

**IN THE MATTER OF THE PATENTS ACT, 1970 AS AMENDED  
BY THE PATENTS (AMENDMENT) ACTS 1999, 2002 AND 2005**

**AND**

**IN THE MATTER OF THE PATENTS RULES, 2003 AS AMENDED BY THE  
THE PATENTS (AMENDMENT) RULES, 2006 AND 2016**

**AND**

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, CHENNAI  
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

In the matter of Pre-grant Opposition under section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005 read with rule 55 of The Patents Rules, 2003 as amended by The Patent (Amendment) Rules 2006 and The Patent (Amendment) Rules 2016

**-And-**

In the matter of Patent Application No. 1310/DELNP/2013 filed on 12<sup>th</sup> February 2013 by Abbvie Bahamas Ltd. of 1 North Waukegan Road North Chicago IL 60064

**..... APPLICANT / RESPONDENT**

**-And-**

In the matter of representation by way of notice of opposition filed by Delhi Network of Positive People (DNP+) of Flat no. A1-5, Property 141 Gali No. 3, Harijan Colony, Neb Sarai, New Delhi, 110068 and the Initiative for Medicines, Access & Knowledge, Inc (I-MAK) of 16192, Coastal Highway, Lewes, Delaware, 19958-9776

**..... OPPONENT/PETITIONER**

**WRITTEN REPRESENTATION BY WAY OF OPPOSITION TO GRANT OF A PATENT**

1. We, the Delhi Network of Positive People (DNP+) of Flat no. A1-5, Property 141 Gali No. 3, Harijan Colony, Neb Sarai, New Delhi, 110068 and the Initiative for Medicines, Access & Knowledge, Inc (I-MAK) of 16192, Coastal Highway, Lewes, Delaware, 19958-9776 (hereinafter as **"Opponent"**) hereby submit a written

representation by way of opposition to patent application no. 1310/DELNP/2013 (herein after as “impugned application”) filed on 12<sup>th</sup> February 2013 entitled “ANTI VIRAL COMPOUNDS” filed by Abbvie Bahamas Ltd. of 1 North Waukegan Road North Chicago IL 60064 (hereinafter, the “**Applicant**”). The impugned patent application is a national phase application of the PCT application PCT/US2011/056045 with an international filing date of 12<sup>th</sup> October 2011. The PCT application is annexed herewith as **Annexure I**.

## **2. Locus Standi**

The Delhi Network of Positive People (DNP+) is a community based non-profit organisation registered as a Trust under Registration No. 8525 representing the needs of people living with HIV/AIDS (“PLHAs”) and Hepatitis C (HCV). The Initiative for Medicines, Access & Knowledge (I-MAK), Inc, is a not-for-profit public service organisation comprising lawyers and scientists working to protect the public domain against undeserved patents to ensure they do not act as a barrier to research and restrict public access to affordable medicines, with its registered address at 16192 Coastal Highway, Lewes, Delaware, 19958-9776, U.S.A. The Opponent makes the present representation under Section 25(1) of the Act in opposing the grant of a patent to the application under no. 1310/DELNP/2013 (hereinafter, the impugned application) in the name of Abbvie Bahamas Ltd.

## **3. Background**

HCV presents a serious global health problem. The virus is transmitted through direct contact with an infected persons blood. Persons with needle-stick injury, health care workers with exposure to blood/blood products, transfusion/blood product recipients, organ transplant recipients and intravenous drug users are some of the populations at risk from HCV. According to the World Health Organization, over 80 million people have chronic HCV infection and are likely to develop liver cancer and/or cirrhosis. The best estimates available show India alone has an estimated 6 million people who are chronically infected with HCV, with 96,000 deaths annually due to the infection. India is also home to 2.1 million

people living with HIV (PLHIV) and applying the global co-infection rate of 2.4% implies that approximately 50,400 people in this community may be co-infected with HCV.

Given the public health crisis around HCV, it is imperative that people living with HCV are able to access the latest and most effective treatments without unmerited patents standing in the way. Undeserved patents of the nature applied for in impugned application affords a company, such as the Applicant, artificial exclusive rights, which then allows it to price a medicine beyond the reach of not only Indian patients, but also many in need in other developing and even developed countries. The Applicant also strategically uses such unmerited patents in its licensing programme in India in order to manage the generic competition and further delay legitimate open competition. By managing the competition the Applicant is able to control the market in India but also in other countries where competitors may otherwise have been able to sell the medicine at more affordable prices.

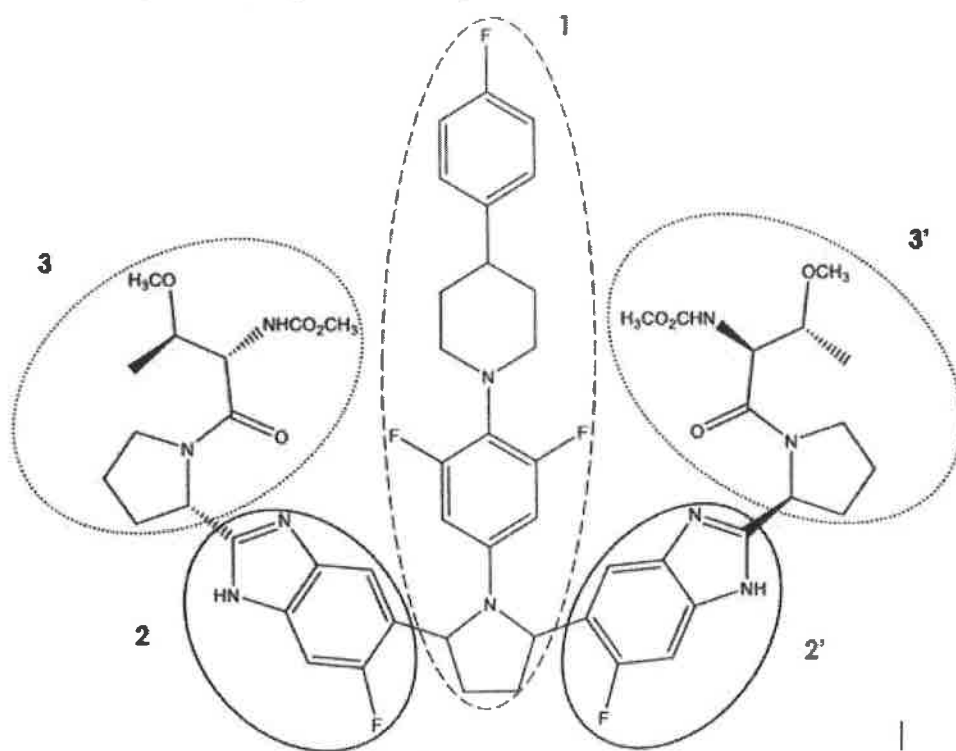
#### **4. Background of the invention:**

4.1 The impugned application titled "Anti viral compounds" has been filed as a national phase application from the PCT application PCT/US2011/056045 (WO/2012/051361) on 12<sup>th</sup> February 2013. The international filing date was 12<sup>th</sup> October 2011. The impugned application application was filed with 22 claims. A request for examination under section 11B and Rule 24(B)(i) of the Indian patents Act (hereinafter, the Act) was filed on 27<sup>th</sup> August 2014 and a First Examination Report (FER) was issued by the Indian Patent Office (IPO) on 7<sup>th</sup> December 2017. The response to the impugned application was filed by the agent of the applicant on 5<sup>th</sup> June 2018. Rule 55 of the Indian Patent Rule says that a pre-grant opposition can be filed from the date of publication till the grant of the patent application. Hence, there is no delay in filing the instant pre-grant opposition.

4.2 The impugned application was filed with 22 claims which correspond to the originally filed claims of the PCT application. While complying with the objections

of the FER under Section 21, the Applicant restricted the number of Claims to 3 on 5<sup>th</sup> June 2018. The said 3 claims pertain to one compound (claim 1) as well as a pharmaceutical composition comprising this compound (claim 2) and its use for the preparation of a medicament for treating a patient with HCV (claim 3). The pending claims as on date are as annexed herewith as **Annexure II**.

4.3 The compound in claim 1 is an HCV NS5A inhibitor also known as pibrentasvir or ABT-530, and is represented by the following formula



Pibrentasvir presents a symmetrical structure with a central core containing a substituted pyrrolidine (1) which serves as a linker for two fluorobenzimidazole (2, 2') bonded to a proline ring which is attached to a N-methoxycarbonyl amino acid (3, 3'). In pibrentasvir, the amino acid is a threonine. The compound is disclosed as Example 3.52 on page 324-5 of International application PCT/US2001/056045 published as WO 2012/051361 (hereafter the '361 application), of which the impugned application is a national phase.

## 5. Grounds of Opposition:

- Section 25(1)(a): that the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from a person under or through whom he claims;
- Section 25(1)(i): that in the case of a convention application, the application was not made within twelve months from the date of the first application for protection for the invention made in a convention country by the applicant or a person from whom he derives title;

Section 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 as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;

- Section 25(1)(f): that 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.

## 6. **DOCUMENTS CITED:**

Document	Publication date
US2011/0207699 ('699)	25 August 2011
WO2010144646 ('646)	16 December 2010
Wagner <i>et al.</i> (2018) <i>J. Med. Chem.</i> <b>61</b> : 4052-4066	13 April 2018
WO2010091413 ('413)	12 August 2010
US20100074863 ('863)	25 March 2010
WO2009003009 ('009)	31 December 2008
US20100267634 ('634)	21 October 2010

## 7. **DETAILED GROUNDS OF OPPOSITION:**

7.1 **Section 25(1)(a):** Why the priority date of the impugned application ought to be October 12, 2011

7.1.1 The impugned application derives its priority from four US applications which are listed:

Priority	Application Number	Priority Date
1	US12/903,822	October 13, 2010

2	US12/964,027	December 09, 2010
3	US61/446,800	February 25, 2011
4	US13/100,827	May 04, 2011

Since the impugned application is a national phase of a PCT application, the right to claim priority is regulated by Article 8 of the Patent Cooperation treaty (PCT) which itself relates to Article 4 of the Stockholm Act of the Paris Convention for the Protection of Industrial Property.

7.1.2 Each of the 4 priority applications listed above were filed in the name of the inventors, *i.e.* with the inventors as applicants. Indeed, at the time these US applications were filed, *i.e.* before entry into force of the America Invents Act (AIA) of 2012, it was required under US law that US applications be filed with the inventors as applicants. In contrast, the '361 application was filed in the name of Abbott Laboratories, *i.e.* with Abbott Laboratories as the applicant.

7.1.3 Accordingly, for the '361 application, and therefore for the impugned application to benefit from the above priority dates, Abbott Laboratories has to be considered the successor in title of the inventors/applicants of the priority applications. The purported assignments of the right to claim priority from the 4 priority applications from the inventors/applicants (assignors) to Abbott Laboratories (assignee) are attached herewith as **Annexures III, IV, V and VI**.

7.1.4 It can be readily seen that while the inventors/applicants (assignors) have executed the purported assignments no legal representative of Abbott Laboratories (assignee) has executed them.

7.1.5 However, for an assignment to be valid under section 67 of the Act, both the assignor and the assignee must execute the assignment.

7.1.6 As such, no valid assignment of the priority rights arising from the above priority filings has occurred within the priority period. Therefore, Abbott Laboratories cannot be considered a successor in title of the inventors/applicants and the impugned application is not entitled to any of the claimed priority dates, *i.e.* its effective date is its filing date (October 12, 2011).

