

Filed on behalf of Petitioner CIPLA LIMITED

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CIPLA LIMITED

Petitioner

v.

GILEAD SCIENCES, INC.,

Patent Owner

Case No.: IPR2025-00033

U.S. Patent No. 11,744,802

Issued: September 5, 2023

Title: THERAPETUTIC COMPOSITIONS FOR TREATMENT OF HUMAN
IMMUNODEFICIENCY VIRUS

DECLARATION OF JEFFREY D. WINKLER, Ph.D.

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I, Jeffrey D. Winkler, Ph.D., hereby declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

1. All of my opinions stated in this Declaration are based on my own personal knowledge and professional judgment. In forming my opinions, I have relied on my knowledge and experience in designing, developing, researching, and teaching the technology referenced in this declaration.

2. I am over 18 years of age and, if I am called upon to do so, I would be competent to testify as to the matters set forth herein. A copy of my current curriculum vitae, which details my education and professional and academic experience, is attached hereto as **Appendix A**. The following provides a brief overview of some of my experience that is relevant to the matters set forth in this declaration.

3. I am the Merriam Professor of Chemistry and Undergraduate Chair in the Department of Chemistry, College of Arts & Sciences, at the University of Pennsylvania.

4. I have forty-one years of experience in organic and medicinal chemistry. I received my undergraduate degree from Harvard College, where I graduated *cum laude* in chemistry in 1977. I received a M.A., M.Phil., Ph.D. from Columbia University in 1981. From 1982 to 1983, I conducted post-doctoral

research at Columbia University as an American Cancer Society Postdoctoral Fellow.

5. From 1983 to 1990, I was an Assistant Professor at the University of Chicago in the Department of Chemistry. From July 1990 until June 1996, I was an Associate Professor in the Department of Chemistry at the University of Pennsylvania. From July 1996 until present, I have been a full Professor in the Department of Chemistry at the University of Pennsylvania. In January 2001, I became the Merriam Professor of Chemistry, a position I still hold today. In July 2018, I became the Undergraduate Chair in the University of Pennsylvania Department of Chemistry.

6. I am a member or founder of several academic programs or institutes dedicated to biomedical research. I am an Affiliate Member of the Ellen and Ronald Caplan Cancer Center at The Wistar Institute and the University of Pennsylvania Cancer Center. I am also founding member of the University of Pennsylvania Center for Cancer Pharmacology. In the context of this work, my laboratory has studied the design and synthesis of new antiviral agents in collaboration with Professor William Degrado, a former colleague at Penn who is currently on the faculty at the University of California at San Francisco, and in my independent work on helical structures that could have anti-HIV activity. So my

laboratory has considerable experience in the design and synthesis of small molecules with anti-viral properties.

7. I co-founded Pinpoint Therapeutics, a company developing novel cancer treatment options aimed to inhibit autophagy. Some of the compounds that we have developed were tested against SARS-COVID-2. I have served as a member of the Scientific Advisory Board of Atrin Pharmaceuticals, a biopharmaceutical company developing proprietary molecules that target DNA damage and response pathways to treat a broad spectrum of cancers.

8. I have received numerous awards recognizing my academic contributions. In 1985, I received the Merck Foundation Award for Faculty Development. From 1987 to 1989, I was an Alfred P. Sloan Research Fellow, a fellowship awarded to early career researchers in recognition of distinguished performance. From 1988 to 1993, I received the NIH-NCI Research Career Development Award. I was awarded the American Cyanamid Young Faculty Award from 1989 to 1993. In 2000, I was awarded the American Chemical Society Cope Scholar Award. In 2014, I became an elected member of the John Morgan Society, the oldest honorific biomedical society in the country. In 2016, I received the Ira H. Abrams Memorial Award for Distinguished Teaching.

9. In conjunction with the above activities, I have co-authored approximately one hundred and fifty papers on the topics of organic chemistry and

medicinal chemistry. In addition to my teaching lectures, I have given approximately 80 invited lectures since 2002.

10. My experience in medical chemistry is extensive, going back to my years of consulting with pharmaceutical companies, where analysis of *in vitro* and *in vivo* data has played an integral role. Over the last twenty years, I have had extensive collaborations with biomedical scientists at the Wistar Institute, the School of Medicine at the University of Pennsylvania, the Childrens' Hospital of Philadelphia and the Massachusetts General Hospital, where the study of structure-activity relationships, the analysis of both *in vitro* and *in vivo* data, and the study of pharmacokinetic properties has been of central importance. Furthermore, as a co-founder of Pinpoint Therapeutics, I have been actively involved in the analysis of both *in vitro* and *in vivo* biological data, as well as the study of the biophysical properties of the molecules that we have invented.

II. SCOPE OF WORK

11. I understand that Cipla is challenging the patentability of the claims 1–13 (hereinafter, “Challenged Claims”) of U.S. Patent No. 11,744,802 (“the ’802 Patent”) in a Petition for *Inter Partes Review* (“Petition”). I have been retained by Cipla Limited (“Cipla”) to provide the Patent Trial and Appeal Board (PTAB) with an overview of important concepts that ordinarily skilled medicinal chemists generally consider when conducting research and development (“R&D”) on small

molecule organic compounds (“small molecules”) designed for the treatment of disease states in the human being. This declaration further provides an overview of general concepts in organic chemistry that an ordinarily skilled medicinal chemist would have known and applied to small molecule pharmaceutical R&D.

12. I have also been retained to provide and/or review the materials I discuss in this declaration and provide my expert opinion in relation to what ordinarily skilled medicinal chemists would have understood, and the actions that they would have taken in view of the state of the art and accumulated knowledge in medicinal chemistry and drug development. In particular, this declaration focuses on the R&D of small molecules for the treatment of HIV, and especially R&D efforts directed to a class anti-HIV drugs known as integrase strand transfer inhibitors (“INSTIs”).

13. My opinions are based on my skills, knowledge, training, education, and experience with medicinal chemistry, organic chemistry, and drug development, including the selection of candidate compounds based on *in vitro* and *in vivo* test data and the selection and preparation of salts of pharmaceutical compounds.

14. In addition to the '802 Patent claims and specification, I have reviewed the record of the exchanges occurring between the USPTO and the applicant as that patent was originally examined.

15. I am being compensated for the time spent working on this matter at my usual and customary hourly rate of \$850 per hour. My compensation is not dependent upon the outcome of, or my testimony in, the present proceeding. I have no other financial interest in the outcome of this proceeding.

16. This declaration sets forth the substance of the facts and opinions on which I base my testimony herein. I understand that this declaration will be filed as evidence in an IPR before the Patent Trial and Appeal Board at the USPTO, and acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

III. THE LEVEL OF ORDINARY SKILL IN THE ART

17. Throughout this declaration, I refer to a person of ordinary skill in the art (“POSA” or “skilled artisan”). As I understand it, this hypothetical person is presumed to have a comprehensive knowledge of the available prior art and a level of skill commensurate with a typical practitioner in the relevant field at the time the earliest application for the ’802 was filed. For the ’802 Patent, I have applied the date of November 9, 2015, which I understand is the earliest priority date to which the ’802 may be entitled.

18. Counsel for Cipla has provided me with the following definition of a POSA:

A POSA is an M.D. or a Ph.D. with at least three years of work experience with HIV therapy and clinical investigations, drug development, medicinal chemistry, pharmaceuticals, pharmacokinetics, and/or pharmaceutical formulations prior to November 9, 2015. The POSA could hold a lesser degree, e.g., a B.S. or Master's degree, so long as that person had at least five years of work experience in the above fields.

A POSA would consult with a collaborative team of skilled artisans in the same or related fields (e.g., MDs and PhDs), including other POSAs (as defined above) with different skill sets, skilled artisans in virology, organic chemistry, pharmacokinetics, pharmacodynamics, and/or conducting clinical trials, as well as artisans skilled in regulatory frameworks under which solid oral dosage forms are developed and approved by the FDA or other regulatory body.

19. I have adopted this definition and applied it in my analysis and opinions herein. Specifically, my opinions are made from the viewpoint of an ordinarily skilled medicinal chemist with specific expertise in, e.g., organic

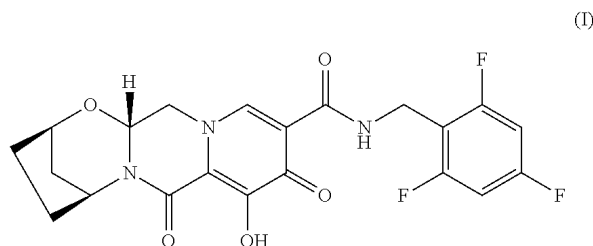
chemistry, drug development and pharmacokinetics. On the basis of my personal knowledge and experience, I am very familiar with the knowledge and practice available to this ordinarily skilled medicinal chemist prior to November 9, 2015.

IV. THE PATENT AT ISSUE – US 11,744,802

20. I understand that the '802 patent was granted to Gilead Sciences, Inc ("Gilead") on September 5, 2023 with thirteen claims, which correspond to the Challenged Claims in Cipla's Petition. I further understand that the '802 patent claims priority to two U.S. provisional applications, the earlier of which was filed on November 9, 2015. For the purposes of this declaration, I was asked to consider the information and knowledge available to a person having ordinary skill in the art ("POSA") in the field of the '802 patent prior to its earliest provisional filing date - November 9, 2015. As such, the publications relied upon herein were available to the public prior to this date and I understand that they constitute prior art to the Challenged claims.

21. I have reviewed and considered the claims, specification, and file history of the '802 patent so as to inform myself about the technical field of the Challenged Claims and further details on the nature of those claims and how they came to be. The Challenged Claims are provided below:

1. A tablet comprising 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

2. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.

3. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.

4. The tablet of claim 1, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

5. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.

6. The tablet of claim 1, wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.

7. The tablet of claim 1, wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.

8. The tablet of claim 1, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

9. The tablet of claim 1, wherein the tablet has a total weight of less than 1000 mg.

10. The tablet of claim 9, wherein the tablet has a total weight of less than 800 mg.

11. The tablet of claim 10, wherein the tablet has a total weight of less than 730 mg.

12. The tablet of claim 1, wherein the tablet contains less than 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

13. The tablet of claim 1, wherein the tablet contains less than 11 % of the compound of Formula I or a pharmaceutically acceptable salt thereof.

22. Briefly, the Challenged Claims are directed to tablet compositions comprising 50 mg of a compound of Formula (I) or a pharmaceutically acceptable salt thereof (e.g., a sodium salt), 25 mg of tenofovir alafenamide (“TAF”) or a pharmaceutically acceptable salt thereof (e.g., TAF fumarate and TAF hemifumarate), and 200 mg of emtricitabine (“FTC”) or a pharmaceutically acceptable salt thereof (e.g., FTC in non-salt form). This declaration focuses primarily on the information and knowledge available to a POSA by November 9, 2015 with regard to the INSTI class of anti-HIV drugs and their salts, of which the compound of Formula (I) in claim 1 was a known member.

23. To the extent that I found the Challenged Claims, or excerpts from the ’802 patent specification (EX-1001) or file history (EX-1002), pertinent to my analysis, I provide further details on those disclosures below.

V. PRIOR ART BACKGROUND AND TECHNICAL TUTORIAL

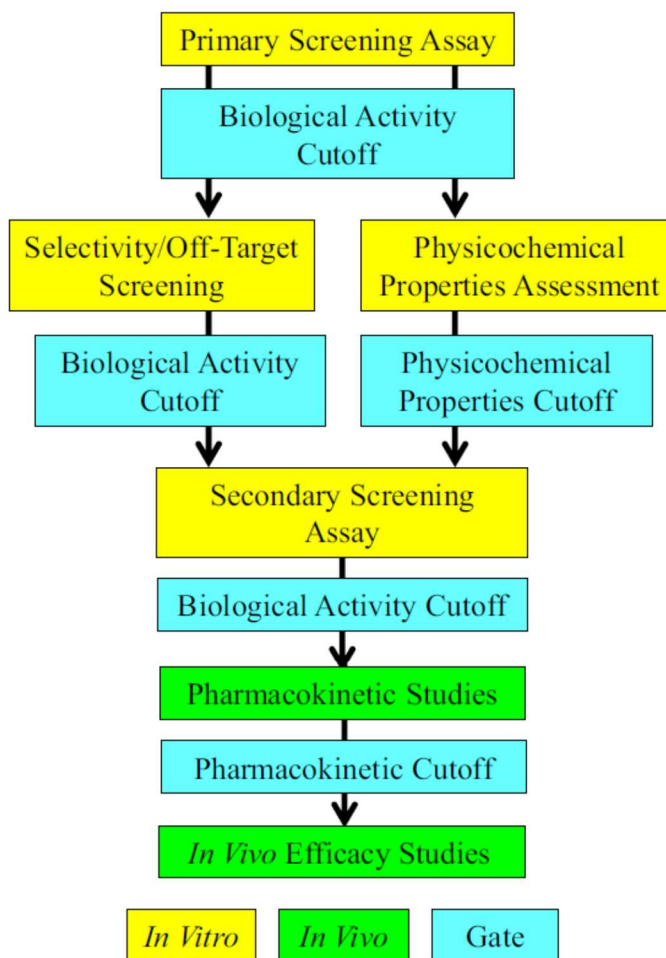
A. General Principles of Drug Discovery and Development

24. Small-molecule drug discovery involves the design, synthesis, and testing of compounds against a biological target (such as an enzyme). The information gained from the biological testing of compounds with different structures, also known as “structure-activity relationship” or “SAR” studies, guides medicinal chemists to design and synthesize a new set of compounds and test them in biological assays, where information gleaned from a prior set of compounds can be used to design and prepare a more optimized set of compounds. Through this iterative experimental process and cycle of drug design, synthesis, and biological testing, medicinal chemists seek to design and discover compounds with improved properties, and the process continues until a suitable compound is selected for clinical development. *See* Benjamin E. Blass, “Drug Discovery and Development: An Overview of Modern Methods and Principles” *in* BASIC PRINCIPLES OF DRUG DISCOVERY AND DEVELOPMENT 203–43 (Academic Press, 2015) (“Blass”) (EX-1047-A); *see also* “Medicinal Chemistry” *in* Blass at 203–43 (EX-1047-B); *see e.g.*, Blass (EX-1047-A) at 20–21. Blass illustrates a lead optimization cycle used by medicinal chemists in drug discovery. Blass (EX-1047-A) at 21.

25. Identifying a compound that is (1) potent against the therapeutic target, and (2) selective over other biological targets, is not the only goal in drug

discovery. Chemists working drug discovery also sought to identify compounds that were novel, that provided improved pharmacokinetic properties, solubility, safety, and stability, as compared to other compounds. Blass (EX-1047A) at 21–22. A useful flow chart describing the process from initial discovery to the choice of a compound for the clinic is commonly referred to as a “screening tree,” as provided below:

FIGURE 1.18 A screening tree is designed to identify lead compounds by establishing a series of qualifications or “gates” that a compound must surpass in order to advance through the process.



See Blass (EX-1047-A) at 22 (Figure 1.18). The process begins with *in vitro* profiling to first assess biological activity, where more potent (and selective)

compounds proceed to *in vivo* profiling to assess pharmacokinetics (PK) and potentially also efficacy in animal models. *Id.*

26. *In vitro* screening is a common way to identify compounds having sufficient potency toward a target of interest, so that a scientist knows whether any particular compound has properties that warrant further investigation using *in vivo* experiments. *See id.* at 22. In general, compounds having higher potency are understood to be capable of being dosed at lower levels. *Id.* And, when lower doses are used, one can expect a decrease in the incidence of side effects compared to higher doses of that compound or other related compounds. *Id.* As an example, a compound with target potency of 5 nM in theory could be provided to a patient at a significantly lower dose than a compound with a target potency of 5 μ M (which is 1000 times more than 5 nM), since the amount of the compound needed to show potency would be three orders-of-magnitude less.

27. The potency of compounds that inhibit a biological target are normally measured in terms of the concentration required to inhibit the function of the target. For example, if an enzyme is the target, the potency of a compound is often defined by the concentration needed to reduce the function of that enzyme (or its activity) by 50%. This is referred to as an **EC₅₀** effective concentration for 50% inhibition. The concentration needed to reduce activity of the enzyme by 90% is referred to as an **EC₉₀**, and for a 95% reduction in activity, the value would be

referred to as an **EC₉₅**), etc. Effective concentrations of compounds may also be referred to as inhibitory concentrations or **IC** values, e.g., **IC₅₀** (concentration that inhibits 50% of target enzyme activity). *See e.g.*, Blass (EX-1047-B) at 206–07. Using this metric, compounds having a smaller **EC₅₀** or **IC₅₀** value are more potent than compounds having a larger value (e.g., 1 nM > 10 nM > 100 nM = 0.1 μM). *See e.g., id.* (FIGS 5.2 and 5.3 showing increased potency with a smaller **IC₅₀** value). **EC** values may also be used in other ways, such as the concentration required to suppress viral replication, as explained further herein.

28. A potent compound, however, is not necessarily a good drug candidate, and the most potent compounds identified in *in vitro* assays are not necessarily (and often are not) the optimal candidates for clinical evaluation. *See e.g.*, Blass (EX-1047-A) at 23. To determine more optimal drug candidates, medicinal chemists conduct additional screening to assess absorption, distribution, metabolism (or biotransformation), and excretion (collectively abbreviated as “ADME”) using additional *in vitro* and especially *in vivo* animal models. *See e.g., id.* at 24-26. This combined analysis provides valuable information for selecting compounds that are “druglike” in nature, and that provide the characteristics needed for a particular use, e.g., a longer half-life, oral bioavailability, etc. as discussed below.

B. ADME and Pharmacokinetics (PK)

29. A pharmaceutical compound can potentially be administered through a variety of routes, including by parenteral (e.g., intravenous (IV) and subcutaneous (SC)) and oral routes. No matter the route of administration, a pharmaceutical compound will encounter several biological processes that can impact its concentration in the body over time. These processes primarily include the extent of absorption, distribution, metabolism, and excretion (ADME) for a given compound.

