The Patents Act, 1970 (As Amended in 2005)
(Section 25(1) & Section 15)

In the matter of Application no. 9313/DELNP/2011 filed in India on 28/11/2011 for Grant of Patent; Corresponding International Patent Application No. PCT/US2010/034600, dated 12/05/2010 Claiming Priority Date 13/05/2009, 10/07/2009, 01/09/2009 of USA;

Applicant: M/S GILEAD SCIENCES, INC.

ATTORNEY PRESENT FOR ARGUMENT: Dr. JYOTI C. RAMANI & Dr. AMRISH TIWARI

Opponent: M/S MSN LABORATORIES PRIVATE LIMITED, C-24, Industrial Estate, Sanath Nagar, Hyderabad 500 018, Telangana, India.

Date of Hearing: 17/01/2023

DEC IS ION

[A] An application titled as **"ANTIVIRAL COMPOUNDS"** was filed in the Patent Office, Delhi on dated 28/11/2011 for grant of Patent. The details of the application are mentioned herein below.

S. No.	Name of the document	Date of filing
1	Publication U/S 11A	22/02/2013
2	Form 18 filing done by…..APPLICANT HIMSELF	16/04/2013
3	FER	13/02/2018
4	Date of reply to FER	10/08/2018
5	Notice of opposition filed via form 7A u/s 25(1) of the Patents Act, 1970 and u/r 55 of the Patents Rules, 2003 (as amended) by M/S MSN LABORATORIES PRIVATE LIMITED (opponent)	31/10/2016
6	Hearing of the pre-grant opposition	17/01/2023
7	Written submission filed by the Applicant	22/01/2023
8	Withdrawal of pregrant opposition by opponent	10/01/2023

[B] The above mentioned application came up for hearing with the following pending objections after the completion of the Examination procedure of the application under section 12 and 13:

Objections

Formal Requirement(s)

1.The person "Sheng, Christopher" is not the inventor of the present application (see Form-1 filed dated 10/08/2018; Form-5 filed dated 28/11/2011 and 10/08/2018), but "Sheng, Christopher" has signed in the Form-1 filed dated 13/01/2012 and 10/08/2018 (in the para 7 of Form-1), please clarify this matter.

Invention u/s 2(1)(ja)

Response filed by applicant dated 10/08/2018 is not satisfactory and therefore, objection regarding inventive step is still maintained.

D1 is directed to Bis-basic ethers and thioethers of fluorenone, fluorenol and fluorene of formula 1; wherein: Z is oxygen, H2 or H, OH. Column 1, line 59 to 64 teaches that these compounds can be used as pharmaceuticals for preventing or inhibiting a viral infection and their use as an antiviral agent. Column 2 teaches fluorenes when Z is H2 and can be shown by the formula (c). D2 is generally directed to antiviral compounds and more specifically directed to compounds which can inhibit the function of NS5A protein encoded by Hepatitis C virus. Compound of Formula (I) disclosed in D2: wherein; R1 and R2 are independently selected fromgroups that include –halo which can be -fluoro. (Page 4, line **4** and line 8), R3 and R4 are each independently selected from hydrogen, R9-C(O)-, and R9-C(S)-. (Page 6, line 10 and 11), X and Yinclude –CH2 group. (Page 3, line 3 and line 5), m and n are independently 0, 1, or 2. (Page 2, last line), q and s are independently 0, 1, 2, 3, or 4. (Page 3, line 1), u and v are independently 0, 1, 2, or 3. (Page 3, line 2), R7 and R8 include –Hydrogen. (Page 4, line 23-24), R5 and R6 (on page 11) as alkyl and each alkyl can optionally form a fused three to six-membered ring with an adjacent carbon atom provide one of the structures shown on page 11. The closest compound disclosed is a symmetric compound as example 24-23 on page 156. In view of the aforesaid, it is seen that compound claimed in claim 1 contains: Difluoro fluorene ring system instead of biphenyl ring, Azaspiro [2.4] heptan-yl and 7- azabicyclo [2.2.1] hept-7-yl instead of two pyrrole ring on either side of the–difluoro fluorene core and Benzimidazole in position of one of the imidazole rings. The teachings/prior arts which motivate a person skilled in the art to modify the compound of D1 to arrive at the structurally closest compound to the compound claimed in the present patent application. The compound of formula 1 of D1 having antiviral activity as a starting compound. The person skilled in the art looking to modify antiviral compound of D1 (particularly for the treatment of Hepatitis C virus) will look for substituent present in known antiviral compounds used for the treatment of Hepatitis C virus, such as the compound disclosed in D2. In view of the teachings of D1 and D2, a person skilled in the art will substitute the substituents present on the benzene ring of the diphenyl component of D2 at the benzene ring of the fluorene compound of D1 in a similar way.

