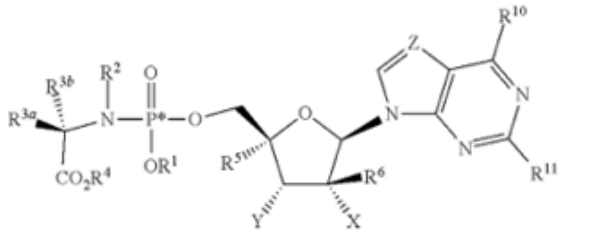
F. Inconsistent Statements By PO Regarding Synthesis At The EPO Opposition Division And Technical Boards Of Appeal

During time periods overlapping with PO's U.S. prosecution of the '361 patent, PO was concurrently opposing the grant of EP 2955190 (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.1030,1031), as it would be difficult or impossible to make them (Ex.1015,¶108).

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

A compound of formula I-6:

I-6



wherein:

(a) R^1 is H, —CH_3, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;

(b) R^2 is H;

(c) R^{3a} is H and R^{3b} is H, —CH_3, —$CH(CH_3)_2$, —$CH_2CH(CH_3)_2$, —$CH(CH_3)CH_2CH_3$, —CH_2Ph or lower cycloalkyl;

(d) R^4 is CH_3, ethyl, n-propyl, or i-propyl;

(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;

(j) Z is N or —CR^{12};

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

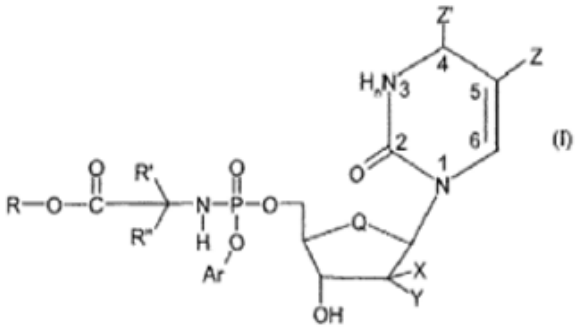
(k) R′ is $C_{1\text{-}6}$ alkyl; and

(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:



(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 -CH_2-;

X is independently selected from the group H, F, Cl, Br, I, OH and methyl (-CH_3);

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 -NH_2 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 the '361 patent claim 1 structure has a purine, the sugar moiety and the phosphoramidate components of the two structures overlap and bear a marked chemical resemblance (Ex.1015,¶108).

Prof. Klibanov has 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 in the scope of X and R^6 of the '361 patent claim 1 (Ex.1015,¶109). PO's litigation submissions to the Opposition Division and the Technical Boards of Appeal of the EPO are, based on Prof. Klibanov's analysis of the chemistry, 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 none of the EPO documents (Exs.1030-1042) submitted by PO were provided or described to the USPTO during prosecution of the '361 patent (Ex.1002).

Prof. Klibanov agrees that certain "compounds within issued claim 1 of the '361 patent cannot be made without at least significant difficulty" based on PO's own positions on non-enablement which he agrees with (Ex.1015,¶110).

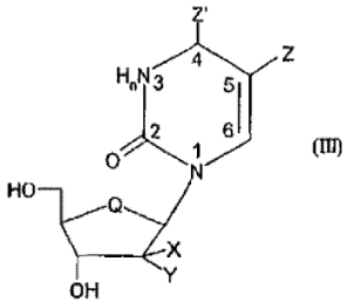
In the following paragraphs, some of the key arguments Gilead (PO) and its experts made to the EPO concerning the difficulty of making nucleosides having certain substitution patterns at the 2'-position are summarized. Specifically, PO's attack on EP'190 included an argument that its claims covered nucleotides with various 2'-substituents, such as 2'-F/OH, but included no specific synthetic routes

to these substitution patterns and, moreover, that these compounds, even if somehow made, would be unstable (Ex.1032,¶134).

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

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. Micklefield to support its positions (Ex.1032).

Specifically, Prof. Micklefield's expert report supporting PO on nucleotide phosphoramidate synthesis in a parallel U.K. proceeding ([2023] EWHC 611 (Pat)) concerning EP'190 was submitted to the EPO Technical Boards of Appeal (Ex.1032). As can be taken from its ¶1 (*id.*), Prof. Micklefield has over 30 years of research experience in bioorganic chemistry, including the design and synthesis of nucleoside and nucleotide analogs.



(III)

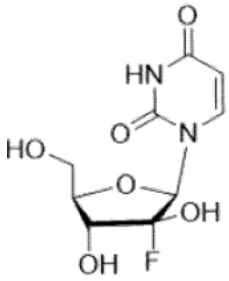
Concerning the 2' position, formula III was defined in EP'190 as "*X is independently selected from the group H, F, Cl, Br, I, OH, and methyl (CH_3); and Y is F*" (Ex.1029,66). Before commenting on any other substitution patterns, Prof.

