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. 2891/DELNP/2013 filed on 2nd April 2013 by Enanta Pharmaceuticals Inc. of 500 Arsenal Street Watertown MA 02472

..... 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. 2891/DELNP/2013 (herein after as "impugned application") filed on 2nd April 2013 entitled "MACROCYCLIC PROLINE DERIVED HCV SERINE PROTEASE INHIBITORS" filed by Enanta Pharmaceuticals Inc. of 500 Arsenal Street Watertown MA 02472 (hereinafter, the "**Applicant**"). The impugned application is a national phase application of the PCT application PCT/US2011/052304 with an international filing date of 20th September 2011. The publication number of this application is WO/2012/040167. The impugned application draws priority from three different patent applications. The earliest priority date of the impugned application is 21st September 2010. 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 impugned application no. 2891/DELNP/2013 in the name of Enanta Pharmaceuticals Inc.

3. Background

HCV presents a serious global health problem. The virus is transmitted through direct contact with an infected person's 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

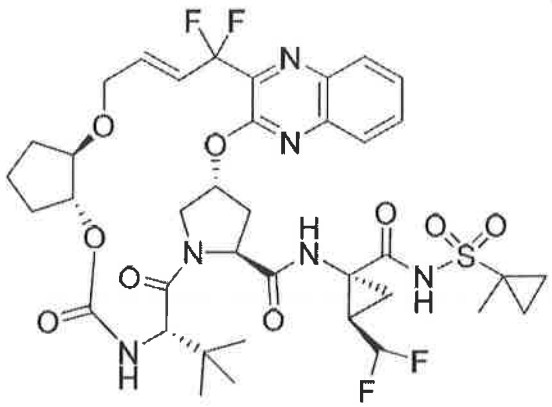
the market in India but also in other countries where competitors may otherwise have been able to sell the medicine at more affordable prices.

4. **Background of the invention:**

4.1 The impugned application titled "Macrocyclic proline derived HCV serine protease inhibitors" has been filed as a national phase application from the PCT application PCT/US2011/052304 (WO/2012/040167) on 2nd April 2013. The international filing date was 20th September 2011. The impugned application was filed with 26 claims. A request for examination under section 11B and Rule 24(B)(i) of the Indian Patents Act (hereinafter, the Act) was filed on 10th October 2013 and a First Examination Report (FER) was issued by the Indian Patent Office (IPO) on 30th May 2018. The response to the FER for the impugned application was filed by the agent of the applicant on 27th August 2018. Rule 55 of the Indian Patent Rule provides 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 26 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 10 on 27th August 2018. The said 10 claims pertain to a compound of the general formula (VII) (claim 1) with multiple possible substituents. The pending claims as on said date are as annexed herewith as **Annexure II**.

4.3 The impugned application claims a compound of the general formula (VII) (claim 1) with multiple possible substituents, as well as a compound of the following structure (claim 10):



This compound pertains to a Hepatitis C virus nonstructural protein 3/4A protease inhibitor also known as glecaprevir or ABT-493. This compound was disclosed as Example 6 on page 25 of the international application PCT/US2011/052304 published as WO2012/040167, of which the 2891 application is a national phase. The said document is already annexed herewith as Annexure I.

5. Grounds of Opposition:

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

6. DOCUMENTS CITED:

Ref. No.	Document
Annexure I	PCT publication of the impugned application

Annexure II	Pending claims of the impugned application
Annexure III	Claims of the priority document US61/504,616
Annexure IV	PCT/US2010/030850 (WO2010/132163)
Annexure V	PCT/US2008/083541 (WO2009/064975)
Annexure VI	PCT/US2007/022460 (WO2008/057209)
Annexure VII	PCT/US2009/033859 (WO2009/108507)
Annexure VIII	PCT/US2009/050915 (WO2010/011566)
Annexure IX	Brunton L.L, Lazo J.G et al, *"Goodman and Gilman's The Pharmacological Basis of Therapeutics" 11th edition, McGraw-Hill*
Annexure X	Tripathi K.D, *"Essentials of Medical Pharmacology"*, 5th edition, Jaypee Brothers Medical Publishers Ltd
Annexure XI	Lawitz et al., (2016) Antimicrobial Agents and Chemotherapy, 60: 1546-1555
Annexure XII	Gentile *et al.*, (2014) *Expert Opin. Investig. Drugs*, **23** : 1-10

7. DETAILED GROUNDS OF OPPOSITION:

7.1 Section 25(1)(e):

Priority claims: The impugned application claims priority from 3 earlier patent applications which are summarized below:

Priority	Application number	Priority date
1	US61/385,058	21 September 2010
2	US61/499,994	22 June 2011
3	US61/504,616	5 July 2011

The earliest priority date for the impugned application is thus 21st September 2010. The impugned application was originally filed with 26 claims. The applicant reduced the claims to 10 in response to the First Examination Report (FER). Claim 1, and therefore related Claims 2-10, of the amended set of claims were not disclosed in either the first or second priority applications. Indeed, the current amended Claim 1 was first claimed in Claim 6 of the priority application No. US 61/504,616. As a result, the claims currently pending at the Indian Patent office

for the impugned application cannot directly and unambiguously be derived from the two earliest priority applications. The claims of the priority application US61/504,616 is annexed herewith the as **Annexure III.**

Accordingly, the earliest effective priority date for the current pending claims derive from US 61/504,616 dated 5 July 2011. In the light of the above, any patent/ application filed prior to the impugned application ought to be treated as prior art for the purpose of the grounds raised in this opposition.