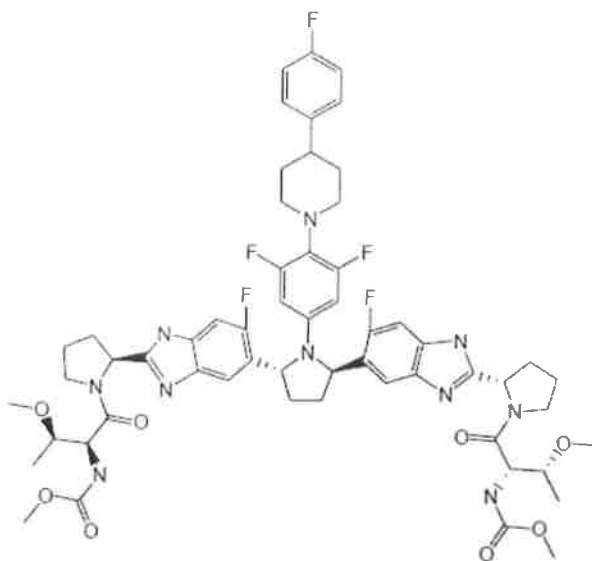
7.1.7 Separately, under section 7(2) of the Act a proof of right document such as an assignment is required to be filed by the applicant of a patent to demonstrate how the said applicant is deriving its title over the subject matter of the patent. This document is required to be filed within 3 months of the application. No such document can be found from the online records of the impugned application which demonstrates that the applicant's 'right' over the subject matter of the impugned application does not stand established. What is filed is a "confirmatory assignment" on 23<sup>rd</sup> February 2015 assigning the impugned application from Abbott, Inc. to Abbvie Bahamas, Ltd. However, the crucial assignment from the inventors to Abbott, Inc. is missing. In the absence of a title in favour of Abbott Laboratories over the subject matter of the impugned application, the applicant is not entitled to claim any right over the impugned application.

7.1.8 Hence, the applicant has *prima facie* wrongfully obtained the invention for the purposes of Section 25(1)(a) and further, as the applicant's predecessor in title, Abbott Laboratories did not secure an assignment of the subject matter of the impugned application from its inventors, the impugned application is not entitled to any of the claimed priority dates, and its effective date ought to be its filing date (October 12, 2011).

7.2. **Section 25(1)(i) read with Section 11:** Arguendo, if Abbott Laboratories was deemed to be the successor in title of the inventors/applicants of the 4 earlier applications from which the priority is claimed by the impugned application, then it is submitted that the impugned application will still not qualify as the corresponding convention application pertaining to US12/903,822 and US12/964,027 for the reasons enumerated hereunder. Hence, for the purposes of Section 11 of the Patents Act, the priority date of the impugned application can at best be considered to be February 25, 2011 (the priority date of US61/446,800) and it ought to be deemed that no corresponding complete specifications have been filed in respect of US12/903,822 and US12/964,027 for the purposes of Section 25(1)(i).

7.2.1 The impugned application claims the compound methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl] pyrrolidin-2-yl}-1H-benzimidazol-

5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate, represented by the following formula:



or a pharmaceutically acceptable salt thereof (claim 1), as well as a pharmaceutical composition comprising said compound (claim 2) and said compound as and when used in the preparation of a medicament for treating a patient infected with HCV (claim 3).

7.2.2 Pending claim 1 of the impugned application is claim 15 of the originally filed claims. Claims 1-14 have been cancelled by the applicant while responding to the FER. Compounds claimed in cancelled claims 1-14 were disclosed in the two earlier priority applications, US12/903,822 of October 13, 2010 and US12/964,027 of December 09, 2010. In view of the cancellation of the claims, the date of filing of the priority applications which pertain to the cancelled claims cannot provide the priority date for the impugned application.

7.2.3 The compound claimed in the currently pending claim 1 was first disclosed in the document US61/446,800. It is not disclosed in the two earlier priority applications, US12/903,822 of October 13, 2010 and US12/964,027 of December 09, 2010. Hence, the effective priority date for the current application should be February 25, 2011 which is the date of filing of the priority application US61/446,800.

### 7.3 Section 25(1)(e): Why the impugned application lacks an inventive step

7.3.1 The impugned application claims compounds, in particular pibrentasvir, which demonstrates anti-HCV activity. The support for the alleged anti-HCV activity of the claimed compound in claim 1 can be found on page 406 lines 22-32 of the complete specification of the impugned application (annexure I), which indicated that when tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each title, including compound of example 3.52 (pibrentasvir) showed an EC50 value of less than about 0.1 nM. However, no detailed experimental results are presented in the application. As such, the impugned application does not provide any evidence demonstrating that pibrentasvir possesses anti-HCV activity.

7.3.2 It is additionally submitted that in the absence of any evidence and data, it is purely conjecture by the applicant that substantially all the compounds described in the impugned application possess the purported anti-HCV activity. The application provides no basis for such a conclusion. Further, on pages 406-407, the applicant discusses the efficacy of certain compounds of the invention using different HCV replicon assays. Some compounds are compared with key compounds of prior applications presented in tables 1-5. Also, there is no mention of Example 3.52 in these paragraphs nor any comparison of the antiviral activity of compound of Example 3.52 with the key compounds of tables 1-5.

7.3.3 In light of the above, on the effective date of the impugned application, it was not credible that the compound of Example 3.52 demonstrates anti-HCV activity.

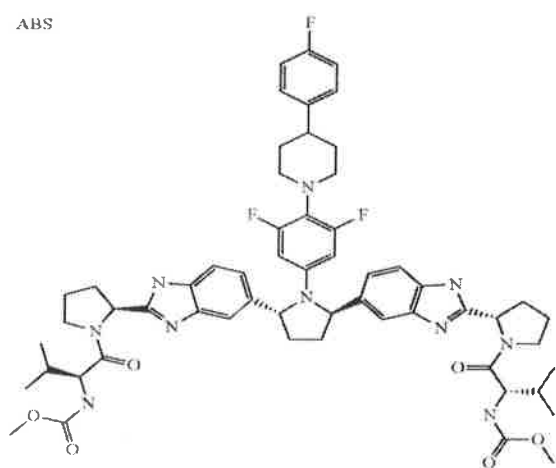
7.3.4 Consequently, the alleged technical advance underlying the impugned application, consisting of pibrentasvir, could at best be the discovery of a compound with an arbitrary chemical structure and not of a compound having a particular activity, such as a NS5A inhibitor activity as this is belied by the applicant's own admission.

7.3.5 Hence the impugned application fails to disclose an inventive step under Section 25(1)(e) and deserves to be refused.

**7.4 Section 25(1)(e): Why the impugned invention suffers from obviousness**

7.4.1 In view of the arguments in paragraph 7.1 establishing that the impugned application cannot be considered to draw priority from any of the prior applications and the priority date should be considered to be from October 12, 2011 i.e. the international filing date, (or at best from February 12, 2011 for the reasons elaborated in 7.2) the Opponents respectfully submit that the impugned application be dismissed on the ground of obviousness due to the lack of priority.

7.4.2 US patent application No. US2011/0207699 annexed herewith as **annexure VII** (hereafter the '699 application), filed by Abbott Laboratories, was published on 25 August 2011, i.e. before the effective date of the impugned application (12 October 2011). This application relates to compounds for inhibiting replication of HCV, as well as compositions comprising these compounds and methods of using these compounds to treat HCV (see paragraph [0002]). The '699 application discloses compounds with a strong structural resemblance with pibrentasvir and which constitute a promising starting point for a development leading to pibrentasvir. In particular, the compound of Example 3.42 (see page 227 of the '699 application), reproduced below, has the same central core as pibrentasvir and very similar lateral chains.



Example 3.42

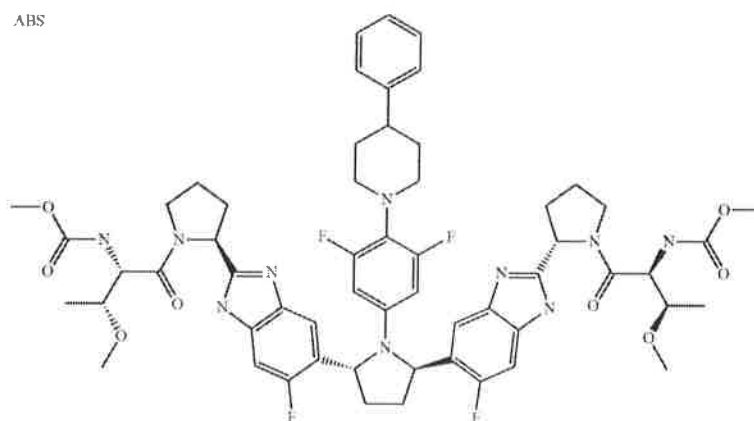
Besides, it is disclosed that this compound showed an EC<sub>50</sub> value of less than about 0.1 nM when tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS. As such, the '699 application is directed to a similar effect as the impugned application, namely providing compounds for use in the treatment of HCV infections, and provides compounds which present structural resemblances with pibrentasvir.

7.4.3 The '699 application therefore qualifies as the closest prior art document. However, the points of difference for the two compound 3.42 and the compound claimed in impugned application are:

- The N-methoxycarbonyl amino acid chain of pibrentasvir comprises a threonine instead of a valine in the compound of Example 3.42;
- The benzimidazole rings of pibrentasvir are substituted by a fluorine atom.

On comparing the compound pibrentasvir with compound of Example 3.42 of the '699 application it is observed that there is no technical advance with respect to the compound of example 3.42, as pibrentasvir is also alleged to have anti-HCV activity in the impugned application. As such, the problem at the basis of pibrentasvir invention described in the impugned application could be simply formulated as providing further anti-HCV compounds to that of Example 3.42.

7.4.4 The '699 application also discloses compound of Example 4.38 (see page 250 of the '699 application) reproduced below which presents structural similarities with example 3.42 and the exact same lateral chains as pibrentasvir, i.e. it comprises a threonine in the N-methoxycarbonyl amino acid chain and fluoro-substituted benzimidazole rings.

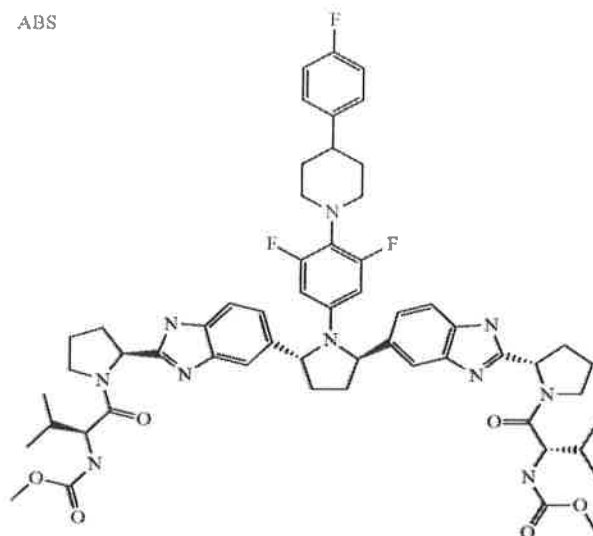


Example 4.38

7.4.5 A person skilled in the art, looking for an alternative anti-HCV compound to the compound of Example 3.42 would have considered other compounds disclosed in the '699 application. Furthermore, it is general technical knowledge that modification of amino acids, substitution with halogens and evaluation of the activity of the modified

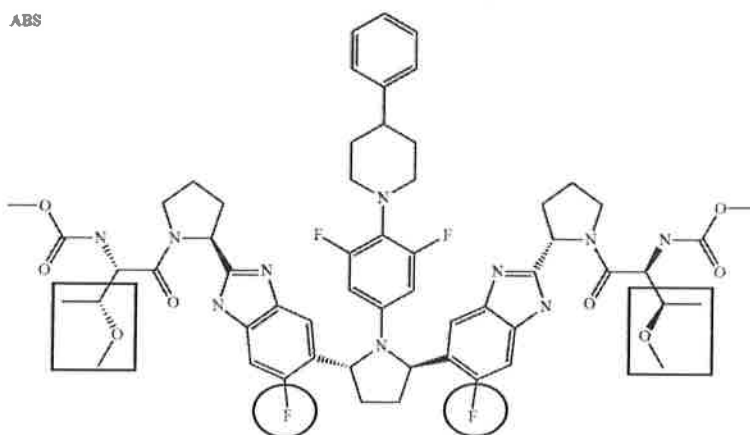
compound constitute routine experiments in the development and optimization of pharmaceutical compounds. Accordingly, the selection of a threonine and fluoro-substituted benzimidazoles already known from the '699 application is an arbitrary choice which does not involve an inventive step.