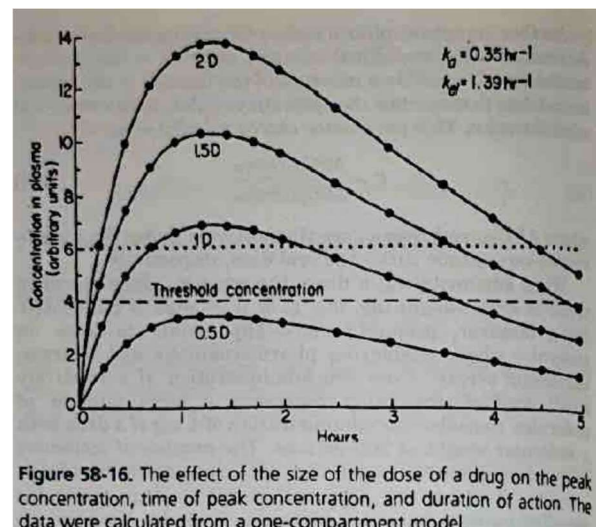
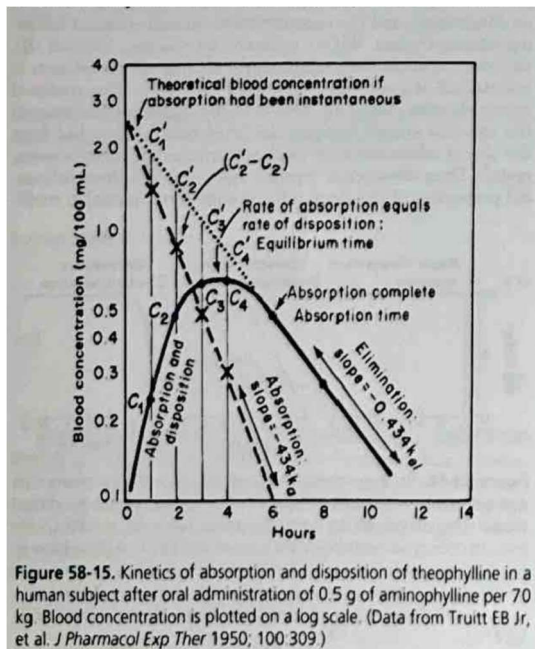
30. *Adsorption* is a measure of a pharmaceutical compound's movement from the site of administration (e.g., oral or subcutaneous (SC)) into the extracellular compartment that can deliver it to the intended site of action. Michael R. Franklin & Donald N. Franz, "Chapter 57: Drug Absorption, Action, and Disposition," in 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1142–70 (Lippincott Williams & Wilkins ed., 2006) ("Remington Chapter 57") (EX-1055-A) at 1156. Most commonly this compartment is the circulatory system, where adsorption is measured by drug concentration in blood plasma after administration. *Id.* at 1157 (Figure 57-12) (showing blood concentration of aminophylline over time after intravenous (IV), rectal, and oral administration). Absorption looks at the increase in compound concentration over time to assess its extent and rate of delivery to the extracellular compartment, e.g., the blood. *Id.* at

1156, 1160. The extent of absorption is called bioavailability, which is usually expressed as the fraction or percent ($F(\%)$) of an administered dose actually absorbed into the bloodstream, and thus available for potential pharmacologic effect. Paul M. Beringer & Michael E. Winter, “Chapter 59: Clinical Pharmacokinetics and Pharmacodynamics,” in 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1191–1205 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 59”) (EX-1055-B) at 1193.

31. On the other hand, distribution, metabolism, and excretion (collectively referred to as “disposition”) are processes that tend to reduce a pharmaceutical compound’s blood concentration over time. Remington Chapter 57 (EX-1055-A) at 1160. *Distribution* speaks to the partitioning of a compound into different locations in the body, e.g., GI, plasma, and tissue distribution. *Id.* at 1160–63. A common measurement for assessing distribution is volume of distribution (V_D or simply V). Remington Chapter 59 (EX-1055-B) at 1193–94. *Metabolism* (or biotransformation) provides an assessment of the body’s ability to convert the desired compound, e.g., through enzymatic oxidation, reduction, or hydrolysis, into another compound that may or may not provide its own pharmacological activity. Remington Chapter 57 (EX-1055-A) at 1163–65. A common site of metabolism is oxidation by the enzyme cytochrome P450 (CYP), particularly including CYP2C and CYP3A, which make up 65% of CYP

concentration in the liver. *Id.* at 1163–64. *Excretion* then assesses the elimination of the desired compound (and its liver metabolites) from the body, primarily though the kidney where these compounds are filtered and then excreted in the urine. *Id.* at 1165–67.

32. Pharmacokinetic (PK) analysis provides a medicinal chemist with a quantitative measure of pharmaceutical compound's concentration in the body over time, where an assessment of ADME, in addition to potency, informs medicinal and drug discovery chemists on the amounts of the compound needed to elicit a therapeutic effect. Raymond E. Galinsky & Craig K. Svensson, "Chapter 58: Basic Pharmacokinetics and Pharmacodynamics," in 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1171–90 (Lippincott Williams & Wilkins ed., 2006) ("Remington Chapter 58") (EX-1055-C) at 1171–73. Blood is the most frequently sampled fluid for assessing PK, where a compound's blood concentration is determined at different times after administration to provide a PK plot. *Id.* at 1171. The following PK plots are representative and provide information on how ADME leads to an initial increase and then a decrease in concentration over time, as well as the impact of dose on blood concentration over time.



Id. at 1182 (FIGS. 58-15 and 58-16). As shown in Figure 58-16, the size of a dose has an impact on the peak concentration of a compound ($C_{\max}$), its time to peak concentration ($T_{\max}$), and its duration of action, i.e., time spent above the “threshold concentration” required for therapeutic activity. Also important is the total concentration of the drug over time as measured by the area under the concentration curve (AUC). As shown above, a combination of this AUC and $C_{\max}$ provides important information on the dose needed to meet or exceed threshold concentration over time, e.g., in Figure 58-16 (above) the 1.5D and 2D doses provided concentrations above the threshold for longer periods of time than the 1D dose, where a 0.5D dose did not reach the threshold at any point. $C_{\max}$ and AUC are thus informative on the dosing frequency needed to elevate plasma

concentrations to or beyond the “threshold concentration” needed for therapeutic activity.

33. An important consideration for PK analysis is the assessment of a pharmaceutical compound’s total clearance rate (**CL**), which provides details on the body’s potential to eliminate the compound (e.g., through metabolism by the liver (**CL_H**) and excretion through the kidney (**CL_R**)). Remington Chapter 58 (EX-1055-C) at 1182–86.

34. A compound’s volume of distribution (**V_D** or simply **V**) and total clearance rate (**CL**) may be used to calculate its elimination rate constant (**K**) and its half-life (**t_{1/2}**) according to the following equations:

$$K = \frac{CL}{V} \qquad t_{1/2} = \frac{(0.693 \times V)}{CL}$$

Remington Chapter 58 (EX-1055-C) at 1176, 1179. Compounds with a larger half-life will remain in the body for a longer period of time compared to compounds having a shorter half-life.

1. Oral PK

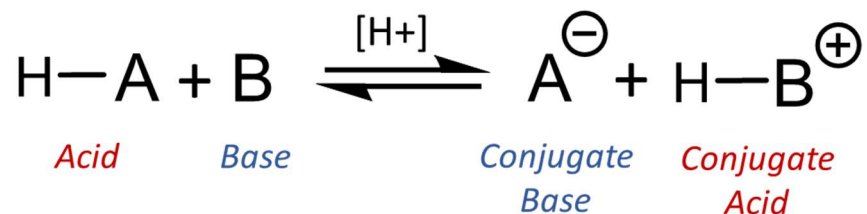
35. Oral administration provides the most convenient route for delivery of pharmaceuticals into circulatory system so that they can reach the intended site of action. Remington Chapter 57 (EX-1055-A) at 1156. However, there is no guarantee that a particular compound will be absorbed through the gastrointestinal

tract in an amount providing sufficiently high blood concentrations (as measured in blood plasma) to be effective. *Id.* As such, a key PK concept for oral dosage forms such as tablets is an assessment of oral bioavailability (**oral F(%)**). As with bioavailability in general, oral bioavailability determines the percent of an orally administered dose actually absorbed into the bloodstream, and thus available for potential pharmacologic effect.

C. Principles of Salt Formation

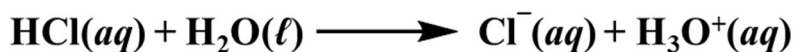
1. Brønsted-Lowry Acid-Base Theory

36. Brønsted-Lowry acid-base theory defines acids and bases in view of their ability to donate or accept a positively charged hydrogen ion (H^+) (also called a “proton”). In this sense, a Brønsted-Lowry acid is a proton (H^+) donor and a Brønsted-Lowry base is a proton (H^+) acceptor. “Chapter 17: Ionic Solutions and Electrolytic Equilibria,” *in* 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 231–49 (Lippincott Williams & Wilkins ed., 2006) (“Remington Chapter 17”) (EX-1055-D) at 235. A Brønsted-Lowry acid that has donated a proton is called a conjugate base, and a Brønsted-Lowry base that has accepted a proton is called a conjugate acid. *Id.* These species are in equilibrium with one another, as shown in the following equation:



The stronger the acid the weaker its conjugate base, and the stronger the base the weaker its conjugate acid. Hydrochloric acid (HCl) being a strong acid means that its conjugate base, chloride ion (Cl^-), does not hold H^+ tightly and is thus a weak conjugate base, whereas water is a weak acid (which holds onto its proton tightly) such that its conjugate base OH^- is a strong conjugate base.

37. A strong acid is one that loses a proton (H^+) easily, meaning that its conjugate base holds that proton weakly and is therefore a weak base. In aqueous solution, a strong acid is one that undergoes essentially complete ionization through proton (H^+) transfer to water to form a hydronium ion (H_3O^+). Examples are hydrochloric acid (HCl), nitric acid (HNO_3) and sulfuric acid (H_2SO_4), all of which are examples of strong acids. Remington Chapter 17 (EX-1055-D) at 236. As an example, when hydrochloric acid is mixed with water, its protons dissociate to form chloride ion (Cl^-) as a conjugate base, and H_3O^+ as the conjugate acid of water (H_2O ; resulting from protonation of the water molecule), as shown in the following reaction equation.

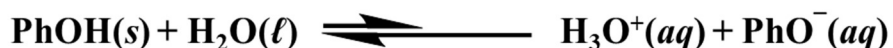


The reaction proceeds completely from left to right as indicated by a single arrow in the equation. *Id.* at 242.

38. On the other hand, a weak acid is one that loses a proton (H^+) with more difficulty, such that its conjugate base holds the proton more tightly and is therefore a stronger base. A weak acid is only partially ionized in water and so an equilibrium exists between the acid and its conjugate base. Remington Chapter 17 (EX-1055-D) at 242. Acetic acid (CH_3COOH) and carbonic acid (H_2CO_3) are examples of weak acids. Their acidic group is a carboxylic acid ($-\text{COOH}$). When acetic acid (CH_3COOH) is mixed with water, the transfer of its protons (H^+) does not proceed to completion. This creates an equilibrium between the acid (CH_3COOH) and base (H_2O) (on the left below), and the conjugate base (CH_3COO^-) and conjugate acid (H_3O^+) on the right below), as indicated by the double arrows in the following reaction equation.



39. The weaker the acid, the less it dissociates in aqueous solution (i.e., water) and so lower amounts of conjugate base and conjugate acid are present in equilibrium. An example is phenol (PhOH), as shown in the equation below.

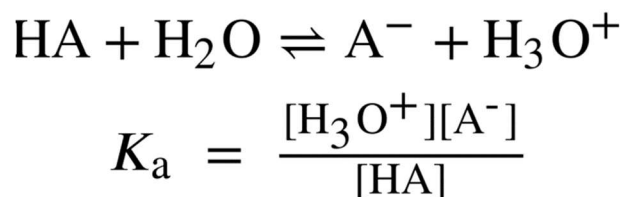


Here, the equilibrium favors the reactants (PhOH (the acid) and H₂O (the base)), as represented by the shorter top arrow to the products (H₃O⁺ (conjugate acid) and PhO⁻ (conjugate base)) and longer bottom arrow back to reactants.

40. Bases are also classified as strong or weak. Remington Chapter 17 (EX-1055-D) at 242. A strong base reacts essentially completely with water by deprotonation to give hydroxide ions (OH⁻). Sodium hydroxide (NaOH) is an example of a strong base.

41. Similar to weak acids, weak bases also exist in equilibrium with their conjugate acids, where particularly weak bases are less prone to accept a proton from an acid, i.e., as illustrated in the reaction above for phenol (PhOH; weak acid) and water (weak base), which favors the reactants at the expense of phenoxide (PhO⁻) and hydronium ion (H₃O⁺). Remington Chapter 17 (EX-1055-D) at 243.

42. The strength of an acid is defined in terms of its acidity (or dissociation) constant (K_a).

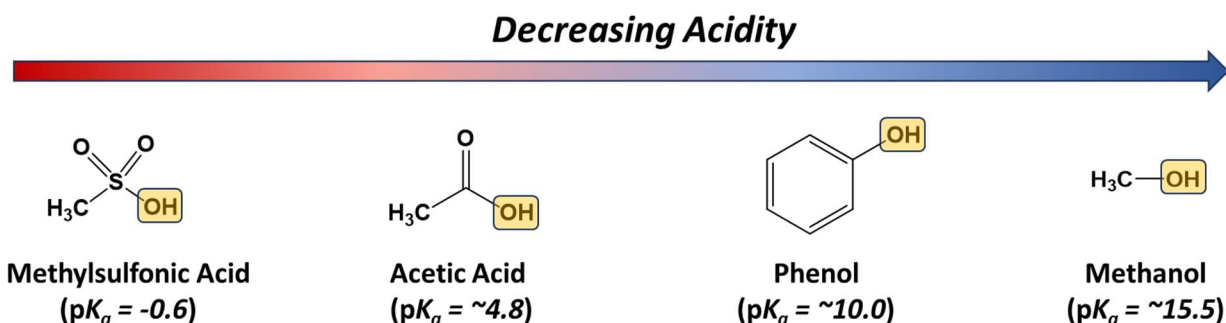


Remington Chapter 17 (EX-1055-D) at 236–37; Alfonso R. Gennaro, “Chapter 25:Organic Pharmaceutical Chemistry,” *in* 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 386–409 (Lippincott Williams and Wilkins ed., 2006)

(“Remington Chapter 25”) (EX-1055-E) at 391. Acidity constants are normally expressed in terms of pK_a , i.e., the negative logarithm of K_a .

$$pK_a = -\log K_a$$

Remington Chapter 25 (EX-1055-E) at 391. Here, a stronger acid has a smaller pK_a and a weaker acid has a larger pK_a . This is shown below for acetic acid and phenol and some other common compounds bearing a hydroxy (-OH) group.

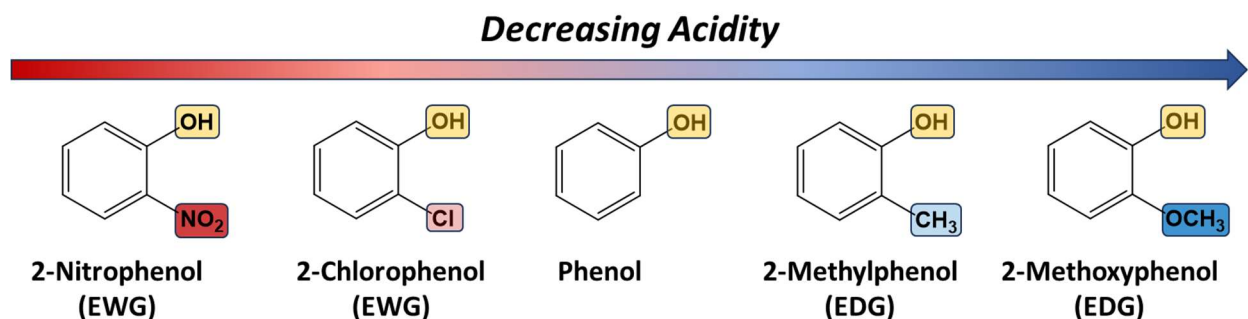


See Frederick G. Bordwell, “Equilibrium Acidities in Dimethyl Sulfoxide Solution,” 21 ACCT. CHEM. RSCH. 456–63 (1988) (“Bordwell”) (EX-1053) at 457 (Table 1) (pK_a values above are in water); *see also* Remington Chapter 25 (EX-1055-E) at 394.

43. The acidity of organic compounds can increase or decrease based on other atoms and/or functional groups in the molecule. Groups that act to withdraw electron density (e.g., nitro and halogen groups) stabilize the conjugate base, leading to an increase in acidity and a lowering of pK_a . On the other hand, groups that act to donate electron density (e.g., ethers and alkyl groups) destabilize the

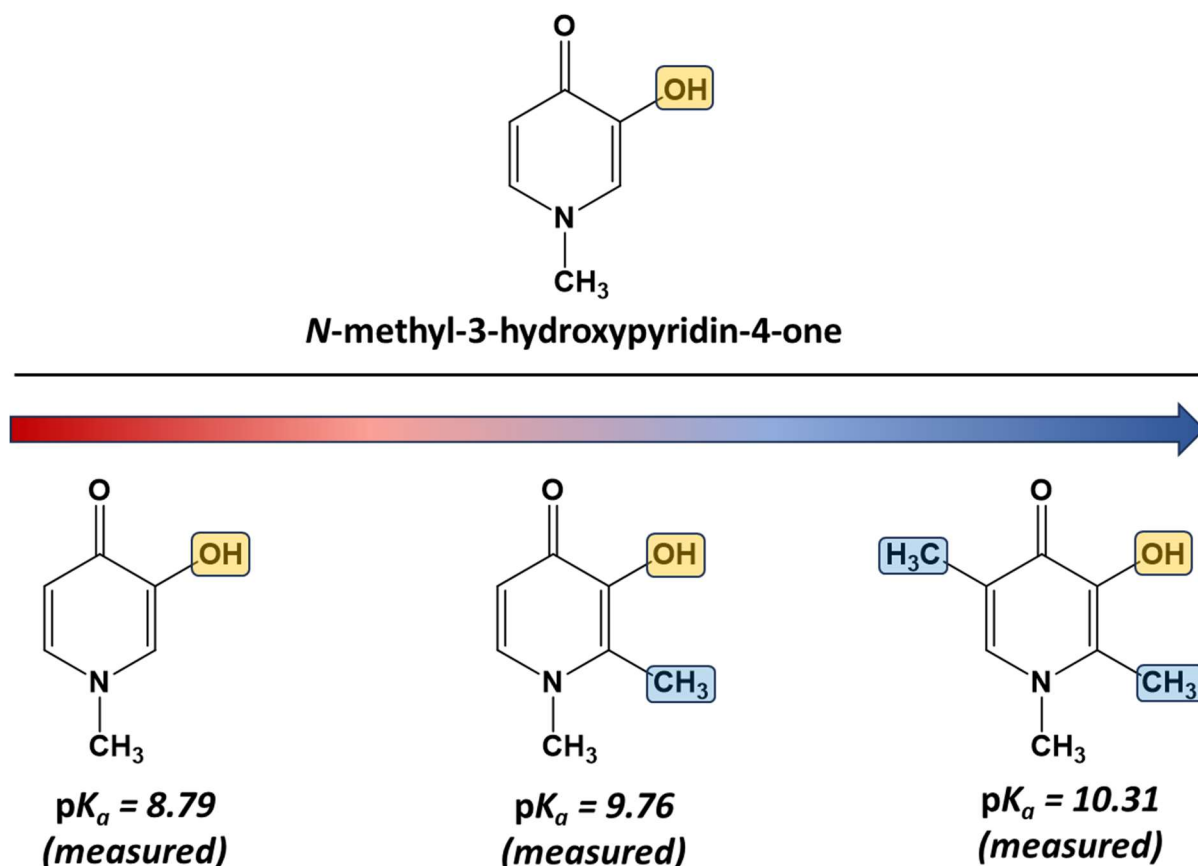
conjugate base, and thus decrease acidity and raise pK_a . Remington Chapter 25 (EX-1055-E) at 392–93.

44. The following illustration applies these concepts to phenol (PhOH). Here, the presence of an electron-withdrawing group (EWG), e.g., nitro ($-\text{NO}_2$) or chlorine ($-\text{Cl}$), stabilizes the conjugate base (PhO^-), and increases the acidity of the corresponding phenolic hydroxy ($-\text{OH}$) group, whereas the presence of an electron-donating group (EDG), e.g., methyl ($-\text{CH}_3$) or a methoxy ($-\text{OCH}_3$), destabilizes the conjugate base (PhO^-) and decreases the acidity of the corresponding acid.