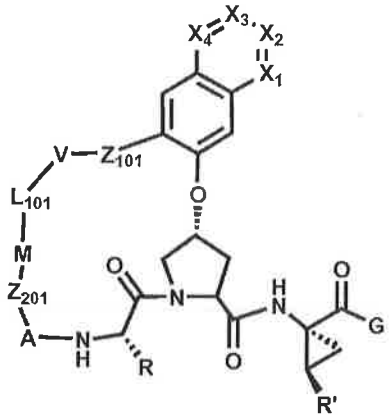
7.2 Lack of Inventive Step in View of WO2010/132163 and WO2009/064975

7.2.1 The impugned application lacks inventive step in light of the following prior publications.

PCT application PCT/US2010/030850 (WO2010/132163), annexed herewith as **Annexure IV**, is a patent application filed by the applicant herein. The international publication date for Annexure IV is 18th November 2010, which is prior to the second priority date for the impugned application i.e. 22nd June 2011.

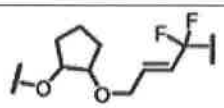
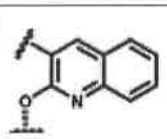
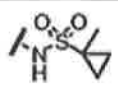
Annexure IV relates to HCV protease inhibitor compounds as can be seen on page 1, lines 12 and 13 and discloses compounds having a strong structural resemblance with compounds of formula (VII) of the impugned application, in particular, glecaprevir claimed in claim 10.

Page 18 of Annexure IV discloses a compound of the following structure:



(X)

with the following substituents (refer to Table 1, page 74 of Annexure IV):

Example #	R	M-L	Ar^2	Ar^1	R'	G
662.			Absent			

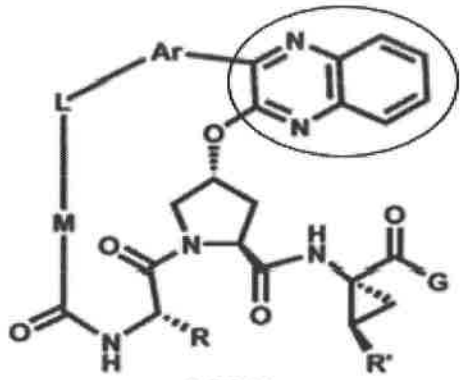
The difference between glecaprevir (compound of claim 10 of the impugned application) and compound of Example 662 of Annexure IV lies in the presence of a quinoxaline instead of a quinoline group (Ar^1 group).

No technical advance can be associated with the difference between glecaprevir (compound of claim 10) and the compound of example 662 of Annexure IV as both the compounds are alleged to have anti-HCV activity. The impugned application also fails to provide comparative data between these two compounds to show there is a technical advance by the presence of quinoxaline.

As such, the problem that the impugned application seeks to target could be simply formulated by providing further anti-HCV compounds of Example 662 of Annexure IV. The quinoxaline group is already mentioned as a possible heteroaryl group in the page 107, line 3 of Annexure IV. This disclosure would prompt any person skilled in the art to try this substituent instead of the quinoline ring.

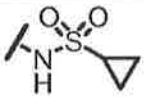
7.2.2 International patent application PCT/US2008/083541 (WO2009/064975) discloses HCV protease inhibitor compounds and was also filed by the applicant herein. This patent application was published on 22nd May 2009, therefore before the effective priority dates of the impugned application. The said patent application is annexed herewith as **Annexure V**. This application relates to HCV protease inhibitor compounds (refer to page 1, lines 10 and 11) which presents structural similarities to the compound of example 662 of Annexure IV.

In particular, Annexure V discloses the following compound of formula XV on page 16 comprising a quinoxaline ring (circled):



(XV)

This compound, with the following substitutions, shares strong structural similarities with glecaprevir, the compound as claimed in claim 10 of the impugned application:

R may be a ter-butyl		Disclosed in example 2 in table 1, page 17 of Annexure V
G may be		Disclosed in example 2 in table 1, page 17 of Annexure V
R' may be		Disclosed in example 2 in table 1, page 17 of Annexure V

In light of the above, any person skilled in the art, looking for an alternative anti-HCV compound to the compound of Example 662 of Annexure IV, would have considered the compound disclosed in Annexure V discussed above. Particularly since quinoxaline and quinoline are both heterocyclic aromatic organic compounds comprising a benzene ring and have approximatively the same molar mass. It is a common practice for a person skilled in the art to substitute one chemical group with another similar functional group in order to find an alternative to the chemical compound. Further, evaluation of the activity of the modified compound constitute routine experiments in the development and optimization of pharmaceutical compounds.

Accordingly, the selection of a quinoxaline instead of a quinoline which was already known from the disclosure of Annexure V is an obvious choice which does not involve any inventive step.

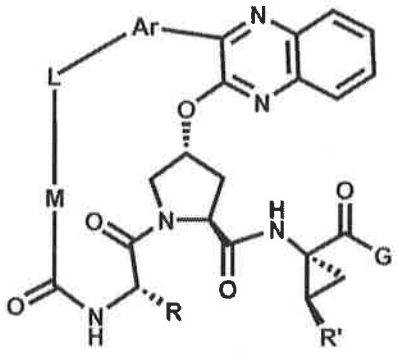
7.3 Lack of Inventive Step in View of WO2009/064975 and WO2008/057209 or WO2009/108507

7.3.1 Without prejudice to the arguments, the impugned application lacks inventive step in light of the following prior publications.

As already set out above, the patent application annexed herewith as **Annexure V** relates to HCV protease inhibitor compounds (refer to page 1, lines 10 and 11).

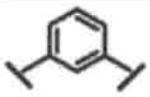
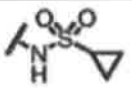
The compounds disclosed in Annexure V have a strong structural resemblance with glecapravir, the compound as claimed in claim 10 of the impugned application.

