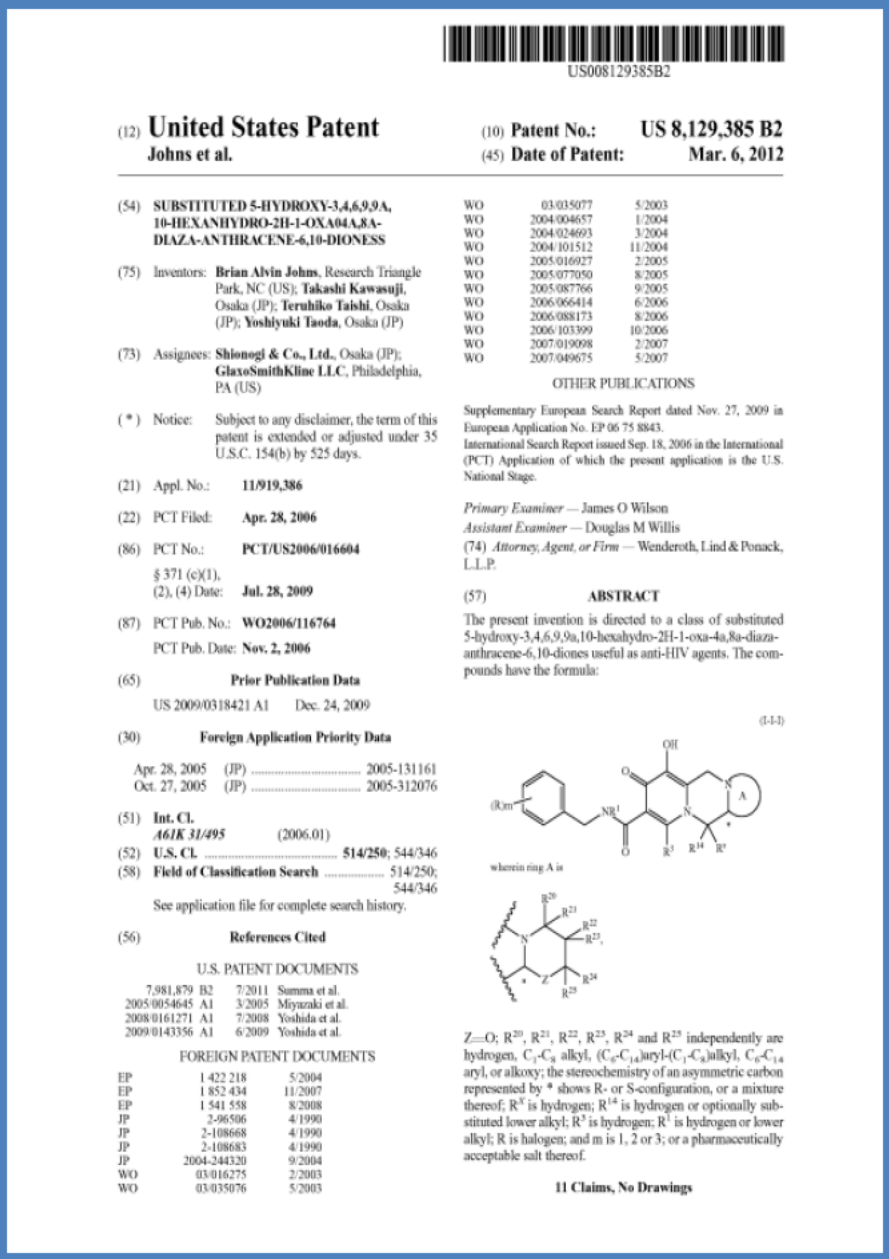
COMPLETE HEALTHCARE MANAGEMENT, CORP.
MARCH 15, 2022



US008129385B2

(12) **United States Patent**
Johns et al.

(10) **Patent No.: US 8,129,385 B2**
(45) **Date of Patent: Mar. 6, 2012**

(54) **SUBSTITUTED 5-HYDROXY-3,4,6,9,9A, 10-HEXANHYDRO-2H-1-OXA04A,8A-DIAZA-ANTHRACENE-6,10-DIONESS**

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(73) Assignees: **Shionogi & Co., Ltd.**, Osaka (JP); **GlaxoSmithKline LLC**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 525 days.

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Oct. 27, 2005 (JP) 2005-312076

(51) **Int. Cl.**
A61K 31/495 (2006.01)

(52) **U.S. Cl.** **514/250**; 544/346

(58) **Field of Classification Search** 514/250; 544/346

See application file for complete search history.

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International Search Report issued Sep. 18, 2006 in the International (PCT) Application of which the present application is the U.S. National Stage.

Primary Examiner — James O Wilson
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(57) **ABSTRACT**

The present invention is directed to a class of substituted 5-hydroxy-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-6,10-diones useful as anti-HIV agents. The compounds have the formula:

(I-I-I)

wherein ring A is

Z=O; R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} independently are hydrogen, C_1-C_8 alkyl, $(C_6$-$C_{14})$aryl-$(C_1$-$C_8)$alkyl, C_6-C_{14} aryl, or alkoxy; the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof; R^X is hydrogen; R^{14} is hydrogen or optionally substituted lower alkyl; R^3 is hydrogen; R^1 is hydrogen or lower alkyl; R is halogen; and m is 1, 2 or 3; or a pharmaceutically acceptable salt thereof.

11 Claims, No Drawings

Substituted 5-hydroxy-3,4,6,9,9a, 10-hexanhydro-2h-1-oxa04a,8a-diaza-anthracene-6,10-dioness

Critical Date: April 28, 2006

Expiration Date: October 5, 2027

Prepared by:

International Patent Reviews

IPR Initial Review

Patent information

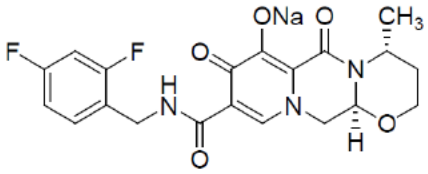
URL	Priority	Expiration	RC*	FC**
https://patents.google.com/patent/US8129385B2	Apr 28, 2006	Oct 5, 2027	37	120

*patent and non-patent literature citations ** citing patents

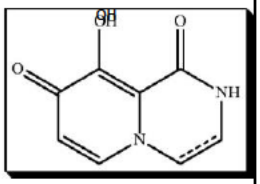
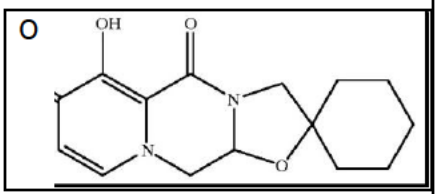
Technology Description & Application Area

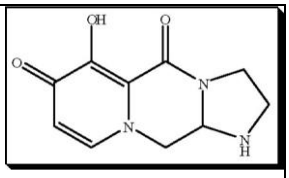
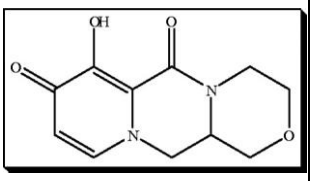
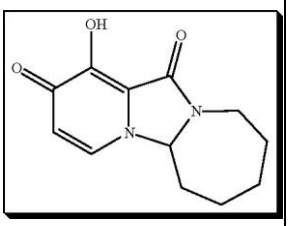
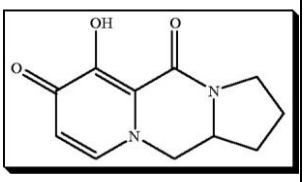
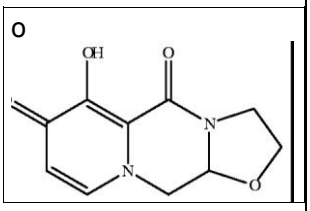
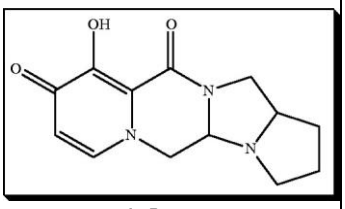
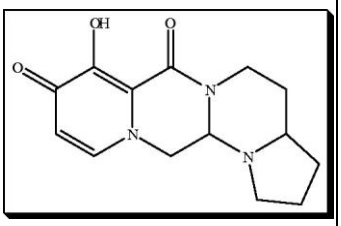
Patent Number	Title	Description/Application Area
8129385	Substituted 5-hydroxy-3,4,6,9,9a,10-hexanhydro-2h-1-oxa04a,8a-diaza-anthracene-6,10-dioness	Compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.

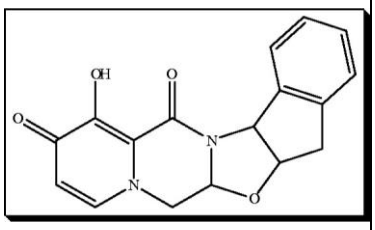
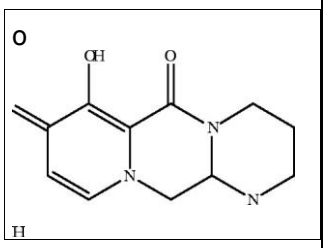
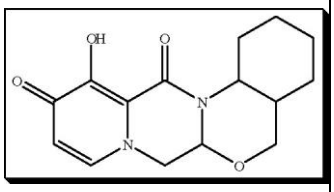
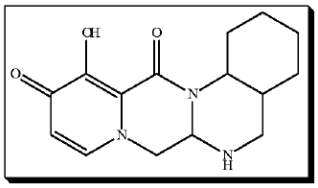
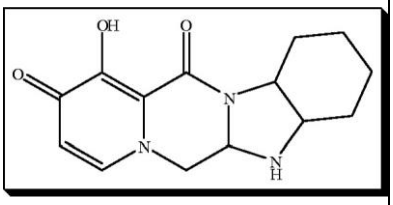
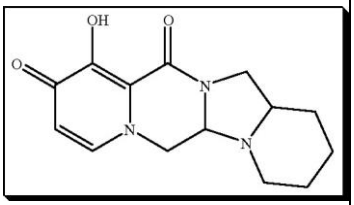
Dolutegravir sodium is: sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol. It has the following structural formula:

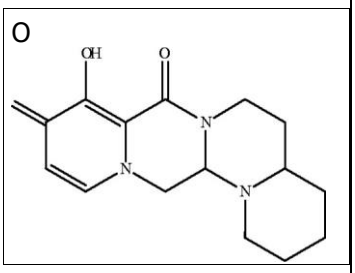
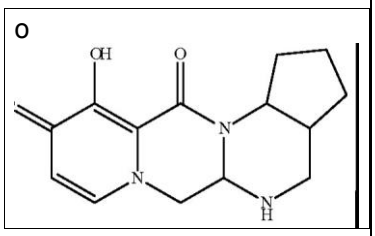
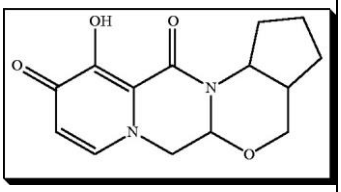


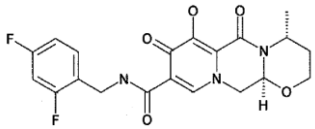
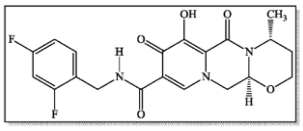
Prosecution History

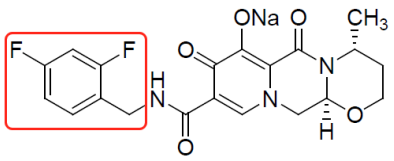
U.S. 8129385	Date	Action/Outcome
Original Filing	Jul 28, 2009	Originally filed with claims 1-56.
Request for Restriction/Election	Jan 27 2011	Group I, claims 1-6, 34, 35 and 50, drawn to substituted 1,8dihydro-2H-pyrido[1,2-a]pyrazine-1,8-diones and simple pharmaceutical compositions of the formula (I), where Z^2 = $(CH_2)_2$- or CH=CH-,  Group II, claims 1-6, 17, 18, 28, 29, 34, 35 and 50, drawn to substituted spiro[cyclohexane-1,2'-oxazolo-[3,2-d]pyrido[1,2a] pyrazine]-5',7'(11'H,11a'H) diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -spirocyclohexane 1,2'-oxazole. 

		Group III, claims 1-18, 22-24, 28, 29, 34, 35 and 50, drawn to substituted dihydro-1H-imidazo[1,2-d]pyrido[1,2-a]pyrazine-5,7(11H, 11aH)-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -imidazole. 
		Group IV, claims 1-16, 34, 35 and 50, drawn to substituted dihydro- 1H-[1-4]oxazino [4,3-d]pyrido[1 ,2-a]pyrazine-6,8(12H,12aH)-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -morpholine. 
		Group V, claims 1-6, 30, 34, 35 and 50, drawn to substituted 2,4b,5,6,7,8,9,10-octahydro-4a,9a-diazobenzo[a]azulene-2, 10-diones and simple pharmaceutical compositions of the formula (I-1I), where ring D = -azepane. 
		Group VI, claims 1-16, 34, 35 and 50, drawn to substituted 2,3,5,7,11, 11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-5,7-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -pyrrole. 
		Group VII, claims 1-18, 22, 23, 28, 29, 31-35 and 50, drawn to substituted 2,3,11,11a-tetrahydrooxazolo[3,2-d]pyrido[1,2-a]pyrazine-5,7-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -tetrahydrooxazole. 
		Group VIII, claims 1-10, 17, 18, 23, 24, 28, 29, 31-35 and 50, drawn to substituted 2,3,4a,5,9,11,13,13a-octahydro-lHpyrido[1,2-apyrrolo[1′,2′:3,4] imidazo[1,2-d]pyrazine-9,11-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -hexahydro-1H-pyrrolo[1,2-c]imidazole. 
		Group IX, claims 1-10, 17, 18, 19, 20, 21, 28, 29, 31, 34, 35 and 50, drawn to substituted 1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrrolo[1,2-c]pyrimidine-7,9-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -octahydropyrrolo[1,2-c].pyrimidine. 

