BEFORE THE CONTROLLER OF PATENTS

PATENT OFFICE, CHENNAI

(SECTION 25(1))

In the matter of PCT National Phase patent

Application No. 8533/DELNP/2012,

filed by

INSTITUT PASTEUR KOREA;

696 Sampyeong-dong Bundang-gu 463-400

Sungnam-si Gyeonggi-do Republic of Korea

And

INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST);101, me de Tolbiac, F-75013 Paris (FR).

1) INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST) ..... applicant,
2) Sankalp Rehabilitation Trust.....Opponent,

HEARING HELD ON 23/08/2023

Present in the hearing (Through video conference):

1) Mr. Amrish Tiwari, Mr. Sanjeeb Tiwari and Dr Jyoti Choithani Ramani of K & S PARTNERS,…….. Applicant
2) Ms Rajeshwari H; Ms. Pragya Singh Thakur; and Ms Prathibha Sankalp M/s RAJESHWARI & ASSOCIATES; on behalf of Sankalp Rehabilitation Trust;-……opponent

Decision

Brief History:

1) The PCT National Phase Patent application no 8533/DELNP/2012 has been filed on 28/09/2012 by the applicants INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST) with a title of

invention " ANTI-INFECTIVE COMPOUNDS" in the Patent Office, Delhi through the patent agent on record M/s. K & S PARTNERS, Intellectual Property Attorneys 109, Sector 44, Gurgaon 122003, National Capital Region, India having the International patent application no PCT/EP2011/001345 dt- 18/03/2011 with a priority no. US61/315,113, 18 Mar 2010 and US61/440, 937, 09 Feb 2011 .

2) The form 18 (Request for Examination) was filed against the said patent application 8533/DELNP/2012 by the agent M/s. K & S PARTNERS within the stipulated time period.

3) The first examination report was issued on 14/01/2019 and reply to first examination report was submitted by applicant on 10/07/2019.

4) The opponent SANKALP REHABILITATION TRUST, M/s RAJESHWARI & ASSOCIATE, has submitted the representation by way of opposition on 29/06/2020.

5) The applicant has submitted the amended claims 1-6 by way of form 13 with govt fees on 05/10/2023.

6) Applicant has submitted the reply statement on 05/10/2023.

7) The pre grant hearing notice was issued on 23/10/2023 scheduled on 24/11/2023.

6) There after applicant and opponent have taken the two time adjournments each and after allowing the adjournments the hearing notice was issued on 23/01/2024 and scheduled on 23/02/2024.

7) The hearing had been conducted and the matter was heard on the scheduled date through VC.

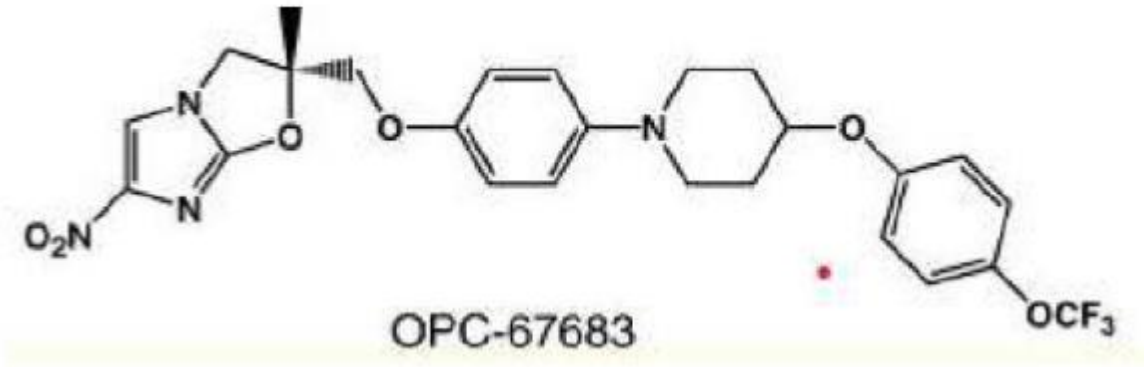
8) The applicant and opponent has submitted the written submission on 29/02/2024 and 28/02/2024 respectively.