ABS

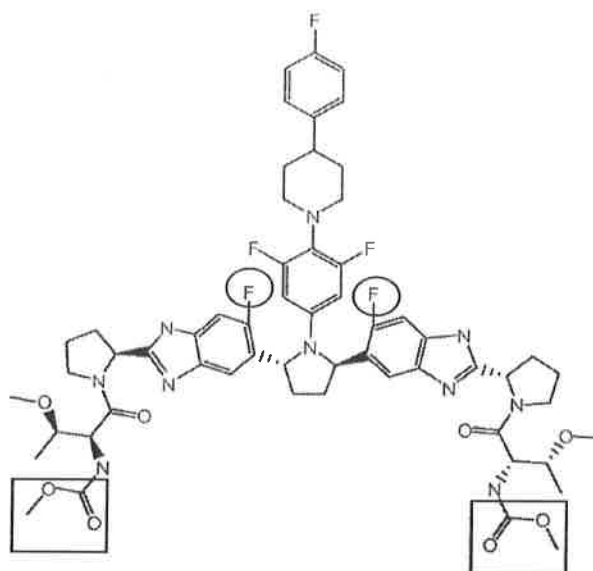


**Example 3.42**

ABS



**Example 4.38**

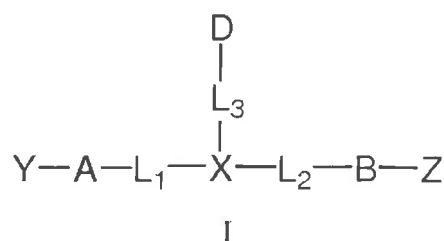


pibrentasvir

7.4.6 The person skilled in the art in order to look for an alternative would have obviously been prompted to adapt the compound of Example 3.42 by replacing the valine by a threonine in the N-methoxycarbonyl amino acid chain and by adding a fluorine atom in each benzimidazole ring, thus arriving to pibrentasvir. Accordingly, pibrentasvir does not involve an inventive step.

7.4.7, The Opponent has put forward alternate arguments in order to establish that the effective priority should be February 25, 2011 in paragraph 7.2 of this opposition. Considering February 25, 2011 as the effective priority date, it is submitted that the impugned application is obvious for *inter alia*, the following reasons:

- (i) The impugned application relates to compounds which are direct-acting antiviral agents and HCV NS5A inhibitors. However NS5A inhibitor compounds for use in HCV therapies, were known at the effective date of the impugned application and pibrentasvir is merely an obvious derivative of compounds disclosed in International application WO2010144646 (hereafter the '646 application) annexed herewith as **Annexure VIII**.
- (ii) The '646 application, filed by Abbott Laboratories, was published on 16 December 2010, i.e. before the effective date of the impugned application. This application relates to compounds effective to inhibit replication of HCV as well as a composition and methods of use comprising these compounds to treat HCV infection. The '646 application discloses compounds having the following general formula (I) (see claim 1 of the '646 application):



wherein:

X is C<sub>3</sub>-C<sub>12</sub>carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R<sub>A</sub>;

L<sub>1</sub> and L<sub>2</sub> are each independently selected from bond or C<sub>1</sub>-C<sub>6</sub>alkylene, C<sub>2</sub>-C<sub>6</sub>alkenylene or C<sub>2</sub>-C<sub>6</sub>alkynylene, each of which is independently optionally substituted at each occurrence with one or more R<sub>L</sub>;

L<sub>3</sub> is bond or -L<sub>4</sub>-K-L<sub>4</sub>'-, wherein K is selected from bond, -O-, -S-, -N(R<sub>B</sub>)-, -C(O)-, -S(O)-, -S(O)-, -OS(O)-, -OS(O)<sub>2</sub>-, -S(O)<sub>2</sub>O-, -S(O)O-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R<sub>B</sub>)-, -N(R<sub>B</sub>)C(O)-, -N(R<sub>B</sub>)C(O)O-, -OC(O)N(R<sub>B</sub>)-, -N(R<sub>B</sub>)S(O)-, -N(R<sub>B</sub>)S(O)<sub>2</sub>-, -S(O)N(R<sub>B</sub>)-, -S(O)<sub>2</sub>N(R<sub>B</sub>)-, -C(O)N(R<sub>B</sub>)C(O)-, -N(R<sub>B</sub>)C(O)N(R<sub>B</sub>')-, -N(R<sub>B</sub>)SO<sub>2</sub>N(R<sub>B</sub>')-, or -N(R<sub>B</sub>)S(O)N(R<sub>B</sub>')-;

A and B are each independently C<sub>3</sub>-C<sub>12</sub>carbocycle or 3- to 12-membered heterocycle and are each independently optionally substituted with one or more R<sub>A</sub>;

D is C<sub>3</sub>-C<sub>12</sub>carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R<sub>A</sub> or D is hydrogen or R<sub>A</sub>;

Y is selected from -T'-C(R<sub>1</sub>R<sub>2</sub>)N(R<sub>3</sub>)-T-R<sub>D</sub>, -T'-C(R<sub>3</sub>R<sub>4</sub>)C(R<sub>5</sub>R<sub>7</sub>)-T-R<sub>D</sub>, -L<sub>K</sub>-T-R<sub>D</sub>, or -L<sub>K</sub>-E;

R<sub>1</sub> and R<sub>2</sub> are each independently R<sub>C</sub>, and R<sub>3</sub> is R<sub>B</sub>; or R<sub>1</sub> is R<sub>C</sub>, and R<sub>2</sub> and R<sub>3</sub>, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R<sub>A</sub>;

R<sub>5</sub>, R<sub>4</sub>, R<sub>6</sub>, and R<sub>7</sub> are each independently R<sub>C</sub>; or R<sub>5</sub> and R<sub>6</sub> are each independently R<sub>C</sub>, and R<sub>4</sub> and R<sub>7</sub>, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R<sub>A</sub>;

Z is selected from -T''-C(R<sub>8</sub>R<sub>9</sub>)N(R<sub>12</sub>)-T-R<sub>D</sub>, -T''-C(R<sub>10</sub>R<sub>11</sub>)C(R<sub>13</sub>R<sub>14</sub>)-T-R<sub>D</sub>, -L<sub>K</sub>-T-R<sub>D</sub>, or -L<sub>K</sub>-E;

R<sub>8</sub> and R<sub>9</sub> are each independently R<sub>C</sub>, and R<sub>12</sub> is R<sub>B</sub> or R<sub>8</sub> is R<sub>C</sub>, and R<sub>9</sub> and R<sub>12</sub>, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R<sub>A</sub>;

$R_{10}$ ,  $R_{11}$ ,  $R_{13}$ , and  $R_{14}$  are each independently  $R_C$ ; or  $R_{10}$  and  $R_{13}$  are each independently  $R_C$ , and  $R_{11}$  and  $R_{14}$ , taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more  $R_A$ ;

$T$  and  $T'$  are each independently selected at each occurrence from bond,  $-L_S-$ ,  $-L_S-M-L_{S'}-$  or  $-L_S-M-L_{S'}-M'-L_{S''}-$ , wherein  $M$  and  $M'$  are each independently selected at each occurrence from bond,  $-O-$ ,  $-S-$ ,  $-N(R_B)-$ ,  $-C(O)-$ ,  $-S(O)_2-$ ,  $-S(O)-$ ,  $-OS(O)-$ ,  $-OS(O)_2-$ ,  $-S(O)_2O-$ ,  $-S(O)O-$ ,  $-C(O)O-$ ,  $-OC(O)-$ ,  $-OC(O)O-$ ,  $-C(O)N(R_B)-$ ,  $-N(R_B)C(O)-$ ,  $-N(R_B)C(O)O-$ ,  $-OC(O)N(R_B)-$ ,  $-N(R_B)S(O)-$ ,  $-N(R_B)S(O)_2-$ ,  $-S(O)N(R_B)-$ ,  $-S(O)_2N(R_B)-$ ,  $-C(O)N(R_B)C(O)-$ ,  $-N(R_B)C(O)N(R_B')-$ ,  $-N(R_B)SO_2N(R_B')-$ ,  $-N(R_B)S(O)N(R_B')-$ ,  $C_3-C_{12}$ carbocycle or 3- to 12-membered heterocycle, and wherein said  $C_3-C_{12}$ carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more  $R_A$ ;

$L_X$  is independently selected at each occurrence from bond,  $-L_S-N(R_B)C(O)-L_{S'}-$  or  $-L_S-C(O)N(R_B)-L_{S'}-$ ; or  $C_1-C_6$ alkylene,  $C_2-C_6$ alkenylene or  $C_2-C_6$ alkynylene, each of which is independently optionally substituted at each occurrence with one or more  $R_1$ ; or  $C_3-C_{12}$ carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more  $R_A$ ;

$E$  is independently selected at each occurrence from  $C_3-C_{12}$ carbocycle or 3- to 12-membered heterocycle, and is independently optionally substituted at each occurrence with one or more  $R_A$ ;

$R_D$  is each independently selected at each occurrence from hydrogen or  $R_A$

$R_A$  is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxy, cyano, or  $-L_S-R_E$ , wherein two adjacent  $R_A$ , taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

$R_B$  and  $R_{B'}$  are each independently selected at each occurrence from hydrogen or  $C_1-C_6$ alkyl,  $C_2-C_6$ alkenyl or  $C_2-C_6$ alkynyl, each of which is independently optionally substituted at amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in  $R_B$  or  $R_{B'}$  is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano,  $C_1-C_6$ alkyl,  $C_2-C_6$ alkenyl,  $C_2-C_6$ alkynyl,  $C_1-C_6$ haloalkyl,  $C_2-C_6$ haloalkenyl or  $C_2-C_6$ haloalkynyl;

$R_C$  is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl or cyano; or  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl or  $C_2$ - $C_6$ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in  $R_C$  is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_6$ haloalkenyl or  $C_2$ - $C_6$ haloalkynyl;