		Group X, claims 1-10, 17, 18, 28, 29, 31, 34, 35 and 50, drawn to substituted 5a,6a,7,11,13,14a'-hexahydro-5H-indeno[1',2':4,5][1,3]oxazolo[3,2'-a]pyrido[1,2-d]pyrazine-11,13-diones and simple pharmaceutical compositions of the formula (I-I), where ring A = -3,3a,8,8a-tetrahydro2H-indeno[1,2-d] oxazole. 
		Group XI, claims 1-21, 28, 29, 31-35 and 50, drawn to substituted 1,2,3,4,6,8, 12, 12a-octahydropyrido[1',2' :4,5]pyrazino[1,2-a]pyrimidine-6,8-diones and simple pharmaceutical compositions of the formula (I-I), where ring A=-hexahydropyrimidine 
		Group XII, claims 1-10, 17-20, 28, 29, 31-35 and 50, drawn to substituted 1,3,4,4a,5,6a,7,11,13,14a-decahydro-2H-pyrido[1',2':4,5]pyrazino[1,2-a][1,3]benzoxine-11,13-diones and simple pharmaceutical compositions of the formula (I-I), where ring A = -octahydro-1H-benzo[d][1,3]oxazine. 
		Group XIII claims 1-10, 17-20, 28, 29, 31-35 and 50 drawn to substituted 1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido [1',2':4,5] pyrazino[1,2-a]quinazoline-11,13-diones and simple pharmaceutical compositions of the formula (I-1), where ring A= -decahydroquinazoline. 
		Group XIV, claims 1-10, 17, 18, 23, 24, 28, 29, 31, 34, 35 and 50, drawn to substituted 2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido [1',2':4,5] pyrazino[1,a]benzimidazole-2,13-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -octahydro-1H-benzo [d]imidazole. 
		Group XV, claims 1-10, 17, 18, 23, 24, 28, 29, 31, 34, 35 and 50, drawn to substituted 1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a] pyrido[1',2':3,4] imidazo[1,2-d]pyrazine-10,12-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -octahydro- 1H-benzo[d]imidazole. 

		Group XVI, claims 1-10, 17-21, 28, 29, 31, 34, 35 and 50, drawn to substituted 2,3,4,4a,5,6,8,10,14,14a-decahydro1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-8,10-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -decahydroquinazoline. 
		Group XVII, claims 1-10, 17-21, 28, 29, 31, 34, 35 and 50, drawn to substituted 2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5] pyrazino[1,2-a]pyramidine-10,12-diones and simple pharmaceutical compositions of the formula (I-1), where ring A = -octahydro-1H-cyclopenta[d]pyrimidine. 
		Group XVIII, claims 1-10, 17-20, 28, 29, 31, 34, 35 and 50, drawn to substituted 1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2' :4,5]pyrazino[1'2-b] [1,3]oxazine10,12-diones and simple pharmaceutical compositions of the formula (I-I), where ring A = -octahydrocyclopenta[d][1,3]oxazine. 
		Group XIX, claims 1-35 and 50, drawn to substituted heterocycles and simple pharmaceutical compositions of the formula (I), formula (I-I) and/or formula (I-Il), where Z^2, ring A and/or ring D, as recited, is not as defined above.
		Group XX, claim 54, drawn to complex pharmaceutical compositions comprising substituted heterocycles of the formula (I), formula (I-1) and/or formula (I-I1) and at least one additional therapeutic agent.
		Group XXI**,** claims 36, 37, 52 and 53, drawn to a process for the preparation of a substituted 2,3,11,11a-tetrahydrooxazolo[3,2-d]pyrido[1,2-a]pyrazine-5,7-dione of the formula (I-20a) or formula (l-20b).
		Group XXII**,** claims 38, 39, 52 and 53, drawn to a process for the preparation of a substituted 2,3,4a,5,9,11, 13,13a-octahydro-1H-pyrido[1,2-a]pyrrolo[1',2':3,4]imidazo[1,2-d]pyrazine-9,11-dione of the formula (I-21a) or formula (I-21 b).
		Group XXIII**,** claims 40, 41, 52 and 53, drawn to a process for the preparation of a substituted 1,2,3,3a,4,5,7,9,13, 13a-decahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrrolo[1,2-c]pyrimidine-7,9-dione of the formula (I-22a) or formula (I-22b).
		Group XXIV**,** claims 42, 43, 52 and 53, drawn to a process for the preparation of a substituted 1,2,3,4,5a,6, 10,12, 14,14a-

		decahydropyrido[1,2-a]pyrido[1',2':3,4]imidazo[1,2-d]pyrazine-10,12-dione of the formula (I-23a) or formula (I-23b). Group XXV**,** claims 44, 45, 52 and 53, drawn to a process for the preparation of a substituted 1,2,3,4,6,8, 12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-6,8-dione of the formula (I-24a) or formula (I-24b). Group XXVI**,** claim 46, 52 and 53, drawn to a process for the preparation of a substituted 1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-11, 13-dione of the formula (I-25). Group XXVII**,** claim 47, 52 and 53, drawn to a process for the preparation of a substituted 2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-10,12-dione of the formula (I-26). Group XXVIII**,** claim 48, 52 and 53, drawn to a process for the preparation of a substituted 1,2,3,3a,4,5a,6,10, 12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[1,2-b][1,3]oxazine-10,12-dione of the formula (I-27). Group XXIX**,** claim 49, drawn to a method of treatment of an HIV infection in a human, comprising administering ... a substituted heterocycle of the formula (I), formula (I-1) and/or formula (I-11). Group XXX, claims 55 and 56, drawn to a method of treatment of an HIV infection in a human, comprising administering ... a complex pharmaceutical composition comprising a substituted heterocycle of the formula (I), formula (I-1) and/or formula (I-11) additional therapeutic agent.
Response to Request for Restriction/Election	Mar 28 2011	Applicants elect to prosecute the invention of Group XIX, with the understanding that such Group includes the following compound, which is compound of Example Y-3 on page 116 of the specification, as the elected provisional species of the elected Group.  Claims 1-11, 13-28, 30-32, 36-48 and 50-56 were canceled. Claim 12 was amended according to claims 17 and 28. New claims 57-62 were added directed to the preferred compounds which are disclosed in the specification.
Non-Final Rejection	May 19 2011	Claims 12, 29, 33-35, 49 and 57-62 are pending. 

		The elected species, shown above, was found to be free of the prior art. Thus, the examiner has expanded the forthcoming prosecution to include all claims relevant to the genus of Group XIX, for a first Office action and prosecution on the merits. Claim 49 was withdrawn from further consideration as being drawn to a nonelected or cancelled invention, there being no allowable generic or linking claim. Various informalities were noted in order to bring the claims into compliance with the elected species. Claims 12 and 33-35 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Various phrases and functionalities were noted. Claims 57 and 58 were allowed.
Applicant Arguments	Aug 19, 2011	Applicant acquiesced to the suggestions and notes from the Non-final Rejection. Claim 35 was cancelled and new claims 63 and 64 added.
Notice of Allowance	Oct 21, 2011	Claims 12, 29, 33, 34 and 57-63 were allowed. "The prior art is silent with respect to substituted 5-hydroxy-3,4,6,9,9a,10-hexahydro-2H1-oxa-4a,8a-diazaanthracene-6,10-diones of the formula (I-1-1) and formula (I-7), as recited in claims 12 and 62, respectively." Specifically, "the limitation …that is not taught or fairly suggested in the prior art is the *halogenated N-benzyl amide* on the periphery of the 5-hydoxy-3,4,6,9,9a,10-hexahydo-2H-1-oxa-4a,8a-diazaanthracene-6,10-dione core." (emphasis in original)  (Figure added for clarity)
Issue Notification	Feb 15 2012	Issue date specified as Mar 6, 2012, for US Patent 8129385

Litigation History U.S. Patent 8129385

VIIV Healthcare Company et al v. Gilead Sciences, Inc. 1-18-cv-00224 (DDE) – Filed Feb 7, 2018
Complaint: Infringement – ANDA

Markman – May 13, 2019:

Term
R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy;

Construction:
R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are each hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy, where (1) each of R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} may be the same as or different from any other R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} and (2) the hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy that comprise each R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are distinct from the hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy that comprise any other R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25}

Motion for Judgment on the Pleading – Feb 5, 2020

Denied
The court denied defendant's motion for judgment on the pleadings that plaintiff's doctrine of equivalents claim was precluded under the disclosure-dedication bar where the disclosure was found in another claim of the patent-in-suit. "The compound recited in claim 6 is a species of the compound genus recited in claim 2 of the patent. Claim 2 discloses a compound with a trifluoro benzyl ring. [Defendant] argues that the disclosure of the trifluoro benzyl ring in claim 2 triggers the disclosure-dedication rule and bars [plaintiff] from alleging that [defendant's HIV drug product] infringes claim 6 under the doctrine of equivalents. . . . By definition, a disclosure in a claim is not dedicated to the public. A patent's claims define the inventor's right to exclude the public from being able to practice the invention; thus, the claims do the exact opposite of dedicating the invention to the public."

Motion for Judgment on the Pleading – Feb 5, 2020

Denied
The court denied defendant's motion for judgment on the pleadings that the court's claim construction specifically precluded plaintiff's doctrine of equivalents claim. "[Defendant] argues that the agreed-upon construction of the 'are independently' limitation specifically excludes [plaintiff] from alleging that [defendant's HIV drug product] equivalently infringes claim 2 because [the drug] has substituents that are located at two Rx's but that are bonded to each other as well as to the ring and therefore are not distinct from one another. . . . Given the parties' fundamental disagreements about the meaning of the agreed-upon construction of 'are independently,' I have decided that it is necessary to revisit claim construction."

Motion to Vacate - Claim Construction Order (Markman) – Feb 5, 2020
The Court's May 13, 2019 Claim Construction Order is VACATED.

Motion for Summary Judgment – Noninfringement – Jul 6, 2020

Denied
The court denied defendant's motion for summary judgment that it did not infringe plaintiffs' HIV drug treatment patents because there were genuine disputes of material fact. "In its concise statement of material undisputed facts filed in support of its motion, [defendant] states that '[t]he terms monocyclic and bicyclic are mutually exclusive.' Plaintiffs deny this asserted fact and cite

record evidence (i.e., expert deposition testimony) that appears on its face to create a genuine issue about whether the terms monocyclic and bicyclic are mutually exclusive. Because there is a disputed fact that [defendant] has said is material to its motion for summary judgment, I will deny the motion."

Motion for Summary Judgment – Noninfringement – Aug 3, 2020

Denied
The court denied defendant's motion for summary judgment that it did not infringe plaintiff's HIV treatment patent under the doctrine of equivalents because plaintiff's expert established a genuine dispute of material fact. "It is undisputed that claim 6 of the [patent] teaches a chemical compound that has among other things a benzyl ring with two fluorines (a difluoro benzyl ring) and that [the accused product] has a benzyl ring with three fluorines (a trifluoro benzyl ring). It is also undisputed that a difluoro benzyl ring is not the same thing as a trifluoro benzyl ring. But it is not clear from the claims or written description of the [patent] that a difluoro benzyl ring necessarily excludes a trifluoro benzyl ring. . . . [Plaintiff] . . . has submitted an expert affidavit to establish, that a trifluoro benzyl ring is not the opposite of and not incompatible with a difluoro benzyl ring."

Motion for Discovery Sanctions -- Issue/Evidence/Terminating

Partial Grant
The court partially granted defendant's motion to sanction plaintiffs for belatedly disclosing that their expert anonymously offered a largely positive review of a scientific article criticized in the expert's report. Instead of granting an adverse jury instruction, the court struck all portions of the expert's report that referenced the article. "[W]hen one reviews the basic facts regarding this dispute, it does not take long to understand why [plaintiff's expert's] reports -- in which he repeatedly noted how '[the article] manuscript was peer reviewed by two scientists with expertise in the field' (but failed to mention that he was one of those two scientists) -- was misleading in a material way. That omission was the kind of thing that screams out its need for correction. . . . [A] jury instruction of the type proposed by Defendant is a very significant remedy, one that could have the effect of influencing the jury's ultimate verdict. In a case involving important, life-sustaining medications and (potentially) billions of dollars in damages, the Court is concerned that imposition of this remedy would unduly distract the factfinder from what really should control the outcome: the merits of the evidence presented by both sides. . . . [T]he right remedy for this violation is that all portions of [the expert's] reports that reference [the article] should be stricken."

Motion for Discovery Sanctions -- Issue/Evidence/Terminating

Partial Grant
The court granted in part plaintiffs' motion to sanction defendant for failing to disclose underlying raw data and documents regarding the accused drug product that were reviewed by its expert when its expert previously served on defendant's advisory board. "Were some of that raw data to contradict the overarching conclusions that [the expert] drew from the two studies, Plaintiffs might want to know that, in order to effectively cross-examine [him]. . . . The subject matter of [his] work on the [advisory board], including his review of the above-referenced candidate protocols, clearly overlaps with that of his expert opinions. . . . Producing these documents and allowing this additional deposition testimony would allow Plaintiffs to cure any prejudice. . . . And the Court finds no evidence of bad faith (and Plaintiffs assert none). Indeed, it is not even clear whether this data (which was otherwise summarized in materials available to Plaintiffs) will even be helpful to Plaintiffs' cause."