9) Submission by the patent agent on behalf of opponent- Sankalp Rehabilitation Trust**:**

a) During hearing and thereafter in submission on 28/02/2024 By the Ms. PRAGYA SINGH THAKUR, FOR RAJESHWARI & ASSOCIATES, the patent agent on behalf of opponent Sankalp Rehabilitation Trust stated that D5 is the closest prior art document since the document discloses compound which are active against MDR/XDR forms of TB. The document discloses a compound denoted therein as OPC-67683 (commonly known as Delamanid) which was found to have potent anti-TB activity in in vitro studies.

b) The opponent also describes that OPC-67683 was also tested in strains of TB which have become resistant to conventional drugs PA-824, RFP (rifampicin), INH (isoniazid), EB (ethambutol), and PZA (pyrazinamide) and was found to be effective against all strains of TB which were resistant to these conventional drugs. The OPC-67683 is a compound which was

already known in the art to be an effective and potent compound against MDR/XDR forms of TB and for which even therapeutic efficacy had been established successfully.



OPC-67683

c) The opponent also states that a person skilled in the art follows the structural scaffold of OPC-67683 and brings about certain minor variations in the structural scaffold of OPC-67683 as per pertinent knowledge in the art before the priority date of the impugned application.

d) The Document D2 is also a document which relates to compounds which known to have good potency against resistant strains of TB. This document teaches that the bicyclic core of OPC-67683 which is imidazo-oxazole can be replaced by imidazo-pyridine without loss of anti-MDR TB activity.

e) The opponent also states that D3 discloses substituted imidazo[1,2-a]pyridines and specifically discloses Compound 33, 34 and 35 with methylene amide bridge between imidazo-pyridine and phenyl.

f) In the document, D5 it is disclosed OPC-67683 was also tested in strains of TB which have become resistant to conventional drugs PA-824, RFP (rifampicin), INH (isoniazid), EB (ethambutol), and PZA (pyrazinamide) and was found to be effective against all strains of TB which were resistant to these conventional drugs and consequently, the compounds of impugned application do not have any technical advancement in respect of OPC-67683.

g) The opponents also states that the applicant has merely provided MIC values of few compounds out of the hundreds of compounds that the Applicant is trying to claims and even in this it is established in the impugned specification that there is no direct correlation between MIC values and efficacy values. This is because in the impugned specification while compound 47 and 54 were tested for their MIC values and in-vitro bactericidal activity (as provided in Example 3 from page 152 to page 153 of the specification), the compounds chosen for in-vivo activity are two completely different compounds namely compound 177 and compound 185(on page 154 of the impugned specification). So from the MIC values

provided no legible conclusion can be drawn of whether these compounds will be effective in-vivo also or not. As per the data provided in specification, there does not seem to be a correlation between the MIC and efficacy.

h) The opponent also states that the presently claimed compound is a new form of the known compound OPC-67683 designed by SAR modification of said compound while the structural scaffold of OPC67683 is preserved and therefore the claimed compounds are derivatives of OPC-67683.

i) The opponents also argued that the data submitted by the Applicant is MIC, which are in-vitro generated values and are not reflective of therapeutic efficacy which is always determined in in-vivo condition.

j) The specification reveals the synthesis of the imidazopyridine general scaffold, generally illustrated in Scheme 1 on page 18. According to the specification, derivatization of imidazopyridine compounds, namely scaffolds Ia and Ib, is carried out through schemes 1-13. The specification lacks guidance for the person skilled in the art engaged in reproducing the impugned invention, especially about the specific compounds like compound 289, on how to combine the various building blocks and the essential reaction conditions required to arrive at the claimed compounds. There is an absence of any synthesis scheme demonstrating the synthesis of claimed compounds, particularly compound 289 by utilizing the compounds from schemes 1-13 as reactants.

k) The opponent also states that in absence of exemplified compounds in the specification for each of the substituents claimed, the disclosure is akin to a jigsaw puzzle being provided to public at large as well as the person skilled in the art and assumption is placed that a person reading the specification would solve this jigsaw puzzle on their own and construe a compound from all the multitude of substituents recited in claim 1 on their own without any undue experimentation and that too when the specification also fails to provide the any synthesis schemes and reaction conditions for arriving at all the compounds claimed in the Markush.