Micklefield asserted at ¶134 (Ex.1032, emphases added) that the synthesis of nucleosides having a 2'-F/OH substitution pattern would not be feasible:

> 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***.

Ex.1015,¶114.

This view is reinforced at his ¶141 (Ex.1032, emphasis added), where Prof. Micklefield stated that "***it would be apparent that 1d is not feasible to synthesise and isolate.***"



(1d)

Ex.1015,¶115.

Prof. Micklefield returns to this point at ¶¶168 and 169 of his expert report and cites to the Seppelt (Ex.1033), Willis (Ex.1034) and Cheburkov (Ex.1035) 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 a-fluoroalcohols could be prepared it [*sic*] ***would undergo facile elimination of HF and would therefore be too unstable for the pharmaceutical applications in mind***.

Ex.1015,¶116.

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,¶¶141,168,169; Ex.1015,¶117). These comments were not limited to pyrimidine phosphoramidates and instead extended to any compound with "an alcohol and a fluorine attached to the same carbon" (Ex.1015,¶117). The fundamental chemical mechanism underlying this view is that the oxygen can form a double bond with the C2'

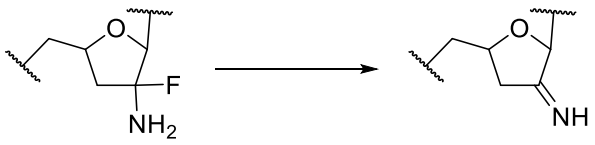
position's carbon, eliminating fluoride and losing a proton in the process, to form HF and a carbonyl group (*id*.).

Compounds of claim 1 wherein X is OH and R^6 is F would thus likely be unstable and eliminate HF (*id*.,¶118). Prof. Klibanov is not aware of any stable drug-like compounds which have an alcohol and a fluorine attached to the same carbon (*id*.).

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) <u>Applying PO's arguments to 2'-F/NH_2 nucleosides</u>

Prof. Klibanov is not aware that PO expressly commented on the 2'-F-2'-NH_2 nucleoside substitution pattern (Ex.1015,¶120).[12] However, the same fundamental chemical reasoning applies, as seen below (*id*.). 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 (*id*.).



[12] The claims of EP'190 did not include 2'F-2'-NH_2 nucleosides.

Compounds of claim 1 of the '361 patent wherein X is NH_2 and R^6 is F, following PO's logic, would likely be unstable and eliminate HF (*id*.,¶121). Additionally, Prof. Klibanov is not aware of any stable drug-like compounds which have an amino and a fluorine attached to the same carbon atom (*id*.).

(iii) <u>Applying PO's arguments to other 2'-position substituents</u>

Claim 1 includes thirty-four different combinations of 2' position substituents of which the synthesis of only one combination is provided (*id*.,¶122). According to PO, its experts, and Prof. Klibanov synthesizing claimed compounds across this entire scope of 2' position substituents would require a substantial research project (*id*.).

Prof. Micklefield emphasized at ¶180 of his expert report that a POSA faced "a research project" within a "new territory" to make nucleosides having new substitution patterns at the 2'-position in nucleosides (Ex.1032, 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.

Ex.1015,¶123.

PO also engaged Prof. Boons as an expert witness concerning EP'190 (Exs.1036,1037). 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, emphases added) highlights the difficulties associated with base coupling to a novel substrate:

> 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***.

Ex.1015,¶124.

PO's Grounds of Appeal (Ex.1038) filed with the EPO concerning EP'190 emphasizes at ¶6.144 (emphasis 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.*

Ex.1015,¶125.

Despite making these statements in Europe detailing the difficulty in preparing 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 in the purine nucleotide prodrug (*id*.,¶126).

(iv) Fluorination chemistry is particularly complicated

According to Prof. Klibanov's technical review, PO took a position at the EPO that was directly inconsistent with the patentability 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 (*id*.,¶127). 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 (*id*.) Prof. Micklefield 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) <u>Delivering a tetra-substituted stereocenter at the 2'-position is challenging</u>

Prof. Micklefield also pointed to "significant challenge[s]" to fluorination of tertiary alkyl groups in ¶139 of his expert report (Ex.1032):

> 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.

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

At ¶184, Prof. Micklefield emphasized the difficulty of obtaining the correct stereochemistry in nucleoside syntheses, which generally introduce stereocenters at several positions (Ex.1032, 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***.

(vii) <u>Nucleoside syntheses would be expected to be challenging and take a long time</u>

Even conducting literature searches on nucleoside synthesis is a lengthy process according to PO. Prof. Micklefield made this point at ¶158 of his expert report (Ex.1032, emphasis added):

> Conducting a comprehensive literature review in relation to any of [2'-F-nucleoside] compounds 1a-1e[13] ***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.

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[13] Compound 1d is the unstable 2'-F/OH nucleoside. Compound 1e is the 2'-F/CH_3 nucleoside. Compounds 1a, 1b, and 1c include 2' substitutions which are not covered by claim 1.