Stipulated/Agreed - Motion to Dismiss - Voluntary Dismissal (FRCP 41(a)) Feb 2, 2022

Case Closed

Current Orange Book Patent Data

Tivicay

Active Ingredient: DOLUTEGRAVIR SODIUM
Proprietary Name: TIVICAY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 10MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N204790
Product Number: 002
Approval Date: Jun 9, 2016
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
002	8129385	10/05/2027	DS	DP			06/15/2016
002	9242986	12/08/2029	DS	DP			06/15/2016

Triumeq

Active Ingredient: ABACAVIR SULFATE; DOLUTEGRAVIR SODIUM; LAMIVUDINE
Proprietary Name: TRIUMEQ
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 600MG BASE;EQ 50MG BASE;300MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N205551
Product Number: 001
Approval Date: Aug 22, 2014
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	8129385	10/05/2027	DS	DP			09/16/2014
001	9242986	12/08/2029	DS	DP			03/10/2016

Juluca

Active Ingredient: DOLUTEGRAVIR SODIUM; RILPIVIRINE HYDROCHLORIDE
Proprietary Name: JULUCA
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE;EQ 25MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N210192
Product Number: 001
Approval Date: Nov 21, 2017
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	7125879	04/21/2025	DS	DP	U-257		12/20/2017
001	8080551	04/11/2023	DS	DP			12/20/2017
001	8101629	08/09/2022		DP			12/20/2017
001	8129385	10/05/2027	DS	DP			12/20/2017
001	9242986	12/08/2029	DS	DP			12/20/2017
001	10426780	01/24/2031	DS	DP	U-257		10/25/2019

Dovato

Active Ingredient: DOLUTEGRAVIR SODIUM; LAMIVUDINE
Proprietary Name: DOVATO
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE;300MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N211994
Product Number: 001
Approval Date: Apr 8, 2019
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	8129385	10/05/2027	DS	DP			04/24/2019
001	9242986	12/08/2029	DS	DP			04/24/2019

Tivicay PD

Active Ingredient: DOLUTEGRAVIR SODIUM
Proprietary Name: TIVICAY PD
Dosage Form; Route of Administration: TABLET, FOR SUSPENSION; ORAL
Strength: EQ 5MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N213983
Product Number: 001
Approval Date: Jun 12, 2020
Applicant Holder Full Name: VIIV HEALTHCARE CO
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	8129385	10/05/2027	DS	DP			06/19/2020
001	9242986	12/08/2029	DS	DP			06/19/2020

Best Potential Prior Art

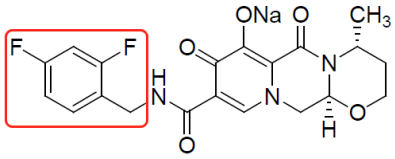
Relevant Patent or Publication	Publication Date
U.S. Pat. Appl. 2005/0054645 A1 to MIYAZAKI et al. "Nitrogen-containing fused ring compound and use thereof as HIV integrase inhibitor"*	Mar 10 2005
WO 2004/096128 A2 to Naidu et al. "HIV Integrase Inhibitors"	Nov 11 2004.
POMMIER, Yves, Allison A. Johnson, and Christophe Marchand. "Integrase inhibitors to treat HIV/AIDS" Nature Reviews Drug Discovery 4.3 (2005): 236-248.	Mar 31 2005
EP 1297834 A1 to Kiyama et al. "Inhibitor for Enzyme Having Two Divalent Metal Ions as Active Centers"	Apr 2 2003
Hazuda et al., "A Naphthyridine Carboxamide Provides Evidence for Discordant Resistance between Mechanistically Identical Inhibitors of HIV-1 Integrase" Proceedings of the National Academy of Sciences of the United States of America, Vol. 101, No. 31, pp. 11233-11238.	Aug 3 2004
WO 2005110414 A2 to Wai et al. "HIV integrase inhibitors"	Nov 24 2005
WO 200230930 A2 to Anthony et al., "Aza- and polyaza-naphthalenyl carboxamides useful as HIV integrase inhibitors"	Apr 18 2002
Barreca et al., "Pharmacophore-Based Design of HIV-1 Integrase Strand-Transfer Inhibitors" J. Med. Chem. 2005, 48, 7084	Nov 3 2005
Chen et al. "Crystal structure of the HIV-1 integrase catalytic core and C-terminal domains: a model for viral DNA binding." Proceedings of the National Academy of Sciences 97.15 (2000): 8233-8238	Jul 18 2000
Costi et al. "6-Aryl-2, 4-dioxo-5-hexenoic acids, novel integrase inhibitors active against HIV-1 multiplication in cell-based assays." Bioorganic & Medicinal chemistry letters 14.7 (2004): 1745-1749.	Apr 30 2004
Dayam, Raveendra, and Nouri Neamati. "Active site binding modes of the β-diketoacids: a multi-active site approach in HIV-1 integrase inhibitor design." Bioorganic & Medicinal chemistry 12.24 (2004): 6371-6381.	Dec 31 2004
Grobler et al. "Diketo acid inhibitor mechanism and HIV-1 integrase: implications for metal binding in the active site of phosphotransferase enzymes." Proceedings of the National Academy of Sciences 99.10 (2002): 6661-6666.	May 7 2002

*on face of patent

Prior Art Analysis

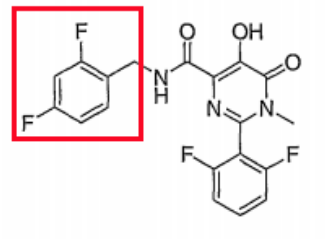
Primary observation

The genesis of the most important and crucial observation with regard to the prior art lies within the Examiner's reasoning behind the Allowance of October 21, 2010 in which it was asserted that "the limitation …that is not taught or fairly suggested in the prior art is the *halogenated N-benzyl amide* on the periphery of the 5-hydoxy-3,4,6,9,9a,10-hexahydo-2H-1-oxa-4a,8a-diazaanthracene-6,10-dione core." The examiner contends that the structure highlighted in this figure is not taught in the prior art:

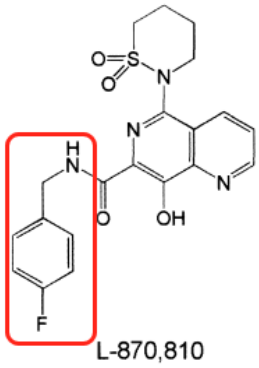


This is clearly and objectively false.

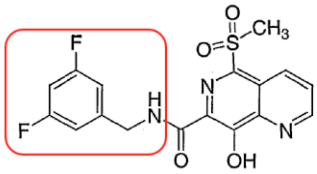
Such a structure is clearly identified and shown in at least the prior art of NAIDUI. Furthermore, the halogenated n-benzyl-amide structures disclosed by NAIDU are, in fact, HIV integrase inhibitors. NAIDU discloses no fewer than 74 HIV integrase inhibitors possessing a *halogenated N-benzyl amide*. Example 8 of Naidu is typical:



A *halogenated N-benzyl amide* functional as an HIV integrase inhibitor is also taught by HAZUDA as L-870,810 an 8-hydroxy-(1,6)-naphthyridine-7-carboxamide pharmacophore (and further mentioned in the review by POMMIER 2005 pg 243 and Fig. 4a):



ANTHONY teaches at least 189 specific compounds useful as an HIV integrase, 72% (137) of which contain a *halogenated N-benzyl amide* moiety. For example, ANTHONY N-(3,5-difluorobenzyl)-8-hydroxy-5-(methylsulfonyl)-1,6-naphthyridine-7-carboxamide (Example 111 page 244):



In all cases, the halogenated benzyl carboxamide moiety is *identical* to that claimed in the '385. How NAIDU, HAZUDA, ANTHONY, and others were overlooked or ignored with refence to the halogenated benzyl carboxamide moiety is puzzling.

Immediately below is a brief synopsis of the prior art. A more detailed analysis of the prior art follows.

SYNOPSIS

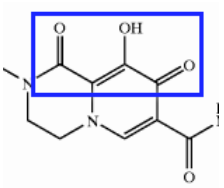
MIYAZAKI: MIYAZAKI teaches nitrogen-containing fused ring structures useful as HIV integrase inhibitors. (MIYAZAKI abstract). MIYAZAKI teaches no fewer than about 440 individual compounds useful as described (MIYAZAKI paras [0215]-[0655]). MIYAZAKI goes on to teach that some of these 440 compounds show better integrase inhibition than others. (MIYAZAKI paras [1509] – [1535], especially Tables 36-46]). Roughly 30% of the compounds specifically disclosed by MIYAZAKI showed the highest activities designated as at least "++++: less than 0.01 μM" activity." (MIYAZAKI para [1513] and Tables 36-46).

Therefore, it is reasonable to assume that POSA, seeking to develop the most effective HIV integrase inhibitor, would look to the most active compounds disclosed by MIYAZAKI in order to begin to design a compound useful for such purpose.

POMMIER 2005: POMMIER 2005 teaches how compounds should be structured in order to interact efficiently with the HIV integrase. POMMIER 2005 teaches that "functional diketo or ß-hydroxy-keto groups are known to have metal-chelating functions, and metal-dependent inhibition by DKAs and DKA-like compounds has been interpreted as indicating a direct interaction of these drugs with the divalent metal in the enzyme [*HIV integrase*] catalytic site. Metal coordination could also be important for shaping the catalytic pocket of integrase and therefore the DKA-binding site" (POMMIER 2005, P 245). POMMIER 2005 further teaches: "The high selectivity of DKAs for the strand-transfer step led to a model in which the two catalytic sites are organized around the **three catalytic DDE residues** and the divalent metal(s) within the integrase–DNA complexes (BOX 3). In this model, the DONOR DNA site binds the donor (viral) DNA end and catalyzes 3'-processing. Consequently, integrase undergoes a structural change that allows the binding of the acceptor (chromosomal) DNA in the acceptor site for strand transfer. DKAs, it is suggested, would bind selectively to a unique conformation of the acceptor site following binding of the viral DNA and 3'-processing, which would then produce the required change in conformation in the acceptor site for accommodating the DKA ligands. According to this scheme, divalent metal coordination would be crucial for DKA binding to the acceptor site (BOX 3, figure part e). This model is supported by scintillation proximity assays with radiolabeled compounds that demonstrated the binding of DKA to an intermediate of the integrase PIC in the presence of Mg^{2+} or Mn^{2+}. DKA binding was shown to require functional integrase, as mutant and catalytically inactive enzymes failed to support DKA binding. Drug binding also requires viral DNA ends, as nonspecific DNA fails to support binding. Finally, DKAs fail to bind in the absence of Mg^{2+} or Mn^{2+} and compete with the strand-transfer target DNA." (POMMIER 2005, P 245; Emphasis added).

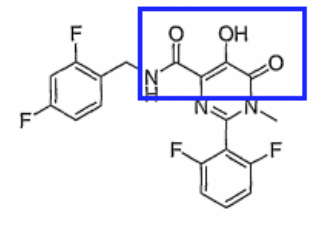
Hence it would have been obvious for a POSA at the time of the invention to begin with or preserve a molecule having the triplanar oxygen triad of a di-keto acid or di-keto aryl or the like in light of POMMIER 2005.

Of the compounds showing the highest levels of integrase inhibition disclosed by MIYAZAKI, **every one of them showed a triad of three oxygens available as a di-keto acid or di-keto-aryl or similar**. Each of the most active compounds in MIYAZAKI exhibited the structural configuration indicated by the blue box below:

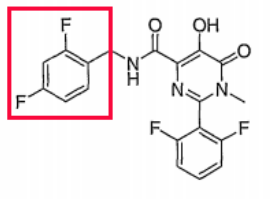


Therefore, it would have been readily obvious to POSA at the time of the invention that an oxygen triad as taught by POMMIER 2005 and exemplified in MIYAZAKI would have been a motif certainly worth incorporating into any molecule putatively directed toward inhibiting HIV integrase activity.

NAIDU: NAIDU also teaches HIV integrase inhibitors with at least 100 specific examples of useful compound. NAIDU indicates that "examples 1-98 were found to have IC50 = 0.002 to 2 μM" (NAIDU pg. 94 ln 15). Hence many of these compounds were shown to be as effective or more than those most active in MIYAZAKI. Like MIYAZAKI, each of the delineated compounds shows the oxygen triad discussed above. (NAIDU generally) as exemplified by Example 8:



However, and more importantly with regard to Allowance, NAIUDU also teaches the utility of incorporating a halogenated N-benzyl amide away from the oxygen triad. At least 74 of the compounds of NAIDU have a mono-, or di--halogenated benzyl amide tail in the molecule. Again, Example 8 is shown below as exemplary:



Of the active compounds taught by NAIDU, every active compound possesses the halogenated N-benzyl amide near the oxygen triad and, further, over 70% of the structures taught have a mono- or di-halogenated benzyl tails. (NAIDU generally). Therefore, it would have been readily obvious to POSA at the time of the invention that a halogenated N-benzyl amide tail such as that taught by NAIDU would have been useful in constructing a compound to inhibit HIV integrase activity. Further given that all of the compounds disclosed by both MIYAZAKI and NAIDU contain the oxygen triad, it would have been obvious for POSA to narrow the genus of MIYAZAKI to include those molecules having a halogenated benzyl tail in order to attempt to maximize HIV integrase inhibition.

MIYAZAKI, in fact, further narrows POSA's choices by teaching only 15 compounds with a N-benzyl amide and, further, only 8 compounds with a halogenated N-benzyl amide (MIYAKAZI Examples 112, 113, 114, 214, 275, 278, 377, and 378). It would have been readily obvious to POSA to include a halogenated N-benzyl amide as

taught by NAIDU and MIYAZAKI as NAIDU focuses exclusively on this tail structure and builds similar structures to those found in MIYAZAKI.