10) **Submission by the patent agent on behalf of applicant-** INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST)**:**

a) During hearing and thereafter in submission on 29/02/2024 By Mr. AMRISH TIWARI & Dr. JYOTI CHOITHANI RAMANI of OF K&S PARTNERS on behalf of, INSTITUT PASTEUR KOREA and INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) (EPST), stated that an object of the present invention is to provide

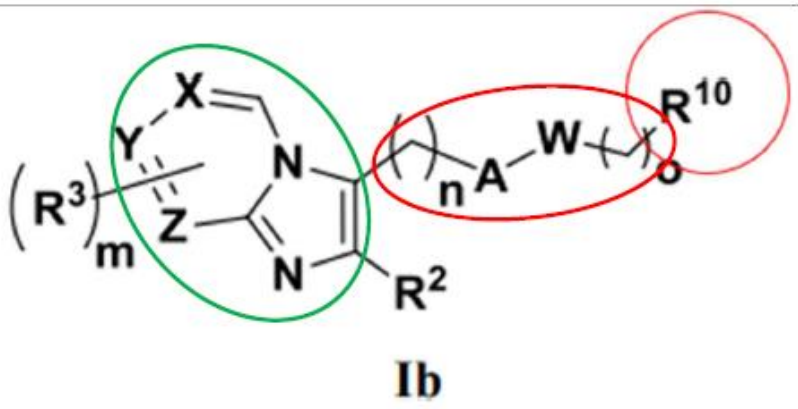
the compound of Markush formula 1(b) claimed in pending claim 1 is provided under on page 8, first compound from top along with definitions of all the substituents till page 9. On page 10, lines 1-3 describes that the compounds have an inhibitory activity on bacterial growth, preferably on the growth of M. tuberculosis, inside a host cell, preferably a macrophage, at a concentration between 1-20 mM, preferably less than 1 mM.

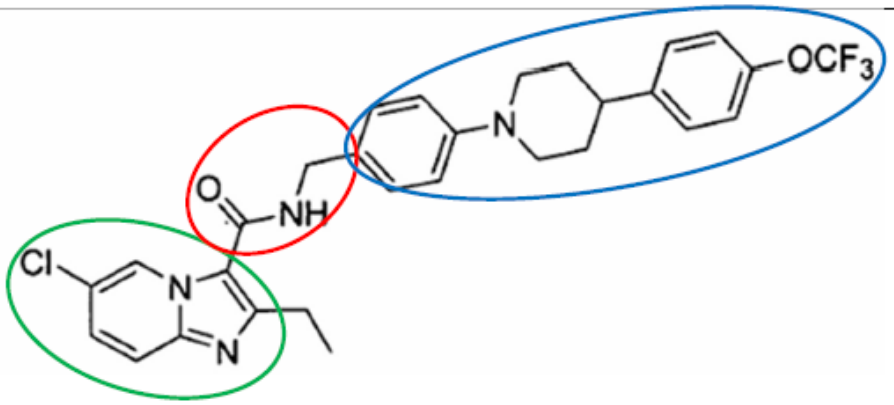
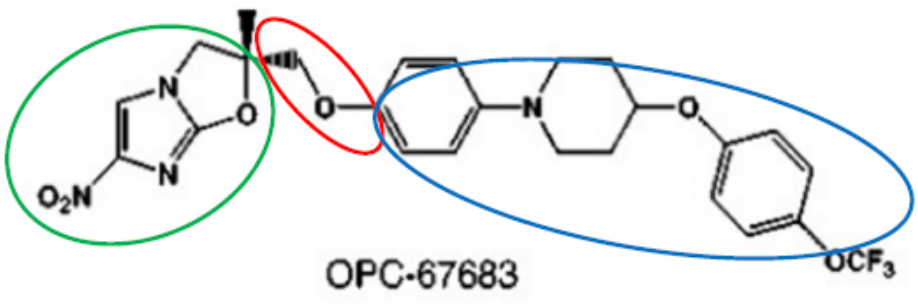
b) The applicant also states that on page 17, last para, Example 2 provides synthesis process for preparation of the claimed compound as outlined in general schemes 1-13. Resulting compounds were examined for inhibitory activity (MIC) using the assays described in example 1 and results are summarized in table 1. The specification discloses a total of 352 compounds along with their synthesis routes as well as their characterization data such as 1H NMR data and mass analysis data. The specification provides for all 352 compounds, the antitubular activity as tested according to Example 1 in Table 1.