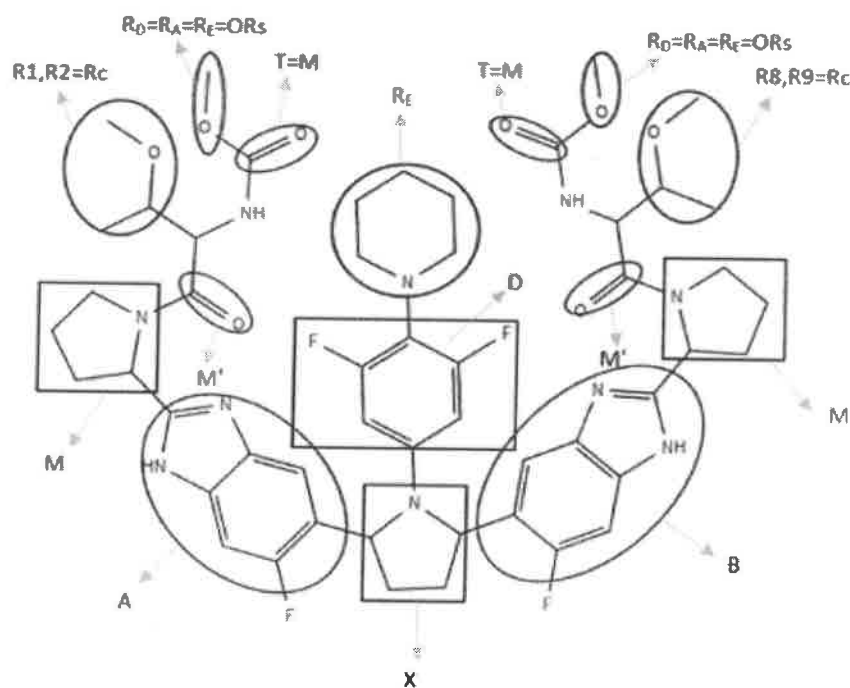
$R_E$  is independently selected at each occurrence from  $-O-R_S$ ,  $-S-R_S$ ,  $-C(O)R_S$ ,  $-OC(O)R_S$ ,  $-C(O)OR_S$ ,  $-N(R_S R_S')$ ,  $-S(O)R_S$ ,  $-SO_2 R_S$ ,  $-C(O)N(R_S R_S')$ ,  $-N(R_S)C(O)R_S'$ ,  $-N(R_S)C(O)N(R_S' R_S'')$ ,  $-N(R_S)SO_2 R_S'$ ,  $-SO_2 N(R_S R_S')$ ,  $-N(R_S)SO_2 N(R_S' R_S'')$ ,  $-N(R_S)S(O)N(R_S' R_S'')$ ,  $-OS(O)-R_S$ ,  $-OS(O)_2-R_S$ ,  $-S(O)_2OR_S$ ,  $-S(O)OR_S$ ,  $-OC(O)OR_S$ ,  $-N(R_S)C(O)OR_S'$ ,  $-OC(O)N(R_S R_S')$ ,  $-N(R_S)S(O)-R_S'$ ,  $-S(O)N(R_S R_S')$  or  $-C(O)N(R_S)C(O)-R_S'$ ; or  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl or  $C_2$ - $C_6$ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl or cyano; or  $C_3$ - $C_6$ carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_6$ haloalkenyl or  $C_2$ - $C_6$ haloalkynyl;

$R_L$  is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxy, cyano,  $-O-R_S$ ,  $-S-R_S$ ,  $-C(O)R_S$ ,  $-OC(O)R_S$ ,  $-C(O)OR_S$ ,  $-N(R_S R_{S'})$ ,  $-S(O)R_S$ ,  $-SO_2 R_S$ ,  $-C(O)N(R_S R_{S'})$  or  $-N(R_S)C(O)R_{S'}$ ; or  $C_3$ - $C_6$ carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl,  $C_2$ - $C_6$ alkynyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_6$ haloalkenyl or  $C_2$ - $C_6$ haloalkynyl;

$L_S$ ,  $L_{S'}$  and  $L_{S''}$  are each independently selected at each occurrence from bond or  $C_1$ - $C_6$ alkylene,  $C_2$ - $C_6$ alkenylene or  $C_2$ - $C_6$ alkynylene, each of which is independently optionally substituted at each occurrence with one or more  $R_L$ ; and

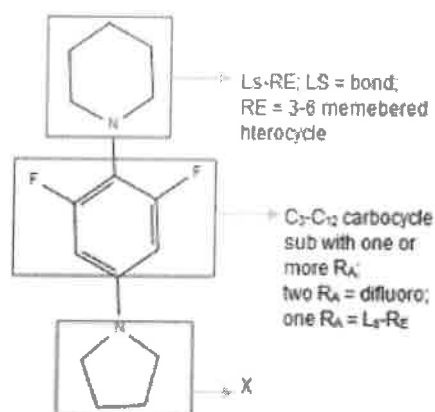
$R_S$ ,  $R_{S'}$  and  $R_{S''}$  are each independently selected at each occurrence from hydrogen;  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_6$ alkenyl or  $C_2$ - $C_6$ alkynyl, each of which is independently optionally

The above highlighted substituents can be deduced into the following structure:

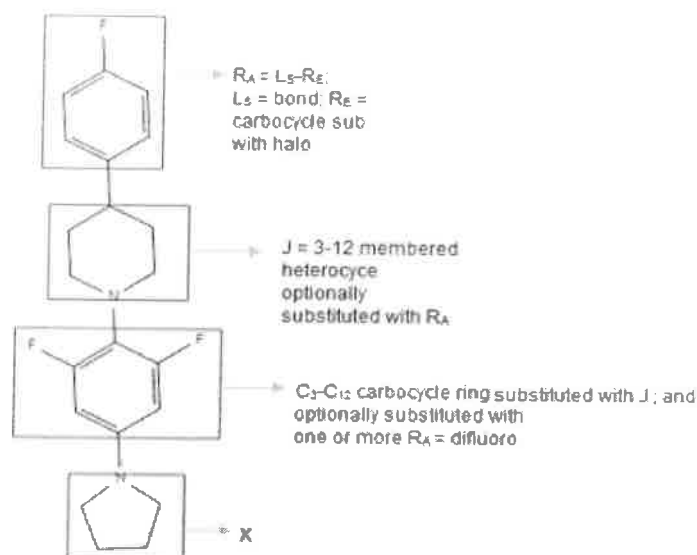


(iii) Thus, the generic disclosure of the impugned application and the disclosure of the '646 application overlap. The difference between pibrentasvir and the compounds disclosed in the '646 application lies in the presence of a fluorophenyl ring in the central core of pibrentasvir. The heterocyclic ring (piperidinyl), as defined under the substituent RE in the '646 application does not include a fluoro-substituted aryl group.

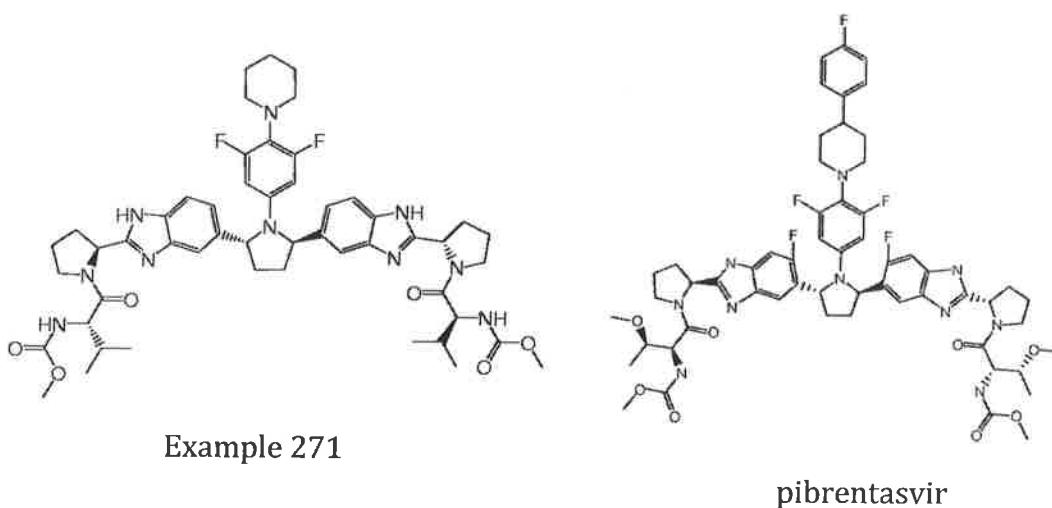
(iv) The substituent "D" in the '646 application includes only a carbocyclic ring substituted with one or more RA (wherein two RA groups can form a difluorophenyl ring and the third RA can be L<sub>S</sub>-RE, in which L<sub>S</sub> = a bond and RE = a 3-6 membered heterocycle = piperidine); this piperidine can be optionally substituted, but the substituents provided does not include the third ring of a halo substituted aryl group (a terminal 4-fluoro phenyl ring), as shown below:



(v) In the impugned application, substituent "D" includes a C<sub>3</sub>-C<sub>12</sub> carbocycle ring substituted with J and optionally with one or more RA. The C<sub>3</sub>-C<sub>12</sub> carbocycle ring substituted with one or more RA is difluorophenyl ring and the substituent J can be a 3-12 membered heterocyclic ring, which in the case of pibrentasvir is piperidine. This ring is further optionally substituted with one or more RA. The RA in this case can be a L<sub>S</sub>-RE, wherein L<sub>S</sub> = a bond and RE = a C<sub>3</sub>-C<sub>6</sub> carbocycle optionally substituted with halogen (4-fluorophenyl) ring, as shown below (see claim 1 of the impugned application).



(vi) The '646 application exemplifies several compounds with structural similarities with pibrentasvir. By way of example, compound of Example 271, reproduced below, has a core structure with strong similarities with pibrentasvir:



Besides, the compound of Example 271 is shown to have an  $EC_{50}$  values of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS (see page 375, line 21 of Annexure VIII). Similarly, the '646 application is directed to a similar effect as the impugned application, namely providing compounds for use as anti-HCV agent, and provides compounds which present structural resemblances with pibrentasvir.

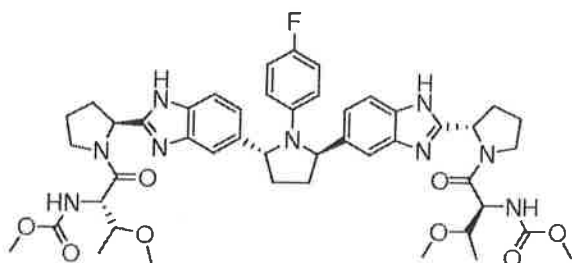
The '646 application therefore qualifies as the closest prior art document to the impugned application.

(vii) The differences between pibrentasvir and the compound of Example 271 of the '646 application is:

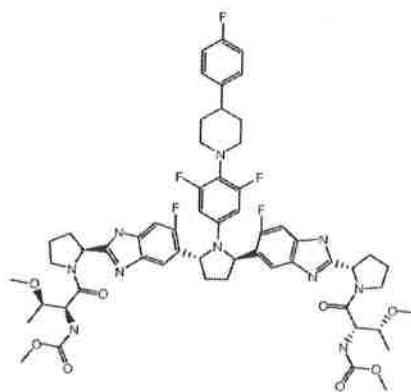
- The substitution of the pyrrolidine is extended in length and comprises an additional fluorophenyl moiety;
- The benzimidazole rings are substituted by a fluorine atom in pibrentasvir;
- The N-methoxycarbonyl amino acid of pibrentasvir comprises a threonine instead of a valine in Example 271 of the '646 application.

No technical advance can be associated to the difference between pibrentasvir and the compound of example 271 of the '646 application, as pibrentasvir is also alleged to have an anti-HCV activity in the impugned application, and no comparative test between compound of example 271 and pibrentasvir is disclosed in the impugned application. As such, the problem at the basis of the claimed invention described in the impugned application could be simply formulated as providing further anti-HCV compounds to those described in the '646 application.

(viii) Another compound disclosed in the '646 application presents N-methoxycarbonyl amino acid and the missing phenyl fluoro ring at the core position. This compound is reproduced below (see page 399, 2nd last compound):



Compound of page 399

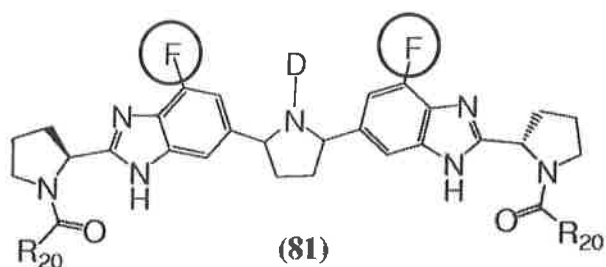


pibrentasvir

The combination of the compound of Example 271 and the compound of page 399 leads to a compound essentially identical to pibrentasvir. The only difference lies in the presence the fluorine atom in the benzimidazole ring of pibrentasvir.