KIYAMA: Finally, KIYAMA teaches inhibitors of HIV integrase activity containing tricyclic ring systems. Like the other prior art presented here, KIYAMA presents the compound in a Markush group comprising many millions of combinations. It will also be noted that KIYAMA also teaches the utility of a triad molecule binding the divalent metal ions in an active site as does POMMIER 2005 above. (KIYAMA pg. 14 para [0028] and following) KIYAMA states that an appropriate atom would be an "atom capable of coordinating to a divalent metal means an atom having at least one lone electron-pair and capable of giving the electrons to a vacant p orbital or d orbital of the divalent metal ion under a physiological condition. As an example of the atom, an oxygen atom capable of coordinating to a divalent metal ion … Those preferred especially are an oxygen atom capable of coordinating to a divalent metal ion" (KIYAMA para [0033]). However, more importantly, KIYAMA teaches "Although in the examples shown above, the ring system is indicated as a 6-membered ring for the purpose of convenience, any number of the ring members may be contemplated. One preferred especially is a 5-membered ring or 6 membered ring, particularly a 5-or 6-membered carbocyclic or heterocyclic ring. While the bond is represented as a single bond also for the purpose of convenience, it can be any possible bond (single bond or double bond) in organic chemistry. Each ring may be fused with several rings (carbocyclic rings or heterocyclic rings) having any ring members." (KIYAMA, Para [0077]).

OBVIOUSNESS OVER THE PRIOR ART

US 8129385B2 is invalid as it fails to meet the requirements of 35 U.S.C § 103[1]. POSA would have had the capacity to find and understand the prior art such that the combination of such prior art renders the current invention obvious. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417, 82 USPQ2d at 1396.

General state of the art at the time of the invention.

At the time of the invention, there was ample and robust research and knowledge focused on identifying and attempting to find treatments for the causes of HIV infections. One of these areas included research into the mode of action of an HIV specific enzyme known as HIV integrase. For example, a review article entitled *Retroviral integrase inhibitors year 2000: update and Perspectives*[2] stated that it was well known at the time of the invention that "HIV-1 integrase is an essential enzyme for retroviral replication and a rational target for the design of anti-AIDS drugs …" and, by at least the year 2000, "several inhibitors with known sites of actions and antiviral activity" had been developed (POMMIER 2000, abstract). The crystal structure of HIV integrase (fundamental to the understanding of how small molecules might interact with the enzyme) had been elucidated as early as 1994.[3] By 1999, a model for binding viral DNA to the HIV integrase had been developed and touted as "promising target for the design of HIV-drugs. The determination of the two domain HIV-1 IN structure, IN52–288, should prove useful for structure-based efforts to design new IN inhibitors, especially those that may act through perturbation of critical interactions between IN and the viral ends."[4] Several active site binding studies

[1] The patent statute was amended in September 2011 by the America Invents Act ("AIA"). See Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 300-01 (2011). The pre-AIA version of § 103 applies in this case. The post-AIA version of this portion of the statute (§ l 12(a)) is identical to the pre-AIA version.
[2] POMMIER, Yves, Christophe Marchand, and Nouri Neamati. "Retroviral integrase inhibitors year 2000: update and perspectives." Antiviral research 47.3 (2000): 139-148.
[3] Dyda, Fred, et al. "Crystal structure of the catalytic domain of HIV-1 integrase: similarity to other polynucleotidyl transferases." Science 266.5193 (1994): 1981-1986. Also: Maignan, Sébastien, et al. "Crystal structures of the catalytic domain of HIV-1 integrase free and complexed with its metal cofactor: high level of similarity of the active site with other viral integrases." Journal of molecular biology 282.2 (1998): 359-368.
[4] Julian, C-H. Chen, et al. "Crystal structure of the HIV-1 integrase catalytic core and C-terminal domains: A model for viral DNA binding." PNAS 97.15 (2000): 8233-8238.

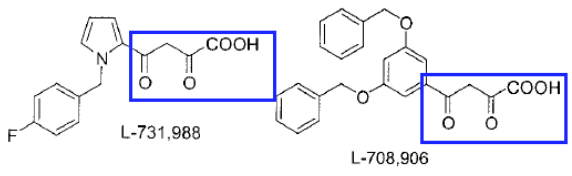
were well entrenched at the time of the invention.[5] In a paper from 2000, Espeth et al. demonstrated that the binding of an integrase inhibitor (in this case L-731,988) competed with the binding of the target DNA at the active site of the integrase.[6]

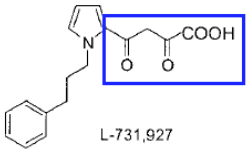
In it's response to opposition of EP3045206, ViiV attempts to imply that as of "the effective date [of the patent] the field of HIV integrase inhibitors was unpredictable. The available structural and mechanistic information about the HIV-1 integrase enzyme was limited and so the rational design of effective compounds was not straightforward."[7] (OPPO para 5.5 pg 11) This is simply untrue. The understanding of the active site and binding characteristics of HIV integrase were very well mapped and characterized at the time of the invention, showing the utility of both the triad and halogenated tail regions of the most significant inhibitors. ViiV goes on to state that "[r]esearch at the effective date was moving in many different directions." (*Id.*) In a general sense, this may have been true. However, all of the "different directions" were predicated on the development of compounds exhibiting the characteristic well identified by many others and summarized by POMMIER 2005. Namely those characteristics based on the efficacy of the DKA and HyAr regions of the active site. Was the state of the art diverse? – Yes. Was it unpredictable? – No. POSA would have know exactly what structural features to incorporate to build an effective HIV integrase inhibitor at the time of the '385.

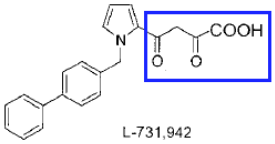
The Oxygen Triad

During the early development of integrase inhibitors, two primary families of inhibitors were studied. These were the integrase binding inhibitors (INBI) and the integrase strand transfer inhibitors (INSTI). Only the integrase strand transfer inhibitors were shown to be effective to treat patients. The first two successful INTSIs developed were raltegravir and elvitegravir with development of dolutegravir being deemed a second generation INTSI. [8]

By late 1999-early 2000, Hazuda and his group had extensively studied the inhibitory activity of various compounds on strand transfer activity in HIV integrases. In a paper published in January 2000, they stated that compounds with a diketo acid moiety were "**the archetype of a new class of integrase inhibitors and novel antiretroviral agents. The compounds are specific inhibitors of integration**, which exert their antiviral effect on HIV-1 solely as a consequence of their ability to inhibit the strand transfer activity of integrase."[9] Hence by no later than 2000, it was well known in the art that a triad of coplanar oxygen atoms were key to inhibiting DNA strand transfer in the active site of HIV integrase (See POMMIER 2000). This triad of oxygen molecules as either diketo acids, diketo aryl compounds or other similar structures were the gold standard for INSTIs. These are a few of the compounds Hazuda referenced in their 2000 journal article (Fig. 1). The diketo acid moiety is highlighted by the blue box:

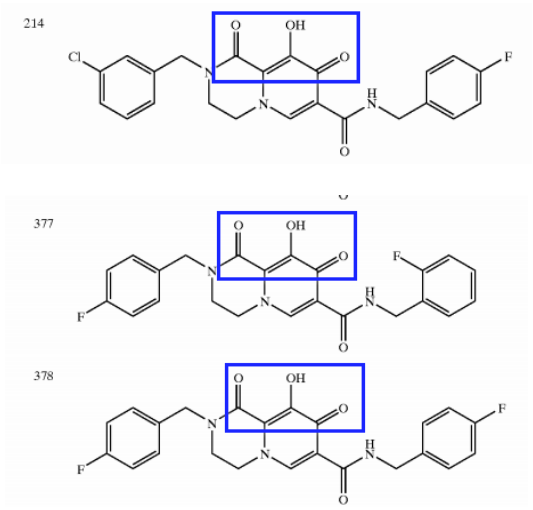






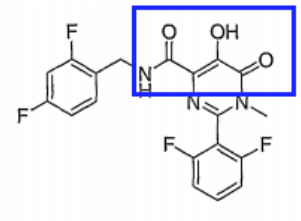
[5] Sotriffer, Christoph A., Haihong Ni, and J. Andrew McCammon. "Active site binding modes of HIV-1 integrase inhibitors." Journal of medicinal chemistry 43.22 (2000): 4109-4117.
[6] Espeseth, Amy S., et al. "HIV-1 integrase inhibitors that compete with the target DNA substrate define a unique strand transfer conformation for integrase." Proceedings of the National Academy of Sciences 97.21 (2000): 11244-11249.
[7] Response to Opposition (O00934EP OPPO 01), EPO Application 16154531.4 from ViiV Healthcare Company et al., May 13 2018.
[8] Thierry, Eloïse, Eric Deprez, and Olivier Delelis. "Different pathways leading to integrase inhibitors resistance." Frontiers in microbiology 7 (2017): 2165.
[9] Hazuda, Daria J., et al. "Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells." Science 287.5453 (2000): 646-650.

MIYAZAKI[10] teaches dozens of compounds with the oxygen triad as well, including compounds 214, 377, and 378.



MIYAZAKI compounds 214, 377, and 378

Likewise, Naidu[11] discloses inhibitors also having the same motif, in this case Example 8.



Naidu Example 8

For illustrative purposes, the structures of raltegravir, elvitegravir, and dolutegravir indicating their coplanar oxygen triads are shown below[12]:

[10] U.S. Patent Appl. 20050054645 A1 "Nitrogen-containing Fused Ring Compound and Use Thereof as HIV Integrase Inhibitor," to MIYAZAKI, et.al, March 10, 2005.
[11] WO 2004096128 A2" HIV Integrase Inhibitors" to Naidu et al, November 11, 2004.
[12] Image from: Hightower, Kendra E., et al. "Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes." Antimicrobial Agents and Chemotherapy 55.10 (2011): 4552-4559.

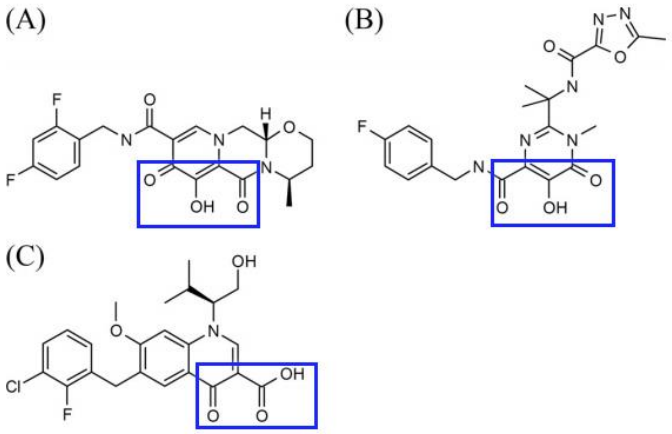
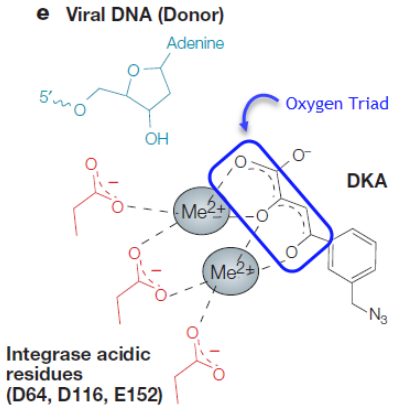


FIG. 1. HIV-1 integrase inhibitors. (A) Dolutegravir (DTG; S/GSK1349572); (B) raltegravir (RAL); (C) elvitegravir (ELV).

At the time of the invention, the mechanism of inhibition of the oxygen this triad was also well known. POMMIER 2005[13] summarizes the knowledge of the direct interaction of this triad with the divalent metal group found inside the catalytic site of the targeted HIV integrase.

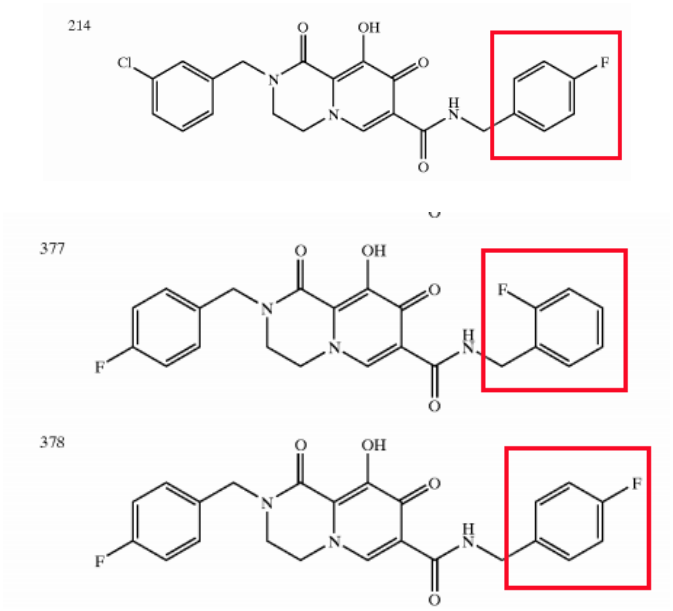
> The high selectivity of DKAs for the strand-transfer step led to a model in which the two catalytic sites are organized around the three catalytic DDE residues and the divalent metal(s) within the integrase–DNA complexes (BOX 3)87. In this model, the DONOR DNA site binds the donor (viral) DNA end and catalyzes 3′-processing. Consequently, integrase undergoes a structural change that allows the binding of the acceptor (chromosomal) DNA in the acceptor site for strand transfer84,87. DKAs, it is suggested, would bind selectively to a unique conformation of the acceptor site following binding of the viral DNA and 3′-processing, which would then produce the required change in conformation in the acceptor site for accommodating the DKA ligands. According to this scheme, divalent metal coordination would be crucial for DKA binding to the acceptor site (BOX 3, figure part e). (From POMMIER 2005).



[13] POMMIER, Yves, Allison A. Johnson, and Christophe Marchand. "Integrase inhibitors to treat HIV/AIDS." Nature Reviews Drug Discovery 4.3 (2005): 236-248.

