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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
THE PATENT OFFICE

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BEFORE THE CONTROLLER OF PATENTS

THE PATENTS ACT, 1970

SECTION 15

In the matter of the Patents Act, 1970 (as amended)

& the Patents Rules, 2003 (as amended)

And

In the matter of Patent Application No. 3865/KOLNP/2007 By

VIIV Health care Company & Shionogi & Co., Ltd.

And

In the matter representation by way of opposition

under Section 25 (1) of the Patent Act

by

1) Delhi Network of People Living with HIV/AIDS(DNP+)
2) Bengal Network of People Living with HIV/AIDS(BNP+)and Mr. Firoz Khan
3) Mr Sanjeev Sharma
4) Dr. Mira Shiva
5) Natco Pharma Limited (settled as per court order)
6) Sankalp Rehabilitation Trust

DECISION

Hearing Notice date	Hearing Date	Remarks
21/08/2025	11/09/2025	Hearing U/S (14)

21/08/2025	09/09/2025 10/09/2025 & 11/09/2025	Hearing u/s 25(1): 11.00AM-2:00PM - Applicant/Opponent: Delhi Network of Positive People on 09-09-20225 2:30-4:00PM Applicant/Opponent: BNP+ and Mr.Firoz Khan on 09-09-2025 11.00AM-2:00 PM Applicant /Opponent :Mr Sanjeev Sharma on 10-09-2025 2:30-4:00 PM- Applicant/ Opponent Ms Mira Shiva on 10-09-2025 11.00AM -2:00PM Applicant/Opponent: Sankalp Rehabilation Trust
21/08/2025	09/09/2025	**Applicant's agent Appeared &** Delhi Network of Positive People's agent didn't appear for hearing
21/08/2025	09/09/2025	**Applicant's & Opponent(s)** BNP+ and Mr.Firoz Khan**'s agent Appeared** for hearing
21/08/2025	10/09/2025	**Applicant's agent Appeared &** Mr Sanjeev Sharma's agent didn't appear for hearing
21/08/2025	10/09/2025	**Applicant's & Opponent** Ms Mira Shiva**'s agent Appeared** for hearing
21/08/2025	11/09/2025	**Applicant's & Opponent** Sankalp Rehabilation Trust**'s agent Appeared** for hearing

1. The present application no. 3865/KOLNP/2007 was refused under section 25(1) of The Patents Act, 1970 (as amended) and corresponding rule 55 of The Patents Rules, 2003 (as amended) on 03/10/2024.
2. An appeal under Section 117(A) of the Indian Patents Act, 1970 (as amended) and Rules made therein and the Hon'ble High court has passed an order [reference no. IA NO: GA-COM/1/2025 on 14/05/2025. The order dated 03/10/2024 of the Controller was unsustainable

and direction as below was passed:

In such circumstances, the appeal stands allowed. In view of the peculiar facts and circumstances of the case the following directions are passed:

(i) To issue a hearing notice within two weeks from the date of this order and dispose of the subject application along with all objections(save and except NATCO) within eight weeks from the date of communication of this order.

(ii) All the documents/publication filed by the appellants in the proceedings under Section 14 and in the pre-grant oppositions proceedings by the respondent no. 2 to respondent no. 7 are to be considered.

(iii) NATCO (respondent no.6) shall withdraw their opposition in terms of the Settlement as enumerated in paragraph 2 above.

(iv) The evidence of all experts to be considered in the proceedings filed by the remaining respondent no. 2 to 5 and the respondent no. 7 (save and except the respondent no.6).

(v) In order to obviate any apprehension of predetermination, the Controller who had passed the impugned order shall not rehear the matter and the subject application along with all the objections are to be considered by any other Controller or Appropriate Hearing Officer.

(vi) With the above directions and to the above extent, IPDPTA/1/2025 stands allowed. It is made clear that there has been no final adjudication on the merits and all questions are left open to be decided in accordance with law.

3. In compliance with the directions of the Hon'ble High Court, the applicant was offered a hearing in respect of the objections under the Patents Act, 1970 vide hearing notice dated 21/08/2025, and the hearing was scheduled as indicated in the table above. All documents and publications filed by the appellants during the proceedings under Section 14, as well as in the pre-grant opposition proceedings by Respondent Nos. 2 to 5 and Respondent No. 7 (**except NATCO Respondent No. 6**), have been taken on record and carefully considered in accordance with the said directions. The hearing notice was issued within two weeks of receipt of the case in the Controller module. However, the applicant filed petitions under Rule 138 (Form-4) seeking one-month extensions three times. Consequently,

disposal of the subject application within eight weeks from the date of communication of the order was not was not practically feasible despite best efforts, and necessary steps were initiated by this office. Upon examination of the record, it is observed that the matter involves six pre-grant oppositions containing voluminous documents, expert evidence, and complex legal as well as technical issues. The following expert evidence relied upon by the appicant has also been taken on record and duly considered:

a) Dr. Brian A. Johns had adduced expert evidence in the pregrant opposition filed by the respondent no. 2, on 26th June 2013.
b) Dr. Sheo Bux Singh had filed evidence in the opposition filed by the respondent no. 2, on 4th February 2016.
c) Dr. Brian A. Johns (in the pre-grant opposition filed by the respondent no. 3) filed on 12th April 2016.
d) Dr. Sheo Bux Singh (in the pre-grant opposition filed by the respondent no. 3) filed on 12th April 2016.
e) Dr. Sheo Bux Singh (in the pre-grant opposition filed by the respondent no. 4) filed on 21.07.2017.
f) Dr. Sheo Bux Singh (in the pre-grant opposition filed by the respondent no. 5) filed on 21.07.2017.

The following objections were conveyed in the instant case;

Objections

Formal Requirement(s)

1. 1. Kindly confirm whether the applicant/agent will be/ will not be attending the scheduled hearing as required u/r 28 (4) of the Patents Rules.

   2. Valid Power of attorney in respect of the person who is attending the hearing should be submitted online before the date of hearing.

   3. With reference to the matter of the application, a hearing u/s 25(1) of the Patent Act , 1970 has been scheduled .You are therefore, required to appear before the Controller for the hearing on the said date and time. You are also requested to prior confirm to the office as well applicant/opponent for attending the same along with precribed fee.

Invention u/s 2(1)(j)

1. The following prior art documents are the closest prior art documents to the claimed subject matter.

   D1: US2005/0054645

   D2: Farnet C.M Et Al: 'Human Immunodeficiency Virus Type 1 cDNA Integration: New Aromatic Hydroxylated Inhibitors and Studies of the Inhibition Mechanism', Antimicrobial Agents & Chemotherapy, 1998, p.2245-2253 (whole document)

   D3: WO2003/035076

   D4: WO2003062204A1

   D5: WO2004/058756

   D6: WO2004035576A2

   D7: WO1999032450A1

   D1 teaches about the numerous polycyclic carbamoylpyridone derivative compounds (general formula I) Wherein R1 is H or methyl; R2 is aryl, unsubstituted or substituted with halogen, alkyl (tert-butyl) or acetylamino; R3 is H; R4 is lower alkyl substituted with aryl (phenyl), which is unsubstituted or substituted with halogen for HIV integrase activity and also mentions their pharmaceutically acceptable salts of the compounds.

   D1 teaches center fused-bicyclic structure, which was attached with halo alkyl/aryl group by amide linkage and the other side is having halo-aryl by alkyl linkage. Therefore, a compound with fused-cyclo system in the centre and halo-substituted alkyl/aryl group on the one end of the compound is similar to the compounds where in center there is fused-tricyclic ring system and at one side it has di-halo substituted aryl group. (Refer abstract, examples 181, 196, 214, 377, 380)

   Further, D2 also teaches various polyhydroxylated aromatic inhibitors of the integrase enzyme and figure 6 discloses various anthrones as potent inhibitors of integrase enzyme. Wherein, it also discloses fused-tricyclic compounds which have the functionality sufficient for the inhibition of purified HIV integrase with hydroxyls on one ring and a carbonyl on the adjacent ring. (Refer figure 6)

   Therefore, from the teachings of D2 it has been anticipated that the compounds comprising fused-tricyclic rings can be utilized for HIV integrase activity.

   Further, D3 teaches similar small molecule chemical compounds which is having dihydroxy-pyrimidine ring structure which was attached to halo-aryl by amide linkage, similar to the claimed compounds and disclosed compounds also been used for inhibition of HIV integrase. (Refer tables 5, 7, 10, 11, 14)

   Further, D4 teaches hydroxy-naphthyridinone carboxamide derivative compounds with halogen substitution at the phenylmethyl ring which is attached to diaza-naphthyridine ring via a carboxamide group used for the inhibition of HIV integrase. (Refer example 1, 4 and table 5)

   Further, D5 teaches hydroxy pyrimidine containing compounds in which phenyl methyl ring is attached to a diaza-bicyclic ring via a carboxamide group for HIV integrase inhibitory activity. D5 also discloses compounds with substitutions pertaining to the presence of halogen substituion at 4-position of phenyl methyl ring which is further attached to pyrdopyrimidine ring which is substituted at 3-position with a hydroxy group and an oxo group at 4-position. (Refer example 2, (M+318), (M+403), (M+417))

Further, D7 teaches about the fused-bicyclic structured compounds with halo-aryl group attached to it by amide group, which is similar to the claimed compounds of present invention. (Refer table 1 and examples)

Therefore, it has been observed that the combined teachings of prior art documents D1 – D7 teaches monocyclic, bicyclic, or tricyclic compounds having apparently similar substituents and intended for the same purpose as claimed in the present application.