However, this possibility is disclosed in the '646 application. See for example the following compounds:

Compound 81, page 91



Example 301, page 372

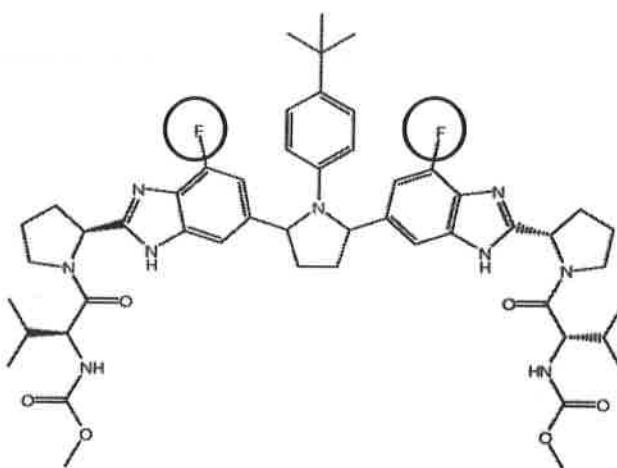
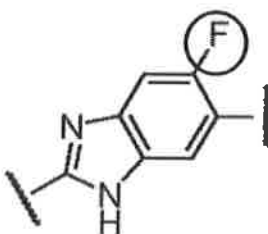
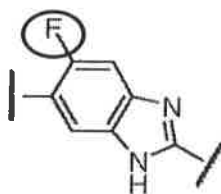


Table 1a.A, page 392



Possible A rings

Table 1b. B – page 393



Possible B72 rings

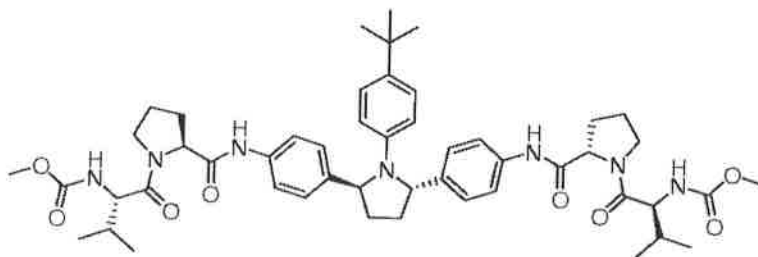
The person skilled in the art, looking for an alternative anti-HCV compound to the compound of Example 271 would have considered other compounds of the '646 application.

(ix) Besides, it is well known that modifications of the central core as well as substitutions with halogens and evaluation of the activity of the modified compound are part of routine experiments in the development and optimization of pharmaceutical compounds.

(x) Accordingly, the selection of a fluoro-substituted benzimidazoles already known from the '646 application is an arbitrary choice which does not involve an inventive step. Furthermore, the addition of a fluorophenyl ring to form a central core with three rings such as compounds of Example 101 page 215, Example 113, page 229 and Example 166 page 279 of the '646 application is also an arbitrary choice which does not involve an inventive step.

(xi) Accordingly, the person skilled in the art would have been prompted to adapt the compound of Example 271 by adding the fluorophenyl ring of compound of page 399 in the central core of compound of example 271 and adding a fluorine atom in each benzimidazole ring of compound of example 271, thus arriving to pibrentasvir. Thus, it can be said pibrentasvir does not involve an inventive step and the alleged invention in the impugned application suffers from obviousness.

(xii) The '646 application also discloses the compound of example 35 reproduced below (see page 134 of the '646 application).



Example 35

This compound pertains to ombitasvir.

Besides this compound shows an EC50 value of less than about 0.1 nM in HCV Ib-Con1 replicon assays in the presence of 5% FBS (see page 135).

The structural differences between compound of example 35 and pibrentasvir are:

- the substitution of the pyrrolidine is extended in length and comprises additional groups;
- pibrentasvir comprises a fluorobenimidazole ring instead of a benzene linked to an amide in ombitasvir;
- the N-methoxycarbonyl amino acid of pibrentasvir comprises a threonine instead of a valine in ombitasvir

However, no technical advance can be attributed to the difference between pibrentasvir and Compound of Example 35 of the '646 application, as pibrentasvir is also alleged to have anti-HCV activity in the '1310 application and no comparative test between compound of Example 35 and pibrentasvir is disclosed in the '1310 application.

A person skilled in the art, looking for an alternative anti-HCV compound to the compound of Example 271 would have considered other compounds of the '646 application. Indeed, in the pharmaceutical field, a well-known technique, for the development and optimization of clinical drug, is to start from a known compound and to apply structural modifications to this compound to analyze the effect on the therapeutic activity (*i.e.* to determine the so-called Structure Activity Relationship (SAT)). Modifications such as the addition of halogen atoms, the replacements of the linker, etc. are routine practice commonly used by the person skilled in the art.

In the present case, the modifications made to the compound of Example 35, namely the replacement of the benzene linked to an amide by a benzimidazole ring, the addition of fluorine atoms on benzimidazole rings, the addition of further groups to the substituted pyrrolidine, and the replacement of the amino acid valine with another amino acid are arbitrary modifications which do not involve an inventive step.

In addition, the inventors themselves admitted that they have modified ombitasvir to design pibrentasvir (Wagner *et al.* (2018) *J. Med. Chem.* **61**: 4052-4066;). The document is annexed herewith as **Annexure IX**. It is, therefore, evident that during the development of pibrentasvir they considered the other analog compounds described in the same

document as ombitasvir, *i.e.* the '646 application and interchanged parts of these compounds with those of ombitasvir.

Accordingly, the selection of a threonine amino acid and a fluoro-substituted benzimidazoles already known from the '646 application is an arbitrary choice which does not involve an inventive step. Furthermore, the modification of the pyrrolidine core by combining the central core of the compound of Example 271 and the 2<sup>nd</sup> last compound of page 399 is also an arbitrary choice, which does not involve an inventive step.

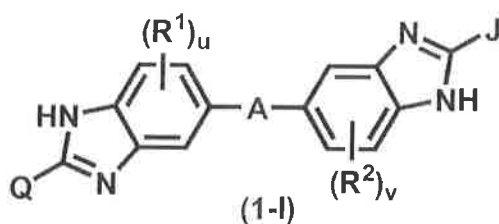
Any person skilled in the art would have been automatically prompted to adapt the compound of Example 35 by replacing the amino acid **changing the central core structure and adding fluoro substituted benzimidazoles, thus arriving to piberntasvir. Accordingly, pibrentasvir does not involve an inventive step.**

**7.6 Without prejudice to the foregoing, if the Patent Office deems 13 Oct 2010 to be the valid priority date for the impugned application, it would be obvious for, *inter alia*, the following reasons:**

(i) This date of October 13, 2010 is obtained from the priority application US12/903,822 which is the earliest priority application. As on October 13, 2010, however, the compound in Claim 1 would have been obvious on account of international application WO2010091413 [hereinafter the '413 application (**Annexure X**)], filed in the name of Enanta Pharmaceuticals, Inc., which was published on 12 August 2010, *i.e.* before the earliest priority date of the impugned application (13 October 2010).

(ii) The '413 application relates to compounds which can inhibit the function of the NS5A protein encoded by HCV, its composition comprising these compounds, methods for inhibiting HCV viral replication, method for treating HCV infection and process of preparation of these compounds (see page 1 lines 5-9).

(iii) The '413 application teaches a compound of the following general structure wherein A can be a heterocyclic ring, wherein the heterocyclic ring can be pyrrolidinyl (see page 67 line 30, page 68 line 7 and claim 1).



wherein:

**A** is independently selected from the group consisting of: aryl, heteroaryl, heterocyclic, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and C<sub>3</sub>-C<sub>8</sub> cycloalkenyl, all optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, -R<sup>10</sup>, -OR<sup>11</sup>, N(R<sup>π</sup>)<sub>2</sub>, -C(O)R<sup>11</sup>, -CO<sub>2</sub>R<sup>11</sup>, -C(O)N(R<sub>n</sub>)<sub>2</sub>, and -N(R<sub>n</sub>)C(O)R<sup>π</sup>;

**R<sup>10</sup>** at each occurrence is independently C<sub>1</sub>-C<sub>4</sub> alkyl optionally with one or more halogen atoms;

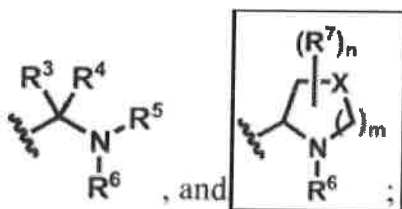
**R<sup>11</sup>** at each occurrence is independently hydrogen or optionally substituted C<sub>i</sub>-C<sub>8</sub> alkyl;

**R<sup>1</sup>** and **R<sup>2</sup>** at each occurrence are each independently selected from the group consisting of: halogen, cyano, optionally substituted C<sub>i</sub>-C<sub>4</sub> alkyl, -O-R<sup>11</sup>, -NRaRb, -C(O)R<sup>11</sup>, -CO<sub>2</sub>R<sup>11</sup>, and -C(O)NRaRb;

Ra and Rb at each occurrence are each independently hydrogen, optionally substituted C<sub>i</sub>-C<sub>8</sub> alkyl, or optionally substituted C<sub>2</sub>-C<sub>8</sub> alkenyl; or Ra and Rb taken together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

**u** and **v** at each occurrence are each independently 0, 1, 2, or 3;

**Q** and **J** at each occurrence are each independently selected from:



wherein,

R<sub>3</sub> and R<sub>4</sub> at each occurrence are each independently hydrogen, optionally substituted C<sub>i</sub>-C<sub>8</sub> alkyl, optionally substituted C<sub>2</sub>-C<sub>8</sub> alkenyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl; or alternatively, R<sub>3</sub> and R<sub>4</sub> taken together with the carbon atom to which they

are attached form optionally substituted C3-C8 cycloalkyl or optionally substituted heterocyclic;

R5 at each occurrence is independently hydrogen, optionally substituted Ci-Cg alkyl, or optionally substituted C3-Cg cycloalkyl;

**R6 at each occurrence is independently** selected from the group consisting of: hydrogen, -C(O)-R12, -C(O)-C(O)-R12, -S(O)<sub>2</sub>-R12, and -C(S)-R12;

**R12 at each occurrence is independently** selected from the group consisting of: -O-R11, -NRaRb, -R13, -NRcRd, -CH(R13)NRaRb and -CH(R13)NRcRd;

**R13 at each occurrence is independently selected from the group consisting of: optionally substituted C1-C8 alkyl, optionally substituted C2-Cg alkenyl, optionally substituted C2-C8 alkynyl, optionally substituted C3-C8 cycloalkyl, optionally substituted C3-Cg cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;**