As for the actual synthesis, according to Prof. Micklefield, this realistically would be much longer, perhaps years, as noted at ¶186 (Ex.1032, emphasis added):

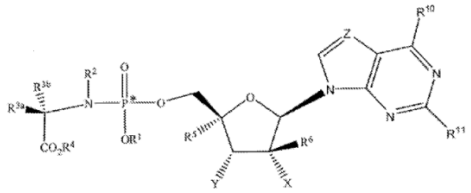
> It is my initial view that if they [i.e., POSAs] were really fortunate (by which I mean they selected a research route that works first time and their syntheses worked as planned), they might be able to make compounds 1a-1c, or 1e in about six months per compound, but the Skilled Chemist ***would need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

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 CH_2F, CHF_2, and CF_3 with the X groups of claim 1 of the '361 patent (Ex.1015,¶134). According to Prof. Klibanov, the POSA would need to do a literature search on at least the thirty-three 2' substitution patterns that PO did not provide the synthesis for (*id*.).

Table 10 (*id*.,¶135) below provides a timeline of positions taken by PO during prosecution of the '361 patent at the USPTO and PO's inconsistent (and 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) 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 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,¶¶134,169. • 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. • 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,¶¶158,186.
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.	

PO's litigation statements, as well as statements by experts presented on its behalf, regarding the state of the art in synthesis of nucleotides are admissible. *Valve Corp. v. Ironburg Inventions Ltd.*, 8 F.4th 1364, 1370 n.6 (Fed. Cir. 2021) ("Generally, the Federal Rules of Evidence apply to IPR proceedings before the Board"); Fed. R. Evid. 801(d)(2) ("Statements that are not hearsay … The statement is offered against an opposing party and … was made by the party in an individual

or representative capacity"). As extensively detailed herein, PO has a long record of statements describing great challenges in deriving useful, active derivatized nucleosides, and thus their prodrugs, at the time of the filing date of the '361 patent. In the opinion of Prof. Klibanov, PO's directly contradicted itself with inconsistent technical statements to the U.S. and European Patent Offices (Ex.1015,¶136).

G. Inconsistent Statements By PO Regarding Anti-HCV Activity of '361 Patent Claim 1 Compounds

Just a handful of N^6-derivatized N^2-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 (compound 72) (Ex.1001,315;Ex.1015,¶137). In addition, no more than 19 compounds out of the entire '361 Supergenus were subjected to biological characterization *in vitro* (Ex.1001,316-320:cols.610-617), only two of which are N^6-derivatized N^2-aminopurine phosphoramidates (Compounds 69 and 70), and ***none*** of which falls within claim 1 of the '361 patent (Ex.1015,¶137). One of the characterized diaminopurine nucleotide prodrugs is a N^6-cyclopentyl derivative and the other is a N^6-azetidine derivative (Compound 69 and Compound 70, respectively), 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).

In Prof. Klibanov's opinion, a POSA would find the '361 patent specification to be a poor, if not impossible, document to use to arrive at the subgenus of claim 1 not only for the reasons explained above, but also because ***no*** biological data whatsoever was provided for any species within claim 1, even though PO took the opportunity to test a range of other compounds (Ex.1015,¶138).

If a POSA somehow overlooked the '361 patent's strong emphasis on the pyrimidine nucleotides and even without any "blaze marks" somehow decided to make a N^6,N^2-diaminopurine nucleotide prodrug instead, then (s)he would have just two structures with *in vitro* biological data to use as a starting point (the N^6-cyclopentyl and N^6-azetidine derivatives (Compounds 69 and 70, respectively)), both of which were intentionally eliminated from claim 1 (Ex.1002,269-272). In Prof. Klibanov's opinion, selecting any other N^6,N^2-diaminopurine compound would be illogical (Ex.1015,¶139). There is no rational reason to select compounds with missing biological data over two compounds with reported activity data (*id*.). And even the two N^6,N^2-diaminopurine compounds described in the '361 patent had no toxicity data (*id*.,).

Prof. Klibanov also reviewed referenced litigation documents that include arguments from PO on the unpredictability of biological activity of nucleotides with

novel substitution patterns (*id*.,¶140). He concluded 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 (*id*.). PO failed to provide these real-time inconsistent statements to the USPTO during prosecution of the '361 patent.