The teachings/prior arts which motivate a person skilled in the art to modify further the compound of Formula-A (See pregrant opposition page no. 10) to arrive at the compound claimed in the present patent application.

I. ‘Azaspiro’ group on left side and ‘Azabicyclo’ group on right side of fluorene ring. The substituents on compound of formula I of D2, R5 and R6 (on page 11 of D2) can be as alkyl and each alkyl can optionally form a fused three to six-membered ring with an adjacent carbon atom provide one of the structures shown on page 11 of D2. In other words, the ‘pyrrole’ ring of a compound of Formula-A (See pre-grant opposition page no. 10) can be fused to form a three to six-membered ring structure [including Azaspiro ring]. Further, D3 teaches compounds, compositions and methods for the treatment of hepatitis C virus (HCV) infection. D3 specifically discloses at page 455, [1363]; example M145, the compound of example M145 having Azaspiro ring instead of pyrrole ring. In view of the teachings of D2 and D3, a person skilled in the art will be motivated to make a drug (against HCV virus) withAzaspiro ring as D2 teaches three to six-membered ring as a possible substituent on pyrrole ring of formula I of D2 and D3 specifically teaches a similar compound with azaspiro ring instead of pyrrole ring. D4 teaches the use of bicyclic ring on drugs which are used for the treatment of Hepatitis C Virus. D4 also specifically discloses the antiviral compound with a bridged bicyclic moiety (Page 45). In view of the teachings of D4, a person skilled in the art will be motivated to make a drug (against HCV virus) with bridged bicyclic moiety as D2 teachesa fused ring (bicyclic ring) as a possible substituent on pyrrole ring of formula I and D4 teaches bridged bicyclic moiety to enhance antiviral activity. Thus a person skilled in the art will consider modifying the pyrrole ring in the compound of Formula-A (See pre-grant opposition page no. 10) with bridge bicyclic moiety to enhance the Antiviral activity. The teaching of D2 and D4, a person skilled in the art will be motivated to use bridged bicyclic moiety by modifying one of the imidazole rings to enhance the antiviral activity due to the following teachings. • D2 teaches a fused ring (bicyclic ring) as a possible substituent on the imidazole ring [i.e. Bridge bicyclic moiety]; • Bridge bicyclic moiety enhances antiviral activity (D4). In order to employ both the modifications (i.e. Azaspiro (fused 3-member ring) and bridge bicyclic moiety), it is obvious for a person skilled in the art to modify the

compound of Formula-A (See pre-grant opposition page no. 10) by modifying one pyrrole ring to Azaspiro ring and modifying the other pyrrole ring so as to get a bridge bicyclic moiety.

II. Difluoro substitution on fluorene ring system D5 describes the effect of fluorine on physicochemical properties at page 637. D5 teaches that the Drug products which are having allylic carbons (next SP3 hybridized carbon to the double bond) **s**ubstituted by fluorine atoms significantly increase the pharmacokinetic properties and bioavailability properties of the said drug. For CH3COOH, the allylic carbon is CH3group and when it is substituted with fluorine atoms (CHF2COOH), its pKa value is significantly changed which will enhance the pharmacokinetic properties and bioavailability properties of the drug products. The teaching of D5 it is obvious for a person skilled in the art to modify compound of Formula-A (See pre-grant opposition page no. 10) with fluorine atom at the allylic carbon atom in the fluorene ring as the same will tend to enhance the pharmacokinetic properties and bioavailability properties of the HCV drug to arrive at Difluoro fluorene ring system of the present patent application.