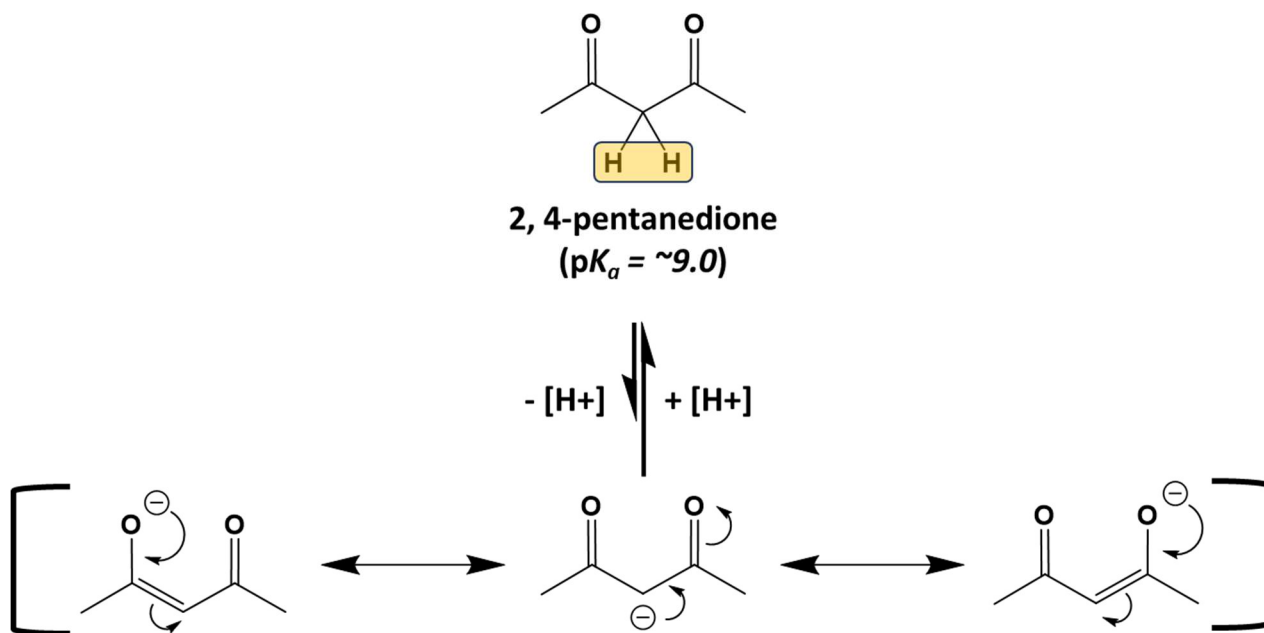
The increase or decrease in acidity compared with the parent compound (PhOH) depends on the strength of the EWG ($-\text{NO}_2 > -\text{Cl}$) and EDG group ($-\text{OMe} > \text{Me}$) (*see above* (increased strength emphasized with darker shading)).

45. Particularly relevant to the issues of this case is the class of weakly acidic 3-hydroxypyridin-4-ones (shown below).



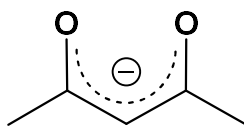
Chen et al., “Prediction of Absolute Hydroxyl pK_a Values for 3-Hydroxypyridin-4-ones,” 3 J. PHYSICAL CHEMISTRY LETTERS 2980–85 (2012) (“Chen”) (EX-1048) at 2980, 2983 (Table 1). The hydroxy group (yellow) in this class of compound has a similar pK_a to phenol at ~ 9 ; however, the pK_a increases (acidity decreases) depending on the presence of additional methyl ($-\text{CH}_3$) groups, which are electron-donating. As shown above, the addition of one $-\text{CH}_3$ group to the ring system leads to an increase in pK_a (decrease in acidity), with a further increase in pK_a (and an even further decrease in acidity) when two $-\text{CH}_3$ groups are added.

46. Acidity is also influenced by resonance where, for example, the movement of electrons through a conjugated system allows for charges to be dispersed over several atoms (electron delocalization). Remington Chapter 25 (EX-1055-E) at 392–96. The presence of different resonance forms tends to stabilize a conjugate base, e.g., an alkoxide ion (O^-), because its negative charge can be distributed amongst more than one atom in a molecule. Stabilization of the conjugate base through resonance acts to increase the acidity of the corresponding acid (and decrease in pK_a). A good example is 2, 4-pentanedione (shown below along with three resonance forms for its conjugate base).



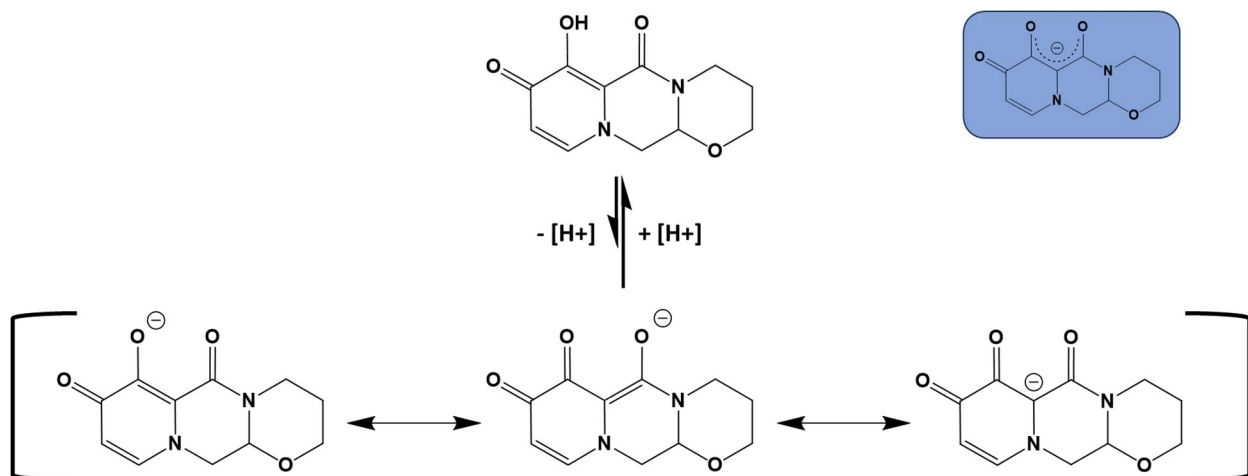
While a hydrogen atom attached to a carbon atom is usually not very acidic (and typically cannot be deprotonated by an aqueous base), a hydrogen (yellow above) on the carbon atom between the carbonyls ($-C=O$), as in 2, 4-pentanedione, is

weakly acidic in water ($pK_a \sim 9.0$). *Id.* at 396. As shown above, there are three different resonance forms (accessible through delocalization of the electron pair ($\ominus$) as shown above with arrows to indicate the movement of electron pairs) for the conjugate base, so that there are three atoms available in the conjugate base that can hold a negative charge, i.e., two oxygen atoms and the carbon atom sitting in between them. This anion stabilized through resonance can also be represented by the following structure, showing the negative charge distributed over a five-atom chain (O-C-C-C-O), and leads to the stabilization of the conjugate base, and therefore increasing the acidity of the starting acid, in this case 2,4-pentanedione.



Conjugate Base of 2, 4-Pentanedione

47. The following diagram shows similar resonance forms available after deprotonation of a tricyclic ring system relevant to the analysis herein. Similar to 2, 4-pentanedione, the conjugate base that is obtained by deprotonation of the hydroxypyridone shown below has three resonance forms that stabilize the resulting anion.



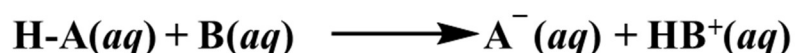
This allows for a similar negative charge distribution over a five-atom chain (O-C-C-C-O) (above in blue) in analogy to 2,4-pentanedione above.

2. Salt Formation with Weakly Acidic Drugs

48. The selection of an appropriate salt form of a new drug substance (or new chemical entity (NCE)) is an important part of pharmaceutical development. It allows pharmaceutical chemists to modify the characteristics of the potential NCE and permits the development of dosage forms with good bioavailability, stability, manufacturability and patient compliance. Bastin et al., “Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities, 4 ORGANIC PROCESS RSCH. & DEV. 427–35 (2000) (“Bastin”) (EX-1049) at 427 (Abstract); Michael J. Bowker, “A Procedure for Salt Selection and Optimization” *in* HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE 161–89 (P. Heinrich Stahl & Camille G. Wermuth eds., 2002) (“Bowker”) (EX-1008) at 162–63. Salts are most commonly employed to increase aqueous

solubility. Bastin (EX-1049) at 428. As such, one of the first physicochemical properties of a potential NCE assessed by the pharmaceutical chemist is the acidity (or basicity) of each functional group in the molecule, as determined by pK_a . *Id.* at 427. This assessment of pK_a allows for the selection of potential salt forming agents (or counterions), e.g., potential bases for the deprotonation of acidic drugs. *Id.* This selection also considers safety of the counterion, such that suitable counterions are selected from lists of pharmaceutically acceptable salts available in the literature. *Id.* at 427–28.

49. A long-known and widely accepted rule of thumb for the formation of a stable salt of a weak acid is the selection of a salt former (e.g., base) that provides a minimum pK_a difference of three units (at least a three order-of-magnitude difference in acidity) between the ionizable group in the potential NCE and the salt forming base itself. *See* Bastin (EX-1049) at 427–28; *see also* Bowker (EX-1008) at 166. A stable salt is said to be irreversible, and so there is little equilibrium back to the free acid. This is shown by the single arrow in the reaction equation below.

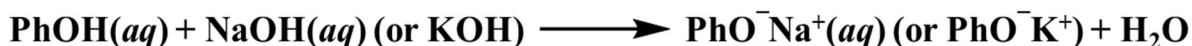


This $\geq$ three pK_a difference was known to be especially important for weak acids (and bases), where equilibration (i.e., dissociation) of the salt back to its free acid and base would be expected for acid-base reactions having smaller pK_a differences, thereby leading to the undesirable formation of mixtures of products. *Id.*

50. After a drug candidate compound has been selected for potential clinical investigation, salt formation is considered one of the first important decisions from a drug development perspective, as salt selection will be used to prepare significant quantities of the desired salt for later toxicological and other evaluations in animal models. The formation of a stable salt is of critical importance for further development. Indeed, a change in a salt form later in development, e.g., in view of instability or otherwise, would require repetition of these and other time consuming and expensive *in vivo* studies. Howard Y. Ando & Galen W. Radebaugh, “Chapter 38: Property-Based Drug Design and Preformulation,” *in* 21 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 720–44 (Lippincott Williams and Wilkins ed., 2006) (“Remington Chapter 38”) (EX-1055-F) at 734.

51. For the weak acids requiring salt formation with a base, this “rule of three” means that the salt-forming base should have a $pK_a \geq 3$ larger than the potential NCE of interest (i.e., it is at least three-order of magnitude less acidity than the free acid). This means, in the case of the weak acid phenol (PhOH) with $pK_a \sim 10$, that the base should have a $pK_a \geq 13$. In terms of pharmaceutically acceptable counterions appearing in marketed drugs, only the alkali metal bases (leading to either Na^+ or K^+ counterions) are strong enough to provide an expectation of irreversible salt formation. It is common knowledge to the

ordinarily skilled medicinal chemist that the strongest bases available for salt formation (in water) with alkali metals are sodium hydroxide (NaOH) and potassium hydroxide (KOH). *See e.g.*, Remington Chapter 38 (EX-1055-F) at 732 ($pK_{a(Na^+)} = 14.77$; $pK_{a(K^+)} = 16.00$); James Wells, “Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances” in 2 PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN 113–38 (M.E. Aulton ed. 1988) (“Wells”) (EX-1050) at 117.



52. Lists of pharmaceutically acceptable salts, including pharmaceutically acceptable salts of acidic compounds, have been available to the public for decades. *See* Berge et al., “Pharmaceutical Salts,” 68 J. PHARM. SCI. 1–19 (1977) (“Berge”) (EX-1051). For example, Berge provided the following compilation of FDA-approved commercially marketed pharmaceutically acceptable cationic salts in use through 1974. Berge (EX-1051) at 2.

Cation	Percent ^a	Cation	Percent ^a
Organic:		Metallic:	
Benzathine ^b	0.66	Aluminum	0.66
Chloroprocaine	0.33	Calcium	10.49
Choline	0.33	Lithium	1.64
Diethanolamine	0.98	Magnesium	1.31
Ethylenediamine	0.66	Potassium	10.82
Meglumine ⁱ	2.29	Sodium	61.97
Procaine	0.66	Zinc	2.95

^a Percent is based on total number of anionic or cationic salts in use through 1974. ^b Camphorsulfonate. ^c 1,2-Ethanedithiolate. ^d Lauryl sulfate. ^e Ethanesulfonate. ^f Glucoheptonate. ^g *p*-Glycollamidophenylarsonate. ^h *N,N'*-Di(dehydroabietyl)ethylenediamine. ⁱ 2-Hydroxyethanesulfonate. ^j 8-Chlorotheophyllinate. ^k *N,N'*-Dibenzylethylenediamine. ^l *N*-Methylglucamine.

As shown above, the most commonly used cations for salt formation at that time were metallic (not organic) salts, and especially salts of sodium (~62% of all FDA-

approved cations), followed by potassium (~10.8%), and calcium (~10.5%). *Id.*

This trend for pharmaceutically acceptable cationic salts continued for decades.

See Paulekuhn et al., “Trends in Active Pharmaceutical Ingredient Salt Selection

Based on Analysis of the Orange Book Database,” 50 J. MED. CHEM. 6665–72

(2007) (“Paulekuhn”) (EX-1009). Indeed, according to Paulekuhn, sodium salts

were by far the most common cationic salts for acidic compounds throughout

history up until 2006, the date range of the newer study. As shown below, sodium

salts made up ~75 percent of all cationic salts overall (through the year 2006), with

much smaller percentages attributed to calcium (6.9%) and potassium (6.3%) and

magnesium (1.2%).

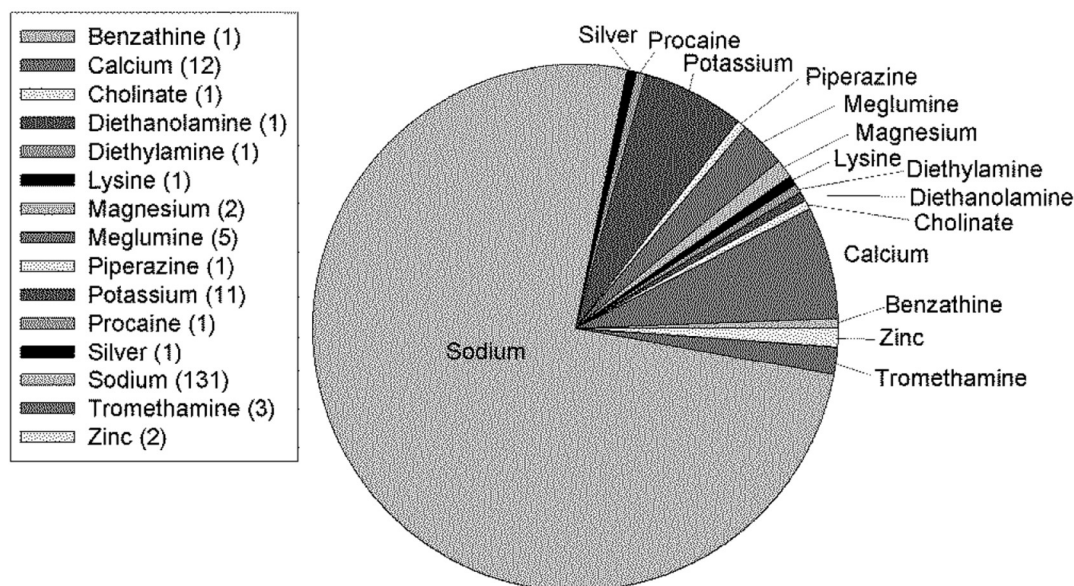


Figure 4. Overall distribution of cations used in APIs of category II in the Orange Book.

Paulekuhn (EX-1009) at 6668 (Table 3 and Figure 4 (above))¹. The trend was the same for cationic salts used in oral dosage forms over the same time period, where sodium salts made up ~65% of salts overall, followed again by potassium and calcium, and then magnesium.

Table 5. Distribution of Cations for API Used in Oral Dosage Forms

	overall (%)	pre-1982 (%)	1982–1986 (%)	1987–1991 (%)	1992–1996 (%)	1997–2001 (%)	2002–2006 (%)
benzathine	1.3	2.3					
calcium	12.0	11.4			11.1		50.0
choline	1.3	2.3					
magnesium	2.7					11.1	16.7
piperazine	1.3	2.3					
potassium	13.3	13.6			33.3		16.7
sodium	65.3	68.2	100.0	83.3	44.4	88.9	16.7
trimethamine	2.7			16.7	11.1		
number of salts	75	44	1	6	9	9	6

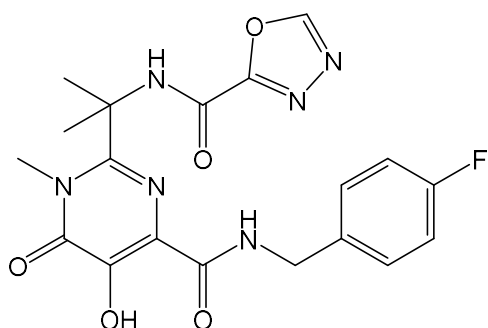
Paulekuhn (EX-1009) at 6669 (Table 5).

D. “Second Generation” Integrase Inhibitors – Structure and Function

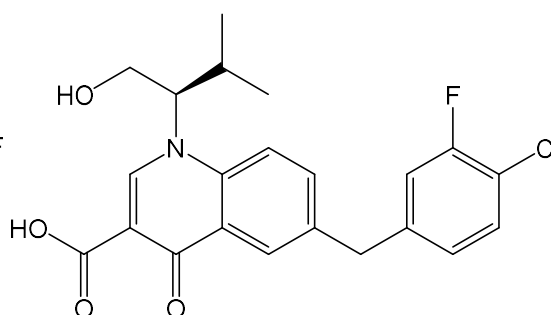
53. Prior to November 9, 2015, there were three FDA-approved INSTIs available for the treatment of HIV in the United States. The approved INSTIs began with Merck’s raltegravir (RAL) (approved in 2007 as Isentress®), followed by Gilead’s elvitegravir (EVG) (approved in 2012 as a component of Stribild® also containing tenofovir disoproxil fumarate (“TDF”), FTC, and the pharmacokinetic booster cobicistat (“COBI”) and then ViiV Healthcare’s dolutegravir (DTG) (approved in 2013 as Tivicay® and approved in 2015 as a component of Triumeq®)

¹ Figure 4 from Paulekuhn refers to the overall distribution of cationic salts in the Orange Book. A POSA would have understood that the Orange Book identifies patents that cover compounds, compositions, and/or methods of treatments for branded drugs approved by the FDA.

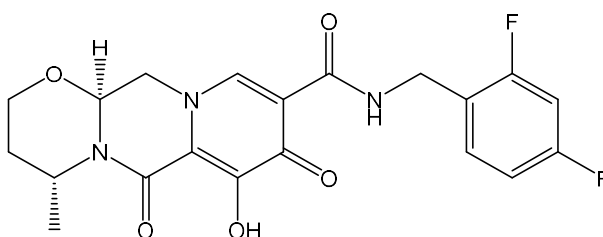
also containing abacavir (“ABC”) and lamivudine (“3TC”)). *See* Highlights and Prescribing Information on Isentress, dated October of 2007 (“Isentress Label”) (EX-1016) at 1; Highlights and Prescribing Information on Stribild, dated August of 2012 (“Stribild Label”) (EX-1019) at 1; Highlights and Prescribing Information on Tivicay, dated August of 2013 (“Tivicay Label”) (EX-1022) at 1; Highlights and Prescribing Information on Triumeq, dated August of 2014 (“Triumeq Label”) (EX-1024) at 1. The chemical structures for RAL, EVG, and DTG as known in the art are provided below.