In particular, Annexure V discloses the following compound of the of formula XV on page 16:

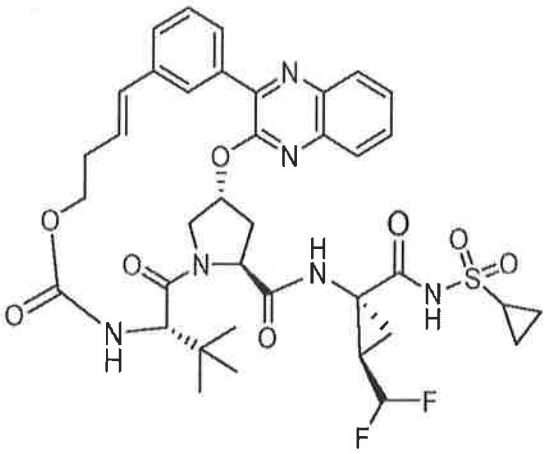
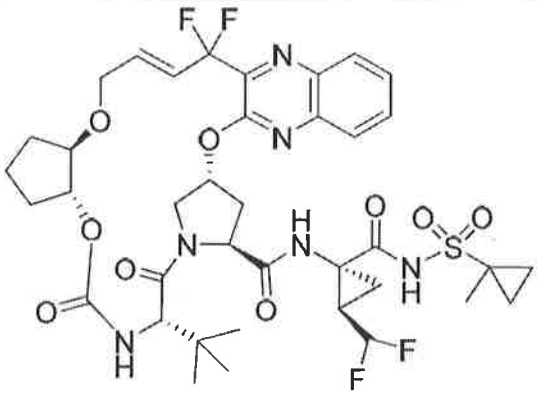


(XV)

with the following substituents (refer to page 17, Table 1):

Example	R	M-L	Ar	R'	G
2.					

The table set out below compares the compound presented in Example 2 of Annexure V against the compound of claim 10 of the impugned application. The comparison makes it sufficiently clear that the two compounds have the same central core and very similar lateral chains:

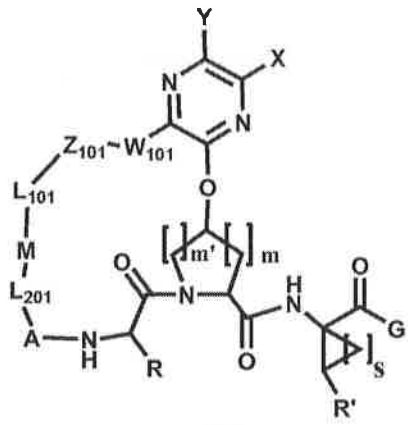
	
Compound of Example 2 (the Annexure V)	Glecaprevir (claim 10 of impugned application)

Moreover, the compound disclosed in Annexure V apart from having structural similarity is also directed to the same purpose as the impugned application that is, it is used in the treatment of HCV infections. The structural dissimilarity between the two compounds is as follows:

i. absence of an aryl group linked to the quinoxaline group in the compound of claim 10 of the impugned application(glecaprevir);
ii. presence of a –O-linkage connecting a cyclopentyl ring with the alkene chain in the compound of claim 10 of the impugned application (glecaprevir);
iii. presence of a difluoro substituent on the alkene chain in in compound of claim 10 of the impugned application (glecaprevir);
iv. presence of a methyl substituent on the terminal cyclopropyl ring in compound of claim 10 of the impugned application (glecaprevir).

No technical advance can be associated with the above identified differences, as the compounds disclosed in Annexure V are also believed to have anti-HCV activity. As such, the basis of the impugned application is simply to identify further anti-HCV compounds. Furthermore, the above identified differences are already

covered by the generic definition provided in Annexure V. This is indicated on page 4 of Annexure V and presented in a table form below. The relevant optional chemical structure is highlighted in the table for ease of deducing the relevant chemical entity of the impugned application (glecaprevir)



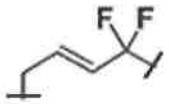
(I)

A is	absent or selected from **-(C=O)-**, -S(O)$_2$, -C=N-OR1 or -C(=N-CN);
L_{201} is	**absent** or [...]
M is	absent or selected from **O**, S, SO, SO_2 or NR1
L_{101} is	absent or selected from -C_1-C_8 alkylene, -C_2-C_8 alkenylene, or -C_2-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C_1-C_8 alkylene, substituted -C_2-C_8 alkenylene, or **substituted -C_2-C_8 alkynylene** each **containing** 0, **1**, 2, or 3 **heteroatoms selected from O**, S or N; -C_3-C_{12} cycloalkylene, or substituted -C_3-C_{12} cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C_3-C_{12} cycloalkenylene, or substituted -C_3-C_{12} cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;
Z_{101} is	**absent** or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl
W_{101} is	**absent** or selected from -O-, -S-, -NR_1-, -C(O)- or -C(O)NR_1-;
X and Y	**taken together with the carbon atoms to which they are attached to form a** carbocyclic moiety or a heterocyclic moiety **selected from aryl**, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocylic;
R_{101} and R_{102} are	independently selected from the group consisting of: (i) hydrogen, halogen, CN, CF_3, N_3, NO_2, OR_1, [...]
R and R' are	each independently selected from the group consisting of: (i) -C_1-C_8 alkyl, -C_2-C_8 alkenyl, or -C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; **substituted -C_1-C_8**