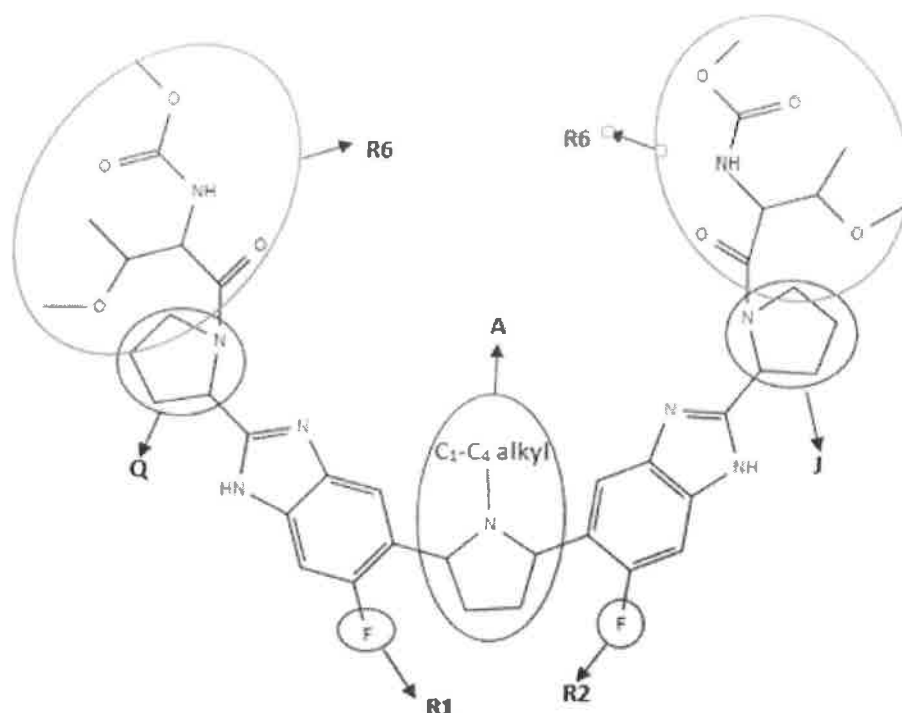
**Rc and Rd at each occurrence are each independently selected from the group consisting of: hydrogen, -R13, -C(O)-R13, -C(O)-OR13, -S(O)<sub>2</sub>-R13, -C(O)N(R13)<sub>2</sub>, and -S(O)<sub>2</sub>N(R13),;**

**m is 0, 1, or 2; n is 0, 1, 2, 3, or 4;**

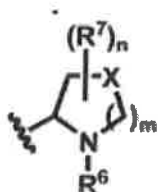
**X at each occurrence is independently selected from O, S, S(O), SO<sub>2</sub>, CH<sub>2</sub>, CHR<sub>7</sub>, and C(R<sub>7</sub>)<sub>2</sub>;** provided that when m is 0, X is selected from CH<sub>2</sub>, CHR<sub>7</sub>, and C(R<sub>7</sub>)<sub>2</sub>; and

**R7 at each occurrence is independently selected from the group consisting of:** halogen, cyano, -O-R11, -NRaRb, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted -C1-C4 alkyl; optionally, two vicinal R7 groups taken together with the two adjacent atoms to which they are attached form a fused, optionally substituted -C3-C8 cycloalkyl or optionally substituted heterocyclic ring; or alternatively and optionally, two terminal R7 groups taken together with the carbon atom to which they are attached form a spiro, optionally substituted C3-C8 cycloalkyl or optionally substituted heterocyclic ring.

The closest compound that can be derived from the above highlighted substituents from '413 can be:



Wherein A = heterocyclic = pyrrolidine ring, optionally substituted with R10 = C1-C4 alkyl; R1 and R2 = halogen = fluoro; Q and J are each independently selected from:

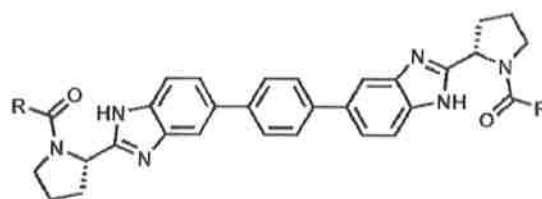


Wherein X = CH<sub>2</sub>; m = 1, n = 0, u = 1 and v = 1 R6 = -C(O)-R12, wherein R12 = -CH(R13)NRcRd; R13 = optionally substituted C1-C8 alkyl; (The page 5-6 discloses that R<sup>13</sup> can be substituted with -O(C<sup>1</sup>-C<sup>4</sup>)alkyl; Rc = Hydrogen; and Rd = -C(O)-OR<sup>13</sup>; wherein R<sup>13</sup> = C<sup>1</sup>-C<sup>8</sup> alkyl = methyl.

Thus the general formula of compounds of the impugned application and of the '413 application overlap.

(iv) The '413 application exemplifies compounds that are structurally close to pibrentasvir as shown below:

Table 1: Compounds 1-1 to 1-219



R is :

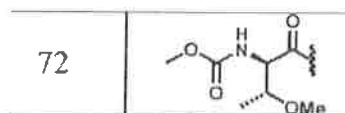
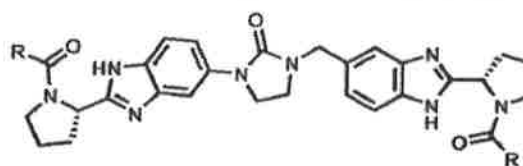
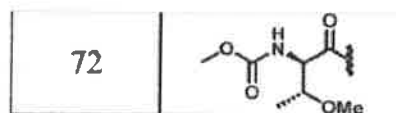


Table 17: Compounds 3-1 to 3-219



R is :



Example 1-72.

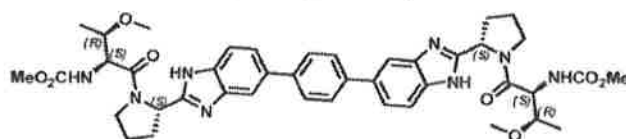
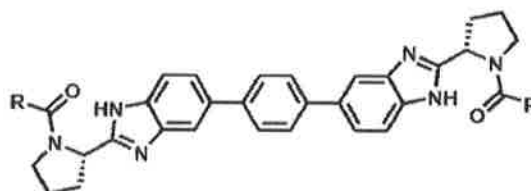


Table 1a: Examples 1-4 to 1-219



R is :

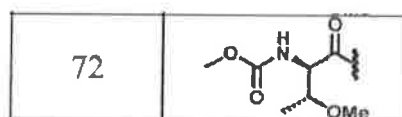
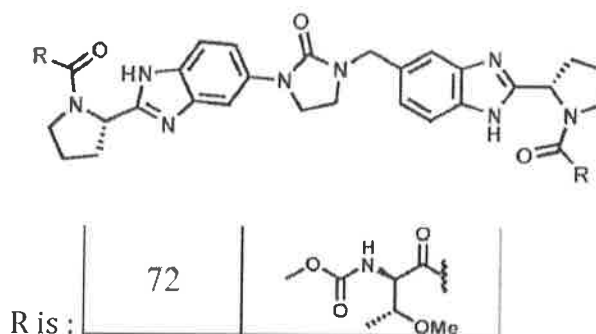


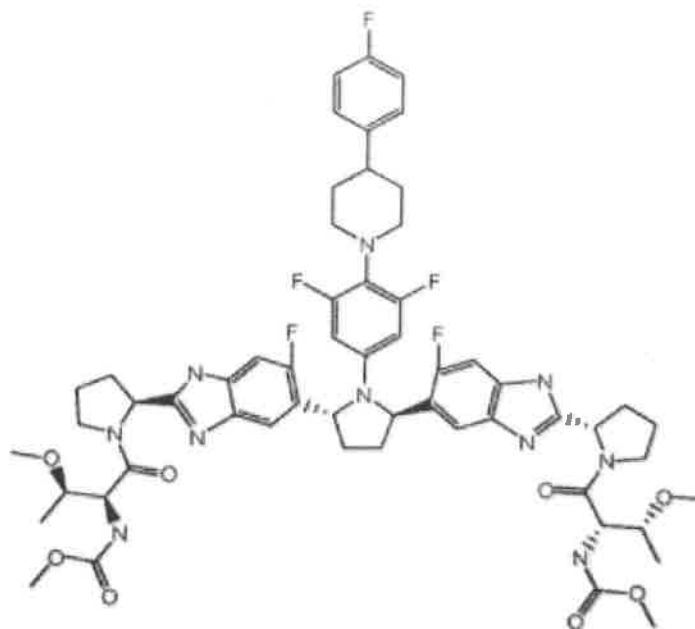
Table 16: Examples 3-1 to 3-219



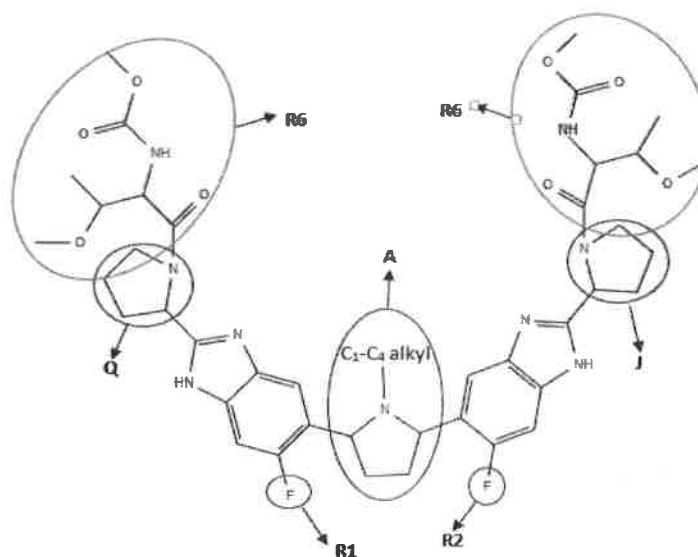
Furthermore, the fluoro substituent on either side of the benzimidazole arms are disclosed in the '413 application (see page 57, compounds 270; page 118 compound 290; and page 130, compound 290).

(v) Besides, the '413 application discloses on page 67 line 30 to page 68 line 7 the definition for the term "heterocyclic", as: *"The terms "heterocyclic" or "heterocycloalkyl" can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, 1,3-dioxolane, **pyrrolidinyl**, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted."* Thus the substituent "A" in the compound of Formula (1-1) includes a pyrrolidine group.

(vi) A comparison between pibrentasvir with that of the closely derived compound from the '413 application, is as below:



pibrentasvir



The '413 application's closest embodiment

Comparing the '413 application with the impugned application, it is noted that both the applications are directed to a similar purpose, that is providing compounds for use as anti-HCV agent, and compounds structurally resemble pibrentasvir.

(vii) The only differences between pibrentasvir and compound 1-72 of the '413 application are:

- The fluoro substituents on the benzimidazole ring of pibrentasvir;

- The central core comprised of a substituted pyrrolidine ring in pibrentasvir.

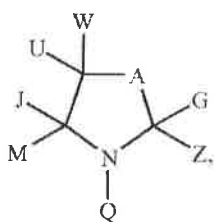
However, no technical advance can be associated to these minor differences between pibrentasvir and compound 1-72 disclosed in the '413 application, as pibrentasvir is also claimed to have anti-HCV activity in the impugned application and no comparative test between pibrentasvir and compound 1-72 is disclosed in the impugned application.

(viii) As such, the problem at the basis of the alleged invention described in the impugned application could be simply formulated as providing further anti-HCV compounds to that described in the '413 application.

(ix) In the '413 application the entire description is based on the presence of a dibenzimidazole linker irrespective of the core and the side linkages remained similar. This would provide a strong motivation to one of skill in the art to keep the dibenzimidazole linker and replace the central core to evaluate the effect in term of efficacy.

(x) The application US20100074863 (**Annexure XI**), hereafter the '863 application, was published on 25 March 2010, *i.e.* before the earliest priority date of the '413 application. This application relates to compounds, compositions and method for inhibiting HCV polymerase, a method for inhibiting HCV viral replication and a method for treating HCV infection.