Raltegravir (RAL)



Elvitegravir (EVG)



Dolutegravir (DTG)

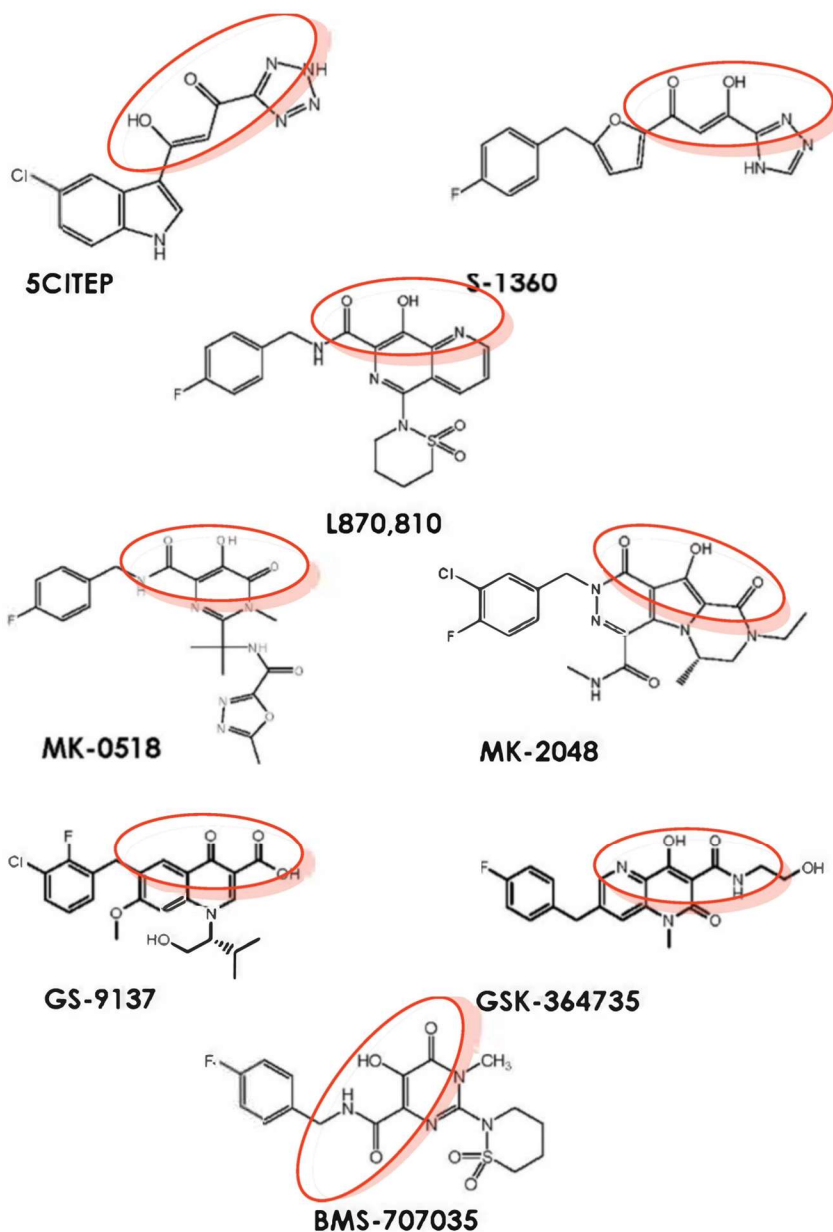
See Isentress Label (EX-1016) at 7 (Section 11); Stribild Label (EX-1019) at 22–23 (Section 11); Tivicay Label (EX-1022) at 14 (Section 11); Triumeq Label (EX-1024) at 17–18 (Section 11); *see also* Johns et al., “Carbamoyl Pyridone HIV-1

Integrase Inhibitors 3. A Diastereomeric Approach to Chiral Nonracemic Tricyclic Ring Systems and the Discovery of Dolutegravir (S/GSK1349572) and (S/GSK1265744),” 56 J. MEDICINAL CHEMISTRY 5901–16 (2013) (“Johns”) (EX-1041) at 5902.

54. RAL was a new class of antiretroviral drug in 2013, and it was the first FDA-approved INSTI, marketed as Isentress[®] which was a tablet containing 400 mg of RAL in a tablet to be given twice-a-day (BID). Isentress Label (EX-1016) at 1, 7 ; EVG followed as a component in Stribild[®] and allowed for once-a-day (QD) administration with food at a 150 mg dose when combined with 150 mg of COBI (as a pharmacokinetic (PK) booster). Stribild Label (EX-1019) at 1, 22–23.

55. And in August of 2013, Tivicay[®] became available with a 50 mg dose of DTG for once-a-day (QD) administration, which (like RAL) did not require co-administration a with PK booster. *See* Tivicay Label (EX-1022) at 1; *see also* Triumeq Label (EX-1024) at 1; Shah et al., “Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV,” 34(5) PHARMACOTHERAPY 506–20 (2014) (“Shah”) (EX-1023) at 506; Dorothy E. Dow & John A. Bartlett, “Dolutegravir, the Second-Generation of Integrase Strand Transfer Inhibitors (INSTIs) for the Treatment of HIV,” 3 INFECTIOUS DISEASES & THERAPY 83–102 (2014) (“Dow”) (EX-1017) at 83.

56. In 2009, Serrao et al. published a review article discussing *inter alia* RAL, EVG, and the birth of the so-called “me-too” HIV-1 INSTIs. Serrao et al., “Raltegravir, elvitegravir, and metoogravir: the birth of the “me-too” HIV-1 integrase inhibitors,” 6 RETROVIROLOGY, Art. 25, 1–14 (2009) (“Serrao”) (EX-1018). At the time of publication, only RAL (MK-0518) had been approved in the U.S., while EVG (GS-9137) was a known INSTI still under clinical development. Serrao describes the birth of the β -diketo acid (“DKA”) pharmacophore class of INSTIs that resulted in the discovery and later approval of RAL. Serrao (EX-1018) at 2. A POSA would understand a pharmacophore to be the functionalities in a molecule that are responsible for its biological activity. Each of the DKA INSTIs discussed in Serrao were understood to be capable of coordinating metal ions in the active site of HIV-1 integrase (“INST”), though these INSTIs possessed different chemical arrangements surrounding the pharmacophore itself. *Id.* (see e.g., Figure 1 (below) providing the chemical structures of known DKA INSTIs including EVG (GS-1937), with the pharmacophores circled in red.



57. Serrao explains that “comparable to every innovation, promising new drugs will be quickly followed into the market by multiple analogs, most striking in their similarity to the original.” Serrao (EX-1018) at 3. These analogs are referred to as “me-too” drugs. Serrao then references an average cost (at the time) of \$2 billion to bring a single drug to market, and the “temptation for

pharmaceutical companies to forego the pains of innovation and rather simply modify current leads.” *Id.*

58. RAL was also known in the art as a “first generation” INSTI. Dow (EX-1017) at 83. Though it provided low nanomolar and strand transfer selective *in vitro* inhibition of INST, multiple treatment resistant-mutations had surfaced in both treatment-naïve and treatment-experienced patients. Serrao (EX-1018) at 3–4 (referring to RAL as a modern blockbuster but detailing mutations in INST that confer robust viral resistance to the drug).

59. Most of the RAL “me-too” drugs shown in Figure 1 (above) comply with the general DKA pharmacophore structural requirements and contain a hydrophobic aromatic (usually fluorobenzyl) component (*see* left side of compounds), and a variable acidic component based on a DKA core (*see* right side of compounds). Serrao (EX-1018) at 2 (Figure 1). This DKA linker usually consists of a gamma-ketone, an enolizable alpha-ketone, and a carboxylic acid (or an acidic or basic bioisostere thereof). *Id.* Based on conclusions drawn from docking studies, Serrao proposed that most of the DKA analogues of RAL may experience a low success rate against RAL-resistant HIV strains. *Id.* at 1 (Abstract). Indeed, this had already been shown for EVG, which provoked the same viral-resistant mutations as RAL in addition to resistance to other mutations. *Id.* at 5, 9–11. For at least this reason, Serrao considered EVG to be a “me-too”

INSTI analog of RAL, and therefore a “first generation” INSTI, as opposed to “second generation” INSTI as defined below. *Id.* at 4–5.

60. Serrao explained the requirements for classifying an INSTI as a “second generation drug,” which included one or more of the avoidances of cross-resistance, novel active substituents, and improved potency and/or decreased toxicity. Serrao (EX-1018) at 4 (Figure 2) (below).

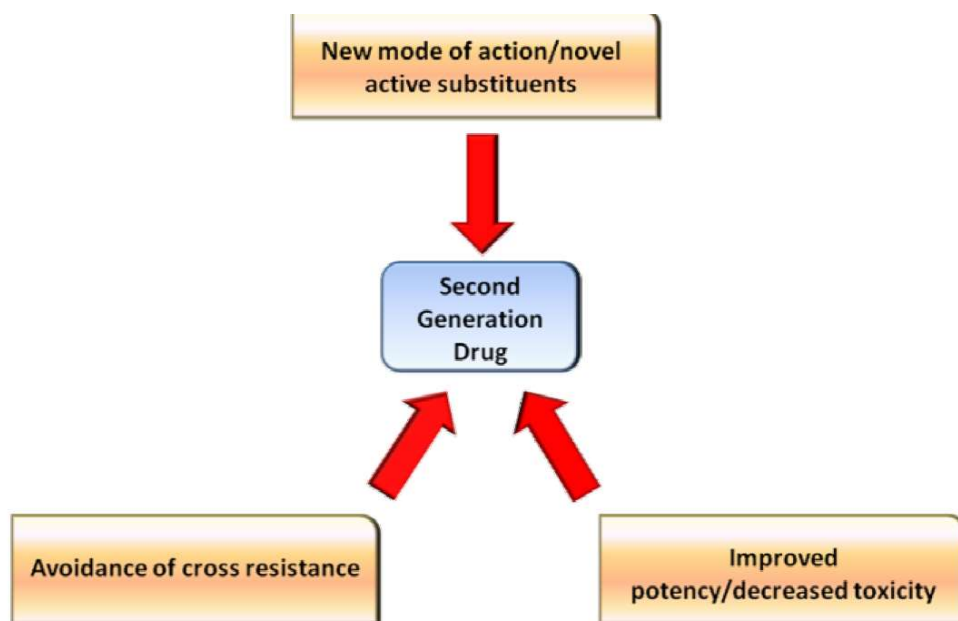
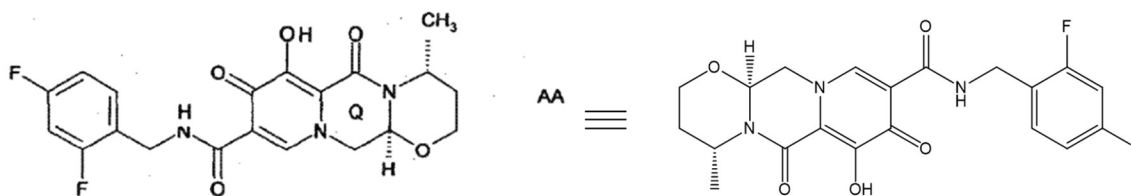


Figure 2
Requirements for "second generation drug" classification.

EVG was not considered to fulfill these requirements, at least because of the large potency losses observed when testing it against a number of INST mutants, including those already resistant to RAL. *Id.* at 9–11, *see e.g.*, Table I (showing that EVG lost potency on the order of 10–100 times for a significant number of

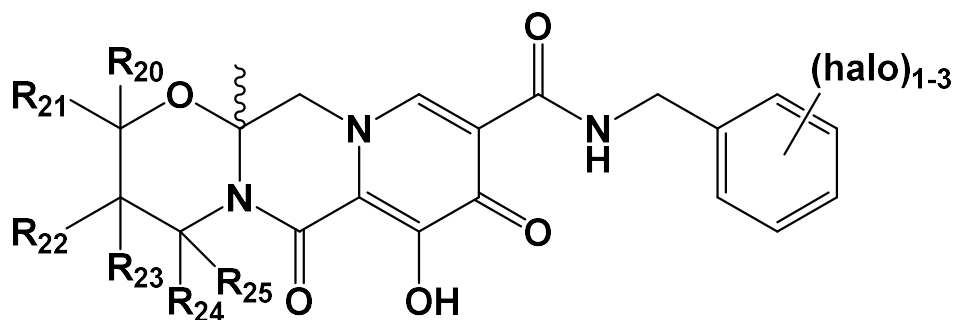
INST mutants); *see also id.* at 5 (noting that EVG provoked the same viral resistance mutations as RAL), 9 (noting that *inter alia* EVG will ultimately experience a low probability of success in viral eradication due to its resistance profile; EVG had already been shown to exhibit near identical resistance profile to RAL).

61. Shortly after Serrao published, a new structural class of INSTIs were disclosed to the public by GlaxoSmithKline (“GSK”) and Shionogi & Co (“Shionogi”). This class included the specific compound **AA** (later known as DTG as approved in 2013).



Compound AA - Dolutegravir (DTG)

See WO 2010/068253 (WO ‘253) (EX-1021) at 2, 7 (right structure above represents compound **AA** (DTG) in the orientation of ’802 patent, claim 1), *see also id.* at 16–22 (synthesis of DTG and its sodium salt). The general INSTI class was also claimed in a patent issued in 2012 (and in force until 2027), which claims a subgenus having the following structure.



See U.S. 8,129,385 ('385 patent) (EX-1057), 177:40-178:36 (claims 1-2 (structure above corresponds to claim 1 generic structure as limited by claim 2)) (claim 2 above provides variables not set by the claim; R₂₀-R₂₅ are defined in claim 1 as hydrogen, C₁-C₈-alkyl, C₆-C₁₄-aryl-C₁-C₈-alkyl, C₆-C₁₄-aryl, or alkoxy); *See also* WO 2006/116764 (WO '764) (EX-1052) at 2-11 (describing broader genera for the INSTIs).

62. At the time of Tivicay[®] approval in 2013, researchers at GSK and Shionogi had also published on the discovery of DTG from an initial compound set designed to bind to the IN active site according to the two-metal chelation model (shown below), i.e., the known model for the DKA INSTIs. Johns (EX-1041) at 5901 (Introduction, Figure 1).

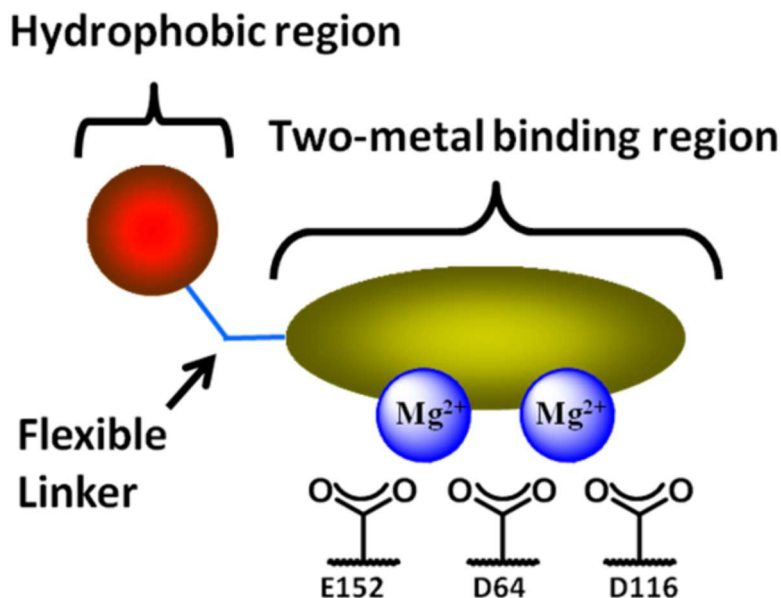


Figure 1. Two-metal binding pharmacophore model for HIV-1 integrase strand transfer inhibitors.

Johns refers to the FDA-approved INSTIs RAL and EVG, noting that:

[B]oth have distinct limitations and leave room for meaningful improvements for patients. Raltegravir is the first-in-class INSTI but requires a high dose of 400 mg twice daily (BID). In addition, three major [INST] signature mutation pathways result in substantial loss of potency of RAL and render it ineffective against these viruses. EVG treatment engenders slightly different resistance pathways, but there is extensive EVG cross resistance among RAL failures. The major advance that EVG provides is the option for once daily dosing. However, this requires the use of a pharmacokinetic boosting agent such as ritonavir or cobicistat to inhibit CYP3A4, which is a primary route of metabolism for EVG.

Johns (EX-1041) at 5901–02.

63. According to Johns, this more recent class of INSTIs, which led to the discovery and development of DTG (compound **3**), was designed to provide more optimal affinity for the IN active site and provide superior *in vitro* inhibitory

affinity compared to related metal-binding scaffolds. Johns at 5902. DTG (compound **3**) was discovered after extensive SAR research from initial monocyclic derivatives such as compound **5** into more elaborate bi- and tricyclic versions (e.g., compounds **6**, **7**, and **8**) as shown in Figure 3 (below; annotated to identify carbons C-2 to C-5, highlighting the two metal binding sites (M1 and M2) of INST, and to add lone electron pairs to the oxygen atoms participating in chelation with the two metal binding sites (M1 and M2)).

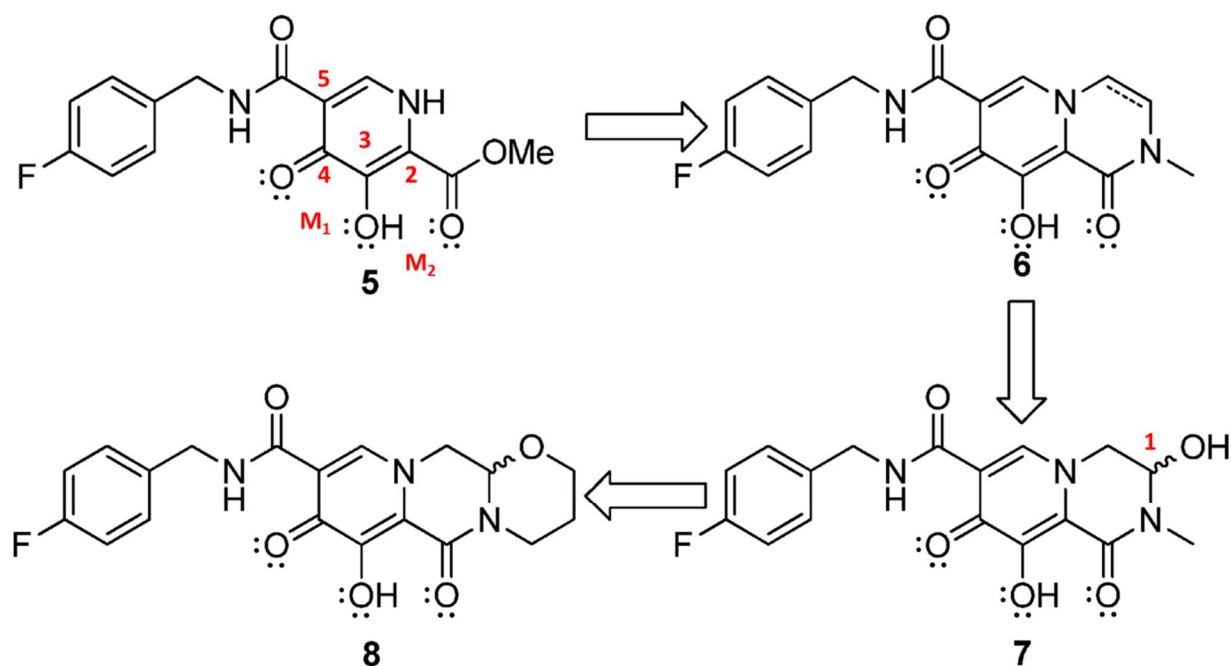


Figure 3. Evolution of the carbomoyl pyridone series.