	alkyl, substituted -C_2-C_8 alkenyl, or substituted -C_2-C_8 alkynyl each containing 0, 1 , 2, or 3 heteroatoms selected from O, S or N; -C_3-C_{12} cycloalkyl, or substituted -C_3- C_{12} cycloalkyl; -C_4-C_{12} alkylcycloalkyl, or substituted -C_4-C_{12} alkylcycloalkyl; -C_3-C_{12} cycloalkenyl, or substituted -C_3-C_{12} cycloalkenyl; - C_4-C_{12} alkylcycloalkenyl, or substituted -C_4-C_{12} alkylcycloalkenyl; (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl; (iii) heterocycloalkyl or substituted heterocycloalkyl; (iv) hydrogen; deuterium;
G is	selected from -OH, **-NHS(O)$_2$-R$_2$**, -NH(SO_2)NR_3R_4, and NR_3R_4;
R2 is	selected from: (i) [...] (ii) [...] (iii) [...] -C_3-C_{12} cycloalkyl, or **substituted -C_3- C_{12} cycloalkyl**; -C_3-C_{12} cycloalkenyl, or substituted -C_3-C_{12} cycloalkenyl; heterocylic; substituted heterocyclic;
m is m' is s is	0, **1**, 2 or 3; 0, **1**, 2 or 3 **1**, 2, 3 or 4

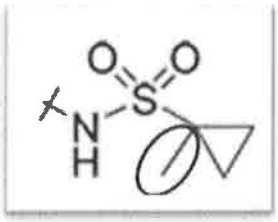
Thus, in view of the general teaching of Annexure V:

- the difluoro-substituent on the alkylene chain (iii), reproduced below,



can be derived from the definition of the L_{101} substituent of the formula (I) of Annexure V; and

- the methyl substituent on the terminal cyclopropyl ring **(iv)**, circled below,



can be derived from the definition of the G and R_2 substituents.

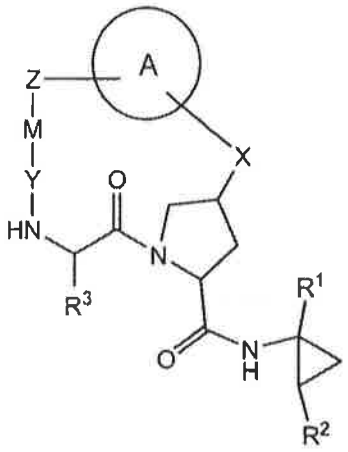
In addition, Table I to III of Annexure V already discloses compounds with a –O-alkene chain which makes it an obvious choice to the person skilled in the art to

employ such linkage and deduce the compound claimed in the impugned application. Any person looking for an alternative anti-HCV compound to the compound of example 2 of Annexure V would have definitely considered the general teaching of Annexure V and would have been able to provide a modified alkene chain with a difluoro-substituent and add a methyl substituent on the terminal cyclopropyl ring. Technically, the only differences between compounds disclosed in the Annexure V and the glecaprevir claimed in claim 10 are:
(i) absence of an aryl group linked to the quinoxaline group in glecaprevir
(ii) presence of a –O-linkage connecting a cyclopentyl ring with the alkene chain.

Thus, the compounds of the impugned application are obvious to a person skilled in the art and lacks inventiveness.

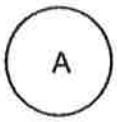
7.3.2 The international patent PCT/US2007/022460 (WO2008/057209) discloses macrocyclic compounds that are useful as inhibitors of the hepatitis C virus NS3 protease and compounds with a strong structural resemblance with compound of example 2 of Annexure V and glecaprevir (compound of claim 10 of the impugned application). This document is annexed here as **Annexure VI**. This patent is filed in the name of Merck & Co., Inc, and Instituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A., and was been published on 15 May 2008, i.e. before the earliest claimed priority date (21 September 2010) in the present application.

Annexure VI discloses a compound of the following formula (I)

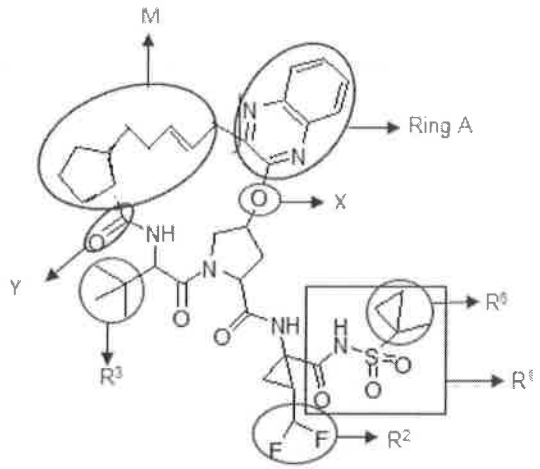
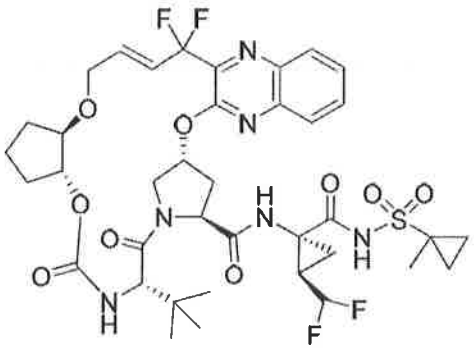


(I)