Some of the key statements Gilead (PO) and its experts made in Europe concern the unpredictability of the biological activity of nucleotides with new substitution patterns. Again, to place these in 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;Ex.1001). PO objected based on the fact that this biological activity was not shown across the full scope of the claims, i.e., for claimed substitution patterns other than the three for which such data were reported (Ex.1038,4,82).[14]

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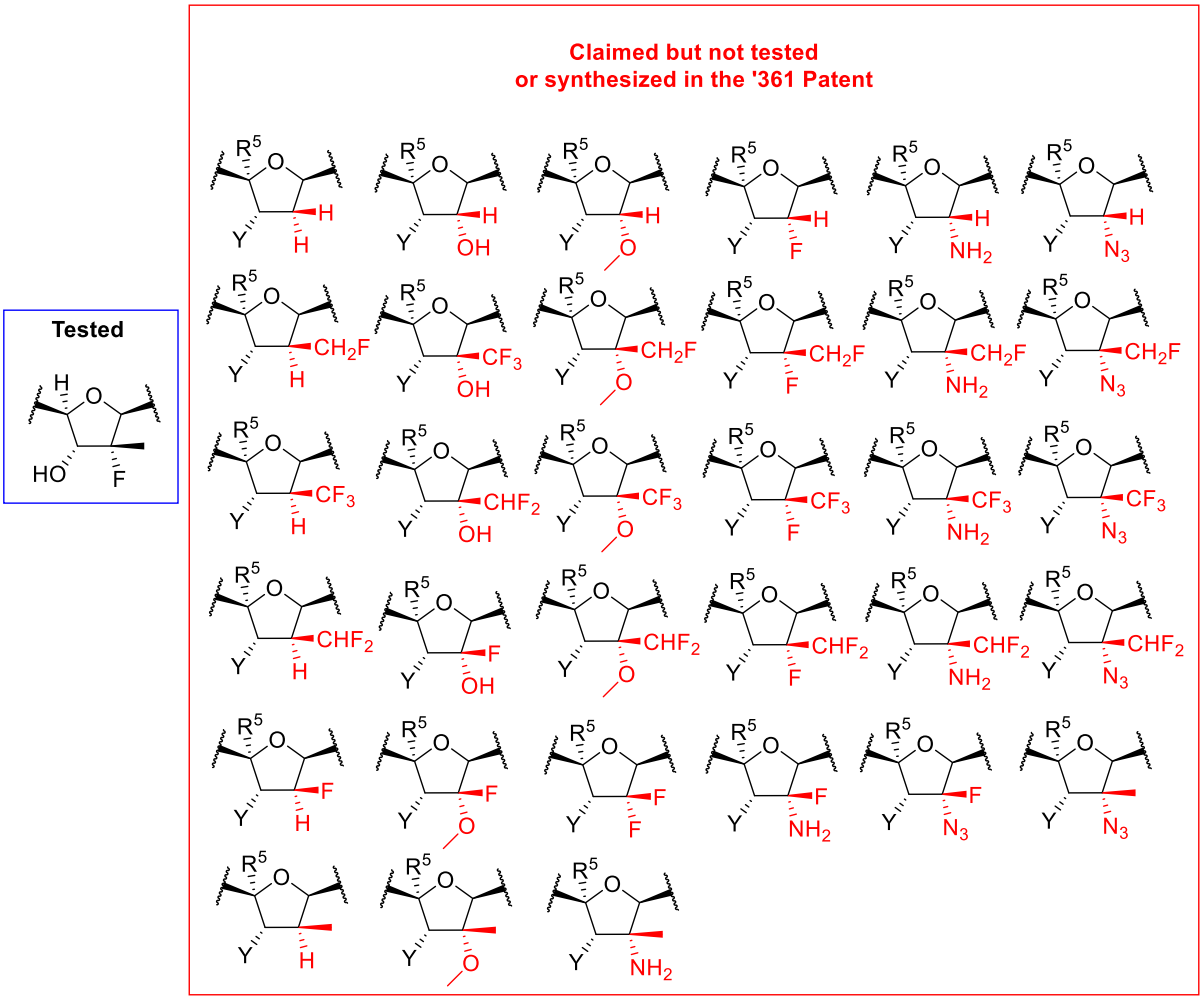
[14] While EP'190 was primarily directed to anti-cancer nucleotides and the '361 patent is directed to anti-viral nucleotides, the breadth of PO's comments regarding the lack of predictability of biological activity stretch across both (Ex.1015,¶142). Further, PO presented an expert (Prof. Götte) to directly bridge its comments to apply to both anti-cancer nucleotides and anti-viral nucleotides (Exs.1040,1041).

In Prof. Klibanov's view, PO's own statements below make clear that, in the view of PO and its experts, the lack of biological activity data in the '361 patent for specific substitution patterns cannot result in a conclusion that useful activity will be achieved across the full scope of claim 1 in the '361 patent (Ex.1015,¶144).

Graphically, the data provided by PO can be compared to the scope claimed in the '361 patent as follows (*id.*):



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[15] 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'-CH_3-up, 2'-F-down); and (ii) two N^6(H),(CH_3),N^2-diaminopurines, one with 2'-F-up, 2'-F-down and the other with 2'-CF_3-up, 2'-F-down. Petitioner also tested N^6(H),(CH_3), N^2 diaminopurine with 2'-F-down and 2'-H-up which showed no activity even at >100 μM. In addition,

According to Prof. Klibanov, 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 have no significant impact on the biological activity:

1) changing 2'-up (Me) to 2'-up (H, CH_2F, CHF_2, CF_3, or F); and at the same time

2) changing 2'-down (F) to 2'-down (H, OH, OCH_3, NH_2, or N_3) (*id*.,¶145).