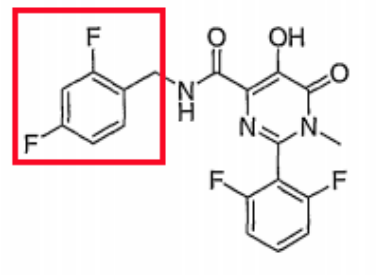
The Halogenated N-benzyl Amide

The second feature common to successful INTSIs was the presence of a halogenated N-benzyl amide moiety. At the time of the invention, it was well known that several highly active INTSIs possessed such a structure. For example, MIYAZAKI discloses at least 6 compounds, including compounds 214, 377, and 378 having a halogenated N-benzyl amide.



MIYAZAKI: Compounds 214, 377 and 378

Likewise, Naidu discloses a total of 74 inhibitors also exhibiting the structure, in this case Example 8 shows a difluoro s-substituted ring linked to the oxygen triad.



Naidu: Example 8

In addition, the two INTSIs known at the time of the invention - raltegravir and elvitegravir - each has a halogen substituted ring linked to the oxygen triad. See (B) and (C) in the figure below (comparative structures from Hightower).

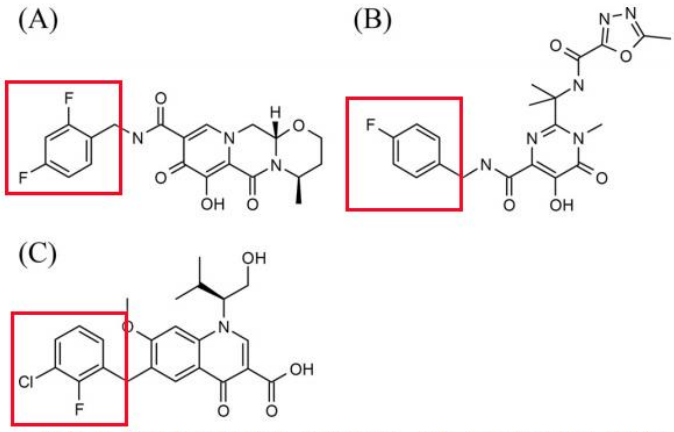
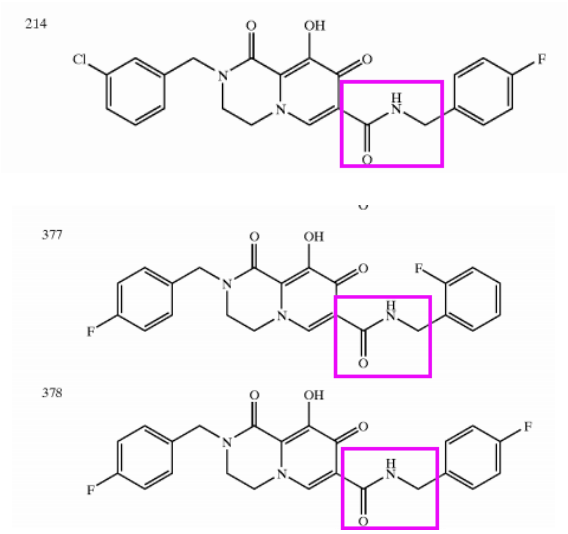


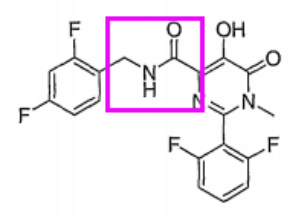
FIG. 1. HIV-1 integrase inhibitors. (A) Dolutegravir (DTG; S/GSK1349572); (B) raltegravir (RAL); (C) elvitegravir (ELV).

The Linker

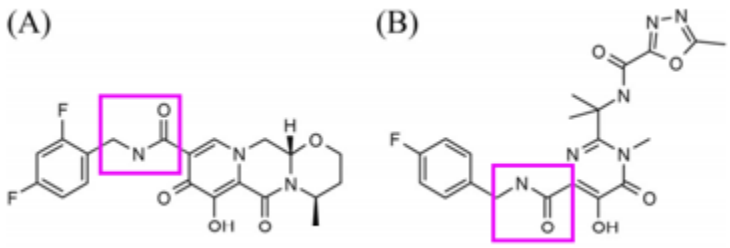
Finally, all of the structures noted above also have a small flexible linker formed between the oxygen triad and the halogenated ring system, usually a carboxamide structure or similar.



MIYAZAKI: Compounds 214, 377 and 378



Naidu: Example 8



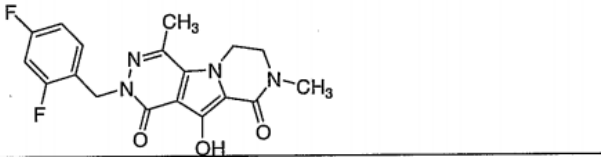
(comparative structures from Hightower).

Hence, it would have been obvious for one of ordinary skill in the art to begin building an HIV integrase inhibitor that is dolutegravir with at least these three structural motifs since all were well known and characterized at the time of the invention.

KIYAMA[14] teaches inhibitors of enzymes having two divalent metal ions as active centers such as HIV integrases. KIYAMA teaches these compounds contain, inter alia, activity tricyclic ring systems and, importantly, the utility of a triad molecule binding the divalent metal ions in an active site as does POMMIER 2005 above. (KIYAMA pg. 14 para [0028] and following) KIYAMA states that an appropriate atom would be an "atom capable of coordinating to a divalent metal means an atom having at least one lone electron-pair and capable of giving the electrons to a vacant p- orbital or d- orbital of the divalent metal ion under a physiological condition.

Finally, WAI[15] teaches HIV integrase inhibitors comprising tricyclic rings with diketo aryl and 2-4-difluoro phenyl, such as, specifically, Example 13:

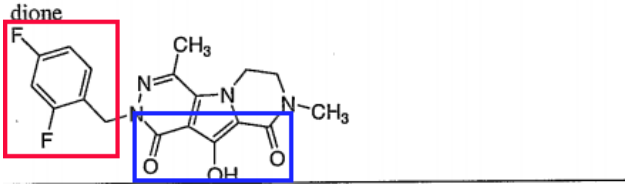
2-(2,4-Difluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrazino[1',2':1,5]-pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-dione



WAI teaches HIV integrase inhibitors as "the compounds prepared in Examples 1- 44 and 47 were tested in the integrase assay and all were found to have IC5o's less than 0.1 micromolar. More generally, the compounds prepared in Examples 1-209 were found to have IC50 values of less than 1 micromolar in the integrase assay. WO'414, P 147, lns1-8.

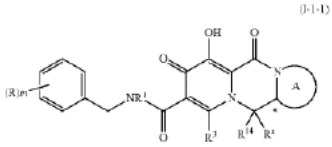
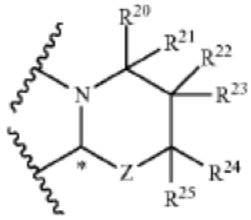
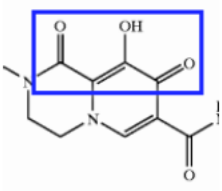
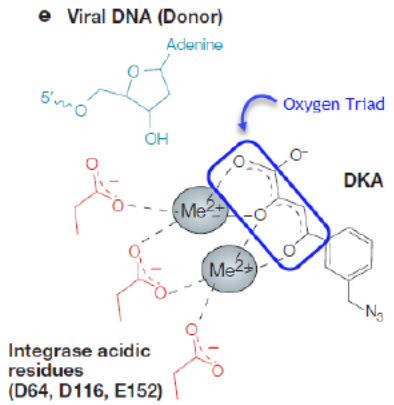
It will be further noted that Example 13 as taught by WAI to be effective as an HIV integrase inhibitor demonstrates the well-known structures (described above) of the triad of three oxygens linked to the halogenated benzyl ring structure as well as teaching the fused ring structure of the claimed compounds:

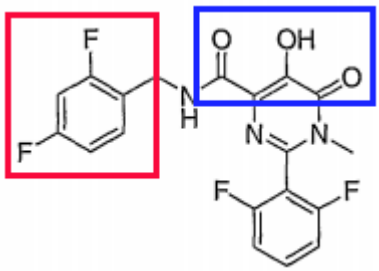
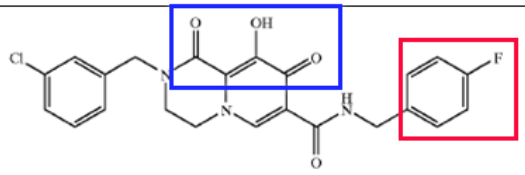
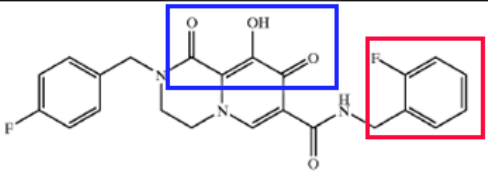
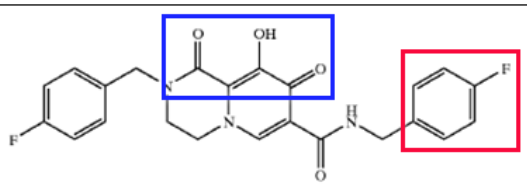
2-(2,4-Difluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrazino[1',2':1,5]-pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-dione



[14] EP 1297834 A1 "Inhibitor for Enzyme Having Two Divalent Metal Ions as Active Centers", Kiyama, et. al., April 2, 2003
[15] WO 2005110414 A2 "Hiv integrase inhibitors" to WAI et al., November 24, 2005

Ground 1 - Claims 1-3, 5-11 of US 8129385 are obvious over MIYAZAKI in light of POMMIER 2005, NAIDU, and KIYAMA.

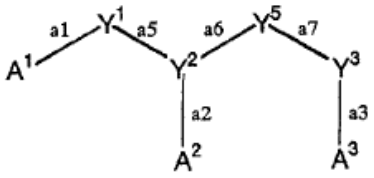
US 8,129,385	MIYAZAKI, POMMIER 2005, NAIDU and KIYAMA
1. A compound of the formula:  Wherein, Ring A is  Z = O; R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy; the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof; R^x is hydrogen; R^{14} is hydrogen or lower alkyl which is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxy, carboxy, halogen, halo lower alkyl, halo lower alkoxy, lower alkyl, lower alkenyl, lower alkynyl. cycloalkyl, cycloalkenyl, lower alkoxy, lower alkenyloxy, lower alkoxycarbonyl, nitro, nitroso, amino, alkylamino,	MIYAZAKI teaches compounds of the formula as claimed, wherein at least one motif encompasses the triad of oxygen molecules as shown in claim 1. Example 214 in part  POMMIER 2005 provides the motivation by teaching that "functional diketo or ß-hydroxy-keto groups are known to have metal-chelating functions, and metal-dependent inhibition by DKAs and DKA-like compounds has been interpreted as indicating a direct interaction of these drugs with the divalent metal in the enzyme [HIV integrase] catalytic site. Metal coordination could also be important for shaping the catalytic pocket of integrase and therefore the DKA-binding site" POMMIER 2005, P 245.  **Part e shows details of the hypothetical binding of DKAs (here MA–DKA; see FIG. 4a) at the interface of the integrase–DNA–divalent metal complex. The processed viral 3′-DNA end (in blue) is bound to integrase (the three acidic catalytic residues (DDE) are shown in red), ready to attack a host DNA phosphodiester bond (see integrase reactions in FIG. 2). It has been proposed that DKAs chelate the metal in the integrase catalytic site and stabilize the macromolecular integrase–DNA complex at the 3′-processing step of the reaction. DKAs could therefore belong to the emerging group of interfacial inhibitors, a class of drugs with a unique new mode of action.** POMMIER 2005, P 245. Therefore, it would have been obvious for POSA to have preserved the diketo moiety of the compounds such as 214, 377 and 378 and all other highly active compounds of MIYASAKI, as it was known that diketo aryl moiety was the key to HIV integrase inhibition in light of the teachings of POMMIER 2005.

acylamino, aralkylamino, aryl, aralkyl. cyano, isocyano, isocyanate, thiocyanate, isothiocyanate, mercapto, alkylthio, alkylsulfonyl, alkylsulfonylamino, carbamoyl, alkylcarbamoyl, sulfamoyl, acyl, formyloxy. haloformyl, oral, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazino, azido, ureido, guanidino, phthalimide, oxo, phosphoric acid, lower alkyl which is substituted with phosphoric acid and may be intervened with a heteroatom, aryl substituted with phosphoric acid, aralkyl substituted with phosphoric acid and hydroxy lower alkyl; R^3 is hydrogen; R^1 is hydrogen or lower alkyl; R is halogen; and m is 1, 2 or 3; or a pharmaceutically acceptable salt thereof.	NAIDU teaches that, in fact, claim 1 encompasses structures of R(m) wherein R is halogen and m is **1, 2, or 3.** There is no disclosure of any preference or technical advantages for substitution with either two Fs or one F atom. By way of example, every compound taught by NAIDU contains N-benzyl amide tail while over 70% of the most active compounds contain a halogenated substituted halogenated N-benzyl amide structure. Further, for example, NAIDU discloses an HIV integrase inhibitor comprising 2-4- difluoro phenyl linked to a diketo aryl via a carboxamide linker as exemplified by Example 8 below.  MIYAZAKI discloses that either 2- or 4- substitution of phenyl ring is possible (compounds 377, 378 and 214), hence it would have been obvious to form a 2-4- difluoro phenyl for compounds 214, 377 or 378 because such moiety has been disclosed in known HIV integrase inhibitors. MIYAZAKI specifically teaches halogenated N-benzyl amide tail structures as discussed. MIYAZAKI specifically discloses various compounds 214, 377 and 378: Compound No. / Structure 214  377  378 

Compounds 214, 377 and 378 all have HIV integrase inhibitory activity with IC_{50} being ++++ (less than 0.01μM). See Para [1513], Table 42 and Table 45. It would have been obvious to these compounds leading compounds for further modifications to enhance HIV integrase inhibition.