Johns (EX-1041) at 5902.

64. According to Johns “a key feature of this novel carbamoyl pyridine motif was the intentional use of a triad of all oxygen-derived lone pairs to serve as the chelating donor atoms toward the two divalent metals (M1 and M2 in Figure 3

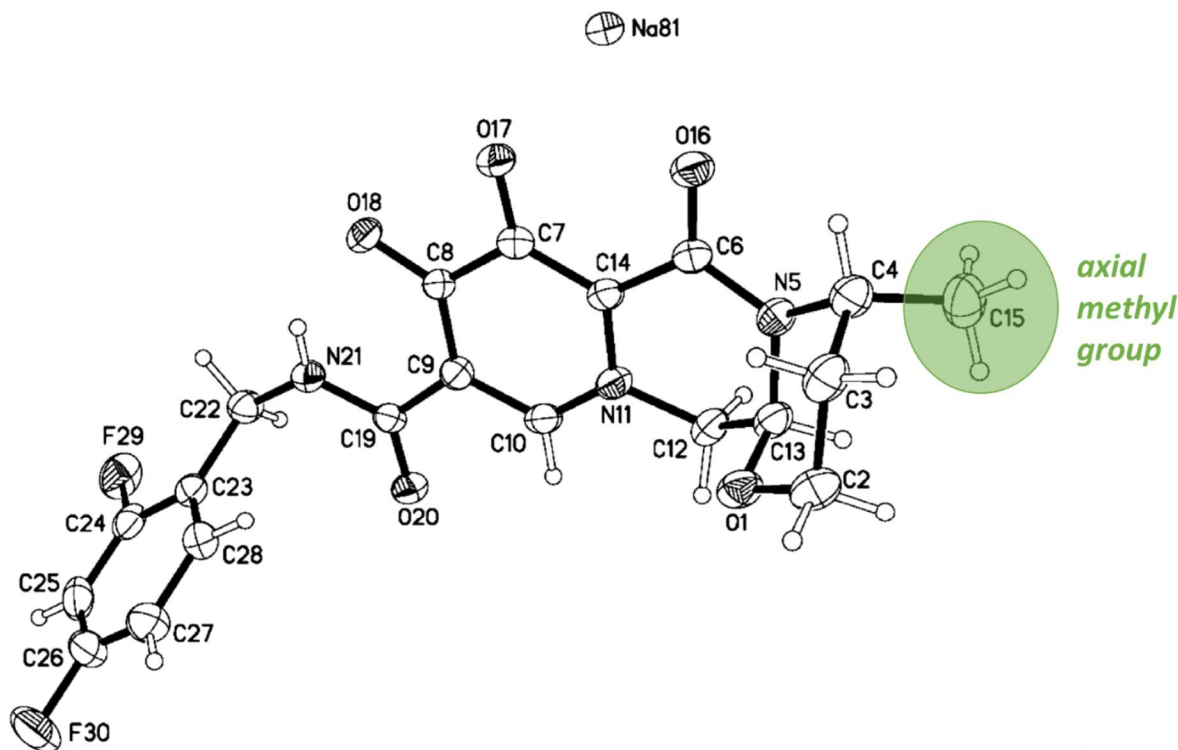
above).” Johns (EX-1041) at 5902. Johns also states that “it is noteworthy that in the case of our system, the 5- and 6-membered rings formed upon metal coordination (M1 and M2 in Figure 3), are reversed relative to the pyrone system [of RAL] ...due to the different positioning of the benzyl carboxamide [linker] (bound to C-4 in RAL (Figure 2) and C-5 in compound **5** (Figure 3)).” *Id.*

65. As shown above in Figure 3, this INSTI series evolved into bicyclic derivatives represented by compound **6** that improved potency toward wild-type INST but maintained problematic resistance mutations. Johns (EX-1041) at 5902. However, when the bicyclic system was further substituted with a hydroxyl moiety on the saturated piperazinone ring (as in **7**, i.e., position 1 as shown in Figure 3 above) significant improvements in the potency against a key integrase mutant (at Q148) were observed. *Id.* Then, to better control stereochemistry, the hydroxy group in compound **7** was tethered into a tricyclic system to provide an aminor, as in compound **8**. *Id.*

66. Compound **8** is a chiral molecule existing as two enantiomers (represented by the wavy line connecting the C-1 carbon to oxygen). After separately testing each enantiomer, Johns observed no chemical stability issues with the aminor (i.e., no interconversion between enantiomers was observed). According to Johns, these isomers had almost identical antiviral activity ($^{pHIV}IC_{50}$ = 2.2 nM for the R-isomer and 1.9 nM for the S-isomer with 1.9 nM for the

racemate) but showed a differential loss in potency against a key Q148K mutant, with the S isomer showing a modest 2.4-fold potency loss (FC) while the R analogue had an 11-fold potency loss. Johns (EX-1041), 5903 (Table 1). As a comparison, RAL (compound **1**) showed a 79-fold loss of potency in the same assay system. Johns (EX-1041) at 5905 (Table 2).

67. Further SAR structural modifications led to DTG (DTG (compound **3**; as disclosed in Johns)). Of all compounds tested in Johns, DTG (compound **3**) provided the smallest loss in potency toward the Q148K mutant (FC = 0.4). *See* Johns (EX-1041) at 5905 (Table 2 - $^{pHIV}IC_{50}$ (compound **3**) = 1.7 nM), 5908 (Table 4). Johns also provided an x-ray crystal structure of DTG sodium, showing DTG's C15 methyl group in an *axial* position on its associated 6-membered ring. *Id.* at 5906 (Figure 4 (below)) (*see* C15 methyl group bound to the C4 carbon on the right most ring, as indicated in green).



A POSA would have appreciated from Johns that placement of the C-4 (as opposed to the C-2/C-3 positions for other compounds in Table 2) methyl group in an *axial* orientation was an important feature for maintaining activity toward the key Q148K mutant that showed resistance to both RAL and EVG. *Id.* at 5905 (Table 2) (compound **3** with an axial C-4 methyl group maintained potency toward Q148K better than all other compounds tested).

68. In sum, of all the compounds tested in Johns, DTG (compound **3**) provided the best ability to maintain potency toward resistant strains of INST which had not been obtained for either RAL or EVG before. As shown in Figure 6 (below), DTG (blue squares in graph) maintained activity against several key INST mutations (as well as others), including the mutations known to confer resistance to

RAL and EVG, most notably Q148K and Q148R, and also EVG resistant strains such as E92Q, N155H, N155S, and N155T. Johns at 5909 (disclosing DTG as having a better resistance profile than compound **4** (S/GSK1265744) as disclosed in Figure 6 of Johns (below)).

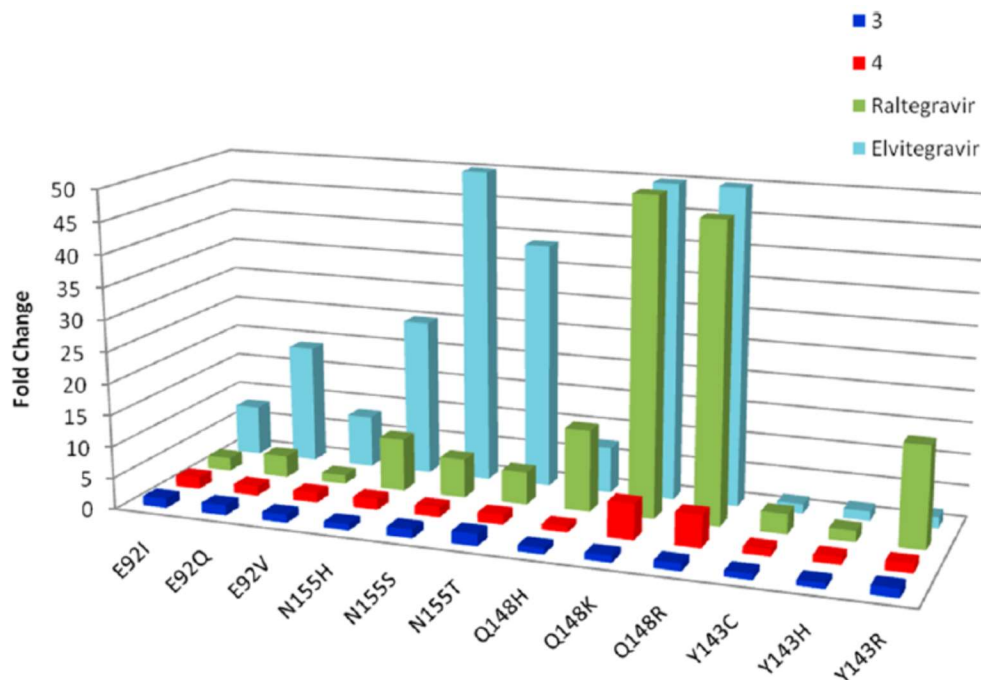


Figure 6. Comparison of Fold Change in HeLa cell IC_{50} of **3** and **4** Against Key IN Resistance Mutations.

Based on its much improved resistance profile, DTG (compound **3**) progressed into animal studies (as its sodium salt) and was found to be suitable for clinical evaluation, where the preclinical data presented in Johns (*see* Table 6 below) demonstrated robust low-dose once-daily PK and associated clinical efficacy. *Id.* at 5909–10.

Table 6. Pharmacokinetic Parameters for Rats, Dogs, and Cynomolgus Monkeys for 3 and 4^a

compd	species	% unbound	Cl ^e (mL/min/kg)	T _{1/2} (h)	V _{dss} (L/kg)	%F	C _{24h} /PAIC ₉₀ ^c
3	rat	0.1	0.23	6.2	0.1	34	18
3	dog ^d	4.6	2.2	5.2	0.3	35	4.6
3	cyno ^d	0.9	2.1	6.0	0.3	25	0.8
3	human	0.7					
4	rat	<0.1	NR ^b	>18	NR ^b	NR ^b	57
4	dog	0.7	0.34	5.7	0.14	8	0.9
4	cyno ^d	0.3	0.32	4.0	0.09	6.2	1.3
4	human	0.4					

^aData represent the mean of at least three replicates. ^bNot reportable due to prolonged exposure and extrapolation in excess of 20% of the total AUC. ^cThe PAIC₉₀ value used was the clinical target of 64 ng/mL for 3 and 166 ng/mL for 4. ^dData represent the average of two independent experiments. ^eLiver blood flow (lbf) = 55/31/44 mL/min/kg for rat/dog/monkey²³

As shown above in Table 6, DTG provided a half-life ($t_{1/2}$) in the range of 5.2–6.2 h depending on the animal studied, and also good oral bioavailability ($F\% = 25$ –35) even though it was dosed as a crystalline solid and its formulation had not yet been optimized. *Id.* at 5909. Related compound 4 showed a significantly lower oral bioavailability ($F\% = 6.2$ –8), though it was administered as a free acid and not as a more soluble salt of its acidic hydroxyl moiety. *Id.*; *see also id.* at 5910 (noting that compound 4 was being evaluated in long-acting parenteral formulations for once-a-month administration, whereas DTG was in the clinic at a dose of 50 mg for once-a-day administration, i.e., oral administration, to naïve and experienced patients and 50 mg twice daily for INSTI-resistant patients).

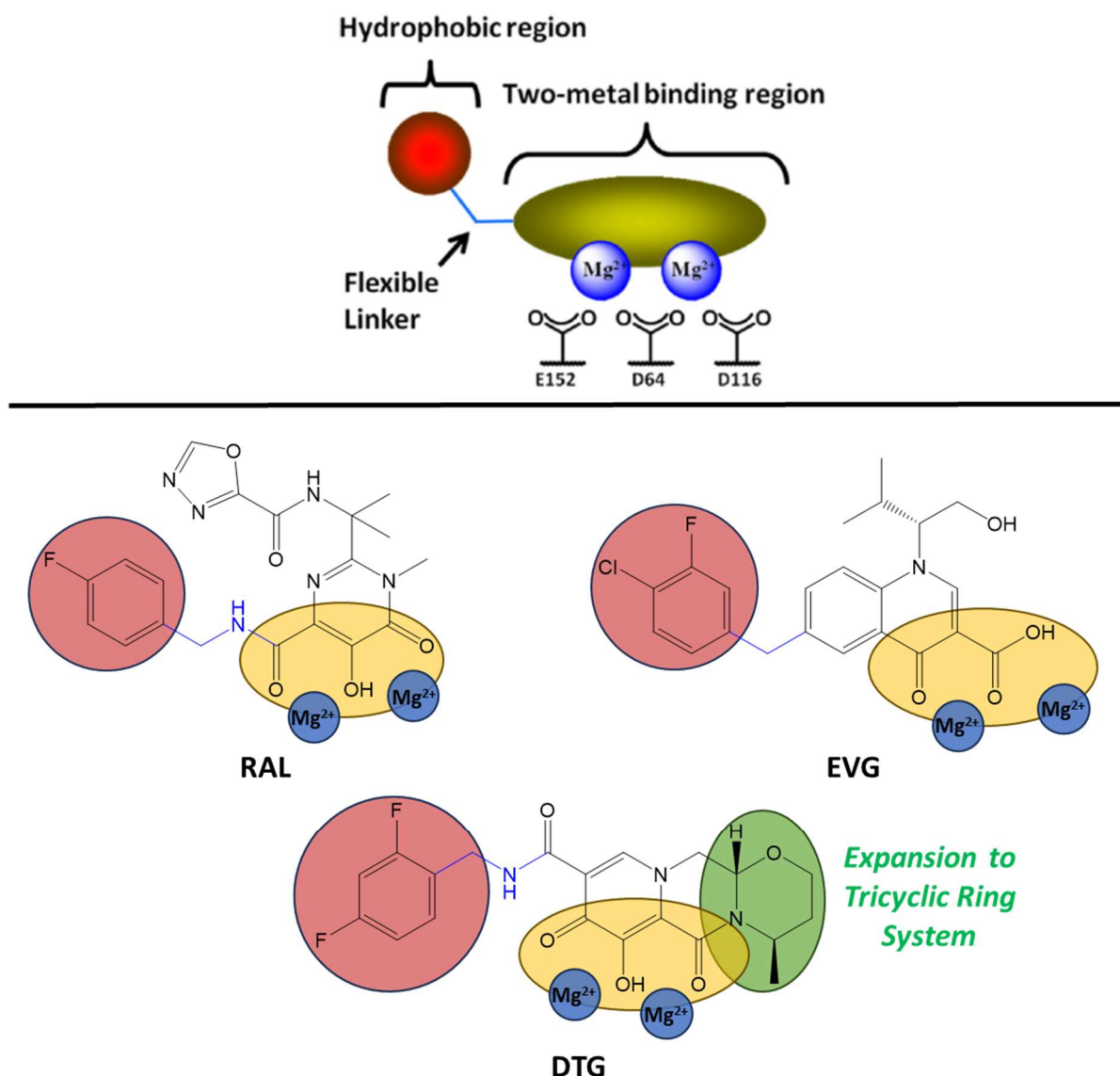
69. In conclusion, Johns stated the following:

By using clinically relevant viral mutations early in the compound triage, we have selected compounds that can add value in the clinical setting for both naïve and experienced patients wherein [INST] mutations may exist. Additionally, by choosing compounds with optimal potency and PK properties likely directly related to serum protein-binding effects, we have discovered INSTi's that have since been proven to be once-daily low-dose antiviral agents. Furthermore, in vitro metabolism and P450 data suggested early that both

compounds would not be subject to significant P450-mediated metabolic pathways and would not require the codosing of a PK enhancer which is necessary for once-daily EVG. The lack of P450 inhibition by the carbamoyl pyridine scaffold is believed to predict a minimal risk for drug–drug interactions. These new INSTi's are potent against wild-type viruses and those containing RAL and EVG signature mutations, thus establishing further differentiation.

Johns (EX-1041) at 5910.

70. Provided below is an illustration I prepared showing the binding of RAL, EVG, and DTG to the active site of INST through magnesium ion coordination. The key expansion of DTG to a tricyclic ring system (compared to the monocycle and bicyclic rings of RAL and EVG, respectively) is highlighted below in green.



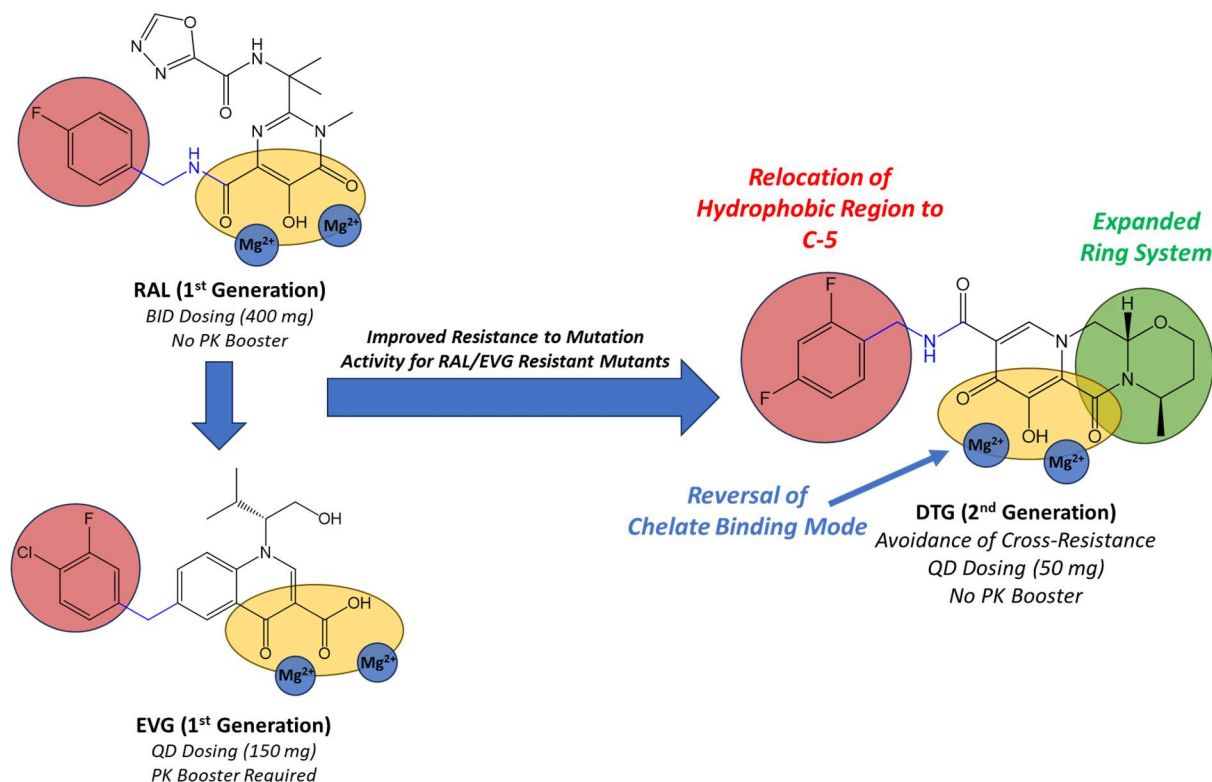
By expanding into a tricyclic scaffold, DTG provided a much improved ability to maintain potency against key mutations of INST, and thus had solved at least one of the key criteria for a “second generation” INSTI described in Serrao, i.e., the avoidance of cross resistance. *See Serrao* (EX-1018) at 4 (Figure 2) (above). It also contained other novel features, including the change from a 6-5 metal chelate (as in RAL) to the 5-6 chelate present in DTG, a repositioning of the hydrophobic

region from the bottom left in RAL and EVG to the top left in DTG, and the expansion of the monocyclic system of RAL and the bicyclic system of EVG into a tricyclic ring system of DTG, thus meeting an additional criteria for a second generation INSTI from Serrao.