PO took the position in its European litigation submissions on EP'190 that this ***assumption*** is incorrect (Ex.1038;Ex.1039;Ex.1015,¶145).

For example, at ¶7.52 of its Grounds of Appeal submitted to the EPO (Ex.1038) PO stated (and Prof. Klibanov agrees (Ex.1015,¶146):

> 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…

Petitioner also tested an $N^6(CH_3)_2$,N^2aminopurine with 2'-F-down and 2'-H-up which showed no activity even at >100 μM. Petitioner is not aware of any combination of substituents with a 2'-hydrogen in the up position active against HCV, nor 2'-hydrogen in the down position active against HCV.

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 the structural features and activity” for the claimed 2’-up (H, CH_2F, CHF_2, CF_3, or F) and 2’-down (H, OH, OCH_3, NH_2, or N_3) compounds (Ex.1015,¶147). According to PO’s own reasoning, therefore, these substitutions are “expected to disturb the pharmacological activity profile” of the tested unclaimed compounds (*id*.).

Specifically with respect to antiviral activity, PO relied on Prof. Matthias Götte as its expert witness in U.K. High Court proceedings (Ex.1040;Ex.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:¶5). 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***.

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

> 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***.

Prof. Götte also illustrated this point using the Perkins reference (Ex.1042) 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 differentiates between DNA viruses or retroviruses and RNA viruses, respectively, as potential targets.

Ex.1015,¶150.

It is highly doubtful that HCV antiviral activity will be achieved in the claimed compounds of the '361 patent, in which X is H (*id*.,¶151).

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 for the activity of claimed compounds with 2'-up (Me). According to Prof. Klibanov, it logically follows 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 (Ex.1015,¶153).

As detailed above, PO's statements regarding the general difficulty in synthesizing and predicting the activity of new nucleoside moieties are directly inconsistent with their presentation of claim 1 which includes thirty-four different 2' substituents combinations for which the synthesis of only one combination is provided. Claim 1 includes at least one 2' substituent combination that PO adamantly states is unstable (F,OH) and covers billions of compounds while only providing the synthesis for one compound covered by the claim.[16]

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

Petitioner's U.S. 2016/0257706 publication ("'706 U.S. Publication," Ex.1020, published on September 8, 2016) describes the synthesis and anti-HCV