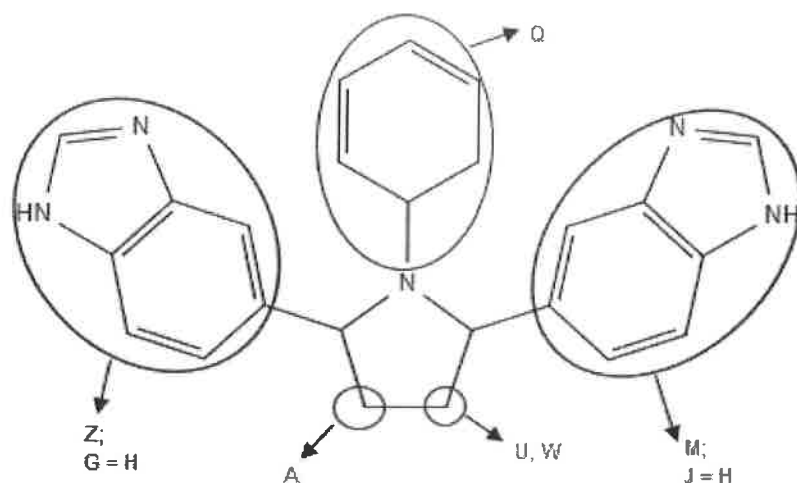
The '863 application teaches a compound represented by formula (I):



Wherein M can be substituted heteroaryl containing at least a nitrogen atom, Q can be R<sub>1</sub>, R<sub>1</sub> can be R<sub>3</sub> which in turn can be substituted aryl, A can be --C(X)(Y), wherein X and Y

are each independently selected from the group consisting of: hydrogen, U is independently X; W is independently Y, Z and J are each independently selected from the group consisting of: --R2, R2 at each occurrence can be independently hydrogen or R3; or R1 and R2 taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclic, G is Hydrogen.

The compound that can be deduced from the above highlighted substituents can be represented below:



wherein M = an optionally substituted heteroaryl or heterocyclic group containing at least a nitrogen atom; J = R2 = H, Q = R1 = R3 = substituted aryl; A == C(X)(Y) = CH2 (X = Y = hydrogen), U = X = H; W = Y = H; Z = R2 = R3 = substituted heteroaryl; and G is hydrogen.

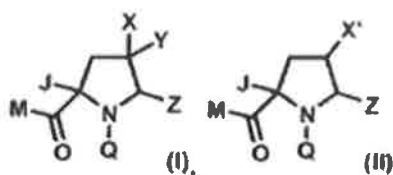
The specification on page 7, paragraph [0059], discloses the definition of the term heteroaryl as: *"The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, **benzimidazolyl**, benzooxazolyl, quinoxalinyl.* Thus, the substituents M and Z includes **benzimidazole rings**.

(xi) Although the above compound is disclosed generically, the publication does not include any specific compound which contains these highlighted substituents, the

reference to this disclosure is on account of its preference of pyrrolidine at the core, which seems to be fixed option according to this disclosure.

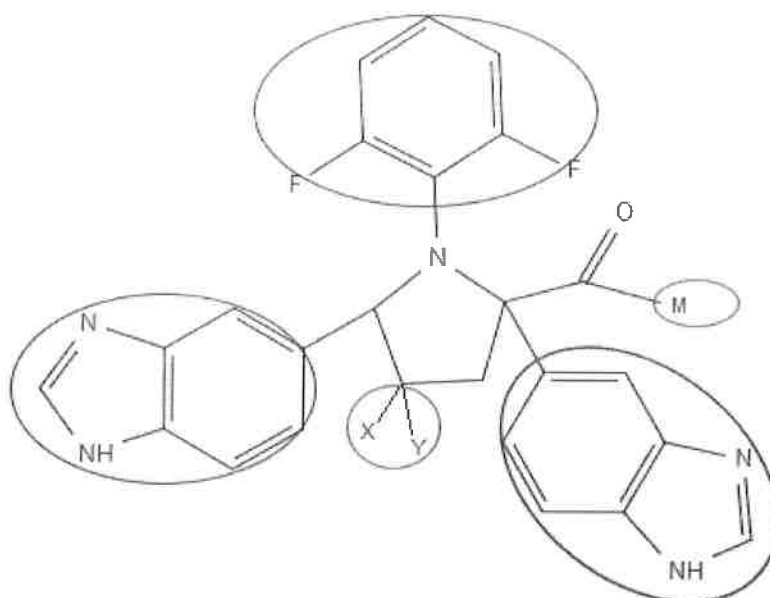
(xii) Additionally, international application WO2009003009 (**Annexure XII**), hereafter the '009 application, assigned to Enanta Pharma, was published on 31 December 2008, *i.e.* before the earliest priority date of the impugned application (13 October 2010).

The '009 application teaches a preference for pyrrolidine core in anti-HCV drugs. In particular, this application discloses compounds represented by Formulae (I) and (II):



or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, prodrug, solvate, or combination thereof, wherein: M at each occurrence can be R<sub>1</sub>, wherein is -R<sub>3</sub>; Wherein R<sub>3</sub> at each occurrence can be substituted aryl or substituted heteroaryl; Q at each occurrence can be -R<sub>3</sub>; X' at each occurrence can be halogen; X at each occurrence can be -X'; Y at each occurrence can be -R<sub>3</sub> or halogen; Z and J at each occurrence are each independently -R<sub>1</sub>.

The closest compounds that can be deduced from the above highlighted substituents can be represented as below:



Wherein Q = R3 = **substituted aryl**;

**Z and J = R1 = R3 = substituted heteroaryl**;

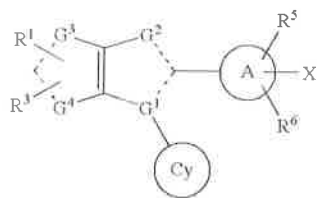
The groups C(=O)M and X, Y (or X') are the elements of difference when compared to the core of the compounds of the WO '361 patent. However, it may be noted that the compounds of WO '009, are capable of inhibiting the replication of an RNA containing virus, specifically HCV and importantly '009 teaches the "fixed" presence of a pyrrolidine core in HCV drugs.

(xiii) In view of the teaching of the '413 application, a person skilled in the art would have a strong motivation to replace the phenyl of compound 1-72 of the '413 application by a pyrrolidine group as disclosed in the the '863 application and the '009 application.

(xiv) Alternatively, application US2009036444, hereafter the '444 application (**Annexure XIII**) assigned to Japan Tobacco and published on 5 February 2009, i.e. before the earliest priority date of the impugned application, relates to a fused ring compound or a pharmaceutically acceptable salt thereof, which shows anti- HCV activity, particularly anti-HCV activity based on an RNA-dependent RNA polymerase inhibitory activity.

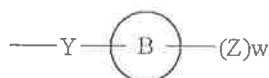
The '444 application covers in claim 1, a fused ring compound represented by the following formula [I] or a pharmaceutically acceptable salt thereof:

[1]

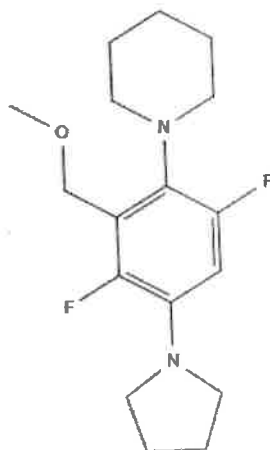


wherein "X", includes compounds of formula:

(13)

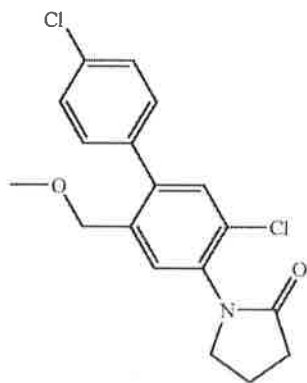


wherein B can be a substituted aryl group (eq. difluorophenyl) and w can be 2 (two substituents on aryl ring); wherein one of Z is a pyrrole ring and the other Z is a piperidiny ring (heterocyclic compound substituted with group D), results in a compound, which can be represented as below:

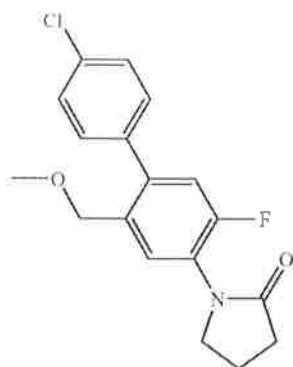


A number of groups that can be used in the place of the variable "X" have been listed from pages 39-68. The following are relevant groups which are similar to the pyrrolidine substitutions as taught in the impugned application:

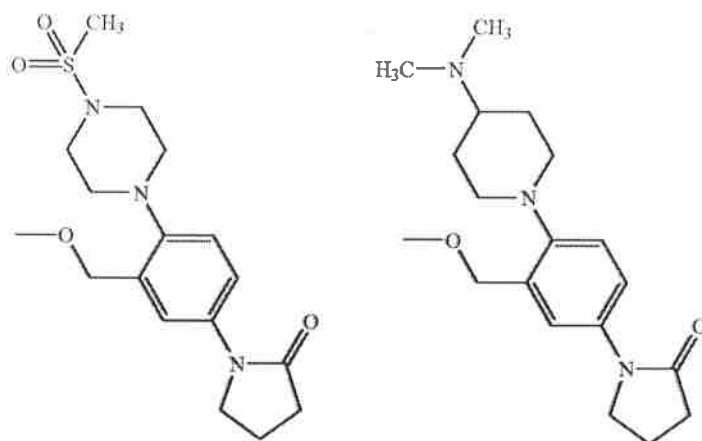
Page 62



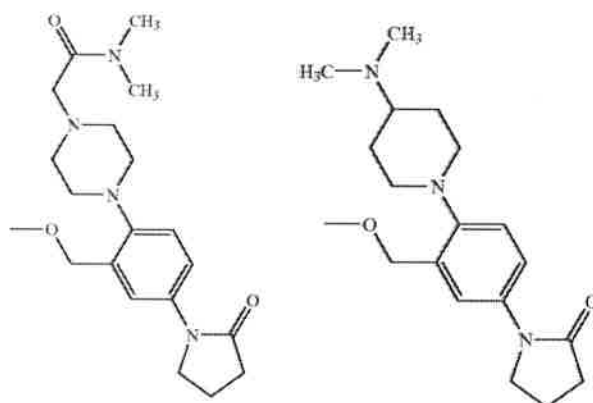
Page 64



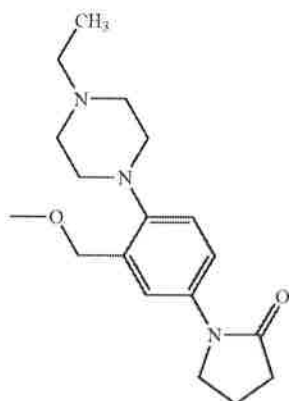
Page 66



Page 67

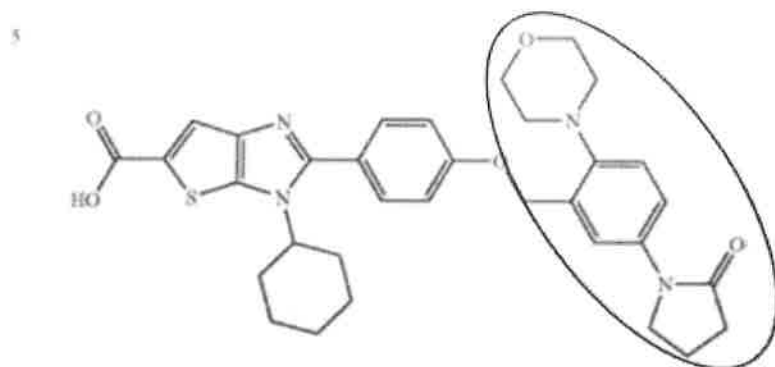


Page 68



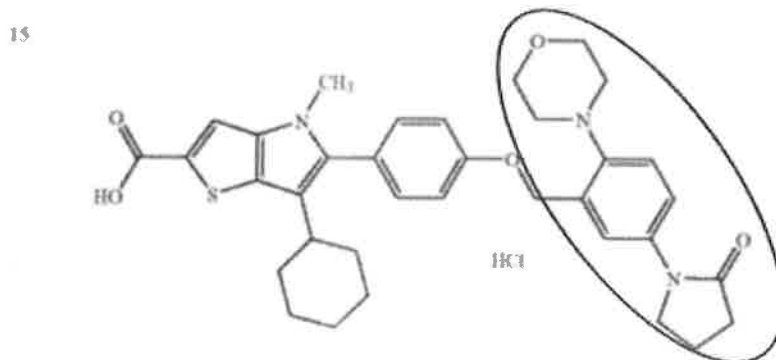
These groups contain a pyrrole ring, attached to an aryl ring, which is further attached to a heterocyclic compound in common. The compounds on page 62 and 64 indicate the presence of halo substitution on the aryl ring.