71. Indeed, by 2014, DTG had been identified as a true second generation INSTI by others in the field. *See* Shah (EX-1023) at 506 (Abstract) (RAL and EVG have a low genetic barrier to resistance; DTG has a higher barrier to resistance), *id.* (identifying DTG as a “second generation” INSTI); Dow (EX-1017) at 83 (Abstract) (“DTG is the only ‘second generation’ INSTI with FDA approval; it has potential advantages over the ‘first generation’ INSTIs, including unboosted daily dosing[, i.e., no need for a pharmacokinetic booster such as COBI], limited cross resistance with raltegravir and elvitegravir, and a high barrier to resistance.”).

72. In sum, researchers at GSK and Shionogi conducted extensive studies, including SAR investigations, in order to improve upon prior DKA-derived INSTIs such as RAL and EVG. By changing the location of the hydrophobic region on the DKA pharmacophore, modifying the chelating donor atoms to a 5-6 arrangement (as opposed to the 6-5 arrangement for RAL and EVG), and expanding into a tricyclic ring system, DTG finally provided the improvements needed to advance INSTIs into the next generation, including improved potency toward resistant

mutants of INST and an avoidance of cross-resistance that was observed with the “first generation” INSTIs RAL and EVG. This improvement through key structural modifications is summarized by the following illustration.

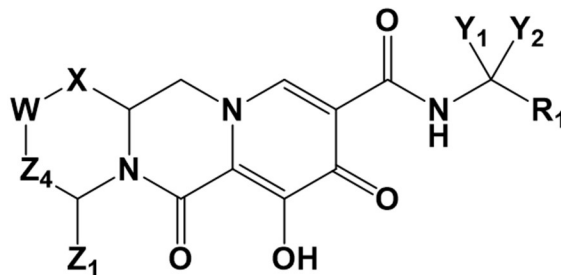


VI. THE EMERGENCE OF GILEAD'S NEXT GENERATION INSTIS AND THE SELECTION OF BICTEGRAVIR AND BICTEGRAVIR SODIUM

73. Around the same time as the approval of ViiV's DTG product Tivicay[®] in 2013, Gilead filed an international (PCT) application directed to “Polycyclic-Carbamoylpyridone Compounds and Their Pharmaceutical Use,” which later published as WO 2014/100323 (EX-1005) (“WO '323”) on June 26, 2014. WO '323 disclosed a class of compounds defined by Formula (I) (below)

and their use in the treatment of HIV infection. WO '323 (EX-1005) at [57]

Abstract.

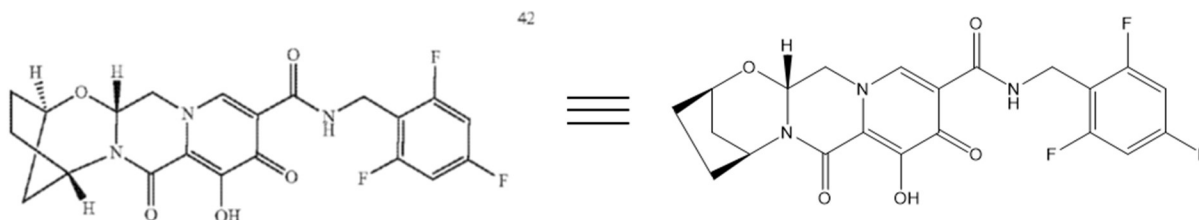


Formula (I)

Id. The compounds of Formula (I) contain a tricyclic ring system with a two-metal chelate binding site (left hand side of structure) and a methylene amide linker (i.e., C(=O)-NH-C(Y₁)(Y₂)-; right-hand side of structure) connected to a halogen substituted phenyl ring (R₁). *Id.* at 3:13–4:4 (defining R₁ as a “phenyl substituted with one or more halogens”).

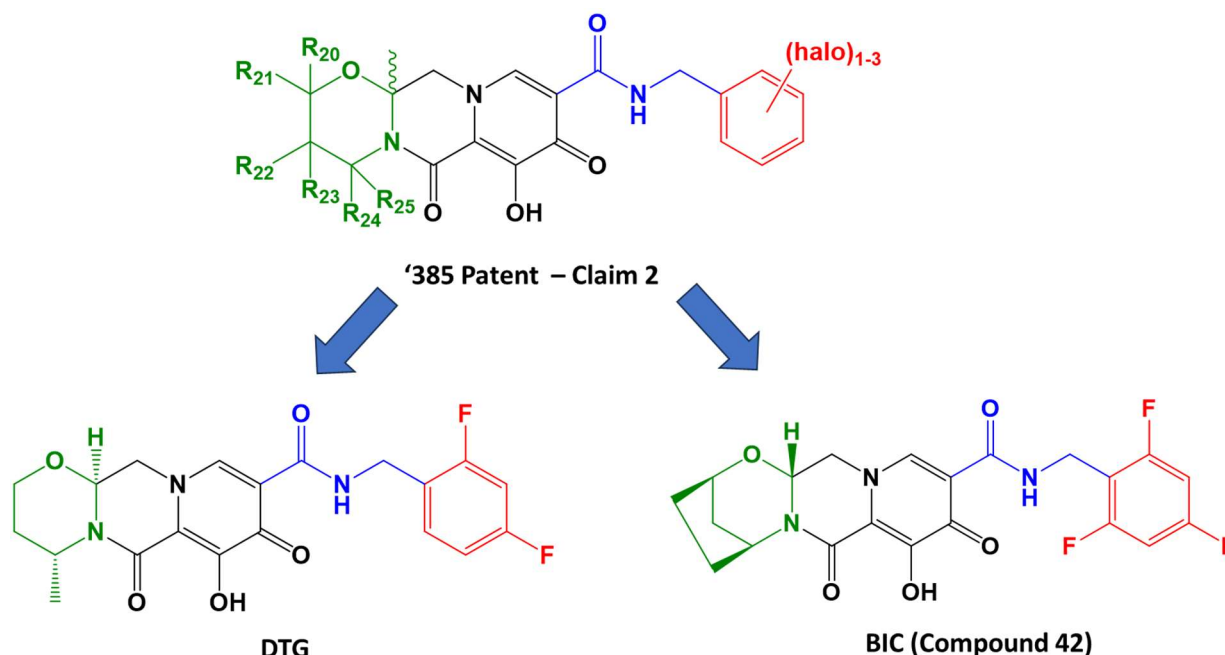
74. According to WO '323, these compounds “may be used to inhibit the activity of HIV integrase [(INST)] and may be used to reduce HIV replication.”

Id. at 3:8–4:4. WO '323 discloses ~100 specific INSTI compounds of Formula (I), including compound **42** which I understand became the INSTI bictegavir (“BIC”) in Gilead’s Biktarvy® approved by the FDA in 2018 (*see below* (left structure = compound **42** (BIC) as appearing in WO '323; right structure = compound **42** (BIC) in the orientation of '802 patent, claim 1)). *Id.* at 99:8–101:25 (Example 42).



Compound 42 (BIC)

The illustration below shows the general structure claimed in the '385 patent (i.e., claim 2) along with the structures for DTG and compound **42** (BIC), each annotated to emphasize their hydrophobic (red), metal chelate region (black), expanded ring system (green), and linker (blue).



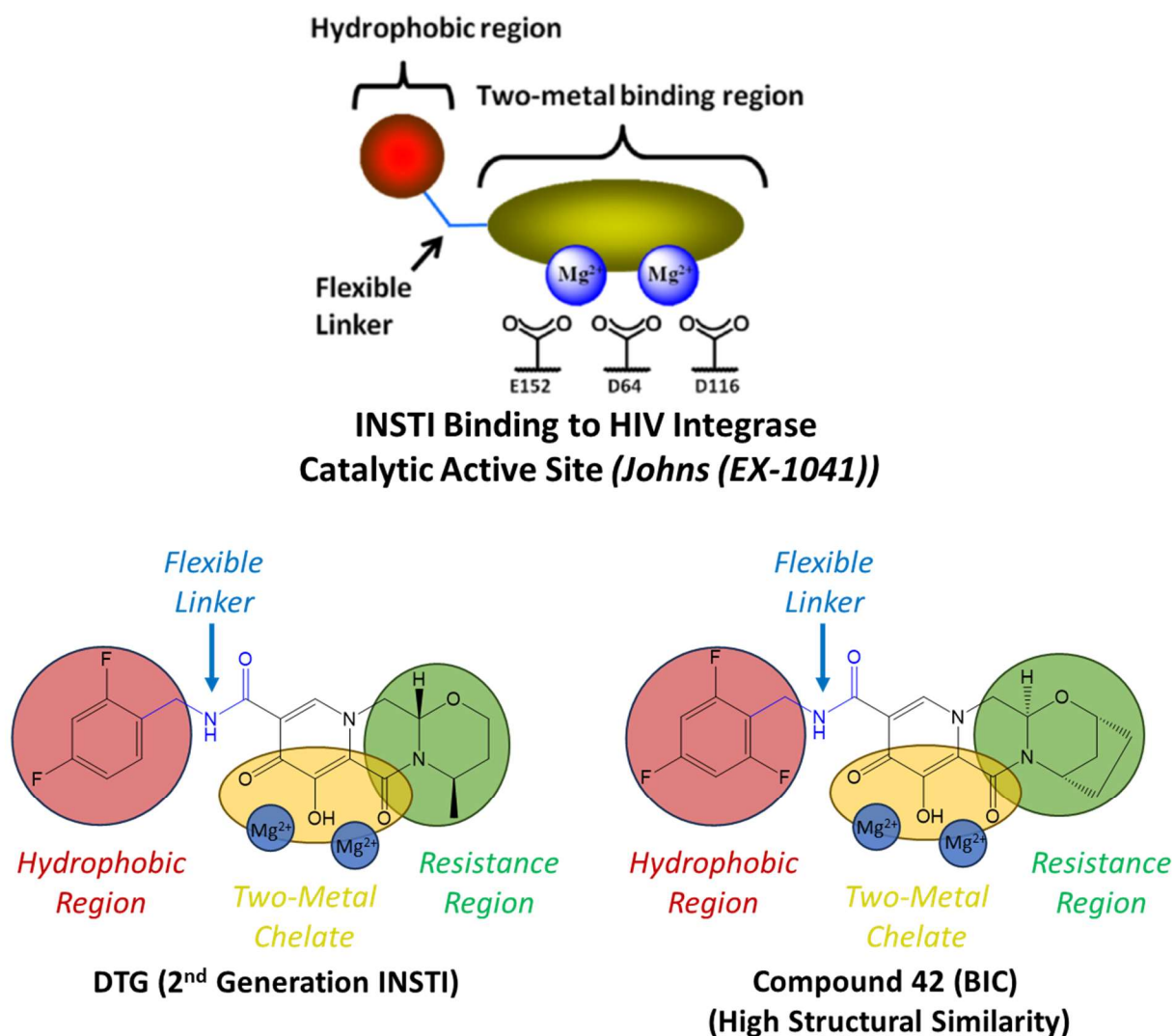
75. In my opinion, a POSA would have immediately appreciated that compound **42** (BIC) bore a close structural similarity to the “second generation” INSTIs studied by Johns and generally claimed in the '385 patent, including the resistance optimized INSTI DTG. This includes an identical metal chelate region

(5-6 arrangement as discussed above; black), an identical linker (blue), a structurally similar fluoro-substituted phenyl hydrophobic region (red) and a structurally similar 6-membered aminal ring system (green) (previously designed by GSK and Shionogi to avoid cross-resistance).

76. The only structural differences between DTG and BIC are: (1) the addition of a fluorine atom to the phenyl group (red) in BIC to provide three fluorine atoms on BIC compared to two fluorine atoms on the phenyl group (red) in DTG; (2) in the resistance region, the addition of a single carbon atom to connect the C-4 methyl group of DTG to the ring carbon adjacent to oxygen in DTG to form the two carbon bridge in BIC (green bold wedges); and (3) the absolute stereochemistry of the methyl (DTG) and methylene (BIC) groups attached to the 6-membered aminal (green; DTG dashed wedge, BIC bold wedges).

77. The following illustration shows how BIC and DTG (structures realigned to fit the binding model) would have been expected to provide similar benefits in view of the two-metal binding model that was well known in the art prior to November 9, 2015.²

² The chemical structures of DTG and BIC have been reoriented to correspond with the binding model in Johns (Ex-1041).



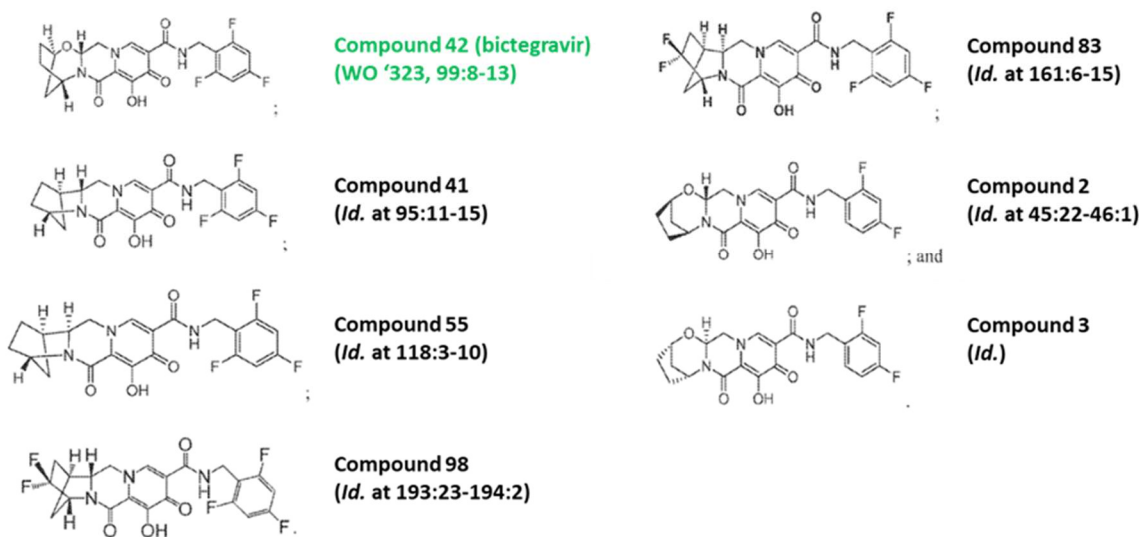
Given that DTG and BIC were both known INSTIs and would have aligned with the INST in a similar fashion, their overall structural similarities would have provided a POSA with the expectation that BIC would have physicochemical and biological properties similar to DTG. This includes a similar binding mode to the active site of INST (yellow above), and an expected high genetic barrier to

resistance and an ability to maintain activity against INST mutations in view of its structurally similar “resistance region” (green).³

A. The Selection of Bictegravir from WO '323

78. WO '323 claims compound **42** (BIC) in a small group of seven INSTI compounds. WO '323 (EX-1005) at 240–41 (claim 32 (annotated below to provide compound numbers from the specification)).

32. A compound of claim 1 selected from:



In my opinion, a POSA would have been particularly drawn to this small group of compounds as a subclass of Gilead's Formula (I) INSTIs and considered them to

³ A POSA would have further appreciated that the conversion of DTG's C4 methyl group (*see* Johns (EX-1041) at 5906 (Figure 4) (crystal structure of DTG sodium) to a two-carbon bridge (as in compound **42**) would be expected to lock the methyl carbon substituent into the *axial* position deemed important to the potency of DTG itself. This would bolster a POSA's expectation that compound **42** would at least maintain (and perhaps improve upon) the high genetic barrier to resistance already observed for DTG.

be of particular importance. Further details from the WO '323 specification make this selection of compounds readily apparent.

79. First, each of the above seven INSTI compounds demonstrated antiviral activity in an assay utilizing HIV-infected MT4 cells, an established metric indicating each compound was potentially useful for “treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms.” WO '323 (EX-1005) at 212–16. Each compound was also found to be particularly potent in the assay. The specification reports each producing EC_{50} values in the range of 1.5–2.5 nM, placing them as among the most potent compounds studied. *Id.* (EC_{50} of all tested compounds ranged from 1.5–422 nM).

80. Second, WO '323 discloses a pharmacokinetics (PK) study of only 11 specific compounds, including all seven of the compounds of claim 32, after IV administration of each compound to beagle dogs. *See id.* at 222–24 (including Table 4 below (IV study emphasized in blue; oral administration study highlighted in yellow; claim 32 compounds emphasized in red)).

Table 4

Compound #	CL (L/h/kg)	V _{ss} (L/kg)	MRT (h)	F (%) aqueous suspension	C _{max} (μM) aqueous suspension	AUC (μM*h) aqueous suspension
98	0.047	0.16	3.3	n/a	n/a	n/a
83	0.161	0.38	2.4	n/a	n/a	n/a
55	0.058	0.24	4.2	n/a	n/a	n/a
77	0.300	0.64	2.2	n/a	n/a	n/a
41	0.015	0.11	7.5	10.7	2.4	16.3
42	0.020	0.15	7.1	28.0	4.5	28.6
47	0.014	0.10	7.4	12.6	2.8	20.4
8	0.498	0.87	1.8	n/a	n/a	n/a
7	0.510	1.20	2.3	n/a	n/a	n/a
3	0.047	0.23	4.9	18.7	1.2	9.2
2	0.030	0.20	6.5	40.7	7.8	66.1

IV Administration  Oral Administration

81. Here, the eleven compounds were first assessed for clearance (CL), steady state volume of distribution (V_{ss}), and mean residence time (MRT) after IV administration. As explained above, (see Paragraphs 31, 33–34 above) a compound's half-life ($t_{1/2}$) is directly linked to its volume of distribution (V) and its clearance (CL) according to the following equation:

$$t_{1/2} = \frac{(0.693 \times V)}{CL}$$

Using the **CL** and **V_{ss}** data from Table 4, a POSA would have calculated the following half-lives for each tested compound (the five compounds having the longest ***t*_{1/2} (h)** values emphasized in bold).

Compound	Half-Life (<i>t</i>_{1/2}) (h)
98	~2.4
83	~1.6
55	~2.9
77	~1.5
41	~5.1
42	~5.2
47	~5.0
8	~1.2
7	~1.6
3	~3.4
2	~4.6

The compounds providing the longest half-lives (compounds **2**, **3**, **41**, **42**, and **47**) also showed the longest mean residence time (**MRT**) according to Table 4 (above).