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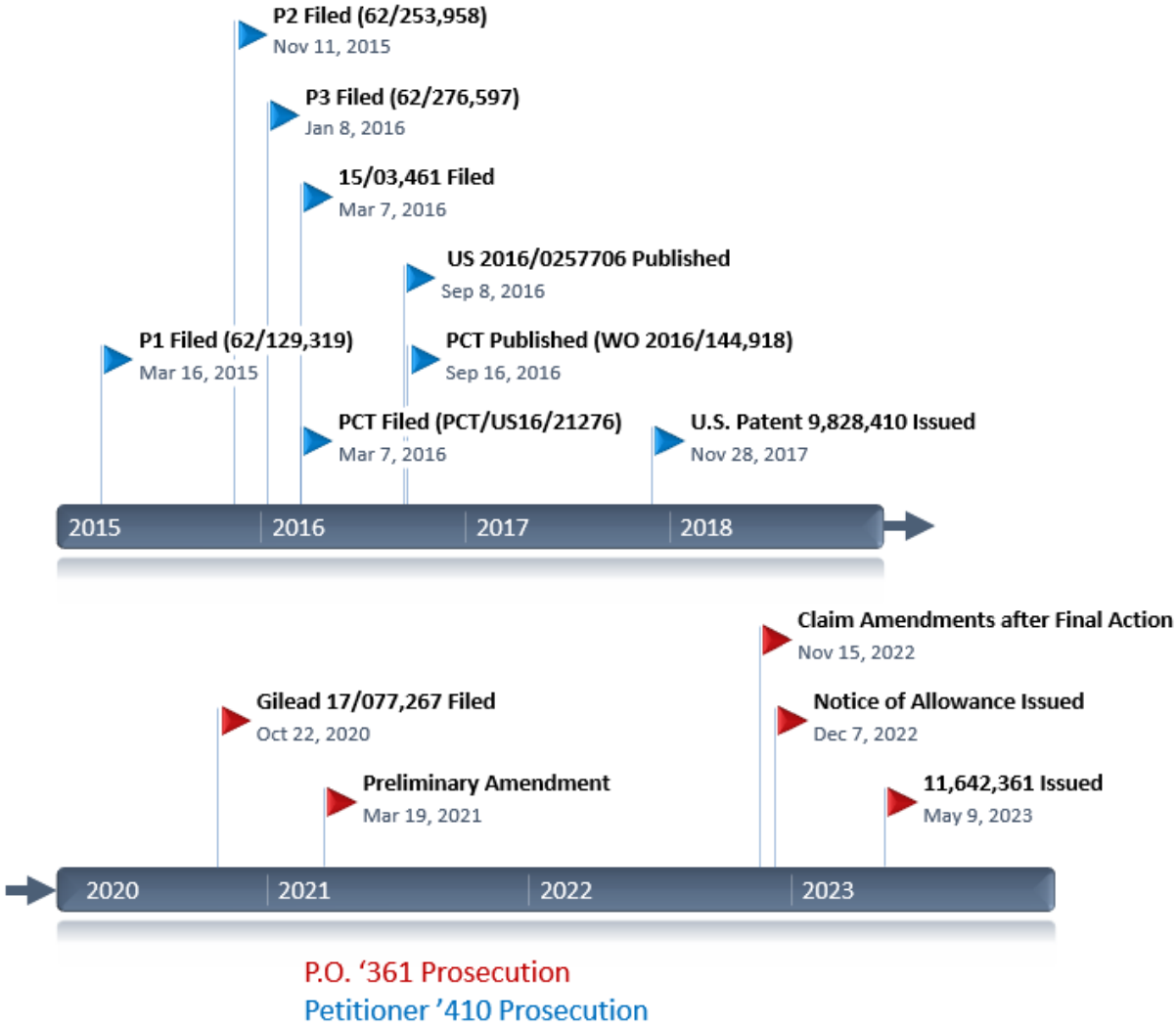
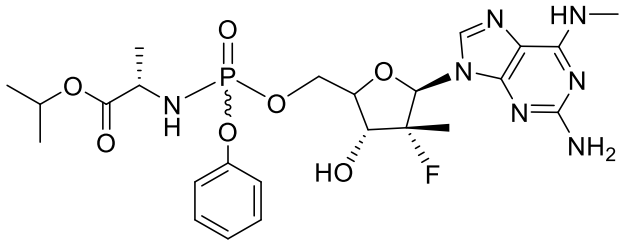
[16] Lead counsel Knowles represents NuCana plc and was involved in the EPO and U.K. litigation matters described in Exs.1030-1035,1037-1041. Both the European and U.K. litigations were decided in favor of Gilead, and they were not appealed.

activity of a compound and its specific stereoisomers that anticipate the subgenus of claim 1 of the ’361 patent (Ex.1015,¶154). As shown in the timeline below the ’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 the ’706 U.S. Publication and thus the publication anticipates claim 1 (*id*.).



Compound 5 is synthesized in Example 1 of the ’706 U.S. Publication (Ex.1020,84).



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 (Ex.1015,¶156).

The ’706 U.S. Publication was not cited by PO to the USPTO during prosecution of the ’361 patent, nor were any of its family members (Ex.1001;Ex.1002).

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.1020,84-85:¶¶[0459]-[0466]). Example 1 provides detailed experimental procedures to synthesize Compound 5 (Ex.1015,¶158). Example 1 also includes the appropriate physicochemical characterization data so that a POSA can ensure that the correct compound was made (*id*.). The characterization techniques used and described include ^{1}H nuclear magnetic resonance (NMR), ^{19}F NMR, ^{31}P NMR, and mass spectrometry (*id*.). The details provided in the ’706 U.S. Publication fully support the synthesis of Compound 5 (*id*.).

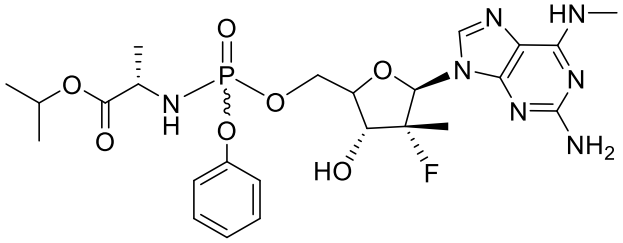
In addition to providing detailed synthetic procedures teaching how to make Compound 5 which anticipates the subgenus of claim 1 of the ’361 patent, the ’706 U.S. Publication also provides biological assays and data for the compound which confirms its’ biological activity (Ex.1015,¶159). In Examples 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.1020,116-127:¶¶[0606]-[0637]).