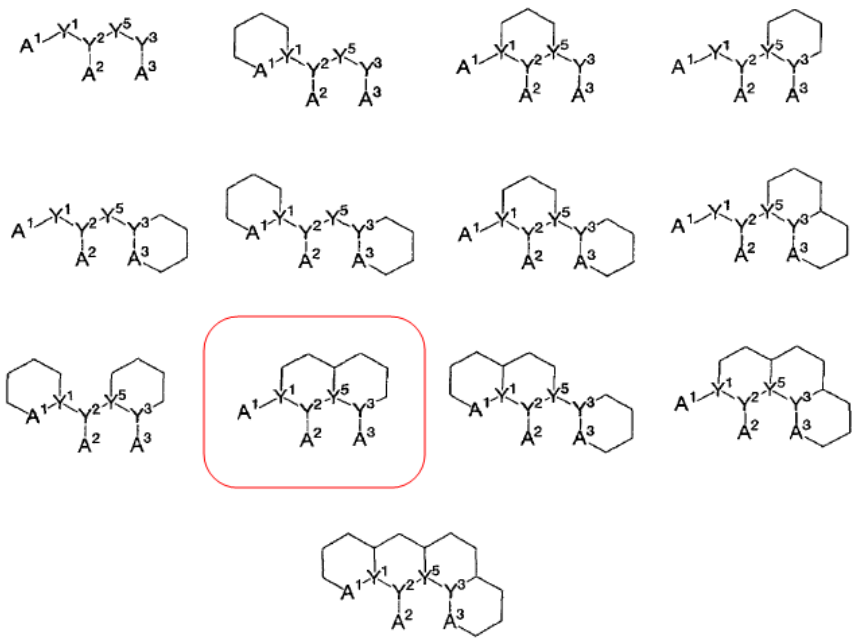
Finally, it would have been obvious to POSA at the time of the invention to form fused tricyclic rings for compounds disclosed by MIYAZAKI because HIV integrase inhibitors with tricyclic rings were well known at the time of the invention as shown by KIYAMA.

For example, KIYAMA teaches HIV integrase inhibitor compound having a structure represented by Formula (III)



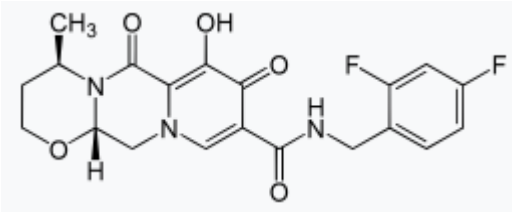
(III)

wherein each symbol is defined as described above may be exemplified by a compound having a skeleton shown below.



See KIYAMA Para [0075]

"wherein atom A1, atom A2 and atom A3 are each independently a nitrogen atom capable of coordinating to a divalent metal ion, oxygen atom capable of coordinating to a divalent metal ion or sulfur atom capable of coordinating to a divalent metal ion, atom Y1 and atom Y3 are each independently a carbon atom, nitrogen atom or sulfur atom, atom Y2 is a carbon atom, atom Y5 is a carbon atom or nitrogen atom,

	bond a1 to bond a3 and bond a5 to bond a7 are each independently a single bond or a double bond, one of bond a2, bond a5 and bond a6 is a double bond, and the other two are single bonds, bond a1, bond a3 and bond a5 to bond a7 may each independently constitute a part of the ring, provided that any adjacent bonds of bond a1 to bond a3 and bond a5 to bond a7 are not double bonds at the same time, may be searched for." KIYAMA Para [0058]. Emphasis added. "Although in the examples shown above, the ring system is indicated as a 6-membered ring for the purpose of convenience, any number of the ring members may be contemplated. One preferred especially is a 5-membered ring or 6 membered ring, particularly a 5-or 6-membered carbocyclic or heterocyclic ring. While the bond is represented as a single bond also for the purpose of convenience, it can be any possible bond (single bond or double bond) in organic chemistry. **Each ring may be fused with several rings (carbocyclic rings or heterocyclic rings) having any ring members**." KIYAMA, Para [0077]. Emphasis added POSA would have rapidly comprehended that HIV inhibitors having tricyclic rings are within the scope and teachings of KIYAMA because it discloses several tricyclic ring systems shown in para [0075] above. It would also have been obvious to fuse a third heterocyclic ring to the bicyclic ring system illustrated above given the disclosures of KIYAMA. It follows, then that one of the structural species specifically encompassed by claim 1 is dolutegravir (also claimed in claims 6-9). Applying the language of the claims with the knowledge provided by MIYAZAKI, NAIDU, and KIYAMA shows that wherein R^{20} is CH_3, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently hydrogen; R^x is hydrogen R^3 is hydrogen; R^1 is hydrogen; R is F; and m is 2. Gives 

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^X is hydrogen; R^{14} is hydrogen; R^3 is hydrogen; m is 1, 2 or 3 and R is halogen.	As set forth in claim 1.
3. A compound according to claim 1 wherein the pharmaceutically acceptable salt is a sodium salt.	MIYAZAKI discloses a pharmaceutically acceptable salt is a sodium salt as well as numerous compounds with sodium salt. "The "pharmaceutically acceptable salt thereof" may be any salt as long as it forms a non-toxic salt with the compounds of the above-mentioned formulas [I], [I]-1, [I]-2, [I]-3 and [I]-4, and can be obtained by a reaction with an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; an organic acid such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoracetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, benzylsulfonic acid and the like; an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like;" US'645, Para [0877] In addition, creation of sodium salt form is a standard procedure in pharmaceutical chemistry and thus obvious.
5. A compound selected from the group consisting of: (3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2R,9aR)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-	As set forth in claim 1 for (4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide, e.g., dolutegravir.

anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2R,9aS)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-6,10-dioxo-2-phenyl-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2R,9aR)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; (3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-	

anthracene-7-carboxylic acid 4-fluoro-benzylamide; (2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; (2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; 5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diazaanthracene-7-carboxylic acid 4-fluorobenzylamide; 5-Hydroxy-3,3-dimethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; 5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-dizazaanthracene-7-carboxylic acid 4-fluorobenzylamide; 5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide;	

5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide; enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.	
6. A compound selected from the group consisting of (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; an enantiomer thereof; diastereomer thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; or a pharmaceutically acceptable salt thereof.	As set forth in claim 1.
7. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide or a pharmaceutically acceptable salt thereof.	As set forth in claim 1
8. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic ac	As set forth in claim 1 {Furthermore, this claim is also invalid for lack of written description as described elsewhere. The specification of '385 did not disclose the sodium salt of the compound claimed in claim 8. It only discloses its base form. See Example Y-3 of the specification.}

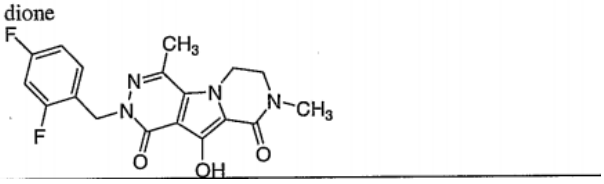
id 2,4-difluoro-benzylamide sodium salt.	
9. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide.	As set forth in claim 1
10. A pharmaceutical composition comprising (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.	The recited compound structure is set forth in claim 1. MIYAZAKI further discloses pharmaceutical composition comprising the HIV integrase inhibitor compound together with a pharmaceutically acceptable carrier or diluent. "Formulation example Formulation Example (a) Compound of Example 1 10g (b) Lactose 50g (c) Cornstarch 15g (d) Carboxymethylcellulose sodium 44g (e) Magnesium stearate 1g" See MIYAZAKI, Para [1536] "[0885] When the compound of the present invention is used as a pharmaceutical preparation, it is admixed with pharmaceutically acceptable carriers, excipients, diluents, extending agents, disintegrants, stabilizers, preservatives, buffers, emulsifiers, flavoring agents, coloring agents, sweetening agents, thickeners, correctives, dissolution aids, and other additives, that are generally known per se, such as water, vegetable oil, alcohol (e.g., ethanol or benzyl alcohol etc.), polyethylene glycol, glycerol triacetate, gelatin, carbohydrate (e.g., lactose, starch etc.), magnesium stearate, talc, lanolin, petrolatum and the like, formed into tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like by a conventional method, and administered systemically or topically, and orally or parenterally." See MIYAZAKI, Para [0885] Emphasis added.
11. A pharmaceutical composition comprising a compound according to any one of claims 1, 5, 6, 7, 8, 9 or 4, or a pharmaceutically acceptable salt thereof, together with a	As set forth in claim 1 and claim 10.

pharmaceutically acceptable carrier or diluent.	

Ground 2 - Claims 1-3, 5-11 of US 8129385 are obvious over MIYAZAKI in light of POMMIER 2005, Naidu, and WAI.

All of the arguments set forth above in Ground 1 as to MIYAZAKI in light of POMMIER 2005 and NAIDU are the same herein for Ground 2. Further, WAI teaches HIV integrase inhibitors comprising tricyclic rings with diketo aryl and halogenated benzyl ring, such as, specifically, Example 13:

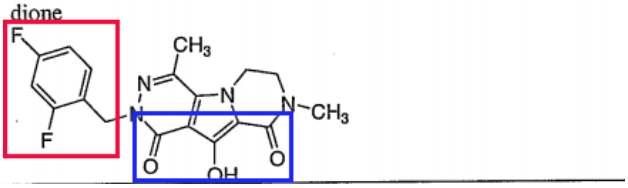
2-(2,4-Difluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrazino[1',2':1,5]-pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-dione



WAI teaches "the compounds prepared in Examples 1- 44 and 47 were tested in the integrase assay and all were found to have IC5o's less than 0.1 micromolar. More generally, the compounds prepared in Examples 1-209 were found to have IC50 values of less than 1 micromolar in the integrase assay. WO'414, P 147, lns1-8.

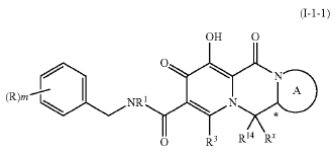
It will be further noted that Example 13 as taught by WAI to be effective as an HIV integrase inhibitor demonstrates the well-known structures (described above) of the triad of three oxygens linked to the halogenated benzyl ring structure as well demonstrates the planar fused rings system as claimed in the '385:

2-(2,4-Difluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrazino[1',2':1,5]-pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-dione



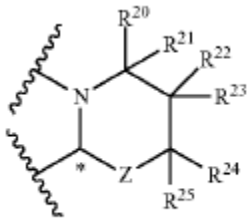
WAI teaches the ring system as a closed, tricyclic, ring system. POSA, using the teachings of MIYAZAKI, POMMIER 2005 and NAIDU in view of WAI would have found it readily obvious to have closed the ring system of MIYAZAKI, for example, to form a stable, tricyclic ring system as taught by WAI.

US 8,129,385	MIYAZAKI, POMMIER 2005, NAIDU and WAI
1. A compound of the formula:	MIYAZAKI teaches compounds of the formula as claimed, wherein at least one motif encompasses the triad of oxygen molecules as shown in claim 1.



Wherein,

Ring A is



Z = O;

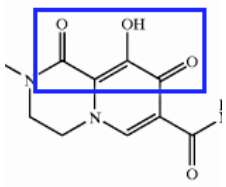
R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently hydrogen, C_1-C_8alkyl, C_6-C_{14}arylC_1-C_8alkyl, C_6-C_{14}aryl, or alkoxy;

the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof;

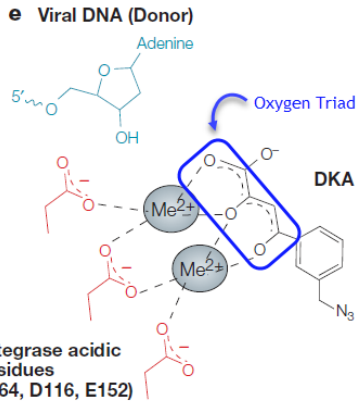
R^x is hydrogen;

R^{14} is hydrogen or lower alkyl which is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxy, carboxy, halogen, halo lower alkyl, halo lower alkoxy, lower alkyl, lower alkenyl, lower alkynyl. cycloalkyl, cycloalkenyl, lower alkoxy, lower alkenyloxy, lower alkoxycarbonyl, nitro, nitroso, amino, alkylamino, acylamino, aralkylamino, aryl, aralkyl. cyano, isocyano, isocyanate, thiocyanate, isothiocyanate, mercapto, alkylthio, alkylsulfonyl, alkylsulfonylamino, carbamoyl, alkylcarbamoyl,

Example 214 in part



POMMIER 2005 provides the motivation by teaching that "functional diketo or ß-hydroxy-keto groups are known to have metal-chelating functions, and metal-dependent inhibition by DKAs and DKA-like compounds has been interpreted as indicating a direct interaction of these drugs with the divalent metal in the enzyme [HIV integrase] catalytic site. Metal coordination could also be important for shaping the catalytic pocket of integrase and therefore the DKA-binding site" POMMIER 2005, P 245.



Part e shows details of the hypothetical binding of DKAs (here MA–DKA; see FIG. 4a**) at the interface of the integrase–DNA–divalent metal complex. The processed viral 3′-DNA end (in blue) is bound to integrase (the three acidic catalytic residues (DDE) are shown in red), ready to attack a host DNA phosphodiester bond (see integrase reactions in** FIG. 2**). It has been proposed that DKAs chelate the metal in the integrase catalytic site and stabilize the macromolecular integrase–DNA complex at the 3′-processing step of the reaction. DKAs could therefore belong to the emerging group of interfacial inhibitors, a class of drugs with a unique new mode of action.**

POMMIER 2005, P 245.

Therefore, it would have been obvious for POSA to have preserved the diketo moiety of the compounds such as 214, 377 and 378 and all other highly active compounds of MIYASAKI, as it was known that diketo aryl moiety was the key to HIV integrase inhibition in light of the teachings of POMMIER 2005.

