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知产视野

Brief Summary of a Medical Invalidation Case

-- One of Top Ten Influential Invalidation Cases

- Patent No. ZL 01820481.3
- Title: Novel Sulfonamides and Their Use as Endothelin Receptor Antagonists
- Patentee: Ekot Rhine medicine Ltd.
- Petitioner: Nanjing Chia-Tai Tianqing Ltd.

The drug "Macitentan" involved in this case is the first oral preparation approved for treating pulmonary hypertension, and can effectively delay the progress of diseases. This case is a patent challenge initiated by the drug imitation applicant aiming at the original drug after the drug imitation application is submitted.

This case has exemplary effects on patent examination with the following aspects: such as understanding of technical terms, identification of priority for Markush compounds and specific compounds, sufficient disclosure of compounds in table, supplementary experimental data and inventiveness judgment of compounds. CNIPA makes No. 48183 Decision of Invalidation Declaration Request and maintains the patent right effective based on the amended text submitted by the patentee.

The amended claims only focus on two compounds, i.e. Compound 104 and "Macitentan", distinct from the chain on the sulfamoyl group, Compound 104 being ethyl and "Maritentan" being propyl.

In addition to structure and preparation method of the compounds, the Description also performs an endothelin-receptor binding inhibition test of the compounds and lists IC50 values against ETA and ETB of 134 specific compounds. For Compound 104, mass spectral data and IC50 values for ETA and ETB are given, no specific preparation is described; for "Macitentan", only the structure is described as a table compound.

Verification of Priority of Specific Compounds

Compound 104 and "Macitentan" are not recorded in the priority document, so one dispute of this case is whether Compound 104 and "Macitentan" can enjoy the priority.

According to the basic principle of novelty, "a formula cannot destroy the novelty of a specific compound in the formula." This means that the Markush formula and the specific compound within its scope cannot be considered as the same technical solution, and thus cannot constitute the inventive

creation of the same subject matter.

Moreover, if any one specific compound in the scope of the Markush formula can be given priority to the prior application as it is covered by the formula, it means that a new specific compound obtained by further research in the Markush formula after the priority date could enjoy the "priority date", which obviously defeats the purpose of the priority system.

Therefore, the Decision deems that, to judge the priority of a specific compound, it depends on whether the specific compound is explicitly or implicitly described in the prior application. The specific compound not explicitly or implicitly described in the prior application cannot enjoy the priority.

Identification of the Sufficient Disclosure of the Compounds in Table

Sufficient disclosure of "Macitentan" is challenged in this case for it is a table compound. In the Decision, Compound 104 was firstly deemed to satisfy the provisions of sufficient disclosure, and based on such conclusion, whether "Macitentan" was sufficiently disclosed or not was further analyzed from three aspects of compound identification, preparation and use.

In terms of compound identification and preparation, first, "Macitentan" is very similar in structure to Compound 104 as aforesaid. From scheme 3 and other similar examples of the Description, the alkyl chain is introduced by reacting an alkylamine as a starting material with an aminosulfonyl chloride, the starting material for introducing the ethyl group is ethylamine when preparing Compound 104, and the ethylamine is only required to be replaced by propylamine when preparing "Macitentan". Second, Compounds 115 and 117 having similar structures with "Macitentan" is prepared in the Description, differing only in that the alkyl chain of Compound 115 is ethyl and the alkyl chain of Compound 117 is butyl. Based on these reasons, a person skilled in the art has no reason to suspect that the introduction of propyl groups according to a similar process would not lead to "Macitentan".

In terms of the use and effect of the compounds, as the Compound 104 and the 'Macitentan' only have one methylene difference, the 'Macitentan' can be reasonably expected to have the technical effect similar to the Compound 104; further, the compounds 115 and 117 only differ by one ethylene group, and the technical effects of the two are equivalent. It can be seen that, the difference of 1-2 carbon atoms between the alkyl chains connected to the aminosulfonamide groups has little influence on the antagonistic performance of the compounds. Moreover, the experimental data submitted later by the patentee also match the expectation.

Therefore, the Decision deems the reasons of unsufficient Disclosure of "Macitentan" provided by the petitioner are not established.

Judgment of Inventiveness of Specific Compounds

Petitioner questioned the inventive step of Compound 104 and "Macitentan" with Compound 7k as the closest prior art and in combination with other evidence and/or general knowledge in the art regarding isosteres.

As for the differences of the technical features,

when comparing Compound 104 and "Macitentan" lies in the sulfonamide moiety at the-4-position of the pyrimidine ring: nitrogen linked sulfonamide group in the patent vs. carbon linked sulfonamide group in the evidence.

As for the technical effect, comparing the IC50 values for ETA and ETB receptors of Compound 104 and "Macitentan" with those of Compound 7k, their effects on endothelin antagonism were essentially equivalent. So, the technical problem actually solved by the invention is to provide a different compound which has an antagonistic effect on both ETA and ETB receptors.

Moreover, it is believed in the prior that the changes in the sulfonamide moiety at the 4-position of the with Compound 7k, the most important difference pyrimidine ring are closely related to the activity of ETA, ETB receptors, and that many of the substituent changes made to the 4-position are directed to changing other moieties while keeping the carbo-linked sulfonamide group. Therefore, based on bioisosteric theory alone, it is not sufficient to deduce that a person skilled in the art could be motivated to replace the carbo-linked sulfonamide group in the evidence with an aza-sulfonamide group.

Therefore, the Decision deems the reasons of inventiveness of "Macitentan" provided by the petitioner are not established.

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Ms. FAN graduated from Jilin University with a B.S. degree in Food Engineering in 2000 and obtained a M.S. degree in Organic Chemistry from Tianjin University in 2004.

From 2008 to 2010, Ms. FAN joined Tee & Howe as a patent engineer.

From 2010 to 2013, Ms. FAN worked at the Patent Examination Cooperation Center of CNIPA as an examiner in the Chemistry Department.

Ms. FAN returned to Tee & Howe in 2013. She is qualified as a patent attorney and an administrative agent ad litem. Currently, she is the manager of the Biotech & Chemistry Patent Department.

With almost 15 years of experience in IP affairs, Ms. FAN specializes in foreign patent translation, prosecution, reexamination and invalidation etc. with a profession in the field of Organic Chemistry. Ms. FAN has served numerous well-known domestic and international companies in IP affairs.

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