c) The applicant also states that page 126, provides support for compound 289, provides its physical properties characterization data such as melting point (164.0 ^{o}C), 1HNMR data. The specification provides activity data for all the compounds from page 155 to 175, particularly, on page 171 for compound 289.

d) The applicant also states that the corresponding patent applications have been granted in all the corresponding countries (total 30) wherever application was filed.

e) The applicant also states that in 2006, D5(Matsumoto et al., 2006) reports Nitro-dihydro-imidazooxazoles as a potent anti-tubercular compound. D5(Matsumoto et al., 2006) discloses compound with totally different core structure with different MOA (mode of action). Title of D5 reads as “Nitro-dihydro-imidazooxasole derivatives” which shows that pharmacore of D5 is different from the pharmacore of the presently claimed compound which is “imidazopyrimidine”. D5 discloses an -O- linkage, in contrast to the amide linkage of Formula Ib.

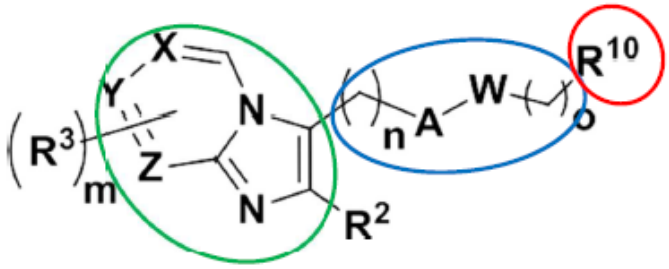
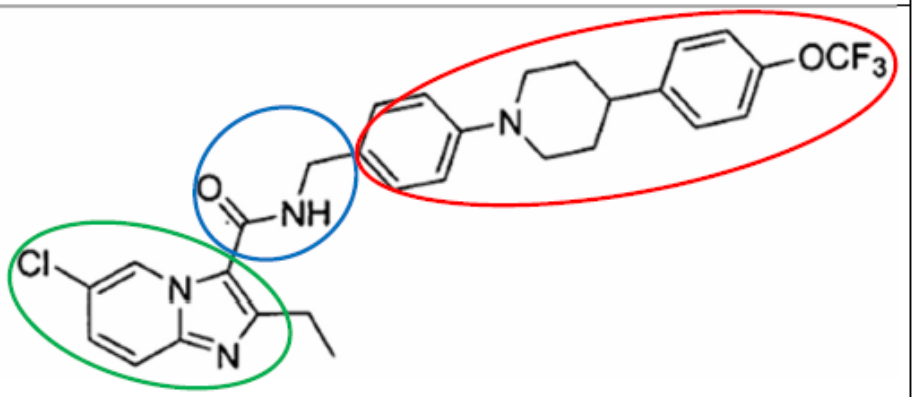
compound of present application	 Ib

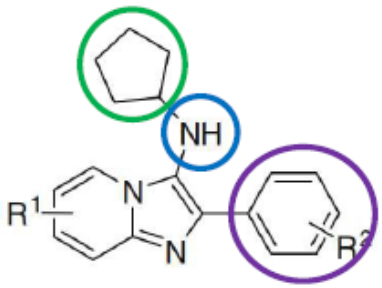
Compound 289 of present invention	
compound of D5	 OPC-67683

f) The applicant also states that the compound of D5 differs from the presently claimed compounds, specifically, compound 289 in respect of at least 4 following features, i.e.,

1. dihydro-imidazooxasole core instead of imidazo[1,2- a]pyridine core;
2. nitro substitution instead of chloro on different central;
3. methylene ether linker instead of alkyl amide linker;
4. different hydrophobic moiety (blue circle) which is aryl or heteroaryl moiety.

g) The applicant also states that the document D2 (2009, Odell et al.,) reports 3-amino-imidazo[1,2-a]pyridine compounds. The compounds of the present application differ from the compounds of D2 in position R2, since R2 of a claimed compounds cannot be any aryl substituent. The compounds of D2 contain 3-amino (NH) “bridge” to a cyclopentyl substituent on the imidazo[1,2-a]pyridine, whereas the presently claimed compounds contain a –(C=O)NH-(CH2)- linkage which further carries an R10 substituent which is different from cyclopentyl group and is selected from mono- and bicyclic aryls and heteroaryls.