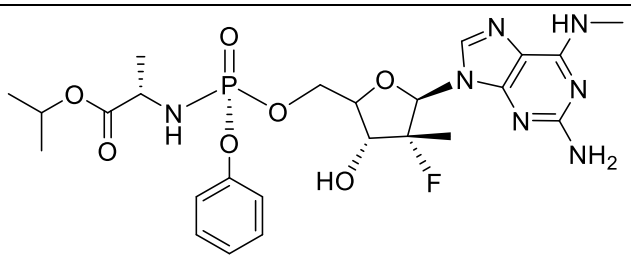
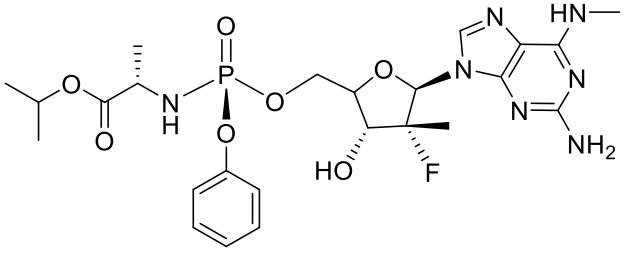
These numerous tests include antiviral activities against six different HCV genotypes, two mutant strains of HCV genotype 1a, one mutant strain of HCV

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*.).

The replicon assay (data shown in Table 7, *id*.,120-127:¶[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 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] (*id*.,116-117) 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

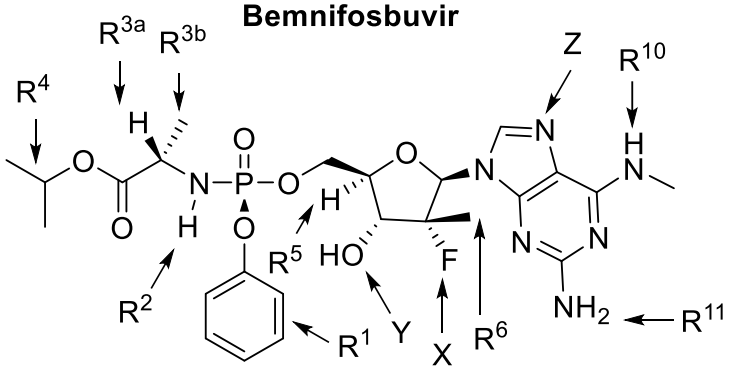
5-1		0.0551	0.282	>100
5-2		0.004	0.028	>100

Stereoisomer 5-2 (which as the hemisulfate salt is referred to as bemnifosbuvir) is now in advanced human clinical trials sponsored by Petitioner for the treatment of both HCV and COVID19.

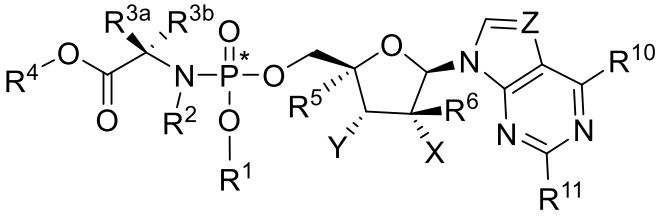
Because, as explained above, claim 1 of the ’361 patent is not entitled to any priority date earlier than November 15, 2022, the claim is invalid as anticipated over the intervening ’706 U.S. Publication (Ex.1020, published on September 8, 2016, and issued as U.S. Patent No. 9,828,410 (Ex.1021)), which 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)). 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 (Ex.1015,¶163):

Bemnifosbuvir



Claim 1



IX. SUMMARY OF CONCLUSIONS

For the reasons explained in detail above, Petitioner urges the Board to institute a Post Grant Review of claim 1 of the '361 patent on the basis that it is more likely than not that (i) claim 1 is invalid for violation of the written description and enablement requirements and (ii) claim 1 is anticipated by Petitioner's earlier '706 U.S. Publication because the '361 claim 1 is entitled to no priority dates before the publication of the '706 U.S. Publication on September 8, 2016.

Respectfully submitted,

Date: August 7, 2023

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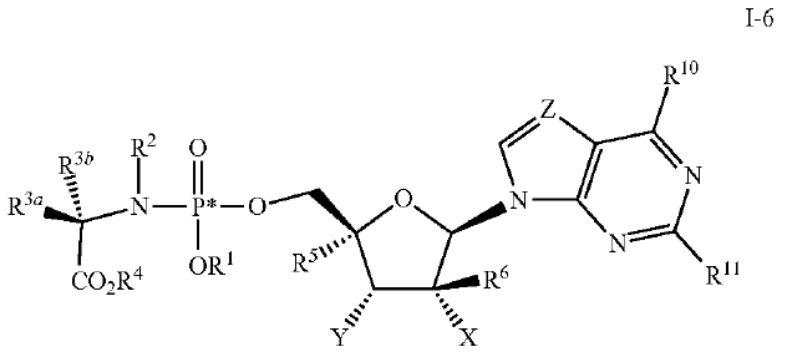
X. APPENDIX: CLAIMS OF THE ’361 PATENT

The claims of the ’361 patent are provided below.