Further, no outstanding advancement achieved upon using claimed compounds over the compounds as disclosed in D1 – D7. Therefore, from the teachings of documents D1 – D7, any person skilled in the art can arrive at the claimed compounds with HIV integrase activity over repeated laboratory experiments.

Accordingly, the claimed subject matter appears obvious to a person skilled in the art, possessing common general knowledge in view of these disclosures. Furthermore, the specification does not provide any comparative data demonstrating that the claimed compounds exhibit any unexpected properties, improved inhibitory activity, or any other advancement in therapeutic efficacy over the prior art compounds. In the absence of such evidence, the subject matter of the present application fails to overcome the objection of lack of inventive step under Section 2(1)(ja) of the Patents Act.

Non-Patentability u/s 3

1. Since the structurally similar compounds and substitutions on them at various positions is known from the cited prior arts (D1-D7). Hence the core structure is known and the equivalent substitutions as taught by the cited document with other groups is considered derivative of known compound without any efficacy with reference to the cited prior arts (D1-D7). The compounds as claimed in the present application are therefore considered derivatives of known compound without any therapeutic efficacy with reference to the cited one. Hence, the subject matter of present claims attracts section 3(d) of The Patents Act.

Other Requirement(s)

1. The disclosure of the compounds as claimed in the present application nees to be provided in the two priority documents. clarify this.

2. These expert opinions with affidavit which are directed by the Hon'ble High Court needs to be claerly reffered in corresponding uploaded documents.

3. The undersigned has initiated steps toward expeditious disposal of the matter as directed by the Hon'ble High Court . While every effort is being made to ensure timely and effective adjudication of the matters, however some reasonable time may be required to ensure due process and proper consideration of all aspects before final disposal. The cooperation of all parties in facilitating the smooth progress of hearings will be greatly appreciated.

4. A hearing u/s 25(1) of Patents Act, 1970 is scheduled to be held on 09/09/2025 to 10-09-2025 . The following is the slot for each opponent:

   11.00AM -2:00PM - Applicant/Opponent 1 Delhi Network of Positive People on 09-09-20225

   2:30-4:00 pm-- Applicant/Opponent 2 BNP+ and Mr.Firoz Khan on 09-09-2025

   11.00AM -2:00 PM Applicant /Opponent 3 Mr Sanjeev Sharma on 10-09-2025

   2:30-4:00 pm- Applicant/ Opponent 4 Ms Mira Shiva on 10-09-2025

   11.00AM -2:00PM Applicant/Opponent 6 Sankalp Rehabilation Trust on 11-09-2025

   2.30 PM section 14 haering

Sufficiency of Disclosure u/s 10 (4)

1. The complete specification fails to comply with the requirements of Section 10(4) of the Patents Act in respect of claims 1 to 4, as it does not provide sufficient and enabling disclosure for the claimed subject matter.

Regarding Claims 1 and 2 (i.e., relevant to Dolutegravir (DTG)), the structure of the compound is not explicitly disclosed in the specification. The process for preparing DTG is not directly described and instead relies on a complex series of cross-referenced examples (A-1, C-1, C-21, Y-3) that require the person skilled in the art to reconstruct synthetic steps, infer structural details from NMR data, and deduce required substitutions without direct teaching. This imposes an undue burden and requires extensive experimentation, which defeats the requirement of enabling disclosure. Furthermore, no data or description of biological activity of DTG is provided in the complete specification.

Further regarding Claims 3 and 4 (i.e., relavent to Cabotegravir (CTG)), although the structure and synthetic example (Z-9) are disclosed and some activity data is provided (page 244), the specification contains inconsistencies related to the starting materials and synthetic pathway. Specifically, there is ambiguity in the reference to compound 106 and the proposed substitution with 3-aminobutanol, which is not clearly linked to CTG in the specification. This creates uncertainty in the reproducibility of the claimed compound and process.

In view of the above, its has been observed that the complete specification fails to sufficiently and clearly describe the invention in a manner that enables a person skilled in the art to carry it out without undue burden, thereby fails to comply with the requirements of Section 10(4) of the Patents Act.

There is no working exapme for the composition as well u/s 10(4)(b) of the Act.

4. The oral arguments presented during the hearing, the written submissions filed thereafter by the Opponent(s), the above-mentioned expert evidence, and all responses submitted by the parties have been taken on record and duly considered for arriving at the present decision. However, for the purpose of determining the patentability of the invention and the grounds raised in the opposition(s), only those documents found to be most relevant have been specifically analyzed herein. It is observed that both the Opponent(s) and the Applicant cited multiple grounds, decisions, and case laws in support of their respective positions. Certain points were found to be irrelevant or superfluous, while others were relevant and required consideration in the matter of the impugned application under pre-grant opposition(s). The numerous preliminary issues, grounds, prior-art documents, and case laws placed on record, along with the written submissions of the Applicant, were examined; however, all of them do not require detailed discussion in this order. Accordingly, only the relevant documents, grounds of opposition, and case laws have been considered. The present decision is based on the disclosure of the invention in the complete specification and claims, analysis of the relevant documents and case laws, and the arguments advanced by the Opponent(s) and the Applicant.

5. Subsequent to the hearing, the Applicant filed written submissions along with a set of amended claims. Claims 3 to 5, which were directed to Cabotegravir, were deleted. In the written submissions, the Applicant stated that they reserve the right to file a divisional application in respect of the deleted claims (i.e., former Claims 3 to 5). The remaining Claims 1, 2, and 6 were accordingly renumbered as Claims 1 to 3 and are reproduced as follows:

1. *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-difluorobenzylamide or a pharmaceutically acceptable salt or solvate thereof.*
2. *The compound as claimed in claim 1 wherein the pharmaceutically acceptable salt is a sodium salt.*

3. *The compound as claimed in claims 1 to 2, as and when used in a pharmaceutical composition comprising a compound as defined in any one of claims 1 or 2 together with a pharmaceutically acceptable carrier.*

6. Documents cited in Hearing Notice:

D1: US2005/0054645

D2: Farnet C.M Et Al: 'Human Immunodeficiency Virus Type 1 cDNA Integration: New Aromatic Hydroxylated Inhibitors and Studies of the Inhibition Mechanism', Antimicrobial Agents & Chemotherapy, 1998, p.2245-2253 (whole document)

D3: WO2003/035076

D4: WO2003062204A1

D5: WO2004/058756

D6: WO2004035576A2

D7: WO1999032450A1

7. **GROUNDS OF OPPOSITION**

Following are the grounds of opposition which were taken by the various opponents in their notice of opposition-

- **Ground I**- Section 25(1) (b): *The invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim*
  The ground regarding lack of novelty was taken by the opponents O1 (at the time of filing the pre grant opposition but did not appear for hearing nor submitted in the submissions after hearing), O3 (has not attended the hearing or submitted any arguments).
- **Ground II**- Section 25(1) (e): *The invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.*
  The ground regarding lack of inventive step was taken by all the opponents O1, O2, O3, O4 and O6.
- **Ground III**- Section 25(1) (f): *The subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.*
  This ground was taken by all the opponents O1,O2, O3, O4, & O6.
- **Ground IV**- Section 25(1)(g): *The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed*.

This ground was taken by the opponents O1, O2, O4, & O6.

- **Ground V**- Section 25(1) (h): *The Applicant has failed to disclose to the Controller the information required under Section 8 or has furnished the information which in any material particular was false to his knowledge.*
  Said ground was dropped by the opponents O2, O4 and O6.

The following is the list of the consolidated documents as provided in the representation filed as prior art by all the six opponents.

S.N	Documents	Opponents
1.	US2005/0054645/EP1544199	O1,O2,03,O4 & O6
2.	JayA.Grobler,PNAS,2002,6661-6666	O1,O2,O4 &O6
3.	WO03/035076	O1,O2,O3,O4
4.	*Amy S Espeseth,PNAS,2000,11244-11249*	O2
5.	Marchand,etal.,JBC,2002,12596-12603	O1,O2,O4
6.	C.M. Farnet et al., Antimicrobial Agents And Chemotherapy, SEP1998, P.2245-2253	O2,O4
7.	HazudaD.J.etal.Science,vol.287,2000"	O6
8.	Wai,J.Med.Chem,2000,43(26),4923-26	O4
9.	Sato et. al., JMedChem,2006,49,1506-08	O4
10.	EP1297834	O6
11.	WO2004/096128	O2,O4,O6
12.	WO2002/030426	O3
13.	WO2004/058756	O1,O3
14.	WO2004/035576	O1
15.	WO2003/0602204	O3
16.	WO1999/032450	O1
17.	Kazuki Hoshino, et.al., Antimicrobial Agents And Chemotherapy, FEB1991,P.309-312	O2,O4
18.	WO2005/110415(PubDate24-Nov-2005)	O4
19.	WO2005/092099	O6
20.	Lazar,Eur.J.Org.Chem.2003,3025-3042	O2,O4
21.	Gould, International Journal Of Pharmaceutics 33 (1986) 201-217 33(1986)201-217	O2,O4
22.	Kenneth R. Morris et.al., Int. J. of Pharmaceutics105(1994)209-217	O2,O4
23.	Johns et al.HIV Integrase Inhibitors: Chapter 6, Published on17 June2013	O1

8. With respect to the objection relating to the priority of the present application, it is observed that the compound of claim 1, namely *(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-difluorobenzylamide*, commercially known as **dolutegravir (DTG)**, as claimed in claims 1–3 of the present application, is not disclosed in either of the priority documents (JP2005-131161 dated 28 April 2005 and JP2005-312076 dated 27 October 2005). Accordingly, the claimed subject matter of claims 1–2 is not entitled to the claimed priority dates, and consequently the effective date of the claimed subject-matter of claims 1-2 is the filing date i.e 28/04/2006.