NAIDU teaches that, in fact, claim 1 encompasses structures of R(m) wherein R is halogen and m is **1, 2, or 3.** There is no disclosure of any preference or technical advantages for substitution with either two Fs or one F atom.

By way of example, every compound taught by NAIDU contains N-benzyl amide tail while over 70% of the most active compounds contain a halogenated substituted halogenated N-benzyl amide structure. Further, for example, NAIDU discloses an HIV integrase inhibitor comprising 2-4-difluoro phenyl linked to a diketo aryl via a carboxamide linker as exemplified by Example 8 below.

sulfamoyl, acyl, formyloxy. haloformyl, oral, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazino, azido, ureido, guanidino, phthalimide, oxo, phosphoric acid, lower alkyl which is substituted with phosphoric acid and may be intervened with a heteroatom, aryl substituted with phosphoric acid, aralkyl substituted with phosphoric acid and hydroxy lower alkyl;

R^3 is hydrogen;

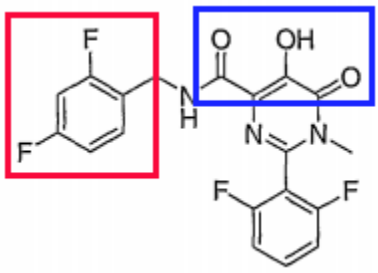
R^1 is hydrogen or lower alkyl;

R is halogen;

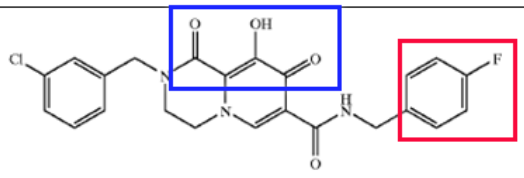
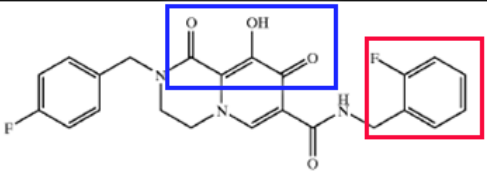
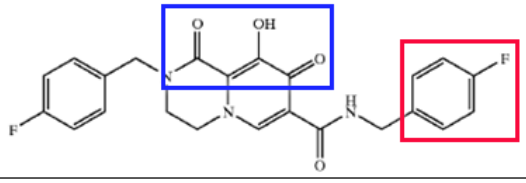
and

m is 1, 2 or 3;

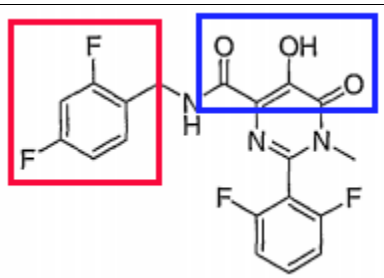
or a pharmaceutically acceptable salt thereof.



MIYAZAKI discloses that either 2- or 4- substitution of phenyl ring is possible (compounds 377, 378 and 214), hence it would have been obvious to form a 2-4- difluoro phenyl for compounds 214, 377 or 378 because such moiety has been disclosed in known HIV integrase inhibitors. MIYAZAKI specifically teaches halogenated N-benzyl amide tail structures as discussed. MIYAZAKI specifically discloses various compounds 214, 377 and 378:

Compound No.	Structure
214	
377	
378	

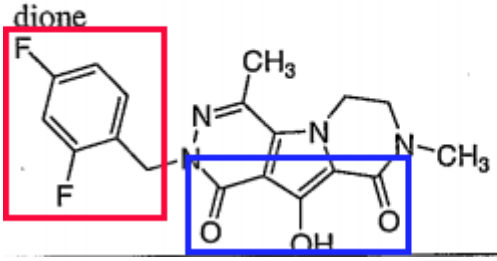
By way of example, every compound taught by NAIDU contains a N-benzyl amide tail structure while over 70% of the most active compounds contain a halogenated substituted benzyl tail. Further, for example, NAIDU discloses an HIV integrase inhibitor comprising 2-4- difluoro phenyl linked to a diketo aryl via a carboxamide linker as exemplified by Example 8 below.



Hence it would have been obvious to form a 2-4- difluoro phenyl for compounds 214, 377 or 378 of MIYAZAKI because such moiety has been disclosed in known HIV integrase inhibitors as taught in NAIDU.

Finally, it would have been obvious to POSA to form the tricyclic ring system as claimed because WAI also teaches HIV integrase inhibitor compound having a structure represented by Example 13:

2-(2,4-Difluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrazino[1',2':1,5]-pyrrolo[2,3-d]pyridazine-1,9(2H,6H)-dione

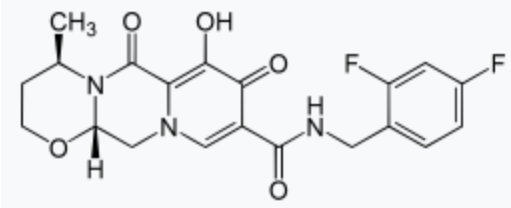


WAI teaches the compound with potent HIV integration inhibition activity possess both the triad of three oxygens linked to the halogenated benzyl ring structure as also disclosed by MIYAZAKI and further teaches the closed tricyclic rings.

See WO'414, P 75.

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds prepared in Examples 1-44 and 47 were evaluated in the integrase assay and all were found to have IC5o's less than 0.1 micromolar. More generally, the compounds prepared in Examples 1-209 were found to have IC50 values of less than 1 micromolar in the integrase assay. WO'414, P 147, lns1-8.

	POSA would have rapidly comprehended that HIV inhibitors having tricyclic rings are within the scope and teachings of WAI because it discloses several tricyclic ring systems. It would also have been obvious to fuse a third heterocyclic ring to the bicyclic ring system illustrated above given the disclosures of WAI. Furthermore, it would have been obvious to adopt the tricyclic ring structure to the compounds 214, 377 and 378 of MIYAZAKI since all are directed to HIV integrase inhibitors with high potency. It follows, then that one of the structural species encompassed by claim 1 is dolutegravir (also claimed in claims 6-9). Applying the language of the claims with the knowledge provided by MIYAZAKI, NAIDU, and WAI shows that wherein R^{20} is CH_3, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} are independently hydrogen; R^x is hydrogen R^3 is hydrogen; R^1 is hydrogen; R is F; and m is 2. Gives 
2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^X is hydrogen; R^{14} is hydrogen; R^3 is hydrogen; m is 1, 2 or 3 and R is halogen.	As set forth in claim 1.
3. A compound according to claim 1 wherein the pharmaceutically acceptable salt is a sodium salt.	MIYAZAKI discloses a pharmaceutically acceptable salt is a sodium salt as well as numerous compounds with sodium salt. "The "pharmaceutically acceptable salt thereof" may be any salt as long as it forms a non-toxic salt with the compounds of the above-mentioned formulas [I], [I]-1, [I]-2, [I]-3 and [I]-4, and can be obtained by a reaction

	with an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; an organic acid such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoracetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, benzylsulfonic acid and the like; an inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like;" US'645, Para [0877] In addition, creation of sodium salt form is a standard procedure in pharmaceutical chemistry and thus obvious.
5. A compound selected from the group consisting of: (3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2R,9aR)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide;	As set forth in claim 1 for (4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide, e.g., dolutegravir.

(2R,9aS)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-6,10-dioxo-2-phenyl-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aS)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2R,9aR)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; (3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; (2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; (2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-	

3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; (2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; 5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diazaanthracene-7-carboxylic acid 4-fluorobenzylamide; 5-Hydroxy-3,3-dimethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide; 5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-dizazaanthracene-7-carboxylic acid 4-fluorobenzylamide; 5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; 5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide; enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.	

6. A compound selected from the group consisting of (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide; an enantiomer thereof; diastereomer thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; or a pharmaceutically acceptable salt thereof.	As set forth in claim 1.
7. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide or a pharmaceutically acceptable salt thereof.	As set forth in claim 1
8. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic ac id 2,4-difluoro-benzylamide sodium salt.	As set forth in claim 1 {Furthermore, this claim is also invalid for lack of written description as described elsewhere. The specification of '385 did not disclose the sodium salt of the compound claimed in claim 8. It only discloses its base form. See Example Y-3 of the specification.}
9. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide.	As set forth in claim 1
10. A pharmaceutical composition comprising (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid	The recited compound structure is set forth in claim 1. MIYAZAKI further discloses pharmaceutical composition comprising the HIV integrase inhibitor compound together with a pharmaceutically acceptable carrier or diluent.

2,4-difluoro-benzylamide or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.	"Formulation example Formulation Example (f) Compound of Example 1 10g (g) Lactose 50g (h) Cornstarch 15g (i) Carboxymethylcellulose sodium 44g (j) Magnesium stearate 1g" See MIYAZAKI, Para [1536] "[0885] When the compound of the present invention is used as a pharmaceutical preparation, it is admixed with pharmaceutically acceptable carriers, excipients, diluents, extending agents, disintegrants, stabilizers, preservatives, buffers, emulsifiers, flavoring agents, coloring agents, sweetening agents, thickeners, correctives, dissolution aids, and other additives, that are generally known per se, such as water, vegetable oil, alcohol (e.g., ethanol or benzyl alcohol etc.), polyethylene glycol, glycerol triacetate, gelatin, carbohydrate (e.g., lactose, starch etc.), magnesium stearate, talc, lanolin, petrolatum and the like, formed into tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like by a conventional method, and administered systemically or topically, and orally or parenterally." See MIYAZAKI, Para [0885] Emphasis added.
11. A pharmaceutical composition comprising a compound according to any one of claims 1, 5, 6, 7, 8, 9 or 4, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.	As set forth in claim 1 and claim 10.

Additional Observation on U.S. 8129385 B2

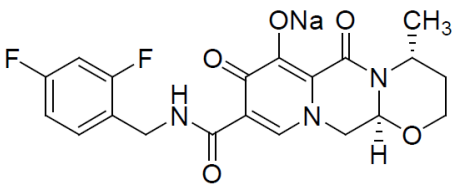
Lack of Written Description (synopsis)

US8129385B2 entitled *Substituted 5-hydroxy-3,4,6,9,9a, 10-hexanhydro-2h-1-oxa04a,8a-diaza-anthracene-6,10-dioness* to Johns et al. is invalid due to its failure to comply with the requirements of 35 U.S.C § 112[16] which provides in pertinent part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ....
>
> Section 112 sets out separate requirements for written description and enablement. See Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1344 (Fed. Cir. 2010) (holding that written description and enablement requirements are separate). Still, these requirements "often rise and fall together." Id. at 1352. (Idenix Pharmaceuticals LLC v Gilead Sciences, DED-1-14-cv-00846-591, pg 16 (hereinafter "Idenix"))

To comply with the written description requirement, a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." Ariad, 598 F.3d at 1351. "[T]he test requires an objective inquiry into the four comers of the specification from the perspective of a person of ordinary skill in the art." *Id*. "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id*. at 1352. However, "a description that merely renders the invention obvious does not satisfy the requirement." *Id*.

The primary active ingredient in each of Tivicay, Tiumeq, Dovato and Juluca is dolutegravir sodium or as it is described on the FDA label (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7olate sodium salt. It will be assumed that allowing for stereochemical variations (i.e. "(4R,12aS)" or "(4R, 9aS)") this is also equivalent for these purposes to (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic ac id 2,4-difluoro-benzylamide sodium salt. Dolutegravir may be represented as:



This compound is claimed generically in at least claims 1-4 and more specifically in at least claim 8.

[16] The patent statute was amended in September 2011 by the America Invents Act ("AIA"). See Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 300-01 (2011). The pre-AIA version of§ 112 applies in this case. The post-AIA version of this portion of the statute (§ l 12(a)) is identical to the pre-AIA version.

Claim 8 reads in its entirety:

> 8. A compound which is (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic ac id 2,4-difluoro-benzylamide **sodium salt**.

However, nowhere in the specification is the compound of claim 8 taught or described sufficiently**. (4R,9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic ac id 2,4-difluoro-benzylamide *sodium salt* is not disclosed**. The compound (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide is mentioned twice in the specification among many dozens of other species of compounds: a) once in a list of dozens of other examples (col 15 ln 1-4) and once as Example Y-3 showing the purported NMR signal of the compound (col 91 lns 40-51).

To show a patent meets the requirements for written description, an applicant must show "possession of the claimed invention by describing the claimed invention *with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention*. Lockwood v. Amer. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) (emphasis added). MPEP 2163 goes on to say an "invention described solely in terms of a method of making and/or its function may lack written descriptive support where there is no described or art-recognized correlation between the disclosed function and the structure(s) responsible for the function. (MPEP 2161 a). For the compounds claimed in the '385 and specifically for that of claim 8, there is no art-recognized correlation between the disclosed function (*i.e.* inhibition of HIV integrase) and the structure responsible for the function (*i.e.* the sodium salt form of compound Y-3). Further, and especially with regard to the Markush claim groups, "*the knowledge and level of skill in the art would not have permitted the ordinary artisan to immediately envisage the claimed product arising from the disclosed process.* See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (**a "laundry list" disclosure of every possible moiety does not necessarily constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species**); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. **The trouble is that there is no such disclosure, easy though it is to imagine it.**" (emphasis in original, bold added)); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("[T]he specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

Because the '385 fails to "describe the technology that is sought to be patented … and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005), at least claim 8 is invalid under 35 U.S.C § 112.

Lack of Enablement (synopsis)

"Enablement is a question of law based on underlying factual findings." MagSil Corp. v. Hitachi Glob. Storage Techs., Inc., 687 F.3d 1377, 1380 (Fed. Cir. 2012). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." Id. (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, Inc. v. Novo NordiskA/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Claims 1-3 describe a very broad genus of compounds presented as a Markush group of substitutions while claims 5-11 describe various structural limitations on the compounds in question. However, the claims are all ONLY structural in nature even though at least claims 1-7, 10 and 11 make mention of the compounds being in a "pharmaceutically acceptable" form. (Noting that Claim 4 is not representative of any derivatives of DTG due to a lack of a methyl group on the terminal oxazine ring.)