III. Replacement of the imidazole group with Benzimidazole group D6 teaches that the compounds of Benzimidazole class are efficient inhibitors of HCV RNA replication in cell culture. D6 also reported the detailed analysis of the mechanism of action of selected Benzimidazole inhibitors. D6 motivates a person skilled in the art to make a drug (against HCV) with Benzimidazole instead imidazole ring in the compound of Formula-A (See pre-grant opposition page no. 10) to enhance the Antiviral activity. A person skilled in the art will be motivated by the teaching of D6 to replace the imidazole group with the Benzimidazole group. On the other hand, a skilled person will also look to maintain the imidazole group which is an essential feature of the compound disclosed in D2. In view of the aforesaid, a person skilled in the art will consider replacing one of the imidazole groups of the compound of Formula-A with the benzimidazole group as shown above and will arrive at the compound claimed in the present application. Thus, as per the submissions made under this section, the present patent application is obvious and devoid of inventive merit on the basis of: Combined teaching of D1, D2, D3, D4, D5, and D6. Hence, in view of the above-cited documents the present claims lack inventive step & fail to meet the requirement of section 2(1)(j)(a) of the Patents Act, 1970.

Non-Patentability u/s 3

Response filed for Non-Patentability is unacceptable because the applicant does not provide any data showing any synergy effect of the pharmaceutical composition claimed in claim 2 and 3 in the complete specification. Hence, claims 2-3 are not allowable u/s 3(e) of the Patents Act 1970.

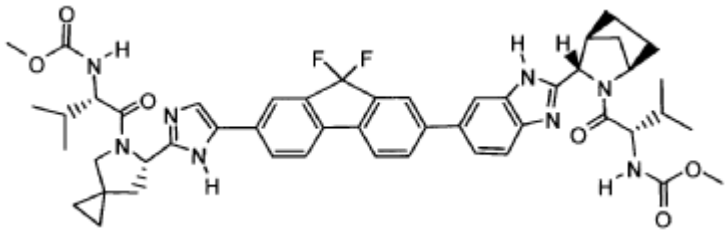
Other Requirement(s)

1. Recitation “further comprising” used in dependent claims is vague and unclear and makes the scope of the claims indefinite for which protection is sought.

2. Claim 3 is inconsistent with claim 2 in respect of the introduction of a NS5B polymerase inhibitor. 3. Claims 1 and 4 have been drafted as separate independent claims, although they refer to the same subject-matter (a compound). Moreover, due to overlapping scope, there is no clear distinction between the independent claims as to the scope of protection sought (under section 10(4)(c) of the Indian Patent Act 1970).

[C] The finally amended claims in response to hearing are reproduced herein below:

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

[D] Pre grant oppositions: One Pregrant Oppositions has been filed against the Grant of the Patent on this application. Filed by M/S MSN LABORATORIES PRIVATE LIMITED, C-24, Industrial Estate, Sanath Nagar, Hyderabad 500 018, Telangana, India. Dated 31 Oct 2016.

In respect of pregrant representations, the applicant had filed reply statements with detailed submissions in reply to each of the grounds in the oppositions on May 10, 2018.

The applicant and the opponent were issued a hearing notice on 22/12/2022. On 10/01/2023, Opponent's agent informed through e-mail that Opponent M/S MSN LABORATORIES PRIVATE LIMITED is no longer interested in pursuing the pregrant and therefore will not be attending the hearing scheduled on 17th January, 2023. Hearing u/s 14 was held on 17/01/2023. The applicant's attorneys attended the said hearing and submitted arguments in favour of their application. In response to hearing held with applicant's agent, two revised claims were filed on 22/01/2023. Applicant's submission is not reproduced here for the sake of brevity and can be seen in electronic file-wrapper of the present Application in Official website.

[E]Observation

The applicant filed written submission on 22/01/2023 and revised claims 1-2 on 22/01/2023 after the hearing. After perusing through the said submission and revised claims, the following observations have been made w.r.t the objections raised in the hearing notice.

(a) Formal requirements-

Formal objections is waived off in view of submission by applicant that "Sheng Christoper" is not the inventor of the present Indian application and his name as one of the inventors has been typed by mistake. The inventor "Sheng, Xiaoning" has signed the Form 1 two times. First time, on his own name and second time on the name of "Sheng Christopher" whose name was mistakenly typed on the execution page of Form 1.

(b) Invention u/s 2(1)(ja)

Following prior art documents were cited by Ld. Examiner (same documents were also cited by the opponent)

D1: US3592819: 13/07/1971
D2: WO2008/021927: 21/02/2008
D3: US20090068140: 12/03/2009
D4: WO2003/006490: 23/01/2003
D5: ChemBioChem 2004, 5, 637-643 entitled "Fluorine in Medicinal Chemistry, 2004.
D6: Journal of Virology 77 (24), 2003, 13225–13231 entitled "Mechanism of Action and Antiviral Activity of Benzimidazole-Based Allosteric Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase" December 2003.