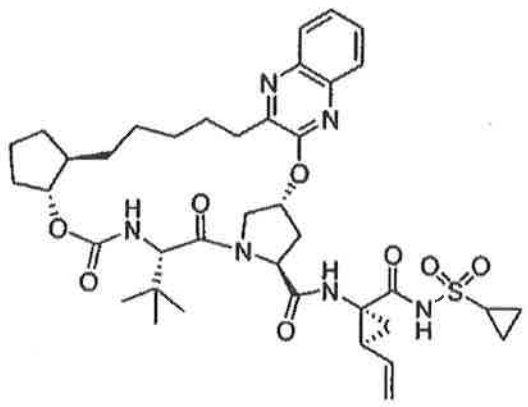
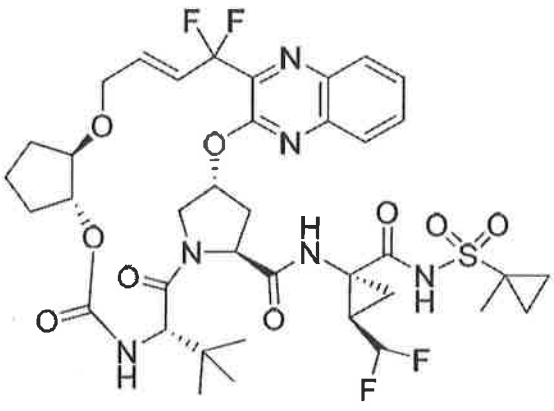
Wherein:

 is	3) **heterocyclic rings in which the heterocyclic ring system attaches to Z and X at points that are two independently selected ring atoms that are either two carbon ring atoms** or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of: b) 8-, 9- or **10-membered** saturated or **unsaturated bicyclic rings with** 1, **2**, or 3 heteroatom ring atoms independently selected from the group consisting of **N**, O or S, and
R^1 is	selected from the group consisting of [...]-**$CONR^{10}SO_2R^6$**
R^2 is	selected from the group consisting of **C_1-C_6 alkyl**, C_2-C_6 alkenyl, and C_3-C_8 cycloalkyl, wherein said R^2 are **substituted** with 0 to 3 independently selected **halogen atoms**;
R^3 is	selected from the group consisting of [...] **C_1-C_8 alkyl**
Y is	selected from the group consisting of **-C(O)-**, [...] -OC(O)-,
M is	selected from the group consisting of [...] **C_2-C_{12} alkenylenes,** wherein said M is substituted with **0 to 2 substituents F** independently selected from the group consisting of [...] **2 adjacent substituents F may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms selected from the group consisting of N**, [...];
R6 is	selected from the group consisting of [...] C_3-C_6 cycloalkyl, [...] wherein said R6 are substituted with 0 to 2 independently selected W substituents, each W is independently selected from the group consisting of [...], **C_1-C_6 alkyl**,
Z is	selected from [...] a **direct bond**
X is	selected from the group consisting of **-O-**, -...

The compound deduced from the above highlighted substituents is represented below:

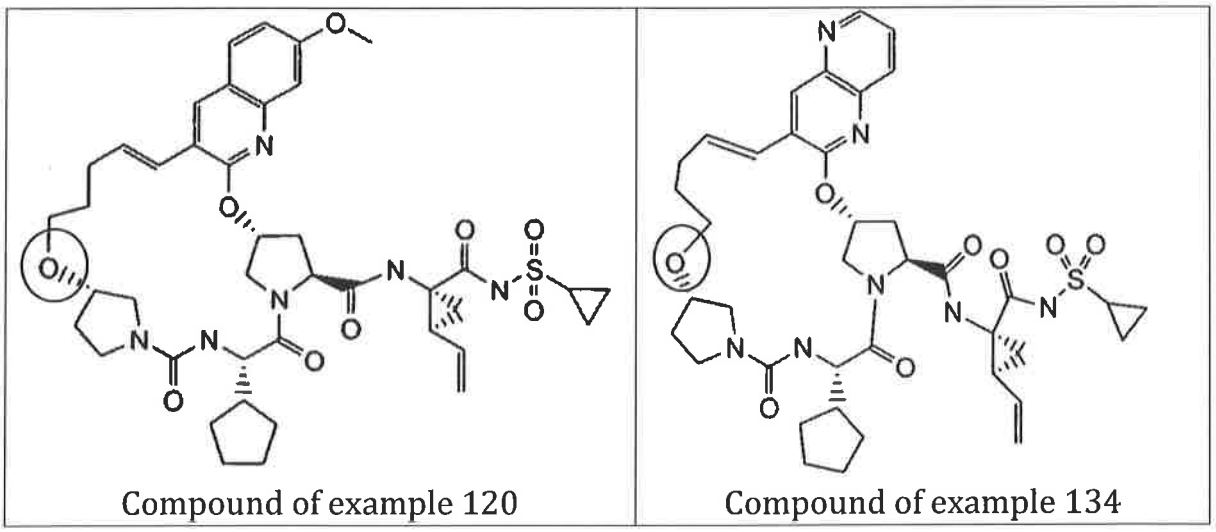
	
Compound that can be deduced from the above highlighted substituents	Glecaprevir which is claim 10 of the impugned application

Additionally, Annexure VI discloses the compound of Example 108 found on page 146 as reproduced below. From the table below it is clear that this compound has the same central core as glecaprevir (compound of claim 10) and similar lateral chains.

	
Compound of Example 108 (of Annexure VI)	Glecaprevir which is claim 10 of the impugned application

This compound comprises the same cyclopentyl ring as glecaprevir (compound of claim 10 of the impugned application) and does not include an aryl ring linked to the quinaxaline group as in glecaprevir (compound of the impugned application).

Furthermore, specific examples disclosed in Annexure VI include compounds which have a C(O)O group as Y group. By way of example, it is possible to mention the compound of example 120 and the compound of example 134 reproduced below with the -O- linkage (circled) between the carbonyl group and the cyclopentyl ring:



Compound of example 120 | Compound of example 134

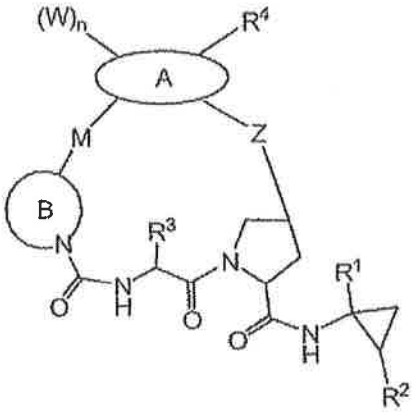
The person skilled in the art looking for alternative compounds to that of the compound of example 2 in Annexure VI would have been able to provide a compound without an aryl group linked the quinoxaline group and to employ a cyclopropyl ring as suggested in the compound of example 108 and a -O-linkage between the carbocyclic ring and the alkene chain as suggested in compounds of examples 120 and 134 without involving any inventive step.