In fact, in order to be useful as an effective, active pharmaceutical ingredient, the molecules must possess some functional limitation. In this case, according to the specification, the invention is related to "a class of substituted 5-hydroxy-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-6,10-diones **useful as anti-HIV agents**" (Abstract, emphasis added). In fact, in order to function as an active anti-viral ingredient as found in the HIV drugs Tivicay, Tiumeq, Dovato, and/or Juluca, the "anti-HIV activity" must be further narrowed to "possess a potent HIV Integrase inhibitory activity"(col 2 lns 8-10)[17]. Thus the claims, in order to be useful as envisioned, must carry both a structural limitation *and* a functional limitation. More specifically, the compounds will be those "substituted 5-hydroxy-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-6,10-diones" that are useful for inhibiting HIV integrase activity.

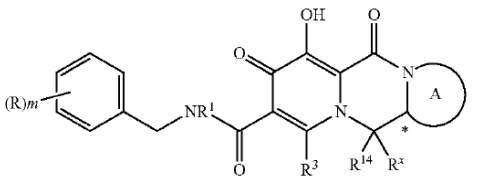
The latter point is most pertinent since it is important to note what is *not* present in the claims themselves. That is, inhibiting HIV integrase activity – which the '385 insists is essential to the teachings and

[17] In the case of HIV infections, integrases are proteins that catalyze retroviral DNA integration into host DNA genomes, thereby introducing the HIV genes into the infected cell. It is an essential step in the replication of retroviruses. If the integrases can be inhibited or inactivated in some way, then the integration of HIV into infected cells can be essentially prevented. (see *The Molecular biology of HIV integrase*, by Craigie Future Virol. 2012 July ; 7(7): 679–686.

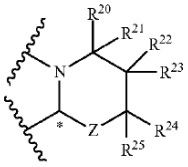
practice of the patent ("polycyclic carbamoylpyri done derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent" (JOHNS col 1 lns 16-20)) - is not found in the claims. In fact, the claims are **not** limited to compounds that possess an inhibitory activity toward any HIV integrase. Therefore, **a "feature which is taught as critical in a specification [e.g. HIV integrase inhibition]and is not recited in the claims should result in a rejection of such claim under the enablement provision section of 35 U.S.C. 112**. See In reMayhew, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976).

Focusing, therefore, on the structural limitations of the claims, an indeterminate number of compounds are envisioned in the Markush language of claims 1-3. The number of compounds encompassed by the claims can easily number into the billions since the compounds of the claims contain multiple locations for numerous chemical substitutions as shown by Formula I-1-1:

(I-1-1)



wherein,
ring A is



Z = O;

And each of R, R1, R3, R14, Rx, R20, R21, R22, R23, R24, and R25 may be occupied by hundreds and hundreds of individual combinations.

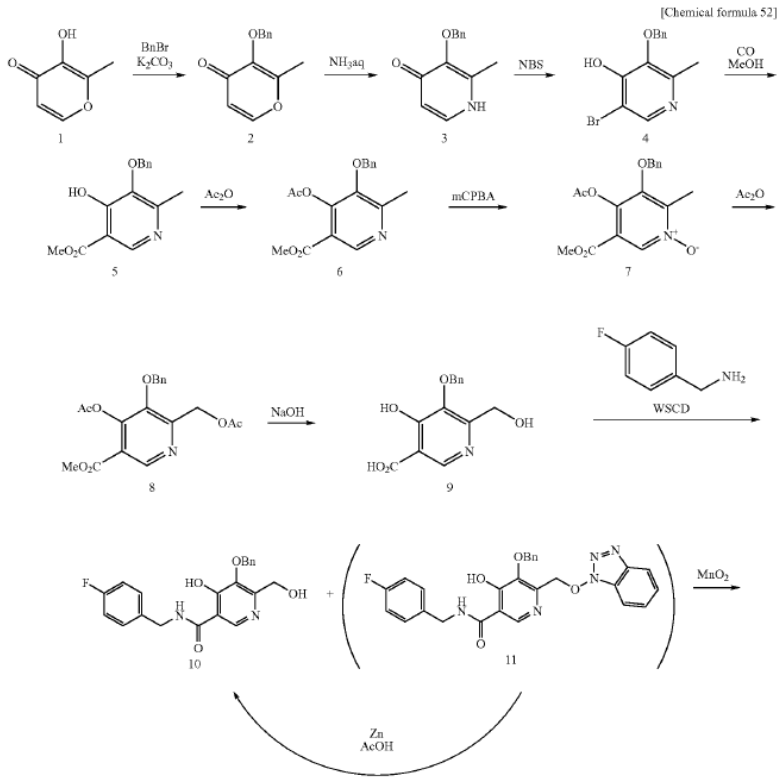
While it is clear that a POSA is capable of working with any number of these compounds, and indeed, theoretically capable of narrowing the number of potential compounds to a workable number of examples based on some functional limitations, there is nothing that leads POSA "for how to navigate from the larger to the smaller category" (Idenix Footnote 13). Therefore, this renders the patent invalid for lack of enablement. In fact, to determine which of the structurally limited compounds of the claims are indeed functional, POSA must test each and every compound using an integrase assay. As to the disclosures in the specification, all experimental determinations of integrase activity are described as IC_{50} values in Experimental Examples 1 and 2 (col 174 ln 44 – col 176 ln 65). **The only experimental examples shown are for compounds C-2, F-2, H-2 (Table 1) and Z-1 through Z-60 (Table 2). None of the compounds tested are dolutegravir**.

Further, it is clear from at least Table 2 of the '385 that a wide variation in integrase inhibitory activity is apparent from a small sample of 60 or so compounds the applicants seemingly randomly chose to test. That is, the range of activities of significant IC_{50} values are categorized as spanning a concentration of inhibitor of from <10nM to >100nM. It would likewise be safe to assume that not all compound disclosed by the massive Markush structural group possess any inhibitory activities toward the target HIV integrase while other possess varying levels of inhibition. Hence the specification and claims are replete with embodiments not within the scope of the patent.

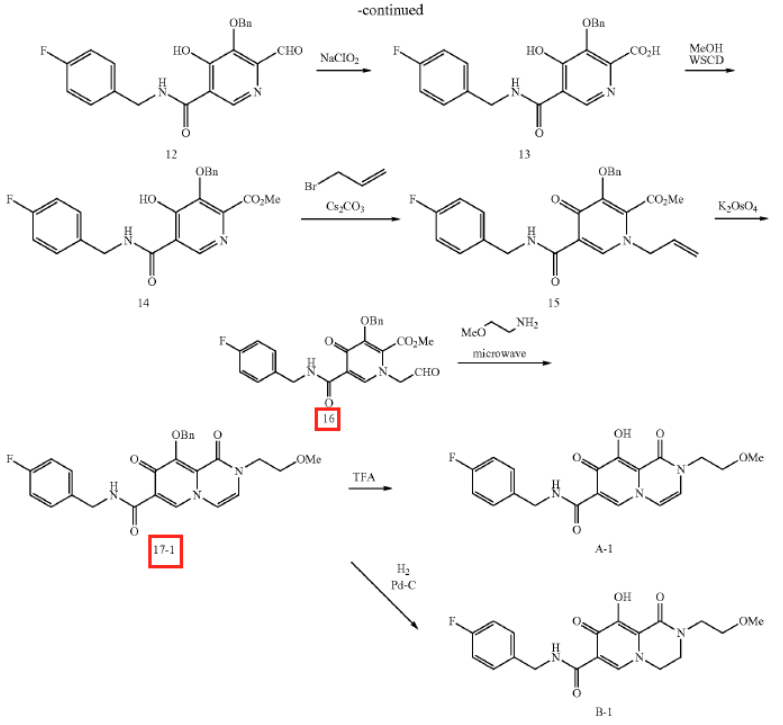
It is further noted that of the billions of structural embodiments, many, if not most, were not readily available to POSA to test for integrase inhibition and would thus have to be synthesized and manufactured by POSA prior to testing. That is, these compounds were not "off the shelf compounds". The synthetic steps for each and every structural molecule are detailed, labor intensive, and not easily automated or routine.

MPEP 2164.06 requires "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis." Using Example Y-3 to show an example of the amount of work to synthesize a single compound: Example Y-3 was synthesized according to steps disclosed in synthesizing compound C-21 (col 91 lns 12-13) wherein compound C-21 is synthesized according to variation on the synthesis of compound C-1 which in itself is based on the synthetic pathway of a combination of compound 16 and compound 33 using compound 55 as an intermediary donor molecule. Compound 33 was itself synthesized using the method of synthesis for compound 17-1 (col 64 ln 45-47). It will be apparent that the synthesis of any one of these compounds is not only *not routine* but each requires considerable time and energy to perform. For example, the pathway for the synthesis of compounds 16 and 17-1 are exemplified in cols 57-56 as :

[Chemical formula 52]



-continued



The enabling description of this pathway alone in the '385 begins at column 59 ln 45 and continues through column 64 ln 11. It includes no less than 17 separate phases and includes **at least 62 hours** specifically referenced for various experimental steps. These procedures *do not include* other physical manipulations that must be performed at each individual stage (*e.g.* filtering, washing, crystalizing, distillation, extractions, gassing, weighing, *etc*.). In fact, Step 4 and Step 17 each (col 61 ln 1-4, col 63 ln 65-67) describe single step processes requiring 18 hours and 20 hours, respectively, during this intermediary synthetic route. In other words, this was not a routine nor automated system. Further it is shown that the synthesis of each and every compound could consume multiple days of effort by POSA. Given the number of compounds exemplified by the Markush groups of claims 1-4, this represents an undue amount of experimentation without further guidance from the specification. And, to be clear, the pathway elucidated above just allows the synthesis of compound C-1. Several other steps are necessary to transition compound C-1 all the way through to C-21 and eventually to Y-3.

POSA would have had to synthesize a significant number of candidate compounds, which would have required a substantial amount of time to find appropriate compounds suitable for the specifications. The synthesis of any one of the claimed compounds "was neither routine nor simple but, instead, required extensive experimentation." (Idenix, pg 31-32) Once synthesized each individual compound would then have to be tested for its ability to inhibit of HIV integrase. This "screening would have taken additional substantial time and effort, on top of the time and effort required to synthesize the compounds." (Idenix, pg 37-38.) In other words, even for compounds satisfying the structural limitations of the claims – it would be necessary to further screen these compounds in order to determine if they also met the functional limitations of the specifications. This screening would have taken **additional substantial time and effort**, on top of the time and effort required to synthesize the compounds.

Hence, even assuming that a POSA would have chosen to focus exclusively on Example Y-3 (*i.e.,* claim 8), the range of possibilities and unpredictability of the art foreclosed mere deductive "visualization" as a successful strategy. Wands requires "that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."

To determine undue experimentation under the *Wands* factors.

> In deciding whether a person having ordinary skill would have to experiment unduly in order to make and use the invention, you may consider several factors:
>
> (1) the quantity of experimentation necessary;
>
> (2) how routine any necessary experimentation is in the relevant field;
>
> (3) whether the patent discloses specific working examples of the claimed invention;

(4) the amount of guidance presented in the patent;

(5) the nature and predictability of the field;

(6) the level of ordinary skill; and

(7) the scope of the claimed invention.

Wands Factor	US'835
the quantity of experimentation necessary	Significant work is necessary to synthesize and screen the universe of the compounds that fall within the scope of the invention. In this case, at least 3-5 days are required for synthesizing each and every claimed compound. And further, this synthesis does not include testing each compound so synthesized for HIV integrase inhibition.
how routine any necessary experimentation is in the relevant field	Some of the synthetic steps were routine, but many of the other synthetic steps were non-routine as exemplified in the 17 step process necessary to make a single intermediate compound described above.
whether the patent discloses specific working examples of the claimed invention	No working examples are disclosed for the pertinent claims. While the patent does disclose some working embodiments, routes for making the claimed molecules, and assays for screening candidates, the claims' structural limitations are enormously broad, and the patent's examples disclose a significant number of possible arrangements which are not pertinent to the claimed compounds.
the amount of guidance presented in the patent	The claims do not actually require a specific inhibition of an HIV integrase by the compound, hence there is little to no guidance for POSA to pursue the operable compounds.
the nature and predictability of the field	The use of such compounds to inhibit the HIV integrase constituted an unpredictable endeavor at the time of the invention.
the level of ordinary skill	Only through experimentation, not prediction, could a POSA determine if a particular compound would meet the functional limitations.
the scope of the claimed invention	The scope of the claims can only be found to support a lack of enablement.

In conclusion:

> Because the Structural Limitations are satisfied by such a large number of compounds, and because of the other *Wands* factors as applied here, the amount of experimentation to refine this broad set of compounds to those that also satisfy the Functional Limitations, given the limited teachings on this point in the patent and the state of the prior art, is an "undue" amount. See generally Erfindergemeinschaft Uropep GBR v. Eli Lilly and Co., 2017 WL 3676736, at *21 (E.D. Tex. Aug. 25, 2017) ("In the context of a disclosure and a field that provides no guidance, aimless plodding through systematic experimentation of a single compound that would take weeks may be undue."); see also Ariad, 598 F.3d at 1353 ("Patents are not awarded for academic theories, no matter how

groundbreaking or necessary to the later patentable inventions of others."). (Idenix pg 45-46)

Thus, the only conclusion that can be reached based is that the asserted claims of the '385 patent are invalid for lack of enablement. The amount of time and effort to synthesize and screen compounds potentially meeting the limitations of the claims of the '385 patent contributes to the lack of enablement, just as it did in Wyeth. See 720 F.3d at 1385 ("**The remaining question is whether having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation. We hold that it does.").**