After careful perusal of the cited documents D1-D6, it is observed that document D1 differs from instant application in that compounds disclosed in D1 are structurally distinct from the compounds of the instant claims. The compounds of the instant claims comprise a 9,9-difluoro-9H-fluorene core, and not a fluorenone or fluorenol or fluorene core as claimed in D1, Further core structure of D1 is differently substituted (substituted with basic ethers or thioethers) compared to instant application claim compound. Further, applicant submitted that D1 broadly states that the compounds can be used for preventing or inhibiting a viral infection but provides activity of only one compound against encephalomyocarditis (Ex. 13, cols. 17-18) therefore a person of skill in the art would not have a reason for expecting a compound useful for treating encephalomyocarditis virus would also be useful in treating HCV. In view of the above, it is clear that compounds of D1 do not provide any teaching or suggestion to arrive at the present invention.

Document D2 differs from compound of instant application claim in that at least D2 fails to disclose a 9,9-difluoro-9H-fluorene core, a benzimidazolyl moiety, azaspiro[2.4]heptan-6-yl moiety, a bridged azabicyclo[2.2.1]heptan-2-yl moiety. Thus, D2 compounds are completely different from the present compound and are not relevant for determining inventive step.

Document D3 differs from compound of instant application claim in that at least D3 fails to disclose a 9,9-difluoro-9H-fluorene core, a benzimidazolyl moiety , a bridged azabicyclo[2.2.1]heptan-2-yl moiety.

Document D4 discloses bridged azabicyclo[2.2.1]heptan-2-yl moiety but compound disclosed in D4 not discloses other part of structure of compound claim in instant application. The applicant has clearly demonstrated in their submission how the current compound differs from the compound of D4.

Document D5 is a general article describing strategies for using fluorine substituents in medicinal chemistry, D5 makes no reference to modifying fluorene cores such as those found in the compounds of the present invention.

Compounds of D6 are structurally distinct from those of the instant claims. Further compounds A and B of D6 comprise a benzimidazolyl moiety substituted by a cyclohexyl ring which is entirely absent in the compounds of the present claims.

Further, it is found that working example has been provided in the complete specification for the preparation of the claimed compound of claim 1 in Example ED' on page 671 of the specification. Also, the specification provides the biological data for antiviral potency of the claimed compound in terms of EC50 value using a Renilla luciferase-based HCV replicon reporter assay on page 947.

In light of the above, it is observed that none of the cited documents D1-D6 of hearing notice either alone or in combination, teaches or suggest the compound as claimed in claim 1.

In view of the written submission by the applicant, it is clear that antiviral compound claimed in present invention are significantly different from the cited documents and thus, the solution proposed in the present invention is non-obvious over the cited prior art and a skilled person had no motivation to obtain the claimed antiviral compound, hence inventive step is acknowledged. In this regard, written argument submitted by the applicant is found persuasive therefore accepted.

(c)Non-Patentability u/s 3

Regarding Section 3(e), it is observed that subject matter of claim 2 relates to a pharmaceutical composition comprising a compound as claimed in claim 1 as an active ingredient, together with pharmaceutically acceptable carrier, wherein, the claimed composition derives its novelty and inventive step from the novel and inventive compound of the invention and the unexpected effect is achieved due to the unexpected effects

from the claimed compound. Accordingly, section 3(e) is not applicable in claim 2. In view of submission and amended claim, objection u/s 3(e) in respect of non- Patent-ability is met with.

(d) Other requirements-

Applicant has deleted claim 3, accordingly this objection stands moot.

To overcome objection u/s 10(4)(c), applicant has amended claim 1 to recite the expression "pharmaceutically acceptable salt thereof" in claim 1 and deleted claim 4.

In view of the above, it is evident that grounds taken by the opponent in opposition are not maintainable as the revised claims 1-2 are inventive over D1-D6 of the hearing notice and thus do constitute an invention u/s2(1)(j) of the Patents Act, 1970. Further, the claims are clear and sufficiently supported by the examples in the specification.

[F] In view of the aforesaid discussion, a patent is granted for the instant application with claims 1-2 dated 22/01/2023 and the opposition filed u/s 25(1) stands disposed off.

DATED: 25/01/2023

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