9. **Ground 1 - Anticipation by prior publication under section 25(1)(b)(ii) of the Patents Act, 1970**

O1 & O3 did not attend the hearing and has also not provided any submissions w.r.t lack of novelty in their submissions. Since the opponents have not provided any substantial evidence to show that the claims lack novelty in view of this document, this ground is not valid. Further, the applicant has shown the specific differences between the compound claimed in present invention and the compound disclosed in the cited prior art document US'645. Thus, in absence of specific disclosure of the claimed compounds in US'645, claims 1-3 are considered to be novel.

I conclude that such a ground of opposition is not validly established by the Opponent(s).

10. **Ground II regarding 25(1)(e)- that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.**

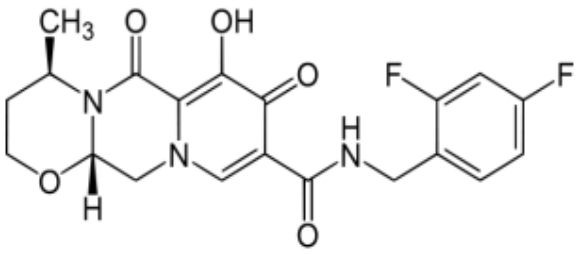
All 5 opponents have provided the following documents to substantiate this ground:

S.No.	Documents	Opponents
1.	US2005/0054645/ EP1544199	O1, O2, 03, O4, O6
2.	Jay A. Grobler, PNAS, 2002, 6661-6666	O1, O2, O4, O6
3.	WO03/035076	O1, O2, O3, O4
4.	Amy S Espeseth, PNAS, 2000, 11244-11249	O2
5.	Marchand, et al., JBC, 2002, 12596-12603	O1, O2, O4
6.	C. M. Farnet et al., Antimicrobial Agents And Chemotherapy, SEP 1998, P. 2245-2253	O2, O4
7.	Hazuda D.J. et al. Science, vol. 287, 2000";	O6
8.	Wai, J. Med. Chem, 2000, 43(26), 4923-26	O4

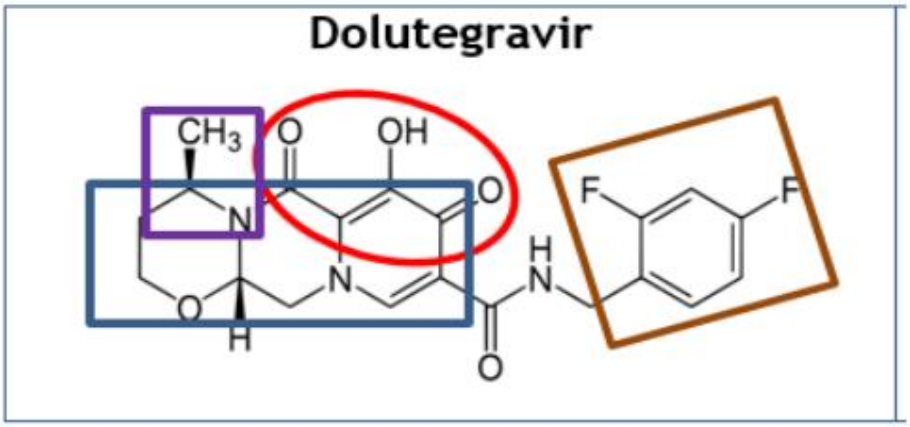
9.	Sato et.al., J Med Chem, 2006, 49, 1506-08	O4
10.	EP1297834	O6
11.	WO2004/096128	O2, O4, O6
12.	WO2002/030426	O3
13.	WO 2004/058756	O1, O3
14.	WO2004/035576	O1
15.	WO2003/0602204	O3
16.	WO1999/032450	O1
17.	Kazuki Hoshino, et.al., Antimicrobial Agents And Chemotherapy, FEB 1991, P. 309-312	O2, O4,
18.	WO2005/110415 (Pub Date 24-Nov-2005)	O4
19.	WO2005/092099	O6
20.	WO1998/34932	O1
21.	WO20030305077	O1
22.	Lazar , Eur. J. Org. Chem. 2003, 3025-3042	
23.	Gould,International Journal Of Pharmaceutics 33	O2, O4
24.	Kenneth R. Morris et.al., Int. J. of Pharmaceutics 105 (1994) 209-217	O2, O4

The invention disclosed in the present application is directed to HIV integrase inhibitors. Integrase inhibitors are a class of antiretroviral drugs that block the action of HIV integrase, an enzyme that is necessary for insertion of the viral genome into the DNA of the host cell. Blockage of HIV integrase results in the inhibition of HIV replication. The amended claims 1-3 of present application is directed to Dolutegravir or a pharmaceutically acceptable salt or its pharmaceutical composition.

Dolutegravir (DTG):



The structure of the compound **Dolutegravir** possesses a characteristic 1,3,4-oxygen triad, wherein the lone pairs of the oxygen atoms facilitate chelation with two divalent metal ions, along with the presence of an oxygen-containing third heterocycle. The compound is non-planar, rigid, and non-aromatic in nature. The core structure of Dolutegravir comprises a complex tricyclic framework containing a methyl-oxazine ring. The methyl-oxazine moiety, together with the presence of a methyl group adjacent to the nitrogen atom, and the stereochemistry of the H/CH_3 arrangement on the methyl-oxazine ring as illustrated below;



In view of the above, the instant application is to be looked as per Indian legislative provisions and jurisprudence regarding the requirement of “Inventive Step” for patentability of an “invention”. Section 2(1)(j) of the Patents Act, 1970 (as amended) defines “invention” as:

“"invention" means a new product or process involving an inventive step and capable of industrial application;”

Section 2(1)(ja) of the Patents Act, 1970 (as amended) defines “inventive step” as:

“inventive step” means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art;

Thus, as per Section 2(1)(ja) of the Patents Act, 1970 (as amended), to be inventive, an invention should:

(involve technical advance as compared to the existing knowledge

OR

have economic significance OR both) AND

be non-obvious to a person skilled in the art.

All the documents cited by the five Opponents have been carefully considered for the purpose of assessing the patentability of the invention and in the context of the grounds raised in the opposition. Only those documents found to be most relevant have been analyzed in detail.

Among the cited prior art(s), **EP1544199** (equivalent to **US2005/0054645**, hereinafter referred to as US '645), **EP1297834**, **WO2004/096128**, Jay A. **Grobler et al.,** published in **Proceedings of the National Academy of Sciences**, 2002, pp. 6661–6666, **C. M. Farnet et al.,** Antimicrobial Agents And Chemotherapy, SEP 1998, P. 2245-2253**,** ***Kasuki Hoshimo*** **et al** and **Sato et al.,** published in **Journal of Medicinal Chemistry**, 2006, Vol. 49, pp. 1506–1508, have been found to be the most relevant for the present determination.

EP1544199 (equivalent to **US2005/0054645)** discloses a comprehensive series of nitrogen-containing condensed heterocyclic compounds as HIV integrase inhibitors, characterized by fused bicyclic pyrido[1,2-a]pyrazine-type ring systems bearing diketo or hydroxy-dione metal-chelating motifs and substituted with benzyl or aryl carboxamide side chains, including halogenated benzyl groups, and provides extensive biological evaluation data in multiple tables; in particular, The core structures of Examples 377 and 378 comprise a relatively planar bicyclic heterocyclic framework lacking stereogenic centres and containing two nitrogen atoms, whereas the presently claimed compound dolutegravir comprises a structurally distinct tricyclic oxa-diaza-anthracene system incorporating an additional fused ring, an oxygen atom within the core, defined stereochemistry. Further, while both examples in this prior art and dolutegravir contain a metal-chelating diketo/enol system and a benzyl carboxamide substituent, US '645 primarily discloses chloro- or fluoro-substituted benzyl groups attached at different positions on the bicyclic core, whereas dolutegravir specifically contains a 2,4-difluorobenzyl amide linked to a stereochemically defined tricyclic scaffold. Accordingly, US '645 establishes highly potent bicyclic integrase inhibitor lead compounds but does not disclose or exemplify the specific tricyclic heterocyclic architecture and stereochemical configuration of dolutegravir, thereby requiring substantial structural modification beyond simple substituent variation to arrive at the claimed compound. The prior art US '645 discloses various integrase inhibitors featuring a diketo acid motif and demonstrates their effectiveness by binding to the Mg^{2+} cofactor. This prior also teaches the use of hydrophobic groups like fluorophenyl linked through amide linkers, which are similar to features found in dolutegravir.

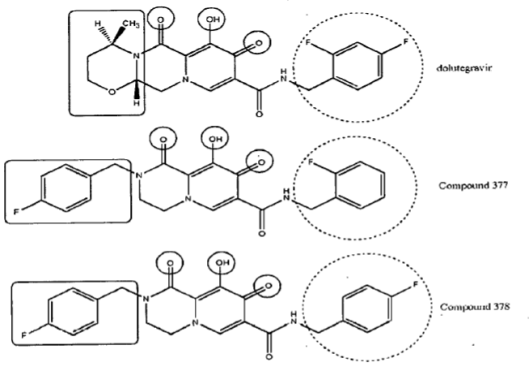


FIGURE – 1

Relevance of fluoro substitution disclosed in US ’645 also discloses compounds with di-fluoro substitutions on the ring structures, which parallels the features of dolutegravir. Examples 377 and 378 of US ’645 are shown to have IC50 of “++++”(table 45) which according to the definition, signifies a value “less than 0.01 μM (10 nM) against HIV integrase”.