7.3.3 International application filed PCT/US2009/033859 (WO2009/108507) filed in the name of Merck & Co., Inc. and Instituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A, was published on 3 September 2009, i.e. before the

earliest claimed priority date of the impugned application (21 September 2010). This document is annexed herewith as **Annexure VII**.

Annexure VII also relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus NS3 protease (refer to page 1, lines 5).

In particular, Annexure VII discloses a compound of the following formula (I) (refer to page 2):

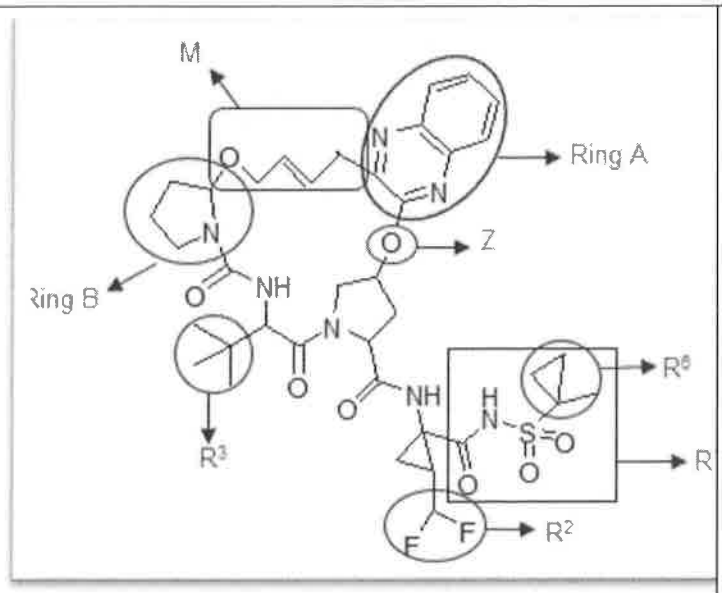


(I)

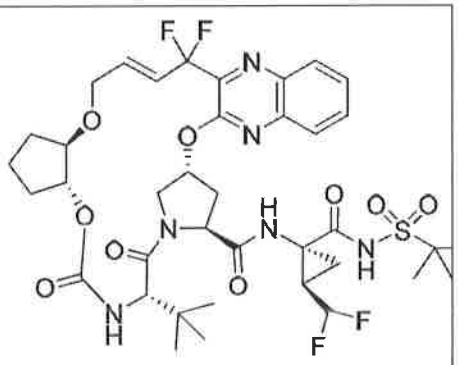
wherein,

n is	**0**,1 or 2
R^1 is	selected from the group consisting of CO^2R^{10}, **$CONR^{10}SO_2R^6$**, $CONR^{10}SO_2NR^8R^9$ and tetrazolyl
R^2 is	selected from the group consisting of **C_{1-6}alkyl**, C_{2-6}alkenyl and C_{3-8}cycloalkyl, wherein said R^2 alkyl, alkenyl or cycloalkyl is **substituted with 0 to 3 halogens**;
R^3 is	selected from the group consisting of **C_{1-8}alkyl**, [...]
ring B is	selected from the group consisting of N-linked 4-to 9-membered heterocycles [...]
M is	selected from the group consisting of C_{3-9}alkylene, **C_{3-9}alkenylene** and C_{3-9}alkynylene, substituted by 0 to 3 substituents selected from the group consisting of C_{1-6}alkyl, $(CH_2)_{0-3}C_{3-8}$cycloalkyl and $(CH_2)_{0-3}$aryl, and **containing 0 or 1 member selected** from the group consisting of **O**, S and NR_{10} group; and
ring A is	selected from the group consisting of **8- to 14-membered fused carbobi-** and carbotri**cyclic ring systems**, **containing 0 to 4 heteroatoms selected from N**, O and S.
R^4 is	selected from the group consisting of **H**, [...]

each W is	independently selected from the group consisting of halogen, OR^1, C_{1-6}alkyl, CN, NO_2, CF_3, CO_2R^{10}, $CON(R^{10})_2$, COR^{10}, $NR^5C(O)R^{10}$, aryl and heteroaryl;
each R^6 is	independently selected from the group consisting of [...]**C_{3-6}cycloalkyl** [...], wherein said R^6 alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is substituted with 0 to 2 **Q substituents**;
each Q is	independently selected from the group consisting of halogen, OR^{10}, **C_{1-6}alkyl**,
each R^{10} is	independently selected from the group consisting of H and C_{1-6}alkyl;
Z is	C_{1-6}alkylene, **C_{0-5}alkylene-O-**,



Compound that can be deduced from the above highlighted substituents



Glecaprevir (claim 10)

In light of the above, it can be concluded that the teachings of Annexure VII provide another path to incorporate a –O- linkage between the cyclopentyl ring and the alkene chain.