1. A compound of formula I-6:



I-6

wherein:

(a) R^1 is H, -CH_3, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;

(b) R^2 is H;

(c) R^{3a} is H and R^{3b} is H, -CH_3, -$CH(CH_3)_2$, -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -CH_2Ph or lower cycloalkyl;

(d) R^4 is CH_3, ethyl, n-propyl, or i-propyl;

(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;

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

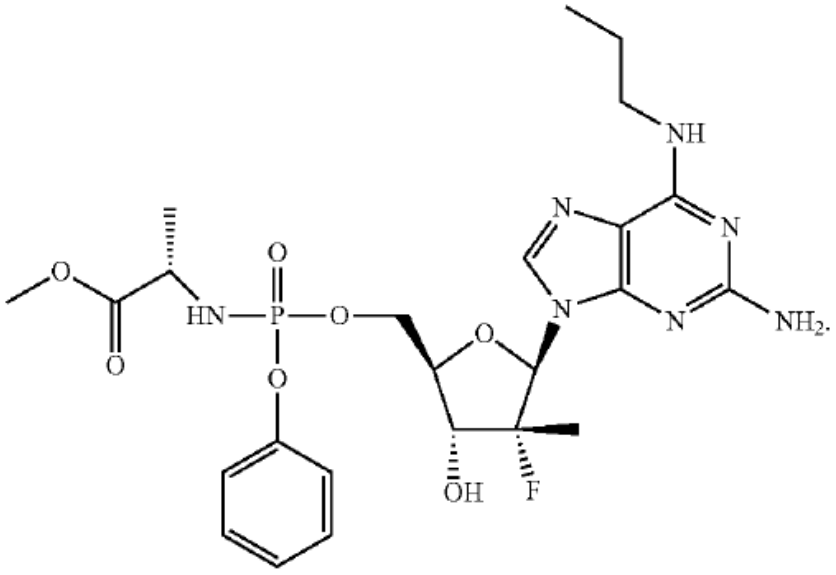
wherein R^{12} is H, halogen, -OR', $-NH_2$, -NHR', $-NR'_2$, $-NO_2$, C_{1-6} alkyl, $-CO_2R'$, $-CONH_2$, -CONHR', $-CONR'_2$, $-CH=CHCO_2H$ or $-CH=CHCO_2R'$;

(k) R' is C_{1-6} alkyl; and

(l) P* is a chiral phosphorus atom;

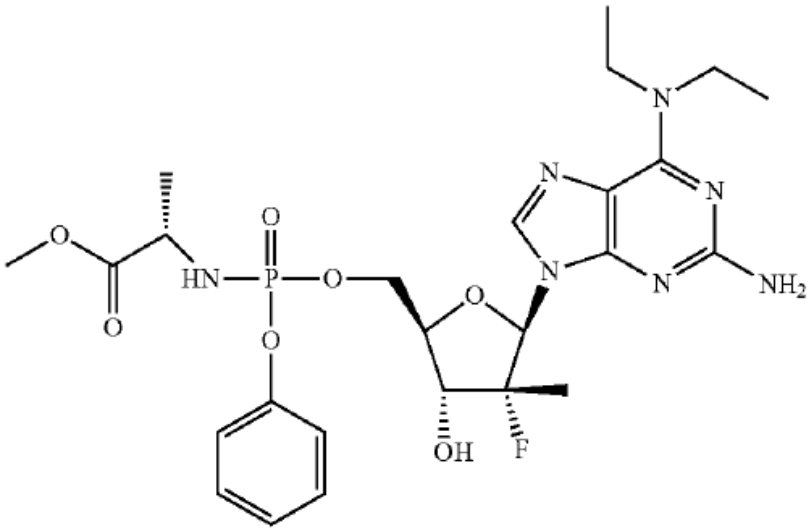
or a pharmaceutically acceptable salt thereof.

2. The compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula:



.

3. A compound which is:



or a pharmaceutically acceptable salt thereof.

XI. CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION OF 37 C.F.R. §42.24

Pursuant to Rule 37 C.F.R. §42.24(d), the undersigned certifies that, based on the word count of the word-processing system used to prepare this paper, the number of words in this Petition is 18,285. This word count does not include the items that may be excluded from the count under 37 C.F.R. §42.24(a), including the table of contents, table of authorities, mandatory notices, list of exhibits, certificate of service and certificate of word count.

Dated: August 7, 2023

Respectfully submitted,
/Anthony R. Prosser/

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XII. CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing petition for Post Grant Review of U.S. Patent No. 11,642,361, including all Exhibits, was served on August 7, 2023, via Express Mail delivery directed to the following correspondence address of record for the patent:

Attn. Joy Lynn Nemirow, Ph.D.
Sheppard Mullin Richter & Hampton LLP
650 Town Center Drive, 10th Floor
Costa Mesa, California 92626

A courtesy copy of the foregoing petition for Post Grant Review of U.S. Patent No. 11,642,361, including all Exhibits, was served on August 7, 2023, via Express Mail delivery directed to the following:

Attn. Deborah H. Telman, Esq.
Executive Vice President, Corporate Affairs and General Counsel
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California 94404

Date: August 7, 2023

/Brent R. Bellows/

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