EP 1297834 discloses integrase inhibitors that chelate divalent metal ions with specific structural features, including tricyclic ring systems and certain binding groups (C=O, C-OH). This prior document which includes tricyclic ring systems, the diagram of which is reproduced below:

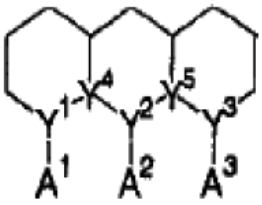
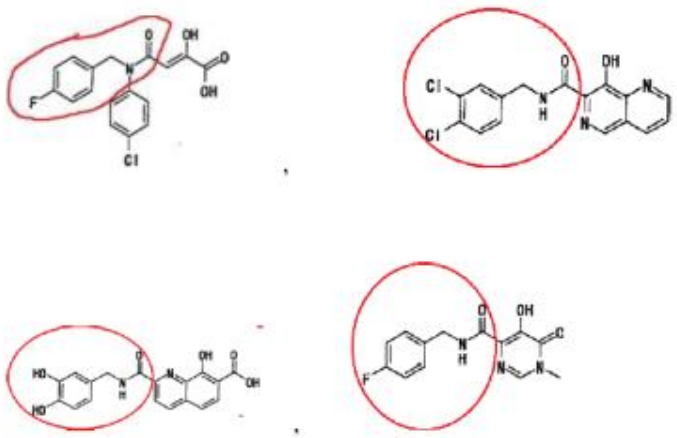


Fig 2. Tricyclic system taught by **EP 1297834**

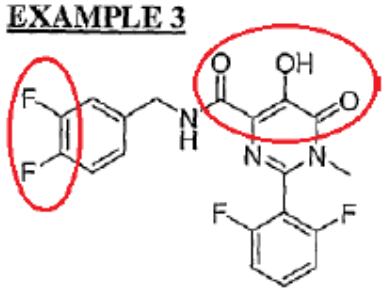
Effective inhibitors are described as having A tricyclic system in a non-planar configuration, Groups capable of chelating metal ions (C=O, C-OH), An additional organic moiety (e.g., halogenated benzylamide).



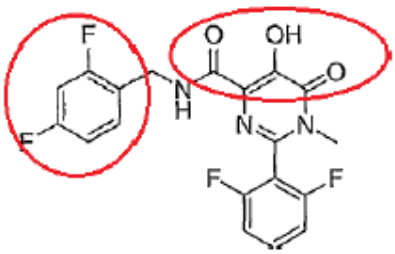
Structure of Ep'834

WO2004/096128 disclsoes presence of difluoro substitution on the benzyl amide group linked to triad containing ring system. This prior art discloses pyrimidine containing HIV integrase inhibitors with two fluorines on the benzene ring at the 2 and 4 position (Example 8) discloses a class of substituted dihydropyrimidine-4-carboxamide derivatives as HIV integrase inhibitors, wherein the core pyrimidine ring is functionalized with hydroxyl and oxo groups forming a metal-chelating motif and is further substituted at the amide position with benzyl or substituted benzyl groups, and the specification provides numerous examples and structural variations demonstrating structure–activity relationships; notably, the document repeatedly discloses and exemplifies compounds containing 2,4-difluorobenzyl amide substituents, along with other halogenated benzyl moieties, and identifies such fluorinated benzyl groups as preferred substituents associated with improved integrase inhibitory activity, thereby teaching the use of 2,4-difluorobenzyl side chains in metal-chelating integrase inhibitor scaffolds. Representative examples are shown below:

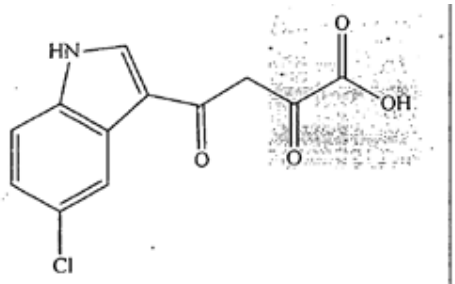
EXAMPLE 3



EXAMPLE 8



Grobler emphasized that diketo acids act as pharmacophores for HIV integrase activity, including their role in catalysis and strand transfer interference



Compound IV, Page-7

Diketo acid may be used to develop prototypes

Grobler discloses the relation between diketo acid inhibitor mechanism and HIV integrase. It states that, binding requires a divalent metal and resistance is metal-dependent with active site mutants displaying resistance only when the enzymes are evaluated in the context of Mg2+. Grobler et al specifically mention that an acidic moiety such as carboxylate or isosteric heterocycle is not required for binding to the enzyme complex but is essential for inhibition and confers distinct metal dependent properties on the inhibitor.

Farnet et al discloses polyhydroxylated aromatic inhibitors of the integrase enzyme. Figure 6 (below) discloses various anthrones (tricyclic) as potent inhibitors of integrase enzyme. Farnet et al also suggests that many of the aromatic polyhydoxylated inhibitors containing diketo motifs may act by blocking the binding of integrase to DNA.

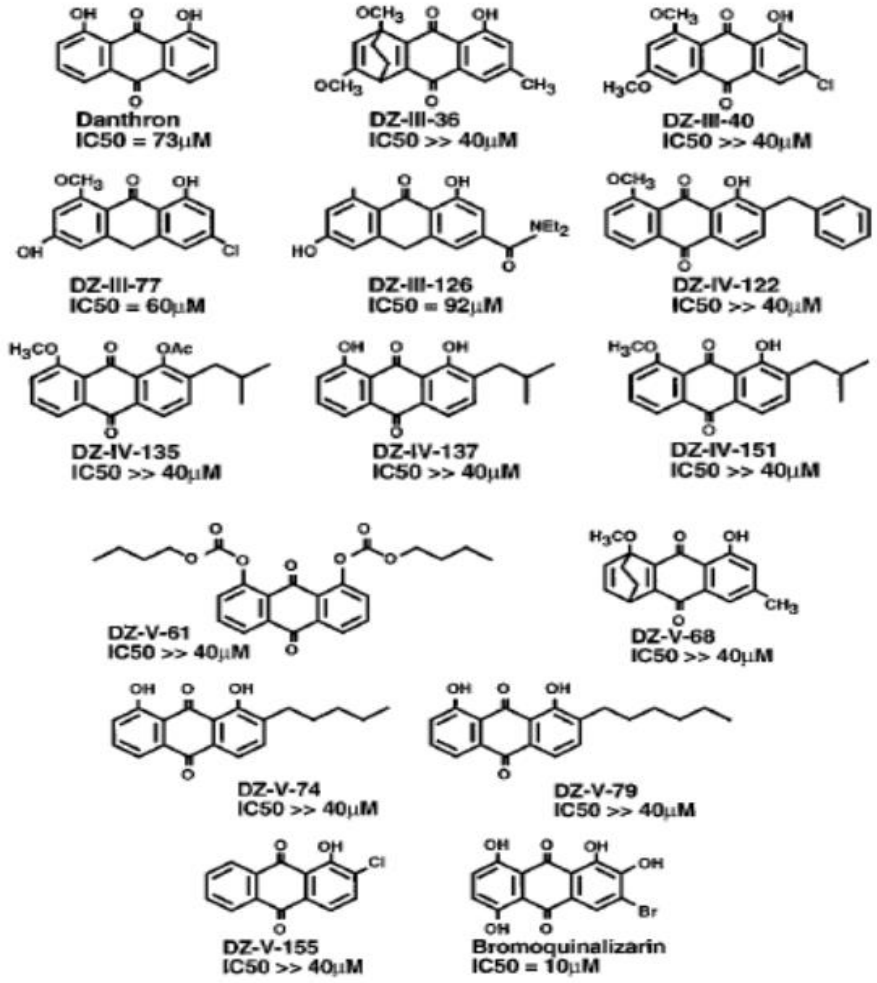


FIG. 6. Anthraquinones and anthrones tested for inhibition of dumbbell disintegration. IC_{50}s are shown beneath each structure.

Sato et al discloses that the core structure of quinolone antibiotics can be used as an alternative to the diketo acid class of HIV-integrase inhibitors. ***Sato et al*** discloses the diketo acid moiety (γ-ketone, enolizable α-ketone, and carboxylic acid) was believed to be essential for the inhibitory activity of this series of integrase inhibitors, and the structures of diketotriazole 2,6 diketotetrazole 3,9 diketopyridine and 7-carbonyl-8-hydroxy-(1,6)-naphthyridine were reported to be bioisosters of the diketo acid pharmacophore (Figure given below).