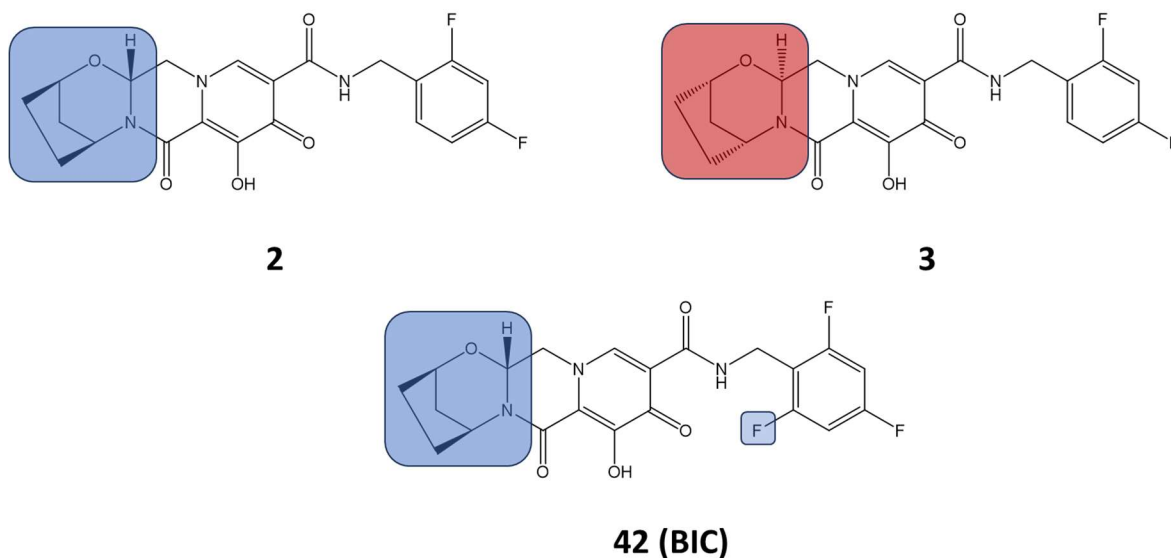
82. As explained above in Section V.D., a POSA would have appreciated that one important goal of INSTI development was to maintain once-a-day administration (like EVG and DTG before), preferably without the need for a pharmacokinetic booster (i.e., COBI as used with EVG in Stribild®). That person would have considered ***t*_{1/2}** and **MRT** as important to that assessment and would have preferred compounds with the longest ***t*_{1/2}** and largest **MRT**. The longest ***t*_{1/2}** and highest **MRT** values from Table 4 are compounds **41**, **42**, and **47**, and a POSA would have preferred them for further study (with potentially also compounds **2** and **3**). Indeed, the remaining compounds **98**, **83**, **55**, **77**, **7**, and **8** provided

significantly shorter half-lives ($t_{1/2}$ = 1.2–2.9 h) and smaller **MRT** values (2.2–4.2 h), and therefore would have been viewed by a POSA as less favorable for once-a-day administration.

83. Third, in the same PK study, only compounds **2**, **3**, **41**, **42**, and **47**, i.e., those with the longest $t_{1/2}$ and largest **MRT**, were investigated further in an oral administration study designed to assess oral bioavailability (**F(%)**), peak plasma concentration (**C_{max}**), and total plasma exposure (**AUC**). See WO '323 (EX-1005) at 223–24 (Table 4) (annotated above in yellow); *see also id.* at 222 (compounds were administered orally as an aqueous suspension with 0.1% Tween 20 and 0.5% HPMC LV100 in Di Water at 1 mg/kg). The tested compounds provided an **F(%)** in the range of 10.7–40.7%, a **C_{max}** in the range of 1.2–7.8 μM , and an **AUC** in the range of 9.2–66.1 $\mu\text{M}\cdot\text{h}$. *Id.* For once-a-day oral administration, a POSA would have desired compounds with higher **F(%)**, **C_{max}** and **AUC** values, given that these values would have established higher concentrations of a compound in the bloodstream. Of the five compounds tested, compounds **42** (BIC) and **2** provided the most desirable **F(%)**, **C_{max}**, and **AUC**. As such, they would have been considered superior candidates for once-a-day oral administration based on their greater bioavailability and the best ability from among the tested compounds to deliver higher blood concentrations for longer periods of time.

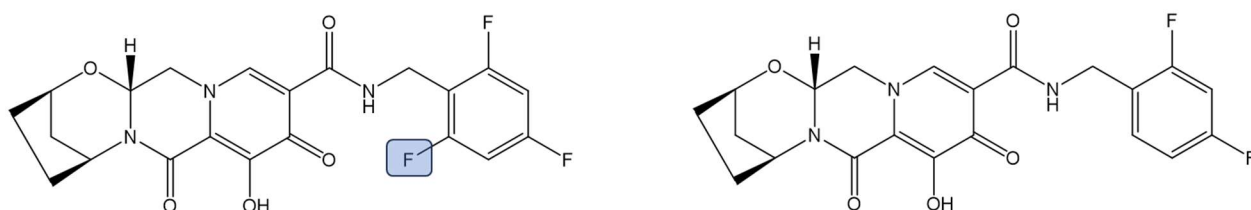
84. In view of the PK data provided in Table 4, a POSA would have identified compound **42** (BIC) as a particularly attractive compound for further study. It provided the longest half-life ($t_{1/2}$) and **MRT** of all compounds tested, and provided good oral bioavailability (similar to that of DTG in Johns; *see* Johns at Table 6 (*supra*); **F(%)** for DTG = 25–35) along with elevated **C_{max}**, and **AUC** values, all desirable for a once-a-day INSTI.⁴ As such, compound **42** along with compound **2** would have been identified as the best candidates for an INSTI intended for oral administration once-daily (as was previously discovered for DTG). In my opinion, a POSA would have viewed compound **42** as providing a

⁴ A POSA would have reasonably expected that the stereochemistry of the bicyclic “resistance region” (leftmost ring in claim 32) of compound **42** (BIC) would be preferred over the opposite stereochemistry. A POSA’s expectation in this regard comes from the comparison of compound **2** and its enantiomer compound **3**. Here, compound **2** (same stereochemical configuration as Compound **42** (BIC)) provided superior **CL** and **MRT**, a superior $t_{1/2}$, and far superior **F (%)**, **C_{max}**, and **AUC** as compared to its enantiomer **3**.



distinct benefit over compound **2** in terms $t_{1/2}$ and **MRT**, while compound **2** would have been viewed as superior in terms of **F(%)** and resultant **C_{max}** and **AUC**. As such, a POSA would have selected each of these compounds based on their distinct respective advantages, but would have dismissed compounds **3**, **41**, and **47** in view of their sub-optimal results in the oral administration experiments from WO '323.

85. In particular, based on its combination of beneficial PK properties, a POSA would have selected compound **42** (BIC) from among the eleven compounds tested in Table 4 and the seven compounds of claim 32 (and also from among the ~100 compounds disclosed in WO '323) for once-a-day administration in the clinic. In my opinion, that a POSA may also have investigated compound **2** does not detract from a POSA's motivation to select compound **42** (BIC) for the same developmental purpose. In fact, a POSA would have considered compounds **2** and **42** to be quite similar when considering their overall balance of relevant PK properties. Moreover, a POSA would have appreciated that these compounds have a large degree of structural similarity, differing only by an additional fluorine atom for compound **42** (as shown below; extra (third) fluorine group highlighted in blue).



Compound 42 (BIC)**Compound 2 (difluoro analogue)**

86. As shown in Table 4, the IV PK data suggested that compound **42** would be superior based on its longer half-life and mean residence time as compared with Compound **2** ($t_{1/2}$ = 5.2 h vs. 4.6 h; **MRT** = 7.1 h vs. 6.5 h), whereas the data indicated better oral PK properties for compound **2** (**F (%)** = 44.7 vs. 28.0; **C_{max}** = 7.8 vs. 4.5; **AUC** = 66.1 vs. 28.6).

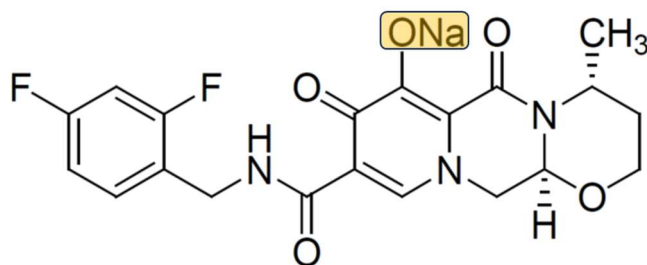
87. As such, it is my opinion that the POSA would have selected compound **42** (BIC) from among the ~100 INSTI compounds from WO '323 as one of the best compounds for once-a-day administration clinical studies. And given its beneficial properties, including low nanomolar potency, longer half-life, larger mean residence time, and good oral bioavailability, a POSA would have reasonably expected that compound **42** (BIC) would be a successful INSTI having advantages similar to structurally related DTG. As such, a POSA would have considered compound **42** (BIC) as a very promising INSTI for use in the treatment of HIV infection, and thus an obvious selection from among the INSTI compounds disclosed in WO '323.

B. The Selection of Bictegravir Sodium

88. WO '323 defines “pharmaceutically acceptable salt” as “a salt that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound.” WO

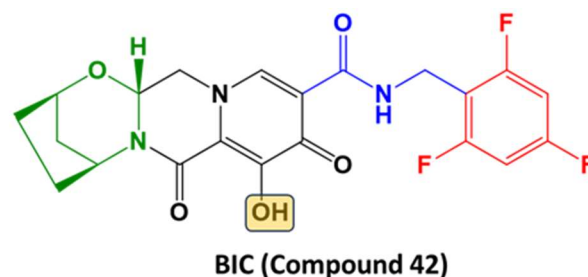
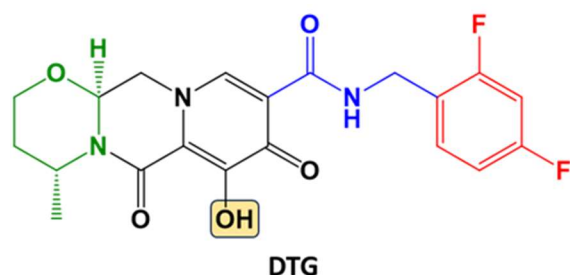
'323 at 14:16-18. This includes “salts derived from an appropriate base, such as an alkali metal (for example, sodium).” *Id.*; *see also id.* at 15:18-20 (metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention, examples being salts containing Li^+ , Na^+ , and K^+).

89. DTG sodium was the preferred form of DTG according to WO '351, and both TIVICAY[®] and TRIUMEQ[®] were marketed with DTG sodium. WO '351 (EX-1006) at 5:10–27;



Tivicay Label (EX-1022) at 14; Triumeq Label (EX-1024) at 17–18; *see also* WO '351 (EX-1006) at 4:12–25 (pointing to the WO 2006/116764 (“WO '764”) (EX-1051) as providing procedures for preparing DTG and its pharmaceutically acceptable salts); WO '764 (EX-1051) at 128–30 (confirming the position of sodium in DTG sodium (as preferred by WO '351) and providing synthetic methods using sodium hydroxide (NaOH)).

90. As shown below, DTG and BIC share significant structural similarity, including an identical metal chelation site (black) containing an acidic hydroxy group (emphasized in yellow).



It is this hydroxy group that interacts with a sodium base (NaOH in WO '764 (EX-1051) to form DTG sodium as preferred by WO '351 and as used in the approved DTG drug products.

91. A POSA would have known that DTG's hydroxy group was the only reasonable functionality for salt formation (as there are no suitable basic sites for conjugate acid salt formation) and would have immediately appreciated the same for compound **42** (BIC). That person would also have expected for the hydroxy groups on DTG and BIC to have similar properties, including similar acidity (both considered weak acids), and that each would form sodium salts (e.g., from NaOH) in the same way. A POSA would have also considered BIC to have a similar acidity to that of DTG, each expected to have a $pK_a \sim 9-10$ (or slightly lower) based on a $pK_a \sim 10$ for phenol and a $pK_a \sim 9$ for 2,4-pentanedione (*see* Section V.C.1-2 above). Indeed, the structural differences between DTG and BIC are distal from their common hydroxy group and therefore would have been expected to have minimal impact on acidity, pK_a and salt formation. Therefore, a POSA would have

reacted compound **42** (BIC) with the strong base NaOH and reasonably expected a stable (and irreversible) salt in direct analogy to DTG sodium as used in Tivicay[®].

92. In sum, a POSA would have been specifically motivated to prepare a pharmaceutically acceptable salt of compound **42** (BIC) with sodium hydroxide (NaOH) to provide BIC sodium and would have expected that it would be stable for the same reasons as the DTG sodium salt used in Tivicay[®]. Indeed, a POSA would have considered sodium salt formation to be a much preferred option (over other salts disclosed in WO '323) for providing a stable (and irreversible) salt with BIC. Thus, a POSA would have selected sodium from among the potential salts described in WO '323 and would have specifically prepared BIC sodium (from NaOH) from among other possibilities given the expectation that the sodium salt would be preferable over than other options given its success with the closely related structure of DTG. Based on the high degree of structural similarity with DTG, and the improved solubility property of DTG sodium relative to the corresponding free acid, a POSA would have also expected for BIC sodium to be more soluble in an aqueous environment than BIC free acid, and thus a more suitable choice for oral administration. *See* Johns (EX-1041) at 5909 (characterizing DTG sodium as a more soluble salt of DTG's acidic hydroxyl moiety). As such, a POSA would have considered BIC sodium to be an obvious

choice for inclusion into a composition for oral administration such as a tablet composition.

93. In addition, Paulekuhn provides a survey on the frequency of different pharmaceutically acceptable counterions appearing in FDA-approved drugs from pre-1982 to 2006. This includes pharmaceutically acceptable cations, of which sodium made up 75.3% of the cations used in APIs overall (62.5 % from 2002–2006). Paulekuhn (EX-1009) at 6667. The sodium cation also accounted for 65.3% of all salts used in oral formulations overall. *Id.* at 6668–69. As such, a POSA would have known that sodium was far and above the most common cation to use with acidic drugs, including weakly acidic drugs like DTG and BIC.

94. Further, Bowker discusses the importance of pK_a when selecting potential salt forming counterions, including cations for acidic drugs, and further explains the need for a pK_a difference of at least three units between the ionizable group, e.g., hydroxy group, and the base employed for deprotonation, i.e., salt formation. Bowker (EX-1008) at 165–66. This represents a difference of acidity of at least three orders of magnitude. A ≥ 3 difference in pK_a was said to be especially important for particularly weak acids to prevent the salt from equilibrating with the free acid (protonated form) in solution. *Id.* Said another way, this is the pK_a difference required to form a stable (i.e., irreversible) salt.

95. Predicting a pK_a of ~ 9 – 10 for DTG and BIC (or slightly lower), a POSA would have looked primarily to bases with a pK_a of ~ 12 or greater, and especially to bases with an even higher pK_a to provide greater confidence of forming an irreversible salt, i.e., that would not dissociate in solution. Even for a weak acid having a pK_a of ~ 8.5 , a POSA would have looked to a pK_a difference >3 to ensure stability and irreversibility. Of the available pharmaceutically acceptable cations, a POSA would have selected sodium hydroxide (NaOH) and potentially also potassium hydroxide (KOH) as the most suitable bases for salt formation.

96. While a POSA may have considered both of these options, they would have been especially drawn to sodium (from NaOH) as the cation for BIC, given that it had already been selected (and preferred) for the structurally similar DTG, and was the most common cation utilized for salt formation with acidic APIs.

97. Thus, a POSA would have been motivated to select the sodium cation (and NaOH as a base) to prepare a salt of BIC. That person would have expected success making BIC sodium given the structural similarities between BIC and DTG, the preference for DTG sodium in WO '351, and the expected >3 pK_a difference between BIC and sodium hydroxide that would have expectedly provided the formation of an irreversible (and stable) salt.

98. In sum, it is my opinion from the viewpoint of a POSA that sodium would have been the most preferred option for salt formation with BIC, and that

BIC sodium would have been preferred over BIC free acid in view of, e.g., its expected increased solubility in aqueous environments (as acknowledged by Johns for DTG), which would have been viewed as a benefit for an oral administration and drug absorption. As discussed above, a POSA would have considered BIC sodium to be an obvious salt to be used in oral dosage forms, e.g., tablets, useful for treating of HIV infection in view of the combination of WO '323 and WO '351, considered in light of the knowledge of a POSA discussed in Section V.

C. The Selection of TAF Fumarate and Hemifumarate, and FTC Free Base.

99. As shown in Section IV of my declaration, each of the Challenged Claims is directed to a tablet containing each of a compound of Formula I (i.e., BIC), tenofovir alafenamide (TAF), and emtricitabine (FTC), each of which may be present as a pharmaceutically acceptable salt thereof. Challenged Claims 2–8 specifically require BIC as a salt and specifically a sodium salt (claims 2, 4, 5, 8) TAF as a salt and specifically TAF fumarate and TAF hemifumarate (claims 4, 5, 8), and emtricitabine as free base (claims 5, 8).

100. WO '351 (discussed above) discloses pharmaceutical combinations containing the “second generation” INSTI DTG along with the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir and prodrugs thereof (TDF and TAF) and the nucleoside reverse transcriptase inhibitor (NRTI) FTC, including pharmaceutical compositions containing each compound, where solid oral dosage

forms are preferred, and tablets are particularly preferred. WO '351 (EX-1006) at [57] (Abstract), 6:24–32 (describing FTC as an NRTI), 9:4–16 (describing tenofovir as an NtRTI), 23:6–8 (stating a particular preference for tablet dosage forms). In a particularly preferred embodiment, the pharmaceutical composition comprises 40 mg to 60 mg of DTG, 150 to 250 mg FTC, 5 mg to 42 mg tenofovir (in particularly TAF), and pharmaceutical excipients. *Id.* at 19:3–12. This includes a specifically preferred embodiment where the composition contains about 50 mg DTG, about 200 mg FTC and about 25 mg of tenofovir (in particular TAF). *Id.* at 19:30–20:12.

101. WO '351 also states a particular preference for DTG as a sodium salt, FTC in the form of its free base, i.e., not in the form of an acid addition salts, and the tenofovir prodrug TAF present in the form of its hemifumarate or fumarate, especially its hemifumarate. WO '351 (EX-1006) at 5:22–27 (DTG), 8:10–11 (FTC), 13:16–18 (TAF).

102. A POSA therefore would have appreciated from WO '351 that FTC as free base and TAF as hemifumarate or fumarate, and especially TAF hemifumarate, as required by one or more of Challenged Claims 4, 5, and 8, were well-known and preferred options for these compounds. In my opinion, a POSA would have selected FTC free base and TAF fumarate and hemifumarate first and foremost over salts of FTC and TAF free base and other salt forms of TAF.

Notably also, WO '323 describes pharmaceutical compositions containing an INSTI, e.g., compound **42** (BIC) and its sodium salt as discussed above, along with an NRTI such as FTC and an NtRTI such as TAF fumarate. WO '323 (EX-1005) at 37:7–11, 38:13–17 (NRTIs), 38:18–21 (NtRTIs), 39:25–27 (disclosing an embodiment where the INSTI, e.g., compound **42** (BIC), is combined with two additional therapeutic agents). Thus, a POSA would have also selected FTC free base and TAF as a fumarate or hemifumarate (and especially TAF fumarate) to combine into a single tablet dosage form along with BIC sodium (as discussed in the preceding section) in view of the combination of WO '323 and WO '351, considered in light of the knowledge of a POSA discussed in Section V.

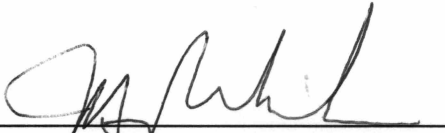
103. In sum, it is my opinion that a POSA would have been particularly motivated to prepare a single tablet containing BIC sodium, TAF fumarate or hemifumarate, and FTC free base as covered by or required by one or more of Challenged Claims 1–8. A POSA would have expected success in the preparation of such a tablet at least in view of Gilead's admission in WO '323 that methods for actually preparing single dosage units such as tablets are “known, or will be apparent, to those skilled in this art.” WO '323, 36:12–18. In view of the analyses and opinions provided above, a POSA would have considered it obvious to prepare a tablet composition containing BIC sodium, TAF fumarate or hemifumarate, and FTC free base.

VII. SUPPLEMENTATION

104. I reserve the right to modify and/or supplement the opinions in this report as appropriate and in response to any new information provided by the Patent Owner, including any allegations of unexpected results or other secondary considerations, and any declarations or additional testimony offered by other expert witnesses.