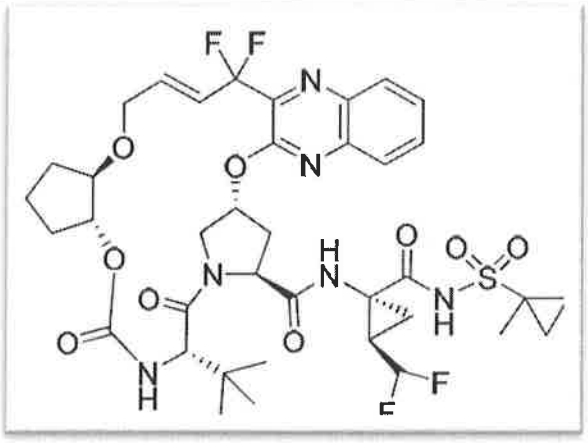
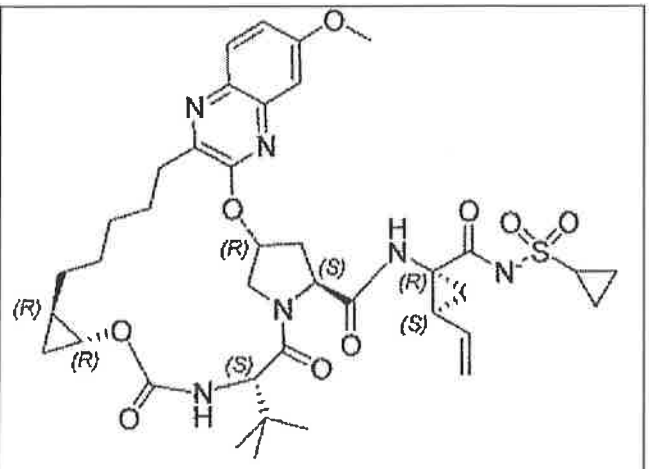
Thus, the subject matter of claims 1 to 10 of the impugned application can be deduced from the prior art and do not involve an inventive step. Hence the impugned application fails to disclose an inventive step under Section 25(1)(e) and should be refused in its entirety.

7.4 Section 25(1)(f) read with Section 3(d):

7.4.1 Glecaprevir, the compound claimed in claim 10, is a new form of grazoprevir, which is a known anti-HCV compound.

Grazoprevir, also known as MK-5172, is a hepatitis C virus protease inhibitor acting against the NS3/4A protease targets. This compound is notably disclosed on page 1 and claimed in claim 1 of International application PCT/US2009/050915 (WO2010/011566), annexed as **Annexure VIII**) filed in the name of Merck & CO., INC. and Instituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A, and published on 28 January 2010, i.e. before the earliest claimed priority date of the impugned application (21 September 2010).

The chemical structures of glecaprevir and grazoprevir are represented below:

	
Glecaprevir (compound of claim 10)	Grazoprevir

7.4.2 The Hon'ble Supreme Court in ***Novartis AG vs Union of India & Others (AIR 2013 SC 1311)*** (hereinafter the "Glivec case"), observed "*[T]he amended portion*

of Section 3(d) clearly sets up a second tier of qualifying standards for chemical substances/pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds".

[Refer to page 56, para 103].

The Supreme Court interpreted "efficacy" as "therapeutic efficacy" stating that the "therapeutic efficacy" of a medicine must be judged strictly and narrowly.

[Refer to page 90, para 180].

The Court also stated that:

"...the physico-chemical properties of beta crystalline form of Imatinib Mesylate, namely (i) more beneficial flow properties, (ii) better thermodynamic stability, and (iii) lower hygroscopicity, may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of section 3(d) of the Act, since these properties have nothing to do with therapeutic efficacy"

[Refer to page 94, para 187]

7.4.3 It is submitted that in pharmacology, intrinsic activity or efficacy refers to the ability of a drug to induce a biological response in its molecular target. Efficacy is defined as *"the generation of a response from the drug receptor complex". Efficacy is that property intrinsic to a particular drug that determines how good an agonist the drug is.*

(See Brunton L.L, Lazo J.G et al, *"Goodman and Gilman's The Pharmacological Basis of Therapeutics" 11th edition, McGraw-Hill, Page 35, lines 1-7,* annexed with this representation as **Annexure IX**).

7.2.4 Another useful and more detailed definition of efficacy is that provided in Tripathi K.D, *"Essentials of Medical Pharmacology",* 5th edition, Jaypee Brothers Medical Publishers Ltd, Page 37, lines 10-13 (annexed with this representation as **Annexure X**) which broadly defines efficacy as *"ability of the drug to activate*

(induce a conformational change in) the receptor consequent to receptor occupation."

7.4.5 Both of the above definitions establish that a mere physical variant of an existing pharmaceutical product lacks the necessary quality of therapeutic efficacy which is a condition precedent to a known substance being considered patentable under the Act. It is also an established position of law that the term "efficacy" in Section 3(d) means therapeutic efficacy for pharmaceutical products.

7.4.6 It is a matter of record that glecaprevir (compound of claim 10) does not show any enhancement of therapeutic efficacy when compared with the known efficacy of grazoprevir. On the contrary, glecaprevir has a lower clinical (i.e. in vivo) antiviral activity than grazoprevir as demonstrated in the citations and table below:

- *"Potent Antiviral Activities of the Direct-Acting Antivirals ABT-493 and ABT-530 with Three-Day Monotherapy for Hepatitis C Virus Genotype 1 Infection patients with HCV genotype 1 infection"* (pages 1546-1555) by Lawitz et al. (2015), which discusses the antiviral activity of the different protease inhibitors of HCV RNA. The document is annexed with this representation as **Annexure XI**. For reducing the HCV RNA level in the patients, a dosage within the range of 100 to 700 mg of NS3/4A inhibitor had to be administered. Glecaprevir falls under this specific category of protease inhibitors.

- *"MK-5172: a second-generation protease inhibitor for the treatment of hepatitis C virus infection"* (Pages 1-10) by Gentile et al., (2014), which mentions that patients with HCV genotype 1 infection were administered with 50 to 800 mg of MK-5172 to inhibit HCV RNA activity. The article (annexed with this representation as **Annexure XII**) also mentions that this category of protease inhibitors also overcomes the drawbacks of the first generation protease inhibitors.