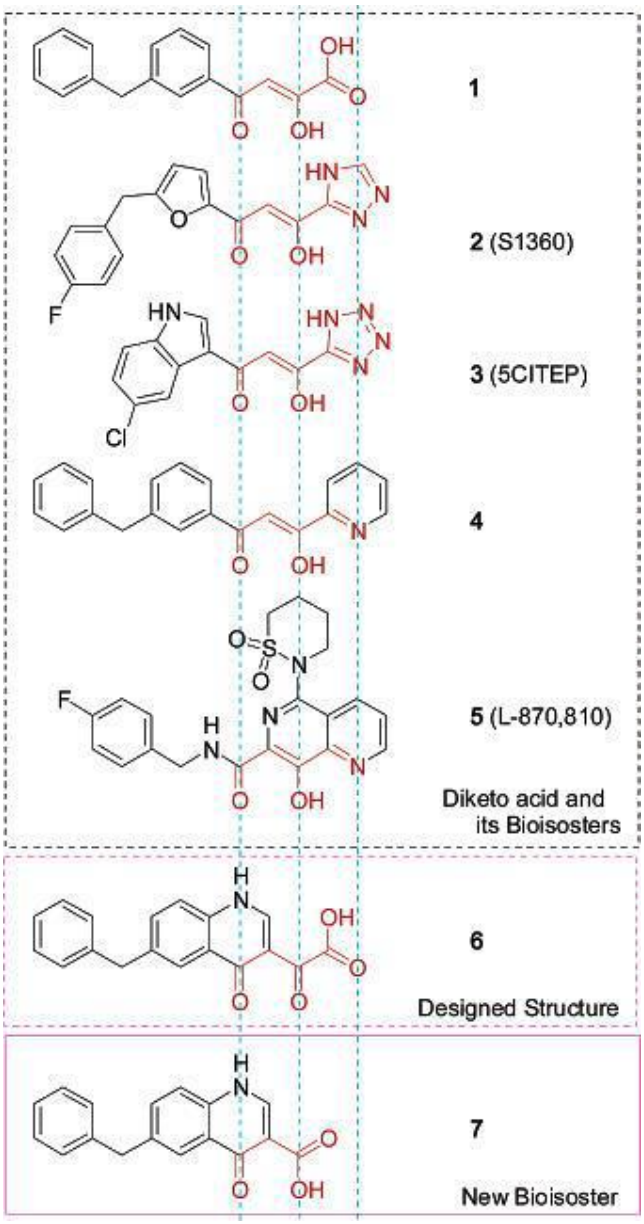


Figure: Structures of the diketo acid family and its new bioisoster

Kasuki Hoshimo et al disclose the antibacterial activity of oflaxacin derivatives and the key role played by presence of methyl group on the oxazine in these derivatives. It discusses the importance of methyl group on oxazine ring and its ability to make the compound less reactive and a more potent inhibitor as compared to the compounds with no methyl groups on the oxazine ring. ***Kasuki Hoshimo* discloses** the correlation between the in vitro inhibitory effects of several quinolones, including four ofloxacin derivatives, on bacterial DNA gyrase from Escherichia coli KL-16 and on topoisomerase II from fetal calf thymus. No correlation was observed between the inhibitions of DNA gyrase activity and topoisomerase II activity. The inhibitory effects of these quinolones against topoisomerase II

were closely correlated with their inhibition of cell growth. Furthermore, among the oxazine derivatives tested, the derilvative with a methyl group at position 3 in an S configuration showed the highest activity against DNA gyrase and derivatives without a methyl group on the oxazine ring were more potent against topoisomerase II than those with a methyl group. Among these derivatives, DR-3355, the S isomer o1 ofloxacin, showed the highest activity against DNA gyrase and low activity against topoisomerase II. These results indicate that the methyl group on the oxazine ring plays an important role in the inhibitory activities of ofloxacin derivatives for these enzymes.

Upon careful consideration of the cited prior art documents, it is observed that certain individual structural features of Dolutegravir are disclosed separately in the prior art(s). As US '645 represents the closest prior art, as it discloses highly potent HIV integrase inhibitors in the form of fused bicyclic heterocyclic compounds, including Examples 377 and 378 exhibiting "++++" inhibitory activity corresponding to IC_{50} values of less than 10 nM, thereby establishing effective lead compounds prior to the filing date. As US '645 discloses integrase inhibitors comprising a diketo acid pharmacophore capable of chelating divalent metal ions through oxygen atoms, and also teaches fluoro-substituted aromatic moieties linked via amide functionalities. DTG differs from 377/378 mainly in Ring expansion (bi → tri), 2, 4- Fluoro substituent, Creation of stereocenters, 1,3-oxazine ring, While both share Metal-chelating diketo acid motif and Benzylamide substituent. As applicant submitted the pharmacokinetic properties of dolutegravir and Compound 378 of US'645. It is apparent that dolutegravir has markedly improved pharmacokinetic properties. In particular, dolutegravir has a total clearance (i.e. the volume of plasma cleared of the drug per unit time) approximately 80 times lower than that of Compound 378 (0.23ml/min/kg versus 17.7 ml/min/kg) and a halflife of over six times longer (6.2 hours versus 1.0 hours).

	Dolutegravir	Compound 378
Pharmacokinetics		
Oral bioavailability	34%[a]	10.0%[c]
Plasma conc. 24 h after PO administration (C_{24h})	1,152 ng/ml[a]	not detectable[c]
Total clearance (CL_{tot})	0.23 ml/min/kg[b]	17.7 ml/min/kg[d]
Half life ($t_{½}$)	6.2 h[b]	1.0 h[d]

[a] determined with Na salt, 5mg/kg PO, [b] determined with Na salt, 1mg/kg IV, [c]determined with free acid, 1mg/5mL/kg (n=2) DMSO/Solutol/50mM N-methylglutamine in 3% mannitol = 10/10/80 (v/w/v) and [d]determined with free acid, 0.5mg/0.8mL/kg (n=2) DMA/PG = 1/1 (v/v)

EP 1297834 discloses tricyclic, non-planar systems containing metal-chelating groups such as C=O and C–OH, along with additional organic substituents. EP 1297834 further establish, as common general knowledge, that HIV integrase inhibition depends on metal chelation by diketo acid–type pharmacophores while WO2004/096128 teaches difluoro substitution on benzylamide groups linked to triad-containing ring systems.

Therefore, none of the cited prior art documents, either individually or in combination, disclose or suggest the specific core structural framework of Dolutegravir, namely:

A tricyclic system incorporating a methyl-oxazine ring as an integral part of the core scaffold;

A saturated methyl-oxazine ring (as opposed to the unsaturated oxazine systems seen in quinolone derivatives); and

The specific stereochemical configuration of the H/CH_3 arrangement on the methyl-oxazine ring, which is critical to the biological profile of Dolutegravir.

While Kazuki Hoshino et al. discuss the role of a methyl group on the oxazine ring in quinolone derivatives such as ofloxacin, those compounds are structurally distinct from Dolutegravir. The quinolone oxazine system disclosed therein contains a double bond and forms part of a fundamentally different antibacterial scaffold. In contrast, Dolutegravir comprises a saturated methyl-oxazine ring embedded within a distinct integrase inhibitor framework. There is no teaching or suggestion in Hoshino et al. that would motivate a person skilled in the art to modify the integrase inhibitor scaffolds disclosed in the cited prior art by incorporating a saturated methyl-oxazine ring at the corresponding position.

Furthermore, the specific stereochemistry of Dolutegravir is not an arbitrary modification but is functionally significant, as evidenced by the lower fold change (FC) in activity relative to its enantiomer. The prior art neither recognizes nor suggests that introduction of such a methyl-oxazine ring with the claimed stereochemical orientation into an integrase inhibitor scaffold would yield improved resistance or activity profiles.

Thus, although certain isolated elements such as metal-chelating oxygen triads, tricyclic systems, or difluoro substitutions are known in the art, the particular structural combination and stereochemically defined methyl-oxazine core of Dolutegravir is neither disclosed nor rendered obvious by the cited documents.

Furthermore, the specific stereochemistry of Dolutegravir is not an arbitrary modification but is functionally significant, as evidenced by the lower fold change (FC) in activity relative to its enantiomer. The prior art neither recognizes nor suggests that introduction of such a methyl-oxazine ring with the claimed stereochemical orientation into an integrase inhibitor scaffold would yield improved resistance or activity profiles.

Thus, although certain isolated elements such as metal-chelating oxygen triads, tricyclic systems, or difluoro substitutions are known in the art, the particular structural combination and stereochemically defined methyl-oxazine core of Dolutegravir is neither disclosed nor rendered obvious by the cited documents.

Collectively, these documents indicate a general motivation to optimise known integrase inhibitors through modification of substituents and scaffolds. However, none of these prior arts, either individually or in combination, discloses or specifically suggests the transformation of the bicyclic

framework of US ’645 into the rigid, stereochemically defined tricyclic oxa-diaza-anthracene system incorporating a 1,3-oxazine ring as present in Dolutegravir, nor do they provide a clear pointer towards the incorporation of such a pharmacophore.The applicant’s later submission, comprising detailed scientific evidence of systematic scaffold evolution, stereochemical optimisation, and structure–activity relationship studies, further identifies Dolutegravir exhibiting an IC_{50} value of 0.5 nM, which represents a marked improvement over the closest prior art compounds disclosed in US ’645. It was submitted in affidavit by Brian A. Johns that *when dosed in patients, dolutegravir demonstrated a long plasma half-life without the need for a pharmacokinetic boosting agent. In monotherapy studies in HIV-infected adults, dolutegravir resulted in a 1.5-2.5 log10 HIV RNA viral load drop. Studies showed the potential for a higher barrier to resistance compared with raltegravir and elvitegravir. Furthermore, dolutegraivr has no or very low cross resistance against raltegravir and elvitegravir-induced HIV mutants, that is, dolutegravir does not have a similar resistance profile as these first generation HIV integrase inhibitors. The markedly different and improved resistance profile result in the enhanced therapeutic efficacy of dolutegravir. Dolutegravir was more effective than raltegravir in HIV integrase inhibitor naïve, treatment experienced patients through 24 weeks, with similar safety and tolerability.*

Proportion of 715 Patients With Plasma HIV-1 RNA <50 c/mL at Week 24

DTG 50 mg QD N=354 n (%)	RAL 400 mg BID N=361 n (%)	% Difference (95% CI)
281	252	
79%	70%	9.7, p = 0.003

This substantial enhancement in inhibitory potency, together with the demonstrated role of the 1,3-oxazine ring in optimising binding geometry and activity, indicates that the claimed compound achieves a technical advance not predictable from the prior art. The development of such a tricyclic, stereochemically defined scaffold with significantly improved biological performance is shown to have required extensive experimental effort and deliberate pharmacophore-driven design rather than routine structural modification. In the absence of any specific teaching in above cited prior arts directing a skilled person to adopt the claimed compound with a reasonable expectation of achieving such superior potency, and having regard to the substantial structural reorganisation involved in progressing from the bicyclic compounds of prior art to the claimed compound, the subject matter of Claims 1-2 cannot be regarded as an obvious outcome. Accordingly, it would not have been obvious to a person skilled in the art, in view of the cited prior art, to arrive at the presently claimed structure

of Dolutegravir. The claimed subject matter therefore involves an inventive step under Section 2(1)(ja) of the Indian Patents Act.