compound of present application	
Compound 289 of present invention	

compound of D2	 **3** and **4**

h) The applicant also states that the document D3(WO2008/082490) is directed towards imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-c]pyridine and imidazo[1,2-d]triazine compounds and their uses as JNK inhibitors for treatment of various cancer.

i) The applicant also states that the document D4 (Kaplancikli et al., 2008) reports hydrazide derivatives of imidazo[1,2- a]pyridine for antituberculosis activity. The presently claimed compounds differ from the compound of D4 in respect of red highlighted group. The linker in the compounds of D4 is sulphide linkage attached to hydrazide moiety through carbonyl group, different from claimed compound linker attaching heterocyclic compounds with imidazole i.e., (-CO-NH-CH2-). Further, claimed compounds do not have R10 as phenyl (green circle). There is no teaching in D4 to replace the highlighted moiety with linker of presently claimed invention.

j) The applicant also states that a potent anti-TB compound does not encompass imidazo[1,2-a]pyridine scaffold. Furthermore, imidazo[1,2-a]pyridine derivatives with new moieties such as semicarbozones, hydrazides, 4-thiazolidinones were investigated for the Anti-TB activity.

k) The applicant also states that the compound of D5 differs from the presently claimed compounds, specifically, compound 289 in respect of at least 4 following features, i.e.,

1. dihydro-imidazooxasole core instead of imidazo[1,2- a]pyridine core;
2. nitro substitution instead of chloro on different central;
3. methylene ether linker instead of alkyl amide linker;
4. different hydrophobic moiety (blue circle) which is aryl or heteroaryl moiety.

Accordingly, compound OPC-67683 cannot be called as a structurally closest known compound for the purpose of section 3(d). Thus, the compounds according to the present invention with distinct moieties are structurally different over the compounds disclosed in the

prior art documents and are not merely a derivative of a known substance. Rather, the compounds according to the present invention are novel and inventive compounds. Hence, the present invention does not come under the purview of the Section 3(d).

l) The applicant states that the specification provides in vitro and intracellular biological assays for the anti-bacterial activity of compound 289. The antibacterial activity is provided on page 171 on the specification, wherein the "+++" indicates activity in the range of < 1 mM.

11) After considering all the arguments by the applicant as well as opponent the following observations are made:

a) The impugned invention relates to the compounds which is used for the treatment of a bacterial infection which is tuberculosis.
b) In the specification the activity data for all the compounds from page 155 to 175, particularly, on page 171 for compound 289 has been described.
c) The cited document D5 described as "Nitro-dihydro-imidazooxasole derivatives" which is different from the claimed compound which is "imidazopyrimidine" wrt the linkage substitutions.
d) It is also to be noted that the compounds as stated in the cited document D2 is 3-amino (NH) "bridge" to a cyclopentyl substituent on the imidazo[1,2-a]pyridine. On the other hand the compounds of the impugned invention is a –(C=O)NH-(CH2)- linkage which further carries an R10 substituent which is different from cyclopentyl group and that is selected from mono- and bicyclic aryls and heteroaryls.
e) On the other hand, in the cited document D3 having the compound with JNK inhibitors and have a different therapeutic activity than the compound of the present application and relates to imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-c]pyridine and imidazo[1,2- d]triazine compounds.
f) It also evident that according to the compound stated in the cited document D4 is different from the claimed compounds of the impugned invention, specifically, compound 289.
g) It is crystal clear from above documents that the compound as disclosed in the cited documents is different from the claimed compounds, specially compound 289 of the impugned invention of the instant application.

h) According to the declaration of the inventor's , the Compound 289 was further tested. In particular, MIC of compound 289 was determined and it shows that at the first concentration giving 90% bacterial growth inhibition compared to DMSO control.

12) In light of the above observations and explanation and all the facts on record, I am of the opinion that the patent application 8533/DELNP/2012 having the amended claims 1-6 are novel and inventive and does not attract u/s 3(d) of the patent act and is proceed for grant and also, I reject the representation made by the opponent u/s 25(1) and pre-grant opposition is disposed off.

Dated 29 th Day of February, 2024.

(Dr. S. J. Sahu)

Jt. Controller of Patents and Designs