* * * * *

I hereby declare that all statements made herein based upon my own knowledge and expertise are true and accurate; that all statements made herein based on information and belief are believed to be true and accurate; and further that these statements were made with the knowledge that willfully false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.



Jeffrey D. Winkler, Ph.D.

10-15-24
Date

Appendix A

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- 2021 Fox Rothschild LLP Expert in organic chemistry
(Vitaworks v. Glanbia)
- 2024 Morrison & Foerster LLP Expert in organic chemistry
(John Gregg v. Cooley, LLP, et. al.; Expert Report)
- 2024 O'Melveny & Myers LLP Expert in organic chemistry Allergan and Abbvie vs. MSN Laboratories Private Limited, MSN Pharmaceuticals Inc., and Sun Pharmaceutical Industries Limited
- 2024 Wilson Sonsini Goodrich & Rosati Expert in organic chemistry
Biohaven Therapeutics, Ltd. and Yale University v. Avilar Therapeutics, Inc. and RA Capital Management GP, LLC
- 2023 Finnegan, Henderson, Farabow, Garrett & Dunner, LLP Expert in organic chemistry (AbbVie and Neurocrine)
- 2023 Sterne Kessler Goldstein & Fox Expert in organic chemistry Catalyst Pharmaceuticals Inc and SERB SA v. Teva Pharmaceuticals (C.A. No. 2:23-cv-01190-MCA-JRA (D.N.J.)), Annora Pharma Private Ltd (C.A. No. 2:23-cv-01194-MCA-JRA (D.N.J.)) and Lupin Ltd. (C.A. No. 2:23-cv-01197-MCA-JRA (D.N.J.)); Expert Report and Deposition)
- 2023 Kirkland & Ellis Expert in organic chemistry (Aerie Pharmaceuticals, Inc., et al. v. Gland Pharma Limited C.A. No. 3:22-cv-01359-GC-LHG (Consolidated))
- 2023 Kirkland & Ellis Expert in organic chemistry (Bristol-Myers Squibb v Handa Oncology No. 3:22-CV-06968-TLT)
- 2023 White and Case LLP Expert in organic chemistry (Servier)

2023 O'Melveny & Myers LLP Expert in organic chemistry
Shionogi & Co., Ltd. and Genentech, Inc. v. Norwich Pharmaceuticals Inc. and Alvogen PB R & D LLC

2023 O'Melveny & Myers LLP Expert in organic chemistry
Amgen v. Araxes Pharma LLC and Wellspring Sciences LLC

2022 Baker Hostetler Expert in organic chemistry
Zanoprima Lifesciences, Ltd. v. Hangsen International Group Ltd.,
No. 22-268 (W.D. Tx.)

2022 Quinn Emanuel Urquhart & Sullivan, LLP Expert in organic chemistry
(Pfizer Inc. v. Regor Therapeutics Inc. et al., Expert Report; No. 3:22-cv-190-JAM (D. Conn.))

2022 Covington & Burling LLP Expert in organic chemistry (Zoegenix International Ltd.)

2022 Cooley LLP Expert in organic chemistry (Scilex Pharmaceuticals, Itochu Chemical Frontier Corporation, and Oishi Koseido Co., Ltd. v. Aveva Drug Delivery Systems, Inc. and Apotex)

2022 Cooley LLP Expert in organic chemistry Biofer S. p. A v. Vifor (International) AG 1:22-cv-02180-AMD-SJB (E.D.N.Y.; Expert Report, Deposition and Trial Testimony)

2022 Jones Day Expert in organic chemistry (Puma Biotechnology; Expert Report)

2021 Venable Expert in organic chemistry (Aerie Pharmaceuticals v. Teva; Expert Report)

2021 Quinn Emanuel Urquhart & Sullivan, LLP Expert in organic chemistry
(Takeda Pharmaceutical Company)

2021 Crowell & Moring LLP Expert in organic chemistry (BrendaRx v. Teva, Cephalon and Eagle)

2021 Cravath Swaine & Moore LLP Expert in organic chemistry
(Vitaworks v. Glanbia; Expert Report and Deposition)

2021 Williams & Connolly LLP Expert in organic chemistry (Singular Genomic Systems)

2021 Dechert LLP Expert in organic chemistry (BioDelivery Sciences International, Inc.)

2021 DLA Piper LLP Expert in organic chemistry (Zoegenix)

- 2021 O'Melveny & Myers LLP Expert in organic chemistry (**Abbvie Inc and Allergan Limited; Expert Report**)
- 2021 **Torys LLP Expert in organic chemistry (Viiv Healthcare Company, Shionogi & Co., Ltd., and Viiv Healthcare ULC v. Sandoz Canada Inc. Canadian Federal Court File No. T-827-20)**
- 2020 **Durie Tangri Expert in organic chemistry (John Gregg v. Cooley, LLP, et. al.; Expert Report)**
- 2020 **Cooley LLP Expert in organic chemistry (Liquidia Technologies v. United Therapeutics Corporation; C.A. No. 20-755-RGA (D. Del.); Expert Report, Deposition, Trial Testimony)**
- 2020 **Fish & Richardson Expert in organic chemistry (GlaxoSmithKline v. Epizyme; Expert Report)**
- 2020 **Winston & Strawn (via IMS Expert Services) Expert in organic chemistry (FWK Holdings, LLC, et. al. v. Merck, Glenmark Pharmaceuticals, et. al.; Expert Report)**
- 2019 **McNeely Hare and War Expert in organic chemistry (Amerigen Pharmaceuticals Ltd v. United Therapeutics Corporation)**
- 2019 **Womble Bond Dickinson Expert in organic chemistry (Ferring Pharmaceuticals Inc. et. al. v. Lupin Inc., No 19-cv-913 (D. Del); Expert Report, Deposition)**
- 2019 **Bereskin & Parr (Canada) Expert in organic chemistry (ViiV Healthcare Co., Shionogi & Co., Ltd., and ViiV Healthcare UK (No. 3) Ltd. v. Gilead Sciences, Inc.; Trial Testimony)**
- 2018 **Baker Hostetler/McGuireWoods Expert in organic and medicinal chemistry (Eli Lilly v. Eagle Pharmaceuticals, Case No. 1:17-cv-1293; Expert Report, Deposition, Trial Testimony)**
- 2018 **Crowell & Moring Expert in organic chemistry (Chen v. Jung and Sawyers, Case No. 2:18-cv-02015-R-KS; Expert Report, Deposition and Trial Testimony)**
- 2017 **Polsinelli PC (via IMS Expert Services) Expert in organic chemistry (Leo Pharma vs. Perrigo; Expert Report and Deposition)**
- 2017 **Durie Tangri Expert in organic chemistry (Plexxikon Inc. v Novartis Pharmaceuticals Corporation; Case 4:17-cv-04405-HSG; Expert Report Deposition and Trial Testimony)**

EDUCATION:

Post-doctoral: Columbia University. January 1982-August 1983.
Research Director: Professor Ronald Breslow.

Graduate: Columbia University. September 1977-December 1981.
M.A. 1978, M.Phil., Ph.D. 1981.
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Undergraduate: Harvard College. September 1973-June 1977.
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**PROFESSIONAL
EXPERIENCE:**

Undergraduate Chair, Department of Chemistry, University
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Affiliate Member, Ellen and Ronald Caplan Cancer Center,
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Merriam Professor of Chemistry,
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Professor, University of Pennsylvania
Department of Chemistry, July 1996-

Founding Member, University of Pennsylvania
Center for Cancer Pharmacology, May 1998-present

Associate Professor, University of Pennsylvania,
Department of Chemistry, July 1990-June 1996

Member, University of Pennsylvania Cancer Center,
July 1993-present

Assistant Professor, University of Chicago,
Department of Chemistry, September 1983-June 1990

AWARDS & HONORS:

Ira H. Abrams Memorial Award for Distinguished Teaching, 2016
Elected Member, John Morgan Society, 2014
Visiting Scholar, Harbin University of Science and Technology, 2013
Fellow, Japan Society for the Promotion of Science, 2010
Lindback Award for Distinguished Teaching, 2007
Philadelphia Organic Chemists' Club Award, 2006
American Chemical Society Cope Scholar Award, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989

Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

PROFESSIONAL ACTIVITIES

Member, American Chemical Society, 1975-present
Founder, Scitemex LLC, 2000-present
Member, Atrin Pharmaceuticals, Scientific Advisor Board, 2013-present
Co-Founder, Pinpoint Therapeutics, 2018-present

INVITED LECTURES AT PHARMACEUTICAL RESEARCH ORGANIZATIONS SINCE 1983:

American Cyanamid/American Home Product (which later became Wyeth), Amgen, Aventis, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb (BMS), Dupont Pharmaceuticals (acquired by BMS), Eli Lilly, Genetics Institute (acquired by Wyeth), GlaxoSmithKline, Incyte, Johnson Matthey, Lederle Laboratories (acquired by Wyeth), Merck, Parke-Davis (acquired by Pfizer), Pfizer, R.W. Johnson, Sepracor (now known as Sunovion), and Wyeth (acquired by Pfizer in 2009)

INVITED LECTURES SINCE 2002:

2002-2003

Plenary Lecturer, French-American Chemical Society, 2002
Pfizer Lecturer, University of Waterloo, 2002
Novartis Lecturer, University of Texas at Austin
University of Rochester
Emory University
Alan Johnson Lecturer, University of Sussex, UK
Invited Speaker, Gordon Research Conference on Natural Products, July 2003

2003-2004

Stanford University
University of California at Berkeley
Glaxo Smith Kline
Amgen
Biogen
Yale University
Boston College
State University of New York at Stony Brook

2004-05

Plenary Speaker, Belgian Organic Chemistry Symposium
Abbott Laboratories Distinguished Lecturer in Organic Synthesis, Notre Dame University
California Institute of Technology

2005-2006

GlaxoSmithKline Symposium Lecture
Wyeth Synthesis Course (Princeton, Collegeville, Pearl River, Cambridge)

2006-2007

Roche Lectureship, University of Colorado
Invited Lecturer, 12th Brazilian Meeting on Organic Synthesis

2007-2008

Bristol-Myers Squibb
University of Wisconsin-Madison

2008-2009

National Taiwan University
National Tsing Hua University, Taiwan
Keynote Speaker, 9th International Symposium on Organic Reactions, 2008 (Chiayi, Taiwan)

2009-2010

Hamilton College
Kyoto University, Katsura Campus
Kyoto University, Yoshida North Campus
Tokyo Institute of Technology
University of Tokyo
Chiba University
Hokkaido University
Tohoku University
Eli Lilly and Company
Pfizer Cambridge

2010-2011

University of Cambridge
University College London
Imperial College London
University of Cardiff
Paristech
University of Lyon
ETH
Invited Lecturer, Breslow Symposium, Anaheim, CA

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Plenary Lecturer, 1st Korea International Forum on Organic Chemistry, Seoul
Frontiers in Chemistry Lecture, Case Western Reserve University
University of Iowa
University of Maryland Eastern Shores
Towson University

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Morgan State University
University of Maryland Eastern Shores
Plenary Lecture, Paquette Symposium, Ohio State University
Amgen (Thousand Oaks, CA)
Harbin Institute of Technology
Shanghai Institute of Organic Chemistry
Peking University
Tsinghua University
University of Science and Technology of China (USTC)
Soochow University
Glaxo (Shanghai)
Fudan University

2013-2014

Muhlenberg College
Cutaneous Oncology Retreat, Villanova Conference Center
Invited Speaker, "PAINS, Promiscuity and Probes-Are Drug and Probe Development Mutually Exclusive?" 248th ACS National Meeting - San Francisco, CA - August 2014

2014-2015

Rider University
University of Maryland Eastern Shores
Wesleyan University

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Bard College
Michigan State University

2016-2017

Louisiana State University
St. Johns University
Hanoi National University

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Radiobiology and Imaging Program, University of Pennsylvania and Abramson Cancer Center

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Philipps-University Marburg
Leibniz Universitat Hannover
ESPCI (Ecole Superiere de Physique et de Chimie Industrielles de La Ville de Paris)
Ecole Polytechnique, Paris

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2021-2022

University of Montreal

2022-2023

Plenary Lecturer, Parsons Symposium, Imperial College, London, UK

2023-2024

State University of New York-ESF

PATENTS AND PATENT APPLICATIONS:

1. J. Winkler, J. Axten, L. Krim, inventors; Trustees of the University of Pennsylvania, applicant; "Novel Dopamine Re-Uptake Inhibitors and Methods of Synthesizing and Using the Same," WO 99/36403, International Publication Date 22 July 1999.
2. N. Dahmane, J. Winkler, inventors; The Wistar Institute and The Trustees of the University of Pennsylvania, assignee; "Steroid-Derived Cycloamine Analogs and Methods for Using the Same in the Prevention or Treatment of Cancer," US 8,575,141 B2, Date of Patent 5 Nov 2013.
3. T. Penning, A. Adeniji, M. Byrns, J. Winkler, B. Twenter, inventors; Trustees of the University of Pennsylvania, applicant; "Bifunctional AKR1C3 Inhibitors/Androgen Receptor Modulators and Methods of Use Thereof," WO 2012/142208 A1, International Publication Date 18 Oct 2012.
4. R. Amaravadi, J. Winkler, inventors; Trustees of the University of Pennsylvania, applicant; "Novel Bisaminoquinoline Compounds, Pharmaceutical Compositions Prepared Therefrom and Their Use," WO 2012/149186 A2, International Publication Date 1 Nov 2012.
5. H. Rubin, T. Yano, S. Kassovska-Bratinova, N. Schechter, J. Teh, J. Winkler, inventors; Trustees of the University of Pennsylvania, application; "Novel Therapeutic Agents," WO 2013/096735 A1, International Publication Date 27 June 2013.
6. T. Penning, A. Adeniji, M. Byrns, J. Winkler, B. Twenter, inventors; Trustees of the University of Pennsylvania, applicant; "Bifunctional AKR1C3 Inhibitors/Androgen Receptor Modulators and Methods of Use Thereof," US 2014/0107085 A1, 17 Apr 2014.
7. N. Dahmane, J. Winkler, A. Isaacs, inventors; The Wistar Institute and Trustees of the University of Pennsylvania, assignees; "Compounds and Methods for the Prevention and Treatment of Cancer," US 8,759,367 B2, 24 June 2014.

8. H. Rubin, T. Yano, S. Kassovska-Bratinova, N. Schechter, J. Teh, J. Winkler, inventors; Trustees of the University of Pennsylvania, applicant; "Novel Therapeutic Agents," US 2014/0371228 A1, 18 Dec 2014.
9. R. Amaravadi, J. Winkler, inventors; Trustees of the University of Pennsylvania, applicant; "Asymmetric Bisaminoquinolines and Bisaminoquinolines with Varied Linkers as Autophagy Inhibitors for Cancer and Other Therapy," WO 2016/022956 A1, International Publication Date 11 Feb 2016.
10. T. Ridky, C. Natale, J. Winkler, R. Cookson, inventors; Trustees of the University of Pennsylvania, applicant; "Compositions and Methods for Increasing, or Preventing or Reversing Loss of Skin Pigmentation in a Mammalian Subject," WO 2016/164450 A1, International Publication Date 13 Oct 2016.
11. R. Amaravadi, J. Winkler, inventors; Trustees of the University of Pennsylvania, applicant; "Dimeric Quinacrine Derivatives as Autophagy Inhibitors for Cancer Therapy," WO 2016/168721 A1.
12. T. Ridky, C. Natale, J. Winkler, inventors; Trustees of the University of Pennsylvania, applicant; "Compounds, Compositions and Methods for Prevention and/or Treatment of Cancer," WO 2017/218191 A1, International Publication Date 21 Dec 2017.
13. P. Mews, S. Berger, J. Winkler, A. Glass, inventors; Trustees of the University of Pennsylvania, applicant; "Compositions and Methods for Inhibiting ACSS2," WO 2019/067528 A1, International Publication Date 04 Apr 2019.
14. S. Berger, P. Mews, J. Winkler, A. Glass, G. Egervari, applicants; Trustees of the University of Pennsylvania, applicant; "Compositions and Methods for Inhibiting ACSS2," WO 2020/069093 A1, International Publication Date 02 Apr 2020.
15. J. Winkler, R. Amaravadi, applicants; Trustees of the University of Pennsylvania, applicant; "Bisaminoquinolines and Bisaminoacridines Compounds and Methods of Their Use," WO 2020/243037 A1, International Publication Date 03 Dec 2020.

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2. G. Stork, C. Shiner, J. Winkler, "Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems," *J. Am. Chem. Soc.* **1982**, *104*, 310-312.
3. G. Stork, J. Winkler, C. Shiner, "Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone," *J. Am. Chem. Soc.* **1982**, *104*, 3767-3768.

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5. J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, R. Breslow, "An Artificial Transaminase Carrying A Synthetic Macrocyclic Binding Group," *J. Am. Chem. Soc.* **1983**, *105*, 7198-7199.
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8. J. Winkler, V. Sridar, "Stereochemical Control of Transannular Radical Cyclizations. A New Approach to the Synthesis of Linearly Fused Cyclopentanoids," *J. Am. Chem. Soc.* **1986**, *108*, 1708-1709.
9. J. Winkler, J. Hey, P. Williard, "Inside-Outside Stereoisomerism: A Synthesis of *trans*-Bicyclo[5.3.1]undecan-11-one," *J. Am. Chem. Soc.* **1986**, *108*, 6425-6427.
10. J. Winkler, P. Hershberger, J. Springer, "A Stereoselective Synthesis of the Azaspiroundecane Ring System of (-)-Histriocotoxin from (+)-Glutamic Acid," *Tetrahedron Lett.* **1986**, 5177-5180.
11. J. Winkler, J. Hey, S. Darling, "Studies Directed Towards the Synthesis of the Taxane Diterpenes: A Remarkable Rearrangement," *Tetrahedron Lett.* **1986**, 5959-5962.
12. J. Winkler, J. Hey, F. Hannon, P. Williard, "Intramolecular Photoaddition of Dioxolenones. An Efficient Method for the Synthesis of Medium-Sized Rings," *Heterocycles* **1987**, *25*, 55-60.
13. J. Winkler, K. Deshayes, "Photodynamic Macrocycles," *J. Am. Chem. Soc.* **1987**, *109*, 2190-2191.
14. J. Winkler, K. Henegar, P. Williard, "Inside-Outside Stereoisomerism II. Synthesis of the Carbocyclic Ring System of the Ingenane Diterpenes *via* the Intramolecular Dioxolenone Photocycloaddition," *J. Am. Chem. Soc.* **1987**, *109*, 2850-2851.
15. K. Henegar, J. Winkler, "A New Method for the Synthesis of Dioxolenones *via* the Carboxylation of Ketone Enolates with Anisyl Cyanoformate," *Tetrahedron Lett.* **1987**, 1051-1054.
16. J. Winkler, C. Muller, R. Scott, "A New Method for the Formation of Nitrogen-Containing Ring Systems *via* the Intramolecular Photocycloaddition of Vinylogous Amides. A Synthesis of Mesembrine," *J. Am. Chem. Soc.* **1988**, *110*, 4831-4832.
17. J. Winkler, J. Hey, P. Williard, "Inside-Outside Stereoisomerism III. The Synthesis of *trans*-Bicyclo[4.3.1]Decan-10-one," *Tetrahedron Lett.* **1988**, 4691-4694.
18. J. Winkler, V. Sridar, "Eight-Membered Ring Templates for Stereoselective Radical Cyclizations," *Tetrahedron Lett.* **1988**, 6219-6222.
19. J. Winkler, K. Deshayes, B. Shao, "Photodynamic Systems for Metal Ion Transport," *J. Am. Chem. Soc.* **1989**, *111*, 769-770.
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