I conclude that such a ground of opposition is not validly established by the Opponent(s).

11. **Ground III- Not patentable under Section 25(1)(f) read with Section 3(d) of the Patents Act.**

3(d); *the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation.--For the purposes of this clause, **salts**, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;

With respect to Section 3(d) of the Patents Act, Examples 377 and 378 of US '645, exhibiting "++++" inhibitory activity corresponding to IC_{50} values of less than 10 nM, represent the closest prior art or known substance, as they these compounds are highly potent HIV integrase inhibitors in the form of fused bicyclic heterocyclic compounds.

It is observed that the complete specification does not expressly provide experimental data demonstrating the inhibitory activity of **Dolutegravir** (referred to therein as "Compound Y3") against HIV integrase. However, pursuant to the directions of the Hon'ble High Court, the expert evidence of Dr. Sheo Bux Singh and Dr. Brian A. Johns have been considered. Accordingly, the activity data relating to Dolutegravir, as furnished in the affidavit(s) filed on record, is taken on record and forms part of the evidentiary material for the purpose of assessment under Section 3(d).

Opponent(s) submitted that *Application as filed, does not show any potential activity of Dolutegravir (which is denoted as "Compound Y3" in the specification) as inhibitor of HIV integrase, let alone enhanced activity as compared to HIV Integrase inhibitor compounds disclosed in prior art documents. The activity pertaining to Dolutegravir has been given only in the affidavits which are dated subsequent to the date of filing of the application. As such, no data is available in the entire specification pertaining any type of beneficial activity of Dolutegravir. Furthermore, the compounds disclosed in prior art are also stated to have same or better activity as that of the exemplified compounds of the impugned application. The HIV integrase activity values stated in impugned application have been compared with those disclosed in some prior art documents in the Table given below:*

Impugned application	Prior art
• 50 Compounds of Z category shown to have best activity i.e. less than 10nM. • Activity of following Compounds shown as: Compound C2 3.3 ng/ml Compound F2 3.8 ng/ml Compound H2 3.2 ng/ml	**EP 1544199** discloses 125 compounds on pages 181 to 188 which have activity of less than 10nM
	WO 2004/096128 discloses on page 401 that "*examples 1 to 98 were found to have IC50 values 0.002 to 2 uM*". It is to be noted that 0.002uM is 2nM.

Thus, the specification as originally filed does not contain any comparative data to establish enhanced efficacy of the compounds of the invention as compared to the HIV Integrase inhibitor compounds disclosed in prior art.

In this regard, the Opponent(s) have relied upon Examples 377 and 378 of EP1544199 as alleged "known substances" against which the Applicant has claimed enhanced efficacy for Dolutegravir. The Opponent(s) have also referred to compounds disclosed in WO2004/096128. However, WO2004/096128 discloses compounds bearing a difluoro substitution on the benzyl amide group attached to a triad-containing ring system. These compounds are structurally distinct and do not possess the characteristic saturated oxazine-containing tricyclic core of Dolutegravir. Accordingly, they cannot be considered structurally relevant or appropriate "known substances" for the purpose of comparison of efficacy as submitted by the Applicant. With respect to Examples 377 and 378 of EP1544199, the Applicant has submitted that Dolutegravir exhibits significant activity against the Q148K resistant mutant HIV integrase enzyme. In his affidavits (Singh-II, para 51 and Singh-IV, para 70), Dr. Sheo Bux Singh has stated that the inventors identified the methyl-substituted compound (with a methyl group adjacent to the nitrogen atom) as unexpectedly demonstrating superior biological activity and favourable pharmaceutical properties, thereby qualifying it as a suitable development candidate. Notably, enhanced activity against the resistant HIV integrase enzyme harbouring the Q148K mutation was shown. Furthermore, Dolutegravir demonstrated a lower fold change (FC) in activity compared to its corresponding enantiomer, indicating a functionally significant stereochemical advantage.

Table 1: Comparison of enantiomeric compounds and their data

Cpd	pHIV IC_{50} (nM)	Q148K (FC)
Dolutegravir	1.7	0.4
Enant-dolutegravir	0.5	2.2

The claimed compound Dolutegravir per se is stated to demonstrate enhanced efficacy over known compound 378 of EP1544199, particularly against resistant mutant strains of HIV integrase.. Accordingly, the claimed compound, Dolutegravir, does not fall within the ambit of Section 3(d) of the Patents Act.

I conclude that such a ground of opposition is not validly established by the Opponent(s).

12. **Ground IV -Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.**

With regard to sufficiency of disclosure of the claimed compound **Dolutegravir**, the applicant has submitted that the compound is disclosed as Example Y-3 at page 116 of the complete specification, wherein a ^1H-NMR spectrum is provided. However, upon careful examination of the complete specification, it is evident that Dolutegravir is not expressly disclosed by name or by structural formula anywhere therein. The compound is merely referred to as "Example Y-3," accompanied only by spectral data.

Example Y-3)

(4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaz a-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

1H-NMR ($CDCl_3$)δ 1.42(3H, d, J=7.0Hz), 1.56(1H, dd, J=2.0, 14.0Hz), 2.19-2.30(1H, m), 4.02(1H, d, J=2.2Hz), 4.05(1H, t, J=2.3Hz), 4.12(1H, dd, J=6.0, 13.6Hz), 4.27(1H, dd, J=4.2, 13.4Hz), 4.64(2H, d, J=5.9Hz), 4.95-5.05(1H, m), 5.26(2H, d, J=4.1, 5.8Hz), 6.75-6.85(2H, m), 7.30-7.40(1H, m), 8.30(1H, s), 10.38(1H, brs), 12.45(1H, s).

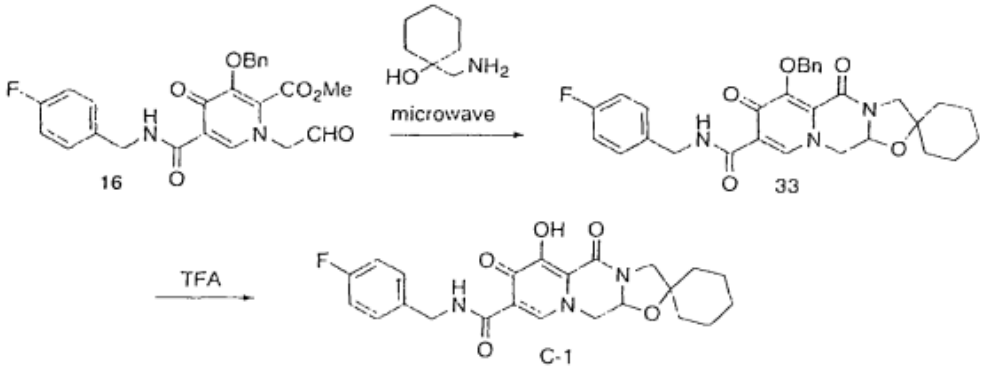
Further, it is observed that the disclosure provides only generic synthetic schemes applicable to compounds of Formula (I) and does not contain any compound-specific worked example or step-by-step method for the preparation of the claimed compound Dolutegravir. Further, the specification does not disclose any experimental HIV integrase inhibitory data or IC_{50} values supporting the claimed technical effect of Dolutegravir is provided in the CS at the time of filing. It is further noted that the

present claims are limited only to a specific molecule, namely Dolutegravir, and its sodium salt, and do not relate to a broad class of compounds. In such circumstances, a specific disclosure of Dolutegravir and its sodium salt is required. However, the disclosure of spectral data, without an accompanying structural formula and preparation, does not amount to disclosure of the compound itself. A person skilled in the art would first be required to derive the complete molecular structure from the NMR data, which, in the present case, involves significant interpretation and assumptions and cannot be considered routine or straightforward.

With respect to the process of preparation, the specification states at page 116 that compounds Y-1 to Y-18 were synthesized "according to the same manner as that of Example C-21." Example C-21 is disclosed at page 91, and reference is made to page 87, which states that compounds C-2 to C-21 may be synthesized using a method similar to that employed for preparing compound C-1. Further, Example C-1 is stated to have been synthesized using compound 33, which in turn is stated to have been prepared according to the method of synthesizing compound 17-1, and ultimately by reference to Example A-1 which is not Dolutegravir.