	Mean decline in plasma HCV RNA level (log_{10} IU/ml)	Reference
Glecapravir	3.8 to 4.3 $logs_{10}$	Annexure XI: Table 2
MK-5172	5.38 log_{10}	Annexure XII: paragraph 3.4

It should be noted that these results obtained *in vivo,* are representative of the clinical, *i.e.* real life data, for establishing the efficacy of the compounds, in comparison to experimental results obtained *in vitro*, e.g. with the replicon assays. Thus, these data are more reliable in comparison to the table presented in page 6 of the FER response filed by the Applicant herein vide a letter dated August 27, 2018.

Besides, claims 1-9 of the impugned application covers a wide variety of compounds within the scope of the broad Markush structure and claims that all the compounds covered have anti-HCV activity. However, the number of claimed variants appear to be disproportionate to what is actually disclosed and supported by pharmacological evidence as disclosed in the complete specification of the invention. Support for the alleged anti-HCV activity of the claimed compound can be found on pages 122 and 123 of the impugned application.

The EC_{50} values of only few compounds are provided in the disclosure of the impugned application. In particular compounds of Examples 1, 2, 4, 5, 6, 8 and 65 falling in the scope of claim 1, when tested using different genotype replicon assays are indicated (refer to pages 122 and 123 of the impugned application). Other than this the impugned application does not provide evidence demonstrating that substantially all the compounds covered by claim 1 possess anti-HCV activity. It may thus be concluded that the impugned application fails to provide the evidence that all the compounds covered within the scope of formula (VII) has any anti-HCV activity at all. In light of the foregoing it is not possible to determine whether the claimed compounds show advanced therapeutic efficacy with respect to the

compounds mentioned in the prior arts and such claims should be dismissed due to lack of inventive step.

Therefore, in light of the above, it is respectfully submitted that the impugned application claims a derivative of a known substance, and therefore the applicant has failed to discharge the onus of fulfilling the requirement under section 3(d) of the Act. Hence, the impugned application cannot be treated as a patentable invention and should be refused under Section 25(1)(f) of the Act.

7.5 Section 25(1)(g): Insufficiency of disclosure

7.5.1 Claims 1 to 9 claim a wide variety of compounds all of which claim to demonstrate anti-HCV activity. The Markush formula claimed in the patent applications claims a large number of compounds and claims that all of them show anti HCV activity. However, whether all claimed variants of the Markush formula actually show anti HCV activity cannot be precisely determined without undue burden of individually testing each of the compounds encompassed within the scope of such an extremely broad Markush structure.

By way of example, if we just consider substituent B of Formula VII it can be seen that B can either be any C_3-C_{12} cycloalkyl or any 4- to 6-membered heterocycloalkyl group which can be substituted by any number of substituents selected from any halo, C_1-C_8 alkyl or C_2-C8 alkenyl. So, it can be concluded that it is not possible for a person skilled in the art to determine the number and nature of different substituents B covered without performing a number of experimentations.

In addition, the synthesis of less than 297 compounds is exemplified in the impugned application, irrespective of the corresponding general formula

considered, while formula (VII) alone likely covers more than about 10^8 different compounds.

Moreover, the impugned patent application only discloses synthesis of around 297 compounds, without considering that formula VII alone encompasses about 10^8 different compounds. So, without providing sufficient clinical data for all the different compounds within the scope of Markush structure of Formula VII, it will be prejudicial to consider that all such compounds show anti HCV activity.

It can thus be concluded that the disclosure of the invention does not commensurate with the broad scope of claims 1 to 9.

7.3.2 Hence, given the absence of evidence demonstrating that substantially all the compounds covered by claim 1 possesses an anti-HCV activity, there is no basis for the Applicant to claim that all compounds of formula (VII) possess purported anti-HCV activity.

7.3.3 In light of the foregoing, the Opponent submits that the compounds of formula (VII) of claims 1 to 9 should be considered as chemical structures resulting from the arbitrary combination of substituents, which therefore do not involve an inventive step and should not be allowed to be patented. Hence, the opponent submits that claim 1 ought to be rejected under u/S 25(1)(g) of the Act due to insufficiency of disclosure.

9. Relief sought:

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

(i) That Indian Application No. 2891/DELNP/2013 in the name of Enanta Pharmaceuticals Inc. 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 12th day of June, 2019.

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Regn no.IN/PA 2802
For and on behalf of the opponents
DNP+ and Initiative for Medicines, Access & Knowledge, Inc (I-MAK)

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

List of Annexures:

Serial No.	Annexure Number	Annexure Details
1.	Annexure I	PCT publication of the impugned application
2.	Annexure II	Pending claims of the impugned application
3.	Annexure III	Claims of the priority document US61/504,616
4.	Annexure IV	PCT/US2010/030850 (WO2010/132163)
5.	Annexure V	PCT/US2008/083541 (WO2009/064975)
6.	Annexure VI	PCT/US2007/022460 (WO2008/057209)
7.	Annexure VII	PCT/US2009/033859 (WO2009/108507)
8.	Annexure VIII	PCT/US2009/050915 (WO2010/011566)
9.	Annexure IX	*Brunton L.L, Lazo J.G et al, "Goodman and Gilman's The Pharmacological Basis of Therapeutics" 11th edition, McGraw-Hill*
10.	Annexure X	*Tripathi K.D, "Essentials of Medical Pharmacology", 5th edition, Jaypee Brothers Medical Publishers Ltd*
11.	Annexure XI	Lawitz et al., (2016) Antimicrobial Agents and Chemotherapy, 60: 1546-1555
12.	Annexure XII	Gentile *et al.*, (2014) *Expert Opin. Investig. Drugs*, **23** : 1-10