Furthermore, the '444 application, discloses on page 101, Table 1, a compound of formula 5:

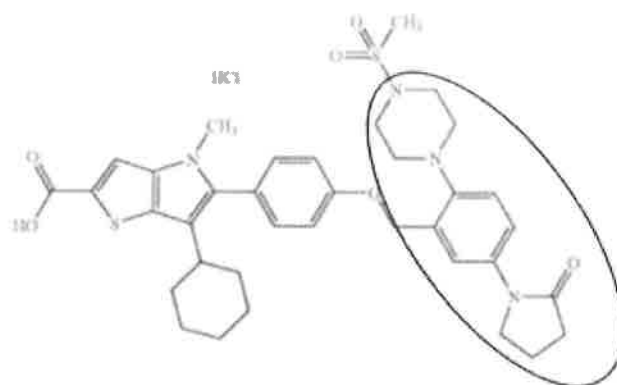


wherein, 2-oxo pyrrolidine is seen attached to a phenyl ring, which in turn is attached to a heterocyclic compound (morpholine).

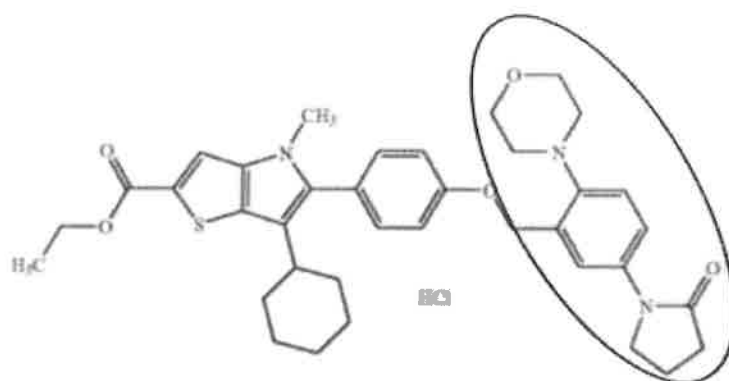
Similarly, the compounds in the Tables 2 and 3 on page 102, compound no. 15 and 18 and table 5 page 104, compound no. 24; all contain a 2-oxo pyrrolidine attached to an aryl ring, which in turn is attached to a heterocyclic compound in common.



18



24



Furthermore, the biological activity of the compounds disclosed in US '444, are provided on page 116:

[0946] The results are shown in Table 18, wherein each symbol means that  $IC_{50}$  falls within the following range.

A:  $0.1 \mu M \leq IC_{50} < 1 \mu M$

B:  $IC_{50} < 0.1 \mu M$

[0947] Reaction mixture: HCV polymerase (0.5  $\mu g/ml$ ) obtained in i), substrate RNA (5  $\mu g/ml$ ) obtained in ii), ATP (50  $\mu M$ ), GTP (50  $\mu M$ ), CTP (50  $\mu M$ ), UTP (2  $\mu M$ ), [5,6- $^3H$ ] UTP (46 Ci/mmol (Amersham), 1  $\mu Ci$ ) 20 mM Tris-HCl (pH 7.5), EDTA (1 mM),  $MgCl_2$  (5 mM), NaCl (50 mM), DTT (1 mM), BSA (0.01%)

TABLE 18

Example	H544 1a 5X $IC_{50}$	H544 1b 3X $IC_{50}$
7	A	B
8	A	A
12	A	A
14	B	B
15	B	B
17	B	B
18	B	B
19	B	B
20	B	B
21	A	B
23	B	B
24	A	A
25	A	B
26	A	B
27	B	B
28	B	B

As can be seen from the above table, the compounds possessing the pyrrolidine group attached to an aryl ring, which in turn is attached to a heterocyclic ring exhibit significant HCV polymerase inhibitory activity.

(xv) Therefore, the above application teaches compounds containing pyrrolidine group attached to an aryl ring, which in turn is attached to a heterocyclic ring to possess greater activity against HCV. Also it may be noted that lead clinical candidates like JTK-109, JTK-652 were evaluated as DAA for HCV therapy and accordingly it may be argued that the claimed pyrrolidine based core is obvious to select from such lead molecules. It may also be possible to combine Japan Tobacco's '444 with Abbott's '634 discussed earlier to show that the pyrrolidine ring in the core can have 3 further ring substitutions.

Hence, the alleged invention in the impugned application should be considered obvious.

**8. Section 25(1)(f):** The impugned application is barred under section 3(d) of the Act

8.1 The compounds from the '646 application are reported to be effective in inhibiting replication of HCV. The specification of '646 reads on page 409, that:

*"In many cases, representative compounds of the present invention can reduce the replication of HCV virus (e.g., in an HCV replicon assay as described above) by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more".*

The specification of '699 application is drafted in the same language as of the impugned application.

8.2 In the impugned application, apart from speculative examples, there is no specific test data provided therein for individual compounds. Furthermore, there are no comparative tests provided in the impugned application which compares the activity of compound of any of the above compounds with the compound of example 3.52 which is pibrentasvir.

8.3 Section 3(d) of the Act bars a new form of a known substance to be considered an invention, unless it results in enhancement of efficacy over the known efficacy of the known substance. Section 3(d) of the Patent Act was amended in 2005 to prevent patents based on modifications of known substances such as combinations and salts, esters, ethers and derivatives of known substances. Under the law each claim that relates to a new form of a known substance has to satisfy section 3(d) of the Patents Act.

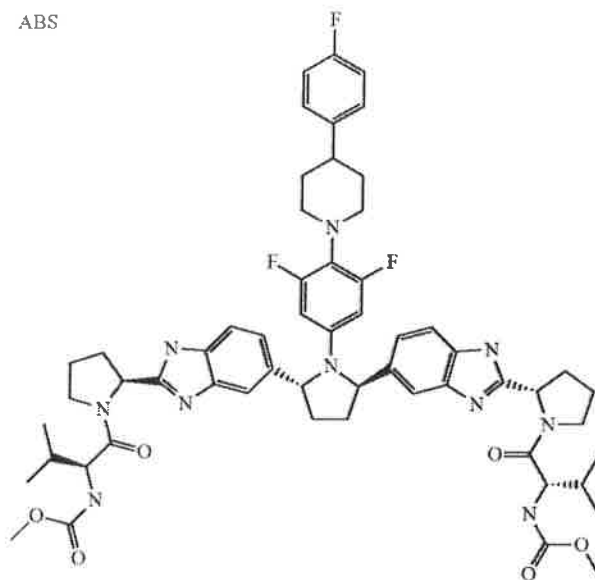
8.4 It is an established position of the law that the section 3(d) has to be satisfied independent of sections 2(1)(j) and 2(1)(ja) [*Novartis AG vs Union Of India and others* (2013 6 SCC 1)]. As held by the Hon'ble Madras High Court, the burden of proof is on the patent applicant to satisfy the requirements of Section 3(d), i.e., that of showing efficacy [*Novartis AG vs Union of India and others*, (2007 4 MLJ 1153), Para 13]. As held by the Hon'ble IPAB, this data is required to be in the complete specification [*Novartis AG vs Union of India and others*, (MIPR, 2009, (2) 0345), para 9(xvii)]. It is also an established position of law that the term efficacy in section 3(d) means therapeutic efficacy for pharmaceutical products [*Novartis AG vs Union Of India and others* (2013 6 SCC 1)].

Hence, the claims of the impugned application fail under section 3(d) of the Patent Act.

8.5 These claims essentially cover compounds already known in prior art. The impugned application does not contain any specific comparative efficacy data with respect to close prior art compounds disclosed and discussed herein, in particular from the '646 and '699 applications.

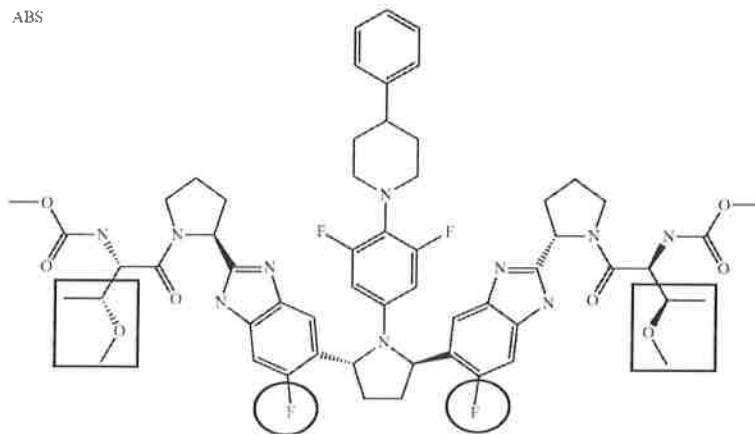
8.6 The compound disclosed and claimed in the impugned application is the "same substance" as compounds disclosed in the '646 and '699, and is merely a predictable variant, as can be clearly seen from the following examples taken from the '699 application.

ABS

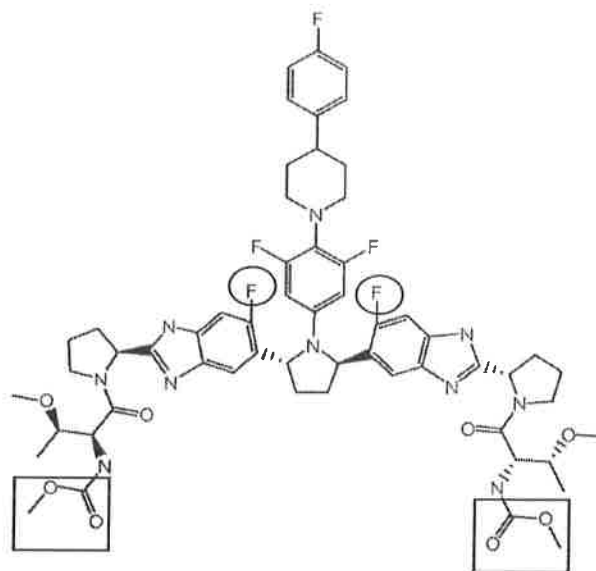


Example 3.42 of the '699 application

ABS



Example 4.38 of the '699 application



Claimed compound of the impugned application (pibrentasvir)

8.7 Therefore, in light of the above it is respectfully submitted that the impugned application claims a derivative of known substances and therefore the applicant has failed to discharge the onus of fulfilling the requirement under section 3(d) of the Act.

## 9. Relief sought:

In light of the grounds stated and the evidence presented above, the Opponents pray:

- (i) That Indian Application No. 1310/DELNP/2013 in the name of Abbvie Bahamas Ltd. be refused;

And in doing so:

- (ii) The Opponents be allowed to make further submissions in the event the Applicant makes any amendments to its claims;
- (iii) The Opponents be permitted to file further evidence if necessary to support its case;

(iv) The Opponents be granted an opportunity of being heard in the matter before any final orders are passed.

Dated this 20<sup>th</sup> day of July 2018.



Sudarshana Bandyopadhyay

Regn. No. IN/PA 2802

For and behalf of

The Delhi Network of Positive People (DNP+) and  
Initiative for Medicines, Access & Knowledge, Inc (I-MAK)

**Address for service in connection with these proceedings is: -**

**Fidus Law Chambers,  
Flat No. 021,  
Mahagun Maestro, Plot F21 A, Sector 50,  
Noida,  
Uttar Pradesh**

**To:  
The Controller of Patents  
The Patent Office  
Boudhik Sampada Bhavan,  
Delhi**