Example C-1

[Chemical formula 55]



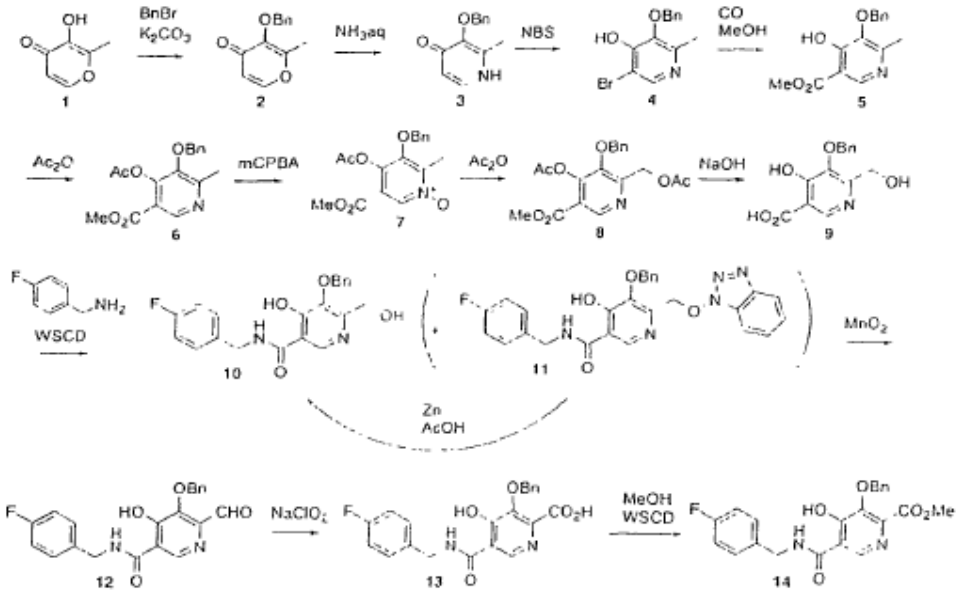
Example A-1)

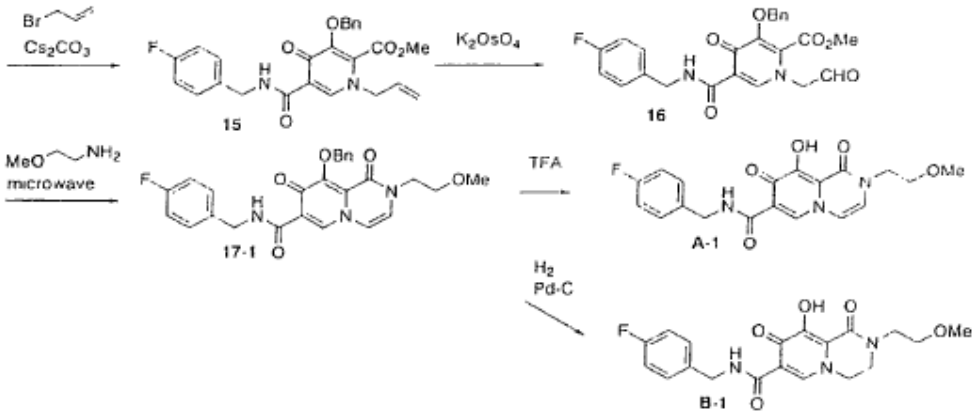
9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,8-dihydro-2H-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluoro-benzylamide

Example B-1)

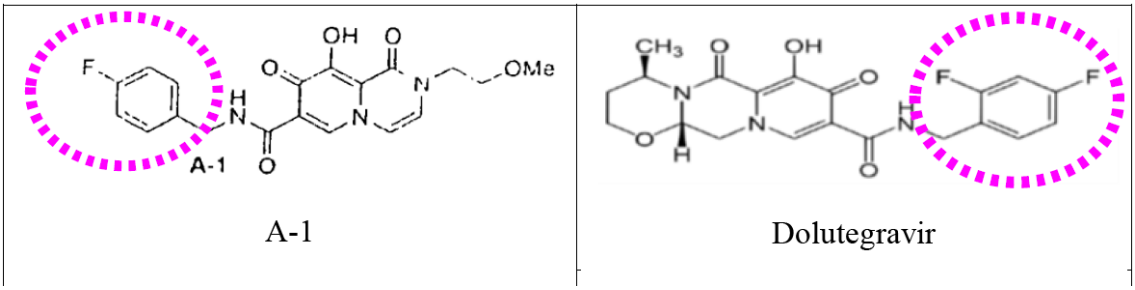
9-Hydroxy-2-(2-methoxy-ethyl)-1,8-dioxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrazine-7-carboxylic acid 4-fluoro benzylamide

[Chemical formula 52]



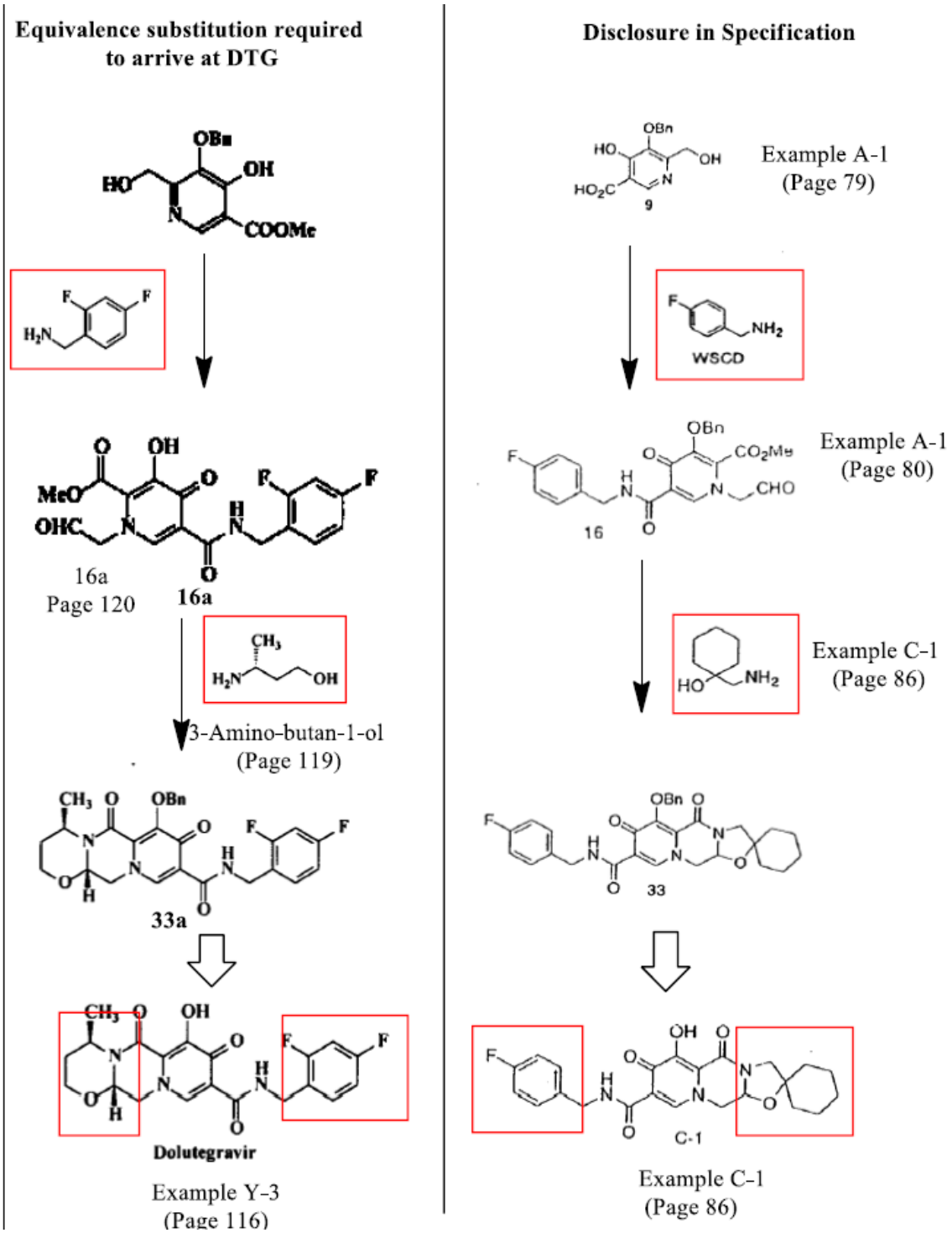


Compound A1 is a product wherein the phenyl ring contains a single fluoro substitution on the phenyl ring whereas the Dolutegravir contains a difluoro system. The figure below illustrates:

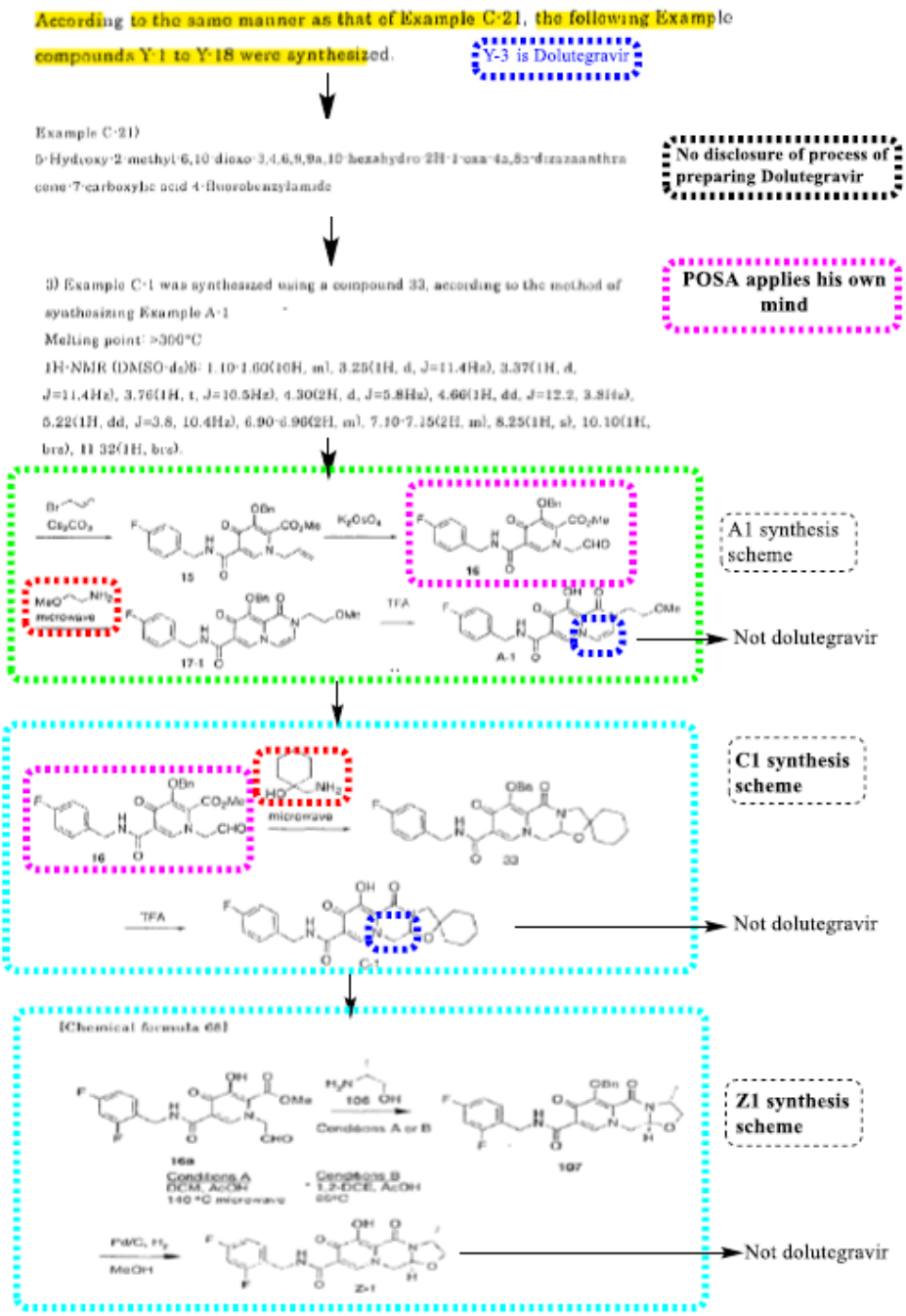


The product obtained from Example A-1 possesses (i) an unsaturation in the ring system, whereas Dolutegravir contains a saturated ring; (ii) a bicyclic ring system, whereas Dolutegravir possesses a tricyclic ring system; and (iii) a phenyl ring bearing a single fluoro substitution, whereas Dolutegravir contains a 2,4-difluoro substitution pattern. Similarly, Example C-1 relates to a compound having structural features distinct from Dolutegravir, including differences in ring system architecture and substitution pattern.

Applicant submitted that a *person skilled in the art would be able to synthesize the compound Dolutegravir by using the below scheme in the manner shown below along with the equivalent reagent as disclosed in the patent specification*.



The combined long route as argued by Applicant is given below for reference.



Thus, even if a person skilled in the art were to follow the cross-referenced synthetic scheme from A-1 through C-1 and C-21, the disclosed process would not yield Dolutegravir. In order to arrive at Dolutegravir, the skilled person would be required to:

(i) first derive the structure from the NMR data of Example Y-3;

(ii) modify the substituent in the A-1 reaction scheme to introduce a 2,4-difluorobenzylamide moiety;

(iii) alter the amino alcohol component used in Example C-1 to obtain the appropriate intermediate;

and
(iv) further modify and convert the resulting intermediate into Dolutegravir.

The product of C-1 process possess a tetracyclic ring system whereas in the Dolutegravir there is a tricyclic ring system. In order to arrive at Dolutegravir, a person skilled in the art would be required to (i) first derive the structure of Dolutegravir from the NMR data disclosed in Example Y-3, (ii) modify the substituent marked in black circle in the reaction scheme of Example A-1 to incorporate a 2,4-difluorobenzylamide moiety to obtain a modified compound 16, (iii) further modify the amino alcohol marked in green circle used in Example C-1 to obtain compound 33, and (iv) finally convert the same into Dolutegravir. These steps are neither disclosed nor suggested in the specification and would require independent inventive effort.

Further, Example C-1 discloses only one starting material (compound 16) for preparation of compounds C-2 to C-21, without identifying the necessary co-reactants or intermediates required to generate structurally diverse products. The specification does not describe any modification of compound 16 that would result in Dolutegravir. Notably, none of the compounds in the C-series or Y-series possess the same saturated oxazine-containing tricyclic system that characterizes Dolutegravir. The significant structural variations among these compounds underscore the absence of enabling guidance regarding the specific reactants, intermediates, and reaction conditions required to synthesize Dolutegravir. Further, it is observed that from Example C-1, a person skilled in the art is informed only about one starting material, namely compound 16, for the preparation of compounds C-2 to C-21. However, the specification does not disclose the identity or structure of the other reactant(s) required for the preparation of compounds C-2 to C-21. Since the invention purports to relate to new compound, such absence of disclosure regarding essential reactants renders the preparation of these compounds impossible without undue experimentation. It is also noted that the specification does not disclose any modification of compound 16 in the reaction scheme, and the use of compound 16 as disclosed cannot result in Dolutegravir. Further, although the specification states that the synthesis scheme of Example C-1 is to be followed for preparing compounds C-2 to C-21, none of the compounds C-2 to C-21 possess a saturated oxazole ring at the terminal end of the tricyclic system, which is a distinguishing structural feature of compound C-1. In light of such significant structural differences, the synthesis scheme of Example C-1 provides no enabling disclosure as to how all compounds of the C-series are to be synthesized. Similarly, none of the compounds Y-1 to Y-18 possess a saturated oxazole ring at the terminal end of the tricyclic system. In view of the substantial structural differences between compound C-1 and the compounds of the Y-series, as well as the variations among the Y-series compounds themselves, the specification fails to disclose which reactants, intermediates, or reaction scheme are to be employed to synthesize the Y-series compounds, including Dolutegravir.

Further, SHEO BUX SINGH in his affidavit mentioned that *The procedure used for preparation of sodium salt of acidic compound DTG is very different than what is described by Philip J. Gould in his publication. Basic amine based pharmaceutical compounds (in the paper by Gould) are paired with acidic reagents to make salts whereas acidic pharmaceutical compounds (DTG) are titrated with basic reagent to make salt. While both processes produce salts the former salt preparation process is opposite of the latter salt preparation process. Therefore, the Opponent clearly 314 49 does not understand the salt formation process.*

With reference to Dolutegravir and its the pharmaceutically acceptable sodium salt, the complete specification neither describes a method to specifically produce the sodium salt of the compound. The disclosure on page 116 of the specification pertains only to Dolutegravir and its isomer namely, compound Y-2 and compound Y-3. Disclosure pertaining to salts in general is given on page 54 of the specification but does not mention any specific pharmaceutical compound, its synthesis or its activity with regards to sodium salt of Dolutegravir.
Also, since the Applicants in claim 1 explicitly claim one specific isomer of Dolutegravir [(4R, 9as)-5-Hydroxy-4-methyl-6, 10-di-oxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a, 8a-diaza-anthracene-7-carboxylix acid 2,4,-difluoro-benzylamide] the specification ought to identify the synthesis of the most active isomer. However, no such disclosure is given in the specification.

In the context of sufficiency under Section 10 of the Act, the disclosure must be such that it enables a person skilled in the art (PSITA) to perform the invention without undue experimentation. A PSITA is a hypothetical person having ordinary skill, relevant qualifications, practical experience, and common general knowledge in the field. The legal standard does not attribute to the skilled person an elevated or creative faculty enabling reconstruction of undisclosed subject matter. The PSITA is not expected to engage in speculative structural derivation, or independent structural redesign in the absence of clear teaching, direction, or enabling guidance in the specification. In medicinal chemistry, even a single substituent modification can introduce structural novelty and unpredictably affect biological activity, physicochemical characteristics, and stereochemical behaviour. Accordingly, if arriving at the claimed invention requires creative modification, selective structural alteration, or multiple non-disclosed steps, the requirement of full and particular description under Section 10 is not satisfied. There is no disclosure in the specification to change the reactant to get dolutegravir and its sodium salt as claimed in claims 1-2**.** Claim 3 is nothing but the application or intend use of the claimed compound. In view of the above, it is concluded that the complete specification fails to provide "BEST MODE" of synthesis of compound Dolutegravir, and is thus, insufficient and consequently the present application is not patentable under Section 10(4) of the Act.

Hence, I conclude that this ground of opposition u/s 25 (1)(g) is validly established by Opponent(s).

13. The instant application does not meet the requirements of section10 of the Patents Act based on the findings from the investigation as well as from the matter presented by the opponents in the pre-grant opposition proceedings as discussed above. Therefore, it is hereby ordered that the invention disclosed and claimed in the instant application 3865/KOLNP/2007 entitled "POLYCYCLIC CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY" has been refused to proceed further under section 15 of the Act and simultaneously, I dispose of the pre-grant opposition as per the provision under Section 25(1) of the Act and corresponding Rules made thereunder.

Dated this 23-02-2026

(Dr. (Miss) Latika Dawara)
Asst. Controller of Patents & Designs
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